UNIVERSITAT DE BARCELONA

Chiral tricyclic lactams as efficient enantiomeric scaffolds for the synthesisof cis-decahydroquinolines substituted on the carbocyclic ring. Total synthesis of *Myrioneuron* alkaloids

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Memòria presentada per Arnau Calbó Zabala per optar al títol de Doctor per la Universitat de Barcelona

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Summary:

The *Myrioneuron* alkaloids constitute a family of natural products found in East and South-East Asia. They feature a *cis*- or *trans*-decahydroquinoline (DHQ) as a common unit, attached to an oxazine, a diazine, or a cyclohexane ring, forming complex polycyclic ring systems. Despite exhibiting promising biological properties, their study has been hindered by the limited quantities available from natural sources.

This thesis presents our advances on the exploration of new cyclocondensation reactions leading to tricyclic lactams bearing substituents at positions of the carbocyclic ring that were previously inaccessible by the group's established methodology. These studies have culminated in the synthesis of various *Myrioneuron* alkaloids.

In the first chapter, the synthesis of *cis*-decahydroquinolines substituted on the carbocyclic ring is explored. Starting from racemic diastereomeric mixtures of dimethyl-2-oxocyclohexanepropionic acids the synthesis of both enantiomers of 7,8-, 6,8-, and 5,8-dimethyl-substituted *cis*-decahydroquinolines is reported. The procedure involves a dynamic kinetic asymmetric transformation in the cyclocondensation of the ketoacids with (*R*)-phenylglycinol to give in each case two major oxazoloquinolone lactams, which differ in the absolute configuration of all the stereogenic centers except that of the chiral inductor. A subsequent two-step stereoselective removal of the phenylethanol residue with simultaneous reduction of the lactam carbonyl afforded the enantiopure *cis*-decahydroquinolines in both enantiomeric series.

The second chapter is centered on the total synthesis of (–)-schoberine B using the previously developed methodology. Firstly, the synthesis of a δ-ketoacid, bearing the appropriate functional groups for the synthesis of the alkaloid, is reported. Subsequently, the application of the aforementioned methodology with this compound allowed the obtention of two major lactams, that differ in the configuration of the four stereocenters on the decahydroquinoline moiety. From the above lactams, the removal of the chiral inductor, the introduction of a 2-piperidone ring, and the closure of the diazine ring completes the first enantioselective total synthesis of the *Myrioneuron* alkaloid (−)-schoberine B and its enantiomer (+)-schoberine B.

In the third chapter, we assess the scope and limitations in the introduction of substituents at the C-7a and/or C-11 positions of simple *(R)*-phenylglycinol-derived oxazolo-DHQs. The reaction of this compound with various electrophiles allowed the regio- and stereoselective formation of various C-7a-subsituted oxazolo-DHQs bearing an all-carbon quaternary stereocenter. In a selected example, the regioselectivity of the process has been successfully modulated leading to the obtention of an 11-

hydroxymethyl-substituted oxazolo-DHQ. A subsequent two-step stereoselective removal of the phenylethanol moiety afforded various C-4a and C-8 substituted *cis*-DHQs. Using this methodology, the most efficient enantioselective synthesis of (+)-myrioxazine A has been achieved.

Resum:

Els alcaloides de *Myrioneuron* són una família de productes naturals que es troben a plantes de l'Est i Sud-est asiàtic. Aquests estan caracteritzats per un anell de *cis*- o *trans*-decahidroquinolina (DHQ) unit a una oxazina, diazina o anell de ciclohexà. Malgrat les seves prometedores propietats biològiques, l'estudi d'aquests alcaloides es veu limitat per les quantitats mínimes en què són obtinguts de fonts naturals.

El primer capítol d'aquesta tesi explora la síntesi de *cis*-decahidroquinolines amb substituents a l'anell carbocíclic. A partir de barreges diastereomèriques de cetoàcids dimetilats, s'aconsegueix la síntesi de 7,8-, 6,8- i 5,8-dimetil *cis*-decahidroquinolines. Aquest procediment implica una reacció de ciclocondensació entre els cetoàcids i un aminoalcohol quiral que dona lloc a l'obtenció estereoselectiva de dos lactams que difereixen en la configuració absoluta de tots els centres estereogènics de l'anell de DHQ. L'eliminació estereoselectiva del fragment de feniletanol de l'inductor quiral ha permès l'obtenció de les corresponents *cis*-decahidroquinolines de manera enantiopura.

El segon capítol se centra en la síntesi total de la (–)-schoberina B fent ús de la metodologia prèviament desenvolupada. Primerament, es duu a terme la síntesi d'un cetoàcid amb els grups funcionals adients per la síntesi. Seguidament, es fa ús de la metodologia desenvolupada al capítol anterior amb aquest cetoàcid. Aquest procés permet l'obtenció estereoselectiva de dos lactams els quals, difereixen en la configuració dels quatre centres estereogènics del nucli decahidroquinolínic. A partir d'aquests lactams, es procedeix a l'eliminació de l'inductor quiral, la introducció d'un anell de 2-piperidona i el tancament de l'anell de diazina per així, completar la primera síntesi total enantioselectiva de l'alcaloide (–)-schoberina B i el seu enantiòmer (+)-schoberina B.

En el tercer capítol, s'ha avaluat l'abast i les limitacions en la introducció de substituents a les posicions C-7a i/o C-11 d'hemiaminals tricíclics derivats del *(R)*-fenilglicinol. La reacció d'aquests compostos amb diversos electròfils ha permès la formació regio- i estereoselectiva de diversos hemiaminals substituïts amb un estereocentre quaternari a la posició 7a. En un cas concret, la regioselectivitat del procés s'ha pogut modular amb èxit, donant lloc a l'obtenció d'un hemiaminal tricíclic substituït a la posició 11. L'eliminació estereoselectiva en dues etapes del residu de feniletanol ha proporcionat diverses *cis*-DHQ substituïdes a C-4a i C-8. Mitjançant aquesta metodologia, s'ha aconseguit la síntesi enantioselectiva més eficient de la (+)-mirioxazina A.

Table of Contents

Dissemination of the Work

Publications:

1) **Generation of acyclic chiral building blocks containing a quaternary stereocenter. Formal synthesis of alkaloids of the leuconolam-leuconoxine-mersicarpine group.** Ordeix, S.; Alcaraz, M.; Llor, N.; Calbó, A.; Bosch, J.; Amat, M. *Tetrahedron,* **2020**, *61*, 131017.
2) **Cyclocondensation reactions of racemic diastereomers of dimethyl-2-oxocyclohexanepropionic acids with (*R*)-phenylglycinol: access to both enantiomers of dimethyl cis-decahydroquinolines.** Calbó, A.; Griera, R.; Bosch, J.; Amat, M. *Org. Chem. Front.* **2023**, *10*, 724-729.
3) **Chiral Aminoalcohol-Derived δ-Lactams Provide Easy Access to Piperidines and Acyclic Five-Carbon Building Blocks Bearing a Tertiary and a Quaternary Stereocenter.** Llor, N.; Peršolja, P.; Calbó, A.; Ordeix, S.; Ramírez, N.; Bosch, J.; Amat, M. *ACS Omega*, **2023**, *8*, 34650-34662.
4) **Total Synthesis of the *Myrioneuron* Alkaloid (–)-Schoberine B and its Enantiomer (+)-Schoberine B.** Calbó, A.; Griera, R.; Bosch, J.; Amat, M. *Adv. Syn. Catal.* **2024**, 10.1002/adsc.202301062

Conferences:

Oral Communication
Calbó A., Colombo E., Griera R., Bosch J., Amat M.
Síntesi enantioselectiva de *cis*-decahydroquinolines: Estudis en la síntesi total de la schoberina B
11a Trobada de Joves Investigadors dels Països Catalans, Vilanova i la Geltrú (Spain), **January-2020**

Poster
Amat M., Griera R., Bosch J., Calbó A.
Synthesis of Enantiopure *cis*-Decahydroquinolines: Towards the Total Synthesis of Schoberine B
1ª Jornada de Jóvenes Investigadores del GEQOR, Online, **June-2021**

Poster
Calbó A., Griera R., Bosch J., Amat M.
Towards the Total Synthesis of Schoberine B
Symposium of the Spanish Royal Society of Chemistry 2021, Online, **September-2021**

Oral Communication
Calbó A., Griera R., Bosch J., Amat M.
Síntesi enantioselectiva de *cis*-decahydroquinolines: Estudis en la síntesi total de la schoberina B
12a Trobada de Joves Investigadors dels Països Catalans, Girona (Spain), **January-2022**

Oral Communication
Calbó A., Griera R., Bosch J., Amat M.
Synthesis of Enantiopure *cis*-Decahydroquinolines: Towards the Total Synthesis of Schoberine B
XXXVIII Reunión Bienal de la Real Sociedad Española de Química, Granada (Spain), **June-2022**

Poster (winner of a poster award sponsored by the Real Sociedad Española de Química)
Calbó A., Griera R., Bosch J., Amat M.
First Total Synthesis of (–)-Schoberine B
XXVIII Reunión Bienal del Grupo Especializado de Química Orgánica, Granada (Spain), **July-2022**

Poster
Amat M., Griera R., Bosch J., Calbó A.
First Total Synthesis of (–)-Schoberine B
XIII Spanish-Italian Symposium on Organic Chemistry, Tarragona (Spain), **September-2022**

Poster
Calbó A., Griera R., Bosch J., Amat M.
First Total Synthesis of (–)-Schoberine B
Ischia Advanced School of Organic Chemistry, Ischia (Italy), **September-2022**

Abbreviations

$[\alpha]^{22}_{D}$	Specific rotation at 22°C in the D line of sodium
Å	Angstrom (10^{-10} m)
acac	Acetylacetonate
AChE	Acetylcholinesterase enzyme
AIBN	Azobisisobutyronitrile
Alloc	Allyloxycarbonyl
AmIn	Aminoindanol
ax	Axial
ax'	Pseudo-axial
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
bz-THQ	5,6,7,8-Tetrahydroquinoline
c	Concentration (mg/mL)
cal	Calorie
Calcd	Calculated
cat	Catalyst
Cbz	Benzyloxycarbonyl
CC_{50}	Concentration of cytotoxicity 50%
COHQ	Cyclohexane-fused octahydroquinolizidine
CuTC	Copper(I) thiophene-2-carboxylate
Cy	Cyclohexane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
Dess-Martin/DMP	1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DHQ	Decahydroquinoline
DIBAL	Diisobutylaluminum hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
D-S	Dean-Stark
DYKAT	Dynamic kinetic asymmetric transformation
EC_{50}	Half maximal effective concentration
e.e.	Enantiomeric Excess
ent	Enantiomer
epi	Epimer
EPO	Erythropoietin
eq	Equatorial
eq'	Pseudo-equatorial
eq.	Equivalent
ESI	Electrospray Ionization
Et	Ethyl
GC-MS	Gas Chromatography/Mass spectrometry

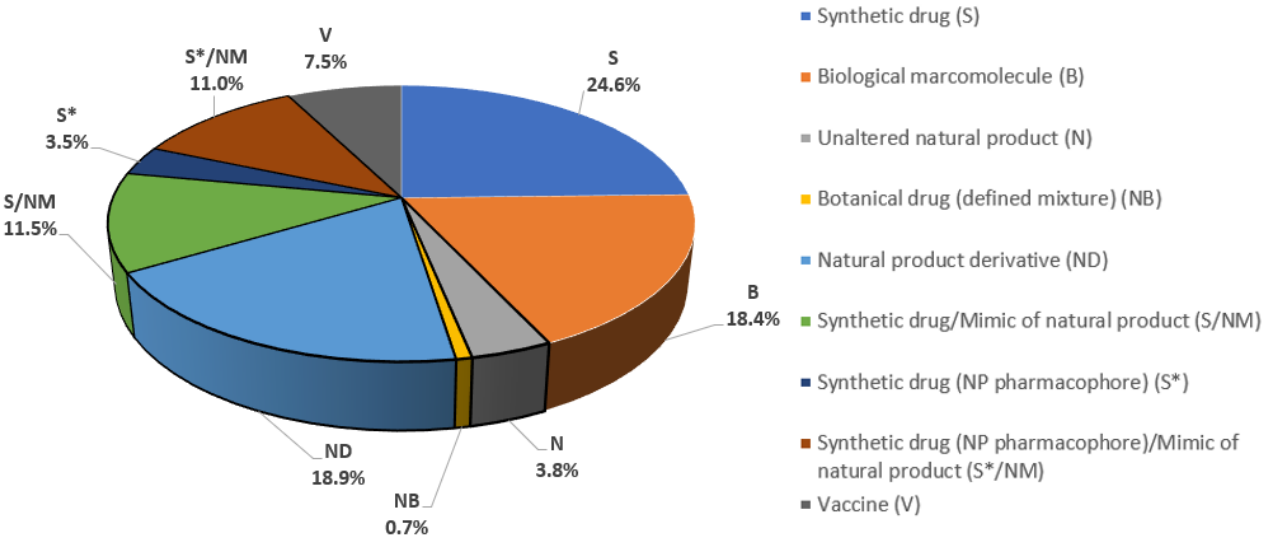
HAT	Hydrogen Atom Transfer
HCV	Hepatitis C Virus
HG-II	Hoveyda–Grubbs second-generation catalyst
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectra
Hz	Hertz
IC_{50}	Half-maximal inhibitory concentration
imid.	Imidazole
***i*-Pr**	Isopropyl
IR	Infrared spectroscopy
IRK	Inward-Rectifier Potassium Channel
J	Coupling Constant
Lawesson Reagent	2,4-Bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LSD	Lysergic acid diethylamide
L-Selectride	Lithium tri-*sec*-butylborohydride
M	Molar Concentration
***m*-CPBA**	3-Chloroperbenzoic acid
Me	Methyl
MOM	Methoxymethyl Ether
mp	Melting Point
Ms	Methanesulfonyl
MS	Molecular Sieves
MVK	Methyl Vinyl Ketone
MW	Molecular weight
nAChRs	Neuronal nicotinic acetylcholine receptors
***n*-Bu**	*n*-Butyl
NCS	*N*-Chlorosuccinimide
***n*-Hex**	*n*-Hexyl
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NP	Natural Product
°C	Degree Celsius
OHQ	Octahydroquinolizidine
PCC	Pyridinium Chlorochromate
Pd(dppf)Cl_2	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PhGly	Phenylglycinol
PhMe	Toluene
PVK	Phenyl Vinyl Ketone
PVS	Phenyl Vinyl Sulfone
Piv	Pivaloyl
ppm	Parts Per Million
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-Toluensulfonic Acid
pyr	Pyridine
RCM	Ring Closing Metathesis

rt	Room Temperature
SI	Selectivity Index
t	Time
TBAF	Tetrabutylammonium Fluoride
TBAI	Tetrabutylammonium Iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
***t*-Bu**	*tert*-butyl
TEA	Triethylamine
TFA	Trifluoroacetic Acid
THF	Tetrahydrofurane
TMS	Trimethylsilane
TOF	Time of Flight
TOS	Target-Oriented Synthesis
Ts	Tosyl
UV	Ultra-Violet Light
XRD	X-Ray Diffraction

1 Introduction and Objectives

Throughout history, the use of natural products (NPs) has played a crucial role in human medicine, as well as in veterinary medicine and agriculture. Traditionally, these products have been employed in the form of folk medicines, potions, remedies, and oils. However, in the early 19th Century, coinciding with the advent of modern medicine,[1] the first pure biologically active compound, morphine, was isolated.[2] The discovery and isolation of natural products have since become an area of great interest.

With the identification of streptomycin in 1940, large efforts were put into the discovery of new natural products and their potential applications. By 1990, 80% of the approved drugs were NPs or analogs.[3] Despite a decline in interest in natural product discovery during the 1990s and early 2000s due to the expansion of synthetic medicinal chemistry, over 49% of the drugs approved between 1984 and 2019 can be traced back to natural products in their original form or as derivatives and analogs (Scheme 1.1).[4]



Scheme 1.1 All new approved drugs from 01/01/1984 to 30/09/2019; *n* = 1881[5]

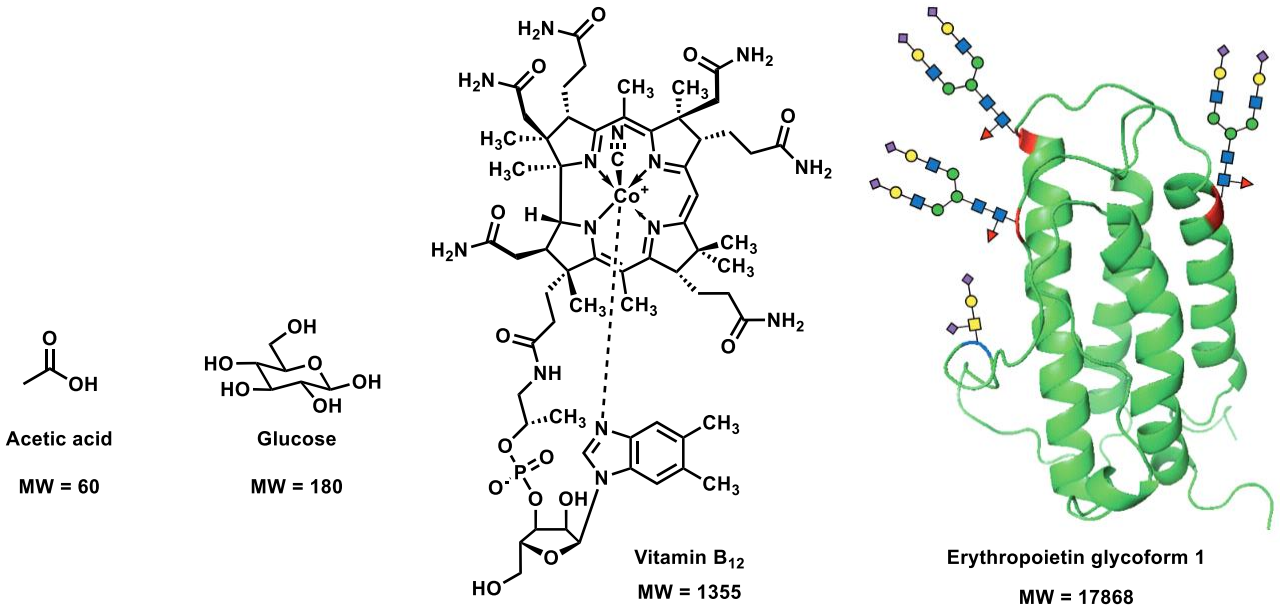
With more than 500.000 NPs reported in the literature,[6] the relevance and demand of NPs is still high. Their complex structures, result of millions of years of evolution, serve as starting point for drug discovery studies. However, these studies are hindered by the minimal amounts in which many of

[1] Sakai, T.; Morimoto, Y. *Pathogens* **2022**, *11*, 1147-1158.
[2] Hamilton, G.R.; Baskett, T.F. *Can. J. Anaesth.* **2000**, *47*, 367-374.
[3] Li, J. W. H.; Vederas, J. C. *Science*. **2009**, *325*, 161-165.
[4] Newman, D.J.; Cragg, G.M. *J. Nat. Prod.* **2020**, *83*, 770-803.
[5] Data extracted from ref 4.
[6] Ntie-Kang, F.; Svozil, D. *Phys. Sci. Rev.* **2020**, *5*, 983245.

these NPs are obtained, especially those from higher plants and marine organisms. To solve this "bottleneck", the synthetical or semi-synthetical production of higher amounts of NPs is essential.[7]

The field of natural product synthesis, also known as "target-oriented synthesis" (TOS), has seen a dramatic change since the first synthesis of urea back in 1828 by Wöhler.[8] The gigantic advancements in the field of chemistry over the last two centuries, marked by the emergence of new reaction methodologies and analytical techniques, allowed the synthesis of natural products with increasing degrees of complexity.

From simple molecules like acetic acid or glucose,[9,10] to more complex macromolecules like vitamin B_{12},[11] to the colossal wild-type erythropoietin (EPO) with a molecular mass of 17868,[12] the synthesis of natural products has propelled significant advancements in scientific knowledge (Scheme 1.2).



Scheme 1.2 Evolution of the targets in natural product synthesis[13]

Furthermore, the synthesis of these natural products has facilitated the synthesis of analogues, contributing to the development of biological probes and novel medicines.

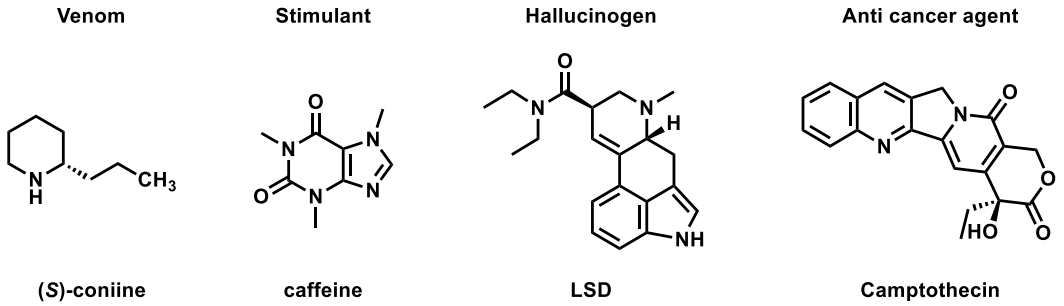
[7] Li, L.; Chen, Z.; Zhang, X.; Jia, Y. *Chem. Rev.* **2018**, *118*, 3752-3832.
[8] Wöhler, F. *Ann. Phys. Chem.* **1828**, *12*, 253.
[9] Kolbe, H. *Ann. Chem. Pharm.* **1845**, *54*, 145.
[10] Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 799-805.
[11] a) Woodward, R.B. *Pure Appl. Chem.* **1968**, *17*, 519-547; b) Woodward, R.B. *Pure Appl. Chem.* **1971**, *25*, 283-304; c) Woodward, R.B. *Pure Appl. Chem.* **1973**, *33*, 145-177; d) Eschenmoser, A.; Wintner C. E. *Science* **1977**, *196*, 1410-1420; e) Eschenmoser, A. *Pure Appl. Chem.* **1963**, *7*, 297-316; f) Eschenmoser, A. *Pure Appl. Chem.* **1971**, *15*, 69; g) Eschenmoser, A. *Naturwissenschaften* **1974**, *61*, 513-525.
[12] a) Wang, P.; Dong, S. W.; Shieh, J. H.; Peguero, E.; Hendrickson, R.; Moore, M. A. S.; Danishefsky, S. J. *Science* **2013**, *342*, 1357-1360; b) Wilson, R. M.; Dong, S. W.; Wang, P.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7646-7665.
[13] Figure of EPO extracted from: Adamíková, J.; Antošová, M.; Polakovič, M. *Biotechnol. Lett.* **2019**, *41*, 483-493.

1.1 Alkaloids

Because of their structural diversity and wide array of biological properties, alkaloids are one of the most important groups of natural products. With more than 20.000 members described in the literature,[14] these secondary metabolites have had, and still have, an important role in society. They are defined as "a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms".[15]

In terms of classification, they are categorized according to their molecular structure, with the two largest groups being the indole alkaloids and isoquinoline alkaloids, consisting of over 4000 compounds each. Additionally, there are other significant groups such as the tropane alkaloids (300 compounds), steroidal alkaloids (450 compounds), and pyridine and pyrrolizidine alkaloids (250 and 570 compounds respectively). Categorization based on botanical origin is also employed. Examples of such classifications include *Papaver* (opium) alkaloids, *Cinchona* alkaloids, *Rauvolfia* alkaloids, *Catharanthus* alkaloids, *Strychnos* alkaloids, ergot alkaloids, cactus alkaloids, and *Solanum* alkaloids. Finally, as they are primarily derived from amino acids such as phenylalanine, tyrosine, or lysine, they can also be classified depending on the amino acid they are biosynthetically made from.[15]

With respect to their biological activities, alkaloids excel in a wide array of applications, being useful as stimulants, hallucinogens, or medicines (Scheme 1.3). These activities can be attributed in part to their chemical properties. Since they are soluble in water under acidic conditions and liposoluble under neutral and basic conditions alkaloids can be transported in their protonated form and cross cell membranes in their neutral form.[16]



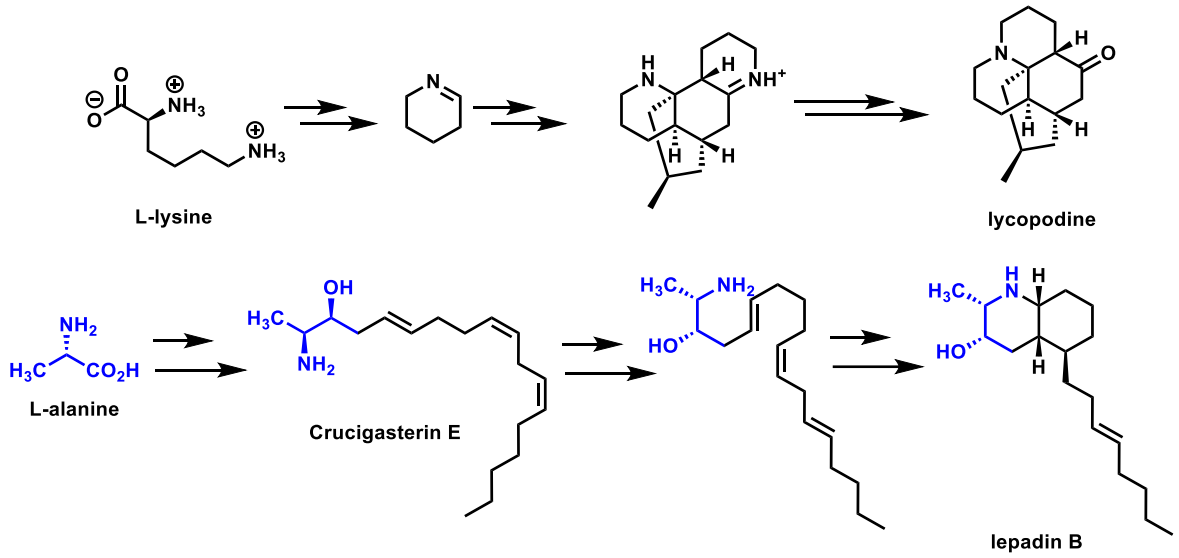
Scheme 1.3 Some examples of different groups of alkaloids and their biological properties

[14] Faisal, S.; Badshah, S. L.; Kubra, B.; Emwas, A. H.; Jaremko, M. *Nat. Prod. Bioprospecting.* **2023**, *13*, 10.1007/s13659-022-00366-9.
[15] Pelletier, S.W. In *Alkaloids: Chemical and Biological Perspectives*, Vol. 1, Wiley, New York, **1985**, pp. 1-31.
[16] Coqueiro, A.; Verpoorte, R. Alkaloids. In *Encyclopedia of Analytical Science*, 3rd ed.; Elsevier, Amsterdam, **2015**; pp. 56-61.

Because of these fascinating properties, there has been a strong focus on the total synthesis of these complex structures throughout the last and the current century.

1.2 Decahydroquinoline Alkaloids

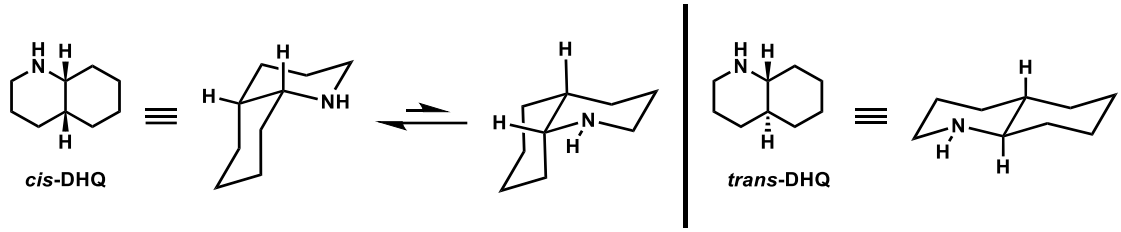
The decahydroquinoline alkaloids are a small group of alkaloids that contain a decahydroquinoline nucleus as a common structural unit. In contrast with other major groups of alkaloids, the DHQ alkaloids do not share a common biosynthetic origin. For instance, plant-derived alkaloids isolated from the *Lycopodium* genus are thought to share similar pathways starting from L-lysine, while marine derived alkaloids isolated from the ascidian *Clavelina lepadiformis*,[17] are assumed to be biosynthetically derived from L- or D-alanine and the corresponding unsaturated fatty acids (Scheme 1.4).[18]



Scheme 1.4 Different biosynthetic origins of the DHQ alkaloids

The decahydroquinoline present in these alkaloids can be found possessing either *cis*- or *trans*-fussed rings. Since *cis*-DHQs possess a more flexible structure, given their conformational equilibrium, the alkaloids have more versatility in their biological activities. On the other hand, *trans*-fused DHQs are rigid structures that confer the corresponding alkaloids the ability of reacting selectively with enzymes and receptors. (Scheme 1.5)

[17] Steffan, B. *Tetrahedron*, **1991**, *47*, 8729-8732.
[18] Pelss, A.; Koskinen, A. M. P. *Chem. Heterocycl. Compd.* **2013**, *49*, 226-240.



Scheme 1.5 Different DHQ fusions and chair structures

Given the vast array of functionalities and patterns of substitution present in these species, DHQ alkaloids are divided according to the source they are obtained from into three main categories:

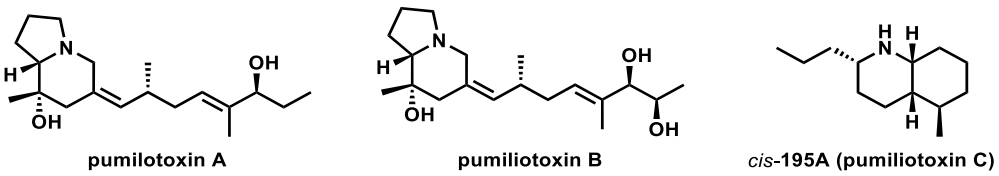
- Amphibian Alkaloids
- Marine Alkaloids
- Plant Alkaloids

1.2.1 Amphibian Alkaloids

Amphibians are a rich provider of alkaloids with more than 800 compounds isolated from their skin extracts.[19] Within this group, more than 50 compound are DHQ alkaloids.[18] These compounds are found in the secretions of the cutaneous venom glands of different genres and species of amphibians: they are found in frogs from the genus *Melanophryniscus* (Bufonidae) in Brazil, Uruguay, and Argentina,[20] in frogs from the genus *Dendrobates, Epipedobates* and *Phyllobates* (Dendrobatidae) in Colombia, Costa Rica, Panama, Brazil, and Bolivia,[21] *Mantella* frogs (Mantellidae) from Madagascar,[22] and *Pseudophryne* frogs (Myobatrachidae) from Australia.[23] Even though these alkaloids are found in a wide array of tropical frogs, it appears that the amphibians don not produce them themselves but acquire them through their diet (ants, beetles, centipedes…).[24] In fact, some DHQ alkaloids have been isolated from Panamanian *Carebarella bicolor* ants.[25]

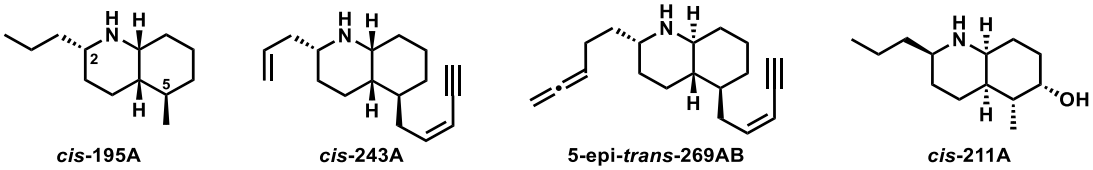
[19] Daly, J.W; Spande, T.F.; Garraffo, H.M. *J. Nat. Prod.* **2005**, *68*, 1556-1575.
[20] a) Garraffo, H. M.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **1993**, *56*, 357-373; b) Daly, J. W.; Wilham, J. M.; Spande, T. F.; Garraffo, H. M.; Gil, R. R.; Silva, G. L.; Vaira, M. *J. Chem. Ecol.* **2007**, *33*, 871-887.
[21] a) Tokuyama, T.; Nismimori, N. *Tetrahedron* **1986**, *42*, 3453-3460; b) Daly, J. W.; Myers, N. W. *Toxicon* **1987**, *25*, 1023-1095; c) Tokuyama,T.; Tsujita, T.; Shimada, A. *Tetrahedron* **1991**, *47*, 5401-5414; d) Mortaria, M. R.; Schwartz, E. N.; Schwartz, C. A.; Pires, O. R. Jr.; Santos, M. M.; Bloch, C. Jr.; Sebben, A. *Toxicon* **2004**, *43*, 303-310; e) Saporito, A.; Donnellya, M. A.; Jainb, P.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Toxicon* **2007**, *50*, 757-778.
[22] a) Garraffo, H.M.; Caceres, J.; Daly, J.W.; Spande, T.F. *J. Nat. Prod.* **1993**, *56*, 1016-1038; b) Daly, J. W.; Higher, R. J.; Myers, C. W. *Toxicon* **1994**, *22*, 905-919; c) Daly, J. W.; Andriamaharavo, N. R.; Andriantsiferana, M.; Myers, C. W. *American Museum Novitates* **1996**, *3177*, 1-34.
[23] Daly, J. W.; Garraffo, H. M.; Pannell, L. K.; Spande, T. F. *J. Nat. Prod.* **1990**, *53*, 407-421.
[24] a) Daly, J. W.; Garraffo, H. M.; Jain, P.; Spande, T. F.; Snelling, R. R.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **2000**, *26*, 73-85; b) Saporito, R. A.; Spande, T. F.; Garraffo, H. M.; Donnelly, M. A. *Heterocycles* **2009**, *79*, 277-297; c) Hantak, M.; Grant, T.; Reinsch, S.; Mcginnity, D.; Loring, M.; Toyooka, N.; Saporito, R. A. *J. Chem. Ecol.* **2013**, *39*, 1400-1406; d) Jones, T. H.; Gorman, J. S. T.; Snelling, R. R.; Delabie, J. H. C.; Blum, M. S.; Garraffo, H. M.; Jain, P.; Daly, J. W.; Spande, T. F. *J. Chem. Ecol.* **1999**, 25, 1179-1193.
[25] Jones, T. H.; Adams, R. M. M.; Spande, T. F.; Garraffo, H. M.; Kaneko, T.; Schultz, T. R. *J. Nat. Prod.* **2012**, *75*, 1930−1936.

The first amphibian alkaloids were isolated and characterized back in 1969 by Daly and coworkers.[26] The skin extracts of *Dendrobates pumilio*, a strikingly colored Panamanian frog, provided the first DHQ alkaloid (*cis*-**195A** - formerly known as pumiliotoxin C), as well as two indozilidine alkaloids: pumiliotoxin A (**307A**) and pumiliotoxin B (**323A**) (Scheme 1.6).



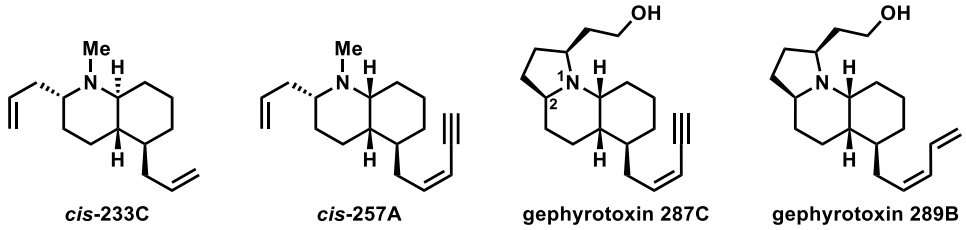
Scheme 1.6 First isolated amphibian alkaloids

Structurally, amphibian sourced DHQ alkaloids are characterized by a 2,5-disubstituted *cis*- or *trans*-fused decahydroquinoline system with alkylic, alkenylic, or alkynylic side chain. Some alkaloids contain allenes, enynynes, conjugated dienes or even, in some minor cases a hydroxy group in the side chain or the C-6 position of the ring (Scheme 1.7).



Scheme 1.7 Examples of DHQ amphibian alkaloids

More complex alkaloids are also found. For instance, DHQ alkaloids obtained from skin extracts *Ameerga picta* are found to be *N*-methylated DHQs, unprecedented in the previously mentioned alkaloids.[27] Skin extracts of the Colombian frog *Dendrobates histrionicus* provided gephyrotoxins 287C and 289B, two *cis*-DHQ alkaloids containing a pyrrolidine ring fused between N-1 and C-2, unique in this class of alkaloids and only found in these compounds (Scheme 1.8).[28]



Scheme 1.8 Additional DHQ amphibian alkaloids with increasing degrees of structural complexity

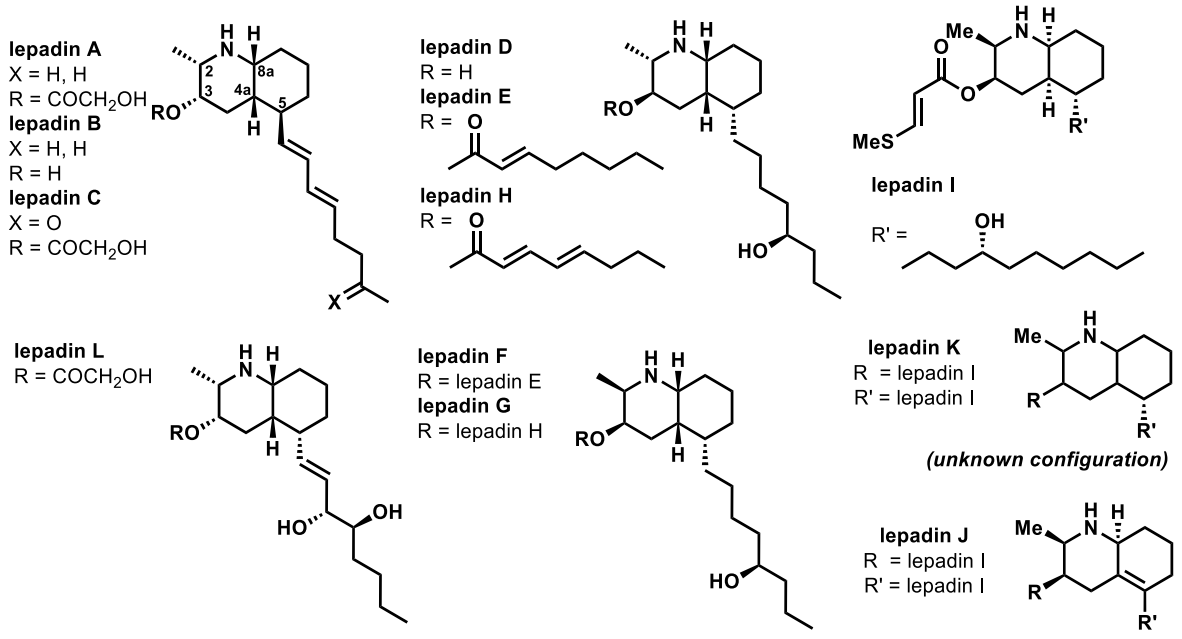
Even though these alkaloids are found in the venom skin extracts, which serve a defensive purpose

[26] Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Liebig's Ann. Chem.* **1969**, *729*, 198-204.
[27] Daly, J. W.; Ware, N.; Saporito, R. A.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2009**, *72*, 1110-1114.
[28] Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128-1140.

for these frogs, they are not as toxic and poisonous as other alkaloids found in such extracts like the indolizidine alkaloids (true pumiliotoxins). Some of them produce a local anesthetic effect by inhibiting the Na^+-K^+ pump in the cell membrane,[29] while others act on the neuronal nicotinic acetylcholine receptors (nAChRs) producing a reversible blockage, useful for the treatment of several neurological disorders such as nicotine addiction, epilepsy, Alzheimer's, or Parkinson's diseases.[30]

1.2.2 Marine Alkaloids

Although most of the marine environment remains unexplored, so far it has provided a considerable number of natural products, including some DHQ alkaloids. Back in 1991, the Steffan group isolated the first marine DHQ alkaloid, lepadin A, from the ascidian *Clavelina lepadiformis*. Since then, 11 more lepadins (B-L) have been isolated from different ascidians and tunicates in different parts of the North Sea, the Coral Sea, the Mediterranean Sea, and the Western Atlantic Ocean (Scheme 1.9).[31]



Scheme 1.9 The lepadin alkaloids

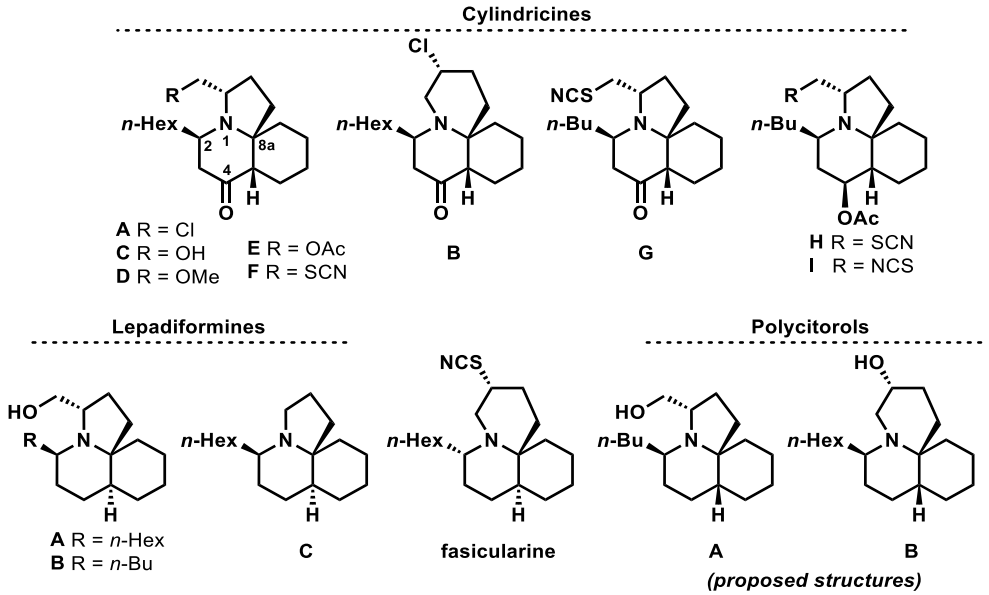
[29] a) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Eldefrawi, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *22*, 565-573; b) Daly, J. W. *Braz. J. Med. Biol. Res.* **1995**, *28*, 1033-1042.

[30] a) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukimoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R. Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5-21; b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227-1240; c) Daly, J. W.; Nishizawa, Y.; Edwards, M. W.; Waters, J. A.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 489-500; d) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; McCloskey, P. J.; Waykole, L.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1207-1212.

[31] a) Steffan, B. *Tetrahedron*, **1991**, *47*, 8729-8732; b) Kubanek, J.; Williams, D.; Dilip de Silva, E.; Allen, T.; Andersen, R. J. *Tet. Lett.* **1995**, *36*, 6189-6192. c) Wright, A.; Goclic, E.; König, G.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067-3075; d) Davis, R.; Carroll, A.; Quinn, R. *J. Nat. Prod.* **2002**, *65*, 454-457; e) Ómarsdóttir, S.; Wang, X.; Liu, H.; Duggan, B.M.; Molinski, T.F. *J. Org. Chem.* **2018**, *83*, 13670-13677; f) Casertano, M.; Genovese, M.; Paoli, P.; Santi, A.; Aiello, A.; Menna, M.; Imperatore, C. *Mar. Drugs* **2022**, *20*, 65-78.

These secondary metabolites are characterized by a 5-alkyl-3-hydroxy-2-methyldeca-(lepadins A–K, L) or octahydroquinoline (lepadin J) nucleus with a diversified array of side chains and relative stereochemical relationships at C-2, C-3, C-4a, C-5, and C-8a.

Shortly after, the cylindricines and lepadiformines were also isolated from marine sources. The cyclindricines were isolated from *Clavelina cylindrica* in the east coast of Tasmania,[32] while the lepadiformines were isolated from *Clavelina lepadiformis*[33] in the north-western coast of Tunisia. Structurally these compounds are characterized by a *cis*- or *trans*-fused DHQ nucleus fused to either a pyrrolidine or a piperidine ring between N-1 and C-8a as well as an aliphatic side chain (*n*-butyl or *n*-hexyl) at C-2. Cylindricines contain an additional oxygenated moiety at the C-4 position of the DHQ nucleus. Fasicularin and polycitorols A and B are closely related structurally to the lepadiformine family but have been isolated from different sources. Fasicularin was isolated from the tunicate *Nephteis fasicularis* in Micronesia,[34] while polycitorols A and B were isolated from the ascidian of the *Polycitoridae* family in Indonesia (Scheme 1.10).[35]



Scheme 1.10 Additional marine sourced DHQ alkaloids

In terms of biological properties, lepadins possess biological activities such as cytotoxicity against cancer cell lines, inhibition of tyrosine kinase and butyrylcholine esterase activity, and antiparasitic

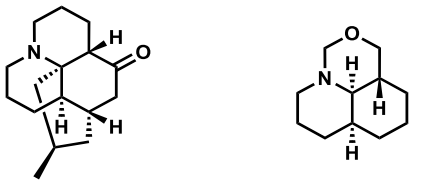
[32] a) Blackman, A.; Li, C. *Tetrahedron* **1993**, *49*, 8645-8656; b) Li, C.; Blackman, A. *Aust. J. Chem.* **1994**, *47*, 1355-1361; c) Li, C.; Blackman, A. *Aust. J. Chem.* **1995**, *48*, 955-965.
[33] a) Biard, J. F.; Guyot, S.; Roussakis, C., Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691-2694; b) Jugé, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J. Y. *Toxicon* **2001**, *39*, 1231-1237.
[34] Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K. *Tetrahedron Lett.* **1997**, *38*, 363-364.
[35] Issa, H. H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trianto, A.; Higa, T. *Mar. Drugs* **2005** *3*, 78-83.

properties.[31f] Lepadiformines have shown cytotoxicity against various tumoral cell lines, as well as an inhibitory effect on the inward-rectifier potassium channel (IRK) used in arterial pressure and cardiac muscle regulation.[33b] Interestingly, fasicularine could be useful against cancer therapy as an adjuvant of DNA-damaging drugs.[34] It also displayed cytotoxic activity against VERO cells.[36] Cylindricines, on the other hand, haven't been properly studied given the low amounts they are extracted from natural sources.

1.2.3 Plant Alkaloids

Plants are the biggest and oldest source of DHQ alkaloids with around 80 compounds isolated to date. Plant derived DHQ alkaloids can be divided into two main families: The *Lycopodium* alkaloids, the largest DHQ family with more than 200 compounds (around 50 with a DHQ nucleus), and the *Myrioneuron* alkaloids, a small family of alkaloids (Scheme 1.11).

Given the importance of the *Myrioneuron* alkaloids in the context of this thesis, they will be discussed in depth in the following section.



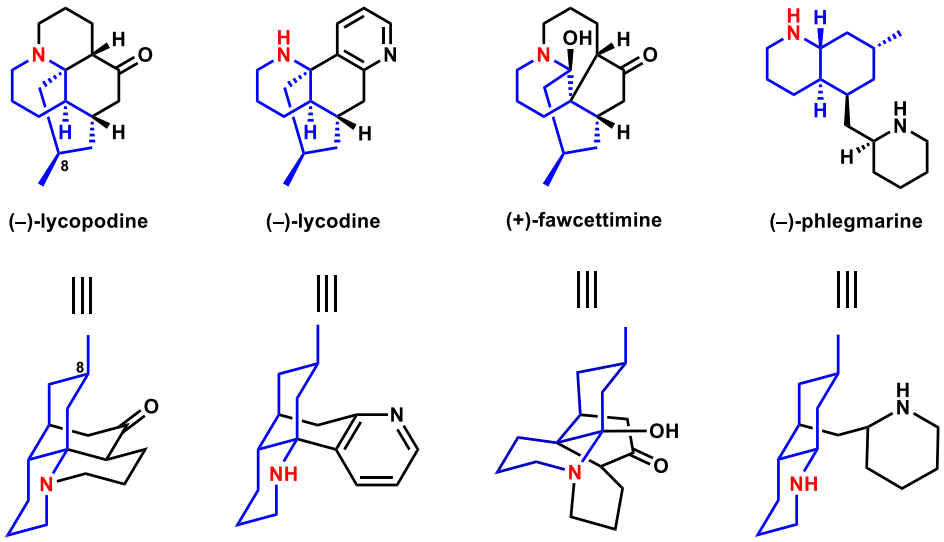
Scheme 1.11 Parent members of the two families of plant derived DHQ alkaloids

Back in 1881 Bödeker isolated the first plant derived DHQ alkaloid, lycopodine, from *Lycopodium complanatum*.[37] Lycopodine is the parent compound of the *Lycopodium* alkaloids, a large family of alkaloids obtained from plants of the *Lycopodium* genera, with more than 500 species distributed along Africa, North and South America and Eurasia. However, of all these species, only around 10% of their compounds have been studied so far. This is attributed to the low abundance and slow growth of these plants that are only found in very specialized habitats. These, added to the inability to cultivate them makes the isolation of new compounds slow and complicated.[38]

Structurally *Lycopodium* alkaloids can be separated into four classes: the lycopodine class, the lycodine class, the fawcettimine class and the miscellaneous group. Representative compounds for

[36] In, J.; Lee, S.; Kwon, Y.; Kim, S. *Chem. Eur. J.* **2014**, *20*, 17433-17442.
[37] Achmatowicz, O.; Uzieblo, W. *Rocz. Chem.* **1938**, *18*, 88-95 (in English 94-95).
[38] Ma, X.; Gang, D.R. *Nat. Prod. Rep.* **2004**, *21*, 752-772.

these structural classes are lycopodine, lycodine, fawcettimine and phlegmarine, respectively (Scheme 1.12).



Scheme 1.12 Parent members of the different classes of *Lycopodium* alkaloids

Structurally, the DHQ alkaloids present in this family are characterized by a *cis*- or *trans*-fused DHQ nucleus with a (*R*)-Me at C-8 (DHQ numbering). Depending on the class, the structures incorporate additional cyclic systems as well as all-carbon quaternary stereocenters, which make *Lycopodium* alkaloids interesting synthetic targets given their complexity.

Because of the difficulties in the obtention of these alkaloids, their biological properties remain mostly unexplored. However, some *Lycopodium* alkaloids have shown an interesting inhibitory effect in acetylcholisterase enzyme (AChE) and noncholinergic neuroprotective effects, which could be useful for the treatment of myasthenia gravis or Alzheimer's disease.[39]

1.3 *Myrioneuron* Alkaloids

The *Myrioneuron* alkaloids are a small but growing family of DHQ alkaloids isolated from plants of the genus *Myrioneuron*.[40] These plants belong to the Rubiaceae family, a large group of flowering plants where important classes of alkaloids, such as purines (caffeine), pyrrolidinoindoline (psychotridine) and quinoline (quinine, camptothecin) alkaloids are found.[41] First discovered by Bodo and colleagues during a screening program of Vietnamese plants with activity against tumor cells, the

[39] a) Herzon, S. B.; Tun, M. K. M. *J. Exp. Pharmacol.* **2012**, *4*, 113-123; Qian, Z. M.; Ke, Y. *Front. Aging Neurosci.* **2014**, *6*, 216; b) Kozikowski, A. P.; Tuckmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641-650; c) Xu, J.; Lacoske, M. H.; Theodorakis, E. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 956-987.
[40] Aquilina, J.M.; Smith, M.W. *Synthesis* **2023**, *55*, 3725-3736.
[41] a) Jannic, V.; Guéritte, F.; Laprévote, O.; Serani, L.; Martin, M. T.; Sévenet, T.; Potier, P. *J. Nat. Prod.* **1999**, 62, 838-843; b) Hart, N. K.; Johns, S. R.; Lamberton, J. A.; Summons, R. E. *Aust. J. Chem*. **1974**, 29, 639-646; c) Aimi, N.; Nishimura, M.; Miwa, A.; Hoshino, H.; Sakai, S. I.; Haginiwa, J. *Tetrahedron Lett*. **1989**, 30, 4991-4994.

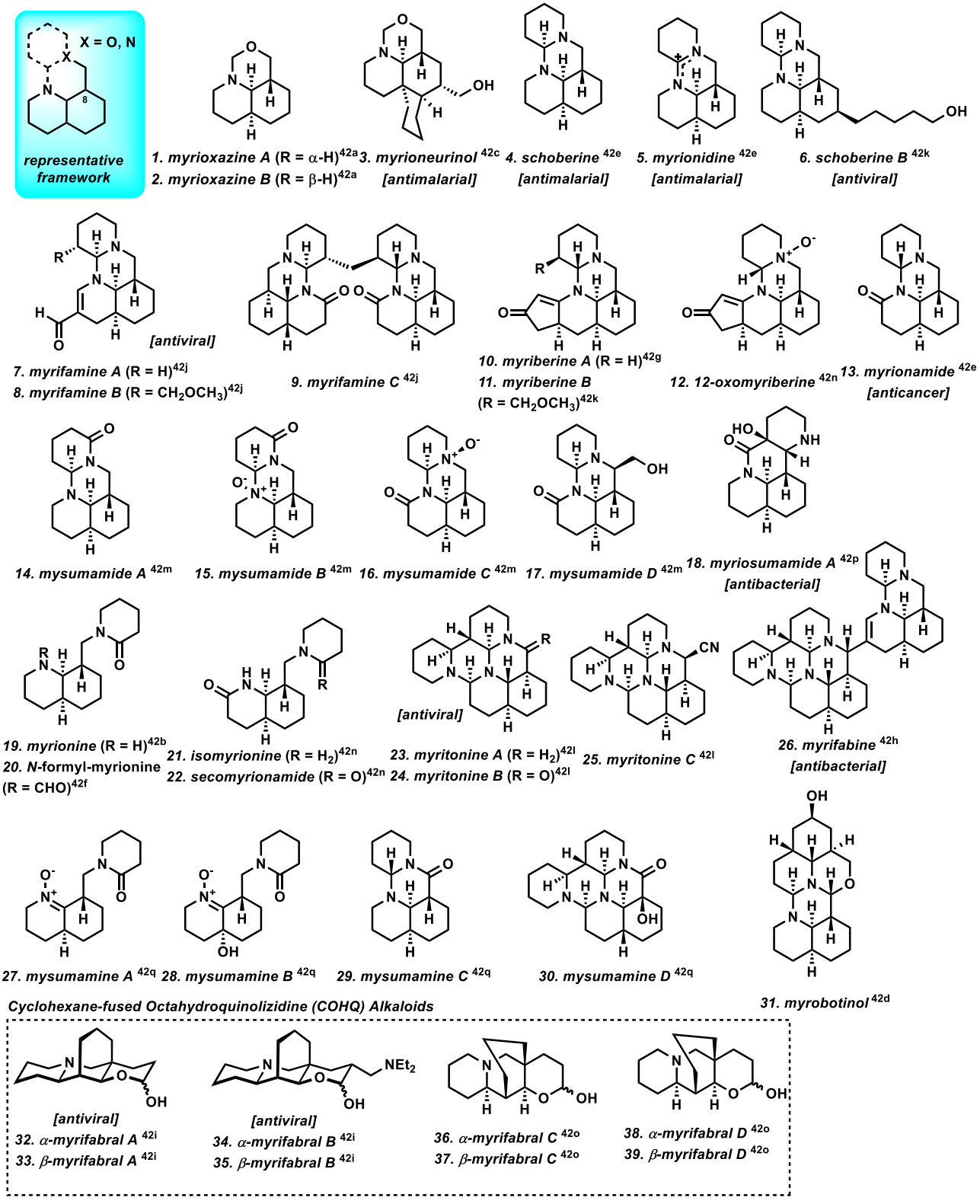
leaf extracts of *Myrioneuron nutans*, a small tree native to North Vietnam, provided two epimeric tricyclic alkaloids: myrioxazine A (**1**) and B (**2**).[42a] Since then, over 35 members have been isolated by the Bodo and Hao groups from various *Myrioneuron* species (*M. nutans*, *M. faberi*, *M. tonkinensis*, and *M. efussum*) all located around the northern part of Vietnam and south of mainland China (Scheme 1.13).[42] Some of these alkaloids have also been found in other plant species. For instance, schoberine (**4**) was isolated from several *Nitraria* species[43] before its isolation from *M. nutans*.[42e]

This family is not only composed of DHQ alkaloids but also few alkaloids containing an octahydroquinolizidine (OHQ) nucleus (**32-39**). They have been isolated from *M. faberi* and included in the family.

Structurally, the DHQ alkaloids of this family are characterized by a *cis*- or *trans*-DHQ ring attached at C-8 to an oxazine, a diazine or a cyclohexane ring forming complex polycyclic ring systems (tri-, tetra-, penta-, hexa-, octa- and decacyclic) with a diversified array of relative stereochemical relationships. In most of the cases, the hydrogen at C-8 has a *trans* relationship with the hydrogens at the ring fusion.

[42] For isolations, see: a) Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2002**, *43*, 7565-7568; b) Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Org. Lett.* **2007**, *9*, 3531-3534; c) Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Tetrahedron* **2007**, *63*, 11244-11249; d) Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *J. Org. Chem.* **2007**, *72*, 9826-9829; e) Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *J. Org. Chem.* **2008**, *73*, 7565-7573; f) Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Eur. J. Org. Chem.* **2009**, 1412-1416; g) Huang, S.-D.; Zhang, Y.; Cao, M.-M.; Di, Y.-T.; Tang, G.-H.; Peng, Z.-G.; Jiang, J.-D.; He, H.-P.; Hao, X.-J. *Org. Lett.* **2013**, *15*, 590-593; h) Cao, M.-M.; Huang, S.-D.; Di, Y.-T.; Yuan, C.-M.; Zuo, G.-Y.; Gu, Y.-C.; Zhang, Y.; Hao, X.-J. *Org. Lett.* **2014**, *16*, 528-531; i) Cao, M.-M.; Zhang, Y.; Li, X.-H.; Peng, Z.-G.; Jiang, J.-D.; Gu, Y.-C.; Di, Y.-T.; Li, X.-N.; Chen, D.-Z.; Xia, C.-F.; He, H.-P.; Li, S.-L.; Hao, X.-J. *J. Org. Chem.* **2014**, *79*, 7945-7950; j) Cao, M.-M.; Zhang, Y.; Huang, S.-D.; Di, Y.-T.; Peng, Z.-G.; Jiang, J.-D.; Yuan, C.-M.; Chen, D.-Z.; Li, S.-L.; He, H.-P.; Hao, X.-J. *J. Nat. Prod.* **2015**, *78*, 2609-2616; k) Cao, M.-M.; Zhang, Y.; Peng, Z.-G.; Jiang, J.-D.; Gao, Y.-J.; Hao, X.-J. *RSC Adv.* **2016**, *6*, 10180-10184; l) Li, X.-H.; Zhang, Y.; Zhang, J.-H.; Li, X.-N.; Cao, M.-M.; Di, Y.-T.; Peng, Z.-G.; Jiang, J.-D.; Hao, X.-J. *J. Nat. Prod.* **2016**, *79*, 1203-1207; m) Zhang, J.-H.; Guo, J.-J.; Yuan, Y.-X.; Fu, Y.-H.; Gu, Y.-C.; Zhang, Y.; Chen, D.-Z.; Li, S.-L.; Di, Y.-T.; Hao, X.-J. *Fitoterapia* **2016**, *112*, 217-221; n) Cao, M.-M.; Zhang, Y.; Huang, S.-D.; Peng, Z.-G.; Jiang, J.-D.; Hao, X.-J. *Tetrahedron Lett.* **2016**, *57*, 4021-4023; o) Cao, M.-M.; Zhang, J.-H.; Zhang, Y.; Peng, Z.-G.; Jiang, J.-D.; Hao, X.-J. *Tetrahedron Lett.* **2016**, *57*, 5632-5635; p) Zhang, J.-H.; Cao, M.; Zhang, Y.; Li, X.-H.; Gu, Y.-C.; Li, X.-N.; Di, Y.-T.; Hao, X.-J. *RSC Adv.* **2022**, *12*, 28147-28151; q) Li, X.-H.; Zhang, J.-H.; Zhang, Y.; Di, Y.-T.; Gu, Y.-C.; Cao, M.; Hao, X.-J. *Phytochem. Lett.* **2023**, *53*, 175-178.

[43] a) Ibragimov, A. A.; Novgorodova, N. Yu.; Aripov, Kh. N. *Chem. Nat. Compd.* **1977**, *13*, 71-74; b) Tulyaganov, T. S. *Chem. Nat. Compd.* **1993**, *29*, 31-34; c) Tulyaganov, T. S.; Allaberdiev, F. Kh. *Chem. Nat. Compd.* **2003**, *39*, 292-293.



Scheme 1.13 The *Myrioneuron* alkaloids

1.3.1 Biological Activity

One of the most interesting and promising aspects of this new family of alkaloids are their biological activities. This is not unusual given that these alkaloids come from the *Rubiaceace* family which contains a wide amount of bioactive natural products.

The most present bioactivity exhibited by these alkaloids is antiviral activity against hepatitis C virus (HCV). Schoberine B, with its unique 5-atom hydroxyalkyl chain, presents inhibitory activity against HCV (EC_{50} = 2.76 μM) with a selectivity index (SI) higher than 36.2 (CC_{50} > 100 μM).[42k] Additional *Myrioneuron* alkaloids present HCV activity, including myrifabrals A (**32**–**33**) and B (**34–35**, EC_{50} = 2.2-4.7, SI >25),[42i] myriberines A (**10**) and B (**11**, EC_{50} = 5.1-8.5 μM, SI >12),[42g,k] myritonines A (**23**) and B (**24**, EC_{50} = 16-17 μM, SI >12),[42l] 12-oxomyriberine (**12**) and isomyrionine (**21**, SI > 15.2 and 36.2, respectively),[42n] and myrifamines A (**7**) and B (**8**, EC_{50} = 0.92-3.3 μM, SI >30.6).[42j]

Antimalarial activity has also been reported. Myrioneurinol (**3**) has shown activity against *Plasmodium falciparum* (IC_{50} = 16.4-21.2 μM). Given its weak inhibition of KB cell proliferation (IC_{50} = 26 μM) it is suspected that this effect is not caused by cytotoxicity.[42c] Myrionidine (**5**) (and its unnatural enantiomer) and schoberine (**4**) possess a more potent activity (IC_{50} = 0.3 and 4.0 μM, respectively) against *P. falciparum*, which again seems not to be related to cytotoxicity (IC_{50} = 6 and 20 μM - against KB cells, respectively).[42e]

Myrifabine (**26**), a decacyclic heterodimeric member of this family, has shown significant cytotoxic effects towards multiple human tumor cell lines (IC_{50} = 16.4–21.2 μM) and against Gram-positive bacteria such as *Staphylococcus aureus* and methicillin-resistant *Stapylococcus aureus* (MIC = 6.3-25.1 μM).[42m] Myrionamide (**13**) showed weak cytotoxicity against HeLa, A549, and COLO-205 cell lines (IC_{50} = 35.2-38.7 μM).[42m]

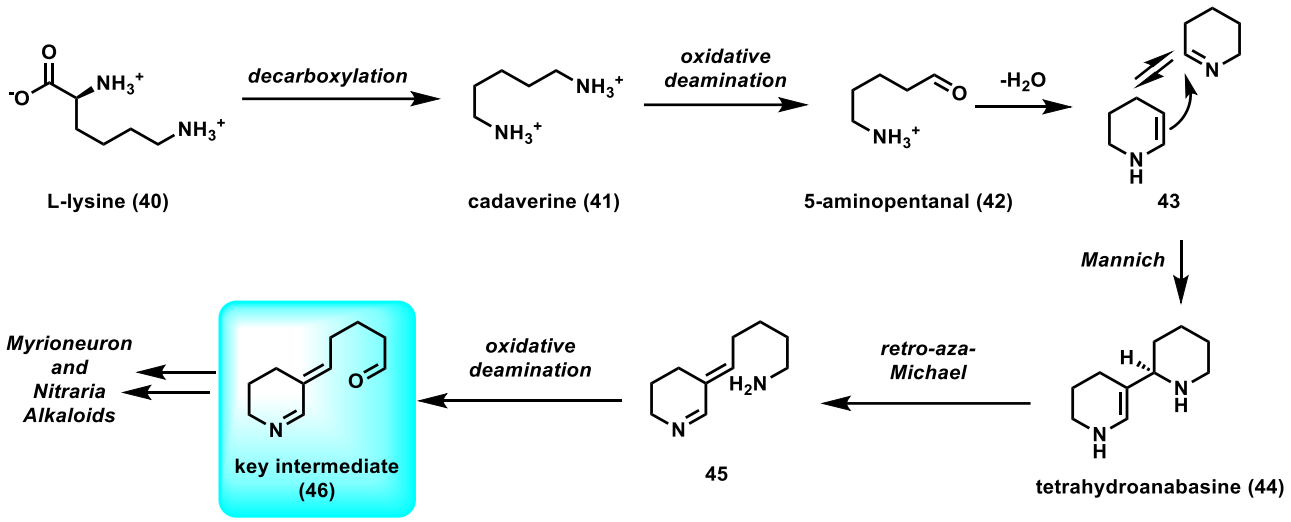
Even though only a small fraction of the compounds has been studied, the *Myrioneuron* alkaloids are likely to exhibit interesting biological properties upon additional biological assays. Further advances in the synthesis of these alkaloids should allow their obtention in enough amounts to facilitate their study.

1.3.2 Proposed Biosynthesis

Like the *Nitraria* alkaloids, the *Myrioneuron* alkaloids are proposed to derive biosynthetically from L-lysine,[44] a common amino acid building block. For the biosynthesis of these molecules, L-lysine (**40**) undergoes a decarboxylation to yield cadaverine (**41**), a C_5 linear symmetric diamine. Oxidative deamination of **41** gives 5-aminopentanal (**42**), which is unstable and cyclizes into Δ^2-piperidine (**43**) [in equilibrium with the corresponding imine (Δ^1-piperidine)]. Dimerization of enamine **43** into

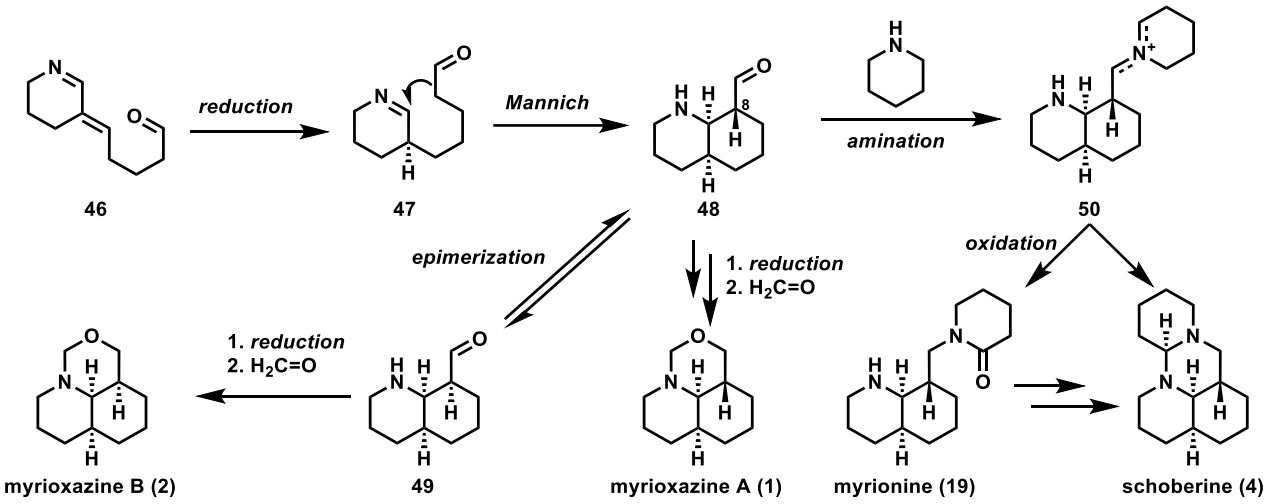
[44] a) Gravel, E.; Poupon, E. *Nat. Prod. Rep.* **2010**, *27*, 32-56; b) Poupon, E.; Gravel, E. *Chem. Eur. J.* **2015**, *21*, 10604-10615.

tetrahydroanabasine (**44**) through a Mannich-type reaction, followed by a retro-aza-Michael reaction and an oxidative deamination ends up key intermediate **46** (Scheme 1.14).[45]



Scheme 1.14 Tetrahydroanabasine divergent evolution in nature

Then, the DHQ scaffold is assembled by reduction of the conjugated double bond of imine **46** followed by a Mannich cyclization to afford *cis*-DHQ intermediate **48**. Simple tricyclic members of the family like myrioxazine A (**1**) and B (**2**) are formed through the reduction of **48** (or **49** after epimerization at C-8) followed by formaldehyde condensation of the resulting aminoalcohol to form the natural products. By incorporating an additional piperidine unit to **48**, additional members of the family such as myrionine (**19**) and schoberine (**4**) can also be constructed (Scheme 1.15).

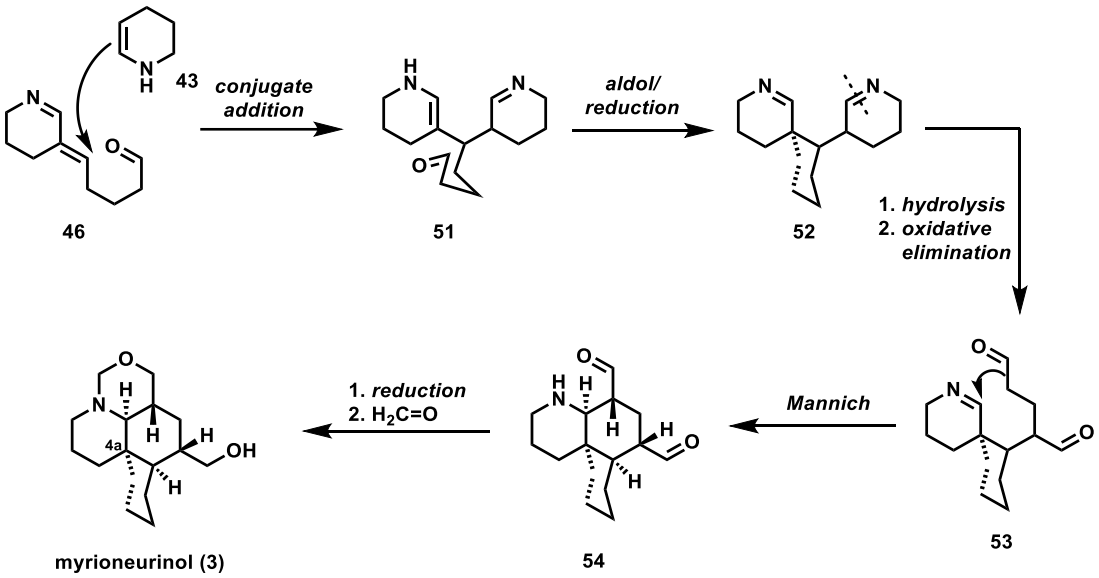


Scheme 1.15 Assembly of simple tricyclic and tetracyclic *Myrioneuron* alkaloids

[45] a) Wanner, M. J.; Koomen, G. J. Stereoselectivity in Synthesis and Biosynthesis of Lupine and Nitraria Alkaloids. In *Studies in Natural Products Chemistry*, Vol. 14; Elsevier, Amsterdam, **1994**; pp. 731-768; b) Wanner, M. J.; Koomen, G. J. *Pure Appl. Chem.* **1994**, *66*, 2239-2242; c) Wanner, M. J.; Koomen, G. J. *Pure Appl. Chem.* **1996**, *68*, 2051-2056.

The use of additional lysine-derived units lead, through similar pathways, to the formation of more complex members of the family like schoberine B (**6**) or the (hetero)dimers and higher oligomers myrobotinol (**31**), myrifabine (**26**), and myrifamine C (**17**).

The biogenesis of myrioneurinol (**3**), on the other hand, differs from the rest of the members of the family given the presence of an all-carbon quaternary stereocenter at C-4a. The biosynthesis of this alkaloid is envisioned to start from key intermmediate **46** which undergoes a conjugate addition from enamine **43** to form intermediate **51**.[42c] Then, the characteristic cyclohexane ring is formed via an enamine-aldol closure followed by deoxygenation to deliver **52** which, upon imine hydrolysis and similar oxidative deamination as seen in Scheme 1.14, gives imine-dialdehyde **53**. Intramolecular Mannich reaction of **53** followed by reduction of dialdehyde **54** and formation of the oxazine ring provides myrioneurinol (Scheme 1.16).



Scheme 1.16 Biosynthesis of myrioneurinol

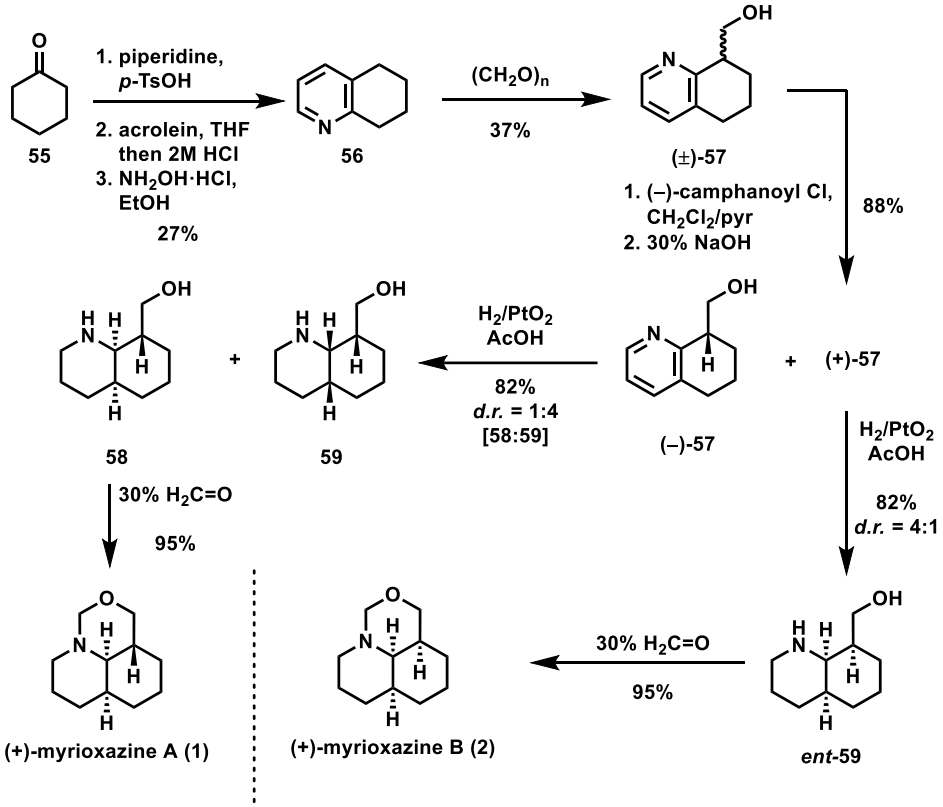
1.3.3 Previous Synthesis of *Myrioneuron* Alkaloids

Given the interesting biological activities and intricate polycyclic systems this family of alkaloids possess, the synthetic interest in this group of compounds has been constant since the first isolation by Bodo. So far, the total synthesis of six alkaloids of the family has been achieved.

1.3.3.1 Total Synthesis of Myrioxazines A and B

During the first isolation and characterization of myrioxazines A (**1**) and B (**2**), Bodo and co-workers synthetized (+)-myrioxazine A and (+)-myrioxazine B, as well as their C-5 and C-10 epimers, which allowed the confirmation of the proposed structures (Scheme 1.17).[42a]

From commercial cyclohexanone **55**, 5,6,7,8-tetrahydroquinoline (bz-THQ) **56** was prepared by Michael addition of acroleine via the enamine of the cyclohexanone, followed by cyclization with hydroxylamine hydrochloride. bz-THQ **56** reacted with paraformaldehyde to provide racemic alcohol (±)-**57**. Racemic resolution of **57** with (–)-camphanoyl chloride followed by hydrolysis of the corresponding ester led to enantiopure (–)-**57** and (+)-**57**. Catalytic hydrogenation of (–)-**57** with PtO_2 afforded aminoalcohols **58** and **59** (*d.r.* = 1:4). Similarly, (+)-**57** provided ***ent*-59** as the major diastereomer. Cyclization of **58** and ***ent*-59** with a 30% formalin solution afforded (+)-myrioxazine A (**1**) and B (**2**), respectively.



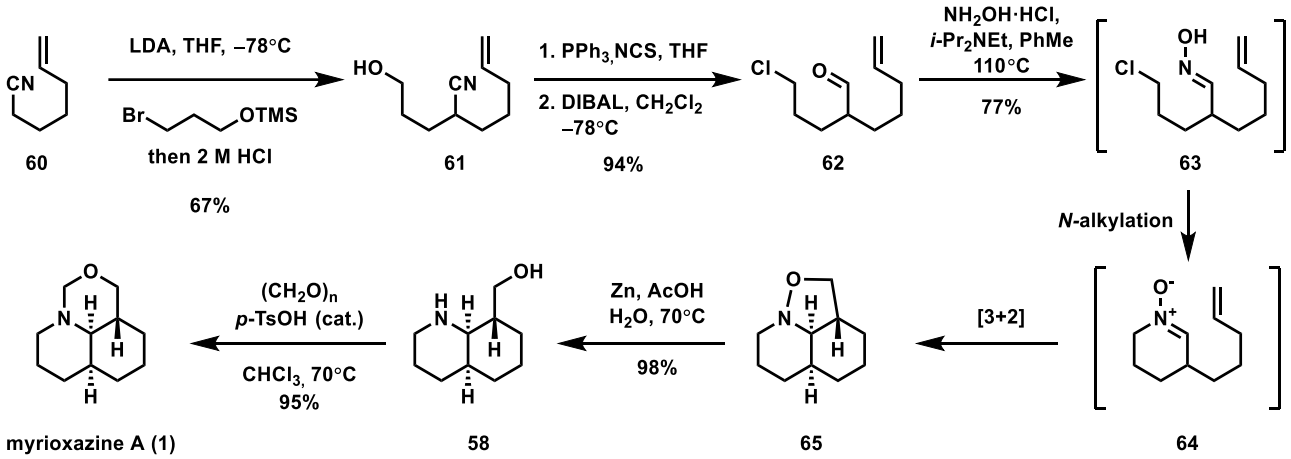
Scheme 1.17 Bodo's total synthesis of (+)-myrioxazine A and (+)-myrioxazine B

With eight steps and overall yields of 0.5% and 5.5% for (+)-myrioxazine A (**1**) and B (**2**), respectively, Bodo's synthesis allowed a concise first approach to the synthesis and structure confirmation of these alkaloids.

Additionally, in 2009, the Coldham group developed a racemic synthesis of myrioxazine A (**1**) by using an acyclic enolizable aldehyde to stereoselectively form the substituted DHQ core via a tandem one-pot reaction involving a condensation, then cyclization (*N*-alkylation), followed by a nitrone dipolar cycloaddition (Scheme 1.18).[46a]

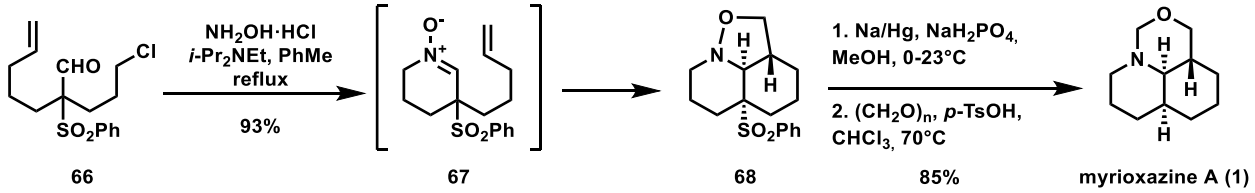
[46] a) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515-1518; b) Coldham, I.; Burrell, A. J. M.; Watson, L.; Oram, N.; Martin, N. G. *Heterocycles* **2012**, *84*, 597-613.

The synthesis starts with alkylation of commercial 6-heptenenitrile (**60**) with (3-bromopropyl)trimethoxysilane followed by acidic deprotection of the trimethylsilyl ether. The resulting alcohol **61** is chlorinated with NCS and PPh_3 and reduced with DIBAL to yield aldehyde **62**. Treatment of the aldehyde with hydroxylamine and *i*-Pr_2NEt initially formed oxime **63** which is *N*-alkylated by the alkyl chloride to form cyclic nitrone **64**. This intermediate undergoes a diastereoselective intramolecular [3+2] cycloaddition with the terminal alkene to provide cycloadduct **65** with the proper relative configuration. The N-O bond of **65** is cleaved by reaction with zinc in acetic acid to give amino alcohol **58**, which upon heating with paraformaldehyde under acid catalysis provided (±)-myrioxazine A (**1**). The synthesis of intermediate **58** also completes the formal synthesis of schoberine (**4**), myrionidine (**5**), and myrionine (**19**).[42e]



Scheme 1.18 Coldham's racemic synthesis of myrioxazine A

In 2012, Coldham reported an additional route to (±)-myrioxazine A by similar means.[46b] In this case, the dipolar cycloaddition cascade was performed with α-sulfonyl aldehyde **66** [readily available from (phenylthio)acetonitrile following similar procedures to the preparation of **62**] to yield cycloadduct **68** (via nitrone **67**). Then, compound **68** was treated with sodium amalgam which promoted the reduction of both the N–O and C–S bonds with retention of configuration followed by formation of the oxazine by heating paraformaldehyde in acid catalysis to provide (±)-myrioxazine A (**1**) (Scheme 1.19).

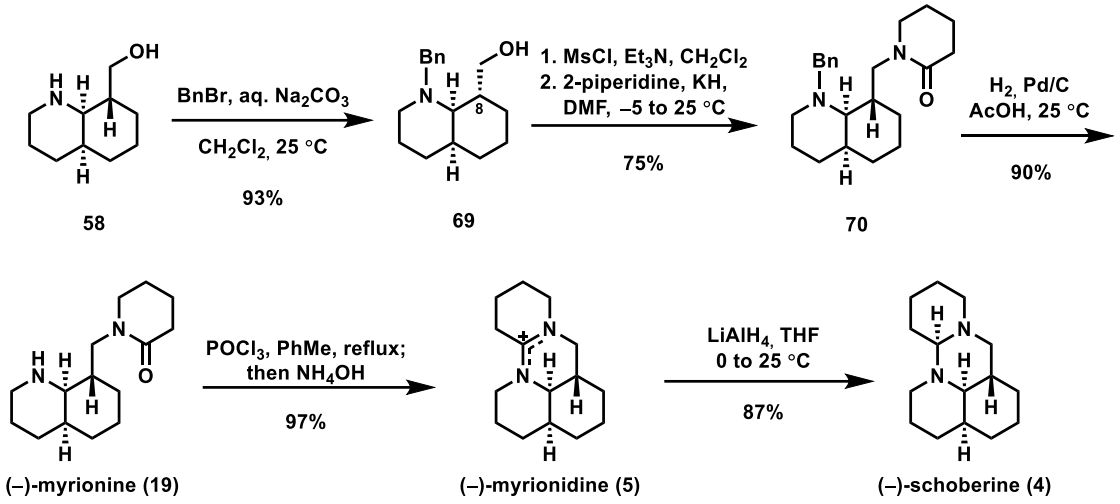


Scheme 1.19 Coldham's second racemic synthesis of myrioxazine A

Three syntheses have been reported for myrioxazine A (**1**) and one for myrioxazine B (**2**). Among them, the most challenging step remains the formation of the DHQ nucleus with an appropriate relative configuration.

1.3.3.2 Total Synthesis of Myrionine, Myrionidine, and Schoberine

Six years after the first studies on the *Myrioneuron* alkaloids, the Bodo group reported the isolation and asymmetric synthesis of three additional alkaloids: myrionine (**19**), myrionidine (**5**), and schoberine (**4**) (Scheme 1.20).[42b,e]



Scheme 1.20 Bodo's total synthesis of (–)-myrionine, (–)-myrionidine, and (–)-schoberine

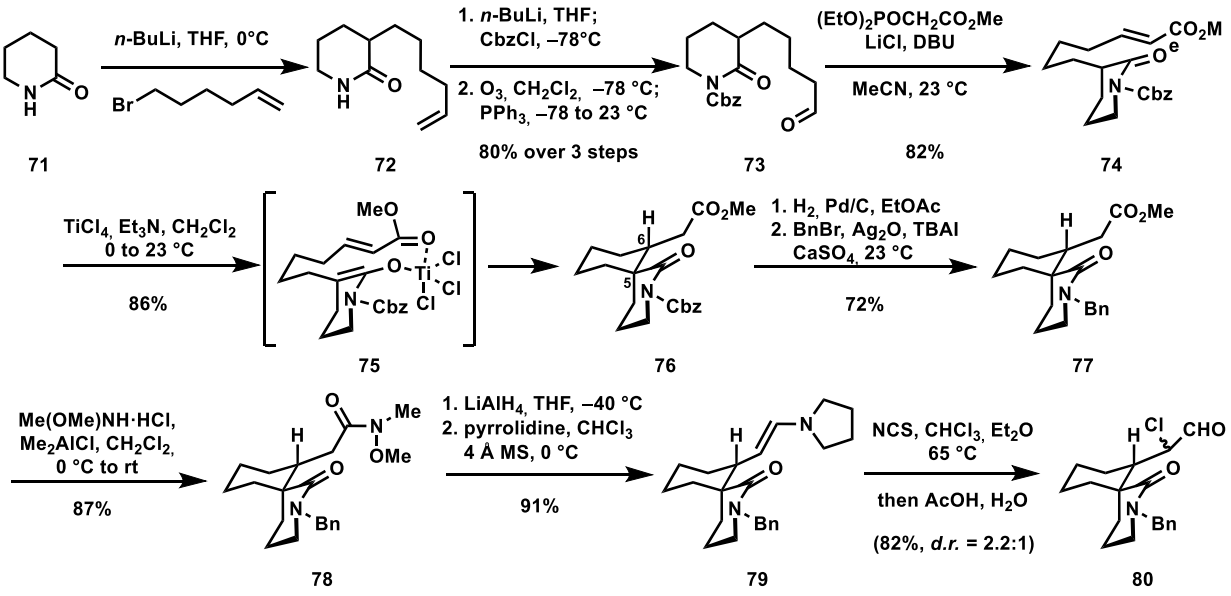
Starting from the previously reported amino alcohol **58** (prepared in seven steps from cyclohexanone **55**, Scheme 1.17) used for the synthesis of myrioxazines A and B, [42a] the amine was protected with benzyl bromide to give *N*-benzyl alcohol **69**. Then, 2-piperidone was introduced into the hydroxymethyl moiety at C-8 through a nucleophilic substitution with the anion of 2-piperidone and a mesylated derivative of **69**. Removal of the benzyl group by catalytic hydrogenation with Pd/C afforded (–)-myrionine (**19**). Then, a dehydrative cyclization via $POCl_3$ and base treatment provided (–)-myrionidine (**5**). Reduction of the amidinium of **5** with lithium aluminum hydride yielded (–)-schoberine (**4**).

1.3.3.3 Total Synthesis of Myrioneurinol

Myrioneurinol, first isolated by Bodo in 2007,[42c] was not synthetized until 2014 by the Weinreb group (Scheme 1.21–Scheme 1.23).[47]

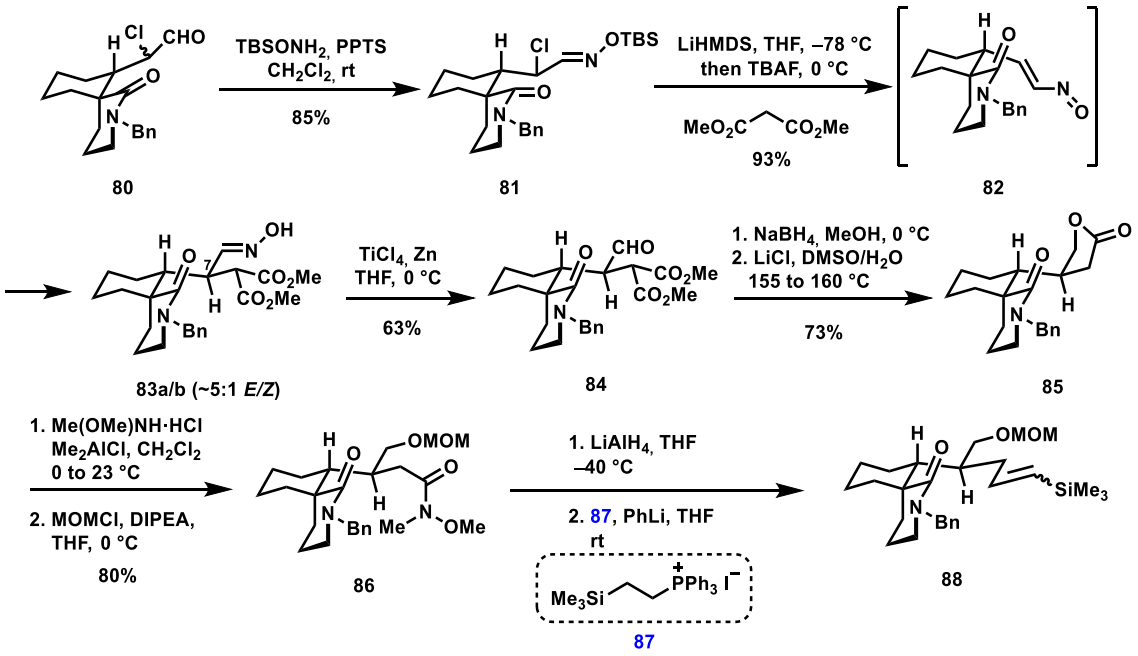
[47] a) Nocket, A. J.; Weinreb, S. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 14162-14165; b) Nocket, A. J.; Feng, Y.; Weinreb, S. M. *J. Org. Chem.* **2015**, *80*, 1116-1129.

δ-Valerolactam (**71**) was *C*-monoalkylared with 6-bromohex-1-one and transformed to lactam **72**. Subsequent *N*-acylation and ozonolysis of the terminal alkene led to benzyloxycarbonyl-protected aldehyde **73** which was subjected to a Horner–Wadsworth–Emmons reaction to provide (*E*)-α-β-unstaturated ester **74**. Soft enolization with titanium tetrachloride led to an intramolecular Michael cyclization to provide spirocycle **76**. This cyclization is thought to occur through titanium enolate **75** which undergoes a conjugate addition to afford the spirocycle with the desired C5/C6 configuration for myrioneurinol. Removal of the Cbz group by catalytic hydrogenation and *N*-benzylation afforded spirocycle **77**. Transformation of **77** into *N*-methoxy-*N*-methylamide **78**, subsequent reduction of the resulting Weinreb amide with $LiAlH_4$ and treatment with pyrrolidine afforded enamine **79**. Treatment of 79 with NCS and acid hydrolysis afforded a diastereomeric mixture of α-chloroaldehyde **80** (Scheme 1.21).



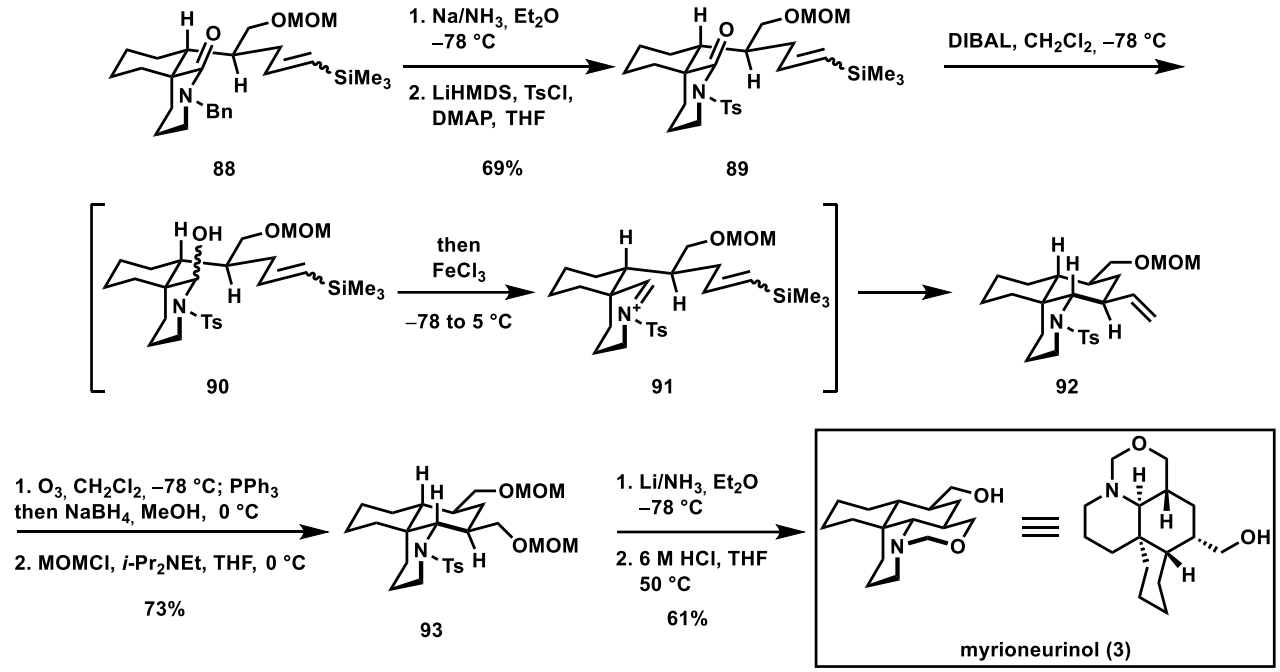
Scheme 1.21 Synthesis of α-chloroaldehyde **80**

Then, α-chloroaldehyde **80** was transformed into *O*-TBS-protected oxime **81** which upon treatment with LiHMDS and dimethyl malonate led to C-7 alkylated product **83** with the desired configuration. The mixture of oximes was cleaved to give aldehyde **84**, which was reduced and decarboxylated to give butyrolactone **85**. Opening of the lactone with *N*,*O*-dimethylhydroxylamine hydrochloride/dimethylaluminium chloride and protection of the resulting alcohol with methoxymethyl chloride afforded compound **86**. Reduction of the amide to an aldehyde and olefination with the Seyferth silylethyl ylide (**87**) provided allylsilane **88** as an *E*/*Z* mixture (Scheme 1.22).



