# Tris(triphenylphosphine)Ruthenium(II) dichloride: a versatile catalystin the synthesis of β-, γ- and δ-lactams from trichloroacetamides and in the isomerization of protected allylamines toz-enamines under microwave activation

Alexandra Georgiana Șandor

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PROGRAMA DE DOCTORAT DE QUÍMICA ORGÀNICA

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Memoria presentada por Alexandra Georgiana Șandor para optar al título de doctor por la Universidad de Barcelona

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https://www.journalcra.com/article/microwave-assisted-benzylic-c-h-activation-using-ruthenium-catalysts-synthesis-%EF%81%A2-lactams

# INDEX

## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| $^{13}C$ NMR | carbon-13 nuclear magnetic resonance |
| $^{1}H$ NMR | proton nuclear magnetic resonance |
| A431 | squamous cell carcinoma |
| $Ac_2O$ | acetic anhydride |
| ACN | acetonitrile |
| AIBN | azobisisobutyronitrile |
| Anisole | methyl phenyl ether |
| aq | aqueous |
| Ar | aryl |
| atm | atmosphere |
| ATRA | atom transfer radical addition |
| ATRC | atom transfer radical cyclization |
| Bn | benzyl |
| $BnNH_2$ | benzylamine |
| br s | broad singlet (spectrum) |
| Bu | butyl |
| $Bu_3P$ | tributylphosphine |
| Bz | benzoyl |
| calcd. | calculated |
| CDT | cyclododecatriene |
| COD | cyclooctadiene |
| COOEt | ethoxycarbonyl |
| COOMe | methoxycarbonyl |
| COSY | spectroscopy correlation |
| d | day (s), doublet (spectrum) |

| | |
|---|---|
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCE | dichloroethane |
| DCM | dichloromethane |
| dd | doublet of doublets (spectrum) |
| DMEM | Dulbecco's Modified Eagle Medium |
| DMF | dimethylformamide |
| DNA | deoxyribonucleic acid |
| ESI-TOF | Electrospray Ionization Time-of-Flight (Mass Spectrometrometry) |
| Et | ethyl |
| $Et_3N$ | triethylamine |
| EtOH | ethanol |
| GLC | gas-Liquid Chromatography |
| h | hour/s |
| HaCaT | immortal human keratinocyte |
| HPLC | high performance liquid chromatography |
| $HPPh_2$ | diphenylphosphine |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single quantum correlation spectroscopy |
| $IC_{50}$ | half maximal inhibitory concentration |
| ISO | International Organization for Standardization |
| *J* | coupling constant |
| LDA | Lithium diisopropylamide |
| L-dopa | L-3,4-dihydroxyphenylalanine |
| LHMDS | Lithium bis(trimethylsilyl)amide solution |
| M | molar |
| m | multiplet (spectrum) |

| | |
|---|---|
| m/z | mass to charge ratio |
| $M^+$ | molecular ion |
| MCF-7 | Michigan Cancer Foundation-*7 breast cancer cell line* |
| Me | methyl |
| MeO | methoxy |
| MeOH | methanol |
| mol | mole (s) |
| MOM | methoxymethyl |
| m.p. | melting point |
| MS | mass spectrometry/ molecular sieves |
| MTT | 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide |
| NBS | *N*-Bromosuccinimide |
| nM | nanometer (unit of measure) |
| NMO | *N*-methylmorpholine *N*-oxide |
| NMR | nuclear Magnetic Resonance Spectroscopy |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| $^n$Pr, *n*Pr | *n*-Propyl |
| NRU | neutral red uptake |
| Ns | nosyl (4-nitrobenzenesulfonyl) |
| p | page |
| P(*t*Bu)$_3$ | tri-*tert*-Butylphospine |
| Ph | phenyl |
| $Ph_3P$ | triphenylphosphine |
| PhH | benzene |
| PhMe | toluene |
| PhO | phenolate |

| | |
|---|---|
| ppm | parts per million |
| *n*$Pr_3P$ | tripropylphosphine |
| q | quadruplet (spectrum) |
| quant. | quantitative |
| quint | quintuplet (spectrum) |
| R | generalized alkyl group or substituent |
| RBC | red blood cells |
| RCM | ring-closing metathesis |
| rfx | reflux |
| rt | room temperature |
| s | singlet (spectrum) |
| t | time, triplet (spectrum) |
| *t*-Bu (*t*Bu, $^t$Bu) | *tert*-butyl |
| TEMPO | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl |
| $Tf_2O$ | trifluoromethanesulfonic anhydride |
| THAHS | tetrahexylammonium hydrogensulfate |
| THF | tetrahydrofuran |
| Ts | tosyl (*p*-toluenesulfonyl) |
| UV | ultraviolet radiation |
| VTMS | vinyloxytrimethylsilane |
| $ZnEt_2$ | diethylzinc |
| β-$CF_3$ | beta-trifluoromethyl |
| γ-$CF_3$ | gamma-trifluoromethyl |
| µW | microwave activation |
| δ | chemical shift |

*CHAPTER 1:*

# ***Introduction and objectives***

In the current PhD thesis are reported the different results related to Tris(triphenylphosphine)ruthenium(II) dichloride ($RuCl_2(PPh_3)_3$) as a powerful and versatile catalyst for the synthesis of β- γ- and δ-lactams and also for the isomerization of protected allylamines to *Z*-enamines under microwave activation.

The first chapter of this thesis is a short overview that opens with the description of $RuCl_2(PPh_3)_3$, its preparation and then describes the numerous chemical transformations in which this catalyst is involved.

The second chapter outlines our results concerning the synthesis of β-lactams from *N*-tethered benzyl trichloroacetamides through a $C(sp^3)$-$C(sp^3)$ bond formation. The latter takes place *via* an unprecedented "Ru" complex promoted activation of a benzylic position in a radical process. In this chapter are also disclosed the results regarding the cytotoxic activity and hemocompatibility studies of six of these lactams.

The third chapter introduces the usage of $RuCl_2(PPh_3)_3$ as a catalyst in the isomerization of *N*-allyl carbamates and *N*-allyl amides to the corresponding *Z*-enecarbamates and *Z*-enamides with very good yields and excellent selectivity.

Finally, the fourth chapter focuses on the synthesis of γ- and δ-lactams from *N*-tethered alkenyl trichloroacetamides in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$. In this part of the work, a reliable diastereoselective Atom Transfer Radical Cyclization is reported from different substrates in very short reaction time and with good yields. The methodology was successfully applied to the synthesis of functionalized indole and morphan scaffolds present in many natural compounds such as the *Daphniphyllum* alkaloids.

## 1.1. A short overview on ruthenium complexes

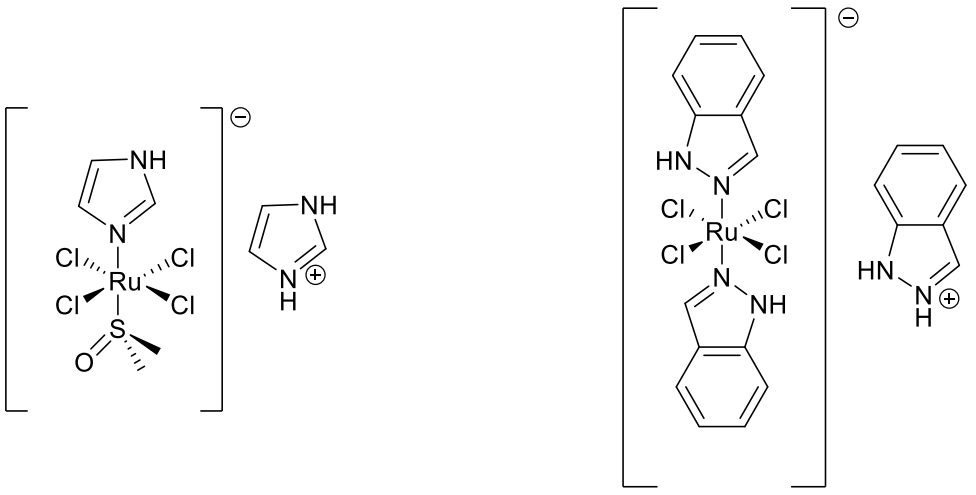
The element ruthenium (Ru) was discovered in 1844 in the Ural Mountains by a Russian scientist called Karl Ernst Claus. He named it “Ruthenium” in honor of his native country after the word “Ruthenia” which was the Latin name for Russia until the end of the 17th century.[1]

Ruthenium is a rare transition metal found in platinum ores as a minor component. Like other metals of the platinum group it is inert to most of other chemicals.

Ru has the widest scope of oxidation states of all elements of the Periodic table (from –2 valent in $Ru(CO)_4^{2-}$ to octavalent in $RuO_4$), and various coordination geometries in each electron configuration.

The ruthenium-based catalysts started to be more explored for their great potential in catalytic reactions and synthetic methods at the beginning of 1980s.

Ruthenium forms a wide range of compounds with carbon-ruthenium bonds that have been considered for cancer therapy (figure 1.1). KP1019 and NAMI-A were discovered after an intense synthetic work carried out in the field of anticancer metal complexes.[2]




**NAMI-A**
(antitumor/antimetastatic)

**KP1019**
(colorectal cancer treatment)

**Figure 1.1.** First ruthenium anticancer compounds in clinical trials.

[1] Pitchkov, V. N. The discovery of ruthenium. *Platin. Met. Rev.* **1996**, *40*, 181-188.
[2] (a) Clarke, M. J. Oncological implications of the chemistry of ruthenium. *Met. Ions. Biol. Syst.* **1980**, *11*, 231-283. (b) Vilar, R. Nucleic acid quadruplexes and metallo-drugs. *Met. Ions Life Sci.* **2018**, *18*, 325-349.

NAMI-A ((ImH)[*trans*-$RuCl_4$(dmso-S)(Im)], Im = imidazole) and KP1019 ((IndH)[*trans*-$RuCl_4(Ind)_2$], Ind = indazole) are structurally related Ru(III) compounds, water-soluble with a low systemic toxicity and moderate stability under physiological conditions as a consequence they are classified as prodrugs.

The pharmacological profile of the two is very distinct, KP1019 has a cytotoxic effect for the treatment of platinum-resistant colorectal cancers, whereas NAMI-A has a non-cytotoxic reputation being effective as an antimetastatic drug. The mechanism of action reveals that KP1019 is able to enter the cells in an appreciable amounts, whereas NAMI-A localizes mostly extracellularly or on the cell membrane.[3]

Among the homogenous catalysts, solutions containing ruthenium trichloride are highly active and used especially for the preparation of other ruthenium complexes that can be divided into five groups according to their supporting ligands:

- Oxo, such as $RuO_4$, $[RuO_2(bpy)\{IO_3(OH)_3\}] \times 1.5H_2O$
- Carbonyl, such as $Ru_3(CO)_{12}$, $[RuCl_2(CO)_3]_2$
- Tertiary phosphines, such as $RuCl_2(PPh_3)_3$, $RuH_2(PPh_3)_4$
- Cyclopentadienyl, such as $RuClCp(PPh_3)_2$, $RuCl_2Cp(PPh_3)$
- Arenes/dienes, such as $[RuCl_2(p\text{-cymene})]_2$, Dichloro(cycloocta-1,5-diene)ruthenium

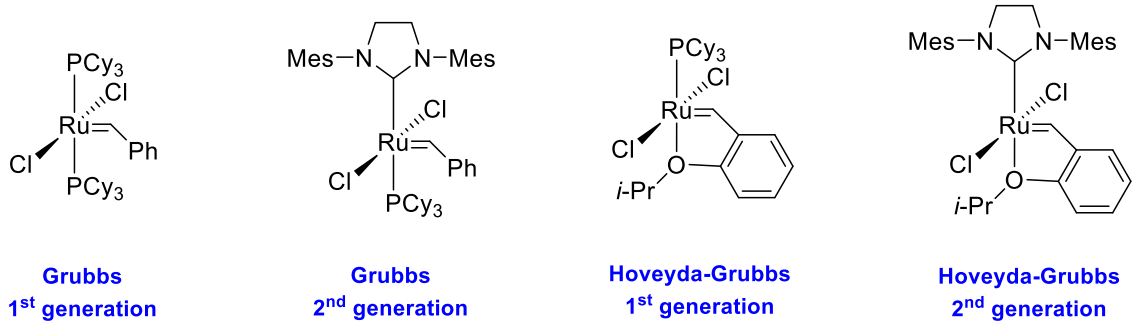
These species have demonstrated abilities to design specific organic transformations, low redox potential, high electron transfer ability, high coordination ability to heteroatoms, Lewis acid acidity or reactivity of metallic species and intermediates.[4]

A large number of reactions were developed using these ruthenium complexes, one of the most important ones being Grubbs (1st and 2nd generation) that have become extremely important in organic synthesis. Grubbs catalysts,

[3] (a) Aitken, J. B.; Antony, S.; Weekley, C.M.; Lai, B.; Spiccia, L.; Harris, H. H. Distinct cellular fates for KP1019 and NAMI-A determined by X-ray fluorescence imaging of single cells. *Metallomics* **2012**, *4*, 1051-1056. (b) Alessio, E.; Messori L. NAMI-A and KP1019/1339, two iconic ruthenium anticancer drug candidates face-to-face: A case story in medicinal inorganic chemistry. *Molecules* **2019**, *24*, 1-20.

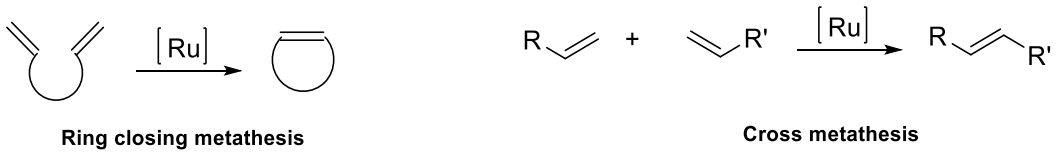
[4] (a) Komiya, S.; Hurano, M. Group 8 (Fe, Ru, Os) metal compounds. Synthesis of organometallic compounds: A practical guide. Komiya, S., Ed. John Wiley & Sons: England, **1997**; pp. 159-203. (b) Naota, T.; Takaya, H.; Murahashi. S.I. Ruthenium-catalyzed reactions for organic synthesis. *Chem. Rev.* **1998**, *98*, 2599–2660.

some of them presented in Figure 1.2, are usually used in olefin metathesis for the generation of new C-C bonds (Figure 1.3).[5] Nevertheless many other non-metathetic behaviours have been reported for theses ruthenium complexes.




**Grubbs 1st generation** | **Grubbs 2nd generation** | **Hoveyda-Grubbs 1st generation** | **Hoveyda-Grubbs 2nd generation**

**Figure 1.2.** Common Grubbs catalysts used in metathesis.




**Ring closing metathesis** | **Cross metathesis**

**Figure 1.3.** Metathetic behaviour of Ruthenium catalysts.

## 1.2. $RuCl_2(PPh_3)_3$ properties and usage in organic synthesis

Tris(triphenylphosphine)ruthenium(II) dichloride or Dichlorotris(triphenyl-phosphine)ruthenium(II) (Figure 1.4) is a coordination complex and the precursor of Grubbs' 1st generation catalyst. It is a red-brown solid or shiny black crystals soluble in organic solvents such as toluene, benzene and dichloromethane. Its molecular formula is $C_{54}H_{45}Cl_2P_3Ru$ with a molecular weight of 958.83 g/mol and a melting point between 132 and 134 °C.

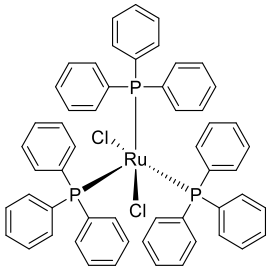



**Figure 1.4.** $RuCl_2(PPh_3)_3$ catalyst (**Ru3**).

[5] Vougioukalakis, G. C.; Grubbs, R. H. Ruthenium-based heterocyclic carbene-coordinated olefin metathesis catalysts. *Chem. Rev.* **2010**, *110*, 1746–1787.

$RuCl_2(PPh_3)_3$ is commercially available but can also be prepared in the laboratory following the synthesis described by Wilkinson in 1966.[6] An excess of triphenylphosphine and ruthenium(III) chloride hydrate are dissolved in boiling ethanol in order to make possible the formation of $RuCl_2(PPh_3)_3$ complex (scheme 1.1). The solvent could also be replaced by methanol or an acetone-water mixture.

$$RuCl_3.xH_2O + PPh_3 \xrightarrow[\text{rfx, 1 h}]{\text{EtOH}} RuCl_2(PPh_3)_3$$
quant.

**Scheme 1.1.** Synthesis of $RuCl_2(PPh_3)_3$.

$RuCl_2(PPh_3)_3$ is an effective catalyst used in oxidations, reductions, cross-couplings, Kharasch addition (ATRA) of a range of halogenated derivatives (Scheme 1.2) and isomerization of a variety of organic compounds.[7]

$$R_2C{=}CH_2 + R'X \longrightarrow R_2CX\text{-}CH_2R'$$

**Scheme 1.2.** Basic Kharasch reaction scheme.

### 1.2.1. $RuCl_2(PPh_3)_3$ in ATRC

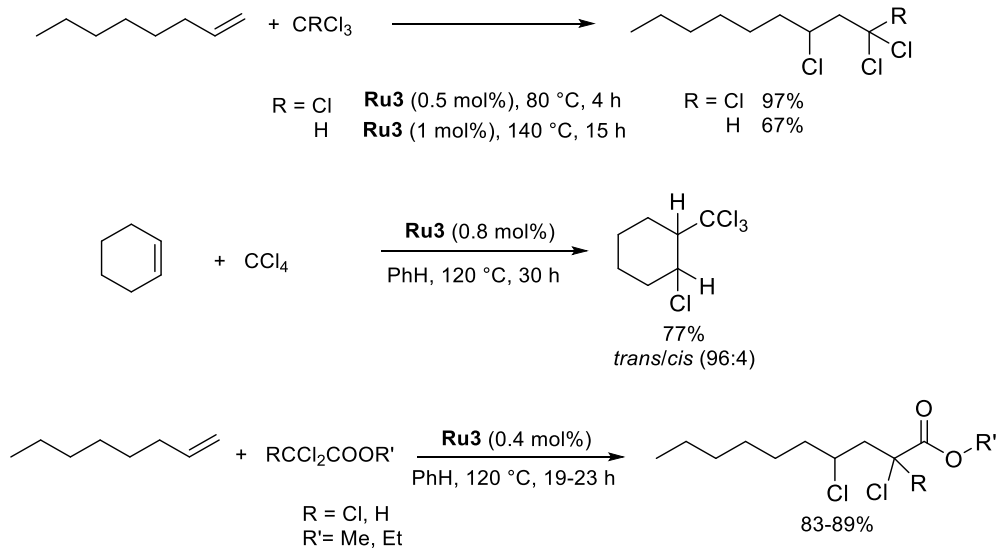
In 1973 Matsumoto *et al*. reported the first intermolecular addition of $CCl_4$ and $CHCl_3$ to terminal olefins catalyzed by $RuCl_2(PPh_3)_3$.[8a] Later, using the same

[6] (a) Samouei, H.; Grushin, V. V. New, Highly Efficient, simple, safe, and scalable synthesis of $[(Ph_3P)_3Ru(CO)(H)_2]$. *Organometallics* **2013**, *32*, 4440-4443. (b) Stephenson, T. A.; Wilkinson, G. New complexes of ruthenium (II) and (III) with triphenylphosphine, triphenylarsine, trichlorostannate, pyridine and other ligands. *J. Inorg. Nucl. Chem*. **1966**, *28*, 945-956. (c) Hallman, P. S; Stephenson, T. A.; Wilkinson, G. Tris(triphenylphosphine)dichlororuthenium(II). *Innorganic Syntheses,* Volume XII, McGraw-Hill Book Company, **1970**, 237-240.

[7] (a) Kharasch M.; Jensen E.; Urry, W.; Addition of carbon tetrachloride and chloroform to olefins. *Science* **1945**; 102 (b) Plummer, J. S., Shun-Ichi, M.; Changjia, Z. Dichlorotris (triphenylphosphine) ruthenium(II), e-EROS Encyclopedia of reagents for organic synthesis, John Wiley, **2010**.

[8] (a) Matsumoto, H.; Nakano, T.; Nagai, Y. Radical reactions in the coordination sphere I. Addition of carbon tetrachloride and chloroform to 1-olefins catalyzed by ruthenium (II) complexes. *Tetrahedron Lett.* **1973**, *14*, 5147-5150. (b) Matsumoto, H.; Nikaido, T.; Nagai, Y. Radical reactions in the coordination sphere II. Stereoselective addition of carbon tetracrloride to cyclohexene catalyzed by dicrlorotris(triphenylphosphine)-rutrenium(II). *Tetrahedron Lett.* **1975**, *16*, 899-902. (c) Matsumoto, H.; Nikaido, T, Nagai, Y. Radical reactions in the coordination sphere. III. Reactions of dichloro- and trichloroacetic acid esters with 1-olefins catalyzed by dichlorotris(triphenylphosphine) ruthenium(II). *J. Org. Chem.* **1976**, *41*, 396–398.

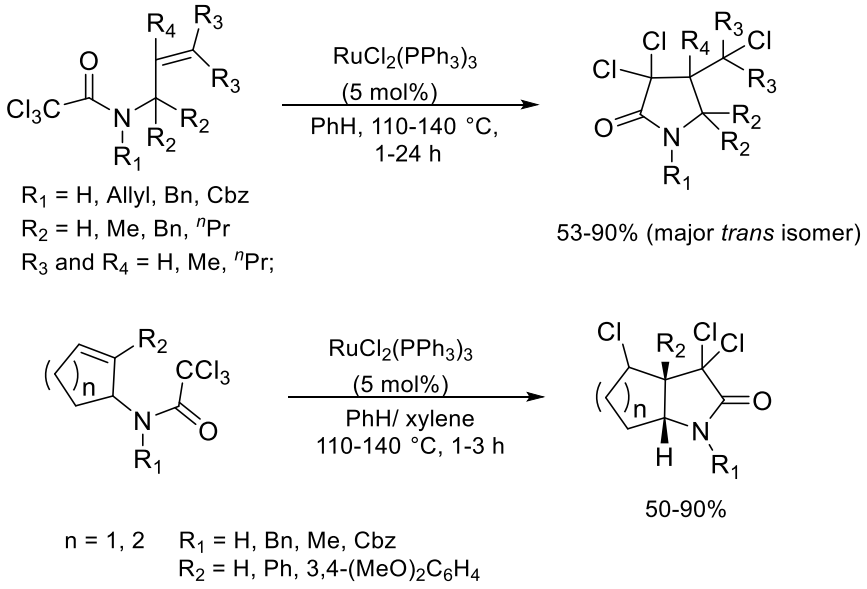
catalyst, the same authors described a stereoselective radical addition of carbon tetrachloride to cyclohexene[8b] and also the reaction of dichloro- and trichloroacetic acid esters with 1-olefins[8c] (Scheme 1.3). This research activity encourages the exploration of numerous other Ru complexes for their ability to catalyze ATRA and ATRC reactions.




**Scheme 1.3.** Intermolecular additions catalyzed by $RuCl_2(PPh_3)_3$.

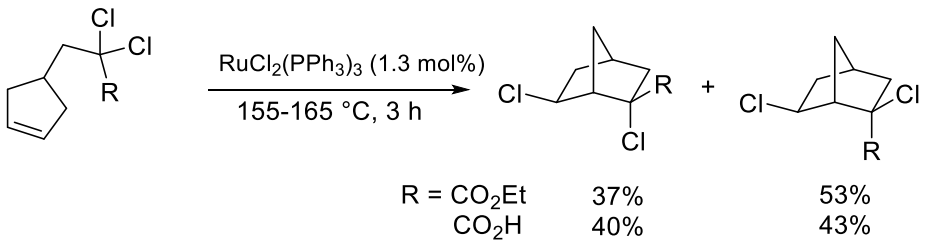
$RuCl_2(PPh_3)_3$ usage for the transformation of trichloroacetamides through ATRC has been outlined in very few examples. Itoh reported the first articles that describe the novel transformation from trichloroacetamides to trichlorinated γ-lactams despite the potential for formation of δ-lactams. The conditions employed involved usage of 5 mol% of **Ru3** catalyst at 110-140 ºC obtaining yields between 53-90% of the corresponding *trans* isomers predominantly. Additionally *cis*-fused hexahydro-oxindoles were also prepared using similar conditions (Scheme 1.4).[9]

[9] (a) Nagashima, H.; Wakamatsu, H.; Itoh, K. A novel preparative method for γ-butyrolactams via carbon-carbon bond formation: copper or ruthenium-catalysed cyclization of *N*-ally trichloroacetamides. *J. Chem. Soc., Chem. Commun.* **1984**, 652-653. (b) Nagashima, H.; Ara, K.; Wakamatsu, H.; Itoh, K. Stereoselective preparation of bicyclic lactams by copper- or ruthenium-catalysed cyclization of *N*-allyltrichloroacetamides: a novel entry to pyrrolidine alkaloid skeletons. *J. Chem. Soc., Chem. Commun.* **1985**, *53*, 518-519. (c) Nagashima, H.; Ozaki, N.; Ishii, M.; Koji,S.; Washiyama, M.; Itoh, K. Transition Metal-Catalyzed Radical Cyclizations: A Low-Temp. process for the cyclization of *n*-protected *n*-allyltrichloroacetamides to trichlorinated γ-lactams and application to the stereoselective preparation of β,γ-disubstituted γ-lactams. *J. Org. Chem.* **1993**, *58*, 464-470.




**Scheme 1.4.** $RuCl_2(PPh_3)_3$ mediated synthesis of γ-lactams (ref. 9).

By the same period, Weinreb *et al.* reported the intramolecular cyclization of unsaturated α,α-dichloro esters, acids and nitriles catalyzed by $RuCl_2(PPh_3)_3$ for the synthesis of functionalized carbocycles (Scheme 1.5).[10]

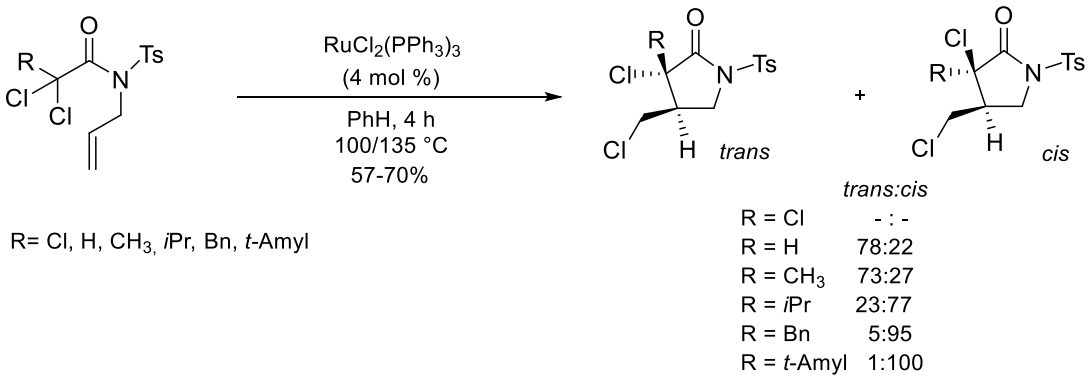



**Scheme 1.5.** A sample of $RuCl_2(PPh_3)_3$ mediated synthesis of carbocycles (ref. 10).

Additionally, Slough reported the synthesis of γ-lactams from α-chloro *N*-tosyl amides in the presence of $RuCl_2(PPh_3)_3$ as a catalyst. The reaction was achieved from a series of substrates varying the substituent on the radical center generated in the first place (R = Cl, H, $CH_3$, *i*Pr, $CH_2Ph$, *tert*-amyl). The reaction takes place with predominant *trans* selectivity and a transition from *trans* to *cis*

[10] (a) Hayes, T. K.; Villani. R.; Weinreb, S. M. Exploratory studies of the transition metal catalyzed intramolecular cyclization of unsaturated α,α-dichloro esters, acids, and nitriles. *J. Amer. Chem. Soc.* **1988**, *110*, 5533-5543. (b) Lee, G. M.; Parvez, M.; Weinreb. S.M. Intramolecular metal catalysed Kharasch cyclizations of olefinic α-halo esters and acids. *Tetrahedron* **1988**, *44*, 4671-4678. (c) Phelps, J. C.; Bergbreiter, D. E.; Lee, G. M.; Villani, R.; Weinreb. S. M. A polyethylene-bound ruthenium(II) catalyst for inter- and intramolecular kharasch reactions. *Tetrahedron Lett*. **1989**, *30*, 3915-3918.

was observed with hindered groups such as *i*-Pr, Bn and *tert*-amyl (Scheme 1.6).[11,12]



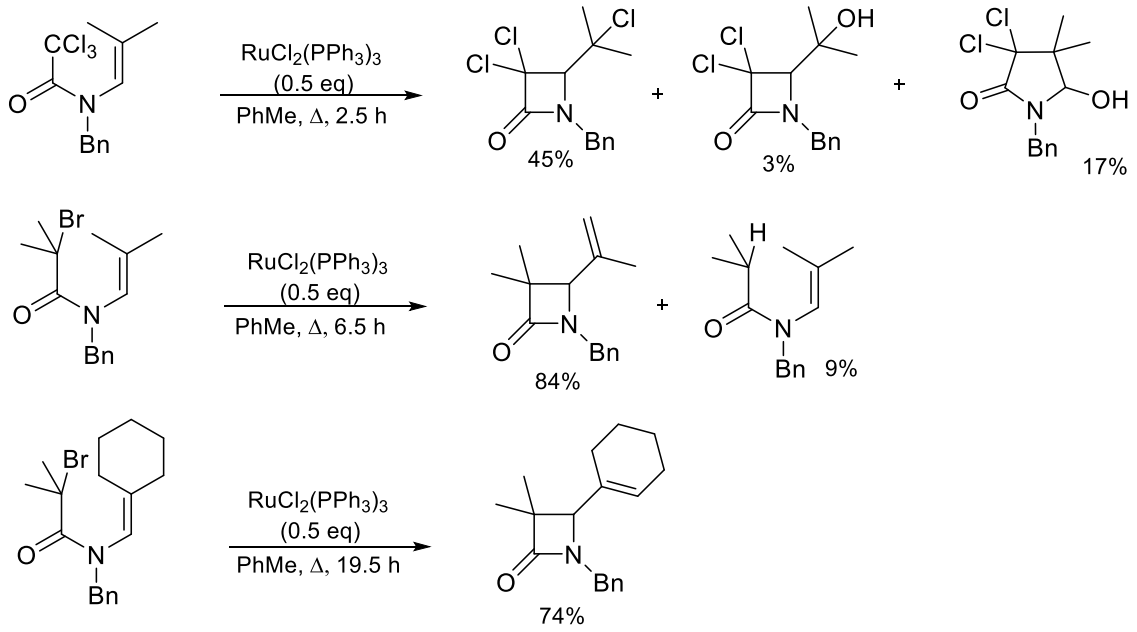

**Scheme 1.6.** *N*-tosyl amides radical cyclization catalyzed by $RuCl_2(PPh_3)_3$.

Parson developed a **Ru3**-mediated ATRC toward the synthesis of β- or γ-lactams starting from *N*-vinylic trichloro- or bromoacetamides in parallel to his work with CuCl. The use of **Ru3** catalyst in toluene afforded the corresponding highly functionalized β-lactams resulting from a 4-*exo* cyclization as the main products. The authors suggested that the β-lactams are formed under a kinetic control whereas the γ-lactams are the thermodynamic products (Scheme 1.7).[13]

[11] Rachita, M. A.; Slough, G. A. Ruthenium (II) catalyzed ring closure of prochiral α-chloro-*N*-tosyl amides: A diastereoselectivity study. *Tetrahedron Lett.* **1993**, *34*, 6821-6824.

[12] Slough, G. A. $(Ph_3P)_3RuCl_2$ catalyzed equilibration and elimination of α-chloro-*N*-tosyl-2-pyrrolidinones: A unique route to unsaturated 2-pyrrolidinones. *Tetrahedron Lett.* **1993**, *34*, 6825-6828.

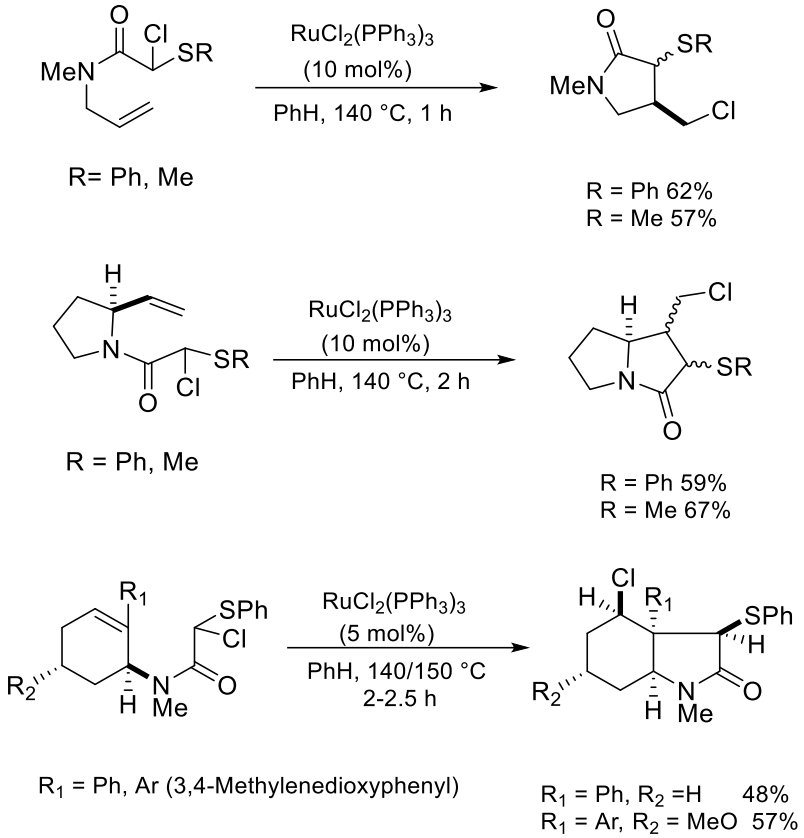
[13] Bryans, J. S.; Chessum, N. E. A.; Parsons, A.F.; Ghelfi, F. The synthesis of functionalised β and γ-lactams by cyclisation of enamides using copper(I) or ruthenium(II). *Tetrahedron Lett.* **2001**, *42*, 2901-2905.




**Scheme 1.7.** Formation of β-lactams catalyzed by $RuCl_2(PPh_3)_3$.

In 1993 Ikeda *et al*. described the synthesis of (-)-trachelanthamidine and a formal total synthesis of (±)-haemanthidine and (±)-pretazettine. One of the key steps of these syntheses is the $RuCl_2(PPh_3)_3$ catalyzed atom transfer radical cyclizations of *N*-allylic-α-chloro-α-thioacetamides to provide the corresponding α-thio-β-chloromethyl substituted γ-lactams with acceptable yields (Scheme 1.8).[14]

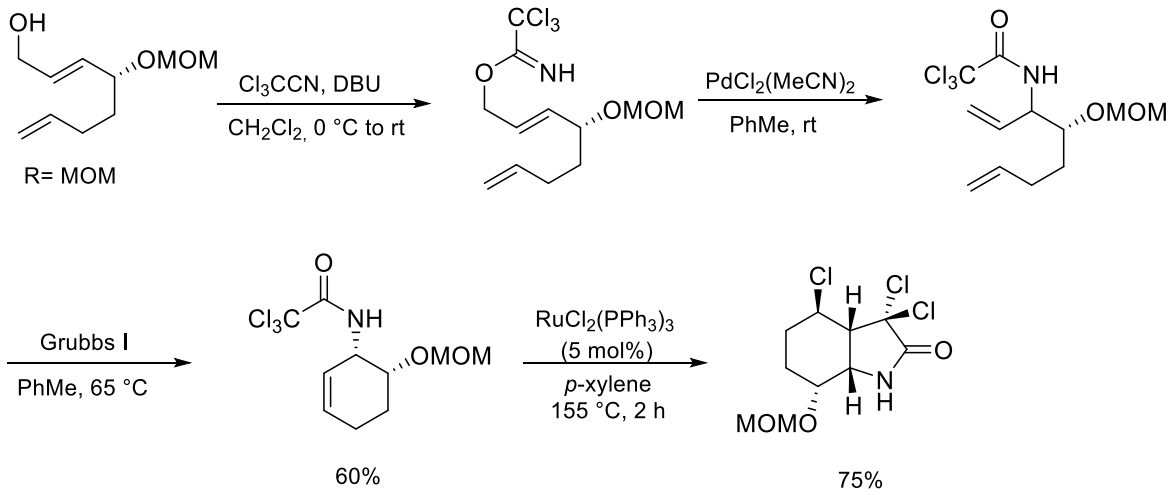
[14] Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamura, N.; Ikeda, M. Ruthenium-catalyzed chlorine atom transfer cyclizations of *N*-allylic α-chloro-α-thioacetamides. Synthesis of (-)-trachelanthamidine and formal total synthesis of (±)-haemanthidine and (±)-pretazettine. *J. Org. Chem.* **1993**, *58*, 2360-2368.




**Scheme 1.8.** Synthesis of γ-lactams by chlorine atom transfer.

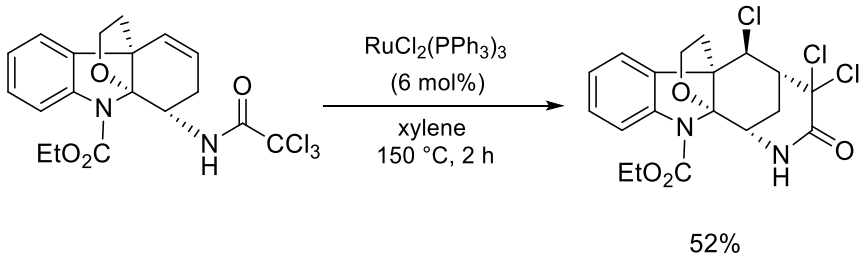
In 2009 Sutherland *et al.* published an elegant work where a tandem MOM-ether directed Overman rearrangement and RCM reaction process were developed for the efficient and highly selective synthesis of cyclopentenyl and cyclohexenyl trichloroacetamides. The latter was then submitted to a Kharasch cyclization in the presence of $RuCl_2(PPh_3)_3$ to provide the corresponding bicyclic amide as a single stereoisomer in 75% yield (Scheme 1.9).[15]

[15] Swift, M. D.; Donaldson, A.; Sutherland, A. Tandem aza-Claisen rearrangement and ring-closing metathesis reactions: the stereoselective synthesis of functionalised carbocyclic amides. *Tetrahedron Lett.* **2009**, *50,* 3241-3244.




**Scheme 1.9.** Overman rearrangement, RCM and kharasch cyclization in the synthesis of functionalized carbocyclic amides.

Finally, in an approach to the pentacyclic core of aspidophylline A, Shi *et al.* described a strategy featuring a CAN-mediated intramolecular azidoalkoxylation of an enecarbamate to construct the fused tetrahydrofuran ring and a $RuCl_2(PPh_3)_3$-catalyzed intramolecular atom transfer radical cyclization to form the azabicycle[3,3,1] fragment as it is indicated in Scheme 1.10.[16]



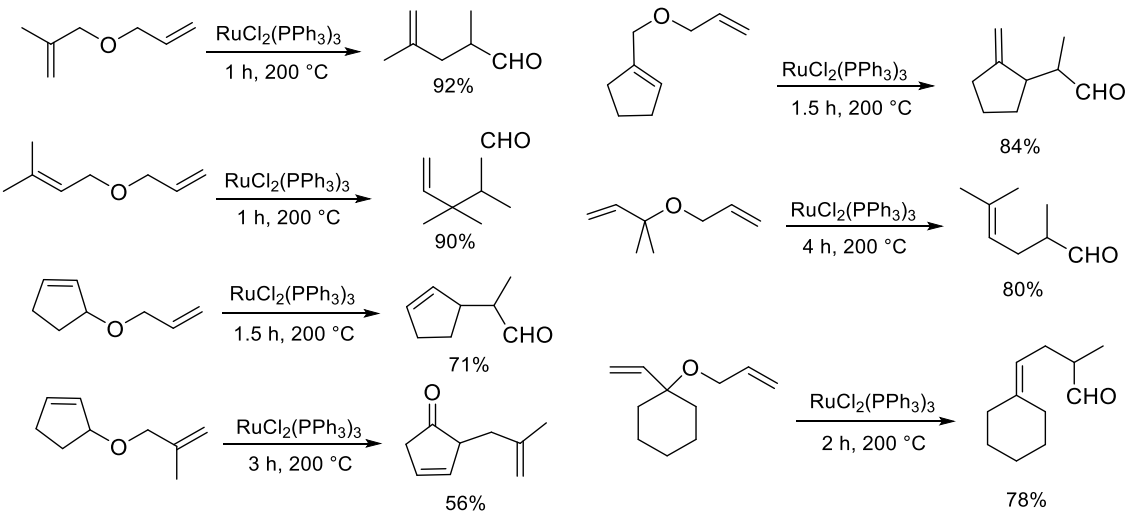

**Scheme 1.10.** Construction of the morphan ring present in aspidophylline A.

## 1.2.2. $RuCl_2(PPh_3)_3$ in isomerization

Besides ATRC, $RuCl_2(PPh_3)_3$ was widely used in isomerization processes as it is outlined in the examples reported bellow.

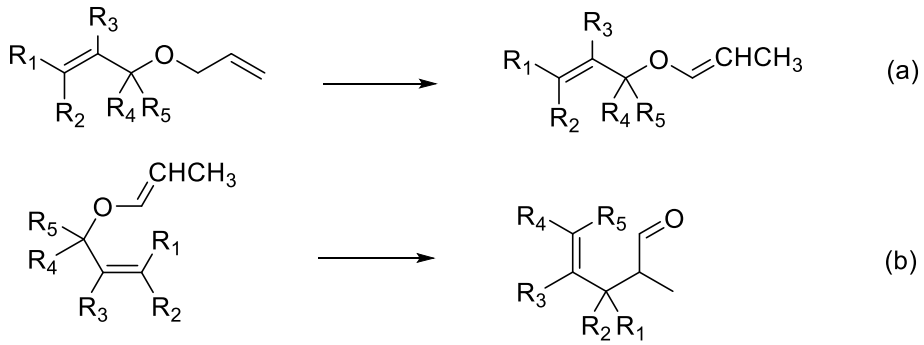
[16] Li, Q.; Li, G.; Ma, S.; Feng, P.; Shi, Y. An approach to the skeleton of aspidophylline A. *Org. Lett.* **2013**, *15*, 2601-2603.

Unsymmetrical diallyl ethers give γ,δ-unsaturated ketones or aldehydes upon heating in the presence of tris(triphenylphosphine)ruthenium dichloride.[17] The selective rearrangement takes place in the presence of 0.1 mol% of catalyst and at 200 °C affording pure carbonyl compounds after the distillation process. Although 2 different isomeric γ,δ-unsaturated carbonyl compounds could be obtained from each diallyl ether, the reaction was highly regiospecific providing the isomers showed in Scheme 1.11 alone.




**Scheme 1.11.** Examples of $RuCl_2(PPh_3)_3$ catalyzed rearrangement of unsymmetrical diallyl ethers.

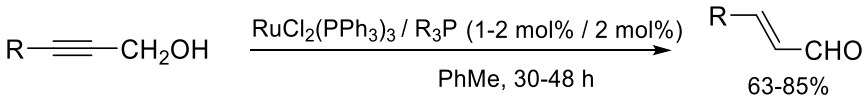
These final aldehydes and ketones are presumably produced by an initial ruthenium catalyzed 1,3-hydrogen shift (Scheme 1.12a) followed by a Claisen rearrangement (Scheme 1.12b).




**Scheme 1.12.** Rearrangement mechanism of unsymmetrical diallyl ethers.

[17] Reuter, J. M.; Salomon, R. G. Ruthenium(II) catalyzed rearrangement of diallyl ethers. a synthesis of γ,δ-unsaturated aldehydes and ketones. *J. Org. Chem.* **1977**, *42*, 3360–3364.

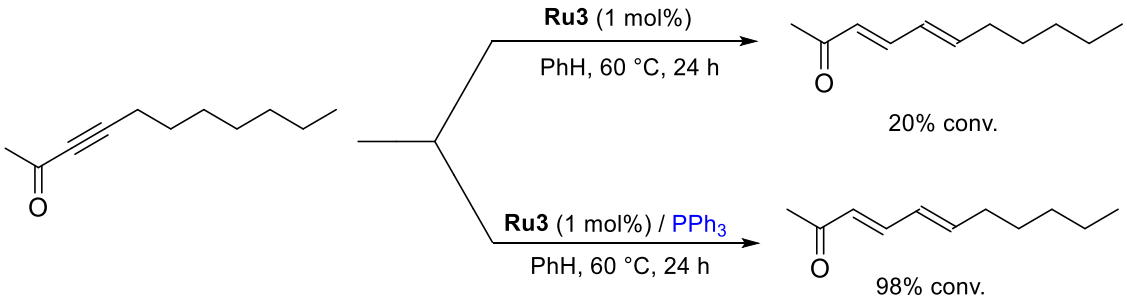
The first example of $RuCl_2(PPh_3)_3$ catalyzed isomerization of 2-ynols to the simple (2*E*)-enals was reported more than three decades ago by Lu *at al.*[18] The stereoselective transformation proceeds in long reaction time (30-48 h) and in the presence of trialkyl phosphine ($R_3P$) under reflux of toluene (Scheme 1.13). Curiously in the absence of a ligand, or using $Ph_3P$ as the ligand, the reaction did not occur.




R = $nC_6H_{13}$, $nC_5H_{11}$, $nC_7H_{15}$, $nC_4H_9$, $C_6H_5$
$R_3P$ = $nBu_3P$/ $iPr_3P$

**Scheme 1.13.** Stereoselective isomerization of 2-ynols to 2-enals.

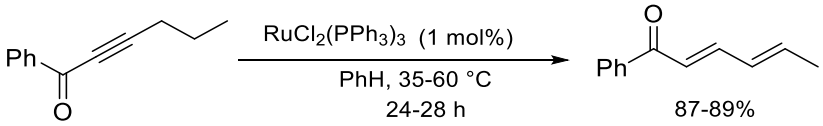
$RuCl_2(PPh_3)_3$ catalyzes the isomerization of *α,β*-ynones to (*E,E*)-α,β,γ,δ-dienones. Indeed successful isomerization of 3-undecyn-2-one to (*3E,5E*)-undeca-3,5-dien-2-one with a 20% rate of conversion took place using 1 mol% of $RuCl_2(PPh_3)_3$ over a 24 h period of time. The presence of an excess of phosphine ligands such as $Ph_3P$ influenced significantly the activity of the catalyst giving a 98% conversion under the same reaction conditions (Scheme 1.14).




**Scheme 1.14.** Effect of $PPh_3$ as a ligand in the isomerization of 3-undecyn-2-one.

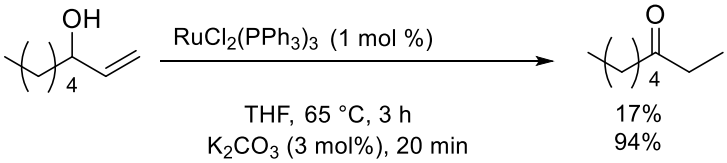
The procedure was successfully applied to prepare several natural compounds among them l-phenyl-(2*E*,4*E*)-hexa-2,4-dienone (capillone), a component of artemisia with medicinal properties (Scheme 1.15).[19]

[18] Ma, D.; Lu, X. A simple route to α,β-unsaturated aldehydes from prop-2-ynols. *J. Chem. Soc. Chem. Commun.* **1989**, *14*, 890-891.
[19] Ma, D.; Yu, Y.; Lu, X. Highly stereoselective isomerization of ynones to conjugated dienones catalyzed by transition-metal complexes. *J. Org. Chem.* **1989**, *54*, 1105-1109.



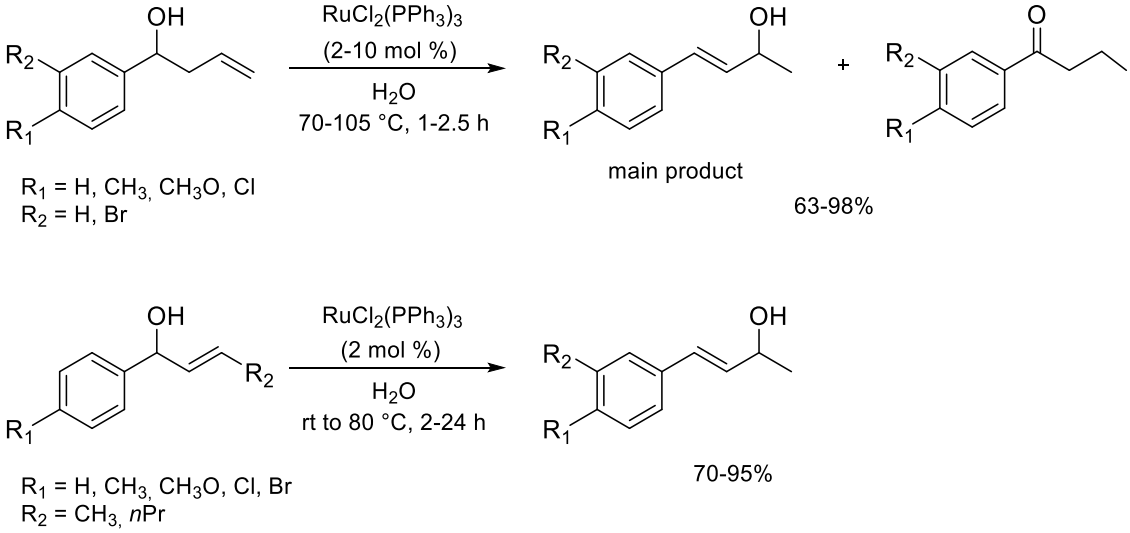

**Scheme 1.15.** Stereoselective isomerization in the synthesis of capillone.

$RuCl_2(PPh_3)_3$ has also been used to convert allylic alcohols to the corresponding saturated ketones. A dramatic rate enhancement was observed when a catalytic amount of a base ($K_2CO_3$) was added to the reaction mixture (Scheme 1.16).[20]




**Scheme 1.16.** Isomerization of 1-octen-3-ol.

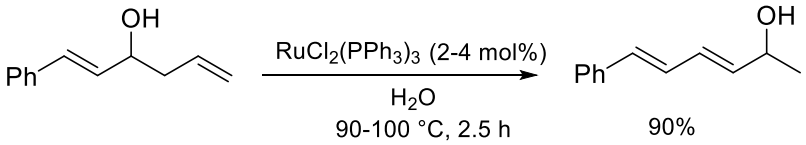
Another example of Isomerization from alkenyl alcohols using $RuCl_2(PPh_3)_3$ as a catalyst in water, was reported by Li *et al.* in 1998.[21] In this investigation the functional groups of homoallylic and allylic alcohols are repositioned to give allylic alcohols with controlled regioselectivity (Scheme 1.17).




**Scheme 1.17.** Isomerization of homoallylic and allylic alcohols in water.

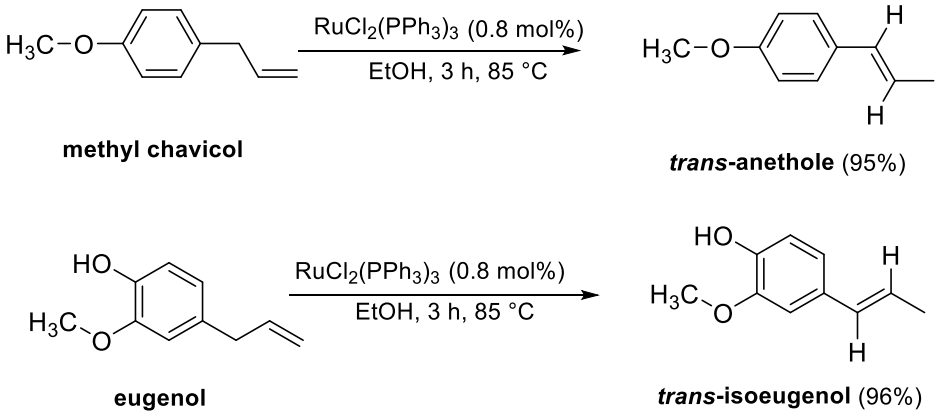
[20] Baeckvall, J.-E.; Andreasson, U. Ruthenium-catalyzed isomerization of allylic alcohols to saturated ketones. *Tetrahedron. Lett.* **1993**, *34*, 5459-5462.
[21] Wang, D.; Chen, D.; Haberman, J. X.; Li, C. J. Ruthenium-catalyzed isomerization of homoallylic alcohols in water. *Tetrahedron* **1998**, *54*, 5129-5142.

When the substrate used has both an allylic and a homoallylic functional groups, the reaction occurs exlusively by rearrangement of the homoallylic group to give the conjugated dienol product (Scheme 1.18).




**Scheme 1.18.** Selective isomerization at the homo-allylic group.

Regioselective synthesis of *trans*-anethole from methyl chavicol via double bond isomerization using $RuCl_2(PPh_3)_3$ catalyst was reported in parallel with the isomerization of eugenol into *trans*-isoeugenol.[22] The highest conversion of both molecules (almost 100%) with 95% of *trans* selectivity was achieved in ethanol using 0.8 mol% of catalyst (Scheme 1.19).

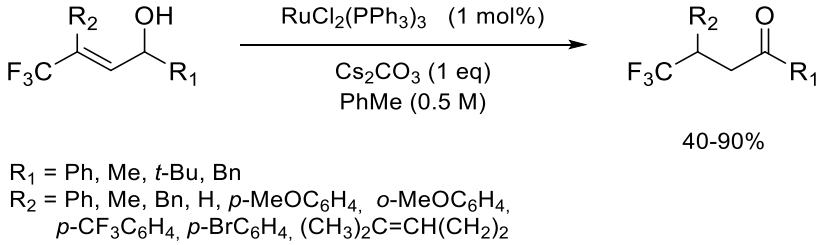



**Scheme 1.19.** Isomerization of methyl chavicol and eugenol.

Renaud and Cahard described the synthesis of β-trifluoromethylated ketones from trifluoromethylated allylic alcohols in the presence of $RuCl_2(PPh_3)_3$ as a catalyst. The ruthenium(II) complex was able to conduct the intramolecular 1,3-hydrogen shift at temperatures comprised between 30 and 70 ºC in toluene and in the presence of $Cs_2CO_3$ (Scheme 1.20).[23] In this work the $CF_3$ group was

[22] Sharma, S. K.; Srivastava, V. K.; Jasra, R. V. Selective double bond isomerization of allyl phenyl ethers catalyzed by ruthenium metal complexes. *J. Mol. Catal. A Chem.* **2006**, *245*, 200–209.
[23] Bizet, V.; Pannecoucke, X.; Renaud, J. L.; Cahard, D. Synthesis of β-$CF_3$ ketones from trifluoromethylated allylic alcohols by ruthenium catalyzed isomerization. *J. Fluor. Chem.* **2013**, *152*, 56-61.

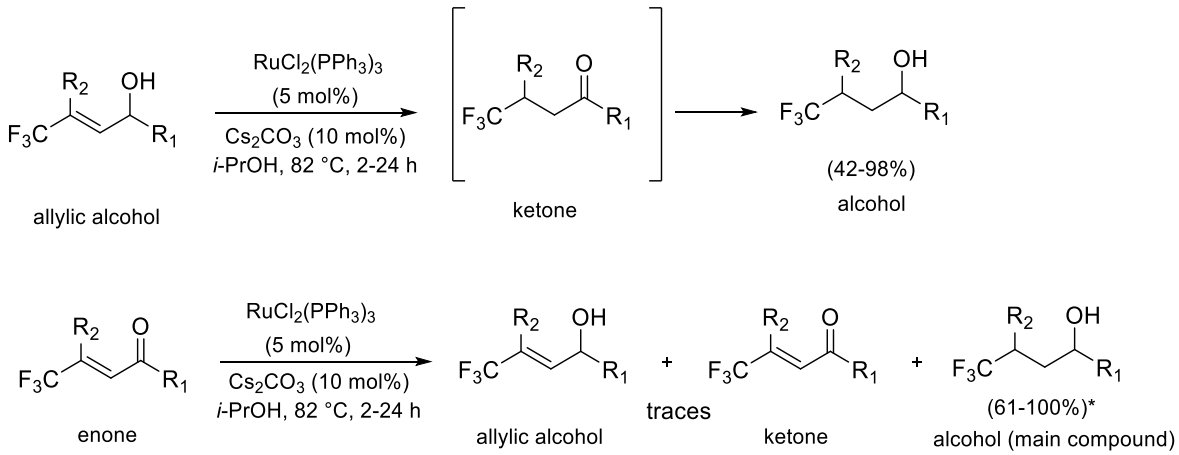
found to strongly accelerate the insertion step compared to non-fluorinated substrates.




$R_1$ = Ph, Me, *t*-Bu, Bn
$R_2$ = Ph, Me, Bn, H, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$, *p*-$CF_3C_6H_4$, *p*-$BrC_6H_4$, $(CH_3)_2C=CH(CH_2)_2$

**Scheme 1.20.** Isomerization of β-trifluoromethylated secondary allylic alcohols conducted by **Ru3** catalyst.

The same authors reported a tandem isomerization-transfer hydrogenation of γ-$CF_3$ allylic alcohols and β-$CF_3$ enones that allows the synthesis of saturated alcohols in high yields. Instead of hydrogen gas, normally necessary in a classical hydrogenation, in this work, 2-propanol was used as a solvent and as the hydrogen source. After a screening of various Ru catalysts and bases, the best combination to obtain the desired saturated alcohol was $RuCl_2(PPh_3)_3/Cs_2CO_3$ in a 1:2 ratio (Scheme 1.21).[24]




$R_1$ = Ph, Me, *t*Bu, Bn
$R_2$ = Ph, Me, Bn, H, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$, *p*-$CF_3C_6H_4$, *p*-$BrC_6H_4$, $(CH_3)_2C=CH(CH_2)_2$
* with 2 exceptions: $R_1$ = Ph, *t*-Bu and $R_2$ = Bn, Ph only traces of alcohol

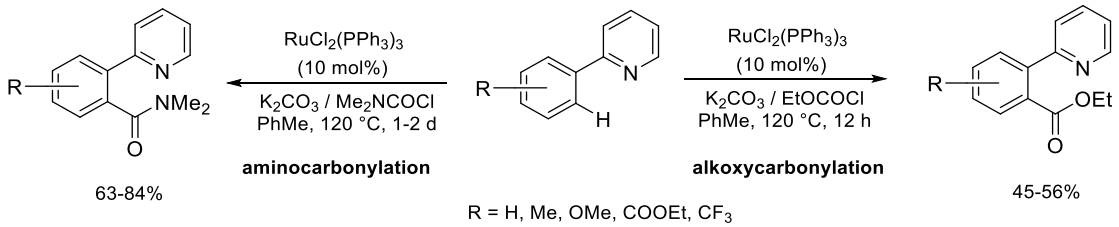
**Scheme 1.21.** Isomerization-transfer hydrogenation of γ-$CF_3$ allylic alcohols and β-$CF_3$ enones to satured alcohols.

[24] Bizet, V.; Pannecoucke, X.; Renaud, J. L.; Cahard, D. Ruthenium-catalyzed one-pot tandem isomerization-transfer hydrogenation reactions of γ-trifluoromethylated allylic alcohols and β-trifluoromethylated enones. *Adv. Synth. Catal.* **2013**, *355*, 1394–1402.

### 1.2.3. $RuCl_2(PPh_3)_3$ in C-H activation reactions

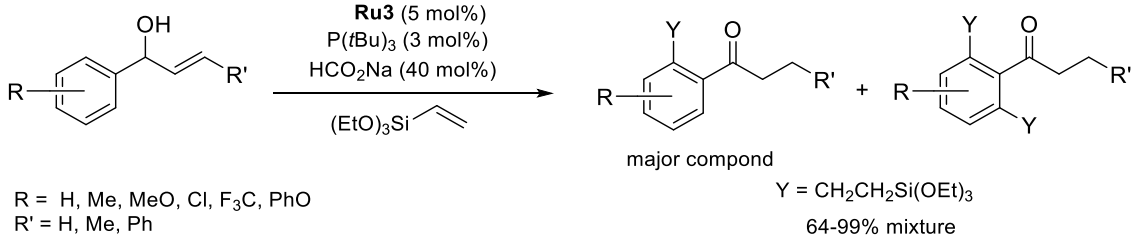
C-C bond formation involving C-H activation and addition on unsaturated substrates has been investigated in the presence of transition metal catalysts.[25]

Kakiuchi *et al.* demonstated that $RuCl_2(Ph_3)_3$ catalyzes the regioselective amino- and alkoxycarbonylations at aromatic C-H bonds using carbamoyl chlorides and alkyl chloroformates respectively without the intervention of an oxidant (Scheme 1.22). A broad generality of amide and ester groups was achieved taking advantage of the wide availability of carbonylating agents.[26]




**Scheme 1.22.** Amino- and alkoxycarbonylations through aromatic C–H activation.

Martín-Matute *et al.* described a general tandem isomerization of allylic alcohols/C-H activation catalyzed by the stable $RuCl_2(PPh_3)_3$ complex. The tandem process affords a variety of ortho alkylated ketones with excellent yields and in very short reaction times (Scheme 1.23).[27]




**Scheme 1.23. Ru3**-catalyzed tandem isomerization/C-H activation/C-C bond formation.

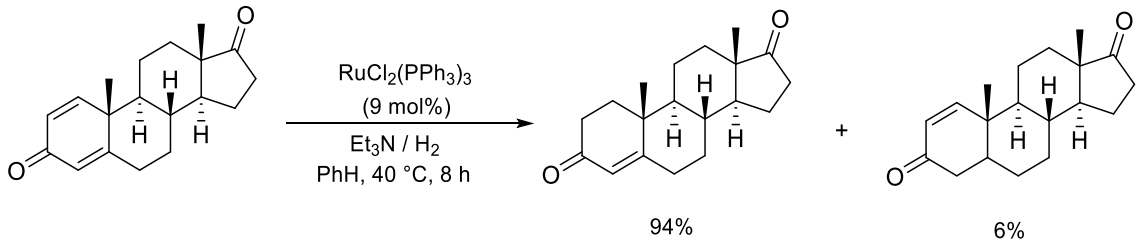
[25] For a review see: Ritleng, V.; Sirlin, C.; Pfeffer, M. Ru-, Rh-, and Pd-catalyzed C-C bond formation involving C-H activation and addition on unsaturated substrates: Reactions and mechanistic aspects. *Chem. Rev.* **2002**, *102*, 1731–1769.

[26] Kochi, T.; Urano, S.; Seki, H. Mizushima, E.; Sato, M.; Kakiuchi, F. Ruthenium-catalyzed amino- and alkoxycarbonylations with carbamoylchlorides and alkyl chloroformates via aromatic C-H bond cleavage. *J. Am. Chem. Soc.* **2009**, *131*, 2792–2793.

[27] Bartoszewicz, A.; Martín-Matute, B. Building molecular complexity via tandem Ru-catalyzed isomerization/C-H activation. *Org. Lett.* **2009**, *11*, 1749-1752.

## 1.2.4. $RuCl_2(PPh_3)_3$ in hydrogenation and hydrogen transfer reactions

Selective hydrogenation of 3-oxo-1,4-diene steroidal compounds in the presence of $RuCl_2(PPh_3)_3$ occurs at a relatively low temperature and under a high hydrogen pressure (10-162 kg/cm$^2$) providing high yields of the corresponding 3-oxo-4-enes (Scheme 1.24).[28] The activity and selectivity of this Ru-complex in the hydrogenation of 1,4-androstadiene-3,17-dione was improved by adding an optimal amount of triethylamine.[29]

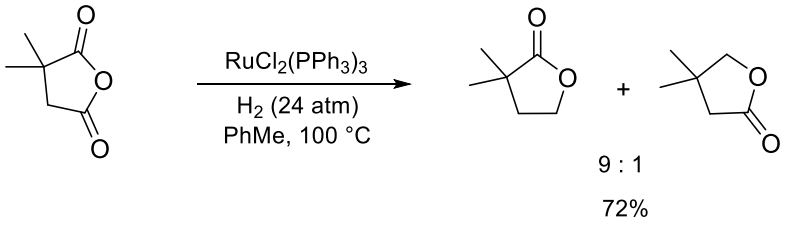



**Scheme 1.24. Ru3**-Hydrogenation of 1,4-androstadiene-3,17-dione.

Other examples of selective hydrogenations using $RuCl_2(PPh_3)_3$ as a catalyst are those of cyclododecatriene(CDT) to cyclododecene, cyclooctadiene (COD) to cyclooctene and ethyl 2-acetyl-4,9-decadienoate to 2-acetyl-4-decenoate obtained with a high selectivity at room temperature.[30]

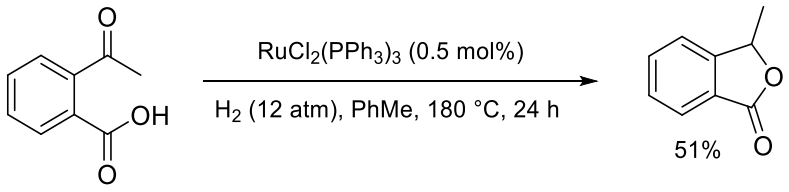
Symmetrical[31] as well as unsymmetrical[32] cyclic anhydrides could be converted in good yields into the corresponding lactones by hydrogenation catalyzed with $RuCl_2(PPh_3)_3$ (Scheme 1.25).

[28] Nishimura, S.; Tsuneda, K. Selective homogeneous hydrogenation of 3-Oxo-1,4-diene steroids with a ruthenium complex as catalyst. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 852.
[29] Nishimura, S.; Ichino, T.; Akimoto, A.; Tsuneda, K. Selective homogeneous hydrogenation of 3-Oxo-1,4-diene steroids. II. Effects of basic additives and of para Substituents on the hydrogenation with dichlorotris(triphenylphosphine)ruthenium. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 279-282.
[30] Tsuji, J.; Suzuki, H. Homogeneous selective hydrogenation of cyclododecatriene, cyclooctadiene, and 1,6-dienes to the corresponding monoenes catalyzed by $RuCl_2(PPh_3)_3$. *Chem. Lett.* **1977**, *6*, 1083-1084.
[31] Lyons, J. E. Homogeneous catalytic hydrogenolysis of the C-O bond: The selective reduction of cyclic carboxylic acid anhydrides to γ-lactones catalysed by [$RuCl_2(Ph_3P)_3$]. *J. C. S. Chem. Commun.* **1975**, *11*, 412–413.
[32] Morand, P.; Kayser, M. Highly regioselective reduction of unsymmetrical cyclic carboxylic acid anhydrides to γ-lactones. *J. C. S. Chem. Commun.* **1976**, 314-315.




**Scheme 1.25. Ru3**-Hydrogenation of 2,2-dimethylsuccinic anhydride.

Following these results, γ-lactones formation was also observed in the $RuCl_2(PPh_3)_3$-catalyzed hydrogenation of some keto acids such as levulinic acid, 3-benzoylpropionic acid and 2-acetylbenzoic acid.[33] The reactions were performed under hydrogen atmosphere in toluene as a solvent and at elevated temperature (180 ºC) with yields from 40 to 86% (Scheme 1.26).




**Scheme 1.26.** An example of **Ru3**-catalyzed hydrogenation of keto acids.

Hydrogen transfer reactions are an alternative method for hydrogenation of organic substrates where hydrogen is added to a molecule from a source other than gaseous $H_2$, being considered a more simple and economical procedure. The donor molecule itself undergoes dehydrogenation during the course of the reaction. Low-valent ruthenium complexes are excellent catalysts for the hydrogen transfer reactions because of their low redox potential and higher affinity toward hetero atom compounds. $RuCl_2(PPh_3)_3$ has been used in hydrogen transfer reactions with alcohols,[34] acids,[35]

[33] Osakada, K.; Ikariya, T.; Yoshikawa, S. Preparation and properties of hydride triphenylphosphine ruthenium complexes with 3-formyl (or acyl) propionate. *J. Organomet. Chem.* **1982**, *231*, 79–90.

[34] (a) Sasson, Y.; Blum, J. Dichlorotris(triphenylphosphine)ruthenium-Catalyzed Hydrogen Transfer from Alcohols to Saturated and Unsaturated Ketones. *J. Org. Chem.* **1975**, *40*, 1887-1896. (b) Sasson, Y.; Albin, P.; Blum, J. Effect of a Ru (II) catalyst on the rate of equilibration of carbinols and ketones. *Tetrahedron Lett.* **1974**, *10*, 833-836.

[35] Maruyama, Y.; Sezaki, T.; Tekawa, M.; Sakamoto, T.; Shimizu, I.; Yamamoto, A. Ruthenium-catalysed reductive cleavage of allylic esters with formic acid and triethylamine. Application to short-step synthesis of α-hydroxy acids. *J. Organomet. Chem.* **1994**, *473*, 257-264.

olefins,[36] ketones,[37] aldehydes,[38] α,β-unsaturated carbonyl compounds,[39] imines,[40] nitro compounds and quinolines[41] (Table 1.1).

[36] Nishiguchi, T.; Imai, H.; Hirose, Y.; Fukuzumi, K. Transfer hydrogenation and transfer hydrogenolysis. VIII. Hydrogen transfer from amines to olefins catalyzed by heterogeneous and homogeneous catalysts. *J. Catal.* **1976**, *41*, 249-257.

[37] (a) Watanabe, Y.; Ohta, T.; Tsuji, Y. Ruthenium-catalyzed reduction of carbonyl compounds using formic acid. *Bull. Chem. Soc. Jpn*. **1982**, 2441-2444. (b) Smith, T. A.; Maitlis, P. M. Methanol as hydrogen-donor in homogeneously catalysed reactions. *J. Organomet. Chem.* **1984**, *269*, 7-9. (c) Smith, T.A.; Maitlis, P.M. Methanol as a hydrogen donor in reactions homogeneously catalysed by Ru and Rh complexes. *J. Organomet. Chem.* **1985**, *289*, 385-395.

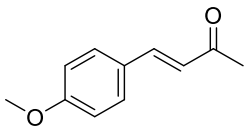
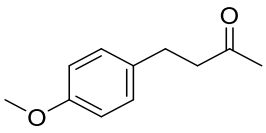
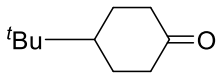
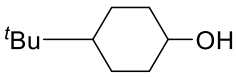
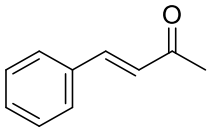
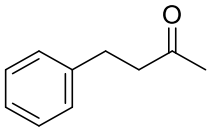
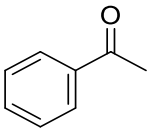
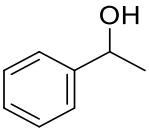
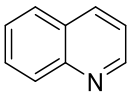
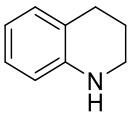
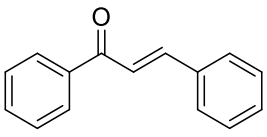
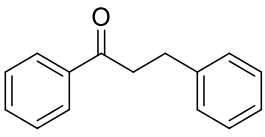
[38] Darensbourg, D.J.; Joo, F.; Kannisto, M.; Katho, A.; Relbensples, J.H. Water-soluble organometallic compounds. 2. catalytic hydrogenation of aldehydes and olefins by new water-soluble 1,3,5-triaza-7-phosphaadamantane complexes of Ruthenium and Rhodium. *Organometallics* **1992**, *11*, 1990–1993.

[39] (a) Sasson, Y.; Blum, J. Homogeneous catalityc transfer-hydrogenenation of α,β-unsaturated carbonyl compounds by dichlorotris(triphenylphosphine)ruthenium (II). *Tetrahedron Lett.* **1971**, *24*, 2167–2170. (b) Blum, J.; Sasson, Y.; Iflah, S. Hydrogen transfer from formyl compounds to α,β-unsaturated ketones by Ru, Rh and Ir Complexes. *Tetrahedron Lett.* **1972**, *11*, 1015–1018. (c) Bar, R.; Sasson, Y. Catalytic reductions with formate ion under phase transfer conditions. *Tetrahedron Lett.* **1981**, *22*, 1709–1710.

[40] Wang, G.Z.; Backvall, J.E. Ruthenium-catalysed transfer hydrogenation of imines by propan-2-ol. *J.C.S. Chem. Comm.* **1992**, 980-982.

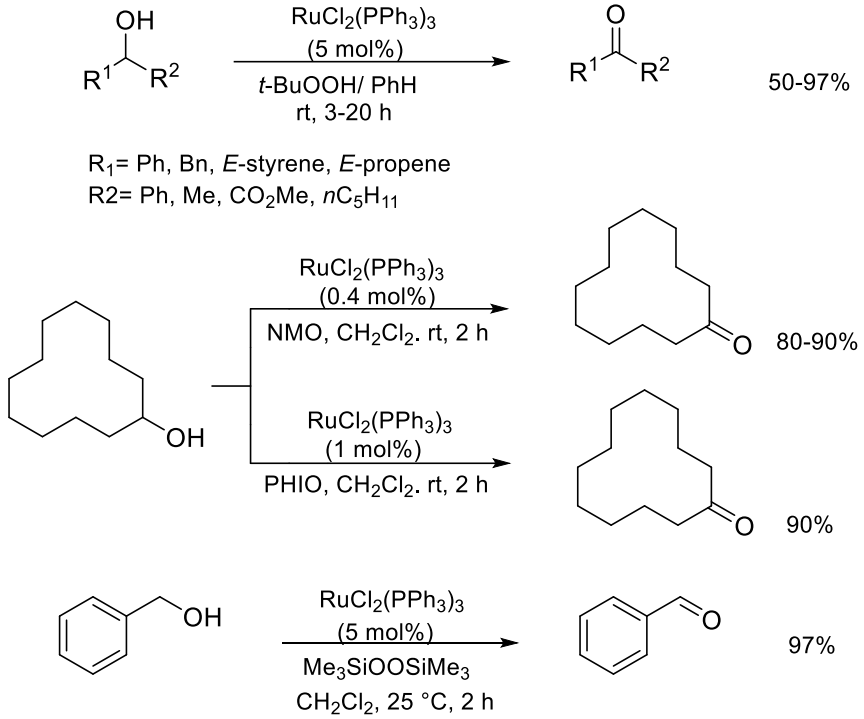
[41] Watanabe, Y.; Ohta, T.; Tsuji, Y.; Hiyoshi, T.; Tsuji, Y. Ruthenium catalyzed reduction of nitroarenes and azaaromatic compounds using formic acid. *Bull. Chem. Soc. Jpn*. **1984**, 2440–2444.

**Table 1.1:** Hydrogen transfer reactions catalyzed by $RuCl_2(PPh_3)_3$

| Hydrogen donor | Hydrogen acceptor | T °C | Product | Conversion (%) |
|---|---|---|---|---|
| BnOH |  | 180 |  | 96 |
| MeOH |  | 145 |  | 77 |
| $HCO_2H$ |  | 97 |  | 90 |
| $HCO_2H$ |  | 125 |  | 54 |
| $HCO_2H$ |  | 18 |  | 76 |
| HCOONa -$H_2O$- THAHS |  | 109 |  | 99 |

### 1.2.5. $RuCl_2(PPh_3)_3$ in oxidation

$RuCl_2(PPh_{3)3}$ catalyzes oxidation of alcohols to ketones by forming various catalytic systems with oxidants such as *t*-BuOOH,[42] *N*-methylmorpholine *N*-oxide (NMO),[43] iodosylbenzene (PHIO)[44] or bis(trimethylsilyl)peroxyde ($Me_3SiOOSiMe_{3)}$[45] as shown in Scheme 1.27.




**Scheme 1.27. Ru3**-catalyzed oxidation of alcohols to ketones.

Additionally, secondary alcohols are readily converted to ketones by an excess of acetone in the presence of a catalytic amount of $RuCl_2(PPh_{3)3}$.[46]

[42] Murahashi, S-I.; Naota, T. Ruthenium-catalyzed oxidations for selective syntheses of ketones and acyl cyanides. Selective acylation of amino compounds with acyl cyanides. *Synthesis* **1993**, *4*, 433-440.

[43] (a) Sharpless, K.B.; Akashi, K.; Oshima, K. Ruthenium catalyzed oxidation of alcohols to aldehydes and ketones by amine-n-oxides. *Tetrahedron Lett.* **1976**, 17 (29), 2503–2506. (b) Vijayasri, K.; Rajaram, J.; Kuriacose, J.C. $RuCl_2(PPh_3)_3$ catalyzed oxidation of secondary alcohols with NMO. *J. Proc. Indian Acad. Sci. (Chem. Sci)* **1986**, *97*, 125-132.

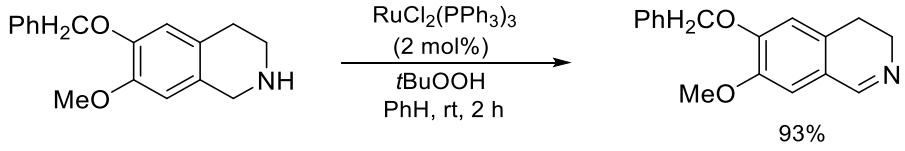
[44] Miiller, P.; Godoy, J. Catalyzed oxidation of alcohols and aldehydes with iodosylbenzene. *Tetrahedron Lett.* **1981**, *22*, 2361-2364.

[45] Kanemoto, S.; Oshima, K.; Matzsubara, S.; Takai, K.; Nozaky, H. Transition-metal catalyzed oxidation of alcohols to aldehydes and ketones by means of $Me_3SiOOSiMe_3$. *Tetrahedron Lett.* **1983**, *24*, 2185-2188.

[46] Wang, G. Z.; Bäckvall, J.E. Ruthenium-catalysed oxidation of alcohols by acetone. *J. C. S. Chem. Comm.* **1992**, *4*, 337-339.

It is worth mentioning that aerobic oxidations of alcohols with $RuCl_2(PPh_3)_3$ catalyst under mild and ambient conditions constitutes an attractive, highly practical and efficient method for the preparation of aldehydes and ketones.[47]

The low-valent ruthenium complex $RuCl_2(PPH_3)_3$ forms a catalytic system with *t*-Butyl hydroperoxide and catalyzes the oxidation of secondary and tertiary amines[48] (Scheme 1.28), amides,[49] phenols,[50] and various linear and cyclic alkanes.[51]




**Scheme 1.28. Ru3**/*t*BuOOH catalyzed oxidation of secondary amines/preparation of 3,4-dihydroisoquinoline.

Finally, both linear and cyclic alkanes can be converted efficiently into the corresponding ketones along with a small amount of alcohols.[52] The system is highly useful for the oxidation of alkylated arenes, one of the examples of these

[47] (a) Matsumoto, M.; Ito, S. Ruthenium-catalysed oxidation of allyl alcohols by molecular oxygen. *J.C.S. Chem. Comm.* **1981**, 907-908. (b) Hanyu, A.; Takezawa, E.; Sakaguchi, S.; Ishii, Y. Selective aerobic oxidation of primary alcohols catalyzed by a $Ru(PPh_3)_3Cl_2$/hydroquinone system. *Tetrahedron Lett.* **1998**, *39*, 5557-5560. (c) Takezawa, E.; Sakaguchi, S.; Ishii, Y. Oxidative cleavage of vic-diols to aldehydes with dioxygen catalyzed by $Ru(PPh_3)_3Cl_2$ on active carbon. *Organic Lett.* **1999**, *1*, 713-715. (d) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. Efficient ruthenium-TEMPO-catalysed aerobic oxidation of aliphatic alcohols into aldehydes and ketones. *Chem. Comm.* **1999**, 1591-1592. (e) Dijksman, A.; Marino-González, A.; Payeras, A. M.; Arends, I. W. C. E.; Sheldon, R. A. Efficient and selective aerobic oxidation of alcohols into aldehydes and ketones using ruthenium/TEMPO as the catalytic system. *J. Am. Chem. Soc.* **2001**, *123*, 6826-6833.

[48] (a) Murahashi, S.; Naota, T.; Taki, H. Ruthenium-catalysed oxidation of secondary amines to lmines using *t*-Butyl hydroperoxide. *J. Chem. Soc., Chem Commun.* **1985**, 613-614. (b) Murahashi, S.; Naota, T.; Yonemura, K. Ruthenium-catalyzed cytochrome P-450 type oxidation of tertiary amines with alkyl hydroperoxides. *J. Am. Chem. Soc.* **1988**, *110*, 8256-8258.

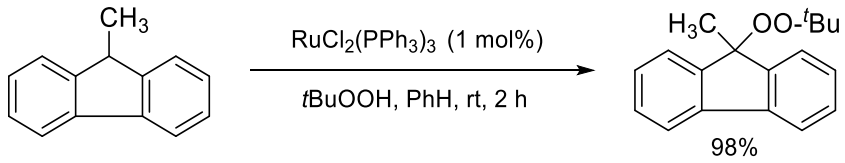
[49] Murahashi, S. I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. Ruthenium-Catalyzed Oxidation of Amides and Lactams with Peroxides. *J. Am. Chem. Soc.* **1990**, *112*, 7820-7822.

[50] (a) Murahashi, S.; Naota, T.; Miyaguchi, N.; Noda, S. Ruthenium-catalyzed oxidation of phenols with alkyl hydroperoxides. *J. Am. Chem. Soc.* **1996**, *5*, 2509-2510. (b) Murahashi, S.; Miyaguchi, N.; Noda, S.*;* Naota, T.; Fujii, A.; Inubushi, Y.; Komiya, N. Ruthenium-catalyzed oxidative dearomatization of phenols to 4-(*tert*-butylperoxy) cyclohexadienones: Synthesis of 2-substituted quinones from *p*-substituted phenols. *Eur. J. Org. Chem.* **2011**, *27*, 5355-5365.

[51] Murahashi. S. Biomimetic oxidation in organic synthesis using transition metal catalysts. *Pure App. Chem.* **1992**, *64*, 403-412.

