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Development of novel MHAT C-C coupling reactions inspired by morphan-containing anticancer compounds

Laura Rodríguez González

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FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

DEPARTAMENT DE FARMACOLOGIA, TOXICOLOGIA I QUÍMICA TERAPÈUTICA

**DEVELOPMENT OF NOVEL MHAT C–C COUPLING
REACTIONS INSPIRED BY MORPHAN-CONTAINING
ANTICANCER COMPOUNDS**

**DESENVOLUPAMENT DE NOVES REACCIONS MHAT D'ACOBLEMENT C–C
INSPIRADES EN COMPOSTOS ANTICÀNCER AMB FRAGMENTS
MORFÀNICS**

LAURA RODRÍGUEZ GONZÁLEZ

2025



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PROGRAMA DE DOCTORAT EN QUÍMICA ORGÀNICA

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Abstract

Natural products have long served as a cornerstone of drug discovery, not only as therapeutic agents but also as key drivers of innovation in organic synthesis. Their intricate structures and remarkable biological activities have inspired the development of new synthetic strategies that enable the efficient construction of complex molecular frameworks. However, the complexity that makes natural products valuable also limits their practical accessibility, often requiring lengthy, low-yielding routes with reduced scalability. To overcome these limitations, two complementary approaches have emerged: function-oriented synthesis (FOS), which simplifies natural product structures while preserving bioactivity, and the development of new synthetic methodologies, allowing for more efficient and selective access to complex molecular architectures (Figure 1).

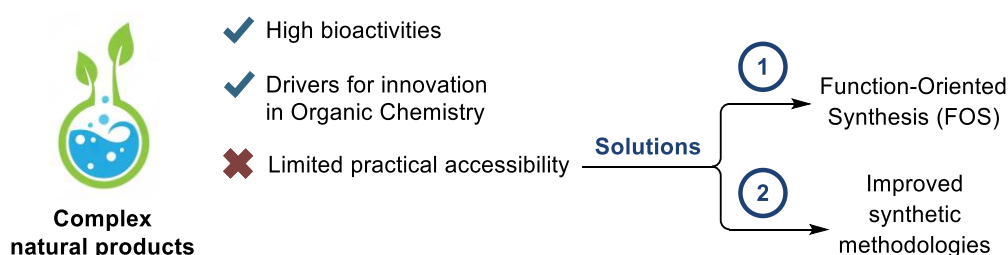
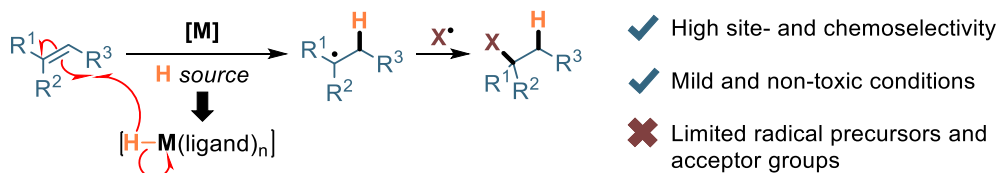


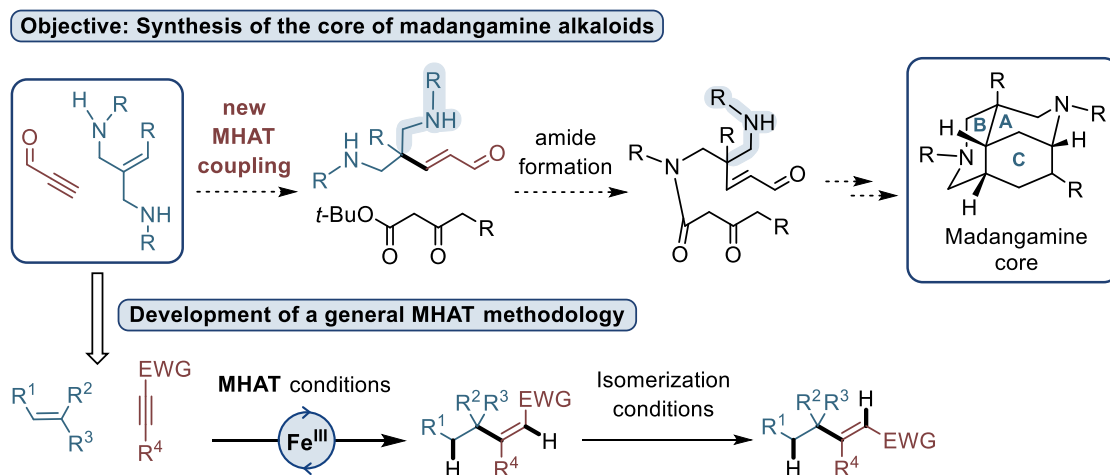
Figure 1: Confronting challenges in natural product synthesis for innovation.

In this context, radical-based transformations have gained increasing attention due to their ability to streamline molecular assembly under mild conditions, expand chemical space, and enable transformations that are difficult to achieve using traditional ionic chemistry. Among these, metal-catalyzed hydrogen atom transfer (MHAT) reactions have emerged as a powerful tool for selective C–C bond formation, proceeding under non-toxic conditions with high site- and chemoselectivity (Scheme 1). Despite their advantages, their full potential remains underexplored, particularly in terms of radical precursors and acceptor groups.



Scheme 1: Metal-Catalyzed Hydrogen Atom Transfer (MHAT).

This thesis aims to expand the utility of MHAT chemistry for the synthesis of bioactive compounds and complex natural products by developing new transformations and disconnection strategies. Firstly, in the context of the synthesis of the core of madangamine alkaloids, a novel MHAT C–C coupling was developed to form a key bond, enabling access to the tricyclic scaffold after classical approaches proved unsuccessful. The reaction involved a Giese addition of electron-deficient alkynes to neutral alkenes (*Scheme 2*), introducing a new disconnection approach to electron-deficient alkenes. This methodology exhibited broad functional group tolerance and proceeded under mild, non-toxic conditions with high atom efficiency and scalability. Furthermore, it enabled control over alkene geometry, favoring the *cis* isomer, which could be readily isomerized to the *trans* form. The method also allowed olefin installation near sterically hindered centers, offering a key advantage over conventional olefination techniques and expanding the synthetic toolbox to access complex molecular frameworks.

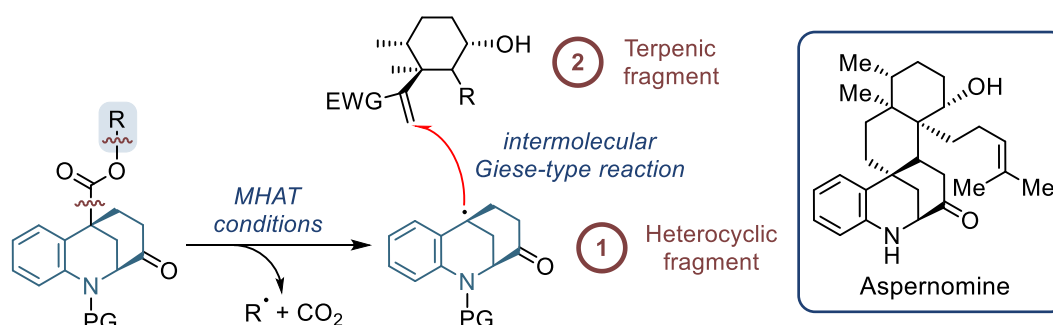


Scheme 2: Use of electron-deficient alkynes as acceptor groups in MHAT reactions to facilitate the synthesis of the core of madangamine alkaloids.

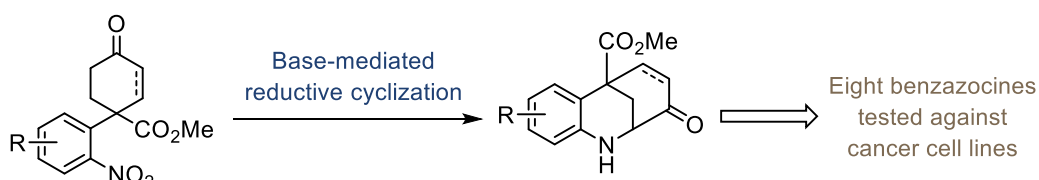
Secondly, with the ultimate goal of achieving the total synthesis of aspernomine, a convergent strategy was proposed, focusing on the preparation of its heterocyclic and terpenic components for late-stage coupling (*Scheme 3a*). Given the complexity of this task, the first step was to apply a function-oriented synthesis strategy to simplify the structure while retaining bioactivity. This approach focused on the synthesis of the 3,4-benzomorphan core, obtained through a base-mediated reductive cyclization of nitrophenyl ketones (*Scheme 3b*). The method provided a concise four-step approach,

achieving high yields of up to 87% in the key cyclization step. Biological evaluation of the analogs showed that their cytotoxicity was generally lower than that of aspernomine, indicating that additional structural elements beyond the core are critical for the full bioactivity of the natural product. Notably, however, the introduction of an enone moiety in the analogs enhanced antiproliferative activity, suggesting that the enone fragment may function as a key pharmacophore, similar to other Michael acceptor-based drugs. Further efforts were directed toward the total synthesis of aspernomine, with a novel MHAT-based methodology proposed to facilitate the coupling of the heterocyclic component to the terpenic fragment, ultimately advancing the synthesis toward its final stages.

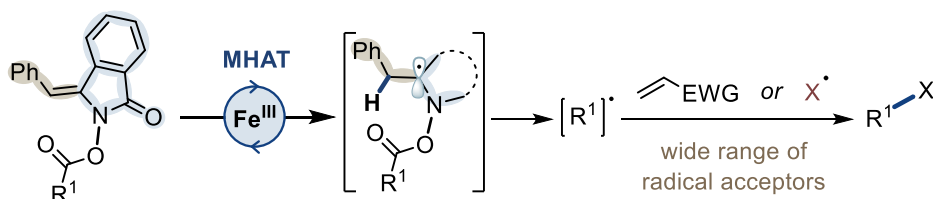
a) Proposed convergent strategy toward aspernomine



b) Synthesis of the heterocyclic fragment



c) Novel MHAT methodology to enable the intermolecular Giese addition



Scheme 3: a) Modular approach for the total synthesis of aspernomine. b) Base-mediated reductive cyclization of nitrophenyl ketones for the synthesis of the 3,4-benzomorphan core. c) MHAT-triggered decarboxylation of redox-active esters.

To achieve this transformation, a new class of redox-active esters (RAEs) was designed by incorporating an alkene fragment into the classical *N*-hydroxyphthalimide framework, facilitating decarboxylation under MHAT conditions (*Scheme 3c*). This modification allowed carboxylic acids to be utilized as radical precursors in MHAT reactions for the first time, expanding the scope of radical sources and broadening the applications of MHAT processes. The strategy also facilitated the generation of primary radicals and enabled the first-ever formation of linearly coupled products under MHAT conditions, complementing the branched products obtained from alkene-based precursors. The versatility of the RAEs was evaluated through Giese-type couplings with electron-deficient alkenes, generating a broad range of radicals. Then, they were further applied in a variety of well-established MHAT reactions, underscoring their potential for diverse synthetic applications.

Keywords: Radical chemistry · MHAT · Iron · Natural products · Anticancer

Resum

Els productes naturals han estat una font d'inspiració en la química orgànica i el desenvolupament de fàrmacs gràcies a la seva complexitat estructural i activitat biològica. No obstant això, aquesta complexitat dificulta la seva síntesi, requerint rutes llargues i poc escalables. Per superar aquestes limitacions, han sorgit dues estratègies: la síntesi orientada a la funció (FOS), que tracta de simplificar estructures mantenint-ne la bioactivitat, i el desenvolupament de noves metodologies sintètiques per a un accés més eficient a estructures complexes.

En aquest context, les transformacions radicalàries han guanyat rellevància per la seva capacitat d'aconseguir acoblaments sota condicions suaus. Entre elles, les reaccions de transferència d'hidrogen catalitzades per metalls (MHAT) han demostrat ser eines versàtils per a la formació selectiva d'enllaços C–C. Malgrat els seus avantatges, encara hi ha marge per ampliar el seu potencial, especialment en l'exploració de nous precursors radicalaris i grups acceptors.

Aquesta tesi busca ampliar l'abast de la química MHAT mitjançant el desenvolupament de noves transformacions per facilitar la síntesi de compostos bioactius i productes naturals. D'una banda, es va desenvolupar una nova metodologia d'acoblament C–C mitjançant MHAT basada en una addició de Giese entre alquins deficients d'electrons i alquens neutres, amb l'objectiu de sintetitzar el nucli tricíclic dels alcaloides de tipus madangamina. Aquesta metodologia va permetre el control de la geometria de l'alquè i va oferir una nova via per sintetitzar alquens electrodeficients.

D'altra banda, es va plantejar una estratègia convergent per a la síntesi de l'aspermomina. En primer lloc, per tal de sintetitzar el fragment de 3,4-benzomorfa es va desenvolupar una ciclació reductiva de nitrofenil cetones, amb una posterior avaluació de les propietats biològiques del nucli tricíclic que va indicar que la seva activitat era més baixa que la del producte natural. Posteriorment, per tal d'unificar el fragment heterocíclic i el fragment terpenic del producte natural es va proposar l'ús d'una nova classe d'èsters redox-actius (RAEs) adaptats a condicions MHAT per fer un acoblament descarboxilatiu. Aquest disseny va permetre, per primer cop, l'ús d'àcids carboxílics com a precursors radicalaris en reaccions MHAT, fent possible així l'accés a productes d'acoblament lineal.

Paraules clau: Química radicalària · MHAT · Ferro · Productes naturals · Anticàncer

List of Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic chemistry have been used following the recommendations from “*Guidelines for Authors*” of *J. Org. Chem.* **2020**.

4CzTPN	2,4,6-tris(4-carbazolyl)-1,3,5-triazine
4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	Acetyl
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
aq.	Aqueous
ATRP	Atom Transfer Radical Polymerization
AZADO	2-azaadamantane- <i>N</i> -oxyl
AZADOL	2-hydroxy-2-azaadamantane
BDE	Bond Dissociation Energy
BDMAP	1,6-bis(dimethylamino)pyrene
BEMP	2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Bn	Benzyl
Boc	<i>tert</i> -butoxycarbonyl
bpy	2,2'-bipyridine
Brettphos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
Bt	Benzotriazole

BuNAH	<i>N</i> -(<i>n</i> -butyl)-1,4-dihydronicotinamide
Bz	Benzoyl
cat	Catechol
cat.	Catalyst or catalytic
Cbs	<i>para</i> -chlorobenzenesulfonyl
Cbz	Benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
cod	1,5-cyclooctadiene
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
δ	Chemical shift
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCE	Dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEMS	Diethoxymethylsilane
DET	Diethyl tartrate
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
dibm	Diisobutyrylmethane

DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
DMIPS	Dimethyl(isopropyl)silyl
DMP	Dess–Martin Periodinane
DMPK	Drug metabolism and pharmacokinetics
DMPU	<i>N,N'</i> -dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
dpm	Dipivaloylmethanate
dppbz	1,2-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dpph	Bis(diphenylphosphino)hydrazine
dtbbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
DTBP	Di- <i>tert</i> -butyl peroxide
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
EDA	Electron Donor–Acceptor
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	Equivalent/s
ESI	Electrospray ionization
<i>et al.</i>	<i>et alii</i> (and others)
EWG	Electron-withdrawing group

F	Faraday constant
FG	Functional Group
FOS	Function-Oriented Synthesis
HAT	Hydrogen Atom Transfer
HE	Hantzsch Ester
HFIP	Hexafluoroisopropanol
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HRMS	High-Resolution Mass Spectrometry
IBX	2-iodo-1,3-benzoxathiol-1,1-dioxide
IC ₅₀	Half-maximal inhibitory concentration
ICTB	Isochromenilium tetrafluoroborate
<i>i</i> Pr	Isopropyl
<i>J</i>	Coupling constant
L	Ligand
LED	Light-Emitting Diode
M	Molar
M ⁺	Molecular ion
<i>m/z</i>	Mass to charge ratio
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
MHAT	Metal-Catalyzed Hydrogen Atom Transfer
MOM	Methoxymethyl
Ms	Mesyl

MS	Molecular Sieves
MTBE	Methyl <i>tert</i> -butyl ether
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MVK	Methyl Vinyl Ketone
MW	Microwaves
Nap	Naphthalene
NHC	<i>N</i> -heterocyclic carbene
NHPI	<i>N</i> -hydroxyphthalimide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NPhth	<i>N</i> -phthalimide
Nu	Nucleophile
<i>o</i> -DCB	<i>ortho</i> -dichlorobenzene
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
PC	Photocatalyst
PCET	Proton-Coupled Electron Transfer
PET	Photoinduced Electron Transfer
PG	Protecting Group
pin	Pinacol
PIFA	Phenyliodine bis(trifluoroacetate)
PMB	<i>para</i> -methoxybenzyl
PMHS	Polymethylhydrosiloxane

ppm	Parts per million
PPTS	Pyridinium <i>para</i> -toluenesulfonate
ppy	2-phenylpyridine
PRE	Persistent Radical Effect
py	Pyridine
R	Generalized alkyl group or substituent
RAE	Redox-Active Ester
rt	Room temperature
SEGPPOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SEM	2-(trimethylsilyl)ethoxymethyl
SES	2-(trimethylsilyl)ethanesulfonyl
SET	Single-Electron Transfer
S _H 2	Bimolecular homolytic substitution
S _H Ar	Homolytic aromatic substitution
<i>t</i> -Bu	<i>tert</i> -butyl
TBABF ₄	Tetrabutylammonium tetrafluoroborate
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TC	Thiophene-2-carboxylate
TDAE	Tetrakis(<i>N,N</i> -dimethylamino)ethylene

TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Teoc	(Trimethylsilyl)ethoxycarbonyl
TES	Triethylsilane
Tf	Triflate
TFA	Trifluoroacetic acid
TFP	Tris(2-furyl)phosphine
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-Layer Chromatography
TM	Transition Metal
TMDS	Tetramethyldisiloxane
TMS	Tetramethylsilane
TOF	Time-of-flight
TPAP	Tetrapropylammonium perruthenate
TPP	Tetraphenylporphyrin
Ts	<i>para</i> -toluenesulfonyl
W	Watts

1. INTRODUCTION AND OBJECTIVES

1.1 INTRODUCTION

1.1.1 Natural products as a source of innovation

Natural products have long served as a source of medicinal bioactive compounds. Iconic examples such as morphine, paclitaxel, and erythromycin demonstrate their remarkable biological activity and structural diversity (*Figure 1.1*). Many of these molecules possess intricate architectures, often featuring novel structural motifs that are rare or unprecedented in synthetic compounds. This complexity represents both an asset and a challenge.¹

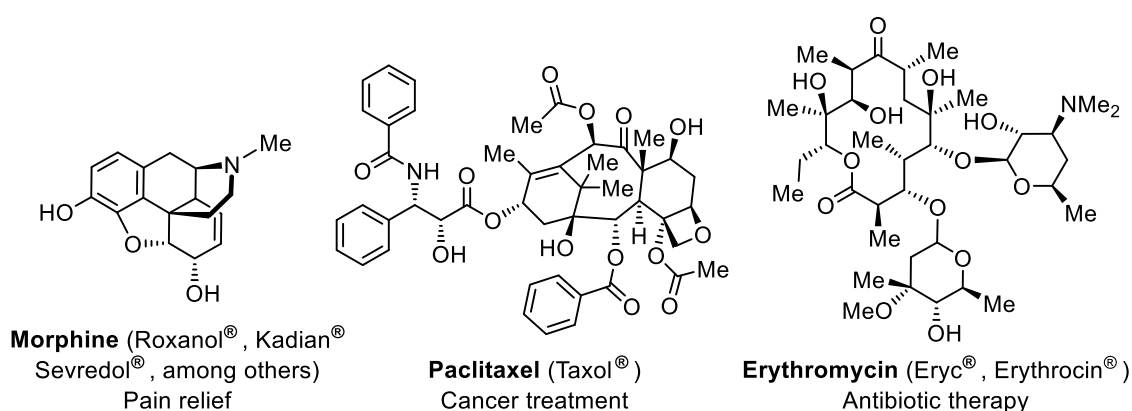


Figure 1.1: Selected examples of bioactive complex natural products.

Natural products provide a wealth of bioactive compounds that inspire the discovery of new pharmaceuticals and drive the development of innovative synthetic methodologies. Their structural complexity propels advances in organic synthesis, enabling chemists to access increasingly sophisticated molecular architectures. As synthetic methods improve, these innovations lead to faster, more efficient strategies for molecule construction, thereby accelerating the discovery of novel drugs.² However, the complexity of natural products also limits their practical accessibility. Many feature densely functionalized, three-dimensional scaffolds that demand precise control over regio-, stereo-, and chemoselectivity during synthesis. Conventional methods often struggle to meet these demands, and even when viable synthetic routes exist, scalability remains a challenge due to lengthy sequences, low yields, and the need for specialized reagents. As a result, despite their therapeutic potential, the widespread use of natural products is hindered by these synthetic and economic limitations.³

To address these challenges and unlock the full potential of natural products, this work explores two complementary strategies: developing new synthetic methodologies to enable novel disconnection approaches and applying function-oriented synthesis (FOS)⁴ (Figure 1.2). The first strategy focuses on advancing chemical synthesis to streamline the construction of complex molecules more efficiently, while minimizing environmental impact. The second, FOS, aims to simplify natural product structures by retaining only the pharmacophoric elements responsible for bioactivity, making them more accessible without compromising their therapeutic potential. Together, these approaches provide a pathway to overcome the barriers posed by natural product complexity and accelerate the discovery of new pharmaceuticals.

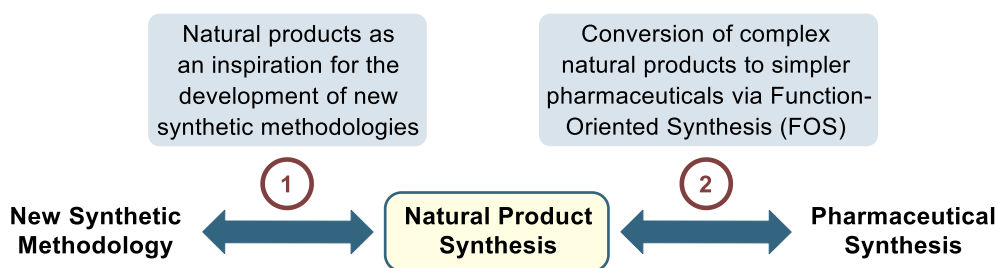


Figure 1.2: Natural products as an inspiration for organic synthesis.

Advancing synthetic methodologies is a key strategy for improving access to natural products. Traditional approaches often rely on resource-intensive, multi-step processes that are inefficient and difficult to scale. Recent innovations in synthetic chemistry focus on designing new reactions and disconnection approaches that reduce the number of steps involved, improving both efficiency and yield.⁵ Green Chemistry principles are also increasingly applied to minimize environmental impact by reducing waste, improving atom economy, and utilizing non-toxic reagents and solvents.⁶ Incorporating earth-abundant metals and bioavailable feedstocks further enhances the sustainability of these methods, making them both practical and environmentally responsible.

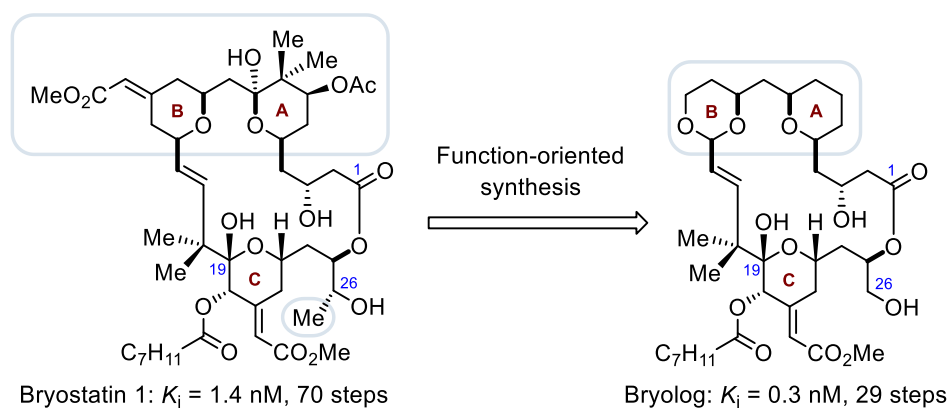
Additionally, there is a growing drive to expand the chemical space beyond the flat, aromatic compounds that currently dominate drug discovery libraries.⁷ These compounds limit the diversity of bioactive molecules that can be explored. To overcome this limitation, there is an increasing push to incorporate more three-dimensional structures, featuring sp^3 -hybridized carbons and chiral centers, into drug design. This

shift aims to create more complex scaffolds that enhance bioactivity by improving molecular interactions with biological targets. These advances not only broaden the scope of molecules for pharmaceutical development but also push the boundaries of synthetic chemistry, opening new avenues for drug discovery.

In addition to advancing synthetic methodologies, function-oriented synthesis offers a pivotal strategy for overcoming the challenges of natural product synthesis. Instead of focusing solely on structural complexity, FOS prioritizes the biological function, aiming to preserve the essential pharmacophores responsible for bioactivity while simplifying the rest of the molecule. While natural products have evolved to interact with specific biological targets, in many cases, only a small fraction of their structure contributes directly to this function. As such, unnecessary complexity can often be eliminated without compromising bioactivity, leading to simpler, synthetically accessible compounds that maintain or even enhance their therapeutic potential. By emphasizing function, FOS facilitates the design of compounds with fewer synthetic steps, greater efficiency, and better scalability for large-scale production.

A representative example of FOS comprises the design of bryostatin analogs (*Scheme 1.1*). Bryostatins are complex molecules with promising anticancer properties.⁸ However, their limited availability due to low yield from marine sources⁹ and complex synthetic routes hampers their broader application.^{10, 11} These natural products exert their biological activity by potently binding to the C1 domain of protein kinase C, with an inhibition constant value of 1.4 nM. Pharmacophoric studies indicated that the carbonyl group at C1, C19, C26 and the lipophilic region of the natural product were the key binding elements. Therefore, Wender and coworkers designed a bryolog with simplified A and B rings and kept the structure of the C ring intact.¹² Moreover, the methyl group at C26 could be removed, enabling closer association in the receptor binding pocket. As a result of the structural modifications, the authors could reduce the number of steps to 29, compared to the 70 steps required for the first reported synthesis of bryostatin 1. Furthermore, the new compound was notably more potent than the natural product.¹³

Ultimately, by combining advances in synthetic methodologies with function-oriented synthesis, chemists can bridge the gap between the complex structures of natural products and their practical application in drug development.



Scheme 1.1: Synthesis of a bryolog with improved activity over bryostatin 1.

These two strategies complement each other: new synthetic methods make complex natural products and their simplified analogs more accessible, while FOS allows for the retention of bioactivity through molecular simplification. Together, they enable the creation of bioactive molecules that are both efficient to synthesize and effective as therapeutics. These approaches not only expand chemical knowledge but also have the potential to deliver significant benefits to society by facilitating the discovery of new pharmaceutical agents and enhancing the sustainability of organic synthesis (*Figure 1.3*).

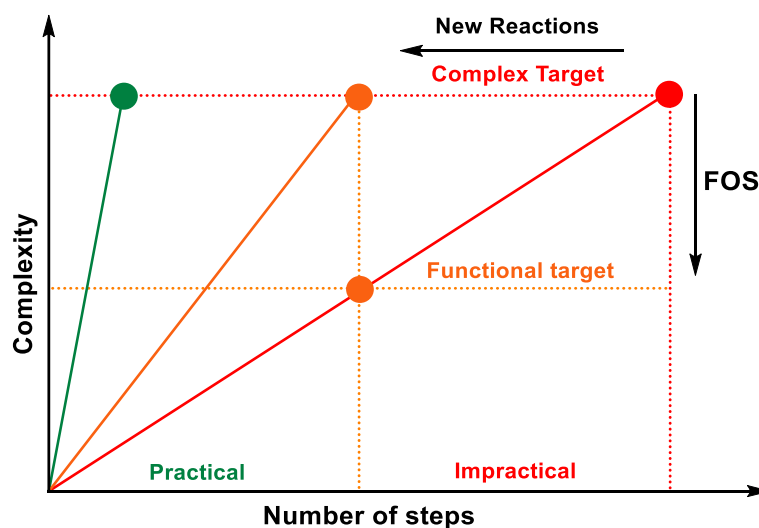


Figure 1.3: Improving access to bioactive compounds via the development of new reactions and the use of FOS.

To implement these strategies and enable the efficient synthesis of both complex natural products and their simplified bioactive analogs, this work will focus on the development of novel methodologies based on metal-catalyzed hydrogen atom transfer (MHAT) C–C coupling reactions. Therefore, the upcoming sections will introduce radical chemistry,

focusing on MHAT reactions, their mechanisms, and their applications in modern synthesis.

1.1.2 Radical reactions in organic synthesis

Radical chemistry has historically been overshadowed by ionic chemistry. In the standard undergraduate organic synthesis curriculum, reactions such as the aldol reaction, the Grignard addition, and pericyclic transformations like the Diels–Alder reaction dominate the discussion. Advanced texts often emphasize the contemporary significance of cross-coupling reactions, yet topics related to radicals receive comparatively little attention.

This lack of attention can be attributed to a perception of radicals as inherently unpredictable and challenging to manage. As highly reactive intermediates, radicals tend to react indiscriminately with most organic molecules, including solvents, and display a defining propensity to react rapidly —often at diffusion-controlled rates— with each other. This reactivity, while advantageous for achieving rapid transformations, poses significant challenges in directing these reactions with precision and selectivity. As a result, radicals have been viewed as both promising and problematic, which has historically contributed to their marginalized status in mainstream organic chemistry.¹⁴

Despite these challenges and misconceptions, a wealth of innovative and elegant chemistry has been achieved over the decades using radical intermediates. In contrast to their ionic counterparts, radical reactions often proceed under milder conditions, exhibiting high chemoselectivity and broad functional group tolerance. These reactions also facilitate the generation of complex molecular structures through tandem processes that are difficult to achieve through ionic mechanisms. Recent advancements have further cemented the significance of radical chemistry in contemporary synthesis. The development of novel methodologies for radical generation under environmentally benign conditions —such as photochemical and electrochemical techniques— has opened new avenues for synthetic transformations. Additionally, the integration of radical chemistry with other fields, including organometallic coupling reactions and organocatalysis, has significantly expanded the scope of possible reactions. As a result, radical chemistry has evolved from a specialized area to a central element in modern synthetic methodology. Its ability to facilitate previously inaccessible transformations

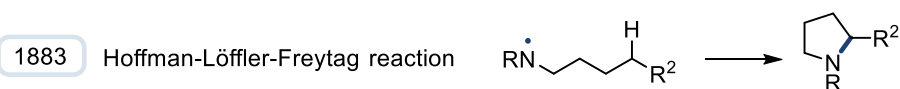
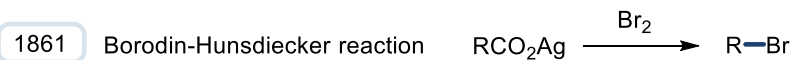
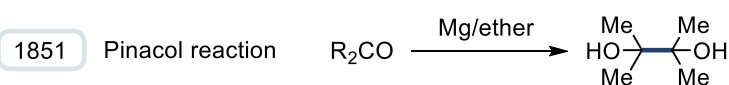
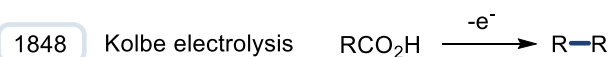
has propelled radical reactions to the forefront of organic synthesis, establishing them as indispensable tools in the development of new chemical entities.

To contextualize the progress in this field, the following scheme highlights some of the most significant milestones in radical chemistry since the 1800s (*Scheme 1.2, a-c*). The history of radical chemistry is marked by pioneering discoveries that predated a complete understanding of these elusive species. Early breakthroughs, such as the Kolbe electrochemical decarboxylation,¹⁵ the Borodin–Hunsdiecker reaction,¹⁶ and the Hofmann–Löffler–Freitag C–H functionalization,¹⁷ showcased the transformative potential of radicals. The pinacol coupling reaction¹⁸ introduced ketyl radicals, paving the way for innovations like the Kagan reagent,¹⁹ first reported in 1977. Its mechanism closely resembles that of the acyloin reaction,²⁰ which drove significant progress in steroid synthesis. The Wohl–Ziegler reaction,²¹ though initially obscure in mechanism, also found wide applications, highlighting the power of radicals.

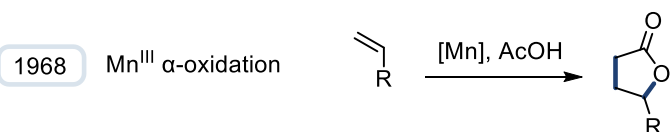
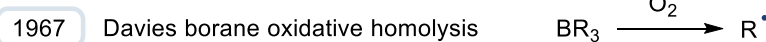
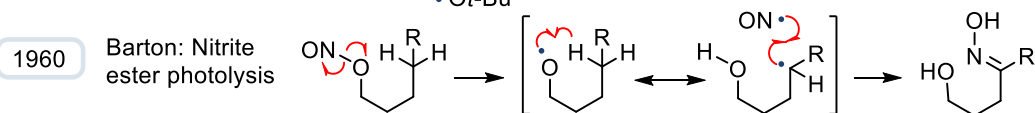
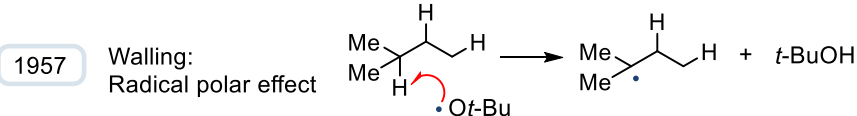
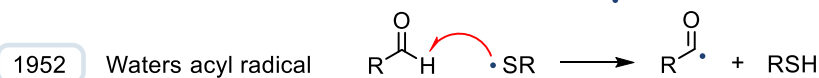
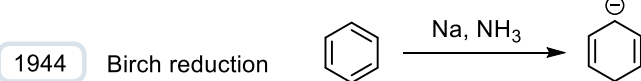
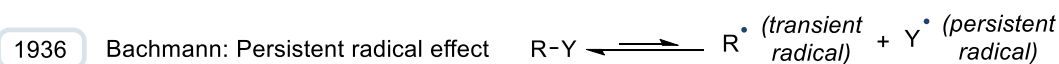
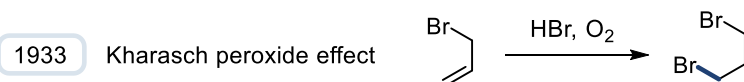
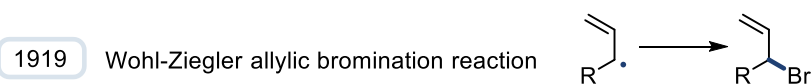
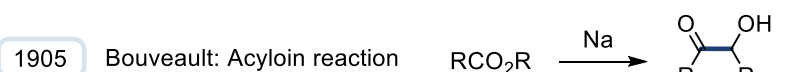
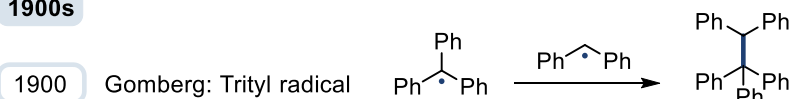
The "rational" era of radical chemistry began with pivotal discoveries in the 20th century. In the 1900s, Gomberg identified the trityl radical,²² the first stable radical, while Kharasch demonstrated the use of radicals in anti-Markovnikov selectivity, a foundation for atom transfer reactions.²³ Bachmann's persistent radical effect (PRE) theory suggested selective coupling between persistent and fleeting radicals, setting the stage for intentional radical design.²⁴ In the mid part of the century, Hey and Waters unraveled homolytic aromatic substitution,²⁵ a cornerstone of arene functionalization, while the Meerwein arylation utilized high-energy aryl radicals in olefin hydroarylation.²⁶ Meanwhile, the Birch reduction offered a novel approach to selectively reducing aromatic systems.²⁷

The 1950s saw further advances with Waters' thiol-catalyzed aldehyde homolysis,²⁸ providing access to acyl radicals and stimulating discussions about radical polar effects, which were extensively studied by Walling years later.²⁹ The development of stannane reagents by Van der Kerk³⁰ enabled mild and selective carbon-centered radical generation. Shortly after, the oxidative homolysis of alkyl boranes by Davies offered an alternative strategy to access these radicals under mild conditions.³¹ In the same period, Barton's nitrite photolysis highlighted radicals' practical utility, enabling the synthesis of aldosterone acetate.³²

1800s



1900s

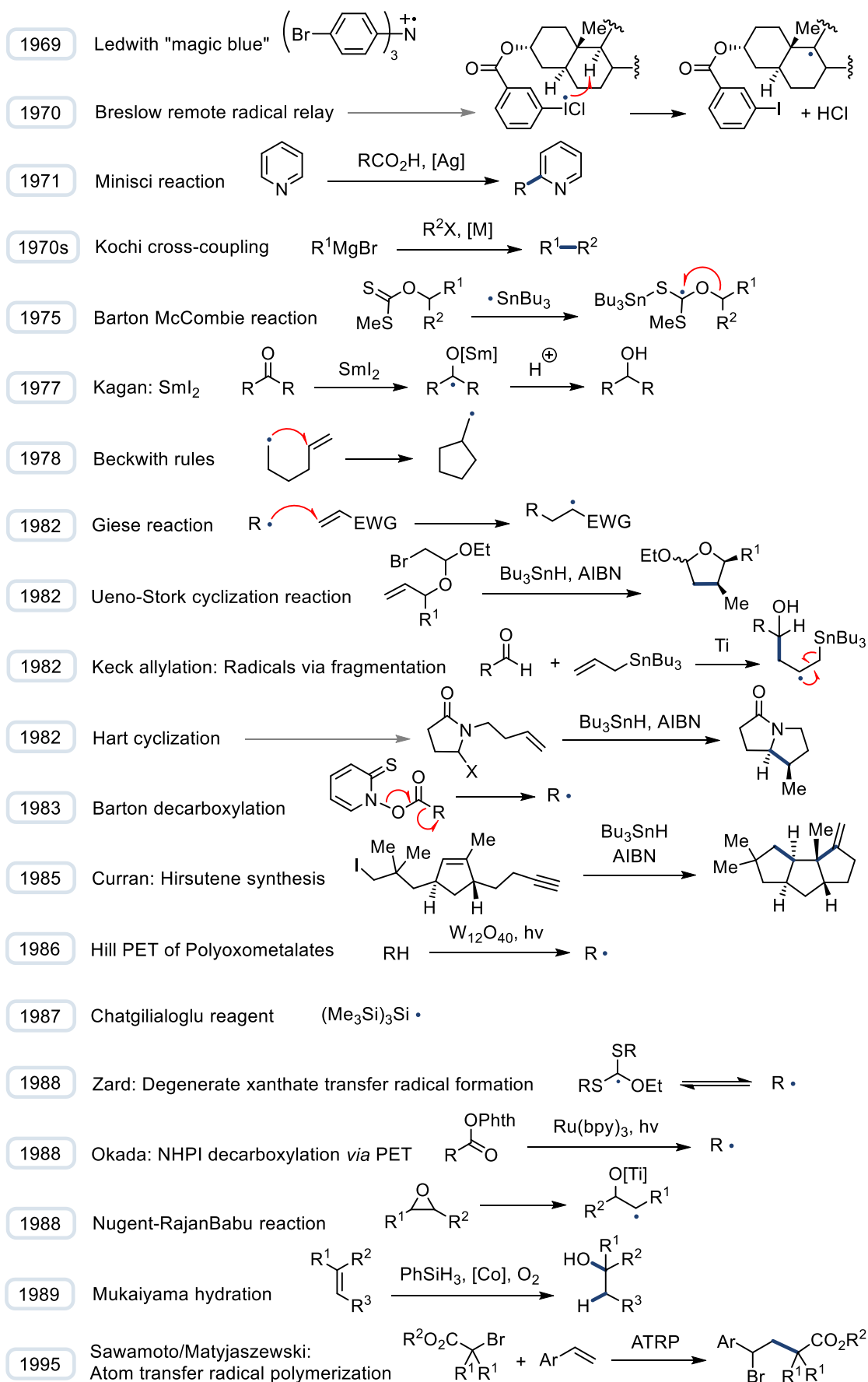


Scheme 1.2: Key milestones in radical chemistry – Part a

By the late 1960s, foundational transformations emerged, including Mn^{III}-mediated oxidative additions to olefins,³³ the generation of cationic radicals using Ledwith's "magic blue" reagent,³⁴ Breslow's remote radical functionalization strategies,³⁵ Minisci's heterocycle C–H alkylation,³⁶ and radical-based cross-coupling chemistry.¹⁴ Barton's decarboxylation and deoxygenation reactions³⁷ highlighted the practical value of radicals in industrial settings. Methodical investigations refined our understanding of radical selectivity, driving progress in synthetic radical chemistry. For instance, the Giese reaction³⁸ arose from studies on radical–olefin interactions, while Beckwith's rules for radical ring closure³⁹ paved the way for cyclizations like the Ueno–Stork⁴⁰ and Hart⁴¹ processes. Keck's allylation avoided premature radical termination via a fragmentation pathway,⁴² and Curran's groundbreaking total syntheses⁴³ underscored the efficiency of radical chain reactions for tandem bond formations.

The 1980s marked the development of "radical clocks", providing key rate constants for various radical processes.⁴⁴ Additionally, researchers expanded the scope of radical precursors, with Hill leveraging polyoxometalates to cleave inert alkane C–H bonds via photoinduced electron transfer (PET).⁴⁵ Zard's xanthate transfer chemistry⁴⁶ revolutionized polymerization and organic synthesis, while Okada's use of PET,⁴⁷ Nugent and RajanBabu's epoxide reduction,⁴⁸ and Mukaiyama's in situ-generated metal hydrides⁴⁹ utilized accessible functional groups like carboxylates, epoxides, and olefins as radical precursors. These advancements brought radical chemistry closer to the forefront of both academic and industrial chemistry, allowing for greater precision and versatility in synthetic applications.

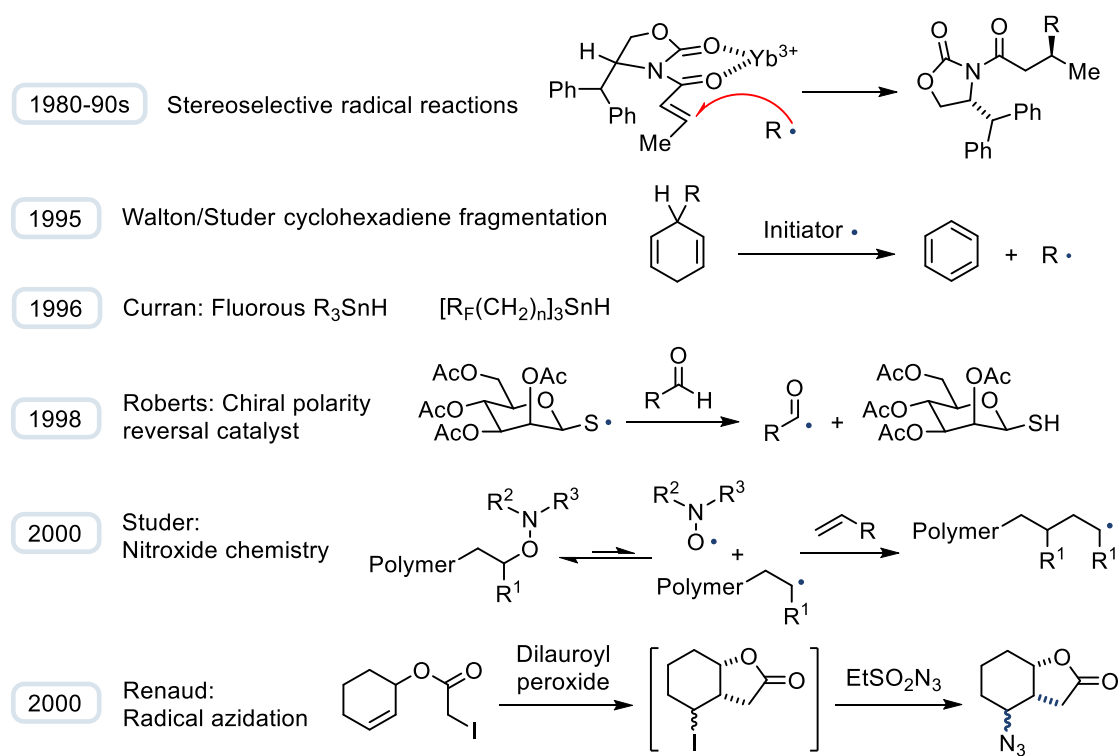
The 1990s ushered in breakthroughs in materials science and organic synthesis. Atom transfer radical polymerization (ATRP) enabled the production of well-defined polymers with precise molecular weights, significantly impacting fields such as coatings, adhesives, and biomedical devices.⁵⁰ Concurrently, key advancements in stereocontrolled radical additions and enantioselective radical processes, such as those developed by Curran, Giese, and Sibi, significantly enhanced the utility of radicals in the synthesis of complex, chiral molecules.⁵¹ In parallel, Roberts's enantioselective hydrosilylation offered an alternative method for controlling chirality, leveraging a thiyl radical as the chiral source.⁵²



Scheme 1.2: Key milestones in radical chemistry – Part b

Innovations like Chatgililoglu's silane reagents,⁵³ Walton and Studer's cyclohexadienes,⁵⁴ and Curran's fluoros stannanes⁵⁵ provided more efficient and selective alternatives to the classical "tin hydride method," overcoming its limitations in controlling radical generation. Furthermore, the exploration of nitroxyl radicals, as studied by Studer,⁵⁶ and radical-based azide transfer, pioneered by Renaud,⁵⁷ expanded the versatility of radical reactions, especially in cyclization and polymerization reactions.

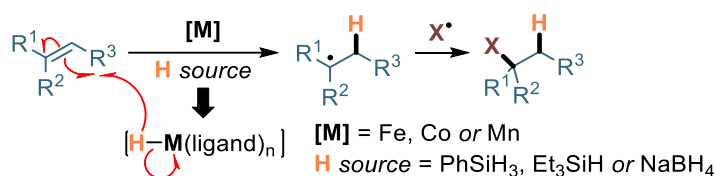
In conclusion, radical chemistry has transformed from a niche area into a vital part of modern organic synthesis. Through decades of innovative research, radical reactions have become essential for creating new chemical transformations and complex molecules. With ongoing advancements, radical chemistry is poised to play a key role in fields such as drug discovery, materials science, and industrial applications, offering exciting prospects for the future of synthetic chemistry.⁵⁸



Scheme 1.2: Key milestones in radical chemistry – Part c

1.1.3 Metal-Catalyzed Hydrogen Atom Transfer (MHAT)

A significant breakthrough in radical chemistry involved the metal-catalyzed generation of radicals from alkenes via hydrogen atom transfer, which initiates coupling reactions. In this method, a non-toxic and abundant metal, such as cobalt, iron, or manganese, is combined with a suitable hydride donor, typically PhSiH_3 , Et_3SiH , or NaBH_4 , to form a metal hydride intermediate (*Scheme 1.3*).⁵⁹ This intermediate then transfers a hydrogen atom to the less substituted carbon of an alkene, generating a carbon-centered radical. This radical is later captured by a suitable acceptor ($\text{X}^\bullet$), resulting in the formation of the corresponding addition product with Markovnikov selectivity.



Scheme 1.3: Radical generation via Metal-Catalyzed Hydrogen Atom Transfer (MHAT).

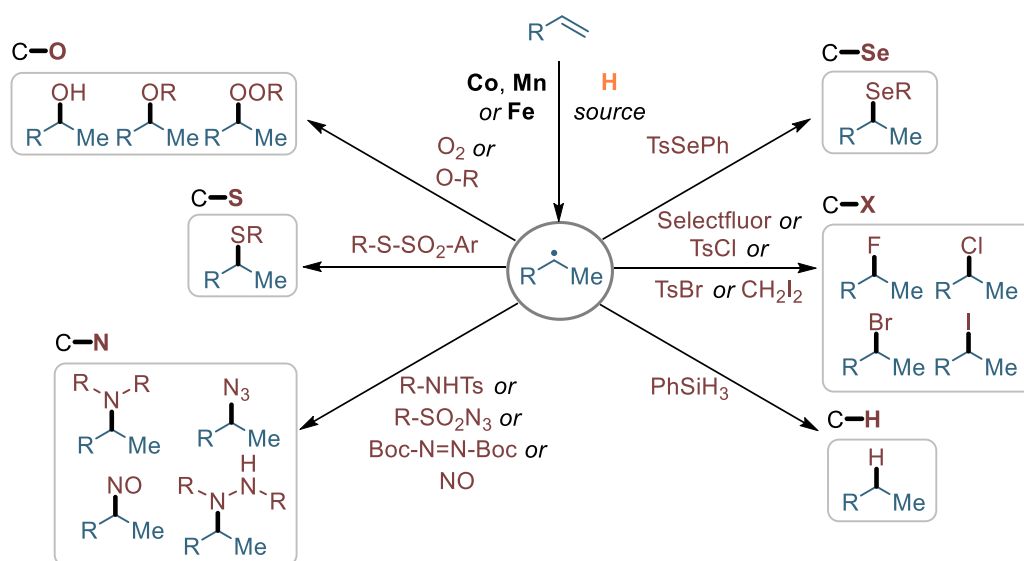
These processes have attracted significant interest from synthetic chemists in recent years, mainly due to the many advantages they offer. One key benefit is that alkenes are stable pro-radicals, allowing them to be incorporated into a synthetic sequence over multiple steps until the desired radical transformation occurs. This makes using MHAT an appealing strategy in the synthesis of complex natural products.⁶⁰ Furthermore, alkenes are inexpensive and widely available, making them excellent starting materials for organic synthesis.

MHAT also offers high chemoselectivity for alkenes,⁶¹ which ensures broad functional group compatibility. Another advantage is its high site selectivity,⁶² enabling the preferential reaction with one alkene over another when substitution patterns differ. The mild conditions under which these processes are typically carried out, often at room temperature, under standard pressure, and without needing to exclude moisture, make them simple to perform. While usually carried out under inert atmospheres, several MHAT processes are even more efficient when exposed to air. Lastly, the use of low amounts of earth-abundant and non-toxic metal catalysts further enhances their appeal compared to traditional radical methods using tin, iridium or ruthenium.

1.1.4 Historical background of MHAT reactions

The first use of an MHAT reaction on a double bond was explored in the 1960s by Kwiatek and Seyler, who successfully hydrogenated various alkenes with a cobalt catalyst.⁶³ In 1982, Drago reported the first selective catalytic oxidation of terminal olefins using cobalt complexes.⁶⁴ However, it was not until 1989 that Mukaiyama's work on the catalytic hydration of alkenes with molecular oxygen, phenylsilane, and $\text{Co}(\text{acac})_2$ sparked significant interest in this type of transformation among organic chemists.⁶⁵ Since then, MHAT reactions have found widespread application in the synthesis of natural products.⁶⁶

Over the years, hydrofunctionalizations of alkenes to form C–O (hydroperoxidation⁶⁷ and hydroalkylation⁶⁸), C–N (hydroamination,⁶⁹ hydrohydrazination, hydroazidation⁷⁰ and nitrosation⁷¹), C–S (hydrothiolation⁷²), C–X (hydrofluorination,⁷³ hydrochlorination,⁷⁴ hydrobromination, and hydroiodination⁷⁵), C–H (hydrogenation⁷⁶) and C–Se (hydroselenation⁷⁷) bonds have been developed using MHAT conditions (*Scheme 1.4*).



Scheme 1.4: Radical-based alkene hydrofunctionalizations enabled by MHAT.

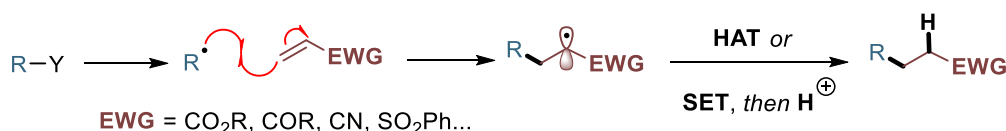
1.1.5 Carbon–Carbon bond formation by MHAT reactions

Although MHAT reactions have been known for a long time, their application in general C–C bond formation has emerged more recently. Since then, they have proven to be a valuable tool in organic synthesis.

As this thesis delves into the development of new MHAT C–C bond-forming reactions, we will briefly outline all the C–C reactions reported to date, classifying them according to the mechanism through which they proceed.

Giese type additions

The Giese reaction involves the formation of a carbon-centered radical from a suitable radical precursor, which selectively adds to a π -bond system conjugated with an electron-withdrawing group (EWG). This process, typically following a regioselective 1,4-addition pathway, creates a new C–C bond and generates an electrophilic radical intermediate. The intermediate may then proceed through a hydrogen atom transfer (HAT) mechanism or undergo single-electron transfer (SET) followed by protonation, ultimately yielding the coupled product (*Scheme 1.5*).⁷⁸

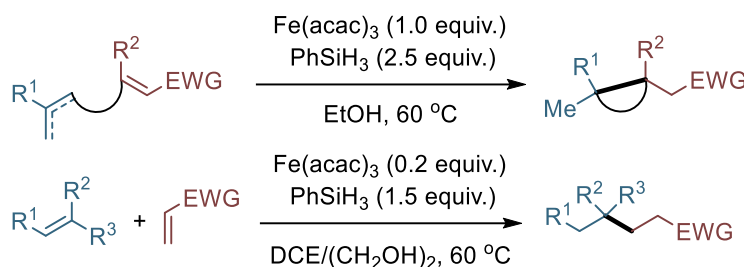


Scheme 1.5: General mechanism of a Giese addition reaction.

Traditional Giese reactions, while highly valuable, have been hampered by the reliance on toxic tin hydride reagents and associated side reactions, such as hydrostannylation and premature hydrogen abstraction. MHAT reactions offer a compelling solution, leveraging metal hydrides to generate radicals under milder, more sustainable conditions and expanding the scope of selective and environmentally friendly transformations.⁷⁹

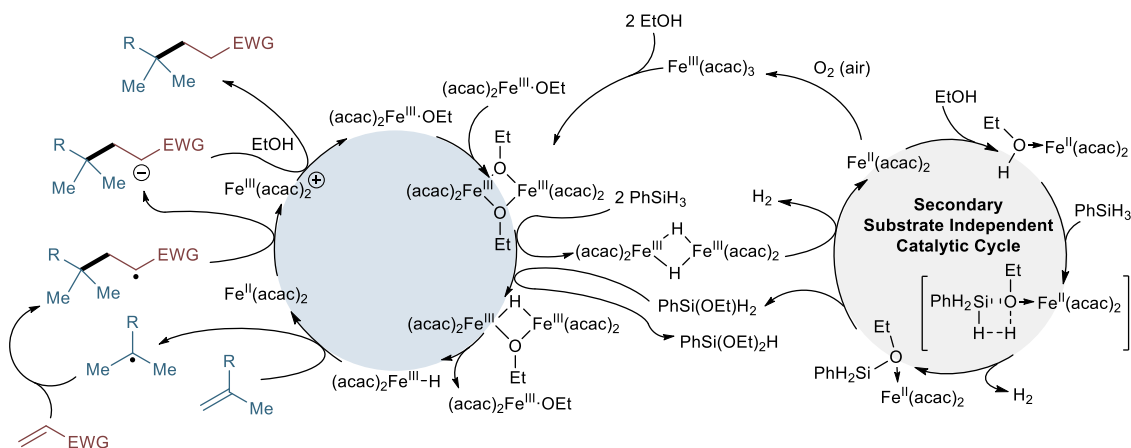
In 2014, Baran and coworkers introduced the first-ever reported MHAT C–C coupling, demonstrating both the intra- and intermolecular coupling between non-activated alkenes and electron-deficient olefins. This approach utilized Fe(acac)₃ as a metal catalyst and PhSiH₃ as a hydride source, enabling the synthesis of diverse structures, including bicyclic systems, cyclopropanes, and vicinal quaternary centers (*Scheme 1.6*).⁸⁰

Baran, 2014

General MHAT
C-C intra- and
intermolecular
couplings

Scheme 1.6: First reported C–C bond-forming MHAT coupling by Baran's group.

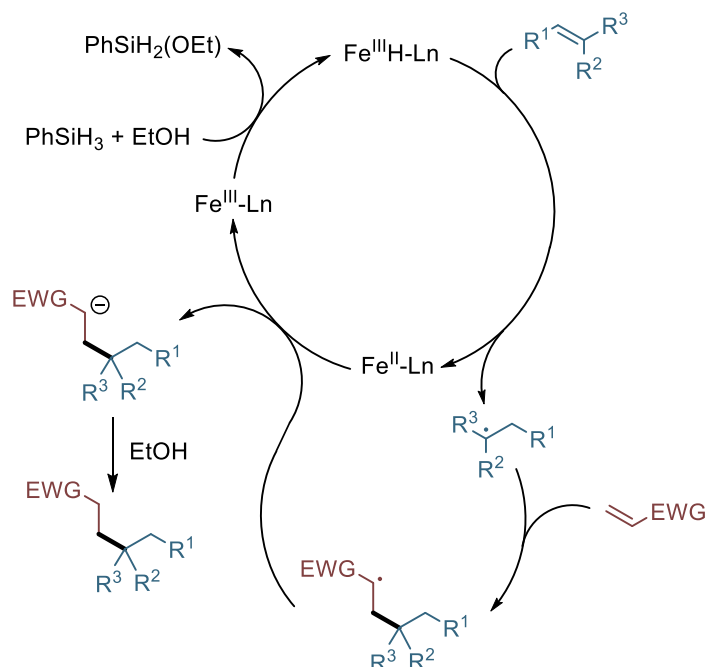
In 2017, Baran and Holland provided experimental evidence to elucidate the mechanism behind this reaction.⁸¹ As shown in *Scheme 1.7*, the process involves a complex catalytic cycle where both the catalyst and hydride source undergo multiple transformations to generate the active metal hydride responsible for radical attack on the alkene, leading to C–C bond formation. Their studies revealed the presence of a secondary catalytic cycle involving Fe^{II} species and PhSiH_3 , independent of the substrate. Additionally, phenylsilane was found to convert into a more reactive ethoxy-substituted analog within this secondary cycle. Notably, excluding air from the reaction prevented the oxidation of Fe^{II} to Fe^{III} .



Scheme 1.7: Mechanistic pathway for the MHAT-triggered Giese addition.

Further insights were provided by Poli and Holland, who employed DFT calculations to analyze this MHAT C–C coupling.⁸² Their findings indicated that Fe species reduce the concentration of free radicals in solution by forming Fe–C and Fe–O bonds. This effect is closely linked to the persistent radical effect (PRE), where the reversible formation of Fe–C bonds stabilizes radicals, prolonging their lifetime and minimizing undesired bimolecular terminations. As a result, PRE enhances cross-coupling selectivity.

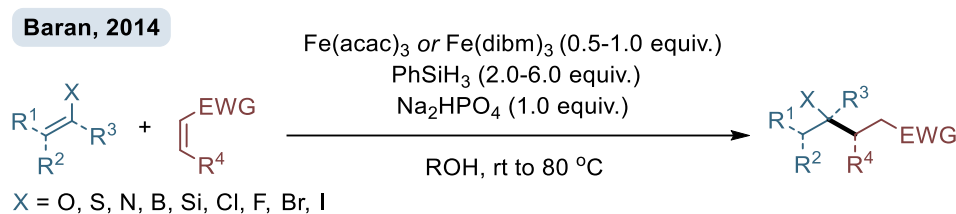
While most subsequent MHAT reaction mechanisms build upon this proposal, a simplified version, omitting the secondary catalytic cycle and depicting the iron species in their monomeric forms, is often presented (*Scheme 1.8*).



Scheme 1.8: Simplified mechanism for the MHAT Giese addition.

For the following reactions, the mechanism will not be outlined as it proceeds analogously to Baran's disclosed pathway.

Shortly after the publication of their Giese addition under MHAT conditions, the scope of the reaction was expanded to include alkenes with a heteroatom adjacent to the carbon on which the radical was formed (*Scheme 1.9*).⁸³

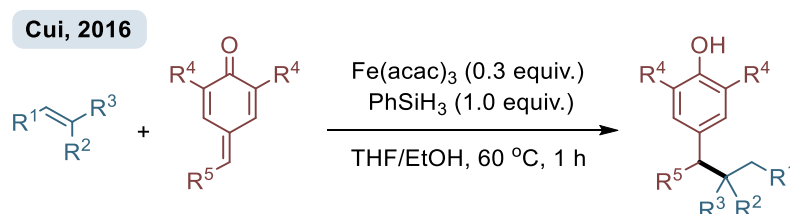


Scheme 1.9: Functionalized olefin cross-coupling for carbon-carbon bond formation.

$\text{Fe}(\text{dibm})_3$ proved to be a more effective catalyst than $\text{Fe}(\text{acac})_3$ due to its increased steric hindrance around the iron center, which allowed for more controlled reactivity. This

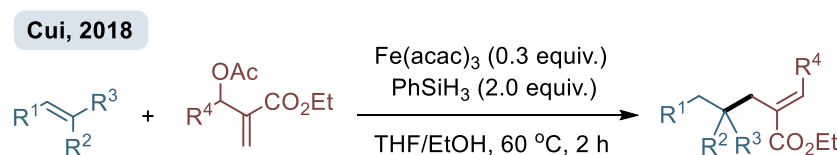
enhanced steric protection helped to avoid unwanted side reactions typically triggered by the presence of a heteroatom. Additionally, Na₂HPO₄ was used as an additive.

In 2016, the group of Cui reported an olefin hydroalkylation with *para*-quinone methides, leveraging the formation of the aromatic phenol ring as the driving force (Scheme 1.10).⁸⁴



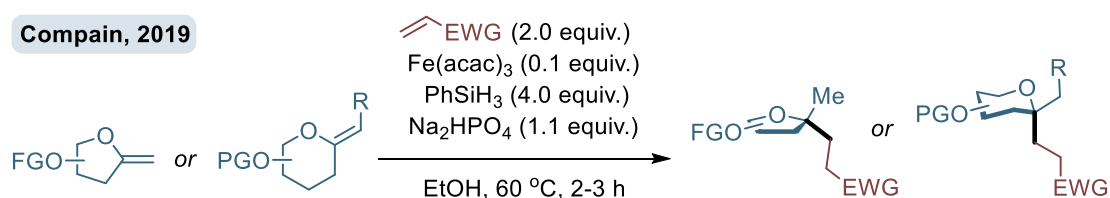
Scheme 1.10: Hydroalkylation of neutral alkenes with *para*-quinone methides by Cui.

Two years later, Cui reported a new approach to the Giese reaction by using Morita–Bailys–Hillman adducts, which contained a leaving group in the α -position of the Michael acceptor.⁸⁵ After the hydroalkylation, an acetate group could be eliminated to regenerate the unsaturation (Scheme 1.11).



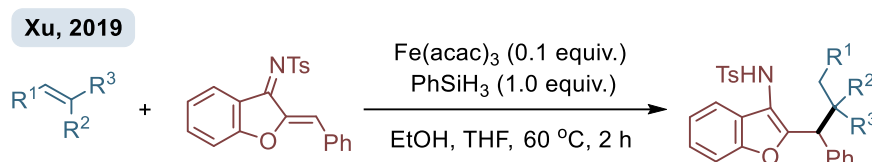
Scheme 1.11: Hydroallylation of unactivated alkenes by Cui.

In 2019, Compain and coworkers developed a method for stereoselective sugar functionalization at the anomeric position using tertiary pseudoanomeric radicals. Their method was successfully applied to both pyrans and furans, achieving precise stereocontrol in the quaternization of the adjacent ether position (Scheme 1.12).⁸⁶



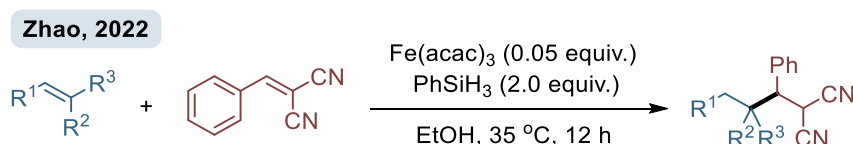
Scheme 1.12: Stereoselective synthesis of *C,C*-glycosides from *exo*-glycals via MHAT.

In the same year, Xu's group introduced a variant of the Giese reaction where unsaturated imines served as radical acceptors in reactions with neutral alkenes, leading to the formation of a diverse range of benzofurans, benzothiophenes, and benzofuran-fused heterocycles (*Scheme 1.13*).⁸⁷



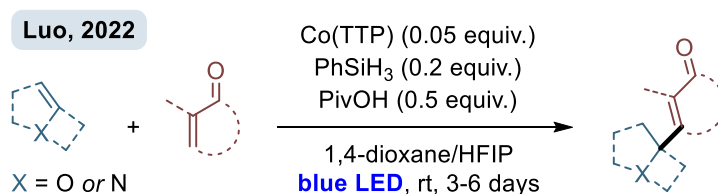
Scheme 1.13: Giese addition to imines by Xu.

To expand the array of acceptors suitable for MHAT, in 2022, Zhao developed a conjugate addition between alkenes and Michael acceptors bearing two nitrile groups. This enabled the synthesis of a diverse array of substituted malononitriles (*Scheme 1.14*).⁸⁸



Scheme 1.14: Synthesis of functionalized malononitriles via MHAT coupling.

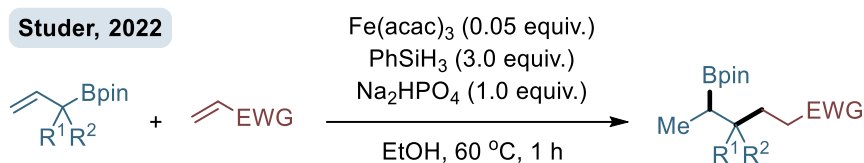
Luo's group used photocatalysis to carry out a dehydrogenative MHAT-initiated Giese reaction using a cobalt catalyst (*Scheme 1.15*). During the reaction, the β -hydrogen of the substrate was transferred to the cobalt species, regenerating the metal hydride and allowing the double bond to reform. As a result, only a catalytic amount of PhSiH_3 was required. However, the method was limited to substrates with an adjacent oxygen atom or 4-membered rings.⁸⁹



Scheme 1.15: Photoinduced Giese addition under MHAT conditions by Luo.

Finally, Studer introduced an alternative to the Baran reaction by reacting allylboronic esters with Michael acceptors. When a metal hydride was added to the alkene, a 1,2-boron shift occurred, forming a more stable radical intermediate, which was then

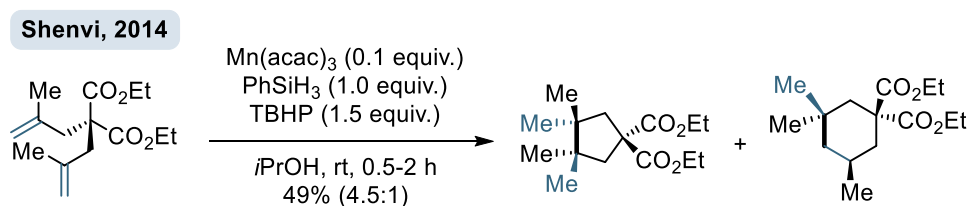
trapped by the Michael acceptor to yield the corresponding borylated compound (Scheme 1.16).⁹⁰



Scheme 1.16: Giese addition with allylborynic esters by Studer et al.

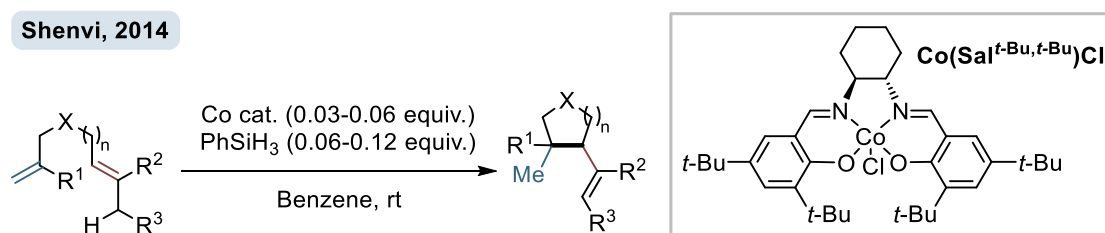
C=C neutral coupling

In 2014, Shenvi's group introduced one of the earliest MHAT C–C couplings proving that non-activated alkene radicals could intermolecularly couple with adjacent neutral alkenes. This study was part of a broader mechanistic investigation into the formation of radical intermediates for hydrogenations using MHAT and was not further developed into a general C–C coupling methodology (Scheme 1.17).⁷⁶



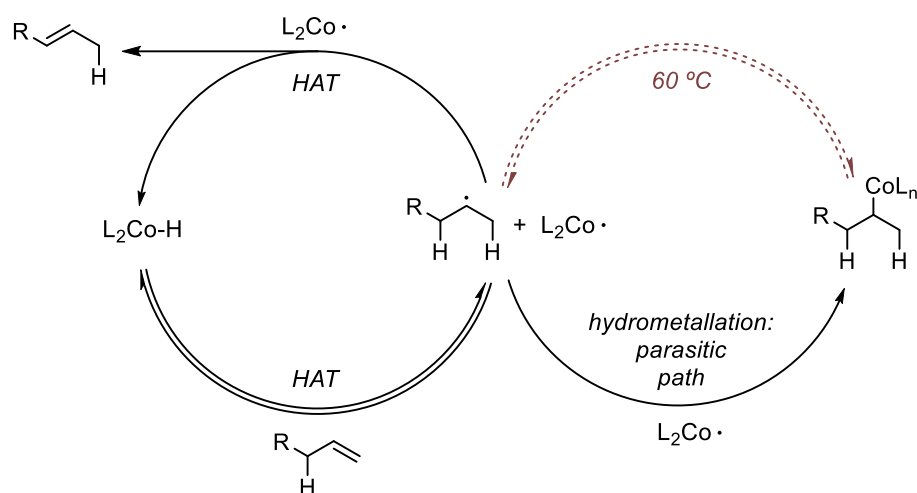
Scheme 1.17: Mn-catalyzed intramolecular coupling between neutral alkenes by Shenvi.

In the same year, Shenvi demonstrated that using a cobalt catalyst in low amounts rendered the radical addition reversible, favoring the formation of more substituted alkenes. When applied to polyenes, the reaction preferentially underwent cycloisomerization yielding products with high efficiency and diastereoselectivity under mild conditions (Scheme 1.18).⁹¹



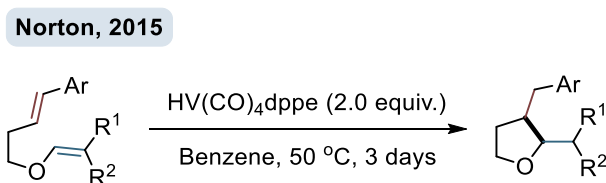
Scheme 1.18: Reversible Co-catalyzed C=C neutral coupling by Shenvi.

Mechanistically, the reaction proceeded through an initial HAT from a Co(salen) hydride complex to the substrate, generating a carbon-centered radical. This radical either underwent productive coupling or collapsed with the metal center in an off-cycle parasitic pathway. At elevated temperatures, C–Co bond homolysis reactivated the catalytic cycle, allowing further radical generation. Overall, the reaction followed a HAT-driven pathway, with radical/metal interactions influencing selectivity and turnover (*Scheme 1.19*). Given that the subsequent reactions proceed via analogous mechanisms, the mechanistic details will not be reiterated for each case.



Scheme 1.19: Mechanistic pathway for the catalytic olefin coupling by Shenvi et al.

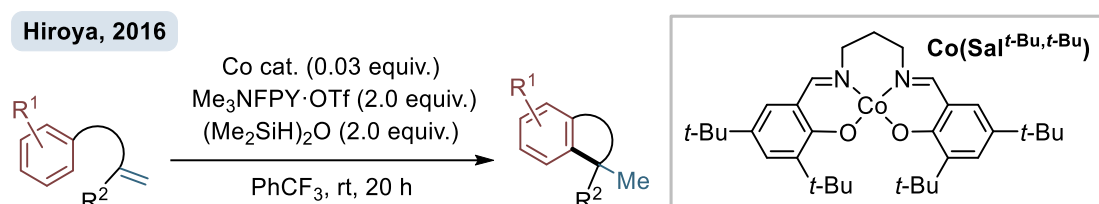
Norton presented a modified version of this reaction to synthesize tetrahydrofuran derivatives. Rather than the typical Fe, Co, or Mn catalysts, they employed $\text{HV}(\text{CO})_4\text{dppe}$ to facilitate these 5-*exo* cyclizations, leveraging the weakness of the V–H bond to drive the equilibrium of the initial $\text{H}\cdot$ transfer toward cyclization (*Scheme 1.20*).⁹²



Scheme 1.20: Norton's MHAT C=C coupling to synthesize substituted tetrahydrofurans.

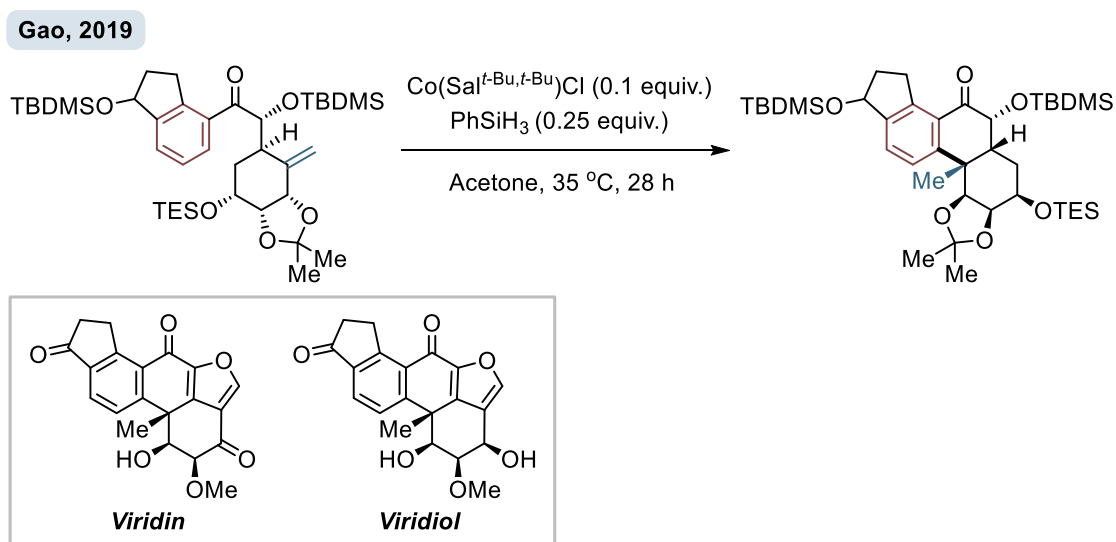
Hiroya broadened the scope of MHAT C=C couplings by introducing an intramolecular hydroarylation of unactivated alkenes, enabling the synthesis of α -mono and α,α -disubstituted six-membered benzocycles. This was achieved using a cobalt catalyst, a

disiloxane reagent as a hydride source, and an *N*-fluoro pyridinium salt, which facilitated the formation of the active catalyst species (Scheme 1.21).⁹³



Scheme 1.21: Co-catalyzed intramolecular hydroarylation of unactivated alkenes.

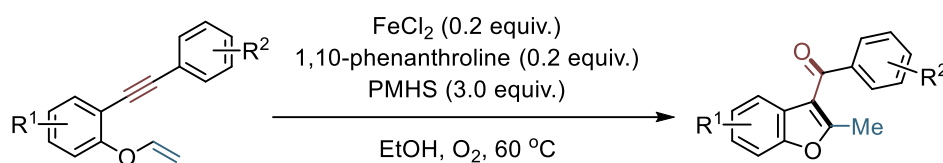
Similarly, Gao and coworkers applied an MHAT hydroarylation as a pivotal step in the synthesis of the aromatic steroids viridin and viridiol using a cobalt catalyst and phenylsilane as a hydride source (Scheme 1.22).⁹⁴



Scheme 1.22: Hydroarylation of alkenes for the synthesis of viridin and viridiol.

In 2019, Wang demonstrated that 1,6-enynes could undergo intramolecular cyclization to form 3-acylbenzofurans and thiophenes, establishing neutral alkynes as viable acceptor groups in MHAT couplings. The metal hydride species facilitated hydrogen transfer to the alkene, generating a radical that added intramolecularly to the triple bond, forming a 5-membered ring. The resulting vinyl radical was then oxidized by oxygen to yield the final product (Scheme 1.23).⁹⁵

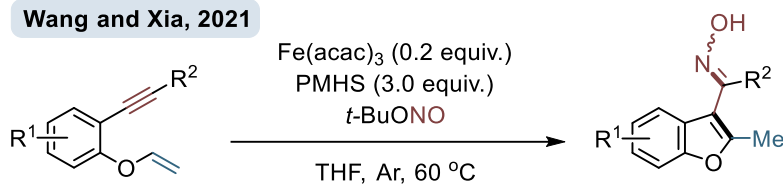
Wang and Xia, 2019



Scheme 1.23: Reductive cyclization of 1,6-enynes under MHAT conditions.

Two years later, the same group expanded the scope of the reaction by trapping the vinyl radical formed after cyclization with NO instead of oxygen. Once trapped, the radical underwent tautomerization, leading to the formation of ketoximes (Scheme 1.24).⁹⁶

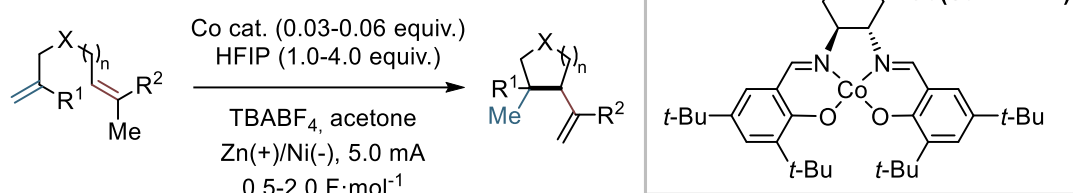
Wang and Xia, 2021



Scheme 1.24: Cyclization of 1,6-enynes for the synthesis of ketoximes by Wang and Xia.

Recently, the Baran group developed a cobalt-mediated electrocatalytic method as an alternative to the cycloisomerization reaction published by Shenvi (see Scheme 1.18).⁹¹ The easily tunable reaction conditions allowed the group to successfully perform over ten different types of reactions, encompassing isomerization, reduction, and hydrofunctionalization strategies (Scheme 1.25).⁹⁷

Baran, 2022

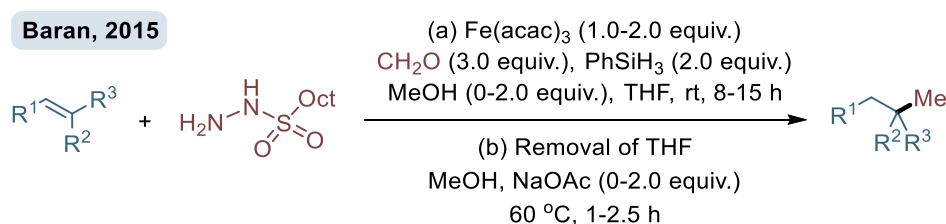


Scheme 1.25: Functionalization of C=C bonds under electrochemical conditions.

Addition to C=X

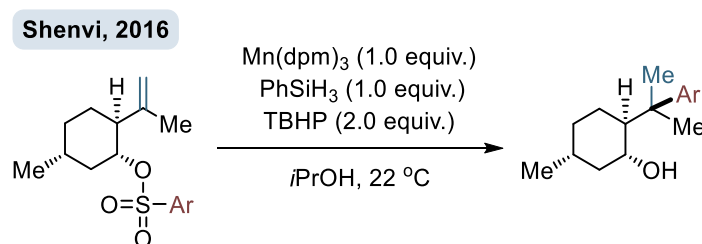
In 2015, Baran's group introduced a hydromethylation method for unactivated alkenes, involving the in situ formation of a tosylhydrazone intermediate from hydrazine and formaldehyde. This intermediate underwent elimination of sulfinic acid and nitrogen, yielding the final methylated product. The approach enabled methylation of mono-, di-,

and trisubstituted alkenes and held promise for late-stage functionalization in the synthesis of natural products and pharmaceuticals (*Scheme 1.26*).⁹⁸



Scheme 1.26: Hydromethylation of neutral alkenes via a tosylhydrazone intermediate.

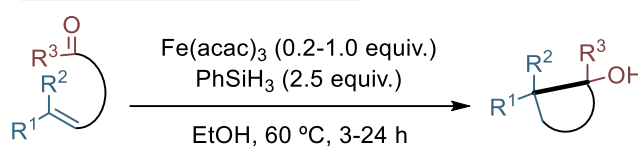
Shortly after, Shenvi disclosed a strategy for constructing 8-arylmenthol-type scaffolds from aryl- and heteroaryl-sulfonated isopulegol derivatives. The approach involved MHAT to the alkene, followed by a Smiles–Truce radical rearrangement that eliminated sulfur dioxide and delivered the hydroarylated terpene with high stereoselectivity (*Scheme 1.27*).⁹⁹



Scheme 1.27: Radical arylation of isopulegol to access 8-arylmenthol derivatives.

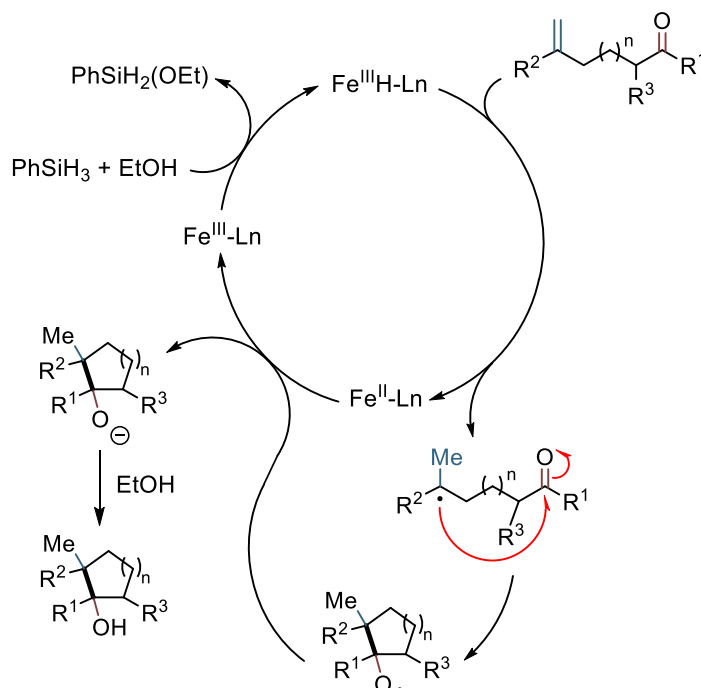
In 2018, our group pioneered the use of carbonyls as acceptors in MHAT reactions.¹⁰⁰ By employing catalytic quantities of $\text{Fe}(\text{acac})_3$ with PhSiH_3 as the hydride donor and ethanol as the solvent at $60\text{ }^\circ\text{C}$, the intramolecular cyclization of various ketoalkenes was achieved, leading to the formation of bi- and tricyclic compounds (*Scheme 1.28*). This reaction is typically challenging due to the inherent instability of the alkoxy radical, which tends to favor the reverse reaction. Nevertheless, the optimized conditions enabled excellent alcohol yields in many instances. Subsequently, this approach was employed to synthesize natural products featuring *trans*-fused hydrindanol frameworks, closely related to the structures of botrydial compounds.¹⁰¹

Bonjoch and Bradshaw, 2018



Scheme 1.28: Radical cyclization of alkene-tethered ketones under MHAT conditions.

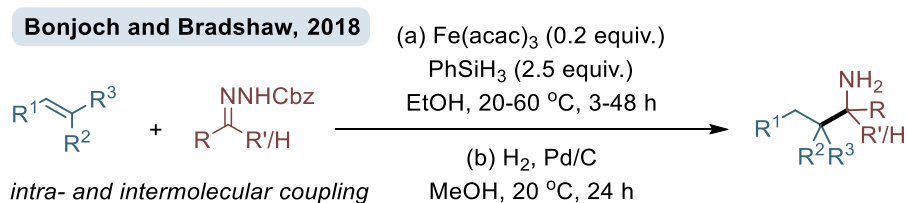
Mechanistically, the reaction proceeded via hydrogen atom transfer (HAT) from the in situ generated $\text{HFe}(\text{acac})_2$ to the olefin, which served as the rate-determining step. This led to the formation of a carbon-centered radical, which then added to the ketone, generating an alkoxy radical. Although the alkoxy radical was less favorable than the ring-opened product, it was converted to an alkoxide through a single-electron transfer from the Fe^{II} species, accompanied by the reoxidation of Fe^{II} to Fe^{III} . This reoxidation enabled the catalytic cycle to continue via $\text{Fe}(\text{acac})_2(\text{OEt})$ (*Scheme 1.29*). Since this mechanism applies to MHAT additions to $\text{C}=\text{X}$ bonds in general, it will serve as a model for the entire section, and detailed mechanisms will not be repeated for the subsequent reactions.



Scheme 1.29: Mechanistic pathway for the addition of neutral alkenes to ketones.

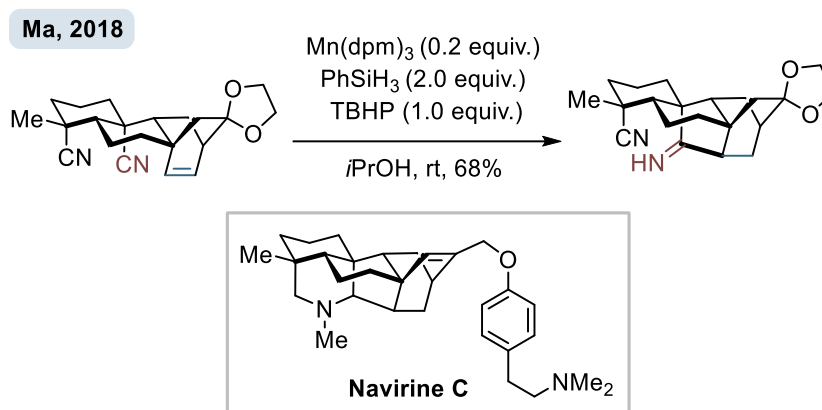
Using analogous conditions, it was observed that the inter- and intramolecular coupling of Cbz-hydrazones with alkenes was also feasible. Subsequent hydrogenation of the

coupled products gave the corresponding α -tertiary amines, which represents a valuable structural motif present in many bioactive compounds and alkaloids (*Scheme 1.30*).¹⁰²



Scheme 1.30: Coupling of alkenes with Cbz-hydrazones by our group.

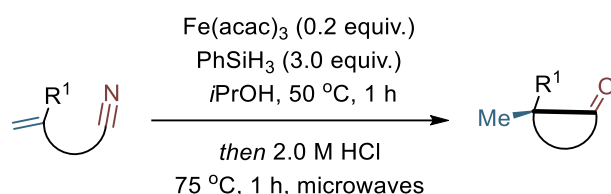
In 2018, Ma and coworkers employed an MHAT reaction to perform an intramolecular reductive cyclization between an alkene and a nitrile, which served as a crucial step in the synthesis of the natural product navirine C (*Scheme 1.31*). Although this was the first reported use of a cyano group in a reductive MHAT coupling reaction, the authors did not extend this approach into a general methodology.¹⁰³



Scheme 1.31: Cyclization between an alkene and a nitrile to access navirine C.

In the same year, Murphy reported an intramolecular cyclization of alkenes and nitriles with $\text{Fe}(\text{acac})_3$ and PhSiH_3 , along with a detailed study of the reaction (*Scheme 1.32*). Following the coupling step, the imine intermediate was treated with acid to afford the desired ketone. This approach offered a novel bond disconnection strategy for ring-closing reactions, enabling the formation of ketones via imine intermediates. Notably, the reaction was highly versatile, facilitating the synthesis of sterically hindered ketones, fused cyclic systems, and spirocycles.¹⁰⁴

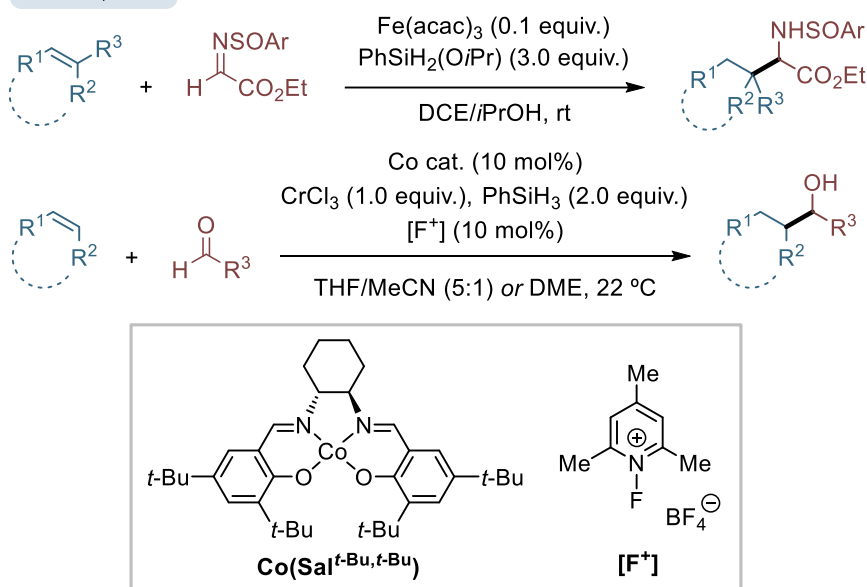
Murphy, 2018



Scheme 1.32: Intramolecular coupling of alkenes and nitriles by Murphy et al.

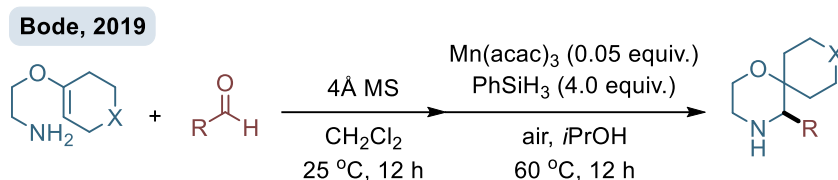
The Shenvi group disclosed a dual catalytic strategy for the reductive coupling of olefins with imines and aldehydes, leveraging distinct mechanistic pathways. Iron catalysis facilitated the coupling with imines via a common radical surrogate, while cobalt catalysis enabled the coupling with aldehydes, followed by a transmetalation step with chromium to generate a carbanion surrogate. Key applications included the efficient synthesis of unnatural amino acids and the late-stage functionalization of complex molecules (Scheme 1.33).¹⁰⁵

Shenvi, 2018



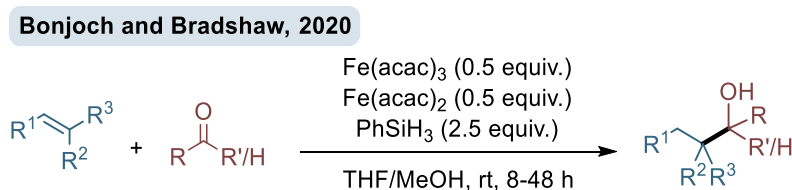
Scheme 1.33: Dual catalysis for the coupling of alkenes with imines and aldehydes.

Soon after, Bode's group showed that imines could participate in intramolecular MHAT cyclization reactions, enabling the synthesis of bridged, spiro, and fused-ring *N*-heterocycles. Given the instability of imines, they were generated in situ from the corresponding amine (Scheme 1.34).¹⁰⁶



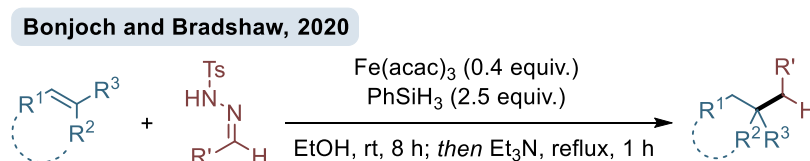
Scheme 1.34: Intramolecular coupling of alkenes with imines by Bode et al.

Following the initial report on intramolecular alkene–carbonyl coupling (see *Scheme 1.28*),¹⁰⁰ our group turned its focus to the intermolecular version. A detailed investigation of the reaction mechanism revealed that the coupling was hindered by the slow reduction of the unstable alkoxy radical to an alkoxide by a Fe^{II} species, formed after the initial atom transfer, which then regenerated Fe^{III} and completed the catalytic cycle. To address this, it was hypothesized that introducing additional Fe^{II} could stabilize the alkoxy radical, facilitating the reaction. Indeed, by employing an $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ combination, good yields of the desired coupled products were achieved (*Scheme 1.35*).¹⁰⁷



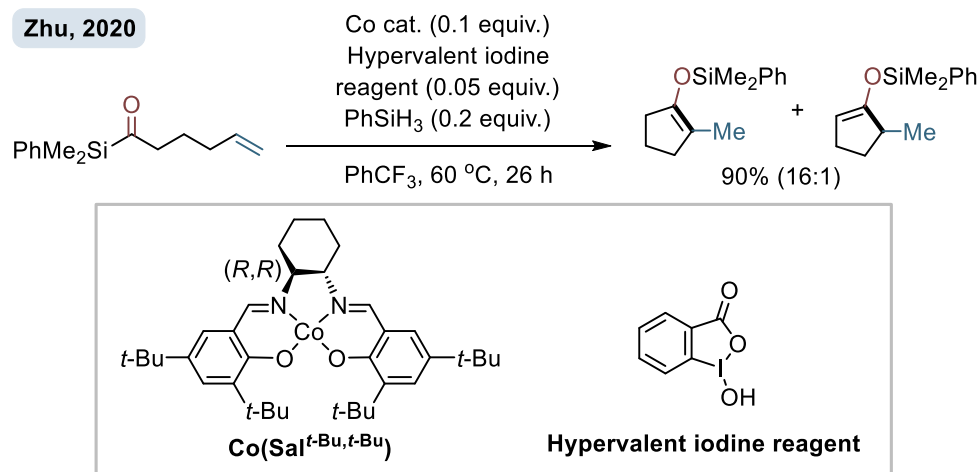
Scheme 1.35: Intermolecular addition of neutral alkenes to aldehydes.

In our efforts to expand the range of compounds accessible through MHAT methodologies, we discovered that tosylhydrazones could effectively couple with unactivated alkenes using $\text{Fe}(\text{acac})_3$ and PhSiH_3 . Following the coupling, the resulting tosylhydrazine was eliminated with Et_3N , leading to alkylated products (*Scheme 1.36*). While this approach was conceptually similar to Baran's methylation reaction (see *Scheme 1.26*),⁹⁸ that reaction was limited to using formaldehyde. In contrast, we demonstrated that a broader range of aldehydes could form the corresponding tosylhydrazones resulting in a general formal alkylation process.¹⁰⁸



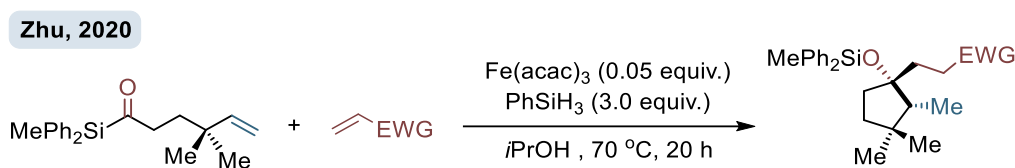
Scheme 1.36: Coupling of tosylhydrazones with unactivated alkenes by our group.

Zhu's group also demonstrated the use of carbonyls as acceptors by addressing the challenge of unfavorable alkoxy radical formation. This was achieved through the use of acylsilanes, leading to the formation of silyl enol ethers. The resulting alkoxy radical promptly underwent a [1,2]-radical Brook rearrangement, effectively trapping the radical and restoring the double bond with the hypervalent iodine reagent acting as an oxidant (*Scheme 1.37*).¹⁰⁹



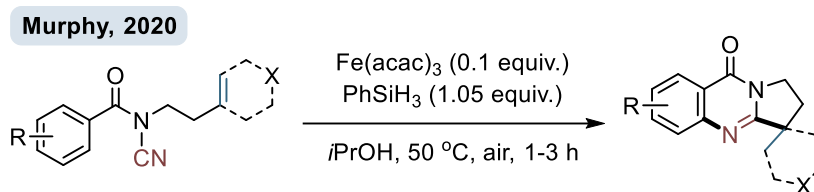
Scheme 1.37: Iron-catalyzed cyclization of unsaturated acylsilanes.

The reaction was further explored in the presence of a Michael acceptor, where the α -siloxy radical was successfully intercepted, yielding the corresponding substituted acylsilanes through a tandem cyclization/Giese addition pathway (*Scheme 1.38*).



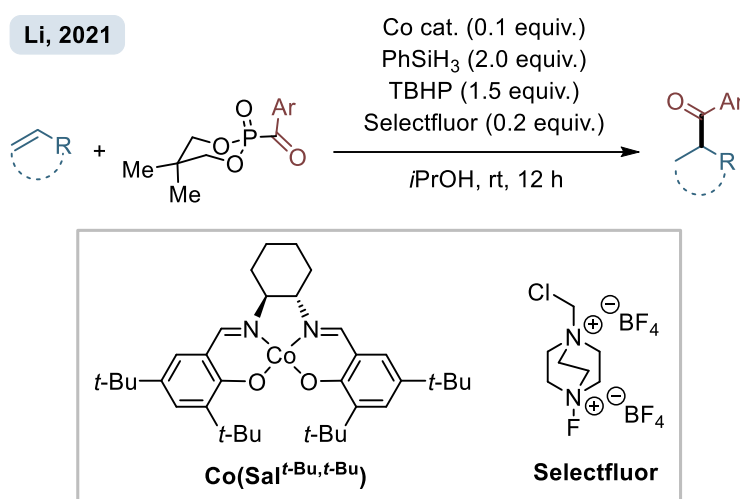
Scheme 1.38: Tandem cyclization and Giese addition of unsaturated acylsilanes.

In 2020, Murphy described a radical domino cyclization of *N*-cyanamide alkenes to synthesize (spiro)quinazolinones using Fe(acac)₃ and PhSiH₃. In this process, atmospheric oxygen played a crucial role by facilitating an oxidation step, ensuring the conversion of the mono-cyclized intermediate into the targeted quinazolinone (*Scheme 1.39*).¹¹⁰



Scheme 1.39: Cyclization reaction for the synthesis of (spiro)quinazolinones.

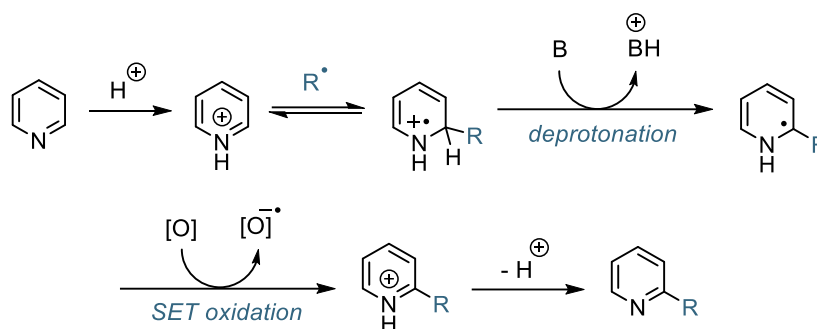
In 2021, Li and coworkers developed a cobalt-catalyzed intermolecular Markovnikov hydroacylation of unactivated alkenes utilizing acylphosphonates as the acyl source. After radical addition to the carbonyl group, a β -scission delivered the hydroacylation product with the elimination of the phosphoryl group (*Scheme 1.40*).¹¹¹



Scheme 1.40: Hydroacylation of neutral alkenes with acylphosphonates as acceptors.

Minisci reactions

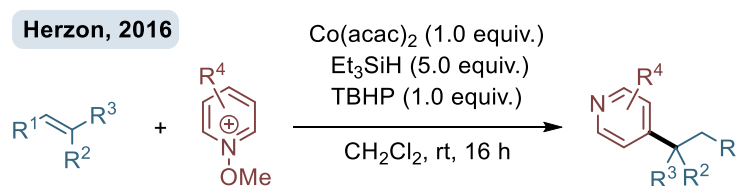
The Minisci reaction involves the addition of nucleophilic carbon-centered radicals to electron-deficient heterocycles, followed by oxidative rearomatization to access functionalized heteroarenes, which are crucial motifs in medicinal chemistry (*Scheme 1.41*).¹¹² Initially based on decarboxylation with stoichiometric silver salts, the reaction has evolved to incorporate various radical generation methods, demonstrating its adaptability to emerging synthetic strategies.¹¹³



Scheme 1.41: Minisci reaction to access functionalized heteroarenes.

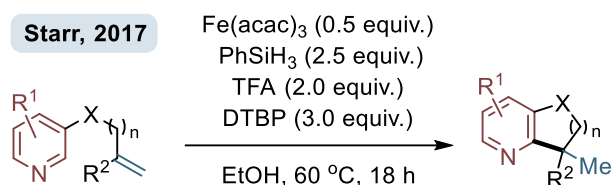
Classical Minisci reactions, despite being powerful, often require metal salts or stoichiometric amounts of peroxides at elevated temperatures. Although photocatalysis has helped reduce the need for high temperatures, it still depends on expensive and potentially toxic Ir and Ru complexes, as well as activated nucleophilic radical sources and strong oxidants. To overcome these challenges, MHAT reactions have emerged as an effective alternative, using metal hydrides to generate radicals under milder, more sustainable conditions.¹¹⁴

In 2016, the Herzon group demonstrated that MHAT conditions could facilitate the Minisci reaction by employing *N*-methoxypyridinium salts as radical acceptors. This approach enabled the hydropyridylation of neutral alkenes with high site-selectivity, allowing for the efficient formation of tertiary and quaternary centers (*Scheme 1.42*).¹¹⁵



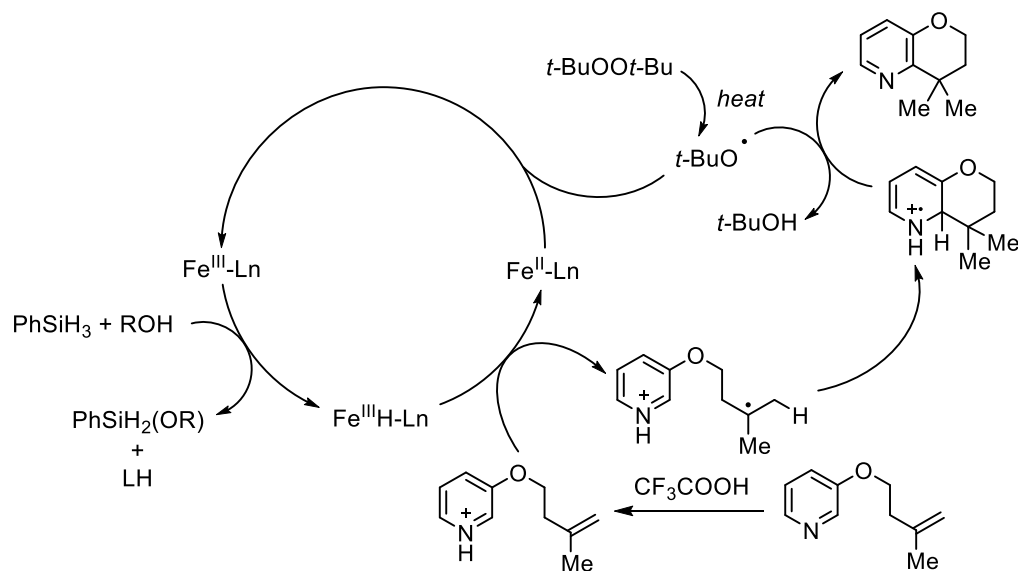
Scheme 1.42: Hydropyridylation of neutral alkenes by Herzon et al.

Starr later reported a method for the intramolecular coupling of olefin chains to pyridines, overcoming the typical requirement for an excess of the radical source in Minisci reactions. The strategy used trifluoroacetic acid for in situ protonation, activating the heterocycle for the transformation. This enabled the construction of valuable scaffolds such as dihydropyrano-pyridines and 1,2,3,4-tetrahydronaphthyridines, showcasing a streamlined approach to accessing structurally complex heterocycles (*Scheme 1.43*).¹¹⁶



Scheme 1.43: Intramolecular hydropyridylation of olefins by Starr et al.

As a representative mechanism for this section, the reaction began with a HAT from the Fe^{III} hydride complex, formed by the reaction of phenylsilane with the iron catalyst, to the olefin, generating a carbon-centered radical. This radical added to the protonated pyridine, forming a radical cation, which was oxidatively rearomatized to yield the desired products. Di-*tert*-butyl peroxide (DTBP) or oxygen from air promoted the rearomatization and regenerated the active Fe^{III} species (*Scheme 1.44*).

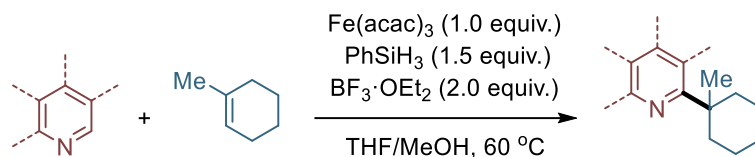
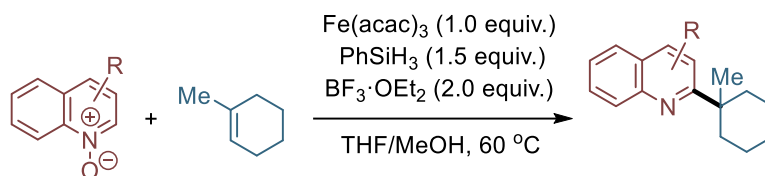


Scheme 1.44: Proposed mechanism for the intramolecular Minisci reaction by Starr.

In 2017, Baran presented a modified approach to the intermolecular Minisci reaction, building on Starr's methodology by substituting TFA with $\text{BF}_3 \cdot \text{OEt}_2$ as the activating acid. While the reaction eliminated the need for a co-oxidant, it required stoichiometric amounts of the iron catalyst. Although some heterocycles yielded regioisomeric mixtures, the use of quinoline and pyridine *N*-oxides enabled selective alkylation at the C2 position, addressing the site-selectivity challenges often encountered in Minisci reactions (*Scheme 1.45*).⁸¹

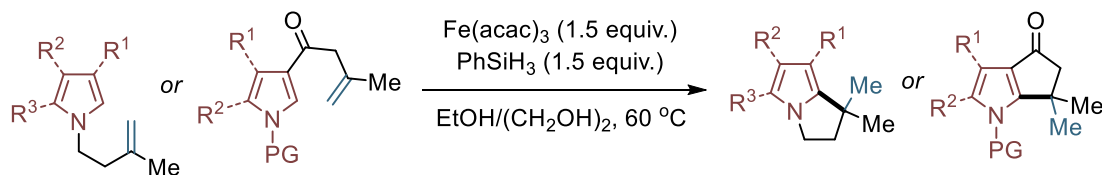
Baran, 2017

a) Olefin-based Minisci reaction:

b) *N*-oxides to give selective C2 alkylation:Scheme 1.45: $\text{BF}_3 \cdot \text{OEt}_2$ -activated MHAT Minisci coupling by Baran et al.

Narang's group recently developed a method for the intramolecular cyclization of alkenyl indoles and pyrroles, enabling the synthesis of fused derivatives. This approach has been successfully utilized in the formal synthesis of bruceolline J as well as the total synthesis of bruceolline E and H (Scheme 1.46).¹¹⁷

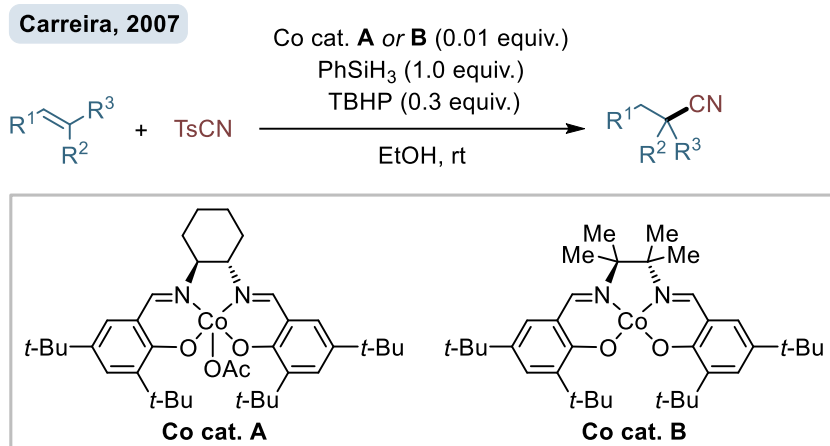
Narang, 2024



Scheme 1.46: MHAT cyclization of alkenyl indoles and pyrroles by Narang et al.

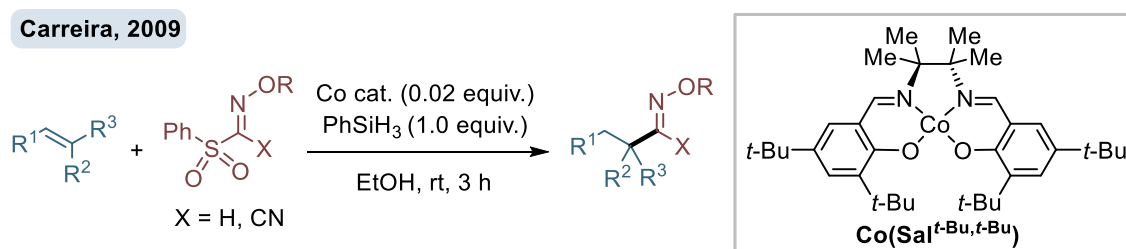
Addition-elimination mechanism

In 2007, Carreira introduced a method for the hydrocyanation of non-activated alkenes, marking the first instance in which cyanides were employed as acceptors in MHAT reactions. This strategy enabled the synthesis of secondary and tertiary nitriles and relied on tosyl cyanide as the cyanide source, a cobalt catalyst, phenylsilane as the hydride donor, and *tert*-butyl hydroperoxide (TBHP) as the oxidizing agent (Scheme 1.47).¹¹⁸



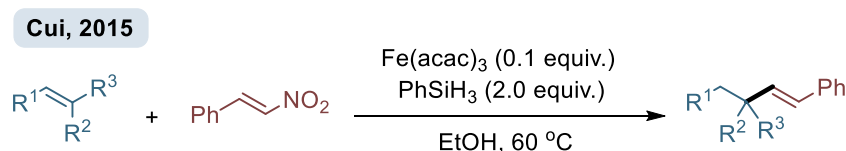
Scheme 1.47: Hydrocyanation of unactivated alkenes via addition-elimination pathway.

In 2009, Carreira also disclosed the use of imines as radical acceptors in MHAT reactions. By employing phenyl sulfonyl oximes, *O*-benzyloximes and oximonitriles could be incorporated onto neutral alkenes with the concomitant elimination of the benzenesulfonyl group using a cobalt catalyst and PhSiH₃ (*Scheme 1.48*).¹¹⁹



Scheme 1.48: First reported example of imines as MHAT radical acceptors by Carreira.

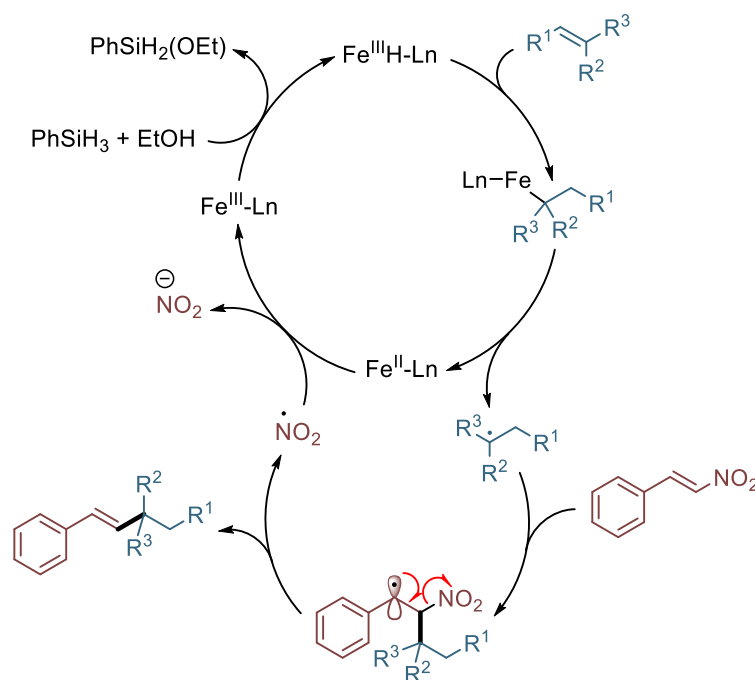
In 2015, Cui described the use of β -nitroalkenes as acceptor groups to produce secondary- and tertiary-alkylated styrene derivatives (*Scheme 1.49*).¹²⁰



Scheme 1.49: MHAT coupling of neutral alkenes with β -nitroalkenes.

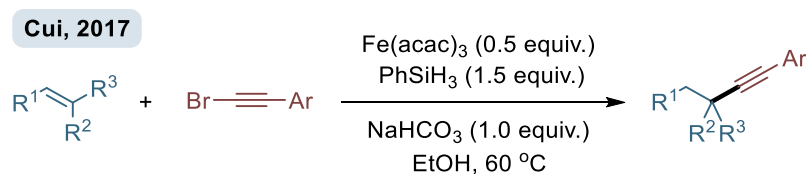
Mechanistically, the reaction proceeded with the conversion of the Fe^{III} catalyst to an iron hydride species in the presence of phenylsilane and ethanol. This Fe^{III}–H species then underwent regioselective addition to the alkene, generating an alkyl radical on the most substituted carbon, which was intercepted by the nitroalkene to form a β -nitro

radical intermediate. Elimination of this intermediate yielded the alkylated styrene product along with a nitro radical, which facilitated the reoxidation of Fe^{II} to Fe^{III} , thereby sustaining the catalytic cycle (*Scheme 1.50*). This mechanistic framework will serve as a model for the entire addition-elimination section, as analogous pathways are expected for the following transformations.



Scheme 1.50: Mechanism for Cui's coupling of neutral alkenes and β -nitrostyrenes.

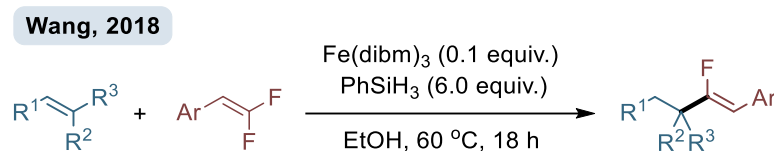
In 2017, the Cui group developed a Fe^{III} -catalyzed hydroalkynylation of unactivated alkenes to form $\text{C}(\text{sp})\text{--C}(\text{sp}^3)$ bonds. The reaction required the addition of NaHCO_3 to neutralize HBr generated during the coupling. This approach successfully enabled the coupling of mono-, di-, and trisubstituted alkenes with a range of aromatic and heterocyclic alkynyl bromides (*Scheme 1.51*).¹²¹



Scheme 1.51: Hydroalkynylation of neutral alkenes by Cui et al.

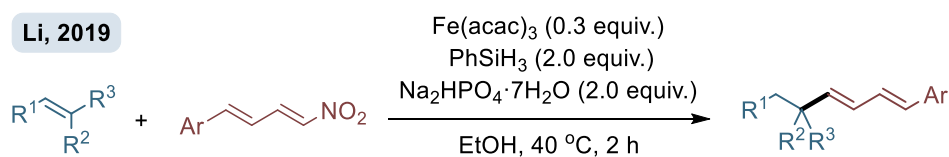
In 2018, Wang developed an iron-catalyzed HAT strategy for the reductive cross-coupling of *gem*-difluoroalkenes with unactivated olefins. The reaction proceeded through β -

fluorine elimination, regenerating the double bond and yielding the corresponding fluoroalkenes with excellent *Z*-selectivity under air- and water-tolerant conditions. The authors also explored the use of mono-fluoroalkenes, enabling the synthesis of alkyl-substituted alkenes (*Scheme 1.52*).¹²²



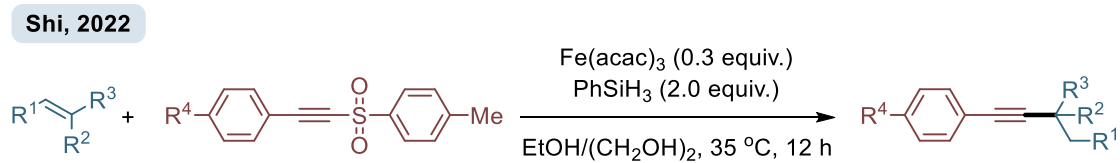
Scheme 1.52: Defluorinative cross-coupling of neutral alkenes and gem-difluoroalkenes.

Soon after, Li's group introduced an iron-catalyzed reductive coupling reaction between nitrodienes and unactivated alkenes, yielding a variety of functionalized dienes. They also discovered that $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ played a critical role as an additive, both accelerating the formation of the hydride source $\text{PhSiH}_2(\text{OEt})$ and preventing catalyst deactivation (*Scheme 1.53*).¹²³



Scheme 1.53: Li's Fe-catalyzed coupling of nitrodienes with neutral alkenes.

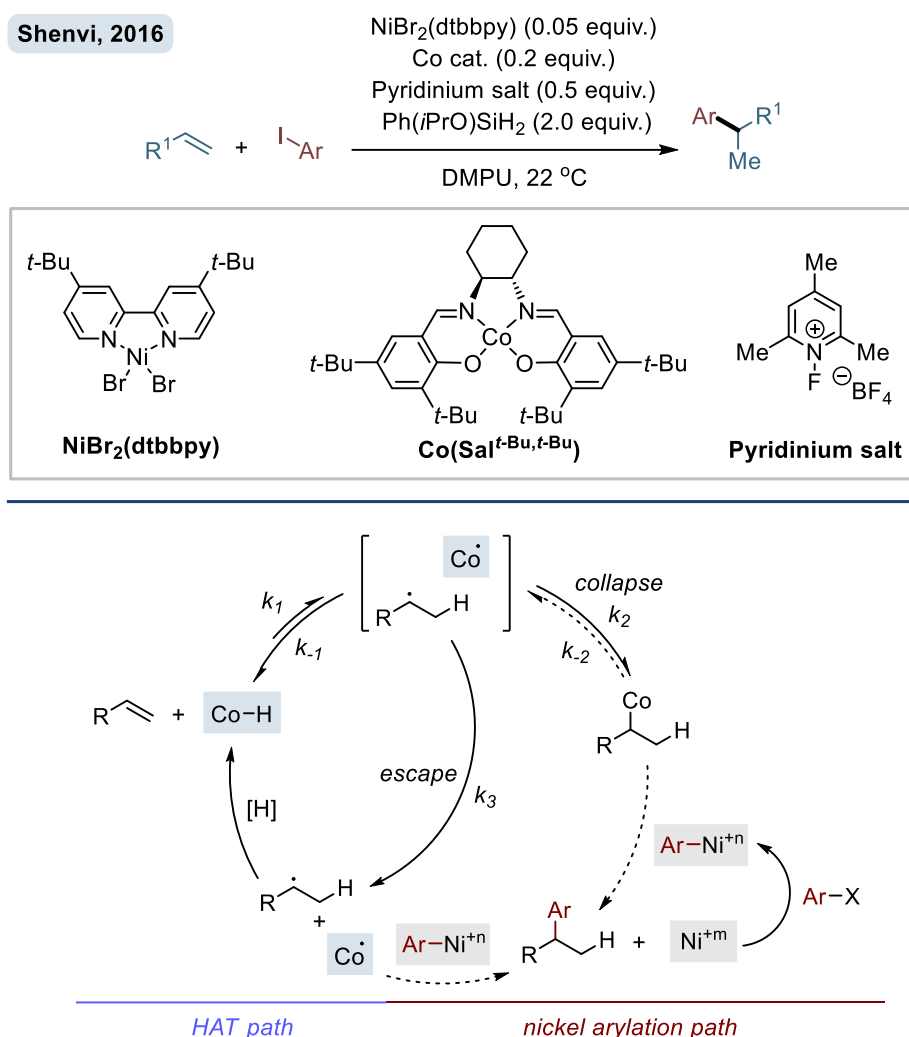
Finally, in 2022, Shi's group reported the coupling of acetylenic sulfones with unactivated alkenes. The methodology was analogous to that described by Cui (see *Scheme 1.51*),¹²¹ albeit with the expulsion of a sulfinic acid instead of HBr (*Scheme 1.54*).¹²⁴



Scheme 1.54: Iron-catalyzed alkynylation of neutral alkenes by Shi et al.

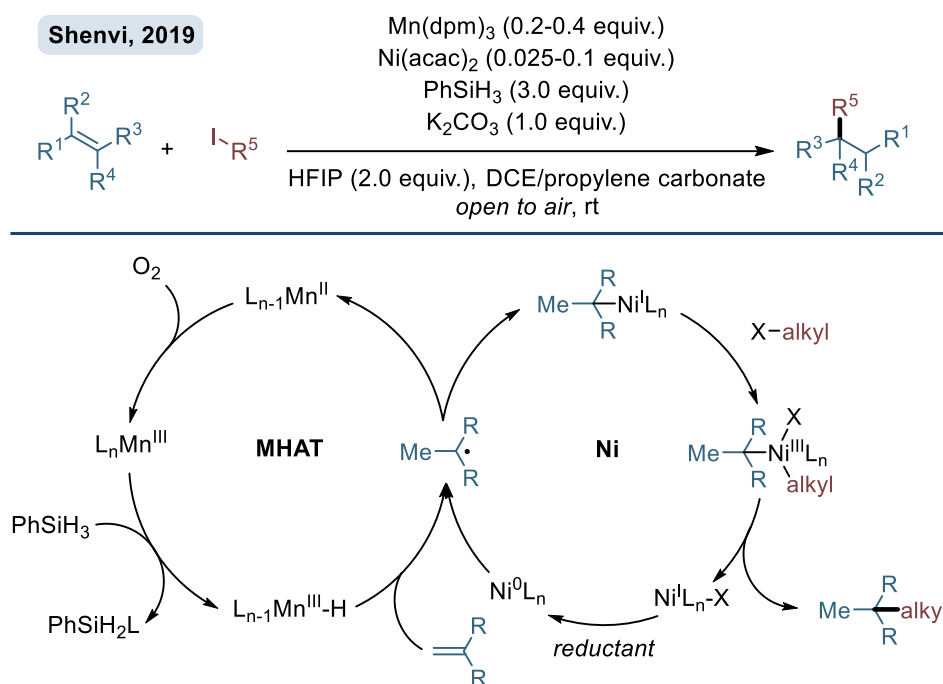
Metal cross-coupling

Shenvi and coworkers reported the hydroarylation of terminal aliphatic olefins with iodoarenes by integrating a cobalt-mediated MHAT catalytic cycle with nickel catalysis. The nickel catalyst formed an arylnickel species, which was intercepted by the alkene cobalt intermediate to yield the coupled products (*Scheme 1.55*).¹²⁵



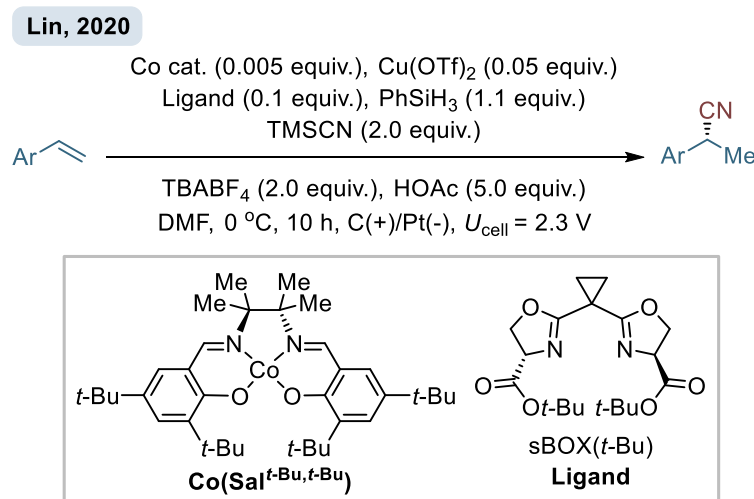
Scheme 1.55: Branch-selective hydroarylation of neutral alkenes with iodoarenes.

Three years later, the same group reported the initial application of alkyl halides as radical acceptors, enabling the synthesis of hydroalkylated compounds featuring tertiary or quaternary carbon centers. This was achieved through a dual Mn/Ni catalytic system, where a secondary or tertiary radical formed via Mn-mediated MHAT was captured by a Ni species originating from the alkyl halide (*Scheme 1.56*).¹²⁶



Scheme 1.56: Dual Mn/Ni-catalyzed hydroalkylation of olefins.

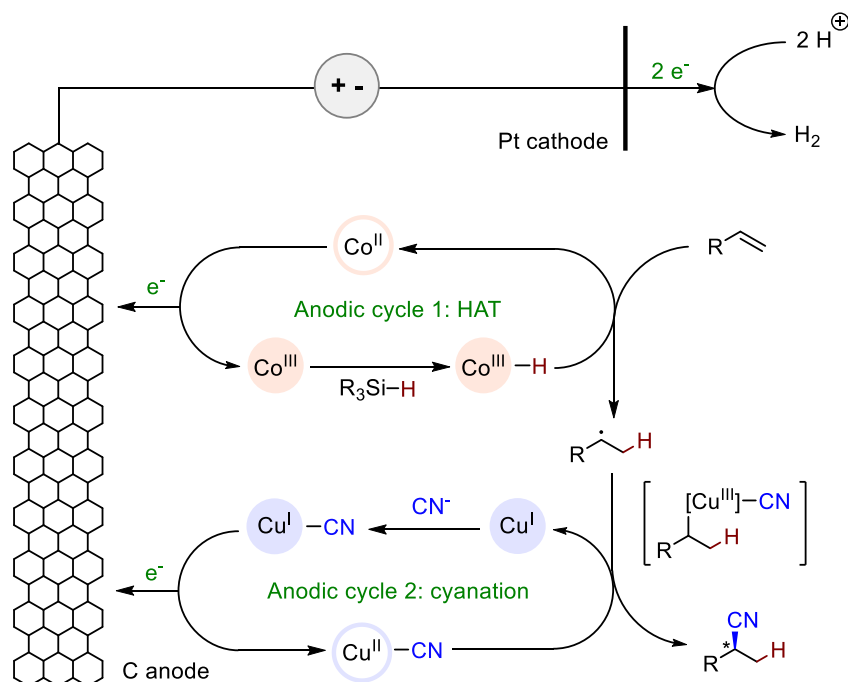
After Carreira's seminal work on the hydrocyanation of alkenes (see Scheme 1.47),¹¹⁸ in 2020, Lin introduced an enantioselective approach that merged cobalt-mediated hydrogen atom transfer with copper-promoted radical cyanation facilitated by a chiral ligand under electrochemical conditions. This method enabled the hydrocyanation of alkenes with high yields and excellent enantiomeric excess (Scheme 1.57).¹²⁷



Scheme 1.57: Dual Co/Cu-catalyzed hydrocyanation of alkenes.

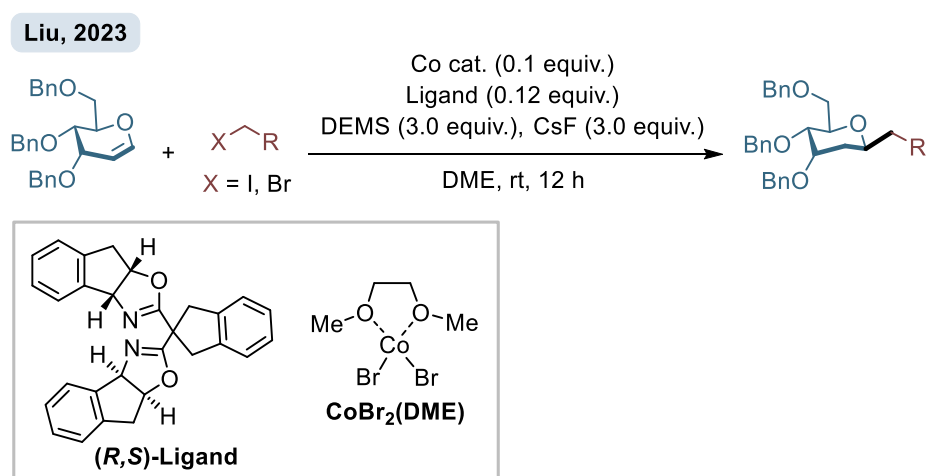
The reaction proceeded through an anodically coupled electrocatalytic system, integrating two metal-mediated radical processes. Initially, a Co^{III}–H species generated

from a Co^{III} precursor and a hydrosilane facilitated HAT to the alkene, yielding a carbon-centered radical. This radical then engaged in a cyanation cycle, undergoing single-electron oxidative addition to a $\text{Cu}^{\text{I}}\text{--CN}$ complex, forming a transient Cu^{III} intermediate. Finally, reductive elimination completed the hydrocyanation, delivering the desired product (*Scheme 1.58*).



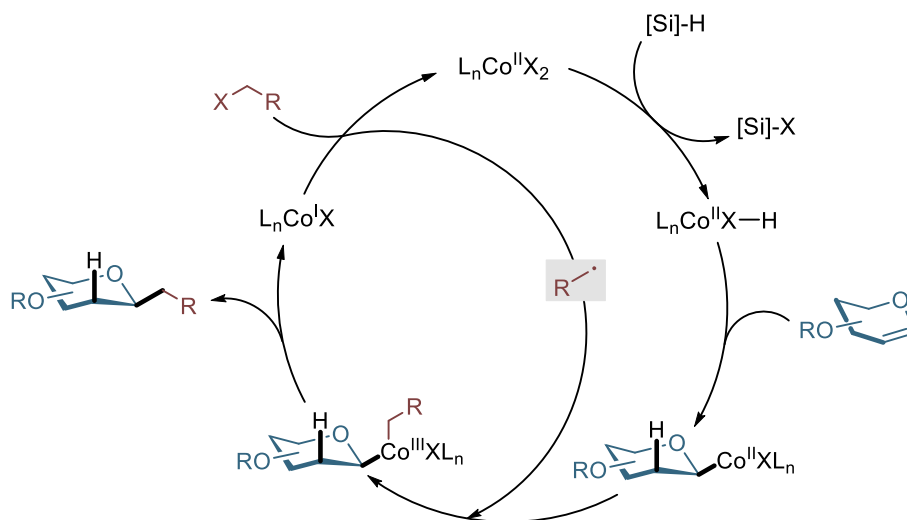
Scheme 1.58: Mechanism of the dual-catalyzed hydrocyanation of alkenes by Lin.

In 2023, Liu introduced a Co^{II} -catalyzed $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ hydroalkylation method for the β -stereoselective synthesis of 2-deoxy-*C*-glycosides from glycals and alkyl halides under mild and non-toxic conditions (*Scheme 1.59*).¹²⁸



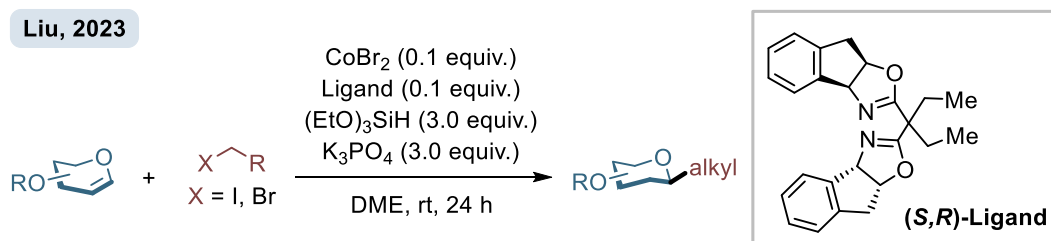
*Scheme 1.59: MHAT β -stereoselective synthesis of 2-deoxy-*C*-glycosides by Liu.*

The glycosyl hydroalkylation reaction proceeded through the initial formation of a cobalt hydride species from the catalyst and silane. This cobalt hydride then inserted into the C=C bond, leading to the formation of an alkyl cobalt intermediate. Rapid capture of the alkyl radical by this intermediate generated a Co^{III} species, which underwent reductive elimination to afford the desired β -2-deoxy-C-glycoside product. Finally, the resulting Co^{I} species was reoxidized to regenerate the active catalyst while simultaneously forming an alkyl radical through its reaction with an alkyl halide (Scheme 1.60).



Scheme 1.60: Mechanistic pathway for the synthesis of 2-deoxy-C-glycosides by Liu.

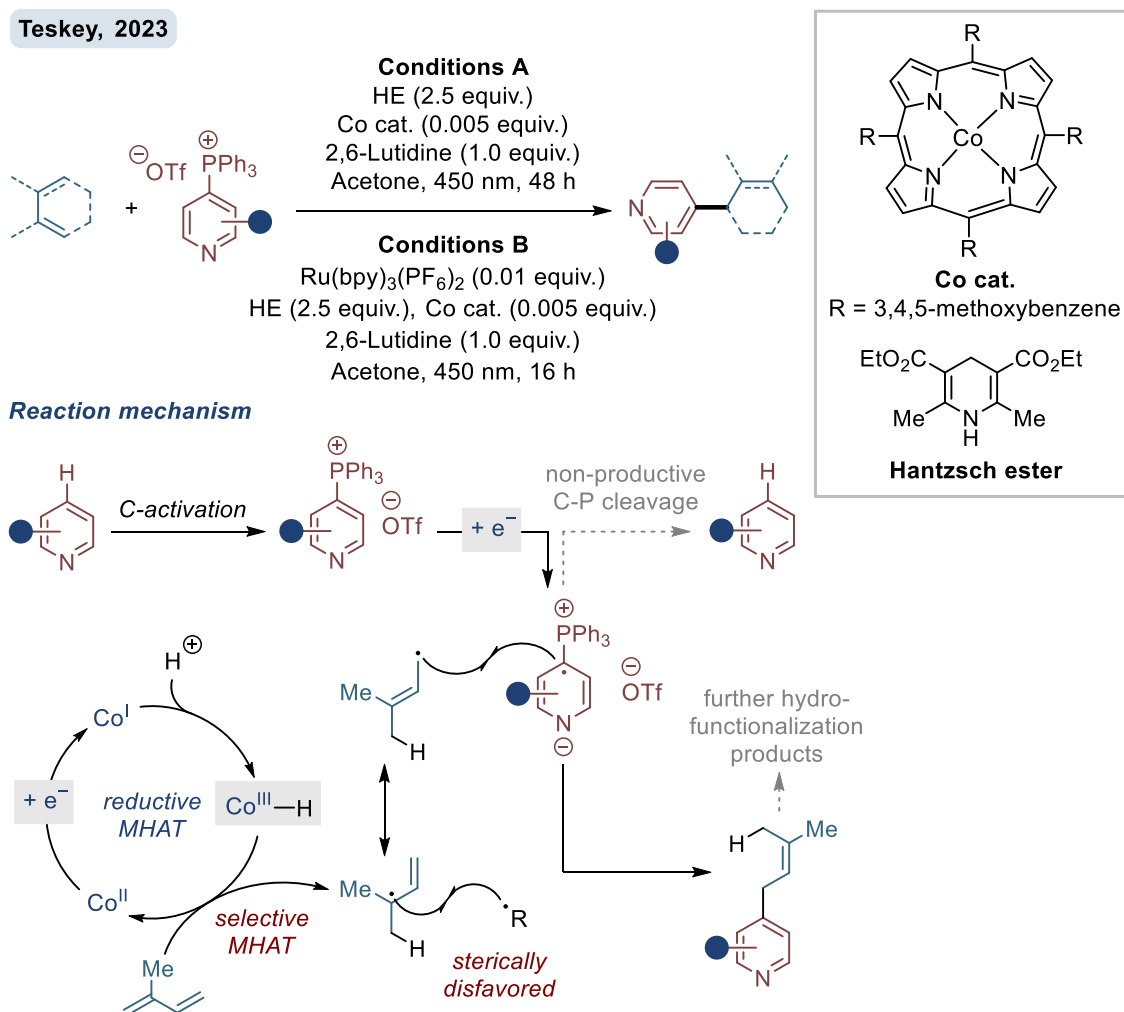
Soon after, Liu's group developed a similar approach for the ligand-controlled, stereoselective C-alkylation of glycals, leading to the synthesis of 2-deoxy- β -C-glycosides. Mechanistic studies suggested that the hydrometallation of the glycal with the coordinated Co–H intermediate represented the rate- and stereoselectivity-determining step in the hydroalkylation (Scheme 1.61).¹²⁹



Scheme 1.61: Co-catalyzed synthesis of 2-deoxy- β -C-glycosides.

Radical–Radical coupling

Instances for the hydroarylation of dienes are scarce, typically requiring dienes stabilized with aromatic groups and electron-rich arenes as coupling partners. To overcome this, in 2023, Teskey presented a method for the selective hydropyridylation of dienes using MHAT under mild, photoinduced, reductive conditions. This approach leveraged a cobalt hydride species which was selective for dienes and pyridyl phosphonium salt radicals to achieve C4-position coupling of a variety of pyridine substrates via a radical–radical reaction. Mechanistically, MHAT from $\text{Co}^{\text{III}}\text{--H}$ to the diene furnished a stabilized allylic radical. Simultaneously, a single-electron reduction generated a C4-centered radical of the pyridyl phosphonium salt, enabling the radical–radical coupling with concomitant removal of PPh_3 (Scheme 1.62).¹³⁰



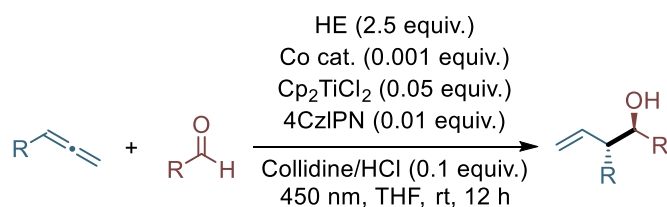
Scheme 1.62: Hydropyridylation of dienes via radical–radical coupling.

Building on Teskey's work, Shi's group later developed a dual Ti- and Co-catalyzed photoinduced strategy for the selective hydrofunctionalization of dienes and allenes with aldehydes.¹³¹

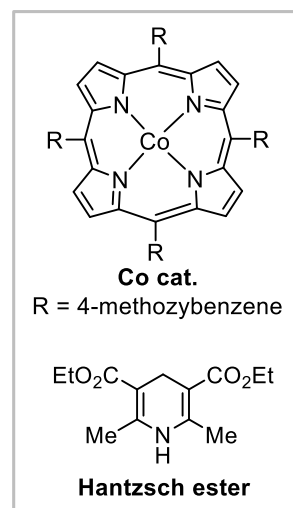
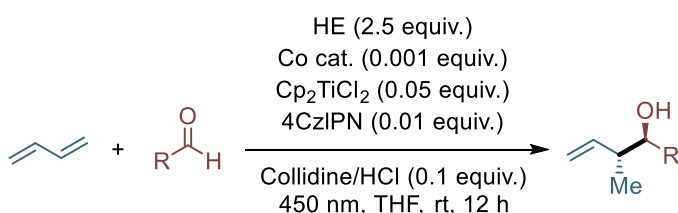
In the postulated mechanism, the photocatalyst triggered the formation of Co^{I} and Ti^{III} . Subsequent protonation of the cobalt species formed $\text{Co}^{\text{III}}\text{--H}$, which transferred a hydride to the selected allene or diene to produce a stabilized allylic radical. This radical was then trapped by Ti^{III} to yield a nucleophilic π -allyltitanium complex, that readily coupled with an aldehyde. Protonation and expulsion of Ti^{IV} released the final product (Scheme 1.63).

Shi, 2024

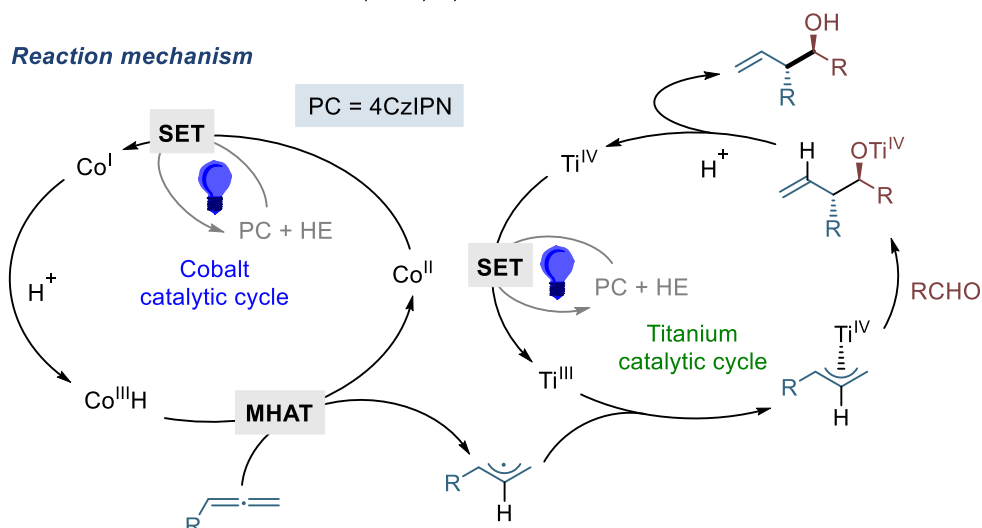
a) Allylation of aldehydes with allenes:



b) Radical crotylation of aldehydes:

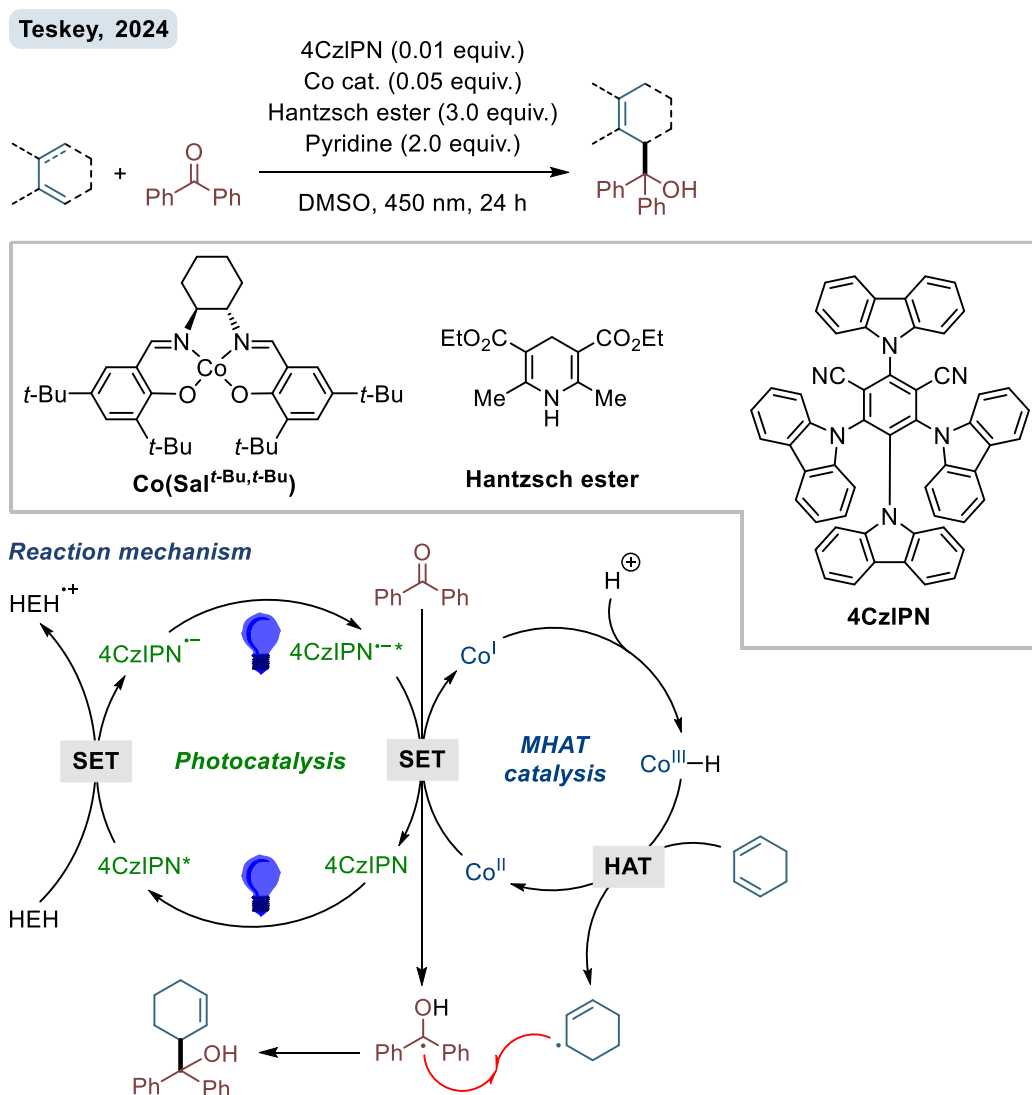


Reaction mechanism



Scheme 1.63: Dual Ti/Co-catalyzed hydrofunctionalization of dienes and allenes by Shi.

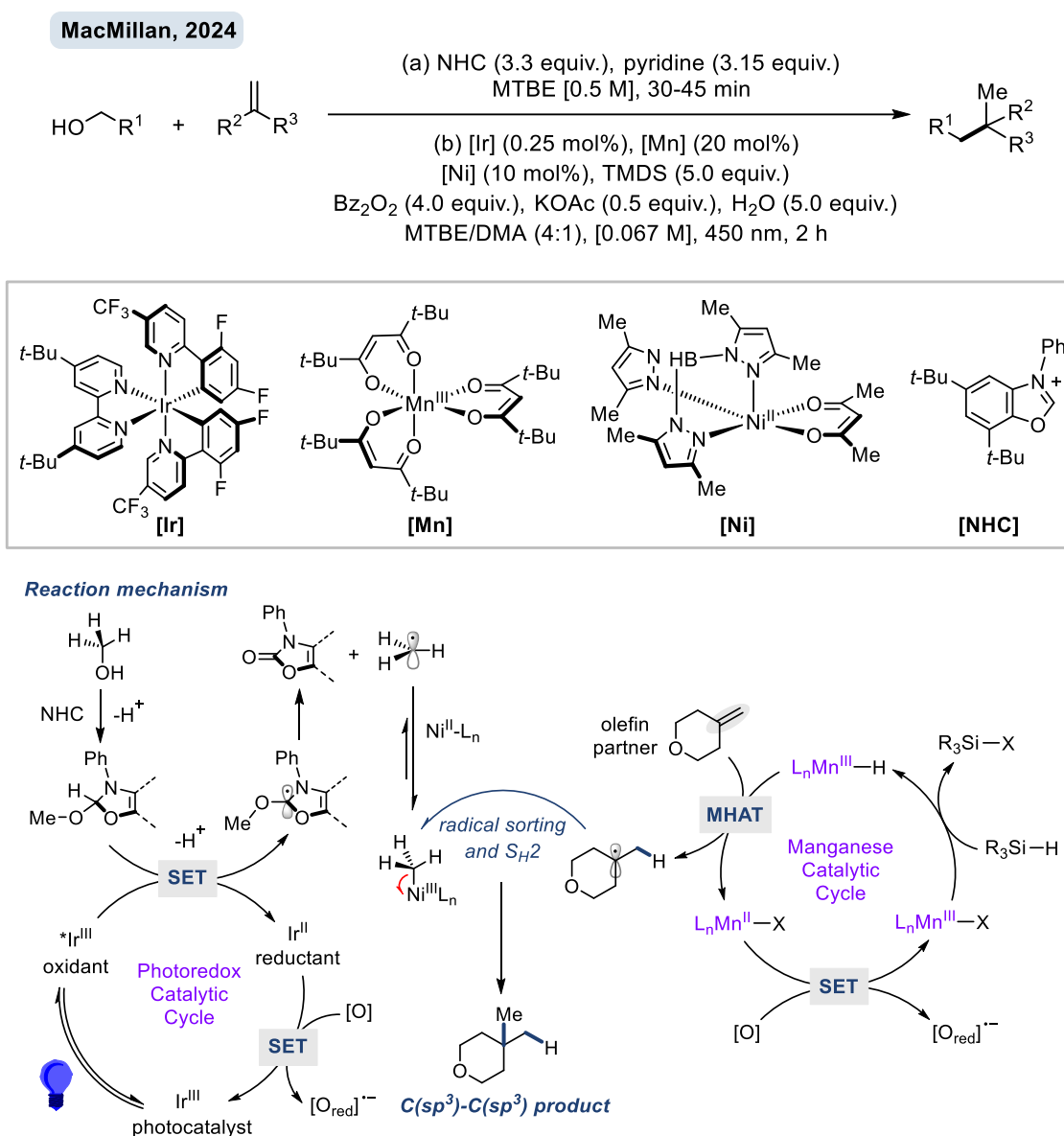
While our group successfully achieved the intermolecular coupling of unactivated alkenes with aldehydes under MHAT conditions (see *Scheme 1.35*),¹⁰⁷ extending this approach to ketones proved challenging. Recently, Teskey and coworkers demonstrated that dienes could be coupled with diaryl ketones under photochemical conditions. In their system, the ketone formed a stable ketyl radical, which engaged in radical–radical coupling with the diene-derived radical generated under MHAT conditions. This mechanism circumvented the formation of an alkoxy radical, enabling the desired intermolecular coupling to proceed with high efficiency (*Scheme 1.64*).¹³²



Scheme 1.64: Photoinduced coupling between dienes and ketones by Teskey.

Aiming to expand the array of coupling partners in MHAT reactions, MacMillan developed an MHAT-triggered metallaphotoredox coupling of alkenes and alcohols (Scheme 1.65). The authors designed an *N*-heterocyclic carbene (NHC) precursor that could be readily coupled with the selected alcohols to promote radical deoxygenation.¹³³

Mechanistically, irradiation in the presence of an Ir^{III} photocatalyst triggered the deoxygenation of the NHC–alcohol adduct to give a carbon-centered primary or secondary radical. Simultaneously, classical Mn^{III}-mediated MHAT to the unactivated alkene furnished a tertiary radical. For the coupling step, the Ni^{II} catalyst intercepted the least substituted radical, in this case the one generated from the alcohol substrate.

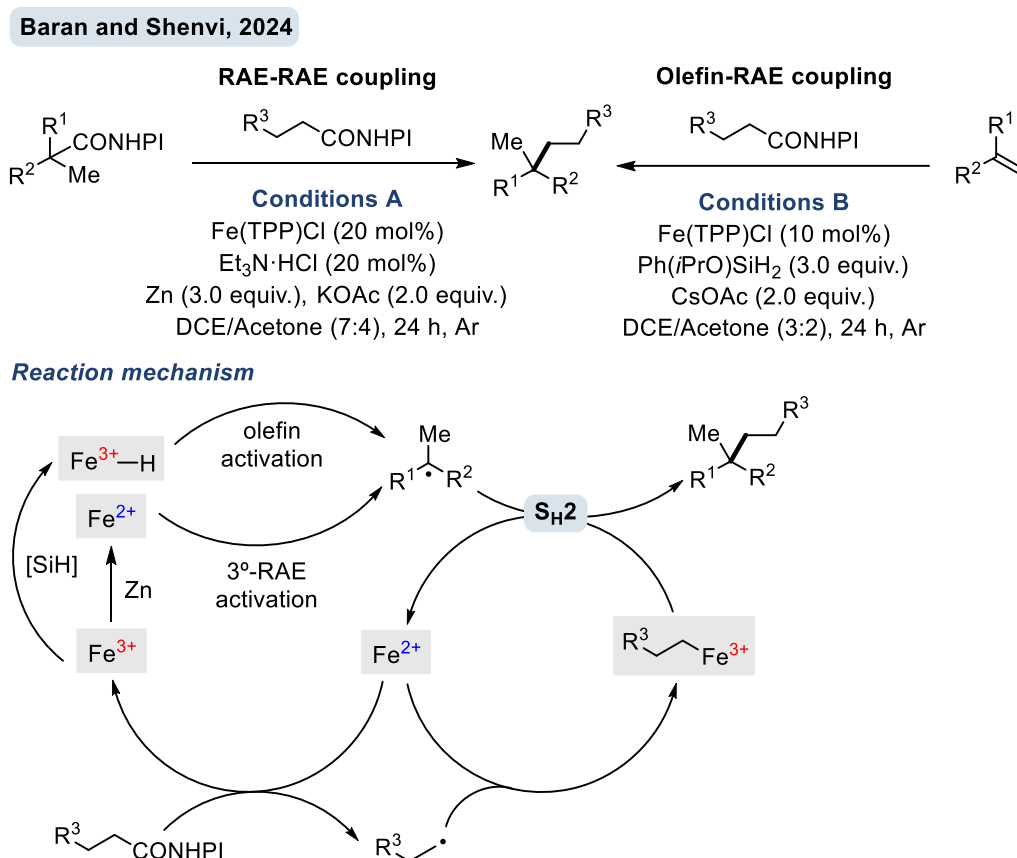


Scheme 1.65: Radical–radical coupling between alkenes and alcohols by MacMillan.

Eventually, the tertiary radical underwent S_H2 displacement with the Ni complex to afford the final product.

Recently, the groups of Baran and Shenvi disclosed an iron-catalyzed radical–radical MHAT coupling of *N*-hydroxyphthalimide (NHPI)-derived redox-active esters (RAEs) and neutral alkenes for the formation of quaternary centers.

Mechanistically, exposure of *gem*-disubstituted alkenes to the Fe^{III} catalyst furnished a tertiary radical via classical MHAT. In the case of the RAEs, Fe^{II} induced their homolytic cleavage to access primary and/or tertiary radicals. Due to their lower stability, primary radicals were preferentially intercepted by Fe^{II} . Eventually, the tertiary radical engaged in an S_H2 process with the iron complex to provide the final quaternized product (Scheme 1.66).¹³⁴



Scheme 1.66: Fe-catalyzed coupling of RAEs and neutral alkenes via an S_H2 process.

1.2 OBJECTIVES

The aim of this thesis is to expand the array of MHAT C–C bond-forming reactions to facilitate the synthesis of bioactive compounds and complex natural products (*Scheme 1.67*).

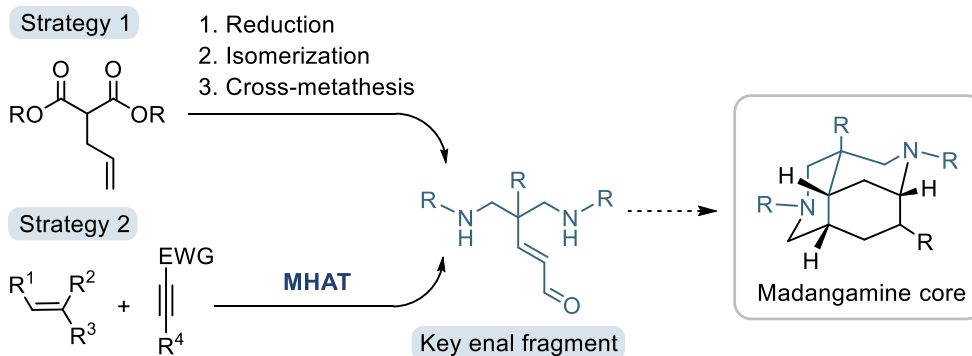
Firstly, we set out to develop an efficient strategy for constructing the azatricyclic core of madangamine alkaloids (*Objective 1*). To do so, we considered two approaches to access the key enal fragment. The more traditional strategy utilized a diester precursor, and the installation of the acrolein fragment via cross-metathesis. Additionally, we proposed an alternative synthetic route that relied on the use of MHAT chemistry. Specifically, we envisaged the formation of a key bond via a previously undisclosed Giese-type addition between an electron-deficient alkyne and a neutral alkene. Establishing the feasibility of this transformation would not only offer a novel strategy toward the madangamine framework but also expand the scope of MHAT C–C bond-forming reactions providing a new disconnection approach to electron-deficient alkenes. The results of this study will be discussed in Chapter 2.

Next, we wanted to explore a modular strategy toward aspernomine. Following a function-oriented synthesis approach, and given the long-term goal of its total synthesis, we first focused on the obtention of its heterocyclic fragment, aiming to determine whether it alone accounts for aspernomine's biological activity—an insight that could streamline the design of bioactive analogs (*Objective 2*). To this end, we developed a base-mediated nitrophenyl reductive cyclization for the synthesis of 3,4-benzomorphans and subsequently conducted biological assays to evaluate their activity. The results of this study will be discussed in Chapter 3.

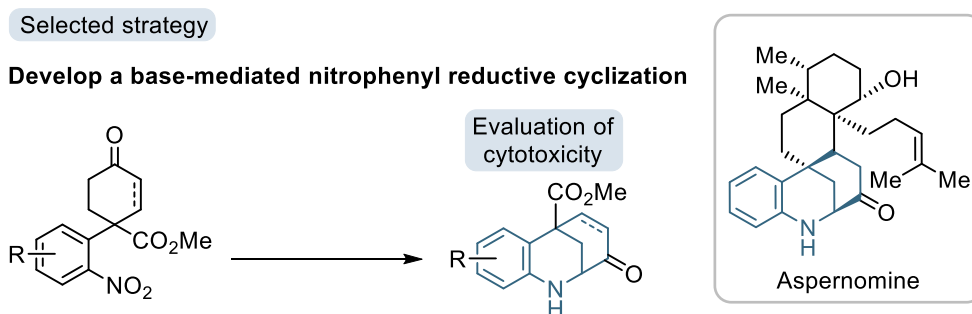
With the 3,4-benzomorphan fragment in hand, we continued our studies toward the synthesis of aspernomine, searching for an efficient strategy to couple the heterocyclic and the terpenic fragments (*Objective 3*). To this end, we proposed an MHAT-triggered decarboxylation of redox-active esters, enabling the formation of non-branched products and leveraging carboxylic acids as radical precursors. This work will be disclosed in Chapter 4.

Objective 1

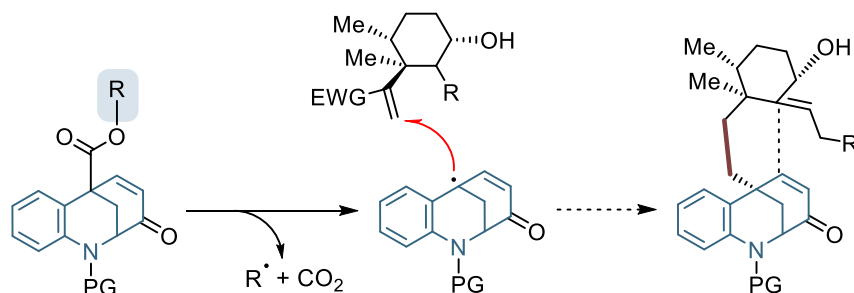
Develop a methodology to access the core of madangamine alkaloids

**Objective 2**

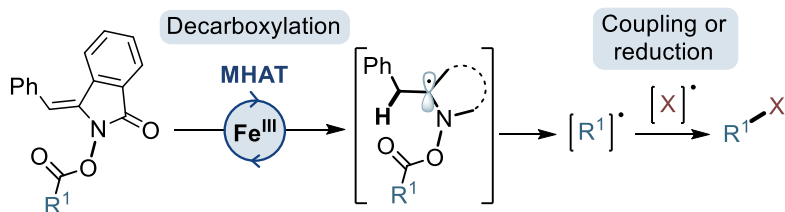
Synthesize the 3,4-benzomorphan fragment embedded in aspernomine

**Objective 3**

Connect the heterocyclic and terpenic fragments of aspernomine

**Selected strategy**

Develop an MHAT-triggered decarboxylation with novel redox-active esters



Scheme 1.67: Main objectives of this work.

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2. ELECTRON-DEFICIENT ALKYNES AS ACCEPTOR GROUPS IN WHAT REACTIONS WITH UNACTIVATED ALKENES

2.1 INTRODUCTION

In this chapter, we develop an MHAT coupling between neutral alkenes and electron-deficient alkynes under mild conditions, employing iron catalysis and phenylsilane as a hydride source. This strategy was inspired by challenges encountered during efforts to synthesize the core of madangamine alkaloids, particularly the installation of alkenes adjacent to sterically hindered centers. The resulting transformation introduces a novel disconnection approach to access electron-deficient alkenes.

2.1.1 Discovery and bioactivity of madangamine alkaloids

Madangamine alkaloids are a family of bioactive marine compounds derived from sponges of the order *Haplosclerida*. In 1994, Andersen isolated the first example of an alkaloid of this group, madangamine A, from the marine sponge *Xetospongia ingens*.¹ Shortly thereafter, the same group isolated madangamines B–E from the same sponge species.² Years later, madangamine F was isolated by Berlinck *et al.* from *Pachychalina alcaloidifera*.³ Madangamines are structurally defined by a pentacyclic fused-ring framework incorporating two nitrogen atoms (*Figure 2.1*). Central to this family is the azatricyclic core, which is consistent across all members. Beyond this core, two linear carbon bridges connect N7 to C9 and N1 to C3, forming the macrocyclic rings D and E, respectively. The structure of ring E is identical in all madangamines except for madangamine F, whereas ring D varies among the different members.

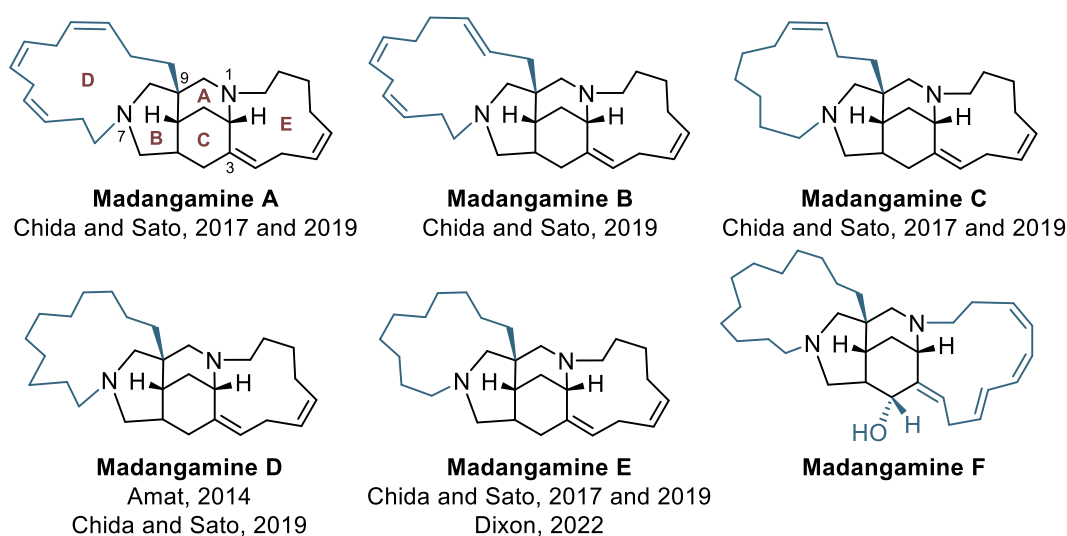


Figure 2.1: Structures of madangamines A to F.

Madangamine alkaloids exhibit potent cytotoxicity against a range of cancer cell lines. Early studies showed that madangamine A was active against murine leukemia P-388, lung A-549, brain U-373, and breast MCF-7 cells.¹ Madangamine D was effective against colon HT-29 and pancreas PSN-1 cells but inactive against lung A-549 and breast MDA-MB-231 cells.⁴ Madangamine F demonstrated significant cytotoxicity against glioblastoma SF-295, breast MDA-MB-435, colon HCT-8, and leukemia HL-60 cells, highlighting the broad anticancer potential of this family.³

In light of these findings, a recent study by Sato and Chida tested madangamines A to E against thirteen cancer cell lines, including A-549 (lung adenocarcinoma), CHL-1 and SK-MEL-28 (melanoma), HCT-116 (colon carcinoma), HeLa (cervical adenocarcinoma), HT-1080 (fibrosarcoma), MCF-7 and MDA-MB-231 (breast carcinoma), Panc-1 and PK-1 (pancreatic carcinoma), PC-3 (prostate adenocarcinoma), T-24 (bladder carcinoma), and THP-1 (acute monocytic leukemia). All compounds inhibited cell growth, with IC₅₀ values probably influenced by the structure of the D ring. Madangamines A and B, with unsaturated D rings, were the most potent, while madangamines D and E, with saturated rings, showed less activity. Notably, madangamine C, featuring a *cis*-olefin in its D ring, was slightly more potent than madangamine E.⁵

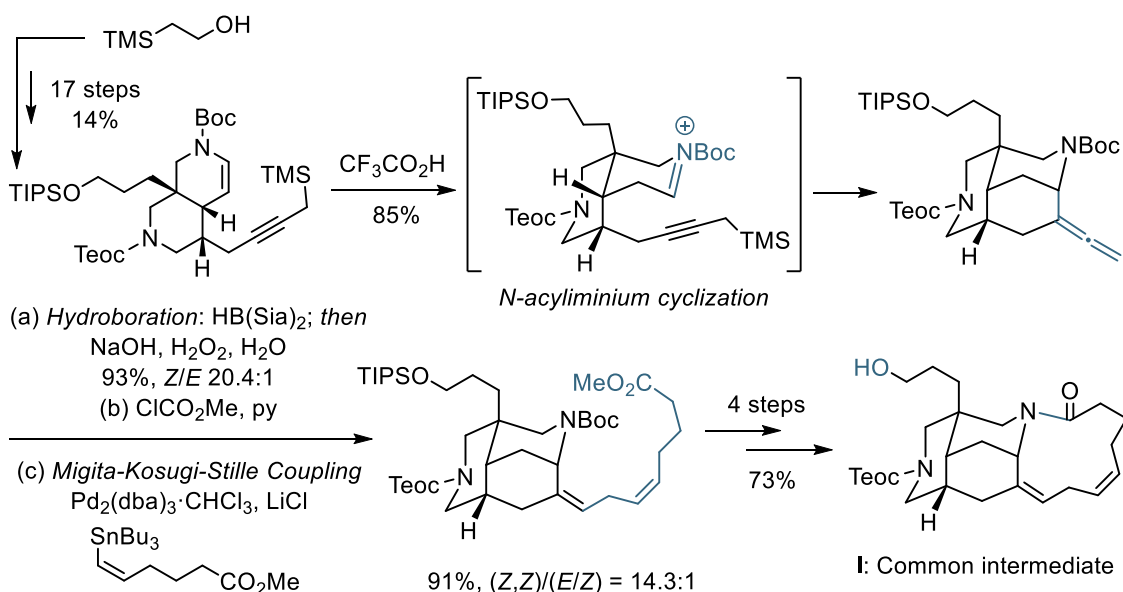
These promising results prompted further studies into the molecular mechanism of these alkaloids. Research by Chida and Sato revealed that madangamine A inhibited autophagy and cell growth in HeLa (cervical adenocarcinoma), HT-1080 (fibrosarcoma), and SK-MEL-28 (melanoma) cells. It also caused lysosomal enlargement and an increase in lysosomal pH, suggesting that its cytotoxicity may be partly due to the inhibition of lysosomal function.⁶

2.1.2 Total syntheses of madangamine alkaloids

The total synthesis of madangamine D was achieved by Amat and Bosch in 2014 in 21 steps (*Scheme 2.1*).⁴ The synthesis began with the cyclocondensation of an oxoester and (*R*)-phenylglycinol, yielding an enantiopure lactam and establishing the stereocenter at C5. Further transformation via seleno derivatives generated an unsaturated intermediate, which underwent stereoselective allylation and ring-closing metathesis to afford a *cis*-octahydroisoquinolone. Selective alkylation from the less hindered face

In 2017, Sato and Chida introduced a stereodivergent strategy for the synthesis of skipped dienes, combining allene hydroboration and Migita–Kosugi–Stille coupling to access all four stereoisomers. This approach facilitated the total synthesis of madangamine alkaloids via a common ABCE-tetracyclic intermediate, with late-stage D ring modifications enabling the obtention of madangamines A, C, and E.⁹ In 2019, the authors expanded this methodology to include the syntheses of madangamines B and D, further showcasing the versatility of their strategy.⁵

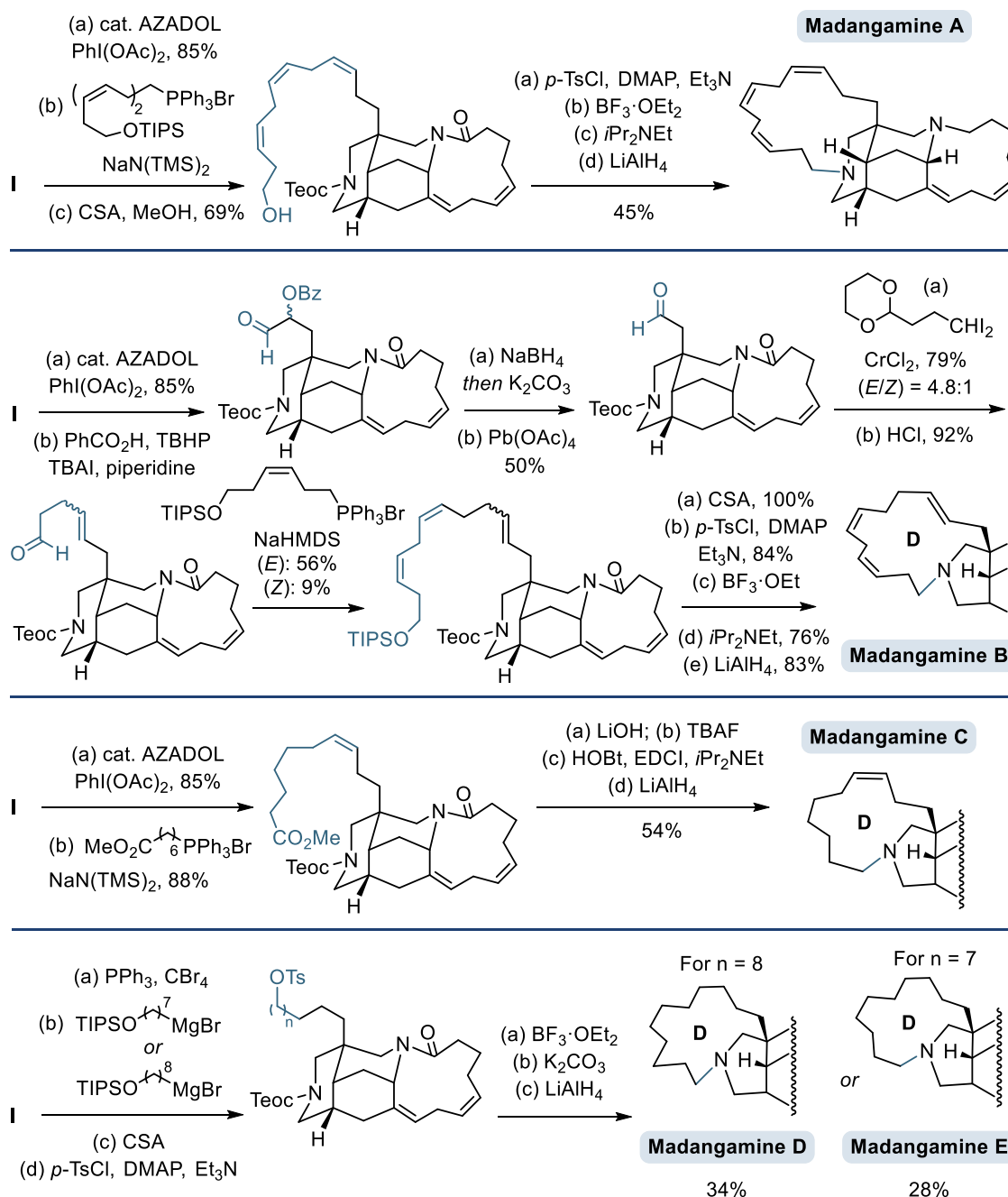
The formation of the tetracycle began by the *N*-acyliminium cyclization of a propargylsilane under acidic conditions. The reaction proceeded via the protonation of the *N*-Boc enamine to form a highly electrophilic *N*-acyliminium cation, which underwent spontaneous cyclization to access an azatricyclic species. *Z*-selective hydroboration of the allene moiety with HB(Sia)₂, followed by Migita–Kosugi–Stille coupling with *Z*-vinyl stannane, afforded the corresponding (*Z,Z*)-diene in 85% yield. Further elaboration of the skipped diene furnished the tetracycle **I**, which served as an advanced common intermediate (*Scheme 2.2*).



Scheme 2.2: Sato and Chida's common intermediate toward madangamines A to E.

Madangamine A was synthesized via Wittig coupling to install the (*Z,Z,Z*)-triene, followed by tosylation, macrocyclic alkylation, and final LiAlH₄ reduction. Madangamine B required a one-carbon dehomologation sequence to prepare an aldehyde, followed by Takai olefination, Wittig coupling, macrocyclic alkylation, and LiAlH₄ reduction.

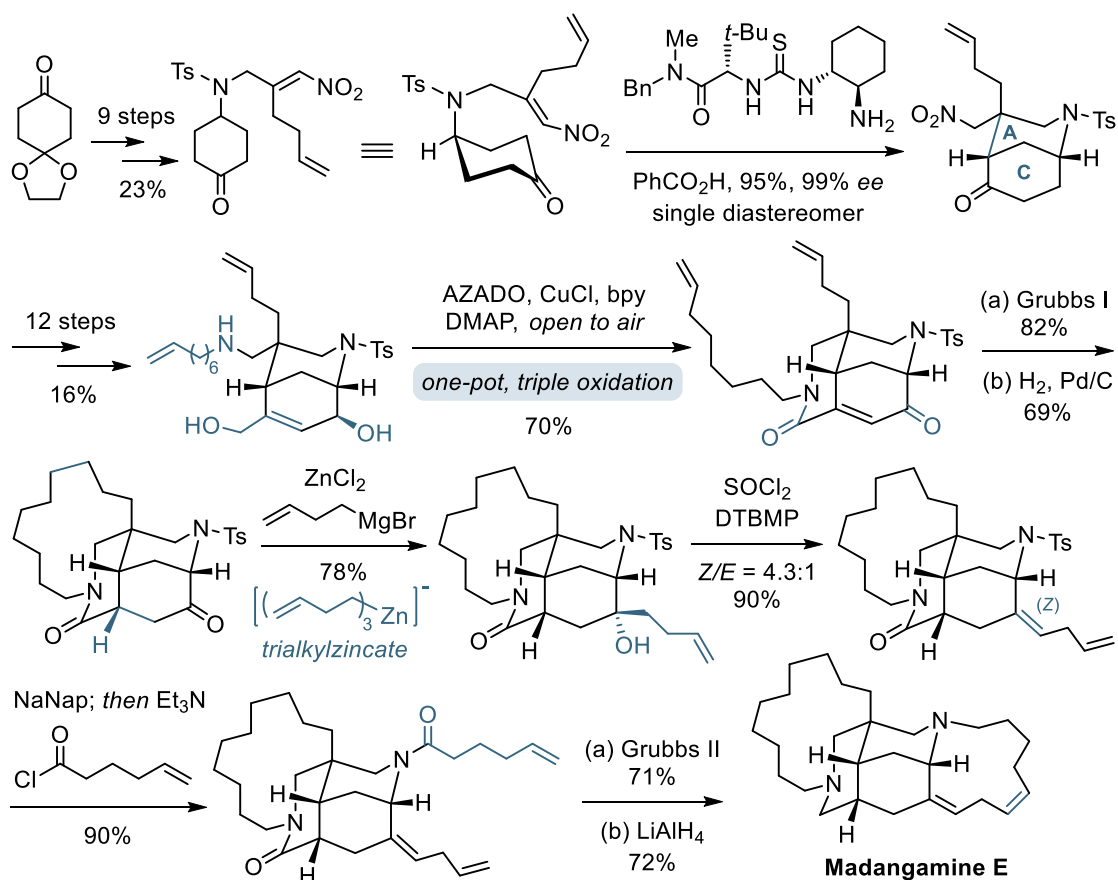
Madangamine C was constructed using AZADOL oxidation, Wittig coupling, macrolactamization, and LiAlH_4 reduction from the common intermediate I. Madangamines D and E were prepared analogously, with Appel bromination, Grignard alkylation, and subsequent tosylation leading to macrocyclic alkylation and final reduction with LiAlH_4 to furnish the saturated 14- and 13-membered D rings, respectively (Scheme 2.3).



Scheme 2.3: Sato and Chida's stereodivergent synthesis of madangamines A to E.

Building on these precedents, Dixon and coworkers recently developed a 30-step linear strategy toward madangamine E, where the stereochemical information was introduced early through the construction of the enantioenriched AC bicyclic core (*Scheme 2.4*).¹⁰

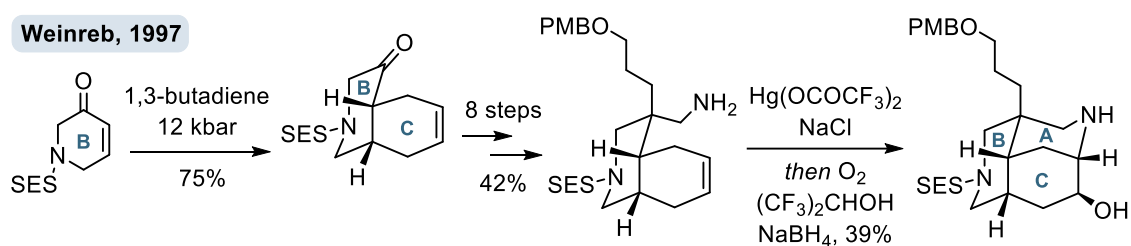
The synthesis began with the elaboration of commercially available 1,4-cyclohexanedione monoethylene acetal to yield an (*E*)-nitroalkene in 23% yield on a multi-gram scale. An unprecedented enantioselective desymmetrizing Michael addition furnished a bicyclic compound containing the A and C rings. Further elaboration led to the obtention of an aminodiol in 12 steps and an overall 16% yield. Formation of the azatricycle proceeded via oxidative lactamization, with concomitant oxidation of the hydroxyl groups. Next, cross-metathesis followed by hydrogenation closed the first macrocycle. A trialkylzincate species facilitated ketone alkylation, yielding a tertiary alcohol, which underwent selective elimination to furnish a (*Z*)-skipped diene. Finally, substitution of the tosyl group with a hexenoate side chain, followed by cross-metathesis and LiAlH₄ reduction, provided madangamine E.



Scheme 2.4: Synthesis of madangamine E by Dixon et al.

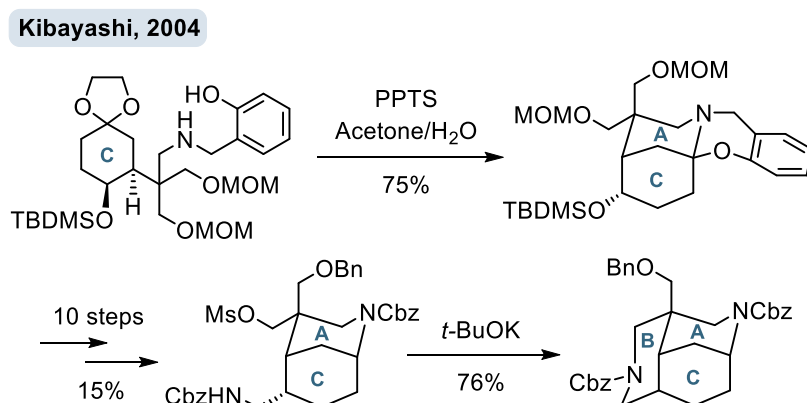
2.1.3 Synthesis of the azatricyclic core of madangamine alkaloids

Besides the total syntheses of madangamine alkaloids outlined in the previous section, there are additional strategies to furnish the ABC azatricyclic core. The first strategy for synthesizing the core of madangamine alkaloids was reported by Weinreb and coworkers in 1997 (*Scheme 2.5*).¹¹ The key bicyclic intermediate was formed via a Diels–Alder reaction between an enone and 1,3-butadiene under high pressure. Subsequent elaboration afforded a primary amine in 42% yield over eight steps. To form the tricycle, the amine was treated with mercuric trifluoroacetate and sodium chloride. Subsequent exposure to oxygen and reduction with sodium borohydride yielded the corresponding alcohol in moderate yield.



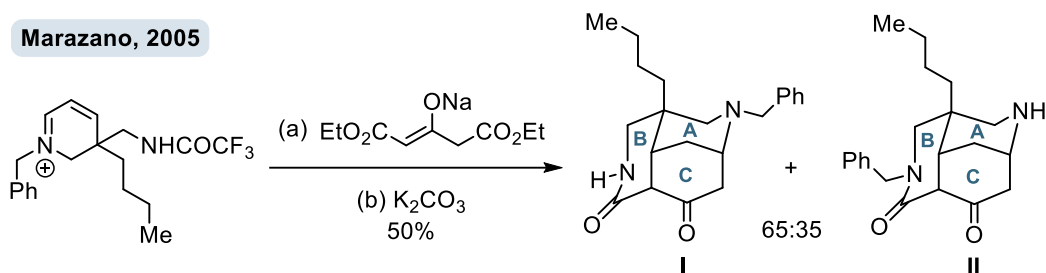
Scheme 2.5: Approach to the core of madangamine A by Weinreb.

In 2004, Kibayashi introduced an alternative strategy focused on the initial construction of the AC bicyclic framework (*Scheme 2.6*).¹² Treatment of an aminophenol precursor with pyridinium *p*-toluenesulfonate (PPTS) in acetone/ H_2O under reflux triggered a deacetalization followed by in situ condensation, yielding a tetracyclic *N,O*-acetal. Subsequent elaboration formed an advanced bicyclic intermediate, which, upon exposure to base, afforded the desired tricyclic structure.



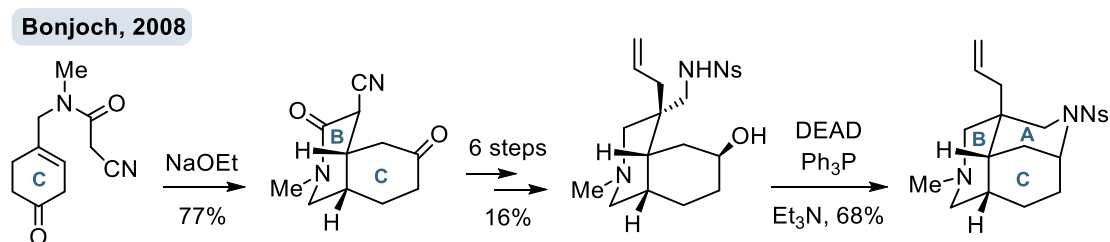
Scheme 2.6: Synthesis of the madangamine core via intramolecular N,O-acetalization.

One year later, Marazano reported a biogenetically inspired strategy for direct access to the madangamine core,¹³ utilizing a dihydropyridinium salt as a precursor (*Scheme 2.7*). Treatment with the sodium salt of acetone dicarboxylate diethyl ether initially yielded a challenging-to-separate mixture of bicyclic adducts. However, subsequent exposure of the crude mixture to base facilitated the formation of tricycles **I** and **II** in 50% overall yield.



Scheme 2.7: Biogenetically inspired approach to the madangamine core by Marazano et al.

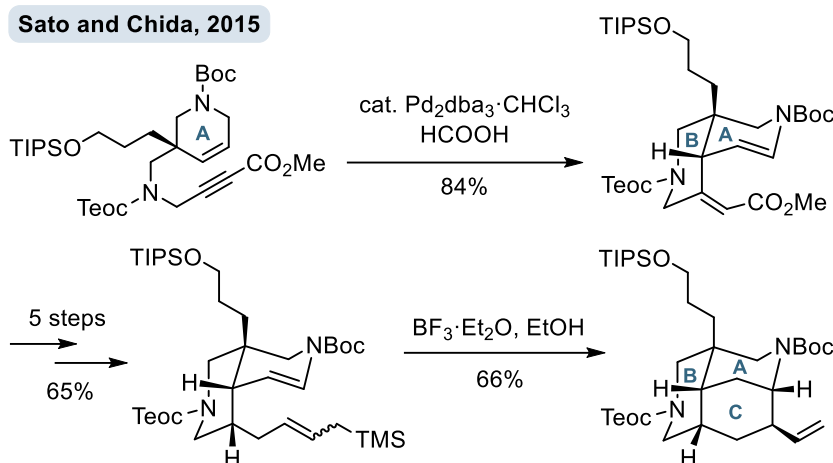
In 2008, our group developed a 10-step sequence for constructing the madangamine core, starting from a 4-(aminomethyl)anisole derivative (*Scheme 2.8*).¹⁴ The formation of ring B was achieved by treating a cyclohexenone with substoichiometric amounts of sodium ethoxide, inducing alkene isomerization followed by a Michael addition, which yielded a *cis*-perhydroisoquinoline in good yield. Subsequent modifications to the bicyclic scaffold furnished an advanced intermediate in moderate yield over several steps. Finally, a Mitsunobu reaction, accompanied by a conformational inversion of the azabicyclic ring system, provided the desired product in 68% yield.



Scheme 2.8: Synthesis of the madangamine core from cis-perhydroisoquinolines.

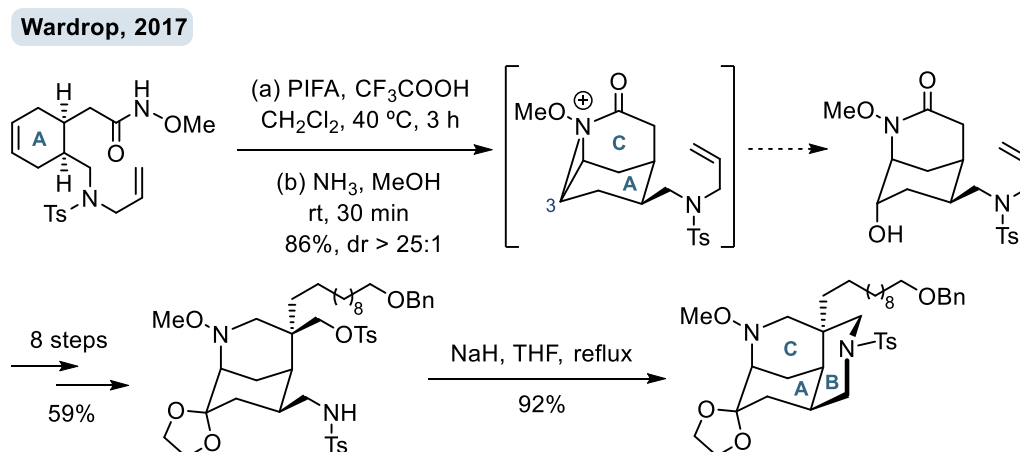
Prior to their total syntheses of madangamines A–E, Sato and Chida proposed a strategy to construct the madangamine core using *N*-acyliminium intermediates (*Scheme 2.9*).¹⁵ The sequence began with the cycloisomerization of an alkynoate, yielding the *cis*-fused AB azabicyclic scaffold. Subsequent elaboration of this scaffold provided an advanced

intermediate in moderate yield over several steps. Finally, direct *N*-acyliminium ion cyclization of the *N*-Boc enamine with boron trifluoride diethyl etherate and ethanol afforded the desired product in high yield.



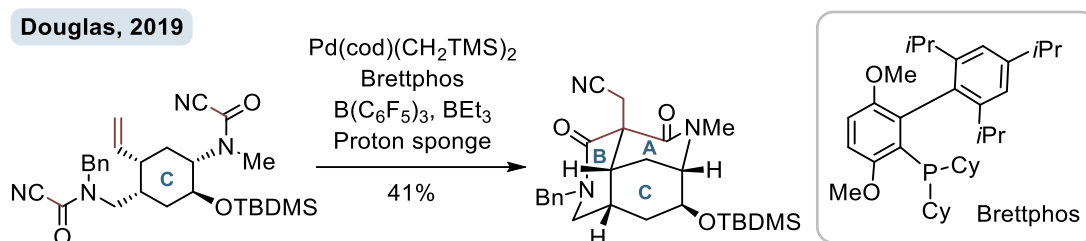
*Scheme 2.9: Formation of the azatricyclic core via an *N*-acyliminium ion cyclization.*

In 2017, Wardrop and coworkers reported a strategy toward the madangamine core featuring a pivotal oxamidation step (*Scheme 2.10*). Cyclization of an unsaturated *O*-alkyl hydroxamate, followed by regioselective ring-opening at C3, yielded a diaxial compound. After further elaboration, the final cyclization was achieved by exposing the intermediate to sodium hydride in refluxing tetrahydrofuran, which induced intramolecular *N*-alkylation and efficiently constructed the ABC madangamine core.¹⁶



*Scheme 2.10: Formation of the ABC tricycle via oxamidation of an unsaturated *O*-alkyl hydroxamate by Wardrop et al.*

More recently, Douglas and coworkers developed a strategy to construct the madangamine core using a cyanoamidation cascade (Scheme 2.11).¹⁷ Starting from a densely functionalized cyclohexane derivative, the cascade formed two new rings and a quaternary stereocenter via two Pd-catalyzed C–C bond activation steps. This one-pot reaction successfully delivered the targeted azatricyclic framework, marking the first use of a tandem approach in madangamine synthesis.

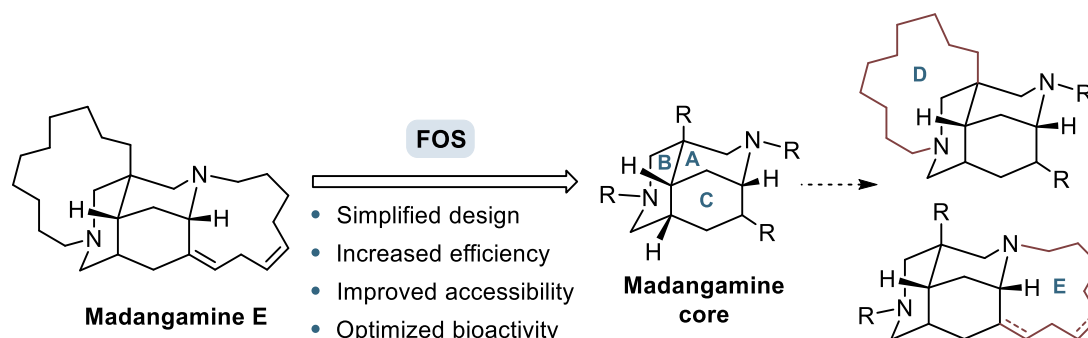


Scheme 2.11: Madangamine core synthesis via C–C activation cascade by Douglas.

2.1.4 Design of a synthesis toward the azatricyclic madangamine core

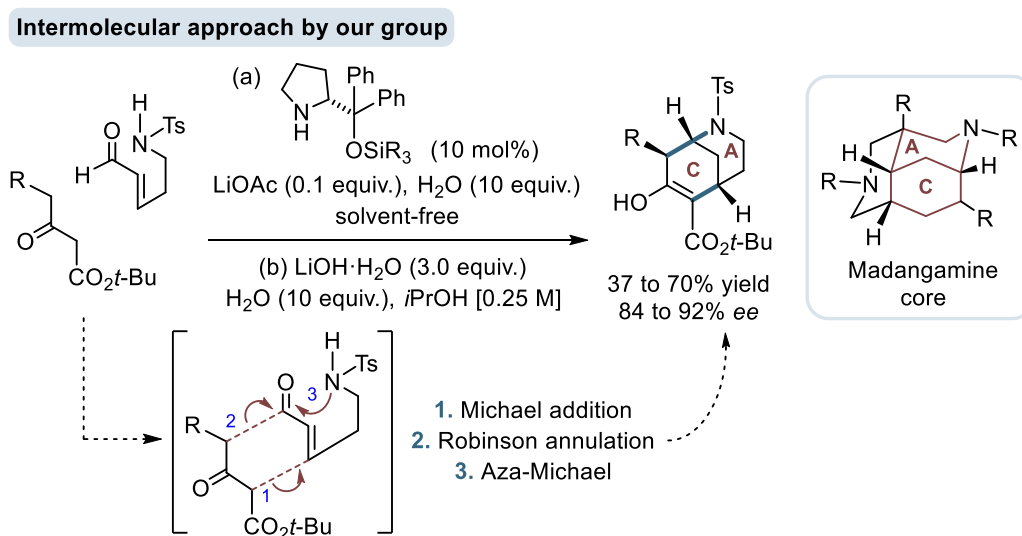
In the previous sections, we have outlined the synthetic strategies described in the literature to access madangamine alkaloids and their azatricyclic core. These approaches often involve numerous steps, resulting in lower overall yields and making it challenging to access analogs suitable for biological testing. Given these limitations, developing a more efficient method to access these structures would be highly valuable, particularly to facilitate the synthesis of bioactive analogs. In this context, FOS represents a promising solution (see Section 1.1.1), as it aims to simplify the structure of the target compounds while retaining or even enhancing their activity, thus avoiding the complexities associated with the full structure of the natural product. In the case of madangamine alkaloids, considering their structural similarities (see Figure 2.1), variations in the macrocyclic rings —such as chain length and degree of unsaturation— are likely not key determinants of bioactivity. In fact, no studies have yet investigated the cytotoxicity of the azatricyclic core or simplified analogs, leaving open the possibility that one or both of the macrocyclic rings may not be essential for biological activity. Based on the insights discussed herein, we aimed to develop an efficient FOS-based strategy for accessing the azatricyclic core of madangamine alkaloids. Once the tricycle was synthesized, we would proceed to evaluate its bioactivity and compare it to that of the natural product. If the activity was found to be lower, suggesting that additional structural elements of the

natural product are necessary for its bioactivity, we would explore the incorporation of one of the macrocyclic rings, either with or without the unsaturations present in the natural product, or longer alkyl chains as substituents to better mimic the lipophilic properties of the original compound. By focusing on these simplified analogs, our goal would be to enhance synthetic efficiency while retaining or improving the pharmacological properties (*Scheme 2.12*).



Scheme 2.12: Application of FOS to obtain bioactive madangamine analogs.

To achieve this, we drew inspiration from previous work in our group. In 2013, a study published by our laboratory described the synthesis of the 2-azabicyclo[3.3.1]nonane scaffold, which constitutes the AC bicycle of the madangamine core, via a sequence that began with a one-pot tandem asymmetric organocatalyzed Michael addition between an enal and a β -ketoester, followed by a domino Robinson annulation to close ring C. A subsequent intramolecular aza-Michael reaction facilitated the closure of ring A and completed the formation of the desired bicycle (*Scheme 2.13*).¹⁸

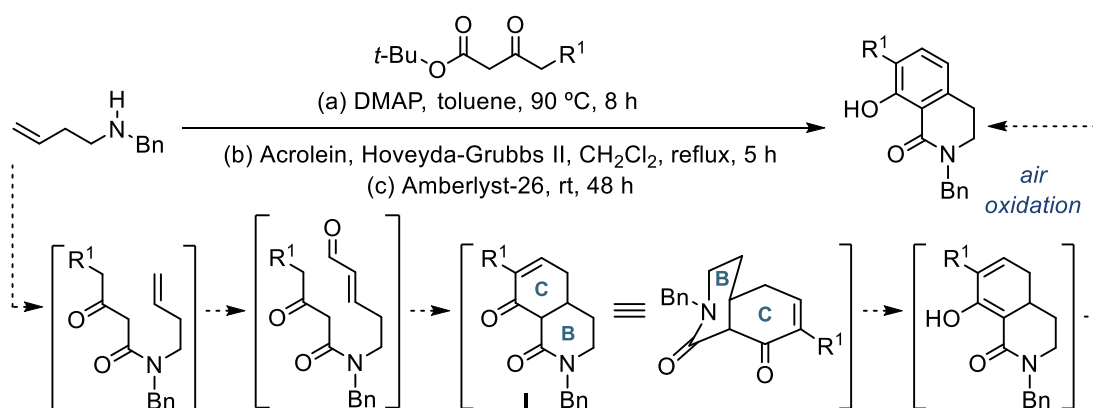


Scheme 2.13: Synthesis of the 2-azabicyclo[3.3.1]nonane framework by our group.

The enal fragment was efficiently prepared in three steps from commercially available 3-buten-1-ol, while β -ketoesters were conveniently accessed via direct acylation of Meldrum's acid. This streamlined approach underscored the accessibility of the complex bicyclic scaffold from simple, readily available starting materials.

In unpublished work, our group also worked on accessing the BC bicycle of madangamine alkaloids using an analogous intramolecular tandem approach (*Scheme 2.14*). The condensation of a β -ketoester with an amine in the presence of DMAP furnished an amide, which upon cross-metathesis with acrolein gave the coupled enal. Then, exposure to basic conditions furnished the targeted bicycle **I**. However, spontaneous oxidation favored by the formation of a stabilized enol triggered aromatization and led to the obtention of a tetrahydroisoquinoline instead of the BC bicycle.

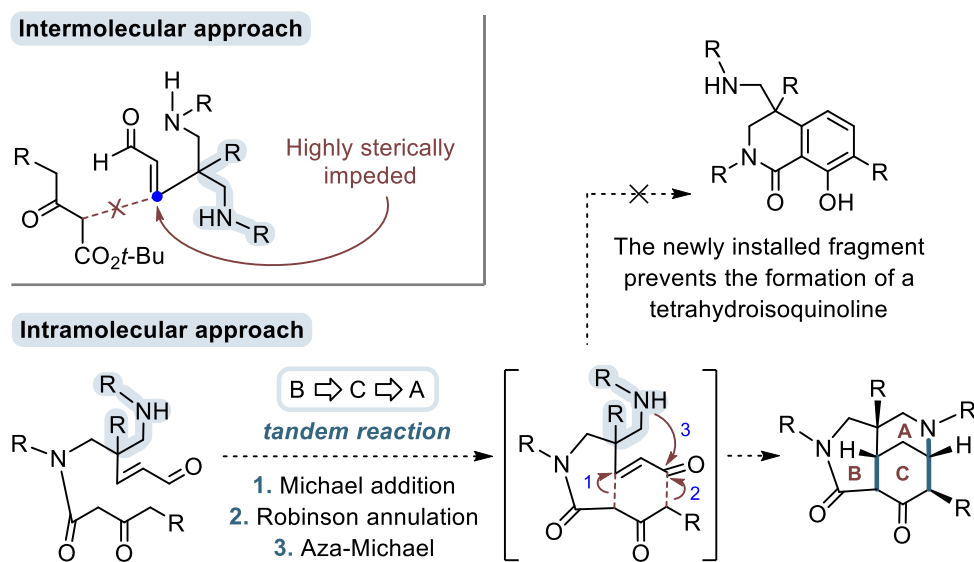
Intramolecular approach by our group



Scheme 2.14: Preliminary studies for the intramolecular assembly of the BC bicycle.

Given that our target structure is a tricyclic system rather than a bicyclic one, a higher level of complexity in the precursors is required for the tandem cyclization. In this context, we anticipated that an intermolecular approach could be hindered by steric impediments in the enal fragment, making tricyclic core formation less favorable. As a result, we proposed that an intramolecular strategy could be more effective by leveraging the precursor's structural complexity. Specifically, incorporating an additional $-\text{CH}_2\text{NHR}$ fragment would help prevent unproductive oxidation of the hydroquinolinic framework by promoting an aza-Michael reaction with the enone, thereby facilitating ring A closure (*Scheme 2.15*). With our targeted enal precursor in hand, the addition of

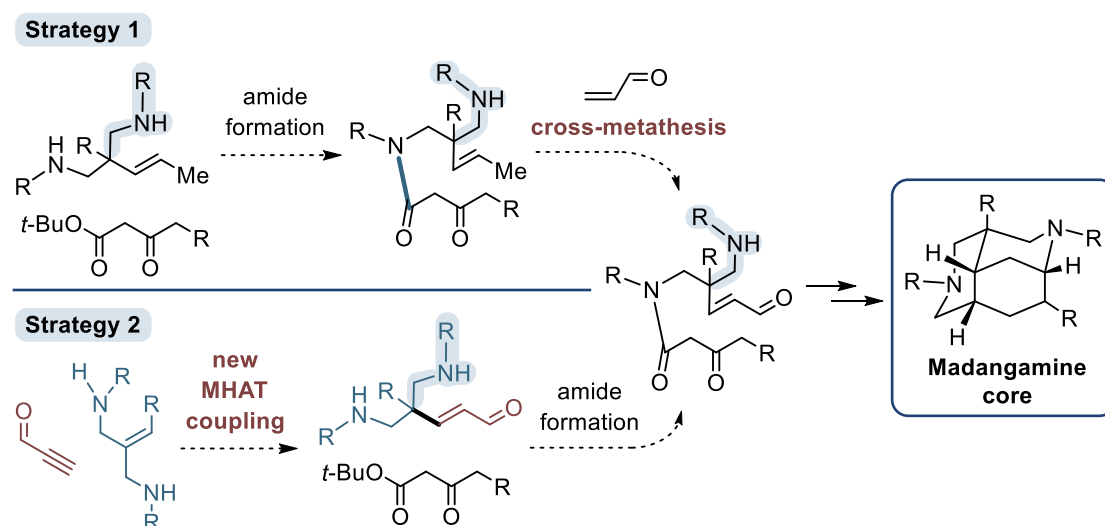
a base or acid could trigger an intramolecular Michael reaction, enabling B ring closure and leading to a Robinson-type cyclization for C ring formation. Finally, the additional amide fragment could undergo an intramolecular aza-Michael reaction to complete the closure of ring A. Notably, this tandem process would constitute a modular and convergent strategy for assembling the core of madangamine alkaloids, offering valuable flexibility in the efficient synthesis of analogs.



Scheme 2.15: Proposed route toward the core of madangamine alkaloids.

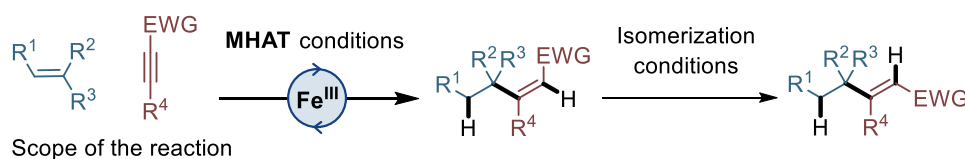
2.2 OBJECTIVES

As outlined in the previous section, the initial objective of this chapter was to design an efficient synthetic route toward the azatricyclic core of madangamine alkaloids via an intramolecular tandem approach. This began with the preparation of an enal precursor, which would serve as the foundation for assembling the targeted tricycle. Our first strategy involved an amide coupling reaction followed by cross-metathesis. Additionally, our second strategy proposed the direct installation of the acrolein moiety by employing a new MHAT C–C coupling reaction, which offered a novel disconnection strategy to access electron-deficient alkenes (*Scheme 2.16*).



Scheme 2.16: Strategies toward the enal precursor of madangamine alkaloids.

Realizing the general potential of this reaction beyond the application to the synthesis of madangamines, the second objective of this chapter was to develop a general MHAT C–C coupling between alkenes and electron-deficient alkynes (*Scheme 2.17*). Once the feasibility of this transformation could be confirmed, we would investigate strategies to selectively access the *cis* and *trans* products. Finally, we would try to broaden the scope of this reaction to include a variety of alkene donors and alkyne acceptors.

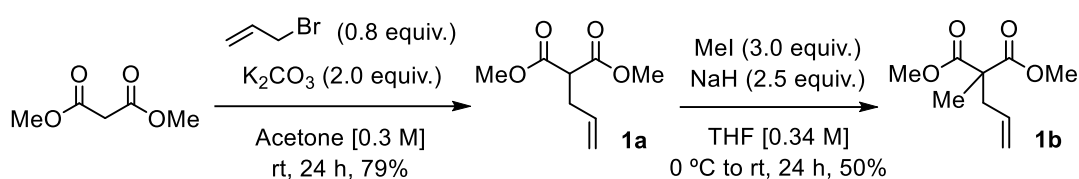


Scheme 2.17: Development of an MHAT C–C coupling between neutral alkenes and electron-deficient alkynes.

2.3 RESULTS AND DISCUSSION

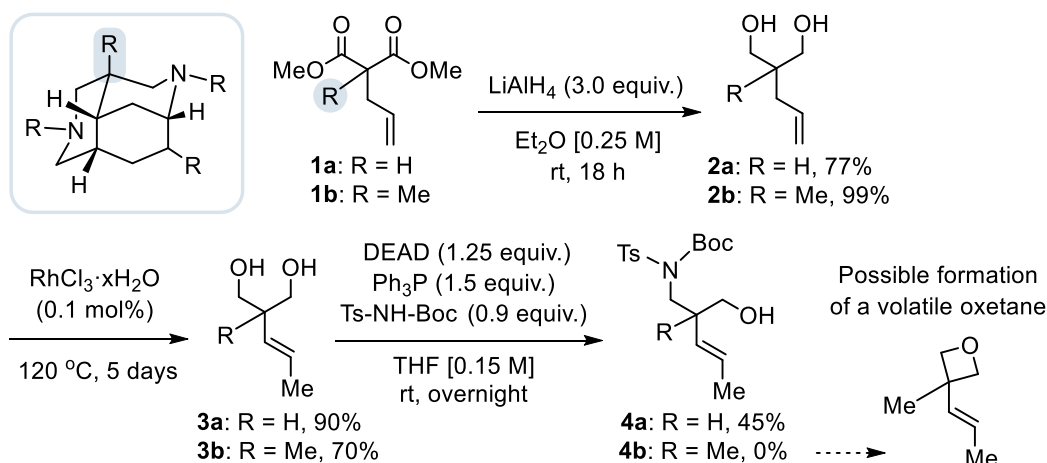
2.3.1 Preliminary studies for the assembly of the enal fragment via cross-metathesis

Our strategy commenced with the preparation of two alternative precursors for the nitrogenated fragment required for the amide coupling. Dimethyl malonate was initially treated with allyl bromide under basic conditions in acetone at room temperature, affording **1a** in 79% yield. A portion of this product was subsequently alkylated with methyl iodide using sodium hydride as a base, furnishing **1b** in 50% yield (*Scheme 2.18*).¹⁹



*Scheme 2.18: Alkylation of dimethyl malonate to access **1a** and **1b**.*

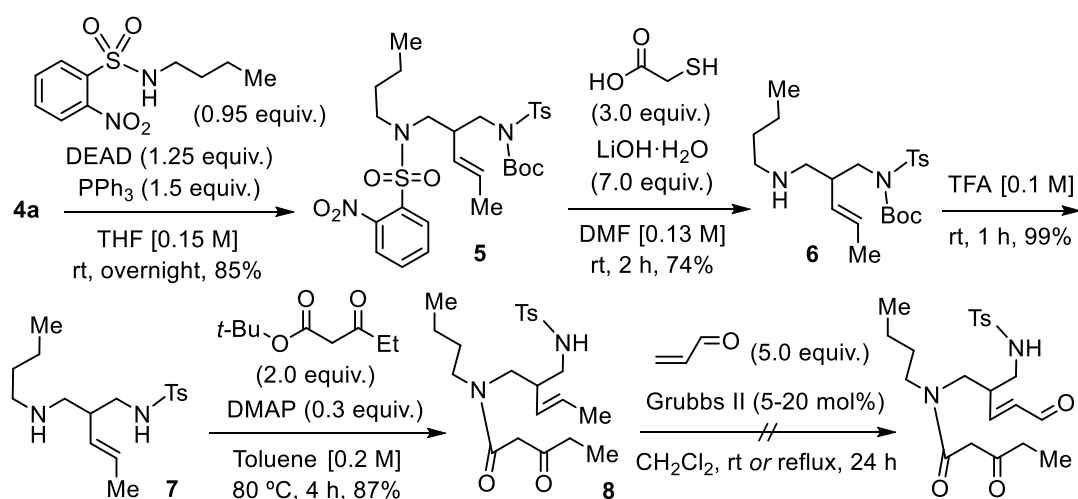
Exposure of **1a** and **1b** to LiAlH_4 in an ether solution at room temperature furnished diols **2a** and **2b** in 77 and 99% yield, respectively (*Scheme 2.19*). Then, both products were treated with RhCl_3 at 120 °C under neat conditions to achieve the isomerization of the unsaturation toward the more stable internal alkenes **3a** and **3b** as *cis/trans* mixtures.²⁰ In the case of alkene **3a**, which does not have a quaternary center, a second isomerization did not take place, most likely due to the steric impediment around the tertiary center.



Scheme 2.19: Initial steps toward the key enal precursor.

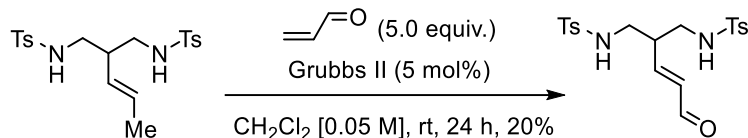
Next, a Mitsunobu reaction with Ts-NH-Boc under standard conditions enabled the installation of the first nitrogenated fragment in **4a**. However, compound **4b** was not observed under these conditions. In light of this result, we postulated that an intramolecular Mitsunobu reaction may have occurred, leading to the formation of a volatile oxetane that could have evaporated. This might be attributed to the Thorpe–Ingold effect,²¹ promoted by the two alkyl chains, which could result in conformational restriction and an enhanced proximity between the two alcohol groups, thereby inducing an otherwise disfavored cyclization.

Given that we could not obtain the expected methylated product **4b**, we decided to carry on with the proposed synthetic route with compound **4a** (Scheme 2.20). The second nitrogenated group was introduced via Mitsunobu reaction with *N*-butyl-2-nitrobenzenesulfonamide, obtaining **5** in 85% yield. Upon removal of the nosyl group with 2-mercaptoacetic acid and LiOH $\cdot$ H₂O to give **6**, and the subsequent elimination of the Boc group with TFA, diamine **7** was formed in 73% yield. The amide coupling between **7** and the selected β -ketoester in the presence of DMAP furnished the coupled product **8** as a complex mixture of rotamers and *cis/trans* isomers. Unfortunately, attempts to complete the cross-metathesis reaction between compound **8** and acrolein were unsuccessful, and the desired product was not obtained.



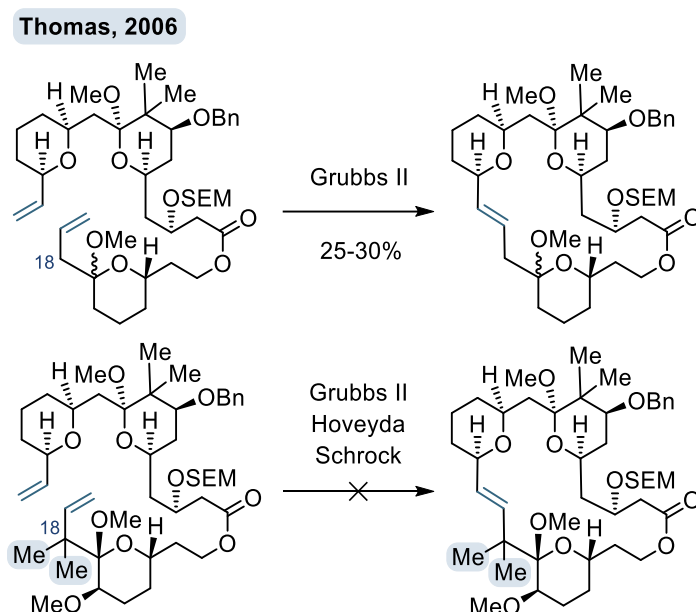
Scheme 2.20: Synthesis of **8** and attempted cross-metathesis with acrolein.

At the same time, work in our group revealed that cross-metathesis of a less impeded related precursor provided the coupled product in 20% yield, which suggested that steric crowding around the alkene was detrimental to the reaction (Scheme 2.21).



Scheme 2.21: Limitations of the cross-metathesis with sterically impeded substrates.

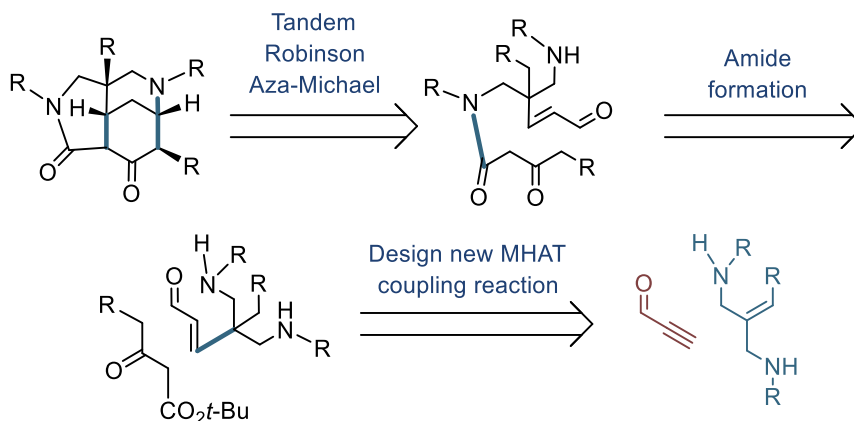
Based on these results, we soon realized that the installation of an olefin adjacent to a congested carbon center via cross-metathesis remains particularly challenging, as noted in previous strategies.²³ For instance, the group of Thomas reported difficulties in performing ring-closing metathesis on certain bryostatin analogs (*Scheme 2.22*).²⁴ Macrolide formation succeeded for substrates lacking geminal dimethyl groups at C18, although with low yields, likely due to the susceptibility of a less hindered terminal alkene to degradation and the absence of the conformational constraints seen in natural bryostatins. However, compounds containing *gem*-dimethyl groups adjacent to the alkene failed to undergo metathesis using a variety of catalysts, yielding complex mixtures instead.



Scheme 2.22: Challenges in ring-closing metathesis to access bryostatin analogs.

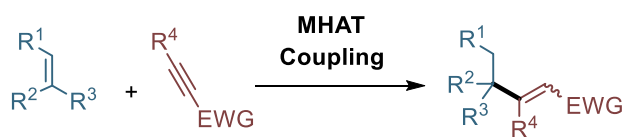
Given this difficulty, the original synthetic strategy was adjusted, and a novel disconnection approach was proposed for the synthesis of the azatricyclic core of madangamines. This new strategy circumvented the need to install the carbonyl group via cross-metathesis in the enal fragment for the tandem reaction. Instead, it introduced

an additional disconnection by leveraging a previously undisclosed MHAT Giese-type coupling between an electron-deficient alkyne and an unactivated olefin (*Scheme 2.23*).²⁵



Scheme 2.23: MHAT-based disconnection approach to madangamines.

The nitrogenated scaffold required for the proposed MHAT coupling can be efficiently accessed from commercially available 2-methylenepropane-1,3-diol via cross-metathesis, followed by the introduction of nitrogen substituents using conventional methods outlined earlier in this section. Given these considerations, we first decided to develop a general methodology (*Scheme 2.24*) to evaluate the reaction's functional group tolerance, providing insights that would later guide its application in the synthesis of the madangamine core.

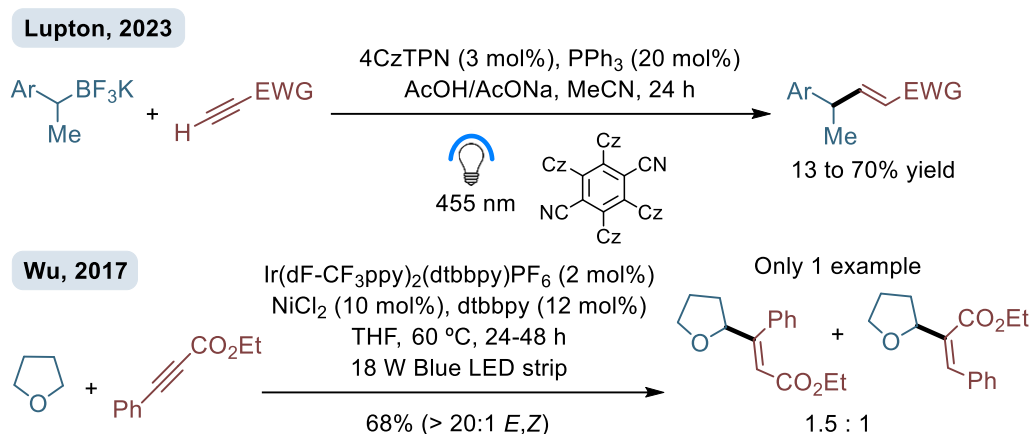


Scheme 2.24: General coupling between alkenes and electron-deficient alkynes.

2.3.2 Background for the newly designed MHAT coupling

Although Giese couplings have been widely studied (see *Section 1.1.4*), reports of such couplings involving electron-deficient alkynes remain scarce (*Scheme 2.25*). Among the few examples described, Lupton reported a radical coupling initiated by the addition of an organophosphine to an ynoate under photochemical conditions.²⁶ In this method, the addition of phosphine generated a more readily reducible intermediate, which subsequently underwent radical–radical coupling with radicals derived from

trifluoroborate derivatives. However, this reaction was limited to boronates containing at least one aromatic group. Similarly, Wu developed a metallaphotoredox approach for alkyne coupling, but demonstrated coupling with an electron-deficient alkyne in only one instance, which resulted in non-regioselective radical coupling.²⁷ Notably, no examples of MHAT-triggered Giese couplings involving electron-deficient alkynes have been reported to date.



Scheme 2.25: Precedents for Giese couplings with electron-deficient alkynes.

The general MHAT coupling proposed herein offers several advantages over the classical Giese coupling. Firstly, the double bond retained in the product serves as a versatile handle for further functionalization, facilitating the synthesis of value-added compounds and broadening the applicability of this methodology beyond traditional Giese coupling.

Additionally, this approach would enable the insertion of an alkene next to a sterically impeded quaternary center, which is essential for preparing the postulated enal precursor for the synthesis of the core of madangamine alkaloids (see *Scheme 2.16*). A typical example of such a quaternary center is the *gem*-dimethyl group, a motif found in bioactive natural products such as cucurbitacin E, bryostatin 1, and arisugacin A (*Figure 2.2*). Despite its biological relevance, the *gem*-dimethyl group is challenging to insert adjacent to an unsaturation. This process typically requires the use of organometallic reagents,²⁸ which, while effective, often exhibit high reactivity and poor compatibility with a broad range of functional groups. These challenges underscore the need for alternative methods that enable this insertion under milder, more selective conditions.

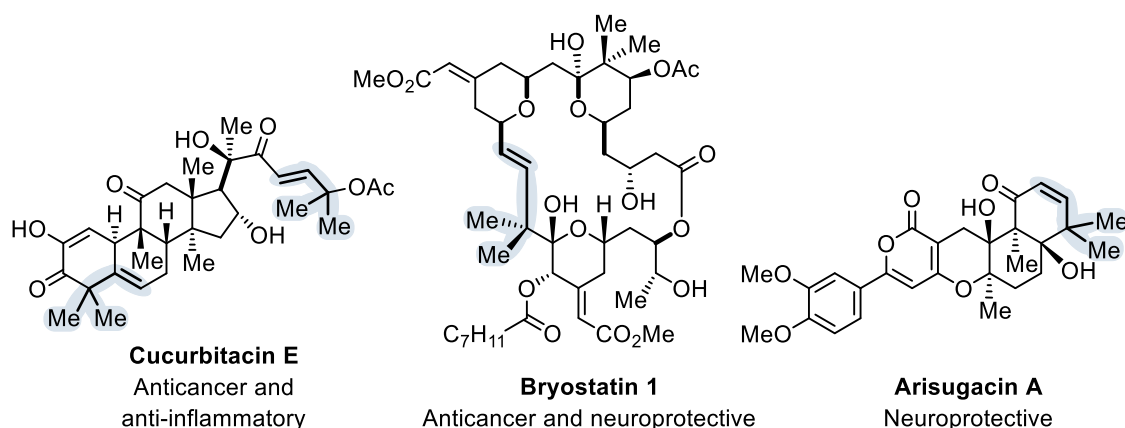


Figure 2.2: Natural products containing a *gem*-dimethyl adjacent to a double bond.