Scheme 1.22 Synthesis of allylsilane **88**

Removal of the *N*-benzyl group with Na/NH_3 and subsequent tosylation of the lactam afforded *N*-sulfonyl lactam **89**. Then, the DHQ nucleus was assembled: lactam **89** was partially reduced to intermediate **90** with DIBAL followed by addition of ferric chloride to form *N*-sulfonyliminium ion/allylsilane **91**, which cyclizes (through the chair-like transition state with the allylsilane moiety) via an intramolecular aza-Sakurai reaction leading to tricycle **92**. Cleavage of the vinyl group by ozonolysis and reduction of the resulting aldehyde followed by protection with methoxymethyl ether afforded the bis(methoxymethyl)-protected ether **93**. Deprotection of the *N*-tosyl with Li/NH_3 and deprotection of the ethers with aqueous HCl allowed the formation of the 1,3-oxazine, producing racemic myrioneurinol (**3**) (Scheme 1.23).



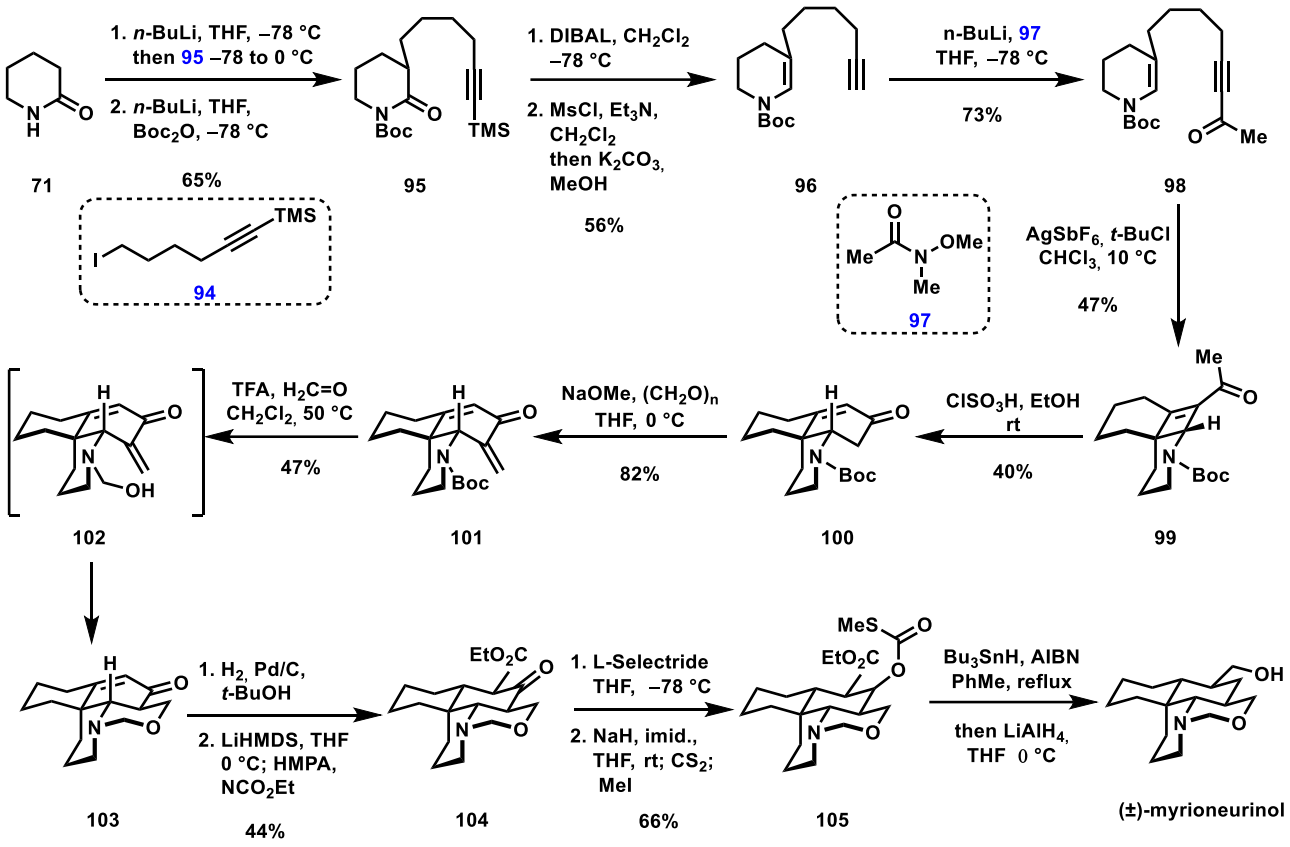
Scheme 1.23 Weinreb's first total synthesis of racemic myrioneurinol

Weinreb's obtention of myrioneurinol (**3**) constitutes the first total synthesis of one of the more complex *Myrioneuron* alkaloids.

In 2022 the Ma group reported a shorter total synthesis of (±)-myrioneurinol (**3**) in 14 steps (Scheme 1.24).[48] Starting from δ-valerolactam (**71**), *N*-Boc protected lactam **95** was synthetized by alkylation with iodosilane **94**. Reduction of the carbonyl lactam followed by elimination afforded enamine-yne **96**. Acetylation of **96** with the Weinreb amide (**97**) yielded **98**. $AgSbF_6$/*t*-BuCl-catalyzed intramolecular [2+2] cycloaddition reaction of alkynone-tethered enamine **98** afforded cyclobutene **99** stereoselectively. Under acidic conditions, a retro–Mannich fragmentation followed by reclosure by Mannich reaction allowed a ring expansion to yield **100** bearing the tricyclic core of the alkaloid. Methylenation of **100** with paraformaldehyde and sodium methoxide provided dione **101**. The assembly of the tetracyclic scaffold of myrioneurinol (**3**) was completed by treatment of **101** with TFA and formalin which, in a cascade fashion, promoted *N*-Boc cleveage, *N*-hydroxymethylation (to intermediate **102**) and an intramolecular oxy Michael addition to yield tetracycle **103**.

Stereoselective hydrogenation followed by α-ethoxycarbonylation provides β-ketoester **104** containing the desired relative configuration of all chiral centers of the final product. Stereoselective reduction of the ketone and conversion of the resulting alcohol into the corresponding xanthate **105** allowed a Barton–McCombie deoxygenation followed by a reduction of the ester with lithium aluminum hydride to furnish (±)-myrioneurinol (**3**) in one step.

[48] Zhang, N.; Jiang, H.; Ma, Z. *Angew. Chem. Int. Ed.* **2022**, *61*, e202200085.



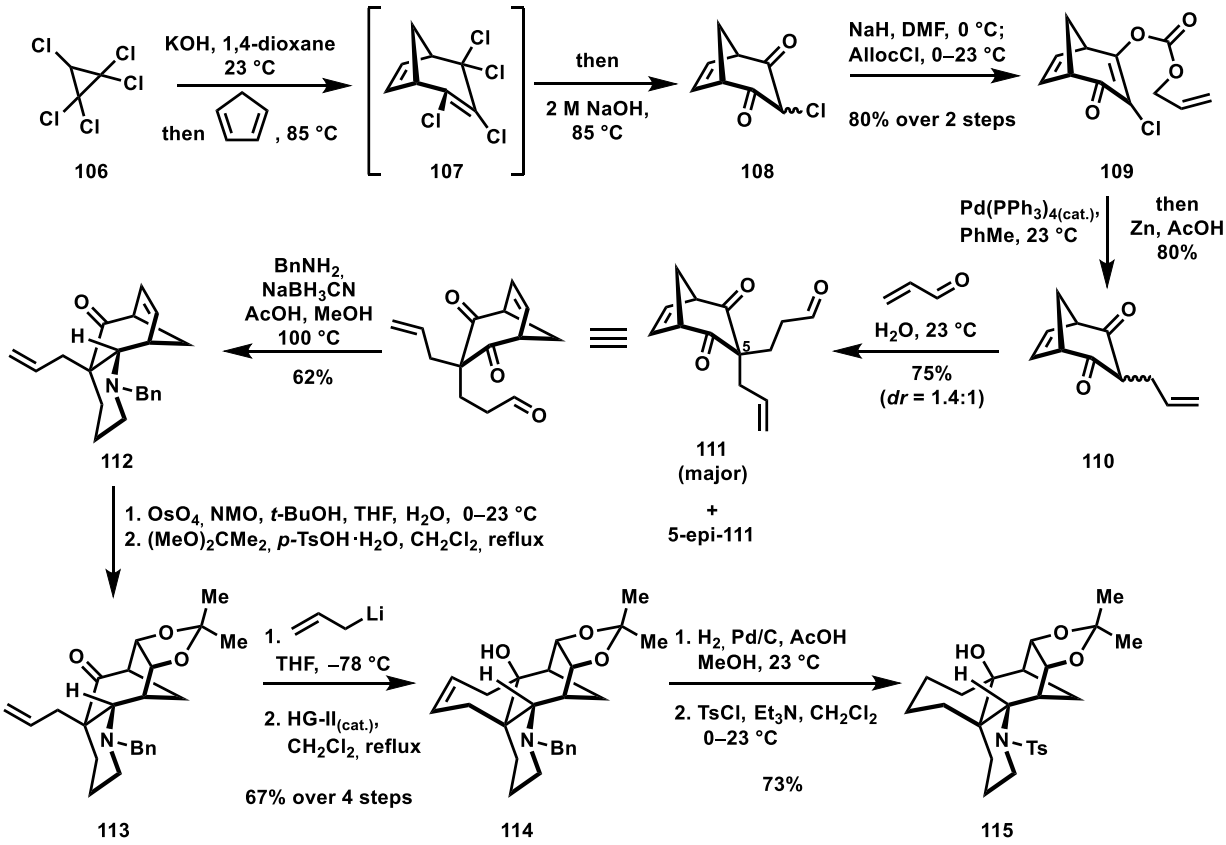
Scheme 1.24 Ma's synthesis of racemic myrioneurinol

Later the same year, the Smith group also reported another synthesis of (±)-myrioneurinol (**3**) (Scheme 1.25–Scheme 1.26).[49]

From pentachlorocyclopropane **106**, a one-pot process started by elimination to the cyclopropene with KOH followed by Diels–Alder cycloaddition with cyclopentadiene, ring-opening to bicycle **107**. Subsequent basic hydrolysis afforded bicyclic chlorodiketone **108**. Enolization and *O*-Alloc acylation provides **109**, which under palladium-catalyzed Tsuji–Trost decarboxylative alkylation furnishes mono-allylated diketone **110** after in situ dichlorination with Zn/AcOH. Michel addition of **110** to acrolein afforded key tricarbonyl precursor **111** with moderate diastereoselectivity (1:1.4 **111**:**5-epi-111**). The epimeric mixture is subjected to a double reductive amination using *N*-benzylamine and sodium cyanoborohydride which desymmetrizes the mixture and yields tricycle **112** as a single diastereomer. Chemoselective dihydroxylation of the bridged alkene and acetonide protection provides ketone **113**. Diastereoselective allylation of ketone **113** followed by ring-closing metathesis (RCM) with Hoveyda–Grubbs second-generation catalyst (HG-II) delivered pentacyclic alkene **114**. Finally, catalytic hydrogenation of the resulting alkene with concomitant hydrogenolysis of the *N*-

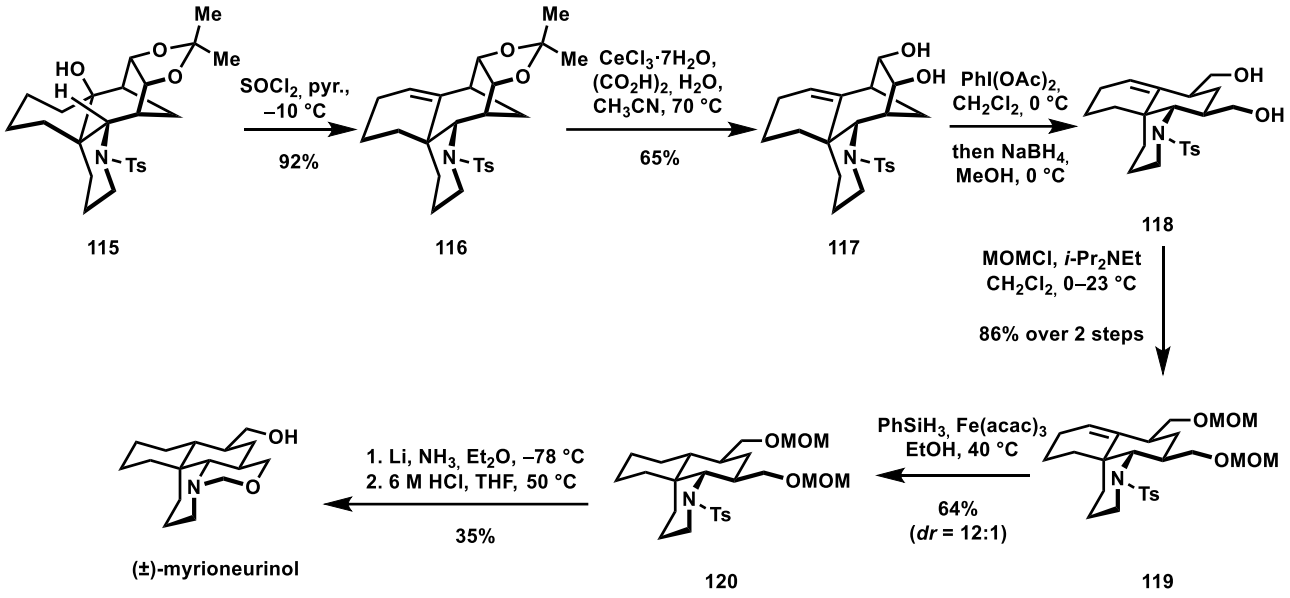
[49] Aquilina, J. M.; Smith, M. W. *J. Am. Chem. Soc.* **2022**, *144*, 11088-11093.

benzyl group followed by reprotection of the secondary amine with tosyl chloride afforded **115** (Scheme 1.25).



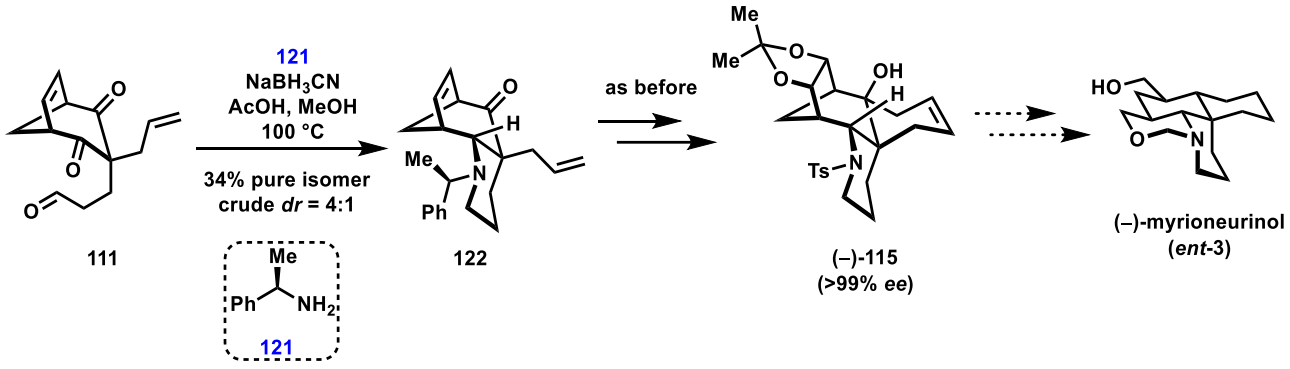
Scheme 1.25 Synthesis of intermediate **115**

Dehydration of **115** to alkene **116** with $SOCl_2$/pyridine followed by acetonide deprotection afforded diol **117**. Oxidative diol cleavage with $PhI(OAc)_2$ and reduction of the resulting aldehydes afforded diol **118**, which upon protection of the primary diols with methoxymethyl chloride and HAT reduction afforded tricycle **120**, known intermediate of the Weinreb synthesis.[47] Tosyl deprotection with Li/NH_3 followed by treatment with 6 M HCl resulted in the cleveage of the distal MOM group and *N*-cyclization with the other MOM to form the 1,3-oxazine ring and yield (±)-myrioneurinol (**3**) (Scheme 1.26).



Scheme 1.26 Completion of Smith's total synthesis of (±)-myrioneurinol

The substitution of benzylamine with (*R*)-α-methylbenzamine (**121**) in the double reductive amination allowed the diasteroselective desymmetrization for one of the two diastereotopic ketones allowing the obtention of pure isomer **122**. Application of the same synthetic sequence allowed the obtention of (–)-**115** and thus, the formal asymmetric synthesis of (–)-myrioneurinol (**3**) (Scheme 1.27).



Scheme 1.27 Smith's enantioselective synthesis of (–)-myrioneurinol

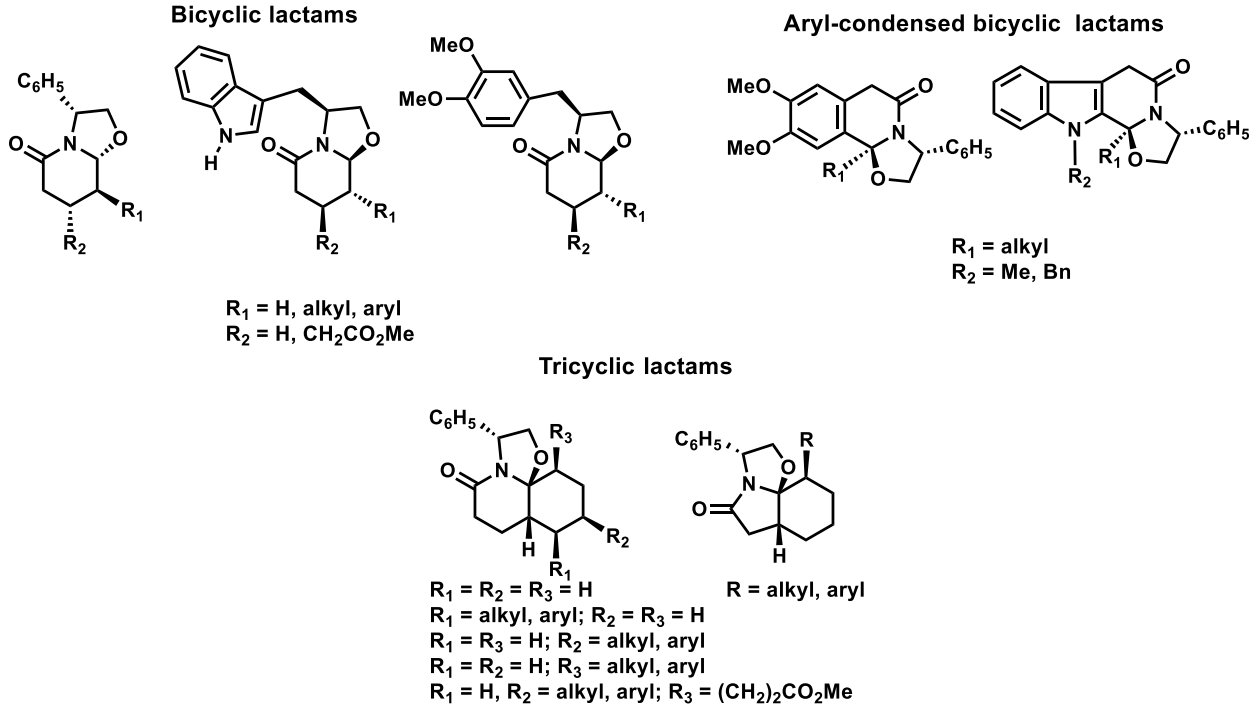
The *Myrioneuron* alkaloids, a recent addition into the DHQ alkaloid family, exhibit intricate structures and promising biological activities. There has been an increaseing interest in isolating and synthesizing these compounds, resulting in the development of novel strategies for the construction of this polycyclic scaffolds. Recent efforts have targeted more complex compounds like myrioneurinol (**3**), but mostly in a racemic manner. Several research groups have successfully achieved the total synthesis of six distinct family members. However, unconquered targets such as myrobotinol (**31**), myrifabine (**26**), and myritonines A–C (**23**–**25**), pose challenges with their extended fused ring systems and varying functionality and connectivity. Pursuing these compounds

will inspire innovative approaches and techniques to achieve these complex structures and will allow further biological studies.

1.4 Previous Accomplishments of the Research Group

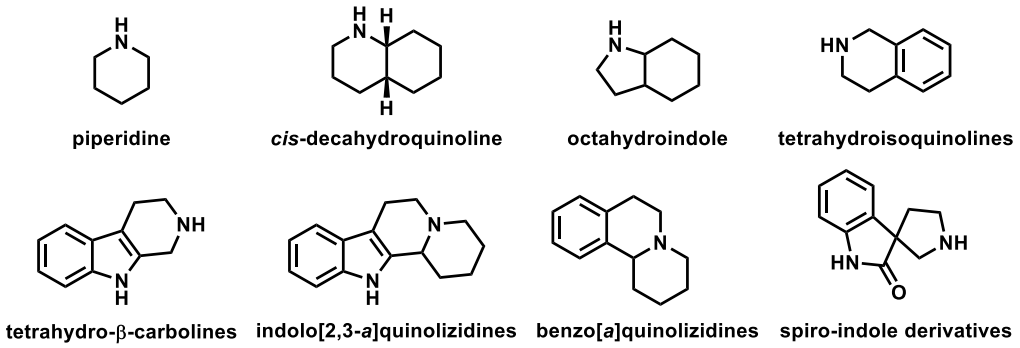
The development of solid and robust methodologies for the obtention of natural products is of utmost importance. Because of that, the research group has accumulated extensive expertise in both natural product synthesis as well as in the creation of sturdy and adaptable frameworks for the synthesis of high-value building blocks.

The group's synthetic methodology is based on the stereoselective formation of chiral bicyclic or tricyclic lactams by cyclocondensation of chiral amino alcohols such as (*R*)-phenylglycinol, (*S*)-tryptophanol, (*S*)-(dimethoxyphenyl)alaninol, or (1*S*, 2*R*)-*cis*-1-amino-2-indanol with simple, racemic or prochiral oxoesters or oxoacids. These processes result in the formation of chiral lactams with multiple stereocenters of a well-defined configuration through highly diastereoselective one-pot reactions (Scheme 1.28).



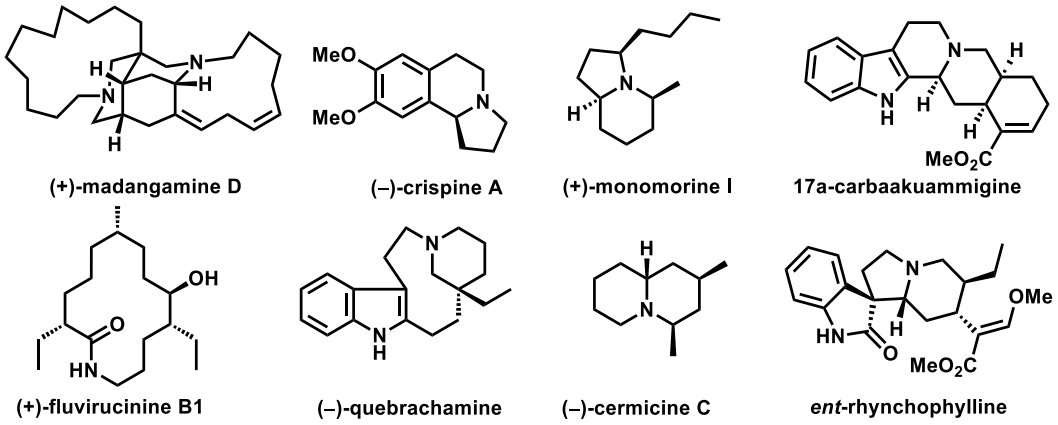
Scheme 1.28 The complete array of chiral platforms used by the group

Derivatization of these lactams has led to the obtention of a wide array of building blocks such as piperidines, *cis*-decahydroquinolines, *cis*- and *trans*-octahydroindoles, tetrahydroisoquinolines, tetrahydro-β-carbolines, indolo[2,3-*a*]quinolizidines, benzo[*a*]quinolizidines, spiro-indole derivatives, and linear amino-alcohols, hydroxy-acids, and hydroxy-nitriles in enantiopure form (Scheme 1.29).



Scheme 1.29 Different cores accessible by the group's methodology

The procedure's versatility and utility has been demonstrated through the total synthesis of multiple natural products. It has proven effective in total synthesis of simple piperidine, indolizidine, quinolizidine alkaloids as well as the synthesis of more complex alkaloids like the indole[50] and rearranged oxindole alkaloids,[51] tetrahydroisoquinoline alkaloids,[52] macrocyclic aza-derivatives,[53] and complex pentacyclic marine alkaloids,[54] among others (Scheme 1.30).



Scheme 1.30 Representation of the array of natural products achievable with the group's methodology

[50] a) Amat, M.; Gómez-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205-1211; b) Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch, J. *Org. Lett.* **2003**, *5*, 3139- 3142; c) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431-4439; d) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681- 8693; e) Amat, M.; Llor, N.; Checa, B.; Pérez, M.; Bosch, J. *Tet. Lett.* **2007**, *48*, 6722- 6725; f) Ordeix, S.; Alcaraz, M.; Llor, N.; Calbó, A.; Bosch, J.; Amat, M. *Tetrahedron* **2020**, *61*, 1-14

[51] Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M.; Bosch, J. *Chem. Commun.* **2013**, *49*, 1954- 1956.

[52] Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2010**, 4017-4026.

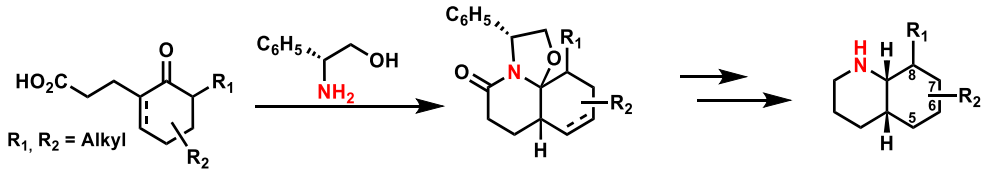
[53] a) Guignard, G.; Llor, N.; Molins, E.; Bosch, J.; Amat, M. *Org. Lett.* **2016**, *18*, 1788-1791; b) Amat, M.; Guignard, G.; Llor, N.; Bosch, J. *J. Org. Chem.* **2014**, *79*, 2792-2802.

[54] Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6202-6205.

1.5 Objectives of the Thesis

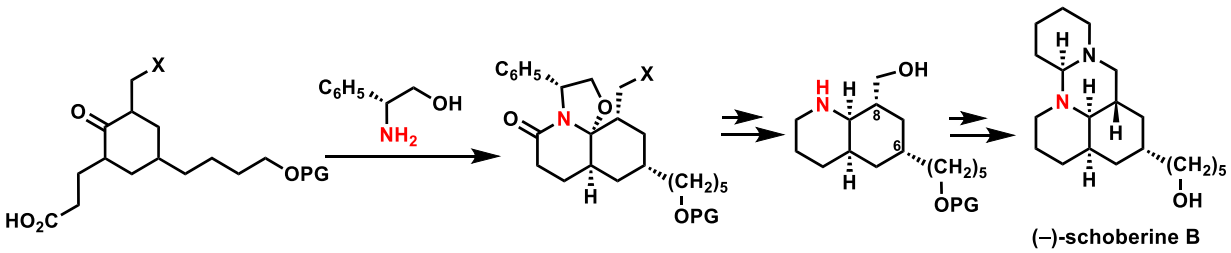
Given the importance outlined in previous sections about the necessity to develop efficient and robust strategies the synthesis of natural products, and the promising biological properties displayed by the *Myrioneuron* alkaloids, we envisioned that this PhD thesis would be focused on the expansion of the group's methodology and its application to the synthesis of *Myrioneuron* alkaloids. Because of that, the main objectives of the thesis are the following:

1. Development of a methodology for the synthesis of disubstituted *cis*-decahydroquinolines at different positions of the carbocyclic ring from chiral tricyclic lactams. We focused on the preparation of enantiopure 5,8-, 6,8-, and 7,8-disubstituted *cis*-DHQs (Scheme 1.31).



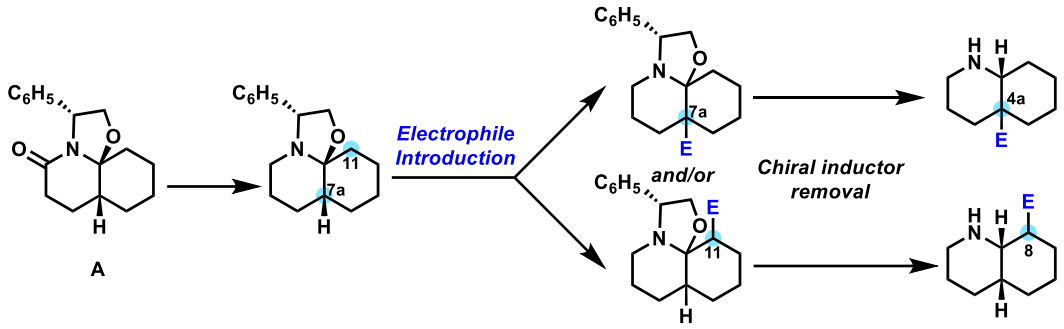
Scheme 1.31 Chapter 1 objectives

2. Application of the above-mentioned methodology to the synthesis of *Myrioneuron* alkaloid (–)-schoberine B (Scheme 1.32).



Scheme 1.32 Chapter 2 objectives

3. Explore the reactivity of the hemiaminal moiety, present in partially reduced derivatives of chiral tricyclic lactam **A**, with electrophiles to potentially obtain C-4a and/or C-8 substituted DHQs (Scheme 1.33).



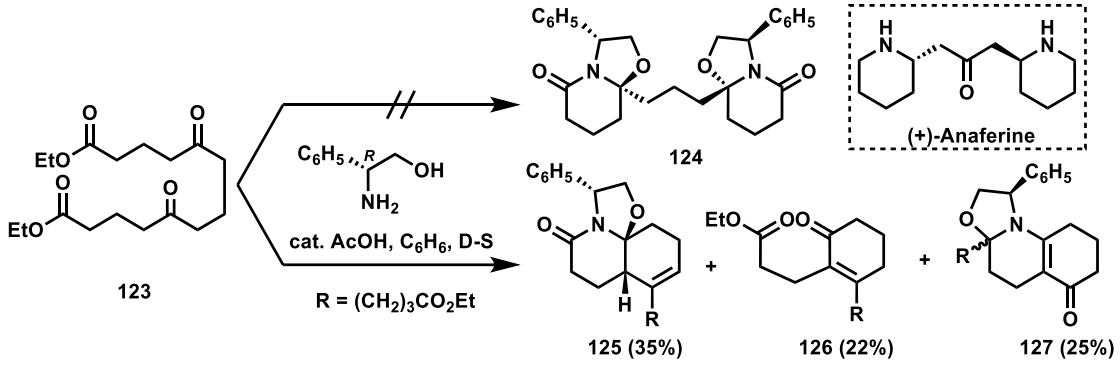
Scheme 1.33 Chapter 3 objectives

2 Enantioselective Synthesis of Disubstituted *cis*-Decahydroquinolines

2.1 Group Precedents on *cis*-Decahydroquinoline Synthesis from Chiral Tricyclic Lactams

2.1.1 Synthesis of C-5 and C-6 Substituted *cis*-Decahydroquinolines from Unsaturated Lactams

In the context of the synthesis of bis-piperidine alkaloids such as (+)-anaferine, it was discovered that the reaction between 1,5-tetracarbonylic compound **123**, *(R)*-phenylglycinol and a catalytic amount of acetic acid at reflux in a Dean-Stark, led to the obtention of enantiopure tricyclic lactam **125** in 35% yield instead of the expected oxazolopiperidine dimer **124**. Cyclohexenone **126** (22%) and hydroquinolone **127** (25%) were also obtained (Scheme 2.1).[55]



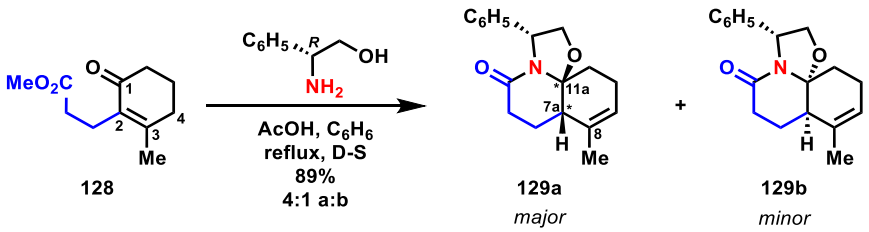
Scheme 2.1 First synthesis of an (*R*)-phenylglycinol derived tricyclic lactam

Further tests concluded that lactam **125** was formed through a highly stereoselective cyclocondensation process by reaction of *(R)*-phenylglycinol with cyclohexenone-based δ-oxoester **126** in refluxing benzene along with catalytic amounts of acetic acid. At the same time **126** could come from an intramolecular aldol cyclization from symmetrical diketone **123**.

2.1.1.1 C-8 Substituted (*R*)-Phenylglycinol-Derived Unsaturated Tricyclic Lactams

Upon using the same reaction conditions with δ-oxoester **128** bearing a methyl group at C-3, the cyclocondensation led to the stereoselective formation of lactam **129a** with good yield (Scheme 2.2).[56]

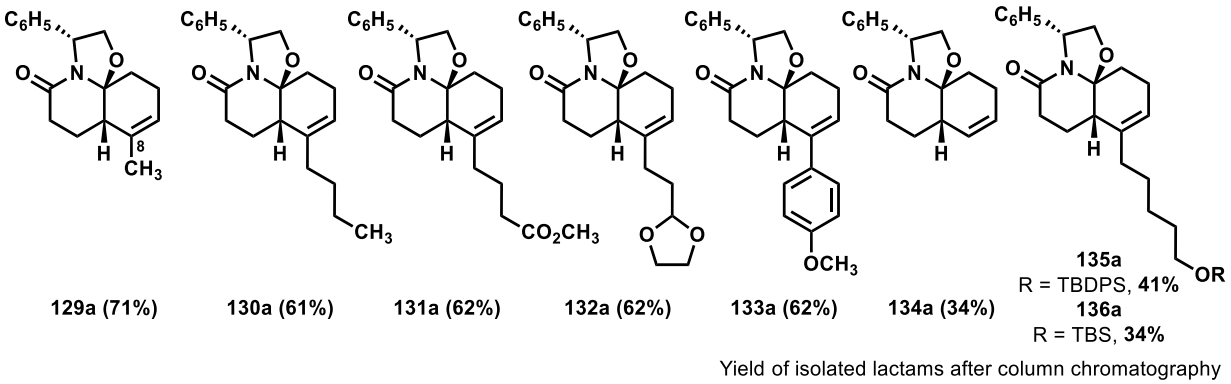
[55] Amat, M.; Griera, R.; Fabregat, R.; Bosch, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3348-3351.
[56] Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794-1797.



Scheme 2.2 Stereoselective formation of C-8 substituted tricyclic lactams

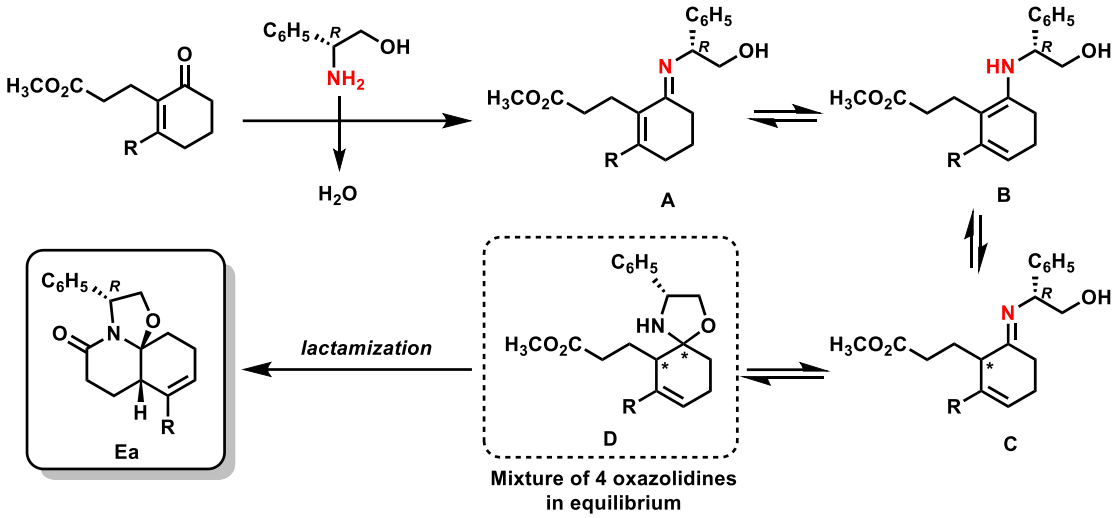
Through this new process, in just one synthetic step, two stereocenters of a well-defined configuration were formed. Additionally, the double bond present in the starting material migrated from C-2/C-3 to C-3/C-4 (cyclohexanone numbering). Minor amounts of diastereomer **129b** were also obtained. No lactams containing a *trans* fusion between C-7a/C-11a, nor lactams with the double bond between C-7a/C-8 were isolated. This could be attributed to the high strain present in these structures.

The cyclocondensation of additional δ-oxoester derivatives bearing different alkylic and arylic substituents at C-3 led to the stereoselective obtention of a library of C-8 substituted tricyclic lactams (**130a-136a**). In terms of stereoselectivity, it appeared that the reaction was not significantly influenced by either the type or the nature of the substituent, as it yielded similar degrees of diastereoselectivity (approximately 4:1) (Scheme 2.3).



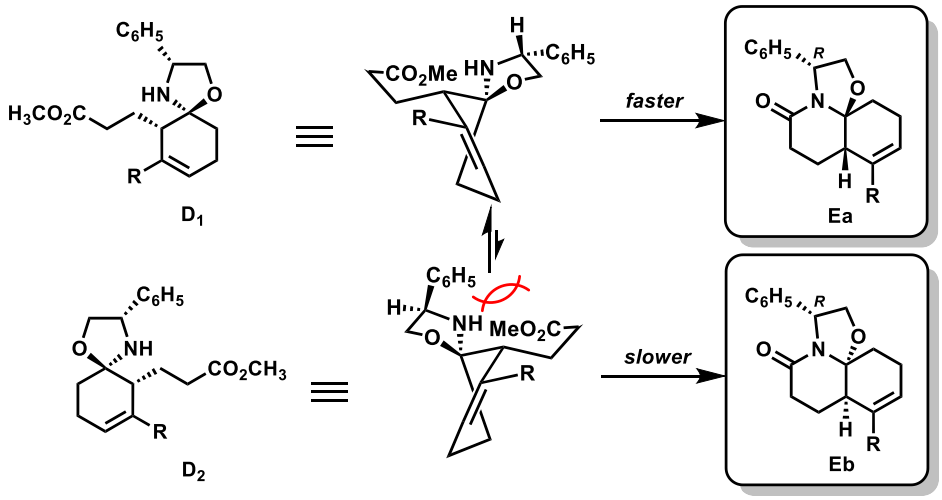
Scheme 2.3 C-8 substituted lactams obtained by cyclocondensation

The proposed mechanism for the formation of these lactams involves the initial generation of imine **A** from the corresponding ketoester and chiral inductor. Dienimine **A** is in equilibrium via dienamine **B** with two diastereomeric imines **C** (one for each configuration of the propionate chain). Cyclization of the alcohol and the imine leads to a mixture of up to 4 chiral oxazolidines which, upon an irreversible lactamization step furnish the corresponding lactams (Scheme 2.4).



Scheme 2.4 Proposed mechanistic pathway for the cyclocondensation reaction

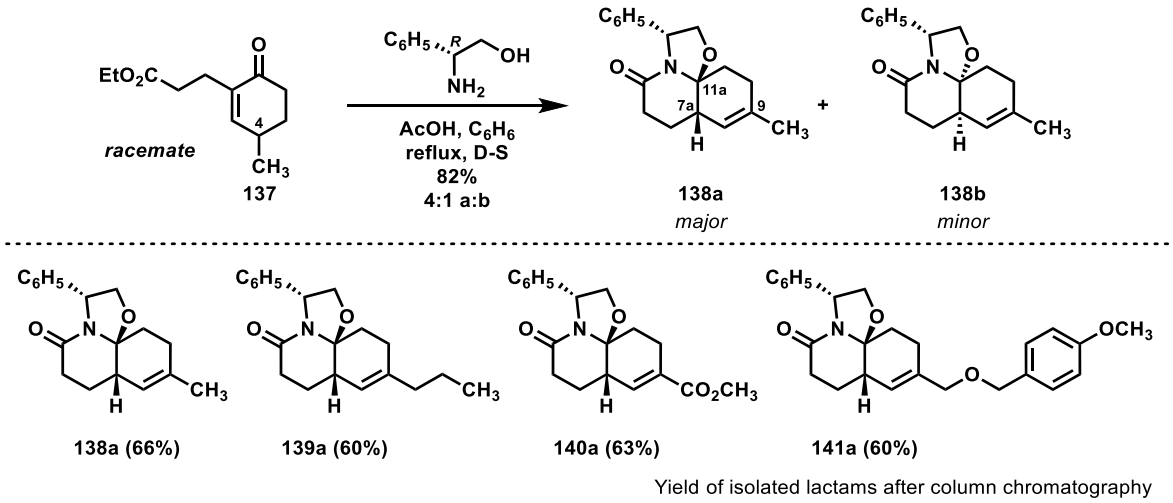
The stereoselective formation of **Ea** can be justified by considering that the lactamization step occurs more rapidly from oxazolidine **D**$_1$ through a chair-like six-membered transition state in which the propionate chain avoids the phenyl group. On the other hand, the obtention of a smaller amount of **Eb** can be accounted for by considering that, from the intermediate spiro-oxazolidine **D**$_2$, the approach of the propionate chain to the nitrogen atom is hindered by the aromatic ring of the chiral inductor, making the lactamization less favorable, and thus, slower (Scheme 2.5).



Scheme 2.5 Lactamization of oxazolidines **D**$_1$ and **D**$_2$

2.1.1.2 C-9 Substituted (*R*)-Phenylglycinol-Derived Unsaturated Tricyclic Lactams

The good results observed in the generation of C-8 substituted unsaturated tricyclic lactams, prompted the group to explore new cyclocondensation reactions from cyclohexenones and (*R*)-phenylglycinol, thus leading to C-9 substituted unsaturated tricyclic lactams. As expected, the cyclocondensation of C-4 substituted δ-oxoester **137** with (*R*)-phenylglycinol led to the stereoselective formation of C-9 substituted lactam **138a** with similar diastereoselectivities and yields. Small amounts of lactams **138b** were also isolated.[57] Similar stereoselectivities were obtained with additional C-9 substituted lactams (**139a**-**141a**) (Scheme 2.6).

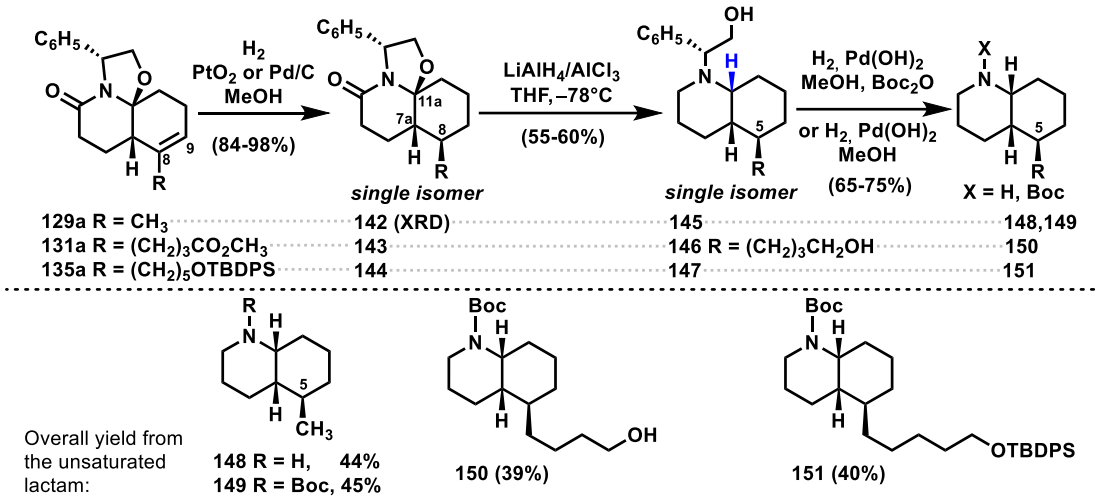


Scheme 2.6 Obtention of C-9 substituted tricyclic lactams

2.1.1.3 C-5 and C-6 Substituted *cis*-DHQs from Tricyclic Lactams

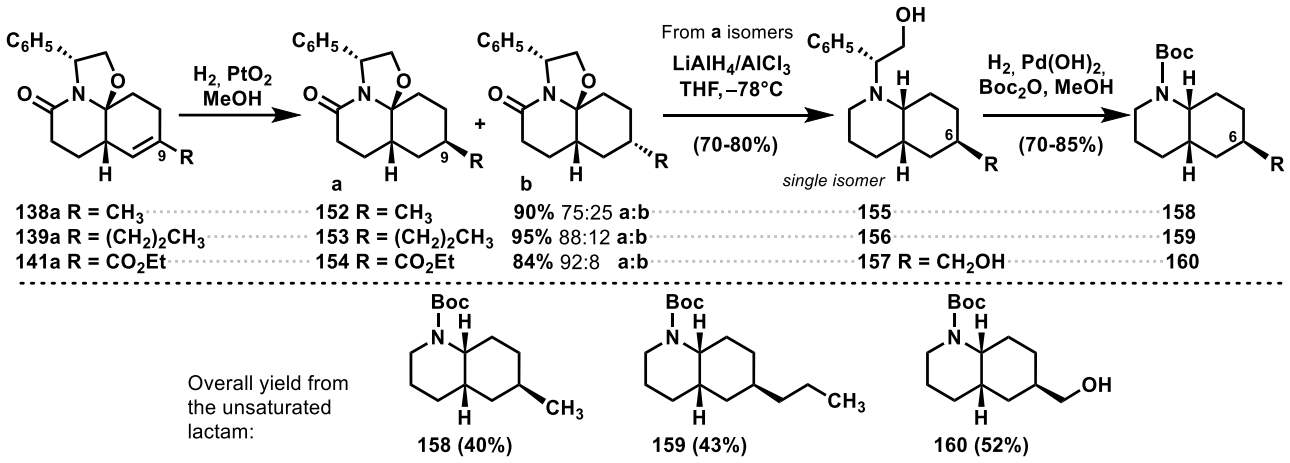
The catalytic hydrogenation of the C-8 substituted lactams (**129a**, **131a**, and **135a**) took place with complete facial selectivity on the C-8/C-9 double bond, yielding the corresponding saturated lactams (**142**-**144**) with excellent yields. XRD analysis of **142** confirmed the absolute configuration of the stereocenters in C-7a, C-8 and C-11a. Reduction of the carbonyl lactam with concomitant reductive opening of the oxazolidine ring promoted by alane ($LiAlH_4$ + $AlCl_3$) led to the obtention of C-5 substituted *cis*-DHQs (**145**-**147**) with complete *cis* selectivity. The stereochemical outcome of this reduction can be rationalized by considering that the reducing reagent coordinates with the oxygen atom of the oxazolidine and that the hydride is delivered from the same face of the C-O bond.[58] Removal of the phenylethanol residue of the chiral inductor by catalytic hydrogenation using the Pearlman's catalyst led to the obtention of the enantiopure C-5 substituted *cis*-DHQs (**148**-**151**) (Scheme 2.7).

[57] Amat, M.; Navío, L.; Llor, N.; Molins, E.; Bosch, J. *Org. Lett.* **2012**, *12*, 210-213.
[58] Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872-7881.



Scheme 2.7 Obtention of C-5 substituted *cis*-decahydroquinolines

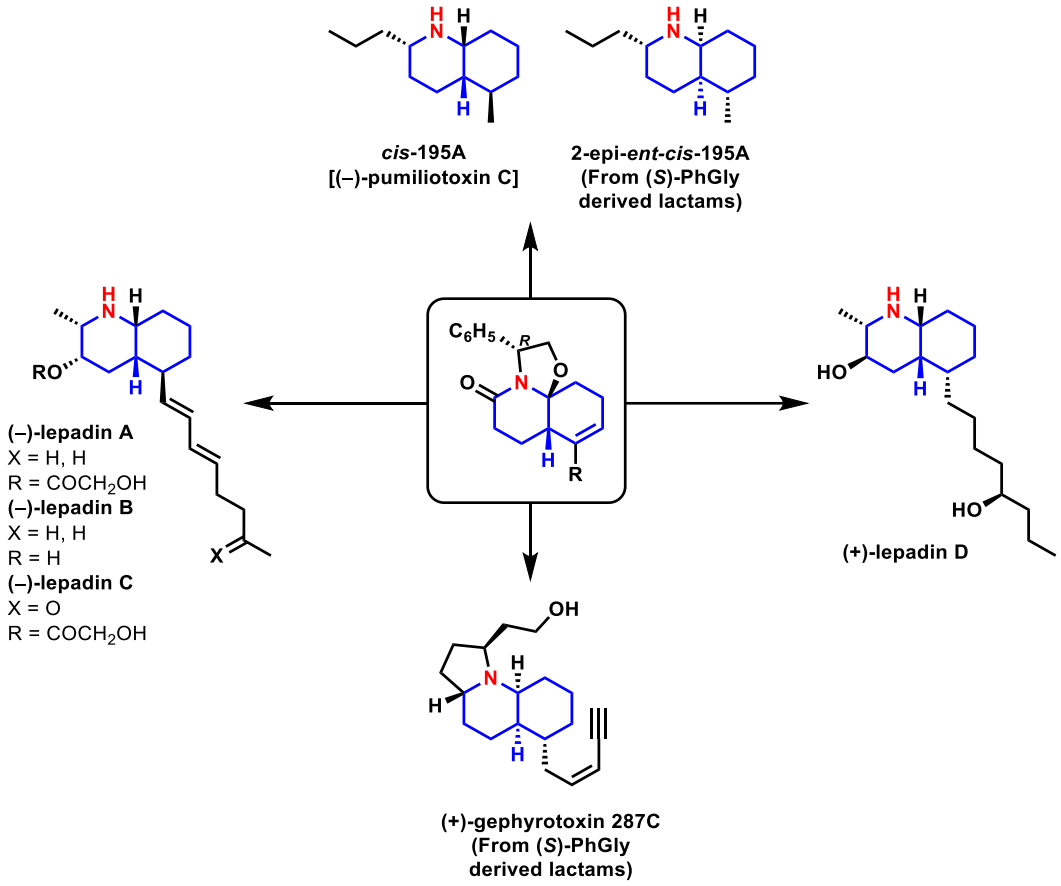
In a similar manner, the reduction of the double bond and removal of the chiral inductor of C-9 substituted tricyclic lactams (**138a-141a**) led to the obtention of enantiopure C-6 substituted *cis*-decahydroquinolines (**158-160**). In this type of substrates, however, the stereoselectivity in the reduction of the double bond was from good to moderate (Scheme 2.8).



Scheme 2.8 Obtention of C-6 substituted *cis*-decahydroquinolines

The synthetic value of the procedure was demonstrated by the total synthesis of a variety of DHQ alkaloids by using various C-8 substituted tricyclic lactams as chiral scaffolds (Scheme 2.9).[58,59]

[59] a) Amat, M.; Fabregat, R.; Griera, R.; Florindo, P.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 3797-3805; b) Amat, M.; Pinto, A.; Griera, R.; Bosch, J. *Chem. Eur. J.* **2015**, *21*, 12804-12808; c) Piccichè, M.; Pinto, A.; Griera, R.; Bosch, J.; Amat, M. *Org. Lett.* **2017**, *19*, 6654-6657.

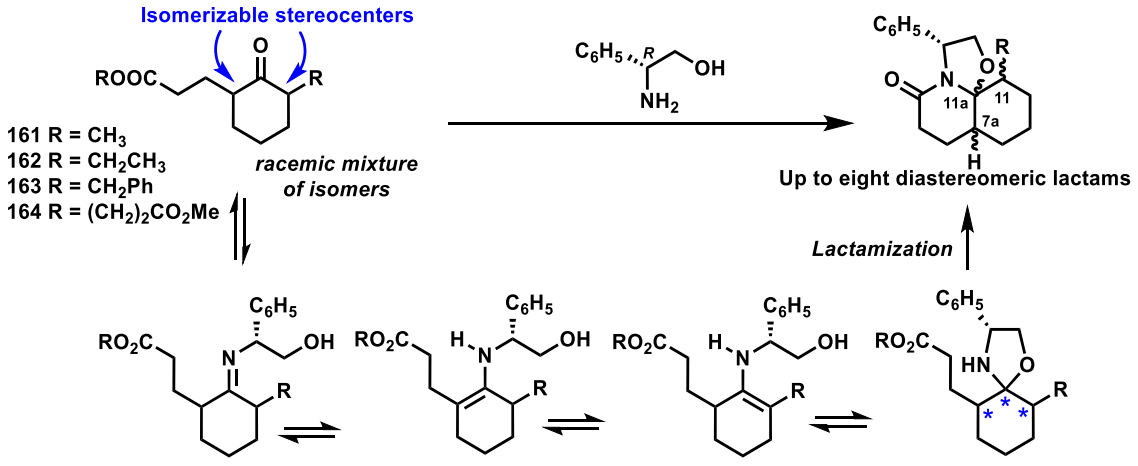


Scheme 2.9 DHQ alkaloids obtained from 8-substituted tricyclic lactams

2.1.2 Preparation of C-8 Substituted and C-6/C-8 Disubstituted *cis*-Decahydroquinolines from Saturated Lactams

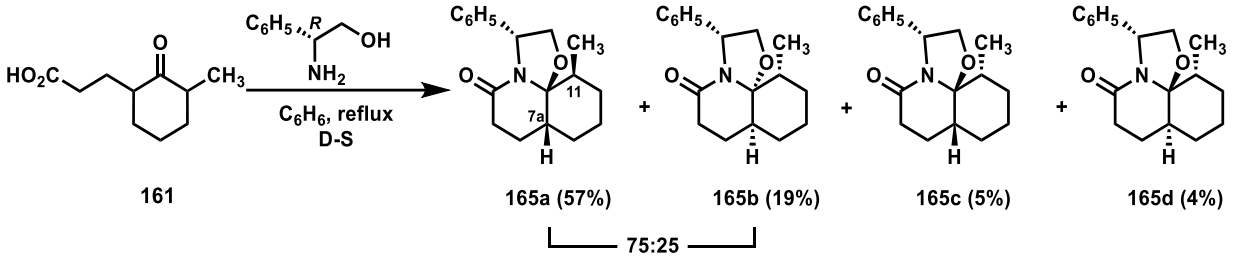
2.1.2.1 C-11 Substituted (*R*)-Phenylglycinol-Derived Tricyclic Lactams

To expand the potential of the methodology for the preparation of *cis*-DHQs with substituents at different positions of the carbocyclic ring, additional studies with δ-ketoacids **161-164** containing different substituents at both isomerizable α positions of the cyclohexanone were performed. The main goal of these studies was to analyze if starting from a mixture of stereoisomers (two pairs of enantiomers) of the cyclohexanone, the isomerization of the stereocenters through the corresponding imine-enamines equilibrium during the cyclocondensation reaction, would lead to the stereoselective formation of one of the eight possible diastereomeric lactams (Scheme 2.10).



Scheme 2.10 Synthetic scheme for the obtention of C-11 substituted tricyclic lactams

Heating a toluene solution of ketoacid **161** and (*R*)-phenylglycinol stereoselectively afforded a mixture of tricyclic lactams **165a** and **165b** in a 75:25 ratio, respectively, in 76% yield. The major isomer **165a** could be isolated in 57% yield after column chromatography. When the reaction was carried out in a multigram scale, two very minor diastereomers **165c** and **165d** could also be isolated (Scheme 2.11).[60]

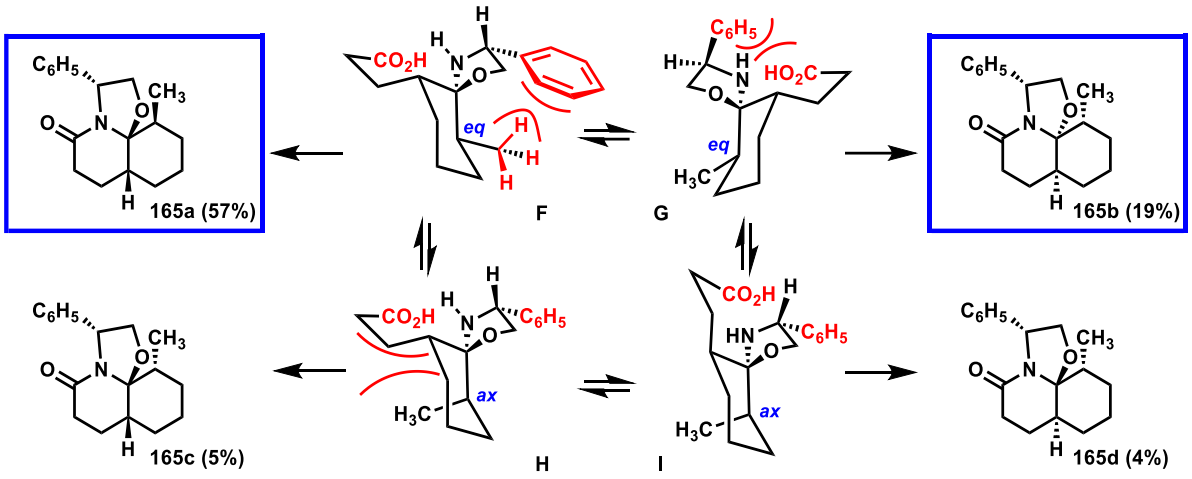


Scheme 2.11 Cyclocondensation of **161** with (*R*)-phenylglycinol

The stereochemical outcome of this reaction can be rationalized by considering that the lactamization step takes place faster from the intermediate oxazolidine **F** in which the approach of the carboxylate to the nitrogen atom during the lactamization step takes place from the less hindered face of the oxazolidine and the methyl substituent is in an equatorial position leading to **165a**. In a similar way, the minor isomer **165b** is formed from the spiro-oxazolidine **G**. However, in this case the lactamization is slower since it takes place from the more hindered face, near to the phenyl of the chiral inductor. Therefore, the absolute configuration of the stereocenter next to the methyl in tricyclic lactams **165a** and **165b** is determined by its equatorial position on the cyclohexane ring of the spiro-oxazolidine intermediate. Formation of the minor isomer **165c**, with an opposite configuration at the stereocenter next to the methyl with respect to the major isomer **165a**, can be justified by considering

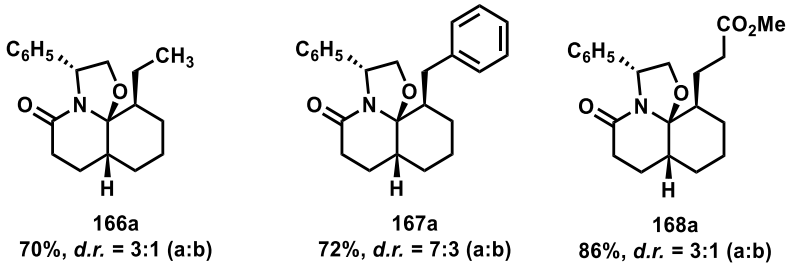
[60] Amat, M.; Ghirardi, E.; Navío, L.; Griera, R.; Llor, N.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2013**, *19*, 16044-16049.

that, in the transition state leading to this major isomer, the equatorial methyl group is located near the phenyl substituent. This steric hindrance is relieved by isomerization to the axial isomer **H**, whose lactamization renders **165c**. However, in **H** the methyl and the propionate chain suffer severe 1,3-diaxial interactions, provoking the isomerization of the stereocenter next to the propionate giving rise to spirooxazolidine **I** whose lactamization affords the highly strained minor isomer **165d** (Scheme 2.12).



Scheme 2.12 Oxazolidine intermediates leading to **165a-165d**

The cyclocondensation of cyclohexanones **162**, **163** and **164** with (*R*)-phenylglycinol exhibited similar yields and stereoselectivities, leading to the stereoselective formation of the C-11 substituted lactams **166a**, **167a**, and **168a**, respectively (Scheme 2.13).

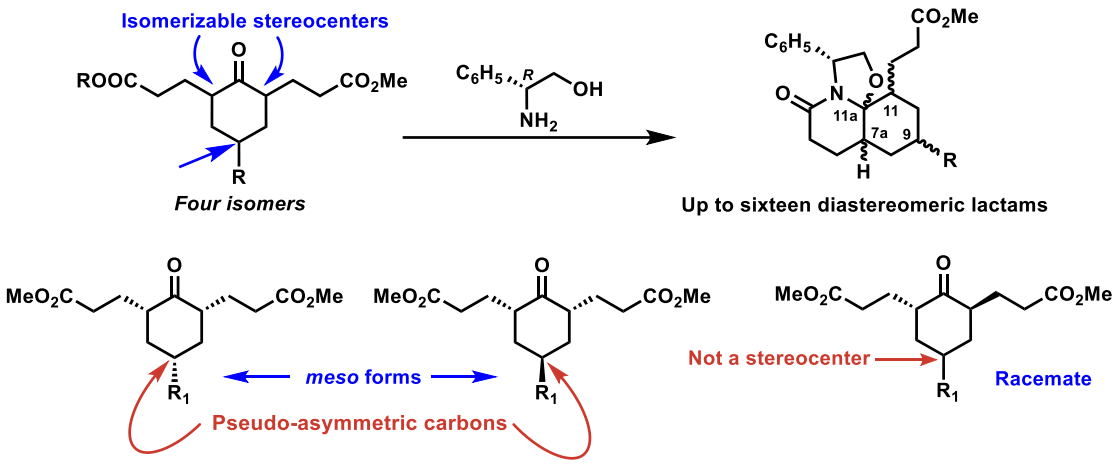


Scheme 2.13 Obtention of C-11 substituted tricyclic lactams

2.1.2.2 C-9 and C-11 Disubstituted (*R*)-Phenylglycinol-Derived Tricyclic Lactams

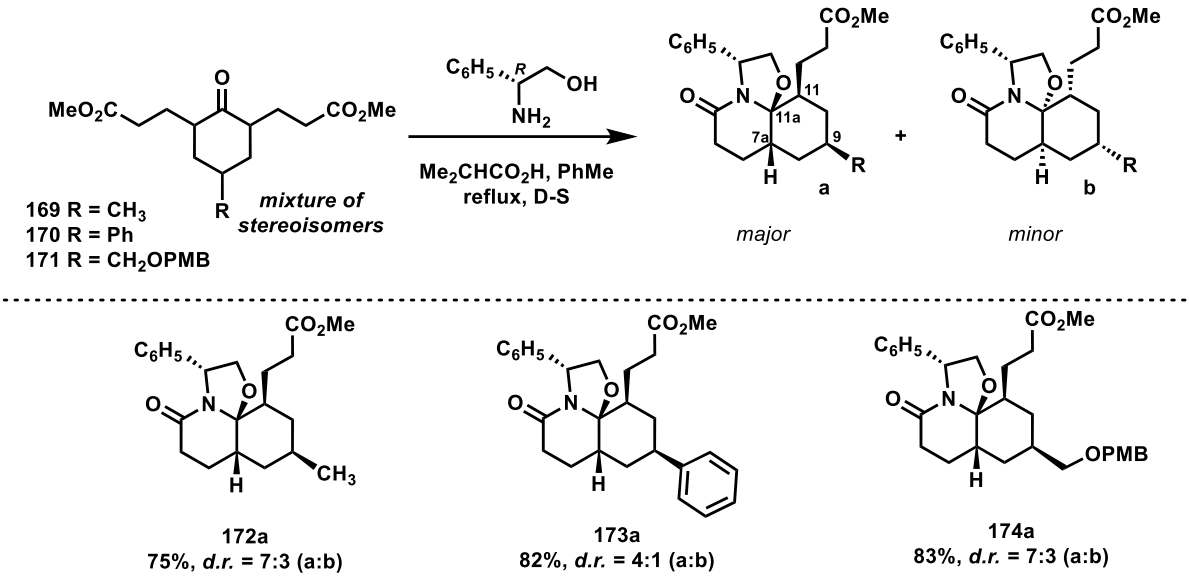
The continuous interest of the research group to find new stereoselective reactions leading to substituted tricyclic lactams as precursors for the synthesis of complex enantiopure *cis*-DHQs stimulated the study of cyclocondensation reactions from cyclohexanones with propionate chains in both α-positions and a carbon substituent at the C-4 position. It has to be considered that this 4-position is not a stereocenter in any of the four diastereomers since in the 2,6-*cis* isomers it is a

pseudo-asymmetric carbon atom, generating two diastereomers both achiral, and in the 2,6-*trans* isomers, which constitute a pair of enantiomers, it is not a stereocenter (Scheme 2.14).



Scheme 2.14 Synthetic strategy for the obtention of 9,11-disubstituted tricyclic lactams

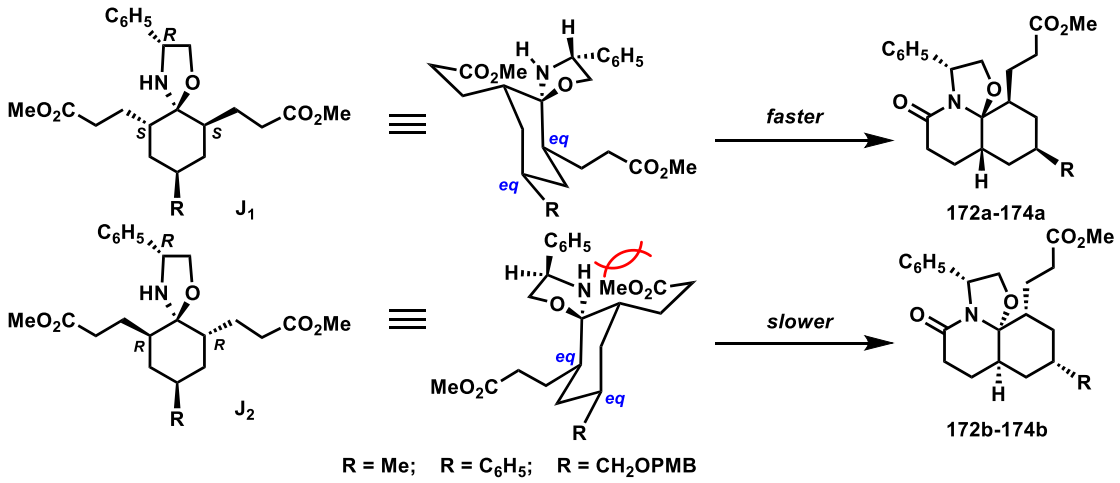
Cyclocondensation reactions of compounds **169-171** with (*R*)-phenylglycinol and isobutyric acid in refluxing toluene, led to the stereoselective obtention of one of the sixteen possible 9,11-disubstituted tricyclic lactams (**172a-174a**), along with a minor diastereomer (**172b-174b**) showing the opposite configuration at the four stereocenters at C-7a, C-9, C-11, and C-11a with good to moderate stereoselectivities and good yields (Scheme 2.15).[60]



Scheme 2.15 Obtention of 9,11-disubstituted tricyclic lactams

The above cyclocondensation reactions from cyclohexanone derivatives, bearing two identical substituents in both α-positions and a carbon substituent at the γ-position, allowed the obtention 9,11-disubstituted lactams in one synthetic step with the formation of four stereocenters of well-defined configuration.

The stereoselectivity observed in the reactions from cyclohexanones **169-171** can be rationalized by considering that the lactamization step occurs faster through those intermediate oxazolidines that contain the propionate chain responsible for the lactamization in an axial position and the rest of the substituents of the carbocyclic ring in an equatorial disposition. The predominance of **172a-174a** lactams is a consequence of the lactamization step occurring faster through oxazolidine $\mathbf{J_1}$, which allows a less-hindered approach of the ester group to the oxazolidine nitrogen atom, *anti* with respect to the phenyl substituent (Scheme 2.16).

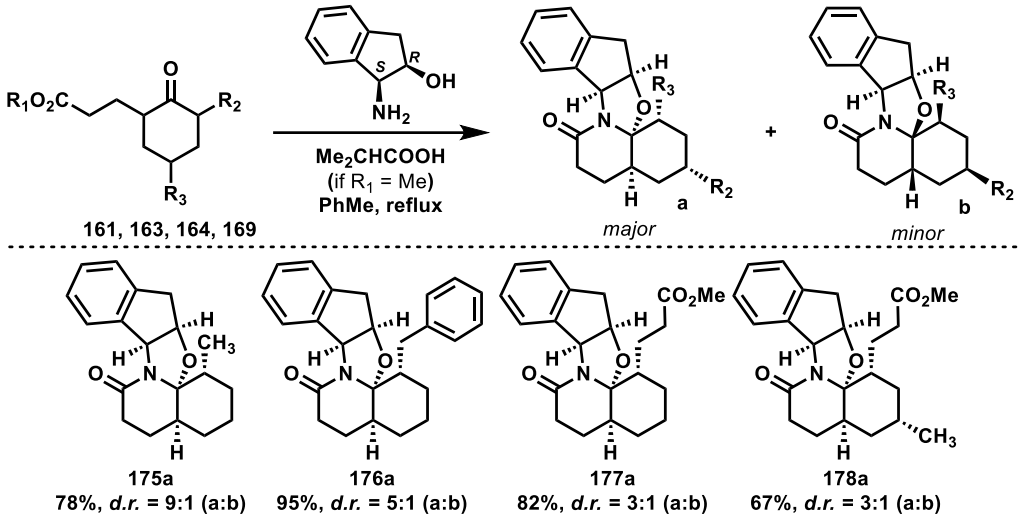


Scheme 2.16 Lactamization step of the most reactive oxazolidine intermediates

2.1.2.3 C-9 Monosubstituted and C-9/C-11 Disubstituted *cis*-1-Amino-2-Indanol-Derived Tricyclic Lactams

The use of *cis*-1-amino-2-indanol, a conformationally rigid analog of phenylglycinol, as chiral inductor slightly improved, in some cases, the stereoselectivity and yield of the cyclocondensation reactions. Thus, starting from cyclohexanone derivatives **161**, **163**, **164**, and **169**, the corresponding lactams **175a-178a** were stereoselectively formed. It is worth mentioning that (1*S*,2*R*)-*cis*-aminoindanol-derived lactams **175a-178a** show an opposite configuration of all chiral centers on the DHQ ring with respect to those previously obtained using (*R*)-phenylglycinol **165a-174a**. This difference can be attributed to the opposite configuration of the stereocenter at the benzylic position in both aminoalcohols. Therefore, the aminoalcohol used, (1*S*,2*R*)-*cis*-aminoindanol, is the equivalent of (*S*)-phenylglycinol (Scheme 2.17).

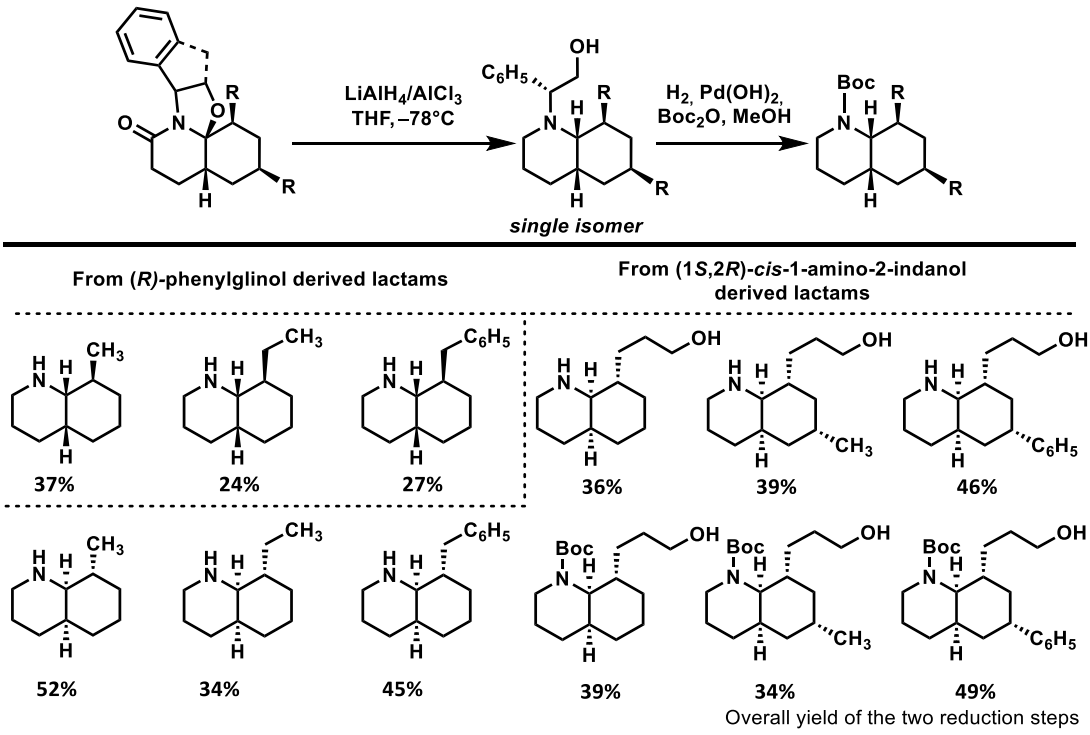
The separation of isomers **a** and **b** of the (1*S*,2*R*)-*cis*-aminoindanol-derived lactams **175-178** became more troublesome, and it had to be performed in subsequent synthetic steps.



Scheme 2.17 (1*S*,2*R*)-*cis*-1-amino-2-indanol derived lactams

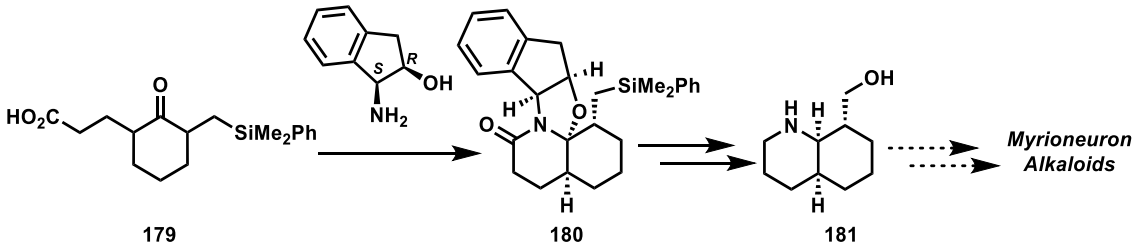
2.1.2.4 Obtention of C-8 Monosubstituted and C-6/C-8 Disubstituted *cis*-DHQs

The removal of the chiral auxiliary was achieved through stereoselective alane ($LiAlH_4$ + $AlCl_3$) reduction of the carbonyl lactam and oxazolidine C-O bond, followed by hydrogenolysis of the benzylic substituent on the nitrogen atom by catalytic hydrogenation with or without Boc_2O, resulting in the formation of the corresponding 6,8-disubstituted and 8-substituted *cis*-decahydroquinolines (Scheme 2.18).



Scheme 2.18 *cis*-DHQs obtained through the methodology

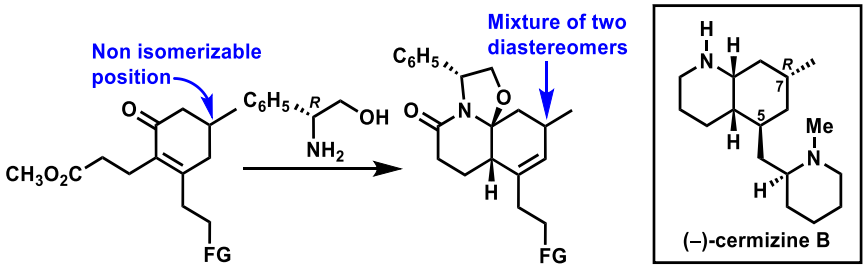
The synthetic utility of the methodology was demonstrated with the formal synthesis of various *Myrioneuron* alkaloids.[60] The cyclocondensation of δ-ketoacid **179** with (1*S*,2*R*)-*cis*-aminoindanol provided pentacyclic lactam **180**. Oxidation of the silyl moiety followed by removal of the chiral inductor afforded aminoalcohol **181**, known precursor of (–)-myrioxazine A,[42a] (–)-myrionine,[42b] (–)-myrionidine,[42e] (–)-schoberine,[42e] and (+)-*N*-formylmyrionine (Scheme 2.19).[42f]



Scheme 2.19 Obtention of intermediate **181**, precursor of multiple *Myrioneuron* alkaloids

2.1.3 Preparation of C-5 and C-7 Monosubstituted, and C-5/C-7 Disubstituted *cis*-DHQs from Saturated Lactams

In subsequent studies, the synthesis of (–)-cermizine B, an alkaloid with a 5,7-disubstituted *cis*-DHQ, was proposed as a target. However, in this case, the stereoselective preparation of the required chiral aminoalcohol-derived tricyclic lactam would involve the use of a cyclohexanone with a methyl in a non-isomerizable position. Therefore, a dynamic kinetic asymmetric transformation (DYKAT)[61] of the racemic cyclohexenone precursor, stereoselectively leading to one diastereomeric tricyclic lactam as a major isomer, was not possible (Scheme 2.20).

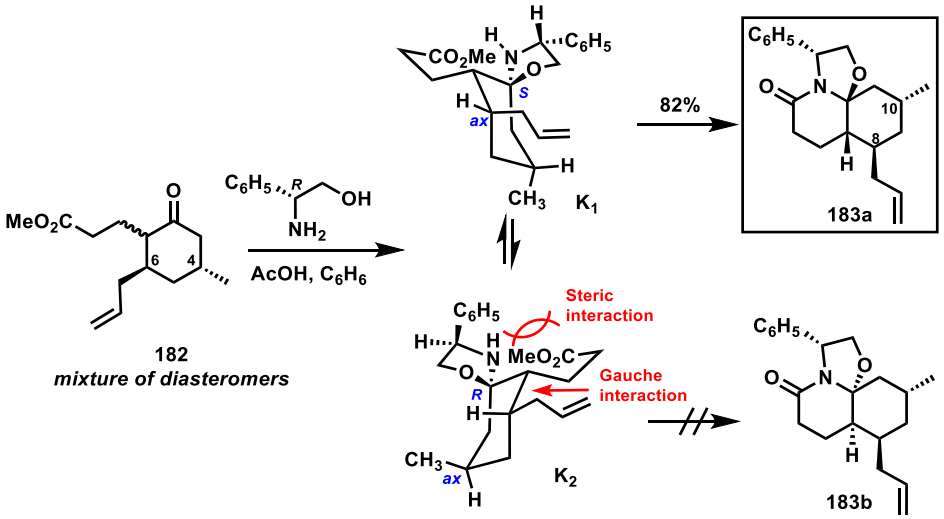


Scheme 2.20 Synthetic approach for the synthesis of the DHQ core of (–)-cermizine B

For this reason, for the synthesis of (–)-cermizine B, the use of the cyclohexanone-propionate **182** bearing substituents of well-defined configuration at C-4 and C-6 was selected to study the preparation of the precursor tricyclic lactam. Compound **182** was prepared in good yields and stereoselectivity from (*R*)-pulegone through a five steps sequence.[62] The cyclocondensation of (*R*)-phenylglycinol with *trans*-4,6-disubstituted δ-ketoester **182** led to the obtention of lactam **183a** as a

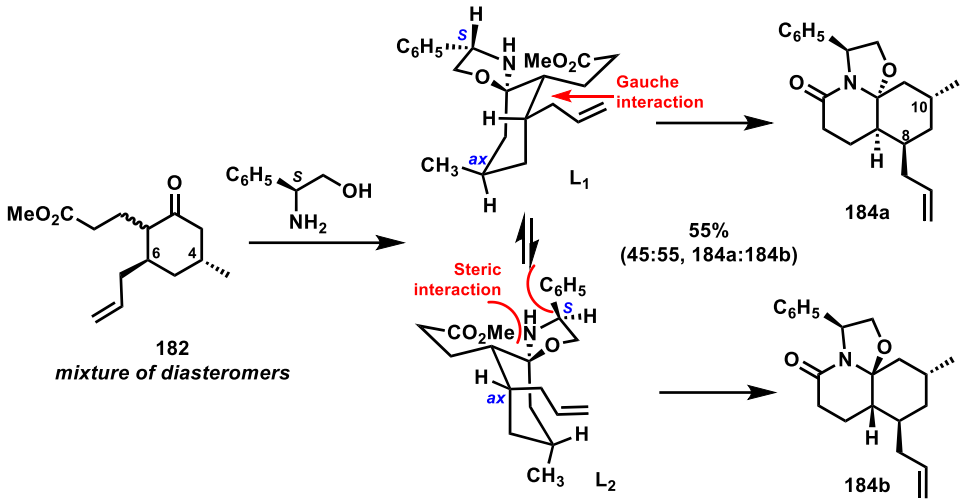
[61] Steinreiber, J.; Faber, K.; Griengl, H. *Chem. Eur. J.* **2008**, *14*, 8060-8072.
[62] Pinto, A.; Griera, R.; Molins, E.; Fernández, I.; Bosch, J.; Amat, M. *Org. Lett.* **2017**, *19*, 1714-1717.

single diastereomer.[62] This complete stereoselectivity can be rationalized by considering that the lactamization step occurs faster through the reactive oxazolidine **K$_1$**, which allows the approach of propionate chain to the nitrogen atom through the less hindered face of the oxazolidine. In the intermediate oxazolidine **K$_2$**, which would have led to the other expected isomer **183b**, the methyl substituent is in an axial position, a gauche interaction between the equatorial allyl substituent and the propionate chain occurs, and the approach of the carboxylate to the nitrogen atom of the oxazolidine ring in the lactamization step takes place from the more hindered face (Scheme 2.21).



Scheme 2.21 Cyclocondensation of ketoacid **182** with (*R*)-phenylglycinol

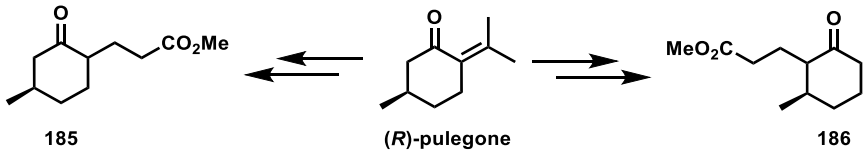
Surprisingly, the cyclocondensation of **182** with (*S*)-phenylglycinol, the enantiomer of the above chiral inductor, led to a nearly equimolecular mixture of lactams **184a** and **184b**. As it can be observed in Scheme 2.22, in the reactive spiro-oxazolidine **L$_1$**, leading **184a**, the methyl substituent is axial and a destabilizing gauche interaction between the propionate chain and the allyl occurs, whereas in the oxazolidine **L$_2$**, precursor of **184b**, the lactamization step takes place from the more hindered face and the allyl group is axial. Therefore, a similar balance of steric interactions occurs from both reactive oxazolidine intermediates.



Scheme 2.22 Cyclocondensation of ketoacid **182** with (*S*)-phenylglycinol

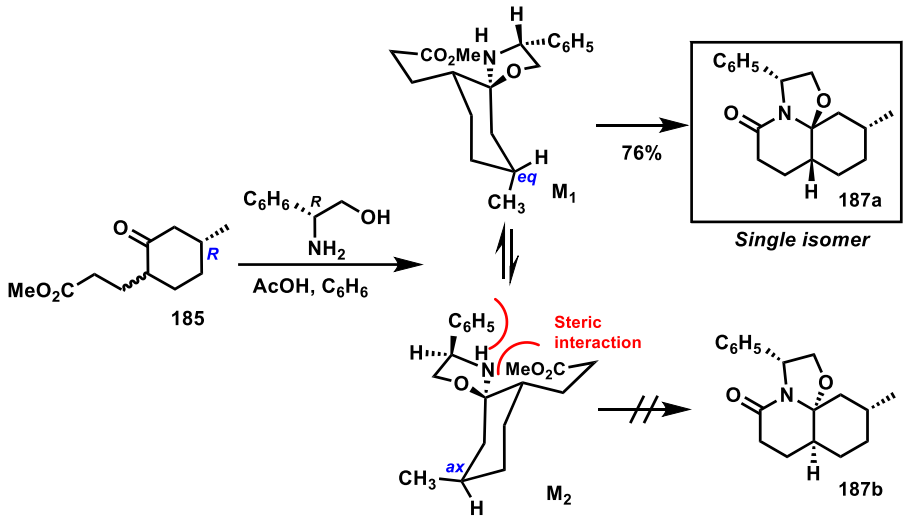
2.1.3.1 Study of the Individual Influence of the Non-Isomerizable Substituents at C-4 and C-6 in the Stereoselectivity of Cyclocondensation Reaction

In order to evaluate the individual influence of the substituents in the above cyclocondensation reactions, cyclohexanones **185** and **186** were prepared from (*R*)-pulegone (Scheme 2.23).



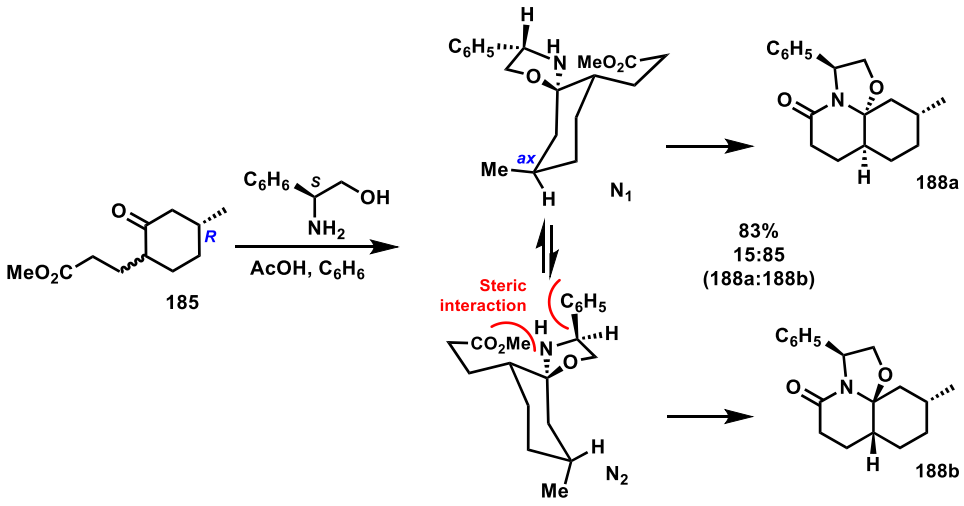
Scheme 2.23 Obtention of ketoacids **185** and **186**

The reaction of **185** with (*R*)-phenylglycinol stereoselectively afforded the tricyclic lactam **187a** as a single isomer. As it can be observed in Scheme 2.24, in the reactive spiro-oxazolidine $\mathbf{M_1}$ the lactamization takes place from the less hindered face of the oxazolidine and the methyl substituent is equatorial, whereas in the intermediate oxazolidine $\mathbf{M_2}$ severe steric interactions occur. Since the dynamic equilibration of isomeric oxazolidines takes place faster than the lactamization step, isomer **187a** is formed in excellent stereoselectivity.



Scheme 2.24 Cyclocondensation of **185** with (*R*)-phenylglycinol

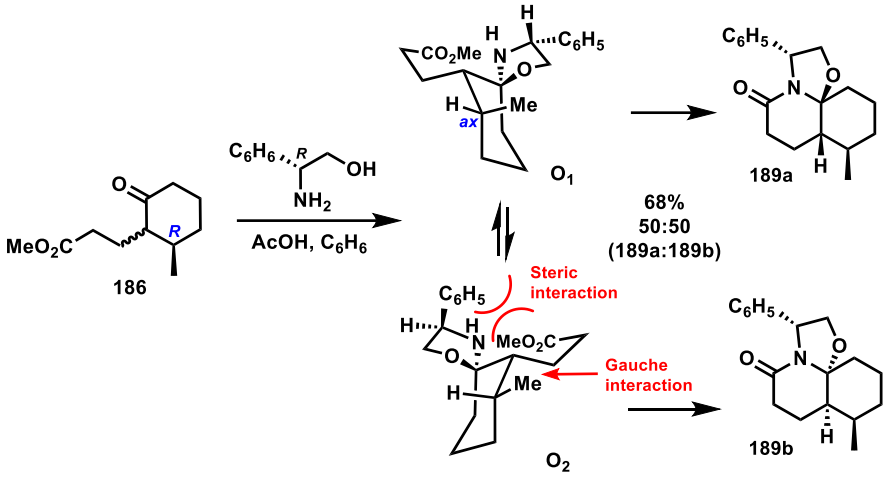
On the other hand, the cyclocondensation of **185** with (*S*)-phenylglycinol unexpectedly afforded the isomer **188b** as the major component of the reaction mixture in a ratio of 15:85 **188a**:**188b**. It is worth mentioning that in the absence of the methyl in the starting oxoester **185**, the major isomer is the demethyl analog of **188a** in a ratio with respect to the demethyl analog of **188b** of 9:1, respectively.[63] This result clearly shows that the axial/equatorial position of the methyl substituent in the reactive spiro-oxazolidine plays a crucial role in the stereoselectivity of the reaction and reveals that the steric interactions of an axial methyl are stronger than the steric hindrance between the phenyl and the carboxylate in the lactamization step (Scheme 2.25).



Scheme 2.25 Cyclocondensation of **185** with (*S*)-phenylglycinol

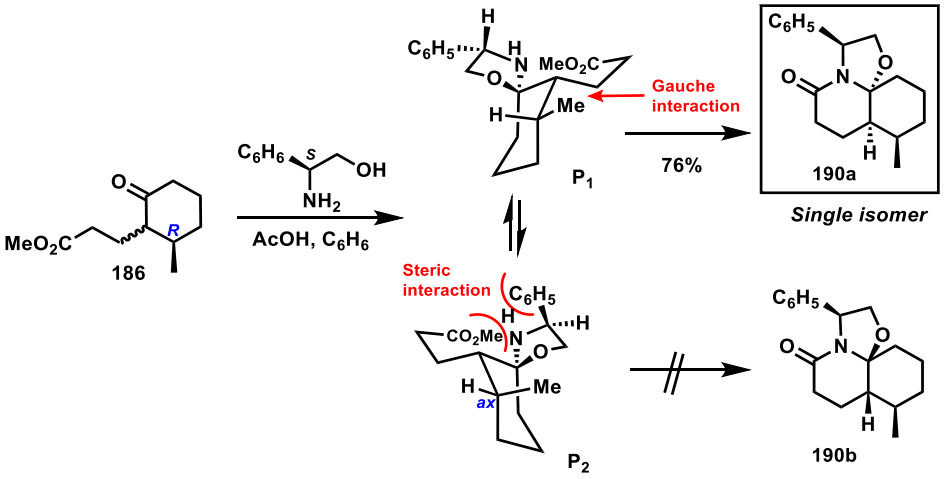
[63] Piccichè, M.; Pinto, A.; Griera, R.; Bosch, J.; Amat, M. *Org. Lett.* **2022**, *24*, 5356-5360.

When cyclohexanone **186** was subjected to reaction with (*R*)-phenylglycinol under the standard conditions, an almost equimolecular mixture of lactams **189a** and **189b** was observed. In this case, the simultaneous effect of both mild steric interactions that appear in the intermediate **O$_2$** (see Scheme 2.26) are similar to the 1,3-axial interactions of the methyl in oxazolidine **O$_1$**, leading to a similar ratio of the resulting compounds **189a** and **189b** (Scheme 2.26).



Scheme 2.26 Cyclocondensation of **186** with (*R*)-phenylglycinol

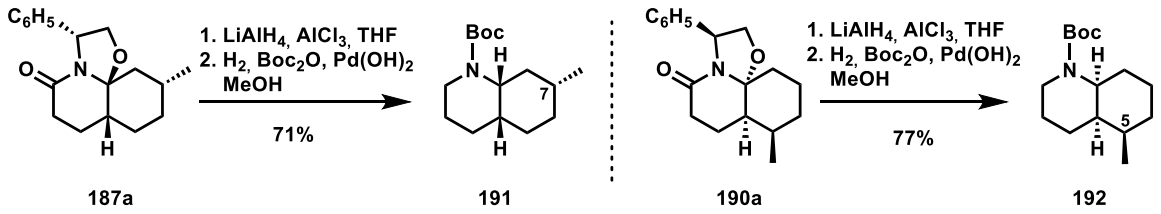
Finally, the cyclocondensation of **186** with (*S*)-phenylglycinol afforded the tricyclic lactam **190a** as a single isomer. This result reveals that the gauche interaction present in intermediate **P$_1$** is a mild destabilizing effect which is overcome by the simultaneous steric interactions in the lactamization step and the 1,3-diaxial interaction of the methyl intermediate **P$_2$** (Scheme 2.27).



Scheme 2.27 Cyclocondensation of **186** with (*S*)-phenylglycinol

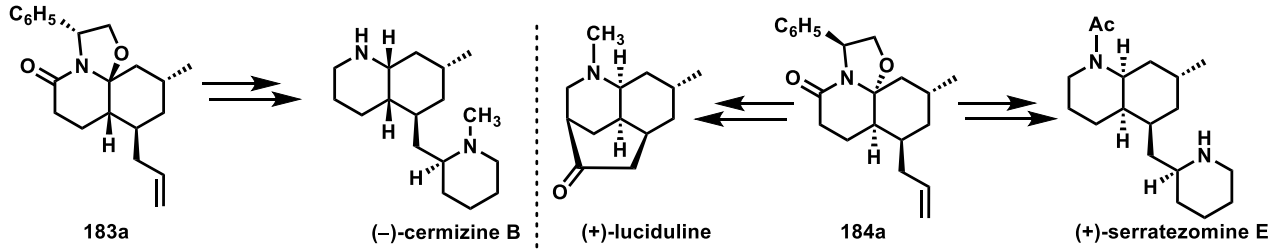
2.1.3.2 Preparation of C-5 and C-7 Monosubstituted *cis*-DHQs

To further illustrate the potential of this procedure, the chiral inductor of the previously obtained lactams was removed to yield the corresponding enantiopure 5-, 7-methyl *cis*-decahydroquinolines (Scheme 2.28).