[52] (a) Murahashi, S.; Oda, Y.; Naota, T. Iron- and ruthenium-catalyzed oxidations of alkanes with molecular oxygen in the presence of aldehydes and acids. *J. Am. Chem. Soc.* **1992**, *114*, 7914-7916. (b) Murahashi, S.; Komiya, N.; Oda, Y.; Kuwabara, T.; Naota, T. Ruthenium-catalyzed oxidation of alkanes with *tert*-butyl hydroperoxide and peracetic acid. *J. Org. Chem.* **2000**, *65*, 9186-9193.

oxidations is displayed in Scheme 1.31 where the oxidation of 9-methyfluorene gave 9-*t*-butyldioxy-9-methylfluorene selectively with a 98% of yield.[53]

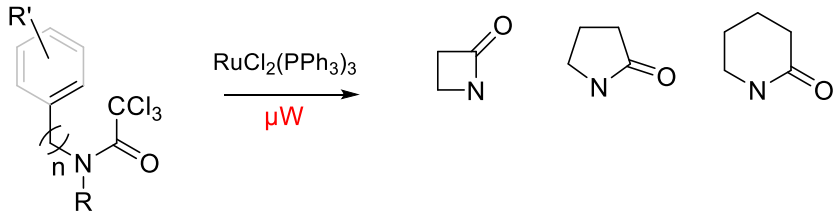



**Scheme 1.31.** Ru-catalyzed oxidation of alkylated arene 9-methyfluorene.

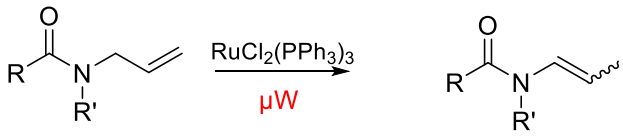
## 1.3. Objectives

The main objective of this PhD thesis is to explore even more the potential of tris(triphenylphosphine)ruthenium(II) dichloride ($RuCl_2(PPh_3)_3$) and demonstrate that it is indeed a potent and versatile catalyst capable of achieving efficient chemical transformations under microwave activation especially in:

1. The synthesis of β-, γ- and δ-lactams using benzylic CH activation or Atom Transfer Radical Cyclizations.




2. The isomerization of tertiary *N*-allyl amides and *N*-allyl carbamates to the corresponding enamides and enecarbamates.




[53] Murahashi, S. I.; Oda, Y.; Naota, T.; Kuwabara, T. Ruthenium-catalyzed cytochrome P-450 type oxidation of alkanes with alkyl hydroperoxides. *Tetrahedron Lett.* **1993**, *34*, 1299-1302.

# CHAPTER 2:

# *Microwave-assisted benzylic C-H activation using ruthenium catalysts. Synthesis of β-lactams*

## 2.1. β-Lactams: a short overview

The β-lactam (2-azetidinone) ring is a four membered lactam found in many natural compounds and medicines especially antibiotics such as penams represented by penicillin G and V, cephems represented by cephalosporin C, monobactams represented by Aztreonam and finally carbapenems represented by Imipenem (Figure 2.1).[1] Nearly all of these antibiotics work by inhibiting bacterial cell wall biosynthesis.

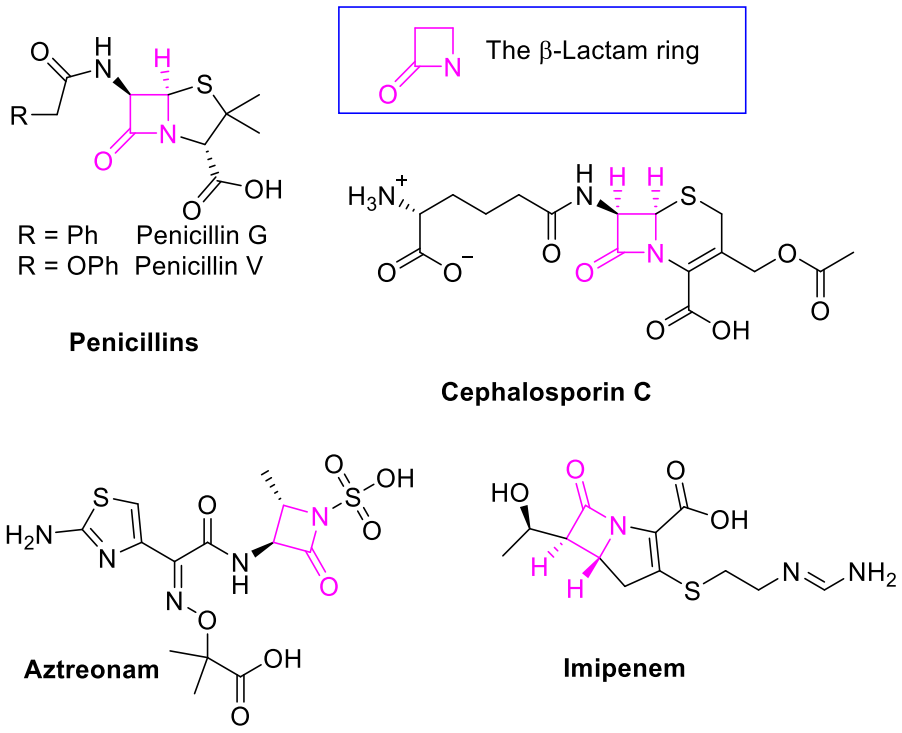



**Figure 2.1.** Chemical structures of some β-lactam antibacterial drugs.

Besides forming part of the core structure of several antibiotic families, the β-lactam ring is found in many other natural and unnatural compounds with diverse activity.[2] For example in 2011, O'Boyle *et al.*[3] described the synthesis of a series of 2-azetidinone derivatives via the Staüdinger reaction. These were then evaluated for antiproliferative, cytotoxic and tubulin-binding activity finding that

[1] Fernandes, R.; Amador, P.; Prudêncio, C. β-Lactams: chemical structure, mode of action and mechanisms of resistance. *Rev. Med. Microbiol*. **2013**, *24*, 7-17.
[2] Gupta, A.; Halve, A. K. β-lactams: a mini review of their biological activity. *Int. J. Pharmaceut. Sci. Res.* **2015**, *6*, 978-987.
[3] O'Boyle, N.M.; Greene, L. M.; Bergin, O.; Fichet, J. B.; McCabe, T.; Lloyd, D. G.; Zisterer, D. M.; Meegan, M. J. Synthesis, evaluation and structural studies of antiproliferative tubulin-targeting azetidin-2-ones. *Bioorg. Med. Chem.* **2011**; *19*, 2306-2325.

the 3-(2-thienyl) and 3-(3-thienyl) analogs (Figure 2.2a) displayed the highest potency in human MCF-7 breast cancer cells with IC50 values of 7 nM and 10 nM respectively, comparable to combretastatin A-4.[4] Additionally, Dou *et al.* have demonstrated that *N*-thiolated β-lactams have tumor cell-killing ability through induction of DNA-damage and subsequent apoptosis (Figure 2.2b).[5] On the other hand, Hussain *et al.*[6] reported the synthesis of β-lactam derivatives with significant antimycobarterial (antitubercular) activity (Figure 2.2c).

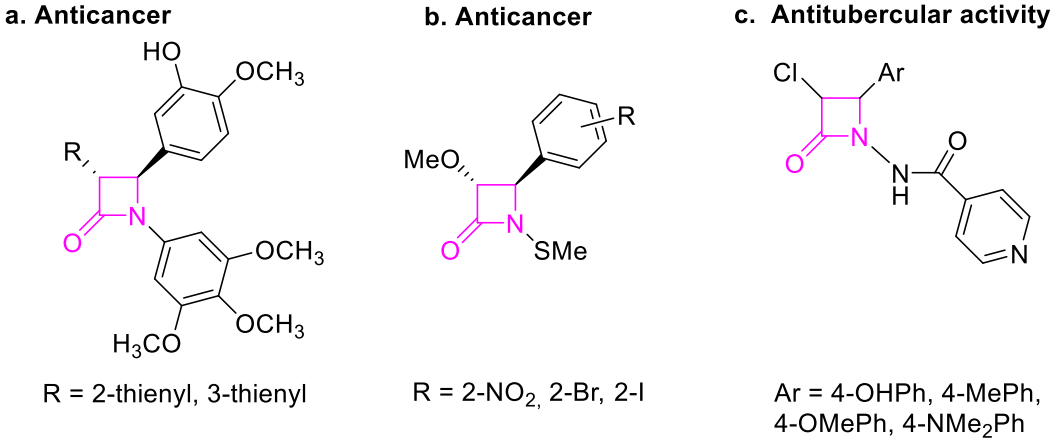



**Figure 2.2**. Structure of β-lactams with cytotoxic and antitubercular activity.

β–Lactams have been prepared using a wide range of strategies,[7] in scheme 2.1 are reported the most outstanding methodologies described so far. Among these are of course the Staudinger procedure,[8] also called the Staudinger ketene-imine non-photochemical 2+2 cycloaddition, the carbonylative ring-

[4]. Cragg, G. M.; Kingston, D. G.; Newman, D. J. Anticancer Agents from Natural Products; CRC press: Florida, **2005**, pp. 123-135.

[5] Smith, D. M.; Kazi, A.; Smith, L.; Long, T. E.; Heldreth, B.; Turos, E.; Dou, Q. P. A novel β–lactam antibiotic activates tumor cell apoptotic program by inducing DNA damage. *Mol. Pharmacol.* **2002**, *61*, 1348-1358.

[6] Hussain, S.; Jadhav, S.; Rai, M.; Farooqui, M. Synthesis, Characterization and Biological Evaluation of N [3-Chloro-2 (aryl)-4-oxoazitidin-1-y] pyridine-4-carboxamide.*Int. J. Drug Des. Discov.* **2011**; *2*, 527-532.

[7] For reviews see: (a) Hosseyni, S.; Jarrahpour, A. recent advances in β–lactams synthesis. *Org. Biomol. Chem.* **2018**, *16*, 6840-6852. (b) Pitts, C. R.; Lectka, T. Chemical Synthesis of β-Lactams: Asymmetric Catalysis and Other Recent Advances. *Chem. Rev.* **2014**, *114*, 7930-7953.

[8] (a) Staudinger, H. Zur Kenntniss der Ketene. Diphenylketen. *Liebigs, Ann. Chem.* **1907**, *356*, (1–2), 51-123. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Asymmetric synthesis of β-lactams through the Staudinger reaction and their use as building blocks of natural and nonnatural products. *Curr. Med. Chem.* **2004**, *11*, 1837-1872. (c) Berry, S.; Bari, S. S.; Banik, B. K.; Bhalla, A. Stereoselective synthesis of novel monocyclic trans-3-halogenated-4-pyrazolyl-β-lactams: potential synthons and promising biologically active agents. *Synth.Commun.* **2017**, *47*, 2239-2246.

opening of aziridines,[9] the Kinugasa reaction which takes place between terminal alkyne and a nitrone in the presence of copper(I),[10] and metal catalyzed C–H insertion of diazoamide carbenes activated by a variety of transition metals such as copper, gold, rhodium[11] and many others.[12]

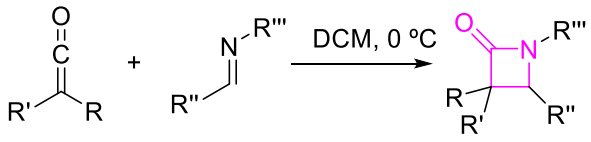
[9] Khumtaveeporn, K.; Alper, H. Transition Metal Mediated Carbonylative Ring Expansion of Heterocyclic Compounds. *Acc. Chem. Res.* **1995**, *28*, 414-422.

[10] For selected examples, see: (a) Kinugasa, M. Hashimoto, S. The reactions of copper(I) phenylacetylide with nitrones. *J. Chem. Soc., Chem. Commun.* **1972**, 466-467; (b) Ahn, C.; Kenninghton, J. W.; DeShong, P. A New Approach to the Synthesis of Monocyclic β-lactam derivatives. *J. Org. Chem.,* **1994**, *59*, 6282–6286. (c) Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198-2200. (d) Kumar, Y.; Singh, P.; Bhargava, G. Cu(I) mediated Kinugasa reactions of α,β-unsaturated nitrones: a facile, diastereoselective route to 3-(hydroxy/bromo)methyl-1-aryl-4-(-styryl)azetidin-2-ones. *New J. Chem.* **2016**, *40*, 8216-8219.

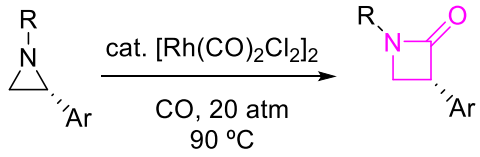
[11] Anada, M.; Watanabe, N.; Hashimoto, S. Highly enantioselective construction of the key azetidin-2-ones for the synthesis of carbapenem antibiotics via intramolecular C–H insertion reactions of α-methoxycarbonyl-α-diazoacetamides catalysed by chiral dirhodium(II) carboxylates. *Chem. Commun.* **1998**, 1517-1518.

[12] For reviews see: (a) Davies, H. M. L.; Beckwith, R. E. J. Catalytic enantioselective C-H activation by means of metal-carbenoid-induced C-H insertion. *Chem. Rev.* **2003**, *103*, 2861-2903. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. Catalytic Carbene Insertion into C-H Bonds. *Chem. Rev.* **2010**, *110*, 704-724.

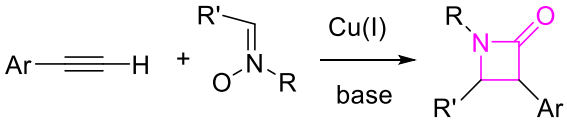
a. The Staudinger ketene imine cycloaddition



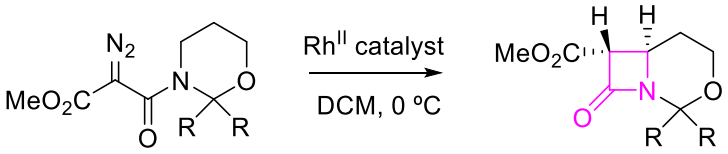

b. Carbonylative ring-opening of aziridines




c. Kinugasa reactions




d. Metal catalyzed C–H insertion of diazoamide carbenes



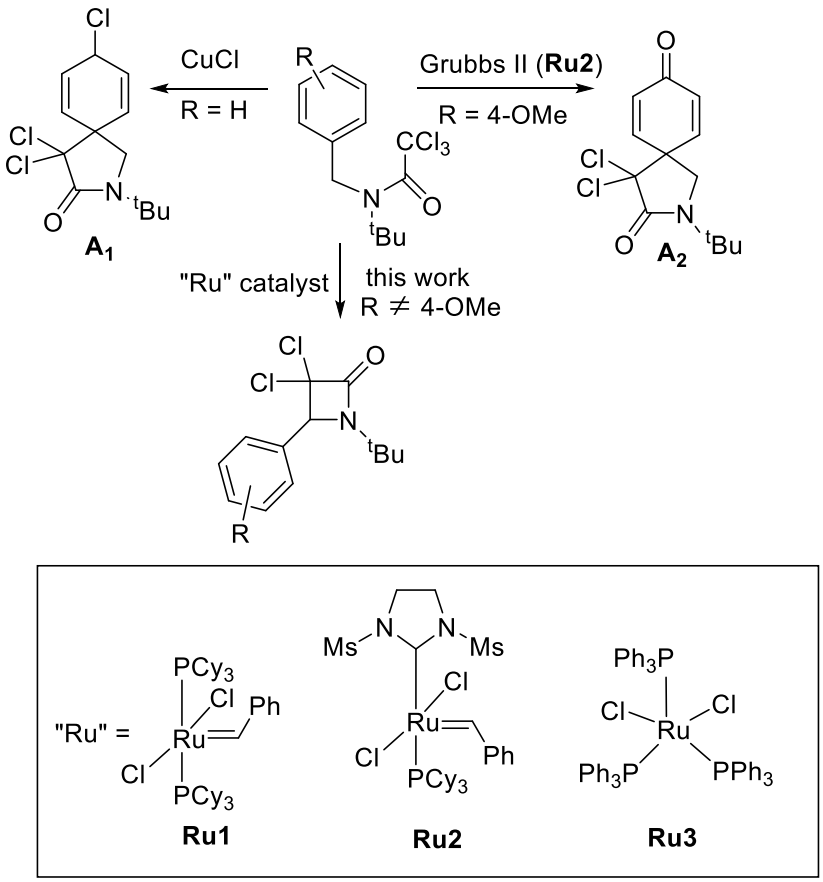

**Scheme 2.1**. Selected examples for the synthesis of β-lactams.

## 2.2. Synthesis of β-lactams in the presence of $RuCl_2(PPh_3)_3$. Our results

Few years ago we reported the first Grubbs' second-generation (**Ru2**) catalyzed intramolecular dearomative ATRC with trichloroacetamides embodying an electron-rich arene for the preparation of 2-azaspirodecadienes **A2**.[13] The investigation was an extension to a previous work where the same reaction leading to **A1** was achieved on unactivated benzenes using Cu(I) as a catalyst (Scheme 2.2).[14]

[13] Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. Atom transfer radical cyclization of trichloroacetamides to electron-rich acceptors using Grubbs' catalysts: Synthesis of the tricyclic framework of FR901483. *J. Org. Chem.* **2014**, *79*, 9365-9372.

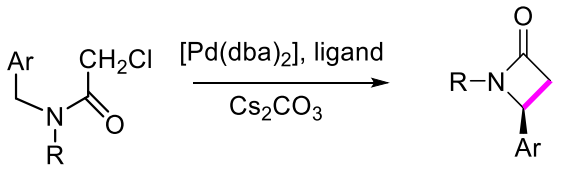
[14] Diaba, F.; Montiel, J. A.; Martínez-Laporta, A.; Bonjoch, J. Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes. *Tetrahedron Lett.* **2013**, *54*, 2619-2622.




**Scheme 2.2**. Group precedents in the synthesis of γ-lactams and actual work.

The reaction which will be developed in this chapter was accidently discovered when dibenzyl trichloroacetamide **1a** (Table 2.1) was submitted to the same reaction conditions in which spiroderivatives type **A2** were isolated. Thus when **1a** was heated with 10% of grubbs catalyst **Ru2** in toluene (0.1 mL) at 160 ºC for 2 h, after chromatography, **2a** was isolated in a 26% yield (Entry 1, Table 2.1). Additionally, *N*,*N*-dibenzyl- and *N*-benzyldichloroacetamides were also isolated in minor yields. To our knowledge, this was an unprecedented ruthenium catalyzed synthesis of β-lactams from readily available *N*-benzyltrichloroacetamides and there is only one example reported in the literature where a saturated $C(sp^3)$-$C(sp^3)$ bond formation is achieved through an asymmetric C-H functionalization from chloroacetamides catalysed by Palladium(0). The reaction takes place in the presence of $Pd(dba)_2$, a bulky taddol

phosphoramidite ligant, adamantly carboxylic acid and $Cs_2CO_3$ in toluene at 110 ºC (Scheme 2.3).[15]




**Scheme 2.3**. Palladium(0) catalyzed synthesis of β-lactams.

It is worth noting that the same reaction, under diluted conditions (1 mL of toluene), did not take place when achieved using standard heating. Nevertheless, under microwave activation and at 100 ºC a full conversion was observed after only 30 min obtaining **2a** in a slightly better yield (Entry 2). After these unexpected results, we started an investigation to explore the scope and limitations of this reaction. In order to improve the reaction yield, we switched to **1b** since the bulky *tert*-butyl substituent on the nitrogen atom is well known to lock the substrate in a conformation prone to cyclization.[16]

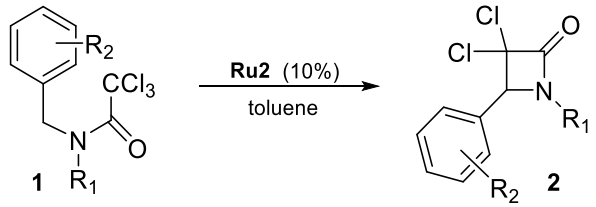
As it was expected, when **1b** was heated at 100 ºC under microwave activation for only 10 min, lactam **2b** was isolated with 48% yield (Entry 3). Reducing the quantity of catalyst although prolonging the reaction time did not improve the final result (Entry 4). When the reaction was carried out at 80 ºC, 20 min were necessary to obtain **2b** with 48% yield (Entry 5). Switching to acetonitrile, a full conversion was observed after only 5 min although the yield for lactam **2b** was lower (Entry 6). We next sought to explore the scope of the reaction on trichloroacetamides **1c**-**1h** with different substituents on the benzene ring. Treatment of substrates **1c**-**1e** all of them with a methyl group in the ortho, meta and para position respectively with **Ru2** (10 mol%) under microwave activation for 10 min and at 100 ºC provided the corresponding lactams **2c**-**2e** with moderate yields (entries 7-9). With anisole derivative **1f**, a similar yield of lactam **2f** was obtained (Entry 10). Even if with these substrates usually some of

[15] Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-lactams by enantioselective palladium(0)-catalyzed C($sp^3$)-H alkylation. *Angew. Chem. Int. Ed.* **2014**, *53*, 9064-9067.
[16] Stork, G., Mah, R. Radical cyclization of allylic haloacetamides a route to *cis*-fused 2-pyrrolidones and piperidones. *Heterocycles* **1989**, *28*, 723-727.

the starting material was recovered, prolonging the reaction time yielded poorer results.

Completely different results were attained with trichloroacetamides **1g** and **1h** with a deactivated benzene ring. Whereas with **1g** a degradation of the starting material was observed (Entry 11), with **1h** lactam **2h** was isolated with a very low yield together with product **3h** which was not observed in the reaction crude but after chromatography using dichloromethane stabilized with ethanol as the eluent (Entry 12). It is worth noting that when dichloromethane stabilized with amylene was used instead in the purification process, we recovered only degradation compounds.

**Table 2.1. Ru2** promoted formation of lactams **2**



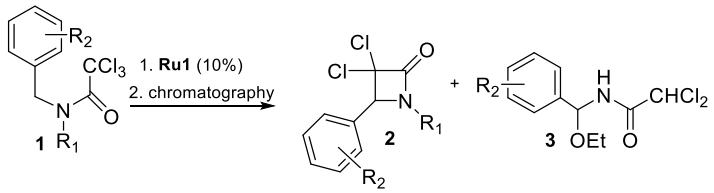

| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|
| **1a** | Bn | H | **1f** | *t*-Bu | 3-OMe |
| **1b** | *t*-Bu | H | **1g** | *t*-Bu | 4-$NO_2$ |
| **1c** | *t*-Bu | 2-Me | **1h** | *t*-Bu | 3,5-diF |
| **1d** | *t*-Bu | 3-Me | | | |
| **1e** | *t*-Bu | 4-Me | | | |

| Entry | **1** | Method[a] | Time (min) | **2**, **3** (yield %) |
|---|---|---|---|---|
| 1 | **1a** | A | 120 | **2a** (26) |
| 2 | **1a** | B | 30 | **2a** (30) |
| 3 | **1b** | B | 10 | **2b** (48) |
| 4 | **1b** | B[b] | 20 | **2b** (38) |
| 5 | **1b** | B[c] | 20 | **2b** (48)[d] |
| 6 | **1b** | B[e] | 5 | **2b** (36) |
| 7 | **1c** | B | 10 | **2c** (30)[f] |
| 8 | **1d** | B | 10 | **2d** (38)[g] |
| 9 | **1e** | B | 10 | **2e** (28) |
| 10 | **1f** | B | 5 | **2f** (25)[h] |
| 11 | **1g** | B | 10 | **2g** (-) |
| 12 | **1h** | B | 5 | **2h** (11)[i], **3h** (24)[j] |

[a] A: 100 mg scale in 0.1 mL of toluene (≈ 0.3 M) at 160 °C. B: 100 mg scale in 1 mL of toluene (≈ 0.3 M) at 100 °C, μW. [b] 5% of **Ru2** was used, 35% of **1b** was recovered. [c] At 80 ºC. [d] 7% of **1b** was recovered. [e] Acetonitrile was used as a solvent. [f] 22% of **1c** was recovered. [g] 20% of **1d** was recovered. [h] 23% of **1f** was recovered. [i] 8% of **1h** was recovered. [j] For the structure of **3h** see table 2.

After these results with **Ru2** we decided to investigate Grubbs' 1st generation catalyst (**Ru1**) using the best reaction conditions established with **Ru2** (Table 2.2). With dibenzyl derivative **1a** the reaction provided lactam **2a** with a comparable yield (Entry 1). Nevertheless, with trichloroacetamide **1b** only **3b** was isolated after chromatography (Entry 2). As it was mentioned before, **3b** was not observed in the crude but isolated after purification. A similar result was achieved with substrates **1g** and **1h** with an unactivated benzene where only **3g** and **3h** were isolated respectively (entries 7 and 8). With tolyl derivatives **1c**-**1e**, besides lactams **2c**-**2e** isolated in modest yields, amides **3c**-**3d** were detected in some fractions after chromatography but were not isolated in pure forms (entries 3-5). It's worth noting that with trichloroacetamide **1c** a better yield of lactam **2c** was obtained (Entry 3). Additionally, with anisole **1f** only **3f** was isolated after purification (Entry 6).

**Table 2.2.** Reactions of trichloroacetamides **1** with **Ru1**[a]



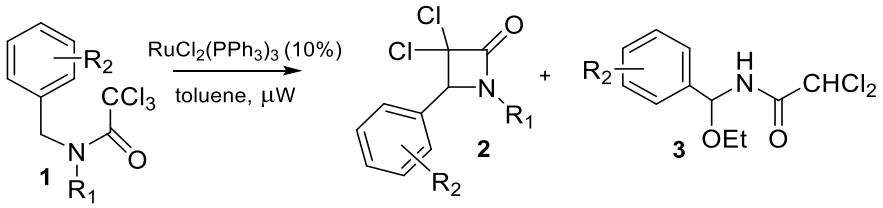

| Entry | **1** | Time (min) | **2** (yield %) | **3** (yield %) |
|---|---|---|---|---|
| 1 | **1a** | 20 | **2a** (28) | **3a** (-) |
| 2 | **1b** | 5 | **2b** (-) | **3b** (38) |
| 3 | **1c** | 10 | **2c** (40) | **3c** (9) |
| 4 | **1d** | 5 | **2d**(16) | **3d** (8)[b] |
| 5 | **1e** | 10 | **2e** (34) | **3e** (-)[c] |
| 6 | **1f** | 5 | **2f** (-)[c] | **3f** (37) |
| 7 | **1g** | 10 | **2g** (-) | **3g** (17) |
| 8 | **1h** | 5 | **2h** (-) | **3h** (46) |

[a] All the reactions were carried out using almost 100 mg scale of **1** in 1 mL of toluene (≈ 0.3 M) at 100 °C, μW. [b] 12% of **1d** was recovered. [c] Only traces were detected.

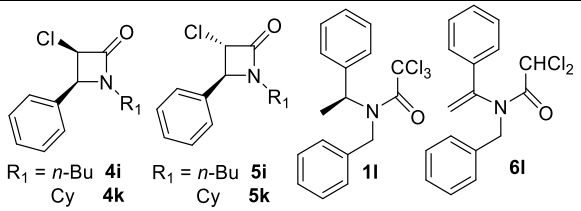
With these results in hand, we set out to explore another more accessible ruthenium catalyst for these unusual reactions (Table 2.3). $RuCl_2(PPh_3)_3$ (**Ru3**) is a commercially available catalyst, more accessible than **Ru2** and is the precursor of **Ru1**. When **1a** was treated with 10% of **Ru3** at 100 °C in toluene for 15 min using microwaves, we were delighted to see that lactam **2a** was isolated

with a modest yield (Table 3, Entry 1). Running the same reaction at 80 °C improved the yield considerably (41%, Entry 2).

**Table 2.3.** $RuCl_2(PPh_3)_3$ promoted formation of lactams **2**[a]




| Entry | $R_1$ | $R_2$ | **1** | T °C | Time (min) | **2**, **3** (yield %) |
|---|---|---|---|---|---|---|
| 1 | Bn | H | **1a** | 100 | 15 | **2a** (20)[b] |
| 2 | Bn | H | **1a** | 80 | 20 | **2a** (41) |
| 3 | *t*Bu | H | **1b** | 100 | 10 | **2b** (49) |
| 4 | *t*Bu | H | **1b** | 80 | 10 | **2b** (58) |
| 5 | *t*Bu | H | **1b** | 80 | 10 | **2b** (55)[c] |
| 6 | *t*Bu | 2-Me | **1c** | 80 | 10 | **2c** (56)[d] |
| 7 | *t*Bu | 3-Me | **1d** | 80 | 10 | **2d** (40), **3d** (8) |
| 8 | *t*Bu | 4-Me | **1e** | 80 | 5 | **2e** (40) |
| 9 | *t*Bu | 3-OMe | **1f** | 80 | 10 | **2f** (18) |
| 10 | *t*Bu | 4-$NO_2$ | **1g** | 80 | 10 | **-** |
| 11 | *t*Bu | 3,5-diF | **1h** | 80 | 10 | **2h** (21), **3h** (18) |
| 12 | *n*-Bu | H | **1i** | 80 | 10 | **2i** (30)[e] |
| 13 | *i*-Pr | H | **1j** | 80 | 10 | **2j** (28[f] |
| 14 | Cy | H | **1k** | 80 | 10 | **2k** (38)[g] |
| 13 | (*S*)-α-MeBn | H | **1l** | 80 | 10 | **6l** (40)[h] |




[a] All the reactions were carried out using 100 mg scale of **1** in 1 mL of toluene (≈ 0.3 M), μW. [b] 6% of **1a** was recovered. [c] With 200 mg of **1b**. [d] 12% of **1c** was recovered. [e] Were also isolated **4i** (4%), **5i** (9%), **1i** (25%). [f] Traces of **4j** and **5j** were detected. [g] Were also isolated **4k** (8%), **5k** (9%). [h] 48% of **1l** was recovered, when the reaction was run for 20 min the yield dropped to 22% even if the conversion was 100% .

Better results were also achieved from trichloacetamides **1b**-**1e** where only lactams **2b**-**2e** were isolated with 40-58% yields (Entries 3-8). Additionally, with electron-poor derivatives **1g** and **1h** a different behaviour was observed. Whereas with **1g** only degradation compounds were detected in the crude, with **1h** a slight improvement in the yield of lactam **2h** was achieved isolated with **3h** (Entry 11). Using catalyst **Ru3** the reaction worked also with amides **1i**-**1k** where the substituents on the nitrogen are *n*butyl, isopropyl and cyclohexyl groups respectively (Entries 12-14). In all cases lactams **2i**-**2k** were isolated with acceptable yields. It is worth noting that with **1i** and **1k,** we isolated also small quantities of the partially reduced lactams **4** and **5**.[17] Finally, with trichloroacetamide **1l**, only dichloroacetamide **6l** was isolated (Entry 13).

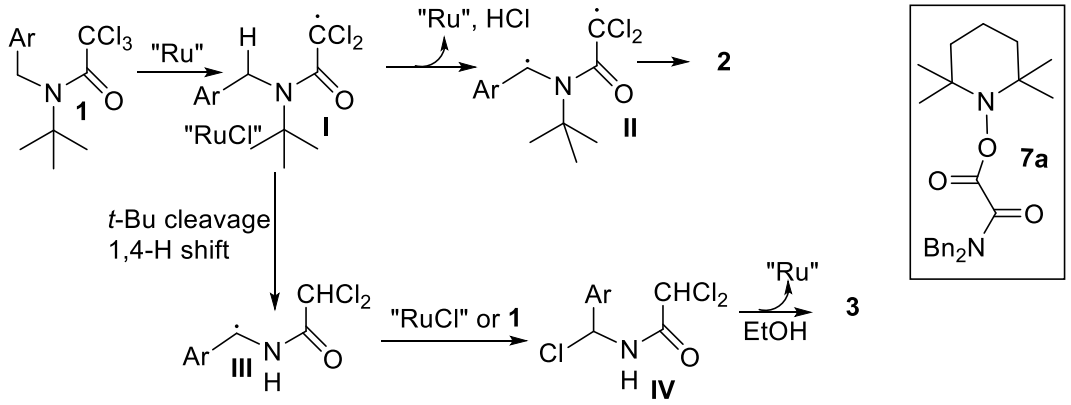
In this investigation we have described an unprecedented behaviour of some ruthenium catalysts leading to β-lactams **2** from trichloroacetamides **1** through benzylic CH activation. The presence of the catalyst is necessary to achieve the process since after heating **1b** alone in toluene at 80 °C under microwave activation for 10 min no reaction took place and **1b** was recovered intact. As it was expected, a radical process is involved in this transformation since running the reaction in the presence of TEMPO either from **1a** or **1b** inhibits the lactam formation. Whereas under microwave activation only degradation compounds were detected in the crude, when **1a** was heated at 160 ºC with **Ru3** (10 mol%) in the presence of 1 equiv. of TEMPO, besides **1a** a small quantity of **7a** was detected resulting from a coupling between TEMPO and the dichlorocarbamoil radical followed by hydrolysis (Scheme 2.4).[18] **7a** was identified by high-resolution mass spectroscopy (ESI-TOF) which confirmed the molecular formula $C_{25}H_{32}N_2O_3$ (calculated for $C_{25}H_{33}N_2O_3$ 409.2486 [M+H]+; found 409.2488). This indicates that the first step of the reaction is abstraction of a chloro atom by the "Ru" catalyst (the modified species) from **1** to generate dichlorocarbamoil radical **I** and "RuCl" complex.[19] Next, we propose that the

[17] Van Driessche, B.; Van Brabandt, W.; D'hooghe, M.; Dejaegher, Y.; De Kimpe, N. Synthesis and reactivity of trans-2-aryl-3-chloroazetidines. *Tetrahedron* **2006**, *62*, 6882-6892.

[18] Baker, A. D.; Wong, D.; Lo, S.; Bloch, M.; Horozoglu, G.; Golman, N. L.; Engel, R. The reaction of *N*-aryl nitrones with dichloroketene: a new synthesis of isatins. *Tetrahedron Lett.* **1978**, *19*, 219-222.

[19] Matsumoto, H.; Nikaido, T.; Nagai, Y. Radical reactions in the coordination sphere. III. Reactions of dichloro- and trichloroacetic acid esters with 1-olefins catalyzed by dichlorotris-(triphenylphosphine)ruthenium(II). *J. Org. Chem.* **1976**, *41*, 396-398.

"RuCl" complex abstracts then a hydrogen atom from radical **I** to generate diradical species **II** with the concomitant release of HCl and regeneration of "Ru" catalyst. Indeed analysis of some reaction crudes in which **Ru3** was successfully used in the synthesis of lactams **2** showed a strong acidic pH of the reaction medium. Next, transient diradical **II** undergoes an intramolecular cross coupling to generate β-lactams **2**. On the other hand amides **3** result from cleavage of the *tert*-butyl group in acid medium[20] and a 1,4-H shift[21] in radical **I** generating radical **III** followed by a chloro atom transfer from "RuCl" complex or amide **1** to provide chloroderivative **IV**. The latter undergoes nucleophilic substitution during purification providing ethers **3**.[22]




**Scheme 2.4.** Proposed mechanism for the formation of **2** and **3**.

As it was mentioned before, ethers **3** were not present in the reaction crudes but were isolated after purification by chromatography using $CH_2Cl_2$ stabilized with ethanol. Formation of chloroderivative **IV** was reinforced by analysis of the reaction mixture when achieved from **1h** and **Ru1** (Table 2.2, Entry 8) since $^1$H NMR spectrum exhibits 2 determinant signals, a singlet at 5.89 ppm and a doublet at 6.32 ppm consistent with a $COCHCl_2$ and a benzylic CHCl respectively. This argument is supported by the experiments achieved with **1l**

[20] Clayden, J.; Stimson, C. C.; Keenan, M. Contra-Friedel–Crafts *tert*-butylation of substituted aromatic rings *via* directed metallation and sulfinylation. *Chem. Comm.* **2006**, 1393-1394.
[21] (a) Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J.; Lago, E.; Molins, E. An unexpected course in the 6-exo radical cyclizations of trichloroacetamides on changing the *N*-substituent from benzyl to α-methylbenzyl. *C. R. Acad. Sci.* **2001**, *4*, 513-521. (b) Nechab, M.; Mondal, S.; Bertrand, M. P. 1,n-Hydrogen-atom transfer (HAT) reactions in which n ≠ 5: an updated inventory. *Chem. Eur. J.* **2014**, *20*, 16034-16059.
[22] Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. Intramolecular reactions of acyclic *N*-acyliminium ions II allyl silanes as nucleophiles. *Tetrahedron Lett.* **1985**, *26*, 3155-3158.

where only alkene **6l** was isolated. With this substrate, we believe that after formation of the dichlorocarbamoil radical, a 1,4-H shift takes place to generate a radical followed by a chloro atom transfer and elimination to furnish **6l**.

## 2.3. Cytotoxic activity of some of the synthesized β-lactams

With the background reported in section 2.1., it was of great interest in this study to investigate and characterize some of the β-lactams prepared, naming **2b**, **2c**, **2e**, **2h**, **2j** and **2k** for their cytotoxic activity and hemocompatibility.[23]

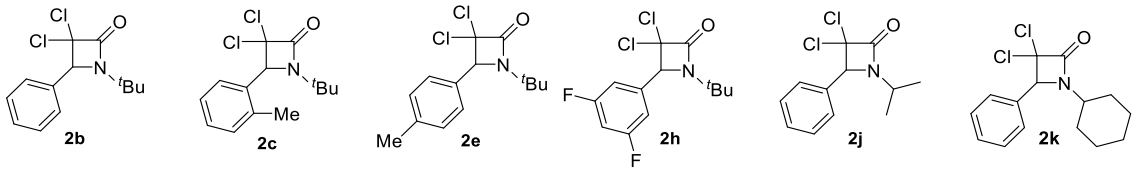



**Figure 2.3.** Selected lactams for cytotoxic and hemocompatibility studies.

### 2.3.1 Hemocompatibility studies

Following the ISO 10993-4 concerning the biological evaluation of medical devices and their interactions with blood, an *in vitro* hemocompatibility assay was carried out.[24] Under the assayed conditions, the determination of the degree of hemolysis produced by the different compounds by incubation with red blood cells (RBC) suspension was performed. The chemical modification on the hemolytic response was evaluated at 2 different concentrations (10 and 80 µg/mL). Table 2.4 shows representative results as a function of the chemical structure. The degree of hemolysis fluctuates slightly, with values ranging between 0.01 and 0.05% for compounds **2b-2j** at concentrations equal to 10 µg/mL. The maximum degree of hemolysis was achieved with compound **2k** with hemolysis close to 0.25 %. By increasing concentration up to 80 µg/mL, no appreciable increase in the hemolytic response was observed. Only under discrete conditions, the hemolysis increase until 2.5 % (compound **2b**). Considering the criteria for which compounds are classified as non-hemolytic (<2%), slightly hemolytic (with values

[23] This part of work was achieved in collaboration with Dr Maria Del Carmen Moran Badenas, Department of Biochemistry and Physiology, University of Barcelona.
[24] ISO 10993-4:2017. Biological evaluation of medical devices-Part 4: Selection of tests for interactions with blood.

2-5%) and hemolytic (values > 5%), it could be concluded that the proposed compounds showed non-hemolytic properties.

**Table 2.4**. Percentage of hemolysis induced by compounds **2b-2k** as a function of the concentration.

| Compound | Hemolysis (%) | |
|---|---|---|
| | **10 µg/mL** | **80 µg/mL)** |
| **2b** | 0.01 ± 0.01 | 2.5 ± 0.97 |
| **2c** | 0.01 ± 0.01 | 0.01 ± 0.01 |
| **2e** | 0.01 ± 0.01 | 0.2 ± 0.23 |
| **2h** | 0.05 ± 0.05 | 0.12 ± 0.09 |
| **2j** | 0.01 ± 0.01 | 0.02 ± 0.02 |
| **2k** | 0.25 ± 0.03 | 0.30 ± 0.21 |

### 2.3.2 Cell viability studies

After ensuring that the selected β-lactams have non-hemolytic character, we were very interested in investigating the cytotoxic activity they induced. For this purpose we used the immortal human keratinocyte (HaCaT) and the squamous cell carcinoma (A431), as close representative skin cell lines with non-tumoral and tumoral characteristics, respectively. Two different end-points, MTT and NRU, were used to assess differences in cell-induced cytotoxicity. In the former method, this offers details about the modification of the metabolic activity of mitochondria inside the cells. In the latter case, however, the derived information is related with the interaction with the plasmatic membrane. Dose–response curves were determined by the MTT[25] and NRU[26] assays using HaCaT and A431 cell lines. Cytotoxicity assays were performed at concentrations ranged between 10 and 250 µg/mL.

[25] For more details about the protocols see the experimental part related to chapter 2.
[26] Repetto, G.; Peso, A.; Zurita, J. L. Neutral red uptake assay for the estimation of cell viability/ cytotoxicity. *Nat. Protoc.* **2008**, *3*, 1125-1131.

The results demonstrated that the cytotoxic response is highly dependent on the structural characteristics of β-lactam compounds and their concentration. In general, cell viability decreases with the increasing of the concentration showing a dose-concentration response (Figure 2.4). However, the final response seems to be a function of the β-lactam derivatives. Compound **2b**, **2e**, **2j**, and **2k** were able to decrease the percentage of viability compared to control cells with values ranged down to 20%, as a function of cell type and endpoint method.

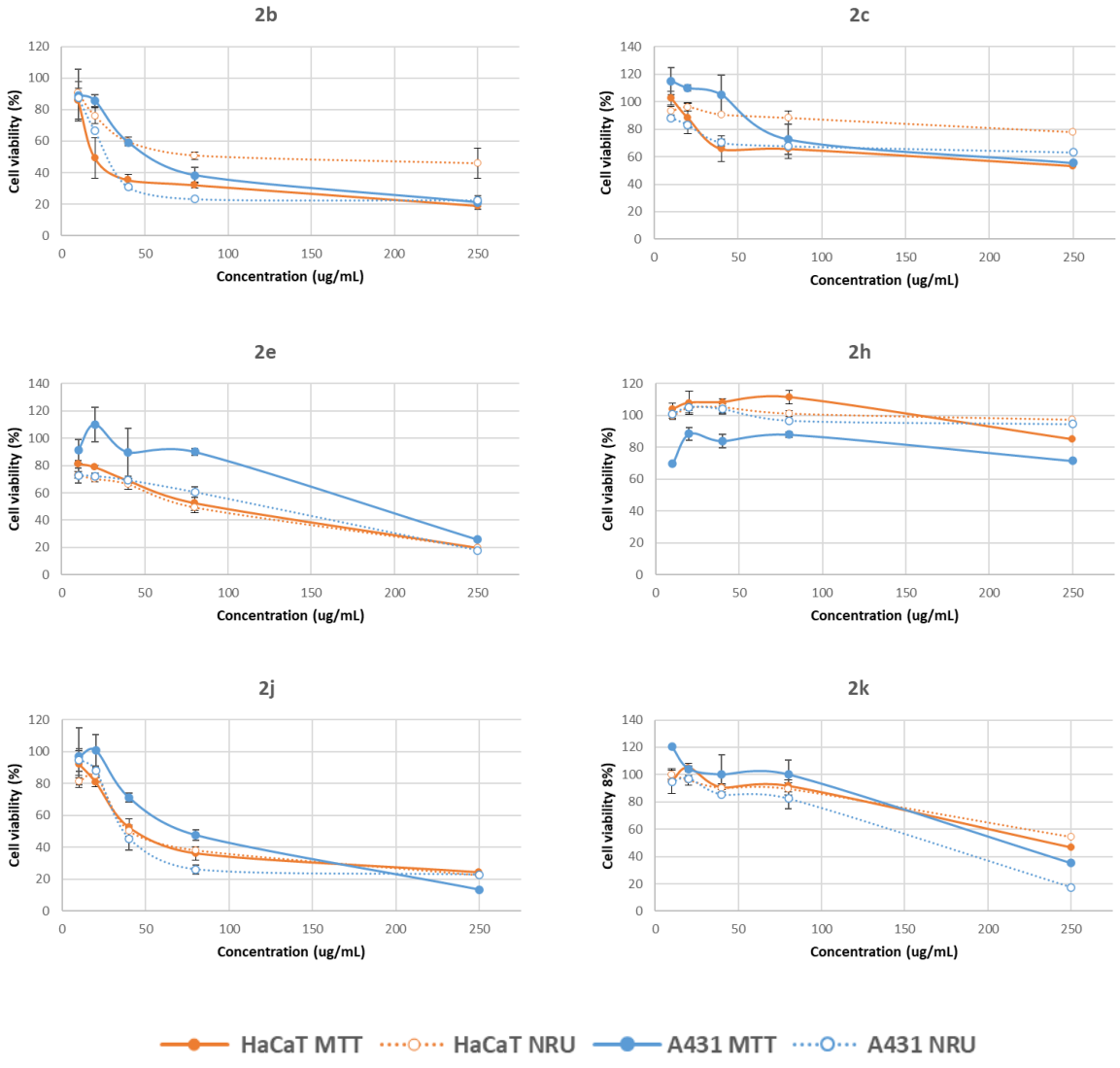



**Figure 2.4.** Concentration-dependent relative viabilities of HaCaT and A431 cells treated with β-lactams derivatives for 24 h determined by MTT (solid lines) and NRU (dotted lines) assays. The data correspond to the average of three independent experiments ± standard deviation.

Compounds **2c** and **2h** however, promote cell viability up to 50% in all cases. Moreover, the structure of the β-lactam determined the selectivity against the cell type and the mode of action. Hence, compound **2e** promotes higher cytotoxicity in HaCaT cells than in A431 cells regardless the concentration range. Meanwhile, oppositely results were observed in the case of compound **2h**. There are not big differences between the cellular responses when the other β-lactams were considered.

As a general trend, these results suggested minor differences between the mode of action of the tested compounds with the plasma membrane and lysosomal accumulation (NRU method) or the modification of the metabolic activity of mitochondria inside the cells (MTT method). In all cases, these compounds can achieve the mitochondrial compartment after alteration of the plasma membrane.

From the fitting of concentration-dependent viabilities curves, the corresponding half-maximal inhibitory concentration ($IC_{50}$) was determined. The obtained results have been summarized in Figure 2.5 and Table 6. The structural characteristics of β-lactam derivatives seem to be the main factor in the tested compounds' cytotoxic response. Compound **2b**, as a reference compound, demonstrated to be the most cytotoxic compound showing the lowest $IC_{50}$ values (20-49 µg/mL and 30-47 µg/mL for HaCaT and A431 cell lines, respectively). The cellular response depends on the nature of the substituent on the benzene ring and its location. Introduction of 2 fluorine atoms (compound **2h**) generates a more biocompatible compound, with $IC_{50}$ values close to 250 µg/mL (A41 cell line) or higher than 250 µg/mL (HaCaT cell line), which corresponds to the highest tested concentration, in an independent manner of the endpoint method.

The location of the methyl group in the benzene ring is also an important parameter on the cell response. Thus, when the $CH_3$ is in the ortho position (compound **2c**) $IC_{50}$ values are close to 250 µg/mL (HaCaT and A41, MTT endpoint) and higher than 250 µg/mL (HaCaT and A431, NRU endpoint). However, when the methyl substituent is in the para position (compound **2e**), the compound preserves the cytotoxic activity with $IC_{50}$ values between 78-93 µg/mL (HaCaT) and 120-180 µg/mL (A431).

Switching from *t*-Bu to *i*-Pr (compound **2j**) have a poor influence on the cytotoxic response since $IC_{50}$ values between 40-42 µg/mL (HaCaT) and 38-76 µg/mL (A431) were found. However, in the case of the cyclohexyl derivative **2k**, limited interaction with the proposed cells was observed as it is indicated by the $IC_{50}$ values close to 220 µg/mL (HaCaT, NRU) or higher than 250 µg/mL (HaCaT, MTT and A41 in all cases).

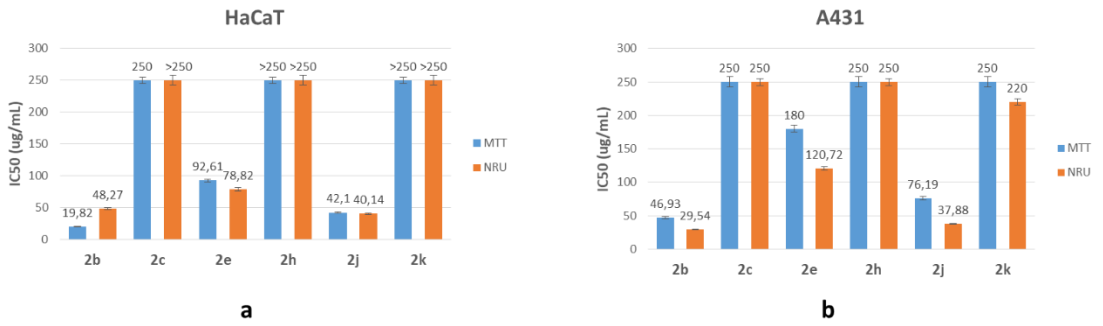
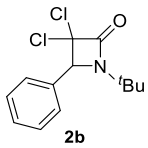



**Figure 2.5**. $IC_{50}$ values of the corresponding β-lactams on HaCaT (a) and A431 (b) cell line as a function of endpoint method. The data correspond to the average of three independent experiments ± standard deviation.

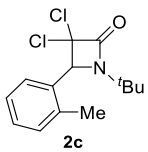
When the $IC_{50}$ values as a function of the endpoint method were compared, the obtained results suggested that, in general, the interaction with the cell membrane is favored. In almost all cases, $IC_{50}$ values corresponding to the NRU method showed lower values than those obtained in the MTT endpoint. Moreover, from the values displayed in Table 2.5, selectivity Index (SI) seems to depend on the endpoint method. In the case of MTT method, poor selectivity was detected. In all cases, SI values are equal or lower than 1, demonstrating no selectivity in the mode of action. However, some selectivity among the proposed cell lines was observed when the NRU endpoint was considered, demonstrating discrete selectivity in the mode of action of almost all compounds (except for compound **2e**).

**Table 2.5**. $IC_{50}$values of the corresponding β-lactams as a function of cell line and endpoint method. Selectivity index against the tumor cell line (A431) in comparison with the non-tumor cell line (HaCaT).

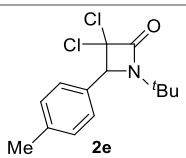
| **Compound** | **$IC_{50}$ HaCaT** (ug/mL) | | **$IC_{50}$ A431** (ug/mL) | | **SI** | |
|---|---|---|---|---|---|---|
| | **MTT** | **NRU** | **MTT** | **NRU** | **MTT** | **NRU** |
| **2b** | 19.82 | 48.27 | 46.93 | 29.54 | 0.42 | 1.63 |
| **2c** | 250 | >250 | 250 | 250 | 1.0 | > 1.0 |
| **2e** | 92.61 | 78.82 | 180 | 120.72 | 0.51 | 0.65 |
| **2h** | >250 | >250 | 250 | 250 | > 1.0 | > 1.0 |
| **2j** | 42.10 | 40.14 | 76.19 | 37.88 | 0.55 | 1.06 |
| **2k** | >250 | >250 | 250 | 220 | > 1.0 | > 1.13 |



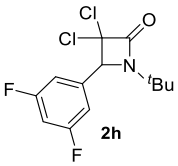
**2b**



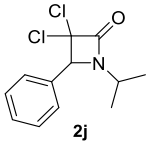
**2c**



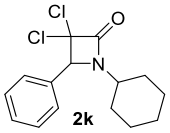
**2e**



**2h**



**2j**



**2k**

# CHAPTER 3:

# *Microwave assisted isomerization of N-allyl carbamates and N-allyl amides to Z-enecarbamates and Z-enamides catalyzed by $RuCl_2(PPh_3)_3$*

## 3.1. Enamides and enecarbamates in natural compounds and organic synthesis

The enamide motif is found in several alkaloids and drug candidates as *E* and the less thermodynamically stable *Z* isomers (Figure 3.1). Moreover, enamides and enecarbamates are stable enamine surrogates with high synthetic potential used in many chemical transformations as a result of the *N*-withdrawing substituent present on the nitrogen atom.[1] Indeed, in contrast to enamines, they are stable to hydrolysis and maintain their predisposition to electrophilic activation.

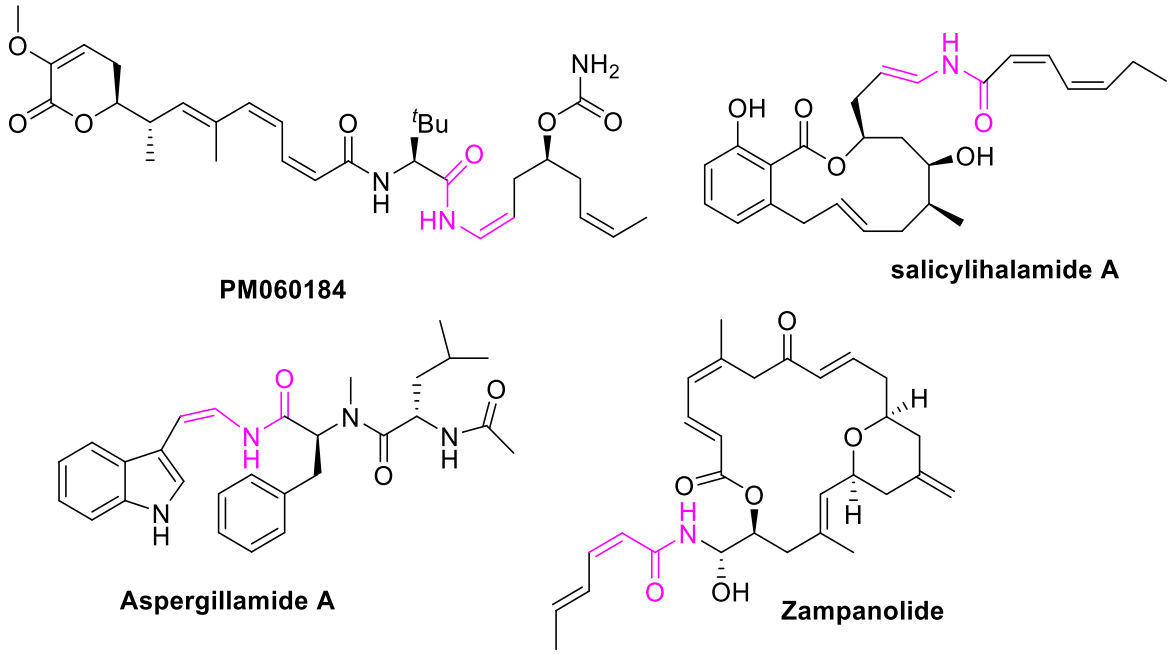


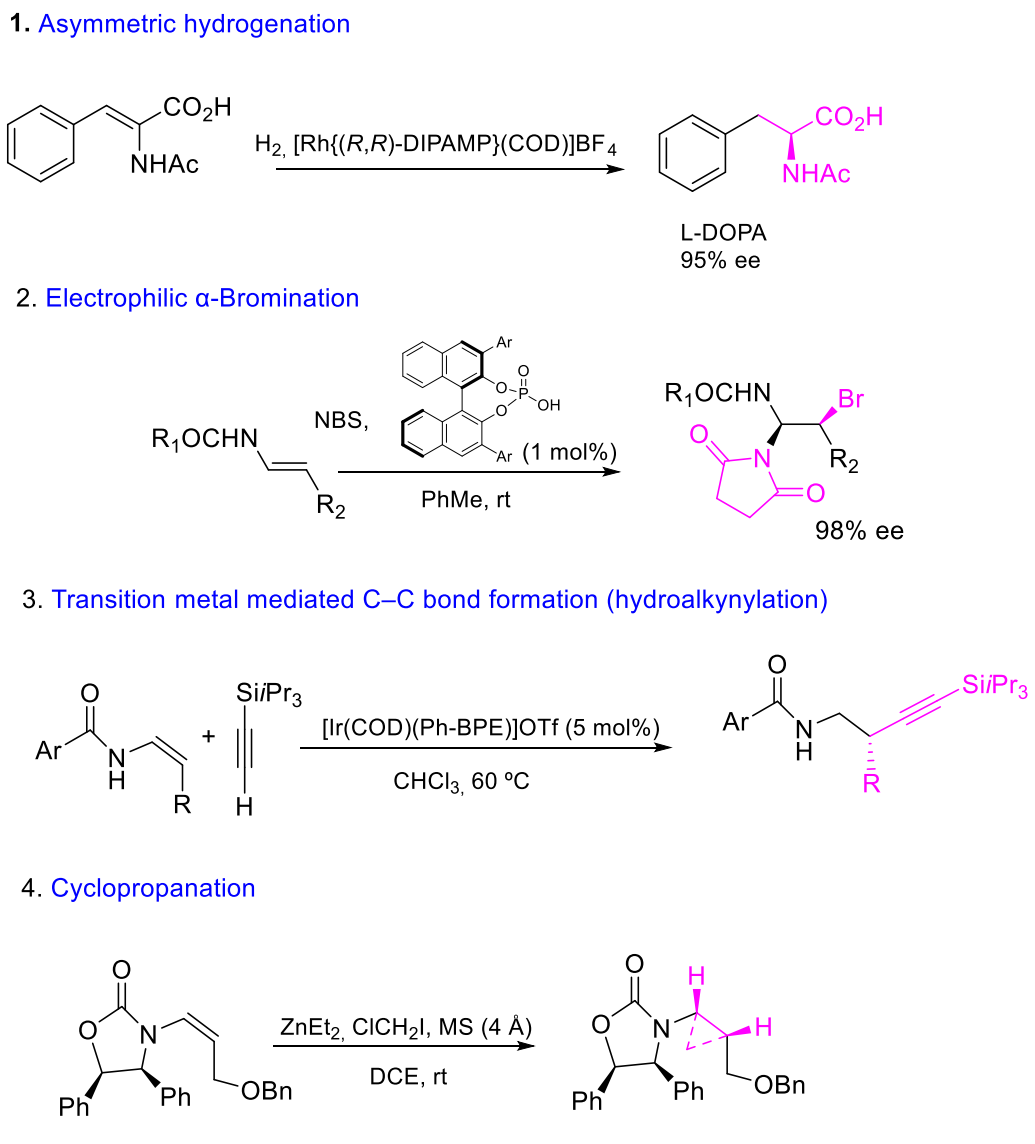

**Figure 3.1**. Natural compounds with the enamide motif with anti-cancer activity.

Thus enamides and enecarbamates have been successfully used in asymmetric hydrogenations catalyzed by transition metal complexes,[1d,2] halo

[1] (a) Matsubara, R.; Kobayashi, S. Enamides and enecarbamates as nucleophiles in stereoselective C–C and C–N bond-forming reactions. *Acc. Chem. Res.* **2008**, *41*, 292-301. (b) Carbery, D. R. Enamides: valuable organic substrates. *Org. Biomol. Chem.* **2008**, *6*, 3455-3460. (c) Nugent, T. C.; El-Shazly, M. Chiral Amine Synthesis-Recent developments and trends for enamide reduction, reductive amination, and imine reduction. *Adv. Synth. Catal.* **2010**, *352*, 753-819. (d) Gopalaiah, K.; Kagan, H. Use of nonfunctionalized enamides and enecarbamates in asymmetric synthesis. *Chem. Rev.* **2011**, *111*, 4599–4657. (e) Bernadat, G.; Masson, G. Enamide derivatives: versatile building blocks for highly functionalized α,β-substituted amines. *Synlett* **2014**, *25*, 2842-2867.

[2] Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. Asymmetric hydrogenation. Rhodium chiral bisphosphine catalyst. *J. Am. Chem. Soc.* **1977**, *99*, 5946-5952.

functionalizations,[3] transition metal mediated C–C bond formations,[4] and cyclopropanations[5] among others (Scheme 3.1).




**Scheme 3.1**. Examples of chemical transformations from enamides and enecarbamates.

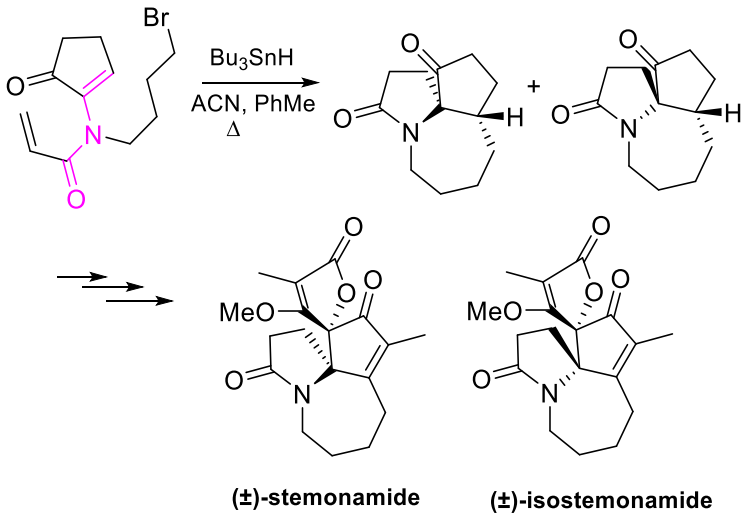
The synthetic potential of enamides and enecarbamates has been readily demonstrated in the total synthesis of several natural and unnatural molecules

[3] Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. Highly enantioselective electrophilic α-bromination of enecarbamates: chiral phosphoric acid and calcium phosphate salt catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 10389-10392.

[4] Bai, X.-Y.; Wang, Z.-X.; Li, B.-J. Iridium-catalyzed enantioselective hydroalkynylation of enamides for the synthesis of homopropargyl amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 9007-9011.

[5] Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, c.; Tang, Y. Stereoselective Simmons-Smith cyclopropanation of chiral enamides. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069-4072

displaying biological activity.[6] One of the outstanding examples was reported in the total syntheses of (±)-stemonamide and (±)-isostemonamide. Indeed starting from an enamide through a 7-endo/5-endo radical-cascade cyclization via α-amidoyl radical in the presence of tributyltin hydride and 1,1′-azobis(cyclohexanecarbonitrile) (ACN) advanced tricyclic intermediates of these natural compounds were achieved (Scheme 3.2).[7]




**Scheme 3.2.** Enamide derivative in the total synthesis of (±)-stemonamide and (±)-isostemonamide.

### 3.2. Synthetic precedents in the preparation of enamides and enecarbamates

Enamides and enecarbamates can be prepared by combining the structure parts, usually two, using traditional methods such as acylation of imines,[8] the Curtius rearrangement of α,β-insaturated acyl azide derivatives,[9]

[6] For representative reviews, see: (a) Courant, T.; Dagousset, G.; Masson, G.; Enamide derivatives: versatile building blocks for total synthesis. *Synthesis* **2015**, *47*, 1799-1826. (b) Cai, X.; Yang, M.; Guo, H. Tertiary enamides: versatile and available substrates in synthetic chemistry. *Curr. Org. Synth.* **2019**, 16, 70−97. (c) Beltran, F.; Miesch, L. Tertiary enamides as versatile and valuable substrates to reach chemical diversity. *Synthesis* **2020**, *52*, 2497-2511. (d) Ninomiya, I.; Naito, T. in "The Alkaloids, Chemistry and Pharmacology", ed. Brossi, A., Vol. 22, Academic Press, New York, **1983**, pp. 189-279.

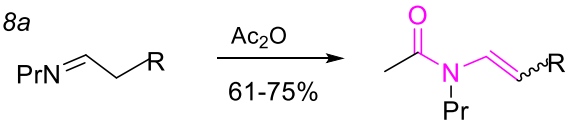
[7] Taniguchi, T.; Tanabe, G.; Muraoka, O.; Ishibashi, H. Total synthesis of (±)-stemonamide and (±)-isostemonamide using a radical cascade. *Org. Lett.* **2008**, *10*, 197-199.

[8] (a) Breederveld, H. The chemistry of the *N*-alkylaldimines. I. The reaction of *N*-alkylaldimines with acetic anhydride. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 401-407. (b) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. β- and γ-Lactams by nickel powder mediated 4-*exo* or 5- *endo* radical cyclisations. A concise construction of the mesembrine skeleton. *Tetrahedron* **1998**, *54*, 1029-1040.

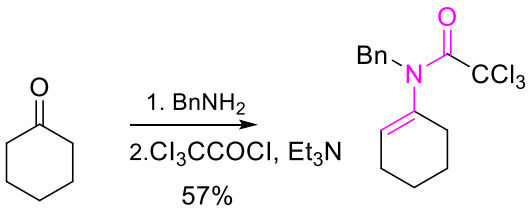
[9] Chuang, T.; Wu, P.J. Synthesis and mechanistic study of isoquinolinones from cinnamoyl azides. *Chin. Chem. Soc.* **2006**, *53*, 413-420.

1. Acylation of imines

*Ref. 8a*

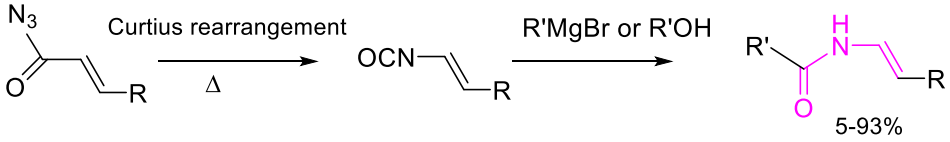



*Ref. 8b*



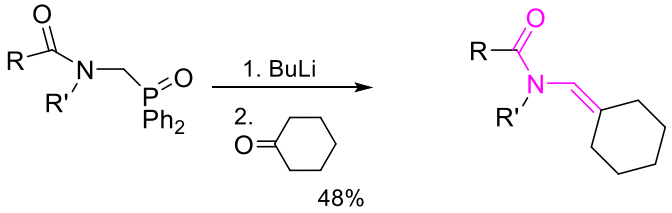

2. Curtius rearrangement

*Ref. 9*



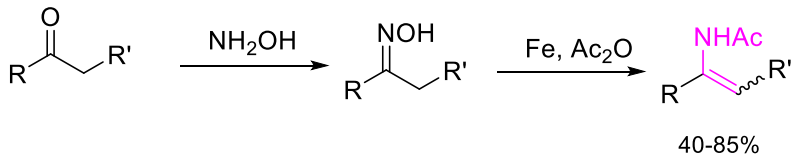

3. Horner-Wittig reaction

*Ref. 10*



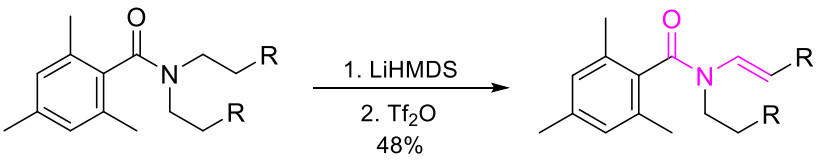

4. Reductive acetylation of ketoximes

*Ref. 11*




5. Dehydrogenation of amides

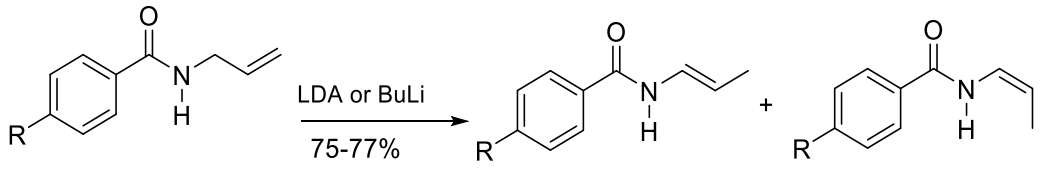
*Ref. 12*




**Scheme 3.3**. Some of the strategies in the synthesis of enamides.

Horner-Wittig reaction,[10] or transformation of a ketone into an oxime followed by subsequent reduction with iron metal in the presence of acetic anhydride[11] (Scheme 3.3). Even though these procedures are still used for the preparation of enamides and enecarbamates, they usually provide a mixture of *E*-*Z* isomers with low to moderate yields. Recently, a direct synthesis of enamides by dehydrogenation on amides using a combination LiHMDS and triflic anhydride was reported providing exclusively *E*-enamides when the reaction was run from acyclic amides (Scheme 3.3).[12]

Another atom-economic synthesis of enamides is the transposition of the terminal carbon–carbon double bond of the corresponding readily available allyl amides.[13] This transformation has been carried out with many experimental procedures. Among these are the use of strong bases such as LDA or BuLi.[14] Thus operating from para-substituted *N*-allylbenzamides, with LDA at -78°C, the corresponding (*E*)-*N*-(prop-I-enyl)benzamide was the major product whereas with *n*butyllithium and the mixture warmed to 0 ºC the (*Z*)-isomer was essentially furnished (Scheme 3.4).



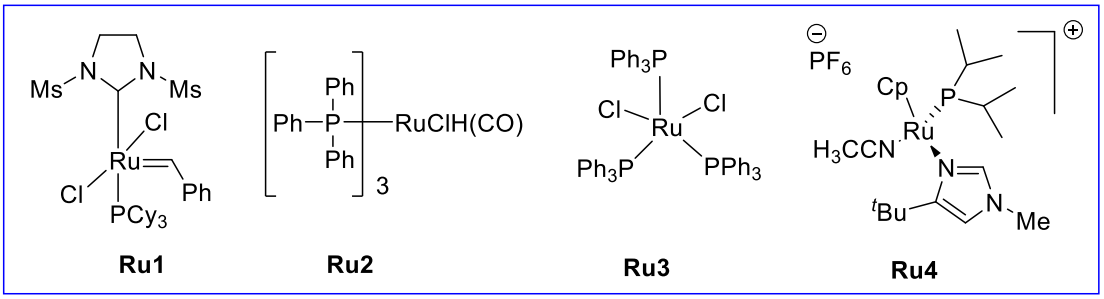

**Scheme 3.4**. Isomerization of allylamides in the presence of strong bases.

The transition metal catalyzed isomerization of *N*-allyl amides to enamides is another alternative which has been explored in the presence of many transition metal complexes.[13]

[10] Broekhof, N.L.J.M.; Jonkers, F.L.; van der Gen, A. Enamine synthesis by the Horner-Wittig reaction. *Tetrahedron Lett.* **1979**, 20, 2453-2456.
[11] Burk, M. J. Casy, G.; Johnson, N. B. A Three-step procedure for asymmetric catalytic reductive amidation of ketones. *J. Org. Chem.* **1998**, *63*, 6084-6085.
[12] Spieß, P.; Berger, M.; Kaiser, D.; Maulide, N. Direct Synthesis of Enamides via Electrophilic Activation of Amides. *J. Am. Chem. Soc.* **2021**, *143*, 10524−10529.
[13] Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. Double bond migration in *N*-allylic systems catalyzed by transition metal complexes. *Coord. Chem. Rev.* **2008**, *252*, 1819-1841.
[14] Ribereau, P.; Delamare, M.; Celanire, S.; Queguiner, G. Selective preparation of (*Z*)- and (*E*)-prop-1-enylamides from *N* –allylbenzamides. *Tetrahedron Lett.* **2001**, *42*, 3571–3573.

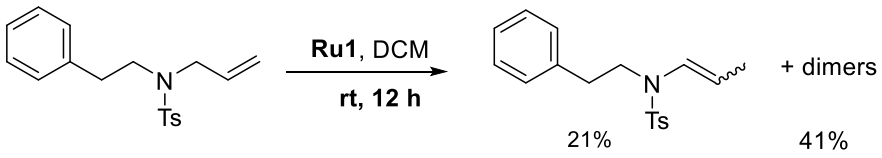
In the presence of ruthenium complexes naming Grubbs' 2nd generation catalyst (**Ru1**) from allyl sulfonamide, the isomerization takes place providing a mixture of *E*/*Z* isomers with a poor yield (Scheme 3.5a).[15] The reaction was also performed from substrates that might experience metathesis as a competitive process to isomerization. In this case the simple addition of vinyloxytrimethylsilane (1 equiv.) is sufficient to provide the corresponding enamide as a mixture of E/Z isomers with good yields (Scheme 3.5b).[16] Isomerization of *N*-allyl-*N*-arylethanamides catalyzed by [$RuClH(CO)(PPh_3)_3$] (**Ru2**) was also investigated. Thus operating from *N*-allyl-*N*-arylethanamides only the corresponding (*E*)-*N*-aryl-*N*-(1-propenyl)ethanamides were isolated with good yields (Scheme 3.5c).[17] In a similar work, using the same catalyst, *N*-allyl 2-iodoacetanilide provided only the (*E*)-enamide with a very good yield (Scheme 3.5d).[18] Additionally, isomerization of *N*-allylphtalimide was achieved in the presence of $RuCl_2(PPh_3)_3$ (**Ru3**) to provide exclusively (*E*)-*N*-propenylphthalimide (Scheme 3.5e).[19] To our knowledge this is the only example where **Ru3** is used as a catalyst for allylamide isomerization. Isomerization of secondary allylamides and alkenes was also performed in the presence of **Ru4** also called the "alkene zipper" to give exclusively the *E*-isomers with supposedly very good NMR yields but confusing experimental data about the catalyst loading and the yields obtained (Scheme 3.5f).[20]

[15] Cadot, C.; Dalko, P. I.; Cossy, J. Olefin isomerization by a ruthenium carbenoid complex. Cleavage of allyl and homoallyl groups. *Tetrahedron Lett.* **2002**, *43*, 1839-1841.
[16] Arisawa, M.; Terada, y.; Nakagawa, M.; Nishida, A. Selective isomerization of a terminal olefin catalyzed by a ruthenium complex: The synthesis of indoles through ring-closing metathesis. *Angew. Chem. Int. Ed.* **2002**, *41*, 4732-4734.
[17] Krompiec, S.; Pigulla, M.; Szczepankiewicz, W.; Bieg, T.; Kuznik, N.; Leszczynska-Sejda, K.; Kubicki, M.; Borowiak, T. Highly selective synthesis of (*E*)-*N*-aryl-*N*-(1-propenyl) ethanamides via isomerization of *N*-allyl ethanamides catalyzed by ruthenium complexes. *Tetrahedron Lett*. **2001**, *42*, 7095–7098.
[18] Dominguez, G.; Casarrubios, L.; Rodriguez-Noriega, J.; Perez-Castells, J. Indole and Quinoline synthesis *via* intramolecular Pauson-Khand reactions of enamines and allylamines. *Helv. Chim. Acta* **2002**, *85,* 2856-2861.
[19] Delogu, G.; Faedda, G.; Gladiali, S. Hydrocarbonylation of unsaturated nitrogen compounds. Synthesis of *N*-protected aminoacid derivatives from *N*-substituted phtalimides. *J. Organomet. Chem.* **1984**, *268*, 167-174.
[20] Larsen, C. R.; Grotjahn, D. B. Stereoselective alkene isomerization over one position. *J. Am. Chem. Soc.* **2012**, *134*, 10357-10360.

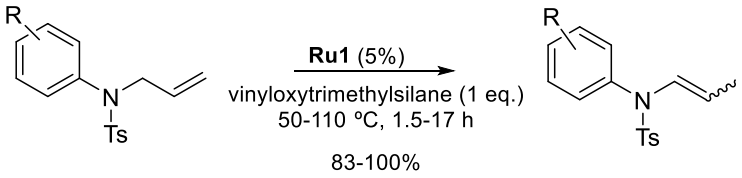



**Ru1** **Ru2** **Ru3** **Ru4**

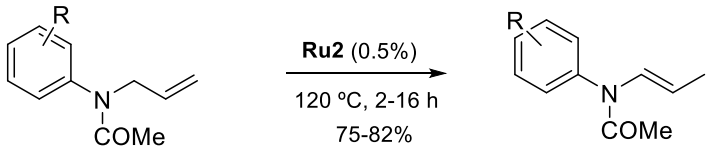
*a.Ref. 15*




*b.Ref. 16*

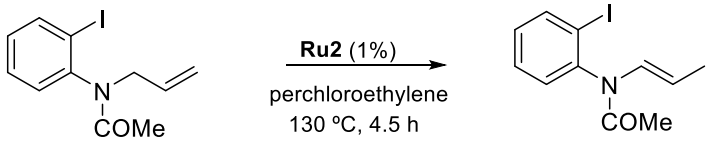



*c. Ref. 17*

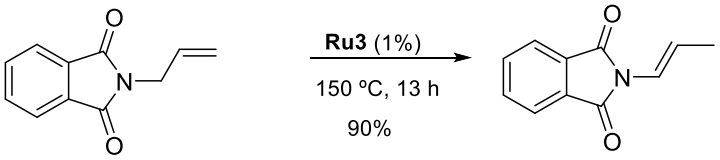



R =H, *o*-Me, *p*-Me, *o*-MeO, *m*-MeO,*p*-MeO,*o*-Cl, *p*-Cl, *o*-Br, *p*-Br

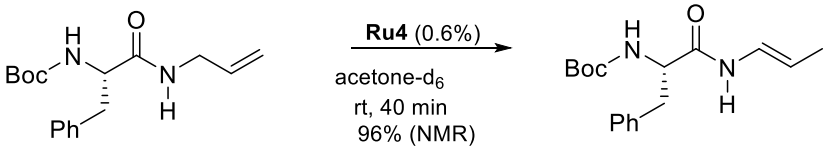
*d. Ref. 18*




*e. Ref. 19*



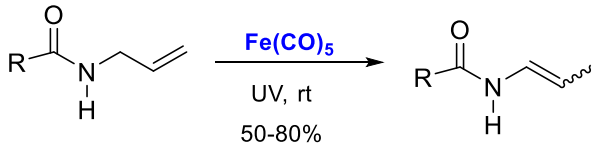

*f. Ref. 20*



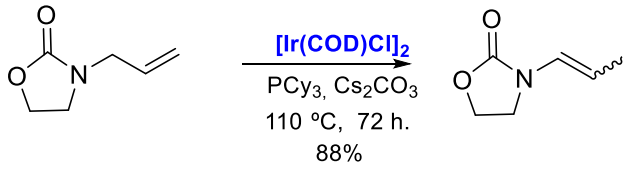

**Scheme 3.5**. Isomerization of allylamides in the presence of Ru catalysts.

The transition metal catalyzed isomerization of *N*-allylamides and *N*-allylcarbamates was also achieved in the presence of Fe (Scheme 3.6a),[21] Ir (Scheme 3.6b),[22] Rh[23] or Ni[24] complexes where a mixture of *E*/*Z* isomers or a strong *E*-selectivity in the isomerization was observed (Scheme 3.6).

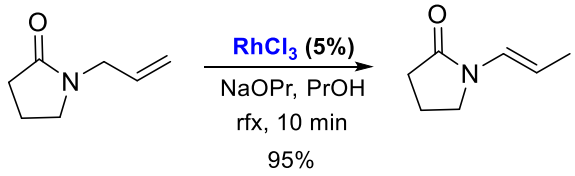
*a. Ref. 21*



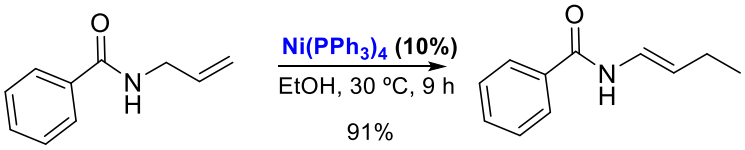

*b. Ref. 22*




*c. Ref. 23*




*d. Ref. 24*




**Scheme 3.6**. Isomerizations of *N*-allyl amides and *N*-allyl carbamates in the presence of Fe, Ir, Rh and Ni complexes.

[21] (a) Hubert, A. J.; Moniotte, P.; Goebbels, G.; Warin, R.; Teyssie, P. Catalysed prototropic rearrangements. Part II. Metal carbonylcatalysed isomerization of *N*-allylamides to prop-2-enyl derivatives. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1954-1957. (b) Sergeyev, S.; Hesse, M. A new convenient method for the preparation of enamides from *N*-allylamides. *Synlett* **2002**, 1313-1317.
[22] Neugnot, B.; Cintrat, J-C; Rousseau, B. A new highly chemoselective isomerization of allylamides. *Tetrahedron* **2004**, *60*, 3575-3579.
[23] Zacuto, M. J.; Xu, F. One-Ste*p RhCl3-catalyzed deprotection of acyclic N-allyl amides. J. Org. Chem.* **2007**, *72*, 6298-6300.
[24] Wang,L.; Liu, C.; Bai, R.; Pana, Y.; Lei, A. Easy access to enamides: a mild nickel-catalysed alkene isomerization of allylamides. *Chem. Commun*. **2013**, *49*, 7923.

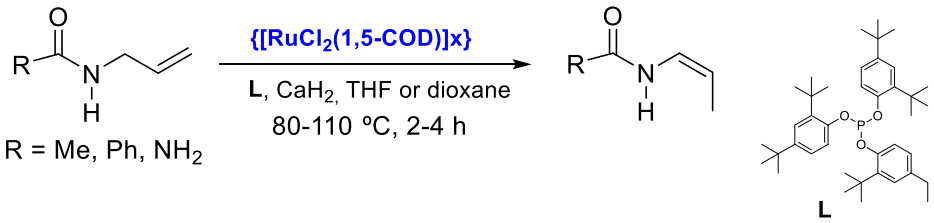
As it was clearly indicated in the examples mentioned before, in the presence of transition metal catalysts, isomerization of *N*-allyl amides and *N*-allyl carbamates usually provides an *E*/*Z*-mixture or the thermodynamically favored *E*-configured enamides or enecarbamates. The achievement of thermodynamically less stable *Z*-configured enamide through double-bond migration is rarely reported, still under-represented and limited to secondary amides (Scheme 3.7).[25] Moreover the examples described are not very clear about the exact proportion of the *Z*/*E* ratio and needed prolonged reaction time to be completed. Additionally, the stereoselective outcome of theses reactions seems to result from a specific coordination of the metal atom with the amide function and the double bond creating a $\pi$ complex in which the rigidity is responsible for the high stereoselectivities observed. In a more recent paper, using $Ni(dppp)Cl_2$ as a catalyst in the presence of $HPPh_2$, Zn and $ZnI_2$, isomerization of secondary amides was carried out at low temperatures (0 ºC-25 ºC) and prolonged time providing a high *Z*-selectivity of the enamides (Scheme 3.7c).[26] Curiously from acyclic tertiary amides, under different reaction conditions no conversion to the *Z* and/or *E* enamides was observed which make the authors suggest that a free NH-group is beneficial, if not crucial, for the nickel-catalysed translocation of the double bond and its stereoselective outcome. Nevertheless cyclic tertiary *N*-allyl derivatives undergo the reaction to give predominantly the *E*-isomers. Finally, an additional example of isomerization leading to *Z*-enamides was reported also in 2017 using $CpRu(CH_3CN)_3PF_6$ as a catalyst. Although the procedure describes an effective access to *Z*-di-, tri-, and tetrasubstituted enamides, it is limited to secondary *N*-allyl amides and prolonged reaction time (1-16 h) was necessary to get full conversions (Scheme 3.7d).[27]

[25] Only few substrates were reported to provide *Z* isomer see: (a) Krompiec, S.; Pigulla, M.; Kuznik, N.; Krompiec, M.; Marciniec, B.; Chadyniak, D.; Kasperczyk, J. Highly selective isomerization of *N*-allylamides catalyzed by ruthenium and rhodium complexes. *J. Mol. Catal. A: Chem.* **2005**, *225*, 91-101. (b) Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialo, J.; Kasperczyk, J. Highly selective isomerization of *N*-allylamides and *N*-allylamines. *Tetrahedron Lett.* **2004**, *45*, 5257-5261 (c) Stille, J. K.; Becker, Y. Isomerization of *N*-allylamides and -imides to aliphatic enamides by iron, rhodium, and ruthenium complexes. *J. Org. Chem.* **1980**, *45*, 2139−2145.