In terms of bioactivity, the *gem*-dimethyl group is a valuable tool in medicinal chemistry, largely because of its unique electronic properties.²⁸ As an electronically neutral and non-polar group, it can be seen as two small, lipophilic lobes projecting from the bioactive conformation. Despite its simplicity, the *gem*-dimethyl fragment can significantly impact pharmacodynamics, molecular structure, drug metabolism and pharmacokinetics (DMPK), and toxicity, as indicated in Figure 2.3. In pharmacodynamics, it enhances target engagement, potency, and selectivity by enforcing a bioactive conformation through rotational restrictions and favorable van der Waals interactions with the binding site. Structurally, it reduces molecular complexity by abolishing chiral centers, improving synthetic accessibility and scalability.

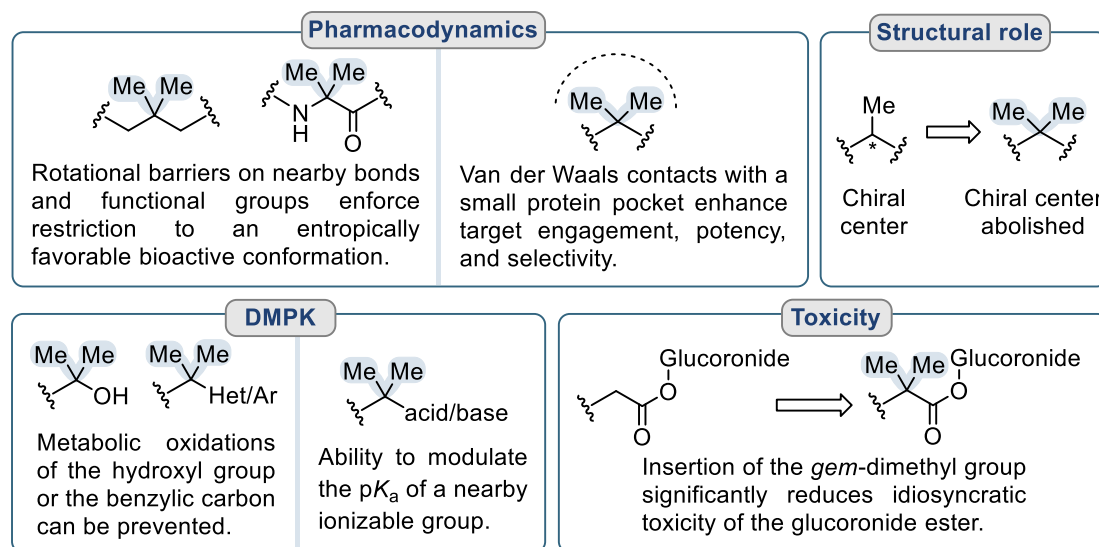


Figure 2.3: Selected examples of the impact of a *gem*-dimethyl group on pharmacodynamics, structure, toxicity, and DMPK.

In terms of DMPK, the *gem*-dimethyl group can contribute to metabolic stability, ultimately increasing compound durability and bioavailability. Additionally, it plays a crucial role in reducing idiosyncratic toxicity and mitigating genotoxicity risks, thereby enhancing the overall safety profile of drug candidates and improving their chances of clinical success.

The methodology proposed herein also provides a new disconnection approach to electron-deficient alkenes. Traditional methods such as the Wittig,²⁹ Horner–Wadsworth–Emmons,³⁰ and Still–Gennari reactions³¹ are widely used to synthesize electron-deficient alkenes. However, they have significant limitations, including the formation of stoichiometric phosphorus byproducts, the need for moisture-sensitive and unstable reagents, and the use of harsh reaction conditions.³² In contrast, our proposed strategy provides a valuable alternative, utilizing readily available and stable starting materials, operating under mild conditions, and proceeding with high atom efficiency, making it a more practical and sustainable approach (Figure 2.4).

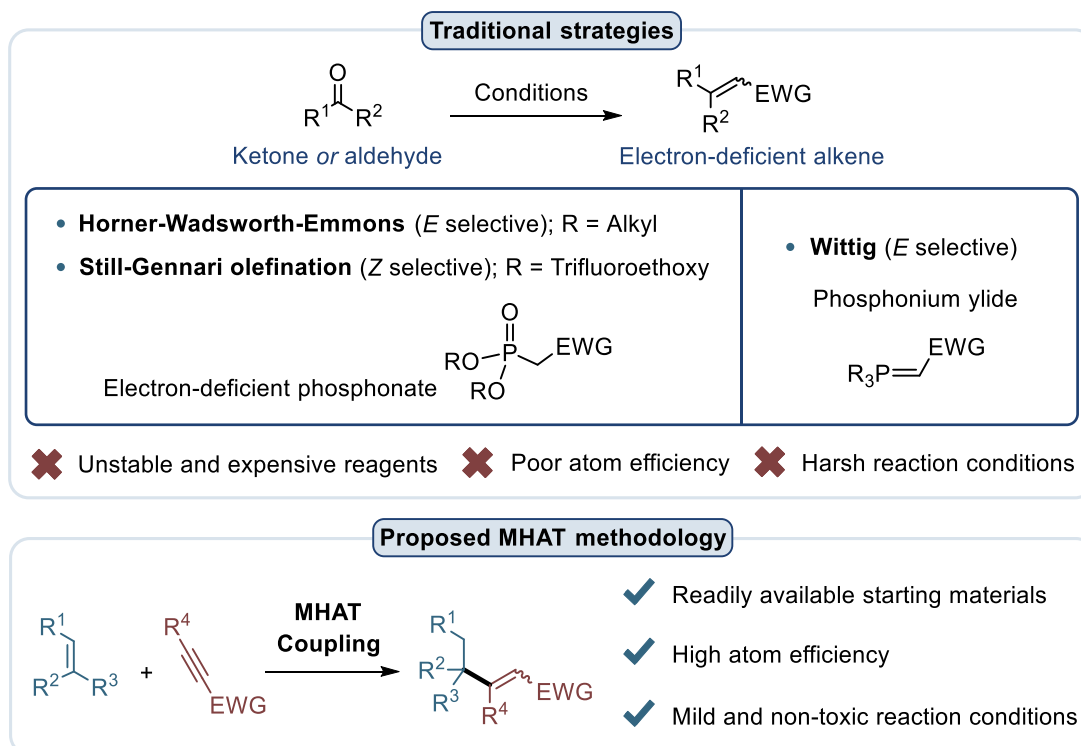
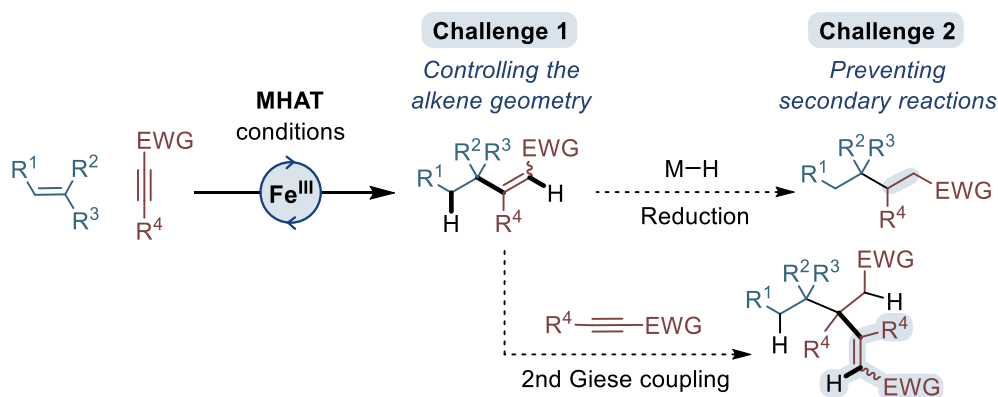


Figure 2.4: Comparison between traditional strategies to access electron-deficient alkenes and our proposed MHAT C–C coupling.

2.3.3 Optimization of the reaction conditions

At the outset of this study, we identified two key challenges: controlling the alkene geometry and preventing secondary reactions, such as reduction by metal hydride species or involvement in a subsequent Giese reaction (Scheme 2.26).



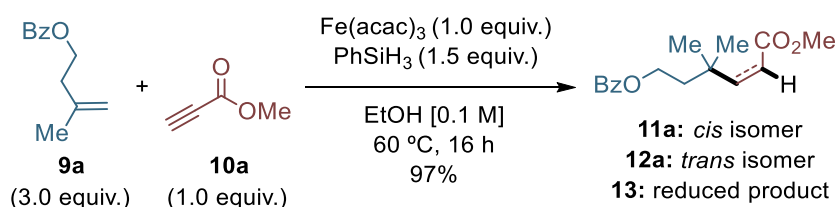
Scheme 2.26: Potential challenges of the proposed MHAT coupling.

We began by studying the reaction of alkene **9a** and methyl propiolate (**10a**). Upon optimization, we found that employing 3.0 equivalents of alkene donor, stoichiometric amounts of acceptor **10a** and Fe(acac)₃ and 1.5 equivalents of phenylsilane as a hydride source in a 0.1 M ethanol solution at 60 °C for 16 hours gave the coupled product in 97% yield, predominantly as the *cis* isomer **11a** (Table 2.1, entry 1). The reaction was performed on a 4.0 mmol scale, showcasing the scalability of the method (for comparison, a 95% yield was achieved on a 0.4 mmol scale). The *trans* isomer **12a** was obtained as a minor product and was easily isolated by column chromatography.

During these optimization studies, we found that decreasing the donor amount (entry 2), changing the solvent (entries 3 and 4), altering the concentration of ethanol (entries 5 and 6), increasing the amount of phenylsilane (entry 7), decreasing the amount of Fe catalyst (entry 8), using a lower temperature (entry 9), increasing the amount of the acceptor (entry 10) or shortening the reaction time (entry 11) was detrimental to the reaction outcome, resulting in either lower yields or significant amounts of the reduced compound **13**. To try to promote the regeneration of the catalyst via oxidation, the reaction was also carried out under open air conditions (entries 12 and 13). However, a lower efficiency was observed when using both stoichiometric and catalytic amounts of Fe(acac)₃, which indicated that the reaction worked better under an argon atmosphere.

A combination of $\text{Fe}(\text{acac})_3$ and $\text{Fe}(\text{acac})_2$ catalysts was also unsuccessful at promoting the reaction (entry 14). While 3.0 equivalents of **9a** were optimal, similar results were achieved with 2.0 equivalents of **9a** (entry 15), offering a more cost-effective option that reduced the consumption of the donor alkene.

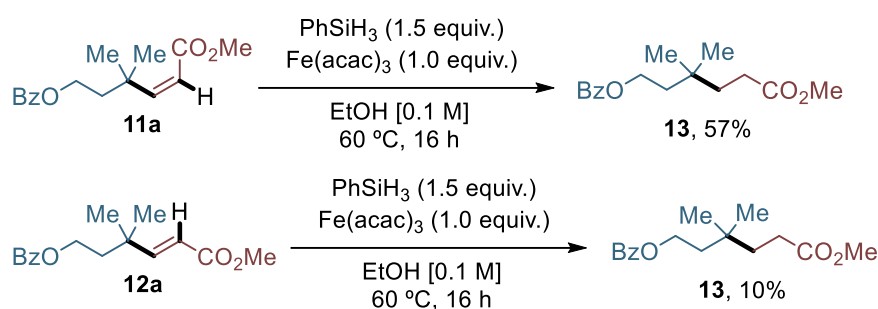
Table 2.1: Optimization of the MHAT coupling conditions.



Entry ^a	Deviation from optimum conditions	Ratio ^b 11a/12a/13	Yield ^c (%)
1	No deviation	62/35/3	97
2	1.0 equiv. of 9a	53/30/17	74
3	THF/MeOH (9:1) as solvent ^d	50/35/15	64
4	DCE as solvent ^d	53/38/9	52
5	EtOH [0.05 M] ^d	51/33/16	74
6	EtOH [0.2 M] ^d	43/32/25	56
7	2.5 equiv. of PhSiH_3 ^d	50/32/18	71
8	0.5 equiv. of $\text{Fe}(\text{acac})_3$ ^d	56/33/11	70
9	25 °C instead of 60 °C ^d	41/39/20	55
10	2.0 equiv. of 10a ^d	50/31/19	69
11	3 h instead of 16 h	62/34/4	84
12	Open air conditions ^e	56/35/9	51
13	Open air conditions	52/36/12	68
14	0.5 equiv. of Fe cat. as $\text{Fe}(\text{acac})_2$	63/31/6	87
15	2.0 equiv. of 9a	63/33/4	92

^aAll reactions were carried out on a 0.4 mmol scale except entry 1, which was carried out on a 4.0 mmol scale (0.4 mmol scale: 95% yield). ^bRatio refers to the proportion of **11a/12a/13** determined by NMR after isolation. ^cCombined yield of **11a** and **12a**. ^d1.0 equiv. of **9a**. ^e0.2 equiv. of $\text{Fe}(\text{acac})_3$ were used.

Interestingly, after extensive optimization, we did not observe the engagement of **11a** and **12a** in a second Giese addition in any case. However, small amounts of reduced compound **13** formed in the coupling process. To investigate the source of the reduced compound, two additional studies were conducted (Scheme 2.27). The *cis* and *trans* isomers **11a** and **12a** were each exposed to the optimal reaction conditions, yielding 57 and 10% of **13**, respectively. Based on these results, it was confirmed that the *cis* isomer was the primary source of the overreduced product.

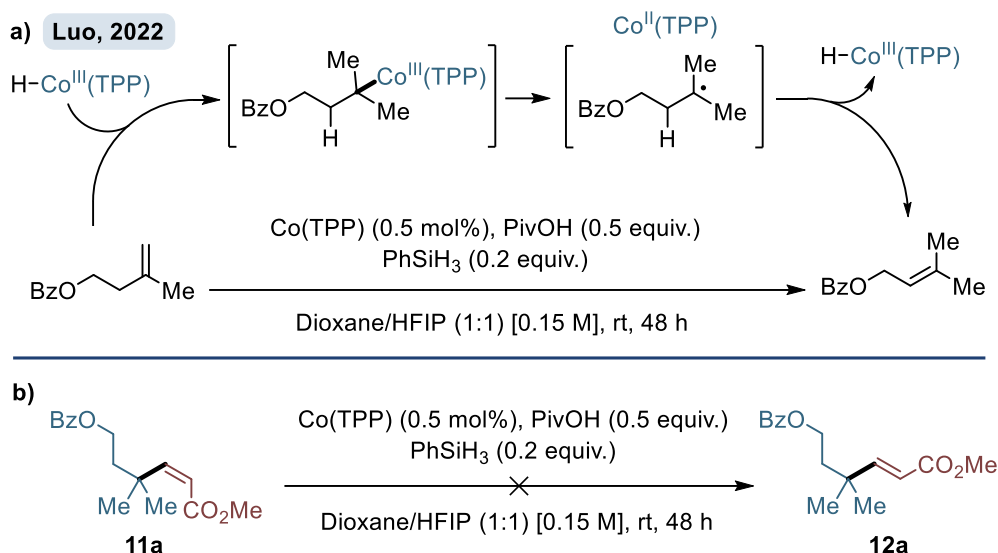


Scheme 2.27: Reduction experiments for compounds **11a** and **12a**.

Given the limited methods available for accessing electron-deficient *Z*-alkenes,³¹ we made an additional effort to enhance the yield of the *cis* product in our reaction. We hypothesized that introducing an electron-deficient alkene as an additive could reduce the required amount of **9a** and minimize the overreduction of the unsaturated products by acting as a scavenger for excess metal hydride species. However, in a competition experiment where 1.0 equivalent of ethyl acrylate (**I**) was added, we observed that electron-deficient alkenes coupled at the same rate as their alkyne counterparts, producing 50% of each coupling product (Table 2.2, entry 1).

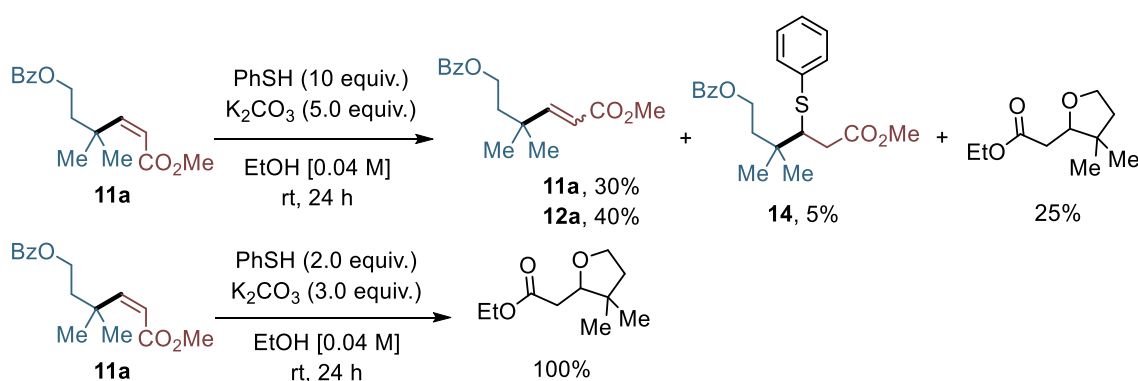
Further studies using internal alkene additives **II** and **III** (entries 2 and 3) and diesters **IV** and **V** (entries 4 and 5) as scavengers resulted in decreased efficiency and large amounts of overreduced compound **13**. The most promising result was obtained using 1.0 equivalent of neutral alkene **VI** (entry 6). Under these conditions, the yield for the **11a/12a** mixture remained unchanged by the addition of **VI** (see Table 2.1, entry 7). However, despite an 11% decrease in the amount of reduced compound, the *cis/trans* ratio was not improved, suggesting that part of the starting material did not react. Variations in the amount of additive or the hydride source led to detrimental effects on the reaction outcome (entries 7 to 9).

regeneration of the active metal hydride species. Applying this reaction conditions to **11a** resulted in complete recovery of the starting material, indicating that no reaction had occurred (Scheme 2.28, b).



Scheme 2.28: a) Proposed isomerization using Luo conditions. b) Attempted isomerization of **11a**.

Next, we explored a coupling reaction with a thiol under basic conditions to generate a sulfide intermediate, which could then be eliminated to yield the desired *trans* product **12a** (Scheme 2.29). Treatment of **11a** with 10 equivalents of thiophenol and 5.0 equivalents of potassium carbonate³⁴ produced a mixture of **11a**, **12a**, and sulfide **14**. Additionally, part of the starting material was hydrolyzed resulting in a cyclized byproduct, reducing the reaction efficiency.



Scheme 2.29: Initial attempts for the isomerization of **11a** via a sulfide intermediate.

Furthermore, handling such large amounts of thiophenol was impractical due to its unpleasant odor. Finally, increasing the base-to-thiol ratio resulted in complete hydrolysis, prompting us to explore alternative strategies involving sulfide formation, oxidation, and elimination.

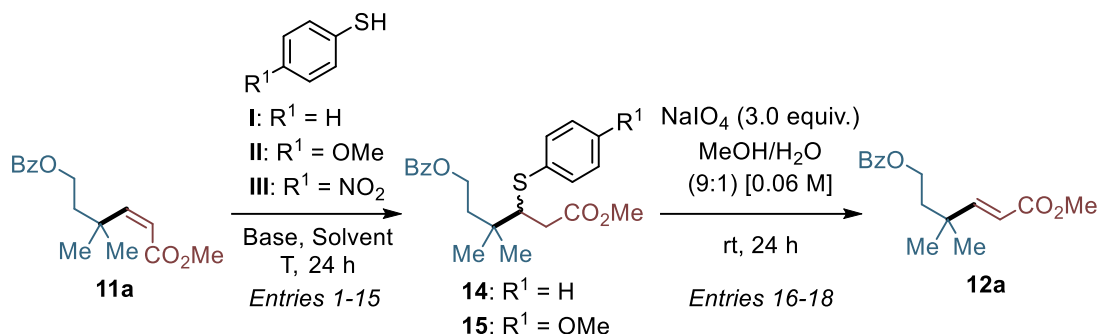
The optimization of the isomerization process was initiated by reacting the *cis* compound **11a** with thiophenol in the presence of several bases (*Table 2.3, entries 1 to 5*). However, only triethylamine provided significant amounts of the desired sulfide, with some *trans* product **12a** also forming due to partial spontaneous elimination of sulfide **14**.

Following the identification of triethylamine as the optimal base, various solvents were evaluated (*entries 6 to 9*). Notably, solvent-free conditions achieved an 85% conversion of the *cis* isomer. Additional optimization revealed that reducing the amount of thiol lowered efficiency (*entry 10*), while increasing the temperature to 40 °C and employing 1.0 equivalent of triethylamine enhanced the conversion, although it reduced the extent of spontaneous sulfide elimination (*entry 11*). Under the optimal conditions (*entry 12*), complete conversion of **11a** was achieved, and applying the same conditions to the *trans* isomer **12a** also produced sulfide **14** (*entry 13*). Testing two alternative thiols (**II** and **III**) demonstrated that 4-methoxythiophenol was similarly effective, whereas the introduction of a nitro group in the aromatic ring completely suppressed the reactivity, probably because of the decreased nucleophilicity of the thiol (*entries 14 and 15*).

In the oxidation step, direct treatment of the crude coupling residue with 3.0 equivalents of sodium periodate did not fully accomplish the oxidation and elimination of **14** (*entry 16*). However, stirring at 70 °C under vacuum for thirty minutes to evaporate the excess of thiol and triethylamine prior to oxidation (*entry 17*) quantitatively yielded *trans* product **12a**. The sulfone spontaneously eliminated during oxidation, producing clean crude products. With 4-methoxythiophenol (**II**) complete oxidation was achieved (*entry 18*), but additional thermolysis of **15** in refluxing toluene was required.

For practical reasons, thiophenol was chosen as the optimal reagent for further studies, as it provided cleaner crude mixtures and caused fewer difficulties during the purification of the isomerized alkenes.

Table 2.3: Optimization of the reaction conditions for the isomerization of the cis/trans mixtures via sulfide formation, oxidation and elimination.



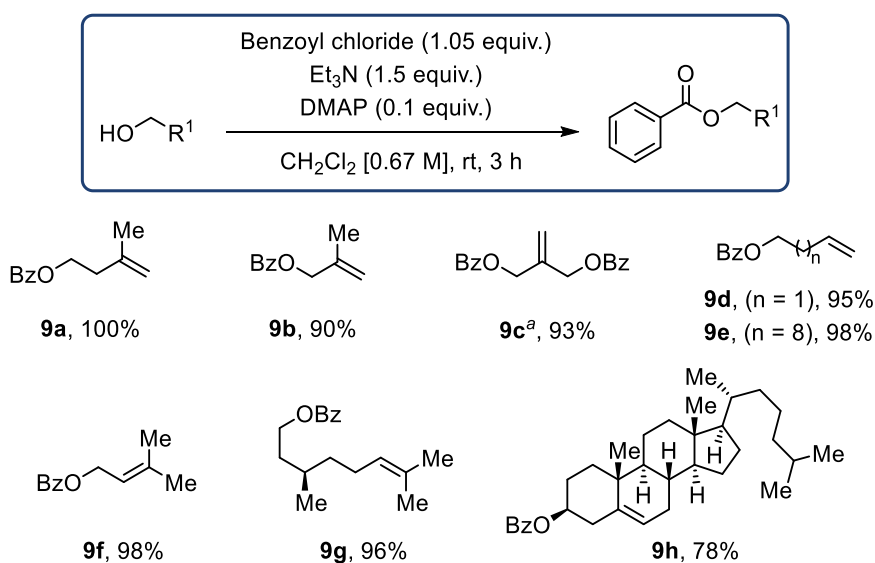
Entry	Reagent	Base	Solvent	T (°C)	Conversion 11a/14 or 15/12a
1	I (2.0 equiv.)	Et ₃ N (0.25 equiv.)	EtOH [0.1 M]	rt	80/10/10
2	I (2.0 equiv.)	Amberlyst® A21 catalyst (0.1 equiv.)	EtOH [0.1 M]	rt	100/0/0
3	I (2.0 equiv.)	PS-BEMP (0.1 equiv.)	EtOH [0.1 M]	rt	95/2/3
4	I (2.0 equiv.)	LiOH (0.1 equiv.)	EtOH [0.1 M]	rt	94/4/2
5	I (2.0 equiv.)	K ₂ CO ₃ (0.1 equiv.)	EtOH [0.1 M]	rt	93/3/4
6	I (2.0 equiv.)	Et ₃ N (0.25 equiv.)	Benzene [0.1 M]	rt	100/0/0
7	I (2.0 equiv.)	Et ₃ N (0.25 equiv.)	CH ₂ Cl ₂ [0.1 M]	rt	100/0/0
8	I (2.0 equiv.)	Et ₃ N (0.25 equiv.)	THF [0.1 M]	rt	100/0/0
9	I (2.0 equiv.)	Et ₃ N (0.25 equiv.)	No solvent	rt	15/51/34
10	I (1.0 equiv.)	Et ₃ N (0.25 equiv.)	No solvent	rt	25/35/40
11	I (1.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	9/52/39
12	I (2.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	0/95/5
13 ^a	I (2.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	0/95/5
14	II (2.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	0/88/12
15	III (2.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	100/0/0
16 ^{b,c}	I (2.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	0/53/47
17 ^{b,d}	I (2.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	0/0/100
18 ^{b,d,e}	II (2.0 equiv.)	Et ₃ N (1.0 equiv.)	No solvent	40	0/0/100

^aIsomer **12a** was used for the coupling with thiophenol. ^b3.0 equivalents of NaIO₄ were added as an oxidant. ^cNo evaporation of the base and thiophenol between the coupling and the oxidation steps. ^dThe residue of the coupling was stirred at 70 °C for thirty minutes under vacuum prior to oxidation. ^eThermolysis of the crude product in a 1.0 M toluene solution at reflux for 2 hours was required.

2.3.4 Substrate scope

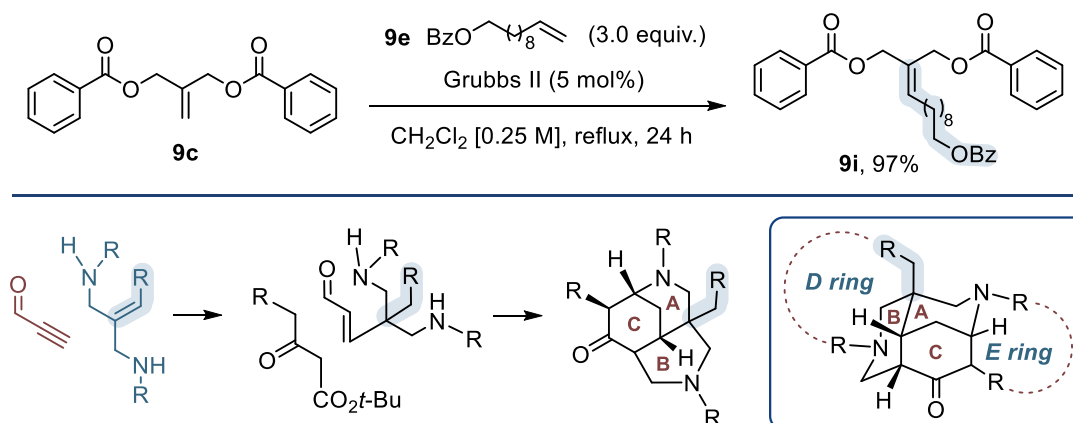
Synthesis of the alkene donors

For the preparation of the alkene donors bearing ester groups, a benzoyl protection of the selected alcohols was carried out with benzoyl chloride, triethylamine and DMAP in a dichloromethane solution for 3 hours at room temperature (Scheme 2.30),³⁵ furnishing the targeted compounds **9a** to **9h** with yields ranging from 90 to 100%.



Scheme 2.30: Benzoyl protection of the MHAT donors. ^a2.0 equiv. of benzoyl chloride, 3.0 equiv. of triethylamine and 0.2 equiv. of DMAP.

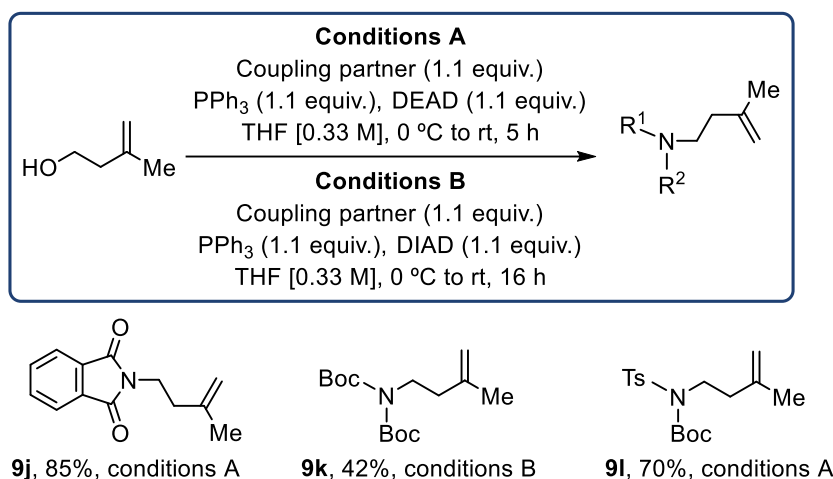
To explore the reaction with a more sterically hindered donor, cross-metathesis between **9c** and **9e** was performed using the second-generation Grubbs catalyst, furnishing the targeted donor alkene **9i** in an excellent 97% yield.



Scheme 2.31: Synthesis of sterically hindered alkene **9i**.

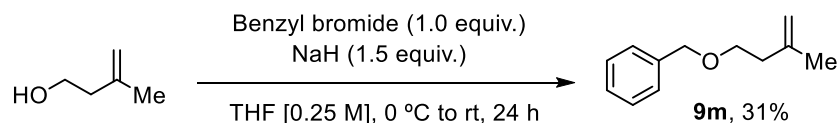
This product was particularly significant due to its structural similarity to the enal building block proposed for the synthesis of the madangamine core. As shown in *Scheme 2.31*, incorporating a long alkyl chain at the terminal position of alkene **9c** would serve as a useful strategy for the formation of macrocycle D.

Alkenes **9j** to **9l**, bearing nitrogenated functionalities, were prepared via nucleophilic substitution of 3-methyl-3-buten-1-ol with the selected nitrogen-containing reagents in the presence of PPh₃ and DEAD or DIAD in an anhydrous THF solution (*Scheme 2.32*).³⁶



*Scheme 2.32: Synthesis of **9j–9l** via nucleophilic substitution.*

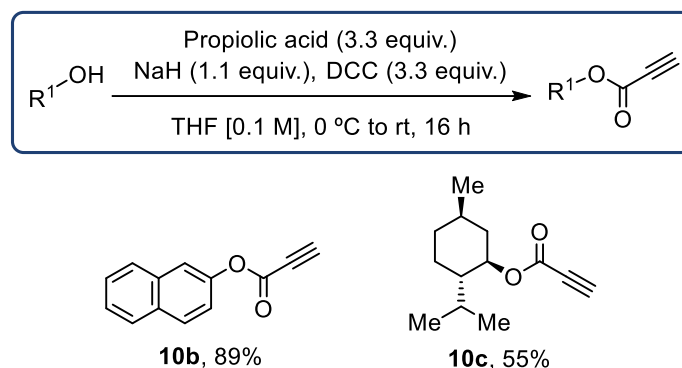
Finally, to evaluate the reaction with a donor bearing an ether group, alkene **9m** was synthesized in 31% yield by treating 3-methyl-3-buten-1-ol with benzyl bromide and sodium hydride in a THF solution for 24 hours (*Scheme 2.33*).³⁷



*Scheme 2.33: Synthesis of alkene donor **9m** with an ether functionality.*

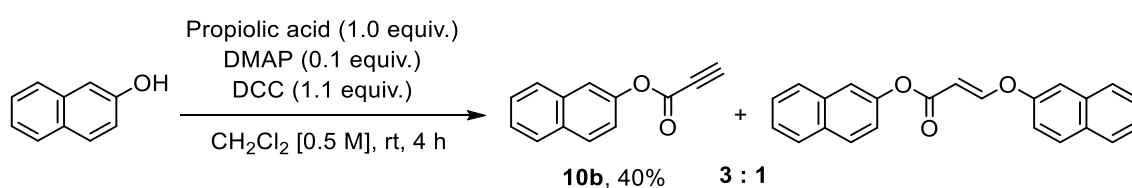
Synthesis of the electron-deficient alkynes

Firstly, electron-deficient alkynes **10b** and **10c** were prepared through the esterification of propiolic acid with sodium hydride and dicyclohexylcarbodiimide (DCC) in a THF solution at room temperature for 16 hours (*Scheme 2.34*).³⁸



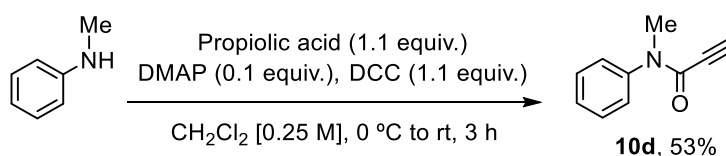
*Scheme 2.34: Esterification of propiolic acid to furnish alkyne acceptors **10b** and **10c**.*

Deprotonation of the alcohol group with sodium hydride prior to the addition of propiolic acid proved essential for the esterification reaction. Previous attempts to achieve the esterification of 2-naphthol by treating a mixture of the alcohol and the acid with 4-dimethylaminopyridine and dicyclohexylcarbodiimide led to a 3:1 inseparable mixture of the desired ester and the 1,4-addition byproduct (*Scheme 2.35*).³⁹



Scheme 2.35: Formation of the 1,4-addition byproduct in the esterification of 2-naphthol.

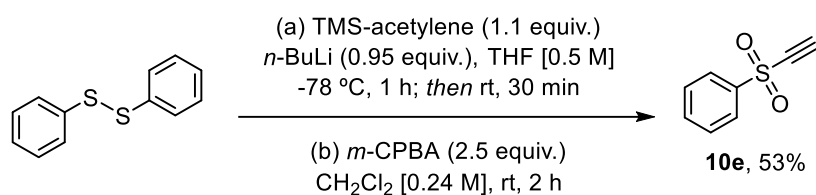
Amide derivative **10d** was obtained in 53% yield by coupling *N*-methylaniline with propiolic acid in the presence of catalytic DMAP and DCC in a dichloromethane solution at room temperature for 3 hours (*Scheme 2.36*).³⁹



*Scheme 2.36: Coupling of propiolic acid with *N*-methylaniline.*

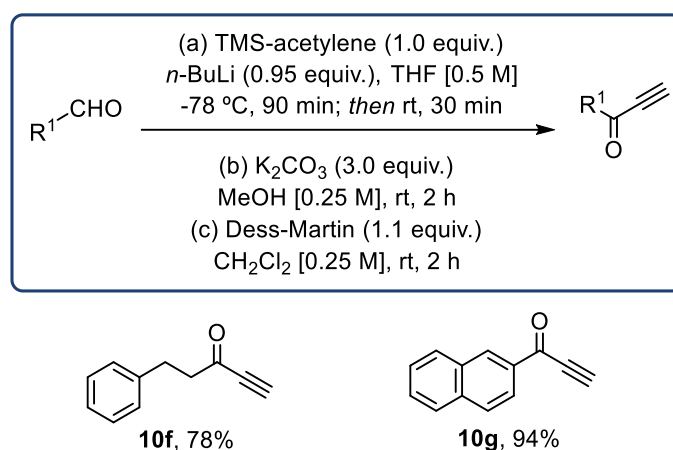
Alkyne acceptors **10e** to **10g** were synthesized using TMS-acetylene to introduce the alkyne fragment. A two-step sequence afforded sulfone **10e** in 53% yield (*Scheme 2.37*). Initially, TMS-acetylene reacted with phenyldisulfide in the presence of *n*-BuLi at -78°C to form trimethylsilyl(phenylthio)acetylene. Without intermediate purification, this

crude product was oxidized with *m*-CPBA, resulting in the formation of the targeted sulfone, with concomitant removal of the trimethylsilyl group.⁴⁰



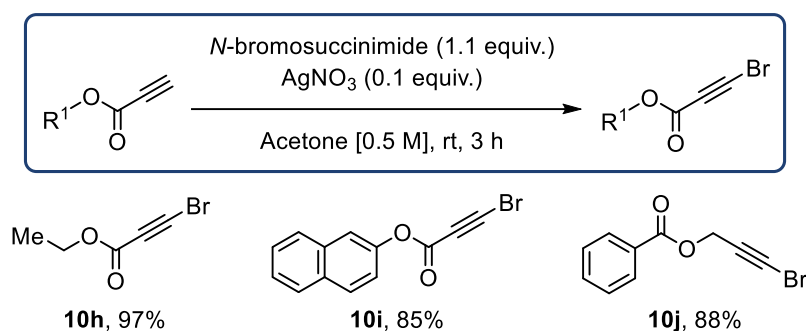
Scheme 2.37: Formation of sulfone 10e from phenyldisulfide.

Ketones **10f** and **10g** were synthesized from 3-phenylpropionaldehyde and 2-naphthaldehyde, respectively, via a three-step sequence.⁴¹ Initially, the aldehydes were treated with TMS-acetylene and *n*-BuLi, yielding TMS-protected alkynyl alcohols. Subsequent exposure to a base facilitated the removal of the TMS group, providing the corresponding alkynyl alcohols. Finally, an oxidation with Dess–Martin periodinane gave access to the targeted ketones (*Scheme 2.38*).



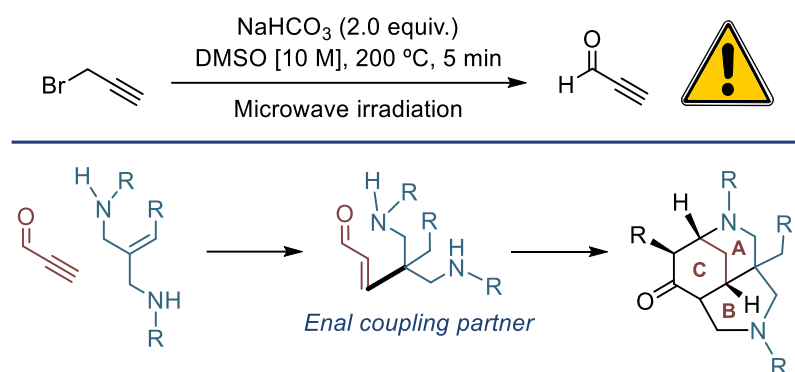
Scheme 2.38: Formation of ketone acceptors 10f and 10g.

Alkynyl bromide precursors **10h** to **10j** were prepared by brominating ethyl propiolate, **10b** and propargyl benzoate, respectively, using silver nitrate and *N*-bromosuccinimide in acetone at room temperature for 3 hours (*Scheme 2.39*).⁴²



Scheme 2.39: Bromination of terminal alkynes to furnish **10h–10j**.

As part of our ongoing efforts to access the core of madangamine alkaloids, we attempted to synthesize propynal, a key acceptor group for the proposed MHAT coupling (Scheme 2.40). However, when a mixture of propargyl bromide and sodium bicarbonate in DMSO was subjected to microwave irradiation,⁴³ a violent reaction occurred, resulting in the complete shattering of the reaction vial. Given the hazardous reactivity and the challenges associated with handling such a volatile compound, we decided to exclude this acceptor group from our studies for the moment.



Scheme 2.40: Attempted synthesis of propynal under microwave irradiation.

Evaluation of the scope of the reaction

With the MHAT coupling and isomerization conditions optimized, along with the successful preparation of the coupling partners, we next explored the versatility of the reaction by examining a diverse range of alkene donors using methyl propiolate as the common acceptor (Table 2.4).

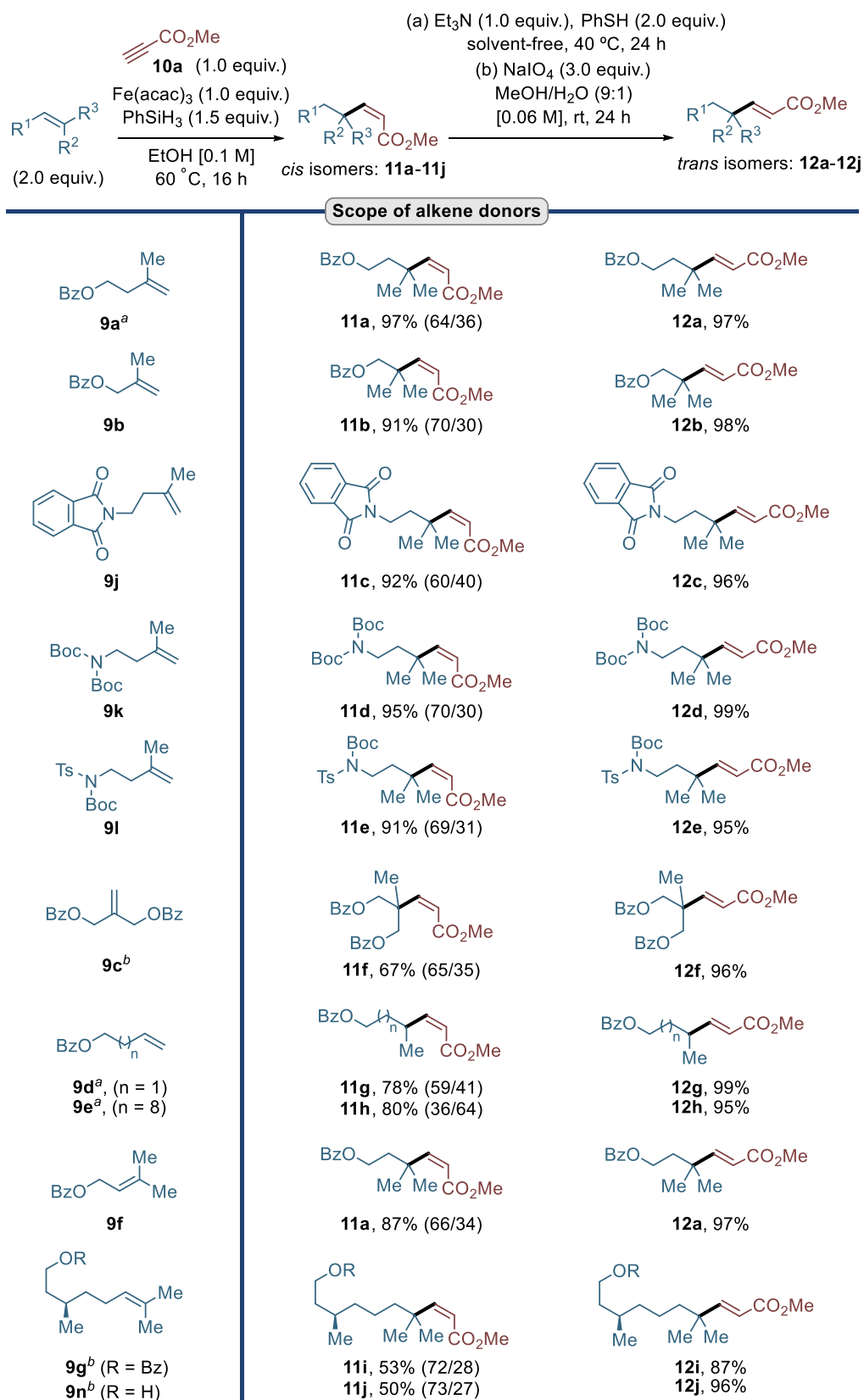
The reaction exhibited a broad functional group tolerance, effectively coupling terminal 2-methyl alkenes which featured ester (**9a** and **9b**), phthalimide (**9j**), carbamate (**9k**), and

sulfonyl functionalities (**9l**), to predominantly yield the *cis* products **11a–11e**. The more sterically congested terminal disubstituted alkene **9c** was also suitable for the coupling. However, a moderate decrease in the yield was observed for the obtention of **11f**. Terminal monosubstituted alkenes **9d** and **9e** led to the formation of the corresponding products **11g–11h**. Interestingly, as the carbon chain lengthened and the protecting group was positioned further from the reactive center, the *trans* isomer emerged as the major product. This shift can be attributed to a reduction in steric hindrance around the alkene, which also led to a slight increase in the amount of the reduced compound. As noted in a previous section (see *Scheme 2.27*), the *cis* isomer is more susceptible to overreduction under the reaction conditions. Consequently, when the double bond is more exposed, the increased reduction of the *cis* isomer naturally results in a higher proportion of the *trans* product.

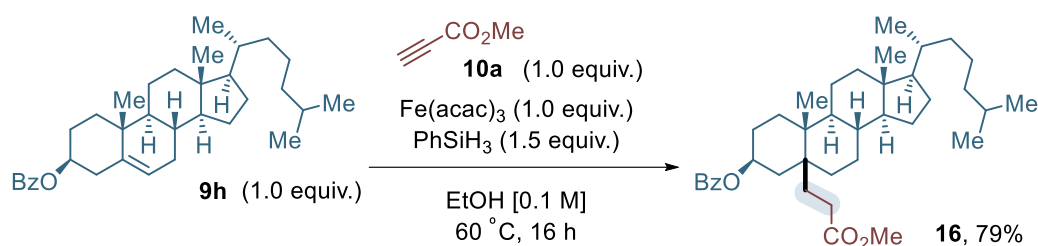
Trisubstituted alkenes were also effective substrates for coupling, with alkene **9f** producing **11a** in a similar manner to the terminal alkene **9a**. The natural product citronellol was also subjected to the coupling reaction, both with and without alcohol protection (**9g** and **9n**, respectively), resulting in products **11i** and **11j**, although in moderate yields, which were attributed to the more remote location of the unsaturation that could trigger overreduction. Notably, all *cis* products could be efficiently isomerized to their respective *trans* compounds **12a–12j** in nearly quantitative yields using the established conditions.

During the investigation of the reaction scope, several donor alkenes were found to be unsuitable for the coupling reaction. Notably, in the case of benzoyl-protected cholesterol **9h**, the coupling product underwent overreduction, yielding compound **16** in 79% yield (*Scheme 2.41*). This outcome was likely influenced by the need to limit the donor alkene to a single equivalent due to purification challenges, which hindered the separation of coupled products from unreacted or reduced alkene. The restricted alkene availability may have contributed to overreduction, as an excess of alkene could have functioned as a hydride scavenger. Moving forward, we propose that the incorporation of an additive as a selective scavenger could help mitigate this issue and enhance the efficiency of the coupling reaction (see *Table 2.2*).

Table 2.4: Study of the scope of the alkene donors in the MHAT coupling.

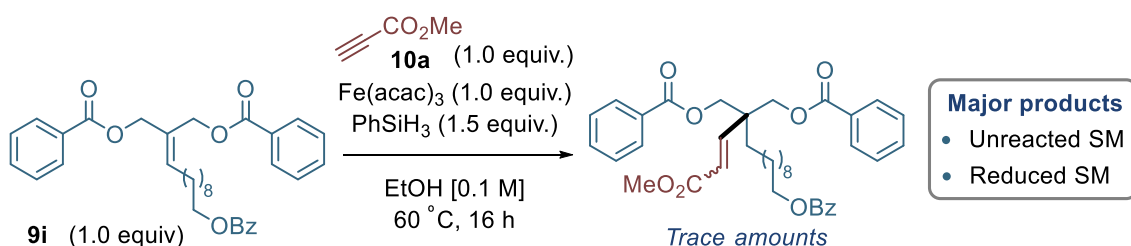


^a3.0 equivalents of donor were used. ^b5.0 equivalents of donor and 0.5 equivalents of PhSiH₃ were used.



Scheme 2.41: MHAT coupling between cholesteryl benzoate and methyl propiolate.

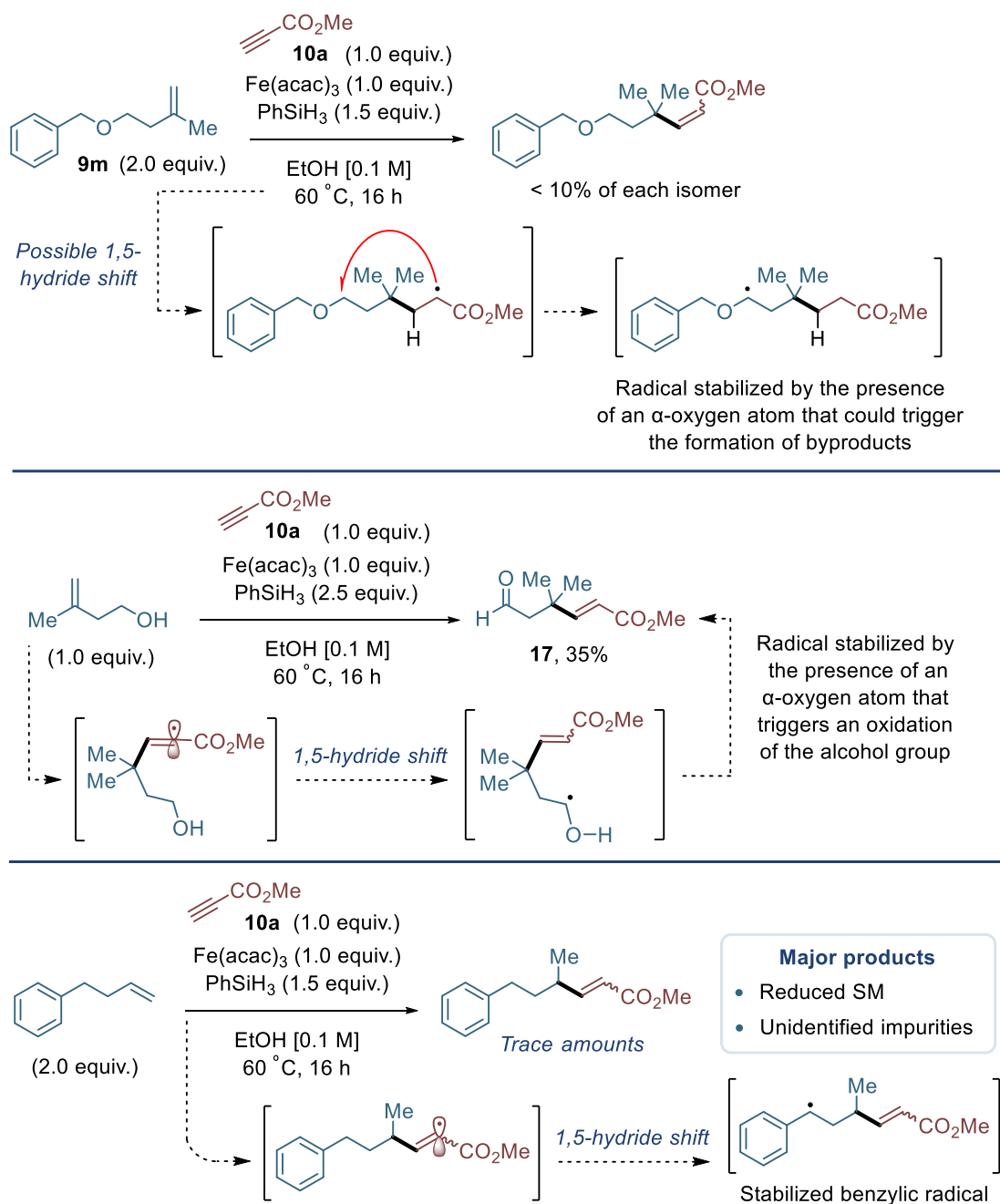
Trisubstituted alkene **9i** produced only trace amounts of the desired *cis/trans* isomers, with most of the donor alkene being recovered either unreacted or in its reduced form (Scheme 2.42). As observed with benzoyl-protected cholesterol (see Scheme 2.41), purification constraints required the use of only one equivalent of the donor alkene, which may have contributed to the low conversion. Additionally, steric hindrance near the double bond likely impeded hydride transfer and the subsequent attack of the acceptor. Given the challenges associated with coupling highly hindered donors, we prioritized the development of a more general methodology applicable to a broader range of substrates, leaving this specific limitation for future studies.



Scheme 2.42: Attempted MHAT coupling of alkene donor **9i**.

The unsaturated ether **9m** yielded only trace amounts of the expected coupled products, which were accompanied by inseparable impurities. Notably, no recovery of the starting material was observed, either in its unreacted or reduced form. This led us to hypothesize that a 1,5-hydride shift might be occurring, generating a stabilized radical adjacent to the oxygen atom and potentially promoting side reactions or degrading the coupling partners (Scheme 2.43). This hypothesis was further supported by the reactivity observed with 3-methylbut-3-en-1-ol, which, under MHAT coupling conditions, led to the formation of aldehyde **17** in 35% yield. Despite TLC analysis indicating efficient conversion, the high volatility of the product limited the isolated yield of the desired compound.

In the case of 4-phenyl-1-butene, even though the majority of the starting material was recovered in its reduced form, a possible 1,5-hydride shift might have triggered the formation of a stabilized benzylic radical, which could have promoted the formation of side products. Given that this reactivity appeared particularly interesting, it was further explored and will be thoroughly discussed in a later section of this chapter.



Scheme 2.43: Proposed 1,5-hydride shift side reaction.

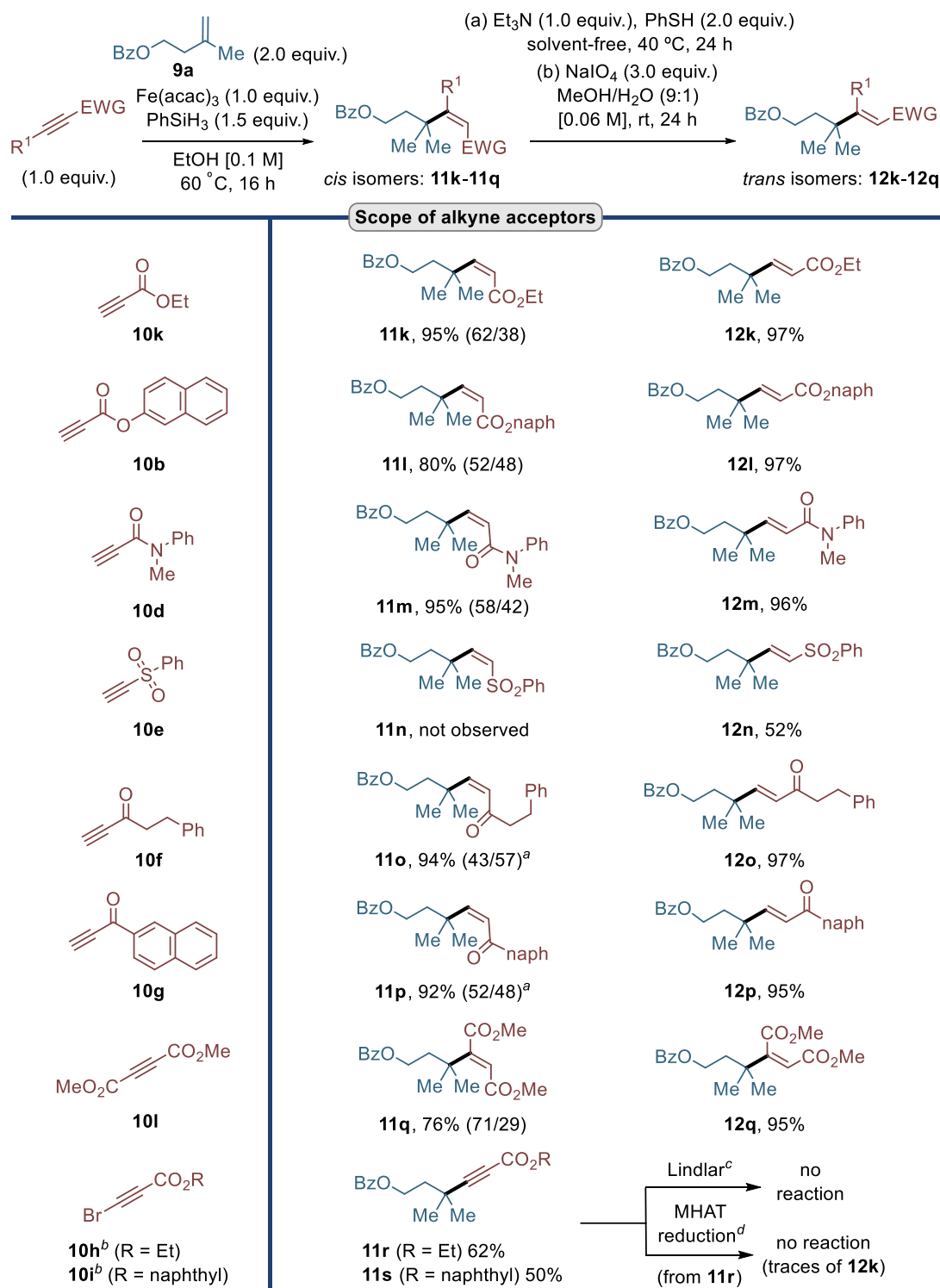
The scope of electron-deficient alkynes was subsequently examined (Table 2.5). Alkyne esters **10k** and **10b**, containing ethyl and naphthyl substituents, respectively, afforded the corresponding products **11k** and **11l**, which were successfully isomerized to the *trans* compounds **12k** and **12l** in nearly quantitative yields. Notably, an increase in the bulkiness of the acceptor caused a slight decrease in the efficiency of the coupling.

Amide **10d** was also an effective acceptor, providing product **11m** which was readily converted into **12m**. In contrast, sulfonamide **10e** only yielded the *trans* product **12n**, with no detection of the *cis* compound **11n**. It remains unclear whether **11n** failed to form under the reaction conditions or underwent rapid isomerization either during the reaction or purification. Ketones **11o** and **11p**, derived from **10f** and **10g**, respectively, underwent spontaneous isomerization to form **12o** and **12p**, suggesting isomerization as the most plausible cause. Nonetheless, the *cis* compounds could be observed via NMR, and estimated ratios are provided post-purification.

Internal alkyne **10l**, bearing a second ester group, also enabled a successful coupling, yielding **11q**, which was subsequently isomerized to **12q** in good yield. In addition, alkynyl bromides were investigated using conditions previously reported by Cui (see Scheme 1.51).⁴⁴ Although Cui's studies were confined to aromatic substituents, our findings indicated that electron-withdrawing groups on the bromoalkyne were compatible as well. Substrates **10h** and **10i** formed alkynes **11r** and **11s**, respectively, through an addition-elimination mechanism rather than a Giese-type pathway.

Although a divergent reduction strategy for selectively accessing *cis* and *trans* alkenes **11k** and **12k** from **11r** was considered, no reaction occurred under Lindlar reduction conditions. MHAT reductive conditions showed a preference for the formation of the *trans* isomer; however, only trace amounts were obtained even with prolonged reaction times. These results highlight the utility of our direct coupling approach in efficiently synthesizing the desired alkene products.

Table 2.5: Study of the scope of the alkyne acceptors in the MHAT coupling.

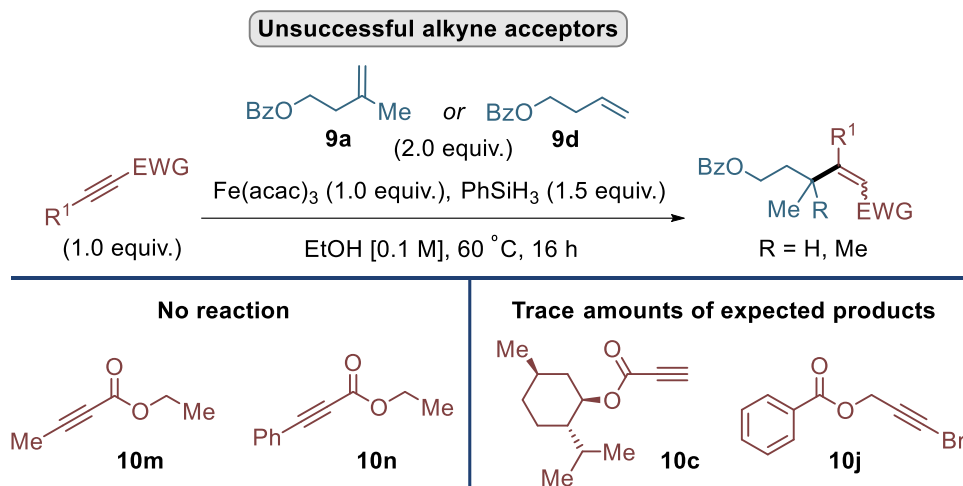


^aThe *cis* product spontaneously isomerized, so the mixture was directly subjected to isomerization conditions. ^b1.0 equiv. of NaHCO₃ was added. ^cConditions: 0.2 equiv. of Lindlar catalyst, 0.15 equiv. of quinoline, MeOH [0.12 M], 25 °C, 24 h. ^dConditions: 1.0 equiv. Fe(acac)₃, 2.5 equiv. PhSiH₃, EtOH [0.1 M], 60 °C, 16 h.

The extensive study of alkyne acceptor scope provided valuable insights into which electron-deficient alkynes were incompatible with the reaction (*Scheme 2.44*). When alkyl and aryl internal alkynes **10m** and **10n** were used as acceptors for the coupling with **9a**, only reduced and unreacted starting material was isolated. To investigate whether steric hindrance around the alkene was hindering the coupling, we also attempted coupling alkene **9d** with alkyne **10m**, but no reaction occurred.

When terminal alkyne **10c** was tested, only trace amounts of the desired products were observed, with most of the starting material recovered either unreacted or reduced, along with unidentified impurities. This outcome suggests that steric effects around the ester functionality may hinder the reaction. Alternatively, a 1,5-hydride transfer of the vinyl radical could generate a stable tertiary radical, potentially leading to degradation or side reactions, similar to the reactivity described in *Scheme 2.43*.

Finally, to confirm that the presence of an electron-withdrawing group on the acceptor was essential for the reaction with alkynyl bromides, we carried out the MHAT coupling with **10j**, but only traces of the coupled product were obtained.

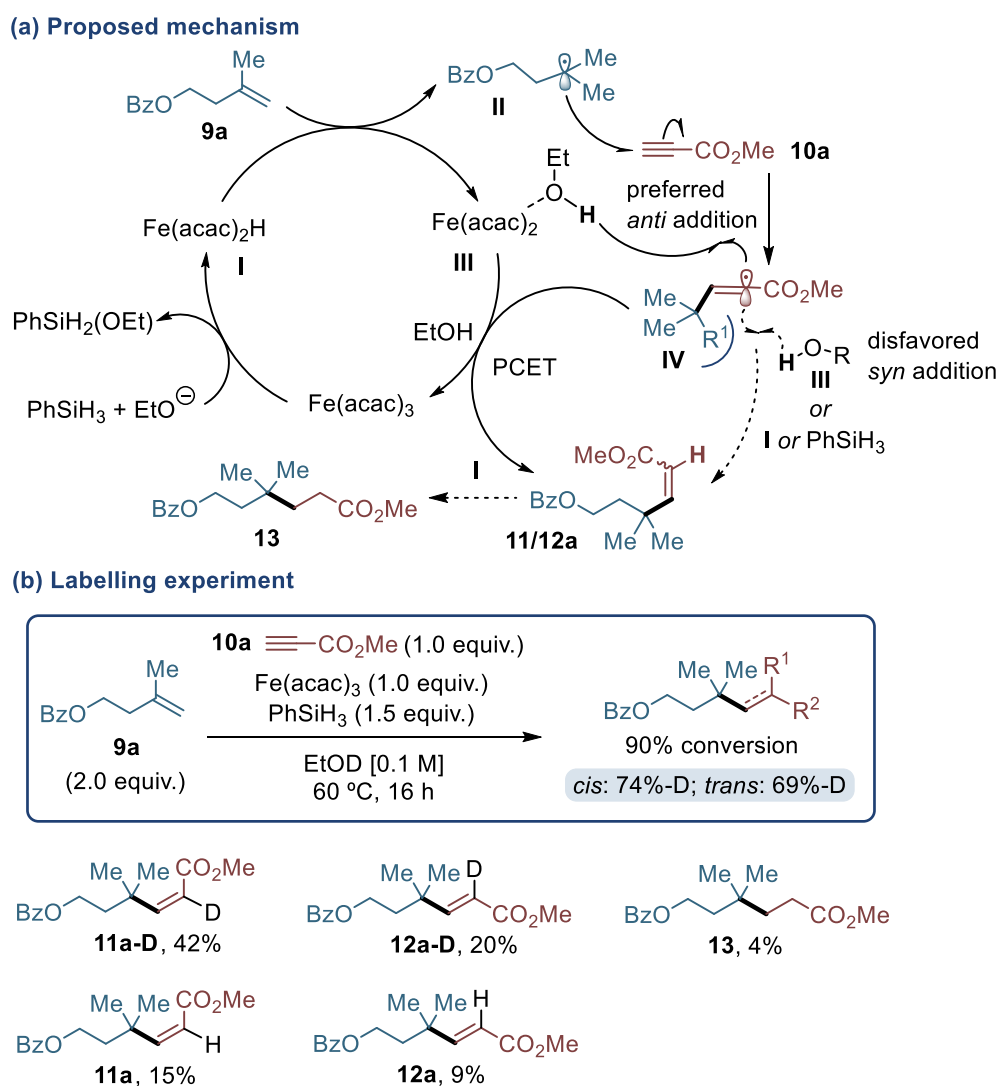


Scheme 2.44: Unsuitable alkyne acceptors for the MHAT coupling.

2.3.5 Mechanistic studies

The proposed mechanism for the reaction is depicted in *Scheme 2.45*. The formation of the iron hydride species $\text{Fe(acac)}_2\text{H}$ (**I**) followed by hydrogen atom transfer (HAT) to alkene **9a** results in the generation of the carbon-centered radical **II**. This radical then reacts with electron-deficient alkyne **10a**, resulting in the formation of vinyl radical **IV**. A

subsequent proton-coupled electron transfer (PCET) from $\text{Fe}(\text{acac})_2 \cdot \text{EtOH}$ (**III**) converts **IV** into either the *cis* product **11a** or the *trans* product **12a**. The preference for the *cis* isomer **11a** arises because PCET occurs more readily on the less sterically hindered face of **IV**, while the formation of the *trans* isomer **12a** involves addition to the more hindered face, making it less favorable. Performing the reaction in EtOD revealed only 74% deuterium incorporation into the *cis* isomer and 69% into the *trans* isomer. This suggests the involvement of an alternative pathway in which vinyl radical **IV** abstracts a hydrogen atom from either phenylsilane or the iron hydride species **I**. Notably, this pathway interferes with the regeneration of the active catalytic species, which could explain why higher $\text{Fe}(\text{acac})_3$ loadings generally improve the reaction outcome.

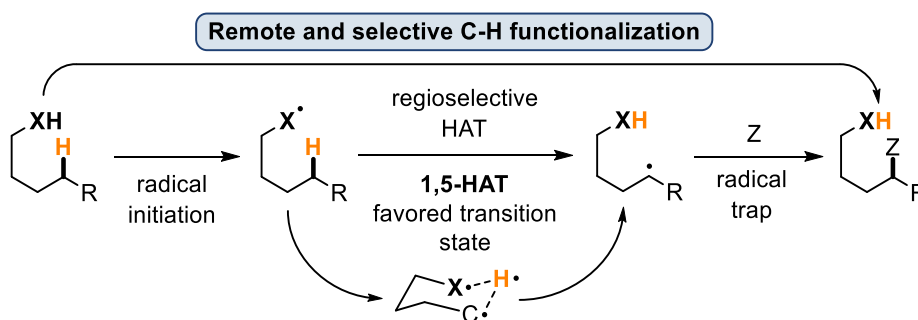


Scheme 2.45: Proposed mechanism for the MHAT coupling and labelling studies.

2.3.6 Transposition of vinyl radicals

As disclosed in *Scheme 2.43*, during the study of the scope of suitable donors for the MHAT coupling, a particular reactivity involving a 1,5-transposition of vinyl radicals was observed. This unexpected behavior suggests a mechanistic pathway worth further investigation. To better understand this reactivity, we will first introduce key concepts related to distal hydrogen atom transfer, a process that plays a fundamental role in radical chemistry.

Hydrogen atom transfer transformations have proven to be a powerful tool for the selective functionalization of remote C–H bonds. Although many HAT events are rapid and exergonic, H $\cdot$ abstraction often exhibits complete δ regioselectivity. The 1,5-HAT pathway is the most frequent due to the involvement of a prearranged six-membered cyclic transition state which is particularly stable (*Scheme 2.46*).⁴⁵

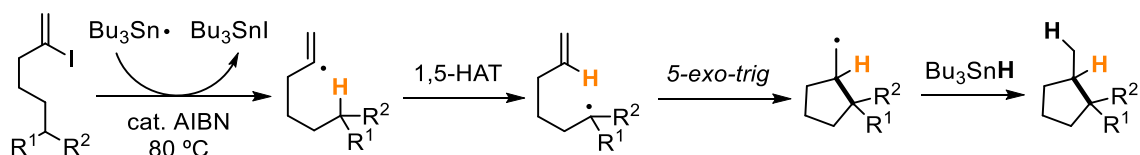


Scheme 2.46: Remote functionalization of C–H bonds via hydrogen atom transfer.

This radical translocation commonly arises from N-, O-, or C-centered radicals. Nitrogen- and oxygen-centered radicals tend to undergo 1,5-HAT more easily for two reasons. Firstly, the formation of these radicals is energetically unfavorable due to the high electronegativity of nitrogen and oxygen. Secondly, the resulting N–H or O–H bonds are stronger than the cleaved C–H bond, providing a thermodynamic driving force that facilitates the reaction.⁴⁶

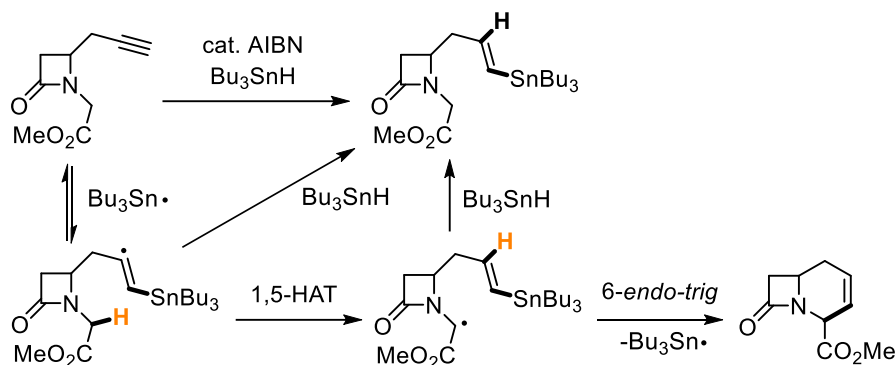
1,5-HAT mediated by C-centered radicals is less common compared to their heteroatom counterparts. As a result, these reactions often require a significant trigger, such as the conversion of a higher-energy C(sp²) vinyl radical to a more stable C(sp³) alkyl radical.⁴⁷ These vinyl radicals can be generated through halogen abstraction or single-electron reduction of the corresponding vinyl halides, or via radical addition to alkynes.

Early studies by Curran and Bachi will be outlined next for a better understanding of this reactivity. In 1988, Curran demonstrated that vinyl iodides could form cyclopentane derivatives by means of a 1,5-translocation of radical sites and subsequent 5-*exo-trig* cyclization.⁴⁸ The reaction utilized Bu_3SnH as an atom transfer agent and AIBN as a radical initiator (*Scheme 2.47*).



Scheme 2.47: Translocation of radical sites via intramolecular 1,5-HAT by Curran.

The generation of vinyl radicals via radical addition to alkynes offers distinct advantages from a synthetic perspective, as it avoids the need to prepare vinyl halides and allows access to more structurally diverse products. In 1993, Bachi and coworkers introduced a strategy for generating vinyl radicals by adding Bu_3SnH radicals to alkynes to achieve distal functionalization.⁴⁹ The resulting radicals underwent 1,5-HAT, followed by 6-*endo-trig* cyclization and β -tin elimination, to yield β -lactam derivatives (*Scheme 2.48*).

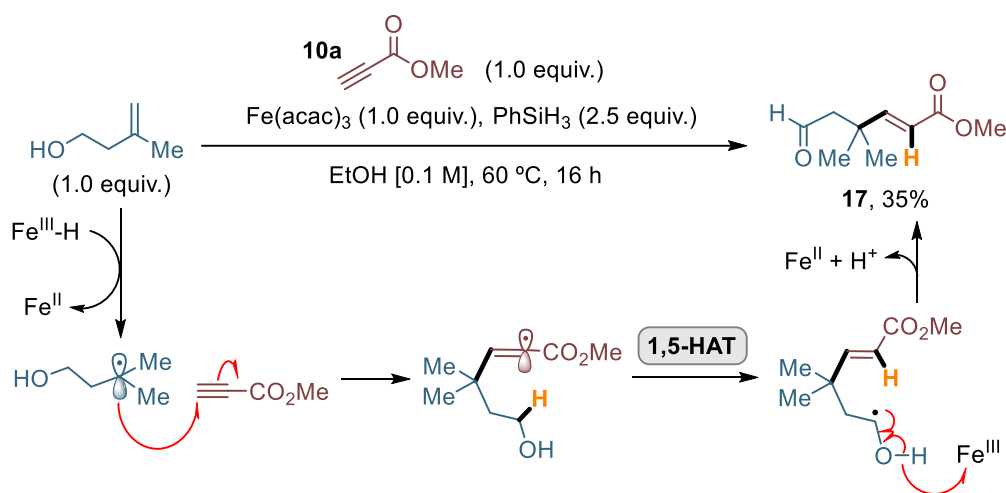


Scheme 2.48: Generation of vinyl radicals with alkyne precursors by Bachi.

Modern strategies for generating vinyl radicals from vinyl halides or alkynes, particularly with the development of tin-free procedures, have greatly expanded their synthetic utility.^{50,51} However, no examples of 1,5-transpositions via the use of MHAT chemistry have been reported to date.

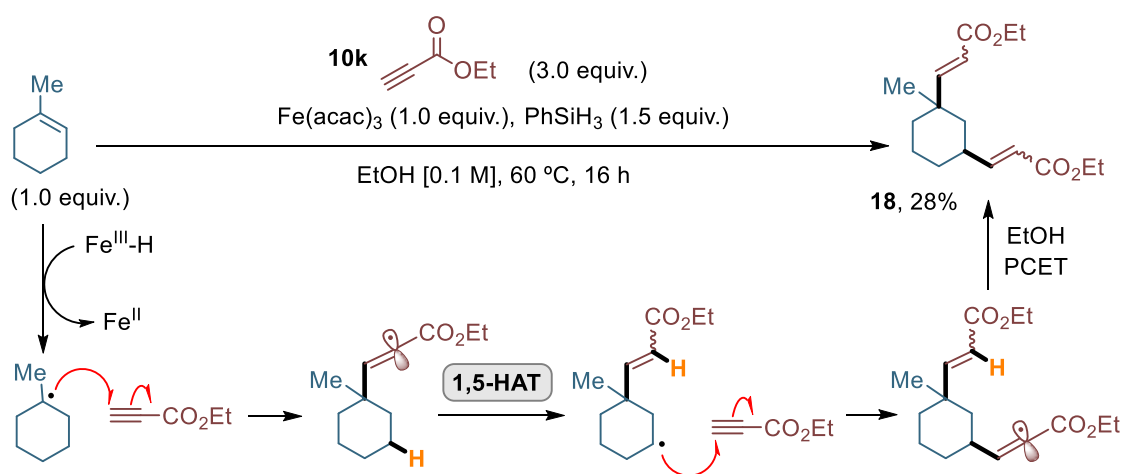
During our investigation of the versatility of the MHAT coupling between alkenes and electron-deficient alkynes, the unexpected oxidized product **17** (*Scheme 2.49*) was

obtained for the coupling of 3-methylbut-3-en-1-ol and methyl propiolate. The reaction was thought to proceed via 1,5-HAT. Firstly, HAT from the metal hydride species to the alkene could generate an alkyl radical, which would then be trapped by the alkyne acceptor. Then, a 1,5-transposition of the unstable vinyl radical would form a stabilized α -oxy radical, which via rearrangement could be converted to aldehyde **17**, with concomitant reduction of Fe^{III} to Fe^{II} and the generation of a proton. Even though an estimated yield is provided, it should be noted that the product was volatile, and considerable amounts were lost by evaporation during the purification process.



Scheme 2.49: 1,5-HAT for the obtention of aldehyde **17**.

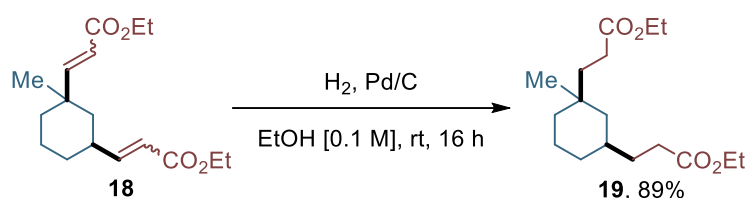
In light of the reactivity observed for 3-methylbut-3-en-1-ol, we identified a similar 1,5-transposition pathway during our exploration of the MHAT coupling between alkenes and electron-deficient alkynes in cyclic frameworks (Scheme 2.50).



Scheme 2.50: 1,5-HAT pathway for 1-methylcyclohexene.

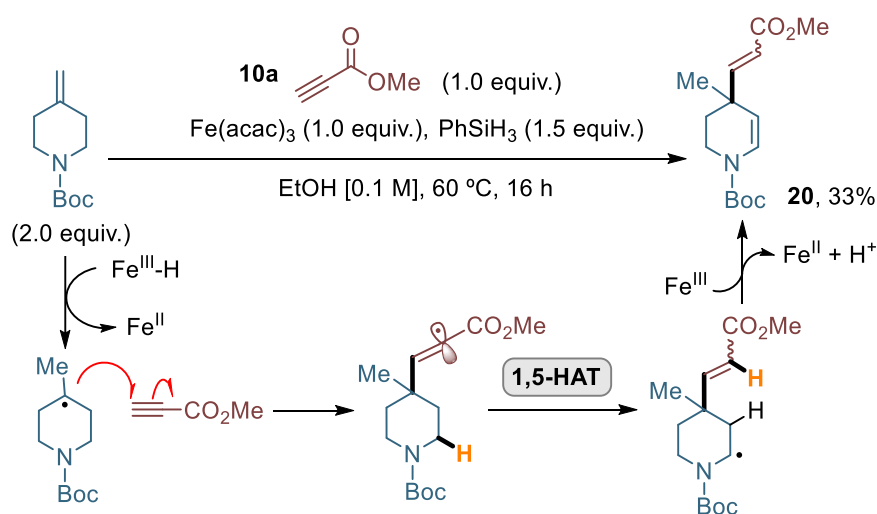
In this case, the reaction proceeded analogously to its acyclic counterparts, with the generation of a vinyl radical followed by a 1,5-HAT. Notably, the process was further extended by a second Giese-type addition, affording the double addition product **18** as a complex mixture of isomers in 28% yield. However, the volatility of both the monoaddition product and the coupling partners made it challenging to determine whether the reaction led to a mixture of mono- and bis-addition products or if the conversion was simply low, leaving a portion of the starting material unreacted.

To address practical challenges, a subsequent hydrogenation step was employed, furnishing **19** in 89% yield (*Scheme 2.51*). While still a mixture, the hydrogenated product exhibited significantly simplified NMR spectra, facilitating characterization.



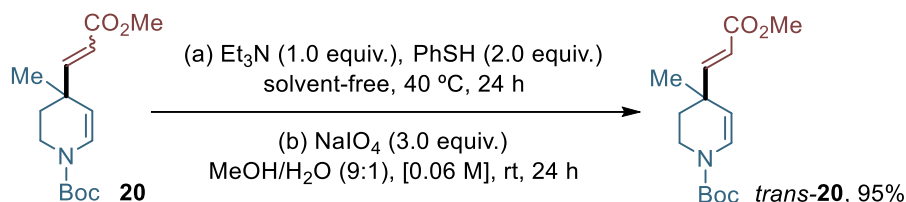
*Scheme 2.51: Hydrogenation of **18** to access reduced compound **19**.*

To further investigate the reactivity observed in cyclic compounds, we conducted the same reaction using an unsaturated piperidine derivative. Instead of yielding the double addition product, the reaction with methyl propiolate, followed by 1,5-HAT, led to the formation of a double bond. The coupled product **20** was obtained as an inseparable mixture of *cis/trans* isomers, along with minor unidentified impurities (*Scheme 2.52*).



*Scheme 2.52: 1,5-HAT transposition to furnish **20**.*

To simplify the mixture, an isomerization sequence was performed, affording *trans*-**20** in 95% yield (Scheme 2.53).

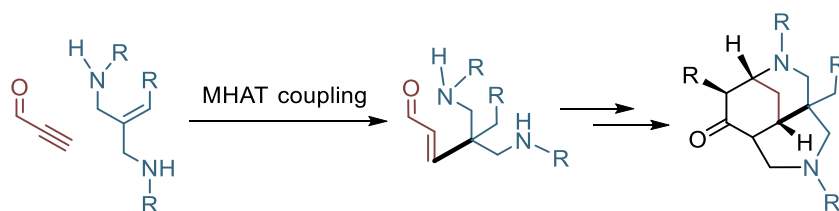


Scheme 2.53: Isomerization of **20** to enable characterization.

Due to the complexity of the results and time constraints, a more detailed investigation of the remote C–H functionalization in the MHAT coupling between alkenes and electron-deficient alkynes was not feasible. Nonetheless, the preliminary findings are promising, and further exploration of this reactivity will be pursued in future studies.

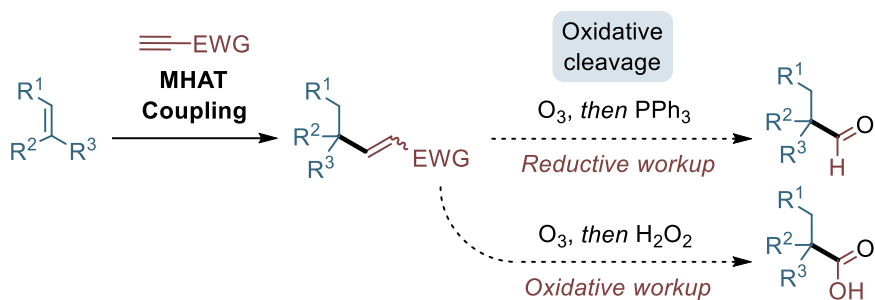
2.3.7 Future work

Throughout this chapter, we have developed a method for synthesizing products featuring an alkene adjacent to a quaternary center. Although some challenges remain, particularly with highly sterically hindered substrates, the strategy outlined in this work provides a valuable tool for advancing the synthesis of the core structure of madangamine alkaloids (Scheme 2.54).



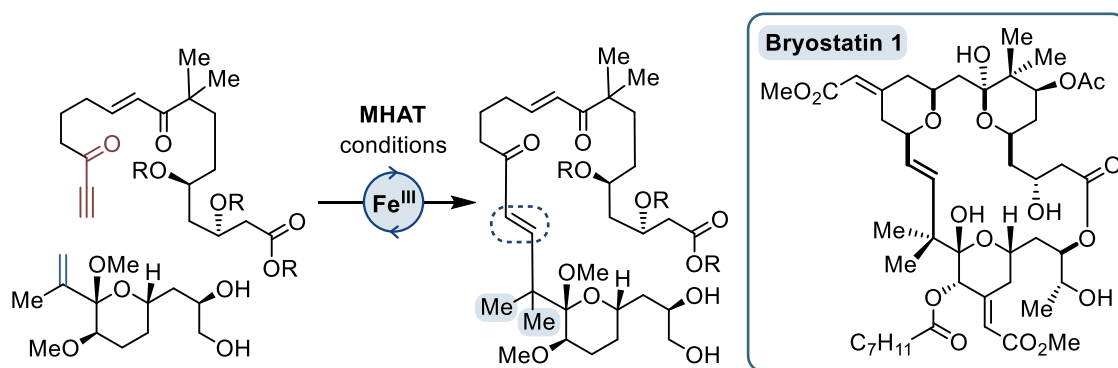
Scheme 2.54: MHAT coupling applied to madangamine core synthesis.

Additionally, the electron-deficient alkenes generated via this methodology could undergo oxidative cleavage, enabling a hydroformylation process.⁵² As proposed in Scheme 2.55, treatment of the coupled products with ozone, followed by triphenylphosphine, would likely cleave the alkene, yielding an aldehyde as the final product. Alternatively, an oxidative workup using H₂O₂ could afford carboxylic acids. These valuable scaffolds could then undergo further functionalization.



Scheme 2.55: Proposed oxidative cleavage of the coupling products.

Finally, our new MHAT coupling offers a potential novel disconnection strategy for bryostatin-related compounds, providing an alternative to cross-metathesis for the modular construction of bryologs through the formation of a key bond (*Scheme 2.56*).⁵³



Scheme 2.56: New disconnection approach to bryostatin-related compounds.

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3. BASE-MEDIATED NITROPHENYL REDUCTIVE CYCLIZATION FOR THE SYNTHESIS OF 3,4-BENZOMORPHANS

3.1 INTRODUCTION

In this chapter, we describe the synthesis of the 3,4-benzomorphan fragment via a nitrophenyl reductive cyclization as a key step in the total synthesis of aspernomine, a natural product isolated from *Aspergillus nomius* that biogenetically derives from anominine. We will begin the chapter by disclosing the previously reported total syntheses of natural products biogenetically related to anominine (Figure 3.1). Then, we will outline known strategies to access the benzomorphan fragment, which we have published as a review during this thesis.¹ Afterward, we will discuss our proposed synthetic route toward the heterocyclic scaffold and the biological testing of the synthesized analogs.²

3.1.1 Exploring anominine and its related metabolites

Frequently, fungi develop specialized structures known as sclerotia, which are crucial for their long-term survival and reproduction. Research conducted by Gloer's team on the sclerotia of *Aspergillus nomius* resulted in the discovery of several bioactive secondary metabolites,³ including anominine,⁴ a complex indole diterpenoid that is likely the biogenetic precursor to other related compounds.

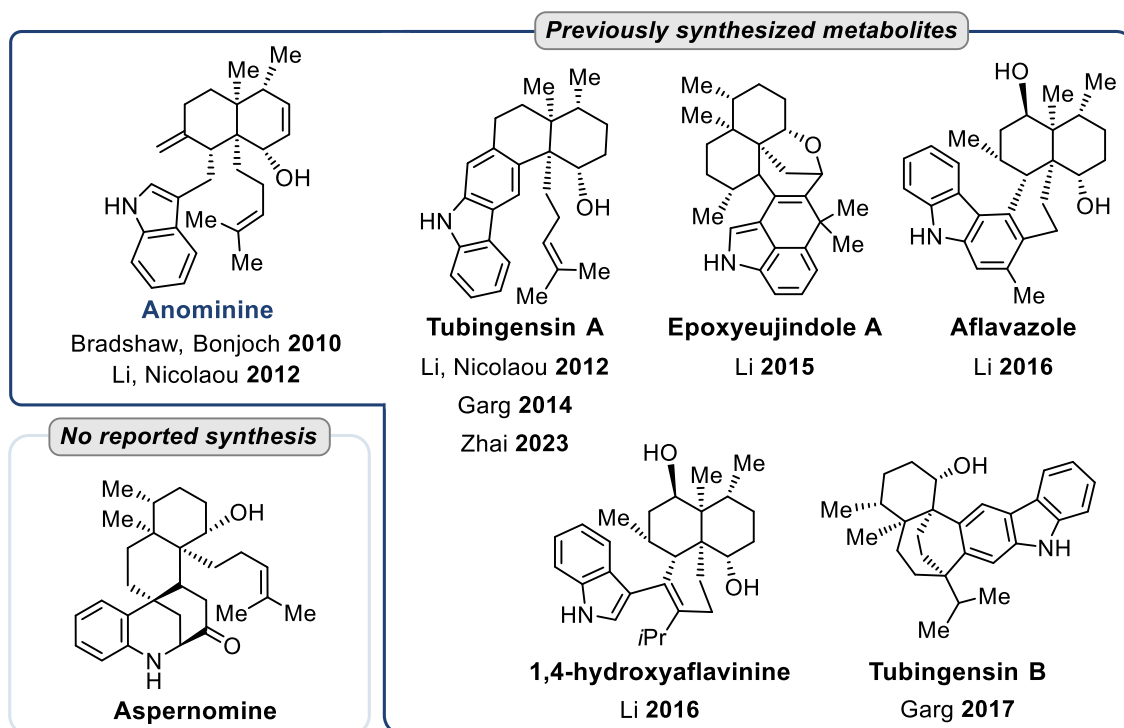


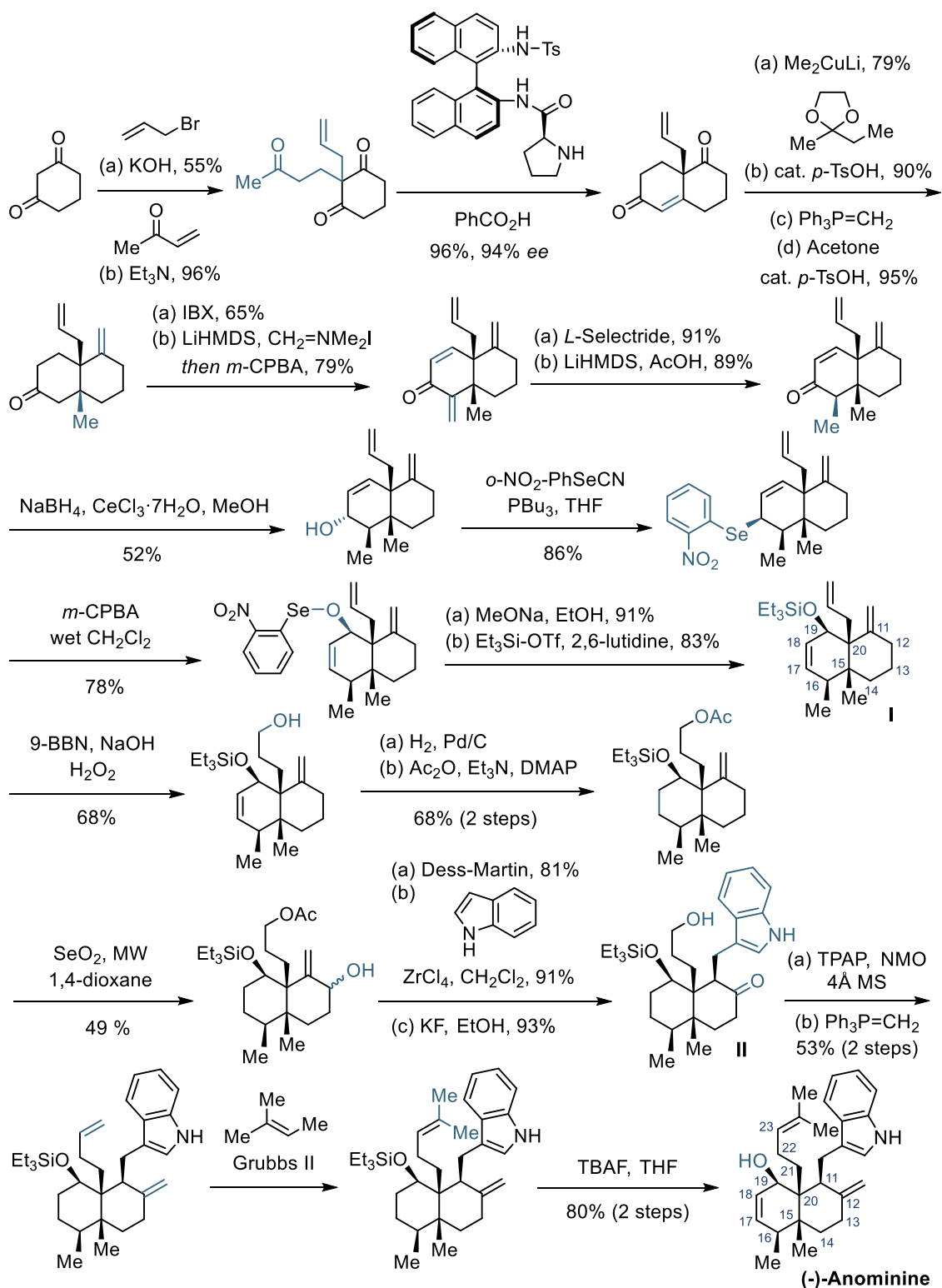
Figure 3.1: Secondary metabolites biogenetically related to anominine.

In earlier work on this natural product, our group accomplished the first total synthesis of (–)-anominine,⁵ establishing its absolute stereochemistry. Since then, the total syntheses of related compounds, including tubingensin A,^{5b,6,7} epoxyeujindole A,⁸ aflavazole,⁹ 1,4-hydroxyaflavinine,⁹ and tubingensin B,¹⁰ have been successfully achieved. However, the synthesis of aspernomine remains unaccomplished. The following section provides a concise overview of these total syntheses.

Total synthesis of (–)-anominine (Bradshaw and Bonjoch, 2010)^{5a}

For the total synthesis of (–)-anominine, our group began to work with 1,3-cyclohexanedione, which was allylated under basic conditions (*Scheme 3.1*). A one-pot asymmetric Robinson annulation furnished a Wieland–Miescher derivative. Then, conjugate addition of Me₂CuLi provided a *cis*-decalin. Temporary protection of the more accessible carbonyl as an acetal allowed Wittig methylenation of the more hindered carbonyl group. Oxidation with IBX then enabled the formation of an endocyclic enone. Methylation with LiHMDS at C16, followed by elimination with *m*-CPBA, yielded an exocyclic enone, which was readily reduced with *L*-Selectride and epimerized. The carbonyl group was then reduced with NaBH₄ and converted into an allylic selenide which upon oxidation under non-anhydrous conditions underwent a sigmatropic rearrangement. The resulting selenate was removed under basic conditions, and the alcohol group was protected with triethylsilane to yield advanced intermediate **I**.

Selective hydroboration of the allylic side chain with 9-BBN generated an alcohol, which underwent selective reduction of the internal double bond due to steric hindrance around the exocyclic olefin. Subsequent protection as an acetate, allylic oxidation with selenium dioxide, and oxidation with Dess–Martin periodinane, enabled the installation of an enone functionality. The conjugate addition of an indole fragment to the enone, mediated by zirconium tetrachloride, followed by treatment with potassium fluoride in refluxing ethanol, furnished the all-*cis* diastereomer **II**, with spontaneous cleavage of the acetate group. The resulting deprotected alcohol was then oxidized to an aldehyde, and both carbonyl groups underwent simultaneous Wittig olefination. Finally, cross-metathesis at the least hindered double bond, followed by deprotection of the silyl group, yielded (–)-anominine.



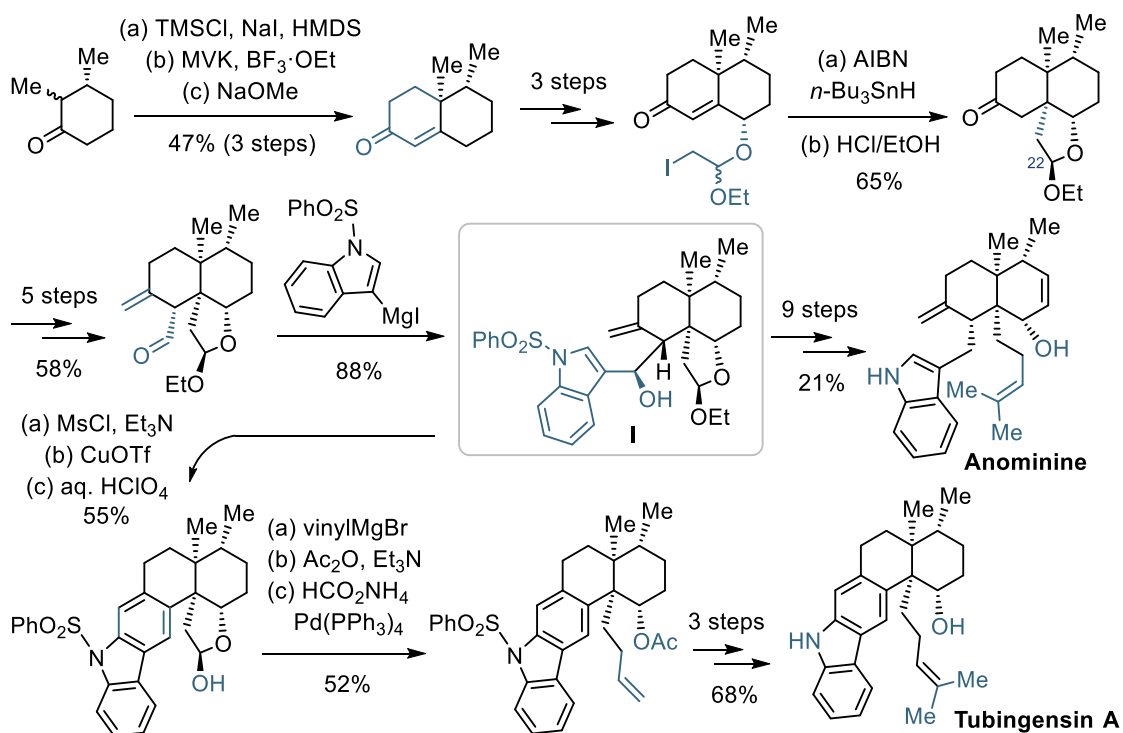
Scheme 3.1: Total synthesis of (–)-anominine by Bradshaw and Bonjoch.

Total synthesis of anominine and tubingensin A (Li and Nicolaou, 2012)^{5b}

After our group disclosed the synthesis of (–)-anominine, Li and coworkers developed a divergent approach to synthesize both anominine and tubingensin A (*Scheme 3.2*). This

route began with the formation of common intermediate **I**, which incorporated all the required stereochemical information for both targets. The synthesis commenced with the formation of a TMS enol ether of a commercially available cyclohexanone, followed by a 1,4-addition and Robinson annulation. Further elaboration of the bicyclic enone provided the iodinated precursor for radical cyclization. Subsequent treatment with AIBN and *n*-Bu₃SnH, followed by epimerization at C22, gave a tricyclic compound. Elaboration of this framework enabled the installation of an indole side chain via reaction with a suitable Grignard reagent, forming key intermediate **I**.

With all stereochemical information introduced, the authors turned their attention to synthesizing anominine. A sequence of nine interconversions including a radical deoxygenation to remove the hydroxyl group, a lactol-opening Grignard reaction, and an efficient side-chain installation delivered anominine in 21% yield from intermediate **I**.



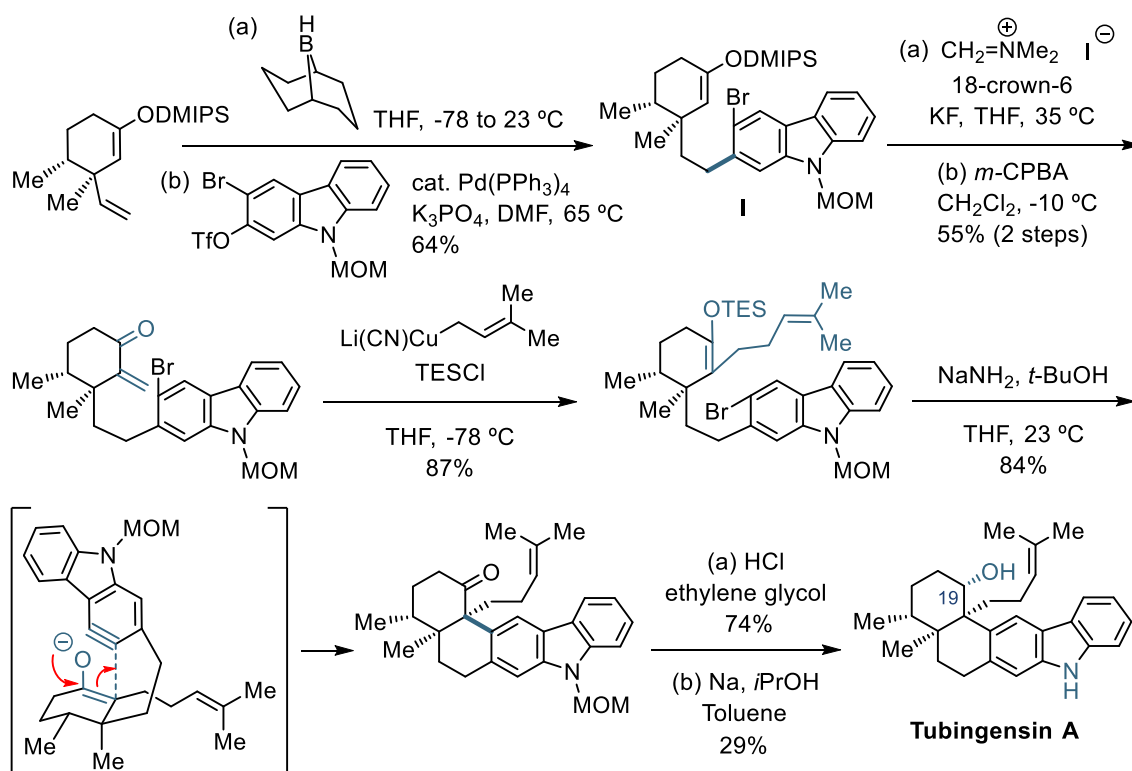
Scheme 3.2: Total synthesis of anominine and tuingensin A by Li and Nicolaou.

Encouraged by these results, the group pursued the synthesis of tuingensin A. Dehydration of **I**, followed by a pivotal CuOTf-promoted 6 π -electrocyclization/aromatization sequence, and deacetalization, furnished a carbazole derivative. A Grignard reaction with vinylMgBr gave the ring-opening addition product, which

underwent bisacetylation and Tsuji reduction to furnish a terminal alkene. Finally, cross-metathesis and deprotection steps enabled the first total synthesis of tubingensin A.

Total synthesis of tubingensin A (Garg, 2014)⁶

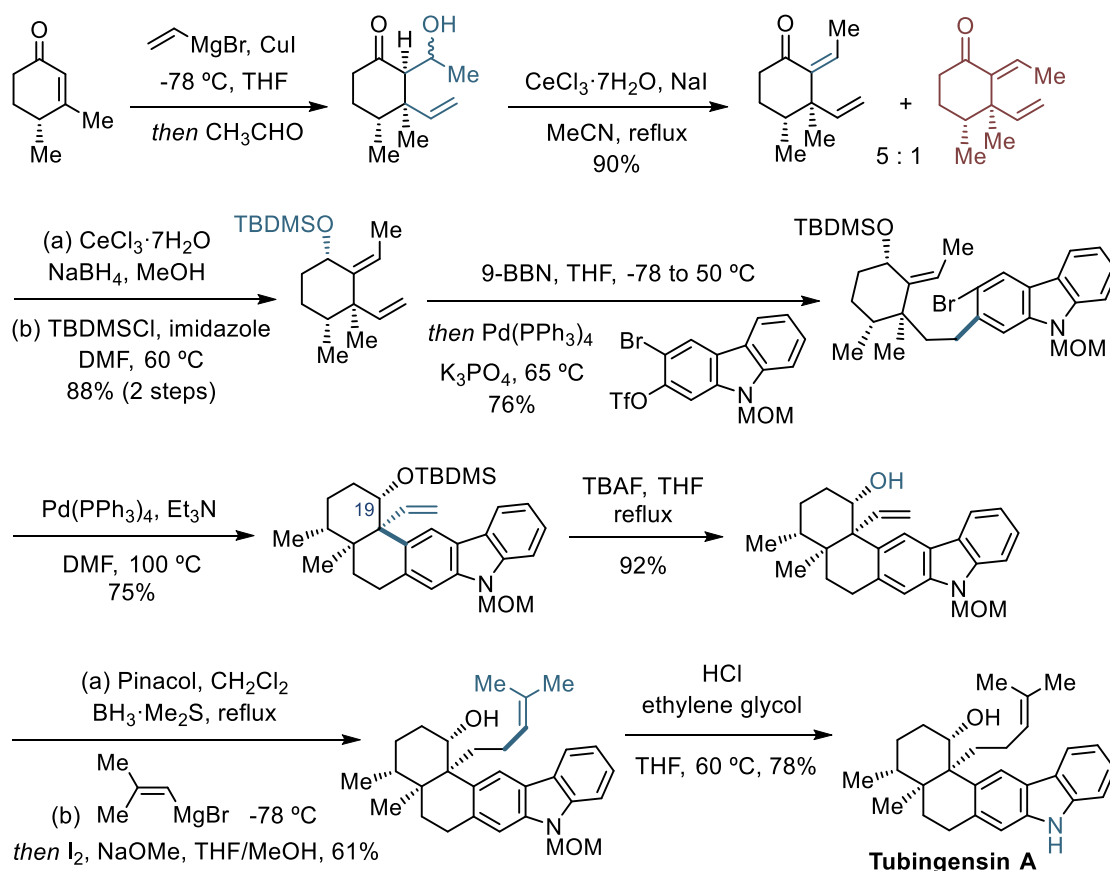
After the group of Li reported their 23 step linear approach toward tubingensin A, Garg employed a modular strategy to connect the terpene and heterocyclic frameworks, shortening the synthesis to only 10 steps from readily available starting materials (Scheme 3.3). A one-pot hydroboration of an enol ether, followed by Suzuki coupling with a carbazole derivative, gave access to **I**. Then, an exocyclic enone was formed in two steps. Subsequent alkylation with a cuprate and trapping of the resultant enolate with TESCl furnished the cyclization precursor, which engaged in the aryne cyclization and enabled the introduction of vicinal quaternary stereocenters present in the natural product with complete diastereoselectivity. To complete the total synthesis only two steps remained. First, removal of the MOM group proceeded smoothly in 74% yield. However, reduction of the carbonyl group proved more challenging, and the best conditions found only gave 29% of the targeted C19 epimer, although it was possible to reoxidize and recycle the undesired epimer.



Scheme 3.3: Total synthesis of tubingensin A by Garg.

Total synthesis of tubingensin A (Zhai, 2023)⁷

Despite Garg's elegant aryne cyclization approach to tubingensin A, some challenges arose. The final reduction of the C19 carbonyl yielded a 1:2 ratio of tubingensin A and its C19 epimer, suggesting that the earlier introduction of the correct stereochemistry could address this. In 2023, Zhai and coworkers developed a modular synthesis to overcome these issues (Scheme 3.4). The synthesis commenced with vinyl cuprate addition to an enone, followed by an aldol reaction to form a β -hydroxy ketone. Treatment with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and NaI in acetonitrile produced a mixture of *Z* and *E* alkenes in a 5:1 ratio. A Luche reduction of the *Z* isomer, followed by hydroxyl protection and sequential hydroboration/Suzuki–Miyaura coupling gave a carbazole derivative. A subsequent intramolecular Heck arylation formed a pentacyclic framework, with the correct stereochemistry at C19. Upon desilylation with TBAF, a Zweifel olefination furnished a trisubstituted alkene. Finally, MOM group removal under acidic conditions gave tubingensin A in 78% yield.

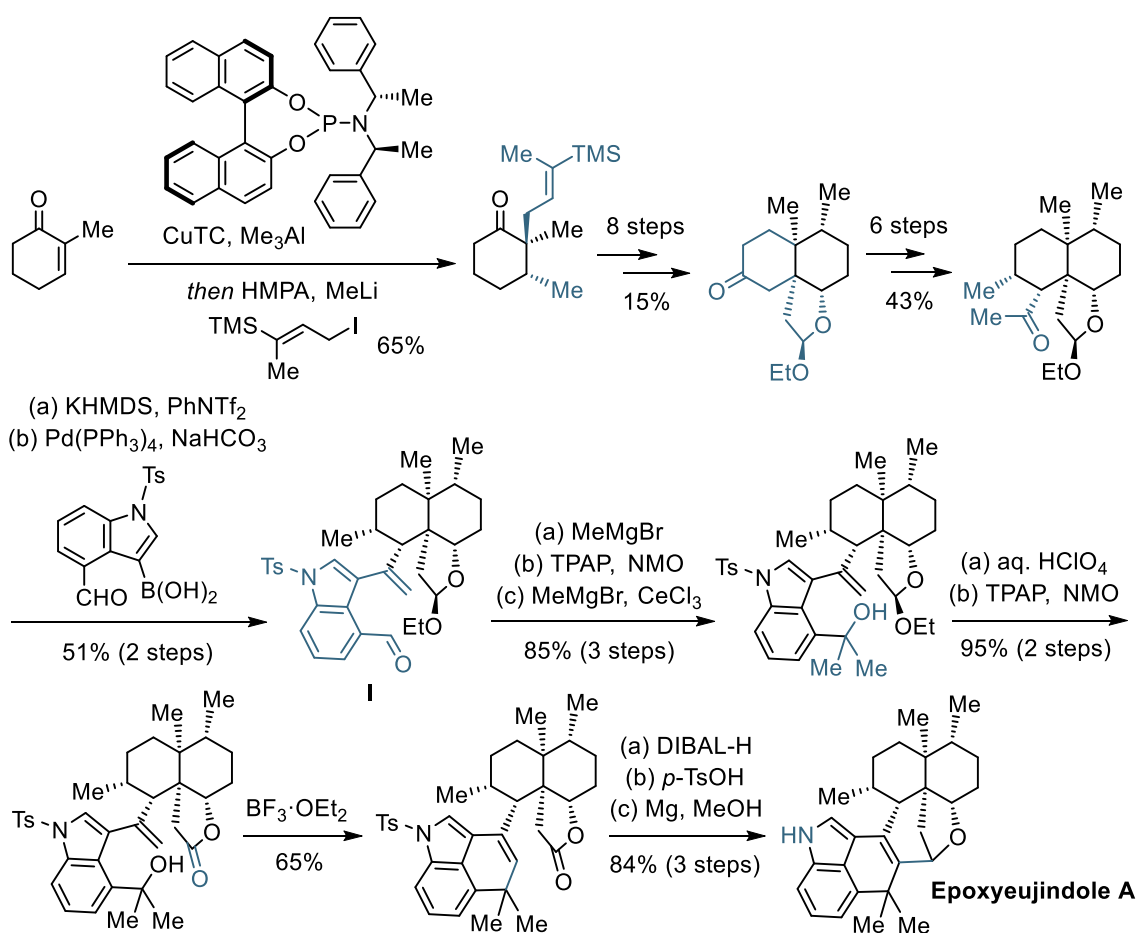


Scheme 3.4: Total synthesis of tubingensin A by Zhai et al.

Total synthesis of epoxyeujindole A (Li, 2015)⁸

In 2015, Li proposed a linear total synthesis of epoxyeujindole A involving 26 steps with a 1% overall yield (Scheme 3.5). The synthesis began with an asymmetric conjugate addition followed by enolate trapping. Elaboration of the resulting cyclohexyl compound over eight steps afforded a tricyclic acetal in 15% yield. Upon subsequent modifications, triflation and a Suzuki–Miyaura coupling with an indole-containing boronic acid furnished aldehyde I.

Two sequential methyl additions converted this aldehyde into a tertiary alcohol. To form the indole-fused ring while avoiding compatibility issues, the acetal motif was protected as a lactone. Then, exposure to $\text{BF}_3 \cdot \text{OEt}_2$ triggered the first cyclization. Finally, hemiacetal formation via DIBAL-H reduction, followed by *p*-TsOH treatment facilitated a Prins cyclization to construct the heptacyclic skeleton. Reductive desulfonation with Mg in MeOH completed the synthesis of epoxyeujindole A.



Scheme 3.5: Total synthesis of epoxyeujindole A by Li.

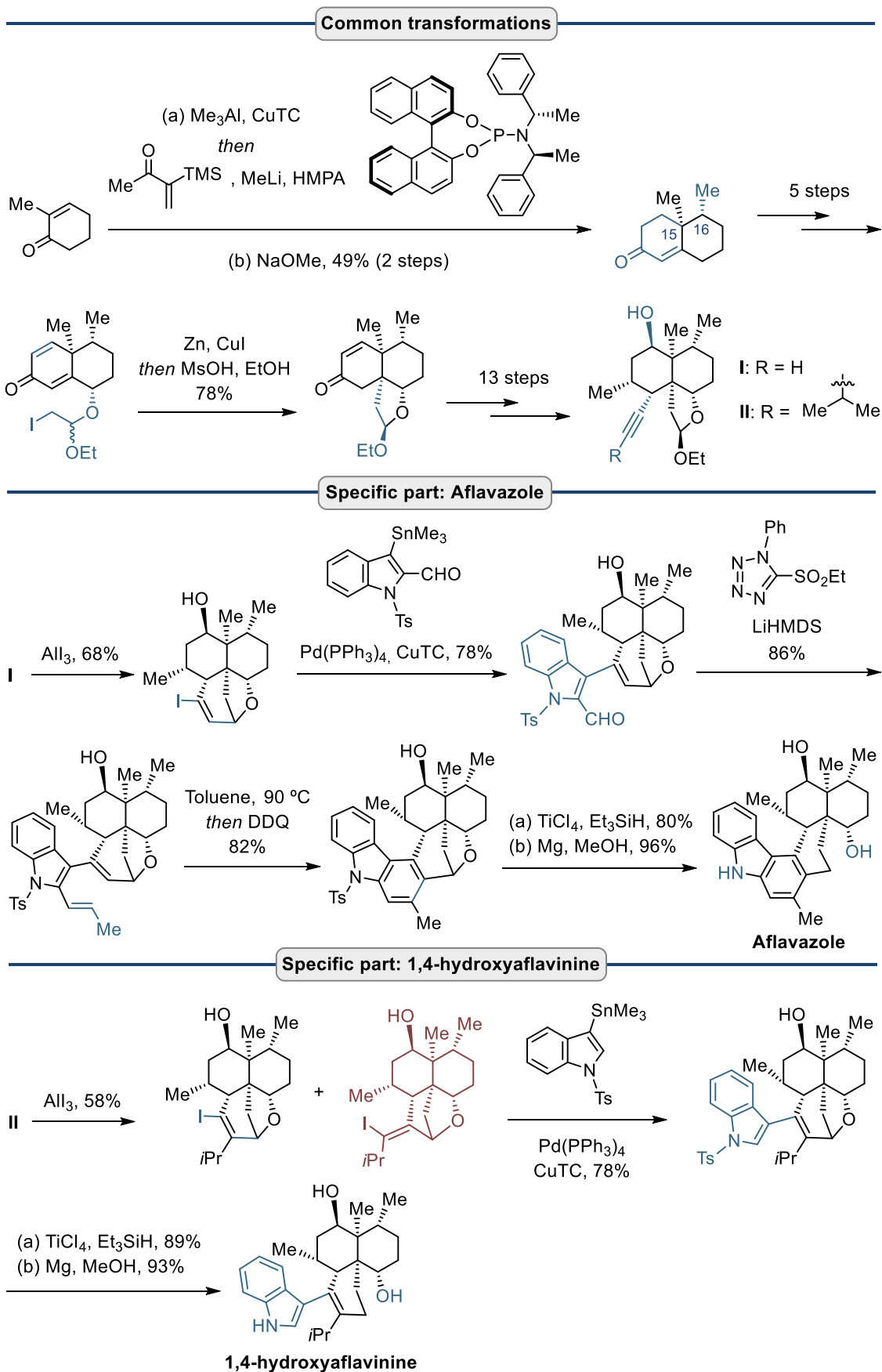
Synthesis of aflavazole and 1,4-hydroxyaflavinine (Li, 2016)⁹

Li and coworkers employed a bioinspired strategy to synthesize aflavazole and 1,4-hydroxyaflavinine, starting from a common intermediate and tailoring final transformations for each compound. This modular approach allowed for efficient synthesis and diversification of the targets (*Scheme 3.6*).

The synthesis began with the formation of analogous intermediates **I** and **II**. Asymmetric 1,4-addition to a cyclohexenone established the stereochemistry at C16. Upon in situ activation with MeLi and HMPA, the enolate reacted with the Stork–Ganem reagent to form an α -silyl ketone bearing the correct stereochemistry at C15, which was then treated with NaOMe. The resulting enone was elaborated in five steps and converted into a bis-enone. Then, Luche cyclization followed by epimerization furnished a tricyclic acetal in 78% yield. This key scaffold was then elaborated in 13 almost identical steps to give alkynes **I** and **II**, which were further derivatized for the syntheses of aflavazole and 1,4-hydroxyaflavinine, respectively.

With alkyne **I** in hand, an extensive optimization for the Prins cyclization was conducted, which revealed that AlI_3 was the most efficient reagent. Next, Stille–Migita reaction enabled the cross-coupling with an indole-derived stannane. Subsequent Julia–Kocienski olefination afforded a triene, which was subjected to 6π -electrocyclization and rearomatized to form the carbazole fragment. Eventually, by means of a reductive cleavage of the benzylic ether with TiCl_4 and Et_3SiH and a desulfonation with Mg, aflavazole could be isolated in 29% global yield from **I**.

For the specific part of the route toward 1,4-hydroxyaflavinine, the group worked with analogous transformations to those used previously. After demonstrating that the key Prins cyclization could take place using a terminal alkyne, internal alkyne **II** underwent the AlI_3 -mediated Prins reaction giving the corresponding cyclized product in 58% yield. However, the five-membered ring side product also formed in 19% yield. Cross-coupling with a Ts-protected indole-derived stannane, followed by reductive C–O cleavage and desulfonation provided 1,4-hydroxyaflavinine in 37% yield from **II**.



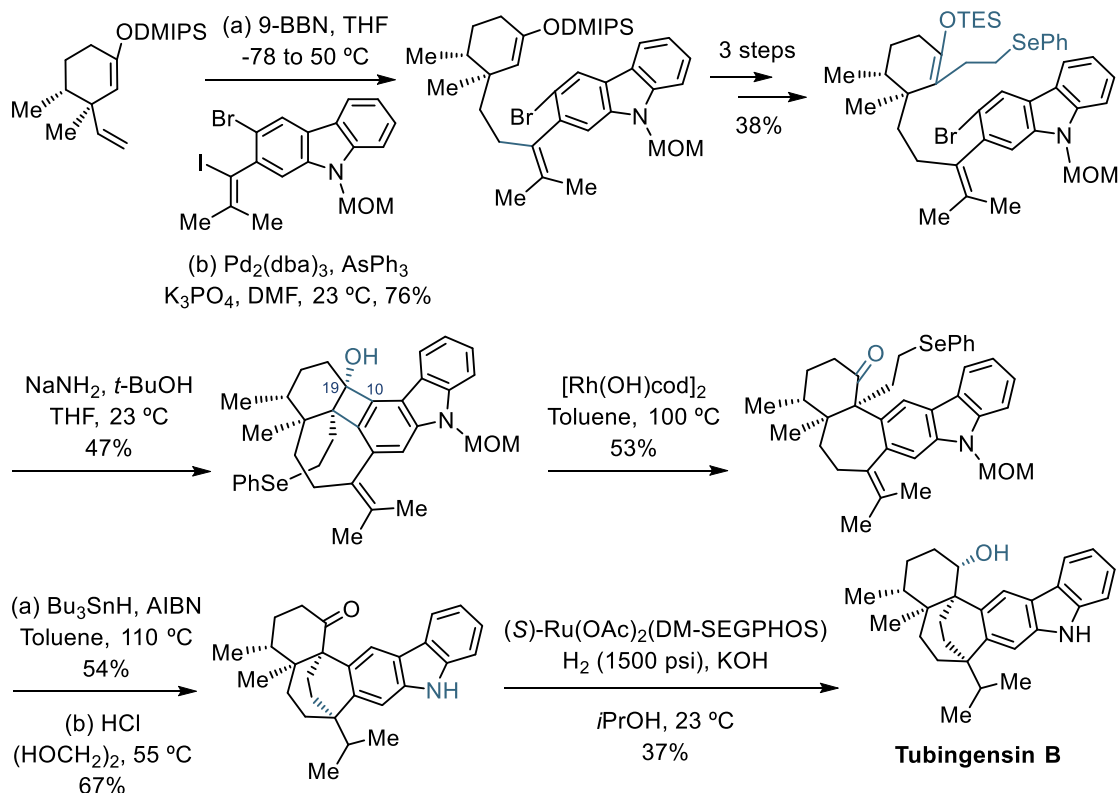
Scheme 3.6: Total syntheses of aflavazole and 1,4-hydroxyaflavinine by Li et al.

Total synthesis of tubingensin B (Garg, 2017)¹⁰

Based on their previous work on the synthesis of tubingensin A, Garg and coworkers also proposed a modular approach toward tubingensin B, which relied on a transient aryne intermediate (Scheme 3.7).

Firstly, the cyclohexyl building block was subjected to hydroboration and then coupled with a dihalocarbazole via a Suzuki–Miyaura reaction. Further elaboration led to the isolation of a phenylselenide, which proved stable in subsequent steps and served as a direct radical cyclization precursor. Next, to form the seven-membered ring, a base-mediated cyclization was used. However, a cyclobutenol moiety with an unwanted C10–C19 bond formed as well, and cleavage under Murakami's mild rhodium-catalyzed ring-opening conditions was required.

To form the remaining C–C bond, an AIBN/Bu₃SnH-mediated radical cyclization was carried out, and subsequent deprotection of the MOM group under acidic conditions was performed. Finally, hydrogenation in the presence of a chiral ligand enabled the diastereoselective reduction of the carbonyl group to access tubingensin B.



Scheme 3.7: Total synthesis of tubingensin B by Garg et al.

3.1.2 Natural products containing the 3,4-benzomorphan scaffold

Notably, many of the compounds discussed in the previous section exhibit potent anti-insectan activity. In contrast, aspernomine stands out as the only cytotoxic member of this metabolite family with demonstrated efficacy against A-549 lung carcinoma, MCF-7 breast adenocarcinoma, and HT-29 colon adenocarcinoma cell lines.¹¹ This suggests that the 3,4-benzomorphan structure can impart significant biological activity when embedded within natural product frameworks, as evidenced by the interesting biological properties of other structurally related compounds (Figure 3.2).

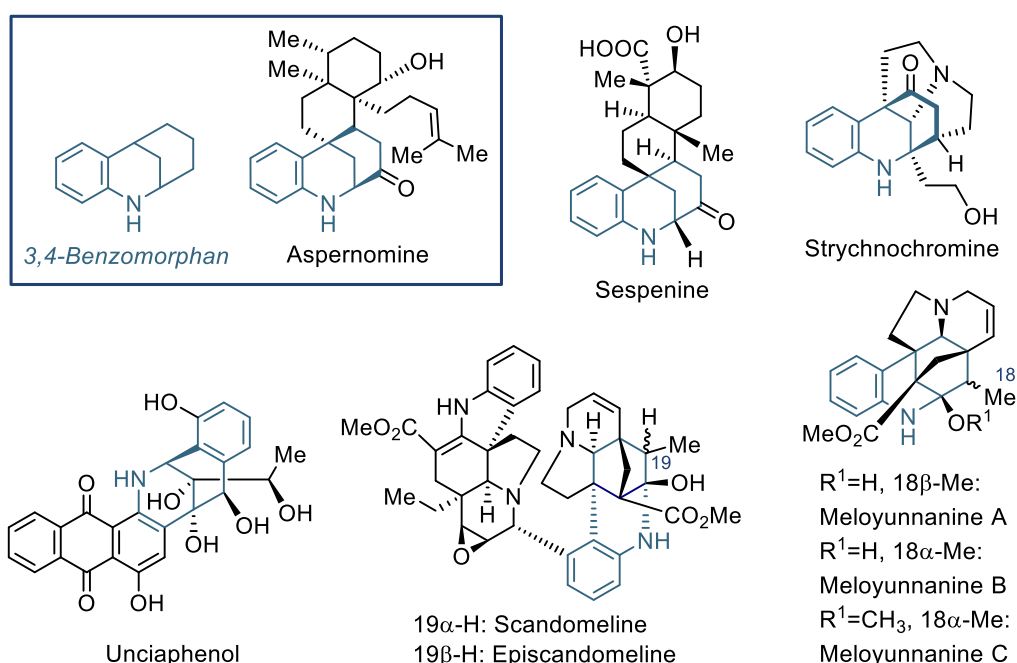


Figure 3.2: Bioactive natural products containing the 3,4-benzomorphan scaffold.

The indole sesquiterpenoid sespentine, isolated from *Streptomyces* —an endophyte from *Kandelia candel*— has demonstrated notable antiviral potential. Its dose-dependent inhibition of herpes simplex virus type 1 (HSV-1) highlights its promise as a therapeutic lead, particularly for addressing viral infections where resistance to existing drugs is a concern.¹² Computational studies have further expanded the scope of sespentine applications. Muhammad *et al.* identified sespentine as the most promising inhibitor of nsp10, a key activator of SARS-CoV-2 replication, among fifty bioactive metabolites from mangrove actinomycetes. Its high binding affinity (−8.8 kcal/mol) and low inhibition constant (0.335 μ M) underscore its potential as a lead compound for developing

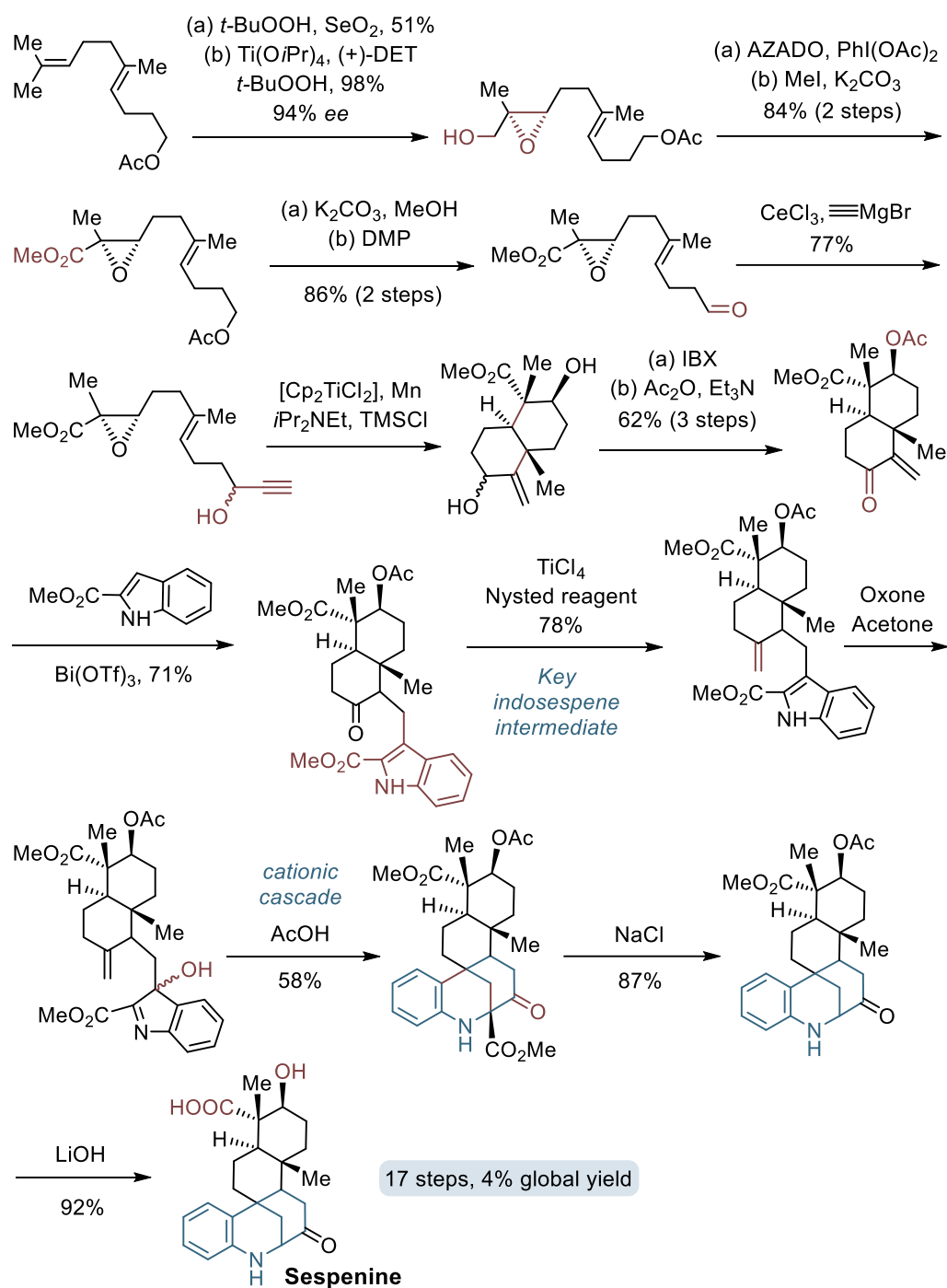
therapeutics against SARS-CoV-2, meriting further exploration through preclinical and clinical evaluations.¹³

Other alkaloids have also shown considerable therapeutic potential. Strychnocromine, an indoline alkaloid isolated from *Strychnos gossweileri*, has demonstrated strong antimalarial activity, effectively inhibiting FCA and W2 strains of *Plasmodium falciparum*. This reinforces the critical role of natural products in addressing multidrug-resistant malaria.¹⁴ Another noteworthy compound is unciaphenol, an oxygenated analog of uncialamycin derived from *Streptomyces*. It has exhibited significant anti-HIV activity and remained effective against strains resistant to existing antiretroviral therapies, offering a promising avenue for overcoming drug resistance in HIV treatment.¹⁵

Investigations into alkaloids derived from the plant species *Melodinus yunnanensis* have led to the discovery of meloyunnanines A–C, a unique class of monoterpenoid indole alkaloids featuring a caged-6/6/5/6/5/5 ring system incorporating a benzazocine scaffold.¹⁶ Despite their structural novelty, these compounds showed minimal cytotoxicity. In contrast, bisindole alkaloids from *Melodinus fusiformis*, such as scandomeline and episcandomeline, have demonstrated greater bioactivity. Notably, episcandomeline exhibited potent cytotoxic effects against the MOLT-4 leukemia cell line, with an IC₅₀ value of 1.5 μ M, comparable to that of cisplatin. This finding underscores its potential as a promising candidate for anticancer drug development, encouraging further structural optimization to enhance selectivity and therapeutic efficacy.^{17,18}

Despite the strong potential of these structures, the lack of prior synthetic examples points out the notable challenges in their preparation. In fact, from all of the natural products listed above, only the total synthesis of sespenine has been reported.

In 2014, the Li group reported the first total synthesis of sespenine, which consisted of 17 steps and achieved an overall 4% yield. Utilizing an indospene-type precursor bearing a C2 methoxycarbonyl substituent, a scalable approach was developed based on an aza-Prins/Friedel–Crafts/retro-Friedel–Crafts reaction cascade to assemble the core of the natural product (Scheme 3.8).¹⁹

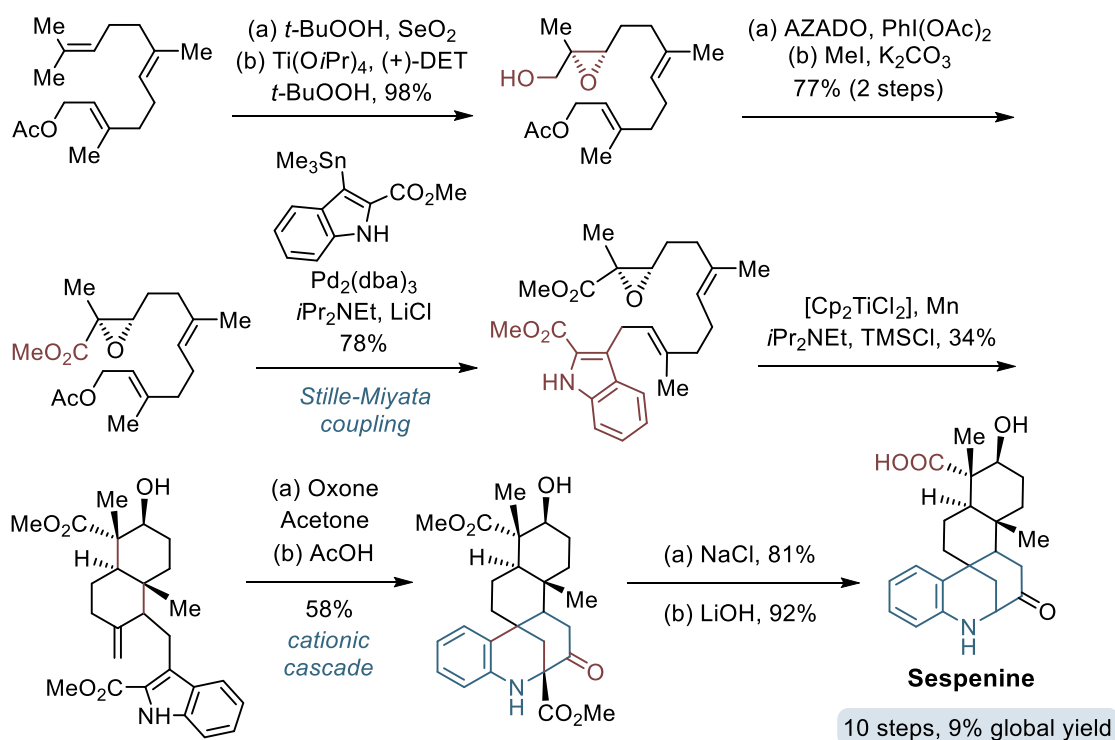


Scheme 3.8: First-generation synthesis of sespenine by Li et al.

Subsequently, in 2016, the group developed an optimized version based on their earlier work, successfully reducing the number of steps to 10 and doubling the overall yield to 9%.²⁰ The improved approach utilized a more advanced starting material, which incorporated the indole fragment prior to the biomimetic cyclization step. This strategic adjustment minimized unnecessary transformations, such as protection and

deprotection steps, thereby streamlining the synthesis and enhancing its efficiency (Scheme 3.9).

The synthesis began with an allylic oxidation and an enantioselective Sharpless epoxidation. This was followed by regioselective oxidation of the alcohol group, using the nitroxyl radical catalyst AZADO and $\text{PhI}(\text{OAc})_2$, after which methylation afforded an ester. The sequence continued with a Stille–Miyata coupling for the early installation of the indole fragment. Then, a Ti^{III} -mediated reductive epoxide-opening radical cyclization produced a *trans*-decalin intermediate bearing a 2-methoxycarbonylindole side chain. Oxidation of this intermediate yielded an isomeric mixture of 3-hydroxyindolenines. Exposure of the major isomer to acidic conditions triggered a cationic cascade comprising a Prins cyclization, a Friedel–Crafts reaction, and a retro-Friedel–Crafts step, giving access to the 3,4-benzomorphan motif. The synthesis ended with a Krapcho demethoxycarbonylation followed by basic hydrolysis, giving sespenine in 9% yield over ten steps.



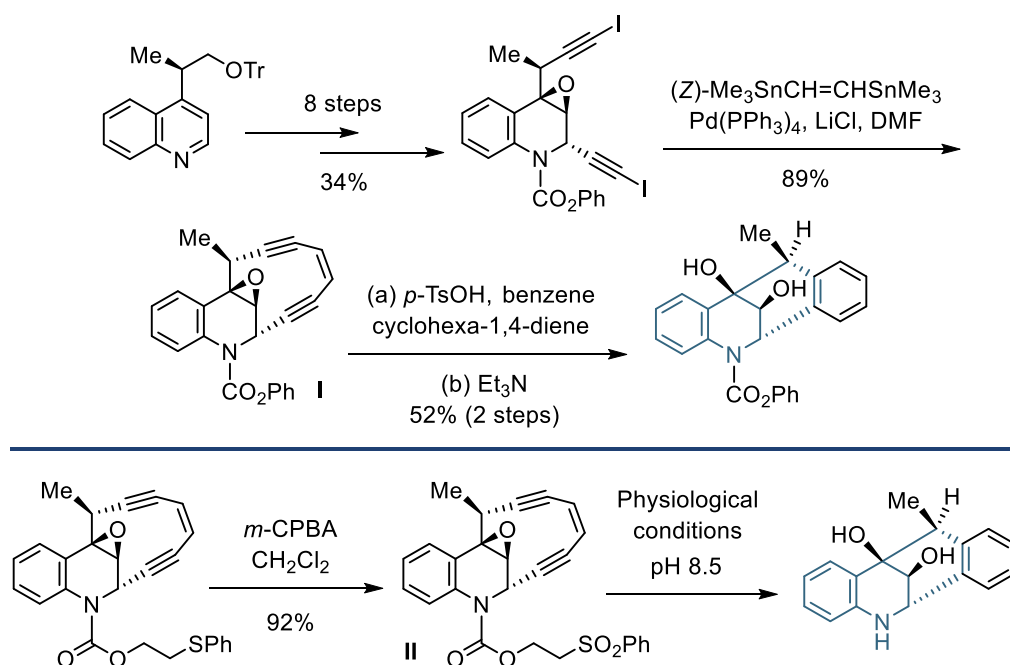
Scheme 3.9: Second-generation synthesis of sespenine by Li et al.

Riva developed a methodology to access a simplified analog of enediyne antibiotics (Scheme 3.10). These bioactive compounds feature a 10-membered 3-ene-1,5-diyne

cyclic scaffold and an epoxide motif with a *trans* relative configuration with respect to the unsaturated ring. Opening of this epoxide promotes a Bergman cycloaromatization to generate the 3,4-benzomorphan scaffold, which could be responsible for their significant bioactivity.²¹

The synthesis of the targeted compound began with the elaboration of a quinoline derivative over eight steps, furnishing a bisiodide intermediate in 34% yield. The key 3-ene-1,5-diyne precursor **I** was formed via a Stille coupling. Subsequent treatment with *p*-TsOH induced epoxide opening and Bergman cyclization, leading to the formation of the azatricyclic product. Although the benzazocine could be successfully synthesized, the epoxide opening of the diyne precursor could not be induced under physiological conditions. To overcome this, the phenyl carbamate protecting group was replaced with a 2-sulfonyl ethyl carbamate, which undergoes β -elimination at pH 8.5.

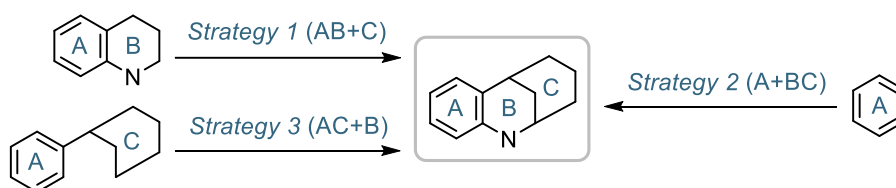
Diyne **I** and **II** were tested for DNA cleavage activity using supercoiled plasmid pBR322. As anticipated, **I** was inactive, whereas the modified enediyne **II** demonstrated activity at concentrations ranging from 1 to 5 μ M via a β -elimination/nitrogen-promoted epoxide opening/cycloaromatization pathway.



Scheme 3.10: Formation of the 3,4-benzomorphan motif via cyclization of enediyne.

3.1.3 Synthetic strategies toward the 3,4-benzomorphan scaffold

This section will outline the reported synthetic methods for constructing this azatricyclic system, categorized by the sequence of ring formation. Strategy 1 involves fusing a preformed tetrahydroquinoline scaffold with ring C. Strategy 2 modifies a phenyl ring to integrate a 2-azabicyclo[3.3.1] nonane structure. Strategy 3 starts with a cyclohexylbenzene framework, which reacts to form the nitrogenated ring of the targeted system, and represents the most common approach (*Scheme 3.11*).



Scheme 3.11: Synthetic approaches toward the 3,4-benzomorphan scaffold.

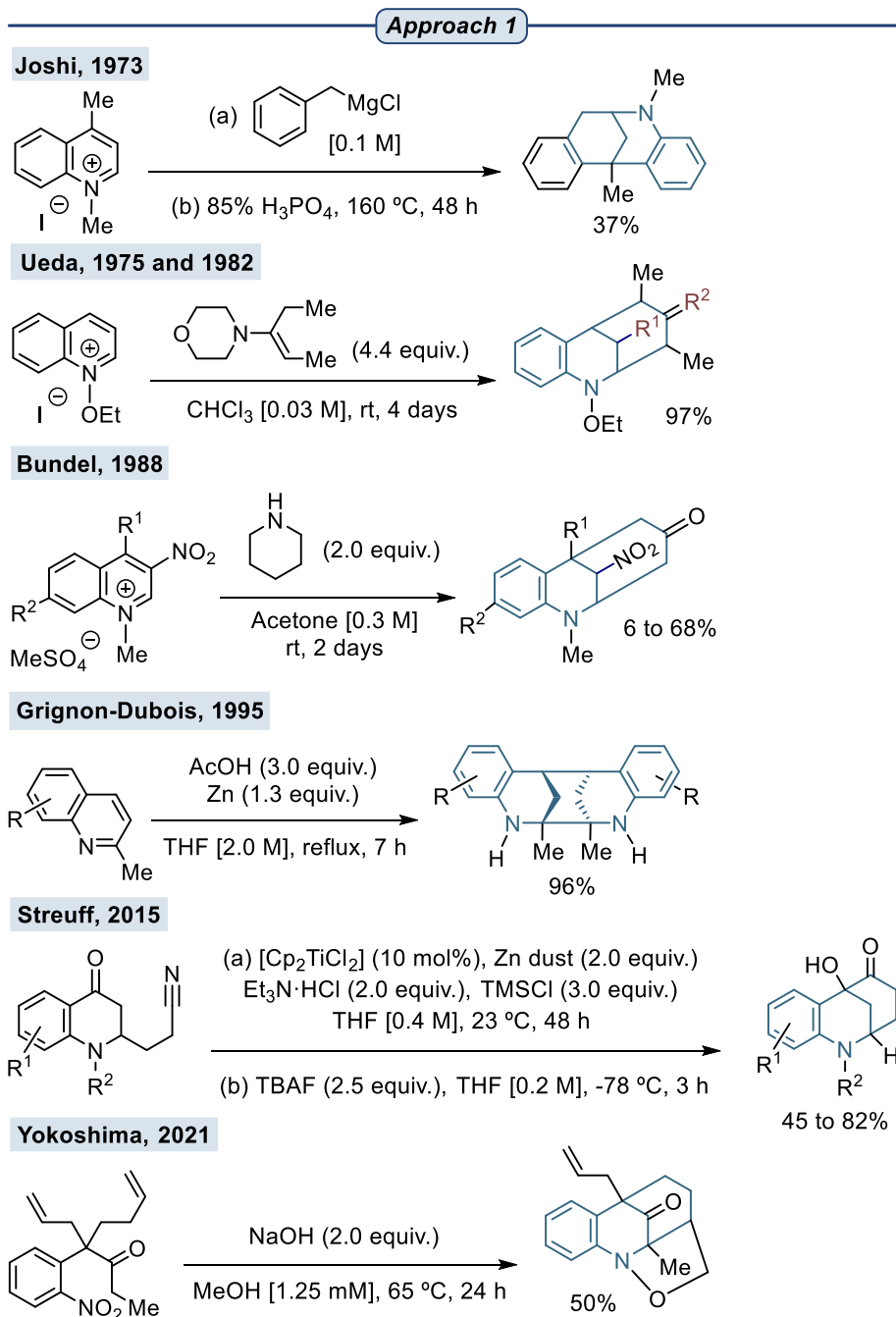
Strategy 1: Starting with a quinoline framework

Between 1970 and 1990, three groups developed strategies to synthesize the hexahydro-2,6-methano-1-benzazocine scaffold using quinolinium salts (*Scheme 3.12*). Joshi first demonstrated that 4-alkyl and 3,4-dialkyl pyridine aryl iodides could undergo Grewe's morphinan synthesis to produce benzomorphan derivatives, yielding a tetracyclic product.²² Shortly after, Ueda and coworkers found that *N*-ethoxyquinolinium salts reacted with enamines at the quinoline 2- and 4-positions, enabling the first synthesis of a tricyclic 3,4-benzomorphan compound.²³ Building on Ueda's work, Bundel showed that ketones reacting at the 2- and 4-positions of 3-nitroquinolinium salts could generate the desired azatricyclic core.²⁴

In 1995, Grignon-Dubois utilized zinc and acetic acid to treat quinaldine, achieving an excellent yield of Heller's dimer. This work marked one of the earliest applications of Zn/AcOH in heteroaromatic chemistry.²⁵

More recently, Streuff introduced a Ti^{III}-catalyzed double-reductive umpolung strategy for efficiently assembling bridged benzazocines from quinolone precursors. The method involved a reductive cross-coupling with a Michael acceptor at the quinolone C2 position, followed by Ti^{III}-mediated reductive ketonitrile cyclization to give the desired benzazocines with yields ranging from 45 to 82%.²⁶

In 2021, Yokoshima demonstrated that ketones bearing a 2-nitrophenyl group at the α -position reacted smoothly with NaOH in methanol at 65 °C. Under these conditions, the generated enolates underwent an intramolecular reaction with the nitro group to give various nitrones, which, upon inter- or intramolecular cycloaddition with alkenes, led to the formation of polycyclic isoxazolidines.²⁷



Scheme 3.12: Synthesis of 3,4-benzomorphans from quinoline precursors.

Strategy 2: Incorporation of 2-azabicyclo[3.3.1]nonane

McWhorter and coworkers employed 2-aryl indole derivatives in the total synthesis of 8-desbromohinckdentine A (*Scheme 3.13*). Their method involved reacting 2-(2-bromophenyl)-3*H*-indol-3-one with 3-butenylmagnesium bromide via a Grignard reaction, resulting in the formation of 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol. Upon treatment with formic acid under reflux, a novel aza-Prins cyclization/phenolium-like rearrangement occurred, accessing a compound containing the 3,4-benzomorphan core along with a pinacol-like rearrangement product.²⁸

In 2009, Yao employed isochromenilium tetrafluoroborate (ICTB) precursors in a metal-free cascade reaction to synthesize polycyclic frameworks with benzazocine cores. While efficient transformations involving ICTBs had been previously reported, this was the first study to describe an extended cationic cascade in which cationic intermediates were trapped to form complex polycyclic structures found in natural products. The process involved a [4+2] cycloaddition between the ICTB precursor and an engineered styrene or allyl group with *N*- or *O*-based functionalities, followed by intramolecular oxonium trapping to yield the cyclized products in good yields.²⁹

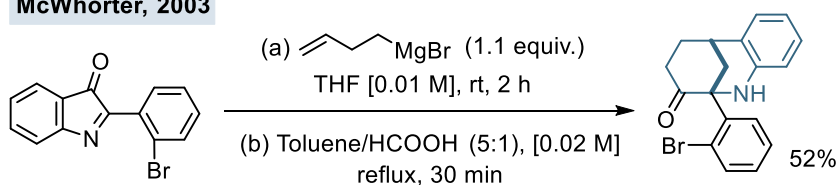
In 2016, Xu proposed a domino approach to synthesize 3,4-benzomorphan derivatives, utilizing a [5+1]/hemiaminalization sequence involving (2-aminoaryl)divinyl ketones, nitroalkanes, and activated methylene reagents under mild conditions, achieving high regio- and stereoselectivity. This method efficiently set four stereocenters in the 3,4-benzomorphan framework without isolating intermediates. Mechanistically, the process started with a DBU-promoted Michael addition between the divinyl ketone and the nucleophile (e.g., nitromethane). After deprotonation, an intramolecular Michael addition occurred, with the nucleophile attacking the less hindered face, thus forming the *anti*-diastereomer of the cyclohexanone intermediate. Finally, an intramolecular semiaminalization of the cyclohexanone led to the benzazocine product.³⁰

Building on a similar electrophilic amination/aza-Prins cyclization/phenolium-like cascade outlined in McWhorter's earlier work, You and coworkers recently introduced an enantioselective approach for synthesizing aza-[3.3.1]-bicyclic enamines and ketones. This innovative approach utilized a specially designed fluorine-containing chiral

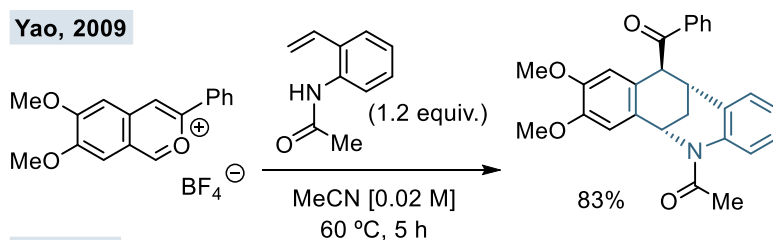
phosphoric acid catalyst, delivering the target products with high yields and excellent enantioselectivities. Notably, the reaction outcome was tunable: the presence or absence of water as an additive selectively steered the pathway toward either enamine or ketone formation.³¹

Approach 2

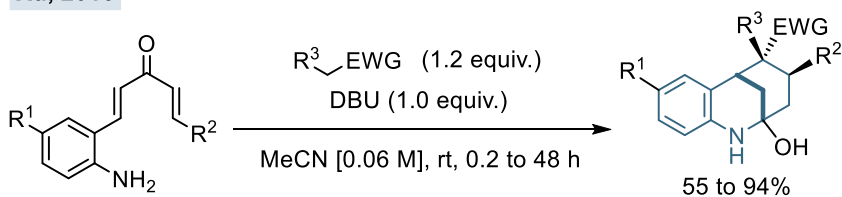
McWhorter, 2003



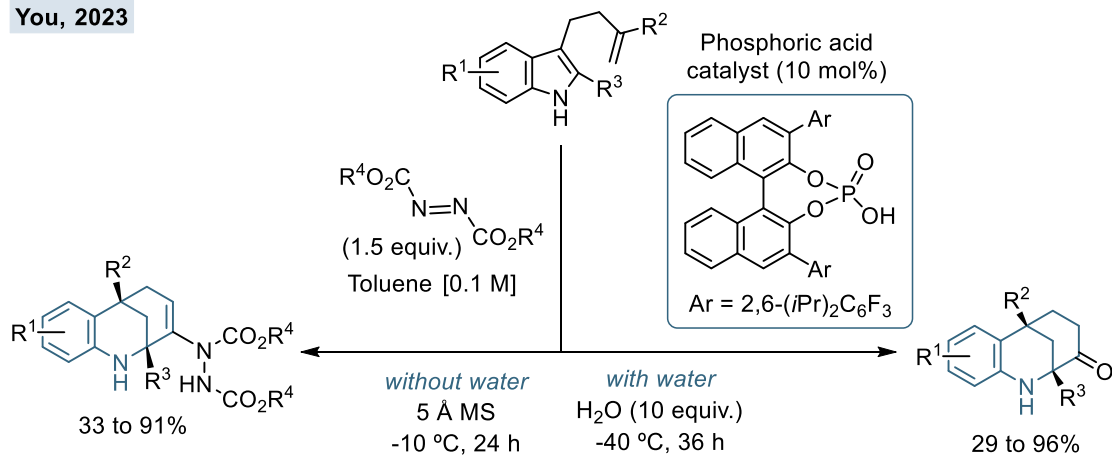
Yao, 2009



Xu, 2016



You, 2023



Scheme 3.13: 3,4-benzomorphane synthesis by 2-azabicyclo[3.3.1]nonane incorporation.

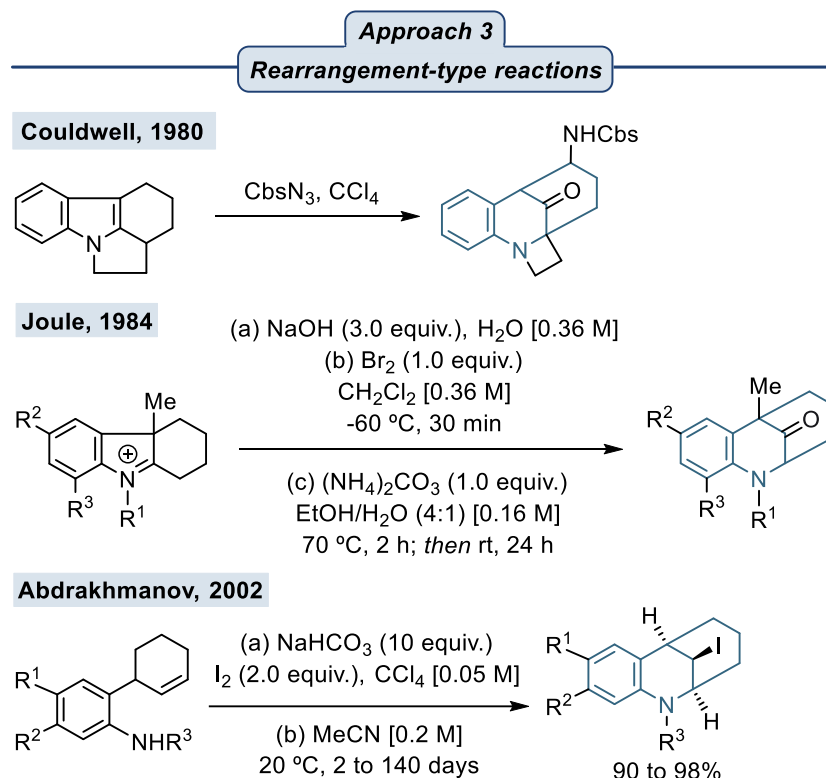
Strategy 3: Formation of the nitrogenated ring

To enhance clarity, this section is organized into four categories based on the type of transformation used to construct the benzazocine core: rearrangement reactions, photochemical processes, palladium-catalyzed methodologies, and redox cyclizations.

Rearrangement-type reactions

Up to now, three approaches toward the azatricyclic structure through a rearrangement of indole-type precursors have been published (*Scheme 3.14*). In 1980, Couldwell demonstrated that by reacting with *p*-chlorobenzenesulfonyl azide in CCl_4 , a tetrahydrocarbazole precursor could rearrange into a tetracyclic 3,4-benzomorphan.³² Building upon this work, Joule proposed an alternative strategy for the formation of the azatricyclic core from tetrahydrocarbazole precursors. The reaction involved the quaternization of an imine, followed by deprotonation to generate an enamine intermediate, which was then brominated. Subsequent rearrangement using ethanolic ammonium carbonate yielded the 3,4-benzomorphan framework.³³

In 2002, Abdrakhmanov discovered that 2-(cyclohex-2-enyl)anilines reacted with iodine and NaHCO_3 in CCl_4 to give hexahydrocarbazoles. These intermediates underwent isomerization in acetonitrile to give benzazocines, although the process could require up to 140 days depending on the substitution pattern.³⁴

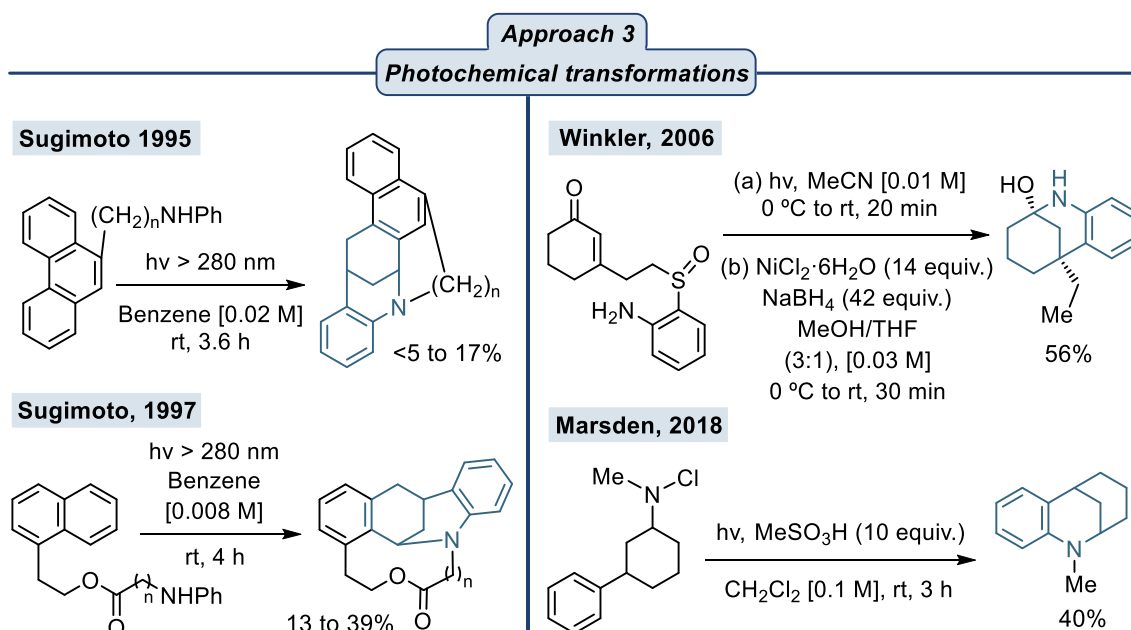


Scheme 3.14: Synthesis of 3,4-benzomorphans via rearrangement-type reactions.

Photochemical transformations

The early syntheses of the desired core using photoirradiation resulted in the formation of intricate polycyclic structures featuring the benzazocine motif (*Scheme 3.15*). In 1995, Sugimoto reported that subjecting 9-(ω -anilinoalkyl)phenanthrenes to irradiation in benzene under anaerobic conditions led to the formation of polycyclic compounds containing the 2-azabicyclo[3.3.1]nonane framework by means of a cyclization at the 6,8-positions of the phenanthrene ring.³⁵ Shortly after, the same group developed an analogous methodology for the synthesis of tricyclic lactones from 2-(1-naphthyl)ethyl ω -anilinoalkanoates, which were subsequently reduced and acetylated.³⁶

Recent approaches to the benzomorphan scaffold include the photoirradiation of simpler substrates, yielding more practical tricyclic products. In 2006, Winkler developed a reductive photochemical rearrangement of aromatic sulfoxides, producing various heterocycles, including a 3,4-benzomorphan.³⁷ In a later study, Marsden presented a metal-free radical approach for the amination of aromatic C–H bonds. This method relied on UV photolysis of secondary *N*-chloroamine precursors, generating a protonated aminium radical that underwent *ortho*-cyclization. Among the examples, the cyclization of an *N*-chloroamine derived from 3-phenylcyclohexylamine produced a 3,4-benzomorphan.³⁸



Scheme 3.15: Synthesis of 3,4-benzomorphans via photochemical reactions.

Palladium-catalyzed reactions

The palladium-catalyzed coupling of aryl halides with ketone enolates efficiently yields α -aryl ketones, but intramolecular applications remain rare despite their potential for synthesizing complex polycycles. In 2001, our group developed a Pd-catalyzed intramolecular coupling of 2-haloanilines with ketone enolates to furnish 2,6-methano-1-benzazocines, optimizing the conditions into three general procedures (*Scheme 3.16*).³⁹ Based on this precedent, in 2016, Jia developed an enantioselective version of the reaction catalyzed by palladium and *L*-proline. The transformation was thought to proceed via an intramolecular Heck reaction of an in situ formed chiral enamine.⁴⁰

Two years later, Banwell introduced a palladium-catalyzed Ullman cross-coupling between β -iodoenones or β -iodoacrylates and *o*-halonitroarenes or *o*-iodobenzonitriles, followed by reductive cyclization to furnish diverse heterocyclic structures, including benzomorphan derivatives.⁴¹

In 2019, Zhou's group designed a palladium/norbornene-catalyzed Catellani-type annulation that featured an *ortho*-C–H amination followed by an intramolecular α -arylation cascade using aryl iodides and functionalized amination reagents. While the approach utilized cyclization precursors similar to those employed in both our work and Jia's, it provided a modular and convergent route to the bridged scaffold, leveraging simpler starting materials.⁴²

Shortly after, Tang developed a palladium-catalyzed dearomative cyclization to construct eight bridged tetracyclic frameworks, including two examples of 3,4-benzomorphans. This approach utilized a site-selective cross-coupling between an aryl halide and the phenol ring, achieving high yields with excellent regio- and chemoselectivity. Additionally, employing a chiral palladium catalyst facilitated the synthesis of enantiomerically enriched bridged structures with up to 99% enantiomeric excess.⁴³

In 2021, Nelson developed a strategy to access 30 diverse tridimensional scaffolds, including three containing the benzazocine core. The process involved an amine-directed C–H (het)arylation of mono- or bicyclic amines, resulting in a *syn*-relationship between the amine and the (het)aryl group, followed by a Pd-catalyzed cyclization.⁴⁴

Approach 3

Palladium-catalyzed reactions

Bonjoch, 2001 and 2003

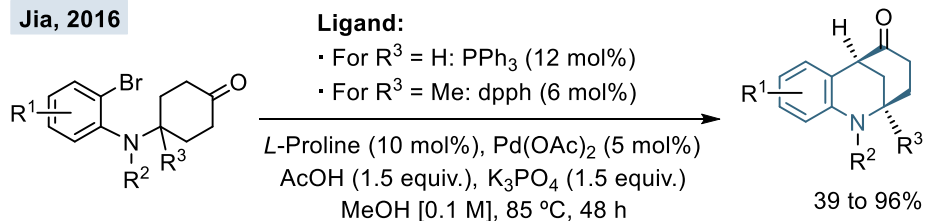


Method A: $\text{Pd}(\text{PPh}_3)_4$ (0.2 equiv.), KOt-Bu (3.0 equiv.), THF [0.020 M], reflux, 3.5 h

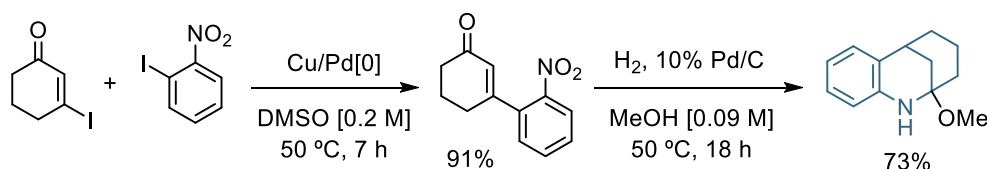
Method B: $\text{PdCl}_2(\text{PPh}_3)_2$ (0.2 equiv.), Cs_2CO_3 (3.0 equiv.), THF [0.028 M], 100–110 °C, sealed tube, 24 h

Method C: $\text{Pd}(\text{PPh}_3)_4$ (0.2 equiv.), K_3PO_4 (3.0 equiv.), THF [0.025 M], 100–110 °C, sealed tube, 24 h

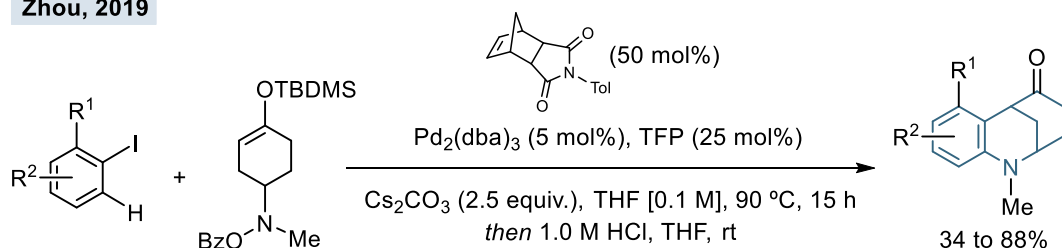
Jia, 2016



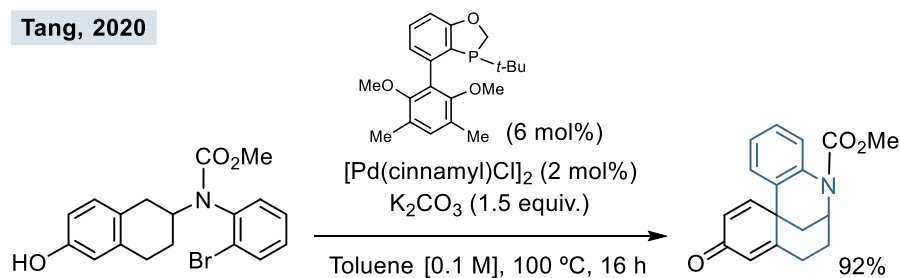
Banwell, 2018



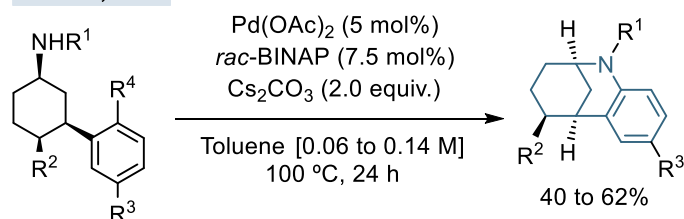
Zhou, 2019



Tang, 2020



Nelson, 2021



Scheme 3.16: Synthesis of 3,4-benzomorphans via Pd-catalyzed reactions.

Redox cyclizations

The first reduction-based routes to the benzazocine scaffold were accidentally discovered by our group while treating various nitrophenyl ketones with different bases. In 1994, efforts to formylate an α -nitrophenyl ketone during the synthesis of *Strychnos* indole alkaloids unexpectedly produced a pyrrolobenzazocine framework via reductive cyclization. The mechanism involved a base-mediated deprotonation of the α -carbon, followed by intramolecular enolate attack on the nitro group with concomitant nitro reduction to a hydroxylamine intermediate, and subsequent amidinium-cation-driven reduction to yield the benzomorphan structure (*Scheme 3.17*).⁴⁵

Years later, our group discovered that propargylic and vinyl iodide precursors could also be transformed into the 3,4-benzomorphan framework under two distinct reaction conditions. The TBAF/DMF cyclization was postulated to proceed via a nucleophilic attack of the enolate on the nitro group, followed by formylation. Reduction and CO₂ elimination would lead to a deprotonated hydroxylamine intermediate, which could undergo further reduction to yield the azatricyclic product. A similar mechanism was proposed for the CuI-promoted reaction, with Cu⁺ as the reducing agent.⁴⁶

In 2007, during studies on the total synthesis of strychnopivotine, our group also observed that a complex aniline was a suitable precursor for the formation of the 3,4-benzomorphan framework by exposure to acidic conditions, which triggered the hydrolysis of the acetal moiety followed by the formation of a hemiaminal species.⁴⁷

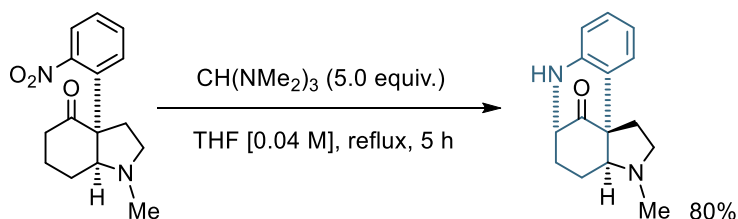
In the context of the first total synthesis of (+)-welwitindolinone A isonitrile by Wood, a substrate containing the benzazocine ring system was isolated by treatment with Kagan's reagent. The starting aniline was exposed to reductive conditions, affording the 3,4-benzomorphan in 19% yield as a result of the 1,4-reduction of the enone moiety.⁴⁸

In 2008, Clive and coworkers introduced a strategy to synthesize linearly fused, angularly fused, and bridged nitrogen heterocycles via a formal oxidative radical cyclization of an sp³-hybridized carbon onto a benzene ring. *p*-Iodophenols, particularly those with a MOM-protected phenolic oxygen, were coupled with amino alcohols to form *N*-aryl amino alcohols. These were then converted into iodide derivatives after nitrogen protection with a carbamate group. Removal of the phenolic protection followed by

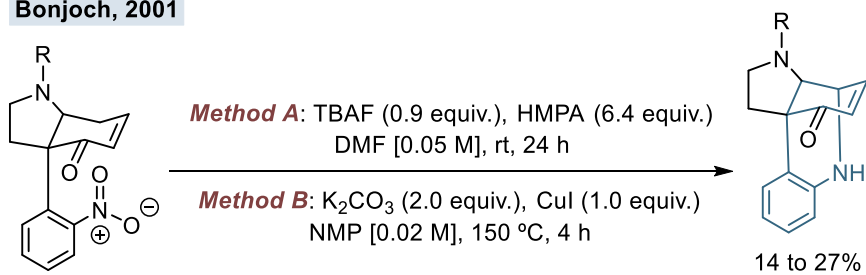
oxidation with $\text{PhI}(\text{OAc})_2$ in methanol yielded cross-conjugated ketones. These underwent 5-, 6-, or 7-*exo-trig* oxidative radical cyclizations, followed by rearomatization under acidic conditions, resulting in nitrogenated heterocycles, including one example featuring the benzazocine core.⁴⁹

Approach 3
Redox cyclizations

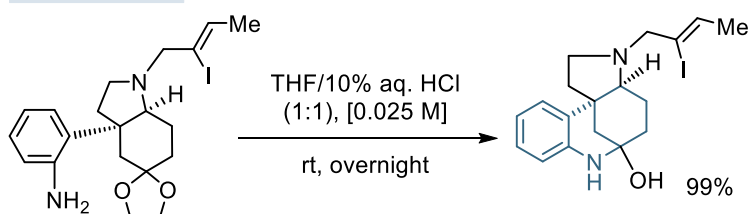
Bonjoch, 1994



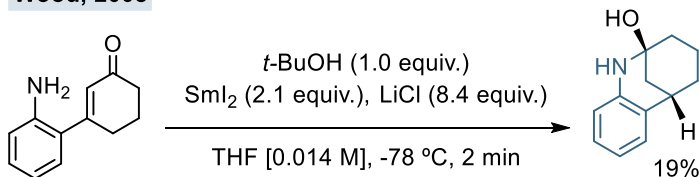
Bonjoch, 2001



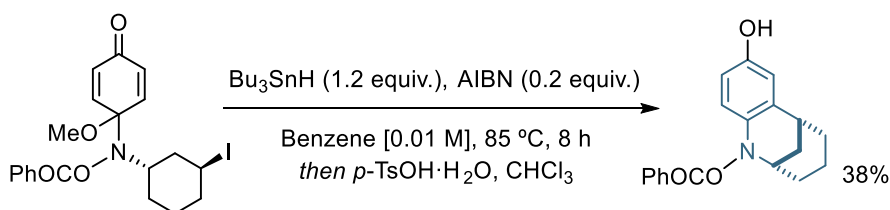
Bonjoch, 2007



Wood, 2008



Clive, 2008

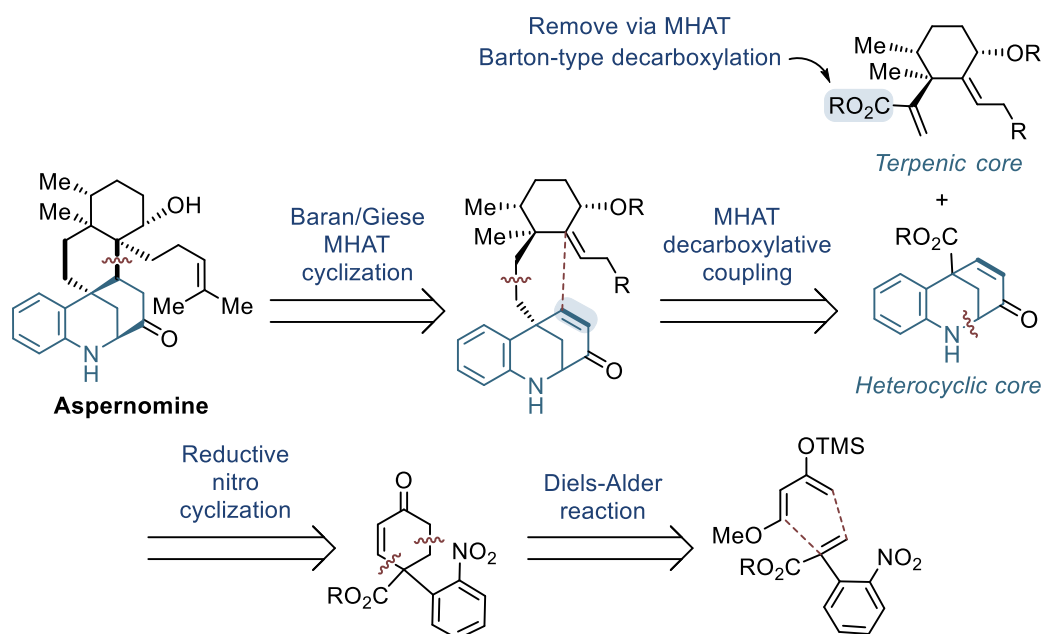


Scheme 3.17: Synthesis of 3,4-benzomorphans via redox cyclizations.

3.1.4 Proposed retrosynthesis of aspernomine

As noted in *Section 3.1.1*, efficient syntheses of anominine-related metabolites often rely on modular strategies, where key fragments are prepared separately and then coupled. Inspired by these approaches, we proposed a convergent strategy for the total synthesis of aspernomine, focusing on the preparation of its heterocyclic and terpenic components for late-stage coupling (*Scheme 3.18*). We aimed to form the key C–C bonds through an MHAT-mediated decarboxylative coupling—the development of which will be discussed in Chapter 4— followed by an MHAT Barton-type decarboxylation to remove the ester group and a classical Giese addition to complete the pentacyclic framework.

The synthesis of the heterocyclic core, which will be discussed in the present chapter, will comprise a Diels–Alder reaction, followed by a base-mediated reductive intramolecular coupling of nitrophenyl ketones, building on precedents discussed earlier in the introduction section (see *Scheme 3.17*). This approach offers an efficient and modular construction of the azatricyclic system, setting the stage for the key coupling between the tricycle and the terpenic fragment.

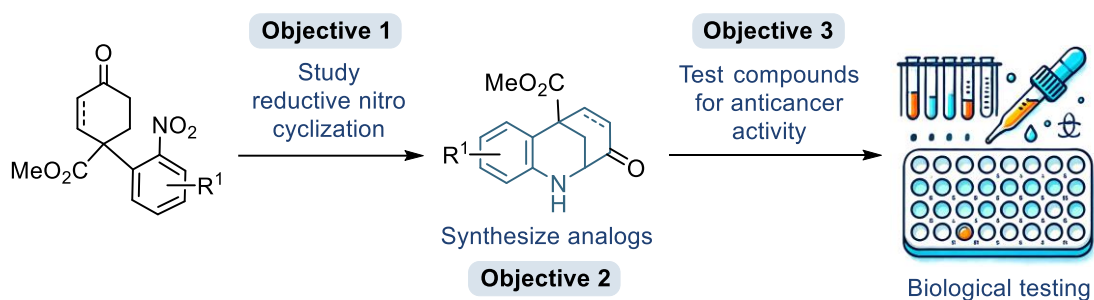


Scheme 3.18: Proposed retrosynthesis toward aspernomine.

3.2 OBJECTIVES

Building on the retrosynthetic framework presented in the preceding section, the main objective of this chapter was to synthesize the 3,4-benzomorphan fragment of aspernomine using nitrophenyl-type precursors (*Scheme 3.19*). Accessing this structure would provide a valuable intermediate for the total synthesis of the natural product. Additionally, from a function-oriented synthesis perspective, we propose that the heterocyclic scaffold is likely responsible for the cytotoxic properties of aspernomine. This hypothesis is supported by the fact that aspernomine is the only member of the anominine family known to possess such biological activity and that uniquely contains a benzomorphan ring system. Consequently, we postulate that synthesizing aspernomine-like benzomorphan derivatives could preserve, or potentially enhance, its bioactivity while simultaneously streamlining the synthetic route.

From a synthetic point of view, the first goal of this chapter would be to determine the optimal conditions for the key cyclization step (*Objective 1*). Next, we would explore the substrate scope by introducing various substituents on the aromatic ring (*Objective 2*). Finally, we would assess the biological properties of the synthesized products to determine whether the bioactivity of aspernomine is dependent on its full structure or primarily on the azatricyclic core (*Objective 3*).

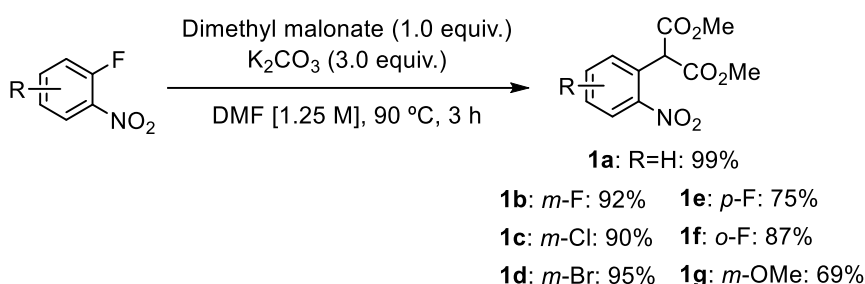


Scheme 3.19: Main objectives of Chapter 3.

3.3 RESULTS AND DISCUSSION

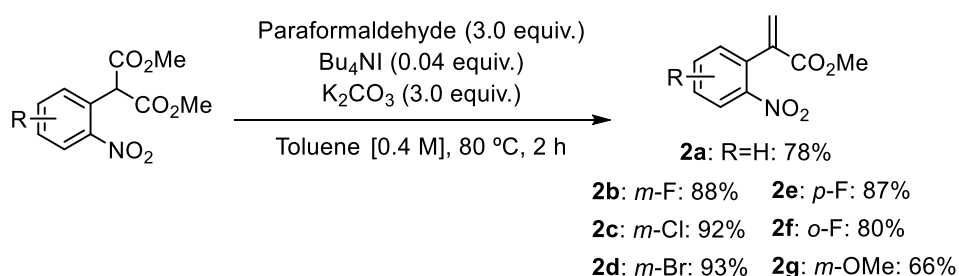
3.3.1 Optimization of the reaction conditions

For the preparation of the dienophile for the Diels–Alder coupling, selected 2-fluoronitrobenzenes were treated with dimethyl malonate and K_2CO_3 in DMF for 3 hours at 90 °C,⁵⁰ obtaining nitromalonates **1a–1g** in yields ranging from 69 to 99%. Notably, the presence of an electron-donating group on the aromatic ring slightly reduced the reaction efficiency. Furthermore, competition in the nucleophilic substitution with a *para*-F substituent also had a minor impact on the yield (*Scheme 3.20*).



Scheme 3.20: Synthesis of malonates 1a–1g.

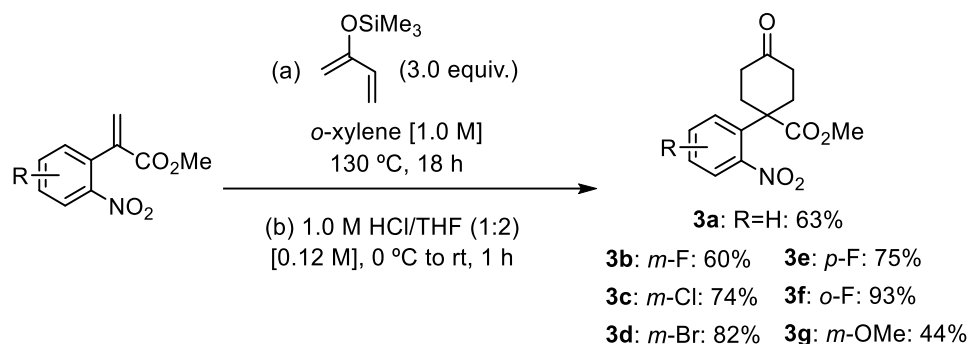
Then, the treatment of malonates **1a–1g** with paraformaldehyde, Bu_4NI and K_2CO_3 in a toluene solution for 2 hours at 80 °C furnished acrylates **2a–2g** in good to excellent yields (*Scheme 3.21*).⁵¹ In this case, the introduction of an electron-withdrawing group in the aromatic ring was beneficial for the efficiency, while the presence of a methoxy group lowered the yield.



Scheme 3.21: Synthesis of acrylates 2a–2g.

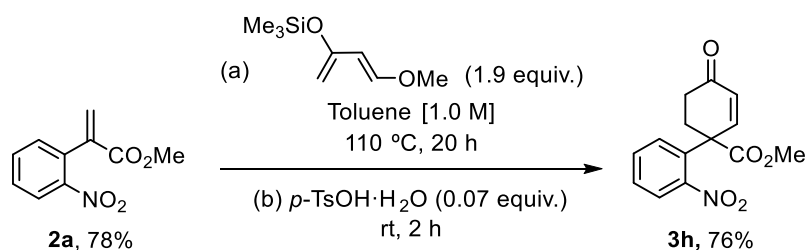
Subsequently, the Diels–Alder coupling of the acrylates with 2-(trimethylsiloxy)-1,3-butadiene in an *o*-xylene solution for 18 hours at 130 °C provided the targeted products as a mixture of the ketone form and the trimethylsilyl enol ether. Therefore, an acidic

hydrolysis of the mixtures was required to obtain nitrophenyl ketones **3a–3g** in yields ranging from 44 to 93%.⁵² As expected, electron-poor aromatic rings gave better yields in the coupling, as they increased the electrophilicity of the dienophile (*Scheme 3.22*).



Scheme 3.22: Synthesis of nitrophenyl ketones 3a–3g via Diels–Alder reaction.

As observed earlier in the proposed retrosynthesis of aspernomine, the required heterocyclic fragment should bear an enone functionality for further elaboration into the natural product. Thus, following an analogous protocol, acrylate **2a** reacted with Danishefsky's diene in toluene for 20 hours at $110\text{ }^\circ\text{C}$ to provide the α,β -unsaturated nitrophenyl ketone **3h** in 76% yield upon acidic hydrolysis (*Scheme 3.23*).⁵³



Scheme 3.23: Synthesis of 3h via Diels–Alder reaction with Danishefsky's diene.

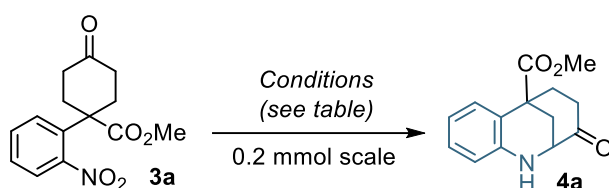
To optimize the cyclization reaction to furnish the azatricyclic core, methyl-1-(2-nitrophenyl)-4-oxocyclohexane carboxylate (**3a**) was selected as a model system due to its structural simplicity. The results are summarized in *Table 3.1*. Based on precedents from our research group,⁴⁵ early attempts using Brederick's reagents were unsuccessful (*entries 1 and 2*). Then, when TBAF and HMPA in DMF were used (*entry 3*),⁴⁶ the cyclized compound **4a** could be observed albeit in low yield and with significant recovery of starting material.

Conducting the reaction in the presence of K_2CO_3 and CuI in DMF provided a better 37% yield (*entry 4*).⁴⁶ However, omitting copper iodide had no effect on the outcome of the reaction (*entry 5*), demonstrating that it did not play a role in the transformation. At this stage, alternative bases such as Cs_2CO_3 and *L*-proline⁵⁴ were evaluated (*entries 6 and 7*). However, Cs_2CO_3 delivered reduced efficiency, while *L*-proline failed to promote the reaction entirely. Then, we discovered that microwave irradiation improved the efficiency and reduced the reaction time from 4 hours to 15 minutes (*entry 8*). Additionally, doubling the amount of potassium carbonate afforded a marginally higher yield (*entry 9*). Under these new conditions, a variety of bases were screened. Among them, only Na_2CO_3 produced results comparable to K_2CO_3 , while KF, K_3PO_4 , and Et_3N showed minimal or no reactivity (*entries 10 to 13*).

As the reaction efficiency remained low, we explored other parameters. First, to increase the solubility of the base, which remained mostly in solid state during the reaction, we performed the cyclization in a DMF/ H_2O (9:1) mixture at 100 °C, but only achieved a 19% yield (*entry 14*). Next, we attempted to promote the cyclization using DMSO as the solvent, given its strong microwave-absorbing properties, but the outcome remained unsatisfactory (*entry 15*). The efficiency of the transformation was improved when NMP was used as the solvent (*entry 16*), and subsequent temperature optimization established 150 °C as optimal for the cyclization (*entries 17 and 18*). Increasing the amount of K_2CO_3 raised the yield to 55%. However, the absence of recovered starting material suggested that part of the substrate was decomposing (*entry 19*). Attempts to mitigate this by enhancing base solubility in MeOH (*entry 20*) or by using *o*-dichlorobenzene to promote microwave absorption (*entry 21*) were unsuccessful.

After optimizing the reaction under microwave irradiation, we tested the best conditions using a heating mantle for 1 hour and adding the substrate over 15 minutes (*entry 22*). Surprisingly, the efficiency remained largely unchanged, providing a 50% yield. A breakthrough came when we diluted the reaction to a 0.01 M concentration, isolating the product in an excellent 82% yield with minimal starting material decomposition (*entry 23*). Finally, scaling up to 1.0 mmol resulted in the obtention of the cyclized product in an 87% yield (*entry 24*).

Table 3.1: Optimization of the reaction conditions for the reductive cyclization.



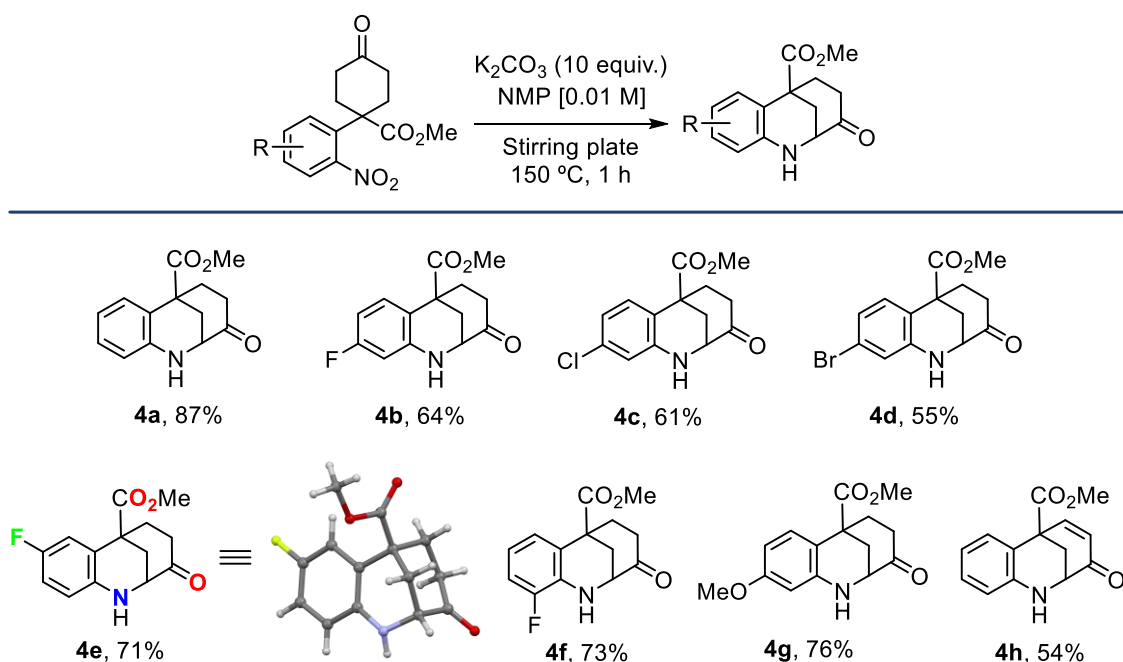
Entry	Solvent ^a	T (°C)	Time	Base	Yield (%)
1	THF	70	5 h	CH(NMe) ₃ (5.0 equiv.)	-
2	THF	70	5 h	CH(NMe) ₂ O ^t -Bu (3.0 equiv.)	-
3	DMF	rt	18 h	TBAF (2.0 equiv.) + HMPA (6.0 equiv.)	13
4	DMF	150	4 h	K ₂ CO ₃ (2.0 equiv.) + CuI (1.0 equiv.)	37
5	DMF	150	4 h	K ₂ CO ₃ (2.0 equiv.)	36
6	DMF	150	4 h	Cs ₂ CO ₃ (2.0 equiv.)	23
7	DMF	150	4 h	L-proline (2.0 equiv.)	-
8	DMF	150 ^b	15 min	K ₂ CO ₃ (2.0 equiv.)	40
9	DMF	150 ^b	15 min	K ₂ CO ₃ (4.0 equiv.)	44
10	DMF	150 ^b	15 min	Na ₂ CO ₃ (4.0 equiv.)	43
11	DMF	150 ^b	15 min	KF (4.0 equiv.)	15
12	DMF	150 ^b	15 min	K ₃ PO ₄ (4.0 equiv.)	4
13	DMF	85 ^b	15 min	Et ₃ N (4.0 equiv.)	-
14	DMF/H ₂ O (9:1)	100 ^b	15 min	K ₂ CO ₃ (4.0 equiv.)	19
15	DMSO	150 ^b	15 min	K ₂ CO ₃ (4.0 equiv.)	27
16	NMP	150 ^b	15 min	K ₂ CO ₃ (4.0 equiv.)	50
17	NMP	100 ^b	15 min	K ₂ CO ₃ (4.0 equiv.)	29
18	NMP	200 ^b	15 min	K ₂ CO ₃ (4.0 equiv.)	34
19	NMP	150 ^b	15 min	K ₂ CO ₃ (10 equiv.)	55
20	MeOH	rt	6 h	K ₂ CO ₃ (10 equiv.)	-
21	<i>o</i> -DCB	150 ^b	15 min	K ₂ CO ₃ (10 equiv.)	-
22 ^c	NMP	150	1 h	K ₂ CO ₃ (10 equiv.)	50
23 ^c	NMP ^d	150	1 h	K ₂ CO ₃ (10 equiv.)	82
24 ^{c,e}	NMP ^d	150	1 h	K ₂ CO ₃ (10 equiv.)	87

^a[0.04 M] unless indicated otherwise. ^bUse of microwaves. ^cAddition of the starting material over 15 minutes. ^d[0.01 M]. ^eThe reaction was carried out on a 1.0 mmol scale.

3.3.2 Substrate scope

Once the optimal reaction conditions for the cyclization of **3a** had been established, we proceeded to examine the scope of the transformation using precursors **3b–3h** (Scheme 3.24). Generally, the introduction of substituents in the aromatic ring resulted in lower but still satisfactory yields. Notably, the presence of halogens at the *meta* position (**4b–4d**) and the incorporation of an enone functionality in **4h** significantly reduced the yields. The latter case posed a particular challenge, as the enone moiety is essential for the proposed synthetic pathway to aspernomine (see Scheme 3.18). In contrast, fluorine atoms at the *para* (**4e**) and *ortho* (**4f**) positions, as well as the presence of an electron-donating group in **4g**, had a less pronounced impact on the reaction efficiency, demonstrating better compatibility with the cyclization conditions.

Among all of the isolated compounds, analog **4e** was the one that exhibited the most crystalline appearance. Therefore, it was selected for X-ray diffraction analysis to confirm its structure.

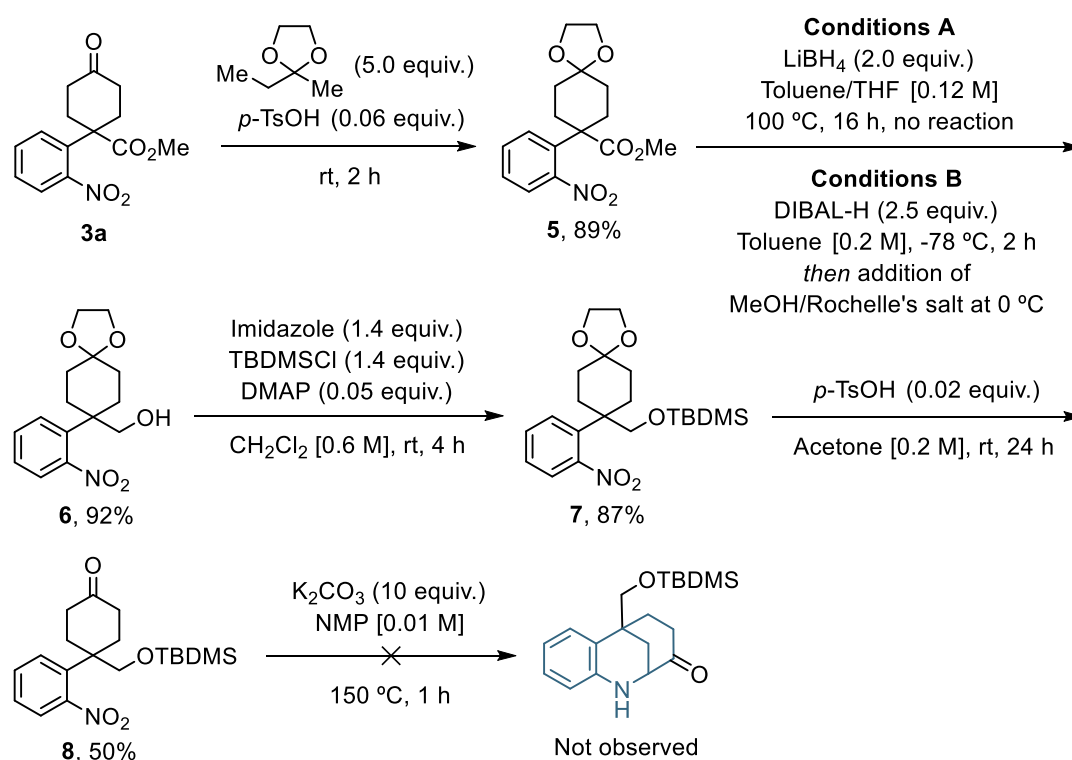


Scheme 3.24: Scope of the reductive cyclization and X-ray of **4e**.

After expanding the scope of nitrophenyl cyclohexanones bearing an ester moiety that could undergo the cyclization reaction, we explored an alternative route toward an ether precursor (Scheme 3.25). To address compatibility issues in subsequent steps, the ketone

functionality in **3a** was acetalized using 2-ethyl-2-methyl-1,3-dioxolane under acidic conditions to give **5** in 89% yield. Then, attempts to reduce the ester with LiBH_4 were unsuccessful with full recovery of the starting material,⁵⁵ but the use of DIBAL-H under previously reported conditions smoothly provided the desired alcohol **6** in 92% yield.⁵⁶

Protection of the alcohol with TBDMS chloride afforded the corresponding silyl ether **7** in 87% yield. At this stage, attempts to deprotect the acetal group to access the key reductive cyclization precursor **8** resulted in a mixture,⁵⁷ with the target compound as the major product alongside inseparable and unidentified impurities. Despite the challenges in isolating the pure compound, we proceeded with the proposed cyclization under optimized conditions. However, subsequent NMR analysis indicated that the product had not formed, and only a complex mixture of unidentified byproducts was observed.



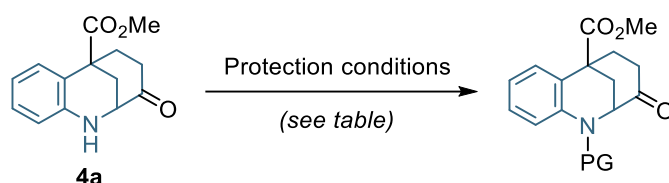
Scheme 3.25: Attempted synthesis of an ether-containing nitrophenyl ketone.

3.3.3 N-protection of the 3,4-benzomorphans derivatives

Upon prolonged storage, the benzazocine compounds exhibited partial degradation. Although the exact identities of the resulting byproducts could not be determined, post-storage filtration through silica revealed a notable decrease in the recovered quantities.

Therefore, with the aim of making these compounds easier to handle, we decided to protect the nitrogen atom using **4a** as a test substrate. However, initial attempts proved more challenging than anticipated, likely due to the poor nucleophilicity of the nitrogen atom caused by the neighboring electron-withdrawing groups. As shown in *Table 3.2*, attempted protection of the aniline using a range of protecting groups including tosyl chloride, benzyl chloroformate, acetic anhydride, methyl chloroformate and benzoyl chloride in the presence of various bases (Et_3N , DIPEA, NaH, K_2CO_3 or NaOH) did not lead to the formation of protected products. Moreover, in all cases, full recovery of starting material was observed.

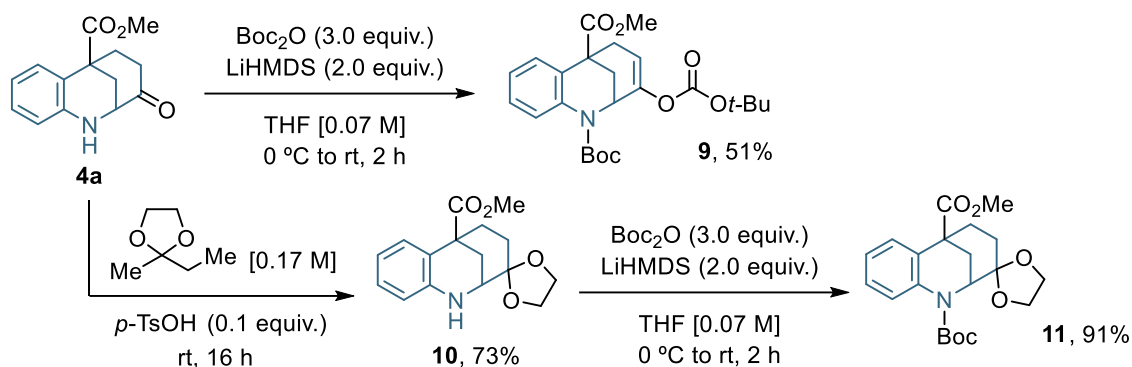
Table 3.2: Initial attempts to protect the nitrogen atom in 3,4-benzomorphan 4a.



Entry	Protecting group	Base	Conditions	Yield (%)
1	Tosyl chloride (1.8 equiv.)	Et_3N (3.0 equiv.) DMAP (1.0 equiv.)	CH_2Cl_2 [0.1 M] rt, 16 h	-
2	Benzyl chloroformate (3.0 equiv.)	DIPEA (4.0 equiv.)	CH_2Cl_2 [0.2 M] rt, 16 h	-
3	Benzyl chloroformate (3.0 equiv.)	NaH (2.0 equiv.) DMAP (0.3 equiv.)	THF [0.07 M] rt, 16 h	-
4	Acetic anhydride (0.08 M)	-	rt, 16 h	-
5	Methyl chloroformate (20 equiv.)	K_2CO_3 (10 equiv.)	DMF [0.08 M] 50 °C, 16 h	-
6	Benzoyl chloride (1.1 equiv.)	NaOH (3.0 equiv.)	Benzene/ H_2O (1:4) [0.08 M], rt, 16 h	-

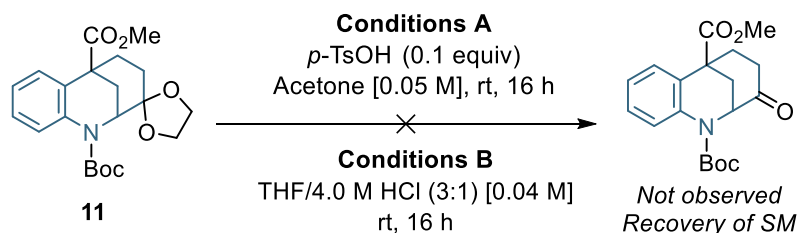
Notably, when the stronger base LiHMDS was used in combination with Boc anhydride, the protection of the nitrogen atom was achieved, accompanied by the unexpected *o*-*tert*-butoxycarbonylation of the ketone to furnish **9** in 51% yield. This suggests that the formation of an enolate occurred prior to the protection step, thereby enhancing the nucleophilic behavior of the aniline. Alongside this product, a portion of the starting material was also recovered (*Scheme 3.26*).

In light of these findings, the α -position of the ketone was blocked through the formation of acetal **10**, which proceeded smoothly in 73% yield. Notably, the nitrogen atom remained unprotonated during acetal protection. Subsequently, the previously established protection conditions were applied, affording the targeted *N*-Boc benzazocine **11** in excellent yield.



Scheme 3.26: N-Boc protection of benzazocine 4a.

With benzazocine **11** in hand, our next objective was the deprotection of the acetal group to regenerate the ketone. However, acidic hydrolysis using *p*-TsOH in acetone or a mixture of THF and aqueous HCl proved unsuccessful, resulting in complete recovery of the starting material (*Scheme 3.27*).



Scheme 3.27: Attempted acetal-deprotecting conditions.

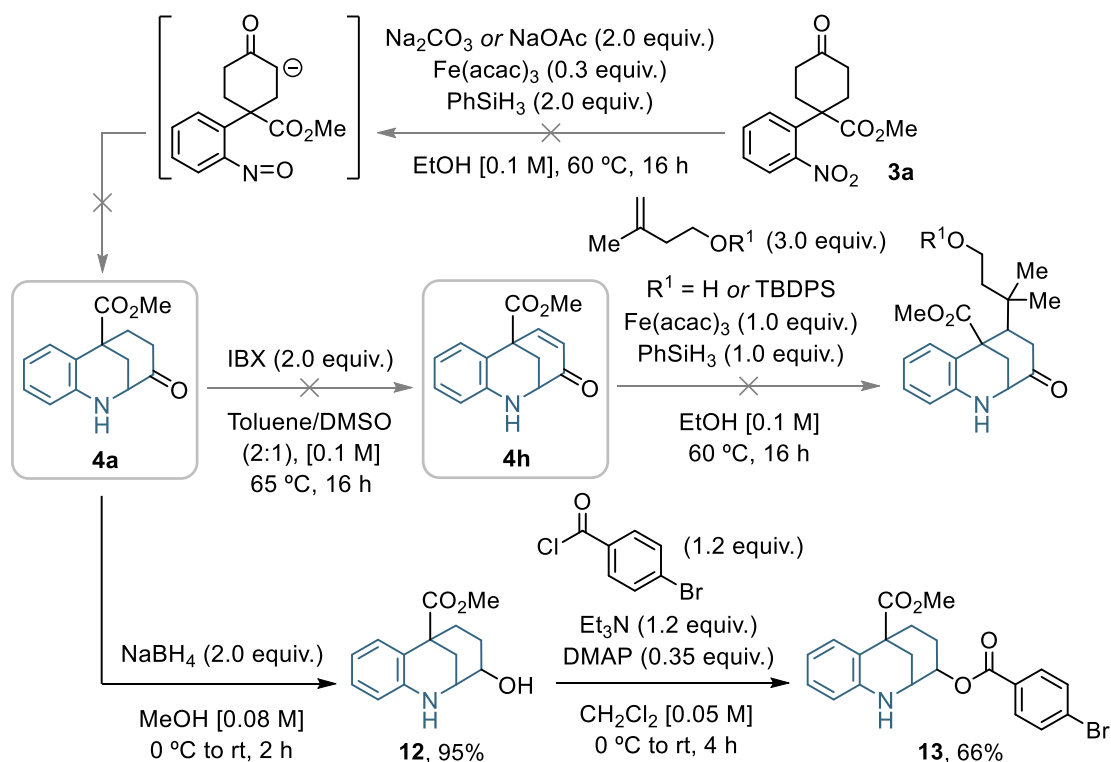
Although this outcome was unexpected and requires further investigation, it suggests that the structural framework is notably stable, likely due to the steric hindrance introduced by the Boc group. This feature could prove advantageous for the subsequent elaboration of the compound. For instance, it may allow for additional transformations involving acidic conditions while retaining the acetal protecting group. Once structural modifications had been introduced, the Boc group could potentially be removed with TFA, followed by acetal deprotection under milder conditions.

3.3.4 Additional reactivity of the 3,4-benzomorphans

During the evaluation of the reaction scope, benzazocine **4h** showed the lowest yield. However, due to limited trials and potential reaction variability, further optimization could improve results, given the precursor's importance for aspernomine synthesis. As an alternative approach, we also attempted to obtain **4h** from **4a** via oxidation with IBX in a toluene/DMSO solution at 65 °C overnight (Scheme 3.28).⁵⁸ Unfortunately, the targeted product did not form, and we only isolated starting material.

To evaluate an alternative to acetal protection, we tested the reduction of **4a** with sodium borohydride, but it yielded a diastereomeric mixture of alcohol **12** instead of a single stereoisomer. Subsequent protection with 4-bromobenzoyl chloride in the presence of triethylamine and DMAP gave **13** in 66% yield. However, the need to work with a mixture of isomers made this approach unsuitable.

Drawing on our expertise in MHAT reactions, we attempted the reductive cyclization of **3a** using Na₂CO₃ or NaOAc as bases, expecting the reaction to proceed via a nitroso intermediate.⁵⁹ However, these conditions failed to yield the desired product, instead producing byproducts containing alcohol or nitroso groups.



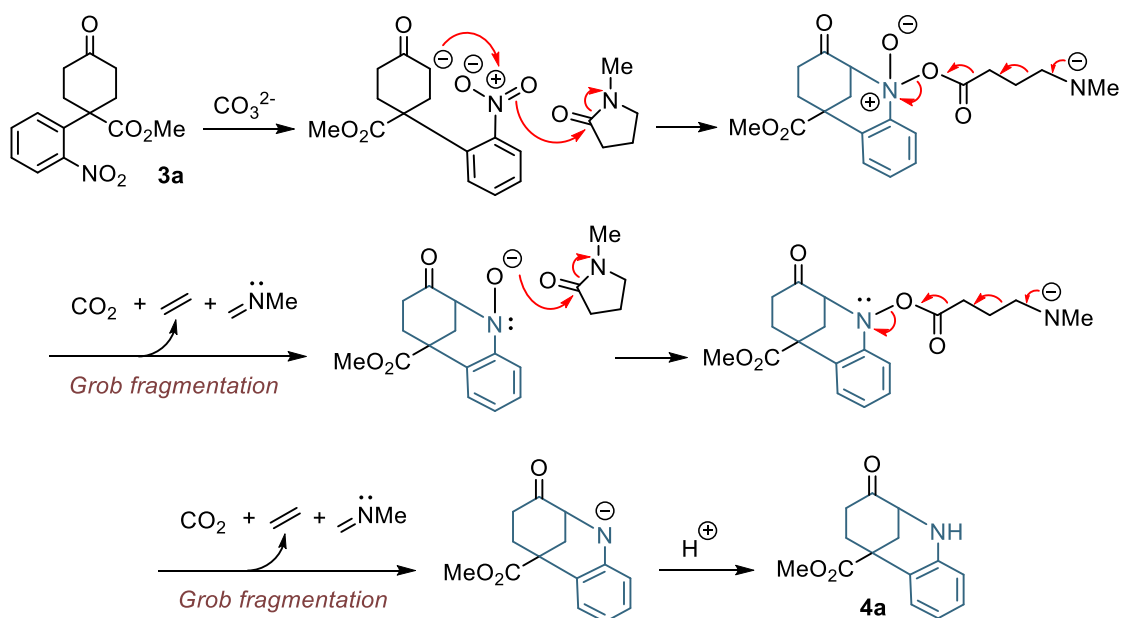
Scheme 3.28: Additional studies on the reactivity of 3,4-benzomorphans.

Next, we also tried a general Giese coupling of two neutral alkenes with the enone functionality in **4h**, but in this case no reaction took place, probably due to the high steric hindrance, and we only recovered the starting material.

3.3.5 Mechanistic discussion

The proposed mechanism for the base-mediated nitrophenyl reductive cyclization of nitrophenyl ketones is described in *Scheme 3.29*.

Firstly, potassium carbonate would abstract an α -proton of the ketone to generate an enolate. This enolate would then attack the nitro group to furnish the six-membered ring and trigger a ring-opening nucleophilic attack on the carbonyl group of NMP, which would generate the five-atom scaffold required for the proposed Grob fragmentation. The electronic rearrangement indicated in the scheme would generate a deprotonated hydroxylamine alongside the elimination of carbon dioxide, ethylene, and *N*-methylmethanimine. The newly generated hydroxylamine could perform a second attack on the carbonyl group of NMP, promoting an iterative sequence that would result in an additional reduction process to yield an amide ion, that could provide the final 3,4-benzomorphan through protonation.



Scheme 3.29: Proposed reaction mechanism for the nitrophenyl reductive cyclization involving a Grob fragmentation.

3.3.6 Study of the biological properties of products **4a** to **4h**

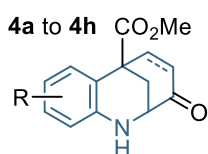
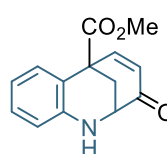
After optimizing the conditions for the synthesis of the 3,4-benzomorphan scaffold, the cytotoxic activity of compounds **4a–4h** was evaluated. To this end, in collaboration with the Department of Biochemistry of the Faculty of Pharmacy at the University of Barcelona, we determined the IC₅₀ of the substrates. This parameter, which refers to the half-maximal inhibitory concentration, is a measure of the effectiveness of a compound in inhibiting cell viability. In this case, the cytotoxicity of the compounds was evaluated using a range of human cancer cell lines. Cells were exposed to increasing concentrations of each compound (from 1 µM to 300 µM) for five days. Viability was assessed using the MTT assay, which measures metabolic activity as an indicator of the amount of cells that are alive and functional. The IC₅₀ value was then determined by calculating the concentration at which 50% of cells were inhibited relative to the untreated controls.

As summarized in *Table 3.3*, the tested benzazocines generally exhibited significantly lower activity against the MCF-7 breast cancer cell line compared to aspernomine (IC₅₀ = 11.7 µM), with IC₅₀ values for products **4a–4g** ranging from 44 to 182 µM. This suggests that cytotoxicity might not be solely attributed to the azatricyclic core and that additional structural features in aspernomine likely contribute to its potency. Moreover, the reduced activity might also be influenced by the presence of an ester group or the racemic nature of the synthesized compounds. For a visual representation of the cytotoxic effects, see *Figure 3.3*, which shows cell images taken using a fluorescent cell imager, illustrating the progression of cell death at increasing concentrations of **4a**.

Remarkably, compound **4h**, which incorporates an enone fragment, displayed a potency of 3.4 µM against the MCF-7 cell line, which is approximately four times higher than that of aspernomine. Therefore, we decided to expand the study to seven additional human cancer cell lines, including PC-3 (prostate), MDA-MB-231 (breast), SKBR-3 (breast), MiaPaCa (pancreas), HeLa (cervix), HT-29 (colon) and 453-WT (breast) cells and evaluate the cytotoxicity using a range of lower concentrations to achieve more accurate results. As shown in the table, in all cases, a higher activity than that of aspernomine was observed, with IC₅₀ values ranging from 2.40 µM to 4.66 µM, establishing benzazocine **4h** as a promising scaffold for further bioactivity studies.

Table 3.3: Activities of benzazocines **4a** to **4h** against the MCF-7 breast cancer cell line. Cytotoxicity of compound **4h** against seven additional cell lines.

General Screening

Compound **4h**

Compound	IC ₅₀ ^a (μM) MCF-7	Cell line	IC ₅₀ ^b (μM)
Aspernomine	11.7	MCF-7 (breast)	3.37
4a (R = H)	77.7		
4b (R = <i>m</i> -F)	77.6	PC-3 (prostate)	2.40
4c (R = <i>m</i> -Cl)	44.3	MDA-MB-231 (breast)	2.56
4d (R = <i>m</i> -Br)	67.8	SKBR-3 (breast)	3.65
4e (R = <i>p</i> -F)	54.2	MiaPaCa (pancreas)	4.32
4f (R = <i>o</i> -F)	77.9	HeLa (cervix)	4.33
4g (R = <i>m</i> -OMe)	182	HT-29 (colon)	4.66
4h	3.4	453-WT (breast)	3.60

IC₅₀ values were determined after 5 days of incubation at increasing concentrations ranging from: ^a25 μM to 300 μM; ^b1 μM to 10 μM.

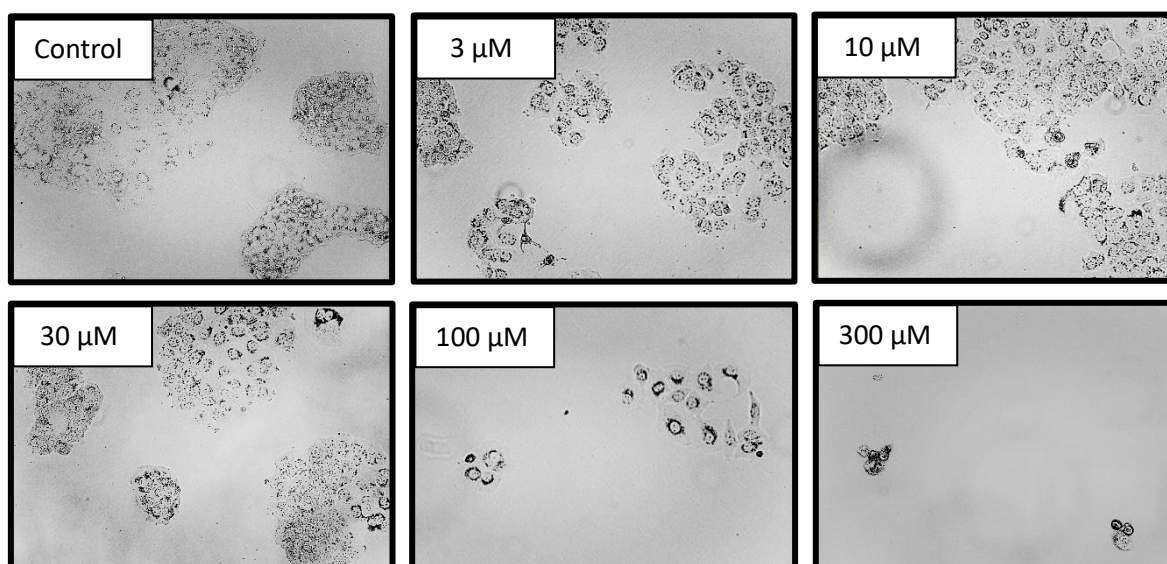
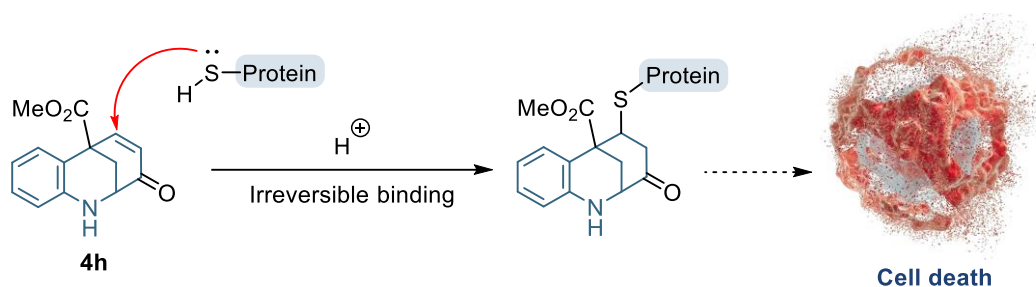


Figure 3.3: Microscopy data of the cytotoxic effect of **4a** against MCF-7 cells: cell death as a function of concentration for IC₅₀ determination.

The increased activity of the enone group may stem from its role as a Michael acceptor, enabling it to irreversibly alkylate cysteine or serine residues through conjugate addition (*Scheme 3.30*). This interaction could result in enzyme inhibition or non-specific protein aggregation, which may contribute to the observed cytotoxicity.⁶⁰ Moreover, it is noteworthy that several cancer therapies incorporate Michael acceptor motifs, underscoring the biosynthetic and therapeutic potential of this structural framework for future research.^{61,62}

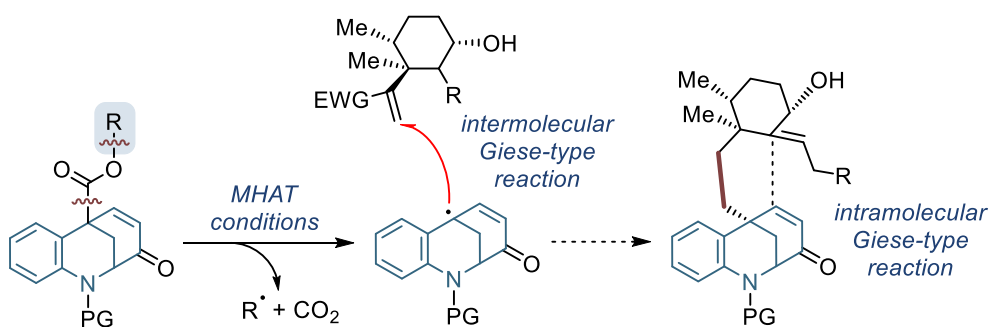


Scheme 3.30: Proposed mechanism of action of benzazocine 4h.

3.3.7 Future work

While this study provides valuable insights into the synthesis and evaluation of the biological properties of the hexahydro-2,6-methano-1-benzazocine framework, several areas remain to be explored.

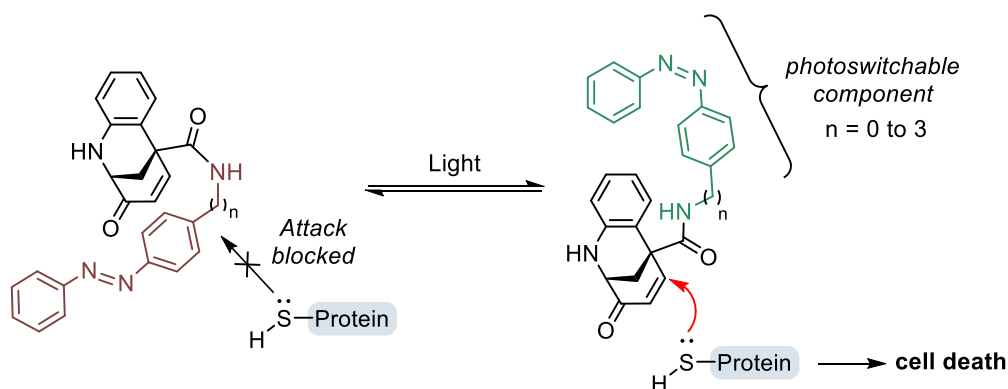
Firstly, with the synthesis of the heterocyclic core of aspernomine accomplished, it is possible to continue making progress in the total synthesis of the natural product. To do so, the conditions for the first connection between the heterocycle and the terpenic fragment via MHAT should be established (*Scheme 3.31*).



Scheme 3.31: Proposed MHAT-triggered decarboxylation for the synthesis of aspernomine.

The proposed strategy requires the design of an -R group that could generate a radical via decarboxylation under MHAT conditions, which has not been previously reported. Then, the radical should engage in a classical Giese addition to give the coupled product. Given the complexity of the coupling partners that are being considered, the methodology should be tested first on simpler substrates, providing a reliable strategy that could be applied to a vast array of compounds. The development and scope of this methodology will be addressed in the following chapter.

Secondly, given the high cytotoxicity of benzazocine **4h**, studying the modulation of its biological activity could be of interest. To achieve this, in future studies of the group we will use an azobenzene photoswitch with varying lengths to control its spatial positioning (*Scheme 3.32*).⁶³



*Scheme 3.32: Use of a photoswitch to modulate the bioactivity of **4h**.*

Photoswitches undergo a reversible transformation between two distinct chemical states when exposed to light, allowing for the control of their physical, chemical, or biological properties. Moreover, light activation of a molecular switch offers several advantages, including precise control over its intensity while remaining traceless, which enables non-invasive manipulation in a variety of applications. Therefore, we believe that this approach may provide a simple and reversible way to modulate the cytotoxicity of **4h**.

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4. MHAT-TRIGGERED DECARBOXYLATION OF ALKENE-FUNCTIONALIZED REDOX-ACTIVE ESTERS

4.1 INTRODUCTION

In this chapter, we present the design of a new class of redox-active esters (RAEs) featuring a novel activation mode based on metal-catalyzed hydrogen atom transfer (MHAT). This approach aims to facilitate the unification of the 3,4-benzomorphan fragment from the previous chapter with the terpenic fragment of aspernomine via decarboxylative coupling.

4.1.1 Historical perspective of redox-active esters

The pursuit of robust, environmentally friendly, atom-efficient, and chemoselective transformations remains a central focus in organic chemistry. To enable the assembly of polyfunctionalized fragments or the late-stage modification of complex molecules containing sensitive functional groups, highly efficient reactions with mild conditions and broad functional group compatibility are essential.¹ In this regard, transition metal-catalyzed cross-couplings have revolutionized synthetic chemistry, offering invaluable tools for producing pharmaceuticals, new chemical entities, and functional materials.²

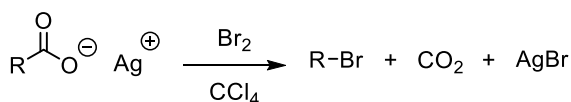
While cross-coupling reactions using C(sp²)-aryl or -alkenyl electrophiles –typically halides or pseudohalides– have been extensively developed, reactions involving alkyl halides remain underexplored due to challenges such as slow oxidative addition and susceptibility to β -hydrogen elimination. In this context, alkyl carboxylic acids have emerged as attractive alternatives, given their abundance, low cost, stability, and ubiquity in nature.³

Decarboxylative coupling reactions proceed through either heterolytic cleavage of the C–COOH bond, which generates synthetically valuable carbanions,⁴ or homolytic cleavage, often from alkyl carboxylic acids or their activated derivatives, resulting in alkyl radicals that can participate in diverse cross-coupling transformations.