Scheme 2.28 Obtention of 5- and 7-methyl-*cis*-DHQs

The usefulness of the methodology was demonstrated with the enantioselective synthesis of (–)-cermizine B from lactam **183a**.[62] The enantioselective total synthesis of (+)-serratezomine E and (+)-luciduline was also accomplished from lactam **184a** (Scheme 2.29).[64]



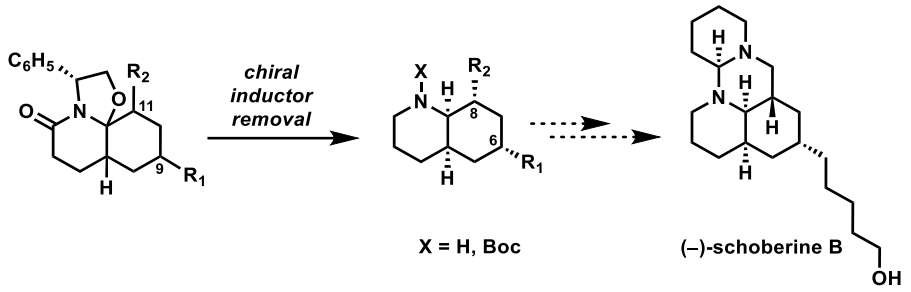
Scheme 2.29 Enantioselective total synthesis of various *Lycopodium* alkaloids

[64] Pinto, A.; Piccichè, M.; Griera, R.; Molins, E.; Bosch, J.; Amat, M. *J. Org. Chem.* **2018**, *83*, 8364-8375.

2.2 Objectives

Considering the good results obtained in previous works on the use (*R*)-phenylglycinol-derived tricyclic lactams for the synthesis of different DHQ alkaloids with substituents on the carbocyclic ring and the rising interest on the recently isolated alkaloids of the *Myrioneuron* family, we decided to expand the scope of the group's methodology by studying the preparation of new tricyclic lactams for the synthesis of disubstituted *cis*-decahydroquinolines. In particular, we focused our attention on the alkaloid (–)-schoberine B, isolated from the species *Myrioneuron faberi*, having an unprecedented 5-carbon chain among lysine-originating alkaloids.

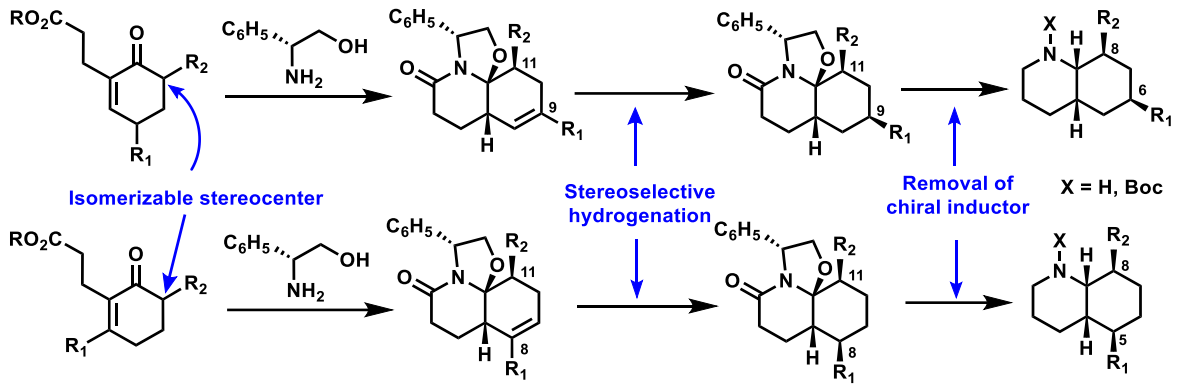
With this purpose in mind, the main goal of the work was to explore an efficient procedure for the stereoselective preparation of chiral amino alcohol-derived tricyclic lactams as precursors of enantiopure 6,8-disubstituted *cis*-DHQs useful for the synthesis of (–)-schoberine B (Scheme 2.30).



Scheme 2.30 Chapter 2 objective

2.3 Enantioselective Synthesis of Disubstituted Azabicycles from (*R*)-Phenylglycinol-Derived Unsaturated Lactams. First approach

Considering the good results observed in the preparation of 8- and 9-substituted tricyclic lactams from unsaturated precursors (see Scheme 2.3 and Scheme 2.6) and of the synthesis of 11-substituted saturated lactams from cyclohexanones with substituents in isomerizable positions (see Scheme 2.11), the first proposal for the synthesis of 6,8-*cis*-disubstituted-*cis*-DHQs involved the cyclocondensation of a 2-cyclohexenone with a C-2 propionate chain and alkyl substituents at the C-4 and C-6 positions. Their reaction with (*R*)-phenylglycinol would lead to the corresponding unsaturated lactams, whose catalytic hydrogenation would provide the desired 9,11-disubstituted tricyclic lactams. As an extension of this study, we decided to explore the preparation of 8,11-disubstituted tricyclic lactams following the same procedure. After removal of the chiral inductor, 6,8- and 5,8-disubstituted DHQs would be obtained (Scheme 2.31).



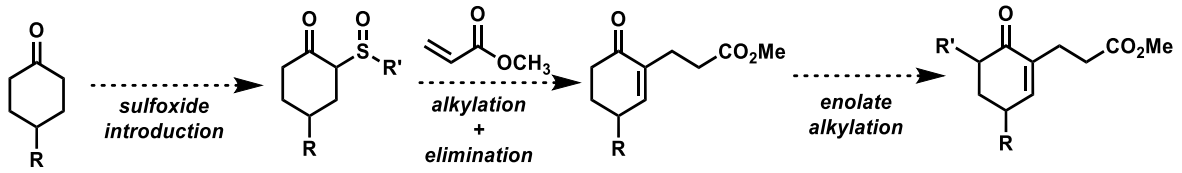
Scheme 2.31 Synthetic scheme for the preparation of disubstituted *cis*-DHQs

Continuing with the research displayed in Section 2.1.1, the cyclocondensation reaction of various disubstituted 1-oxocyclohexenepropionate derivatives with (*R*)-phenylglycinol was studied. To do that the preparation various precursors containing a methyl group at C-6 and an alkylic or arylic substituent at C-3/4 of the ring was first needed.

2.3.1 Preparation of Starting Materials

2.3.1.1 Preparation of C-4/C-6 Disubstituted 1-Oxocyclohexenepropionate Derivatives

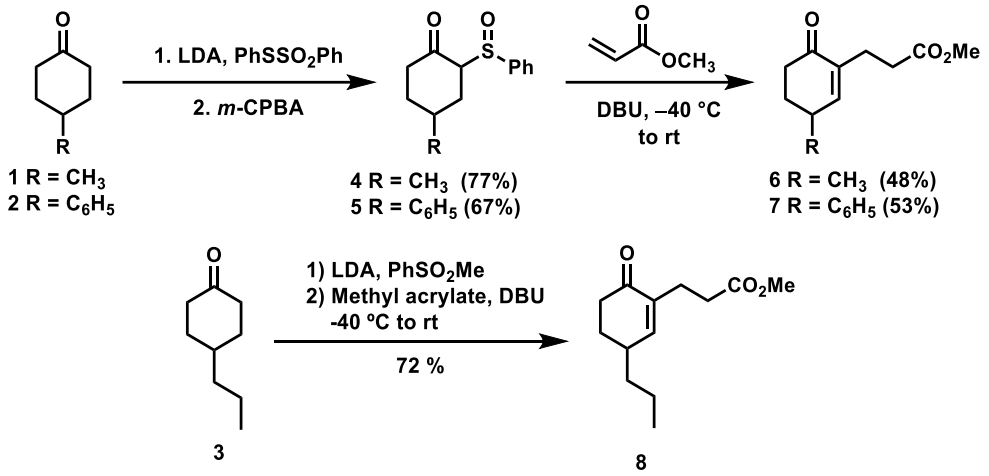
Since the required starting materials for the cyclocondensation reaction are not commercially available, we resorted to a synthetic approach previously used by the group, for the obtention of these intermediates.[57] The synthetic strategy involved the introduction of a sulfoxide moiety into the α-position of various 4-substituted cyclohexanones followed by a conjugate addition of the enolate of the β-ketosulfoxide to methyl acrylate. Elimination of the sulfoxide would provide the corresponding cyclohexenone derivative. Enolate alkylation of the remaining α position would provide the desired starting materials (Scheme 2.32).



Scheme 2.32 Synthetic strategy

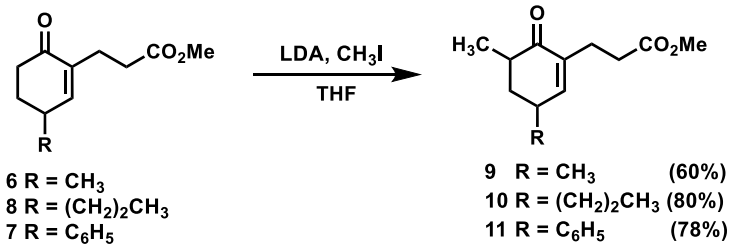
Starting from cyclohexanones **1** and **2**, treatment with LDA and *S*-phenyl benzenethiosulfonate followed by oxidation with *m*-CPBA led to the obtention of sulfoxides **4** and **5** with good yields. Conjugate addition of the sulfoxides **4** and **5** under mild basic conditions to methyl acrylate at –40 °C followed by elimination of the sulfoxide at room temperature led to the obtention of δ-ketoesters **6** and **7**. Alternatively, δ-ketoester **8** was easily obtained by reaction of the lithium enolate of 4-propylcyclohexanone **3** with methyl benzenesulfinate. Alkylation of the resulting β-ketosulfoxide

with methyl vinyl ketone followed by elimination of the sulfoxide led to **8** in just two steps. The use of the later approach constituted a faster and more efficient sequence to the obtention of these intermediates (Scheme 2.33).



Scheme 2.33 Preparation of 4-substituted δ-ketoesters **6-8**

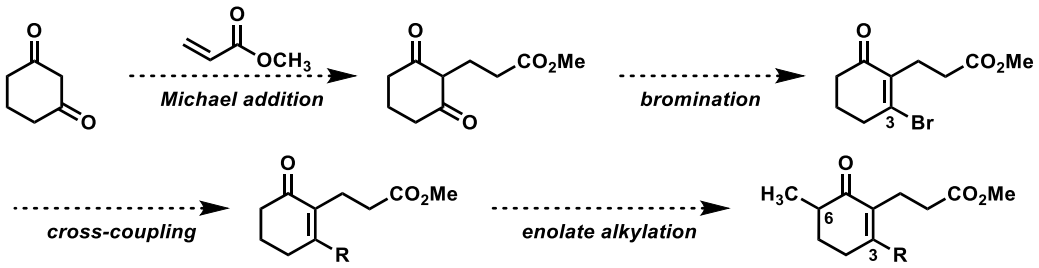
Enolate alkylation of δ-ketoesters **6-8** with methyl iodide led to the obtention of 4,6-disubstituted δ-ketoesters **9-11** in good yields (Scheme 2.34).



Scheme 2.34 Preparation of 3,5-disubstituted δ-ketoesters **9-11**

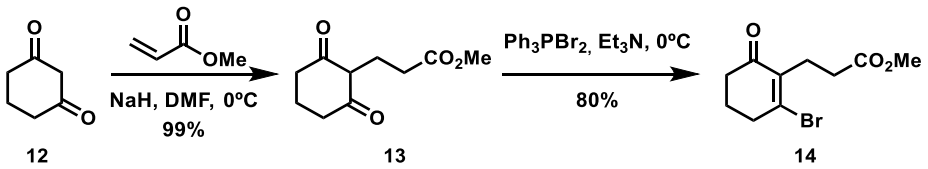
2.3.1.2 Preparation of C-3/C-6 Disubstituted 1-Oxocyclohexenepropionate Derivatives

For the synthesis of 3,6-disubstituted 1-oxocyclohexenylpropionate derivatives, the devised strategy involved first the introduction of the propionate chain on the carbocyclic ring via Michael addition of 1,3-cyclohexadione to methyl acrylate, followed by a bromination to provide the corresponding β-bromoenone. Then, a cross-coupling reaction would allow the easy introduction of alkylic and arylic substituents at the C-3 position of the cyclohexenone. Finally, an enolate alkylation would provide the corresponding 3,6-disubstituted 1-oxocyclohexenepropionate derivatives (Scheme 2.35).[56]



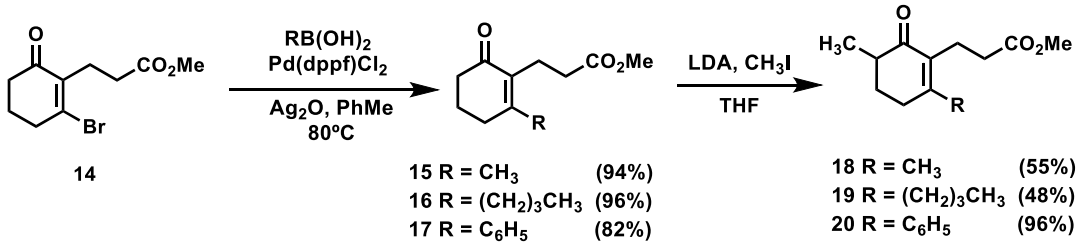
Scheme 2.35 Synthetic strategy

Starting from 1,3-cyclohexadione **12**, δ-diketoester **13** was easily prepared by conjugate addition of the sodium enolate of 1,3-cyclohexadione with methyl acrylate. Then, **13** was transformed into β-bromoenone **14** by treatment with triphenylphosphine dibromide (Scheme 2.36).[65]



Scheme 2.36 Preparation of β-bromoenone **14**

Suzuki coupling of various alkyl and aryl boronic acids with **14**, allowed the introduction of alkylic and arylic substituents to provide 3-susbtituted δ-ketoesters **15-17**. Enolate alkylation of these cyclohexenones with methyl iodide gave the corresponding disubstituted δ-ketoesters **18-20** with good yields (Scheme 2.37).



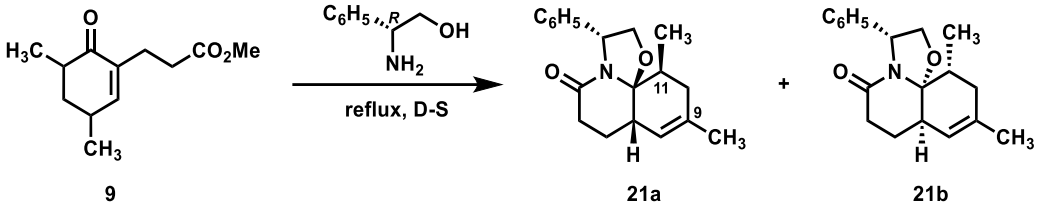
Scheme 2.37 Preparation of 3,6-disubstituted δ-ketoesters **18-20**

2.3.2 Cyclocondensation Reaction

2.3.2.1 Studies on the Preparation of C-9/C-11 Disusbtituted Tricyclic Lactams

With the required ketoesters in hand, the study of their cyclocondensation reactions with enantiopure amino alcohols was next. 4,6-Dimethyl δ-ketoester **9** was subjected to reaction with (*R*)-phenylglycinol under different reaction conditions. The results are summarized in Table 2.1.

[65] Piers, E.; Nagakura, I. *J. Org. Chem*. **1975,** *40*, 2694-2696.

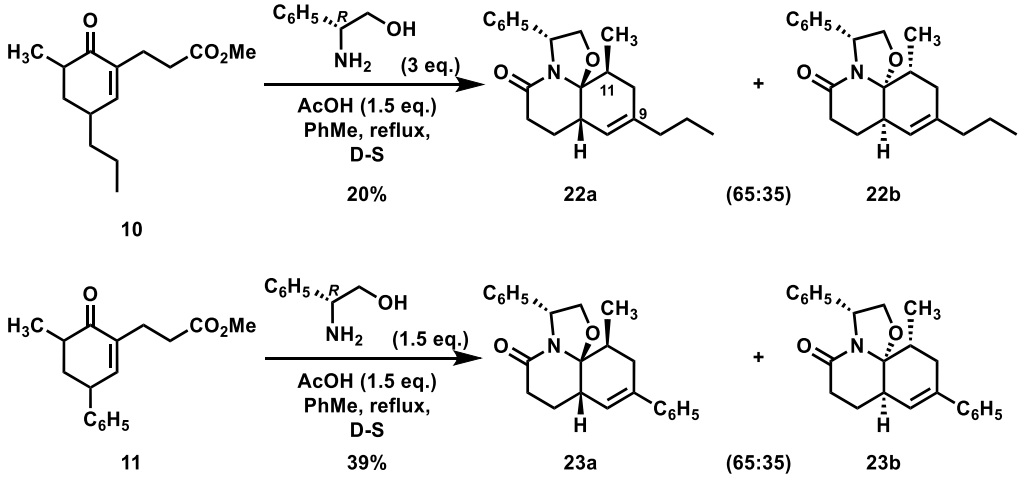


	eq. (*R*)-PhGly	Solvent	t (h)	eq. AcOH added	Yield (%)	a:b
1	1.5 x 2	PhMe	96	1.5	32	63:37
2	1.5 x 2	PhMe	96	1.5 x 2	23	64:36
3	1.5 x 4	C_6H_6	72	1.5 x 4	12	66:34

Table 2.1 Cyclocondensation reaction of ketoester **9** with (*R*)-phenylglycinol

The cyclocondensation of **9** with (*R*)-phenylglycinol in refluxing toluene in the presence of 1.5 equivalents of acetic acid using a Dean-Stark apparatus, led to the stereoselective obtention of lactams **21a** and **21b** with an average stereoselectivity of 64:36 among all the assays. The increase of acetic acid drastically reduced the yield of the reaction. Additional tests concluded that neither the change of solvent, nor the addition of more equivalents of the chiral amino acid led to an increase of the yield but to a decrease.

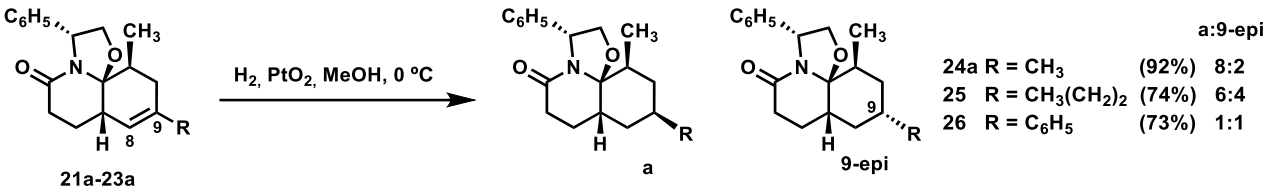
Similarly, the cyclocondensation of ketoesters **10** and **11** under the previously reported conditions (Entry 1, Table 2.1), led to the obtention of lactams **22a**-**22b** and **23a**-**23b** with similar stereoselectivities. In the case of lactams **23a**-**23b**, a lower amount of chiral inductor was required, and the yield was higher. This could be attributed to the formation of a conjugated electronic system between the double bond and the aromatic ring (Scheme 2.38).



Scheme 2.38 Cyclocondensation of ketoesters **10** and **11** with (*R*)-phenylglycinol

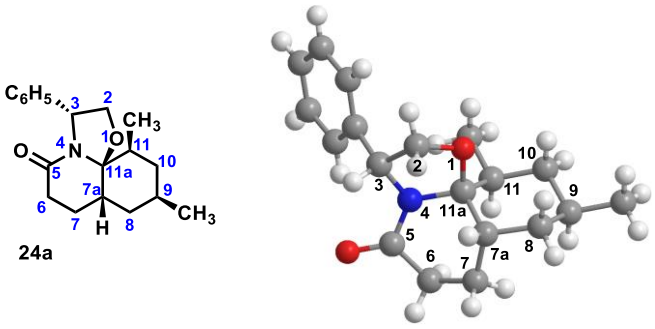
In all the cyclocondensation processes, few traces of a minor lactam were also observed that could not be isolated in pure form. On the grounds of previous assays of the group on the obtention of C-11 substituted lactams, the minor isomer is thought to be a C-11 epimer of **21a**-**23a**.

Catalytic hydrogenation in presence of the Adam's catalyst in methanol at 0 °C of lactams **21a**-**23a** allowed the reduction of the C-8/C-9 double bond to provide lactams **24a**-**26a** (Scheme 2.39).



Scheme 2.39 Hydrogenation assays of lactams **21a-23a**

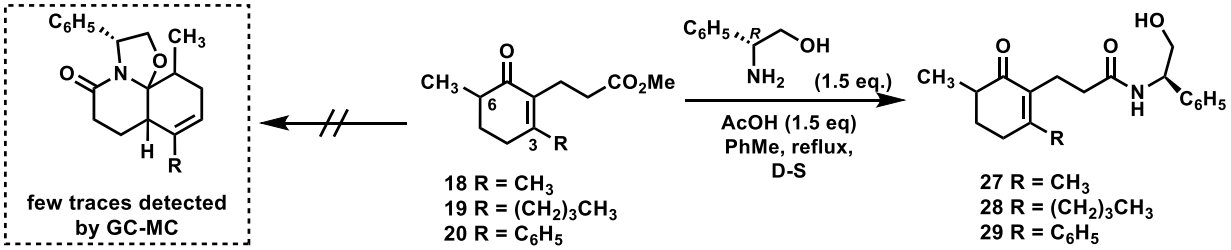
In terms of yield and stereoselectivity, it appears that the size of the C-9 substituent has a significant influence. Upon increasing the size of the substituent, both the yield and stereoselectivity undergo a decline with the later achieving a 1:1 ratio when R is a phenyl group. On the other hand, the obtention of a crystal of **24a** allowed the determination of its absolute configuration by XRD analysis (Scheme 2.40).



Scheme 2.40 Structure obtained from XRD analysis of **24a** crystal

2.3.2.2 Preparation of C-8/C-11 Disubstituted Lactams

At the same time, the cyclocondensation of 3,6-disubstituted δ-ketoesters **18**-**20** with (*R*)-phenylglycinol was tested (Scheme 2.41).



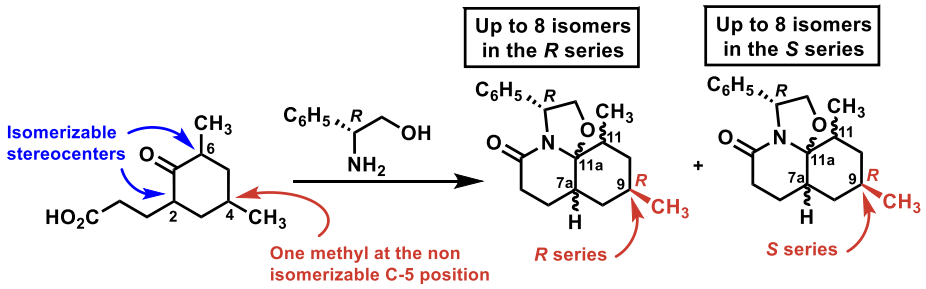
Scheme 2.41 Cyclocondensation outcome of ketoesters **18**-**20** with (*R*)-phenylglycinol

Unfortunately, cyclocondensation products were only observed in trace amounts by GC-MS. Instead, amides **27**-**29** were detected. In comparison to previous studies (Section 2.1.2), it can be concluded that the presence of a substituent at C-3 greatly reduces the cyclocondensation yield.

The synthesis of disubstituted tricyclic lactams from their unsaturated precursors proved to be less efficient in terms of chemical yield and stereoselectivity than initially anticipated. Accordingly, the procedure is not useful under a synthetic standpoint and a new approach had to be devised.

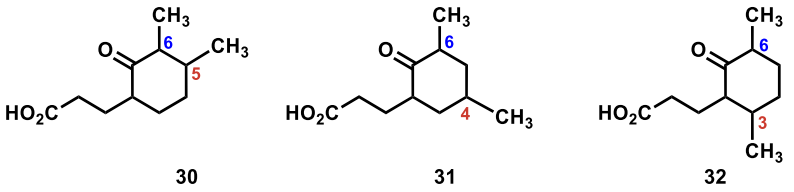
2.4 Enantioselective Synthesis of Disubstituted Azabicycles from (*R*)-Phenylglycinol-Derived Saturated Lactams. Second Approach

Considering the above adverse results, we decided to explore alternative cyclocondensation processes starting from disubstituted cyclohexanone derivatives as starting materials. As mentioned in the objectives section of this chapter, the final goal was to set up an efficient procedure for the preparation of enantiopure 6,8-disubstituted *cis*-DHQs from tricyclic lactams and its application to the synthesis of (–)-schoberine B. As proof of concept, we decided to analyze the stereoselectivity in the generation of 9,11-dimethyl tricyclic lactams from racemic diastereomeric mixtures of 1-oxocyclohexanepropionates bearing two methyl groups at the C-4 and C-6 positions. However, in this case, the stereocenter at C-4 is not isomerizable and the reaction can provide two series of lactams differing, at least, in the configuration C-9. Consequently, an *R* series (C-9 with an *R* configuration) in which up to 8 diastereomers differing in the configuration at C-7a, C-11, and C-11a can be formed and an *S* series (C-9 with an *S* configuration) in which a similar mixture of 8 diastereomers can also be generated. Obviously, the highest possible yield in the formation of one or a mixture of diastereomeric lactams for each series is 50%. Therefore, the first goal was to analyze the stereoselectivity in the formation of a major isomer of the corresponding tricyclic lactam in each series (Scheme 2.42).



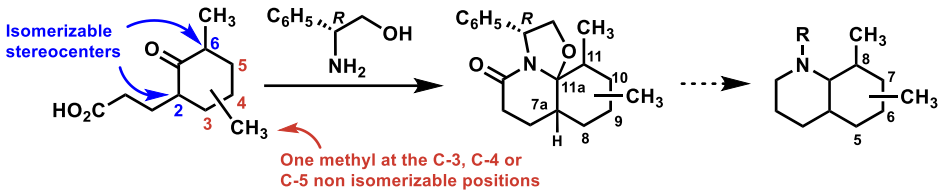
Scheme 2.42 Expected cyclocondensation outcome

To analyze the scope of the procedure and the influence of the position of the methyl substituents in non-isomerizable stereocenters in the stereoselectivity of the reaction, we decided to carry out cyclocondensation reactions from cyclohexanones **30, 31**, and **32** (Scheme 2.43).



Scheme 2.43 Cyclocondensation precursors

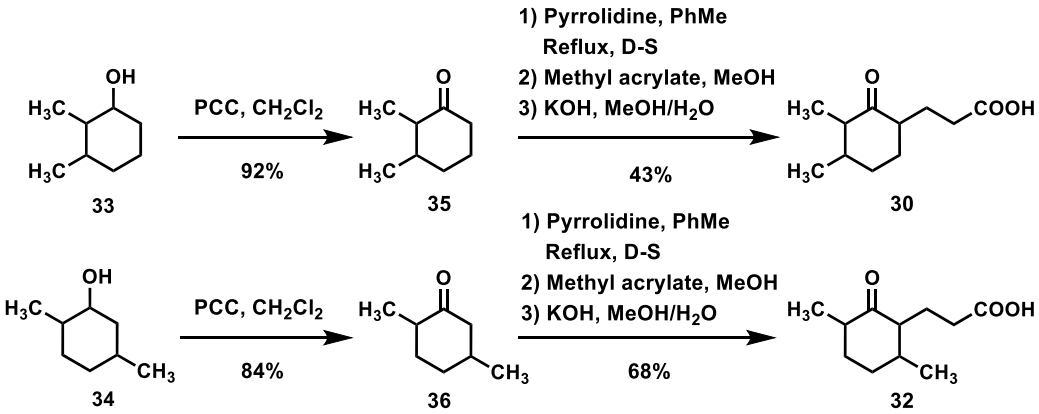
The corresponding tricyclic lactams would be advanced precursors for the synthesis of enantiopure 5,8-, 6,8-, and 7,8-dimethyl DHQs (Scheme 2.44).



Scheme 2.44 Synthetic scheme of the new approach

2.4.1 Preparation of Starting Materials

The 2,3- and 2,5-dimethyl cyclohexan-1-ols **33** and **34**, both commercially available, were used for the synthesis of cyclohexanonepropionates **30** and **32**. Pyridinium chlorochromate oxidation of the alcohols **33** and **34** provided dimethylcyclohexanones **35** and **36** in good yields.[66] Alkylation of the pyrrolidine-derived enamines of **35** and **36** with methyl acrylate followed by hydrolysis of the resulting ester, provided δ-ketoacids **30** and **32** (Scheme 2.45).

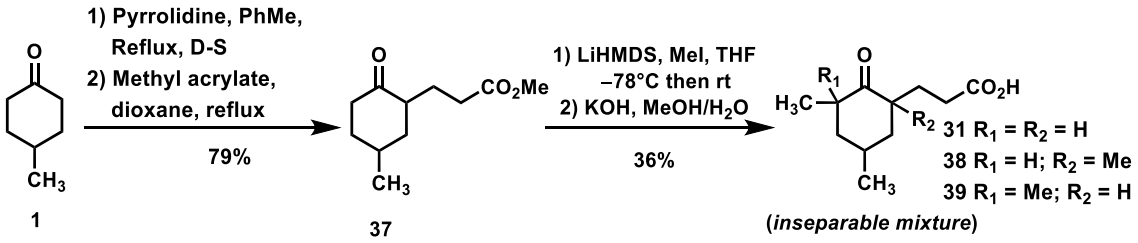


Scheme 2.45 Synthesis of dimethylated δ-ketoacids **30** and **32**

On the other hand, the synthesis of ketoacid **31** was performed using a different sequence. Starting from 4-methylcyclohexanone **1**, the propionate moiety was introduced by treatment of its pyrrolidine enamine with methyl acrylate to provide δ-ketoester **37** in good yield. Subsequent introduction of the

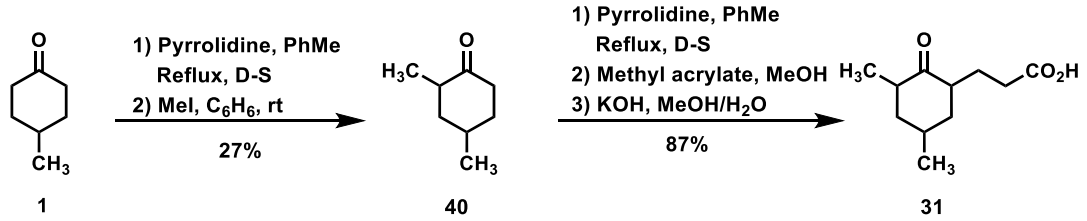
[66] a) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **2000**, *65*, 7145-7150; b) Abe, H.; Ogura, Y.; Kobayashi, T.; Ito, H. *Org. Lett.* **2017**, *19*, 5996-5999.

methyl group through the lithium enolate of **37** afforded an inseparable mixture of the desired product and dialkylation byproducts (**38**-**39**) (Scheme 2.46).



Scheme 2.46 First approach to **31**

The addition of HMPA to the reaction mixture did not improve the above results.[67] To circumvent the di- and polyalkylation associated with alkali enolates,[68] we switched the order of introduction of substituents (Scheme 2.47).



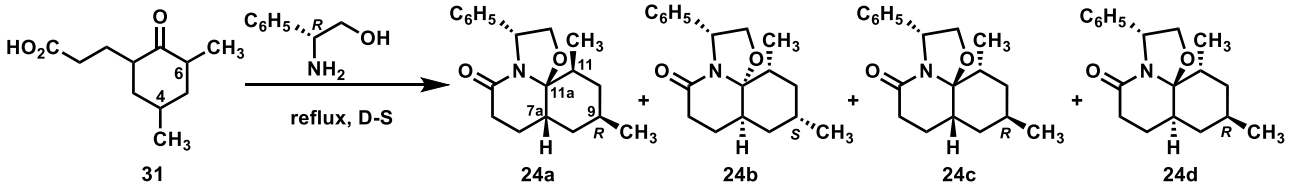
Scheme 2.47 Synthesis of 3,5-dimethyl δ-ketoacid **31**

Enamine alkylation of the pyrrolidine-derived enamine of **1** with methyl iodide afforded 2,4-dimethylcyclohexanone **40**.[69] The subsequent introduction of the propionate chain from the pyrrolidine enamine of **40** and methyl acrylate followed by ester hydrolysis using the above-mentioned conditions afforded the dimethylated δ-ketoacid **31**.

2.4.2 Cyclocondensation Reaction

With the ketoacids in hand, we studied the cyclocondensation of ketoacid **31** with (*R*)-phenylglycinol (Table 2.2).

[67] Suzuki, M.; Koyama, H.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 259-268.
[68] Streitwieser, A.; Kim, Y.-J.; Wang, D.Z.-R. *Org. Lett.* **2001**, *3*, 2599-2601.
[69] Oritani, T.; Kondo, H.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 263-264.



	eq. (*R*)-PhGly	Solvent	t (h)	24a[2]	24b[2]	24c[2]	24d[2]
1	1.5	C_6H_6	24 h	31%	34%	2%	4%
2	3	C_6H_6	72 h	26%	21%	-[3]	-[3]
3	3[1]	PhMe	72 h	26%	34%	-[3]	-[3]

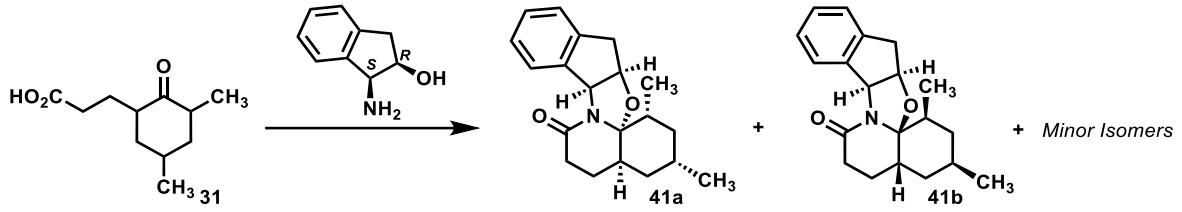
[1] 2 additions of 1.5 eq of (*R*)-phenylglycinol; [2] Yield after flash chromatography; [3] Detected but not isolated.

Table 2.2 Cyclocondensation assays of **31**

To our delight, heating a mixture of ketoacid **31** and (*R*)-phenylglycinol in refluxing benzene for 24 h stereoselectively led to the formation of tricyclic lactams **24a** (9*R* series; 31%) and **24b** (9*S* series; 34%), showing an opposite configuration at the four stereocenters on the carbocyclic ring. Two minor diastereomeric lactams, **24c** (2%), differing in the configuration at the C-11 position, and **24d** (4%) differing in the configuration at the C-7a and C-11 positions, in both cases with respect to the major isomer **24a**, were also isolated in the 9*R* series. Lactam **24b** was isolated as the only isomer in the 9*S* series. Given that the C-5 stereocenter of **31** is not isomerizable, the cyclocondensation reaction yields two sets of lactams (*R/S* series), with a maximum achievable yield of 50%.

Additional experiments were conducted to test if the yield and stereoselectivity could be improved. Using the same chiral inductor, different amounts of (*R*)-phenylglycinol as well as a higher boiling point solvent were tested but neither improved the yield (Entries 2 and 3, Table 2.2). The use of the corresponding methyl ester of the 4,6-dimethyl-1-oxocyclohexanonepropionic acid **31** in the cyclocondensation reaction did not improve the results either.

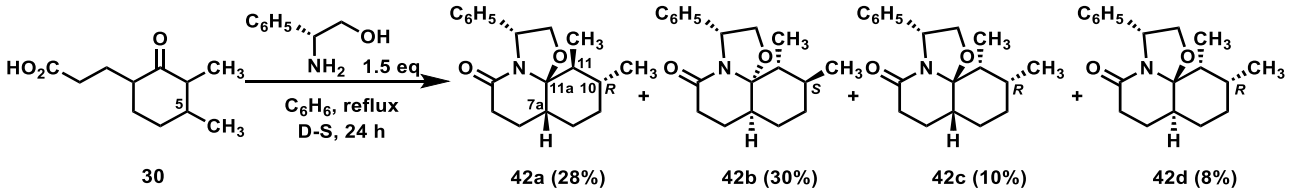
Finally, when the conformationally more rigid (1*S*,2*R*)-aminoindanol, instead of (*R*)-phenylglycinol, was used an inseparable mixture of mainly lactams **41a** and **41b** was obtained in slightly higher overall yields (Table 2.3). Unfortunately, lactams **41a** and **41b** could not be separated by chromatographic methods (column chromatography or GC-MS), and the ratio of isomers could not be determined. For this reason, no further studies were performed using this chiral inductor.



	eq. (1*S*,2*R*)-*cis*-AmIn	Solvent	t (h)	Overall yield
1	1.5	C_6H_6	24 h	74%
2	3	C_6H_6	72 h	73%
3	3	PhMe	72 h	67%

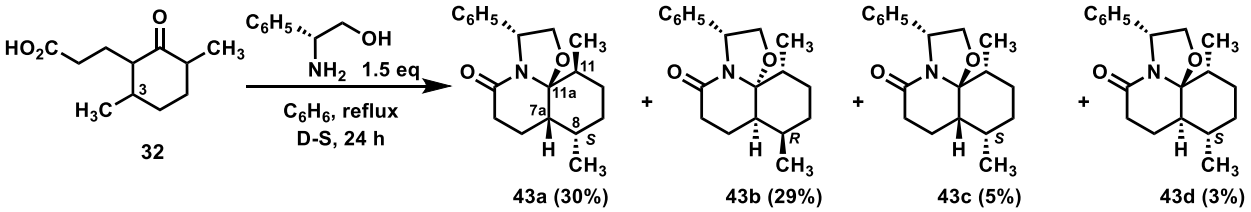
Table 2.3 Cyclocondensation assays of **31** with (1*S*, 2*R*)-*cis*-aminoindanol

With the cyclocondensation parameters optimized, ketoacid **30** was next tested (Scheme 2.48). Thus, cyclocondensation of ketoacid **30** with (*R*)-phenylglycinol stereoselectively afforded lactams **42a** (10*R* series) and **42b** (10*S* series) in 28% and 30% yield, respectively. Small amounts of diastereomers **42c** (10%) and **42d** (8%) were also isolated from the reaction mixture.



Scheme 2.48 Cyclocondensation of ketoacid **30** with (*R*)-phenylglycinol

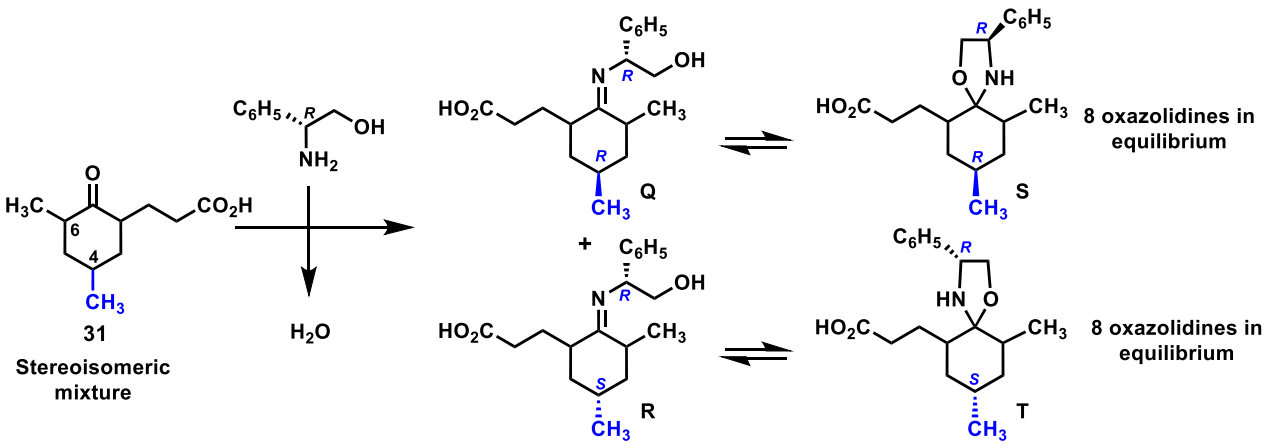
The cyclocondensation of **32** with (*R*)-phenylglycinol provided similar results (Scheme 2.49). Tricyclic lactams **43a** (8*S* series) and **43b** (8*R* series) were obtained in 30% and 29% yield, respectively. Again, only very minor amounts of other two diastereomers, **43c** (5%) and **43d** (3%).



Scheme 2.49 Cyclocondensation of ketoacid **32** with (*R*)-phenylglycinol

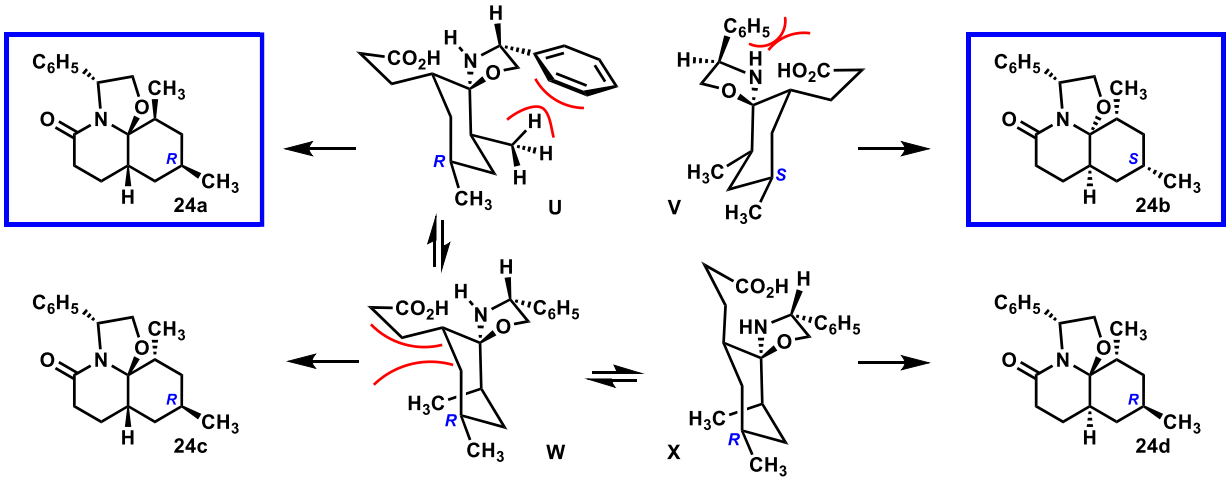
The stereoselectivity observed for the formation of lactams **24a/24b**, **42a/42b**, **43a/43b** can be rationalized by considering the previously described cyclocondensation mechanism with additional considerations. Taking the cyclocondensation of **31** as example, reaction of this ketoacid with (*R*)-phenylglycinol leads to the formation of imines **Q** (*R* series) and **R** (*S* series) (mixture of isomers at the isomerizable stereocenters). Addition of the hydroxy group to the imine lead to the formation of 16 intermediate spiro-oxazolidines **S** (*R* series) and **T** (*S* series). Eight of them for each configuration

of the non-isomerizable stereocenter and in equilibrium through the corresponding imine-enamines (Scheme 2.50).



Scheme 2.50 Generation of oxazolidines **S-T**

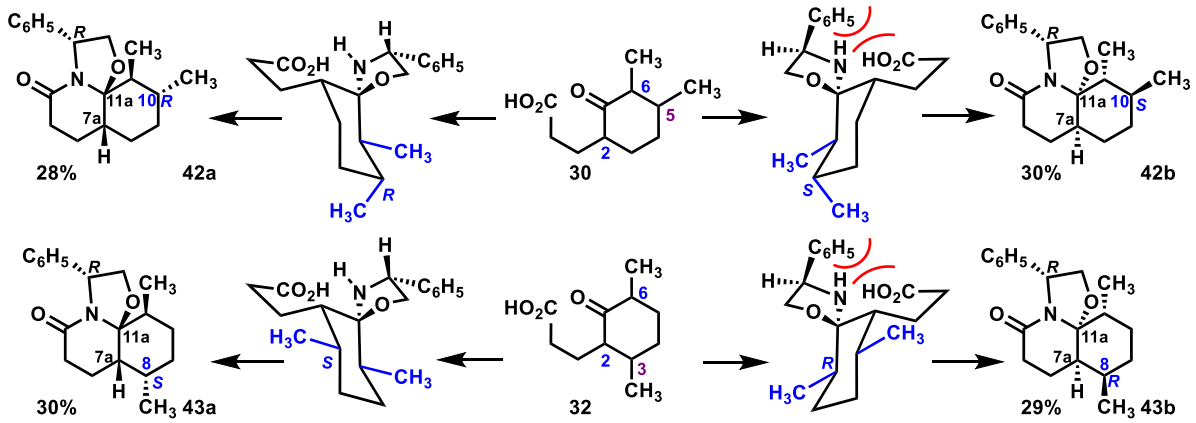
Then, lactamization occurs faster through those oxazolidines containing both methyl groups in equatorial position (**U** and **V**), leading to the stereoselective formation of lactams **24a** and **24b**. The formation of two minor isomers, **24c** and **24d**, in the 9*R* series can be attributed to the severe steric interactions in **U** between the phenyl group and the isomerizable equatorial methyl substituent, which induce a configurational change of this stereocenter via the equilibrium oxazolidine-imine-enamine. However, in oxazolidine **W**, which is the precursor of lactam **24c**, the isomerizable methyl substituent shows a 1,3-diaxial interaction with the propionate chain. This strain is released in oxazolidine **X**, generated by an inversion in the configuration of the stereocenter next to this chain, again via the equilibrium oxazolidine-imine-enamine. Oxazolidine **X** is the precursor of the highly strained lactam **24d**, with a *trans* fusion of the two six-membered rings (Scheme 2.51).



Scheme 2.51 Oxazolidine intermediates leading to all the lactams obtained in the cyclocondensation of **31**

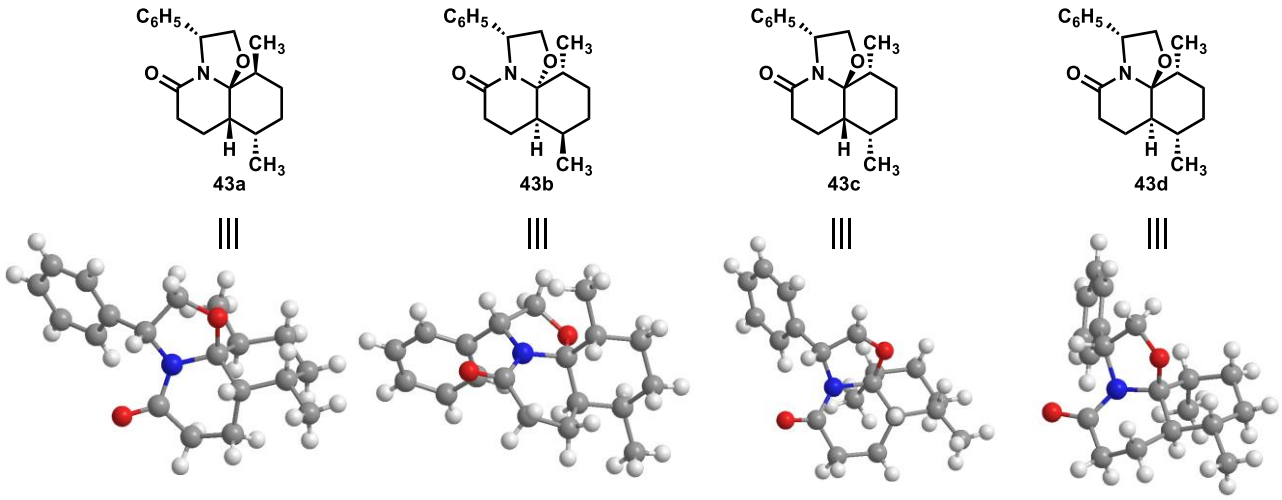
The C_6H_5/CH_3 interactions do not exist in the spiro-oxazolidine **V** (9*S* series), since the phenyl substituent is on the opposite face of the oxazolidine ring, so a single lactam **24b** was formed in this series. The moderate yield (34%) in the cyclocondensation leading to **24b** in comparison with the overall yield for the lactams in the 9*R* series (**24a** + **24c** + **24d**; 37%) could be accounted for by considering that in **24b**, the carboxylate approaches the nitrogen from the more hindered face of the oxazolidine, next to the phenyl substituent. It is worth mentioning that the formation of two minor diastereomers with the same relative configuration at the C-7a, C-11 and C-11a positions as lactams **24c** and **24d** were already observed in the cyclocondensation of ketoacid **165a** (R = CH_3, C-4 demethyl analog of **31**) with (*R*)-phenylglycinol but at the time couldn't be identified (see Scheme 2.11).[60]

The formation of the two major isomers **42a/42b** from cyclohexanone **30** and **43a/43b** from **32** can be justified taking into account the same mechanistic considerations described for the formation of **24a/24b** from **31**. As it can be observed in Scheme 2.52, the relative configuration of the two methyl substituents *cis* (in **24a/24b**) or *trans* (in **42a/42b** and **43a/43b**) is determined by their equatorial position in the reactive spiro-oxazolidine intermediate.



Scheme 2.52 Intermediate oxazolidines leading to lactams **42a-43a** and **42b-43b**

The absolute configuration of all lactams except for **24c** and **42c** was unequivocally determined by XRD analysis (Scheme 2.53).



Scheme 2.53 Structures obtained from XRD analysis of all the lactams obtained from the cyclocondensation of **32**

Furthermore, upon comparing the NMR data of each series of compounds, signals with diagnostic value for various positions within the molecule are revealed. As depicted in Figure 2.1, the chemical shifts of positions C-2, C-3, and C-5 enable the precise identification of the configuration at positions C-7a, C-11, and C-11a.[70]

[70] Additional ^{1}H and ^{13}C NMR stacked spectra and ^{13}C NMR tables of lactams **165, 24, 42, 43a-d** in Section 6.1

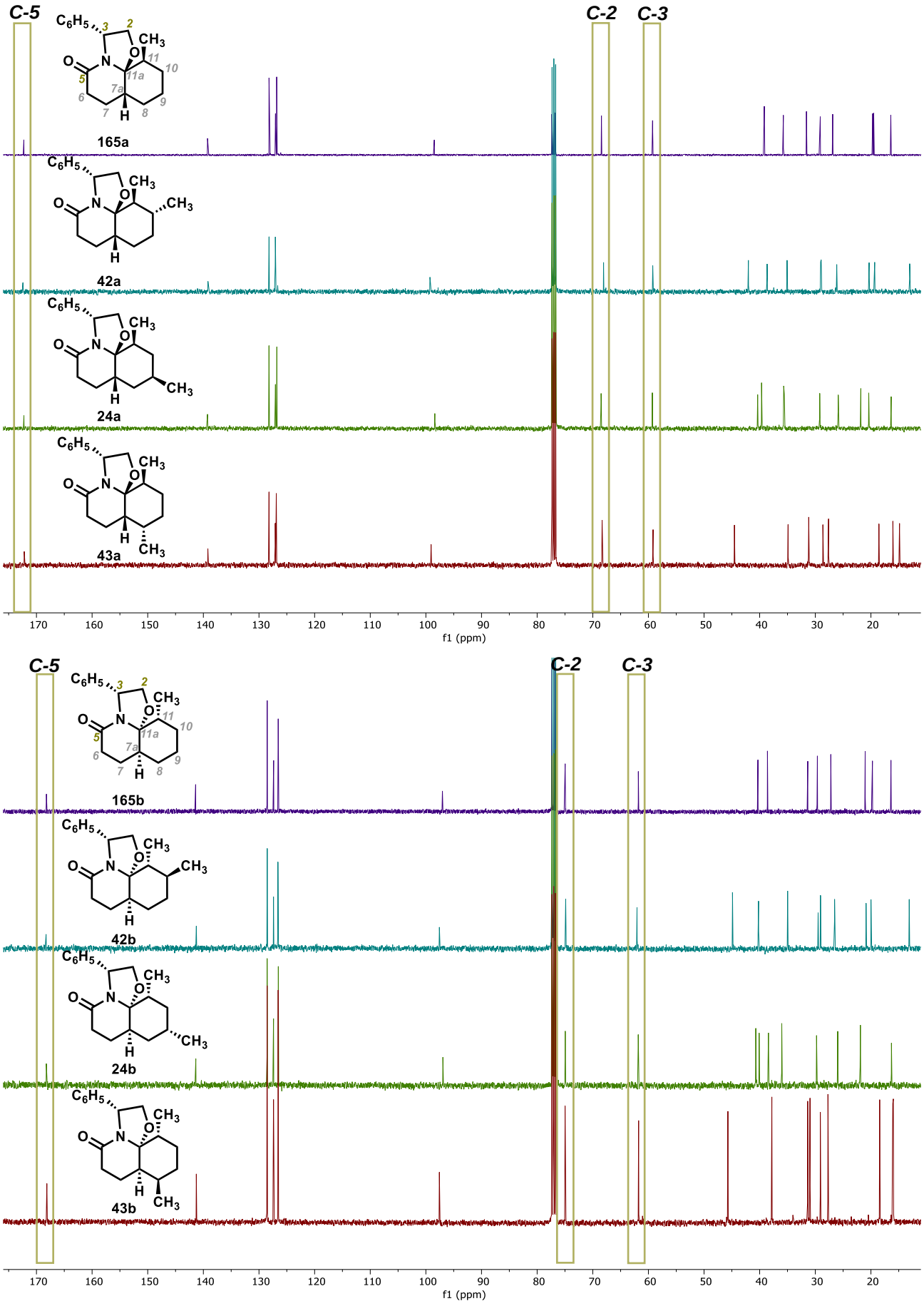
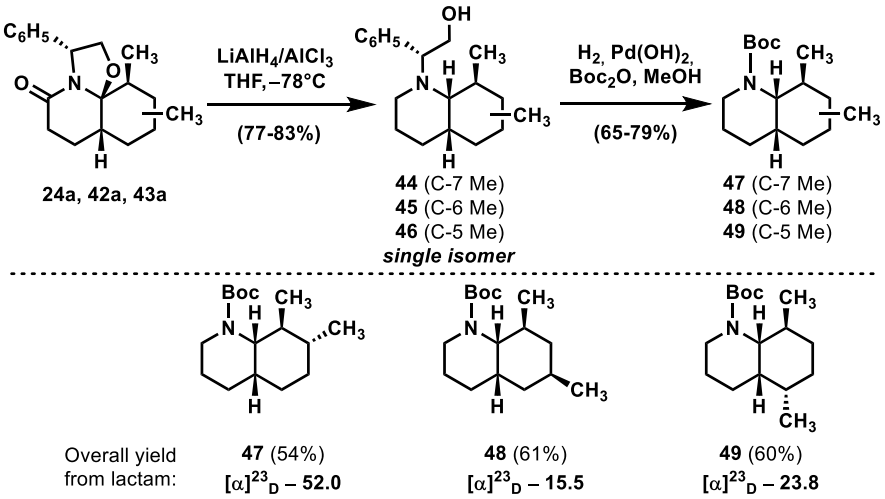


Figure 2.1 ^{13}C Stacked spectra of **165a-b**, **24a-b**, **42a-b**, and **43a-b**

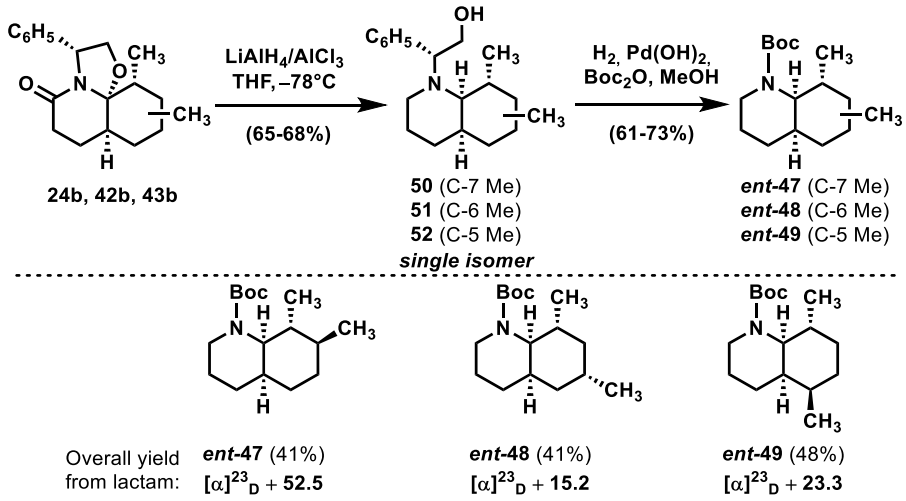
2.4.3 Obtention of Disubstituted *cis*-Decahydroquinolines

To demonstrate the synthetic utility of this new contribution to the methodologies developed in the group for the synthesis of enantiopure *cis*-DHQ, we aimed to remove the chiral inductor of the major lactams of each sequence using the two-step reductive removal of the chiral inductor previously reported. Treatment of lactams **24a**, **42a**, and **43a** with $LiAlH_4$ and $AlCl_3$ promoted the reduction of the lactam carbonyl as well as the stereoselective ring opening of the oxazolidine to give *cis*-decahydroquinolines **44-46** in good yields. Removal of the 2-phenylethanol moiety was completed by catalytic hydrogenation using Perlman's catalyst in the presence of Boc_2O to provide the target enantiopure 7,8-, 6,8-, and 5,8-dimethyl-*cis*-decahydroquinolines **47**, **48**, and **49** (Scheme 2.54).



Scheme 2.54 Chiral inductor removal of lactams **24a**, **42a**, and **43a**

Similarly, the removal of the chiral inductor from lactams **24b**, **42b**, and **43b** allowed the obtention of the corresponding enantiomers (***ent*-47**, ***ent*-48**, and ***ent*-49**) with good yields (Scheme 2.55).



Scheme 2.55 Chiral inductor removal of lactams **24b**, **42b**, and **43b**

2.5 Conclusions

Starting from racemic diastereomeric mixtures of dimethyl-1-oxocyclohexanepropionic acids (**30**-**32**) the synthesis of enantiopure 7,8-, 6,8-, and 5,8-dimethyl-substituted *cis*-decahydroquinolines (**47**, **48**, and **49**) and their enantiomers (***ent*-47**, ***ent*-48**, and ***ent*-49**) has been achieved. The procedure involves a dynamic kinetic asymmetric transformation in the cyclocondensation of ketoacids **30**-**32** with (*R*)-phenylglycinol to give in each case two major oxazoloquinolone lactams (**24a**/**24b**, **42a**/**42b**, **43a**/**43b**), which differ in the absolute configuration of all the stereogenic centres except that of the chiral inductor. A subsequent two-step stereoselective removal of the phenylglycinol moiety with simultaneous reduction of the lactam carbonyl affords the enantiopure *cis*-decahydroquinolines in both enantiomeric series.[71]

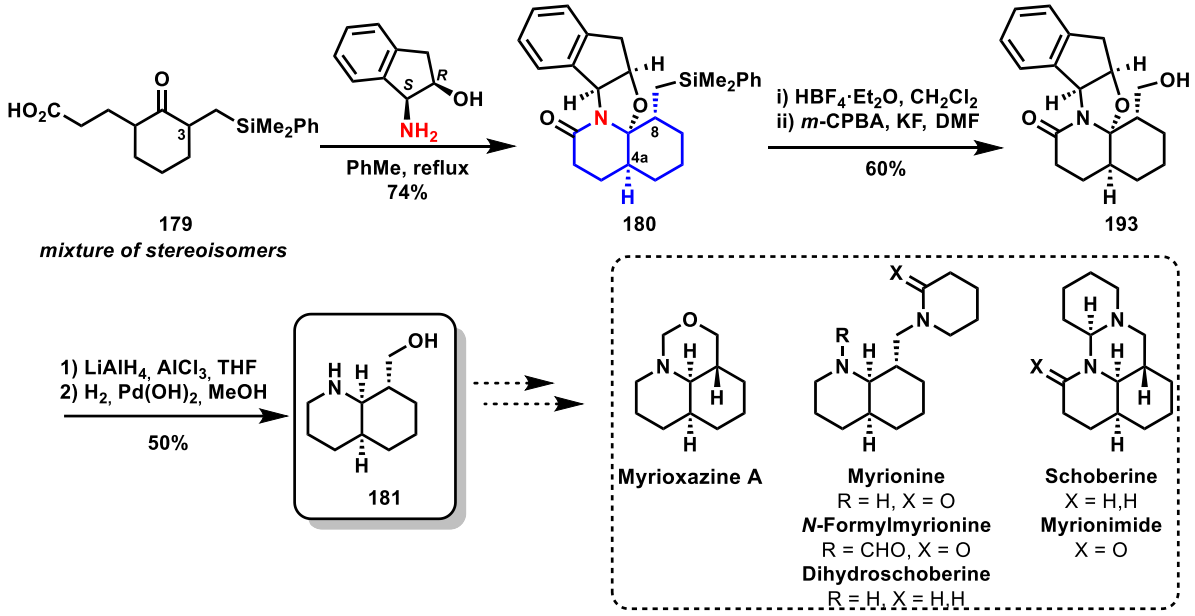
The development of this methodology opens the door to the synthesis of alkaloids containing a 6,8-disubstituted-*cis*-DHQ nucleus.

[71] Calbó, A.; Griera, R.; Bosch, J.; Amat, M.; *Org. Chem. Front.* **2023**, *10*, 724-729.

3 Total Synthesis of (–)-Schoberine B and its Enantiomer (+)-Schoberine B

3.1 Synthesis of *Myrioneuron* Alkaloids: Group Precedents

For an introduction to the isolation, structural features, biological activities, biosynthesis, and total synthesis of alkaloids of the *Myrioneuron* family, see Section 1.3 in Chapter 1 of this Doctoral Thesis. As outlined there, the *Myrioneuron* family is an interesting group of alkaloids not only because of their bioactivities but also because of their structural diversity and various degrees of complexity. Few syntheses have been described for a limited group of the more accessible members of this family. This gives the opportunity for the development of novel approaches for the synthesis of the more inaccessible alkaloids of this family. The research group is no stranger to the synthesis of *Myrioneuron* alkaloids and has contributed to the formal synthesis of some members within this group (Scheme 3.1).[60]



Scheme 3.1 Formal synthesis of various *Myrioneuron* alkaloids

The synthetic strategy involved the formation of a chiral *cis*-aminoindanol derived lactam bearing a DHQ nucleus with a substituent at C-8 and its conversion into the known 8-hydroxymethyl-DHQ **181,** previously reported by Bodo in the context of their synthesis of *Myrioneuron* alkaloids.[42a,b,e,f] Thus, starting from a stereoisomeric mixture of δ-ketoacid **179**, the cyclocondensation with (1*S*,2*R*)-*cis*-1-amino-2-indanol led to the stereoselective obtention of lactam **180**, thus assembling the DHQ core of the desired targets with the proper configuration of C-4a and C-8 (DHQ numbering). Subsequent Flemming–Tamao oxidation allowed the transformation of the dimethylphenylsilyl moiety into the corresponding alcohol and thus, afforded lactam **193**.[72] Removal of the indanol moiety through the parallel reduction of the lactam and stereoselective oxazolidine opening followed by

[72] Fleming, I.; Henning, R.; Parker, D.C; Plaut, H.E.; Sanderson, P.E.J. *Chem. Soc. Perkin Trans.* **1995**, *1*, 317-337.

catalytic hydrogenation provided amino alcohol **181**, known precursor of (–)-myrioxazine A,[42a] (–)-myrionine,[42b] (–)-myrionidine,[42e] (–)-schoberine,[42e] and (+)-*N*-formylmyrionine.[42f] With the experience accumulated in the group on the synthesis of alkaloids of this family, and the prior extension of the group's methodology to obtain disusbstituted *cis*-DHQ, we focused our attention to more complex *Myrioneuron* alkaloids.

3.2 Schoberine B

From the aerial parts of *Myrioneuron faberi*, a small plant found in multiple regions of main-land China and North-Vietnam, (–)-schoberine B was first isolated by Cao and coworkers back in 2016 (Figure 3.1) [42k].

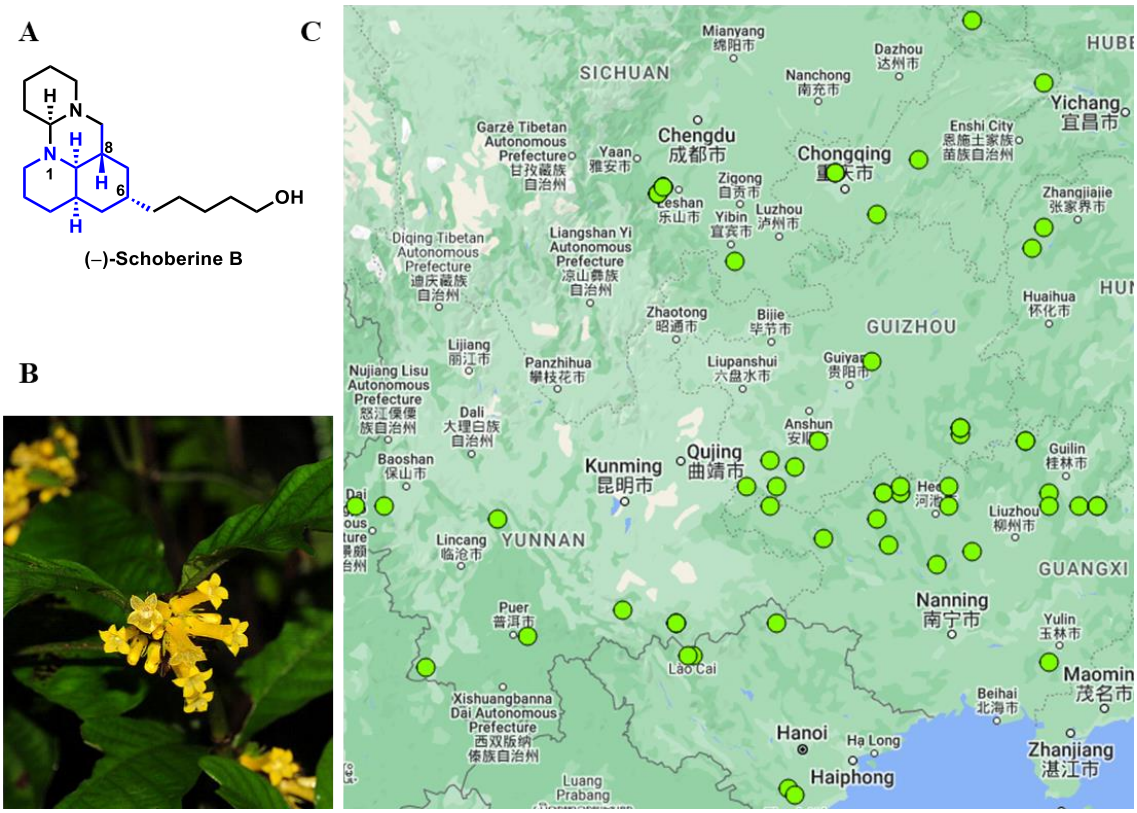


Figure 3.1 A. Structure of (–)-schoberine B; **B.** Photo of *Myrioneuron faberi* [73] **C.** Locations where *Myrioneuron faberi* has been found[74]

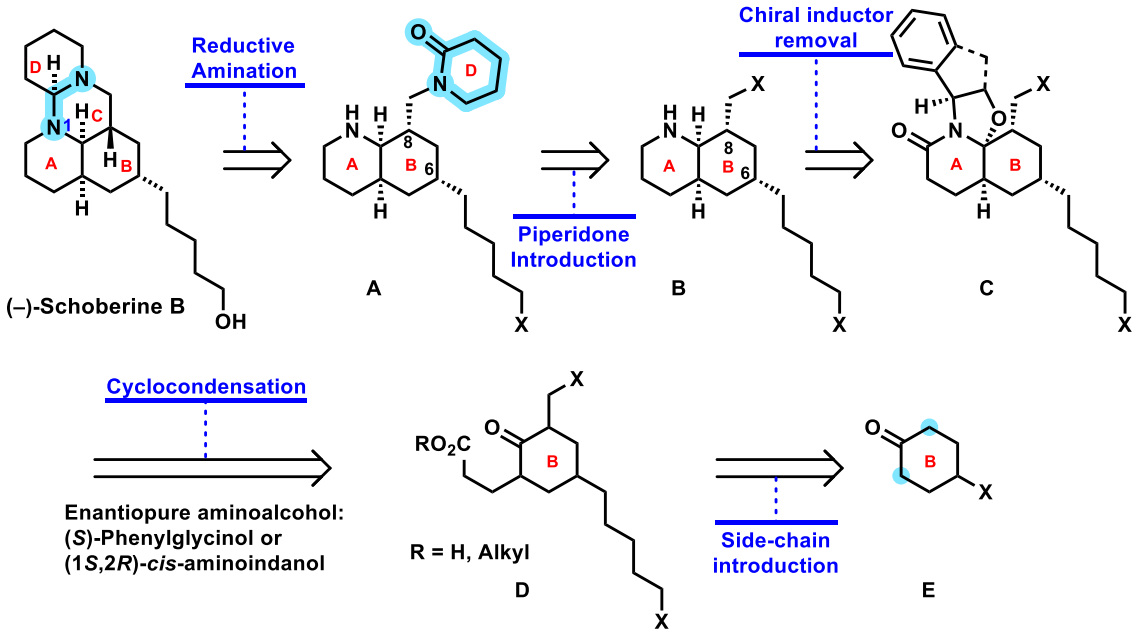
Its structure features a diazatetracyclic skeleton containing a *cis*-DHQ nucleus with a fused pyrido[1,2-*a*]pyrimidine. A 5-carbon atom chain, hydroxylated at the terminal position and unique

[73] Liu, J. Nature Library. A Librarian's Nature Journal. *Mycetia Faberi* http://naturelib.net/plantae/mycetia-faberi/ (accessed Sept. 2023).
[74] Map generated with data from: *Myrioneuron faberi* Hemsl. in GBIF Backbone Taxonomy. Checklist dataset https://doi.org/10.15468/39omei (accessed Sept. 2023)

among the DHQ alkaloids of this family, is found attached at C-6. In terms of biological properties, as mentioned in Section 1.3.1, it provides inhibitory activity against HCV.

3.3 Retrosynthetic Analysis

Based on previous synthesis of *Myrioneuron* alkaloids,[42e] we envisioned that (–)-schoberine B could be accessed from *cis*-decahydroquinoline **A** through a stereoselective reductive amination. At the same time, intermediate **A** could be accessed from *cis*-DHQ **B** by introducing a piperidone moiety into the functionalized one carbon substituent at C-8. The intermediate 6,8-disubstituted *cis*-DHQ **B** could be accessed by using the methodology developed in the previous chapter. Therefore, compound **B** could be obtained from lactam **C** through the removal of the chiral inductor and **C** could be accessed by the stereoselective cyclocondensation of δ-ketoacid/ester **D** and a chiral aminoalcohol. Finally, **D** could be obtained from cyclohexanone **E** by addition of the corresponding side chains (Scheme 3.2).



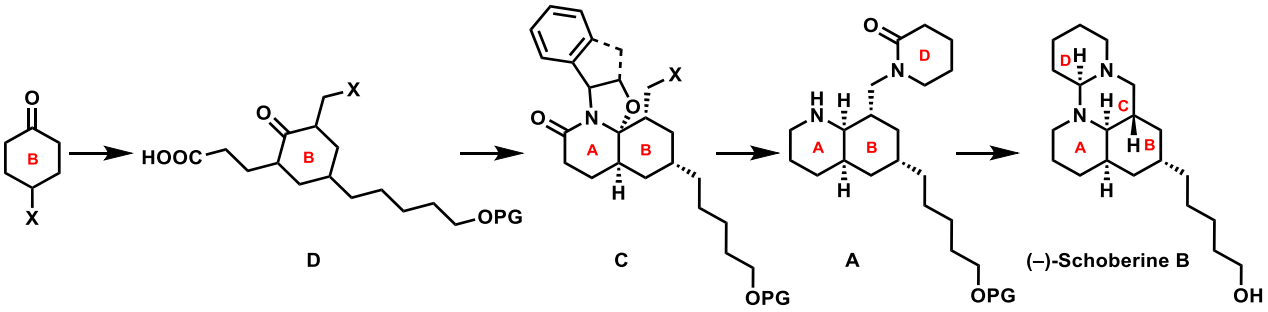
Scheme 3.2 Retrosynthetic analysis of (–)-schoberine B

3.4 Objectives

Given the retrosynthetic analysis proposed for this alkaloid, we envisioned that the total synthesis of (–)-schoberine B could be divided into 4 main objectives:

1) Obtention of ketoacid derivative **D** with substituents that allow the generation of a 6,8-disusbtituted *cis*-DHQ with suitable substituents to achieve the synthesis.
2) Assembly of lactam **C** using the previously developed methodology and thus assemble the A and B rings (*cis*-DHQ) of the product.

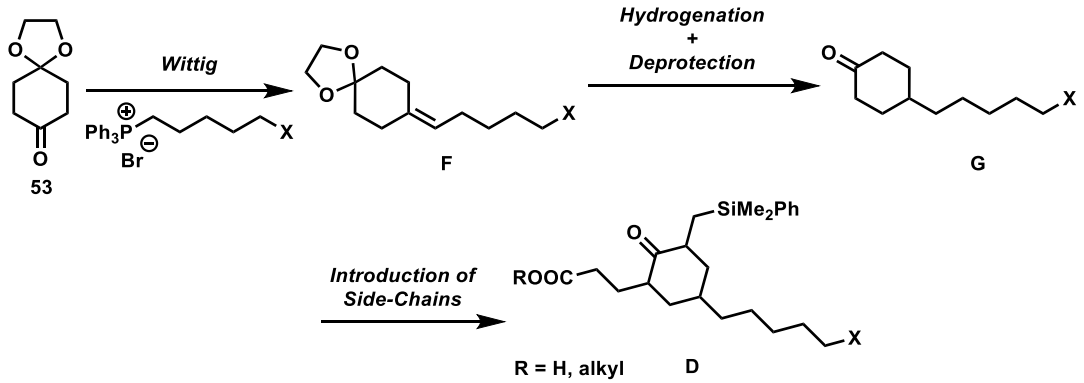
3) Removal of the chiral inductor and introduction of the D-ring to obtain 6,8-disubstiuted *cis*-DHQ **A**.
4) Stereoselective assembly of the tetracyclic structure and obtention of the alkaloid.



Scheme 3.3 Stages of (–)-schoberine B synthesis

3.5 Synthesis of the Cyclocondensation Precursor

For the obtention of compound **D**, we envisioned that it could be accessed from 1,4-cyclohexanedione monoethylene acetal **53**. First, a Wittig reaction, should allow the introduction of the 5-carbon aliphatic chain to provide acetal **F**. Reduction of the resulting double bond and acetal deprotection would furnish cyclohexanone **G** which would then be subjected to the alkylation of both α-positions of the cyclohexanone. On the grounds of our previous experience in the formal synthesis of *Myrioneuron* alkaloids, we envisaged the introduction of a [dimethyl(phenyl)silyl]methyl substituent as a surrogate of a hydroxymethyl that in subsequent steps would be used to introduce a 2-piperidone (D ring) (Scheme 3.4).

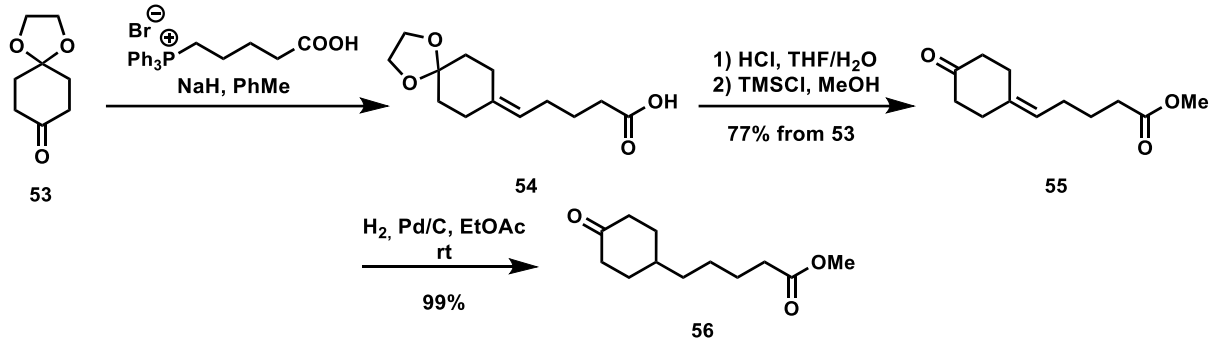


Scheme 3.4 Synthetic strategy for the synthesis of δ-ketoacid **C**

3.5.1 First Approach

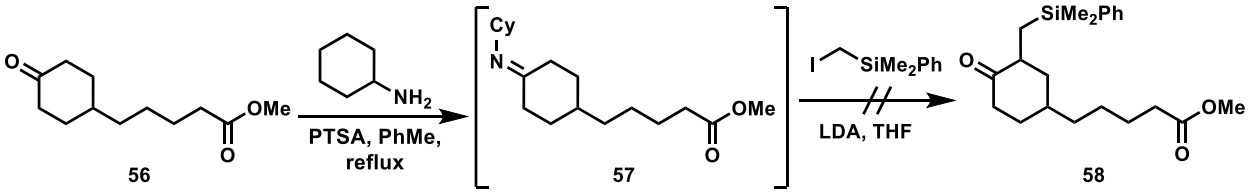
Starting from commercially available 1,4-cyclohexadione(monoethylene)acetal **53**, we performed a Wittig reaction using (4-carboxybutyl)triphenylphosphonium bromide and sodium hydride in toluene

to provide acid **54**.[75] Then, acid hydrolysis of the acetal and transformation of the carboxylic acid into the corresponding methyl ester with trimethylsilyl chloride, afforded ketoester **55** in good yield. Catalytic hydrogenation of **55** in presence of palladium afforded ketoester **56** in almost quantitative yield (Scheme 3.5).



Scheme 3.5 Obtention of ketoester **56**

Then, ketone **56** was transformed into cyclohexylamine-derived imine **57** and the introduction of the [dimethyl(phenyl)silyl]methyl moiety was attempted (Scheme 3.6).



Scheme 3.6 Alkylation attempt of **56**

However, attempts to alkylate the aza-enolate of cyclohexyl-imine **57** with (iodomethyl)dimethyl-(phenyl)silane[76] did not furnish ketoester **58**. In most cases, even the starting material was not recovered. Modification of the reaction conditions, such as the temperature or the base amount were unsuccessful. Upon inspecting the preparation of similar but simpler substrates,[77] it was concluded that the presence of an ester was incompatible with the alkylation through the aza-enolate of **57**. The use of alternative nucleophilic species derived from **56** also did not yield the alkylation product. In light of the results, we decided to slightly change the strategy for the synthesis of the cyclocondensation precursor.

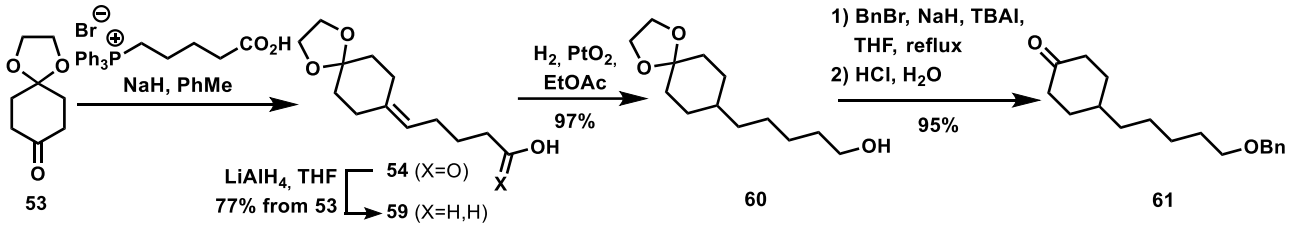
[75] Harada, K.; Mizukami, J.; Kadowaki, S.; Matsuda, I.; Watanabe, T.; Oe, Y.; Kodama, Y.; Aoki, K.; Suwa, K.; Fukuda, S.; Yata, S.; Inaba, T. *Bioorg. Med. Chem. Lett.* **2018,** *28*, 1228-1233.

[76] Prepared starting from (chloromethyl)dimethyl(phenyl)silane through a Finkelstein reaction as described in: Mercadante, M. A.; Kelly, C. B.; Hamlin, T. A.; Delle Chiaie, K.R.; Drago, M. D.; Duffy, K. K.; Dumas, M. T.; Fager, D. C.; Glod, B. L.C.; Hansen, K. E.; Hill, C. R.; Leising, R. M.; Lynes, C. L.; MacInnis, A.E.; McGohey, M. R.; Murray, S. A.; Piquette, M. C.; Roy, S. L.; Smith, R.M.; Sullivan, K. R.; Truong, B. H.; Vailonis, K. M.; Gorbatyuk, V.; Leadbeater, N. E.; Tilley, L. J. *Chem. Sci.* **2014**, *5*, 3983−3994.

[77] Ghirardi, E. Enantio- and Diastereoselective Cyclocondensation Reactions. Stereocontrolled Access to Azabicycles and Application to Natural Product Synthesis. Ph.D. Thesis, Universitat de Barcelona, Barcelona, Spain, 2016.

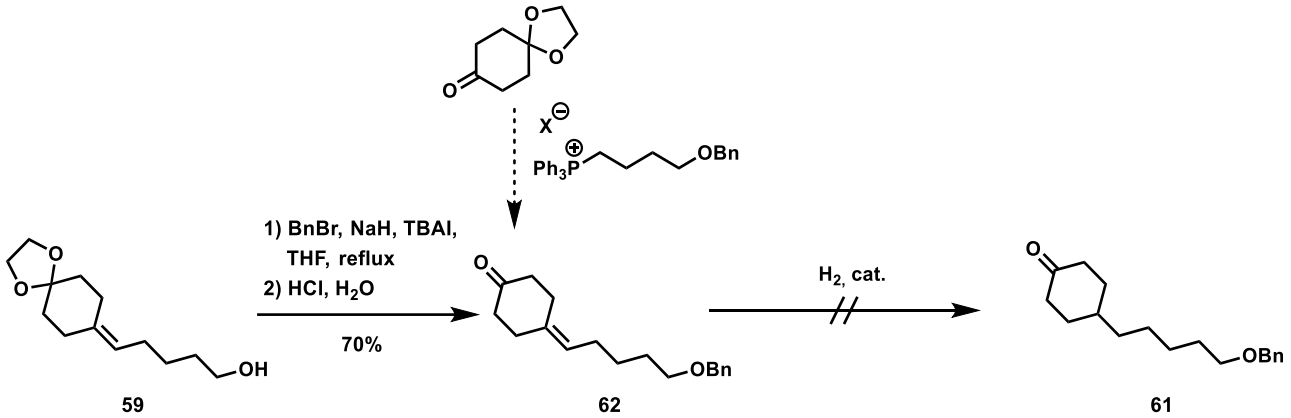
3.5.2 Second Approach

Given the difficulties encountered in the first approach, attributable to the ester functionality, we decided to change the pending group in the aliphatic chain and employ a benzylic ether. With this purpose in mind, we first performed the same Wittig reaction to provide acid **54**. Lithium aluminum hydride reduction of **54** provided alcohol **59** in good yield and the subsequent hydrogenation of the double bond in presence of platinum oxide afforded alcohol **60** with excellent yield. Protection of the aliphatic alcohol with benzyl bromide followed by acid-mediated acetal hydrolysis gave ketone **61** in good yield (Scheme 3.7).



Scheme 3.7 Synthesis of ketone **61**

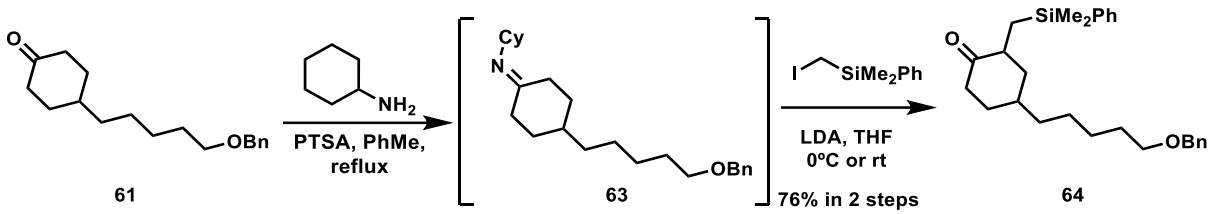
With the aim of simplifying the sequence leading to **61** from **53**, we envisioned the incorporation of the aliphatic chain with the benzylated alcohol already present. However, we first decided to test the hydrogenation of the double bond in the presence of the benzyl ether. Benzylation of alcohol **59** and deprotection of the corresponding acetal provided ketone **62** in good yield. Unfortunately, upon testing various hydrogenation conditions, none of the assays yielded the desired product **61**. The use of harsher hydrogenation conditions afforded the reduction product but also promoted the hydrogenolysis of the benzyl ether. Given these results, this approach was discarded (Scheme 3.8).



Scheme 3.8 Strategy simplification assays

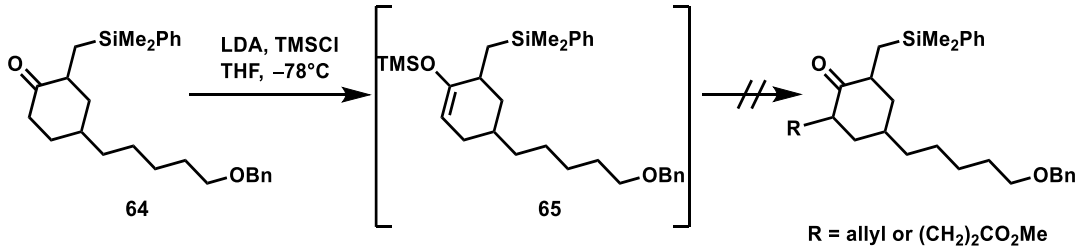
With ketone **61** in hand, we proceeded with the introduction of the methylsilyl moiety. Using the same procedure as with **56** (Scheme 3.6), ketone **61** was transformed into cyclohexylamine-derived imine **63** under standard conditions. Then, treatment of imine **63** with lithium(diisopropyl)amide

generated the corresponding aza-enolate which, upon addition (iodomethyl)dimethyl(phenyl)silane, provided ketone **64** in good yield (Scheme 3.9).



Scheme 3.9 Obtention of ketone **64**

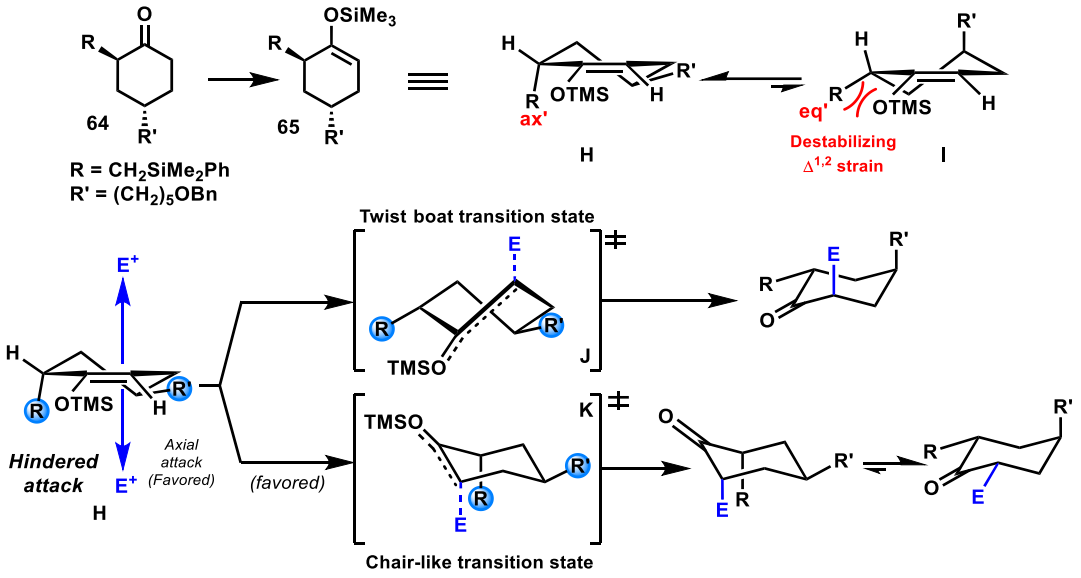
Next, to obtain the required precursor for the cyclocondensation studies, the introduction of a propionate on the free α-position of ketone **64** chain was required. Initially, the classical Stork enamine alkylation with methyl acrylate, which was successfully used for the preparation of the dimethyl analogue **31** (Scheme 2.47), was attempted. However, all efforts to prepare enamine derivatives of **64** resulted in failure. For this reason, the trimethylsilyl enol ether **65** was regioselectively prepared by treatment of **64** with LDA and TMSCl at low temperature.[78] Again, the introduction of a propionate or an allyl chain by treatment of **65** with methyl acrylate or diallyl carbonate, respectively, did not afford the expected result (Scheme 3.10).



Scheme 3.10 First approach for the alkylation of **64**

The justification for this occurrence can be found in the transition states leading to the desired alkylated products (Scheme 3.11).[79]

[78] House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* **1964**, *34*, 2324-2336.
[79] Stoltz, B.M.; Bennett, N.B.; Duquette, D.C.; Goldberg, A.F.G.; Liu, Y.; Loewinger, M. Alkylations of Enols and Enolates. In *Comprehensive Organic Synthesis*, Vol. 3, Elsevier, Amsterdam, **2014**, pp. 1-55.

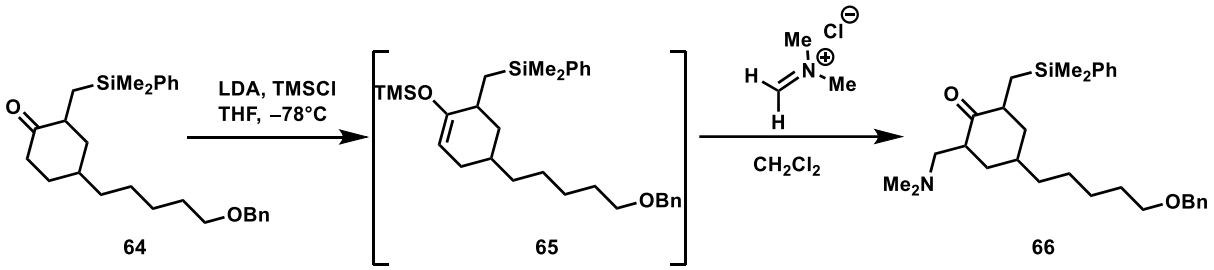


Scheme 3.11 Stereoelectronic issues leading to the alkylation of 2,4-disubstituted cyclohexanones

The spectroscopic data indicates that compound **64** contains R and R' in a *trans* disposition. Upon its transformation into silyl enol ether **65**, it would adopt an energy-minimized half-chair conformation (**H**) in which these substituents would be in a pseudo-axial disposition to avoid repulsive interactions between the trimethylsilyloxy and the R substituent ($\Delta^{1,2}$-strain), interactions that would occur in chair conformation **I**. An axial attack of the electrophile, under stereoelectronic control, from the *Si* face (below) would lead to the formation of a more stable chair-like transition state **K** than the attack from the *Re* face (above) which would lead to the formation of twist-boat transition state **J**, energetically less favorable. However, the axial attack of electrophiles such as methyl acrylate or diallyl carbonate from the *Si* face is severely hindered by the bulky alkyl axial substituent R in a relative 1,3-position with respect to the nucleophilic carbon of the silyl enol ether.

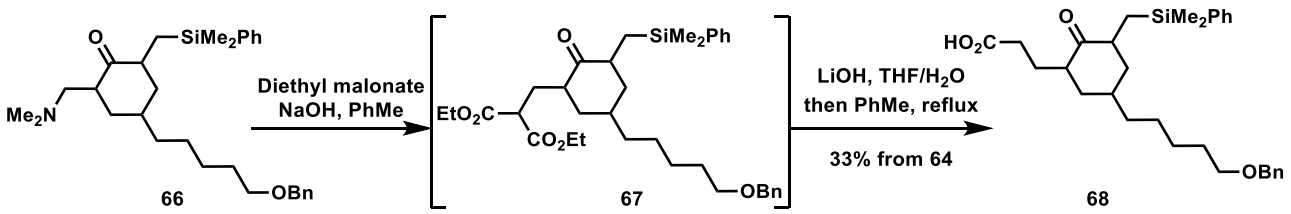
To circumvent this problem, we performed a multistep procedure consisting of treatment of trimethylsilyl enol ether **65** with the highly reactive cationic Böhme salt (an Eschenmoser salt analogous with a chlorine counteranion) that allows the α-aminomethyl alkylation of sterically hindered ketones.[80] This reaction satisfactorily afforded the corresponding (dimethylamino)methyl cyclohexanone derivative **66** (Scheme 3.12).[81]

[80] Kinast, G.; Tietze, L-F. *Angew. Chem. Int. Ed.* **1976**, *15*, 239-240.
[81] Danishefsky, S.; Prisbylla, M.; Lipisko, B. *Tetrahedron Lett.* **1980**, *21*, 805-808.



Scheme 3.12 Synthesis of ketoamine **66**

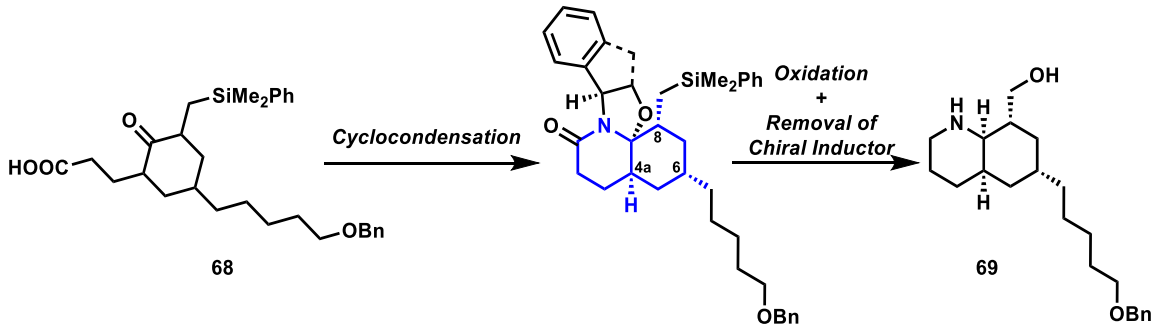
Subsequent addition of diethyl malonate to **66** under basic conditions, to afford diester **67**,[82] followed by hydrolysis of the resulting diester and thermal decarboxylation conducted to δ-ketoacid **68** (Scheme 3.13).