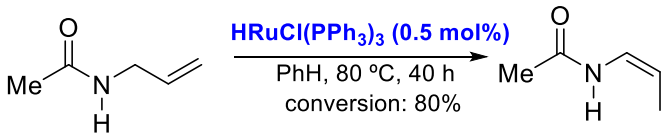
[26] Weber, F.; Steinlandt, P. S.; Ballmann, M.; Hilt, g. Structure-dependent nickel-catalysed transposition of *N*-allylamides to *E*- or *Z*-enamides. *Synthesis* **2017,** *49*, 440-450.

[27] Trost, B. M.; Cregg, J. J.; Quach, N. Isomerization of *N*-allyl amides to form geometrically defined di-, tri-, and tetrasubstituted enamides. *J. Am. Chem. Soc.* **2017**, *139*, 5133−5139.

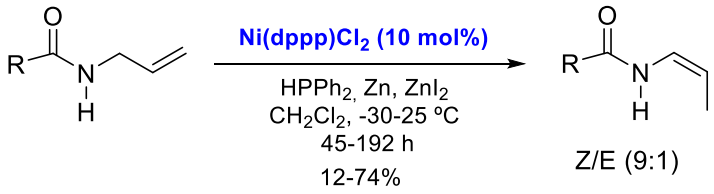
*a. Ref. 25a, 25b the authors do not provide information about the yield or the Z/E ratio*



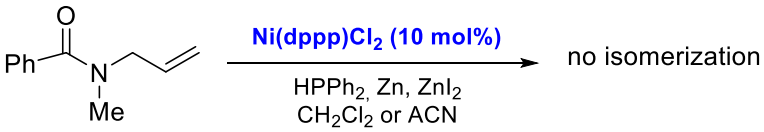

*b. Ref. 25c, only 1 example providing the Z-isomer but no yield*



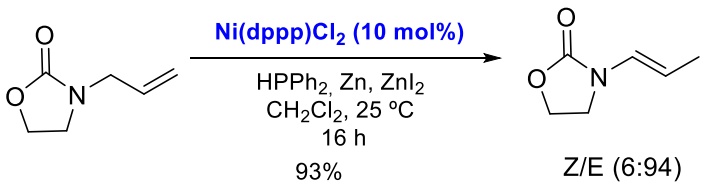

*c. Ref. 26, with tertiary acyclic amide no isomerization takes place*



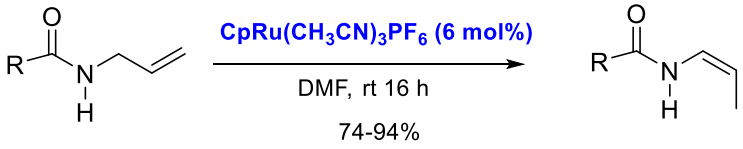

R = Me, *n*Hp, Bn, Ph, O*t*Bu, OBn




With cyclic tertiary *N*-allyl derivatives exclusively the *E*-isomers




*d. Ref. 27*



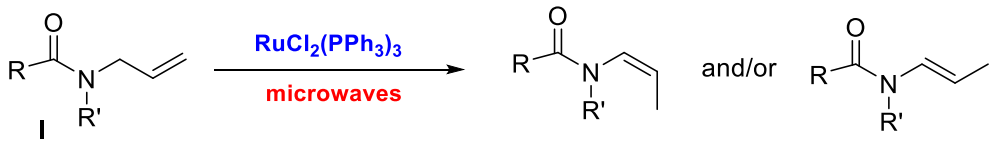

R = Ph, vinyl, $CH_2CH_2NHBoc$

**Scheme 3.7**. Synthesis of *Z*-enamides and *Z*-enecarbamates.

In conclusion isomerizations in the presence of transtion metal catalysts are limited to secondary amides, prolonged reactions are necessary to achieve full conversion and in most cases a mixture of *Z*/*E* isomers is obtained.

### 3.3. Isomerization of *N*-allyl carbamates and *N*-allyl amides in the presence of $RuCl_2(PPh_3)_3$. Our results

As it was reported in the introduction (Chapter 1), the aim of this part of the thesis is to investigate the isomerization process from tertiary allyl carbamates and allyl amides type **I** in the presence of $RuCl_2(PPh_3)_3$ and under microwave activation.




**I**

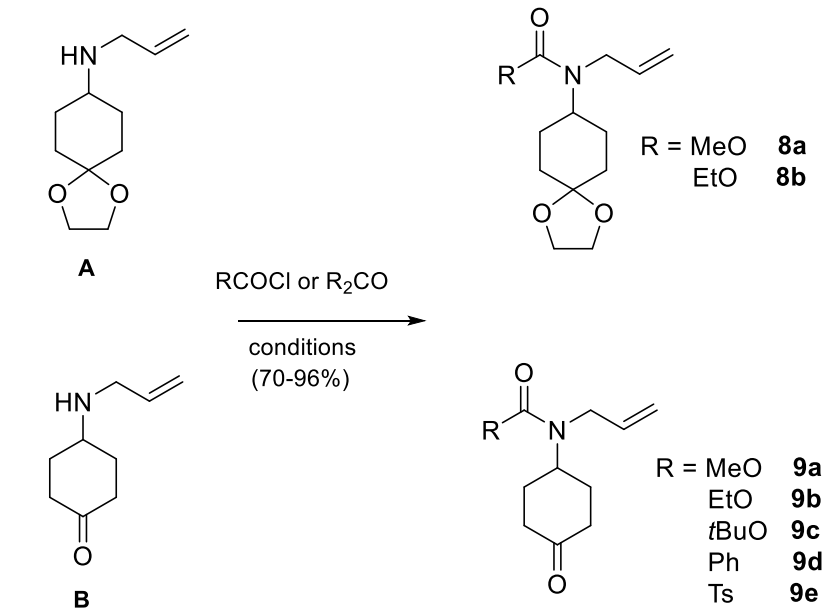
R = Oalkyl, alkyl, aryl

R'≠ H

**Scheme 3.8**. Aim of this investigation.

To start our study we decided to prepare carbamates and amides **8** and **9** since their precursors were already available in the laboratory from a previous work (Scheme 3.9).[28]

[28] For the preparation of **8** we followed the same procedure reported in: Diaba, F.; Bonjoch, J. Asymmetric synthesis of 2-azabicyclo[3.3.1]nonanes by a microwave-assisted organocatalysed tandem desymmetrisation and intramolecular aldolisation. *Org. Biomol. Chem.* **2009**, *7*, 2517-2519.




R = MeO, EtO ($K_2CO_3$, ACN, rt overnight ref. 28)
R = *t*BuO ($Boc_2O$, $CH_2Cl_2$, rt, overinght)
R = Ph ($Et_3N$, $CH_2Cl_2$, rt, overinght)
R = Ts (TsCl, $CH_2Cl_2$, at 0 ºC for 15 min then at rt for 2 h)

**Scheme 3.9.** Synthesis of **8** and **9**.

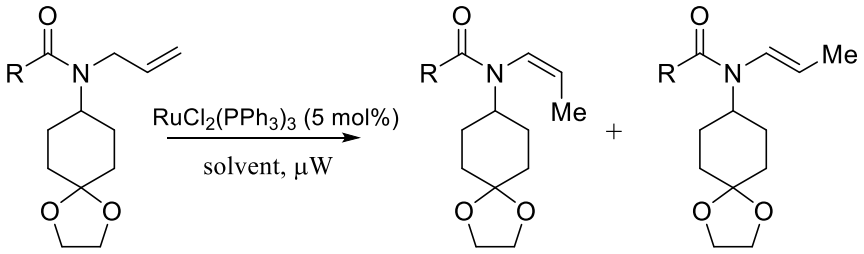
Using the classical procedures, described already in the research group, secondary amines **A** and **B** were treated with methyl or ethyl chloroformate in the presence of a base yielding **8a**, **8b**, **9a** and **9b** with good yields. **9c** and **9d** result from reaction of **B** with di-*tert*-butyl dicarbonate and benzoyl chloride respectively (Scheme 3.9).

Having in hand substrates **8** and **9** we started our investigation by screening the reaction conditions with carbamate **8a** and **8b** (Table 3.1).

Following our previous work (Chapter 2) we decided to run the first reaction from **8a** (0.44 mmol) in toluene as a solvent (1 mL) at 100 ºC using microwave activation. After 75 minutes of irradiation, only a modest conversion was observed (33%) providing after purification the *Z* derivative **10a** with a low yield (Entry 1). It's worth noting that prolonging the reaction further than 75 min did not bring better results. Nevertheless, to our big delight, an almost full conversion was achieved by simply increasing the temperature of the reaction under microwave activation to 120 ºC (Entry 2). Indeed in the $^1$H NMR spectrum of the crude the signals of **8a** almost disappeared revealing mainly the ones belonging to *Z*-

derivative **10a** (Figure 3.2). After purification by chromatography we were able to isolate as the major product **10a** with an excellent yield and the minor *E* derivative **11a** in pure forms despite their similar polarity.

**Table 3.1**. Screening of the isomerization conditions from **8a** and **8b**.[a]




R = MeO (**8a**), EtO (**8b**) **10a**, **10b** **11a**, **11b**

| Entry | **8** | Solvent | Temp.(ºC) | Time (min) | **10**, **11** (yield %) | **10**/**11** |
|---|---|---|---|---|---|---|
| 1 | **8a** | PhMe | 100 | 75 | 30[b] | 7/1 |
| 2 | **8a** | PhMe | 120 | 75 | 82 | **10/1** |
| 3 | **8a** | ACN | 120 | 75 | - | - |
| 4 | **8a** | THF | 120 | 75 | 38 | 2/1 |
| 5 | **8a** | DMF | 120 | 75 | 76 | 4/1 |
| 6 | **8a** | PhMe | 120 | 60 | 80 | **11/1** |
| 7 | **8a**[c] | DCM | 50 | 90 | - | - |
| 8 | **8a**[d] | PhMe | 100 | 45 | 55 | 1/3 |
| 9 | **8a** | PhMe | 140 | 30 | 90 | 1.1/1 |
| 10 | **8a** | PhMe | 160 | 30 | 94 | 1/2.3 |
| 11 | **8a** | PhMe | 180 | 30 | 93 | 1/2 |
| 12 | **8a** | PhMe | 180 | 10 | 93 | 1/1.9 |
| 13 | **8b** | PhMe | 120 | 45 | 90 | **11/1** |

[a] Unless otherwise noted, the reactions were carried out with 0.44 mmol of **8a** or **8b** in 1 mL of solvent under microwave activation. [b] 67% of starting material (**8a**) was recovered. [c] Using conventional heating in the presence of vinyloxytrimethylsilane (10 equiv.) and Grubbs' second-generation catalyst (5%). [d] Using the same conditions reported in c but under microwave activation.

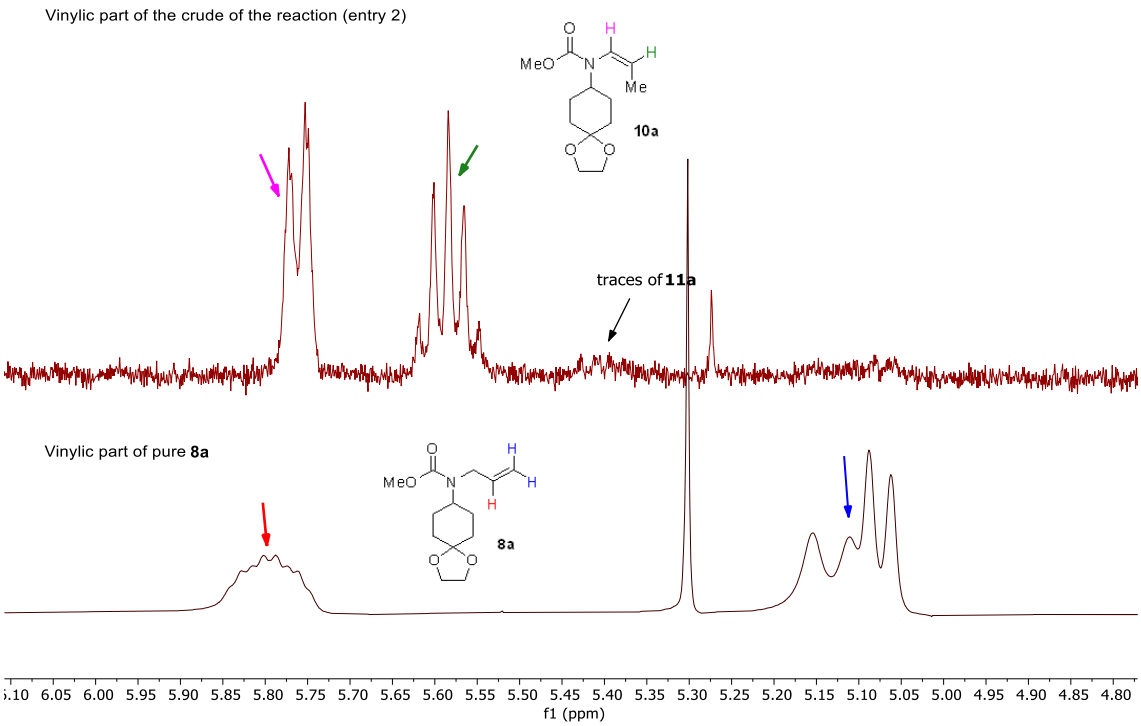



**Figure 3.2**. $^{1}$H NMR spectra of **8a** and the crude of the isomerization reaction (Table 3.1, Entry 2).

The reaction was also carried out under the same conditions using acetonitrile, tetrahydrofuran and dimethylformamide respectively. Whereas the isomerization in ACN did not take place at all and only **8a** was present in the reaction mixture (Entry 3), the reaction in THF and DMF provided a mixture of **10a** and **11a** with lower yields and worse diastereoselectivities (Entries 4 and 5). With these results in hand we decided to maintain toluene as the solvent of the reaction. Reducing the time from 75 to 60 min affects slightly the conversion ratio and the diastereoselectivity of the process (Entry 6). Additionally, we also checked the isomerization process under the conditions reported by Nishida *et al.*,[16] in the presence of vinyloxytrimethylsilane (10 equiv.) and Grubbs' second-generation catalyst (5%), after 90 min of heating at 50 ºC only **8a** was present in the reaction mixture (Entry 7). Nevertheless, using the same conditions in toluene as a solvent instead of DCM and under microwave activation, after 45 min of heating at 100 ºC, a full conversion was achieved but both the yield and the diastereoselectivity were modest (Entry 8).

Next we decided to investigate the influence of the reaction temperature on the course of the reaction under microwave activation. At 140 ºC, a full conversion was achieved after only 30 min providing a mixture of **10a** and **11a** in a 1.1/1 ratio and a very good yield (Entry 9). At 160 ºC and after the same reaction time the *E* isomer **11a** was the main compound of the reaction (Entry 10). At 180 ºC the reaction was first carried out for 30 min but then a simple $^{1}$H NMR checking showed that it was over after only 10 min providing a mixture of **10a** and **11a** in similar yields and diastereoselectivity as before (Entries 11 and 12). These results showed clearly that rising the temperature of the reaction favors the formation of the thermodynamically more stable *E*-enamides.

Additionally, the reaction from **8b,** with an ethoxy instead of a methoxy group, followed the same scenario affording after only 45 min of reaction at 120 ºC, **10b** as the major isomer in a very good yield (Entry 13).

Identification of **10a** and **11a** as well as **10b** and **11b** was possible by simply comparing the vinylic protons coupling constants. As it was reported before,[25] the coupling constant in the *Z*-isomer is smaller (≈ 7 Hz) than the *E*-isomer (≈ 13 Hz). Moreover, the vinylic protons in the *Z*-isomer are shielded (the proton on the carbon linked to the nitrogen) and deshielded (the other proton) in comparison with the *E*-isomers. Additionally, the methyl group in the latter appears at lower field in contrast to the former (Figure 3.3).

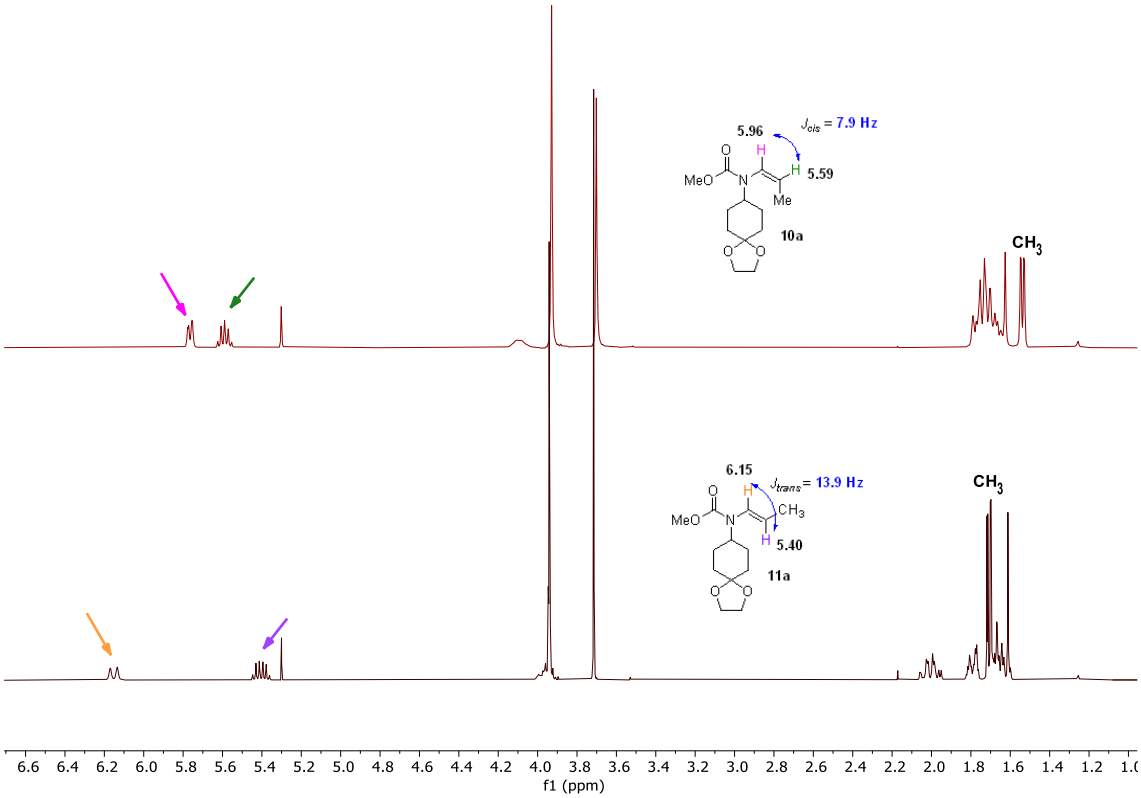
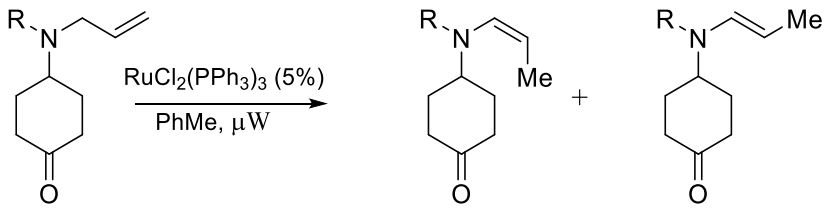



**Figure 3.3**. Comparison of $^{1}$H NMR spectra of **10a** and **11a**.

The optimized conditions were then applied to carbamates and amides **9a**-**9e** (Table 3.2). From **9a**-**9d** and as in the previous reactions with **8a**, a full conversion was attained after 75 min of heating at 120 ºC to provide mainly the *Z*-derivatives **12a**-**12d** with excellent yields (Entries 1, 5-8). Curiously, from tosylate derivative 9e, no reaction takes place (Entry 8). The influence of the reaction temperature on the *Z*/*E* ratio was also investigated with **9a** providing similar results as before (Figure 3.4).

**Table 3.2**. Isomerization reactions from **9a**-**9e**.[a]




**9** **12** **13**

| Entry | R | 9 | Temp. ºC | Time (min)[b] | Yield (%) | **12/13** |
|---|---|---|---|---|---|---|
| 1 | **$CO_2Me$** | **9a** | 120 | 75 | 89 | 10/1 |
| 2 | | **9a** | 140 | 30 | 92 | 3.9/1 |
| 3 | | **9a** | 160 | 30 | 96 | 1/2.5 |
| 4 | | **9a** | 180 | 30 | 84 | 1/2.2 |
| 5 | **$CO_2Et$** | **9b** | 120 | 75 | 88 | 10/1 |
| | | | 120 | 45 | 85 | 13:1 |
| 6 | **$CO_2tBu$** | **9c** | 120 | 75 | 95 | 15/1 |
| 7 | **COPh** | **9d** | 120 | 75 | 90 | 29/1 |
| 8 | **Ts** | **9e** | 120 | 75 | - | - |

[a] Unless otherwise noted, the reactions were carried out with 0.44 mmol of **9** in 1 mL of toluene under microwave activation. [b]Time necessary for a full conversion .

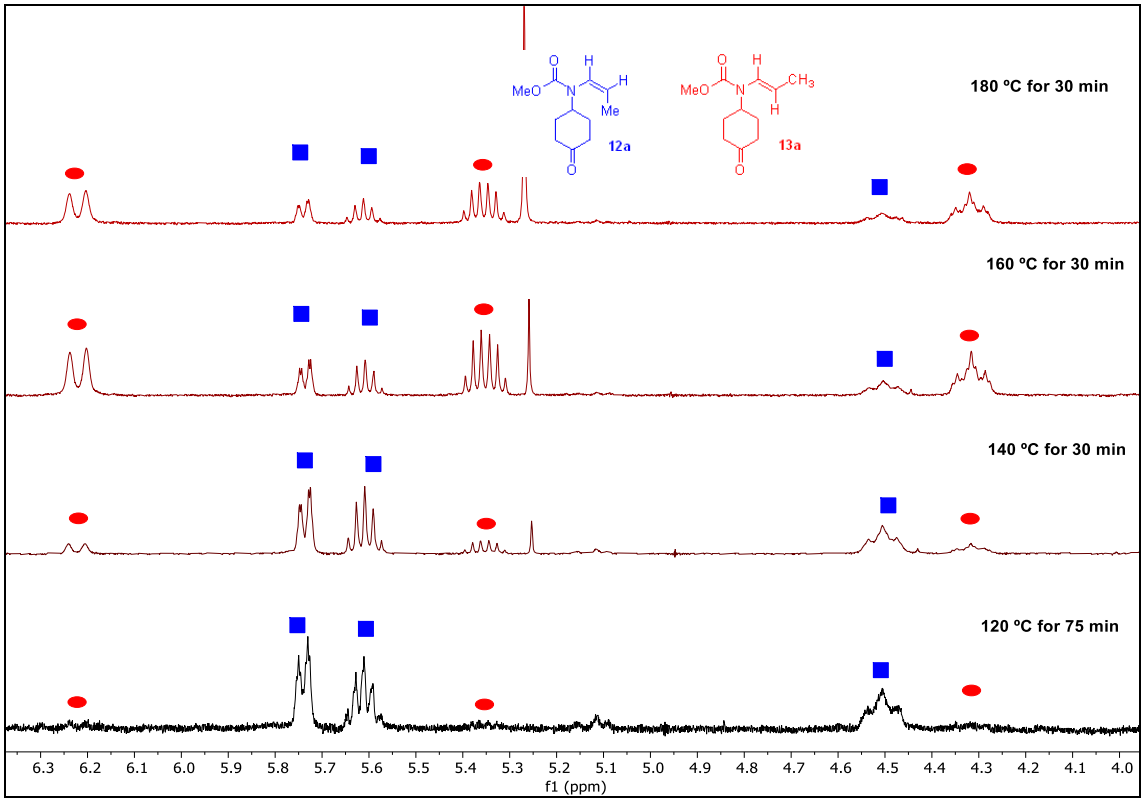
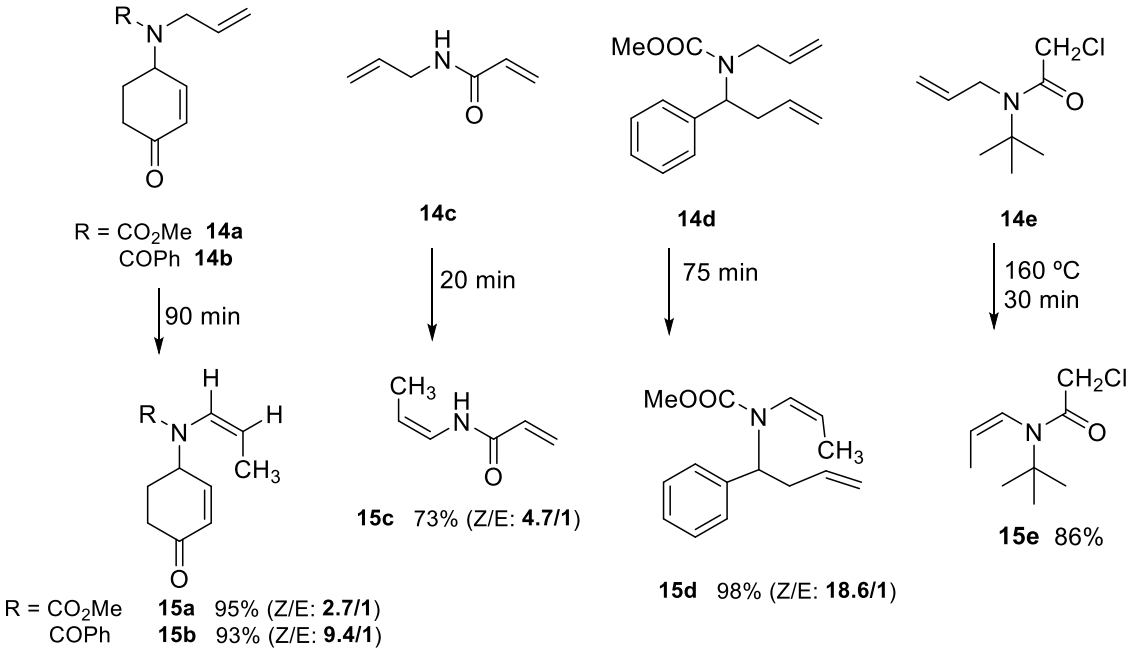



**Figure 3.4.** $^1$H NMR spectra of the isomerization from **9a** achieved at different temperatures (comparison of the *Z*/*E* ratio).

Finally the isomerization process was successfully extended to substrates **14** with different pattern providing mainly or exclusively the corresponding *Z*-enamides with good to excellent yields (Scheme 3.10). In the case of **14a** and **14b** the isomerization takes place only on the terminal double bond providing better *Z*-selectivity with the latter. On the other hand from **14d**, despite the presence of another terminal alkenyl chain only **15d** was isolated with an excellent yield and streoselectivity. Finally, It is worth noting that from **14e**, no ATRC takes place and only *Z*-**15e** was isolated as a single stereoisomer.

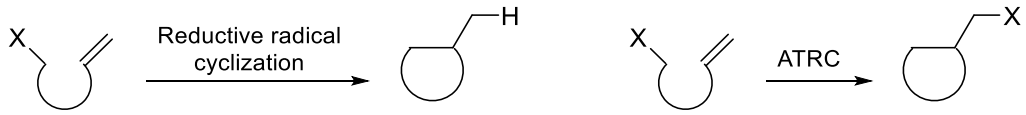



**Scheme 3.10**. *Z*-Isomerization from substrates **14**.

# CHAPTER 4:
# *Microwave assisted synthesis of γ- and δ-lactams from trichloro- and dichloroacetamides catalyzed by $RuCl_2(PPh_3)_3$*

## 4.1. Atom transfer radical reactions

Among the radical processes, atom transfer radical additions (ATRA) and atom transfer radical cyclizations (ATRC) are considered important and useful tools for the formation of C-C bonds. In contrast to the radical reductive procedures, in this type of reactions, known also as the Kharasch additions or cyclizations,[1] the halogen (X) present in the substrate and which abstraction is part of the propagation step, is retained in the final compound (Scheme 4.1). In consequence the generated intermediates possess a potentially useful carbon-halogen bond that allows post-cyclization manipulation if required to access more advanced structures.[2]




**Scheme 4.1.** Reductive radical cyclization *vs* ATRC.

Atom transfer radical additions and cyclizations in the presence of transition metal catalysts specially derived from iron, copper, ruthenium or nickel are well documented.[3] In this last part of the thesis, will be reported our results related to the synthesis of γ- and δ-lactams from alkenyl tethered trichloroacetamides in the presence of $RuCl_2(PPh_3)_3$ using microwave activation. As it was outlined in chapter 1, this catalyst has been successfully used in the synthesis of the above mentioned heterocycles but the processes involved were

[1] (a) Kharasch, M. S.; Engelmann, H.; Mayo, F. R. Atom transfer radical reactions as a tool for olefin functionalization. *J. Org. Chem*. **1937**, 2, 288-302. (b) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. Addition of carbon tetrachloride and chloroform to olefins. *Science* **1945**, *102*, 128-128.

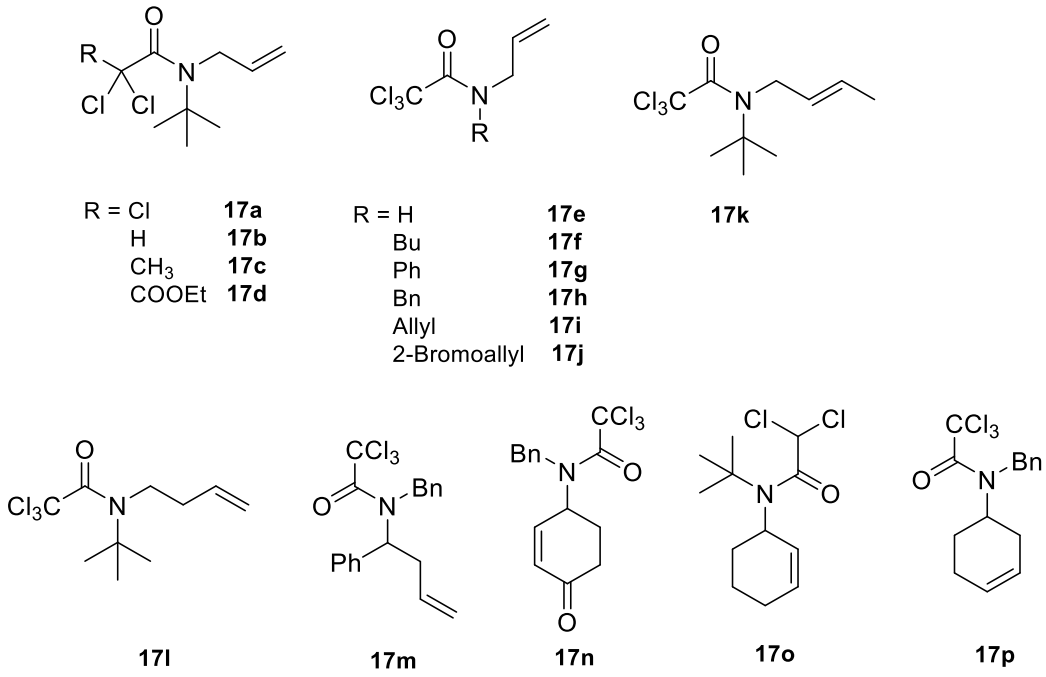
[2] For reviews see: a) Iqbal, J.; Bhatia, B.; Nayyar, N.K. Transition metal-promoted free-radical reactions in organic synthesis: the formation of carbon-carbon bonds. *Chem. Rev*. **1994**, 94, 519–564; b) Clark, A.J. Atom transfer radical cyclisation reactions mediated by copper complexes. *Chem. Soc. Rev.* **2002**, 31, 1-11; (c) MuñozMolina, J. M.; Belderrain, T. R.; Pérez, P. J. Atom transfer radical reactions as a tool for olefin functionalization – on the way to practical applications. *Eur. J. Inorg. Chem*. **2011**, 3155–3164. (d) Curran, D. P. The design and application of free radical chain reactions in organic synthesis. Part 1. *Synthesis* **1988**, 417–439.

[3] See for example: (a) Minisci, F. Free-radical additions to olefins in the presence of redox systems. *Acc. Chem.Res.* **1975**, *8*, 165-171. (b) Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Belluš, D. Convenient approaches to heterocycles via coppercatalysed additions of organic polyhalides to activated oleffns. *Tetrahedron* **1985**, *41*, 4057-4078. (c) Severin, K. Ruthenium catalysts for the Kharasch reaction. *Curr. Org.Chem.* **2006**, *10*, 217-224. (d) Grove, M. D.; Van Koten, G.; Verschuuren, A. H. M. New Homogeneous catalysts in the addition of polyhalogenoalkanes to olefins; organonickel(II) Complexes $[Ni\{C_6H_3(CH_2NMe_2)2\text{-}o,o'\}X]$ (X = Cl, Br, I). *J. Mol.Catal.* **1988**, *45*, 169-174.

achieved at high temperatures and using long reaction times. Thus we decided to investigate the compatibility of the ATRC in the presence of $RuCl_2(PPh_3)_3$ and microwave activation with the aim of improving the reaction conditions, the yield and also the stereoselectivity.

## 4.2. ATRC catalyzed by $RuCl_2(PPh_3)_3$ in the synthesis of γ- and δ-lactams from trichloro- and dichloroacetamides. Our results

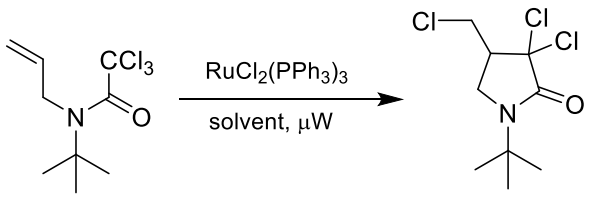
The investigation started with usage of this catalyst in combination with microwave activation for the preparation of γ- and δ–lactams and also for the preparation of these embedded in bicyclic structures such as indoles and morphans from trichoroacetamides and α,α-dichloroamides with a suitable alkenyl chain. For this purpose we choose the already available substrates (**17a**-**17p**) listed below to carry out our investigation (Scheme 4.2).




**Scheme 4.2.** Substrates used in the ATRC mediated by **Ru3** catalyst.

To optimize the reaction conditions, we carried out our primary study on trichloroacetamide **17a** with a *t*-butyl group on the nitrogen since the presence of the latter can accelerate the reaction (Table 4.1).

**Table 4.1**. Screening of the ATRC reaction conditions for **17a.**[a]




**17a** **18a**

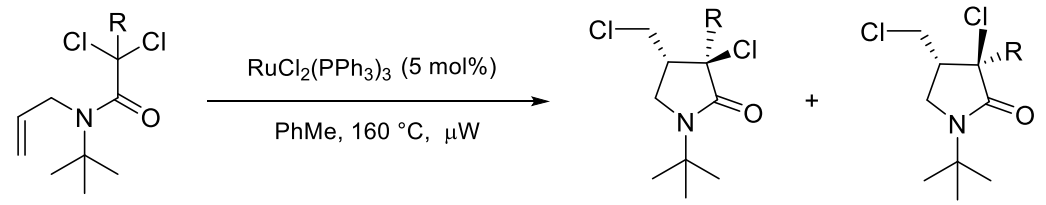
| Entry | **Ru3** (mol%) | Solvent | Temp (ºC) | Time (min) | **18a** Yield (%) | **17a** (%) |
|---|---|---|---|---|---|---|
| 1 | 5 | PhMe | 140 | 75 | 0 | 100 |
| 2 | 10 | PhMe | 160 | 30 | 79 | traces |
| 3 | 5 | PhMe | 160 | 30 | 82 | traces |
| 4 | 5 | PhMe | 160 | 15 | 83 | traces |
| 5 | 5 | PhMe | 160 | 10 | 79 | traces |
| 6 | 2.5 | PhMe | 160 | 20 | 61 | 12 |
| 7 | 3 | PhMe | 160 | 60 | 71 | 5 |
| 8 | 5 | ACN | 160 | 15 | 0 | 100 |

[a] Unless otherwise noted, the reactions were carried out with 0.386 mmol of **17a** in 1 mL of solvent under microwave activation. All products were separated through column chromatography and analysed by NMR spectroscopy.

Hence the first reaction from **17a** was achieved using the conditions reported in the literature but with microwave irradiation.[4] When **17a** was heated at 140 ºC in toluene for more than 1 h with 5 mol% of catalyst, the reaction did not take place and **17a** was recovered (Entry 1). Only by increasing the temperature to 160 °C, almost a full conversion was observed after 15 min of reaction leading to γ-lactam **18a** with an excellent yield (Entry 4). Shortening the reaction time or decreasing the catalyst loading did not bring any improvement to the reaction yield (Entries 5-7). It's worth noting that when the reaction was run in acetonitrile under the optimized conditions no reaction takes place (Entry 8). The best conditions were then applied to **17b-17d** where one of the chloro atoms was substituted by a hydrogen, a methyl and an ester group respectively. In all cases the reaction proceeds successfully providing the corresponding γ-lactams (**18** and **19**) with good yields for almost all the substrates (Table 4.2). The diastereomers formed in each case were separated and identified by NMR spectroscopy.

[4] See for example ref. 9 in the introduction.

**Table 4.2.** $RuCl_2(PPh_3)_3$ catalyzed ATRC reaction from substrates **17b-17d.**[a]




R = H **17b**
$CH_3$ **17c**
COOEt **17d**

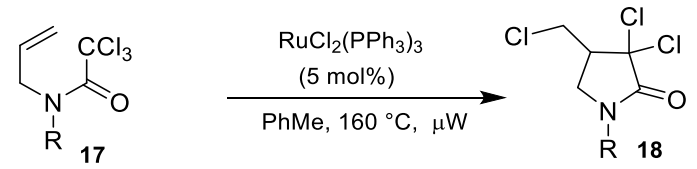
**18** **19**

| Entry | **17** | Time (min) | **18/19** (yield %) | **18/19** | **17** (%) |
|---|---|---|---|---|---|
| 1 | **17b** | 15 | 75 | 1.7/1[b] | traces |
| 2 | **17c** | 15 | 52 | 1.5/1 | 29 |
| 3 | **17c** | 30 | 80 | 2.5/1 | traces |
| 4 | **17d** | 15 | 70 | 1.8/1 | 10 |
| 5 | **17d** | 10 | 77 | 2.1/1 | traces |

[a] Unless otherwise noted, the reactions were carried out with 0.386 mmol of **17b, 17c** or **17d** in 1 mL of solvent under microwave activation. All products were separated through column chromatography and analysed by NMR spectroscopy. [b] **19b** was not isolated in pure form.

We also investigated the reaction from trichloroacetamides **17e**-**17j** with different substituents on the nitrogen (Table 4.3). In all cases the corresponding γ-lactams were obtained with good yields even if with some substrates (**17e**, **17g** and **17 j**) 30 to 45 min were necessary to achieve a full conversion.

**Table 4.3.** $RuCl_2(PPh_3)_3$ catalyzed ATRC reaction for substrates **17e-17j**[a]



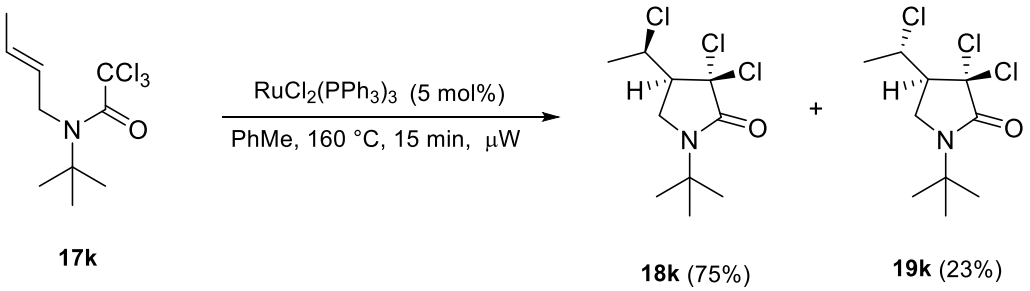

R = H **17e**
*n*Bu **17f**
Ph **17g**
Bn **17h**
Allyl **17i**
2-Bromoallyl **17j**

| Entry | **17** | Time (min) | **18** (yield %) | **17** (%) |
|---|---|---|---|---|
| 1 | **17e** | 15 | 62 | 8 |
| 2 | **17e** | 30 | 68 | 7 |
| 3 | **17f** | 15 | 90 | 0 |
| 4 | **17g** | 15 | 48 | 45 |
| 5 | **17g** | 45 | 84 | 13 |
| 6 | **17h** | 15 | 78 | traces |
| 7 | **17i** | 15 | 78 | traces |
| 8 | **17j** | 15 | 69 | 20 |
| 9 | **17j** | 30 | 67 | 11 |

[a] Unless otherwise noted, the reactions were carried out with 0.386 mmol of **17e-17j** in 1 mL of toluene under microwave activation. All products were separated through column chromatography and analysed by NMR spectroscopy.

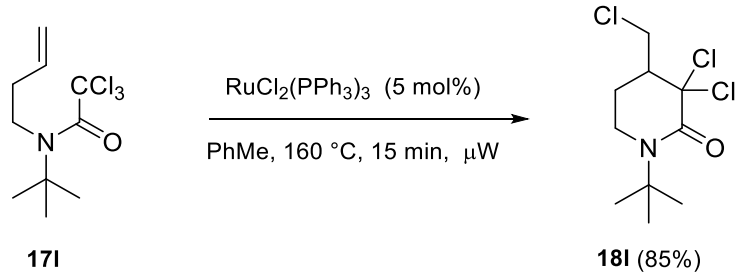
Additionally, we investigated the efficacy of the process varying the nature of the radical acceptor (the alkenyl chain) in trichloroacetamides **17k-17p**.

In the case of **17k** with a methyl group on the terminal carbon of the allyl double bond, the cyclization occurs providing lactams **18k** and **19k** with an excellent yield and a good diastereoselectivity (Scheme 4.3)




**Scheme 4.3.** ATRC from **17k.**

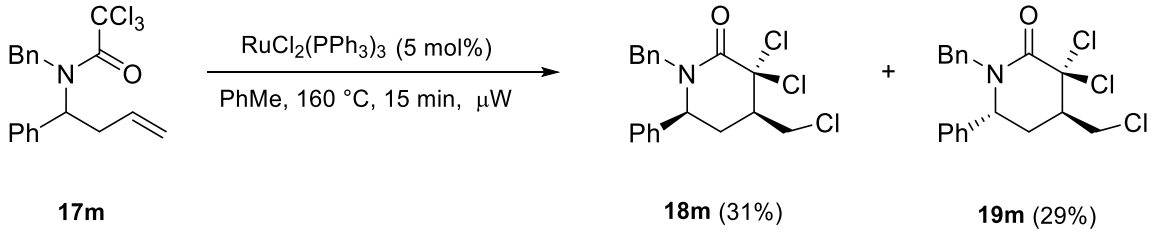
Operating from butenyl derivative **17l**, only δ-lactam **18l** resulting from a *6-exo-trig* radical cyclization was obtained with a very good yield (Scheme 4.4)




**17l** **18l** (85%)

**Scheme 4.4.** ATRC from **17l**.

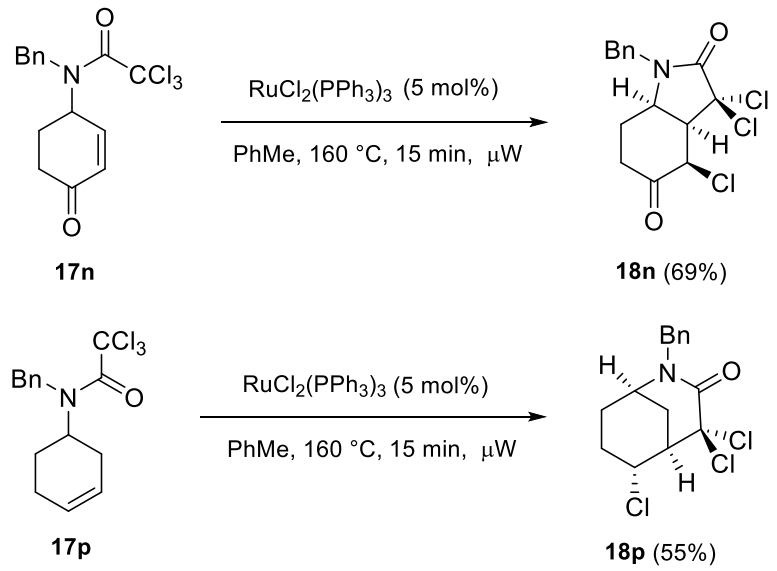
Furthermore, from trichloroacetamide **17m**, the corresponding δ-lactam as a mixture of diastereomers (**18m** and **19m**) in almost an equimolar proportion was produced (Scheme 4.5).




**17m** **18m** (31%) **19m** (29%)

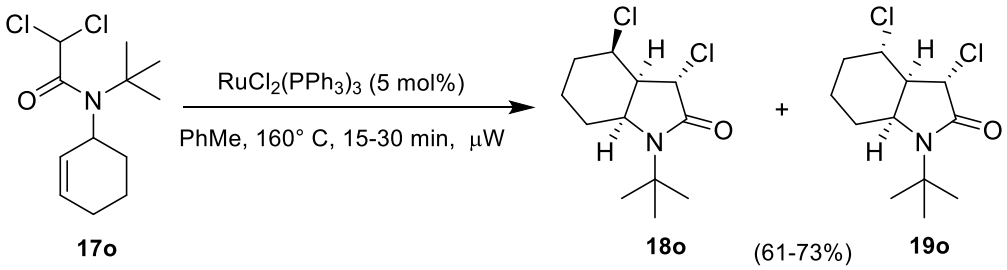
**Scheme 4.5.** ATRC from **17m**.

The procedure was also successfully extended to trichloroacetamides **17n** and **17p**. In both cases the reaction was completely diastereoselective proving the corresponding indole and morphan derivatives with acceptable to good yields (Scheme 4.6). It is worth mentioning that with substrate **17p**, a fair amount of starting material (20%) was recovered and we believe that the yield could be improved by prolonging the reaction time.



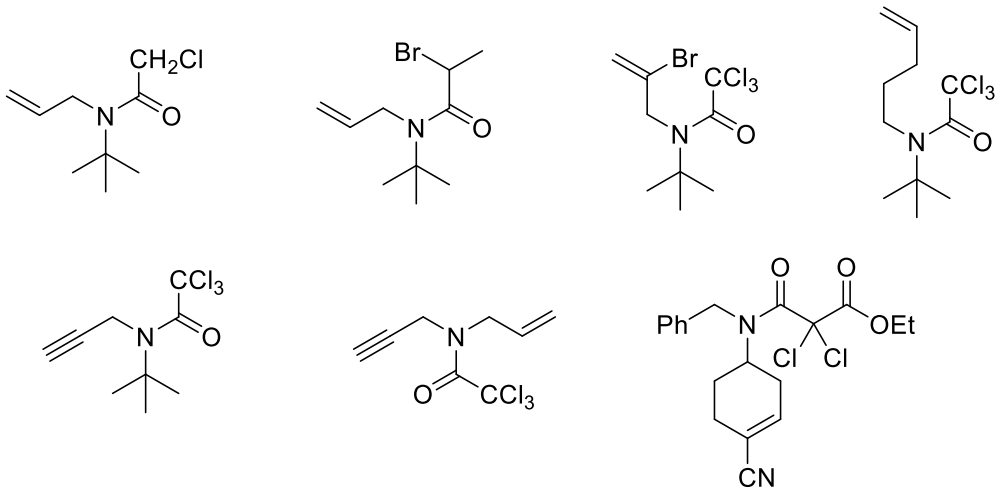

**Scheme 4.6.** ATRC from **17n** and **17p**.

Finally, we checked also the reaction from dichloroacetamide **17o**. After 15 min of irradiation under the same conditions reported previously, a mixture of diastereomers **18o** and **19o** was isolated in a 3.6:1 ratio. In this case, the reaction was not complete since some of **17o** (about 25%) was recovered after chromatography and due to the lack of time we were not able to optimize the reaction from this substrate (Scheme 4.7).




**Scheme 4.7.** ATRC from **17o**.

It is worth mentioning that not all the substrates that we investigated in this part of the thesis gave good results. In Scheme 4.8 are listed the α-haloamides derivatives with which the reaction did not take place. In these cases, instead of the expected lactams a mixture of unidentified products or the initial starting materials were recovered.



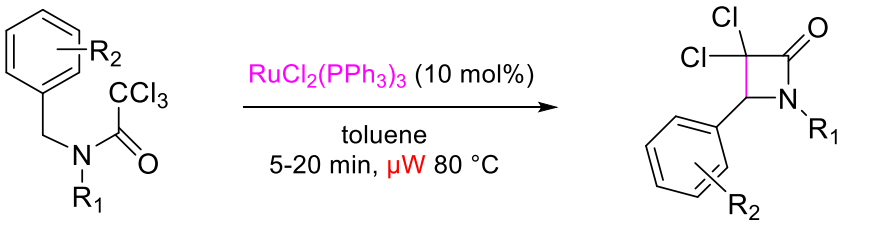

**Scheme 4.8.** Substrates which reactions were unsuccessful.

*CHAPTER 5:*

# ***Conclusions***

In the research work presented in this PhD thesis, we have demonstrated that tris(triphenylphosphine)ruthenium(II) dichloride is truly a versatile and potent catalyst capable of achieving different chemical transformations under microwave activation.

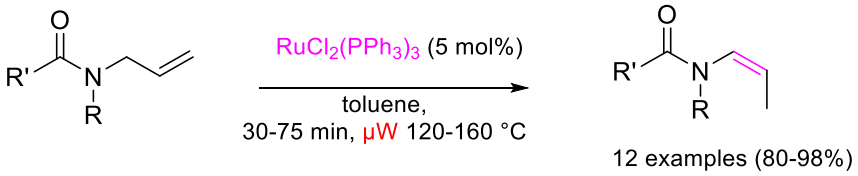
First, a new behaviour of $RuCl_2(PPh_3)_3$ leading to β-lactams from *N*-tethered benzyl trichloroacetamides through benzylic CH activation was discovered and established. The simplicity of the process and the challenging unprecedented reaction involved for this $C(sp^3)$-$C(sp^3)$ bond formation bring new insights into the chemistry of ruthenium catalysts. Future efforts will be steered toward expanding the reaction to more substrates for the synthesis of other nitrogen heterocycles and also to shed more light on the mechanism of this radical transformation.




11 examples (18-58%)

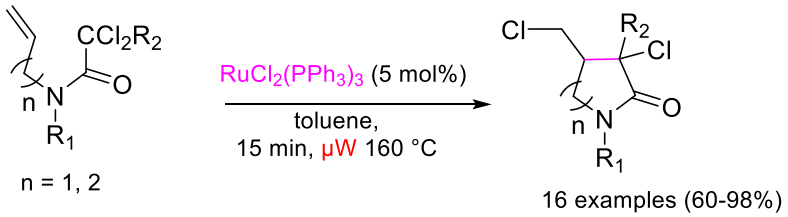
Some of the β-lactams prepared naming **2b**, **2c**, **2e**, **2h**, **2j** and **2k** were evaluated for their cytotoxic activity and hemocompatibility. The results showed that the proposed compounds have non-hemolytic properties and that the cytotoxic response is highly dependent on the structure and the concentrations of these β-lactams. Compound **2b** was found to be the most cytotoxic of the list showing the lowest IC50 values (20-49 μg/mL and 30-47 μg/mL for HaCaT and A431 cell lines, respectively).

In the second place, $RuCl_2(PPh_3)_3$ was successfully used in protected allylamines isomerization under microwave activation.




The isomerization process proceeds from tertiary *N*-allyl carbamates and *N*-allyl amides to provide the corresponding enecarbamates and enamides with a very good yields and excellent *Z*-selectivity. The reactions are achieved in very short reaction time and the nature of the protective group on the nitrogen seems to have a big influence on the course of the reaction. It is worth noting that $RuCl_2(PPh_3)_3$ was used herein for the first time in this type of transformations.

Finally, even if ATRC in the presence of $RuCl_2(PPh_3)_3$ were already reported in the literature from alkenyl tethered trichloroacetamides, in this last part of the work we have showed that these reactions can be achieved under microwave activation. Hence we were able to access several γ- and δ-lactams in very short reaction times and with very good yields. The process was extended to α,α-dichloroamides and the reactions in almost all cases are diastereoselective. Studies are underway to discover more potential of this ruthenium complex.



*CHAPTER 6:*

# ***Experimental part***

## General information

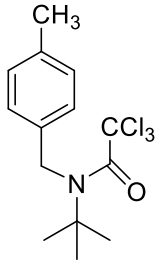
NMR spectra were recorded in $CDCl_3$ and the chemical shifts of $^1H$ spectra are reported in ppm downfield ($\delta$) from $Me_4Si$, $^{13}C$ NMR spectra are referenced to the deuterated solvent signal ($CDCl_3$: 77.00 ppm). All NMR data assignments are supported by gCOSY and gHSQC experiments. The high resolution ESI mass spectra were obtained from an Agilent LC/MSD-TOF mass spectrometer. Analytical thin-layer chromatography was performed on $SiO_2$ (Merck silica gel 60 $F_{254}$) with a fluorescent indicator ($\lambda$ = 254 nm), and the spots were located by UV light and/or with 1% aqueous $KMnO_4$ solution or anisaldehyde. Chromatography refers to flash chromatography and was carried out on $SiO_2$ (Carlo Erba silica gel 60A, 35-70 $\mu$m). Drying of organic extracts during workup of reactions was performed over anhydrous $Na_2SO_4$. Solvent evaporation was accomplished with a rotatory evaporator. All yields refer to chromatographically and spectroscopically (NMR) pure material. Microwave irradiation experiments were performed using a single-mode Discover System from CEM Corporation using standard Pyrex vessel (capacity 10 mL)

## *6.1. Experimental part of chapter 2*

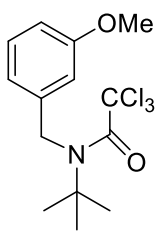
### 1. Synthesis of trichloroacetamides 1a-1l[1]

For the preparation of trichloroacetamides **1e**-**1g** and **1l** we followed the same procedure reported in ref.1 isolating **1e** (40%), **1f** (50%), **1g** (30%) and **1l** (70%).

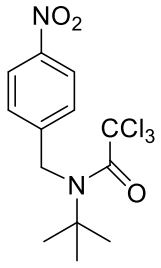
***N-tert*-Butyl-2,2,2-trichloro-*N*-(4-methylbenzyl)acetamide (1e)**. IR (NaCl, neat): 2998, 2973, 2923, 2867, 2857, 1685 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.41 (s, 9H, *t*-Bu), 2.34 (s, 3H, $CH_3$), 4.99 (brs, 2H, $CH_2Ar$), 7.15 (brs, 4H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.0 ($CH_3$), 28.1 ($CH_3$), 50.8 ($CH_2Ar$), 61.8 (C), 95.4 ($CCl_3$), 126.4, 129.1 (ArCH), 135.5 (C), 136.8 (C), 160.8 (CO). HRMS (ESI-TOF): Calcd for $C_{14}H_{19}Cl_3NO$ $[M+H]^+$ 322.0527; found 322.0528.



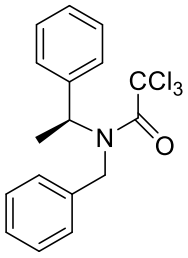

***N-tert*-Butyl-2,2,2-trichloro-*N*-(3-methoxybenzyl)acetamide (1f)**. IR (NaCl, neat): 3001, 2965, 2937, 1685, 1601 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.44 (s, 9H, *t*-Bu), 3.80 (s, 3H, $CH_3$), 5.01 (brs, 2H, $CH_2Ar$), 6.76-6.89 (m, 3H, ArH), 7.26 (t, *J* = 7.8 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 28.0 ($CH_3$), 50.9 ($CH_2Ar$), 55.2 ($CH_3$), 61.9 (C), 95.2 ($CCl_3$), 112.3, 118.7, 129.5 (ArCH), 140.3 (C), 159.7 (C), 160.7 (CO). HRMS (ESI-TOF): Calcd for $C_{14}H_{19}Cl_3NO_2$ $[M+H]^+$ 338.0476; found 338.0464.




***N-tert*-Butyl-2,2,2-trichloro-*N*-(4-nitrobenzyl)acetamide (1g)**. IR (NaCl, neat): 3081, 2981, 2934, 2676, 1688, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.44 (s, 9H, *t*-Bu), 5.15 (brs, 2H, $CH_2Ar$), 7.48 (d, *J* = 6.7 Hz, 2H, ArH), 8.24 (d, *J* = 6.7 Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 28.1 ($CH_3$), 50.6 ($CH_2Ar$), 62.2 (C), 94.9 ($CCl_3$), 123.9, 127.2 (ArCH), 146.4 (C), 147.2 (C), 160.6 (CO). HRMS (ESI-TOF): Calcd for $C_{13}H_{16}Cl_3N_2O_3$ $[M+H]^+$ 353.0221; found 353.0224.

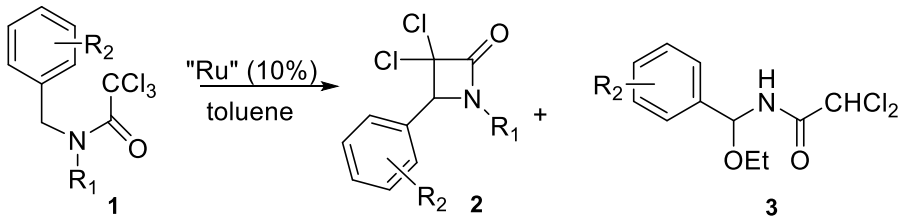



[1] For the preparation of **1a**-**1d** and **1h-1k** see: Diaba, F.; Montiel, J. A.; Martinez-Laporta, A.; Bonjoch, J. *Tetrahedron Lett.* **2013**, 54, 2619.

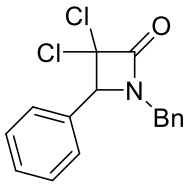
**(*S*)-*N*-Benzyl-2,2,2-trichloro-*N*-(1-phenylethyl)acetamide (1l)**. IR (NaCl, neat): 

3106, 3088, 3062, 3030, 2988, 2939, 1673, 1602 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.58 (s, 3H, $CH_3$), 3.88 (brd, *J* = 15.8 Hz, 1H, $CH_2Ar$), 4.76 (brd, *J* = 15.8 Hz, 1H, $CH_2Ar$), 5.93 (brs, 1H), 6.96-7.43 (m, 10H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 17.9 ($CH_3$), 49.4 ($CH_2Ar$), 57.3 (CHAr), 93.7 ($CCl_3$), 126.6, 126.9, 127.8, 128.4, 128.7 (ArCH), 137.3 (C), 139.1 (C), 161.2 (CO). HRMS (ESI-TOF): Calcd for $C_{17}H_{17}Cl_3NO$ $[M+H]^+$ 356.0370; found 356.0369; Calcd for $C_{17}H_{20}Cl_3N_2O$ $[M+NH_4]^+$ 373.0636; found 373.0636.

## 2. General procedure for the reaction of trichloroacetamides 1 with "Ru" catalysts



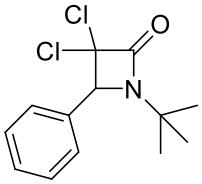

In a 10 mL vessel was placed trichloroacetamide **1** (100 mg, 0.32 mmol) and ruthenium catalyst (0.032 mmol, 10%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 5 to 30 min at 80 ºC or 100 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) **2** and/or **3** were isolated.[2]

**1-Benzyl-3,3-dichloro-4-phenylazetidin-2-one (2a).** IR (NaCl, neat): 3088, 

3064, 3032, 2923, 2852, 1790 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 3.88 (d, *J* = 15.0 Hz, 1H, $CH_2N$), 4.77 (s, 1H, H-4), 4.90 (d, *J* = 15.0 Hz, 1H, $CH_2N$), 7.05-7.10 (m, 2H, ArH), 7.15-7.20 (m, 2H, ArH), 7.23-7.28 (m, 3H, ArH), 7.35-7.40 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 45.0 ($CH_2N$), 73.2 (C-4), 84.8 (C-3), 128.1, 128.4, 128.8, 129.1, 129.9 (ArH), 131.7, 133.5 (C), 161.7 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{14}Cl_2NO$ $[M+H]^+$ 306.0447; found 306.0450.

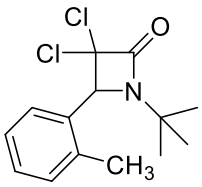
[2] For the yields of pure compounds from **1a**-**1l** see the tables in chapter 2.

**1-(*tert*-Butyl)-3,3-dichloro-4-phenylazetidin-2-one (2b).** mp 81-83 ºC; IR



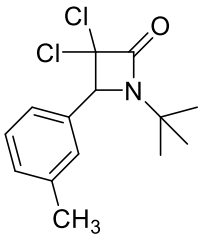
(NaCl, neat): 3065, 3036, 2976, 2931, 2872, 2856, 1778 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 9H, *t*-Bu), 5.05 (s, 1H, H-4), 7.35-7.46 (m, 5H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 27.9 ($CH_3$), 55.7 (C), 73.6 (C-4), 83.4 (C-3), 128.5, 129.7 (ArH), 134.6 (C), 161.6 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{16}Cl_2NO$ $[M+H]^+$ 272.0603; found 272.0606.

**1-(*tert*-butyl)-3,3-dichloro-4-(*o*-tolyl)azetidin-2-one (2c).** IR (NaCl, neat):



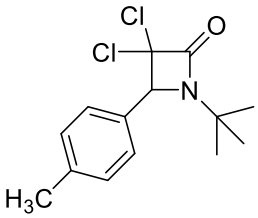
3074, 3029, 2980, 2937, 2876, 1769 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 9H, *t*-Bu), 2.44 (s, 3H, $CH_3$), 5.31 (s, 1H, H-4), 7.22-7.37 (m, 4H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 19.7 ($CH_3$), 27.8 ($CH_3$), 55.5 (C), 69.9 (C-4), 83.2 (C-3), 125.8, 126.9, 129.0, 130.6 (ArCH), 133.2 (C), 136.5 (C), 161.9 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO$ $[M+H]^+$ 286.0760; found 286.0761.

**1-(*tert*-butyl)-3,3-dichloro-3-(*p*-tolyl)azetidin-2-one (2d).** IR (NaCl, neat):



3029, 2975, 2926, 2871, 1781 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 9H, *t*-Bu), 2.40 (s, 3H, $CH_3$), 5.00 (s, 1H, H-4), 7.15-7.34 (m, 4H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 21.4 ($CH_3$), 27.9 ($CH_3$), 55.7 (C), 73.6 (C-4), 83.8 (C-3), 128.4, 130.4 (ArCH), 134.5 (C), 138.3 (C), 161.7 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO$ $[M+H]^+$ 286.0760; found 286.0764.

**1-(*tert*-butyl)-3,3-dichloro-4-(*p*-tolyl)azetidin-2-one (2e).** IR (NaCl, neat):



3053, 3028, 2976, 2934, 2873, 1778 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 9H, *t*-Bu), 2.39 (s, 3H, $CH_3$), 5.01 (s, 1H, H-4), 7.23 (d, *J* = 8.5 Hz, 2H, ArH), 7.26 (d, *J* = 8.5 Hz, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 21.3 ($CH_3$), 27.9 ($CH_3$), 55.6 (C), 73.5 (C-4), 83.5 (C-3), 128.2, 129.2 (ArCH), 131.5 (C), 139.8 (C), 161.7 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO$ $[M+H]^+$ 286.0760; found 286.0766.

**1-(*tert*-Butyl)-3,3-dichloro-4-(3-methoxyphenyl)azetidin-2-one (2f).** IR (NaCl, neat): 3071, 3060, 3064, 2975, 2935, 2876, 2853, 2837, 1778 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 9H, *t*-Bu), 3.84 (s, 3H, $CH_3O$), 5.01 (s, 1H, H-4), 6.89 (m, 1H, ArH), 6.93-6.98 (m, 2H, ArH), 7.34 (t, *J* = 7.9 Hz, 1H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 27.9 ($CH_3$), 55.3 ($CH_3O$), 55.7 (C), 73.5 (C-4), 83.4 (C-3), 113.8, 115.0, 120.5, 129.6 (ArCH), 136.1 (C), 159.7 (C), 161.6 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}Cl_2NO_2$ $[M+H]^+$ 302.0709; found 302.0709.

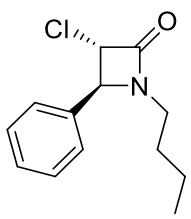
**1-(*tert*-butyl)-3,3-dichloro-4-(3,5-difluorophenyl)azetidin-2-one (2h)**. IR (NaCl, neat): 3094, 3063, 2977, 2931, 2875, 2855, 1784 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.35 (s, 9H, *t*-Bu), 4.99 (s, 1H, H-4), 6.84-6.96 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 27.9 ($CH_3$), 56.0 (C), 72.4 (C-4), 83.0 (C-3), 105.3 (t, *J* = 25.1 Hz, 1C, ArCH), 111.0 (brs, 2C, ArCH), 138.8 (t, *J* = 8.6 Hz, ArC), 161.3 (C-2), 163.0 (dd, *J* = 249.3, 12.4 Hz, 2C, C-F). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{14}Cl_2F_2NO$ $[M+H]^+$ 308.0415; found 308.0412.

**1-Butyl-3,3-dichloro-4-phenylazetidin-2-one (2i).** IR (NaCl, neat): 3065, 3035, 2960, 2932, 2873, 1789 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.3 Hz, 3H, $CH_3$), 1.29-1.41 (m, 2H, $CH_2$), 1.51-1.60 (m, 2H, $CH_2$), 2.96 (dt, *J* = 14.0, 6.6 Hz, 1H), 3.62 (dt, *J* = 14.0, 7.8 Hz, 1H), 5.05 (s, 1H, H-4), 7.05-7.10 (m, 2H, ArH), 7.28-7.32 (m, 2H, ArH), 7.43-7.49 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 13.5 ($CH_3$), 20.0 ($CH_2$), 29.1 ($CH_2$), 40.9 ($CH_2$), 74.0 (C-4), 84.7 (C-3), 128.1, 128.8, 129.9 (ArCH), 132.0 (C), 161.8 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{16}Cl_2NO$ $[M+H]^+$ 272.0603; found 272.0604.

**(3*RS*,4*SR*)-1-Butyl-3-chloro-4-phenylazetidin-2-one (4i)**. IR (NaCl, neat): 3063, 3035, 2958, 2925, 2871, 1770 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.26-1.38 (m, 2H), 1.45-1.56 (m, 2H), 2.90-2.99 (m, 2H), 3.55 (dt, *J* = 14.0, 7.7 Hz, 1H), 4.46 (d, *J* = 4.9 Hz, H-4), 5.10 (d, *J* = 4.9 Hz, 1H, H-3), 7.25-7.30 (m, 2H, ArH), 7.37-7.47 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 13.5 ($CH_3$), 20.2 ($CH_2$), 29.3 ($CH_2$), 40.9 ($CH_2$), 60.9 (C-3), 61.0 (C-3), 128.2, 128.5, 129.1 (ArCH),

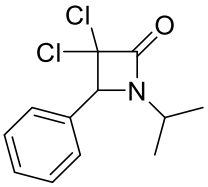
133.2 (C), 164.3 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{17}ClNO$ $[M+H]^+$ 238.0993; found 238.0997.

**(3*RS*,4*RS*)-1-Butyl-3-chloro-4-phenylazetidin-2-one (5i)**. IR (NaCl, neat):



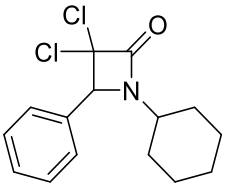
3064, 3032, 2958, 2931, 2872, 1772 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.24-1.36 (m, 2H, $CH_2$), 1.44-1.53 (m, 2H, $CH_2$), 2.86 (dt, *J* = 14.1, 7.0 Hz, 1H), 3.52 (dt, *J* = 14.1, 7.6 Hz, 1H), 4.49 (brd, *J* = 1.7 Hz, H-4), 4.54 (d, *J* = 1.7 Hz, 1H, H-3), 7.30-7.33 (m, 2H, ArH), 7.37-7.47 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 13.5 ($CH_3$), 20.0 ($CH_2$), 29.4 ($CH_2$), 40.8 ($CH_2$), 63.1 (C-4), 66.0 (C-3), 126.6, 129.3, 129.4 (ArCH), 135.2 (C), 163.8 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{17}ClNO$ $[M+H]^+$ 238.0993; found 238.0993.

**1-Isopropyl-3,3-dichloro-4-phenylazetidin-2-one (2j).** IR (NaCl, neat): 2954,



2923, 2852, 1789 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.40 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.75 (hept, *J* = 6.8 Hz, 1H), 5.03 (s, 1H, H-4), 7.05-7.10 (m, 2H, ArH), 7.33-7.37 (m, 2H, ArH), 7.41-7.47 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 20.1 ($CH_3$), 20.8 ($CH_3$), 46.5 (CH), 73.3 (C-4), 84.0 (C-3), 128.3, 128.7, 129.9 (ArCH), 133.1 (C), 161.5 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{14}Cl_2NO$ $[M+H]^+$ 258.0447; found 358.0447.

**3,3-Dichloro-1-cyclohexyl-4-phenylazetidin-2-one (2k).** IR (NaCl, neat): 3035,



2933, 2857, 1784 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.103-1.36 (m, 4H), 1.58 (m, 1H), 1.65-1.90 (m, 4H), 2.08 (dm, *J* = 12.6 Hz, 1H), 3.40 (tt, *J* = 11.4, 3.8 Hz, 1H), 5.05 (s, 1H, H-4), 7.05-7.10 (m, 2H, ArH), 7.32-7.37 (m, 2H, ArH), 7.42-7.47 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 24.7 ($CH_2$), 25.0 (2 $CH_2$), 30.2 ($CH_2$), 30.9 ($CH_2$), 53.8 (CH), 73.2 (C-4), 84.1 (C-3), 128.3, 128.6, 129.8 (ArCH), 133.2 (C), 161.5 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{18}Cl_2NO$ $[M+H]^+$ 298.0760; found 398.0762.

**(3*RS*,4*SR*)-3-Chloro-1-cyclohexyl-4-phenylazetidin-2-one (4k)**. IR (NaCl, neat): 3031, 2932, 2855, 1761 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.99-1.30 (m, 4H), 1.51-1.70 (m, 3H), 1.76 (m, 1H), 1.84 (m, 1H), 2.03 (dm, *J* = 12.5 Hz, 1H), 3.43 (tt, *J* = 11.5, 3.9 Hz, 1H), 4.97 (brd, *J* = 5.0 Hz, H-4), 5.03 (brd, *J* = 5.0 Hz, 1H, H-3), 7.30-7.35 (m, 2H, ArH), 7.38-7.45 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 24.9 ($CH_2$), 25.0 ($CH_2$), 25.1 ($CH_2$), 30.4 ($CH_2$), 31.3 ($CH_2$), 53.6 (CH), 60.0 (C-4), 60.2 (C-3), 128.3, 128.4, 129.1 (ArCH), 134.4 (C), 164.0 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{19}ClNO$ $[M+H]^+$ 264.1150; found 264.1154.

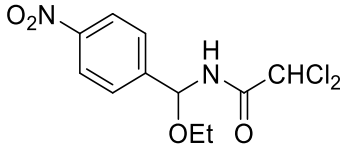
**(3*RS*,4*RS*)-3-Chloro-1-cyclohexyl-4-phenylazetidin-2-one (5k)**. IR (NaCl, neat): 3031, 2931, 2855, 1768 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.97-1.30 (m, 4H), 1.50-1.70 (m, 3H), 1.71-1.82 (m, 2H), 2.00 (dm, *J* = 12.5 Hz, 1H), 3.38 (tt, *J* = 11.4, 3.8 Hz, 1H), 4.44 (brd, *J* = 1.7 Hz, H-4), 4.53 (brd, *J* = 1.7 Hz, 1H, H-3), 7.33-7.40 (m, 5H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 24.9 ($CH_2$), 25.0 ($CH_2$), 25.1 ($CH_2$), 30.4 ($CH_2$), 31.2 ($CH_2$), 53.5 (CH), 62.6 (C-4), 65.1 (C-3), 126.7, 129.1, 129.3 (ArCH), 136.7 (C), 163.6 (C-2). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{19}ClNO$ $[M+H]^+$ 264.1150; found 264.1153.

**2,2-Dichloro-*N*-(ethoxyphenylmethyl)acetamide (3b)**. IR (NaCl, neat): 3260, 3060, 3005, 2974, 2922, 2853, 1673 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.30 (t, *J* = 7.0 Hz, 3H, $CH_3$), 3.68 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.81 (dq, *J* = 9.4, 7.0 Hz, 1H), 5.97 (s, 1H, $CHCl_2$), 6.22 (d, *J* = 9.3 Hz, 1H), 6.87 (brd, *J* = 9.1 Hz, 1H, NH), 7.33-7.48 (m, 5H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 15.1 ($CH_3$), 64.5 ($CH_2$), 66.4 ($CHCl_2$), 80.7 (CH), 125.8, 128.7, 128.8 (ArCH), 138.4 (C), 164.3 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{13}Cl_2NNaO_2$ $[M+Na]^+$ 284.0216; found 284.0227.

**2,2-Dichloro-*N*-[ethoxy(3-methoxyphenyl)methyl]acetamide (3f)**. IR (NaCl, neat): 3261, 3061, 3005, 2977, 2925, 2855, 2835, 1674 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.30 (t, *J* = 7.0 Hz, 3H, $CH_3$), 3.67 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.80 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.82 (s, 3H, $CH_3$), 5.97 (s, 1H, $CHCl_2$), 6.18 (d, *J* = 9.4 Hz, 1H), 6.85 (brs, 1H, NH), 6.90 (ddd, *J* = 8.2, 2.6, 0.7 Hz, 1H, ArH), 6.99-7.05 (m,

2H, ArH), 6.90 (t, *J* = 8.0 Hz, 1H, ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 15.1 ($CH_3$), 55.3 ($CH_3$), 64.5 ($CH_2$), 66.3 ($CHCl_2$), 80.6 (CH), 111.4, 114.3, 118.0, 129.9 (ArCH), 140.0, 159.9 (C), 164.2 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{14}Cl_2NO_3$ $[M-H]^-$ 290.0356; found 290.0360.

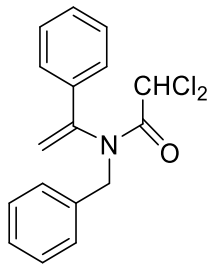
**2,2-Dichloro-*N*-[ethoxy(4-nitrophenyl)methyl]acetamide (3g)**. IR (NaCl, neat): 3234, 3062, 3012, 2978, 2916, 1685 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.33 (t, *J* = 7.0 Hz, 3H, $CH_3$), 3.71 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.86 (dq, *J* = 9.4, 7.0 Hz, 1H), 6.00 (s, 1H, $CHCl_2$), 6.32 (d, *J* = 9.4 Hz, 1H), 6.83 (brd, *J* = 9.1 Hz, 1H, NH), 7.65 (dd, *J* = 9.0, 0.6 Hz, 2H, ArH), 8.25 (d, *J* = 9.0 Hz, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 15.0 ($CH_3$), 64.9 ($CH_2$), 66.2 ($CHCl_2$), 79.8 (CH), 123.9, 127.0 (ArCH), 128.3 (ArC), 145.3 (C), 164.5 (CO). HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $C_{11}H_{11}Cl_2N_2O_4$ 305.0101; found 305.0115.




**2,2-Dichloro-*N*-[ethoxy(3,5-difluorophenyl)methyl]acetamide (3h)**. IR (NaCl, neat): 3276, 3057, 3005, 2981, 2930, 2915, 2901, 2889, 1685 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.31 (t, *J* = 7.0 Hz, 3H, $CH_3$), 3.68 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.82 (dq, *J* = 9.4, 7.0 Hz, 1H), 5.98 (s, 1H, $CHCl_2$), 6.19 (d, *J* = 9.4 Hz, 1H), 6.80 (tt, *J* = 8.8, 2.4 Hz, 1H, ArH), 6.80 (brs, 1H, NH), 6.96-7.03 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 15.0 ($CH_3$), 64.8 ($CH_2$), 66.2 ($CHCl_2$), 79.6 (CH), 104.2 (t, *J* = 25.1 Hz, 1C, ArCH), 109.1 (d, *J* = 26.4 Hz, 2C, ArCH), 109.1 (d, *J* = 11.6 Hz, 1C, ArC), 163.1 (dd, *J* = 248.1, 12.5 Hz, 2C, CF), 164.4 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{10}Cl_2F_2NO_2$ $[M-H]^-$ 296.0062; found 296.0052.

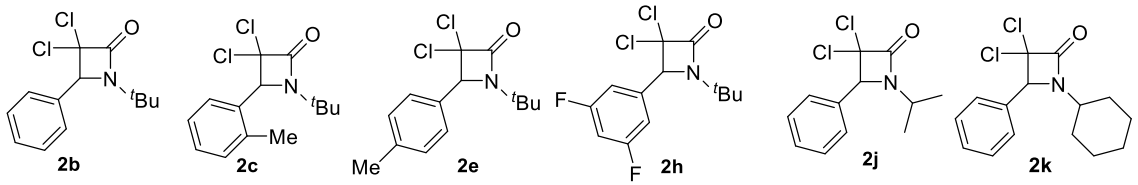



***N*-Benzyl-2,2-dichloro-*N*-(1-phenylvinyl)acetamide (6l).** From **1l** (100 mg, 0.28 mmol) and $RuCl_2(PPh_3)_3$ (27 mg, 0.028 mmol, 10%) in toluene (1 mL). The mixture was heated with stirring to 80 ºC using microwave irradiation for 10 min. After chromatography (hexane-$CH_2Cl_2$, 1:0 to 1:1) **6l** was isolated (36 mg, 40%). In this reaction 48 mg of **1l** was also recovered. IR (NaCl, neat): 3061, 3029, 2952, 2924, 2854, 1690, 1625, 1576 cm$^{-1}$; $^1$H NMR



($CDCl_3$, 400 MHz): δ 4.66 (brs, 2H, $CH_2Ar$), 4.98 and 5.70 (2 s, 1H each, $=CH_2$), 6.38 (s, 1H, $CHCl_2$), 7.21-7.30 (m, 5H, ArH), 7.37-7.45 (m, 5H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 50.7 ($CH_2Ar$), 64.0 ($CHCl_2$), 116.0 ($=CH_2$), 126.0, 127.9, 128.5, 129.2, 129.3, 129.9 (ArCH), 134.0 (C), 135.8 (C), 144.5 (C), 164.8 (CO). HRMS (ESI-TOF): Calcd for $C_{17}H_{16}Cl_2NO$ $[M+H]^+$ 320.0603; found 320.0603.

## 3. Cytotoxic activity and hemocompatibility studies of some of the synthesized lactams




Selected lactams for cytotoxic and hemocompatibility studies

### 3.1. Materials and methods

#### 3.1.1. Materials

Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), L-glutamine solution (200 mM), trypsin-EDTA solution (170,000U/L trypsin and 0.2 g/L EDTA), penicillin–streptomycin solution (10,000 U/mL penicillin and 10 mg/mL streptomycin) and phosphate buffered saline (PBS) were obtained from Lonza (Verviers, Belgium). 2,5-Diphenyl-3,-(4,5-dimethyl-2-thiazolyl) tetrazolium bromide (MTT) and neutral red dye (NR) were from Sigma–Aldrich (St.Louis, MO, USA). The 75 $cm^2$ flasks and 96-well plates were obtained from TPP (Trasadingen, Switzerland). All other reagents were of analytical grade.

#### 3.1.2. Methods

##### 3.1.2.1. *In vitro* assay with Human erythrocytes

**3.1.2.1.1** *Obtention and extraction of the erythrocytes*

Human blood samples were obtained from the Banc de Sang i Teixits de Barcelona from the Catalan Department of Health. Blood was deposited in tubes

with anticoagulant EDTA-$K_3$. Blood samples were centrifugated at 3000 rpm at 4 ºC for 10 min (Megafuge 2.0 R. Heraeus Instruments) to induce sedimentation. Plasma was extracted with a Pasteur pipette. Next, the residual pellet was washed with PBS pH 7.4. This procedure was repeated three times to remove residual leukocytes and platelets and to concentrate the erythrocytes. Following the last wash, the erythrocytes suspension was diluted (1:1) in PBS pH 7.4, to obtain suitable erythrocytes suspension (cell density of $8 \times 10^9$ cell/mL).

### 3.1.1.2. Hemolysis assay

The hemolysis assay determined the capability of the different compounds to induce lysis of the erythrocyte membrane. A stock solution of 1 mg/mL in PBS pH 7.4.of each compound was prepared. Different volumes (10-80 µL) were placed in polystyrene tubes, and an aliquot of 25 µL of the erythrocyte suspensions was added to each tube. The final volume was 1 mL. The tubes were incubated at room temperature by rotatory conditions. After that, the tubes were centrifugated at 10.000 rpm for 5 min. The supernatants absorbance at 540 nm (Shimadzu UV-160A) was compared with those of the control samples hemolysed with distilled water (positive control). Negative control was obtained by incubating an aliquot of 25 µL of the erythrocyte suspension with PBS pH 7.4.