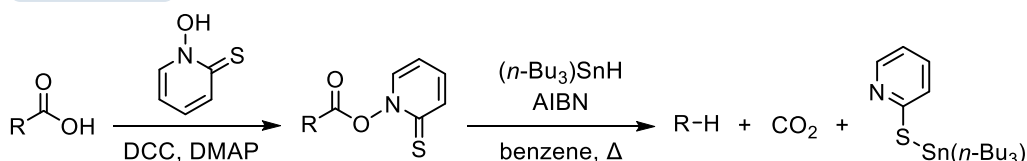
Classical methods for the decarboxylation of carboxylic acids via homolytic cleavage include the Hunsdiecker reaction, developed by Heinz and Cläre Hunsdiecker in the 1930s. This reaction relies on the oxidative decarboxylation of the silver salt of a carboxylic acid in the presence of an external oxidant, generating an alkyl radical. The radical is subsequently trapped by a halogen, producing an alkyl halide in a

transformation known as decarboxylative halogenation. Another significant strategy is the Barton reaction, which employs *N*-hydroxy-2-thiopyridone esters that undergo decarboxylation to generate alkyl radicals capable of participating in functional group interconversion reactions (Scheme 4.1).⁵

Hunsdiecker, 1936



Barton, 1984



Scheme 4.1: Classical methods for the homolytic decarboxylation of carboxylic acids.

Despite their utility, Barton esters are often limited in application due to their thermal and photochemical instability and their tendency to undergo undesired side reactions, such as radical recombination with reactive 2-pyridylthiyl radicals, leading to byproducts like (alkylthio)pyridines. In recent years, *N*-(acyloxy)phthalimides (NHPI esters) have emerged as promising alternatives to Barton esters, offering several advantages for radical-mediated cross-coupling reactions (Figure 4.1). NHPI esters are not only more stable, with a significantly higher N–O bond dissociation energy (BDE $\approx$ 75 kcal/mol), but they are also more easily synthesized. They can be prepared from the corresponding carboxylic acids and *N*-hydroxyphthalimide (NHPI) under standard coupling conditions, making them a more practical option compared to Barton esters.⁶

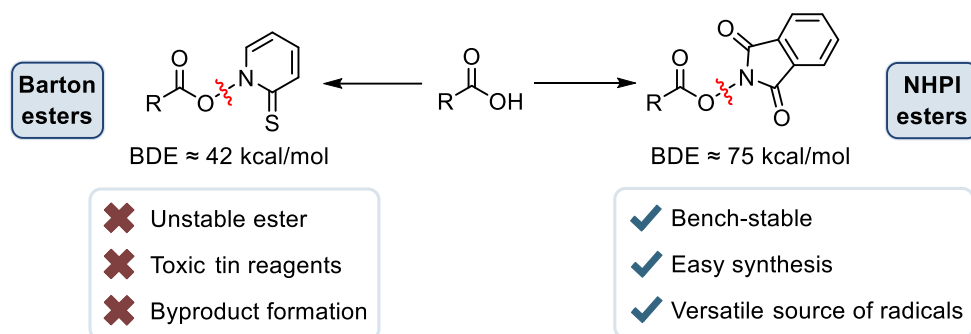
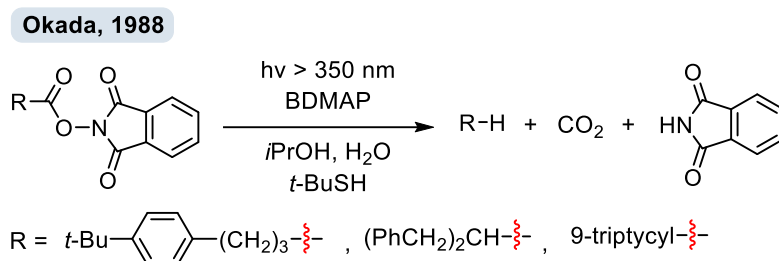


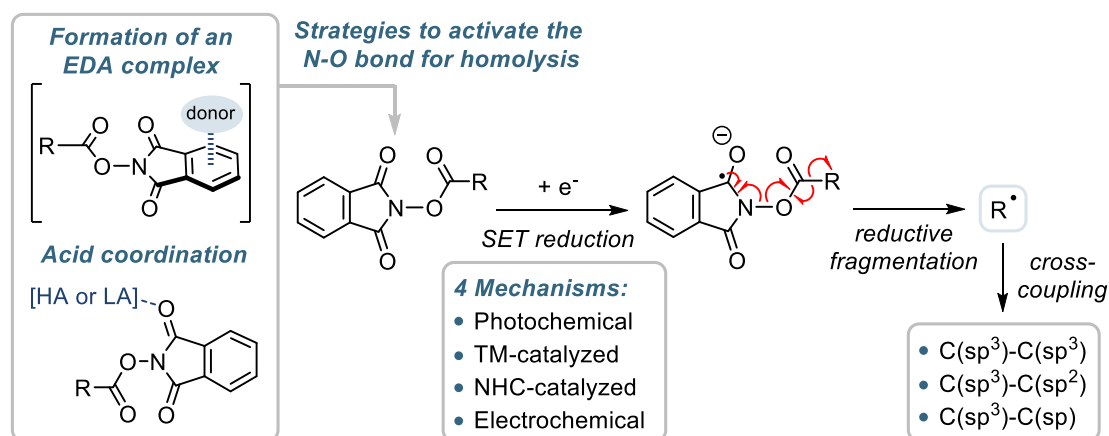
Figure 4.1: Advantages of NHPI esters compared to Barton esters.

Their utility as radical precursors was first demonstrated by Okada and coworkers in 1988, who successfully generated C(sp³)-centered radicals by irradiating NHPI esters in the presence of the photoreductant 1,6-bis(dimethylamino)pyrene (BDMAP) (Scheme 4.2).⁷



Scheme 4.2: First reported example of the use of NHPI esters by Okada.

Mechanistically, these redox-active esters undergo reductive decarboxylative fragmentation to generate radicals, which can then be trapped with a vast array of acceptors. This reduction, facilitated by single-electron transfer (SET), can proceed via a photochemical, transition metal (TM)-catalyzed, *N*-heterocyclic carbene (NHC)-catalyzed or electrochemical pathway, with factors such as electron donors, Brønsted and Lewis acids, and charge-transfer complexes influencing the reaction outcome (Scheme 4.3).⁸



Scheme 4.3: Mechanism and activation modes involved in radical generation with RAEs.

In the following sections, we will briefly describe the main characteristics of each of the mechanistic pathways available for the decarboxylative C–C couplings involving NHPI esters, using a representative example for each case.

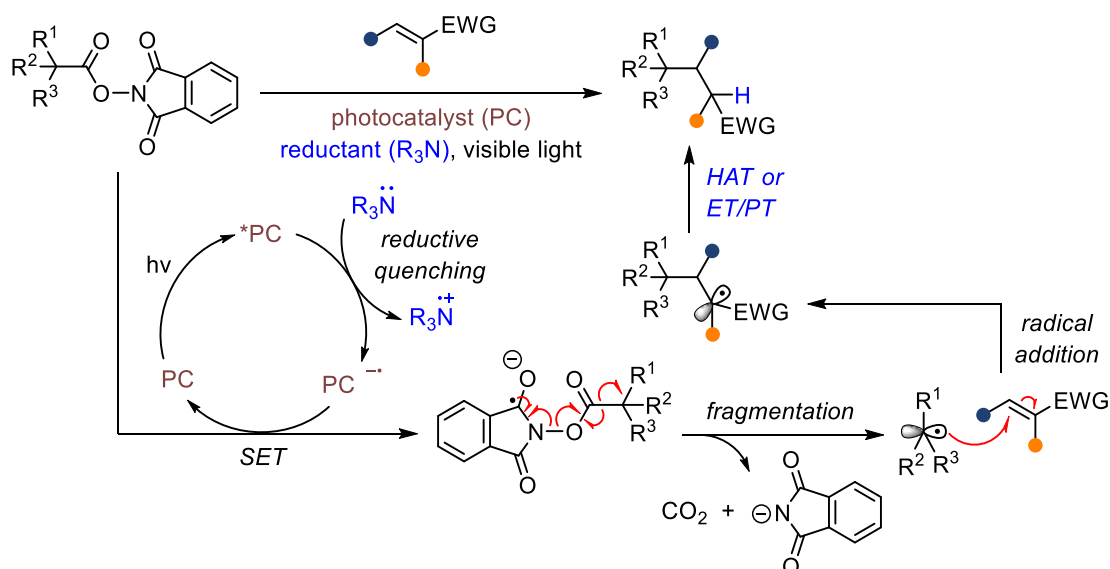
4.1.2 Photoinduced cross-couplings

The use of visible-light irradiation is the most commonly employed activation mode for RAEs. When a photocatalyst absorbs light, it enters an excited state (*PC) that can engage in single-electron transfer following four mechanistic pathways:

Reductive quenching mechanism

A widely used transformation involving NHPI esters is the Giese-type addition, typically carried out under net reductive conditions.⁹ This process frequently operates via a reductive quenching photocatalytic cycle, in which the photocatalyst oxidizes a donor to produce a highly reducing species (*Scheme 4.4*).

Under visible-light irradiation, the photocatalyst absorbs light and enters an excited state (*PC), where it can be reduced by an electron donor, generating a reduced photocatalyst (PC^{-•}). This highly reducing species facilitates the one-electron reduction of the NHPI ester, producing a radical anion intermediate. This intermediate undergoes fragmentation through N–O bond cleavage and decarboxylation, yielding an alkyl radical along with the release of a phthalimide anion and carbon dioxide. The radical then reacts with an olefin acceptor to form an advanced intermediate, which is subsequently converted into the final conjugate addition product via either hydrogen atom transfer or sequential electron and proton transfer.

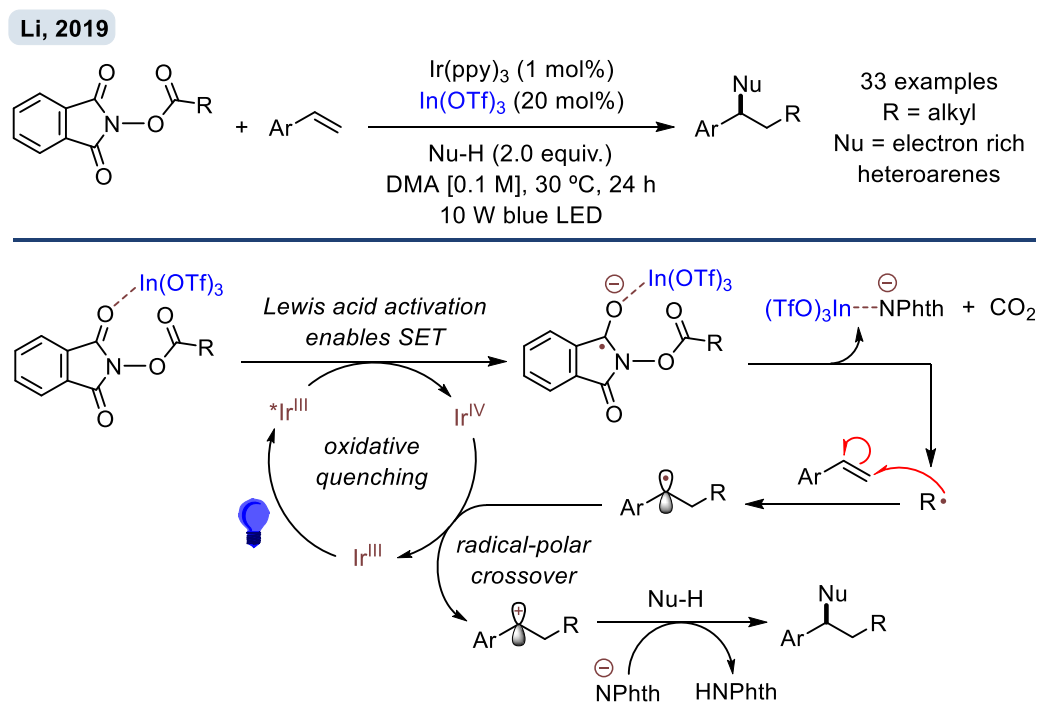


Scheme 4.4: Giese addition via NHPI activation under reductive quenching mechanism.

Oxidative quenching mechanism

In this oxidative pathway, the excited photocatalyst triggers the one-electron reduction of an acceptor substrate. As a representative example, in 2019, Li reported an $\text{In}(\text{OTf})_3$ -promoted strategy for the photoredox-mediated alkylarylation of styrenes using alkyl *N*-hydroxyphthalimide esters and arenes via an oxidative quenching path (Scheme 4.5).¹⁰

In the proposed mechanism, the RAE –which was activated by Lewis acid coordination– underwent single-electron reduction via oxidative quenching of the excited iridium catalyst ($^*\text{Ir}^{\text{III}}$), furnishing a radical anion and the corresponding Ir^{IV} complex. Following decarboxylation and addition to styrene, a benzylic radical was generated. A subsequent radical-polar crossover resulted in the formation of a cationic species, accompanied by the regeneration of the catalyst. Finally, a nucleophilic addition led to the formation of the coupled product.



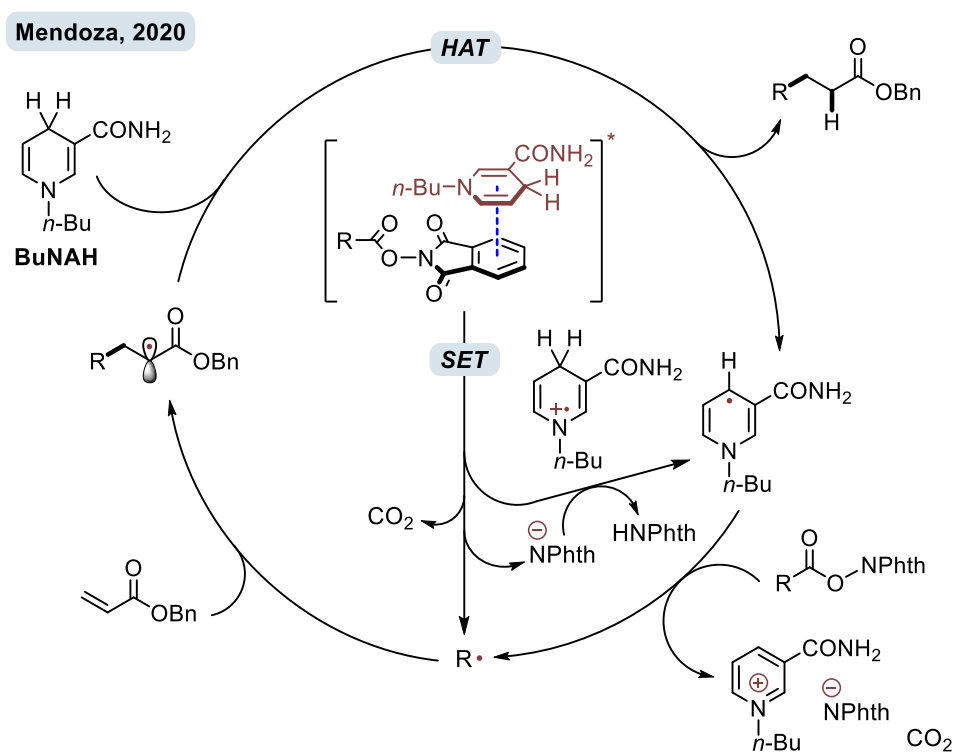
Scheme 4.5: Photoredox alkylarylation of styrenes via oxidative quenching mechanism.

Activation via charge-transfer complex formation

An alternative activation pathway for NHPI esters involves π -stacking interactions between the phthalimide ring and an electron-rich species, leading to the formation of

charge-transfer complexes. Depending on the specific system, this process may or may not require an external photocatalyst to initiate decarboxylation.

For instance, a Giese-type addition mediated by an electron donor–acceptor (EDA) complex was reported by Mendoza in 2020 (Scheme 4.6).¹¹ The reaction was initiated by the formation of the photoactive complex between the reductant *N*-(*n*-butyl)-1,4-dihydronicotinamide (BuNAH) and the NHPI ester. Upon irradiation with visible light, the complex underwent a photoinduced single-electron transfer, producing the substrate radical and the nicotinyl radical. Subsequently, the substrate radical added to the Michael acceptor, forming an open-shell intermediate. This intermediate was reduced via a BuNAH-mediated hydrogen atom transfer, which regenerated the nicotinyl radical. Finally, the aromatization of this radical triggered the expulsion of a pyridinium ion, thereby propagating the radical chain.

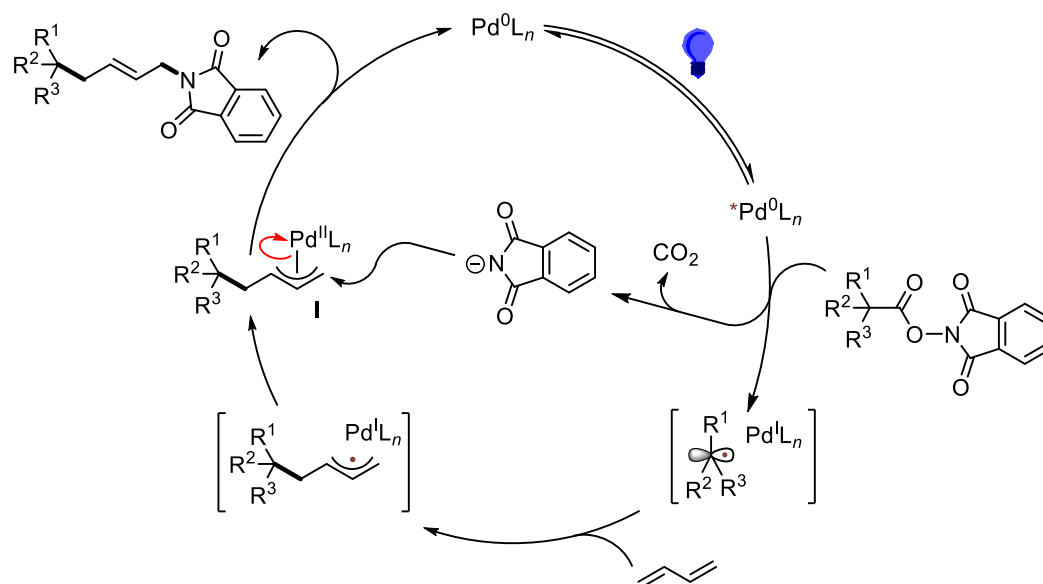


Scheme 4.6: Giese addition via NHPI activation through EDA complex formation.

Photoinduced transition metal-catalyzed mechanism

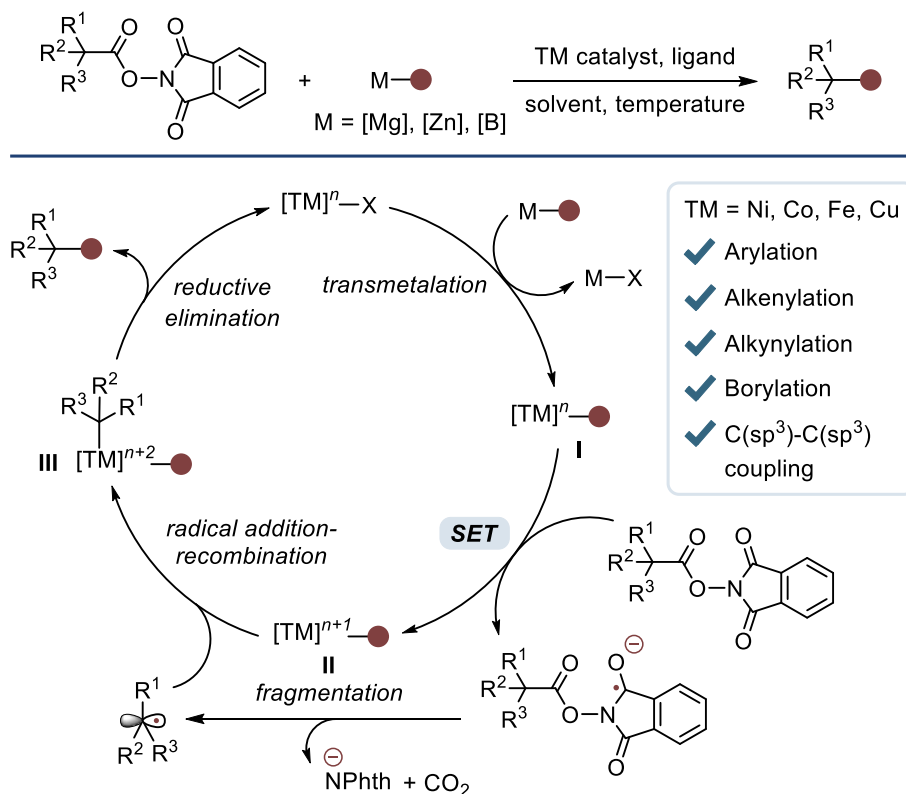
Photoactive catalysts can be generated in situ by combining simple transition metal salts with appropriate ligands. Unlike traditional photoredox catalysts based on ruthenium and iridium, these TM catalysts serve a dual purpose: facilitating photoinduced electron

As a representative example, in 2020, Glorius and coworkers developed a photoinduced Pd-catalyzed aminoalkylation of 1,3-dienes (*Scheme 4.7*).¹³ Mechanistically, the reaction started by the photoexcitation of a Pd⁰ species, which enabled the activation of the RAE via SET to furnish a hybrid alkyl–Pd^I radical species. A subsequent reaction with 1,3-butadiene resulted in the formation of a hybrid allyl–Pd^I complex, which was readily converted to the π-allylpalladium intermediate **I** upon radical recombination. Finally, a nucleophilic attack of the phthalimide anion to **I** would give access to the coupled product, completing the catalytic cycle.



4.1.3 Initiation by metal catalysts and stoichiometric reductants

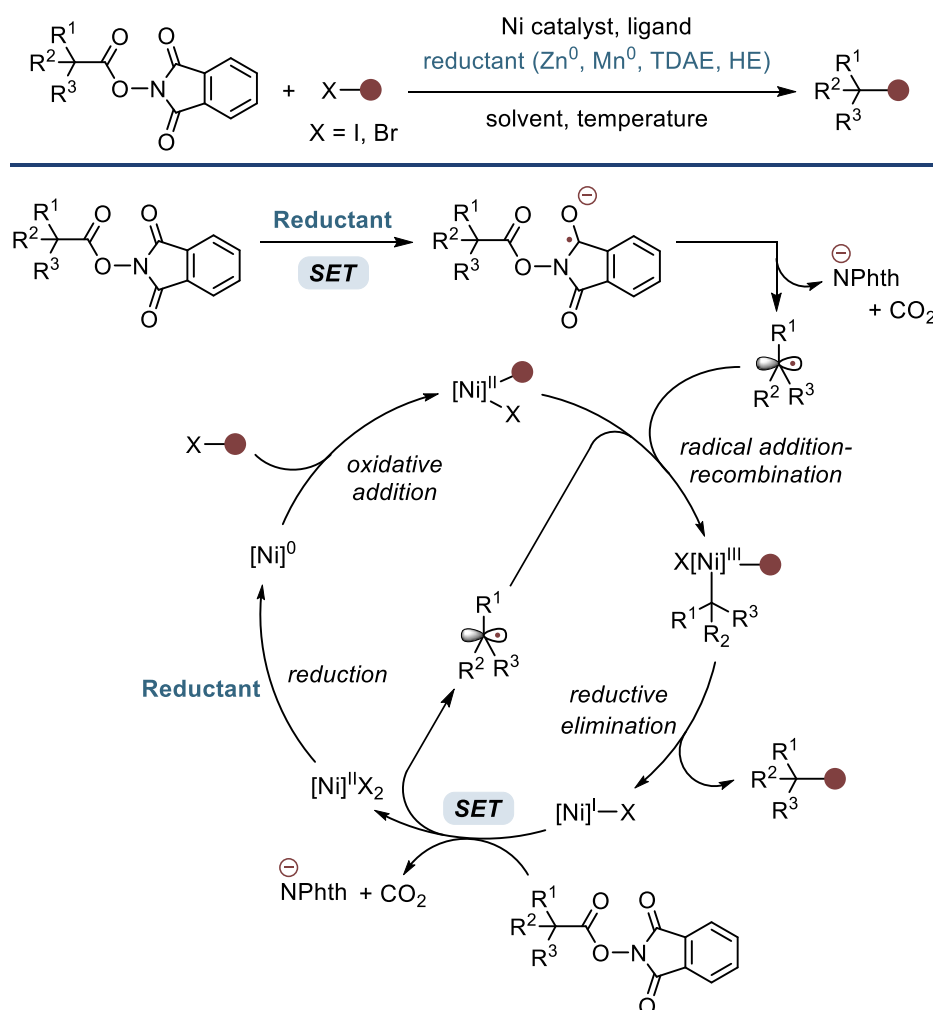
Transition metals can also promote the activation of NHPI esters without the need for a photocatalyst. Typically, two distinct approaches can be depicted. First, the decarboxylative cross-coupling of NHPI esters with organometallic reagents has been facilitated by nickel, cobalt, iron, and copper catalysts.¹⁴ The process generally begins with transmetalation of the organometallic coupling partner to the transition metal catalyst, forming intermediate **I**. This intermediate serves as a reducing agent, transferring an electron to the RAE to generate a radical anion and the oxidized metal complex **II**. After fragmentation, the resulting alkyl radical is captured by complex **II** to form intermediate **III**, which undergoes reductive elimination to yield the cross-coupling product (Scheme 4.8).



Scheme 4.8: Coupling of NHPI esters and organometallic reagents via TM catalysis.

The second category of reactions, known as cross-electrophile coupling,³ comprises the nickel-catalyzed reaction of NHPI esters with aryl or vinyl halides under reducing conditions (Scheme 4.9).¹⁵ The catalytic sequence begins with the oxidative addition of an organohalide to a Ni^0 catalyst, forming a Ni^{II} complex. Simultaneously, the NHPI ester

undergoes single-electron transfer activation facilitated by a reductant, leading to a radical intermediate. This radical interacts with the Ni^{II} complex to generate an oxidized Ni^{III} species, which then undergoes reductive elimination to yield the desired cross-coupling product. The process also produces a Ni^{I} intermediate, which can trigger additional SET steps, sustaining the cycle. Finally, the Ni^0 catalyst is regenerated by the reductant, allowing the catalytic cycle to continue.

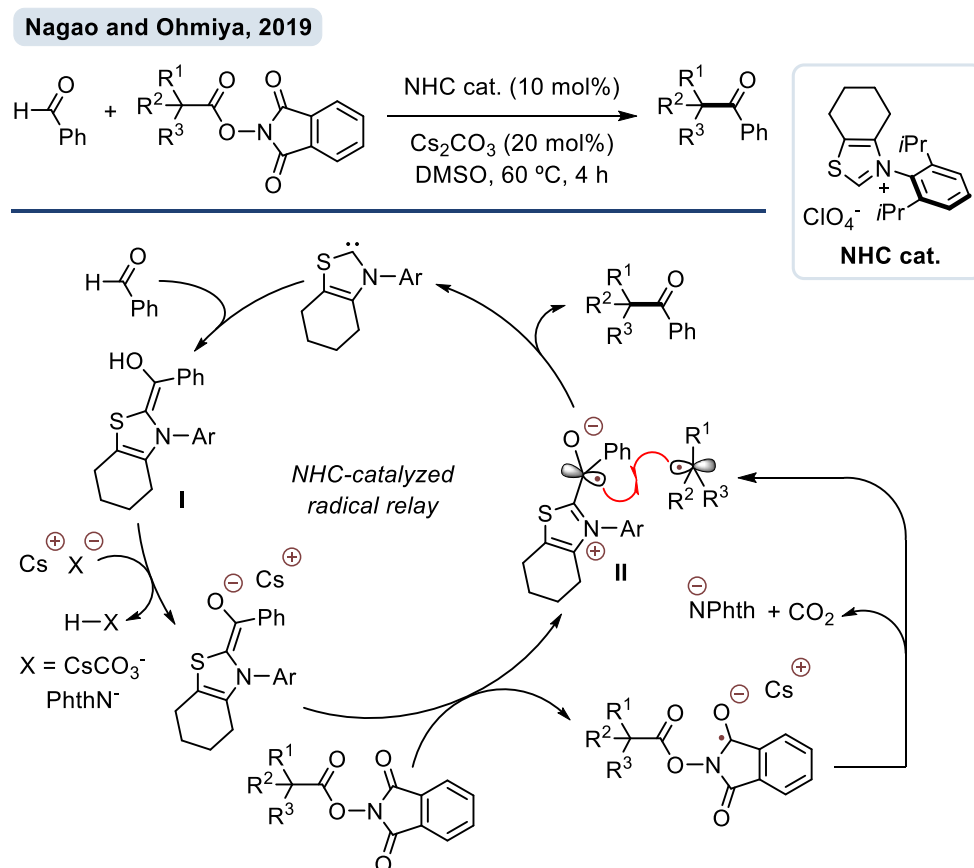


Scheme 4.9: TM-catalyzed cross-electrophile coupling of NHPI esters.

4.1.4 N-Heterocyclic Carbene (NHC) catalysis

An alternative approach for activating NHPI esters involves the use of NHC catalysts (Scheme 4.10). For example, in 2019, Nagao and Ohmiya reported a decarboxylative coupling reaction between aryl aldehydes and RAEs derived from tertiary or secondary alkyl carboxylic acids, leading to the formation of aryl alkyl ketones.¹⁶ The mechanism began with the reaction of benzaldehyde and the NHC catalyst, furnishing Breslow

intermediate **I**. Cesium carbonate then deprotonated the enol, forming an enolate which promoted the reduction of the NHPI ester, yielding the persistent radical **II** and triggering the formation of an alkyl radical via decarboxylation. Finally, radical–radical coupling, followed by NHC catalyst elimination, delivered the coupled ketone.



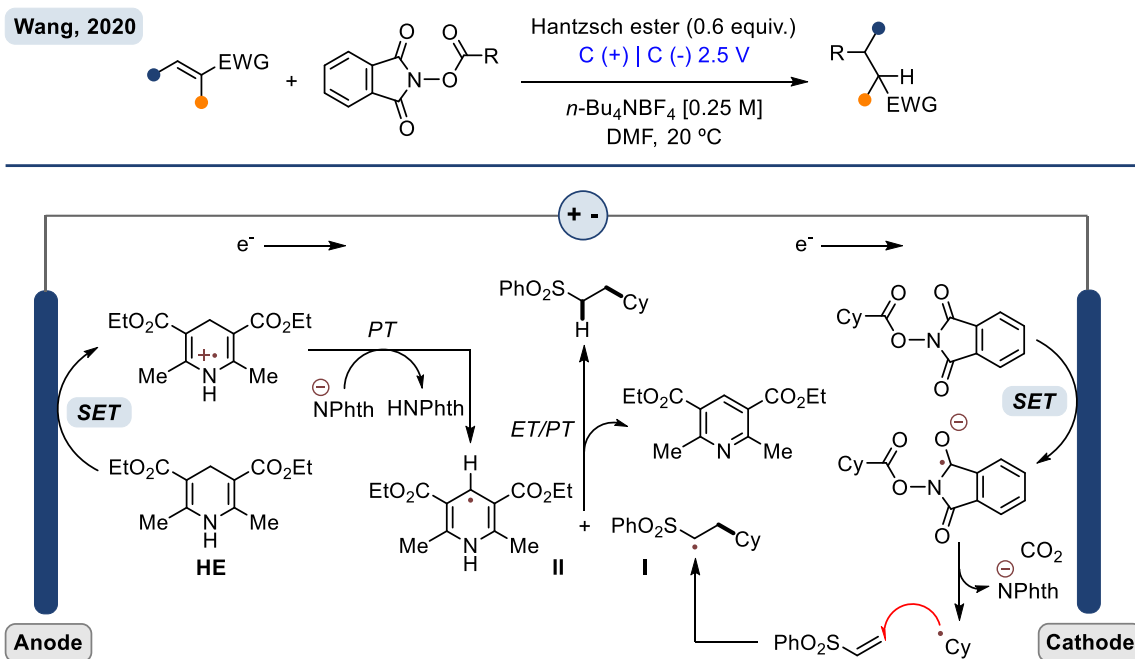
Scheme 4.10: NHC-catalyzed decarboxylative coupling of NHPI esters and aldehydes.

4.1.5 Mechanisms under electrochemical activation

The electrochemical activation of NHPI esters offers notable benefits over alternative approaches. It enables single-electron reduction using affordable carbon-based cathodes, thereby eliminating the need for expensive metal photocatalysts or external reductants.

As a selected example involving this mechanistic pathway, in 2020, Wang and coworkers designed a Giese-type addition in an undivided cell using graphite electrodes (*Scheme 4.11*).¹⁷ Under these conditions, the NHPI ester underwent activation via single-electron transfer at the cathode surface, generating the corresponding radical anion. This was followed by fragmentation, producing a cyclohexyl radical, which subsequently added to

the terminal carbon of the radical acceptor, forming intermediate **I**. In the complementary redox half-reaction, Hantzsch ester (HE) underwent anodic oxidation to yield a radical cation, which likely transferred a proton to the phthalimide anion, producing radical species **II**. Finally, the interaction between intermediates **I** and **II** via sequential electron transfer and proton transfer (ET/PT) resulted in the formation of the hydroalkylation product and the pyridine byproduct.



Scheme 4.11: Giese addition using NHPI esters via electrochemical activation.

4.1.6 Acceptor groups in NHPI-mediated couplings

As outlined in the previous sections, NHPI esters have long been valuable in organic chemistry due to their versatile reactivity. Recently, interest in their chemistry has grown, driven by efforts to expand the scope of accessible products. This has included the exploration of novel radical acceptors, enabling the development of innovative methodologies. The following section summarizes acceptor groups used for functionalizing RAE-derived radicals, starting with C–heteroatom bond formation (Figure 4.2).

Significant advances in C–N coupling have emerged recently. In 2017, Fu utilized the phthalimide anion generated from RAE decarboxylation to synthesize protected amines,¹⁸ a strategy later expanded by Zheng.¹⁹ Shortly after, Hu developed a

photoredox Cu-catalyzed process that efficiently coupled arylamines, sulfonamides, amides, and ureas,²⁰ later extending the method to imines.²¹

In 2020, Lopchuck introduced diazirine-based amination, offering access to amines, hydrazines, and heterocycles,²² a strategy complemented by Liao's alternative catalytic system for analogous products.²³ In 2021, Ohmiya reported a method for the *N*-alkylation of sulfonamides with both aliphatic and aromatic substrates.²⁴

In 2023, Wang introduced a Ni-catalyzed strategy for efficiently synthesizing tertiary amines, which proved highly effective for late-stage functionalization of drugs and natural products.²⁵ Shortly after, he disclosed an electrochemical approach for the obtention of anilines using nitroarene precursors.²⁶ That same year, Cornella employed bismuth radical catalysis to couple alkyl radicals with heteroaromatic compounds.²⁷ Finally, in 2024, Bao and Yu developed complementary mild TMSN₃-based protocols for the efficient synthesis of carbamoyl azides.²⁸

Considering C–O couplings, only one precedent has been reported to date: the aminoxylation of RAEs using TEMPO. The resulting products were converted into aliphatic alcohols via reduction with zinc in acetic acid, demonstrating the synthetic utility of this strategy.²⁹

The first precedent regarding the halogenation of RAEs was reported in 1989 by Okada and coworkers, who described a chlorodecarboxylation of carboxylic acid precursors under light irradiation in the presence of CCl₄.³⁰ In 2015, MacMillan and coworkers developed a photoinduced coupling method to synthesize alkyl fluorides via radical trapping, utilizing Selectfluor as an electrophilic fluorinating agent.³¹ However, while these examples highlight early innovations in the field, the majority of halogenation strategies for RAEs rely on halide salts as halogen sources.^{19,32}

In 2020, Zheng and Wang developed C–S bond-forming strategies using disulfides and *S*-aryl benzenethiosulfonates. Zheng's approach utilized visible-light-induced ruthenium catalysis,³³ while Wang's method, in contrast, employed manganese mediation under light-free conditions. Notably, Wang's work also enabled the formation of C–Se, C–Te, and C–P bonds, showcasing the broad versatility of this approach.³⁴ More recently,

Aggarwal and coworkers developed a cost-effective method for the thiocyanation of RAEs under dual photoredox-Cu catalysis.^{32c}

The formation of C–B bonds has also been extensively investigated over the past decade, consistently employing diboron reagents for the synthesis of boronic esters.³⁵ When B₂(OH)₄ was used as the boron source, the resulting boronic acids were derivatized in situ to boronic esters or alkyltrifluoroborates, simplifying their handling and expanding their utility.³⁶

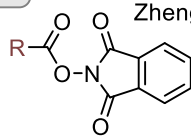
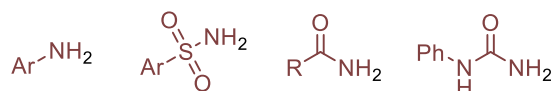
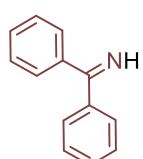
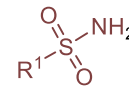
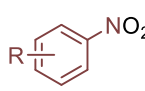
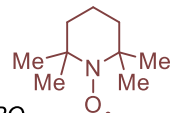
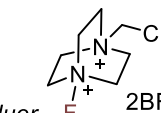
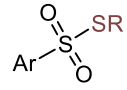
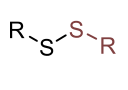
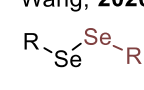
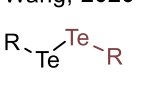
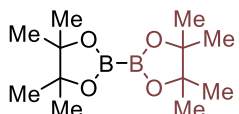
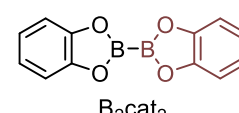
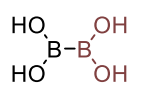
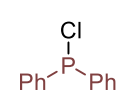
C-X Couplings					
C-N  Fu, 2017 Zheng, 2023 via decarboxylation	Hu, 2018 				Hu, 2020 
Lopchuk, 2020 Liao, 2021 	Ohmiya, 2021 	Wang, 2023 BzONBn ₂	Wang, 2023 	Cornella, 2023 	Bao, 2024 Yu, 2024 TMSN ₃
C-O Liang, 2018  TEMPO	C-F MacMillan, 2015  Selectfluor	C-Cl Okada, 1989 CCl ₄	Zheng, 2023 n-Bu ₄ NCl	Aggarwal, 2023 LiCl	
C-Br Zheng, 2023 n-Bu ₄ NBr	Aggarwal, 2023 LiBr	C-I Chen, 2020 NaI	Shang, 2020 LiI	Zheng, 2023 n-Bu ₄ NI	
C-S Wang, 2020 Zheng, 2020 	Wang, 2020 Zheng, 2020 	Aggarwal, 2023 KSCN	C-Se Wang, 2020 	C-Te Wang, 2020 	
C-B Li, 2017 Baran, 2017 Glorius, 2017  B ₂ pin ₂	Aggarwal, 2017 Shuto, 2019  B ₂ cat ₂	Li, 2017 Novák, 2024 	C-P Wang, 2020 		

Figure 4.2: Suitable acceptors for the formation of C–heteroatom bonds.

Focusing on C–C bond-forming reactions (*Figure 4.3*), a wide range of precursors have been explored. In 2015, Overman and coworkers developed a photoinduced Ru-catalyzed coupling to access alkylated products. Allyl and vinyl halides underwent addition-fragmentation to furnish the desired products, while coupling with electron-deficient alkenes proceeded via Giese addition. Notably, neutral alkenes also served as effective coupling partners.⁹ More recently, other research groups have further expanded the chemical diversity accessible using these precursors.^{11,34,37} For example, Mendoza employed neutral alkenes in a cyclopropanation strategy, significantly broadening the reaction's applicability.³⁸

In 2018, Wang's group developed a cobalt-catalyzed decarboxylative Negishi coupling of redox-active aliphatic esters with organozinc reagents, enabling the formation of alkyl–alkenyl and alkyl–alkynyl coupling products under mild conditions, without the need for ligands or additives.^{14b} Shortly thereafter, Ohmiya employed NHC catalysis to promote the decarboxylative coupling of aryl aldehydes with alkyl carboxylic acid-derived redox-active esters, resulting in the formation of aryl alkyl ketones under mild, transition-metal-free conditions.¹⁶

Building on their previous work on the dehalogenative alkenylation of vinyl bromides, in 2020, Wang demonstrated that allyl sulfones were also well-suited for the transformation.³⁴ In the same year, Liu developed a photoinduced Cu-catalyzed asymmetric decarboxylative alkynylation with terminal alkynes.³⁹

A particularly interesting application of RAE precursors is the possibility of engaging in doubly decarboxylative couplings. These reactions can provide cross-coupled compounds, as studied by Baran,⁴⁰ or lead to dimerized products, which have been investigated by Che and coworkers. Che's work was further extended to incorporate cyanide acceptors.⁴¹

More recently, two new acceptors have been used. Xie developed a Ni-catalyzed radical–radical coupling between RAEs and carboxylic acids to form alkylated or acylated products.⁴² In the same year, Yang employed malonates as acceptors, enabling the formation of quaternary stereocenters via Ir, Fe, and N triple catalysis.⁴³

Regarding strategies for the arylation of RAE-derived radicals, the use of arylzinc reagents and aryl halides has been widely explored.^{14a,15a,44} These methods show broad functional group tolerance and are applicable to heteroaromatic substrates.

C-C Couplings				
Overman, 2015 X = Cl, Br allylation	Overman, 2015 Mendoza, 2020 Giese-addition	Overman, 2015 Mendoza, 2019 alkylation	Overman, 2015 Reisman, 2017 and 2023 Wang, 2020 X = Cl, Br alkenylation	Wang, 2018 R_2Zn or $R-ZnOPiv$ alkenylation alkynylation
Ohmiya, 2019 acylation	Wang, 2020 alkenylation	Liu, 2020 alkynylation	Che, 2020 Baran, 2022 and 2023 dimerization (Che) cross-coupling (Baran)	
Che, 2020 $TMSCN$ cyanation	Xie, 2024 alkylation or acylation	Yang, 2024 alkylation	Arylations Baran, 2016 Wang, 2018 Mercado, 2019 $Ar-Zn-R$	Weix, 2016 Bio, 2018 Shui, 2024 Sevov, 2024 X = Cl, Br, I, OTf

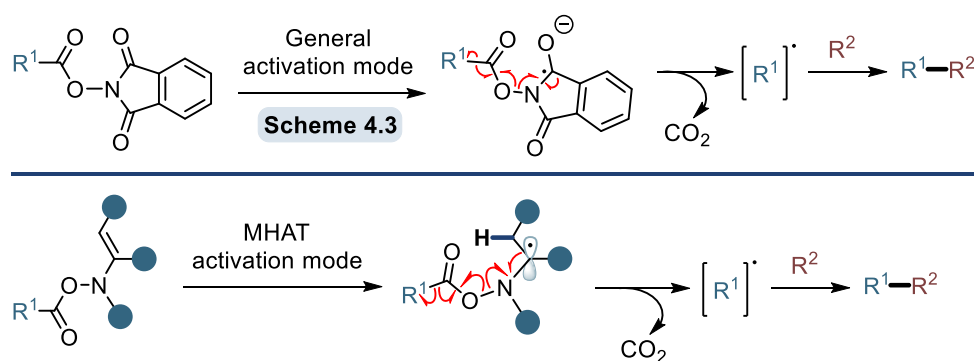
Figure 4.3: Suitable acceptors for the formation of C–C bonds.

4.1.7 Use of RAEs in MHAT reactions

Following the comprehensive overview of MHAT chemistry presented in Chapter 1, this platform has proven to be a powerful tool for unlocking new reactivities and expanding chemical space. However, two defining features of MHAT reactions –the use of alkenes as radical precursors and Markovnikov selectivity– can also be viewed as potential limitations. While alkenes are among the most abundant feedstock chemicals, the chemical space accessible through these transformations is constrained by the structural diversity of the starting materials. Furthermore, the inherent Markovnikov selectivity of MHAT reactions, although advantageous for the generation of branched products⁴⁵ and sterically impeded centers,⁴⁶ precludes access to primary radicals, thereby ruling out the formation of linearly coupled products. Therefore, overcoming these drawbacks could significantly broaden the applicability and scope of MHAT processes.

In this chapter, we have outlined how the use of RAEs gives access to a variety of primary, secondary, and tertiary radicals by selecting suitable carboxylic acid precursors. Moreover, carboxylic acids represent one of the most widely commercially available, structurally diverse, stable, and inexpensive feedstocks for chemical synthesis.⁴⁷

While the use of NHPI esters as precursors in MHAT reactions could potentially address the aforementioned limitations, the conditions required for their cleavage, usually involving complexation and single-electron transfer, are not possible under MHAT conditions. A recent breakthrough from the Shenvi and Baran laboratories demonstrated the use of NHPI esters in MHAT radical–radical coupling reactions with Fe(TPP)Cl as the catalyst (see *Scheme 1.66*).⁴⁸ However, this protocol, which employs an S_H2 coupling mechanism,⁴⁹ is also incompatible with classical MHAT reactions. The reason behind this incompatibility lies in the need for the iron catalyst to cleave the NHPI ester and bind the resulting primary radical for attack by another radical species. This makes it unavailable to participate as a nucleophilic radical with other acceptor groups. We therefore set out to design a novel RAE that could serve as a direct surrogate for alkenes in MHAT reactions in a “plug-and-play” manner. We proposed to incorporate an alkene “trigger” that upon exposure to MHAT conditions would result in the formation of a radical adjacent to the N–O bond in an analogous manner to classical NHPI esters. This radical should spontaneously fragment, providing access to a broad range of decarboxylated radical intermediates (*Scheme 4.12*).



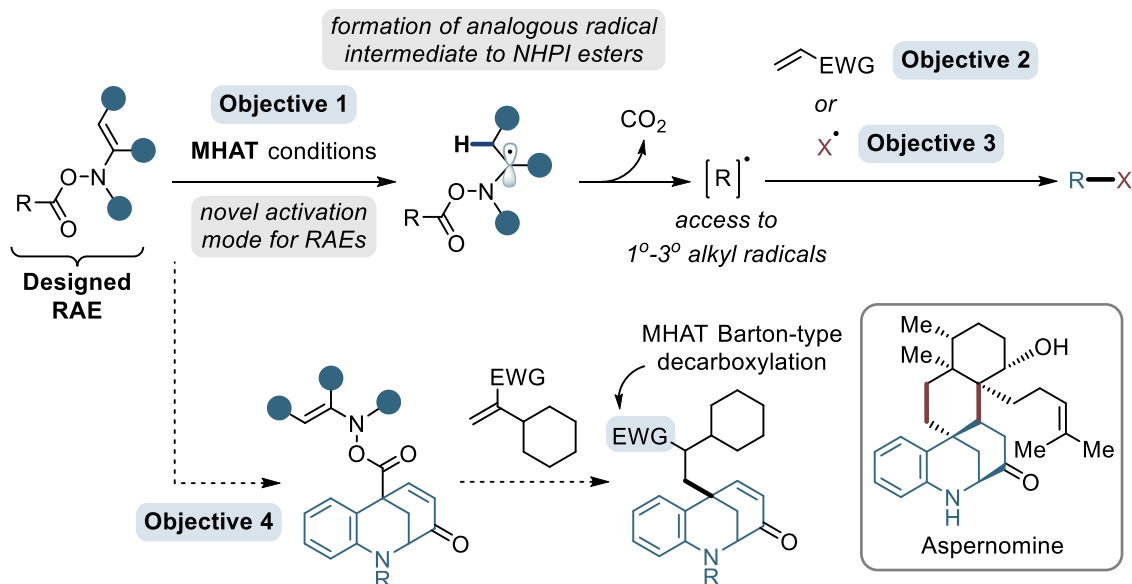
Scheme 4.12: Conventional and MHAT activation modes for RAE coupling.

4.2 OBJECTIVES

Based on the retrosynthesis proposed for aspernomine, this chapter focuses on developing an MHAT reaction to couple RAEs with electron-deficient alkenes using simpler substrates (*Scheme 4.13*).

The first objective was to design an engineered RAE compatible with an MHAT activation mode, which has not been reported previously. The second goal was to optimize the reaction conditions and evaluate the versatility of the decarboxylative coupling with electron-deficient alkenes, with a particular focus on accessing linearly coupled products. Thirdly, we aimed to expand the range of acceptor groups suitable for coupling with the redox-active esters.

Finally, after developing the novel MHAT coupling, the last objective would be to continue making progress in the total synthesis of aspernomine by studying the coupling of the heterocyclic and terpenic fragments using a simplified structure for the terpene, followed by the removal of the electron-withdrawing group by developing an MHAT Barton-type decarboxylation procedure.



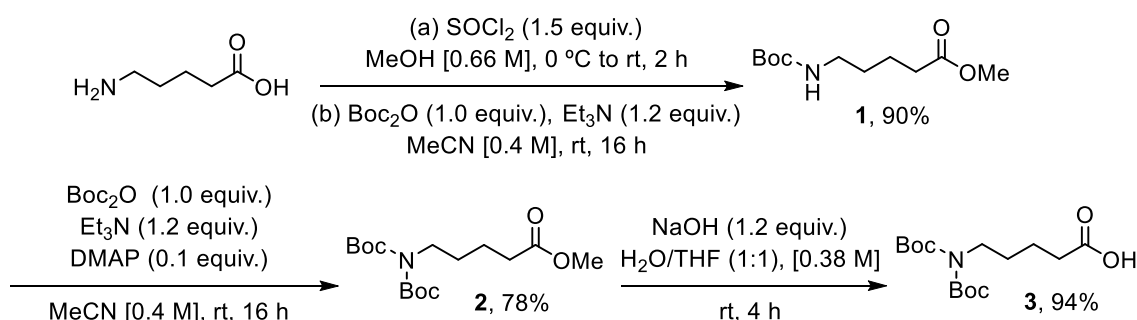
Scheme 4.13: Main objectives of Chapter 4.

4.3 RESULTS AND DISCUSSION

4.3.1 Design of a suitable RAE

Synthesis of the model carboxylic acid

N,N-di-Boc-aminovaleric acid was selected as the model substrate because, upon decarboxylation, it generates a primary radical that leads to non-volatile products. For its preparation, a four-step sequence starting from aminovaleric acid was required (Scheme 4.14). The synthesis began with the esterification of 5-aminovaleric acid using thionyl chloride in methanol, followed by treatment with Boc anhydride and triethylamine in acetonitrile at room temperature to furnish monoprotected amine **1** in 90% yield.⁵⁰ Although the initial protection step proceeded under mild conditions, introducing the second Boc group to form **2** required the use of 4-dimethylaminopyridine (DMAP) as a catalyst to enhance the electrophilicity of Boc anhydride.⁵¹ Finally, hydrolysis of the ester was performed in a biphasic H₂O/THF mixture in the presence of sodium hydroxide to afford **3** in 94% yield.

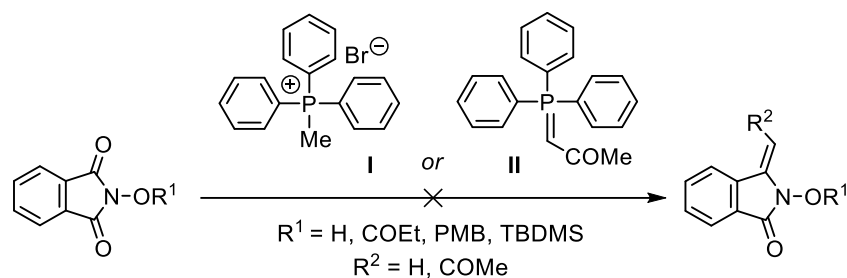


Scheme 4.14: Synthesis of *N,N*-di-Boc-aminovaleric acid.

Synthesis of the RAE precursor

Initial studies aimed at accessing a novel RAE precursor capable of triggering decarboxylation under MHAT conditions involved the installation of a double bond in *N*-hydroxyphthalimide via Wittig coupling under previously reported conditions (Table 4.1).⁵² Despite exploring multiple protection conditions and various phosphonium ylides, no reaction occurred, consistently yielding only a mixture of starting materials.

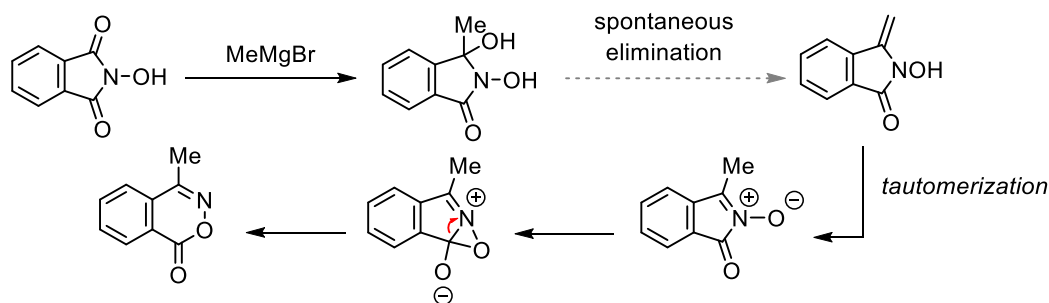
Table 4.1: Attempts at the installation of a double bond in *N*-hydroxyphthalimide via Wittig coupling.



Entry	R ¹	R ²	Reagent	Conditions	Yield
1	H	H	I (1.0 equiv.)	Toluene [0.08 M], BuLi (1.0 equiv.) ^a	-
2	H	H	I (2.5 equiv.)	Toluene [0.08 M], BuLi (2.5 equiv.) ^a	-
3	COEt	H	I (1.0 equiv.)	Toluene [0.08 M], BuLi (1.0 equiv.) ^a	-
4	COEt	H	I (2.5 equiv.)	Toluene [0.08 M], BuLi (2.5 equiv.) ^a	-
5	H	COMe	II (1.0 equiv.)	Toluene [0.04 M] ^a	-
6	COEt	COMe	II (1.0 equiv.)	Toluene [0.04 M] ^a	-
7	TBDMS	COMe	II (1.0 equiv.)	Toluene [0.04 M] ^a	-
8	H	COMe	II (1.0 equiv.)	DMSO [0.17 M] ^b	-
9	PMB	COMe	II (1.0 equiv.)	DMSO [0.17 M] ^b	-
10	H	COMe	II (1.0 equiv.)	THF [0.1 M] ^c	-

^aReflux, 3 h. ^bMicrowaves, 150 °C, 20 min. ^crt, 16 h.

Then, we considered the use of a Grignard reagent to attack one of the carbonyl groups in *N*-hydroxyphthalimide, but attempts were also unsuccessful (Scheme 4.15).⁵³ It was hypothesized that the issues could arise from a rearrangement process described in the literature,⁵⁴ triggered by the spontaneous elimination of the hydroxyl group.

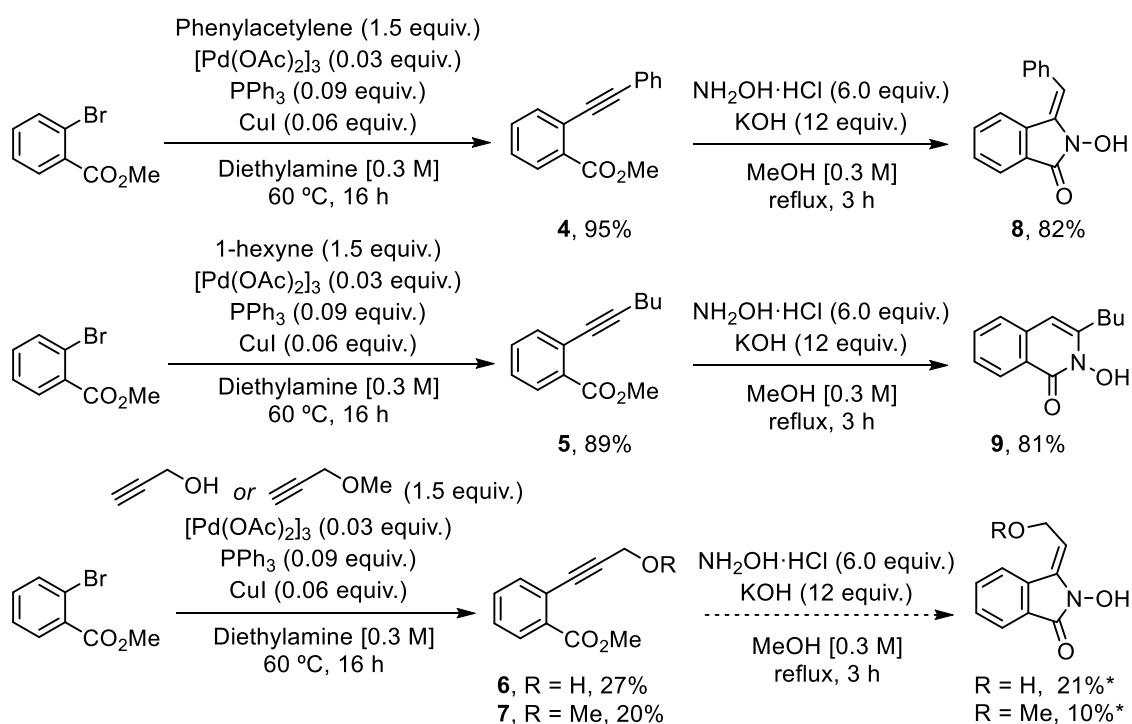


Scheme 4.15: Attempts at an olefination of *N*-hydroxyphthalimide using Grignard reagents.

The tautomerization of the expected product might lead to a nitron, which could then undergo further rearrangement to form an oxaziridine. However, we isolated a complex mixture and were unable to identify any of the byproducts formed.

Given the inability to access the olefinated products using *N*-hydroxyphthalimide as the precursor, an alternative strategy was adopted, starting from a commercially available bromoester, which led to the desired products through a two-step synthesis.⁵⁵

First, a Sonogashira coupling between methyl 2-bromobenzoate and selected alkynes furnished alkynes **4** to **7**.⁵⁶ Upon treatment with hydroxylamine hydrochloride under basic conditions, these alkynes yielded hydroxamic acids containing an unsaturated moiety. The cyclization led to either a five- or six-membered ring, dictated by the alkyl substituent and whether the process followed an *exo* or *endo* pathway. As shown in *Scheme 4.16*, alkynes **4** and **5** smoothly underwent in situ cyclization to afford **8** and **9**, respectively. However, precursors **6** and **7** did not efficiently undergo cyclization, providing only low yields of the desired products along with unidentified impurities. Due to these limitations, they were deemed unsuitable for further study and subsequently discarded.

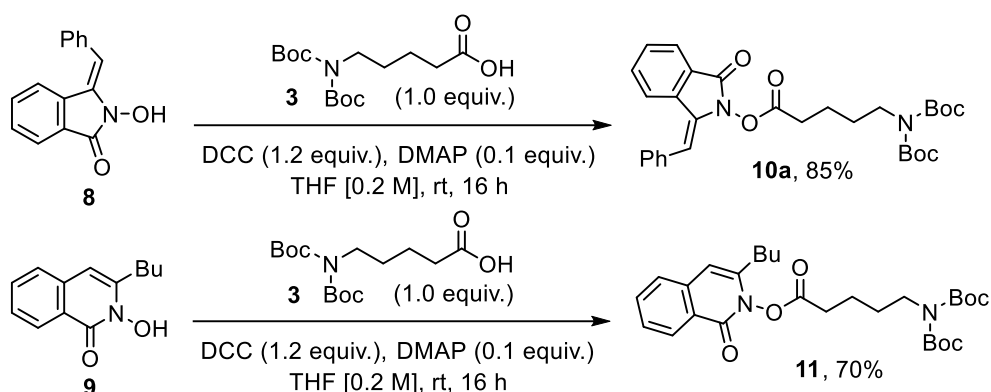


* The products could not be characterized as they were isolated alongside unidentified impurities.

*Scheme 4.16: Two-step synthesis of hydroxamic acids **8** and **9**.*

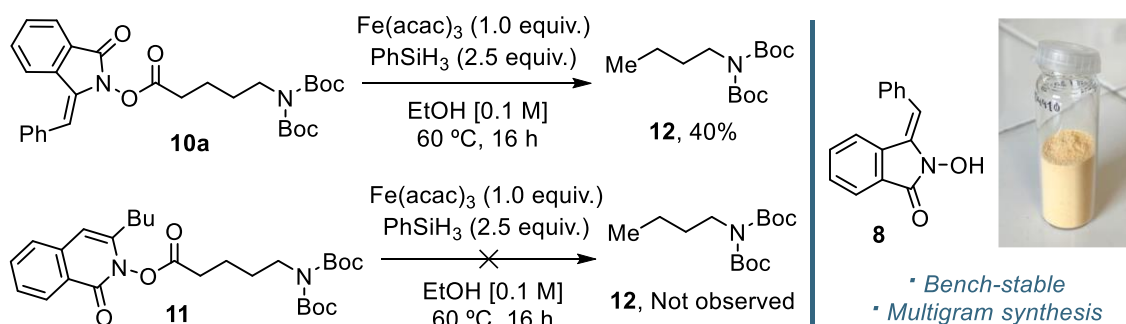
Initial decarboxylation studies

With the engineered redox-active ester precursors **8** and **9** in hand, we proceeded to study their coupling with *N,N*-di-Boc-aminovaleric acid via a Steglich esterification in the presence of *N,N*-dicyclohexylcarbodiimide (DCC) and DMAP (Scheme 4.17),⁵⁷ which successfully gave **10a** and **11** in 85 and 70% yield, respectively.



Scheme 4.17: Formation of **10a** and **11** via Steglich esterification.

At this point, we initiated preliminary decarboxylation studies to evaluate whether the engineered RAEs could be activated under MHAT conditions. Treating **10a** with phenylsilane and Fe(acac)₃ in ethanol at 60 °C for 16 hours yielded the decarboxylated product **12** in 40% yield, confirming the feasibility of the reaction. However, treatment of **11** under the same conditions resulted only in the recovery of starting material (Scheme 4.18). Consequently, redox-active ester precursor **8** was selected for further studies, as it performed well in all stages and was readily scalable, enabling the efficient preparation of large quantities.



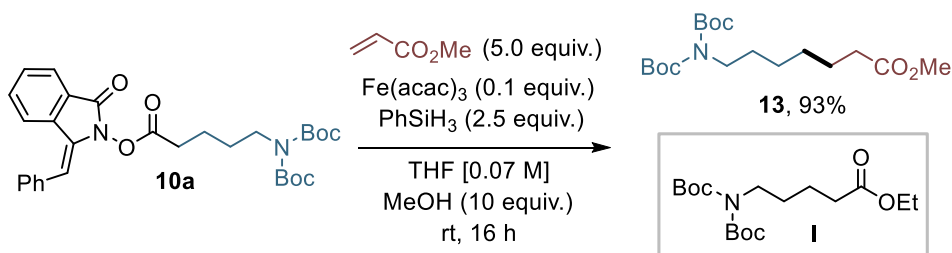
Scheme 4.18: Preliminary decarboxylation studies of **10a** and **11**, leading to the selection of **8** as the redox-active ester precursor for further investigation.

4.3.2 RAE-mediated Giese addition under MHAT conditions

4.3.2.1 Optimization of the reaction conditions

Despite the moderate yield of the preliminary decarboxylation studies, this result provided a proof of concept, demonstrating that the decarboxylative radical process was viable under MHAT conditions. With this validation, we next explored the Giese-type coupling of **10a** with methyl acrylate as the acceptor (*Table 4.2*). Upon optimization, we found that **13** could be formed in 93% yield when performing the reaction between **10a** and 5.0 equivalents of methyl acrylate in the presence of 0.1 equivalents of Fe(acac)₃ and 2.5 equivalents of PhSiH₃ in THF, with 10 equivalents of methanol as an additive, at room temperature for 16 hours (*entry 1*). The use of heating and ethanol as the solvent led to significant formation of the transesterification product **I** (*entries 2 and 3*).

Table 4.2: Optimization of the MHAT coupling conditions.

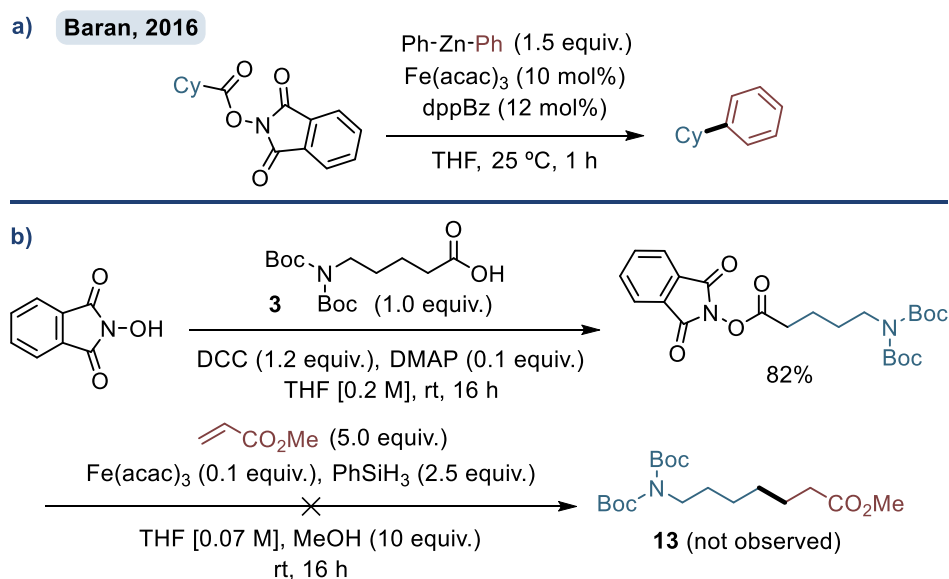


Entry ^a	Deviation from optimum conditions	Yield ^b
1	No deviation	93
2	60 °C instead of rt, EtOH as solvent	55
3	EtOH as solvent	74
4	DCE instead of THF/MeOH	2
5	10 equiv. of acceptor	35
6	2.0 equiv. of acceptor	74
7	0.25 equiv. of Fe(acac) ₃	89
8	0.5 equiv. of Fe(acac) ₃	90
9	1.0 equiv. of PhSiH ₃	64
10	Co(acac) ₃ instead of Fe(acac) ₃	-
11	Mn(dpm) ₃ instead of Fe(acac) ₃	-

^aAll reactions were carried out on a 0.2 mmol scale except the optimized reaction which was carried out on a 1.0 mmol scale (91% on a 0.2 mmol scale). ^bAll yields are isolated yields.

Replacing EtOH with DCE as the solvent (*entry 4*) to prevent transesterification led to only trace amounts of the coupled product, indicating that an alcoholic solvent was essential. Adjusting the acceptor amount (*entries 5 and 6*) proved detrimental, while varying the iron catalyst loading had little effect (*entries 7 and 8*), with a slight yield improvement at lower loadings. Reducing PhSiH₃ from 2.5 to 1.0 equivalent lowered the yield (*entry 9*). Finally, replacing Fe(acac)₃ with Co(acac)₃ or Mn(dpm)₃ (*entries 10 and 11*) completely suppressed reactivity, leading to full recovery of the starting material.

In 2016, Baran and coworkers reported a decarboxylative cross-coupling of RAEs with arylzinc compounds, utilizing a Fe(acac)₃-based catalytic cycle (*Scheme 4.19, a*).^{44a} To evaluate whether classical *N*-hydroxyphthalimide esters could also undergo decarboxylation under MHAT conditions, we synthesized a conventional precursor and subjected it to the reaction (*Scheme 4.19, b*). This experiment aimed to determine if the process was driven by radical formation at the carbonyl group via SET or initiated through the precursor's alkene fragment via HAT from the metal hydride species. However, treatment of the redox-active ester under the optimal conditions led to no detectable formation of **13**, nor the reduced compound **12**. Likewise, the addition of 1.0 equivalent of Fe(acac)₂ –since Fe^{II} is known to cleave RAEs (see *Scheme 1.66*)– led to a similar outcome. These results indicated that the alkene fragment in our novel redox-active ester was essential to initiate decarboxylative coupling under MHAT conditions.



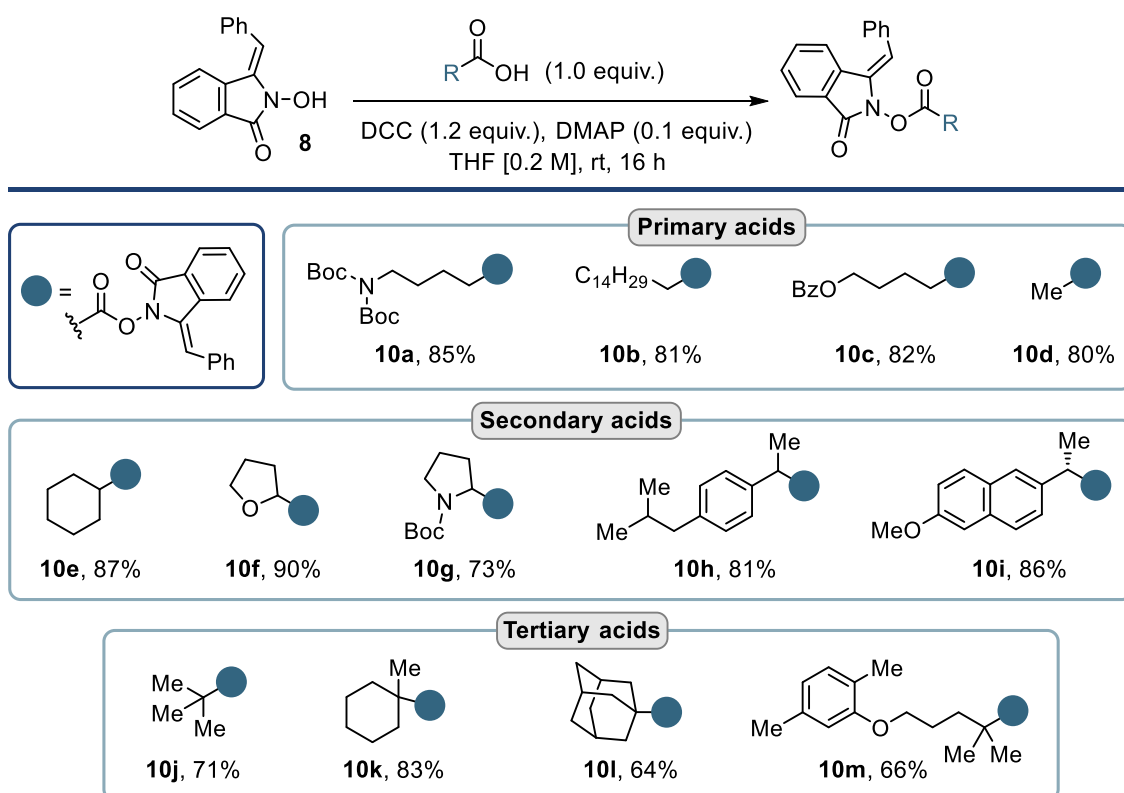
Scheme 4.19: a) Baran's Barton-type decarboxylation process. b) Testing of classical NHPI esters under our MHAT conditions.

4.3.2.2 Substrate scope

Synthesis of the RAEs

To study the scope of carboxylic acids suitable for the MHAT coupling, we conducted a coupling of selected primary, secondary, and tertiary acids with hydroxamic acid **8** via a Steglich esterification to give the additional precursors **10b** to **10m** (Table 4.3).⁵⁷

Table 4.3: Synthesized RAEs for the MHAT decarboxylative coupling.



Scope of the reaction

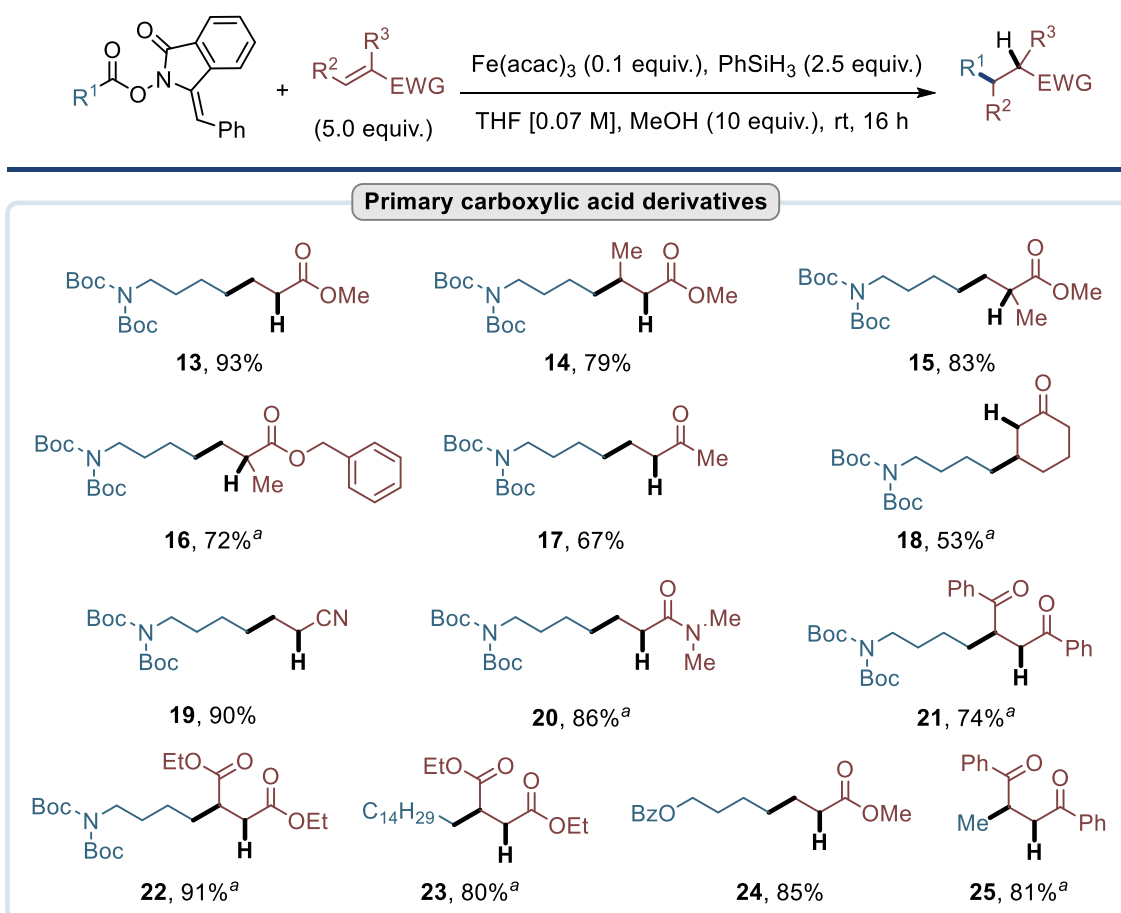
With the optimal conditions established, we explored the reaction scope of primary carboxylic acids (Table 4.4). The coupling with **10a** demonstrated broad compatibility with various Michael acceptors bearing diverse electron-withdrawing groups, including esters with different substitution patterns (**14–16**), ketones (**17–18**), nitriles (**19**), and amides (**20**). Additionally, acceptors bearing two electron-withdrawing groups were effective coupling partners (**21–22**).

Beyond these, other primary radical donors (**10b–10d**) were evaluated, demonstrating high efficiencies (**23–25**). Notably, the methyl radical donor **10d** was of particular interest,

as methyl incorporation is highly valued in medicinal chemistry due to its profound pharmacological impact, commonly referred to as the "magic methyl" effect. This phenomenon has been linked to significant potency increases, sometimes exceeding 1000-fold, primarily due to induced conformational changes that enhance target binding. Additional factors, such as a reduced desolvation penalty and enhanced hydrophobic interactions, further contribute to its widespread relevance in drug design.⁵⁸

With these results in hand, our methodology proved to be effective for the generation of linearly coupled products; an otherwise inaccessible transformation in classical MHAT reactions that employ alkenes as radical precursors.

Table 4.4: Scope of primary acids for the MHAT decarboxylative coupling.



^a2.0 equivalents of the acceptor were used in cases where it was non-volatile to simplify purification.

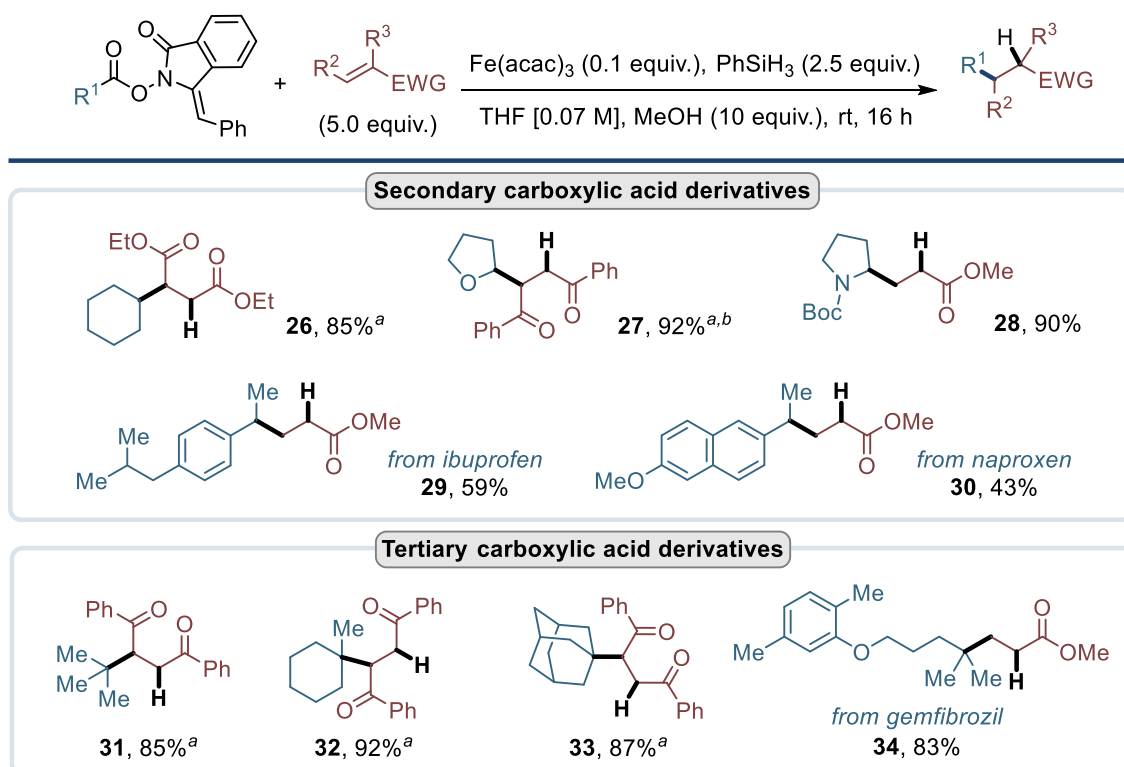
We next investigated secondary radical precursors (*Table 4.5*). For predicted volatile products, an acceptor with two electron-withdrawing groups was used instead of methyl acrylate. Cyclohexane carboxylic acid (**10e**), tetrahydro-2-furoic acid (**10f**), and *N*-Boc

proline derivatives (**10g**) coupled efficiently, affording **26–28** in excellent yields. The presence of a stabilizing heteroatom enhanced the coupling efficiency without requiring alternative iron catalysts, which are typically needed when using alkenes as radical precursors to mitigate unwanted side reactions caused by the Lewis acidity of the metal.⁵⁹

In contrast, benzylic radicals exhibited somewhat lower yields, with derivatives from ibuprofen (**10h**) and naproxen (**10i**) giving **29** and **30** in 59 and 43% yield, respectively. This could be due to the particular stability of these radicals, which may lead to the formation of byproducts such as the protodecarboxylated donors, that could be observed during the purification process.

Finally, all studied tertiary radical precursors (**10j–10l**) performed exceptionally well, enabling the coupling of *tert*-butyl (**31**), methylcyclohexane (**32**), and adamantane (**33**) fragments. Moreover, the ester derived from gemfibrozil (**10m**) successfully coupled with methyl acrylate, furnishing **34** in 83% yield.

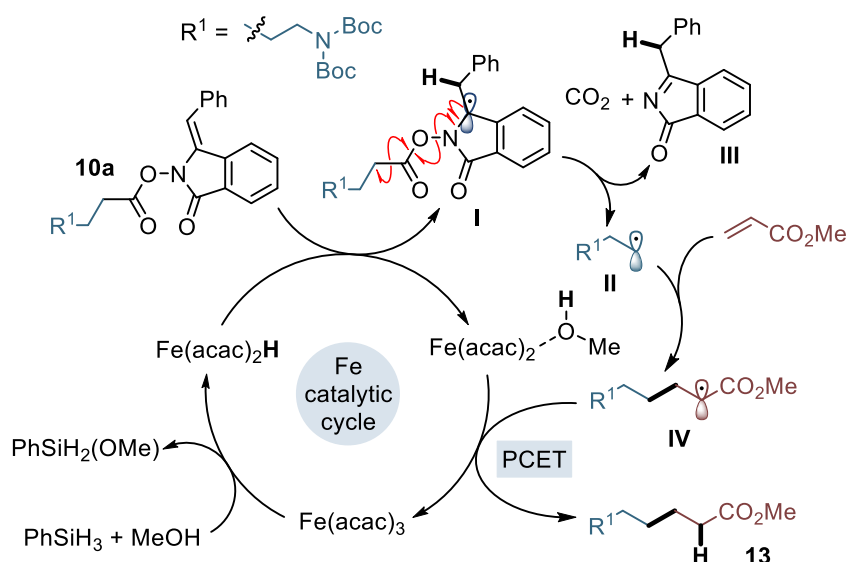
Table 4.5: Scope of secondary and tertiary acids for the MHAT decarboxylative coupling.



^a2.0 equivalents of the acceptor were used in cases where it was non-volatile to simplify purification. ^bIsolated as a 60:40 mixture of diastereoisomers.

4.3.2.3 Mechanism of the reaction

Our proposed reaction mechanism begins with the generation of an iron hydride species,⁶⁰ which subsequently adds to the alkene fragment of **10a** (Scheme 4.20). This leads to the formation of intermediate **I**, featuring a radical adjacent to the nitrogen atom. This radical then triggers decarboxylation, releasing carbon dioxide and generating the primary radical species **II** along with intermediate **III**. The alkyl radical **II** undergoes coupling with methyl acrylate to form **IV**, which is then reduced via a proton-coupled electron transfer (PCET)⁶¹ process involving the Fe^{II} species and a molecule of MeOH. This reduction yields **13** while simultaneously oxidizing Fe^{II} to Fe^{III}, thereby completing the catalytic cycle.



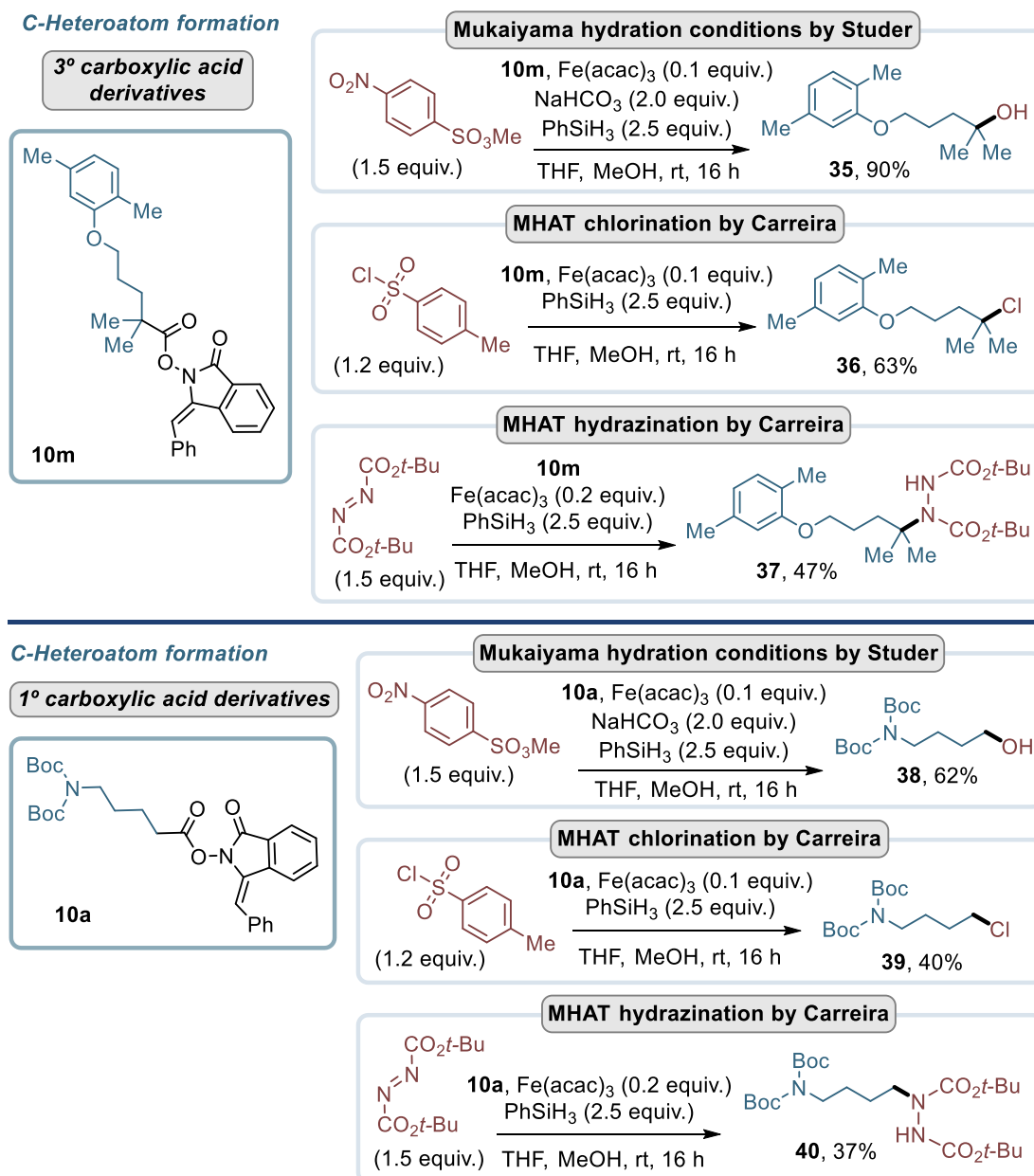
Scheme 4.20: Proposed mechanism for the RAE-mediated Giese addition under MHAT conditions.

4.3.3 Use of RAEs as radical precursors in established MHAT reactions

After thoroughly investigating the novel Giese coupling between redox-active esters and electron-deficient alkenes, we demonstrated that our procedure could generate a wide range of radical species. We next explored the applicability of these donors across a broader scope of established MHAT reactions, starting with C–heteroatom bond-forming couplings (Scheme 4.21).

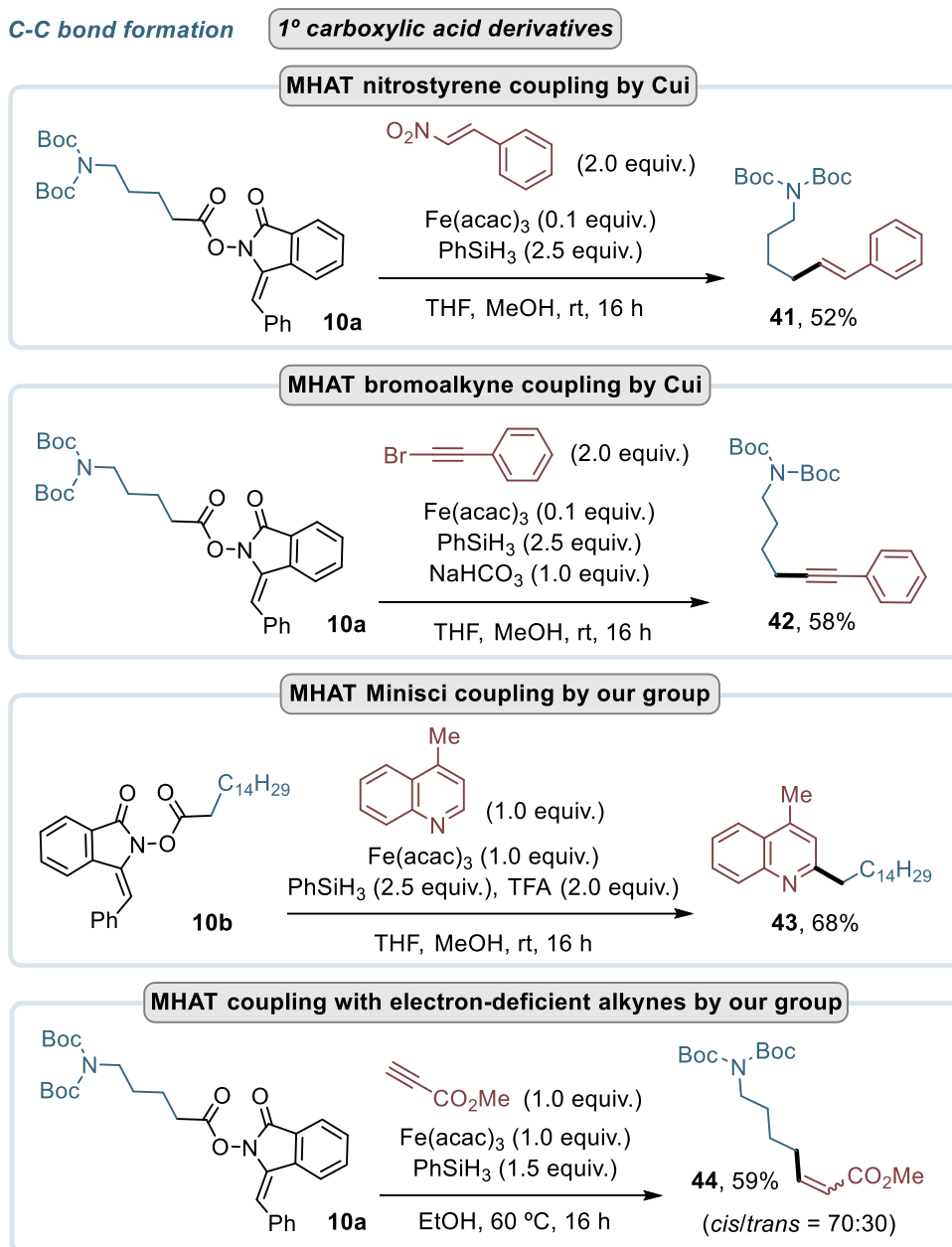
We initially selected tertiary RAE **10m**, given the enhanced stability of the resulting radical. Studer's Mukaiyama-type hydration, utilizing methyl 4-nitrobenzenesulfonate as

the acceptor, afforded alcohol **35** in excellent yield.⁶² Likewise, Carreira's hydrochlorination with TsCl provided chloride **36**,⁶³ while his hydrazination strategy, employing di-*tert*-butyl azodicarboxylate, successfully furnished **37**.⁶⁴ Using **10a** as a donor under Studer's hydration conditions gave primary alcohol **38** in 62% yield, while chlorination and hydrazination under Carreira's conditions provided the targeted compounds **39** and **40** in 40 and 37% yield, respectively. Although the yields were lower, likely due to the instability of the primary radical favoring reduction, it is noteworthy that these compounds are not accessible via classical MHAT couplings with alkenes.



Scheme 4.21: C-Heteroatom MHAT reactions with primary and tertiary RAEs.

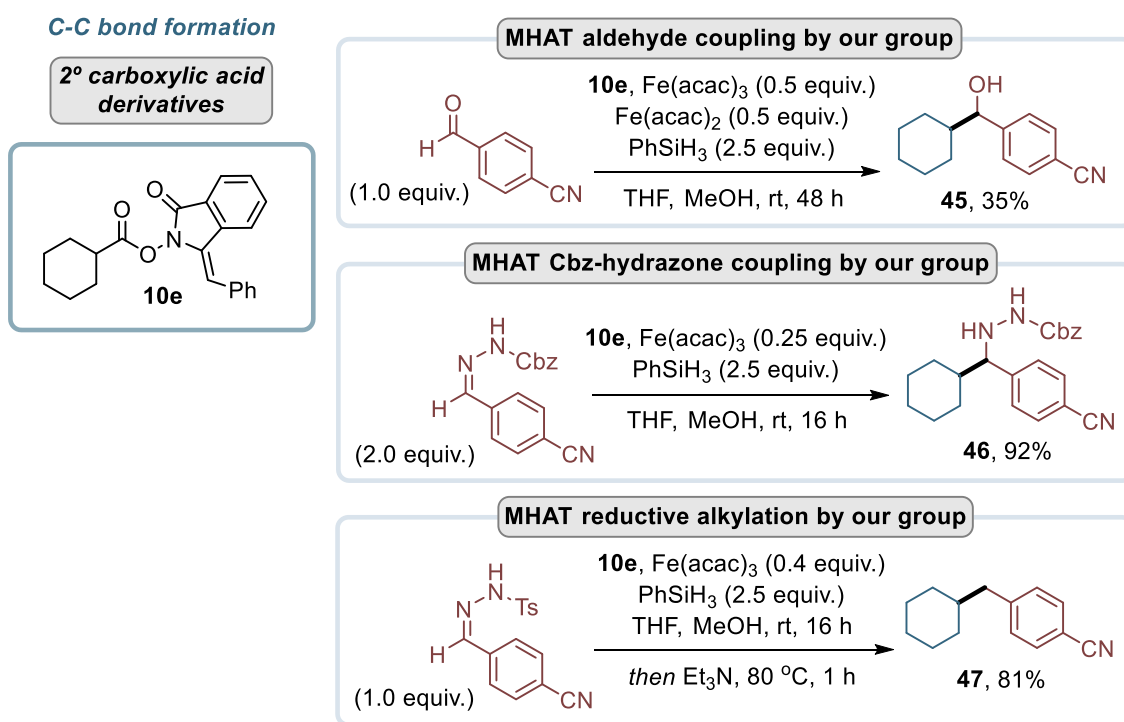
Next, we investigated C–C bond-forming reactions (Scheme 4.22). The coupling of RAE **10a** with nitrostyrene⁶⁵ and (bromoethynyl)benzene,⁶⁶ as reported by Cui, successfully yielded the linear products **41** and **42** in 52 and 58% yield, respectively. Leveraging our group's expertise in utilizing heterocycles as acceptors in MHAT reactions, we achieved the intermolecular Minisci coupling of **10b** with lepidine, affording heterocycle **43** in 68% yield. In this case, the RAE derived from palmitic acid was employed instead of **10a** to avoid stability issues caused by exposing the Boc protecting groups to TFA.⁶⁷



Scheme 4.22: C–C MHAT reactions with primary RAEs.

Finally, we applied our newly developed MHAT hydroalkylation strategy using electron-deficient alkynes as acceptors to **10a**, furnishing the unsaturated alkene **44** in 59% yield as a mixture of *cis* and *trans* isomers.⁶⁸ However, due to the presence of inseparable impurities, only the *cis* isomer could be successfully isolated and characterized.

Based on previous work in our group using aldehydes,⁶⁹ Cbz-hydrazones,⁷⁰ and Ts-hydrazones⁷¹ as acceptors in MHAT reactions, the redox-active ester **10e** underwent C–C bond-forming couplings to give alcohol **45**, hydrazine **46**, and alkylation product **47** after cleavage of the hydrazine intermediate with triethylamine (*Scheme 4.23*). Unfortunately, these reactions failed when using a primary RAE, yielding only the corresponding protodecarboxylated product. This outcome was mainly attributed to the reduced reactivity of carbonyl-type acceptors in MHAT reactions, particularly when compared to electron-deficient alkenes, resulting in competitive quenching of the initial primary alkyl radical via hydrogen atom transfer by the metal hydride species.



Scheme 4.23: C–C MHAT reactions with secondary RAEs.

In summary, these results showcase the broad potential of our MHAT-triggered decarboxylation of RAEs, enabling transformations beyond the reach of classical alkene-based methods, and highlighting the versatility of this approach in both C–heteroatom and C–C bond-forming reactions.

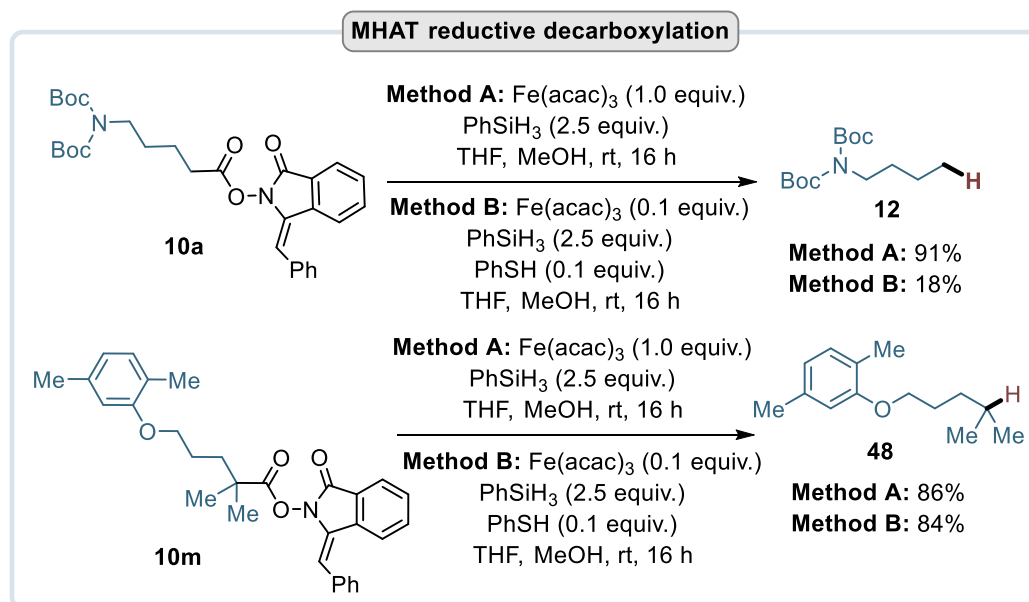
4.3.4 Barton-like decarboxylation of our engineered RAEs

With a methodology in hand to potentially enable the coupling of the benzomorphan core to the terpenic fragment of aspernomine via a Giese-type addition under MHAT conditions, we next turned our attention to the removal of the ester group (see *Scheme 3.18*). The synthesis of complex molecules often relies on the strategic incorporation of functional groups to selectively activate specific sites, directing reactivity and enabling precise bond formation. However, to achieve the desired molecular architecture, these functional groups typically need to be removed. As a result, various methodologies have been developed to achieve their reductive elimination in the final stages of synthesis.⁷²

In our particular case, the target was a methyl ester, which is usually removed via conversion to the corresponding carboxylic acid.⁷³ Conventional strategies, such as the classical Barton decarboxylation and photocatalytic approaches, are hindered by unstable reagents, toxic conditions, and scalability issues.⁷⁴ Therefore, we envisioned that our newly developed MHAT activation mode for RAEs could provide an effective platform for the decarboxylative reduction of carboxylic acids.

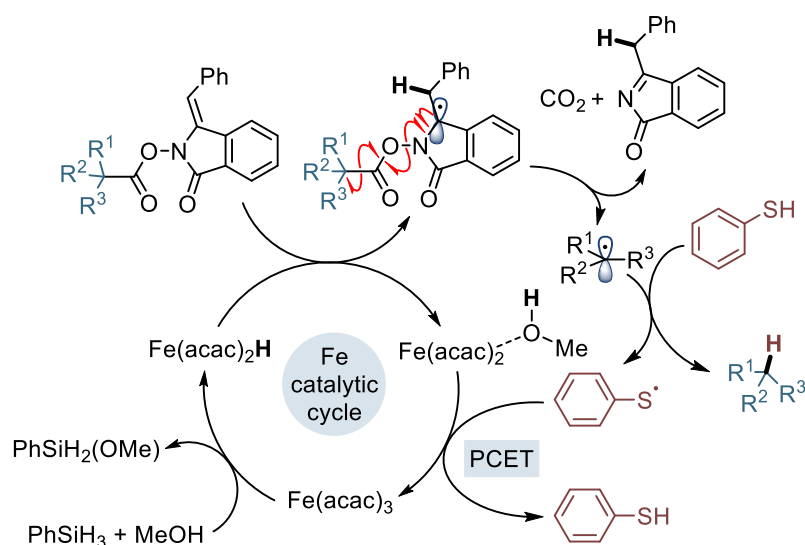
During our exploration of the decarboxylative functionalization of RAEs under MHAT conditions, several unsuccessful attempts led to the formation of overreduced products. Consequently, our initial studies focused on applying the reaction conditions without an acceptor group. Treatment of **10a** and **10m** in the absence of an acceptor and with stoichiometric Fe(acac)₃ (Method A) yielded excellent results, providing the decarboxylated products **12** and **48** in high yields. This approach offered a simple, efficient, and mild method for performing Barton-type decarboxylations (*Scheme 4.24*).

Subsequently, a catalytic version of the reaction incorporating 0.1 equivalents of thiophenol as an additive, based on the conditions developed by West for the hydrogenation of alkenes (Method B),⁷⁵ was tested. This method yielded nearly identical results for **10m** compared to the stoichiometric version. However, for **10a**, only an 18% yield of the desired decarboxylation product **12** was obtained, likely due to preferential quenching of the primary radical by the metal hydride. This was attributed to the absence of a persistent radical effect, which led to premature consumption of the catalyst before the reaction could complete.



Scheme 4.24: Initial studies of the MHAT-triggered reductive decarboxylation.

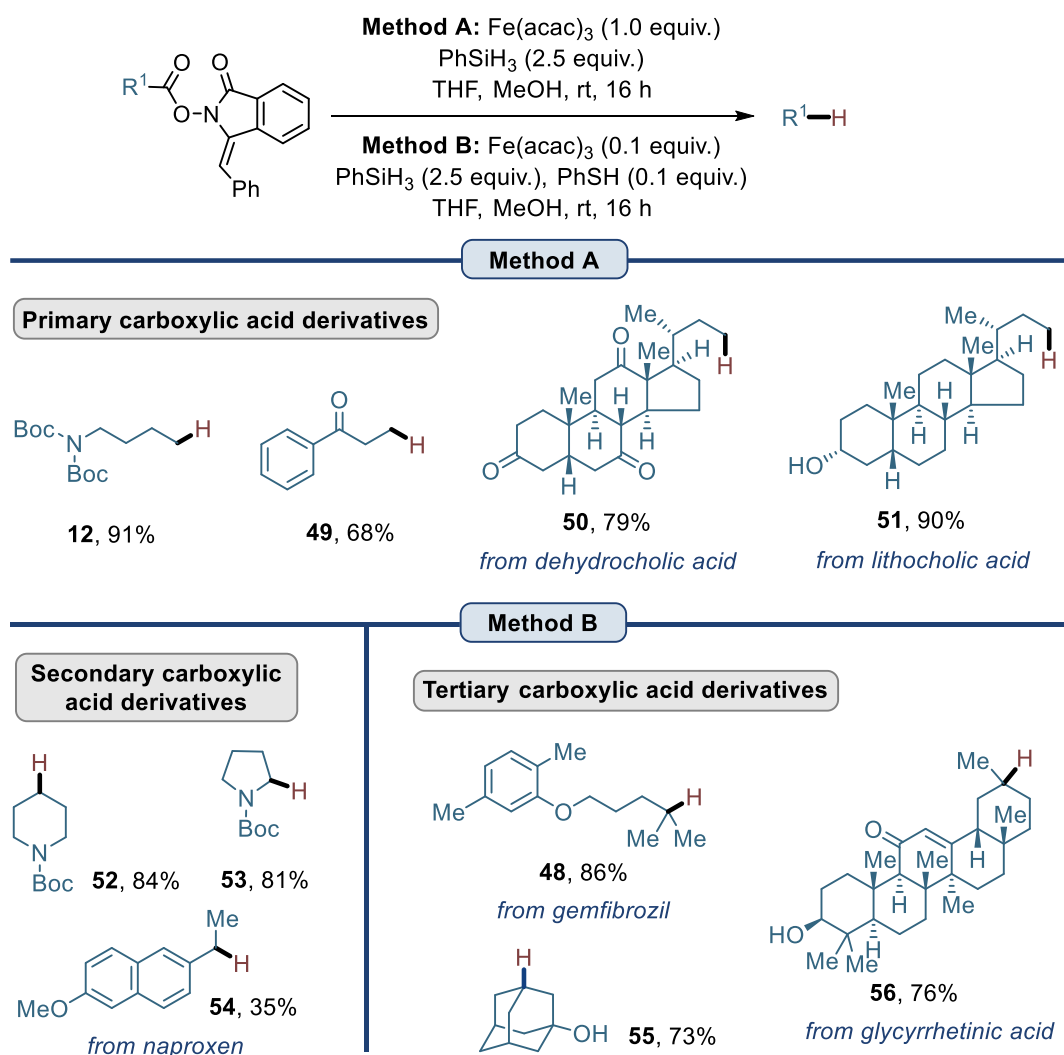
Mechanistically, the catalytic decarboxylation of RAEs via Method B begins identically to our previously proposed pathway (see Scheme 4.20). However, upon the formation of the alkyl radical species, a reductive quenching with thiophenol furnishes the protodecarboxylated compound alongside a phenylthiyl radical, which then undergoes reduction through a proton-coupled electron transfer (PCET) process, involving the Fe^{II} species and a molecule of MeOH. This process regenerates both the iron catalyst and thiophenol, thereby completing the catalytic cycle (Scheme 4.25).



Scheme 4.25: Proposed catalytic cycle for the reductive decarboxylation of RAEs.

With the conditions for RAE reduction established, we assessed the reaction's versatility using stoichiometric conditions (Method A) for primary acid-derived esters and catalytic conditions (Method B) for secondary and tertiary acid-derived esters. As shown in *Table 4.6*, a wide variety of carboxylic acids, regardless of their substitution pattern, were successfully reduced to give the decarboxylated compounds **49–56**. Notably, the reaction demonstrated broad functional group tolerance and remained unaffected by the presence of heteroatoms at the α -position of the radical. Furthermore, this strategy enabled the decarboxylation of several bioactive products, including dehydrocholic acid, lithocholic acid, naproxen, gemfibrozil, and glycyrrhetic acid.

Table 4.6: Initial evaluation of the scope of the MHAT reductive decarboxylation.

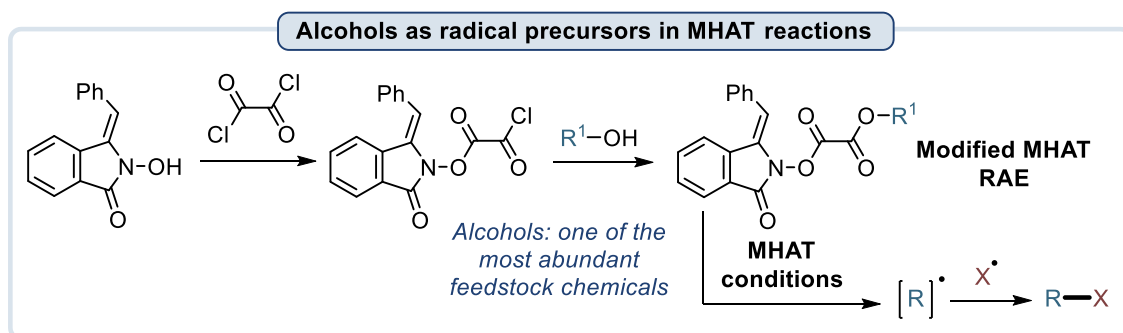


In summary, we have developed an unprecedented class of redox-active esters featuring a novel activation mode based on MHAT, enabling carboxylic acids to serve as surrogates

for alkenes across a broad range of MHAT transformations. Unlike the Markovnikov-selective reactivity of alkenes, these RAEs facilitate the formation of linearly coupled products in MHAT reactions for the first time. Furthermore, our reductive decarboxylation method expands the utility of this strategy. Together, these advancements significantly extend the scope of MHAT chemistry and lay the groundwork for future developments in novel MHAT couplings, a direction our group is actively pursuing.

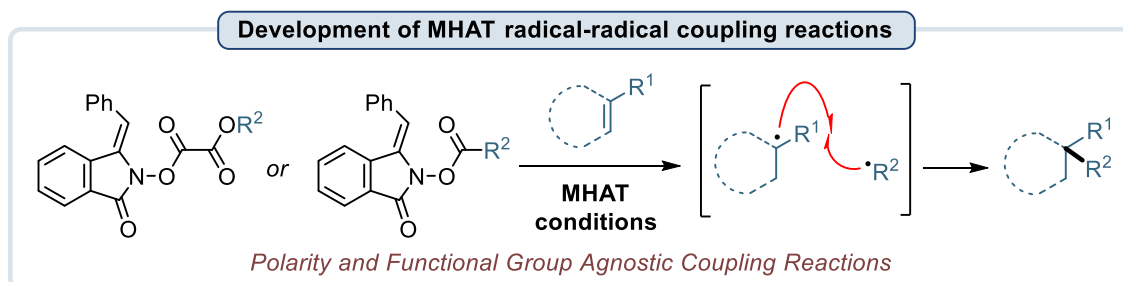
4.3.5 Future work

As future work, we aim to broaden the range of chemical feedstocks available as radical precursors in MHAT reactions. In this context, we propose modifying the RAE precursor developed in this chapter via coupling with oxalyl chloride to enable the direct use of alcohols as a radical source,⁴⁹ further expanding the scope and applicability of this strategy (Scheme 4.26).



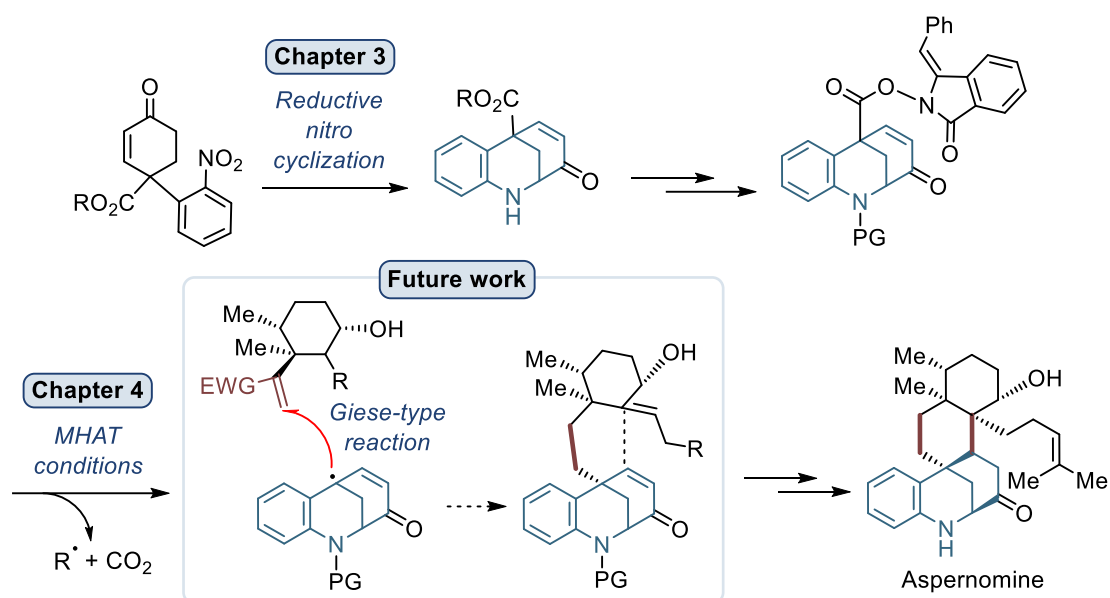
Scheme 4.26: Proposed MHAT coupling using alcohols as radical precursors.

Secondly, upon the expansion of the chemical space accessible via MHAT reactions, we would work toward the development of MHAT radical–radical couplings using the engineered RAEs to couple carboxylic acids or alcohols to neutral alkenes (Scheme 4.27).



Scheme 4.27: Proposed radical–radical MHAT coupling using engineered RAEs.

Finally, building on the methodology developed in Chapter 3 for constructing the azatricyclic core of aspernomine and the novel MHAT-triggered decarboxylation of RAEs introduced in Chapter 4, future work will focus on evaluating the coupling between the heterocyclic and terpenic fragments of the natural product (*Scheme 4.28*). The initially devised route proposed an intermolecular Giese addition to form this key bond, and this remains the primary approach moving forward. However, the exploration of alternative coupling reactions in this chapter suggests that other strategies could also be considered in future studies.



Scheme 4.28: Proposed studies toward the total synthesis of aspernomine.

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5. CONCLUSIONS

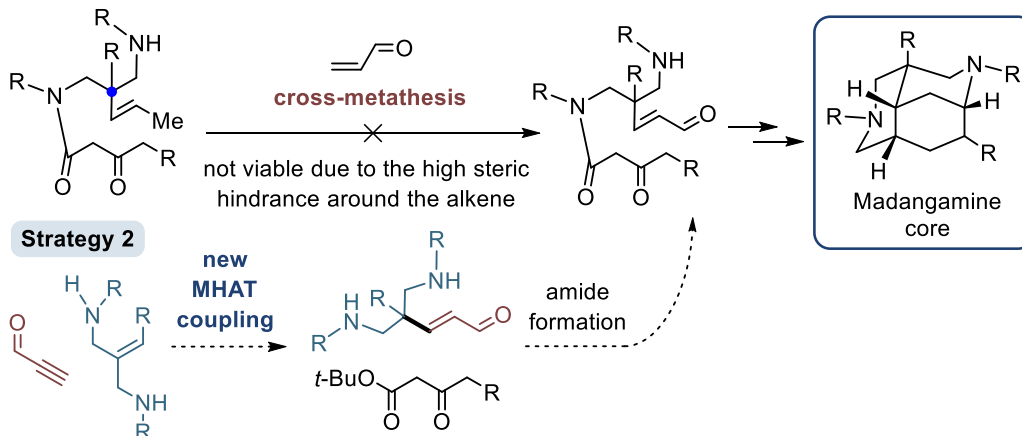
Throughout this work, the development of novel synthetic methodologies guided by a function-oriented synthesis approach has proven to be a powerful strategy for the design and synthesis of bioactive compounds. Based on the results obtained, we can conclude the following:

CHAPTER 2:

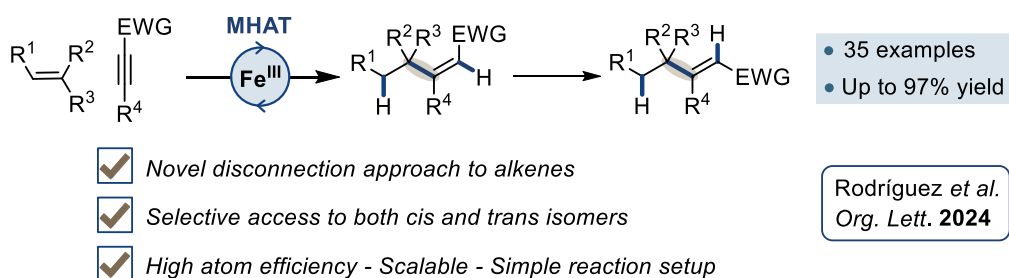
1. An efficient synthetic route was proposed to access the azatricyclic core of madangamine alkaloids via an intramolecular tandem approach, beginning with the preparation of a suitable enal precursor. The initial strategy to prepare this precursor, involving a cross-metathesis to install an acrolein fragment, failed due to significant steric hindrance around the alkene, thereby revealing a notable gap in the literature regarding the construction of such structural motifs. This limitation prompted the development of an alternative approach, featuring a novel MHAT C-C coupling reaction to access electron-deficient alkenes (Scheme 5.1, a).

a) Synthesis of the core of madangamine alkaloids

Strategy 1



b) Hydroalkylation with electron-deficient alkynes



Scheme 5.1: a) Attempted strategies to access the core of madangamine alkaloids. b) MHAT Giese-type addition of electron-deficient alkynes to neutral alkenes.

2. A novel MHAT strategy was developed for the selective reductive coupling of neutral alkenes with electron-deficient alkynes (*Scheme 5.1, b*), representing a new disconnection approach to electron-deficient alkenes. This method demonstrated excellent functional group tolerance, enabling the efficient coupling of alkenes bearing ester, phthalimide, carbamate, and sulfonyl groups with a variety of electron-deficient alkynes, including esters, amides, and ketones. The reaction proceeded under mild, non-toxic conditions with high atom efficiency and scalability.

3. The strategy allowed for control over alkene geometry, predominantly yielding the *cis* isomer, which could be readily isomerized to the *trans* form. The method also enabled the installation of olefins adjacent to sterically hindered centers, providing a key advantage over traditional olefination techniques and expanding the synthetic toolbox for constructing complex molecular frameworks. This approach lays a solid foundation for the future synthesis of the madangamine core, although detailed optimization is still needed. Due to time constraints, this aspect falls beyond the scope of this thesis, but it will be further developed in future studies.

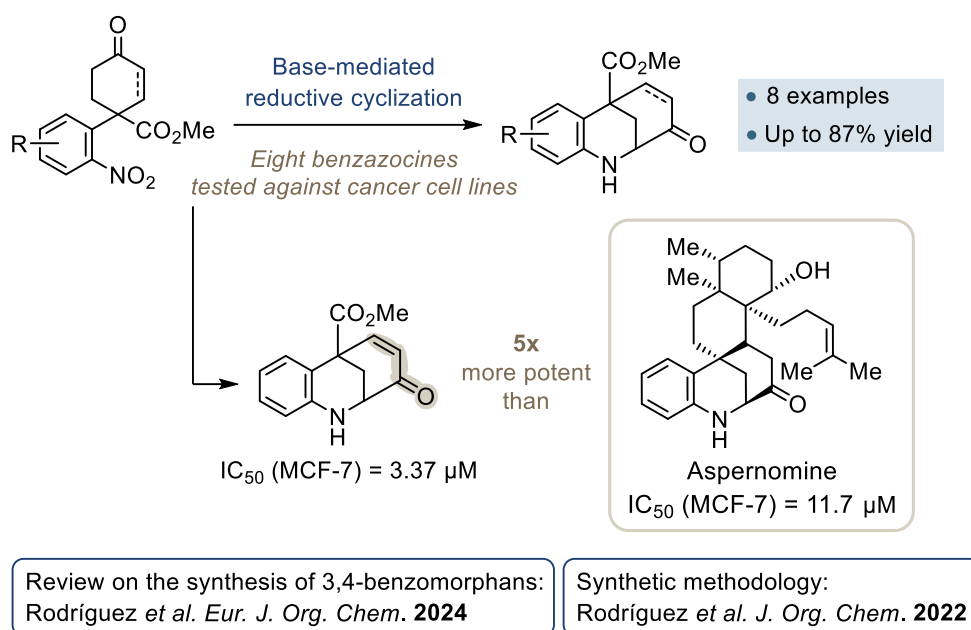
CHAPTER 3:

4. This chapter proposed a modular approach for the synthesis of aspernomine. Given the complexity of the target and guided by a function-oriented synthesis perspective, we focused on constructing the 3,4-benzomorphan fragment. A thorough review of the literature revealed the absence of synthetic strategies capable of positioning the necessary functional groups within the azatricyclic core for further elaboration toward the natural product. This research was published as a review during the course of this thesis.

5. A base-mediated nitrophenyl reductive cyclization strategy was developed to efficiently construct the 3,4-benzomorphan scaffold with the required functional groups for subsequent elaboration into aspernomine (*Scheme 5.2*). This approach enabled a concise, four-step synthesis of these valuable benzazocine derivatives.

6. The biological evaluation of the synthesized benzazocines revealed that, while the core structure alone exhibited lower cytotoxicity than aspernomine, the introduction of an enone moiety significantly enhanced antiproliferative activity against human cancer

cell lines. This suggested that the enone fragment could serve as a key pharmacophore, potentially contributing to the enhanced bioactivity, similarly to other Michael acceptor-based drugs that are used in cancer treatment through mechanisms such as irreversible cysteine or serine alkylation. Although the saturated analogs displayed reduced activity, the well-documented bioactivity of 3,4-benzomorphan-containing compounds highlights their potential for future investigation in other therapeutic areas, including antiviral and antibacterial applications.



Scheme 5.2: Base-mediated reductive cyclization of nitrophenyl ketones.

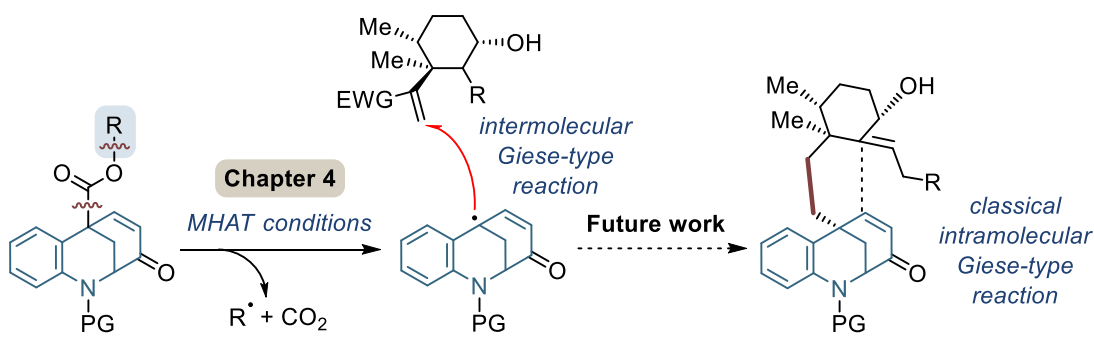
CHAPTER 4:

7. To continue making progress in the total synthesis of aspernomine, a previously undisclosed MHAT decarboxylative Giese addition was devised to form the first key bond between the heterocyclic and terpenic fragments (Scheme 5.3, a). To achieve this, a novel class of redox-active esters was developed by incorporating an alkene fragment into the classical *N*-hydroxyphthalimide framework. This modification enabled decarboxylation under MHAT conditions, allowing carboxylic acids to be used as radical precursors in MHAT reactions for the first time. This approach introduced an accessible radical source, broadening the scope of MHAT processes and unlocking new synthetic applications (Scheme 5.3, b).

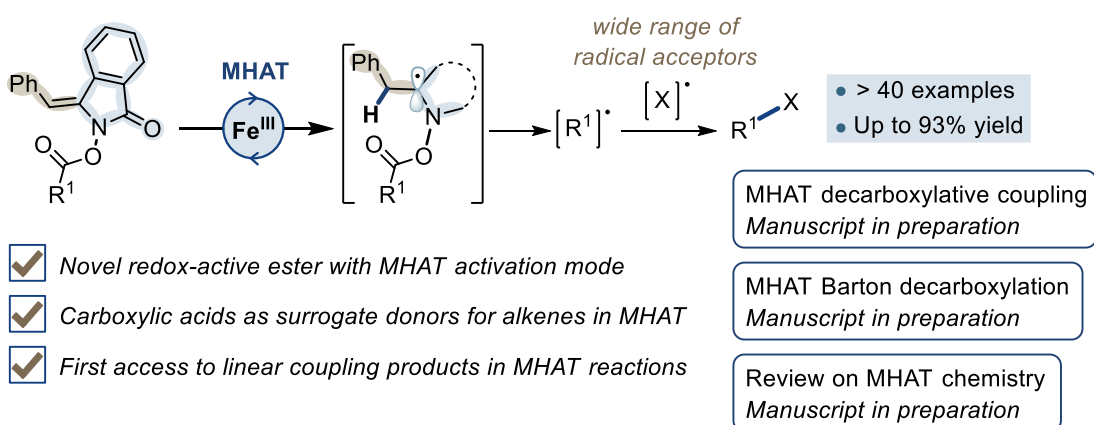
8. The methodology granted access to primary radicals, enabling the formation of linearly coupled products under MHAT conditions for the first time. This approach complements the formation of branched products observed with alkene-based precursors, providing a new avenue for selective coupling reactions.

9. The scope of the RAEs was thoroughly examined through a Giese-type coupling with electron-deficient alkenes, demonstrating that a wide range of radicals could be generated from these carboxylic acid-derived precursors. To further explore their applicability, the RAEs were successfully employed in a broad spectrum of well-established MHAT reactions, underscoring their versatility and potential for diverse synthetic applications.

a) **Required methodology for the total synthesis of aspernomine**



b) **MHAT-triggered decarboxylation of RAEs**



Scheme 5.3: a) Proposed route toward the synthesis of aspernomine. b) Development of a novel MHAT activation mode for the decarboxylation of redox-active esters.

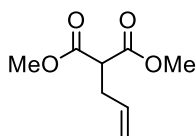
6. EXPERIMENTAL SECTION

General information

All reactions were carried out under an argon atmosphere using dry, freshly distilled solvents under anhydrous conditions. Analytical thin-layer chromatography (TLC) was performed on SiO₂ (Merck silica gel 60 F₂₅₄), and the spots were located with 1% aqueous KMnO₄ or 2% ethanolic anisaldehyde solutions. Chromatography refers to flash column chromatography and was carried out on SiO₂ (SDS silica gel 60 ACC, 35-75 μm, 230-240 mesh ASTM). Organic layers were dried over anhydrous Na₂SO₄ during reaction workup. Solvents were removed under reduced pressure using a rotary evaporator. NMR spectra were recorded in CDCl₃ unless stated otherwise. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane or the residual solvent peak. All NMR signal assignments were supported by gCOSY and gHSQC experiments. High-resolution mass spectra (HRMS) were recorded using an electrospray ionization (ESI) source with a time-of-flight (TOF) analyzer (Agilent Technologies).

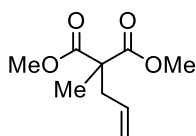
2. ELECTRON-DEFICIENT ALKYNES AS ACCEPTOR GROUPS IN MHAT REACTIONS WITH UNACTIVATED ALKENES

PRELIMINARY STUDIES FOR THE ASSEMBLY OF THE MADANGAMINE CORE



*Dimethyl 2-allylmalonate (1a).*¹ To a suspension of K₂CO₃ (16.6 g, 120

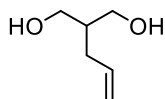
mmol, 2.0 equiv.) in acetone (200 mL, 0.3 M) was added dimethyl malonate (7.92 g, 60 mmol, 1.0 equiv.) dropwise, and the resulting solution was left to stir for 15 minutes. Then, allyl bromide (5.80 g, 4.2 mL, 48 mmol, 0.8 equiv.) was added and the solution was stirred for 24 hours at room temperature. Upon completion, the reaction was quenched with a saturated solution of NH₄Cl and subsequently extracted with dichloromethane (3 × 80 mL), dried with Na₂SO₄ and concentrated under reduced pressure. Purification by chromatography (Hex → Hex/AcOEt 10%) gave **1a** (6.52 g, 79%) as a colorless liquid. Spectral data were identical to those previously reported.^[1] ¹H NMR (400 MHz, CDCl₃) δ 5.83 – 5.69 (m, 1H), 5.15 – 5.08 (m, 1H), 5.07 – 5.02 (m, 1H), 3.73 (s, 6H), 3.46 (t, *J* = 7.6 Hz, 1H), 2.68 – 2.60 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 169.4, 134.0, 117.8, 52.6, 51.5, 33.0 ppm.



Dimethyl 2-allyl-2-methylmalonate (1b). To a solution of NaH (1.87 g, 78

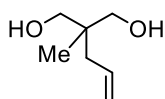
mmol, 2.5 equiv.) in THF (91 mL, 0.34 M) was added dimethyl 2-allylmalonate (5.35 g, 31 mmol, 1.0 equiv.) and the resulting mixture was stirred for 1 h at 0 °C. After, methyl iodide (13.2 g, 5.8 mL, 93 mmol, 3.0 equiv.) was added dropwise and the solution was stirred for 24 hours at room temperature. Upon completion, the reaction was quenched with a saturated solution of NH₄Cl and THF was evaporated. The solution was then extracted with diethyl ether (3 × 40 mL), dried with Na₂SO₄ and concentrated under reduced pressure. Purification by chromatography (Hex → Hex/AcOEt 10%) gave **1b** (2.89 g, 50%) as a colorless liquid. Spectral data were identical to those previously reported.^[2] ¹H NMR (400 MHz, CDCl₃) δ 5.75 – 5.61 (m, 1H), 5.14 – 5.09 (m, 1H), 5.09 –

5.06 (m, 1H), 3.71 (s, 6H), 2.61 (d, $J = 7.4$ Hz, 2H), 1.40 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 172.5, 132.7, 119.3, 53.8, 52.6, 40.3, 20.0 ppm.



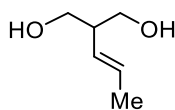
2-allylpropane-1,3-diol (2a). To a solution of LiAlH_4 (4.10 g, 108 mmol, 3.0

equiv.) in diethyl ether (144 mL, 0.25 M) at 0 °C was added 2-allylpropane-1,3-diol (6.20 g, 36 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 18 hours. Upon completion, the reaction was quenched with a 15% NaOH aqueous solution and subsequently stirred for 30 minutes at room temperature. Then, the crude mixture was filtered through Celite, dried with Na_2SO_4 and concentrated under reduced pressure to give **2a** (3.22 g, 77%) as a colorless oil. Spectral data were identical to those previously reported.^[3] ^1H NMR (400 MHz, CDCl_3) δ 5.78 (ddt, $J = 17.2, 10.1, 7.1$ Hz, 1H), 5.12 – 4.95 (m, 2H), 3.86 – 3.72 (m, 2H), 3.71 – 3.57 (m, 2H), 2.80 (s, 2H), 2.12 – 1.98 (m, 2H), 1.95 – 1.74 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 136.3, 116.7, 65.7, 41.9, 32.6 ppm.



2-allyl-2-methylpropane-1,3-diol (2b). To a solution of LiAlH_4 (1.43 g, 37.8

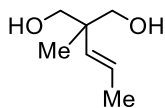
mmol, 3.0 equiv.) in diethyl ether (50 mL, 0.25 M) at 0 °C was added dimethyl 2-allyl-2-methylmalonate (2.35 g, 12.6 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 18 hours. Upon completion, the reaction was quenched with a 15% NaOH aqueous solution and subsequently stirred for 30 minutes at room temperature. Then, the crude mixture was filtered through Celite, dried with Na_2SO_4 and concentrated under reduced pressure to give **2b** (1.62 g, 99%) as a colorless oil. Spectral data were identical to those previously reported.^[4] ^1H NMR (400 MHz, CDCl_3) δ 5.91 – 5.76 (m, 1H), 5.14 – 5.07 (m, 1H), 5.09 – 5.05 (m, 1H), 3.59 – 3.47 (m, 4H), 2.79 (s, 2H), 2.11 (d, $J = 7.5$ Hz, 2H), 0.83 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 134.3, 118.0, 70.2, 39.4, 38.8, 18.6 ppm.



2-(prop-1-en-1-yl)propane-1,3-diol (3a).⁵ 2-allylpropane-1,3-diol (4.07 g,

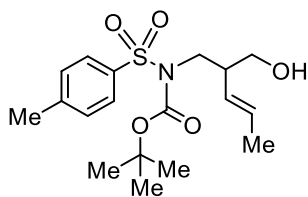
35 mmol, 1.0 equiv.) was treated with $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ (Rh 38-40%, 25 mg, 0.1 mol%) at 120 °C for 5 days. Purification by chromatography ($\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{MeOH}$ 4%) gave **3a** (3.66 g, 90%) as a yellow oil. The product was isolated as a 1:4 *cis/trans* mixture. ^1H NMR (400

MHz, CDCl₃) δ 5.73 – 5.55 (m, 1H), 5.27 (ddq, J = 15.5, 8.1, 1.7 Hz, 0.78H), 5.16 (ddq, J = 11.3, 9.6, 1.8 Hz, 0.22H), 3.68 (d, J = 6.3 Hz, 4H), 2.96 – 2.82 (m, 0.3H), 2.54 – 2.38 (m, 1.6H), 1.74 – 1.64 (m, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 129.2, 128.6, 128.2, 126.9, 65.4, 65.2, 46.9, 41.8, 18.4, 13.5 ppm.



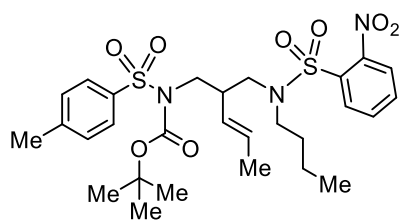
(*E*)-2-methyl-2-(prop-1-en-1-yl)propane-1,3-diol (**3b**).⁵ Dimethyl 2-allyl-2-

methylmalonate (1.05 g, 8.0 mmol, 1.0 equiv.) was treated with RhCl₃·xH₂O (Rh 38-40%, 6 mg, 0.1 mol%) at 120 °C for 5 days. Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 4%) gave **3b** (740 mg, 70%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.58 (dq, J = 15.8, 6.3 Hz, 1H), 5.39 (dd, J = 15.8, 1.6 Hz, 1H), 3.61 – 3.46 (m, 4H), 2.48 – 2.38 (m, 2H), 1.71 (dd, J = 6.3, 1.6 Hz, 3H), 0.99 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 133.8, 126.0, 69.5, 42.7, 19.3, 18.6 ppm.



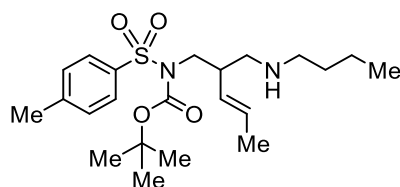
tert-butyl-(2-(hydroxymethyl)pent-3-en-1-yl)(tosyl)carbamate

(**4a**). To a solution of *tert*-butyl tosylcarbamate (1.76 g, 6.5 mmol, 0.9 equiv.) and triphenylphosphine (2.83 g, 10.8 mmol, 1.5 equiv.) in tetrahydrofuran (48 mL, 0.15 M) was added diethyl azodicarboxylate (40% solution in toluene, 4.1 mL, 9.0 mmol, 1.25 equiv.) dropwise and the solution was stirred for 10 minutes at room temperature. Then, 2-(prop-1-en-1-yl)propane-1,3-diol (840 mg, 7.2 mmol, 1.0 equiv.) was added and the reaction was stirred at room temperature overnight. Upon completion, the solvent was evaporated under reduced pressure. Purification by chromatography (Hex/AcOEt 2.5% → Hex/AcOEt 25%) gave **4a** (1.08 g, 45%) as a yellow oil. The product was isolated as a 1:6 *cis/trans* mixture. ¹H NMR (500 MHz, CDCl₃) δ 7.78 – 7.74 (m, 2H), 7.33 – 7.27 (m, 2H), 5.77 – 5.61 (m, 1H), 5.49 – 5.39 (m, 1H), 3.97 – 3.86 (m, 1H), 3.84 – 3.74 (m, 1H), 3.68 (dd, J = 11.3, 4.9 Hz, 1H), 3.65 – 3.58 (m, 1H), 2.73 – 2.63 (m, 1H), 2.44 (s, 3H), 1.72 (dd, J = 6.9, 1.8 Hz, 0.5H), 1.70 (dd, J = 6.4, 1.6 Hz, 2.6H), 1.33 (s, 1.5H), 1.33 (s, 7.4H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 151.8, 144.5, 137.4, 129.40, 129.35, 129.0, 128.0, 84.9, 62.9, 48.0, 45.9, 28.0, 21.8, 18.4 ppm.



tert-butyl-(2-(((*N*-butyl-2-nitrophenyl)sulfonamido)

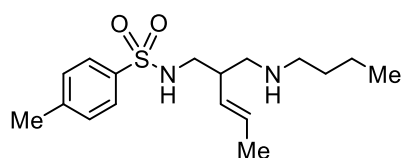
methyl)pent-3-en-1-yl)(tosyl)carbamate (**5**). To a solution of *N*-butyl-2-nitrobenzenesulfonamide (245 mg, 0.95 mmol, 0.95 equiv.) and triphenylphosphine (393 mg, 1.5 mmol, 1.5 equiv.) in tetrahydrofuran (7 mL, 0.15 M) was added diethyl azodicarboxylate (40% solution in toluene, 0.6 mL, 1.25 mmol, 1.25 equiv.) dropwise and the solution was stirred for 10 minutes at room temperature. Then, *tert*-butyl-(2-(hydroxymethyl)pent-3-en-1-yl)(tosyl)carbamate (370 mg, 1.0 mmol, 1.0 equiv.) was added and the reaction was stirred at room temperature overnight. Upon completion, the solvent was evaporated under reduced pressure. Purification by chromatography (Hex/AcOEt 2.5% → Hex/AcOEt 25%) gave **5** (518 mg, 85%) as a yellow oil. The product was isolated as a 1:3 *cis/trans* mixture. ^1H NMR (500 MHz, CDCl_3) δ 8.07 – 8.02 (m, 1H), 7.78 – 7.72 (m, 2H), 7.70 – 7.65 (m, 2H), 7.64 – 7.60 (m, 1H), 7.31 – 7.27 (m, 2H), 5.69 – 5.60 (m, 0.3H), 5.60 – 5.49 (m, 0.7H), 5.24 – 5.06 (m, 1H), 3.86 – 3.78 (m, 1H), 3.77 – 3.69 (m, 1H), 3.53 – 3.36 (m, 2H), 3.36 – 3.21 (m, 2H), 2.96 – 2.82 (m, 1H), 2.43 (s, 3H), 1.63 (dd, $J = 6.9, 1.8$ Hz, 1H), 1.58 (dd, $J = 6.5, 1.5$ Hz, 3H), 1.53 – 1.40 (m, 2H), 1.32 (s, 9H), 1.28 – 1.16 (m, 2H), 0.89 – 0.79 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 151.11, 151.06, 148.10, 148.06, 144.3, 137.5, 134.14, 134.06, 133.4, 131.7, 131.2, 130.4, 129.34, 129.28, 129.0, 128.8, 128.6, 128.1, 128.0, 124.3, 84.5, 84.3, 49.2, 49.1, 48.93, 48.85, 46.9, 46.7, 42.4, 36.2, 31.1, 29.4, 29.2, 28.0, 21.7, 19.9, 18.2, 13.8, 13.4 ppm.



tert-butyl (E)-(2-((butylamino)methyl)pent-3-en-1-yl)

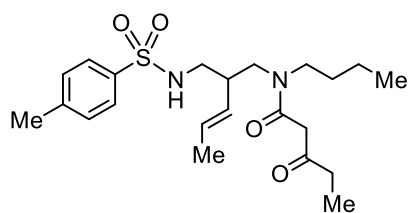
(tosyl)carbamate (**6**).⁶ To a solution of *tert*-butyl-(2-(((*N*-butyl-2-nitrophenyl)sulfonamido)methyl)pent-3-en-1-yl)(tosyl)carbamate (125 mg, 0.20 mmol, 1.0 equiv.) in DMF (1.5 mL, 0.13 M) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (59 mg, 1.4 mmol, 7.0 equiv.) and mercaptoacetic acid (55 mg, 42 μL , 0.60 mmol, 3.0 equiv.), and the resulting solution was stirred for 2 hours at room temperature. Upon completion, the crude mixture was

diluted with water (4 mL) and subsequently extracted with dichloromethane (3×4 mL). Then, the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography ($\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{MeOH}$ 5%) gave **6** (63 mg, 74%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.80 – 7.73 (m, 2H), 7.27 (dd, $J = 8.6, 0.7$ Hz, 2H), 5.63 – 5.53 (m, 1H), 5.24 (ddd, $J = 15.3, 9.3, 1.7$ Hz, 1H), 3.89 – 3.83 (m, 1H), 3.79 (dd, $J = 14.4, 8.2$ Hz, 1H), 2.84 – 2.75 (m, 1H), 2.72 (dd, $J = 11.7, 5.1$ Hz, 1H), 2.68 – 2.61 (m, 2H), 2.58 (dd, $J = 11.7, 8.7$ Hz, 1H), 2.42 (s, 3H), 1.67 (ddd, $J = 8.1, 6.6, 1.7$ Hz, 3H), 1.55 – 1.45 (m, 2H), 1.35 – 1.31 (m, 2H), 1.31 (s, 9H), 0.90 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 151.2, 144.2, 137.6, 130.0, 129.9, 129.3, 128.1, 84.2, 51.2, 49.5, 49.3, 43.6, 31.5, 28.0, 21.7, 20.5, 18.3, 14.1 ppm.



N-(2-((butylamino)methyl)pent-3-en-1-yl)-4-

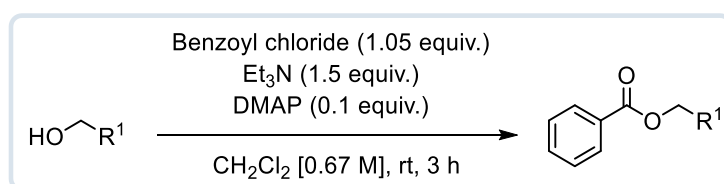
methylbenzenesulfonamide (**7**). A solution of *tert*-butyl-(2-((butylamino)methyl)pent-3-en-1-yl) (tosyl)carbamate (42 mg, 0.10 mmol, 1.0 equiv) was dissolved in trifluoroacetic acid (1 mL, 0.1 M), and the resulting mixture was stirred for 1 hour at room temperature. Upon completion, the solvent was evaporated and the crude product was redissolved in dichloromethane (5 mL) and sodium bicarbonate (5 mL). Then, the aqueous layer was extracted with dichloromethane (3×4 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The targeted product **7** was isolated as a yellow oil in a 3:7 *cis/trans* mixture (32 mg, 99%). No further purification was required. ^1H NMR (400 MHz, CDCl_3) δ 7.75 – 7.70 (m, 2H), 7.33 – 7.26 (m, 2H), 5.61 – 5.43 (m, 1H), 5.11 (ddq, $J = 15.4, 8.0, 1.7$ Hz, 0.8H), 5.00 (ddq, $J = 11.2, 9.5, 1.8$ Hz, 0.3H), 3.03 – 2.86 (m, 2H), 2.75 – 2.66 (m, 0.4H), 2.66 – 2.44 (m, 4H), 2.42 (s, 3H), 2.35 – 2.25 (m, 1H), 1.62 (ddd, $J = 6.4, 1.7, 0.7$ Hz, 2H), 1.58 (dd, $J = 6.9, 1.8$ Hz, 1H), 1.48 – 1.36 (m, 2H), 1.38 – 1.27 (m, 2H), 0.94 – 0.88 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 143.2, 137.3, 129.8, 129.7, 128.8, 128.4, 127.8, 127.2, 54.4, 54.1, 49.70, 49.66, 48.0, 47.9, 41.0, 36.0, 32.11, 32.08, 21.6, 20.5, 18.2, 14.1, 13.4 ppm.



N-butyl-*N*-(2-(((4-methylphenyl)sulfonamido)methyl)

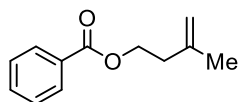
pent-3-en-1-yl)-3-oxopentanamide (**8**). A solution of *N*-(2-((butylamino)methyl)pent-3-en-1-yl)-4-methylbenzenesulfonamide (60 mg, 0.19 mmol, 1.0 equiv.), *tert*-butyl 3-oxopentanoate (64 mg, 0.37 mmol, 2.0 equiv.) and 4-dimethylaminopyridine (7 mg, 0.06 mmol, 0.3 equiv.) in toluene (1 mL, 0.2 M) was stirred for 4 hours at 80 °C. Upon completion, the crude mixture was concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 4%) gave **8** (68 mg, 87%) as a colorless oil. The product was isolated as a complex mixture of isomers and rotamers. ¹H NMR (400 MHz, CDCl₃) δ 7.75 – 7.68 (m, 2H), 7.29 – 7.23 (m, 2H), 5.87 – 5.69 (m, 1H), 5.66 – 5.46 (m, 1H), 5.36 – 5.21 (m, 1H), 3.57 (dd, *J* = 13.8, 8.6 Hz, 1H), 3.50 – 3.43 (m, 2H), 3.24 – 3.01 (m, 3H), 2.99 – 2.87 (m, 1H), 2.82 – 2.72 (m, 1H), 2.56 – 2.46 (m, 2H), 2.45 – 2.41 (m, 1H), 2.43 – 2.37 (m, 3H), 1.70 – 1.58 (m, 4H), 1.55 – 1.40 (m, 2H), 1.35 – 1.21 (m, 2H), 1.14 (t, *J* = 7.5 Hz, 0.7H), 1.03 (t, *J* = 7.3 Hz, 2.4H), 0.92 (t, *J* = 7.3 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 204.8, 179.7, 172.3, 167.7, 142.9, 137.3, 129.9, 129.7, 129.6, 129.5, 129.2, 128.7, 128.6, 128.3, 128.2, 127.5, 127.1, 127.0, 85.2, 50.0, 48.9, 48.7, 48.4, 48.2, 47.2, 47.0, 46.7, 45.9, 44.9, 44.3, 44.2, 44.1, 42.8, 41.3, 36.5, 36.4, 35.9, 30.8, 30.7, 30.6, 29.2, 29.0, 21.5, 20.13, 20.05, 20.0, 18.1, 13.7, 13.2, 10.9, 7.6 ppm.

SYNTHESIS OF THE ALKENE DONORS AND ALKYNE ACCEPTORS

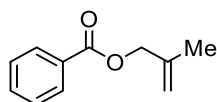


General method for the benzoyl protection:⁷ To a solution of the selected alcohol (1.0 equiv.) and triethylamine (1.5 equiv.) in dichloromethane (0.67 M) was added 4-dimethylaminopyridine (0.1 equiv.) under an argon atmosphere. Then, the solution was cooled to 0 °C with an ice bath and benzoyl chloride (1.05 equiv.) was added dropwise. After stirring the solution for 3 hours at room temperature, the mixture was diluted with dichloromethane and subsequently washed with water and 10% citric acid. The organic

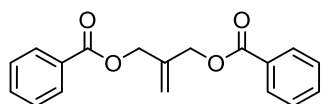
layer was dried with sodium sulfate and concentrated. The corresponding product was purified by flash column chromatography on silica gel.



3-methylbut-3-en-1-yl benzoate (9a). The title compound was prepared according to the general procedure using 3-methylbut-3-en-1-ol (1.72 g, 2.0 mL, 20 mmol, 1.0 equiv.), benzoyl chloride (2.95 g, 2.4 mL, 21 mmol, 1.05 equiv.), triethylamine (3.04 g, 4.2 mL, 30 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (244 mg, 2.0 mmol, 0.1 equiv.) in dichloromethane (30 mL, 0.67 M). Purification by chromatography (Hex → Hex/AcOEt 10%) gave **9a** (3.80 g, 100%) as a colorless oil. Spectral data were identical to those previously reported.^[8] ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.01 (m, 2H), 7.58 – 7.52 (m, 1H), 7.47 – 7.40 (m, 2H), 4.87 – 4.80 (m, 2H), 4.44 (t, *J* = 6.8 Hz, 2H), 2.49 (t, *J* = 6.7 Hz, 2H), 1.82 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.7, 141.8, 133.0, 130.5, 129.7, 128.5, 112.5, 63.3, 36.9, 22.6 ppm.

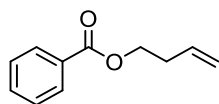


2-methylallyl benzoate (9b). The title compound was prepared according to the general procedure using methallyl alcohol (721 mg, 840 μL, 10 mmol, 1.0 equiv.), benzoyl chloride (1.48 g, 1.2 mL, 10.5 mmol, 1.05 equiv.), triethylamine (1.52 g, 2.1 mL, 15 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (122 mg, 1.0 mmol, 0.1 equiv.) in dichloromethane (15 mL, 0.67 M). Purification by chromatography (Hex → Hex/AcOEt 10%) gave **9b** (1.59 g, 90%) as a colorless oil. Spectral data were identical to those previously reported.^[9] ¹H NMR (400 MHz, CDCl₃) δ 8.11 – 8.04 (m, 2H), 7.61 – 7.52 (m, 1H), 7.50 – 7.40 (m, 2H), 5.11 – 5.06 (m, 1H), 5.02 – 4.96 (m, 1H), 4.75 (s, 2H), 1.85 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.4, 140.1, 133.1, 130.3, 129.7, 128.5, 113.1, 68.2, 19.7 ppm.



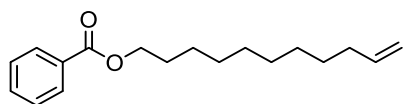
2-methylenepropane-1,3-diyl dibenzoate (9c). The title compound was prepared according to a modification of the general procedure using 2-methylenepropane-1,3-diol (705 mg, 650 μL, 8.0 mmol, 1.0 equiv.), benzoyl chloride (2.25 g, 1.9 mL, 16 mmol, 2.0 equiv.), triethylamine (2.43 g, 3.3 mL, 24 mmol, 3.0 equiv.)

and 4-dimethylaminopyridine (195 mg, 1.6 mmol, 0.2 equiv.) in dichloromethane (12 mL, 0.67 M). Purification by chromatography (Hex → Hex/AcOEt 25%) gave **9c** (2.20 g, 93%) as a colorless solid. Spectral data were identical to those previously reported.^[10] ¹H NMR (400 MHz, CDCl₃) δ 8.10 – 8.01 (m, 4H), 7.56 (ddt, *J* = 8.0, 6.9, 1.4 Hz, 2H), 7.48 – 7.38 (m, 4H), 5.45 (s, 2H), 4.96 (s, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.3, 138.8, 133.3, 130.0, 129.8, 128.5, 117.4, 65.3 ppm.



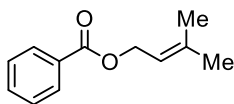
But-3-en-1-yl benzoate (9d). The title compound was prepared

according to the general procedure using 3-buten-1-ol (1.44 g, 1.7 mL, 20 mmol, 1.0 equiv.), benzoyl chloride (2.95 g, 2.4 mL, 21 mmol, 1.05 equiv.), triethylamine (3.04 g, 4.2 mL, 30 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (244 mg, 2.0 mmol, 0.1 equiv.) in dichloromethane (30 mL, 0.67 M). Purification by chromatography (Hex → Hex/AcOEt 10%) gave **9d** (3.35 g, 95%) as a colorless oil. Spectral data were identical to those previously reported.^[11] ¹H NMR (400 MHz, CDCl₃) δ 8.08 – 8.01 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 5.88 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.22 – 5.14 (m, 1H), 5.15 – 5.07 (m, 1H), 4.38 (t, *J* = 6.7 Hz, 2H), 2.57 – 2.49 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.7, 134.2, 133.0, 130.5, 129.7, 128.5, 117.5, 64.1, 33.3 ppm.

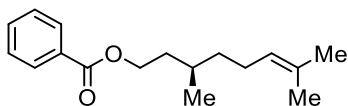


Undec-10-en-1-yl benzoate (9e). The title compound

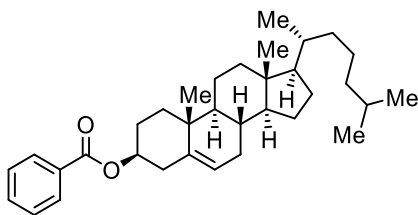
was prepared according to the general procedure using undec-10-en-1-ol (1.36 g, 1.6 mL, 8.0 mmol, 1.0 equiv.), benzoyl chloride (1.18 g, 1.0 mL, 8.4 mmol, 1.05 equiv.), triethylamine (1.21 g, 1.7 mL, 12 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (98 mg, 0.80 mmol, 0.1 equiv.) in dichloromethane (12 mL, 0.67 M). Purification by chromatography (Hex → Hex/AcOEt 10%) gave **9e** (2.15 g, 98%) as a colorless oil. Spectral data were identical to those previously reported.^[12] ¹H NMR (400 MHz, CDCl₃) δ 8.08 – 8.01 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (ddt, *J* = 17.1, 2.2, 1.5 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 4.32 (t, *J* = 6.7 Hz, 2H), 2.09 – 1.98 (m, 2H), 1.82 – 1.71 (m, 2H), 1.49 – 1.24 (m, 12H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.8, 139.3, 132.9, 130.7, 129.7, 128.4, 114.3, 65.3, 33.9, 29.6, 29.5, 29.4, 29.2, 29.1, 28.9, 26.2 ppm.



3-methylbut-2-en-1-yl benzoate (9f). The title compound was prepared according to the general procedure using 3-methyl-2-buten-1-ol (689 mg, 810 μ L, 8.0 mmol, 1.0 equiv.), benzoyl chloride (1.18 g, 1.0 mL, 8.4 mmol, 1.05 equiv.), triethylamine (1.21 g, 1.7 mL, 12 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (98 mg, 0.80 mmol, 0.1 equiv.) in dichloromethane (12 mL, 0.67 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **9f** (1.49 g, 98%) as a colorless oil. Spectral data were identical to those previously reported.^[13] ^1H NMR (400 MHz, CDCl_3) δ 8.08 – 8.01 (m, 2H), 7.58 – 7.50 (m, 1H), 7.47 – 7.37 (m, 2H), 5.53 – 5.41 (m, 1H), 4.82 (d, J = 7.2 Hz, 2H), 1.78 (d, J = 6.9 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.8, 139.3, 132.9, 130.7, 129.7, 128.4, 118.8, 62.0, 25.9, 18.2 ppm.



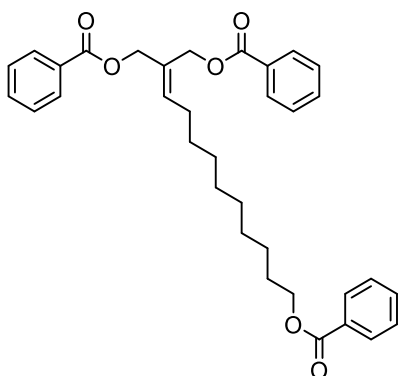
(R)-3,7-dimethyloct-6-en-1-yl benzoate (9g). The title compound was prepared according to the general procedure using citronellol (1.25 g, 1.5 mL, 8.0 mmol, 1.0 equiv.), benzoyl chloride (1.18 g, 1.0 mL, 8.4 mmol, 1.05 equiv.), triethylamine (1.21 g, 1.7 mL, 12 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (98 mg, 0.80 mmol, 0.1 equiv.) in dichloromethane (12 mL, 0.67 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **9g** (2.00 g, 96%) as a colorless oil. Spectral data were identical to those previously reported.^[14] ^1H NMR (400 MHz, CDCl_3) δ 8.08 – 8.00 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 5.15 – 5.05 (m, 1H), 4.44 – 4.29 (m, 2H), 2.12 – 1.91 (m, 2H), 1.88 – 1.76 (m, 1H), 1.72 – 1.63 (m, 4H), 1.63 – 1.52 (m, 4H), 1.47 – 1.35 (m, 1H), 1.31 – 1.19 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.8, 132.9, 131.5, 130.7, 129.7, 128.5, 124.7, 63.6, 37.1, 35.6, 29.7, 25.8, 25.5, 19.7, 17.8 ppm.



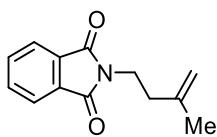
Cholesteryl benzoate (9h). The title compound was prepared according to the general procedure using cholesterol (2.32 g, 6.0 mmol, 1.0 equiv.), benzoyl chloride (886 mg, 730 μ L, 6.3 mmol, 1.05 equiv.), triethylamine (0.91 g,

1.3 mL, 9.0 mmol, 1.5 equiv.) and 4-dimethylaminopyridine (73 mg, 0.60 mmol, 0.1 equiv.) in dichloromethane (9 mL, 0.67 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **9h** (2.29 g, 78%) as a white solid. Spectral data were identical to those previously reported.^[15] ¹H NMR (400 MHz, CDCl₃) δ 8.08 – 8.01 (m, 2H), 7.59 – 7.50 (m, 1H), 7.47 – 7.39 (m, 2H), 5.42 (d, *J* = 5.0 Hz, 1H), 4.87 (dtd, *J* = 12.0, 8.5, 4.5 Hz, 1H), 2.47 (d, *J* = 7.4 Hz, 2H), 2.01 (ddt, *J* = 16.8, 9.3, 4.2 Hz, 3H), 1.92 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.89 – 1.76 (m, 1H), 1.79 – 1.67 (m, 1H), 1.66 – 1.42 (m, 6H), 1.43 – 1.06 (m, 11H), 1.07 (s, 3H), 1.07 – 0.95 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.87 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.69 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.1, 139.8, 132.9, 131.0, 129.7, 128.4, 122.9, 74.7, 56.9, 56.3, 50.2, 42.5, 39.9, 39.7, 38.4, 37.2, 36.8, 36.3, 36.0, 32.1, 32.0, 28.4, 28.2, 28.0, 24.5, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0 ppm.

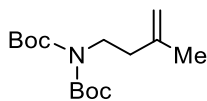
Synthesis of 2-(10-(benzoyloxy)decylidene)propane-1,3-diyl dibenzoate (**9i**)



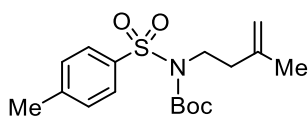
To a solution of 2-methylenepropane-1,3-diyl dibenzoate (296 mg, 1.0 mmol, 1.0 equiv.) and undec-10-en-1-yl benzoate (823 mg, 3.0 mmol, 3.0 equiv.) in degassed dichloromethane (4 mL, 0.25 M) was added Grubbs II catalyst (42 mg, 0.05 mmol, 0.05 equiv.) and the resulting mixture was heated at reflux for 24 hours. Upon completion, the solvent was evaporated under reduced pressure. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **9i** (527 mg, 97%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.06 – 8.03 (m, 2H), 8.03 – 7.99 (m, 4H), 7.58 – 7.49 (m, 3H), 7.47 – 7.40 (m, 2H), 7.42 – 7.35 (m, 4H), 5.95 (t, *J* = 7.5 Hz, 1H), 5.00 (s, 2H), 4.92 (s, 2H), 4.34 – 4.27 (m, 2H), 2.25 (q, *J* = 7.4 Hz, 2H), 1.80 – 1.69 (m, 2H), 1.48 – 1.37 (m, 4H), 1.37 – 1.23 (m, 8H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 166.8, 166.6, 166.5, 137.7, 133.10, 133.06, 132.9, 130.7, 130.3, 130.2, 129.77, 129.75, 129.7, 129.2, 128.47, 128.45, 67.7, 65.3, 65.2, 60.7, 29.6, 29.5, 29.41, 29.37, 29.3, 28.8, 28.0, 26.2 ppm.

Synthesis of 2-(3-methylbut-3-en-1-yl)isoindoline-1,3-dione (9j)¹⁶

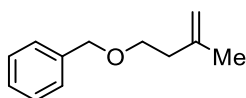
To a solution of 3-methyl-3-buten-1-ol (861 mg, 1.0 mL, 10 mmol, 1.0 equiv.), phthalimide (1.62 g, 11 mmol, 1.1 equiv.) and PPh_3 (2.89 g, 11 mmol, 1.1 equiv.) in anhydrous THF (30 mL, 0.33 M) was added diethyl azodicarboxylate (1.92 g, 1.7 mL, 11 mmol, 1.1 equiv.) dropwise at 0 °C and the resultant solution was left to stir at room temperature for 5 hours. Afterward, the reaction mixture was concentrated under vacuum. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **9j** (1.83 g, 85%) as a colorless oil. Spectral data were identical to those previously reported.^[17] ^1H NMR (400 MHz, CDCl_3) δ 7.85 – 7.79 (m, 2H), 7.72 – 7.67 (m, 2H), 4.76 – 4.69 (m, 1H), 4.69 – 4.64 (m, 1H), 3.82 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 1.80 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 168.4, 142.3, 134.0, 132.2, 123.3, 112.9, 36.6, 36.5, 22.2 ppm.

Synthesis of di-*tert*-butyl (3-methylbut-3-en-1-yl)carbamate (9k)¹⁸

To a solution of 3-methyl-3-buten-1-ol (431 mg, 510 μL , 5.0 mmol, 1.0 equiv.), di-*tert*-butyl-iminodicarboxylate (1.19 g, 5.5 mmol, 1.1 equiv.) and PPh_3 (1.44 g, 5.5 mmol, 1.1 equiv.) in anhydrous THF (15 mL, 0.33 M) was added diisopropyl azodicarboxylate (1.11 g, 1.1 mL, 5.5 mmol, 1.1 equiv.) dropwise at 0 °C and the resulting solution was left to stir at room temperature for 16 hours. The solvent was evaporated, and the residue was suspended in Et_2O . After filtration, the organic extracts were concentrated. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **9k** (599 mg, 42%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.77 – 4.72 (m, 1H), 4.72 – 4.67 (m, 1H), 3.69 – 3.61 (m, 2H), 2.26 (t, J = 6.4 Hz, 2H), 1.75 (s, 3H), 1.49 (s, 18H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 152.6, 142.8, 112.3, 82.2, 45.3, 37.3, 28.2, 22.5 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{15}\text{H}_{28}\text{NO}_4^+$ 286.2013, found 286.2015.

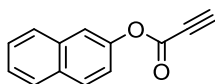
Synthesis of *tert*-butyl (3-methylbut-3-en-1-yl)(tosyl)carbamate (9l)¹⁶

To a solution of 3-methyl-3-buten-1-ol (431 mg, 510 μ L, 5.0 mmol, 1.0 equiv.), *tert*-butyl tosylcarbamate (1.49 g, 5.5 mmol, 1.1 equiv.) and PPh₃ (1.44 g, 5.5 mmol, 1.1 equiv.) in anhydrous THF (15 mL, 0.33 M) was added diethyl azodicarboxylate (958 mg, 860 μ L, 5.5 mmol, 1.1 equiv.) dropwise at 0 °C and the resulting solution was left to stir at room temperature for 5 hours. Afterward, the reaction mixture was concentrated under vacuum. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **9l** (1.19 g, 70%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.76 (m, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 4.84 – 4.73 (m, 2H), 3.96 – 3.88 (m, 2H), 2.48 – 2.44 (m, 2H), 2.43 (s, 3H), 1.79 (s, 3H), 1.34 (s, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 151.0, 144.2, 142.3, 137.7, 129.3, 128.0, 112.7, 84.2, 46.0, 38.4, 28.0, 22.6, 21.7 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₇H₂₆NO₄S⁺ 340.1577, found 340.1575.

Synthesis of (((3-methylbut-3-en-1-yl)oxy)methyl)benzene (9m)

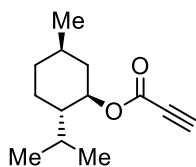
A solution of sodium hydride (540 mg, 22.5 mmol, 1.5 equiv.) in tetrahydrofuran (60 mL, 0.25 M) was cooled at 0 °C with an ice bath. Then, 3-methyl-3-buten-1-ol (1.29 g, 1.5 mL, 15 mmol, 1.0 equiv.) and benzyl bromide (2.52 g, 1.8 mL, 15 mmol, 1.0 equiv.) were added dropwise and the resulting mixture was left to stir at room temperature for 24 hours. After completion of the reaction, the mixture was cooled at 0 °C and acidified with a saturated solution of NH₄Cl. Then, tetrahydrofuran was evaporated under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 $\times$ 30 mL). The combined organic layers were dried with Na₂SO₄ and the solvent was evaporated. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **9m** (824 mg, 31%) as a colorless liquid. Spectral data were identical to those previously reported.^[19] ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 4.83 – 4.71 (m, 2H), 4.53 (s, 2H), 3.59 (t, *J* = 6.9 Hz, 2H), 2.36 (t, *J* = 6.9 Hz, 2H), 1.75 (s, 3H) ppm.

Synthesis of 2-naphthyl propiolate (**10b**)



A solution of 2-naphthol (577 mg, 4.0 mmol, 1.0 equiv.) in tetrahydrofuran (20 mL, 0.2 M) at 0 °C was treated with sodium hydride (dry 90%, 117 mg, 4.4 mmol, 1.1 equiv.). On a separate flask, a solution of propiolic acid (925 mg, 810 μ L, 13.2 mmol, 3.3 equiv.) in tetrahydrofuran (20 mL, 0.2 M) at 0 °C was treated sequentially with dicyclohexylcarbodiimide (2.72 g, 13.2 mmol, 3.3 equiv.) and the above naphthyl mixture. The resulting solution was allowed to stir at room temperature for 16 hours. Upon completion of the reaction, the solvent was evaporated and the residue was treated with acetonitrile (40 mL). Then, the mixture was filtered and concentrated under reduced pressure. Purification by chromatography (Hex $\rightarrow$ Hex/Et₂O 20%) gave **10b** (691 mg, 89%) as a white solid. Spectral data were identical to those previously reported.^[20] ¹H NMR (400 MHz, CDCl₃) δ 7.91 – 7.79 (m, 3H), 7.64 (d, J = 2.4 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.28 (dd, J = 8.9, 2.4 Hz, 1H), 3.11 (s, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 151.2, 147.5, 133.7, 131.9, 129.9, 128.0, 127.0, 126.3, 120.5, 118.7, 77.1, 74.4 ppm.

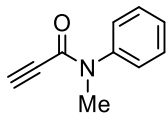
Synthesis of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl propiolate (**10c**)



A solution of menthol (625 mg, 4.0 mmol, 1.0 equiv.) in tetrahydrofuran (20 mL, 0.2 M) at 0 °C was treated with sodium hydride (dry 90%, 117 mg, 4.4 mmol, 1.1 equiv.). On a separate flask, a solution of propiolic acid (925 mg, 810 μ L, 13.2 mmol, 3.3 equiv.) in tetrahydrofuran (20 mL, 0.2 M) at 0 °C was treated sequentially with dicyclohexylcarbodiimide (2.72 g, 13.2 mmol, 3.3 equiv.) and the above menthol mixture. The resulting solution was allowed to stir at room temperature for 16 hours. Upon completion of the reaction, the solvent was evaporated and the residue was treated with acetonitrile (40 mL). Then, the mixture was filtered and concentrated under reduced pressure. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **10c** (573 mg, 55%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.80 (td, J = 10.9, 4.4 Hz, 1H),

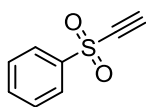
2.86 (s, 1H), 2.09 – 1.98 (m, 1H), 1.96 – 1.84 (m, 1H), 1.77 – 1.63 (m, 2H), 1.53 – 1.39 (m, 2H), 1.13 – 0.98 (m, 2H), 0.91 (dd, $J = 6.8, 3.7$ Hz, 7H), 0.77 (d, $J = 7.0$ Hz, 3H) ppm.

Synthesis of *N*-methyl-*N*-phenylpropiolamide (**10d**)²¹



To a solution of *N*-methylaniline (536 mg, 541 μ L, 5.0 mmol, 1.0 equiv.) in dichloromethane (20 mL, 0.25 M) was added dicyclohexylcarbodiimide (1.13 g, 5.5 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (61 mg, 0.50 mmol, 0.1 equiv.) and the resulting mixture was stirred for 10 minutes at 0 °C. After, propiolic acid (385 mg, 341 μ L, 5.5 mmol, 1.1 equiv.) was added dropwise and the solution was left to stir at room temperature for 3 hours. Upon completion of the reaction, the mixture was filtered through Celite, diluted with a saturated Na_2CO_3 solution (15 mL) and extracted with dichloromethane (3×15 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 , filtered, and concentrated under vacuum. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **10d** (422 mg, 53%) as a brown solid. Spectral data were identical to those previously reported.^[22] ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.32 (m, 3H), 7.32 – 7.25 (m, 2H), 3.60 (s, 0.4H, [m]), 3.33 (s, 2.6H, [M]), 3.28 (s, 0.1H, [m]), 2.81 (s, 0.8H, [M]); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 153.1, 142.7, 129.4 (m), 129.3 (M), 128.3 (m), 127.3 (m), 127.2 (M), 125.5 (M), 80.2 (m), 79.6 (M), 76.4, 39.6 (m), 36.6 (M) ppm.

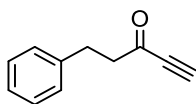
Synthesis of (ethynylsulfonyl)benzene (**10e**)²³



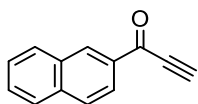
To a solution of trimethylsilylacetylene (648 mg, 939 μ L, 6.6 mmol, 1.1 equiv.) in anhydrous tetrahydrofuran (12 mL, 0.5 M) was added *n*-BuLi (1.6 M in hexane, 3.6 mL, 5.7 mmol, 0.95 equiv.) dropwise at -78 °C under argon. The solution was left to stir for 30 minutes and a solution of phenyl disulfide (1.31 g, 6.0 mmol, 1.0 equiv.) in tetrahydrofuran (2 mL) was added dropwise. After stirring the solution for 1 hour at -78 °C, the reaction was stirred for an additional 30 minutes at room temperature and subsequently quenched with water. The mixture was extracted with diethyl ether (3×30 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4 ,

filtered, and concentrated. The residue was dissolved in dichloromethane (25 mL, 0.24 M) and *m*CPBA (2.59 g, 15.0 mmol, 2.5 equiv.) was added portionwise. The resulting solution was left to stir at room temperature for 2 hours and subsequently treated with a saturated solution of Na₂SO₃ and extracted with dichloromethane (3 × 20 mL). The organic layer was treated with silica for 2 hours at room temperature, filtered and concentrated. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **10e** (528 mg, 53%) as a colorless liquid. Spectral data were identical to those previously reported.^[23] ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 7.97 (m, 2H), 7.77 – 7.67 (m, 1H), 7.66 – 7.56 (m, 2H), 3.48 (s, 1H) ppm.

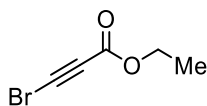
Synthesis of 5-phenylpent-1-yn-3-one (**10f**)



To a solution of trimethylsilylacetylene (491 mg, 692 μL, 5.0 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (10 mL, 0.5 M) was added *n*-BuLi (1.6 M in hexane, 3.0 mL, 4.75 mmol, 0.95 equiv.) dropwise at -78 °C under argon. The solution was left to stir for 30 minutes and 3-phenylpropionaldehyde (671 mg, 664 μL, 5.0 mmol, 1.0 equiv.) was added dropwise. After stirring the solution for 1 hour at -78 °C, the reaction was stirred for an additional 30 minutes at room temperature and subsequently quenched with water. The mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered, and concentrated. The residue was dissolved in methanol (20 mL, 0.25 M) and potassium carbonate (2.07 g, 15 mmol, 3.0 equiv.) was added in one portion. The mixture was allowed to stir at room temperature for 2 hours and then filtered through a silica plug. Afterward, the crude product was dissolved in anhydrous dichloromethane (20 mL, 0.25 M) and Dess-Martin reagent (2.33 g, 5.5 mmol, 1.1 equiv.) was added. The solution was left to stir for 2 hours and subsequently concentrated. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **10f** (617 mg, 78%) as a colorless liquid. Spectral data were identical to those previously reported.^[24] ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.23 (m, 2H), 7.25 – 7.16 (m, 3H), 3.23 (s, 1H), 3.04 – 2.96 (m, 2H), 2.97 – 2.88 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 186.4, 140.1, 128.7, 128.5, 126.5, 81.5, 79.0, 47.1, 29.7 ppm.

Synthesis of 1-(naphthalen-2-yl)prop-2-yn-1-one (10g)²⁵

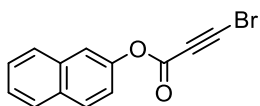
To a solution of trimethylsilylacetylene (628 mg, 911 μ L, 6.4 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (13 mL, 0.5 M) was added *n*-BuLi (1.6 M in hexane, 3.8 mL, 6.08 mmol, 0.95 equiv.) dropwise at $-78\text{ }^{\circ}\text{C}$ under argon. The mixture was left to stir for 30 minutes and a solution of 2-naphthaldehyde (1.00 g, 6.4 mmol, 1.0 equiv.) in tetrahydrofuran (2 mL) was added dropwise. After stirring for 1 hour at $-78\text{ }^{\circ}\text{C}$, the reaction was stirred for an additional 30 minutes at room temperature and subsequently quenched with water. The mixture was extracted with ethyl acetate (3×30 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. The residue was dissolved in methanol (26 mL, 0.25 M) and potassium carbonate (2.65 g, 19.2 mmol, 3.0 equiv.) was added in one portion. The mixture was allowed to stir at room temperature for 2 hours and then filtered through a silica plug. Afterward, the crude product was dissolved in anhydrous dichloromethane (26 mL, 0.25 M) and Dess-Martin reagent (2.97 g, 7.0 mmol, 1.1 equiv.) was added. The solution was left to stir for 2 hours and subsequently concentrated. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **10g** (1.08 g, 94%) as a white solid. Spectral data were identical to those previously reported.^[26] ^1H NMR (400 MHz, CDCl_3) δ 8.77 – 8.71 (m, 1H), 8.13 (dd, $J = 8.7, 1.8$ Hz, 1H), 8.01 (dd, $J = 8.1, 1.3$ Hz, 1H), 7.93 – 7.85 (m, 2H), 7.64 (ddd, $J = 8.2, 6.9, 1.4$ Hz, 1H), 7.58 (ddd, $J = 8.2, 6.9, 1.3$ Hz, 1H), 3.51 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 177.4, 136.4, 133.8, 133.5, 132.5, 130.0, 129.4, 128.8, 128.1, 127.2, 123.7, 80.8, 80.5 ppm.

Synthesis of ethyl 3-bromopropiolate (10h)²⁷

To a solution of ethyl propiolate (491 mg, 506 μ L, 5.0 mmol, 1.0 equiv.) in acetone (10 mL, 0.5 M) was added silver nitrate (85 mg, 0.50 mmol, 0.1 equiv.) and the solution was left to stir at room temperature for 5 minutes. Afterward, *N*-bromosuccinimide (979 mg, 5.5 mmol, 1.1 equiv.) was added and the reaction was stirred at room temperature for 3 hours. The resulting mixture was filtered and concentrated under vacuum. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%)

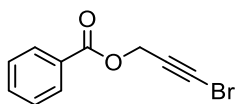
gave **10h** (858 mg, 97%) as a colorless oil. Spectral data were identical to those previously reported.^[27] ^1H NMR (400 MHz, CDCl_3) δ 4.23 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 152.6, 73.0, 62.6, 52.5, 14.1 ppm.

Synthesis of naphthalen-2-yl 3-bromopropiolate (**10i**)²⁷



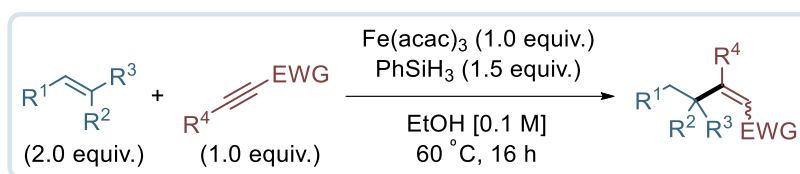
To a solution of naphthalen-2-yl propiolate (260 mg, 1.33 mmol, 1.0 equiv.) in acetone (2.7 mL, 0.5 M) was added silver nitrate (23 mg, 0.13 mmol, 0.1 equiv.) and the solution was left to stir at room temperature for 5 minutes. Afterward, *N*-bromosuccinimide (260 mg, 1.46 mmol, 1.1 equiv.) was added and the reaction was stirred at room temperature for 3 hours. The resulting mixture was filtered and concentrated under vacuum. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **10i** (310 mg, 85%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.90 – 7.76 (m, 3H), 7.61 (d, J = 2.2 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.25 (dd, J = 8.9, 2.4 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 151.0, 147.6, 133.7, 131.8, 129.8, 127.93, 127.90, 127.0, 126.3, 120.5, 118.6, 72.6, 55.6 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{13}\text{H}_8\text{BrO}_2^+$ 274.9702, found 274.9705.

Synthesis of 3-bromoprop-2-yn-1-yl benzoate (**10j**)²⁷

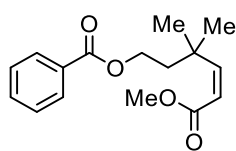


To a solution of prop-2-yn-1-yl benzoate (641 mg, 4.0 mmol, 1.0 equiv.) in acetone (8 mL, 0.5 M) was added silver nitrate (68 mg, 0.40 mmol, 0.1 equiv.) and the resulting mixture was stirred for 5 minutes at room temperature. Then, *N*-bromosuccinimide (783 mg, 4.4 mmol, 1.1 equiv.) was added and the reaction was stirred for 3 hours at room temperature. The resulting mixture was filtered and concentrated under vacuum. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **10j** (844 mg, 88%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.10 – 8.04 (m, 2H), 7.61 – 7.55 (m, 1H), 7.49 – 7.41 (m, 2H), 4.95 (s, 2H) ppm.

MHAT COUPLING BETWEEN UNBIASED ALKENES AND ELECTRON-DEFICIENT ALKYNES

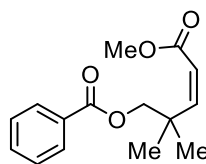


General method for the MHAT reaction between non-activated alkenes and electron-deficient alkynes: To a solution of the selected alkene (2.0 equiv.) in ethanol (0.1 M) was added the selected electron-deficient alkyne (1.0 equiv.) and Fe(acac)₃ (1.0 equiv.). The resulting mixture was degassed for 5 minutes with argon and, subsequently, PhSiH₃ (1.5 equiv.) was added dropwise. The suspension was heated at 60 °C with a heating mantle for 16 hours and the resulting mixture was concentrated. The corresponding product was purified by flash column chromatography on silica gel.



(*Z*)-6-methoxy-3,3-dimethyl-6-oxohex-4-en-1-yl benzoate (**11a**). The

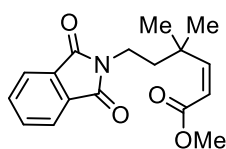
title compound was prepared according to a modification of the general procedure using 3-methylbut-3-en-1-yl benzoate (2.28 g, 12 mmol, 3.0 equiv.), methyl propiolate (336 mg, 350 μ L, 4.0 mmol, 1.0 equiv.), Fe(acac)₃ (1.41 g, 4.0 mmol, 1.0 equiv.) and PhSiH₃ (649 mg, 740 μ L, 6.0 mmol, 1.5 equiv.) in ethanol (40 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12a** (64:36) (1.07 g, 97%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.06 – 7.99 (m, 2H), 7.58 – 7.51 (m, 1H), 7.47 – 7.40 (m, 2H), 6.03 (d, *J* = 13.0 Hz, 1H), 5.75 (d, *J* = 13.1 Hz, 1H), 4.37 (t, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 2.09 (t, *J* = 7.1 Hz, 2H), 1.28 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.9, 166.7, 153.8, 133.0, 130.5, 129.7, 128.5, 119.7, 62.7, 51.5, 40.6, 36.2, 28.0 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₆H₂₁O₄⁺ 277.1434, found 277.1433.



(*Z*)-5-methoxy-2,2-dimethyl-5-oxopent-3-en-1-yl benzoate (**11b**). The

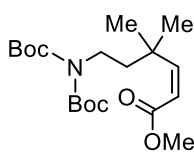
title compound was prepared according to the general procedure using 2-methylallyl benzoate (282 mg, 1.6 mmol, 2.0 equiv.), methyl propiolate (67 mg, 71 μ L, 0.80 mmol,

1.0 equiv.), $\text{Fe}(\text{acac})_3$ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH_3 (130 mg, 148 μL , 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/ AcOEt 25%) gave **11/12b** (70:30) (191 mg, 91%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.07 – 8.00 (m, 2H), 7.60 – 7.51 (m, 1H), 7.49 – 7.39 (m, 2H), 6.11 (d, J = 13.0 Hz, 1H), 5.83 (d, J = 13.0 Hz, 1H), 4.33 (s, 2H), 3.70 (s, 3H), 1.34 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.7, 166.6, 151.2, 133.1, 130.4, 129.7, 128.5, 120.7, 72.6, 51.6, 37.8, 24.5 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{15}\text{H}_{19}\text{O}_4^+$ 263.1278, found 263.1277.



(*Z*)-methyl-6-(1,3-dioxoisindolin-2-yl)-4,4-dimethylhex-2-enoate

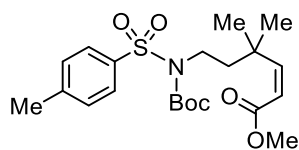
(11c). The title compound was prepared according to the general procedure using 2-(3-methylbut-3-en-1-yl)isoindoline-1,3-dione (344 mg, 1.6 mmol, 2.0 equiv.), methyl propiolate (67 mg, 71 μL , 0.80 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH_3 (130 mg, 148 μL , 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/ AcOEt 25%) gave **11/12c** (60:40) (222 mg, 92%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.84 – 7.78 (m, 2H), 7.71 – 7.65 (m, 2H), 6.01 (d, J = 13.1 Hz, 1H), 5.75 (d, J = 13.1 Hz, 1H), 3.71 (s, 3H), 3.70 – 3.64 (m, 2H), 1.95 – 1.86 (m, 2H), 1.26 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 168.3, 166.9, 152.9, 133.9, 132.3, 123.2, 120.0, 51.5, 40.5, 36.3, 34.8, 27.5 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{17}\text{H}_{20}\text{NO}_4^+$ 302.1387, found 302.1387.



(*Z*)-methyl-6-((di-tert-butoxycarbonyl)amino)-4,4-dimethylhex-2-enoate

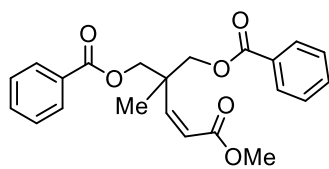
(11d). The title compound was prepared according to the general procedure using di-tert-butyl (3-methylbut-3-en-1-yl)carbamate (457 mg, 1.6 mmol, 2.0 equiv.), methyl propiolate (67 mg, 71 μL , 0.80 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH_3 (130 mg, 148 μL , 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/ AcOEt 25%) gave **11/12d** (70:30) (282 mg, 95%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.97 (d, J = 13.1 Hz, 1H), 5.73 (d, J = 13.1 Hz, 1H), 3.69 (s, 3H), 3.59 – 3.52 (m, 2H), 1.79 – 1.72 (m, 2H), 1.49 (s, 18H), 1.20 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.0, 153.2, 152.5, 119.6, 82.2, 51.4, 43.4, 41.6,

36.2, 28.2, 27.0 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{19}H_{34}NO_6^+$ 372.2381, found 372.2383.



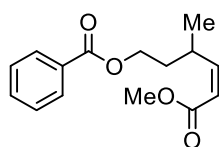
(*Z*)-methyl-6-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)

sulfonamido)-4,4-dimethylhex-2-enoate (**11e**). The title compound was prepared according to the general procedure using *tert*-butyl (3-methylbut-3-en-1-yl)(tosyl)carbamate (407 mg, 1.2 mmol, 2.0 equiv.), methyl propiolate (50 mg, 54 μ L, 0.60 mmol, 1.0 equiv.), $Fe(acac)_3$ (212 mg, 0.60 mmol, 1.0 equiv.) and $PhSiH_3$ (97 mg, 110 μ L, 0.90 mmol, 1.5 equiv.) in ethanol (6 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12e** (69:31) (232 mg, 91%) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.01 (d, J = 13.1 Hz, 1H), 5.78 (d, J = 13.1 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.71 (s, 3H), 2.42 (s, 3H), 2.03 – 1.94 (m, 2H), 1.32 (s, 9H), 1.25 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.0, 152.7, 150.9, 144.1, 137.6, 129.3, 128.0, 120.0, 84.2, 51.5, 44.2, 42.5, 36.4, 28.0, 27.3, 21.7 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{21}H_{32}NO_6S^+$ 426.1945, found 426.1948.



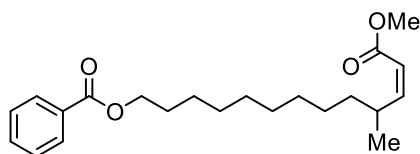
(*Z*)-2-(3-methoxy-3-oxoprop-1-en-1-yl)-2-methylpropane-1,3-

diyl dibenzoate (**11f**). The title compound was prepared according to a modification of the general procedure using 2-methylenepropane-1,3-diyl dibenzoate (1.19 g, 4.0 mmol, 5.0 equiv.), methyl propiolate (67 mg, 71 μ L, 0.80 mmol, 1.0 equiv.), $Fe(acac)_3$ (283 mg, 0.80 mmol, 1.0 equiv.) and $PhSiH_3$ (43 mg, 49 μ L, 0.40 mmol, 0.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12f** (65:35) (205 mg, 67%) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 4H), 7.59 – 7.51 (m, 2H), 7.46 – 7.39 (m, 4H), 6.17 (d, J = 13.1 Hz, 1H), 5.99 (d, J = 13.1 Hz, 1H), 4.61 (d, J = 0.8 Hz, 4H), 3.71 (s, 3H), 1.49 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 166.2, 146.9, 133.2, 130.0, 129.8, 128.6, 122.9, 68.1, 51.8, 41.6, 19.3 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{22}H_{23}O_6^+$ 383.1489, found 383.1489.



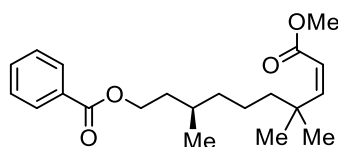
(*Z*)-6-methoxy-3-methyl-6-oxohex-4-en-1-yl benzoate (**11g**). The title

compound was prepared according to a modification of the general procedure using but-3-en-1-yl benzoate (529 mg, 3.0 mmol, 3.0 equiv.), methyl propiolate (84 mg, 88 μ L, 1.0 mmol, 1.0 equiv.), Fe(acac)₃ (353 mg, 1.0 mmol, 1.0 equiv.) and PhSiH₃ (162 mg, 184 μ L, 1.5 mmol, 1.5 equiv.) in ethanol (10 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12g** (59:41) (205 mg, 78%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.08 – 8.00 (m, 2H), 7.59 – 7.50 (m, 1H), 7.48 – 7.39 (m, 2H), 6.03 (dd, *J* = 11.5, 10.2 Hz, 1H), 5.77 (dd, *J* = 11.5, 0.9 Hz, 1H), 4.38 – 4.24 (m, 2H), 3.85 – 3.71 (m, 1H), 3.64 (s, 3H), 1.95 – 1.83 (m, 1H), 1.82 – 1.68 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.7, 154.5, 132.9, 130.5, 129.7, 128.4, 119.0, 63.3, 51.2, 35.8, 30.1, 20.5 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₅H₁₉O₄⁺ 263.1278, found 263.1279.

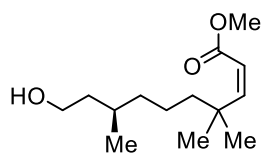


(*Z*)-13-methoxy-10-methyl-13-oxotridec-11-en-1-yl

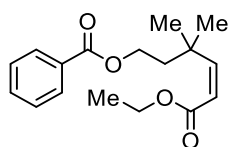
benzoate (**11h**). The title compound was prepared according to a modification of the general procedure using undec-10-en-1-yl benzoate (659 mg, 2.4 mmol, 3.0 equiv.), methyl propiolate (67 mg, 71 μ L, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12h** (36:64) (231 mg, 80%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.08 – 8.00 (m, 2H), 7.58 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 5.97 (dd, *J* = 11.6, 10.2 Hz, 1H), 5.71 (dd, *J* = 11.5, 0.9 Hz, 1H), 4.31 (t, *J* = 6.7 Hz, 2H), 3.70 (s, 3H), 3.54 – 3.42 (m, 1H), 1.81 – 1.70 (m, 2H), 1.48 – 1.37 (m, 2H), 1.38 – 1.19 (m, 12H), 0.99 (d, *J* = 6.7 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.0, 166.8, 156.8, 132.9, 130.7, 129.7, 128.5, 117.9, 65.3, 51.1, 37.1, 32.9, 29.8, 29.6, 29.4, 28.9, 27.5, 26.2, 20.4 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₂₂H₃₃O₄⁺ 361.2373, found 361.2377.

*(Z),(R)*-10-methoxy-3,7,7-trimethyl-10-oxodec-8-en-1-yl

benzoate (**11i**). The title compound was prepared according to a modification of the general procedure using (*R*)-3,7-dimethyloct-6-en-1-yl benzoate (1.04 g, 4.0 mmol, 5.0 equiv.), methyl propiolate (67 mg, 71 μ L, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (43 mg, 49 μ L, 0.40 mmol, 0.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12i** (72:28) (147 mg, 53%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.00 (m, 2H), 7.59 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 5.92 (d, *J* = 13.1 Hz, 1H), 5.69 (d, *J* = 13.1 Hz, 1H), 4.42 – 4.28 (m, 1H), 3.69 (s, 3H), 1.86 – 1.74 (m, 1H), 1.71 – 1.60 (m, 1H), 1.61 – 1.51 (m, 1H), 1.52 – 1.42 (m, 2H), 1.39 – 1.15 (m, 4H), 1.15 (s, 6H), 0.95 (d, *J* = 6.5 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.4, 166.8, 154.4, 132.9, 130.7, 129.7, 128.5, 118.9, 63.7, 51.4, 43.4, 37.8, 37.2, 35.7, 30.1, 27.3, 22.2, 19.7 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₂₁H₃₁O₄⁺ 347.2217, found 347.2218.

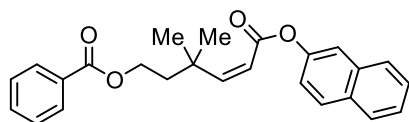
Methyl (*R,Z*)-10-hydroxy-4,4,8-trimethyldec-2-enoate (**11j**). The

title compound was prepared according to a modification of the general procedure using (*R*)-3,7-dimethyloct-6-en-1-ol (938 mg, 6.0 mmol, 5.0 equiv.), methyl propiolate (101 mg, 106 μ L, 1.2 mmol, 1.0 equiv.), Fe(acac)₃ (424 mg, 1.2 mmol, 1.0 equiv.) and PhSiH₃ (65 mg, 74 μ L, 0.60 mmol, 0.5 equiv.) in ethanol (12 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12j** (73:27) (145 mg, 50%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.92 (d, *J* = 13.1 Hz, 1H), 5.69 (d, *J* = 13.1 Hz, 1H), 3.69 (s, 3H), 3.69 – 3.58 (m, 2H), 1.65 – 1.49 (m, 3H), 1.51 – 1.39 (m, 2H), 1.40 – 1.30 (m, 1H), 1.32 – 1.18 (m, 3H), 1.14 (s, 6H), 1.14 – 1.07 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.4, 154.5, 118.8, 61.3, 51.4, 43.3, 40.0, 37.9, 37.2, 29.5, 27.4, 27.3, 22.2, 19.8 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₄H₂₇O₃⁺ 243.1955, found 243.1957.



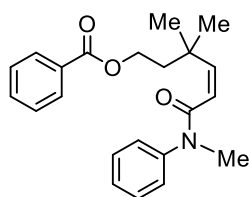
(*Z*)-6-ethoxy-3,3-dimethyl-6-oxohex-4-en-1-yl benzoate (**11k**). The

title compound was prepared according to the general procedure using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), ethyl propiolate (78 mg, 80 μ L, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12k** (62:38) (221 mg, 95%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.06 – 7.99 (m, 2H), 7.54 (ddt, J = 8.0, 6.8, 1.4 Hz, 1H), 7.47 – 7.39 (m, 2H), 6.00 (d, J = 13.1 Hz, 1H), 5.75 (d, J = 13.1 Hz, 1H), 4.37 (t, J = 7.1 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 2.09 (t, J = 7.2 Hz, 2H), 1.31 – 1.25 (m, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.7, 166.6, 153.1, 133.0, 130.6, 129.7, 128.4, 120.2, 62.7, 60.4, 40.6, 36.2, 28.0, 14.3 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₇H₂₃O₄⁺ 291.1591, found 291.1590.



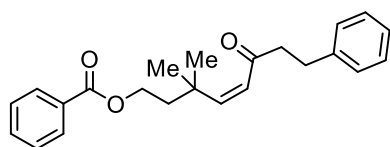
(*Z*)-3,3-dimethyl-6-(naphthalen-2-yloxy)-6-oxohex-4-

en-1-yl benzoate (**11l**). The title compound was prepared according to the general procedure using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), naphthalen-2-yl propiolate (157 mg, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12l** (52:48) (249 mg, 80%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.00 (m, 2H), 7.87 – 7.74 (m, 3H), 7.58 (d, J = 2.3 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.51 – 7.37 (m, 4H), 7.28 – 7.22 (m, 1H), 6.28 (d, J = 12.9 Hz, 1H), 6.04 (d, J = 13.0 Hz, 1H), 4.43 (t, J = 7.1 Hz, 2H), 2.17 (t, J = 7.1 Hz, 2H), 1.37 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.7, 164.6, 157.1, 148.3, 133.9, 133.0, 131.6, 130.5, 129.7, 129.5, 128.5, 127.9, 127.8, 126.6, 125.8, 121.3, 119.3, 118.7, 62.6, 40.4, 36.4, 28.1 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₂₅H₂₅O₄⁺ 389.1747, found 389.1749.



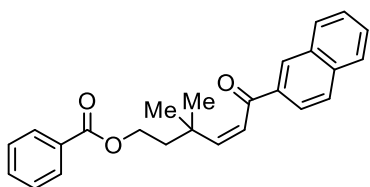
(Z)-3,3-dimethyl-6-(methyl(phenyl)amino)-6-oxohex-4-en-1-yl

benzoate (**11m**). The title compound was prepared according to the general procedure using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), *N*-methyl-*N*-phenylpropiolamide (127 mg, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12m** (58:42) (267 mg, 95%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.98 (m, 1.7H), 7.98 – 7.94 (m, 0.3H), 7.71 – 7.67 (m, 0.1H), 7.57 – 7.51 (m, 1.0H), 7.42 (t, *J* = 7.6 Hz, 2.0H), 7.36 (t, *J* = 7.5 Hz, 1.7H), 7.30 – 7.22 (m, 1.2H), 7.17 (d, *J* = 7.7 Hz, 1.5H), 7.03 (td, *J* = 7.7, 1.1 Hz, 0.2H), 6.83 – 6.77 (m, 0.1H), 5.60 (d, *J* = 13.0 Hz, 0.8H), 5.52 (d, *J* = 13.0 Hz, 0.8H), 4.44 (t, *J* = 6.8 Hz, 0.3H), 4.31 (t, *J* = 7.2 Hz, 1.5H), 3.32 (s, 2.4H), 3.20 (s, 0.4H), 2.27 (t, *J* = 6.8 Hz, 0.3H), 1.98 (t, *J* = 7.2 Hz, 1.7H), 1.48 (s, 0.8H), 1.25 (s, 5.7H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 168.7, 167.7, 166.7, 166.6, 151.1, 146.6, 144.6, 143.9, 132.9, 132.9, 130.6, 130.2, 129.7, 129.5, 129.2, 128.4, 127.5, 127.0, 126.3, 122.9, 121.9, 120.5, 108.3, 62.7, 62.2, 41.4, 39.8, 36.9, 36.2, 35.1, 29.8, 27.6, 26.3 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₂₂H₂₆NO₃⁺ 352.1907, found 352.1908.



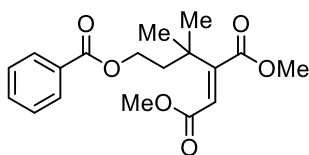
(Z)-3,3-dimethyl-6-oxo-8-phenyloct-4-en-1-yl benzoate

(**11o**). The title compound was prepared according to the general procedure using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), 5-phenylpent-1-yn-3-one (127 mg, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **11/12o** (43:57) (264 mg, 94%) as a colorless oil. The product was not stable and isomerized into the *trans* isomer prior to full characterization. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₂₃H₂₇O₃⁺ 351.1955, found 351.1955.



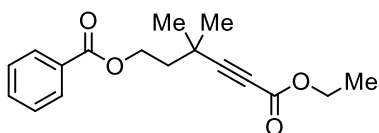
(Z)-3,3-dimethyl-6-(naphthalen-2-yl)-6-oxohex-4-en-1-yl

benzoate (**11p**). The title compound was prepared according to the general procedure using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), 1-(naphthalen-2-yl)prop-2-yn-1-one (144 mg, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **11/12p** (52:48) (274 mg, 92%) as a colorless oil. However, the product was not stable and isomerized into the *trans* isomer prior to full characterization. HRMS (ESI) m/z : [M+H]⁺: calculated for C₂₅H₂₅O₃⁺ 373.1798, found 373.1804.



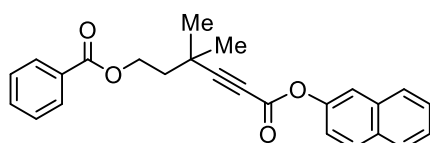
(Z)-dimethyl 2-(4-(benzoyloxy)-2-methylbutan-2-yl)fumarate

(**11q**). The title compound was prepared according to the general procedure using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), dimethyl but-2-ynedioate (114 mg, 98 μ L, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH₃ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11/12q** (71:29) (203 mg, 76%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.01 (dd, J = 8.4, 1.4 Hz, 2H), 7.57 – 7.50 (m, 1H), 7.45 – 7.38 (m, 2H), 6.38 (s, 1H), 4.37 (t, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.72 (s, 3H), 2.23 (t, J = 7.0 Hz, 2H), 1.32 (s, 6H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 168.8, 167.3, 166.6, 149.0, 132.9, 130.6, 129.6, 128.4, 125.2, 62.5, 52.2, 52.1, 39.7, 38.0, 27.7 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₈H₂₃O₆⁺ 335.1489, found 335.1488.

6-ethoxy-3,3-dimethyl-6-oxohex-4-yn-1-yl benzoate (**11r**).

The title compound was prepared according to a modification of the general procedure using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), ethyl 3-bromopropiolate (142 mg, 0.80 mmol, 1.0 equiv.), Fe(acac)₃ (283 mg, 0.80 mmol, 1.0

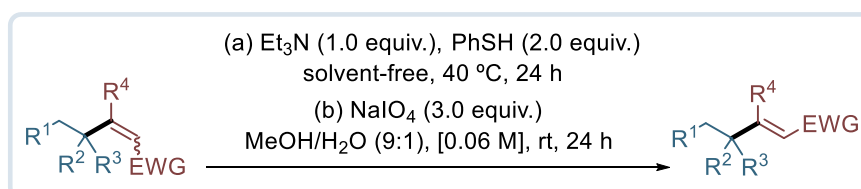
equiv.), NaHCO_3 (67 mg, 0.80 mmol, 1.0 equiv.), and PhSiH_3 (130 mg, 148 μL , 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11r** (143 mg, 62%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.07 – 8.01 (m, 2H), 7.59 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 4.51 (t, J = 6.8 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 1.99 (t, J = 6.8 Hz, 2H), 1.37 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.6, 154.0, 133.1, 130.3, 129.7, 128.5, 94.0, 73.7, 62.3, 62.0, 40.7, 30.2, 28.8, 14.2 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{17}\text{H}_{21}\text{O}_4^+$ 289.1434, found 289.1432.



3,3-dimethyl-6-(naphthalen-2-yloxy)-6-oxohex-4-

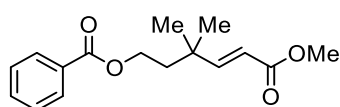
yn-1-yl benzoate (**11s**). The title compound was prepared according to a modification of the general procedure using 3-methylbut-3-en-1-yl benzoate (228 mg, 1.2 mmol, 2.0 equiv.), naphthalen-2-yl 3-bromopropiolate (165 mg, 0.60 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (212 mg, 0.60 mmol, 1.0 equiv.), NaHCO_3 (50 mg, 0.60 mmol, 1.0 equiv.), and PhSiH_3 (98 mg, 111 μL , 0.90 mmol, 1.5 equiv.) in ethanol (6 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **11s** (116 mg, 50%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.12 – 8.04 (m, 2H), 7.89 – 7.76 (m, 3H), 7.58 – 7.52 (m, 2H), 7.49 (ddd, J = 7.6, 5.3, 1.6 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.23 (dd, J = 8.9, 2.3 Hz, 1H), 4.55 (t, J = 6.7 Hz, 2H), 2.04 (t, J = 6.8 Hz, 2H), 1.43 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.7, 152.3, 147.9, 133.8, 133.1, 131.8, 130.3, 129.8, 129.7, 128.5, 127.90, 127.85, 126.8, 126.1, 120.9, 118.7, 97.1, 73.3, 62.1, 40.7, 30.4, 28.7 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{25}\text{H}_{23}\text{O}_4^+$ 387.1591, found 387.1591.

ISOMERIZATION OF THE *CIS*/*TRANS* MIXTURES OF THE MHAT COUPLING



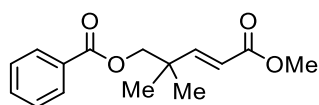
General method for the isomerization of the *cis*/*trans* mixtures of the MHAT reaction between non-activated alkenes and electron-deficient alkynes: To the purified

cis/trans mixture (1.0 equiv.) obtained in the MHAT coupling was added triethylamine (1.0 equiv.) and thiophenol (2.0 equiv.) and the resulting solution was stirred at 40 °C in an oil bath for 24 hours. Then, triethylamine was evaporated by heating at 70 °C in an oil bath and applying vacuum for 30 minutes. Afterward, the crude mixture was dissolved in MeOH/H₂O (9:1, 0.06 M) and sodium periodate (3.0 equiv.) was added portionwise. After stirring for 24 hours at room temperature, the mixture was extracted with dichloromethane. The organic layer was dried with sodium sulfate and concentrated. The corresponding product was purified by flash column chromatography on silica gel.



(*E*)-6-methoxy-3,3-dimethyl-6-oxohex-4-en-1-yl benzoate

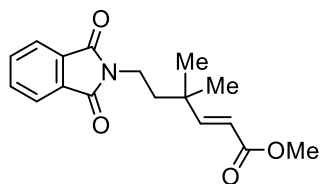
(12a). The title compound was prepared according to the general procedure using the **11a** and **12a** mixture (100 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12a** (97 mg, 97%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.97 (m, 2H), 7.58 – 7.50 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 15.9 Hz, 1H), 5.77 (d, *J* = 16.0 Hz, 1H), 4.31 (t, *J* = 6.9 Hz, 2H), 3.68 (s, 3H), 1.89 (t, *J* = 6.9 Hz, 2H), 1.16 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.4, 166.6, 157.3, 133.0, 130.3, 129.7, 128.5, 118.0, 62.0, 51.6, 40.6, 36.0, 26.8 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₆H₂₁O₄⁺ 277.1434, found 277.1436.



(*E*)-5-methoxy-2,2-dimethyl-5-oxopent-3-en-1-yl benzoate

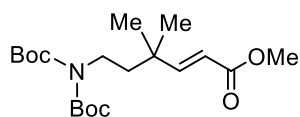
(12b). The title compound was prepared according to the general procedure using the **11b** and **12b** mixture (94 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12b** (93 mg, 98%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.98 (m, 2H), 7.60 – 7.53 (m, 1H), 7.48 – 7.40 (m, 2H), 7.04 (d, *J* = 16.0 Hz, 1H), 5.90 (d, *J* = 16.0 Hz, 1H), 4.17 (s, 2H), 3.74 (s, 3H),

1.21 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.3, 166.5, 154.4, 133.2, 130.1, 129.7, 128.6, 119.4, 71.7, 51.8, 37.7, 24.0 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{15}\text{H}_{19}\text{O}_4^+$ 263.1278, found 263.1278.



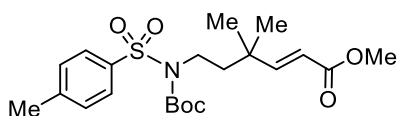
Methyl (E)-6-(1,3-dioxoisindolin-2-yl)-4,4-dimethylhex-2-

enoate (**12c**). The title compound was prepared according to the general procedure using the **11c** and **12c** mixture (108 mg, 0.36 mmol, 1.0 equiv.) triethylamine (36 mg, 50 μL , 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μL , 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/ H_2O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12c** (104 mg, 96%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.84 – 7.78 (m, 2H), 7.72 – 7.66 (m, 2H), 6.89 (d, J = 16.0 Hz, 1H), 5.77 (d, J = 16.0 Hz, 1H), 3.67 – 3.62 (m, 2H), 3.61 (s, 3H), 1.83 – 1.75 (m, 2H), 1.14 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 168.3, 167.2, 156.5, 134.0, 132.2, 123.3, 118.1, 51.5, 39.8, 36.2, 34.5, 26.4 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{17}\text{H}_{20}\text{NO}_4^+$ 302.1387, found 302.1388.



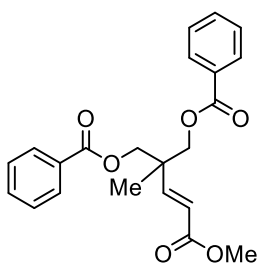
(E)-methyl-6-((di-tert-butoxycarbonyl)amino)-4,4-dimethylhex-

2-enoate (**12d**). The title compound was prepared according to the general procedure using the **11d** and **12d** mixture (134 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μL , 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μL , 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/ H_2O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12d** (132 mg, 99%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 6.91 (d, J = 16.0 Hz, 1H), 5.75 (d, J = 16.0 Hz, 1H), 3.71 (s, 3H), 3.53 – 3.44 (m, 2H), 1.67 – 1.60 (m, 2H), 1.49 (s, 18H), 1.09 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.4, 157.3, 152.3, 118.0, 82.4, 51.6, 43.1, 40.4, 35.9, 28.2, 26.4 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{19}\text{H}_{33}\text{NNaO}_6^+$ 394.2200, found 394.2212.



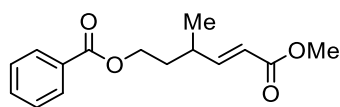
(E)-methyl-6-((N-(tert-butoxycarbonyl)-4-

methylphenyl)sulfonamido)-4,4-dimethylhex-2-enoate (**12e**). The title compound was prepared according to the general procedure using the **11e** and **12e** mixture (153 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12e** (146 mg, 95%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.79 – 7.72 (m, 2H), 7.32 – 7.27 (m, 2H), 6.95 (d, J = 16.0 Hz, 1H), 5.81 (d, J = 16.0 Hz, 1H), 3.78 – 3.69 (m, 5H), 2.43 (s, 3H), 1.92 – 1.79 (m, 2H), 1.33 (s, 9H), 1.14 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.4, 156.9, 150.9, 144.3, 137.5, 129.4, 127.9, 118.3, 84.3, 51.6, 43.9, 41.6, 36.1, 28.0, 26.4, 21.7 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₂₁H₃₂NO₆S⁺ 426.1945, found 426.1948.

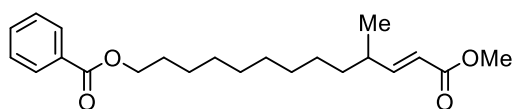


(E)-2-(3-methoxy-3-oxoprop-1-en-1-yl)-2-methylpropane-1,3-diyl

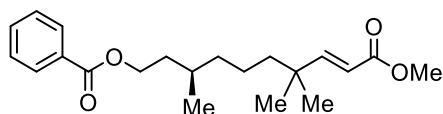
dibenzoate (**12f**). The title compound was prepared according to the general procedure using the mixture of **11f** and **12f** (138 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12f** (132 mg, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.97 (m, 4H), 7.62 – 7.52 (m, 2H), 7.49 – 7.39 (m, 4H), 7.10 (d, J = 16.2 Hz, 1H), 6.05 (d, J = 16.2 Hz, 1H), 4.50 – 4.34 (m, 4H), 3.75 (s, 3H), 1.34 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.7, 166.3, 149.4, 133.4, 129.8, 128.6, 121.8, 67.7, 51.9, 41.4, 19.5 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₂₂H₂₃O₆⁺ 383.1489, found 383.1488.

*(E)*-6-methoxy-3-methyl-6-oxohex-4-en-1-yl benzoate (**12g**).

The title compound was prepared according to the general procedure using the **11g** and **12g** mixture (94 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12g** (93 mg, 99%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.98 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.38 (m, 2H), 6.91 (dd, J = 15.7, 8.0 Hz, 1H), 5.84 (dd, J = 15.7, 1.1 Hz, 1H), 4.33 (qt, J = 11.2, 6.5 Hz, 2H), 3.70 (s, 3H), 2.66 – 2.47 (m, 1H), 1.86 (q, J = 6.6 Hz, 2H), 1.14 (d, J = 6.7 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.1, 166.6, 153.4, 133.1, 130.3, 129.7, 128.5, 120.2, 62.9, 51.6, 34.9, 33.9, 19.5 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₅H₁₉O₄⁺ 263.1278, found 263.1277.

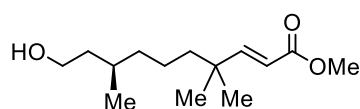
*(E)*-13-methoxy-10-methyl-13-oxotridec-11-en-1-yl benzoate (**12h**).

The title compound was prepared according to the general procedure using the **11h** and **12h** mixture (130 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12h** (123 mg, 95%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.08 – 8.02 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 – 7.40 (m, 2H), 6.87 (dd, J = 15.7, 7.9 Hz, 1H), 5.77 (dd, J = 15.7, 1.2 Hz, 1H), 4.31 (t, J = 6.7 Hz, 2H), 3.73 (s, 3H), 2.37 – 2.22 (m, 1H), 1.82 – 1.72 (m, 2H), 1.49 – 1.39 (m, 2H), 1.39 – 1.19 (m, 12H), 1.04 (d, J = 6.7 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.5, 166.8, 155.2, 132.9, 130.7, 129.6, 128.4, 119.3, 65.2, 51.5, 36.7, 36.1, 29.7, 29.60, 29.57, 29.4, 28.8, 27.3, 26.1, 19.5 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₂₂H₃₃O₄⁺ 361.2373, found 361.2373.

*(R,E)*-10-methoxy-3,7,7-trimethyl-10-oxodec-8-en-1-yl benzoate (**12i**).

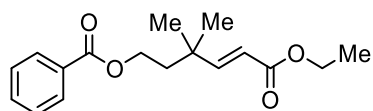
The title compound was prepared according to the general procedure

using the **11i** and **12i** mixture (125 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12i** (109 mg, 87%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 7.99 (m, 2H), 7.59 – 7.50 (m, 1H), 7.48 – 7.38 (m, 2H), 6.92 (d, J = 15.9 Hz, 1H), 5.71 (d, J = 16.0 Hz, 1H), 4.41 – 4.27 (m, 2H), 3.72 (s, 3H), 1.85 – 1.71 (m, 1H), 1.69 – 1.48 (m, 3H), 1.40 – 1.10 (m, 6H), 1.03 (s, 6H), 0.94 (d, J = 6.5 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.7, 166.8, 158.8, 132.9, 130.6, 129.7, 128.5, 117.5, 63.6, 51.6, 42.6, 37.7, 36.9, 35.7, 30.0, 26.48, 26.46, 22.0, 19.7 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₂₁H₃₁O₄⁺ 347.2217, found 347.2216.



Methyl (R,E)-10-hydroxy-4,4,8-trimethyldec-2-enoate (12j).

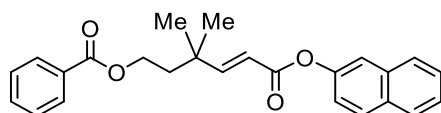
The title compound was prepared according to the general procedure using the **11j** and **12j** mixture (87 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12j** (84 mg, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 6.91 (d, J = 16.0 Hz, 1H), 5.70 (d, J = 16.0 Hz, 1H), 3.72 (s, 3H), 3.71 – 3.57 (m, 2H), 1.63 – 1.47 (m, 2H), 1.40 – 1.04 (m, 7H), 1.03 (s, 6H), 0.86 (d, J = 6.6 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.8, 158.9, 117.4, 61.2, 51.6, 42.6, 40.0, 37.8, 37.0, 29.5, 26.5, 26.4, 22.0, 19.7 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₄H₂₇O₃⁺ 243.1955, found 243.1956.



(E)-6-ethoxy-3,3-dimethyl-6-oxohex-4-en-1-yl benzoate (12k).

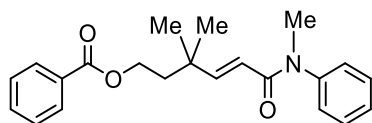
The title compound was prepared according to the general procedure using the **11k** and **12k** mixture (105 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12k** (101 mg, 97%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.04 – 7.98 (m, 2H), 7.58 – 7.51 (m, 1H), 7.46 –

7.39 (m, 2H), 6.99 (d, $J = 15.9$ Hz, 1H), 5.77 (d, $J = 15.9$ Hz, 1H), 4.32 (t, $J = 6.9$ Hz, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 1.90 (t, $J = 6.9$ Hz, 2H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.17 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.0, 166.7, 157.0, 133.0, 130.3, 129.7, 128.5, 118.4, 62.0, 60.4, 40.6, 36.0, 26.8, 14.4 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{17}\text{H}_{23}\text{O}_4^+$ 291.1591, found 291.1594.



(*E*)-3,3-dimethyl-6-(naphthalen-2-yloxy)-6-oxohex-

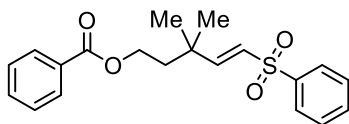
4-en-1-yl benzoate (**12l**). The title compound was prepared according to the general procedure using the **11l** and **12l** mixture (140 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μL , 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μL , 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/ H_2O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12l** (136 mg, 97%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.04 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.83 (d, $J = 8.8$ Hz, 2H), 7.81 – 7.74 (m, 1H), 7.56 – 7.51 (m, 1H), 7.50 (d, $J = 1.8$ Hz, 1H), 7.47 (ddd, $J = 7.9, 5.7, 1.6$ Hz, 2H), 7.46 – 7.37 (m, 2H), 7.26 (d, $J = 15.9$ Hz, 1H), 7.18 (dd, $J = 8.9, 2.3$ Hz, 1H), 6.03 (d, $J = 16.0$ Hz, 1H), 4.38 (t, $J = 6.7$ Hz, 2H), 1.97 (t, $J = 6.8$ Hz, 2H), 1.25 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.7, 165.5, 159.5, 148.5, 133.9, 133.1, 131.6, 130.2, 129.7, 129.4, 128.6, 127.9, 127.8, 126.6, 125.8, 121.4, 118.7, 117.6, 62.0, 40.7, 36.4, 26.8 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{25}\text{H}_{25}\text{O}_4^+$ 389.1747, found 389.1749.



(*E*)-3,3-dimethyl-6-(methyl(phenyl)amino)-6-oxohex-4-

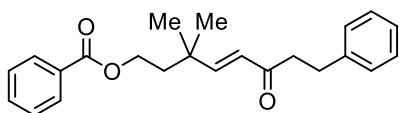
en-1-yl benzoate (**12m**). The title compound was prepared according to the general procedure using the **11m** and **12m** mixture (127 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μL , 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μL , 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/ H_2O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12m** (121 mg, 96%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.00 (dd, $J = 8.3, 1.4$ Hz, 2H), 7.58 – 7.52 (m, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.42 – 7.33 (m, 2H), 7.31 – 7.25 (m, 1H), 7.15 – 7.08 (m, 2H), 6.91 (d, $J = 15.5$ Hz, 1H), 5.66 (d, $J = 15.5$ Hz, 1H), 4.21 (t, $J = 7.0$

Hz, 2H), 3.33 (s, 3H), 1.80 (t, $J = 7.0$ Hz, 2H), 1.00 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.6, 166.4, 153.4, 143.8, 133.0, 130.4, 129.7, 129.6, 128.5, 127.5, 127.3, 118.6, 62.2, 40.4, 37.5, 35.8, 26.9 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_3^+$ 352.1907, found 352.1908.



(E)-3,3-dimethyl-5-(phenylsulfonyl)pent-4-en-1-yl

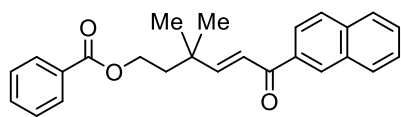
benzoate (12n). The title compound was prepared according to the general procedure for the MHAT reaction between non-activated alkenes and electron-deficient alkynes (see page 260) using 3-methylbut-3-en-1-yl benzoate (304 mg, 1.6 mmol, 2.0 equiv.), (ethynylsulfonyl)benzene (133 mg, 0.80 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (283 mg, 0.80 mmol, 1.0 equiv.) and PhSiH_3 (130 mg, 148 μL , 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12n** (149 mg, 52%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.06 – 7.99 (m, 2H), 7.87 – 7.80 (m, 2H), 7.64 – 7.52 (m, 2H), 7.54 – 7.46 (m, 2H), 7.49 – 7.40 (m, 2H), 7.06 (d, $J = 15.3$ Hz, 1H), 6.28 (d, $J = 15.3$ Hz, 1H), 4.28 (t, $J = 6.9$ Hz, 2H), 1.91 (t, $J = 6.9$ Hz, 2H), 1.17 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.6, 154.5, 140.7, 133.4, 133.2, 130.1, 129.7, 129.4, 128.6, 128.2, 127.7, 61.6, 40.3, 36.4, 26.5 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{20}\text{H}_{23}\text{O}_4\text{S}^+$ 359.1312, found 359.1310.



(E)-3,3-dimethyl-6-oxo-8-phenyloct-4-en-1-yl benzoate

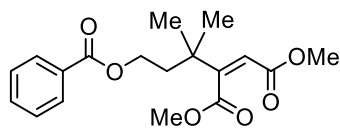
(12o). The title compound was prepared according to the general procedure using the **11o** and **12o** mixture (126 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μL , 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μL , 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/ H_2O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12o** (122 mg, 97%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.03 – 7.95 (m, 2H), 7.58 – 7.51 (m, 1H), 7.46 – 7.37 (m, 2H), 7.31 – 7.22 (m, 2H), 7.22 – 7.12 (m, 3H), 6.81 (d, $J = 16.2$ Hz, 1H), 6.04 (d, $J = 16.2$ Hz, 1H), 4.30 (t, $J = 6.9$ Hz, 2H), 2.88 (ddd, $J = 8.3, 6.5, 1.8$ Hz, 2H), 2.79 (ddd, $J = 8.7, 6.7, 1.8$ Hz, 2H), 1.88 (t, $J = 6.9$ Hz, 2H), 1.15 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 199.7, 166.6, 155.2, 141.3, 133.1, 130.2, 129.7, 128.6, 128.51, 128.49, 126.7, 126.2,

62.0, 42.2, 40.6, 36.0, 30.1, 26.8 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{23}H_{27}O_3^+$ 351.1955, found 351.1952.



(*E*)-3,3-dimethyl-6-(naphthalen-2-yl)-6-oxohex-4-en-1-yl

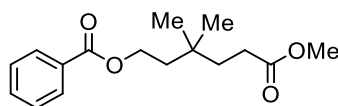
benzoate (**12p**). The title compound was prepared according to the general procedure using the mixture of **11p** and **12p** (134 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12p** (127 mg, 95%) as a colorless oil. 1H NMR (400 MHz, CDCl₃) δ 8.45 – 8.40 (m, 1H), 8.04 – 7.94 (m, 4H), 7.93 – 7.84 (m, 2H), 7.63 – 7.57 (m, 1H), 7.59 – 7.51 (m, 1H), 7.52 – 7.46 (m, 1H), 7.37 (t, J = 7.7 Hz, 2H), 7.17 (d, J = 15.7 Hz, 1H), 7.02 (d, J = 15.7 Hz, 1H), 4.41 (t, J = 6.9 Hz, 2H), 2.00 (t, J = 7.0 Hz, 2H), 1.29 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, CDCl₃) δ 190.7, 166.7, 157.4, 135.54, 135.47, 133.0, 132.6, 130.2, 130.1, 129.69, 129.66, 128.6, 128.5, 128.4, 127.9, 126.8, 124.6, 122.2, 62.1, 40.6, 36.5, 27.0 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{25}H_{25}O_3^+$ 373.1798, found 373.1798.