Scheme 3.13 Synthesis of ketoacid **68**

3.6 Assembly of the C-6/C-8 Disubstituted *cis*-DHQ Core

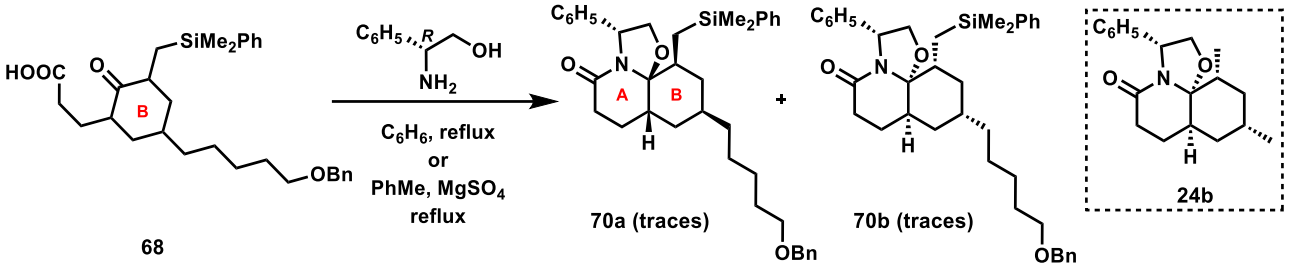
With the obtention of δ-ketoacid **68** the assembly of DHQ core was next. For that, we planned on using the cyclocondensation studied in the previous chapter to obtain a lactam with the desired configuration at C-4a, C-6, and C-8 (DHQ numbering). Following the same sequence employed in previous synthesis,[60] oxidation of the silyl moiety followed by the stereoselective removal of the chiral inductor would provide 6,8-disubstituted *cis*-DHQ **69** bearing the appropriate functionalities (Scheme 3.14).



Scheme 3.14 Synthetic strategy for the obtention of **69**

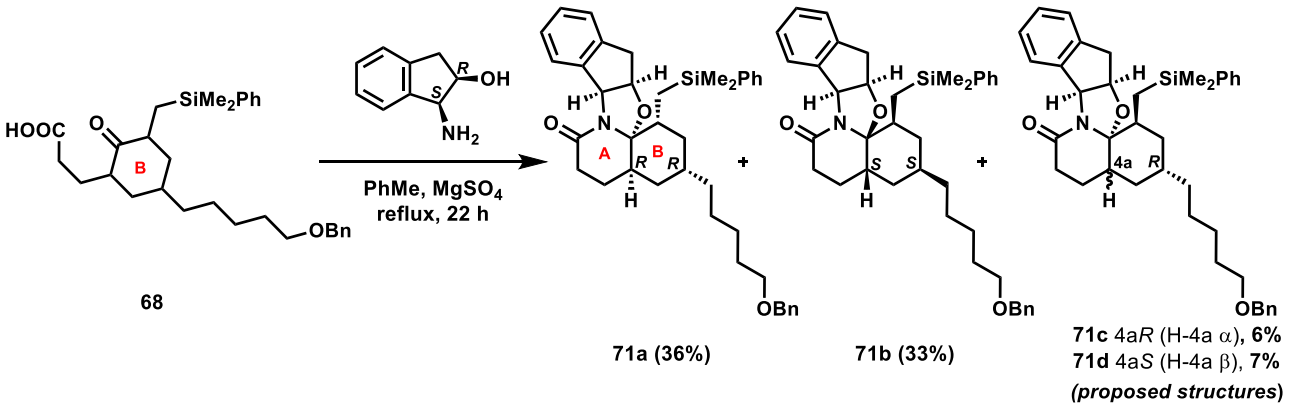
[82] House, H. O.; Schellenbaum, M. *J. Org. Chem.* **1963**, *28*, *1*, 34-38.

Initially, the cyclocondensation of **68** was attempted using the conditions developed in the previous chapter: (*R*)-phenylglycinol in refluxing benzene. This approach had previously led to the stereoselective formation of disubstituted lactam **24b**, which contained the desired configuration in the DHQ ring for the synthesis of the alkaloid. Unfortunately, starting material was mostly recovered, with small amounts of the expected lactams (**70a** and **70b**). Slight changes in the reaction parameters proved unsuccessful. The use of a higher boiling point solvent or the addition of magnesium sulfate as a drying agent to the reaction vessel seemed to yield similar results (Scheme 3.15).



Scheme 3.15 Cyclocondensation of **68** with (*R*)-phenylglycinol

On the other hand, the use of (1*S*,2*R*)-*cis*-aminoindanol, a rigid analog of (*R*)-phenylglycinol, in refluxing toluene with anhydrous $MgSO_4$ as drying agent,[60,77] allowed the stereoselective obtention of lactams **71a** and **71b** in good yields. As seen in the previous chapter, the major products of the cyclocondensation differ in the configuration of the four stereocenters on the decahydroquinoline moiety (Scheme 3.16).

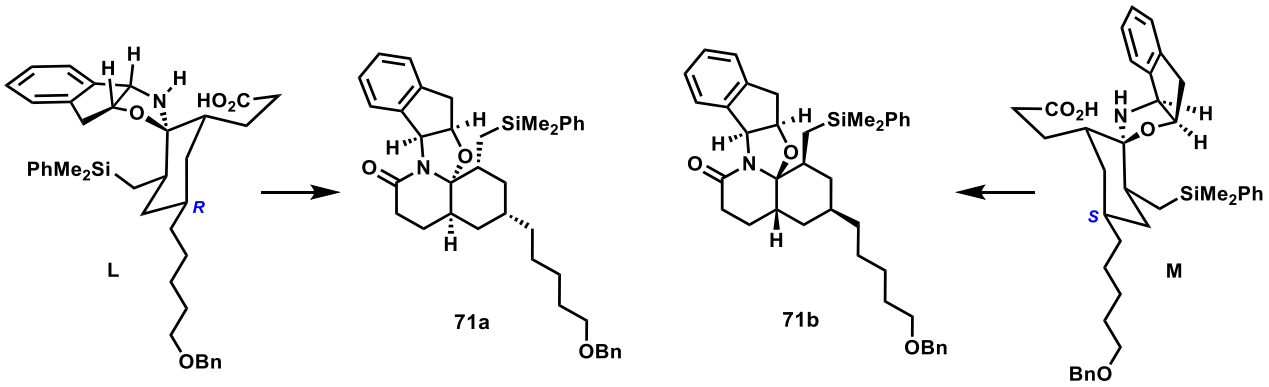


Scheme 3.16 Cyclocondensation of **68** with (1*S*,2*R*)-*cis*-aminoindanol

Lactam **71a** was isolated together with small amounts of **71c**, a C-8 epimer of **71a**, which could not be separated by column chromatography at this stage, in 42% yield. Lactam **71b** was obtained in 33% yield. A fourth lactam, **71d** was also isolated in small amount. The configuration of the major products was deduced by comparison with similar compounds previously prepared by the group. In the case of the minor isomers the proposed structures are based on the cyclocondensation assays performed in

Chapter 2 in which, all minor isomers of the cyclocondensation were determined by XRD analysis.[71,83]

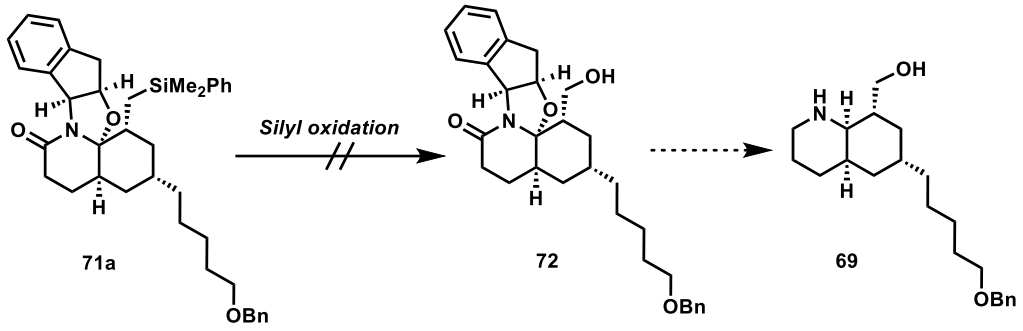
The high stereoselectivity and stereochemical outcome in the formation of lactams **71a** and **71b** can be rationalized by considering that the reaction of (1*S*,2*R*)-*cis*-aminoindanol with oxoacid **68** can afford a mixture of up to sixteen diastereomeric spiro-oxazolidines.[84] The eight oxazolidine intermediates having an *R* configuration at the non-isomerizable stereocenter are in equilibrium through the corresponding imine-enamines resulting from opening of the oxazolidine. The subsequent irreversible lactamization takes place preferentially from oxazolidine **L**, in which the two substituents on the cyclohexane ring are equatorial, leading to lactam **71a**. The same mechanistic considerations can be used to explain the stereoselective formation of lactam **71b**. From the eight diastereomeric oxazolidines in equilibrium having an *S* configuration at the non-isomerizable stereocenter, the lactamization step takes place faster from oxazolidine **M** (Scheme 3.17).



Scheme 3.17 Cyclocondensation pathway for the obtention of **71a** and **71b**

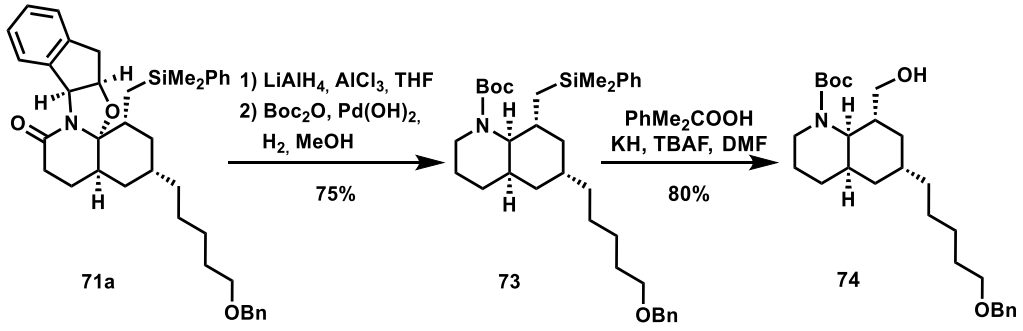
After assembling the AB ring system, we proceeded with the oxidation of the dimethylphenyl silyl group of **58a** to transform it into the corresponding hydroxyl group (Scheme 3.18).

[83] (1*S*,2*R*)-*cis*-aminoindanol is the equivalent of (*S*)-phenylglycinol; therefore, the minor lactams contain the opposite configuration to those isolated in Section 2.4.2.
[84] See Scheme 2.50 for oxazolidine formation.



Scheme 3.18 First attempt on the synthesis of aminoalcohol **69**

However, none of the Fleming-Tamao oxidation methods provided alcohol **72**. In most instances, complex crude mixtures were obtained. As a result, we prioritized the removal of the chiral inductor through the previously mentioned two-step reductive removal process. Lactam **71a**, displaying the appropriate configuration at the four stereocenters of the decahydroquinoline nucleus for the synthesis of (–)-schoberine B, was treated with $LiAlH_4$ to reduce the carbonyl of the lactam with concomitant stereoselective oxazolidine ring opening. Subsequent *N*-debenzylation by catalytic hydrogenation using the Pearlman´s catalyst in the presence of Boc_2O stereoselectively afforded the *cis*-decahydroquinoline **73** as a single isomer in good overall yield. With *cis*-DHQ **73** in hand, we revisited the oxidation experiments. Given our previous results, we opted for the modified oxidation conditions developed by Worpel.[85] In contrast to the conventional Tamao-Fleming acidic conditions ($HBF_4{\cdot}Et_2O$, *m*-CPBA, KF), which produced a complex mixture of byproducts, the utilization of cumene hydroperoxide as an oxidant under basic conditions provided *cis*-DHQ **74** in good yield (Scheme 3.19).



Scheme 3.19 Synthesis of *cis*-DHQ **74**

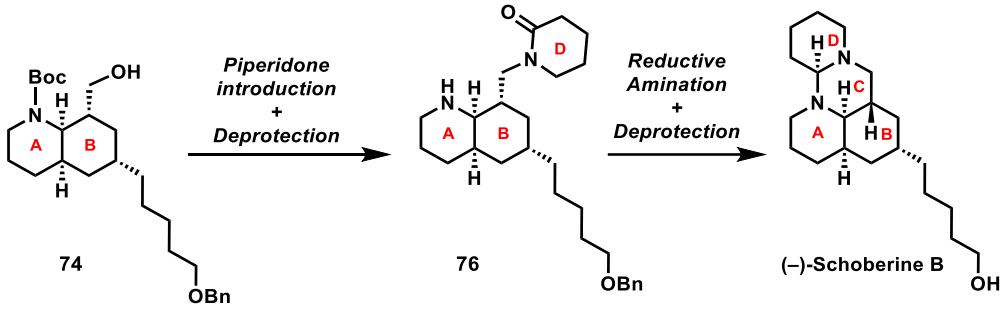
The Woerpel variation of the Fleming-Tamao method proves to be a superior unmasking technique, as it eliminates the need for harsh reagents like HBF_4, Br_2, or $Hg(OAc)_2$, typically used to introduce

[85] a) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044-6046; b) Gilles, P.; Py, S. *Org. Lett.* **2012**, *14*, 1042-1045.

a heteroatom prior to oxidation in the acidic and electrophilic variants of this reaction.[86] This, in turn, allows for the presence of a broader range of functionalities.

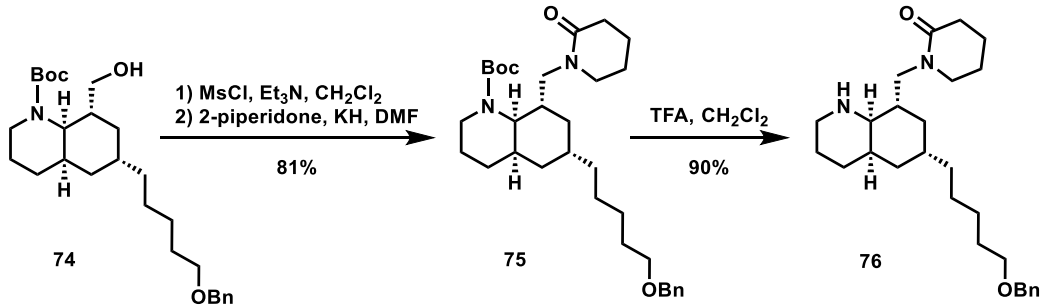
3.7 Synthesis of (–)-Schoberine B

With an efficient procedure for the preparation of *cis*-DHQ **74**, the only remaining steps involved the incorporation of the C and D rings of the natural product. To achieve this, we were inspired by the work of Bodo on the synthesis of schoberine, a similar alkaloid lacking the hydroxypentyl substituent.[42e] Introduction of a 2-piperidone on the hydroxymethyl substituent, followed by closure of the C ring would complete the tetracyclic skeleton of (–)-schoberine B (Scheme 3.20).



Scheme 3.20 Synthetic strategy for the late stages of the synthesis

Introduction of the piperidine D-ring was performed by first transforming the hydroxyl group of **74** into a methanesulfonyl ester using standard procedures followed by treatment of the resulting sulfonate with the anion of 2-piperidone to afford *cis*-DHQ **75** in good yield. TFA-promoted deprotection of the *N*-Boc moiety afforded secondary amine **76** with excellent yield (Scheme 3.21).

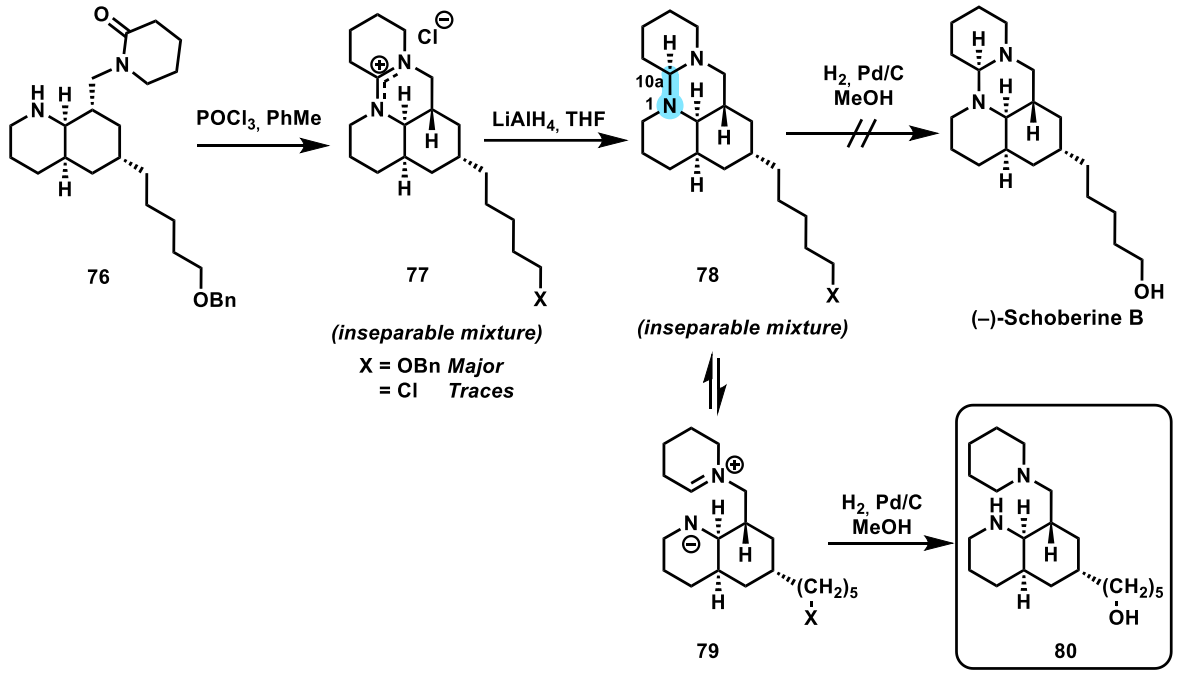


Scheme 3.21 Obtention of *cis*-DHQ **76**

Closure of the diazine C-ring was carried out by treatment of **76** with $POCl_3$ under refluxing toluene to provide intermediate iminium salt **77**.[42e] Treatment of **76** with $POCl_3$ provoked a partial deoxychlorination of the benzyl ether. The formation of this byproduct was minimized by shortening the reaction time but was detrimental for the overall yield of the transformation. Reduction of the

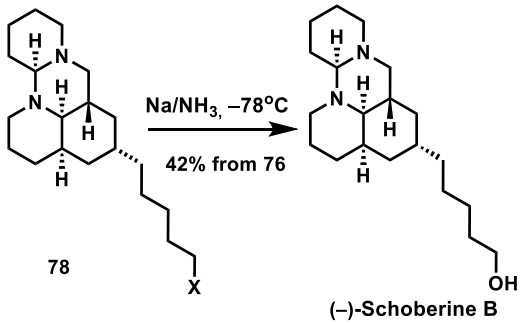
[86] a) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29-31; b) Fleming, I.; Sanderson, P.E.J. *Tetrahedron Lett.* **1987**, *28*, 4229-4232.

iminium salt with lithium aluminum hydride afforded aminal **78**. The removal of the benzyl group by catalytic hydrogenation cleaved aminal moiety between N-1 and C-10a and afforded tricyclic amine **80** instead of the target molecule. A revision of old literature on *Myrioneuron* alkaloids revealed that schoberine undergoes a similar reduction under catalytic hydrogenation conditions. [87] This is caused by an equilibrium present between aminal **78** and the iminium salt **79**, which in the presence of hydrogenation conditions, reduces to **80** (Scheme 3.22).



Scheme 3.22 Synthesis of aminal **78** and obtention of byproduct **80**

To circumvent this reactivity issue, we removed the benzyl group with sodium in liquid ammonia (Scheme 3.23).

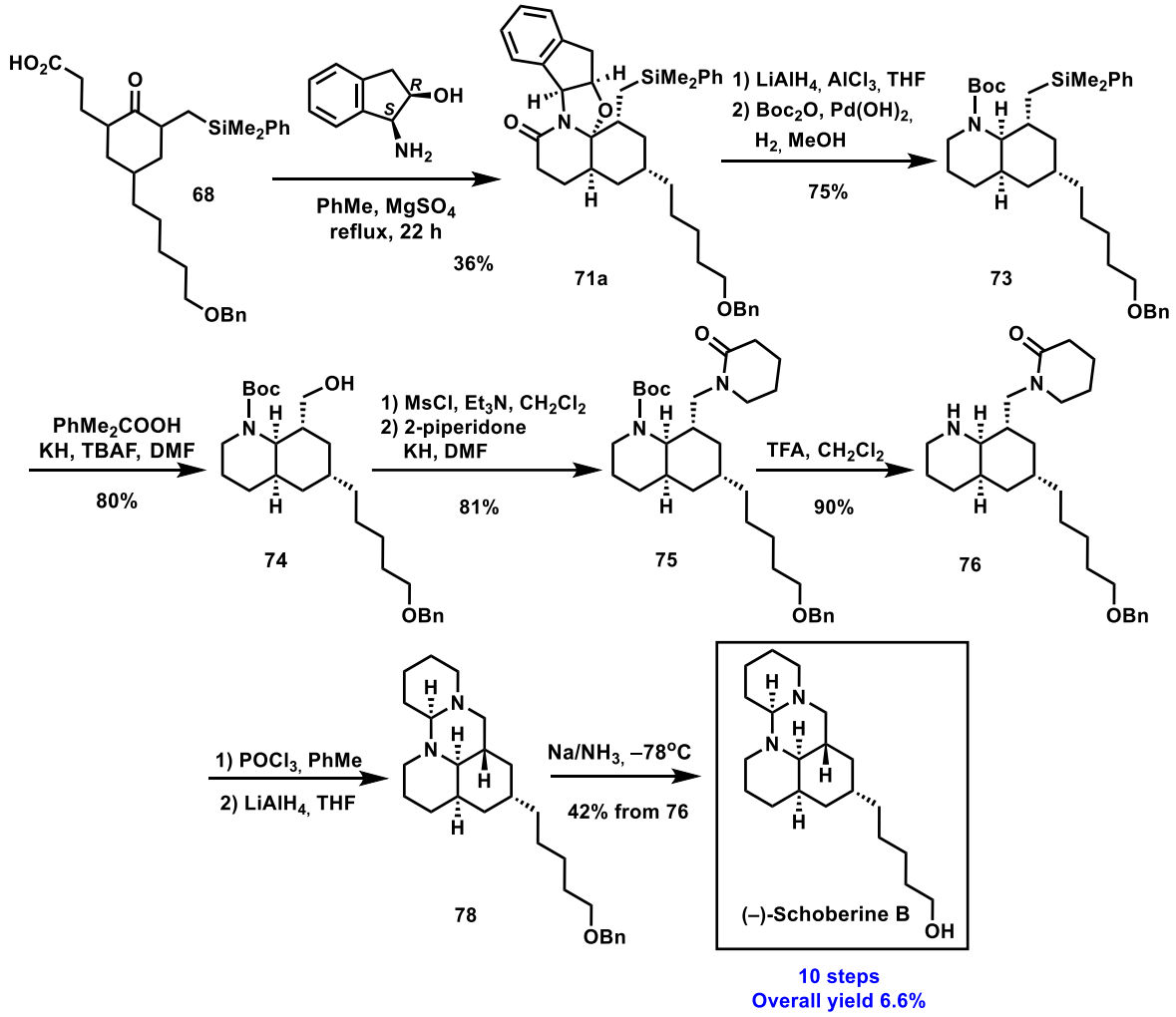


Scheme 3.23 Obtention of (–)-schoberine B

[87] a) Tashkhodzhaev, B.; Ibragimov, A.A.; Ibragimov, B.T.; Yunusov, S.Yu. *Chem. Nat. Compd*. **1989**, *25*, 24-28. b) Tulyaganov, T. S.; Allaberdiev, F. Kh. *Chem. Nat. Compd.* **2001**, *37*, 556-558.

This deprotection method allowed the removal of the benzyl group with and completed the first total synthesis (–)-schoberine B. The synthesis of this alkaloid was achieved in 10 steps from cyclohexanone **68** in an overall yield of 6.6% (Scheme 3.24).

NMR data and specific rotation of synthetic (–)-schoberine B were coincident with those reported in the literature for the natural product confirming the proposed structure (See Section 6.2).[42k]

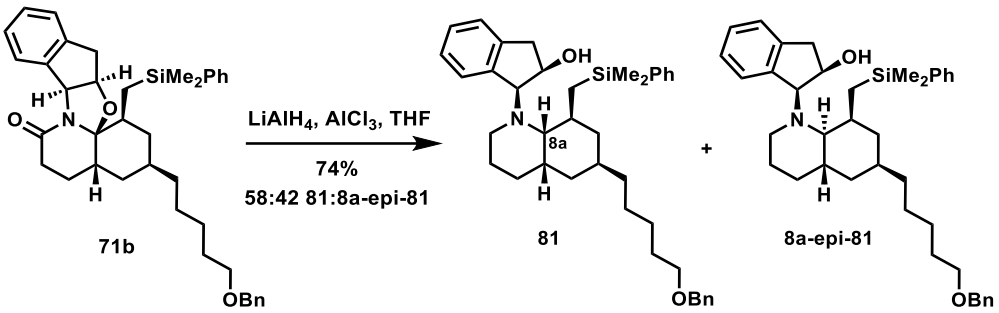


Scheme 3.24 Synthesis of (–)-schoberine B from ketoacid **68**

3.8 Synthesis of (+)-Schoberine B

To demonstrate the synthetic utility of chiral lactams obtained by cyclocondensation of racemic disubstituted 1-oxocyclohexanepropionates and enantiopure aminoalcohols for the preparation of both enantiomers of *cis*-decahydroquinoline derivatives of biological interest, we decided to synthesize (+)-schoberine B, the enantiomer of the natural product. To do that we first performed the reductive removal of the chiral inductor of lactam **71b**. Surprisingly, treatment with $LiAlH_4$ and $AlCl_3$ did not took place with the high *cis*-selectivity observed in previous works and afforded a mixture of

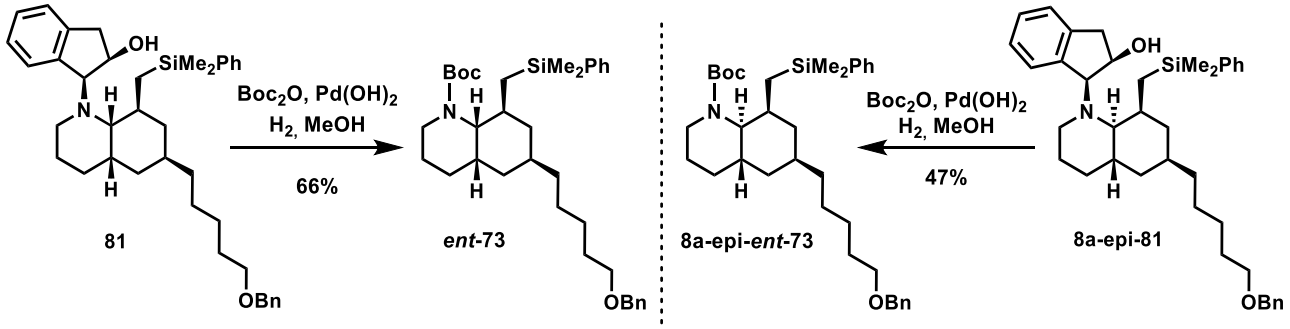
disubstituted *cis*- and *trans*-decahydroquinolines **81** and **8a-epi-81** as an almost equimolecular mixture, in good yield (Scheme 3.25).



Scheme 3.25 Reduction of **71b**

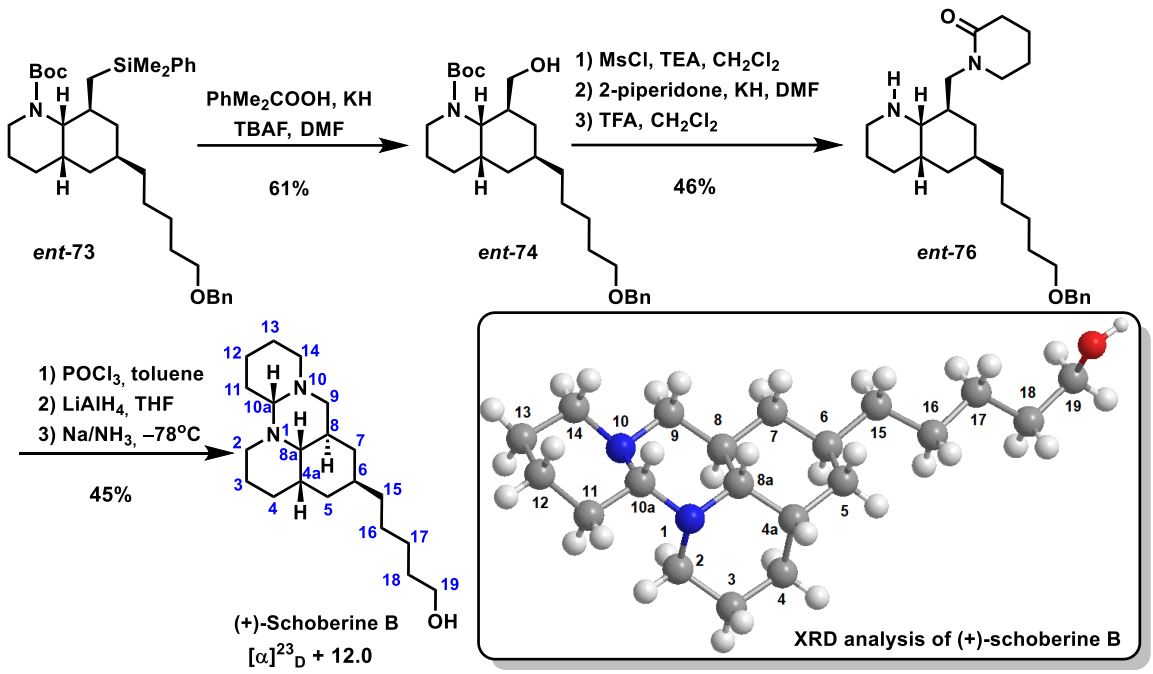
This stereochemical result could be attributed to the steric hindrance provoked by the bulky dimethylphenylsilyl group and dihydroindene moiety of the chiral inductor which lie over the *Re* face of the intermediate iminium salt, hampering the approach of the reducing aluminum reagent.

Debenzylation of **81** and **8a-epi-81** led to the obtention of *cis*-DHQ ***ent*-73** and *trans*-DHQ **8a-epi-*ent*-73** (Scheme 3.26).



Scheme 3.26 Debenzylation of **81** and **8a-epi-81**

Isomer ***ent*-73** was transformed into (+)-schoberine B by using the same synthetic sequence described above for the synthesis of (–)-schoberine B. NMR data of synthetic (+)-schoberine B were coincident with those reported in the literature for the natural product. On the other hand, its specific rotation matched the absolute value described for the natural product but with the opposite sign. Additionally, this isomer was successfully crystallized, and its structure confirmed by XRD analysis (Scheme 3.27).



Scheme 3.27 Obtention of (+)-schoberine B

3.9 Conclusions

We have thus accomplished the first enantioselective total synthesis of (–)-schoberine B in 10 steps from cyclohexanone **68**, achieving an overall yield of 6.6%. Additionally, the synthesis of its enantiomer, (+)-schoberine B, was also completed. These syntheses involved a key stereoselective cyclocondensation process, enabling the generation and definition of more than half of the stereocenters present in the target molecule in a single step. The stereoselective obtention of lactams **71a** and **71b** with opposite configurations in the DHQ nucleus allowed the synthesis of both enantiomers of the natural product and the confirmation of its structure spectroscopically and by XRD analysis.[88]

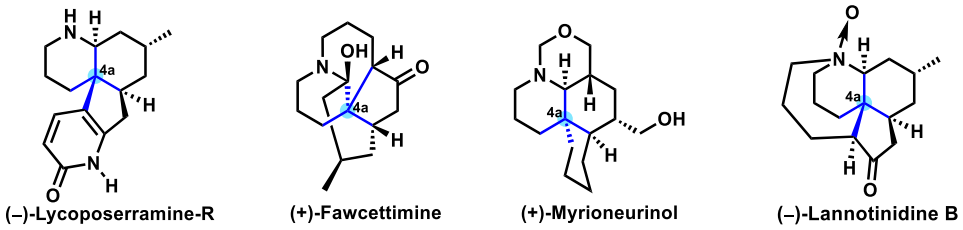
These results highlight and reinforce the robustness and usefulness of the synthetic methodology developed in the previous chapter and manifest its potential for the synthesis of other alkaloids containing disubstituted *cis*-DHQs.

[88] Calbó, A.; Griera, R.; Bosch, J.; Amat, M. *Adv. Synth. Catal.* **2024**, 10.1002/adsc.202301062.

4 Enantioselective Synthesis of C-4a/C-8 Substituted *cis*-Decahydroquinolines

Organic compounds containing all-carbon-substituted quaternary stereocenters are widely present in many natural products as well as biologically interesting molecules as they usually display unique bioactivities due to their rigid three-dimensional structure. However, the stereocontrolled generation of all-carbon quaternary carbon centers with a well-defined configuration constitutes one of the more challenging issues in organic synthesis due to the steric hindrance imposed by four different carbon substituents.[89]

Decahydroquinolines with an all-carbon-substituted quaternary stereocenter at C-4a constitute a structural motif present in many natural products. Thus, as mentioned in Section 1.2, some DHQ alkaloids belonging to the *Myrioneuron* or *Lycopodium* families contain this structural feature at the C-4a fused position (Scheme 4.1).

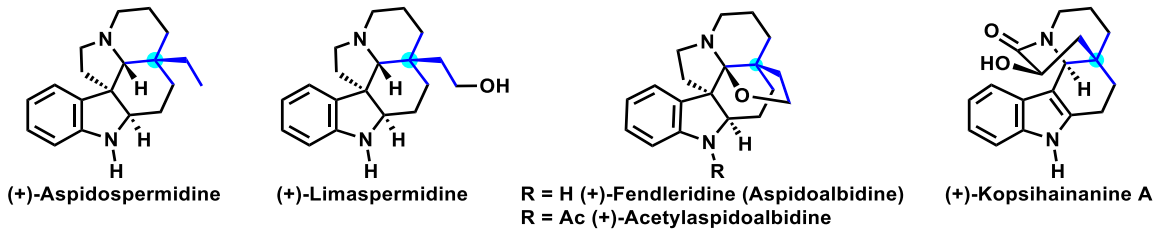


Scheme 4.1 DHQ alkaloids containing quaternary stereocenters

On the other hand, the alkaloids of the *Aspidosperma* family, widely used in traditional medicine due to their pharmacological properties and biological activities, contain highly congested polycyclic frameworks with multiple chiral centers. These intricate molecular structures, along with their pharmacological properties, have spurred intense investigation over the past few decades on their synthesis.[90] A structural feature common to all the *Aspidosperma* alkaloids is the presence of a quaternary stereocenter at the C-4a position of the decahydroquinoline moiety (Scheme 4.2).

[89] a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388-401; b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367; c) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181-191; d) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B.M. *Acc. Chem. Res.* **2015**, *48*, 740-751; e) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330-7396; f) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908-8976; g) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333-9403; h) Feng, J.; Holmes, M.; Krische, M. J. *Chem. Rev.* **2017**, *117*, 12564-12580; i) Li, Y.; Xu, S. *Chem. Eur. J.* **2018**, *24*, 16218-16245; j) Ping, Y.; Li, Y.; Zhu, J.; Kong, W. *Angew. Chem. Int. Ed.* **2019**, *58*, 1562-1573.

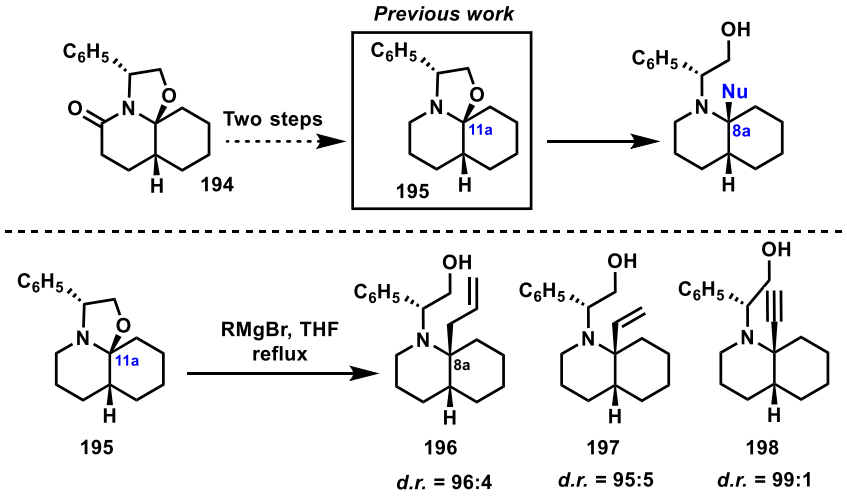
[90] a) Saxton J. E. Synthesis of the *Aspidosperma* Alkaloids. In *The Alkaloids: Chemistry and Biology*, Vol. 50, Academic Press, San Diego, **1998**; pp. 343-376; b) Ishikura, M; Yamada, K.; Abe, T. *Nat. Prod. Rep.* **2010**, *27*, 1630-1680; c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694-752; d) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2015**, *32*, 1389-1471.



Scheme 4.2 *Aspidosperma* alkaloids

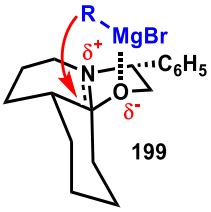
4.1 Decahydroquinolines with Quaternary Stereocenters: Group Precedents

In previous work, the group prepared oxazolo-decahydroquinoline **195** by chemoselective reduction of the carbonyl present in the unsubstituted chiral phenyl glycinol-derived tricyclic lactam **194** and demonstrated its synthetic utility in the stereoselective generation of C-8a quaternary stereocenters. Treatment of **194** with allyl, vinyl or ethynyl magnesium bromide afforded compounds **196**, **197**, and **198**, respectively, in excellent stereoselectivity and good to moderate yields.[63] It is worth mentioning that tricyclic lactam **194** was unreactive when treated with a variety of nucleophiles due to amide-like nature of the nitrogen (Scheme 4.3).



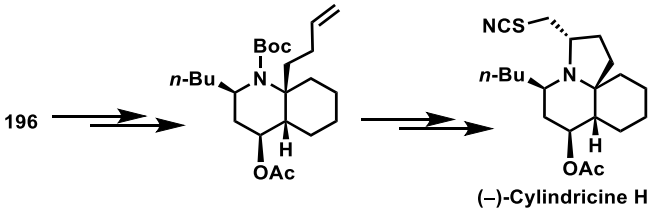
Scheme 4.3 Obtention of C-8a substituted *cis*-DHQs

The proposed mechanism involves the coordination of the Grignard reagent to the oxygen atom of the oxazolidine generating an incipient iminium ion (**199**) which undergoes the attack of the carbon nucleophile from the same face of the C-O bond leading to the *cis* isomer (Scheme 4.4).



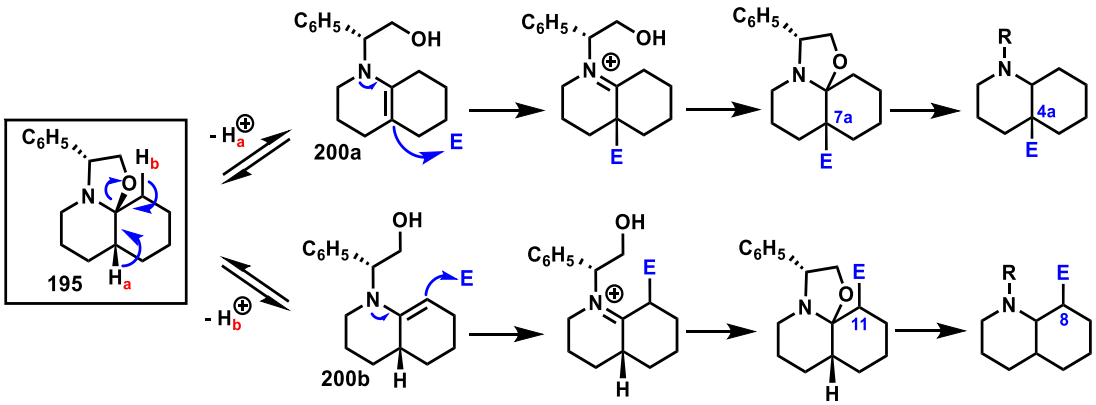
Scheme 4.4 Proposed intermediate for the introduction of nucleophiles into C-8a position

The synthetic utility of this procedure was demonstrated with the total synthesis of the marine alkaloid (–)-cylindricine H from the allyl-derivative **196** (Scheme 4.5).[63]



Scheme 4.5 (–)-Cylindricine H total synthesis

In the present work, we decided to further explore the versatility of oxazolo-DHQ **195** for the preparation of C-4a or C-8 substituted DHQs. Thus, potentially, **195** can afford two regioisomeric enamines, **200a** and **200b**, which can interact with appropriate electrophiles to give C-7a or C-11 substituted oxazolo-DHQs, respectively. Subsequent removal of the 2-phenylethanol residue of the chiral inductor would provide the target C-4a or C-8 substituted DHQs (Scheme 4.6).



Scheme 4.6 Potential reactivity of **195** with electrophiles

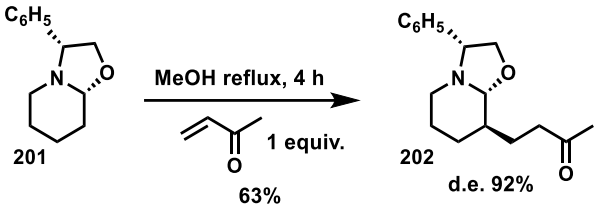
4.2 Objectives

Therefore, the main objective of the work included in this chapter was to assess the scope and limitations in the introduction of substituents at the C-4a and/or C-8 positions of the DHQ nucleus from (*R*)-phenylglycinol oxazolo-DHQ **195** by considering its hemiaminal moiety a latent form of enamines **200a** and **200b**. In particular, we focused our interest on the control of the stereo- and regioselectivities by manipulating the reaction conditions and/or the selection of the electrophile.

4.3 Enantioselective Synthesis of C-4a Substituted Decahydroquinolines

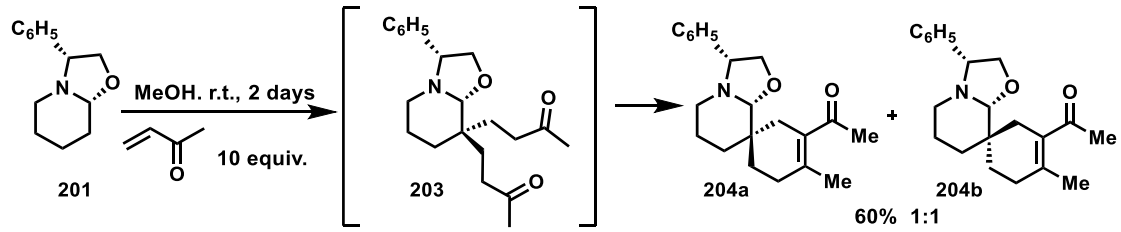
4.3.1 (*R*)-Phenylglycinol-Derived Oxazolopiperidines as 2-Piperideine (enamine) Equivalents. The H.-P. Husson work.

In the context of his studies on the use of phenylglycinol-derived oxazolopiperidines, H.-P. Husson reported that treatment of compound **201** with one equivalent of methyl vinyl ketone (MVK) in refluxing methanol for a short period of time stereoselectively afforded the 3-oxobutyl derivative **202**, by conjugate addition of the enamine resulting from opening of the oxazolidine **202** to the enone.[91] The stereochemical outcome of the reaction was rationalized by the authors invoking stereoelectronic and steric effects. However, the equilibration of diastereomers of **202** through the corresponding enamine to give the thermodynamically more stable isomer (**202**) cannot be discarded (Scheme 4.7).



Scheme 4.7 Reaction of **201** with MVK

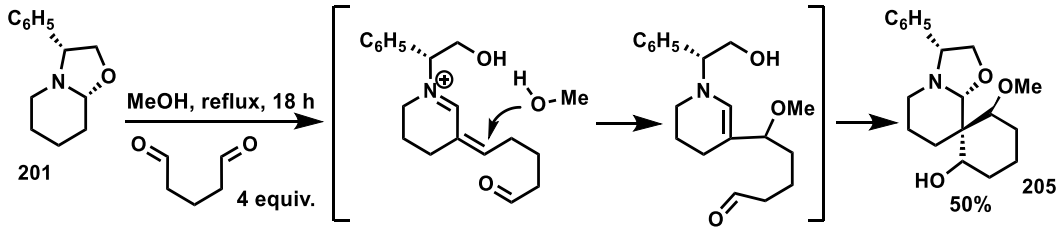
When increasing the amount of methyl vinyl ketone to 10 equivalents and the reaction mixture was left to stir at room temperature for two days, two sequential conjugate additions, through the corresponding enamines, took place. The resulting 8,8-bis-3-oxobutyl derivative **203** undergoes an intramolecular aldol reaction affording an equimolecular mixture of the two diastereomeric spiranic compounds **204a** and **204b** (Scheme 4.8).



Scheme 4.8 Obtention of spiranic compounds **204a** and **204b** from **195**

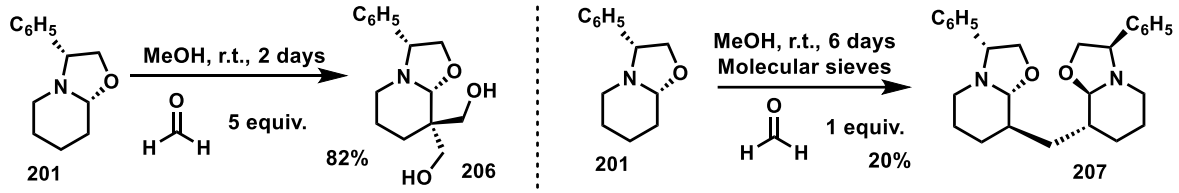
The use of glutaraldehyde as electrophile, instead of methyl vinyl ketone, provokes a double nucleophilic addition of the corresponding enamines to both carbaldehydes, leading again to a spiranic compound (**205**) (Scheme 4.9).

[91] Poupon, E.; François, D.; Kunesch, Husson, H.-P. *J. Org. Chem.* **2004**, *69*, 3836-3841.



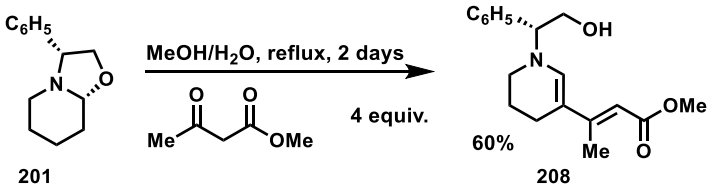
Scheme 4.9 Obtention of spiranic compound **205** from **195**

Treatment of compound **201** at room temperature with an excess of formaldehyde for two days afforded in 82% yield the bis-methanolic product **206** resulting from a double addition, whereas when using one equivalent of formaldehyde for a long reaction time, the dimeric compound **207** was observed in low yield (Scheme 4.10).



Scheme 4.10 Obtention of compounds **206** and **207** from **195**

Finally, the reaction of **201** with methyl 3-oxobutanoate provided the vinylogous urethane **208** resulting from addition of the enamine to the ketone followed by dehydration. In this case, the thermodynamically more stable conjugated system present in tetrahydropyridine **208** is obtained instead of the corresponding bicyclic oxazolopiperidine (Scheme 4.11).

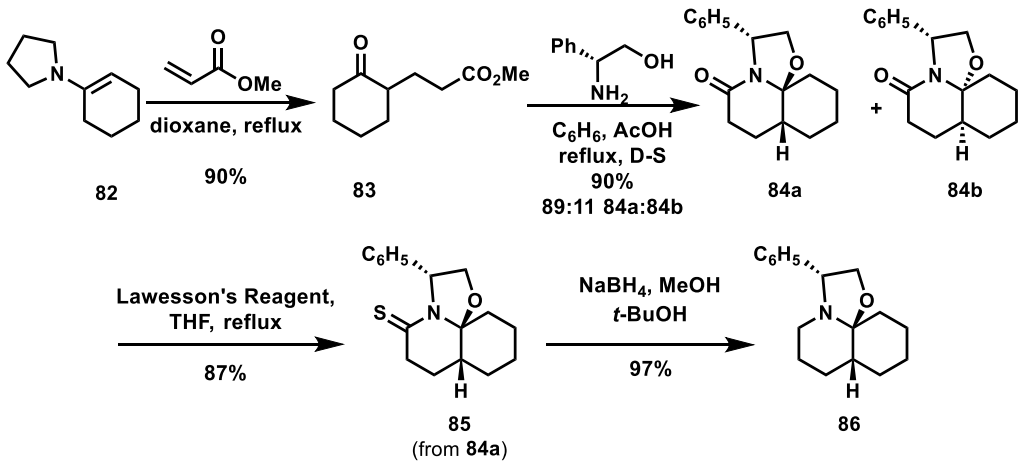


Scheme 4.11 Obtention of compound **208** from **195**

4.3.2 Preparation of Starting Material

In order to prepare the required oxazolodecahydroquinoline **86,** we followed the protocol reported by the group.[63] Addition of the commercially available 1-pyrrolidino-1-cyclohexene **82** to methyl acrylate followed by cyclocondensation of the resulting ketoester **83** with (*R*)-phenylglycinol provided lactam **84a** in excellent stereoselectively and high yield. Treatment of tricyclic lactam **84a** with Lawesson's reagent gave thiolactam **85**, which was chemoselectively reduced with sodium

borohydride. In this way, the oxazolo-DHQ **86** was obtained in excellent yield and no by-products resulting from the reductive opening of the oxazolidine moiety were observed (Scheme 4.12).[92]



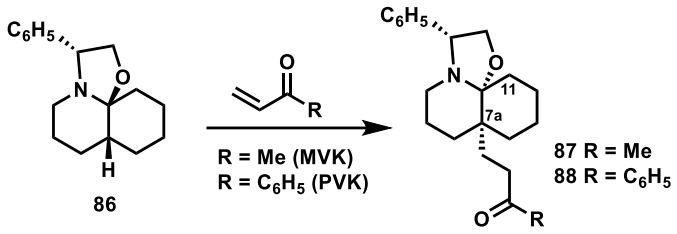
Scheme 4.12 Synthetic sequence for the obtention of amine **86**

4.3.3 Alkylation Assays

With amine **86** in hand, we proceeded to evaluate its behavior as a latent form of an enamine by treatment with a variety of electrophiles. For our first studies we decided to use methyl vinyl ketone, which had been successfully employed by H.-P. Husson and coworkers in their studies from (*R*)-phenylglycinol-derived oxazolopiperidine **195** (Scheme 4.7).[91] After several assays, we observed the best yields when heating a methanolic solution of **86** and 5 equivalents of methyl vinyl ketone under reflux temperature for 24 h. (Table 4.1, Entry 1) In all cases, the desired compound **87**, resulting from the attack of the intermediate enamine from the C-7a position, was observed as the only regio- and stereoisomer (Table 4.1). Similar results were observed when using phenyl vinyl ketone under the same reaction conditions. Thus, compound **88** was obtained in 76% yield again as the only regio- and stereoisomer detectable by spectroscopic methods (Table 4.1, Entry 4). The use of other solvents in the above reactions, such as dioxane or toluene, afforded the expected compounds **87** and **88** in lower yields.

The formation of **87** and **88** from the oxazolo-DHQ **86** can be considered a remarkable result as an all-carbon quaternary stereocenter is generated by means of an enamine intermediate (see Scheme 4.6) in which the only stereocenter is in an exocyclic position and on a substituent for which a free conformational rotation around the C-N bond is assumed. Therefore, a 1,4-chiral induction takes place from a single stereocenter located in a conformationally flexible position.

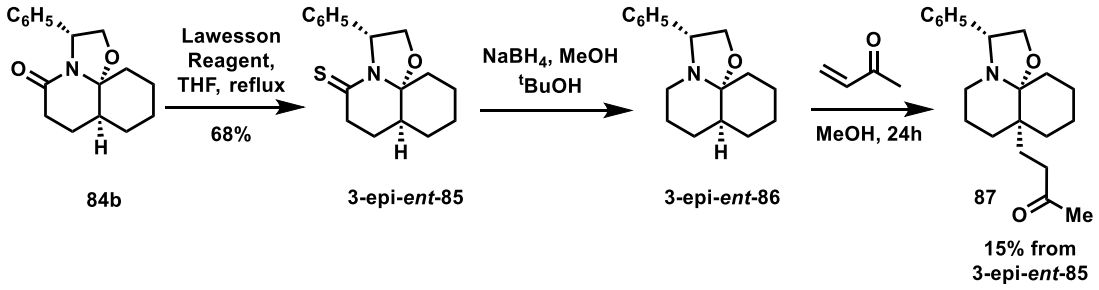
[92] The enumeration of compounds found in both the precedents and results sections adheres to distinct sequences.



Entry	Enone[1]	Solvent[2]	Product	Yield (%)
1	MVK	MeOH	**87**	69
2	MVK	Dioxane	**87**	65
3	MVK	PhMe	**87**	44
4	PVK	MeOH	**88**	76
5	PVK	Dioxane	**88**	43
6	PVK	PhMe	**88**	48

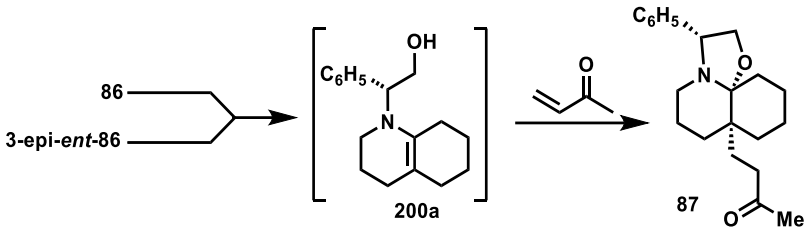
Table 4.1 Alkylation assays of **86** with MVK and PVK. [1] All reactions were carried out using 5 equivalents of MVK or PVK; [2] All reactions were performed at reflux temperature for 24 h.

To gain further insight about the reaction pathway, we subjected lactam **84b** to the same 2-step reductive treatment as **84a**. However, we observed that the resulting compound **3-epi-*ent*-86** was more unstable than its diastereomer **86** and, in addition, under the reaction conditions of the thioamide reduction, it underwent a partial reductive opening of the oxazolidine ring. For this reason, the crude mixture resulting from treatment of thioamide **3-epi-*ent*-85** with $NaBH_4$ was immediately subjected to reaction with methyl vinyl ketone under the same conditions as with **86** (Scheme 4.13).



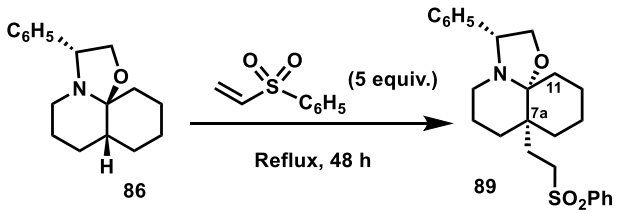
Scheme 4.13 Alkylation assay of **3-epi-*ent*-86** with methyl vinyl ketone

To our delight, amine **87** was obtained as the sole product, which confirmed that the alkylation reaction proceeds through the same enamine intermediate **200a**, in which the stereocenters at the C-7a and C-11a of **86** and **3-epi-*ent*-86** have been destroyed (Scheme 4.14). Again, as in the alkylation of **86**, no C-11 substituted products were detected in any of the assays.



Scheme 4.14 Alkylation of **86** and **3-epi-*ent*-86** through the same enamine intermediate **200a**

In order to increase the scope of the procedure, additional electrophiles were next tested. Treatment of the oxazolo-DHQ **86** with phenyl vinyl sulfone under the best reaction conditions observed in previous essays afforded compound **89** in poor yield (Table 4.2, Entry 1). An analysis of the reaction mixture revealed the presence of a compound resulting from the addition of methanol to phenyl vinyl sulfone, which is probably responsible for the consumption of the reagent. A change in the solvent from methanol to dioxane provided the desired product **89** in 51% yield, whereas in toluene a moderate 45% yield was observed. It is worth mentioning that compound **89** could not be separated from phenyl vinyl sulfone by column chromatography and this reagent had to be removed in subsequent steps. The phenyl-sulfone present in compound **89** constitutes a point of diversity due to the variety of further transformations in which this functional group can participate.[93]



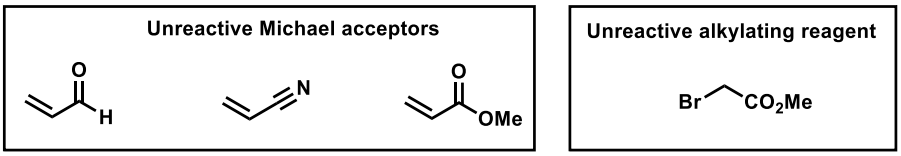
Entry	Solvent	Yield (%)[1]
1	MeOH	27
2	Dioxane	51
3	PhMe	45

Table 4.2 Alkylation assays of **86** with PVS. [1] Yield calculated by ^{1}H-NMR from a mixture of **89** and phenyl vinyl sulfone.

The absolute configuration of the quaternary stereocenter at C-7a was unambiguously determined by X-ray crystallographic analysis of a derivative of **89** (Scheme 4.22).

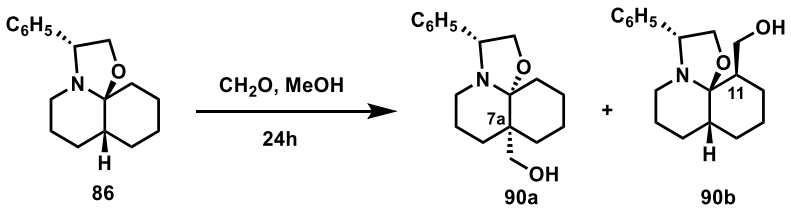
All attempts to induce the reaction of **86** with other Michael acceptors, such as acrylaldehyde, acrylonitrile or methyl acrylate, under the above reaction conditions, resulted in failure. Similarly, the alkylating reagent methyl bromoacetate did not afford the expected product (Scheme 4.15).

[93] Lo, J.C.; Kim, D.; Pan, C.-M.; Edwards, J.T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P.L.; Baran, P.S. *J. Am. Chem. Soc.* **2017**, *139*, 2484-2503.



Scheme 4.15 Unreactive electrophiles tested with **86**

Finally, we screened various conditions for the introduction of a hydroxymethyl moiety at the C-7a position. Reaction of **86** with paraformaldehyde in refluxing methanol gave a 1:1 mixture of C-7a and C-11 (**90a/90b**) alkylated products in low yield. However, the use of formalin, a more reactive source of purely monomeric formaldehyde,[94] in refluxing methanol provided a mixture of the C-7a and C-11 alkylated products **90a** and **90b** in a ratio 17:83, respectively, from which the major regioisomer **90b** was isolated in 42% yield after column chromatography. To our delight, when the same reaction was performed at room temperature, the C-7a product **90a** was obtained exclusively in good yield and absolute stereoselectivity (Table 4.3).



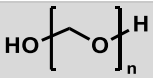
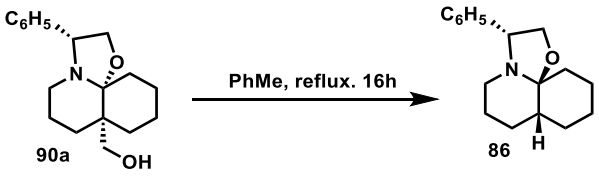
Entry	Formaldehyde source	Temperature	Yield (%)	90a:90b
1		Reflux	22	48:52
2		Reflux	51	17:83
3	(37% w/w in H_2O)	r.t.	73	100:0

Table 4.3 Alkylation assays of amine **86**. All reactions were carried out in MeOH for 24 h.

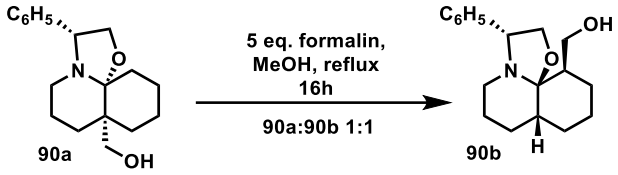
This behavior induced us to suspect that the reaction of **86** with formaldehyde is a reversible reaction and that under kinetic control, the C-7a alkylated amine **90a** is the only product of the reaction, while under thermodynamic control the C-11 alkylated amine **90b** is regioselectively formed. To further explore this hypothesis, we conducted two different assays. First, we heated at reflux temperature a solution of **90a** in toluene in the absence of formalin. After 16 h we observed the formation of the starting oxazolo-DHQ **86**. This reaction clearly indicates that the reaction of **86** with formaldehyde to give the C-7a substituted regioisomer **90a** is a reversible process (Scheme 4.16).

[94] Liu, X.-L.; Liao, Y.-H.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2010**, *75*, 4872-4875.



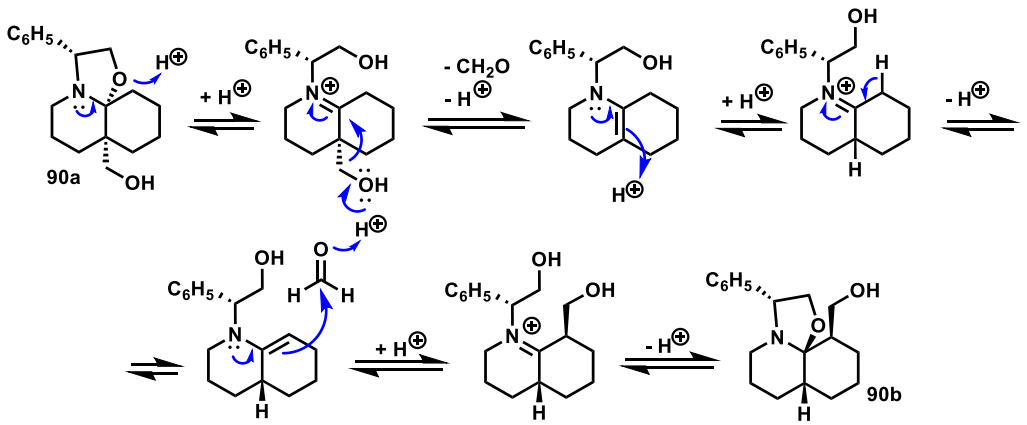
Scheme 4.16 Dealkylation of **91a**

On the other hand, when a methanolic solution of **90a** containing 5 equivalents of formalin was heated at reflux temperature for 16 h an equimolecular mixture of both regioisomers **90a** and **90b** was obtained. No further experiments at longer reaction times to figure out the ratio of **90a** and **90b** in the equilibrium were performed (Scheme 4.17).



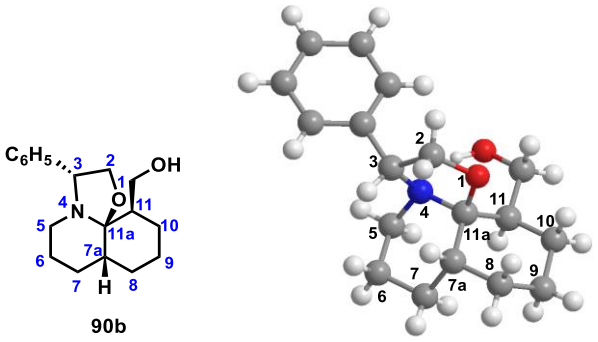
Scheme 4.17 Additional experiments with amine **90a**

The transformation of **90a** into its regioisomer **90b** can be rationalized following the mechanism depicted in Scheme 4.18.



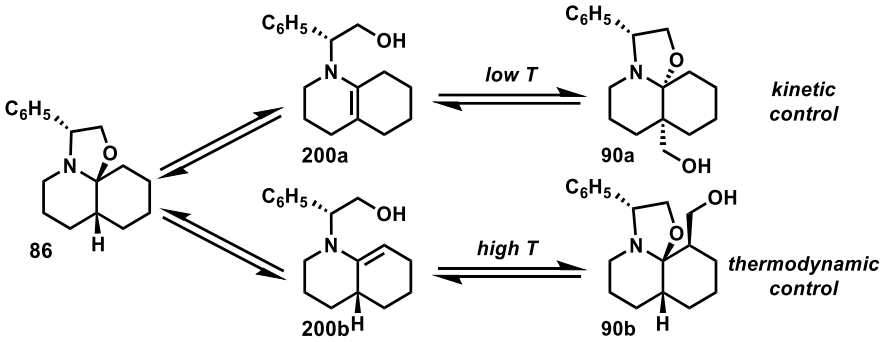
Scheme 4.18 Proposed mechanism for the transformation of **90a** to **90b**

The absolute configuration of the stereocenters of **90b** was unambiguously determined by XRD analysis (Scheme 4.19).



Scheme 4.19 XRD analysis of **90b**

From these experiments it can be concluded that the reaction of formaldehyde with amine **86** is a process governed by equilibrium reactions and that, depending on the reaction conditions, the regioselectivity can be modulated to favor the obtention of the C-7a or the C-11 alkylated products **90a** or **90b,** respectively (Scheme 4.20).



Scheme 4.20 The alkylation of amine **86** with formalin

The stereochemical outcome of the above reactions of **86** with Michael acceptors and formaldehyde is difficult to rationalize and theoretical calculations are necessary to provide some light about the course of the reaction. A speculation for the stereoselective attack of the electrophile by the *Re* face of the beta position of the enamine **200a** would consider that the phenylethanol of the chiral inductor, with a free rotation around the exocyclic C-N bond, induces a particular conformation of the two six-membered rings of the DHQ nucleus avoiding steric interactions of the bulky phenyl substituent and the hydroxymethyl group with the hydrogens of the C-2 and C-8 positions of the DHQ. In the more stable conformation, the attack of the electrophile would take place axial, under stereoelectronic control, leading to a chair-like transition state, energetically more favorable that the boat-like transition state that would result from the attack of the electrophile from the opposite face of the enamine (Figure 4.1).

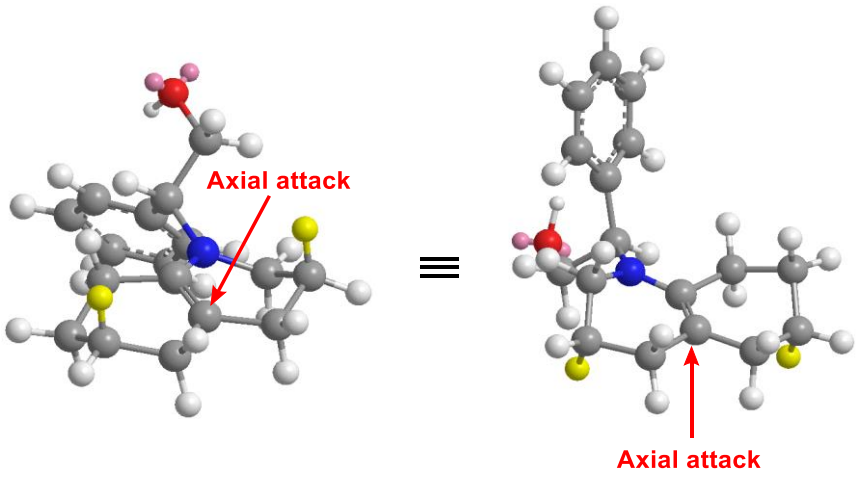
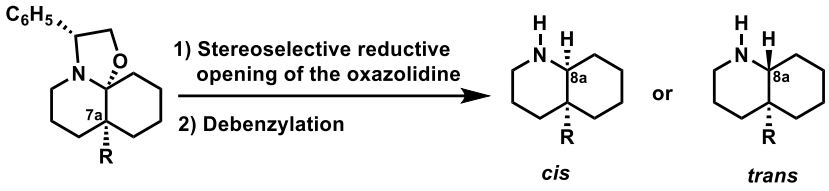


Figure 4.1 Plausible conformation of intermediate **200a**

4.3.4 Obtention of C-4a and C-8 Substituted *cis*-DHQs

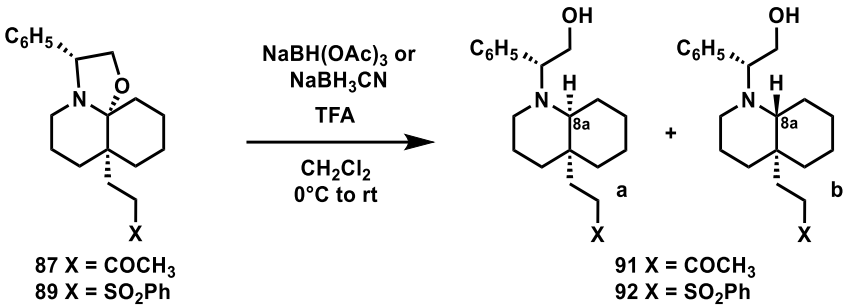
The transformation of the C-7a substituted oxazolo-DHQs into *cis* or *trans* DHQs having an all-carbon quaternary stereocenter at C-4a required the removal of the phenylethanol moiety of the chiral inductor following a two-step sequence, the reductive opening of the oxazolidine ring and the removal of the resulting benzylic appendage on the nitrogen. The first step involves the cleavage of the C-O bond and, consequently, the generation of the stereocenter of the C-8a position of the DHQ. Thus, we decided to assay different reducing reagents with the final aim of controlling the stereoselective formation of *cis* or *trans*-DHQs (Scheme 4.21).



Scheme 4.21 Synthetic strategy for the obtention of C-4a substituted DHQs

Considering that compound **87** has a ketone function, we first selected $NaBH(OAc)_3$ and $NaBH_3CN$, two mild borohydride reagents that should chemoselectively provoke the reductive opening of the oxazolidine ring without affecting the ketone present in its side chain.[95] Reduction of amines **87** and **89** with $NaBH(OAc)_3$ in the presence of TFA, led to the *cis*-fused DHQs **91a** and **92a** in moderate stereoselectivity and chemical yields (Table 4.4, Entries 1-2). However, the use of $NaBH_3CN$ under similar conditions afforded the *trans* fused DHQs **91b** and **92b** as the major isomers but, again, in low stereoselectivity (Table 4.4, Entries 3-5).

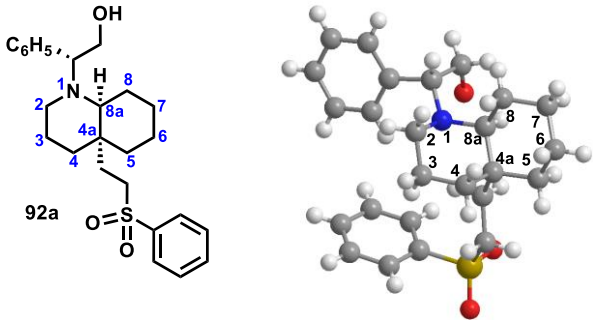
[95] a) Hart, D.J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757-5770. b) Pelletier, S.W.; Mody, N.V.; Venkov, A.P.; Desai, H.K.; *Tetrahedron Lett.* **1979**, *51*, 4939-4940.



Entry	Substrate	Hydride	t (°C)	T (h)	Product	Yield (%)	Ratio a:b
1	**87**	$NaBH(OAc)_3$	25	4	**91**	77	81:19
2	**89**	$NaBH(OAc)_3$	25	72	**92**	56	84:16
3	**87**	$NaBH_3CN$	25	4	**91**	69	30:70
4	**87**	$NaBH_3CN$	0	24	**91**	88	33:67
5	**89**	$NaBH_3CN$	25	72	**92**	74	46:54

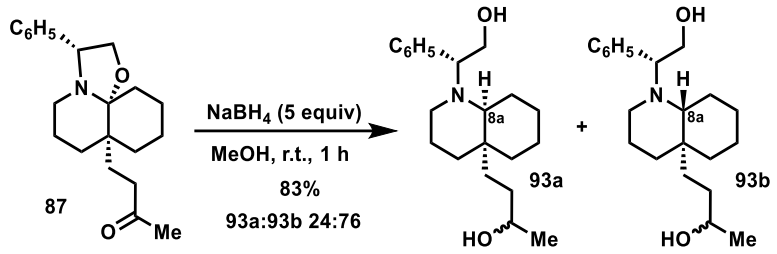
Table 4.4 All reactions were carried out in CH_2Cl_2 and in the presence of 0.5 equivalents of TFA.

The obtention of a crystal of *cis*-DHQ **92a** allowed the determination of its absolute configuration by XRD and revealed the configuration of the C-4a quaternary stereocenter (Scheme 4.22).



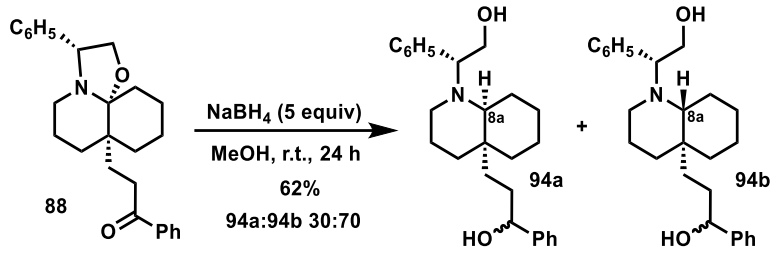
Scheme 4.22 Structure of compound **92a** elucidated by XRD analysis

The moderate stereoselectivities observed in the above reductions, induced us to test $NaBH_4$ for the reductive opening of the oxazolidine ring of **87**. Stirring a methanolic solution of **87** with an excess of $NaBH_4$ at room temperature for 1 h afforded a 24:76 mixture of *cis* **93a** and *trans* **93b**, respectively, in good chemical yield (Scheme 4.23). Therefore, the $NaBH_4$, as $NaBH_3CN$, induce the selective formation of the *trans*-DHQ isomer although in better yield and diastereomeric ratio.



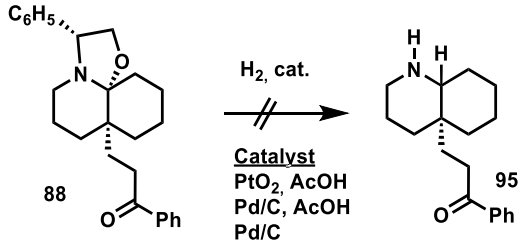
Scheme 4.23 $NaBH_4$ reduction of **87**

The good results observed in the reduction of **87** with $NaBH_4$ induced us to study the reductive opening of the oxazolidine ring present in the phenyl-ketone **88** with this hydride. Under the same conditions used for **87**, compound **88** afforded a 30:70 mixture of *cis* **94a** and *trans* **94b** in moderate yield (Scheme 4.24).



Scheme 4.24 $NaBH_4$ reduction of **88**

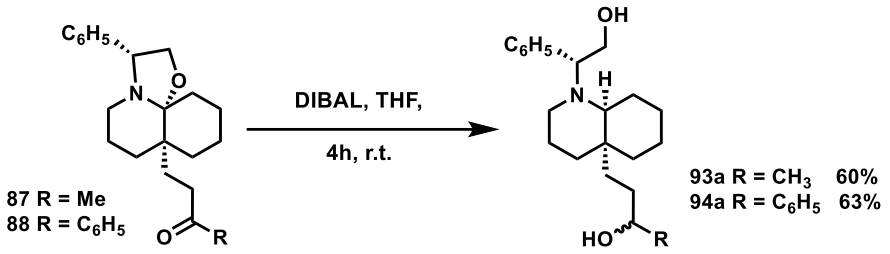
Attempts to provoke the hydrogenolysis of the benzylic C-N bond and of the C-O bond of the oxazolidine of **88** in a one pot reaction by catalytic hydrogenation under several reaction conditions resulted in failure and only complex mixtures were obtained. Preliminary analysis of the crude by ^1H NMR showed that the process was not stereoselective (Scheme 4.25).



Scheme 4.25 Attempts on the one-pot removal of the chiral inductor of **88**

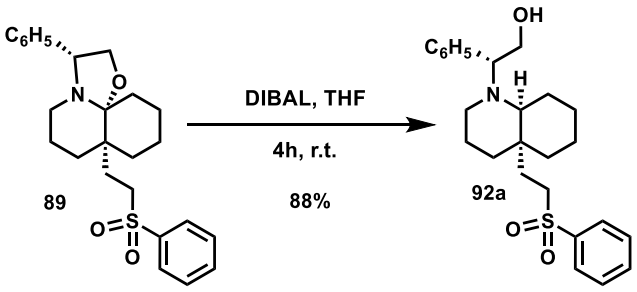
Given the poor stereoselectivities observed in previous reductions and the technical difficulties affronted with the purification of some of the resulting epimeric mixtures, we decided to try diisobutylaluminium hydride (DIBAL), a bulkier analogue of alane (Scheme 4.26). Treatment of a THF solution of compound **87** with DIBAL at room temperature allowed the isolation of compound **93a** in moderate chemical yield but in excellent stereoselectivity in the formation of the *cis* isomer. Unfortunately, the ketone present in the 3-oxo-butyl chain was reduced to the corresponding alcohol.

A similar result was observed when the phenyl-ketone **88** was subjected to reduction under similar reaction conditions. Compound **94a** was isolated in excellent stereoselectivity in the formation of the *cis* isomer, but as a mixture of diastereomers in the stereocenter next to the hydroxy group.



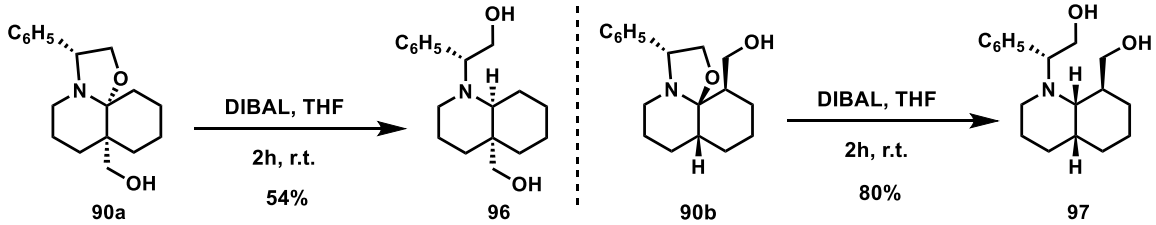
Scheme 4.26 DIBAL-promoted reduction of **87** and **88**

Compound **92a**, with a 2-(phenylsulfonyl)ethyl appendage at the quaternary stereocenter, was obtained in excellent yield and stereoselectivity by treatment of **89** with DIBAL under the same reaction conditions as before (Scheme 4.27).



Scheme 4.27 DIBAL-promoted reduction of **89**

Finally, the regioisomeric C-4a and C-8 hydroxymethyl compounds **96** and **97** were stereoselectively obtained by reduction of the oxazolo-DHQs **90a** and **90b** (Scheme 4.28).

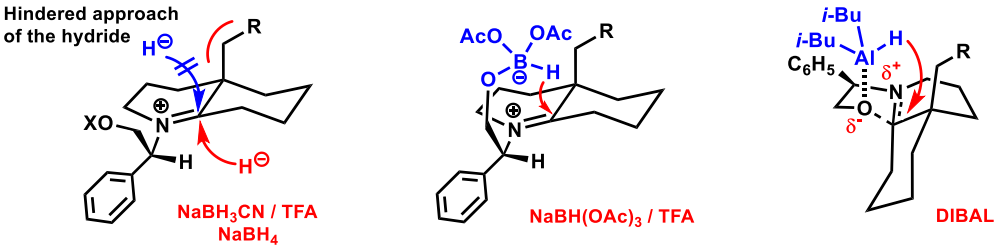


Scheme 4.28 DIBAL-promoted reduction of **90a** and **90b**

The differences observed in the stereoselectivity of the reductive opening of the oxazolidine ring using the above-mentioned conditions could be rationalized as follows (Scheme 4.29). The reactions with $NaBH_3CN$ and $NaBH(OAc)_3$ are carried out in the presence of TFA which provokes the generation of an iminium ion that undergoes the attack of the hydride. When using $NaBH_3CN$, the approach of the reagent to the *Re* face of the electrophilic carbon of the iminium salt is hindered by the presence of the substituent at the C-4a position, and the reduction takes place mainly from the

opposite side affording the *trans* isomer, although in moderate stereoselectivity. However, with $NaBH(OAc)_3$, presumably, an intermediate resulting from the substitution of an acetoxy group by the oxygen of the chiral inductor is formed and the delivery of the hydride takes place intramolecularly.[96] Therefore, in this case, the facial selectivity of the reduction depends on the relative stability of the conformations around the exocyclic C-N bond connecting the DHQ and the chiral inductor. A conformation in which the bulky phenyl group lies away from the C-8 carbon of the intermediate iminium salt, in order to avoid steric interactions, would induce the intramolecular attack of the reductant from the *Re* face to give mainly the *cis* isomer.

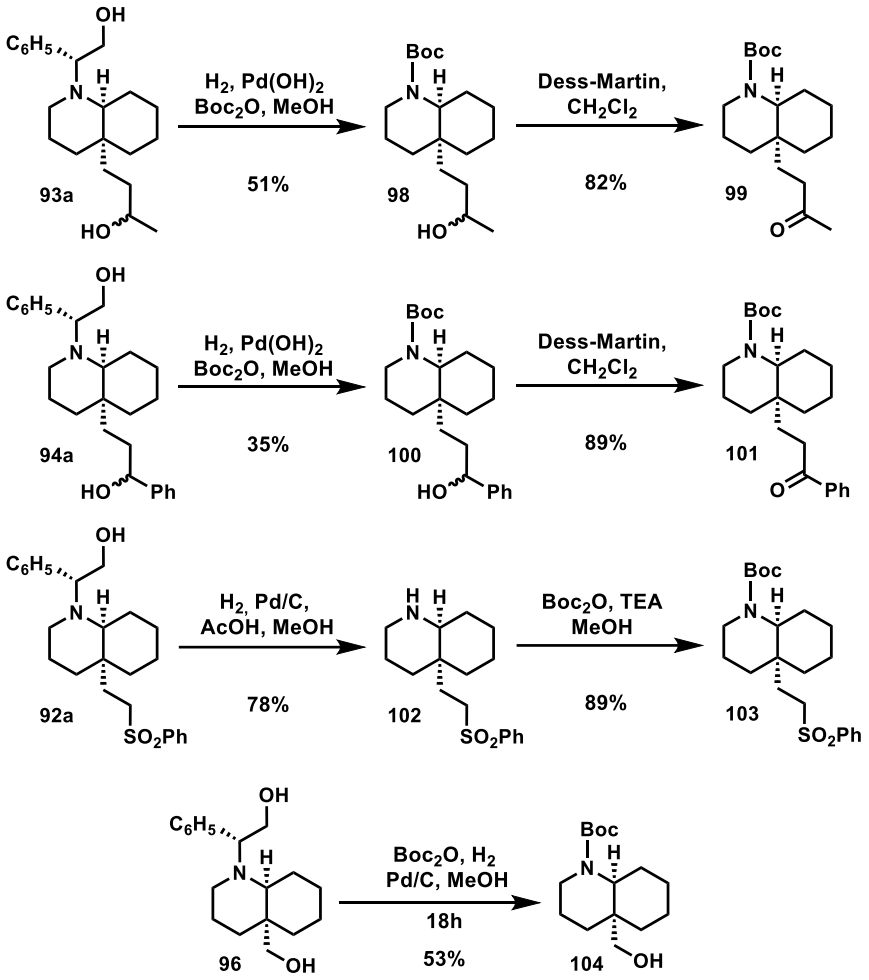
Finally, DIBAL, an electrophilic reducing reagent, coordinates with the oxygen atom of the oxazolidine ring generating an incipient iminium ion. The delivery of the hydride takes place from the same face of the C-O bond leading to the *cis* isomer in excellent stereoselectivity.



Scheme 4.29 Reduction intermediates depending on the reducing agent used

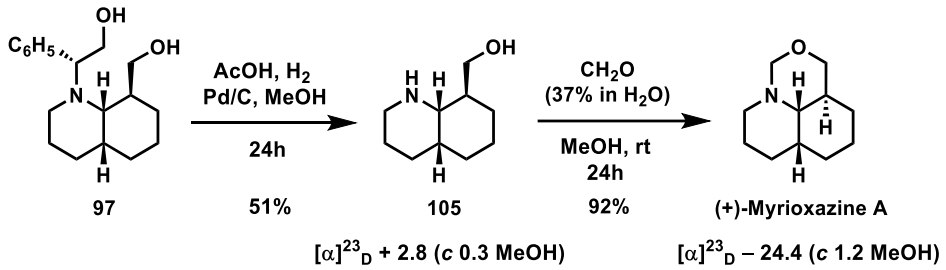
Removal of the 2-phenylethanol moiety of the chiral inductor of compounds **92a**, **93a**, **94a** and **96** was carried out by hydrogenolysis of the benzylic C-N bond with molecular hydrogen in the presence of a catalyst. In the case of **93a** and **94a**, the resulting N-Boc protected product was subjected to oxidation of the secondary alcohol. In this way, the enantiopure C-4a substituted *cis*-DHQs **99**, **101**, **103**, and **104** were obtained (Scheme 4.30).

[96] a) Canesi, S.; Bouchu, D.; Ciufolini, M.A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4336-4338; b) Ge, H.M.; Zhang, L.-D.; Tan, R.X.; Yao, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 12323-12325; c) Kurose, T.; Tsukano, C.; Takemoto, Y. *Org. Lett*, **2017**, *19*, 4762-4765.



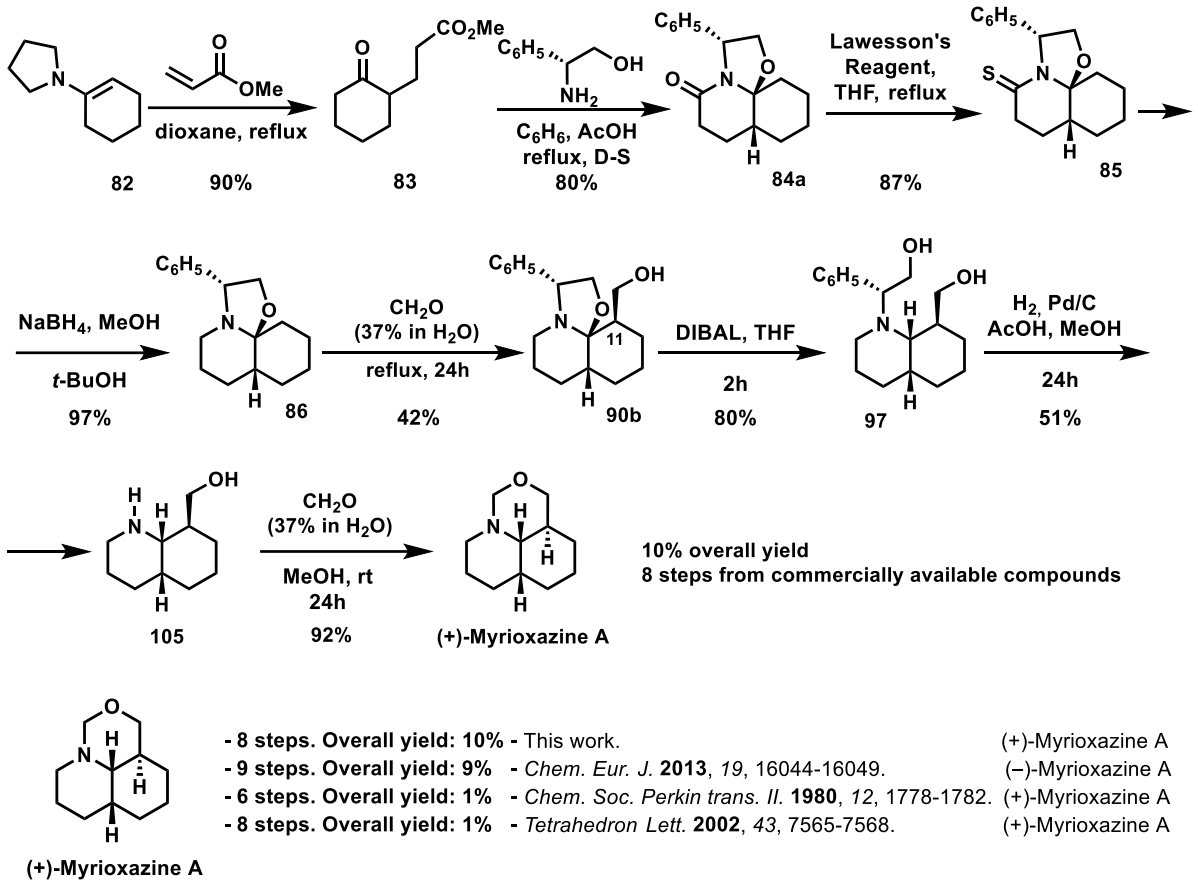
Scheme 4.30 Obtention of C-4a substituted *cis*-DHQs

Removal of the benzylic substituent of compound **97** by catalytic hydrogenation led to the *cis*-DHQ **105**, a known precursor of several *Myrioneuron* alkaloids. In our hands, treatment of **105** with formalin in methanol allowed the closure of the oxazine ring, completing the total synthesis of (+)-myrioxazine A (Scheme 4.31).



Scheme 4.31 Total synthesis of (+)-myrioxazine A

Thus, we have carried out the total synthesis of (+)-myrioxazine A in eight steps from commercially available compounds, in an overall yield of 10% and without the use of protecting groups (Scheme 4.32).



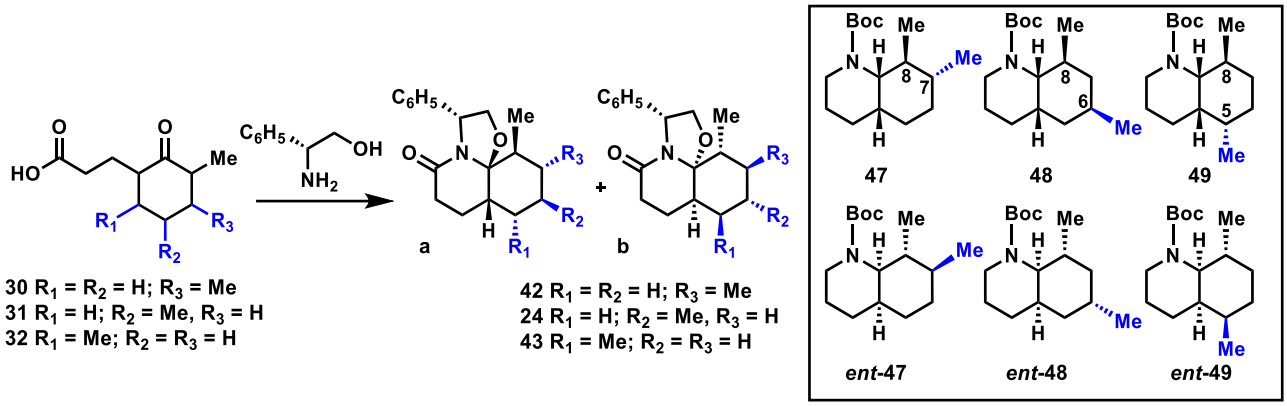
Scheme 4.32 Current enantioselective total syntheses of myrioxazine A

4.4 Conclusions

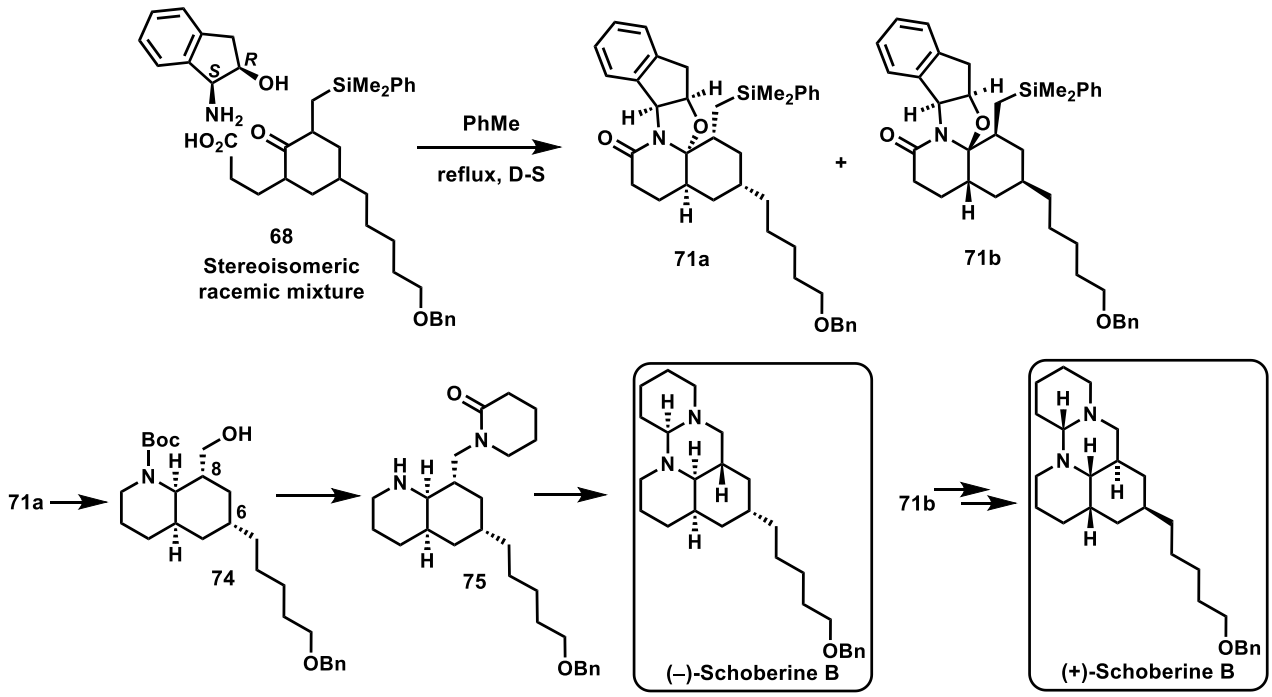
In the last chapter of this thesis, we have explored the reactivity of the hemiaminal moiety present in amine **86** with electrophiles. Vinyl ketones, phenyl vinyl sulfone and formaldehyde have been introduced stereo- and regioselectively at C-7a. The alkylation of the C-11 position has also been achieved with formaldehyde by increasing the system's temperature. The reductive opening of the oxazolidine with DIBAL proved to be the most stereoselective method for the obtention of *cis*-DHQ among the tested reducing agents. Catalytic hydrogenation allowed the elimination of the phenylethanol moiety and the obtention of C-4a and C-8 susbstituted *cis*-DHQs. The modulation of the regioselectivity for the introduction of hydroxymethyl units and the overall good yields for the obtention of *cis*-DHQ **105** allowed the completion of the most efficient enantioselective synthesis of (+)-myrioxazine A

5 Conclusions

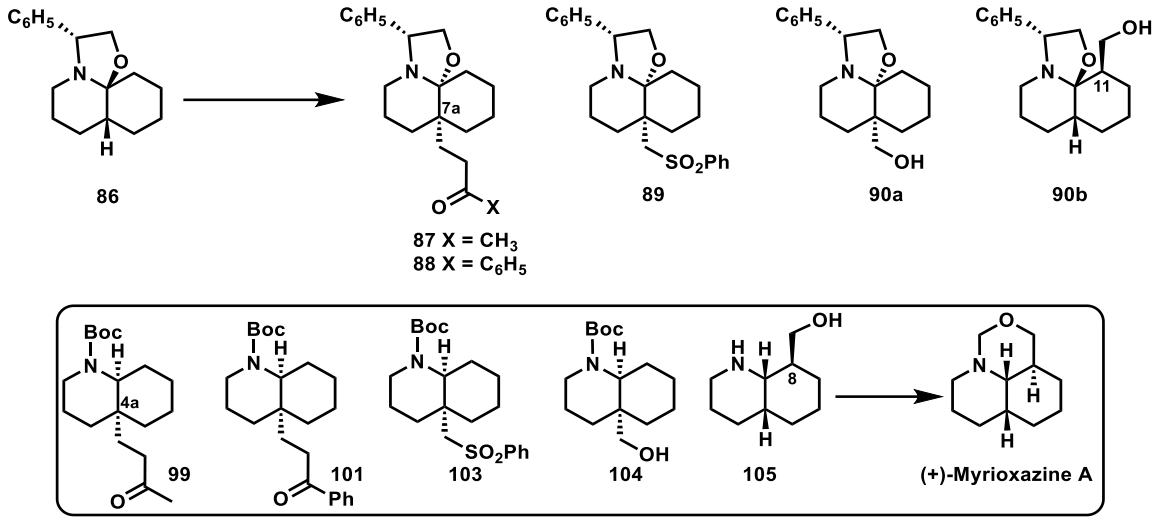
1. Cyclocondensation of (*R*)-phenylglycinol with a stereoisomeric mixture of δ-oxoacids **30-32**, bearing one substituent at a non-isomerizable position of the carbocyclic ring, led to the stereoselective obtention of lactams **24a/24b**, **42a/42b**, and **43a/43b** with opposite the absolute configuration of all the stereogenic centres in the DHQ ring. Stereoselective removal of the phenylethanol residue led to the obtention of enantiopure *cis*-DHQs in both enantiomeric series.