The hemolysis degree was determined by the following equation:

Hemolysis (%) = $100 \times (Abs – Ab_0)/(Abs_{100} – Abs_0)$ where Abs, $Abs_0$, and $Abs_{100}$ are the absorbance of test samples, the suspension treated with isotonic physiological buffer saline (PBS), and the suspension of complete hemolysis treated with distilled water, respectively.

### 3.1.2.2. Cell cultures

The immortal human keratinocyte (HaCaT) and the squamous cell carcinoma (A431) were obtained from Celltec UB. Cells were grown in DMEM medium (4.5 g/L glucose) supplemented with 10 % (v/v) FBS, 2 mM L-glutamine, 100 U/ mL penicillin and 100 µg/ mL streptomycin at 37 ºC, 5% $CO_2$. Cells were routinely cultured in 75 $cm^2$ culture flasks and were trypsinized using trypsin-EDTA when the cells reached approximately 80 % confluence.

### 3.1.2.3. Cell viability assays

HaCaT cells ($1 \times 10^5$ cells/ mL) and A431 ($5 \times 10^4$ cells/mL) were grown at the defined densities into the central 60 wells of a 96-well plate. Cells were incubated for 24 h under 5% $CO_2$ at 37 ºC. Then, the spent medium was removed and cells were incubated for 24 h with the corresponding compound solutions (1 mg/mL) previously diluted in the minimum amount of DMF and then in DMEM medium supplemented with 5% FBS (100 µL) at the required concentration range (10–250 µg/mL).

#### 3.1.2.3.1. NRU assay

Neutral red uptake (NRU) assay is based in the accumulation of the dye in the lysosomes of viable cells. After the cells were incubated for 24 h with the corresponding systems, the medium was removed, and the compounds solutions were incubated for 3 h with the NR dye (Sigma-Aldrich) solution (50 µg/mL) dissolved in the medium without FBS and phenol red (Lonza). Cells were then washed with sterile PBS, followed by adding 100 µL of a solution containing 50% ethanol absolute and 1% acetic acid in distilled water to extract the dye. To help the total dissolution of the dye, plates were placed in a microtitre-plate shaker for 5 min at room temperature. The absorbance of the resulting solutions was measured at 550 nm ( Bio-Rad 550 microplate reader). Finally, the effect of each treatment was calculated as the percentage of tetrazolium salt reduction by viable cells against the control cells (cells without any treatment).

#### 3.1.2.3.2. MTT assay

Only living cells can reduce the yellow tetrazolium salt, 2,5-diphenyl-3, -(4,5-dimethyl-2-thiazolyl) tetrazolium bromide (MTT) to insoluble purple formazan crystals. After 24 h of incubation of the cells with the corresponding NPs, the medium was removed, and 100 µL of MTT (Sigma–Aldrich) in PBS (5 mg/mL) diluted 1:10 in culture medium without phenol red and absence of FBS (Lonza) was added to the cells. After 3 h of incubation the medium was removed. Thereafter, 100 µL of DMSO (Sigma–Aldrich) was added to each well to dissolve the purple formazan crystals. Agitation, determination of the absorbance of the extracted solution, and the effect of each treatment measured at the same conditions that on 3.1.2.3.1.

#### 3.1.2.3.3. Selectivity towards cancer cells

The corresponding half-maximal inhibitory concentration ($IC_{50}$) values for the different formulations as a function of cell line and endpoint were determined from the fitting of concentration-dependent viabilities curves.

The corresponding selectivity indexes toward cancer cells were calculated as the following ratio:

SI = $IC_{50}$ (non-tumoral cell line)/$IC_{50}$ (tumoral cell line)

where HaCaT keratinocytes were used as closely representative of skin model cell lines under normal conditions.

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Usuari: san / Mostra: ZAS088-16
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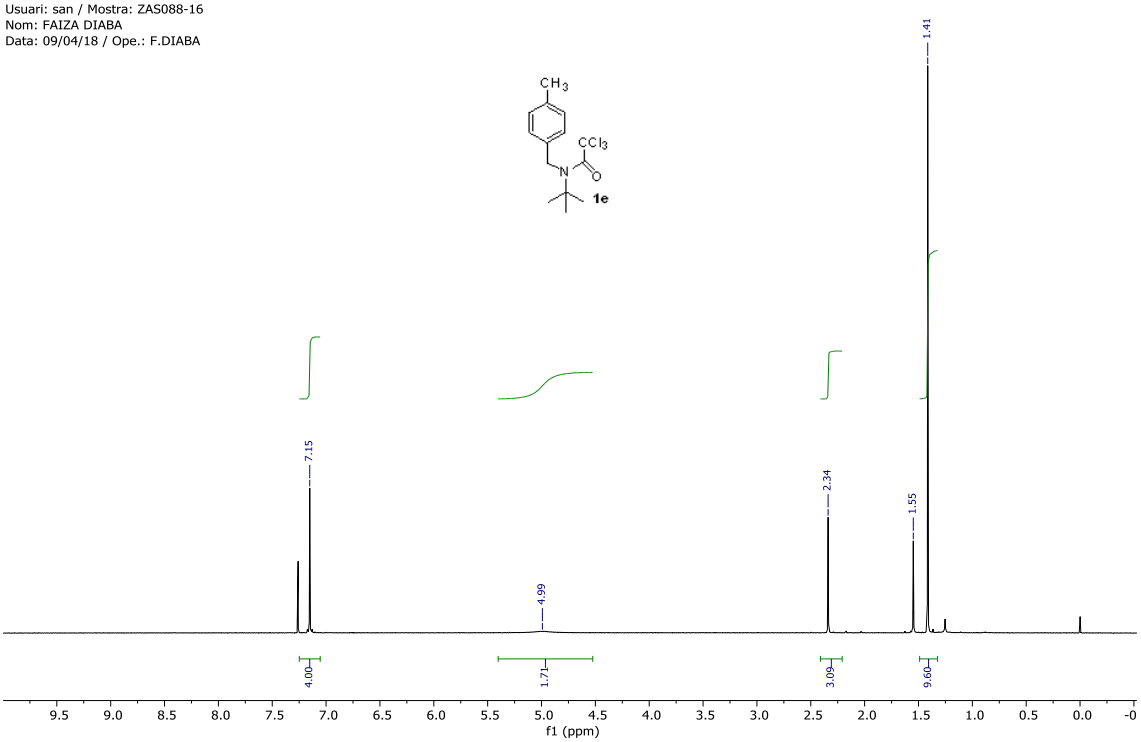


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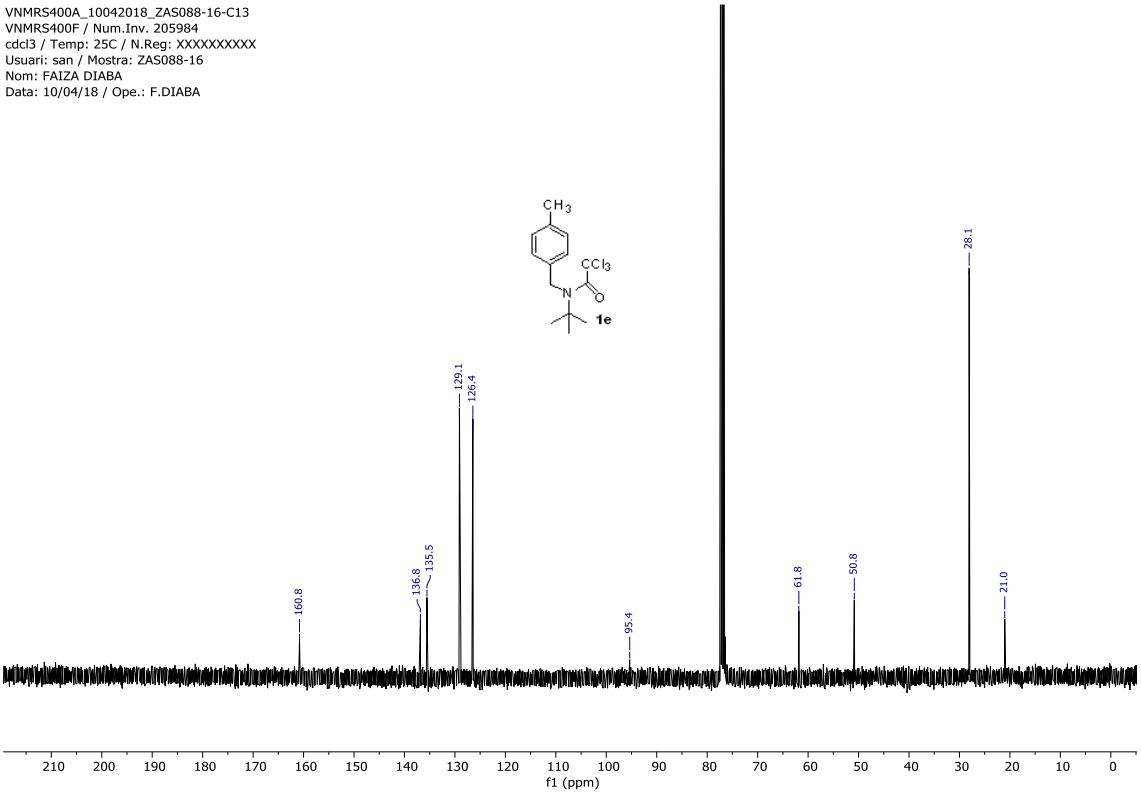
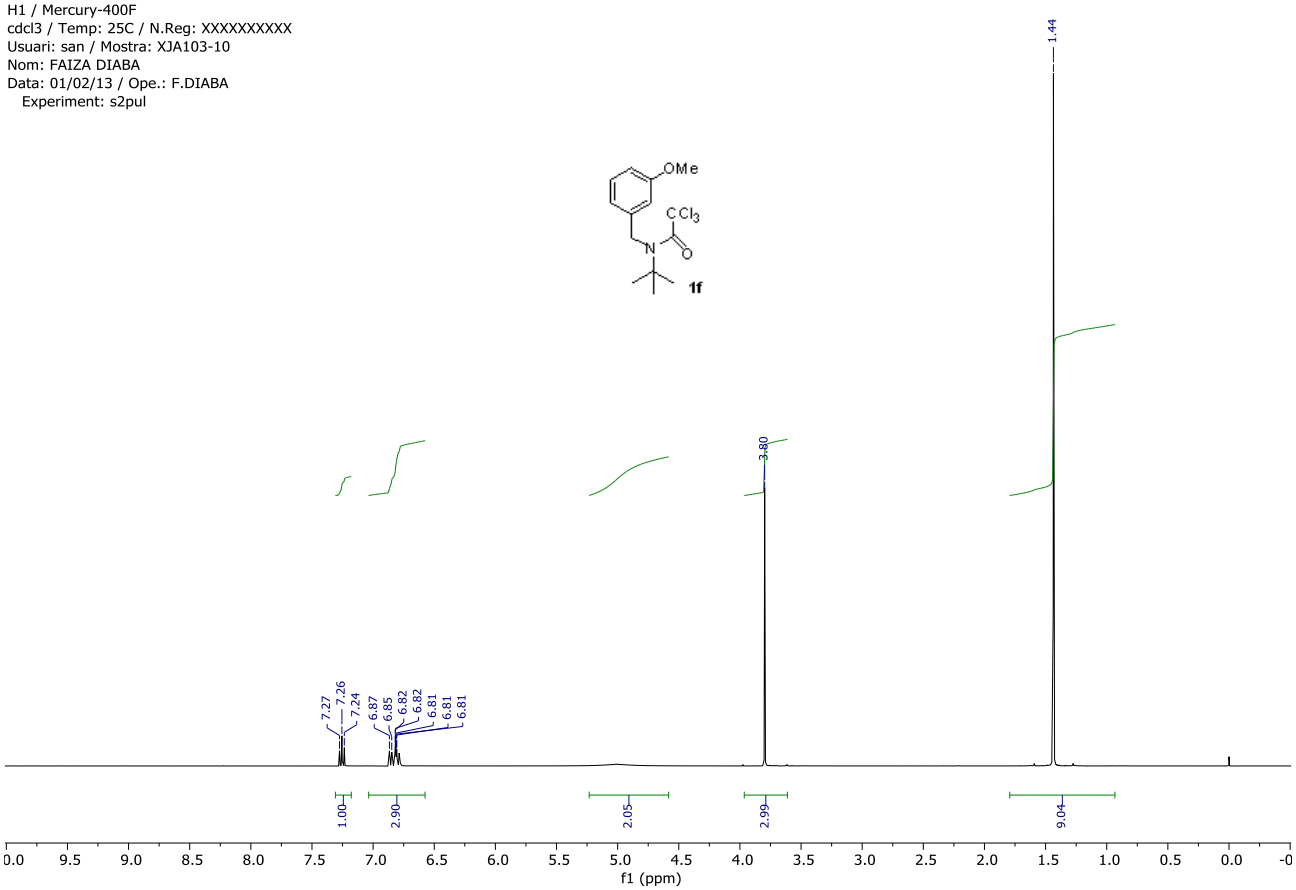
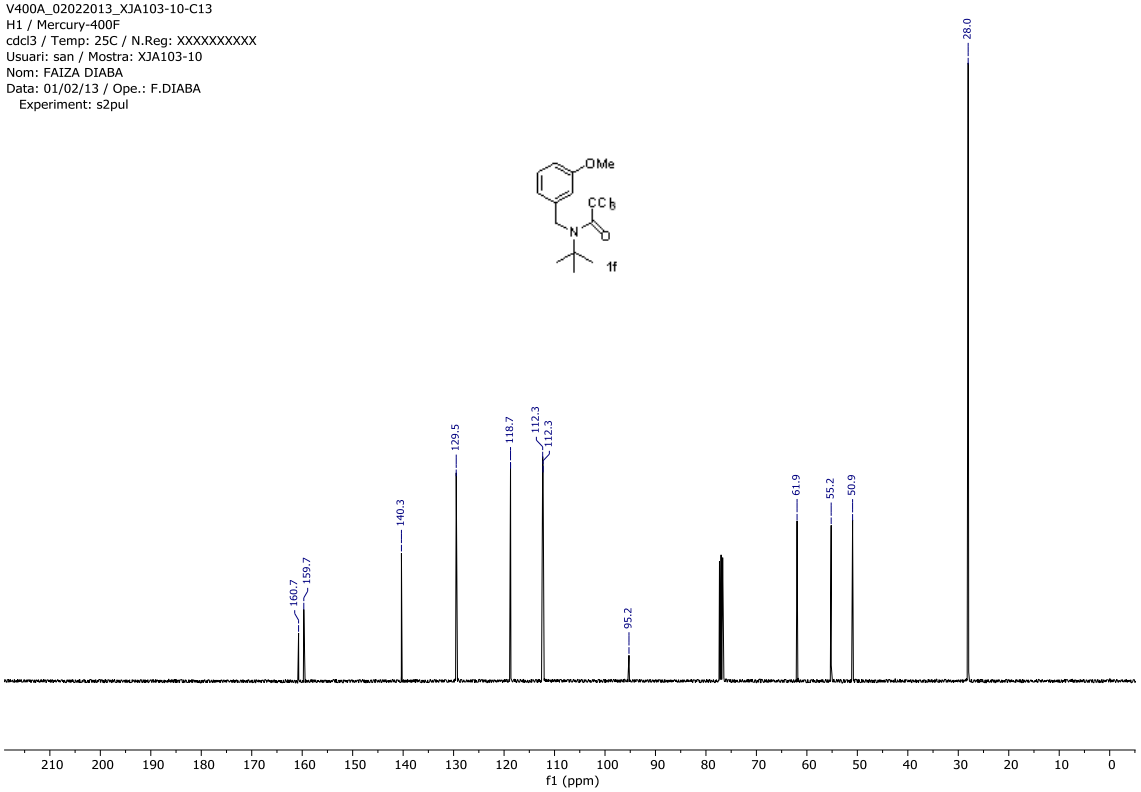
Nom: FAIZA DIABA
Data: 10/04/18 / Ope.: F.DIABA



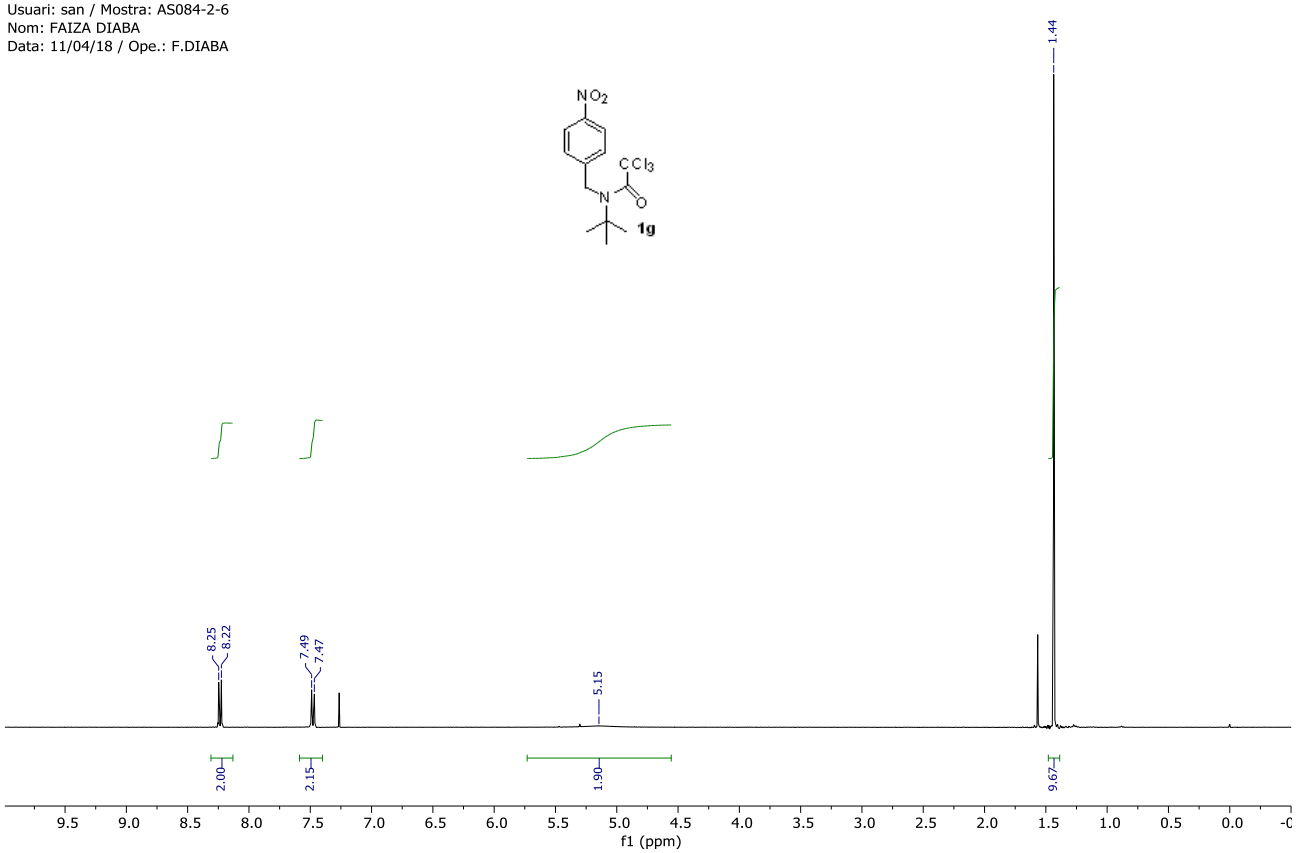
V400A_02022013_XJA103-10-H1
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA103-10
Nom: FAIZA DIABA
Data: 01/02/13 / Ope.: F.DIABA
Experiment: s2pul



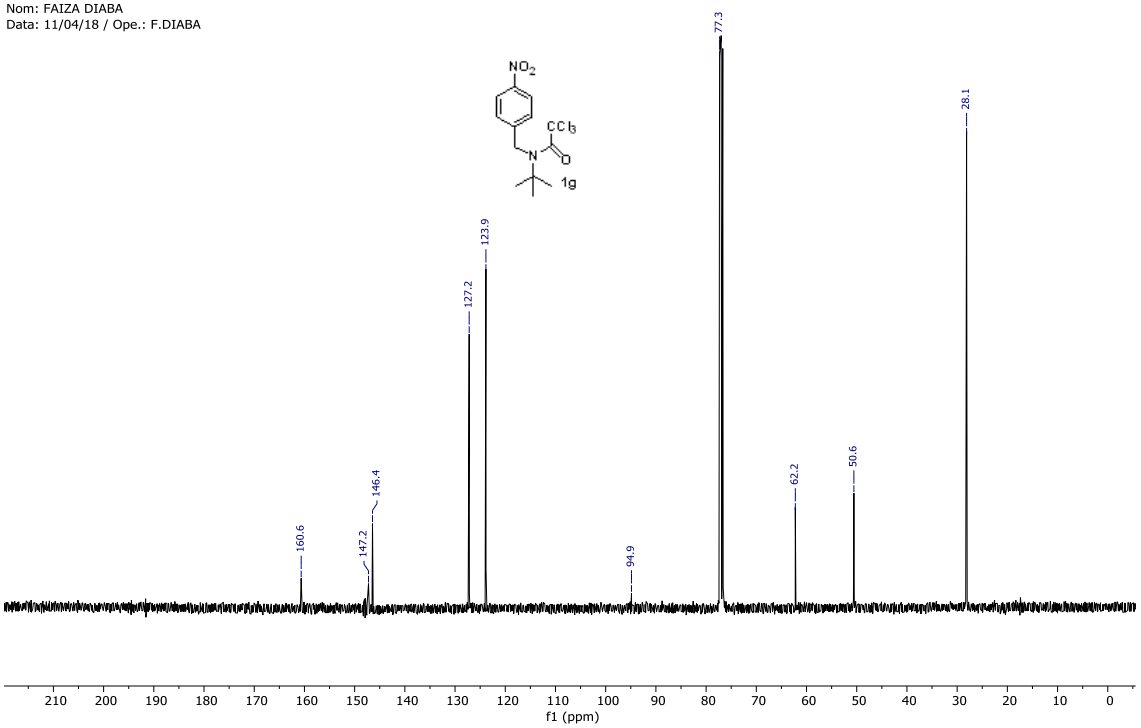

V400A_02022013_XJA103-10-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA103-10
Nom: FAIZA DIABA
Data: 01/02/13 / Ope.: F.DIABA
Experiment: s2pul

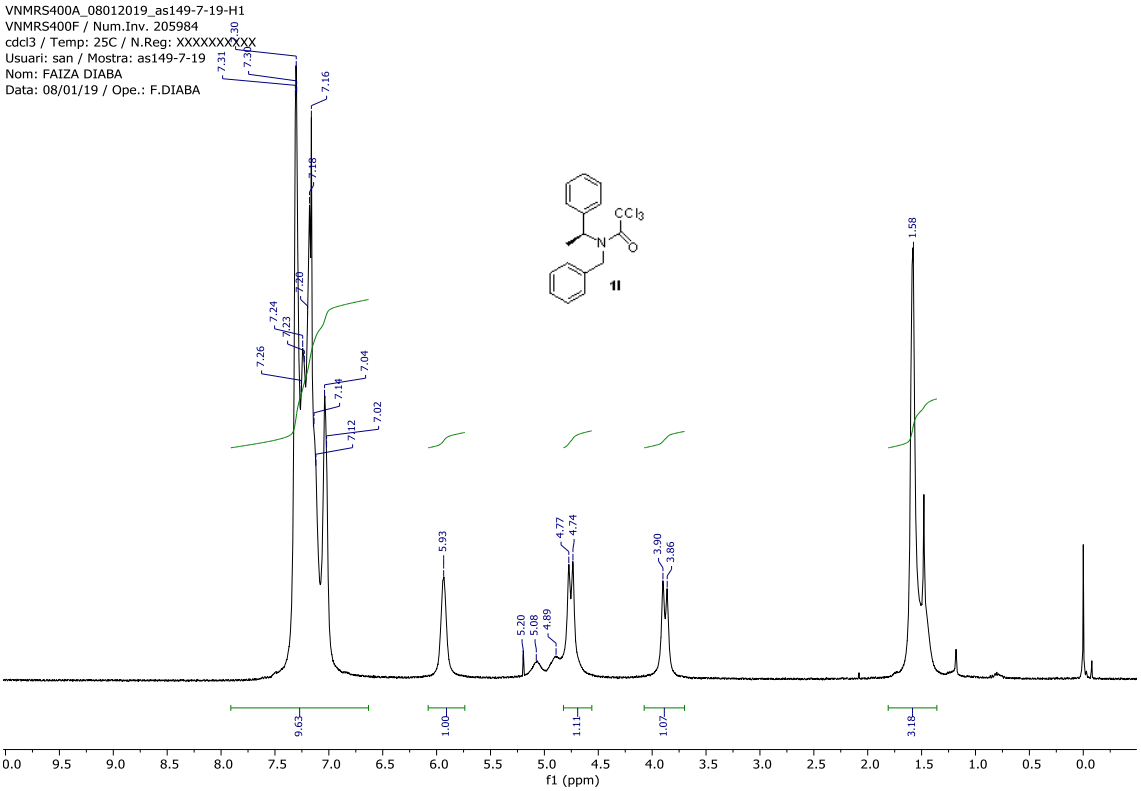


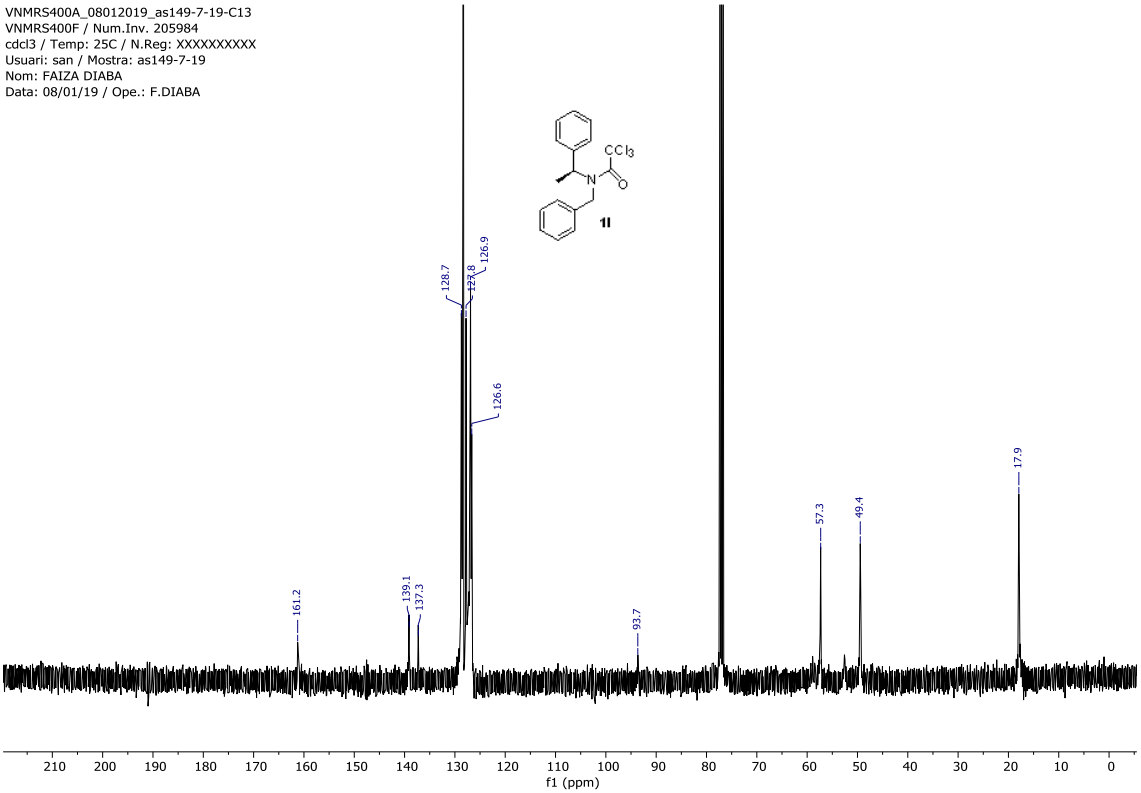
M400AFF_11042018_AS084-2-6-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS084-2-6
Nom: FAIZA DIABA
Data: 11/04/18 / Ope.: F.DIABA



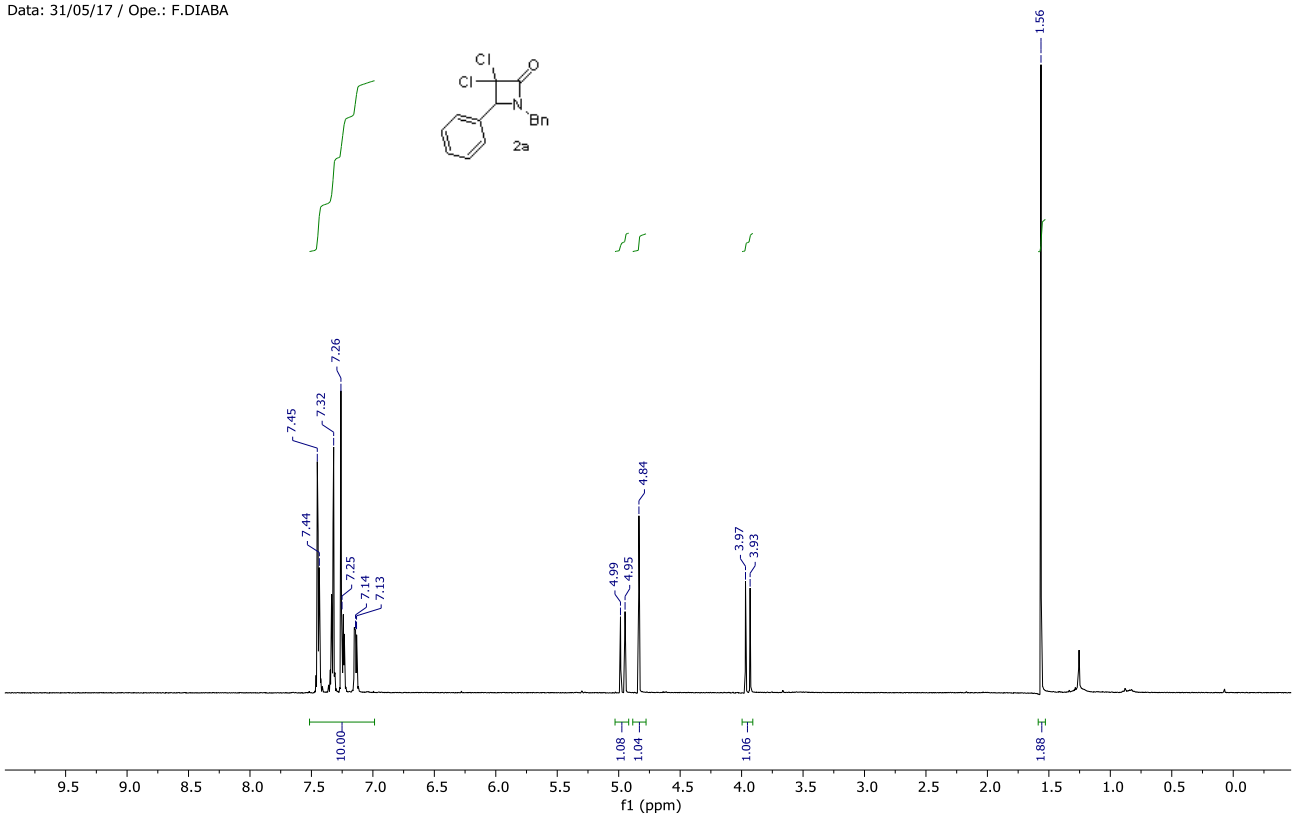

VNMRS400A_11042018_AS084-2-6-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS084-2-6
Nom: FAIZA DIABA
Data: 11/04/18 / Ope.: F.DIABA



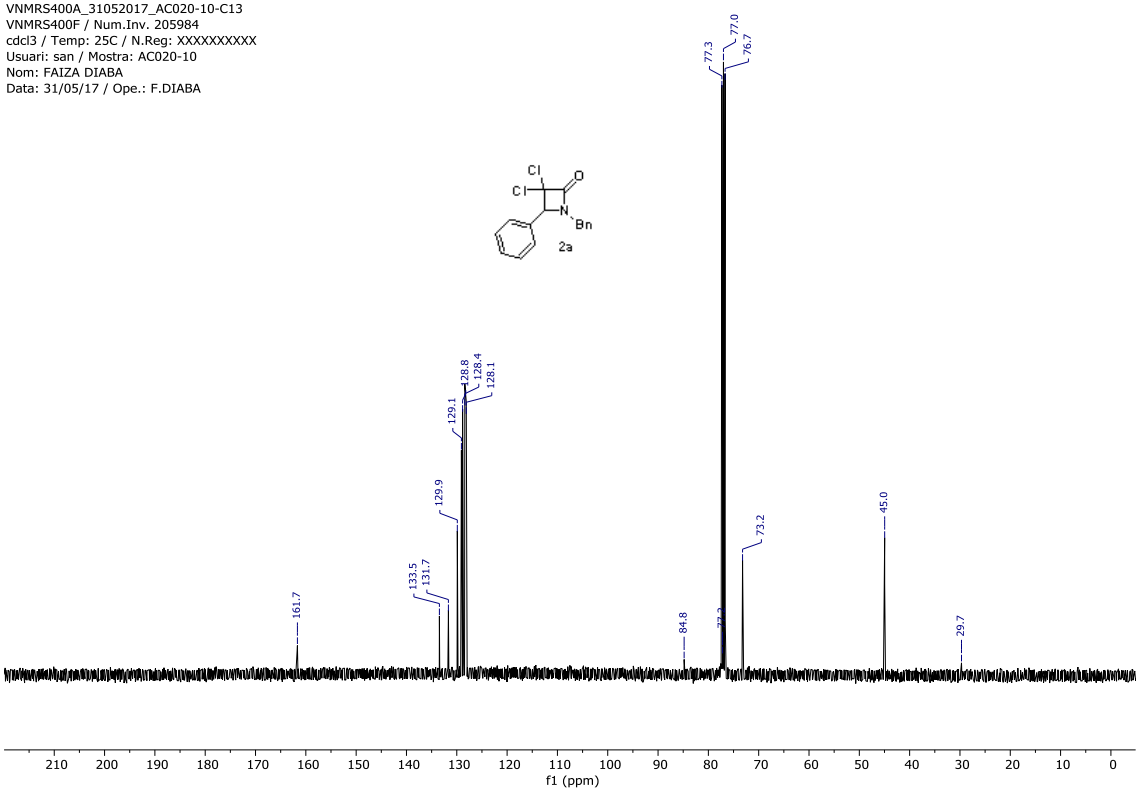

VNMRS400A_08012019_as149-7-19-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as149-7-19
Nom: FAIZA DIABA
Data: 08/01/19 / Ope.: F.DIABA
CCl3
N
O
1l
7.31
7.30
7.16
7.18
7.20
7.24
7.23
7.26
7.04
7.14
7.12
7.02
5.93
5.20
5.08
4.89
4.77
4.74
3.90
3.86
1.58
9.63
1.00
1.11
1.07
3.18
f1 (ppm)


VNMRS400A_08012019_as149-7-19-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as149-7-19
Nom: FAIZA DIABA
Data: 08/01/19 / Ope.: F.DIABA
CCl3
N
O
1l
128.7
126.9
126.6
161.2
139.1
137.3
93.7
57.3
49.4
17.9
f1 (ppm)

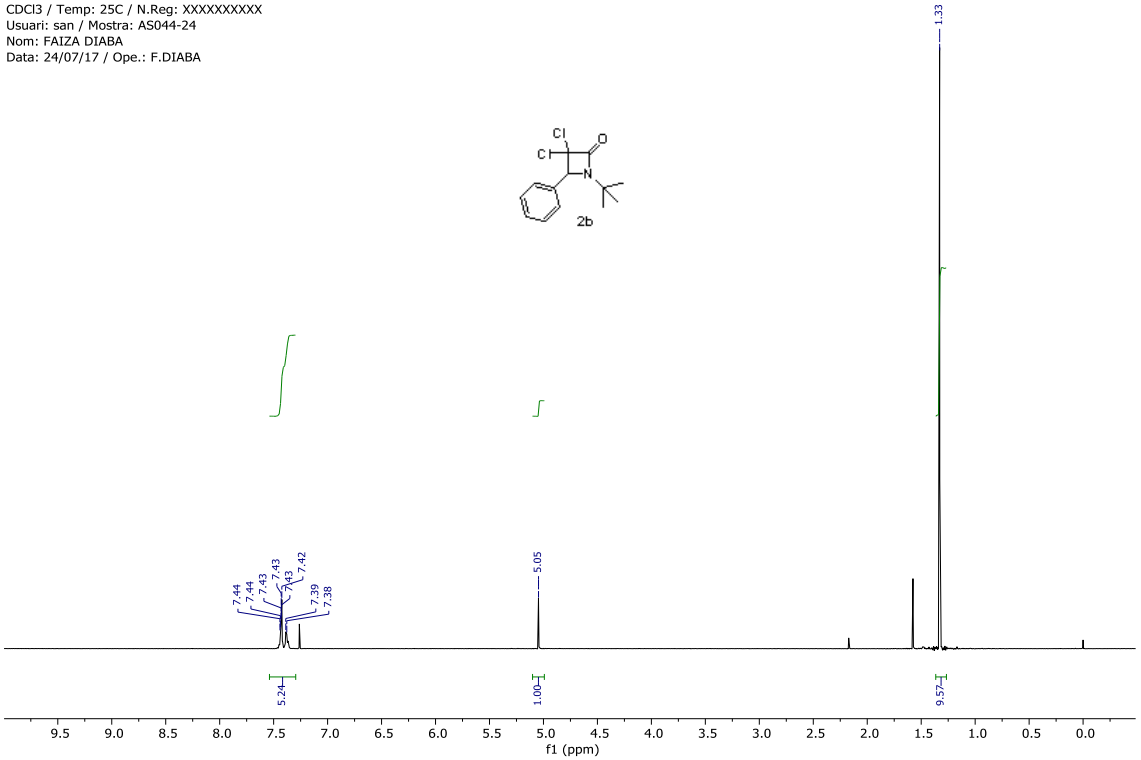
VNMRS400A_31052017_AC020-10-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AC020-10
Nom: FAIZA DIABA
Data: 31/05/17 / Ope.: F.DIABA



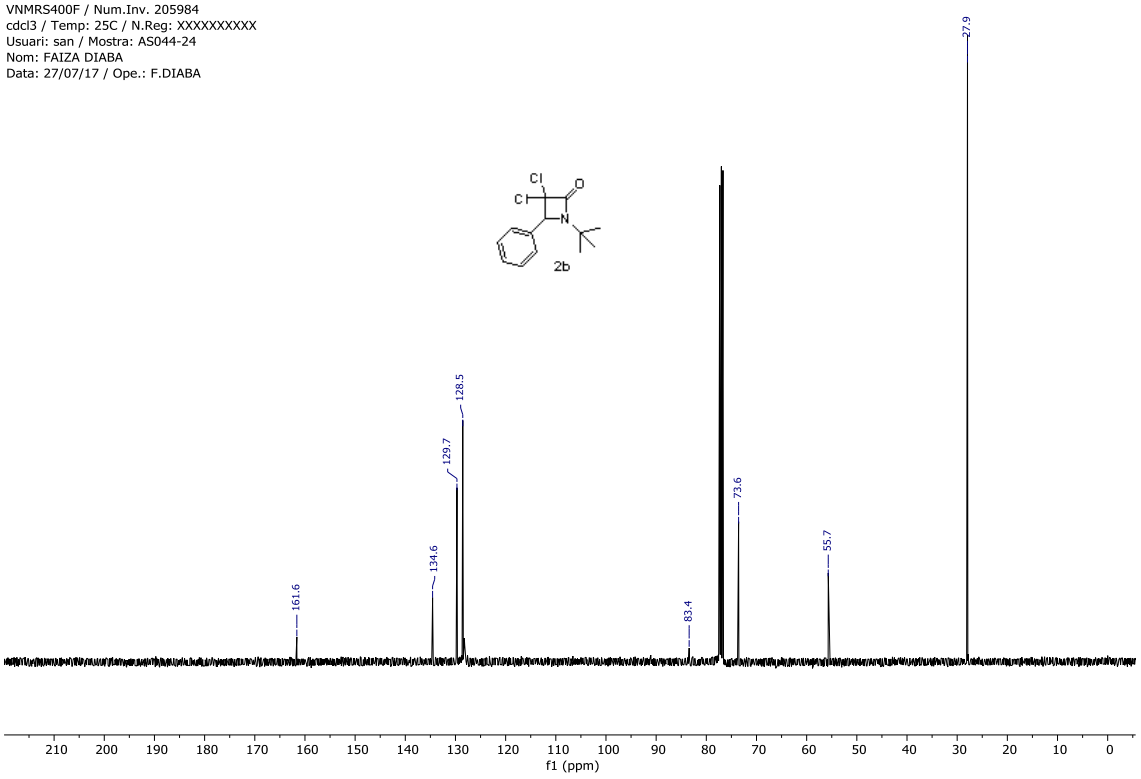

VNMRS400A_31052017_AC020-10-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AC020-10
Nom: FAIZA DIABA
Data: 31/05/17 / Ope.: F.DIABA



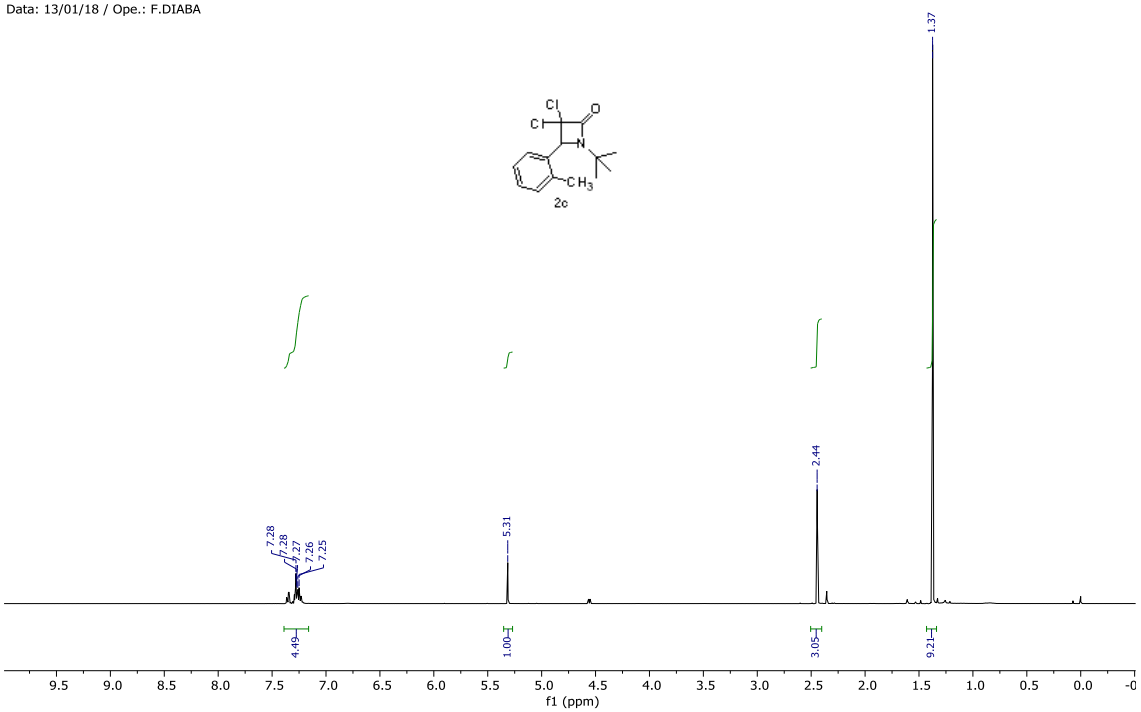
M400AFF_24072017_AS044-24-H1
M400F / Num.Inv. 1009191
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS044-24
Nom: FAIZA DIABA
Data: 24/07/17 / Ope.: F.DIABA




VNMRS400A_27072017_AS044-24-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS044-24
Nom: FAIZA DIABA
Data: 27/07/17 / Ope.: F.DIABA

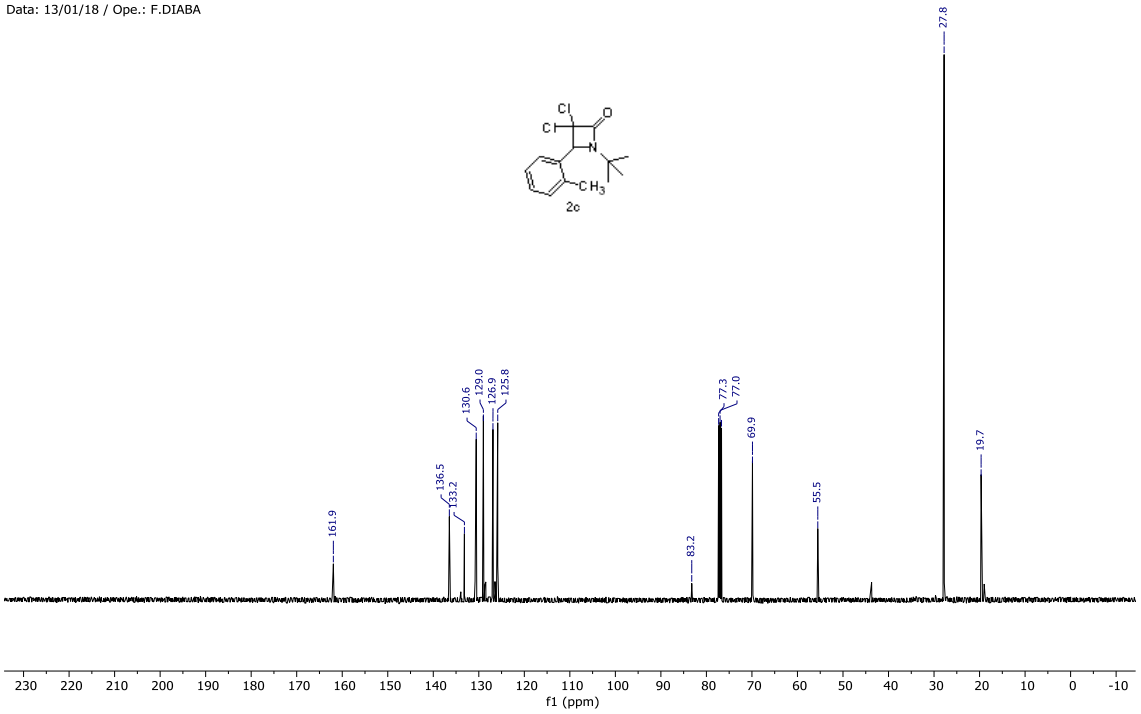


VNMRS400A_13012018_AS071-2-6-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS071-2-6
Nom: FAIZA DIABA
Data: 13/01/18 / Ope.: F.DIABA



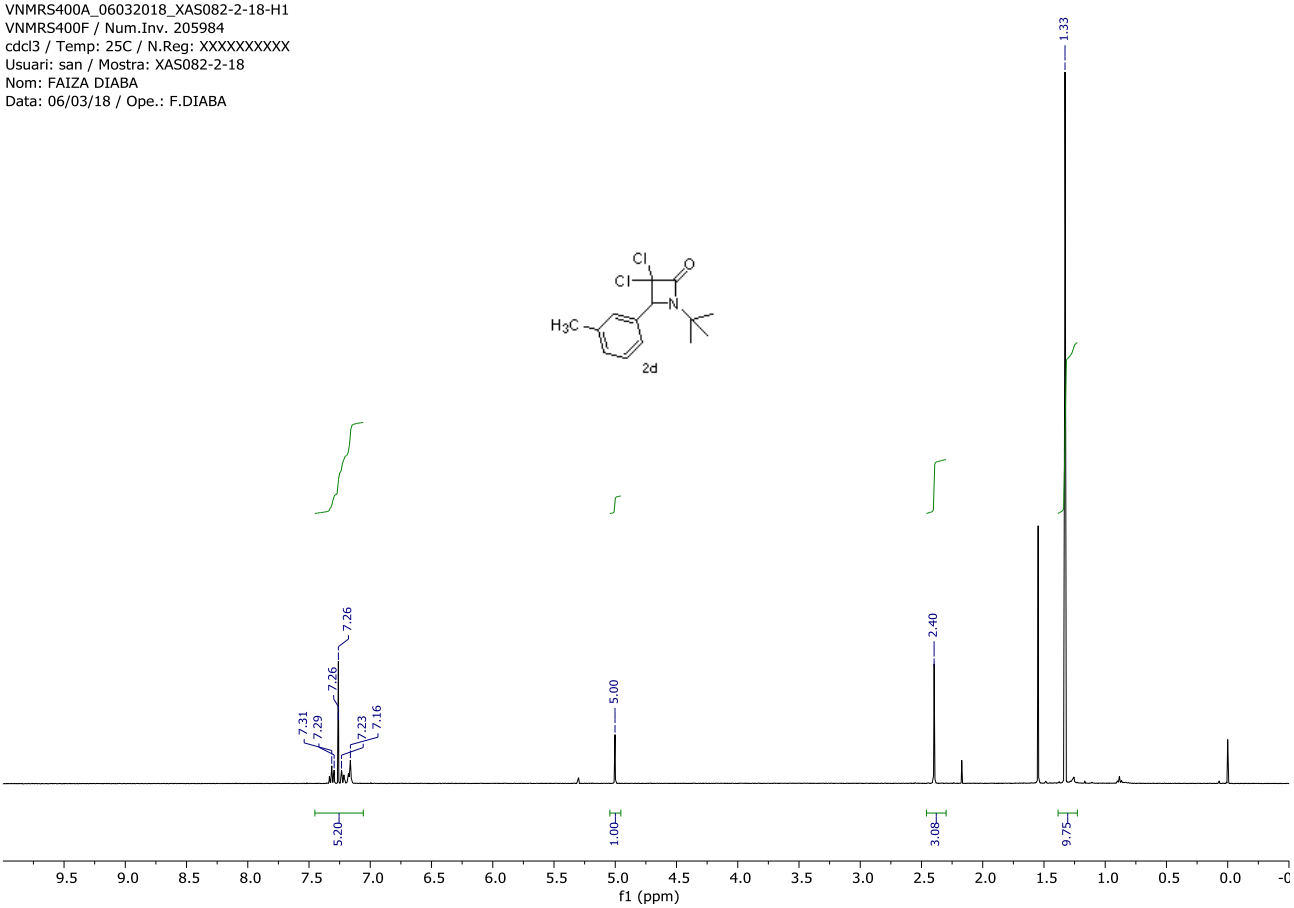

2c

VNMRS400A_13012018_AS071-2-6-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS071-2-6
Nom: FAIZA DIABA
Data: 13/01/18 / Ope.: F.DIABA

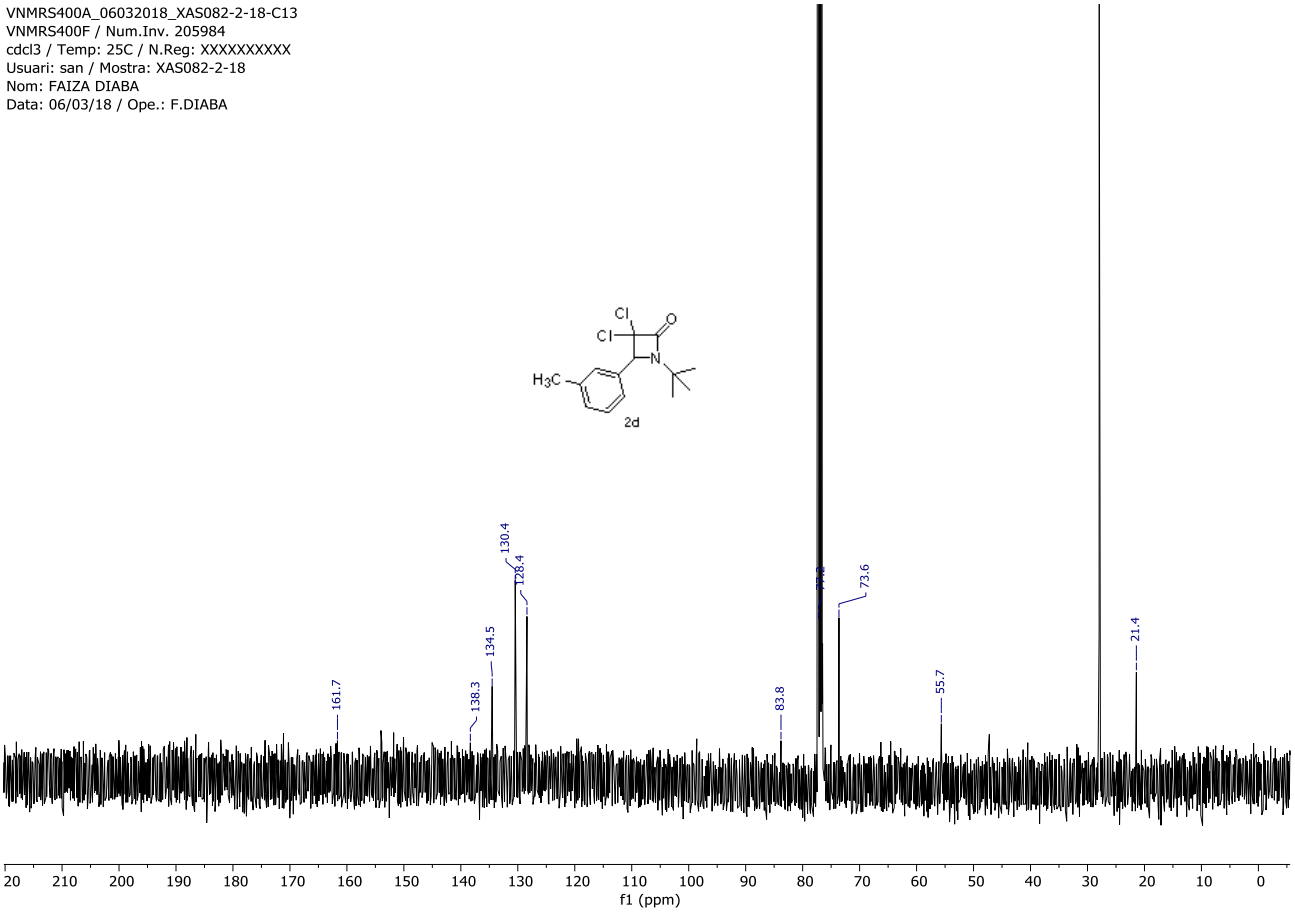



2c

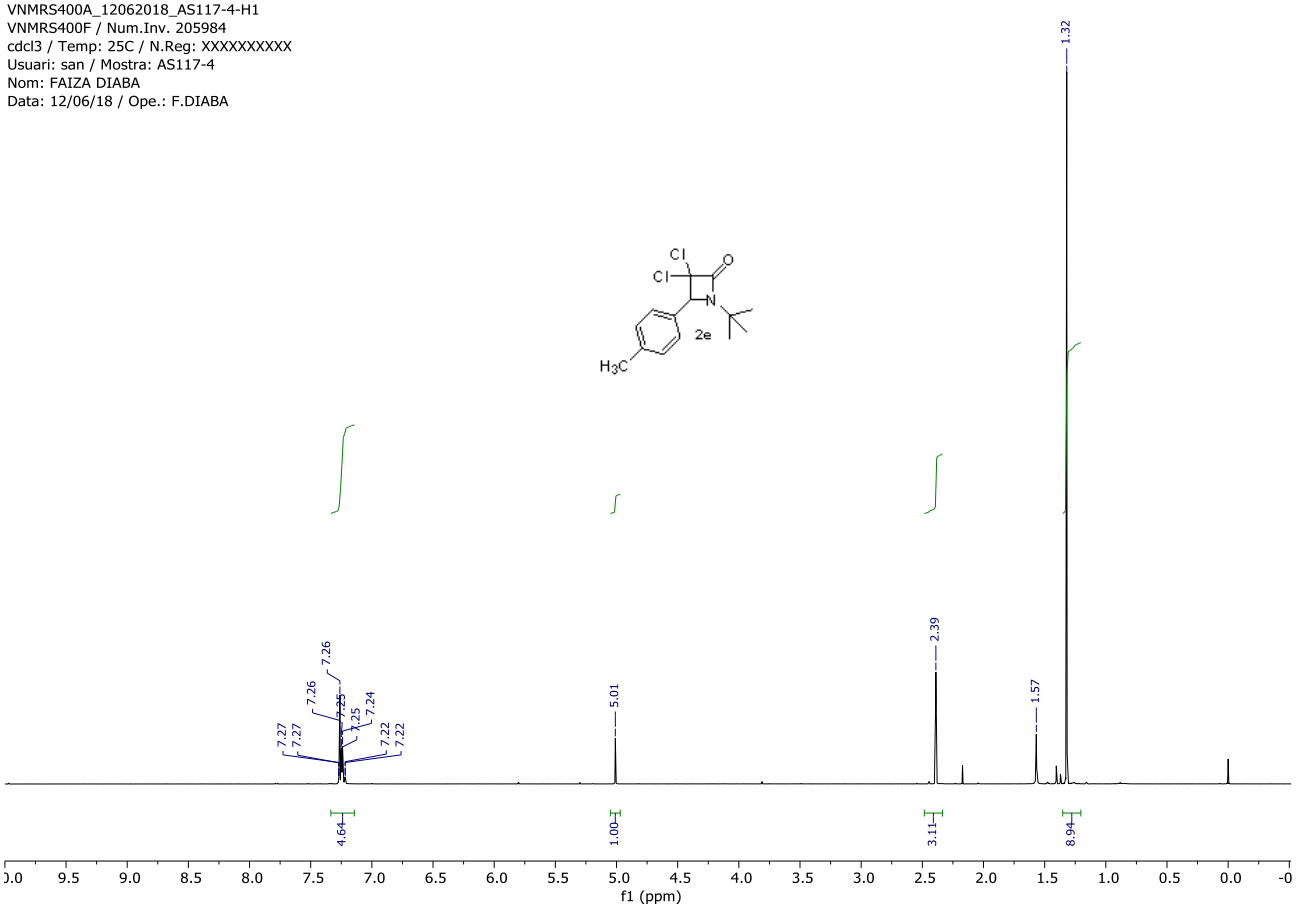
VNMRS400A_06032018_XAS082-2-18-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS082-2-18
Nom: FAIZA DIABA
Data: 06/03/18 / Ope.: F.DIABA



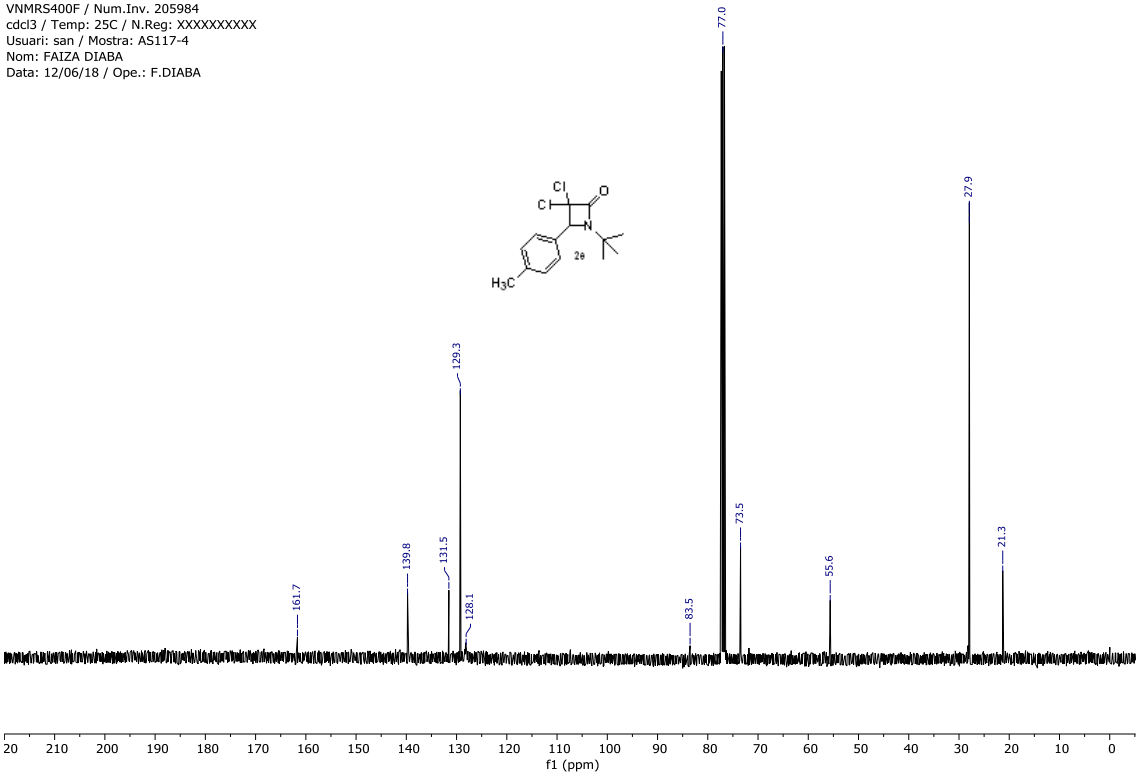

VNMRS400A_06032018_XAS082-2-18-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS082-2-18
Nom: FAIZA DIABA
Data: 06/03/18 / Ope.: F.DIABA



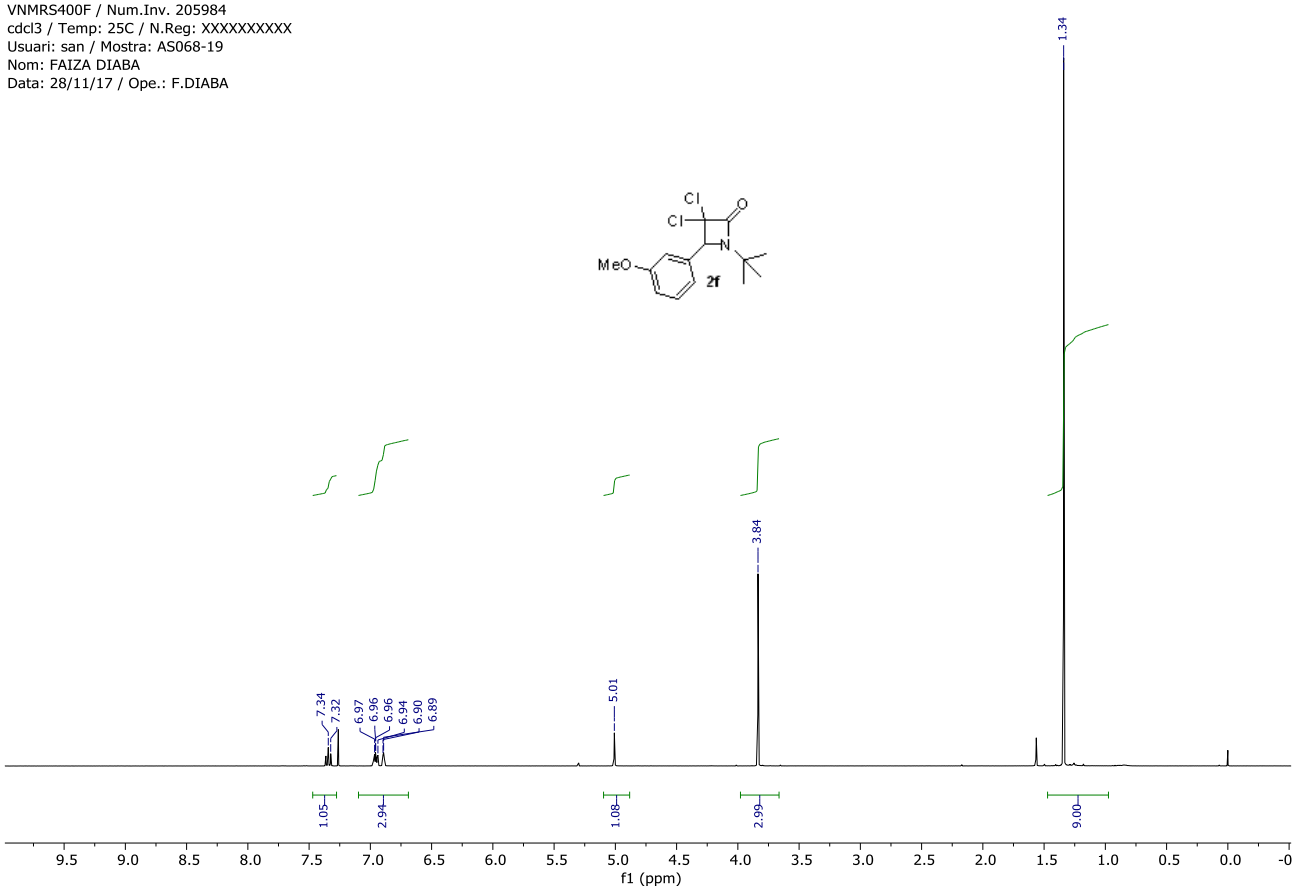
VNMRS400A_12062018_AS117-4-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS117-4
Nom: FAIZA DIABA
Data: 12/06/18 / Ope.: F.DIABA



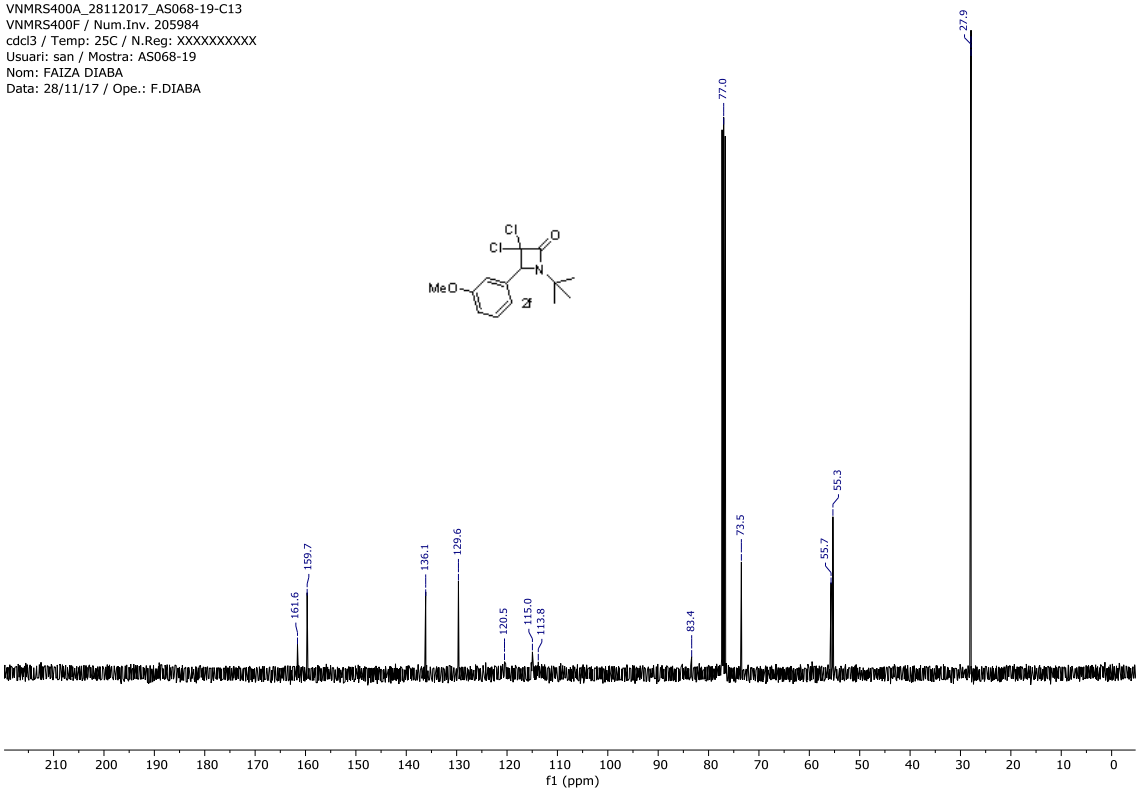

VNMRS400A_12062018_AS117-4-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS117-4
Nom: FAIZA DIABA
Data: 12/06/18 / Ope.: F.DIABA



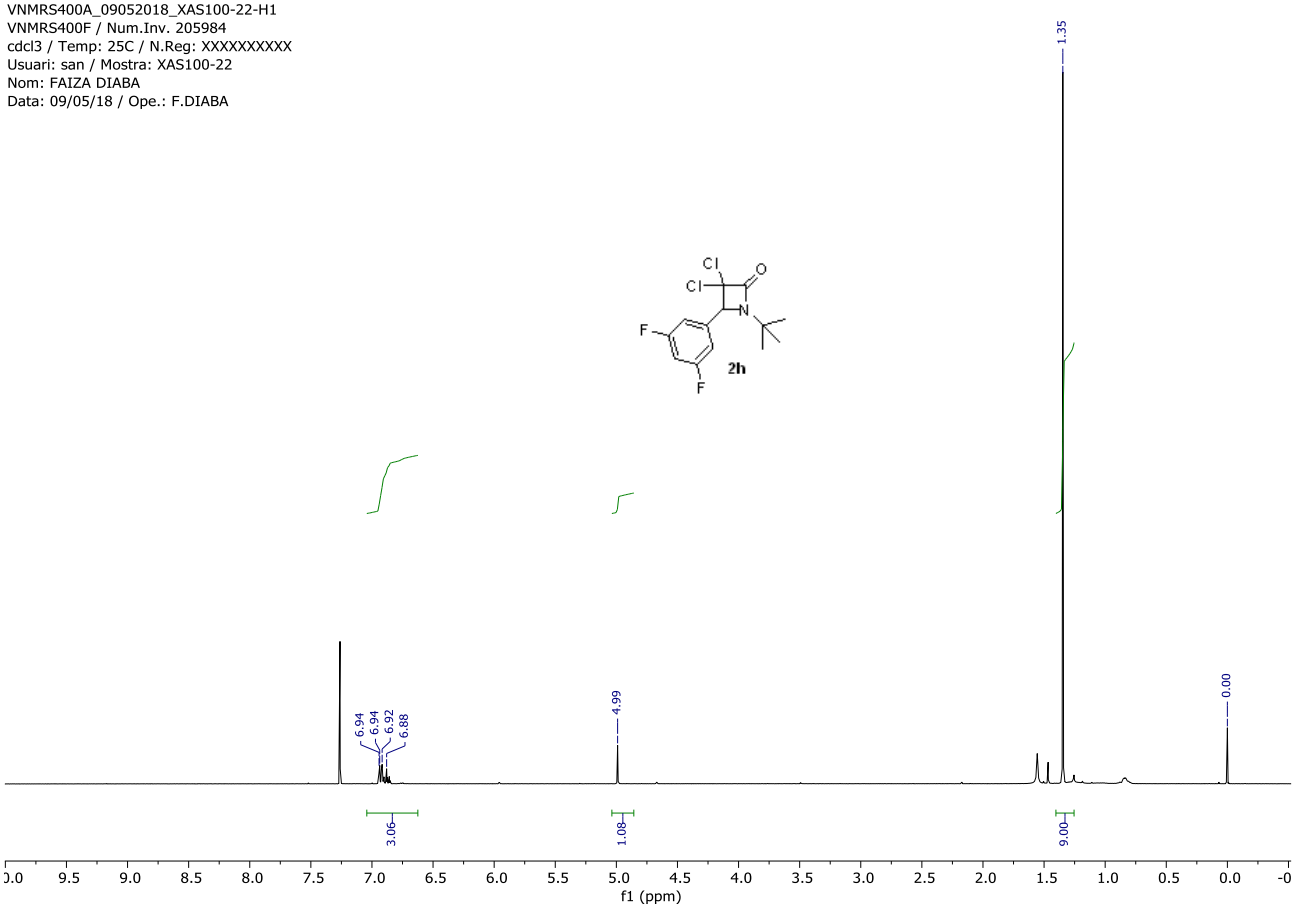
VNMRS400A_28112017_AS068-19-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS068-19
Nom: FAIZA DIABA
Data: 28/11/17 / Ope.: F.DIABA



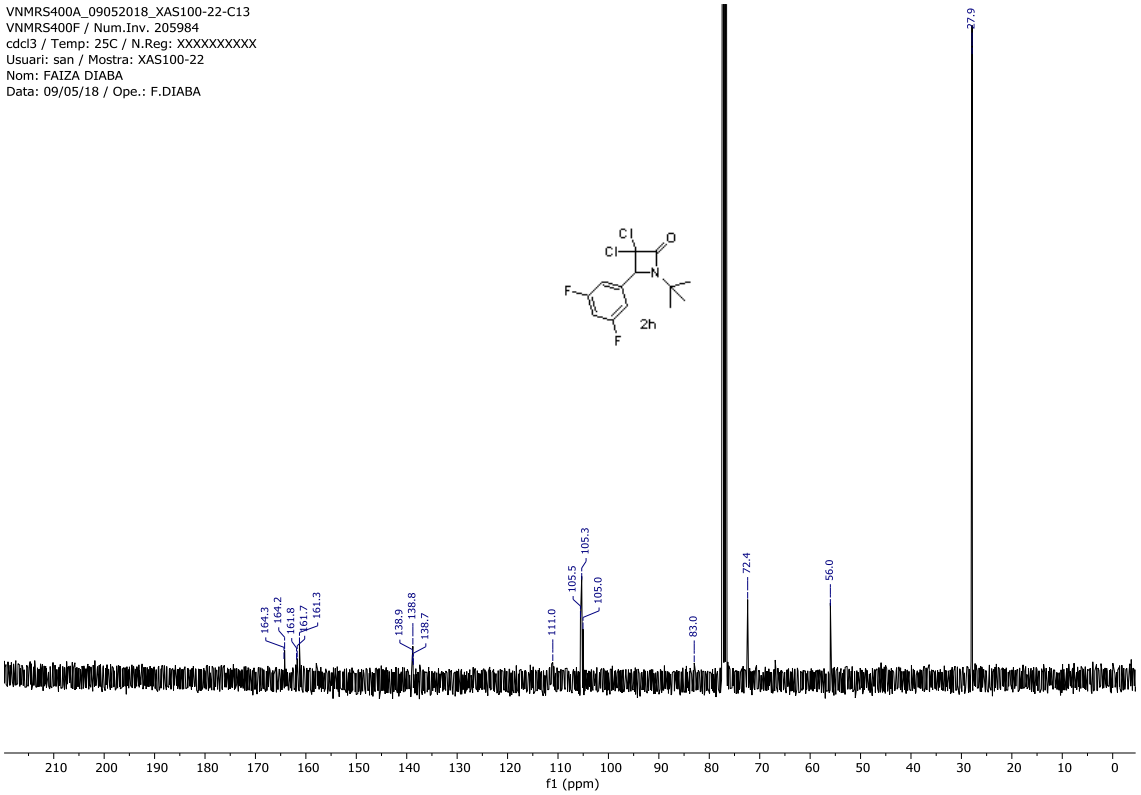

VNMRS400A_28112017_AS068-19-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS068-19
Nom: FAIZA DIABA
Data: 28/11/17 / Ope.: F.DIABA



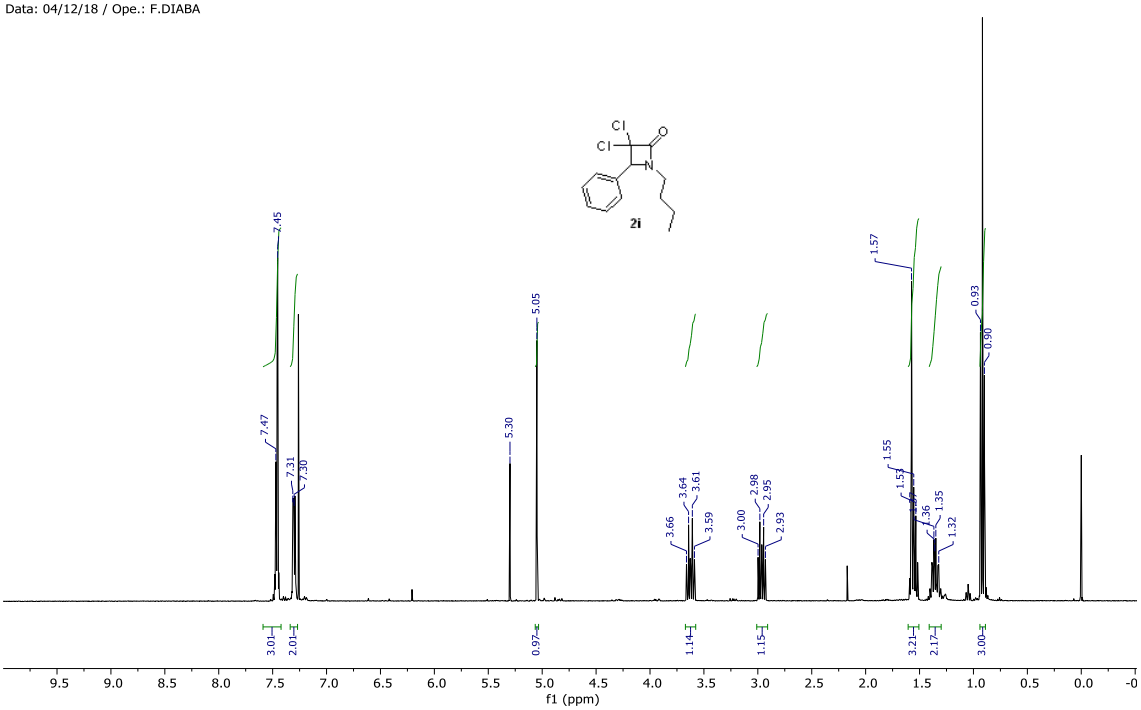
VNMRS400A_09052018_XAS100-22-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS100-22
Nom: FAIZA DIABA
Data: 09/05/18 / Ope.: F.DIABA



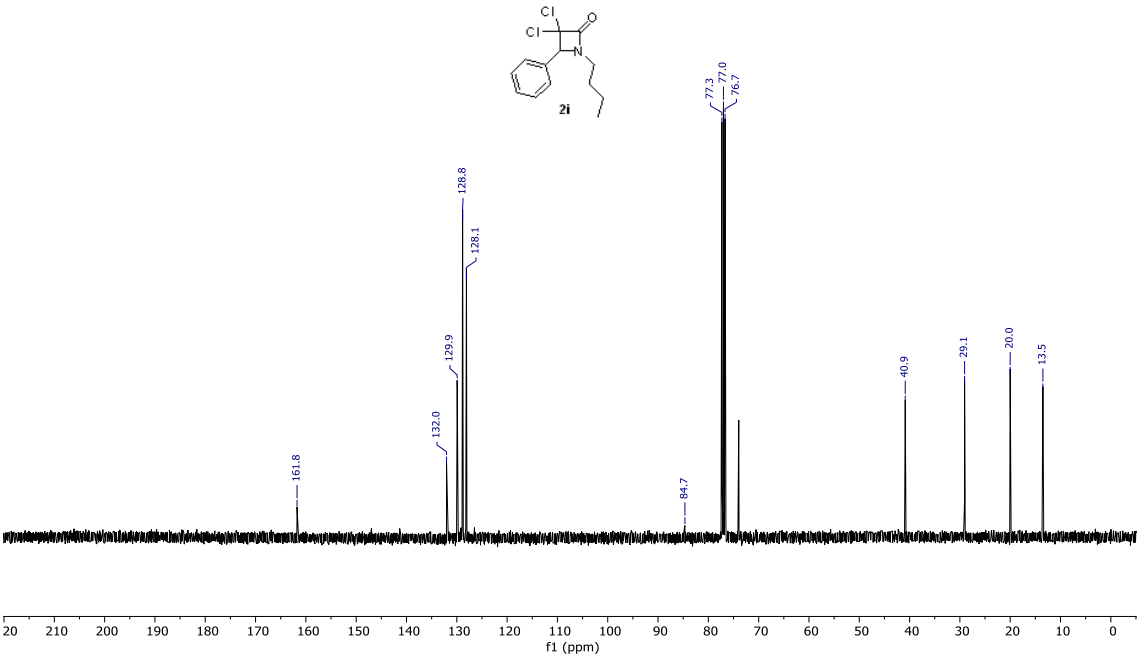

VNMRS400A_09052018_XAS100-22-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS100-22
Nom: FAIZA DIABA
Data: 09/05/18 / Ope.: F.DIABA