(*E*)-dimethyl 2-(4-(benzoyloxy)-2-methylbutan-2-yl)maleate

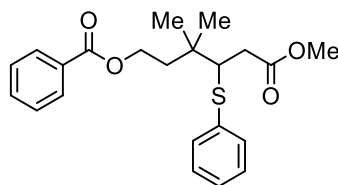
(**12q**). The title compound was prepared according to the general procedure using the **11q** and **12q** mixture (120 mg, 0.36 mmol, 1.0 equiv.), triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.), thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and sodium periodate (231 mg, 1.08 mmol, 3.0 equiv.) in (9:1) MeOH/H₂O (6 mL, 0.06 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **12q** (114 mg, 95%) as a colorless oil. 1H NMR (400 MHz, CDCl₃) δ 8.04 – 7.98 (m, 2H), 7.55 (ddt, J = 8.0, 6.9, 1.4 Hz, 1H), 7.46 – 7.39 (m, 2H), 5.88 (s, 1H), 4.36 (t, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 2.00 (t, J = 7.0 Hz, 2H), 1.25 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, CDCl₃) δ 168.8, 166.6, 165.5, 158.5, 133.0, 130.3, 129.7, 128.5, 117.8, 62.0, 52.4, 52.0, 39.4, 38.0, 27.1 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{18}H_{23}O_6^+$ 335.1489, found 335.1488.

Synthesis of (Z)-6-methoxy-3,3-dimethyl-6-oxohexyl benzoate (**13**)



The title compound was isolated during the synthesis of **11/12a** according to a modification of the general procedure for the MHAT reaction between non-activated alkenes and electron-deficient alkynes (see page 260) using 3-methylbut-3-en-1-yl benzoate (2.28 g, 12 mmol, 3.0 equiv.), methyl propiolate (336 mg, 350 μ L, 4.0 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (1.41 g, 4.0 mmol, 1.0 equiv.) and PhSiH_3 (649 mg, 740 μ L, 6.0 mmol, 1.5 equiv.) in ethanol (40 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **13** (33 mg, 3%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.08 – 7.98 (m, 2H), 7.61 – 7.50 (m, 1H), 7.47 – 7.37 (m, 2H), 4.38 (t, J = 7.3 Hz, 2H), 3.65 (s, 3H), 2.38 – 2.28 (m, 2H), 1.71 (t, J = 7.2 Hz, 2H), 1.68 – 1.63 (m, 2H), 0.98 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.6, 166.8, 133.0, 130.5, 129.7, 128.5, 62.2, 51.7, 39.7, 37.0, 32.2, 29.5, 27.1 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{16}\text{H}_{23}\text{O}_4^+$ 279.1591, found 279.1592.

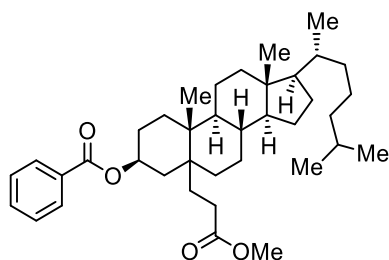
Synthesis of 6-methoxy-3,3-dimethyl-6-oxo-4-(phenylthio)hexyl benzoate (**14**)



To the purified *cis/trans* mixture of **11a** and **12a** (100 mg, 0.36 mmol, 1.0 equiv.) obtained in the MHAT coupling was added triethylamine (36 mg, 50 μ L, 0.36 mmol, 1.0 equiv.) and thiophenol (79 mg, 73 μ L, 0.72 mmol, 2.0 equiv.) and the resulting mixture was stirred at 40 $^\circ\text{C}$ in an oil bath for 24 hours. Then, triethylamine was evaporated by heating at 70 $^\circ\text{C}$ in an oil bath and applying vacuum for 30 minutes. Purification by chromatography of the Michael adduct (Hex $\rightarrow$ Hex/AcOEt 10%) gave **14** (139 mg, 100%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.05 – 7.97 (m, 2H), 7.59 – 7.47 (m, 3H), 7.47 – 7.38 (m, 2H), 7.30 – 7.21 (m, 2H), 7.22 – 7.13 (m, 1H), 4.43 – 4.25 (m, 2H), 3.63 – 3.56 (m, 4H), 2.86 (dd, J = 15.9, 4.1 Hz, 1H), 2.59 (dd, J = 15.9, 10.0 Hz, 1H), 2.01 (ddd, J = 14.1, 8.2, 6.1 Hz, 1H), 1.87 (ddd, J = 13.9, 8.3, 6.5 Hz, 1H), 1.11 (s, 3H), 1.10 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 172.6, 166.7, 136.6, 133.0, 131.7, 130.4, 129.7, 129.1,

128.4, 127.0, 62.0, 56.9, 51.9, 38.1, 38.0, 37.4, 25.2, 25.1 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{22}H_{27}O_4S^+$ 387.1625, found 387.1627.

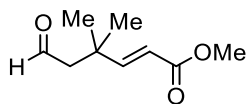
Synthesis of (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-5-(3-methoxy-3-oxopropyl)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl benzoate (16).



The title compound was prepared according to a modification of the general procedure for the MHAT reaction between non-activated alkenes and electron-deficient alkynes (see page 260) using cholesteryl benzoate (393 mg, 0.80 mmol, 1.0 equiv.), methyl propiolate (67 mg, 71 μ L, 0.80 mmol, 1.0 equiv.), $Fe(acac)_3$ (283 mg, 0.80 mmol, 1.0 equiv.) and $PhSiH_3$ (130 mg, 148 μ L, 1.2 mmol, 1.5 equiv.) in ethanol (8 mL, 0.1 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 10%) gave **16** (366 mg, 79%) as a white solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.3, 1.4 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.46 – 7.37 (m, 2H), 5.18 (qt, J = 9.0, 4.3 Hz, 1H), 3.71 (s, 3H), 2.70 – 2.50 (m, 3H), 2.20 (td, J = 14.0, 3.3 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.83 (td, J = 10.2, 5.0 Hz, 3H), 1.79 – 1.64 (m, 2H), 1.65 – 1.56 (m, 4H), 1.56 – 1.26 (m, 10H), 1.23 (dd, J = 12.1, 7.2 Hz, 2H), 1.18 – 0.95 (m, 8H), 0.91 – 0.83 (m, 12H), 0.62 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.0, 166.0, 132.7, 131.1, 129.6, 128.4, 72.6, 56.3, 54.3, 51.9, 47.0, 44.6, 43.1, 42.7, 41.6, 39.7, 38.1, 36.3, 35.8, 35.7, 34.9, 29.6, 29.5, 28.5, 28.21, 28.16, 27.9, 24.6, 23.9, 23.0, 22.7, 21.6, 18.8, 15.6, 10.9 ppm.

1,5-TRANSPOSITIONS OF VINYL RADICALS

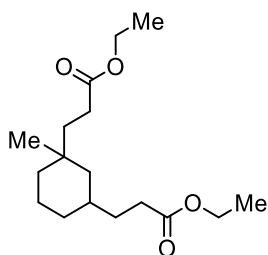
Synthesis of methyl (*E*)-4,4-dimethyl-6-oxohex-2-enoate (17)



To a solution of 3-methylbut-3-en-1-ol (86 mg, 101 μ L, 1.0 mmol, 1.0 equiv.) in ethanol (10 mL, 0.1 M) was added methyl propiolate (84 mg, 88 μ L, 1.0 mmol, 1.0 equiv.) and $Fe(acac)_3$ (353 mg, 1.0 mmol, 1.0 equiv.). The resulting mixture was degassed for 5 minutes with argon and, subsequently, $PhSiH_3$ (270 mg, 307 μ L, 2.5 mmol,

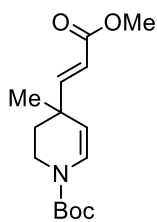
2.5 equiv.) was added dropwise. The suspension was heated at 60 °C with a heating mantle for 16 hours and the resulting mixture was concentrated. Purification by chromatography (Hex → Hex/AcOEt 50%) gave **17** (60 mg, 35%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 9.70 (t, $J = 2.8$ Hz, 1H), 7.03 (d, $J = 16.0$ Hz, 1H), 5.81 (d, $J = 16.0$ Hz, 1H), 3.75 (s, 3H), 2.44 (d, $J = 2.8$ Hz, 2H), 1.22 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 201.5, 167.2, 155.7, 118.6, 54.4, 51.8, 36.0, 27.0 ppm.

Synthesis of diethyl 3,3'-(1-methylcyclohexane-1,3-diyl)dipropionate (**19**)



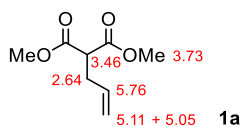
To a solution of 1-methyl-1-cyclohexene (96 mg, 101 μL , 1.0 mmol, 1.0 equiv.) in ethanol (10 mL, 0.1 M) was added ethyl propiolate (294 mg, 303 μL , 3.0 mmol, 3.0 equiv.) and $\text{Fe}(\text{acac})_3$ (353 mg, 1.0 mmol, 1.0 equiv.). The resulting mixture was degassed for 5 minutes with argon and, subsequently, PhSiH_3 (162 mg, 184 μL , 1.5 mmol, 1.5 equiv.) was added dropwise. The suspension was heated at 60 °C with a heating mantle for 16 hours and then concentrated. Purification by chromatography (Hex → Hex/AcOEt 50%) gave diethyl 3,3'-(1-methylcyclohexane-1,3-diyl)diacrylate (**18**) (82 mg, 28%) as a complex mixture of isomers that could not be characterized. Then, the product (82 mg, 0.28 mmol, 1.0 equiv.) was dissolved in ethanol (2.8 mL, 0.1 M) and palladium on carbon (5 wt.% loading, 18 mg, 8.5 μmol , 0.03 equiv.) was added in one portion. The resulting solution was stirred for 16 hours at room temperature under a hydrogen atmosphere. Purification by chromatography (Hex → Hex/AcOEt 50%) gave **19** (74 mg, 89%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.16 – 4.05 (m, 4H), 2.32 – 2.23 (m, 3H), 2.22 – 2.13 (m, 1H), 1.74 – 1.66 (m, 1H), 1.66 – 1.57 (m, 1H), 1.55 – 1.33 (m, 8H), 1.28 – 1.19 (m, 6H), 1.10 – 0.96 (m, 1H), 0.85 (s, 1H), 0.82 (s, 2H), 0.79 – 0.67 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.7, 174.6, 174.2, 60.41, 60.38, 60.33, 60.31, 44.4, 44.3, 41.0, 37.4, 37.2, 33.2, 33.0, 32.8, 32.74, 32.69, 32.4, 32.1, 31.1, 29.5, 29.3, 29.0, 22.0, 21.9, 21.7, 14.4 ppm.

Synthesis of *tert*-butyl (*E*)-4-(3-methoxy-3-oxoprop-1-en-1-yl)-4-methyl-3,4-dihydropyridine-1(2*H*)-carboxylate (*trans*-20**)**

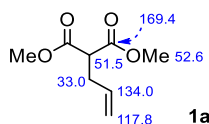
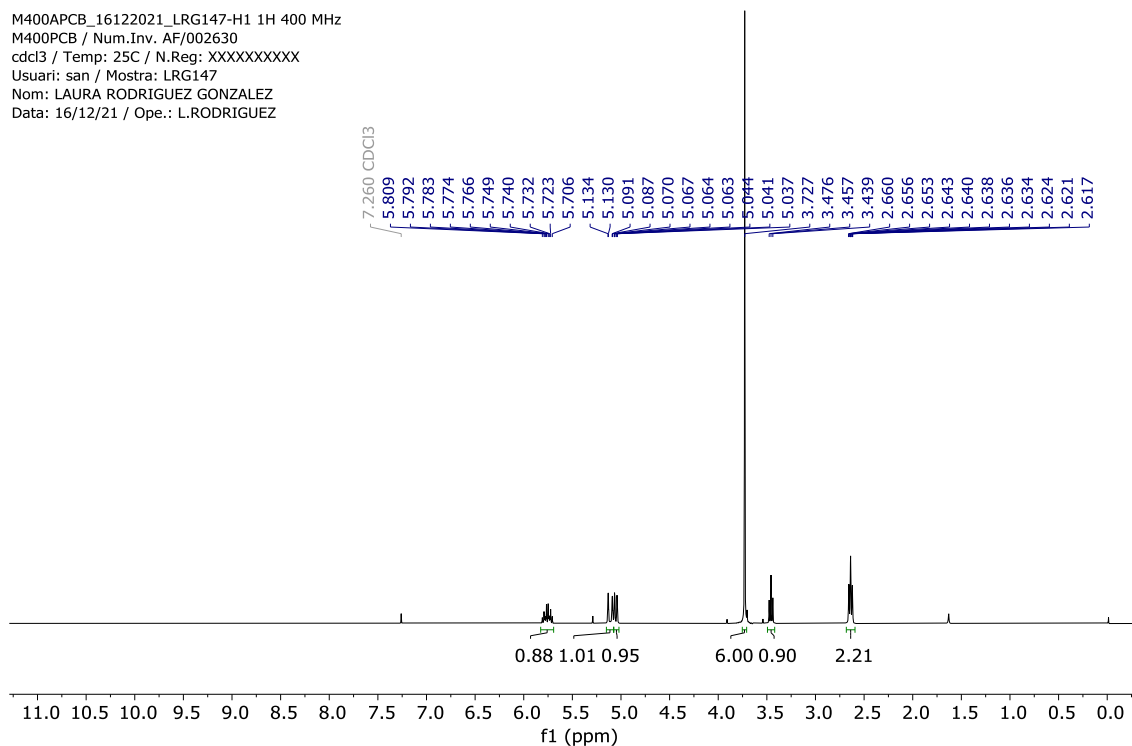


To a solution of *tert*-butyl 4-methylenepiperidine-1-carboxylate (395 mg, 2.0 mmol, 2.0 equiv.) in ethanol (10 mL, 0.1 M) was added methyl propiolate (84 mg, 88 μ L, 1.0 mmol, 1.0 equiv.) and Fe(acac)₃ (353 mg, 1.0 mmol, 1.0 equiv.). The resulting mixture was degassed for 5 minutes with argon and, subsequently, PhSiH₃ (162 mg, 184 μ L, 1.5 mmol, 1.5 equiv.) was added dropwise. The suspension was heated at 60 °C with a heating mantle for 16 hours and subsequently concentrated. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave *tert*-butyl 4-(3-methoxy-3-oxoprop-1-en-1-yl)-4-methyl-3,4-dihydropyridine-1(2*H*)-carboxylate (**20**) (93 mg, 33%) as a complex mixture of isomers that could not be characterized. The mixture of isomers was treated with triethylamine (33 mg, 0.33 mmol, 1.0 equiv.) and thiophenol (73 mg, 67 μ L, 0.66 mmol, 2.0 equiv.) and stirred at 40 °C in an oil bath for 24 hours. Then, triethylamine was evaporated by heating at 70 °C in an oil bath and applying vacuum for 30 minutes. The crude residue was dissolved in MeOH/H₂O (9:1, 5.5 mL, 0.06 M) and sodium periodate (213 mg, 1.0 mmol, 3.0 equiv.) was added portionwise. After stirring the solution for 24 hours at room temperature, the mixture was extracted with dichloromethane. The organic layer was dried with sodium sulfate and concentrated. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave *trans*-**20** (88 mg, 95%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 6.93 (d, *J* = 8.4 Hz, 0.3H), 6.85 (d, *J* = 15.7 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 0.5H), 5.75 (d, *J* = 15.7 Hz, 1H), 4.62 (d, *J* = 8.4 Hz, 0.4H), 4.51 (d, *J* = 8.4 Hz, 0.6H), 3.82 – 3.64 (m, 1H), 3.72 (s, 3H), 3.20 (ddd, *J* = 13.1, 10.7, 3.5 Hz, 1H), 1.86 – 1.57 (m, 3H), 1.48 (s, 9H), 1.17 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.4, 156.0, 152.7, 152.2, 125.8, 125.5, 120.4, 110.0, 109.6, 81.2, 81.0, 51.7, 39.3, 38.2, 36.0, 35.8, 34.1, 28.4, 27.5 ppm.

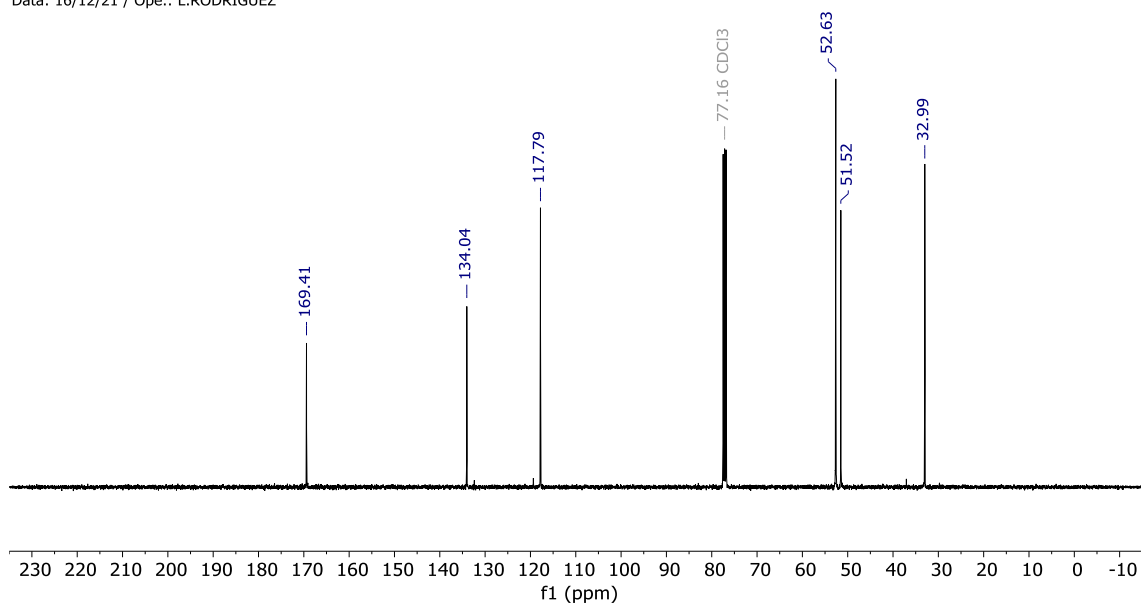
COPIES OF NMR SPECTRA

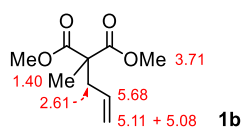


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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG147
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 16/12/21 / Ope.: L.RODRIGUEZ

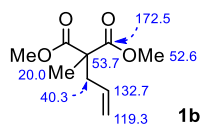
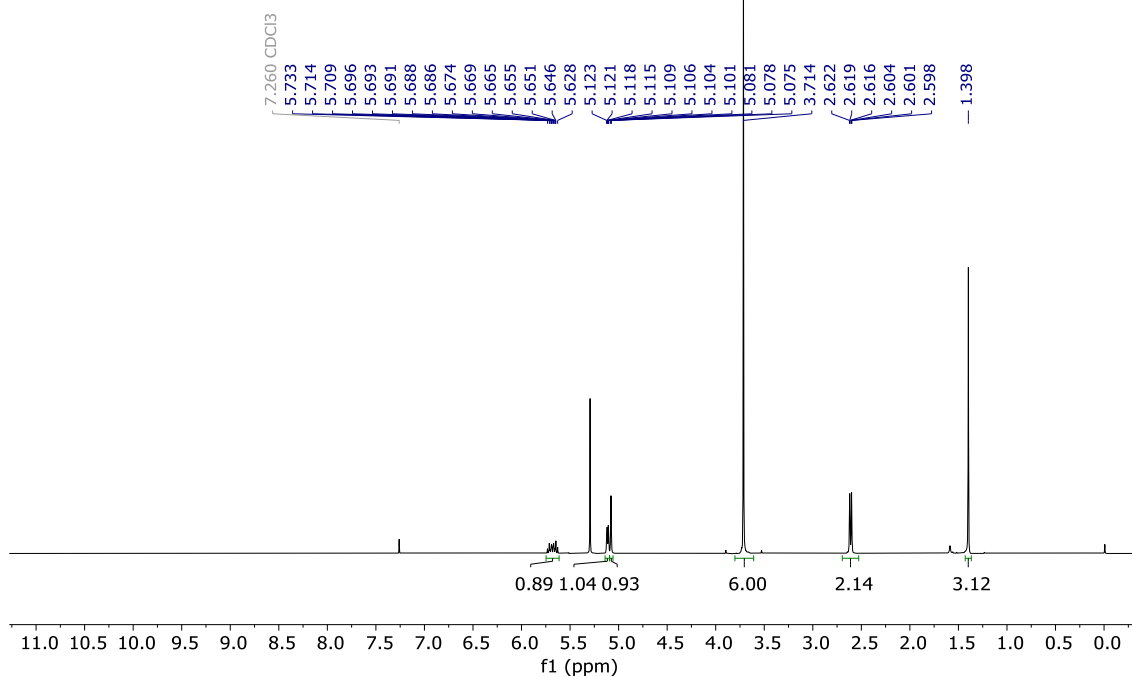


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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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Nom: LAURA RODRIGUEZ GONZALEZ
Data: 16/12/21 / Ope.: L.RODRIGUEZ

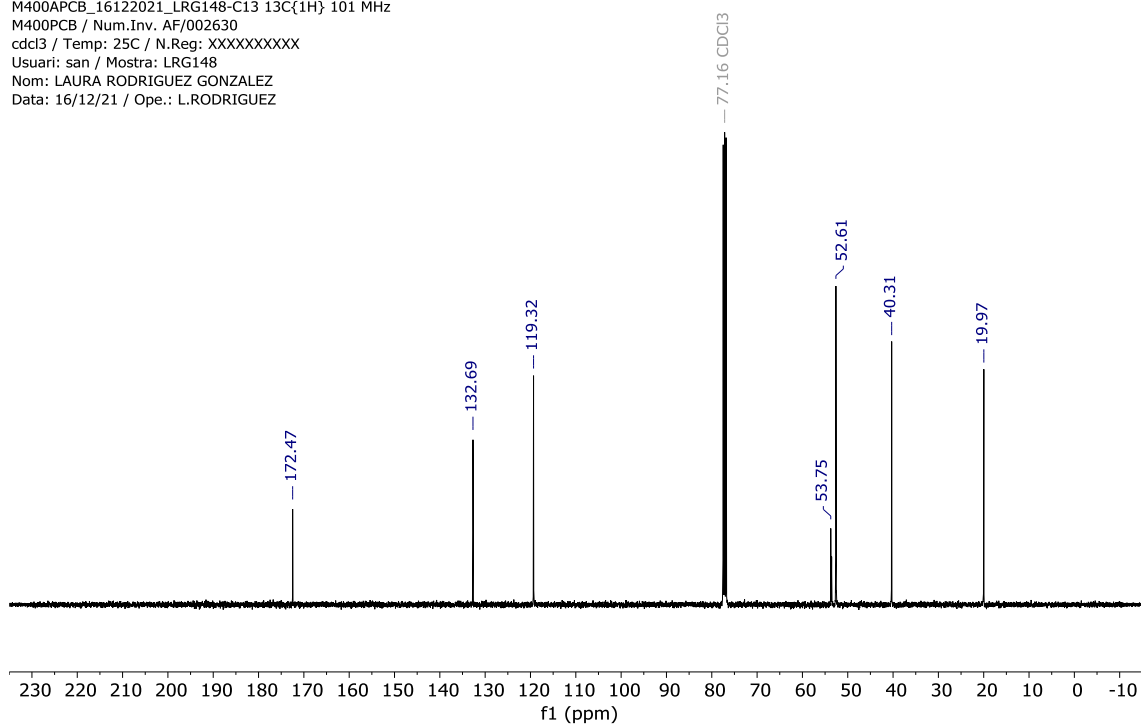


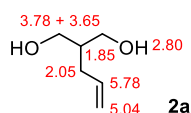


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 Data: 16/12/21 / Ope.: L.RODRIGUEZ

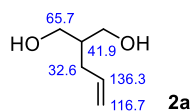
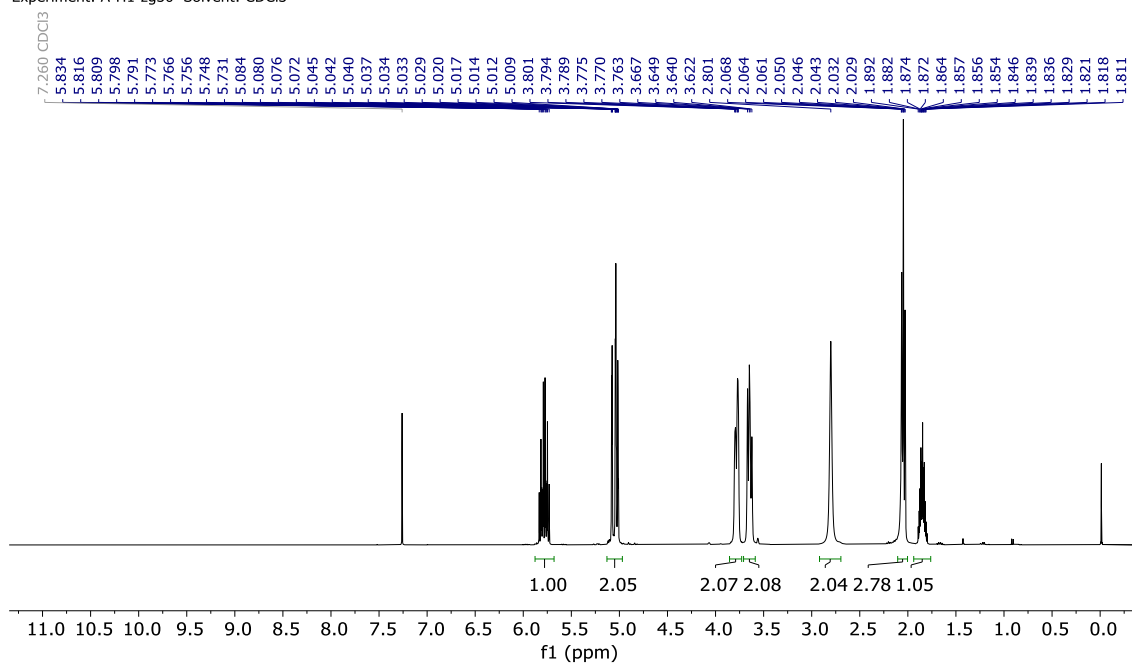


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 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 16/12/21 / Ope.: L.RODRIGUEZ

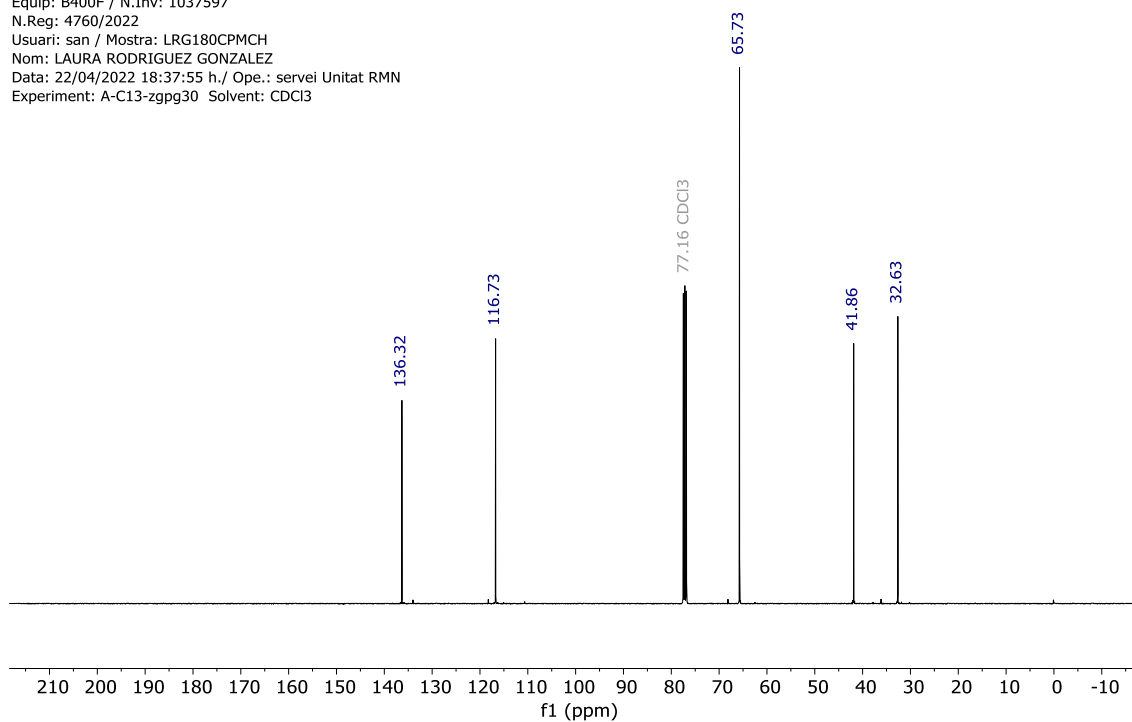


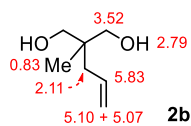


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 N.Reg: 4760/2022
 Usuari: san / Mostra: LRG180CPMCH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 22/04/2022 18:37:55 h./ Ope.: servei Unitat RMN
 Experiment: A-H1-zg30 Solvent: CDCl3

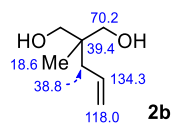
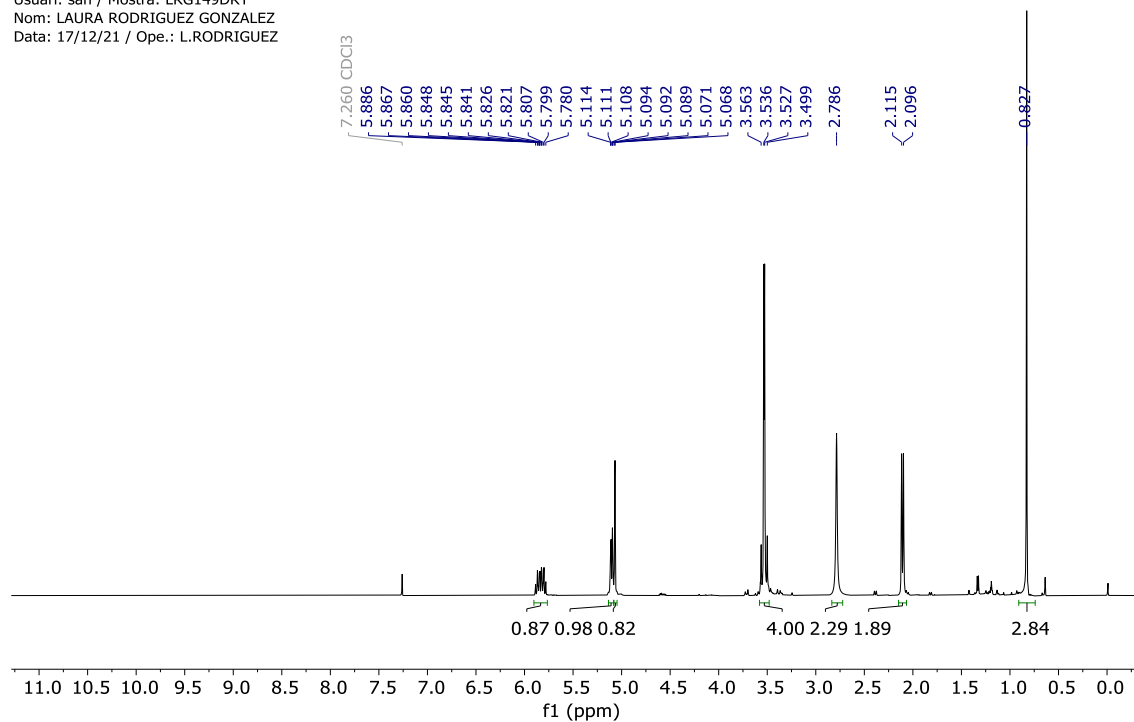


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 N.Reg: 4760/2022
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 Experiment: A-C13-zgpg30 Solvent: CDCl3

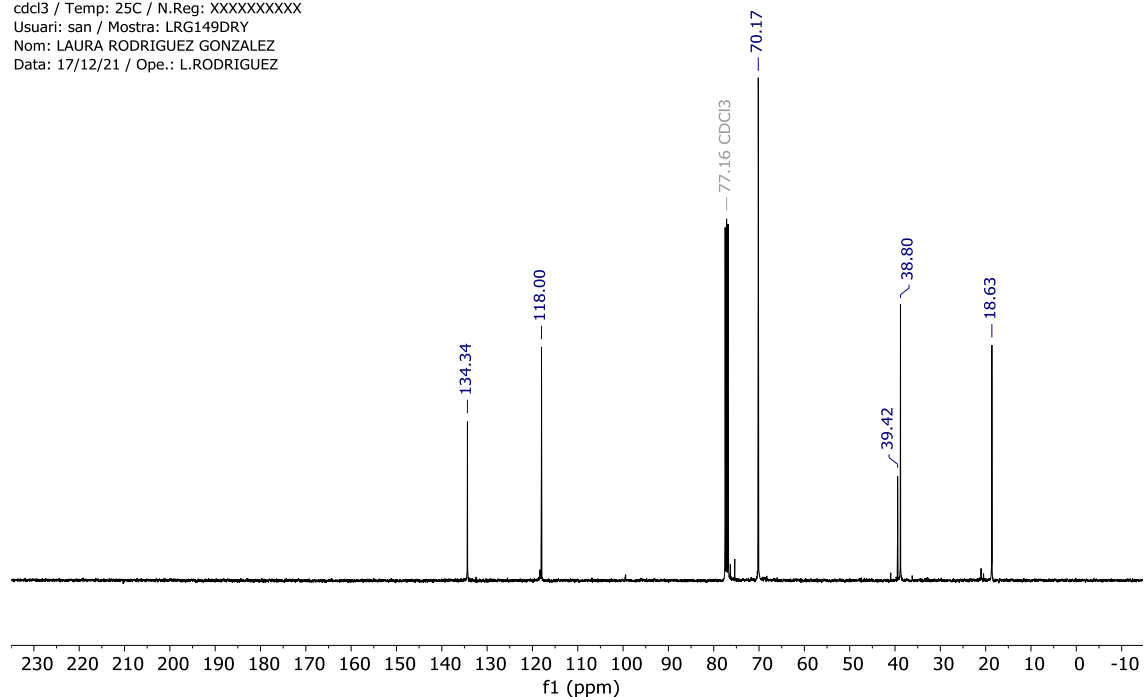


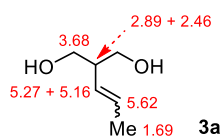


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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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Nom: LAURA RODRIGUEZ GONZALEZ
Data: 17/12/21 / Ope.: L.RODRIGUEZ

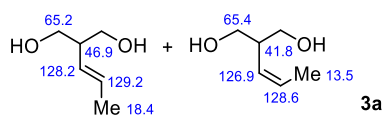
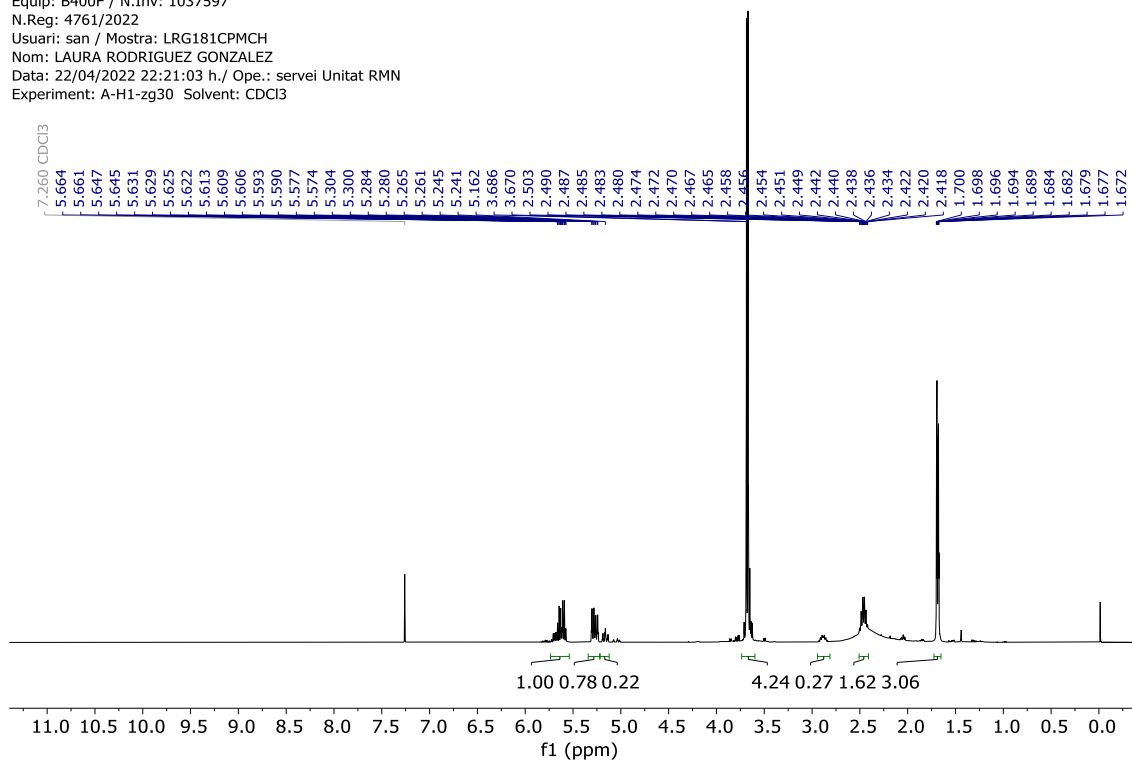


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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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Nom: LAURA RODRIGUEZ GONZALEZ
Data: 17/12/21 / Ope.: L.RODRIGUEZ

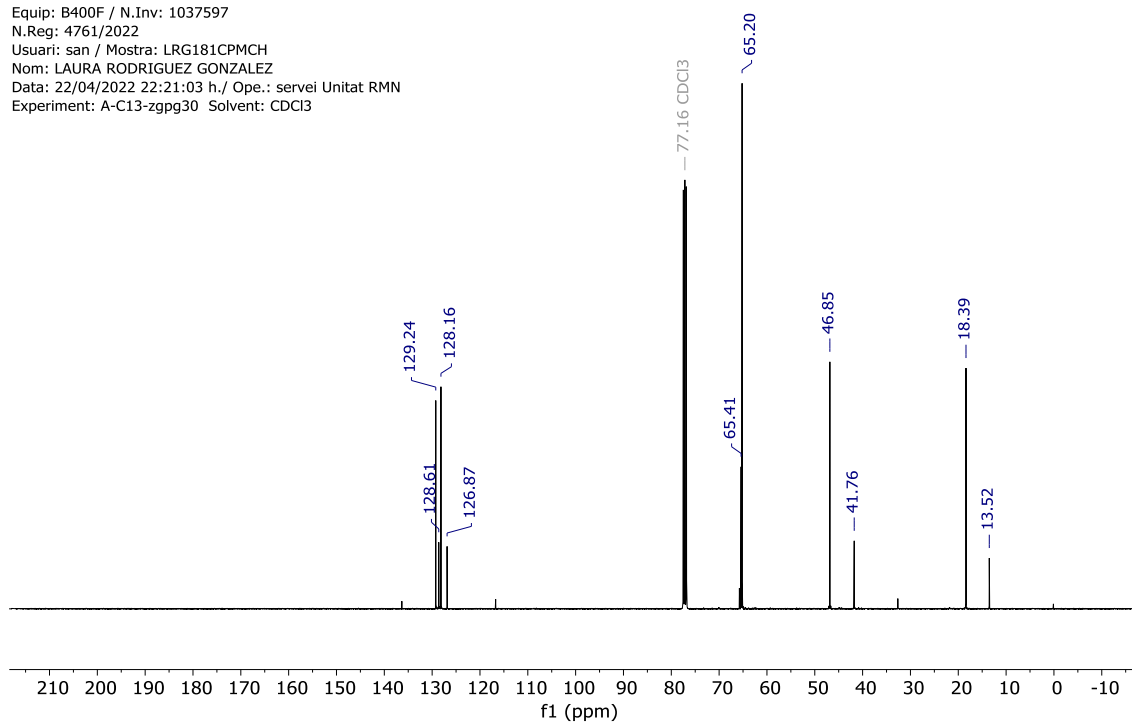


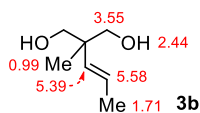


LRG181CPMCH.1.fid
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 N.Reg: 4761/2022
 Usuari: san / Mostra: LRG181CPMCH
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 Experiment: A-H1-zg30 Solvent: CDCl3

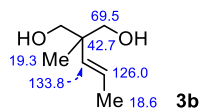
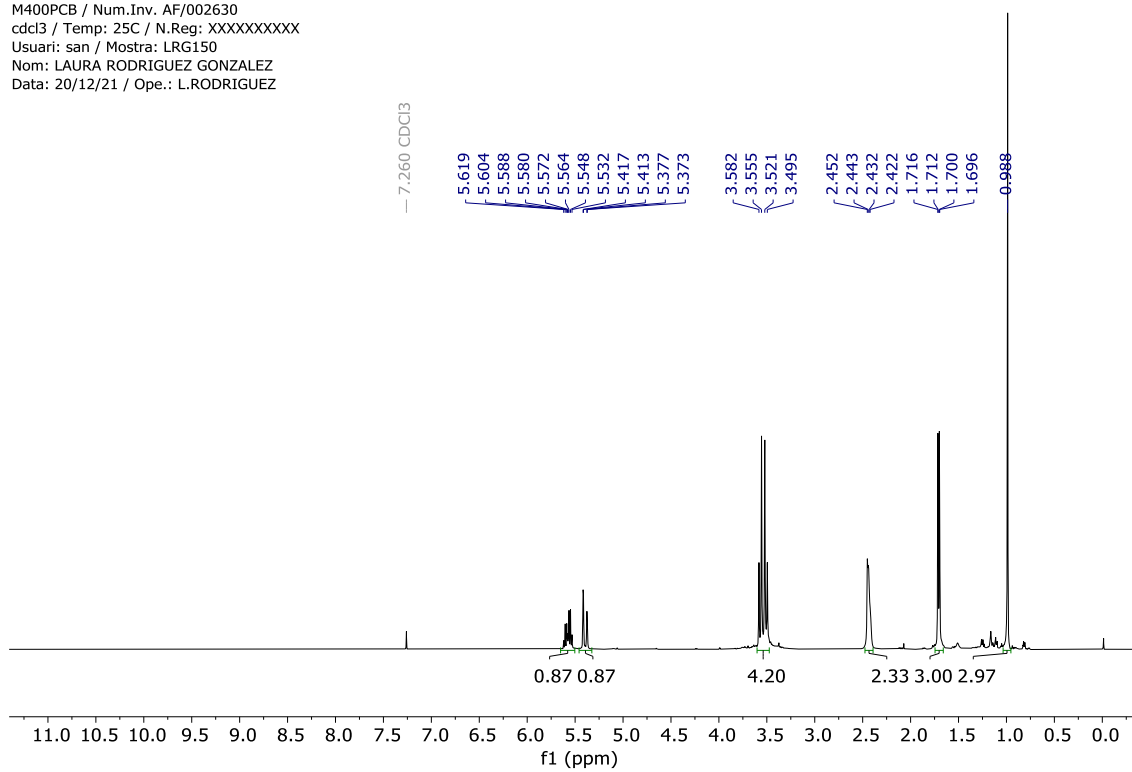


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 N.Reg: 4761/2022
 Usuari: san / Mostra: LRG181CPMCH
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 Experiment: A-C13-zgpg30 Solvent: CDCl3

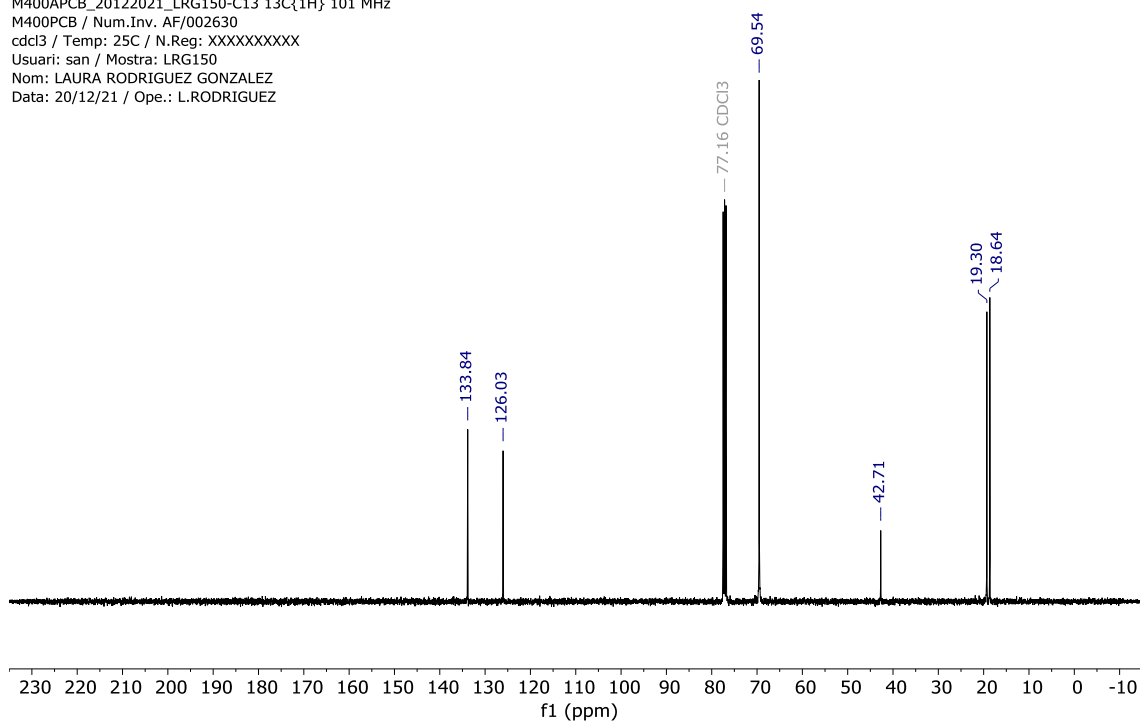


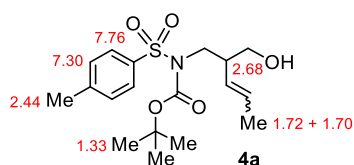


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Data: 20/12/21 / Ope.: L.RODRIGUEZ

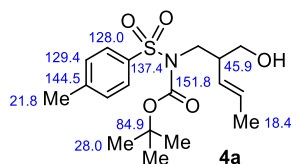
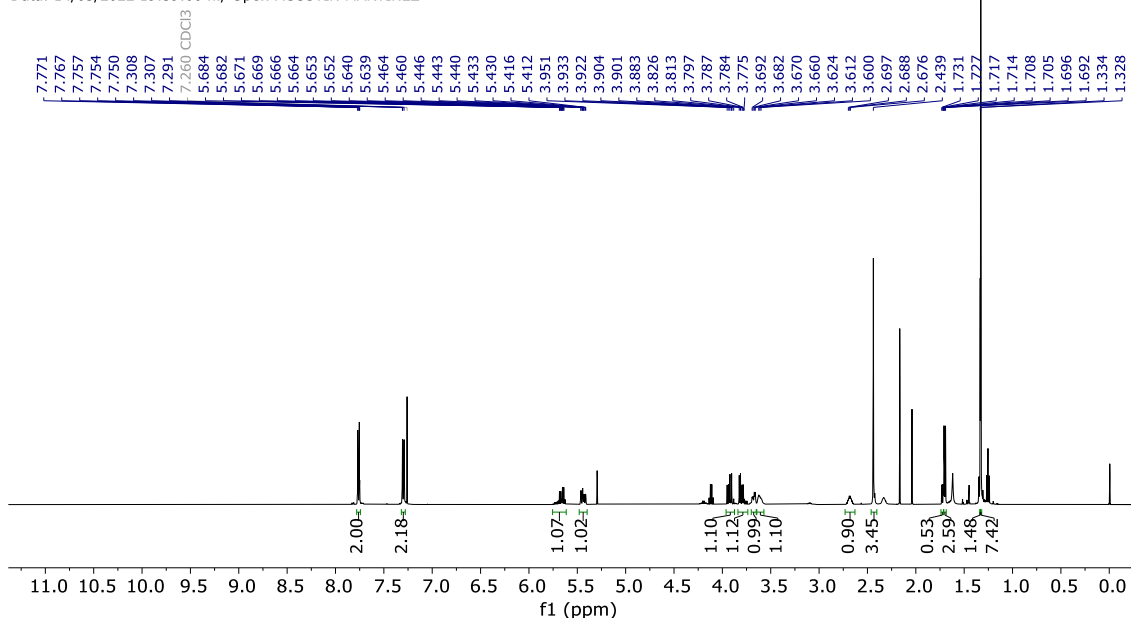


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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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Data: 20/12/21 / Ope.: L.RODRIGUEZ



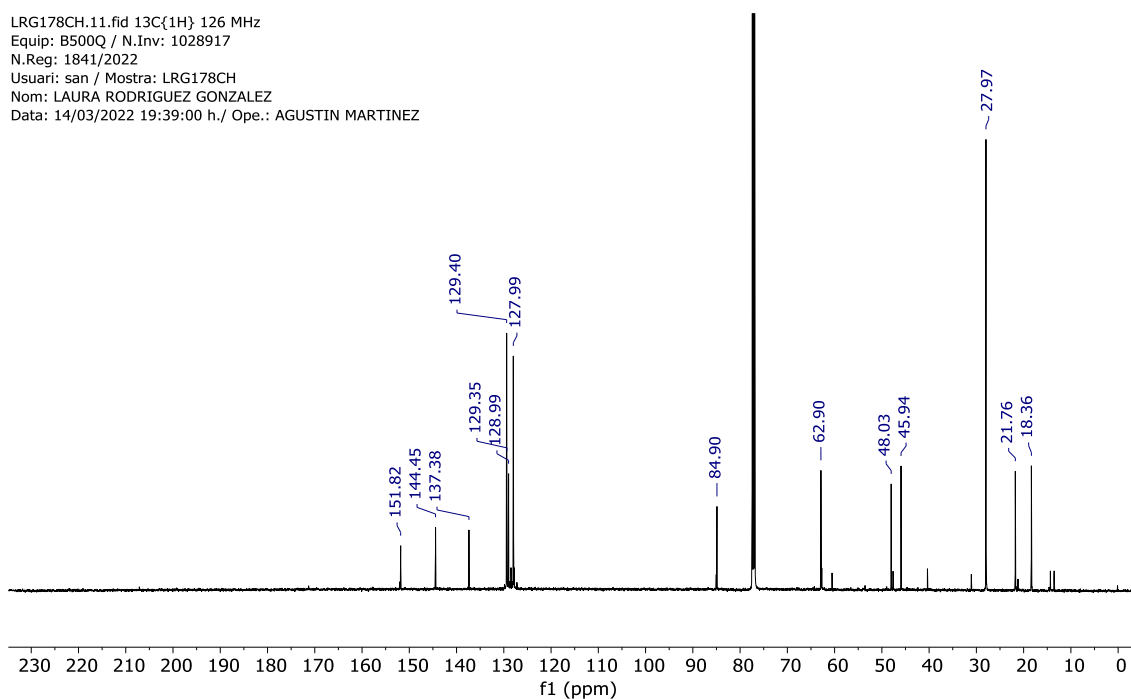


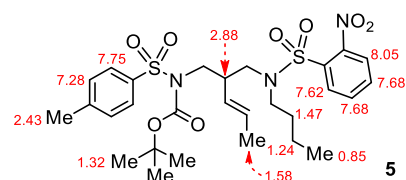
san-1841-2022.10.fid 1H 500 MHz
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 N.Reg: 1841/2022
 Usuari: san / Mostra: LRG178CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/03/2022 19:39:00 h./ Ope.: AGUSTIN MARTINEZ



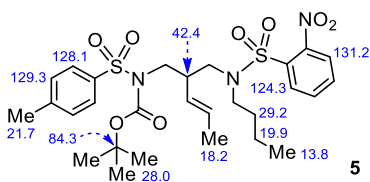
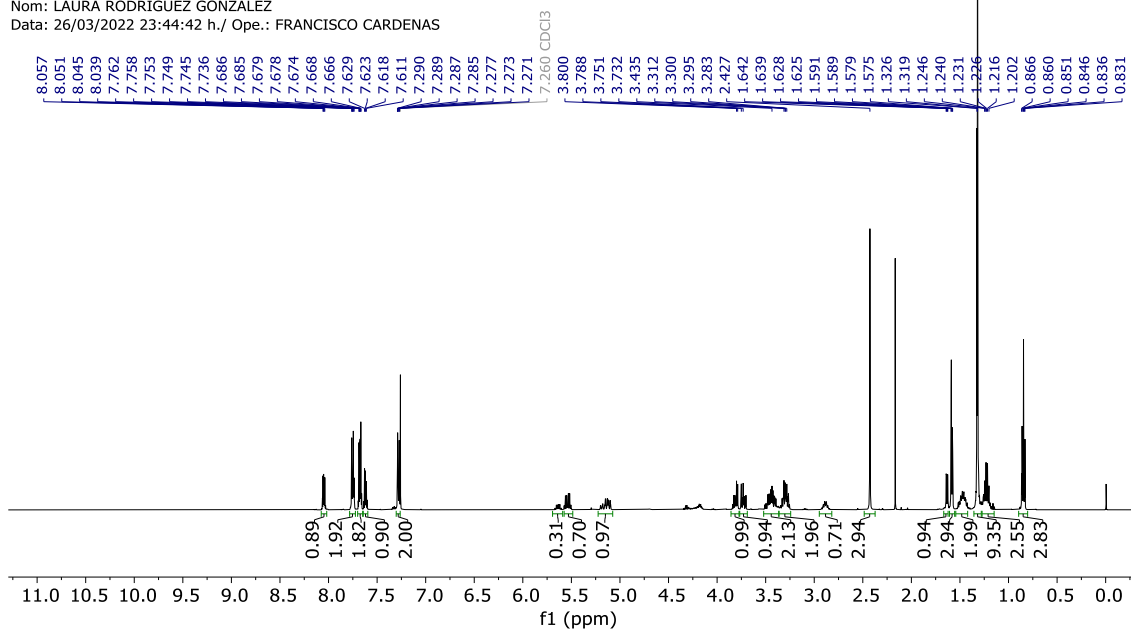
Signals corresponding to the major *trans* isomer.

LRG178CH.11.fid 13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 1841/2022
 Usuari: san / Mostra: LRG178CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/03/2022 19:39:00 h./ Ope.: AGUSTIN MARTINEZ

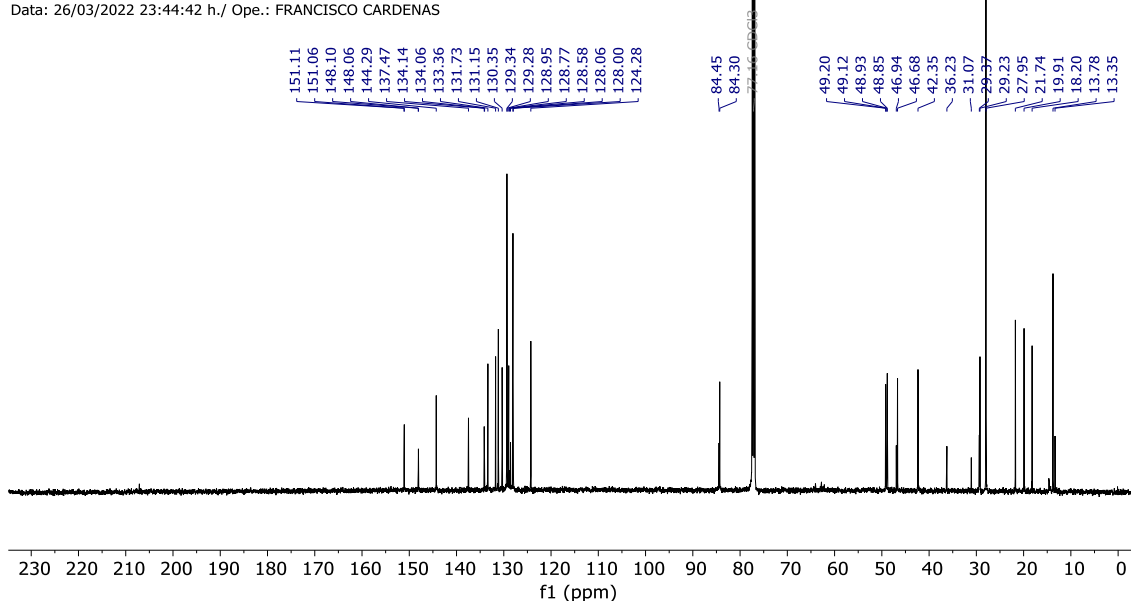


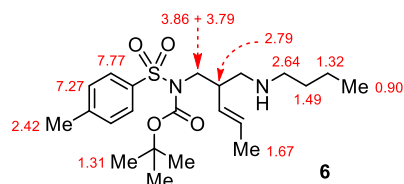


san-2870-2022.10.fid 1H 500 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 2870/2022
 Usuari: san / Mostra: LRG189T42T46
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/03/2022 23:44:42 h./ Ope.: FRANCISCO CARDENAS

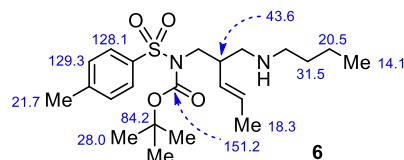
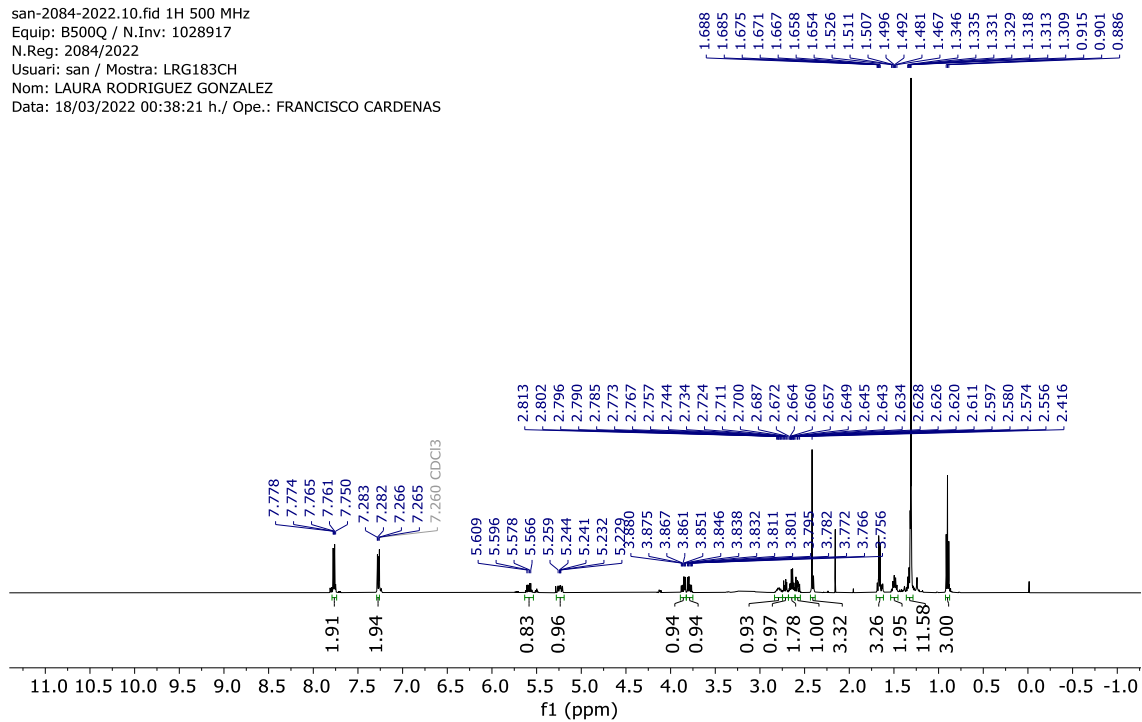


LRG189T42CHT46.11.fid 13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 2870/2022
 Usuari: san / Mostra: LRG189T42T46
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/03/2022 23:44:42 h./ Ope.: FRANCISCO CARDENAS

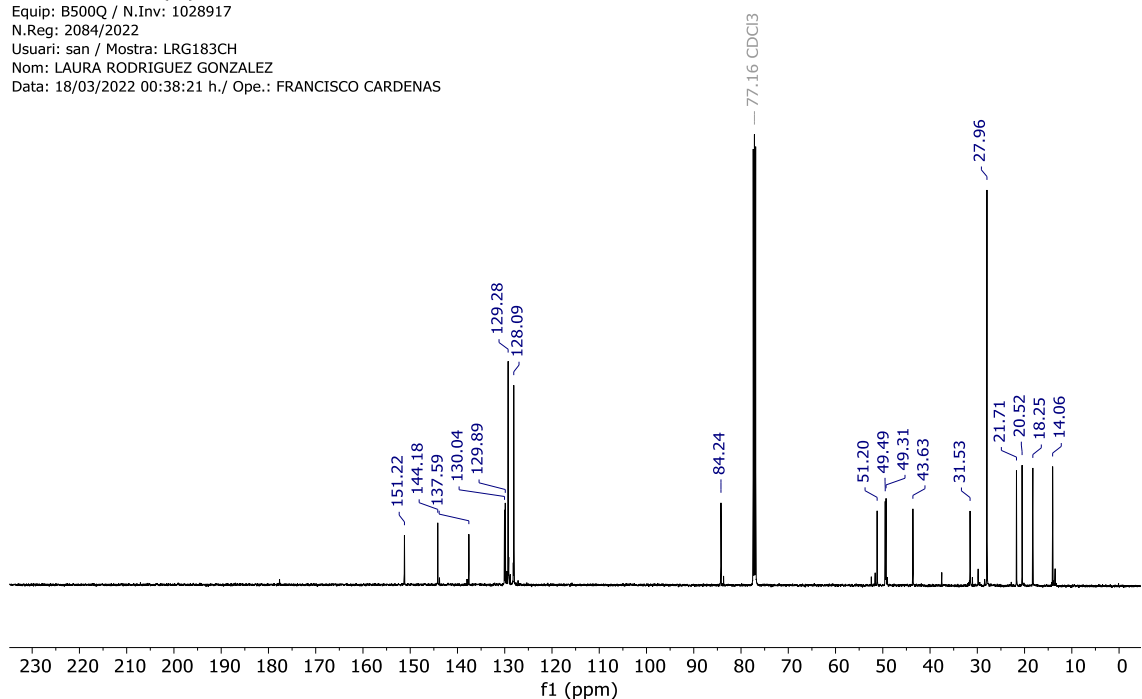




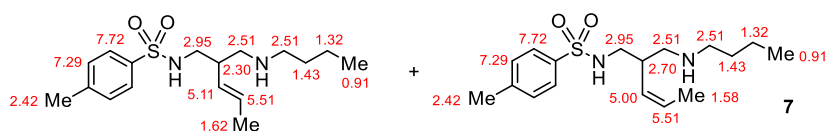
san-2084-2022.10.fid ^1H 500 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 2084/2022
 Usuari: san / Mostra: LRG183CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/03/2022 00:38:21 h./ Ope.: FRANCISCO CARDENAS



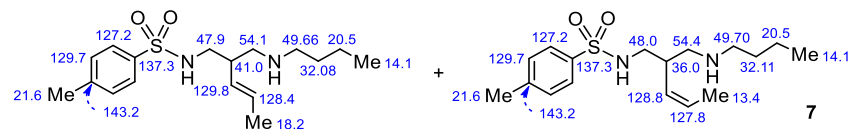
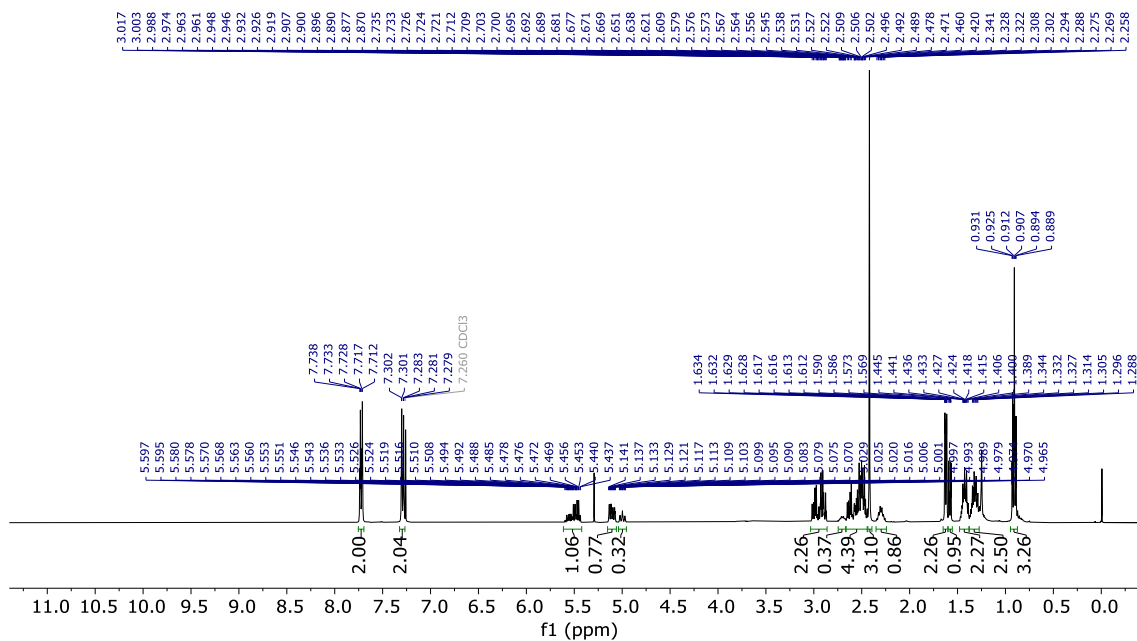
LRG183CH.11.fid ^{13}C { ^1H } 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 2084/2022
 Usuari: san / Mostra: LRG183CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/03/2022 00:38:21 h./ Ope.: FRANCISCO CARDENAS



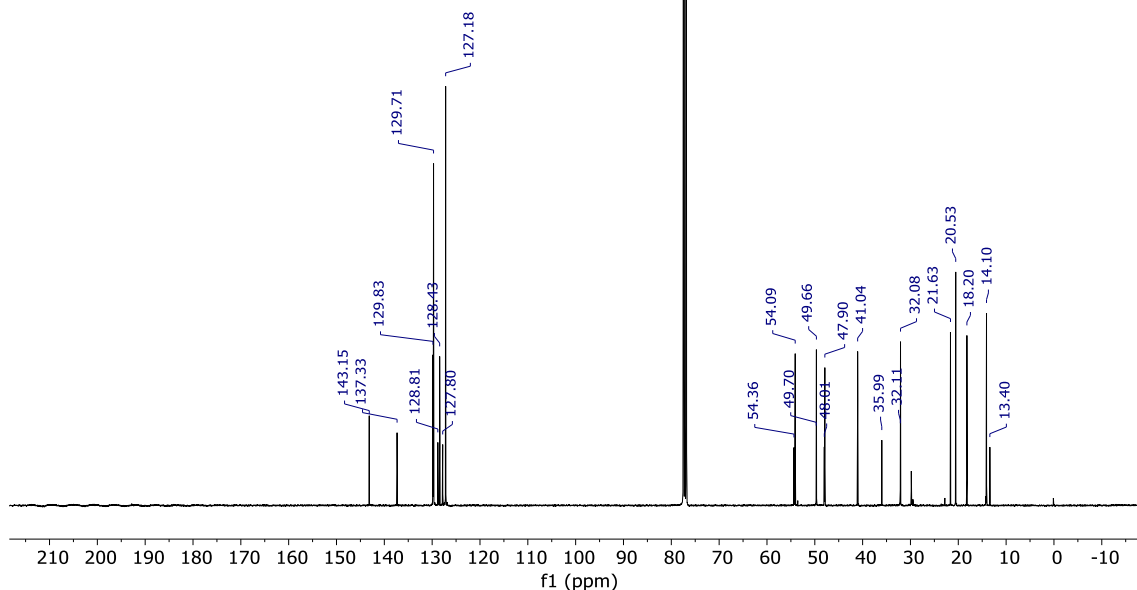
Experimental Section: Chapter 2

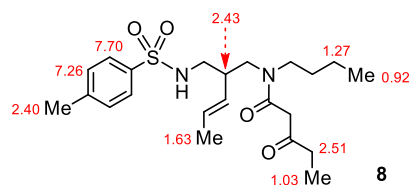


LRG204CH.1.fid
 Equip: B400F / N.Inv: 1037597
 N.Reg: 5105/2022
 Usuari: san / Mostra: LRG204CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/04/2022 17:21:51 h./ Ope.: servei Unitat RMN
 Experiment: A-H1-zg30 Solvent: CDCl3

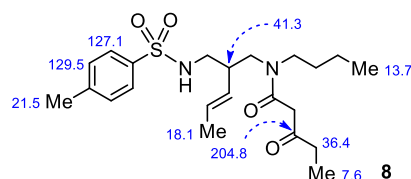
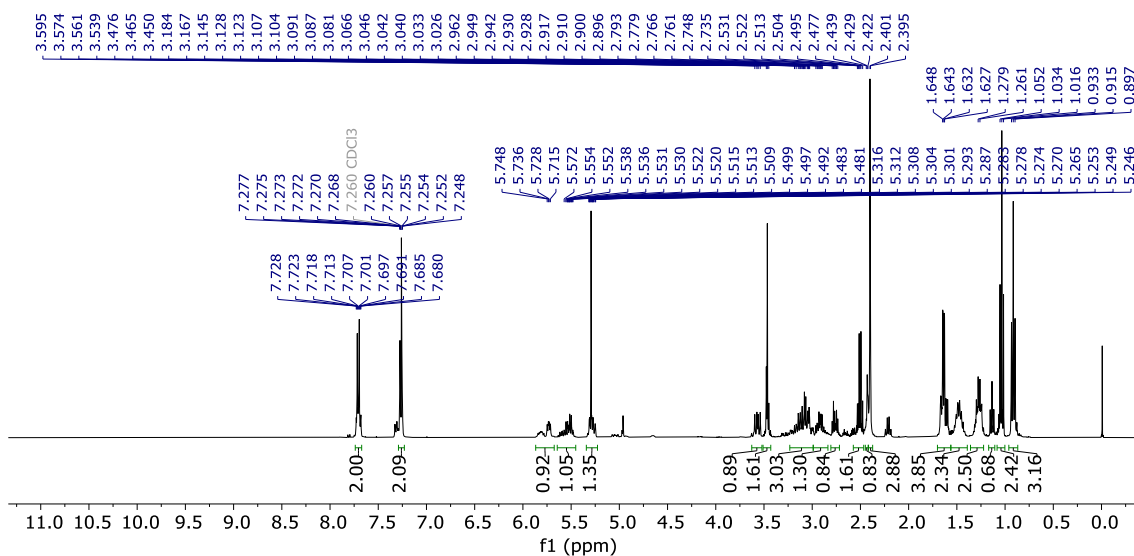


LRG204CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 5105/2022
 Usuari: san / Mostra: LRG204CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/04/2022 17:21:51 h./ Ope.: servei Unitat RMN
 Experiment: A-C13-zgpg30 Solvent: CDCl3

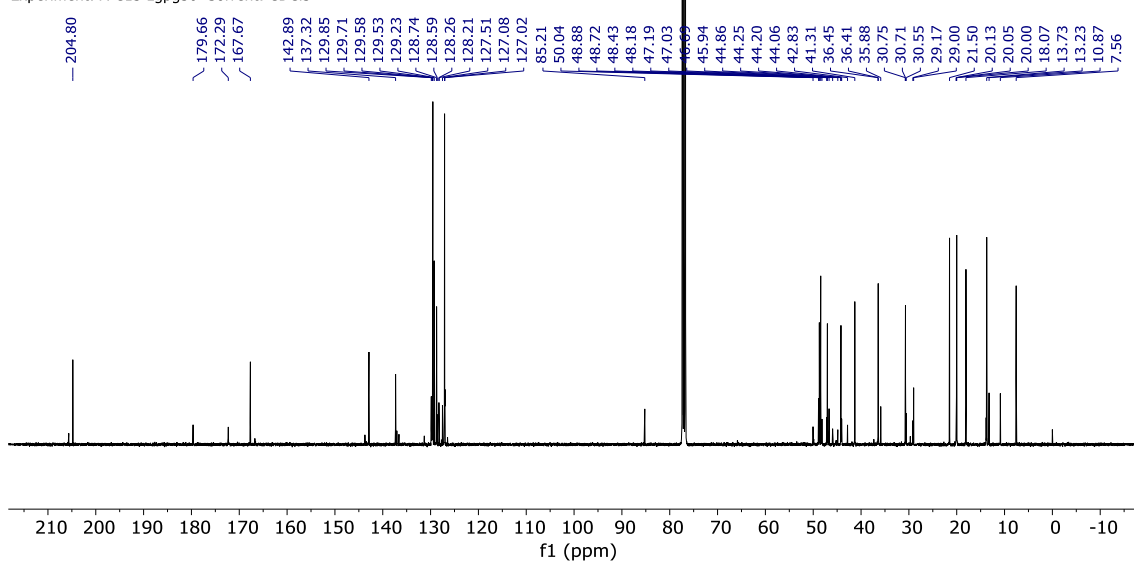


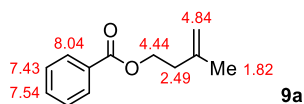


LRG205CH.1.fid ^1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 5395/2022
 Usuari: san / Mostra: LRG205Control
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 28/04/2022 15:42:01 h./ Ope.: servei Unitat RMN
 Experiment: A-H1-zg30 Solvent: CDCl_3

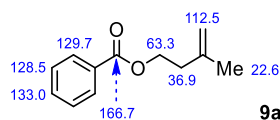
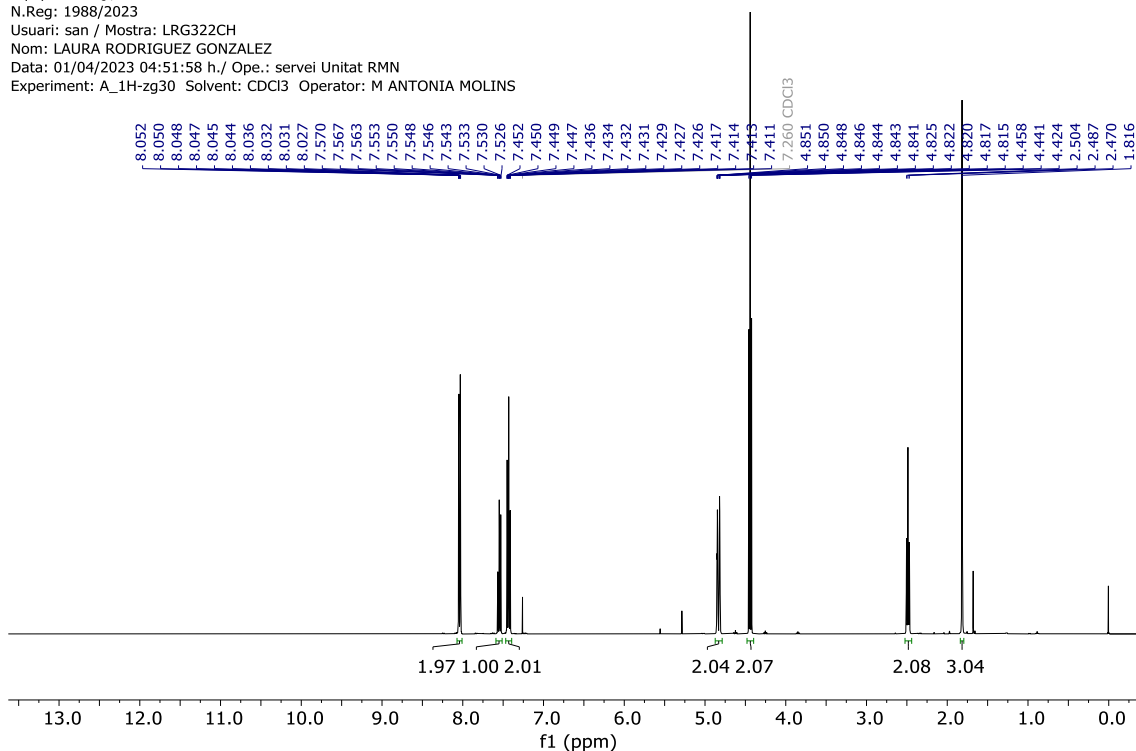


LRG205CH.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 5395/2022
 Usuari: san / Mostra: LRG205Control
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 29/04/2022 05:16:46 h./ Ope.: servei Unitat RMN
 Experiment: A-C13-zpg30 Solvent: CDCl_3

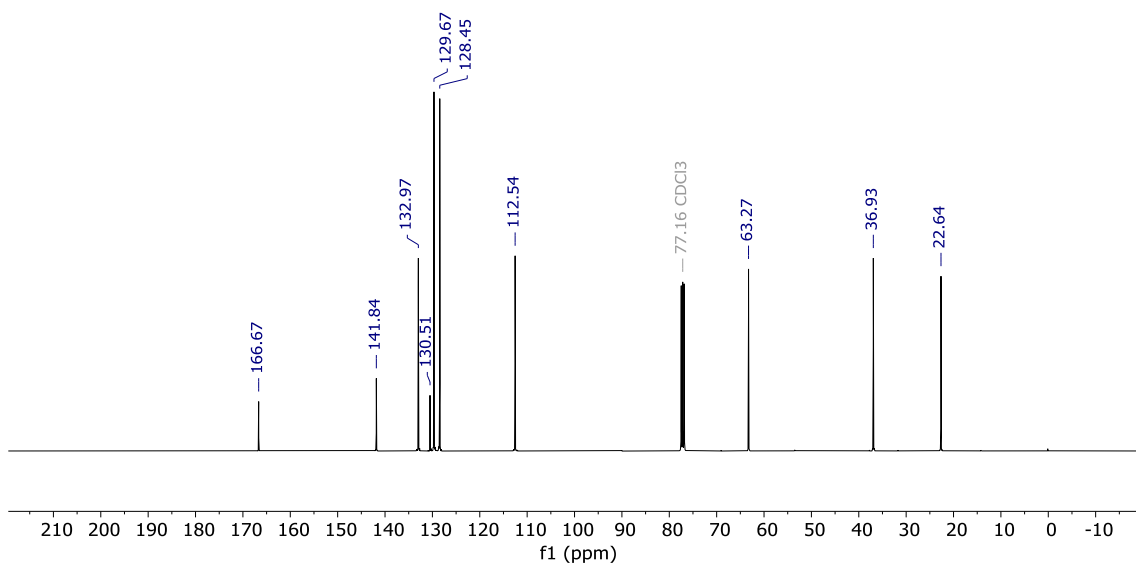


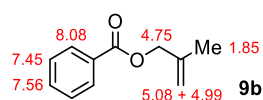


san-1988-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1988/2023
 Usuari: san / Mostra: LRG322CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 01/04/2023 04:51:58 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator: M ANTONIA MOLINS

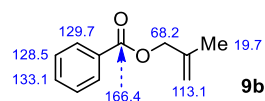
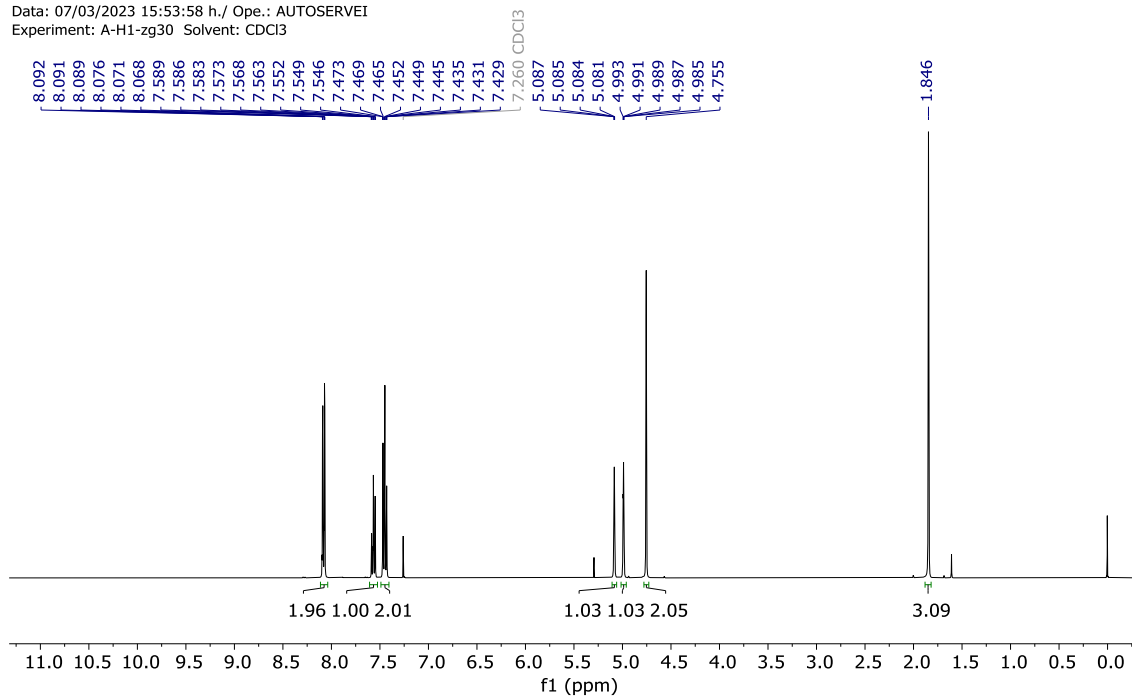


san-1988-2023.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1988/2023
 Usuari: san / Mostra: LRG322CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 01/04/2023 04:51:58 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpgp30 Solvent: CDCl3 Operator: M ANTONIA MOLINS

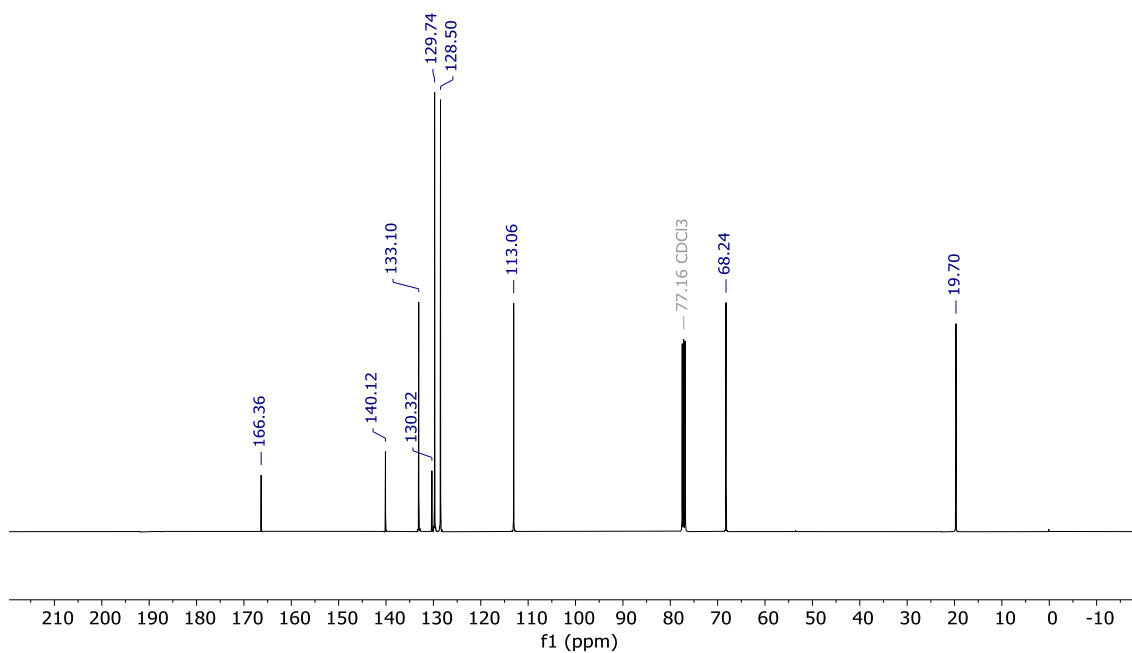


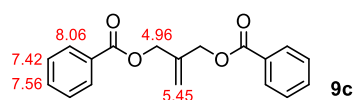


LRG339COL.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030307
 Usuari: san / Mostra: LRG339COL
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/03/2023 15:53:58 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

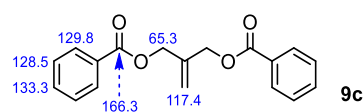
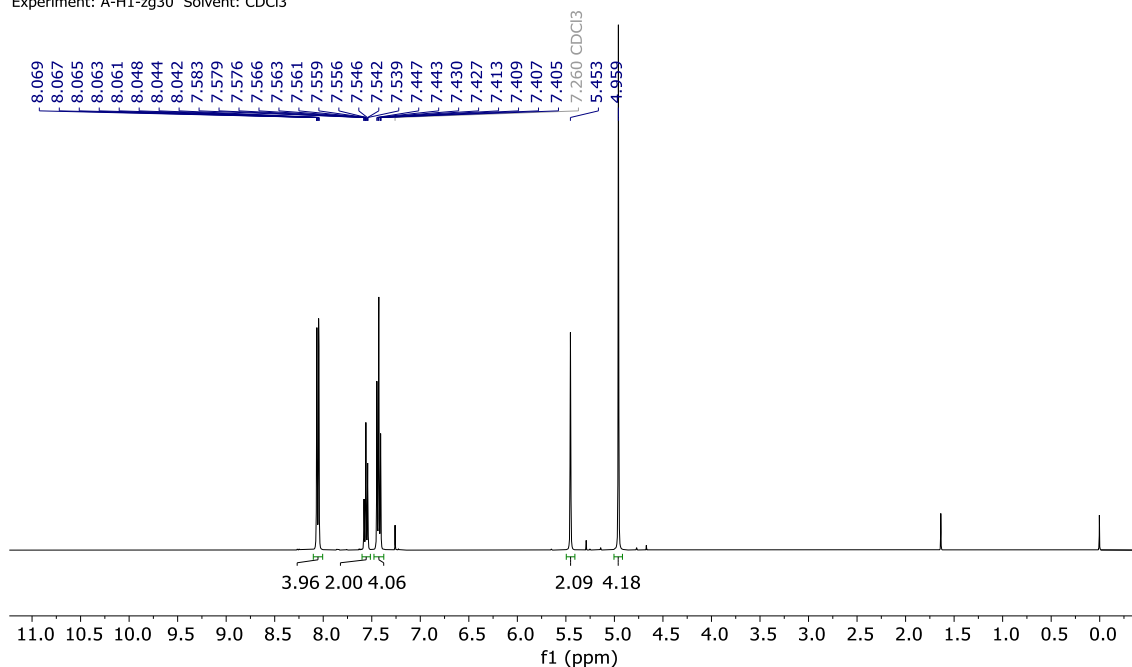


san-1990-2023.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1990/2023
 Usuari: san / Mostra: LRG339CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 01/04/2023 08:02:53 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl₃ Operator: M ANTONIA MOLINS

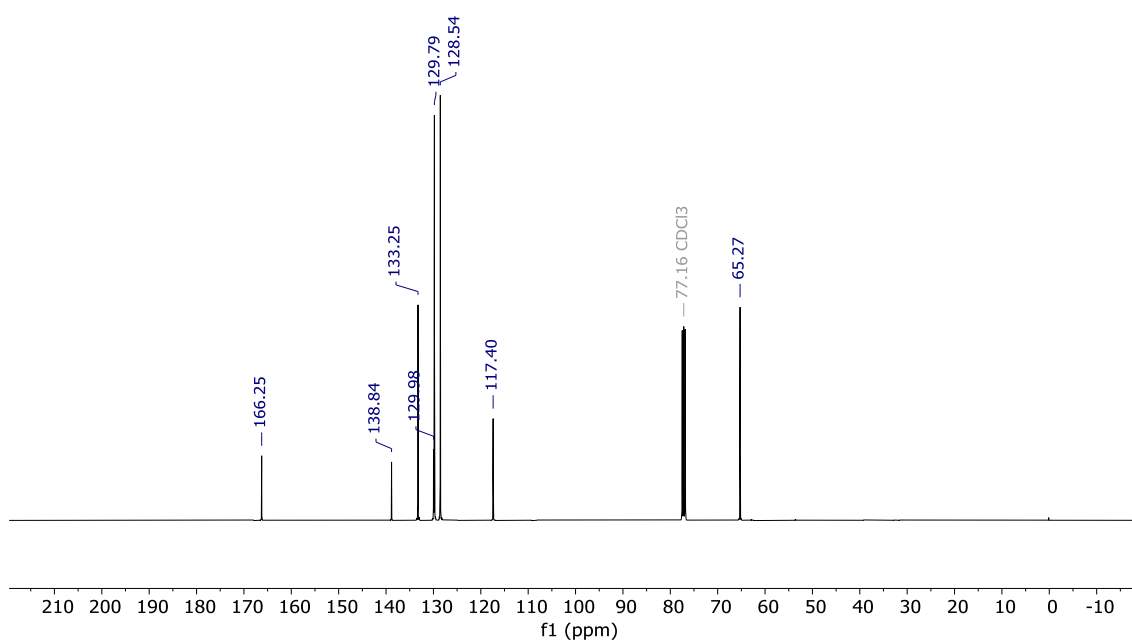


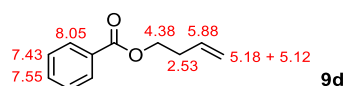


LRG370T13T17.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040346
 Usuari: san / Mostra: LRG370T13T17
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/04/2023 14:47:36 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

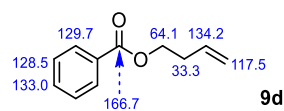
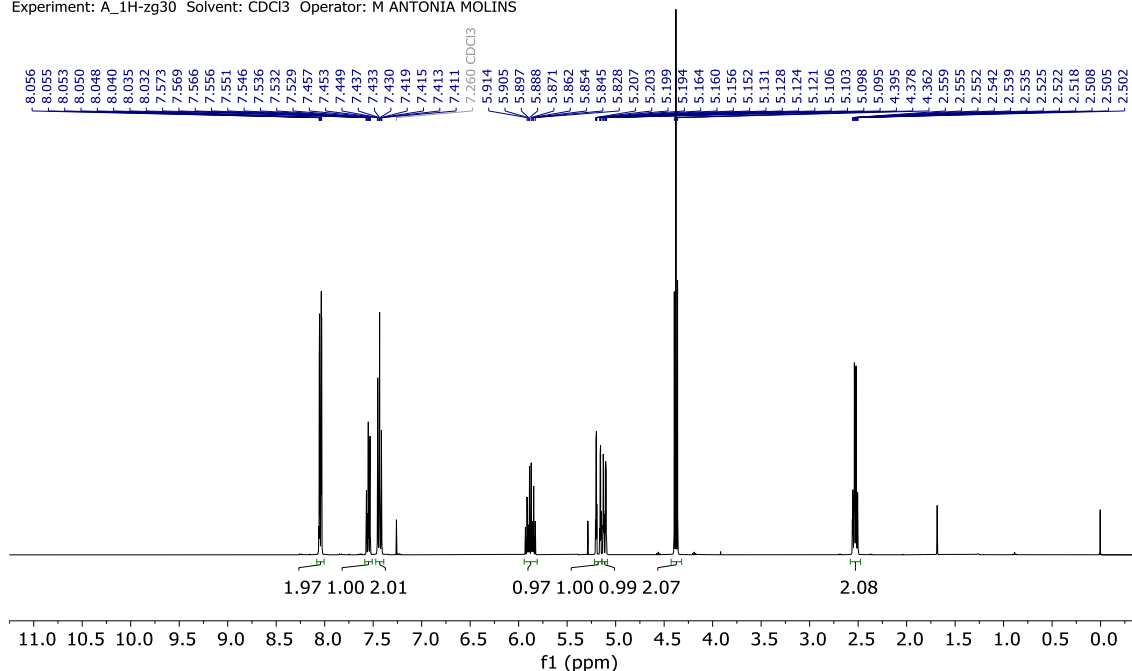


san-2230-2023.4.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2230/2023
 Usuari: san / Mostra: LRG370CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 20/04/2023 02:40:18 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator: M ANTONIA MOLINS

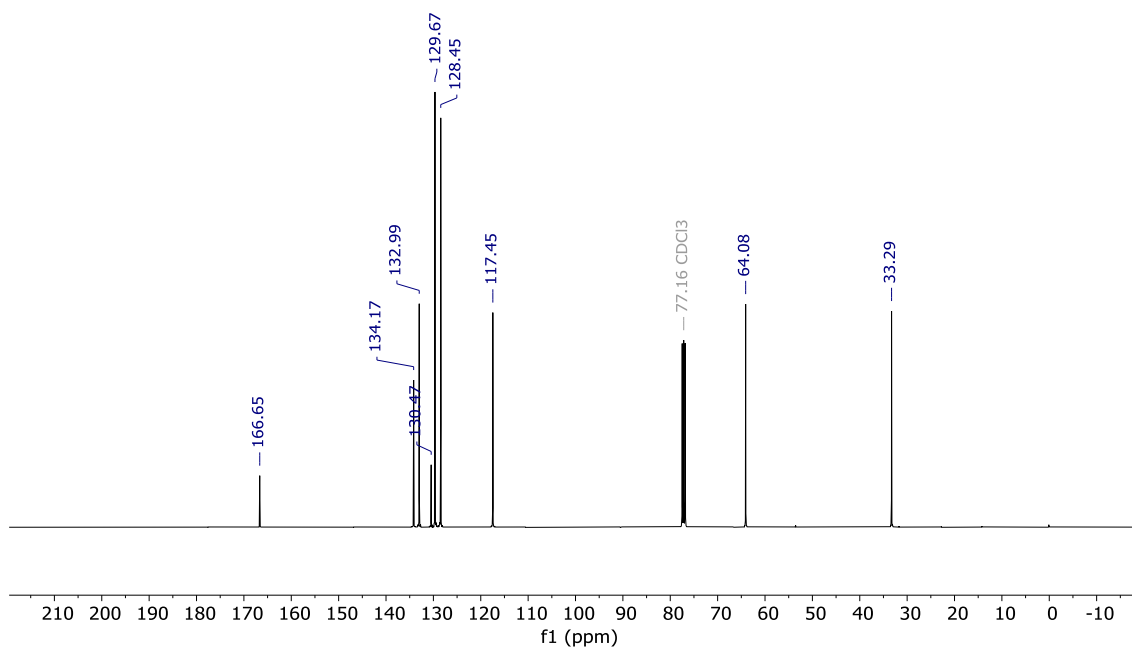


**9d**

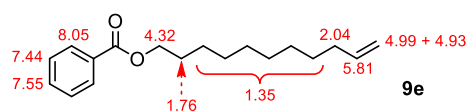
san-1991-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1991/2023
 Usuari: san / Mostra: LRGJPB525CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 01/04/2023 11:14:09 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator: M ANTONIA MOLINS

**9d**

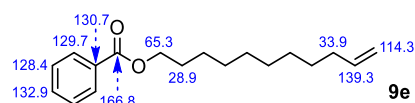
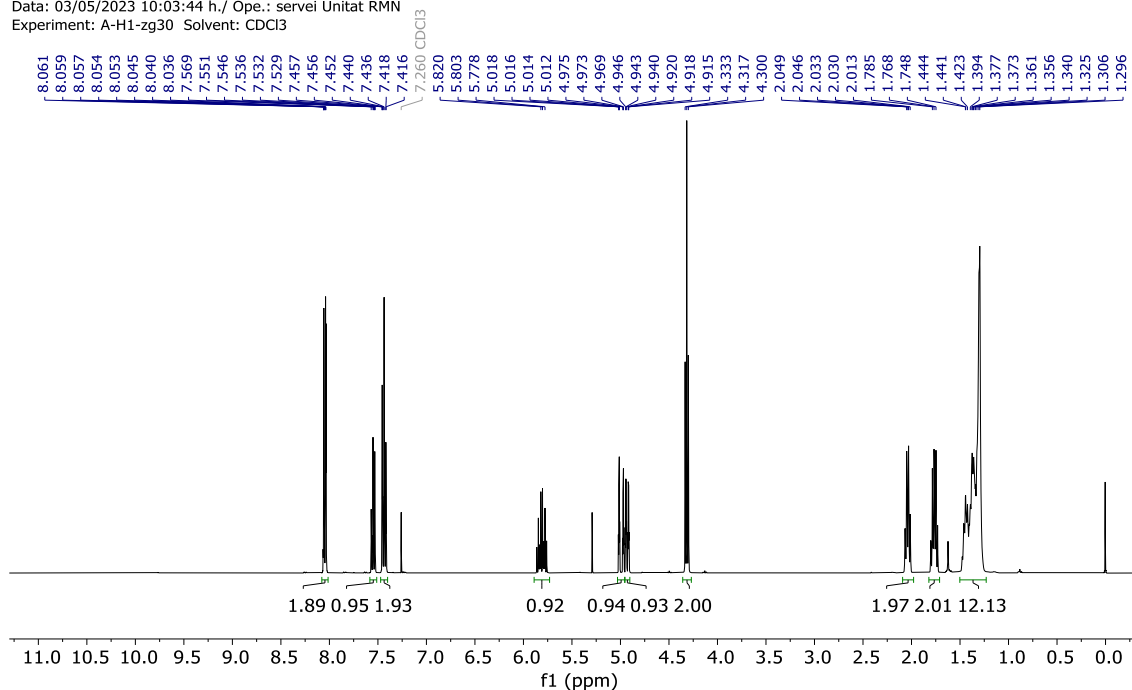
san-1991-2023.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1991/2023
 Usuari: san / Mostra: LRGJPB525CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 01/04/2023 11:14:09 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator: M ANTONIA MOLINS



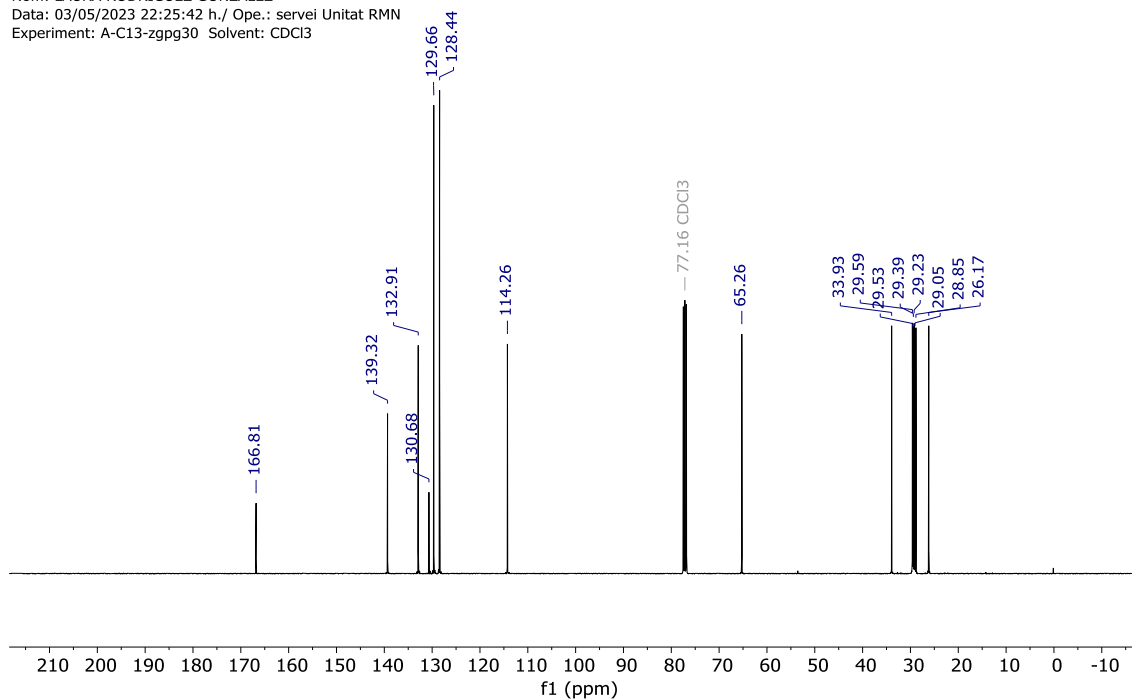
Experimental Section: Chapter 2

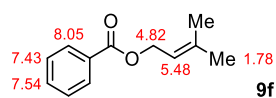


2585-2023_B400FA_04052023_LRG325CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 2585/2023
 Usuari: san / Mostra: LRG325CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/05/2023 10:03:44 h./ Ope.: servei Unitat RMN
 Experiment: A-H1-zg30 Solvent: CDCl₃

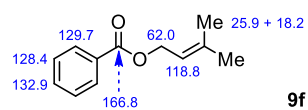
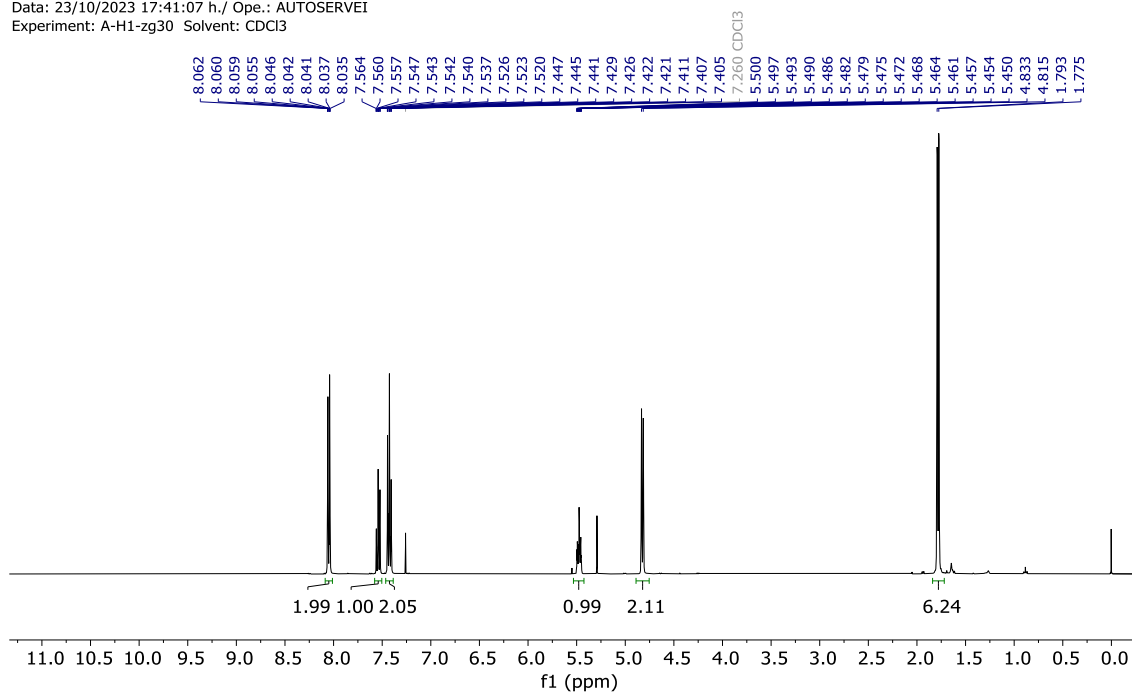


2585-2023_B400FA_04052023_LRG325CH.4.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 2585/2023
 Usuari: san / Mostra: LRG325CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/05/2023 22:25:42 h./ Ope.: servei Unitat RMN
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

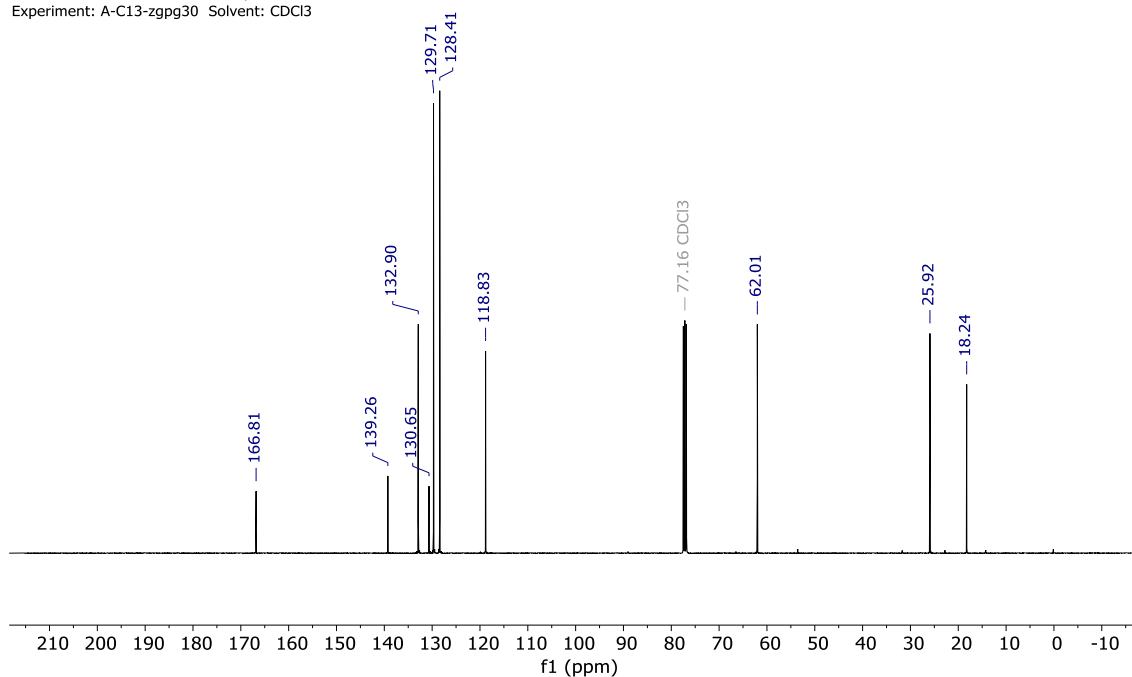




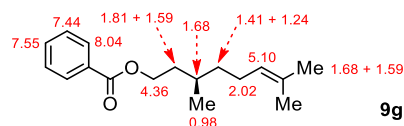
23100207_B400FA_23102023_LRG483COLT4T18.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100207
 Usuari: san / Mostra: LRG483COLT4T18
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 23/10/2023 17:41:07 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



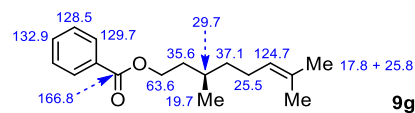
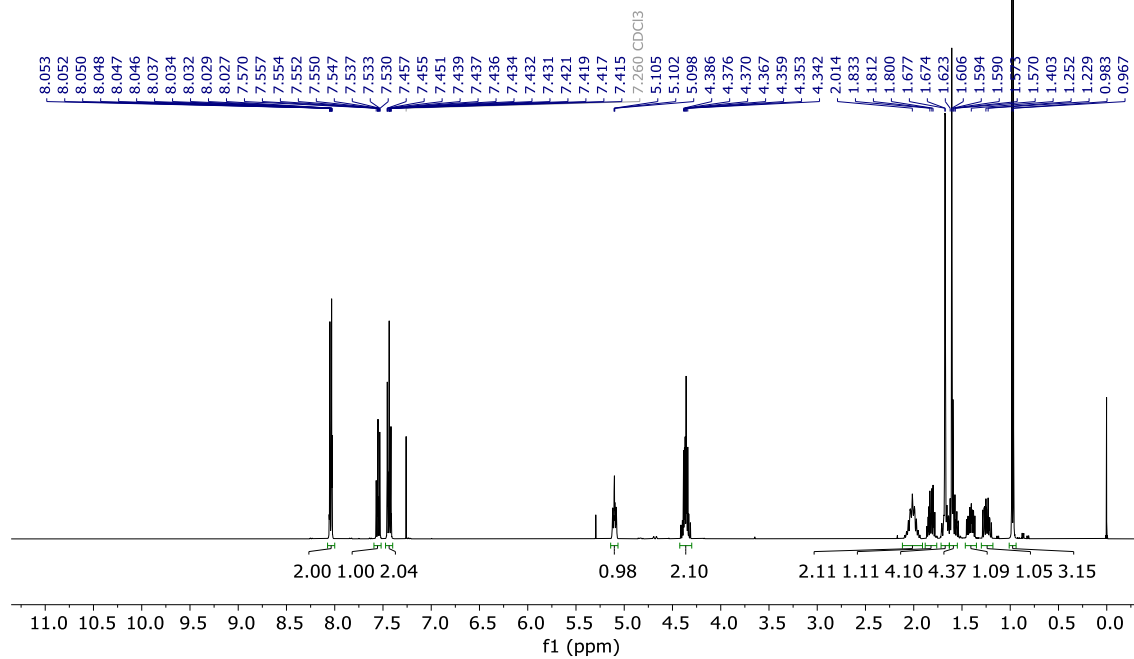
23100211_B400FA_23102023_LRG483CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100211
 Usuari: san / Mostra: LRG483CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 23/10/2023 20:27:31 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



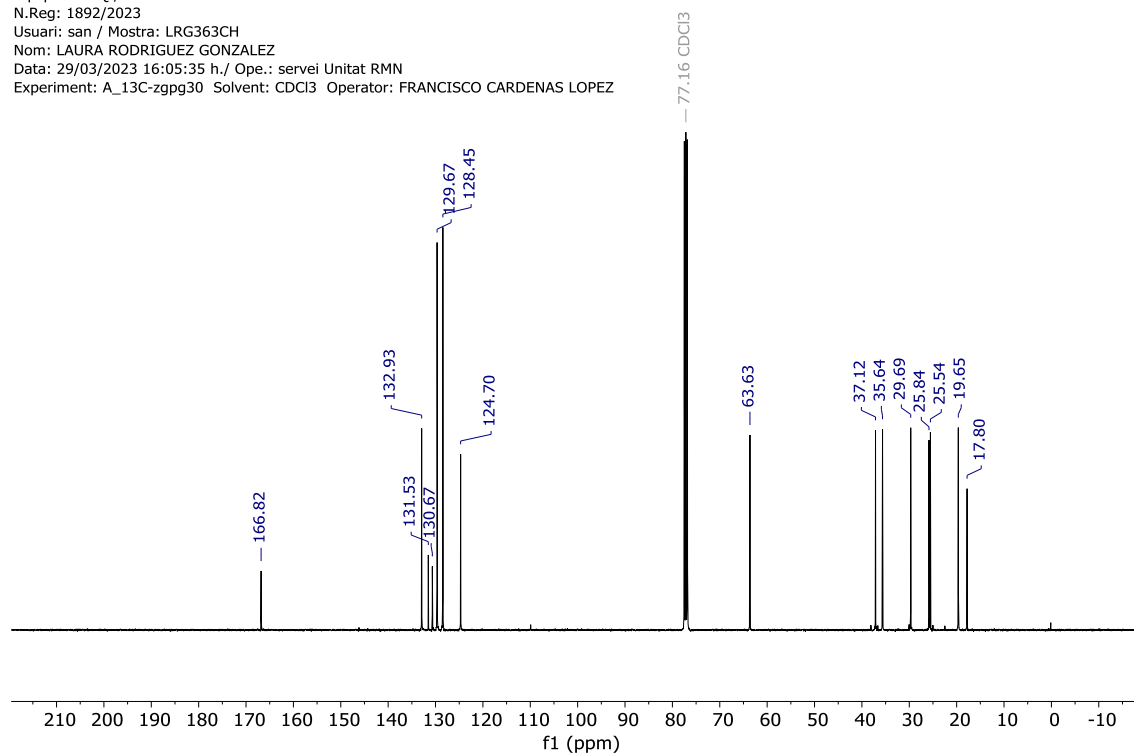
Experimental Section: Chapter 2

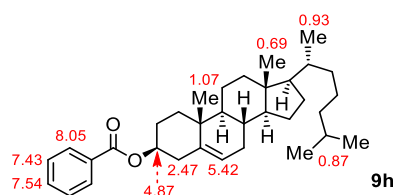


san-1892-2023.1.fid ^1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1892/2023
 Usuari: san / Mostra: LRG363CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 29/03/2023 15:42:23 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl_3 Operator: FRANCISCO CARDENAS LOPEZ

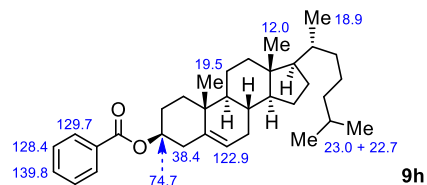
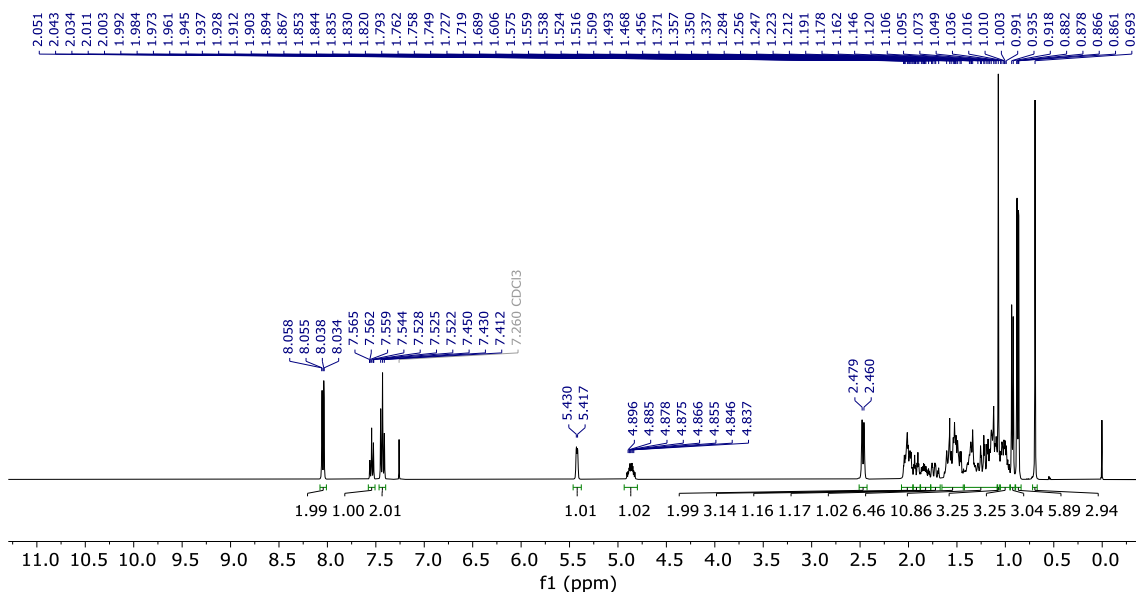


san-1892-2023.3.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1892/2023
 Usuari: san / Mostra: LRG363CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 29/03/2023 16:05:35 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl_3 Operator: FRANCISCO CARDENAS LOPEZ

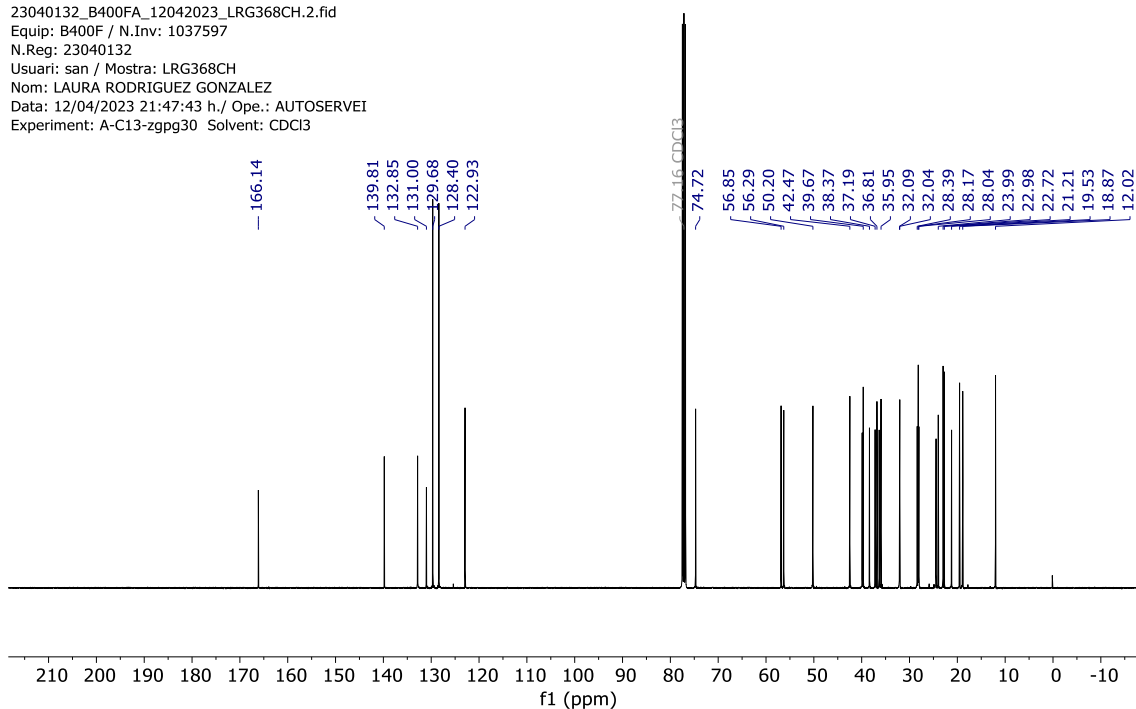


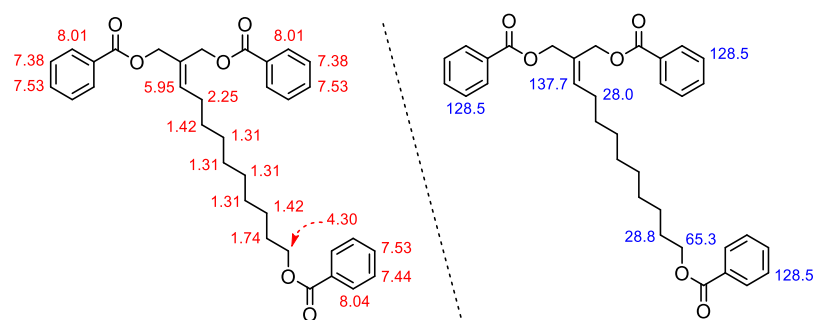


23040132_B400FA_12042023_LRG368CH.1.fid
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040132
 Usuari: san / Mostra: LRG368CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 12/04/2023 15:07:47 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

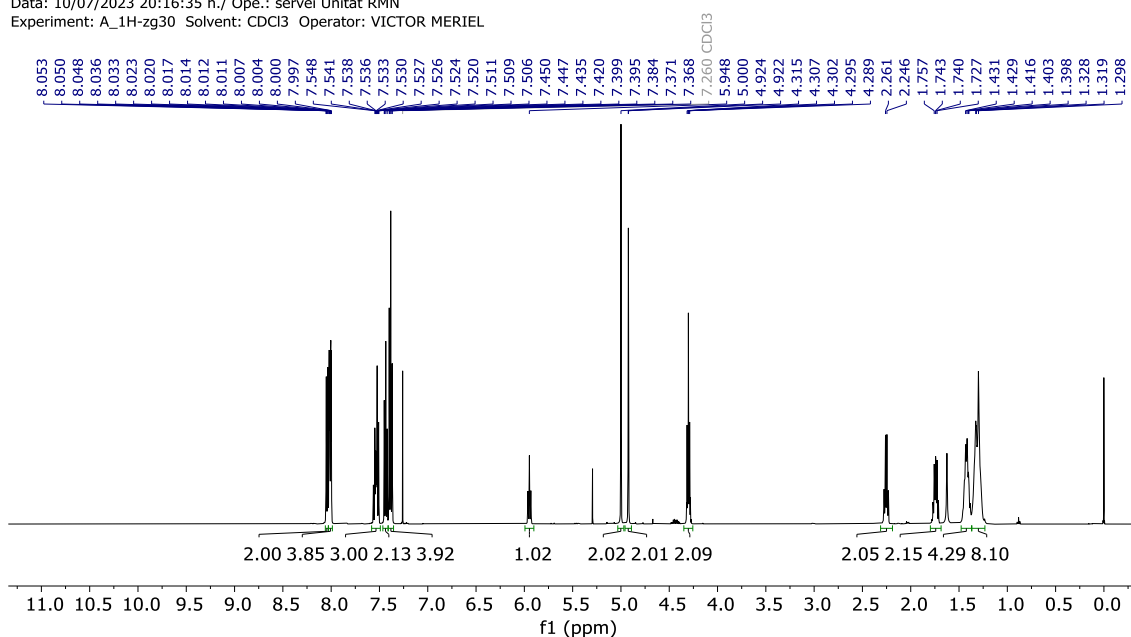


23040132_B400FA_12042023_LRG368CH.2.fid
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040132
 Usuari: san / Mostra: LRG368CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 12/04/2023 21:47:43 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

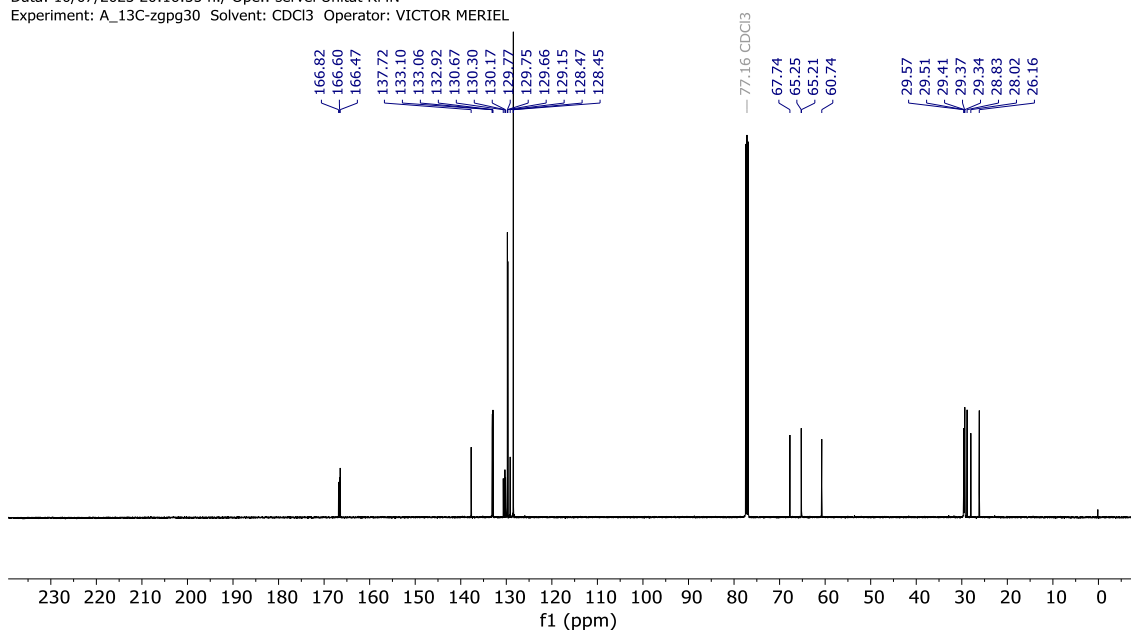


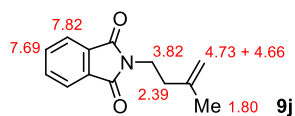


san-4004-2023.10.fid 1H 500 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 4004/2023
 Usuari: san / Mostra: LRG428CH500
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/07/2023 20:16:35 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: VICTOR MERIEL

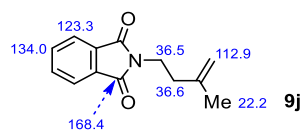
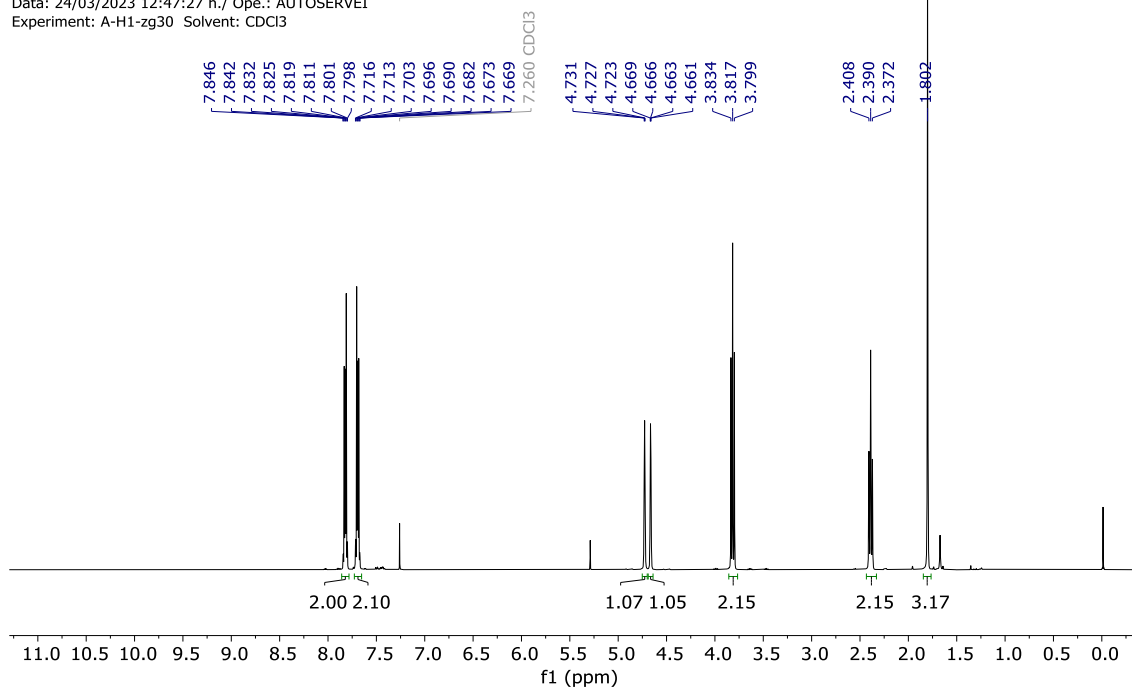


4004-2023_B500QA_10072023_LRG428CH500.11.fid 13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 4004/2023
 Usuari: san / Mostra: LRG428CH500
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/07/2023 20:16:35 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpgp30 Solvent: CDCl₃ Operator: VICTOR MERIEL

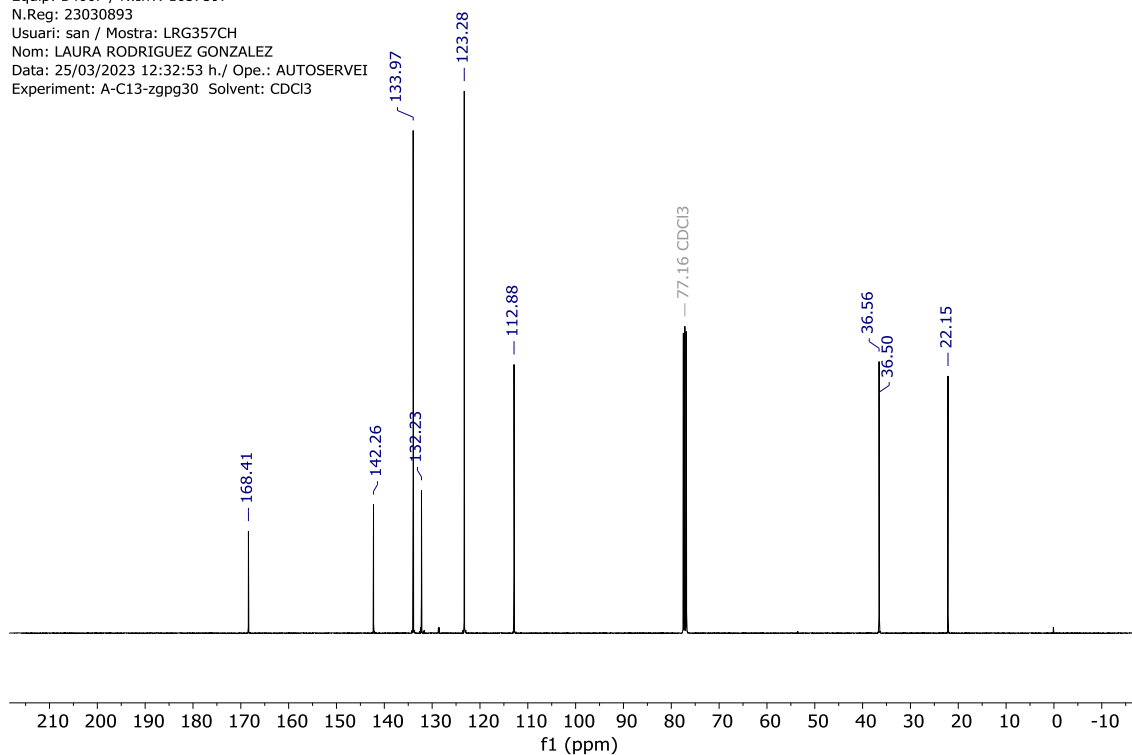




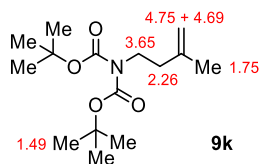
LRG357CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030893
 Usuari: san / Mostra: LRG357CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 24/03/2023 12:47:27 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



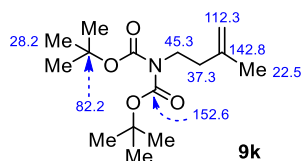
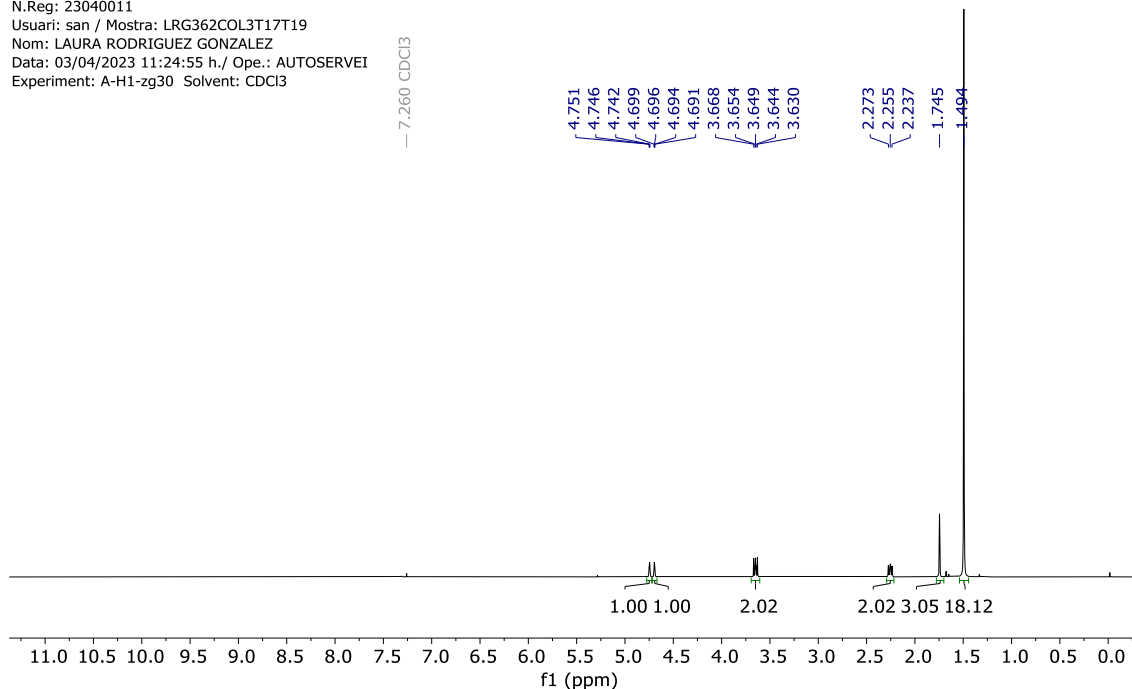
LRG357CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030893
 Usuari: san / Mostra: LRG357CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 25/03/2023 12:32:53 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



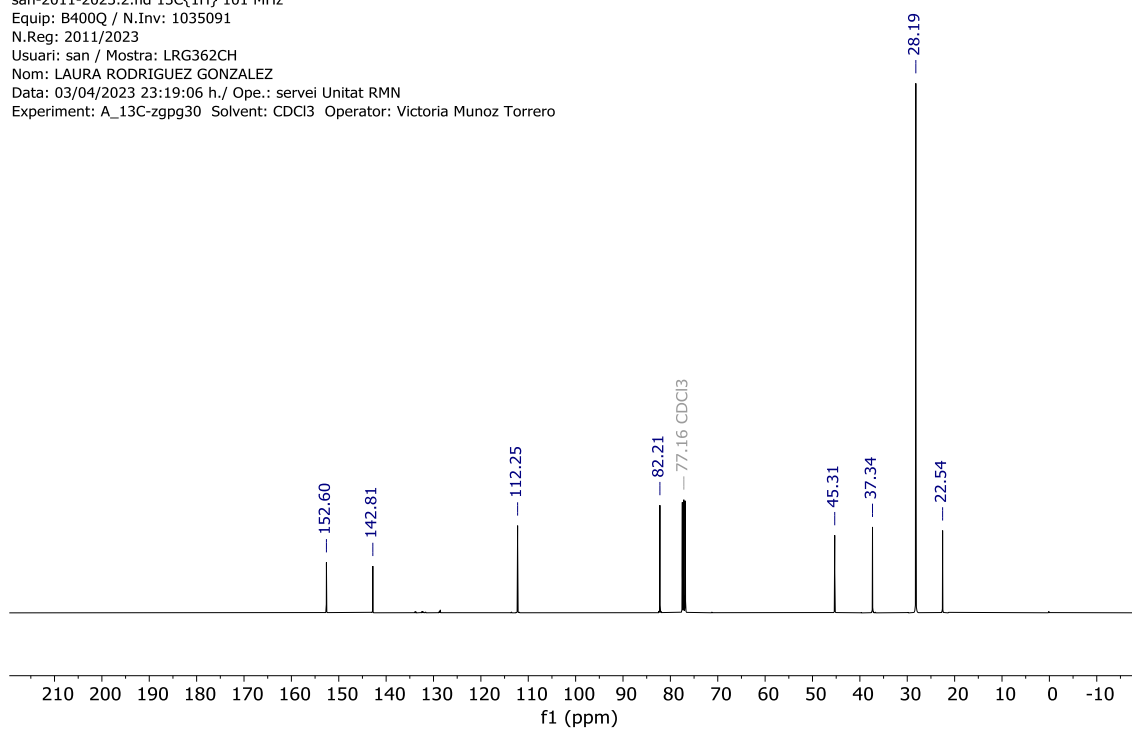
Experimental Section: Chapter 2

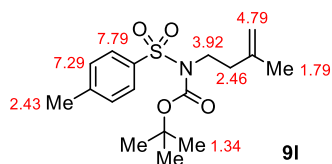


23040011_B400FA_03042023_LRG362COL3T17T19.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040011
 Usuari: san / Mostra: LRG362COL3T17T19
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/04/2023 11:24:55 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

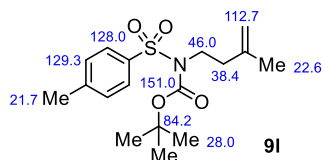
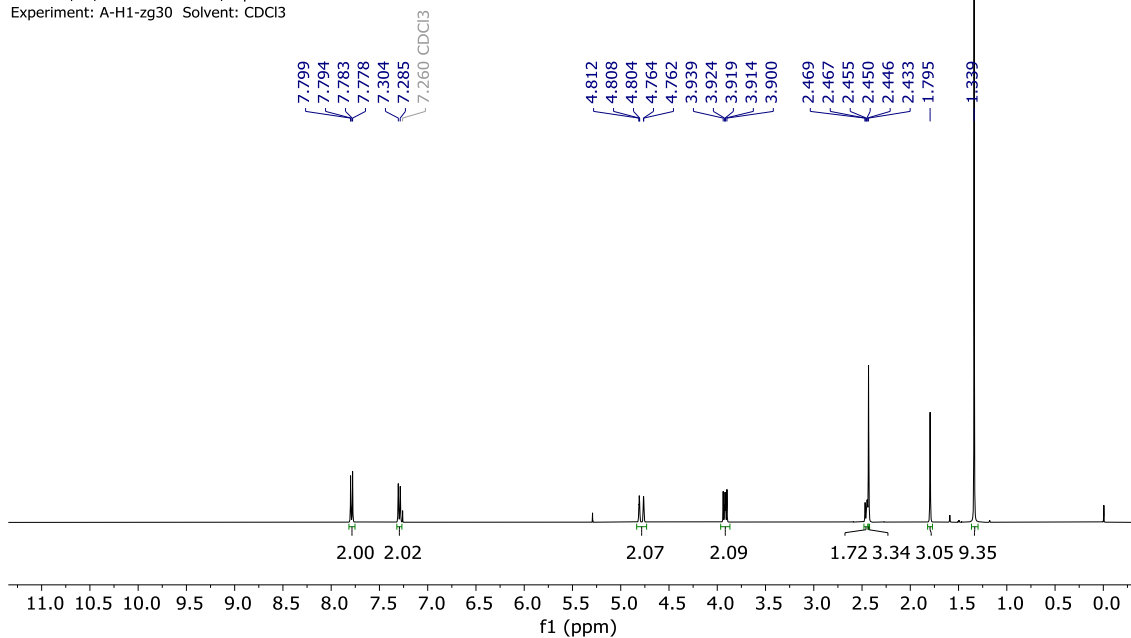


san-2011-2023.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2011/2023
 Usuari: san / Mostra: LRG362CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/04/2023 23:19:06 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl₃ Operator: Victoria Munoz Torrero

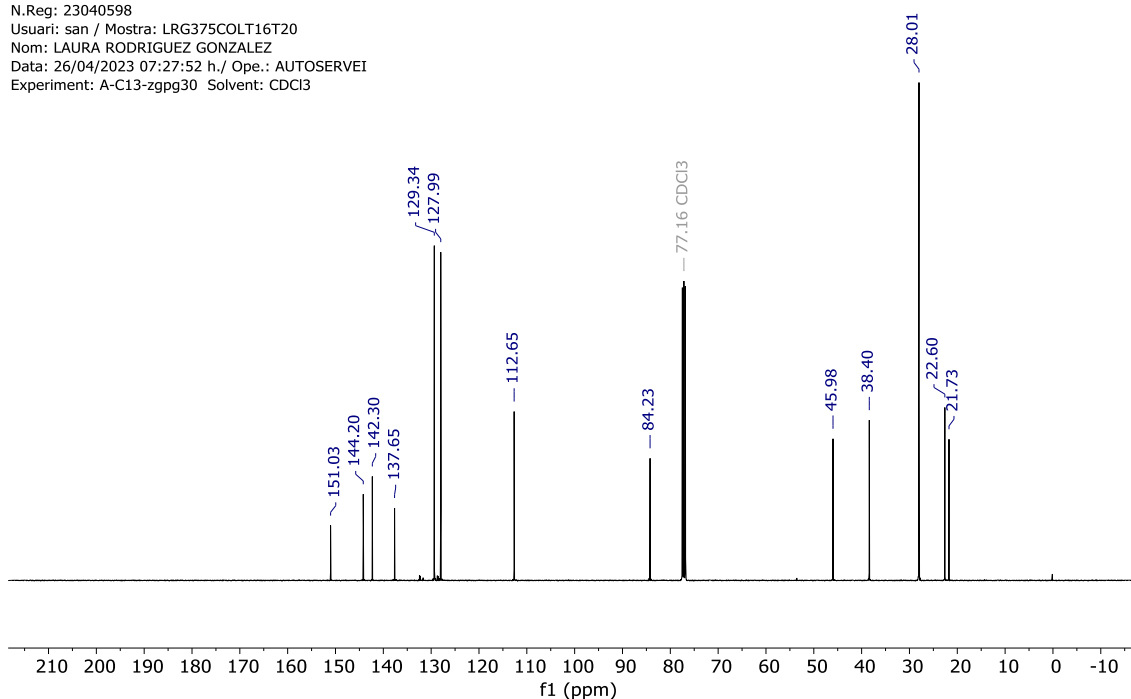


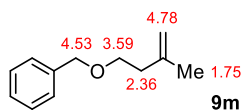


23040598_B400FA_26042023_LRG375COLT16T20.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040598
 Usuari: san / Mostra: LRG375COLT16T20
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 25/04/2023 16:35:45 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

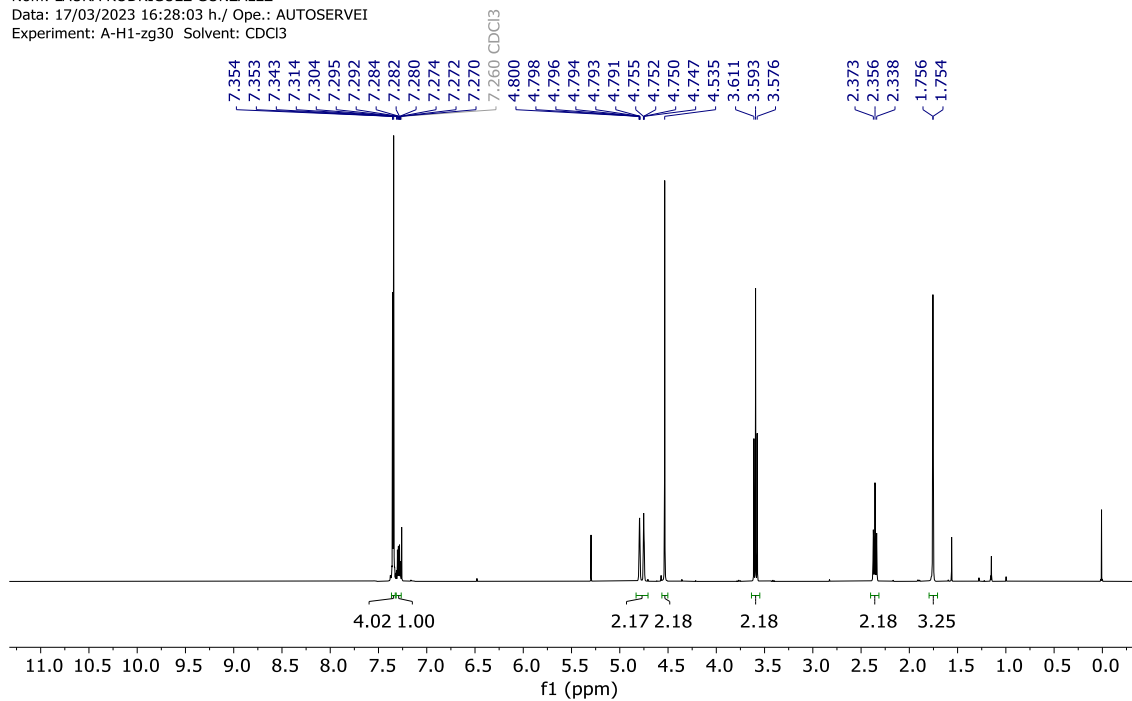


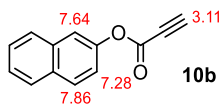
23040598_B400FA_26042023_LRG375COLT16T20.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040598
 Usuari: san / Mostra: LRG375COLT16T20
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/04/2023 07:27:52 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpgp30 Solvent: CDCl3



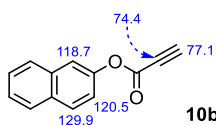
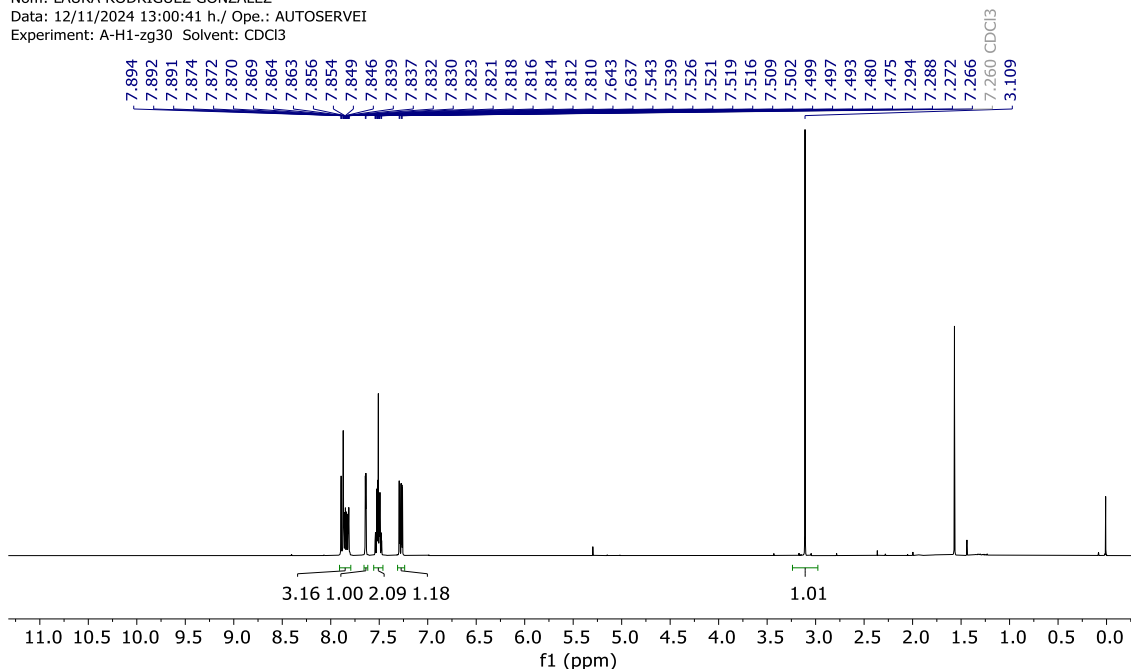


LRG354COLT15T17.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030621
 Usuari: san / Mostra: LRG354COLT15T17
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 17/03/2023 16:28:03 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

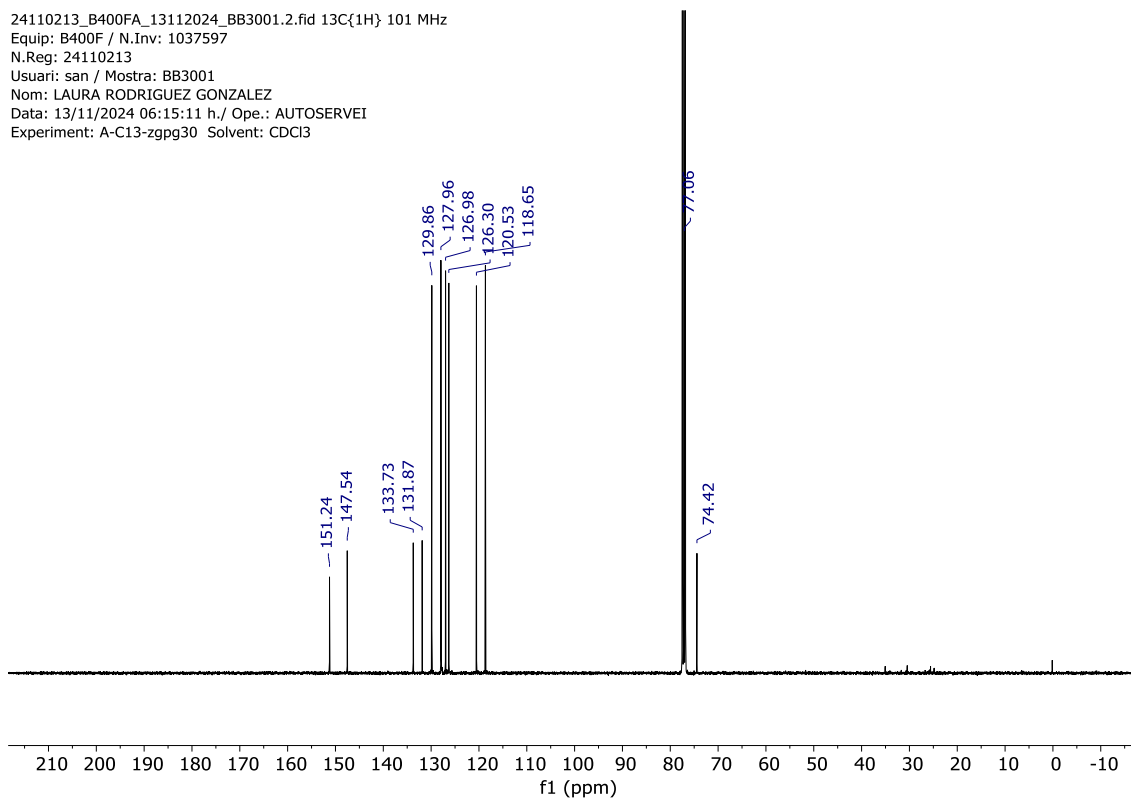


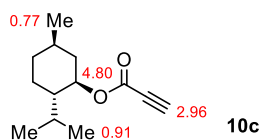


24110213_B400FA_12112024_BB3001.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24110213
Usuari: san / Mostra: BB3001
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 12/11/2024 13:00:41 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3

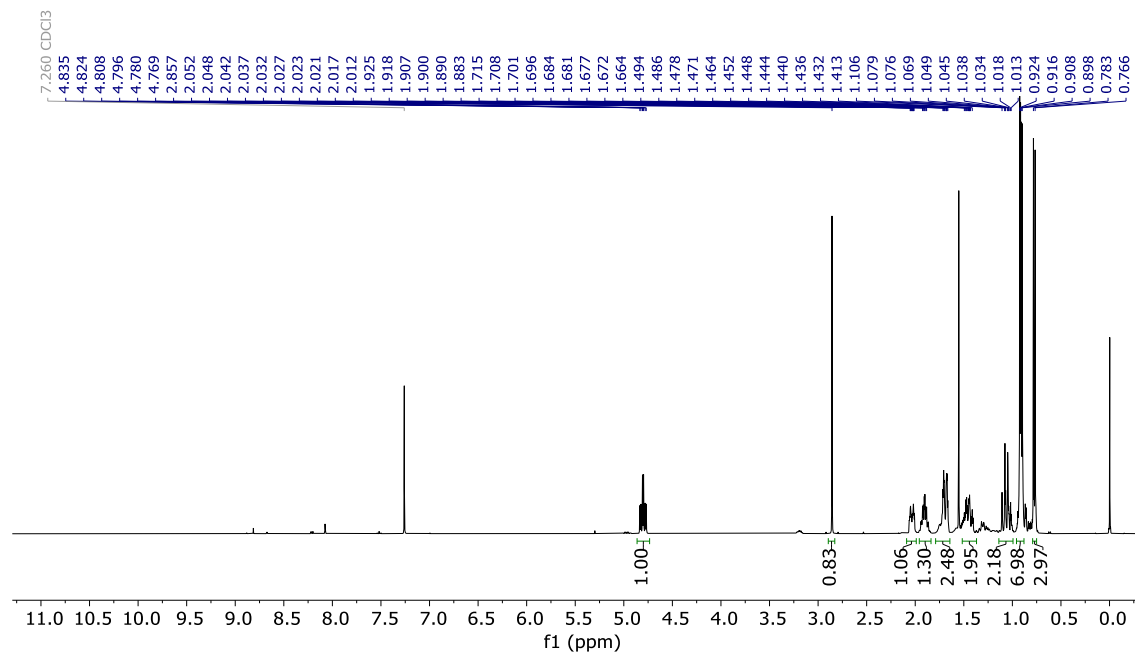


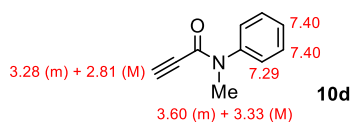
24110213_B400FA_13112024_BB3001.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24110213
Usuari: san / Mostra: BB3001
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 13/11/2024 06:15:11 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3



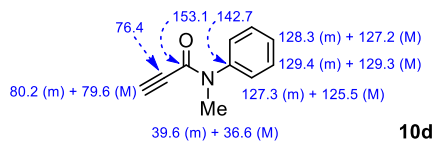
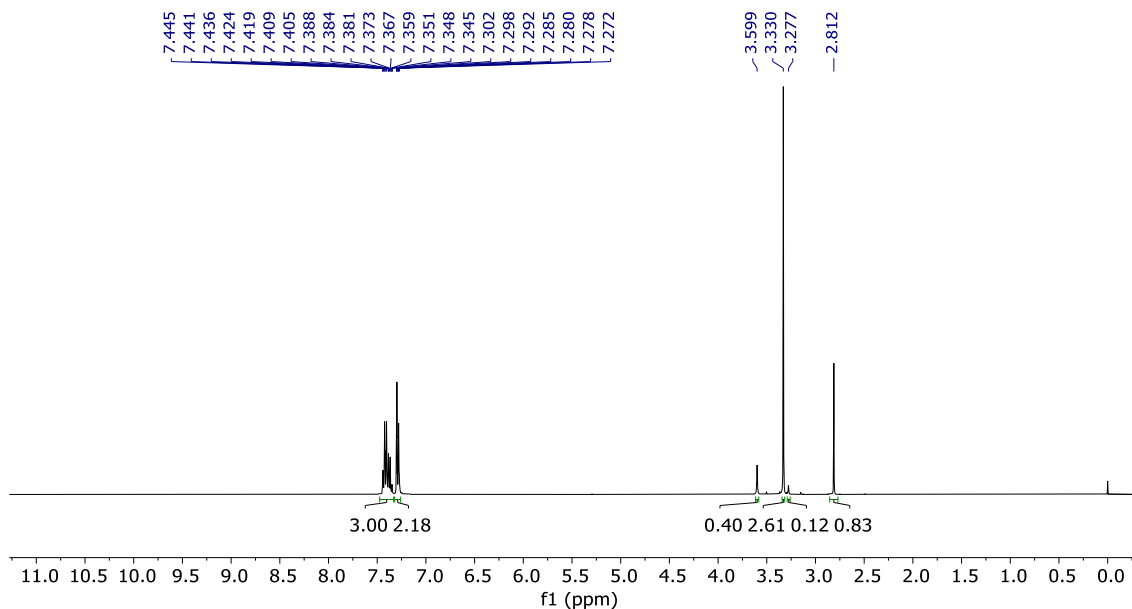


LRG382REC.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23050196
 Usuari: san / Mostra: LRG382REC
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 05/05/2023 16:38:19 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

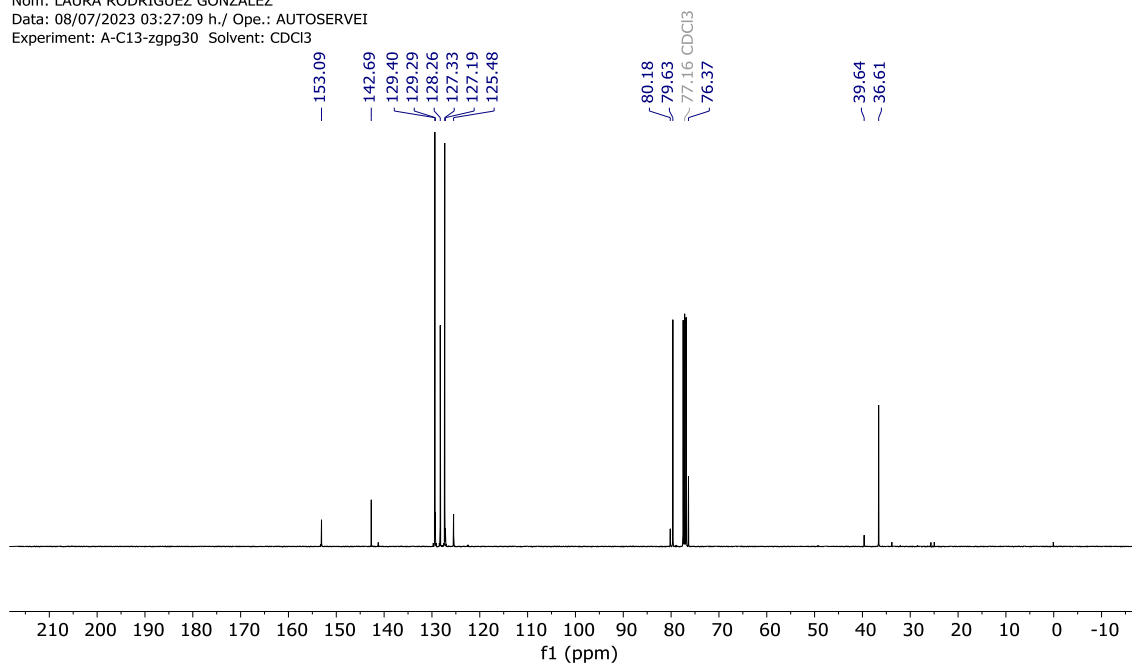


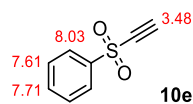


23070179_B400FA_08072023_LRG396CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070179
 Usuari: san / Mostra: LRG396CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/07/2023 15:23:51 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

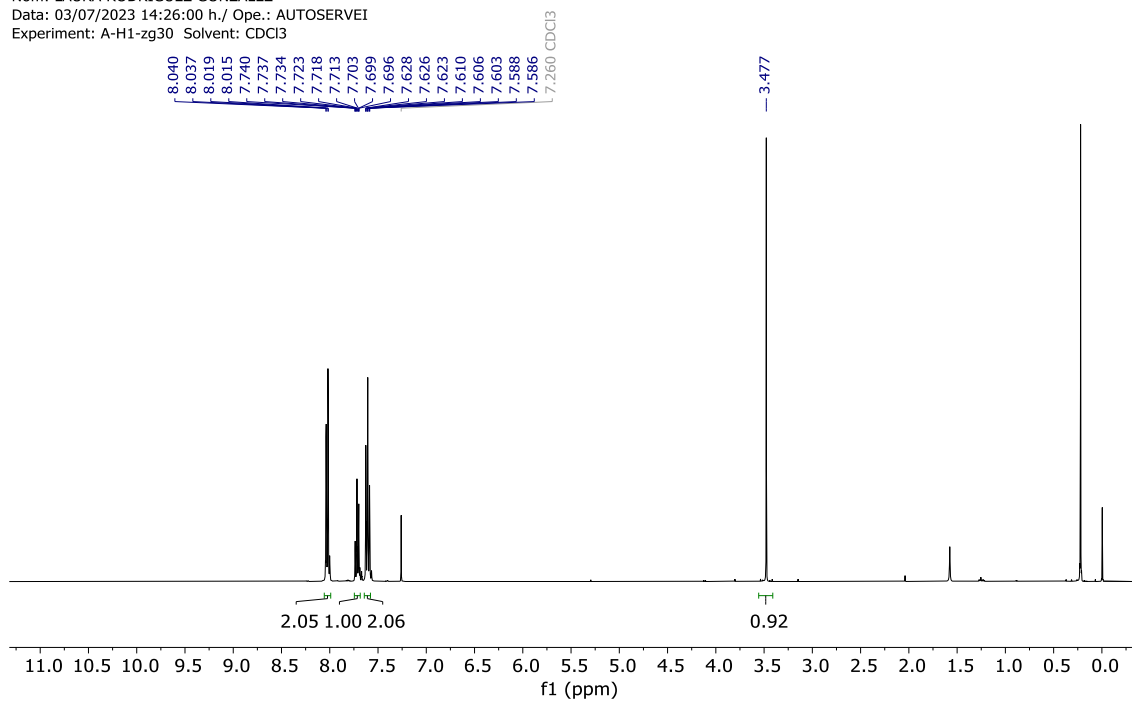


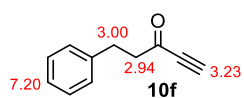
23070179_B400FA_08072023_LRG396CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070179
 Usuari: san / Mostra: LRG396CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/07/2023 03:27:09 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



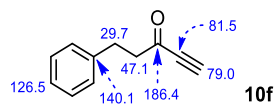
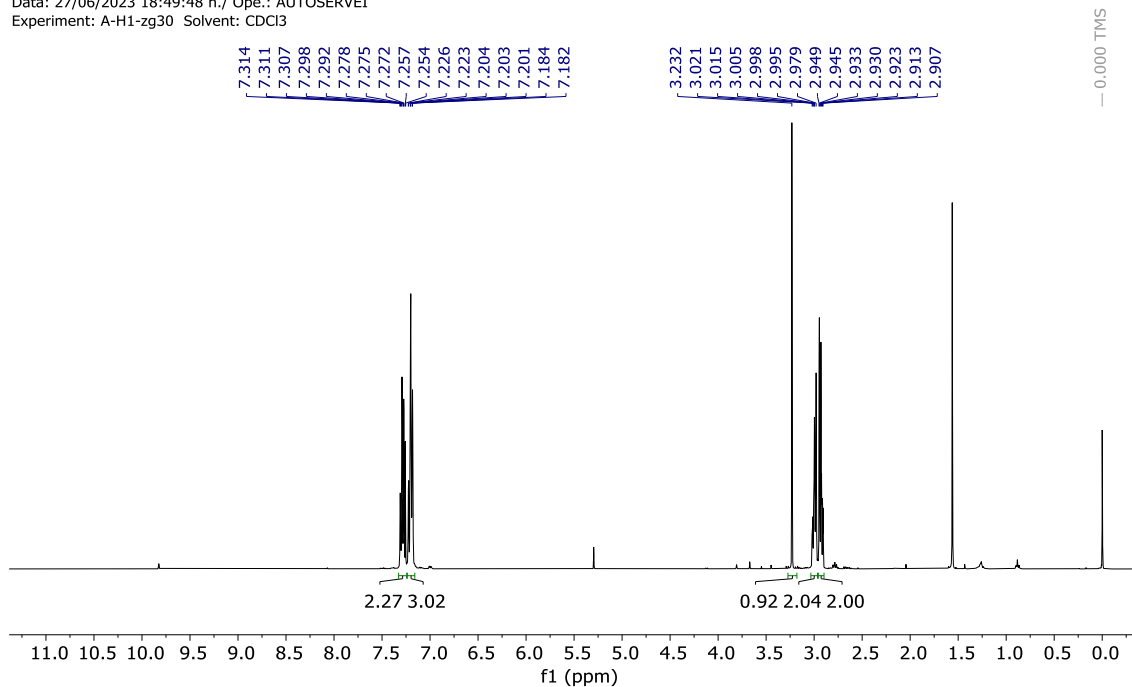


LRG415COLT12T18.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070012
 Usuari: san / Mostra: LRG415COLT12T18
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/07/2023 14:26:00 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

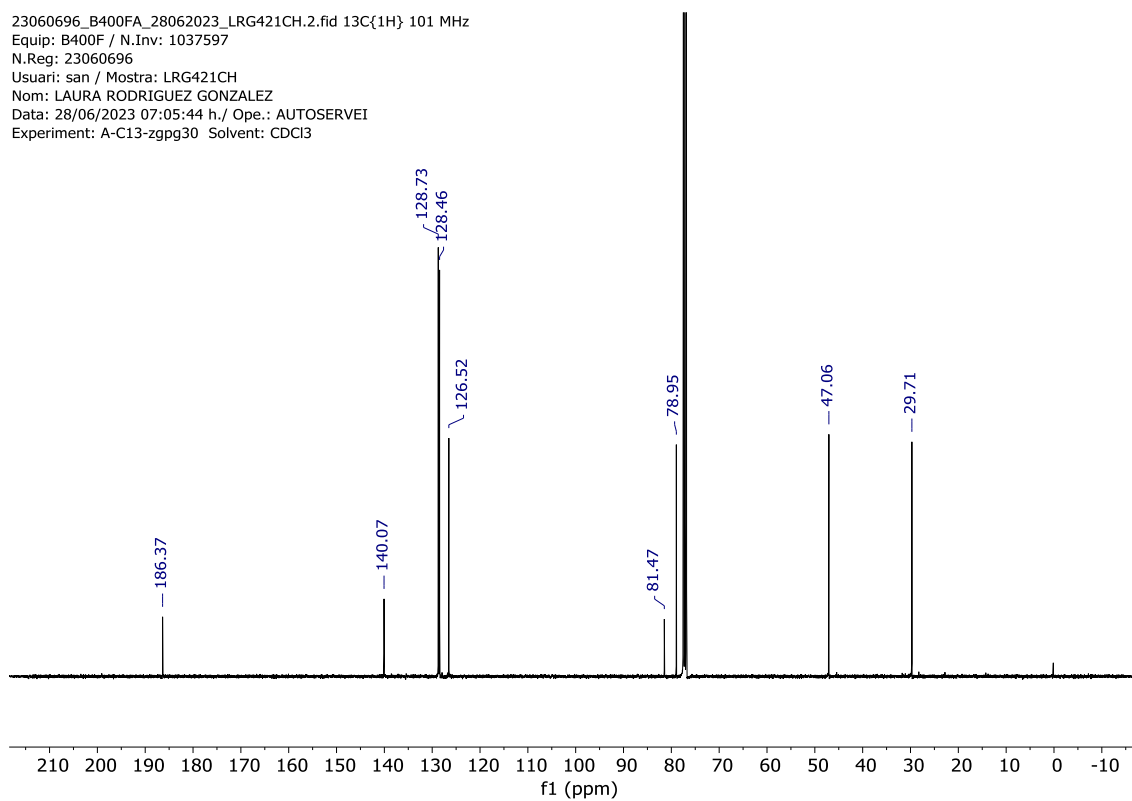


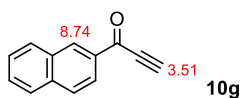


23060696_B400FA_28062023_LRG421CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060696
 Usuari: san / Mostra: LRG421CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/06/2023 18:49:48 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

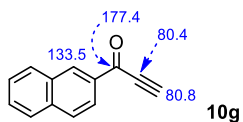
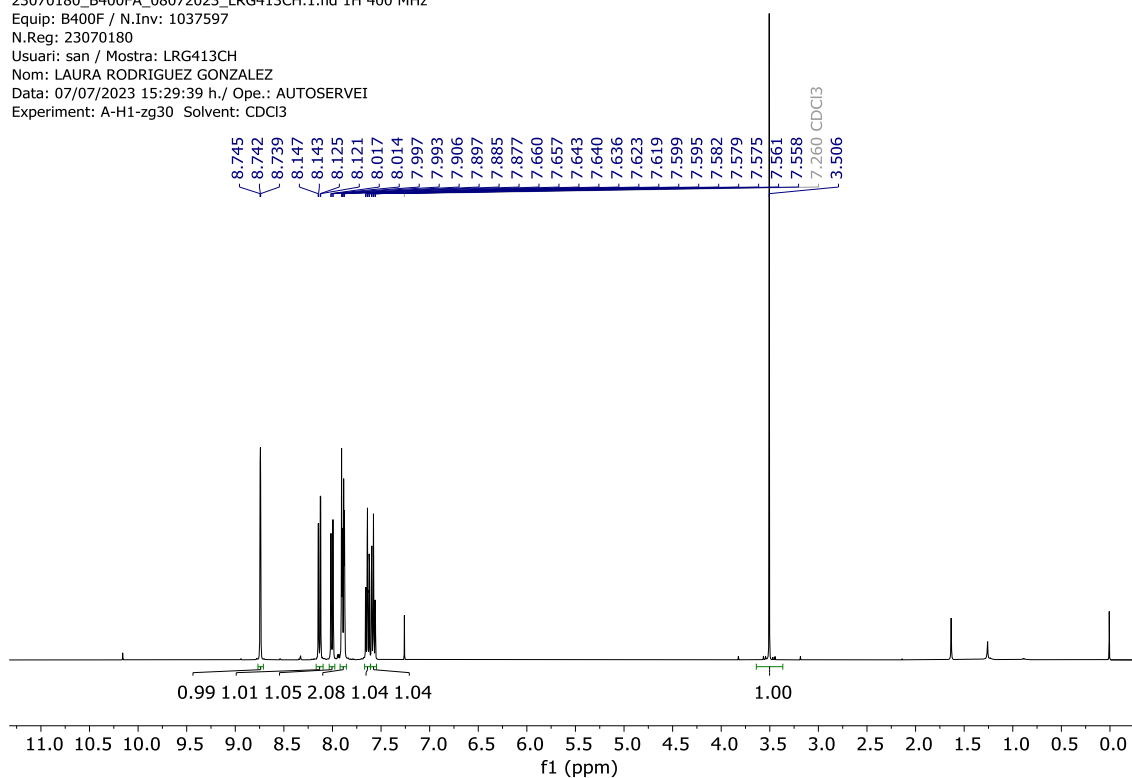


23060696_B400FA_28062023_LRG421CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060696
 Usuari: san / Mostra: LRG421CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 28/06/2023 07:05:44 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

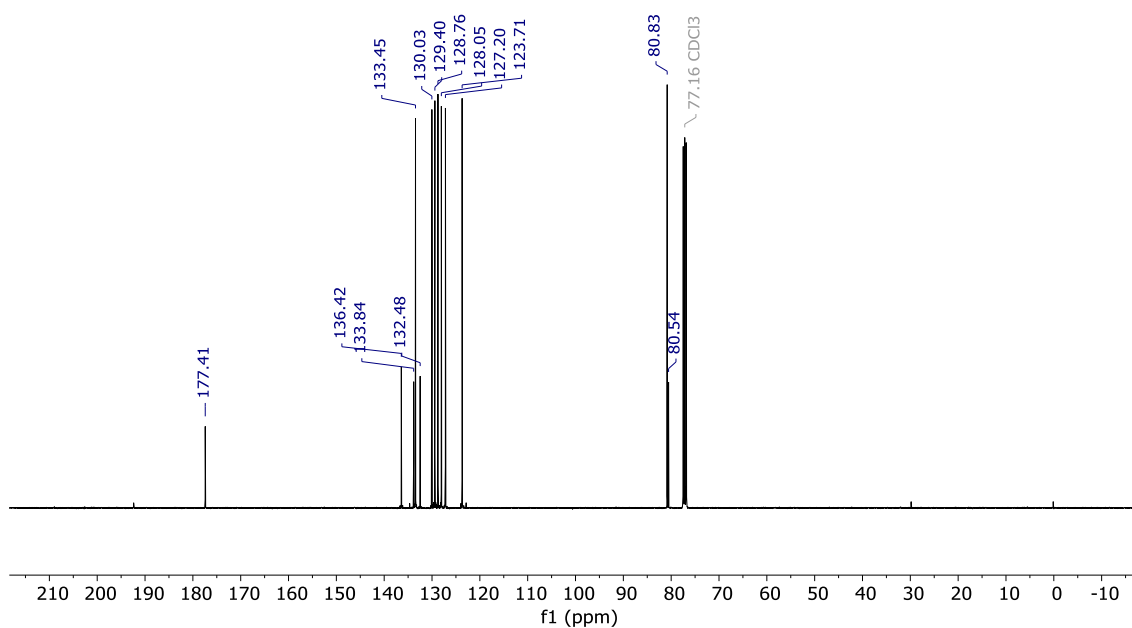


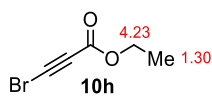


23070180_B400FA_08072023_LRG413CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070180
 Usuari: san / Mostra: LRG413CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/07/2023 15:29:39 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

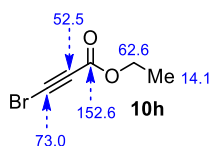
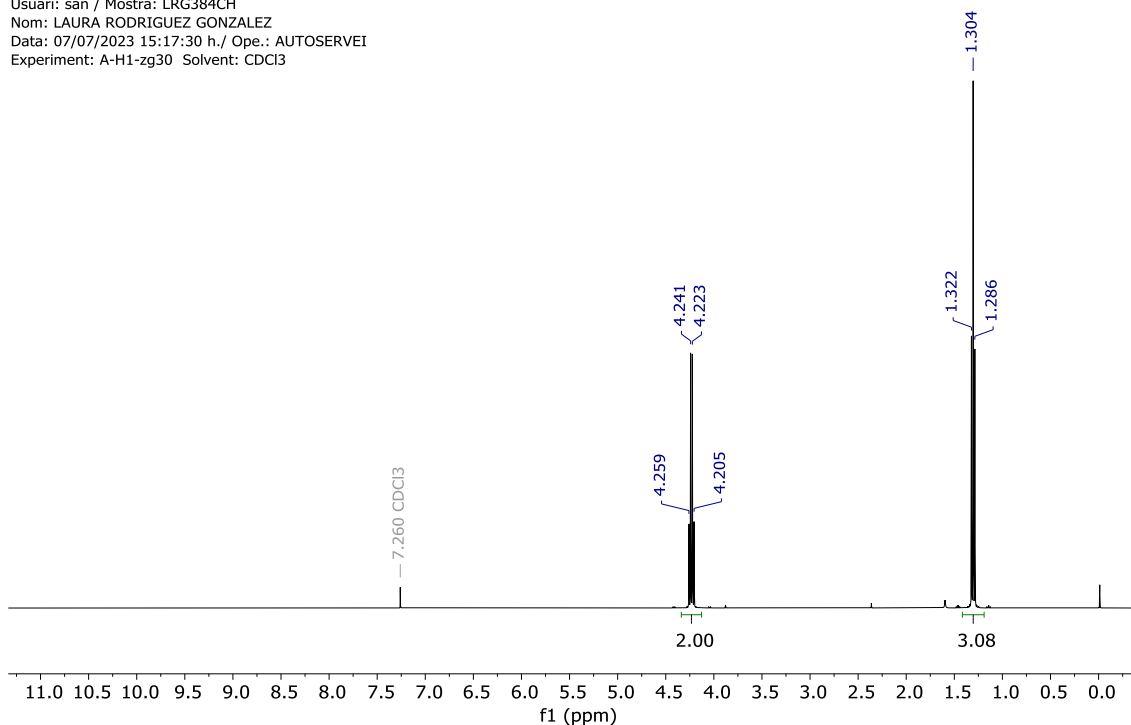


23070180_B400FA_08072023_LRG413CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070180
 Usuari: san / Mostra: LRG413CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/07/2023 06:13:49 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

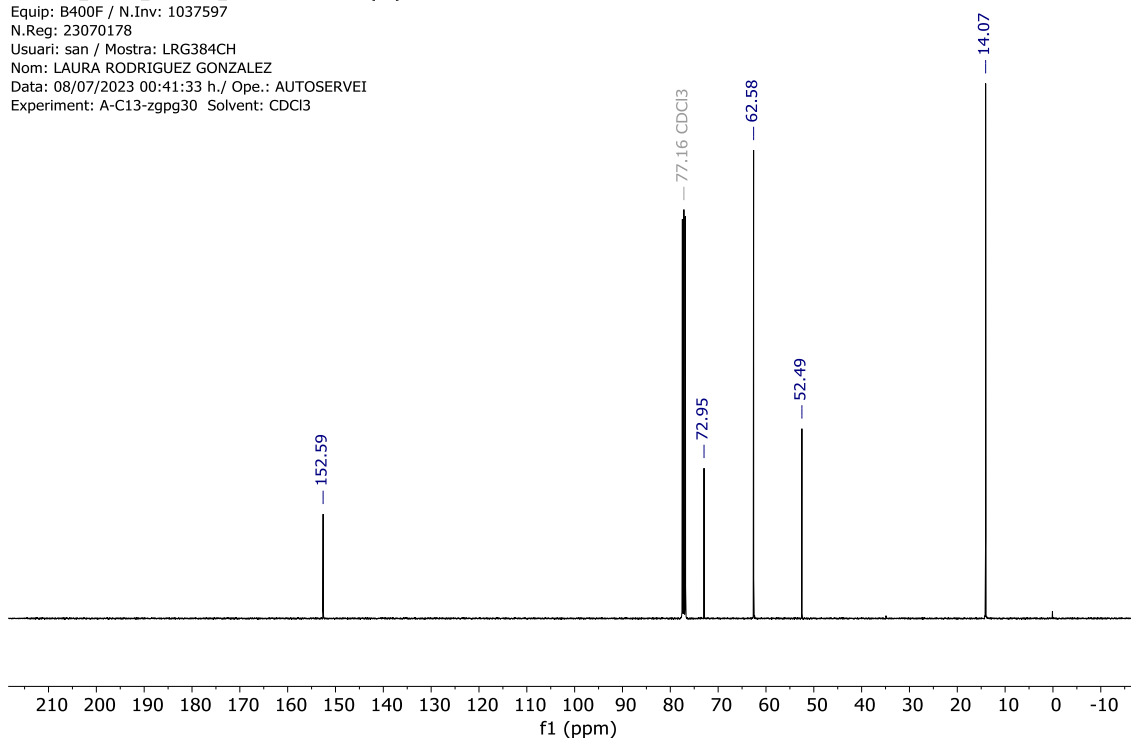




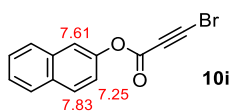
23070178_B400FA_08072023_LRG384CH.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 23070178
Usuari: san / Mostra: LRG384CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 07/07/2023 15:17:30 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3



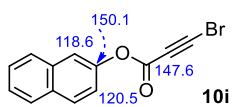
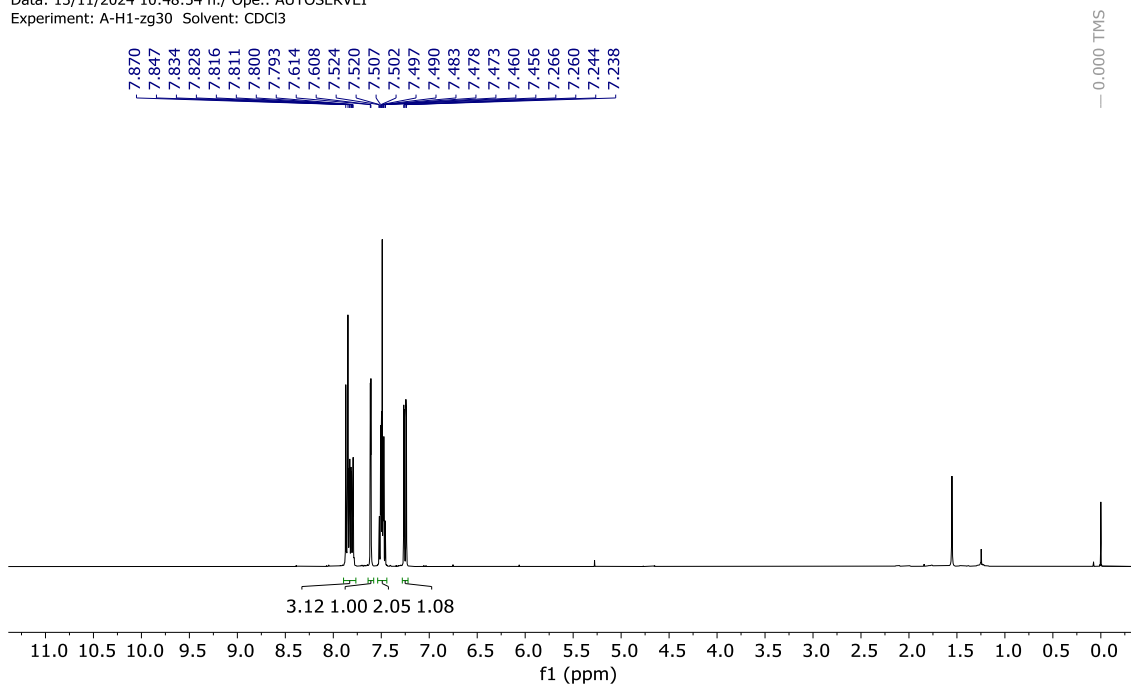
23070178_B400FA_08072023_LRG384CH.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 23070178
Usuari: san / Mostra: LRG384CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 08/07/2023 00:41:33 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgp30 Solvent: CDCl3



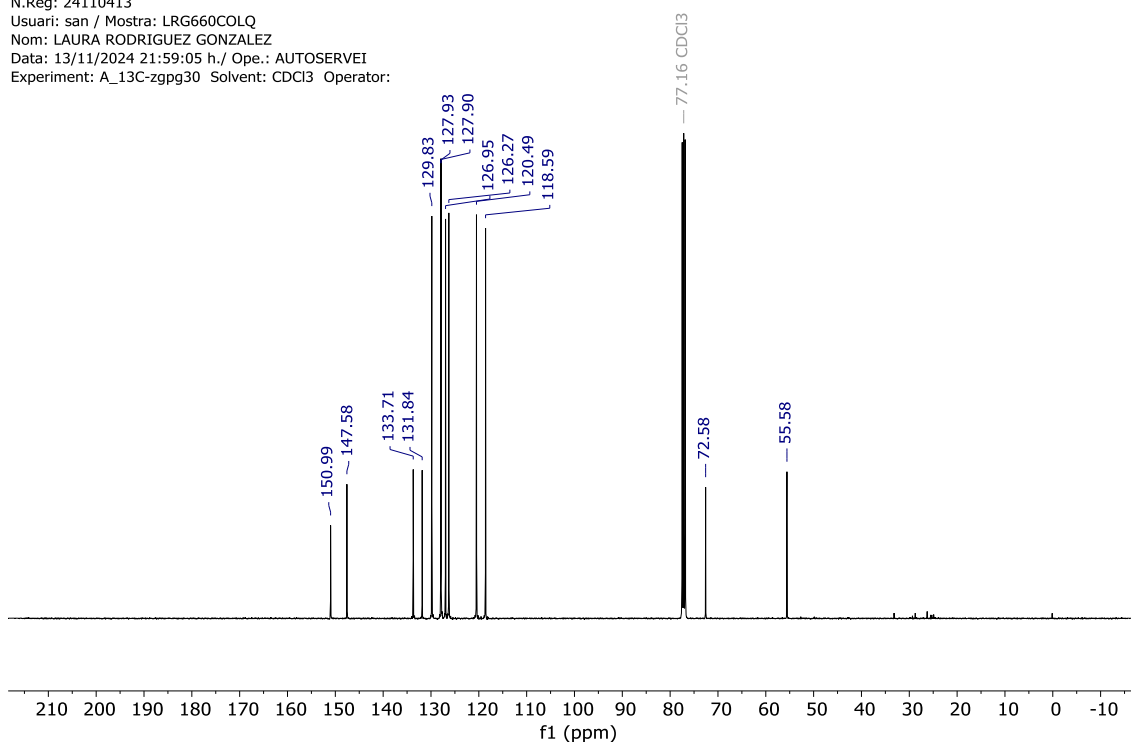
Experimental Section: Chapter 2

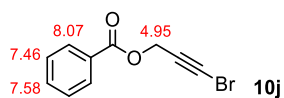


24110250_B400FA_13112024_LRG660T11.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24110250
 Usuari: san / Mostra: LRG660T11
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 13/11/2024 10:48:54 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

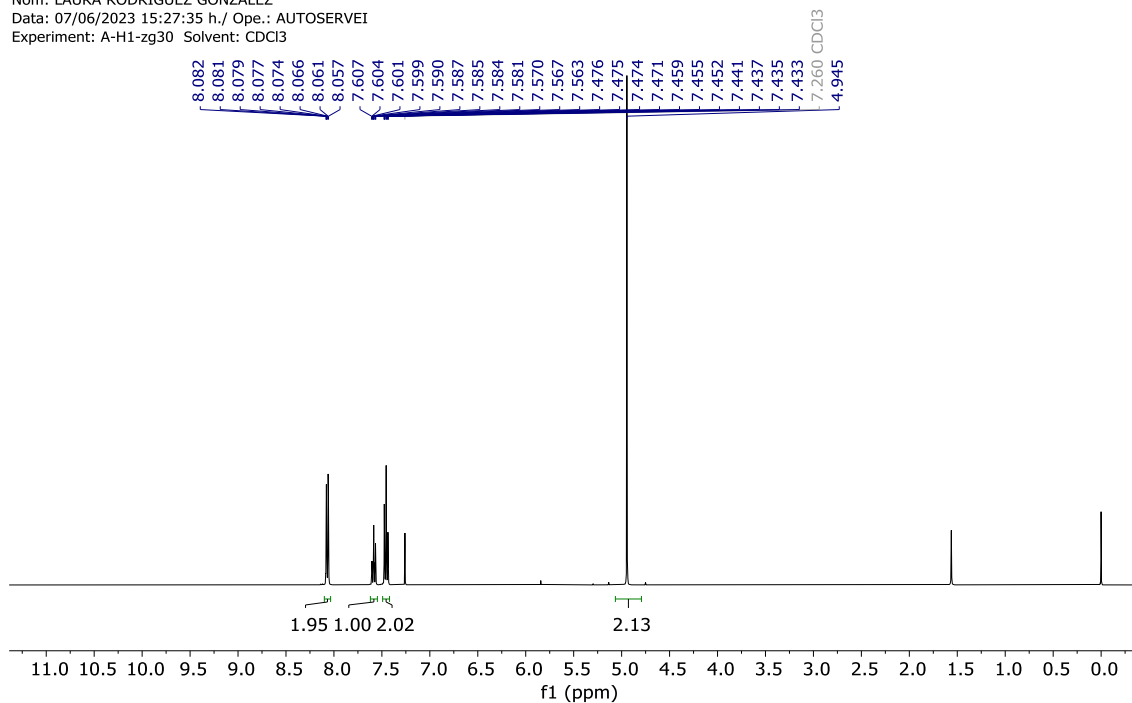


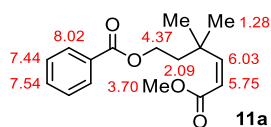
auto-13112024-105914.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 24110413
 Usuari: san / Mostra: LRG660COLQ
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 13/11/2024 21:59:05 h./ Ope.: AUTOSERVEI
 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator:



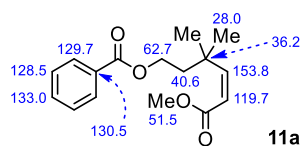
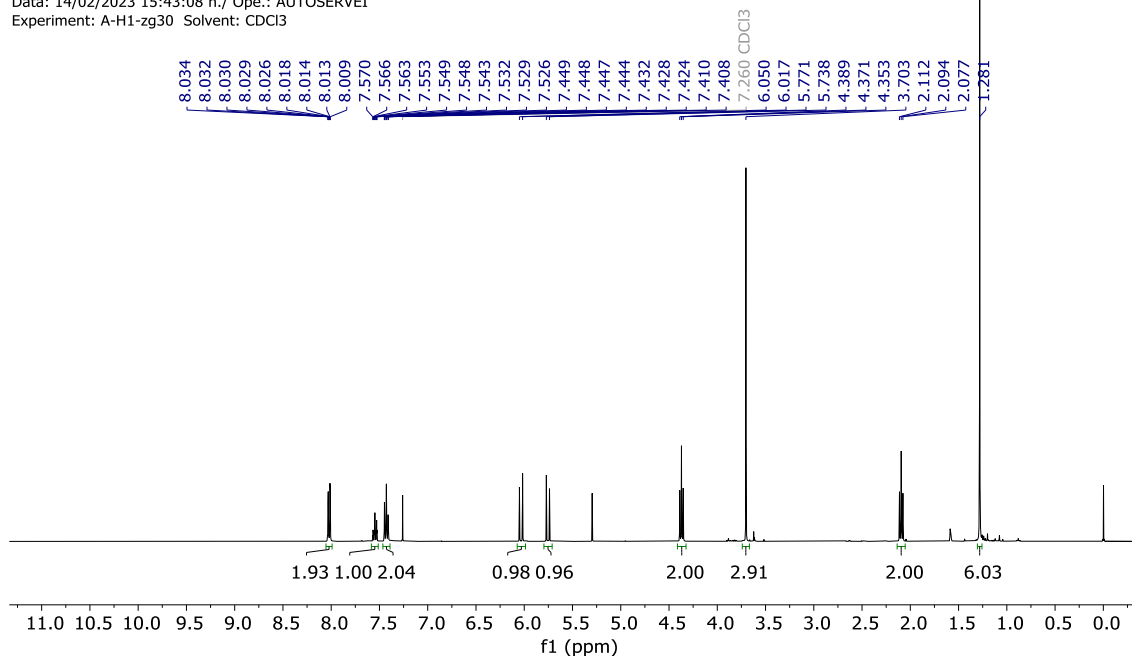


LRG400COLT21T23.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 23060130
Usuari: san / Mostra: LRG400COLT21T23
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 07/06/2023 15:27:35 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl₃

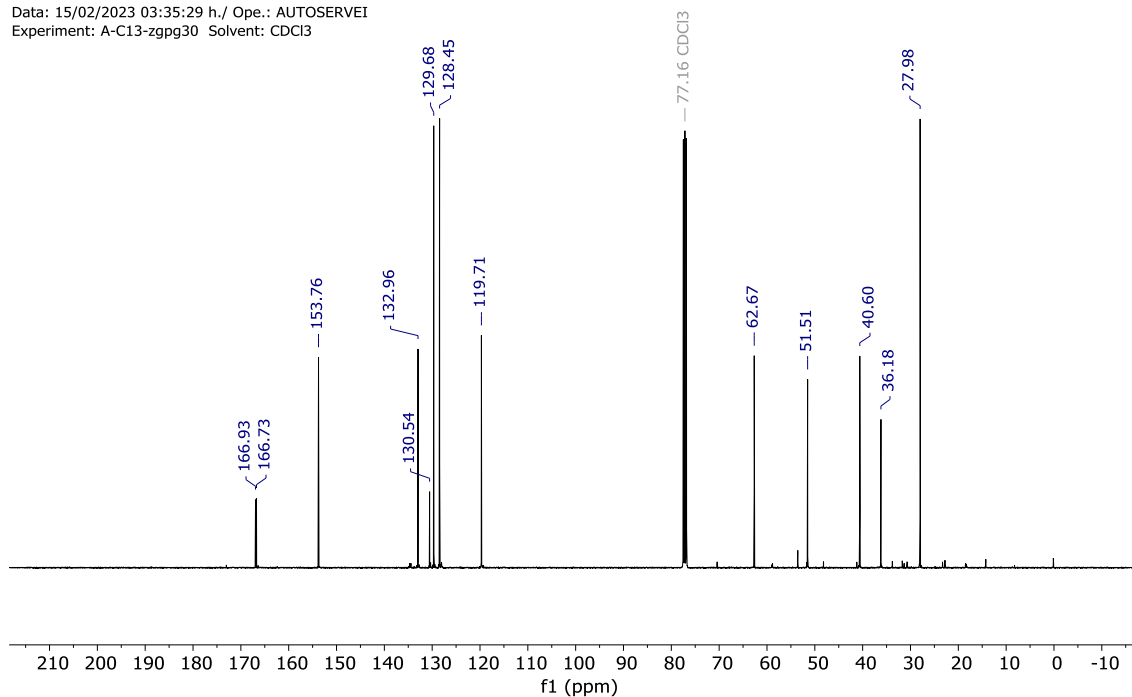


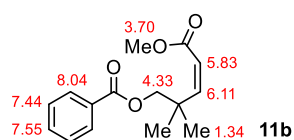


LRG320COLT21T22.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23020561
 Usuari: san / Mostra: LRG320COLT21T22
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/02/2023 15:43:08 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

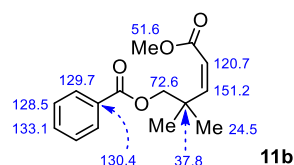
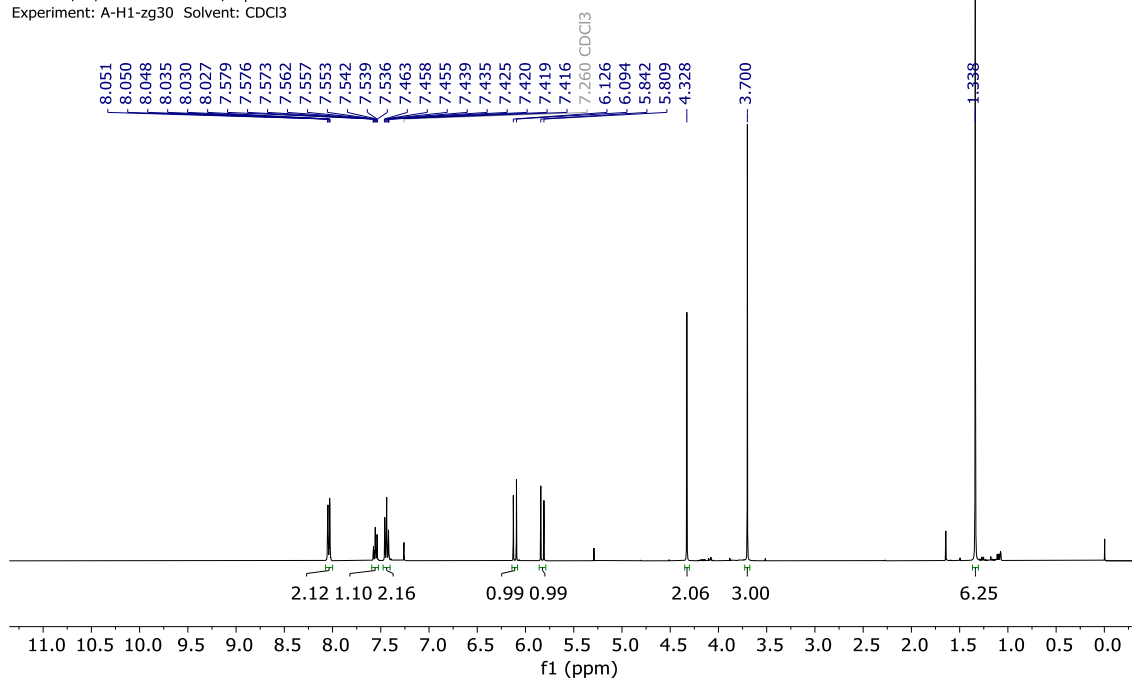


LRG320CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23020581
 Usuari: san / Mostra: LRG320CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/02/2023 03:35:29 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

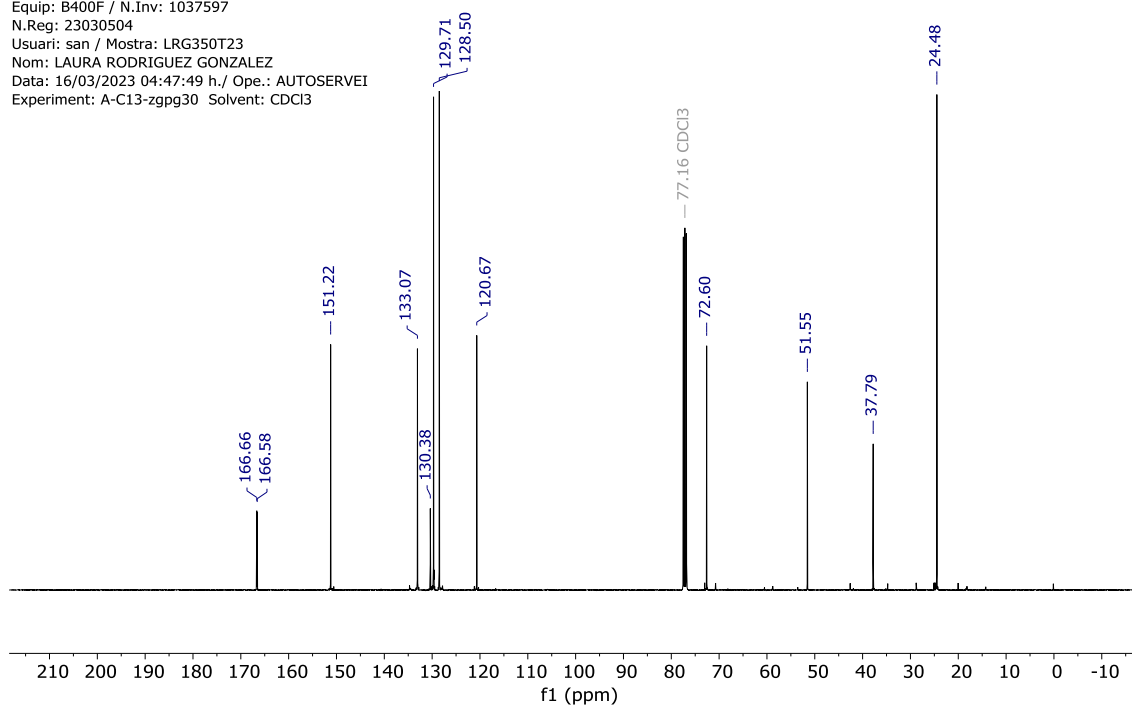


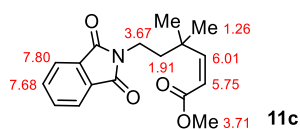


23030506_B400FA_15032023_LRG351T24T27.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030506
 Usuari: san / Mostra: LRG351T24T27
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/03/2023 13:33:59 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

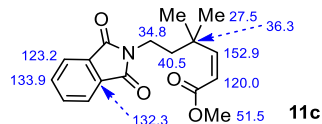
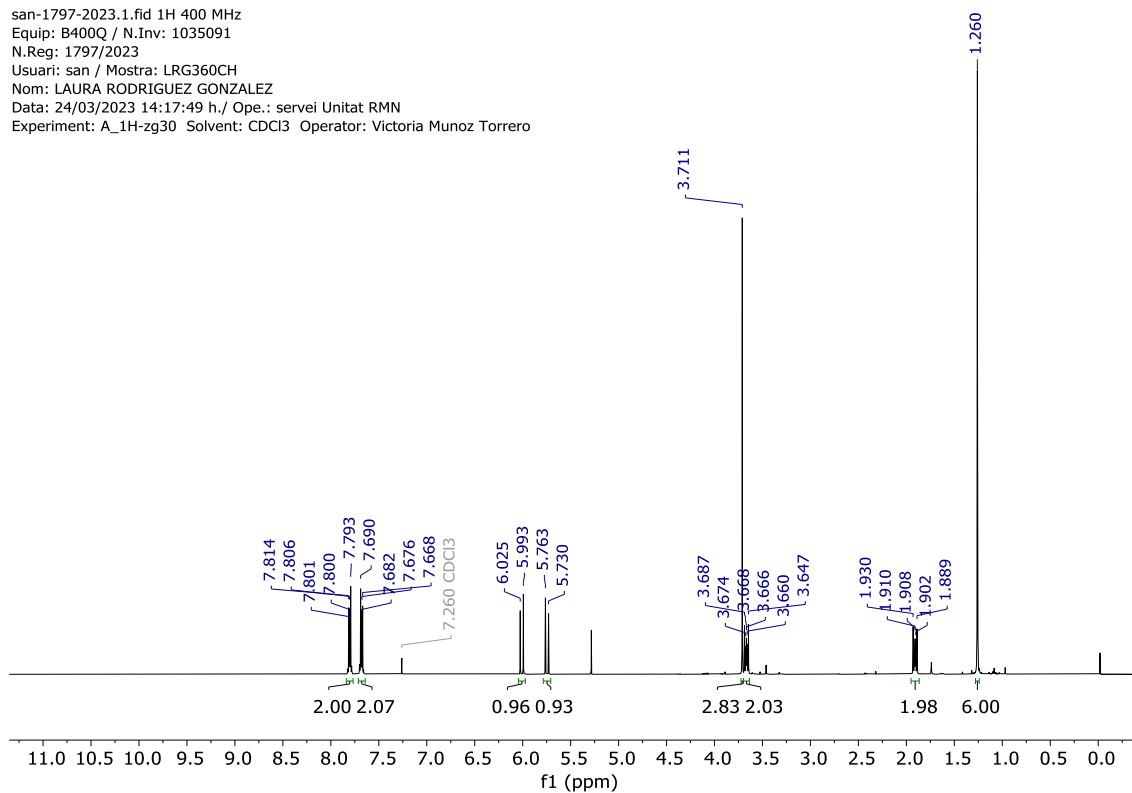


LRG351T24T27CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030504
 Usuari: san / Mostra: LRG350T23
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 16/03/2023 04:47:49 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpgp30 Solvent: CDCl3

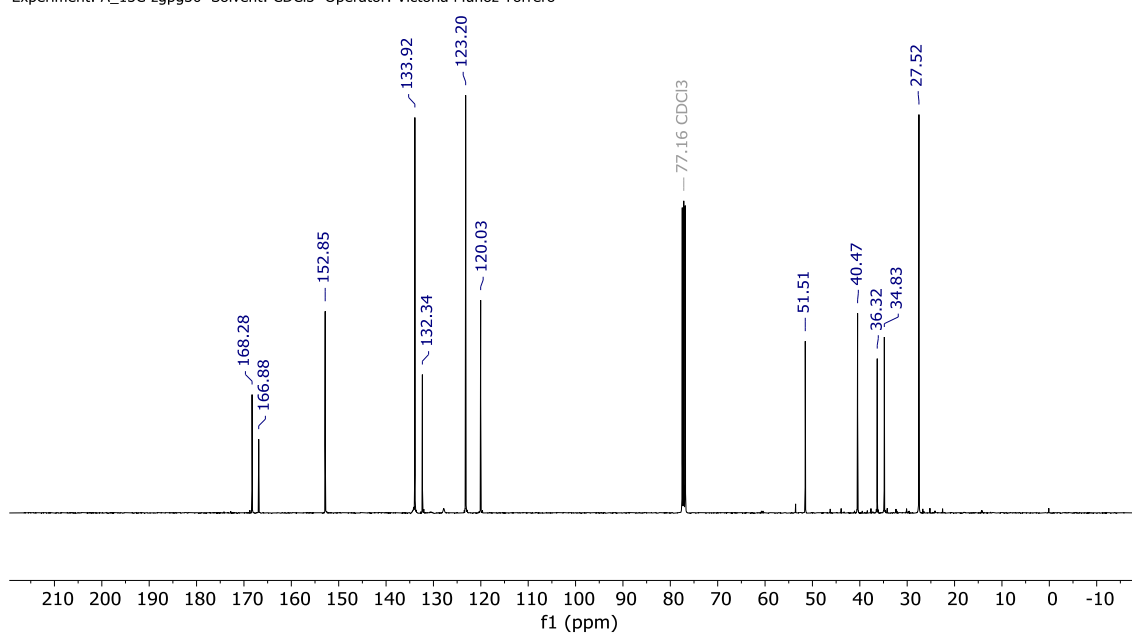


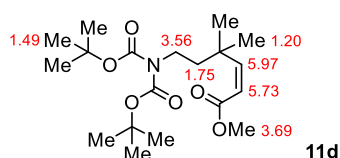


san-1797-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1797/2023
 Usuari: san / Mostra: LRG360CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 24/03/2023 14:17:49 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: Victoria Munoz Torrero

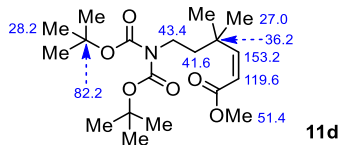
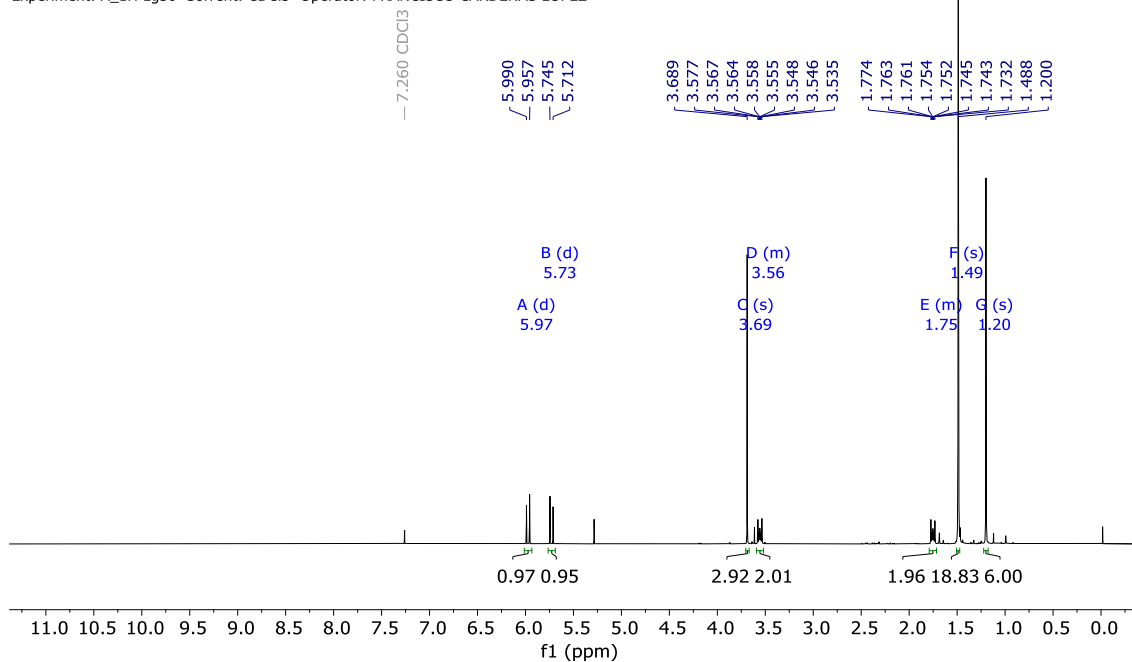


san-1797-2023.5.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1797/2023
 Usuari: san / Mostra: LRG360CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 24/03/2023 16:20:34 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpg30 Solvent: CDCl₃ Operator: Victoria Munoz Torrero

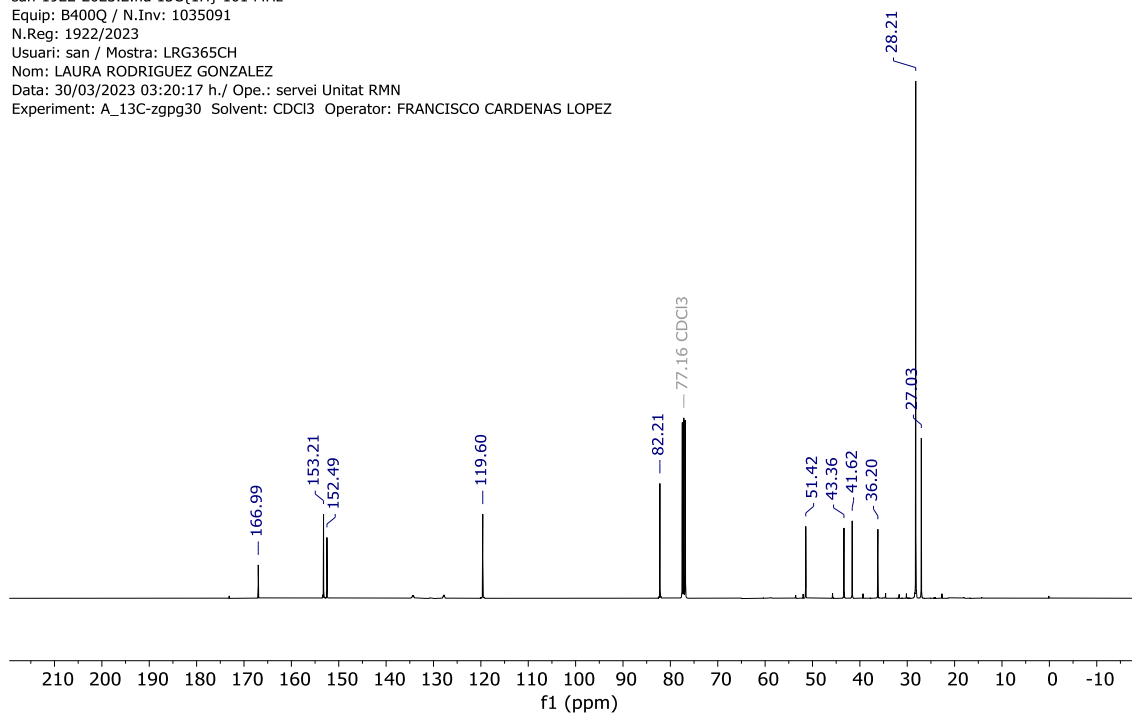


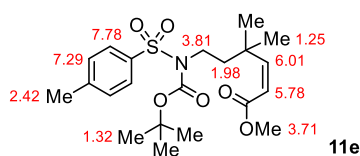


san-1922-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1922/2023
 Usuari: san / Mostra: LRG365CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 30/03/2023 03:20:17 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator: FRANCISCO CARDENAS LOPEZ

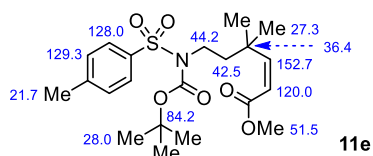
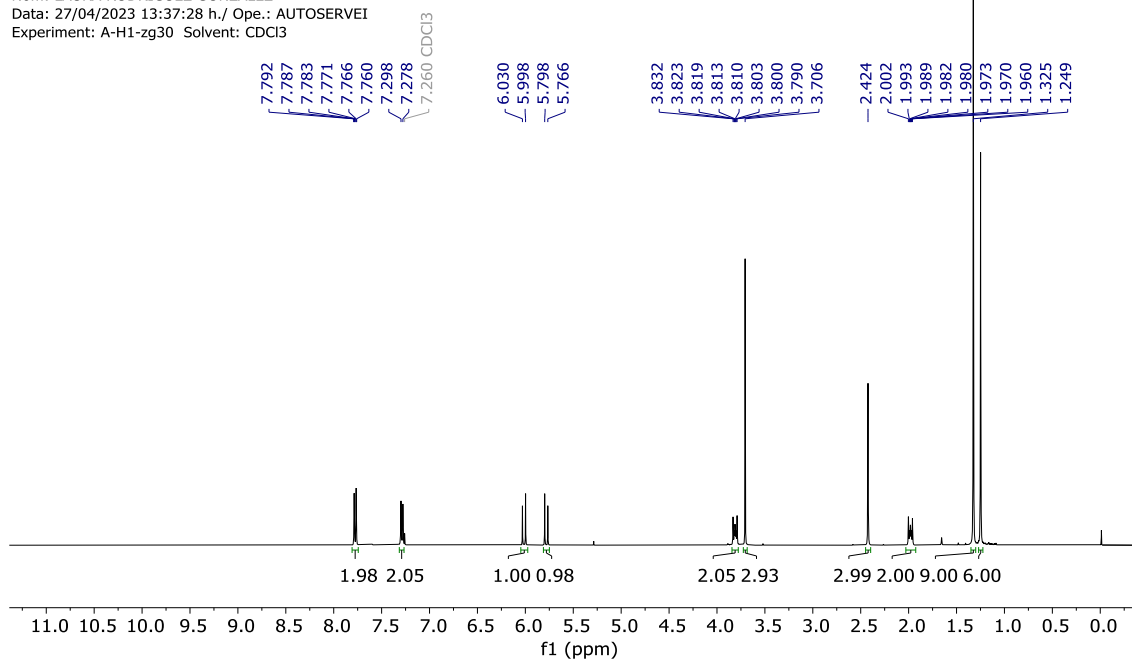


san-1922-2023.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1922/2023
 Usuari: san / Mostra: LRG365CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 30/03/2023 03:20:17 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl₃ Operator: FRANCISCO CARDENAS LOPEZ

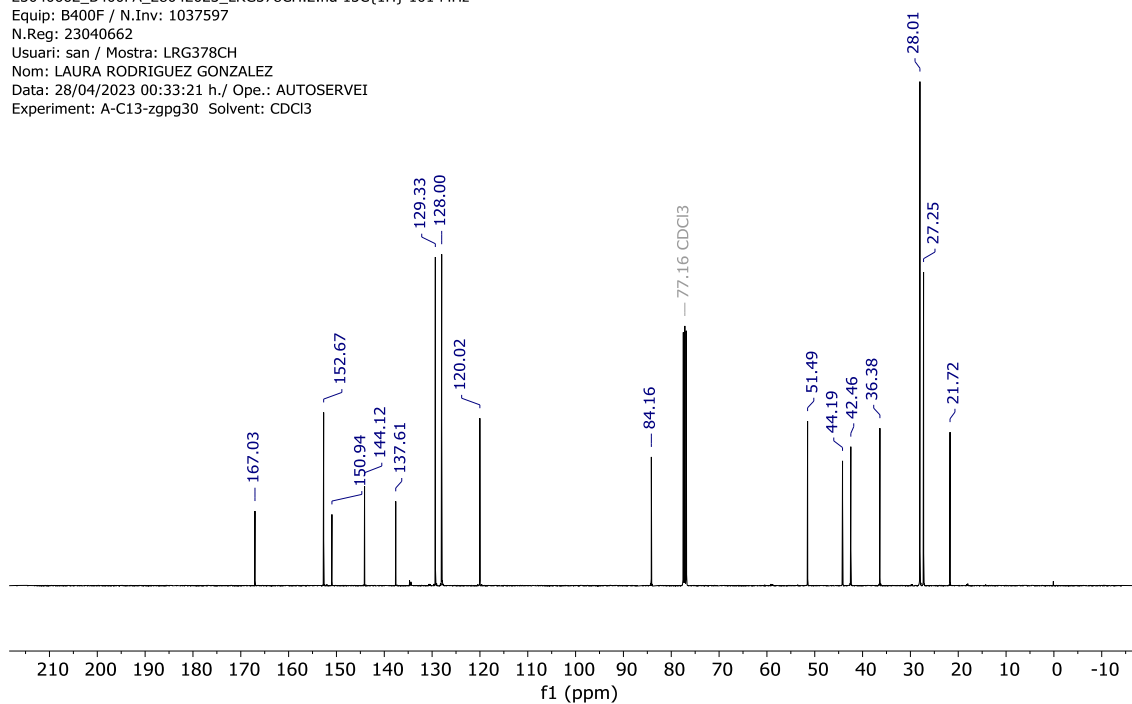


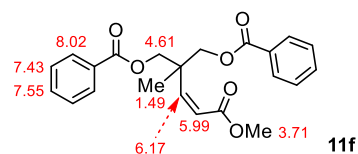


23040662_B400FA_27042023_LRG378CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040662
 Usuari: san / Mostra: LRG378CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/04/2023 13:37:28 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

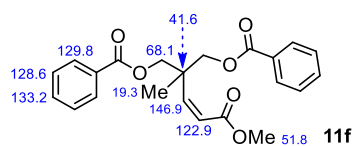
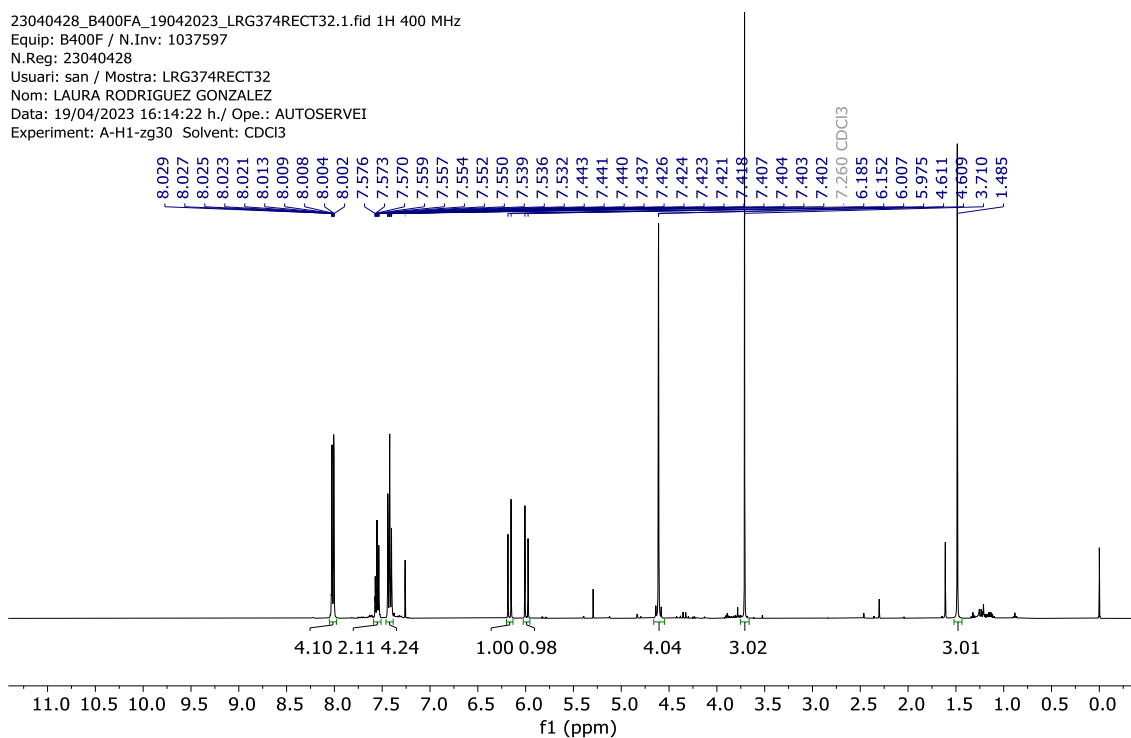


23040662_B400FA_28042023_LRG378CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040662
 Usuari: san / Mostra: LRG378CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 28/04/2023 00:33:21 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

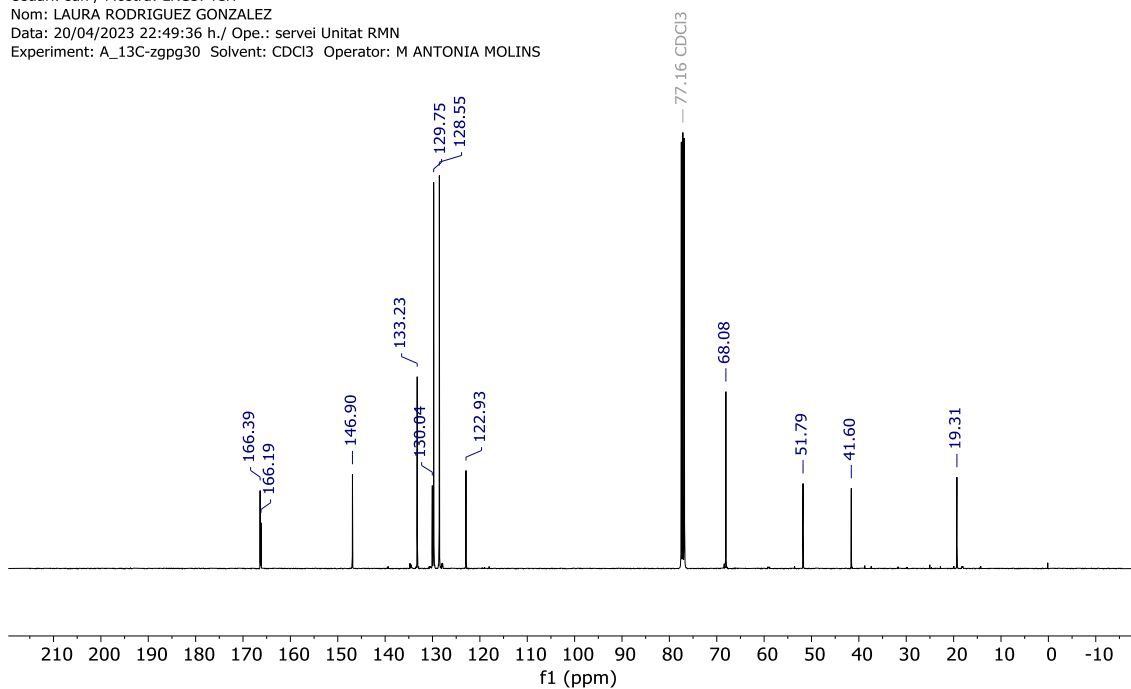




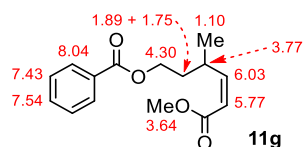
23040428_B400FA_19042023_LRG374RECT32.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23040428
 Usuari: san / Mostra: LRG374RECT32
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/04/2023 16:14:22 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