2. Application of the above methodology to ketoacid **68** allowed the stereoselective obtaining of lactams **71a** and **71b**, which were transformed into both enantiomers of schoberine B, thus completing its first total synthesis.



3. Reaction of amine **86** with vinyl ketones, phenyl vinyl sulfone and formaldehyde led to the regio- and stereoselective obtention of C-7a alkylation products. A variation of the temperature in the formaldehyde alkylation allowed the modulation of the regioselectivity to obtain either the C-7a product or the C-11 product as major regioisomer. DIBAL-promoted stereoselective oxazolidine ring opening followed by catalytic hydrogenation allowed the obtention of C-4a and C-8 substituted *cis*-DHQs. The obtention of *cis*-DHQ **105** allowed the obtention of the most efficient synthesis of (+)-myrioxazine A.



6 Experimental Procedures and Spectroscopic Data

6.1 ^{1}H and ^{13}C NMR Tables and Spectra Comparisons – Chapter 2

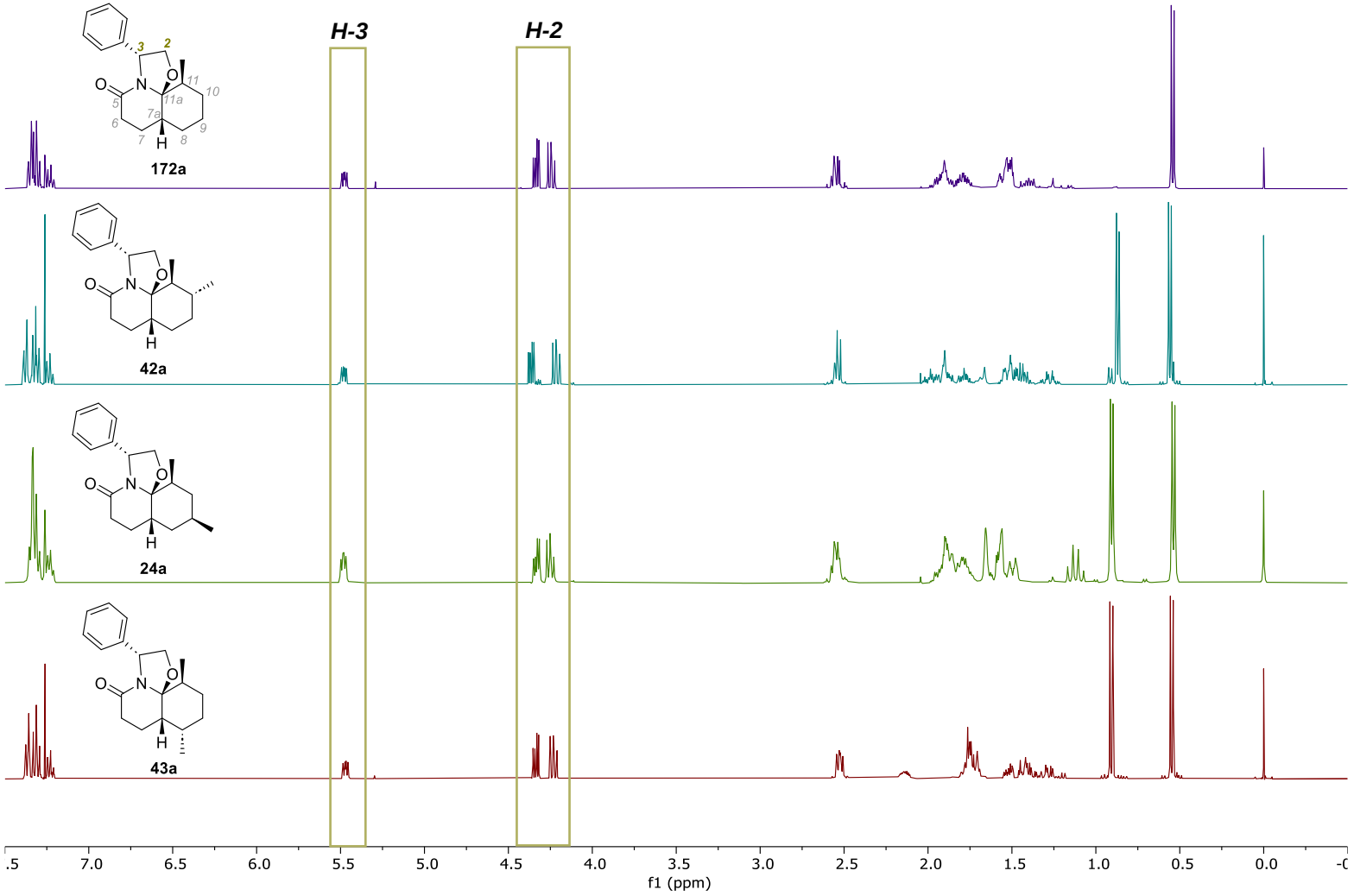


Figure 6.1 ^{1}H NMR stacked spectra of **172a**, **24a**, **42a**, and **43a** displaying diagnostic signals.

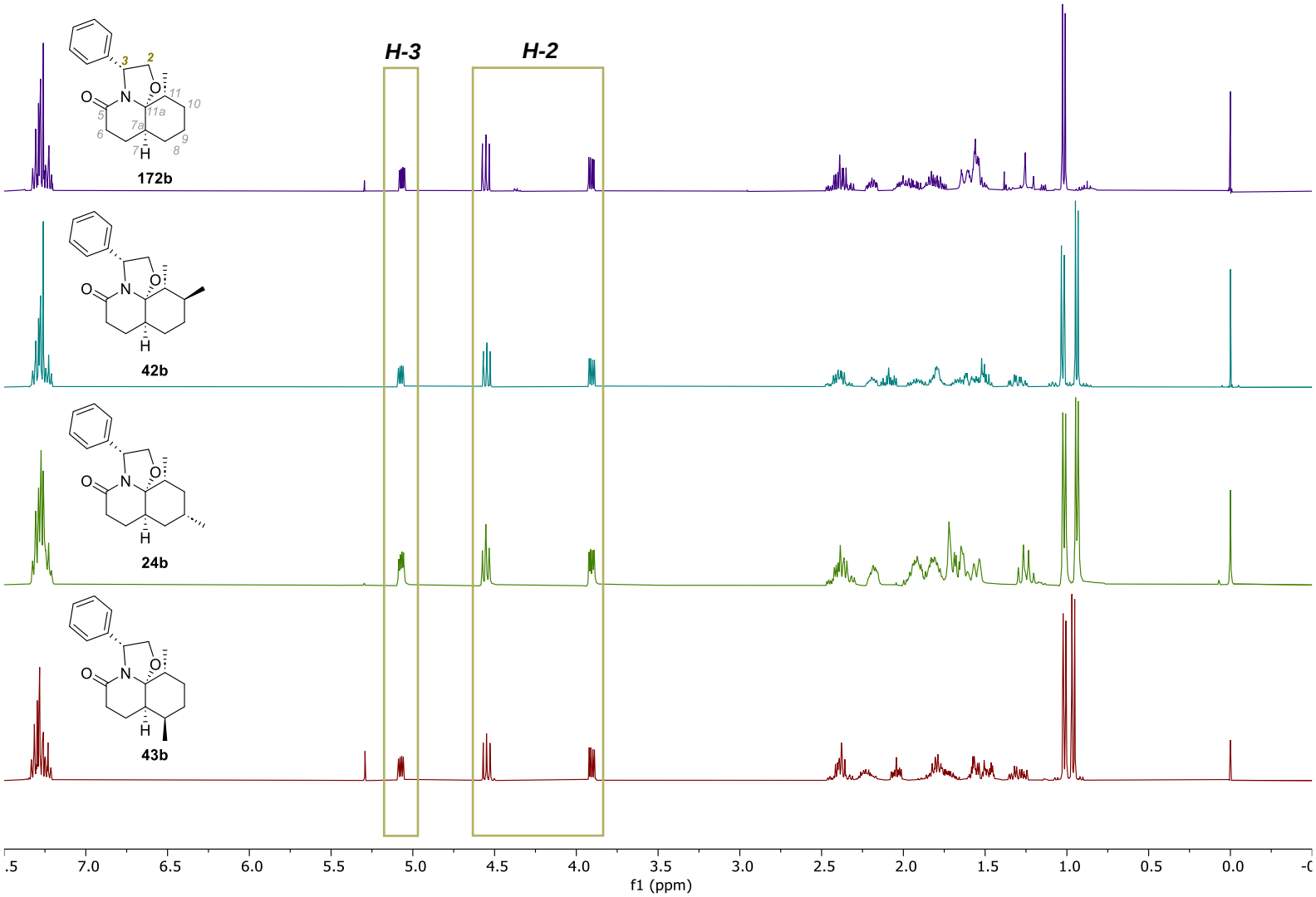


Figure 6.2 ^{1}H NMR stacked spectra of **172b**, **24b**, **42b**, and **43b** displaying diagnostic signals.

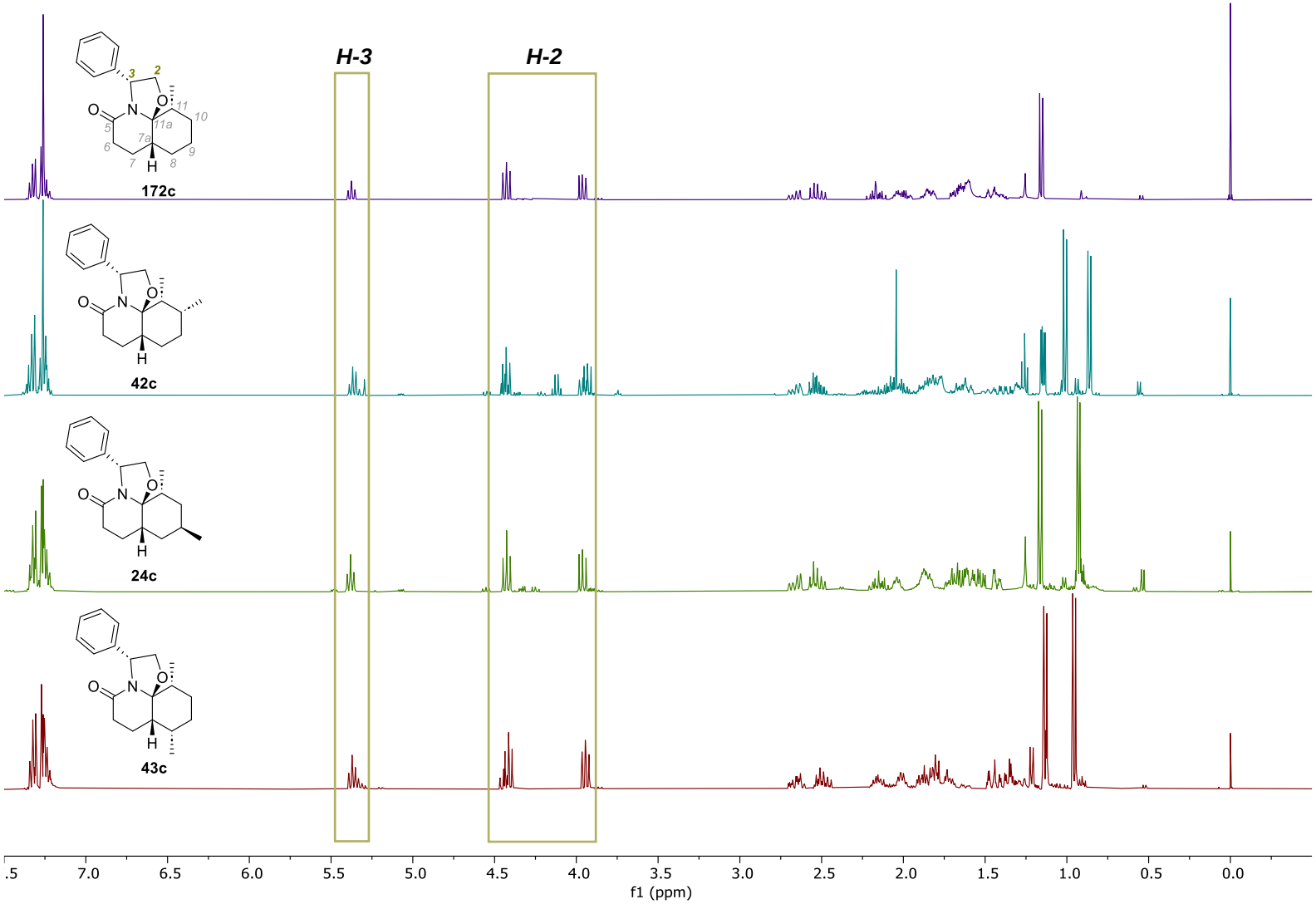


Figure 6.3 ^{1}H NMR stacked spectra of **172c**, **24c**, **42c**, and **43c** displaying diagnostic signals.

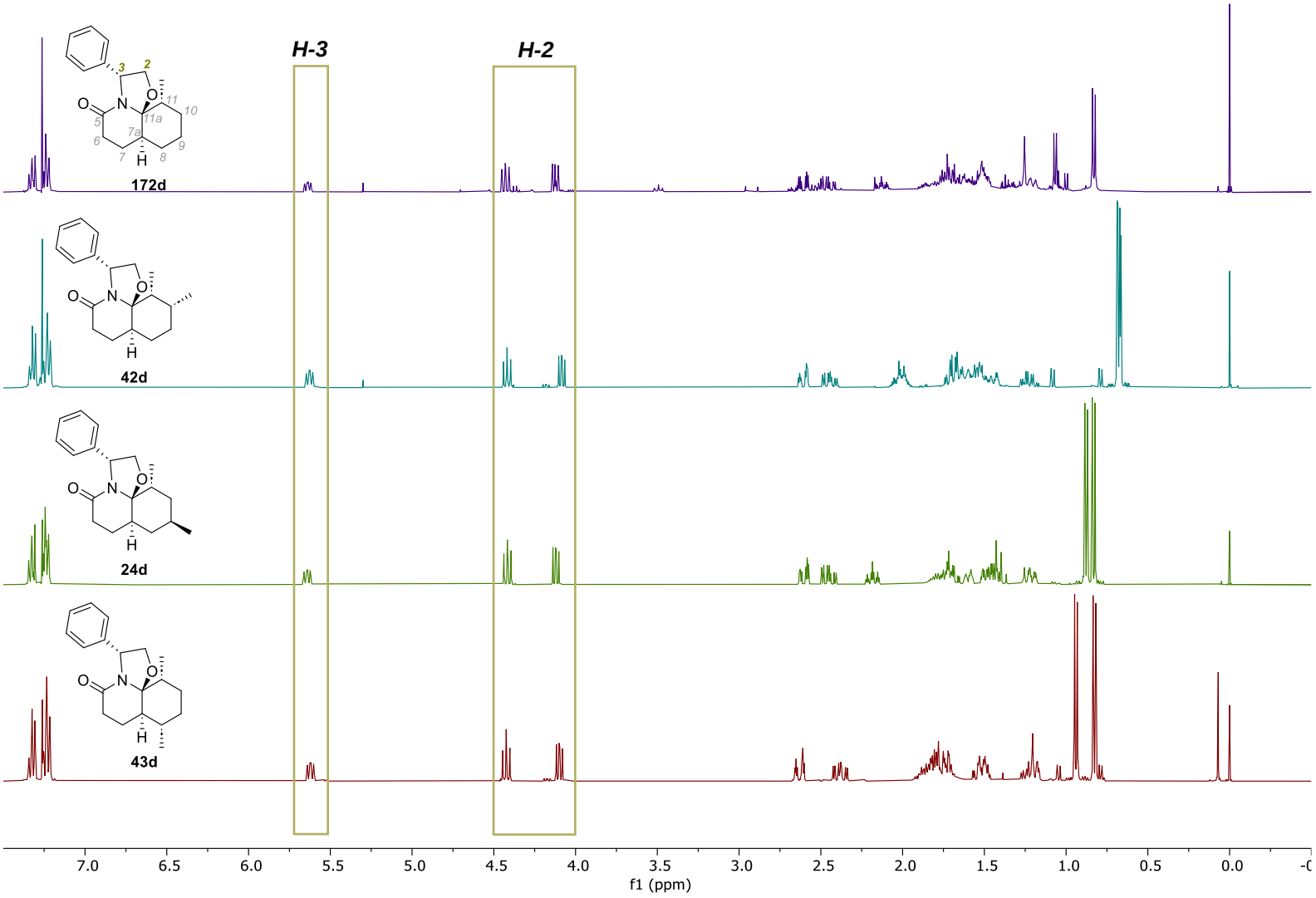


Figure 6.4 ^{1}H NMR stacked spectra of **172d**, **24d**, **42d**, and **43d** displaying diagnostic signals.

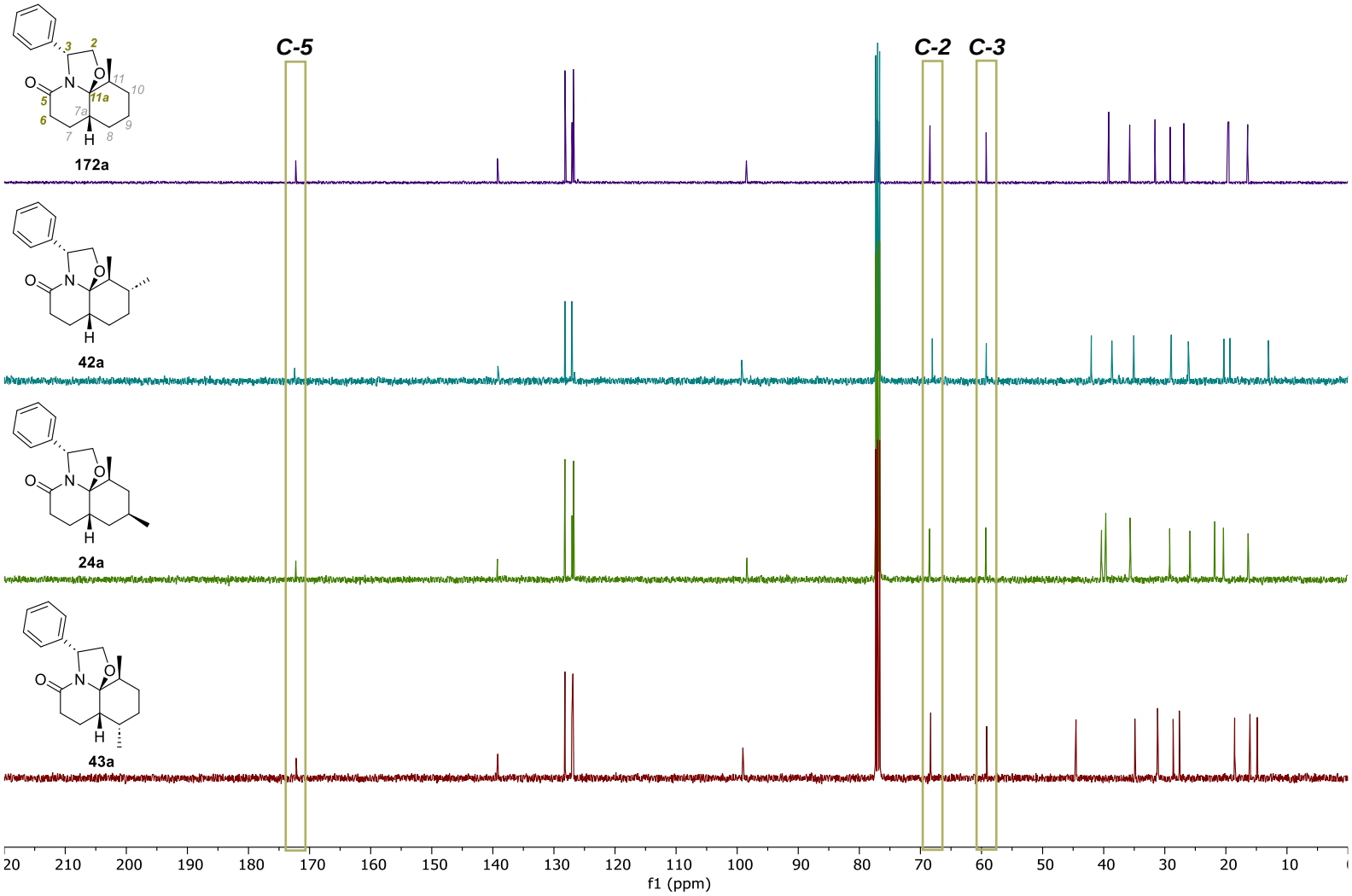


Figure 6.5 ^{13}C NMR stacked spectra of **172a**, **24a**, **42a**, and **43a** displaying diagnostic signals.

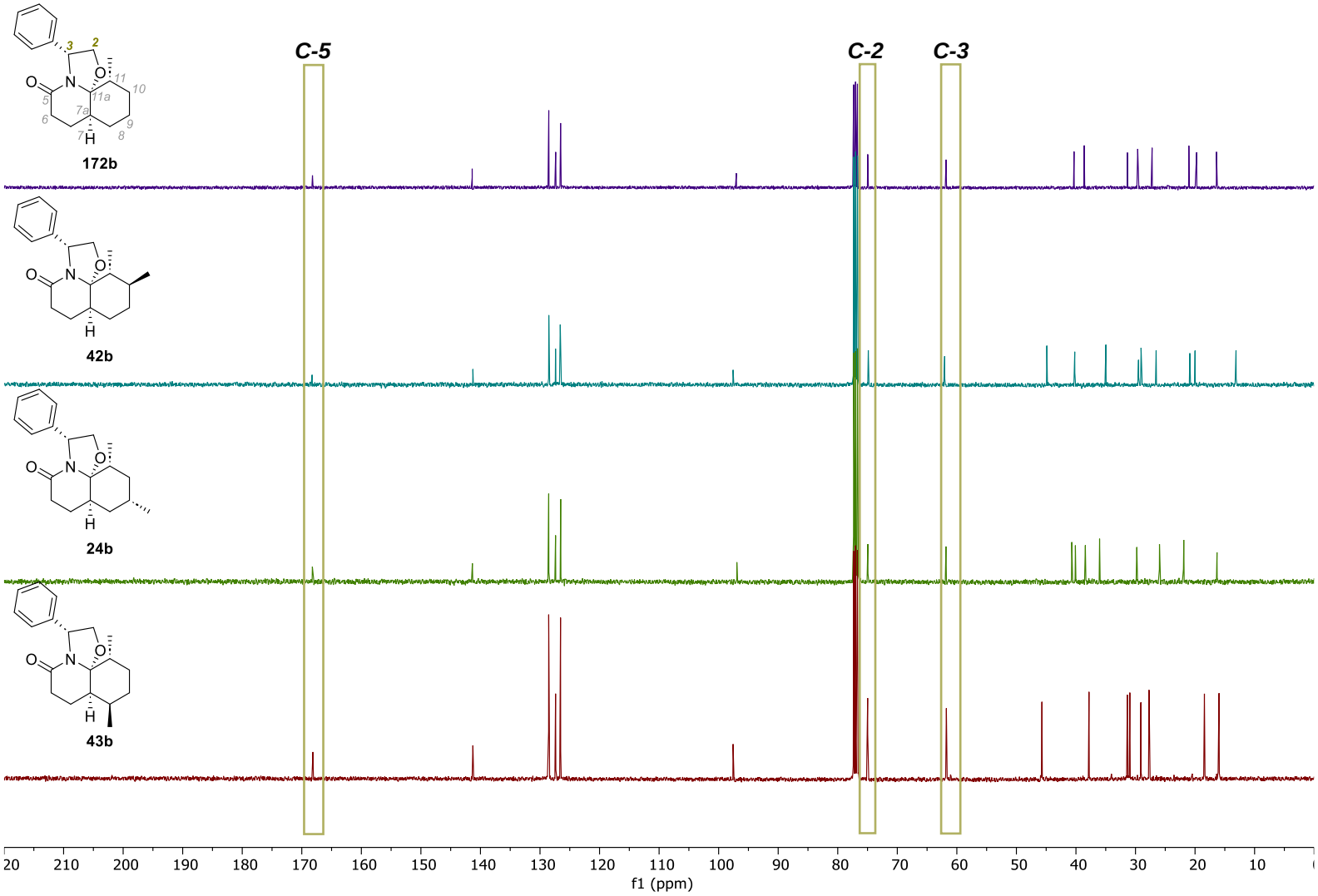


Figure 6.6 ^{13}C NMR stacked spectra of **172b**, **24b**, **42b**, and **43b** displaying diagnostic signals.

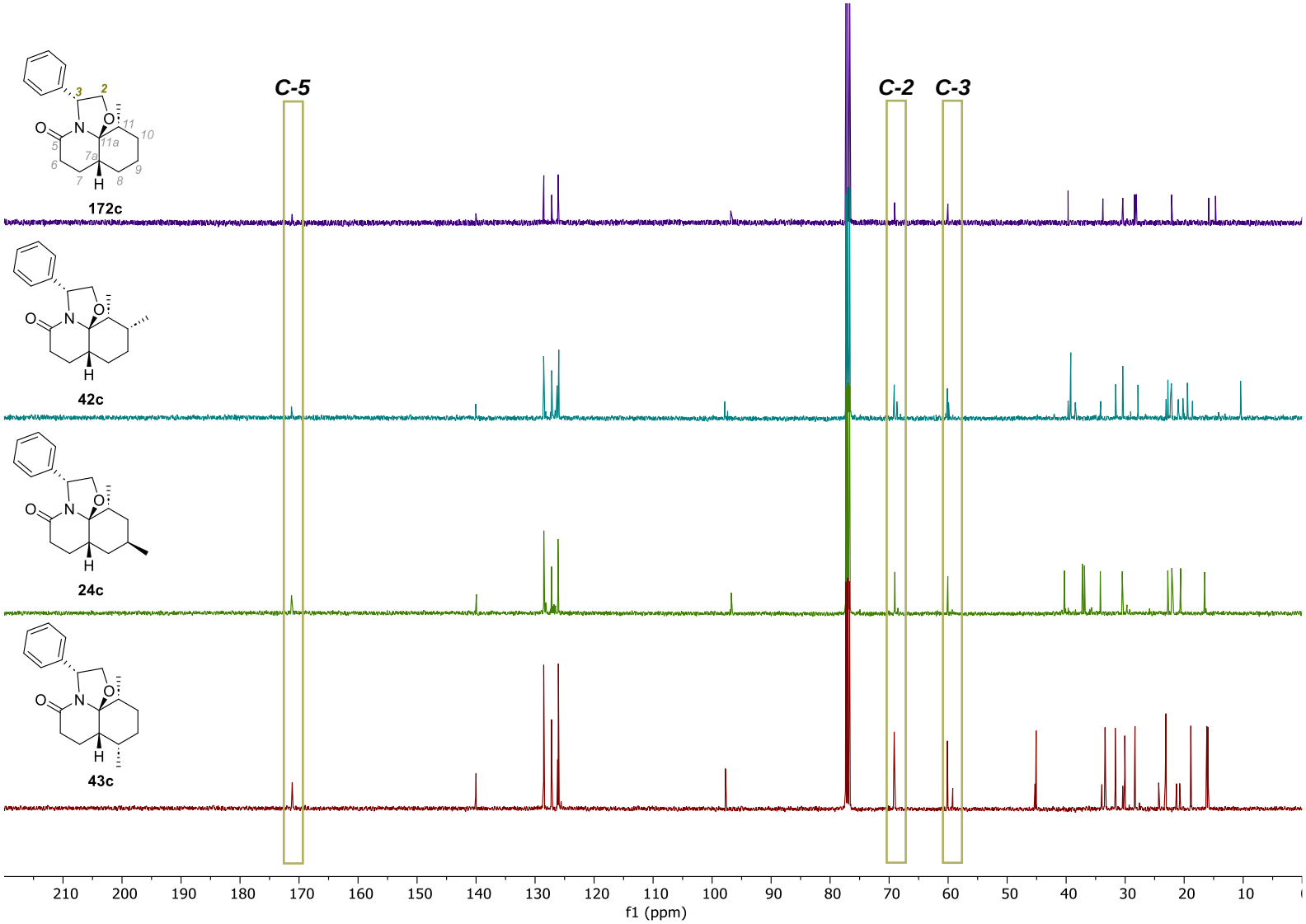


Figure 6.7 ^{13}C NMR stacked spectra of **172c**, **24c**, **42c**, and **43c** displaying diagnostic signals.

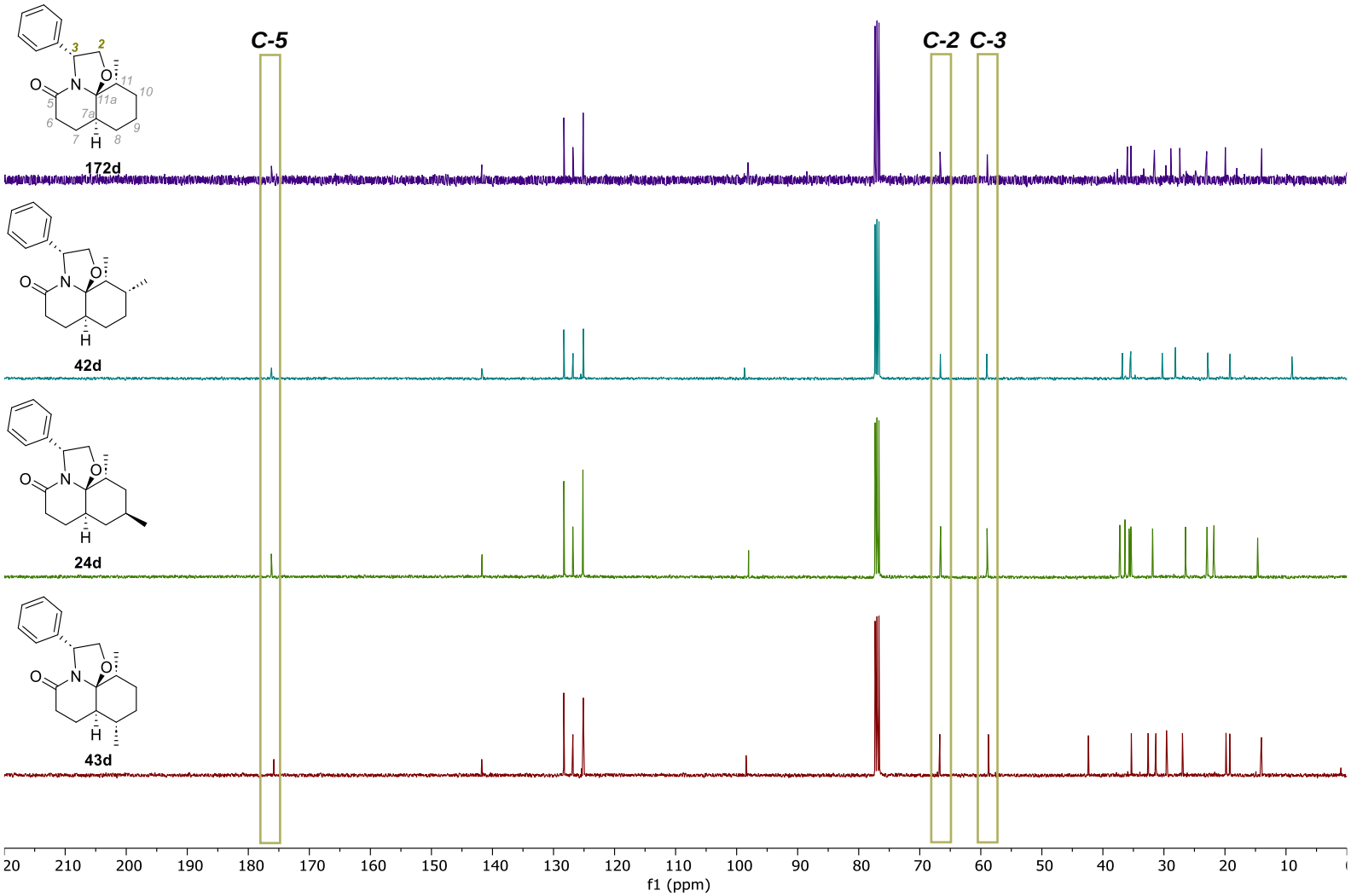


Figure 6.8 ^{13}C NMR stacked spectra of **172d**, **24d**, **42d**, and **43d** displaying diagnostic signals.

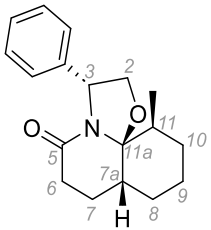
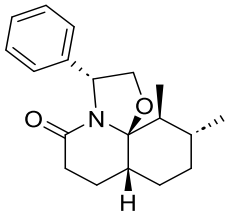
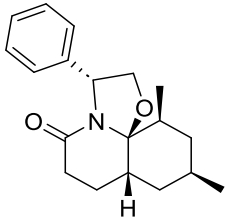
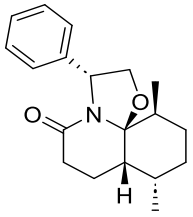
	C-2	**C-3**	**C-5**	**C-6**	**C-7**	**C-7a**	**C-8**	**C-9**	**C-10**	**C-11**	**C-11a**	**CH_3C-11**	**CH_3C-8/9/10**
 **172a**	68.4	59.2	172.2	29.1	19.5	39.1	26.8	19.7	31.6	35.7	98.5	16.4	-
 **42a**	68.1	59.2	172.4	29.0	19.3	38.7	26.1	28.9	35.1	42.0	99.3	13.0	20.3
 **24a**	68.4	59.2	172.1	29.1	20.3	39.6	35.6	25.8	40.3	35.5	98.3	16.3	21.8
 **43a**	68.3	59.2	172.2	28.6	14.9	44.5	31.2	31.2	27.6	34.9	99.1	16.1	18.6

Table 6.1 ^{13}C NMR chemical shift values of **172a**, **24a**, **42a**, and **43a**.

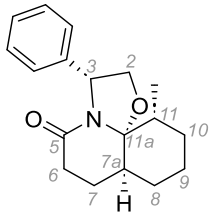
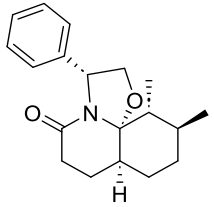
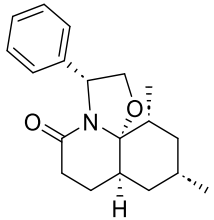
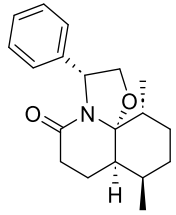
	C-2	**C-3**	**C-5**	**C-6**	**C-7**	**C-7a**	**C-8**	**C-9**	**C-10**	**C-11**	**C-11a**	**CH_3C-11**	**CH_3C-8/9/10**
 **172b**	74.9	61.8	168.2	29.6	21.0	40.3	27.2	19.7	31.3	38.6	97.0	16.4	-
 **42b**	74.9	62.0	168.3	29.5	20.9	40.2	26.5	29.1	35.0	44.9	97.6	20.0	13.1
 **24b**	74.8	61.7	168.1	29.7	21.8	40.6	35.9	38.2	40.0	25.9	96.8	16.2	21.8
 **43b**	75.0	61.8	168.1	29.1	16	45.7	37.8	31.0	27.7	31.4	97.6	18.4	16.1

Table 6.2 ^{13}C NMR chemical shift values of **172b**, **24b**, **42b**, and **43b**.

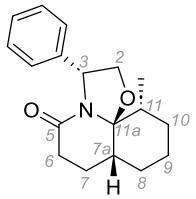
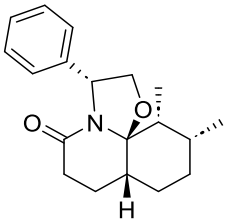
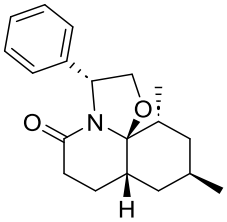
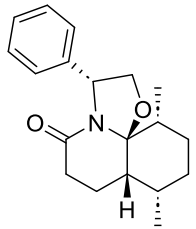
	C-2	**C-3**	**C-5**	**C-6**	**C-7**	**C-7a**	**C-8**	**C-9**	**C-10**	**C-11**	**C-11a**	**CH_3C-11**	**CH_3C-8/9/10**
 **172c**	69.1	60.0	171.2	30.4	22.1	39.7	28.1	28.4	14.7	33.8	96.8	15.8	-
 **42c**	69.1	60.1	171.5	30.4	22.7	39.2	27.8	22.8	31.6	39.2	97.8	10.4	19.4
 **24c**	69.0	60.0	171.3	30.5	22.8	40.3	37.2	20.6	36.9	34.2	96.7	16.5	22.1
 **43c**	69.1	60.1	171.1	30.0	16.1	45.1	31.7	28.3	23.1	33.4	97.7	15.9	18.9

Table 6.3 ^{13}C NMR chemical shift values of **172c**, **24c**, **42c**, and **43c**.

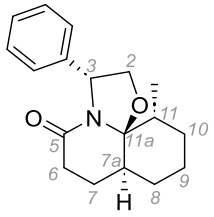
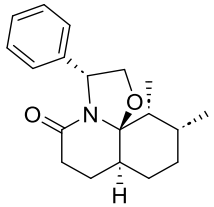
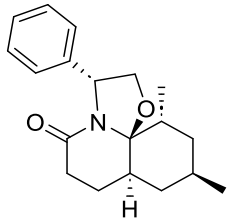
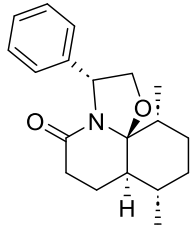
	C-2	**C-3**	**C-5**	**C-6**	**C-7**	**C-7a**	**C-8**	**C-9**	**C-10**	**C-11**	**C-11a**	**CH_3C-11**	**CH_3C-8/9/10**
 **172d**	66.7	58.9	176.2	35.4	23.0	36.0	28.8	27.4	19.9	31.5	98.1	14.0	-
 **42d**	66.6	59.0	176.2	35.4	22.8	36.8	28.1	28.1	30.3	35.5	98.7	19.2	9.0
 **24d**	66.6	59.0	176.2	35.4	22.9	35.7	37.2	26.4	36.4	31.8	98.0	14.6	21.8
 **43d**	66.7	58.8	175.8	35.3	19.2	42.4	32.6	27.0	29.6	31.3	98.4	14.0	19.8

Table 6.4 ^{13}C NMR chemical shift values of **172d**, **24d**, **42d**, and **43d**

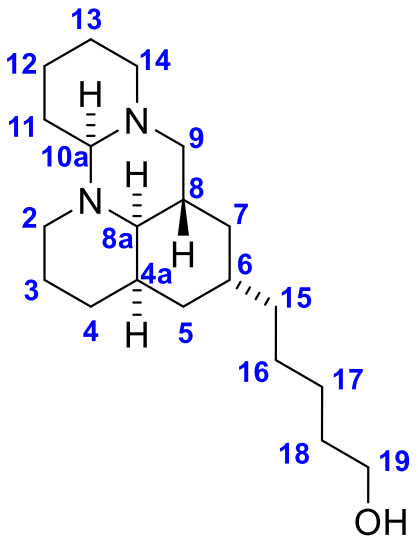
6.2 Comparison of the ^{1}H and ^{13}C NMR Data of Natural and Synthetic (–)-Schoberine B

Proton number	**Synthetic $CDCl_3$, δ_{1H} (mult, *J* in Hz)**	**Synthetic Pyr-d_5, δ_{1H} (mult, *J* in Hz)**	**Natural[42k] Pyr-d_5, δ_{1H} (mult, *J* in Hz)**
2	2.90-2.69 (m)	2.92-2.85 (m)	2.92 (m)
3		1.73-1.61 (m), 1.59-1.42 (m)	1.69 (m), 1.58 (m)
4		1.73-1.61, 1.31-1.22	1.69 (m), 1.28 (m)
4a	1.99-1.92 (m)	1.99-1.91 (m)	1.97 (m)
5		1.59-1.42 (m), 1.16-1.08 (m)	1.55 (m), 1.13 (m)
6		1.39-1.31 (m)	1.40 (m)
7	1.59-1.50 (m), 0.52 (q, 12.0)	1.59-1.42, 0.45 (t, 12.0)	1.47 (m), 0.46 (q, 12.0)
8	2.20 (qt, 11.2, 3.6)	2.17 (qt, 11.6, 4.0)	2.19 (m)
8a	2.51 (dd, 11.2, 4.8)	2.49 (dd, 10.8, 4.8)	2.52 (dd, 10.8, 4.8)
9	2.90-2.69 (m), 1.77-1.67 (m)	2.78 (dd, 12.8, 4.0), 1.73-1.61 (m)	2.81 (dd, 10.8, 3.6), 1.68 (m)
10a	2.90-2.69 (m)	2.92-2.85 (m)	2.92 (m)
11		1.86-1.75 (m), 1.73-1.61 (m)	1.75 (m), 1.68 (m)
12		1.73-1.61 (m), 1.31-1.22 (m)	1.70 (m), 1.25 (m)
13		1.59-1.42 (m)	1.52 (m), 1.46 (m)
14	2.90-2.69 (m), 1.91 (td, 12.0, 3.6)	2.76-2.71 (m), 1.86-1.75 (m)	2.78 (d, 11.4), 1.86 (td, 12.0, 2.4)
15		1.16-1.08 (m)	1.13 (m)
16		1.39-1.31 (m)	1.35 (m)
17		1.59-1.42 (m)	1.52 (m)
18		1.86-1.75 (m)	1.80 (m)
19	3.62 (t, 6.8)	3.91 (t, 6.4)	3.92 (t, 6.0)

Table 6.5 ^{1}H NMR values of synthetic (–)-schoberine B in $CDCl_3$ and pyr-d_5, natural (–)-schoberine B in pyr-d_5.

Carbon number	**Synthetic $CDCl_3$, δ_{13C}**	**Synthetic Pyr-d_5, δ_{13C}**	**Natural[42k] Pyr-d_5, δ_{13C}**	**Variation $\Delta\delta_{13C}$ (ppm)**
2	39.8	40.6	40.7	-0.1
3	26.2	27.2	27.2	0
4	25.4	26.4	26.3	0.1
4a	35.5	36.4	36.4	0
5	38.5	39.4	39.3	0.1
6	31	31.8	31.8	0
7	36.8	37.6	37.6	0
8	26	27.1	27.1	0
8a	65.1	66	66	0
9	63.6	64.7	64.6	0.1
10a	82.5	83.2	83.2	0
11	29.9	30.6	30.5	0.1
12	24.6	25.6	25.5	0.1
13	25.4	26.4	26.3	0.1
14	56.2	56.8	56.8	0
15	37.1	38.1	38.1	0
16	26.8	27.6	27.7	-0.1
17	26.6	27.3	27.3	0
18	32.8	34.2	34.2	0
19	62.8	62.6	62.6	0

Table 6.6 ^{13}C NMR values of synthetic (–)-schoberine B in $CDCl_3$ and pyr-d_5, natural (–)-schoberine B in pyr-d_5, and the variation of ppm values between the synthetic and the isolated alkaloid.

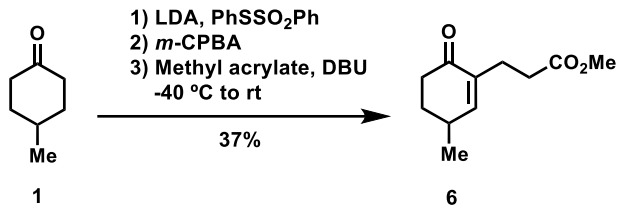


6.3 General Experimental Procedures

General Procedures. All air sensitive reactions were performed under a dry argon or atmosphere with dry, freshly distilled solvents using standard procedures. For reactions that require heating, a hot plate magnetic stirrer with an aluminum heating block was used. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvent was accomplished with a rotatory evaporator. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by either UV or a 1% $KMnO_4$ solution. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh) or amino functionalized SiO_2 (silica gel 60, 200 mesh). NMR spectra were recorded at 400 or 500 MHz (^1H) and 100.6 or 125 MHz (^{13}C), and chemical shifts are reported in δ values, in parts per million (ppm) relative to Me_4Si (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (*J*) in hertz (Hz), integrated intensity, and assignment (when possible). IR spectra were performed in a spectrophotometer Nicolet Avatar 320 FT-IR and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured on Perkin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HMRS) were performed by *Centres Científics i Tecnològics de la Universitat de Barcelona* using an electrospray ionization (ESI) source and a Time of Flight (TOF) analyzer.

6.4 Experimental Procedures and Spectroscopic Data – Chapter 2

Methyl 3-methyl-6-oxocyclohexenepropionate (6):



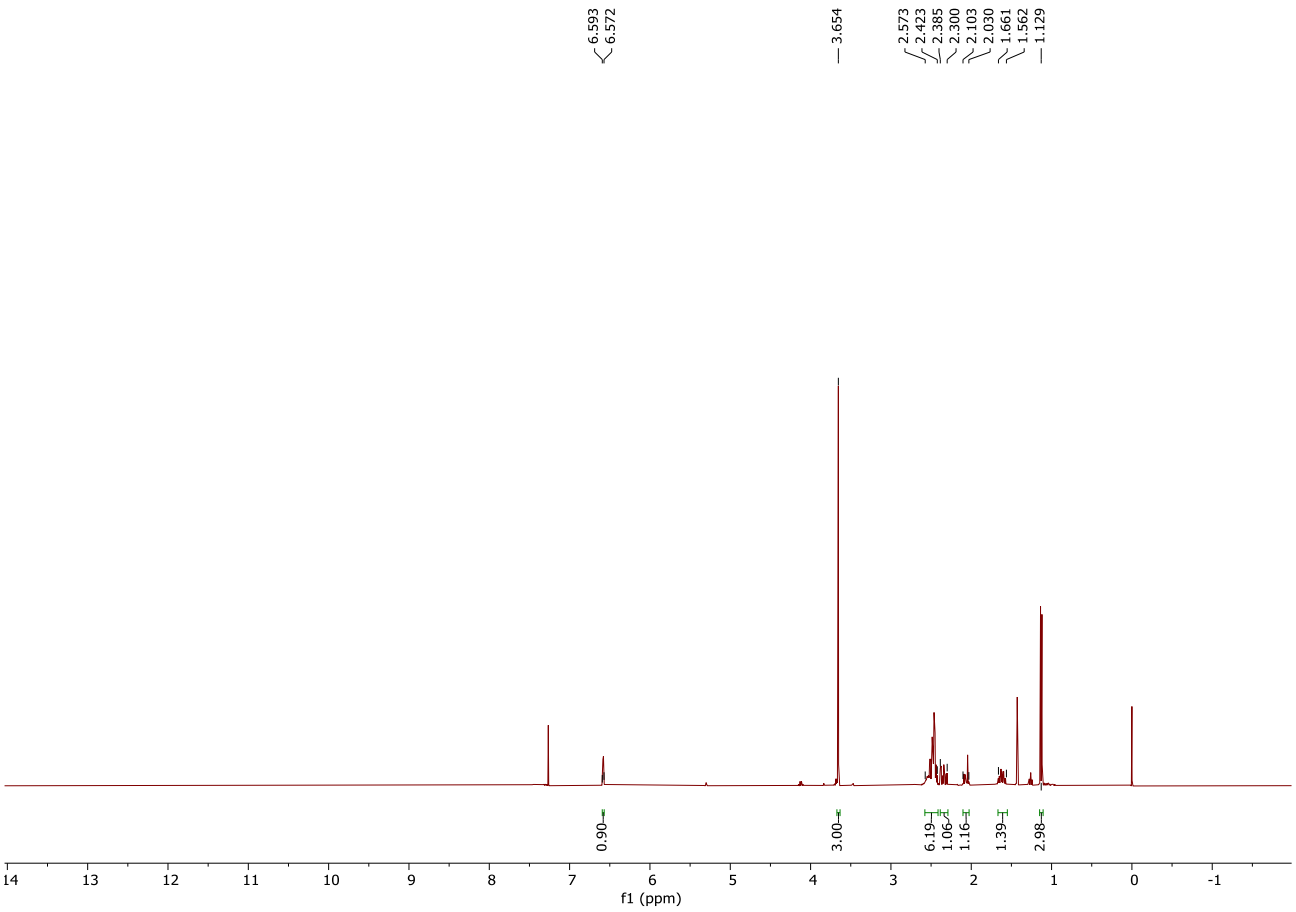
1 6

*First step***:** A solution of LDA (9.4 mL of a 2M solution in THF/heptane/ethylbenzene, 18.72 mmol) was added, under inert atmosphere, to a solution of 4-methylcyclohexanone (2.2 mL, 17.83mmol) in anhydrous THF (180 mL) at –78°C, and the mixture was stirred at this temperature for 30 min. Then, a solution of $PhSSO_2Ph$ (4.46 g, 17.83 mmol) in THF (20 mL) was added and stirring was continued at –78 °C for 1 h and at room temperature for 1 h more. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated.

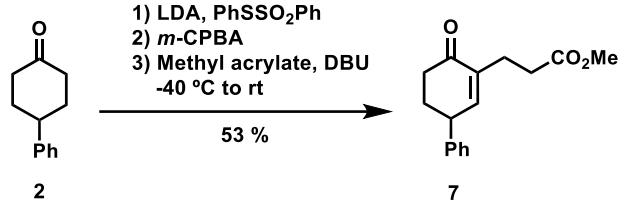
Second step: A solution of *m*-CPBA (3.99 g, 17.83 mmol, 77%) in CH_2Cl_2 (40 mL) was added at –78 °C to a solution of the above crude in CH_2Cl_2 (360 mL). After 5 min, saturated aqueous $Na_2S_2O_3$ was added, and the mixture was cooled down. The resulting mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered and concentrated under vacuum. Flash column chromatography (8:2 to 2:3 hexane–EtOAc) afforded a mixture of sulfoxides (3.263 g, 16.63 mmol).

Third step: DBU (2.3 mL, 15.19 mmol) and methyl acrylate (1.3 mL, 13.81 mmol) were sequentially added to a solution of the above sulfoxide (3.26 g, 13.81 mmol) in DMF (145 mL) at –40 °C, under Ar atmosphere. The mixture was stirred at 10 °C for 1.5 h. Then, saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with Et_2O. The organic extracts were dried, filtered and stirred at room temperature for 23.5 h. The solvent was evaporated under reduced pressure. Flash column chromatography (hexane to 8:2 hexane–EtOAc) afforded the ketoester **6** (1.30 g, 37%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59-6.57 (m, 1H), 3.66 (s, 3H), 2.57-2.42 (m, 6H), 2.39-2.29 (m, 1H), 2.11-2.02 (m, 1H), 1.66-1.56 (m, 1H), 1.13 (d, J = 7.2 Hz, 3H).


6.593
6.572
3.654
2.573
2.423
2.385
2.300
2.103
2.030
1.661
1.562
1.129
0.90
3.00
6.19
1.06
1.16
1.39
2.98
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

Methyl 3-Phenyl-6-oxocyclohexenepropionate (7):

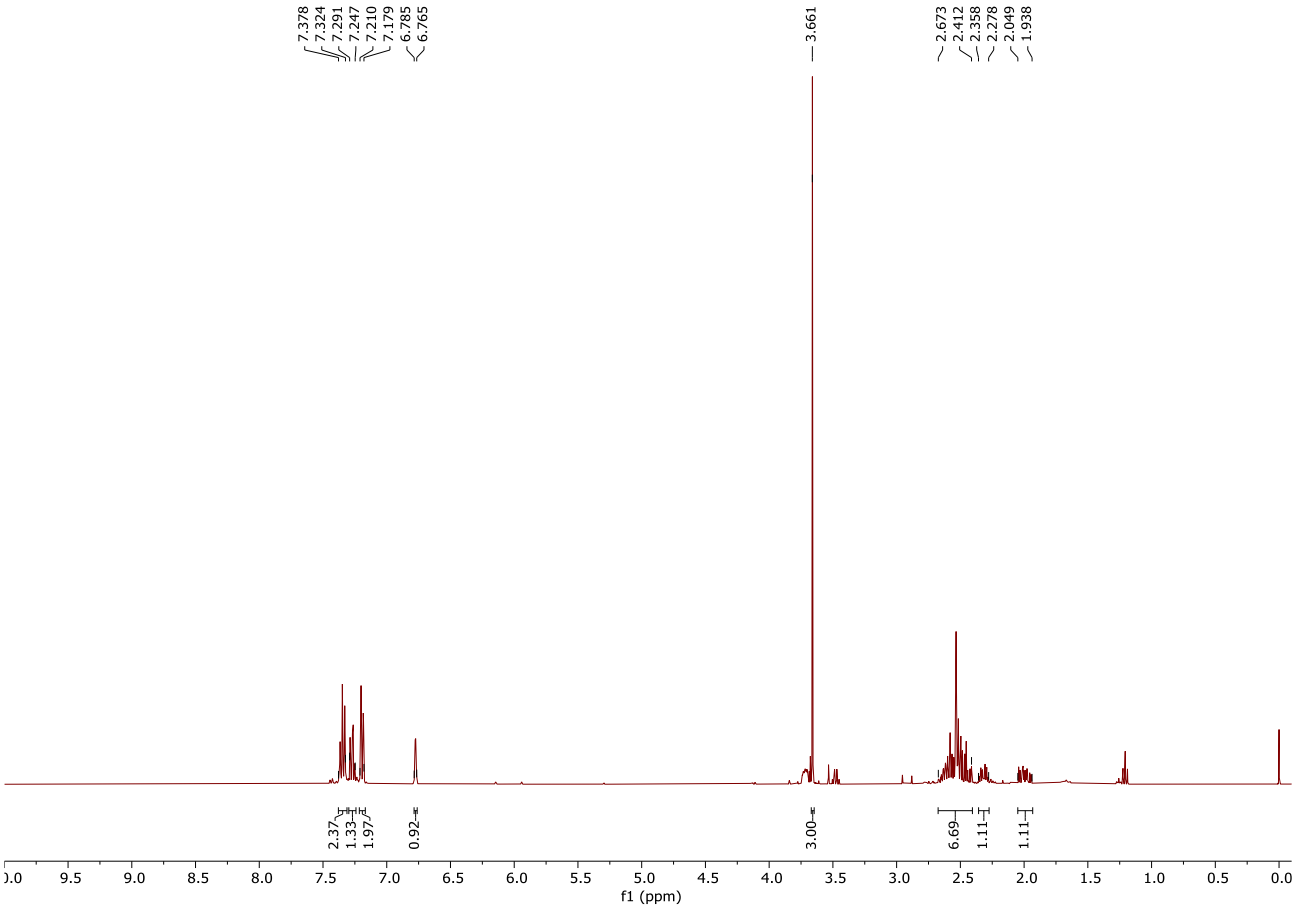


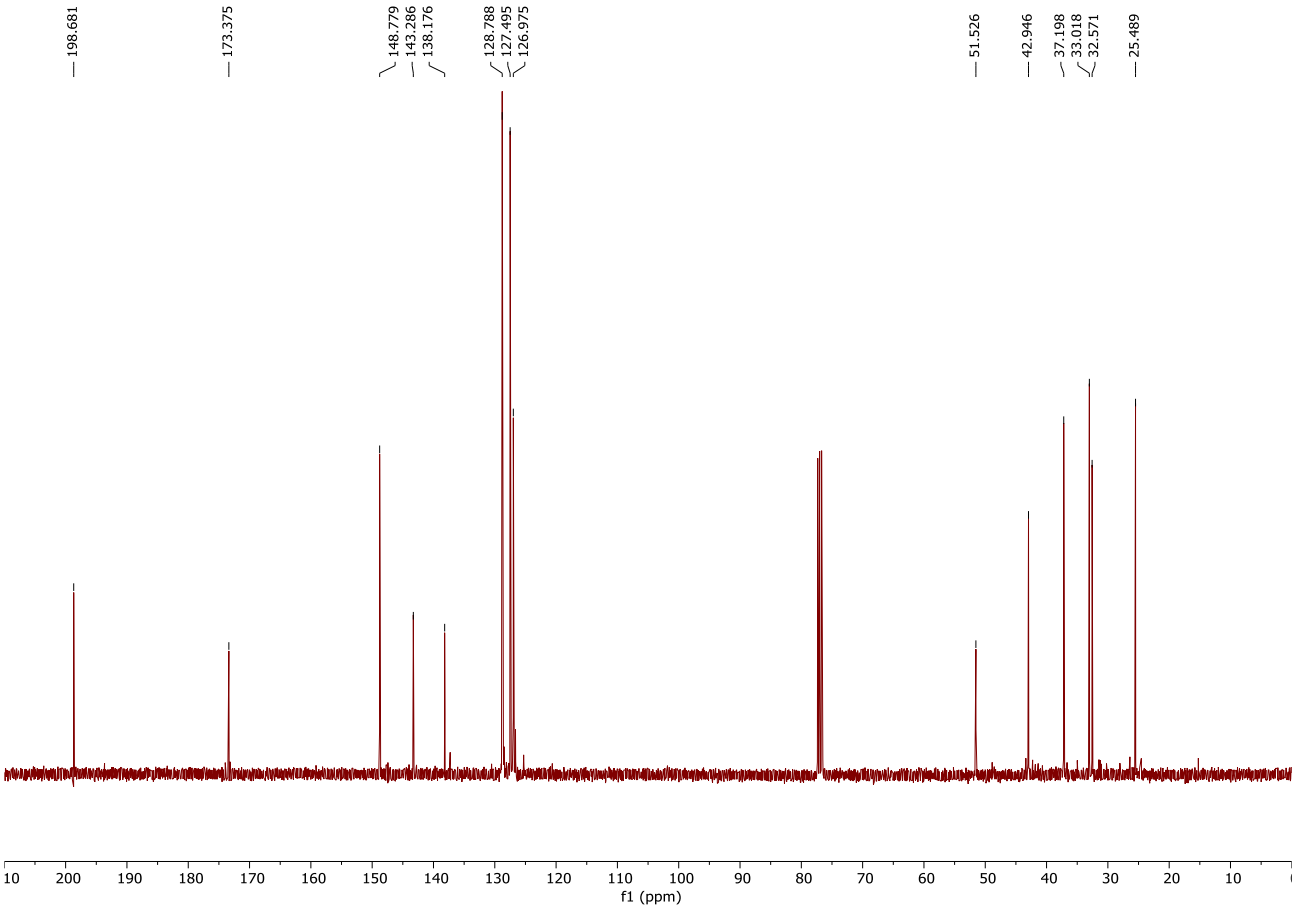
2 7

Operating as described for the preparation of **6**, from 4-phenylcyclohexanone (2.00 g, 11.48 mmol), LDA (6.0 mL of a 2M solution in THF/heptane/ethylbenzene, 12 mmol) in THF (120 mL), and $PhSSO_2Me$ (2.88 g, 11.48 mmol) in THF (20 mL), and then *m*-CPBA (2.57 g, 11.48 mmol, 77%) in CH_2Cl_2 (260 mL) a mixture of sulfoxides (2.30 g, 11.72 mmol) was obtained after flash chromatography (8:2 to 0:1 hexane–EtOAc). Then, DBU (450 µL, 2.95 mmol) and methyl acrylate (250 µL, 13.81 mmol) were added to the solution of sulfoxides in DMF (30 mL). The residue was purified by flash chromatography (hexane to 9:1 hexane–EtOAc) to give ketoacid **7** (1.03 g, 35%).

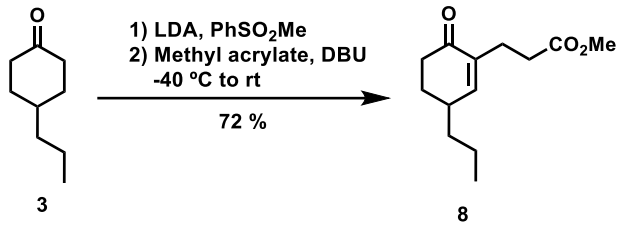
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 2H, ArH), 7.29-7.25 (m, 1H, ArH), 7.21-7.18 (m, 2H ArH), 6.78- 6.76 (m, 1H, H-2), 3.66 (s, 3H, CH_3), 2.67-2.41 (m, 7H), 2.36-2.28 (m, 1H), 2.05-1.94 (m, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.7 (CO), 173.4 (COO), 148.8 (C-2), 143.3 (C-1), 138.2 (C-Ar), 128.8 (CH-Ar), 127.5 (CH-Ar), 127.0 (CH-Ar), 51.5 (CH_3), 42.9 (C-3), 37.2 (CH_2), 33.0 (CH_2), 32.6 (CH_2), 25.5 (CH_2).


7.378
7.324
7.291
7.247
7.210
7.179
6.785
6.765
3.661
2.673
2.412
2.358
2.278
2.049
1.938
2.37
1.33
1.97
0.92
3.00
6.69
1.11
1.11
f1 (ppm)


198.681
173.375
148.779
143.286
138.176
128.788
127.495
126.975
51.526
42.946
37.198
33.018
32.571
25.489
f1 (ppm)

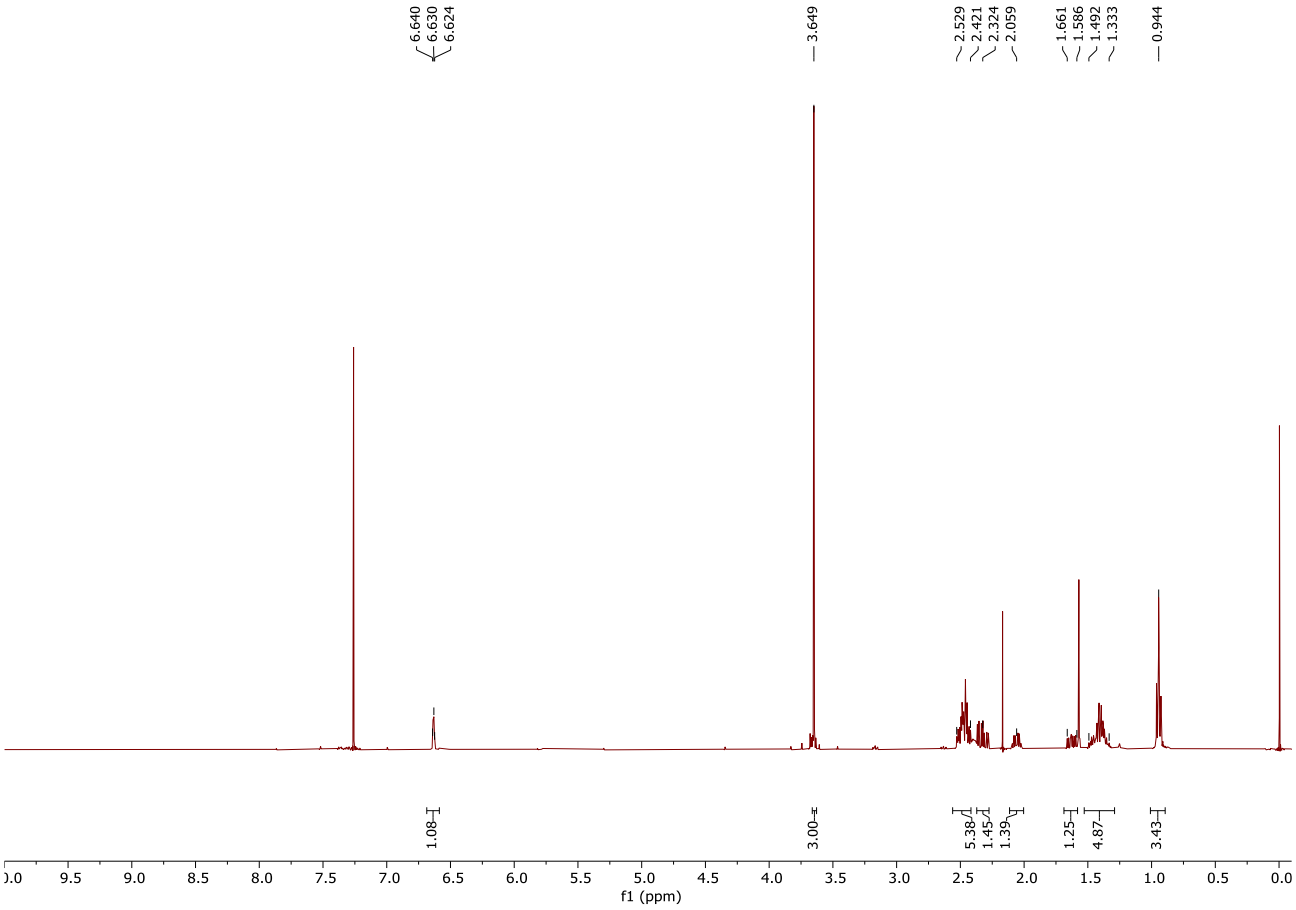
Methyl 3-propyl-6-oxocyclohexenepropionate (8):



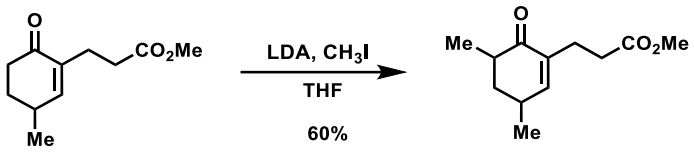
First step: NaHMDS (55.6 mL of a 1M solution in THF, 55.63 mmol) was added to a solution of 4-propylcyclohexanone (6.0 g, 42.85 mmol) in THF (214 mL) at 0 °C. After 20 min, $PhSO_2Me$ (8.66 g, 55.63 mmol) was added, and the reaction was allowed to warm to rt and stirred for 5 h. The solution was quenched with saturated aqueous NH_4Cl, the aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was chromatographed (8:2 hexane–EtOAc to EtOAc) to afford a mixture of sulfoxides (1.1 g, 3.12 mmol).

Second step: DBU (6.5 mL, 42.82 mmol) was slowly added to a solution of the above sulfoxide in DMF (210 mL) at –40 °C, and the mixture was stirred for 20 min. Methyl acrylate (3.8 mL, 42.82 mmol) was added and stirred for 1 h at this temperature. After this time, the reaction was allowed to warm to room temperature for 10 min and then to 40 °C for 2 h. The mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (99:1 to 9:1 hexane–EtOAc) affording compound **8** (6.9 g, 72%) as an oil.

^1H NMR (400 MHz, $CDCl_3$) δ 6.64-6.63 (m, 1H, H-2), 3.65 (s, 3H, CH_3O), 2.53-2.42 (m, 5H), 2.32 (ddd, *J* = 16.8, 12.4, 4.8 Hz, 1H), 2.05 (dcd, J = 18.0, 4.4, 0.8 Hz, 1H), 1.66-1.59 (m, 1H), 1.49-1.33 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 3H).


6.640
6.630
6.624
3.649
2.529
2.421
2.324
2.059
1.661
1.586
1.492
1.333
0.944
1.08
3.00
5.38
1.45
1.39
1.25
4.87
3.43
f1 (ppm)

Methyl 3,5-dimethyl-6-oxocyclohexenepropionate (9).



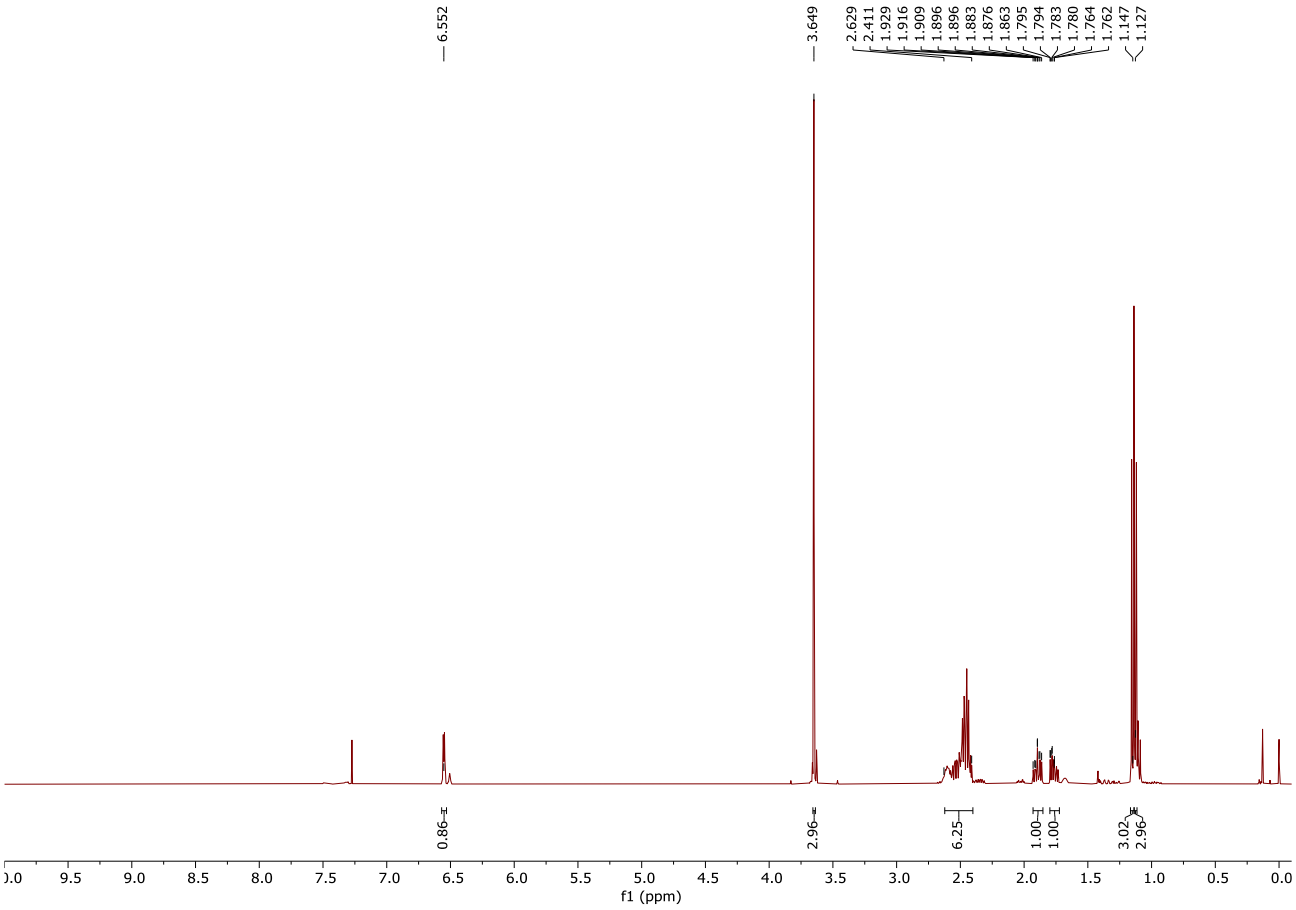
6 9

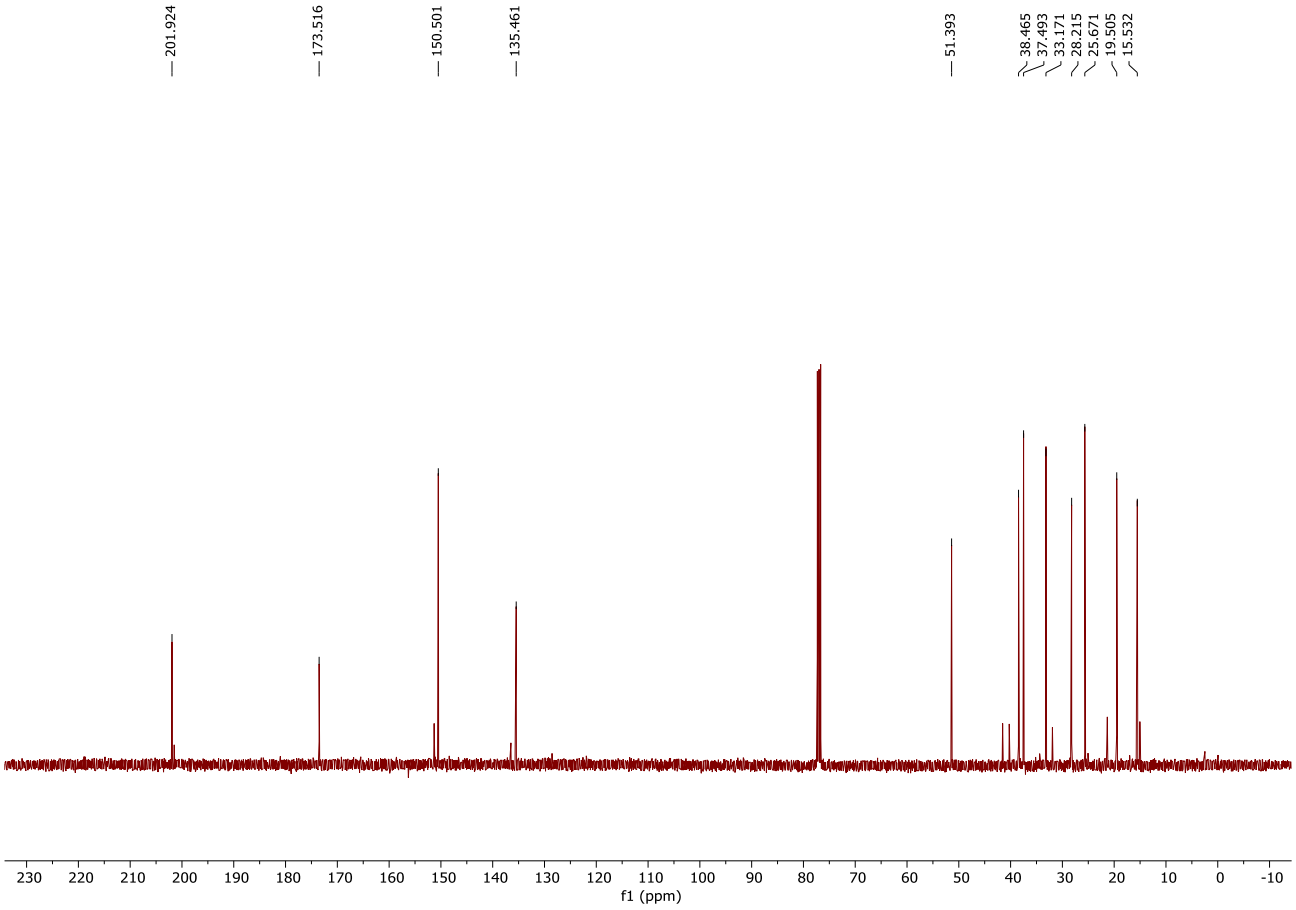
LiHMDS (7.0 mL of a 1 M solution in THF, 7.0 mmol) was added dropwise to a solution of ketoester **x** (1.31 g, 6.67 mmol) in anhydrous THF (15 mL) at –78 °C, and the mixture was stirred at this temperature for 30 min. Then, MeI (2.1 mL, 33.33 mmol) was added at –78 °C, and the stirring was continued at room temperature for 16 hours. Saturated aqueous NH_4Cl (7.5 mL) was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated. Flash chromatography (from hexane to 9:1 hexane–EtOAc) afforded ketoester **9** (840 mg, 60%, diastereomeric mixture) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, *J* = 3.7 Hz, H-2), 3.65 (s, 3H, CH_3O), 2.41-2.62 (m, 6H), 1.90 (ddd, *J* = 13.2, 8.0, 5.2 Hz, 1H, H-4_{ax}), 1.74 (dddd, *J* = 13.2, 6.0, 4.8, 0.4 Hz, 1H, H-4_{ec}), 1.14 (d, *J* = 7.2 Hz, 3H, CH_3), 1.13 (d, *J* = 7.2 Hz, 3H, CH_3).

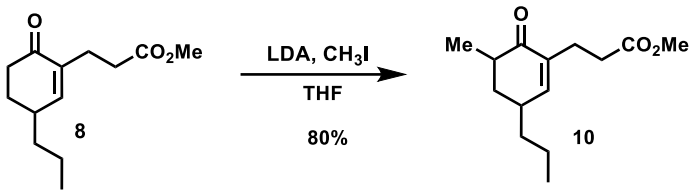
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.90 (CO), 173.50 (COO), 150.48 (C-2), 135.45 (C-1), 51.39 (O*C*H_3), 38.46 (CH), 37.49 (CH_2), 33.17 (CH_2), 28.21 (CH_2), 25.67 (CH), 19.5 (CH_3), 15.3 (CH_3).

HRMS Calcd for [$C_{12}H_{18}O_3$+H^+]: 211.1329; found 211.1328.


6.552
3.649
2.629
2.411
1.929
1.916
1.909
1.896
1.896
1.883
1.876
1.863
1.795
1.794
1.783
1.780
1.764
1.762
1.147
1.127
0.86
2.96
6.25
1.00
1.00
3.02
2.96
f1 (ppm)


201.924
173.516
150.501
135.461
51.393
38.465
37.493
33.171
28.215
25.671
19.505
15.532
f1 (ppm)

Methyl 3-Butyl-5-methyl-6-oxocyclohexenepropionate (10):

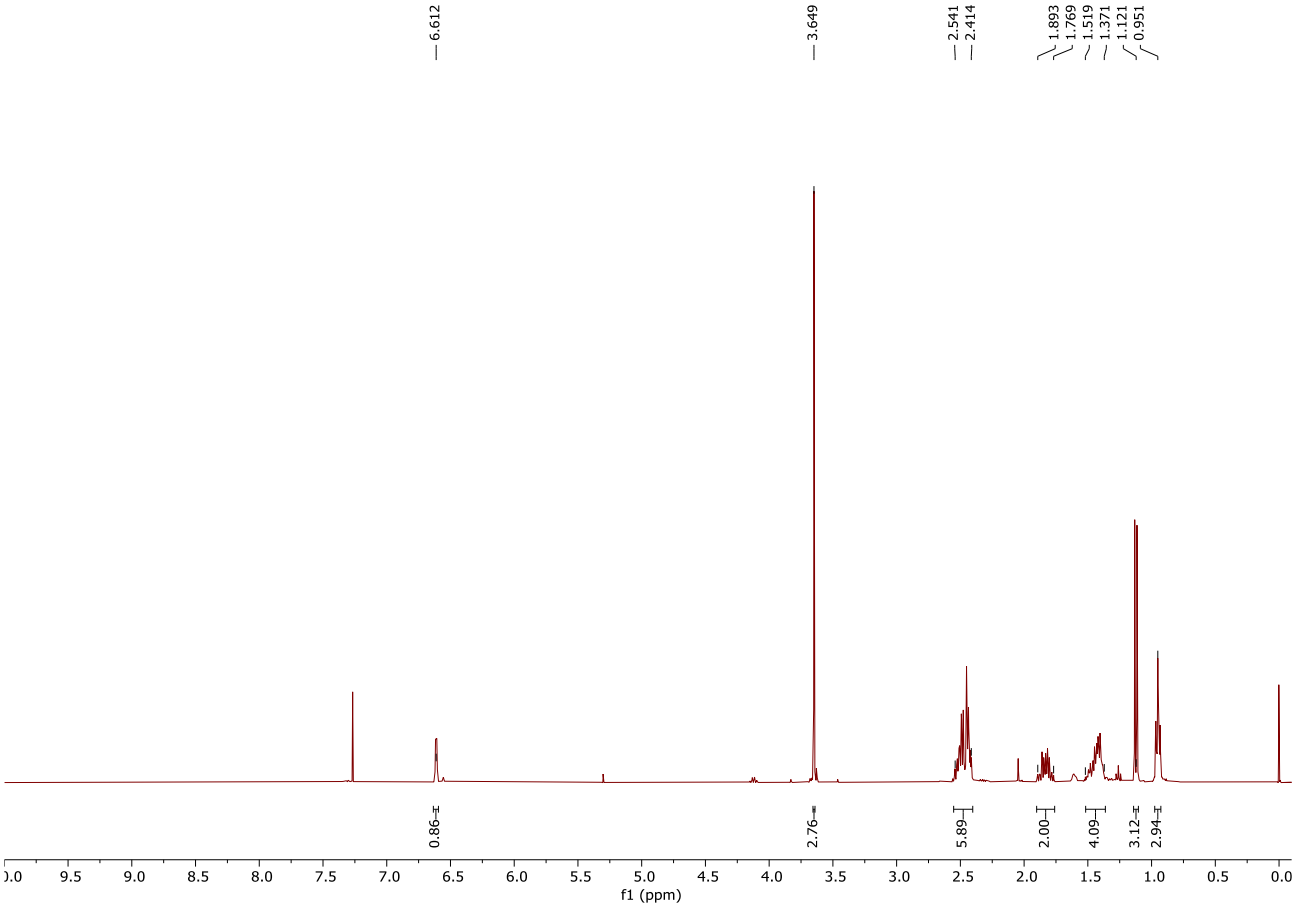


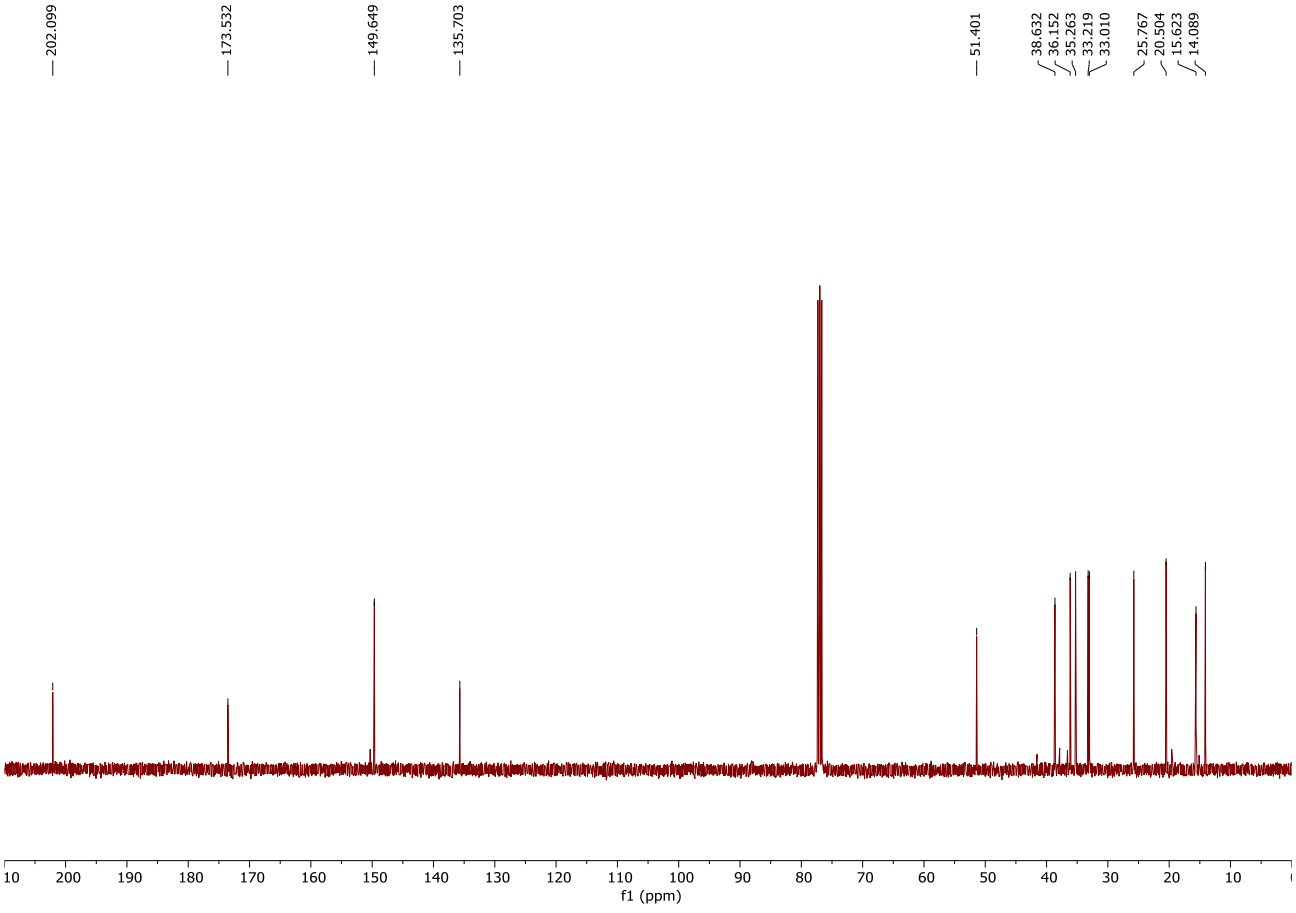
Operating as described in the preparation of ketoester **9**, LiHMDS (2.0 mL of a 1M solution in THF, 2.0 mmol), MeI (0.6 mL, 9.52 mmol) and ketoester **8** (427 mg, 1.90 mmol) in anhydrous THF (5.0 mL), ketoester **10** (364 mg, 80%, diastereomeric mixture) was obtained after flash column chromatography (hexane to 9:1 hexane–EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, *J* = 3.6 Hz, 1H), 3.65 (s, 3H), 2.54-2.41 (m, 6H), 1.89-1.77 (m, 2H), 1.52-1.37 (m, 2H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 6.8 Hz, 3H).

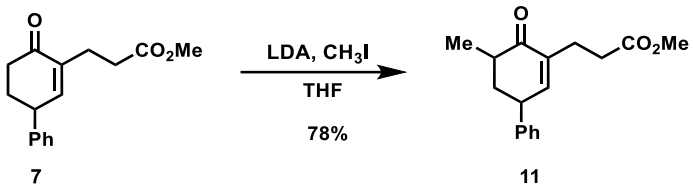
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.1 (CO), 173.5 (COO), 149.6 (C-2), 135.7 (C-3), 51.4 (CH_3O), 38.6 (CH), 36.1 (CH_2), 35.2 (CH_2), 33.2 (CH_2), 33.0 (CH), 25.8 (CH_2), 20.5 (CH_2), 15.6 (CH_3), 14.1 (CH_3).

HRMS Calcd for [$C_{14}H_{22}O_3$ +H^+]: 239.1642; found 239.1639


6.612
3.649
2.541
2.414
1.893
1.769
1.519
1.371
1.121
0.951
0.86
2.76
5.89
2.00
4.09
3.12
2.94
f1 (ppm)


202.099
173.532
149.649
135.703
51.401
38.632
36.152
35.263
33.219
33.010
25.767
20.504
15.623
14.089
f1 (ppm)

Methyl 3-phenyl-5-methyl-6-oxocyclohexenepropionate (11).



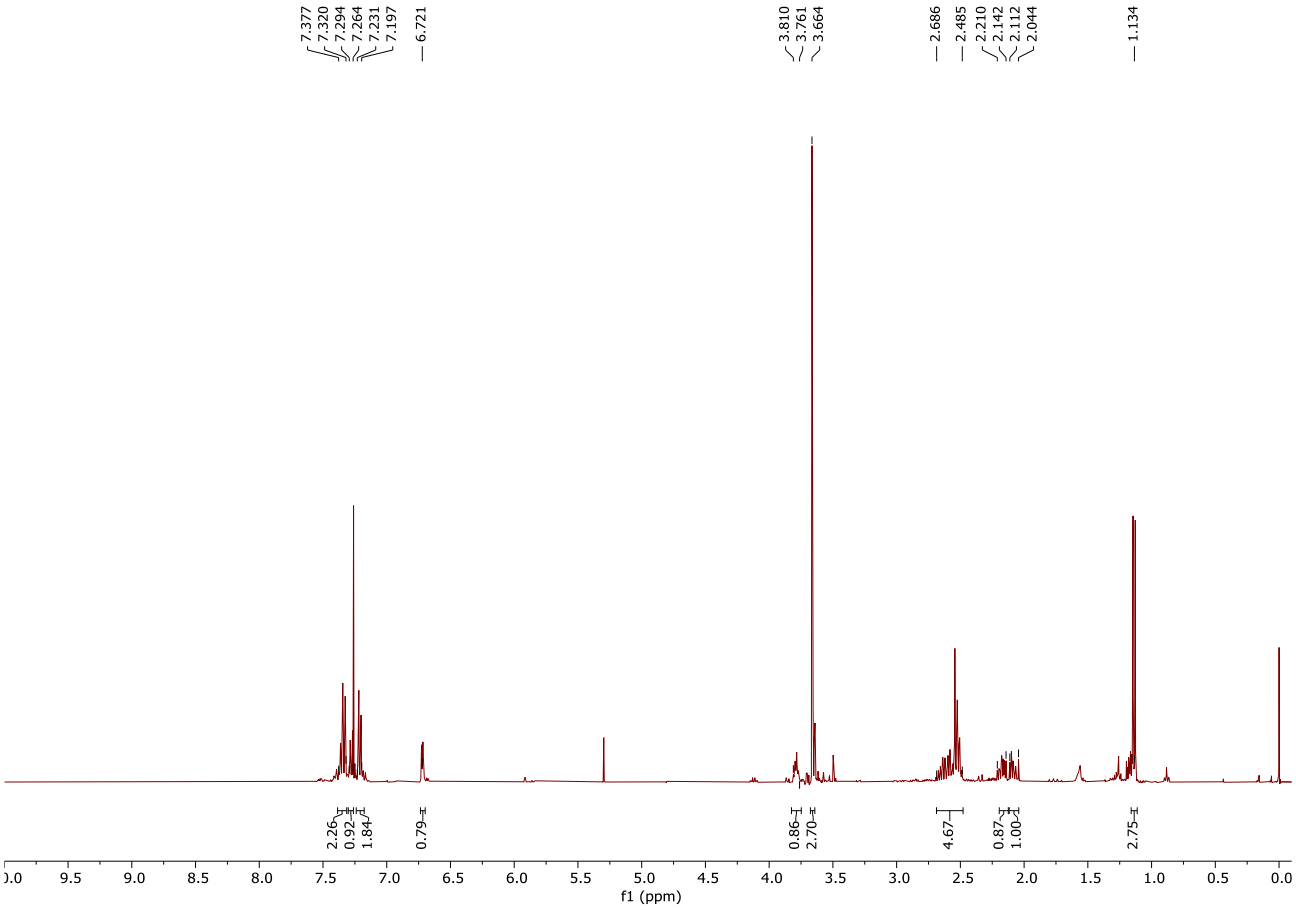
7 11

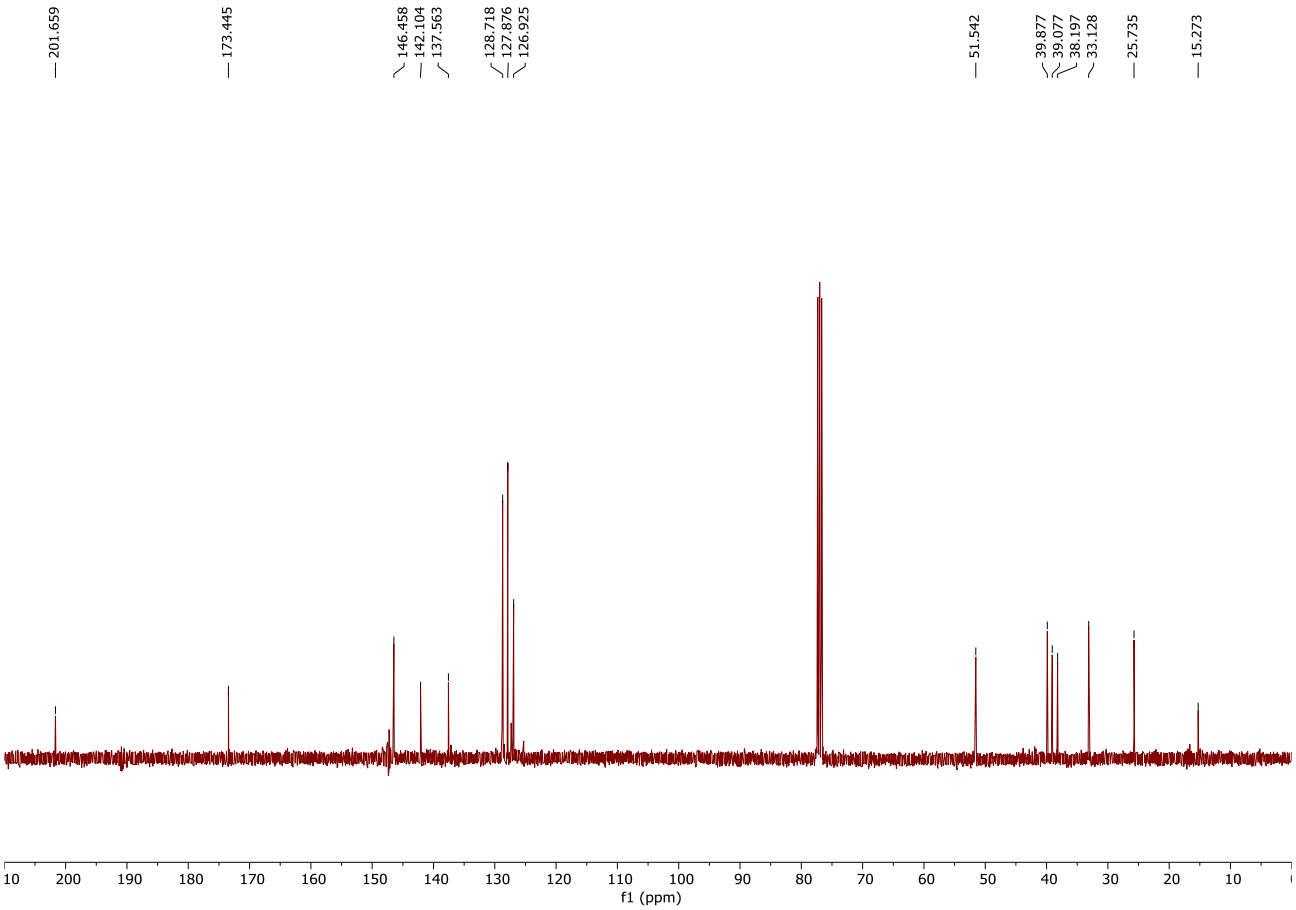
Operating as described in the preparation of ketoester **9**, LiHMDS (3.9 mL of a 1M solution in THF, 3.9 mmol), MeI (1.2 mL, 18.84 mmol) and ketoester **7** (0.971 g, 3.77 mmol) in anhydrous THF (8.5 mL), ketoester **11** (799 mg, 78%, diastereomeric mixture) was obtained after flash column chromatography (hexane to 9:1 hexane–EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 2H, ArH), 7.29-7.26 (m, 1H, ArH), 7.23-7.20 (m, 2H, ArH), 6.72 (d, *J* = 4.4 Hz, 1H, H-2), 3.81-3.76 (m, 1H), 3.66 (s, 3H, CH_3O), 2.69-2.49 (m, 5H), 2.21-2.14 (m, 1H), 2.11-2.04 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H, CH_3).