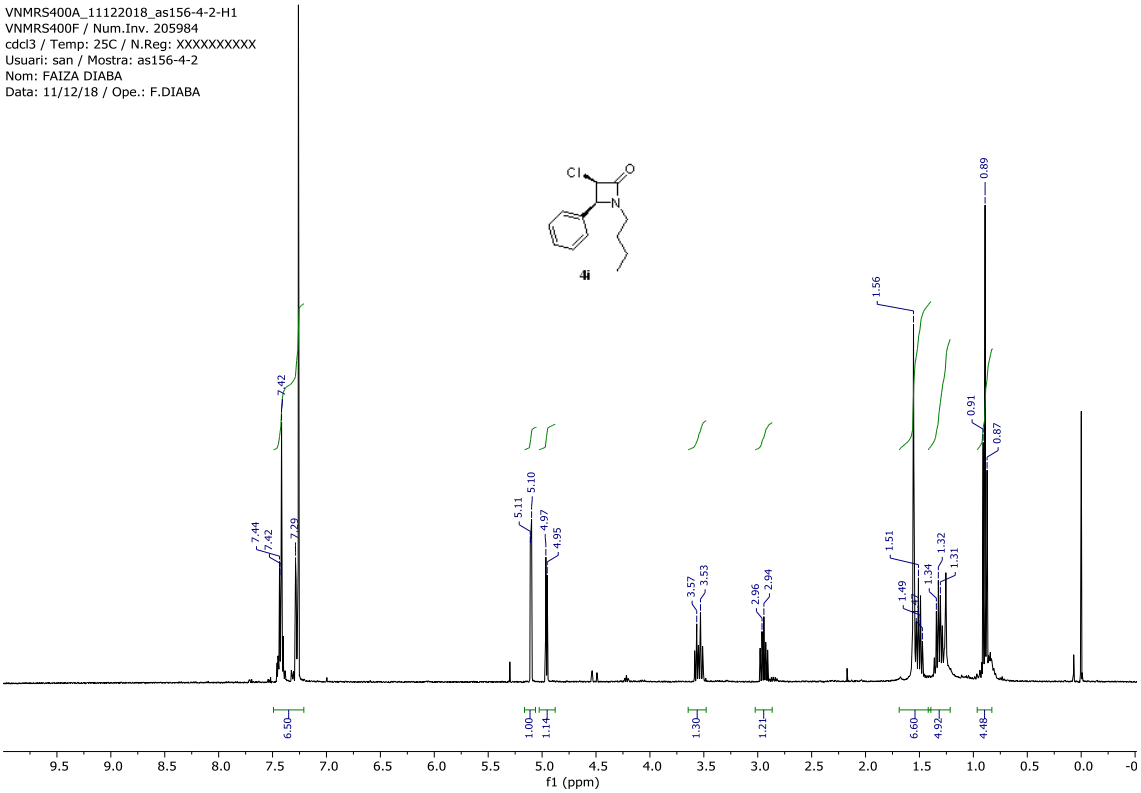


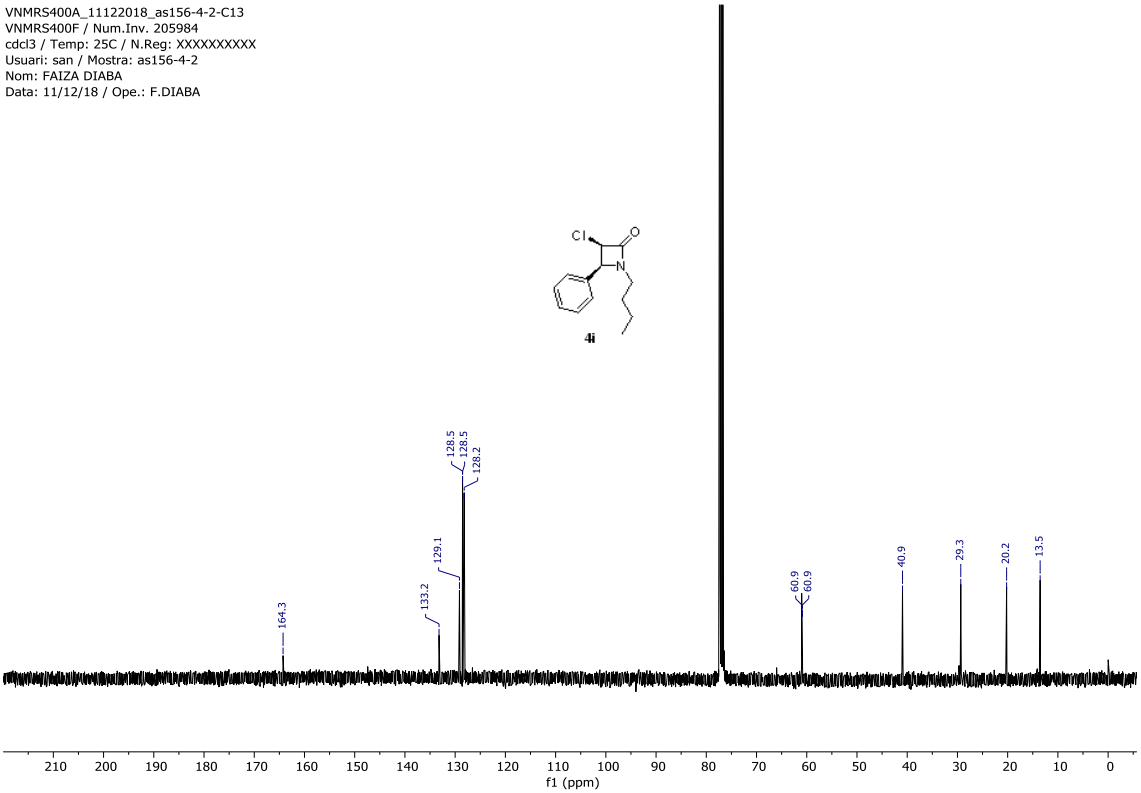
VNMRS400A_04122018_as156-13-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as156-13
Nom: FAIZA DIABA
Data: 04/12/18 / Ope.: F.DIABA

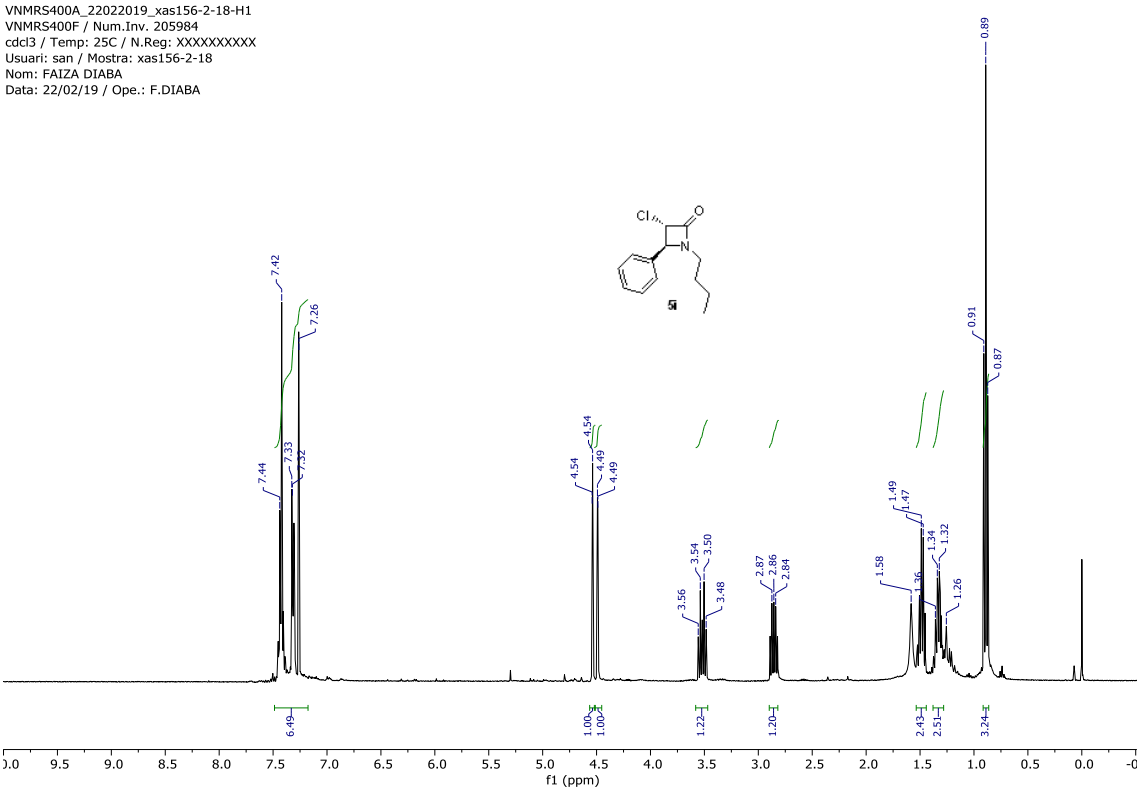


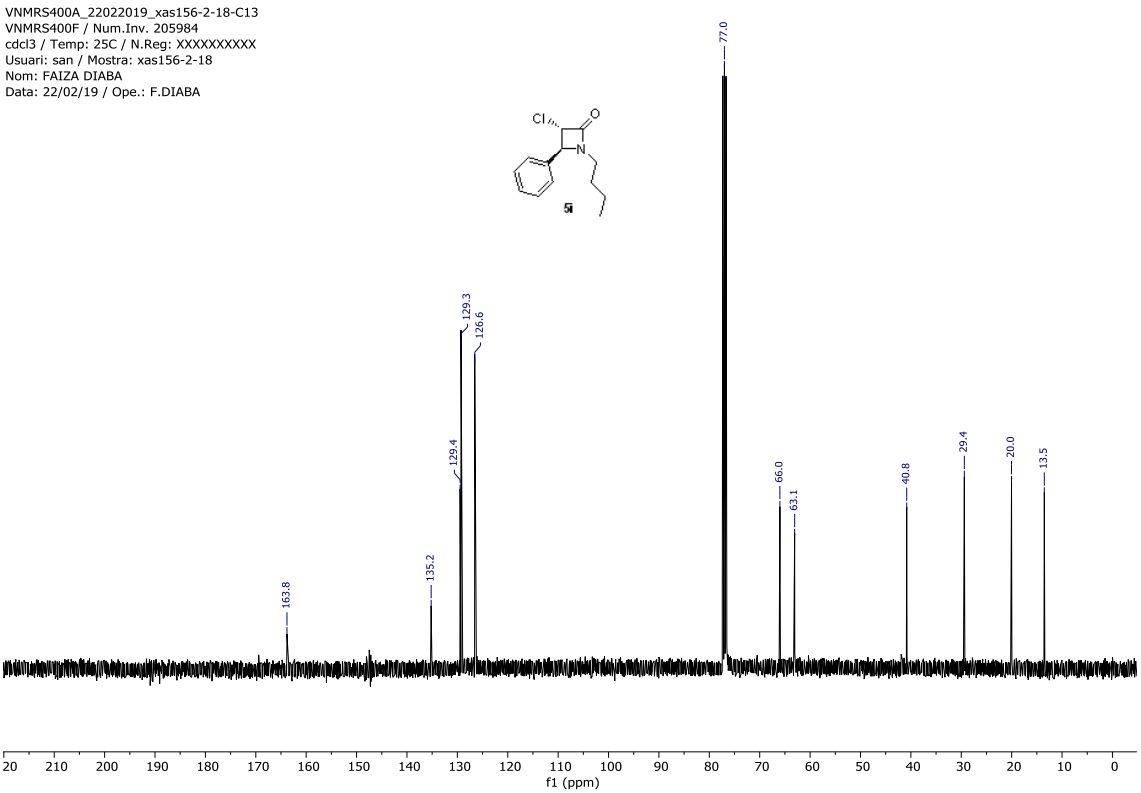

VNMRS400A_04122018_as156-13-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as156-13
Nom: FAIZA DIABA
Data: 04/12/18 / Ope.: F.DIABA



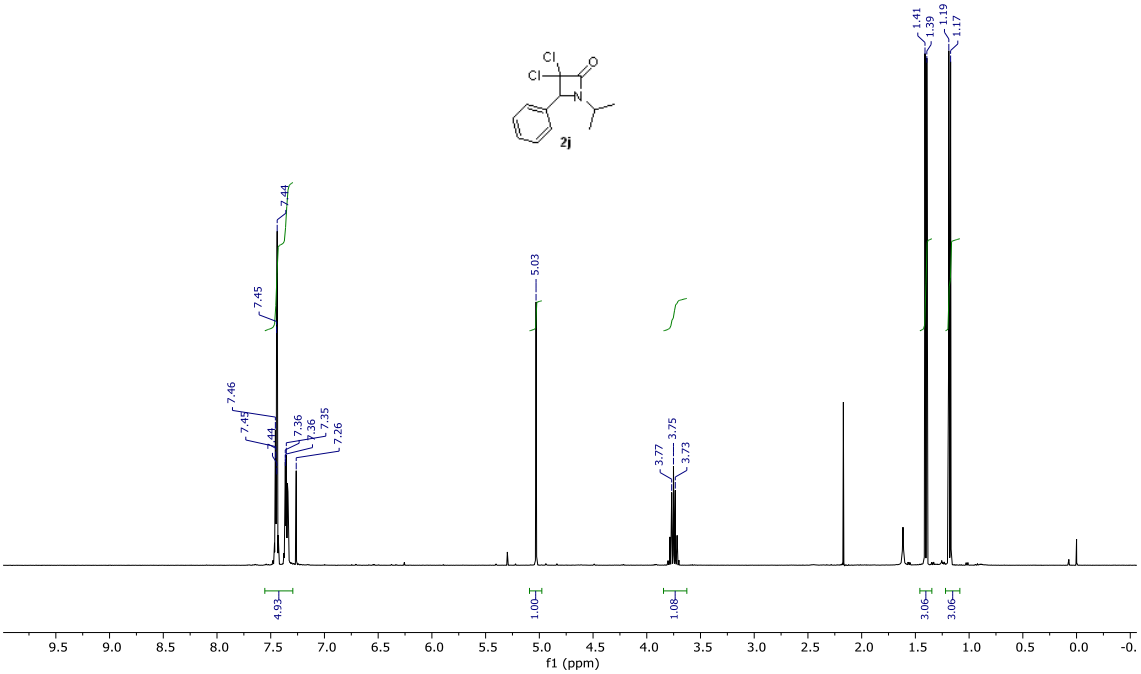

VNMRS400A_11122018_as156-4-2-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as156-4-2
Nom: FAIZA DIABA
Data: 11/12/18 / Ope.: F.DIABA
4i
7.44
7.42
7.29
5.11
5.10
4.97
4.95
3.57
3.53
2.96
2.94
1.56
1.51
1.49
1.34
1.32
1.31
0.91
0.89
0.87
6.50
1.00
1.14
1.30
1.21
6.60
4.92
4.48
f1 (ppm)


VNMRS400A_11122018_as156-4-2-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as156-4-2
Nom: FAIZA DIABA
Data: 11/12/18 / Ope.: F.DIABA
4i
164.3
133.2
129.1
128.5
128.5
128.2
60.9
60.9
40.9
29.3
20.2
13.5
f1 (ppm)

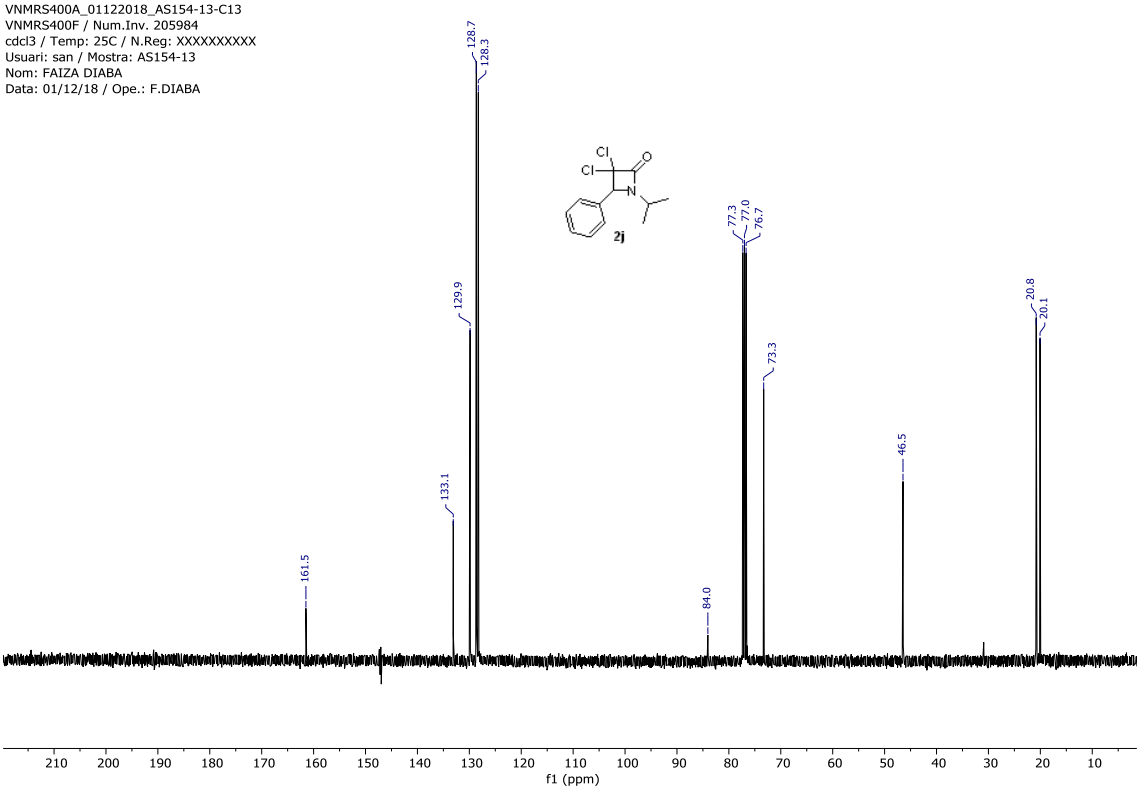

VNMRS400A_22022019_xas156-2-18-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xas156-2-18
Nom: FAIZA DIABA
Data: 22/02/19 / Ope.: F.DIABA
5i
f1 (ppm)

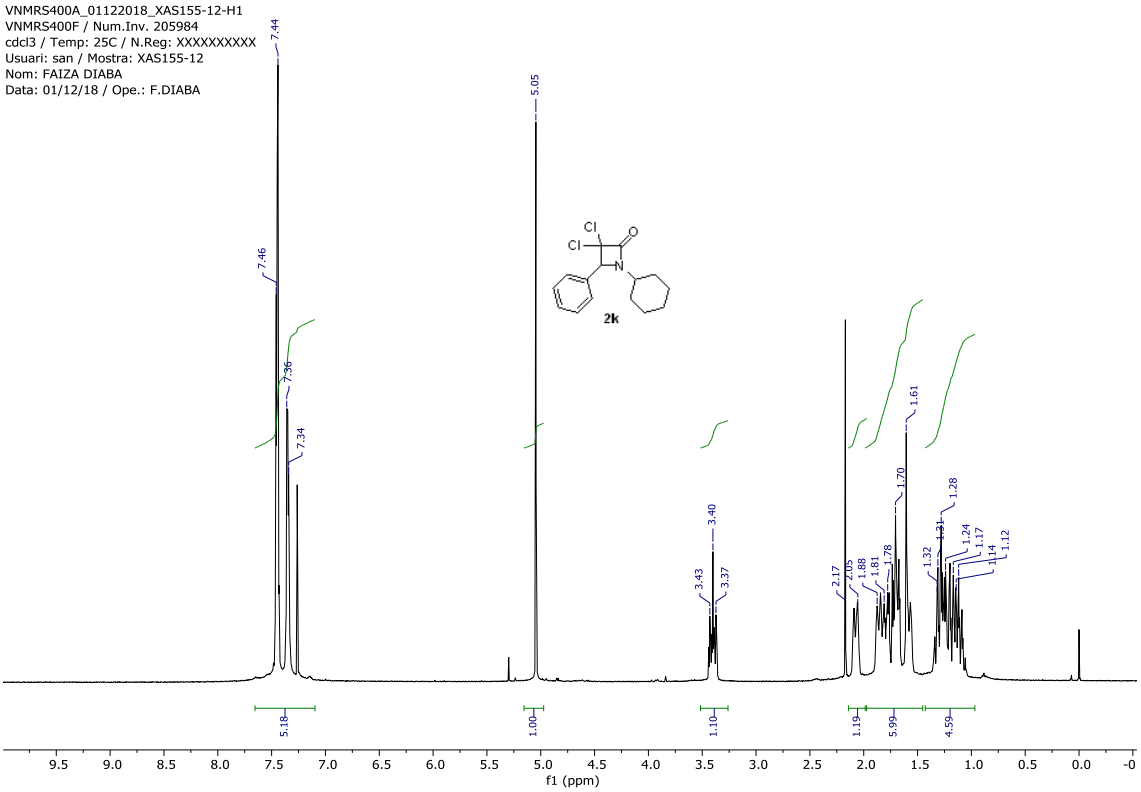

VNMRS400A_22022019_xas156-2-18-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xas156-2-18
Nom: FAIZA DIABA
Data: 22/02/19 / Ope.: F.DIABA
5i
f1 (ppm)

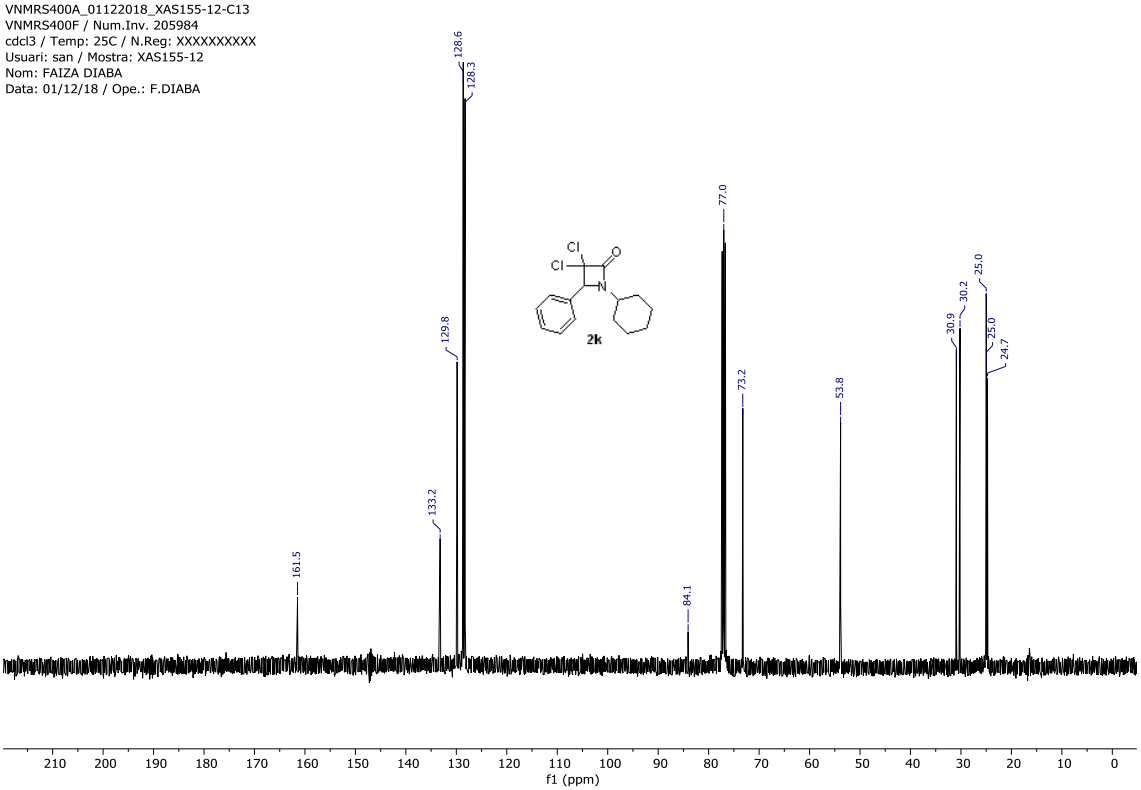
VNMRS400A_01122018_AS154-13-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS154-13
Nom: FAIZA DIABA
Data: 01/12/18 / Ope.: F.DIABA

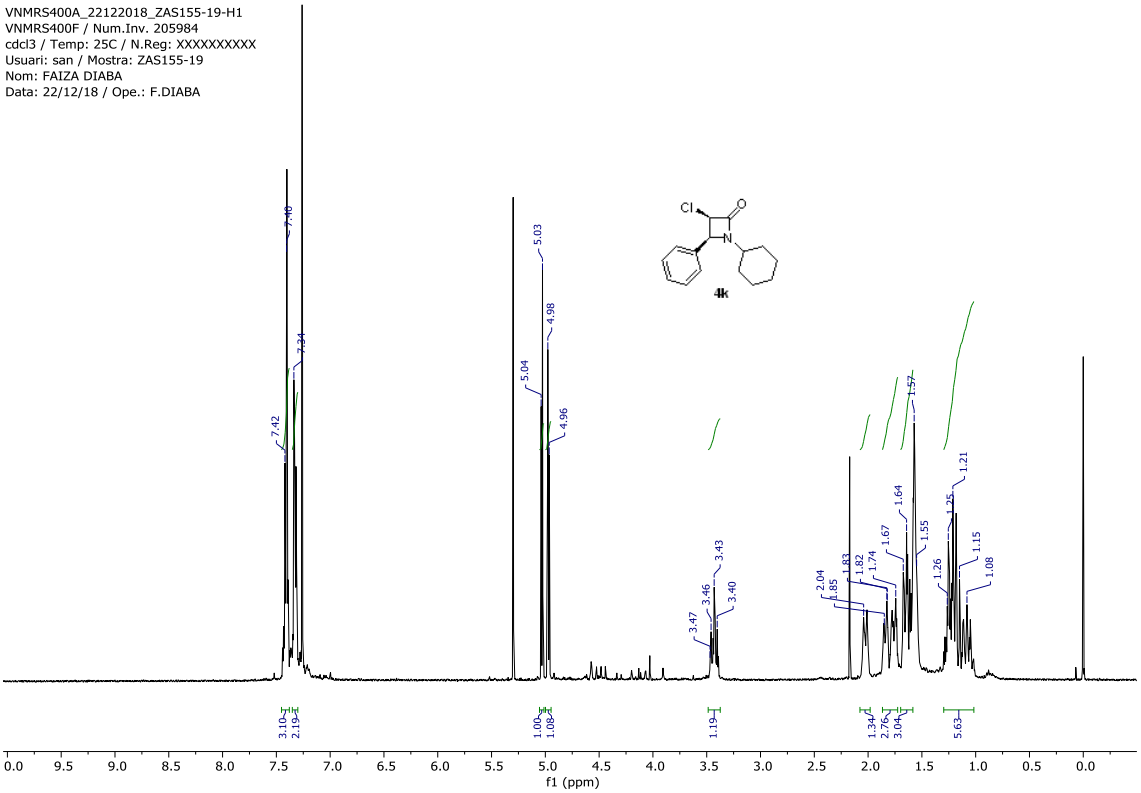


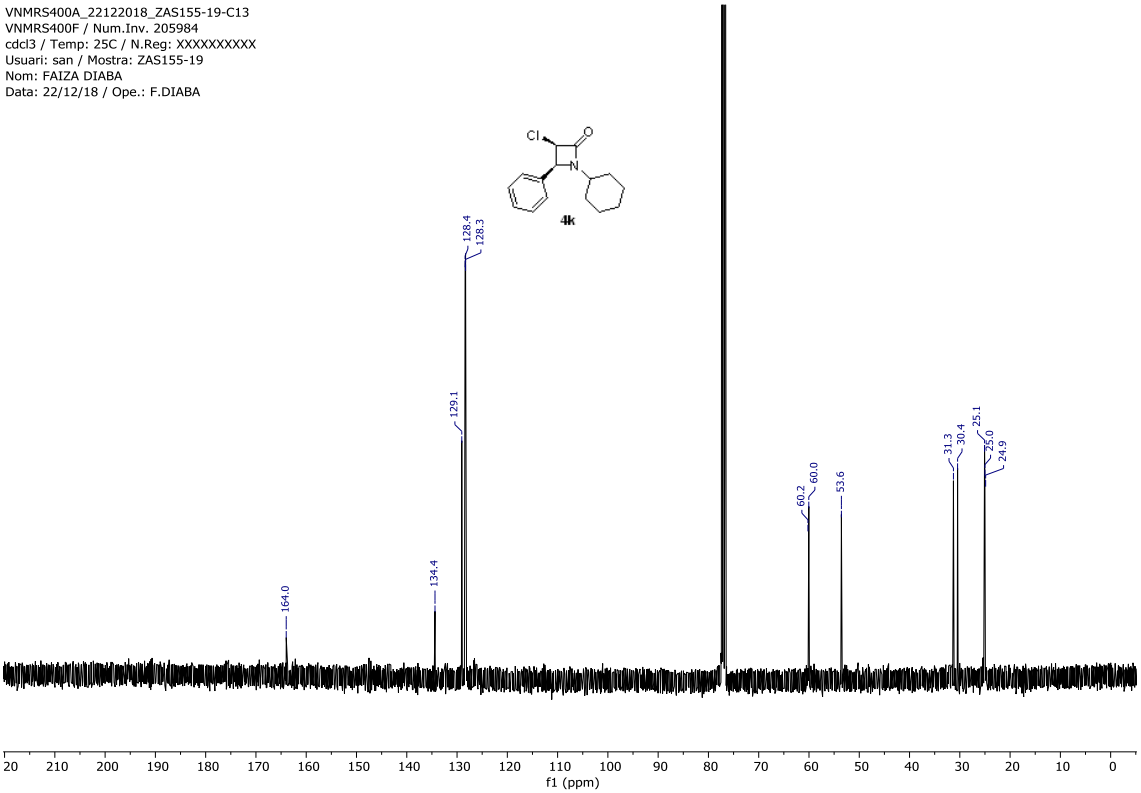

VNMRS400A_01122018_AS154-13-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS154-13
Nom: FAIZA DIABA
Data: 01/12/18 / Ope.: F.DIABA

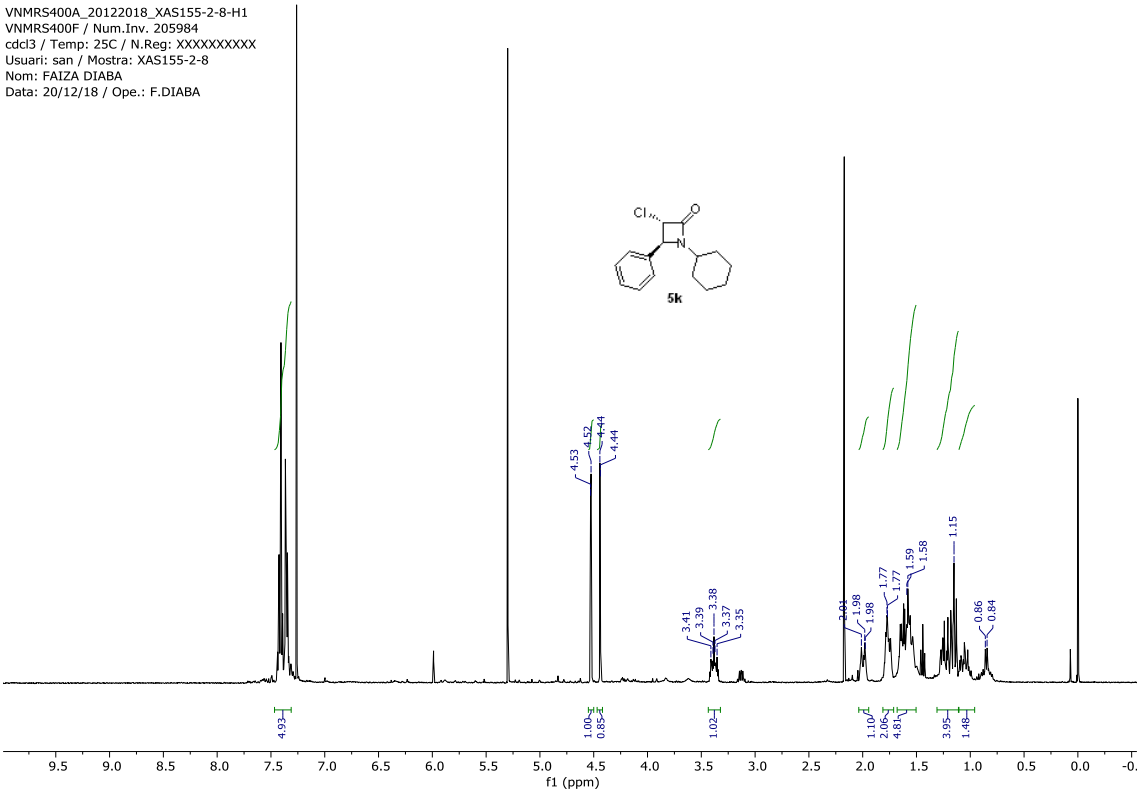



VNMRS400A_01122018_XAS155-12-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS155-12
Nom: FAIZA DIABA
Data: 01/12/18 / Ope.: F.DIABA
Cl
Cl
O
N
2k
7.44
7.46
7.36
7.34
5.05
3.40
3.43
3.37
2.17
2.08
1.88
1.81
1.78
1.70
1.61
1.32
1.28
1.31
1.24
1.17
1.14
1.12
5.18
1.00
1.10
1.19
5.99
4.59
f1 (ppm)


VNMRS400A_01122018_XAS155-12-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS155-12
Nom: FAIZA DIABA
Data: 01/12/18 / Ope.: F.DIABA
Cl
Cl
O
N
2k
128.6
128.3
129.8
133.2
161.5
84.1
77.0
73.2
53.8
30.9
30.2
25.0
25.0
24.7
f1 (ppm)


VNMRS400A_22122018_ZAS155-19-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ZAS155-19
Nom: FAIZA DIABA
Data: 22/12/18 / Ope.: F.DIABA
4k
f1 (ppm)


VNMRS400A_22122018_ZAS155-19-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ZAS155-19
Nom: FAIZA DIABA
Data: 22/12/18 / Ope.: F.DIABA
4k
f1 (ppm)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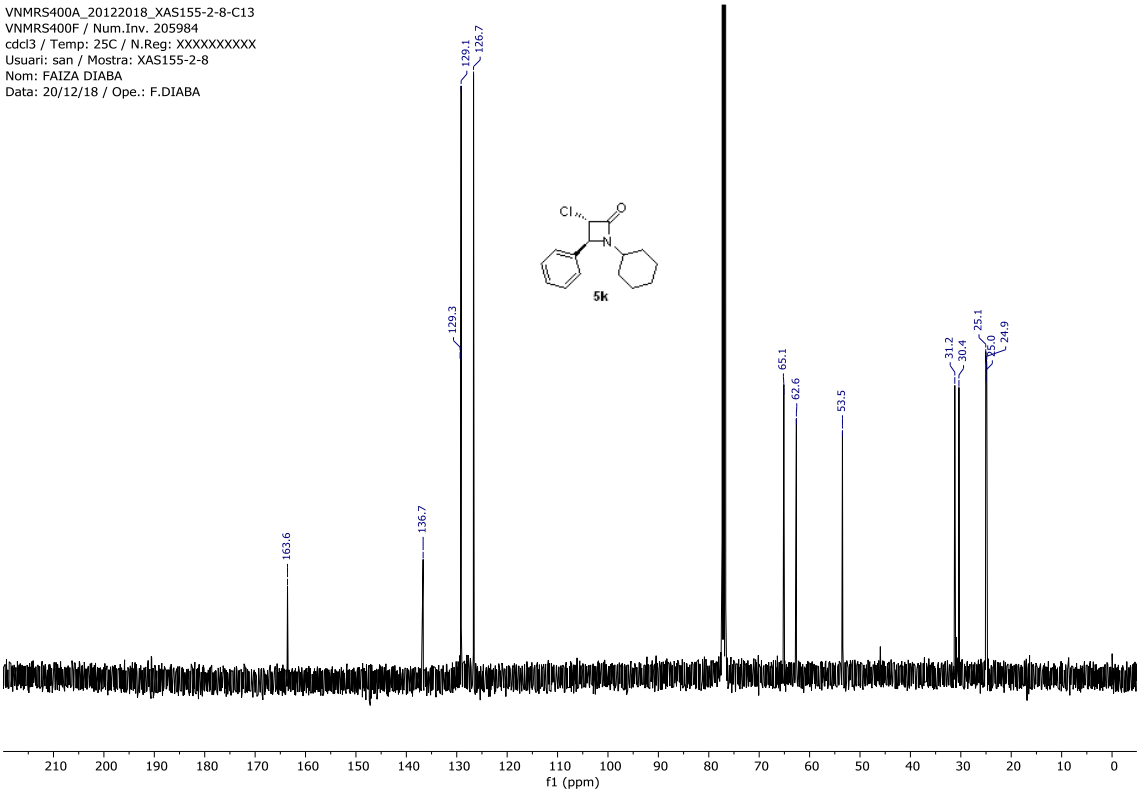
Data: 20/12/18 / Ope.: F.DIABA
5k
f1 (ppm)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Data: 20/12/18 / Ope.: F.DIABA
5k
f1 (ppm)

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Usuari: san / Mostra: AS051-9-24
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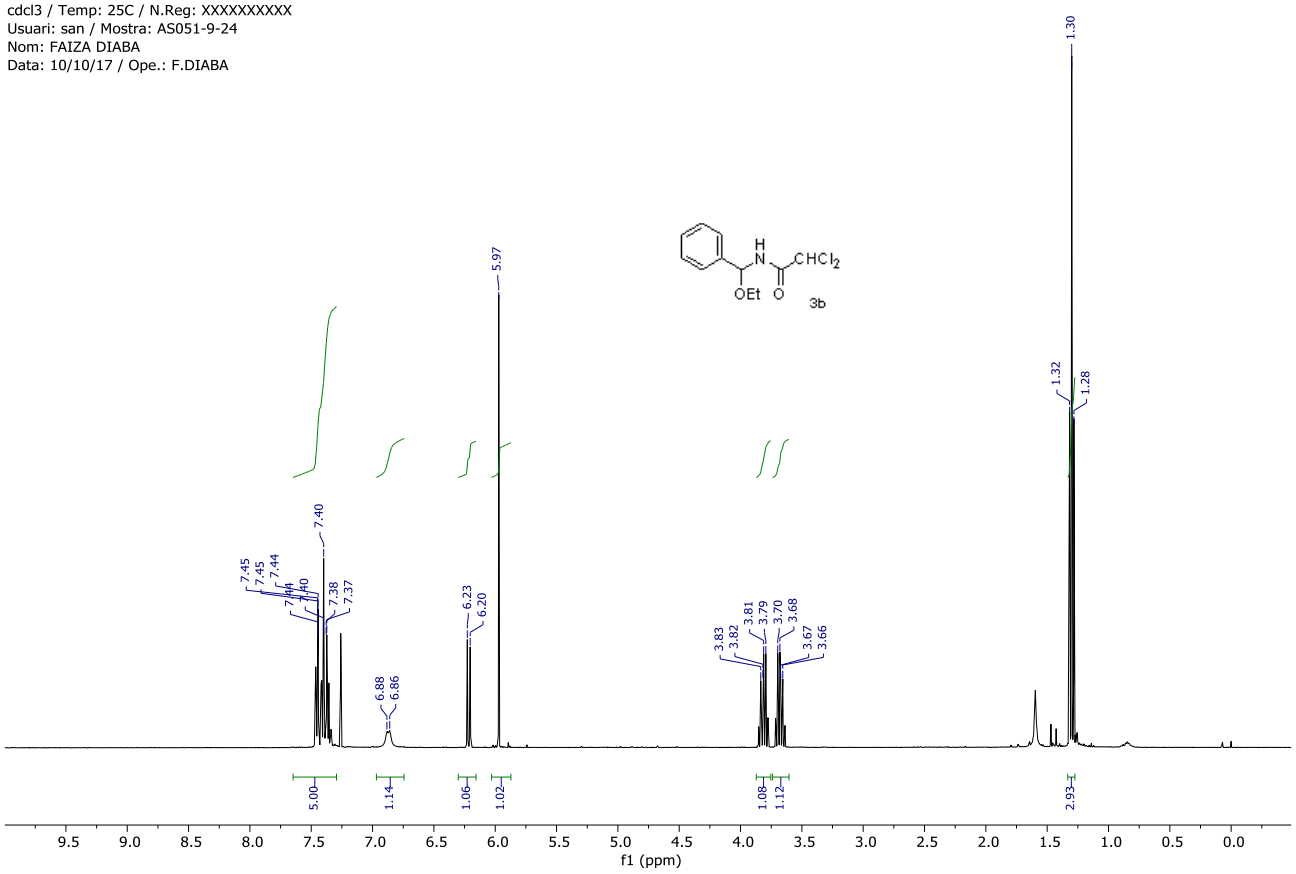
Data: 10/10/17 / Ope.: F.DIABA

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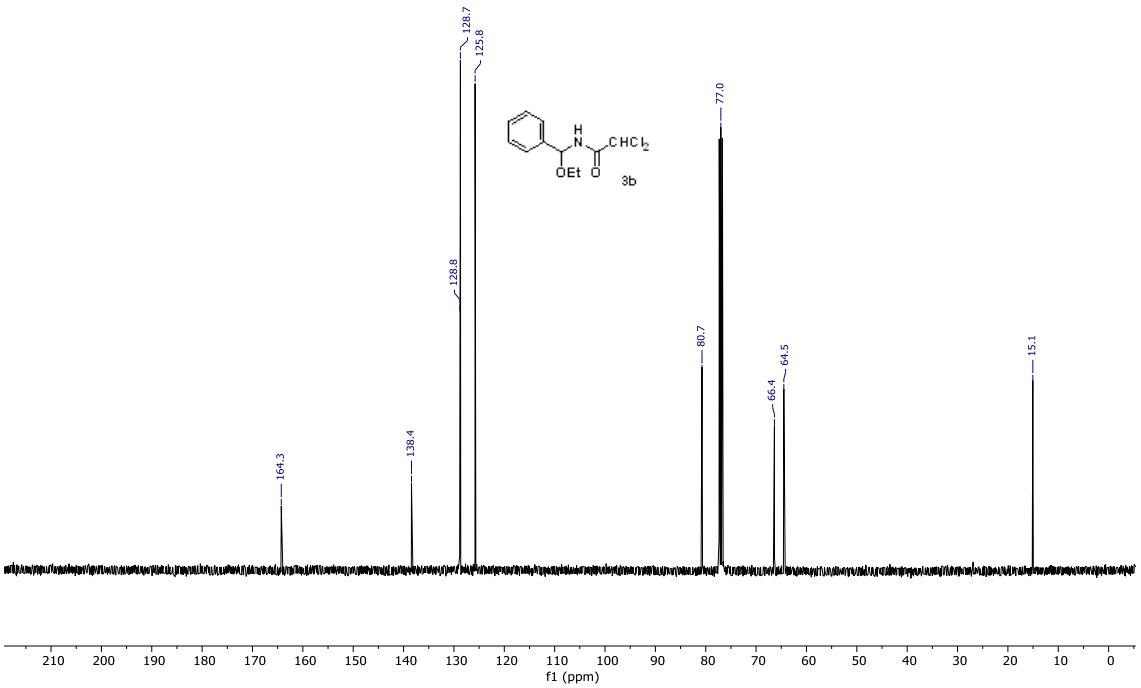
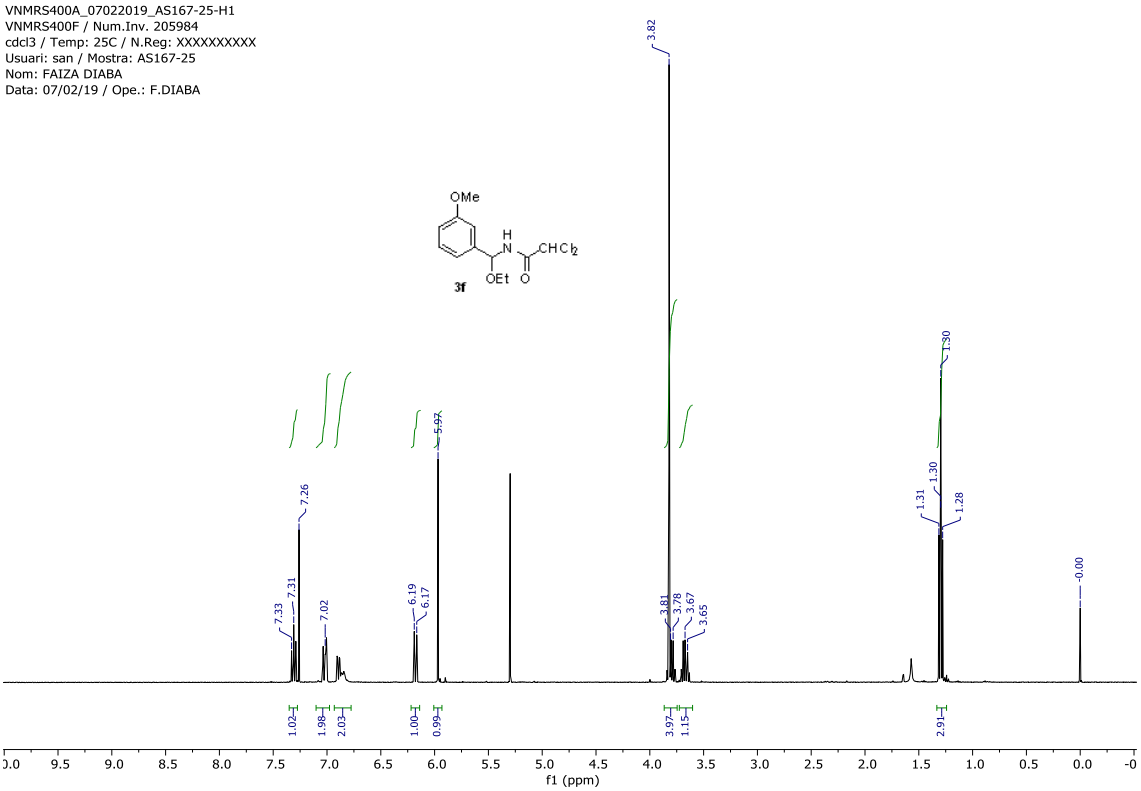
Nom: FAIZA DIABA
Data: 10/10/17 / Ope.: F.DIABA

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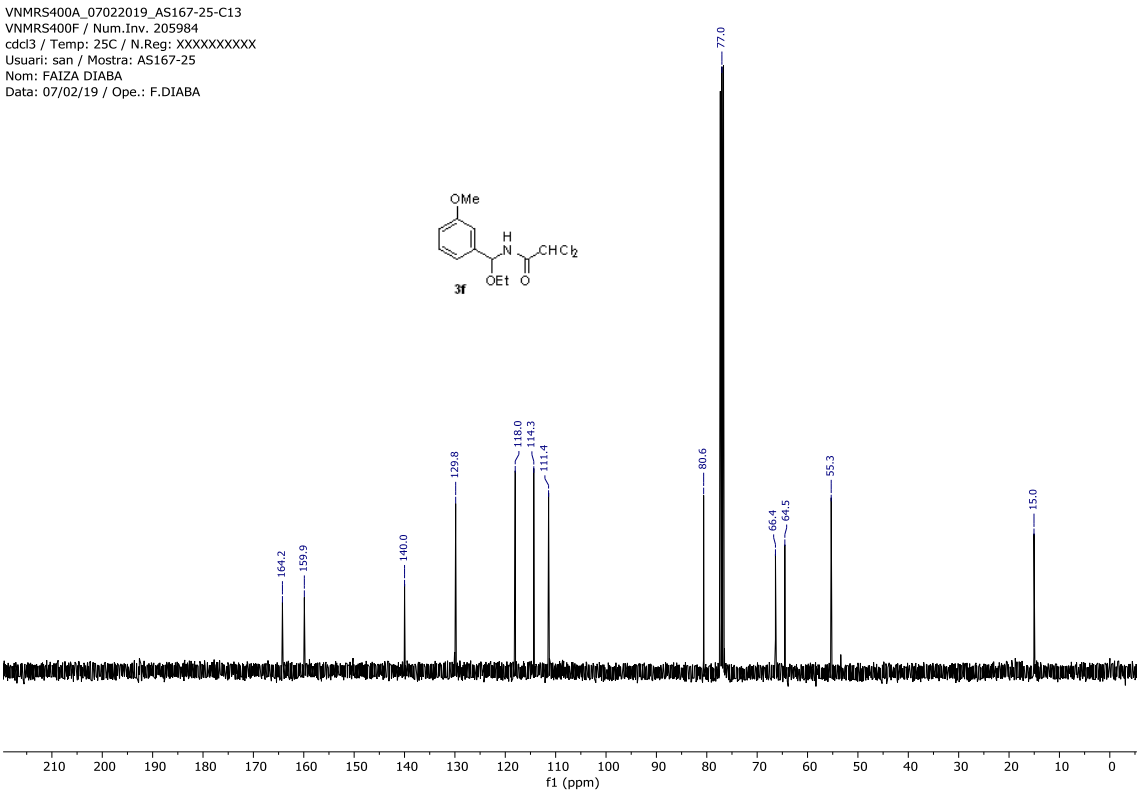
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS167-25
Nom: FAIZA DIABA
Data: 07/02/19 / Ope.: F.DIABA
OMe
H
N
CHCl2
OEt O
3f
3.82
1.30
5.97
7.26
1.31
1.30
1.28
7.33
7.31
7.02
6.19
6.17
3.81
3.78
3.67
3.65
-0.00
1.02
1.98
2.03
1.00
0.99
3.97
1.15
2.91
f1 (ppm)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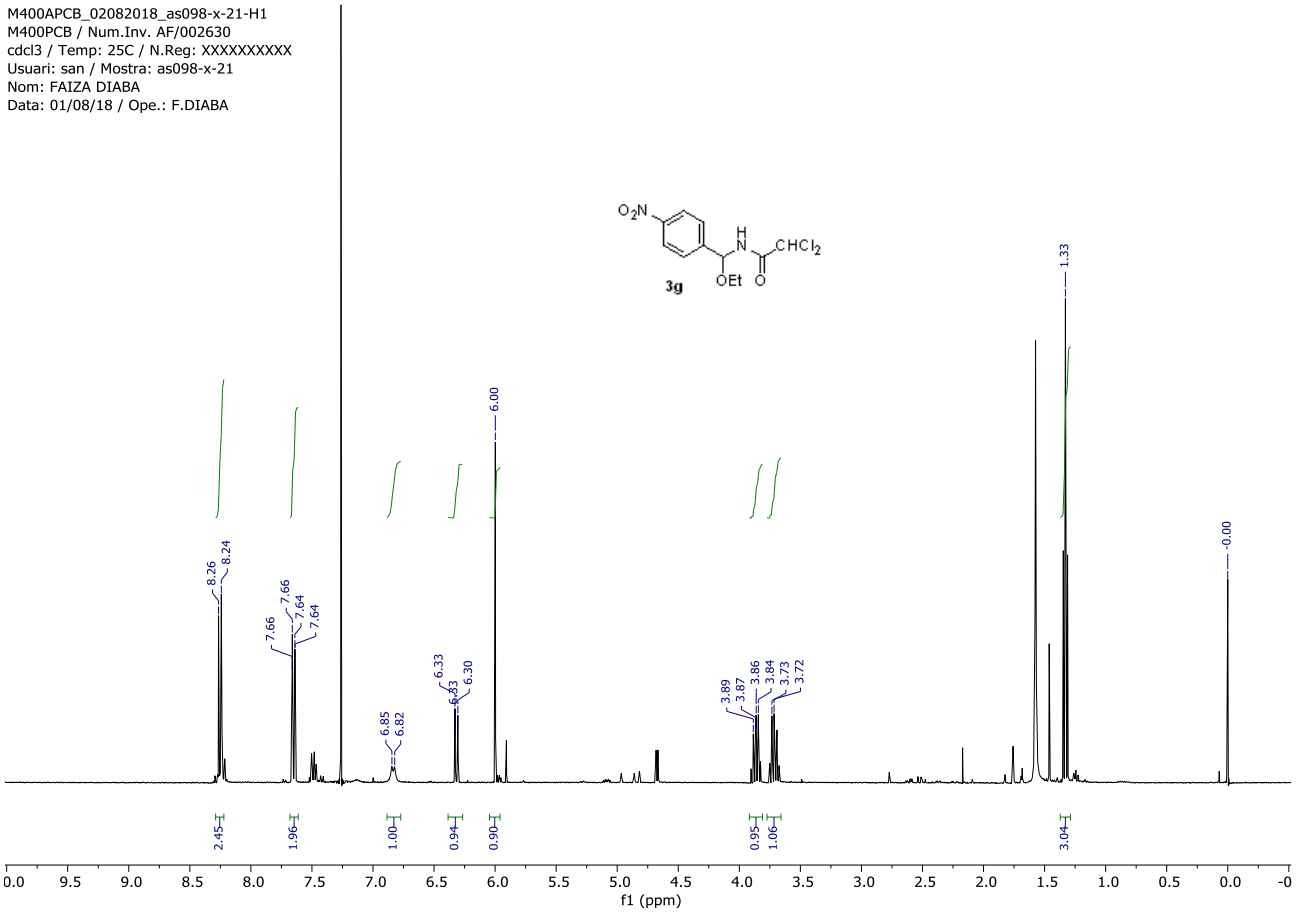
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS167-25
Nom: FAIZA DIABA
Data: 07/02/19 / Ope.: F.DIABA
OMe
H
N
CHCl2
OEt O
3f
77.0
118.0
114.3
111.4
129.8
80.6
55.3
66.4
64.5
15.0
164.2
159.9
140.0
f1 (ppm)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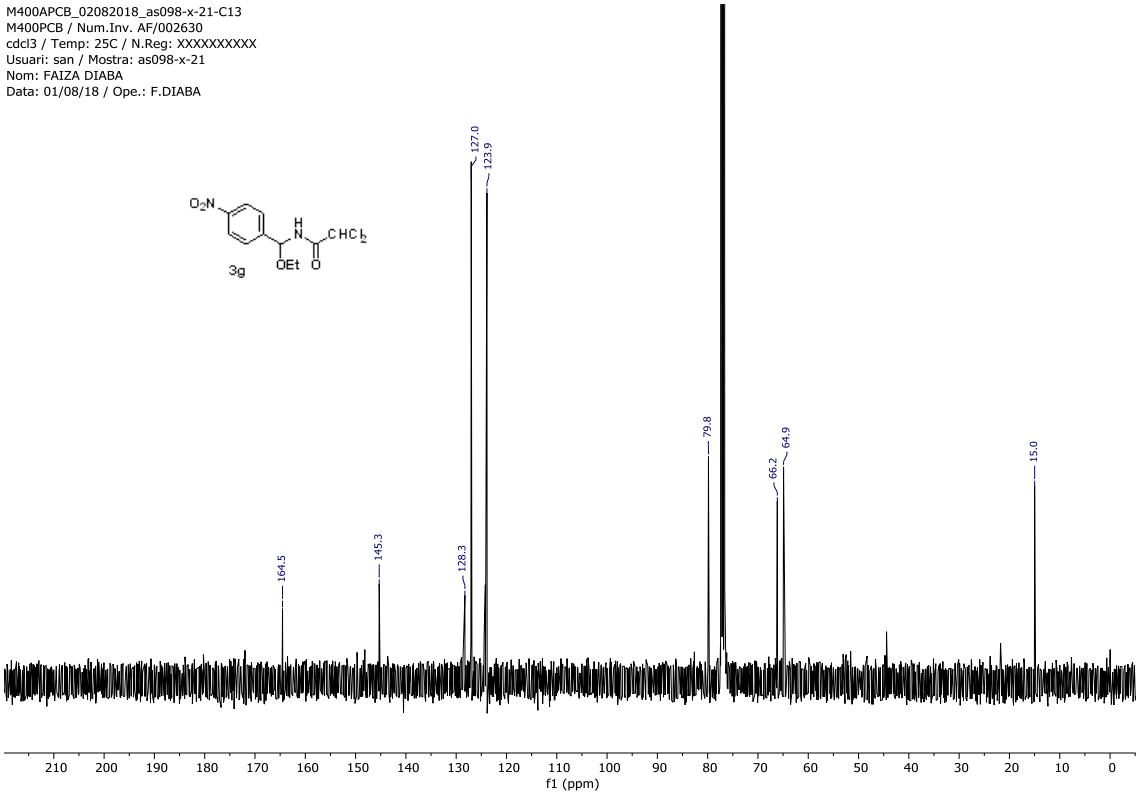
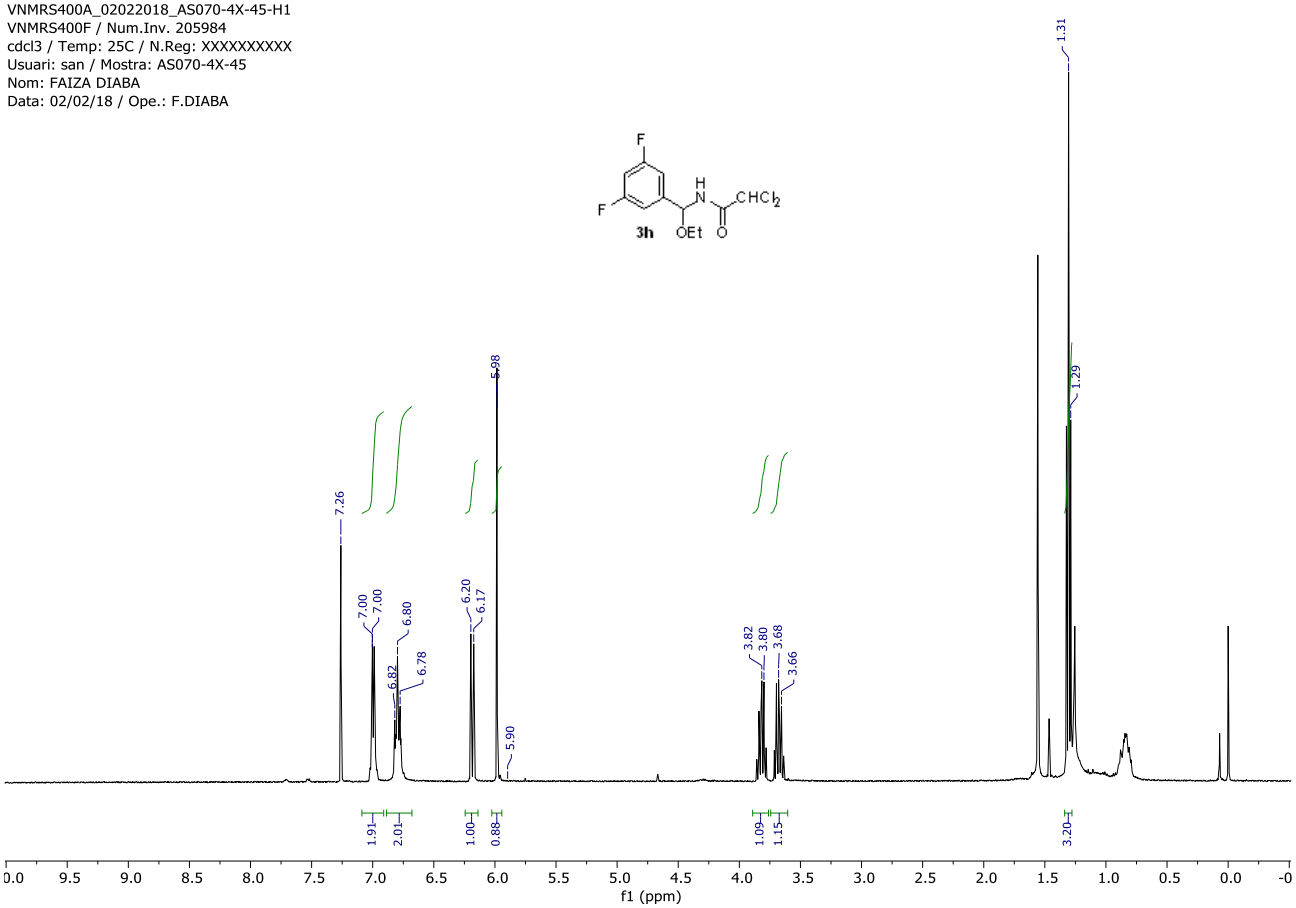
M400PCB / Num.Inv. AF/002630
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as098-x-21
Nom: FAIZA DIABA
Data: 01/08/18 / Ope.: F.DIABA
3g
8.26
8.24
7.66
7.66
7.64
7.64
6.85
6.82
6.33
6.33
6.30
6.00
3.89
3.87
3.86
3.84
3.73
3.72
1.33
-0.00
2.45
1.96
1.00
0.94
0.90
0.95
1.06
3.04
f1 (ppm)


M400APCB_02082018_as098-x-21-C13
M400PCB / Num.Inv. AF/002630
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as098-x-21
Nom: FAIZA DIABA
Data: 01/08/18 / Ope.: F.DIABA
3g
164.5
145.3
128.3
127.0
123.9
79.8
66.2
64.9
15.0
f1 (ppm)

VNMRS400A_02022018_AS070-4X-45-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS070-4X-45
Nom: FAIZA DIABA
Data: 02/02/18 / Ope.: F.DIABA




VNMRS400A_02022018_AS070-4X-45-C13
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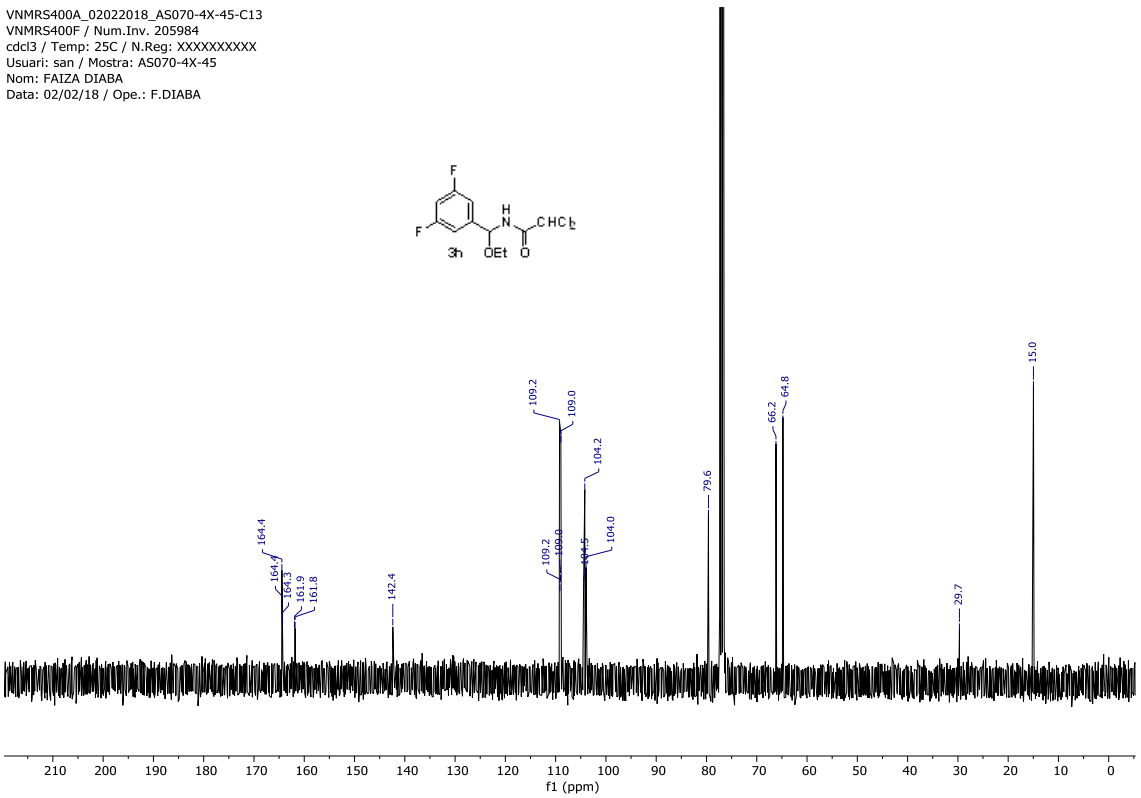
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS070-4X-45
Nom: FAIZA DIABA
Data: 02/02/18 / Ope.: F.DIABA



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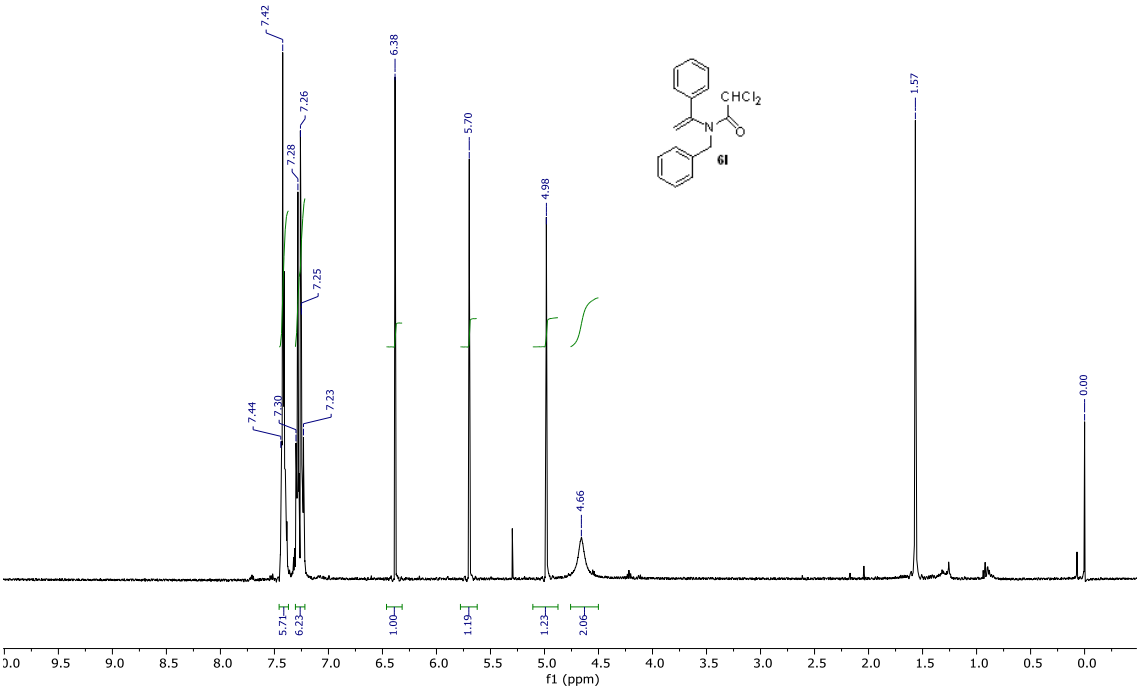
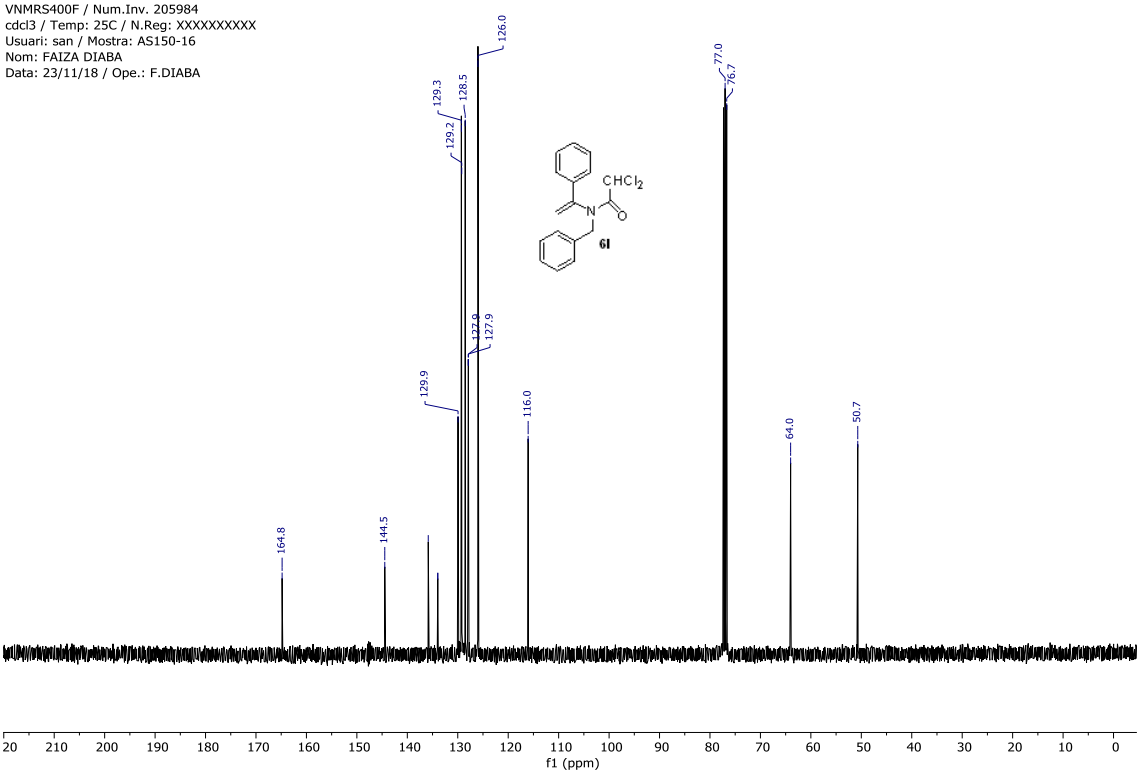
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS150-16
Nom: FAIZA DIABA
Data: 22/11/18 / Ope.: F.DIABA




VNMRS400A_23112018_AS150-16-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS150-16
Nom: FAIZA DIABA
Data: 23/11/18 / Ope.: F.DIABA

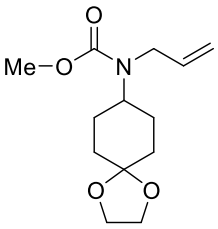


## *6.2. Experimental part of chapter 3*

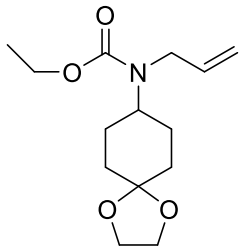
### 1. Synthesis of protected allylamines

- **Synthesis of 8a** and **8b**

For the preparation of **8a** and **8b** we followed the classical procedures reported in the literature[3] isolating **8a** (93%) and **8b** (98%).



***Methyl* allyl(1,4-dioxaspiro[4.5]decan-8-yl)carbamate (8a).** $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 1.57-1.84 (m, 4H, H-10, H-9), 3.70 (s, 4H, H-6, H-7), 3.79 (brs, 2H, $CH_2N$), 3.92-3.96 (m, 4H, H-8, $CH_3$), 3.98-4.19 (zm, 2H, H-2, H-3), 5.07 (d, *J* = 10.3, 1H, $CH_2CH$), 5.13 (d, *J* = 17.5 Hz, 1H, $CH_2CH$), 5.70-5.90 (m, 1H, $CHCH_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 27.8 ($CH_2Ar$), 34.0 ($CH_2Ar$), 44.8 ($CH_2N$), 52.5 ($CH_3$), 64.2 (CHAr), 64.3 (C-2, C-3), 107.7 (CAr), 115.6 ($CH_2CH$), 135.8 ($CHCH_2$), 156.7 (CO).



***Ethyl* allyl(1,4-dioxaspiro[4.5]decan-8-yl)carbamate (8b).** IR (NaCl, neat): 3080, 2879, 1694, 1467, 1448, 1413 $cm^{-1}$; $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, *J* = 7.08 Hz, 3H, $CH_3$), 1.53-1.74 (m, 4H, H-10, H-9), 1.74-1.92 (m, 4H, H-6, H-7), 3.75 (brs, 2H, $CH_2N$), 3.93 (m, 5H, H-8, H-2, H-3), 4.14 (q, *J* = 6.3 Hz, 2H, $CH_2O$), 5.07 (dd, *J* = 10.3, 1.8 Hz, 1H, $CH_2CH$), 5.13 (d, *J* = 17.2 Hz, 1H, $CH_2CH$), 5.79 (tt, *J* = 10.3, 5.1 Hz, 1H, $CHCH_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 14.6 ($CH_3$), 27.8 ($CH_2Ar$), 34.0 ($CH_2Ar$), 44.8 ($CH_2N$), 61.1 ($CH_2O$), 64.2 (CHAr), 64.3 (C-2, C-3), 107.8 (CAr), 115.5 ($CH_2CH$), 135.9 ($CHCH_2$), 156.2 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{24}NO_4$ $[M+H]^+$ 270.1700; found 270.1705.

- **Synthesis of 9a-9e**

For the preparation of **9a**-**9e** we followed the same procedures reported in ref.3 isolating **9a** (73%), **9b** (84%), **9c** (99%) and **9d** (91%), **9e** (93%).

[3] Diaba, F.; Montiel, J. A.; Serban, G.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 3860−3863.

**Methyl allyl (4-oxocyclohexyl) carbamate (9a).** IR (NaCl, neat): 3081, 2955, 2873, 2360, 2341, 1698, 1546, 1469 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.81-2.00 (m, 2H, H-6), 2.00-2.15 (m, 2H, H-2), 2.35-2.54 (m, 4H, H-3, H-5), 3.73 (s, 3H, $CH_3O$), 3.82 (s, 2H, $CH_2N$), 4.39 (bs, 1H, H-1), 5.03-5.23 (m, 2H, $CH_2CH$), 5.8 (ddt, *J* = 16.17, 10.62 Hz, $CHCH_2$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 29.8 ($CH_2Ar$), 39.9 ($CH_2Ar$), 45.8 ($CH_2N$), 52.6 ($CH_3O$), 54.0 (CHAr), 116.1 ($CH_2CH$), 135.4 ($CHCH_2$), 156.4 (CO), 209.5 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$ 212.1281; found 212.1280.

**Ethyl allyl (4-oxocyclohexyl) carbamate (9b).** IR (NaCl, neat): 3081, 2956, 1693, 1469, 1450, 1414 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.28 (td, *J* = 7.12, 2.78 Hz, 3H, $CH_3$), 1.94 (d, *J* = 14.45 Hz, 2H, H-6), 2.00-2.10 (m, 2H, H-2), 2.36-2.54 (m, 4H, H-3, H-5), 3.81 (s, 2H, $CH_2N$), 4.18 (qd, *J* = 7.10, 2.72 Hz, 2H, $CH_2O$), 4.42 (bs, 1H, H-1), 5.06-5.20 (m, 2H, $CH_2CH$), 5.80 (dtt, *J* = 15.68, 5.48, 2.64 Hz, $CHCH_2$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 14.6 ($CH_3$), 29.9 ($CH_2Ar$), 40.0 ($CH_2Ar$), 45.7 ($CH_2N$), 53.8 (CHAr), 61.4 ($CH_2O$), 116.1 ($CH_2CH$), 135.5 ($CHCH_2$), 156.0 (CO), 209.6 (CAr)**.** HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{20}NO_3$ $[M+H]^+$ 226.1438; found 226.1437.

***tert*-Butyl allyl(4-oxocyclohexyl)carbamate (9c).** IR (NaCl, neat): 3081, 3005, 2974, 2872, 1720, 1693, 1654, 1454 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.47 (s, 9H, *t*-Bu), 2.00-2.09 (m, 4H, H-2, H-6), 2.35-2.53 (m, 4H, H-3, H-5), 3.75 (s, 2H, $CH_2N$), 4.44 (bs, 1H, H-1), 5.01-5.18 (m, 2H, $CH_2CH$), 5.70-5.86 (m, 1H, $CHCH_2$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 28.4 ($CH_3$), 30.01 ($CH_2Ar$), 40.1 ($CH_2Ar$), 45.7 ($CH_2N$), 53.4 (C-1), 80.0 (CCH3), 115.7 ($CH_2CH$), 135.8 ($CHCH_2$), 155.2 (CO), 209.8 (C-4). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{24}NO_3$ $[M+H]^+$ 254.1751; found 254.1754.

***N*-Allyl-*N*-(4-oxocyclohexyl)benzamide (9d).** IR (NaCl, neat): 3061, 2955, 2360, 2341, 1715, 1632, 1494, 1412 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.11 (s, 4H, H-2, H-6), 2.45 (s, 4H, H-3, H-5), 3.92 (s, 2H, $CH_2N$), 4.77 (bs, 1H, H-1), 5.15 (d, *J* = 10.42 Hz, 2H, $CH_2CH$), 5.79 (bs, 1H, $CHCH_2$), 7.34-7.47 (m, 5H, CHPh); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 29.6 ($CH_2Ar$), 39.9 ($CH_2Ar$), 49.0 ($CH_2N$), 53.1 (C-1), 117.0 ($CH_2CH$), 126.2(CHPh), 128.5(CHPh), 129.5(CPh), 135.2 ($CHCH_2$), 136.9 (CO), 209.5 (C-4). HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1485; found 258.1488.

***N*-Allyl-4-methyl-*N*-(4-oxocyclohexyl)benzenesulfonamide (9e).** IR (NaCl, neat): 3069, 2955, 2872, 2359, 1716, 1641, 1597, 1494 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.82-1.96 (m, 4H, H-2, H-6), 2.32-2.42 (m, 4H, H-3, H-5), 2.43 (s, 3H, $CH_3$), 3.84 (d, *J* = 6.06, 1.49 Hz, 2H, $CH_2N$), 4.22 (m, 1H, H-1), 5.11 (dq, *J* = 10.19, 1.35 Hz, 1H, $CH_2CH$), 5.19 (dq, *J* = 17.16, 1.24 Hz, 1H, $CH_2CH$), 5.74-5.89 (m, 1H, $CHCH_2$), 7.70-7.75 (m, 2H, CHAr), 7.28-7.34 (m, 2H, CHAr); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 21.5 (CH3), 30.03 ($CH_2Ar$), 40.0 ($CH_2Ar$), 46.6 ($CH_2N$), 56.7 (C-1), 80.0 (CCH3), 117.4 ($CH_2CH$), 126.9(CHAr), 129.8(CHAr), 136.0 ($CHCH_2$), 138.0 (CS), 143.4 ($CCH_3$), 208.7 (C-4). HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{22}NO_3S$ $[M+H]^+$ 308.1315; found 308.1312.

- **Synthesis of 14a and 14b**

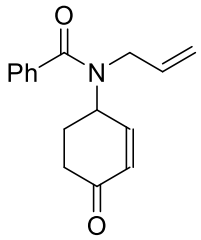
Allylamines **14a** and **14b** were prepared from **9a** and **9d** reapectively following the experimental reported previously [4] isolating **14a** (75%) and **14b** (82%)

**Methyl allyl(4-oxocyclohex-2-en-1-yl)carbamate (14a).** IR (NaCl, neat): 3364, 2981, 2361, 1689, 1455, 1410, 1382 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.27 (tdf, *J* = 7.09, 1.84 Hz, 1H, H-6) 2.19 (bs, 1H, H-6), 2.19 (s, 1H, H-5), 2.4-2.6 (m, 1H, H-5), 3.82 (s, 3H, $CH_3$), 4.19 (qd, *J* = 7.08, 1.67 Hz, 2H, $CH_2N$), 4.7 (s, 1H, H-1), 4.99 (bs, 1H,

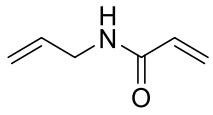
[4] Nicolaou, K. C.; Montagnon, T.; Baran, P. S. ; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245-2258.

$CH_2CH$), 5.16 (d, *J* = 11.05 Hz, 1H, $CH_2CH$), 5.76-5.91 (m, 1H, $CHCH_2$), 6.04 (d, *J* = 10.31 Hz, 1H, H-3), 6.85 (dft, *J* = 10.34, 1.43 Hz, 1H, H-2); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 14.6 (C-6), 36.9 (C-5), 47.2 ($CH_2N$), 54.1 ($CH_3$), 61.7 (CHAr), 116.6 ($CH_2CH$), 130.6 (C-3), 134.9 ($CHCH_2$), 152.2 (H-2), 156.0 (CO), 197.9 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$ 224.1281; found 224.1284.

***N*-Allyl-*N*-(4-oxocyclohex-2-en-1-yl) benzamide (14b).** IR (NaCl, neat): 3059, 2954, 1683, 1633, 1601, 1577, 1493, 1405 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 1H, H-6), 2.46 (s, 1H, H-6), 2.59 (s, 2H, H-5), 3.89 (d, *J* = 15.25 Hz, 2H, $CH_2N$), 4.77 (bs, 1H, H-1), 5.20 (dt, *J* = 10.36, 1.34 Hz, 2H, $CH_2CH$), 5.78 (bs, 1H, H-2), 6.07 (ddd, *J* = 10.32, 2.84, 1.08 Hz, 1H, H-3), 6.94 (s, 1H, $CHCH_2$), 7.39-7.47 (m, 5H, CHPh); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 27.6 (C-6), 36.9 (C-5), 50.3 ($CH_2N$), 53.4 (C-1), 117.9 ($CH_2CH$), 126.5 (CHPh), 128.6 (CHPh), 129.9 (C-3), 134.3 (C-2), 135.9 (CPh), 152.3 ($CHCH_2$), 172.0 (CO), 197.5 (C-4)**.** HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332; found 256.1326.

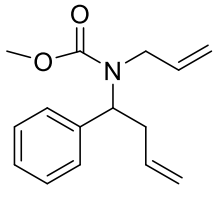



- **Synthesis of *N*-allylacrylamide (14c)**




**14c** was prepared from acryloyl chloride and allylamine following the experimental reported previously.[5]

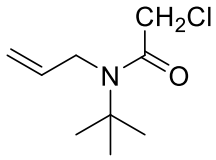
**Methyl allyl(1-phenylbut-3-en-1-yl)carbamate (14d).** IR (NaCl, neat): 3077, 3029, 2979, 2953, 1698, 1642, 1602, 1454 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.73 (m, 2H, $CH_2CHN$), 3.55 (dd, *J* =15.95, 6.58 Hz, 1H, $CH_2N$), 3.66 (s, 1H, $CH_2N$), 3.72 (s, 3H, $CH_3$), 4.89-5.00 (m, 2H, $CH_2CH$), 5.03-5.16 (m, 2H, $CH_2CH$), 5.40 (s, 1H, CHN), 5.51-5.68 (m, 1H, $CHCH_2$), 5.79 (ddt, *J* =17.01, 10.22, 6.74 Hz, 1H, $CHCH_2$), 7.26 (t, *J* =4.49 Hz, 3H, CHAr), 7.32 (d, *J* =4.93 Hz, 2H, CHAr); $^{13}C$ NMR




[5] Qu, Q.; Liu, G.; Lv, X.; Zhang, B.; An, Z. *ACS Macro Lett.* **2016**, *5*, 316−320.

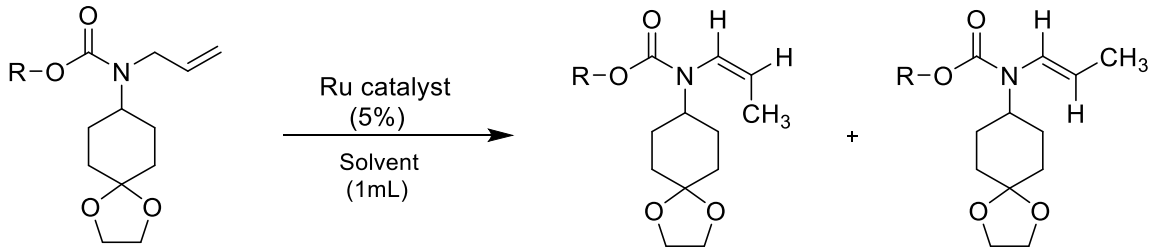
($CDCl_3$, 100 MHz): δ 35.5 ($CH_2CHN$), 46.2 ($CH_2N$), 52.6 ($CH_3$), 58.5 (CHN), 116.0 ($CH_2CH$), 117.4 ($CH_2CH$), 127.5 (CHAr), 128.0 (CHAr), 128.3 (CHAr), 134.9 ($CHCH_2$), 135.3 ($CHCH_2$), 139.7 (CO), 157.1 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1489; found 246.1481.