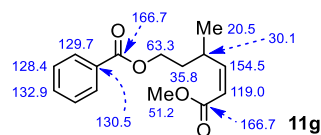
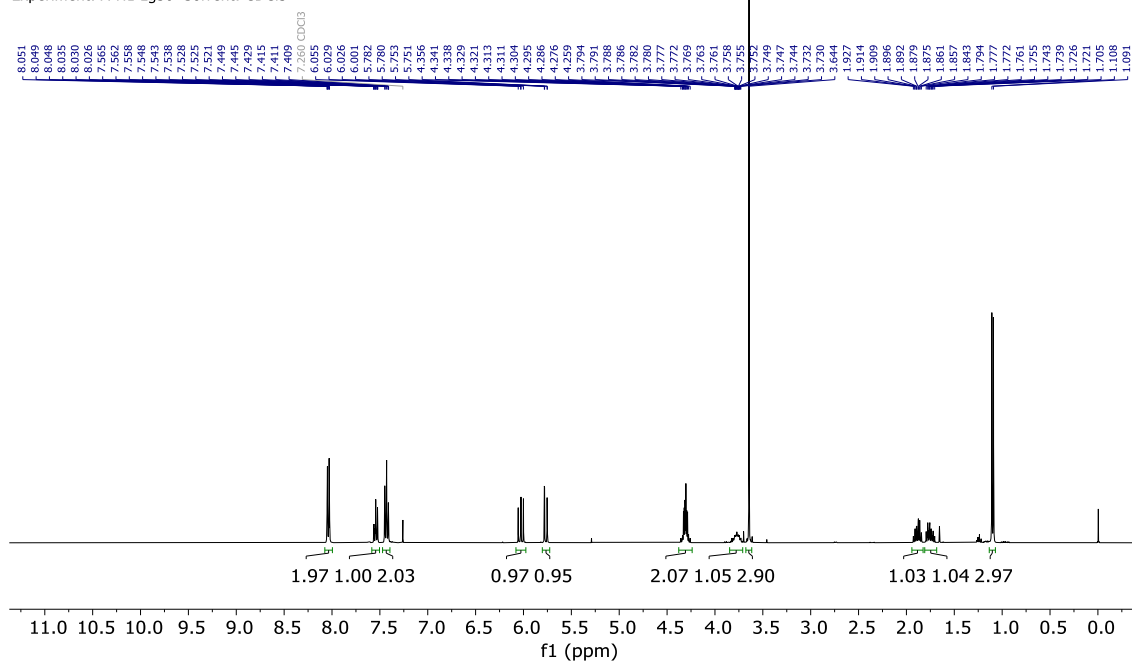
san-2256-2023.4.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2256/2023
 Usuari: san / Mostra: LRG374CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 20/04/2023 22:49:36 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator: M ANTONIA MOLINS



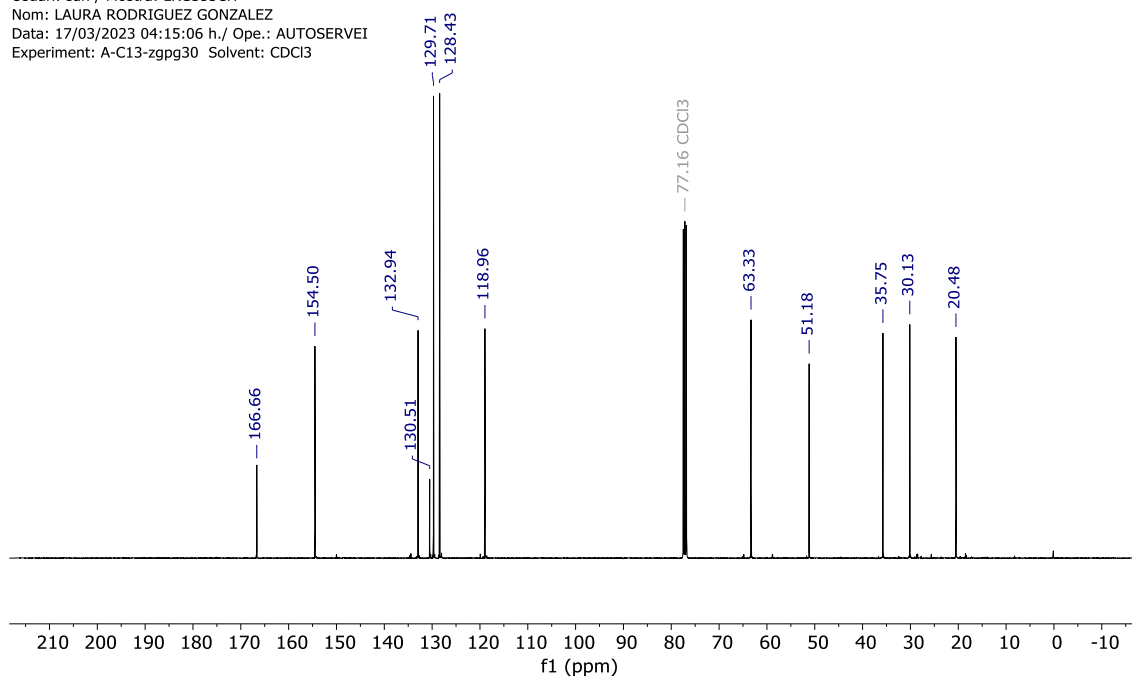
Experimental Section: Chapter 2

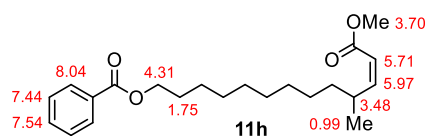


23030566_B400FA_17032023_LRG353CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030566
 Usuari: san / Mostra: LRG353CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 16/03/2023 15:39:19 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

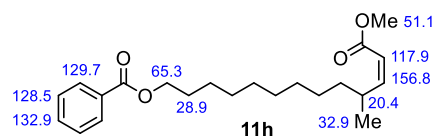
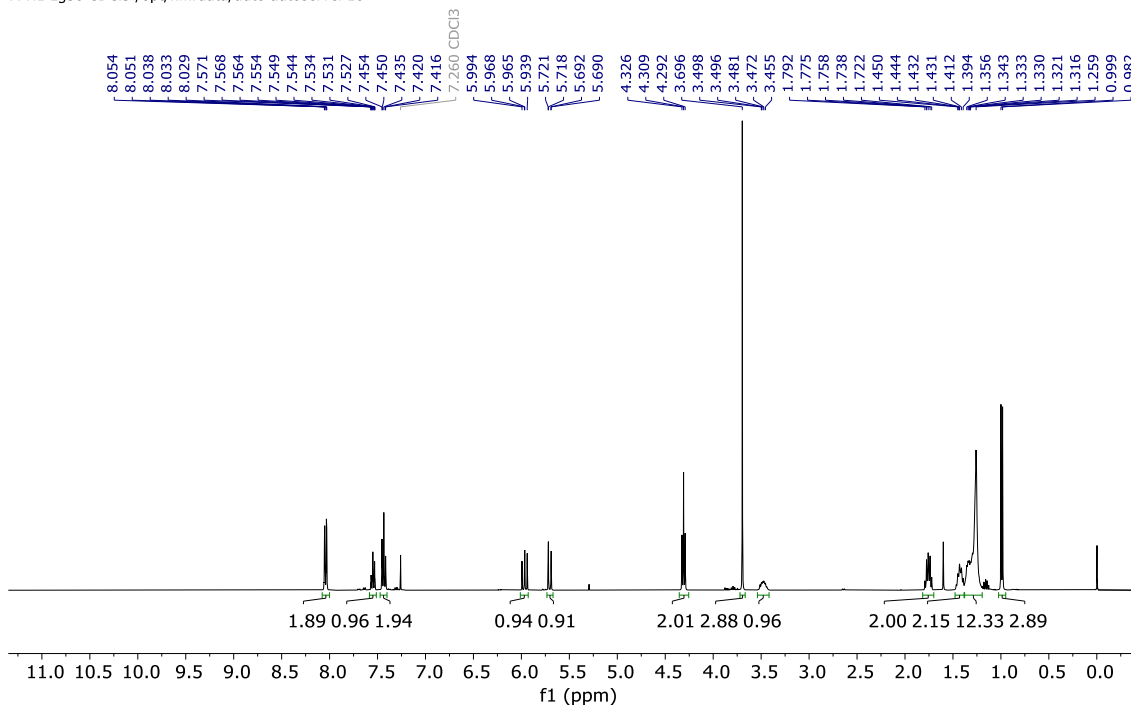


23030566_B400FA_17032023_LRG353CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23030566
 Usuari: san / Mostra: LRG353CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 17/03/2023 04:15:06 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

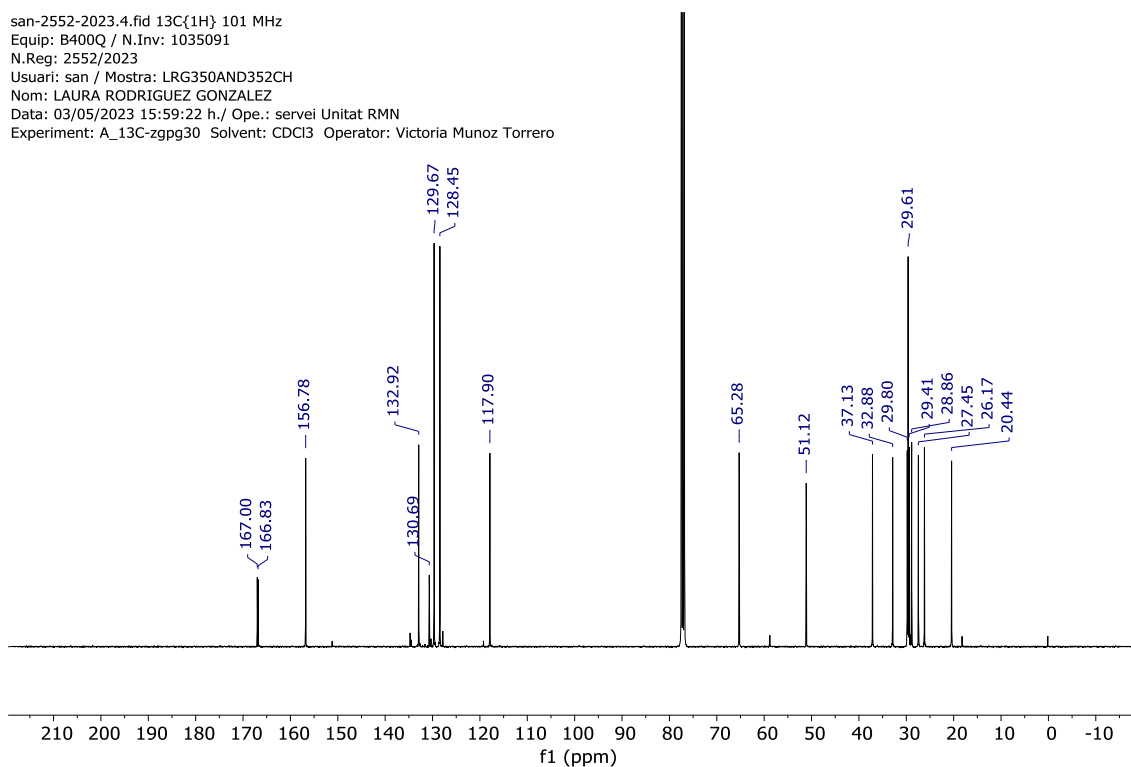


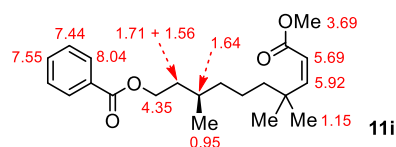


LRG350+352T21.1.fid 1H 400 MHz
Register 23050015
A-H1-zg30 CDCl₃ /opt/nmrdata/auto autoservei 16

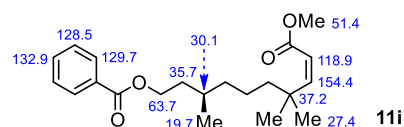
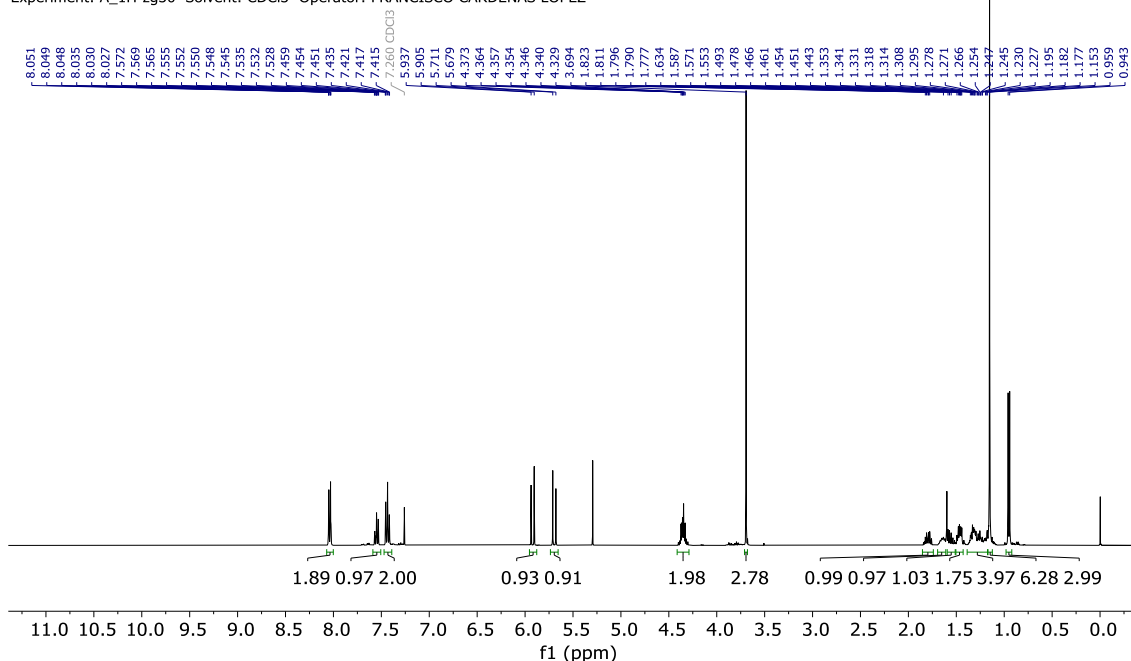


san-2552-2023.4.fid 13C{1H} 101 MHz
Equip: B400Q / N.Inv: 1035091
N.Reg: 2552/2023
Usuari: san / Mostra: LRG350AND352CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 03/05/2023 15:59:22 h./ Ope.: servei Unitat RMN
Experiment: A_13C-zgpg30 Solvent: CDCl₃ Operator: Victoria Munoz Torrero

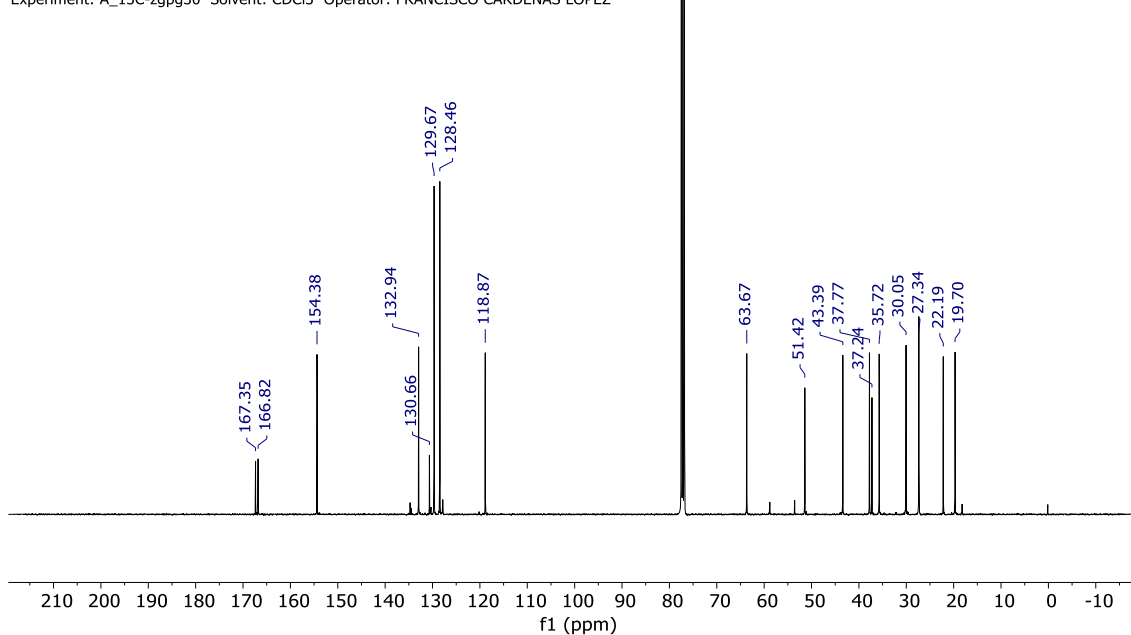


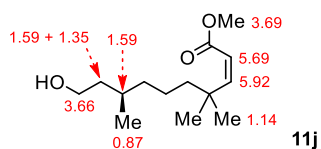


san-1891-2023.1.fid ^1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1891/2023
 Usuari: san / Mostra: LRG364CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 29/03/2023 17:19:06 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl_3 Operator: FRANCISCO CARDENAS LOPEZ

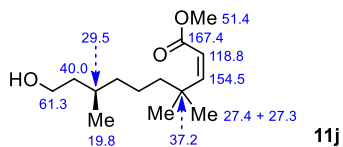
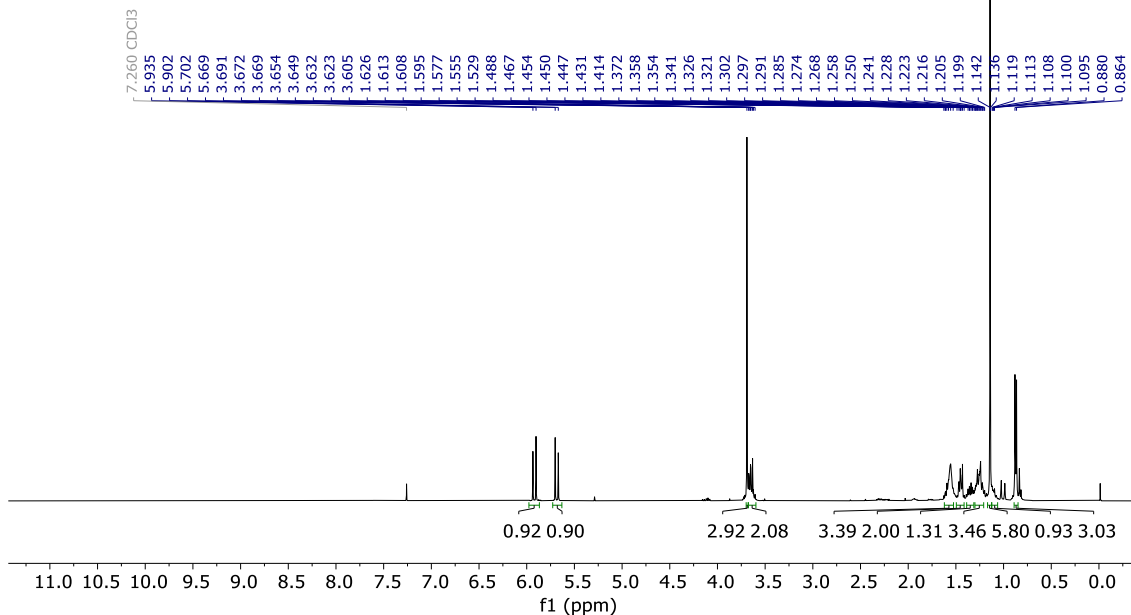


san-1891-2023.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 1891/2023
 Usuari: san / Mostra: LRG364CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 29/03/2023 17:19:06 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl_3 Operator: FRANCISCO CARDENAS LOPEZ

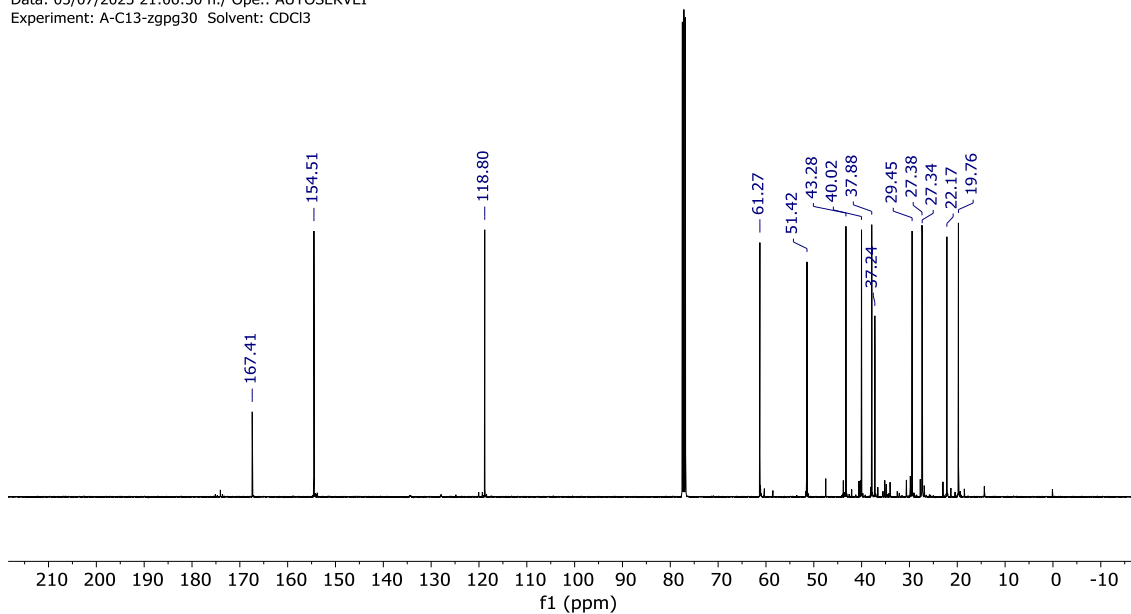




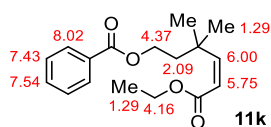
23070080_B400FA_05072023_LRG426COLT34.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070080
 Usuari: san / Mostra: LRG426COLT34
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 05/07/2023 11:44:19 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



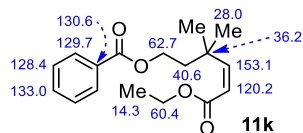
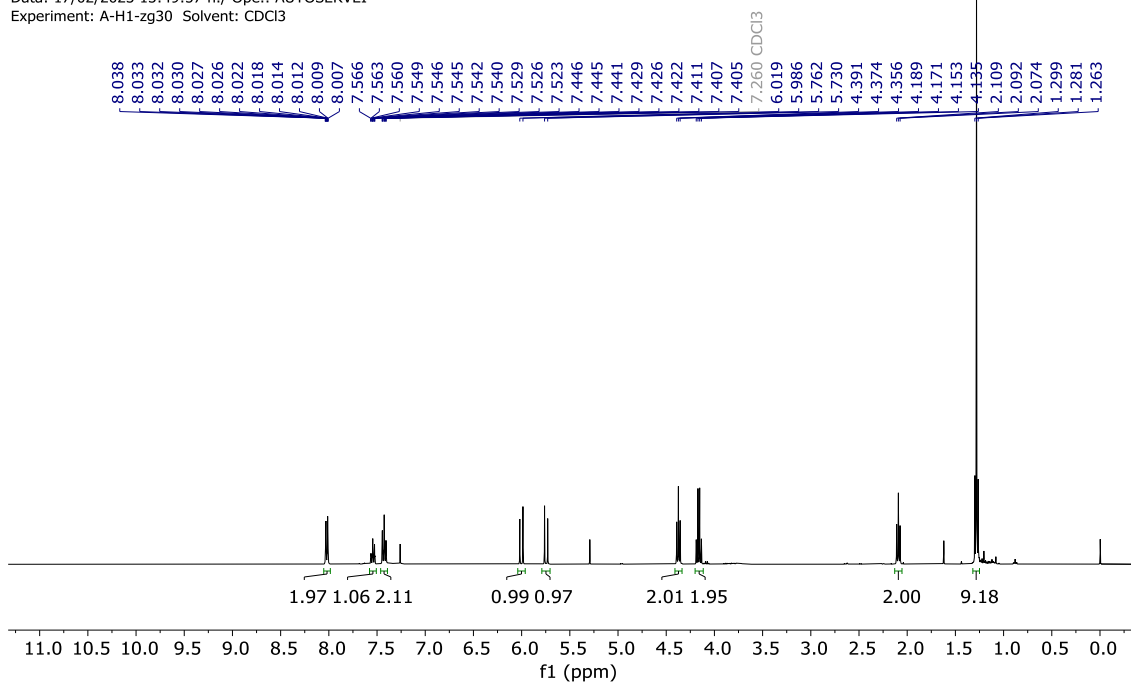
23070073_B400FA_05072023_LRG426CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070073
 Usuari: san / Mostra: LRG426CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 05/07/2023 21:06:50 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



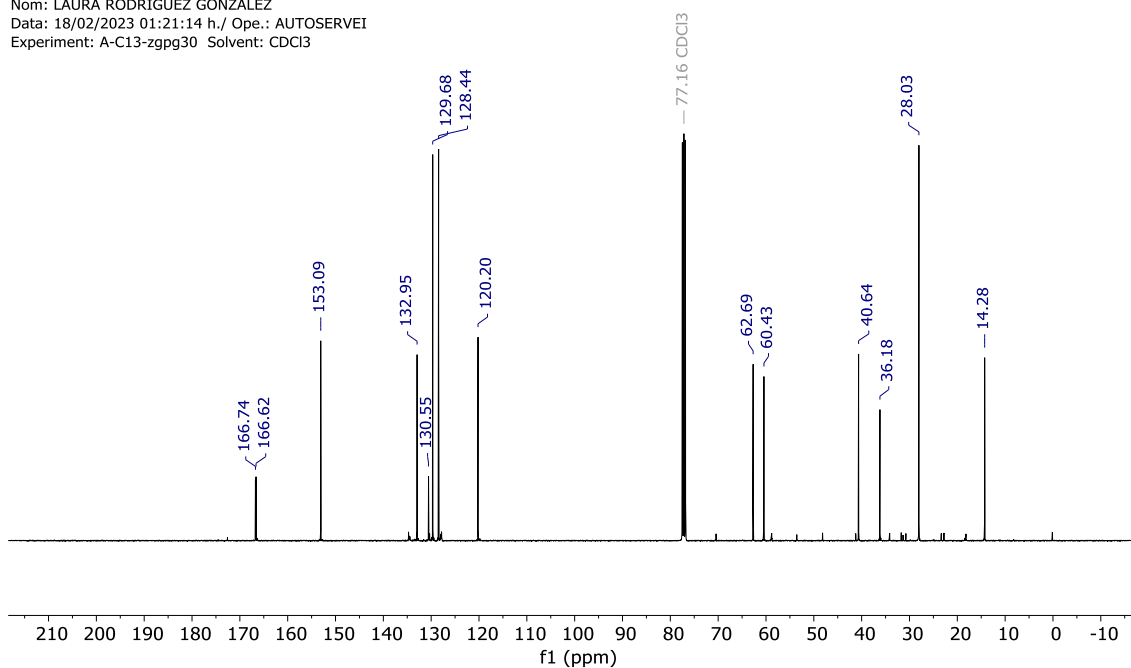
Experimental Section: Chapter 2

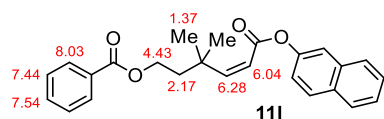


LRG323CHcomp.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23020706
 Usuari: san / Mostra: LRG323CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 17/02/2023 13:49:57 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

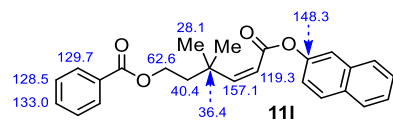
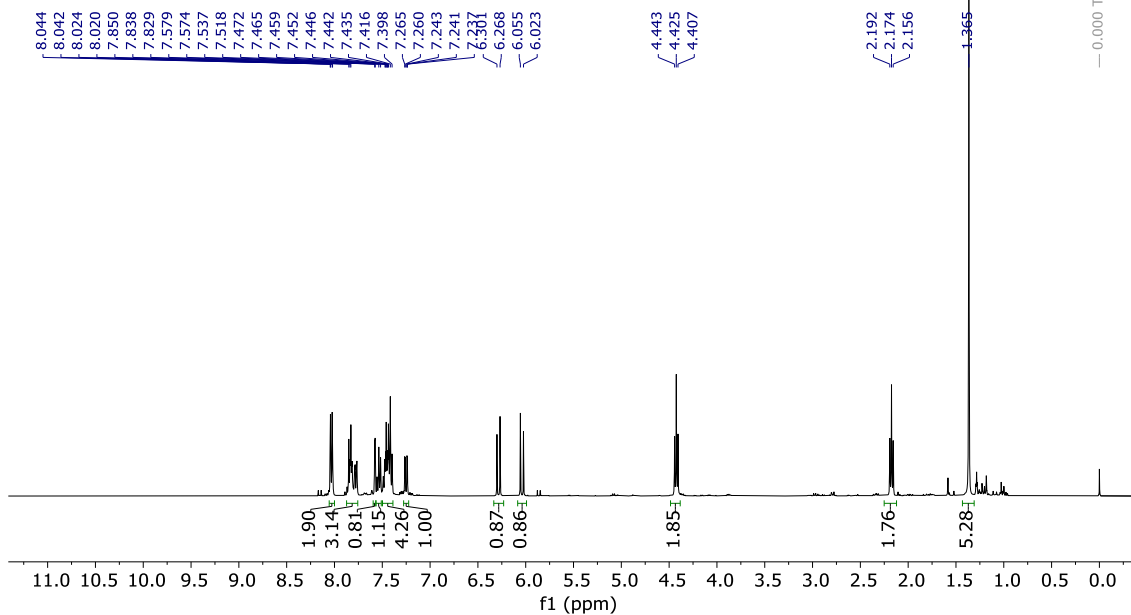


LRG323CHcomp.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23020706
 Usuari: san / Mostra: LRG323CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/02/2023 01:21:14 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

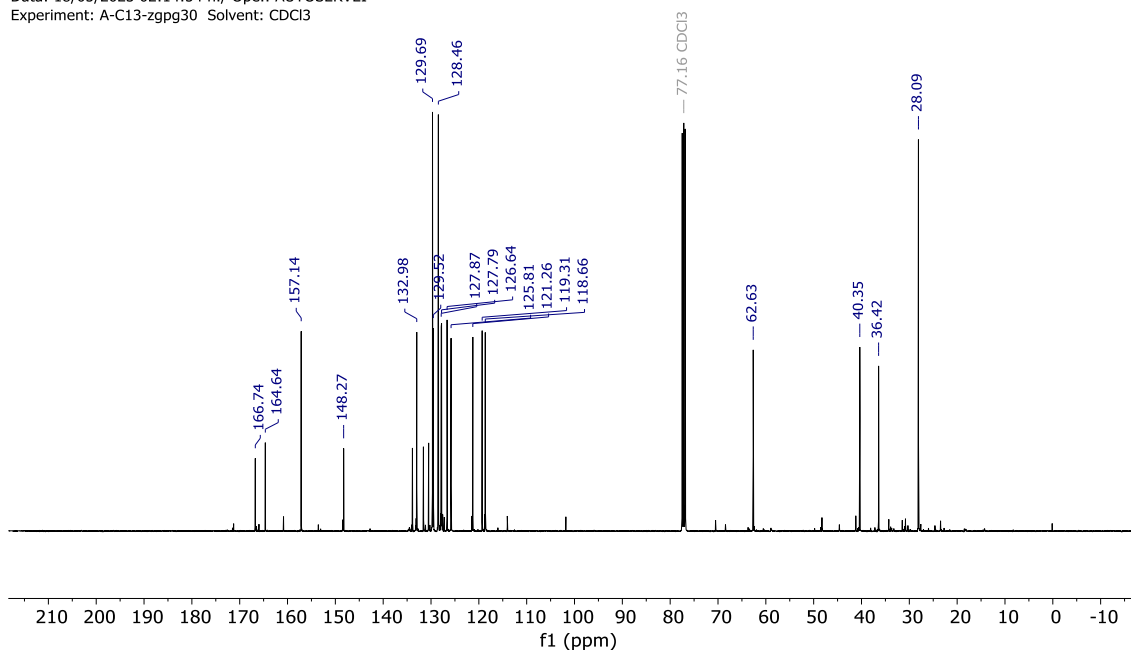


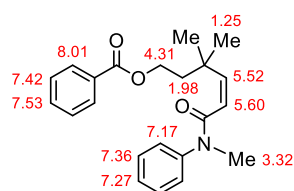


23050548_B400FA_18052023_LRG389COL1T25T26CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23050548
 Usuari: san / Mostra: LRG389COL1T25T26CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 17/05/2023 15:34:14 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



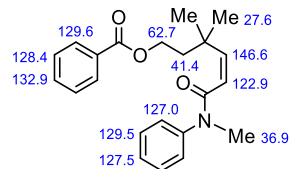
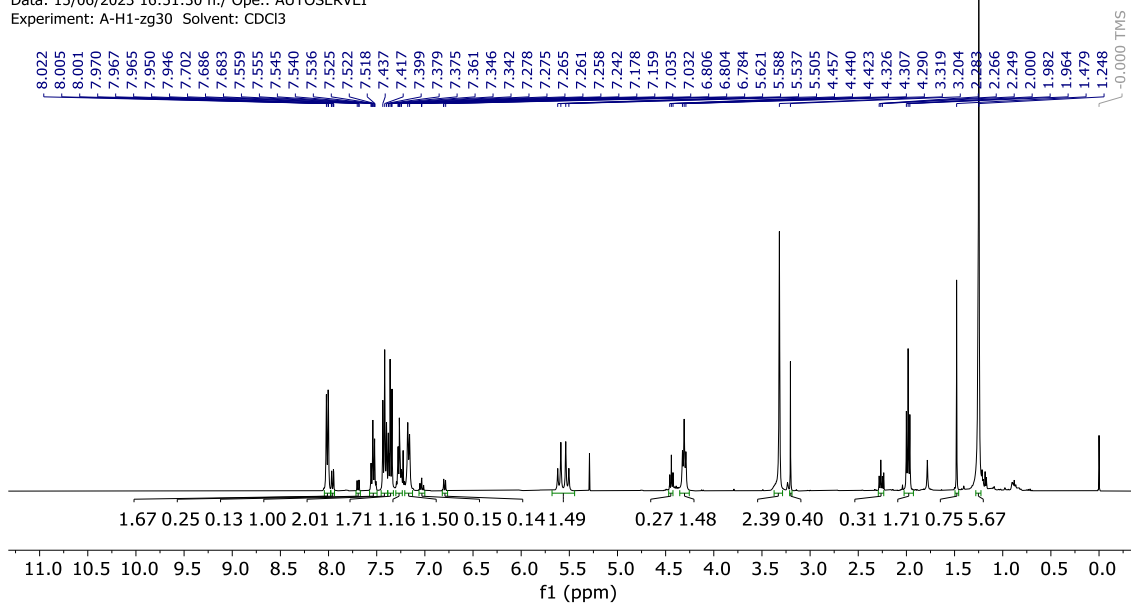
23050548_B400FA_18052023_LRG389COL1T25T26CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23050548
 Usuari: san / Mostra: LRG389COL1T25T26CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/05/2023 02:14:54 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃





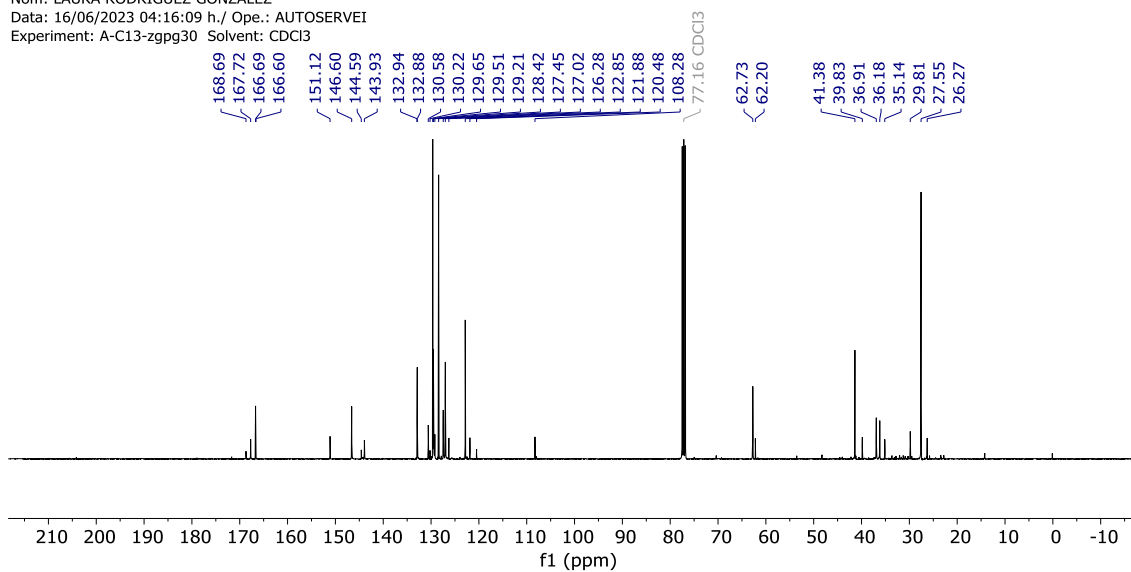
Major rotamer 11m

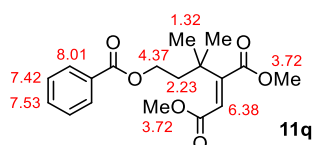
23060362_B400FA_15062023_LRG401RECT37T38.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060362
 Usuari: san / Mostra: LRG401RECT37T38
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/06/2023 16:51:30 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



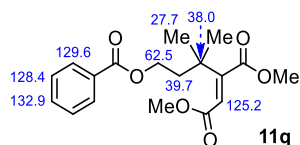
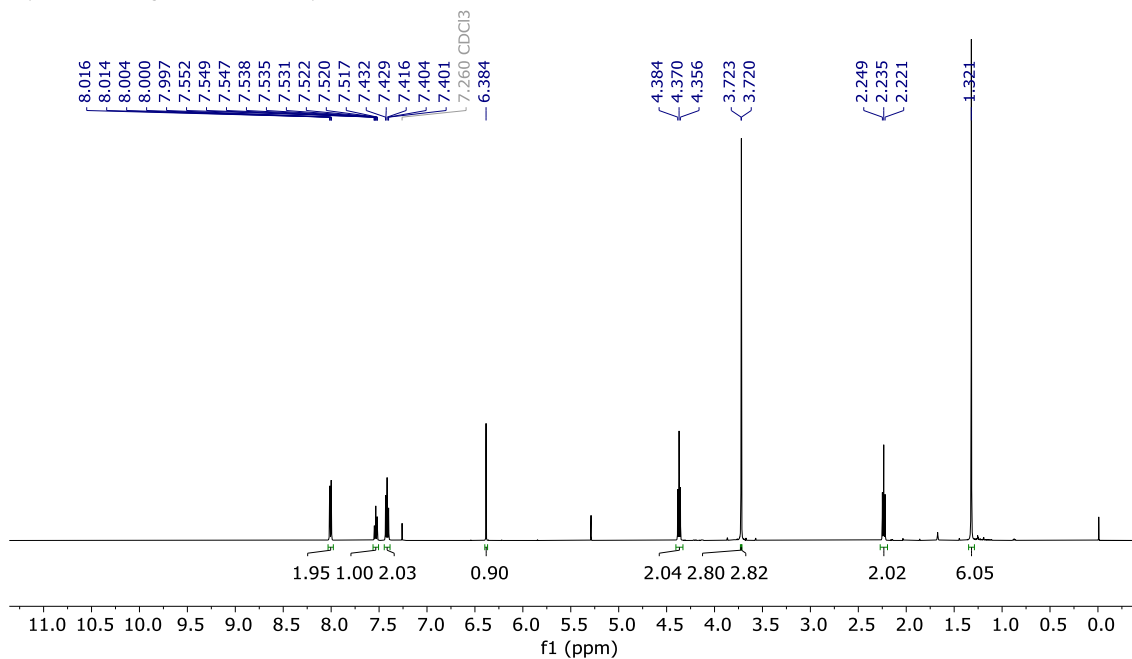
Major rotamer 11m

23060362_B400FA_16062023_LRG401RECT37T38.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060362
 Usuari: san / Mostra: LRG401RECT37T38
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 16/06/2023 04:16:09 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

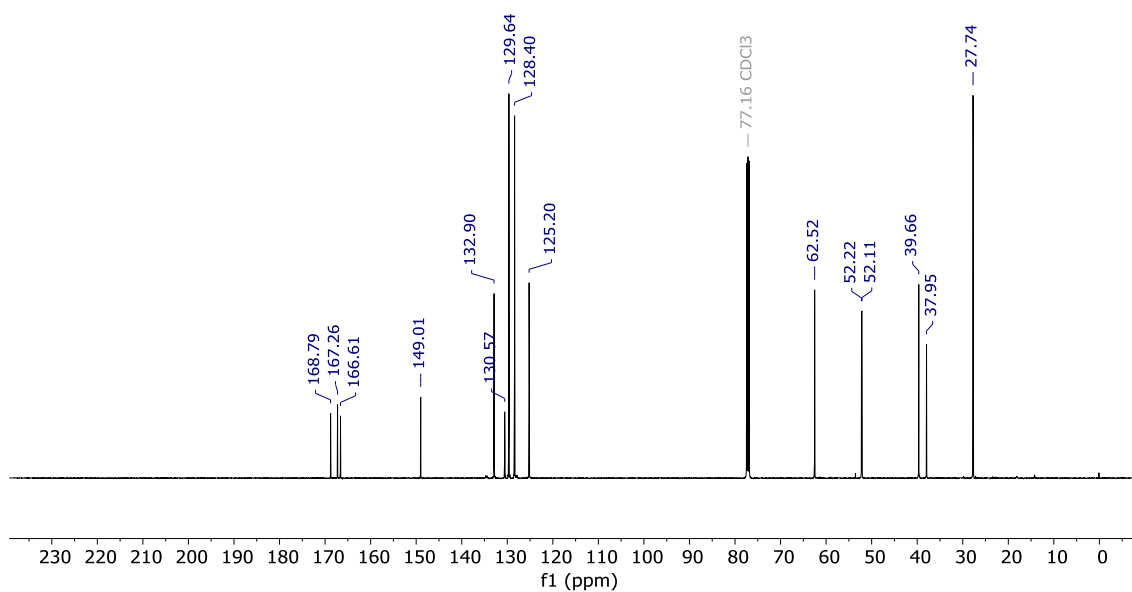




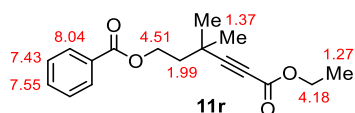
san-2381-2023.10.fid 1H 500 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 2381/2023
 Usuari: san / Mostra: LRG377CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/04/2023 00:33:49 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: M. ANTONIA MOLINS



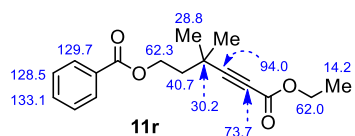
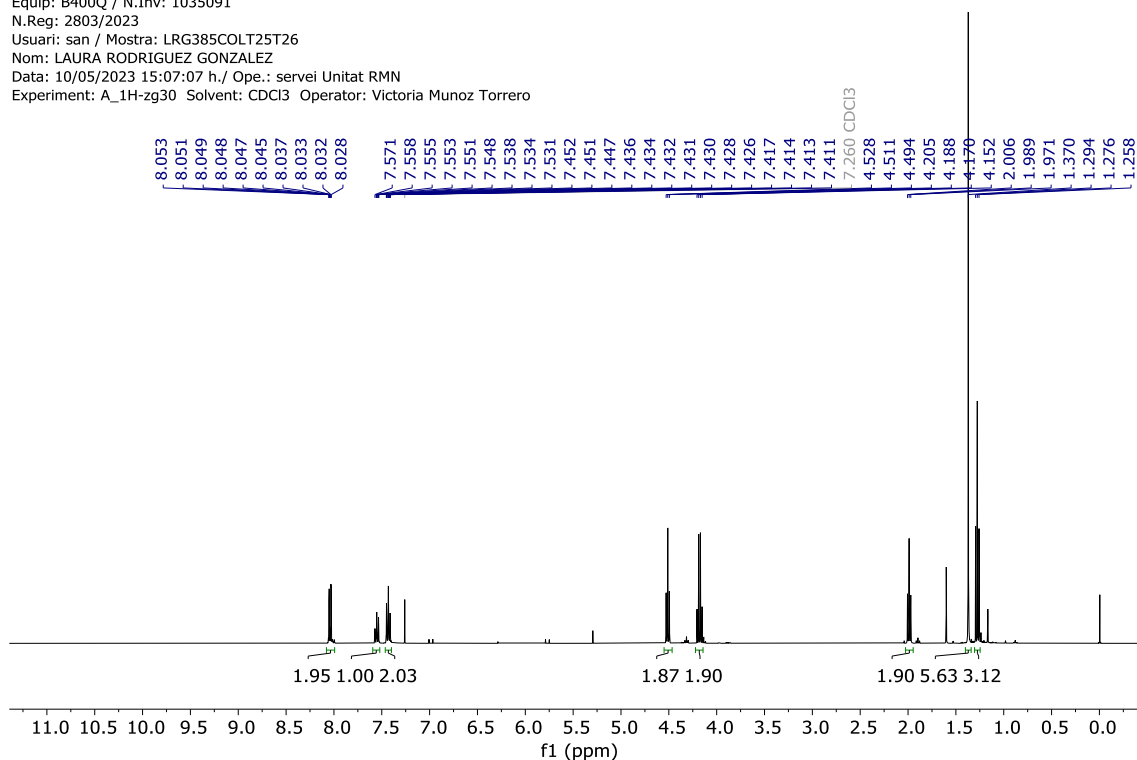
2604230430-2381-2023_B500QA_26042023_LRG377CH.13.fid 13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 2381/2023
 Usuari: san / Mostra: LRG377CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/04/2023 01:55:38 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpgp30 Solvent: CDCl₃ Operator: M. ANTONIA MOLINS



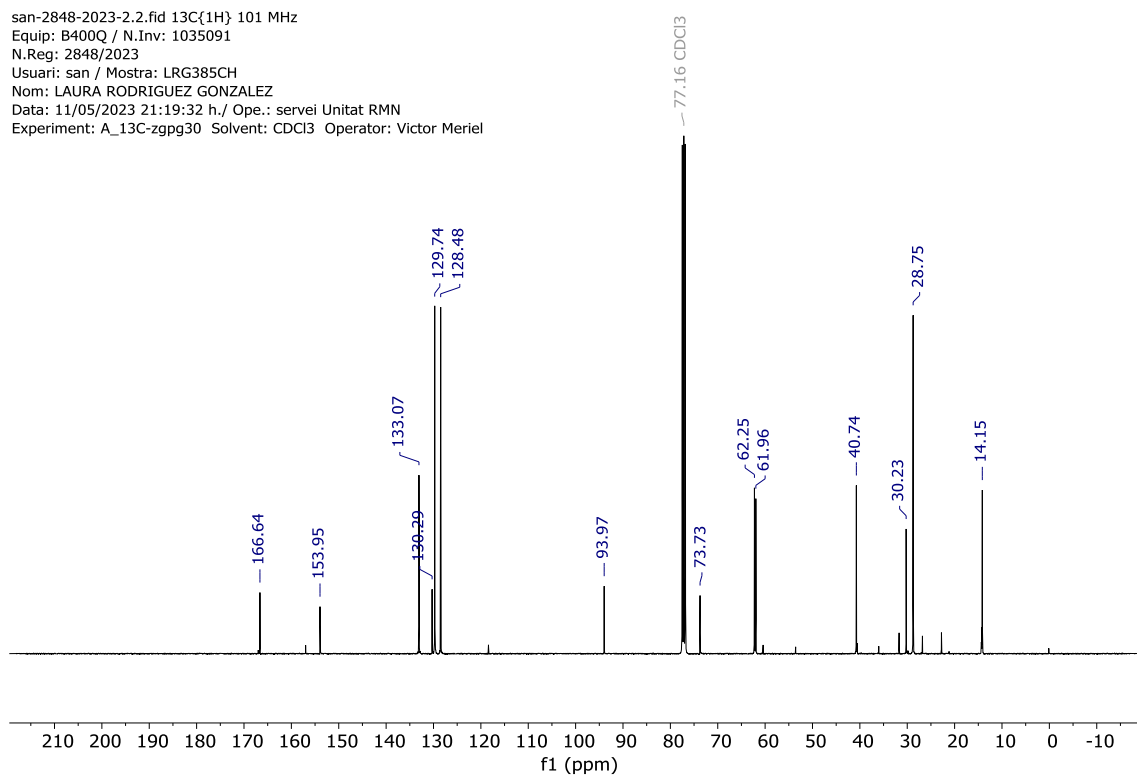
Experimental Section: Chapter 2

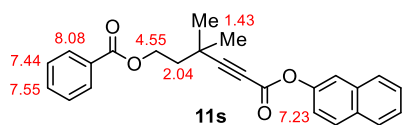


san-2803-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2803/2023
 Usuari: san / Mostra: LRG385COLT25T26
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/05/2023 15:07:07 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: Victoria Munoz Torrero

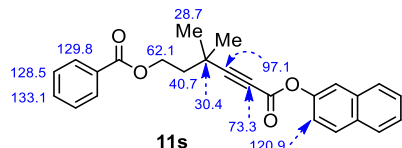
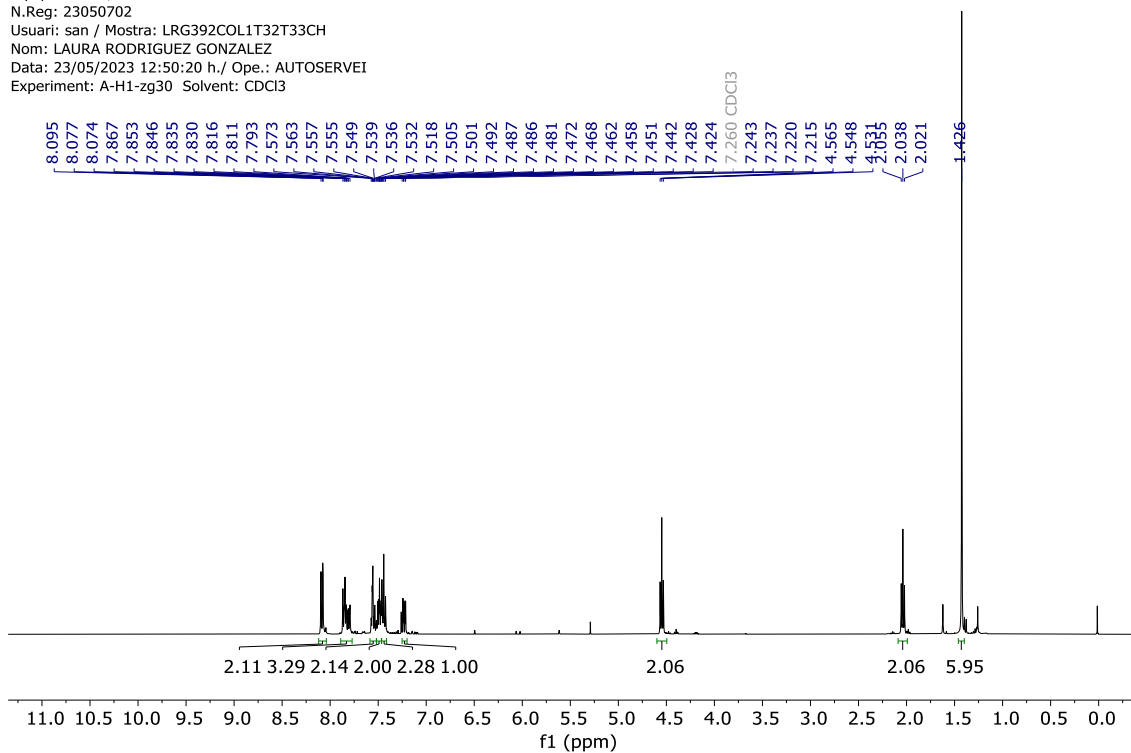


san-2848-2023-2.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2848/2023
 Usuari: san / Mostra: LRG385CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 11/05/2023 21:19:32 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl₃ Operator: Victor Meriel

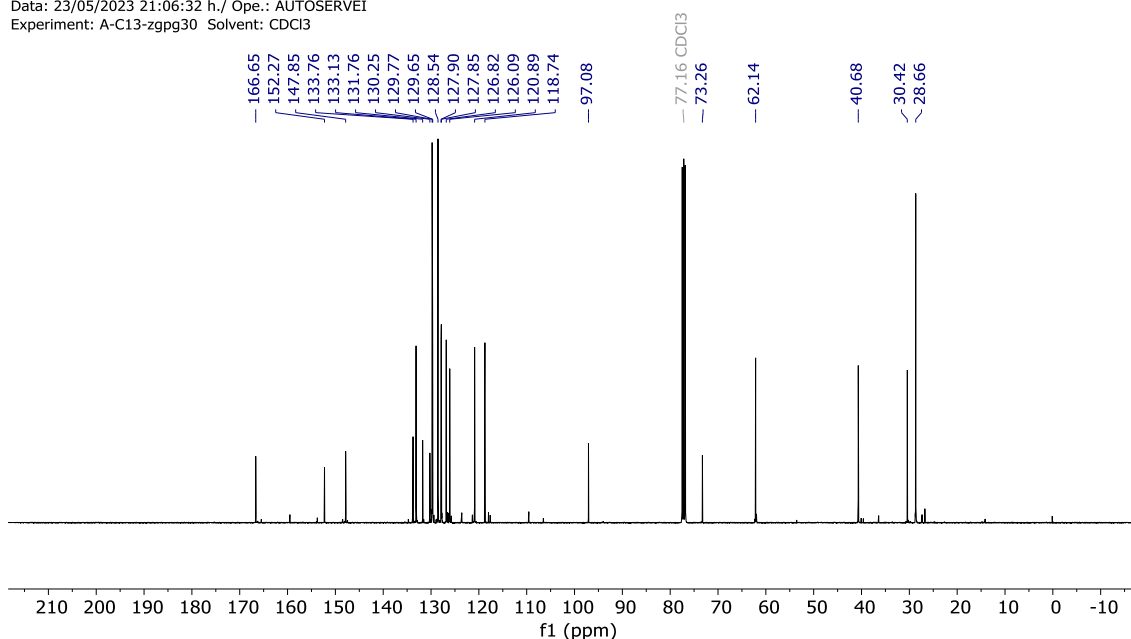




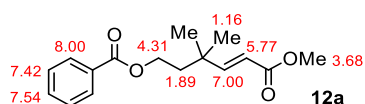
23050702_B400FA_23052023_LRG392COL1T32T33CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23050702
 Usuari: san / Mostra: LRG392COL1T32T33CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 23/05/2023 12:50:20 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



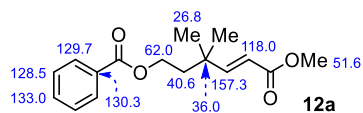
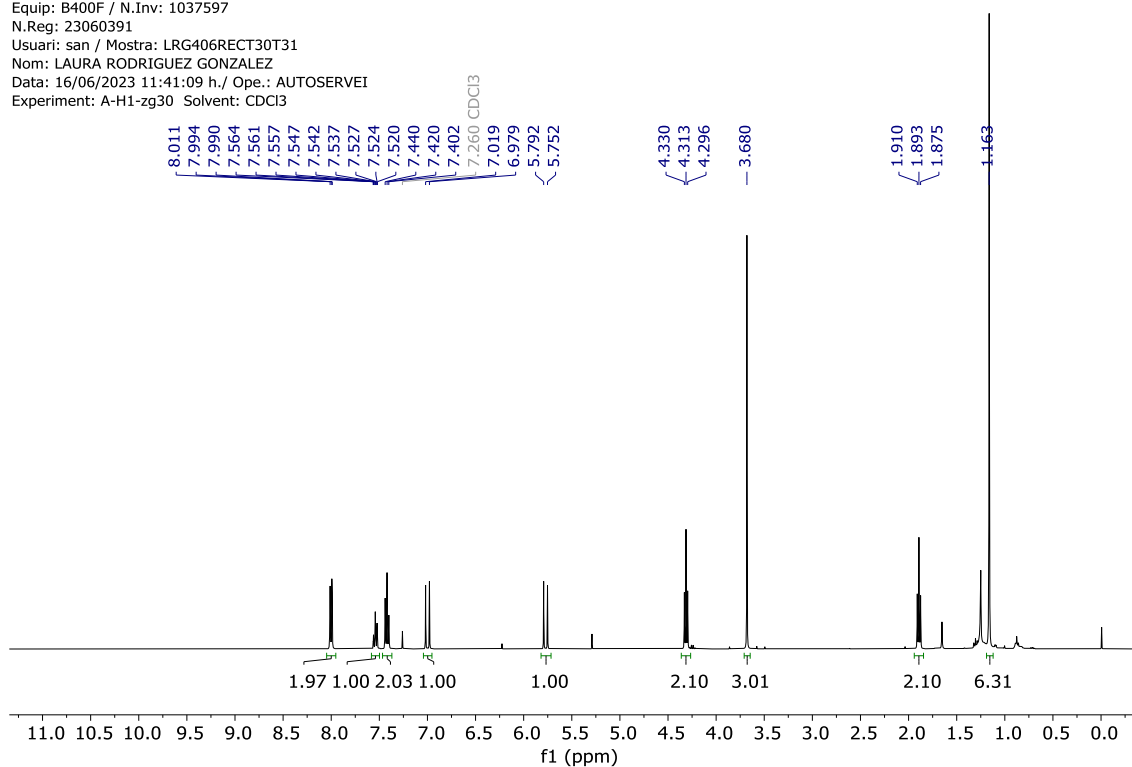
23050702_B400FA_23052023_LRG392COL1T32T33CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23050702
 Usuari: san / Mostra: LRG392COL1T32T33CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 23/05/2023 21:06:32 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpg30 Solvent: CDCl3



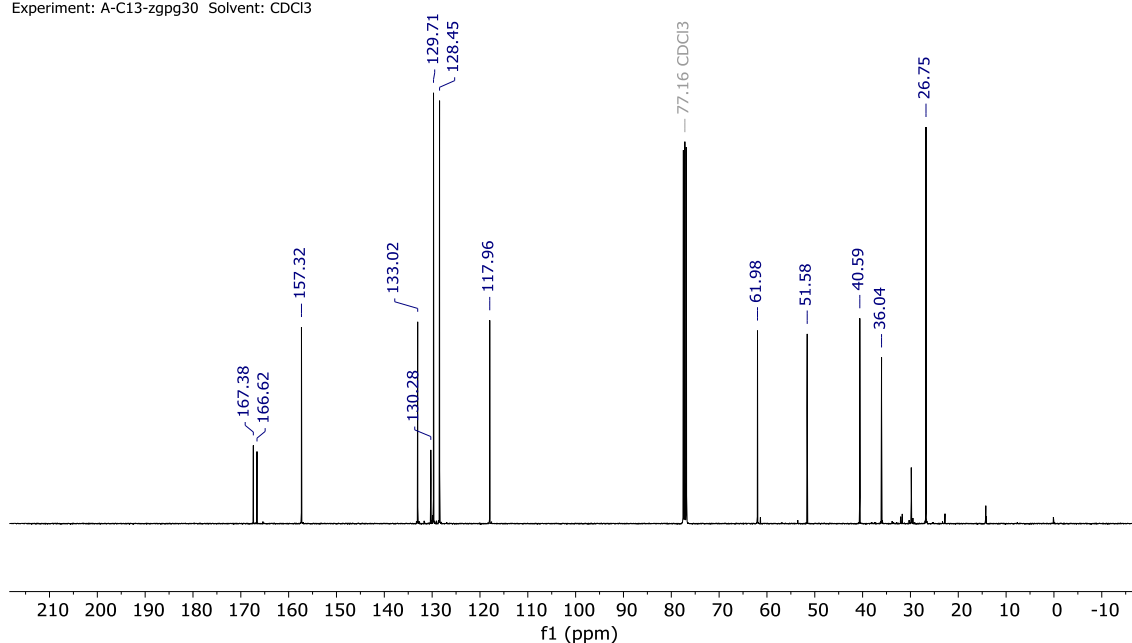
Experimental Section: Chapter 2

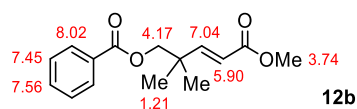


23060391_B400FA_16062023_LRG406RECT30T31.1.fid ^1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060391
 Usuari: san / Mostra: LRG406RECT30T31
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 16/06/2023 11:41:09 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl_3

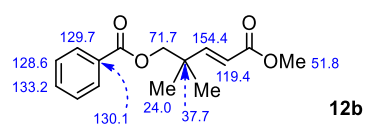
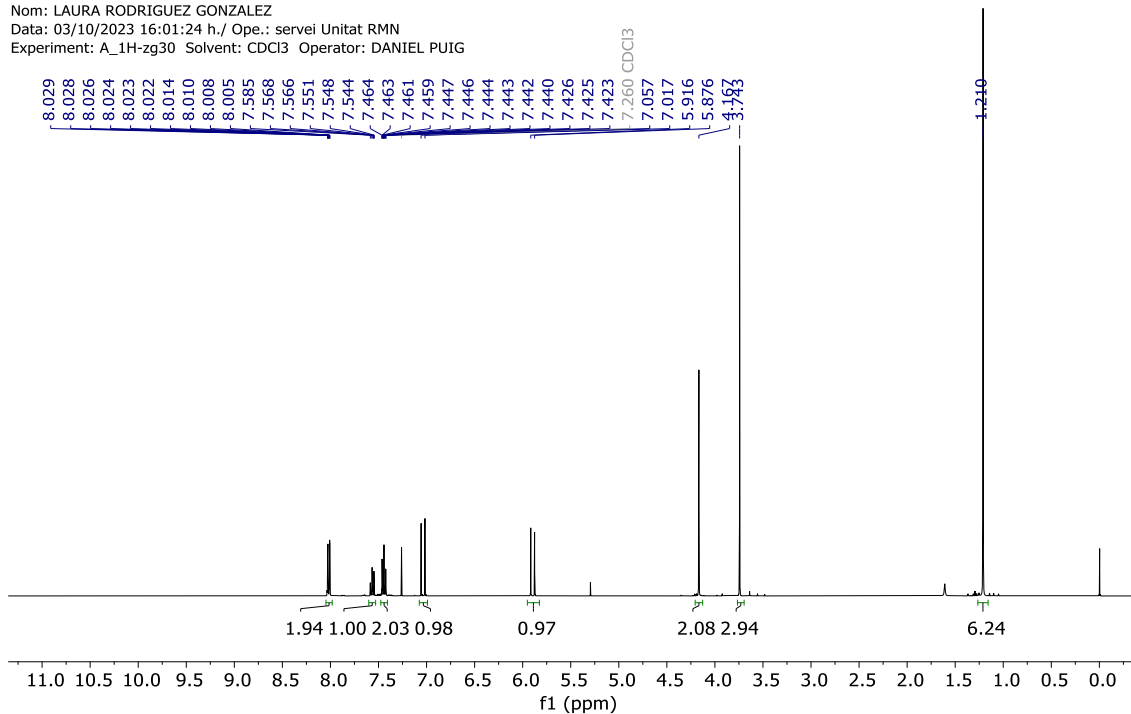


23060392_B400FA_17062023_LRG406RECT30T31CH.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060392
 Usuari: san / Mostra: LRG406RECT30T31CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 16/06/2023 22:46:14 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl_3

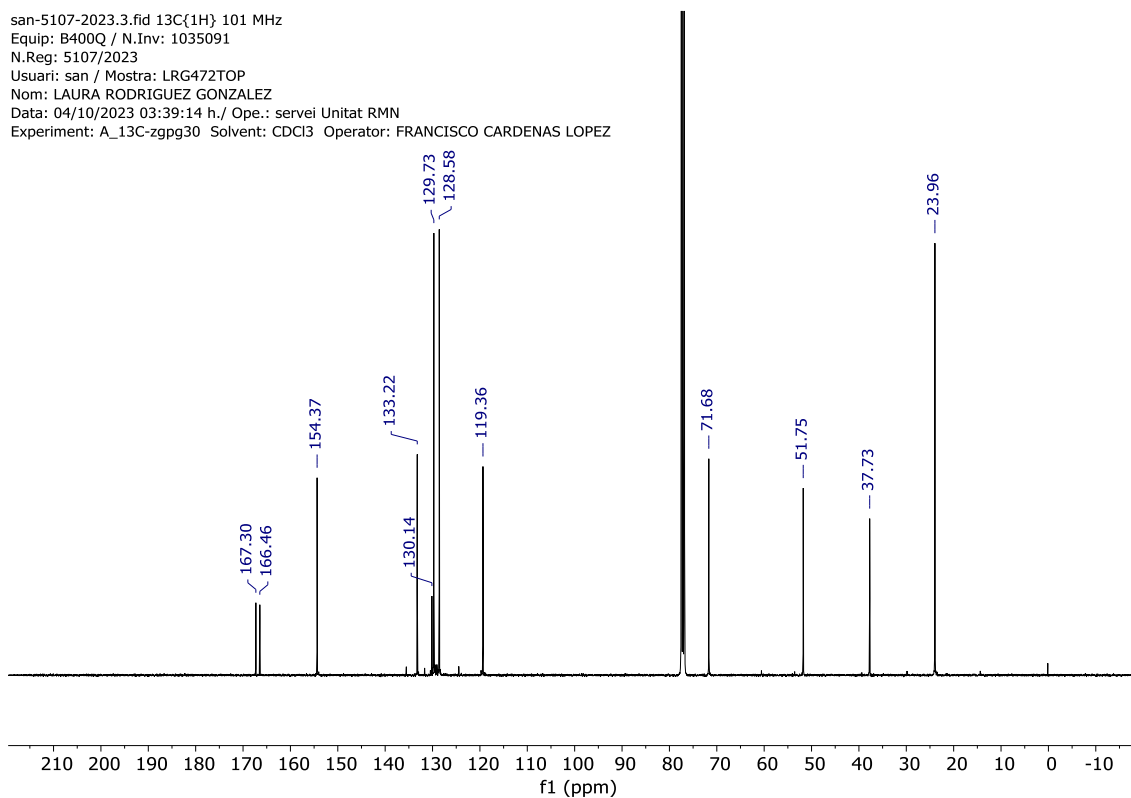


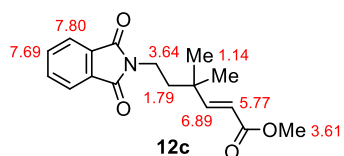
**12b**

san-5107-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 5107/2023
 Usuari: san / Mostra: LRG472TOP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/10/2023 16:01:24 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: DANIEL PUIG

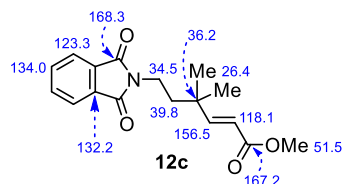
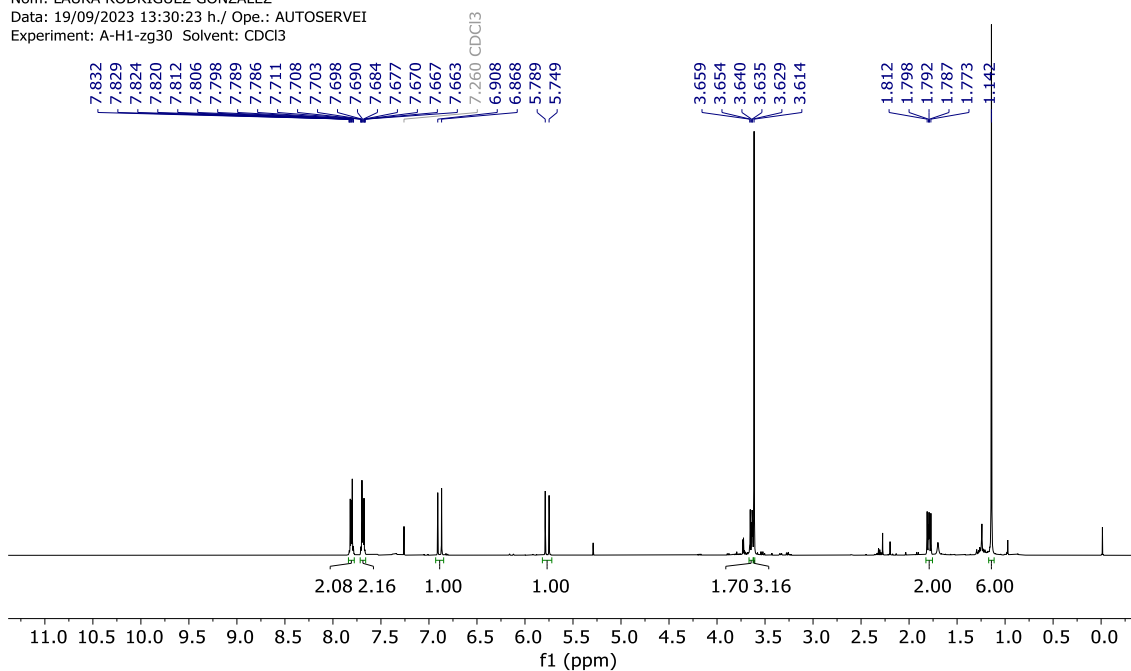
**12b**

san-5107-2023.3.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 5107/2023
 Usuari: san / Mostra: LRG472TOP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 04/10/2023 03:39:14 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpgg30 Solvent: CDCl₃ Operator: FRANCISCO CARDENAS LOPEZ

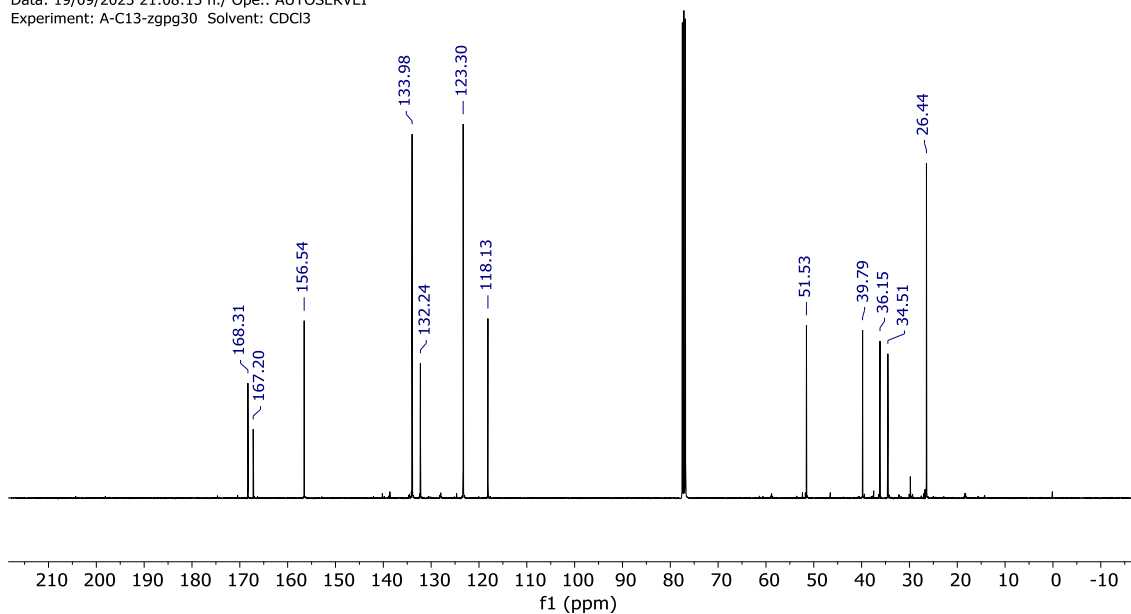




23090335_B400FA_19092023_LRG456COLT34.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23090335
 Usuari: san / Mostra: LRG456COLT34
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/09/2023 13:30:23 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



23090332_B400FA_19092023_LRG456CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23090332
 Usuari: san / Mostra: LRG456CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/09/2023 21:08:15 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



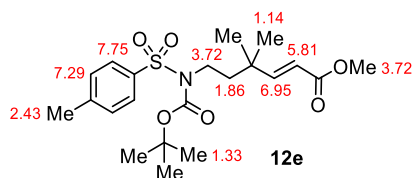


Data: 25/10/2023 11:39:26 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3

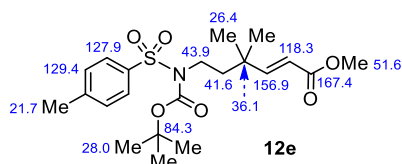
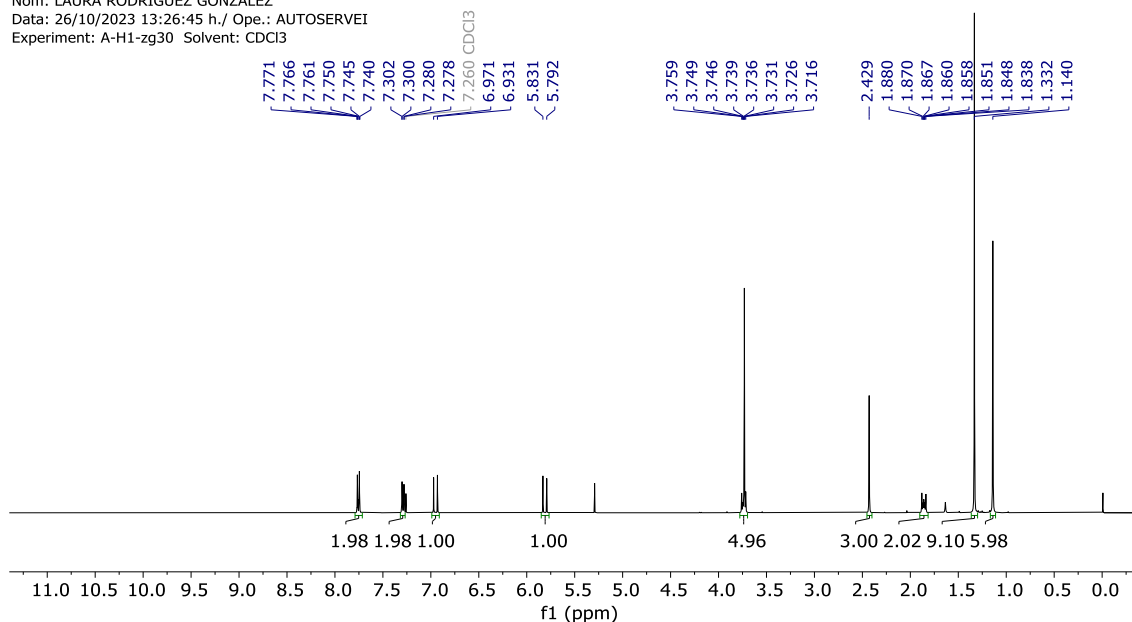


Data: 25/10/2023 22:04:40 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3

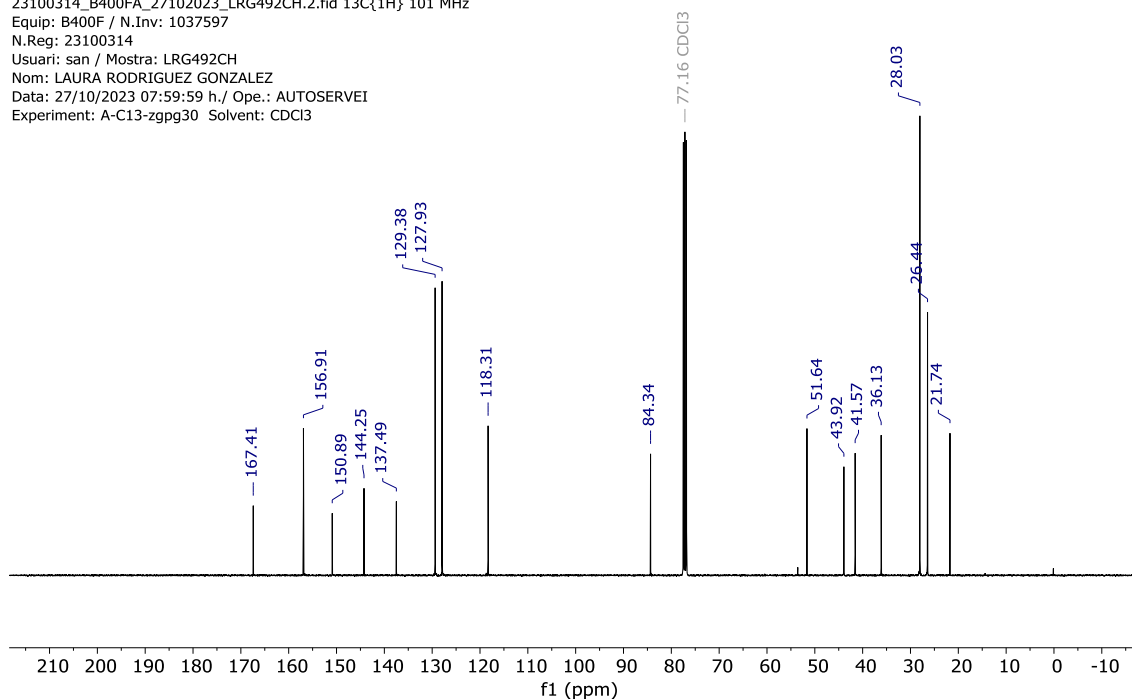


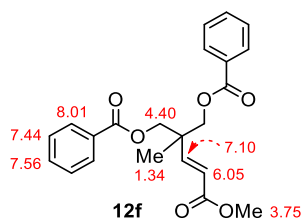


23100314_B400FA_26102023_LRG492CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100314
 Usuari: san / Mostra: LRG492CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 26/10/2023 13:26:45 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

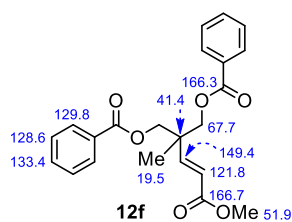
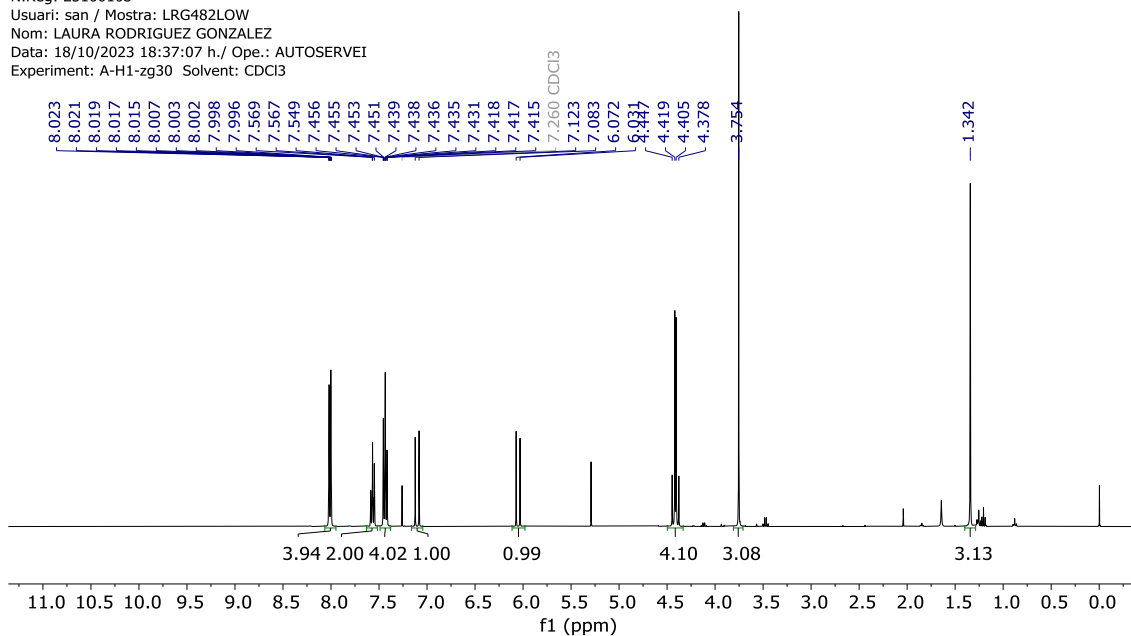


23100314_B400FA_27102023_LRG492CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100314
 Usuari: san / Mostra: LRG492CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/10/2023 07:59:59 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

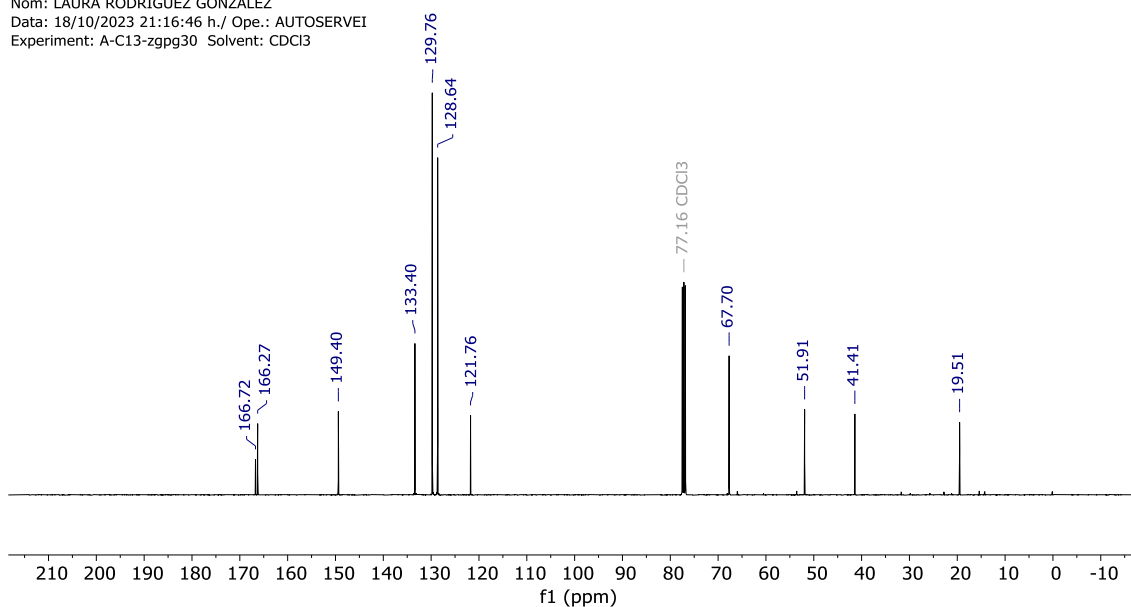


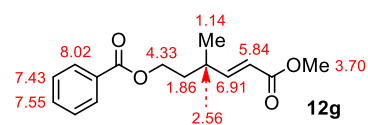


23100103_B400FA_18102023_LRG482LOW.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100103
 Usuari: san / Mostra: LRG482LOW
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/10/2023 18:37:07 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

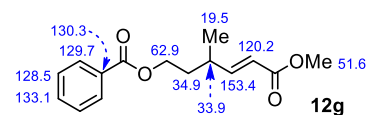
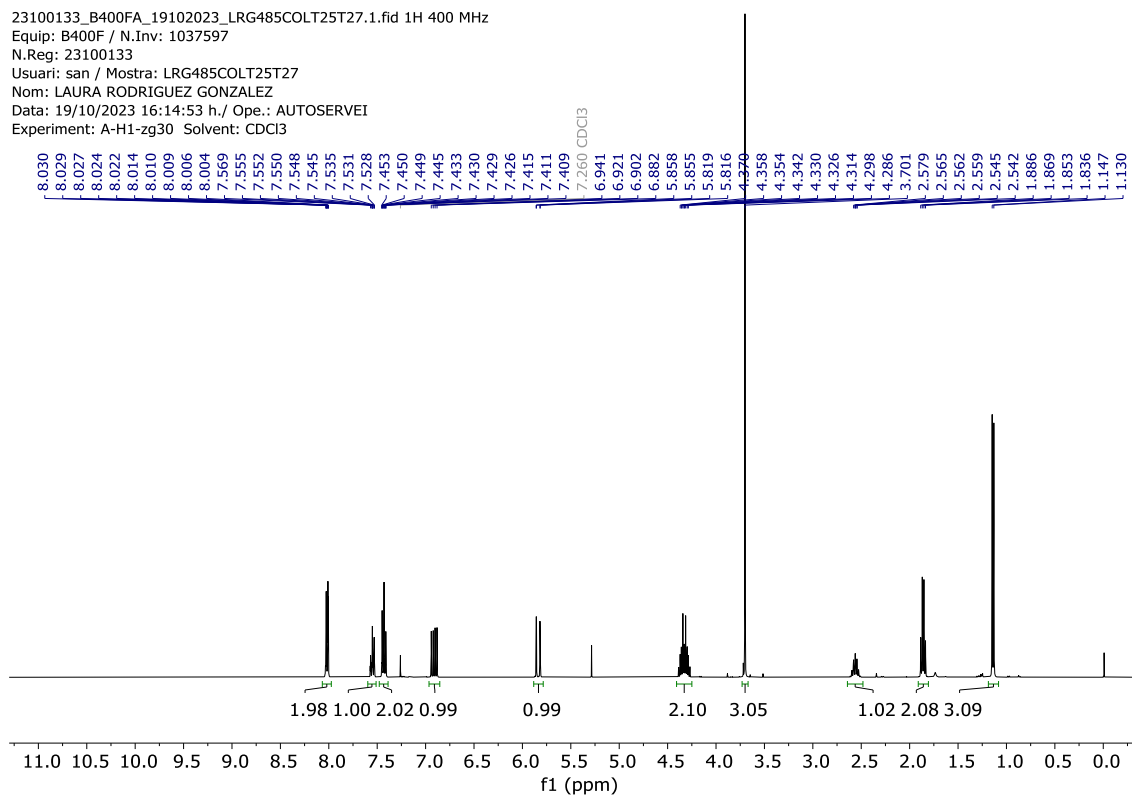


23100056_B400FA_18102023_LRG482CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100056
 Usuari: san / Mostra: LRG482CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/10/2023 21:16:46 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpgp30 Solvent: CDCl3

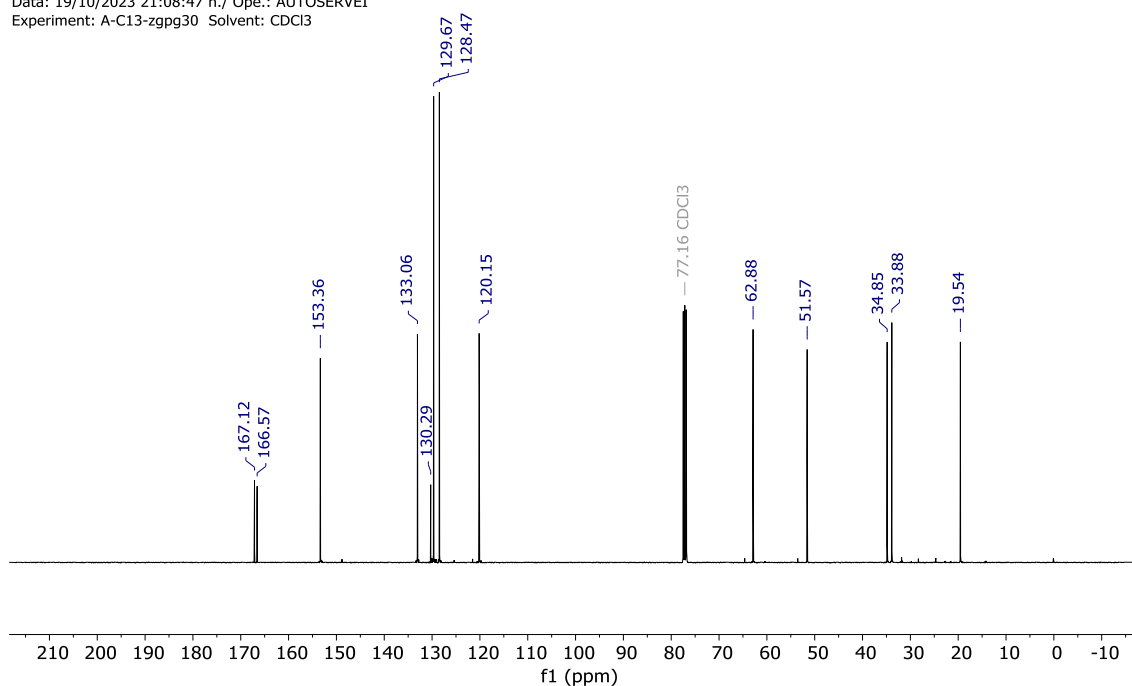


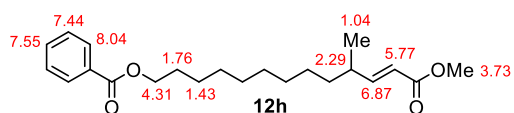


23100133_B400FA_19102023_LRG485COLT25T27.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100133
 Usuari: san / Mostra: LRG485COLT25T27
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/10/2023 16:14:53 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

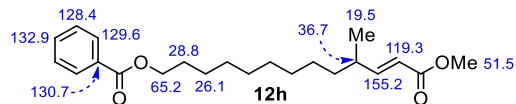
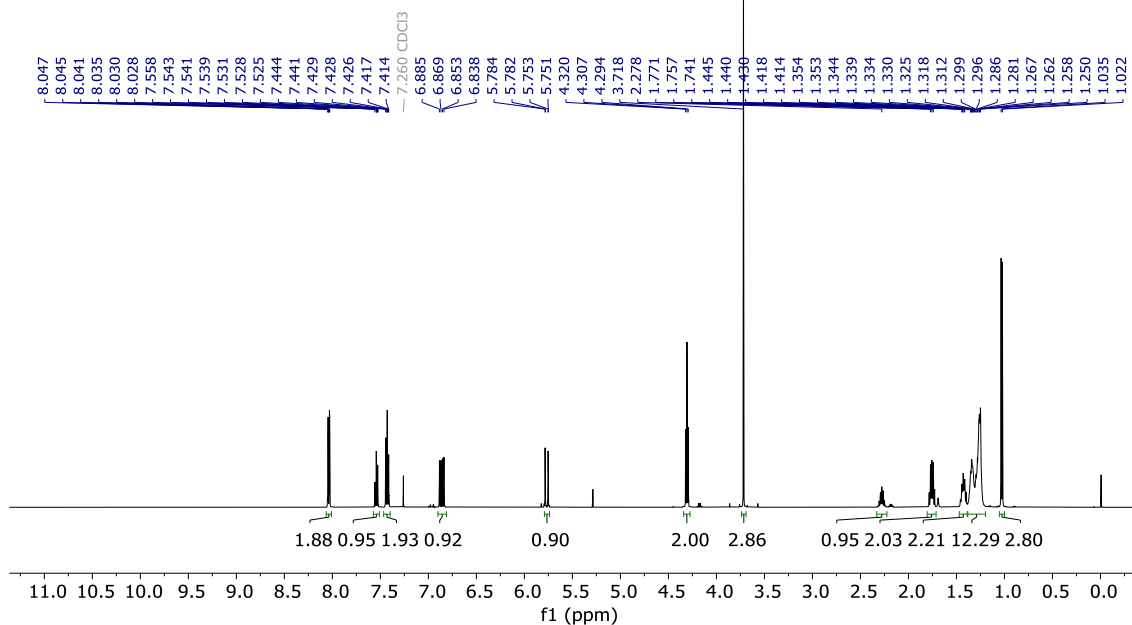


23100121_B400FA_19102023_LRG484CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100121
 Usuari: san / Mostra: LRG484CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/10/2023 21:08:47 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

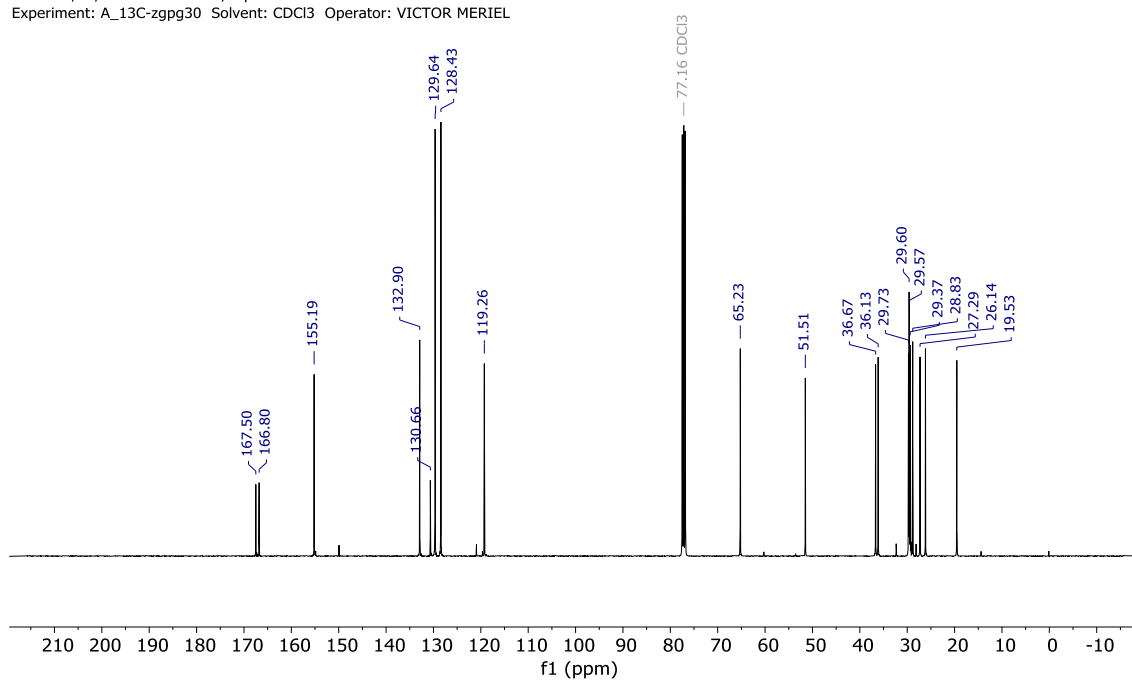




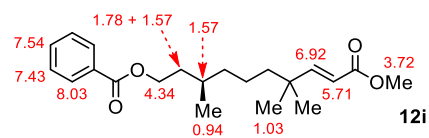
5488-2023_B500QA_10102023_LRG476COLT24T25.10.fid 1H 500 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 5488/2023
 Usuari: san / Mostra: LRG476COLT24T25
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/10/2023 11:07:42 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: DANIEL PUIG



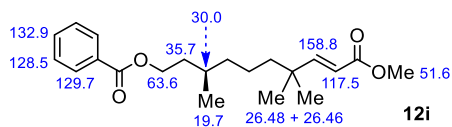
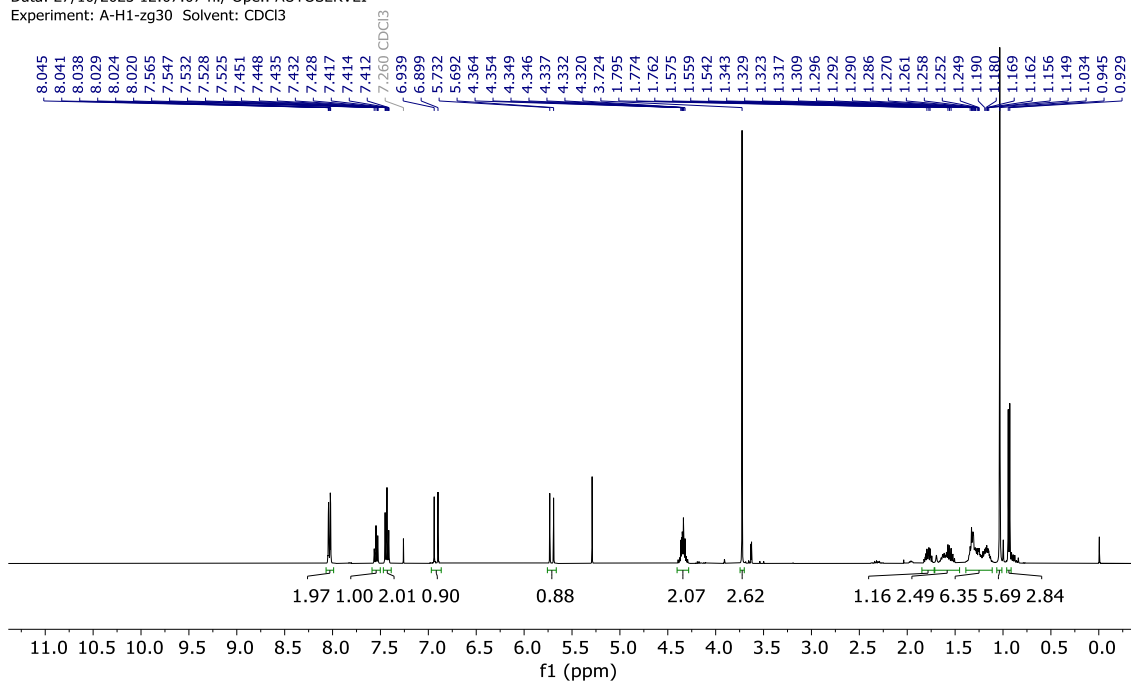
san-5488-2023.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 5488/2023
 Usuari: san / Mostra: LRG476COLT24T25
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/10/2023 17:03:23 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpgp30 Solvent: CDCl₃ Operator: VICTOR MERIEL



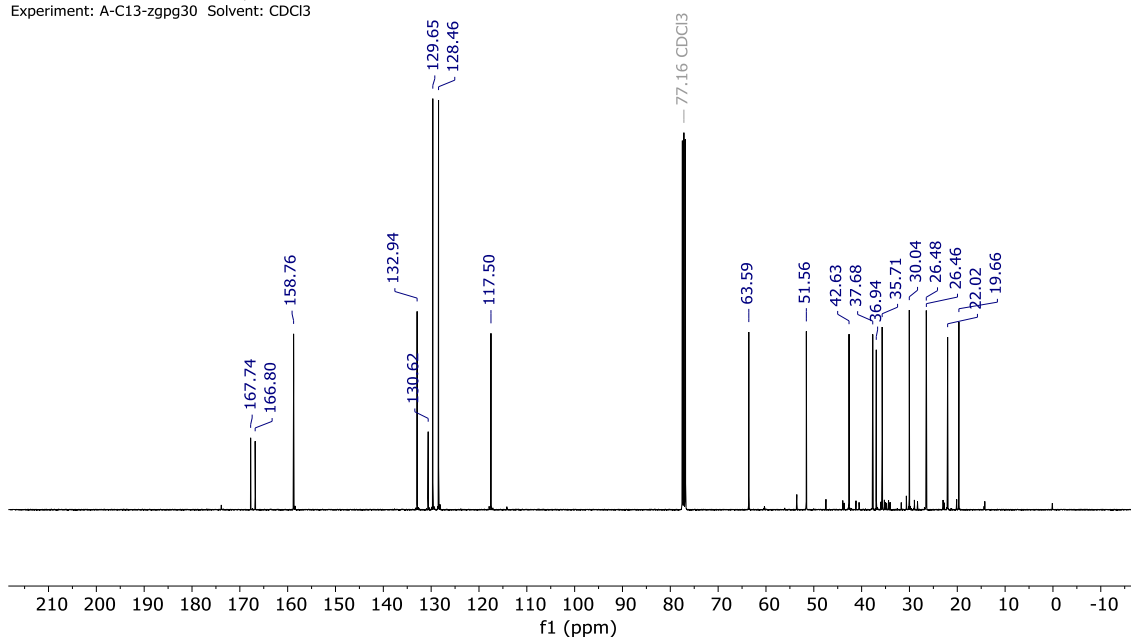
Experimental Section: Chapter 2

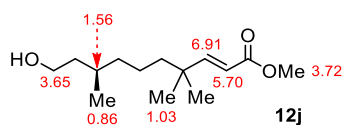


23100356_B400FA_27102023_LRG495COLT16T18.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100356
 Usuari: san / Mostra: LRG495COLT16T18
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/10/2023 12:07:07 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

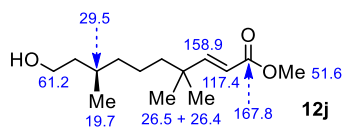
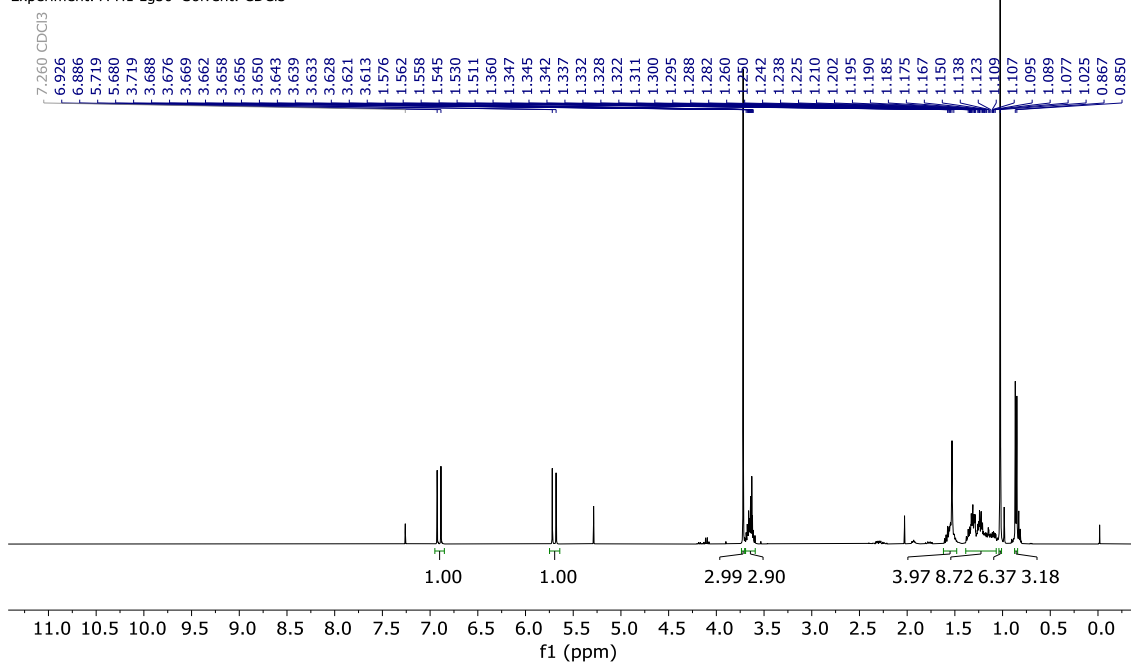


23100341_B400FA_27102023_LRG495CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23100341
 Usuari: san / Mostra: LRG495CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/10/2023 22:32:02 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

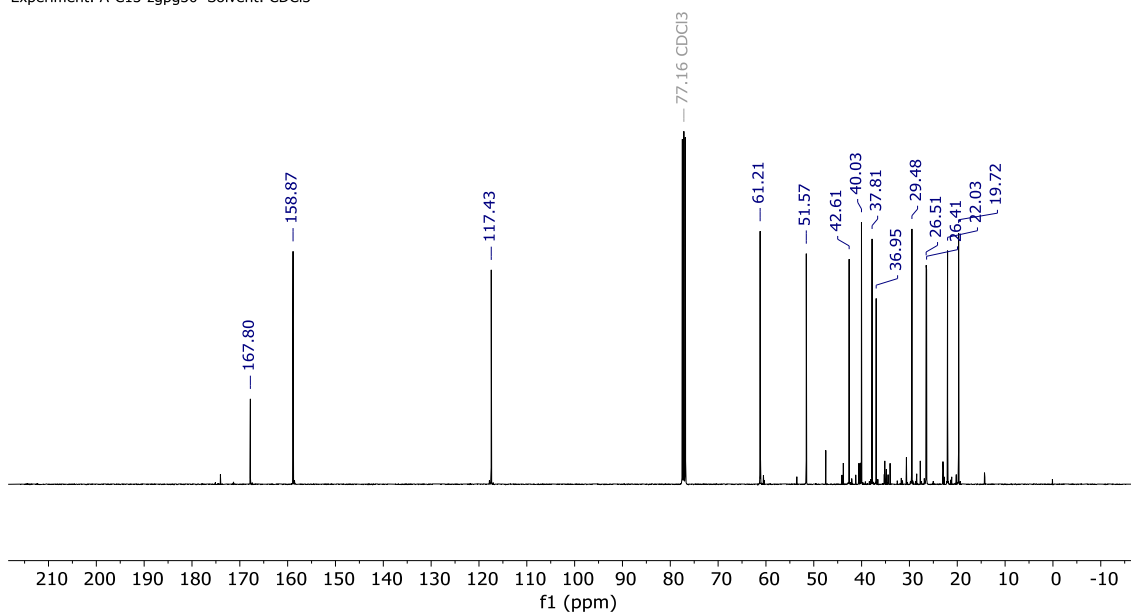




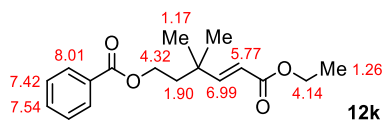
23110776_B400FA_28112023_LRG509COLT37T39.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23110776
 Usuari: san / Mostra: LRG509COLT37T39
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 28/11/2023 12:06:30 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



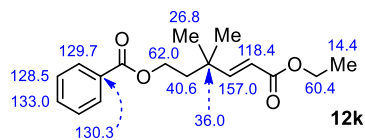
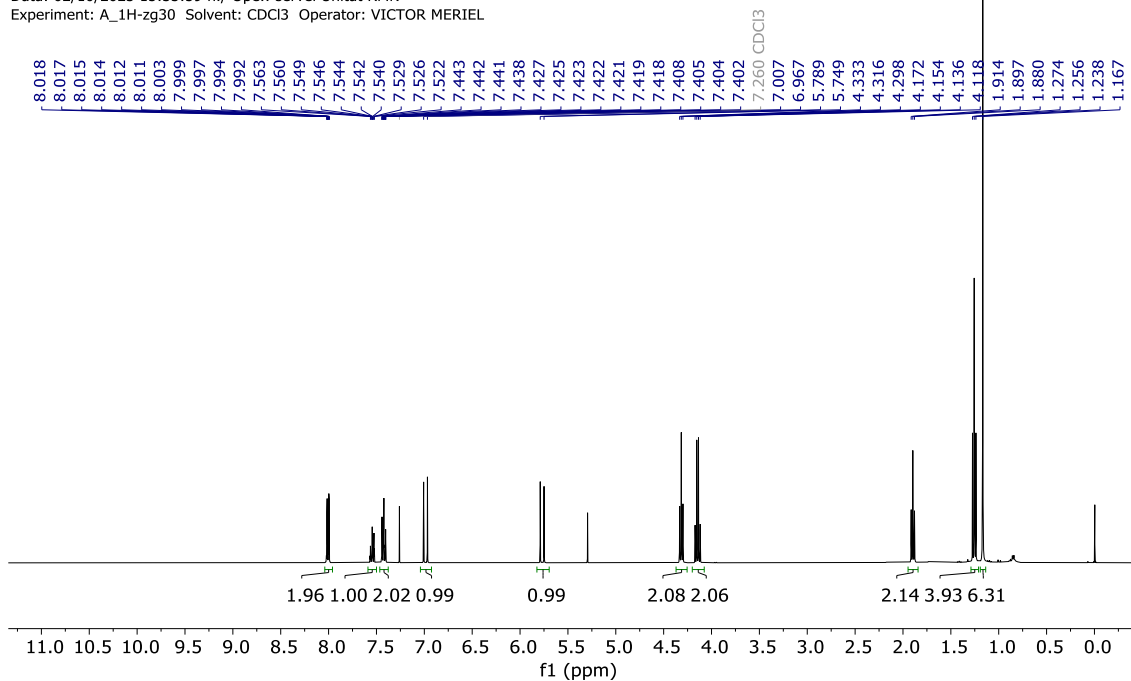
23110760_B400FA_28112023_LRG509CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23110760
 Usuari: san / Mostra: LRG509CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 28/11/2023 21:07:53 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpg30 Solvent: CDCl₃



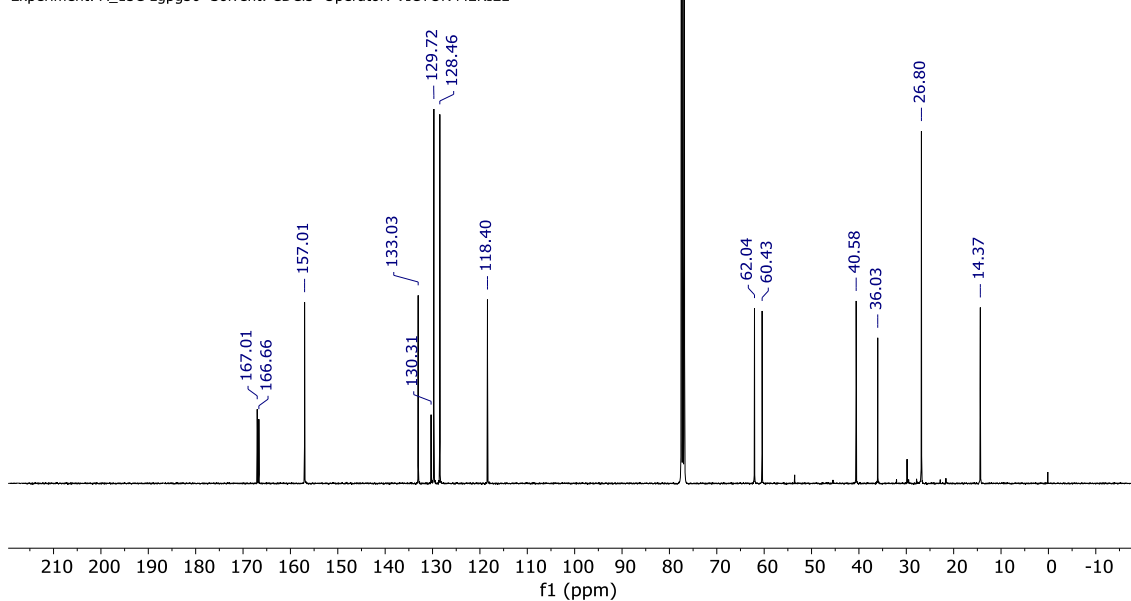
Experimental Section: Chapter 2

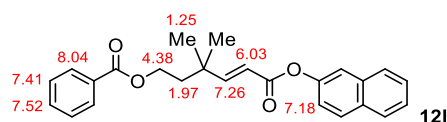


san-5030-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 5030/2023
 Usuari: san / Mostra: LRG470PROD
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 02/10/2023 15:33:59 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator: VICTOR MERIEL

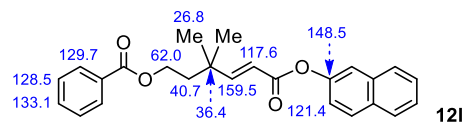
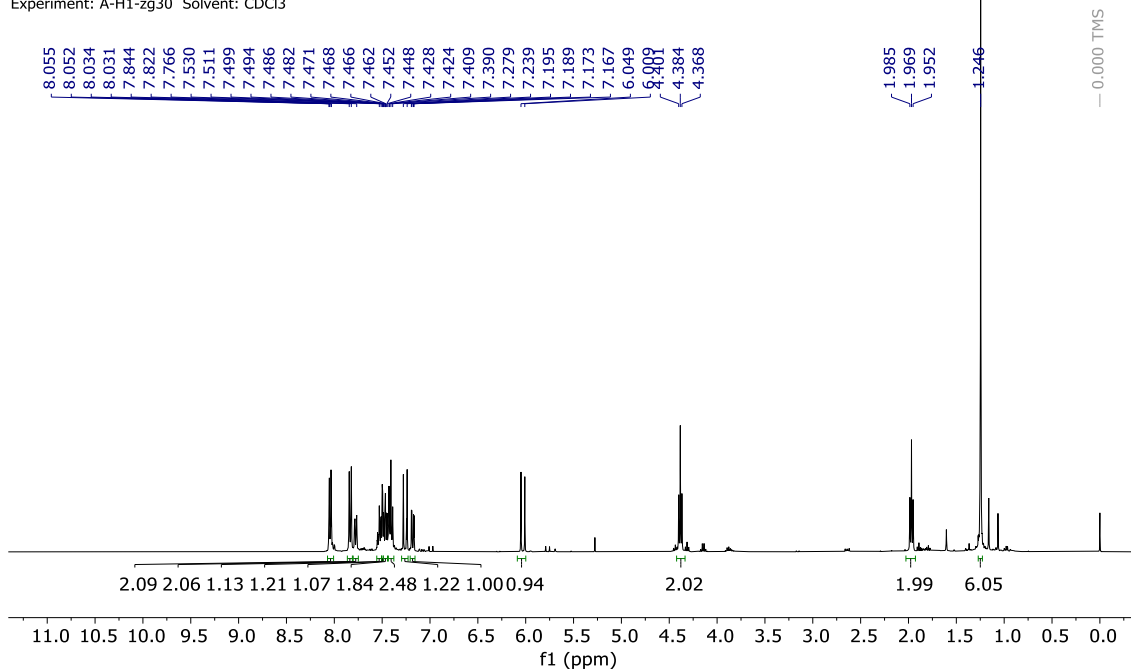


san-5030-2023.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 5030/2023
 Usuari: san / Mostra: LRG470PROD
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/10/2023 03:35:44 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator: VICTOR MERIEL

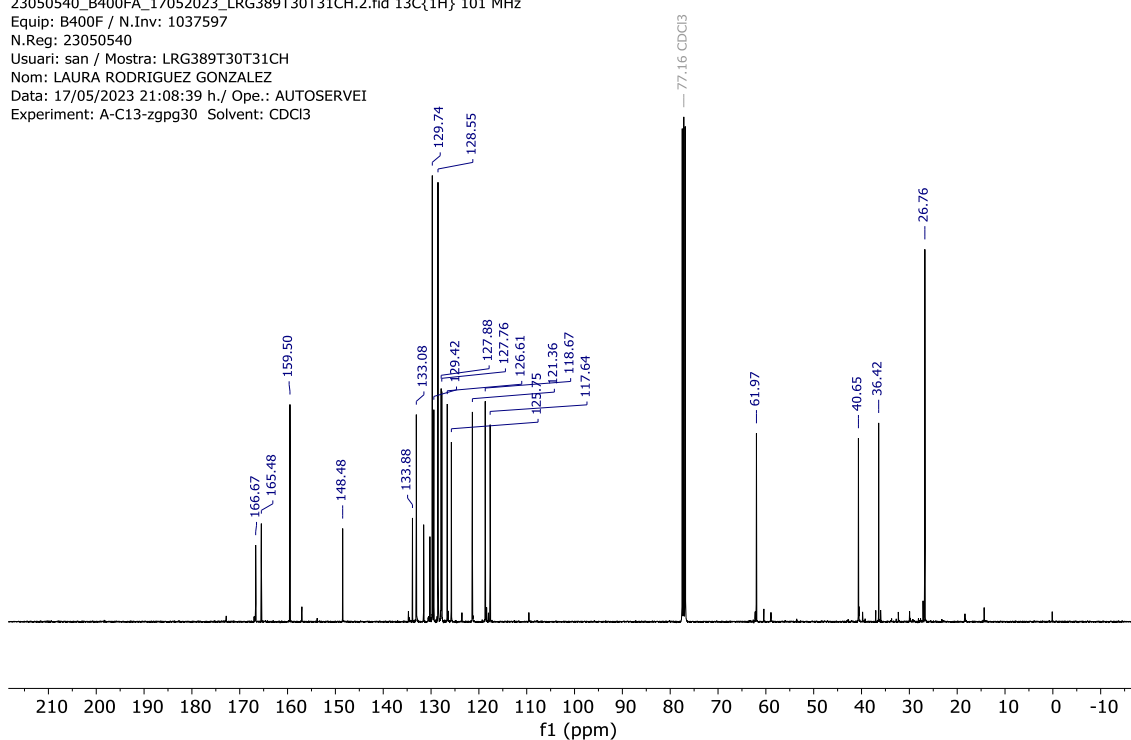




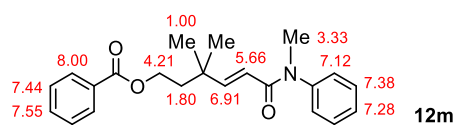
23050540_B400FA_17052023_LRG389T30T31CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23050540
 Usuari: san / Mostra: LRG389T30T31CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 17/05/2023 14:13:42 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



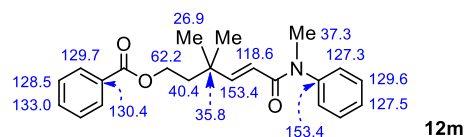
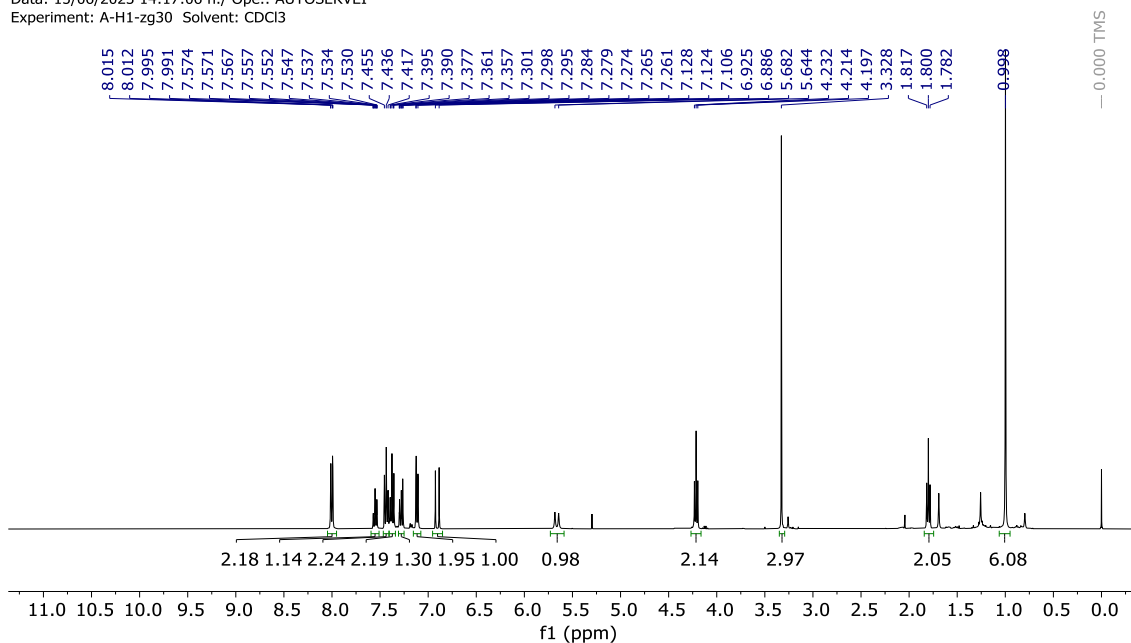
23050540_B400FA_17052023_LRG389T30T31CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23050540
 Usuari: san / Mostra: LRG389T30T31CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 17/05/2023 21:08:39 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



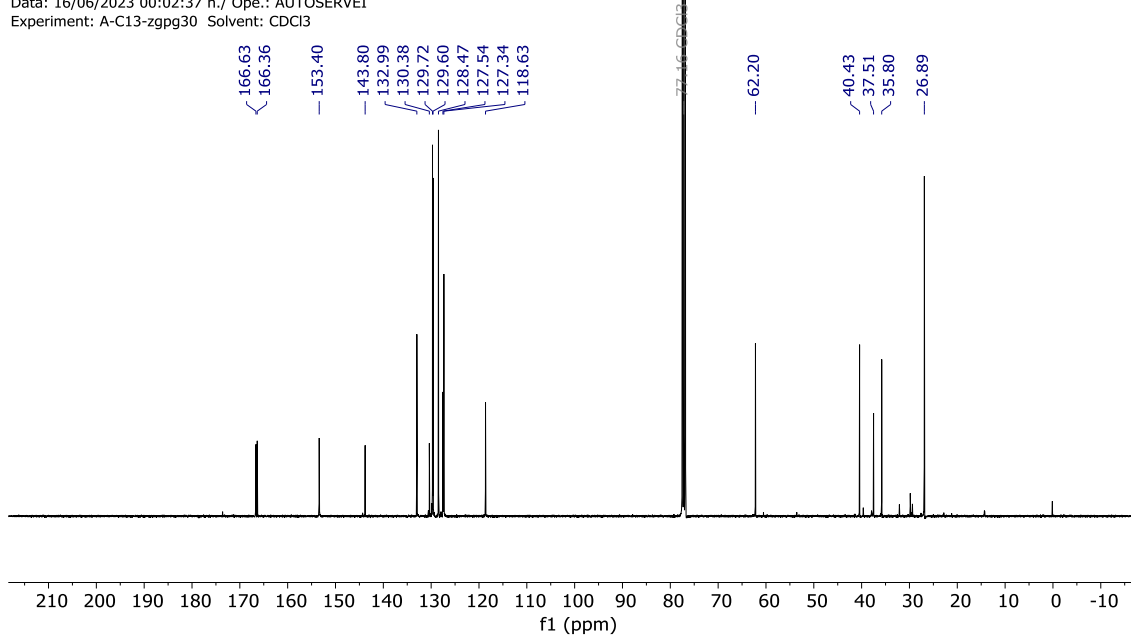
Experimental Section: Chapter 2

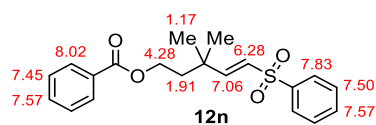


23060349_B400FA_15062023_LRG401COLT41T42.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060349
 Usuari: san / Mostra: LRG401COLT41T42
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/06/2023 14:17:06 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

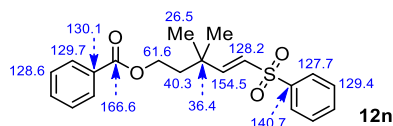
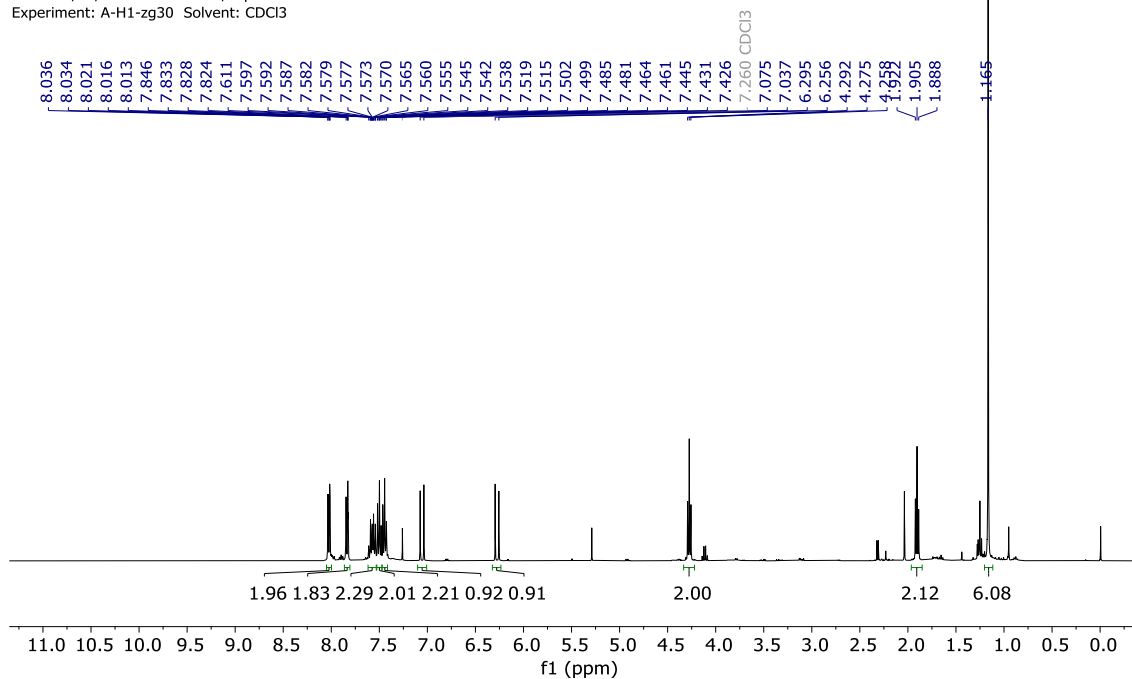


23060352_B400FA_16062023_LRG401T41T42CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23060352
 Usuari: san / Mostra: LRG401T41T42CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 16/06/2023 00:02:37 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

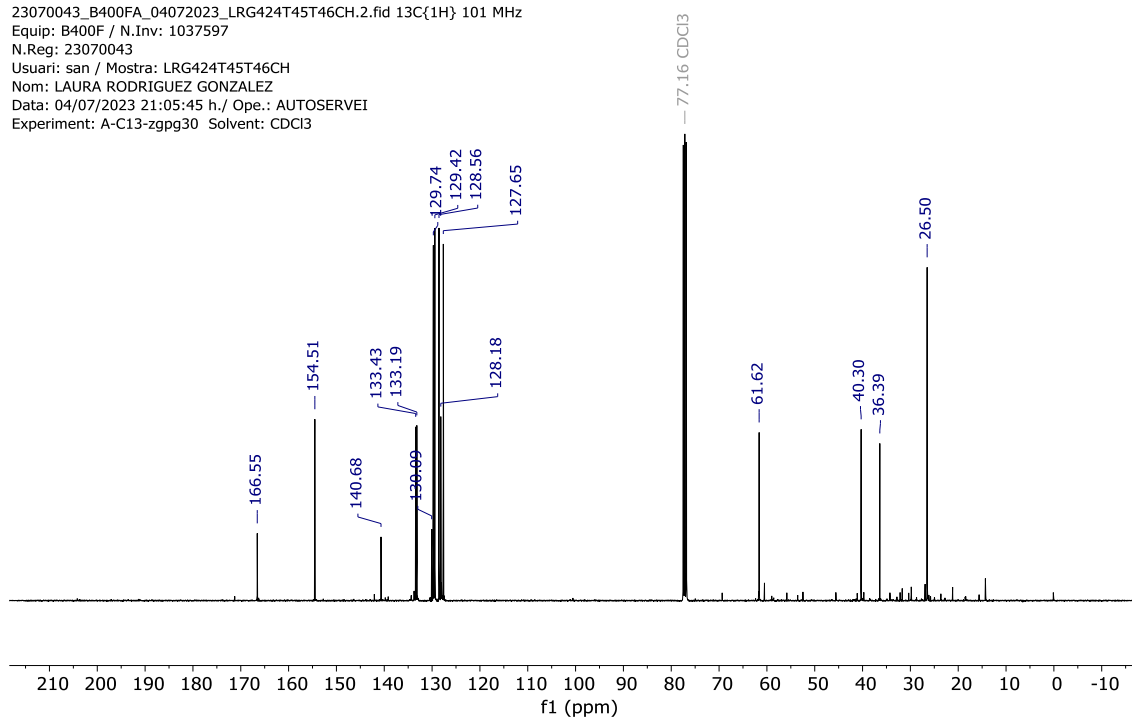




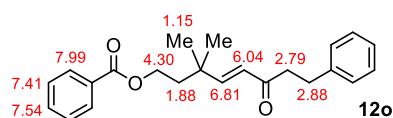
23070039_B400FA_04072023_LRG424COLT45T46.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070039
 Usuari: san / Mostra: LRG424COLT45T46
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 04/07/2023 10:51:45 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



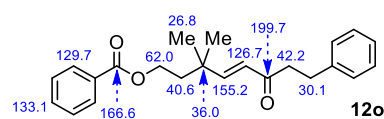
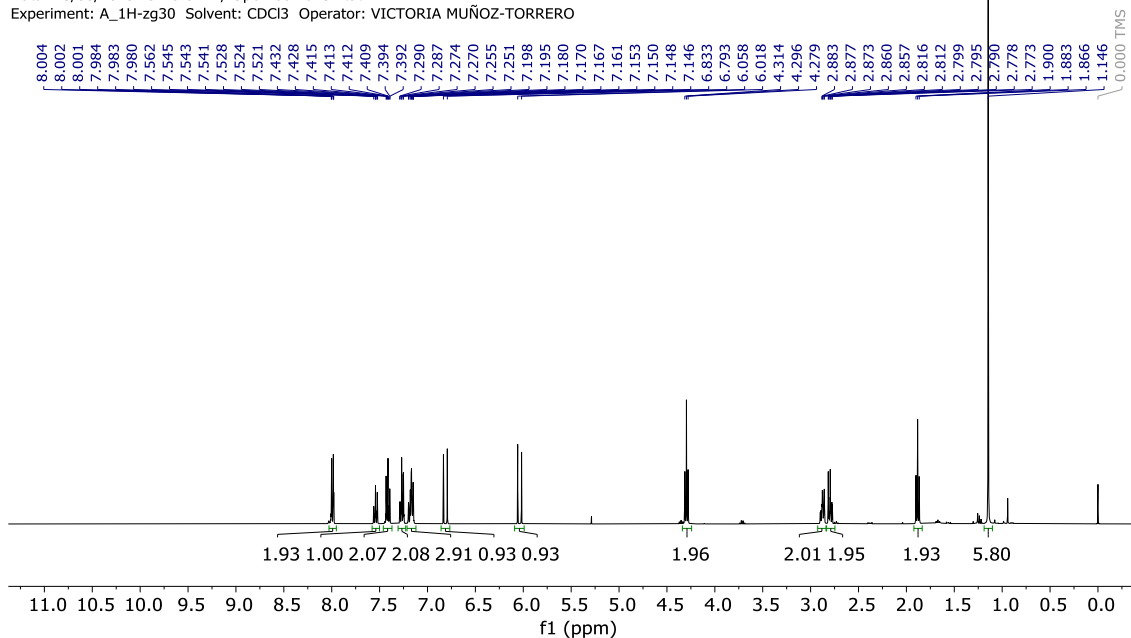
23070043_B400FA_04072023_LRG424T45T46CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 23070043
 Usuari: san / Mostra: LRG424T45T46CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 04/07/2023 21:05:45 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



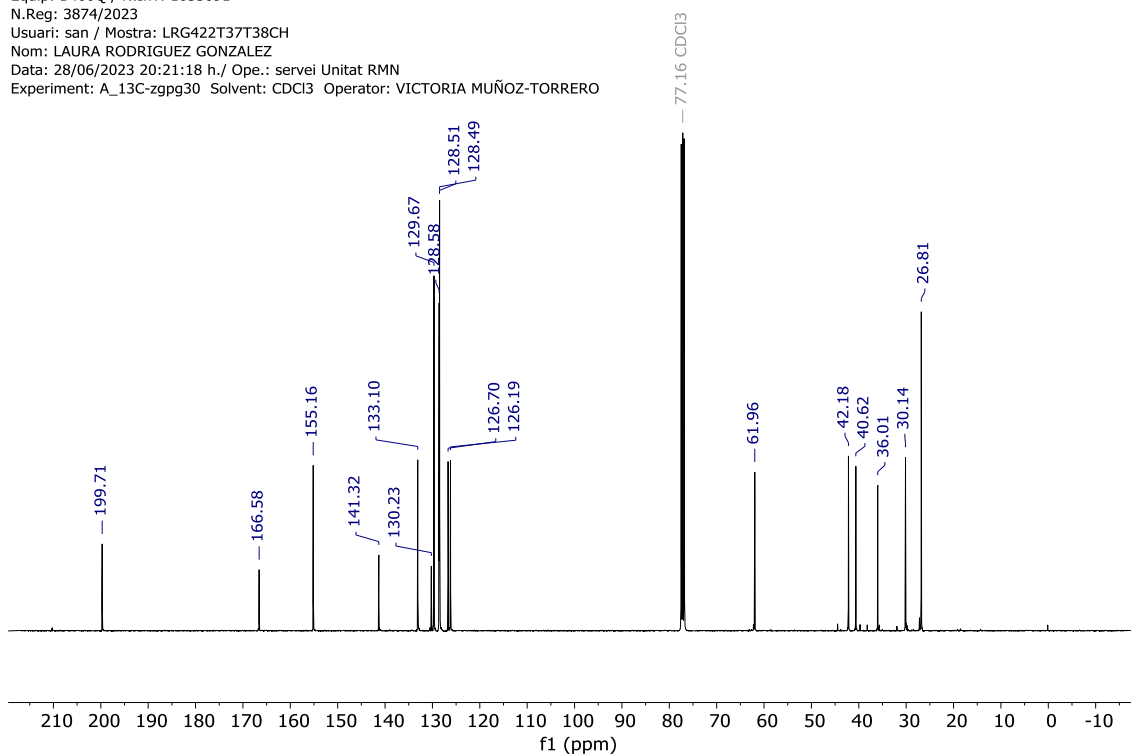
Experimental Section: Chapter 2

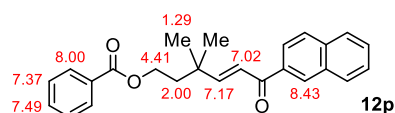


san-3874-2023.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 3874/2023
 Usuari: san / Mostra: LRG422T37T38CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 28/06/2023 19:16:02 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: VICTORIA MUÑOZ-TORRERO

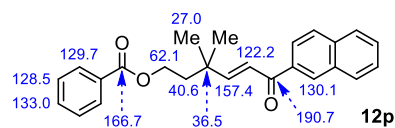
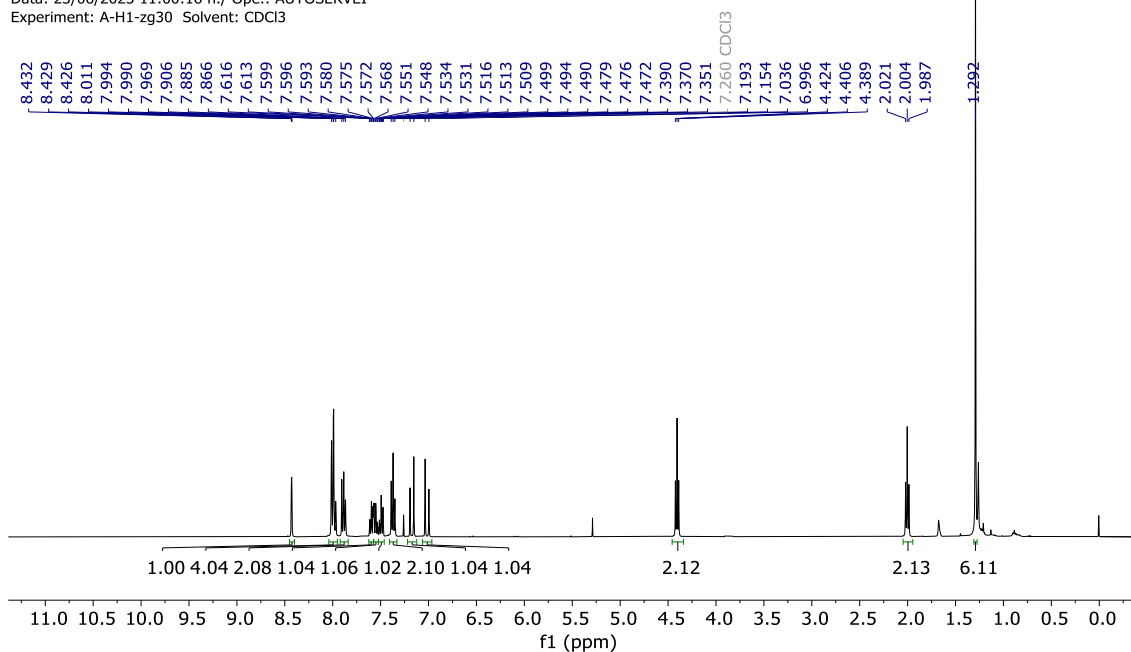


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 N.Reg: 3874/2023
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 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 28/06/2023 20:21:18 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpg30 Solvent: CDCl₃ Operator: VICTORIA MUÑOZ-TORRERO

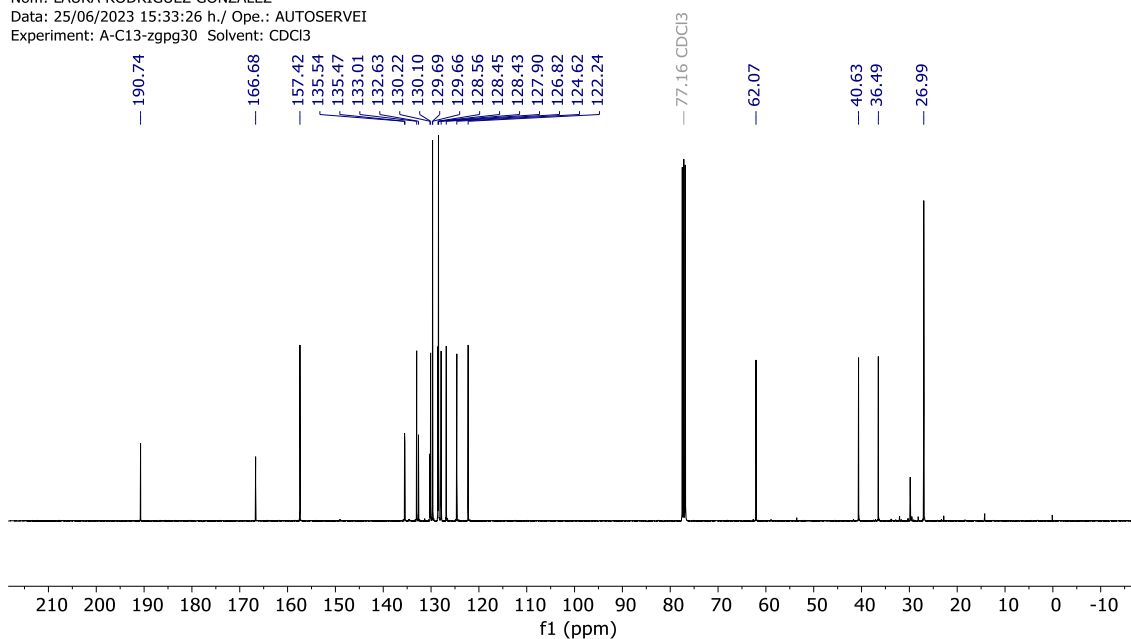


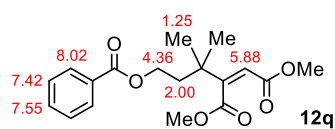


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 Usuari: san / Mostra: LRG417COLT40
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 Data: 23/06/2023 11:00:16 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

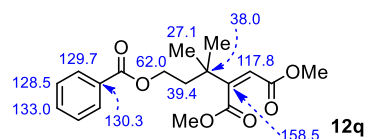
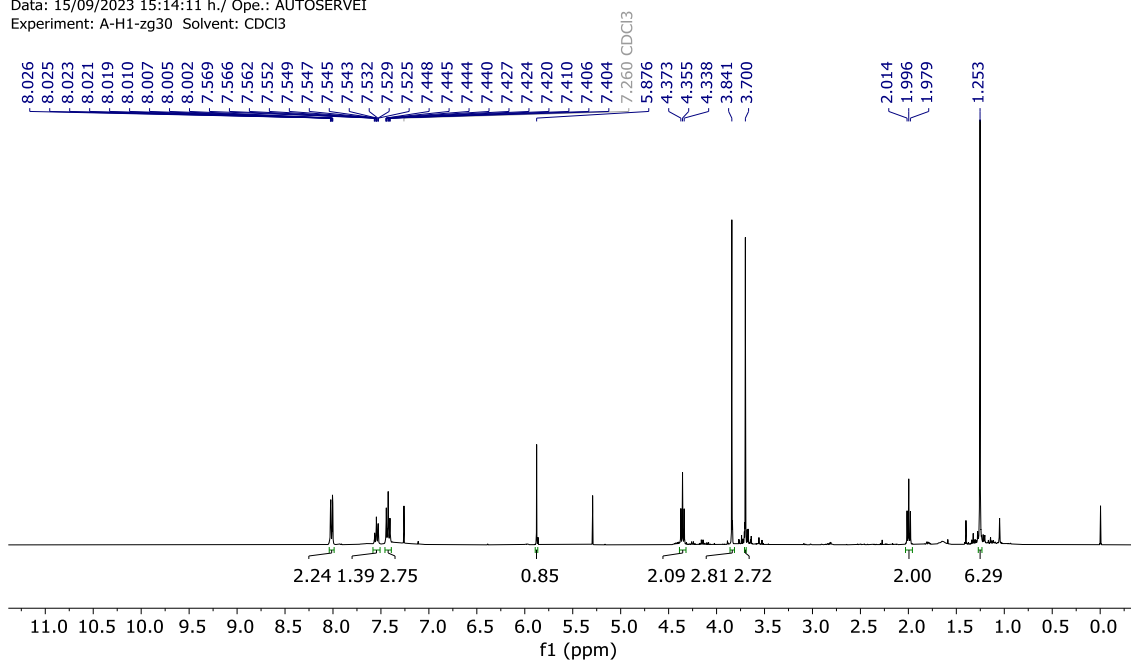


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 Usuari: san / Mostra: LRG417T40CH
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 Experiment: A-C13-zpgp30 Solvent: CDCl₃

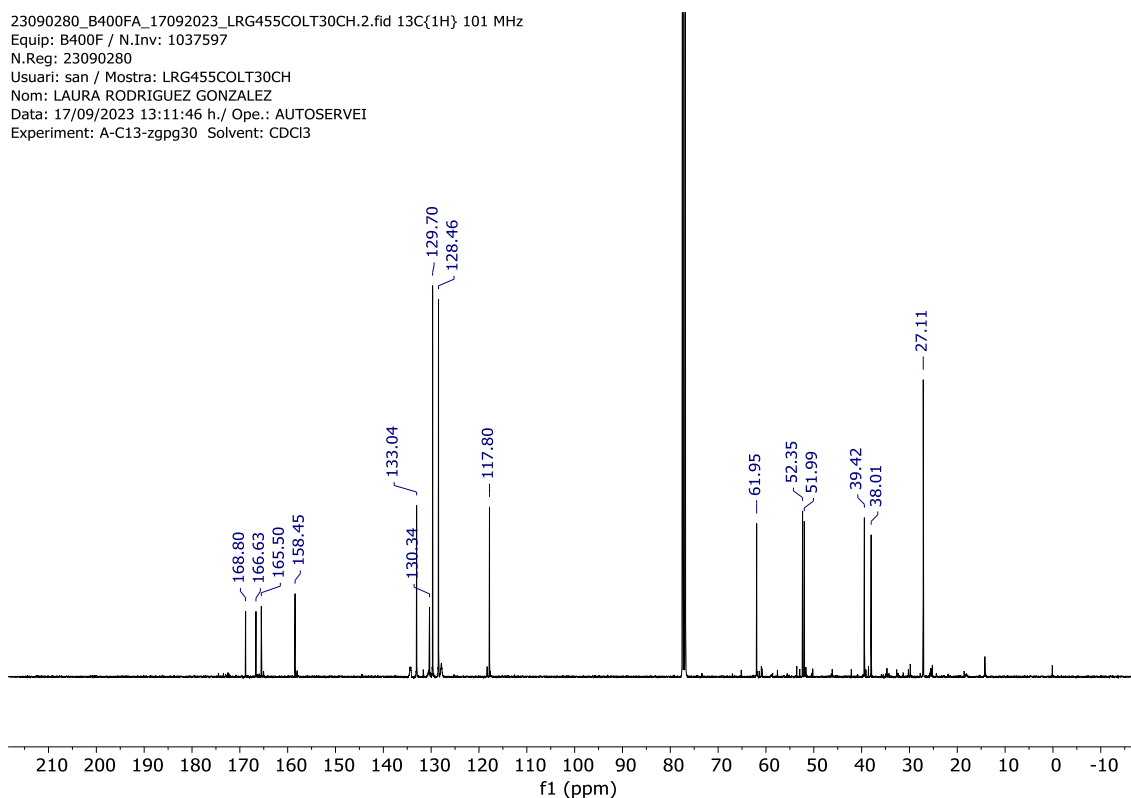


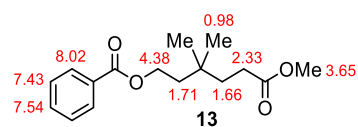


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 Experiment: A-H1-zg30 Solvent: CDCl₃

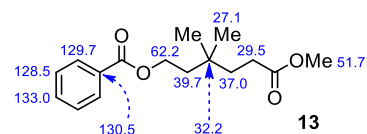
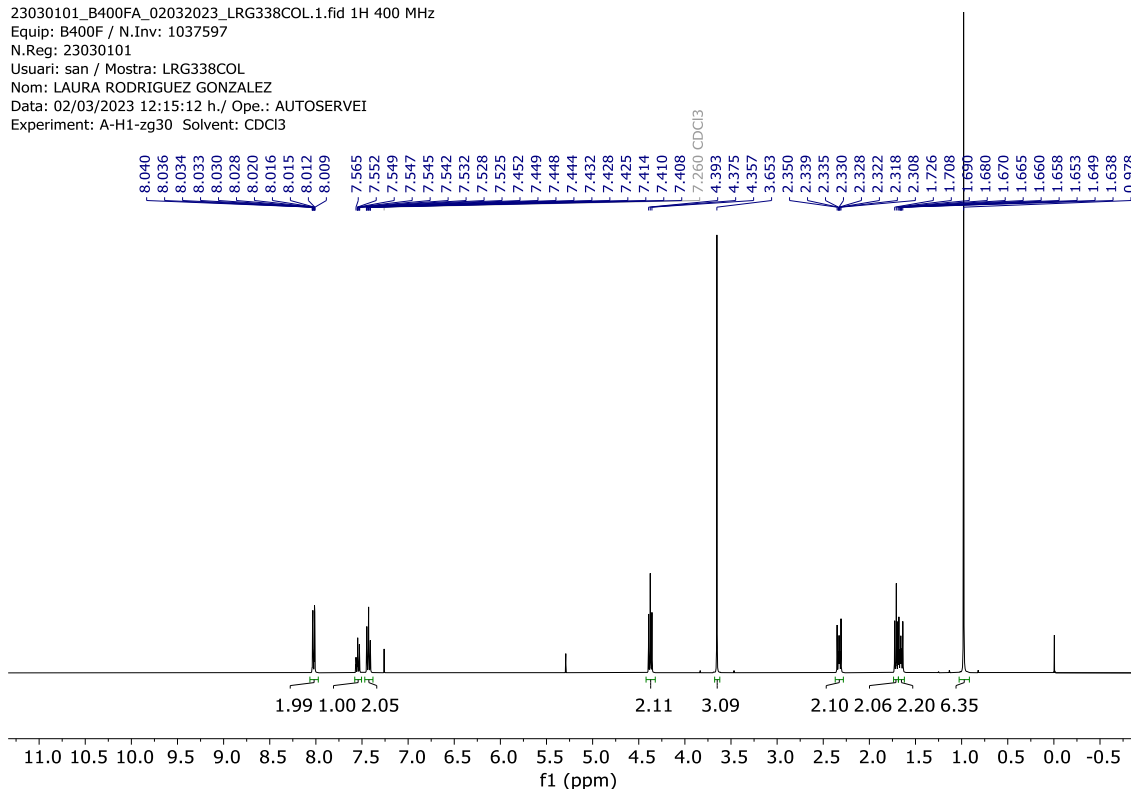


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 Data: 17/09/2023 13:11:46 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpg30 Solvent: CDCl₃

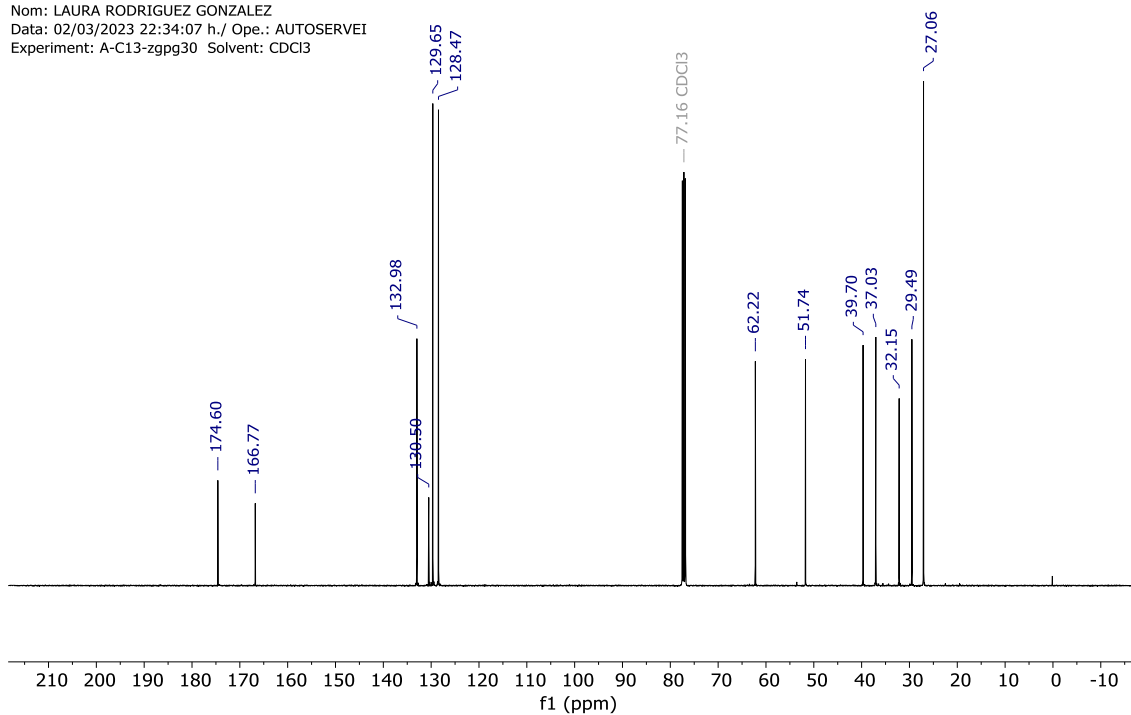


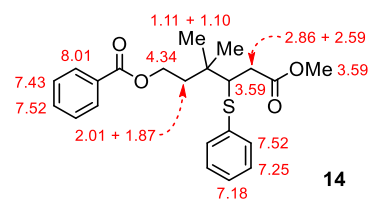


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 Usuari: san / Mostra: LRG338COL
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 Experiment: A-H1-zg30 Solvent: CDCl_3

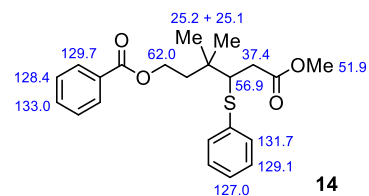
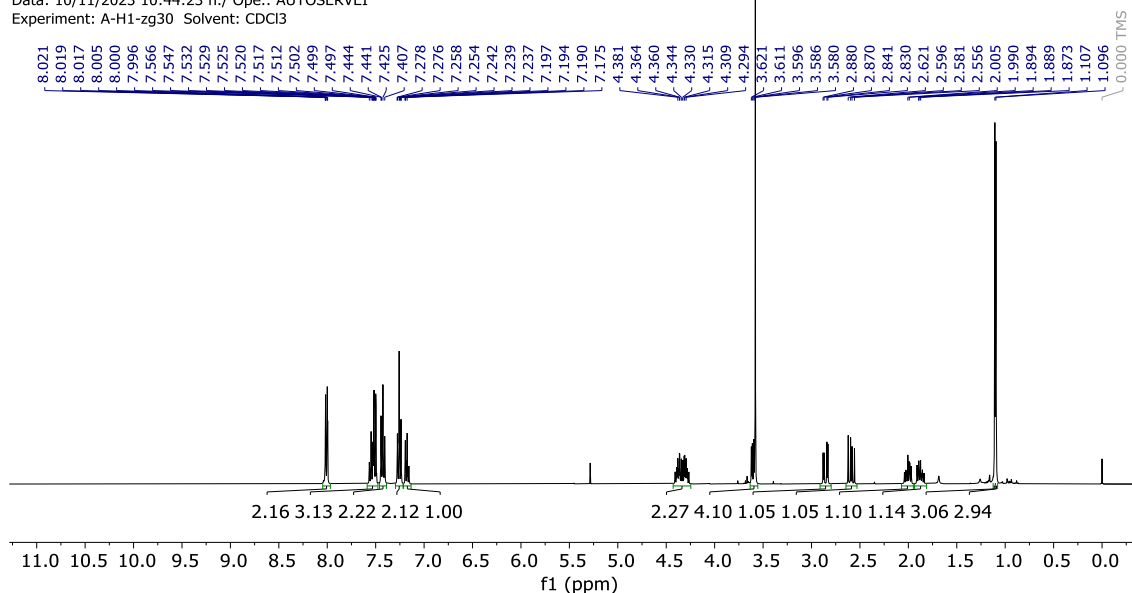


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 N.Reg: 23030101
 Usuari: san / Mostra: LRG338COL
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 Data: 02/03/2023 22:34:07 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl_3

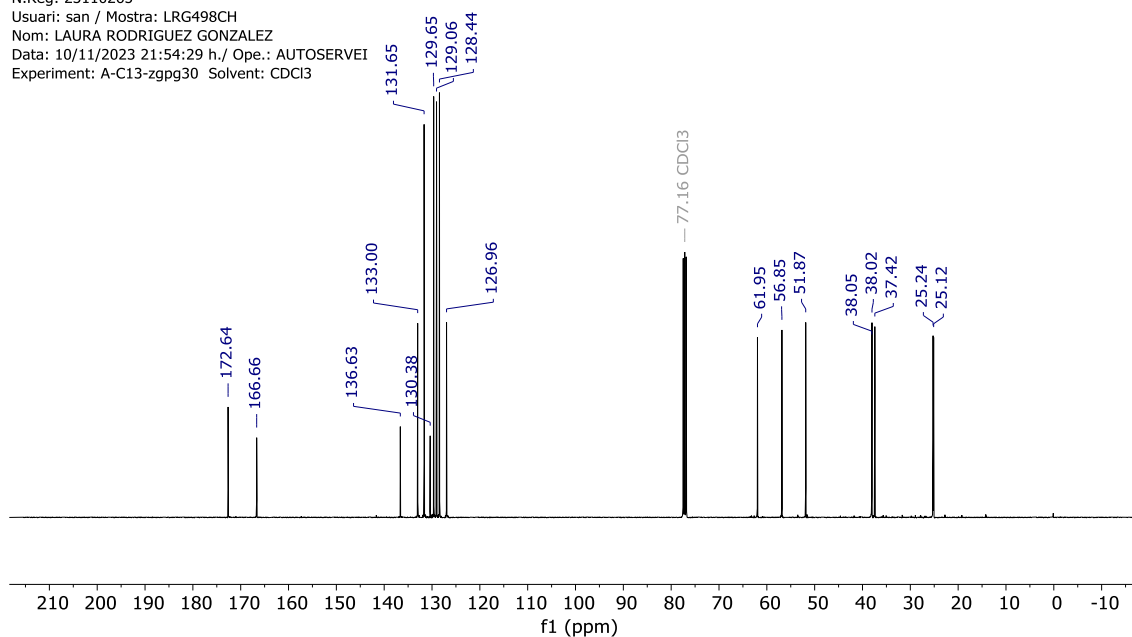


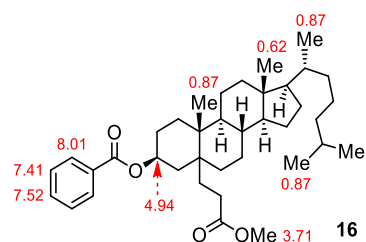


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 Data: 10/11/2023 10:44:23 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

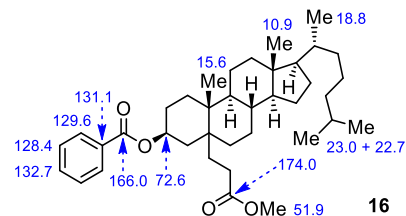
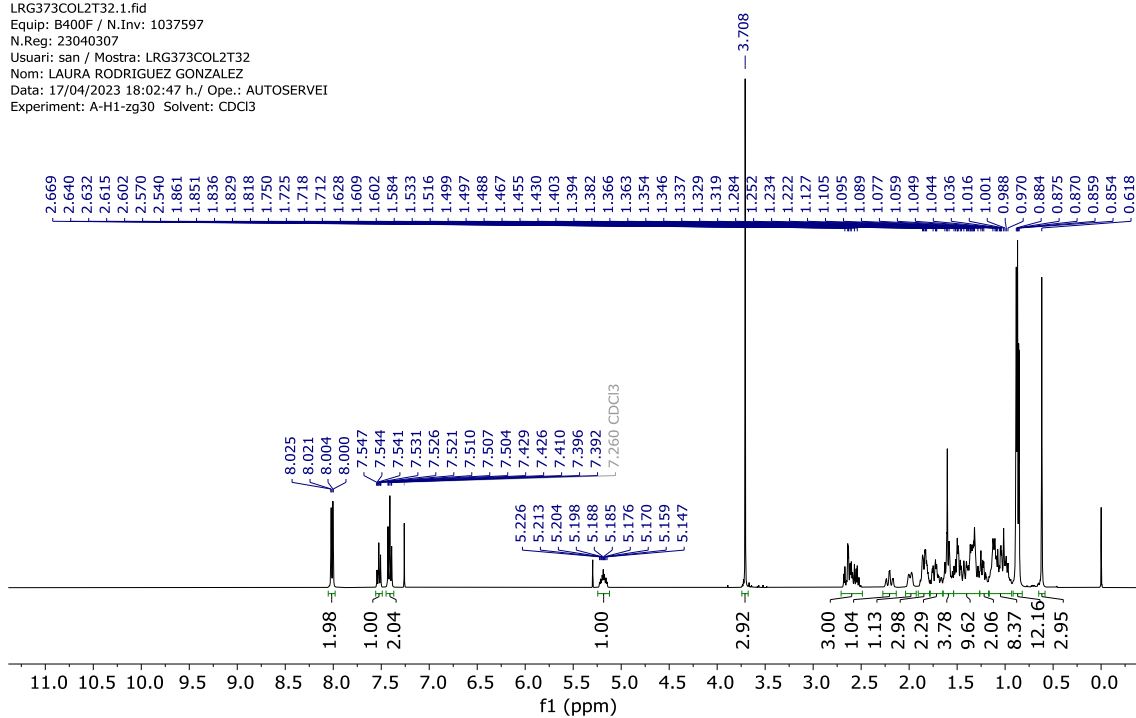


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 Experiment: A-C13-zgpg30 Solvent: CDCl3

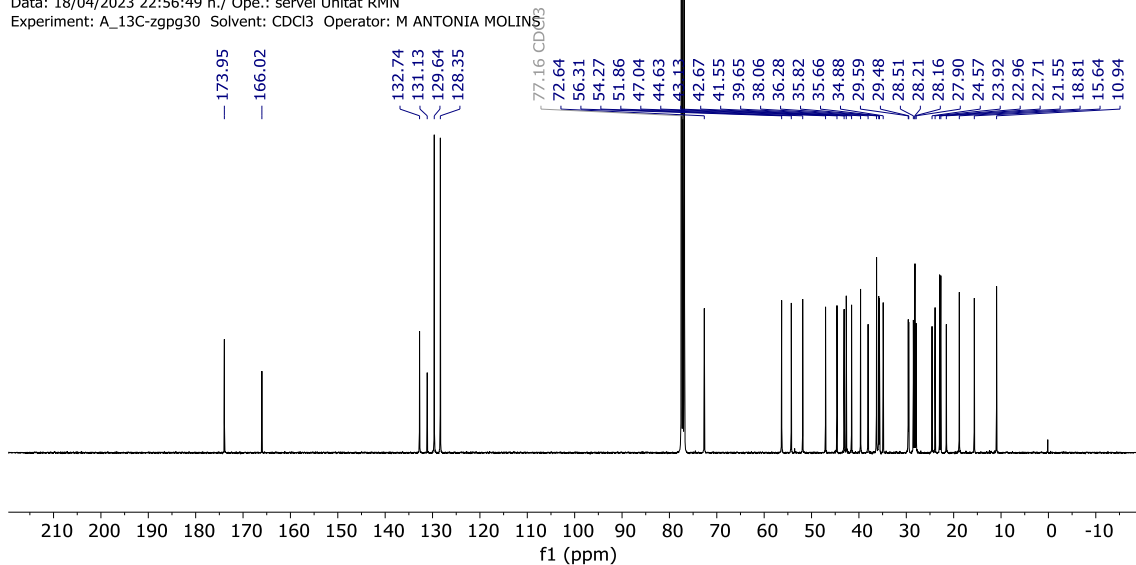




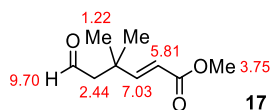
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 Usuari: san / Mostra: LRG373COL2T32
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 Experiment: A-H1-zg30 Solvent: CDCl3



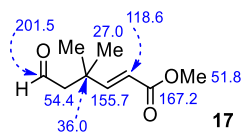
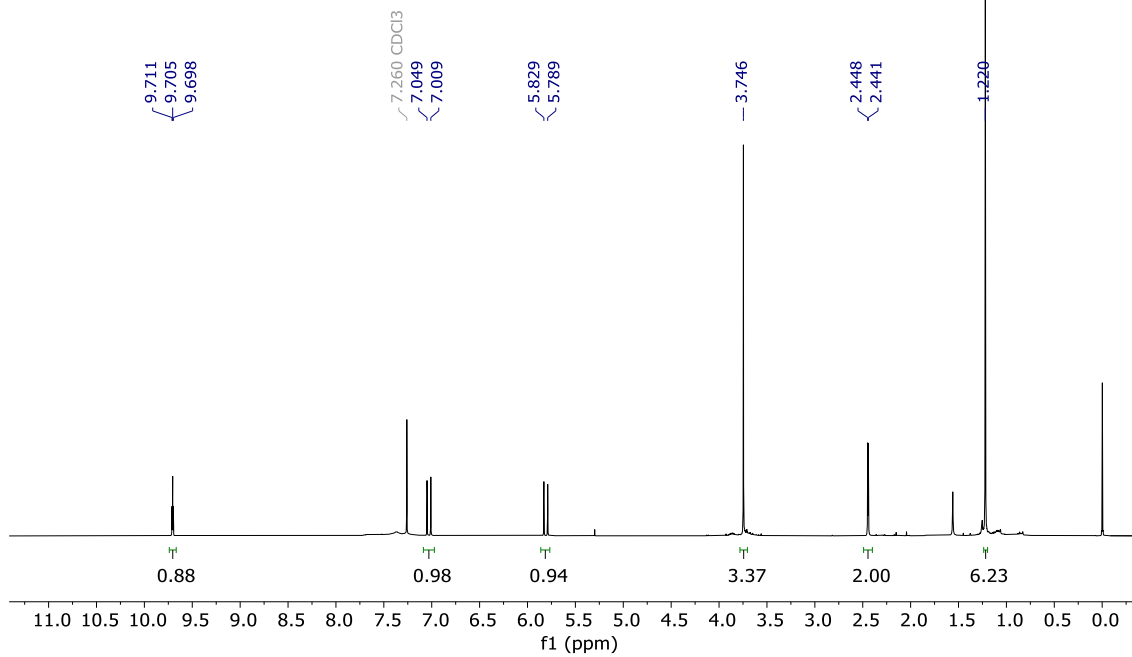
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 Nom: LAURA RODRIGUEZ GONZALEZ
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 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator: M ANTONIA MOLINS



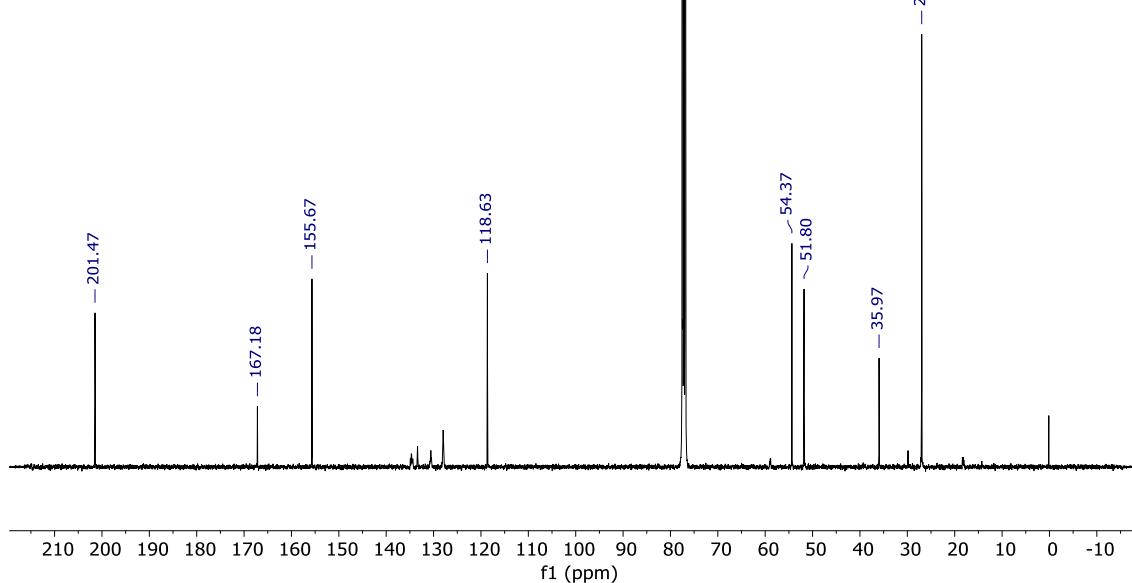
Experimental Section: Chapter 2

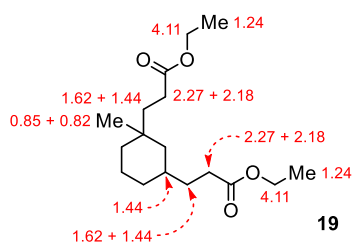


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 Equip: B400Q / N.Inv: 1035091
 N.Reg: 668/2023
 Usuari: san / Mostra: LRG314CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/02/2023 07:50:53 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator: FRANCISCO CARDENAS LOPEZ



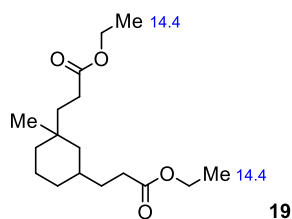
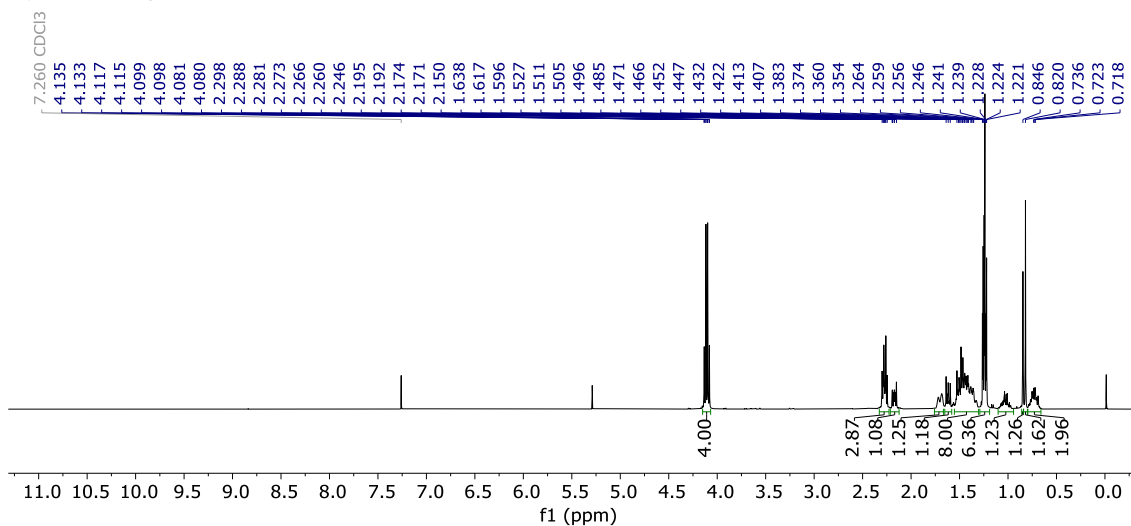
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 Experiment: A_13C-zpgp30 Solvent: CDCl3 Operator: FRANCISCO CARDENAS LOPEZ



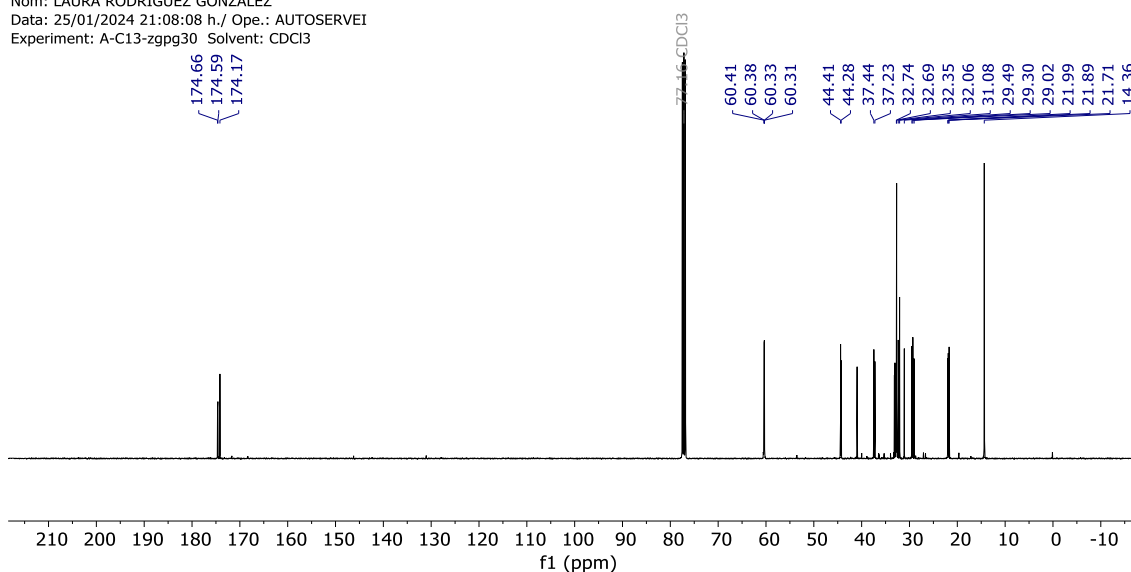


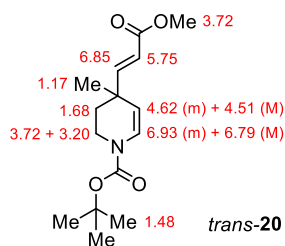
Product isolated as a mixture of diastereomers

LRG525COLT13T14CH.1.fid 1H 400 MHz
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 Usuari: san / Mostra: LRG525COLT13T14CH
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 Data: 25/01/2024 09:24:25 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

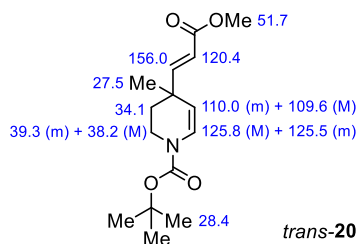
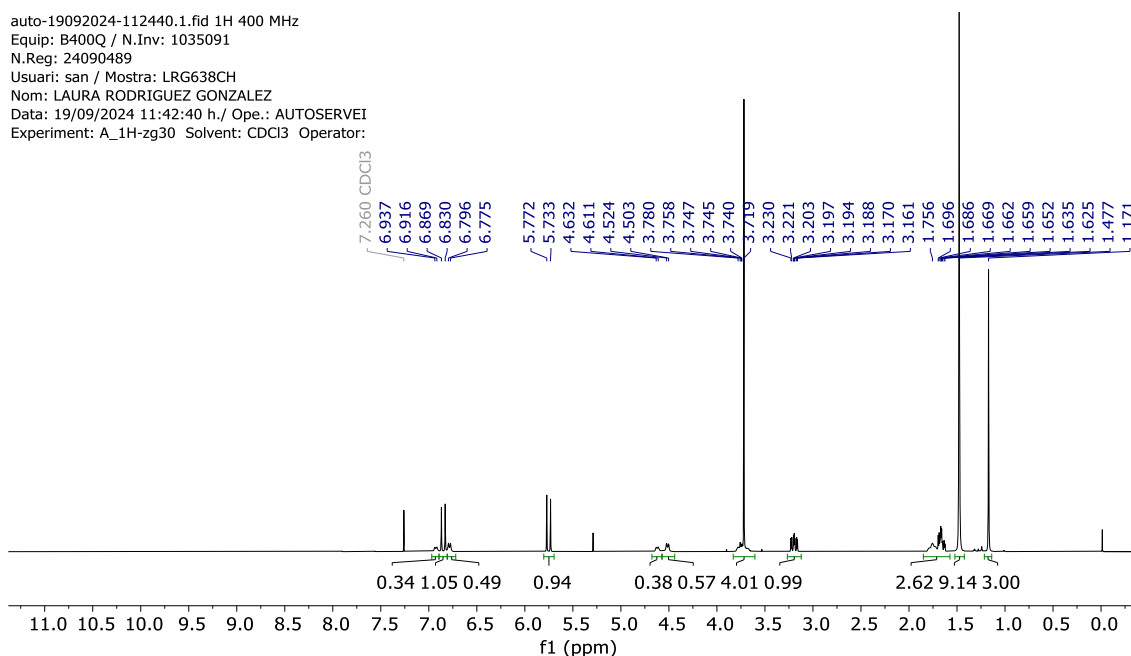


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 Experiment: A-C13-zgpg30 Solvent: CDCl3

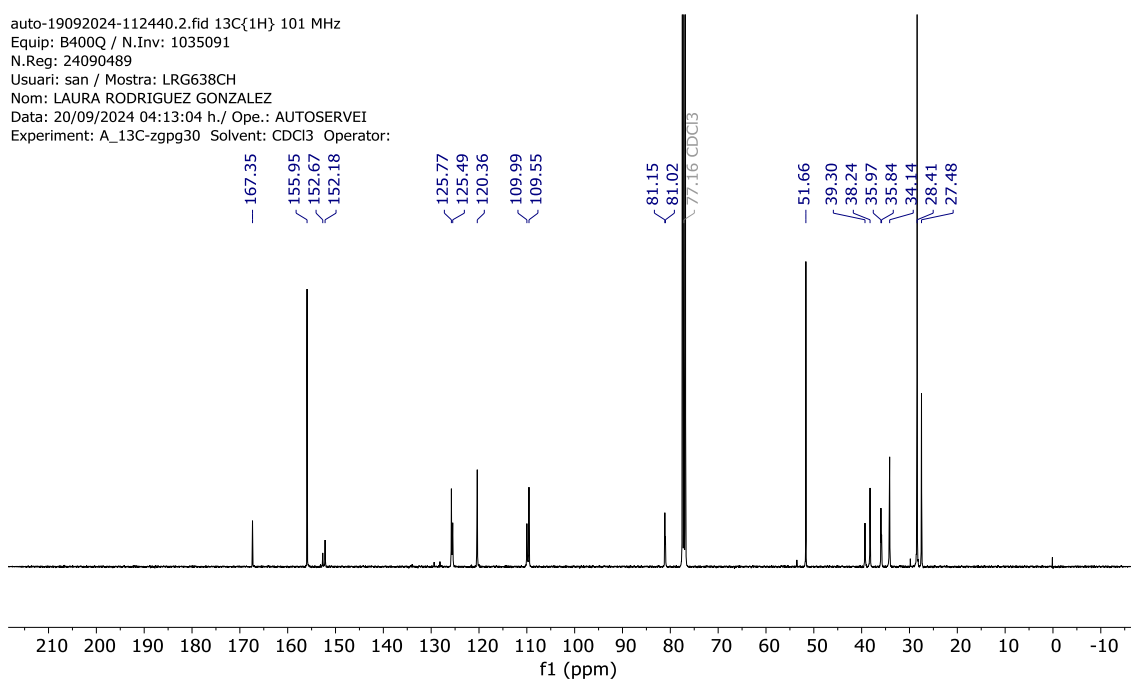




auto-19092024-112440.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
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 Usuari: san / Mostra: LRG638CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/09/2024 11:42:40 h./ Ope.: AUTOSERVEI
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator:



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 N.Reg: 24090489
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 Nom: LAURA RODRIGUEZ GONZALEZ
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 Experiment: A_13C-zgpg30 Solvent: CDCl₃ Operator:



References for the Experimental Section of Chapter 2

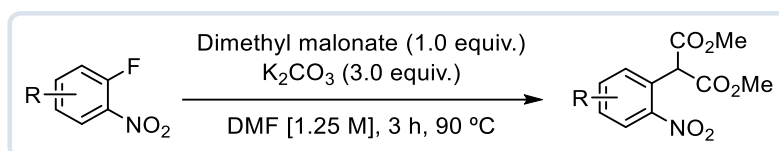
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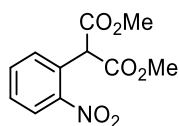
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3. BASE-MEDIATED NITROPHENYL REDUCTIVE CYCLIZATION FOR THE SYNTHESIS OF 3,4-BENZOMORPHANS

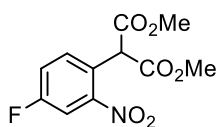
SYNTHESIS OF THE CYCLIZATION PRECURSORS



General method for the synthesis of nitrophenyl malonates:¹ Dimethyl malonate (1.0 equiv.), potassium carbonate (3.0 equiv.), and the selected 2-fluoronitrobenzene (1.0 equiv.) were charged in a round-bottom flask. Then, dimethylformamide (1.25 M) was added to the mixture. The resulting brown suspension was heated at 90 °C for 3 hours. After cooling to room temperature, the mixture was diluted with ice–water (3 mL/mmol) and Et₂O (3 mL/mmol). The aqueous layer was then extracted three times with Et₂O. The combined organic layers were washed with brine, dried, and evaporated. The corresponding nitrophenyl malonate was purified by flash column chromatography on silica gel.

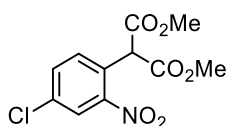


Dimethyl 2-(2-nitrophenyl)malonate (1a). The title compound was prepared according to the general procedure using 2-fluoro-1-nitrobenzene (6.01 g, 4.5 mL, 42.6 mmol, 1.0 equiv.), dimethyl malonate (5.63 g, 4.9 mL, 42.6 mmol, 1.0 equiv.), and potassium carbonate (17.7 g, 128 mmol, 3.0 equiv.) in DMF (34 mL, 1.25 M). Purification by chromatography (CH₂Cl₂) gave **1a** (10.7 g, 99%) as a yellow oil. Spectral data were identical to those previously reported.^[1] ¹H NMR (500 MHz, CDCl₃) δ 8.07 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.65 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 7.56 – 7.49 (m, 2H), 5.33 (s, 1H), 3.80 (s, 6H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 167.8, 148.9, 133.7, 131.5, 129.5, 128.0, 125.4, 54.2, 53.3 ppm.



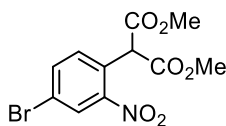
Dimethyl 2-(4-fluoro-2-nitrophenyl)malonate (1b). The title compound

was prepared according to the general procedure using 2,5-difluoronitrobenzene (1.59 g, 1.1 mL, 10 mmol, 1.0 equiv.), dimethyl malonate (1.32 g, 1.2 mL, 10 mmol, 1.0 equiv.), and potassium carbonate (4.15 g, 30 mmol, 3.0 equiv.) in DMF (8 mL, 1.25 M). Purification by chromatography (CH₂Cl₂) gave **1b** (2.50 g, 92%) as a pale-yellow solid. Spectral data were identical to those previously reported.^[2] ¹H NMR (400 MHz, CDCl₃) δ 7.79 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.55 (dd, *J* = 8.8, 5.3 Hz, 1H), 7.38 (ddd, *J* = 8.8, 7.2, 2.8 Hz, 1H), 5.31 (s, 1H), 3.80 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.6, 163.2, 160.7, 149.5, 149.4, 133.4, 133.3, 124.1, 124.0, 121.1, 120.9, 113.2, 113.0, 53.5, 53.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -109.08 (td, *J* = 7.6, 5.1 Hz) ppm.



Dimethyl 2-(4-chloro-2-nitrophenyl)malonate (1c). The title

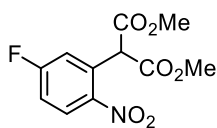
compound was prepared according to the general procedure using 4-chloro-1-fluoro-2-nitrobenzene (1.00 g, 670 μL, 5.7 mmol, 1.0 equiv.), dimethyl malonate (753 mg, 650 μL, 5.7 mmol, 1.0 equiv.), and potassium carbonate (2.37 g, 17.1 mmol, 3.0 equiv.) in DMF (4.6 mL, 1.25 M). Purification by chromatography (CH₂Cl₂) gave **1c** (1.47 g, 90%) as a yellow solid. Spectral data were identical to those previously reported.^[2] ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 2.2 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 5.29 (s, 1H), 3.80 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.4, 149.2, 135.5, 133.7, 132.8, 126.5, 125.5, 53.6, 53.5 ppm.



Dimethyl-2-(4-bromo-2-nitrophenyl)malonate (1d). The title

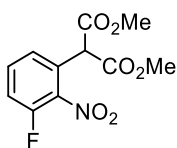
compound was prepared according to the general procedure using 5-bromo-2-fluoronitrobenzene (1.65 g, 920 μL, 7.5 mmol, 1.0 equiv.), dimethyl malonate (991 mg, 860 μL, 7.5 mmol, 1.0 equiv.), and potassium carbonate (3.11 g, 22.5 mmol, 3.0 equiv.) in DMF (6 mL, 1.25 M). Purification by chromatography (CH₂Cl₂) gave **1d** (2.36 g, 95%) as a pale-yellow solid. Spectral data were identical to those previously reported.^[3] ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 2.1 Hz, 1H), 7.77 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.42 (d, *J*

= 8.4 Hz, 1H), 5.27 (s, 1H), 3.79 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.3, 149.2, 136.7, 133.0, 128.3, 126.9, 122.9, 53.7, 53.5 ppm



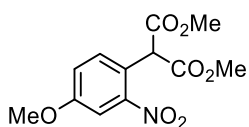
Dimethyl 2-(5-fluoro-2-nitrophenyl)malonate (1e). The title compound

was prepared according to the general procedure using 2,4-difluoronitrobenzene (1.61 g, 1.1 mL, 10.1 mmol, 1.0 equiv.), dimethyl malonate (1.33 g, 1.2 mL, 10.1 mmol, 1.0 equiv.), and potassium carbonate (4.19 g, 30.3 mmol, 3.0 equiv.) in DMF (8 mL, 1.25 M). Purification by chromatography (Hex/AcOEt 2.5% $\rightarrow$ Hex/AcOEt 50%) gave **1e** (2.05 g, 75%) as a white solid. Spectral data were identical to those previously reported.^[4] ^1H NMR (400 MHz, CDCl_3) δ 8.15 (dd, J = 9.1, 5.1 Hz, 1H), 7.28 – 7.18 (m, 2H), 5.40 (s, 1H), 3.82 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.3, 166.2, 163.6, 144.9, 131.4, 131.3, 128.3, 128.2, 118.9, 118.7, 116.6, 116.4, 54.1, 53.5; ^{19}F NMR (376 MHz, CDCl_3) δ -101.88 to -102.02 (m) ppm.



Dimethyl-2-(3-fluoro-2-nitrophenyl)malonate (1f). The title compound

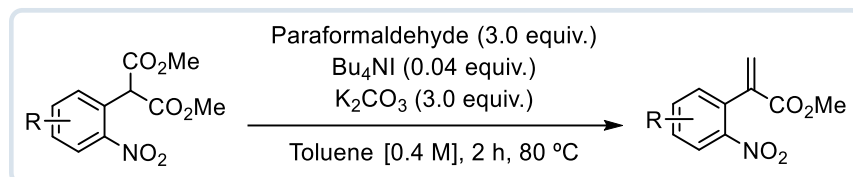
was prepared according to the general procedure using 2,6-difluoronitrobenzene (1.00 g, 670 μL , 6.3 mmol, 1.0 equiv.), dimethyl malonate (832 mg, 720 μL , 6.3 mmol, 1.0 equiv.), and potassium carbonate (2.62 g, 18.9 mmol, 3.0 equiv.) in DMF (5 mL, 1.25 M). Purification by chromatography (CH_2Cl_2) gave **1f** (1.48 g, 87%) as a pale-yellow solid. Spectral data were identical to those previously reported.^[5] ^1H NMR (400 MHz, CDCl_3) δ 7.56 (ddd, J = 8.2, 8.2, 5.3 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.29 (ddd, J = 9.3, 8.2, 1.0 Hz, 1H), 4.86 (s, 1H), 3.80 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.0, 155.6, 153.0, 139.8, 139.6, 132.7, 132.6, 128.0, 126.38, 126.35, 117.7, 117.5, 53.5, 52.6, 52.5; ^{19}F NMR (376 MHz, CDCl_3) δ -121.26 (dd, J = 9.5, 5.2 Hz) ppm.



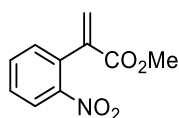
Dimethyl-2-(4-methoxy-2-nitrophenyl)malonate (1g). The title

compound was prepared according to the general procedure using 4-fluoro-3-nitroanisole (993 mg, 5.8 mmol, 1.0 equiv.), dimethyl malonate (766 mg, 670 μL , 5.8

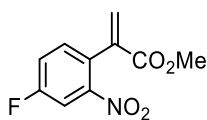
mmol, 1.0 equiv.), and potassium carbonate (2.41 g, 17.4 mmol, 3.0 equiv.) in DMF (4.6 mL, 1.25 M). Purification by chromatography (CH₂Cl₂) gave **1g** (1.13 g, 69%) as a white solid. Spectral data were identical to those previously reported.^[1] ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 2.7 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.17 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.25 (s, 1H), 3.88 (s, 3H), 3.79 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 168.1, 159.9, 149.5, 132.4, 120.0, 119.9, 110.3, 56.1, 53.5, 53.2 ppm.



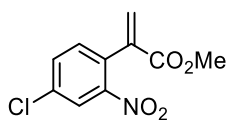
General method for the synthesis of acrylates:⁶ To a solution of the selected diester (1.0 equiv.) in toluene (0.4 M) at room temperature were added paraformaldehyde (3.0 equiv.), tetrabutylammonium iodide (0.04 equiv.), and potassium carbonate (3.0 equiv.). The resulting mixture was stirred at 80 °C for 2 hours. After cooling to room temperature, water (2.5 mL/mmol) was added and the aqueous phase was extracted three times with toluene. The combined organic layers were washed with brine, dried, and evaporated. The corresponding acrylate was purified by flash column chromatography on silica gel.



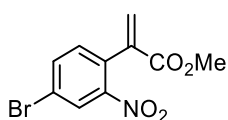
Methyl 2-(2-nitrophenyl)acrylate (2a). The title compound was prepared according to the general procedure using dimethyl (2-nitrophenyl)malonate (10.7 g, 42.2 mmol, 1.0 equiv.), paraformaldehyde (3.80 g, 126.6 mmol, 3.0 equiv.), tetrabutylammonium iodide (624 mg, 1.69 mmol, 0.04 equiv.), and potassium carbonate (17.5 g, 126.6 mmol, 3.0 equiv.) in toluene (100 mL, 0.4 M). Purification by chromatography (CH₂Cl₂) gave **2a** (6.85 g, 78%) as a yellow oil. Spectral data were identical to those previously reported.^[6] ¹H NMR (400 MHz, CDCl₃) δ 8.12 (ddd, *J* = 8.1, 1.3, 0.4 Hz, 1H), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 7.39 (ddd, *J* = 7.6, 1.5, 0.4 Hz, 1H), 6.55 (d, *J* = 0.9 Hz, 1H), 5.88 (d, *J* = 0.9 Hz, 1H), 3.73 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 165.4, 148.0, 139.9, 133.8, 133.1, 132.3, 129.5, 127.6, 124.7, 52.4 ppm.



Methyl 2-(4-fluoro-2-nitrophenyl)acrylate (2b). The title compound was prepared according to the general procedure using dimethyl 2-(4-fluoro-2-nitrophenyl)malonate (2.39 g, 8.8 mmol, 1.0 equiv.), paraformaldehyde (793 mg, 26.4 mmol, 3.0 equiv.), tetrabutylammonium iodide (129 mg, 0.35 mmol, 0.04 equiv.), and potassium carbonate (3.65 g, 26.4 mmol, 3.0 equiv.) in toluene (22 mL, 0.4 M). Purification by chromatography (CH₂Cl₂) gave **2b** (1.74 g, 88%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.84 (ddd, *J* = 8.3, 2.2, 0.7 Hz, 1H), 7.42 – 7.33 (m, 2H), 6.54 (d, *J* = 0.7 Hz, 1H), 5.86 (d, *J* = 0.7 Hz, 1H), 3.72 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 165.2, 163.4, 160.9, 148.5, 148.4, 139.0, 133.8, 133.7, 129.23, 129.20, 128.0, 121.0, 120.8, 112.7, 112.4, 52.5; ¹⁹F NMR (376 MHz, CDCl₃) δ –109.31 to –109.43 (m) ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₀H₉FO₄⁺ 226.0510, found 226.0519.

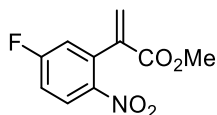


Methyl 2-(4-chloro-2-nitrophenyl)acrylate (2c). The title compound was prepared according to the general procedure using dimethyl 2-(4-chloro-2-nitrophenyl)malonate (1.41 g, 4.9 mmol, 1.0 equiv.), paraformaldehyde (441 mg, 14.7 mmol, 3.0 equiv.), tetrabutylammonium iodide (74 mg, 0.20 mmol, 0.04 equiv.), and potassium carbonate (2.03 g, 14.7 mmol, 3.0 equiv.) in toluene (12 mL, 0.4 M). Purification by chromatography (CH₂Cl₂) gave **2c** (1.09 g, 92%) as a yellow oil. Spectral data were identical to those previously reported.^[6] ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 2.1 Hz, 1H), 7.62 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 0.8 Hz, 1H), 5.88 (d, *J* = 0.8 Hz, 1H), 3.72 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 165.1, 148.3, 139.0, 135.3, 133.8, 133.3, 131.5, 128.2, 125.0, 52.5 ppm.

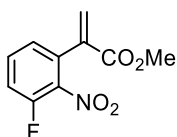


Methyl 2-(4-bromo-2-nitrophenyl)acrylate (2d). The title compound was prepared according to the general procedure using dimethyl 2-(4-bromo-2-nitrophenyl)malonate (2.19 g, 6.6 mmol, 1.0 equiv.), paraformaldehyde (595 mg, 19.8 mmol, 3.0 equiv.), tetrabutylammonium iodide (103 mg, 0.28 mmol, 0.04 equiv.), and potassium carbonate (2.74 g, 19.8 mmol, 3.0 equiv.) in toluene (17 mL, 0.4 M).

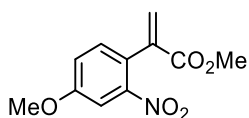
Purification by chromatography (CH₂Cl₂) gave **2d** (1.76 g, 93%) as a yellow solid. Spectral data were identical to those previously reported.^[6] ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 2.1 Hz, 1H), 7.78 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 0.7 Hz, 1H), 5.89 (d, *J* = 0.8 Hz, 1H), 3.73 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 165.0, 148.3, 139.0, 136.7, 133.4, 131.9, 128.1, 127.8, 122.7, 52.5 ppm.



Methyl 2-(5-fluoro-2-nitrophenyl)acrylate (2e). The title compound was prepared according to the general procedure using dimethyl 2-(5-fluoro-2-nitrophenyl)malonate (1.95 g, 7.2 mmol, 1.0 equiv.), paraformaldehyde (649 mg, 21.6 mmol, 3.0 equiv.), tetrabutylammonium iodide (107 mg, 0.29 mmol, 0.04 equiv.), and potassium carbonate (2.99 g, 21.6 mmol, 3.0 equiv.) in toluene (18 mL, 0.4 M). Purification by chromatography (CH₂Cl₂) gave **2e** (1.40 g, 87%) as a pale-yellow solid. Spectral data were identical to those previously reported.^[6] ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 9.0, 5.0 Hz, 1H), 7.20 (ddd, *J* = 9.1, 7.2, 2.8 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.56 (d, *J* = 0.6 Hz, 1H), 5.88 (d, *J* = 0.6 Hz, 1H), 3.73 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.3, 164.9, 163.7, 144.1, 139.3, 136.3, 136.2, 128.1, 127.7, 127.6, 119.4, 119.2, 116.4, 116.2, 52.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -103.04 to -103.14 (m) ppm.

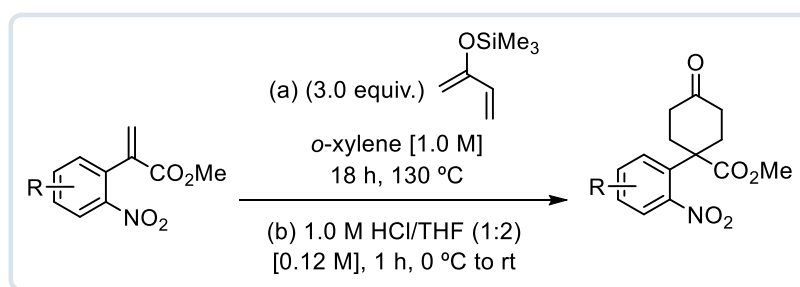


*Methyl 2-(3-fluoro-2-nitrophenyl)acrylate (2f).*⁷ The title compound was prepared according to the general procedure using dimethyl 2-(3-fluoro-2-nitrophenyl)malonate (1.46 g, 5.4 mmol, 1.0 equiv.), paraformaldehyde (486 mg, 16.2 mmol, 3.0 equiv.), tetrabutylammonium iodide (81 mg, 0.22 mmol, 0.04 equiv.), and potassium carbonate (2.24 g, 16.2 mmol, 3.0 equiv.) in toluene (14 mL, 0.4 M). Purification by chromatography (CH₂Cl₂) gave **2f** (970 mg, 80%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.53 (ddd, *J* = 8.5, 7.8, 5.1 Hz, 1H), 7.29 (ddd, *J* = 9.8, 8.5, 1.3 Hz, 1H), 7.20 – 7.15 (m, 1H), 6.61 (s, 1H), 5.96 (s, 1H), 3.76 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 164.8, 155.8, 153.3, 137.2, 137.1, 133.6, 132.83, 132.75, 130.5, 126.79, 126.76, 117.8, 117.6, 52.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -121.03 (dd, *J* = 9.9, 4.9 Hz) ppm. HRMS (ESI) *m/z* [M + Na]⁺: calculated for C₁₀H₈FNNaO₄⁺ 248.0335, found 248.0328.

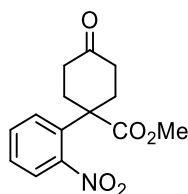


Methyl 2-(4-methoxy-2-nitrophenyl)acrylate (2g). The title

compound was prepared according to the general procedure using dimethyl 2-(4-methoxy-2-nitrophenyl)malonate (0.99 g, 3.5 mmol, 1.0 equiv.), paraformaldehyde (315 mg, 10.5 mmol, 3.0 equiv.), tetrabutylammonium iodide (52 mg, 0.14 mmol, 0.04 equiv.), and potassium carbonate (1.45 g, 10.5 mmol, 3.0 equiv.) in toluene (9 mL, 0.4 M). Purification by chromatography (Hex/AcOEt 5% → Hex/AcOEt 25%) gave **2g** (554 mg, 66%) as a pale-yellow solid. Spectral data were identical to those previously reported.^[6] ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 2.6 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.48 (d, *J* = 1.0 Hz, 1H), 5.82 (d, *J* = 1.0 Hz, 1H), 3.90 (s, 3H), 3.71 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 165.8, 160.2, 148.6, 139.6, 133.1, 127.0, 125.3, 120.0, 109.6, 56.1, 52.4 ppm.

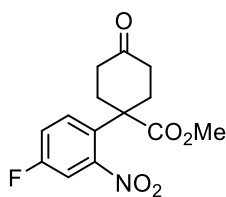


General method for the synthesis of the cyclization precursors:⁸ To a solution of the selected acrylate (1.0 equiv.) in *o*-xylene (1.0 M) was added 2-(trimethylsiloxy)-1,3-butadiene (3.0 equiv.) under an argon atmosphere. The reaction tube was sealed, and the mixture was heated at 130 °C for 18 hours. After cooling to room temperature, the solvent was evaporated and the crude product was dissolved in tetrahydrofuran (0.18 M). The mixture was cooled to 0 °C, and 1.0 M hydrochloric acid (2.8 mL/mmol) was added dropwise. After stirring the solution for 1 hour, tetrahydrofuran was evaporated and the aqueous layer was diluted and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. The corresponding product was purified by flash column chromatography on silica gel.



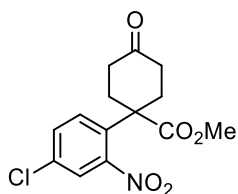
Methyl 1-(2-nitrophenyl)-4-oxocyclohexanecarboxylate (3a). The title

compound was prepared according to the general procedure using methyl-2-(2-nitrophenyl)acrylate (1.49 g, 7.2 mmol, 1.0 equiv.) and 2-(trimethylsiloxy)-1,3-butadiene (3.07 g, 3.8 mL, 21.6 mmol, 3.0 equiv.) in *o*-xylene (7.2 mL, 1.0 M). The residue was hydrolyzed in a (1:2) v/v 1.0 M hydrochloric acid/tetrahydrofuran mixture (0.12 M). Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 0.5%) gave **3a** (1.26 g, 63%) as a pale-brown solid. ¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.80 (m, 1H), 7.66 – 7.62 (m, 2H), 7.50 – 7.44 (m, 1H), 3.71 (s, 3H), 2.78 – 2.59 (m, 4H), 2.42 – 2.24 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 209.5, 174.1, 149.6, 135.8, 133.1, 128.6, 128.5, 125.9, 52.6, 48.7, 37.7, 33.2 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₆NO₅⁺ 278.1023, found 278.1019.



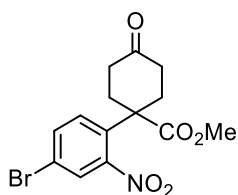
Methyl 1-(4-fluoro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (3b). The title

compound was prepared according to the general procedure using methyl-2-(4-fluoro-2-nitrophenyl)acrylate (1.51 g, 6.7 mmol, 1.0 equiv.) and 2-(trimethylsiloxy)-1,3-butadiene (2.86 g, 3.5 mL, 20.1 mmol, 3.0 equiv.) in *o*-xylene (6.7 mL, 1.0 M). The residue was hydrolyzed in a (1:2) v/v 1.0 M hydrochloric acid/tetrahydrofuran mixture (0.12 M). Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 0.3%) gave **3b** (1.18 g, 60%) as a pale-brown solid. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 9.0, 5.3 Hz, 1H), 7.57 (dd, *J* = 7.9, 2.8 Hz, 1H), 7.36 (ddd, *J* = 8.9, 7.0, 2.9 Hz, 1H), 3.71 (s, 3H), 2.81 – 2.58 (m, 4H), 2.42 – 2.20 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 209.2, 173.9, 162.4, 159.9, 150.1, 150.0, 132.1, 132.0, 130.2, 130.1, 120.2, 119.9, 113.8, 113.6, 52.7, 48.4, 37.6, 33.4; ¹⁹F NMR (471 MHz, CDCl₃) δ -110.94 (td, *J* = 7.4, 5.2 Hz) ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅FO₅⁺ 296.0929, found 296.0936.



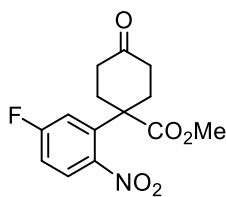
Methyl 1-(4-chloro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate

(3c). The title compound was prepared according to the general procedure using methyl-2-(4-chloro-2-nitrophenyl)acrylate (1.04 g, 4.3 mmol, 1.0 equiv.) and 2-(trimethylsiloxy)-1,3-butadiene (1.84 g, 2.2 mL, 12.9 mmol, 3.0 equiv.) in *o*-xylene (4.3 mL, 1.0 M). The residue was hydrolyzed in a (1:2) v/v 1.0 M hydrochloric acid/tetrahydrofuran mixture (0.12 M). Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 1%) gave **3c** (990 mg, 74%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.82 (dd, *J* = 2.1, 0.6 Hz, 1H), 7.63 – 7.56 (m, 2H), 3.71 (s, 3H), 2.80 – 2.58 (m, 4H), 2.41 – 2.20 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 209.1, 173.7, 149.9, 134.48, 134.47, 133.0, 129.7, 126.0, 52.7, 48.5, 37.6, 33.2 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅ClNO₅⁺ 312.0633, found 312.0640.



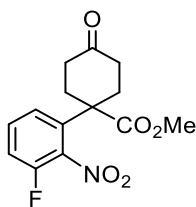
Methyl 1-(4-bromo-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate

(3d). The title compound was prepared according to the general procedure using methyl-2-(4-bromo-2-nitrophenyl)acrylate (1.66 g, 5.8 mmol, 1.0 equiv.) and 2-(trimethylsiloxy)-1,3-butadiene (2.48 g, 3.1 mL, 17.4 mmol, 3.0 equiv.) in *o*-xylene (5.8 mL, 1.0 M). The residue was hydrolyzed in a (1:2) v/v 1.0 M hydrochloric acid/tetrahydrofuran mixture (0.12 M). Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 0.3%) gave **3d** (1.68 g, 82%) as a pale-yellow solid. Spectral data were identical to those previously reported.^[8] ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 3.71 (s, 3H), 2.80 – 2.68 (m, 2H), 2.68 – 2.58 (m, 2H), 2.41 – 2.30 (m, 2H), 2.30 – 2.20 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 209.1, 173.6, 150.0, 136.0, 135.0, 129.9, 128.8, 121.9, 52.7, 48.6, 37.6, 33.2 ppm.



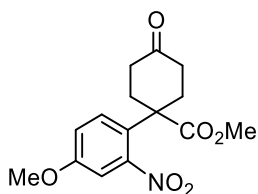
Methyl 1-(5-fluoro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate

(3e). The title compound was prepared according to the general procedure using methyl-2-(5-fluoro-2-nitrophenyl)acrylate (1.37 g, 6.1 mmol, 1.0 equiv.) and 2-(trimethylsiloxy)-1,3-butadiene (2.60 g, 3.2 mL, 18.3 mmol, 3.0 equiv.) in *o*-xylene (6.1 mL, 1.0 M). The residue was hydrolyzed in a (1:2) v/v 1.0 M hydrochloric acid/tetrahydrofuran mixture (0.12 M). Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 0.3%) gave **3e** (1.35 g, 75%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (dd, *J* = 9.0, 5.4 Hz, 1H), 7.33 (dd, *J* = 10.4, 2.7 Hz, 1H), 7.16 (ddd, *J* = 8.9, 6.6, 2.7 Hz, 1H), 3.71 (s, 3H), 2.84 – 2.71 (m, 2H), 2.71 – 2.60 (m, 2H), 2.43 – 2.32 (m, 2H), 2.30 – 2.18 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 209.1, 173.5, 166.0, 163.4, 145.5, 140.2, 140.1, 128.84, 128.75, 116.2, 116.0, 115.5, 115.2, 52.7, 48.7, 37.5, 33.1; ¹⁹F NMR (376 MHz, CDCl₃) δ –102.61 (dt, *J* = 10.6, 6.1 Hz) ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅FNO₅⁺ 296.0929, found 296.0932.



Methyl 1-(3-fluoro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (3f).

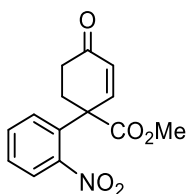
The title compound was prepared according to the general procedure using methyl-2-(3-fluoro-2-nitrophenyl)acrylate (1.40 g, 6.2 mmol, 1.0 equiv.) and 2-(trimethylsiloxy)-1,3-butadiene (2.65 g, 3.2 mL, 18.6 mmol, 3.0 equiv.) in *o*-xylene (6.2 mL, 1.0 M). The residue was hydrolyzed in a (1:2) v/v 1.0 M hydrochloric acid/tetrahydrofuran mixture (0.12 M). Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 1.5%) gave **3f** (1.70 g, 93%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.54 (td, *J* = 8.3, 5.7 Hz, 1H), 7.38 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.27 (td, *J* = 8.6, 1.1 Hz, 1H), 3.76 (s, 3H), 2.72 – 2.59 (m, 4H), 2.46 – 2.34 (m, 2H), 2.34 – 2.19 (m, 2H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 208.7, 173.2, 155.7, 153.7, 139.7, 139.6, 135.2, 131.94, 131.88, 123.29, 123.27, 116.8, 116.6, 53.1, 49.29, 49.28, 37.8, 33.2; ¹⁹F NMR (471 MHz, CDCl₃) δ –122.49 (ddd, *J* = 8.9, 5.7, 1.3 Hz) ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅FNO₅⁺ 296.0929, found 296.0933.



Methyl 1-(4-methoxy-2-nitrophenyl)-4-oxocyclohexane-1-

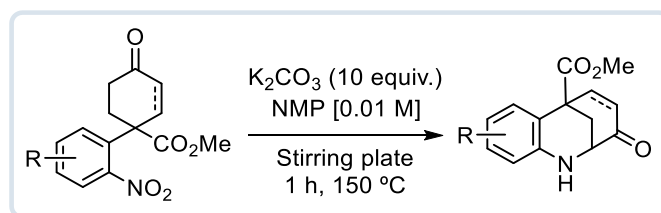
carboxylate (3g). The title compound was prepared according to a modification of the general procedure using methyl-2-(4-methoxy-2-nitrophenyl)acrylate (1.07 g, 4.5 mmol, 1.0 equiv.) and 2-(trimethylsiloxy)-1,3-butadiene (2.56 g, 3.2 mL, 18 mmol, 4.0 equiv.) in *o*-xylene (4.5 mL, 1.0 M). The residue was hydrolyzed in a (1:2) v/v 1.0 M hydrochloric acid/tetrahydrofuran mixture (0.12 M). Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 1%) gave **3g** (616 mg, 44%) as a green solid. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.9 Hz, 1H), 7.33 (d, *J* = 2.8 Hz, 1H), 7.14 (dd, *J* = 8.9, 2.9 Hz, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 2.77 – 2.55 (m, 4H), 2.40 – 2.21 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 209.7, 174.4, 159.1, 150.1, 129.5, 127.4, 118.7, 111.2, 56.0, 52.6, 48.2, 37.8, 33.4 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₅H₁₈NO₆⁺ 308.1129, found 308.1128.

Synthesis of methyl 1-(2-nitrophenyl)-4-oxo-2-cyclohexene-1-carboxylate (**3h**)⁹

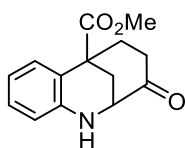


A solution of methyl 2-(2-nitrophenyl)acrylate (1.26 g, 6.1 mmol, 1.0 equiv.) and 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (2.00 g, 11.6 mmol, 1.9 equiv.) in toluene (6.1 mL, 1.0 M) was heated at reflux in a sealed tube for 20 hours. Afterward, solid *p*-toluenesulfonic acid monohydrate (82 mg, 0.43 mmol, 0.07 equiv.) was added to the mixture. The resulting solution was stirred for 2 hours, diluted with ethyl acetate (60 mL), washed with water (25 mL) and brine (25 mL), dried with sodium sulfate, and concentrated. Purification by chromatography (Hex/AcOEt 2.5% → Hex/AcOEt 50%) gave **3h** (1.28 g, 76%) as a yellow oil. Spectral data were identical to those previously reported.^[9] ¹H NMR (400 MHz, CDCl₃) δ 8.00 (ddd, *J* = 8.1, 1.5, 0.4 Hz, 1H), 7.64 (ddd, *J* = 7.9, 7.4, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.1, 7.5, 1.4 Hz, 1H), 7.46 (ddd, *J* = 7.8, 1.4, 0.4 Hz, 1H), 6.79 (d, *J* = 10.2 Hz, 1H), 6.32 (d, *J* = 10.2 Hz, 1H), 3.69 (s, 3H), 3.30 – 3.18 (m, 1H), 3.00 – 2.89 (m, 1H), 2.46 – 2.30 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ

198.0, 171.0, 148.7, 147.5, 135.8, 133.5, 132.3, 130.4, 129.0, 126.2, 52.9, 34.4, 32.3 ppm.

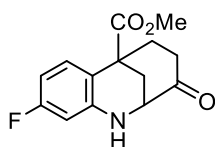


General method for the synthesis of the cyclized products: A solution of potassium carbonate (10 equiv.) in *N*-methylpyrrolidinone (90 mL/mmol) under an argon atmosphere was heated to 150 °C in a preheated oil bath. Then, a solution of the selected Diels–Alder product (1.0 equiv.) in NMP (10 mL/mmol) was added dropwise to the reaction mixture over 15 min. After this time, the solution was vigorously stirred for 1 hour. The resulting dark brown mixture was filtered through Celite to retain the salts and subsequently evaporated to dryness. The corresponding product was purified by flash column chromatography on silica gel.



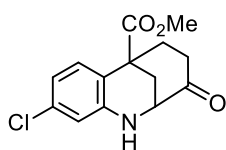
Methyl 3-oxo-2,3,4,5-tetrahydro-2,6-methanobenzo[b]azocine-6

(1H)-carboxylate (4a). The title compound was prepared according to the general procedure using methyl 1-(2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (277 mg, 1.0 mmol, 1.0 equiv.) and potassium carbonate (1.38 g, 10 mmol, 10 equiv.) in *N*-methylpyrrolidinone (100 mL, 0.01 M). Purification by chromatography (CH₂Cl₂) gave **4a** (213 mg, 87%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.12 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 6.97 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.72 (ddd, *J* = 7.8, 7.3, 1.2 Hz, 1H), 6.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.49 (s, 1H), 3.86 – 3.82 (m, 1H), 3.76 (s, 3H), 2.63 (dt, *J* = 13.2, 3.7 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.35 – 2.23 (m, 3H), 2.17 (ddd, *J* = 13.2, 2.9, 1.5 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 208.3, 175.3, 141.7, 128.9, 126.9, 121.1, 118.3, 114.4, 57.3, 52.6, 44.7, 38.8, 34.7, 32.8 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₆NO₃⁺ 246.1125, found 246.1125.



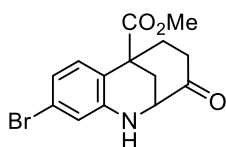
Methyl 9-fluoro-3-oxo-2,3,4,5-tetrahydro-2,6-methanobenzo[b]

azocine-6(1H)-carboxylate (4b). The title compound was prepared according to the general procedure using methyl 1-(4-fluoro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (89 mg, 0.30 mmol, 1.0 equiv.) and potassium carbonate (415 mg, 3.0 mmol, 10 equiv.) in *N*-methylpyrrolidinone (30 mL, 0.01 M). Purification by chromatography (CH₂Cl₂) gave **4b** (51 mg, 64%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.93 (dd, *J* = 8.6, 6.1 Hz, 1H), 6.42 (td, *J* = 8.5, 2.5 Hz, 1H), 6.30 (dd, *J* = 10.3, 2.6 Hz, 1H), 4.61 (s, 1H), 3.85 – 3.81 (m, 1H), 3.76 (s, 3H), 2.59 (dt, *J* = 13.3, 3.7 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.35 – 2.22 (m, 3H), 2.17 (dd, *J* = 13.3, 2.9 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 207.9, 175.0, 164.4, 162.0, 143.3, 143.2, 128.5, 128.4, 116.91, 116.88, 105.5, 105.2, 101.0, 100.7, 57.1, 52.7, 44.3, 38.8, 34.5, 32.9; ¹⁹F NMR (471 MHz, CDCl₃) δ –113.62 (ddd, *J* = 10.3, 8.3, 6.1 Hz) ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅FNO₃⁺ 264.1036, found 264.1032.



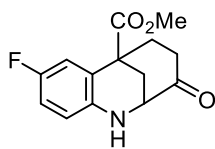
Methyl 9-chloro-3-oxo-2,3,4,5-tetrahydro-2,6-methanobenzo[b]

azocine-6(1H)-carboxylate (4c). The title compound was prepared according to the general procedure using methyl 1-(4-chloro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (56 mg, 0.18 mmol, 1.0 equiv.) and potassium carbonate (249 mg, 1.8 mmol, 10 equiv.) in *N*-methylpyrrolidinone (18 mL, 0.01 M). Purification by chromatography (CH₂Cl₂) gave **4c** (31 mg, 61%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 6.91 (d, *J* = 8.3 Hz, 1H), 6.69 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.60 (d, *J* = 2.1 Hz, 1H), 4.56 (s, 1H), 3.86 – 3.81 (m, 1H), 3.76 (s, 3H), 2.58 (dt, *J* = 13.3, 3.7 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.37 – 2.23 (m, 3H), 2.18 (dd, *J* = 13.3, 2.9 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 207.7, 174.8, 142.8, 134.4, 128.2, 119.6, 118.4, 114.0, 57.1, 52.7, 44.4, 38.6, 34.5, 32.7 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅ClNO₃⁺ 280.0740, found 280.0739.



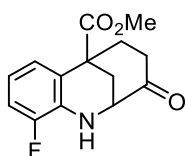
Methyl 9-bromo-3-oxo-2,3,4,5-tetrahydro-2,6-methanobenzo[b]

azocine-6(1H)-carboxylate (4d). The title compound was prepared according to the general procedure using methyl 1-(4-bromo-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (64 mg, 0.18 mmol, 1.0 equiv.) and potassium carbonate (249 mg, 1.8 mmol, 10 equiv.) in *N*-methylpyrrolidinone (18 mL, 0.01 M). Purification by chromatography (CH₂Cl₂) gave **4d** (32 mg, 55%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 6.88 – 6.79 (m, 2H), 6.75 (dd, *J* = 1.6, 0.6 Hz, 1H), 4.58 (s, 1H), 3.87 – 3.80 (m, 1H), 3.76 (s, 3H), 2.57 (dt, *J* = 13.3, 3.7 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.36 – 2.23 (m, 3H), 2.17 (dd, *J* = 13.3, 2.9 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 207.7, 174.8, 143.1, 128.4, 122.4, 121.2, 120.0, 116.9, 57.0, 52.7, 44.5, 38.6, 34.5, 32.6 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅BrNO₃⁺ 324.0230, found 324.0215.

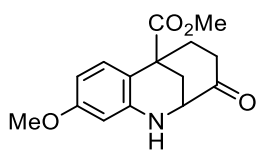


Methyl 8-fluoro-3-oxo-2,3,4,5-tetrahydro-2,6-methanobenzo[b]

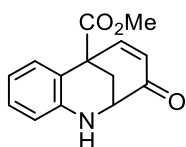
azocine-6(1H)-carboxylate (4e). The title compound was prepared according to the general procedure using methyl 1-(5-fluoro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (53 mg, 0.18 mmol, 1.0 equiv.) and potassium carbonate (249 mg, 1.8 mmol, 10 equiv.) in *N*-methylpyrrolidinone (18 mL, 0.01 M). Purification by chromatography (CH₂Cl₂) gave **4e** (34 mg, 71%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 6.85 (ddd, *J* = 8.8, 8.0, 2.9 Hz, 1H), 6.75 (dd, *J* = 9.5, 2.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.82 (ddt, *J* = 3.6, 2.9, 1.3 Hz, 1H), 3.78 (s, 3H), 2.59 (dt, *J* = 13.3, 3.7 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.38 – 2.21 (m, 3H), 2.18 (dd, *J* = 13.3, 2.9 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 208.0, 174.7, 157.1, 154.7, 138.1, 121.8, 116.1, 115.8, 115.34, 115.26, 113.4, 113.2, 57.2, 52.8, 44.5, 38.6, 34.7, 32.6; ¹⁹F NMR (376 MHz, CDCl₃) δ –126.05 (td, *J* = 8.8, 4.7 Hz) ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₅FNO₃⁺ 264.1030, found 264.1031.



Methyl 10-fluoro-3-oxo-2,3,4,5-tetrahydro-2,6-methanobenzo[b]azocine-6(1H)-carboxylate (4f). The title compound was prepared according to the general procedure using methyl 1-(3-fluoro-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (53 mg, 0.18 mmol, 1.0 equiv.) and potassium carbonate (249 mg, 1.8 mmol, 10 equiv.) in *N*-methylpyrrolidinone (18 mL, 0.01 M). Purification by chromatography (CH_2Cl_2) gave **4f** (35 mg, 73%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 6.95 (ddd, J = 11.0, 8.1, 1.3 Hz, 1H), 6.78 (dt, J = 7.8, 1.1 Hz, 1H), 6.64 (td, J = 8.0, 5.3 Hz, 1H), 4.68 (s, 1H), 3.97 – 3.92 (m, 1H), 3.77 (s, 3H), 2.62 (dt, J = 13.4, 3.8 Hz, 1H), 2.49 – 2.37 (m, 1H), 2.38 – 2.24 (m, 3H), 2.24 – 2.17 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 207.6, 174.8, 151.5, 149.5, 130.8, 130.7, 123.21, 123.19, 122.03, 122.01, 117.3, 117.2, 114.3, 114.1, 56.5, 52.7, 44.6, 44.5, 38.7, 34.6, 32.7; ^{19}F NMR (471 MHz, CDCl_3) δ -137.17 (dd, J = 11.1, 5.3 Hz) ppm. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$: calculated for $\text{C}_{14}\text{H}_{15}\text{FNO}_3^+$ 264.1036, found 264.1031.



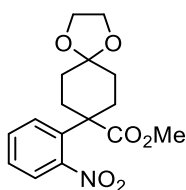
Methyl 9-methoxy-3-oxo-2,3,4,5-tetrahydro-2,6-methanobenzo[b]azocine-6(1H)-carboxylate (4g). The title compound was prepared according to the general procedure using methyl 1-(4-methoxy-2-nitrophenyl)-4-oxocyclohexane-1-carboxylate (55 mg, 0.18 mmol, 1.0 equiv.) and potassium carbonate (249 mg, 1.8 mmol, 10 equiv.) in *N*-methylpyrrolidinone (18 mL, 0.01 M). Purification by chromatography (CH_2Cl_2) gave **4g** (38 mg, 76%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 6.88 (d, J = 8.6 Hz, 1H), 6.31 (dd, J = 8.6, 2.5 Hz, 1H), 6.12 (d, J = 2.5 Hz, 1H), 3.81 (t, J = 3.3 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.60 (dt, J = 13.2, 3.7 Hz, 1H), 2.46 – 2.35 (m, 1H), 2.36 – 2.19 (m, 3H), 2.16 (dd, J = 13.2, 2.9 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 208.4, 175.4, 160.2, 142.8, 127.9, 113.9, 104.7, 99.3, 57.3, 55.3, 52.6, 44.2, 38.8, 34.7, 33.2 ppm. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$: calculated for $\text{C}_{15}\text{H}_{18}\text{NO}_4^+$ 276.1236, found 276.1236.



Methyl 3-oxo-2,3-dihydro-2,6-methanobenzo[b]azocine-6(1H)-

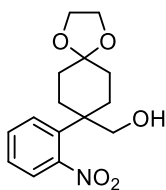
carboxylate (4h). The title compound was prepared according to the general procedure using methyl 1-(2-nitrophenyl)-4-oxocyclohex-2-ene-1-carboxylate (275 mg, 1.0 mmol, 1.0 equiv.) and potassium carbonate (1.38 g, 10 mmol, 10 equiv.) in *N*-methylpyrrolidinone (100 mL, 0.01 M). Purification by chromatography (CH₂Cl₂) gave **4h** (131 mg, 54%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.45 (dd, *J* = 10.1, 2.1 Hz, 1H), 7.12 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.69 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 6.61 (ddd, *J* = 8.1, 1.3, 0.5 Hz, 1H), 6.22 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.74 (s, 1H), 4.03 – 3.96 (m, 1H), 3.87 (s, 3H), 2.51 – 2.42 (m, 1H), 2.42 – 2.33 (m, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 193.8, 173.0, 151.2, 140.1, 129.4, 128.1, 125.8, 117.9, 117.6, 115.2, 53.8, 53.0, 46.5, 29.9 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₁₄H₁₄NO₃⁺ 244.0968, found 244.0965.