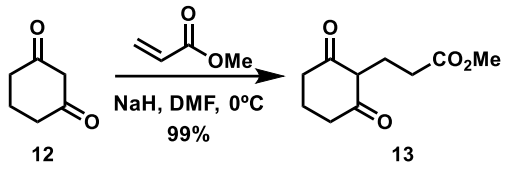
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.7 (CO), 173.4 (COO), 146.5 (C-2), 142.1 (C-Ar), 137.6 (C-1), 128.7 (CH-Ar), 127.9 (CH-Ar), 126.9 (CH-Ar), 51.5 (CH_3O), 39.9 (CH), 39.1 (CH_2), 38.2 (CH), 33.1 (CH_2), 25.7 (CH_2), 15.3 (CH_3).

HRMS Calcd for [$C_{17}H_{20}O_3$+H^+]: 273.1485; found 273.1481.


7.377
7.320
7.294
7.264
7.231
7.197
6.721
3.810
3.761
3.664
2.686
2.485
2.210
2.142
2.112
2.044
1.134
2.26
0.92
1.84
0.79
0.86
2.70
4.67
0.87
1.00
2.75
f1 (ppm)

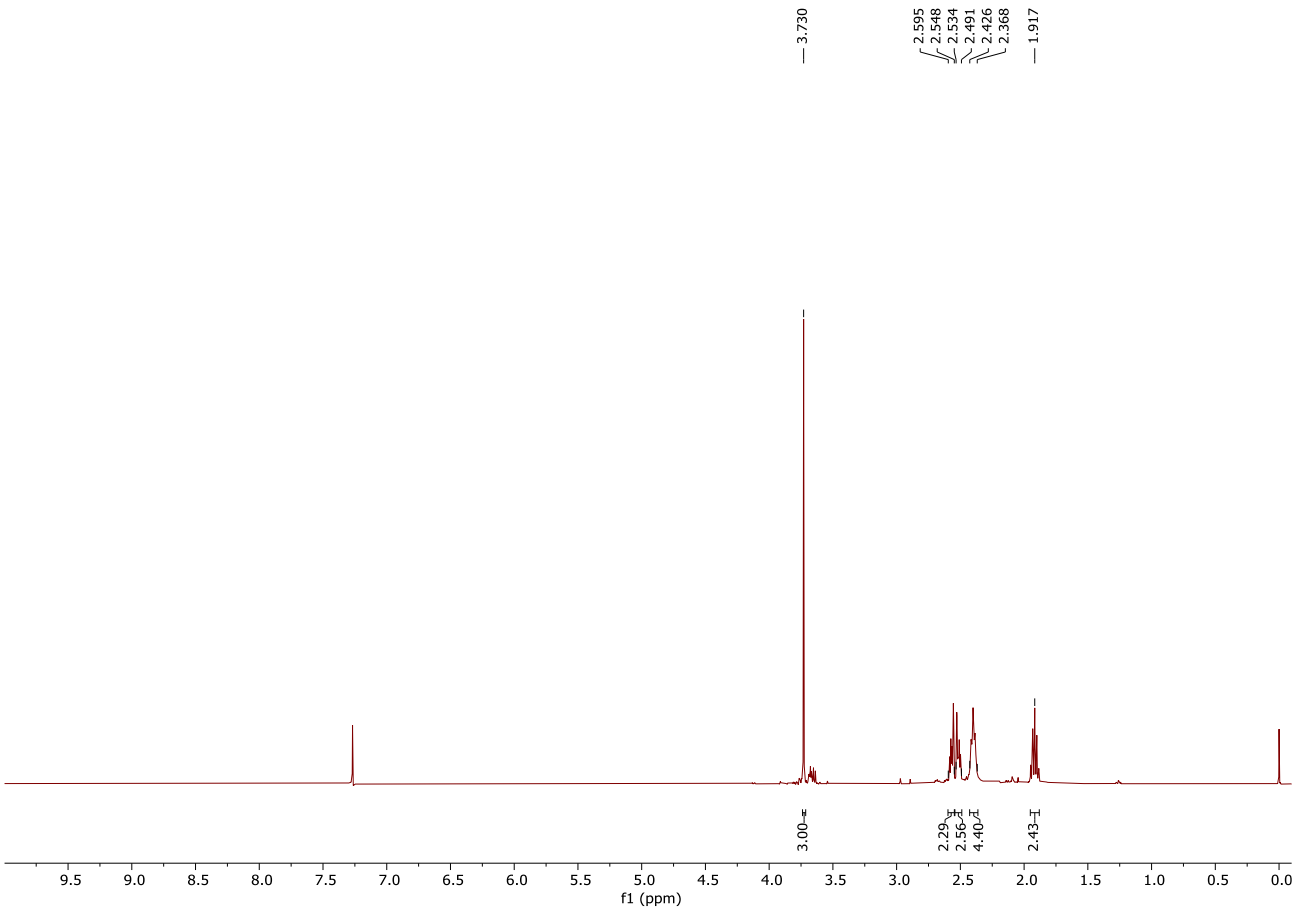

201.659
173.445
146.458
142.104
137.563
128.718
127.876
126.925
51.542
39.877
39.077
38.197
33.128
25.735
15.273
f1 (ppm)

Methyl 2,6-dioxocyclohexanepropionate (13):

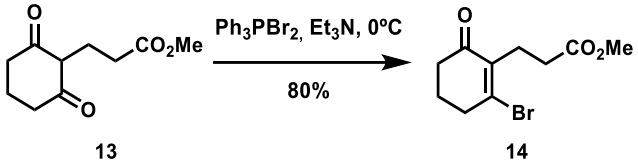


A solution of 1,3-cyclohexanedione **12** (31 g, 0.268 mmol, 97%) in anhydrous DMF (119 mL) was added to a suspension of NaH (6.77 g, 0.268 mmol, 95%) in anhydrous DMF (150 mL) at 0 °C. After 30 minutes at 0 °C, methyl acrylate (29 mL, 0.322 mmol) was added, and the mixture was heated to 80 °C for 6 h. The reaction mixture was cooled to room temperature and 2M HCl was added until pH = 1, and the crude mixture was extracted with EtOAc. The organic extracts were dried and concentrated to afford pure compound **13** (52.5 g, 99%) as a brown gum.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H, CH_3), 2.59-2.55 (m, 2H), 2.53-2.49 (m, 3H), 2.43-2.37 (m, 4H), 1.92 (quint, *J* = 6.0 Hz, 2H, H-4).


3.730
2.595
2.548
2.534
2.491
2.426
2.368
1.917
3.00
2.29
2.56
4.40
2.43
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

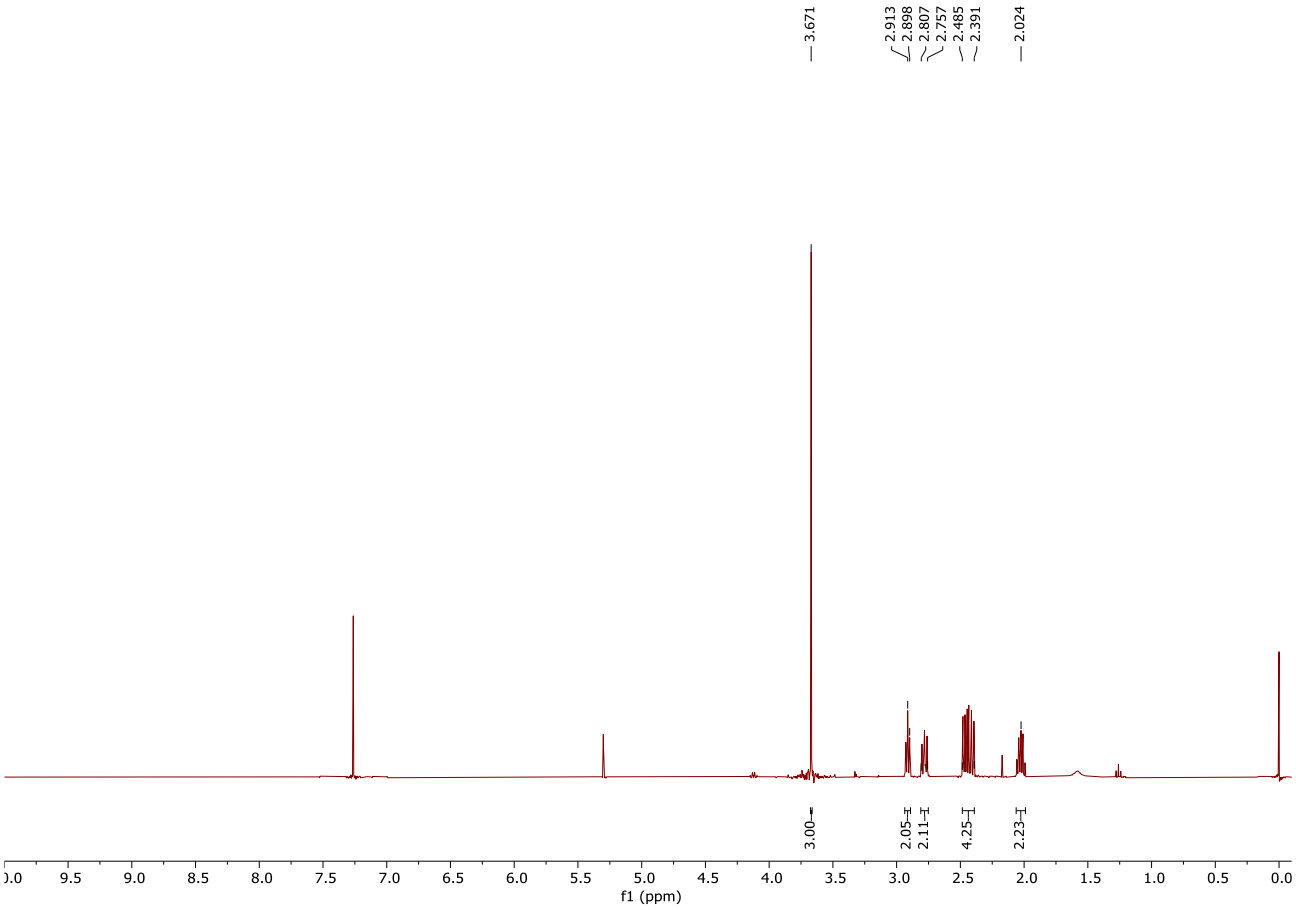
Methyl 2-Bromo-6-oxocyclohexenepropionate (14):



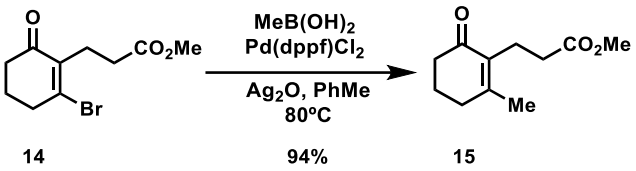
13 14

Et_3N (5.8 mL, 41.7 mmol) and methyl 2,6-dioxocyclohexanepropionate **13** (7.87 g, 39.69 mmol) were added to a solution of Ph_3PBr_2 (18.32 g, 41.7 mmol, 96%) in CH_2Cl_2 (130 mL) at room temperature, and the mixture was stirred for 17 h. Then, the solvent was evaporated Flash column chromatography (9:1 hexane–EtOAc), afforded ketoester **14** (8.192.4 g, 80%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H, CH_3), 2.91 (t, *J* = 6.0 Hz, 2H), 2.81-2.76 (m, 2H), 2.48-2.39 (m, 2H), 2.02 (quint, *J* = 6.0 Hz, 2H, H-4).


3.671
2.913
2.898
2.807
2.757
2.485
2.391
2.024
3.00
2.05
2.11
4.25
2.23
f1 (ppm)

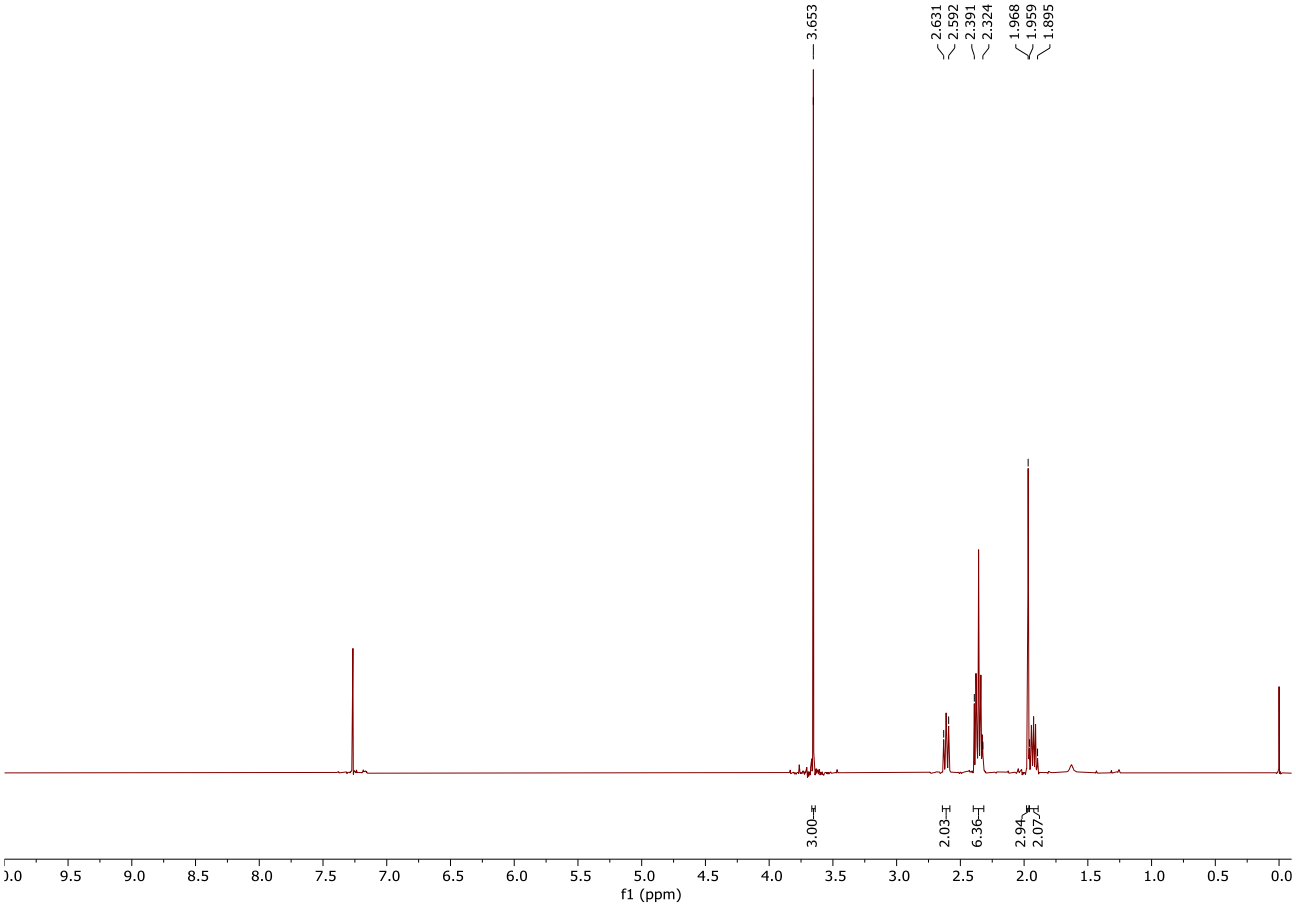
Methyl 2-Methyl-6-oxocyclohexenepropionate (15).



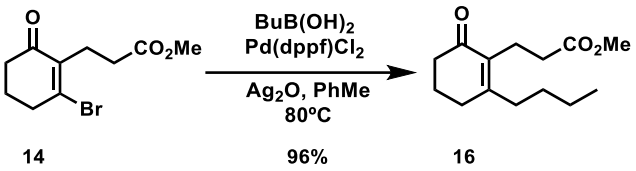
14 94% 15

(dppf)$PdCl_2$ (42 mg, 0.057 mmol), methylboronic acid (229 mg, 3.83 mmol), Ag_2O (887 mg, 3.83 mmol) and K_2CO_3 (794 mg, 5.75 mmol) were sequentially added, under Ar atmosphere, to a solution of bromoenone **14** (500 mg, 1.92 mmol) in anhydrous and deoxygenated toluene (12 mL). The black mixture was stirred at 80 °C for 16 h. After cooling to room temperature, Et_2O was added, and the resulting suspension was filtered over Celite®. The filtrate was washed with H_2O, dried, filtered and evaporated to give ketoester **15** (353 mg, 94%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H, OCH_3), 2.63-2.59 (m, 2H), 2.39-2.32 (m, 6H), 1.97 (s, 3H, CH_3), 1.96-1.89 (m, 2H).


3.653
2.631
2.592
2.391
2.324
1.968
1.959
1.895
3.00
2.03
6.36
2.94
2.07
f1 (ppm)

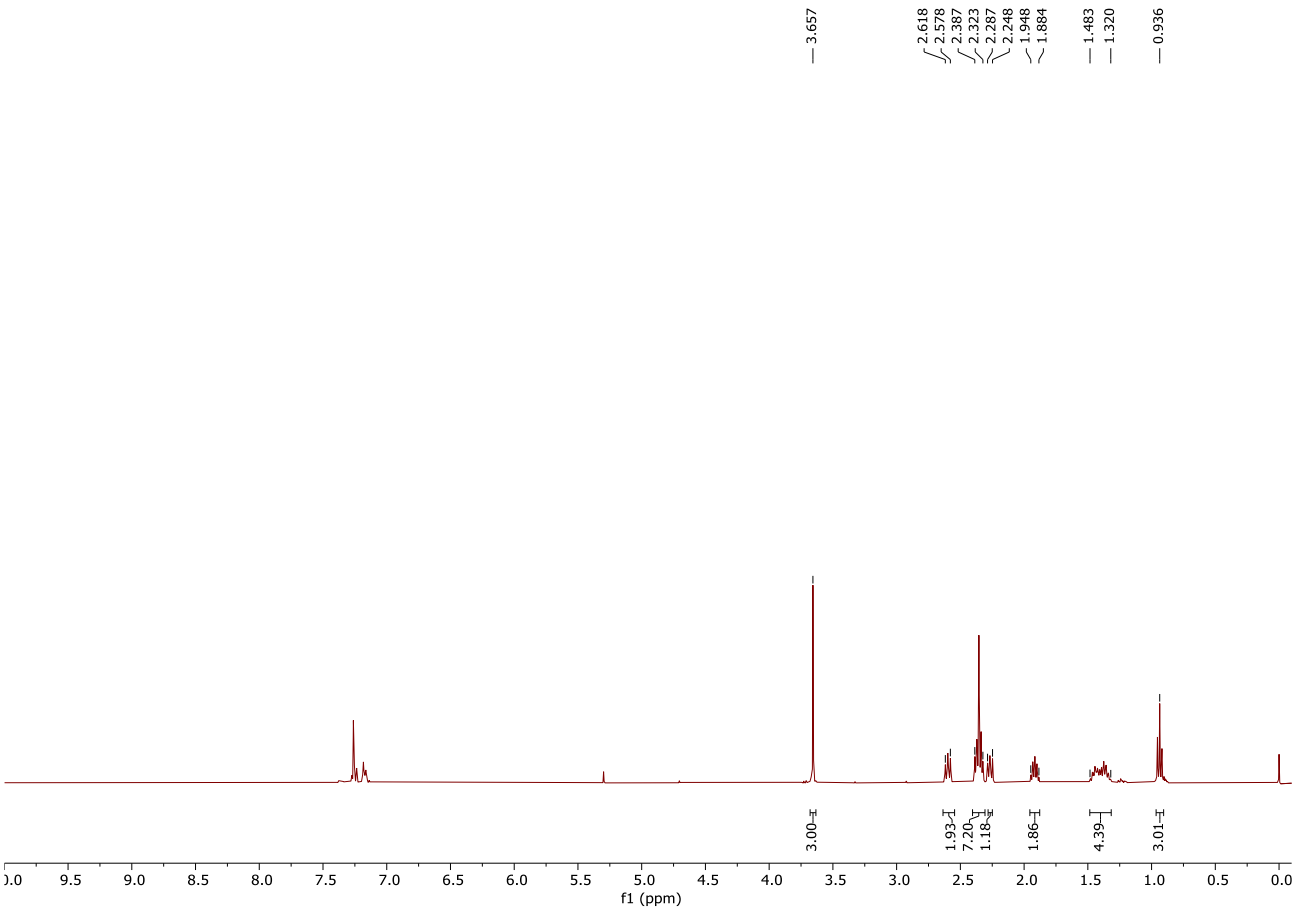
Methyl 2-Butyl-6-oxocyclohexenepropionate (16):



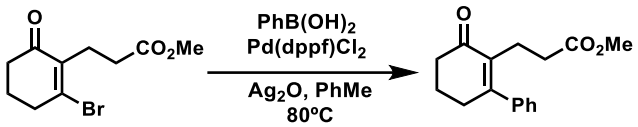
14 **96%** **16**

Operating as in the preparation of **15**, (dppf)$PdCl_2$ (84 mg, 0.115 mmol), butylboronic acid (820 mg, 8.04 mmol), Ag_2O (1.78 g, 7.66 mmol), K_2CO_3 (1.59 g, 11.49 mmol), and bromoenone **14** (1.00 g, 3.83 mmol) in anhydrous and deoxygenated toluene (23 mL) gave ketoester **16** (875 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.62-2.58 (m, 2H), 2.39-2.32 (m, 7H), 2.29-2.25 (m, 1H) 1.92 (m, 2H), 1.48-1.32 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H).


3.657
2.618
2.578
2.387
2.323
2.287
2.248
1.948
1.884
1.483
1.320
0.936
3.00
1.93
7.20
1.18
1.86
4.39
3.01
f1 (ppm)

Methyl 2-Phenyl-6-oxocyclohexenepropionate (17):



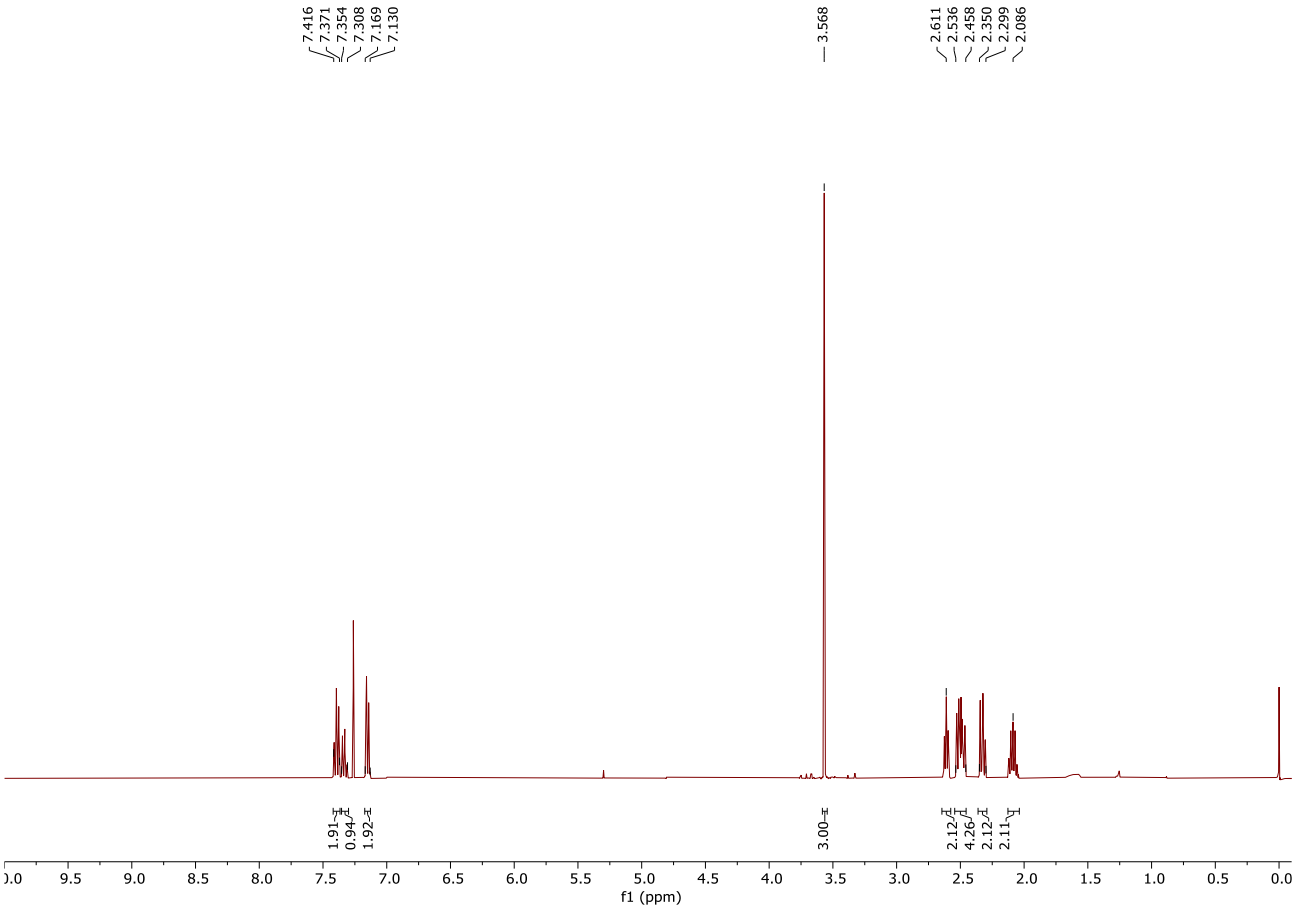
14 82% 17

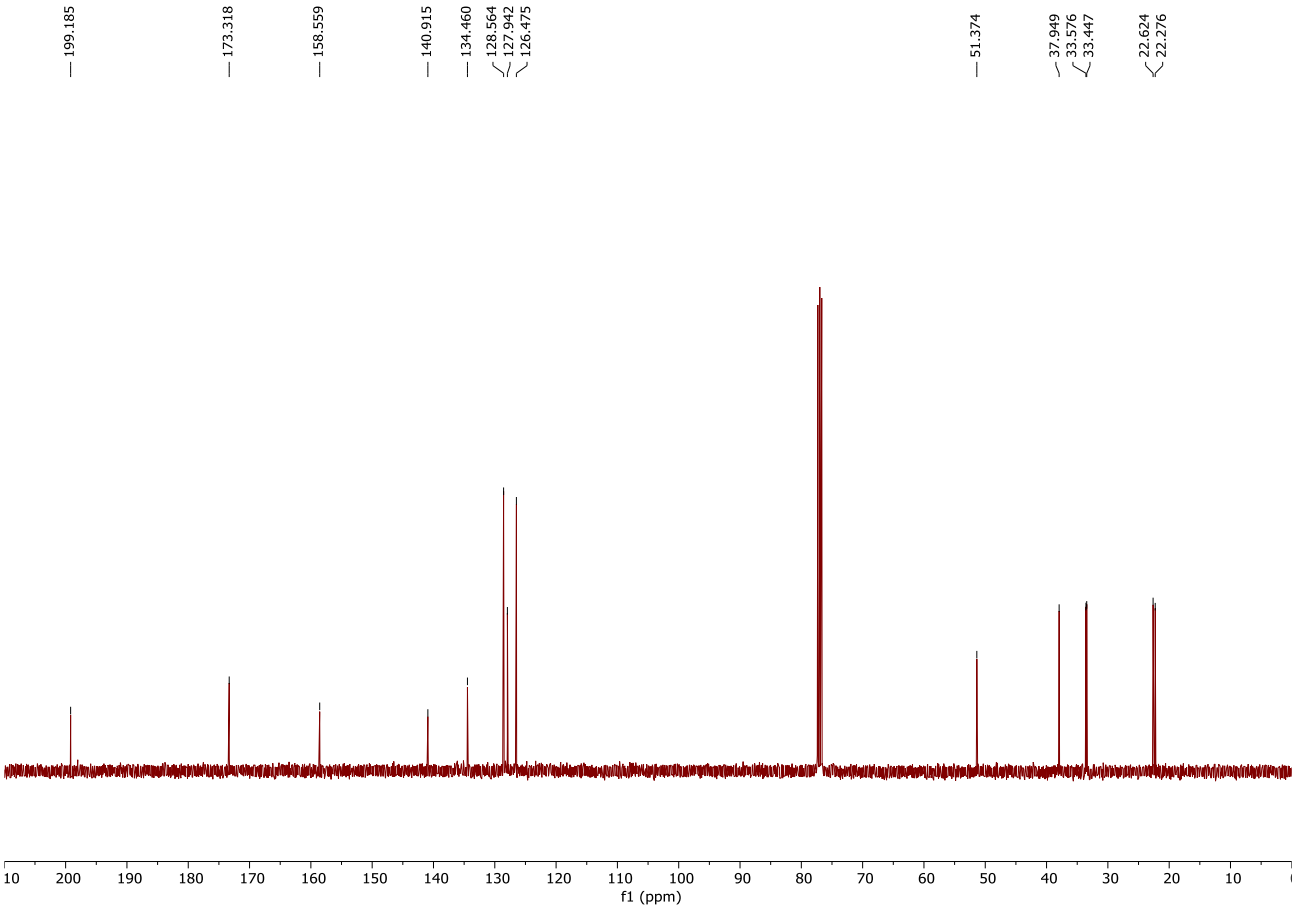
Operating as in the preparation of **15**, (dppf)$PdCl_2$ (84 mg, 0.115 mmol), phenylboronic acid (980 mg, 8.04 mmol), Ag_2O (1.78 g, 7.66 mmol), K_2CO_3 (1.59 g, 11.49 mmol), and bromoenone **14** (1.00 g, 3.83 mmol) in anhydrous and deoxygenated toluene (23 mL) gave ketoester **17** (809 mg, 82%) after flash column chromatography (hexane to 7:3 hexane–EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H, ArH), 7.35-7.31 (m, 1H, ArH), 7.17-7.13 (m, 2H, ArH), 3.57 (s, 3H CH_3O), 2.61 (t, *J* = 6.0 Hz, 2H, H-5), 2.54-2.46 (m, 4H), 2.35-2.30 (m, 2H), 2.09 (quint, *J* = 6.0 Hz, 2H, H-4).

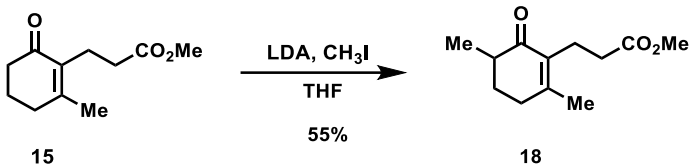
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.2 (CO), 173.3 (COO), 158.6 (C), 140.9 (C), 134.5 (C-Ar), 128.6 (CH-Ar), 127.9 (CH-Ar), 126.5 (CH-Ar), 51.4 (CH_3O), 37.9 (CH_2), 33.6 (CH_2), 33.4 (CH_2), 22.6 (CH_2), 22.3 (CH_2).

HRMS Calcd for [$C_{16}H_{18}O_3 + H^+$]: 259.1329; found 259.1329.


7.416
7.371
7.354
7.308
7.169
7.130
3.568
2.611
2.536
2.458
2.350
2.299
2.086
1.91
0.94
1.92
3.00
2.12
4.26
2.12
2.11
f1 (ppm)


199.185
173.318
158.559
140.915
134.460
128.564
127.942
126.475
51.374
37.949
33.576
33.447
22.624
22.276
f1 (ppm)

Methyl 2,5-dimethyl-6-oxocyclohexenepropionate (18).



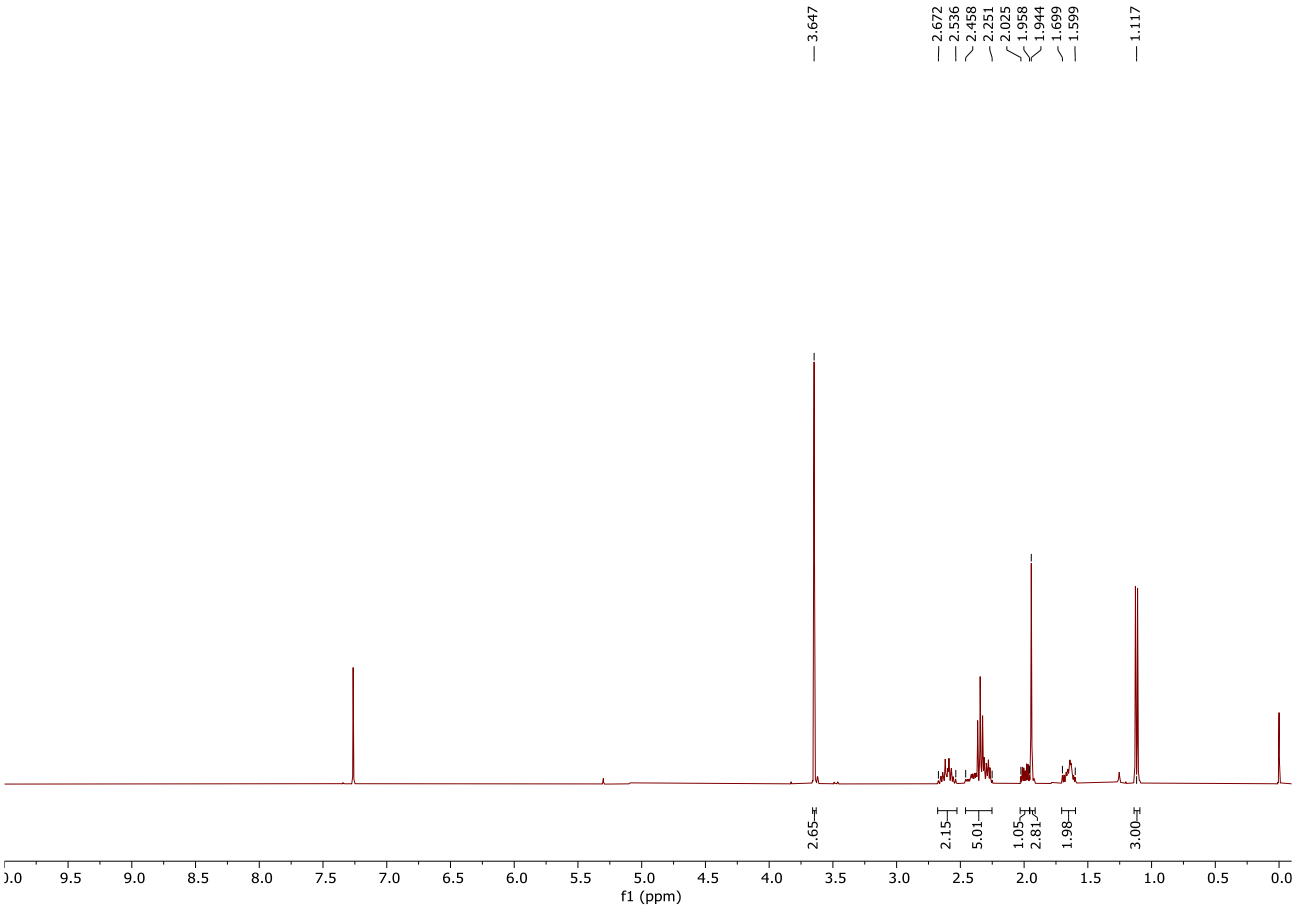
15 18

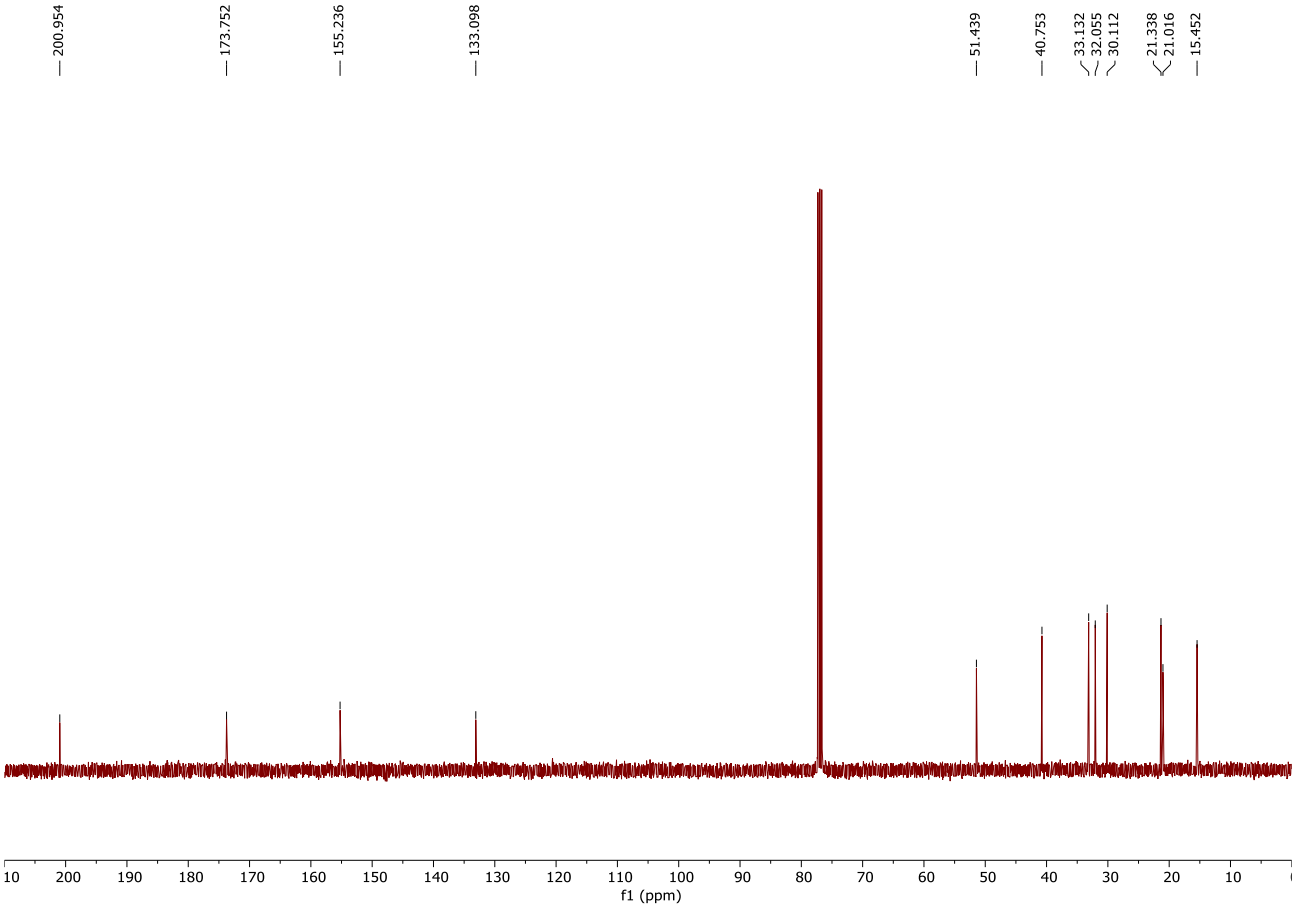
Operating as described in the preparation of ketoester **9**, LiHMDS (1.9 mL of a 1M solution in THF, 1.89 mmol), MeI (0.6 mL, 8.99 mmol) and ketoester **15** (353 mg, 1.80 mmol) in anhydrous THF (4 mL), ketoester **18** (209 mg, 55%) was obtained after flash column chromatography (hexane to 9:1 hexane–EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H, CH_3O), 2.67-2.54 (m, 2H), 2.46-2.25 (m, 5H), 2.03-1.96 (m, 1H), 1.94 (s, 3H, CH_3C-2), 1.70- 1.60 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H, CH_3C-5).

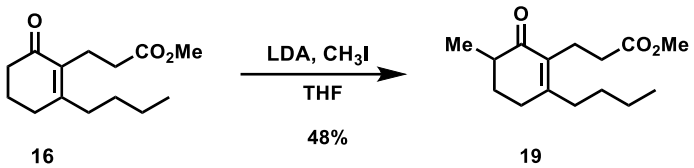
^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 201.0 (CO), 173.8 (COO), 155.2 (C-2), 133.1 (C-1), 51.5 (CH_3O), 40.8 (C-5), 33.2 (CH_2), 32.1 (CH_2), 30.1 (CH_2), 21.4 (CH_2), 21.0 (CH_3), 15.5 (CH_3).

HRMS Calcd for [$C_{12}H_{18}O_3 + H^+$]: 211.1329; found 211.1331.


3.647
2.672
2.536
2.458
2.251
2.025
1.958
1.944
1.699
1.599
1.117
2.65
2.15
5.01
1.05
2.81
1.98
3.00
f1 (ppm)


200.954
173.752
155.236
133.098
51.439
40.753
33.132
32.055
30.112
21.338
21.016
15.452
f1 (ppm)

Methyl 2-butyl-5-methyl-6-oxocyclohexenepropionate (19):



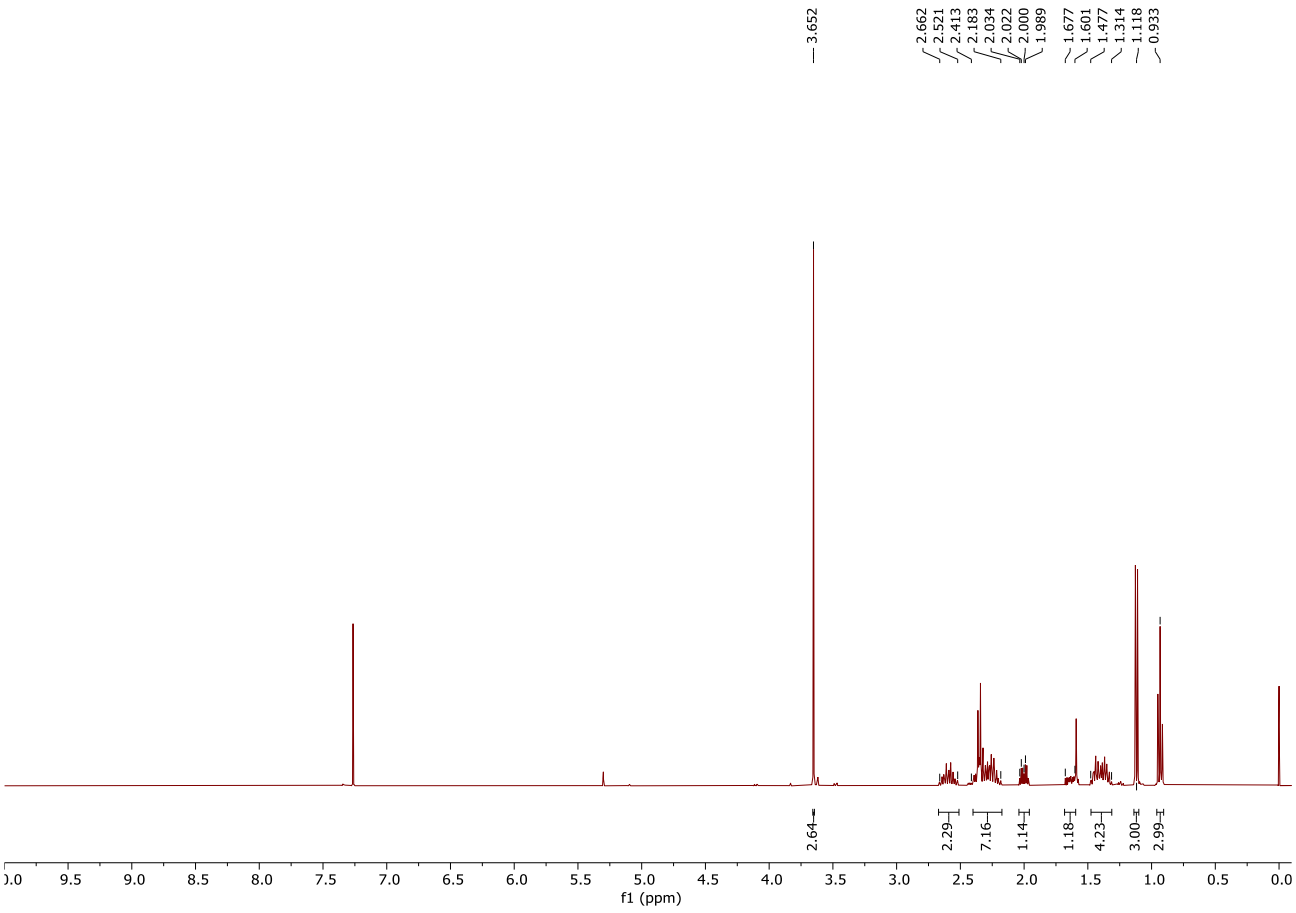
16 19

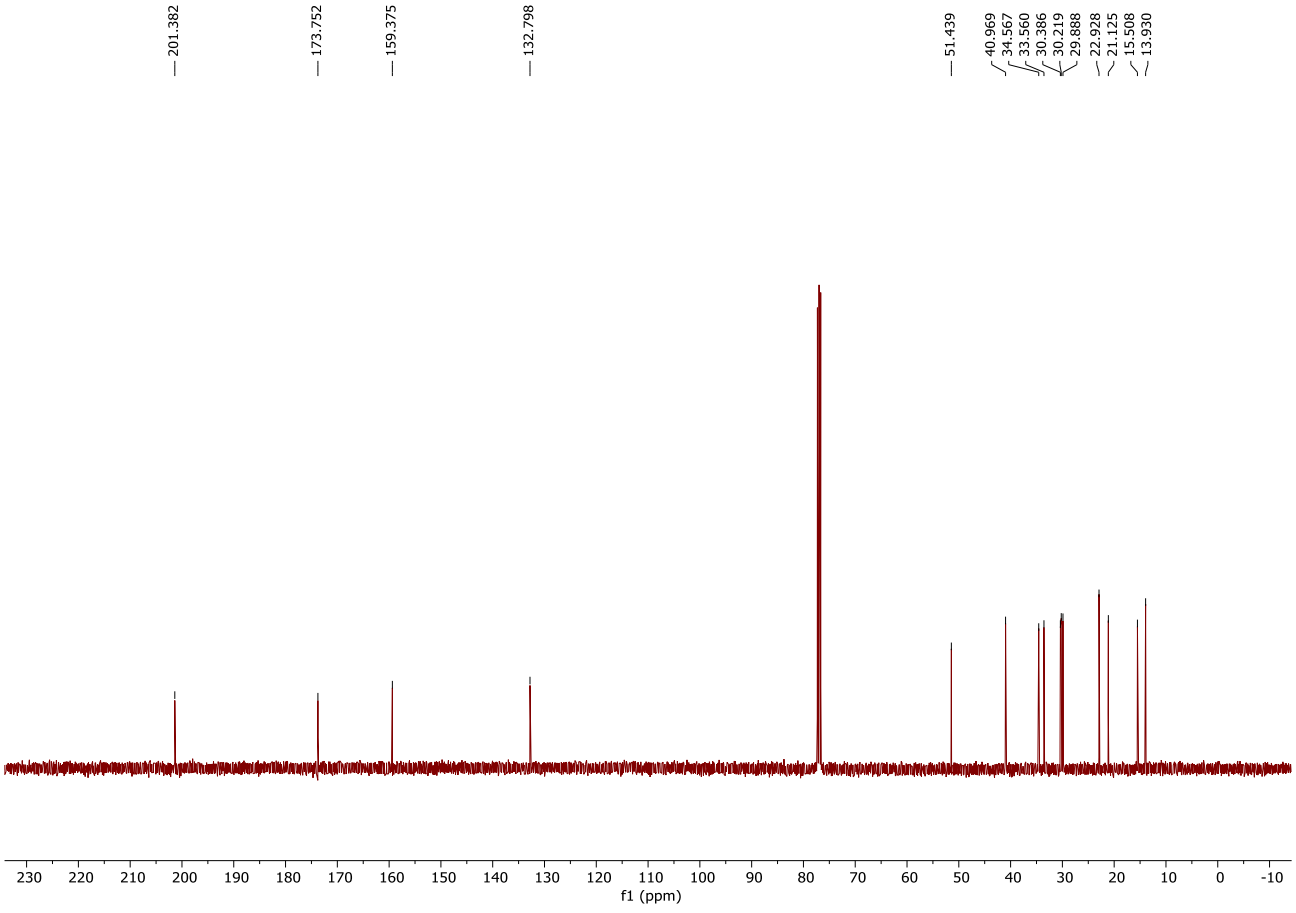
Operating as described in the preparation of ketoester **9**, LiHMDS (3.8 mL of a 1 M solution in THF, 3.86 mmol), MeI (1.2 mL, 18.35 mmol) and ketoester **16** (875 mg, 3. 67 mmol) in anhydrous THF (8.5 mL), ketoester **19** (447 mg, 48%) was obtained after flash column chromatography (hexane to 9:1 hexane–EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H, CH_3O), 2.66-2.52 (m, 2H), 2.41-2.18 (m, 7H), 2.00 (dq, *J* = 13.2, 4.8 Hz, 1H), 1.68-1.60 (m, 1H), 1.48-1.31 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H, CH_3), 0.93 (t, *J* = 7.2 Hz, 3H, CH_3).

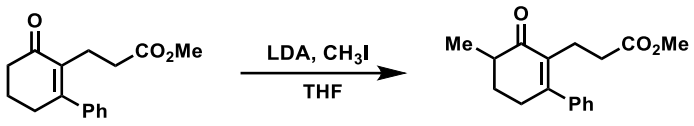
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.4 (CO), 173.8 (COO), 159.4 (C-2), 132.8 (C-1), 51.5 (CH_3), 41.0 (C-5), 34.6 (CH_2), 33.6 (CH_2), 30.4 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 22.9 (CH_2), 21.1 (CH_2), 15.5 (CH_3), 13.9 (CH_3).

HRMS Calcd for [$C_{15}H_{24}O_3 + H^+$]: 253.1798; found 253.1803.


3.652
2.662
2.521
2.413
2.183
2.034
2.022
2.000
1.989
1.677
1.601
1.477
1.314
1.118
0.933
2.64
2.29
7.16
1.14
1.18
4.23
3.00
2.99
f1 (ppm)


201.382
173.752
159.375
132.798
51.439
40.969
34.567
33.560
30.386
30.219
29.888
22.928
21.125
15.508
13.930
f1 (ppm)

Methyl 2-phenyl-5-methyl-6-oxocyclohexenepropionate (20):



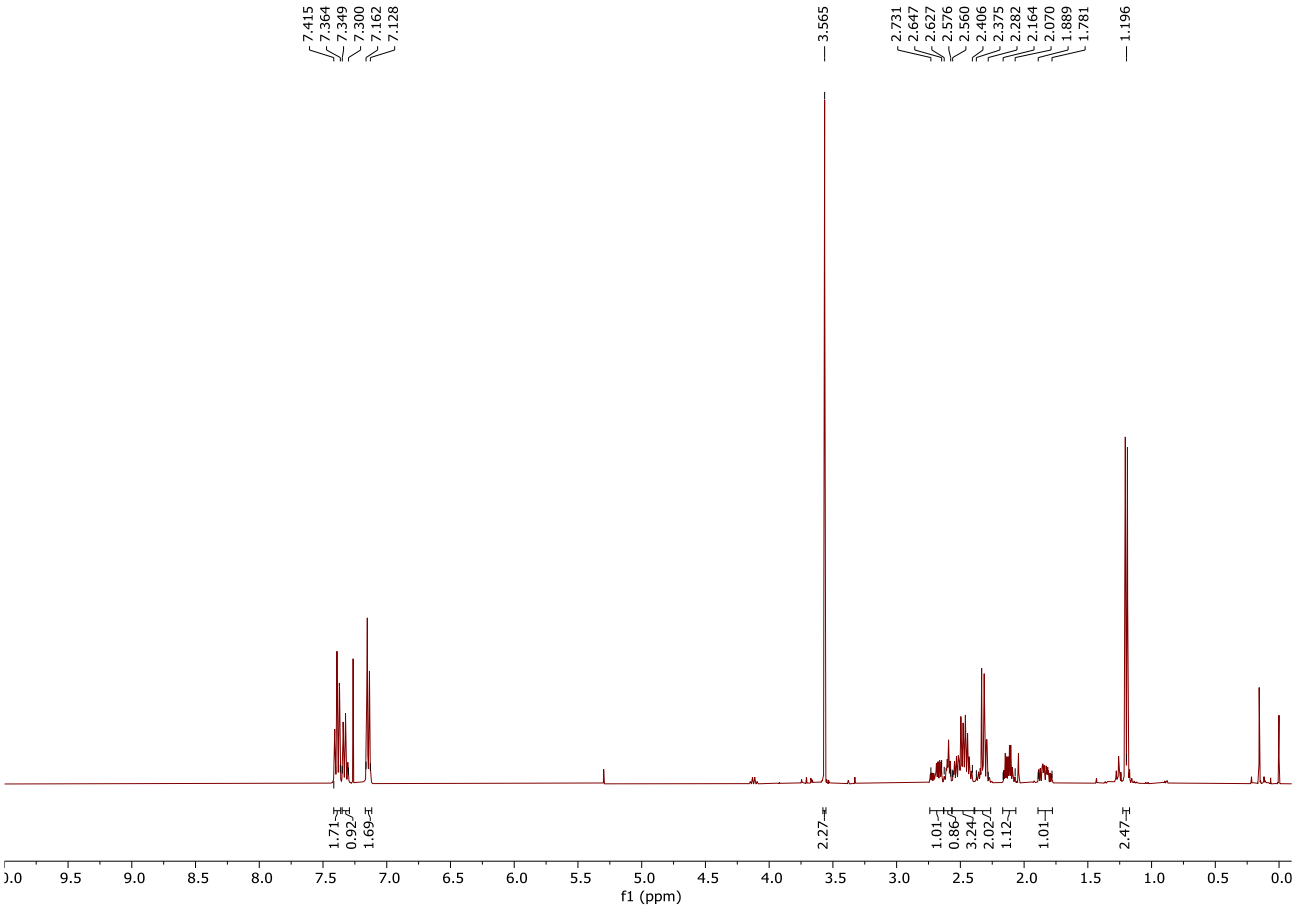
17 20

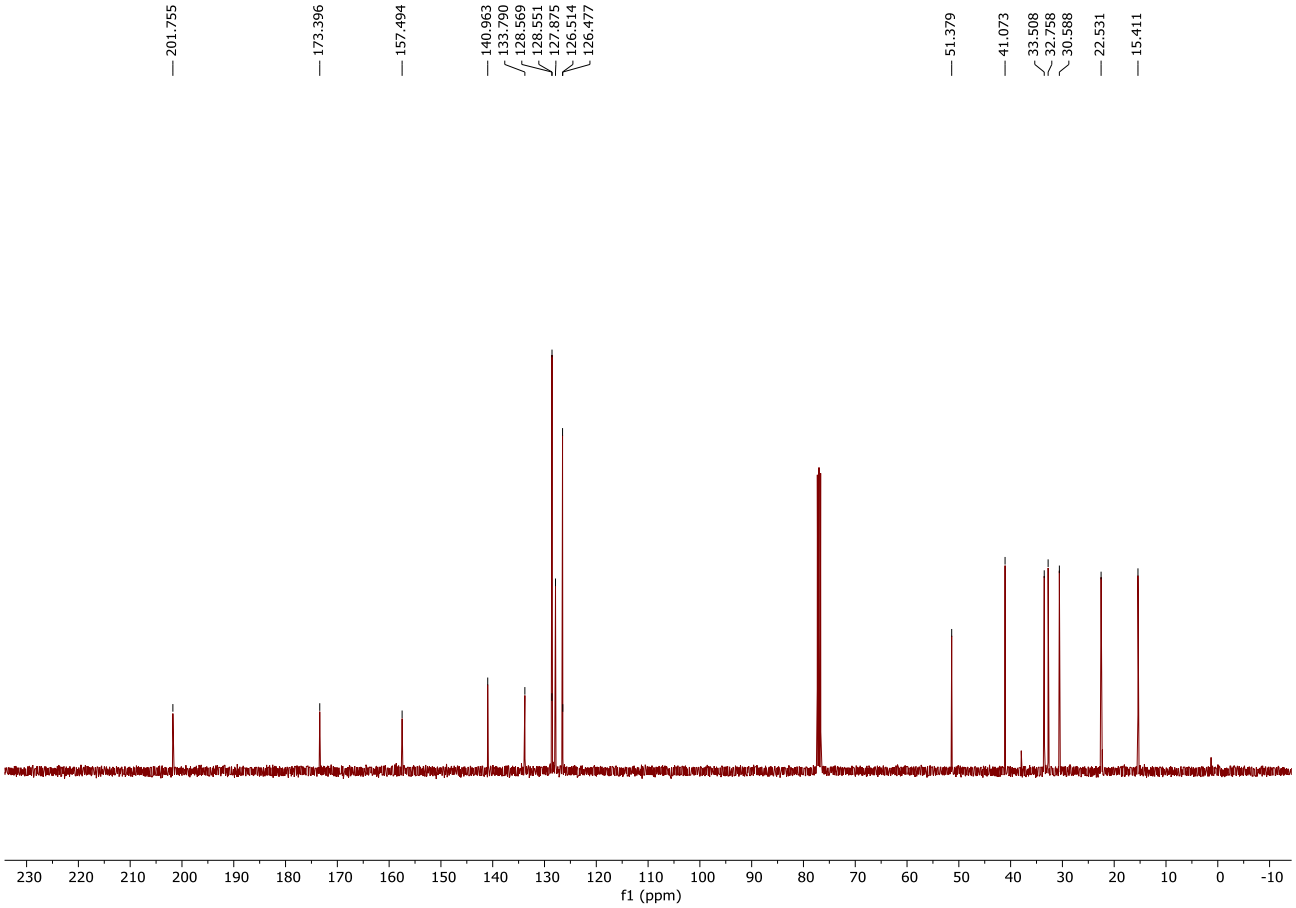
Operating as described in the preparation of ketoester **9**, LiHMDS (2.7 mL of a 1 M solution in THF, 2.73 mmol), MeI (0.8 mL, 13.0 mmol) and ketoester **17** (671 mg, 2.60 mmol) in anhydrous THF (6 mL), ketoester **20** (676 mg, 96%) was obtained after flash column chromatography (hexane to 9:1 hexane–EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 2H, ArH), 7.35-7.30 (m, 1H, ArH), 7.16-7.13 (m, 2H, ArH), 3.56 (s, 3H, CH_3O), 2.73-2.65 (m, 1H), 2.63-2.58 (m, 1H), 2.56-2.41 (m, 3H), 2.37-2.28 (m, 2H), 2.16-2.07 (m, 1H), 1.89-1.78 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H, CH_3).

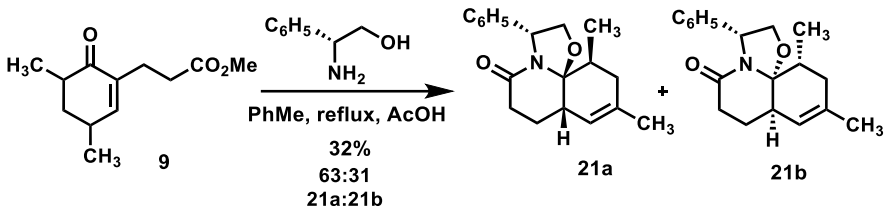
^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 201.7 (CO), 173.4 (COO), 157.5 (C-2), 140.9 (C-1), 133.8 (C-Ar), 128.6 (CH-Ar), 127.9 (CH-Ar), 126.5 (CH-Ar), 51.4 (CH_3O), 41.1 (C-5), 33.5 (CH_2), 32.7 (CH_2), 30.6 (CH_2), 22.5 (CH_2), 15.4 (CH_3).

HRMS Calcd for [$C_{17}H_{20}O_3 + H^+$]: 273.1485; found 273.1489.


7.415
7.364
7.349
7.300
7.162
7.128
3.565
2.731
2.647
2.627
2.576
2.560
2.406
2.375
2.282
2.164
2.070
1.889
1.781
1.196
1.71
0.92
1.69
2.27
1.01
0.86
3.24
2.02
1.12
1.01
2.47
f1 (ppm)


201.755
173.396
157.494
140.963
133.790
128.569
128.551
127.875
126.514
126.477
51.379
41.073
33.508
32.758
30.588
22.531
15.411
f1 (ppm)

(3*R*,7a*S*,11*S*,11a*S*)- and (3*R*,7a*R*,11*R*,11a*R*)-9,11-Dimethyl-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (21a and 21b).



(*R*)-Phenylglycinol (792 mg, 5.78 mmol) was added to a solution of ketoester **9** (810 mg, 3.85 mmol) and AcOH (0.33 mL, 5.78 mmol) in toluene (30 mL). The mixture was heated at reflux for 48 h with azeotropic elimination of H_2O produced by a Dean-Stark apparatus. Additional (*R*)-phenylglycinol (792 mg, 5.78 mmol) was added, and the stirring was continued at reflux temperature for 48 h. After cooling, the mixture was concentrated under reduced pressure, and the resulting residue was dissolved in EtOAc. The resulting solution was washed with saturated aqueous $NaHCO_3$, dried, filtered, and concentrated. Flash column chromatography (95:5 to 1:1 hexane–EtOAc) afforded **21a** (250 mg, 22%) and **21b** (110 mg, 10%)

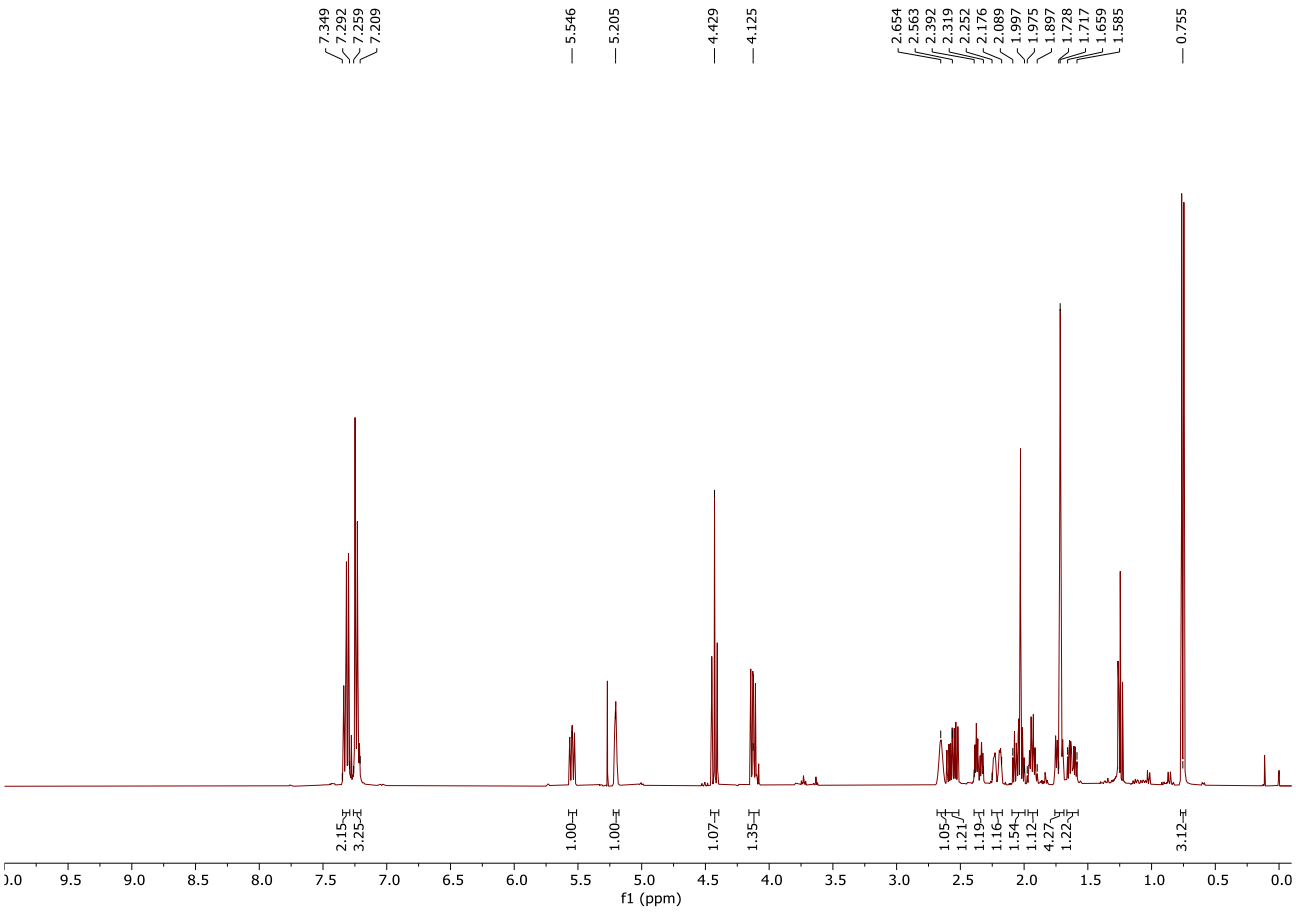
21a:

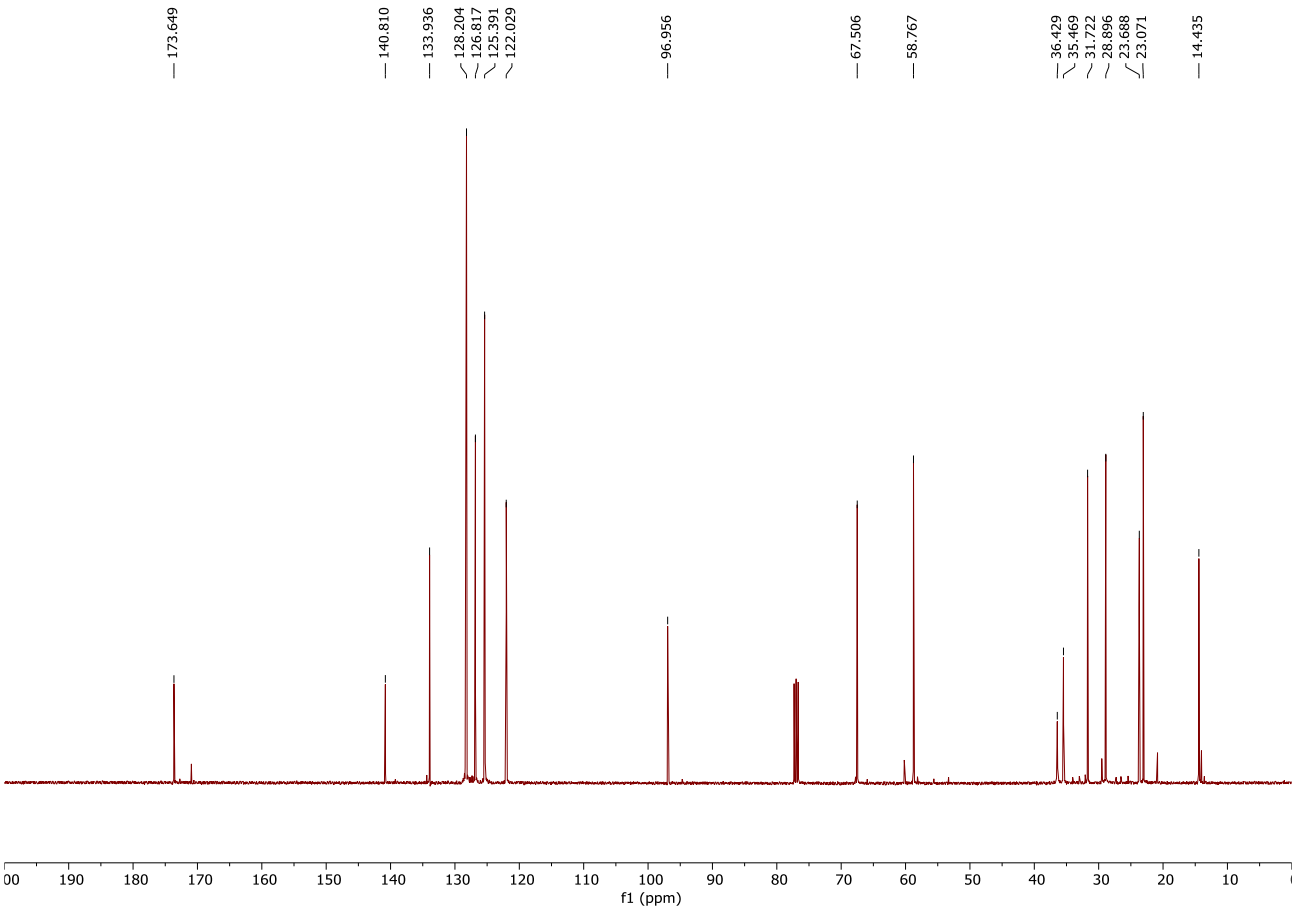
$[\alpha]^{23}_D$ –16.72 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$ COSY, *g*-HSQC) δ 7.35-7.29 (m, 2H, ArH), 7.26-7.21 (m, 3H, ArH), 5.55 (dd, *J* = 8.4, 6.0 Hz, 1H, H-3), 5.20 (m, 1H, H-8), 4.43 (t, *J* = 8.4 Hz, 1H, H-2_a), 4.13 (dd, *J* = 8.4, 6.0 Hz, 1H, H-2_b), 2.65 (m, 1H, H-7a), 2.56 (ddd, *J* = 17.6, 11.2, 6.4 Hz, 1H, H-6_a), 2.39-2.32 (m, 1H, H-6_b), 2.25-2.18 (m, 1H, H-10_a), 2.09-2.00 (m, 1H, H-7_a), 1.98-1.90 (m, 1H, H-11), 1.73 (dd, *J* = 17.2, 5.6 Hz, 1H, H-10_b), 1.72 (s, 3H, CH_3C-9), 1.66-1.59 (m, 1H, H-7_b), 0.75 (d, *J* = 7.6 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6 (CO), 140.8 (C-Ar), 133.9 (C-9), 128.2 (CH-Ar), 126.8 (CH-Ar), 125.4 (CH-Ar), 122.0 (C-8), 97.0 (C-11a), 67.5 (C-2), 58.8 (C-3), 36.4 (C-7a), 35.5 (C-10), 31.7 (C-11), 28.9 (C-6), 23.7 (C-7), 23.1 (CH_3C-9), 14.4 (CH_3C-11).

HRMS Calcd for [$C_{19}H_{23}NO_2 + H^+$]: 298.1802; found 298.1807.


7.349
7.292
7.259
7.209
5.546
5.205
4.429
4.125
2.654
2.563
2.392
2.319
2.252
2.176
2.089
1.997
1.975
1.897
1.728
1.717
1.659
1.585
0.755
2.15
3.25
1.00
1.00
1.07
1.35
1.05
1.21
1.19
1.16
1.54
1.12
4.27
1.22
3.12
f1 (ppm)


173.649
140.810
133.936
128.204
126.817
125.391
122.029
96.956
67.506
58.767
36.429
35.469
31.722
28.896
23.688
23.071
14.435
f1 (ppm)

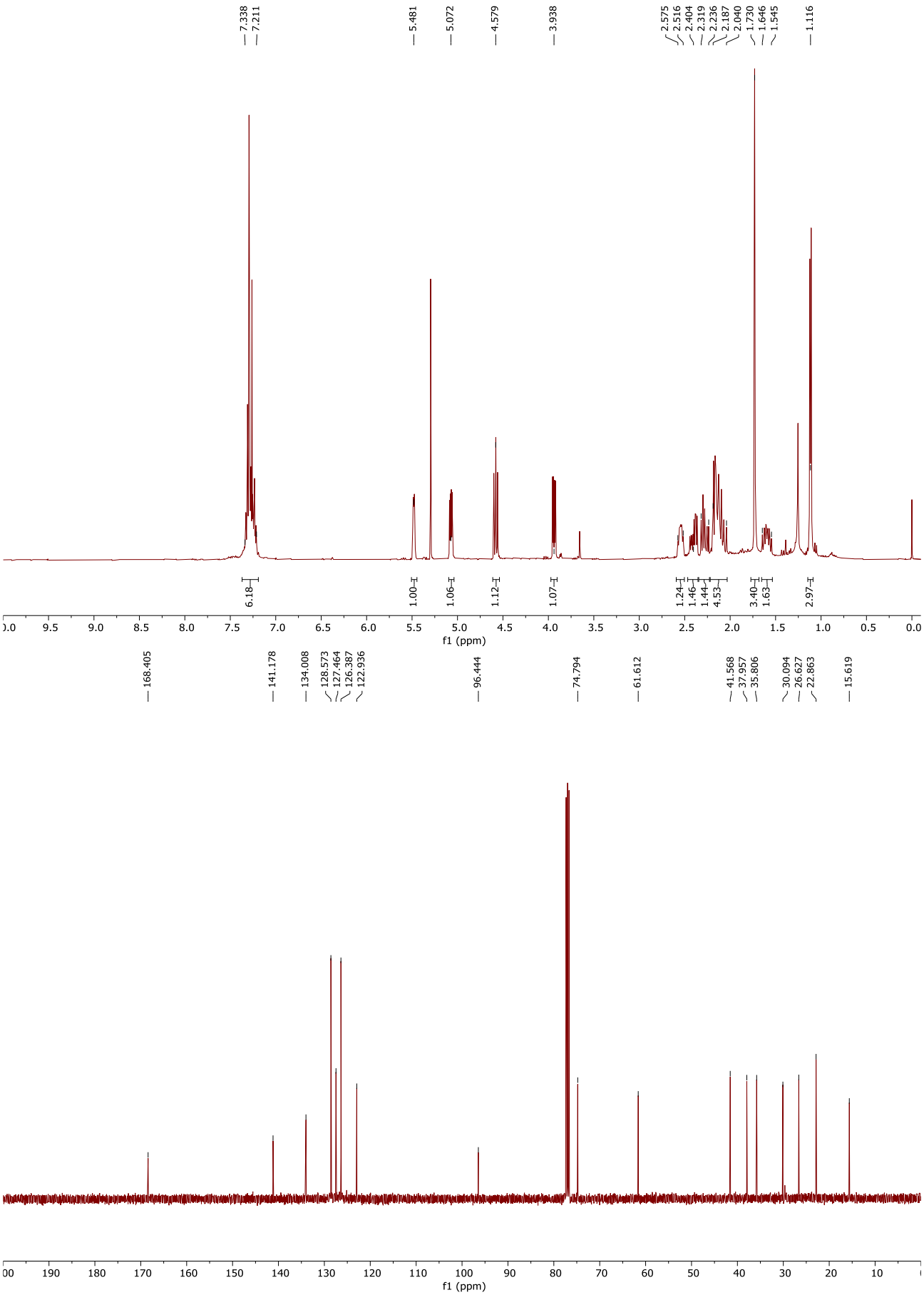
21b:

$[\alpha]^{22}_{D}$ + 4.12 (*c* 1.00, MeOH).

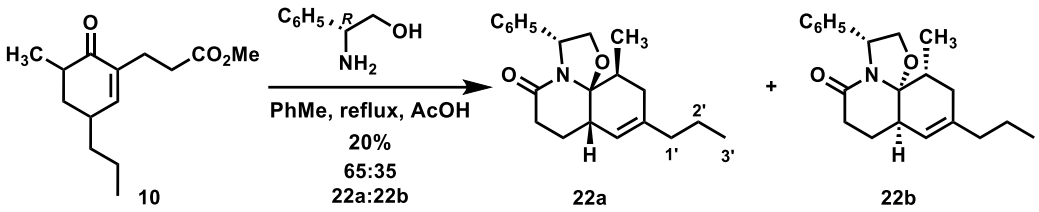
^{1}H NMR (400 MHz, $CDCl_3$ COSY, *g*-HSQC) δ 7.34-7.21 (m, 5H, ArH), 5.48 (m, 1H, H-8), 5.07 (dd, *J* = 7.6, 4.0 Hz, 1H, H-3_a), 4.58 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2), 3.94 (dd, *J* = 8.8, 4.0, 1H, H-2_b), 2.57-2.52 (m, 1H, H-7a), 2.40 (ddd, *J* = 18.0, 8.8, 5.2 Hz, 1H, H-6_a), 2.32-2.24 (m, 1H, H-6_b), 2.19-2.04 (m, 4H, H-7_a, H-11, and H-11), 1.73 (s, 3H, CH_3C-9), 1.65-1.55 (m, 1H, H-7_b), 1.12 (d, *J* = 6.4 Hz, 3H, CH_3C-11).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (CO), 141.2 (C-Ar), 134.0 (C-9), 128.6 (CH-Ar), 127.5 (CH-Ar), 126.4 (CH-Ar), 122.9 (C-8), 96.4 (C-11a), 74.8 (C-2), 61.6 (C-1), 41.6 (C-7a), 38.0 (C-10), 35.8 (C-11), 30.1 (C-6), 26.6 (C-7), 22.9 (CH_3C-9), 15.6 (CH_3C-11).

HRMS Calcd for $[C_{19}H_{23}NO_2+H^+]$: 298.1802; found 298.1801.


7.338
7.211
5.481
5.072
4.579
3.938
2.575
2.516
2.404
2.319
2.236
2.187
2.040
1.730
1.646
1.545
1.116
6.18
1.00
1.06
1.12
1.07
1.24
1.46
1.44
4.53
3.40
1.63
2.97
f1 (ppm)
168.405
141.178
134.008
128.573
127.464
126.387
122.936
96.444
74.794
61.612
41.568
37.957
35.806
30.094
26.627
22.863
15.619
f1 (ppm)

(3*R*,7a*S*,11*S*,11a*S*)- and (3*R*,7a*R*,11*R*,11a*R*)-11-Methyl-5-oxo-3-phenyl-9-propyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (22a and 22b):



Operating as described in the preparation of lactam **21a**, from a diastereomeric mixture of keto ester **10** (364 mg, 1.53 mmol), *(R)*-phenylglycinol (628 mg, 4.58 mmol), and AcOH (0.13 mL, 2.29 mmol) in toluene (12 mL), lactams **22a** (64 mg, 13%) and **22b** (35 mg, 7%), were obtained after flash column chromatography (95:5 to 1:1 hexane–EtOAc).

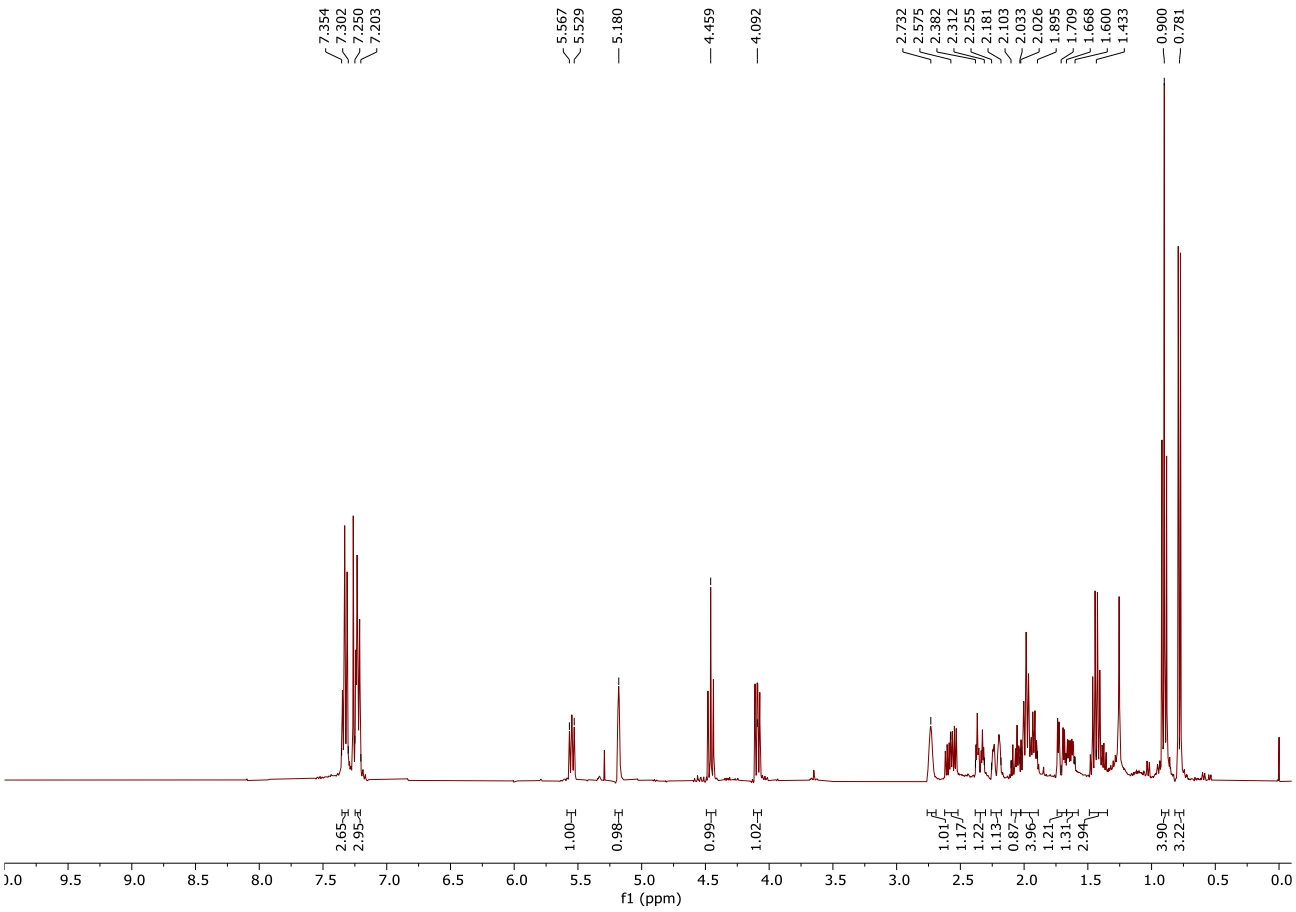
22a:

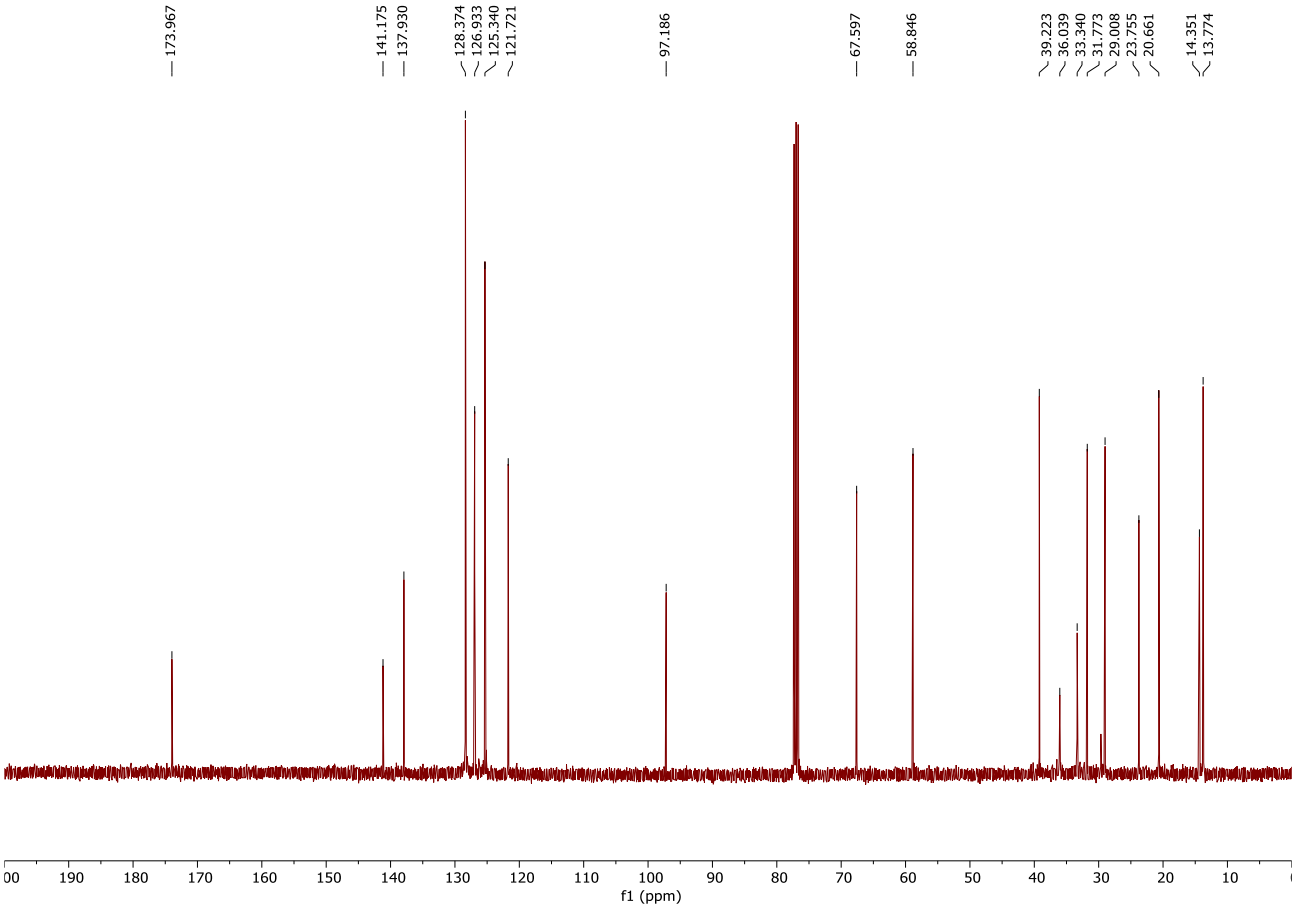
$[\alpha]^{23}_{D}$ –13.41 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$ COSY, *g*-HSQC) δ 7.35-7.30 (m, 2H, ArH), 7.25-7.20 (m, 3H, ArH), 5.57-5.53 (m, 1H, H-3), 5.18 (m, 1H, H-8), 4.46 (t, *J* = 8.4 Hz, 1H, H-2_a), 4.09 (dd, *J* = 8.4, 6.4 Hz, 1H, H-2_b), 2.73 (m, 1H, H-7a), 2.57 (ddd, *J* = 18.0, 12.0, 5.6 Hz, 1H, H-6_a), 2.38-2.31 (m, 1H, H-6_b), 2.25-2.18 (m, 1H, H-10_a), 2.10-2.03 (m, 1H, H-7_a), 2.03-1.90 (m, 3H, H-1' and H-11), 1.71 (dd, *J* = 17.2, 4.4 Hz, 1H, H-10_b), 1.67-1.60 (m, 1H, H-7), 1.43 (q, *J* = 7.2 Hz, 2H, H-2'), 0.90 (t, *J* = 7.2 Hz, 3H, H-3'), 0.78 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.0 (CO), 141.2 (C-Ar), 137.9 (C-9), 128.4 (CH-Ar), 126.9 (CH-Ar), 125.3 (CH-Ar), 121.7 (C-8), 97.2 (C-11a), 67.6 (C-2), 58.8 (C-3), 39.2 (C-1'), 36.0 (C-7a), 33.3 (C-10), 31.8 (C-11), 29.0 (C-6), 23.8 (C-7), 20.7 (C-2'), 14.4 (CH_3C-11), 13.8 (C-3').

HRMS Calcd for [$C_{21}H_{27}NO_2 + H^+$]: 326.2115; found 326.2115.