- **Synthesis of *N*-Allyl-*N*-(*tert*-butyl)-2-chloroacetamide (14e).**



**14e** was prepared following the procedure reported in the literature.[6]

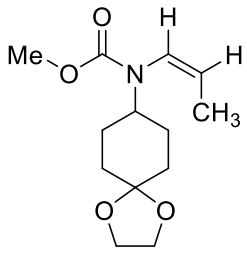
2. **General procedure for the isomerization of protected allylamines 8a and 8b in the presence of Ru catalysts**




$R_1$= MeO **(8a)**, EtO **(8b)** **10a, 10b** **11a, 11b**

In a 10 mL vessel allylamine **8** was placed (0.443 mmol) and ruthenium catalyst (0.022 mmol, 5%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 45 min at 120 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) **10** and/or **11** were isolated.

**Methyl (*Z*)-prop-1-en-1-yl(1,4-dioxaspiro[4.5]decan-8-yl)carbamate (10a).** IR

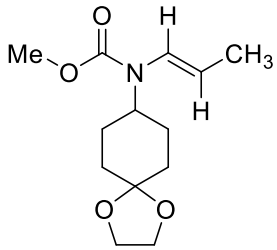


(NaCl, neat): 3032, 2949, 2878, 1698, 1659, 1446, 1398 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.54 (dd, *J* = 6.86, 1.79 Hz, 3H, $CH_3CH$), 1.62-1.81 (m, 8H, $CH_2Ar$), 3.70 (s, 3H, $CH_3O$), 3.93 (s, 4H, H-2, H-3), 4.10 (bs, 1H, H-8), 5.53-5.64 (m, 1H, $CHCH_3$), 6.15 (dq, *J* = 7.94, 1.81 Hz, 1H, CHN); $^{13}C$ NMR

[6] Zhang, Z.; Zhu, L.; Li, C. *Chin. J. Chem.* **2019**, *37*, 452-456.

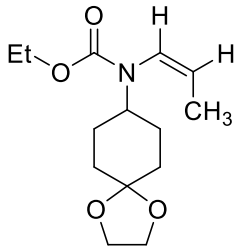
($CDCl_3$, 100 MHz): δ 12.5 ($CH_3CH$), 27.2($CH_2Ar$), 33.8($CH_2Ar$), 52.7 ($CH_3O$), 54.9 (CHAr), 64.3 (C-2), 64.3 (C-3), 107.8 (CAr), 123.4 (CHN), 127.2 ($CHCH_3$), 155.3 (CO); HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{22}NO_4$ $[M+H]^+$ 256.1543; found 256.1543.

**Methyl (*E*)-prop-1-en-1-yl(1,4-dioxaspiro[4.5]decan-8-yl)carbamate (11a).** IR



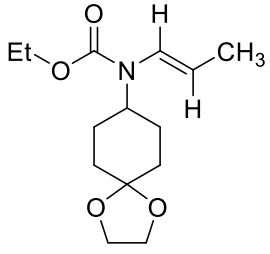
(NaCl, neat): 3383, 2935, 2360, 2341, 1704, 1662, 1443 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.62-1.68 (m, 4H, H-10, H-9), 1.71 (dd, *J* = 6.67, 1.67 Hz, 3H, $CH_3CH$), 1.74-1.83 (m, 2H, H-6), 1.93-2.08 (m, 2H, H-7), 3.72 (s, 3H, $CH_3O$), 3.92-3.97 (m, 4H, H-2, H-3), 3.94 (s, 1H, H-8), 5.40 (dq, *J* = 13.48, 6.67 Hz, 1H, $CHCH_3$), 6.15 (d, *J* = 14.08 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 15.5 ($CH_3CH$), 27.3 ($CH_2Ar$), 34.1 ($CH_2Ar$), 52.7 ($CH_3O$), 55.2 (CHAr), 64.3 (C-2, C-3), 107.8 (CAr), 117.1 ($CHCH_3$), 125.8 (CHN), 155.4 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{22}NO_4$ $[M+H]^+$ 256.1543; found 256.1543.

**Ethyl (*Z*)-prop-1-en-1-yl(1,4-dioxaspiro[4.5]decan-8-yl)carbamate (10b).** IR



(NaCl, neat): 3029, 2954, 2871, 1716, 1694, 1660, 1531 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.27 (td, *J* = 7.08, 6.64 Hz, 3H, $CH_3CH_2$), 1.56 (dd, *J* = 6.86, 1.78 Hz, 3H, $CH_3CH$), 1.80-1.97 (m, 2H, H-10), 2.00-2.14 (m, 2H, H-9), 2.36-2.50 (m, 4H, H-6, H-7), 2.51 (dd, *J* = 14.25, 5.9 Hz, 4H, H-2, H-3), 4.17 (qt, *J* = 7.13, 1.12 Hz, 2H, $CH_2O$), 4.52 (t, *J* = 12.25 Hz, 1H, H-8), 5.6 (dq, *J* = 7.85, 6.85 Hz, 1H, $CHCH_3$), 5.75 (dq, *J* = 7.84, 1.76 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 12.6 ($CH_3CH$), 14.7 ($CH_3CH_2$), 29.3 ($CH_2Ar$), 39.8 ($CH_2Ar$), 40.0 (C-2, C-3), 54.0 (CHAr), 61.6 ($CH_2O$), 108.4 (CAr), 123.1 (CHN), 127.5 ($CHCH_3$), 154.8 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{24}NO_4$ $[M+H]^+$ 270.1700; found 270.1703.

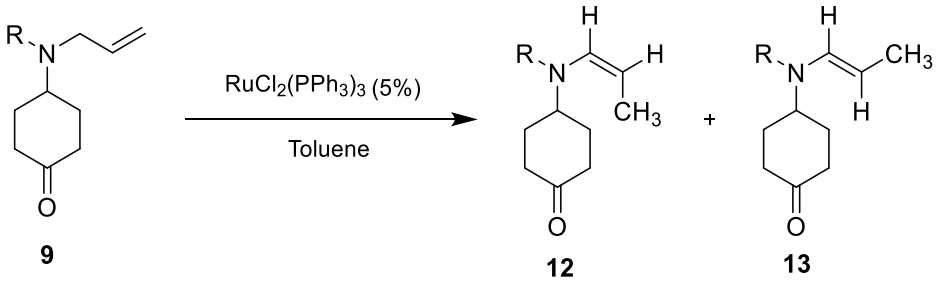
**Ethyl (*E*)-prop-1-en-1-yl(1,4-dioxaspiro[4.5]decan-8-yl)carbamate.(11b)** IR



(NaCl, neat): 2940, 2880, 1703, 1662, 1465, 1432, 1411, 1371 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.28 (tt, *J* = 7.08, 1.15 Hz, 3H, $CH_3CH_2$), 1.57-1.68 (m, 4H, H-10, H-9), 1.64-1.74 (m, 3H, $CH_3CH$), 1.74-1.84 (m, 2H, H-6), 1.96-2.11 (m, 2H, H-7), 3.88-4.01 (m, 5H, H-8, H-2, H-3), 4.16 (qt, *J* = 7.13,

1.12 Hz, 2H, $CH_2O$), 5.38 (dqd, *J* = 13.42, 6.68, 1.45 Hz, 1H, $CHCH_3$), 6.19 (d, *J* = 14.20 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 14.6 ($CH_3CH_2$), 15.6 ($CH_3CH$), 27.2 ($CH_2Ar$), 34.2 ($CH_2Ar$), 55.1 (CHAr), 61.5 ($CH_2O$), 64.3 (C-2), 64.3 (C-3), 107.8 (CAr), 115.7 ($CHCH_3$), 126.0 (CHN), 154.9 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{24}NO_4$ $[M+H]^+$ 270.1700; found 270.1707.

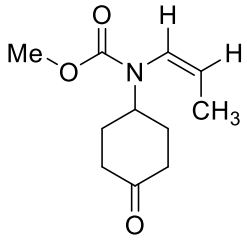
3. **General procedure for the isomerization of protected allylamines 9a-9d in the presence of $RuCl_2(PPh_3)_3$**




R = MeO (**9a**), EtO (**9b**)
*t*-BuO (**9c**), Ph (**9d**), Ts (**9e**)

In a 10 mL vessel allylamine **9** was placed (0.443 mmol) and ruthenium catalyst (0.022 mmol, 5%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 45-75 min at 120 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) 1**2** and/or **13** were isolated.

**Methyl (*Z*)-(4-oxocyclohexyl)(prop-1-en-1-yl)carbamate. (12a)** IR (NaCl, neat): 3346, 3029, 2953, 2869, 1715, 1658, 1531, 1447 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.56 (dd, *J* = 6.84, 1.75 Hz, 3H, $CH_3CH$), 1.80-1.96 (m, 2H, H-6), 2.04-2.13 (m, 2H, H-2), 2.36-2.55 (m, 4H, H-3, H-5), 3.73 (s, 3H, $CH_3O$), 4.51 (t, *J* = 12.17 Hz, 1H, H-1), 5.62 (dq, *J* =7.82, 6.83 Hz, 1H, $CHCH_3$), 5.75 (dq, *J* =7.82, 1.77 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 12.5 ($CH_3CH$), 29.3 ($CH_2Ar$), 39.8 ($CH_2Ar$), 52.9 ($CH_3O$), 54.2 (CHAr), 123.1 ($CH_2CH$), 127.8 (CHAr), 155.3 (CO), 209.5 (CAr); HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$ 212.1281; found 212.1276.



**Methyl (*E*)-(4-oxocyclohexyl)(prop-1-en-1-yl)carbamate (13a).** IR (NaCl, neat): 3355, 2955, 2885, 1713, 1663, 1530, 1445 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.72 (dd, *J* = 6.68, 1.68 Hz, 3H, $CH_3CH$), 1.98-2.08 (m, 2H, H-6), 2.13-2.28 (m, 2H, H-2), 2.38-2.52 (m, 4H, H-3, H-5), 3.74 (s, 3H, $CH_3O$), 4.33 (tt, *J* = 11.92, 3.97 Hz, 1H, H-1), 5.36 (dq, *J* =14.13, 6.68 Hz, 1H, $CHCH_3$), 6.22 (d, *J* =14.09 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 15.4 ($CH_3CH$), 29.1 ($CH_2Ar$), 40.0 ($CH_2Ar$), 52.8 ($CH_3O$), 54.5 (CHAr), 116.7 ($CH_2CH$), 126.2 (CHAr), 155.1 (CO), 209.7 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$ 212.1281; found 212.1276.

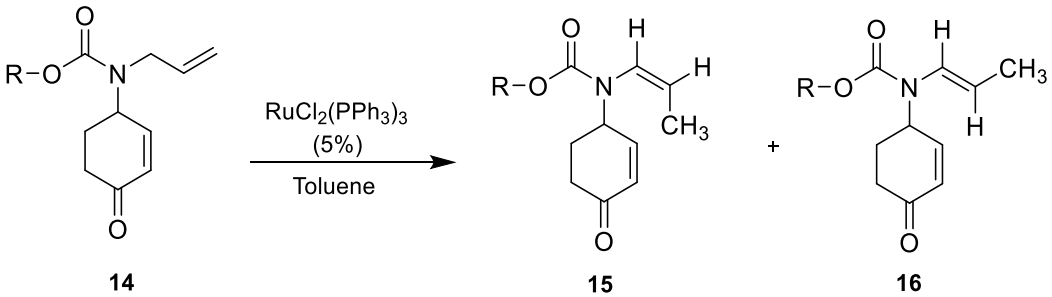
**Ethyl (*Z*)-(4-oxocyclohexyl)(prop-1-en-1-yl)carbamate (12b).** IR (NaCl, neat): 3350, 3030, 2976, 2915, 2871, 1716, 1660, 1532 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.26 (td, *J* = 7.11, 0.71 Hz, 3H, $CH_3CH_2$), 1.56 (ddd, *J* = 6.84, 1.77, 0.70 Hz, 3H, $CH_3CH$), 1.80-1.97 (m, 2H, H-6), 2.02-2.14 (m, 2H, H-2), 2.36-2.55 (m, 4H, H-3, H-5), 4.17 (qd, *J* = 7.12, 0.70 Hz, $CH_2O$), 4.52 (t, *J* = 12.03 Hz, 1H, H-1), 5.54-5.66 (m, 1H, $CHCH_3$), 5.75 (dqd, *J* =7.83, 1.76, 0.66 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 12.6 ($CH_3CH$), 14.6 ($CH_3CH_2$), 29.3 ($CH_2Ar$), 39.8 ($CH_2Ar$), 54.0 (CHAr), 61.6 ($CH_2O$), 123.2 (CHN), 127.5 ($CHCH_3$) , 154.8 (CO), 209.6 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{20}NO_3$ $[M+H]^+$ 226.1438; found 226.1436.

**Ethyl (*E*)-(4-oxocyclohexyl)(prop-1-en-1-yl)carbamate (13b).** IR (NaCl, neat): 3094, 2959, 2938, 2887, 2050, 1983, 1704, 1662 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.29 (t, *J* = 7.12 Hz, 3H, $CH_3CH_2$), 1.72 (dd, *J* = 6.65, 1.67 Hz, 3H, $CH_3CH$), 1.97-2.07 (m, 2H, H-6), 2.15-2.35 (m, 2H, H-2), 2.45 (dd, *J* = 9.38, 4.64 Hz, 4H, H-3, H-5), 4.18 (q, *J* = 7.12 Hz, $CH_2O$), 4.31 (s, 1H, H-1), 5.33 (dq, *J* =13.54, 6.58 Hz, 1H, $CHCH_3$), 6.27 (d, *J* =14.12 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 14.6 ($CH_3CH_2$), 15.4 ($CH_3CH$), 29.0 ($CH_2Ar$), 40.1 ($CH_2Ar$), 54.4 (CHAr), 61.7 ($CH_2O$), 120.4 ($CHCH_3$), 126.4 (CHN) , 154.6 (CO), 209.8 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{20}NO_3$ $[M+H]^+$ 226.1438; found 226.1435.

***tert*-Butyl *(Z)*-(4-oxocyclohexyl)(prop-1-en-1-yl)carbamate (12c).** IR (NaCl, neat): 3029, 2973, 2930, 2870, 1719, 1692, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.46 (s, 9H, *t*-Bu), 1.56 (dd, *J* = 6.85, 1.79 Hz, $CH_3CH$), 1.85 (qd, *J* = 12.81, 5.04 Hz, 2H, H-6), 2.00-2.13 (m, 2H, H-2), 2.35-2.53 (m, 4H, H-3, H-5), 4.48 (bs, 1H, H-1), 5.54 (dq, *J* = 7.85, 6.85 Hz, 2H, $CHCH_3$), 5.71 (dq, *J* = 7.83, 1.79 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 12.7 ($CH_3$), 28.3 ($CH_3$-*t*Bu), 29.4 ($CH_2Ar$), 39.9 ($CH_2Ar$), 53.5 (C-1), 80.0 (CCH3), 123.5 (CHN), 126.7 ($CHCH_3$), 158.4 (CO), 209.8 (C-4).

**(*Z*)-*N*-(4-Oxocyclohexyl)-*N*-(prop-1-en-1-yl)benzamide (12d).** IR (NaCl, neat): 3029, 2914, 2870, 1716, 1638, 1578, 1537, 1446 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.24 (dd, *J* = 6.98, 1.79 Hz, 3H, $CH_3$), 1.93 (qd, *J* = 12.77, 4.54 Hz, 2H, H-2), 2.16-2.27 (m, 2H, H-6), 2.44 (dt, *J* = 4.92, 2.24 Hz, 1H, H-3), 2.48 (dt, *J* =4.70, 2.32 Hz, 1H, H-3), 2.50-2.64 (m, 2H, H-5), 4.99 (bs, 1H, H-1), 5.35 (q, *J* = 7.18, $CHCH_3$), 6.02 (dq, *J* = 7.86, 1.82 Hz, 1H, CHCH) 7.28-7.35 (m, 3H, CHPh), 7.46-7.53 (m, 2H, CHPh); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 12.5 ($CH_3$), 29.0 ($CH_2Ar$), 39.8 ($CH_2Ar$), 52.6 (H-1), 125.7 (CHCH), 127.5 (CHPh), 128.0 (CHPh), 128.0 ($CHCH_3$), 129.9 (CPh), 170.6 (CO), 209.5 (C-4). HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1485; found 258.1485.

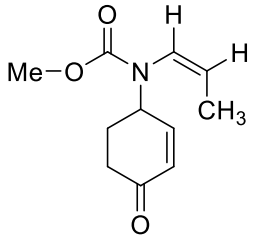
4. **Reaction of protected allylamines 14a and 14b with $RuCl_2(PPh_3)_3$**




**14** **15** **16**

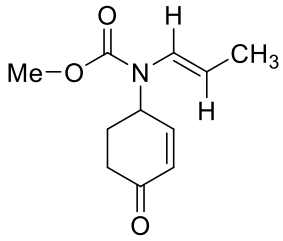
In a 10 mL vessel allylamine **14** was placed (0.443 mmol) and ruthenium catalyst (0.022 mmol, 5%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 90-120 min at 120-140 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) **15** and/or **16** were isolated.

**Methyl (*Z*)-(4-oxocyclohex-2-en-1-yl)(prop-1-en-1-yl)carbamate (15a).** IR



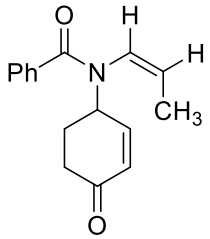
(NaCl, neat): 3031, 2954, 2918, 1693, 1660, 1536, 1447 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.61 (dd, *J* = 6.93, 1.77 Hz, 3H, $CH_3$), 2.13-2.28 (m, 2H, H-6), 2.39-2.53 (m, 1H, H-5), 2.54-2.64 (m, 1H, H-5), 3.75 (s, 3H, $CH_3O$), 5.03 (s, 1H, H-1), 5.60 (dq, *J* = 7.89, 6.90 Hz, 1H, $CHCH_3$), 5.80 (dq, *J* = 7.86, 1.78 Hz, 1H, H-3), 6.04 (ddd, *J* = 10.31, 2.77, 1.13 Hz, 1H, CHCH), 6.84 (ddd, *J* = 10.40, 2.22, 1.30 Hz, 1H, H-2); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 12.7 ($CH_3$), 27.4 (C-6), 36.7 (C-5), 53.1 ($CH_3O$), 54.3 (CHAr), 124.1 (C-3), 126.9 ($CHCH_3$), 130.5 (CHCH), 151.2 (C-2), 152.3 (CO), 197.8 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.1125; found 210.1124.

**Methyl (*E*)-(4-oxocyclohex-2-en-1-yl)(prop-1-en-1-yl)carbamate (16a).** IR



(NaCl, neat): 2955, 1708, 1684, 1584, 1444, 1308, 1377 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.68 (dd, *J* = 6.61, 1.64 Hz, 3H, $CH_3$), 2.09-2.21 (m, 2H, H-6), 2.41-2.57 (m, 1H, H-5), 2.54-2.64 (m, 1H, H-5), 3.78 (s, 3H, $CH_3O$), 5.10 (s, 1H, H-1), 5.17 (dq, *J* = 13.44, 6.64 Hz, 1H, $CHCH_3$), 6.02 (ddd, *J* = 10.36, 2.97, 1.17 Hz, 1H, H-3), 6.54 (d, *J* = 14.56 Hz, 1H, CHCH), 6.93 (dt, *J* = 10.40, 2.11 Hz, 1H, H-2); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 15.5 ($CH_3$), 26.9 (C-6), 37.1 (C-5), 53.2 ($CH_3O$), 53.4 (CHAr), 109.8 ($CHCH_3$), 126.1 (CHCH), 128.8 (C-3), 153.1 (C-2), 154.5 (CO), 197.7 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.1125; found 210.1127.

**(*Z*)-*N*-(4-Oxocyclohex-2-en-1-yl)-*N*-(prop-1-en-1-yl)benzamide.(15b)** IR

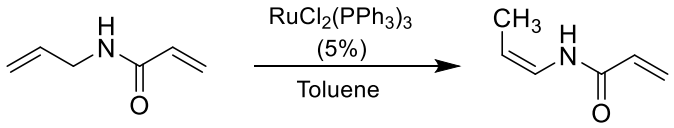


(NaCl, neat): 3059, 3034, 2955, 1716, 1681, 1635, 1601, 1578, 1530 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.26 (dd, *J* = 7.05, 1.78 Hz, 3H, $CH_3$), 2.15-2.37 (m, 2H, H-6), 2.50-2.67 (m, 2H, H-5), 5.36 (p, *J* = 7.18, $CHCH_3$), 5.57 (bs, 1H, H-1), 6.05 (dq, *J* = 7.88, 1.83 Hz, 1H, H-2), 6.12 (ddd, *J* = 10.32, 2.84, 1.08 Hz, 1H, H-3), 6.91 (dt, *J* = 10.34, 2.02 Hz, 1H, CHCH), 7.51-7.39 (m, 3H, CHPh), 7.51-7.57 (m, 2H, CHPh); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 12.7 ($CH_3$), 26.9 ($CH_2Ar$), 36.6 ($CH_2Ar$), 52.6 (H-1), 126.3 (H-2), 127.6 ($CHCH_3$), 127.6 (CHPh), 128.3 (CHPh),

130.3 (CHPh), 131.1 (H-3), 135.7 (CPh), 150.05 (CHCH), 170.6 (CO), 197.9 (C-4). HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332; found 256.1326.

**7. Reaction of 14c with $RuCl_2(PPh_3)_3$**

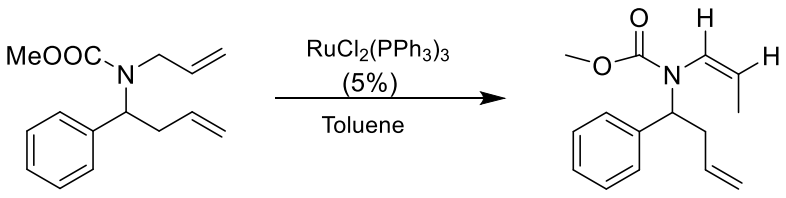
In a 10 mL vessel allylamine **14c** was placed (49.2 mg, 0.443 mmol) and ruthenium catalyst (0.022 mmol, 5%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 30 min at 120 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) **15** and/or **16** were isolated.




**14c** **15c**

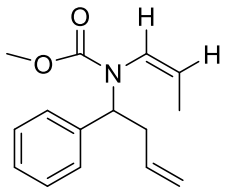
**(*Z*)-*N*-(Prop-1-en-1-yl)acrylamide (15c).** IR (NaCl, neat): 3253, 3194, 3055, 2922, 2855, 2779, 1658, 1625, 1537 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.31 (dd, *J* =6.8, 1.6 Hz, 3H, $CH_3$), 5.17-5.31 (m, 2H, $CH_2CH_3$), 5.69 (dd, *J* =10.3, 1.3 Hz, 1H, $CH_2CH$), 6.09 (q, *J* =12.9 Hz, 1H, $CH_2CH$), 6.35 (dd, *J* =16.9, 3.1 Hz, 1H, CHCO), 6.77-6.89 (m, 1H, CHNH), 7.13 (bs, 1H, NH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 14.8 ($CH_3$), 108.9 ($CH_2CH_3$), 123.1 ($CH_2CH$), 127.5 (CHNH), 130.2 (CHCO), 162.1 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_9H_{10}NO$ $[M+H]^+$ 112.0757; found 112.0757.

**8. Reaction of 14d with $RuCl_2(PPh_3)_3$**

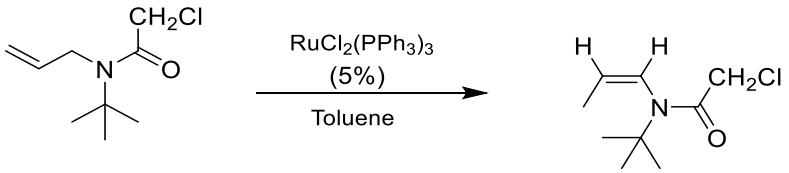



**14d** **15d**

In a 10 mL vessel allylamine **14d** was placed (109 mg, 0.443 mmol) and ruthenium catalyst (0.022 mmol, 5%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 75 min at 120 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) **15d** was isolated.

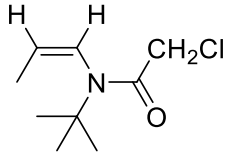
**Methyl *(Z)*-(1-phenylbut-3-en-1-yl)(prop-1-en-1-yl)carbamate (15d).** IR (NaCl, 
neat): 3064, 3030, 2978, 2951, 2916, 1698, 1160, 1445 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.31 (dd, *J* =6.8, 1.64 Hz, 3H, $CH_3$), 2.61-2.78 (m, 2H, $CH_2CHN$), 3.73 (d, *J* =2.17 Hz, 3H, $CH_3O$), 5.03-5.17 (m, 2H, $CH_2CH$), 5.48 (dq, *J* =7.85, 6.73 Hz, 1H, $CHCH_3$), 5.51 (s, 1H, CHN), 5.57 (dq, *J* =7.96, 1.66 Hz, 1H, $CHCH_2$), 5.79 (dddd, *J* =17.34, 10.22, 7.24, 6.19 Hz, 1H, CHNCO), 7.22-7.36 (m, 5H, CHAr). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 12.8 ($CH_3$), 35.2 ($CH_2CHN$), 52.8 ($CH_3O$), 58.9 (CHN), 117.4 ($CH_2CH$), 123.0 ($CHCH_2$), 126.9 ($CHCH_3$), 127.5 (CHAr), 127.9 (CHAr), 128.2(CHAr), 134.8 (CHNCO), 139.3 (CO), 157.5 (CAr). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1489; found 246.1484.

## 9. Reaction of 14e with $RuCl_2(PPh_3)_3$

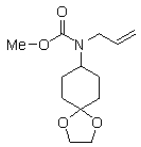



**14e** **15e**

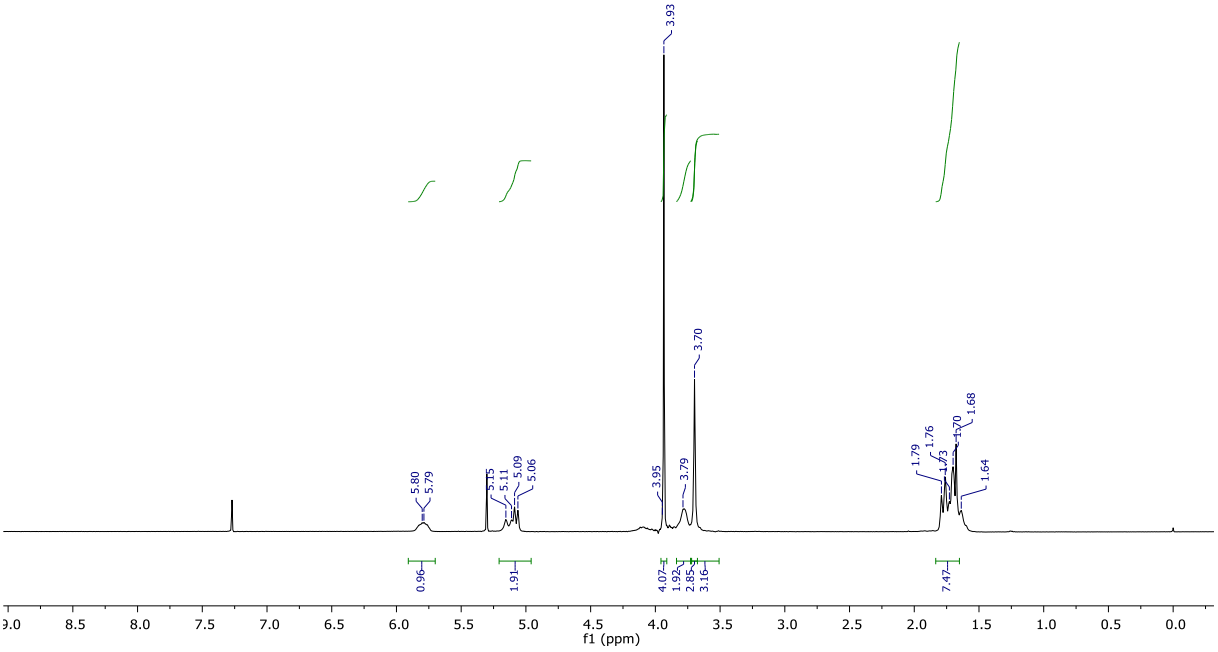
In a 10 mL vessel allylamine **14e** was placed (73 mg, 0.386 mmol) and ruthenium catalyst (0.019 mmol, 5%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 30 min at 160 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) **15e** and/or **16e** were isolated.

**(*Z*)-*N*-(*tert*-Butyl)-2-chloro-*N*-(prop-1-en-1-yl)acetamide (15e).** IR (NaCl, 
neat): 3027, 2976, 2935, 1670, 1649 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.41 (s, 9H, *t*-Bu), 1.68 (dd, *J* =6.94, 1.88 Hz, 3H, $CH_3$), 3.95 (s, 1H, $CH_2Cl$), 4.03 (m, 1H, $CH_2Cl$), 5.72 (dqd, *J* =7.85, 6.89, 0.97 Hz, $CHCH_3$), 6.05 (dt, *J*=7.69, 1.90 Hz, 1H, CHN); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 12.3 ($CH_3$), 28.1 (*t*-Bu), 44.6 ($CH_2Cl$), 58.7 (CN), 127.9 (CHN), 129.1 ($CHCH_3$), 165.8 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_9H_{17}ClNO$ $[M+H]^+$ 134.0367; found 134.0368.

M400AFF_27112019_AS245-3-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS245-3
Nom: ALEXANDRA SANDOR
Data: 27/11/19 / Ope.: A.SANDOR

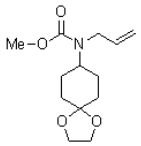


**8a**

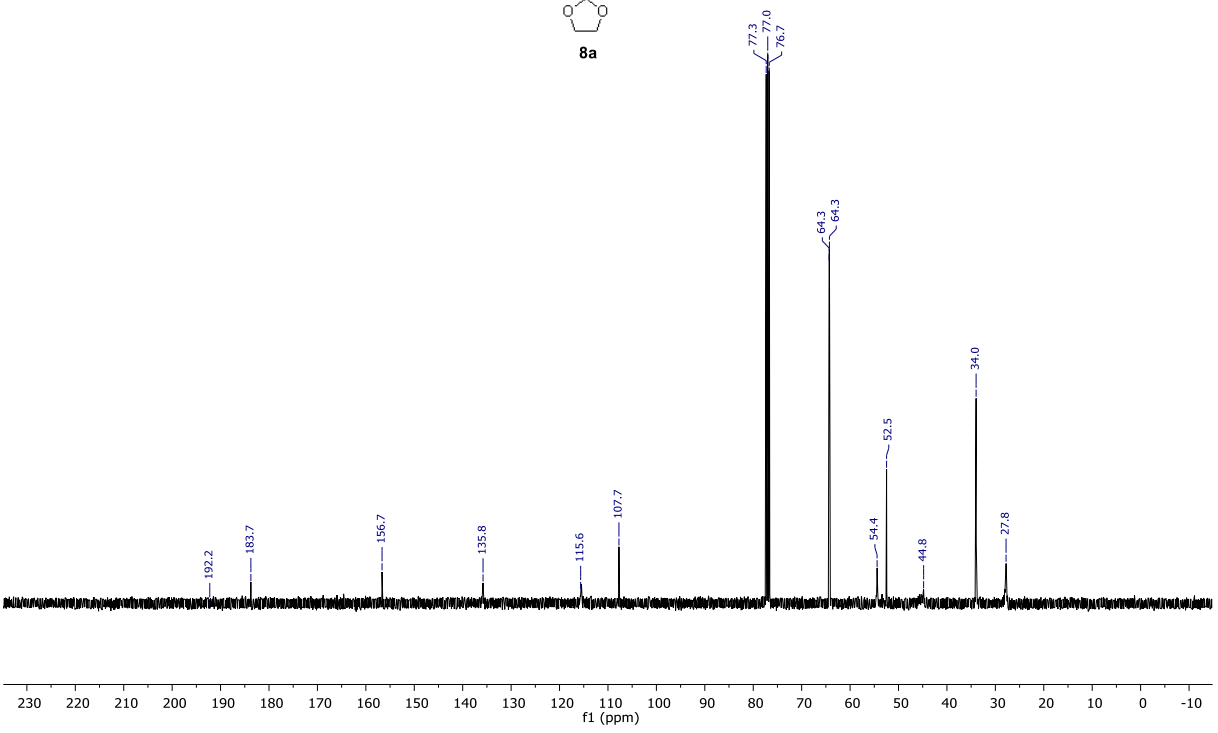



7.

M400AFF_28112019_AS245-3-C13
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS245-3
Nom: ALEXANDRA SANDOR
Data: 27/11/19 / Ope.: A.SANDOR



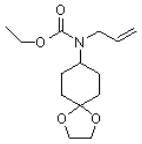
**8a**



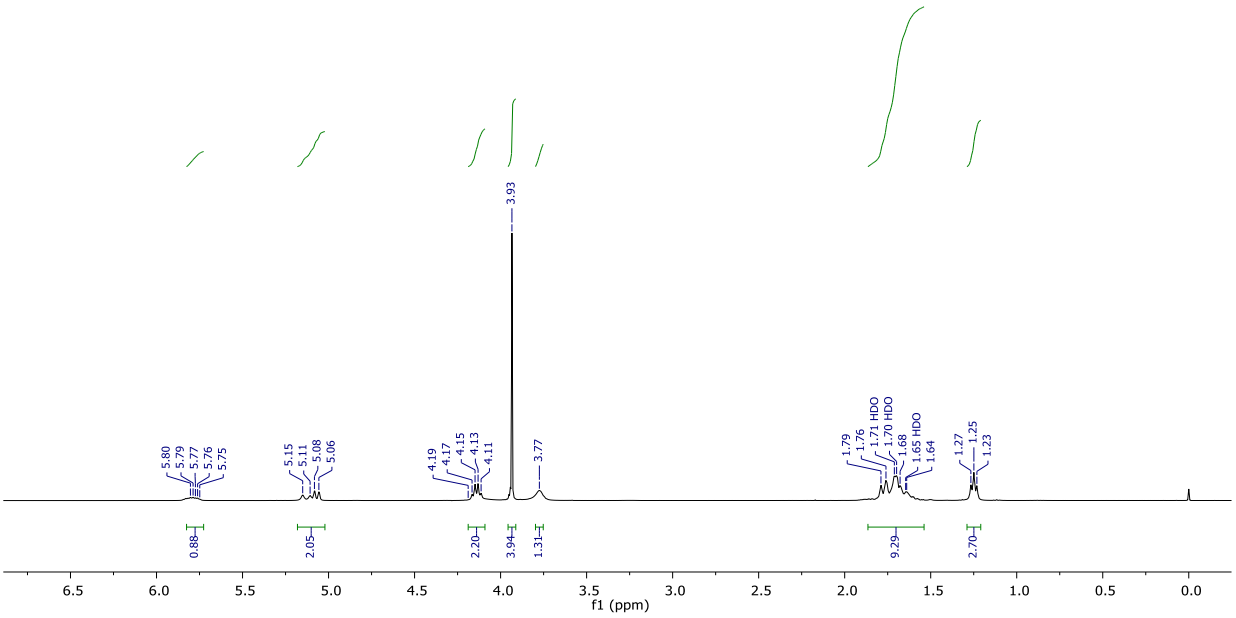

8.

9.

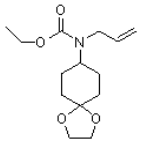
VNMRS400A_12112019_AS222-4-H1_rep_17_19_54
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 18
Usuari: san / Mostra: AS222-4
Nom: ALEXANDRA SANDOR
Data: 12/11/19 / Ope.: V.MERIEL



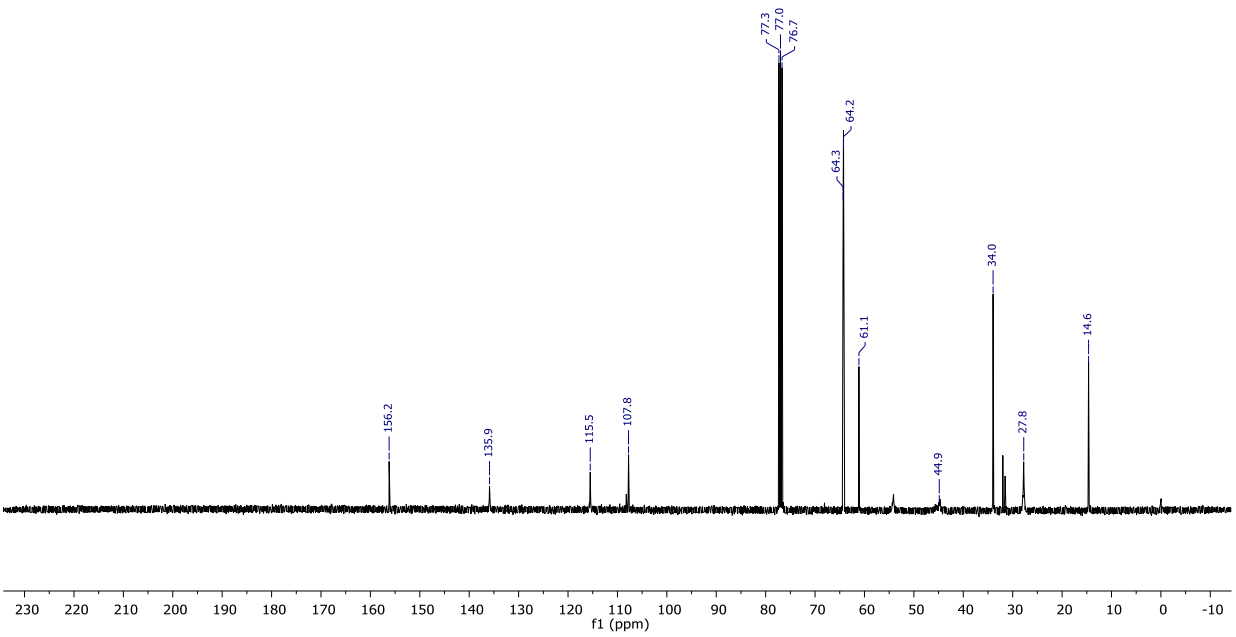
**8b**




VNMRS400A_12112019_AS222-4-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 18
Usuari: san / Mostra: AS222-4
Nom: ALEXANDRA SANDOR
Data: 12/11/19 / Ope.: V.MERIEL

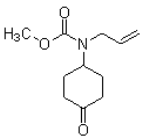


**8b**

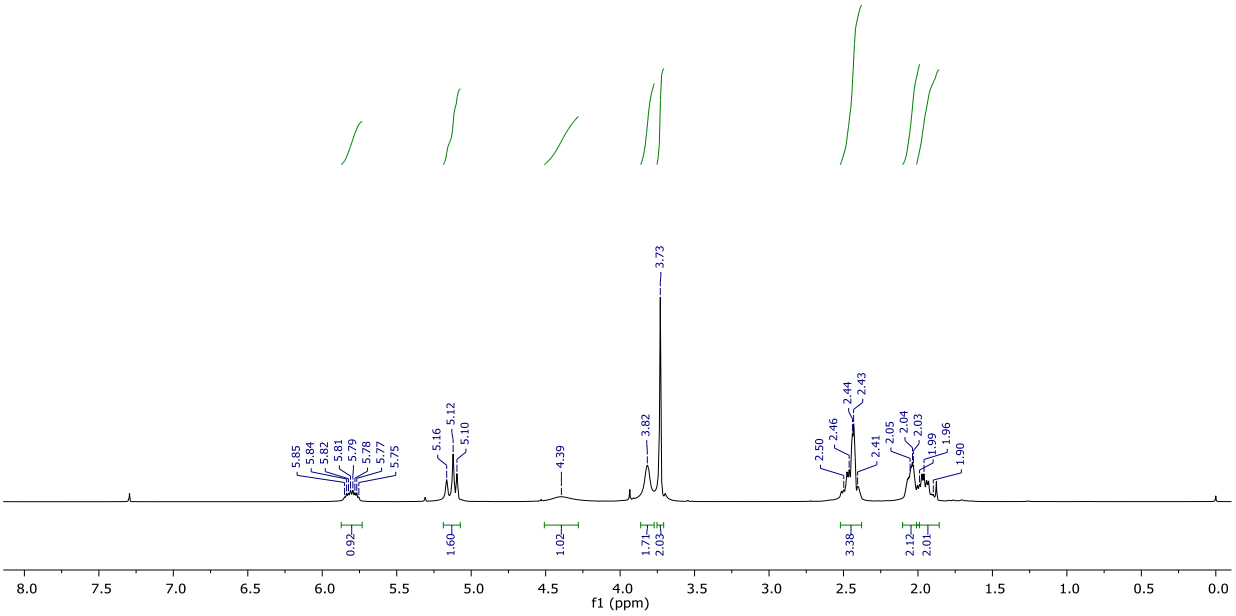


10.

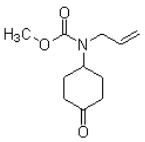
VNMRS400A_30012020_AS288_27-H1_rep_17_21_10
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: SAN
Usuari: san / Mostra: AS288_27
Nom: ALEXANDRA SANDOR
Data: 30/01/20 / Ope.: A.GALLEN



**9a**



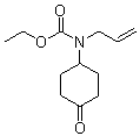

VNMRS400A_30012020_AS288_27-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: SAN
Usuari: san / Mostra: AS288_27
Nom: ALEXANDRA SANDOR
Data: 30/01/20 / Ope.: A.GALLEN



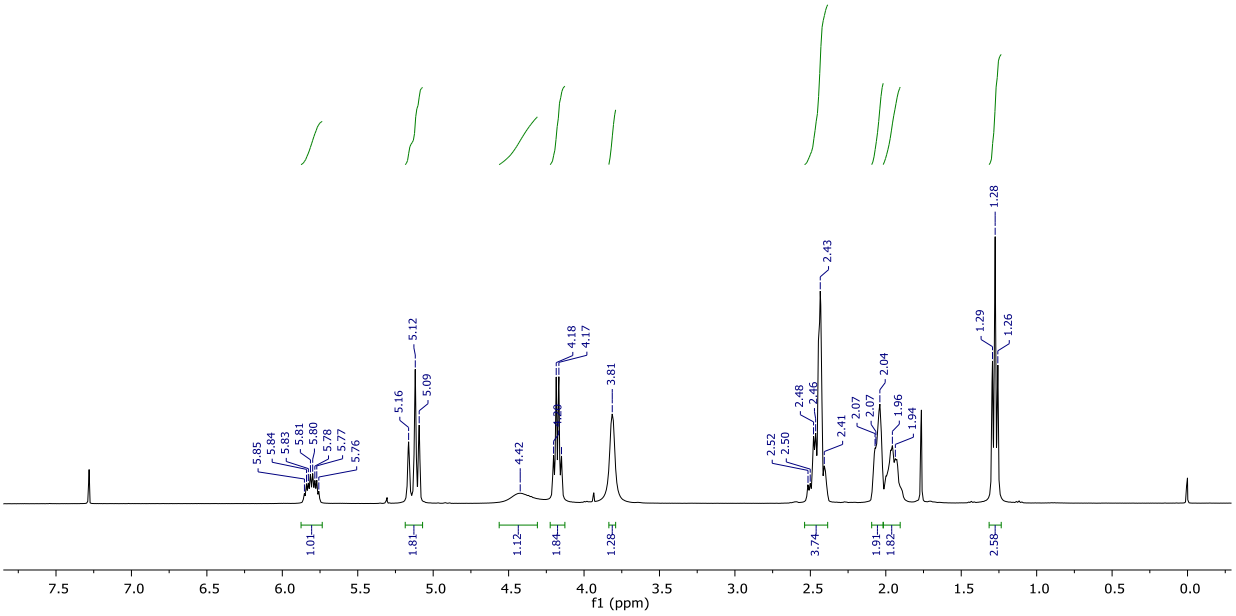
**9a**

11.

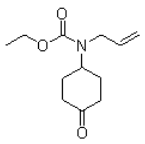
VNMRS400A_30102019_AS226-5-H1_rep_21_08_37
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 3
Usuari: san / Mostra: AS226-5
Nom: ALEXANDRA SANDOR
Data: 30/10/19 / Ope.: F.CARDENAS



**9b**




VNMRS400A_30102019_AS226-5-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 3
Usuari: san / Mostra: AS226-5
Nom: ALEXANDRA SANDOR
Data: 30/10/19 / Ope.: F.CARDENAS



**9b**

12.

VNMRS400A_30092020_AS350-ALL-H1
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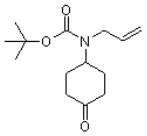
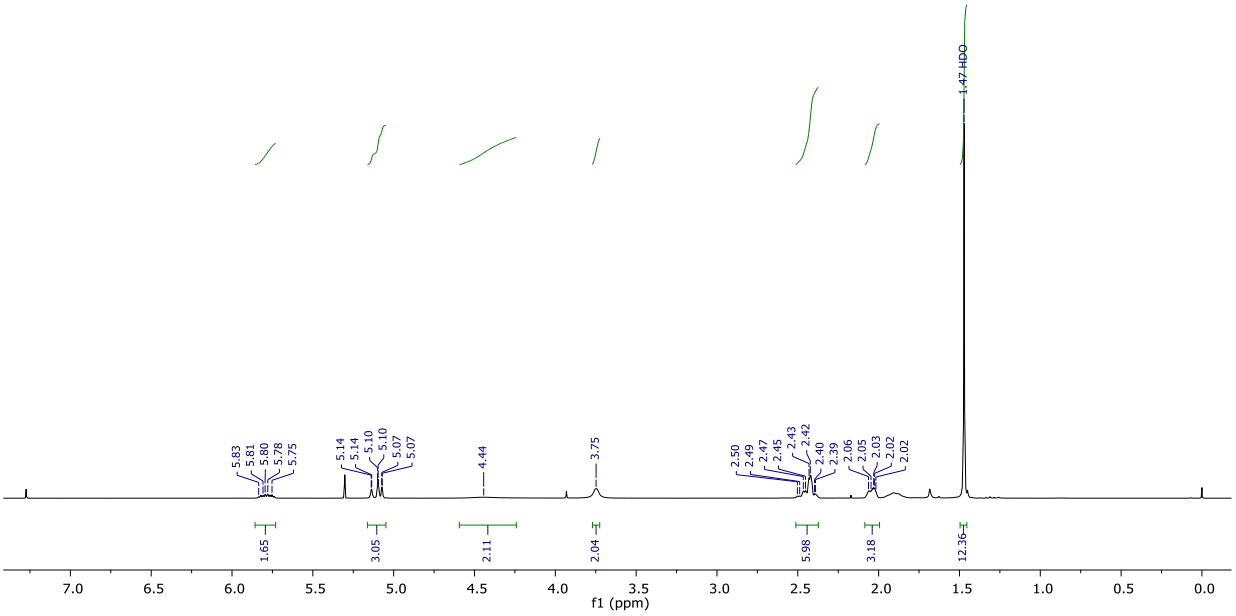
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS350-ALL
Nom: ALEXANDRA SANDOR
Data: 30/09/20 / Ope.: A.SANDOR



**9c**

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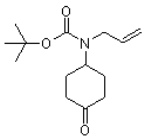
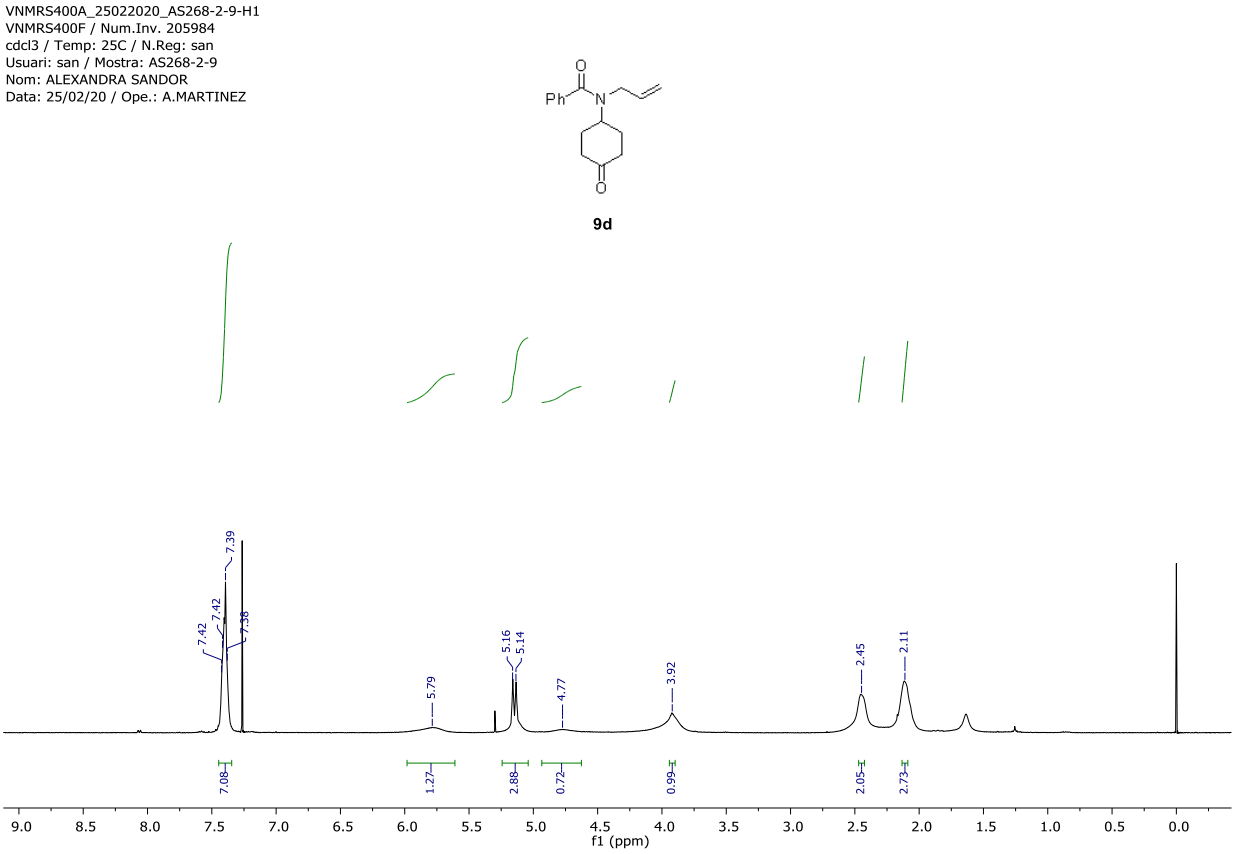
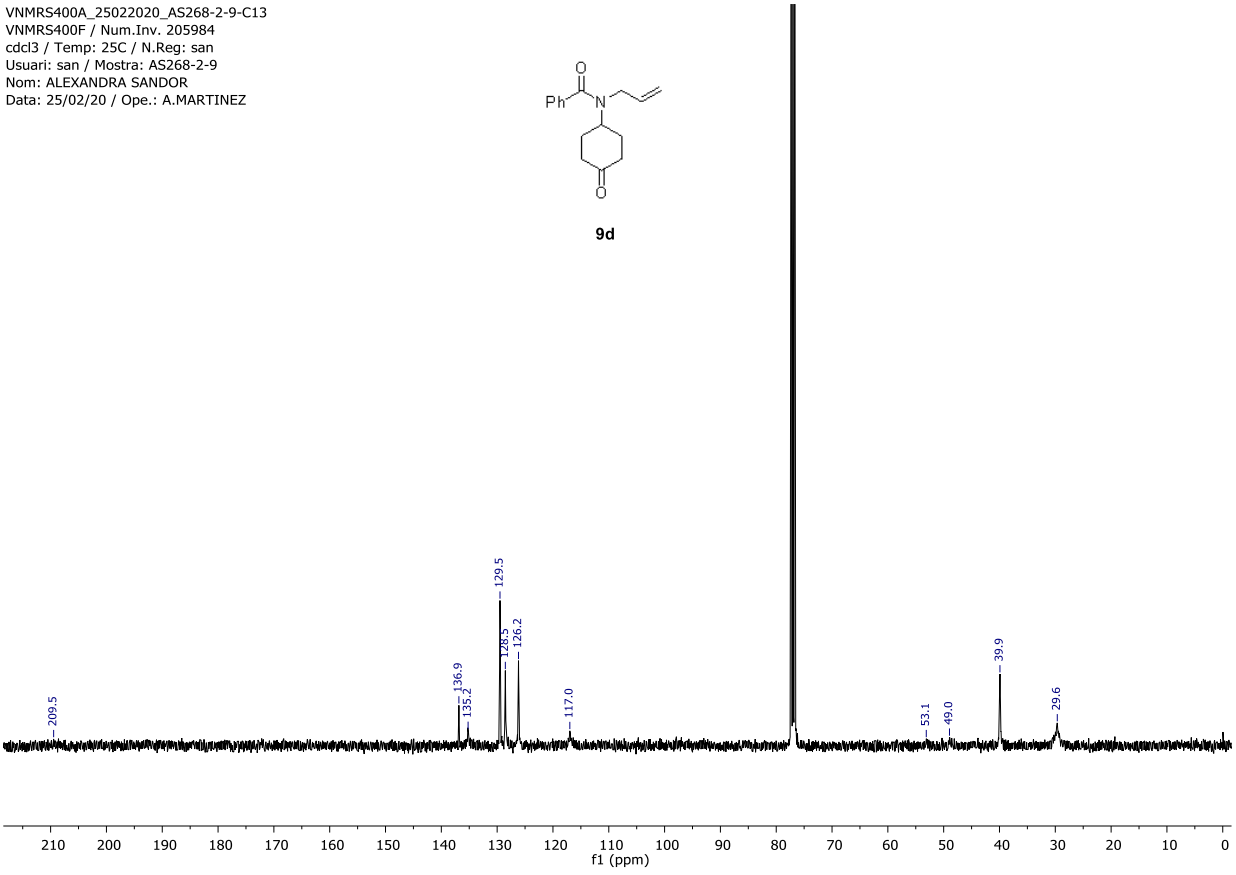
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS350-ALL
Nom: ALEXANDRA SANDOR
Data: 30/09/20 / Ope.: A.SANDOR



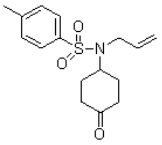
**9c**

13.

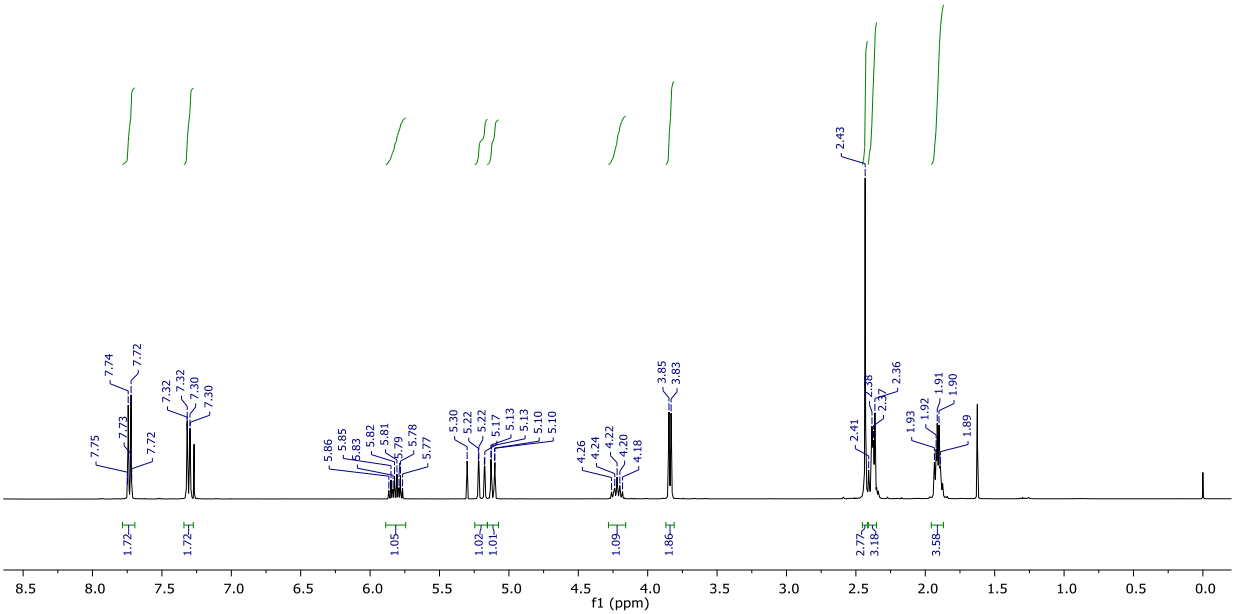

VNMRS400A_25022020_AS268-2-9-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: san
Usuari: san / Mostra: AS268-2-9
Nom: ALEXANDRA SANDOR
Data: 25/02/20 / Ope.: A.MARTINEZ
Ph
N
O
O
9d
7.42
7.42
7.39
7.38
5.79
5.16
5.14
4.77
3.92
2.45
2.11
7.08
1.27
2.88
0.72
0.99
2.05
2.73
f1 (ppm)


VNMRS400A_25022020_AS268-2-9-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: san
Usuari: san / Mostra: AS268-2-9
Nom: ALEXANDRA SANDOR
Data: 25/02/20 / Ope.: A.MARTINEZ
Ph
N
O
O
9d
209.5
136.9
135.2
129.5
128.5
126.2
117.0
53.1
49.0
39.9
29.6
f1 (ppm)

VNMRS400A_11022020_AS298-4-H1_rep_17_39_47
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: san
Usuari: san / Mostra: AS298-4
Nom: ALEXANDRA SANDOR
Data: 11/02/20 / Ope.: A.GALLEN



**9e**




VNMRS400A_11022020_AS298-4-C13
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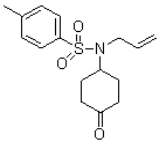
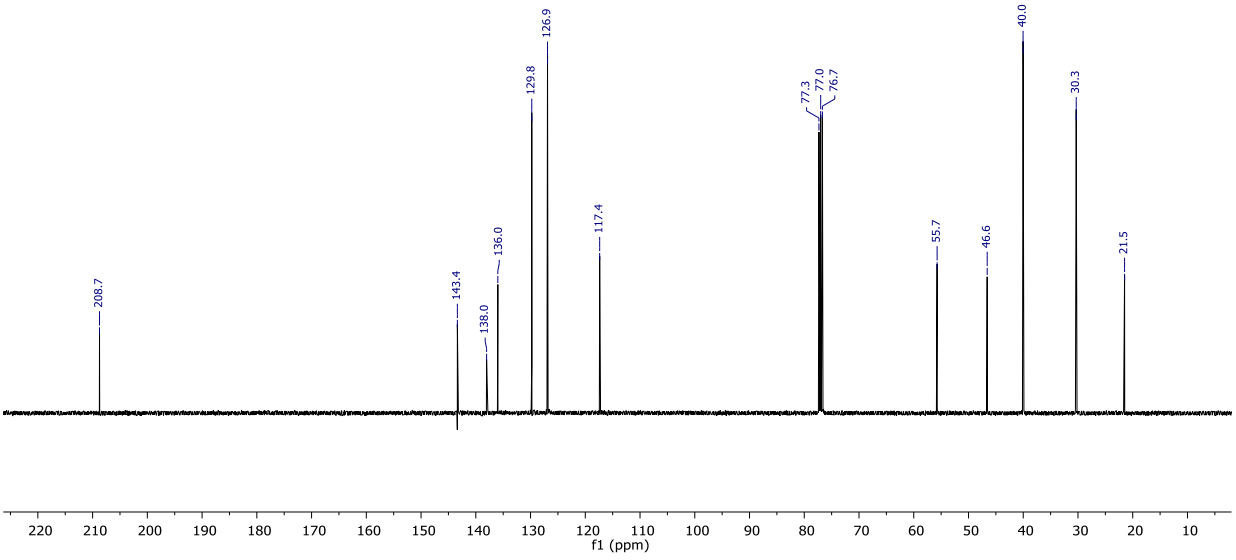
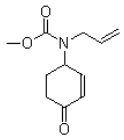
cdcl3 / Temp: 25C / N.Reg: san
Usuari: san / Mostra: AS298-4
Nom: ALEXANDRA SANDOR
Data: 11/02/20 / Ope.: A.GALLEN



**9e**

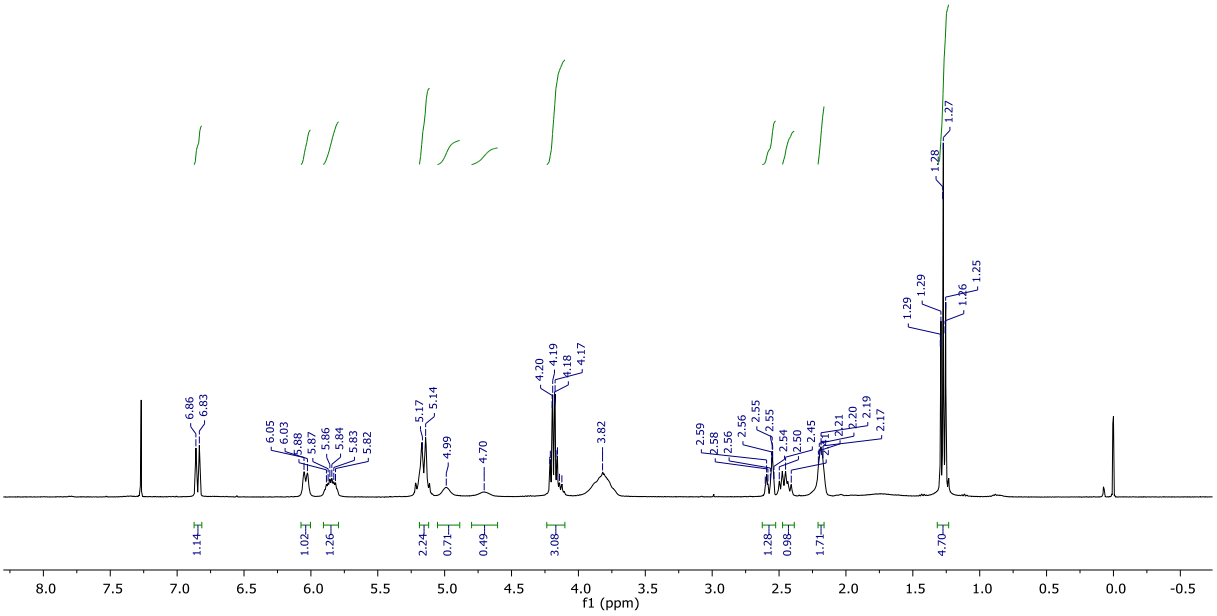


VNMRS400A_19112019_AS238-CRU-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 24
Usuari: san / Mostra: AS238-CRU
Nom: ALEXANDRA SANDOR
Data: 19/11/19 / Ope.: V.MERIEL

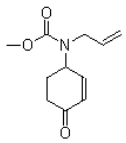


**14a**

14.

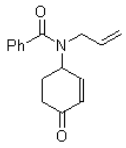



VNMRS400A_20112019_AS238-CRU-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 24
Usuari: san / Mostra: AS238-CRU
Nom: ALEXANDRA SANDOR
Data: 20/11/19 / Ope.: V.MERIEL

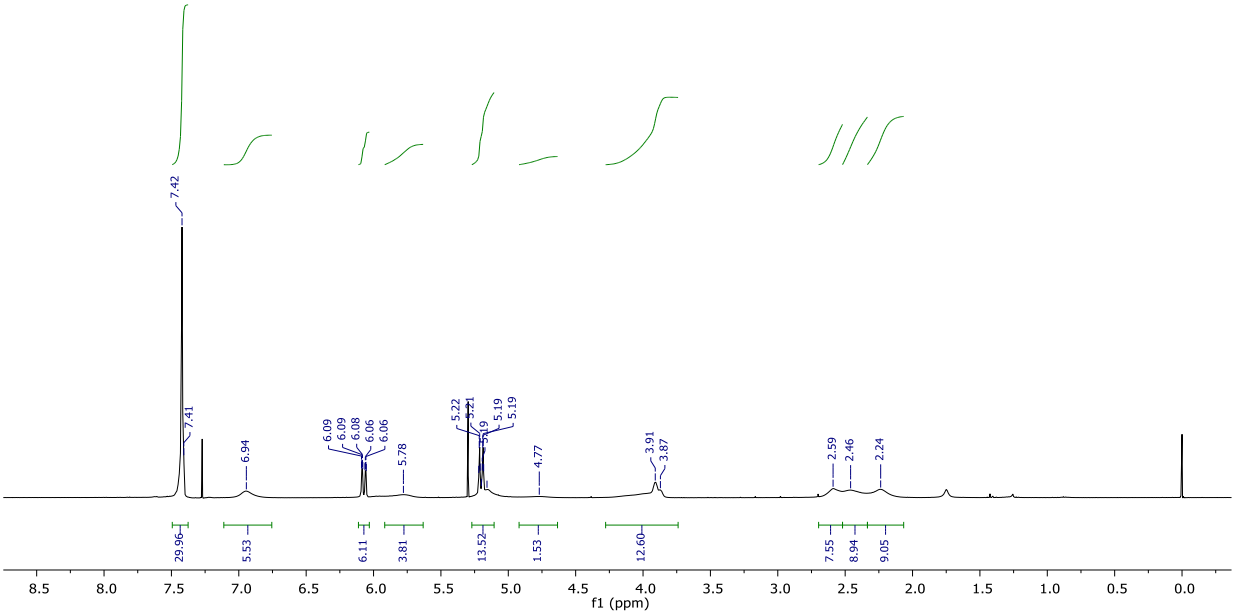


**14a**

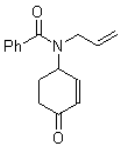
VNMRS400A_22092020_AS343-2-66-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS343-2-66
Nom: ALEXANDRA SANDOR
Data: 22/09/20 / Ope.: A.SANDOR



**14b**



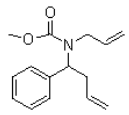

VNMRS400A_22092020_AS343-2-66-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS343-2-66
Nom: ALEXANDRA SANDOR
Data: 22/09/20 / Ope.: A.SANDOR



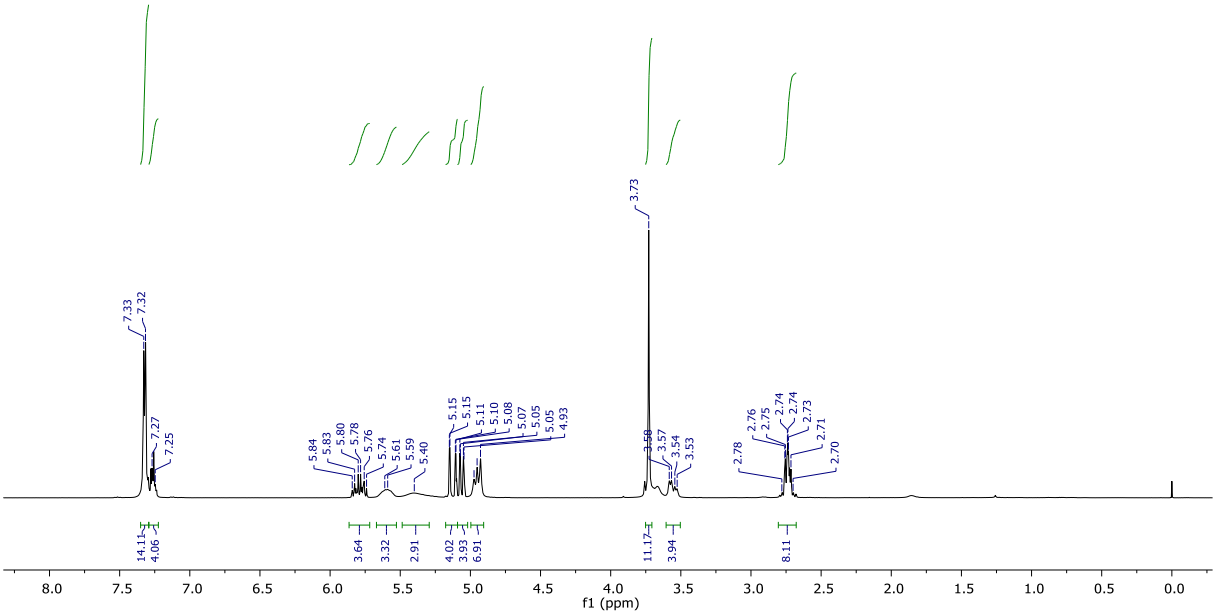
**14b**

15.

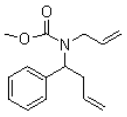
VNMRS400A_02032020_AS310-23-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: san
Usuari: san / Mostra: AS310-23
Nom: FAIZA DIABA
Data: 02/03/20 / Ope.: A.GALLEN



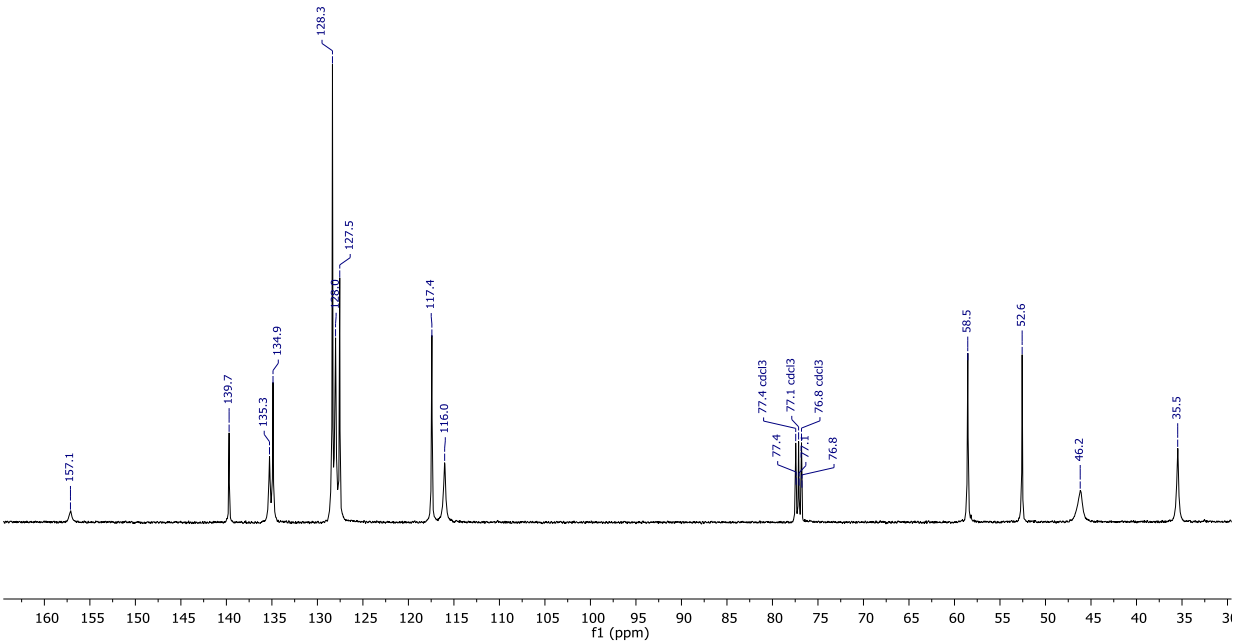
**14d**



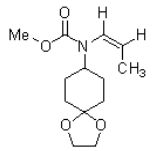

VNMRS400A_29022020_XAS310-23-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS310-23
Nom: FAIZA DIABA
Data: 29/02/20 / Ope.: F.DIABA



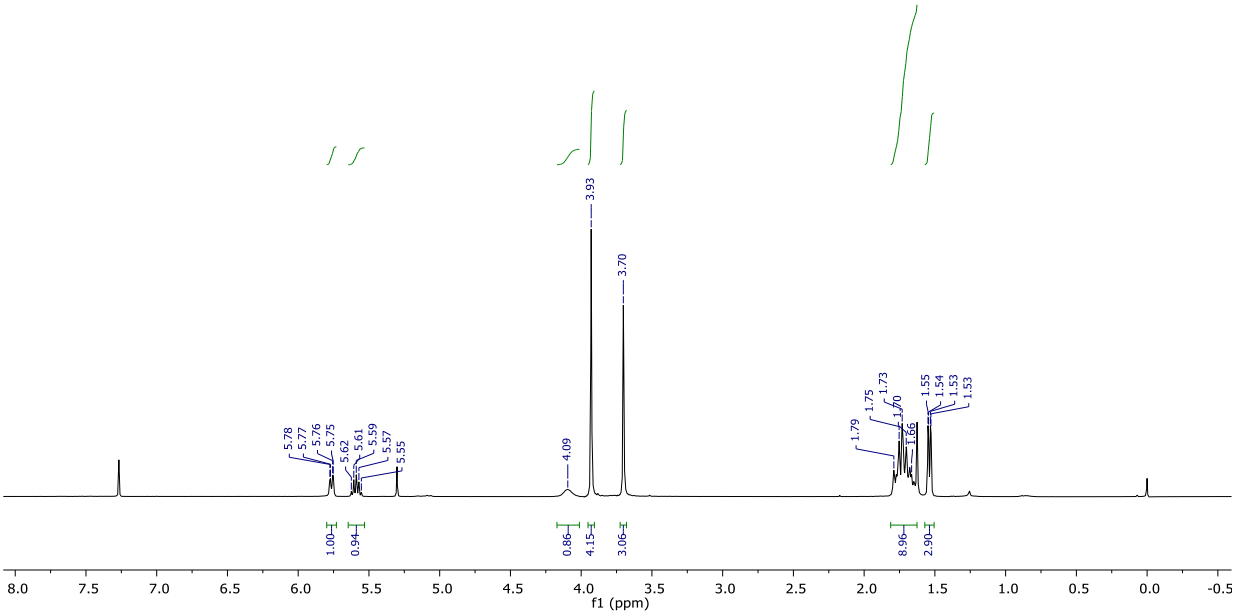
**14d**



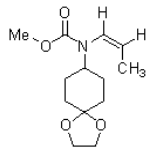
M400AFF_05122019_as252-57-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as252-57
Nom: ALEXANDRA SANDOR
Data: 05/12/19 / Ope.: A.SANDOR



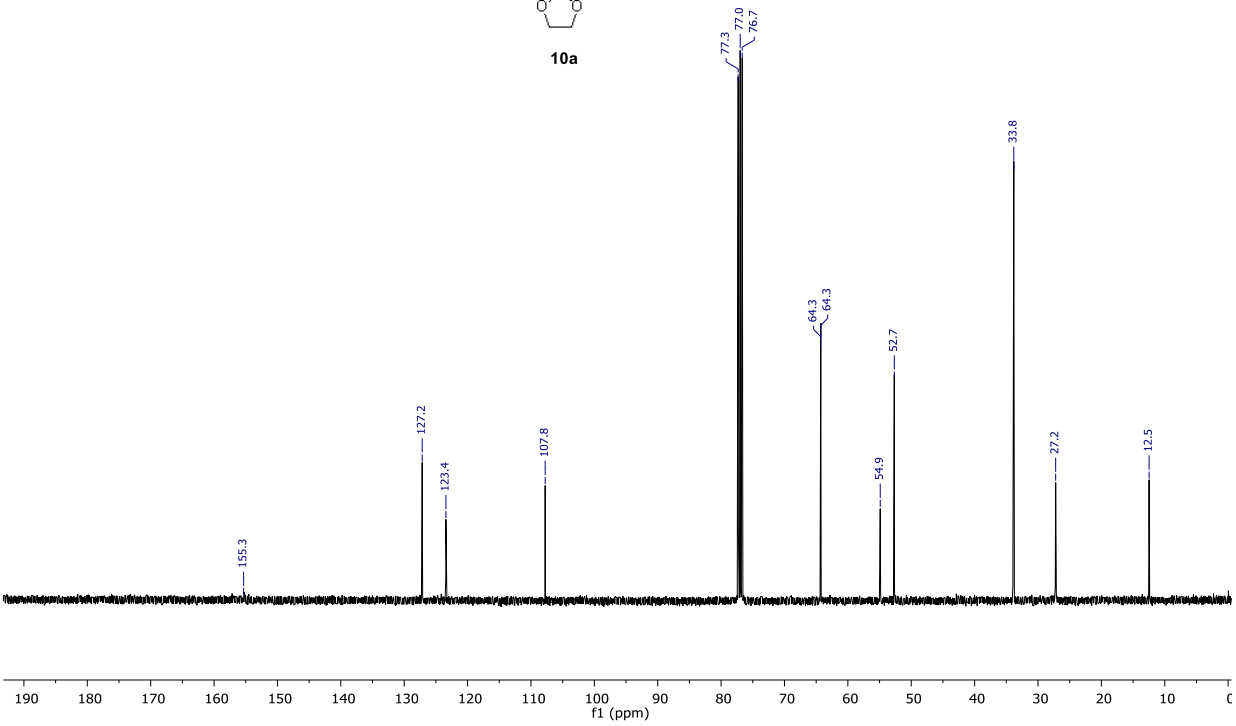
**10a**




VNMRS400A_09122019_AS252-57-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 43
Usuari: san / Mostra: AS252-57
Nom: ALEXANDRA SANDOR
Data: 09/12/19 / Ope.: V.MERIEL

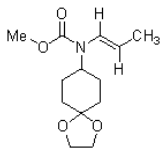


**10a**

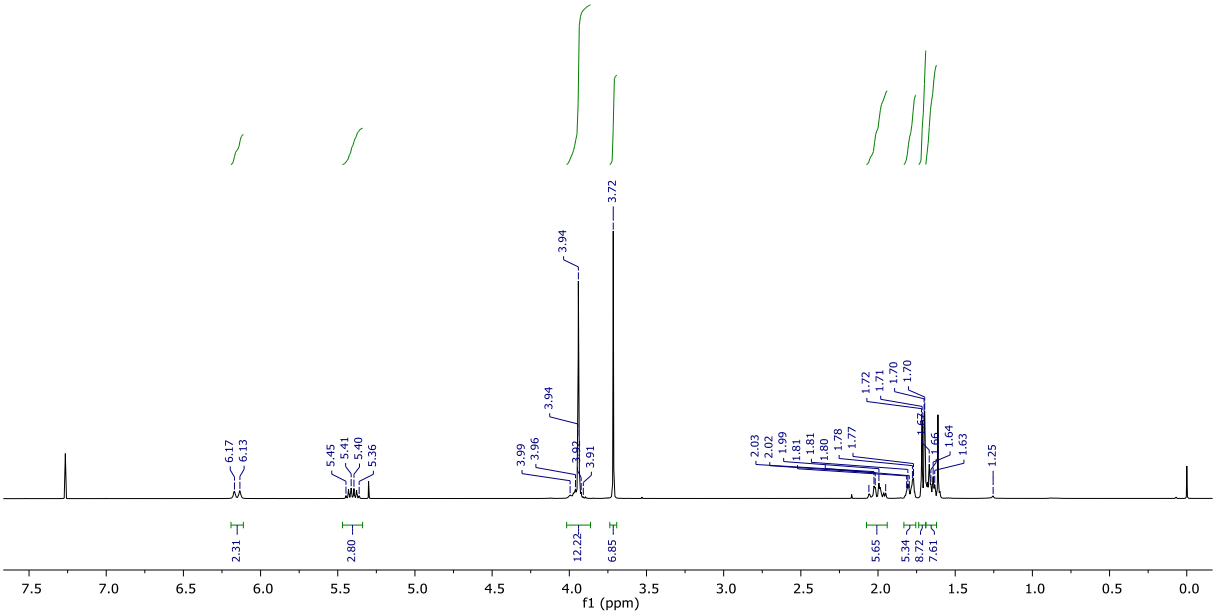


16.

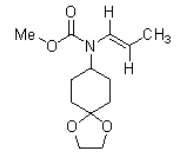
VNMRS400A_05122019_AS252-29-H1_rep_21_52_07
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 43
Usuari: san / Mostra: AS252-29
Nom: ALEXANDRA SANDOR
Data: 05/12/19 / Ope.: V.MERIEL



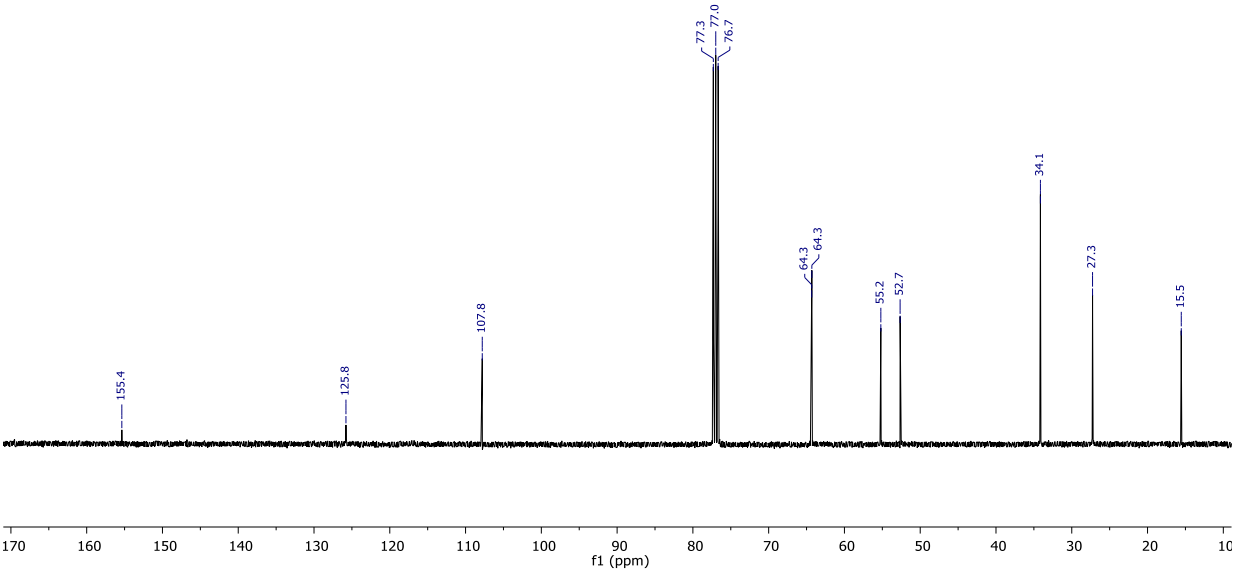
**11a**




VNMRS400A_06122019_AS252-29-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 43
Usuari: san / Mostra: AS252-29
Nom: ALEXANDRA SANDOR
Data: 06/12/19 / Ope.: V.MERIEL

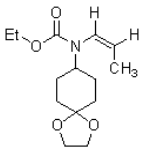


**11a**

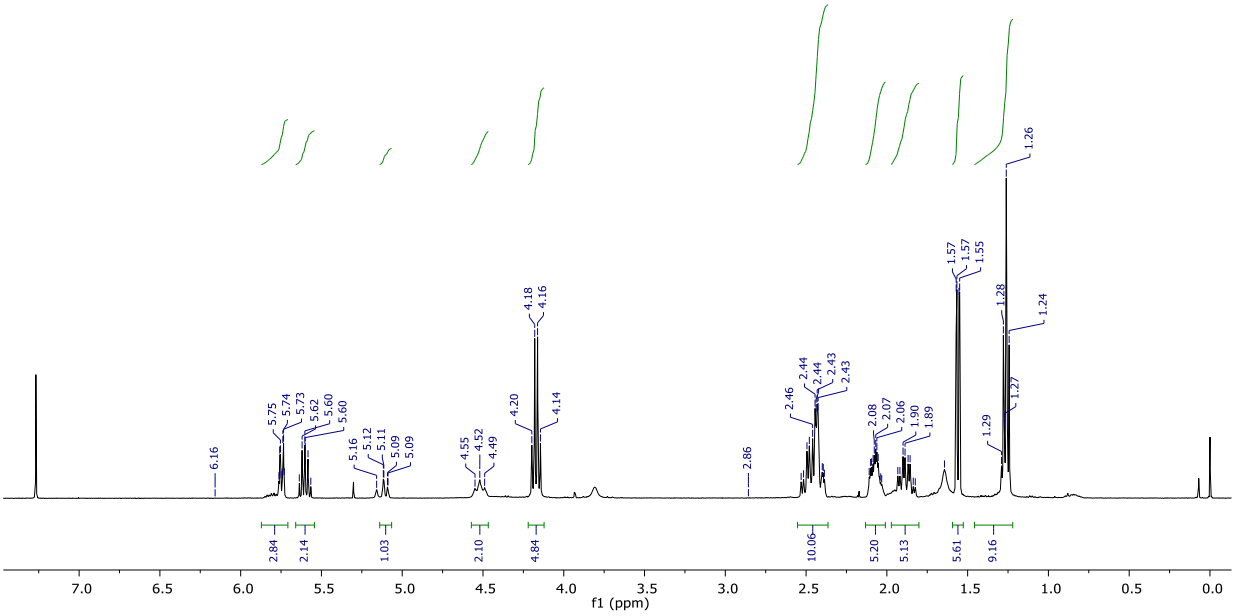


17.