Synthesis of methyl 8-(2-nitrophenyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (**5**)



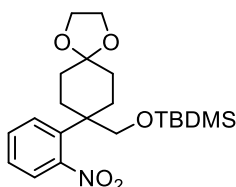
A solution of the precursor **3a** (100 mg, 0.36 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (4 mg, 0.022 mmol, 0.06 equiv.) in 2-ethyl-2-methyl-1,3-dioxolane (209 mg, 230 μL, 1.8 mmol, 5.0 equiv.) was stirred for 2 hours at room temperature. Then, the reaction was quenched with a saturated solution of NaHCO₃ and extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂) gave **5** as a colorless oil (102 mg, 89%). ¹H NMR (400 MHz, CDCl₃) δ 7.71 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.67 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.1, 7.3, 1.5 Hz, 1H), 7.40 (ddd, *J* = 8.0, 7.3, 1.3 Hz, 1H), 3.99 – 3.86 (m, 4H), 3.68 (s, 3H), 2.44 – 2.33 (m, 2H), 2.20 – 2.10 (m, 2H), 1.98 – 1.87 (m, 2H), 1.64 – 1.53 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 174.8, 149.9, 135.8, 132.5, 129.6, 128.1, 125.5, 107.9, 64.5, 64.4, 52.3, 49.1, 31.7, 31.6 ppm.

Synthesis of (8-(2-nitrophenyl)-1,4-dioxaspiro[4.5]decan-8-yl)methanol (**6**)¹⁰



A solution of **5** (139 mg, 0.43 mmol, 1.0 equiv.) in toluene (2.1 mL, 0.2 M) was cooled at -78 °C. Then, DIBAL-H (1.0 M in toluene, 1.1 mL, 1.08 mmol, 2.5 equiv.) was added dropwise and the resulting mixture was stirred at -78 °C for 2 hours. Upon completion, the reaction was quenched with methanol and Rochelle's salt at 0 °C and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 1%) gave **6** as a colorless oil (116 mg, 92%). ¹H NMR (400 MHz, MeOD) δ 7.71 – 7.64 (m, 1H), 7.62 – 7.54 (m, 1H), 7.48 – 7.42 (m, 2H), 3.97 – 3.89 (m, 2H), 3.89 – 3.85 (m, 2H), 3.72 (s, 2H), 2.29 – 2.13 (m, 2H), 1.83 (ddd, *J* = 14.5, 13.4, 3.2 Hz, 2H), 1.72 – 1.61 (m, 2H), 1.39 (td, *J* = 13.6, 3.5 Hz, 2H); ¹³C{¹H} NMR (101 MHz, MeOD) δ 153.8, 133.5, 133.4, 131.7, 128.9, 125.3, 109.5, 70.9, 65.3, 65.2, 46.8, 32.8, 30.4 ppm.

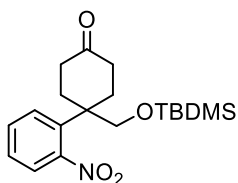
Synthesis of *tert*-butyldimethyl((8-(2-nitrophenyl)-1,4-dioxaspiro[4.5]decan-8-yl)methoxy) silane (**7**)



To a solution of **6** (270 mg, 0.92 mmol, 1.0 equiv.) in dichloromethane (1.5 mL, 0.6 M) were added imidazole (88 mg, 1.29 mmol, 1.4 equiv.), *tert*-butyldimethylsilyl chloride (194 mg, 1.29 mmol, 1.4 equiv.) and 4-dimethylaminopyridine (6 mg, 0.05 mmol, 0.05 equiv.) and the resulting mixture was stirred for 4 hours at room temperature. Upon completion, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with ammonium chloride (10 mL) and brine (10 mL), dried with Na₂SO₄ and concentrated under reduced pressure. Purification by chromatography (CH₂Cl₂) gave **7** as a colorless oil (327 mg, 87%). ¹H NMR (400 MHz, MeOD) δ 7.67 – 7.62 (m, 1H), 7.55 (ddd, *J* = 8.2, 6.4, 2.4 Hz, 1H), 7.47 – 7.40 (m, 2H), 3.96 – 3.90 (m, 2H), 3.90

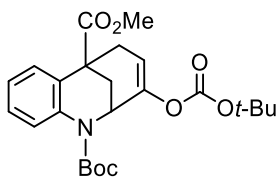
– 3.84 (m, 2H), 3.77 (s, 2H), 2.30 – 2.14 (m, 2H), 1.79 (td, $J = 14.1, 3.2$ Hz, 2H), 1.71 – 1.60 (m, 2H), 1.39 (td, $J = 13.5, 3.4$ Hz, 2H), 0.83 (s, 9H), -0.11 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, MeOD) δ 153.7, 133.9, 133.5, 131.4, 128.9, 125.2, 109.6, 71.9, 65.3, 65.2, 46.7, 32.9, 30.6, 26.3, 19.1, -5.6 ppm.

Synthesis of 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(2-nitrophenyl)cyclohexan-1-one (8**)¹¹**



To a solution of **7** (306 mg, 0.75 mmol, 1.0 equiv.) in acetone (3.8 mL, 0.2 M) was added *p*-toluenesulfonic acid monohydrate (3 mg, 0.015 mmol, 0.02 equiv.) in one portion and the solution was stirred for 24 hours at room temperature. Then, the reaction was quenched with a saturated solution of NaHCO_3 and acetone was evaporated under reduced pressure. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers were washed with a saturated solution of NaHCO_3 (10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography (Hex/AcOEt 10%) gave **8** as a yellow oil alongside smaller amounts of unidentified impurities. However, a tentative yield (137 mg, 50%) is provided. ^1H NMR (400 MHz, MeOD) δ 7.80 – 7.72 (m, 1H), 7.68 – 7.59 (m, 1H), 7.58 – 7.48 (m, 2H), 3.88 (s, 2H), 2.60 – 2.46 (m, 2H), 2.39 – 2.09 (m, 4H), 1.97 (ddd, $J = 14.3, 13.2, 4.7$ Hz, 2H), 0.84 (s, 9H), -0.09 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, MeOD) δ 212.5, 153.7, 133.7, 132.3, 131.9, 129.5, 125.5, 71.6, 46.6, 38.9, 32.6, 26.3, 19.1, -5.6 ppm.

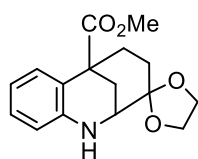
Synthesis of 1-(*tert*-butyl) 6-methyl 3-((*tert*-butoxycarbonyl)oxy)-2,5-dihydro-2,6-methanobenzo[*b*]azocine-1,6-dicarboxylate (9**)**



A solution of benzazocine **4a** (49 mg, 0.20 mmol, 1.0 equiv.) and di-*tert*-butyl dicarbonate (131 mg, 0.60 mmol, 3.0 equiv.) in anhydrous tetrahydrofuran (3 mL, 0.07 M) was cooled to 0 °C. Then, a 1.0 M solution of LiHMDS in THF (0.40 mL,

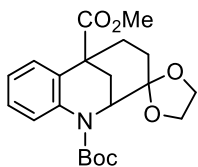
0.40 mmol, 2.0 equiv.) was added dropwise, and the mixture was stirred at room temperature for 2 hours. After this time, the reaction was quenched with water and subsequently dried with sodium sulfate. The resulting mixture was filtered and concentrated in vacuo. Purification by chromatography (Hex/AcOEt 5% → Hex/AcOEt 25%) gave **9** as a yellow oil (45 mg, 51%). ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, J = 8.5 Hz, 1H), 7.19 (ddd, J = 8.6, 7.1, 1.7 Hz, 1H), 7.08 (dd, J = 7.8, 1.7 Hz, 1H), 6.99 (ddd, J = 8.1, 7.1, 1.3 Hz, 1H), 5.50 – 5.43 (m, 2H), 3.72 (s, 3H), 2.86 (dt, J = 17.8, 1.6 Hz, 1H), 2.58 – 2.46 (m, 2H), 2.16 (dd, J = 12.7, 3.7 Hz, 1H), 1.55 (s, 9H), 1.51 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 175.5, 152.9, 151.9, 145.2, 136.5, 128.3, 127.5, 126.6, 124.2, 123.8, 116.0, 83.4, 81.8, 52.7, 49.0, 45.1, 37.4, 32.4, 28.5, 27.9 ppm. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$: calculated for $\text{C}_{24}\text{H}_{32}\text{NO}_7^+$ 446.2173, found 446.2175.

Synthesis of methyl 1',2',4',5'-tetrahydro-6'H-spiro[[1,3]dioxolane-2,3'-[2,6] methano benzo [b]azocine]-6'-carboxylate (10**)**



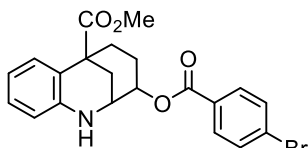
A solution of benzazocine **4a** (123 mg, 0.50 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol, 0.1 equiv.) in 2-ethyl-2-methyl-1,3-dioxolane (3 mL, 0.17 M) was stirred at room temperature overnight. Afterward, the reaction was quenched with solid potassium carbonate, filtered, and concentrated in vacuo. Purification by chromatography (Hex/AcOEt 1% → Hex/AcOEt 50%) gave **10** as a yellow oil (106 mg, 73%). ^1H NMR (400 MHz, CDCl_3) δ 7.04 (ddd, J = 8.0, 7.2, 1.5 Hz, 1H), 6.84 (dd, J = 7.7, 1.5 Hz, 1H), 6.61 (ddd, J = 7.5, 7.4, 1.2 Hz, 1H), 6.55 (dd, J = 8.1, 1.2 Hz, 1H), 4.05 – 3.88 (m, 4H), 3.74 (s, 3H), 3.31 – 3.25 (m, 1H), 2.34 (ddd, J = 12.8, 3.8, 2.8 Hz, 1H), 2.22 (dd, J = 12.8, 2.8 Hz, 1H), 2.17 – 1.98 (m, 2H), 1.57 – 1.48 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 176.2, 143.5, 128.2, 126.5, 122.3, 117.3, 114.2, 110.2, 65.3, 64.6, 52.24, 52.16, 44.7, 35.3, 30.2, 28.0 ppm. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$: calculated for $\text{C}_{16}\text{H}_{20}\text{NO}_4^+$ 290.1387, found 290.1389.

Synthesis of 1'-(*tert*-butyl) 6'-methyl 4',5'-dihydro-2'*H*-spiro[[1,3]dioxolane-2,3'-[2,6]methanobenzo[*b*]azocine]-1',6'-dicarboxylate (11)



A solution of benzazocine **10** (58 mg, 0.20 mmol, 1.0 equiv.) and di-*tert*-butyl dicarbonate (131 mg, 0.60 mmol, 3.0 equiv.) in anhydrous tetrahydrofuran (3 mL, 0.07 M) was cooled to 0 °C. Then, a 1.0 M solution of LiHMDS in THF (0.40 mL, 0.40 mmol, 2.0 equiv.) was added dropwise, and the mixture was stirred at room temperature for 2 hours. After this time, the reaction was quenched with water and subsequently dried with sodium sulfate. The resulting mixture was filtered and concentrated in vacuo. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **11** as a colorless oil (71 mg, 91%). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.19 (ddd, *J* = 8.7, 6.6, 2.3 Hz, 1H), 7.00 – 6.89 (m, 2H), 4.70 – 4.65 (m, 1H), 4.13 – 3.98 (m, 3H), 3.98 – 3.90 (m, 1H), 3.73 (s, 3H), 2.38 (dt, *J* = 13.0, 3.4 Hz, 1H), 2.20 (dd, *J* = 13.0, 3.2 Hz, 1H), 2.11 (td, *J* = 13.6, 4.3 Hz, 1H), 1.95 (ddt, *J* = 13.3, 5.3, 2.6 Hz, 1H), 1.56 (s, 9H), 1.54 – 1.47 (m, 1H), 1.24 (td, *J* = 14.0, 5.2 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 176.0, 154.0, 137.9, 127.4, 126.9, 126.2, 123.0, 122.4, 108.2, 81.8, 65.2, 65.1, 53.1, 52.4, 45.8, 35.1, 30.5, 29.2, 28.5 ppm. HRMS (ESI) *m/z* [M + H]⁺: calculated for C₂₁H₂₈NO₆⁺ 390.1911, found 390.1910.

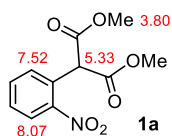
Synthesis of methyl 3-((4-bromobenzoyl)oxy)-2,3,4,5-tetrahydro-2,6-methanobenzo[*b*]azocine-6(1*H*)-carboxylate (13)



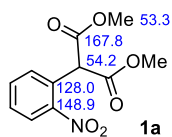
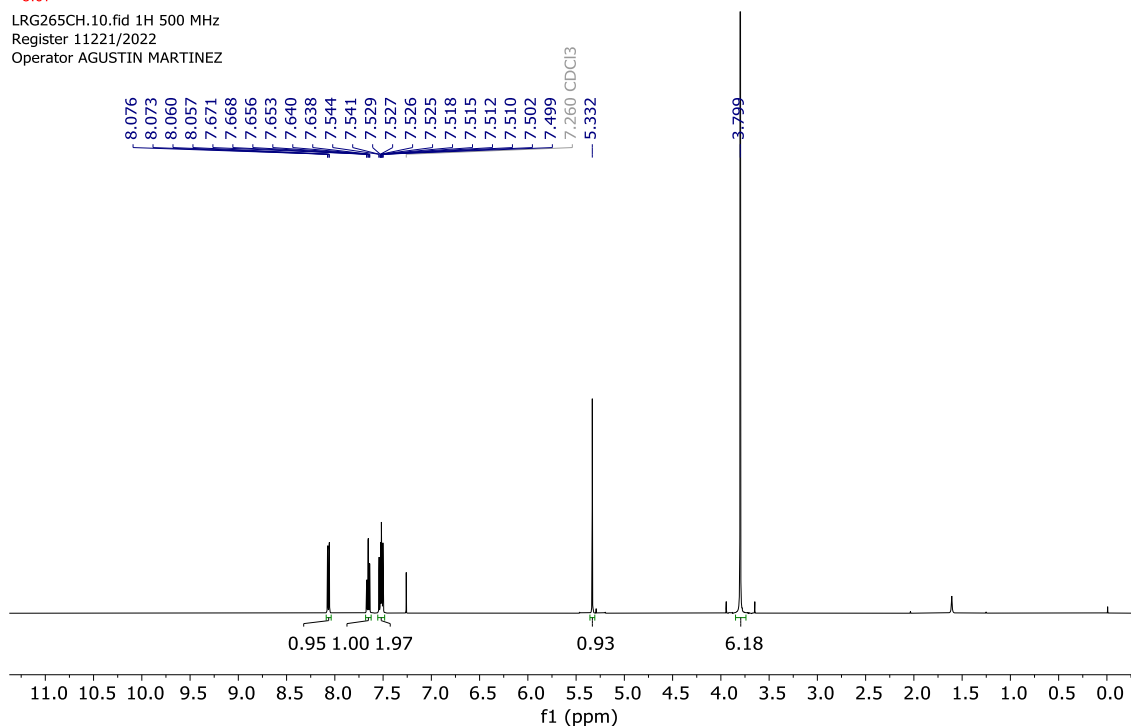
A solution of **4a** (57 mg, 0.24 mmol, 1.0 equiv.) in methanol (3 mL, 0.08 M) was cooled to 0 °C. Then, sodium borohydride (18 mg, 0.48 mmol, 2.0 equiv.) was added in one portion and the resulting mixture was stirred for 2 hours. Upon completion, the reaction was quenched with a saturated solution of NaHCO₃ and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried with Na₂SO₄, filtered and concentrated under reduced pressure. Methyl 3-hydroxy-2,3,4,5-tetrahydro-2,6-methanobenzo[*b*]azocine-6(1*H*)-carboxylate

(**12**) was isolated as a colorless oil without further purification (56 mg, 95%). The product was then dissolved in dichloromethane (4.6 mL, 0.05 M) and the resulting solution was cooled to 0 °C. After, DMAP (1 mg, 0.008 mmol, 0.35 equiv.), triethylamine (28 mg, 39 μ L, 0.28 mmol, 1.2 equiv.) and 4-bromobenzoyl chloride (61 mg, 0.28 mmol, 1.2 equiv.) were added in one portion. The mixture was stirred at room temperature for 4 hours and, upon completion, the reaction was diluted with water (5 mL) and extracted with dichloromethane (3 $\times$ 5 mL). The combined organic layers were washed with brine (5 mL), dried with Na₂SO₄, filtered and concentrated under reduced pressure. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **13** as a colorless oil (65 mg, 66%). The NMR data reported correspond to the major isomer. ¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.87 (m, 2H), 7.63 – 7.57 (m, 2H), 7.10 – 7.03 (m, 1H), 6.85 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 6.68 – 6.60 (m, 2H), 5.05 (ddd, J = 11.8, 5.2, 2.9 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.80 – 3.73 (m, 3H), 2.57 – 2.46 (m, 1H), 2.19 (ddt, J = 13.6, 5.3, 3.0 Hz, 1H), 2.10 (dd, J = 13.6, 4.1 Hz, 1H), 2.06 – 1.99 (m, 1H), 1.99 – 1.89 (m, 1H), 1.64 (qd, J = 13.2, 4.9 Hz, 1H) ppm.

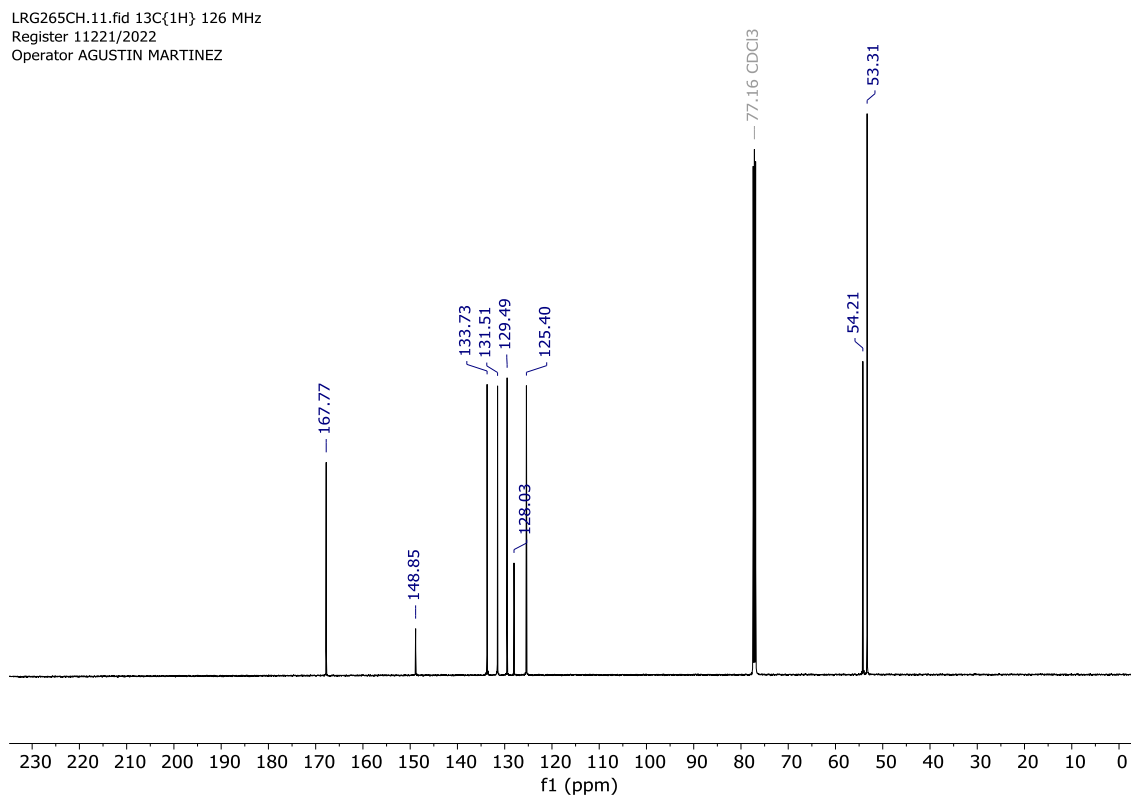
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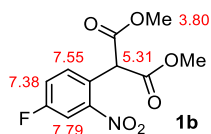


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Operator AGUSTIN MARTINEZ

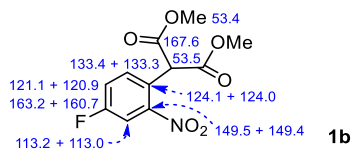
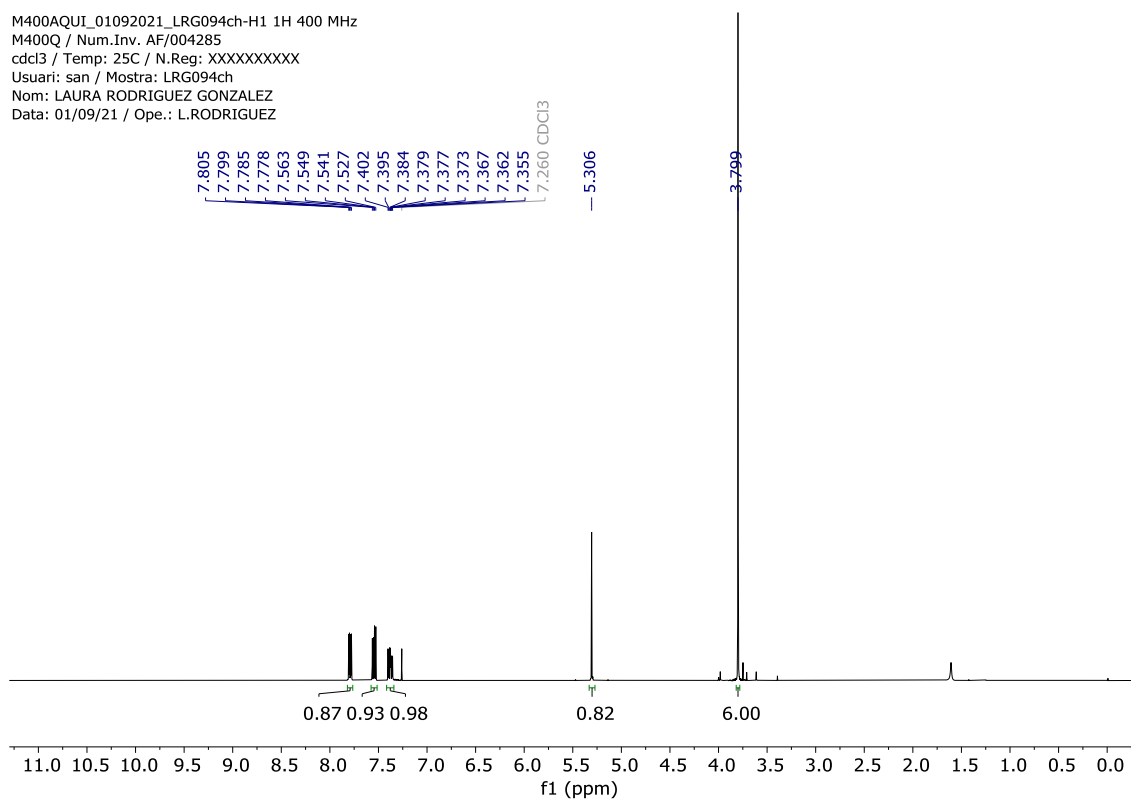


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Register 11221/2022
Operator AGUSTIN MARTINEZ

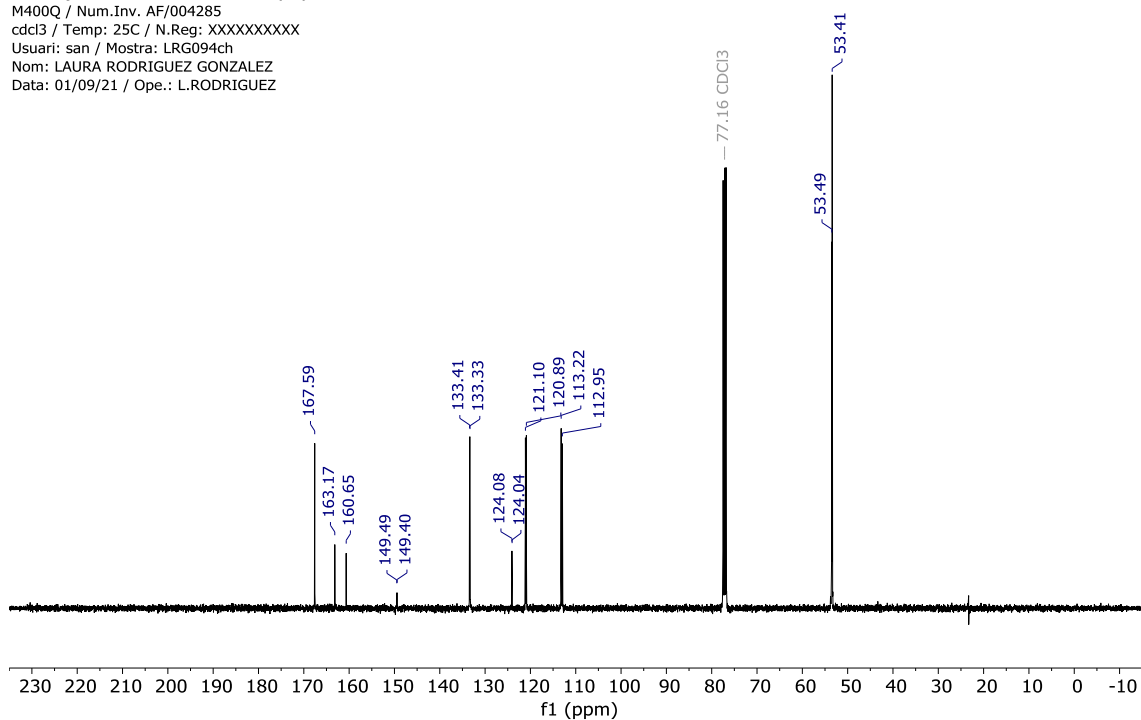


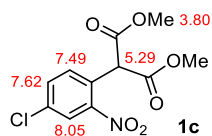


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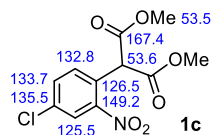
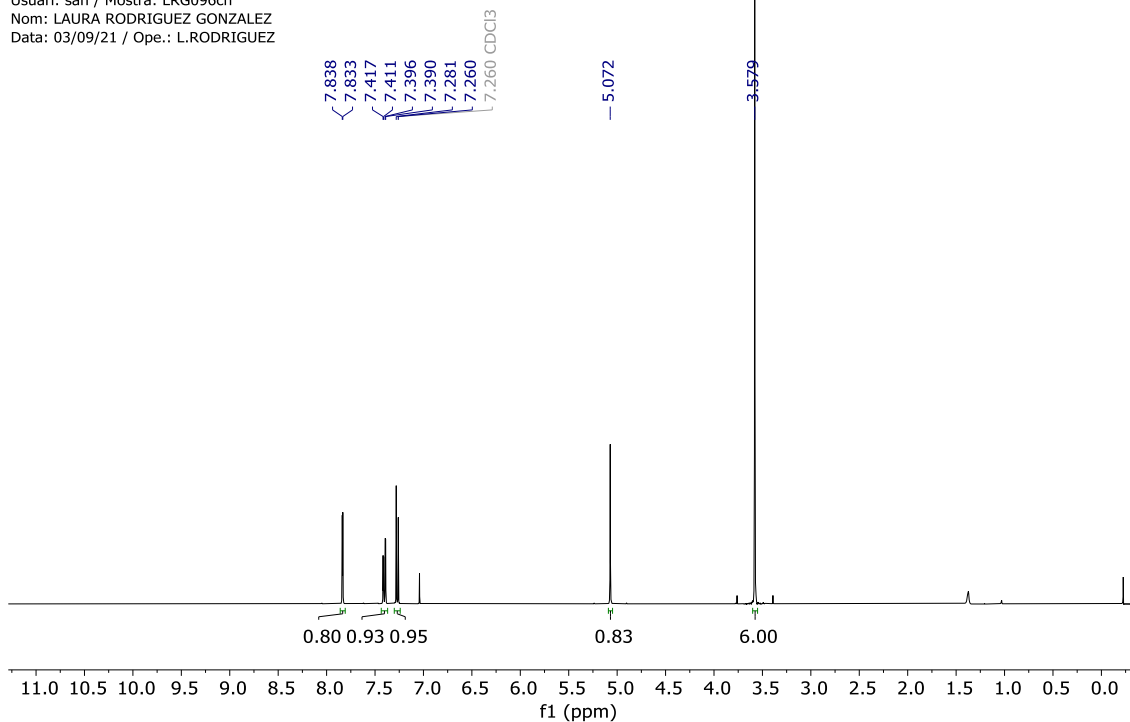


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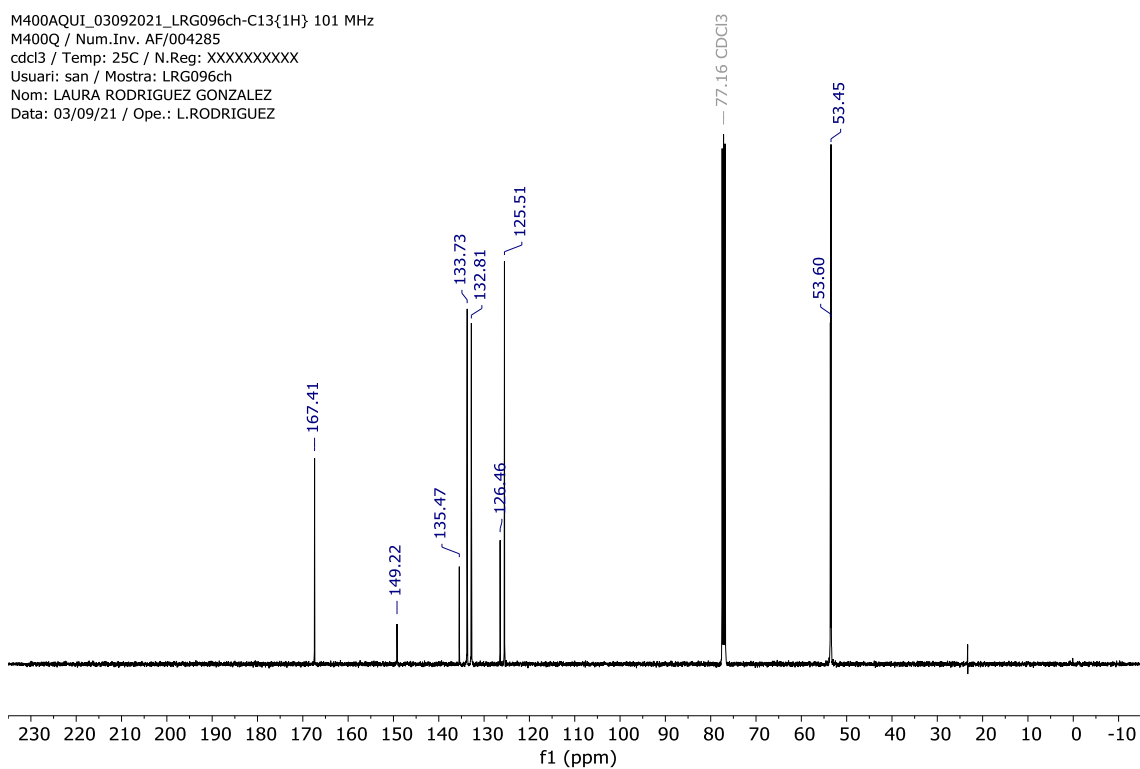


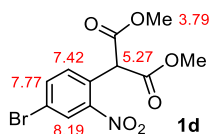


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Data: 03/09/21 / Ope.: L.RODRIGUEZ

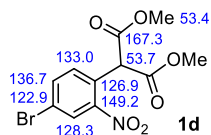
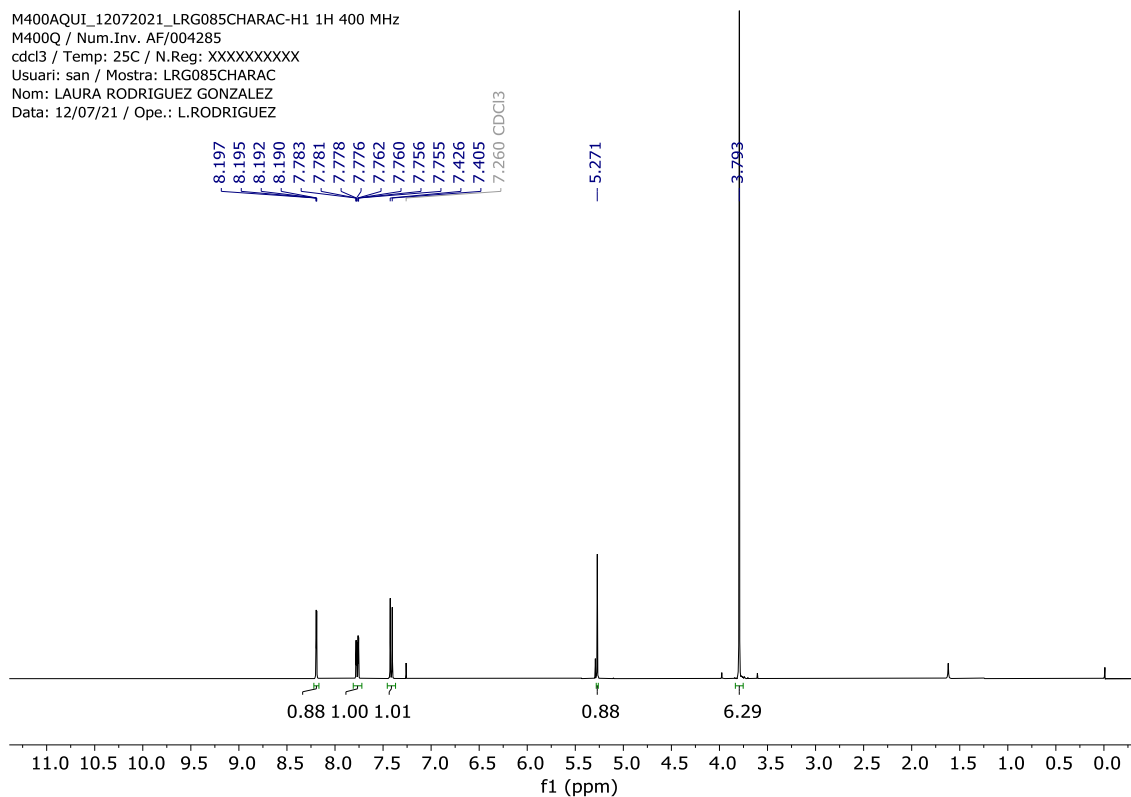


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Data: 03/09/21 / Ope.: L.RODRIGUEZ

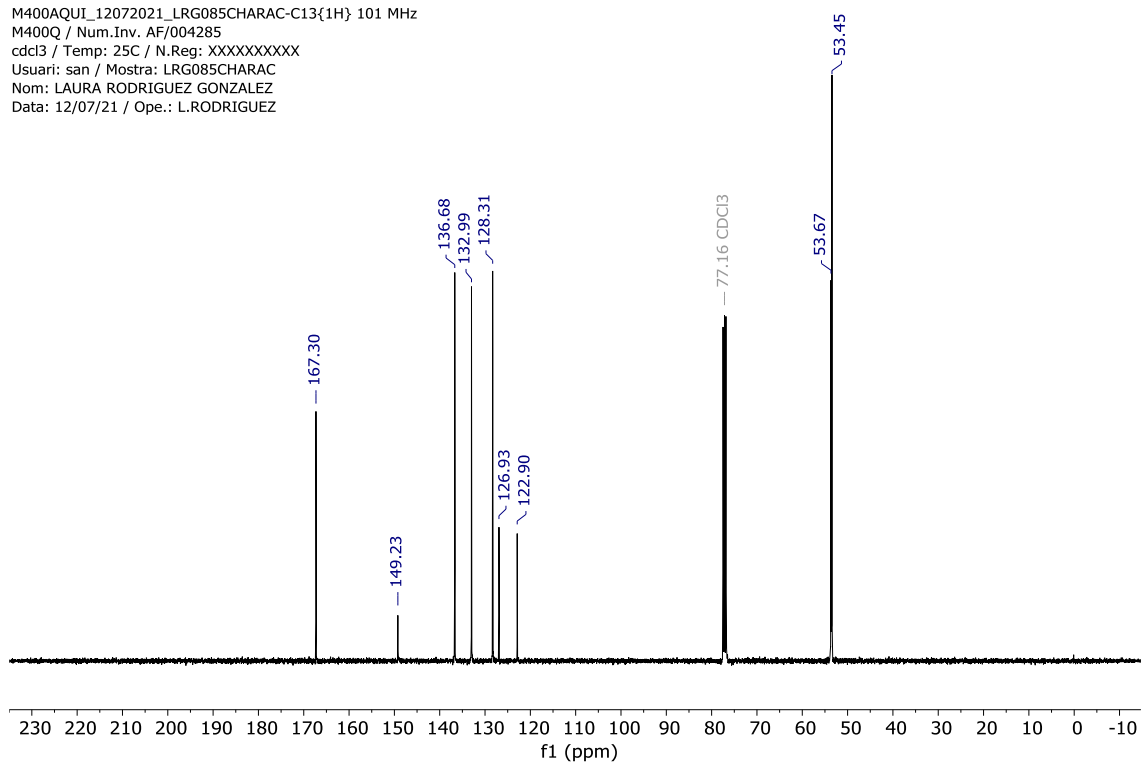


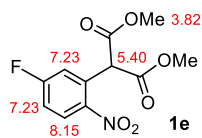


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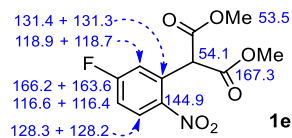
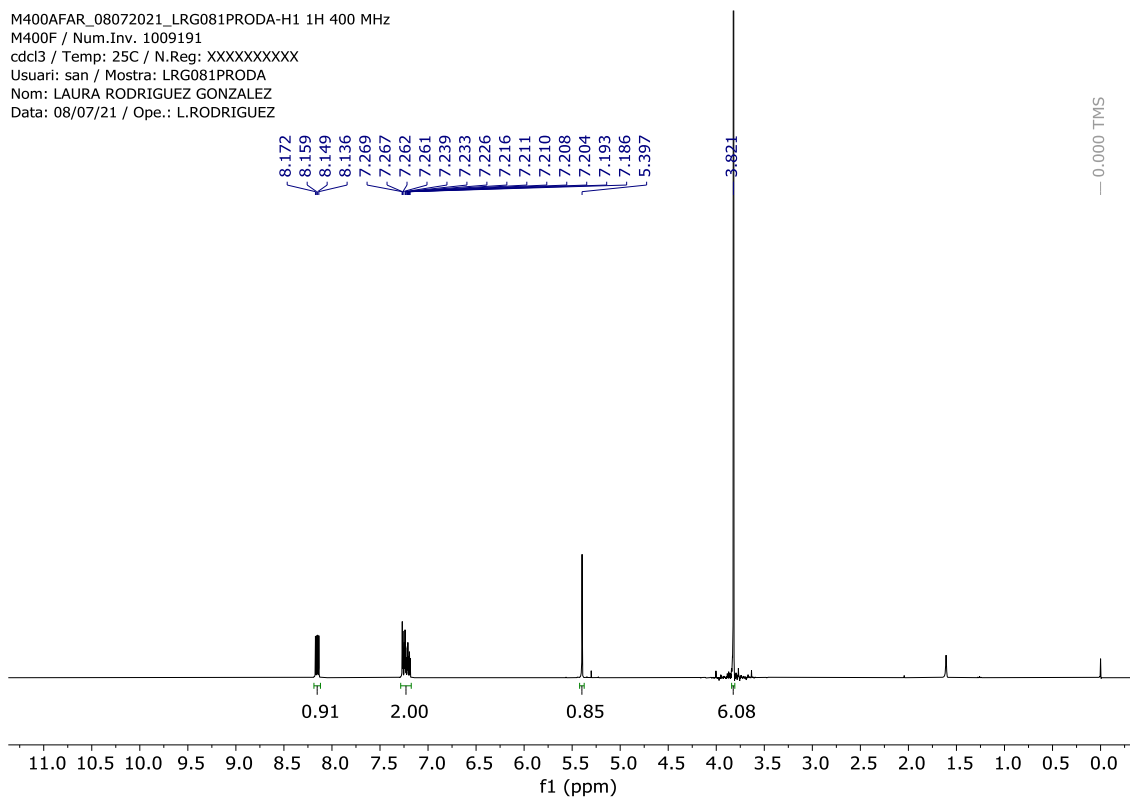


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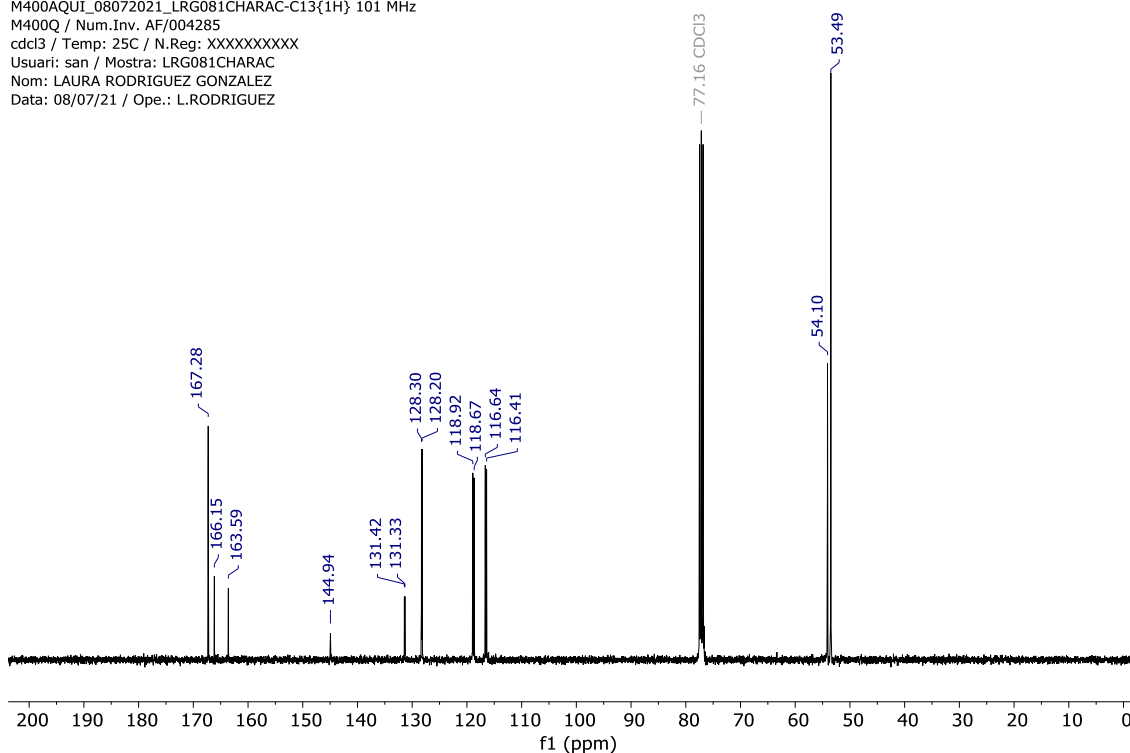


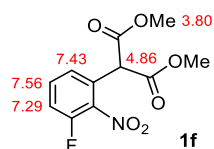


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Data: 08/07/21 / Ope.: L.RODRIGUEZ

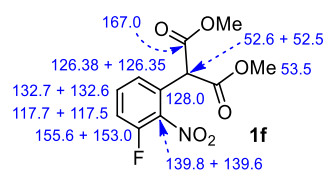
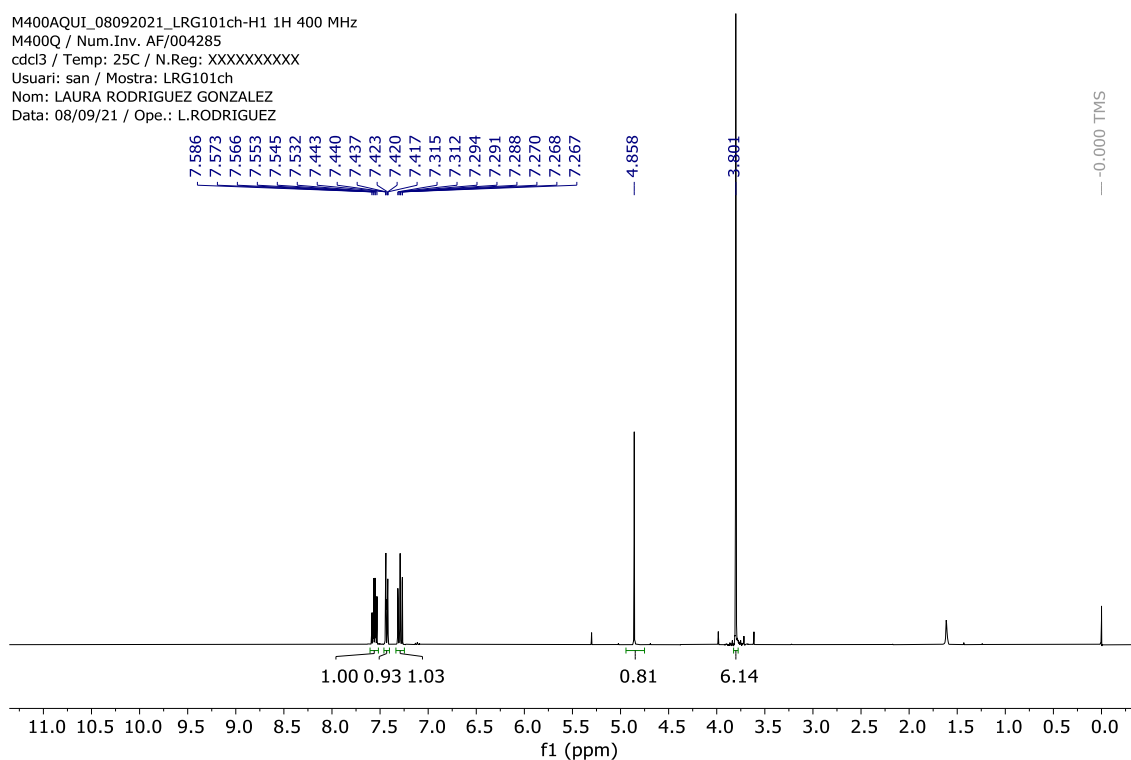


M400AQUI_08072021_LRG081CHARAC-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG081CHARAC
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 08/07/21 / Ope.: L.RODRIGUEZ

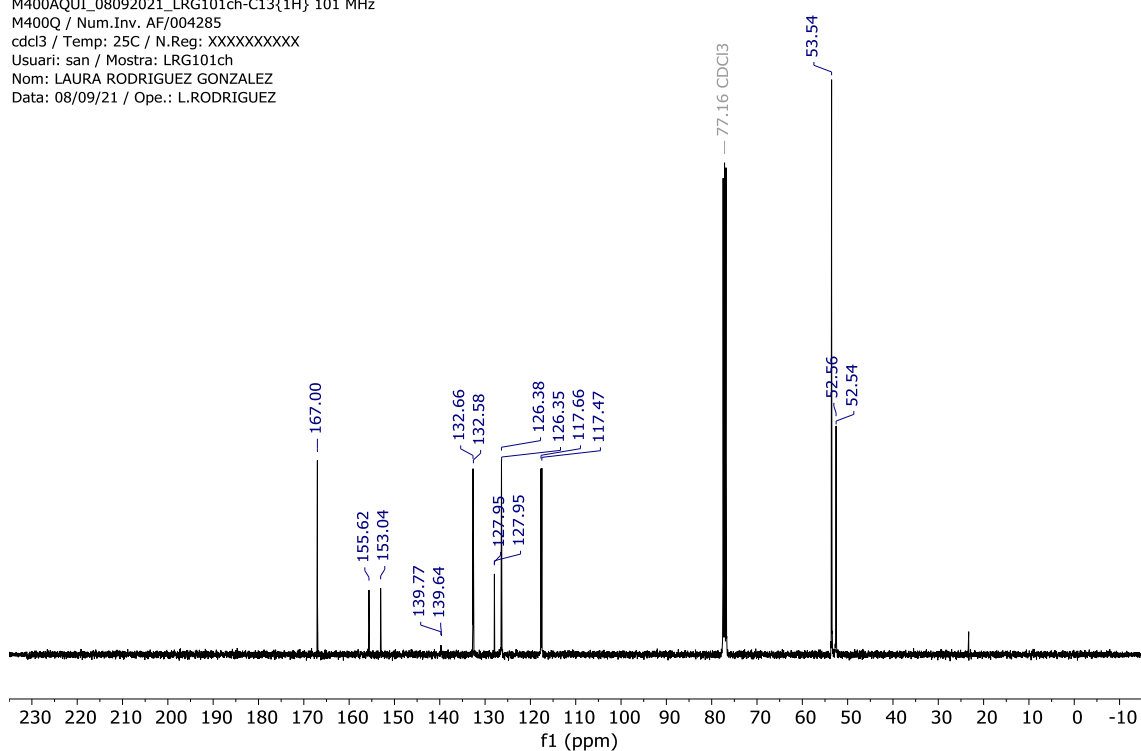


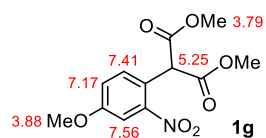


M400AQUI_08092021_LRG101ch-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG101ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/09/21 / Ope.: L.RODRIGUEZ

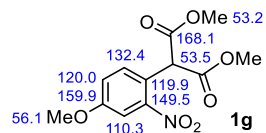
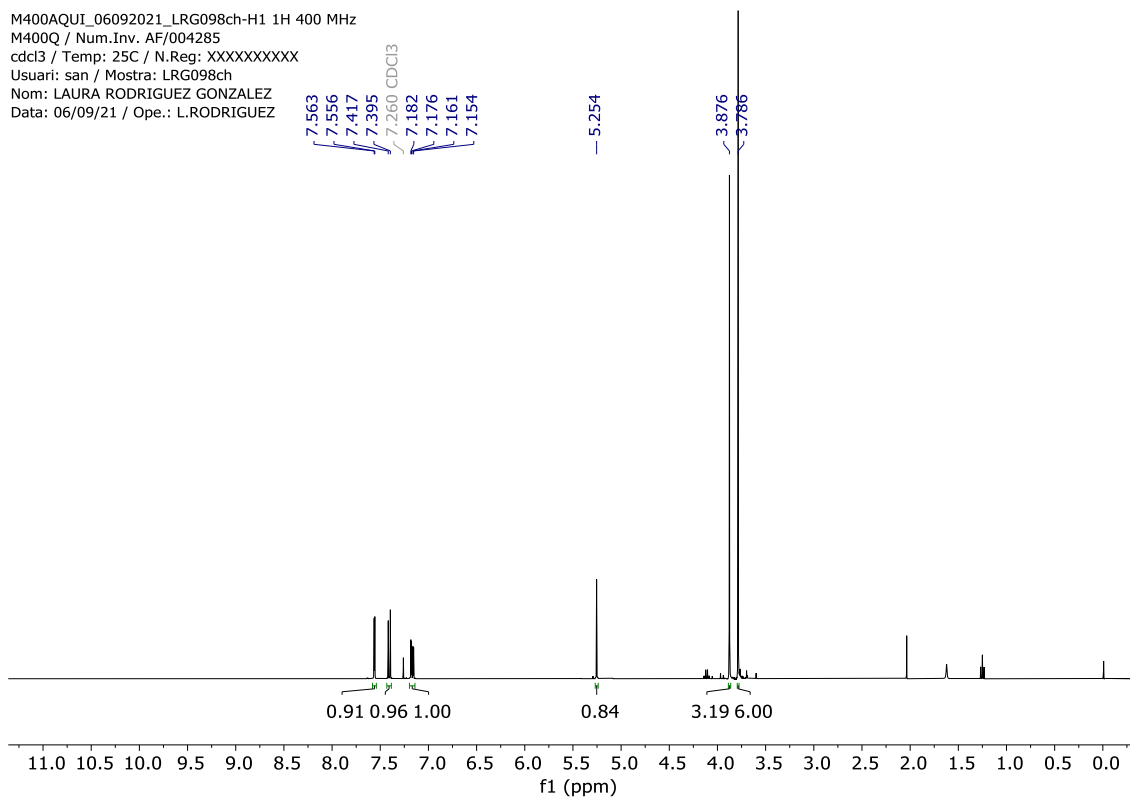


M400AQUI_08092021_LRG101ch-C13{1H} 101 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG101ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/09/21 / Ope.: L.RODRIGUEZ

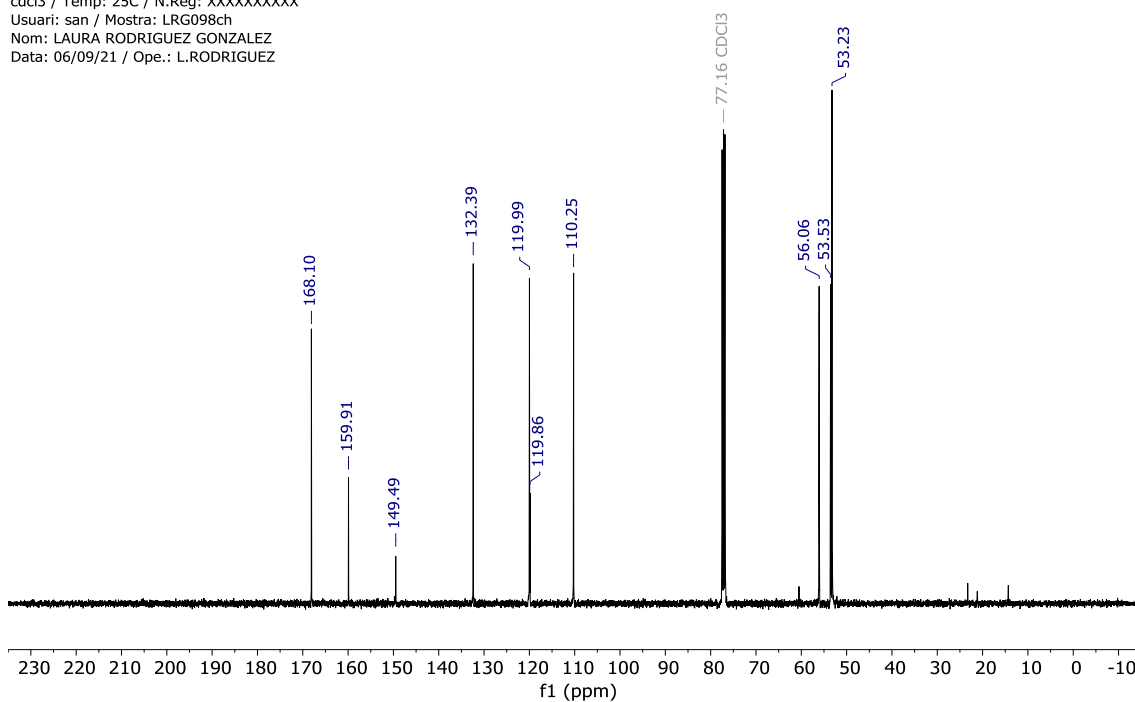


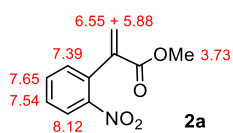


M400AQUI_06092021_LRG098ch-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG098ch
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 06/09/21 / Ope.: L.RODRIGUEZ

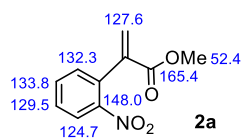
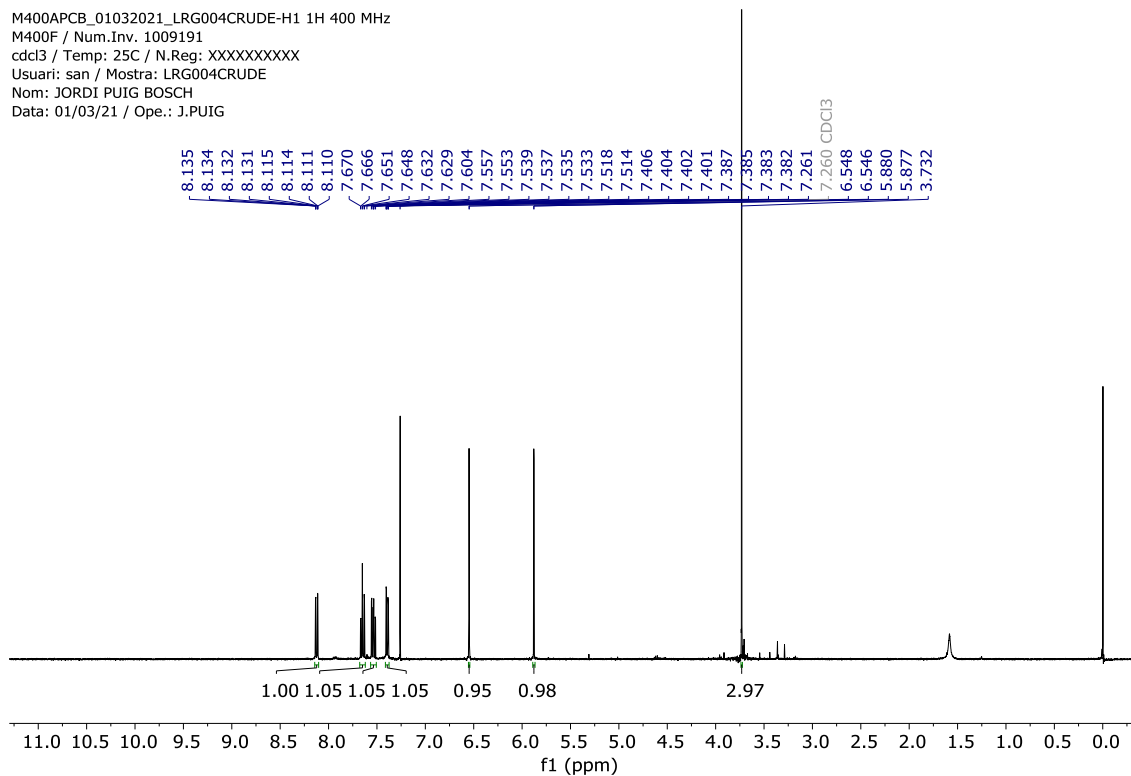


M400AQUI_06092021_LRG098ch-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG098ch
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 06/09/21 / Ope.: L.RODRIGUEZ

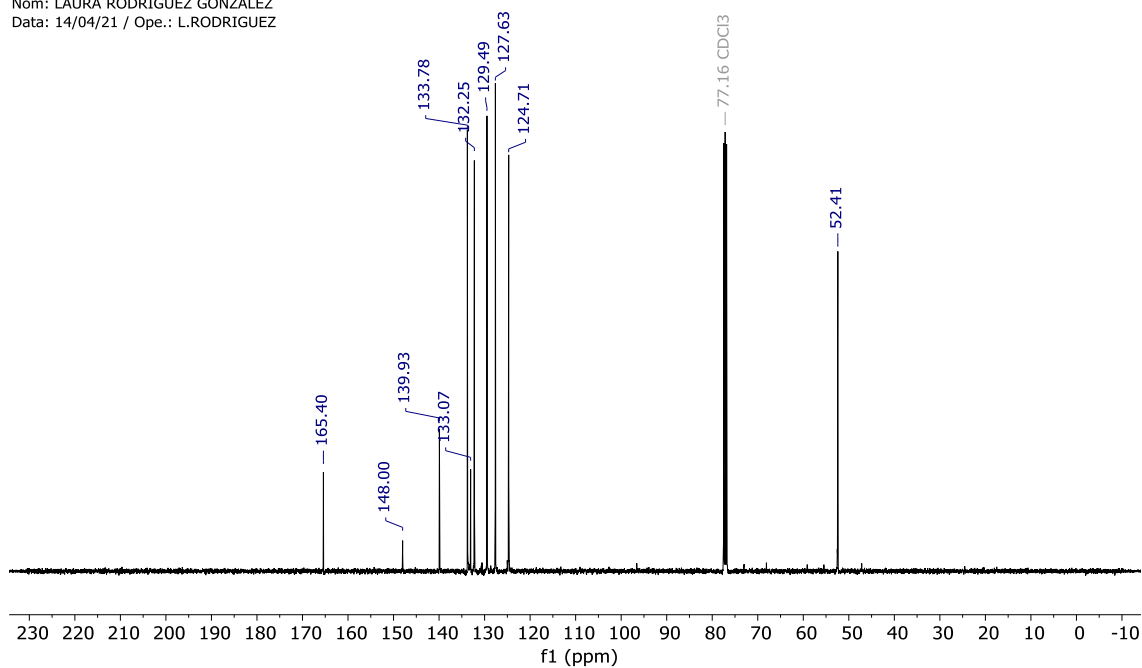




M400APCB_01032021_LRG004CRUDE-H1 1H 400 MHz
 M400F / Num.Inv. 1009191
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG004CRUDE
 Nom: JORDI PUIG BOSCH
 Data: 01/03/21 / Ope.: J.PUIG

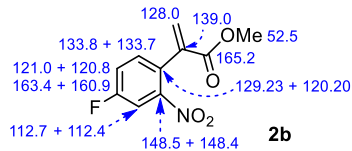
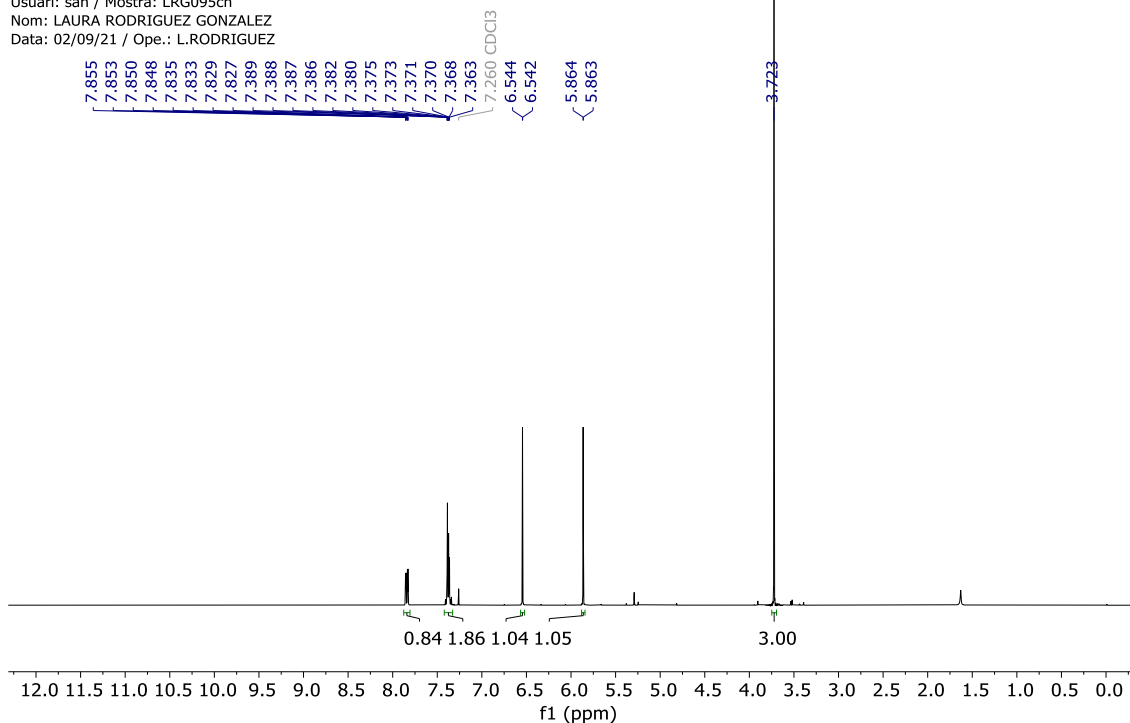


VNMRS400A_14042021_LRG023CH-C13{1H} 101 MHz
 VNMRS400F / Num.Inv. 205984
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG023CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/04/21 / Ope.: L.RODRIGUEZ

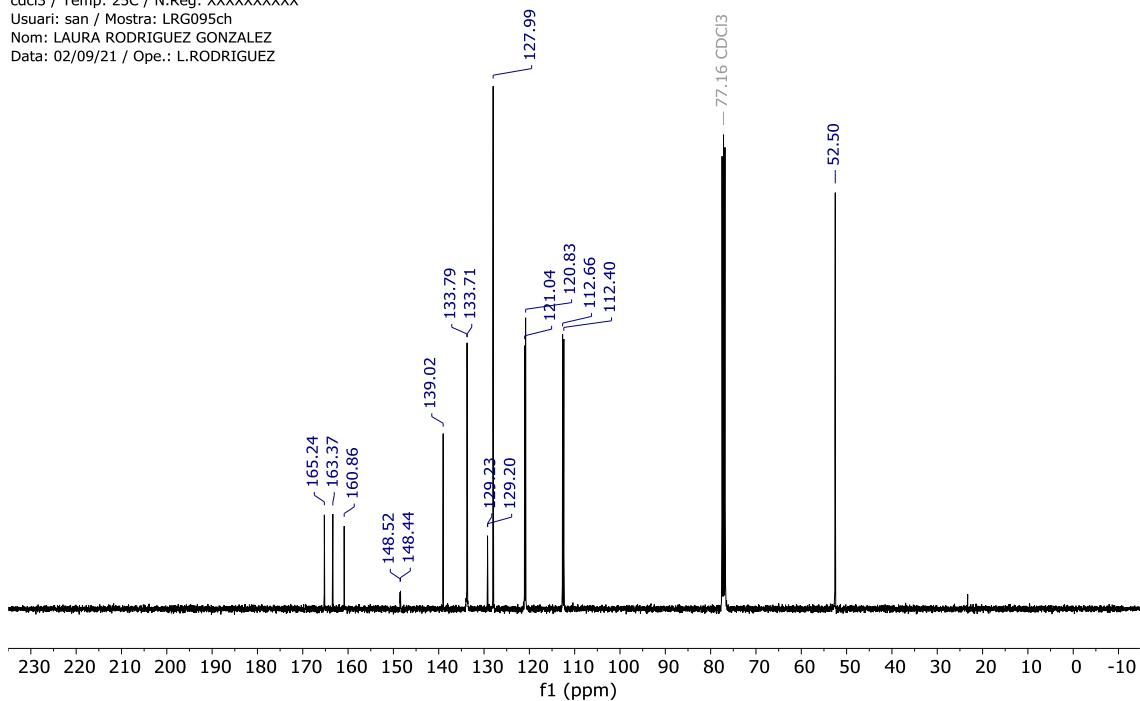


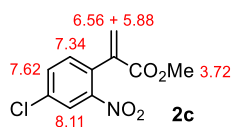


M400AQUI_02092021_LRG095ch-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: LRG095ch
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 02/09/21 / Ope.: L.RODRIGUEZ

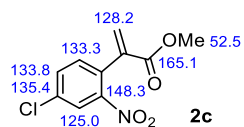
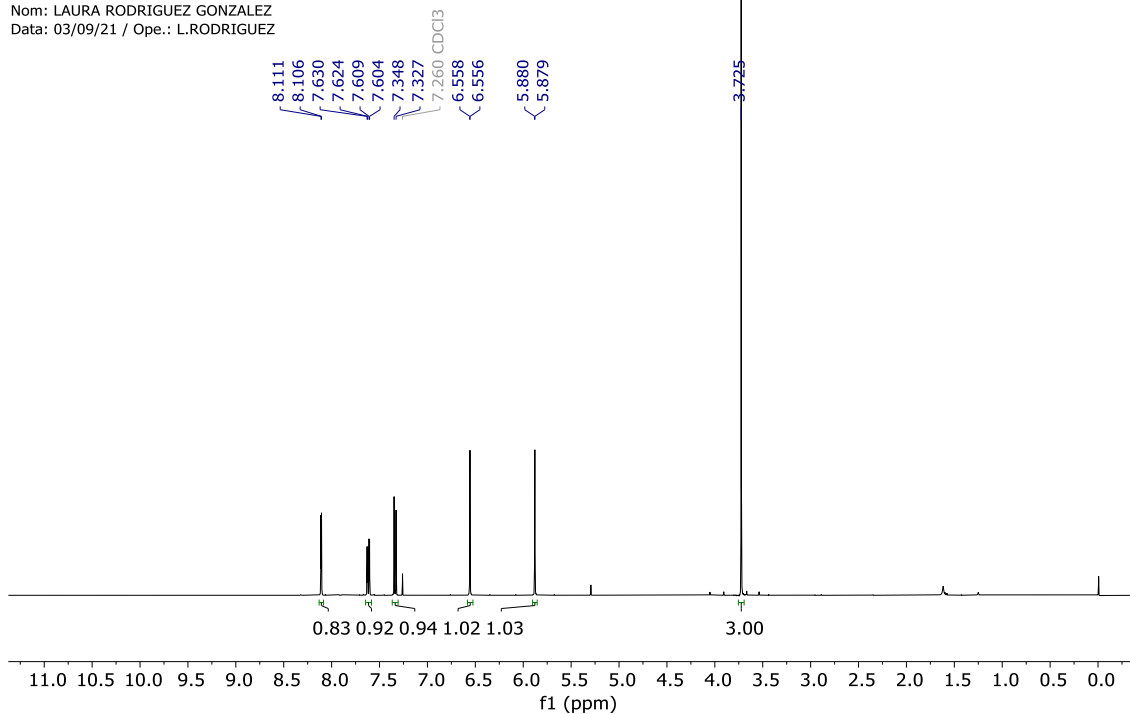


M400AQUI_02092021_LRG095ch-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: LRG095ch
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 02/09/21 / Ope.: L.RODRIGUEZ

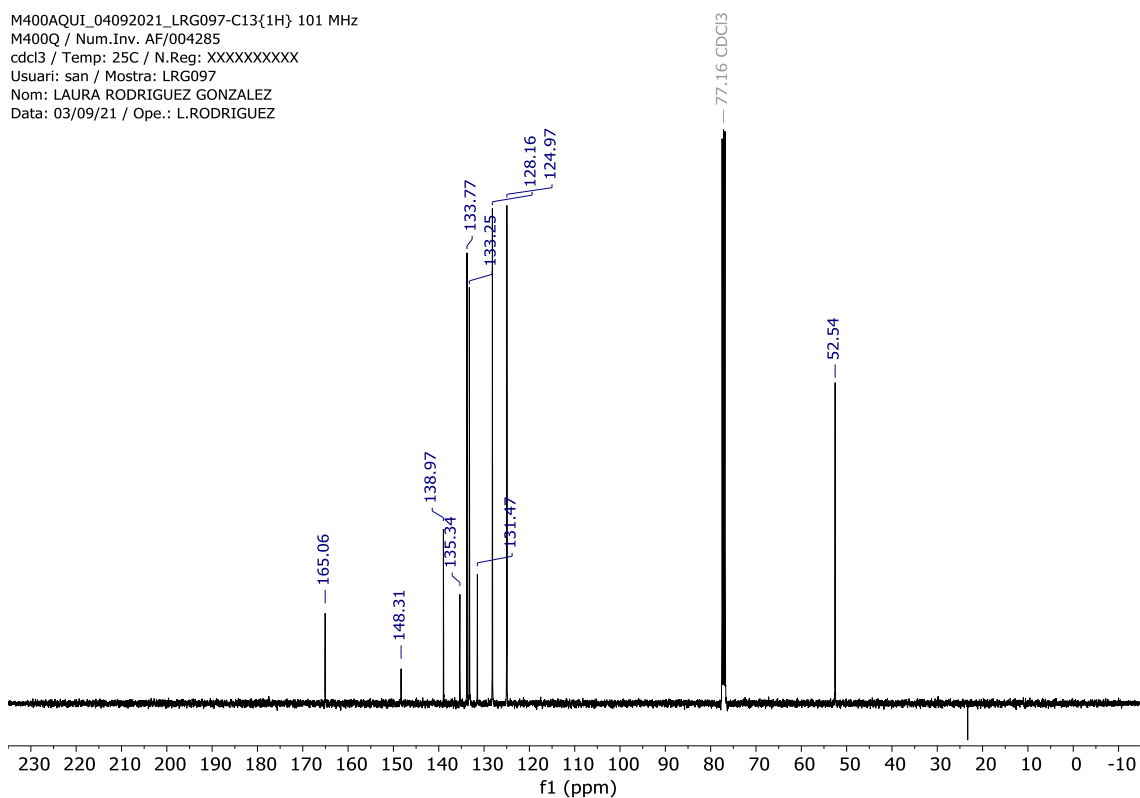




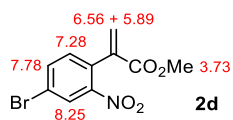
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 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG097
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/09/21 / Ope.: L.RODRIGUEZ



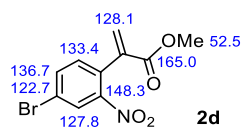
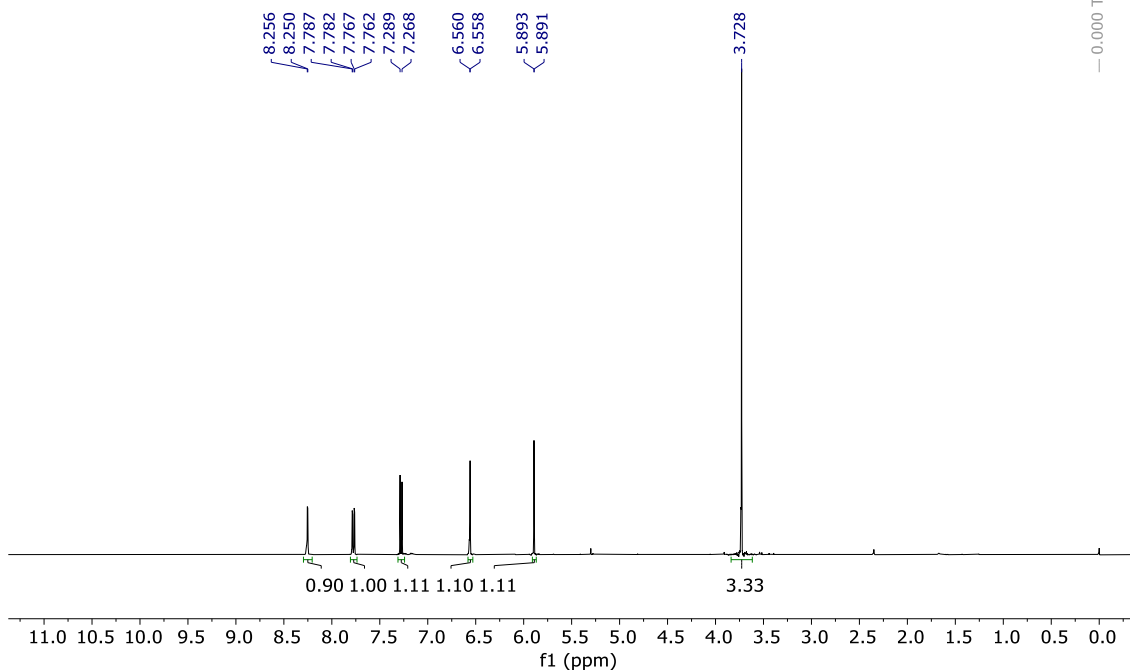
M400AQUI_04092021_LRG097-C13{1H} 101 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG097
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/09/21 / Ope.: L.RODRIGUEZ



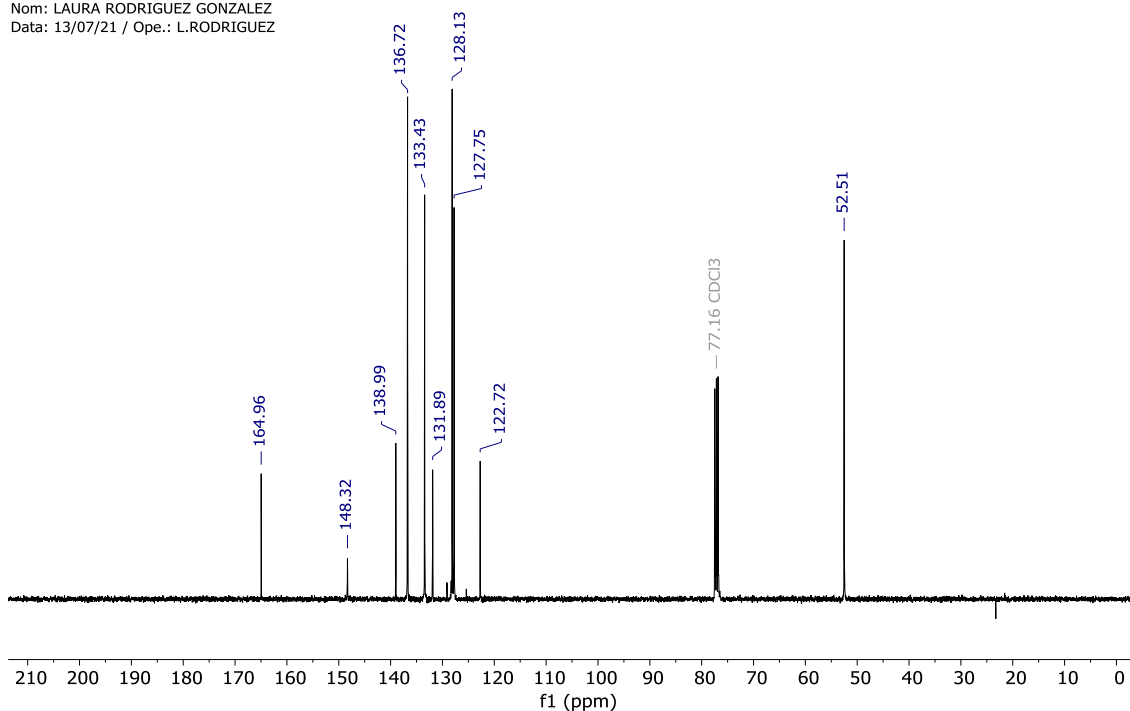
Experimental Section: Chapter 3

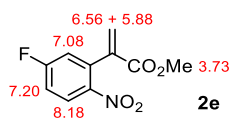


M400AFAR_13072021_LRG086-H1 1H 400 MHz
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: LRG086
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 13/07/21 / Ope.: L.RODRIGUEZ

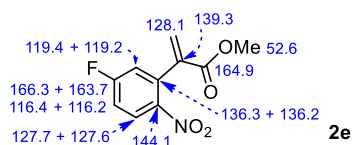
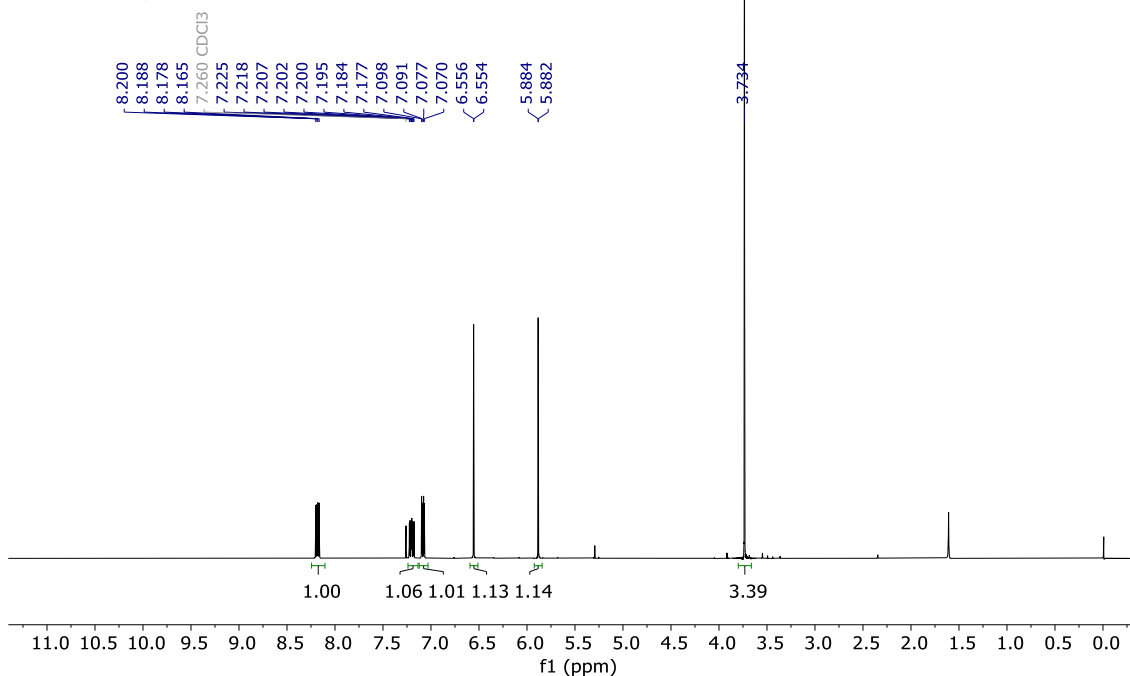


M400AQUI_13072021_LRG086CHARAC-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: LRG086CHARAC
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 13/07/21 / Ope.: L.RODRIGUEZ

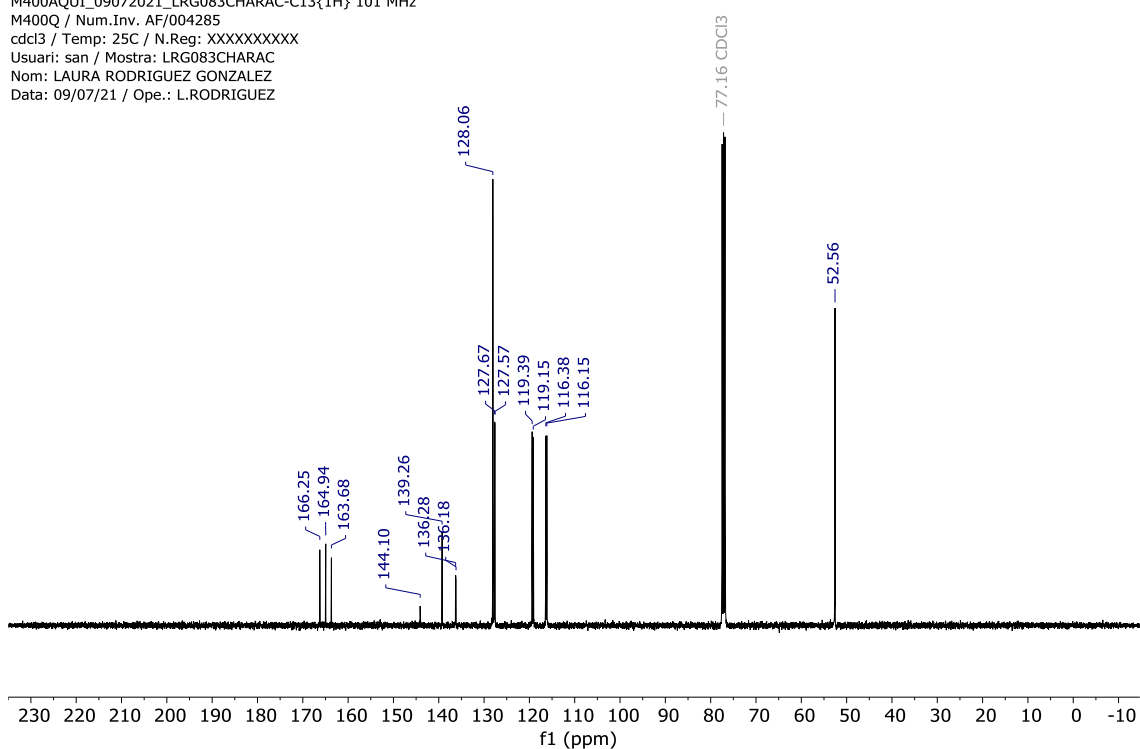




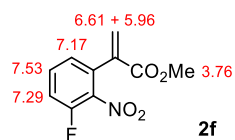
M400AQUI_09072021_LRG083CHARAC-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG083CHARAC
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 09/07/21 / Ope.: L.RODRIGUEZ



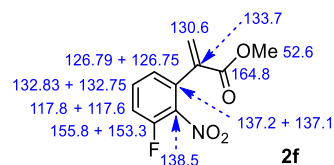
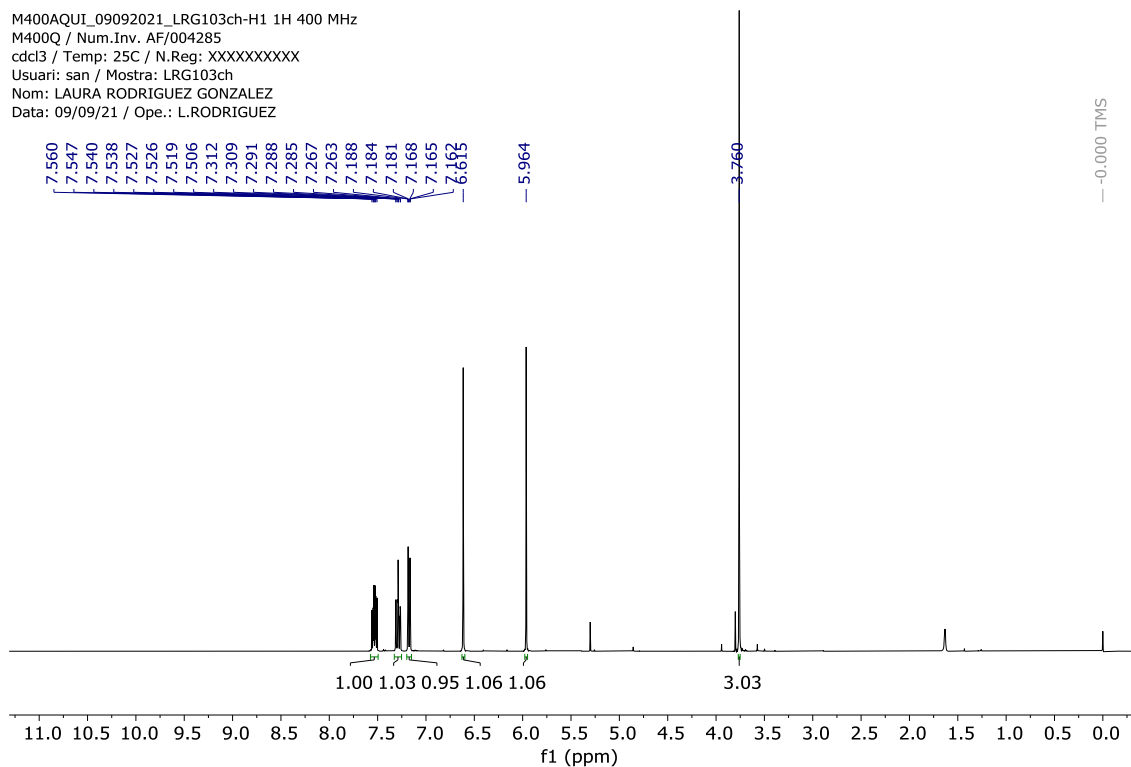
M400AQUI_09072021_LRG083CHARAC-C13{1H} 101 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG083CHARAC
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 09/07/21 / Ope.: L.RODRIGUEZ



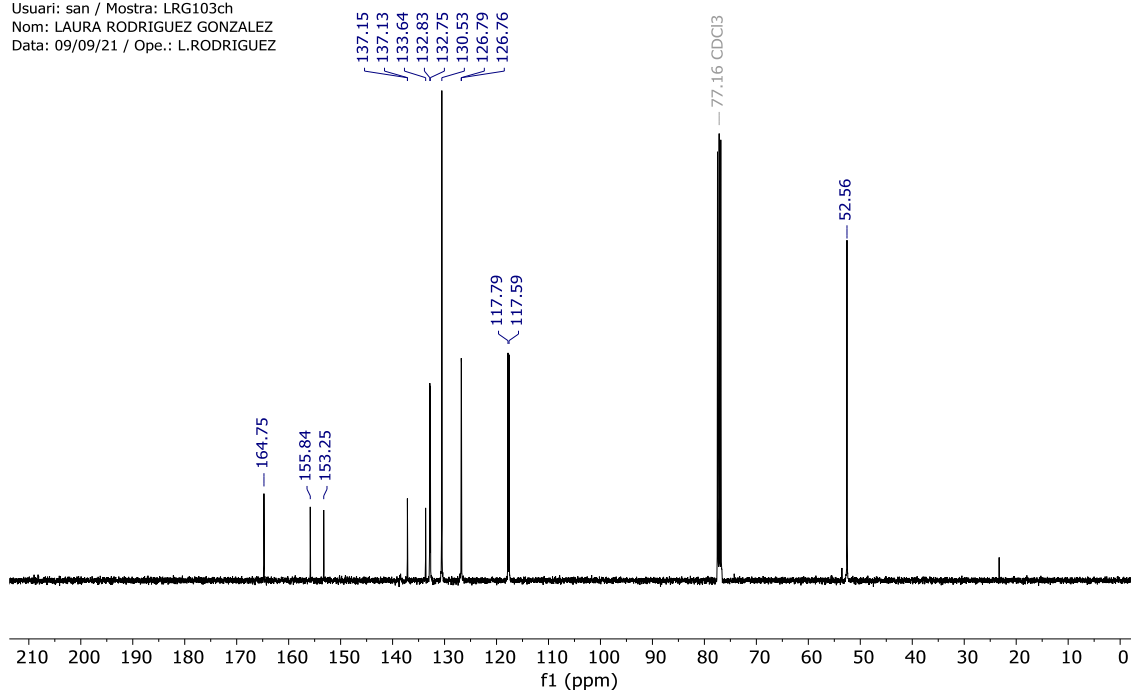
Experimental Section: Chapter 3

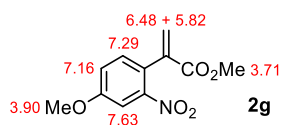


M400AQUI_09092021_LRG103ch-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG103ch
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 09/09/21 / Ope.: L.RODRIGUEZ

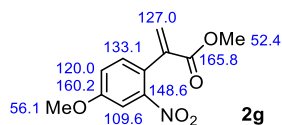
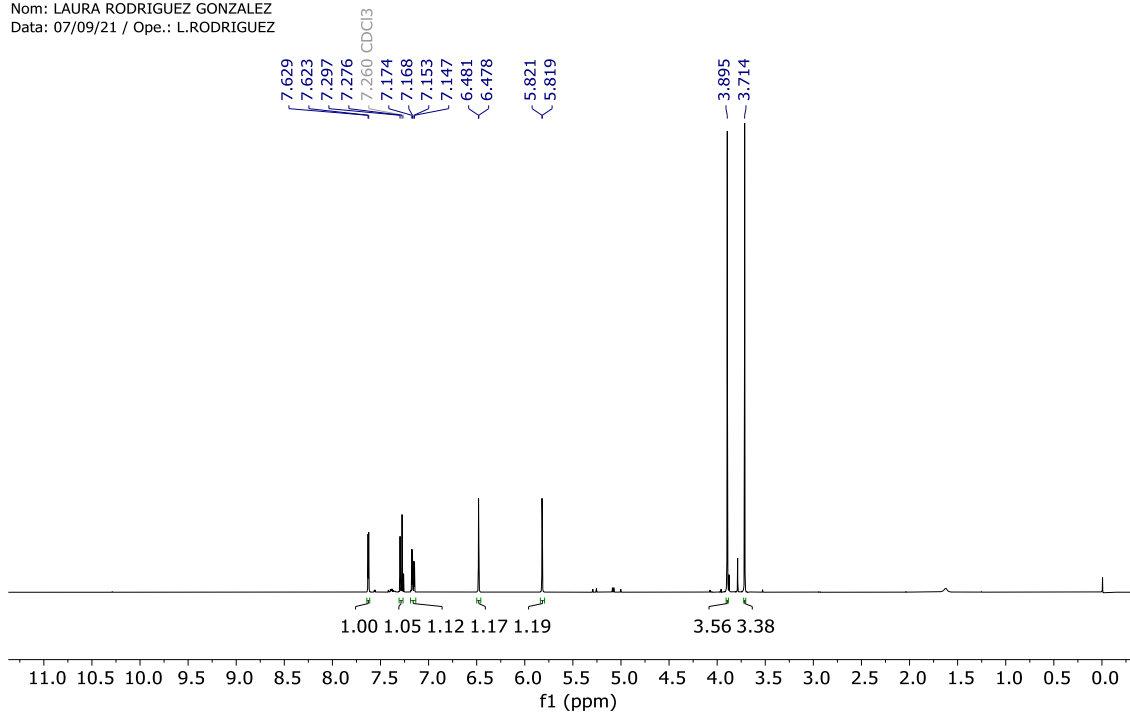


M400AQUI_09092021_LRG103ch-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG103ch
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 09/09/21 / Ope.: L.RODRIGUEZ

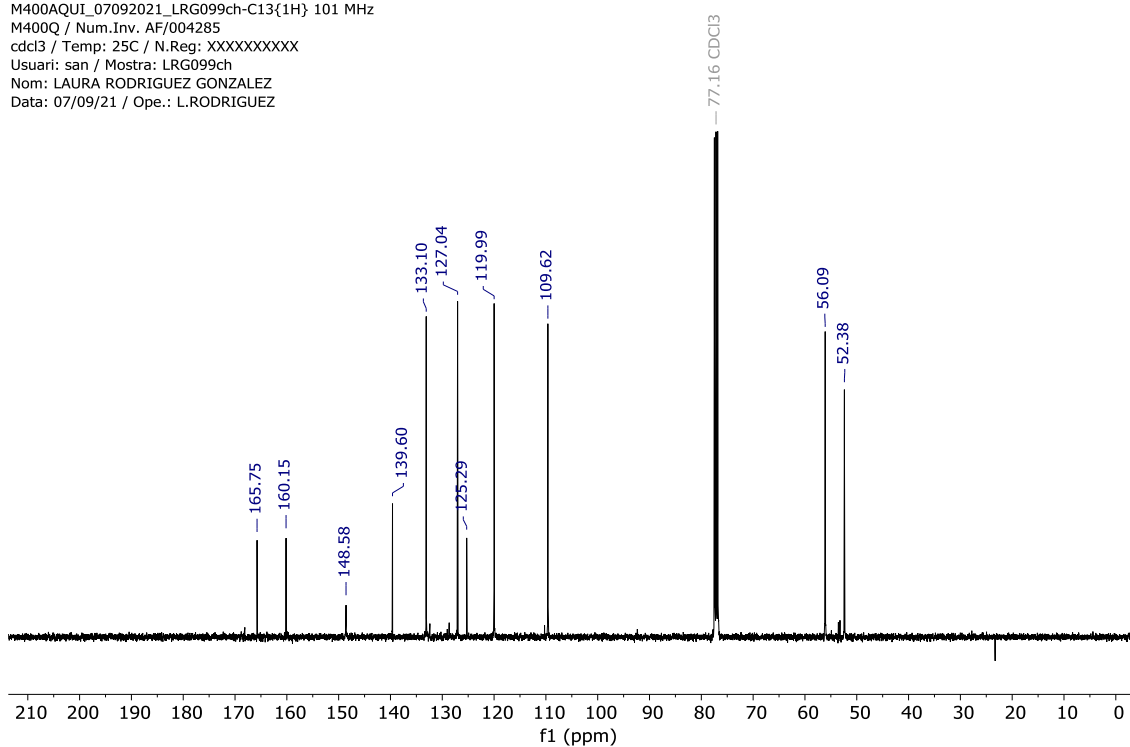


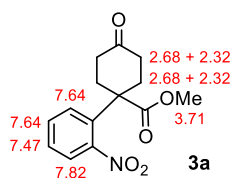


M400AQUI_07092021_LRG099ch-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG099ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/09/21 / Ope.: L.RODRIGUEZ

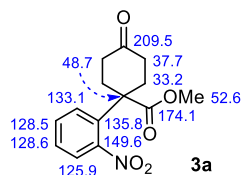
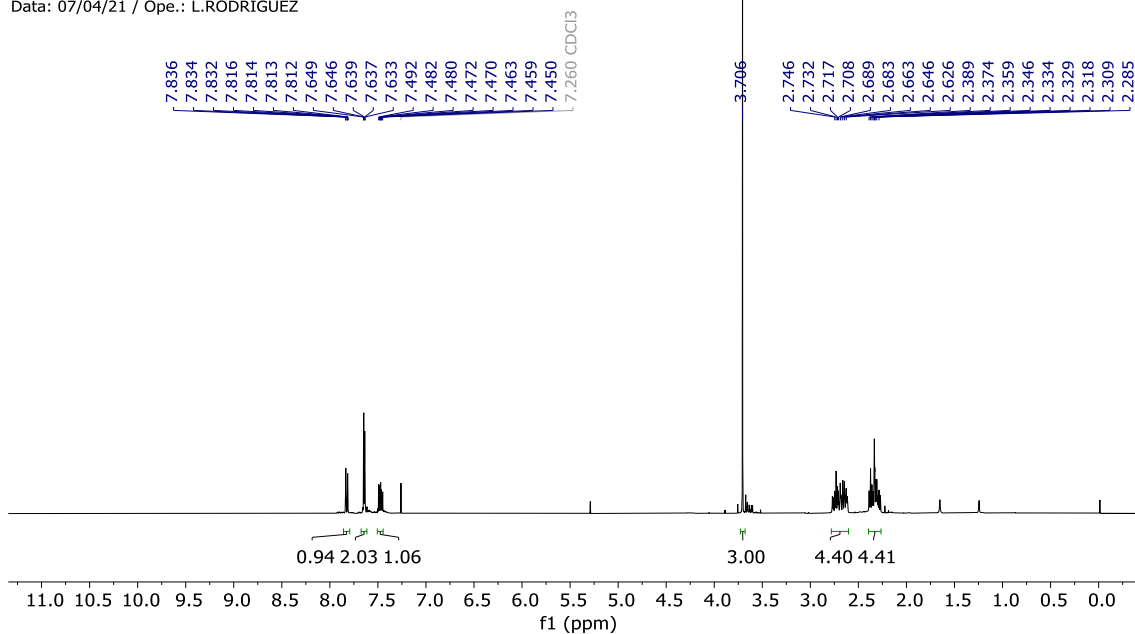


M400AQUI_07092021_LRG099ch-C13{1H} 101 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG099ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/09/21 / Ope.: L.RODRIGUEZ

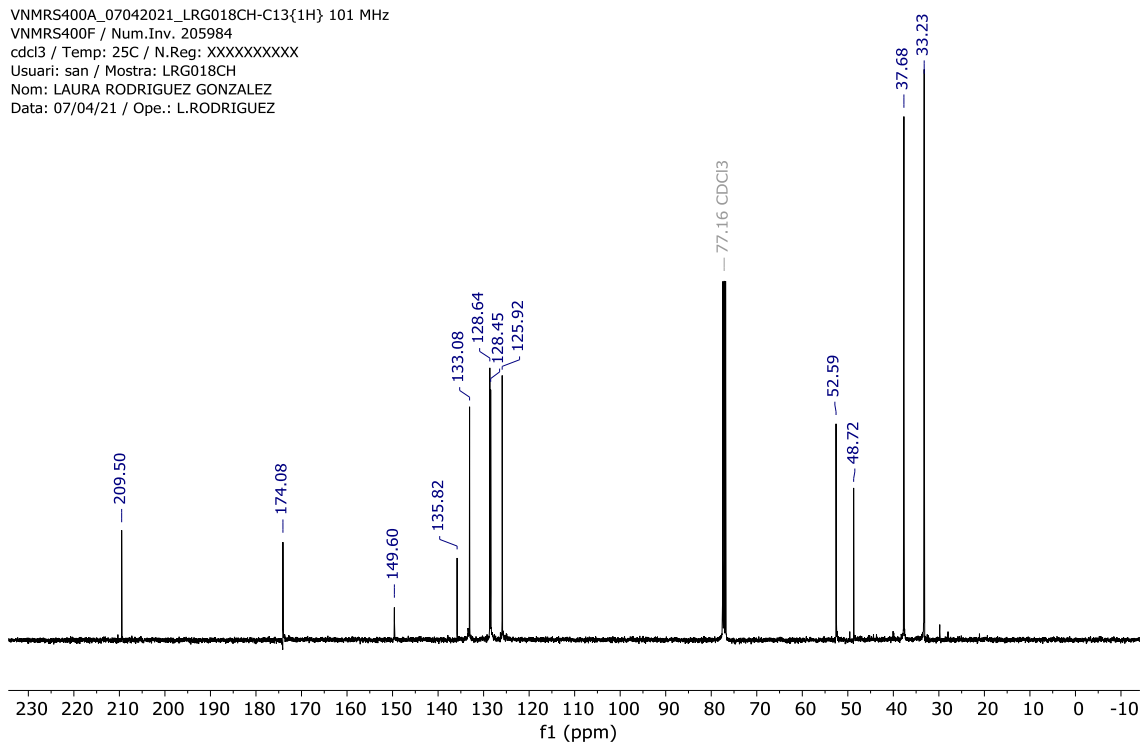


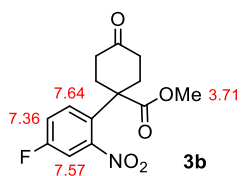


VNMRS400A_07042021_LRG018CH-H1 1H 400 MHz
 VNMRS400F / Num.Inv. 205984
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
 Usuari: san / Mostra: LRG018CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/04/21 / Ope.: L.RODRIGUEZ

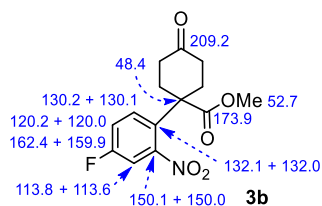
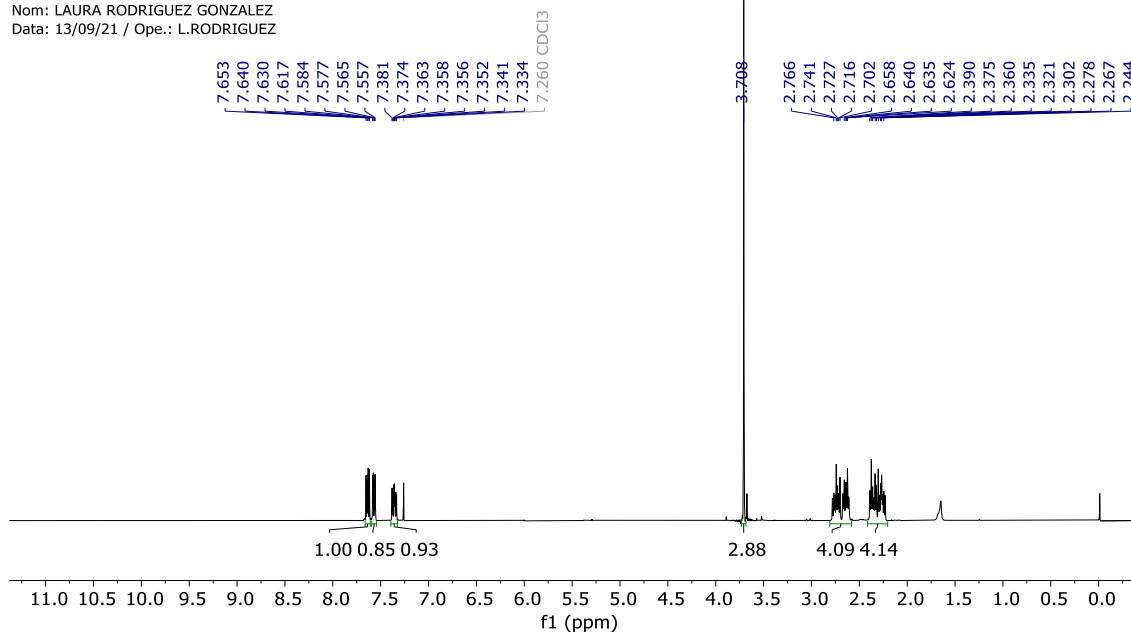


VNMRS400A_07042021_LRG018CH-C13{1H} 101 MHz
 VNMRS400F / Num.Inv. 205984
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
 Usuari: san / Mostra: LRG018CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/04/21 / Ope.: L.RODRIGUEZ

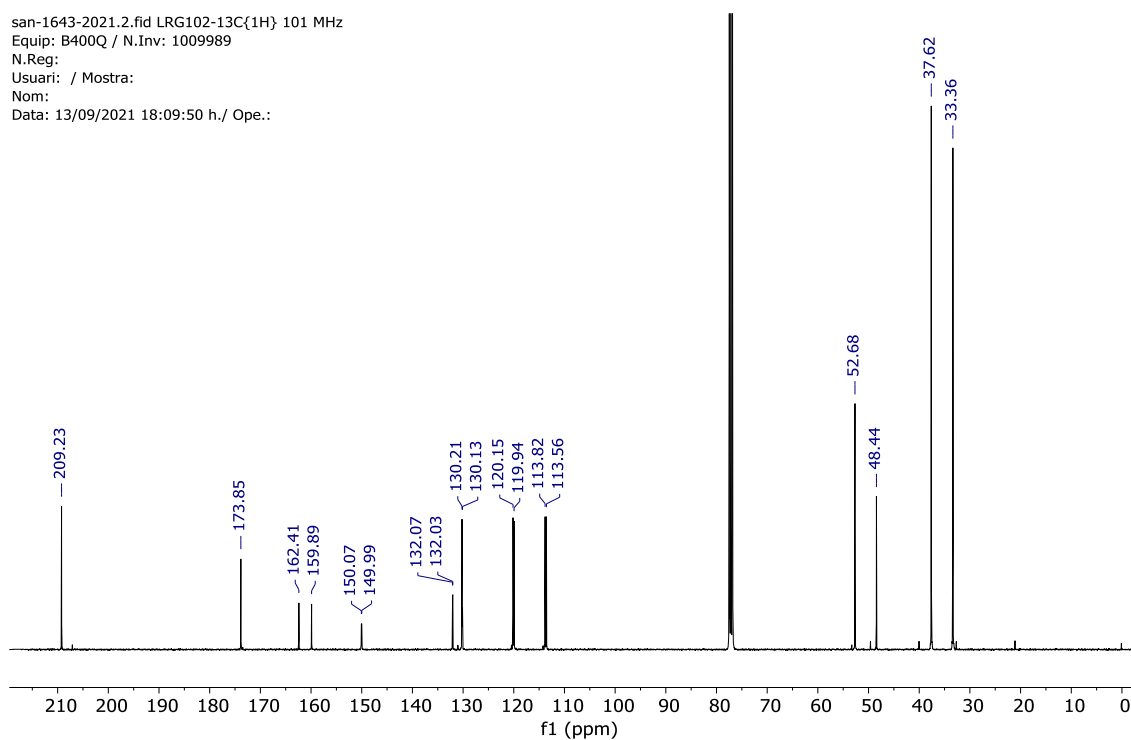


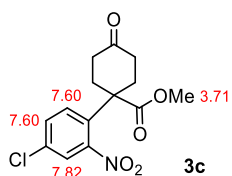


M400AQUI_13092021_LRG102TEST-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG102TEST
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 13/09/21 / Ope.: L.RODRIGUEZ

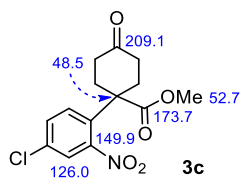
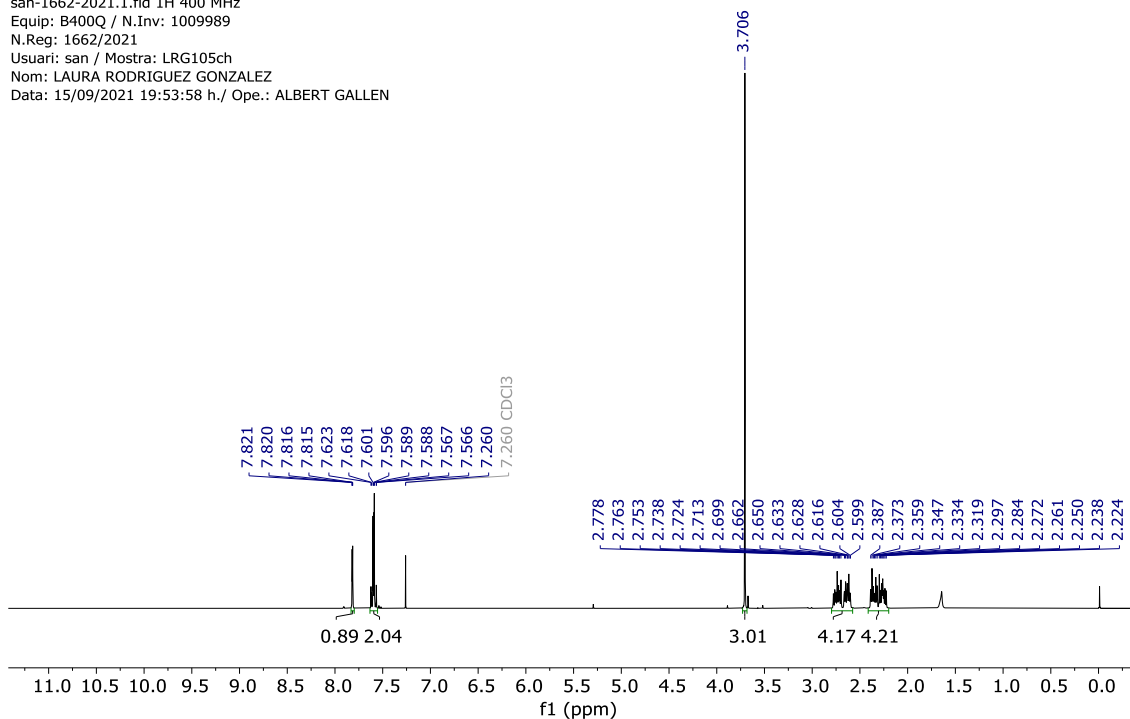


san-1643-2021.2.fid LRG102-13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1009989
 N.Reg:
 Usuari: / Mostra:
 Nom:
 Data: 13/09/2021 18:09:50 h./ Ope.:

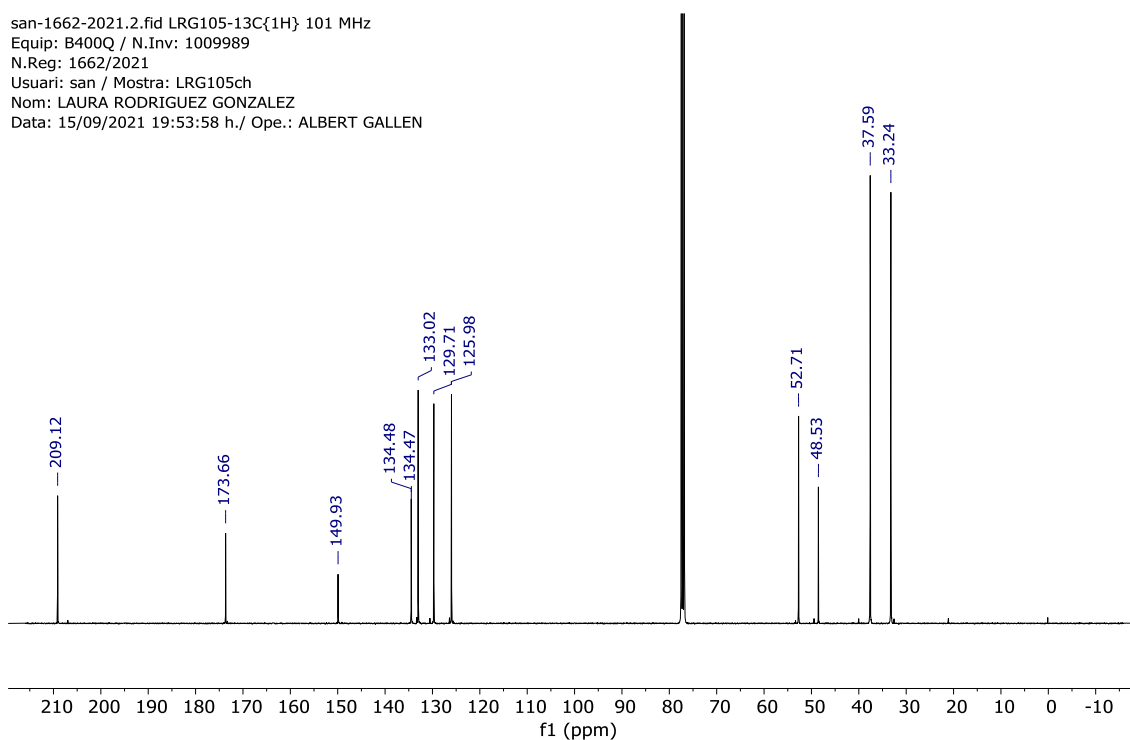


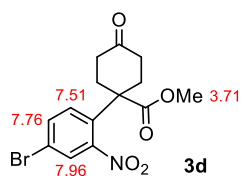


san-1662-2021.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1009989
 N.Reg: 1662/2021
 Usuari: san / Mostra: LRG105ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/09/2021 19:53:58 h./ Ope.: ALBERT GALLEN

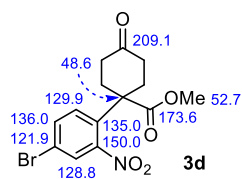
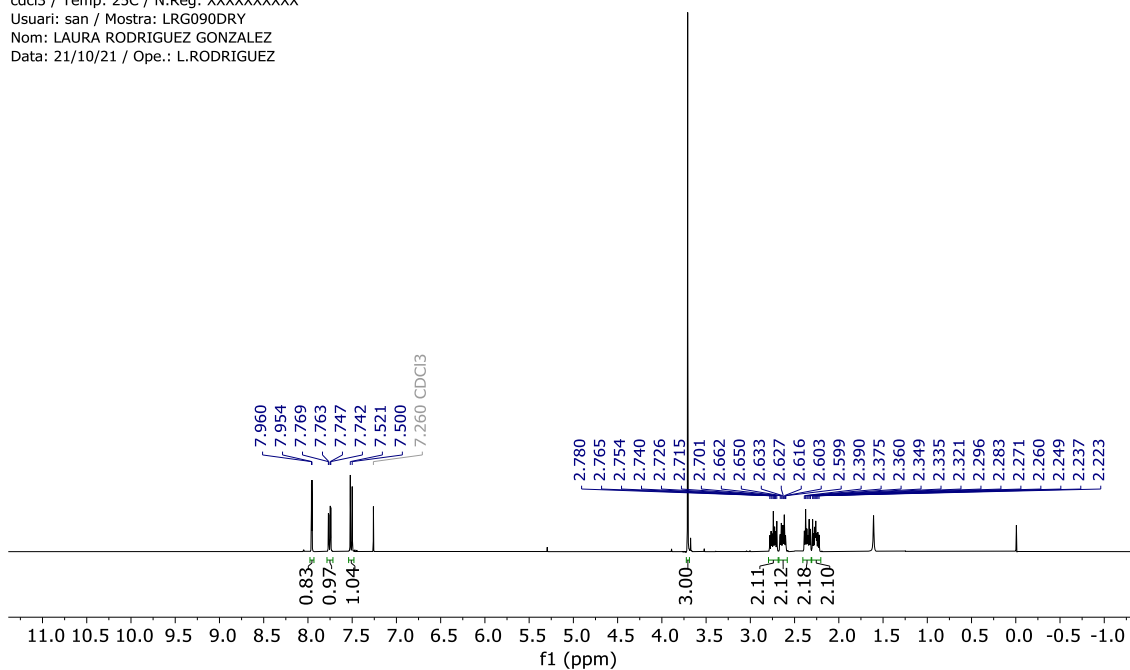


san-1662-2021.2.fid LRG105-13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1009989
 N.Reg: 1662/2021
 Usuari: san / Mostra: LRG105ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/09/2021 19:53:58 h./ Ope.: ALBERT GALLEN

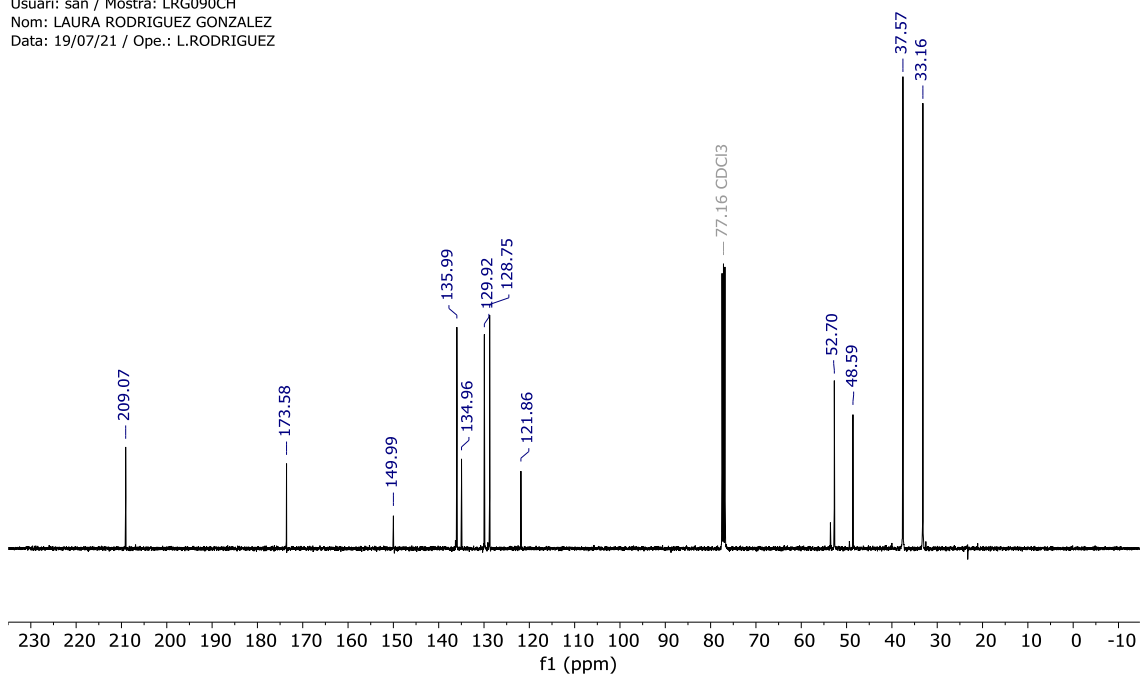


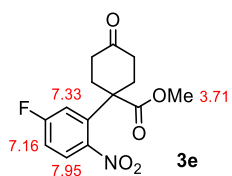


M400AQUI_21102021_LRG090DRY-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG090DRY
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 21/10/21 / Ope.: L.RODRIGUEZ

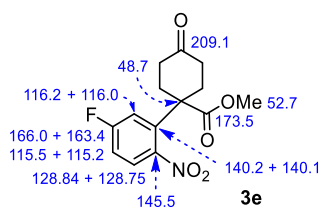
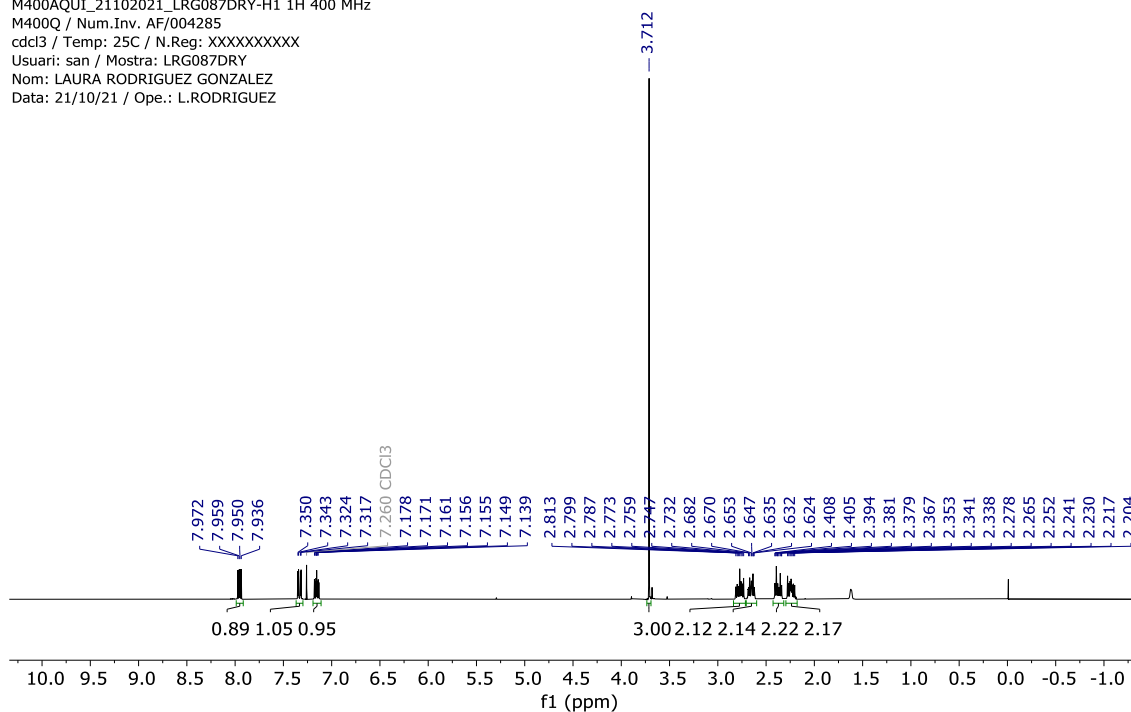


M400AQUI_19072021_LRG090CH-C13{1H} 101 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG090CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/07/21 / Ope.: L.RODRIGUEZ

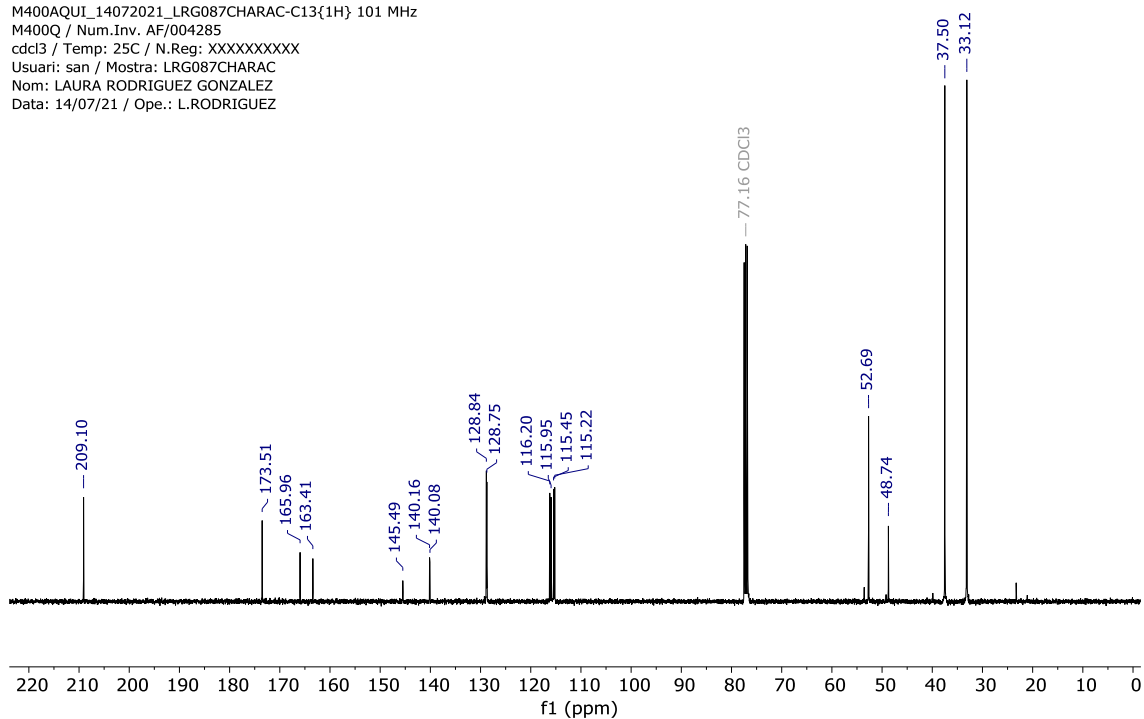


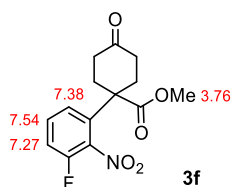


M400AQUI_21102021_LRG087DRY-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG087DRY
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 21/10/21 / Ope.: L.RODRIGUEZ

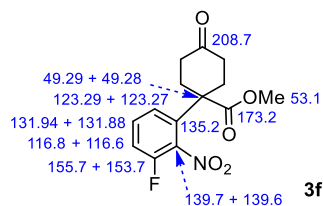
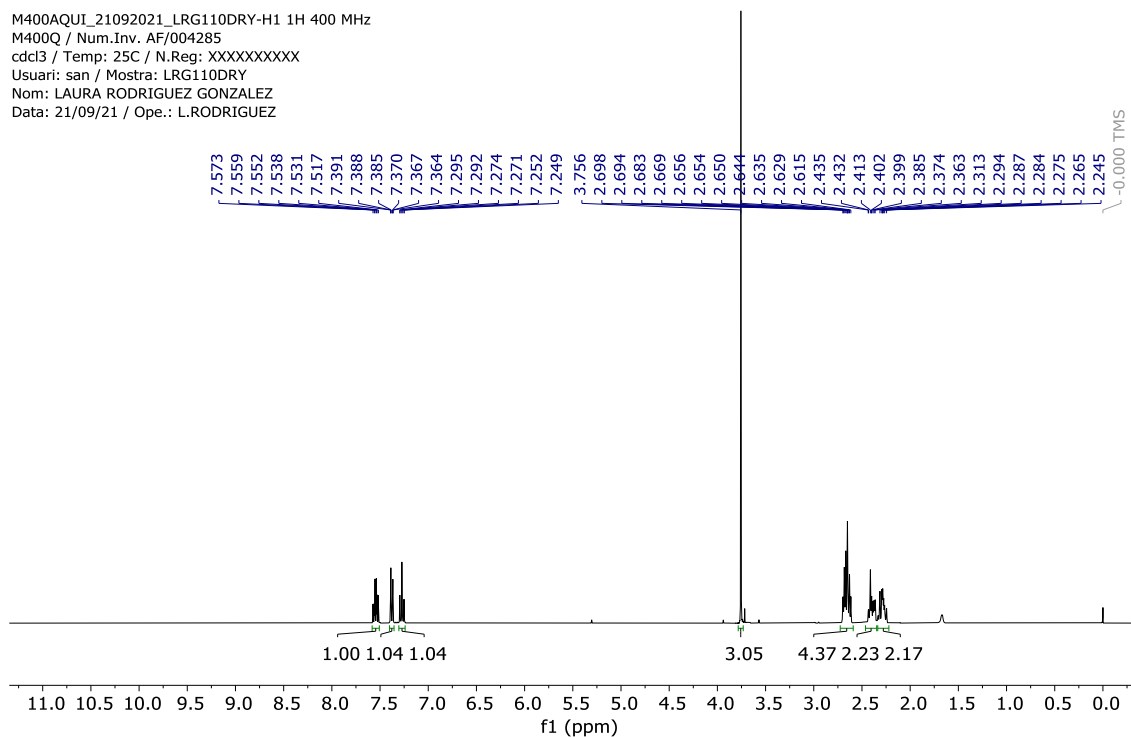


M400AQUI_14072021_LRG087CHARAC-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG087CHARAC
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 14/07/21 / Ope.: L.RODRIGUEZ

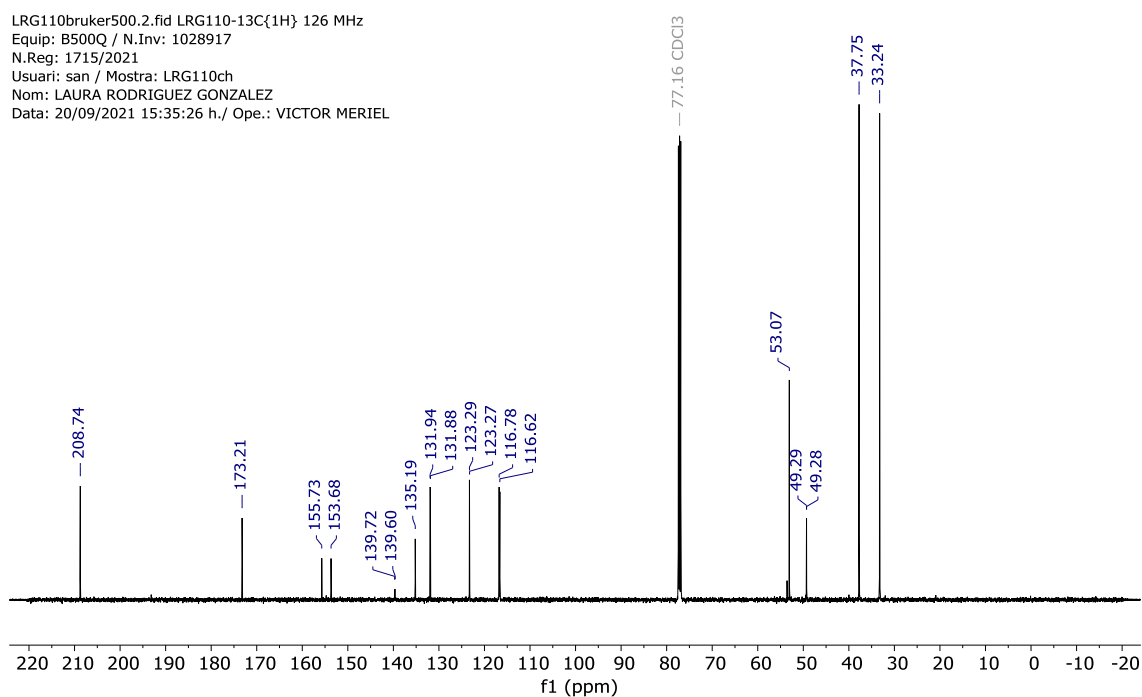


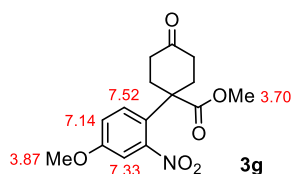


M400AQUI_21092021_LRG110DRY-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG110DRY
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 21/09/21 / Ope.: L.RODRIGUEZ

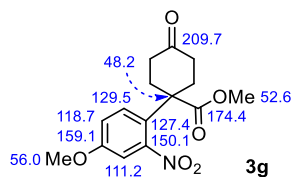
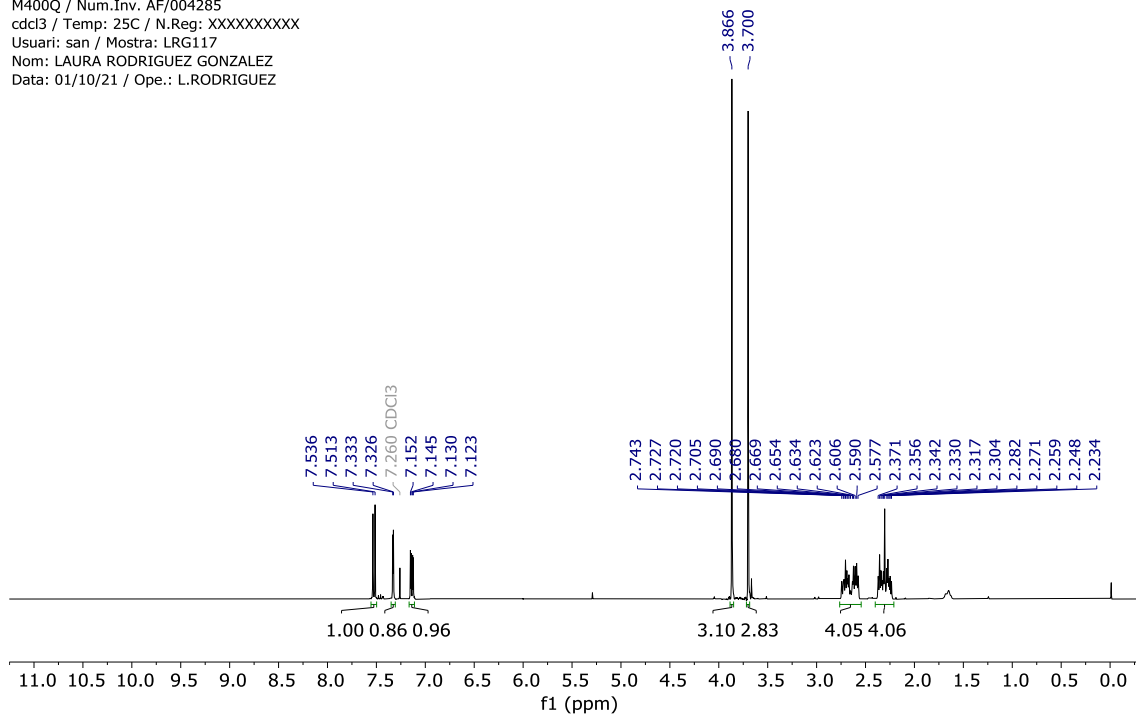


LRG110bruker500.2.fid LRG110-13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 1715/2021
 Usuari: san / Mostra: LRG110ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 20/09/2021 15:35:26 h. / Ope.: VICTOR MERIEL

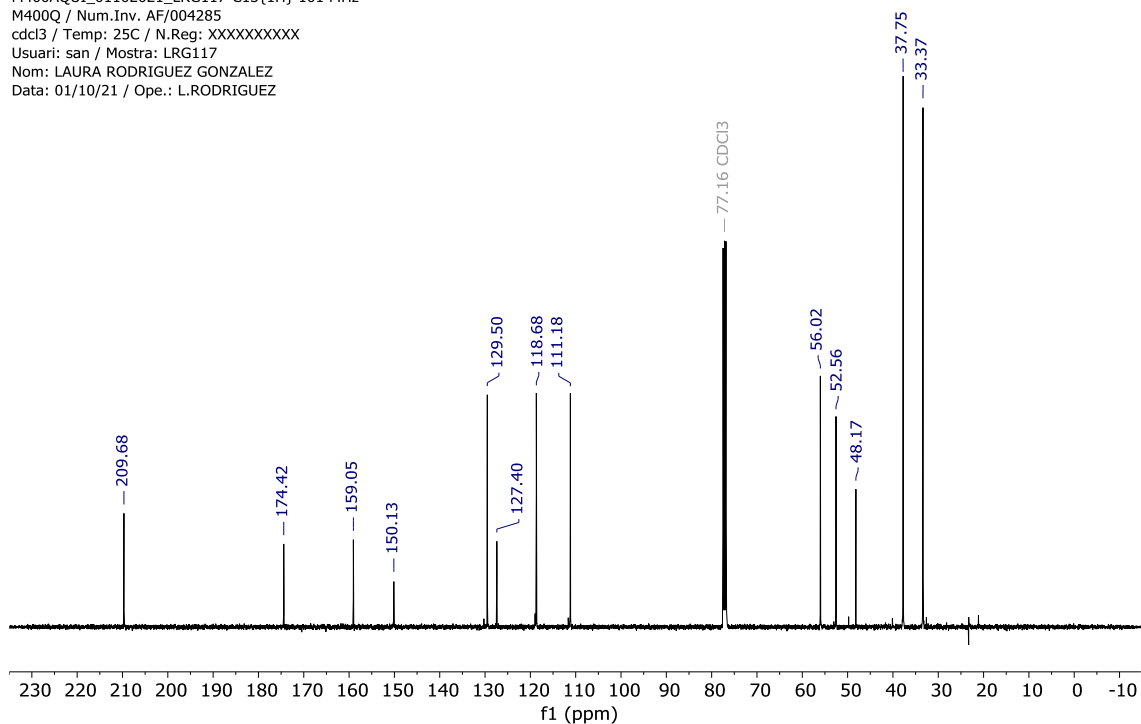


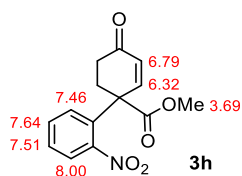


M400AQUI_01102021_LRG117-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG117
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 01/10/21 / Ope.: L.RODRIGUEZ

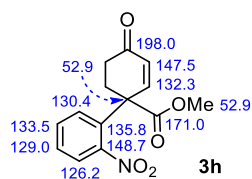
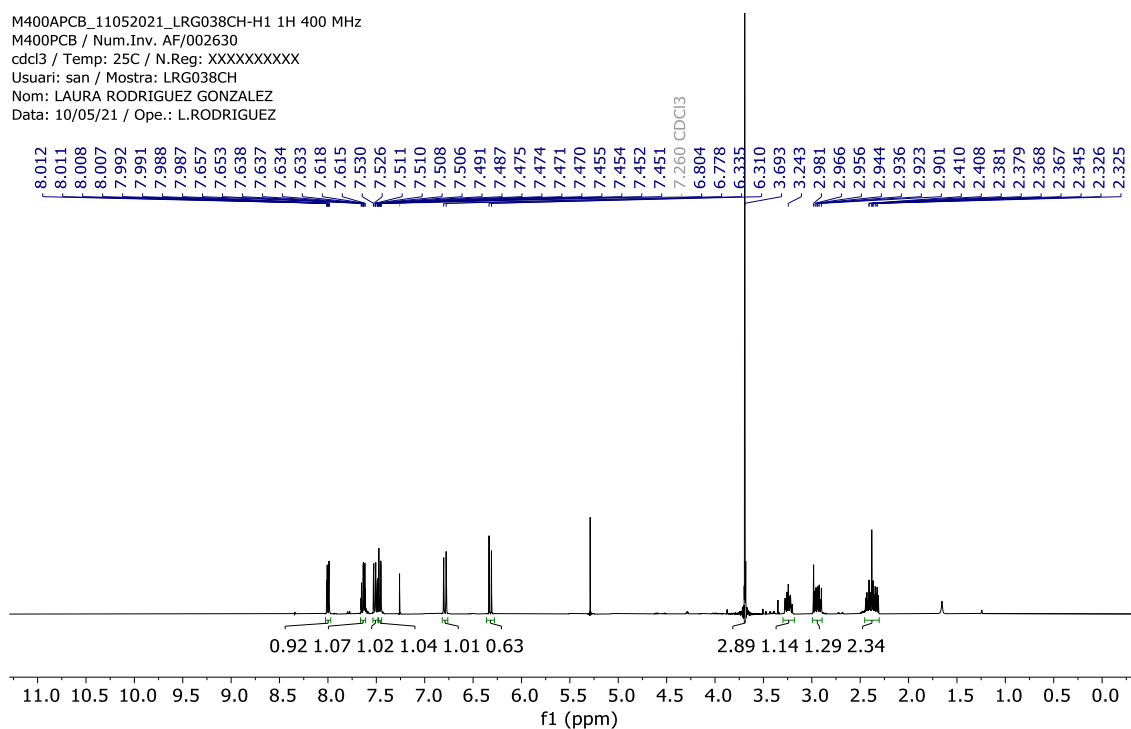


M400AQUI_01102021_LRG117-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG117
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 01/10/21 / Ope.: L.RODRIGUEZ

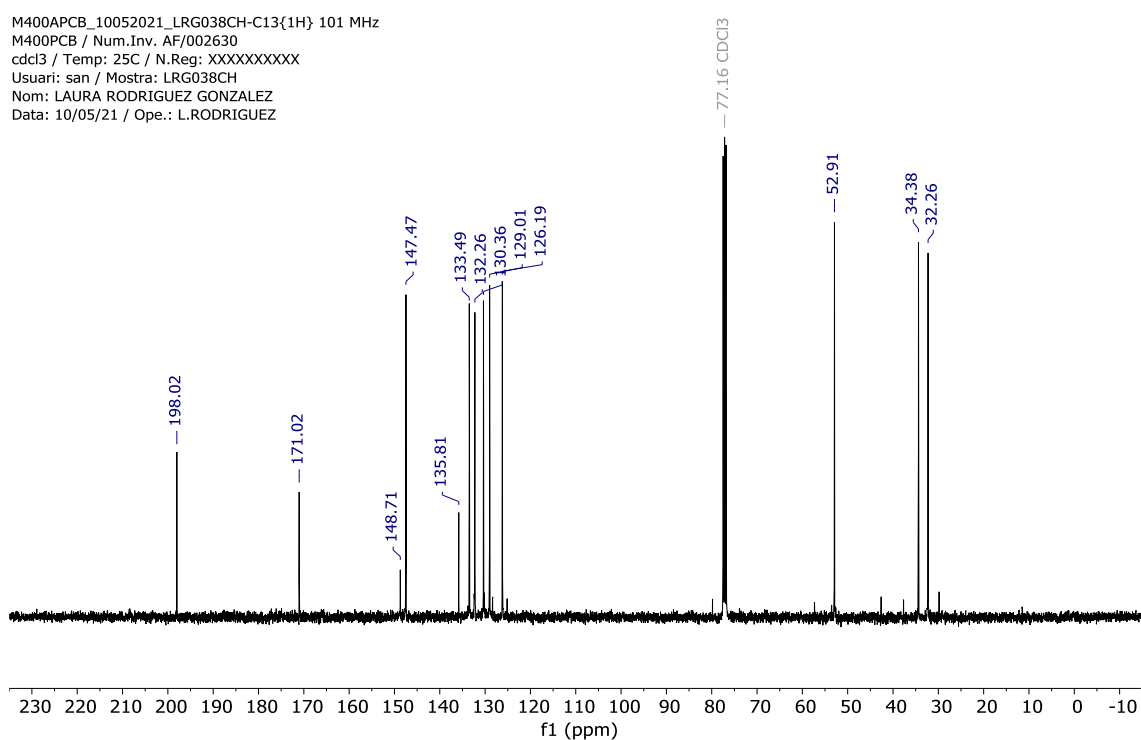


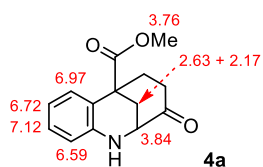


M400APCB_11052021_LRG038CH-H1 1H 400 MHz
 M400PCB / Num.Inv. AF/002630
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG038CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/05/21 / Ope.: L.RODRIGUEZ

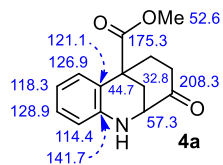
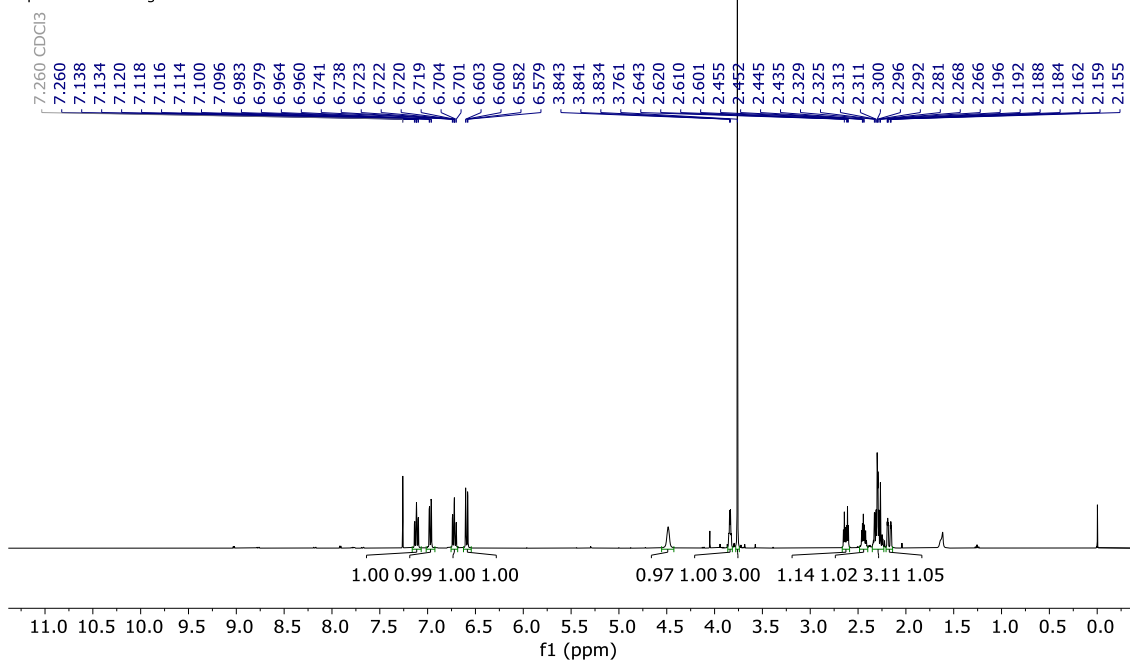


M400APCB_10052021_LRG038CH-C13{1H} 101 MHz
 M400PCB / Num.Inv. AF/002630
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG038CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/05/21 / Ope.: L.RODRIGUEZ

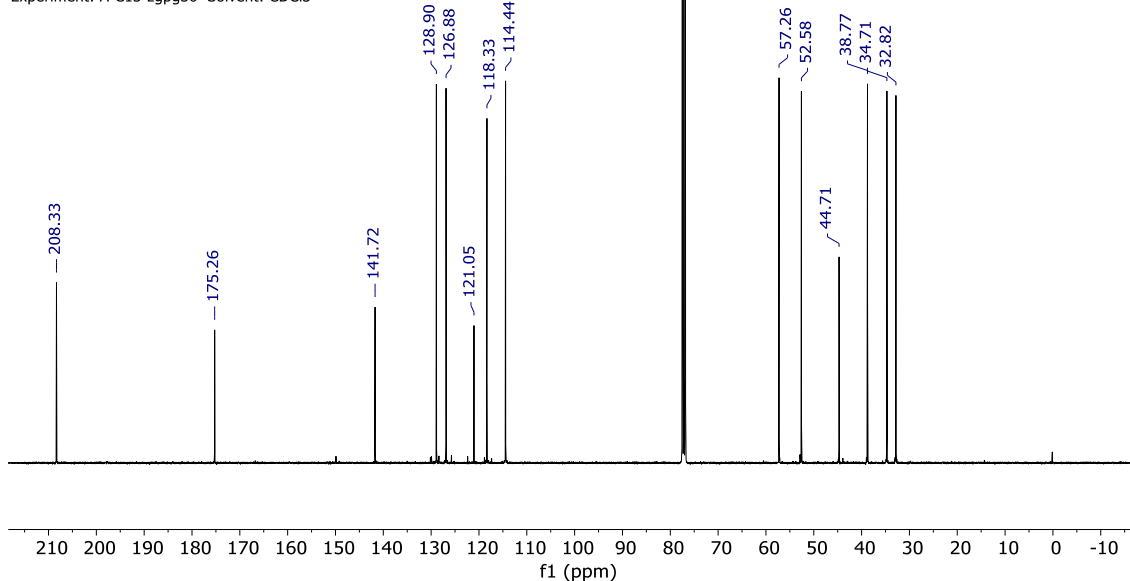


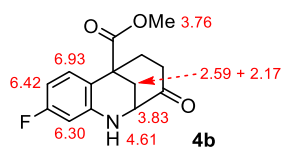


22070260_B400FA_12072022_LRG236P4A.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 22070260
 Usuari: san / Mostra: LRG236P4A
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 12/07/2022 10:26:27 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

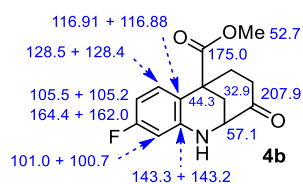
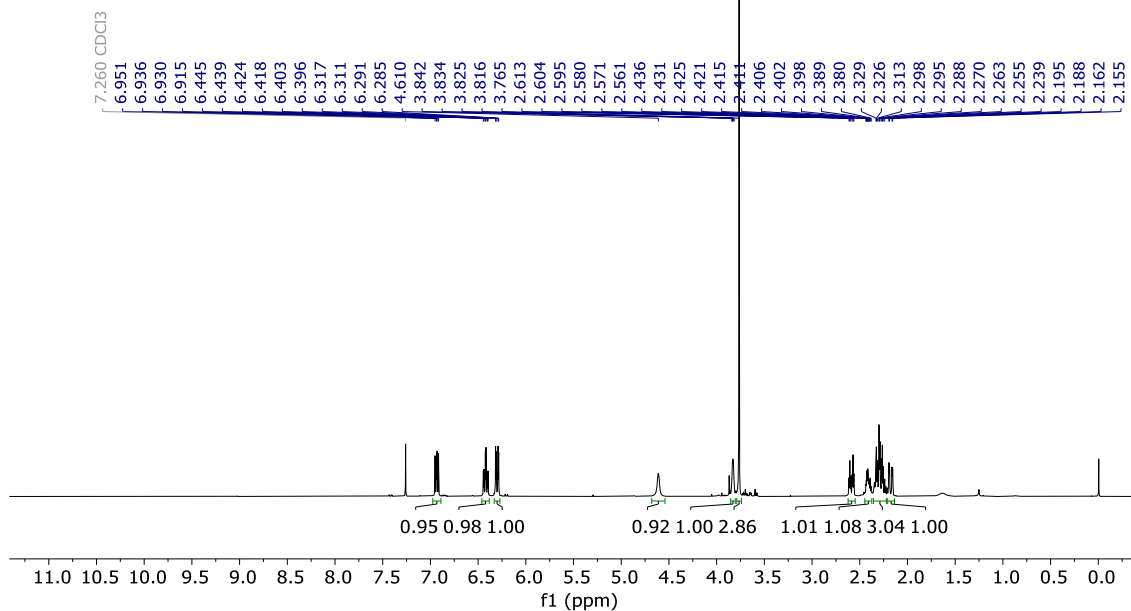


22070260_B400FA_13072022_LRG236P4A.2.fid 13C{H1} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 22070260
 Usuari: san / Mostra: LRG236P4A
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 13/07/2022 03:51:34 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

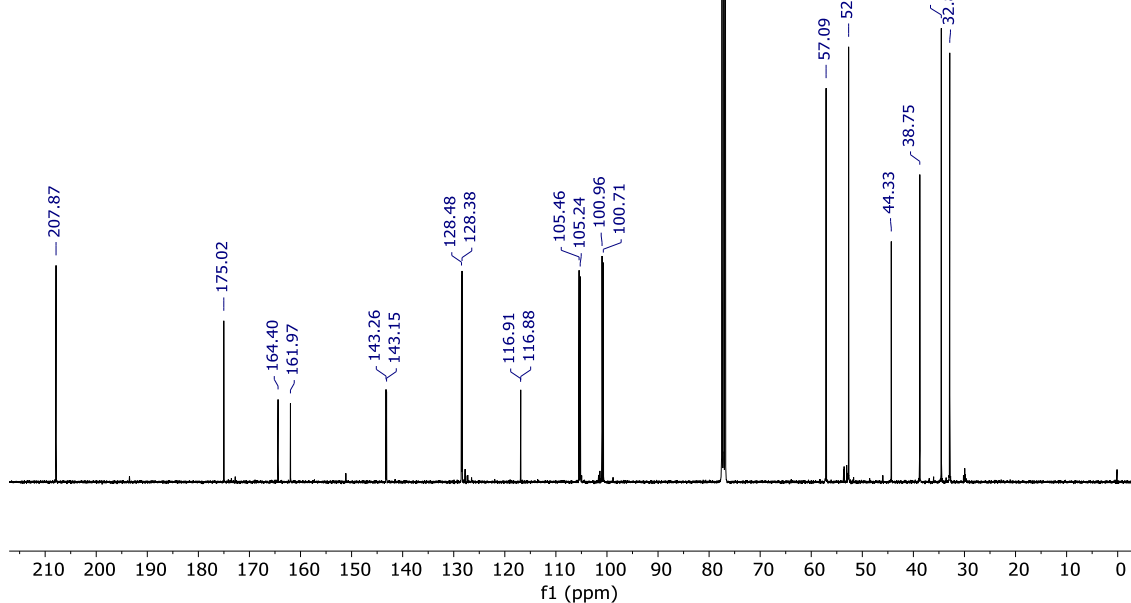


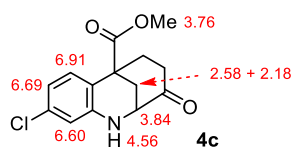


22070385_B400FA_14072022_LRG237PROD4B.1.fid 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 22070385
 Usuari: san / Mostra: LRG237PROD4B
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/07/2022 13:33:23 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

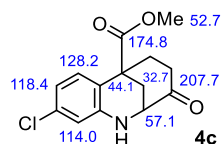
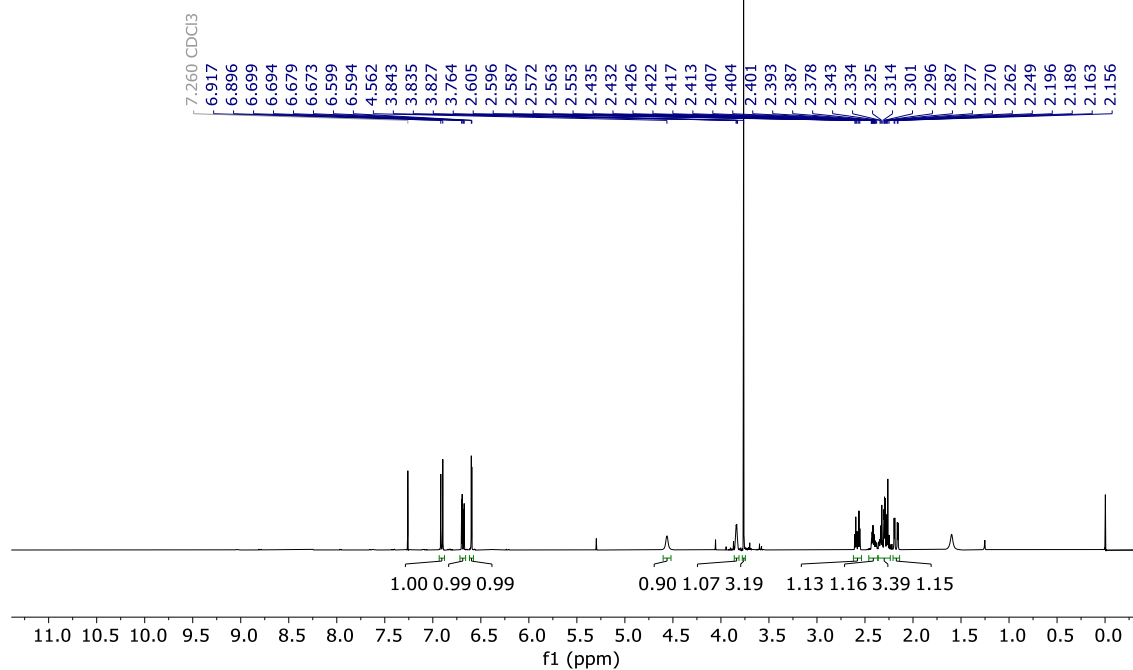


22070326_B400FA_14072022_LRG237P4B.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 22070326
 Usuari: san / Mostra: LRG237P4B
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/07/2022 05:01:50 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

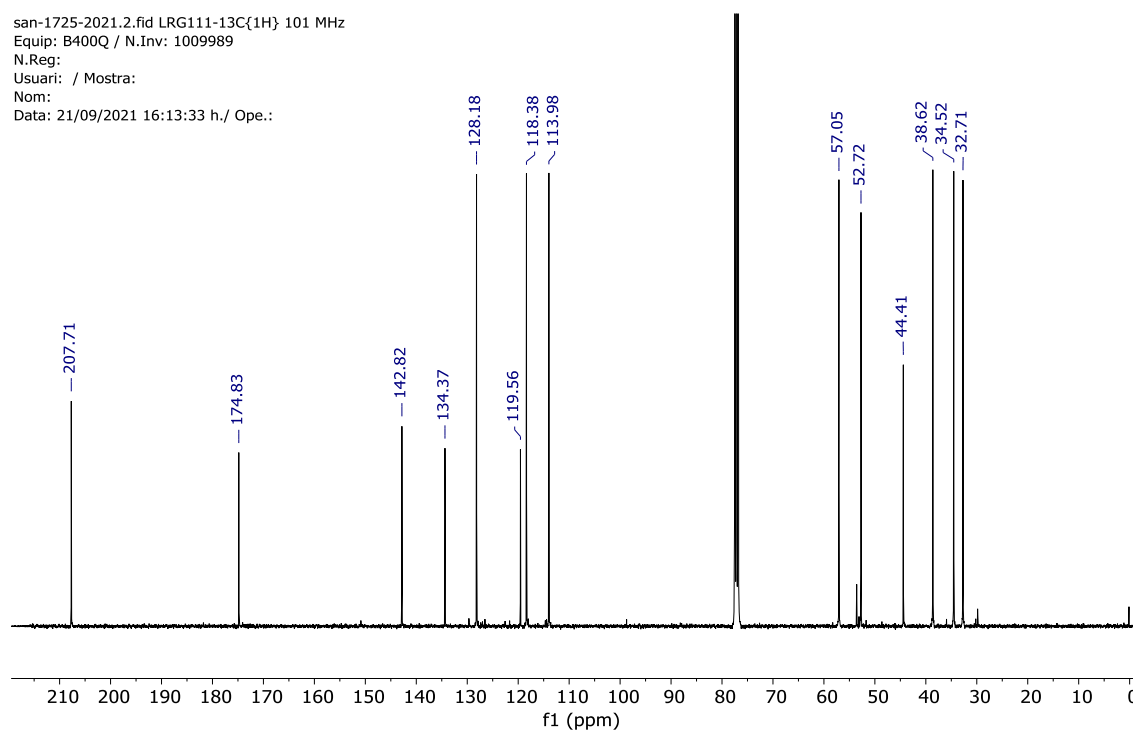


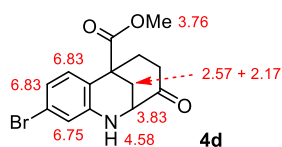


M400AQUI_22092021_LRG111dry-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG111dry
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 22/09/21 / Ope.: L.RODRIGUEZ

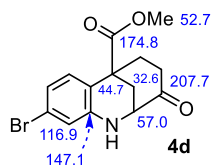
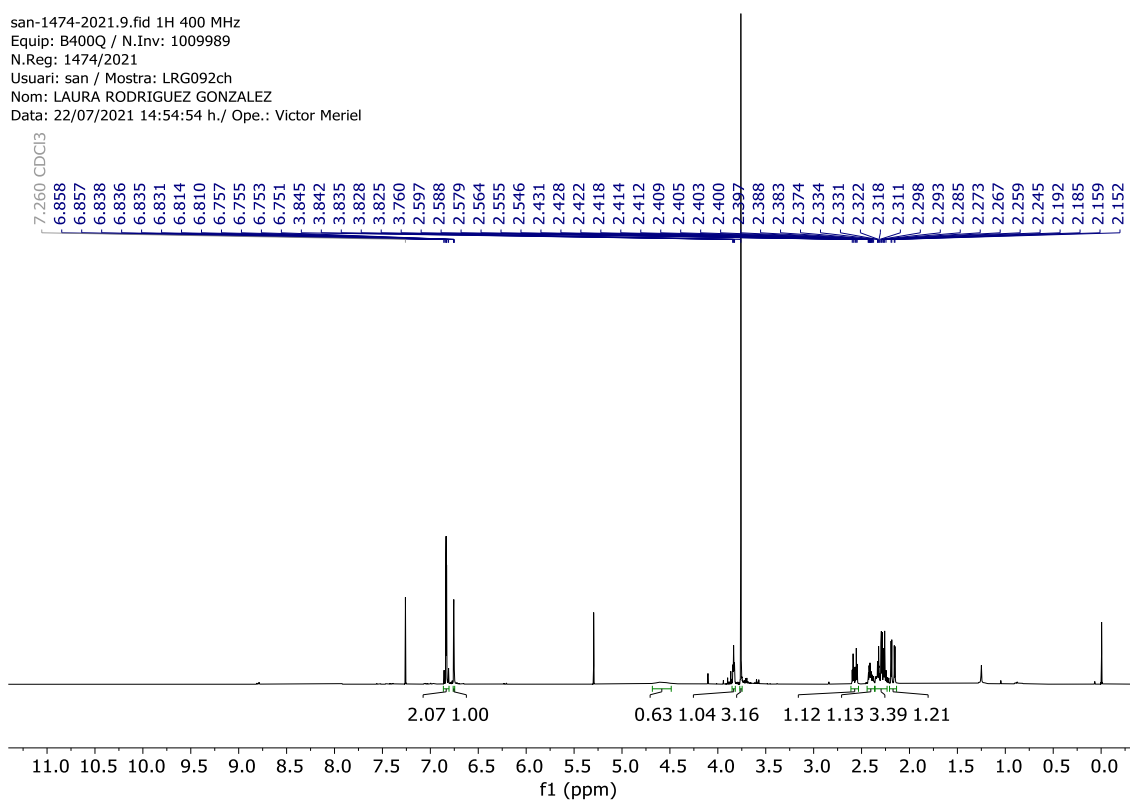


san-1725-2021.2.fid LRG111-13C{1H} 101 MHz
Equip: B400Q / N.Inv: 1009989
N.Reg:
Usuari: / Mostra:
Nom:
Data: 21/09/2021 16:13:33 h./ Ope.:

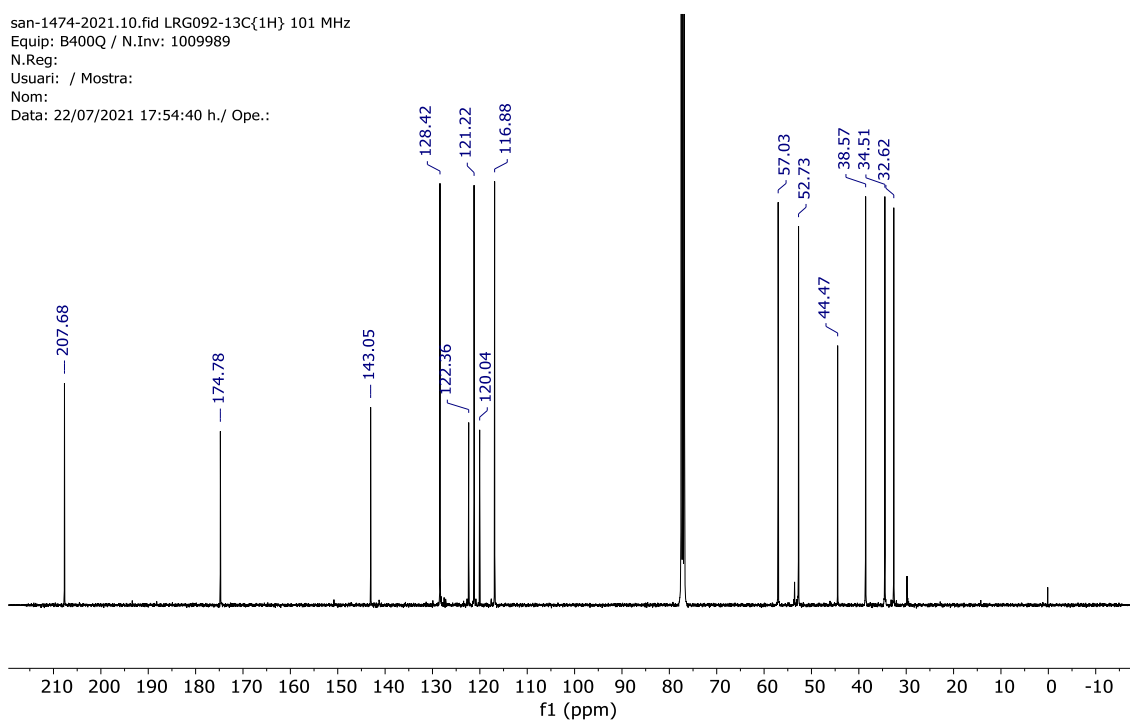


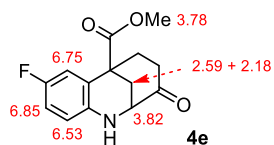


san-1474-2021.9.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1009989
 N.Reg: 1474/2021
 Usuari: san / Mostra: LRG092ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 22/07/2021 14:54:54 h./ Ope.: Victor Meriel

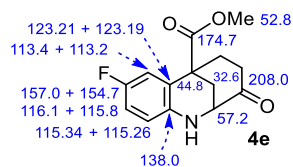
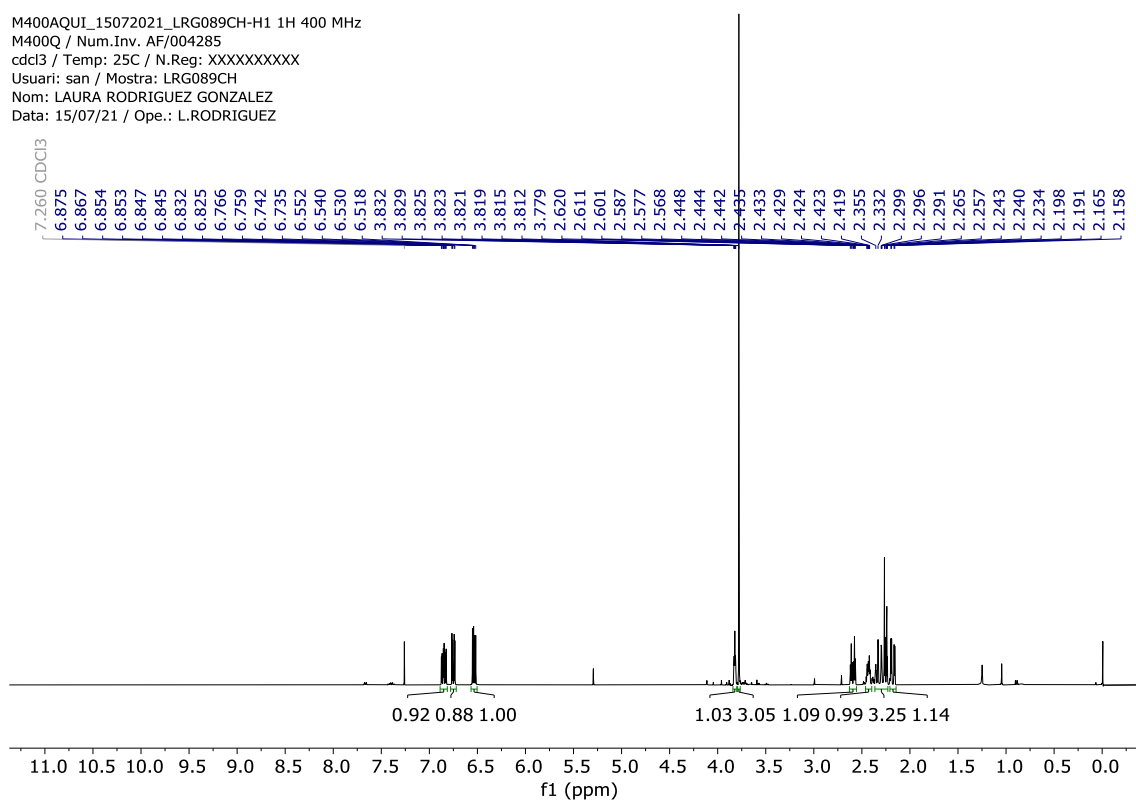


san-1474-2021.10.fid LRG092-13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1009989
 N.Reg:
 Usuari: / Mostra:
 Nom:
 Data: 22/07/2021 17:54:40 h./ Ope.:

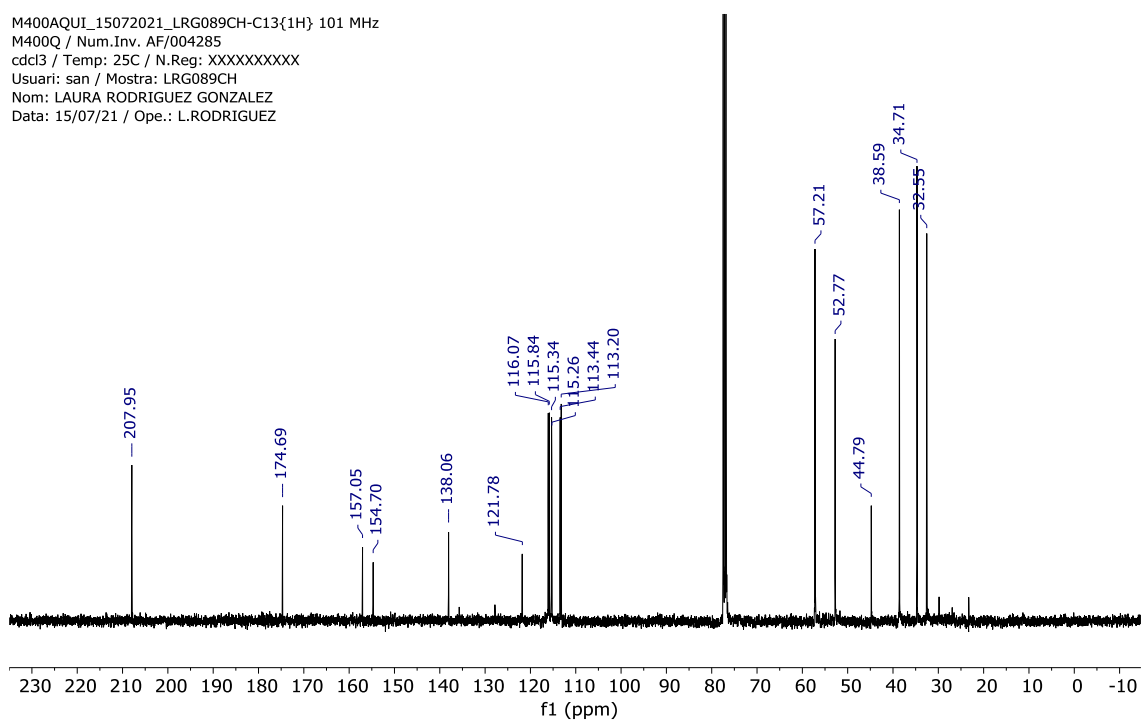


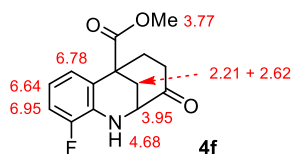


M400AQUI_15072021_LRG089CH-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG089CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 15/07/21 / Ope.: L.RODRIGUEZ

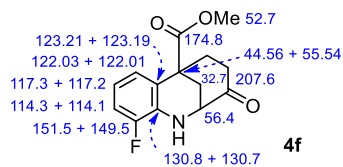
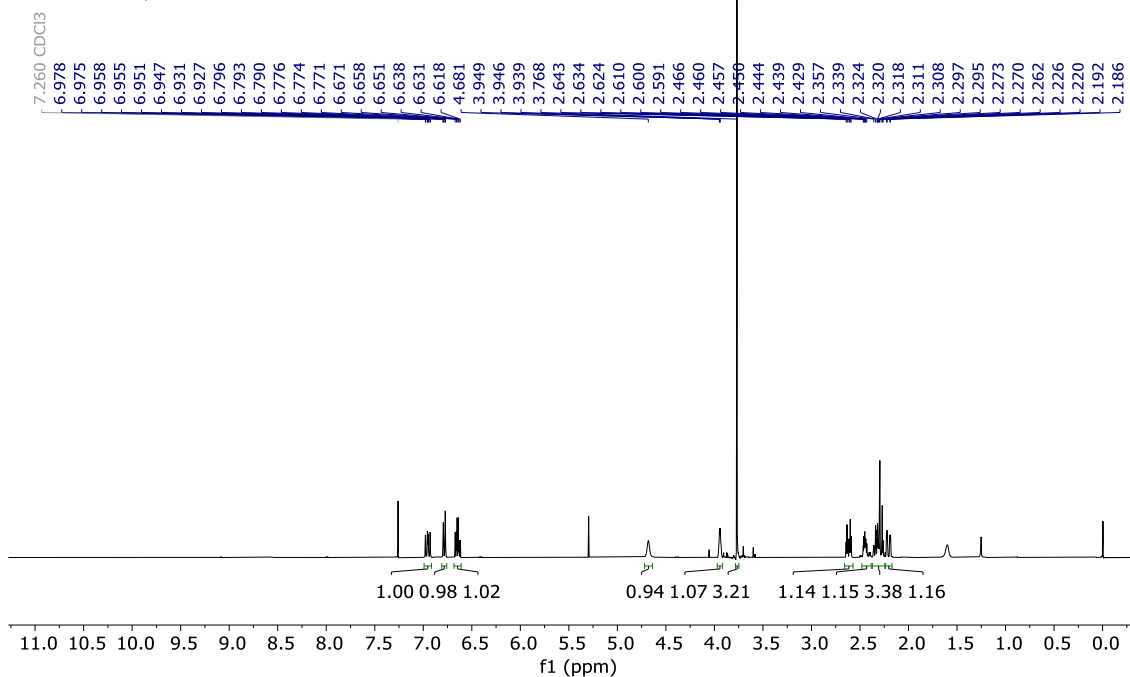


M400AQUI_15072021_LRG089CH-C13{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG089CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 15/07/21 / Ope.: L.RODRIGUEZ

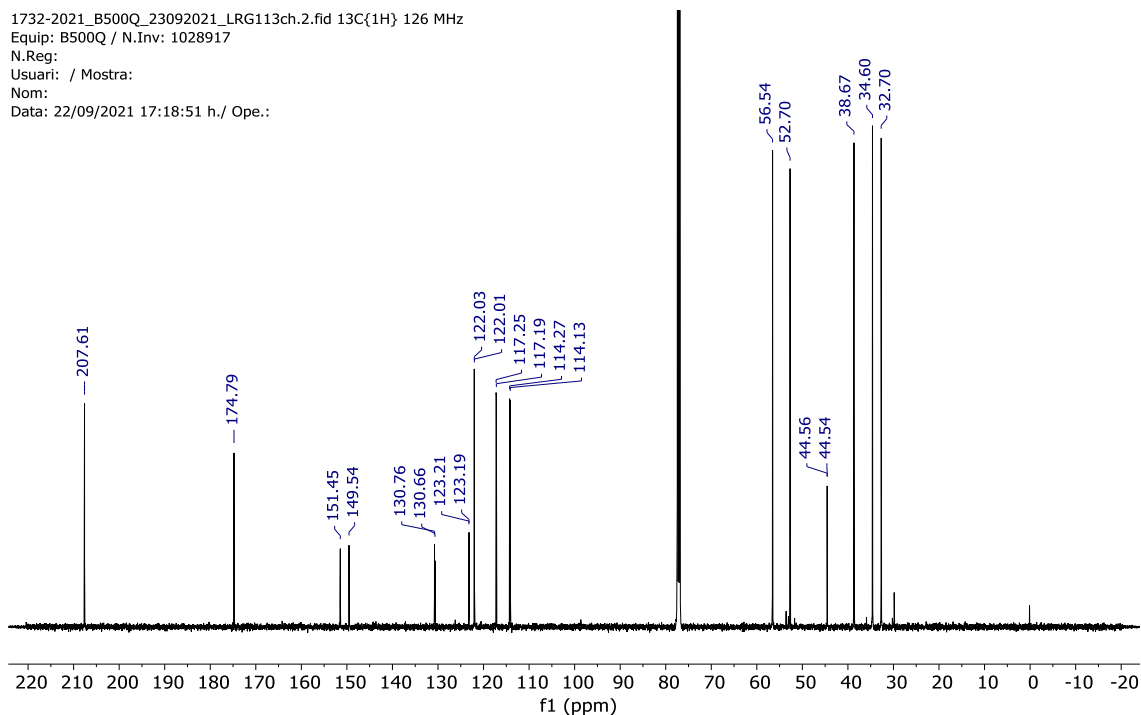


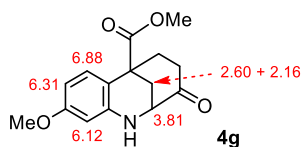


M400AQUI_22092021_LRG113ch-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG113ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 22/09/21 / Ope.: L.RODRIGUEZ

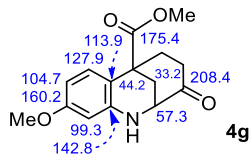
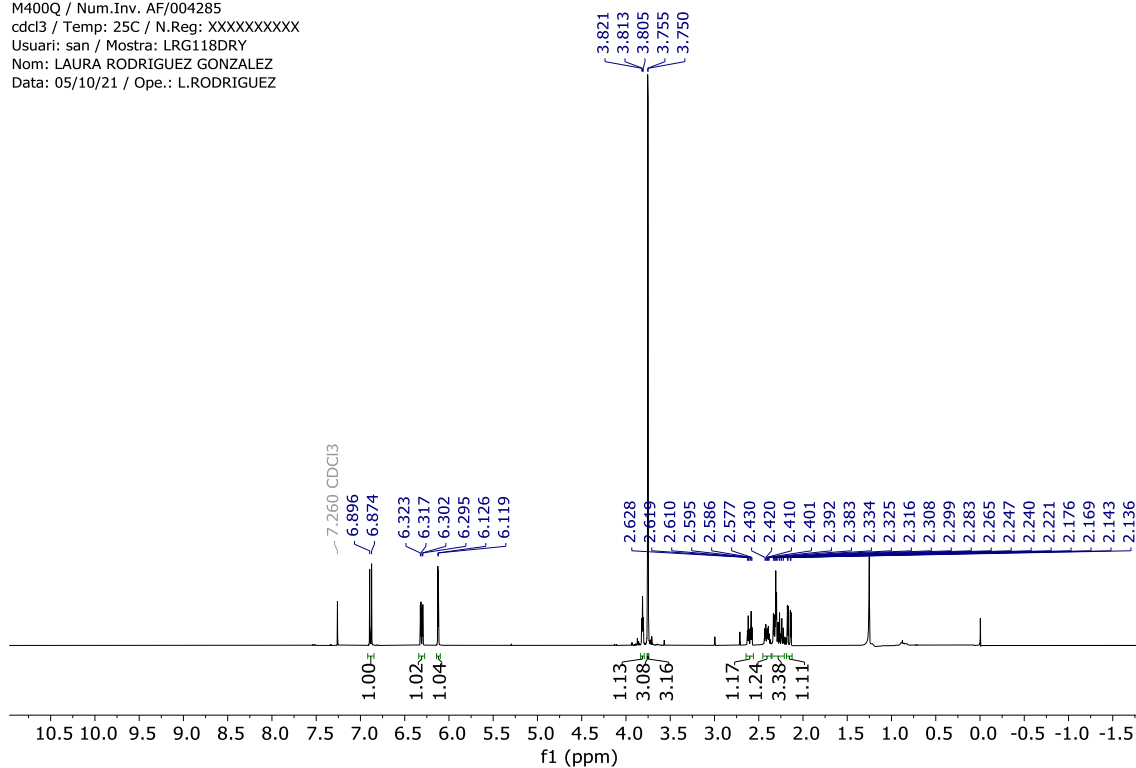


1732-2021_B500Q_23092021_LRG113ch.2.fid 13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg:
 Usuari: / Mostra:
 Nom:
 Data: 22/09/2021 17:18:51 h./ Ope.:

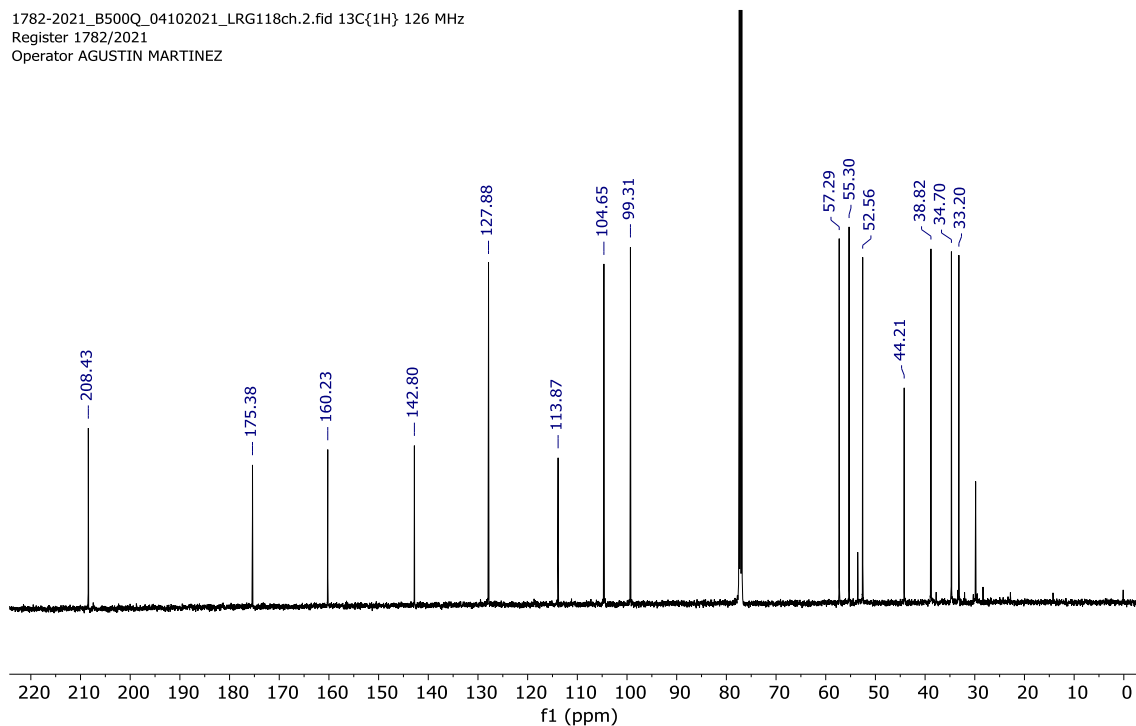


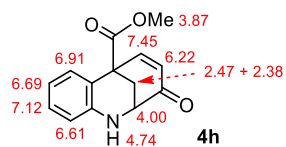


M400AQUI_05102021_LRG118DRY-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG118DRY
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 05/10/21 / Ope.: L.RODRIGUEZ

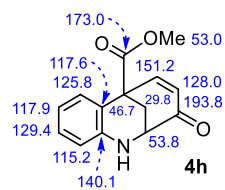
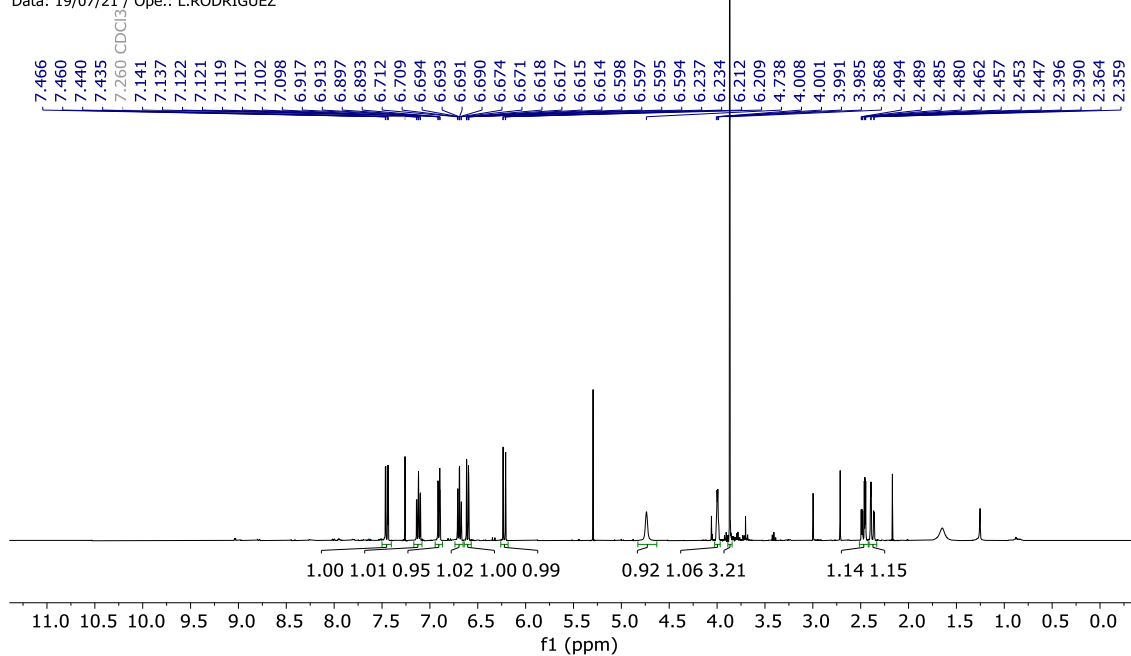


1782-2021_B500Q_04102021_LRG118ch.2.fid 13C{1H} 126 MHz
Register 1782/2021
Operator AGUSTIN MARTINEZ

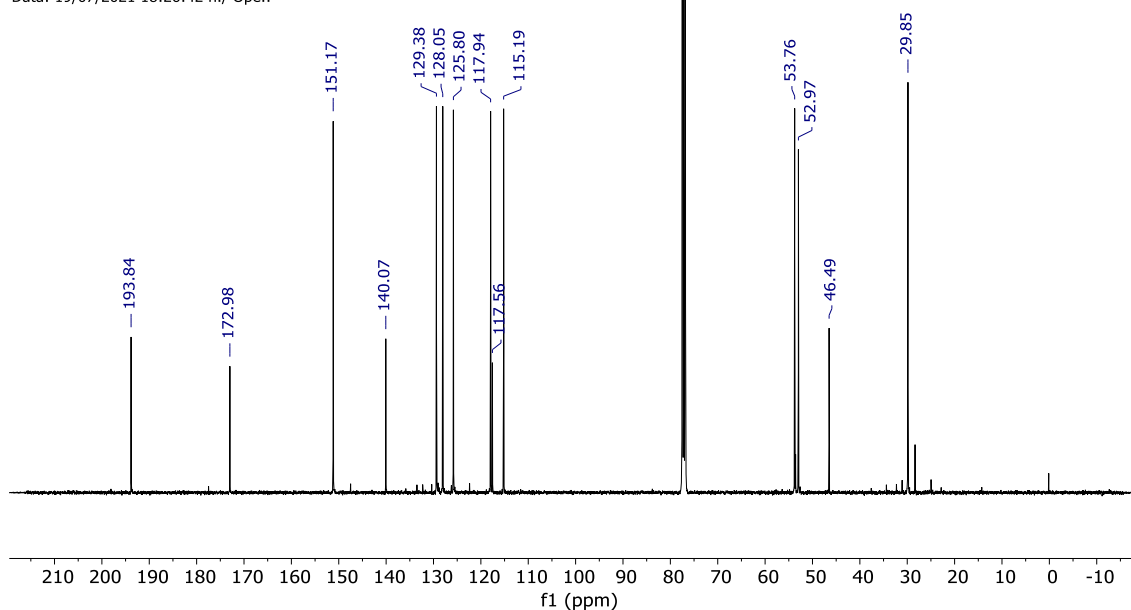


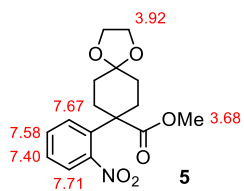


M400AQUI_19072021_LRG091-H1 1H 400 MHz
 M400Q / Num.Inv. AF/004285
 cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
 Usuari: san / Mostra: LRG091
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/07/21 / Ope.: L.RODRIGUEZ

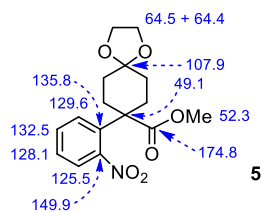
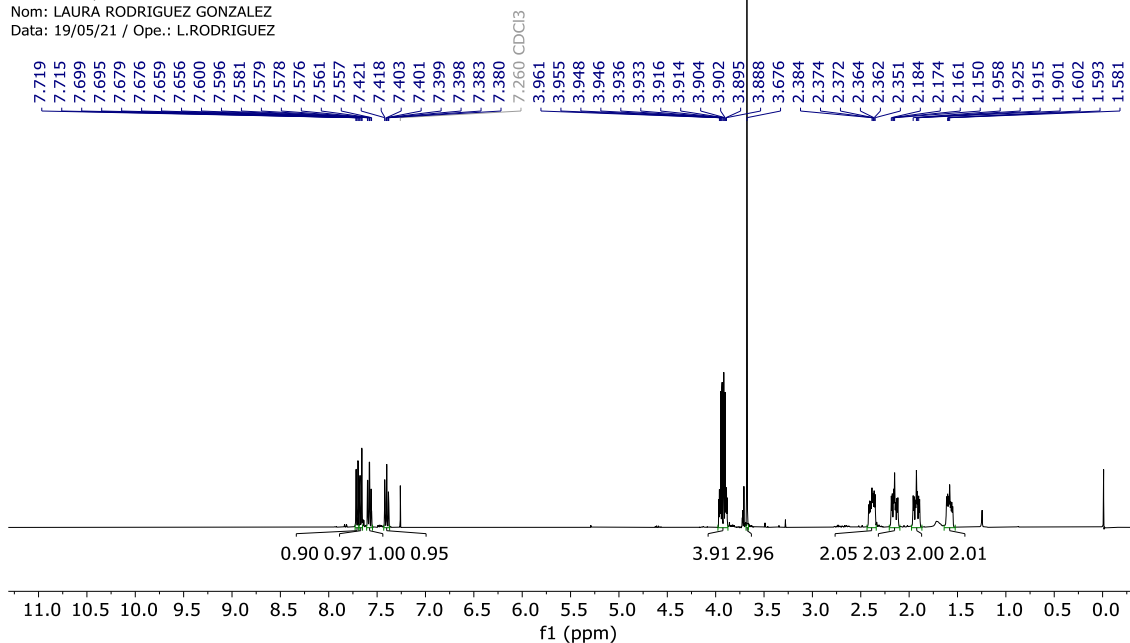


san-1455-2021.2.fid LRG091-13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1009989
 N.Reg:
 Usuari: / Mostra:
 Nom:
 Data: 19/07/2021 18:26:42 h./ Ope.:

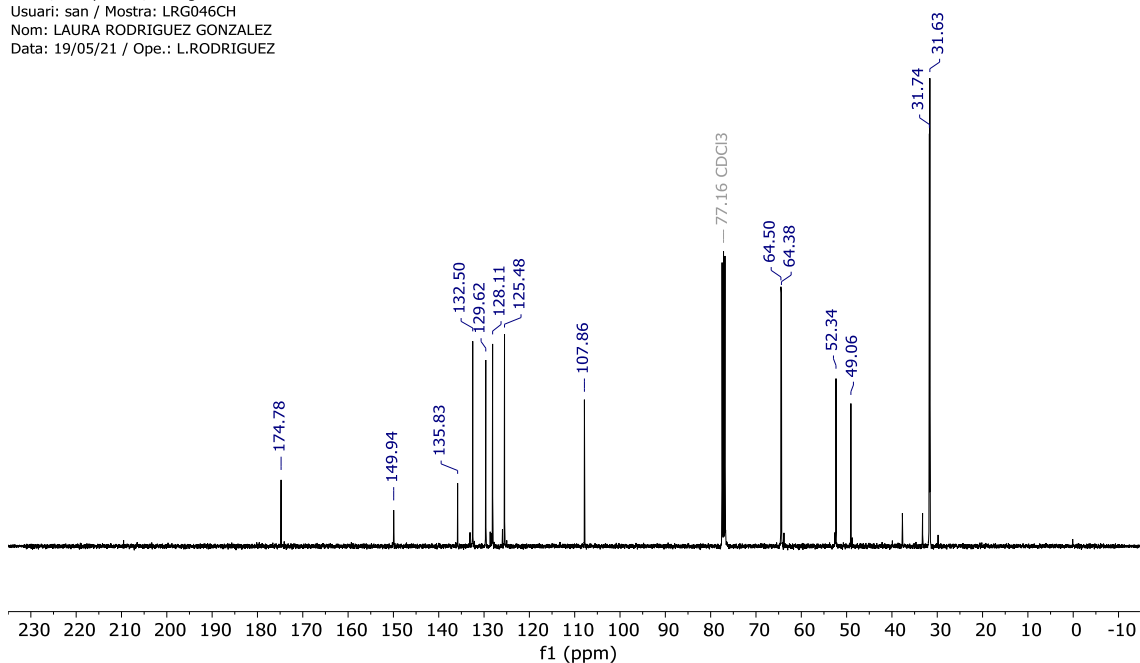


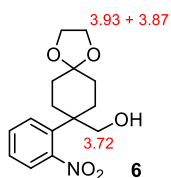


M400AQUL_19052021_LRG046CH-H1 1H 400 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG046CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 19/05/21 / Ope.: L.RODRIGUEZ

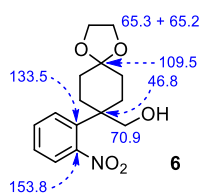
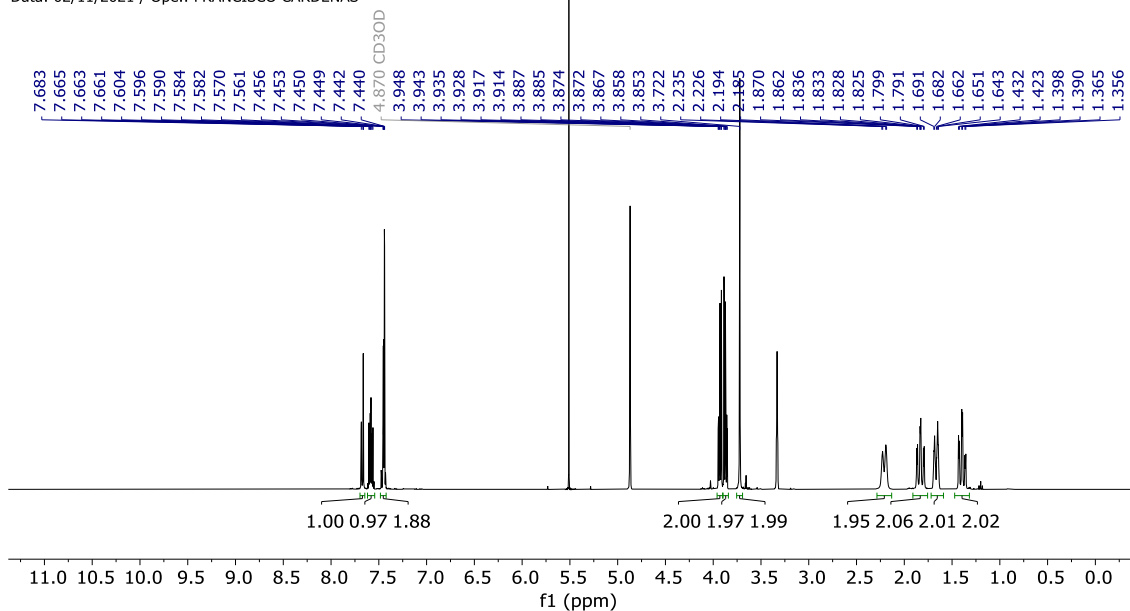


M400AQUL_19052021_LRG046CH-C13 13C{1H} 101 MHz
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: LRG046CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 19/05/21 / Ope.: L.RODRIGUEZ

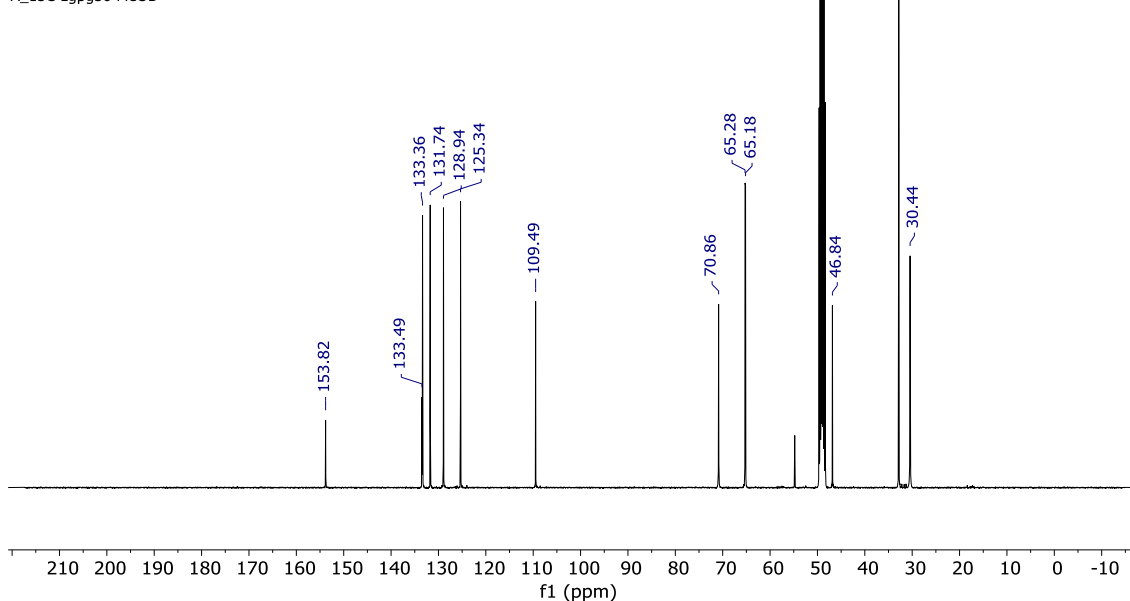




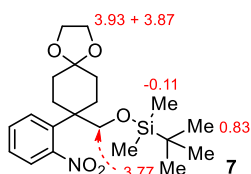
san-2012-2021.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2012/2021
 Usuari: san / Mostra: LRG138
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 02/11/2021 / Ope.: FRANCISCO CARDENAS



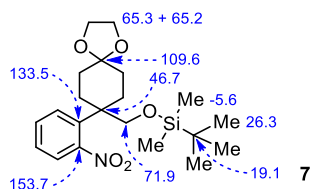
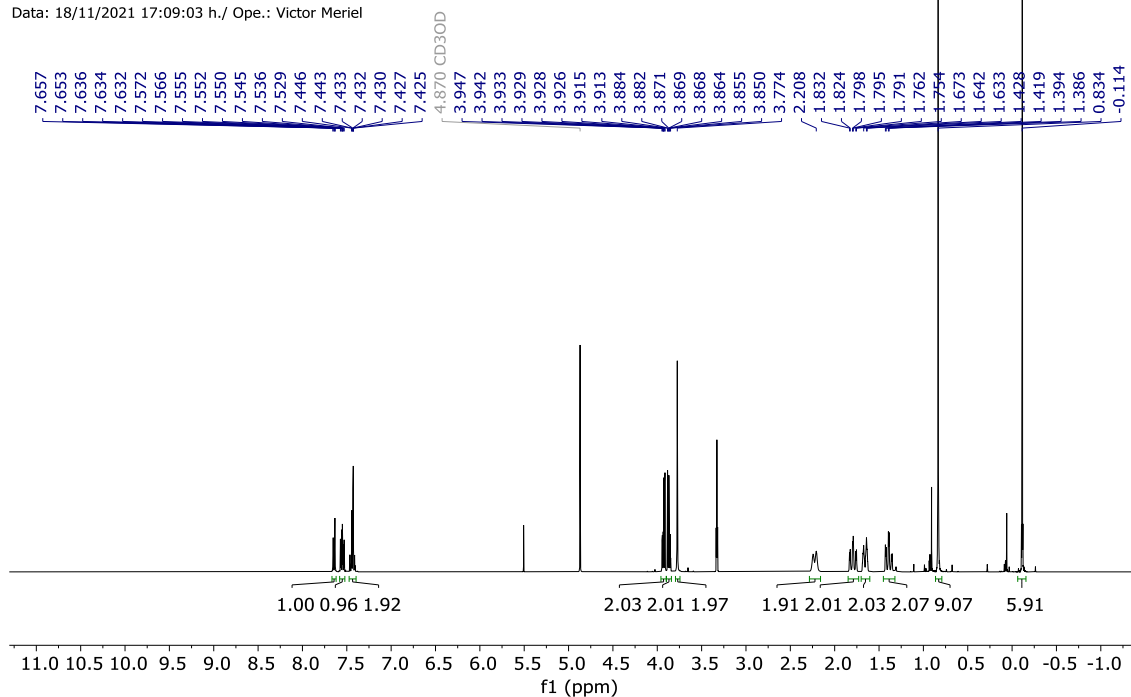
san-2012-2021.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2012/2021
 Usuari: san / Mostra: LRG138
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 02/11/2021 / Ope.: FRANCISCO CARDENAS
 A_13C-zpgg30 MeOD



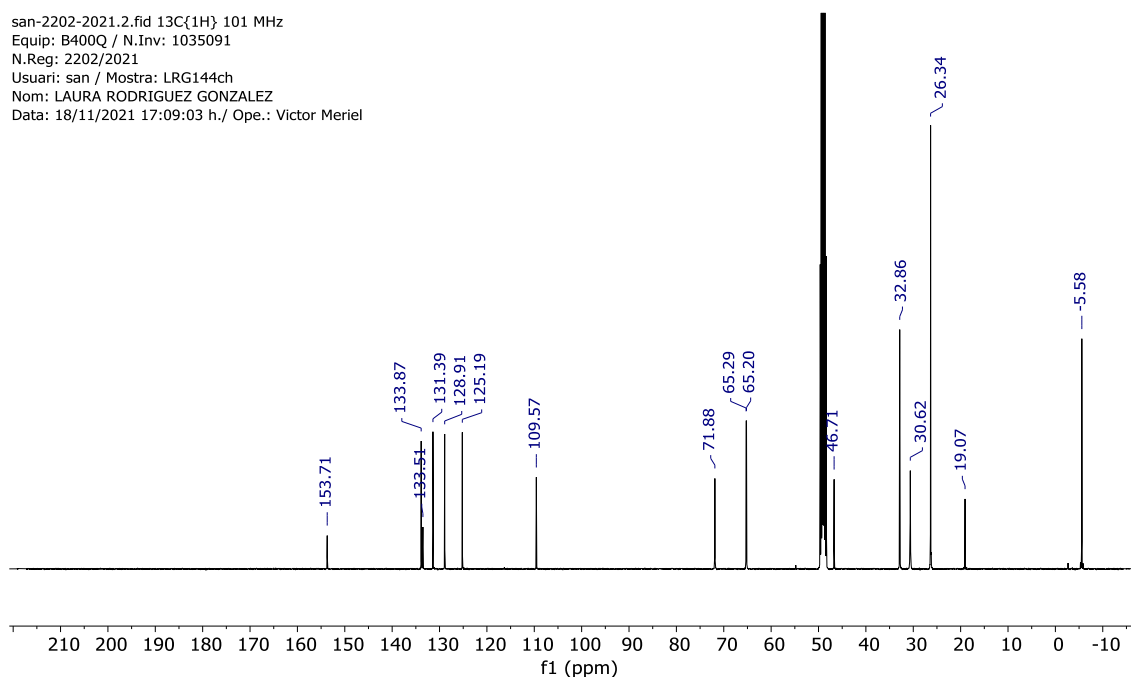
Experimental Section: Chapter 3

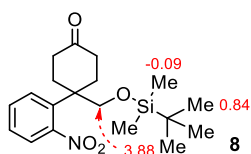


san-2202-2021.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2202/2021
 Usuari: san / Mostra: LRG144ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/11/2021 17:09:03 h./ Ope.: Victor Meriel

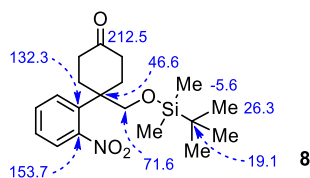
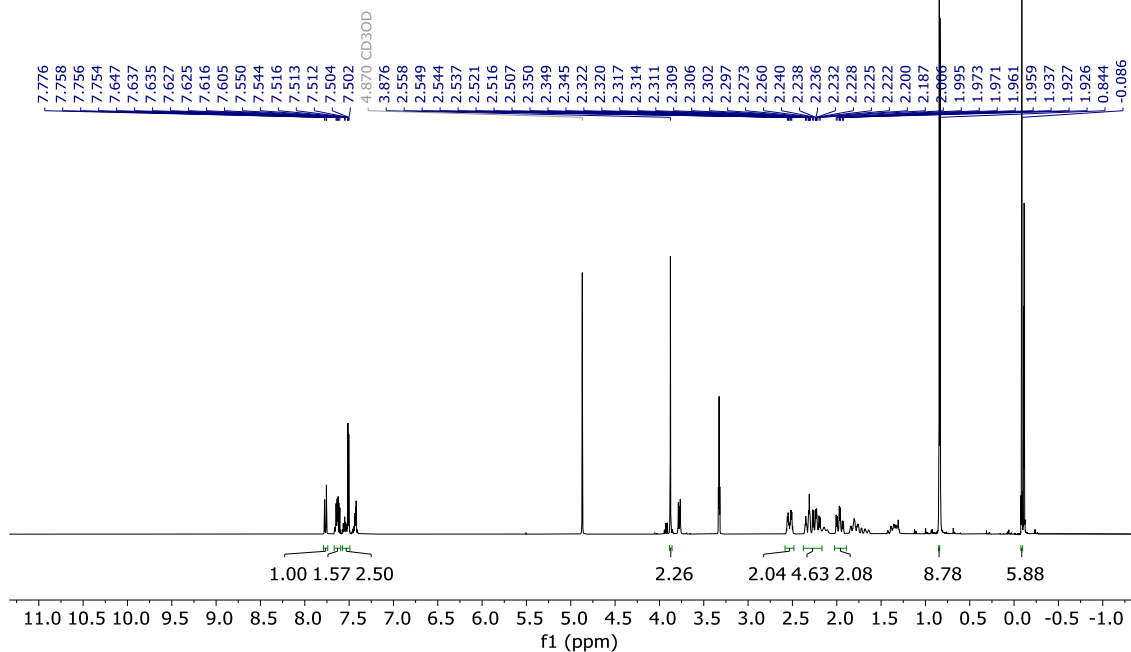


san-2202-2021.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2202/2021
 Usuari: san / Mostra: LRG144ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/11/2021 17:09:03 h./ Ope.: Victor Meriel

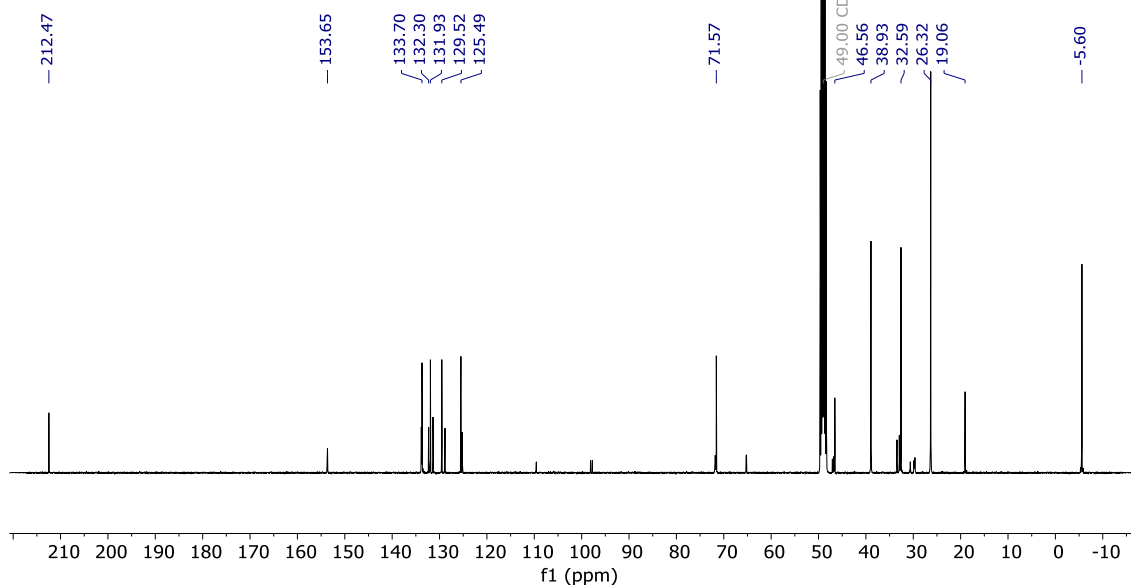


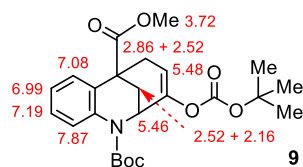


san-2203-2021.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2203/2021
 Usuari: san / Mostra: LRG145ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/11/2021 21:29:35 h./ Ope.: Victor Meriel

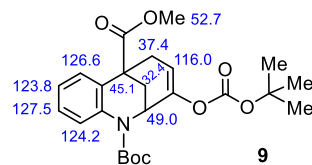
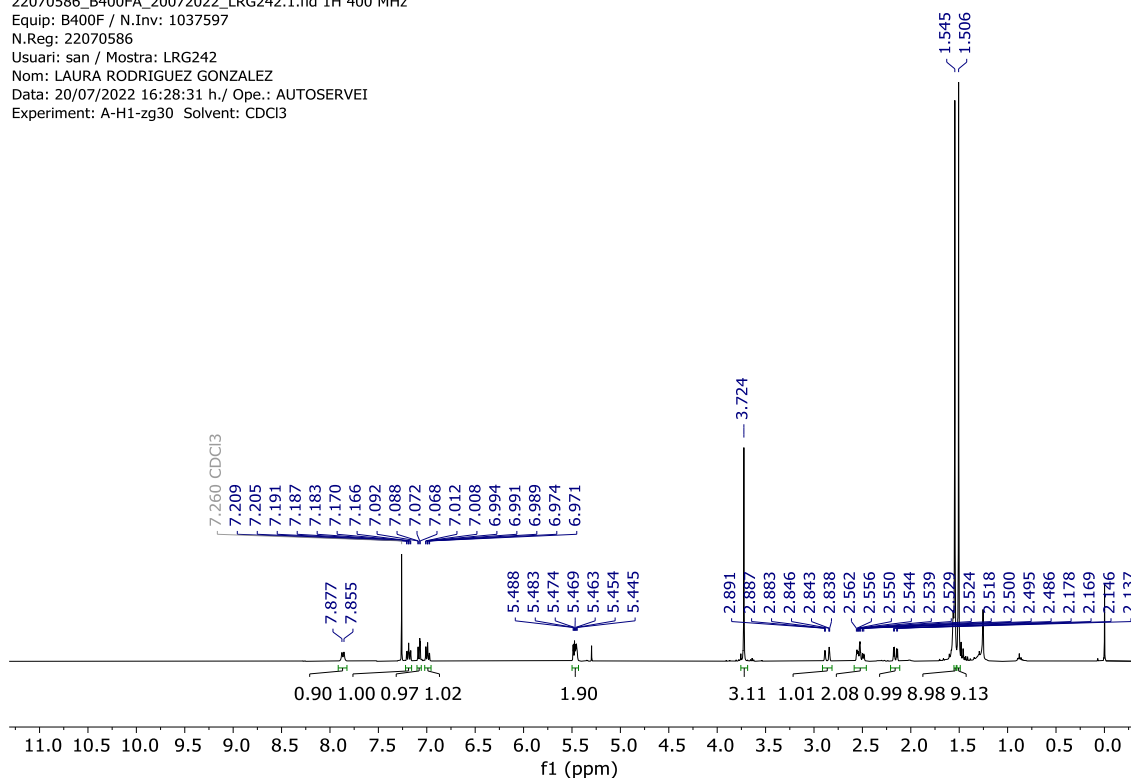


san-2203-2021.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 2203/2021
 Usuari: san / Mostra: LRG145ch
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 18/11/2021 21:29:35 h./ Ope.: Victor Meriel

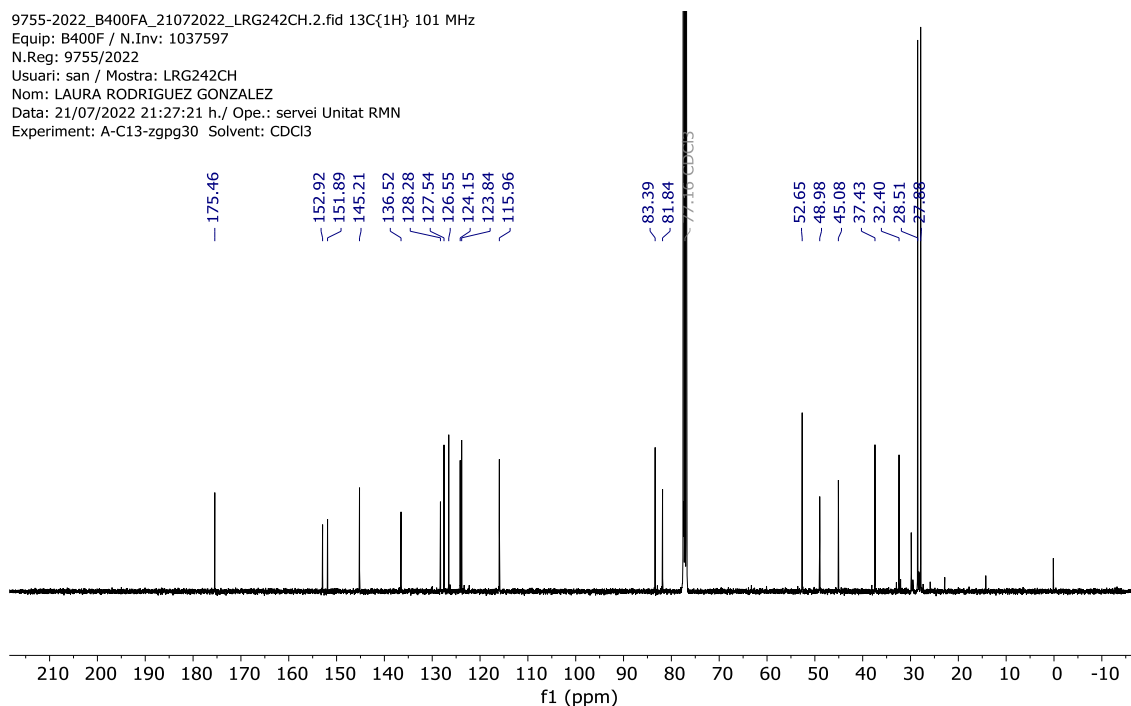


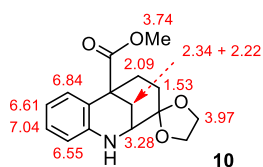


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 Experiment: A-H1-zg30 Solvent: CDCl_3

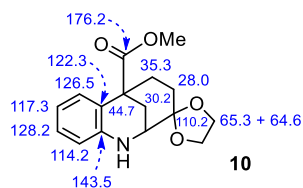
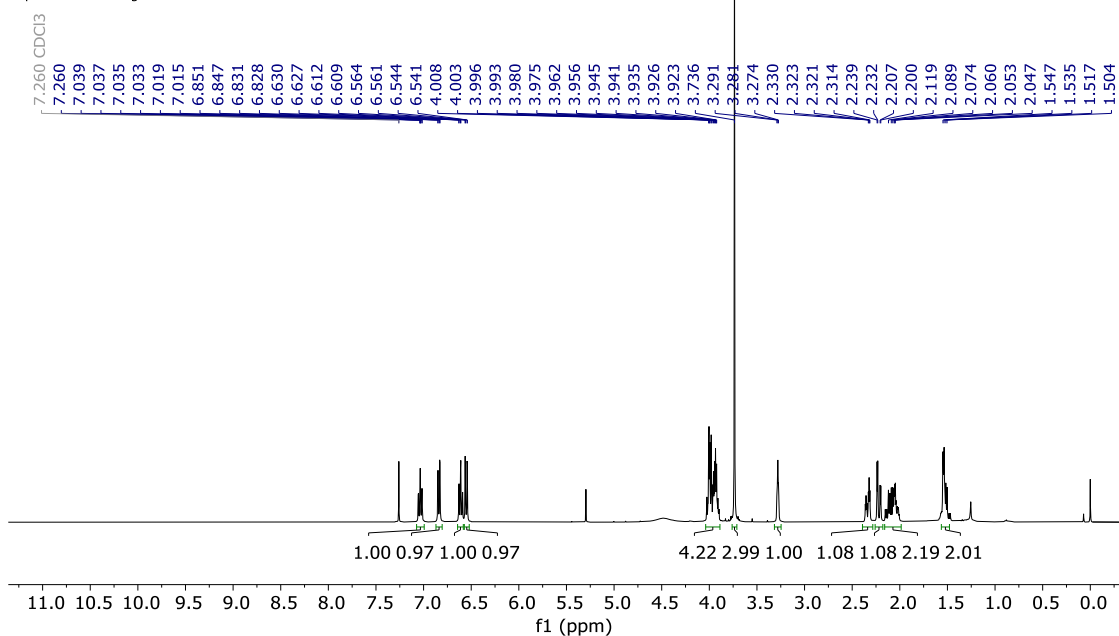


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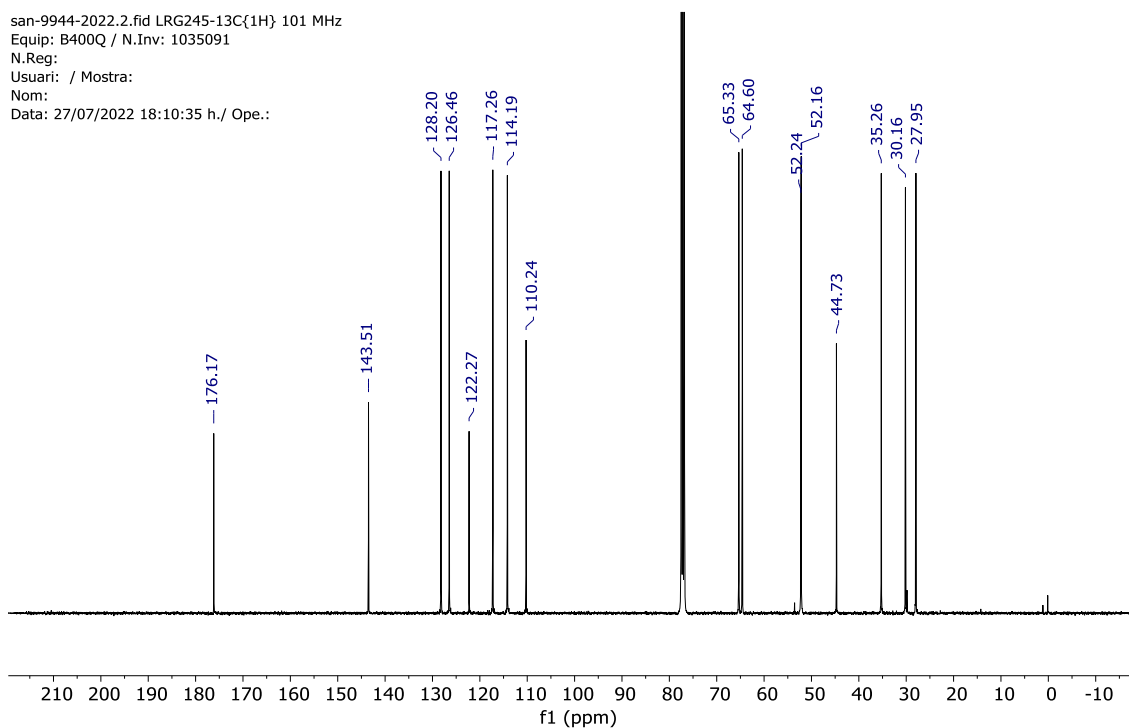


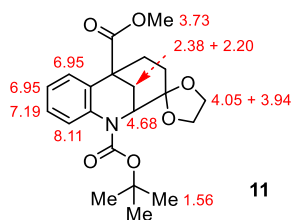


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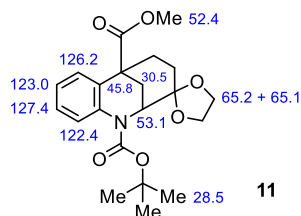
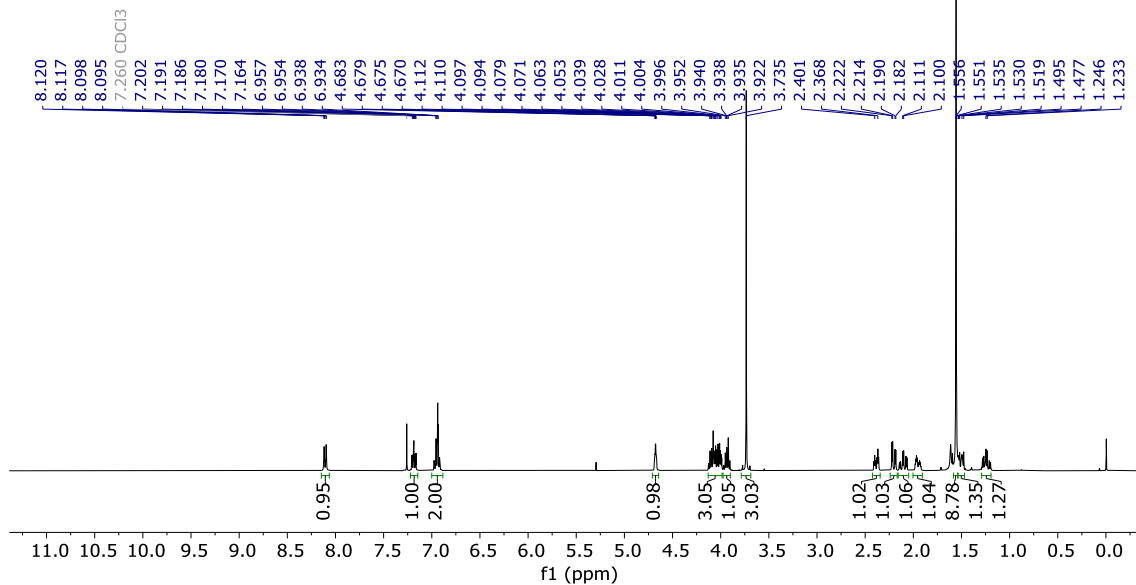


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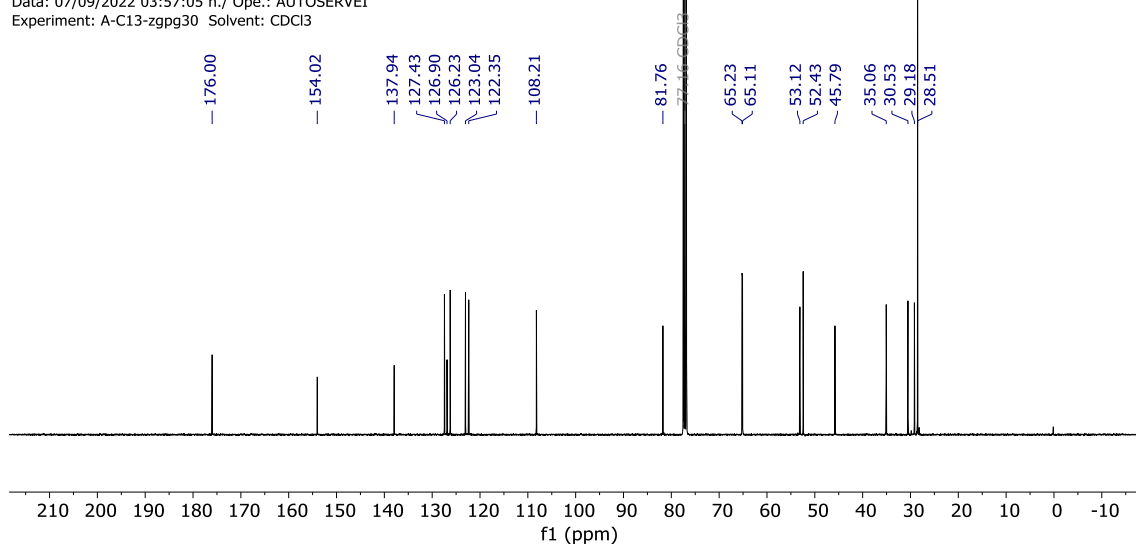


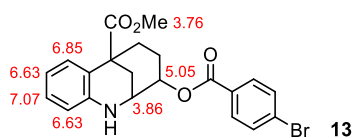


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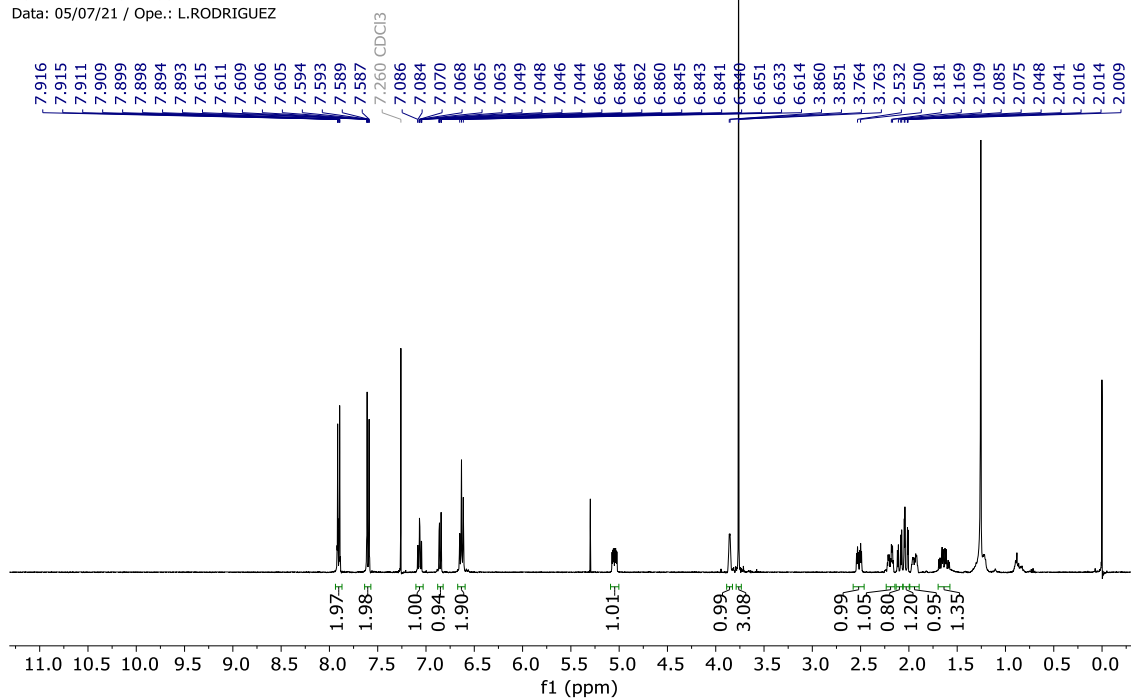


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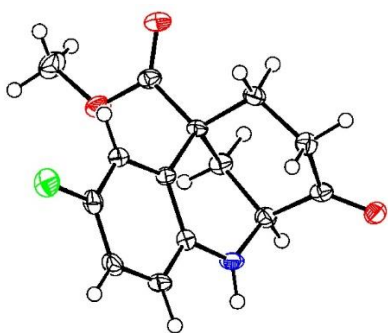




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Nom: LAURA RODRIGUEZ GONZALEZ
Data: 05/07/21 / Ope.: L.RODRIGUEZ



X-Ray Crystallographic Data for Compound **4e** (CCDC 2145263)



Compound **4e** was crystallized from a mixture of dichloromethane and hexane through vapor diffusion.