7.354
7.302
7.250
7.203
5.567
5.529
5.180
4.459
4.092
2.732
2.575
2.382
2.312
2.255
2.181
2.103
2.033
2.026
1.895
1.709
1.668
1.600
1.433
0.900
0.781
2.65
2.95
1.00
0.98
0.99
1.02
1.01
1.17
1.22
1.13
0.87
3.96
1.21
1.31
2.94
3.90
3.22
f1 (ppm)


173.967
141.175
137.930
128.374
126.933
125.340
121.721
97.186
67.597
58.846
39.223
36.039
33.340
31.773
29.008
23.755
20.661
14.351
13.774
f1 (ppm)

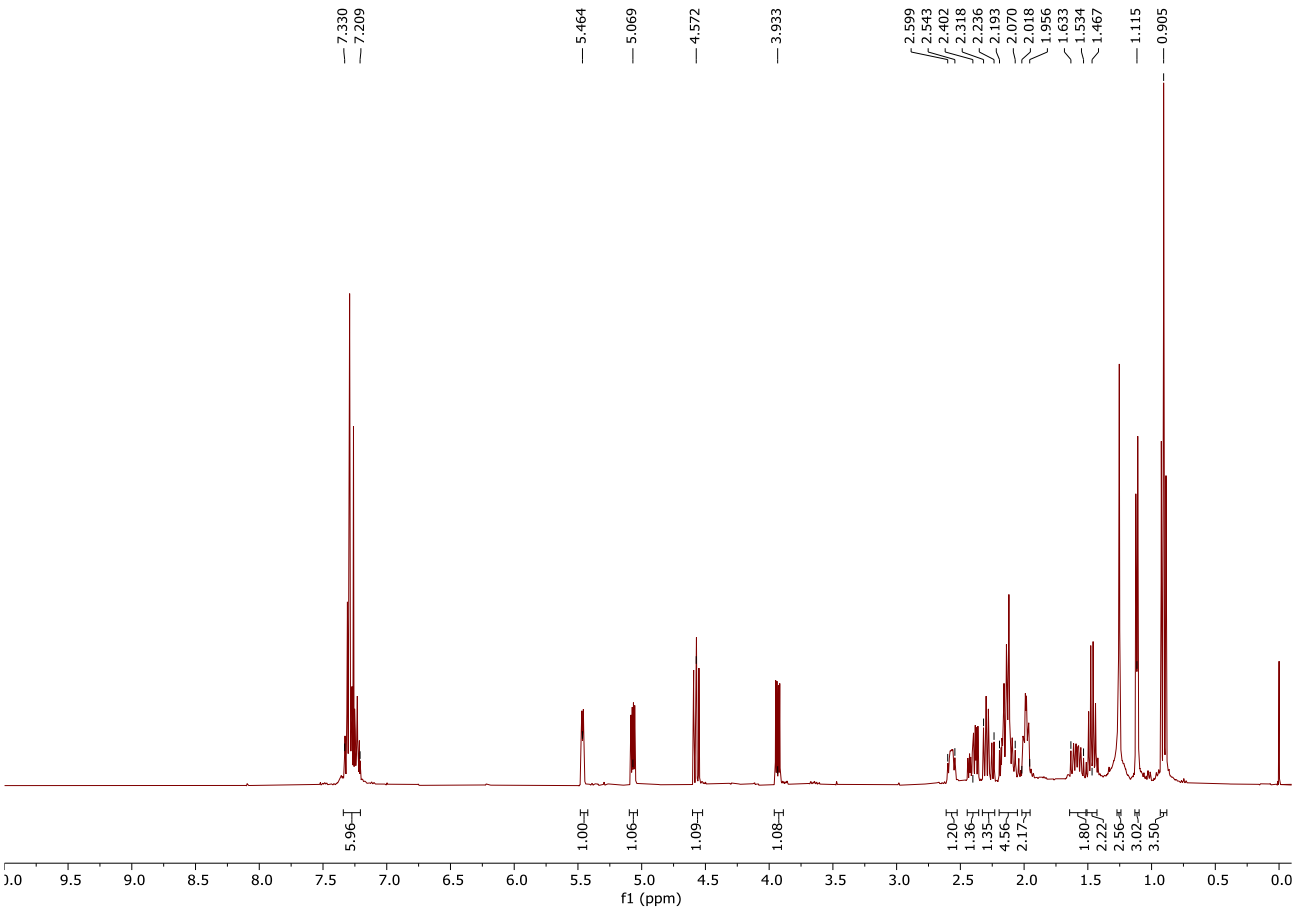
22b:

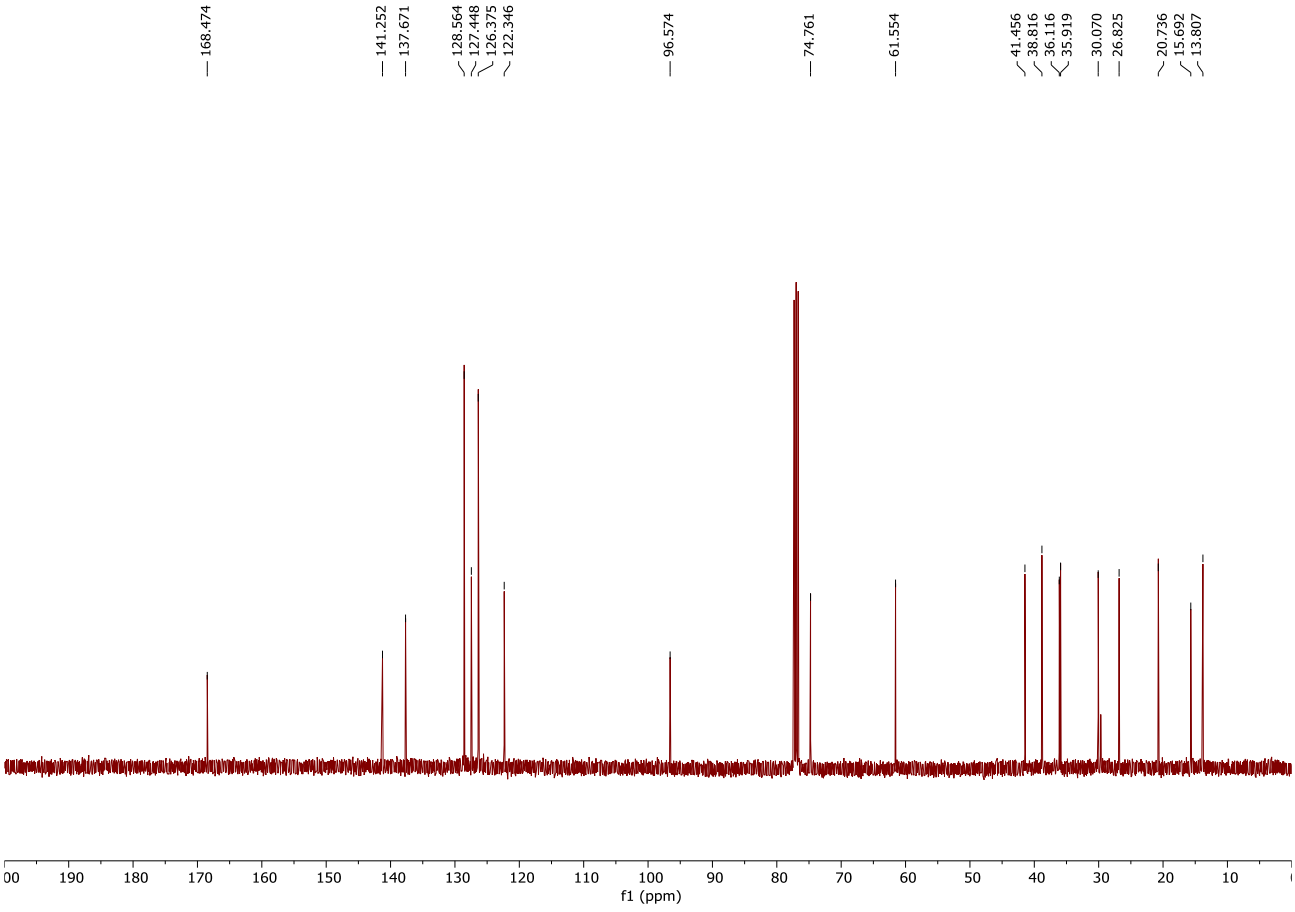
$[\alpha]^{22}_{D}$ + 4.22 (c. 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$ COSY, *g*-HSQC) δ 7.33-7.21 (m, 5H, ArH), 5.46 (d, *J* = 4.8 Hz, 1H, H-8), 5.07 (dd, *J* = 7.6, 4.0 Hz, 1H, H-3), 4.57 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2_a), 3.93 (dd, *J* = 8.8, 4.0 Hz, 1H, H-2_b), 2.60- 2.54 (m, 1H, H-7a), 2.40 (ddd, *J* = 18.0, 8.8, 5.6 Hz, 1H, H-6_a), 2.32-2.24 (m ,1H, H-6_b), 2.19-2.07 (m, 4H, H-7_a, H-10 and H-11), 2.02-1.96 (m, 2H, H-1'), 1.63-1.53 (m, 1H, H-7_b), 1.47 (q, *J* = 7.6 Hz, 1H, H-2'), 1.11 (d, *J* = 7.6 Hz, 3H, CH_3C-11), 0.91 (t, *J* = 7.6 Hz, 3H, H-3').

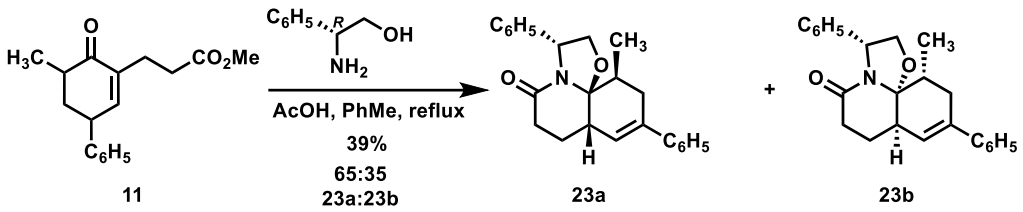
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.5 (CO), 141.3 (C-Ar), 137.7 (C-9), 128.6 (CH-Ar), 127.4 (CH-Ar), 126.4 (CH-Ar), 122.3 (C-8), 96.6 (C-11a), 74.8 (C-2), 61.6 (C-3), 41.5 (C-7a), 38.8 (C-1'), 36.1 (C-10), 35.9 (C-11), 30.1 (C-6), 26.8 (C-7), 20.7 (C-2'), 15.7 (CH_3C-11), 13.8 (C-3').

HRMS Calcd for [$C_{21}H_{27}NO_2 + H^+$]: 326.2115; found 326.2119.


7.330
7.209
5.464
5.069
4.572
3.933
2.599
2.543
2.402
2.318
2.236
2.193
2.070
2.018
1.956
1.633
1.534
1.467
1.115
0.905
5.96
1.00
1.06
1.09
1.08
1.20
1.36
1.35
4.56
2.17
1.80
2.22
2.56
3.02
3.50
f1 (ppm)


168.474
141.252
137.671
128.564
127.448
126.375
122.346
96.574
74.761
61.554
41.456
38.816
36.116
35.919
30.070
26.825
20.736
15.692
13.807
f1 (ppm)

(3*R*,7a*S*,11*S*,11a*S*)- and (3*R*,7a*R*,11*R*,11a*R*)-11-Methyl-5-oxo-3,9-diphenyl-2,3,5,6,7,7a,10,11-octahydro-oxazolo[2,3-*j*]quinoline (23a and 23b):



Operating as described in the preparation of lactam **21a**, from a diastereomeric mixture of keto ester **x** (793 mg, 2.92 mmol), *(R)*-phenylglycinol (600 mg, 4.38 mmol), and AcOH (0.25 mL, 4.38 mmol) in toluene (18 mL), lactams **23a** (265 mg, 25%) and **23b** (146 mg, 14%), were obtained after flash column chromatography (95:5 to 1:1 hexane–EtOAc).

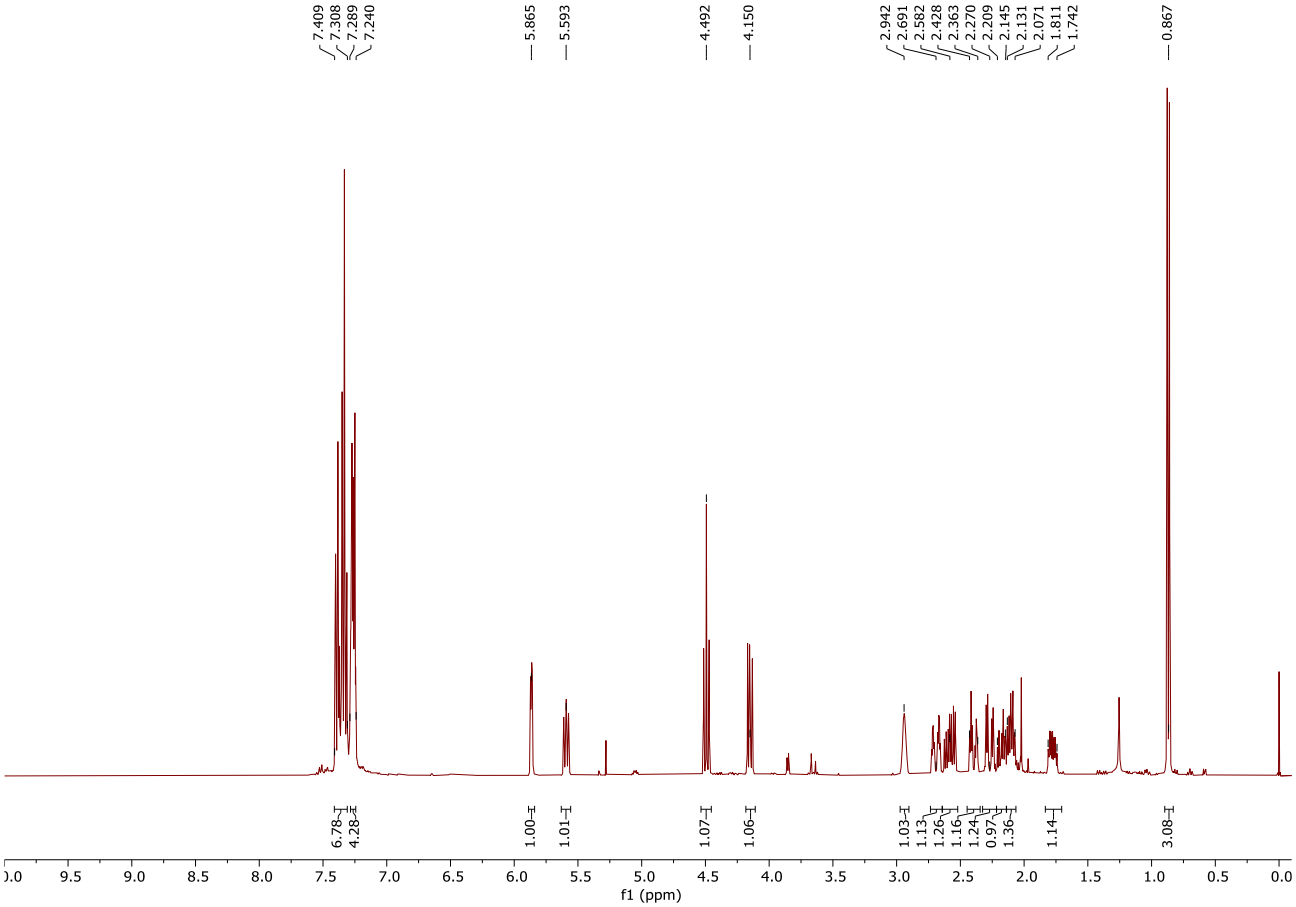
23a:

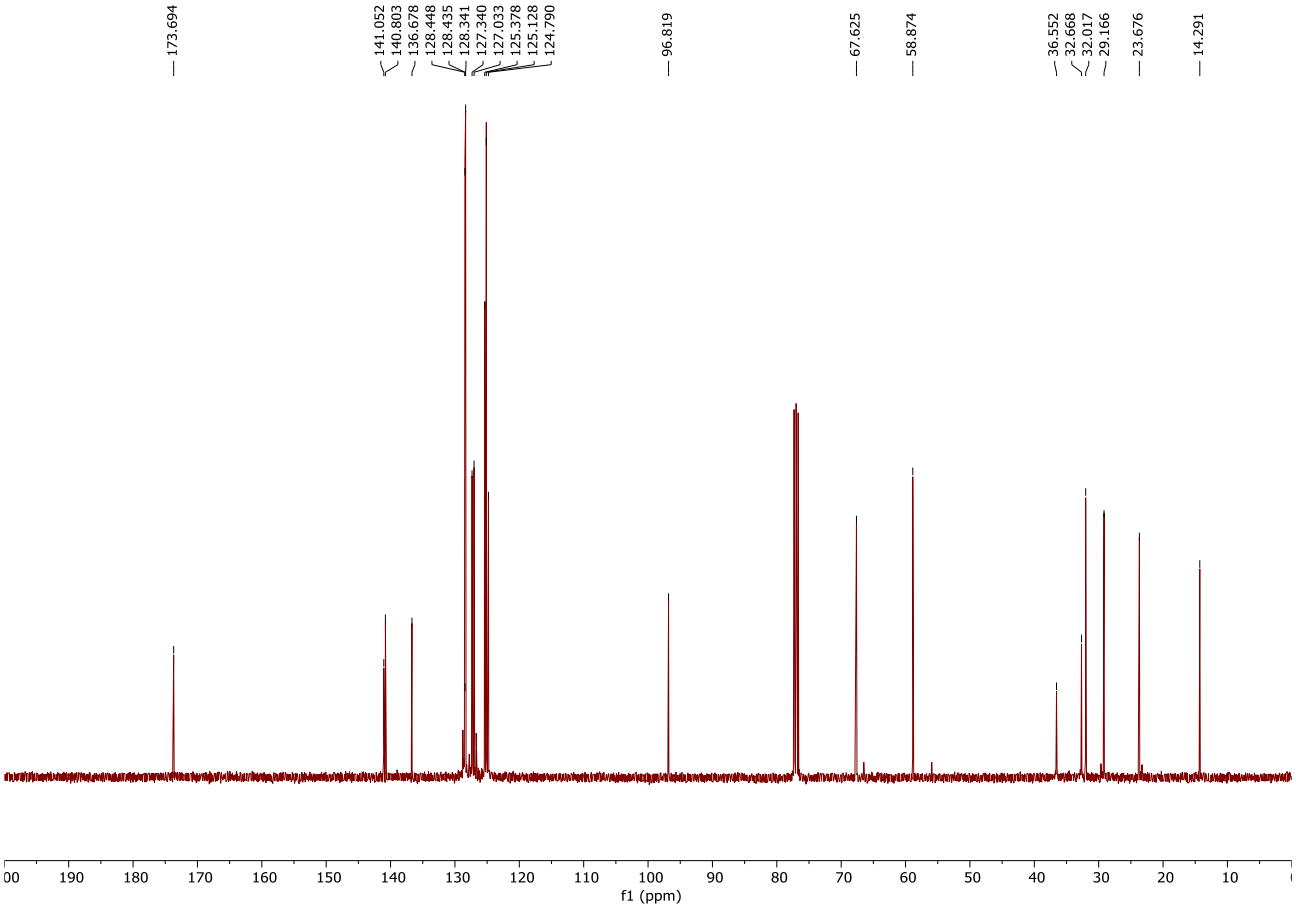
$[\alpha]^{23}_{D}$ –19.94 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$ COSY, *g*-HSQC) δ 7.41-7.31 (m, 6H, ArH), 7.29-7.24 (m, 4H, ArH), 5.87 (dd, *J* = 4.0, 1.6 Hz, 1H, H-8), 5.59 (dd, *J* = 8.4, 6.4 Hz, 1H, H-3), 4.49 (t, *J* = 8.4 Hz, 1H, H-2_a), 4.15 (dd, *J* = 8.4, 6.4 Hz, 1H, H-2_b), 2.94 (m, 1H, H-7a), 2.69 (ddt, *J* = 17.2, 4.8, 2.4 Hz, 1H, H-10_a), 2.58 (ddd, *J* = 16.4, 12.0, 6.0 Hz, 1H, H-6_a), 2.43-2.36 (m, 1H, H-6_b), 2.27 (dd, *J* = 17.2, 12.0 Hz, 1H, H-10_b), 2.21-2.14 (m, 1H, H-7_a), 2.13-2.07 (m, 1H, H-11), 1.81-1.74 (m, 1H, H-7_b), 0.87 (d, *J* = 6.8 Hz, 1H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.7 (CO), 141.1 (C-Ar), 140.8 (C-Ar), 136.7 (C-9), 128.5 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 127.3 (CH-Ar), 127.0 (CH-Ar), 125.4 (CH-Ar), 125.1 (CH-Ar), 124.8 (C-9), 96.8 (C-11a), 67.6 (C-2), 58.9 (C-3), 36.6 (C-7a), 32.7 (C-6), 32.0 (C-11), 29.2 (C-10), 23.7 (C-7), 14.3 (CH_3C-11).

HRMS Calcd for [$C_{24}H_{25}NO_2$+H^+]: 360.1958; found 360.1955.


7.409
7.308
7.289
7.240
5.865
5.593
4.492
4.150
2.942
2.691
2.582
2.428
2.363
2.270
2.209
2.145
2.131
2.071
1.811
1.742
0.867
6.78
4.28
1.00
1.01
1.07
1.06
1.03
1.13
1.26
1.16
1.24
0.97
1.36
1.14
3.08
f1 (ppm)


173.694
141.052
140.803
136.678
128.448
128.435
128.341
127.340
127.033
125.378
125.128
124.790
96.819
67.625
58.874
36.552
32.668
32.017
29.166
23.676
14.291
f1 (ppm)

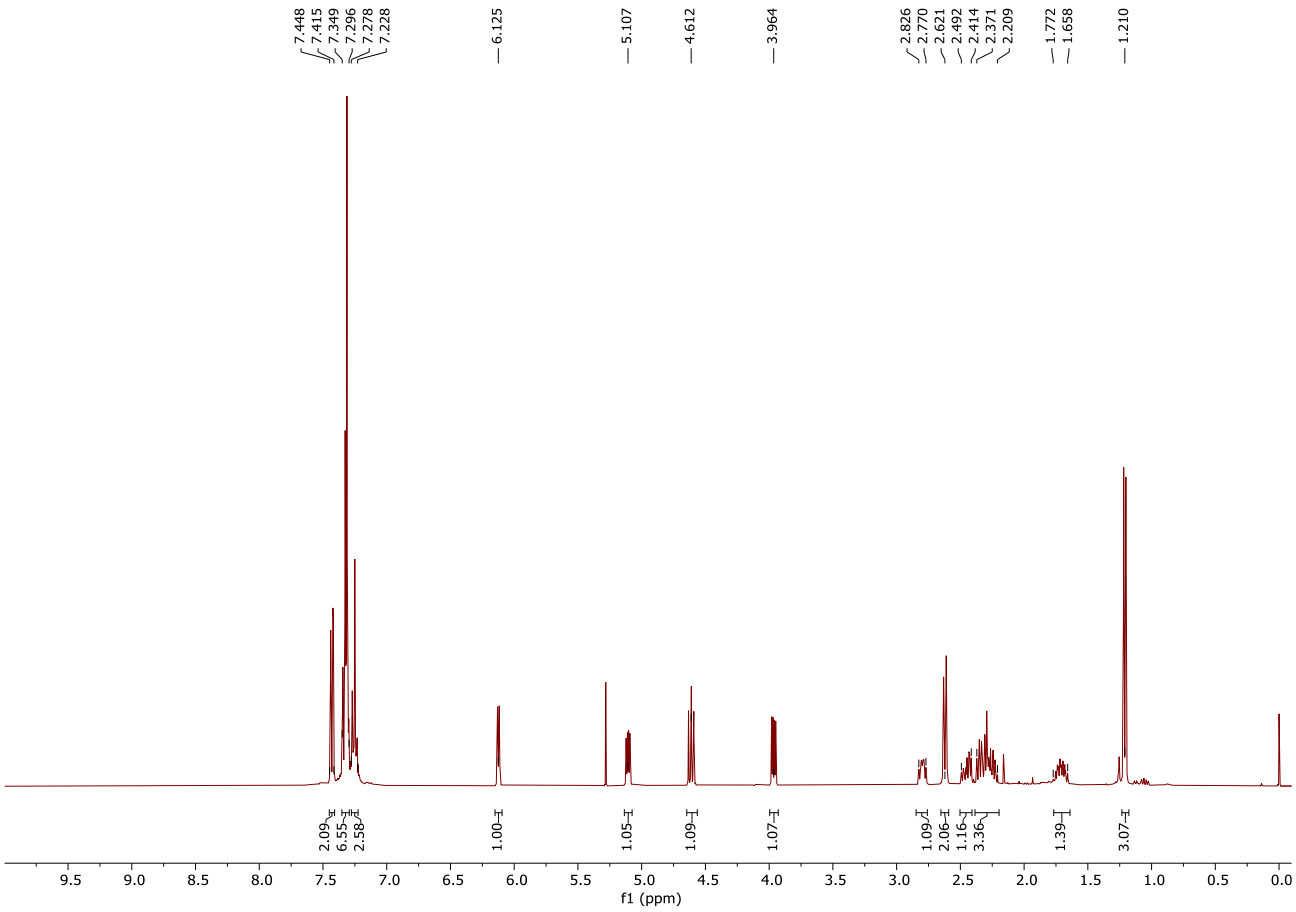
23b:

$[\alpha]^{22}_{D}$ + 8.91 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$ COSY, *g*-HSQC) δ 7.45-7.41 (m, 2H, ArH), 7.35-7.30 (m, 6H, ArH), 7.28-7.23 (m, 2H, ArH), 6.12 (dt, *J* = 5.2, 1.6 Hz, 1H, H-8), 5.11 (dd, *J* = 7.6, 4.0 Hz, 1H, H-3), 4.61 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2_a), 3.96 (dd, *J* = 8.8, 4.0 Hz, 1H, H-2_b), 2.83-2.77 (m, 1H, H-7a), 2.62 (dt, *J* = 8.4, 1.6 Hz, 2H, H-10), 2.49-2.41 (m, 1H, H-6), 2.37-2.21 (H-6_b, H-7_a and H-11), 1.77-1.66 (m, 1H, H-7_b), 1.21 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.3 (CO), 141.1 (C-Ar), 140.6 (C-Ar), 136.2 (C-9), 128.6 (CH-Ar), 128.3 (CH-Ar), 127.5 (CH-Ar), 127.2 (CH-Ar), 126.4 (CH-Ar), 125.3 (CH-Ar), 125.2 (C-8), 96.2 (C-11a), 74.8 (C-2), 61.5 (C-3), 41.8 (C-7a), 36.1 (C-11), 35.1 (C-10), 30.0 (C-6), 26.4 (C-7), 15.7 (CH_3-11).

HRMS Calcd for [$C_{24}H_{25}NO_2$ +H^+]: 360.1958; found 360.1957.


7.448
7.415
7.349
7.296
7.278
7.228
6.125
5.107
4.612
3.964
2.826
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2.621
2.492
2.414
2.371
2.209
1.772
1.658
1.210
2.09
6.55
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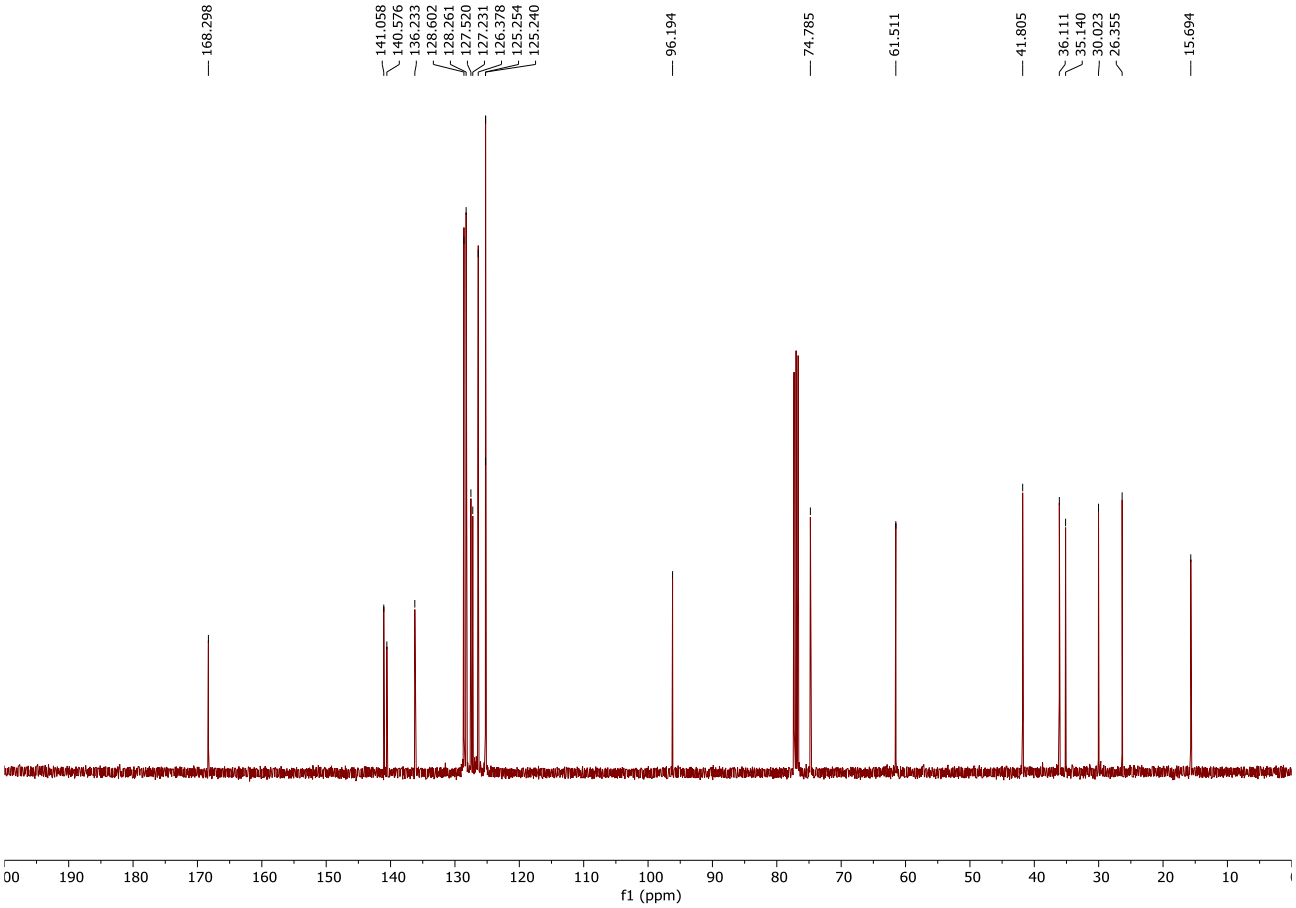
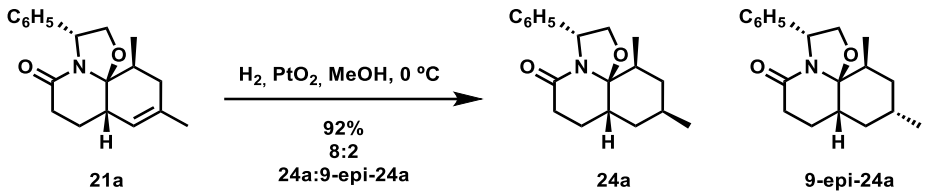
1.07
1.09
2.06
1.16
3.36
1.39
3.07
f1 (ppm)


168.298
141.058
140.576
136.233
128.602
128.261
127.520
127.231
126.378
125.254
125.240
96.194
74.785
61.511
41.805
36.111
35.140
30.023
26.355
15.694
f1 (ppm)

(3*R*,7a*S*,9*R*,11*S*,11a*S*)-9,11-Dimethyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (24a):



20% PtO_2 (9 mg) was added to a solution of lactam **21a** (46 mg, 0.155 mmol) in EtOAc (3.5 mL). The mixture was stirred under hydrogen atmosphere at 0 °C for 15 h. Then, the catalyst was removed by filtration over Celite®. Flash column chromatography (hexane to 75:25 hexane–EtOAc) to give an 8:2 mixture of **24a** and **9-epi-24a** (42.5 mg, 92%).

24a:

CCDC number: 2217478

mp: 82-84 °C (hexane–CH_2Cl_2).

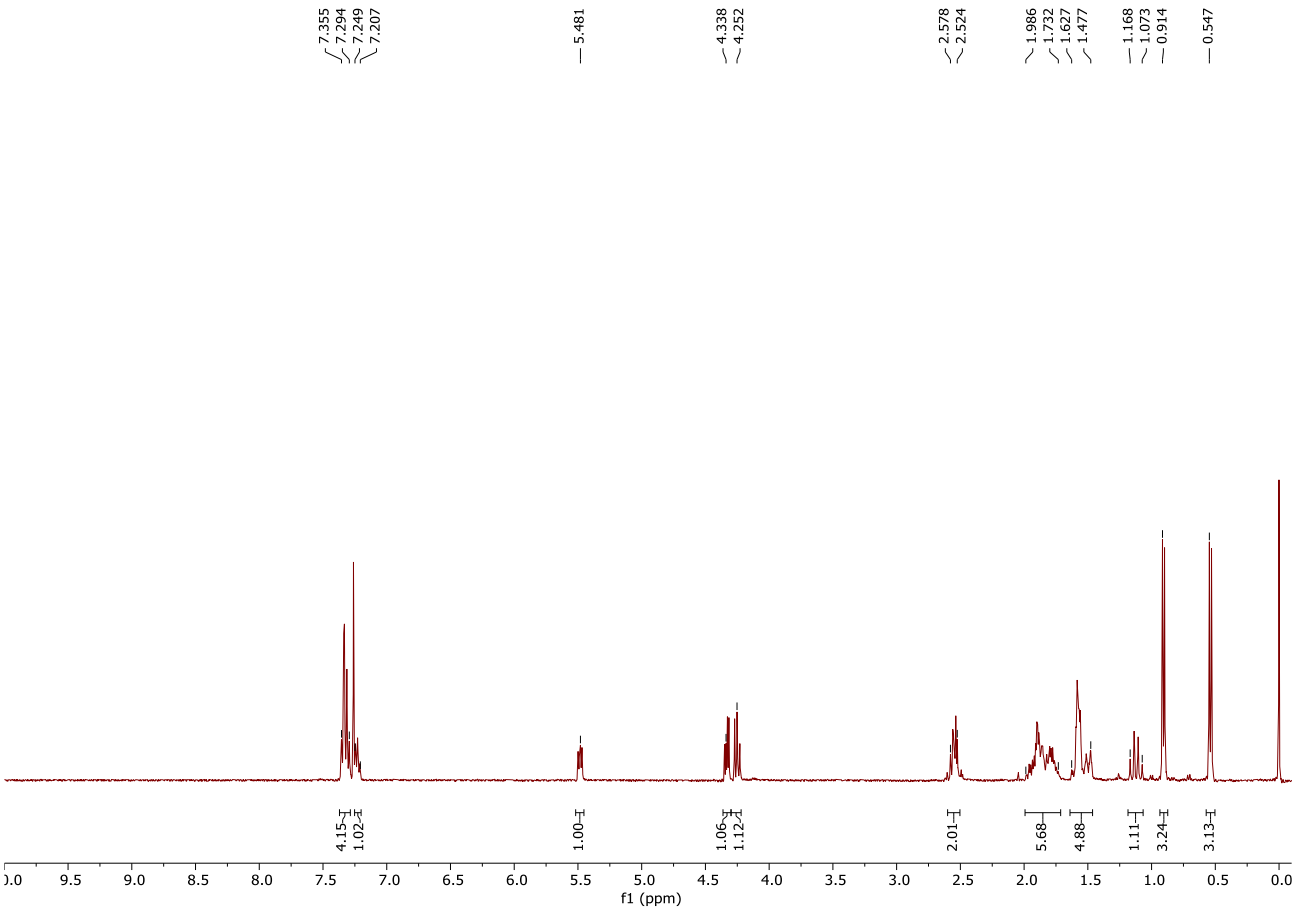
$[\alpha]^{23}_D$ – 153.3 (*c* 1.04, $CHCl_3$).

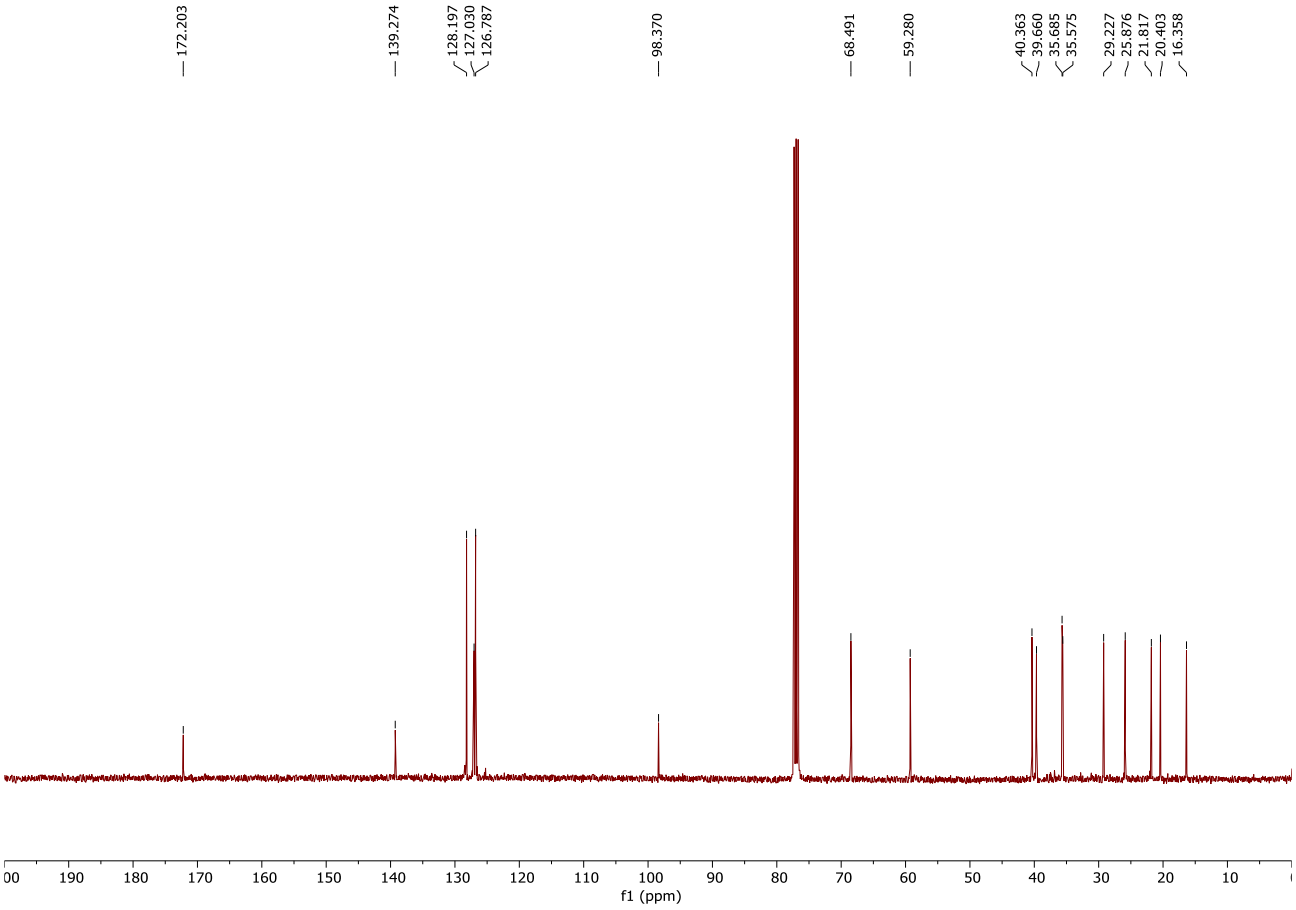
IR (NaCl): 1658 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.35-7.20 (m, 5H, ArH), 5.47 (dd, *J* = 7.2, 4.4 Hz, 1H, H-3), 4.32 (dd, *J* = 8.8, 4.4 Hz, 1H, H-2), 4.24 (dd, *J* = 8.8, 7.2 Hz, 1H, H-2), 2.61-2.47 (m, 2H, H-6), 1.98-1.74 (m, 5H, H-7, H-7a, H-9 and H-11), 1.59-1.55 (m, 2H, H-8), 1.51-1.47 (m, 1H, H-10), 1.12 (q, *J* = 12.8 Hz, 1H, H-10), 0.90 (d, *J* = 6.4 Hz, 3H, CH_3C-9), 0.53 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

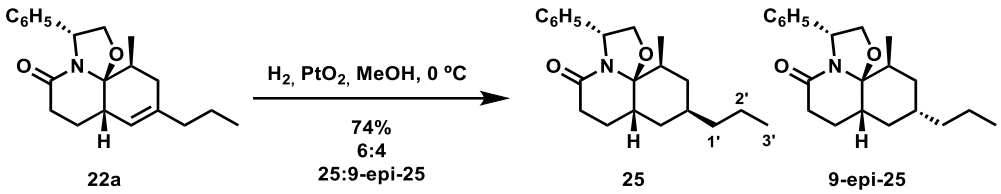
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1 (CO), 139.2 (C-Ar), 127.0 (CH-Ar), 128.1 (CH-Ar), 126.7 (CH-Ar), 98.3 (C-11a), 68.4 (C-2), 59.2 (C-3), 40.3 (C-10), 35.6 (C-8), 29.1 (C-6), 39.6 (C-7a), 35.5 (C-11), 25.8 (C-9), 21.8 (CH_3C-9), 20.3 (C-7), 16.3 (CH_3C-11).

HRMS Calcd for [$C_{19}H_{25}NO_2 + H^+$]: 300.1958; found 300.1962.


7.355
7.294
7.249
7.207
5.481
4.338
4.252
2.578
2.524
1.986
1.732
1.627
1.477
1.168
1.073
0.914
0.547
4.15
1.02
1.00
1.06
1.12
2.01
5.68
4.88
1.11
3.24
3.13
f1 (ppm)


172.203
139.274
128.197
127.030
126.787
98.370
68.491
59.280
40.363
39.660
35.685
35.575
29.227
25.876
21.817
20.403
16.358
f1 (ppm)

(3*R*,7a*S*,9*R*,11*S*,11a*S*)-11-Methyl-5-oxo-3-phenyl-9-propyldecahydrooxazolo[2,3-*j*]quinolone (25):



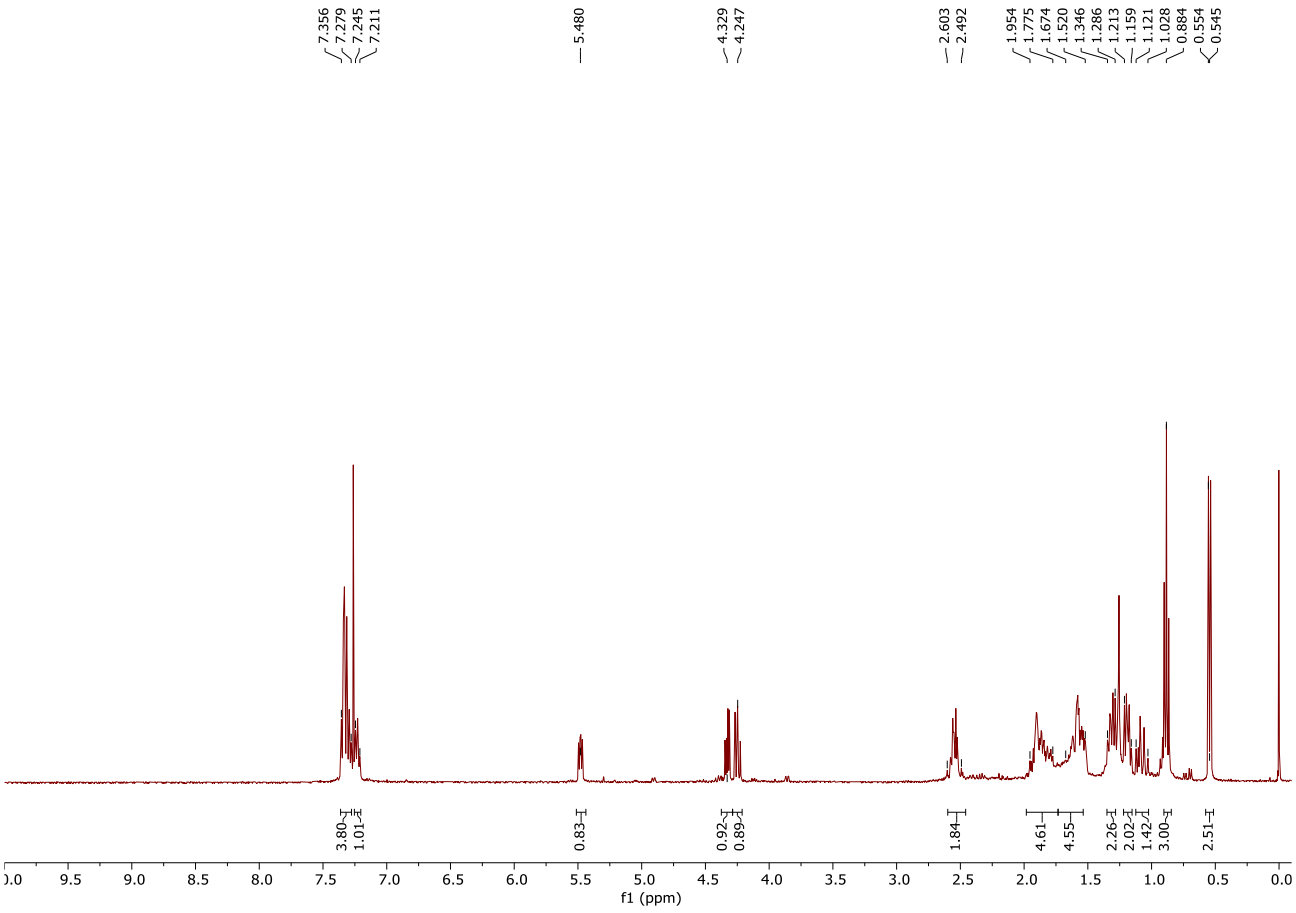
Operating as in the preparation of decahydroquinoline **24a**, from lactam **22a** (46 mg, 0.155 mmol) and 28% PtO_2 (12.6 mg) in EtOAc (3.5 mL), a 6:4 mixture of lactams **25** and **9-epi-25** (34 mg, 72%) was obtained after flash column chromatography (hexane to 75:25 hexane–EtOAc) as a yellowish oil:

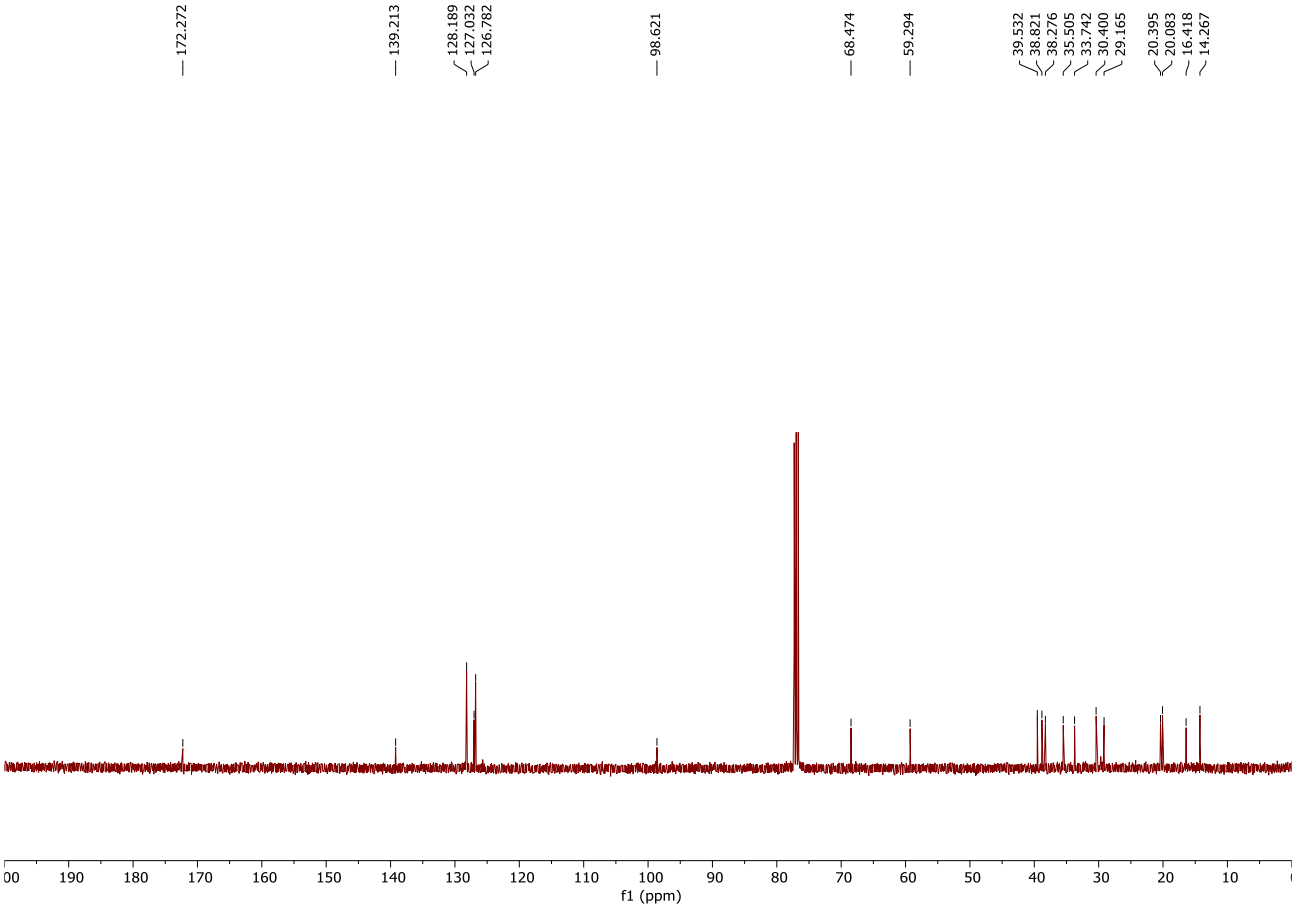
An enriched fraction of **25**:

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.36-7.28 (m, 4H, ArH), 7.24-7.21 (m, 1H, ArH), 5.48 (dd, *J* = 7.6, 4.8 Hz, 1H, H-3), 4.33 (dd, *J* = 9.2, 4.8 Hz, 1H, H-2_a), 4.25 (dd, *J* = 9.2, 7.6 Hz, 1H, H-2_b), 2.60- 2.49 (m, 2H, H-6), 1.95-1.77 (m, 4H, H-7, H-7a and H-11), 1.67-1.52 (m, 4H, H-8_a, H-9 and H-10), 1.35-1.29 (m, 2H, H-2'), 1.21-1.16 (m, 2H, H-1'), 1.12-1.03 (m, 1H, H-8_b), 0.88 (t, *J* = 7.2 Hz, 3H, H-3'), 0.55 (d, *J* = 6.4 Hz, 3H, CH_3C-11).

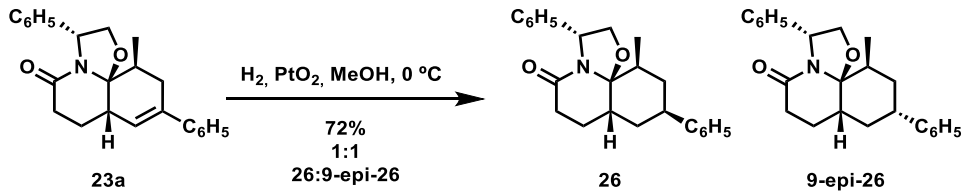
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.3 (CO), 139.2 (C-Ar), 128.2 (CHAr), 127.0 (CHAr), 126.8 (CHAr), 98.6 (C-11a), 68.5 (C-2), 59.3 (C-3), 39.5 (C-7a), 38.8 (C-1'), 38.3 (C-8), 35.5 (C-11), 33.7 (C-10), 30.4 (C-9), 29.2 (C-6), 20.4 (C-7), 20.1 (C-2'), 16.4 (CH_3C-11), 14.3 (C-3').

HRMS Calcd for [$C_{21}H_{29}NO_2$ + H^+]: 328.2271; found 328.2269.


7.356
7.279
7.245
7.211
5.480
4.329
4.247
2.603
2.492
1.954
1.775
1.674
1.520
1.346
1.286
1.213
1.159
1.121
1.028
0.884
0.554
0.545
3.80
1.01
0.83
0.92
0.89
1.84
4.61
4.55
2.26
2.02
1.42
3.00
2.51
f1 (ppm)


172.272
139.213
128.189
127.032
126.782
98.621
68.474
59.294
39.532
38.821
38.276
35.505
33.742
30.400
29.165
20.395
20.083
16.418
14.267
f1 (ppm)

(3*R*,7a*S*,9*R*,11*S*,11a*S*)-11-Methyl-5-oxo-3,9-diphenyl-decahydrooxazolo[2,3-*j*]quinoline (26):



Operating as in the preparation of decahydroquinoline **24a**, from lactam **23a** (66 mg, 0.18 mmol) and 20% PtO_2 (13 mg) in EtOAc (4.0 mL), a 1:1 mixture of lactams **26** and **9-epi-26** (48 mg, 72%) was obtained after flash column chromatography (hexane to 85:15 hexane–EtOAc) as a yellowish oil:

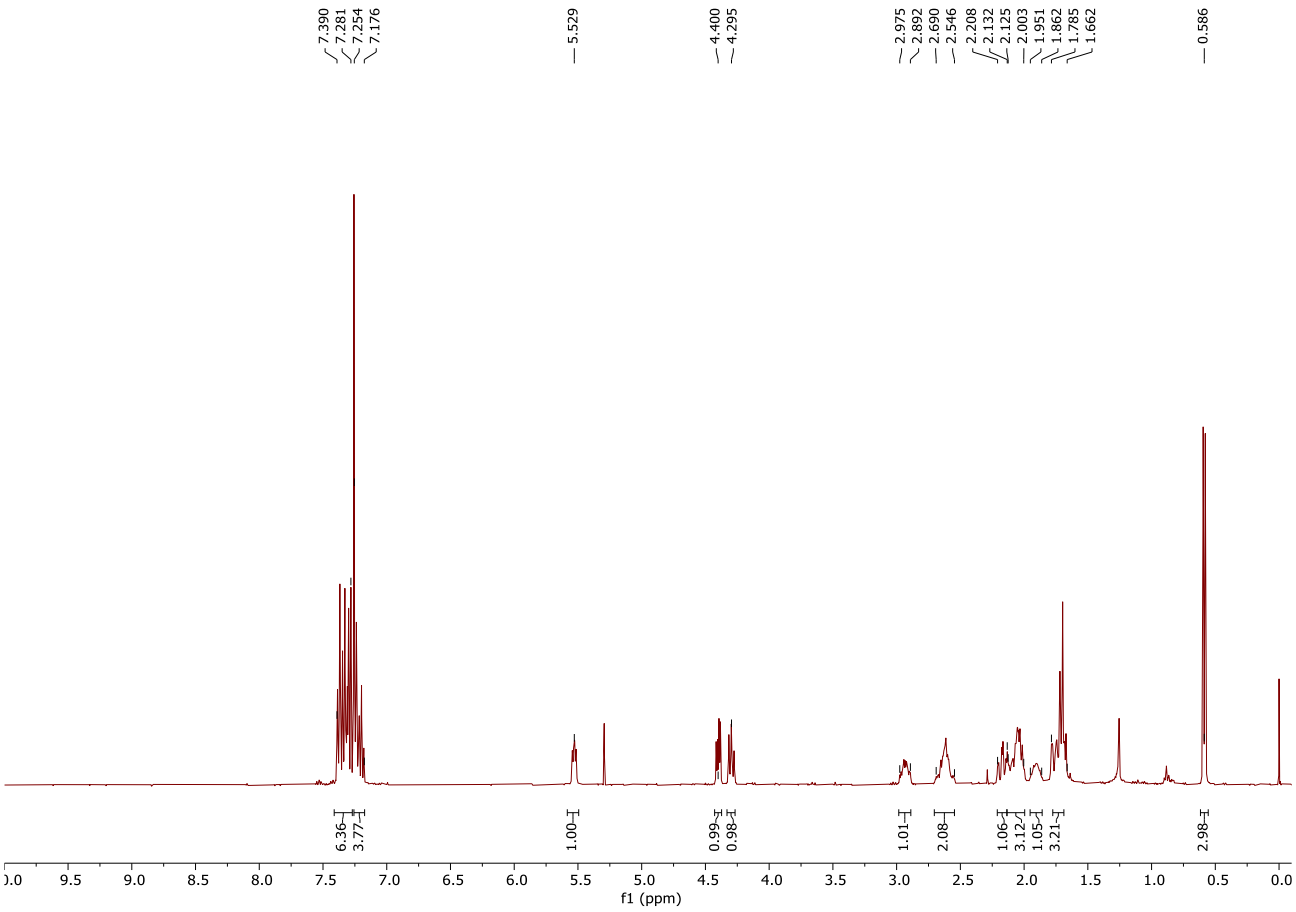
26:

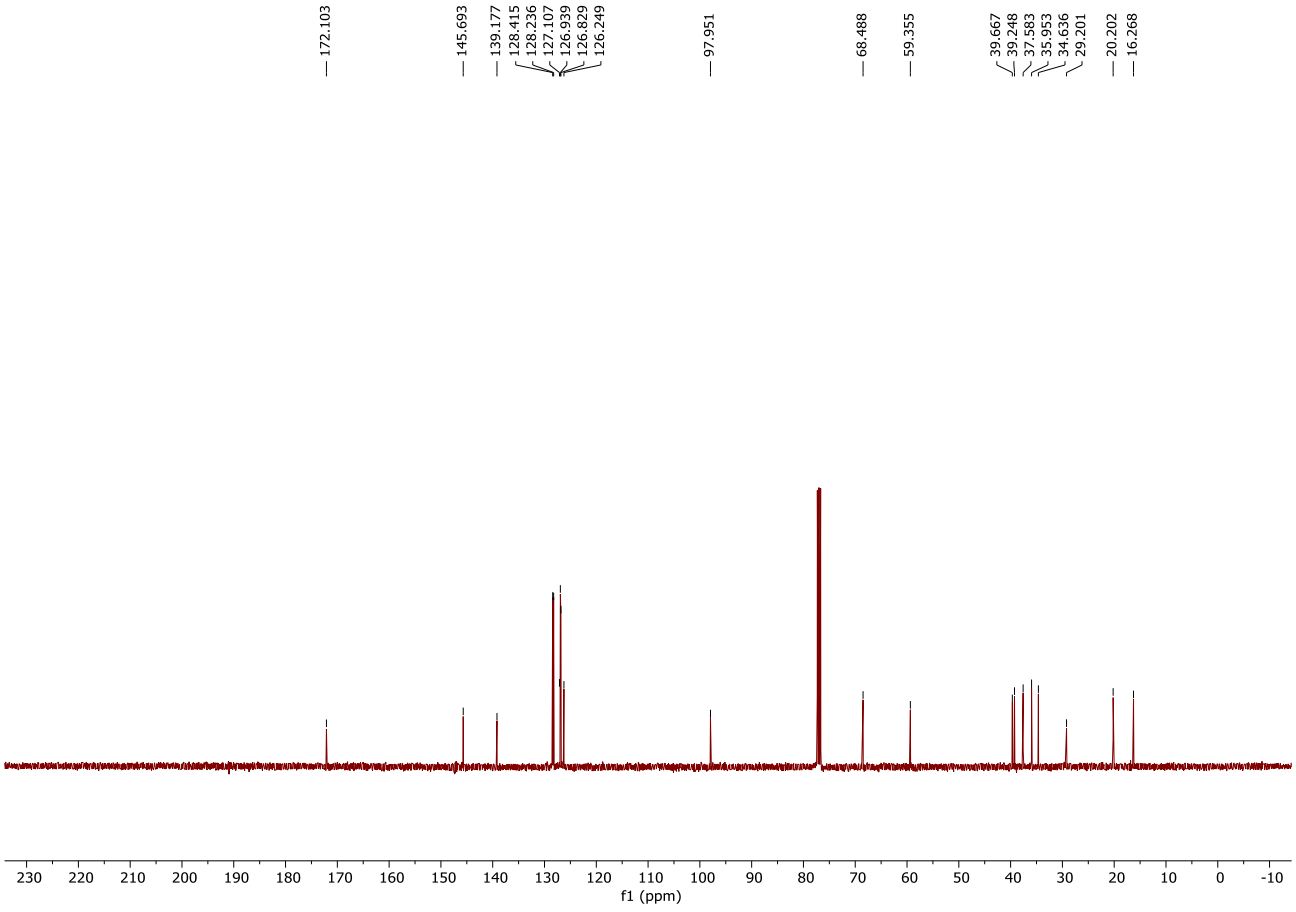
$[\alpha]^{22}_{D}$ –9.25 (*c* 1.0, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.39-7.28 (m, 6H, ArH), 7.25-7.18 (m, 4H, ArH), 5.53 (dd, *J* = 7.2, 4.4 Hz, 1H, H-3), 4.40 (dd, *J* = 8.8, 4.4 Hz, 1H, H-2_a), 4.30 (dd, *J* = 8.8, 7.2 Hz, 1H, H-2_b), 2.98-2.89 (m, 1H, H-7a), 2.69-2.55 (m, 2H, H-6), 2.21-2.13 (m ,1H, H-8_a), 2.13-2.00 (m, 3H, H-7_a, H-9 and H-11), 1.95-1.86 (m, 1H, H-7_b), 1.79-1.66 (m, 1H, H-7_b), 0.59 (d, *J* = 6.4 Hz, 3H, CH_3C-11);

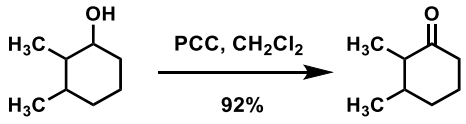
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1 (CO), 145.7 (C-Ar), 139.2 (C-Ar), 128.4 (CHAr), 128.2 (CHAr), 127.1 (CHAr), 126.9 (CHAr), 126.8 (CHAr), 126.2 (CHAr), 98.0 (C-11a), 68.5 (C-2), 59.4 (C-3), 39.7 (C-9), 39.2 (C-10), 37.6 (C-7a), 36.0 (C-11), 34.6 (C-8), 29.2 (C-6), 20.2 (C-7), 16.3 (CH_3C-11);

HRMS Calcd for [$C_{24}H_{27}NO_2 + H^+$]: 362.2115; found 362.2117.


7.390
7.281
7.254
7.176
5.529
4.400
4.295
2.975
2.892
2.690
2.546
2.208
2.132
2.125
2.003
1.951
1.862
1.785
1.662
0.586
6.36
3.77
1.00
0.99
0.98
1.01
2.08
1.06
3.12
1.05
3.21
2.98
f1 (ppm)


172.103
145.693
139.177
128.415
128.236
127.107
126.939
126.829
126.249
97.951
68.488
59.355
39.667
39.248
37.583
35.953
34.636
29.201
20.202
16.268
f1 (ppm)

2,3-Dimethylcyclohexanone (35):

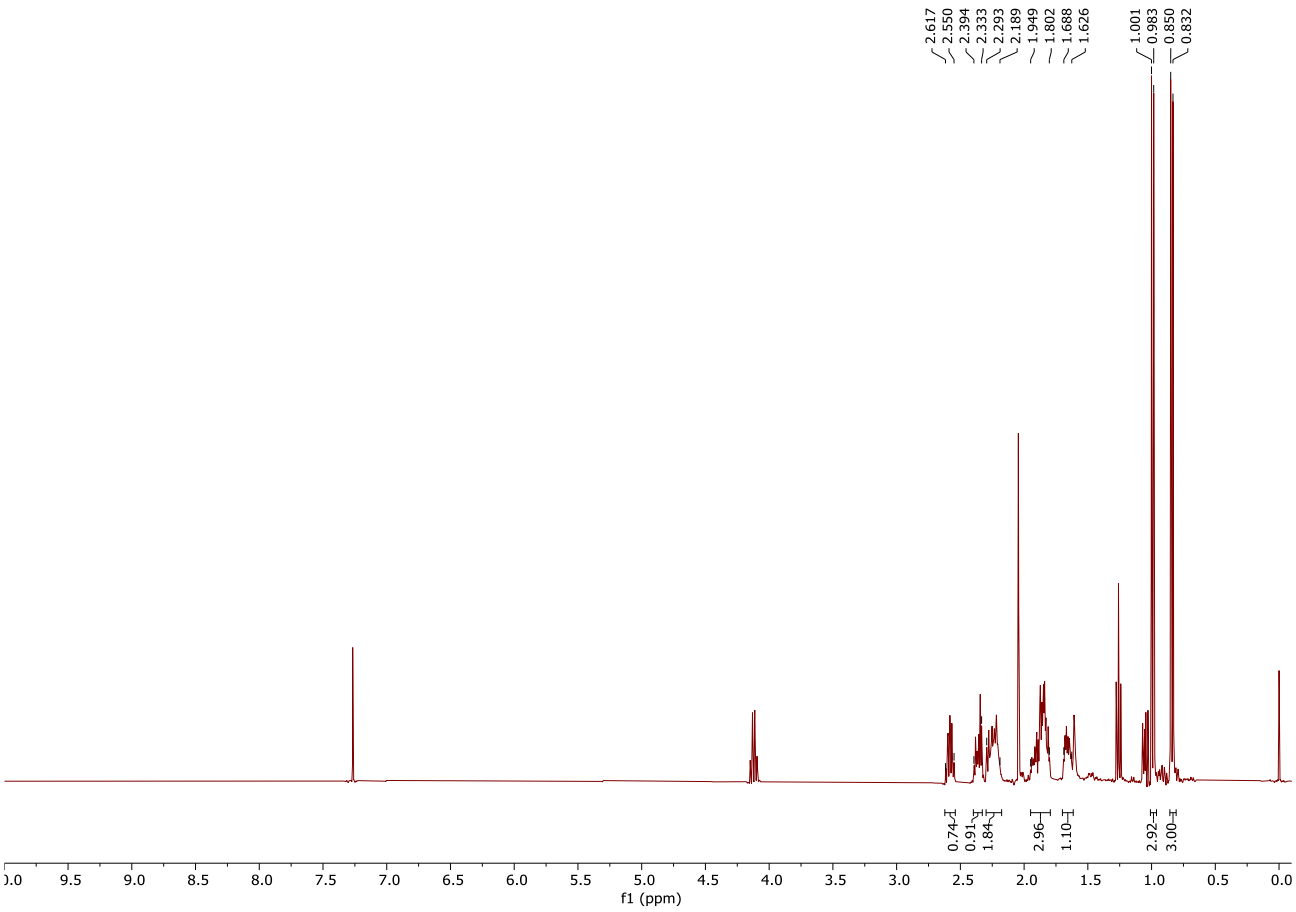


33 35

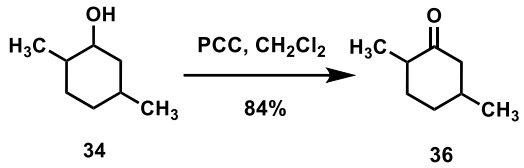
Pyridinium chlorochromate (10.10 g, 115.00 mmol) was added to a solution of 2,3-dimethylcyclohexanol **33** (5.00 g, 38.22 mmol) in CH_2Cl_2 (75 mL) and the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered over silica and Celite®, rinsing with eluent hexane/EtOAc (from 9:1 to 7:3), and the filtrate was concentrated to afford 2,3-dimethylcyclohexanone **35** (4,42 g, 92%) as a yellowish oil.[97]

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (d, *J* = 7.2 Hz, 3H, CH_3), 0.98 (d, *J* = 7.2 Hz, 3H, CH_3), 1.62-1.68 (m, 1H), 1.79-1.94 (m, 3H), 2.18-2.29 (m, 2H), 2.33-2.39 (m, 1H), 2.54-2.61 (m, 1H).

[97] Compound described in: Abe, H.; Ogura, Y.; Kobayashi, T.; Ito, H. *Org. Lett.* **2017**, *19*, 5996-5999.


2.617
2.550
2.394
2.333
2.293
2.189
1.949
1.802
1.688
1.626
1.001
0.983
0.850
0.832
0.74
0.91
1.84
2.96
1.10
2.92
3.00
f1 (ppm)

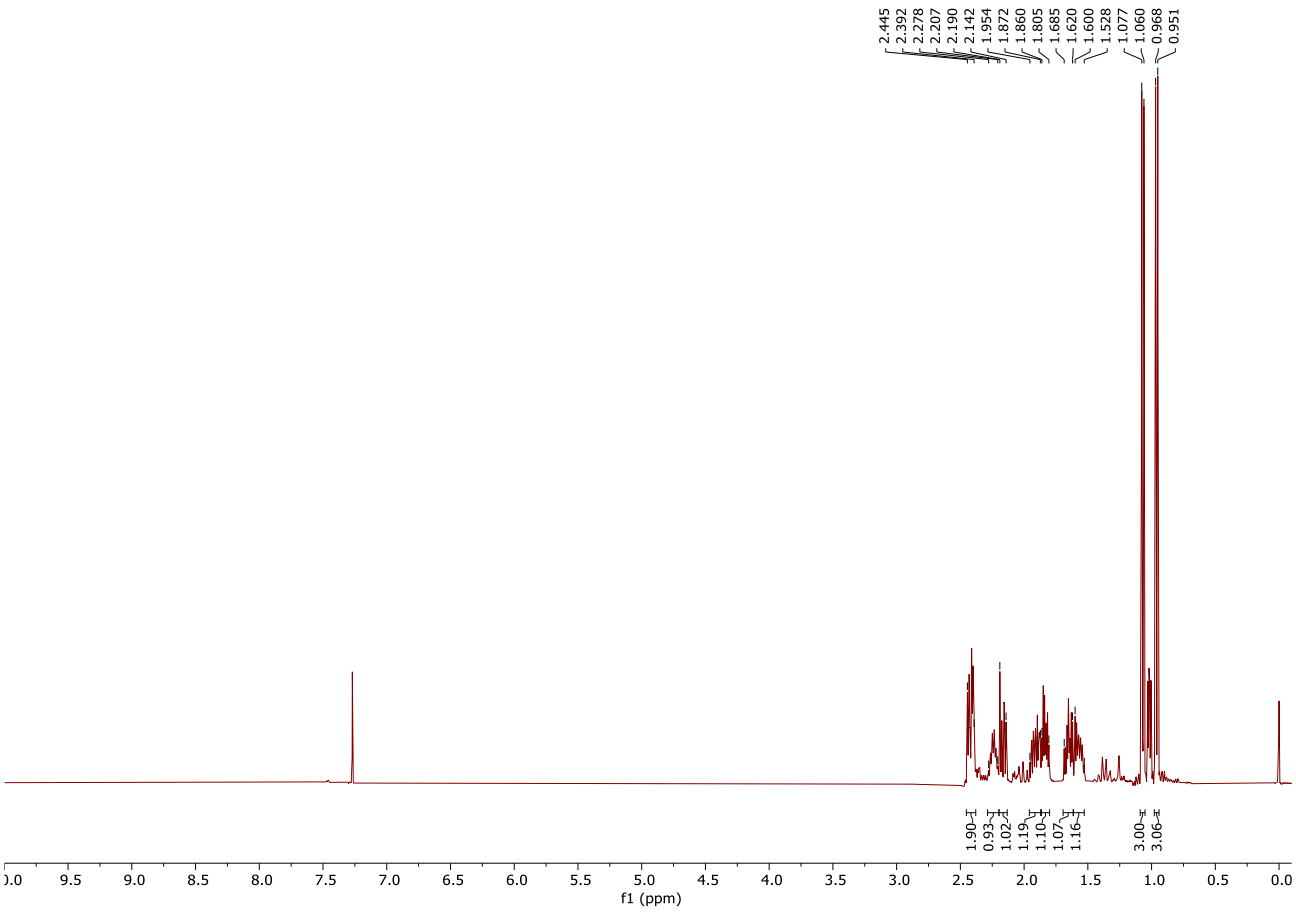
2,5-Dimethylcyclohexanone (36):



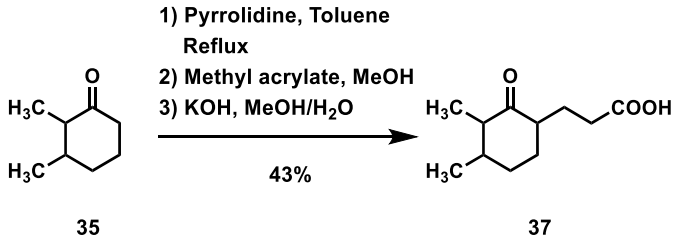
34 36

Operating as described in the preparation of ketone **35**, from PCC (10.18 g, 46.32 mmol) and 2,5-dimethylcyclohexanol (5.01 g, 38.60 mmol) in CH_2Cl_2 (75 mL), 2,5-dimethylcyclohexanone **36** was obtained as a colorless liquid (4.15 g, 84%):

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, J = 6.9 Hz, 3H, CH_3), 1.07 (d, J = 6.8 Hz, 3H, CH_3), 1.53-1.60 (m, 1H), 1.62-1.69 (m, 1H), 1.81-1.86 (m, 1H), 1.87-1.95 (m, 1H), 2.14-2.19 (m, 1H), 2.21-2.28 (m, 1H), 2.39-2.44 (m, 2H).


2.445
2.392
2.278
2.207
2.190
2.142
1.954
1.872
1.860
1.805
1.685
1.620
1.600
1.528
1.077
1.060
0.968
0.951
1.90
0.93
1.02
1.19
1.10
1.07
1.16
3.00
3.06
f1 (ppm)

3,4-Dimethyl-2-oxocyclohexanepropionic acid (37):



35 37

First Step: A solution of 2,3-dimethylcyclohexanone **35** (racemic mixture of diastereomers; 4.44 g, 35.2 mmol) and pyrrolidine (5.11 g, 71.8 mmol) in toluene (10 mL) was heated at reflux temperature under Dean Stark conditions. After 15 h, the mixture was cooled and concentrated. Methyl acrylate (3.46 mL, 38.7 mmol) was added to a solution of the above residue in methanol (11 mL) and the mixture was stirred at reflux temperature for 4 h. Then, a buffer solution (15 mL, HOAc–H_2O–NaOAc 25 mL:25 mL:12.5 g) was added and the reflux was continued for 1 h. After cooling to room temperature, the mixture was diluted with Et_2O, and washed with 2 M aqueous HCl and brine. The organic phase was dried and concentrated.

Second Step: KOH (2.3 g, 34.8 mmol, 85%) was added to a solution of the above crude in MeOH–H_2O (60 mL:30 mL), and the mixture was stirred at room temperature for 6 h. Then, the mixture was washed with CH_2Cl_2. The combined aqueous extracts were acidified to pH 2-3 by addition of 2 M aqueous HCl and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a diastereomeric mixture of keto acids **37** (3.01 g, 43%) as an off-white solid.

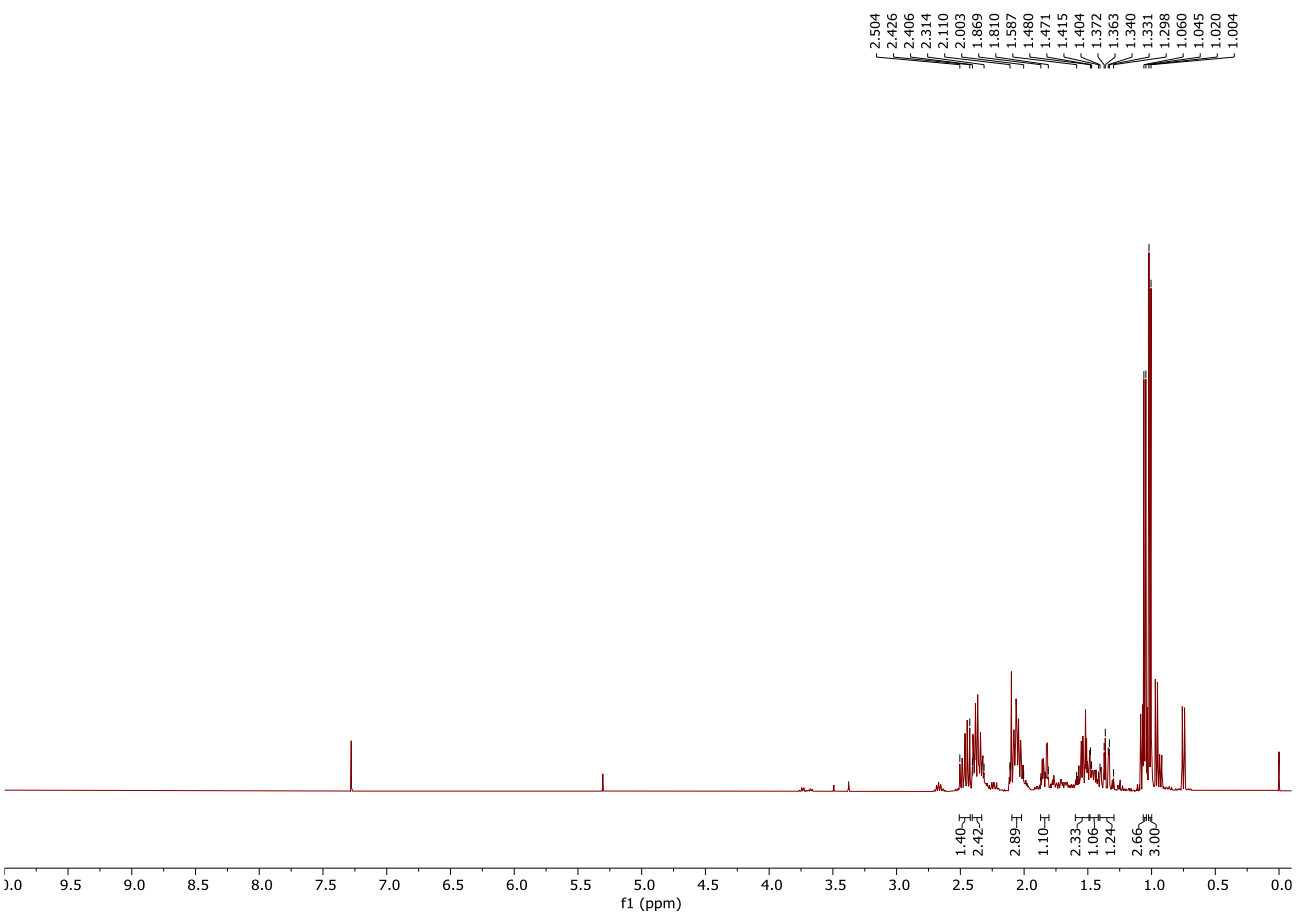
mp 60-64 °C (hexane–CH_2Cl_2).

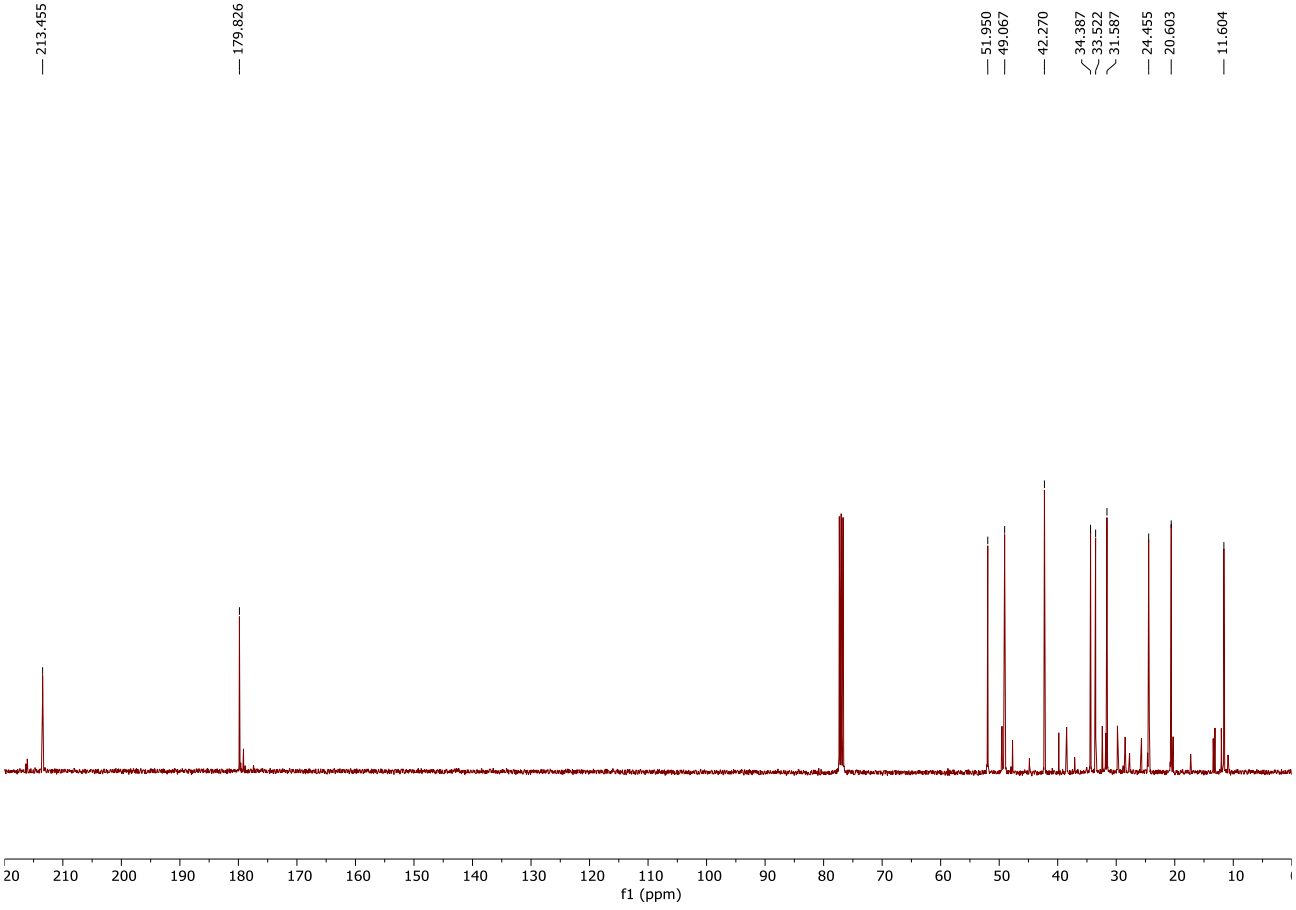
IR (NaCl): 1701 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 9.93 (br s, 1H, COOH); 2.43-2.50 (m, 1H); 2.41-2.31 (m, 2H), 2.11- 2.00 (m, 3H), 1.87-1.81 (m, 1H), 1.59-1.48 (m, 2H), 1.47-1.42 (m, 1H), 1.35 (qd, J = 12.8, 3.6 Hz, 1H), 1.05 (d, J = 6.2 Hz, 3H, CH_3), 1.01 (d, J = 6.2 Hz, 3H, CH_3).

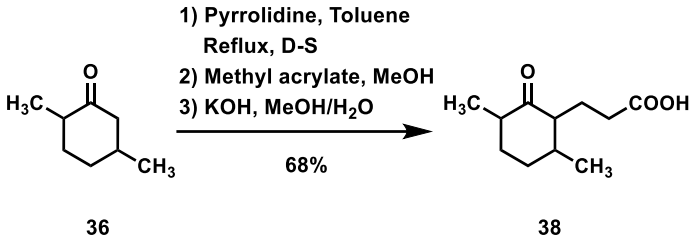
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.5 (CO), 179.8 (CO_2), 51.9 (CH), 49.1 (CH), 42.3 (CH), 34.4 (CH_2), 33.5 (CH_2), 31.6 (CH_2), 24.5 (CH_2), 20.6 (CH_3), 11.6 (CH_3).

HRMS Calcd for [$C_{11}H_{18}O_3 – H^+$]: 197.1183; found 197.1187.


2.504
2.426
2.406
2.314
2.110
2.003
1.869
1.810
1.587
1.480
1.471
1.415
1.404
1.372
1.363
1.340
1.331
1.298
1.060
1.045
1.020
1.004
1.40
2.42
2.89
1.10
2.33
1.06
1.24
2.66
3.00
f1 (ppm)


213.455
179.826
51.950
49.067
42.270
34.387
33.522
31.587
24.455
20.603
11.604
f1 (ppm)

3,6-Dimethyl-2-oxocyclohexanepropionic acid (38):



36 38

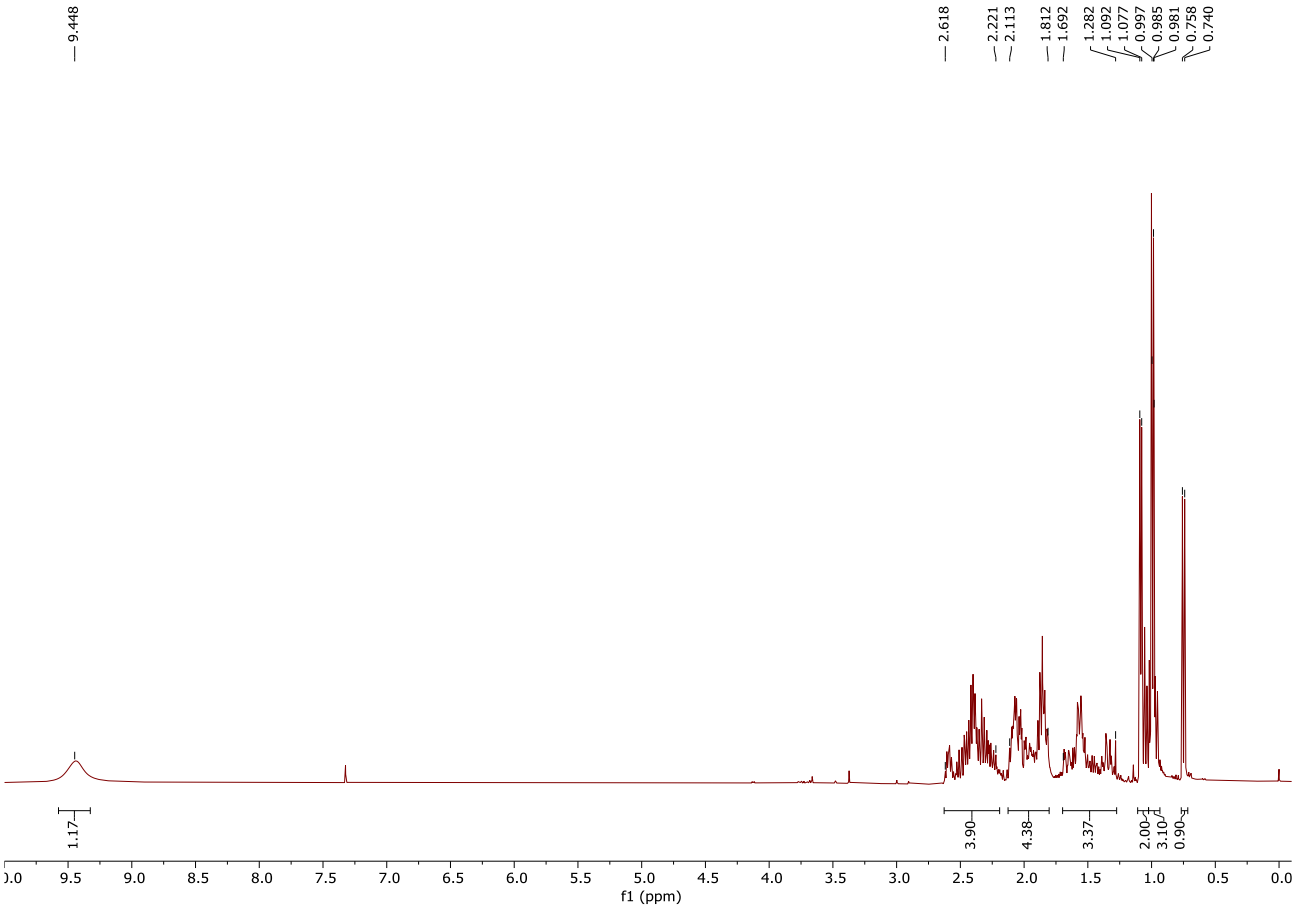
Operating as described in the preparation of keto acids **4**, from pyrrolidine (3.96 g, 55.6 mmol), 2,5-dimethylcyclohexanone **x** (racemic mixture of diastereomers; 3.51 g, 27.8 mmol) in toluene (25 mL), methyl acrylate (5 mL, 55.6 mmol) in MeOH (25 mL), and KOH (3.67 g, 55.6 mmol) in MeOH–H_2O (72 mL:36 mL), a diastereomeric mixture of keto acids **6** (3.75 g, 68% from **3**) was obtained as a yellowish oil:

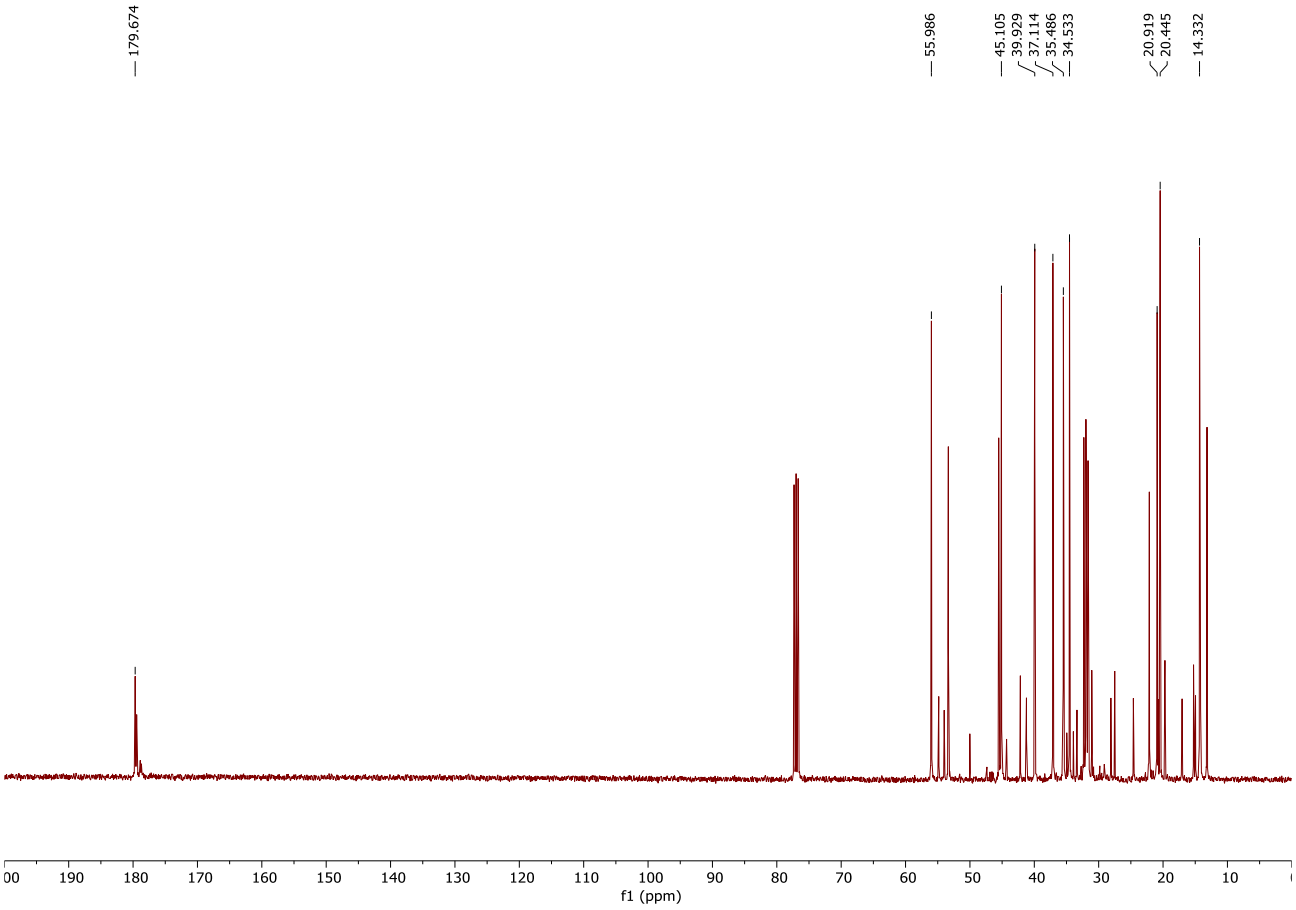
IR (NaCl): 1708 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 9.45 (br s, OH) 2.62-2.21 (m, 3H), 2.11-1.81 (m, 4H), 1.69-1.28 (m, 3H), 0.75 and 0.98 and 1.08 [(d, J = 7.2 Hz), (d, J = 6.4 Hz) and (d, J = 4.0 Hz), 6H, $2CH_3$].

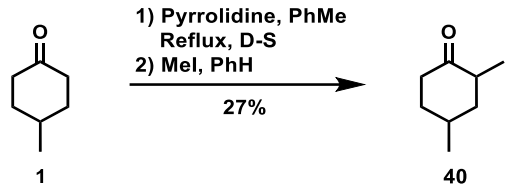
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.6 (CO), 179.7 (COO), 56.0 (CH), 45.1 (CH), 39.9 (CH), 37.1 (CH_2), 35.5 (CH_2), 34.5 (CH_2), 20.9 (CH_2), 20.4 (CH_3), 14.3 (CH_3).

HRMS Calcd for [$C_{11}H_{18}O_3 + H^+$]: 199.1329; found 197.1332.