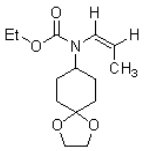
VNMRS400A_03112020_AS244-2-18-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS244-2-18
Nom: ALEXANDRA SANDOR
Data: 03/11/20 / Ope.: A.SANDOR



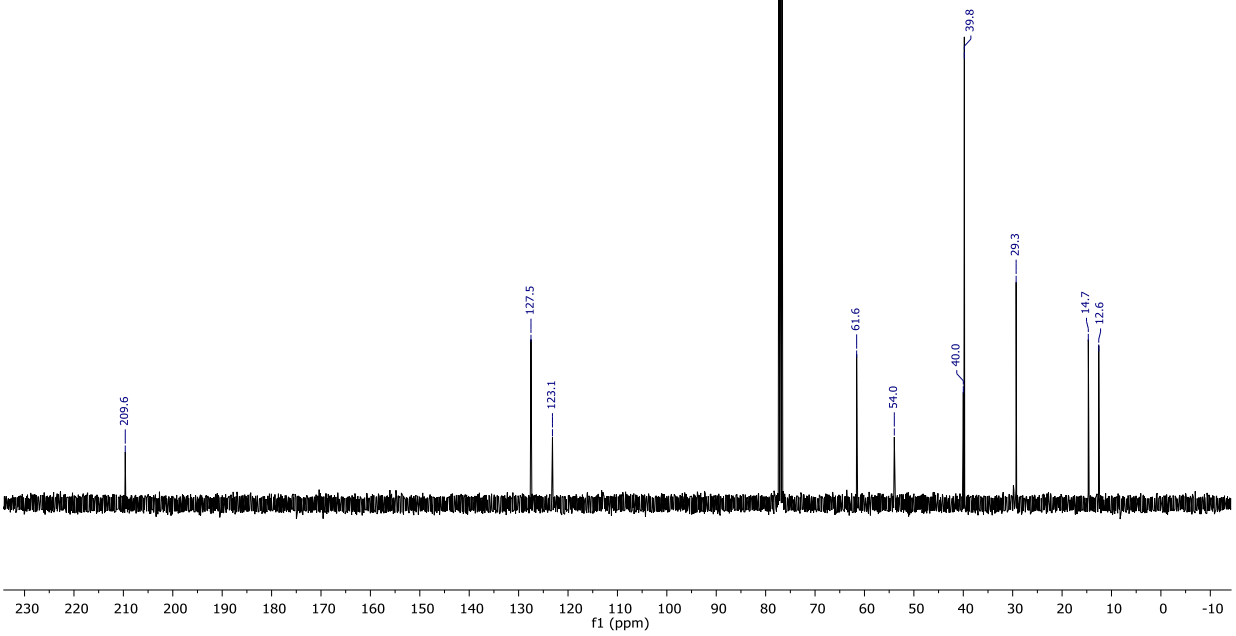
**10b**



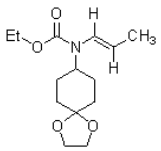

VNMRS400A_03112020_AS244-2-18-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS244-2-18
Nom: ALEXANDRA SANDOR
Data: 03/11/20 / Ope.: A.SANDOR



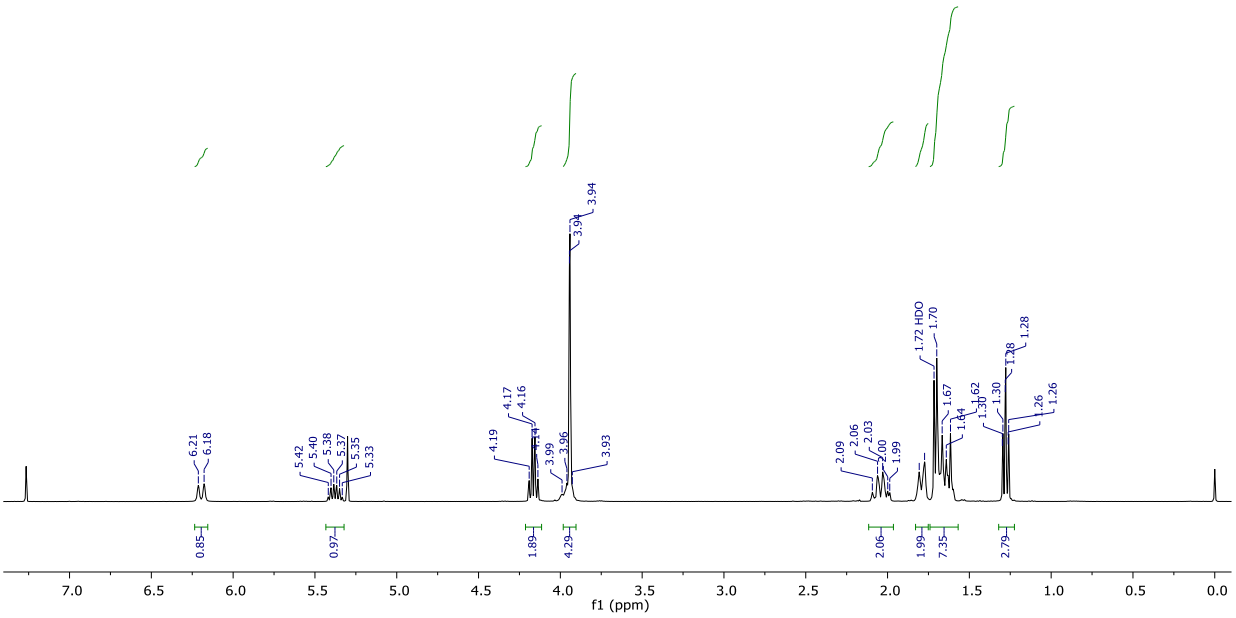
**10b**



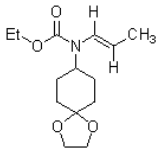
VNMRS400A_11112019_AS223-7-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 17
Usuari: san / Mostra: AS223-7
Nom: ALEXANDRA SANDOR
Data: 11/11/19 / Ope.: V.MERIEL



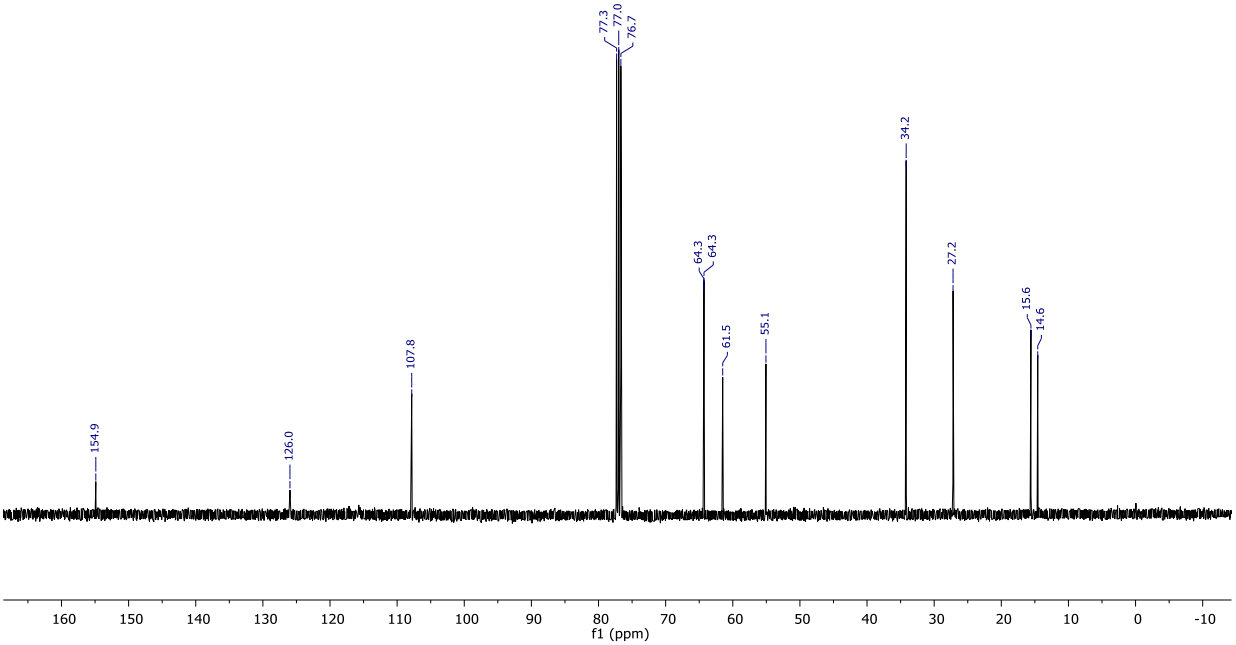
**11b**



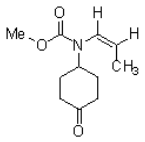

VNMRS400A_23102019_XAS223-7-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS223-7
Nom: FAIZA DIABA
Data: 23/10/19 / Ope.: F.DIABA



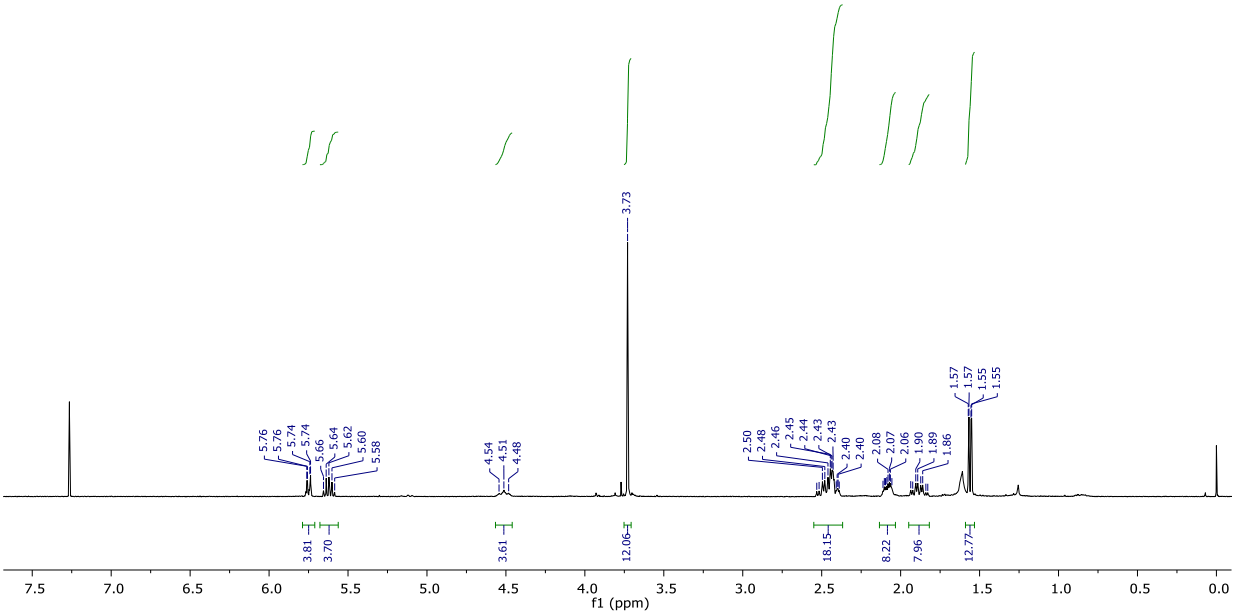
**11b**



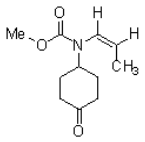
VNMRS400A_02112020_as327-cis-25-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as327-cis-25
Nom: ALEXANDRA SANDOR
Data: 02/11/20 / Ope.: A.SANDOR



**12a**

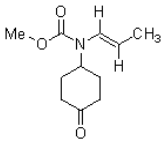



VNMRS400A_02112020_as327-cis-25-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as327-cis-25
Nom: ALEXANDRA SANDOR
Data: 02/11/20 / Ope.: A.SANDOR

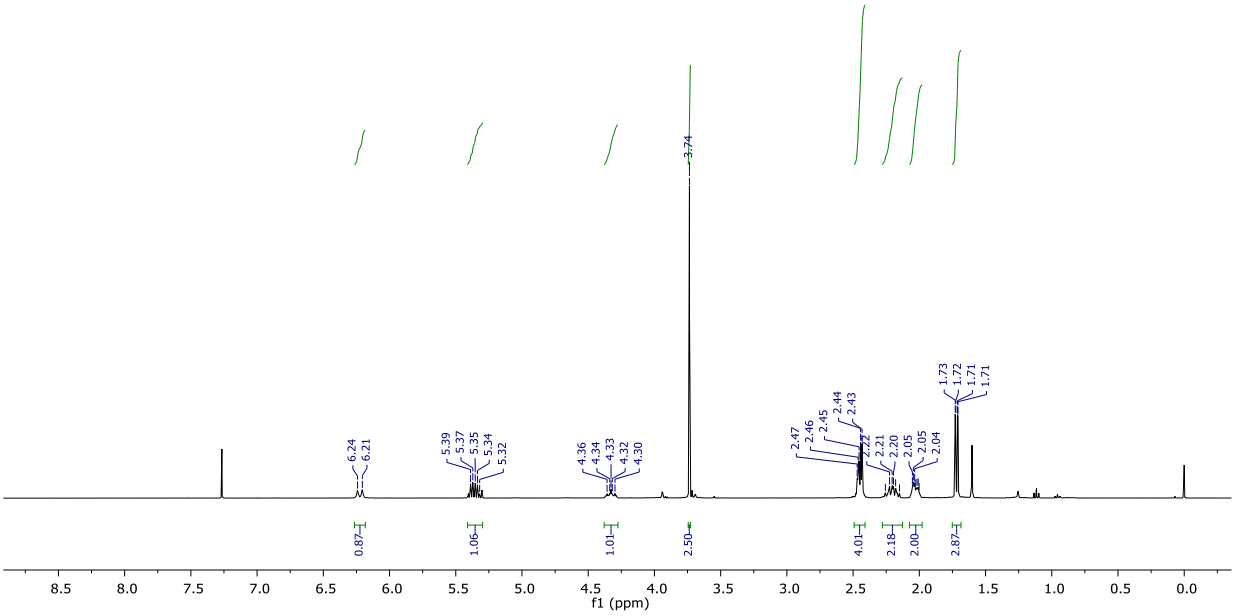


**12a**

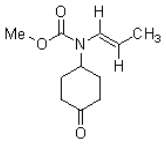
VNMRS400A_27102020_AS327-F2-28-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS327-F2-28
Nom: ALEXANDRA SANDOR
Data: 27/10/20 / Ope.: A.SANDOR



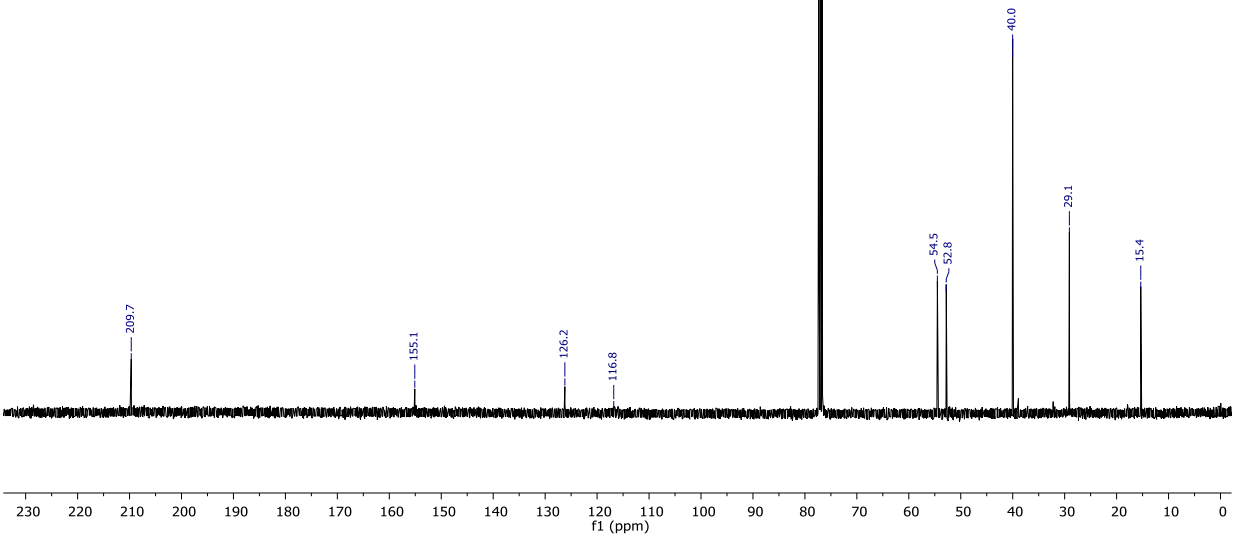
**13a**



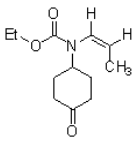

VNMRS400A_28102020_AS327-F2-28-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS327-F2-28
Nom: ALEXANDRA SANDOR
Data: 28/10/20 / Ope.: A.SANDOR



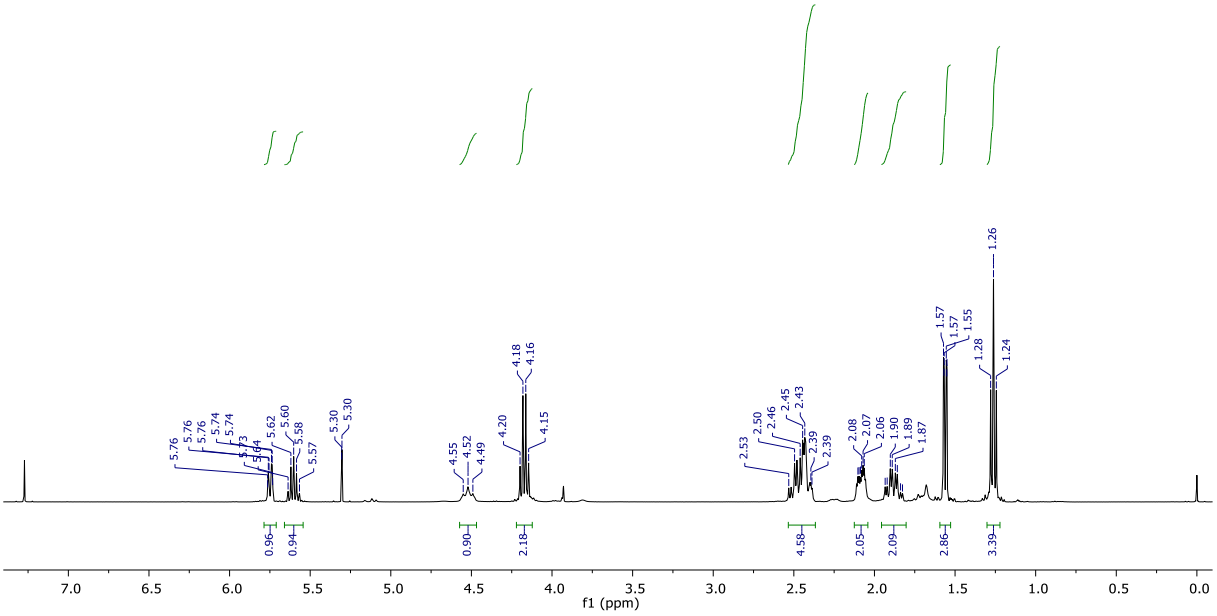
**13a**



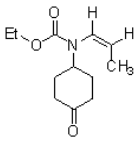
VNMRS400A_07122020_as382-35-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as382-35
Nom: ALEXANDRA SANDOR
Data: 07/12/20 / Ope.: A.SANDOR



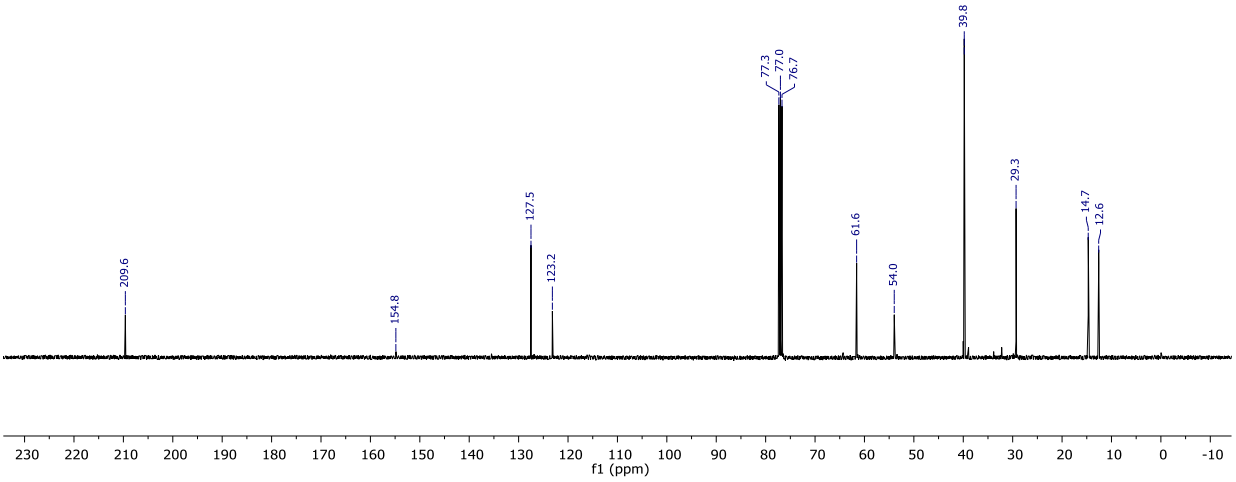
**12b**



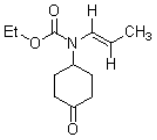

VNMRS400A_07122020_as382-35-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as382-35
Nom: ALEXANDRA SANDOR
Data: 07/12/20 / Ope.: A.SANDOR



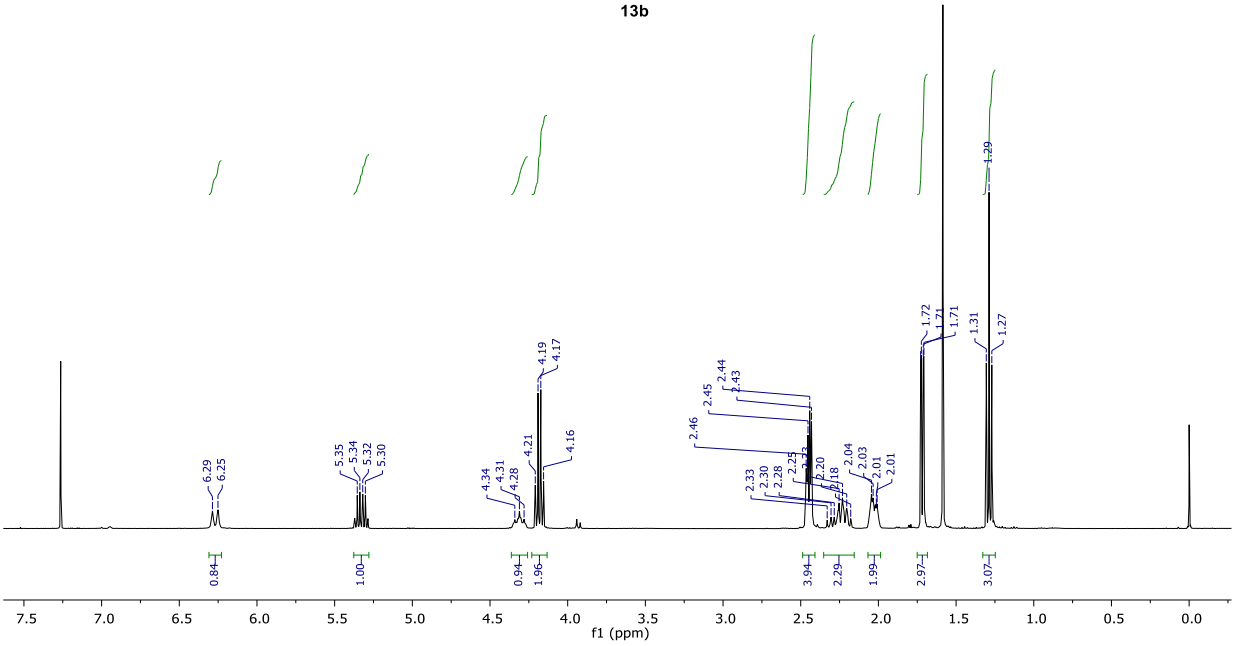
**12b**



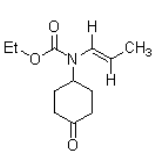
VNMRS400A_29102020_AS229-2-22-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS229-2-22
Nom: ALEXANDRA SANDOR
Data: 29/10/20 / Ope.: A.SANDOR



13b

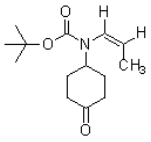



VNMRS400A_29102020_AS229-2-22-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS229-2-22
Nom: ALEXANDRA SANDOR
Data: 29/10/20 / Ope.: A.SANDOR

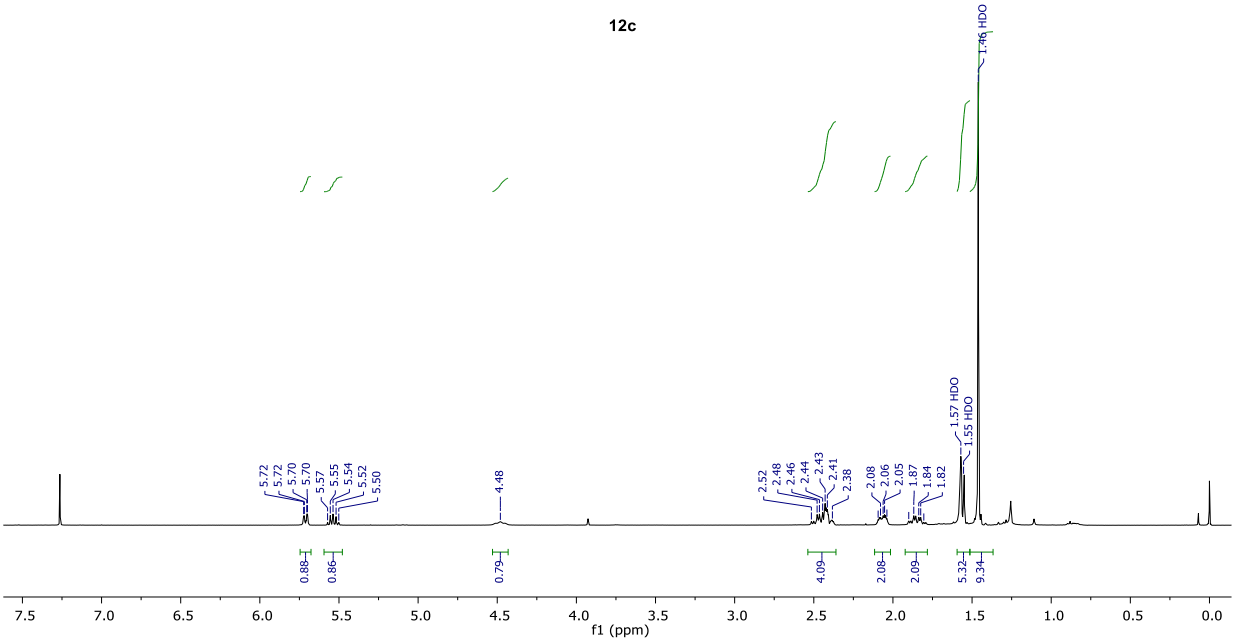


13b

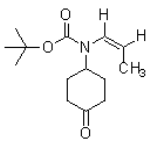
VNMRS400A_04102020_XAS351-45-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS351-45
Nom: FAIZA DIABA
Data: 04/10/20 / Ope.: F.DIABA



**12c**

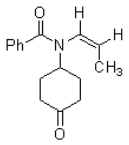



VNMRS400A_04102020_XAS351-45-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAS351-45
Nom: FAIZA DIABA
Data: 04/10/20 / Ope.: F.DIABA

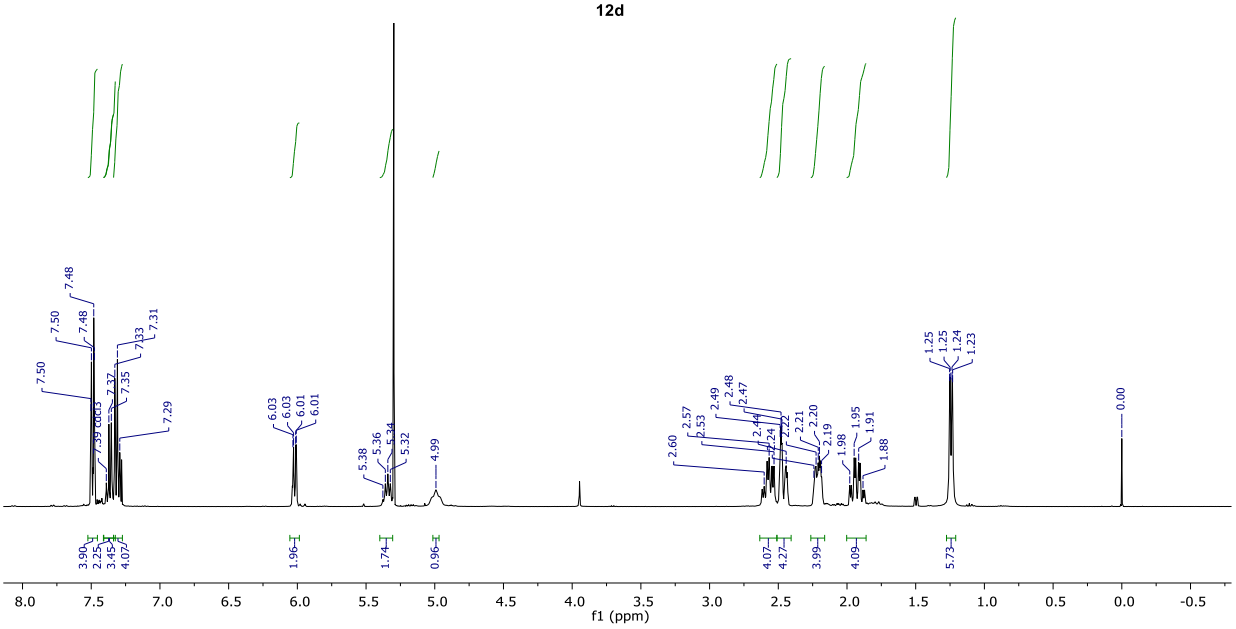


**12c**

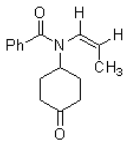
VNMRS400A_25062020_as304-8y11-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as304-8y11
Nom: ALEXANDRA SANDOR
Data: 25/06/20 / Ope.: A.SANDOR



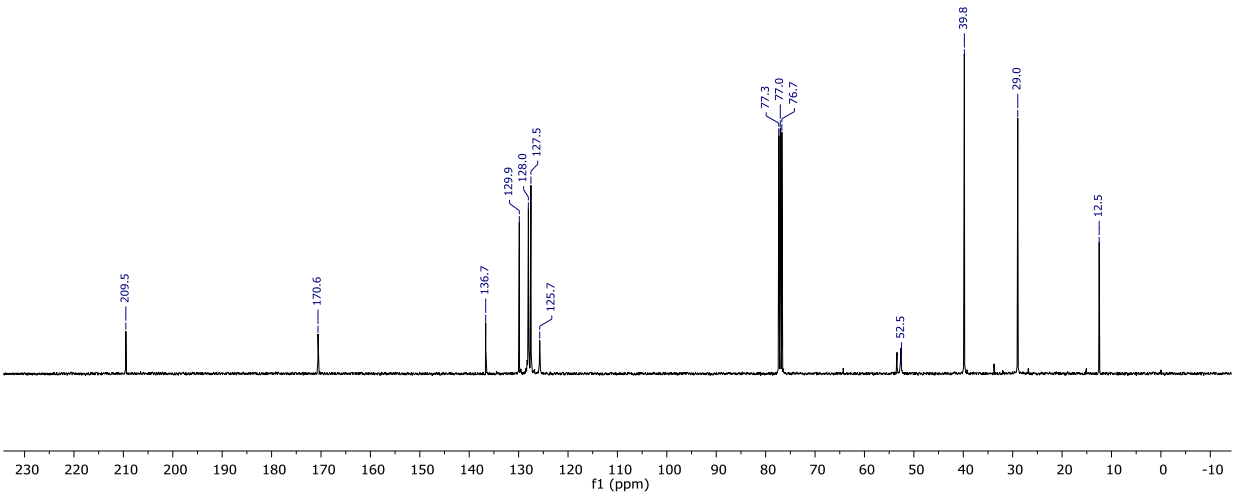
**12d**



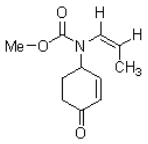

VNMRS400A_25062020_as304-8y11-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as304-8y11
Nom: ALEXANDRA SANDOR
Data: 25/06/20 / Ope.: A.SANDOR



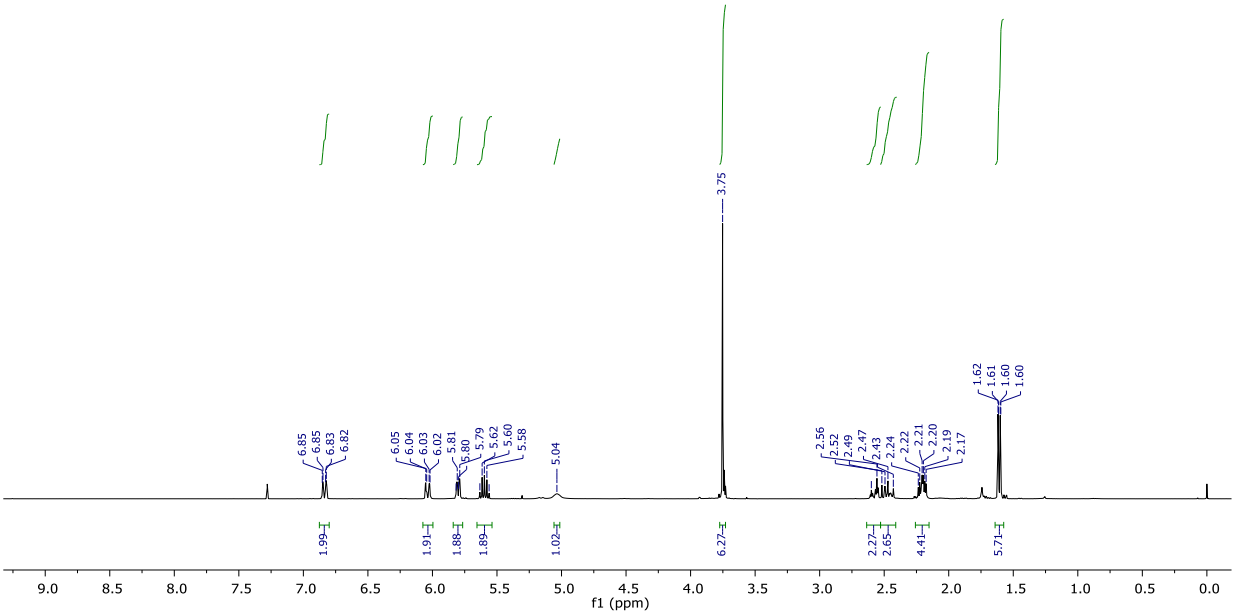
**12d**



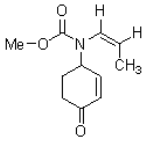
VNMRS400A_28092020_AS-345-2-30-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 1
Usuari: san / Mostra: AS-345-2-30
Nom: ALEXANDRA SANDOR
Data: 28/09/20 / Ope.: V.MERIEL



**15a**




VNMRS400A_28092020_AS-345-2-30-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: 1
Usuari: san / Mostra: AS-345-2-30
Nom: ALEXANDRA SANDOR
Data: 28/09/20 / Ope.: V.MERIEL



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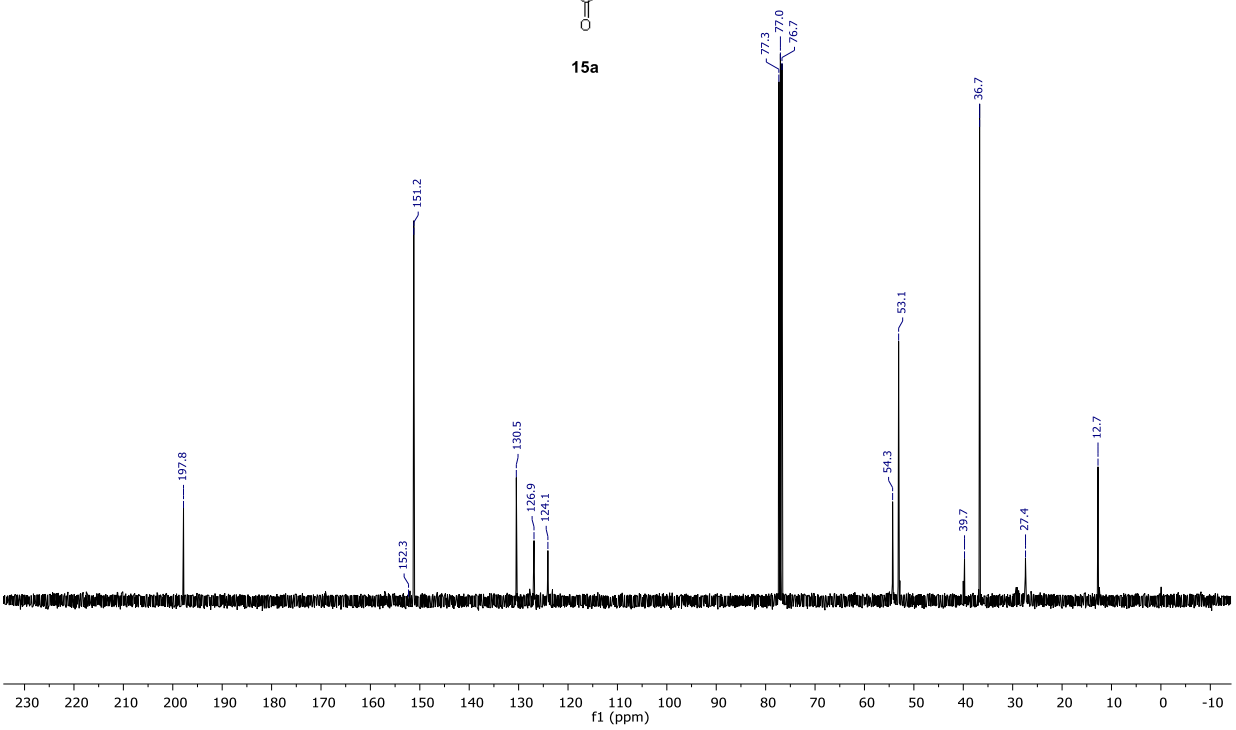

AS315-20-H1_rep_23_54_46
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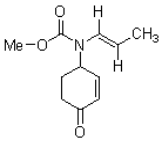
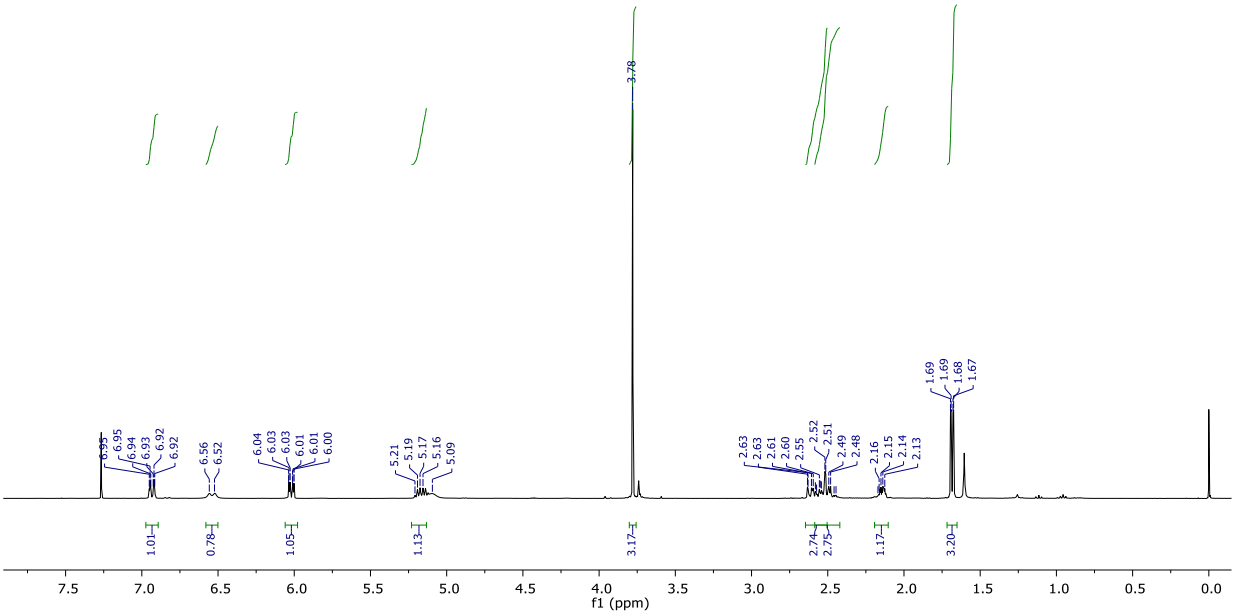
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS315-20
Nom: ALEXANDRA SANDOR
Data: 18/06/20 / Ope.: A.SANDOR



**16a**




AS315-20-C13
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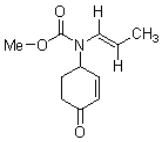
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS315-20
Nom: ALEXANDRA SANDOR
Data: 18/06/20 / Ope.: A.SANDOR



**16a**

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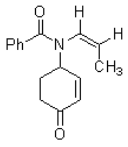
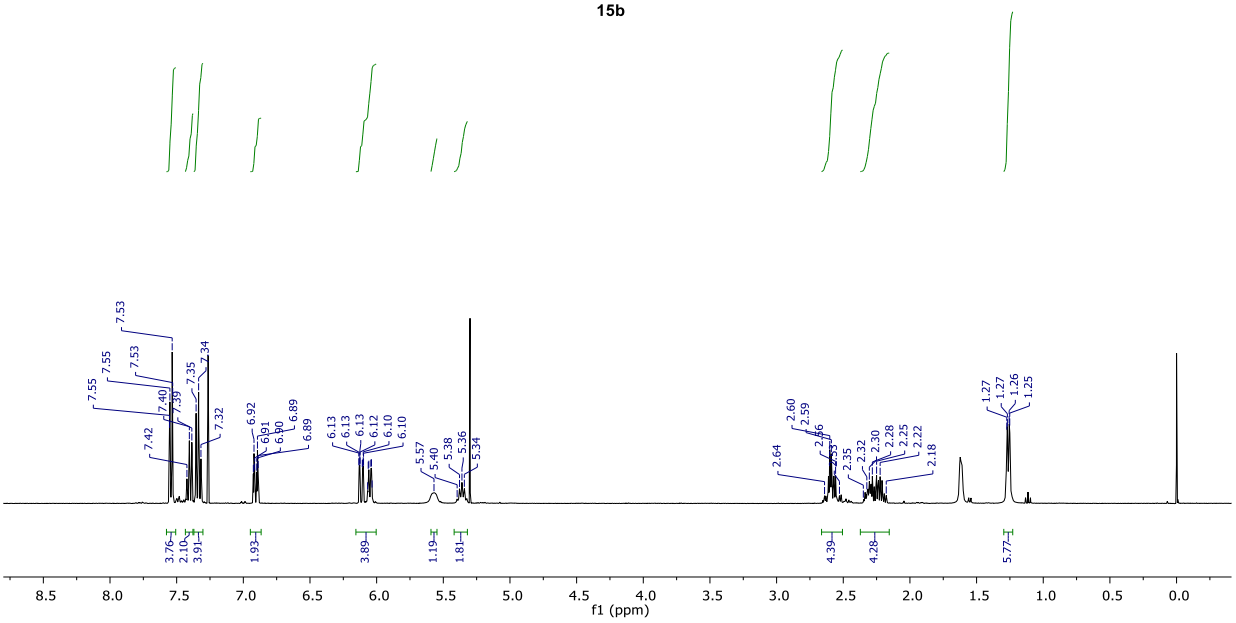
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as329-21
Nom: ALEXANDRA SANDOR
Data: 24/07/20 / Ope.: A.SANDOR



**15b**

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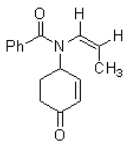
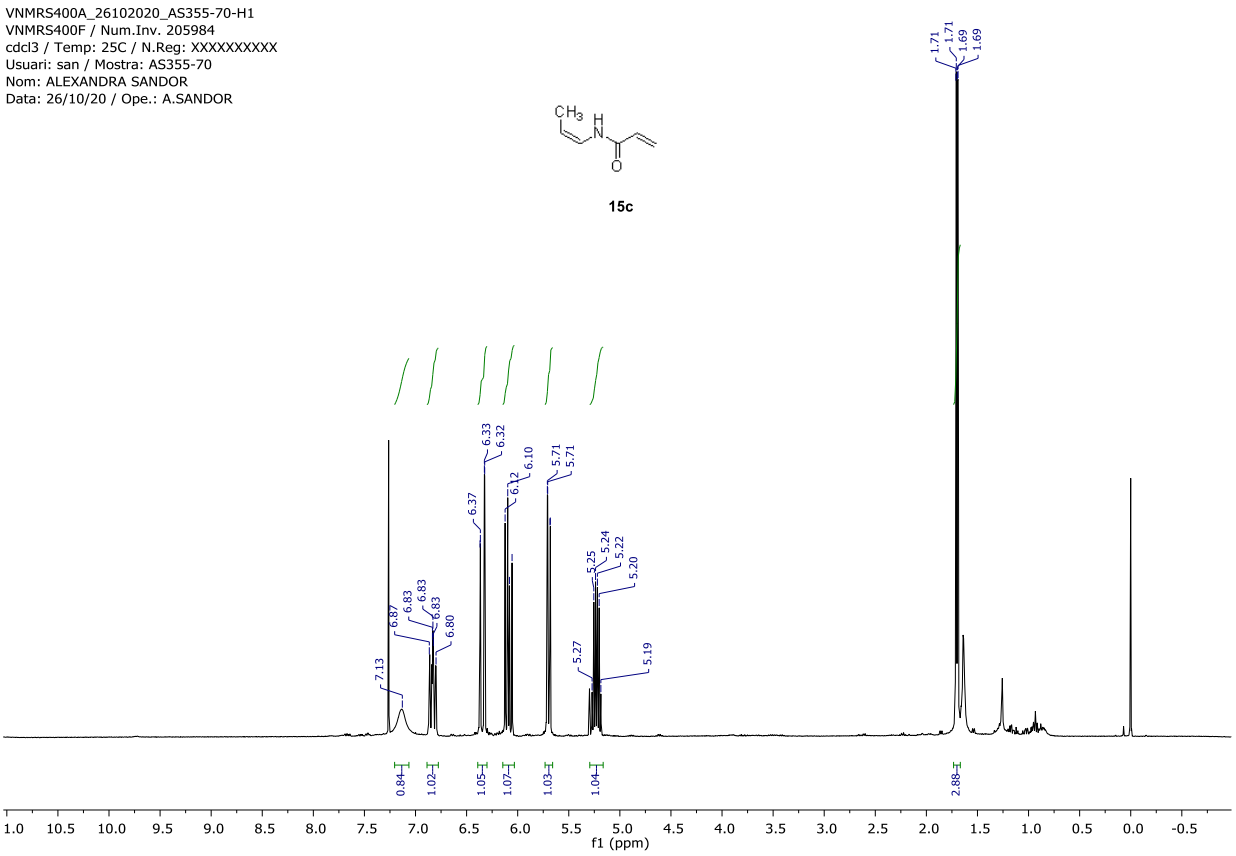
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as329-21
Nom: ALEXANDRA SANDOR
Data: 24/07/20 / Ope.: A.SANDOR



**15b**

**18.**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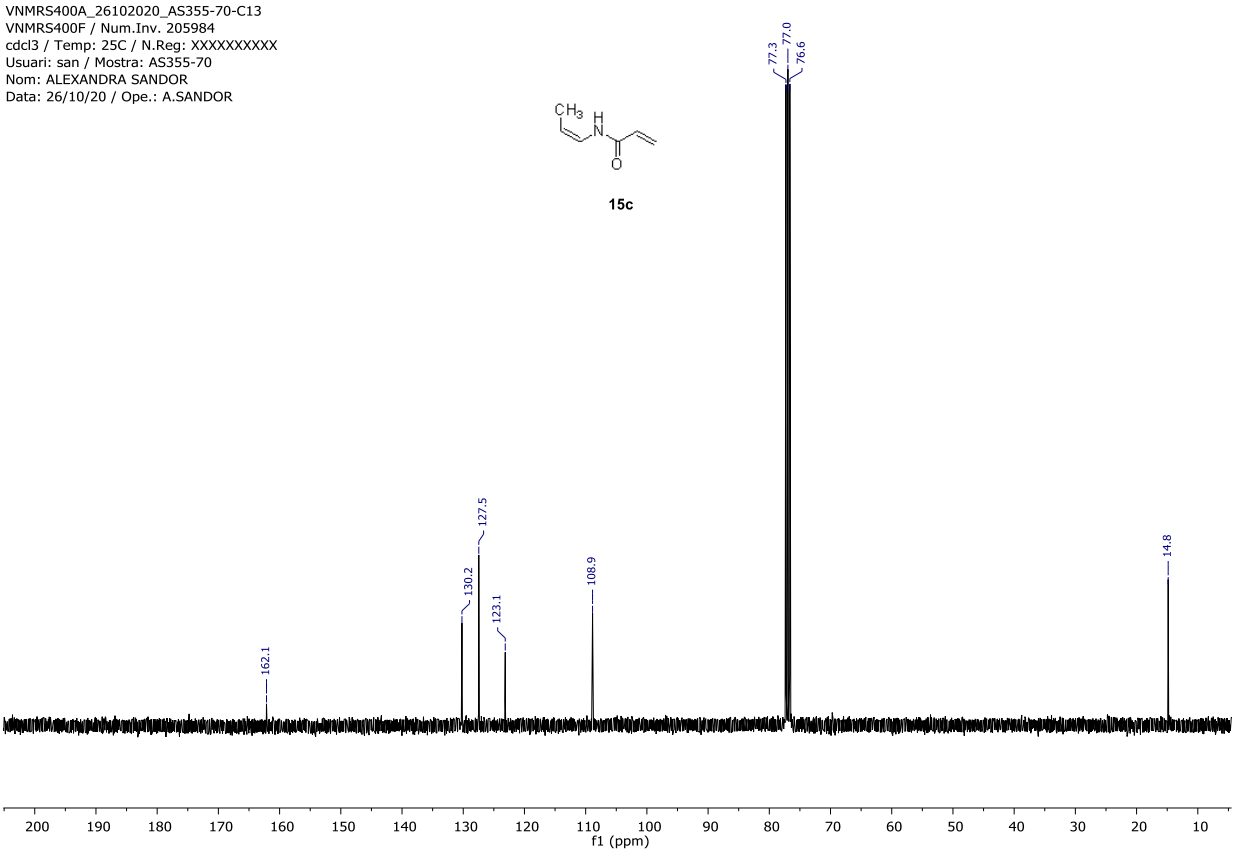
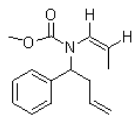
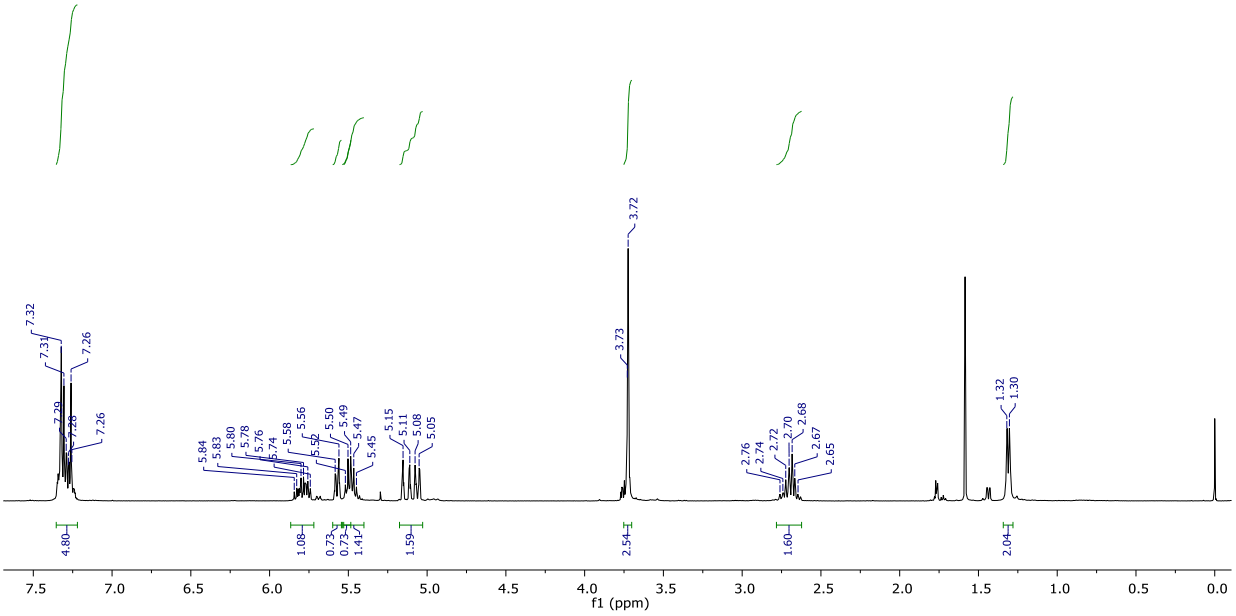
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS355-70
Nom: ALEXANDRA SANDOR
Data: 26/10/20 / Ope.: A.SANDOR
15c
f1 (ppm)


VNMRS400A_26102020_AS355-70-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS355-70
Nom: ALEXANDRA SANDOR
Data: 26/10/20 / Ope.: A.SANDOR
15c
f1 (ppm)

VNMRS400A_29102020_AS353-23-13-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS353-23-13
Nom: ALEXANDRA SANDOR
Data: 29/10/20 / Ope.: A.SANDOR



**15d**

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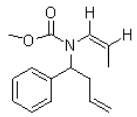
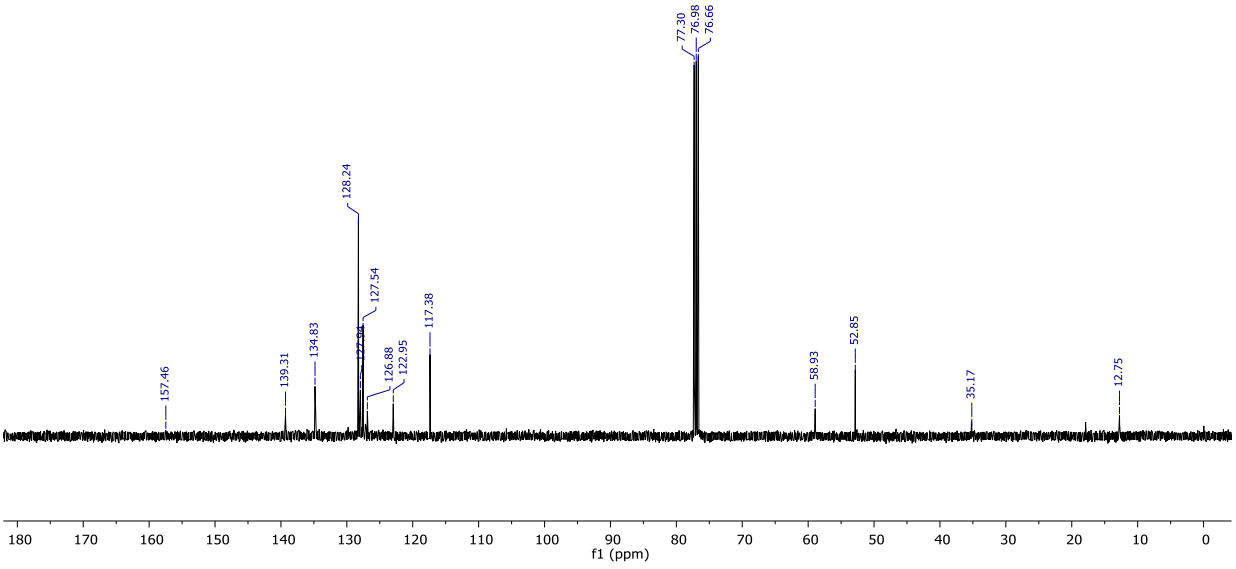
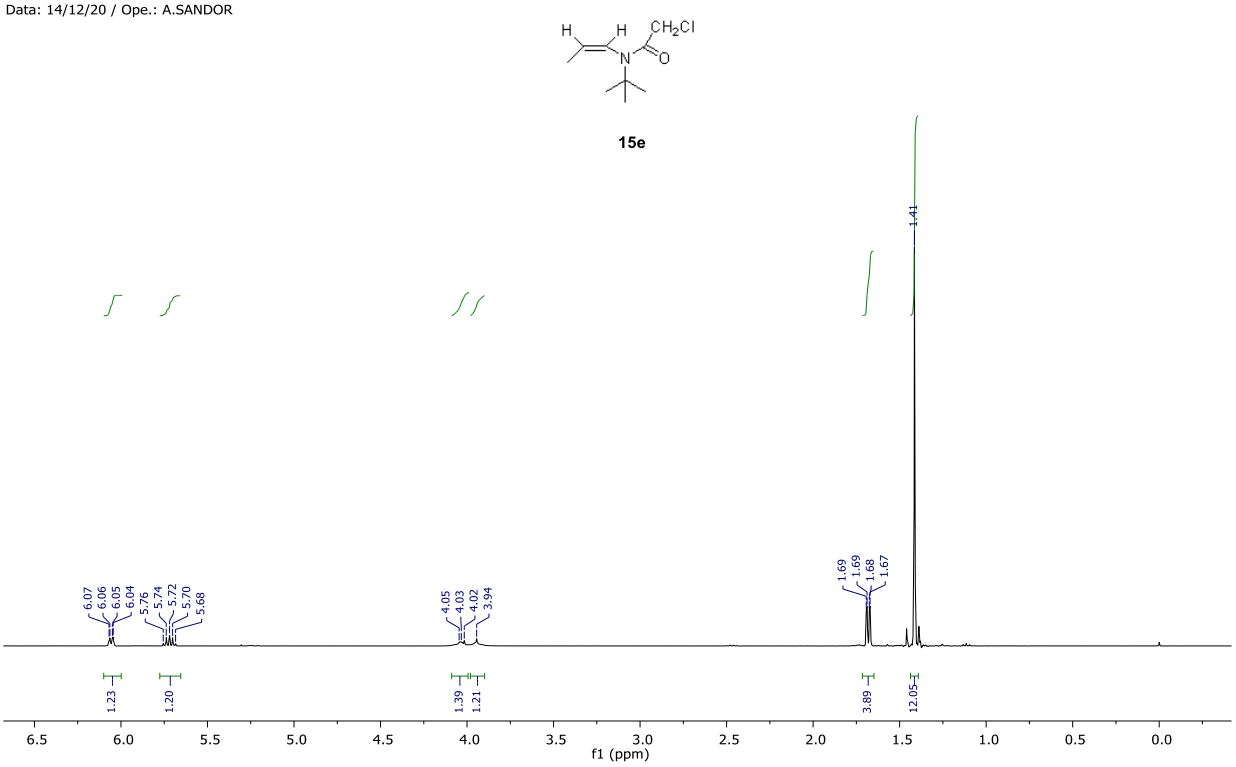
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS353-23-13
Nom: ALEXANDRA SANDOR
Data: 29/10/20 / Ope.: A.SANDOR



**15d**

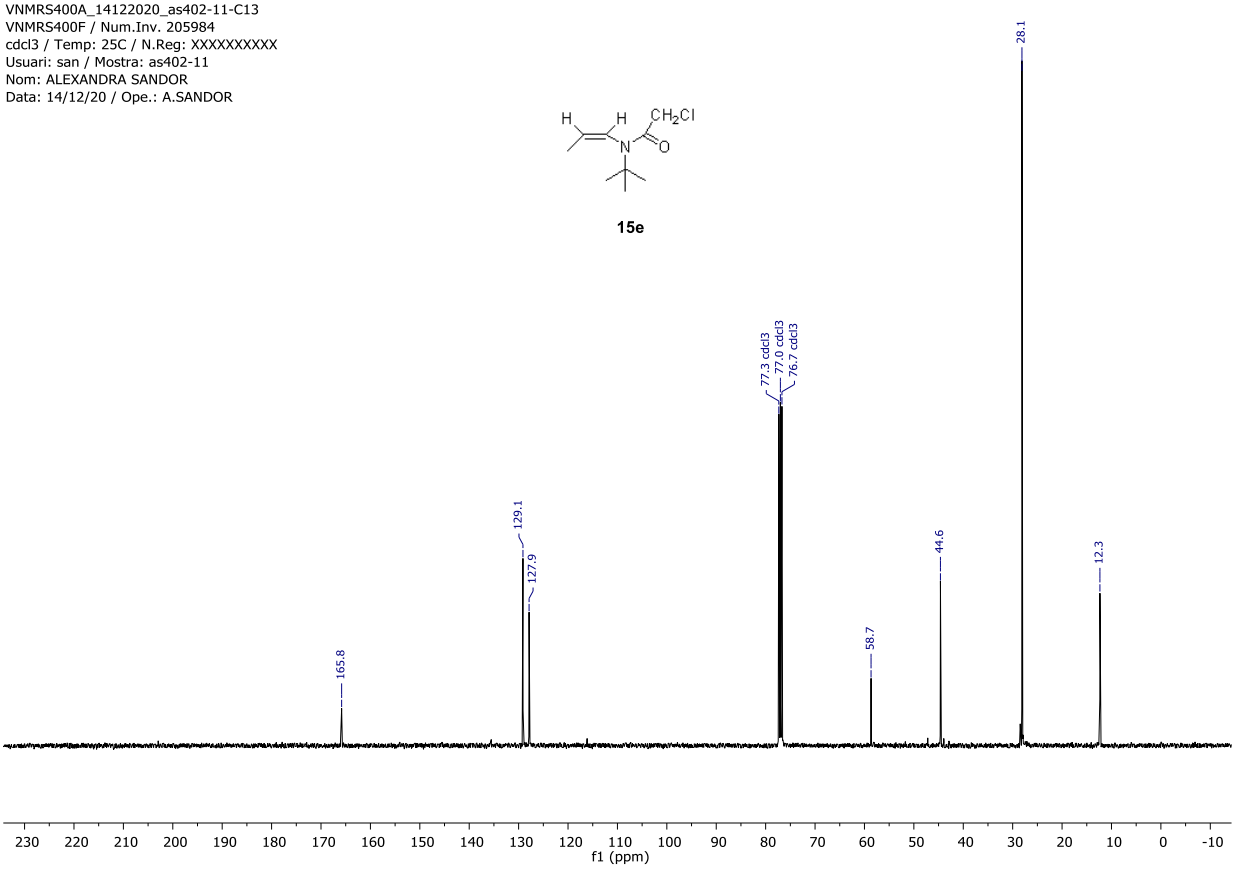


M400AFF_14122020_AS402-11-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS402-11
Nom: ALEXANDRA SANDOR
Data: 14/12/20 / Ope.: A.SANDOR




15e

VNMRS400A_14122020_as402-11-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as402-11
Nom: ALEXANDRA SANDOR
Data: 14/12/20 / Ope.: A.SANDOR




15e

19.

### *6.3. Experimental part of chapter 4*

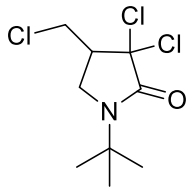
#### 1. Synthesis of trichloro- and dichloroacetamides 17

Starting materials of this part of the work (**17a**-**17p**) were prepared in the context of another project

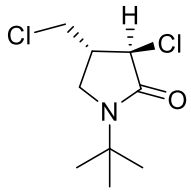
#### 2. General procedure for the reaction of trichloro- and dichloroacetamides 17 with $RuCl_2(PPh_3)_3$

In a 10 mL vessel were placed chloroacetamide **17** (0.386 mmol) and $RuCl_2(PPh_3)_3$ (0.019 mmol, 5 mol%) in toluene (1 mL). The mixture was heated with stirring using microwave irradiation for 15 min (**17a**, **17b**, **17f**, **17h**-**17p**), 30 min (**17c**-**17e**) or 45 min (**17g**) at 160 ºC. After chromatography (hexane-$CH_2Cl_2$, 9:1 to $CH_2Cl_2$) **18** and/or **19** were isolated.

***1*-(*tert*-Butyl)-3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one (18a).** IR (NaCl, neat): $cm^{-1}$; 2978, 2937, 2874, 1715, 1667 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H, *t*-Bu), 2.95-3.03 (m, 1H, CH), 3.22 (dd, *J* = 10.10, 8.22 Hz, 1H, CH2Cl), 3.68-3.75 (m, 2H, $CH_2Cl$, $CH_2N$), 3.99 (dd, *J* = 11.2, 4.2 Hz, 1H, $CH_2N$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 27.2 ($CH_3$), 41.2 (C-5), 46.0 (CH2), 51.0 (CH), 55.6 (C), 85.0 (C-3), 165.6 (CO). HRMS (ESI-TOF): Calcd for $C_9H_{15}Cl_3NO$ $[M+H]^+$ 258.0214; found 258.0211.




**(3*RS*,4*RS*)-1-(*tert*-Butyl)-3-chloro-4-(chloromethyl)-pyrrolidin-2-one (18b).** IR (NaCl, neat): 2979, 2938, 2910, 2875, 1760, 1731, 1704, 1698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H, *t*-Bu), 2.66-2.77 (m, 1H, H-4), 3.31 (dd, *J* = 10.0, 7.3 Hz, 1H, $CH_2Cl$), 3.60-3.82 (m, 3H, $CH_2Cl$, H-5), 4.25 (d, *J* = 8.2 Hz, 1H, H-3); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 27.4 ($CH_3$), 43.6 (C-5), 44.3 (C-4), 45.9 ($CH_2Cl$), 58.1 (C-3), 55.1 (C), 168.4 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_9H_{16}Cl_2NO$ $[M+H]^+$ 224.0603; found 224.0602.



**(3*RS*,4*RS*)-1-(*tert*-Butyl)-3-chloro-4-(chloromethyl)-3-methylpyrrolidin-2-one (18c).** IR (NaCl, neat): 3003, 2974, 2930, 2872, 1686, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.42 (s, 9H, *t*-Bu), 1.73 (s, 3H, $CH_3$), 2.39-2.50 (m, 1H, H-4), 3.15 (ddd, *J* = 9.9, 9.1, 0.5 Hz, 1H, $CH_2Cl$), 3.63 (dd, *J* = 10.0, 6.9 Hz, 1H, $CH_2Cl$), 3.66-3.72 (m, 1H, H-5), 3.82 (dd, *J* =11.2, 5.1 Hz, 1H, H-5); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 24.7($CH_3$), 27.4($CH_3$), 42.3 (C-5), 46.5 (C-4), 47.1 ($CH_2Cl$), 54.8 (C), 70.6 (C-3), 171.0 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{10}H_{18}Cl_2NO$ $[M+H]^+$ 238.076; found 238.0762.

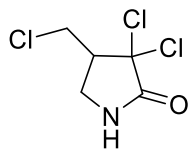
**(3*RS*,4*SR*)-1-(*tert*-Butyl)-3-chloro-4-(chloromethyl)-3-methylpyrrolidin-2-one (19c).** IR (NaCl, neat): 3345, 2976, 2929, 1698, 1479, 1406, 1365 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.42 (s, 9H, *t*-Bu), 1.59 (s, 3H, $CH_3$), 2.79-2.89 (m, 1H, H-4), 3.31 (ddd, *J* = 10.2, 4.4, 0.6 Hz, 1H, $CH_2Cl$), 3.37-3.45 (m, 1H, H-5), 3.70-3.77 (m, 2H, $CH_2Cl$, H-5); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.2($CH_3$), 27.3($CH_3$), 42.5 (C-5), 45.8 ($CH_2Cl$), 47.5 (C-4), 54.8 (C), 69.3 (C-3), 170.9 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{10}H_{18}Cl_2NO$ $[M+H]^+$ 238.076; found 238.0767.

**Ethyl (3*RS*,4*SR*)-1-(*tert*-Butyl)-3-chloro-4-(chloromethyl)-2-oxopyrrolidine-3-carboxylate (18d).** IR (NaCl, neat): 2976, 2935, 1704, 1698, 1478, 1457 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.29-1.37 (m, 3H, $CH_3$), 1.42 (s, 9H, *t*-Bu), 3.18 (t, *J* = 9.7 Hz, 1H, $CH_2Cl$), 3.35-3.45 (m, 1H, H-4), 3.56-3.79 (m, 3H, $CH_2Cl$, H-5), 4.20-4.42 (m, 2H, $CH_2O$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 14.0 ($CH_3$), 27.3 ($CH_3$), 41.5 (H-5), 44.1 (C-4), 46.3 ($CH_2Cl$), 55.4 (C), 63.5 ($CH_2O$), 72.3 (C-3), 166.3 (C-2), 167.0 (CO)**.** HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{20}Cl_2NO_3$ $[M+H]^+$ 296.0815; found 296.0814.

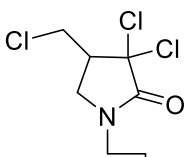
**Ethyl (3*RS*,4*RS*)-1-(*tert*-Butyl)-3-chloro-4-(chloromethyl)-2-oxopyrrolidine-3-carboxylate (19d).** IR (NaCl, neat): 2973, 2935, 2908, 2872, 1758, 1705 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.32 (t, *J* = 7.2 Hz, 3H, $CH_3$), 1.44 (s, 9H, *t*-Bu), 2.96-3.06 (m, 1H, H-4), 3.32 (t, *J* = 9.4 Hz, 1H, $CH_2Cl$), 3.41 (t, *J* = 10.9 Hz, 1H, H-5), 3.71-3.79 (m, 1H, $CH_2Cl$), 3.84 (dd, *J* = 11.0, 4.5 Hz, 1H, H-5), 4.19-4.39 (m,

2H, $CH_2O$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 14.0 ($CH_3$), 27.3 ($CH_3$), 41.2 (C-5), 47.1 ($CH_2Cl$), 49.0 (C-4), 56.0 (C), 63.4 ($CH_2$), 94.9 (C-3), 165.3 (C-2), 166.8 (CO)**.** HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{20}Cl_2NO_3$ $[M+H]^+$ 296.0815; found 296.0816.

**3,3-Dichloro-4-(chloromethyl)pyrrolidin-2-one (18e).** IR (NaCl, neat): 3261, 3006, 2961, 2924, 2854, 1734, 1650, 1481 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.14-3.24 (m, 1H, H-4), 3.28 (dd, *J* = 10.08, 8.5 Hz, 1H, $CH_2Cl$), 3.67-3.80 (m, 2H, $CH_2Cl$, $CH_2N$), 3.99 (dd, *J* = 11.3, 4.36 Hz, 1H, $CH_2N$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 40.9 (C-5), 43.5 ($CH_2Cl$), 53.5 (C-4), 82.9 (C-2), 169.1 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_5H_7Cl_3NO$ $[M+H]^+$ 201.9588; found 201.959.




**1-Butyl-3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one (18f).** IR (NaCl, neat): 2960, 2932, 2872, 1727, 1483, 1447, 1431 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.27-1.42 (m, 2H, $CH_2$), 1.49-1.63 (m, 2H, $CH_2$), 3.05-3.15 (m, 1H, H-4), 3.21-3.36 (m, 2H, $CH_2Cl$, $CH_2N$), 3.47 (dt, *J* = 13.7, 7.5 Hz, 1H, $CH_2N$), 3.60 (dd, *J* = 10.1, 6.9 Hz, 1H, $CH_2Cl$), 3.68-3.79 (m, 1H, H-5), 4.01 (dd, *J* = 11.2, 4.2 Hz, 1H, zH-5); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 13.6 ($CH_3$), 19.8 ($CH_2$), 28.9 ($CH_2$), 41.2 (C-5), 43.7 ($CH_2N$), 47.8 ($CH_2Cl$), 51.7 (C-4), 83.8 (C-3), 165.9 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_9H_{15}Cl_3NO$ $[M+H]^+$ 258.0214; found 258.0214



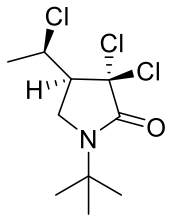

**3,3-Dichloro-4-(chloromethyl)-1-phenylpyrrolidin-2-one (18g).** IR (NaCl, neat): 1708, 1594, 1495, 1473, 1459, 1410 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.20-3.31 (m, 1H, H-4), 3.74 (ddd, *J* = 10.0, 8.4, 0.5 Hz, 1H, H-5), 3.80-3.88 (m, 1H, $CH_2Cl$), 4.01-4.15 (m, 2H, $CH_2Cl$, H-5), 7.19-7.31 (m, 1H, ArH), 7.33-7.52 (m, 2H, ArH), 7.58-7.68 (m, 2H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 41.0 ($CH_2Cl$), 49.1 (C-5), 51.1 (C-4), 84.0 (C-3), 120.2 (CHAr), 126.2 (CHAr), 129.2 (CHAr), 137.9 (CAr), 16.4 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{11}H_{11}Cl_3NO$ $[M+H]^+$ 277.9901; found 277.9899.

**1-Benzyl-3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one (18h).** IR (NaCl, neat): 3063, 3030, 2926, 2878, 1731, 1604, 1585, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 3.01-3.16 (m, 2H, H-4, $CH_2Cl$), 3.40-3.53 (m, 1H, $CH_2Cl$), 3.63-3.73 (m, 1H, H-5), 3.95 (dd, *J* = 11.2, 3.72 Hz, 1H, H-5), 4.45 (d, *J* = 14.7 Hz, 1H, $CH_2N$), 4.63 (d, *J* = 14.7 Hz, 1H, $CH_2N$), 7.21-7.29 (m, 2H, ArH), 7.30-7.42 (m, 3H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 41.0 (H-5), 47.2 ($CH_2Cl$), 47.9 ($CH_2N$), 51.6 (H-4), 83.7 (C-3), 128.2 (CHAr), 128.3 (CHAr), 129.1 (CHAr), 134.5 (CAr), 166.0 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{13}Cl_3NO$ $[M+H]^+$ 292.0057; found 292.0062.

**1-Allyl-3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one (18i).** IR (NaCl, neat): 3085, 3015, 2961, 2923, 1731, 1644 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 3.06-3.16 (m, 1H, H-4), 3.23 (ddd, *J* = 10.2, 8.2, 0.5 Hz, 1H, $CH_2Cl$), 3.59 (ddd, *J* = 10.2, 7.0, 0.6 Hz, 1H, $CH_2Cl$), 3.74 (ddd, *J* = 11.3, 10.1, 0.6 Hz, 1H, H-5), 3.91-4.05 (m, 3H, H-5, $CH_2N$), 5.24-5.32 (m, 2H, $CH_2$), 5.66-5.81 (m, 1H, CH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 41.1 (C-5), 46.4 ($CH_2N$), 47.4 ($CH_2Cl$), 51.7 (C-4), 83.6 (C-3), 119.7 ($CH_2$), 130.5 (CH), 165.7 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_8H_{11}Cl_3NO$ $[M+H]^+$ 241.9901; found 241.9898.

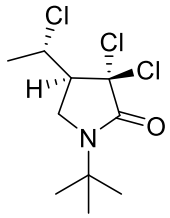
**1-(2-Bromoallyl)-3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one (18j).** IR (NaCl, neat): 2961, 2920, 2849, 1730, 1629 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.09-3.22 (m, 1H, H-4), 3.31 (ddd, *J* = 10.1, 8.1, 0.7 Hz, 1H, $CH_2Cl$), 3.57-3.65 (m, 1H, $CH_2Cl$), 3.71-3.81 (m, 1H, H-5), 4.02 (ddd, *J* = 11.3, 4.3, 0.74 Hz, 1H, H-5), 4.17 (d, *J* =15.4 Hz, 1H, $NCH_2$), 4.32 (d, *J* =15.4 Hz, 1H, $NCH_2$), 5.67-5.73 (d, *J* = 2.24 Hz, 1H, $CH_2$), 5.86-5.89 (d, *J* = 2.00 Hz, 1H, $CH_2$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 40.9 (C-5), 47.3 ($CH_2Cl$), 51.6 ($NCH_2$), 51.8 (C-4), 83.2 (C-3), 121.0 ($CH_2$), 125.9 (CBr), 165.9 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_8H_{10}BrNO$ $[M+H]^+$ 319.9006; found 319.9003.

**(*RS*)-1-(*tert*-Butyl)-3,3-dichloro-4-((*SR*)-1-chloroethyl)pyrrolidin-2-one (18k).**



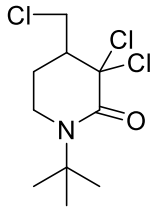
IR (NaCl, neat): 3131, 2979, 2935, 2913, 2873, 1724 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.44 (s, 9H, *t*-Bu), 1.84 (d, *J* = 6.5 Hz, 3H, $CH_3$), 2.81 (ddd, *J* = 9.9, 9, 7.2 Hz, 1H, H-4), 3.17 (dd, *J* = 10.3, 9.0, 1H, $CH_2$), 3.74 (dd, *J* = 10.3, 7.2 Hz, 1H, $CH_2$), 4.33 (dq, *J* = 9.9, 6.5 Hz, 1H, CHCl); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 23.8 ($CH_3$), 27.2 ($CH_3$), 46.9 (C-5), 55.5 (C-4), 55.6 (C), 56.9 (CCl), 84.8 (C-3), 165.7 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{10}H_{17}Cl_3NO$ $[M+H]^+$ 272.0370; found 272.0363

**(*RS*)-1-(*tert*-Butyl)-3,3-dichloro-4-((*RS*)-1-chloroethyl)pyrrolidin-2-one (19k).**



IR (NaCl, neat): 3001, 2981, 2934, 2914, 1715, 1670 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.44 (s, 9H, *t*-Bu), 1.53 (d, *J* = 6.7 Hz, 3H, $CH_3$), 2.94-3.01 (m, 1H, H-4), 3.18-3.24 (m, 1H, $CH_2$), 3.52-3.57 (m, 1H, $CH_2$), 4.39-4.48 (m, 1H, CHCl); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.9 ($CH_3$), 27.2 ($CH_3$), 44.4 (C-5), 54.3 (CCl), 54.7 (C-4), 55.6 (C), 85.4 (C-3), 165.9 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{10}H_{17}Cl_3NO$ $[M+H]^+$ 272.0370; found 272.0366.

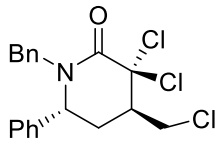
**1-(*tert*-Butyl)-3,3-dichloro-4-(chloromethyl)piperidin-2-one (18l).** IR (NaCl, neat): 3008, 2967, 2931, 2870, 1672, 1631 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.46 (s, 9H, *t*-Bu), 1.79-1.96 (m, 1H, H-5), 2.33-2.43 (m, 1H, H-5), 2.66 (dddd, *J* = 12.6, 10.1, 3.5, 2.4 Hz, 1H, H-4), 3.31 (dddd, *J* = 13.1, 11.9, 4.8, 1.1 Hz, 1H, H-6), 3.50-3.61 (m, 2H, H-6, $CH_2Cl$), 4.13 (dd, *J* = 11.1, 3.2 Hz, 1H, $CH_2Cl$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 23.4 (C-5), 27.6 ($CH_3$), 43.0 (C-6), 44.0 ($CH_2Cl$), 51.8 (C-4), 59.0 (C), 87.2 (C-3), 163.2 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{10}H_{17}Cl_3NO$ $[M+H]^+$ 272.0370; found 272.0363.