A yellow prism-like specimen of $C_{14}H_{14}FNO_3$, approximate dimensions 0.060 mm x 0.200 mm x 0.250 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a D8 Venture system equipped with a multilayer monochromator and a Mo microfocus ($\lambda = 0.71073 \text{ \AA}$).

The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 47049 reflections to a maximum θ angle of 26.54° ($0.80 \text{ \AA}$ resolution), of which 10273 were independent (average redundancy 4.580, completeness = 99.7%, $R_{\text{int}} = 5.62\%$, $R_{\text{sig}} = 4.53\%$) and 8314 (80.93%) were greater than $2\sigma(F^2)$. The final cell constants of $a = 9.0069(16) \text{ \AA}$, $b = 9.7444(17) \text{ \AA}$, $c = 56.483(10) \text{ \AA}$, $\beta = 91.350(3)^\circ$, volume = $4956.0(15) \text{ \AA}^3$, are based upon the refinement of the XYZ-centroids of reflections above $20 \sigma(I)$. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6152 and 0.7454.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P 1 21/n 1$, with $Z = 16$ for the formula unit, $C_{14}H_{14}FNO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 698 variables converged at $R1 = 8.23\%$, for the observed data and $wR2 = 16.61\%$ for all data. The goodness-of-fit was 1.186. The largest peak in the final difference electron density synthesis was $0.320 \text{ e}^-/\text{\AA}^3$ and the largest hole was $-0.327 \text{ e}^-/\text{\AA}^3$ with an RMS deviation of $0.067 \text{ e}^-/\text{\AA}^3$. On the basis of the final model, the calculated density was 1.411 g/cm^3 and $F(000)$, 2208 e^- .

Identification code	D43ZB157_0m_a	
Empirical formula	C14 H14 F N O3	
Formula weight	263.26	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 9.0069(16) Å	$\alpha = 90^\circ$.
	b = 9.7444(17) Å	$\beta = 91.350(3)^\circ$.
	c = 56.483(10) Å	$\gamma = 90^\circ$.
Volume	4956.0(15) Å ³	
Z	16	
Density (calculated)	1.411 Mg/m ³	
Absorption coefficient	0.109 mm ⁻¹	
F(000)	2208	
Crystal size	0.250 x 0.200 x 0.060 mm ³	
Theta range for data collection	2.121 to 26.539°.	
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -70 ≤ l ≤ 70	
Reflections collected	47049	
Independent reflections	10273 [R(int) = 0.0562]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7454 and 0.6152	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	10273 / 0 / 698	
Goodness-of-fit on F ²	1.186	
Final R indices [I > 2sigma(I)]	R1 = 0.0823, wR2 = 0.1588	
R indices (all data)	R1 = 0.1012, wR2 = 0.1661	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.320 and -0.327 e.Å ⁻³	

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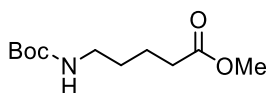
¹¹ Lutz, V.; Park, N.; Rothe, C.; Krüger, C.; Baro, A.; Laschat, S. Doing it Twice: Asymmetric Deprotonation/Alkylation of Weiss Diketone Derivatives as Key Steps in the Functionalization of Bicyclo[3.3.0]octanes. *Eur. J. Org. Chem.* **2013**, *2013*, 761–771.

<https://doi.org/10.1002/ejoc.201201409>

4. MHAT-TRIGGERED DECARBOXYLATION OF ALKENE-FUNCTIONALIZED REDOX-ACTIVE ESTERS

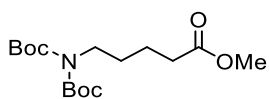
DESIGN OF A SUITABLE REDOX-ACTIVE ESTER PRECURSOR

Synthesis of methyl 5-((*tert*-butoxycarbonyl)amino)pentanoate (**1**)^{1,2}



To a solution of 5-aminovaleric acid (2.93 g, 25 mmol, 1.0 equiv.) in methanol (38 mL, 0.66 M) at 0 °C was added thionyl chloride (4.46 g, 2.7 mL, 37.5 mmol, 1.5 equiv.) dropwise and the resulting mixture was left to stir at room temperature for 2 hours. Afterward, the solvent and the excess of thionyl chloride were evaporated and the residue was dissolved in acetonitrile (63 mL, 0.4 M). Triethylamine (3.04 g, 4.2 mL, 30 mmol, 1.2 equiv.) and Boc₂O (5.46 g, 25 mmol, 1.0 equiv.) were slowly added and the solution was left to stir at room temperature for 16 hours. Then, the solvent was evaporated, and ethyl acetate (40 mL) and 1.0 M hydrochloric acid (40 mL) were added. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **1** (5.20 g, 90%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.67 (s, 3H), 3.12 (t, *J* = 6.9 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.72 – 1.60 (m, 2H), 1.57 – 1.48 (m, 2H), 1.44 (s, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 174.0, 156.1, 79.3, 51.7, 40.3, 33.7, 29.6, 28.5, 22.2 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₁H₂₂NO₄⁺ 232.1543, found 232.1547.

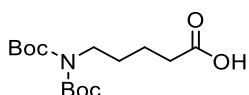
Synthesis of methyl 5-((*di-tert*-butoxycarbonyl)amino)pentanoate (**2**)³



To a solution of methyl 5-((*tert*-butoxycarbonyl)amino)pentanoate (3.47 g, 15 mmol, 1.0 equiv.), DMAP (183 mg, 1.5 mmol, 0.1 equiv.) and triethylamine (1.82 g, 2.5 mL, 18 mmol, 1.2 equiv.) in acetonitrile (38 mL, 0.4 M) was added Boc₂O (3.27 g, 15 mmol, 1.0 equiv.) and the resulting mixture was left to stir at room temperature for 16 hours. Then, the solvent was evaporated, and ethyl acetate (30 mL) and 1.0 M hydrochloric acid (30 mL) were added. The two phases were separated, and

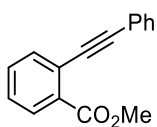
the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **2** (3.88 g, 78%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 3H), 3.57 (t, *J* = 6.9 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.67 – 1.57 (m, 4H), 1.50 (s, 18H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 173.9, 152.7, 82.3, 51.6, 46.0, 33.8, 28.6, 28.2, 22.3 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₆H₃₀NO₆⁺ 332.2068, found 332.2070.

Synthesis of 5-((di-*tert*-butoxycarbonyl)amino)pentanoic acid (**3**)



To a solution of methyl 5-((di-*tert*-butoxycarbonyl)amino)pentanoate (4.97 g, 15 mmol, 1.0 equiv.) in a (1:1) THF/H₂O mixture (40 mL, 0.38 M) was added sodium hydroxide (720 mg, 18 mmol, 1.2 equiv.) and the resulting mixture was stirred at room temperature for 4 hours. Then, the mixture was neutralized with a 10% solution of citric acid (50 mL) and subsequently extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **3** (4.48 g, 94%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.62 – 3.51 (m, 2H), 2.42 – 2.32 (m, 2H), 1.68 – 1.56 (m, 4H), 1.49 (s, 18H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 179.4, 152.8, 82.4, 46.0, 33.7, 28.5, 28.2, 22.0 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₅H₂₈NO₆⁺ 318.1911, found 318.1911.

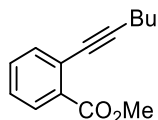
Synthesis of methyl 2-(phenylethynyl)benzoate (**4**)⁴



A mixture of methyl 2-bromobenzoate (5.16 g, 3.4 mL, 24 mmol, 1.0 equiv.), CuI (274 mg, 1.44 mmol, 0.06 equiv.), PPh₃ (567 mg, 2.16 mmol, 0.09 equiv.) and [Pd(OAc)₂]₃ (162 mg, 0.72 mmol, 0.03 equiv.) was dissolved in degassed diethylamine (80 mL, 0.3 M). Afterward, phenylacetylene (3.68 g, 4.0 mL, 36 mmol, 1.5 equiv.) was added dropwise and the resulting mixture was heated at 60 °C for 16 hours. Then, the solution was concentrated under vacuum. Purification by chromatography (Hex → Hex/AcOEt 25%) gave **4** (5.38 g, 95%) as a yellow oil. Spectral data were identical to those previously reported.^[5] ¹H NMR (400 MHz, CDCl₃) δ 7.98 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.61 – 7.55 (m, 2H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 – 7.32 (m, 4H), 3.97 (s, 3H); ¹³C{¹H}

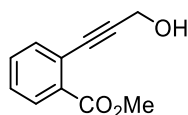
NMR (101 MHz, CDCl_3) δ 166.9, 134.1, 132.0, 131.9, 131.8, 130.6, 128.7, 128.5, 128.0, 123.8, 123.5, 94.5, 88.4, 52.3 ppm.

Synthesis of methyl 2-(hex-1-yn-1-yl)benzoate (**5**)⁴

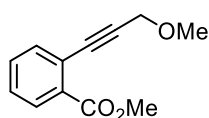


A mixture of methyl 2-bromobenzoate (2.15 g, 1.4 mL, 10 mmol, 1.0 equiv.), CuI (114 mg, 0.60 mmol, 0.06 equiv.), PPh_3 (236 mg, 0.90 mmol, 0.09 equiv.) and $[\text{Pd}(\text{OAc})_2]_3$ (67 mg, 0.30 mmol, 0.03 equiv.) was dissolved in degassed diethylamine (33 mL, 0.3 M). Afterward, 1-hexyne (1.23 g, 1.7 mL, 15 mmol, 1.5 equiv.) was added dropwise and the resulting mixture was heated at 60 °C for 16 hours. Then, the solution was concentrated under vacuum. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **5** (1.92 g, 89%) as a yellow oil. Spectral data were identical to those previously reported.^[6] ^1H NMR (400 MHz, CDCl_3) δ 7.87 (ddd, J = 7.8, 1.5, 0.5 Hz, 1H), 7.50 (ddd, J = 7.8, 1.4, 0.5 Hz, 1H), 7.40 (td, J = 7.6, 1.5 Hz, 1H), 7.29 (td, J = 7.6, 1.4 Hz, 1H), 3.91 (s, 3H), 2.47 (t, J = 7.1 Hz, 2H), 1.68 – 1.57 (m, 2H), 1.56 – 1.44 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.2, 134.3, 132.1, 131.6, 130.2, 127.2, 124.6, 96.1, 79.3, 52.2, 30.9, 22.1, 19.6, 13.8 ppm.

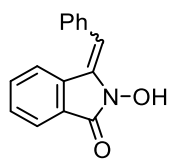
Synthesis of methyl 2-(3-hydroxyprop-1-yn-1-yl)benzoate (**6**)⁴



A mixture of methyl 2-bromobenzoate (2.15 g, 1.4 mL, 10 mmol, 1.0 equiv.), CuI (114 mg, 0.60 mmol, 0.06 equiv.), PPh_3 (236 mg, 0.90 mmol, 0.09 equiv.) and $[\text{Pd}(\text{OAc})_2]_3$ (67 mg, 0.30 mmol, 0.03 equiv.) was dissolved in degassed diethylamine (33 mL, 0.3 M). Afterward, propargyl alcohol (841 mg, 870 μL , 15 mmol, 1.5 equiv.) was added dropwise and the resulting mixture was heated at 60 °C for 16 hours. Then, the solution was concentrated under vacuum. Purification by chromatography (Hex/AcOEt 10% $\rightarrow$ Hex/AcOEt 50%) gave **6** (513 mg, 27%) as a yellow oil. Spectral data were identical to those previously reported.^[7] ^1H NMR (400 MHz, CDCl_3) δ 7.92 (dd, J = 7.9, 1.4 Hz, 1H), 7.53 (dd, J = 7.7, 1.4 Hz, 1H), 7.44 (td, J = 7.6, 1.4 Hz, 1H), 7.35 (td, J = 7.6, 1.4 Hz, 1H), 4.55 (d, J = 2.6 Hz, 2H), 3.90 (s, 3H), 2.72 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.7, 134.3, 131.9, 131.8, 130.4, 128.1, 123.4, 92.9, 84.3, 52.4, 51.8 ppm.

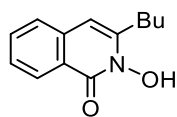
Synthesis of methyl 2-(3-methoxyprop-1-yn-1-yl)benzoate (7**)⁴**

A mixture of methyl 2-bromobenzoate (2.15 g, 1.4 mL, 10 mmol, 1.0 equiv.), CuI (114 mg, 0.60 mmol, 0.06 equiv.), PPh₃ (236 mg, 0.90 mmol, 0.09 equiv.) and [Pd(OAc)₂]₃ (67 mg, 0.30 mmol, 0.03 equiv.) was dissolved in degassed diethylamine (33 mL, 0.3 M). Afterward, methyl propargyl ether (1.05 g, 1.3 mL, 15 mmol, 1.5 equiv.) was added dropwise and the resulting mixture was heated at 60 °C for 16 hours. Then, the reaction mixture was concentrated under vacuum. Purification by chromatography (Hex/AcOEt 2.5% → Hex/AcOEt 25%) gave **7** (408 mg, 20%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (ddd, *J* = 7.9, 1.5, 0.6 Hz, 1H), 7.56 (ddd, *J* = 7.7, 1.4, 0.5 Hz, 1H), 7.45 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 4.38 (s, 2H), 3.91 (s, 3H), 3.49 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.6, 134.4, 132.0, 131.8, 130.4, 128.2, 123.3, 90.4, 85.1, 60.7, 57.8, 52.3 ppm.

Synthesis of 3-benzylidene-2-hydroxyisoindolin-1-one (8**)⁸**

A mixture of potassium hydroxide (14.2 g, 254 mmol, 12 equiv.) and hydroxylamine hydrochloride (8.80 g, 127 mmol, 6.0 equiv.) was dissolved in anhydrous methanol (70 mL, 0.3 M). Afterward, methyl 2-(phenylethynyl)benzoate (**4**) (4.98 g, 21.1 mmol, 1.0 equiv.) was added dropwise and the resulting mixture was heated at reflux for 3 hours. Then, the solution was concentrated under vacuum. The crude product was dissolved in dichloromethane and washed with 1.0 M HCl. Purification by chromatography (Hex/AcOEt 10% → AcOEt) gave **8** as a light orange solid (4.11 g, 82%). The NMR data reported correspond to the major isomer, with a 91/9 proportion of *E/Z* isomers. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.65 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.69 (td, *J* = 7.6, 1.2 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.55 (td, *J* = 7.5, 0.8 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.22 (m, 1H), 6.88 (s, 1H); ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆) δ 163.2, 134.5, 133.9, 132.3, 131.6, 130.6, 129.3, 127.6, 127.1, 125.5, 122.4, 120.0, 106.8 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₅H₁₂NO₂⁺ 238.0863, found 238.0863.

Synthesis of 3-butyl-2-hydroxyisoquinolin-1(2*H*)-one (**9**)⁵

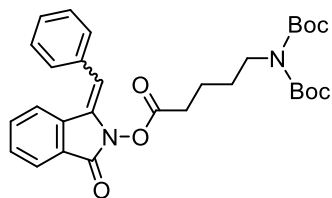


A mixture of potassium hydroxide (5.40 g, 96 mmol, 12 equiv.) and hydroxylamine hydrochloride (3.30 g, 48 mmol, 6.0 equiv.) was dissolved in anhydrous methanol (27 mL, 0.3 M). Afterward, methyl 2-(hex-1-yn-1-yl)benzoate (**5**) (1.73 g, 8.0 mmol, 1.0 equiv.) was added dropwise and the resulting mixture was heated at reflux for 3 hours. Then, the solution was concentrated under vacuum. The crude product was dissolved in dichloromethane and washed with 1.0 M HCl. Purification by chromatography (Hex/AcOEt 10% → AcOEt) gave **9** as a light orange solid (1.41 g, 81%). ¹H NMR (400 MHz, CDCl₃) δ 8.35 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.42 (s, 1H), 2.90 – 2.77 (m, 2H), 1.81 – 1.68 (m, 2H), 1.54 – 1.38 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 157.8, 140.5, 135.5, 131.8, 126.9, 126.0, 125.8, 122.3, 103.9, 30.5, 29.8, 22.5, 14.0 ppm.

SYNTHESIS OF THE REDOX-ACTIVE ESTERS

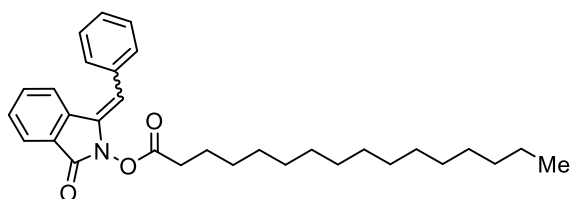
General method for the synthesis of the redox-active esters:⁹ A solution of the selected acid (1.0 equiv.), 3-benzylidene-2-hydroxyisoindolin-1-one (1.0 equiv.), dicyclohexylcarbodiimide (1.2 equiv.) and DMAP (0.1 equiv.) in THF (0.2 M) was left to stir for 16 hours at room temperature. Afterward, the reaction mixture was concentrated under vacuum. The corresponding product was purified by flash column chromatography on silica gel.

- PRIMARY ACIDS 10a to 10d**



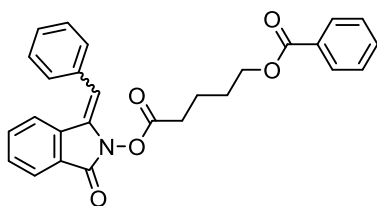
1-benzylidene-3-oxoisoindolin-2-yl 5-(bis(tert-butoxycarbonyl)amino)pentanoate (**10a**). The title compound was prepared according to the general procedure using 5-((di-*tert*-butoxycarbonyl)amino)pentanoic acid (**3**) (1.71 g, 5.4 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisoindolin-1-one (**8**) (1.28 g, 5.4 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (1.34 g, 6.5 mmol, 1.2 equiv.) and DMAP (66 mg, 0.54 mmol,

0.1 equiv.) in THF (27 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **10a** (2.46 g, 85%) as a white solid in a 81/19 proportion of *E/Z* isomers. ^1H NMR (400 MHz, CDCl_3) δ 7.93 – 7.85 (m, 1H), 7.78 – 7.71 (m, 1H), 7.69 – 7.63 (m, 1H), 7.58 – 7.49 (m, 1H), 7.43 – 7.32 (m, 4H), 7.34 – 7.25 (m, 1H), 6.70 (s, 0.2H), 6.68 (s, 0.8H), 3.71 – 3.58 (m, 0.1H), 3.43 (t, $J = 6.8$ Hz, 1.7H), 2.27 – 2.09 (m, 1H), 1.82 – 1.65 (m, 1H), 1.65 (s, 1H), 1.50 (s, 16H), 1.41 – 1.30 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 169.4, 166.8, 164.0, 152.6, 135.0, 133.2, 131.9, 130.1, 130.0, 129.6, 128.0, 127.8, 125.5, 124.1, 119.9, 106.8, 82.3, 45.7, 30.2, 28.22, 28.16, 21.3 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{NaO}_7^+$ 559.2415, found 559.2418.



1-benzylidene-3-oxoisindolin-2-yl

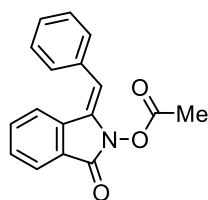
palmitate (**10b**). The title compound was prepared according to the general procedure using palmitic acid (385 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **10b** (578 mg, 81%) as a yellow oil in a 94/6 proportion of *E/Z* isomers. ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, $J = 7.5$ Hz, 1H), 7.75 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.70 – 7.61 (m, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.44 – 7.37 (m, 2H), 7.40 – 7.31 (m, 2H), 7.32 – 7.26 (m, 1H), 6.68 (s, 0.9H), 6.46 (s, 0.1H), 2.21 – 2.06 (m, 1H), 1.76 – 1.59 (m, 1H), 1.44 – 0.99 (m, 26H), 0.87 (t, $J = 6.8$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 169.8, 164.2, 135.1, 133.21, 133.16, 132.0, 130.1, 129.6, 128.0, 127.8, 125.6, 124.2, 119.9, 106.9, 32.1, 30.6, 29.83, 29.80, 29.79, 29.76, 29.7, 29.49, 29.45, 29.2, 28.8, 24.1, 22.8, 14.3 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{31}\text{H}_{42}\text{NO}_3^+$ 476.3159, found 476.3157.



5-((1-benzylidene-3-oxoisindolin-2-yl)oxy)-5-oxopentyl

benzoate (**10c**). The title compound was prepared according to the general procedure

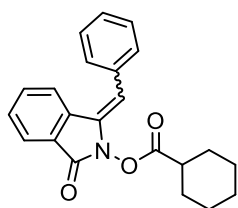
using 5-(benzyloxy)pentanoic acid (333 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisoindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **10c** (542 mg, 82%) as a yellow oil in a 94/6 proportion of *E/Z* isomers. ^1H NMR (500 MHz, CDCl_3) δ 8.02 (dd, $J = 8.4, 1.3$ Hz, 1H), 7.90 (dt, $J = 7.6, 1.0$ Hz, 1H), 7.76 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.68 (td, $J = 7.6, 1.1$ Hz, 1H), 7.60 – 7.51 (m, 1H), 7.48 – 7.41 (m, 1H), 7.43 – 7.38 (m, 1H), 7.37 – 7.30 (m, 1H), 7.30 – 7.23 (m, 1H), 6.69 (s, 1H), 6.56 (s, 0.1H), 4.18 (t, $J = 6.2$ Hz, 1H), 2.34 – 2.19 (m, 1H), 1.87 – 1.72 (m, 1H), 1.63 – 1.40 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.4, 166.6, 164.2, 135.1, 133.3, 133.2, 133.1, 132.0, 130.4, 130.1, 129.72, 129.68, 128.5, 128.1, 127.9, 125.5, 124.2, 120.0, 106.9, 64.3, 30.1, 27.8, 20.9 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{27}\text{H}_{24}\text{NO}_5^+$ 442.1649, found 442.1651.



(*E*)-1-benzylidene-3-oxoisoindolin-2-yl acetate (**10d**). The title

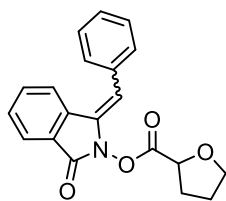
compound was prepared according to the general procedure using acetic acid (90 mg, 86 μL , 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisoindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **10d** (335 mg, 80%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.90 (ddd, $J = 7.6, 1.2, 0.8$ Hz, 1H), 7.76 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.67 (ddd, $J = 7.8, 7.4, 1.2$ Hz, 1H), 7.54 (td, $J = 7.5, 1.0$ Hz, 1H), 7.43 – 7.29 (m, 5H), 6.71 (s, 1H), 1.65 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.8, 163.8, 135.0, 133.2, 133.1, 131.8, 130.0, 129.7, 128.1, 127.8, 125.6, 124.2, 119.9, 106.9, 17.2 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{17}\text{H}_{14}\text{NO}_3^+$ 280.0968, found 280.0968.

• **SECONDARY ACIDS 10e to 10i**



1-benzylidene-3-oxoisindolin-2-yl cyclohexanecarboxylate (10e).

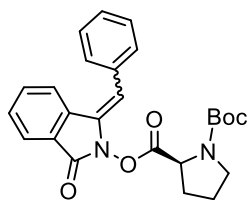
The title compound was prepared according to the general procedure using cyclohexanecarboxylic acid (192 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisoindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **10e** (453 mg, 87%) as a yellow oil in a 93/7 proportion of *E/Z* isomers. ^1H NMR (400 MHz, CDCl_3) δ 7.92 – 7.85 (m, 1H), 7.78 – 7.71 (m, 1H), 7.66 (td, J = 7.6, 1.2 Hz, 1H), 7.53 (td, J = 7.5, 1.0 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.40 – 7.32 (m, 2H), 7.32 – 7.26 (m, 1H), 6.67 (s, 0.9H), 6.44 (s, 0.1H), 2.06 – 1.92 (m, 1H), 1.89 – 1.75 (m, 1H), 1.74 – 1.61 (m, 1H), 1.59 – 1.46 (m, 2H), 1.44 – 0.94 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 172.0, 164.6, 135.3, 133.4, 133.2, 132.3, 130.2, 129.6, 128.0, 127.7, 125.6, 124.1, 119.9, 107.0, 40.5, 28.7, 27.8, 25.5, 25.2, 25.0 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{22}\text{H}_{22}\text{NO}_3^+$ 348.1594, found 348.1593.



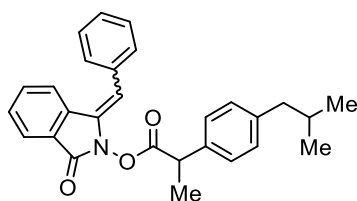
1-benzylidene-3-oxoisindolin-2-yl tetrahydrofuran-2-carboxylate (10f).

The title compound was prepared according to the general procedure using tetrahydro-2-furoic acid (174 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisoindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **10f** (453 mg, 90%) as a yellow oil. The product was isolated as a mixture of *E/Z* and *R/S* isomers and a tentative assignation is provided. ^1H NMR (400 MHz, CDCl_3) δ 7.93 – 7.84 (m, 1H), 7.79 (dt, J = 7.9, 0.9 Hz, 0.2H), 7.75 (d, J = 7.8 Hz, 0.9H), 7.71 – 7.60 (m, 1H), 7.57 – 7.50 (m, 1H), 7.47 – 7.40 (m, 2H), 7.42 – 7.33 (m, 2H), 7.36 – 7.26 (m, 1H), 6.71 (s, 0.8H), 6.56 (s, 0.2H), 4.32 (s, 0.3H), 4.00 – 3.90 (m, 0.5H), 3.89 – 3.75 (m, 2H), 2.28 – 1.98 (m, 1H), 1.96

– 1.59 (m, 2H), 1.34 – 1.10 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 169.9, 169.0, 138.3, 135.3, 135.1, 133.4, 133.2, 132.4, 132.3, 132.1, 130.2, 129.9, 129.7, 129.4, 128.5, 128.2, 128.0, 127.8, 125.3, 124.2, 123.7, 120.0, 119.9, 107.3, 106.0, 75.0, 74.5, 69.6, 69.5, 30.4, 29.1, 25.0 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{20}\text{H}_{18}\text{NO}_4^+$ 336.1230, found 336.1227.



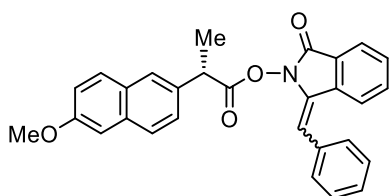
2-(1-benzylidene-3-oxoisindolin-2-yl) 1-(tert-butyl) (R)-pyrrolidine-1,2-dicarboxylate (**10g**). The title compound was prepared according to the general procedure using *N*-Boc-L-proline (323 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **10g** (476 mg, 73%) as a yellow oil in a 88/12 proportion of *E/Z* isomers. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 7.6 Hz, 0.7H), 7.88 (dt, J = 7.6, 1.0 Hz, 0.3H), 7.79 (dt, J = 7.7, 0.9 Hz, 0.2H), 7.74 (d, J = 7.8 Hz, 0.9H), 7.70 – 7.61 (m, 1H), 7.58 – 7.49 (m, 1H), 7.52 – 7.40 (m, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.33 – 7.25 (m, 1H), 6.64 (s, 0.8H), 6.55 (s, 0.1H), 4.37 – 4.11 (m, 1H), 3.48 – 3.10 (m, 2H), 1.75 – 1.23 (m, 13H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 169.6, 168.9, 165.0, 153.7, 138.3, 135.6, 135.1, 133.4, 133.2, 132.4, 130.4, 129.8, 129.4, 128.5, 128.4, 128.1, 127.8, 125.3, 124.3, 123.7, 120.0, 107.1, 106.0, 81.0, 56.7, 46.3, 46.0, 28.2 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_5^+$ 435.1914, found 435.1918.



1-benzylidene-3-oxoisindolin-2-yl 2-(4-isobutylphenyl)

propanoate (**10h**). The title compound was prepared according to the general procedure using 2-(4-isobutylphenyl)propanoic acid (309 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **10h** (517 mg, 81%)

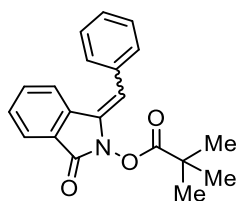
as a yellow oil. The product was isolated as a mixture of *E/Z* and *R/S* isomers and a tentative assignation is provided. ^1H NMR (400 MHz, CDCl_3) δ 7.92 – 7.82 (m, 1H), 7.78 – 7.69 (m, 1H), 7.64 (td, J = 7.6, 1.2 Hz, 1H), 7.51 (td, J = 7.5, 1.0 Hz, 1H), 7.48 – 7.31 (m, 4H), 7.30 – 7.20 (m, 1H), 7.07 (s, 2H), 6.98 – 6.88 (m, 1H), 6.85 – 6.76 (m, 1H), 6.69 (s, 0.6H), 6.61 (s, 0.4H), 3.52 – 3.38 (m, 0.4H), 3.16 (q, J = 7.2 Hz, 0.6H), 2.49 – 2.32 (m, 2H), 1.82 (hept, J = 6.8 Hz, 1H), 1.44 (d, J = 6.9 Hz, 1.3H), 1.03 (d, J = 7.3 Hz, 1.9H), 0.88 (d, J = 6.6 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 171.4, 171.1, 165.1, 164.3, 141.0, 140.8, 135.9, 135.6, 135.2, 133.2, 132.2, 130.2, 129.63, 129.56, 129.3, 128.1, 127.9, 127.2, 124.2, 119.9, 107.6, 106.9, 45.2, 42.4, 42.2, 30.2, 22.5, 19.0, 18.5 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{28}\text{H}_{28}\text{NO}_3^+$ 426.2064, found 426.2069.



1-benzylidene-3-oxoisindolin-2-yl

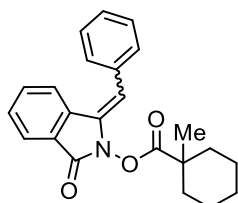
(S)-2-(6-methoxynaphthalen-2-yl)propanoate (**10i**). The title compound was prepared according to the general procedure using *(S)*-2-(6-methoxynaphthalen-2-yl)propanoic acid (345 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **10i** (580 mg, 86%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.95 – 7.80 (m, 1H), 7.78 – 7.60 (m, 3H), 7.59 – 7.48 (m, 2H), 7.48 – 7.30 (m, 3H), 7.30 – 7.21 (m, 2H), 7.18 – 6.95 (m, 4H), 6.86 – 6.78 (m, 0.2H), 6.70 (s, 0.4H), 6.58 (s, 0.4H), 4.28 (s, 0.2H), 3.90 (s, 2.7H), 3.75 – 3.56 (m, 0.4H), 3.40 – 3.24 (m, 0.4H), 1.83 – 1.41 (m, 2H), 1.15 (d, J = 7.4 Hz, 1H) ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{29}\text{H}_{24}\text{NO}_4^+$ 450.1700, found 450.1707.

• TERTIARY ACIDS 10j to 10m



1-benzylidene-3-oxoisindolin-2-yl pivalate (10j). The title

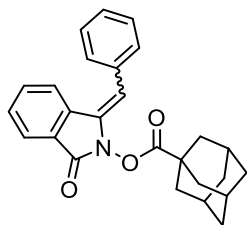
compound was prepared according to the general procedure using pivalic acid (153 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **10j** (342 mg, 71%) as a yellow oil in a 88/12 proportion of *E/Z* isomers. ^1H NMR (400 MHz, CDCl_3) δ 7.88 (dt, $J = 7.6, 1.0$ Hz, 1H), 7.74 (dt, $J = 7.9, 1.0$ Hz, 1H), 7.65 (td, $J = 7.6, 1.2$ Hz, 1H), 7.52 (td, $J = 7.5, 1.0$ Hz, 1H), 7.48 – 7.40 (m, 2H), 7.40 – 7.31 (m, 2H), 7.32 – 7.23 (m, 1H), 6.67 (s, 0.9H), 6.42 (s, 0.1H), 1.47 (s, 1H), 0.95 (s, 8H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.7, 165.4, 135.6, 133.6, 133.3, 132.9, 130.2, 129.6, 128.2, 127.9, 125.5, 124.1, 120.0, 109.3, 107.4, 38.2, 27.3, 26.6 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{20}\text{H}_{20}\text{NO}_3^+$ 322.1438, found 322.1433.



1-benzylidene-3-oxoisindolin-2-yl 1-methylcyclohexane-1-

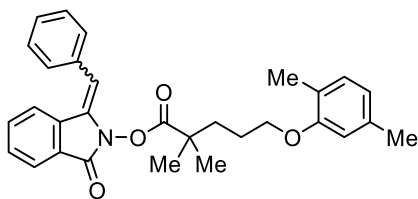
carboxylate (10k). The title compound was prepared according to the general procedure using 1-methylcyclohexane-1-carboxylic acid (213 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 25%) gave **10k** (450 mg, 83%) as a yellow oil in a 84/16 proportion of *E/Z* isomers. ^1H NMR (400 MHz, CDCl_3) δ 7.92 – 7.83 (m, 1H), 7.75 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.66 (td, $J = 7.6, 1.2$ Hz, 1H), 7.53 (td, $J = 7.5, 1.0$ Hz, 1H), 7.51 – 7.44 (m, 2H), 7.47 – 7.38 (m, 1H), 7.40 – 7.32 (m, 2H), 7.31 – 7.24 (m, 1H), 6.66 (s, 0.9H), 6.45 (s, 0.2H), 2.29 (s, 0.4H), 1.98 – 1.84 (m, 1H), 1.81 – 1.38 (m, 6H), 1.38 – 1.23 (m, 1H), 1.23 – 0.97 (m, 4H), 0.96 (s, 0.2H), 0.68 (s, 2.6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.2, 165.8, 135.8, 133.5, 133.3,

133.1, 130.4, 129.6, 128.8, 128.3, 127.9, 125.6, 124.2, 120.0, 107.5, 42.7, 35.8, 35.2, 25.6, 22.8, 22.7 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{23}H_{24}NO_3^+$ 362.1751, found 362.1755.



1-benzylidene-3-oxoisindolin-2-yl (1S,3S)-adamantane-1-

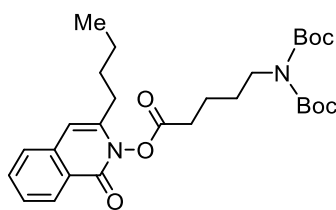
carboxylate (10l). The title compound was prepared according to the general procedure using adamantane-1-carboxylic acid (270 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **10l** (384 mg, 64%) as a yellow oil in a 87/13 proportion of *E/Z* isomers. 1H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 1H), 7.78 – 7.71 (m, 1H), 7.66 (td, J = 7.6, 1.2 Hz, 1H), 7.53 (td, J = 7.5, 1.0 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.43 – 7.33 (m, 2H), 7.33 – 7.26 (m, 1H), 6.66 (s, 0.9H), 6.41 (s, 0.1H), 2.22 – 2.16 (m, 0.8H), 2.16 – 2.09 (m, 0.5H), 1.92 – 1.83 (m, 3H), 1.82 – 1.76 (m, 1H), 1.69 – 1.48 (m, 11H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.6, 165.4, 135.6, 133.6, 133.2, 132.9, 130.3, 129.6, 128.8, 128.3, 127.7, 125.6, 124.2, 119.9, 109.3, 107.3, 40.3, 38.8, 37.9, 36.4, 36.2, 27.8, 27.7 ppm. HRMS (ESI) m/z : $[M+H]^+$: calculated for $C_{26}H_{26}NO_3^+$ 400.1907, found 400.1909.



1-benzylidene-3-oxoisindolin-2-yl 5-(2,5-

dimethylphenoxy)-2,2-dimethylpentanoate (10m). The title compound was prepared according to the general procedure using 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid (375 mg, 1.5 mmol, 1.0 equiv.), 3-benzylidene-2-hydroxyisindolin-1-one (**8**) (356 mg, 1.5 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (371 mg, 1.8 mmol, 1.2 equiv.) and DMAP (18 mg, 0.15 mmol, 0.1 equiv.) in THF (7.5 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **10m** (465 mg, 66%) as a yellow oil in a 89/11 proportion of *E/Z* isomers. 1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dt,

$J = 7.7, 1.0$ Hz, 1H), 7.74 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.66 (td, $J = 7.6, 1.2$ Hz, 1H), 7.53 (td, $J = 7.5, 1.0$ Hz, 1H), 7.49 – 7.42 (m, 2H), 7.34 (t, $J = 7.5$ Hz, 2H), 7.29 – 7.21 (m, 1H), 6.99 (d, $J = 7.4$ Hz, 1H), 6.69 – 6.61 (m, 2H), 6.58 (s, 1H), 6.45 (s, 0.1H), 3.81 (t, $J = 5.8$ Hz, 2H), 2.31 (s, 3H), 2.21 – 2.11 (m, 3H), 1.76 – 1.39 (m, 4H), 0.94 (s, 3H), 0.93 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.2, 165.6, 157.1, 136.6, 135.7, 133.5, 133.4, 133.0, 130.33, 130.29, 129.7, 128.3, 127.9, 125.5, 124.2, 123.6, 120.7, 120.0, 112.0, 109.4, 107.5, 67.9, 41.7, 37.2, 24.68, 24.65, 24.3, 21.5, 15.9 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{30}\text{H}_{32}\text{NO}_4^+$ 470.2326, found 470.2329.



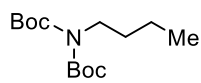
3-butyl-1-oxoisoquinolin-2(1H)-yl 5-(bis(tert-butoxycarbonyl)

amino)pentanoate (11). The title compound was prepared according to a modification of the general procedure using 5-((di-*tert*-butoxycarbonyl)amino)pentanoic acid (**3**) (855 mg, 2.7 mmol, 1.0 equiv.), 3-butyl-2-hydroxyisoquinolin-1(2H)-one (**9**) (587 mg, 2.7 mmol, 1.0 equiv.), dicyclohexylcarbodiimide (670 mg, 3.24 mmol, 1.2 equiv.) and DMAP (33 mg, 0.27 mmol, 0.1 equiv.) in THF (14 mL, 0.2 M). Purification by chromatography (Hex → Hex/AcOEt 50%) gave **11** (976 mg, 70%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.34 (d, $J = 8.4$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 6.29 (s, 1H), 3.64 (t, $J = 7.0$ Hz, 2H), 2.85 – 2.62 (m, 2H), 2.60 – 2.46 (m, 2H), 1.90 – 1.78 (m, 2H), 1.80 – 1.70 (m, 2H), 1.70 – 1.61 (m, 2H), 1.51 (s, 18H), 1.47 – 1.38 (m, 2H), 0.96 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 169.9, 157.9, 152.8, 142.2, 136.4, 132.7, 128.0, 126.3, 125.8, 125.4, 103.6, 82.4, 45.8, 31.2, 30.7, 29.8, 28.6, 28.2, 22.3, 22.0, 14.0 ppm.

MHAT DECARBOXYLATION OF THE REDOX-ACTIVE ESTERS

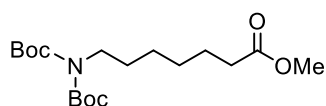
General method for the MHAT-triggered decarboxylation: To a solution of the selected redox-active ester (1.0 equiv.) in THF (0.07 M) and methanol (10 equiv.) was added $\text{Fe}(\text{acac})_3$ (0.1 equiv.) and the acceptor of choice (5.0 equiv.). The resulting mixture was degassed for 5 minutes with argon and, subsequently, PhSiH_3 (2.5 equiv.) was added dropwise. The suspension was left to stir at room temperature for 16 hours and the

resulting mixture was concentrated. The corresponding product was purified by flash column chromatography on silica gel.



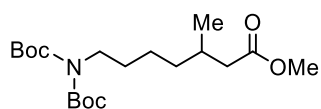
Di-tert-butyl butylcarbamate (12). The title compound was prepared

according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (215 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (141 mg, 0.40 mmol, 1.0 equiv.), and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **12** (100 mg, 91%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.59 – 3.48 (m, 2H), 1.58 – 1.50 (m, 2H), 1.49 (s, 18H), 1.36 – 1.23 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.9, 82.1, 46.4, 31.3, 28.2, 20.1, 13.9 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₄H₂₇NNaO₄⁺ 296.1832, found 296.1839.



Methyl 7-((di-tert-butoxycarbonyl)amino)heptanoate (13). The

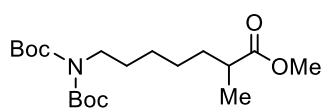
title compound was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), methyl acrylate (86 mg, 91 μ L, 1.0 mmol, 5.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **13** (67 mg, 93%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 3H), 3.57 – 3.50 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.68 – 1.50 (m, 4H), 1.49 (s, 18H), 1.39 – 1.21 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 174.3, 152.9, 82.2, 51.6, 46.5, 34.1, 29.0, 28.2, 26.6, 25.0 ppm. HRMS (ESI) *m/z*: [M+Na]⁺: calculated for C₁₈H₃₃NNaO₆⁺ 382.2200, found 382.2191.



Methyl 7-((di-tert-butoxycarbonyl)amino)-3-methylheptanoate

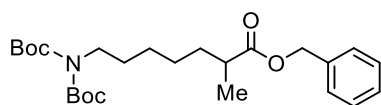
(14). The title compound was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), methyl

crotonate (100 mg, 106 μ L, 1.0 mmol, 5.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **14** (59 mg, 79%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.65 (s, 3H), 3.53 (t, J = 7.5 Hz, 2H), 2.28 (dd, J = 14.7, 6.0 Hz, 1H), 2.10 (dd, J = 14.7, 8.1 Hz, 1H), 2.01 – 1.86 (m, 1H), 1.63 – 1.50 (m, 2H), 1.49 (s, 18H), 1.38 – 1.12 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 173.8, 152.9, 82.2, 51.5, 46.5, 41.7, 36.5, 30.4, 29.3, 28.2, 24.3, 19.7 ppm. HRMS (ESI) m/z : [M+Na]⁺: calculated for C₁₉H₃₅NNaO₆⁺ 396.2357, found 396.2352.



Methyl 7-((di-tert-butoxycarbonyl)amino)-2-methylheptanoate

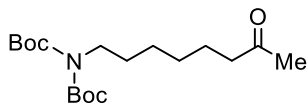
(15). The title compound was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), methyl methacrylate (100 mg, 106 μ L, 1.0 mmol, 5.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **15** (62 mg, 83%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.65 (s, 3H), 3.57 – 3.48 (m, 2H), 2.48 – 2.35 (m, 1H), 1.71 – 1.49 (m, 3H), 1.49 (s, 18H), 1.45 – 1.34 (m, 1H), 1.34 – 1.21 (m, 4H), 1.13 (d, J = 7.0 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 177.4, 152.9, 82.2, 51.6, 46.5, 39.5, 33.9, 29.0, 28.2, 27.1, 26.9, 17.2 ppm. HRMS (ESI) m/z : [M+Na]⁺: calculated for C₁₉H₃₅NNaO₆⁺ 396.2357, found 396.2347.



Benzyl 7-((di-tert-butoxycarbonyl)amino)-2-methylheptanoate

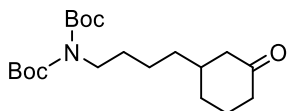
(16). The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), benzyl methacrylate (70 mg, 67 μ L, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **16** (65 mg, 72%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.27 (m,

5H), 5.11 (s, 2H), 3.58 – 3.47 (m, 2H), 2.58 – 2.38 (m, 1H), 1.73 – 1.51 (m, 3H), 1.50 (s, 18H), 1.48 – 1.36 (m, 1H), 1.36 – 1.20 (m, 4H), 1.16 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 176.7, 152.9, 136.4, 128.7, 128.3, 128.2, 82.2, 66.1, 46.5, 39.6, 33.8, 29.0, 28.2, 27.1, 26.9, 17.2 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{25}\text{H}_{39}\text{NNaO}_6^+$ 472.2670, found 472.2661.



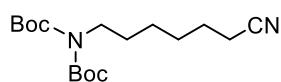
Di-tert-butyl (7-oxooctyl)carbamate (17). The title compound

was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), 3-buten-2-one (70 mg, 81 μL , 1.0 mmol, 5.0 equiv.) and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **17** (46 mg, 67%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 3.60 – 3.47 (m, 2H), 2.41 (t, $J = 7.4$ Hz, 2H), 2.12 (s, 3H), 1.66 – 1.51 (m, 4H), 1.50 (s, 18H), 1.36 – 1.22 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 209.3, 152.9, 82.2, 46.5, 43.8, 30.0, 29.0, 28.2, 26.8, 23.9 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{18}\text{H}_{33}\text{NNaO}_5^+$ 366.2251, found 366.2259.



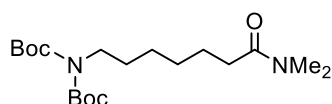
Di-tert-butyl (4-(3-oxocyclohexyl)butyl)carbamate (18). The title

compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), 2-cyclohexen-1-one (38 mg, 38 μL , 0.40 mmol, 2.0 equiv.) and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **18** (39 mg, 53%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 3.60 – 3.49 (m, 2H), 2.46 – 2.30 (m, 2H), 2.30 – 2.19 (m, 1H), 2.11 – 1.94 (m, 2H), 1.95 – 1.83 (m, 1H), 1.83 – 1.68 (m, 1H), 1.72 – 1.59 (m, 1H), 1.62 – 1.51 (m, 2H), 1.50 (s, 18H), 1.43 – 1.23 (m, 5H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 212.0, 152.9, 82.3, 48.3, 46.4, 41.6, 39.2, 36.4, 31.3, 29.2, 28.2, 25.4, 24.1 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{20}\text{H}_{35}\text{NNaO}_5^+$ 392.2407, found 392.2403.



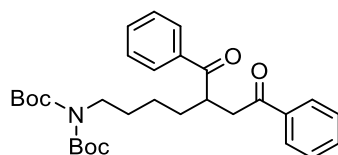
Di-tert-butyl (6-cyanoheptyl)carbamate (19). The title compound

was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), acrylonitrile (53 mg, 65 μ L, 1.0 mmol, 5.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **19** (59 mg, 90%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.60 – 3.48 (m, 2H), 2.32 (t, *J* = 7.1 Hz, 2H), 1.71 – 1.59 (m, 2H), 1.62 – 1.51 (m, 2H), 1.49 (s, 18H), 1.49 – 1.40 (m, 2H), 1.38 – 1.25 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.9, 119.8, 82.3, 46.3, 28.8, 28.5, 28.2, 26.1, 25.4, 17.2 ppm. HRMS (ESI) *m/z*: [M+Na]⁺: calculated for C₁₇H₃₀N₂NaO₄⁺ 349.2098, found 349.2103.



Di-tert-butyl (7-(dimethylamino)-7-oxoheptyl)carbamate (20).

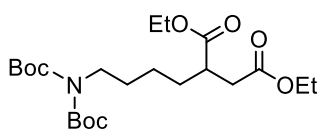
The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), *N,N*-dimethylacrylamide (40 mg, 42 μ L, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ AcOEt) gave **20** (64 mg, 86%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.59 – 3.47 (m, 2H), 2.99 (s, 3H), 2.93 (s, 3H), 2.34 – 2.24 (m, 2H), 1.68 – 1.50 (m, 4H), 1.49 (s, 18H), 1.41 – 1.22 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 173.2, 152.9, 82.2, 46.5, 37.4, 35.5, 33.4, 29.4, 29.1, 28.2, 26.8, 25.3 ppm. HRMS (ESI) *m/z*: [M+Na]⁺: calculated for C₁₉H₃₆N₂NaO₅⁺ 395.2516, found 395.2523.



Di-tert-butyl (5-benzoyl-7-oxo-7-phenylheptyl) carbamate (21).

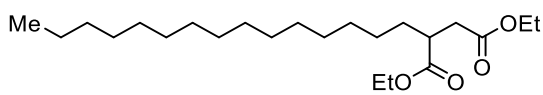
The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), *trans*-1,4-diphenyl-2-butene-1,4-dione (95 mg, 0.40 mmol, 2.0 equiv.) and

PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **21** (75 mg, 74%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.09 – 8.02 (m, 2H), 8.00 – 7.93 (m, 2H), 7.61 – 7.51 (m, 2H), 7.53 – 7.40 (m, 4H), 4.21 – 4.08 (m, 1H), 3.72 (dd, J = 18.0, 9.2 Hz, 1H), 3.58 – 3.45 (m, 2H), 3.16 (dd, J = 18.0, 4.1 Hz, 1H), 1.86 – 1.70 (m, 1H), 1.65 – 1.48 (m, 3H), 1.47 (s, 18H), 1.40 – 1.23 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 203.3, 198.7, 152.9, 136.9, 136.7, 133.3, 133.1, 128.8, 128.7, 128.6, 128.3, 82.3, 46.2, 41.3, 40.8, 32.3, 29.2, 28.2, 24.7 ppm. HRMS (ESI) m/z : [M+Na]⁺: calculated for C₂₀H₃₅NNaO₅⁺ 532.2670, found 532.2673.



Diethyl 2-(4-((di-tert-butoxycarbonyl)amino)butyl)succinate (22).

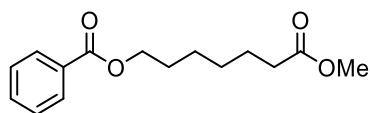
The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), diethyl maleate (69 mg, 65 μ L, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **22** (81 mg, 91%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.19 – 4.07 (m, 4H), 3.57 – 3.49 (m, 2H), 2.86 – 2.73 (m, 1H), 2.68 (dd, J = 16.4, 9.3 Hz, 1H), 2.40 (dd, J = 16.3, 5.1 Hz, 1H), 1.72 – 1.57 (m, 2H), 1.61 – 1.49 (m, 2H), 1.49 (s, 18H), 1.36 – 1.25 (m, 2H), 1.27 – 1.19 (m, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 174.9, 172.0, 152.8, 82.3, 60.7, 46.2, 41.4, 36.2, 31.8, 29.0, 28.2, 24.3, 14.34, 14.29 ppm. HRMS (ESI) m/z : [M+Na]⁺: calculated for C₂₂H₃₉NNaO₈⁺ 468.2568, found 468.2573.



Diethyl 2-pentadecylsuccinate (23).

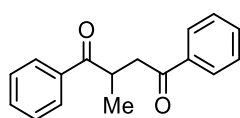
The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl palmitate (**10b**) (95 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), diethyl maleate (69 mg, 65 μ L, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$

Hex/AcOEt 25%) gave **23** (62 mg, 80%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.21 – 4.07 (m, 4H), 2.86 – 2.75 (m, 1H), 2.68 (dd, J = 16.3, 9.4 Hz, 1H), 2.40 (dd, J = 16.3, 5.1 Hz, 1H), 1.69 – 1.56 (m, 1H), 1.55 – 1.42 (m, 1H), 1.33 – 1.18 (m, 32H), 0.92 – 0.82 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 175.2, 172.2, 60.7, 60.6, 41.4, 36.3, 32.11, 32.06, 29.82, 29.79, 29.76, 29.7, 29.6, 29.53, 29.50, 27.0, 22.8, 14.4, 14.30, 14.25 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{23}\text{H}_{45}\text{O}_4^+$ 385.3312, found 385.3320.



7-methoxy-7-oxoheptyl benzoate (**24**). The title compound

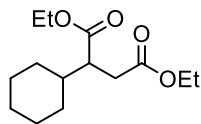
was prepared according to the general procedure using 5-((1-benzylidene-3-oxoisindolin-2-yl)oxy)-5-oxopentyl benzoate (**10c**) (88 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), methyl acrylate (86 mg, 91 μL , 1.0 mmol, 5.0 equiv.) and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **24** (45 mg, 85%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.07 – 8.01 (m, 2H), 7.59 – 7.52 (m, 1H), 7.47 – 7.40 (m, 2H), 4.31 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.72 – 1.61 (m, 2H), 1.52 – 1.42 (m, 2H), 1.44 – 1.34 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 174.3, 166.8, 133.0, 130.6, 129.7, 128.5, 65.0, 51.6, 34.1, 28.9, 28.7, 25.9, 24.9 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{15}\text{H}_{21}\text{O}_4^+$ 265.1434, found 265.1440.



2-methyl-1,4-diphenylbutane-1,4-dione (**25**). The title compound was

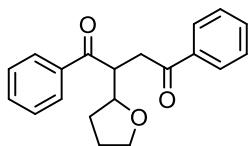
prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl acetate (**10d**) (56 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), (*E*)-1,4-diphenylbut-2-ene-1,4-dione (95 mg, 0.40 mmol, 2.0 equiv.) and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **25** (41 mg, 81%) as a colorless oil. Spectral data were identical to those previously reported.^[10] ^1H NMR (400 MHz, CDCl_3) δ 8.10 – 8.03 (m, 2H), 8.03 – 7.96 (m, 2H), 7.62 – 7.52 (m, 2H), 7.54 – 7.41 (m, 4H), 4.26 – 4.12 (m, 1H), 3.73 (dd, J = 18.0, 8.4 Hz, 1H), 3.12 (dd, J = 18.0, 4.9 Hz, 1H), 1.29 (d, J = 7.2 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz,

CDCl₃) δ 203.6, 198.6, 136.8, 136.2, 133.3, 133.1, 128.8, 128.70, 128.65, 128.2, 42.5, 36.4, 18.1 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₇H₁₇O₂⁺ 253.1223, found 253.1227.



Diethyl 2-cyclohexylsuccinate (26). The title compound was

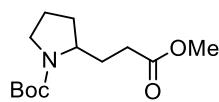
prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl cyclohexanecarboxylate (**10e**) (69 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), diethyl maleate (69 mg, 65 μ L, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **26** (44 mg, 85%) as a colorless oil. Spectral data were identical to those previously reported.^[11] ¹H NMR (400 MHz, CDCl₃) δ 4.23 – 4.02 (m, 4H), 2.76 – 2.62 (m, 2H), 2.51 – 2.35 (m, 1H), 1.79 – 1.68 (m, 2H), 1.70 – 1.53 (m, 4H), 1.29 – 1.20 (m, 7H), 1.21 – 0.94 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 174.6, 172.7, 60.7, 60.5, 47.2, 40.1, 33.6, 30.7, 30.2, 26.5, 26.3, 14.4, 14.3 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₄H₂₅O₄⁺ 257.1747, found 257.1747.



1,4-diphenyl-2-(tetrahydrofuran-2-yl)butane-1,4-dione (27). The title

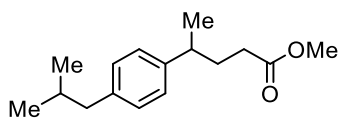
compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl tetrahydrofuran-2-carboxylate (**10f**) (67 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), (*E*)-1,4-diphenylbut-2-ene-1,4-dione (95 mg, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **27** (57 mg, 92%) as a colorless oil. A 60/40 mixture of stereoisomers was obtained; spectroscopic data correspond to the major isomer. ¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.08 (m, 2H), 7.99 – 7.91 (m, 2H), 7.61 – 7.51 (m, 2H), 7.53 – 7.44 (m, 2H), 7.48 – 7.40 (m, 2H), 4.40 (ddd, J = 10.2, 7.1, 3.2 Hz, 1H), 4.22 – 4.12 (m, 1H), 3.91 – 3.83 (m, 1H), 3.80 (dd, J = 18.0, 10.1 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.21 (dd, J = 18.0, 3.2 Hz, 1H), 2.01 – 1.79 (m, 3H), 1.78 – 1.64

(m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 202.0, 198.3, 137.9, 136.6, 133.4, 133.0, 128.8, 128.68, 128.66, 128.2, 79.9, 68.4, 46.1, 37.8, 29.0, 25.8 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{20}\text{H}_{21}\text{O}_3^+$ 309.1485, found 309.1487.



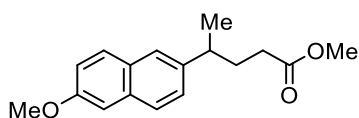
tert-butyl 2-(3-methoxy-3-oxopropyl)pyrrolidine-1-carboxylate (28).

The title compound was prepared according to the general procedure using 2-(1-benzylidene-3-oxoisindolin-2-yl) 1-(*tert*-butyl) pyrrolidine-1,2-dicarboxylate (**10g**) (87 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), methyl acrylate (86 mg, 91 μL , 1.0 mmol, 5.0 equiv.) and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **28** (46 mg, 90%) as a colorless oil. Spectral data were identical to those previously reported.^[12] ^1H NMR (400 MHz, CDCl_3) δ 3.86 – 3.75 (m, 1H), 3.66 (s, 3H), 3.46 – 3.33 (m, 1H), 3.32 – 3.21 (m, 1H), 2.32 (t, J = 7.8 Hz, 2H), 2.05 – 1.75 (m, 4H), 1.74 – 1.56 (m, 2H), 1.45 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.0, 154.9, 79.4, 56.7, 51.7, 46.4, 31.3, 30.6, 29.9, 28.7, 23.5 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_4^+$ 258.1700, found 258.1704.



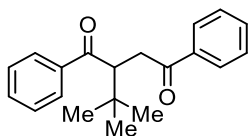
Methyl 4-(4-isobutylphenyl)pentanoate (29).

The title compound was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 2-(4-isobutylphenyl)propanoate (**10h**) (85 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), methyl acrylate (86 mg, 91 μL , 1.0 mmol, 5.0 equiv.) and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **29** (29 mg, 59%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.07 (s, 4H), 3.62 (s, 3H), 2.77 – 2.59 (m, 1H), 2.43 (d, J = 7.1 Hz, 2H), 2.30 – 2.08 (m, 2H), 2.02 – 1.73 (m, 3H), 1.26 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.6 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.4, 143.5, 139.6, 129.3, 126.8, 51.6, 45.2, 39.2, 33.4, 32.5, 30.4, 22.6, 22.3 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{16}\text{H}_{24}\text{NaO}_2^+$ 271.1669, found 271.1669.



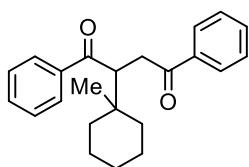
Methyl-4-(6-methoxynaphthalen-2-yl)pentanoate (30). The

title compound was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (**10i**) (90 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), methyl acrylate (86 mg, 91 μ L, 1.0 mmol, 5.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **30** (23 mg, 43%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, *J* = 8.5, 3.0 Hz, 2H), 7.53 (d, *J* = 1.7 Hz, 1H), 7.30 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.17 – 7.09 (m, 2H), 3.91 (s, 3H), 3.61 (s, 3H), 2.95 – 2.76 (m, 1H), 2.32 – 2.13 (m, 2H), 2.08 – 1.89 (m, 2H), 1.34 (d, *J* = 6.9 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 174.3, 157.4, 141.4, 133.4, 129.2, 127.2, 126.2, 125.4, 118.9, 105.7, 55.4, 51.6, 39.5, 33.3, 32.5, 22.4 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₇H₂₁O₃⁺ 273.1485, found 273.1485.



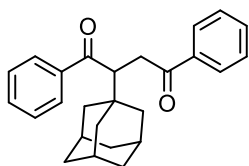
2-(tert-butyl)-1,4-diphenylbutane-1,4-dione (31). The title

compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl pivalate (**10j**) (64 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), (*E*)-1,4-diphenylbut-2-ene-1,4-dione (95 mg, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **31** (50 mg, 85%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.14 – 8.09 (m, 2H), 7.99 – 7.92 (m, 2H), 7.58 – 7.49 (m, 2H), 7.52 – 7.43 (m, 2H), 7.47 – 7.38 (m, 2H), 4.05 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.88 (dd, *J* = 17.9, 11.0 Hz, 1H), 3.23 (dd, *J* = 17.9, 2.4 Hz, 1H), 0.98 (s, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 204.4, 199.5, 140.0, 136.8, 133.3, 132.5, 128.7, 128.64, 128.56, 128.2, 49.4, 39.0, 33.6, 28.8 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₂₀H₂₃O₂⁺ 295.1693, found 295.1686.



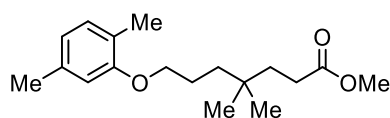
2-(1-methylcyclohexyl)-1,4-diphenylbutane-1,4-dione (**32**). The title

compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 1-methylcyclohexane-1-carboxylate (**10k**) (72 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), (*E*)-1,4-diphenylbut-2-ene-1,4-dione (95 mg, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **32** (62 mg, 92%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.16 – 8.09 (m, 2H), 8.00 – 7.92 (m, 2H), 7.58 – 7.49 (m, 2H), 7.52 – 7.43 (m, 2H), 7.47 – 7.38 (m, 2H), 4.11 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.87 (dd, *J* = 17.9, 10.9 Hz, 1H), 3.24 (dd, *J* = 18.0, 2.5 Hz, 1H), 1.59 – 1.45 (m, 3H), 1.49 – 1.35 (m, 2H), 1.38 – 1.24 (m, 3H), 1.26 – 1.08 (m, 2H), 1.04 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 204.9, 199.7, 140.5, 136.8, 133.3, 132.4, 128.6, 128.5, 128.2, 50.2, 38.0, 37.2, 36.7, 26.1, 22.0, 21.8, 20.3 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₂₃H₂₇O₂⁺ 335.2006, found 335.2001.

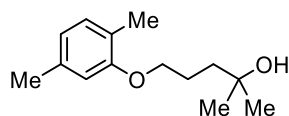


2-((3*R*,5*R*,7*R*)-adamantan-1-yl)-1,4-diphenylbutane-1,4-dione (**33**).

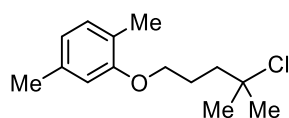
The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl (1*S*,3*S*)-adamantane-1-carboxylate (**10l**) (80 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), (*E*)-1,4-diphenylbut-2-ene-1,4-dione (95 mg, 0.40 mmol, 2.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **33** (65 mg, 87%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.18 – 8.10 (m, 2H), 8.00 – 7.92 (m, 2H), 7.58 – 7.51 (m, 2H), 7.53 – 7.44 (m, 2H), 7.47 – 7.38 (m, 2H), 3.94 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.84 (dd, *J* = 17.5, 11.0 Hz, 1H), 3.27 (dd, *J* = 17.6, 2.1 Hz, 1H), 1.99 – 1.89 (m, 3H), 1.78 – 1.56 (m, 9H), 1.56 – 1.46 (m, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 204.1, 199.7, 140.1, 136.8, 133.2, 132.5, 128.7, 128.6, 128.5, 128.2, 50.5, 40.9, 37.3, 36.9, 35.8, 28.7 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₂₆H₂₉O₂⁺ 373.2162, found 373.2178.

*Methyl 7-(2,5-dimethylphenoxy)-4,4-dimethylheptanoate*

(34). The title compound was prepared according to the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**10m**) (94 mg, 0.20 mmol, 1.0 equiv.), Fe(acac)₃ (7 mg, 0.02 mmol, 0.1 equiv.), methyl acrylate (86 mg, 91 μ L, 1.0 mmol, 5.0 equiv.) and PhSiH₃ (54 mg, 61 μ L, 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μ L, 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **34** (49 mg, 83%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.01 (d, J = 7.5 Hz, 1H), 6.69 – 6.63 (m, 1H), 6.62 (s, 1H), 3.91 (t, J = 6.4 Hz, 2H), 3.67 (s, 3H), 2.34 – 2.25 (m, 5H), 2.18 (s, 3H), 1.82 – 1.69 (m, 2H), 1.65 – 1.55 (m, 2H), 1.43 – 1.32 (m, 2H), 0.91 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 175.0, 157.2, 136.6, 130.4, 123.7, 120.8, 112.1, 68.5, 51.7, 38.0, 36.5, 32.4, 29.5, 26.9, 24.4, 21.6, 15.9 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₈H₂₉O₃⁺ 293.2111, found 293.2110.

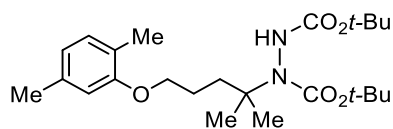
*5-(2,5-dimethylphenoxy)-2-methylpentan-2-ol (35).*¹³

The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**10m**) (188 mg, 0.40 mmol, 1.0 equiv.), methyl 4-nitrobenzenesulfonate (130 mg, 0.60 mmol, 1.5 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), NaHCO₃ (67 mg, 0.80 mmol, 2.0 equiv.) and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **35** (80 mg, 90%) as a colorless oil. Spectral data were identical to those previously reported.^[14] ¹H NMR (400 MHz, CDCl₃) δ 7.01 (d, J = 7.4 Hz, 1H), 6.67 (d, J = 7.1 Hz, 1H), 6.64 (s, 1H), 3.97 (t, J = 6.3 Hz, 2H), 2.31 (s, 3H), 2.18 (s, 3H), 1.95 – 1.84 (m, 2H), 1.72 – 1.62 (m, 2H), 1.27 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 157.1, 136.6, 130.5, 123.7, 120.9, 112.2, 70.9, 68.4, 40.5, 29.5, 24.7, 21.5, 16.0 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₄H₂₃O₂⁺ 223.1693, found 223.1695.



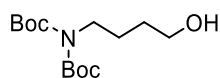
2-((4-chloro-4-methylpentyl)oxy)-1,4-dimethylbenzene

(**36**).¹⁵ The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**10m**) (188 mg, 0.40 mmol, 1.0 equiv.), tosyl chloride (92 mg, 0.48 mmol, 1.2 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **36** (61 mg, 63%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.02 (d, J = 7.4 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.64 (s, 1H), 3.99 (t, J = 5.9 Hz, 2H), 2.32 (s, 3H), 2.19 (s, 3H), 2.08 – 1.96 (m, 2H), 2.00 – 1.91 (m, 2H), 1.63 (s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 157.1, 136.6, 130.5, 123.7, 120.9, 112.1, 70.9, 67.8, 42.8, 32.6, 25.6, 21.6, 15.9 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₄H₂₂ClO⁺ 241.1354, found 241.1356.



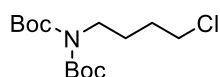
Di-tert-butyl 1-(5-(2,5-dimethylphenoxy)-2-methylpentan

-2-yl)hydrazine-1,2-dicarboxylate (**37**).¹⁶ The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**10m**) (188 mg, 0.40 mmol, 1.0 equiv.), di-tert-butyl diazene-1,2-dicarboxylate (138 mg, 0.60 mmol, 1.5 equiv.), Fe(acac)₃ (28 mg, 0.08 mmol, 0.2 equiv.), and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **37** (82 mg, 47%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 6.62 (s, 1H), 6.18 (s, 0.6H), 5.89 (s, 0.3H), 3.93 (t, J = 6.3 Hz, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 2.13 – 1.99 (m, 1H), 1.91 – 1.69 (m, 3H), 1.54 – 1.41 (m, 21H), 1.31 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 157.1, 156.6, 156.2, 154.9, 154.4, 136.6, 130.4, 123.7, 120.8, 112.1, 81.5, 81.0, 80.8, 68.3, 62.0, 36.9, 28.44, 28.38, 27.1, 26.5, 24.9, 21.5, 16.0 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₂₄H₄₁N₂O₅⁺ 437.3010, found 437.3012.



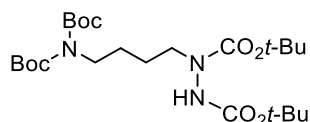
*tert-butyl (tert-butoxycarbonyl)(4-hydroxybutyl)carbamate (38).*¹³ The

title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (150 mg, 0.28 mmol, 1.0 equiv.), Fe(acac)₃ (11 mg, 0.03 mmol, 0.1 equiv.), NaHCO₃ (47 mg, 0.56 mmol, 2.0 equiv.), methyl 4-nitrobenzenesulfonate (91 mg, 0.42 mmol, 1.5 equiv.), and PhSiH₃ (76 mg, 86 μ L, 0.70 mmol, 2.5 equiv.) in THF (4 mL, 0.07 M) and methanol (90 mg, 114 μ L, 2.8 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **38** (50 mg, 62%) as a colorless oil. Spectral data were identical to those previously reported.^[17] ¹H NMR (400 MHz, CDCl₃) δ 3.64 (t, *J* = 6.3 Hz, 2H), 3.60 – 3.55 (m, 2H), 1.68 – 1.59 (m, 2H), 1.59 – 1.52 (m, 2H), 1.48 (s, 18H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.9, 82.4, 62.6, 46.1, 29.8, 28.2, 25.4 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₄H₂₈NO₅⁺ 290.1962, found 290.1962.



*tert-butyl (tert-butoxycarbonyl)(4-chlorobutyl)carbamate (39).*¹⁵

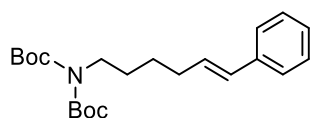
The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (214 mg, 0.40 mmol, 1.0 equiv.), tosyl chloride (92 mg, 0.48 mmol, 1.2 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **39** (49 mg, 40%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.60 (t, *J* = 7.0 Hz, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 1.85 – 1.67 (m, 4H), 1.50 (s, 18H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.8, 82.5, 45.7, 44.8, 30.0, 28.2, 26.5 ppm. HRMS (ESI) *m/z*: [M+H]⁺: calculated for C₁₄H₂₇ClNO₄⁺ 308.1623, found 308.1625.



Di-tert-butyl 1-(4-(bis(tert-butoxycarbonyl)amino)butyl)

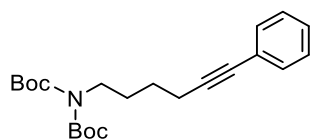
*hydrazine-1,2-dicarboxylate (40).*¹⁶ The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (214 mg, 0.40 mmol, 1.0 equiv.), di-*tert*-butyl diazene-1,2-dicarboxylate (138 mg, 0.60 mmol, 1.5 equiv.), Fe(acac)₃ (28 mg,

0.08 mmol, 0.2 equiv.), and PhSiH_3 (108 mg, 123 μL , 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μL , 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **40** (75 mg, 37%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 6.40 (s, 0.7H), 6.12 (s, 0.3H), 3.60 – 3.50 (m, 2H), 3.48 – 3.36 (m, 2H), 1.57 – 1.52 (m, 4H), 1.50 – 1.47 (m, 20H), 1.45 (s, 9H), 1.44 (s, 7H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 155.5, 155.2, 152.9, 152.8, 82.3, 81.1, 50.6, 49.2, 46.2, 46.1, 28.3, 28.2, 26.3, 25.5, 25.1, 24.8 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{24}\text{H}_{46}\text{N}_3\text{O}_8^+$ 504.3279, found 504.3277.



*Di-tert-butyl (E)-(6-phenylhex-5-en-1-yl)carbamate (41).*¹⁸ The

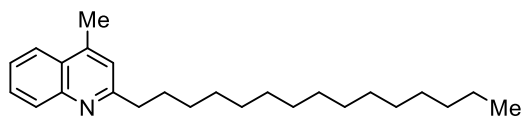
title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), (*E*)-(2-nitrovinyl)benzene (60 mg, 0.40 mmol, 2.0 equiv.), and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **41** (39 mg, 52%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.29 (m, 2H), 7.32 – 7.24 (m, 2H), 7.23 – 7.14 (m, 1H), 6.38 (d, J = 15.9 Hz, 1H), 6.20 (dt, J = 15.8, 6.8 Hz, 1H), 3.63 – 3.54 (m, 2H), 2.23 (qd, J = 7.1, 1.4 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.50 (s, 18H), 1.50 – 1.41 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 152.9, 137.9, 130.7, 130.3, 128.6, 127.0, 126.1, 82.2, 46.4, 32.8, 28.8, 28.2, 26.7 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{22}\text{H}_{33}\text{NNaO}_4^+$ 398.2302, found 398.2310.



*Di-tert-butyl (6-phenylhex-5-yn-1-yl)carbamate (42).*¹⁹ The title

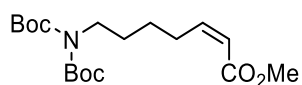
compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(*tert*-butoxycarbonyl)amino)pentanoate (**10a**) (107 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (7 mg, 0.02 mmol, 0.1 equiv.), (bromoethynyl)benzene (72 mg, 0.40 mmol, 2.0 equiv.), NaHCO_3 (17 mg, 0.20 mmol, 1.0 equiv.) and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$

Hex/AcOEt 25%) gave **42** (43 mg, 58%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.33 (m, 2H), 7.30 – 7.22 (m, 3H), 3.68 – 3.56 (m, 2H), 2.44 (t, J = 7.0 Hz, 2H), 1.83 – 1.69 (m, 2H), 1.68 – 1.55 (m, 2H), 1.50 (s, 18H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 152.8, 131.7, 128.3, 127.7, 124.1, 90.0, 82.3, 81.1, 46.1, 28.5, 28.2, 26.2, 19.4 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{22}\text{H}_{31}\text{NNaO}_4^+$ 396.2145, found 396.2154.



4-methyl-2-pentadecylquinoline (**43**).²⁰

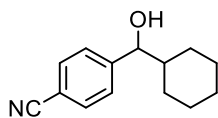
The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl palmitate (**10b**) (142 mg, 0.30 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (106 mg, 0.30 mmol, 1.0 equiv.), lepidine (43 mg, 40 μL , 0.30 mmol, 1.0 equiv.), TFA (68 mg, 46 μL , 0.60 mmol, 2.0 equiv.), and PhSiH_3 (81 mg, 92 μL , 0.75 mmol, 2.5 equiv.) in THF (4.5 mL, 0.07 M) and methanol (96 mg, 122 μL , 3.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **43** (72 mg, 68%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, J = 8.4 Hz, 1H), 7.95 (dd, J = 8.3, 1.4 Hz, 1H), 7.68 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.51 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.15 (d, J = 1.1 Hz, 1H), 3.00 – 2.84 (m, 2H), 2.69 (d, J = 1.0 Hz, 3H), 1.86 – 1.73 (m, 2H), 1.48 – 1.18 (m, 24H), 0.92 – 0.82 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 162.8, 147.4, 144.8, 129.4, 129.2, 126.9, 125.7, 123.7, 122.2, 39.2, 32.1, 30.3, 29.84, 29.81, 29.79, 29.76, 29.70, 29.68, 29.5, 22.8, 18.9, 14.3 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{25}\text{H}_{40}\text{N}^+$ 354.3155, found 354.3151.



Methyl (Z)-7-(bis(tert-butoxycarbonyl)amino)hept-

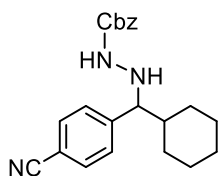
2-enoate (*cis*-**44**).²¹ The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(bis(tert-butoxycarbonyl)amino)pentanoate (**10a**) (215 mg, 0.40 mmol, 2.0 equiv.), $\text{Fe}(\text{acac})_3$ (72 mg, 0.20 mmol, 1.0 equiv.), methyl propiolate (17 mg, 18 μL , 0.20 mmol, 1.0 equiv.), and PhSiH_3 (32 mg, 37 μL , 0.30 mmol, 1.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **44** (42 mg, 59%, 70:30 mixture of *cis* and *trans* isomers) as a colorless oil. Spectroscopic data correspond to the major *cis* isomer. ^1H NMR (400 MHz, CDCl_3) δ 6.20 (dt, J = 11.5, 7.5 Hz,

1H), 5.78 (dt, $J = 11.5, 1.7$ Hz, 1H), 3.70 (s, 3H), 3.61 – 3.53 (m, 2H), 2.67 (qd, $J = 7.5, 1.8$ Hz, 2H), 1.68 – 1.55 (m, 4H), 1.50 (s, 18H), 1.50 – 1.39 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.9, 152.8, 150.4, 119.7, 82.2, 51.2, 46.3, 28.81, 28.75, 28.2, 26.4 ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$: calculated for $\text{C}_{18}\text{H}_{31}\text{NNaO}_6^+$ 380.2044, found 380.2057.



4-(cyclohexyl(hydroxy)methyl)benzonitrile (**45**).²² The title

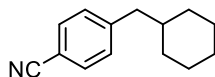
compound was prepared according to a modification of the general procedure by treating 1-benzylidene-3-oxoisindolin-2-yl cyclohexanecarboxylate (**10e**) (69 mg, 0.20 mmol, 1.0 equiv.) with $\text{Fe}(\text{acac})_3$ (35 mg, 0.10 mmol, 0.5 equiv.), $\text{Fe}(\text{acac})_2$ (25 mg, 0.10 mmol, 0.50 equiv.), 4-formylbenzonitrile (26 mg, 0.20 mmol, 1.0 equiv.), and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.) for 48 hours. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **45** (15 mg, 35 %) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 7.9$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 4.48 (d, $J = 6.4$ Hz, 1H), 1.92 – 1.51 (m, 5H), 1.47 – 1.36 (m, 1H), 1.31 – 0.86 (m, 5H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 149.0, 132.1, 127.4, 119.1, 111.2, 78.6, 45.2, 29.4, 28.2, 26.4, 26.2, 26.1 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{14}\text{H}_{18}\text{NO}^+$ 216.1383, found 216.1377.



Benzyl-2-((4-cyanophenyl)(cyclohexyl)methyl)hydrazine-1-

carboxylate (**46**).²³ The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl cyclohexanecarboxylate (**10e**) (69 mg, 0.20 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (18 mg, 0.05 mmol, 0.25 equiv.), benzyl-2-(4-cyanobenzylidene)hydrazine-1-carboxylate (112 mg, 0.40 mmol, 2.0 equiv.), and PhSiH_3 (54 mg, 61 μL , 0.50 mmol, 2.5 equiv.) in THF (3 mL, 0.07 M) and methanol (64 mg, 81 μL , 2.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **46** (67 mg, 92 %) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, $J = 7.8$ Hz, 2H), 7.38 (d, $J = 7.8$ Hz, 2H), 7.36 – 7.23 (m, 5H), 6.07 (s, 1H), 5.17 – 4.96 (m, 2H), 3.96 (d, $J = 6.7$ Hz, 1H), 1.88 (d, $J = 12.6$ Hz, 1H), 1.75 (d, $J = 13.1$ Hz, 1H), 1.69 – 1.51 (m, 3H), 1.40 (d, $J = 13.1$ Hz, 1H), 1.31 – 0.95 (m, 4H), 0.90 – 0.71 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz,

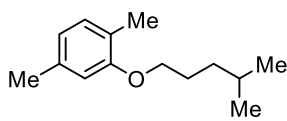
CDCl_3) δ 157.2, 146.6, 135.9, 132.0, 129.4, 128.7, 128.5, 128.2, 119.0, 111.2, 69.8, 67.3, 42.1, 30.0, 29.2, 26.3, 26.13, 26.07 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{22}\text{H}_{26}\text{N}_3\text{O}_2^+$ 364.2020, found 364.2023.



4-(cyclohexylmethyl)benzonitrile (**47**).²⁴ The title

compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl cyclohexanecarboxylate (**10e**) (104 mg, 0.30 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (42 mg, 0.12 mmol, 0.4 equiv.), N' -(4-cyanobenzylidene)-4-methylbenzenesulfonohydrazide (90 mg, 0.30 mmol, 1.0 equiv.), and PhSiH_3 (81 mg, 92 μL , 0.75 mmol, 2.5 equiv.) in THF (4.5 mL, 0.07 M) and methanol (96 mg, 122 μL , 3.0 mmol, 10 equiv.). After the MHAT coupling, triethylamine (121 mg, 166 μL , 1.2 mmol, 4.0 equiv.) was added and the mixture was heated at reflux for 1 hour. Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **47** (48 mg, 81%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 2.53 (d, J = 7.1 Hz, 2H), 1.76 – 1.59 (m, 5H), 1.59 – 1.45 (m, 1H), 1.30 – 1.06 (m, 3H), 1.03 – 0.85 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 147.3, 132.0, 130.0, 119.4, 109.6, 44.3, 39.7, 33.1, 26.5, 26.3 ppm. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$: calculated for $\text{C}_{14}\text{H}_{18}\text{N}^+$ 200.1434, found 200.1432.

For the MHAT-mediated Barton-type decarboxylation of **49**, **50**, **51**, **52**, **55** and **56**, the corresponding redox-active esters were prepared according to the general procedure shown in page 425.

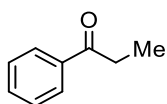


1,4-dimethyl-2-((4-methylpentyl)oxy)benzene (**48**).

Method A: The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**10m**) (188 mg, 0.40 mmol, 1.0 equiv.), $\text{Fe}(\text{acac})_3$ (141 mg, 0.40 mmol, 1.0 equiv.), and PhSiH_3 (108 mg, 123 μL , 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μL , 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **48** (71 mg, 86%) as a colorless oil.

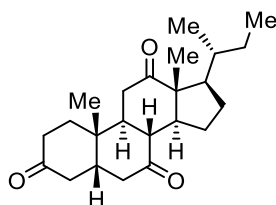
Method B:²⁵ The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**10m**) (188 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), thiophenol (4 mg, 4 μ L, 0.04 mmol, 0.1 equiv.) and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **48** (69 mg, 84%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, J = 7.5 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.66 (s, 1H), 3.95 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H), 2.21 (s, 3H), 1.89 – 1.77 (m, 2H), 1.72 – 1.59 (m, 1H), 1.44 – 1.34 (m, 2H), 0.96 (d, J = 6.6 Hz, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 157.3, 136.6, 130.4, 123.8, 120.7, 112.1, 68.3, 35.5, 27.9, 27.4, 22.7, 21.6, 15.9 ppm. HRMS (ESI) m/z : [M+H]⁺: calculated for C₁₄H₂₃O⁺ 207.1743, found 207.1749.



Propiophenone (**49**). **Method A:** The title compound was prepared

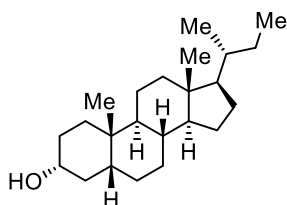
according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 4-oxo-4-phenylbutanoate (159 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (141 mg, 0.40 mmol, 1.0 equiv.), and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 5%) gave **49** (36 mg, 68%) as a colorless oil. Spectral data were identical to those previously reported.^[26] ¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.92 (m, 2H), 7.58 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 3.00 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 201.0, 137.0, 133.0, 128.7, 128.1, 31.9, 8.3 ppm.



(*5S,8R,9S,10S,13R,14S,17R*)-17-((*R*)-*sec*-butyl)-10,13-dimethyl

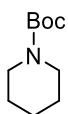
dodecahydro-3H-cyclopenta[a]phenanthrene-3,7,12(2H,4H)-trione (**50**). **Method A:** The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl (*R*)-4-((*5S,8R,9S,10S,13R,14S,17R*)-10,13-dimethyl-

3,7,12-trioxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (248 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (141 mg, 0.40 mmol, 1.0 equiv.), and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **50** (113 mg, 79%) as a white solid. Spectral data were identical to those previously reported.^[27] ¹H NMR (400 MHz, CDCl₃) δ 2.97 – 2.77 (m, 3H), 2.39 – 1.91 (m, 12H), 1.89 – 1.78 (m, 1H), 1.65 – 1.55 (m, 1H), 1.53 – 1.43 (m, 1H), 1.39 (s, 3H), 1.34 – 1.09 (m, 4H), 1.06 (s, 3H), 0.90 – 0.78 (m, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 212.3, 209.3, 209.0, 57.0, 51.9, 49.2, 47.0, 45.7, 45.6, 45.1, 42.9, 38.8, 37.5, 36.6, 36.1, 35.4, 28.0, 27.8, 25.3, 22.0, 18.5, 12.0, 11.0 ppm.



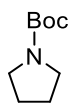
(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((*R*)-sec-butyl)-10,13-

dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (**51**). **Method A:** The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl (4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (238 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (141 mg, 0.40 mmol, 1.0 equiv.), and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 50%) gave **51** (120 mg, 90%) as a colorless oil. Spectral data were identical to those previously reported.^[28] ¹H NMR (400 MHz, CDCl₃) δ 3.62 (tt, *J* = 11.1, 4.7 Hz, 1H), 1.96 (dt, *J* = 12.3, 3.1 Hz, 1H), 1.90 – 1.70 (m, 4H), 1.70 – 1.61 (m, 1H), 1.61 – 1.45 (m, 4H), 1.45 – 1.17 (m, 11H), 1.18 – 0.95 (m, 7H), 0.91 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H), 0.64 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 72.0, 56.7, 55.9, 42.8, 42.3, 40.6, 40.3, 37.2, 36.6, 36.0, 35.5, 34.7, 30.7, 28.4, 28.3, 27.4, 26.6, 24.4, 23.5, 21.0, 18.2, 12.2, 10.5 ppm.

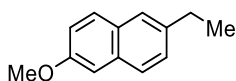


tert-butyl piperidine-1-carboxylate (**52**). **Method B:** The title compound was prepared according to a modification of the general procedure using 4-(1-benzylidene-

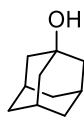
3-oxoisindolin-2-yl) 1-(*tert*-butyl) piperidine-1,4-dicarboxylate (179 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), thiophenol (4 mg, 4 μ L, 0.04 mmol, 0.1 equiv.) and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **52** (62 mg, 84%) as a yellow oil. Spectral data were identical to those previously reported.^[29] ¹H NMR (400 MHz, CDCl₃) δ 3.38 – 3.27 (m, 4H), 1.60 – 1.51 (m, 2H), 1.51 – 1.45 (m, 4H), 1.43 (s, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 155.1, 79.2, 44.8, 28.6, 25.8, 24.6 ppm.



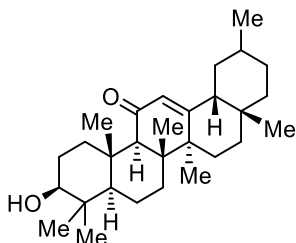
tert-butyl pyrrolidine-1-carboxylate (**53**). **Method B:** The title compound was prepared according to a modification of the general procedure using 2-(1-benzylidene-3-oxoisindolin-2-yl) 1-(*tert*-butyl) pyrrolidine-1,2-dicarboxylate (174 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), thiophenol (4 mg, 4 μ L, 0.04 mmol, 0.1 equiv.) and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **53** (55 mg, 81%) as a colorless oil. Spectral data were identical to those previously reported.^[30] ¹H NMR (400 MHz, CDCl₃) δ 3.35 – 3.22 (m, 4H), 1.87 – 1.75 (m, 4H), 1.44 (s, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 154.8, 79.0, 45.9, 28.7, 25.5 ppm.



2-ethyl-6-methoxynaphthalene (**54**). **Method B:** The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 3-(6-methoxynaphthalen-2-yl)propanoate (180 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), thiophenol (4 mg, 4 μ L, 0.04 mmol, 0.1 equiv.) and PhSiH₃ (108 mg, 123 μ L, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μ L, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex $\rightarrow$ Hex/AcOEt 25%) gave **54** (26 mg, 35%) as a colorless solid. Spectral data were identical to those previously reported.^[31] ¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.63 (m, 2H), 7.59 – 7.54 (m, 1H), 7.33 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.17 – 7.09 (m, 2H), 3.92 (s, 3H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 157.2, 139.6, 133.0, 129.3, 129.0, 127.7, 126.8, 125.6, 118.7, 105.8, 55.4, 29.0, 15.8 ppm.



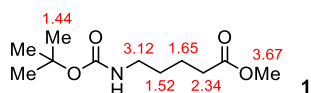
Adamantan-1-ol (55). **Method B:** The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl (1*R*,3*S*,5*R*,7*S*)-3-hydroxyadamantane-1-carboxylate (166 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), thiophenol (4 mg, 4 μL, 0.04 mmol, 0.1 equiv.) and PhSiH₃ (108 mg, 123 μL, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μL, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex → Hex/AcOEt 25%) gave **55** (44 mg, 73%) as a colorless solid. Spectral data were identical to those previously reported.^[32] ¹H NMR (400 MHz, CDCl₃) δ 2.19 – 2.09 (m, 3H), 1.71 (d, *J* = 3.0 Hz, 6H), 1.68 – 1.49 (m, 7H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 68.4, 45.4, 36.2, 30.8 ppm.



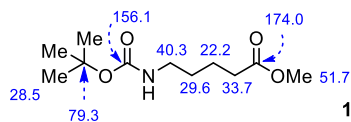
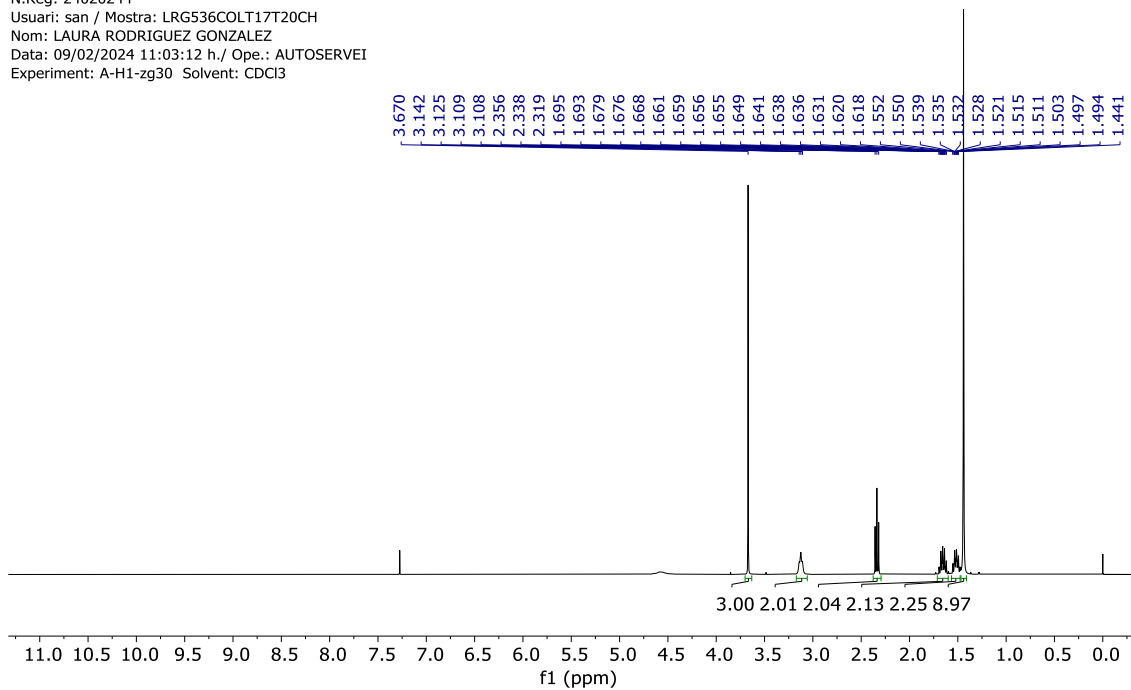
(4a*R*,6a*S*,6b*R*,8a*R*,10*S*,12a*S*,12b*R*,14b*R*)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydropicen-13(2*H*)-one (56). **Method B:** The title compound was prepared according to a modification of the general procedure using 1-benzylidene-3-oxoisindolin-2-yl 2-((4a*R*,6a*S*,6b*R*,10*S*,12a*S*,12b*R*,14b*S*)-10-hydroxy-4a,6a,6b,9,9,12a-hexamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicen-2-yl)acetate (276 mg, 0.40 mmol, 1.0 equiv.), Fe(acac)₃ (14 mg, 0.04 mmol, 0.1 equiv.), thiophenol (4 mg, 4 μL, 0.04 mmol, 0.1 equiv.) and PhSiH₃ (108 mg, 123 μL, 1.0 mmol, 2.5 equiv.) in THF (6 mL, 0.07 M) and methanol (128 mg, 162 μL, 4.0 mmol, 10 equiv.). Purification by chromatography (Hex → Hex/AcOEt 25%) gave **56** (130 mg, 76%) as a white solid. Spectral data were identical to those previously reported.^[27] ¹H NMR (400 MHz, CDCl₃) δ 5.60 (s, 0.8H), 5.59 (s, 0.2H), 3.23 (dd, *J* = 10.9, 5.4 Hz, 1H), 2.79 (dt, *J* = 13.5, 3.5 Hz, 1H), 2.34 (s, 1H), 2.11 – 1.95 (m, 2H), 1.83 (ddd, *J* = 13.7, 11.1, 4.6 Hz, 1H), 1.72 – 1.56 (m, 5H), 1.55 – 1.34 (m, 10H), 1.29 (td, *J* = 13.7, 4.1 Hz, 2H), 1.14 (s, 8H), 1.04 – 0.93 (m, 6H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.83 (s, 3H), 0.81 (s, 3H), 0.70 (dd, *J* = 11.7, 2.0 Hz, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 200.6, 171.1, 170.6, 128.1, 78.9,

61.9, 55.1, 51.8, 45.6, 45.54, 45.50, 43.53, 43.46, 41.5, 41.0, 39.3, 37.9, 37.2, 34.4, 33.5, 33.0, 32.9, 32.5, 30.8, 29.1, 28.9, 28.2, 27.8, 27.4, 26.9, 26.77, 26.76, 26.63, 26.56, 23.5, 22.5, 18.83, 18.81, 17.6, 17.0, 16.5, 15.7 ppm.

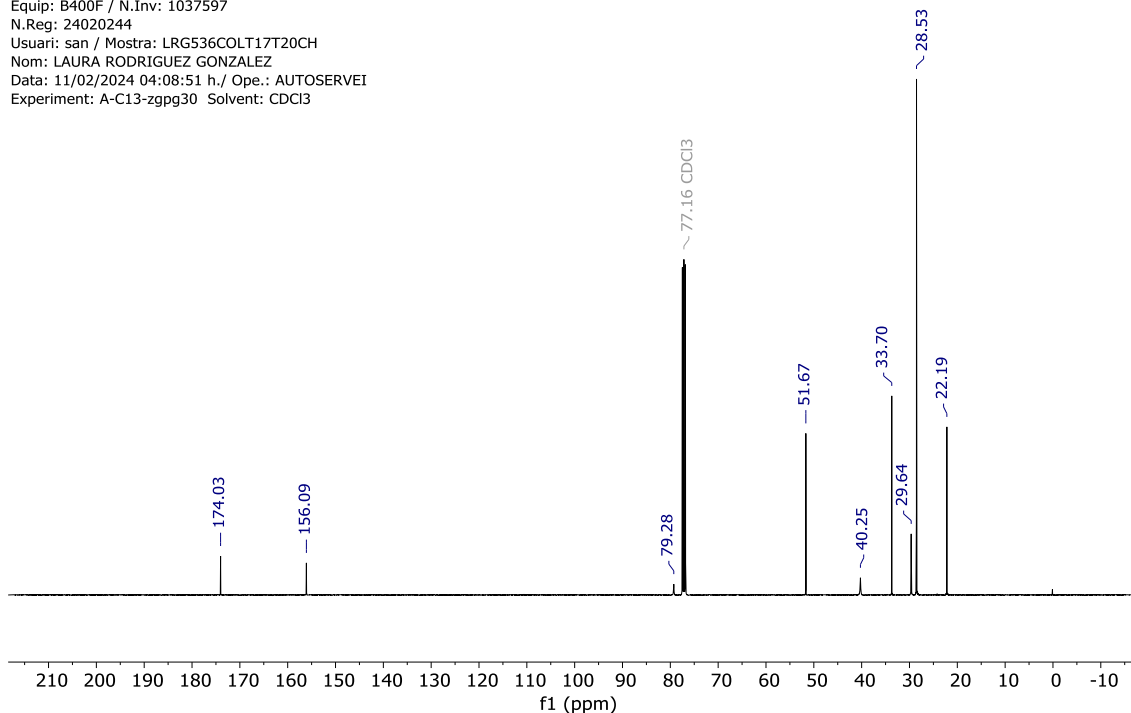
COPIES OF NMR SPECTRA

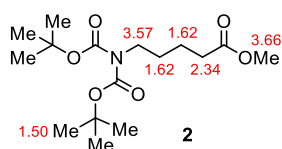


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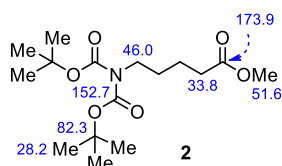
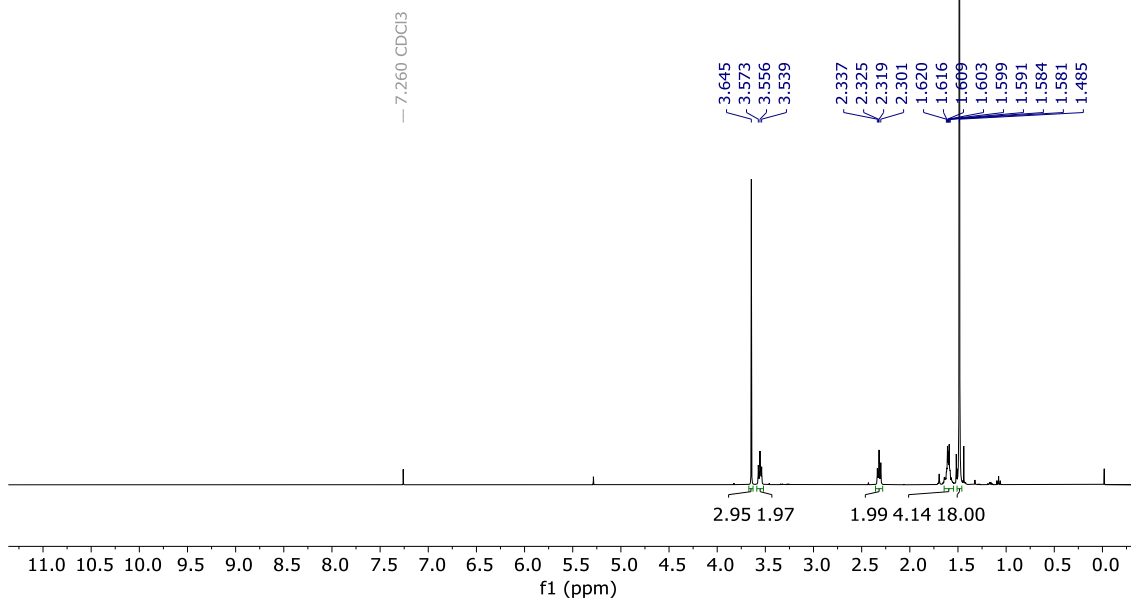


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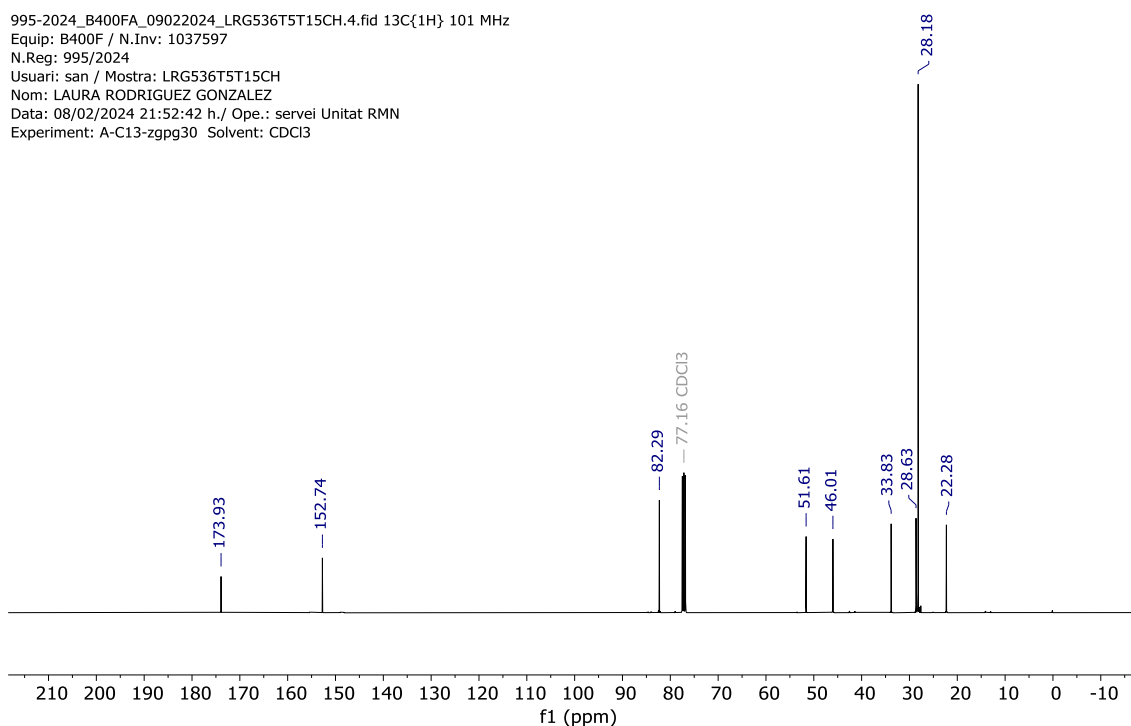




995-2024_B400FA_09022024_LRG536T5T15CH.1.fid ^1H 400 MHz
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Experiment: A-H1-zg30 Solvent: CDCl_3

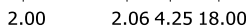


995-2024_B400FA_09022024_LRG536T5T15CH.4.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
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Usuari: san / Mostra: LRG536T5T15CH
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Experiment: A-C13-zgpg30 Solvent: CDCl_3



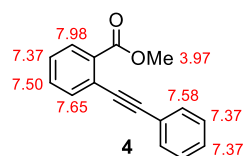


— 7.260 CDCI3

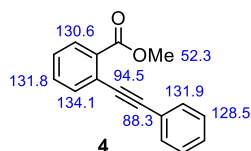
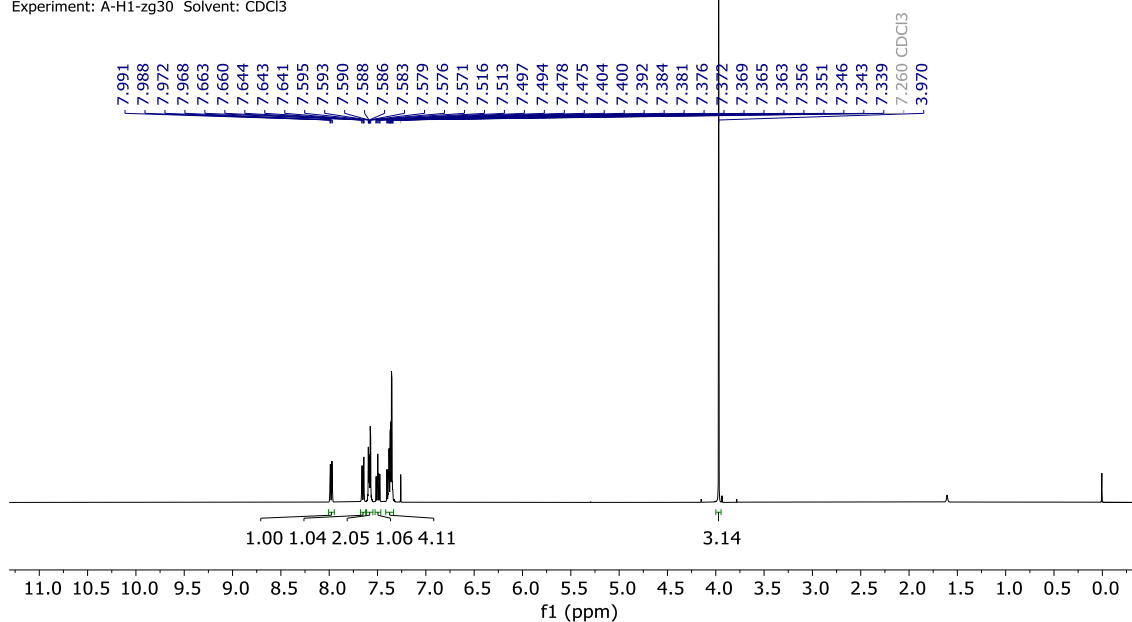


✓ 28 19

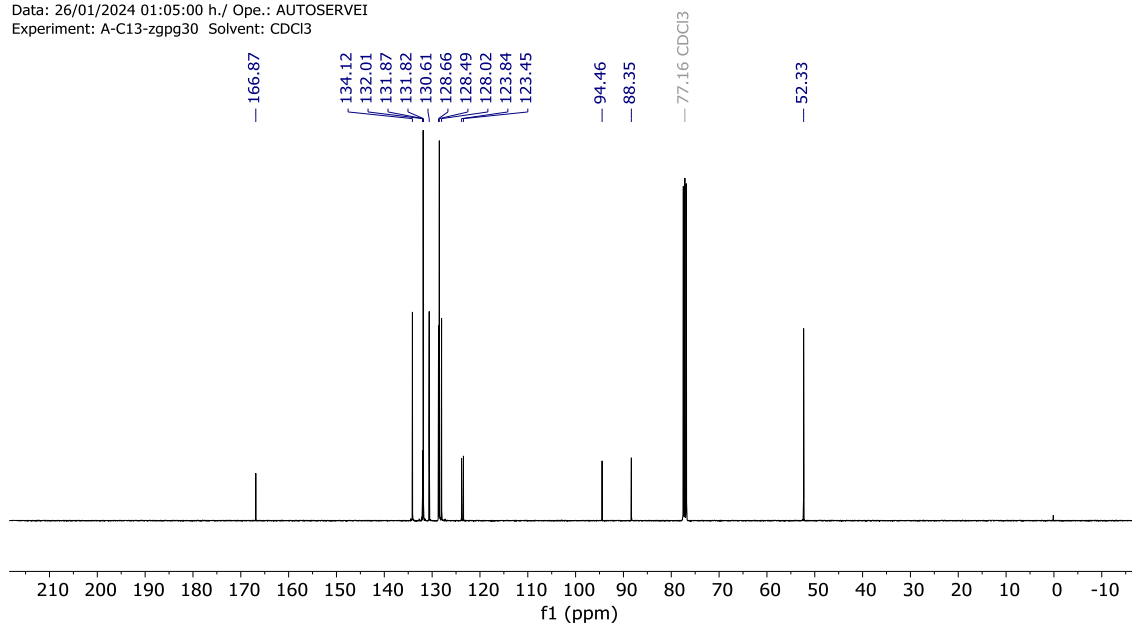




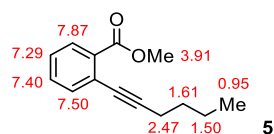
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Usuari: san / Mostra: LRG526COLT17T22
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 25/01/2024 15:14:54 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3



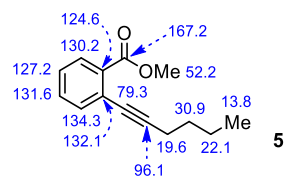
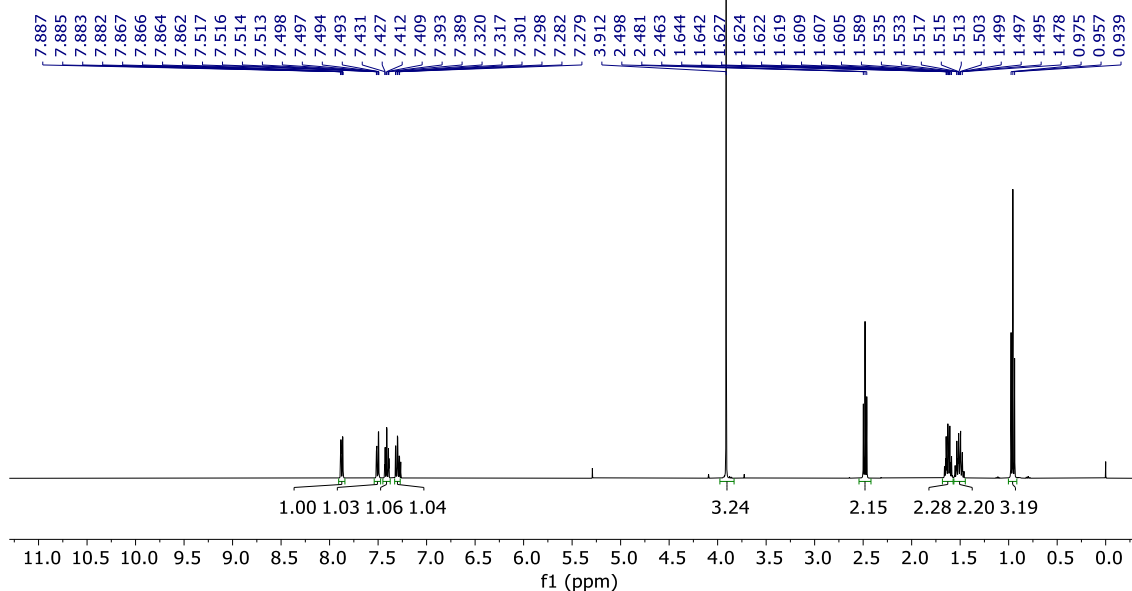
24010559_B400FA_26012024_LRG526COLT17T22.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24010559
Usuari: san / Mostra: LRG526COLT17T22
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 26/01/2024 01:05:00 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3



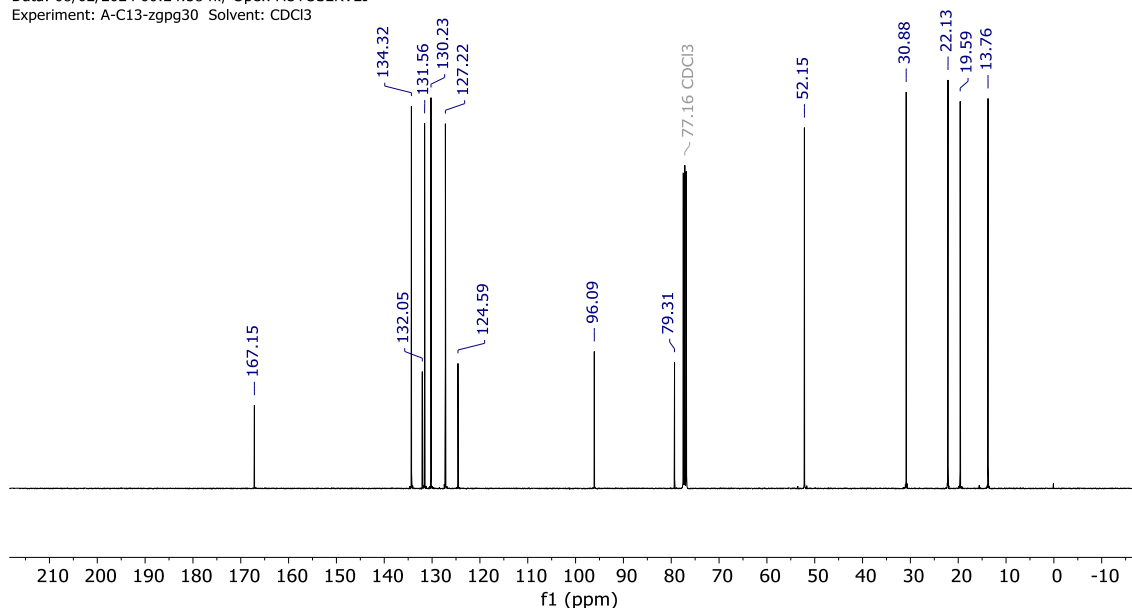
Experimental Section: Chapter 4

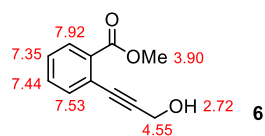


24020175_B400FA_07022024_ASV002COLT11T13.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24020175
 Usuari: san / Mostra: ASV002COLT11T13
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/02/2024 16:53:29 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

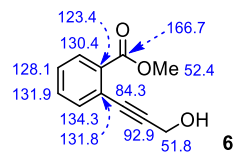
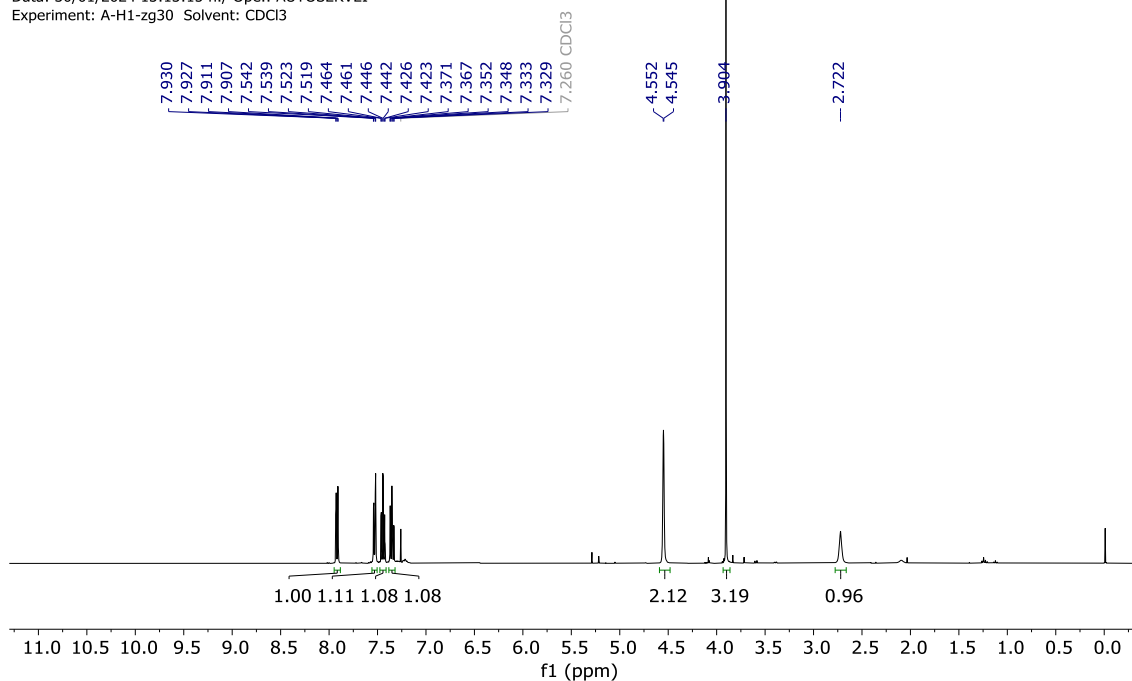


ASV002CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24020155
 Usuari: san / Mostra: LRG536COLT5T15
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/02/2024 00:24:58 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

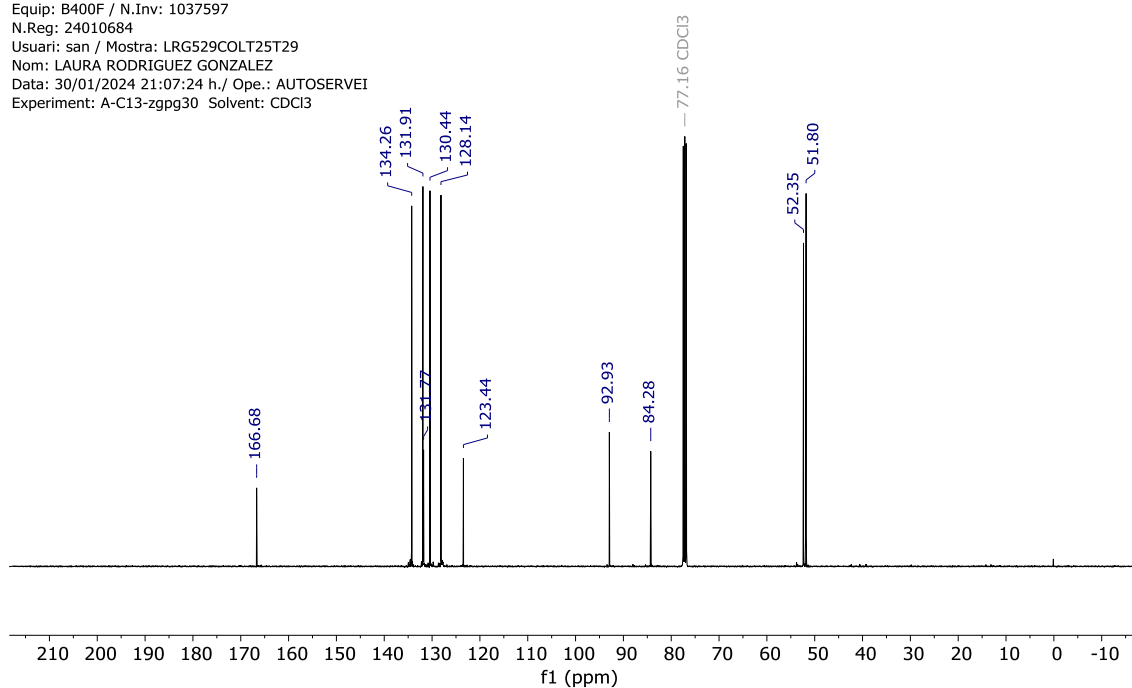




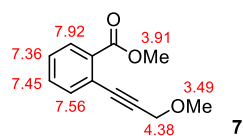
24010684_B400FA_30012024_LRG529COLT25T29.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24010684
Usuari: san / Mostra: LRG529COLT25T29
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 30/01/2024 13:13:15 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3



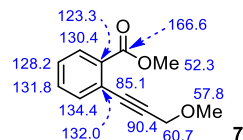
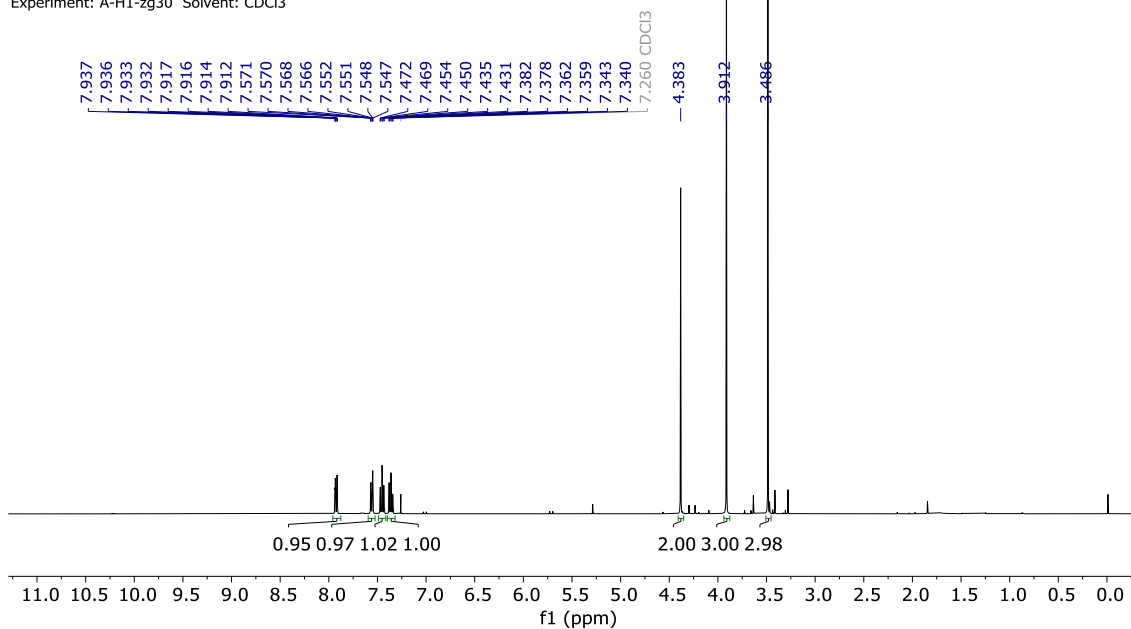
24010684_B400FA_30012024_LRG529COLT25T29.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24010684
Usuari: san / Mostra: LRG529COLT25T29
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 30/01/2024 21:07:24 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3



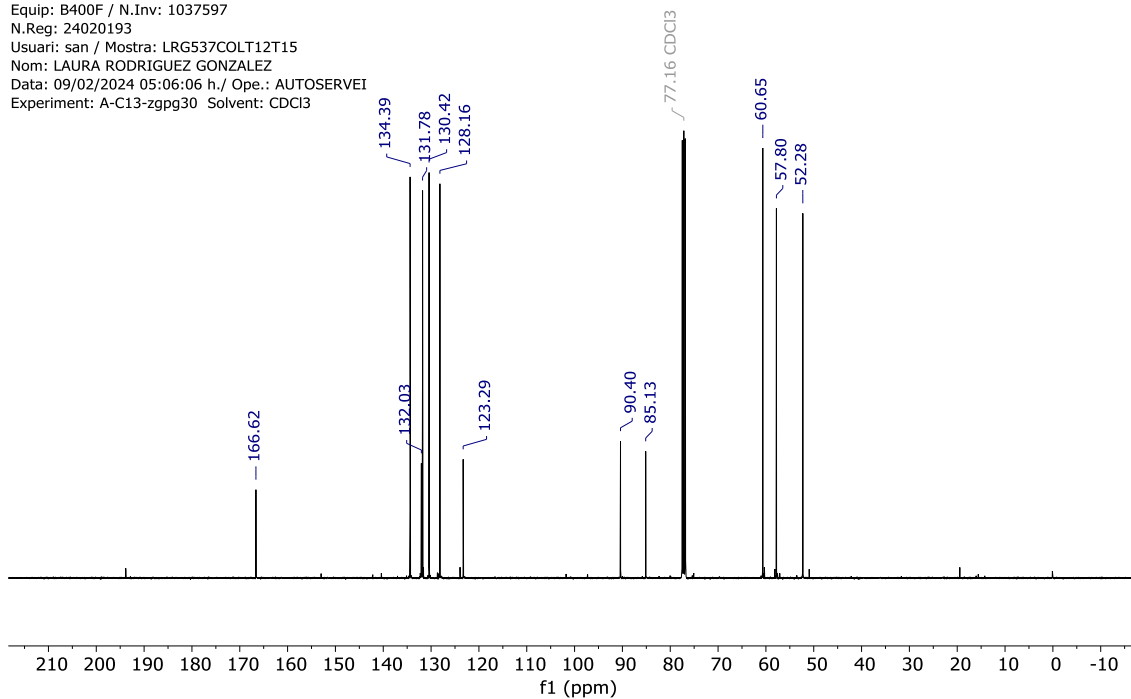
Experimental Section: Chapter 4

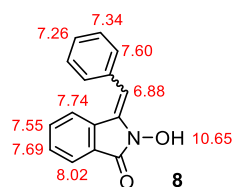


24020193_B400FA_08022024_LRG537COLT12T15.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24020193
 Usuari: san / Mostra: LRG537COLT12T15
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/02/2024 15:20:26 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

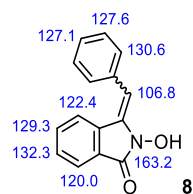
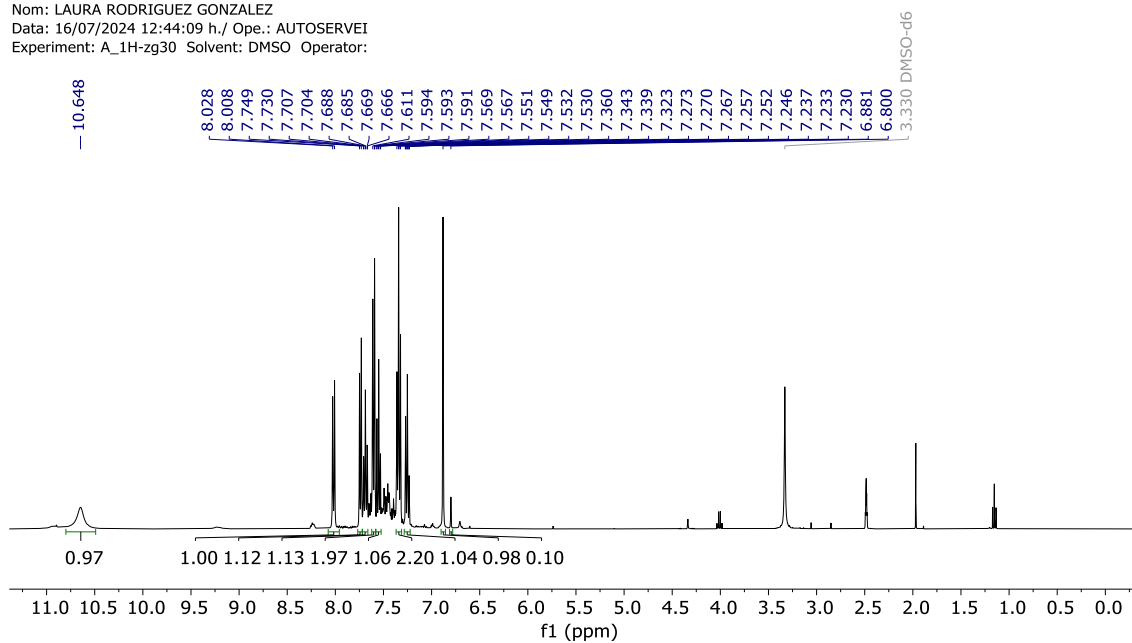


24020193_B400FA_09022024_LRG537COLT12T15.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24020193
 Usuari: san / Mostra: LRG537COLT12T15
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 09/02/2024 05:06:06 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

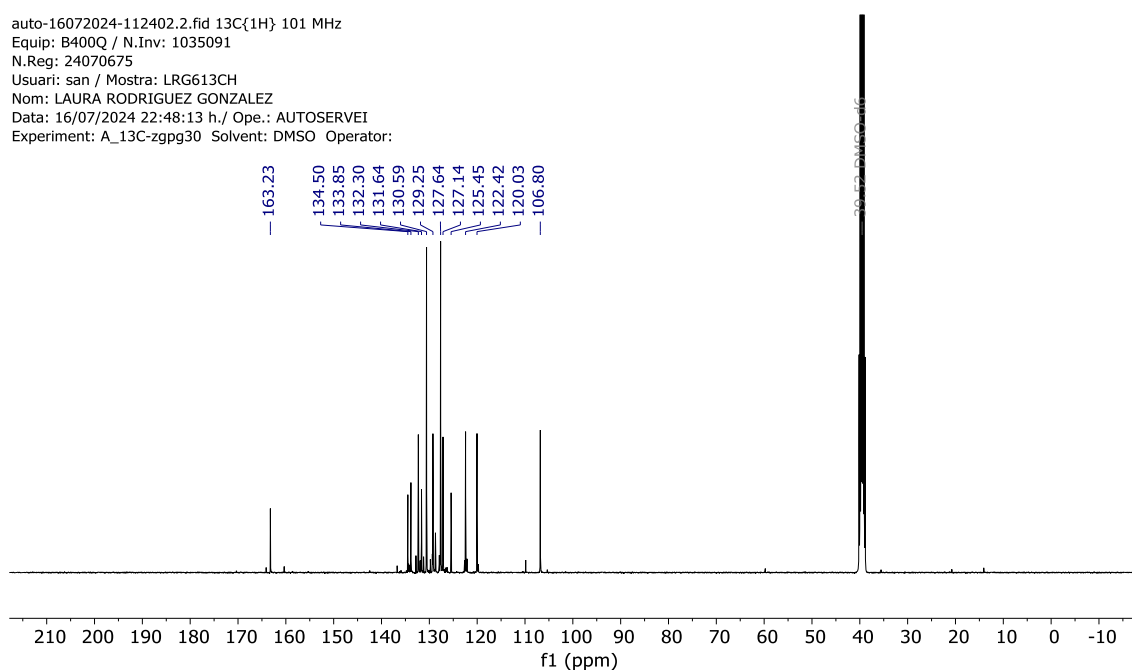




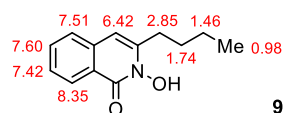
auto-16072024-112402.1.fid 1H 400 MHz
Equip: B400Q / N.Inv: 1035091
N.Reg: 24070675
Usuari: san / Mostra: LRG613CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 16/07/2024 12:44:09 h./ Ope.: AUTOSERVEI
Experiment: A_1H-zg30 Solvent: DMSO Operator:



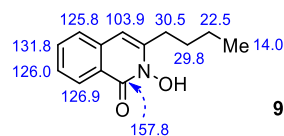
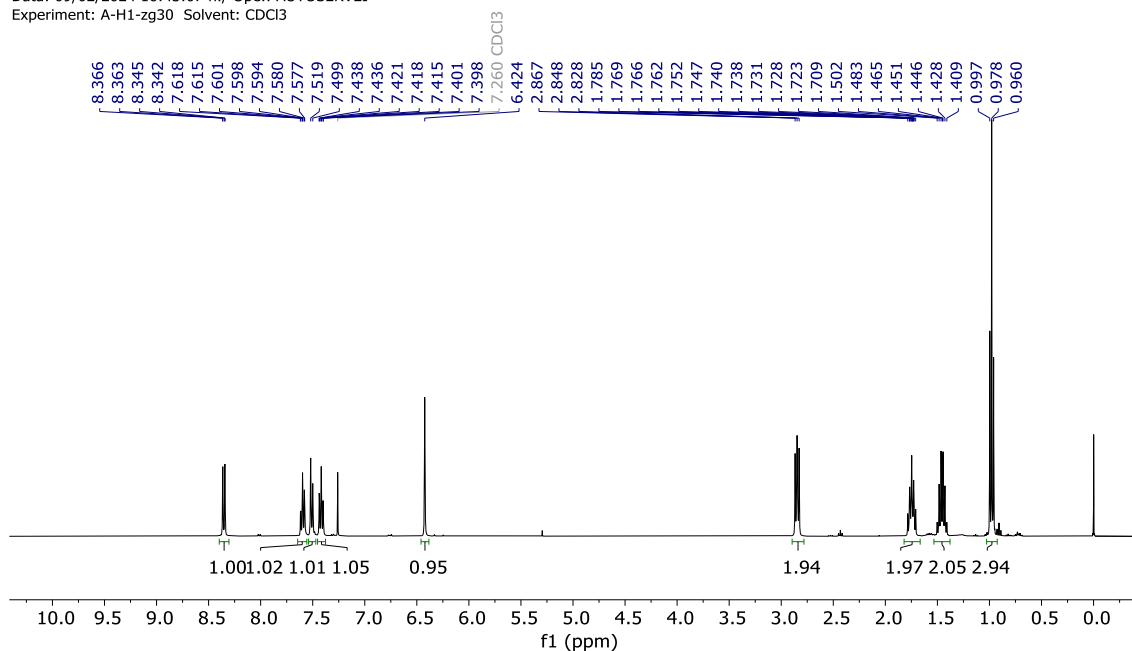
auto-16072024-112402.2.fid 13C{1H} 101 MHz
Equip: B400Q / N.Inv: 1035091
N.Reg: 24070675
Usuari: san / Mostra: LRG613CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 16/07/2024 22:48:13 h./ Ope.: AUTOSERVEI
Experiment: A_13C-zpgp30 Solvent: DMSO Operator:



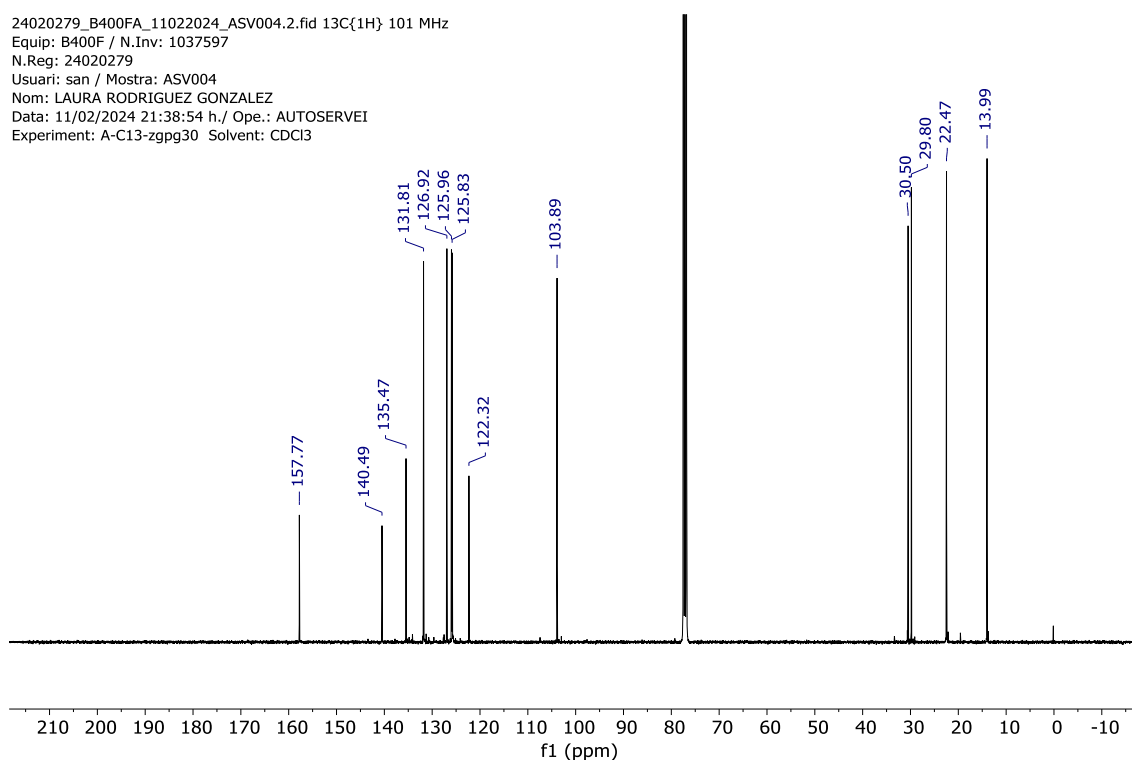
Experimental Section: Chapter 4

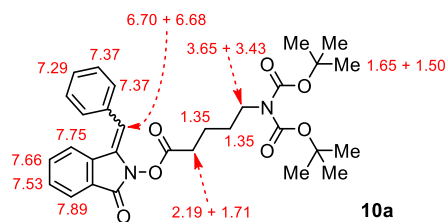


24020279_B400FA_11022024_ASV004.1.fid 1H 400 MHz
 Equip: B400F / N.Inv.: 1037597
 N.Reg: 24020279
 Usuari: san / Mostra: ASV004
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 09/02/2024 16:43:07 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

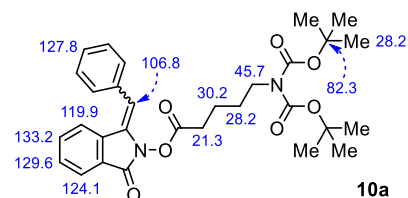
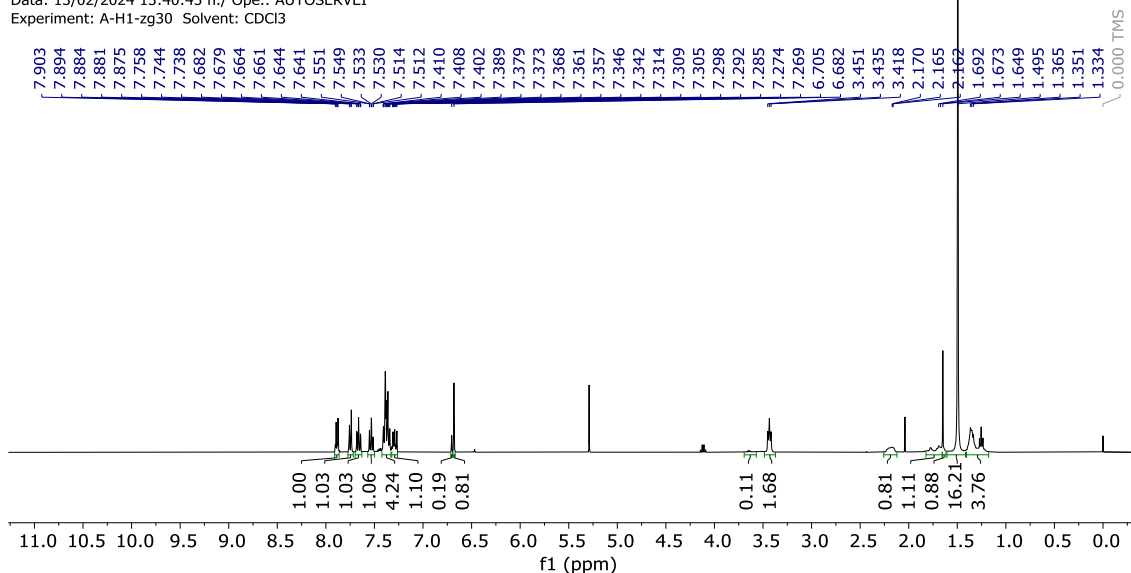


24020279_B400FA_11022024_ASV004.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv.: 1037597
 N.Reg: 24020279
 Usuari: san / Mostra: ASV004
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 11/02/2024 21:38:54 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

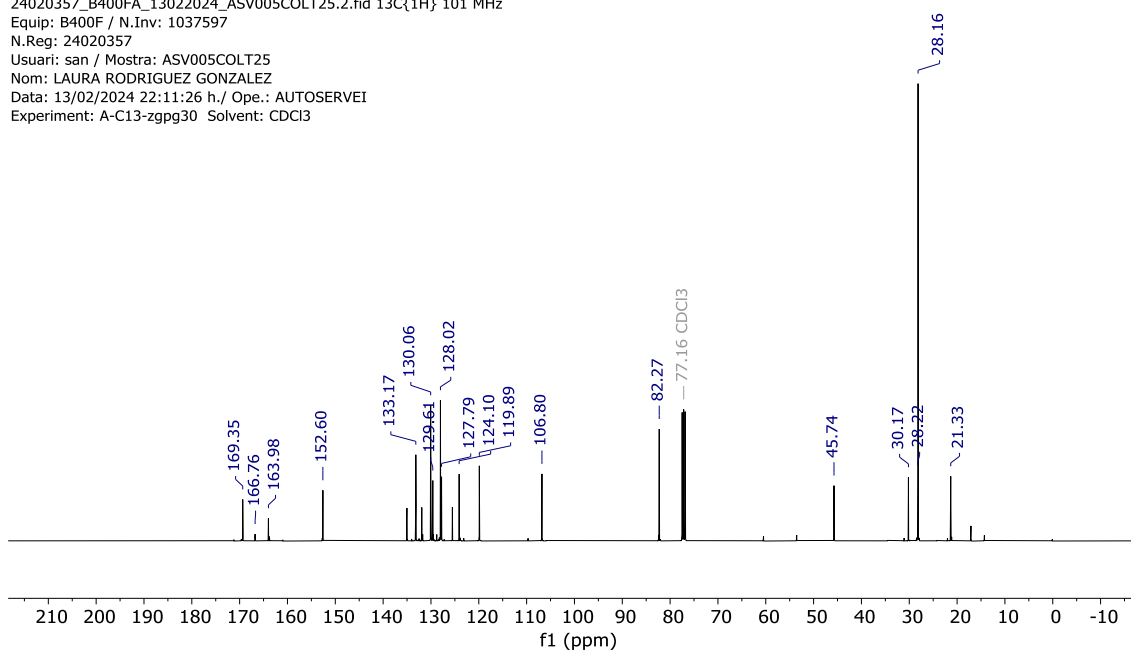


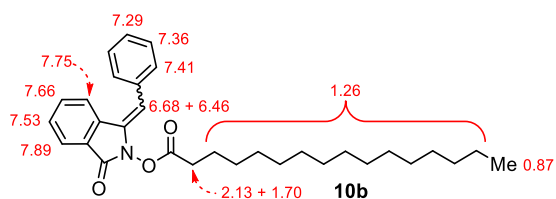


24020357_B400FA_13022024_ASV005COLT25.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24020357
Usuari: san / Mostra: ASV005COLT25
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 13/02/2024 13:40:45 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3



24020357_B400FA_13022024_ASV005COLT25.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24020357
Usuari: san / Mostra: ASV005COLT25
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 13/02/2024 22:11:26 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3





ASV029-20-25.1.fid ^1H 400 MHz

Equip: B400F / N.Inv: 1037597

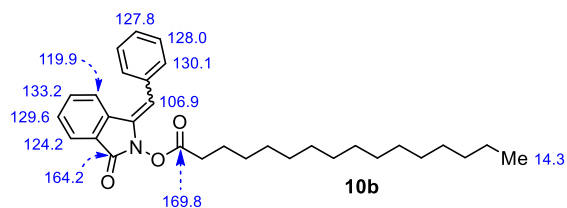
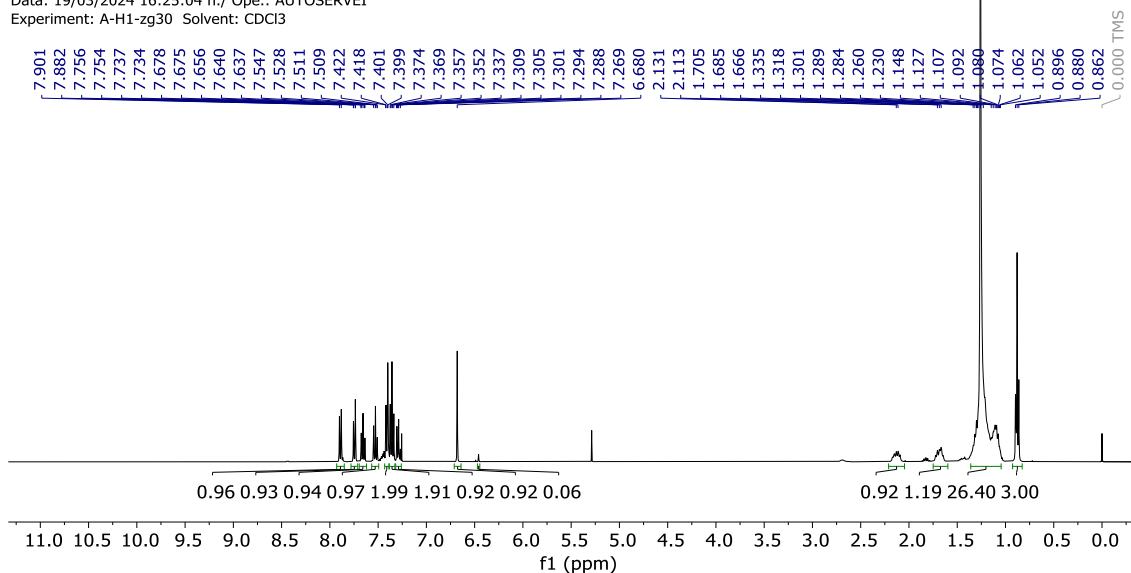
N.Reg: 24030748

Usuari: san / Mostra: ASV029-20-25

Nom: AINA SERRA VERT

Data: 19/03/2024 16:25:04 h./ Ope.: AUTOSERVEI

Experiment: A-H1-zg30 Solvent: CDCl_3



ASV029-20-25.2.fid ^{13}C { ^1H } 101 MHz

Equip: B400F / N.Inv: 1037597

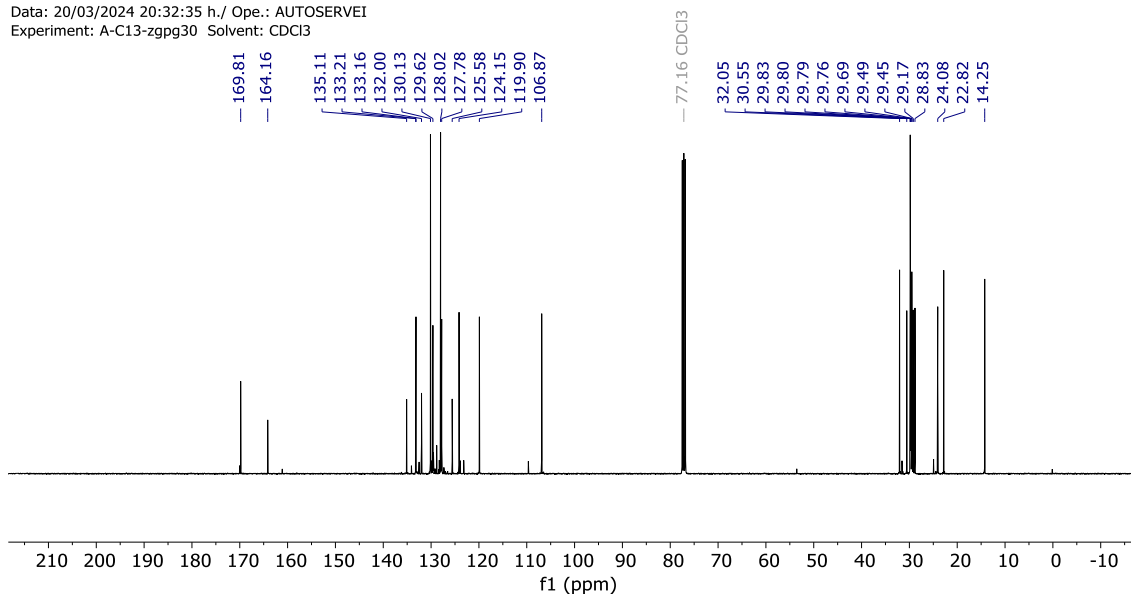
N.Reg: 24030799

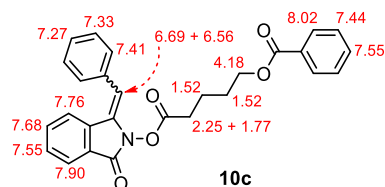
Usuari: san / Mostra: ASV029-20-25

Nom: AINA SERRA VERT

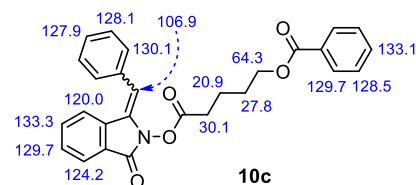
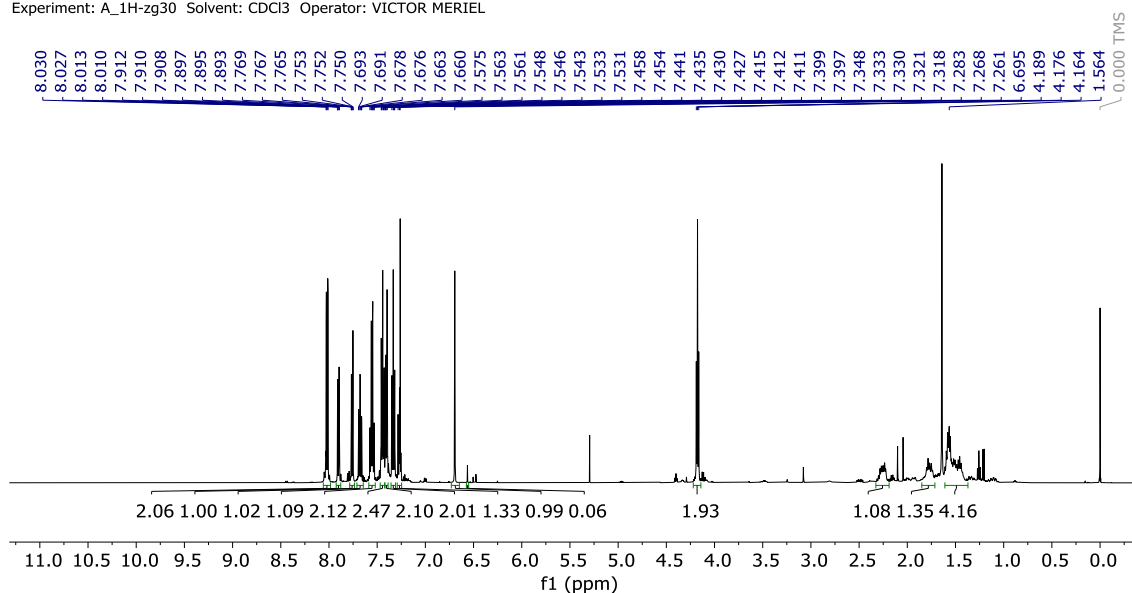
Data: 20/03/2024 20:32:35 h./ Ope.: AUTOSERVEI

Experiment: A-C13-zpgp30 Solvent: CDCl_3

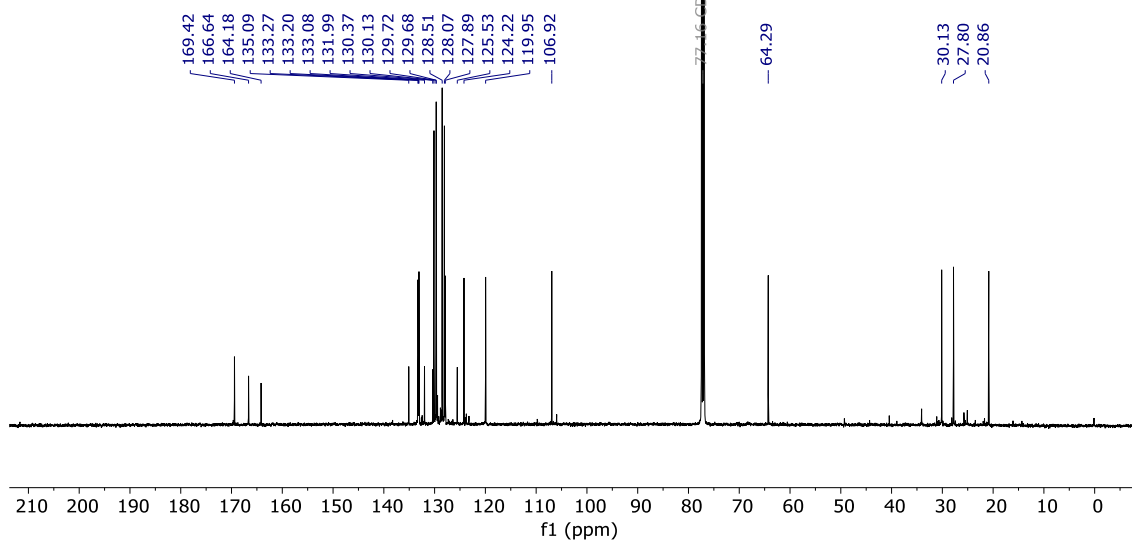


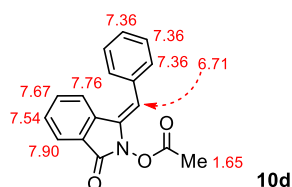


5923-2024_B500QA_14062024_ASV061CH.10.fid 1H 500 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 5923/2024
 Usuari: san / Mostra: ASV061CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/06/2024 14:13:22 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator: VICTOR MERIEL

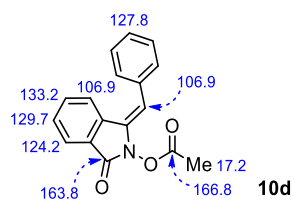
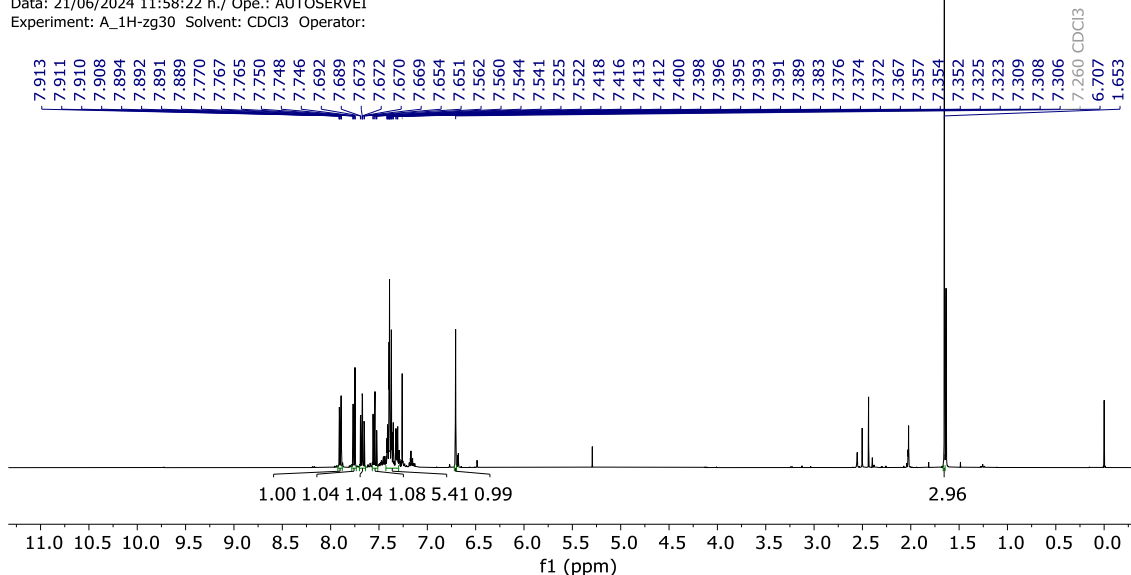


5923-2024_B500QA_14062024_ASV061CH.11.fid 13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 5923/2024
 Usuari: san / Mostra: ASV061CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/06/2024 14:13:22 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zpgp30 Solvent: CDCl3 Operator: VICTOR MERIEL

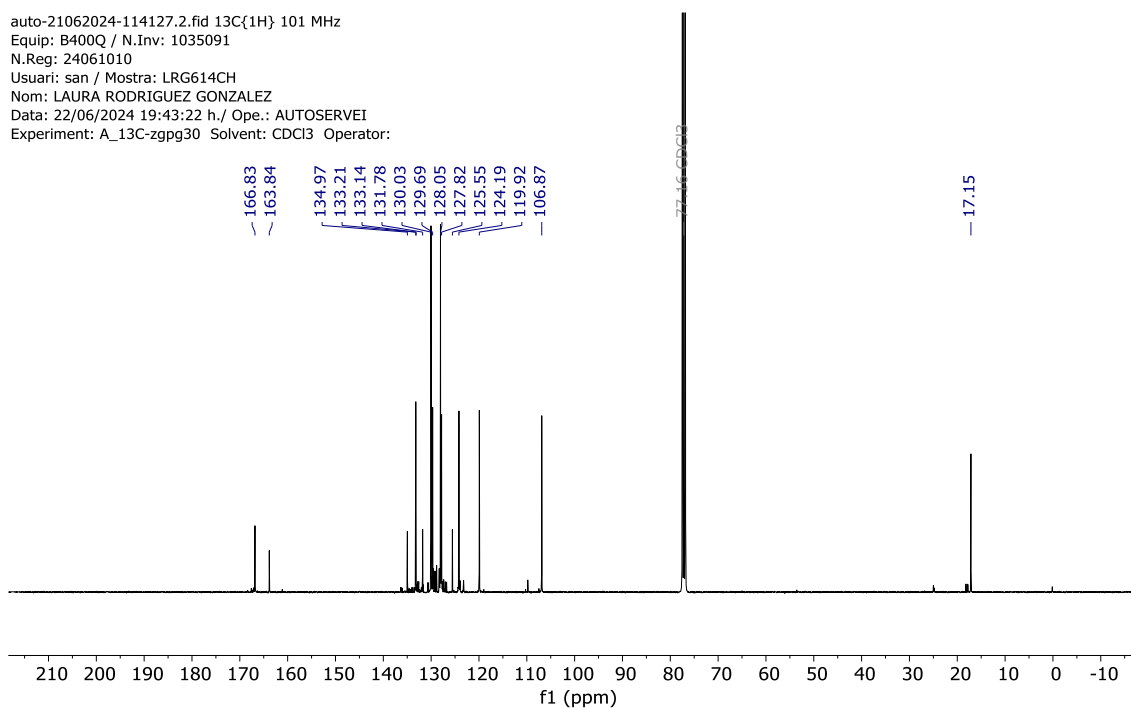


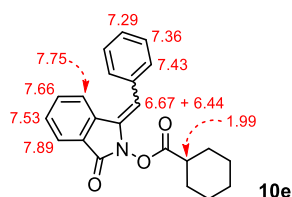


auto-21062024-114127.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 24061010
 Usuari: san / Mostra: LRG614CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 21/06/2024 11:58:22 h./ Ope.: AUTOSERVEI
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator:

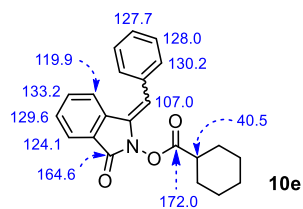
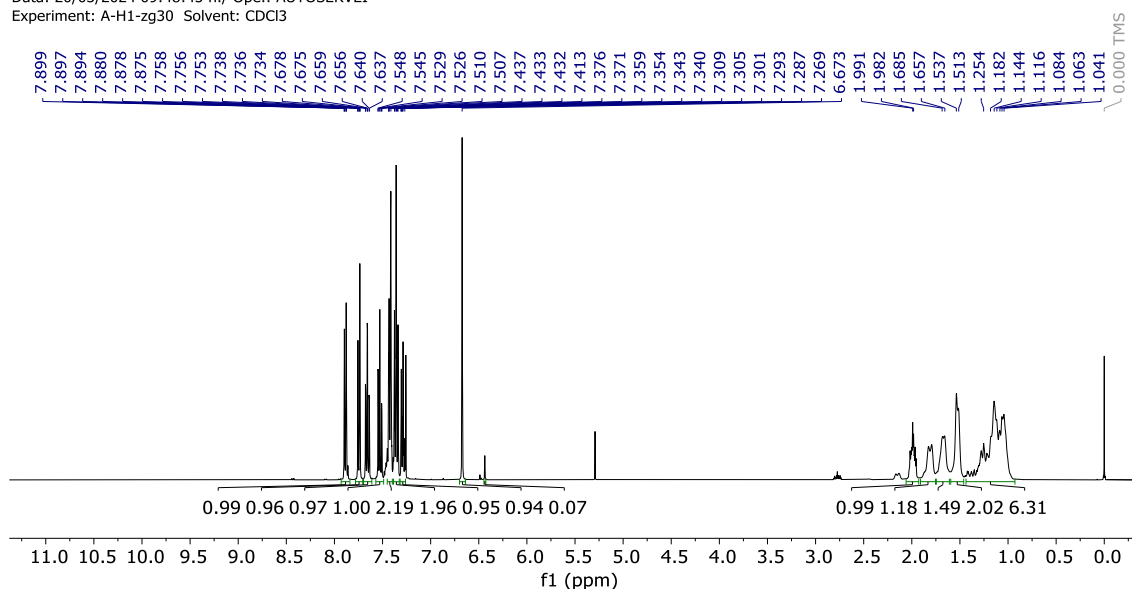


auto-21062024-114127.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 24061010
 Usuari: san / Mostra: LRG614CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 22/06/2024 19:43:22 h./ Ope.: AUTOSERVEI
 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator:

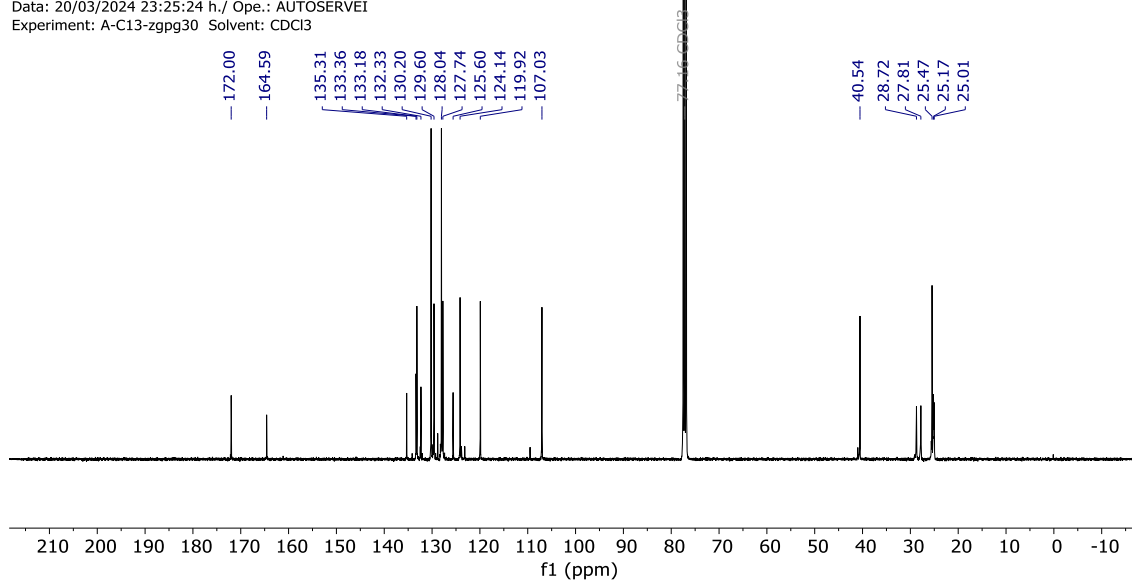


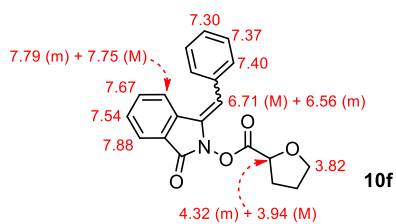


ASV030-19-24.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24030800
Usuari: san / Mostra: ASV030-19-24
Nom: AINA SERRA VERT
Data: 20/03/2024 09:48:45 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl₃

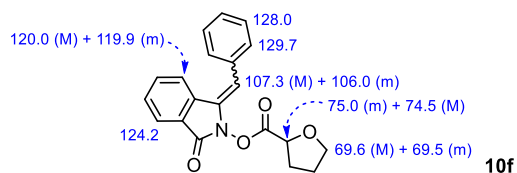
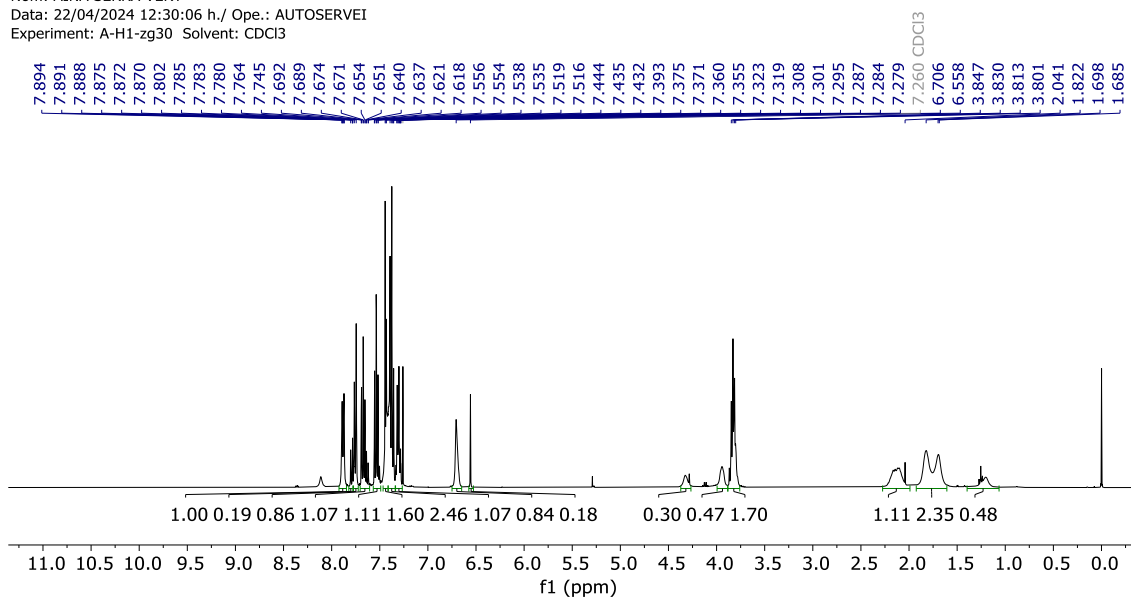


ASV030-19-24.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24030800
Usuari: san / Mostra: ASV030-19-24
Nom: AINA SERRA VERT
Data: 20/03/2024 23:25:24 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zpgg30 Solvent: CDCl₃

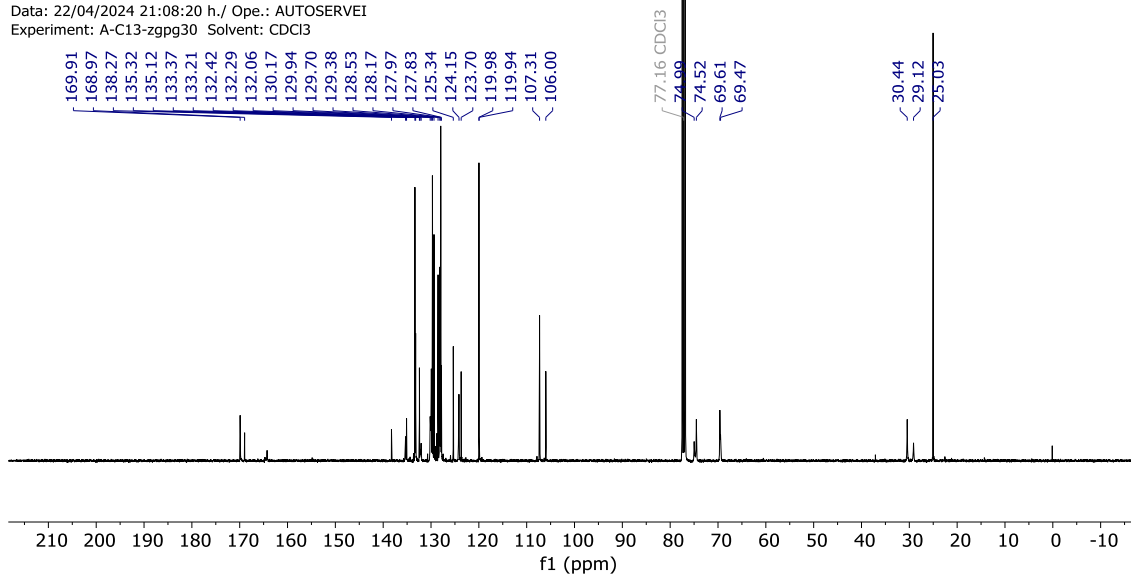


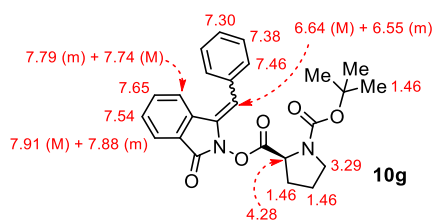


24040948_B400FA_22042024_ASV036-2-23-24.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040948
 Usuari: san / Mostra: ASV036-2-23-24
 Nom: AINA SERRA VERT
 Data: 22/04/2024 12:30:06 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

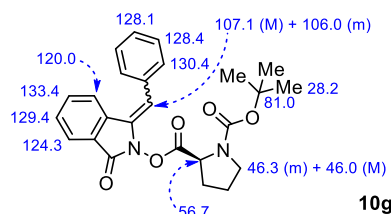
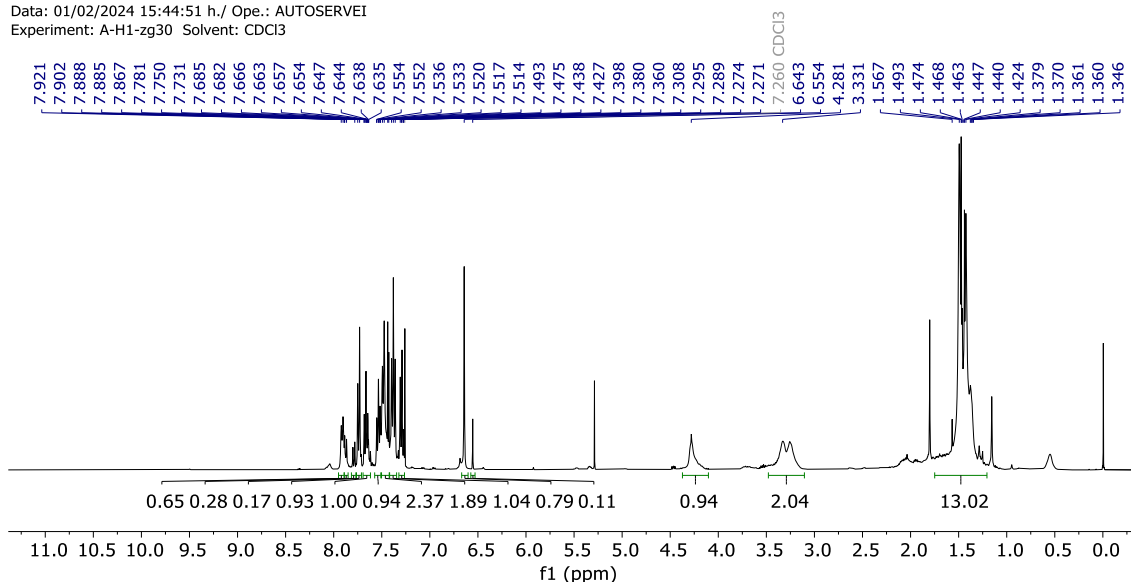


24040948_B400FA_22042024_ASV036-2-23-24.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040948
 Usuari: san / Mostra: ASV036-2-23-24
 Nom: AINA SERRA VERT
 Data: 22/04/2024 21:08:20 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpg30 Solvent: CDCl3

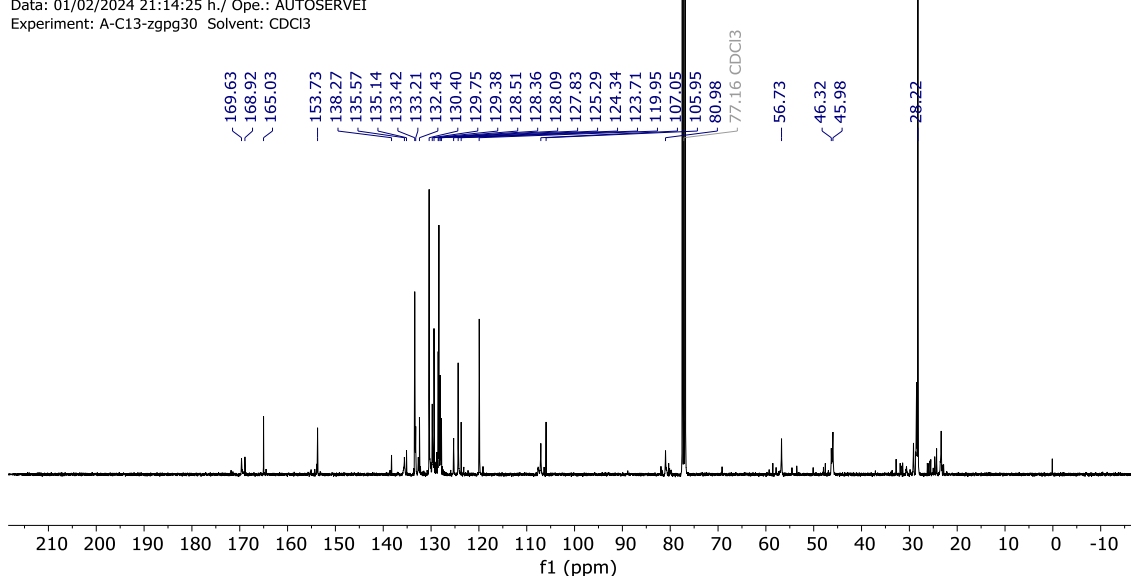




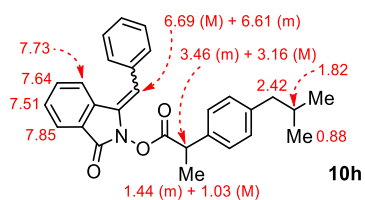
LRG531T29DRY.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24020028
Usuari: san / Mostra: LRG531T29DRY
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 01/02/2024 15:44:51 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3



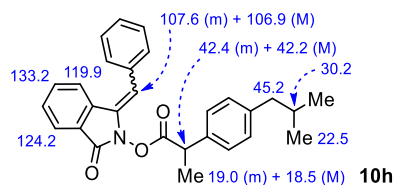
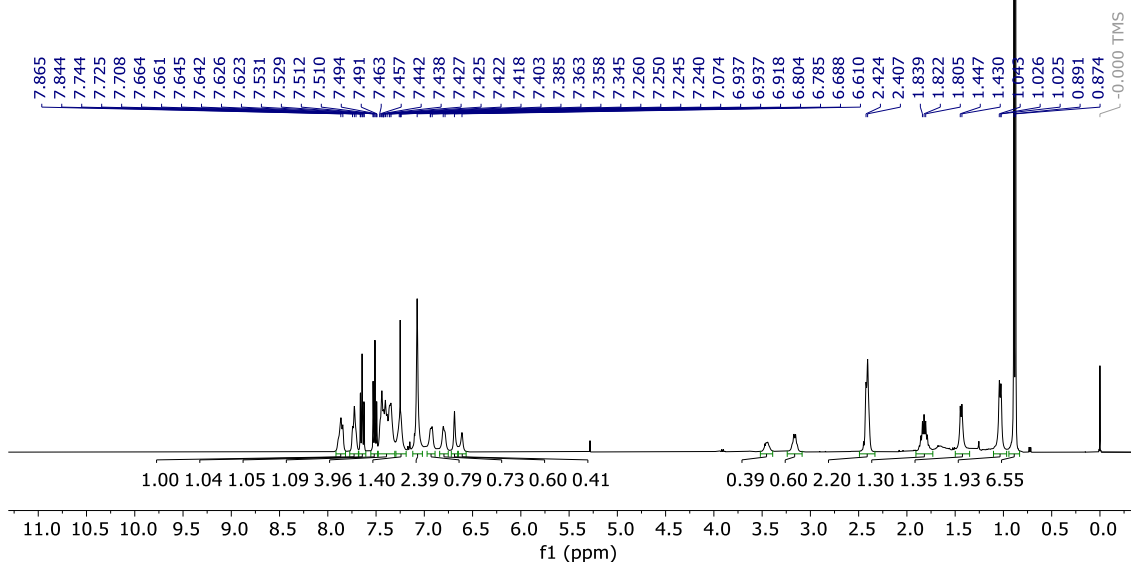
LRG531CH.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24020001
Usuari: san / Mostra: LRG531CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 01/02/2024 21:14:25 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3



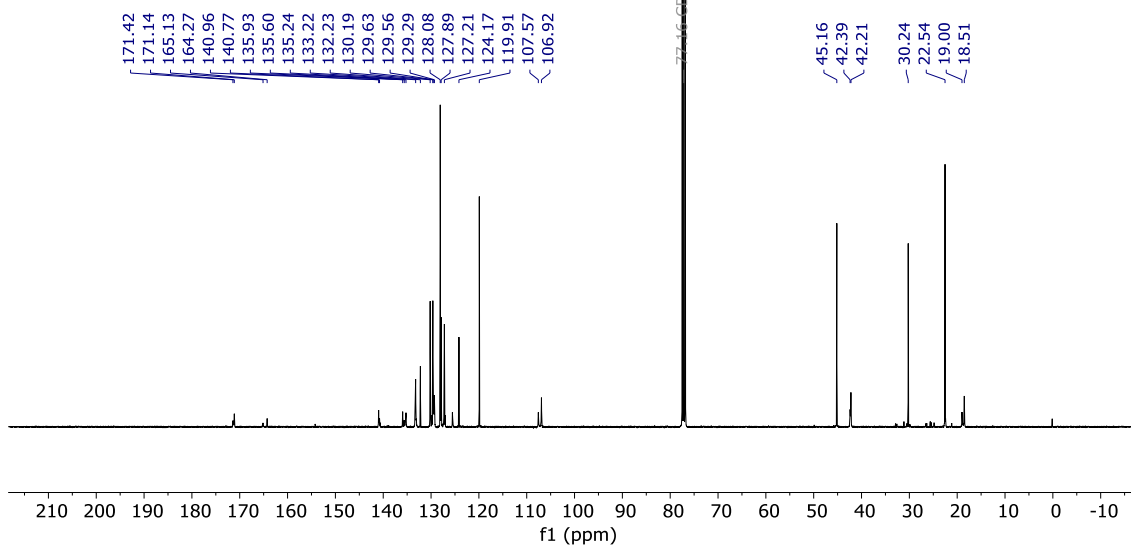
Experimental Section: Chapter 4

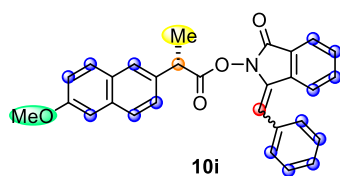


24050623_B400FA_16052024_ASV054-PREP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050623
 Usuari: san / Mostra: ASV054-PREP
 Nom: AINA SERRA VERT
 Data: 15/05/2024 15:28:25 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



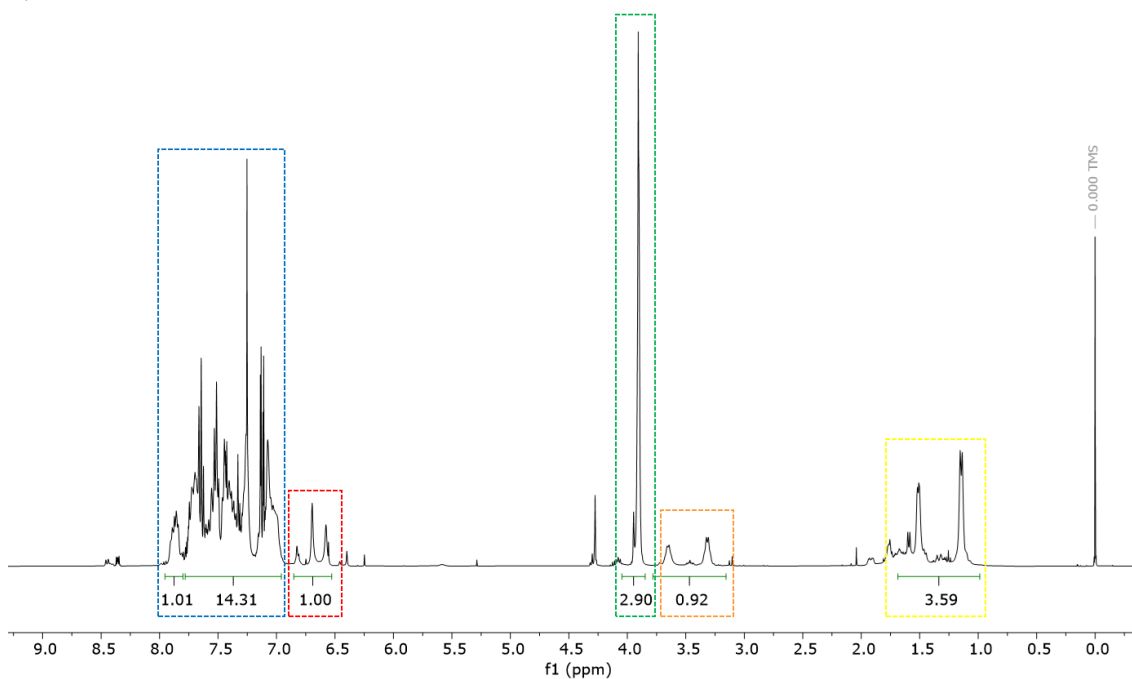
24050623_B400FA_16052024_ASV054-PREP.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050623
 Usuari: san / Mostra: ASV054-PREP
 Nom: AINA SERRA VERT
 Data: 16/05/2024 01:08:00 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

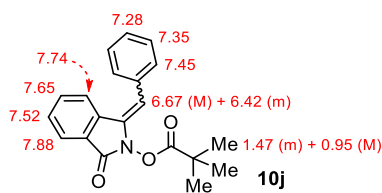




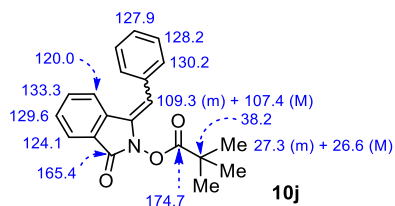
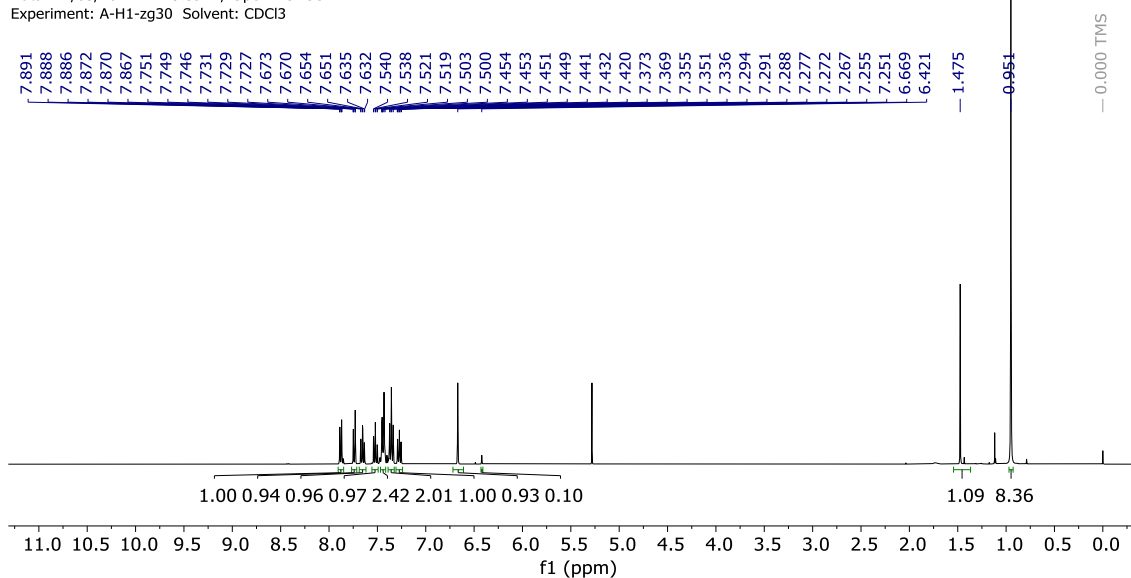
This product was isolated as a complex mixture of isomers and rotamers that made it impossible to interpret the ^{13}C spectrum. Therefore, only the data corresponding to the ^1H NMR (400 MHz) spectrum is reported herein.