**(4*RS*,6*SR*)-1-Benzyl-3,3-dichloro-4-(chloromethyl)-6-phenylpiperidin-2-one (18m).** IR (NaCl, neat): 3086, 3063, 3029, 2966, 2931, 1681, 1603, 1585 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.28-2.37 (m, 2H, H-5), 2.74-2.83 (m, 1H, H-4), 3.44-3.59 (m, 2H, $CH_2Cl$, $CH_2Bn$), 4.04 (dd, *J* = 11.1, 2.97 Hz, 1H, $CH_2Cl$), 4.63 (dd, *J* = 5.5, 2.6 Hz, 1H, H-6), 5.59 (d, *J* = 14.8 Hz, 1H, $CH_2Bn$), 7.06-7.23 (m, 5H, ArH), 7.25-7.49 (m, 5h, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 31.0 (C-5), 43.5 ($CH_2Cl$), 47.2 (C-4), 49.7

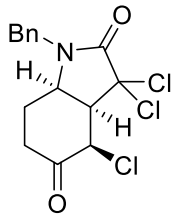
($CH_2Bn$), 58.1 (C-6), 85.4 (C-3), 126.0 (ArCH), 127.9, 128.0 (ArCH), 128.3, 128.9 (ArCH), 129.4 (ArCH), 135.8 (ArC), 138.6 (ArC), 164.2 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{19}H_{19}Cl_3NO$ $[M+H]^+$ 382.0527; found 382.0515.

**(4*RS*,6*RS*)-1-Benzyl-3,3-dichloro-4-(chloromethyl)-6-phenylpiperidin-2-one**



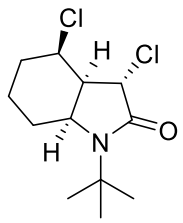

**(19m).** IR (NaCl, neat): 3086, 3063, 3029, 2926, 2849, 1730, 1676, 1603 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.0-2.13 (m, 1H, H-5), 2.60 (ddd, *J* = 14.6, 5.8, 2.9, 1H, H-5), 2.69-2.78 (m, 1H, H-4), 3.47-3.6 (m, 2H, $CH_2Cl$, $CH_2Bn$), 4.2 (dd, *J* = 11.1, 2.9 Hz, 1H, $CH_2Cl$), 4.33 (dd, *J* = 11.6, 5.8 Hz, 1H, H-6), 5.35 (d, *J* = 14.6 Hz, 1H, $CH_2Bn$), 6.94-7.22 (m, 5H, ArH), 7.22-7.48 (m, 5H, ArH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 32.8 (C-5), 43.8 ($CH_2Cl$), 48.3 ($CH_2Bn$), 50.5 (C-4), 60.1 (C-6), 85.3 (C-3), 127.8 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 129.2 (ArCH), 135.8 (ArC), 139.8 (ArC), 164.1 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{19}H_{19}Cl_3NO$ $[M+H]^+$ 382.0527; found 382.0514.

**(3a*RS*,4*RS*,7a*RS*)-1-Benzyl-3,3,4-trichlorohexahydro-2H-indole-2,5(3H)-dione (18n).**




IR (NaCl, neat): 3064, 3029, 2949, 2923, 1737, 1731, 1715 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.00-2.15 (m, 1H, H-7), 2.18-2.28 (m, 1H, H-7), 2.46 (dt, *J* = 17.2, 4.3 Hz, 1H, H-6), 2.70 (ddd, *J* = 17.0, 13.0, 6.0 Hz, 1H, H-6), 3.44 (dd, *J* = 8.2, 5.0 Hz, 1H, CH), 3.82 (m, *J* = 11.4, 8.2, 5.1 Hz, 1H, NCH), 4.26 (d, *J* = 15.0 Hz, 1H, $CH_2Ar$), 4.9 (d, *J* = 4.6, 1H, ClCH), 4.94 (s, 1H, $CH_2Ar$), 7.24-7.30 (m, 2H, ArCH), 7.33-7.43 (m, 3H, ArCH); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 24.6 (C-7), 32.8 (C-6), 46.2 ($CH_2Ar$), 52.3 (NCH), 57.2 (ClCH), 57.3 (CH), 82.6 ($CCl_2$), 128.1(ArCH), 128.6(ArCH), 129.2 (ArCH), 134.4 (C), 165.4 (CO), 199.2 (CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{15}H_{15}Cl_3NO_2$ $[M+H]^+$ 346.0163; found 346.0158.

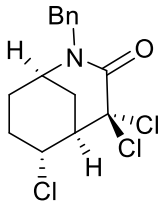
**(3*RS*,3a*RS*,4*SR*,7a*RS*)-1-(*tert*-Butyl)-3,4-dichlorooctahydro-2*H*-indol-2-one**




**(18o).** IR (NaCl, neat): 2949, 2869, 1704, 1480, 1459, 1393 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.07-1.26 (m, 2H, $CH_2$), 1.44 (s, 9H, *t*-Bu), 1.56-1.68 (m, 1H, $CH_2$), 1.76-1.89 (m, 1H, $CH_2$), 1.94-2.07 (m, 1H, $CH_2$), 2.15-2.26 (m, 1H, $CH_2$), 2.71 (dd, *J* =12.3, 6.6 Hz, 1H, H-3a), 3.88-3.99 (m, 1H, H-4), 4.27 (d, *J* =12.2 Hz, 1H, H-7a), 4.65 (bs, 1H, H-3); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 17.1 ($CH_2$), 28.0 ($CH_3$), 28.5 ($CH_2$), 31.7 ($CH_2$), 51.7 (C-3a), 52.6 (C-4), 55.2 (C), 56.7 (C-3), 58.2 (C-7a), 167.8

(CO). HRMS (ESI-TOF) *m/z*: calcd for $C_{12}H_{20}Cl_2NO$ $[M+H]^+$ 264.0916; found 264.0916.

**(1*RS*,5*RS*,6*RS*)-2-benzyl-4,4,6-trichloro-2-azabicyclo[3.3.1]nonan-3-one (18p).**




The spectroscopic data of this product matches the ones reported previously.[7]

[7] Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.; Pérez, P. J.; Belderrain, T. R.. *Chem. Commun.* **2012**, *48*, 8799–8801.

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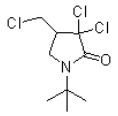
Data: 01/12/20 / Ope.: A.SANDOR




**18a**

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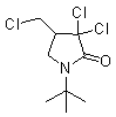


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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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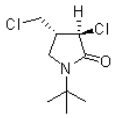
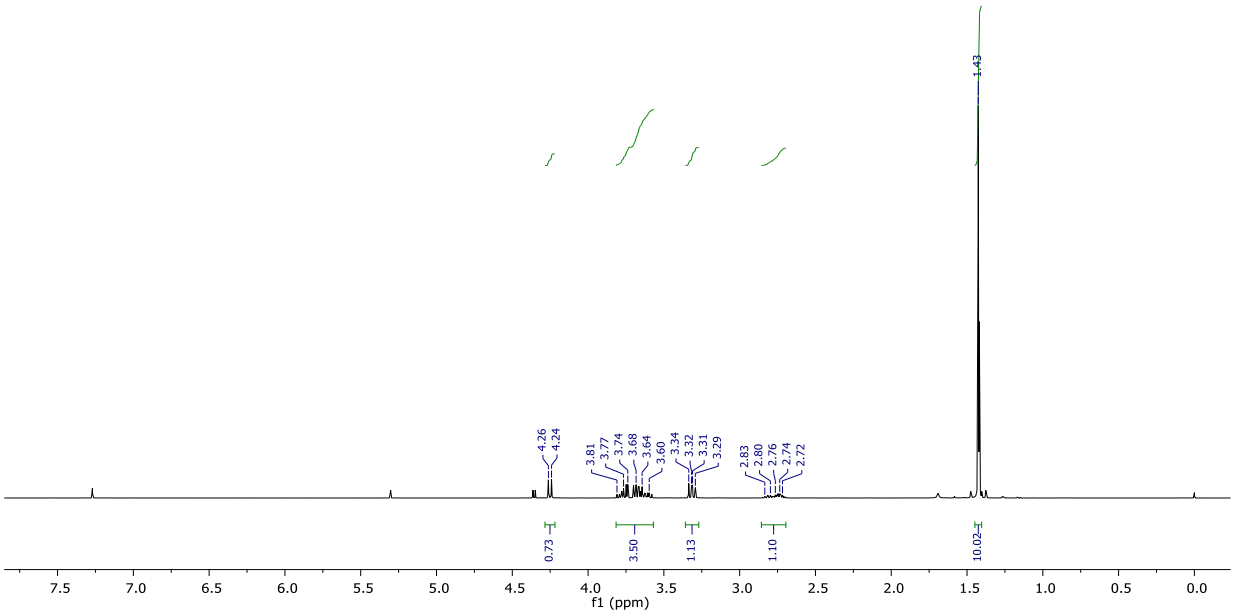
Data: 17/12/20 / Ope.: A.SANDOR



**18b**

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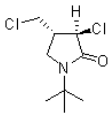
Data: 17/12/20 / Ope.: A.SANDOR



**18b**

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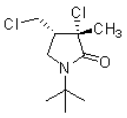
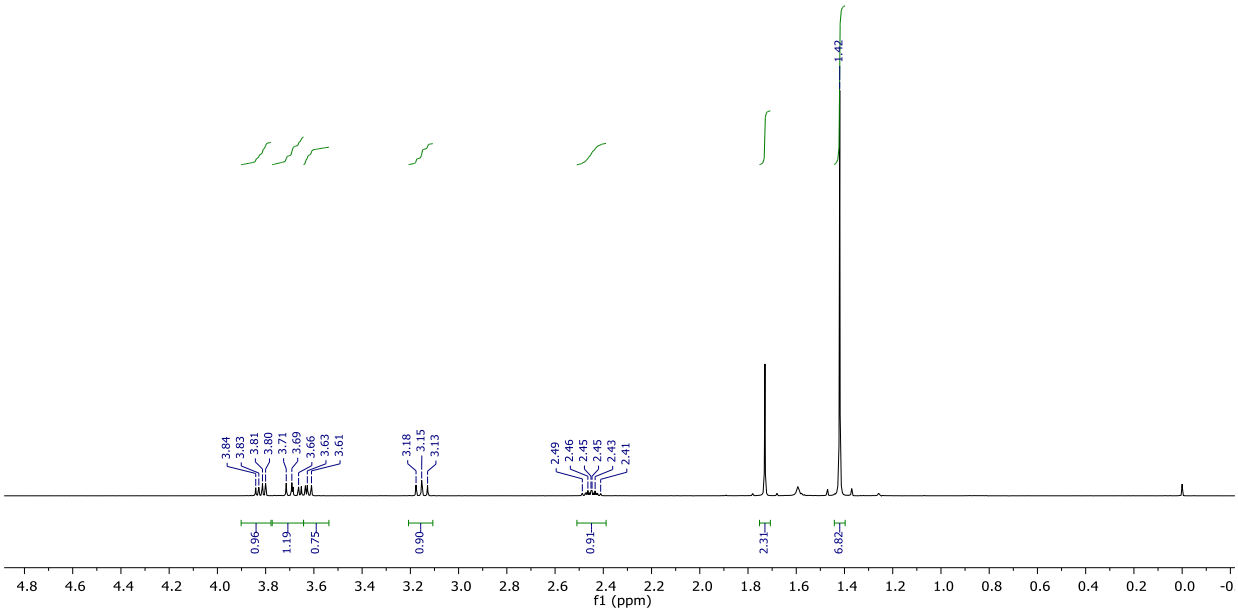
Data: 25/01/21 / Ope.: F.DIABA



18c

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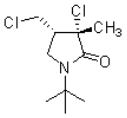

18c

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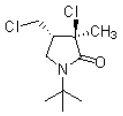
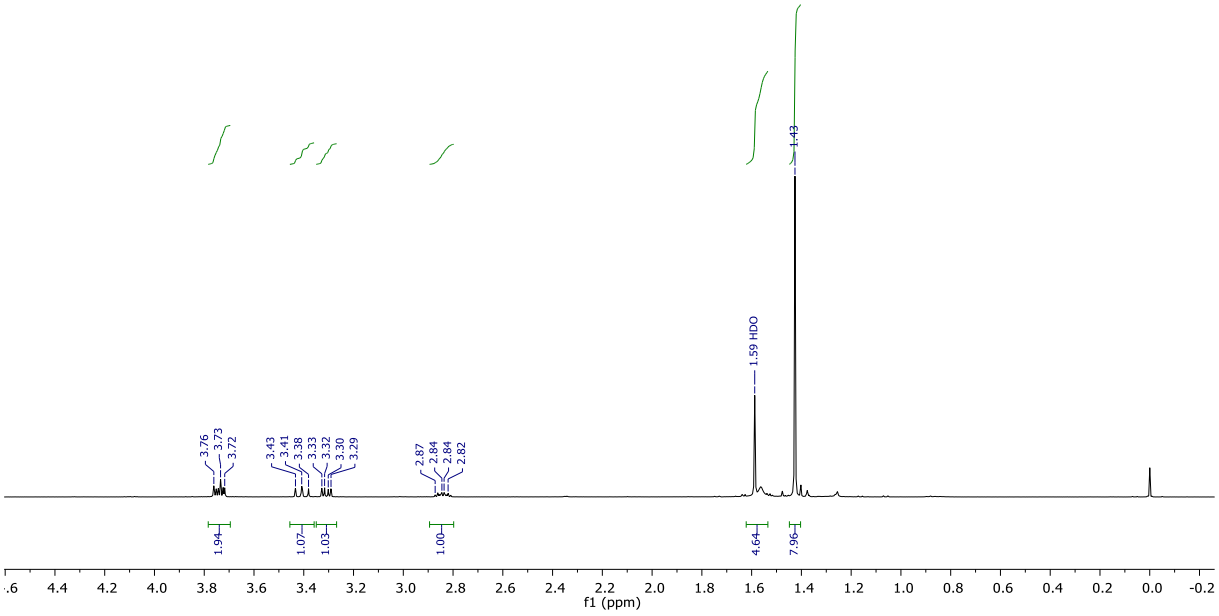
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS411-2-19
Nom: ALEXANDRA SANDOR
Data: 26/01/21 / Ope.: A.SANDOR



**19c**

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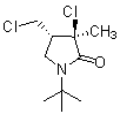

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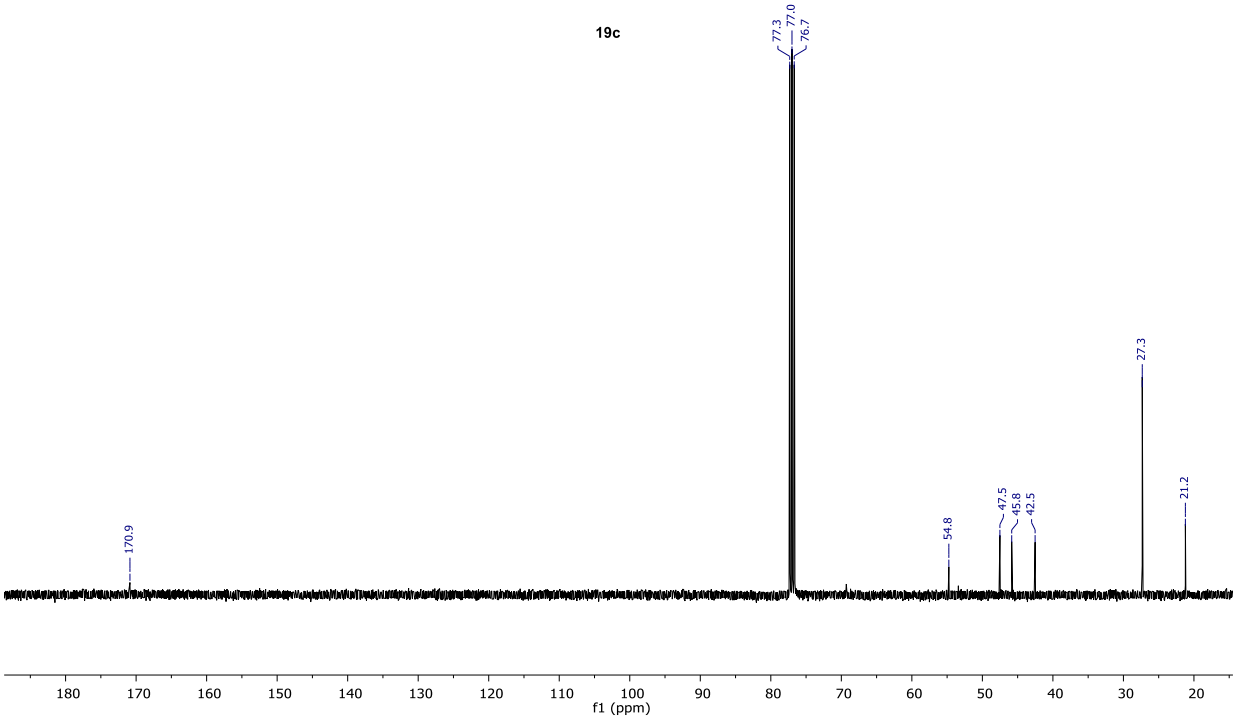

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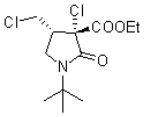
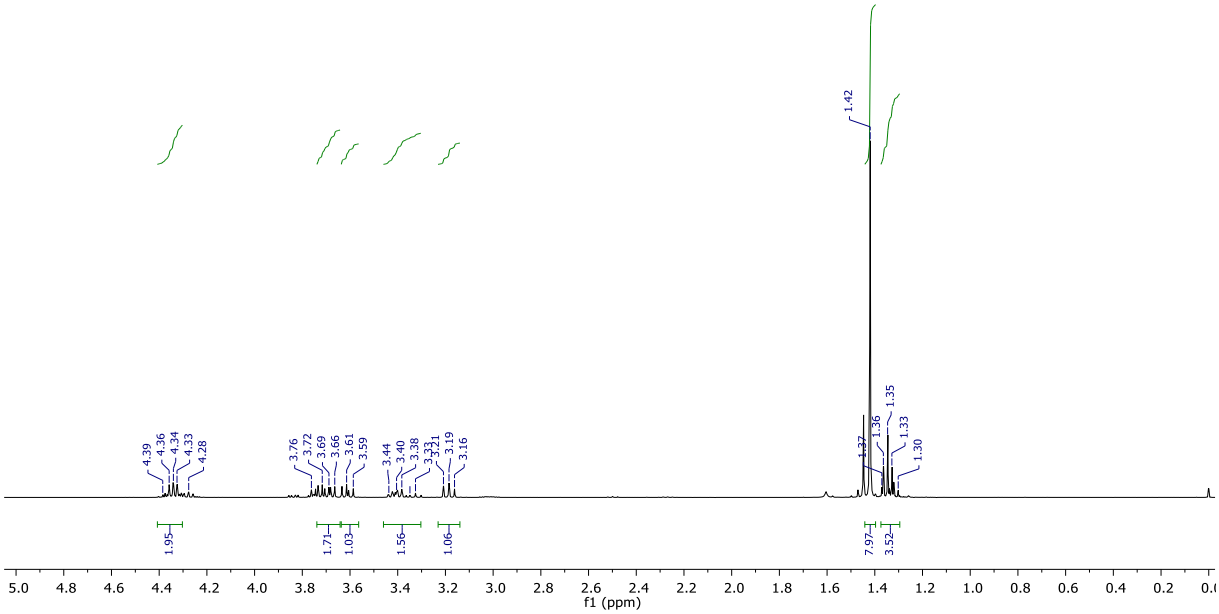
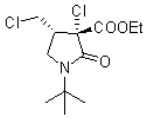
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as401-2-8
Nom: ALEXANDRA SANDOR
Data: 16/12/20 / Ope.: A.SANDOR




**18d**




VNMRS400A_17122020_as401-2-8-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as401-2-8
Nom: ALEXANDRA SANDOR
Data: 17/12/20 / Ope.: A.SANDOR

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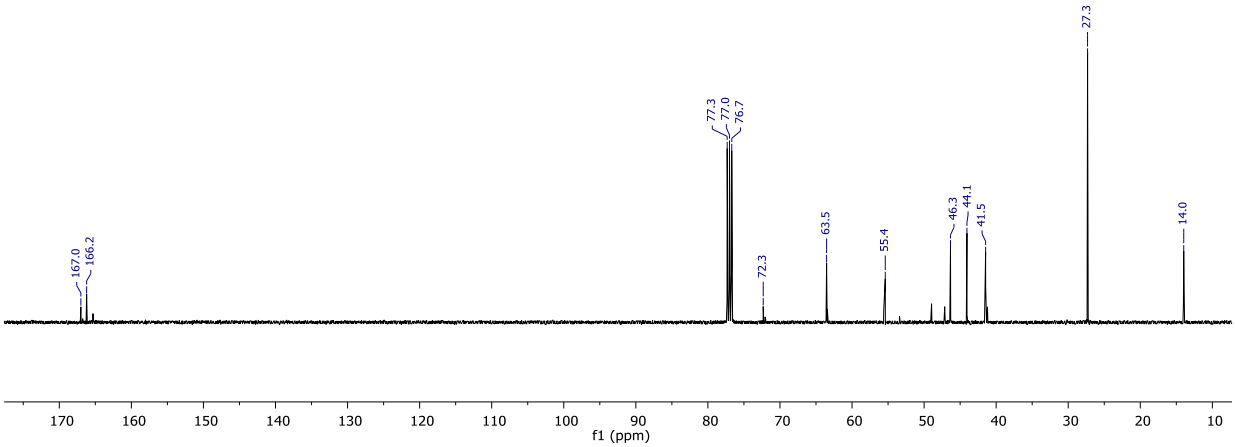
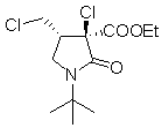


VNMRS400A_16122020_as401-2-16-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as401-2-16
Nom: ALEXANDRA SANDOR
Data: 16/12/20 / Ope.: A.SANDOR

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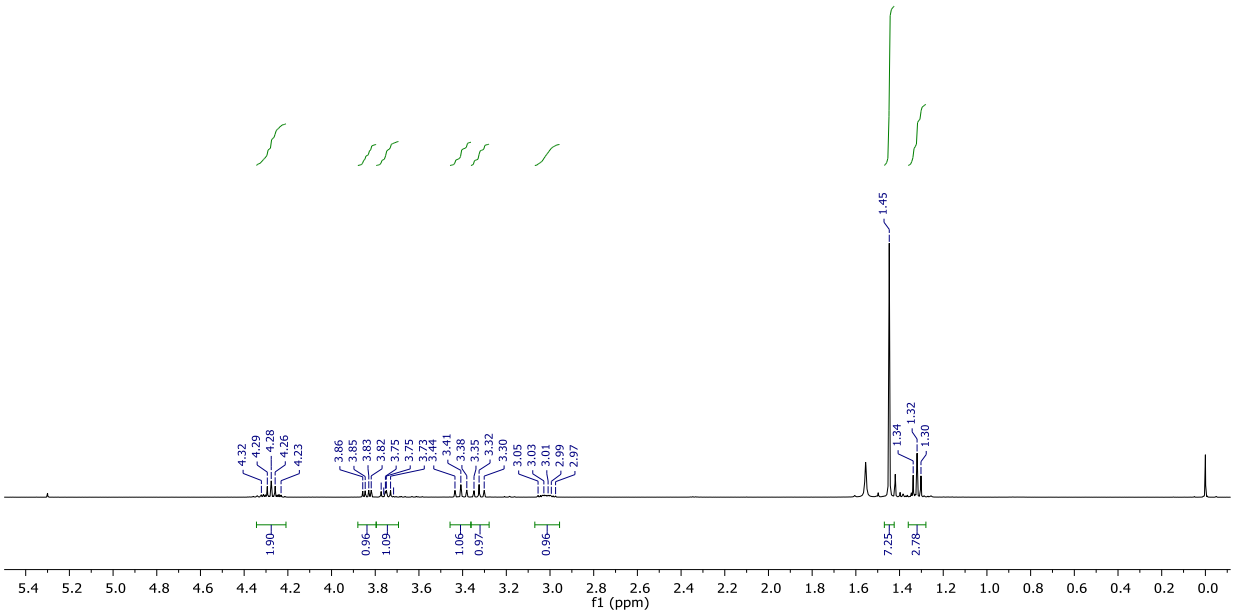
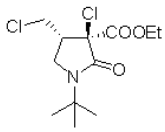
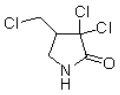



VNMRS400A_16122020_as401-2-16-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as401-2-16
Nom: ALEXANDRA SANDOR
Data: 16/12/20 / Ope.: A.SANDOR




**19d**

VNMRS400A_04022021_as416-21y23-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as416-21y23
Nom: ALEXANDRA SANDOR
Data: 04/02/21 / Ope.: A.SANDOR



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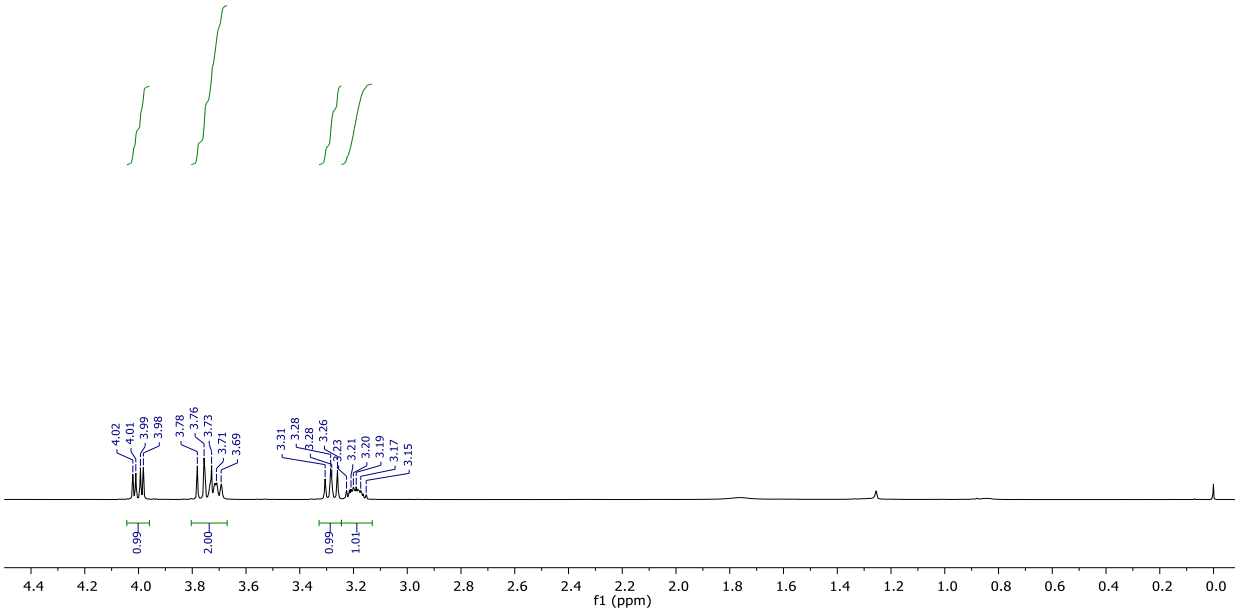
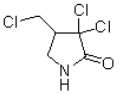



VNMRS400A_04022021_as416-21y23-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as416-21y23
Nom: ALEXANDRA SANDOR
Data: 04/02/21 / Ope.: A.SANDOR



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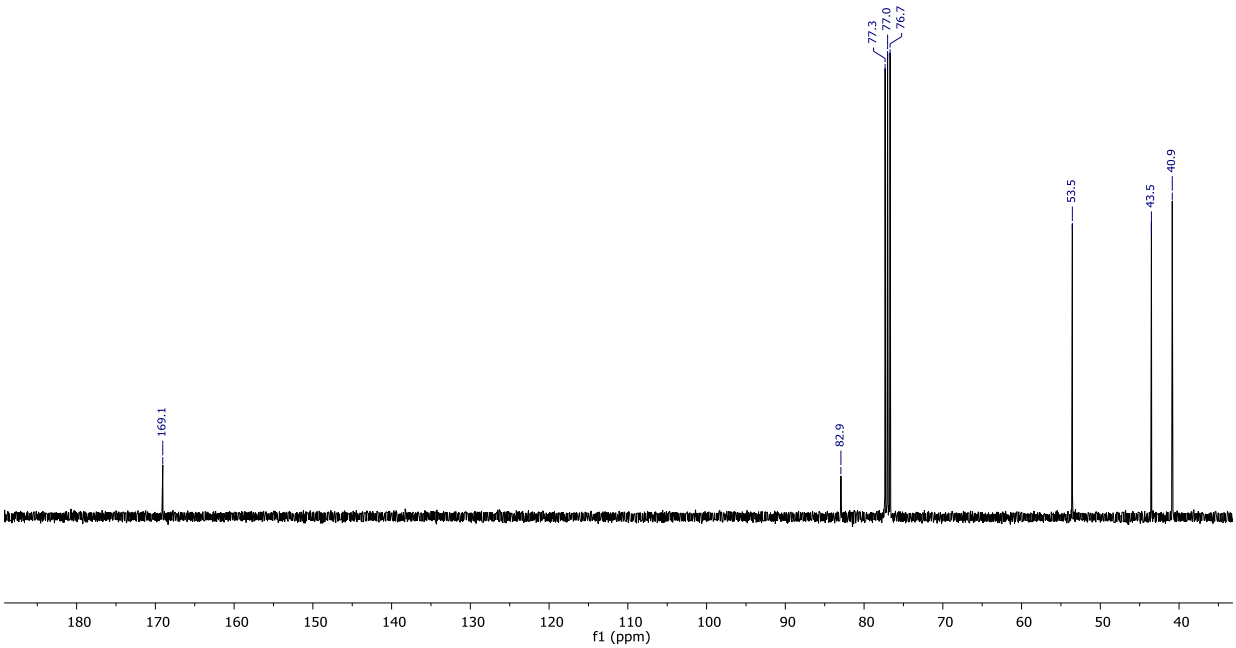
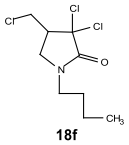
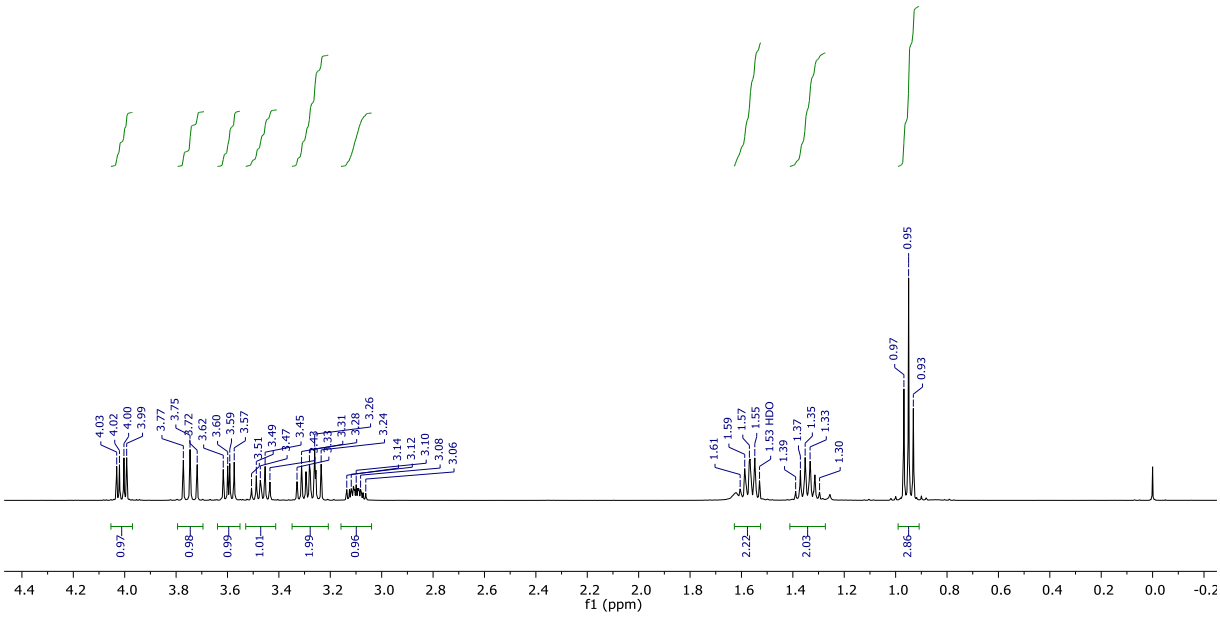


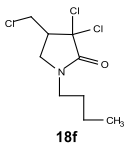
VNMRS400A_27012021_AS414-14-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS414-14
Nom: ALEXANDRA SANDOR
Data: 27/01/21 / Ope.: A.SANDOR




**18f**




VNMRS400A_27012021_AS414-14-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS414-14
Nom: ALEXANDRA SANDOR
Data: 27/01/21 / Ope.: A.SANDOR

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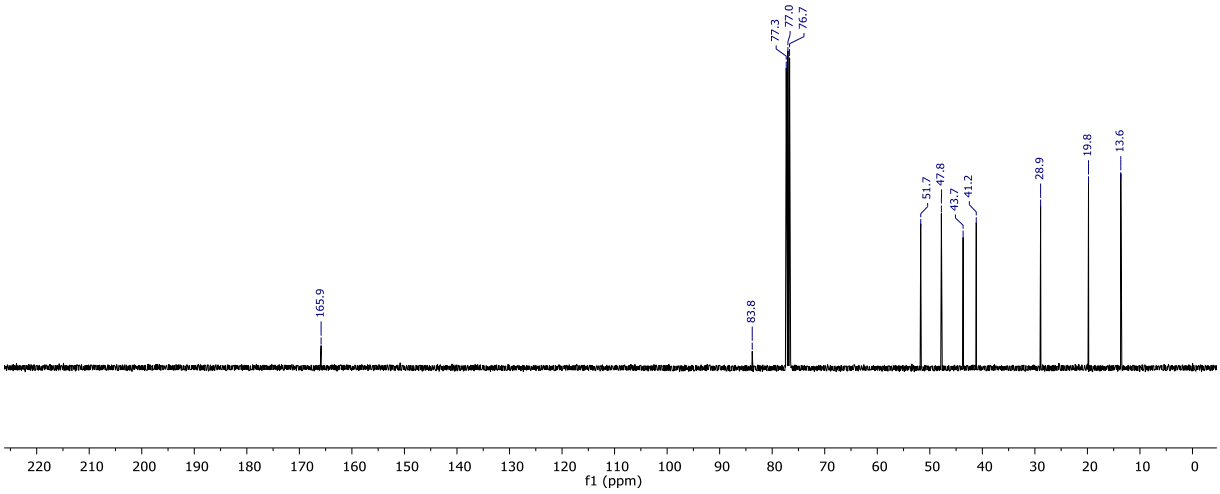
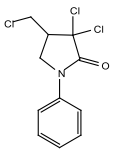


VNMRS400A_26012021_AS413-28-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS413-28
Nom: ALEXANDRA SANDOR
Data: 26/01/21 / Ope.: A.SANDOR



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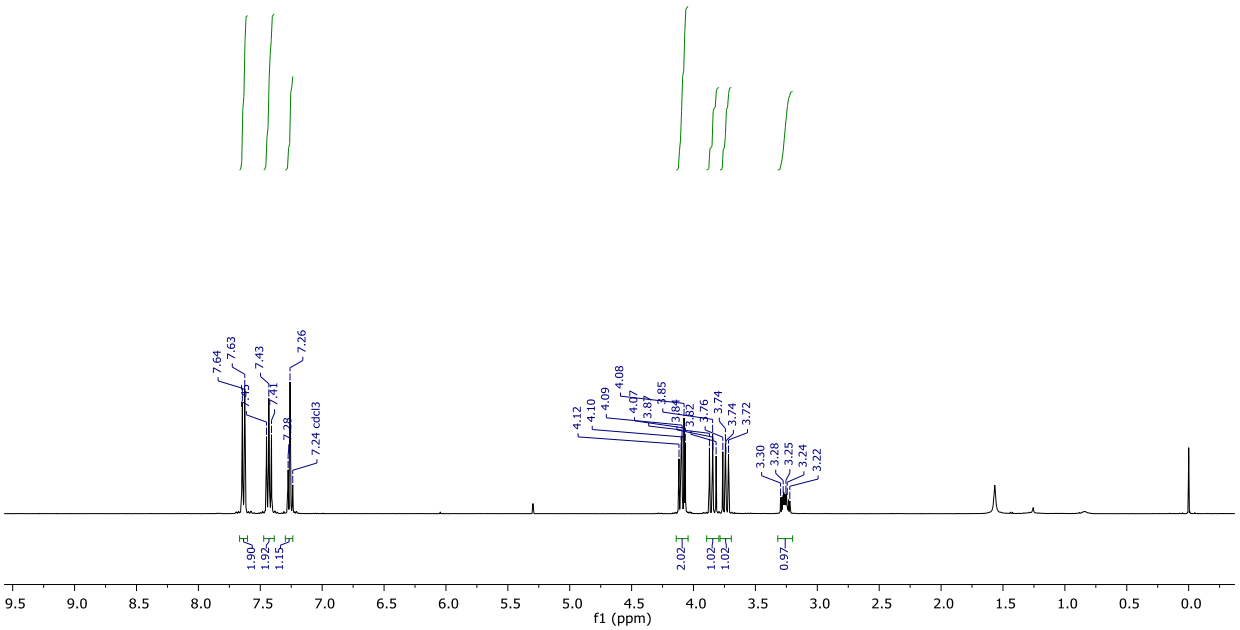
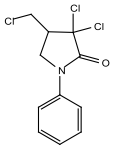
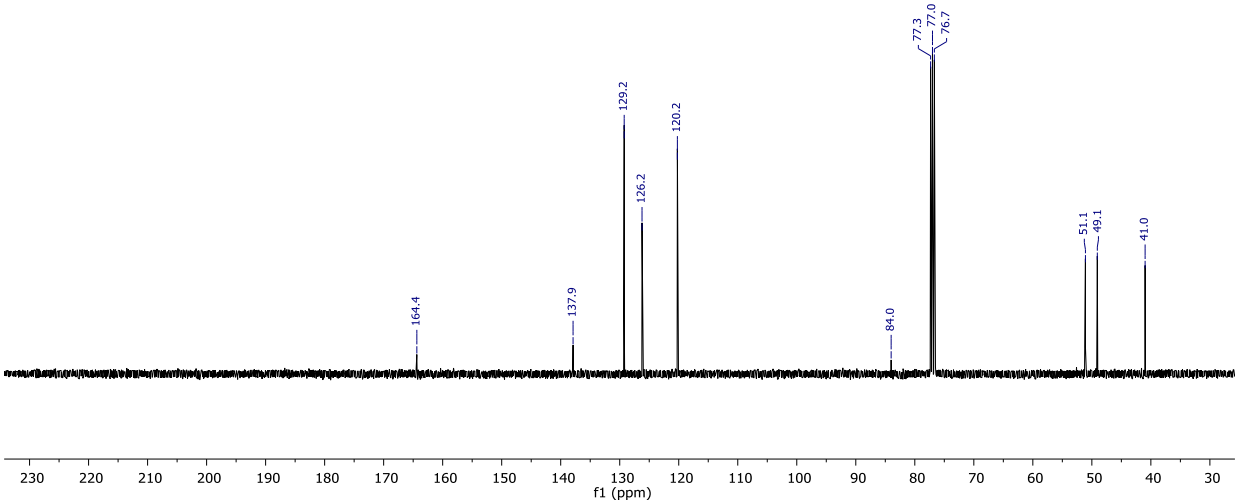


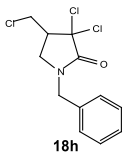

VNMRS400A_26012021_AS413-28-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS413-28
Nom: ALEXANDRA SANDOR
Data: 26/01/21 / Ope.: A.SANDOR



18g



VNMRS400A_04022021_as417-8-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as417-8
Nom: ALEXANDRA SANDOR
Data: 04/02/21 / Ope.: A.SANDOR

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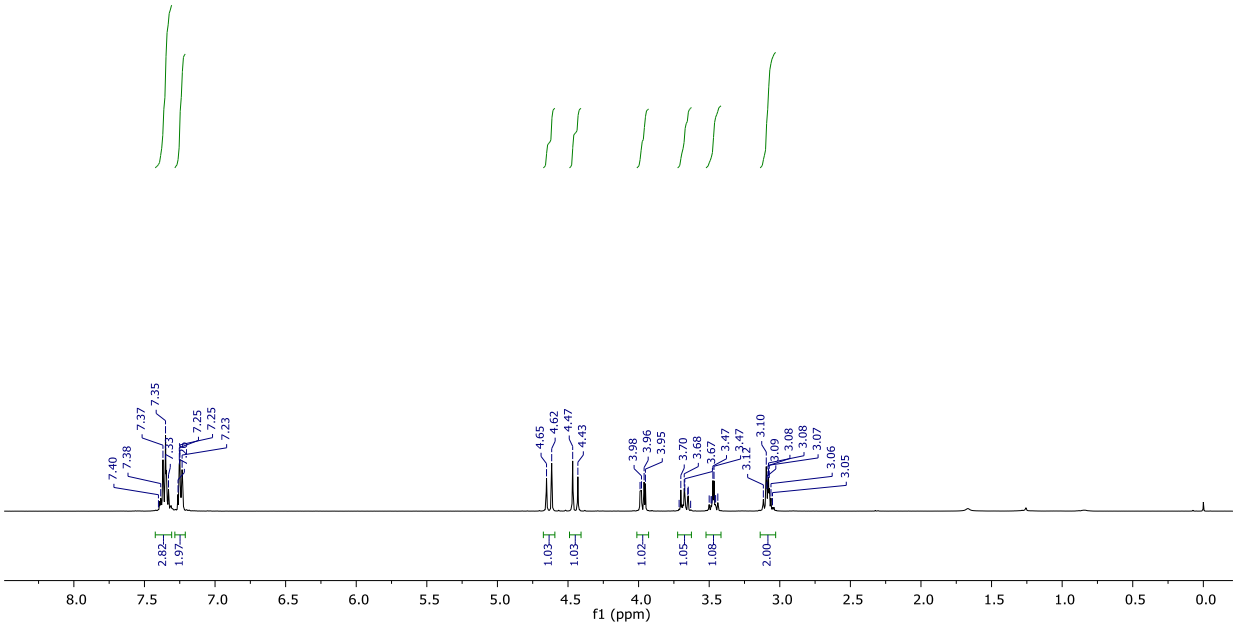
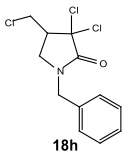



VNMRS400A_04022021_as417-8-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as417-8
Nom: ALEXANDRA SANDOR
Data: 04/02/21 / Ope.: A.SANDOR

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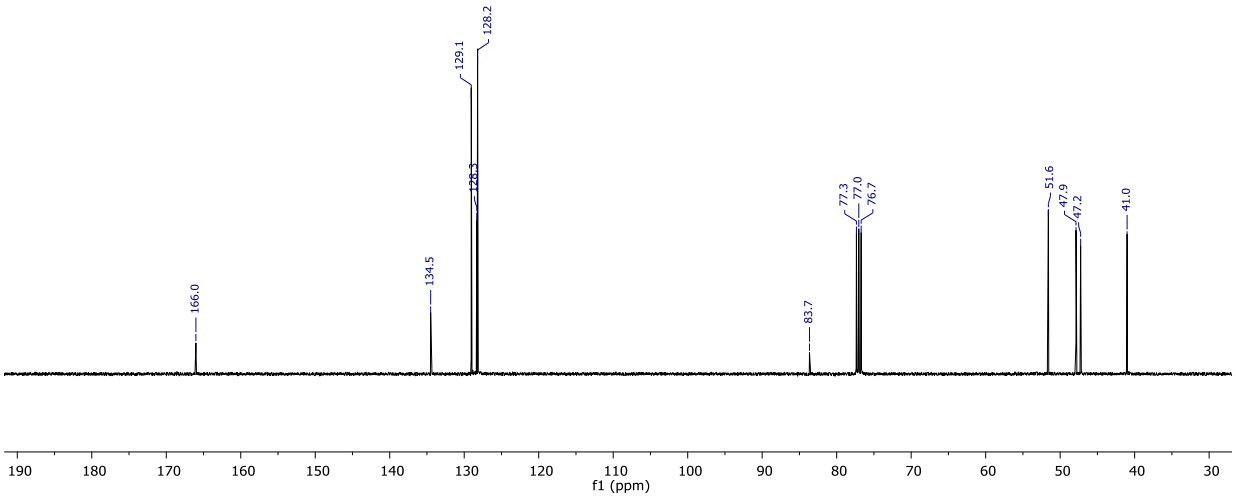
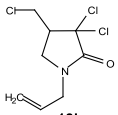


VNMRS400A_18122020_as404-2-20-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as404-2-20
Nom: ALEXANDRA SANDOR
Data: 18/12/20 / Ope.: A.SANDOR

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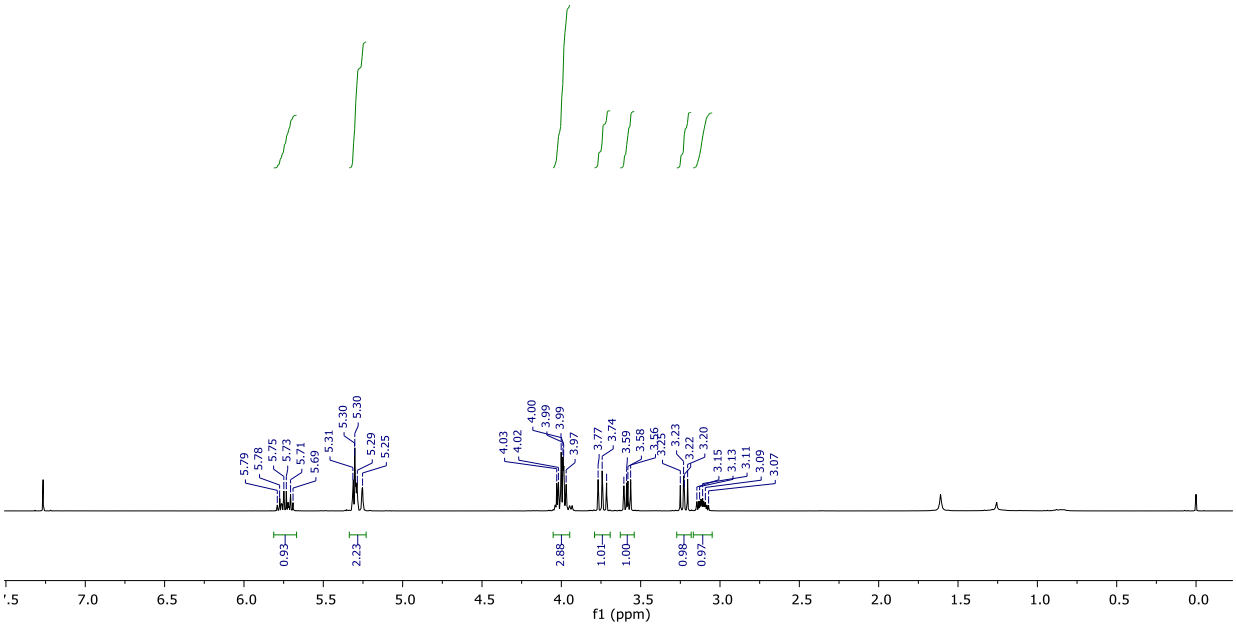
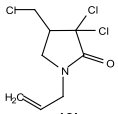



VNMRS400A_18122020_as404-2-20-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as404-2-20
Nom: ALEXANDRA SANDOR
Data: 18/12/20 / Ope.: A.SANDOR

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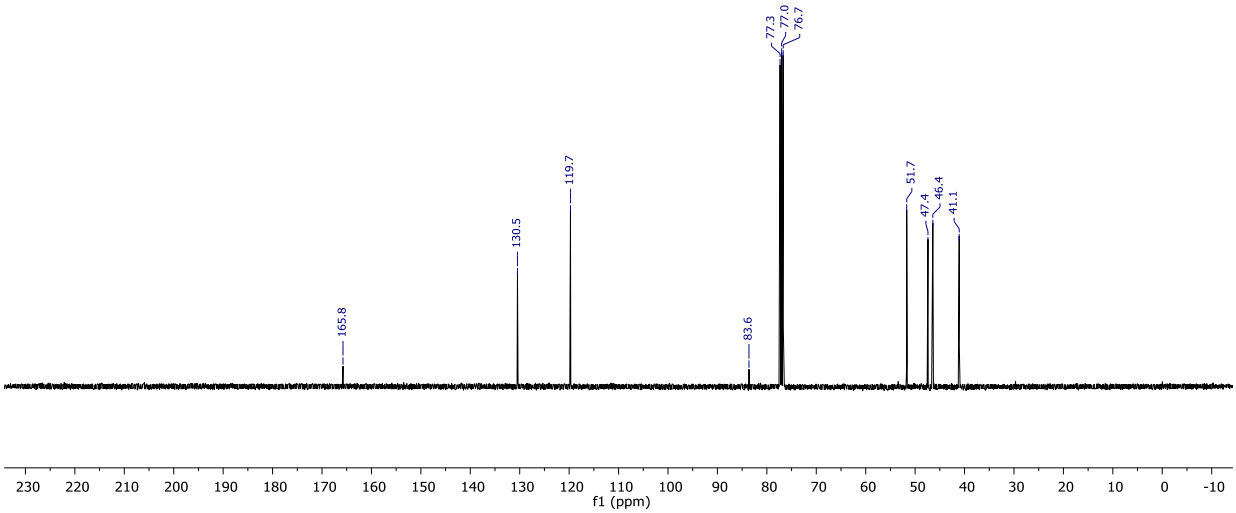
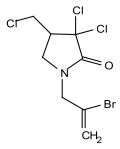


VNMRS400A_10122020_as397-2-40-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as397-2-40
Nom: ALEXANDRA SANDOR
Data: 10/12/20 / Ope.: A.SANDOR

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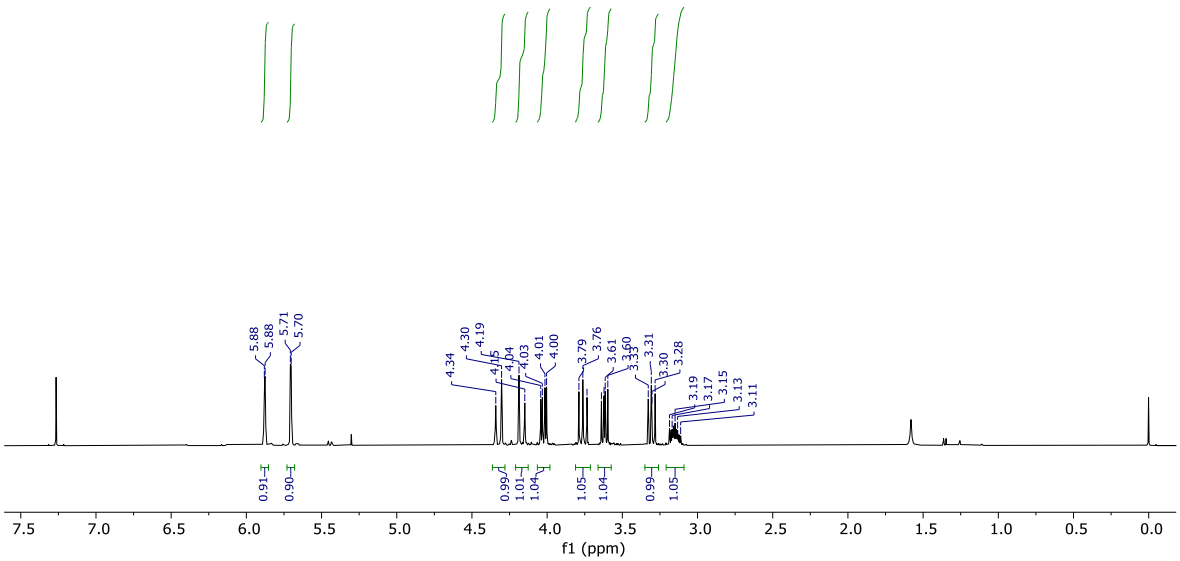
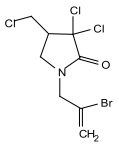



VNMRS400A_10122020_as397-2-40-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as397-2-40
Nom: ALEXANDRA SANDOR
Data: 10/12/20 / Ope.: A.SANDOR

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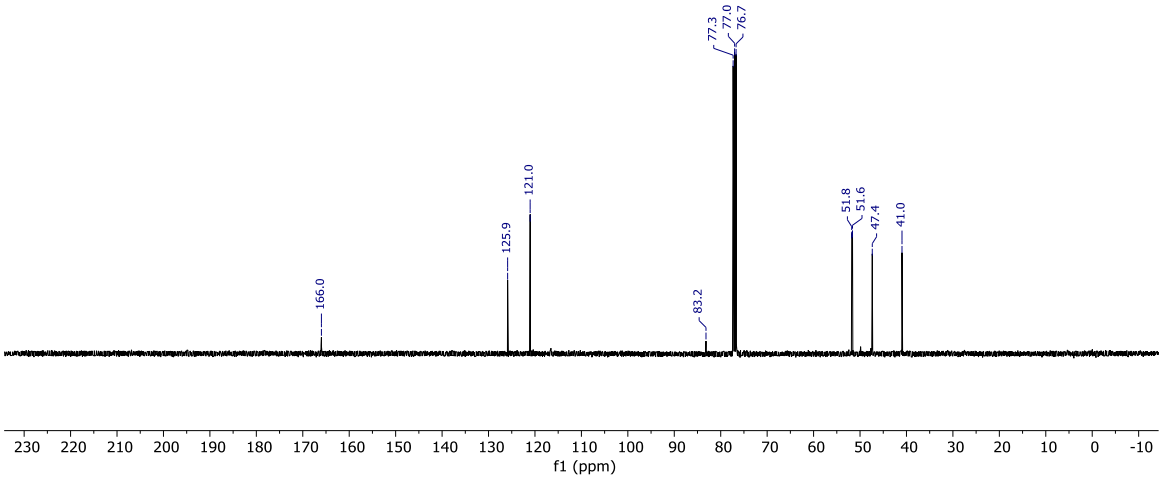
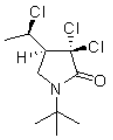


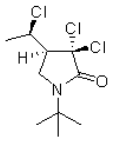
VNMRS400A_07122020_as395-13-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as395-13
Nom: ALEXANDRA SANDOR
Data: 07/12/20 / Ope.: A.SANDOR



18k




VNMRS400A_08122020_as395-13-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as395-13
Nom: ALEXANDRA SANDOR
Data: 08/12/20 / Ope.: A.SANDOR



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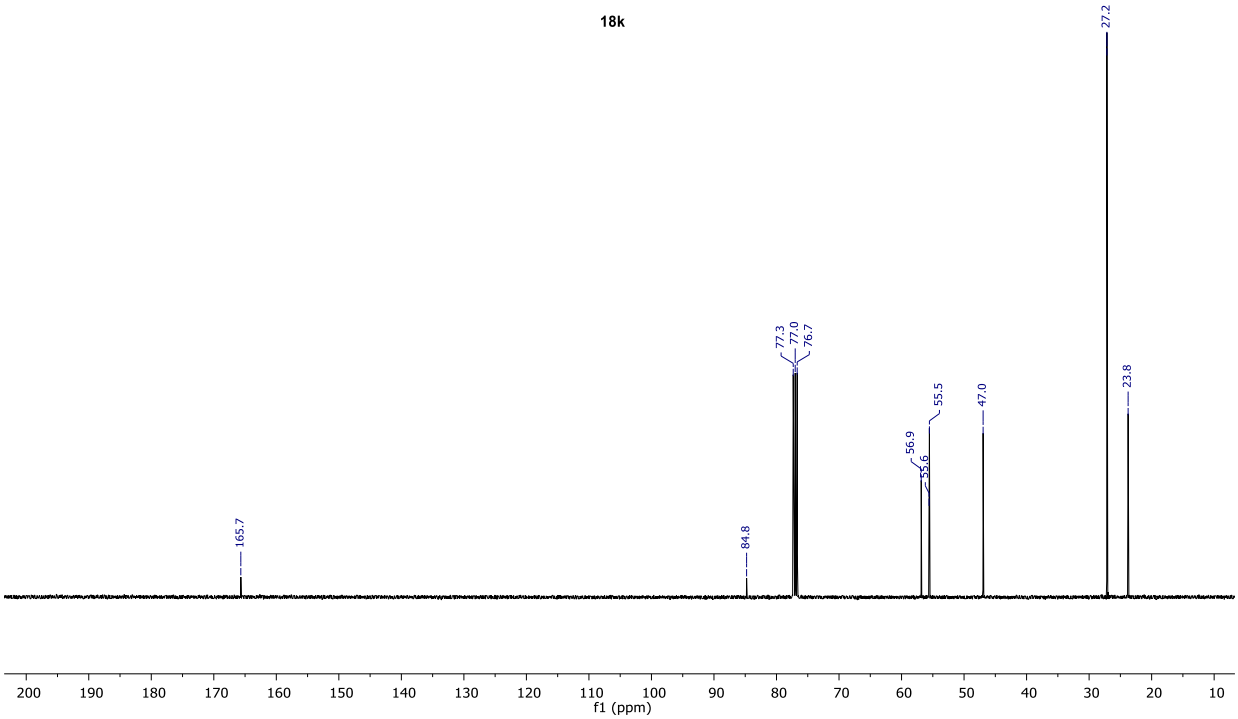
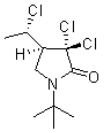


VNMRS400A_08122020_as395-18-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as395-18
Nom: ALEXANDRA SANDOR
Data: 08/12/20 / Ope.: A.SANDOR



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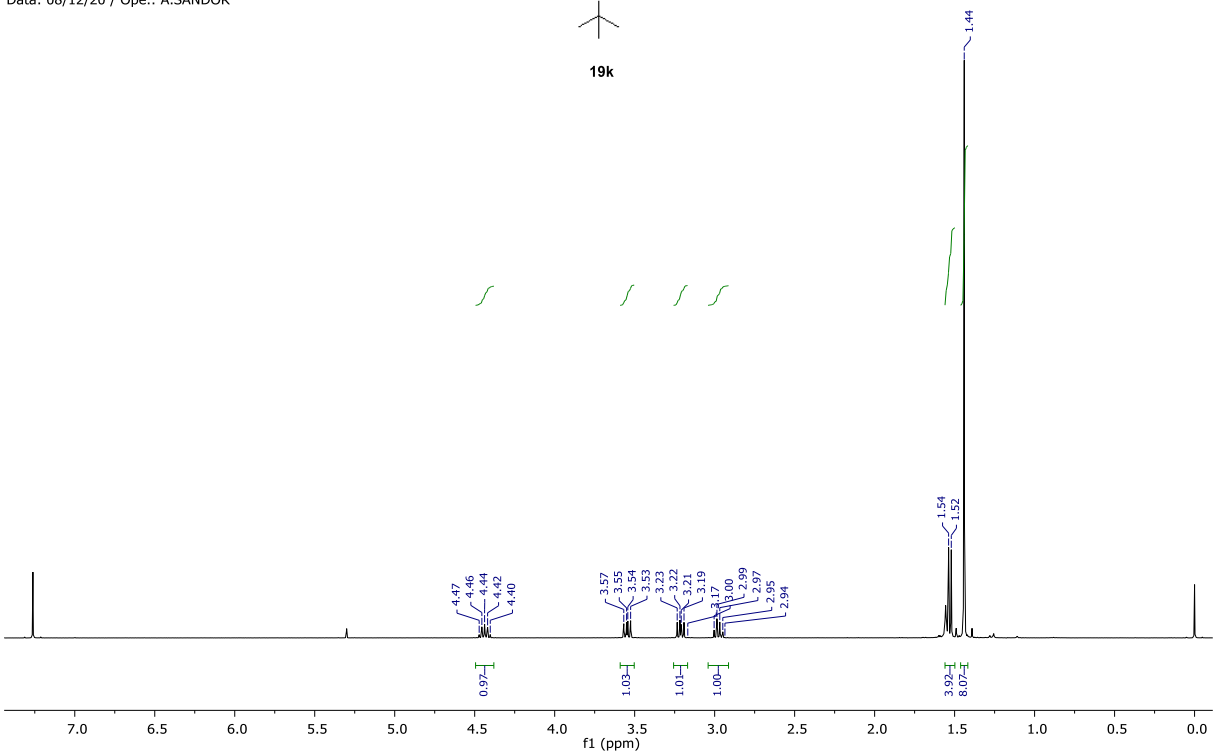
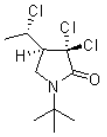



VNMRS400A_08122020_as395-18-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as395-18
Nom: ALEXANDRA SANDOR
Data: 08/12/20 / Ope.: A.SANDOR



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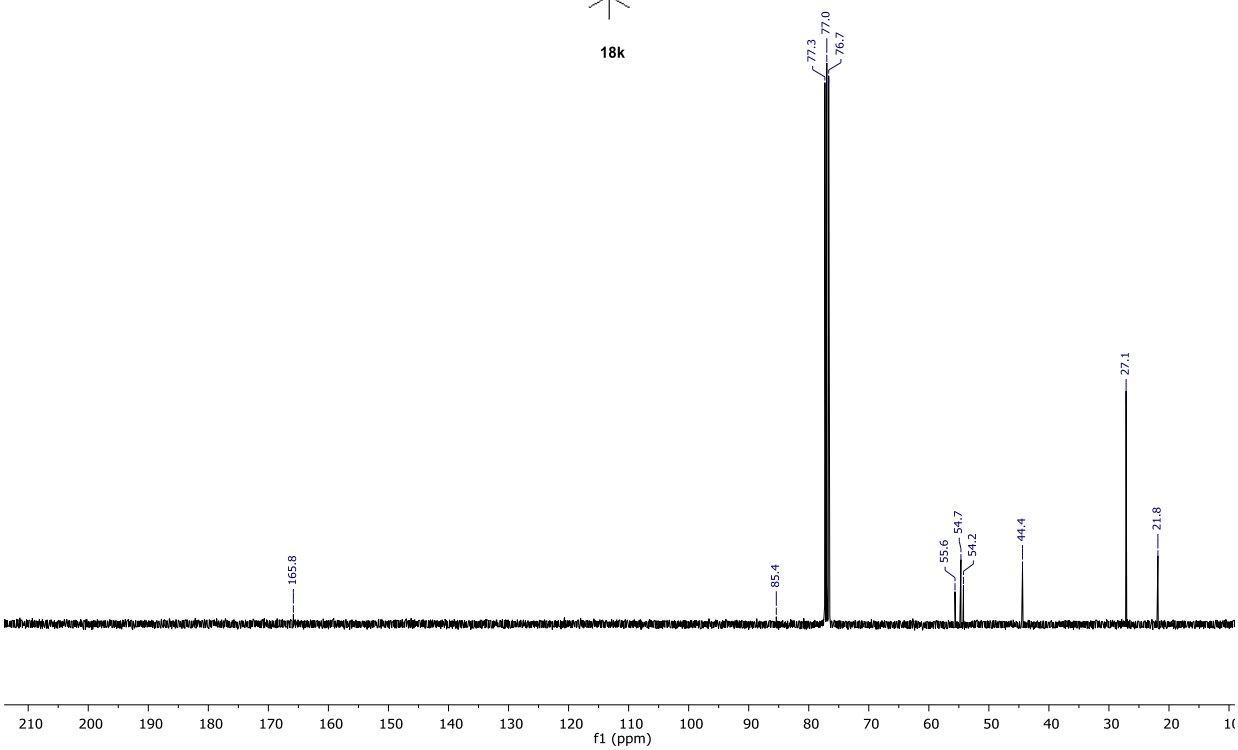
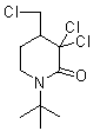
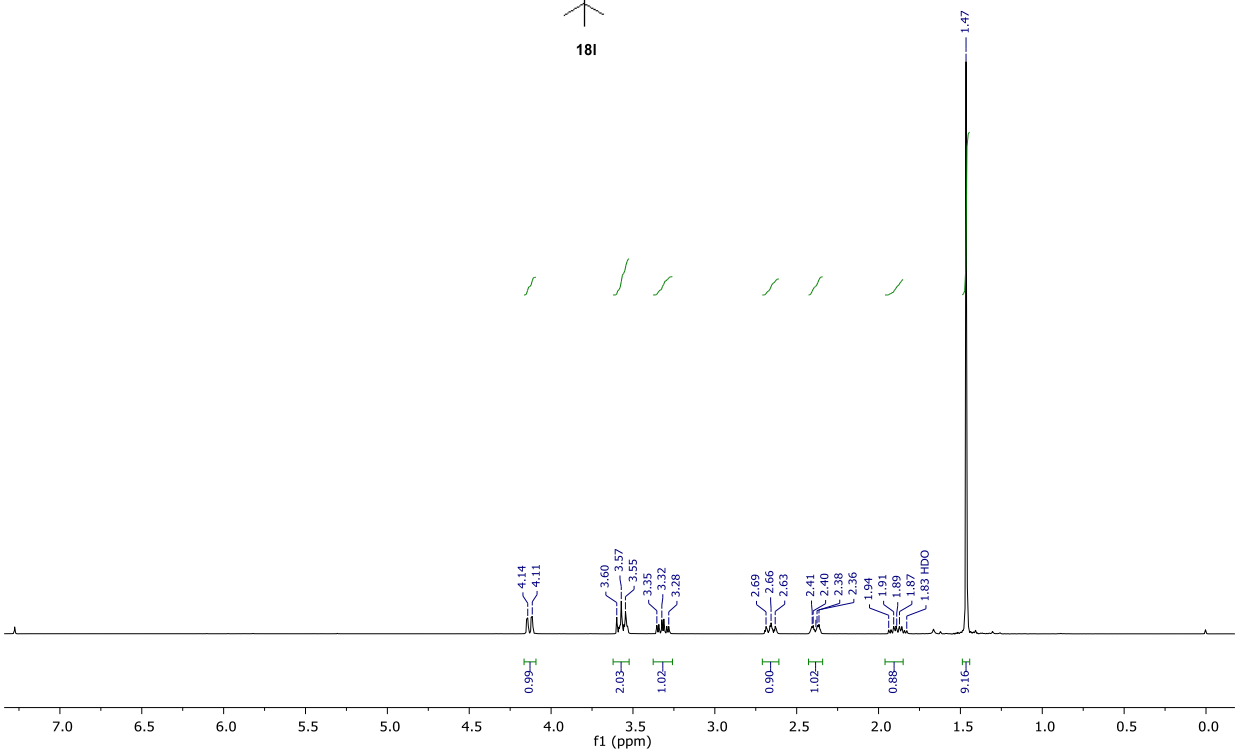


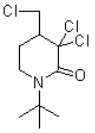
M400AFF_13122020_AS400-7-H1_rep_20_18_01
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS400-7
Nom: ALEXANDRA SANDOR
Data: 13/12/20 / Ope.: A.SANDOR



**18l**




VNMRS400A_14122020_as400-7-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as400-7
Nom: ALEXANDRA SANDOR
Data: 14/12/20 / Ope.: A.SANDOR



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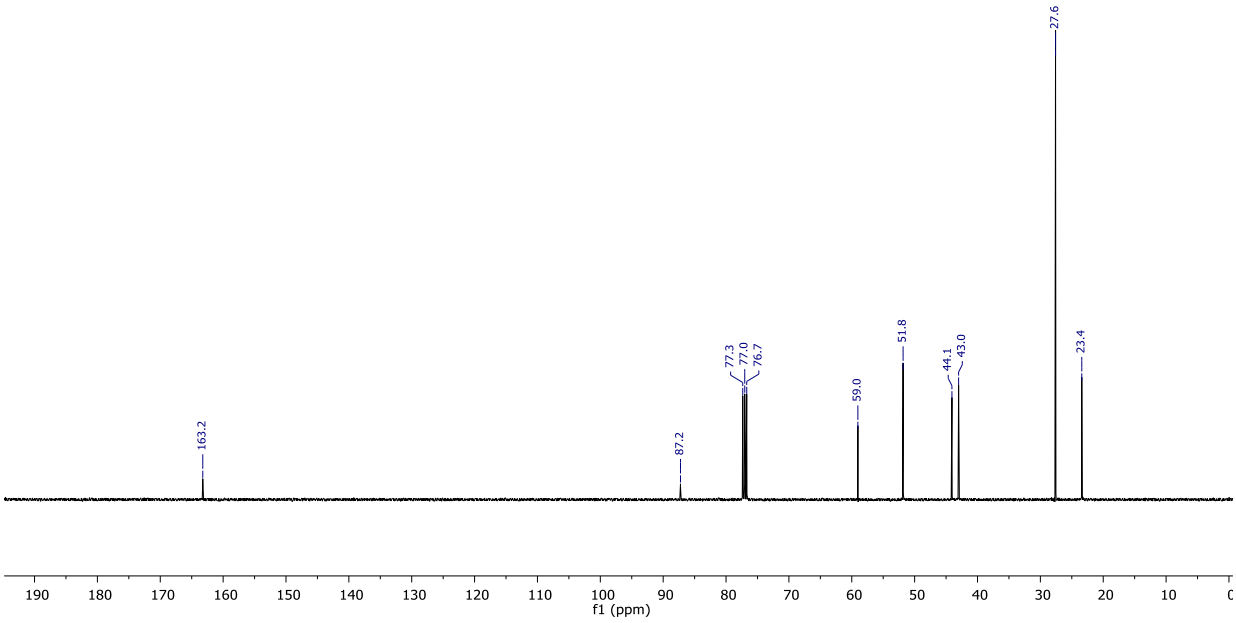
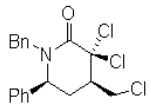


VNMRS400A_09122020_Xas396-11-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xas396-11
Nom: ALEXANDRA SANDOR
Data: 09/12/20 / Ope.: A.SANDOR

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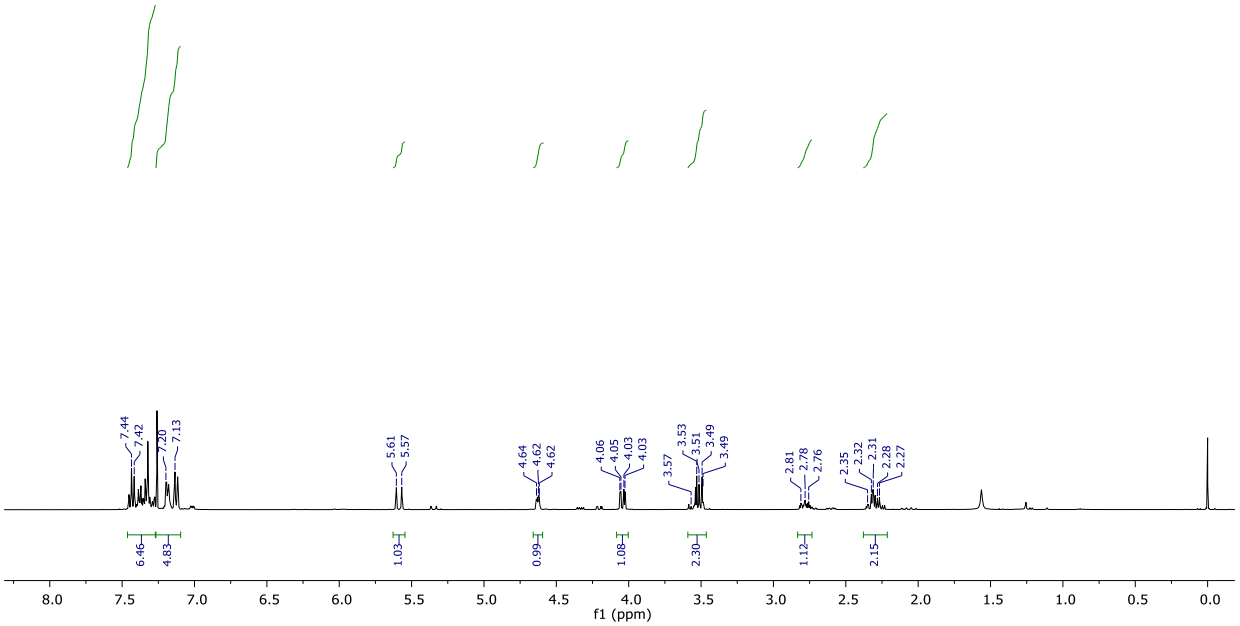
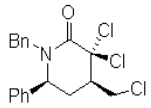



VNMRS400A_09122020_Xas396-11-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xas396-11
Nom: ALEXANDRA SANDOR
Data: 09/12/20 / Ope.: A.SANDOR

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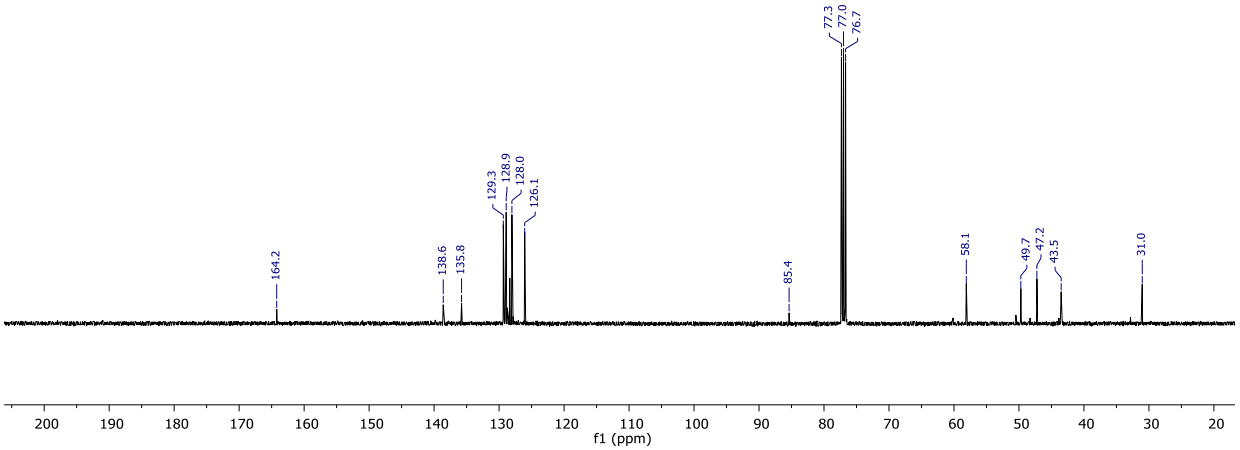

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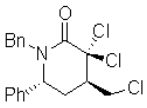
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xas396-9
Nom: ALEXANDRA SANDOR
Data: 09/12/20 / Ope.: A.SANDOR

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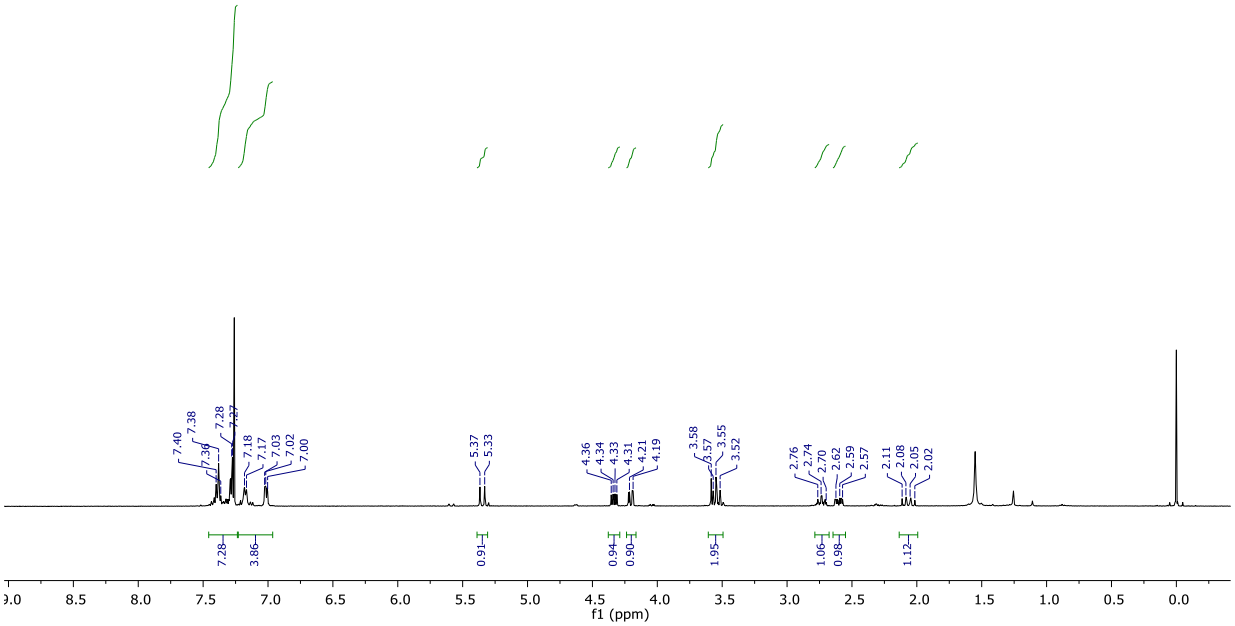


VNMRS400A_09122020_Xas396-9-C13
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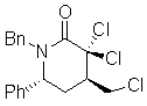
Nom: ALEXANDRA SANDOR
Data: 09/12/20 / Ope.: A.SANDOR




**19m**

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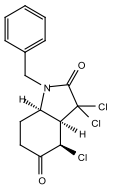
Usuari: san / Mostra: as392-2-all
Nom: ALEXANDRA SANDOR
Data: 04/12/20 / Ope.: A.SANDOR



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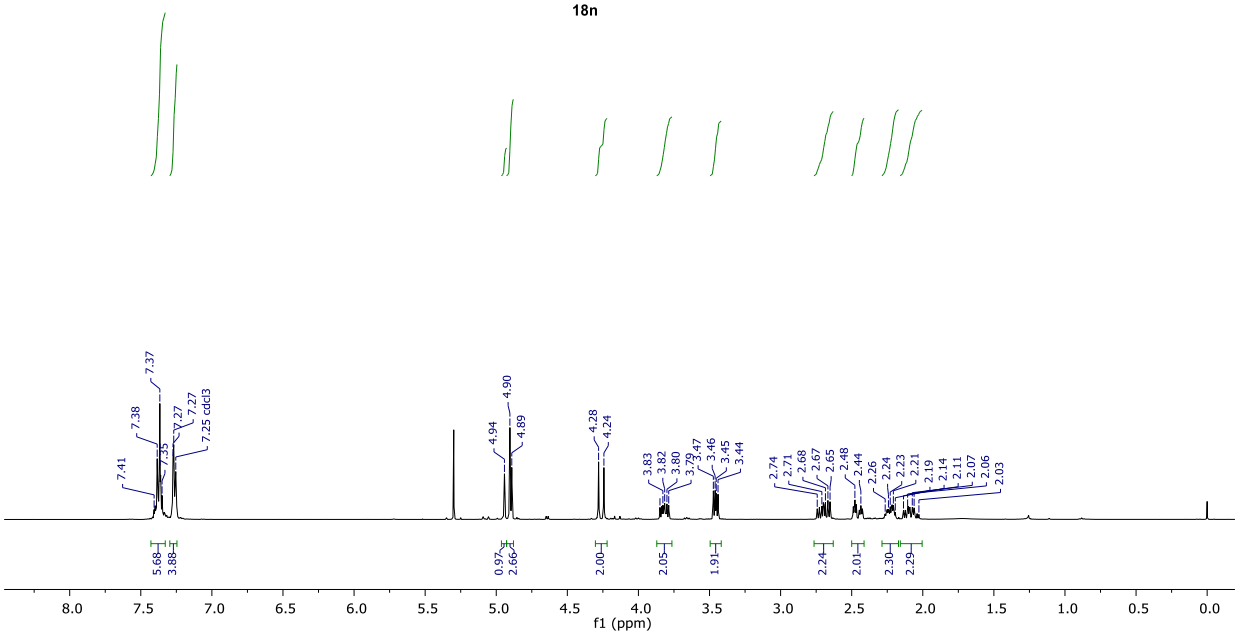


VNMRS400A_04122020_as392-2-all-C13
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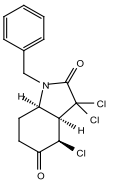
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: as392-2-all
Nom: ALEXANDRA SANDOR
Data: 04/12/20 / Ope.: A.SANDOR



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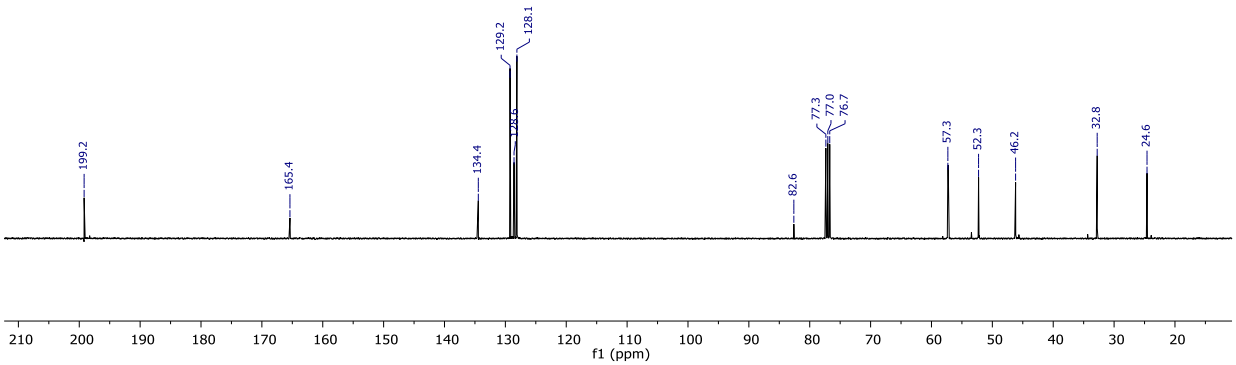

VNMRS400A_28012021_AS415-2-10-H1
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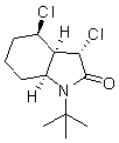
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AS415-2-10
Nom: ALEXANDRA SANDOR
Data: 28/01/21 / Ope.: A.SANDOR



**18o**




VNMRS400A_28012021_AS415-2-10-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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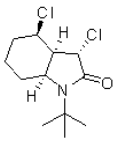
Nom: ALEXANDRA SANDOR
Data: 28/01/21 / Ope.: A.SANDOR



**18o**