ASV050-30-32.1.fid
Equip: B400F / N.Inv: 1037597
N.Reg: 24041199
Usuari: san / Mostra: ASV050-30-32
Nom: AINA SERRA VERT
Data: 26/04/2024 13:18:57 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3

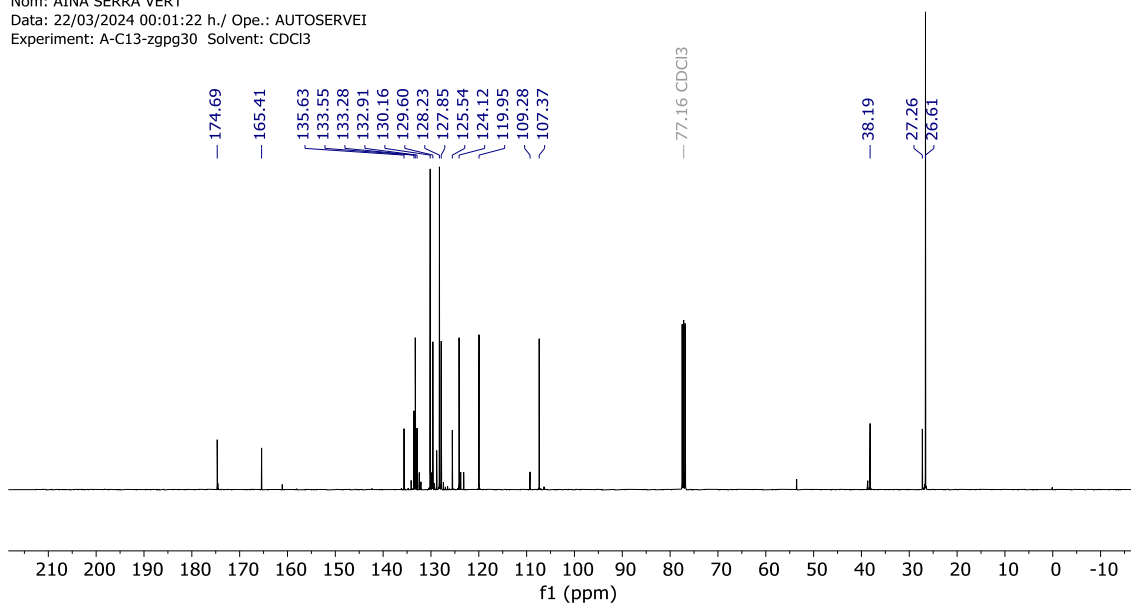


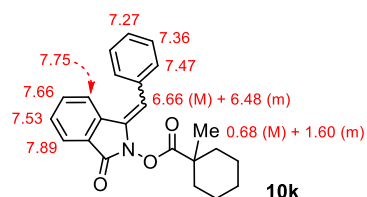


ASV031-21-24CH.1.fid ^1H 400 Mhz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030897
 Usuari: san / Mostra: ASV031-21-24
 Nom: AINA SERRA VERT
 Data: 21/03/2024 14:28:39 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl_3

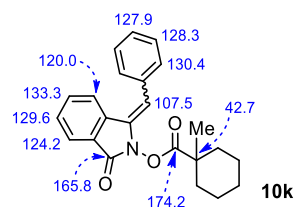
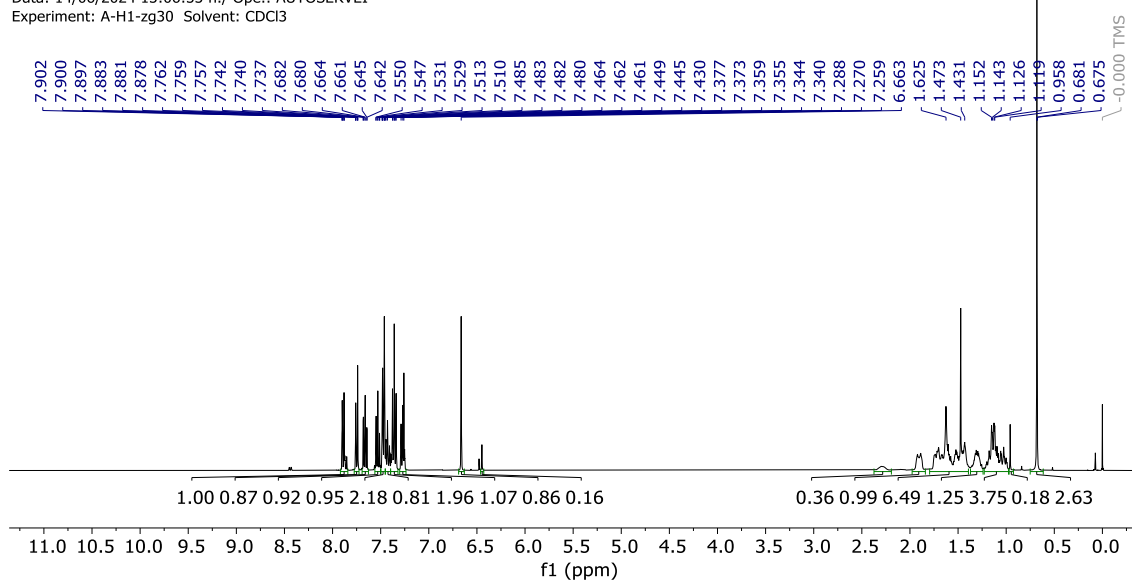


ASV031-21-24CH.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030897
 Usuari: san / Mostra: ASV031-21-24
 Nom: AINA SERRA VERT
 Data: 22/03/2024 00:01:22 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl_3

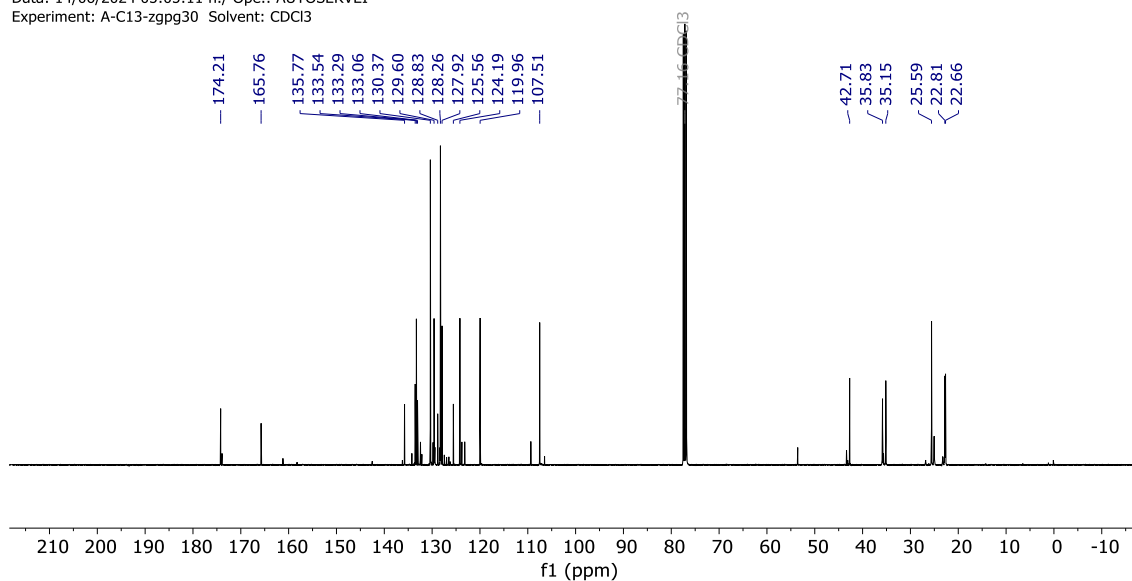


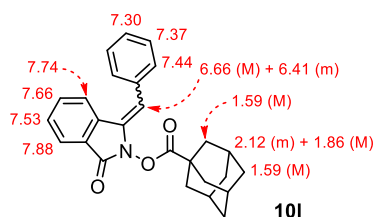


24060403_B400FA_14062024_LRG611DRY.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24060403
Usuari: san / Mostra: LRG611DRY
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 14/06/2024 13:06:33 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3

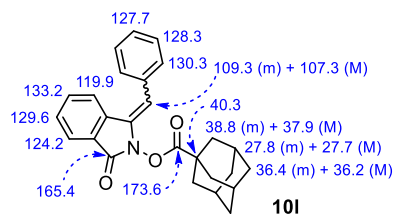
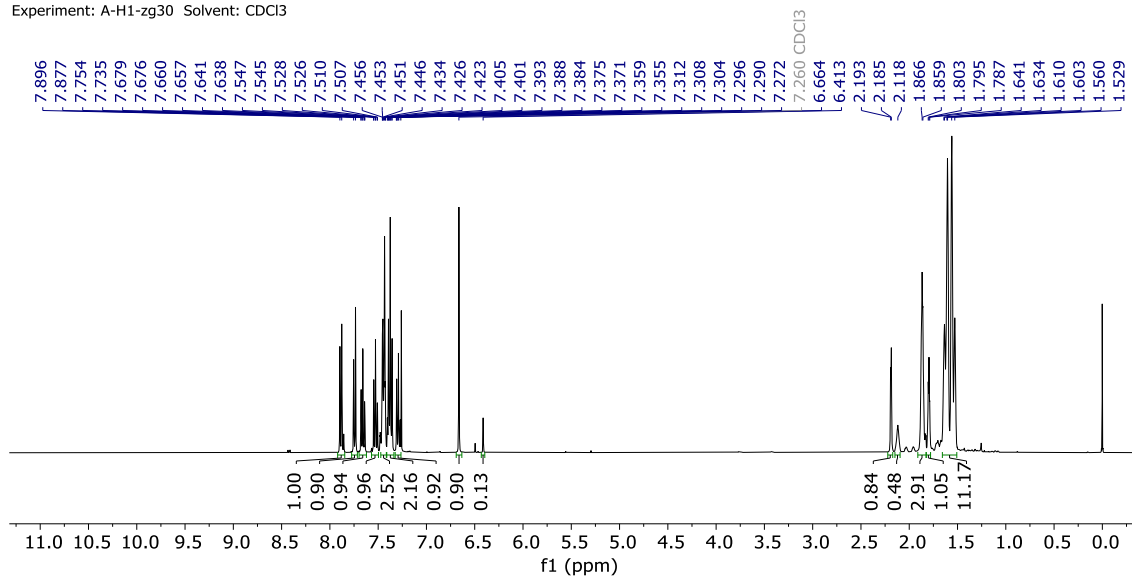


24060346_B400FA_14062024_LRG611COLT21T23.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24060346
Usuari: san / Mostra: LRG611COLT21T23
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 14/06/2024 05:05:11 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3

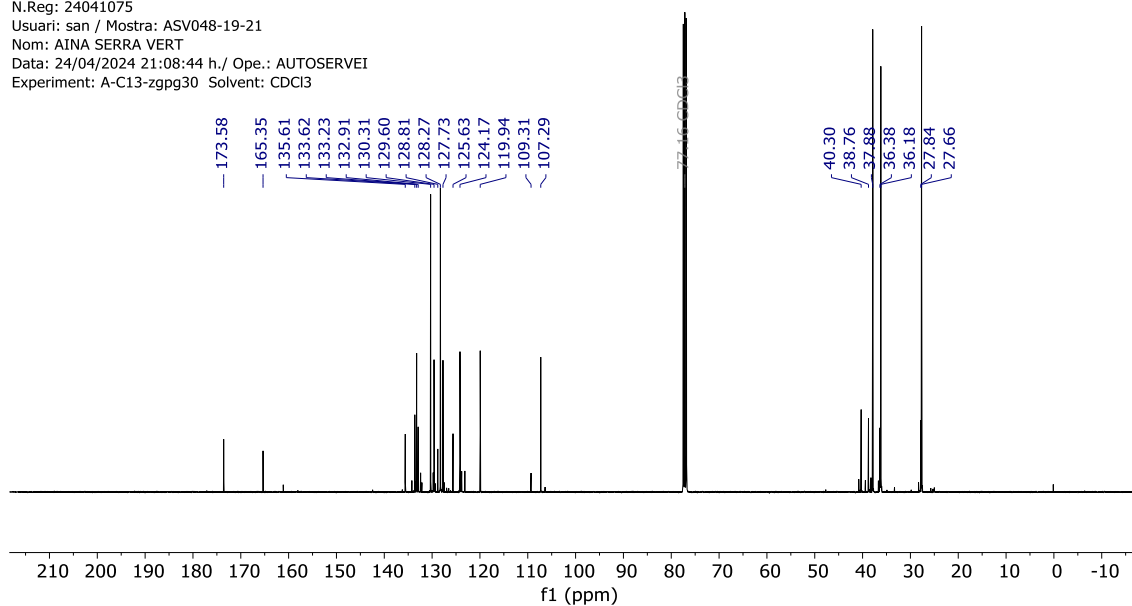


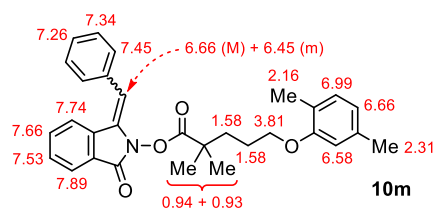


24041075_B400FA_24042024_ASV048-19-21.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24041075
 Usuari: san / Mostra: ASV048-19-21
 Nom: AINA SERRA VERT
 Data: 24/04/2024 13:15:16 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

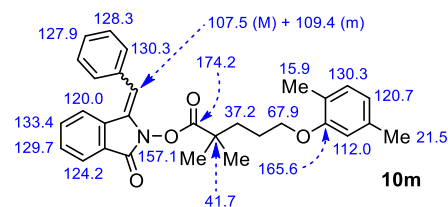
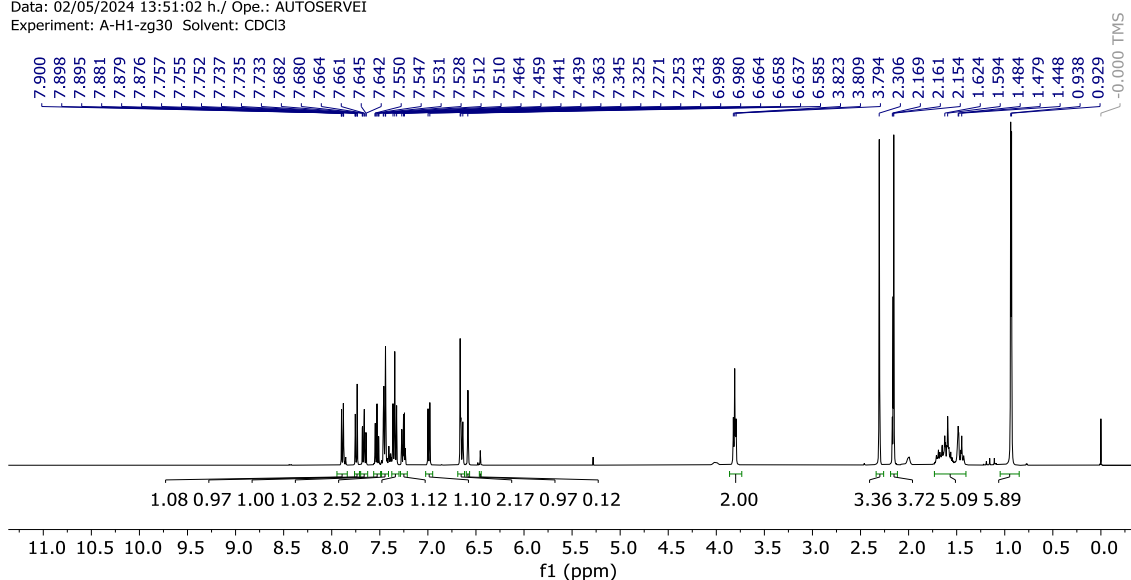


24041075_B400FA_24042024_ASV048-19-21.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24041075
 Usuari: san / Mostra: ASV048-19-21
 Nom: AINA SERRA VERT
 Data: 24/04/2024 21:08:44 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

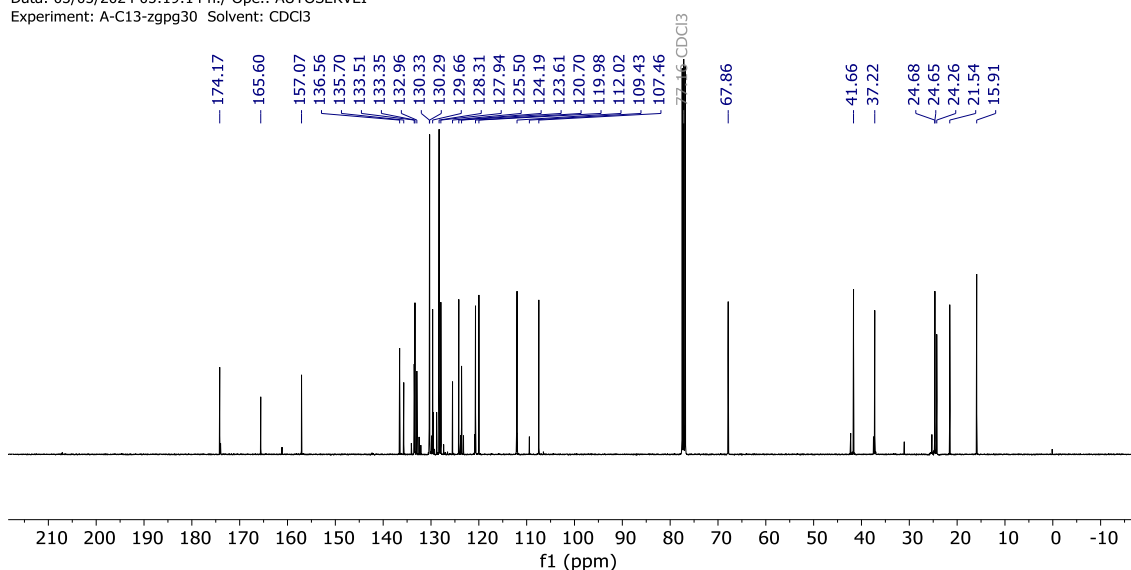


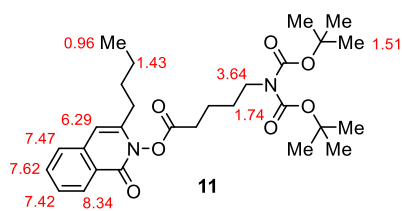


24050020_B400FA_02052024_ASV052T22.1.fid ^1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050020
 Usuari: san / Mostra: ASV052T22
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 02/05/2024 13:51:02 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

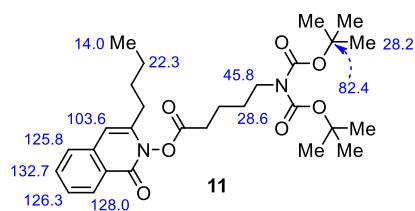
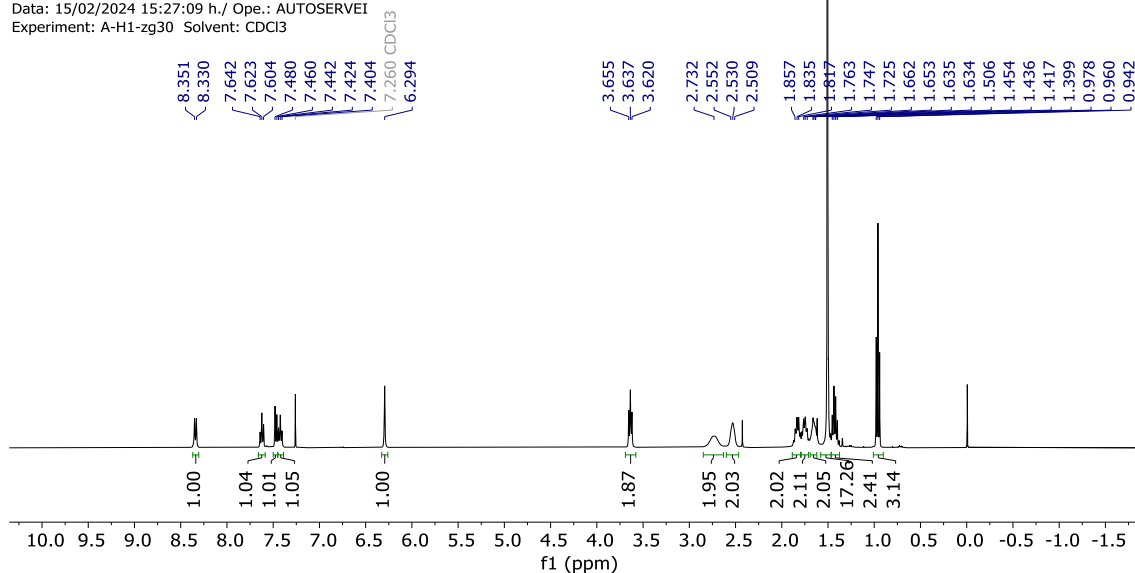


24050033_B400FA_03052024_ASV052-22-24.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050033
 Usuari: san / Mostra: ASV052-22-24
 Nom: AINA SERRA VERT
 Data: 03/05/2024 05:19:14 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

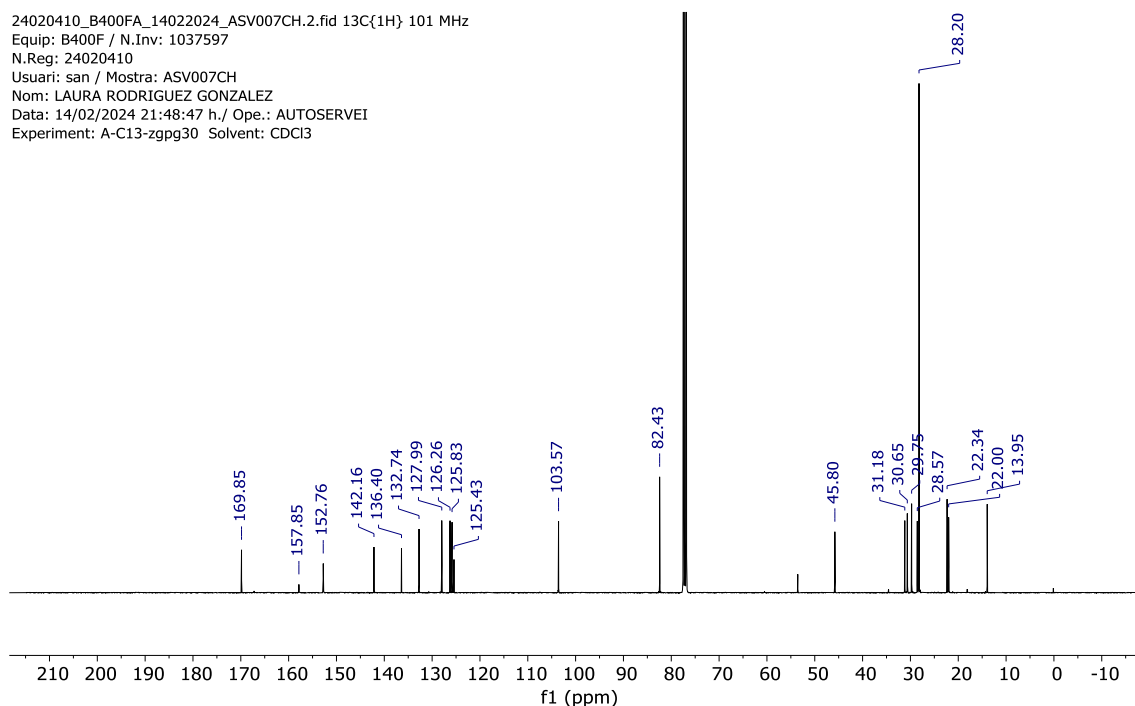


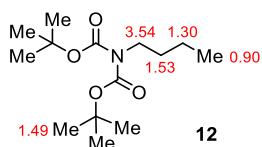


24020465_B400FA_15022024_ASV007DRY.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24020465
 Usuari: san / Mostra: ASV007DRY
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/02/2024 15:27:09 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

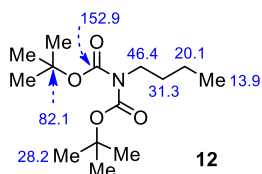
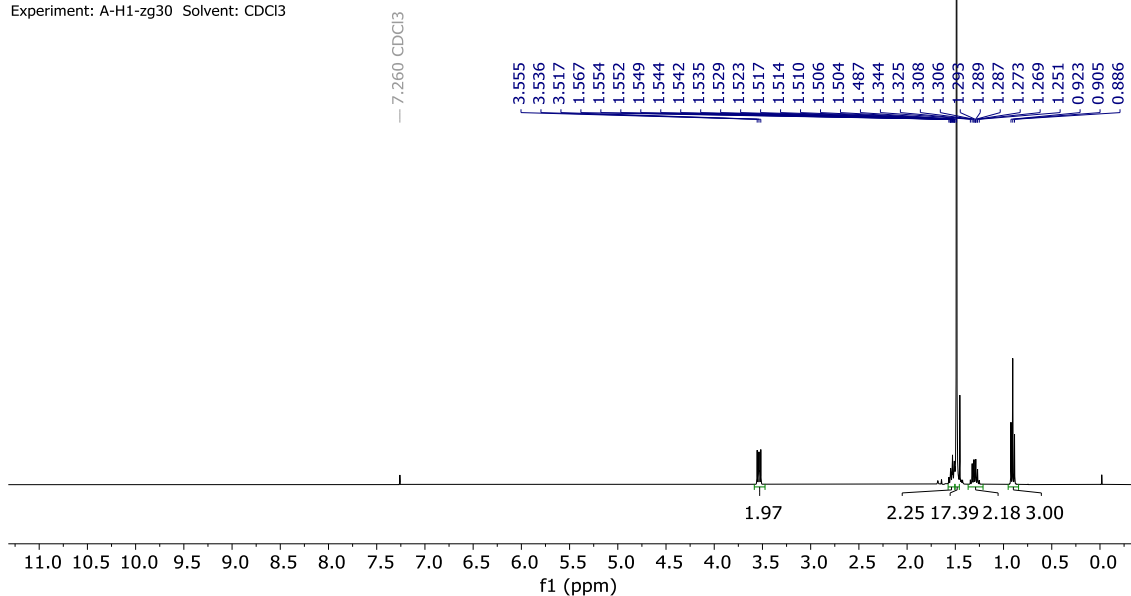


24020410_B400FA_14022024_ASV007CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24020410
 Usuari: san / Mostra: ASV007CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/02/2024 21:48:47 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

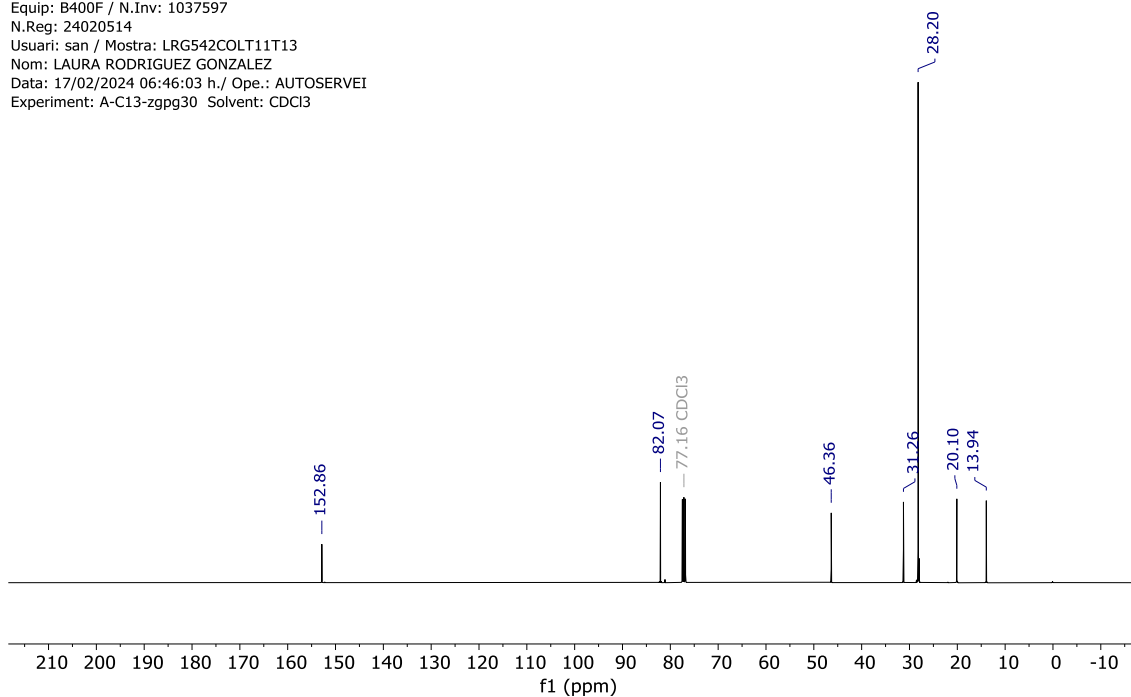




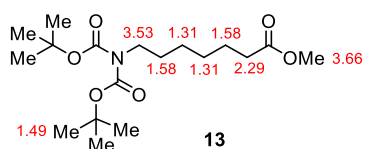
24020514_B400FA_17022024_LRG542COLT11T13.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24020514
Usuari: san / Mostra: LRG542COLT11T13
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 16/02/2024 15:15:24 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3



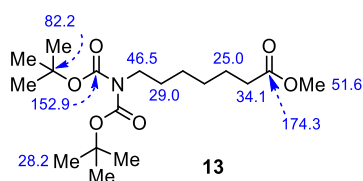
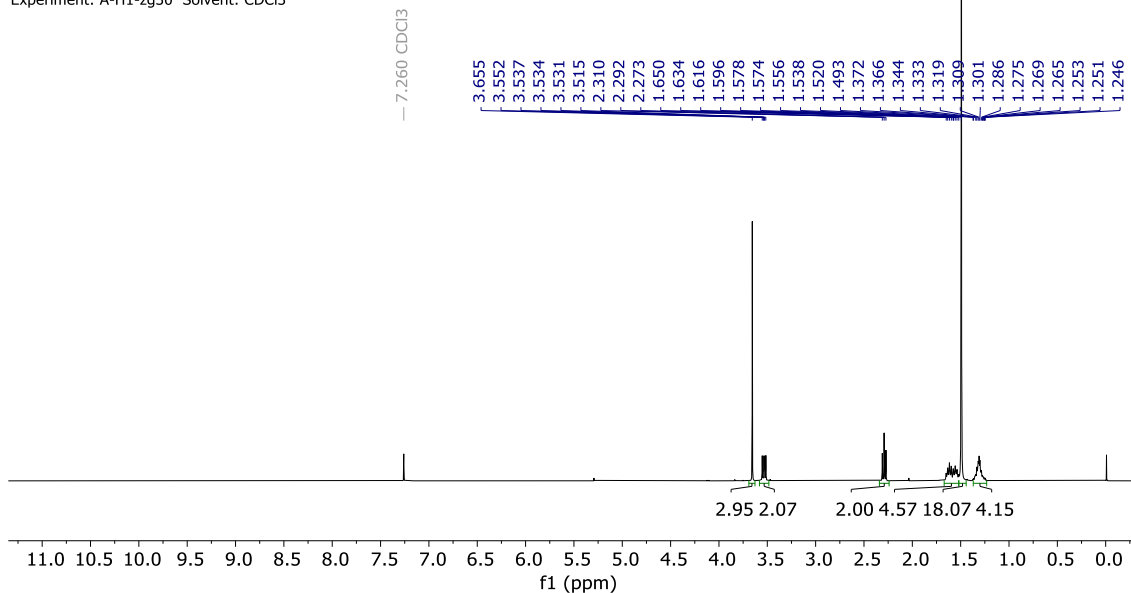
24020514_B400FA_17022024_LRG542COLT11T13.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24020514
Usuari: san / Mostra: LRG542COLT11T13
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 17/02/2024 06:46:03 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zpgp30 Solvent: CDCl3



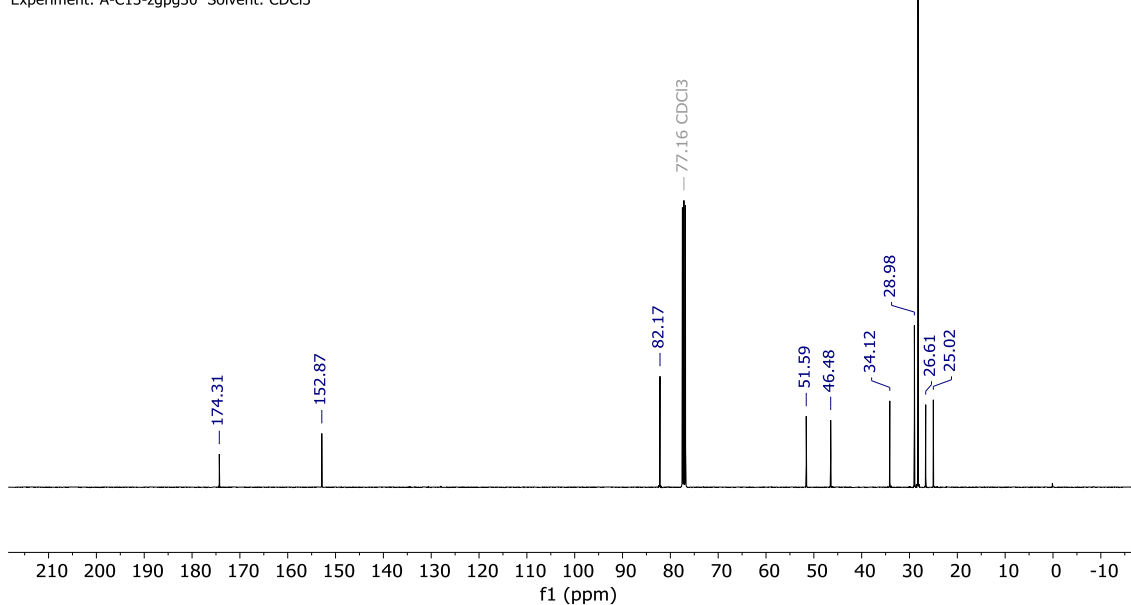
Experimental Section: Chapter 4

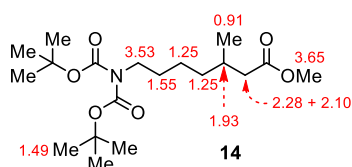


24030080_B400FA_04032024_LRG554PREP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030080
 Usuari: san / Mostra: LRG554PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 04/03/2024 16:50:23 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

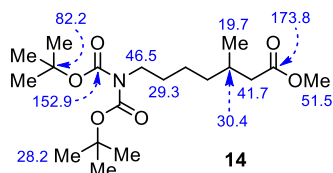
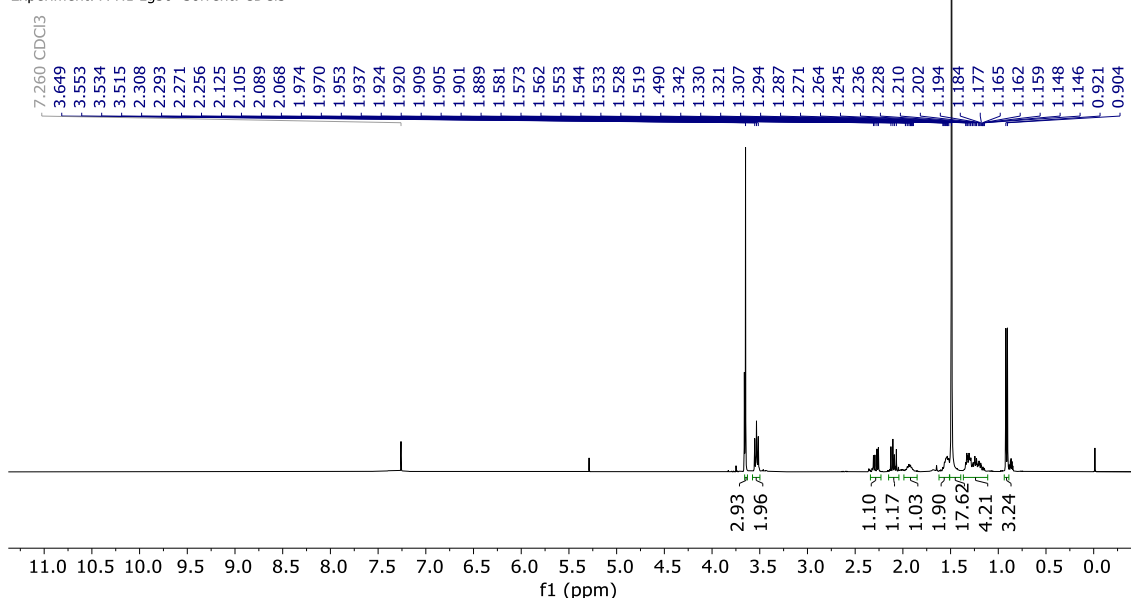


24030080_B400FA_05032024_LRG554PREP.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030080
 Usuari: san / Mostra: LRG554PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 05/03/2024 07:30:57 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

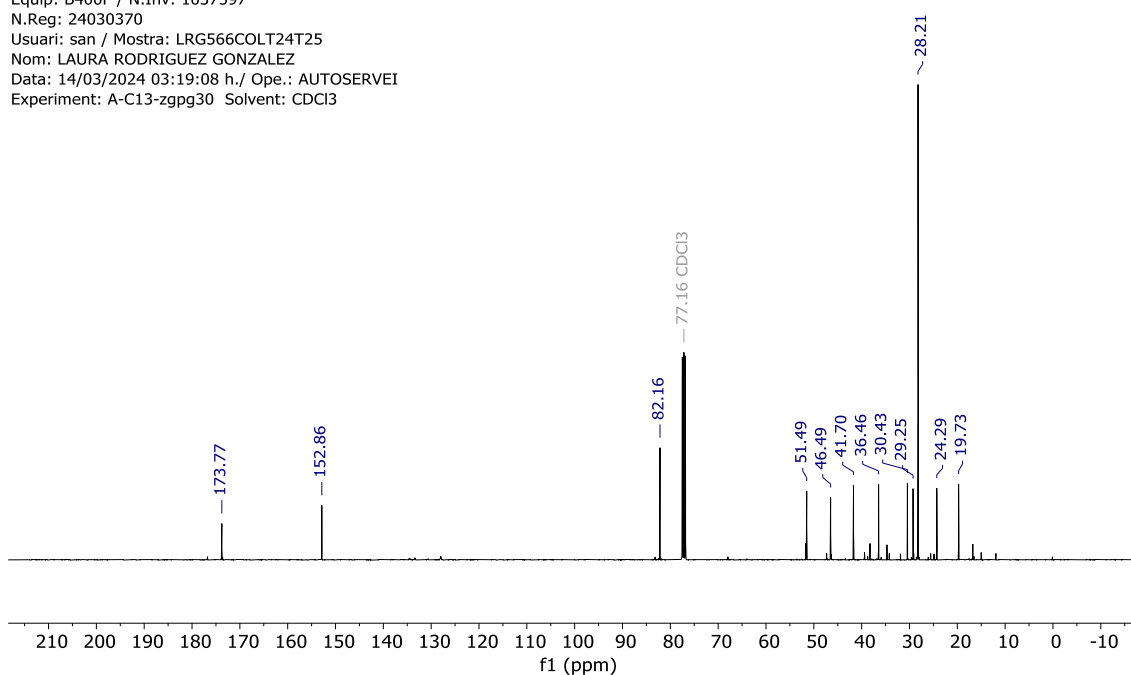




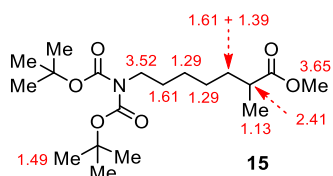
24030370_B400FA_13032024_LRG566COLT24T25.1.fid ^1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24030370
Usuari: san / Mostra: LRG566COLT24T25
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 13/03/2024 11:37:53 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl_3



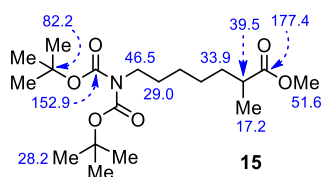
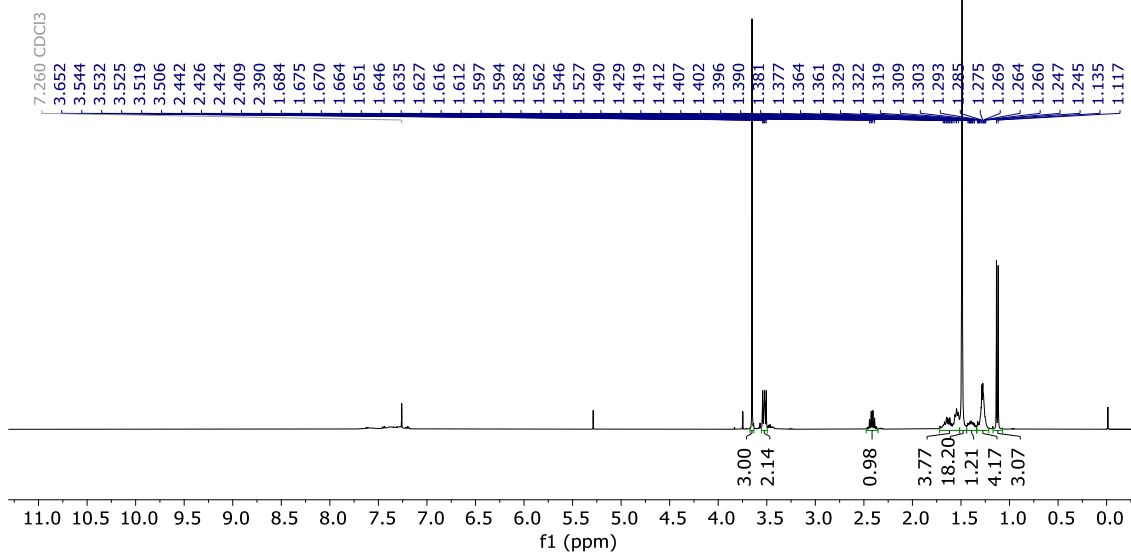
24030370_B400FA_14032024_LRG566COLT24T25.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24030370
Usuari: san / Mostra: LRG566COLT24T25
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 14/03/2024 03:19:08 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl_3



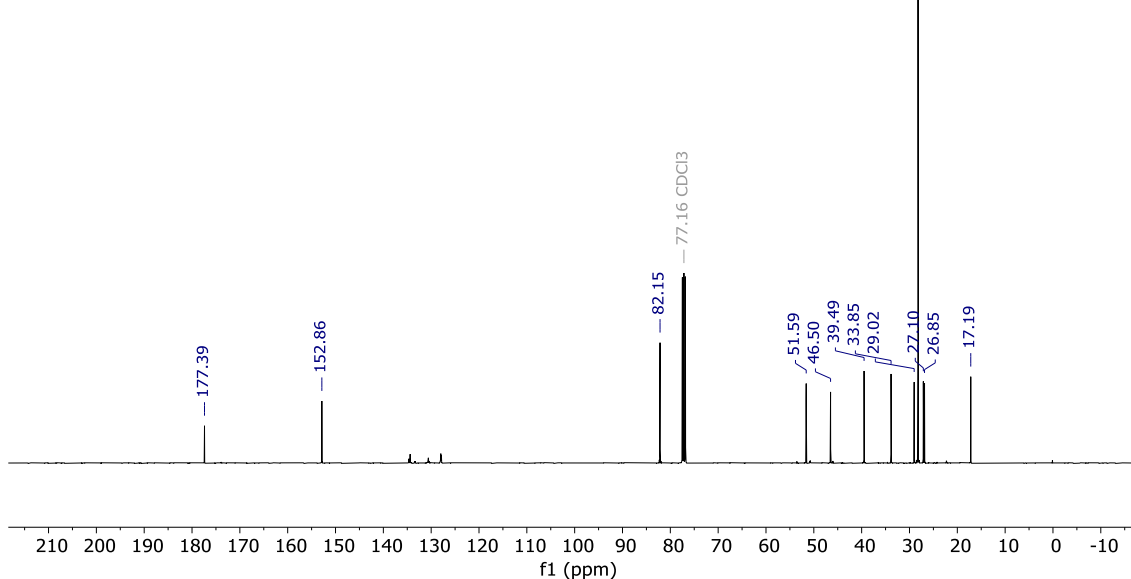
Experimental Section: Chapter 4

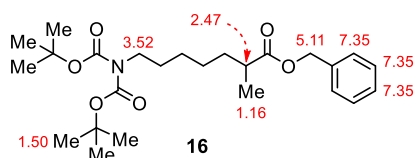


24030732_B400FA_19032024_LRG568COLT26T27.1.fid ^1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030732
 Usuari: san / Mostra: LRG568COLT26T27
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/03/2024 14:42:24 h. / Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl_3

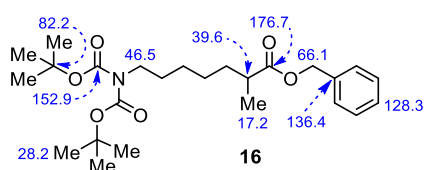
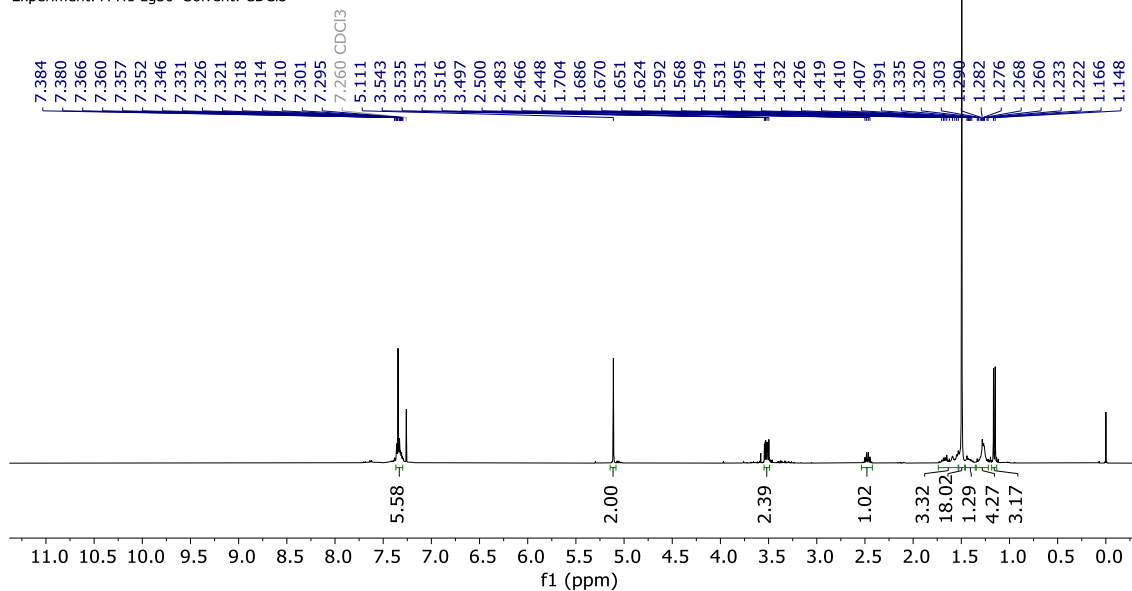


LRG568COLT26T27.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030721
 Usuari: san / Mostra: LRG570COLT27T28
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 20/03/2024 00:57:48 h. / Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl_3

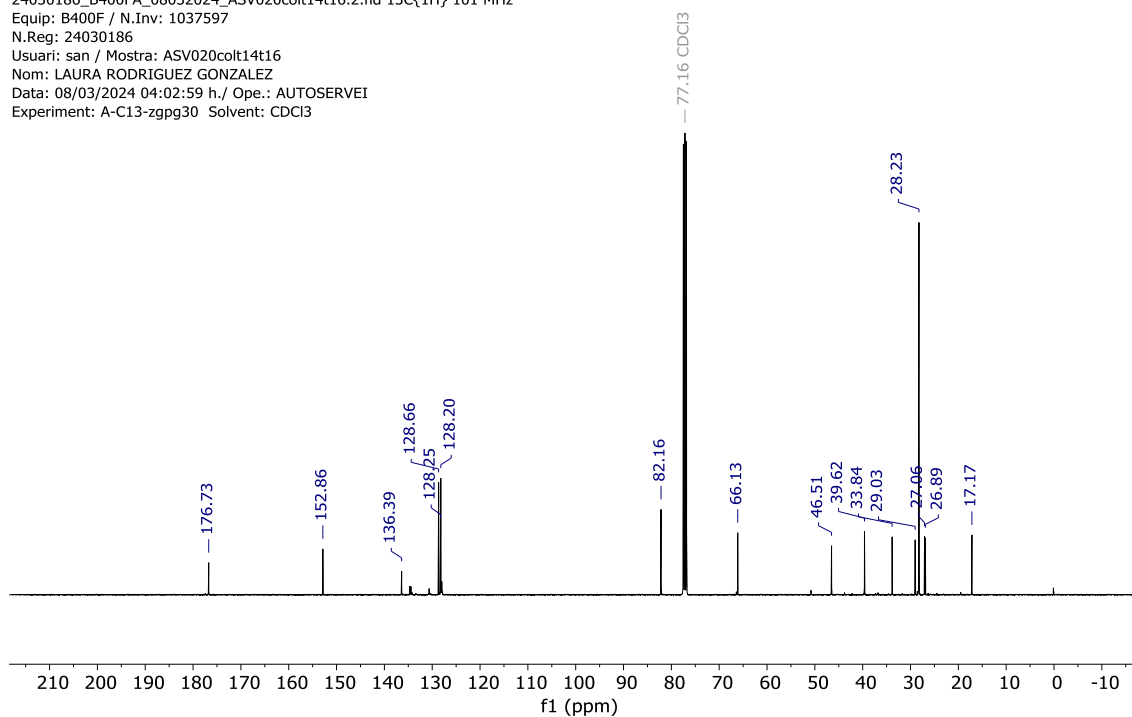




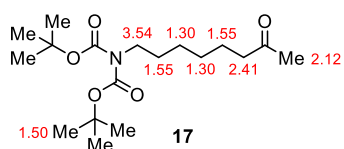
24030199_B400FA_07032024_ASV020-18-19.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030199
 Usuari: san / Mostra: ASV020-18-19
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/03/2024 16:15:15 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



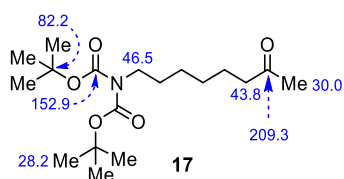
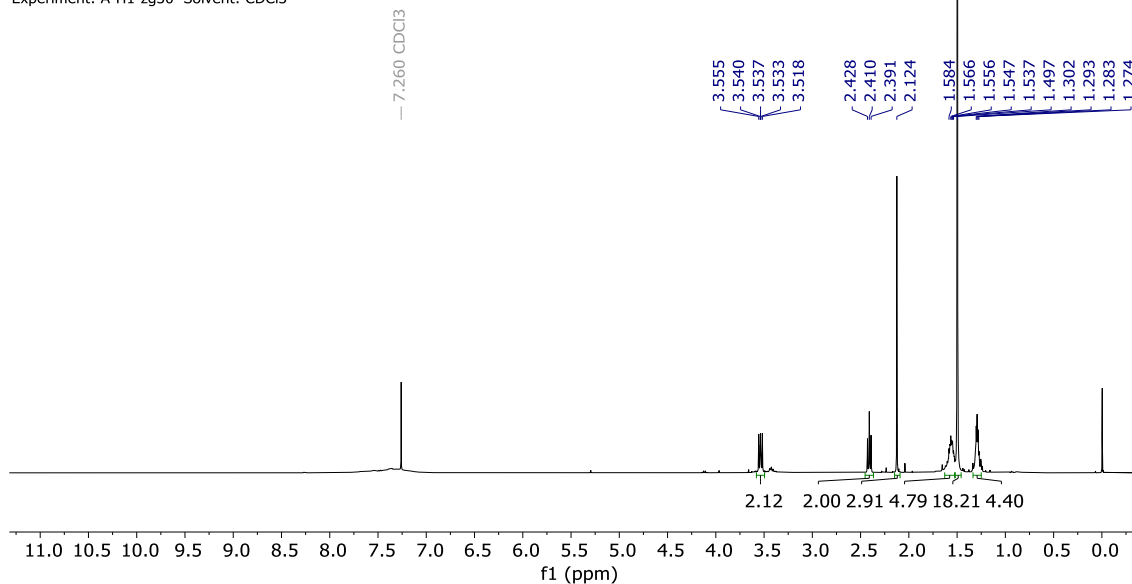
24030186_B400FA_08032024_ASV020colt14t16.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030186
 Usuari: san / Mostra: ASV020colt14t16
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/03/2024 04:02:59 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



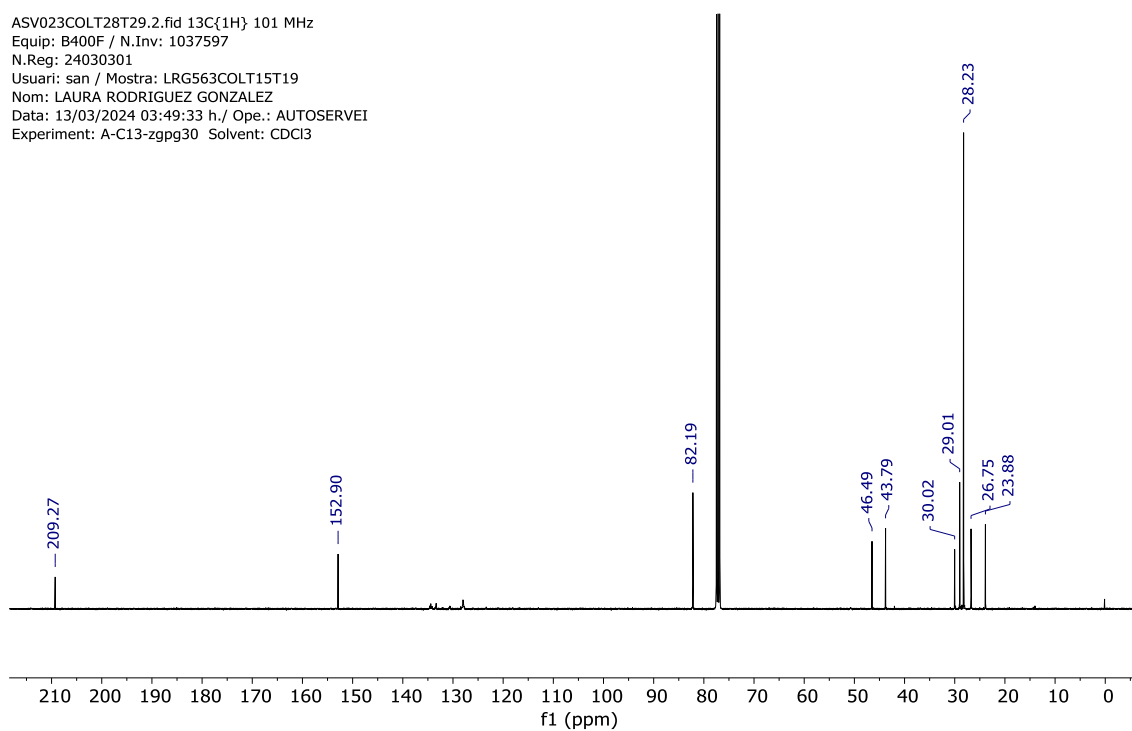
Experimental Section: Chapter 4

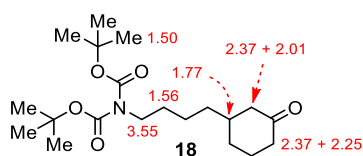


24030306_B400FA_12032024_ASV023-27-28.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030306
 Usuari: san / Mostra: ASV023-27-28
 Nom: AINA SERRA VERT
 Data: 12/03/2024 12:37:41 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

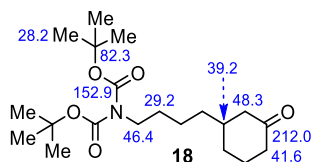
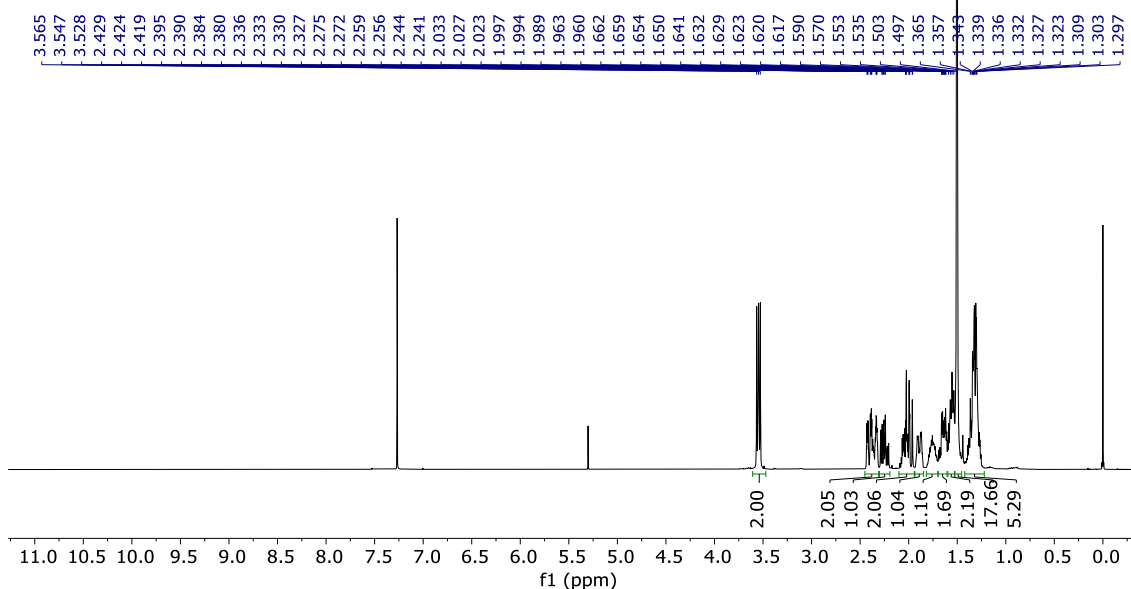


ASV023COLT28T29.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030301
 Usuari: san / Mostra: LRG563COLT15T19
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 13/03/2024 03:49:33 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

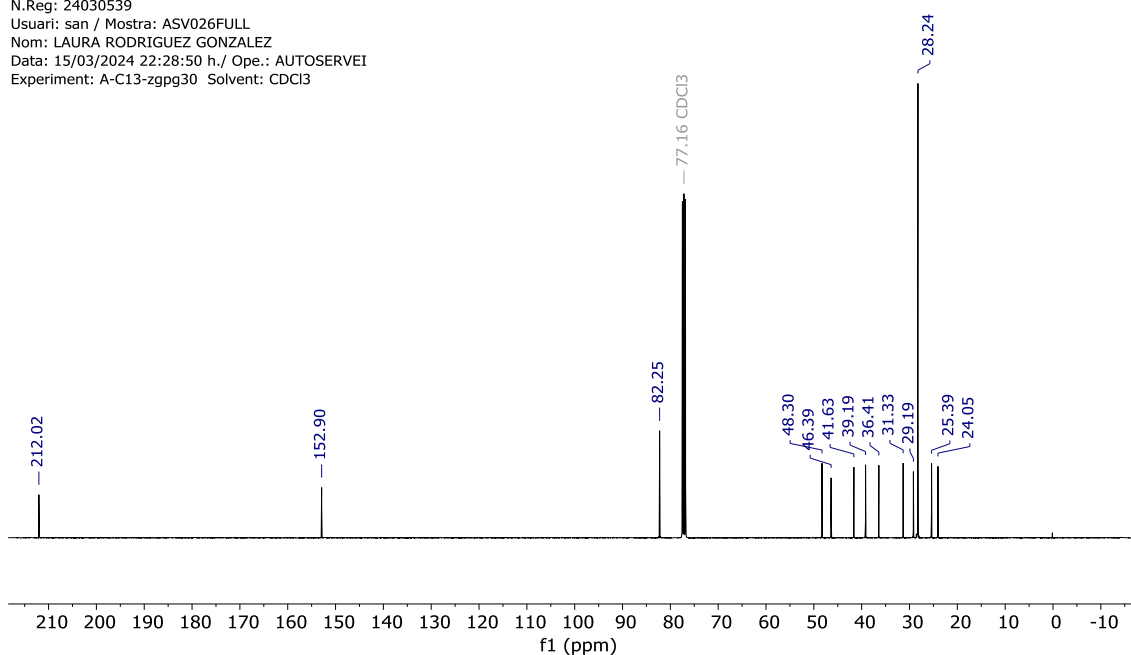




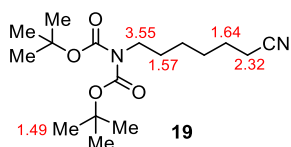
24030532_B400FA_15032024_ASVO26PREPCH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030532
 Usuari: san / Mostra: ASVO26PREPCH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/03/2024 09:59:31 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



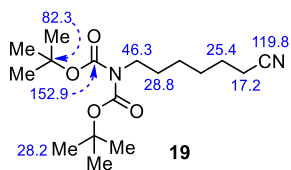
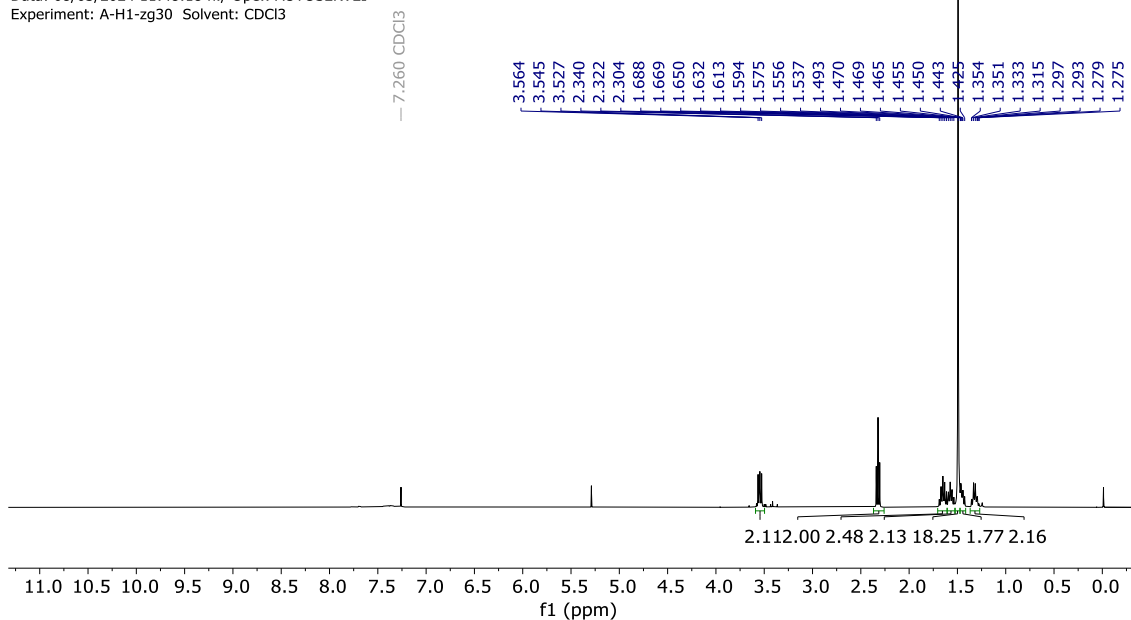
24030539_B400FA_16032024_ASVO26FULL.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030539
 Usuari: san / Mostra: ASVO26FULL
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/03/2024 22:28:50 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



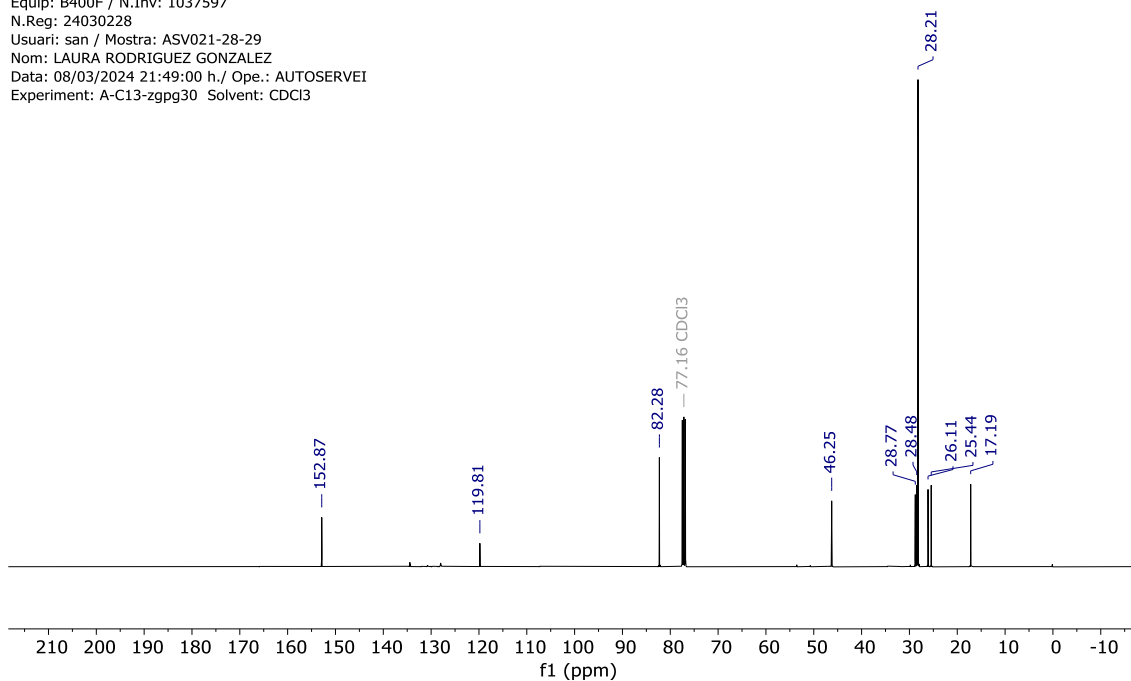
Experimental Section: Chapter 4

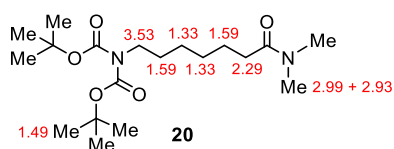


24030228_B400FA_08032024_ASV021-28-29.1.fid ^1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030228
 Usuari: san / Mostra: ASV021-28-29
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/03/2024 11:48:18 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl_3

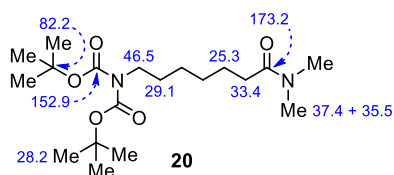
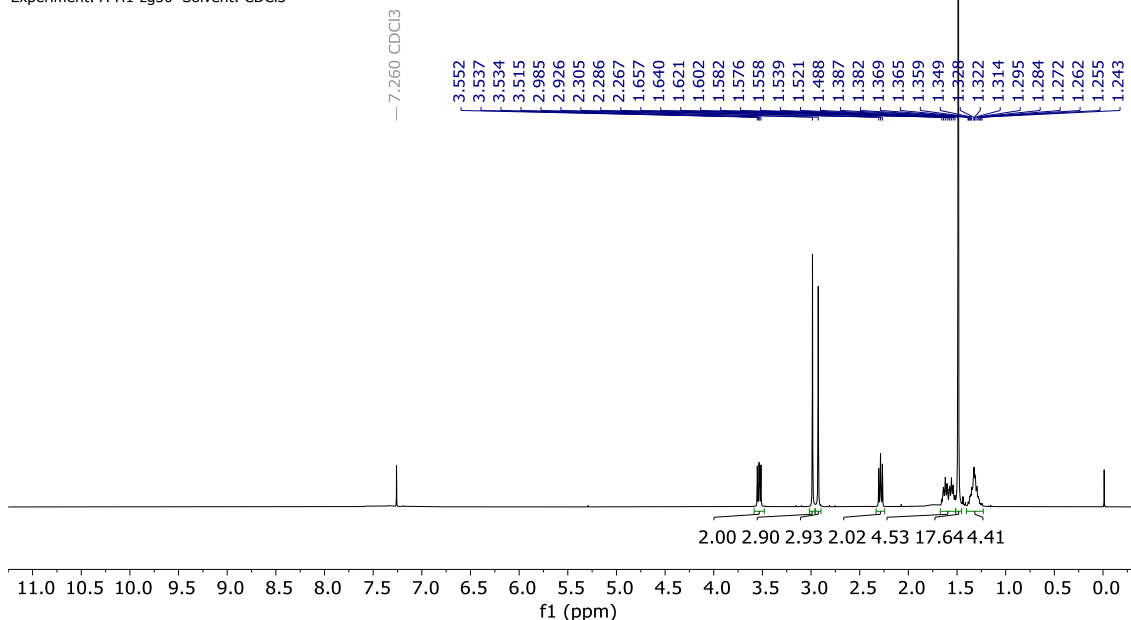


24030228_B400FA_08032024_ASV021-28-29.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030228
 Usuari: san / Mostra: ASV021-28-29
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/03/2024 21:49:00 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl_3

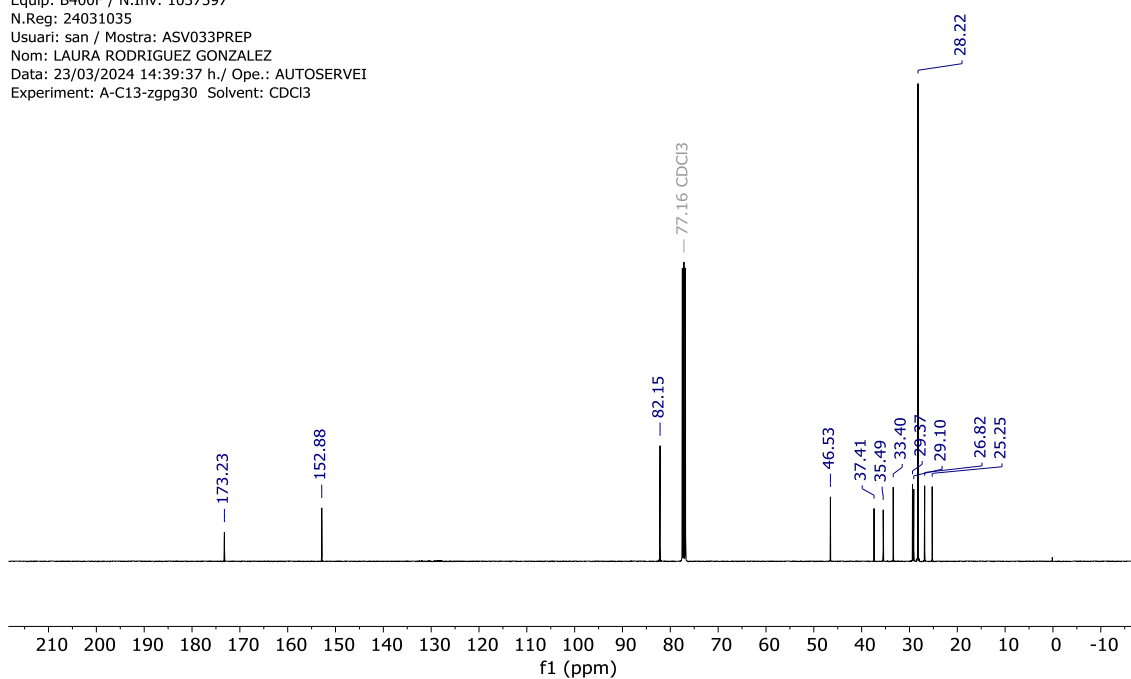


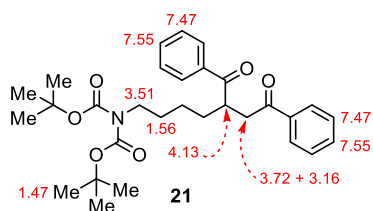


24031035_B400FA_22032024_ASV033PREP.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24031035
Usuari: san / Mostra: ASV033PREP
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 22/03/2024 18:03:28 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3

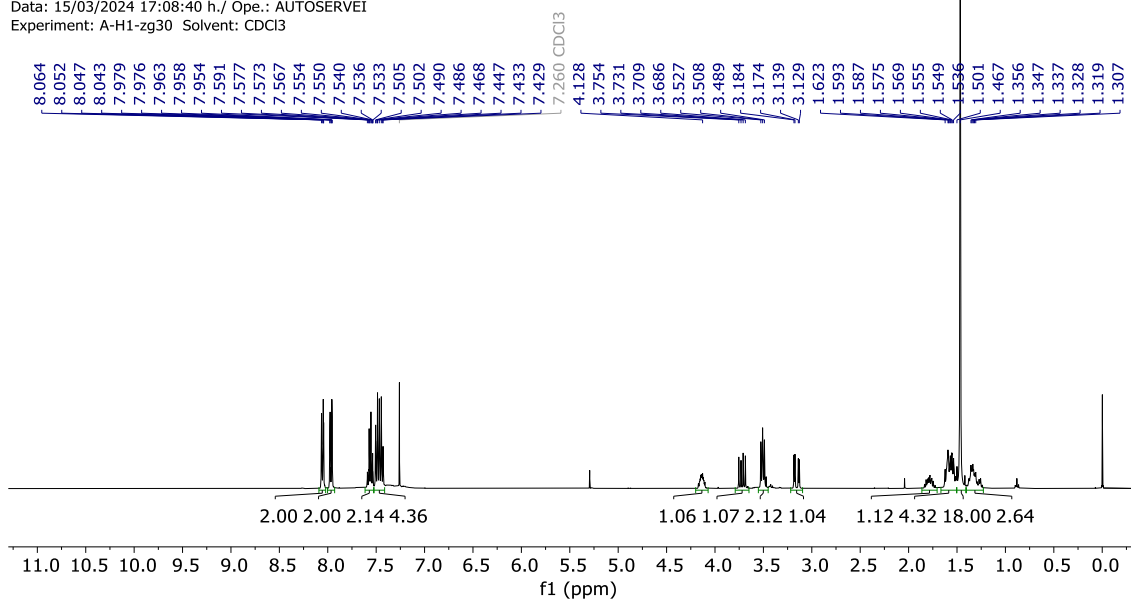


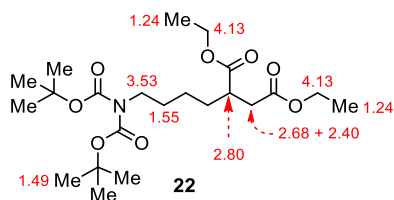
24031035_B400FA_23032024_ASV033PREP.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24031035
Usuari: san / Mostra: ASV033PREP
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 23/03/2024 14:39:37 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl3



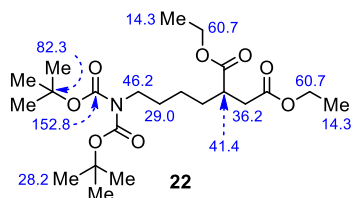
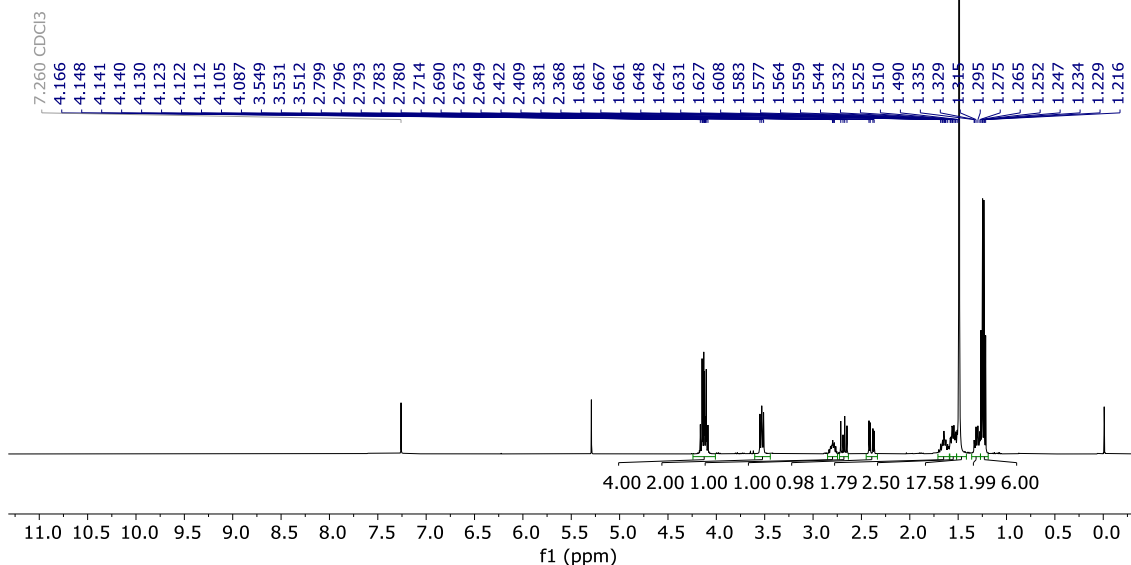


24030576_B400FA_16032024_ASV027T25CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030576
 Usuari: san / Mostra: ASV027T25CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/03/2024 17:08:40 h. / Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

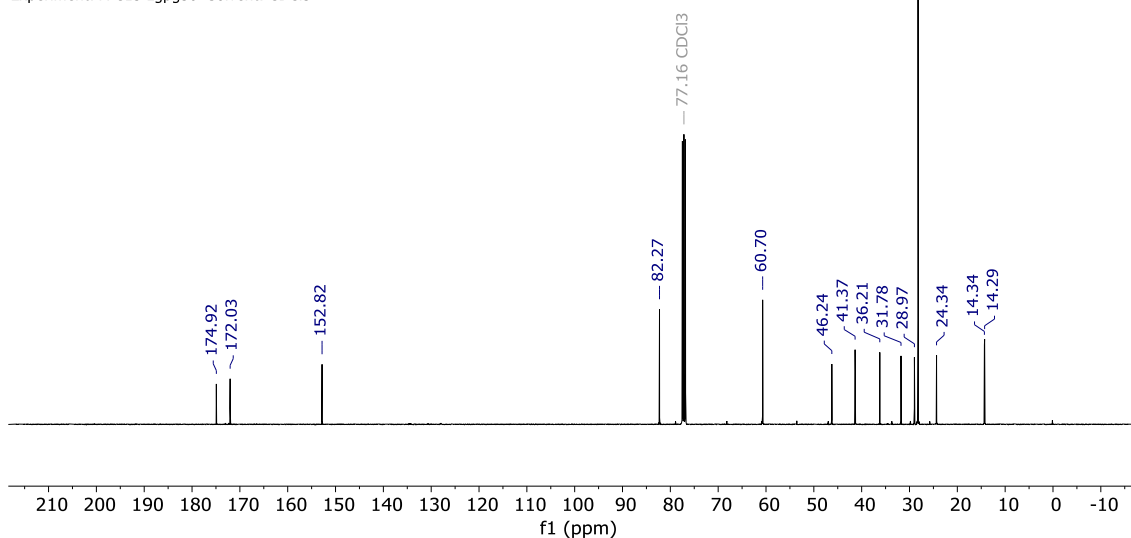




24030464_B400FA_14032024_LRG567COLT29.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030464
 Usuari: san / Mostra: LRG567COLT29
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/03/2024 12:23:46 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



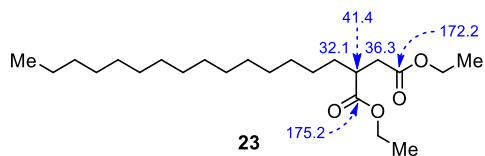
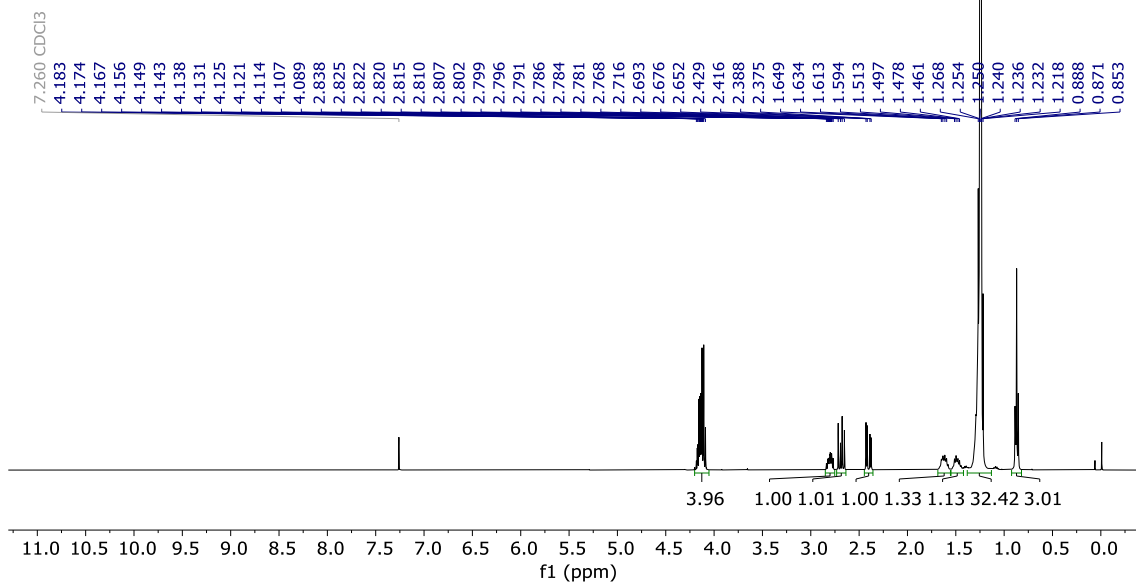
24030464_B400FA_15032024_LRG567COLT29.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24030464
 Usuari: san / Mostra: LRG567COLT29
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 15/03/2024 02:40:21 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



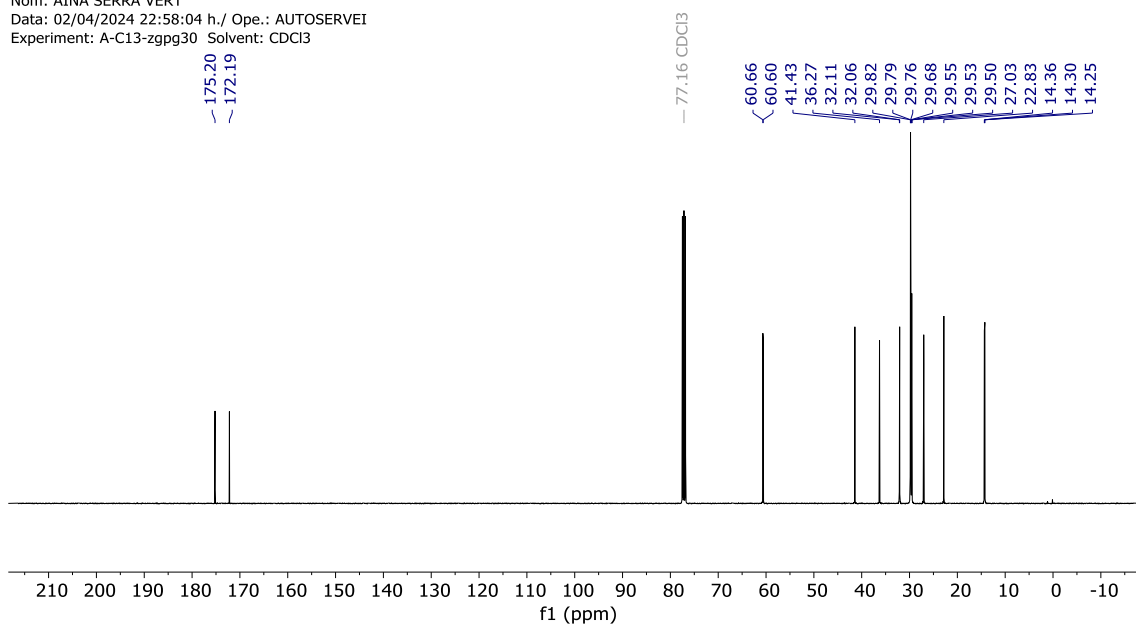
Experimental Section: Chapter 4

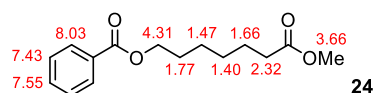


24040027_B400FA_02042024_ASV032-prep.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040027
 Usuari: san / Mostra: ASV032-prep
 Nom: AINA SERRA VERT
 Data: 02/04/2024 15:08:09 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



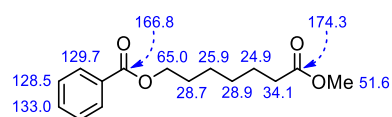
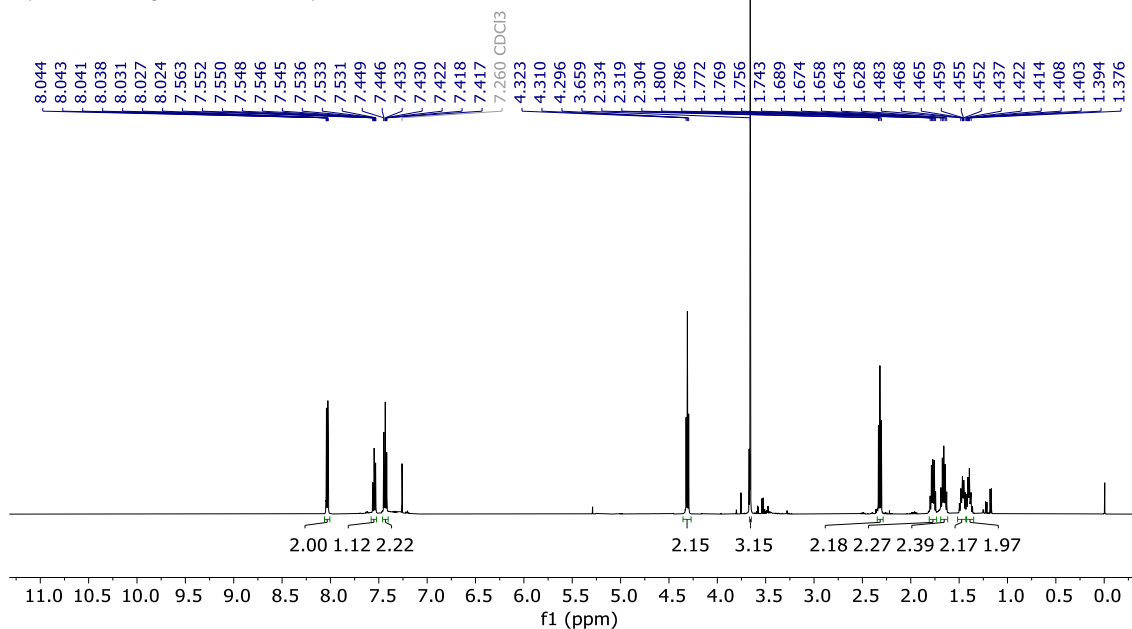
24040027_B400FA_02042024_ASV032-prep.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040027
 Usuari: san / Mostra: ASV032-prep
 Nom: AINA SERRA VERT
 Data: 02/04/2024 22:58:04 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3





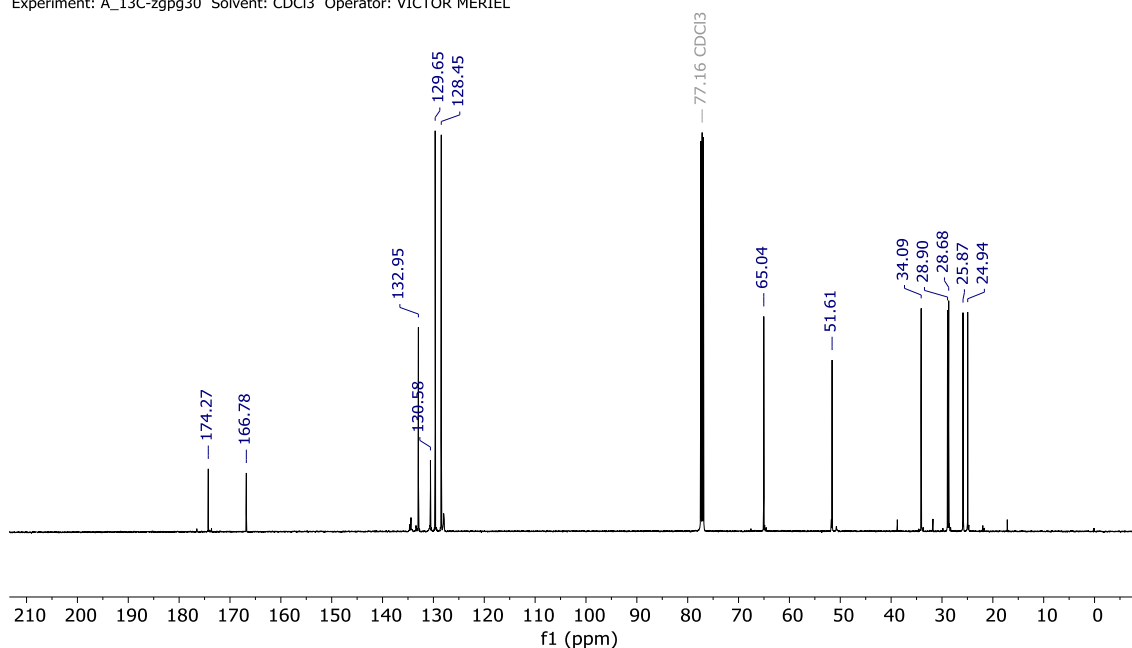
24

5924-2024_B500QA_14062024_ASV062CH.10.fid 1H 500 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 5924/2024
 Usuari: san / Mostra: ASV062CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/06/2024 18:36:45 h./ Ope.: servei Unitat RMN
 Experiment: A_1H-zg30 Solvent: CDCl₃ Operator: VICTOR MERIEL

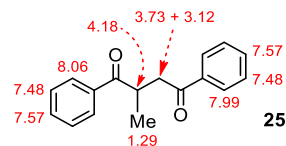


24

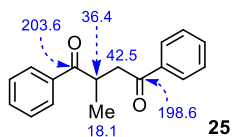
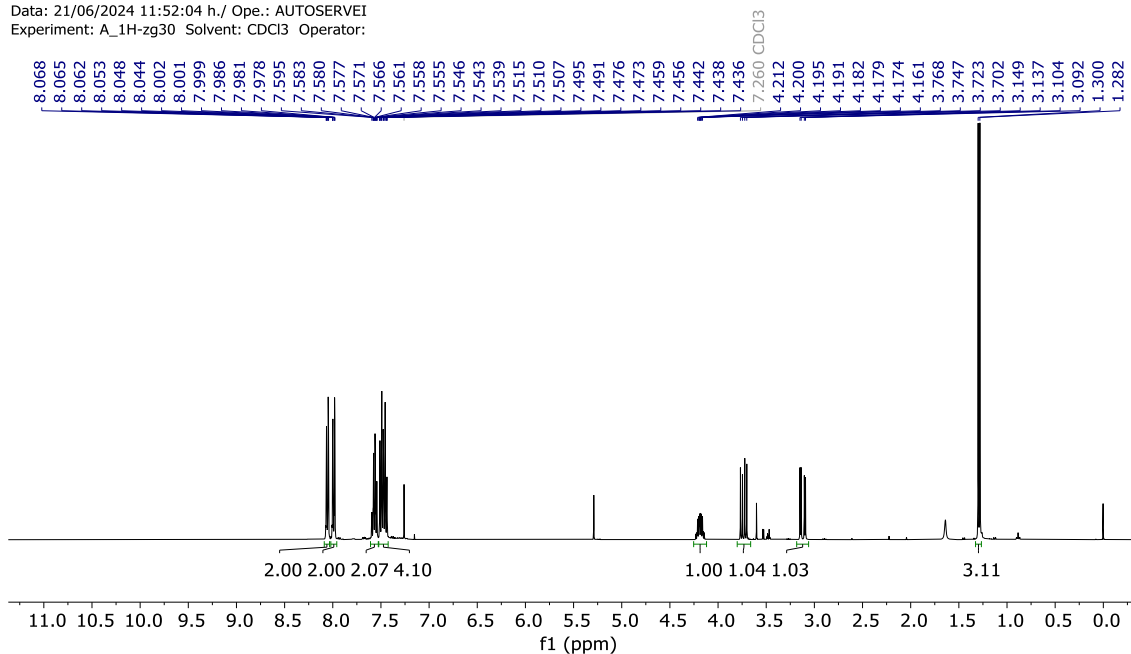
5924-2024_B500QA_14062024_ASV062CH.11.fid 13C{1H} 126 MHz
 Equip: B500Q / N.Inv: 1028917
 N.Reg: 5924/2024
 Usuari: san / Mostra: ASV062CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 14/06/2024 18:36:45 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl₃ Operator: VICTOR MERIEL



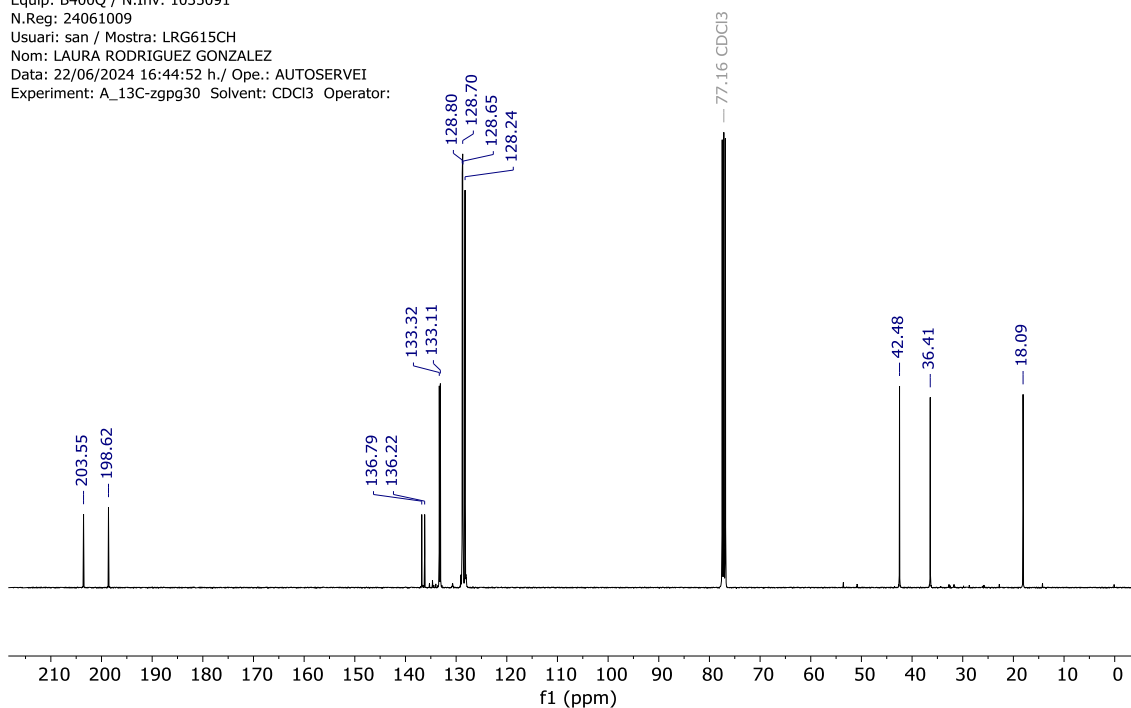
Experimental Section: Chapter 4

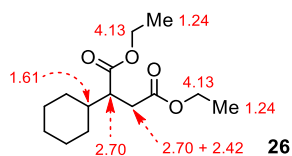


auto-21062024-113955.1.fid 1H 400 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 24061009
 Usuari: san / Mostra: LRG615CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 21/06/2024 11:52:04 h./ Ope.: AUTOSERVEI
 Experiment: A_1H-zg30 Solvent: CDCl3 Operator:

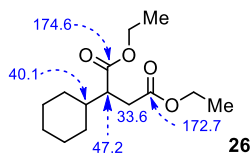
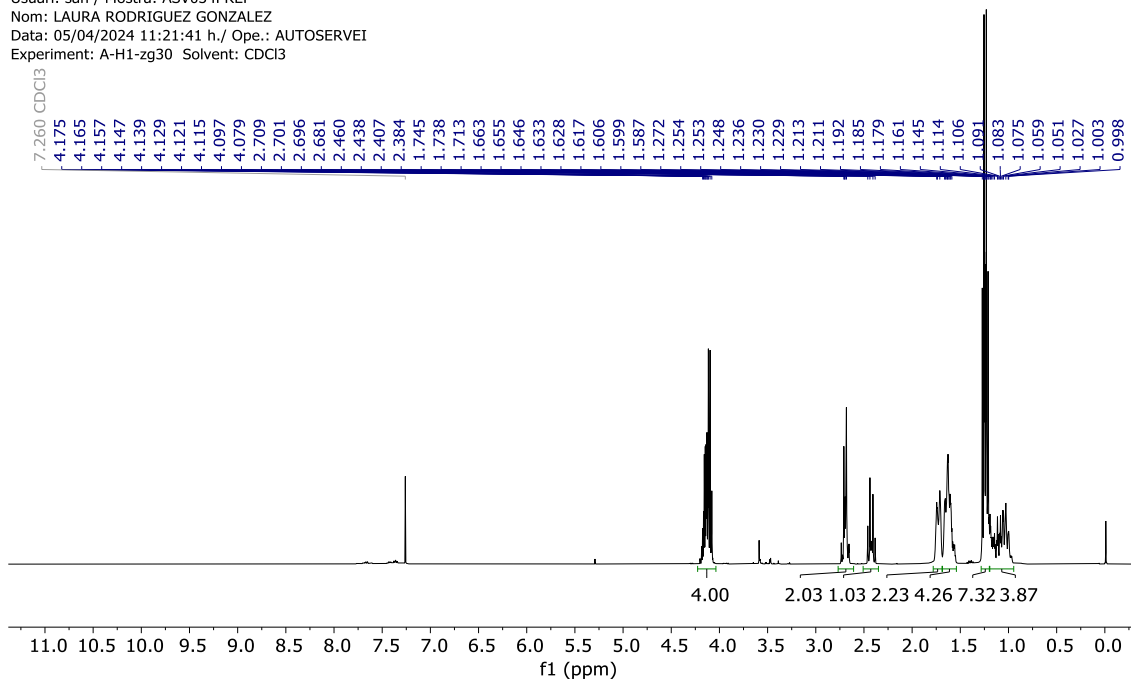


auto-21062024-113955.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 24061009
 Usuari: san / Mostra: LRG615CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 22/06/2024 16:44:52 h./ Ope.: AUTOSERVEI
 Experiment: A_13C-zgpg30 Solvent: CDCl3 Operator:

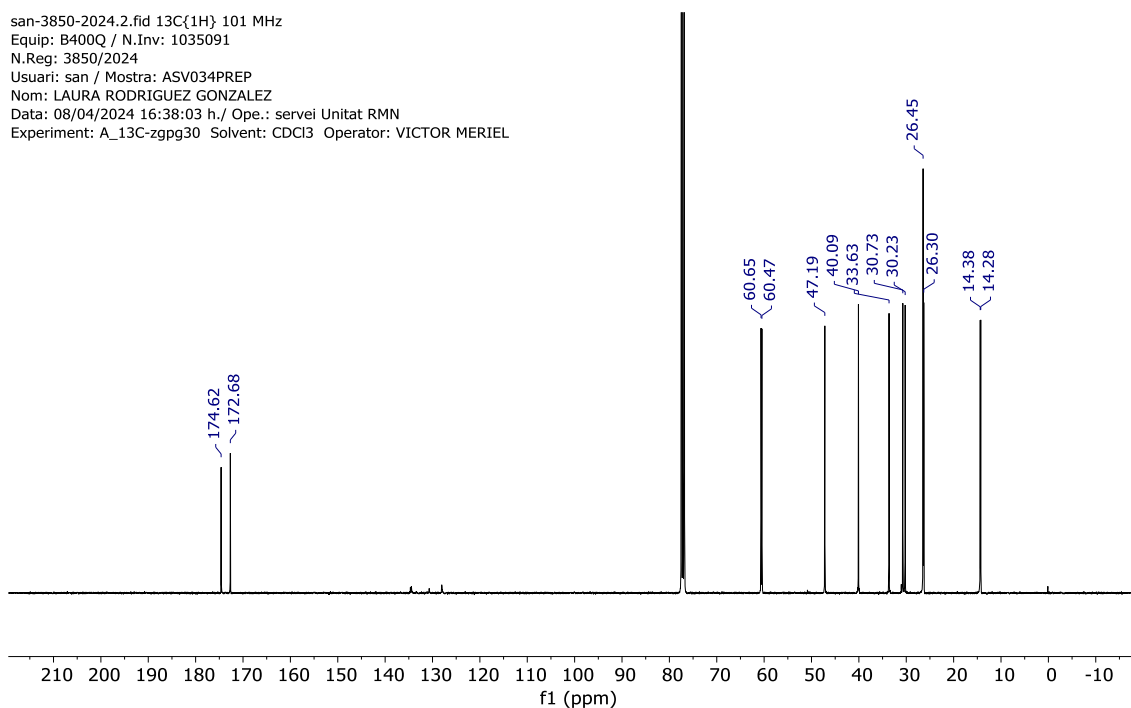


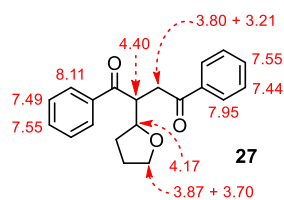


24040210_B400FA_05042024_ASVO34PREP.1.fid ^1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040210
 Usuari: san / Mostra: ASVO34PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 05/04/2024 11:21:41 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl_3

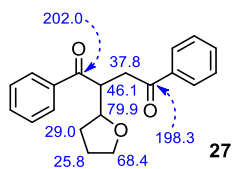
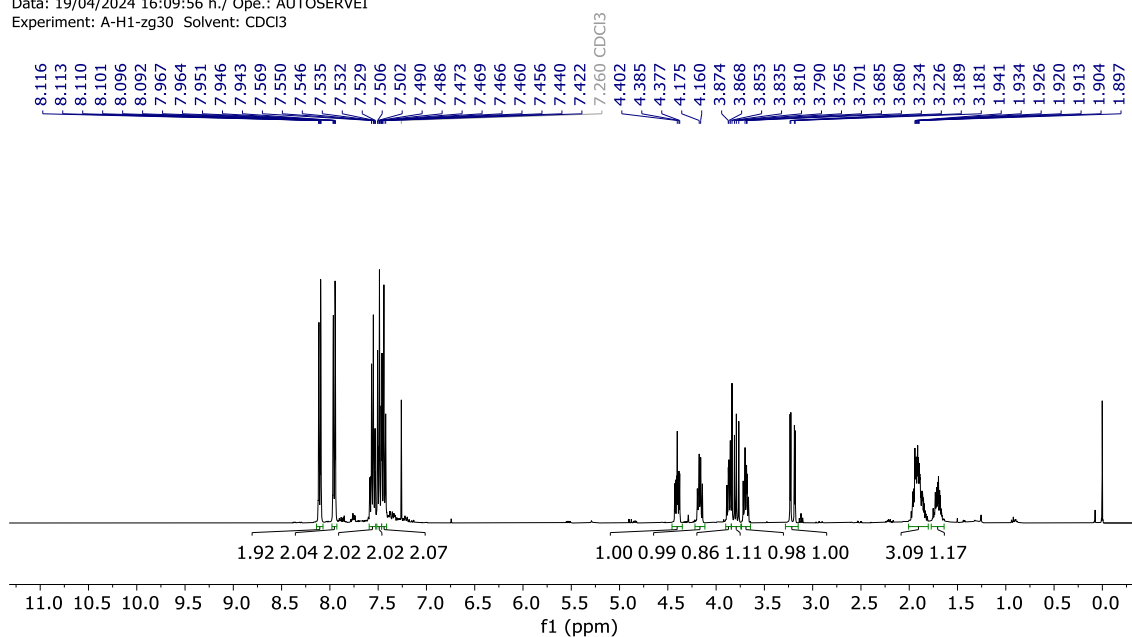


san-3850-2024.2.fid $^{13}\text{C}\{^1\text{H}\}$ 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 3850/2024
 Usuari: san / Mostra: ASVO34PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/04/2024 16:38:03 h./ Ope.: servei Unitat RMN
 Experiment: A_13C-zgpg30 Solvent: CDCl_3 Operator: VICTOR MERIEL

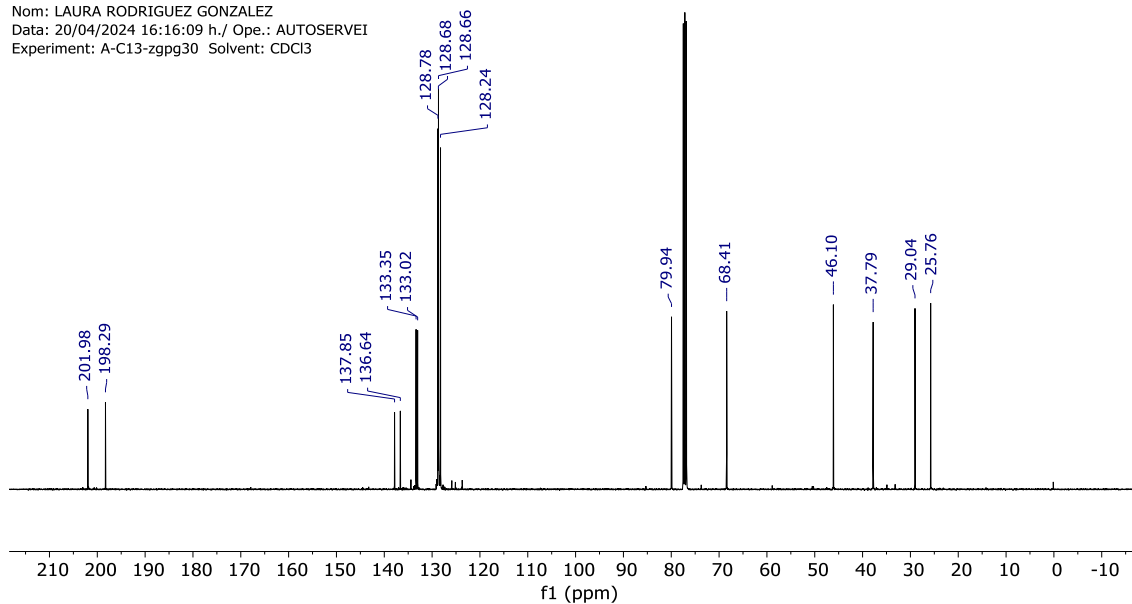


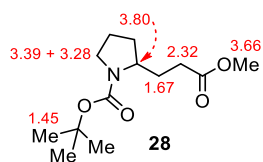


24040898_B400FA_19042024_ASVO44PREPMID.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040898
 Usuari: san / Mostra: ASVO44PREPMID
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/04/2024 16:09:56 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

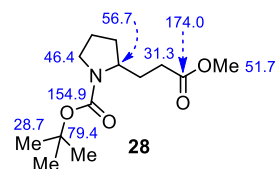
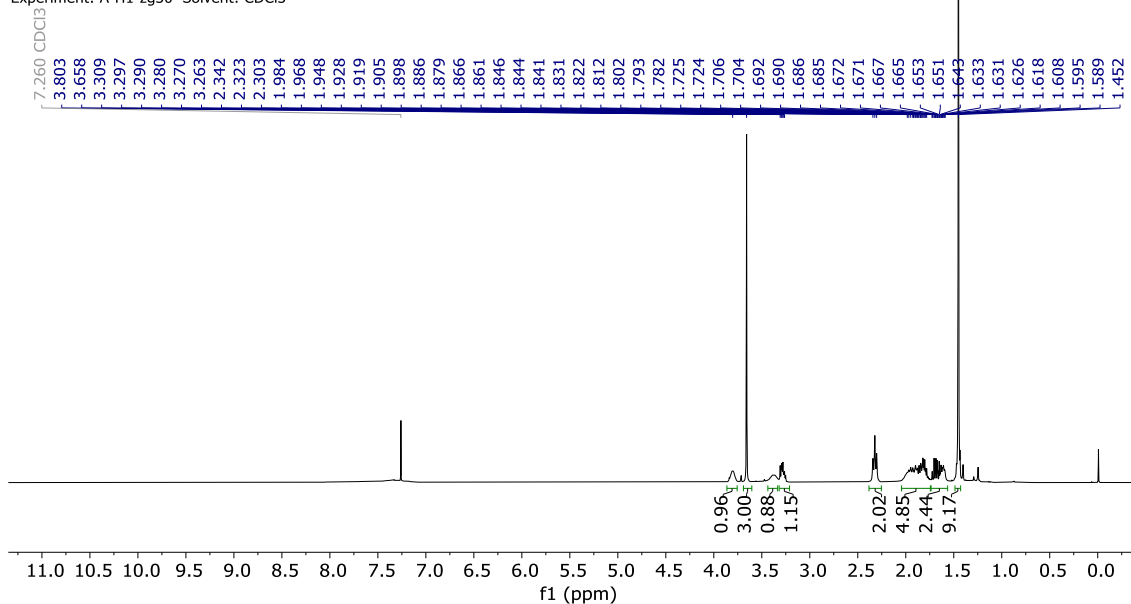


24040898_B400FA_20042024_ASVO44PREPMID.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040898
 Usuari: san / Mostra: ASVO44PREPMID
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 20/04/2024 16:16:09 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

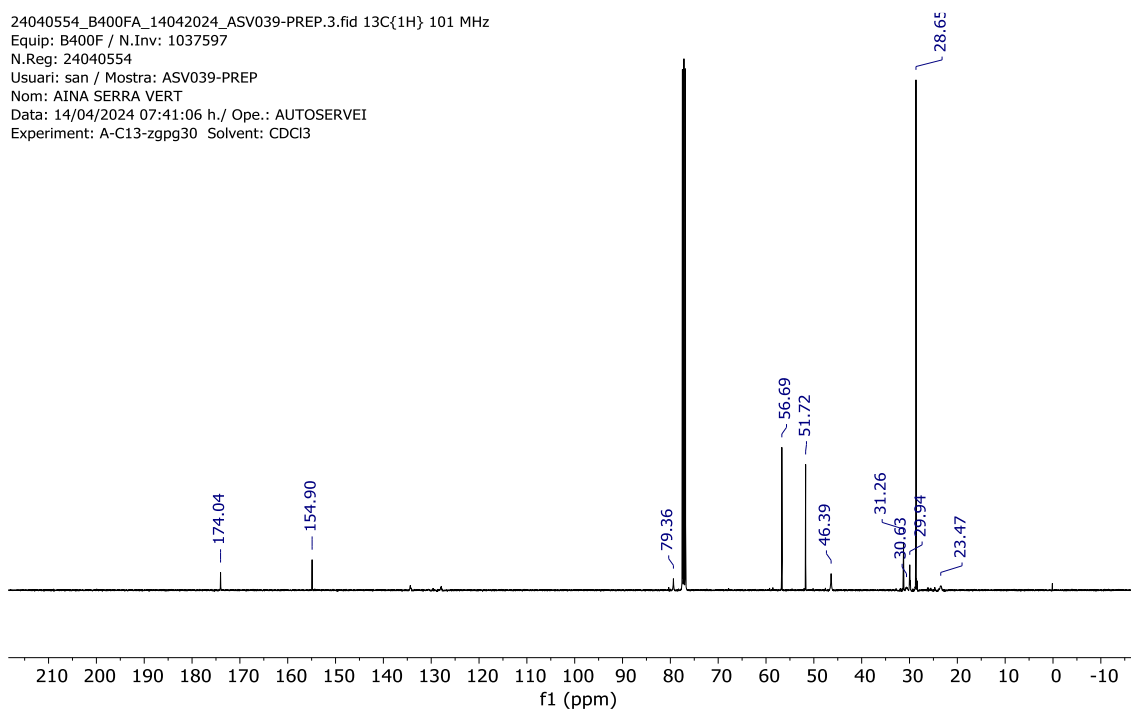




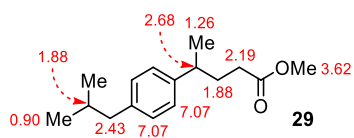
24040554_B400FA_12042024_ASV039-PREP.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24040554
Usuari: san / Mostra: ASV039-PREP
Nom: AINA SERRA VERT
Data: 12/04/2024 11:17:58 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl₃



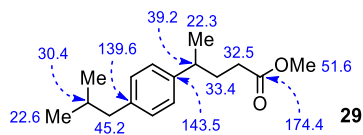
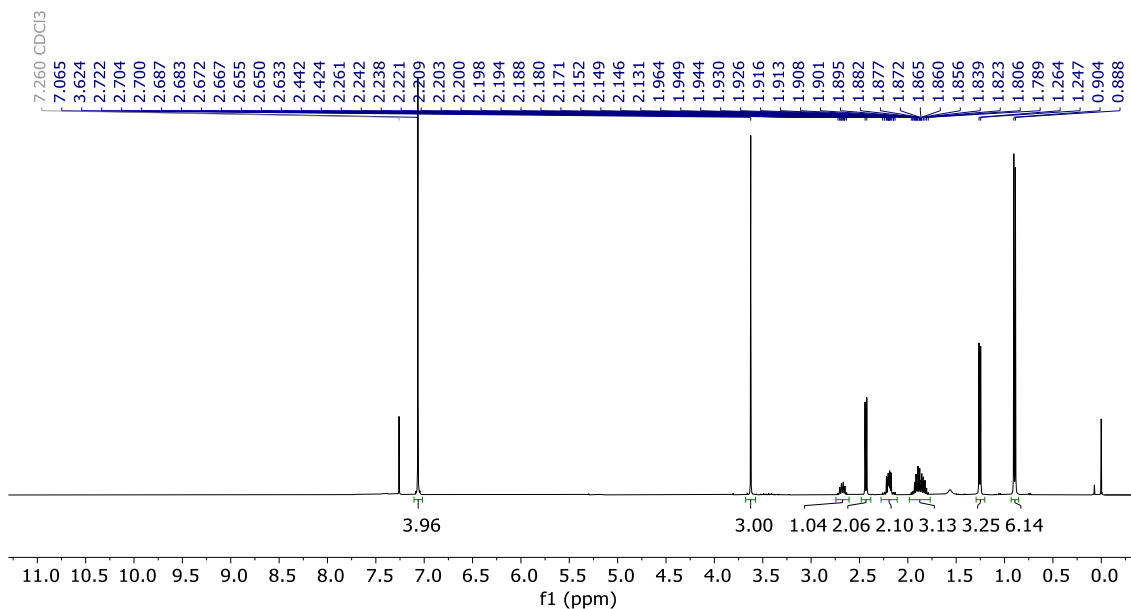
24040554_B400FA_14042024_ASV039-PREP.3.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24040554
Usuari: san / Mostra: ASV039-PREP
Nom: AINA SERRA VERT
Data: 14/04/2024 07:41:06 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl₃



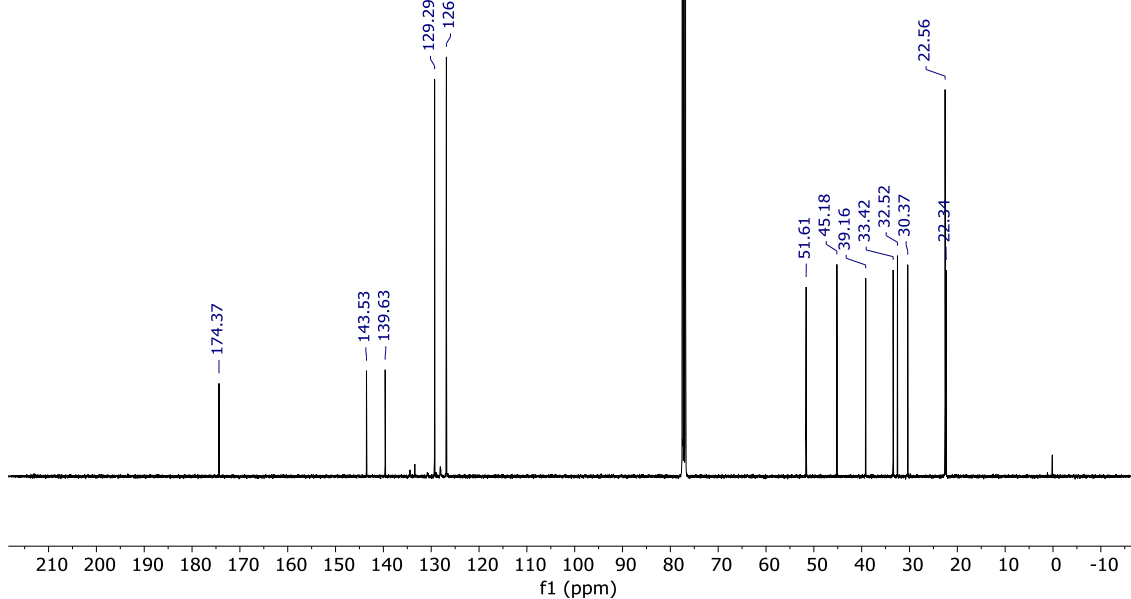
Experimental Section: Chapter 4

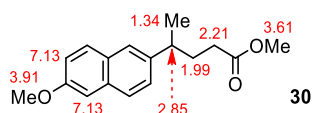


24050321_B400FA_09052024_ASV055-PREP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050321
 Usuari: san / Mostra: ASV055-PREP
 Nom: AINA SERRA VERT
 Data: 09/05/2024 13:12:17 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

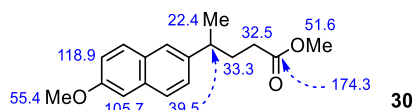
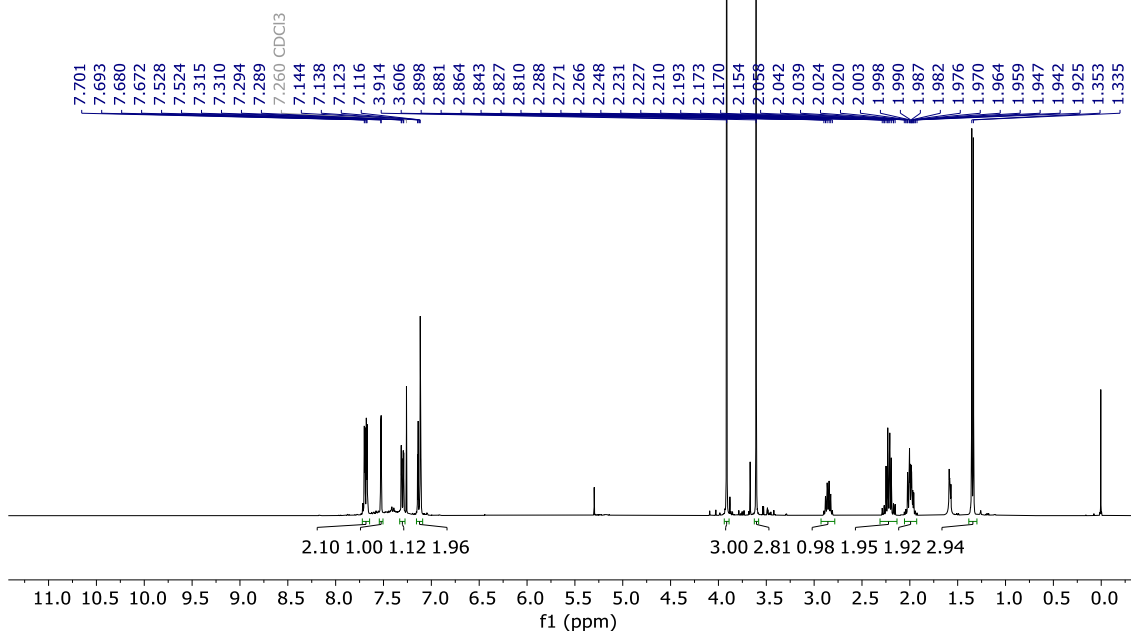


24050321_B400FA_09052024_ASV055-PREP.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050321
 Usuari: san / Mostra: ASV055-PREP
 Nom: AINA SERRA VERT
 Data: 09/05/2024 21:58:25 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

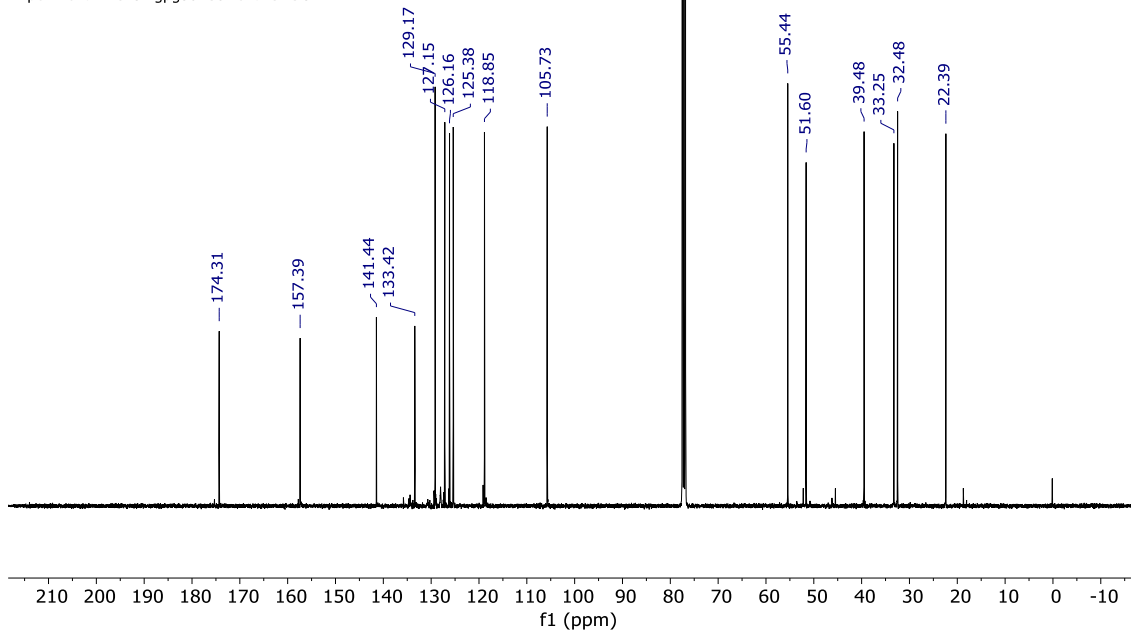


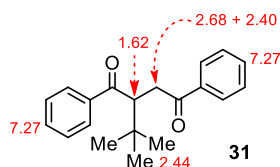


24041304_B400FA_30042024_ASV051-17-19.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24041304
Usuari: san / Mostra: ASV051-17-19
Nom: AINA SERRA VERT
Data: 30/04/2024 13:35:23 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl3

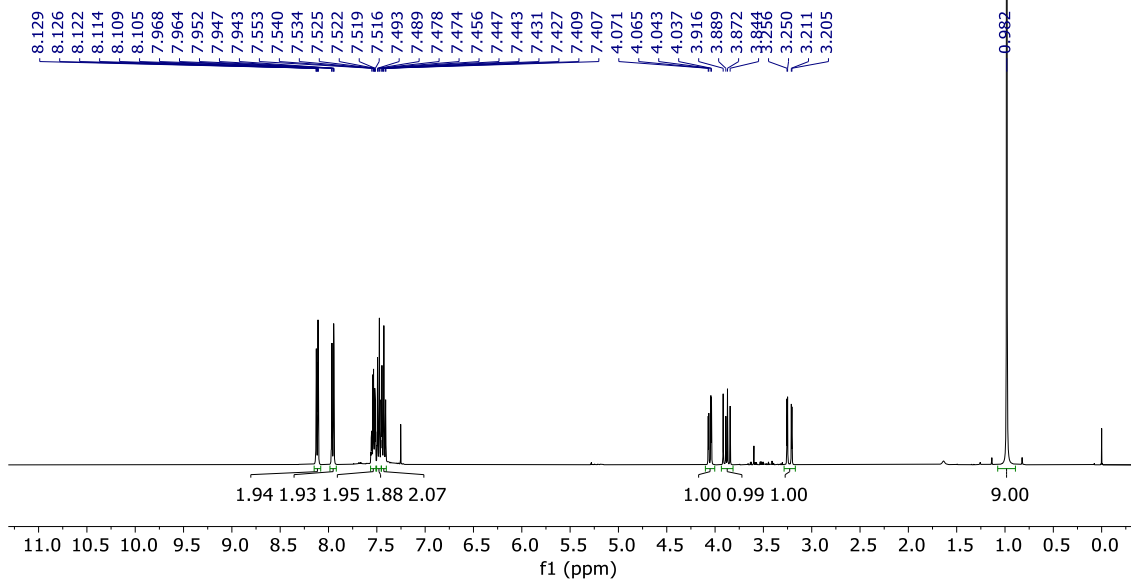


24041311_B400FA_01052024_ASV051-17-19-BO.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24041311
Usuari: san / Mostra: ASV051-17-19-BO
Nom: AINA SERRA VERT
Data: 30/04/2024 21:58:08 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zpgp30 Solvent: CDCl3

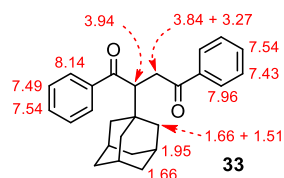




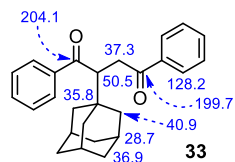
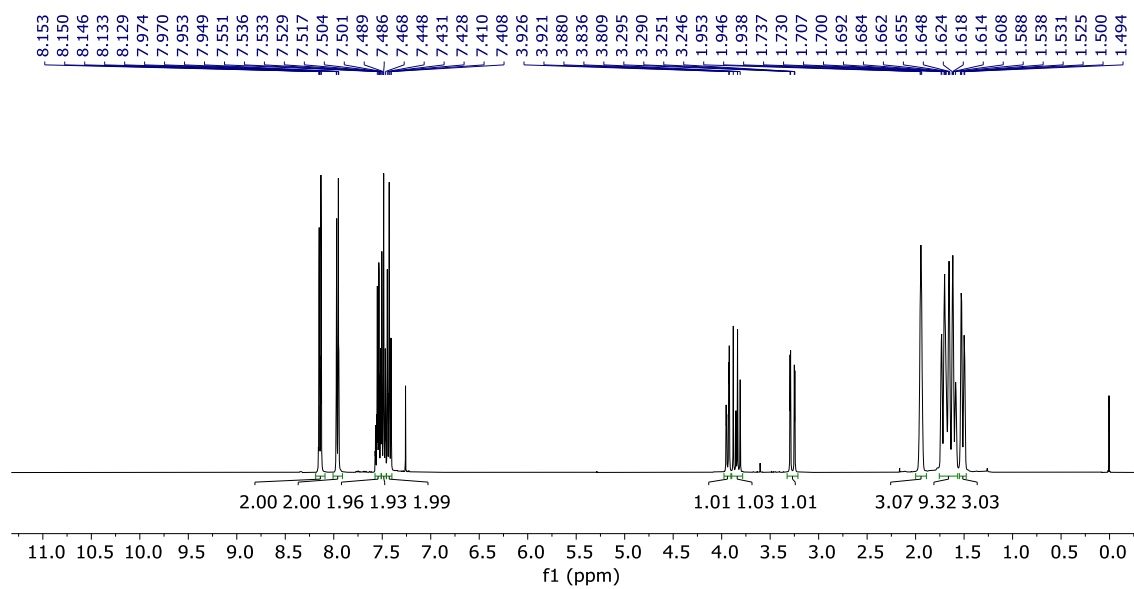
24040432_B400FA_11042024_LRG579CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040432
 Usuari: san / Mostra: LRG579CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/04/2024 15:09:50 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



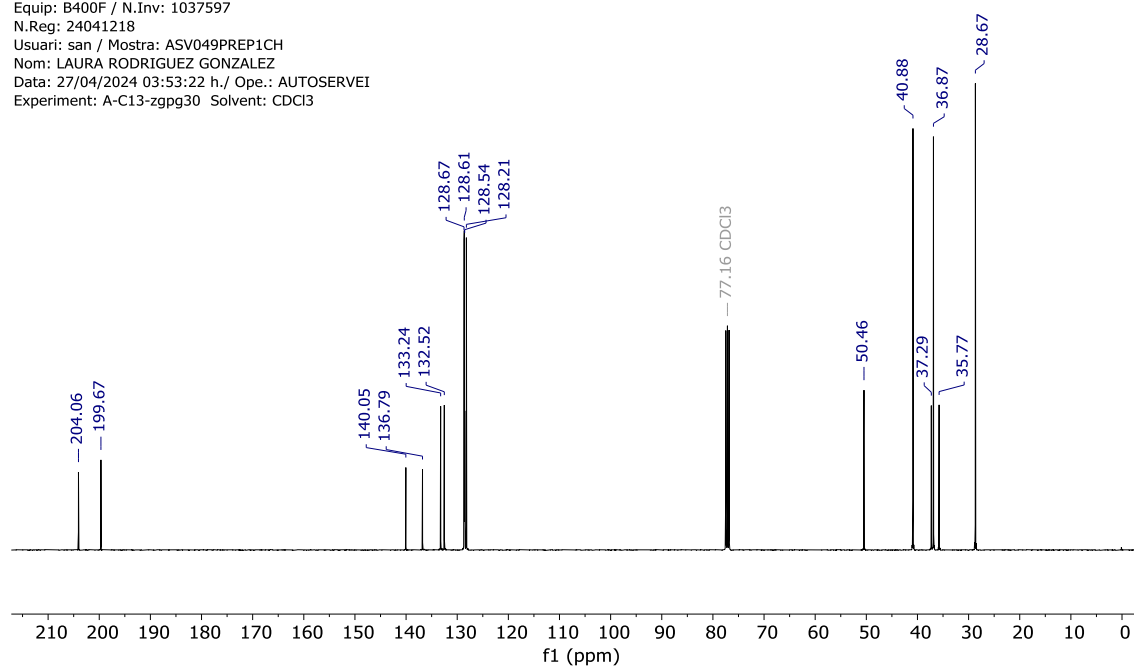
Experimental Section: Chapter 4

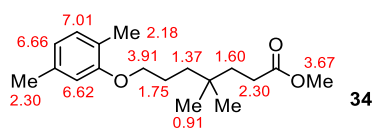


24041200_B400FA_26042024_ASV049-PREP-1.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24041200
 Usuari: san / Mostra: ASV049-PREP-1
 Norm: AINA SERRA VERT
 Data: 26/04/2024 13:25:03 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

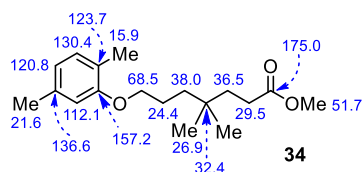
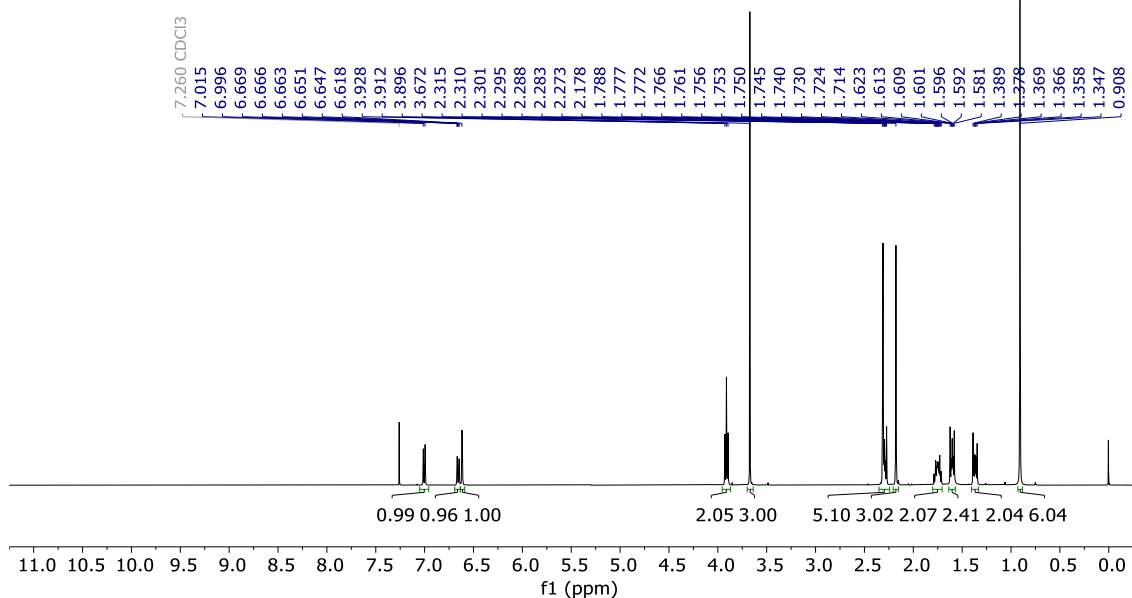


24041218_B400FA_27042024_ASV049PREP1CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24041218
 Usuari: san / Mostra: ASV049PREP1CH
 Norm: LAURA RODRIGUEZ GONZALEZ
 Data: 27/04/2024 03:53:22 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

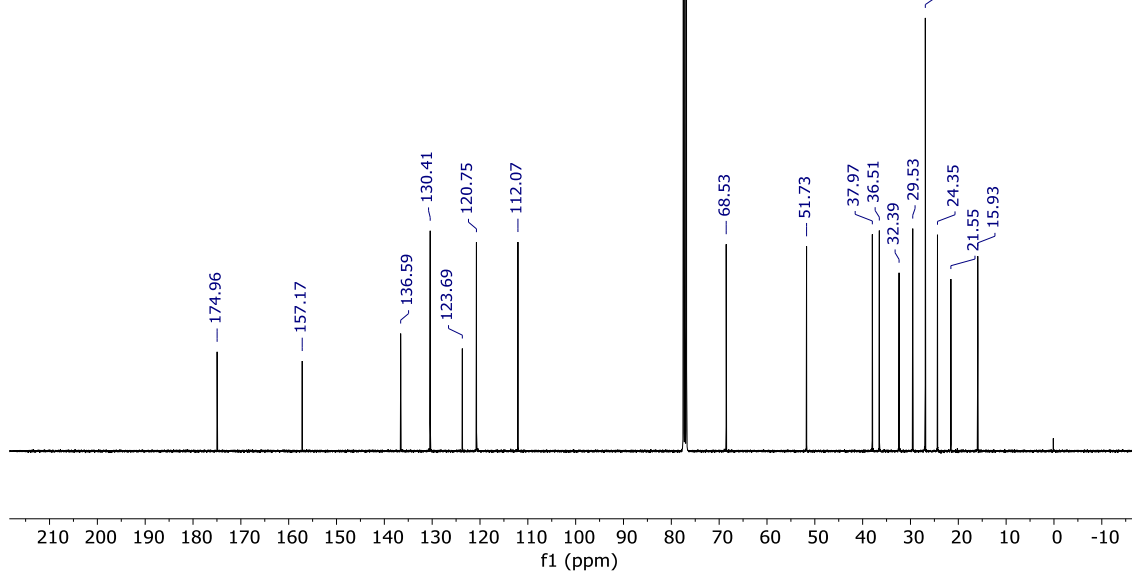




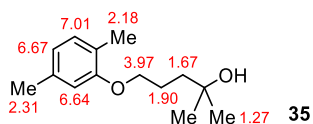
24050271_B400FA_08052024_ASV053-PREP1.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050271
 Usuari: san / Mostra: ASV053-PREP1
 Nom: AINA SERRA VERT
 Data: 08/05/2024 15:33:28 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



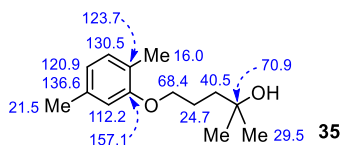
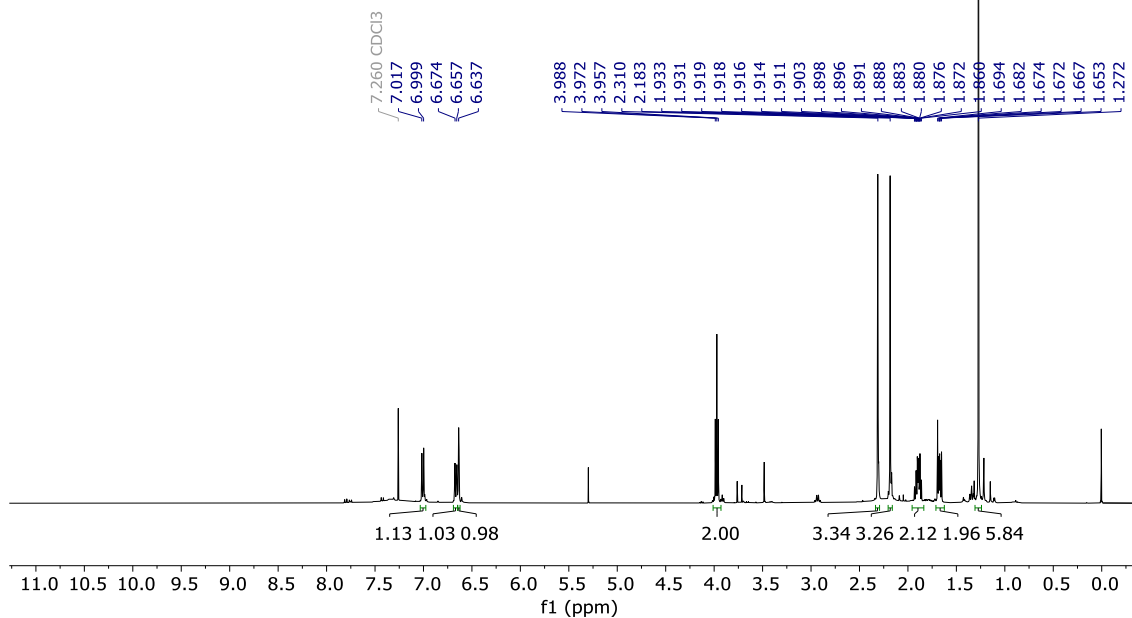
24050271_B400FA_08052024_ASV053-PREP1.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050271
 Usuari: san / Mostra: ASV053-PREP1
 Nom: AINA SERRA VERT
 Data: 08/05/2024 21:08:53 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



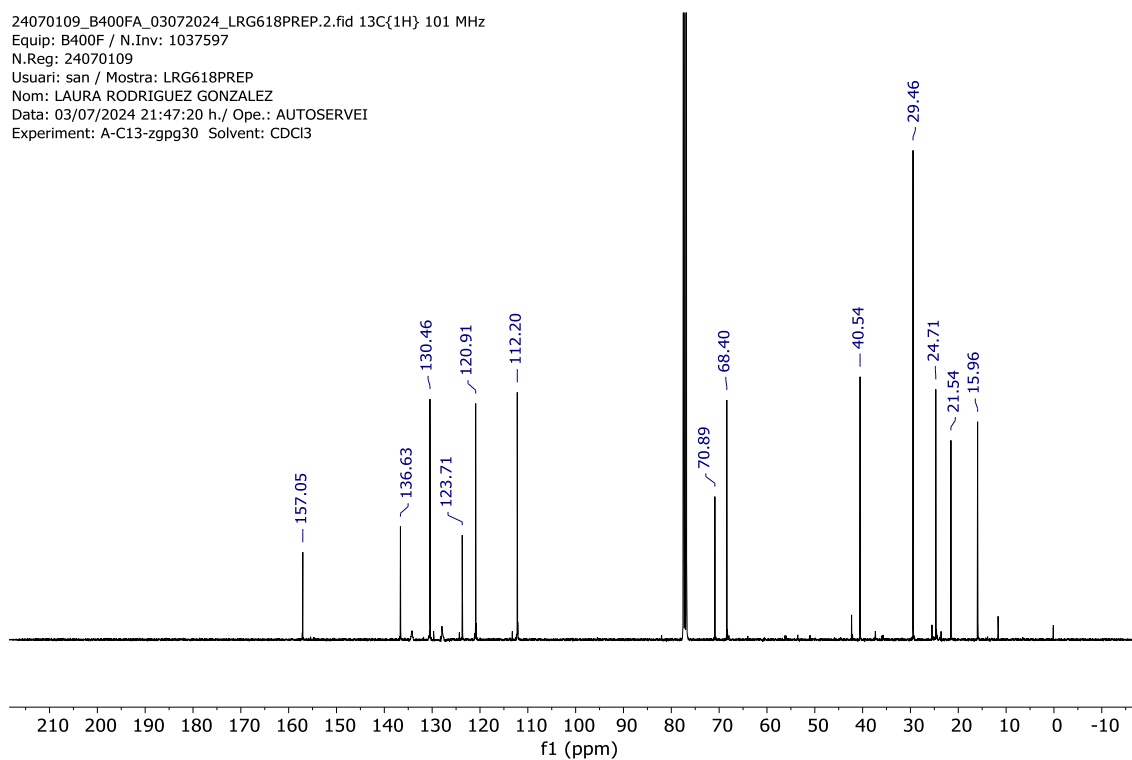
Experimental Section: Chapter 4

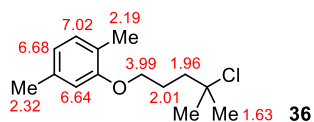


24070110_B400FA_03072024_LRG618PREPTOP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24070110
 Usuari: san / Mostra: LRG618PREPTOP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/07/2024 09:36:38 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

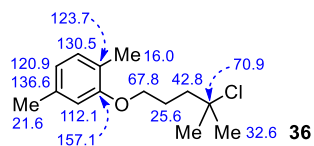
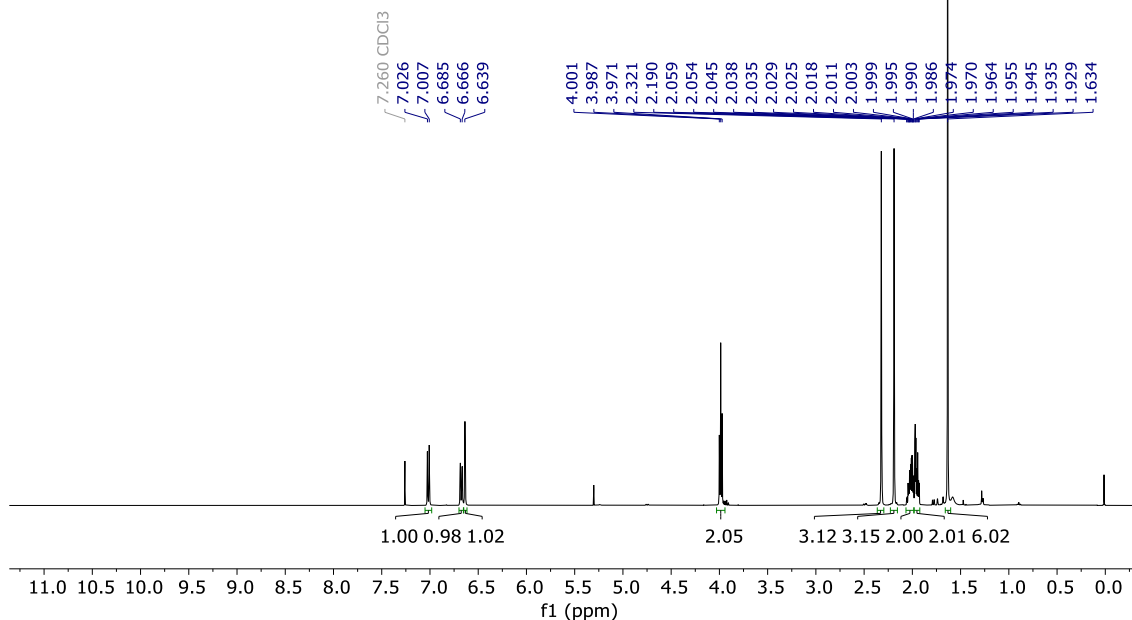


24070109_B400FA_03072024_LRG618PREP.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24070109
 Usuari: san / Mostra: LRG618PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/07/2024 21:47:20 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

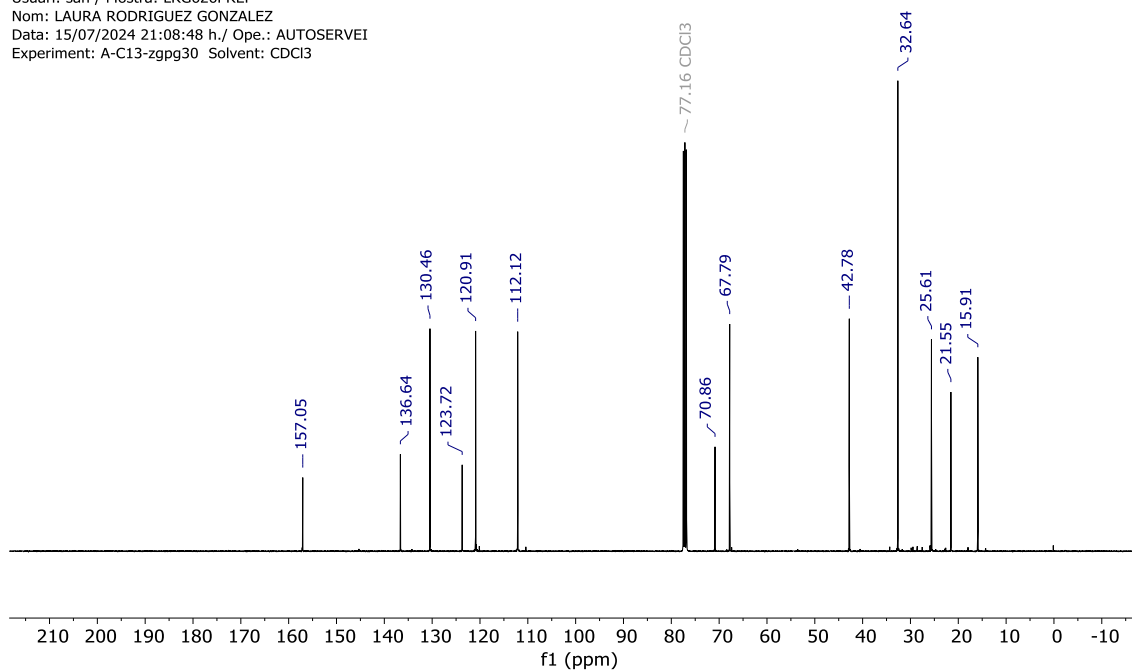


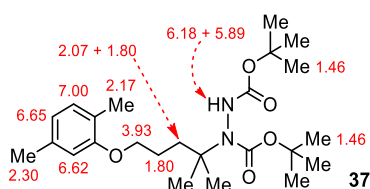


24070614_B400FA_15072024_LRG626PREP.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24070614
Usuari: san / Mostra: LRG626PREP
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 15/07/2024 13:07:39 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl₃



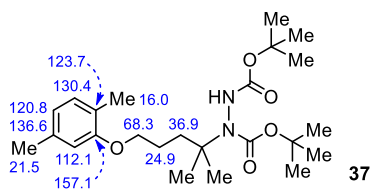
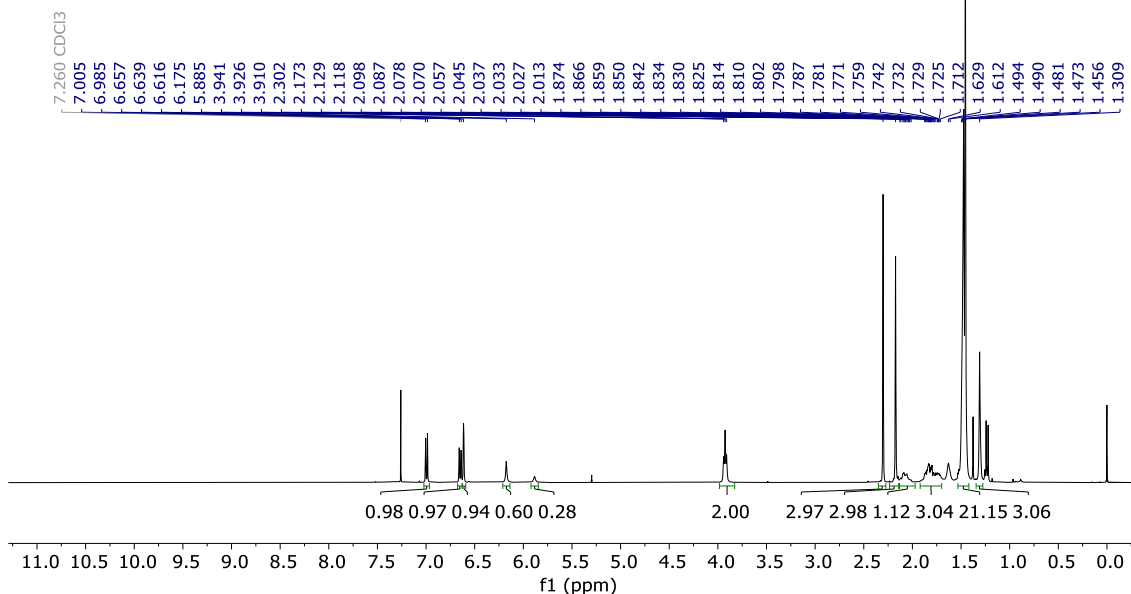
24070614_B400FA_15072024_LRG626PREP.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24070614
Usuari: san / Mostra: LRG626PREP
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 15/07/2024 21:08:48 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl₃



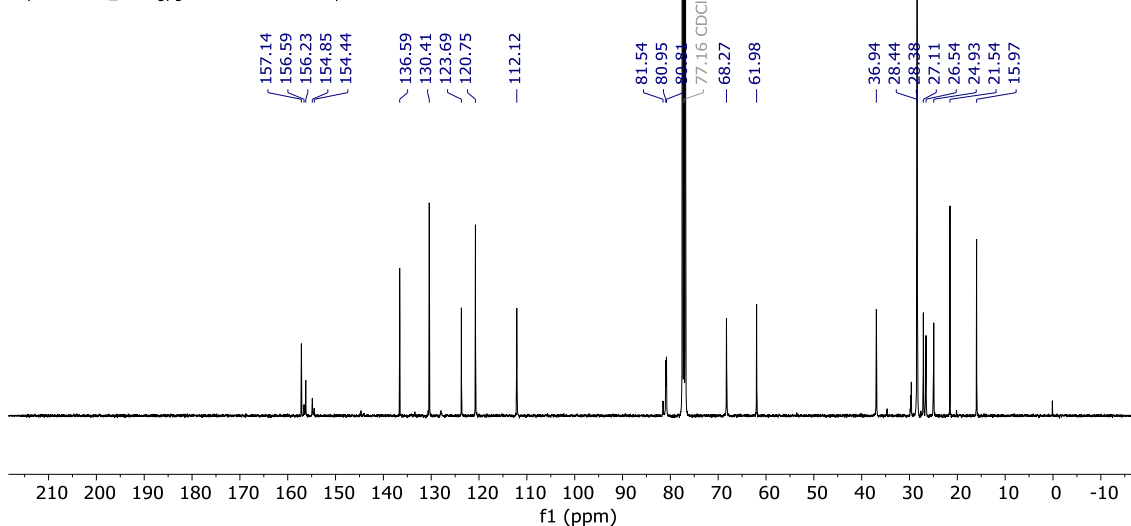


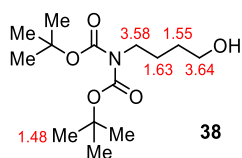
37 The product was isolated as a mixture of rotamers

24070286_B400FA_05072024_LRG621PREPTOP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24070286
 Usuari: san / Mostra: LRG621PREPTOP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 05/07/2024 13:28:34 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

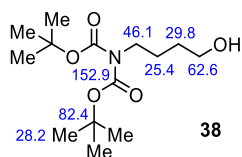
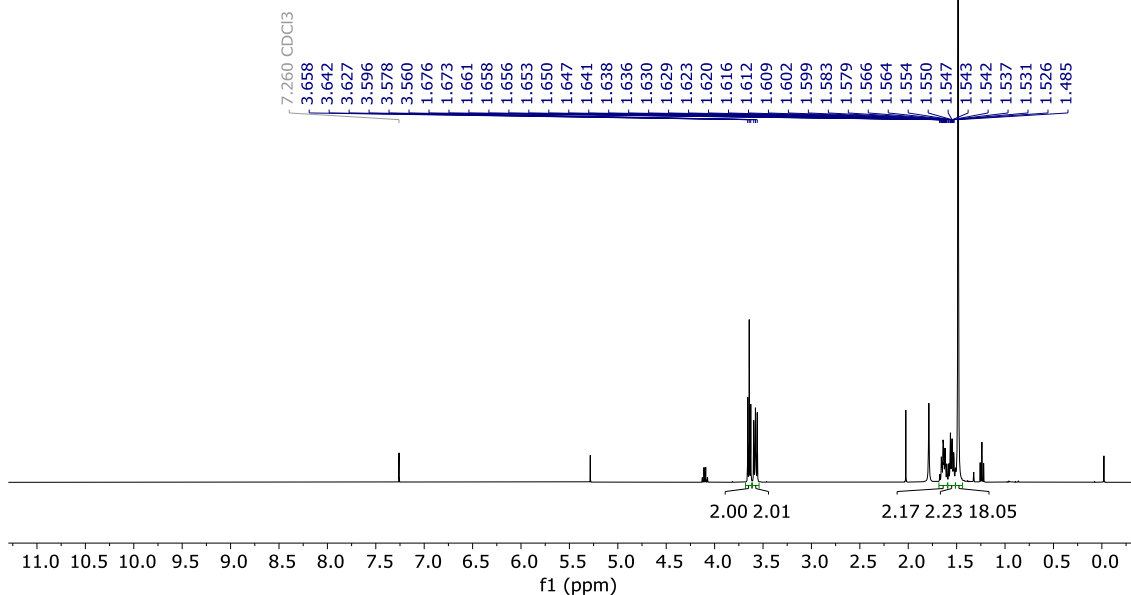


auto-05072024-141116.2.fid 13C{1H} 101 MHz
 Equip: B400Q / N.Inv: 1035091
 N.Reg: 24070272
 Usuari: san / Mostra: LRG621PREPTOPCH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 06/07/2024 11:19:03 h./ Ope.: AUTOSERVEI
 Experiment: A_13C-zpgg30 Solvent: CDCl3 Operator:

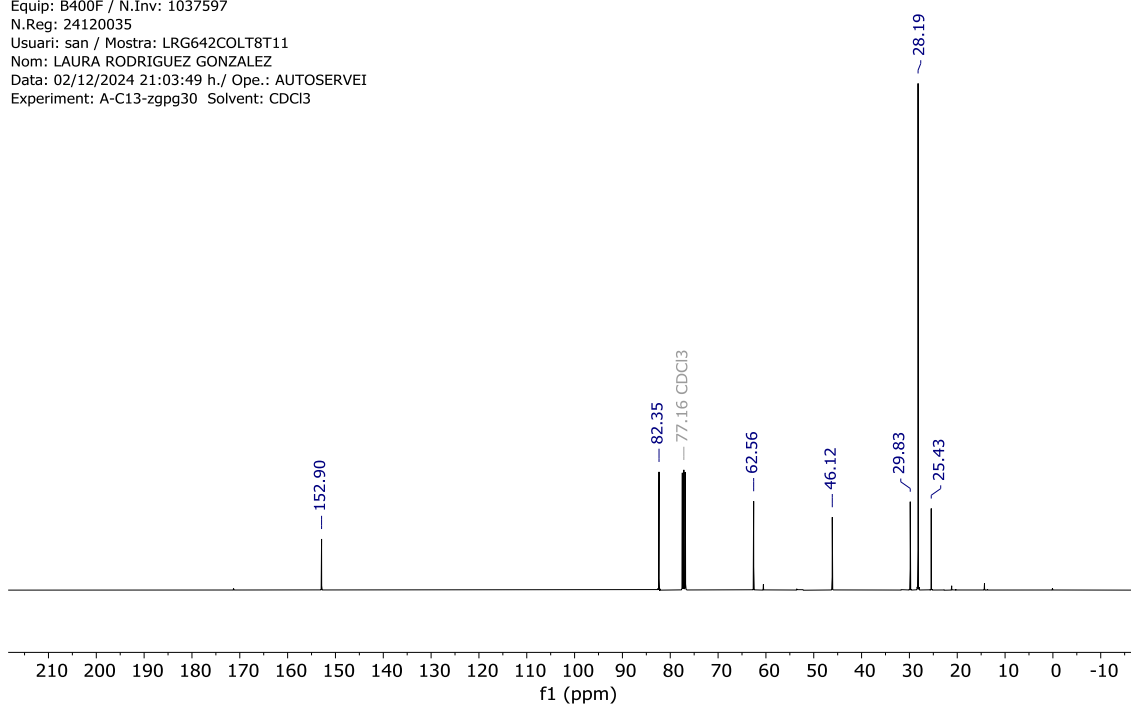




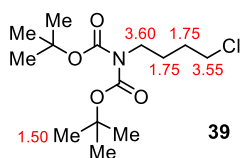
24120035_B400FA_02122024_LRG642COLT8T11.1.fid 1H 400 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24120035
Usuari: san / Mostra: LRG642COLT8T11
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 02/12/2024 17:40:13 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl₃



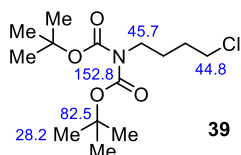
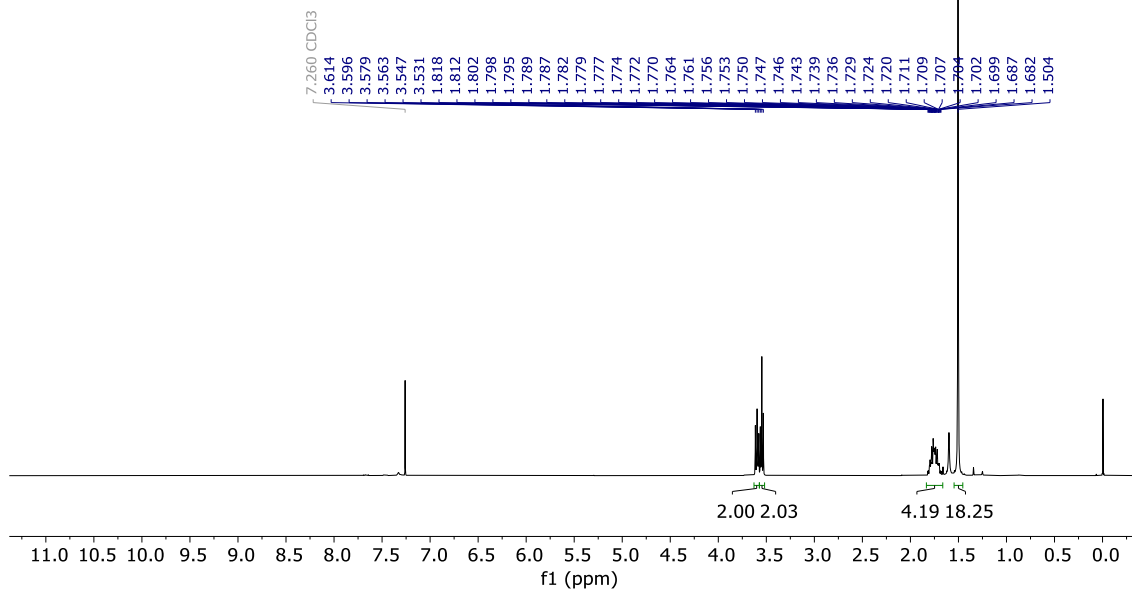
24120035_B400FA_02122024_LRG642COLT8T11.2.fid 13C{1H} 101 MHz
Equip: B400F / N.Inv: 1037597
N.Reg: 24120035
Usuari: san / Mostra: LRG642COLT8T11
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 02/12/2024 21:03:49 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl₃



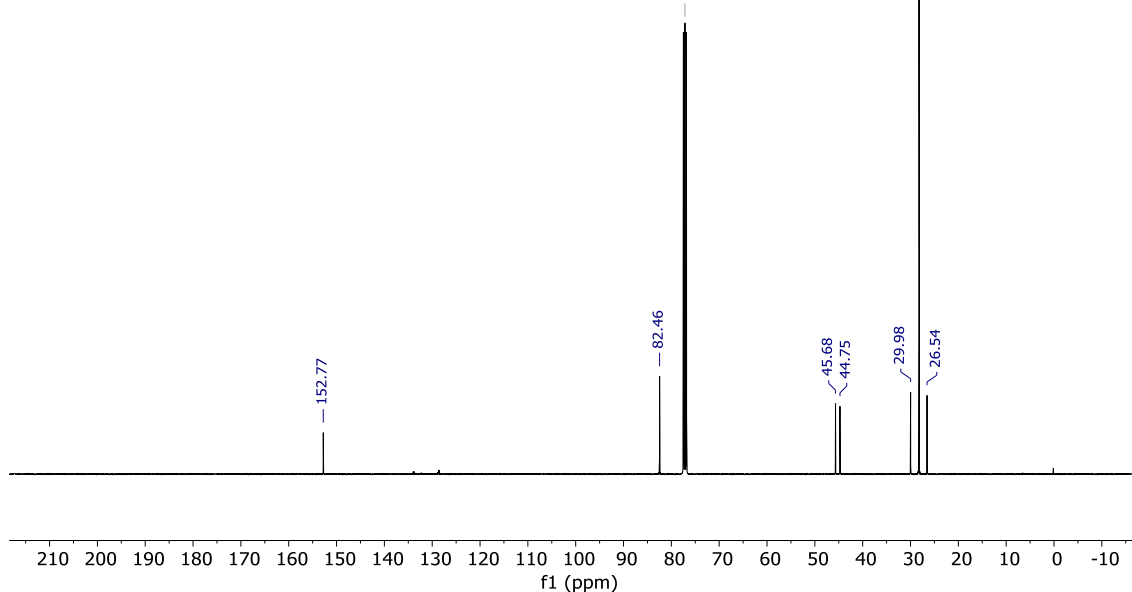
Experimental Section: Chapter 4

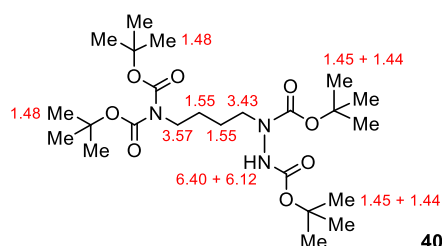


LRG677COLT10T11.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24120162
 Usuari: san / Mostra: LRG677COLT10T11
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 09/12/2024 16:42:50 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃



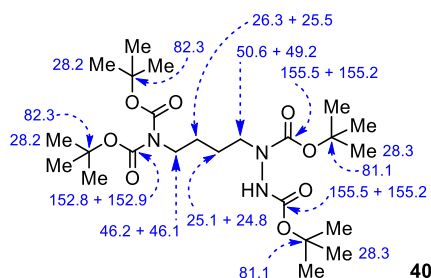
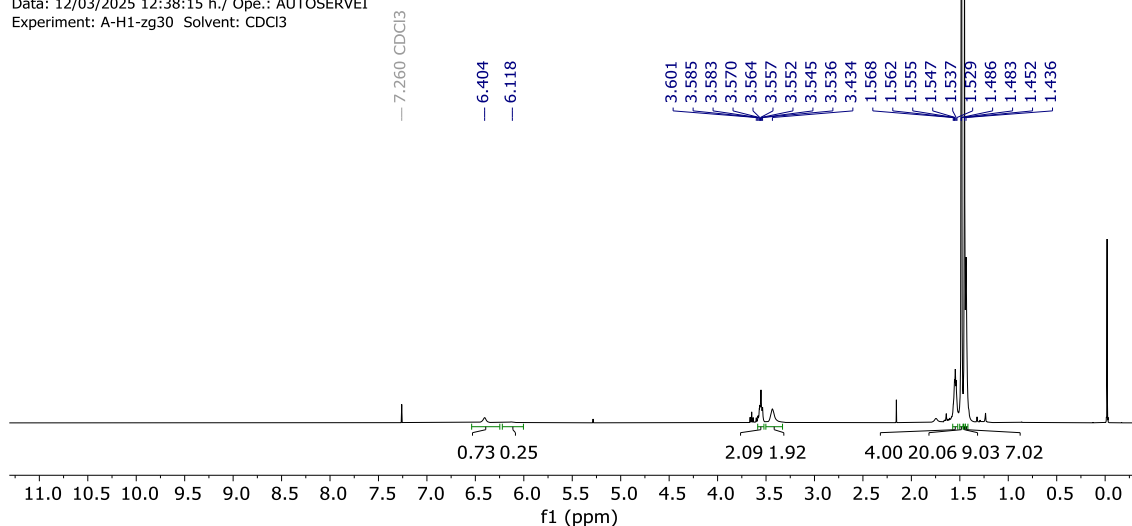
LRG677COLT10T11.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24120162
 Usuari: san / Mostra: LRG677COLT10T11
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 09/12/2024 23:52:26 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃



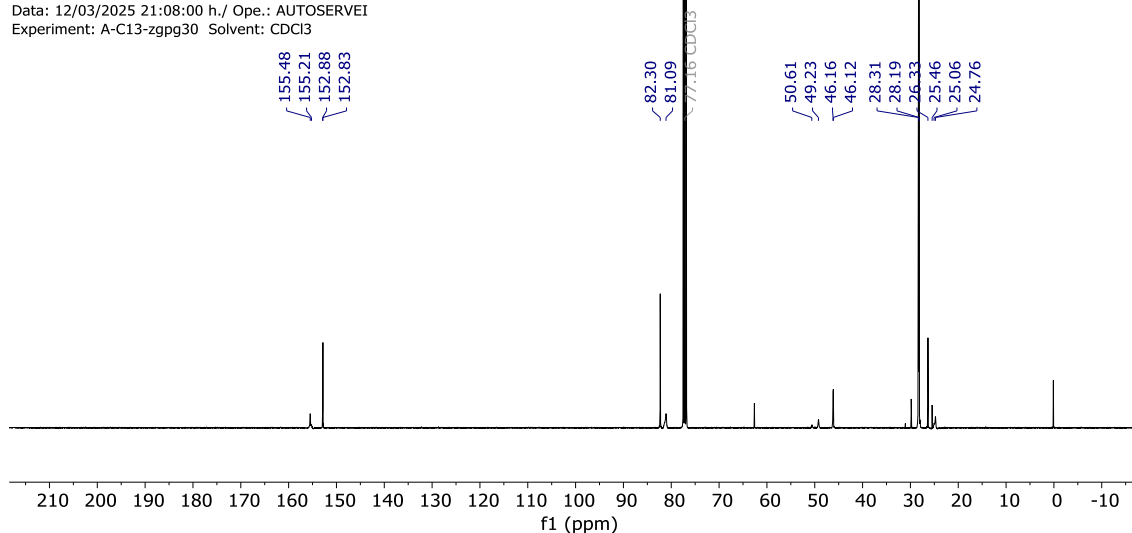


40 The product was isolated as a mixture of rotamers

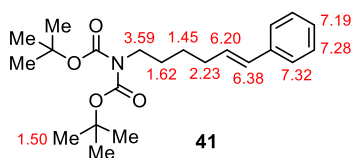
25030299_B400FA_12032025_BB3013CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 25030299
 Usuari: san / Mostra: BB3013CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 12/03/2025 12:38:15 h. / Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



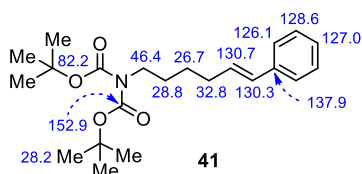
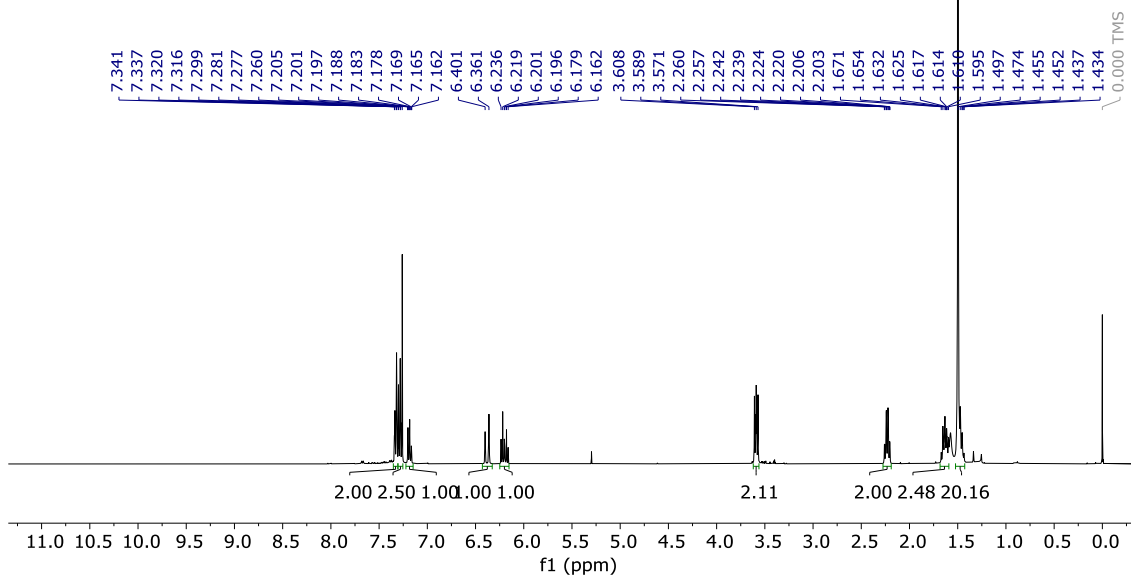
25030299_B400FA_12032025_BB3013CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 25030299
 Usuari: san / Mostra: BB3013CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 12/03/2025 21:08:00 h. / Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



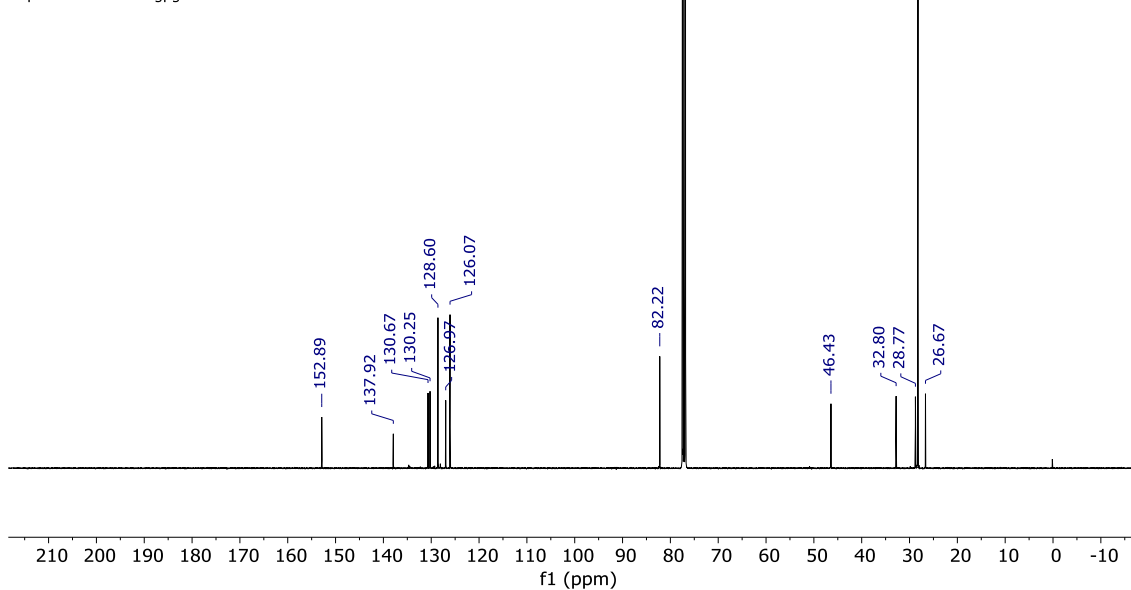
Experimental Section: Chapter 4

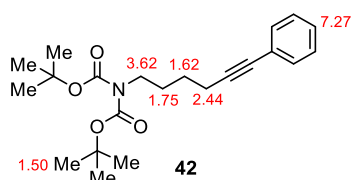


4123-2024_B400FA_12042024_LRG580PREPCH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 4123/2024
 Usuari: san / Mostra: LRG580PREPCH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 12/04/2024 19:19:50 h./ Ope.: servei Unitat RMN
 Experiment: A-H1-zg30 Solvent: CDCl3

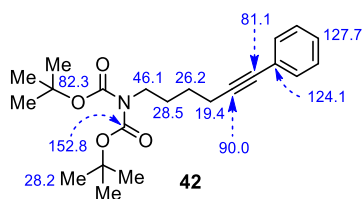
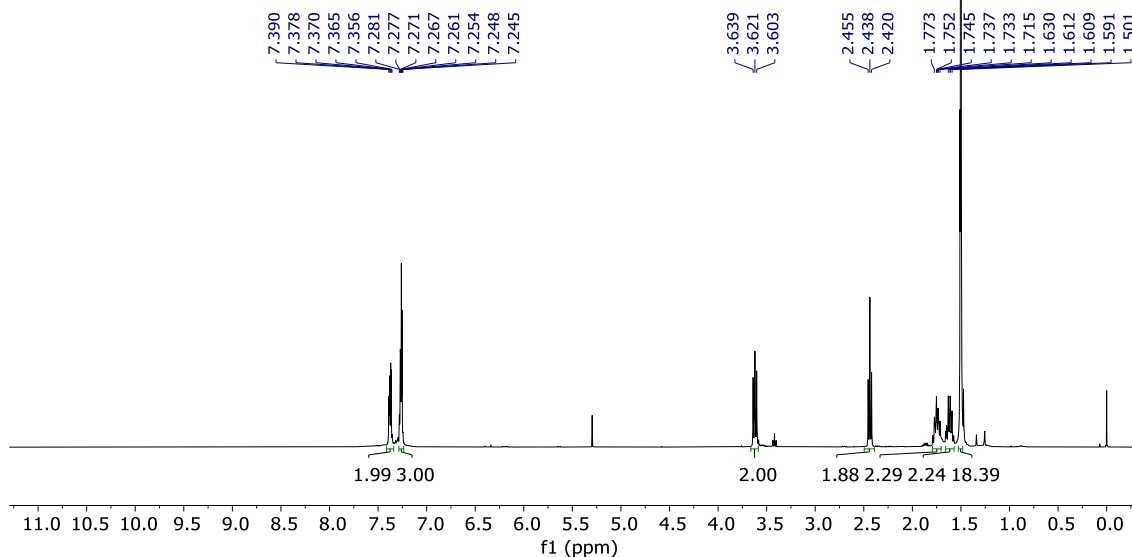


4123-2024_B400FA_12042024_LRG580PREPCH.4.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 4123/2024
 Usuari: san / Mostra: LRG580PREPCH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 12/04/2024 20:12:14 h./ Ope.: servei Unitat RMN
 Experiment: A-C13-zgpg30 Solvent: CDCl3

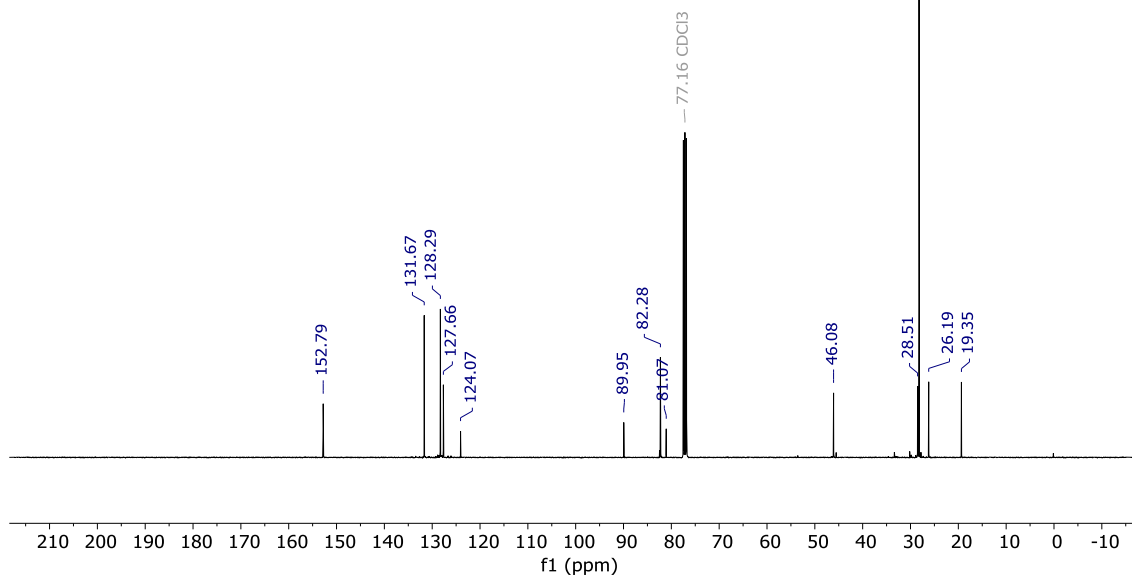




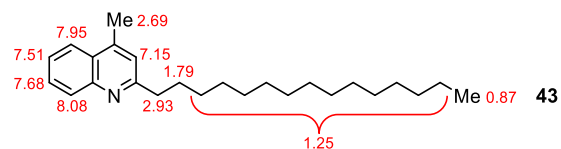
24040430_B400FA_11042024_LRG578CH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040430
 Usuari: san / Mostra: LRG578CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 10/04/2024 15:00:13 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



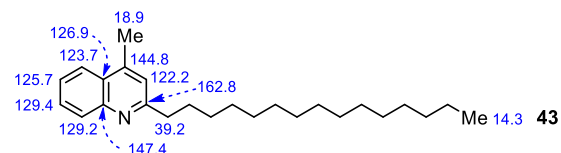
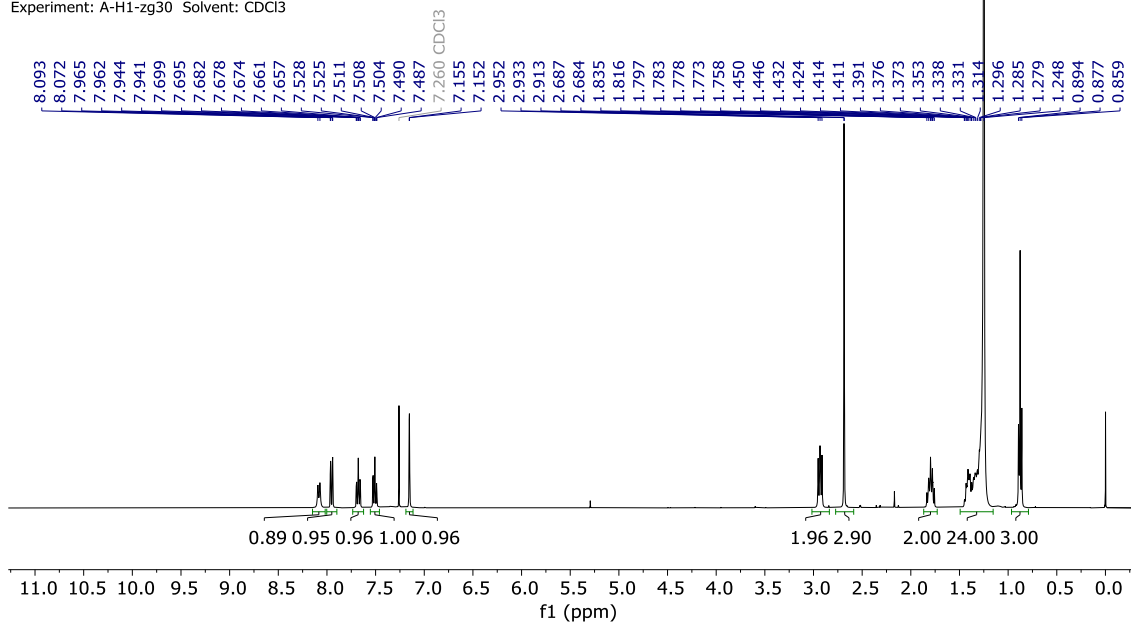
24040430_B400FA_11042024_LRG578CH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040430
 Usuari: san / Mostra: LRG578CH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 11/04/2024 03:06:13 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



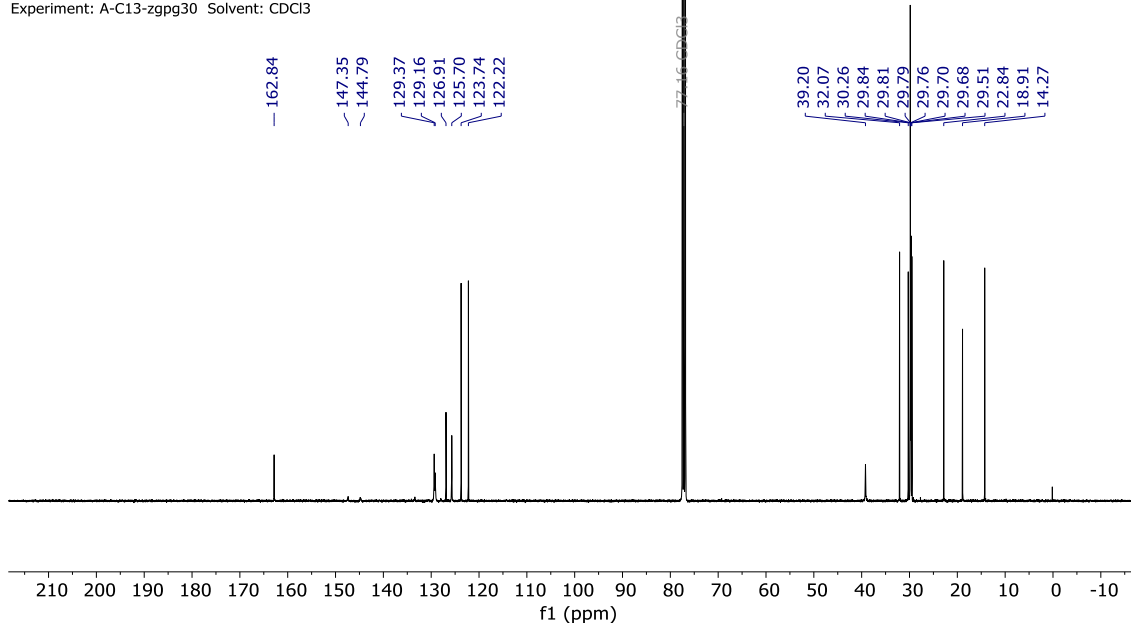
Experimental Section: Chapter 4

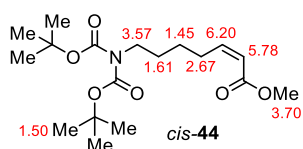


24050285_B400FA_08052024_LRG595PREP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050285
 Usuari: san / Mostra: LRG595PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 08/05/2024 17:10:21 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

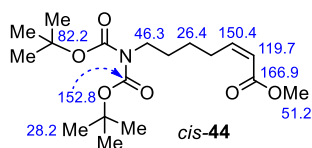
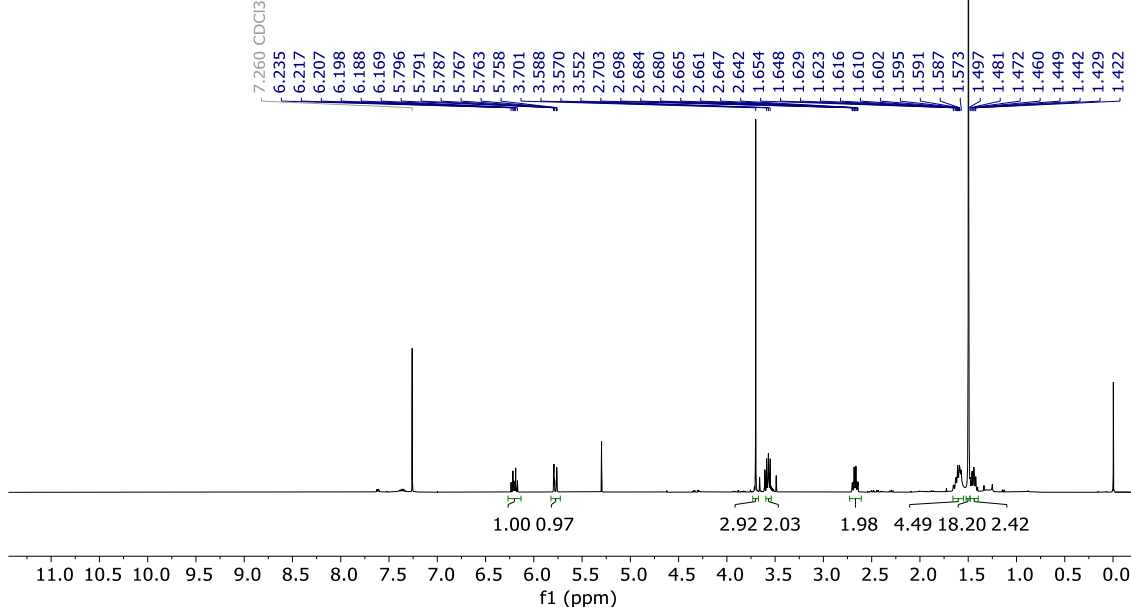


24050285_B400FA_09052024_LRG595PREP.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050285
 Usuari: san / Mostra: LRG595PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 09/05/2024 02:31:11 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

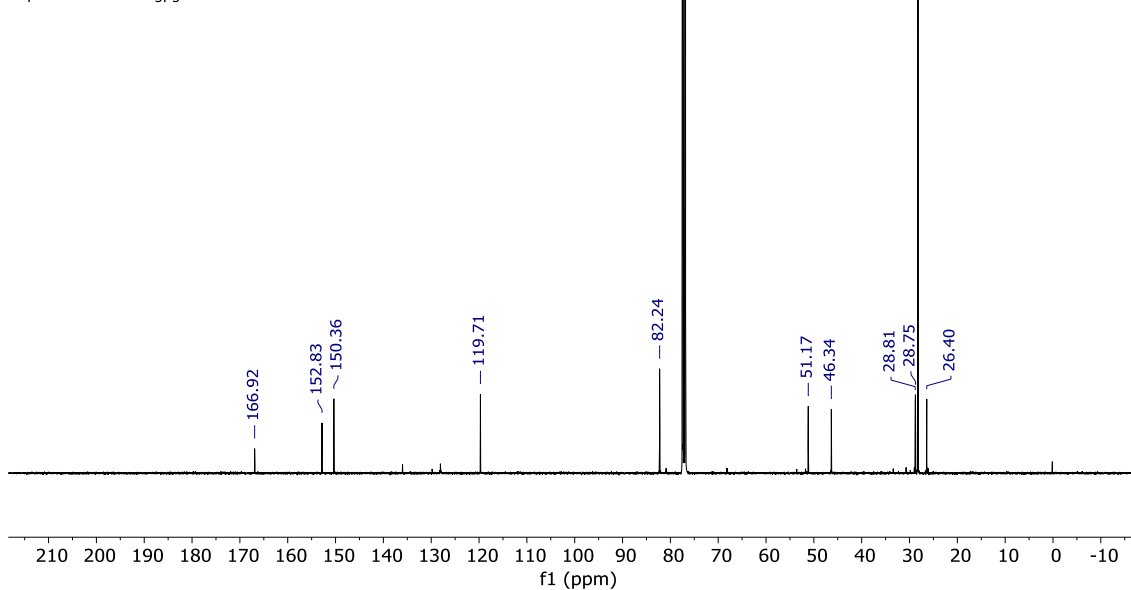


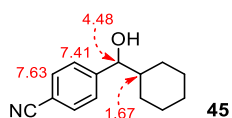


24040836_B400FA_20042024_LRG583PREPCH.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040836
 Usuari: san / Mostra: LRG583PREPCH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/04/2024 15:37:57 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

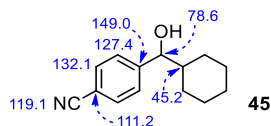
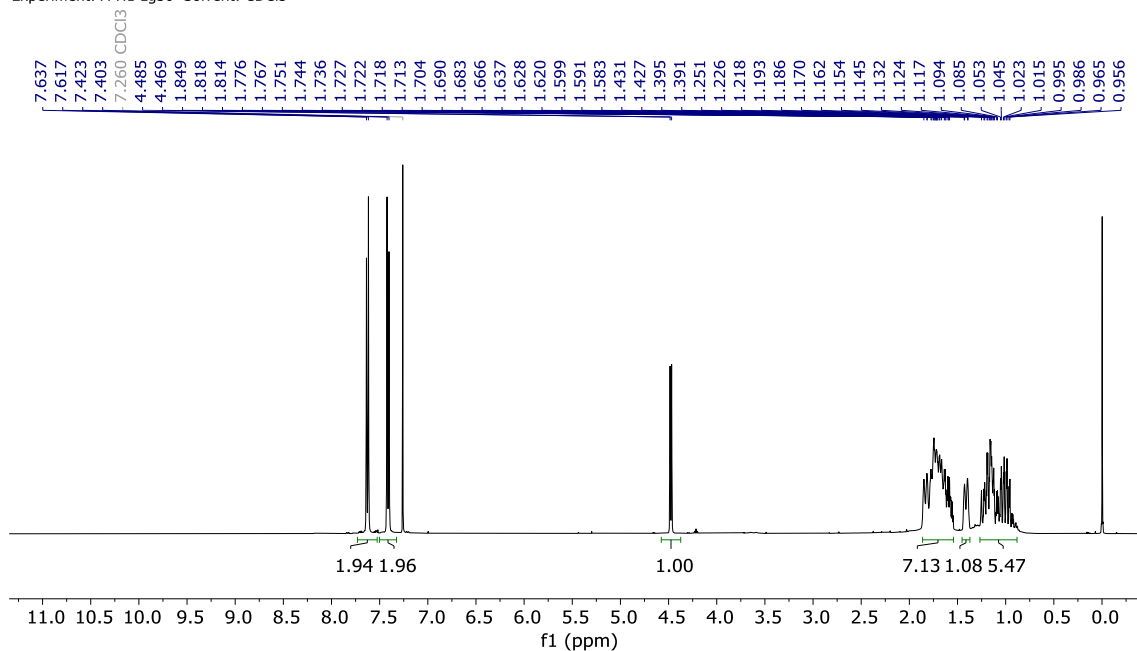


24040836_B400FA_20042024_LRG583PREPCH.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24040836
 Usuari: san / Mostra: LRG583PREPCH
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/04/2024 23:23:08 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpgp30 Solvent: CDCl₃

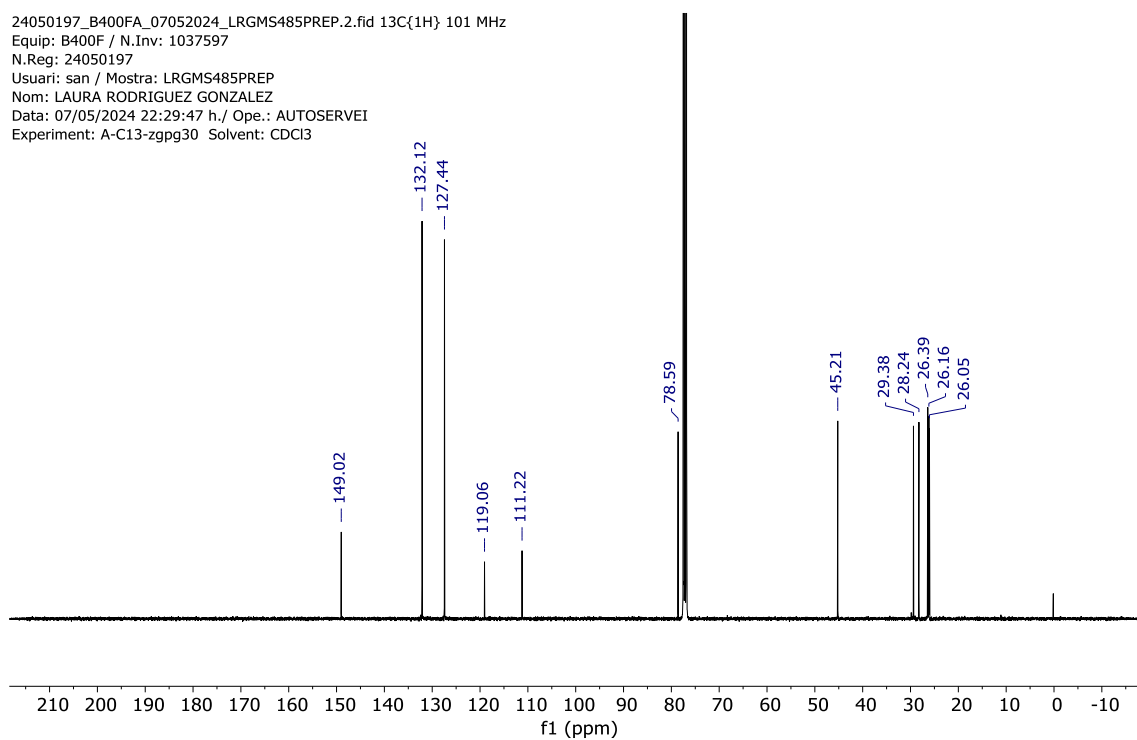


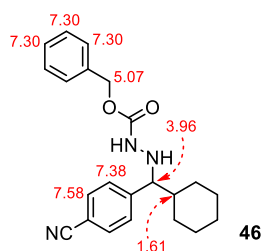


24050197_B400FA_07052024_LRGMS485PREP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050197
 Usuari: san / Mostra: LRGMS485PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/05/2024 12:08:07 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

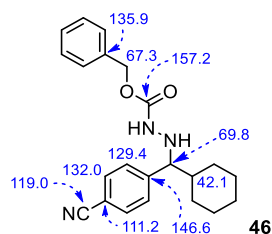
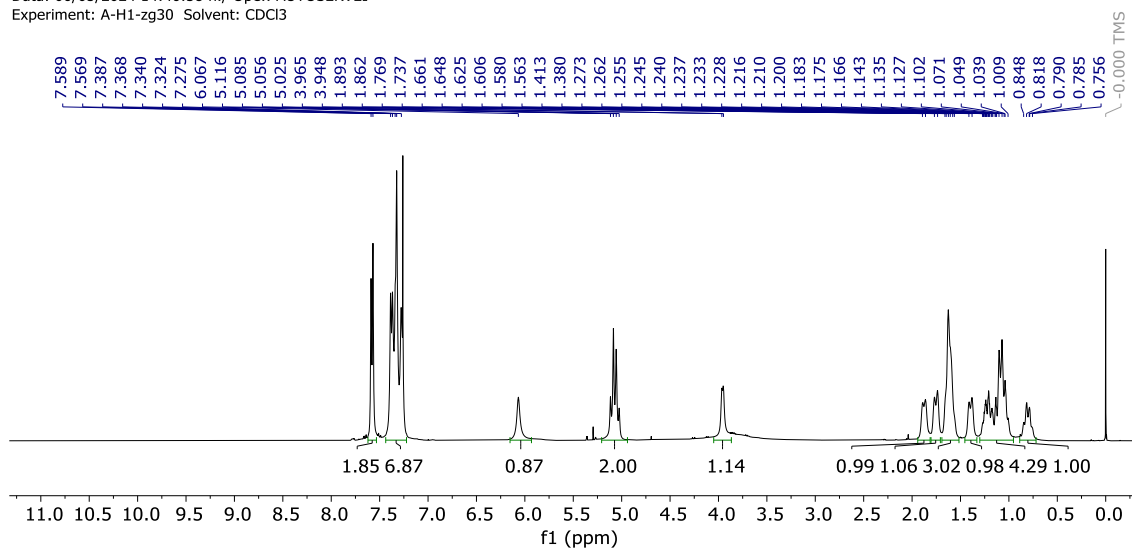


24050197_B400FA_07052024_LRGMS485PREP.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050197
 Usuari: san / Mostra: LRGMS485PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/05/2024 22:29:47 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

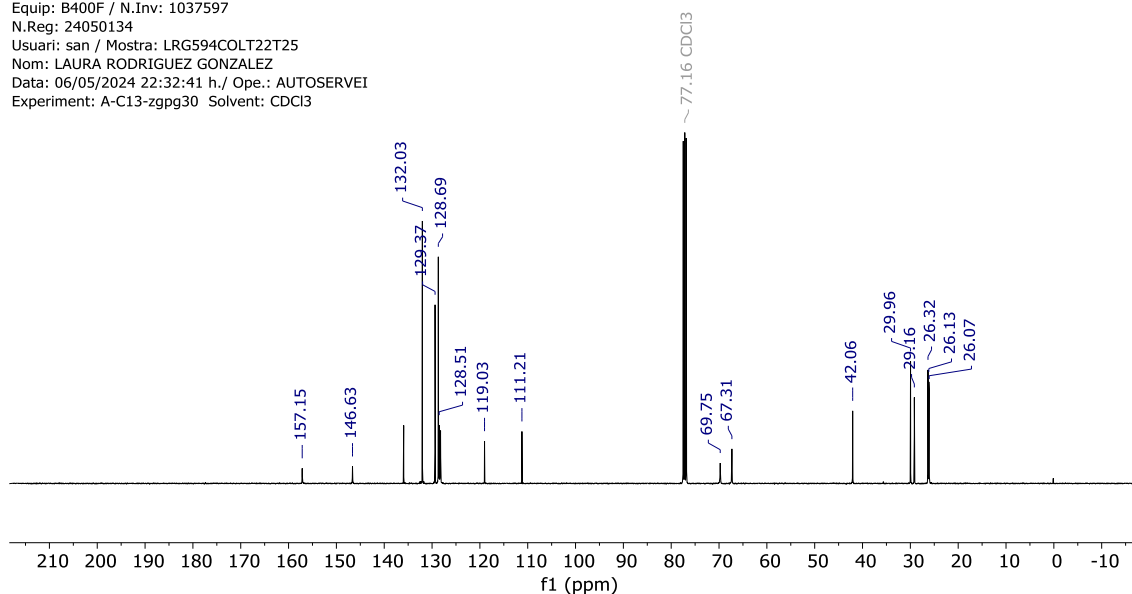




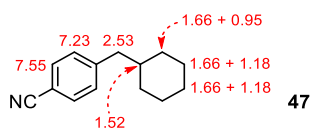
24050149_B400FA_06052024_LRG594DRY.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050149
 Usuari: san / Mostra: LRG594DRY
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 06/05/2024 14:46:38 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



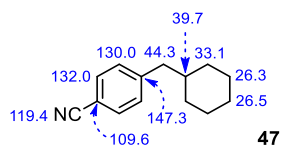
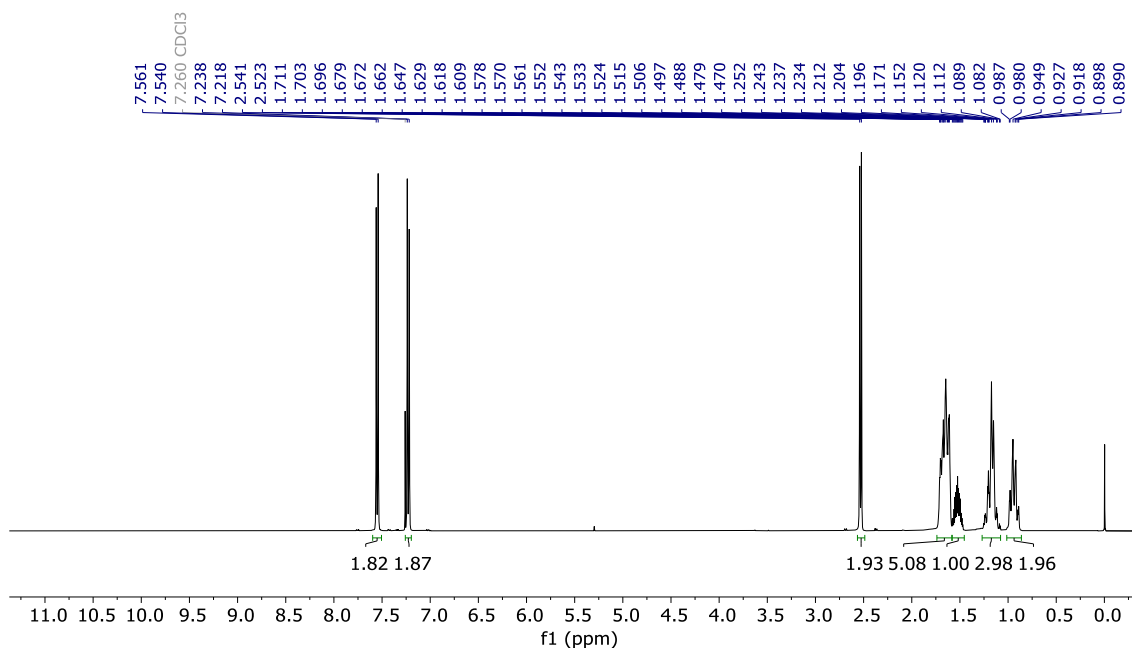
24050134_B400FA_06052024_LRG594COLT22T25.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050134
 Usuari: san / Mostra: LRG594COLT22T25
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 06/05/2024 22:32:41 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpgp30 Solvent: CDCl3



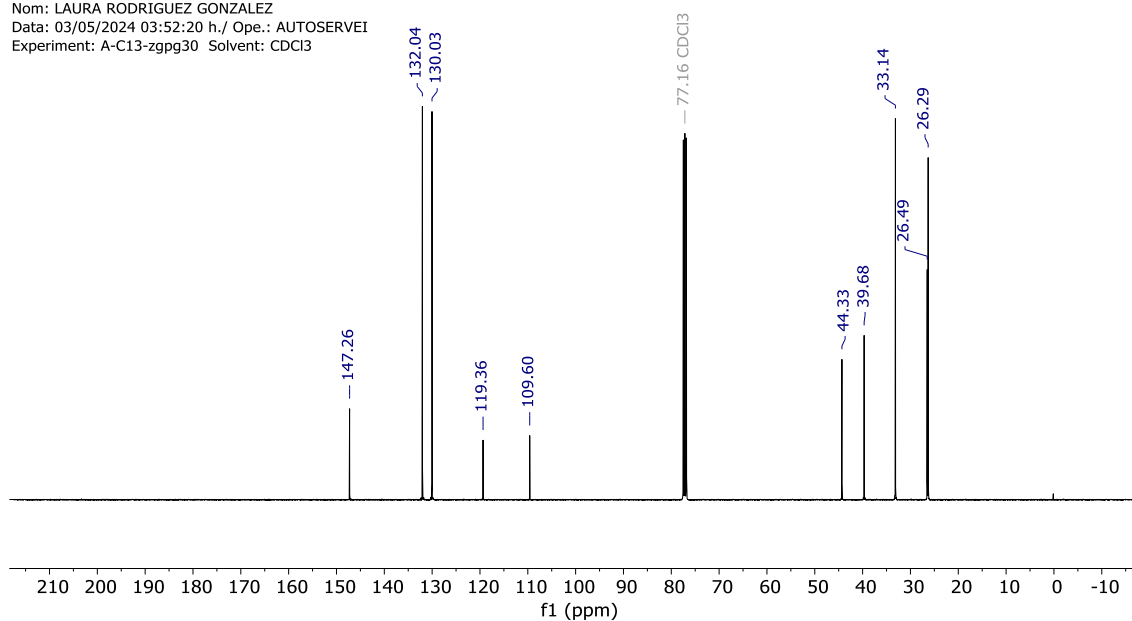
Experimental Section: Chapter 4

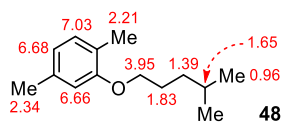


24050019_B400FA_02052024_LRG591PREP.1.fid 1H 400 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050019
 Usuari: san / Mostra: LRG591PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 02/05/2024 13:45:58 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

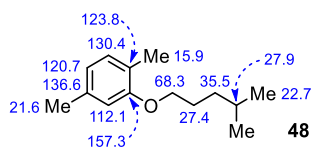
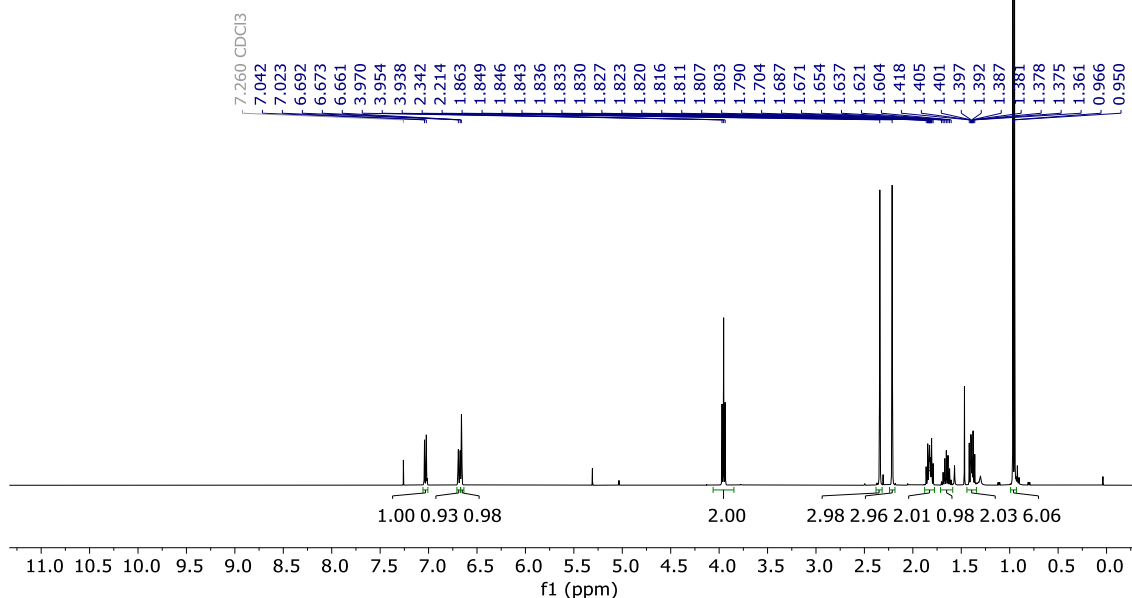


24050019_B400FA_03052024_LRG591PREP.2.fid 13C{1H} 101 MHz
 Equip: B400F / N.Inv: 1037597
 N.Reg: 24050019
 Usuari: san / Mostra: LRG591PREP
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/05/2024 03:52:20 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3

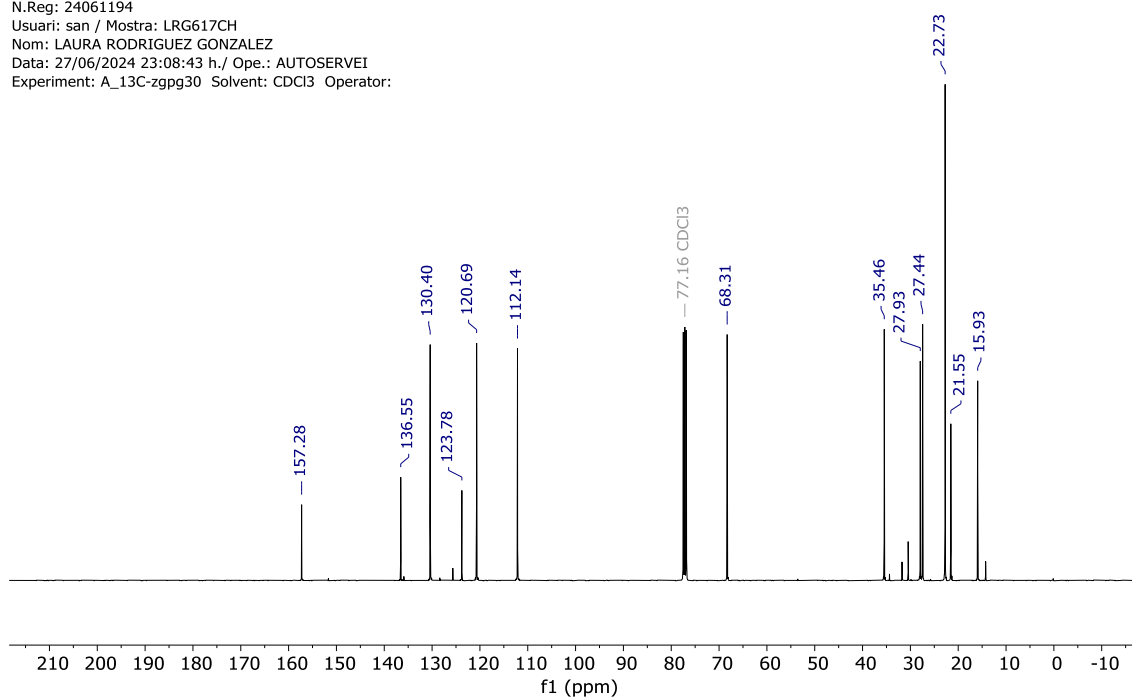




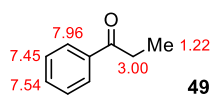
auto-27062024-123559.1.fid 1H 400 MHz
Equip: B400Q / N.Inv: 1035091
N.Reg: 24061192
Usuari: san / Mostra: LRG617COLT10T15
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 27/06/2024 12:42:11 h./ Ope.: AUTOSERVEI
Experiment: A_1H-zg30 Solvent: CDCl₃ Operator:



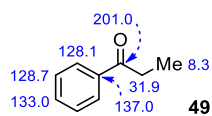
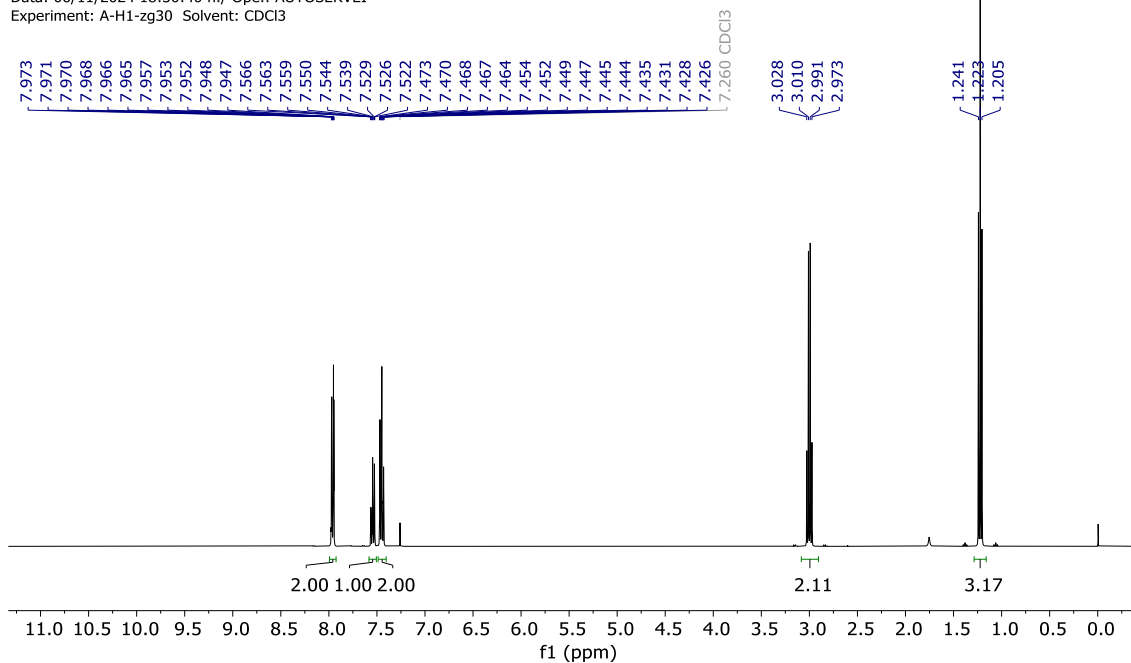
auto-27062024-130906.2.fid 13C{1H} 101 MHz
Equip: B400Q / N.Inv: 1035091
N.Reg: 24061194
Usuari: san / Mostra: LRG617CH
Nom: LAURA RODRIGUEZ GONZALEZ
Data: 27/06/2024 23:08:43 h./ Ope.: AUTOSERVEI
Experiment: A_13C-zpgp30 Solvent: CDCl₃ Operator:



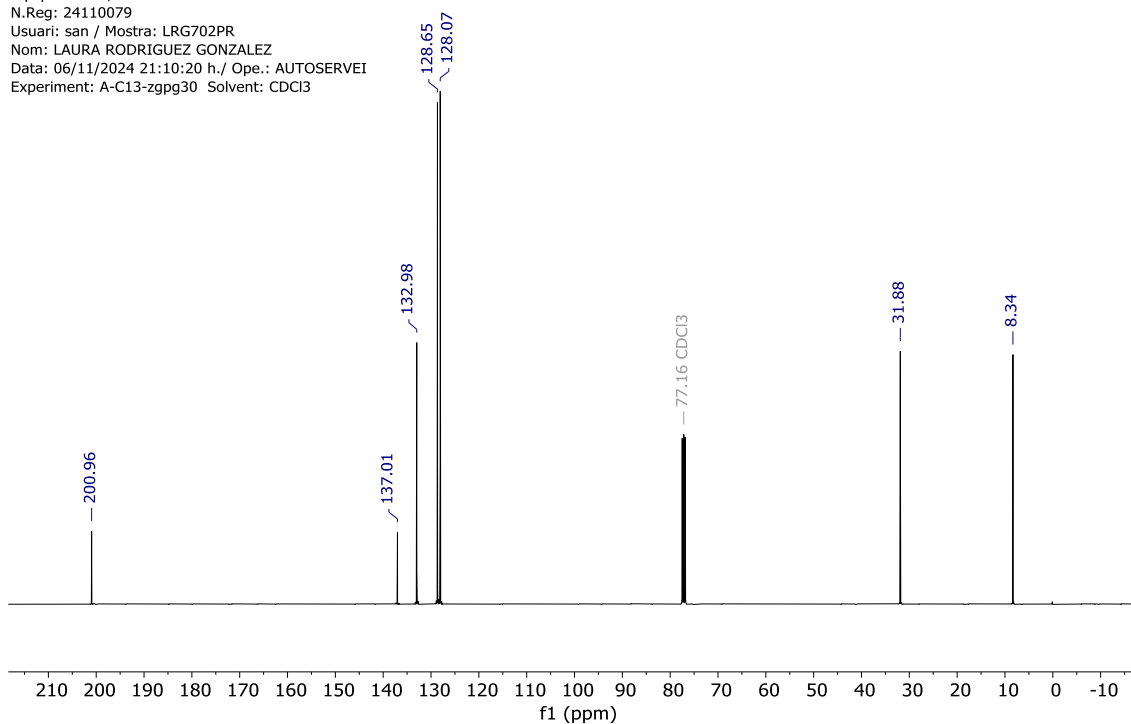
Experimental Section: Chapter 4

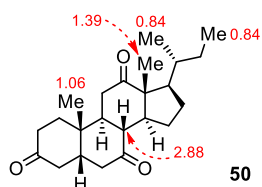


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 Equip: B400F / N.Inv: 1037597
 N.Reg: 24110079
 Usuari: san / Mostra: LRG702PR
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 06/11/2024 18:30:40 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

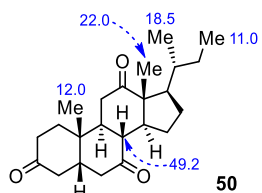
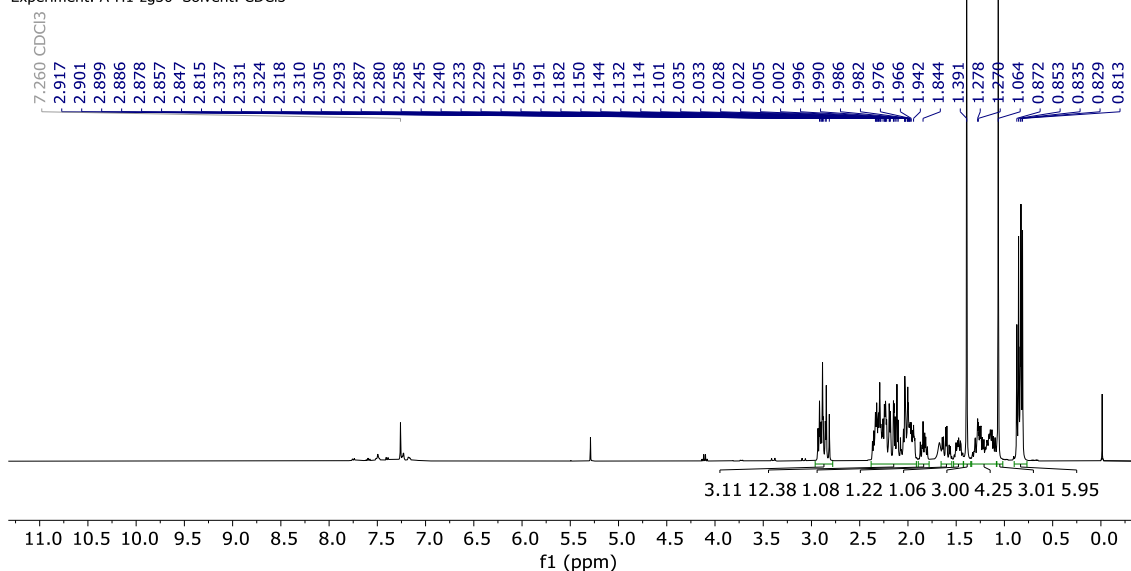


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 N.Reg: 24110079
 Usuari: san / Mostra: LRG702PR
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 06/11/2024 21:10:20 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl₃

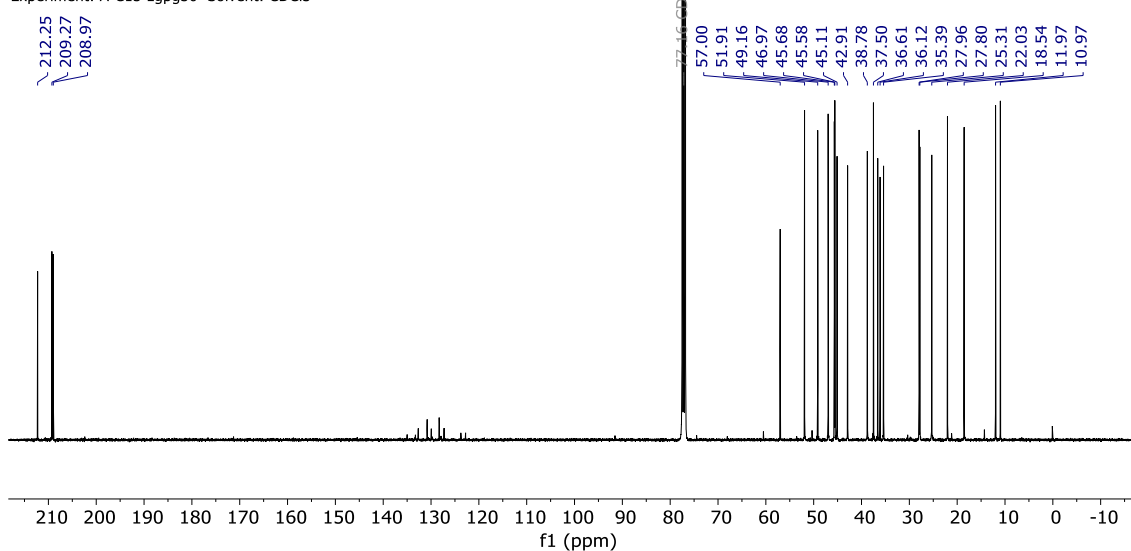


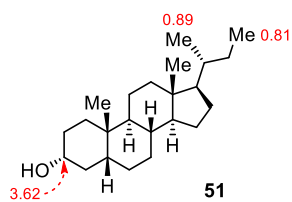


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 Usuari: san / Mostra: LRG667COLT22T24
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/11/2024 10:41:56 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

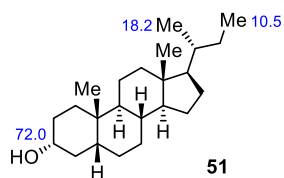
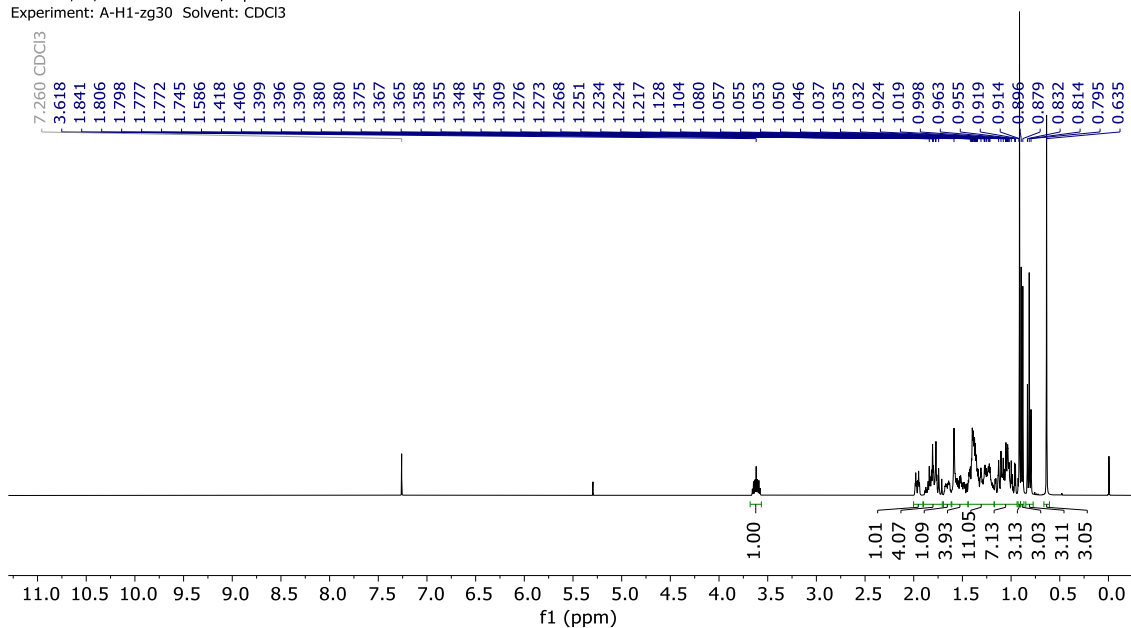


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 Usuari: san / Mostra: LRG667COLT22T24
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/11/2024 22:41:52 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpg30 Solvent: CDCl3

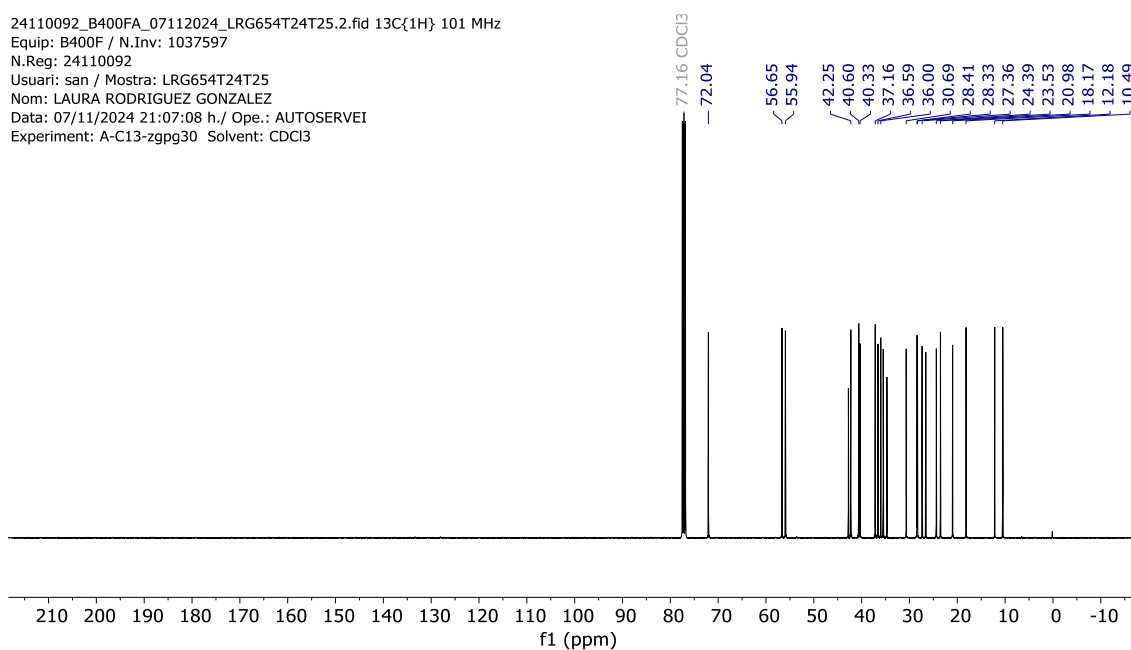


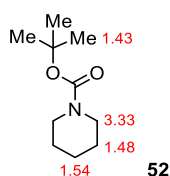


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 Equip: B400F / N.Inv: 1037597
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 Usuari: san / Mostra: LRG654T24T25
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 07/11/2024 11:17:32 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3

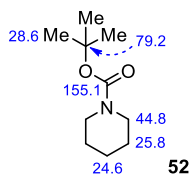
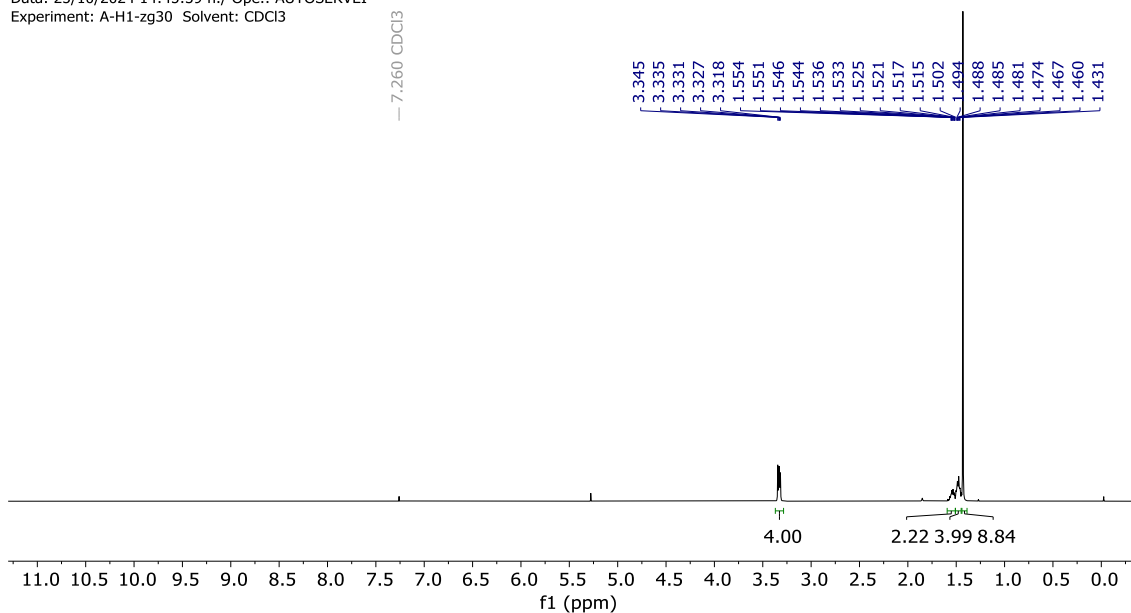


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 Data: 07/11/2024 21:07:08 h./ Ope.: AUTOSERVEI
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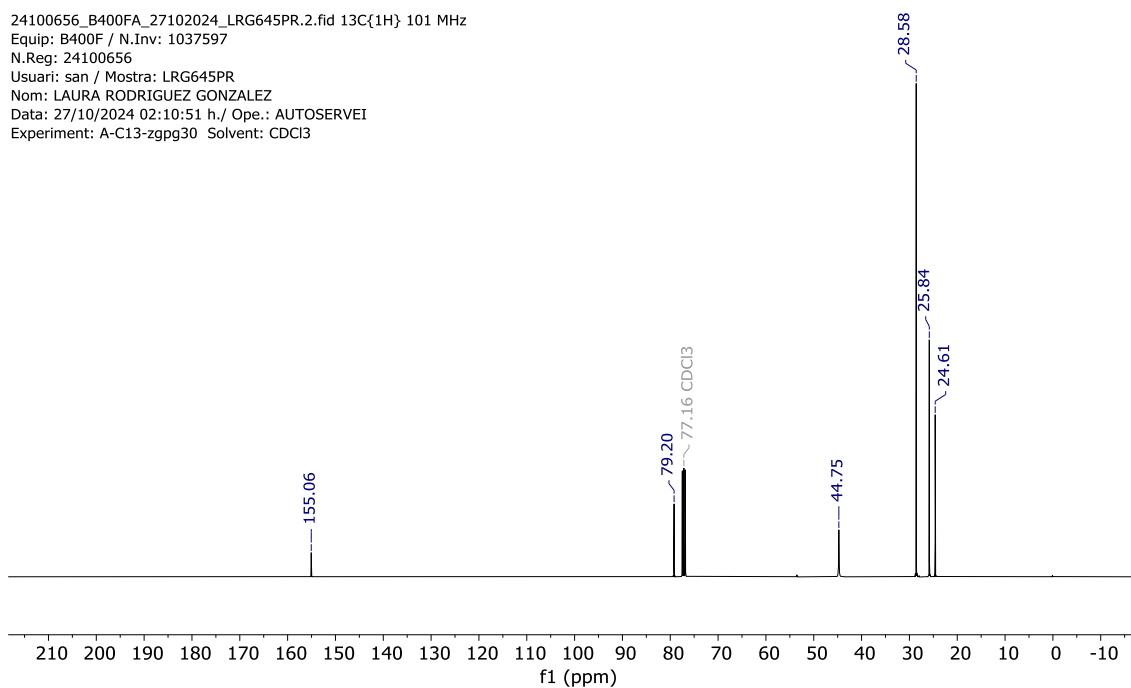




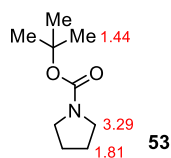
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 N.Reg: 24100656
 Usuari: san / Mostra: LRG645PR
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 25/10/2024 14:45:39 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



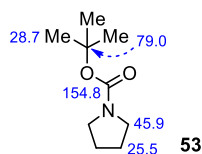
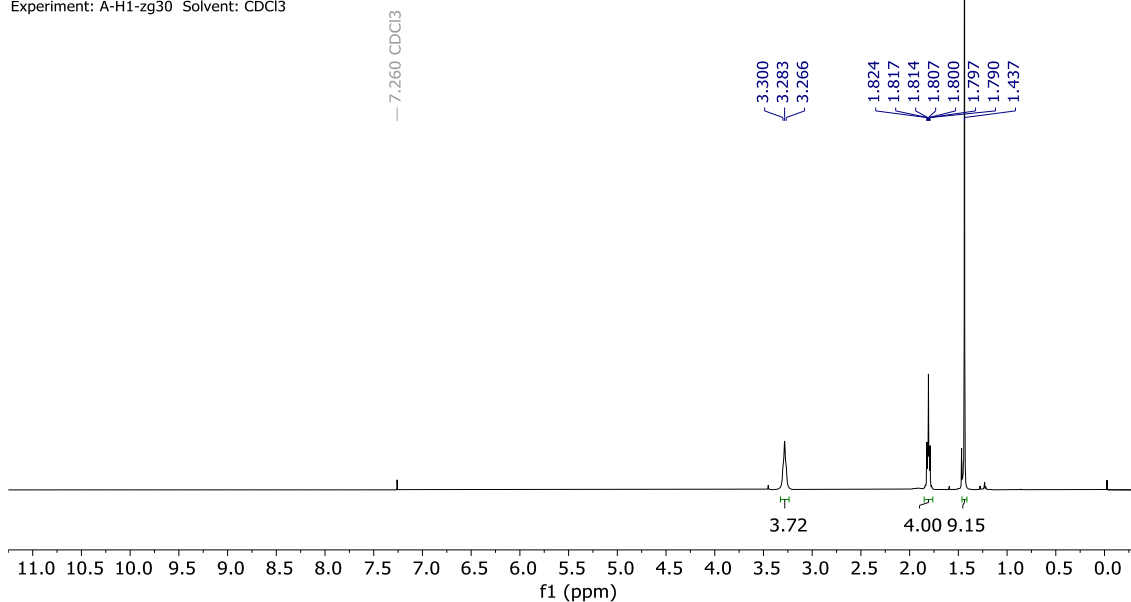
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 Usuari: san / Mostra: LRG645PR
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 27/10/2024 02:10:51 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



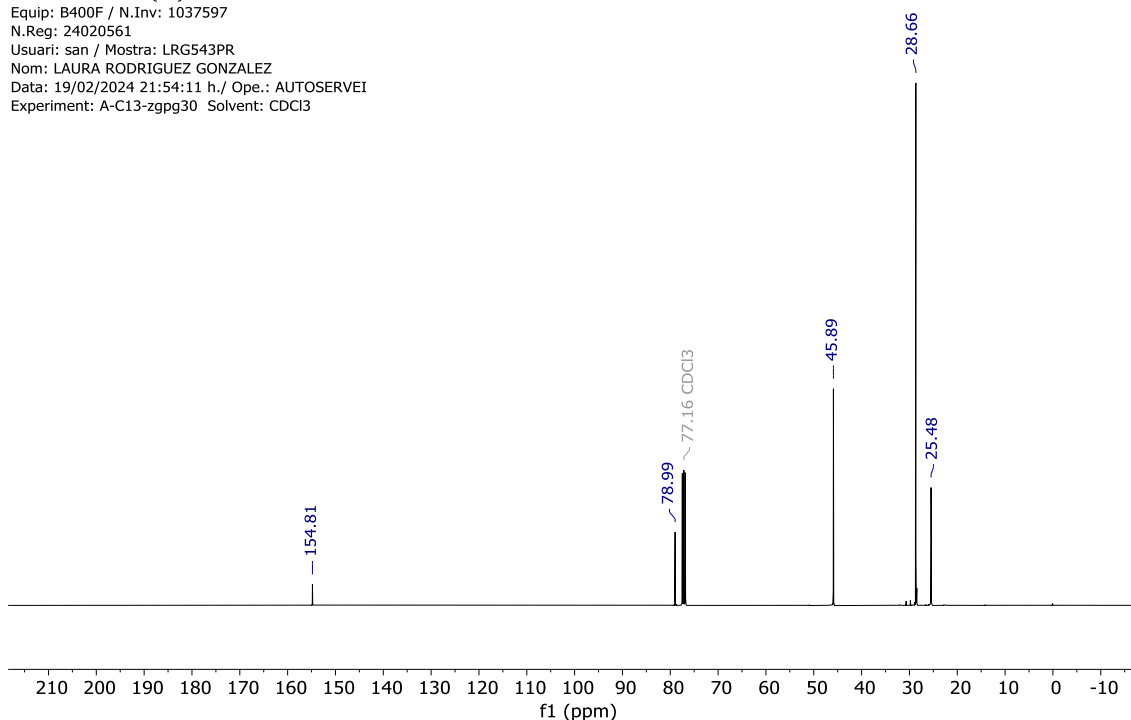
Experimental Section: Chapter 4

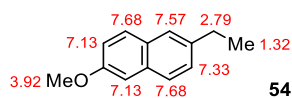


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 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/02/2024 15:49:34 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl₃

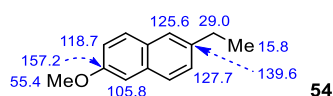
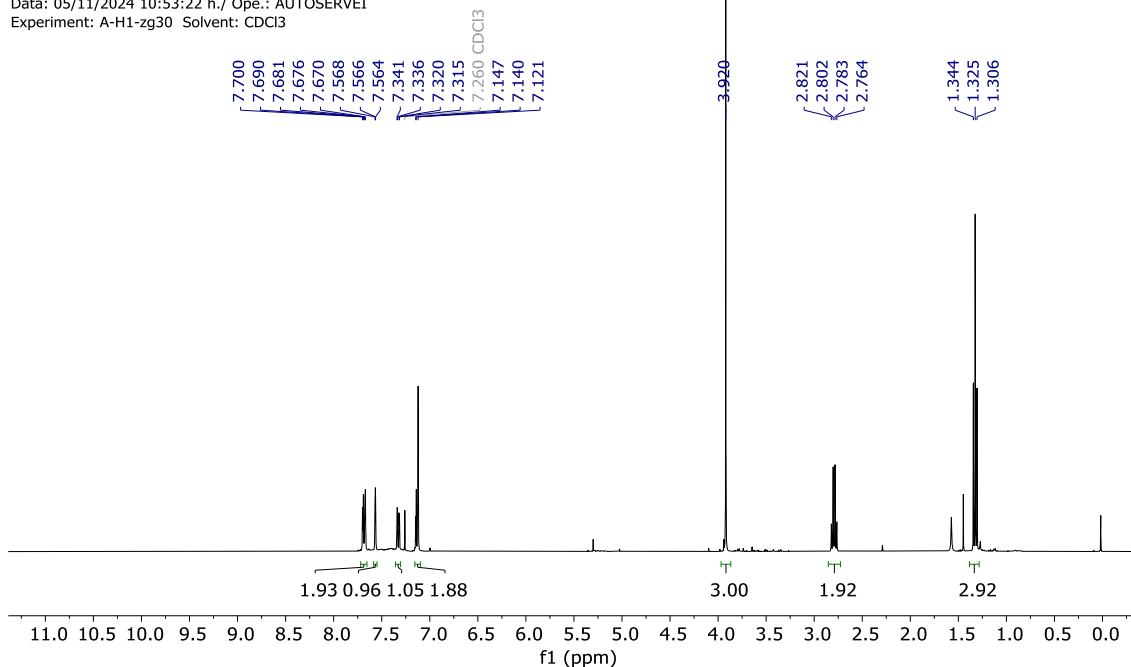


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 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 19/02/2024 21:54:11 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zpgp30 Solvent: CDCl₃

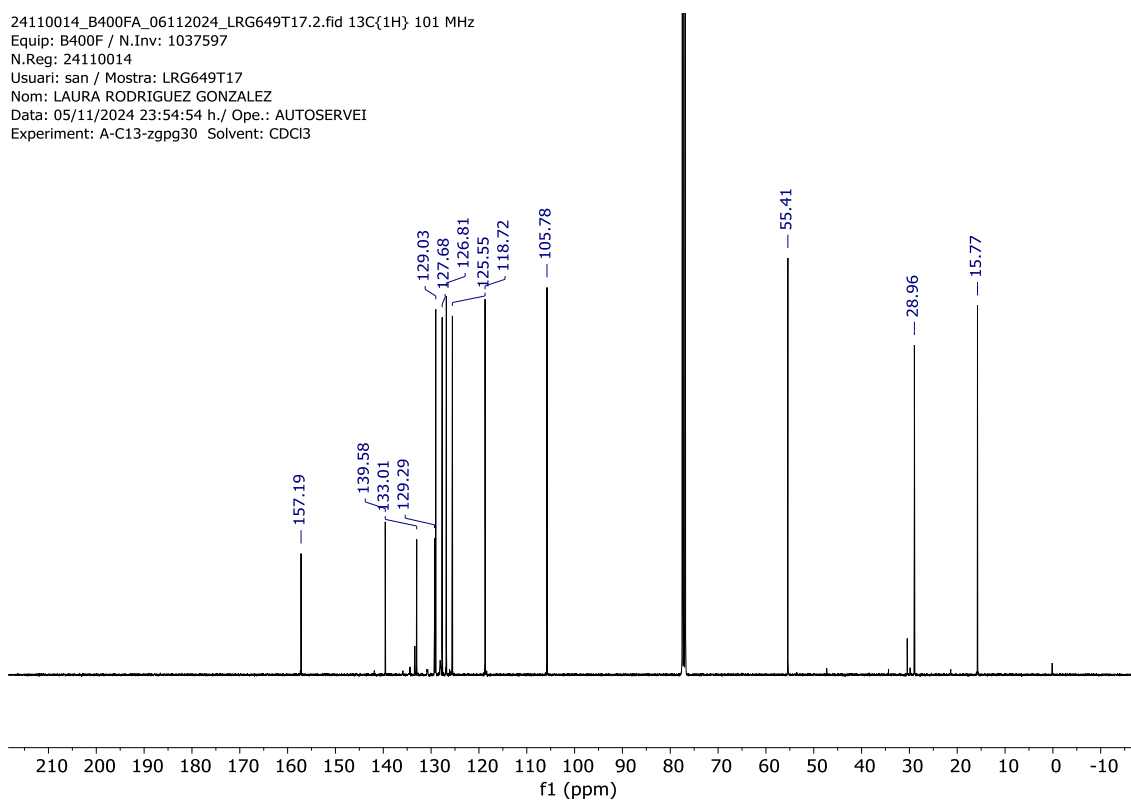




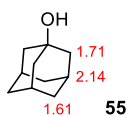
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 Data: 05/11/2024 10:53:22 h. / Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



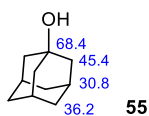
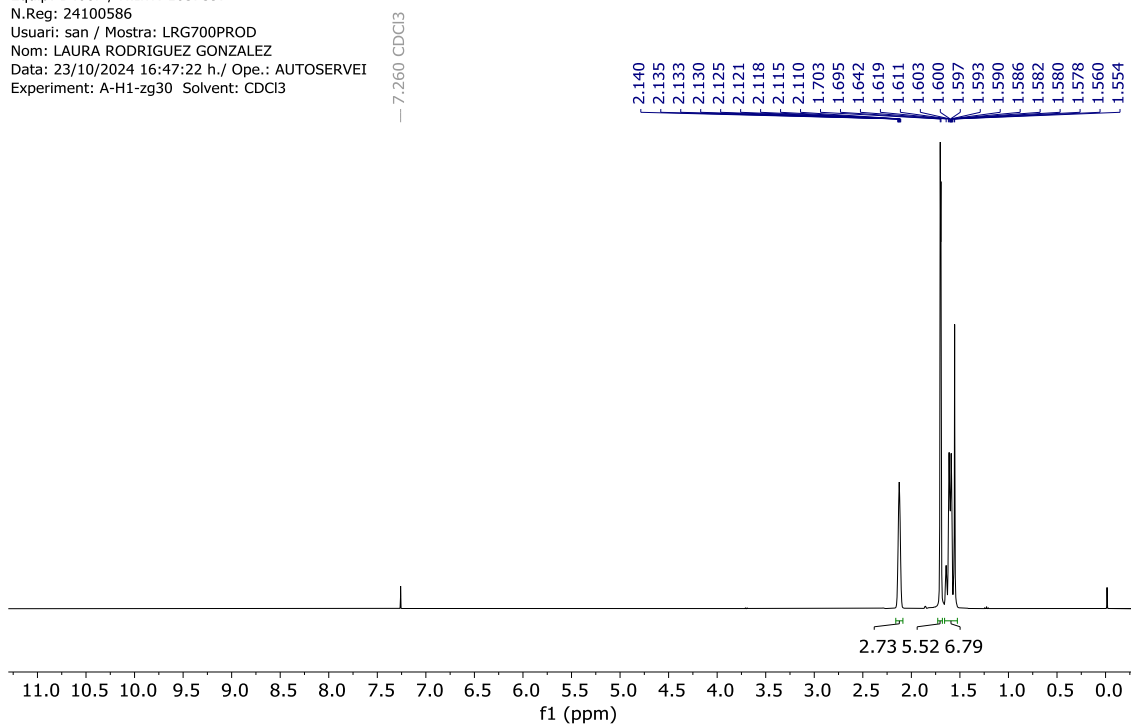
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 Data: 05/11/2024 23:54:54 h. / Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



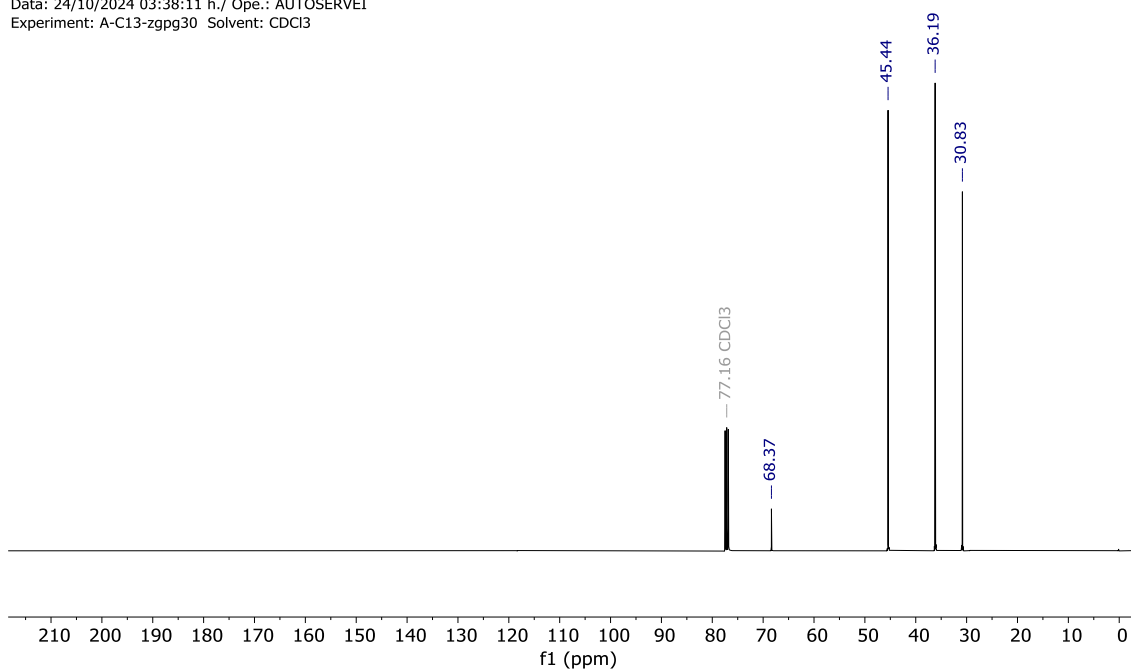
Experimental Section: Chapter 4

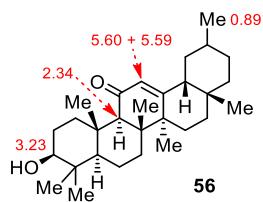


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Usuari: san / Mostra: LRG700PROD
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Data: 23/10/2024 16:47:22 h./ Ope.: AUTOSERVEI
Experiment: A-H1-zg30 Solvent: CDCl₃

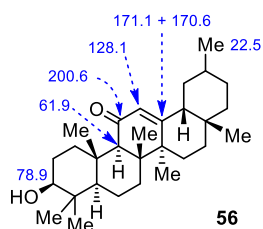
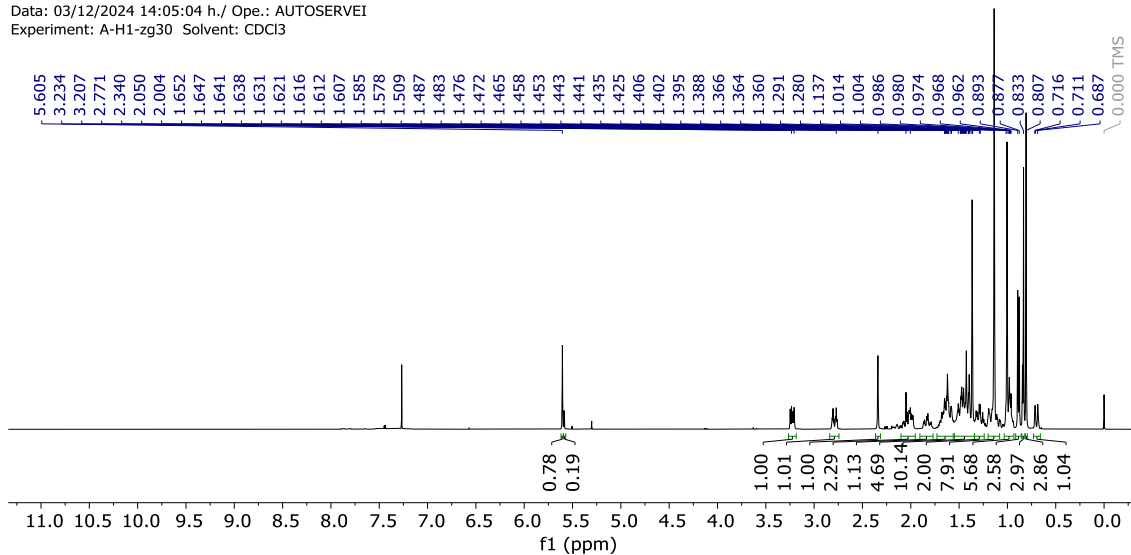


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Usuari: san / Mostra: LRG700PROD
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Data: 24/10/2024 03:38:11 h./ Ope.: AUTOSERVEI
Experiment: A-C13-zgpg30 Solvent: CDCl₃

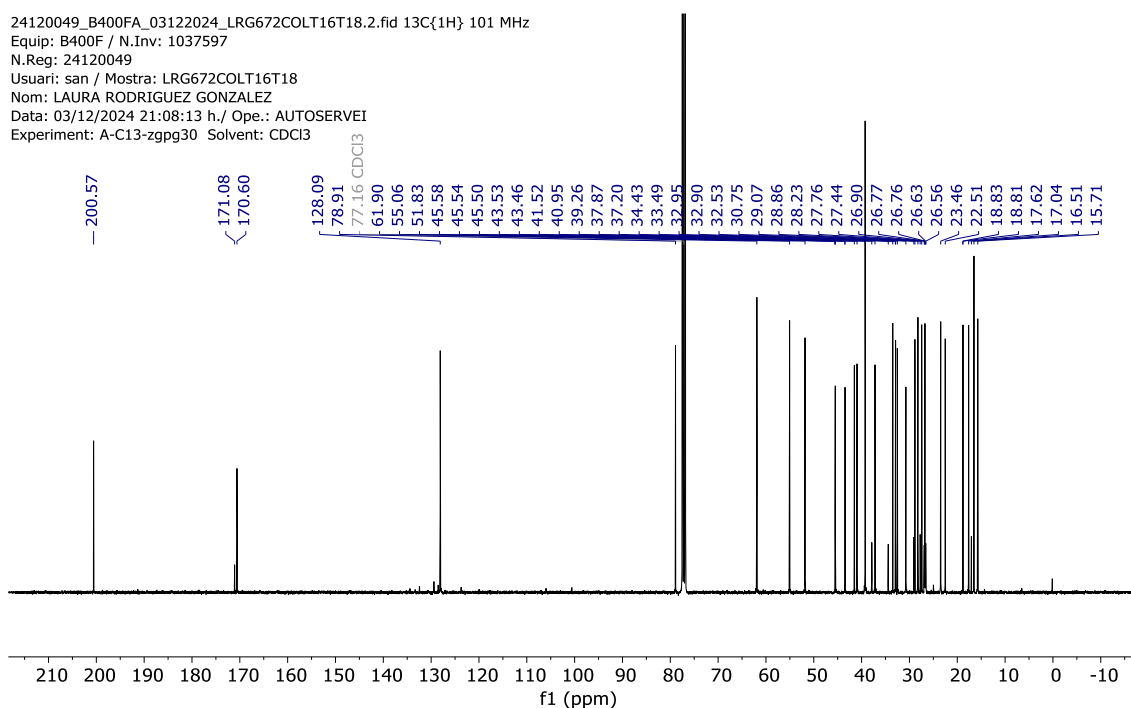




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 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/12/2024 14:05:04 h./ Ope.: AUTOSERVEI
 Experiment: A-H1-zg30 Solvent: CDCl3



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 N.Reg: 24120049
 Usuari: san / Mostra: LRG672COLT16T18
 Nom: LAURA RODRIGUEZ GONZALEZ
 Data: 03/12/2024 21:08:13 h./ Ope.: AUTOSERVEI
 Experiment: A-C13-zgpg30 Solvent: CDCl3



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