9.448
2.618
2.221
2.113
1.812
1.692
1.282
1.092
1.077
0.997
0.985
0.981
0.758
0.740
1.17
3.90
4.38
3.37
2.00
3.10
0.90
f1 (ppm)


179.674
55.986
45.105
39.929
37.114
35.486
34.533
20.919
20.445
14.332
f1 (ppm)

2,4-Dimethylcyclohexanone (40):

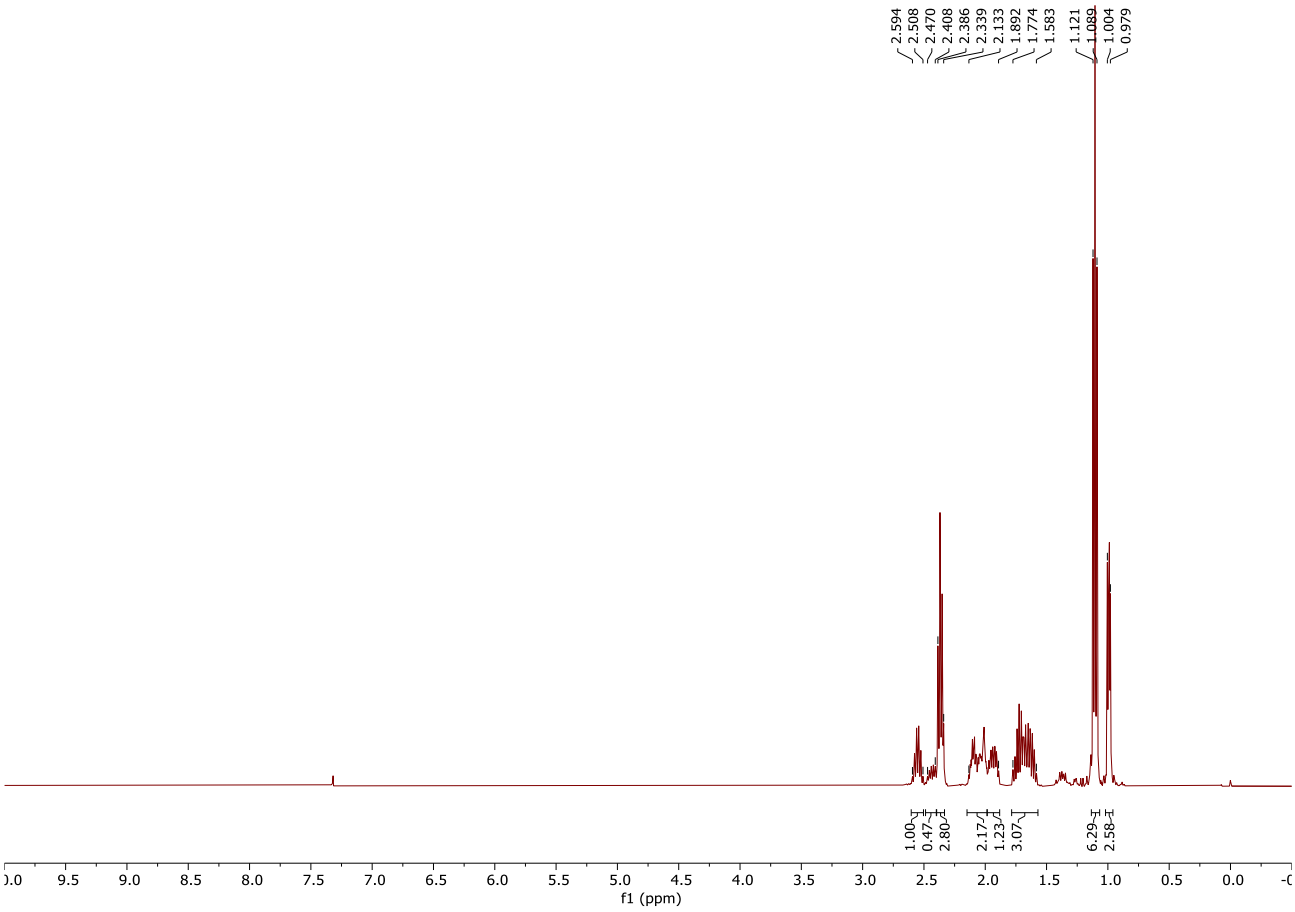


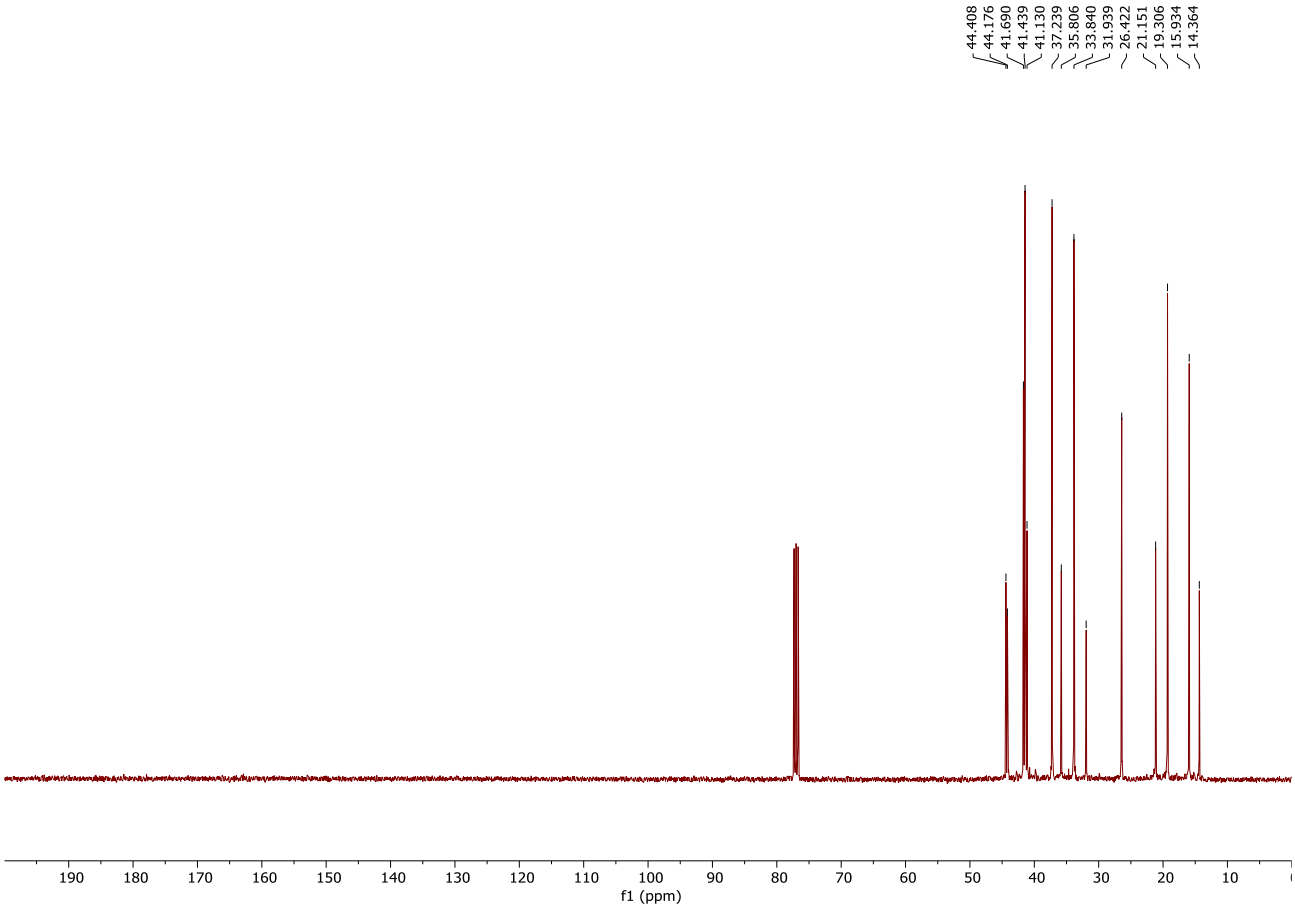
A solution of 4-methylcyclohexanone (5.0 mL, 40.7 mmol) and pyrrolidine (6.12 mL, 73.34 mmol) in toluene (20 mL) was heated at reflux temperature under Dean Stark conditions. After 15 h, the mixture was cooled and concentrated. Methyl iodide (5.1 mL, 81.5 mmol) was added to a solution of the above residue in benzene (50 mL) and the mixture was stirred at room temperature for 24 h. Then, a buffer solution (30 mL; HOAc–H_2O–NaOAc, 25 mL: 25 mL: 12.5 g) was added and the mixture was heated at reflux temperature for 1 h. After cooling, the mixture was diluted with Et_2O, washed with 2 M aqueous HCl (2 x 20 mL) and brine (2 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (9:1 hexane–Et_2O) afforded ketone **40** (1.41 g, 27 %, 7:3 *cis:trans* mixture[98]) as colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.98-1.00 (m, 6H, CH_3), 1.09-1.12 (m, 6H, CH_3), 1.12-1.13 (m, 1H), 1.34-1.42 (m, 1H) 1.58-1.77 (m, 3H), 1.89-2.13 (m, 5H), 2.34- 2.39 (m, 4H), 2.41-2.47 (m, 1H), 2.51-2.59 (m, 1H).

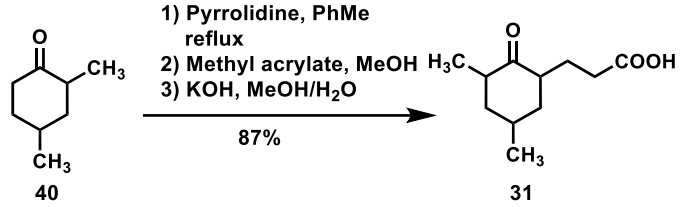
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.4 and 15.9 (CH_3), 19.3 and 21.2 (CH_3), 26.4 and 31.9 (CH), 33.8 and 35.8 (CH_2), 37.2 (CH_2), 41.1 and 41.4 (CH_2), 41.7 and 44.2 (CH), 44.4 (CH_2), 213.4 and 214.7 (CO).

[98] *cis* isomer described in: Snider, B. B.; Lu, Q. *J. Org. Chem*. **1994**, *59*, 8065-8070


2.594
2.508
2.470
2.408
2.386
2.339
2.133
1.892
1.774
1.583
1.121
1.089
1.004
0.979
1.00
0.47
2.80
2.17
1.23
3.07
6.29
2.58
f1 (ppm)


44.408
44.176
41.690
41.439
41.130
37.239
35.806
33.840
31.939
26.422
21.151
19.306
15.934
14.364
f1 (ppm)

3,5-Dimethyl-2-oxocyclohexanepropionic acid (31):



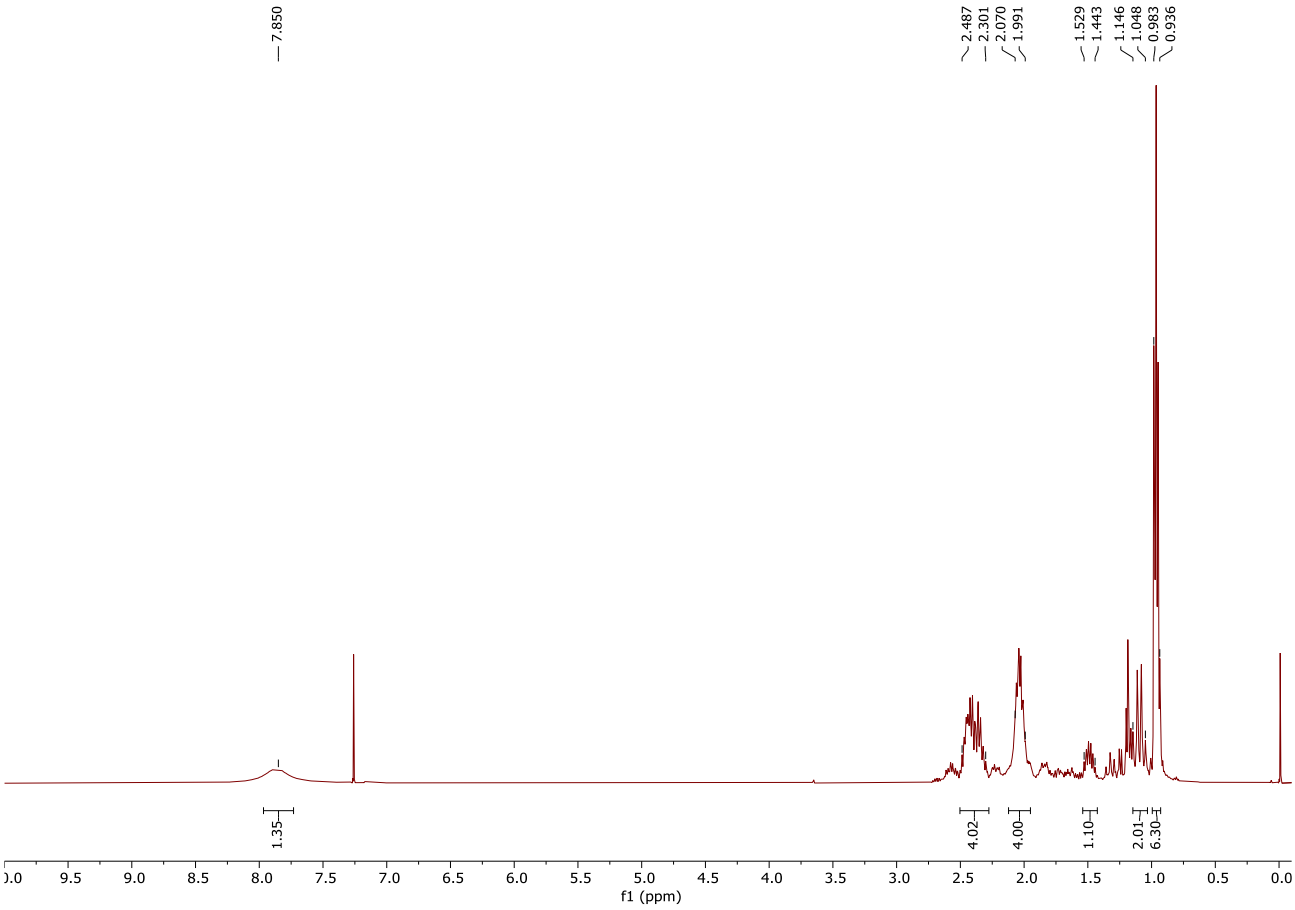
Operating as described in the preparation of keto acid **37**, from pyrrolidine (1.7 mL, 21.2 mmol), 2,4-dimethylcyclohexanone **40** (racemic mixture of diastereomers; 1.34 g, 10.6 mmol) in toluene (11 mL), methyl acrylate (0.95 mL, 10.6 mmol) in MeOH (14 mL), and KOH (772 mg, 11.7 mmol, 85%) in MeOH–H_2O (24 mL:12 mL), a diastereomeric mixture of keto acids **31** (1.83 g, 87%) was obtained as a colorless oil:

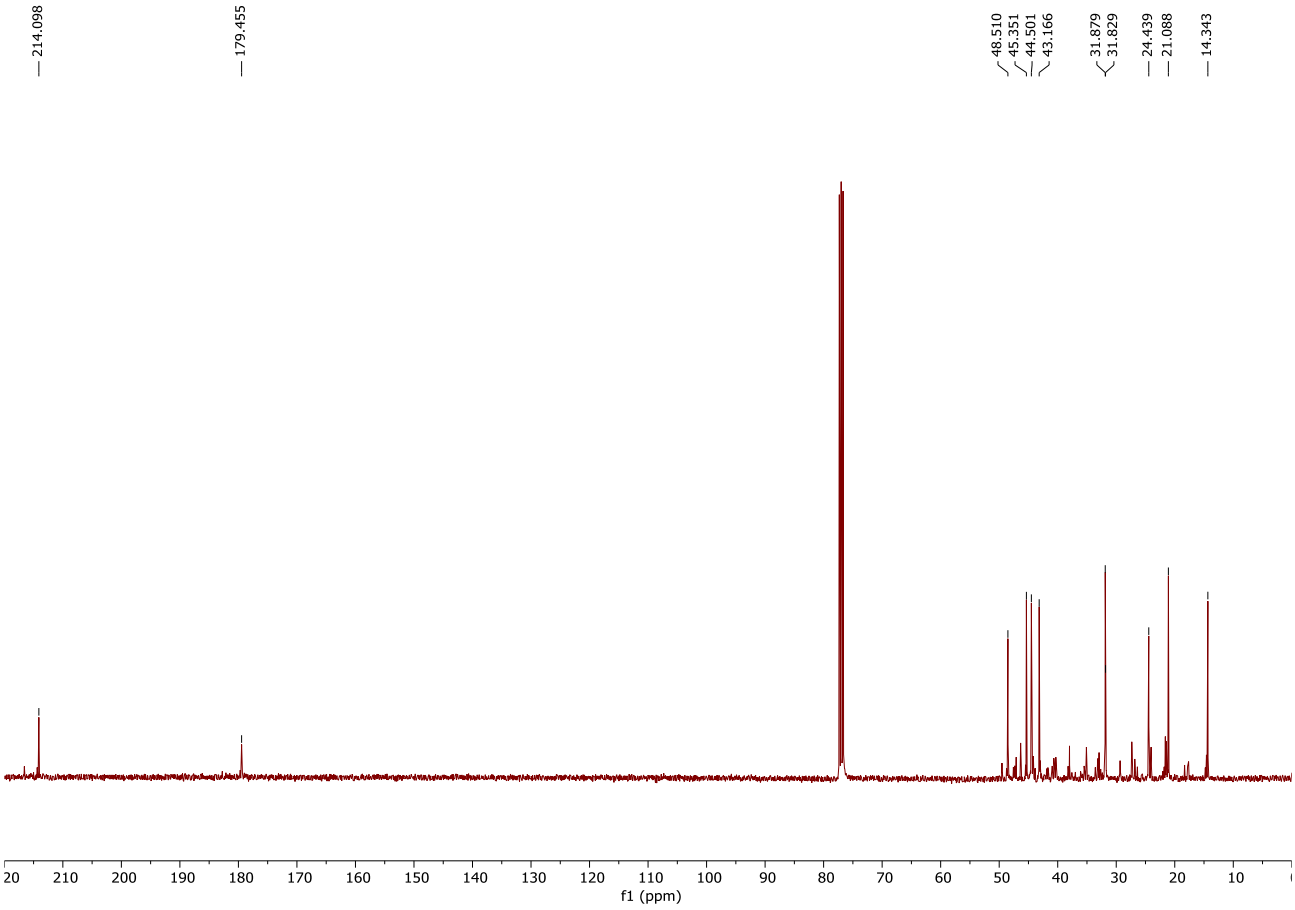
IR (NaCl): 1709 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.85 (br s, 1H, COOH); 2.50-2.33 (m, 4H), 2.10-2.01 (m, 4H), 1.55-1.46 (m 1H), 1.16-1.06 (m, 2H), 1.00-0.95 (m, 6H, CH_3).

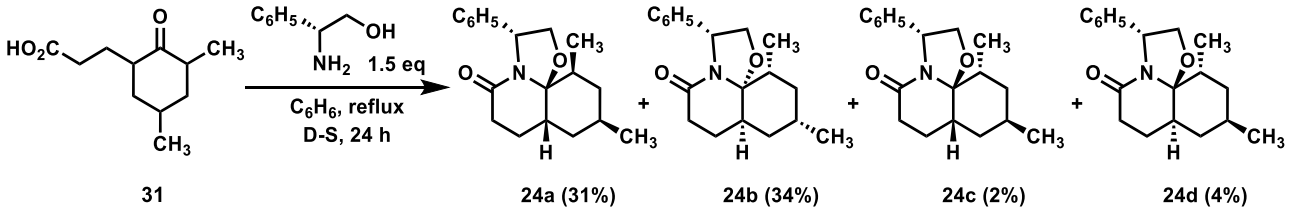
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.1 (CO); 179.4 (CO_2), 48.5 (CH), 45.3 (CH_2), 44.5 (CH), 43.2 (CH_2), 31.9 (CH), 31.8 (CH_2), 24.4 (CH_2), 21.1 (CH_3), 14.3 (CH_3).

HRMS Calcd for [$C_{11}H_{18}O_3 – H^+$]: 197.1183; found 197.1191.


7.850
2.487
2.301
2.070
1.991
1.529
1.443
1.146
1.048
0.983
0.936
1.35
4.02
4.00
1.10
2.01
6.30
f1 (ppm)


214.098
179.455
48.510
45.351
44.501
43.166
31.879
31.829
24.439
21.088
14.343
f1 (ppm)

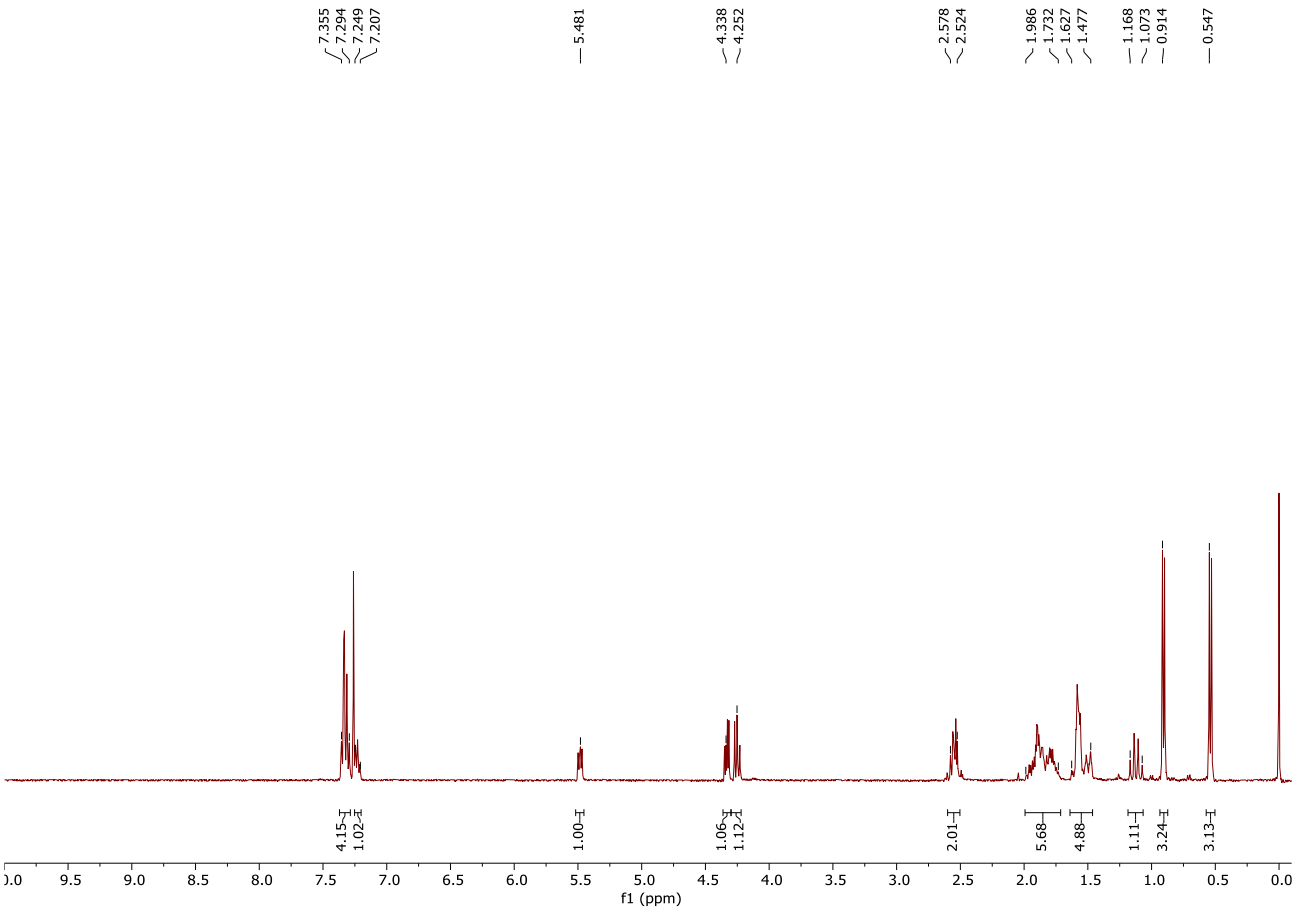
(3*R*,7a*S*,9*R*,11*S*,11a*S*)-9,11-Dimethyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (24a) and its (3*R*,7a*R*,9*S*,11*R*,11a*R*), (3*R*,7a*S*,9*R*,11*R*,11a*S*) and (3*R*,7a*R*,9*R*,11*R*,11a*S*) isomers (24b, 24c and 24d, respectively):



(*R*)-phenylglycinol (1.13 g, 8.2 mmol) was added to a solution of a diastereomeric mixture of keto acids **31** (1.07 g, 5.4 mmol) in benzene (55 mL). The mixture was heated at reflux under Dean Stark conditions for 24 h. After cooling, the solvent was evaporated, and the resulting residue was suspended in EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$, dried and evaporated. Flash chromatography (9:1 to 1:1 hexane–EtOAc) afforded lactams **24a** (502 mg, 31%), **24b** (543 mg, 34%), **24c** (29 mg, 2 %), and **24d** (59 mg, 4%) as colorless solids (**24c** as a colorless gum).

24a:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H, ArH), 5.47 (dd, *J* = 7.2, 4.4 Hz, 1H, H-3), 4.32 (dd, *J* = 8.8, 4.4 Hz, 1H, H-2), 4.24 (dd, *J* = 8.8, 7.2 Hz, 1H, H-2), 2.61-2.47 (m, 2H, H-6), 1.98-1.74 (m, 5H, H-7, H-7a, H-9 and H-11), 1.59-1.55 (m, 2H, H-8), 1.51-1.47 (m, 1H, H-10), 1.12 (q, *J* = 12.8 Hz, 1H, H-10), 0.90 (d, *J* = 6.4 Hz, 3H, CH_3C-9), 0.53 (d, *J* = 6.8 Hz, 3H, CH_3C-11);


7.355
7.294
7.249
7.207
5.481
4.338
4.252
2.578
2.524
1.986
1.732
1.627
1.477
1.168
1.073
0.914
0.547
4.15
1.02
1.00
1.06
1.12
2.01
5.68
4.88
1.11
3.24
3.13
f1 (ppm)

24b:

CCDC number: 2217476

mp: 66-68 °C (hexane–CH_2Cl_2).

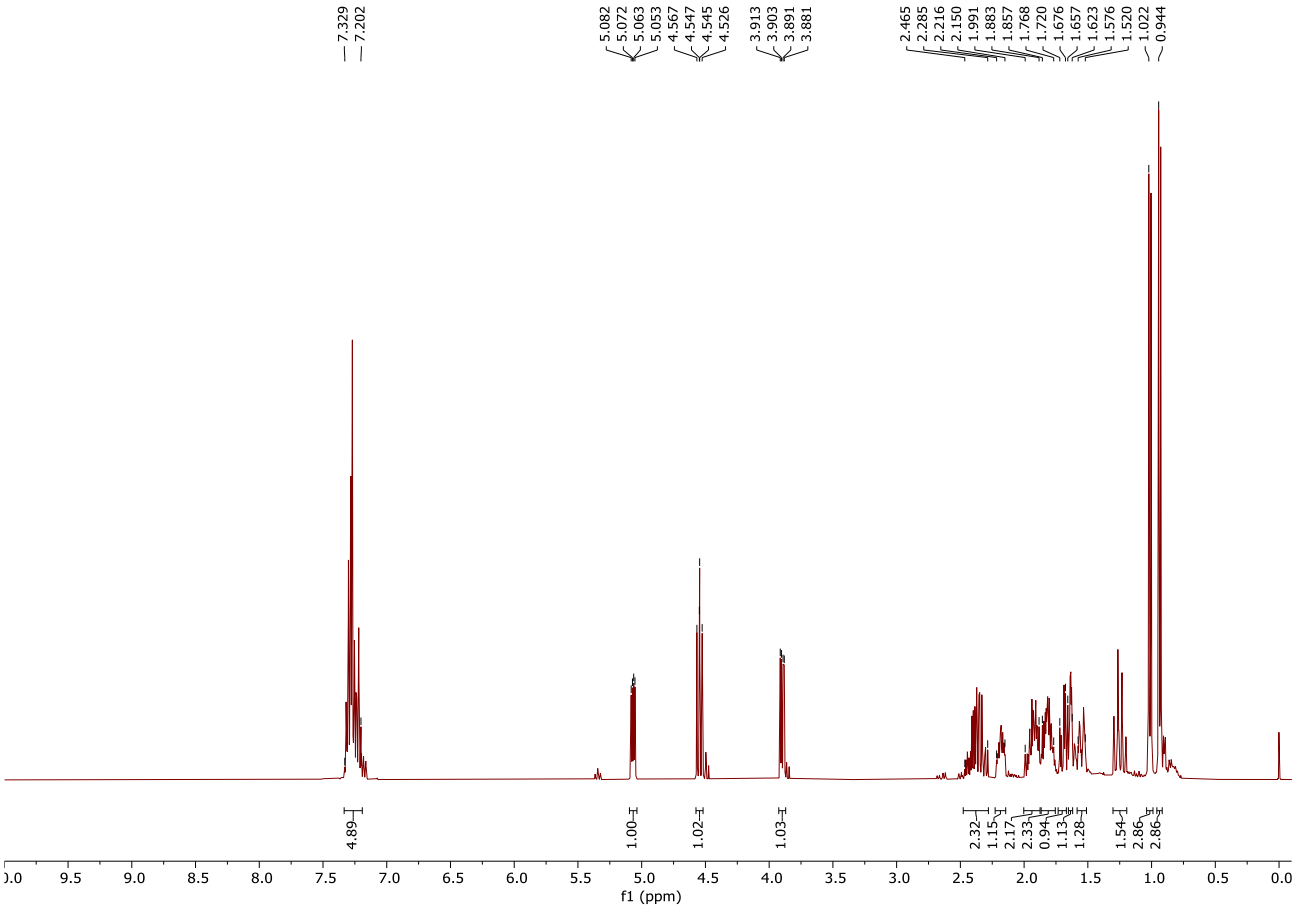
$[\alpha]^{23}_D$ + 32.7 (*c* 0.99, $CHCl_3$).

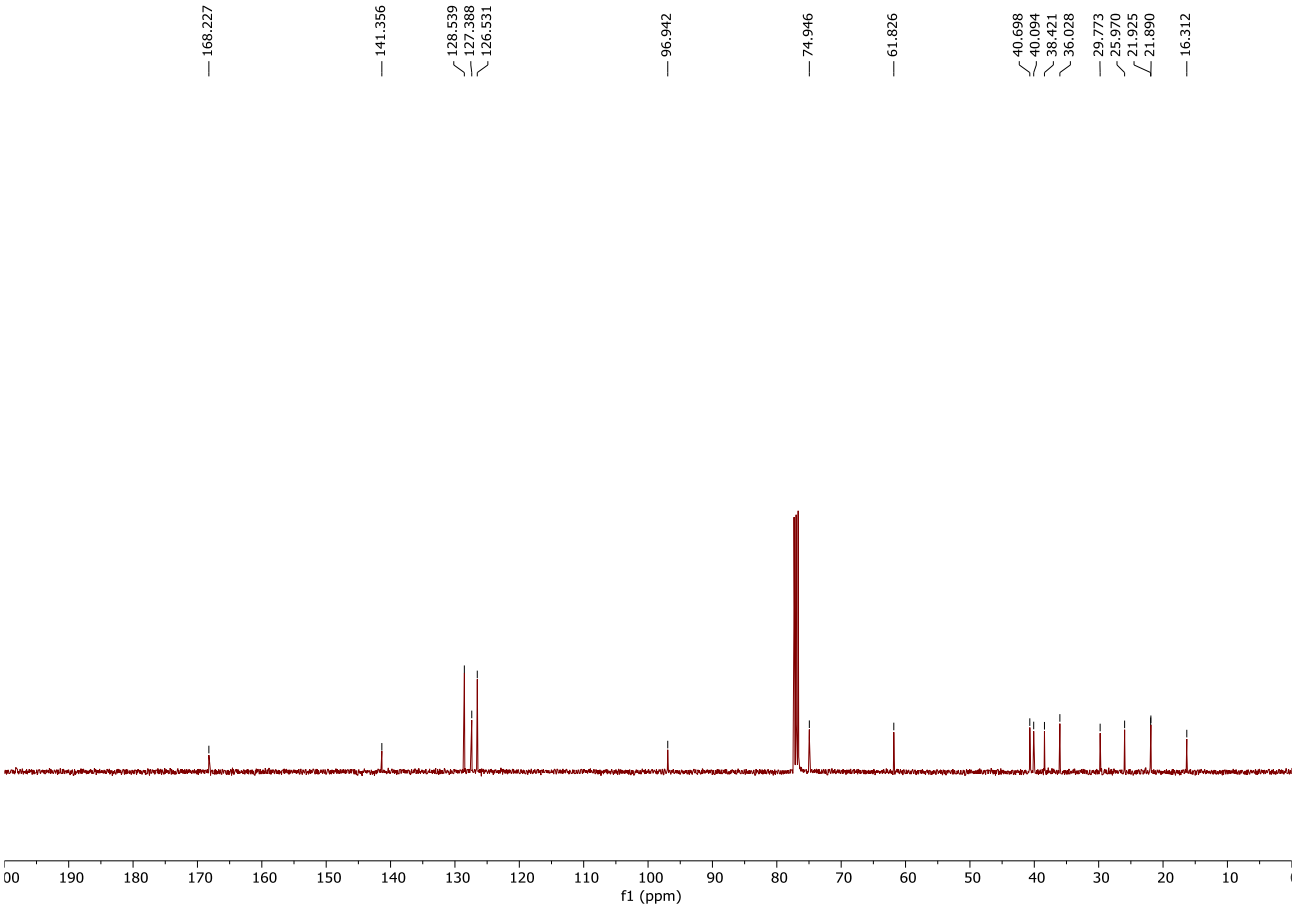
IR (NaCl): 1662 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.33-7.20 (m, 5H, ArH), 5.07 (dd, *J* = 7.6, 4.0 Hz, 1H, H-3), 4.55 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2), 3.90 (dd, *J* = 8.8, 4.0 Hz, 1H, H-2), 2.46-2.28 (m, 2H, H-6), 2.22-2.15 (m, 1H, H-7a), 1.97-1.87 (m, 2H, H-7 and H-9), 1.87-1.77 (m, 2H, H-7 and H-11), 1.69 (m, 1H, H-8), 1.63 (m, 1H, H-8), 1.58-1.52 (m, 1H, H-10), 1.25 (q, *J* = 12.5 Hz, 1H, H-10), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3C-9), 0.93 (d, *J* = 6.4 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.1 (CO), 141.3 (C-Ar), 127.3 (CH-Ar), 128.4 (CH-Ar), 126.4 (CH-Ar), 96.8 (C-11a), 74.8 (C-2), 61.7 (C-3), 40.6 (C-7a), 40.0 (C-10), 38.2 (C-9), 35.9 (C-8), 29.7 (C-6), 25.9 (C-11), 21.8 (*C*H_3C-9 and C-7), 16.2 (*C*H_3C-11).

HRMS Calcd for [$C_{19}H_{25}NO_2$ + H^+]: 300.1958; found 300.1962.


7.329
7.202
5.082
5.072
5.063
5.053
4.567
4.547
4.545
4.526
3.913
3.903
3.891
3.881
2.465
2.285
2.216
2.150
1.991
1.883
1.857
1.768
1.720
1.676
1.657
1.623
1.576
1.520
1.022
0.944
4.89
1.00
1.02
1.03
2.32
1.15
2.17
2.33
0.94
1.13
1.28
1.54
2.86
2.86
f1 (ppm)


168.227
141.356
128.539
127.388
126.531
96.942
74.946
61.826
40.698
40.094
38.421
36.028
29.773
25.970
21.925
21.890
16.312
f1 (ppm)

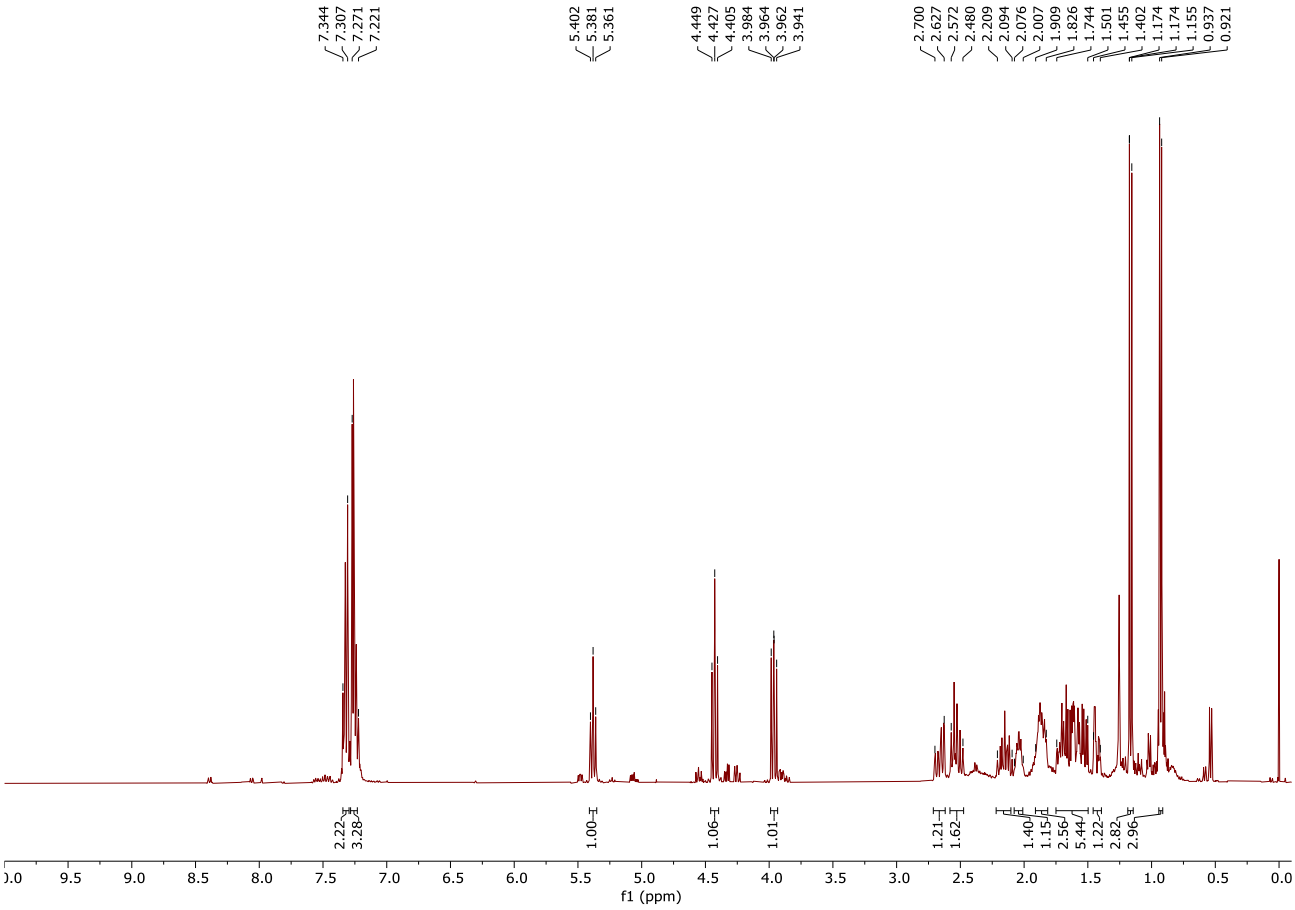
24c:

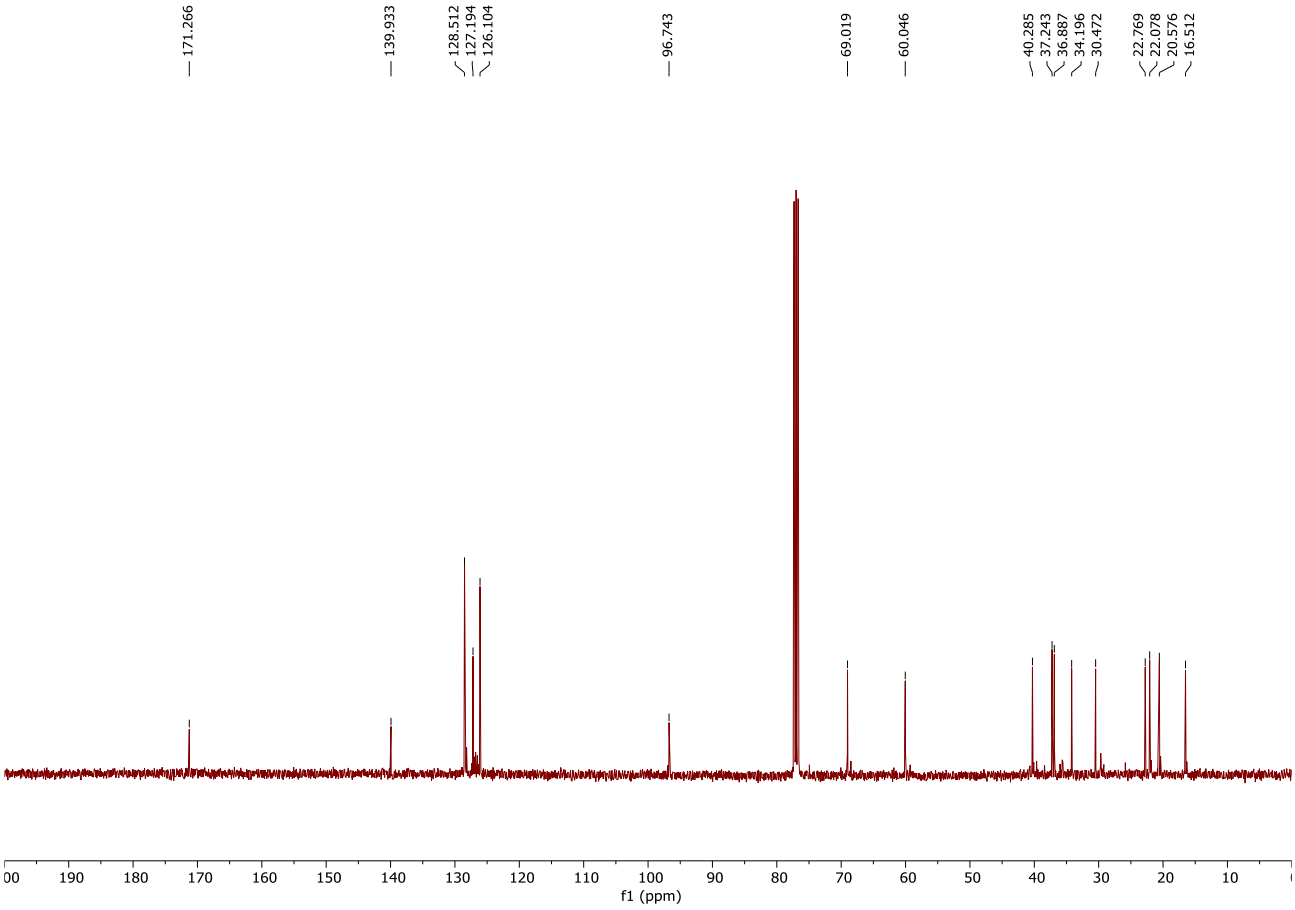
IR (NaCl): 1656 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, *g*-HSQC) δ 7.34-7.31 (m, 2H, ArH), 7.27-7.22 (m, 3H, ArH), 5.38 (t, *J* = 8.4 Hz, 1H, H-3), 4.43 (t, *J* = 8.8 Hz, 1H, H-2), 3.96 (dd, *J* = 8.8, 8 Hz, 1H, H-2), 2.70-2.63 (m, 1H, H-6), 2.57-2.48 (m, 1H, H-6), 2.21-2.09 (m, 1H, H-7), 2.08-2.01 (m, 1H, H-11), 1.91-1.83 (m, 2H, H-7a and H-9), 1.74-1.50 (m, 4H, H-7, H-8 and H-10), 1.46-1.40 (m, 1H, H-8), 1.16 (d, *J* = 7.6 Hz, 3H, CH_3C-11), 0.93 (d, *J* = 6.4 Hz, 3H, CH_3C-9).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.3 (CO), 139.9 (C-Ar), 127.2 (CH-Ar), 128.5 (CH-Ar), 126.1 (CH-Ar), 96.7 (C-11a), 69.0 (C-2), 60.0 (C-3), 40.3 (C-7a), 37.2 (C-8), 36.9 (C-10), 34.2 (C-11), 30.5 (C-6), 22.8 (C-7), 22.1 (*C*H_3C-9), 20.6 (C-9), 16.5 (*C*H_3C-11).

HRMS Calcd for [$C_{19}H_{25}NO_2 + H^+$]: 300.1958; found 300.1952.


7.344
7.307
7.271
7.221
5.402
5.381
5.361
4.449
4.427
4.405
3.984
3.964
3.962
3.941
2.700
2.627
2.572
2.480
2.209
2.094
2.076
2.007
1.909
1.826
1.744
1.501
1.455
1.402
1.174
1.155
0.937
0.921
2.22
3.28
1.00
1.06
1.01
1.21
1.62
1.40
1.15
2.56
5.44
1.22
2.82
2.96
f1 (ppm)


171.266
139.933
128.512
127.194
126.104
96.743
69.019
60.046
40.285
37.243
36.887
34.196
30.472
22.769
22.078
20.576
16.512
f1 (ppm)

24d:

CCDC number: 2217477

mp: 119-121 °C (hexane–CH_2Cl_2).

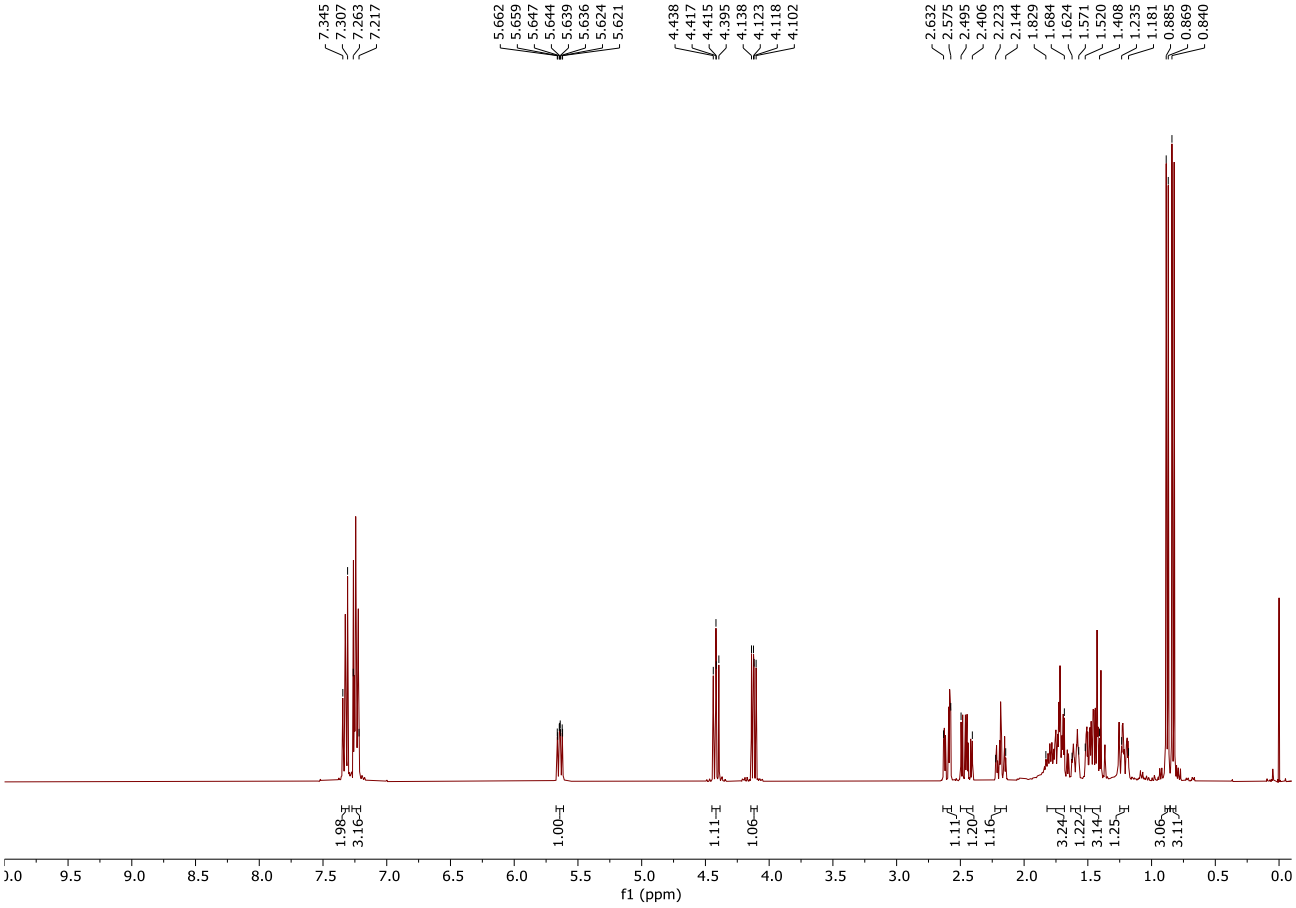
$[\alpha]^{23}_D$ – 193.3 (*c* 1.01, $CHCl_3$).

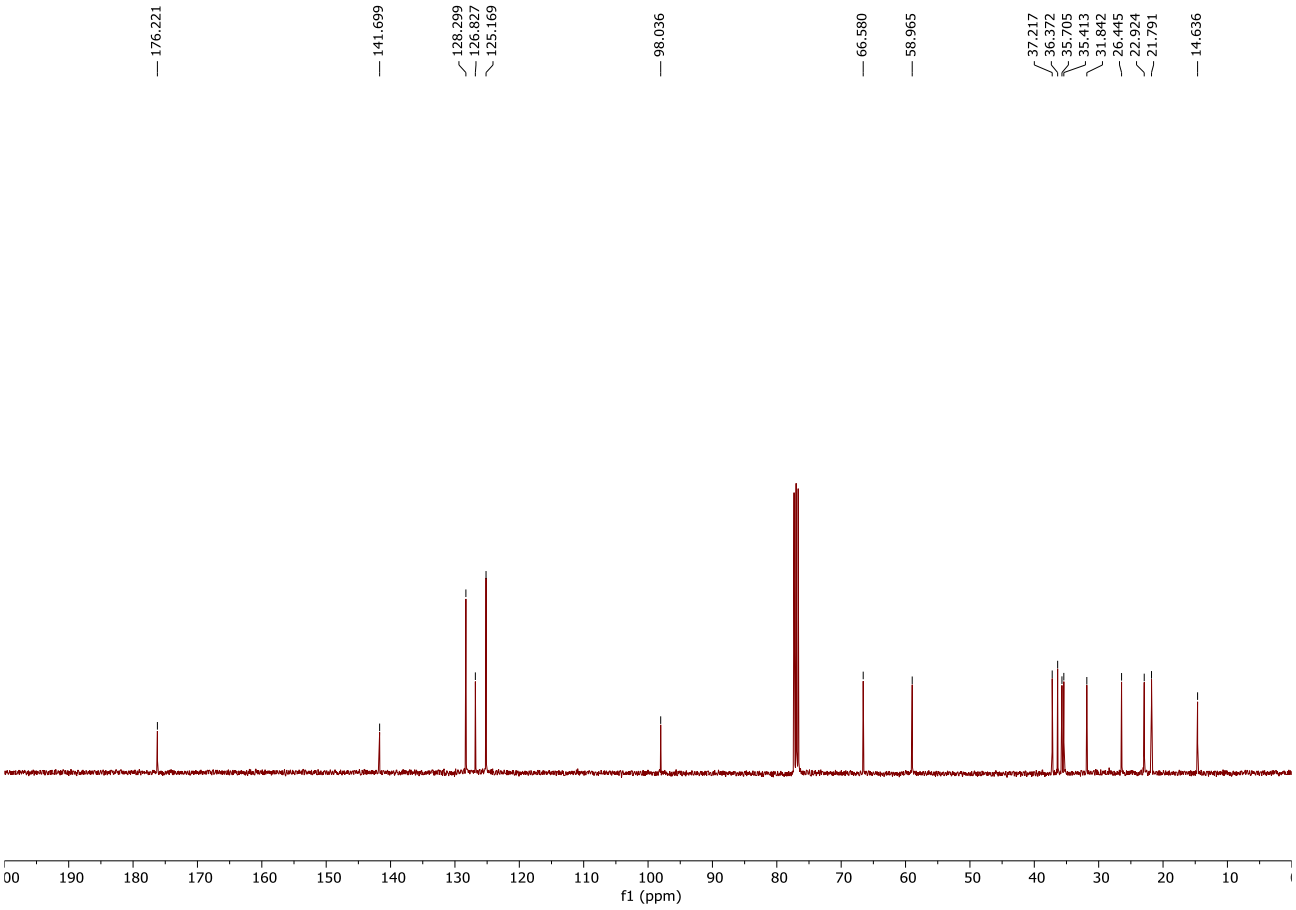
IR (NaCl): 1668 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.34-7.31 (m, 2H, ArH), 7.26-7.22 (m, 3H, ArH), 5.64 (dd, *J* = 8.8, 6.0 Hz, 1H, H-3), 4.42 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 4.12 (dd, *J* = 8.0, 6.0 Hz, 1H, H-2), 2.60 (dd, *J* = 16.8, 3.6 Hz, 1H, H-6), 2.45 (dd, *J* = 14.0, 5.2 Hz, 1H, H-6), 2.18 (tt, *J* = 12.4, 2.8 Hz, 1H, H-7a), 1.83-1.68 (m, 3H, H-7, H-9 and H-11) , 1.62-1.57 (m, 1H, H-8), 1.52-1.41 (m, 3H, H-7, H-8 and H-10), 1.23-1.18 (m, 1H, H-10), 0.87 (d, *J* = 6.4 Hz, 3H, CH_3C-9), 0.83 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

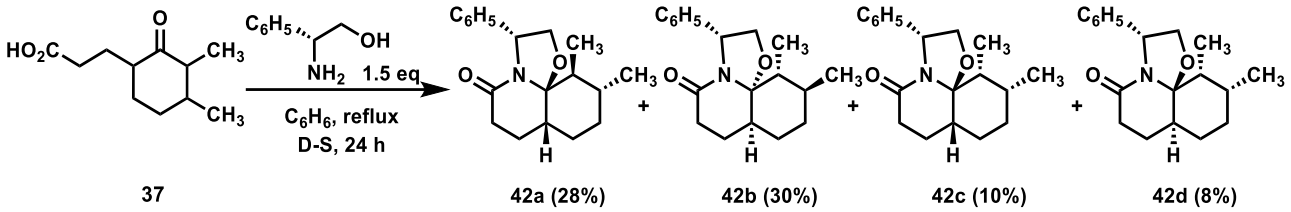
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.2 (CO), 141.7 (C-Ar), 126.8 (CH-Ar), 128.3 (CH-Ar), 125.2 (CH-Ar), 98.0 (C-11a), 66.6 (C-2), 59.0 (C-3), 37.2 (C-8), 36.4 (C-10), 35.7 (C-7a), 35.4 (C-6), 31.8 (C-11), 26.4 (C-9), 22.9 (C-7), 21.8 (*C*H_3C-9), 14.6 (*C*H_3C-11).

HRMS Calcd for [$C_{19}H_{25}NO_2$ + H^+]: 300.1958; found 300.1952.


7.345
7.307
7.263
7.217
5.662
5.659
5.647
5.644
5.639
5.636
5.624
5.621
4.438
4.417
4.415
4.395
4.138
4.123
4.118
4.102
2.632
2.575
2.495
2.406
2.223
2.144
1.829
1.684
1.624
1.571
1.520
1.408
1.235
1.181
0.885
0.869
0.840
1.98
3.16
1.00
1.11
1.06
1.11
1.20
1.16
3.24
1.22
3.14
1.25
3.06
3.11
f1 (ppm)


176.221
141.699
128.299
126.827
125.169
98.036
66.580
58.965
37.217
36.372
35.705
35.413
31.842
26.445
22.924
21.791
14.636
f1 (ppm)

(3*R*,7a*R*,10*R*,11*S*,11a*R*)-10,11-Dimethyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (42a) and its (3*R*,7a*S*,10*S*,11*R*,11a*S*), (3*R*,7a*R*,10*R*,11*R*,11a*R*) and (3*R*,7a*S*,10*R*,11*R*,11a*R*) isomers (42b, 42c and 42d, respectively):



37 42a (28%) 42b (30%) 42c (10%) 42d (8%)

Operating as described in the preparation of lactams **24a-24d**, from a diastereomeric mixture of keto acids **37** (2.88 g, 14.53 mmol) and *(R)*-phenylglycinol (2.99 g, 21.8 mmol) in benzene (150 mL), lactams **42a** (1.21 g, 28%), **42b** (1.32 g, 30 %), **42c** (0.41 g, 10 %), and **42d** (0.36 g, 8%) were obtained after flash column chromatography (9:1 to 1:1 hexane–EtOAc) as colorless solids (**42c** as a colorless gum).

42a:

CCDC number: 2217474

mp: 71-75 °C (hexane–CH_2Cl_2).

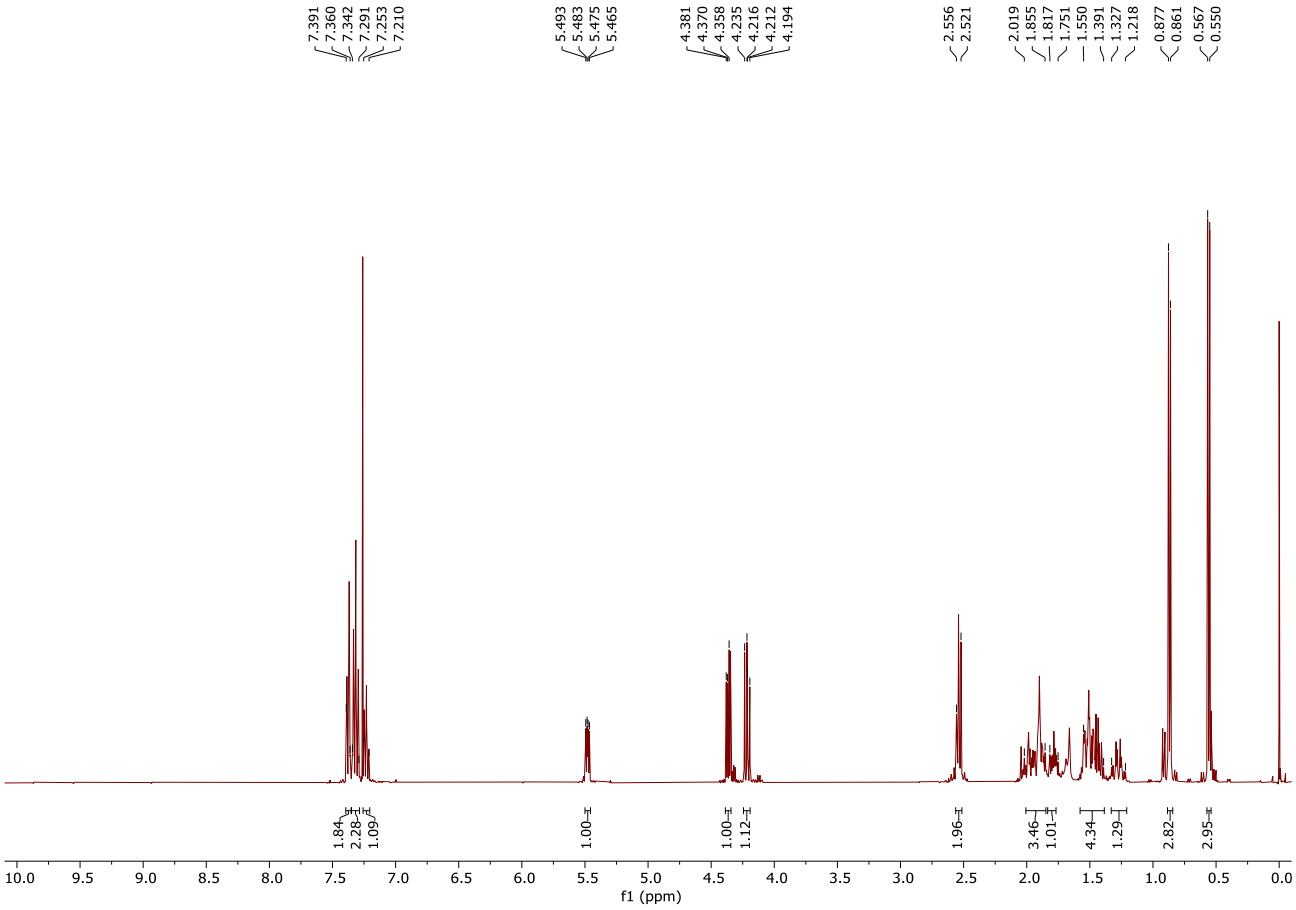
$[\alpha]^{23}_D$ – 181.4 (*c* 1.00, $CHCl_3$).

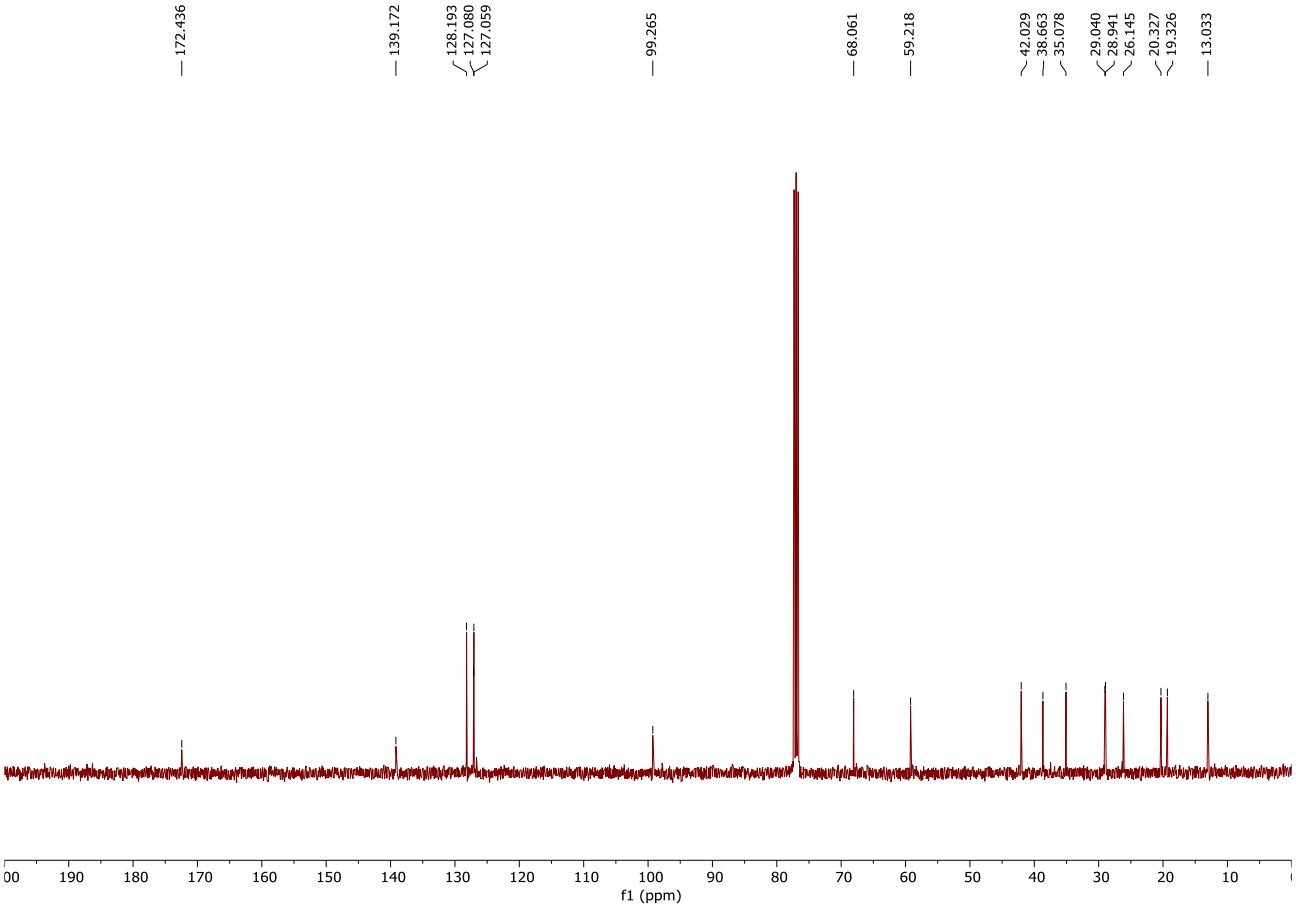
IR (NaCl): 1654 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.39-7.36 (m, 2H, ArH), 7.34-7.29 (m, 2H, ArH), 7.25-7.21 (m, 1H, ArH), 5.48 (dd, *J* = 7.4, 4.2 Hz, 1H, H-3), 4.36 (dd, *J* = 9.2, 4.2 Hz, 1H, H-2), 4.21 (dd, *J* = 9.2, 7.4 Hz, 1H, H-2), 2.56-2.52 (m, 2H, H-6), 2.02-1.85 (m, 3H, H-7, H-7a and H-8), 1.82-1.75 (m, 1H, H-7), 1.55-1.39 (m, 4H, H-8, H-9, H-10 and H-11), 1.33-1.22 (m, 1H, H-9), 0.87 (d, *J* = 6.4 Hz, 3H, CH_3C-11), 0.56 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (CO), 139.2 (C-Ar), 128.2 (CH-Ar), 127.1 (CH-Ar), 127.1 (CH-Ar), 99.3 (C-11a), 68.1 (C-2), 59.2 (C-3), 42.0 (C-11), 38.7 (C-7a), 35.1 (C-10), 29.0 (C-6), 28.9 (C-9), 26.1 (C-8), 20.3 (CH_3-C10), 19.3 (C-7), 13.0 (CH_3-C11).

HRMS Calcd for [$C_{19}H_{25}NO_2$ + H^+]: 300.1958; found 300.1960.


7.391
7.360
7.342
7.291
7.253
7.210
5.493
5.483
5.475
5.465
4.381
4.370
4.358
4.235
4.216
4.212
4.194
2.556
2.521
2.019
1.855
1.817
1.751
1.550
1.391
1.327
1.218
0.877
0.861
0.567
0.550
1.84
2.28
1.09
1.00
1.00
1.12
1.96
3.46
1.01
4.34
1.29
2.82
2.95
f1 (ppm)


172.436
139.172
128.193
127.080
127.059
99.265
68.061
59.218
42.029
38.663
35.078
29.040
28.941
26.145
20.327
19.326
13.033
f1 (ppm)

42b:

CCDC number: 2217475

mp: 92-95 °C (hexane–CH_2Cl_2).

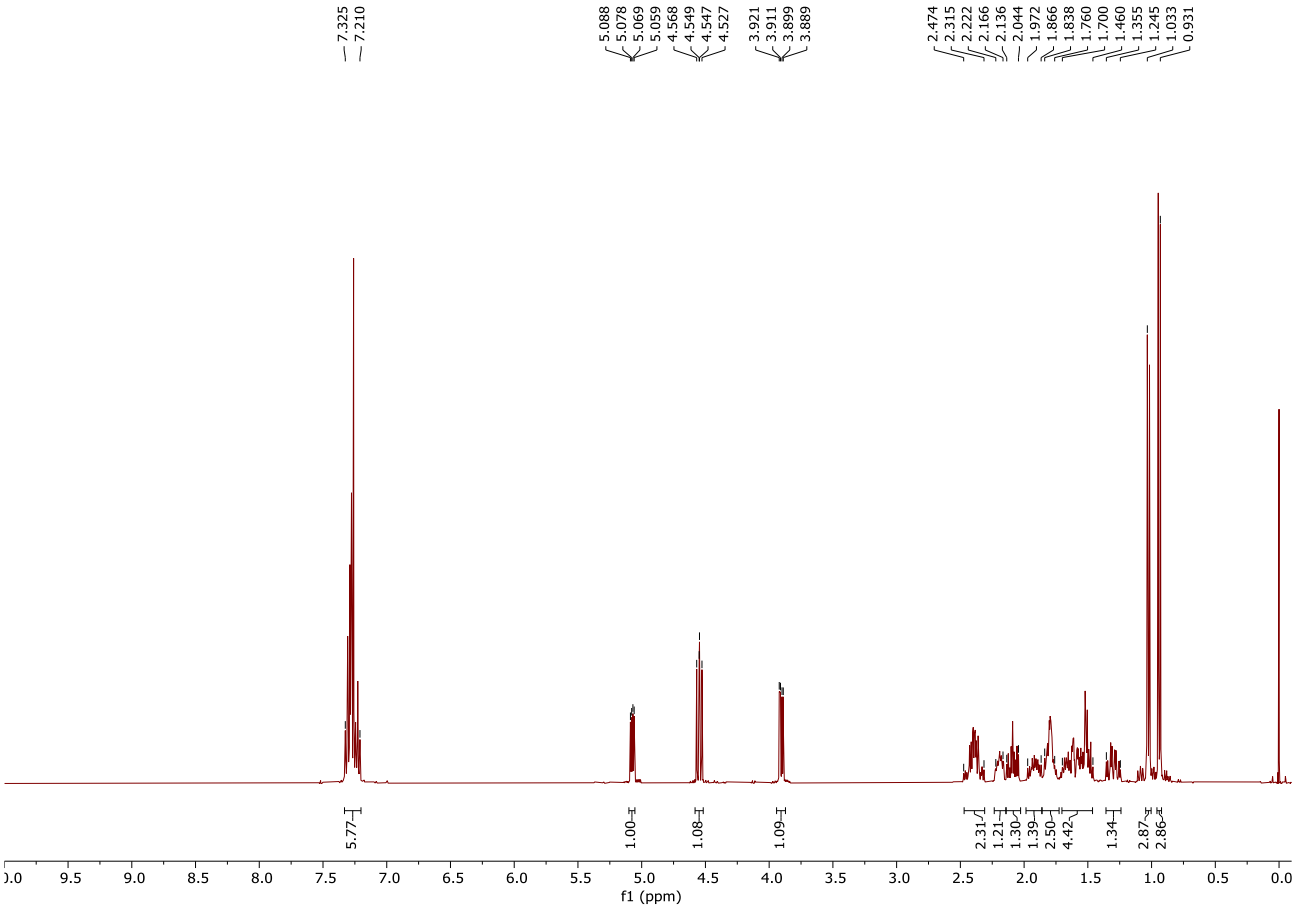
$[\alpha]^{23}_D$ + 43.2 (*c* 1.02, $CHCl_3$).

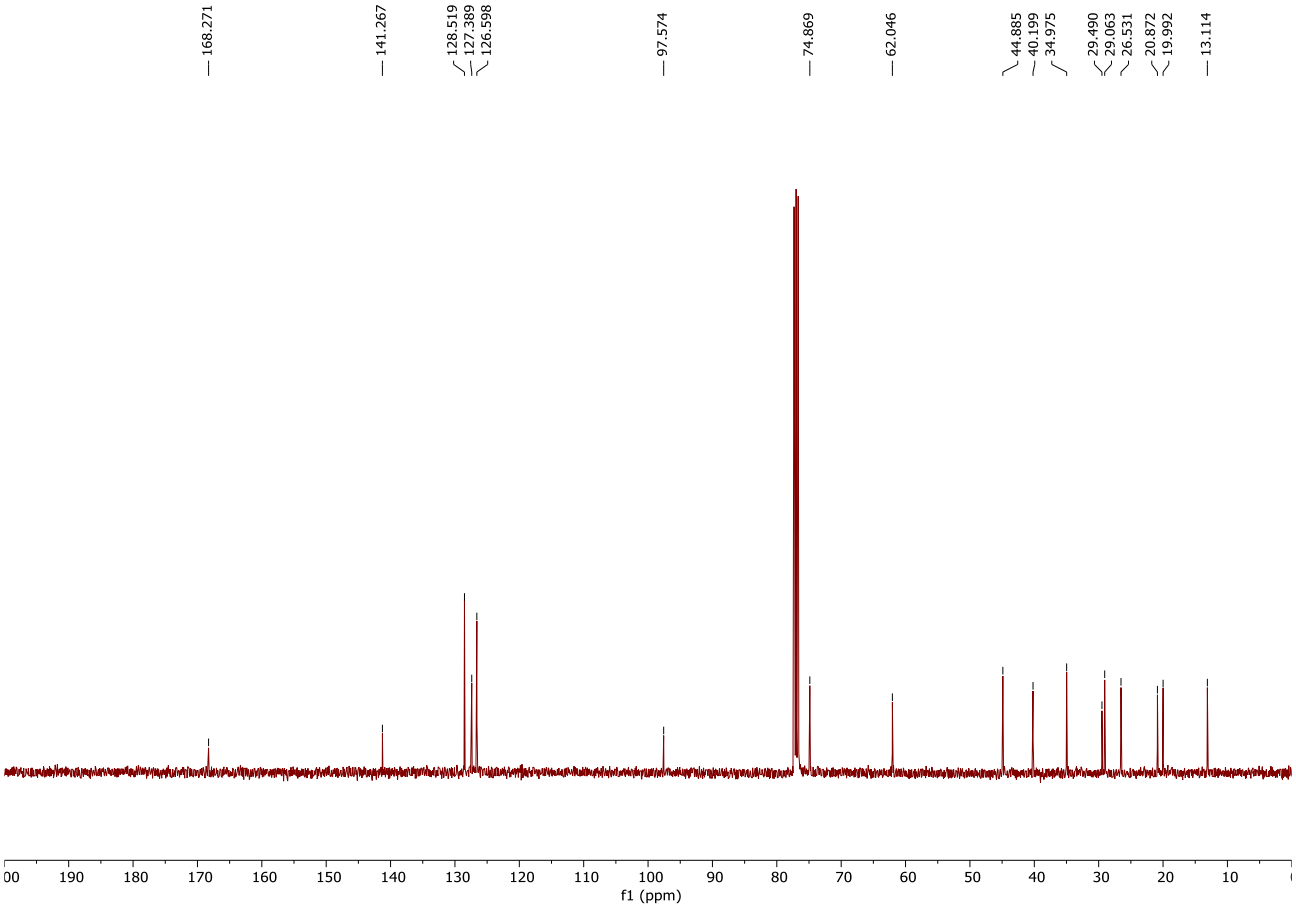
IR (NaCl): 1654 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.33-7.21 (m, 5H, ArH), 5.07 (dd, *J* = 7.6, 4.0 Hz, 1H, H-3), 4.55 (dd, *J* = 8.6, 7.6 Hz, 1H, H-2), 3.91 (dd, *J* = 8.6, 4.0 Hz, 1H, H-2), 2.44-2.31 (m, 2H, H-6), 2.23-2.16 (m, 1H, H-7a), 2.14-2.04 (m, 1H, H-8), 1.97-1.87 (m, 1H, H-7), 1.83-1.76 (m, 1H, H-7), 1.70-1.46 (m, 4H, H-8, H-9, H-10 and H-11), 1.35-1.24 (m, 1H, H-9), 1.02 (d, *J* = 6.8 Hz, 3H, CH_3), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.3 (CO), 141.3 (C-Ar), 127.4 (CH-Ar), 128.5 (CH-Ar), 126.6 (CH-Ar), 97.6 (C-11a), 74.9 (C-2), 62.0 (C-3), 44.9 (C-11), 40.2 (C-7a), 35.0 (C-10), 29.5 (C-6), 29.1 (C-9), 26.5 (C-8), 20.9 (C-7), 20.0 (CH_3-C11), 13.1 (CH_3-C10).

HRMS Calcd for [$C_{19}H_{25}NO_2 + H^+$]: 300.1958; found 300.1950.


7.325
7.210
5.088
5.078
5.069
5.059
4.568
4.549
4.547
4.527
3.921
3.911
3.899
3.889
2.474
2.315
2.222
2.166
2.136
2.044
1.972
1.866
1.838
1.760
1.700
1.460
1.355
1.245
1.033
0.931
5.77
1.00
1.08
1.09
2.31
1.21
1.30
1.39
2.50
4.42
1.34
2.87
2.86
f1 (ppm)


168.271
141.267
128.519
127.389
126.598
97.574
74.869
62.046
44.885
40.199
34.975
29.490
29.063
26.531
20.872
19.992
13.114
f1 (ppm)

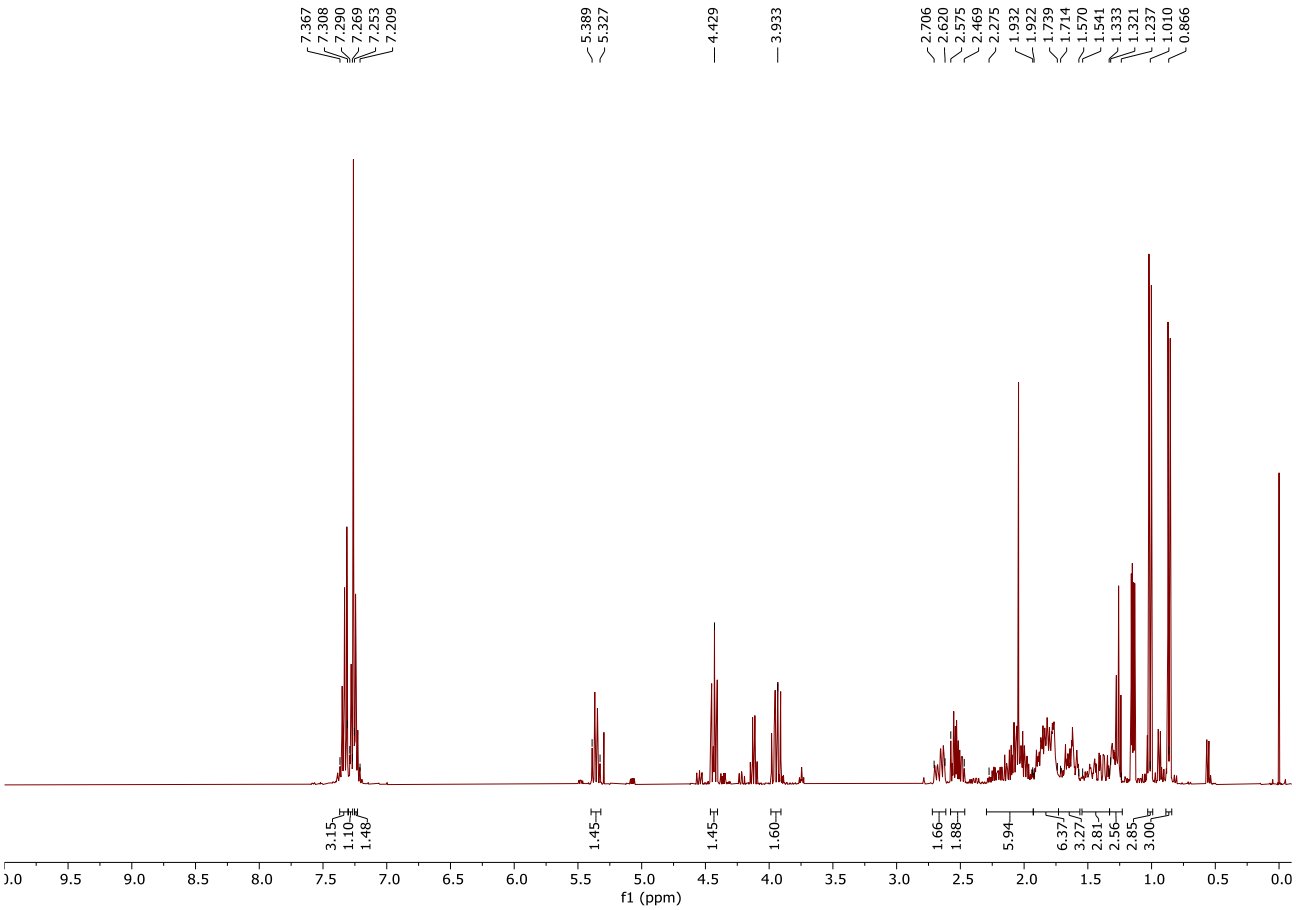
42c:

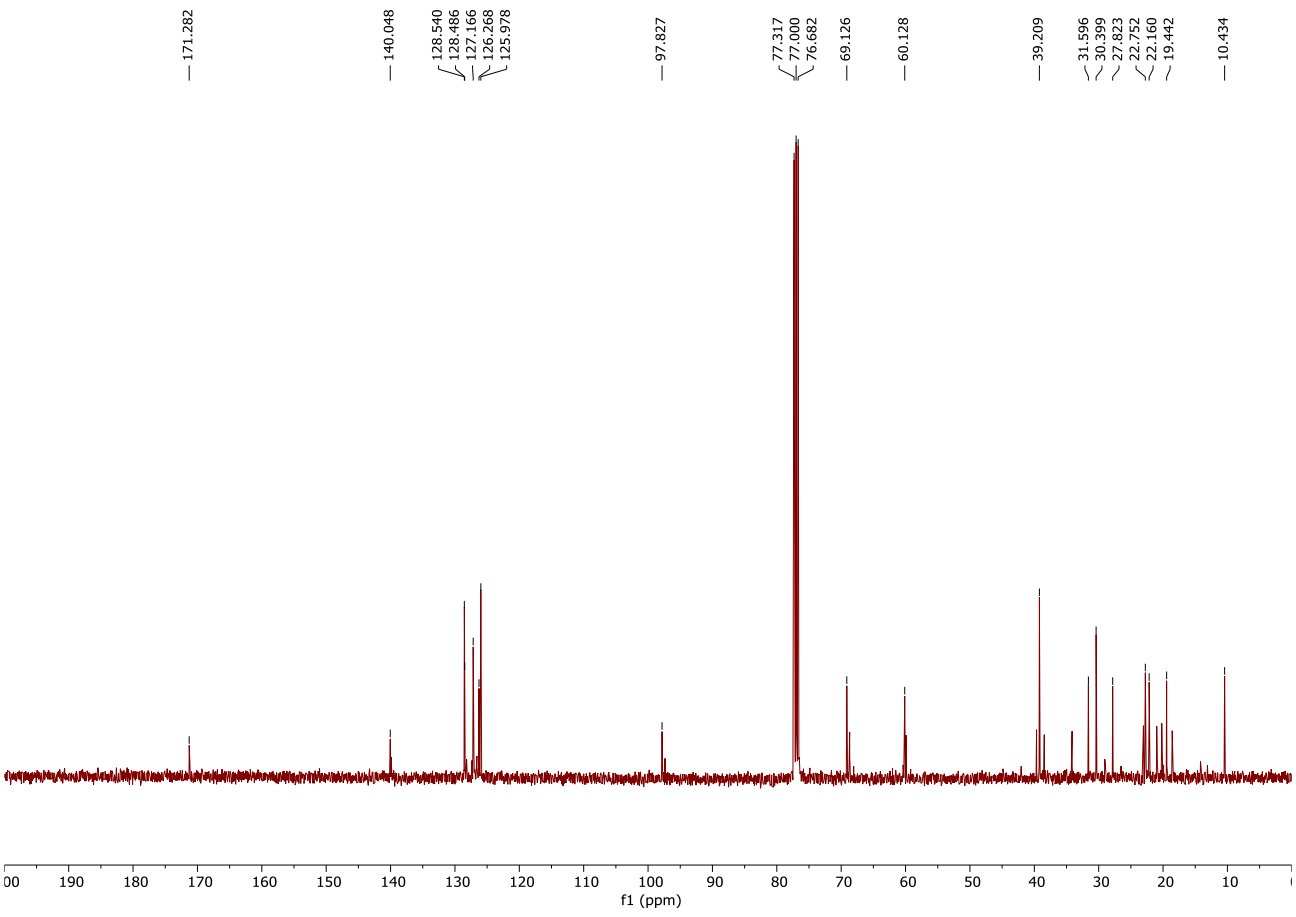
IR (NaCl): 1658 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.36-7.31 (m, 3H, ArH), 7.29-7.27 (m, 1H, ArH), 7.25-7.23 (m, 1H, ArH), 5.39-5.33 (m, 1H, H-3), 4.45-4.41 (m, 1H, H-2), 3.95-3.91 (m, 1H, H-2), 2.70-2.63 (m, 1H, H-6), 2.58-2.47 (m, 1H, H-6), 2.20-1.96 (m, 3H, H-7, H-8 and H-10), 1.90-1.77 (m, 2H, H-7a and H-11), 1.69-1.58 (m, 2H, H-7 and H-8), 1.45-1.35 (m, 1H, H-9), 1.31-1.25 (m, 1H, H-9), 1.01 (d, J = 7.6 Hz, 3H, CH_3), 0.86 (d, J = 6.8 Hz, 3H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.3 (CO), 140.0 (C-Ar), 126.0 (CH-Ar), 128.5 (CH-Ar), 127.2 (CH-Ar), 97.8 (C-11a), 69.1 (C-2), 60.1 (C-3), 39.2 (C-7a and C-11), 31.6 (C-10), 30.4 (C-6), 27.8 (C-8), 22.8 (C-9), 22.2 (C-7), 19.4 (CH_3C-10), 10.4 (CH_3C-11).

HRMS Calcd for [$C_{19}H_{25}NO_2 + H^+$]: 300.1958; found 300.1958.


7.367
7.308
7.290
7.269
7.253
7.209
5.389
5.327
4.429
3.933
2.706
2.620
2.575
2.469
2.275
1.932
1.922
1.739
1.714
1.570
1.541
1.333
1.321
1.237
1.010
0.866
3.15
1.10
1.48
1.45
1.45
1.60
1.66
1.88
5.94
6.37
3.27
2.81
2.56
2.85
3.00
f1 (ppm)


171.282
140.048
128.540
128.486
127.166
126.268
125.978
97.827
77.317
77.000
76.682
69.126
60.128
39.209
31.596
30.399
27.823
22.752
22.160
19.442
10.434
f1 (ppm)

42d:

CCDC number: 2217480

mp: 87-92 °C (hexane–CH_2Cl_2).

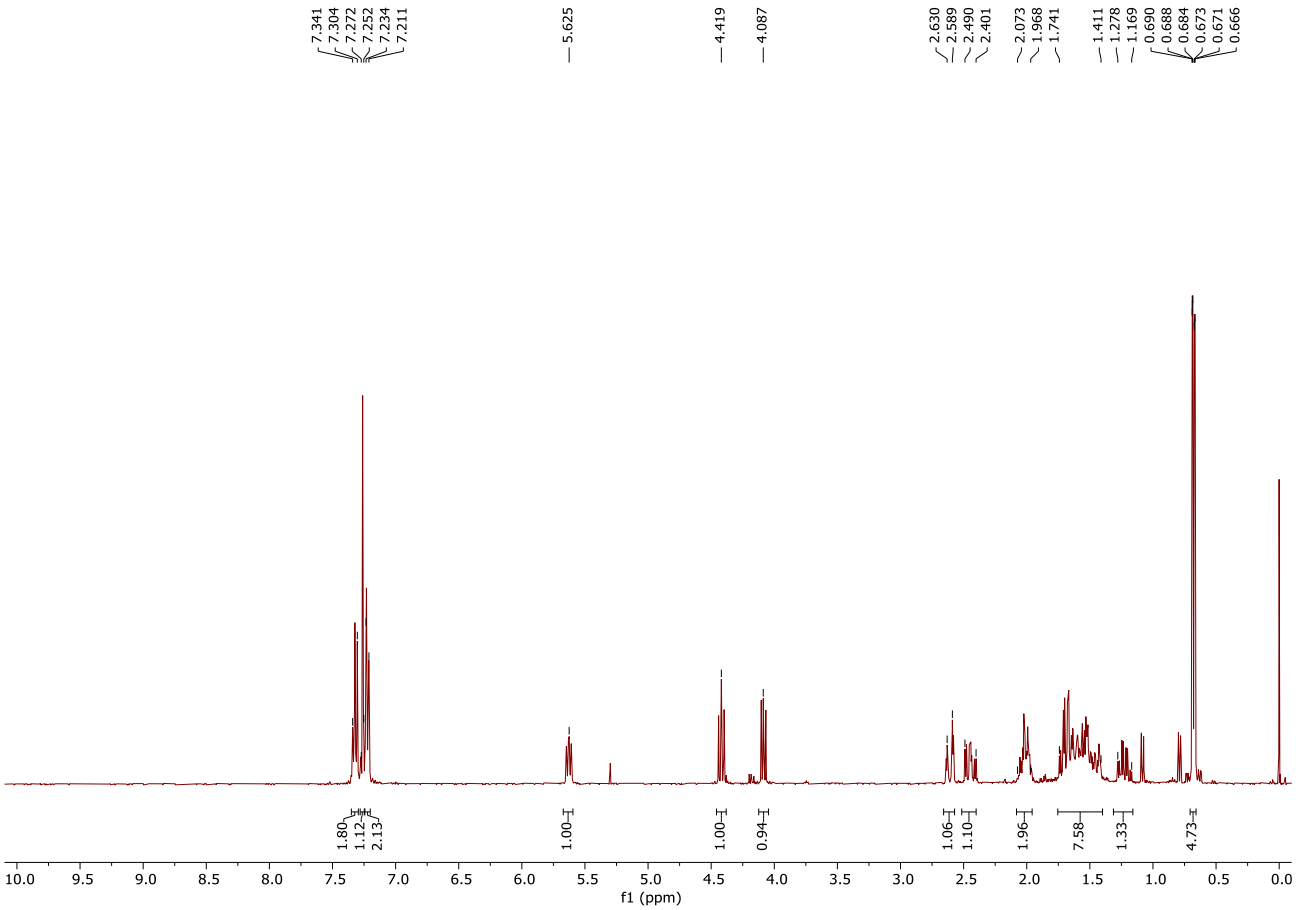
$[\alpha]^{23}_D$ – 181.5 (*c* 1.00, $CHCl_3$).

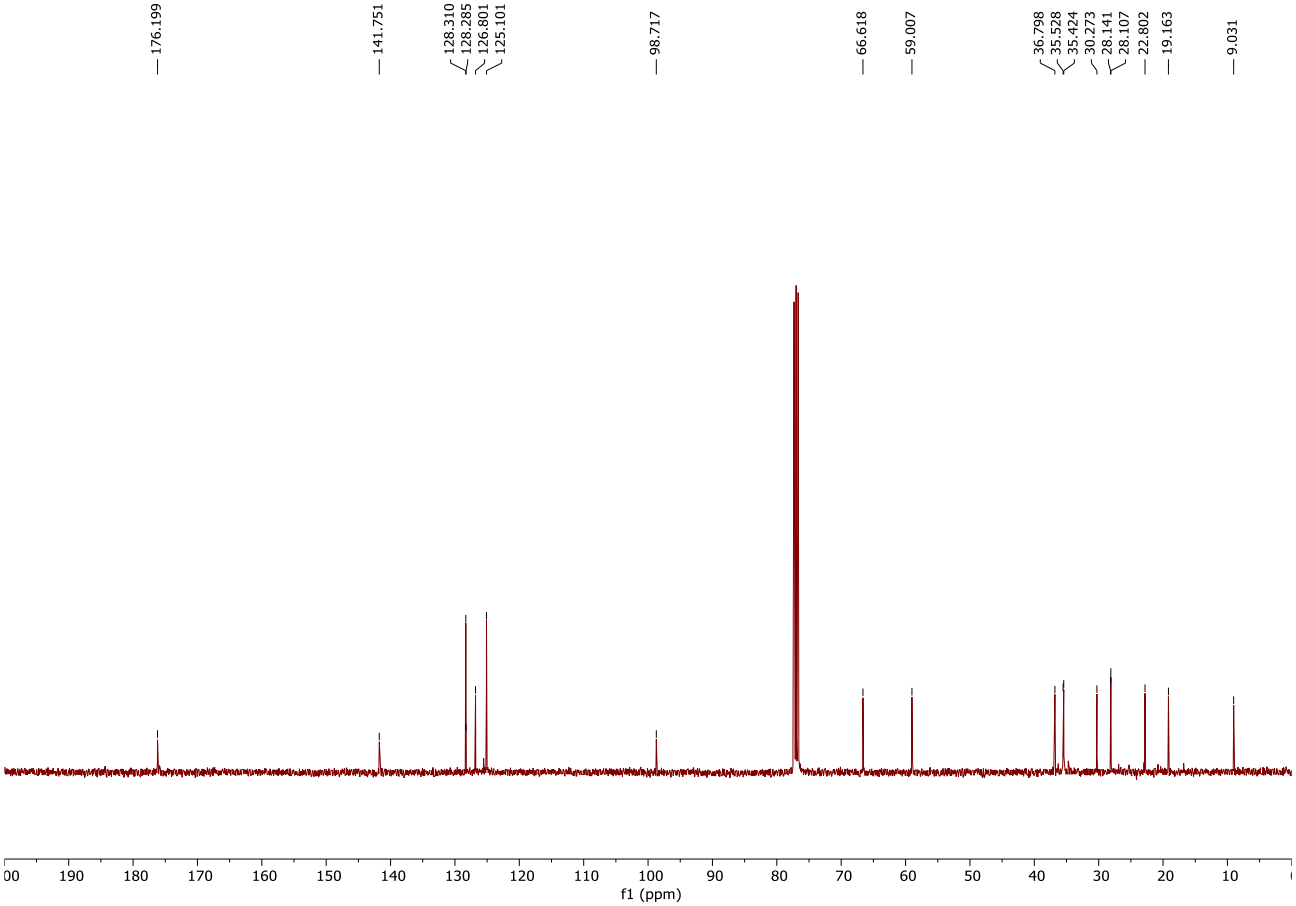
IR (NaCl): 1664 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.34-7.30 (m, 2H, ArH), 7.27-7.25 (m, 1H, ArH), 7.23-7.21 (m, 2H, ArH), 5.63 (dd, *J* = 8.8, 6.4 Hz, 1H, H-3), 4.42 (t, *J* = 8.8 Hz, 1H, H-2), 4.08 (dd, *J* = 8, 6.4 Hz, 1H, H-2), 2.64-2.58 (m, 1H, H-6), 2.49- 2.40 (m, 1H, H-6), 2.06-1.98 (m, 2H, H-7a and H-11), 1.74-1.41 (m, 7H, H-7, H-8, H-9 and H-10), 1.22 (qd, *J* = 13.2, 4.8 Hz, 1H, H-9), 0.68 (d, *J* = 7.0 Hz, 3H, CH_3C-10), 0.67 (d, *J* = 7.0 Hz, 3H, CH_3C-11).

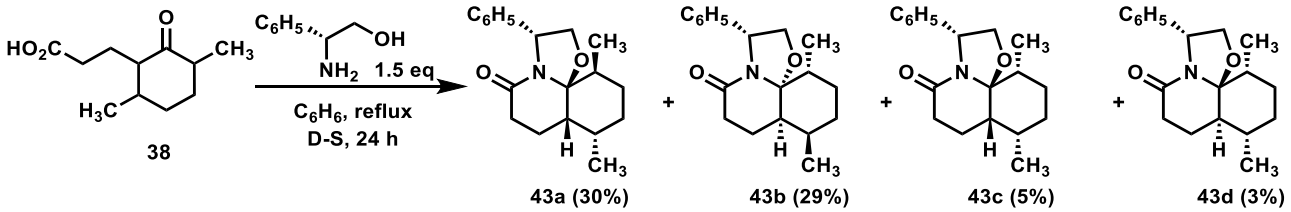
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.2 (CO), 141.8 (C-Ar), 126.8 (CH-Ar), 125.1 (CH-Ar), 128.3 (CH-Ar), 98.7 (C-11a), 66.6 (C-2), 59.0 (C-3), 36.8 (C-7a), 35.5 (C-11), 35.4 (C-6), 30.3 (C-10), 28.1 (C-9 and C-8), 22.8 (C-7), 19.2 (*C*H_3C-11), 9.0 (*C*H_3C-10).

HRMS Calcd for [$C_{19}H_{25}NO_2 + H^+$]: 300.1958; found 300.1957.


7.341
7.304
7.272
7.252
7.234
7.211
5.625
4.419
4.087
2.630
2.589
2.490
2.401
2.073
1.968
1.741
1.411
1.278
1.169
0.690
0.688
0.684
0.673
0.671
0.666
1.80
1.12
2.13
1.00
1.00
0.94
1.06
1.10
1.96
7.58
1.33
4.73
f1 (ppm)


176.199
141.751
128.310
128.285
126.801
125.101
98.717
66.618
59.007
36.798
35.528
35.424
30.273
28.141
28.107
22.802
19.163
9.031
f1 (ppm)

(3*R*,7a*S*,8*S*,11*S*,11a*S*)-8,11-Dimethyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (43a) and its (3*R*,7a*R*,8*R*,11*R*,11a*R*) (3*R*,7a*S*,8*S*,11*R*,11a*S*), and (3*R*,7a*R*,8*S*,11*R*,11a*S*) isomers (43b, 43c and 43d, respectively):



Operating as described in the preparation of lactams **24a-24d**, from a diastereomeric mixture of keto acids **38** (4.48 g, 22.58 mmol) and *(R)*-phenylglycinol (4.65 g, 33.86 mmol) in benzene (220 mL), lactams **43a** (2.00 g, 30%), **43b** (1.96 g, 29 %), **43c** (0.34 g, 5 %), and **43d** (0.18 g, 3 %) were obtained after flash column chromatography (9:1 to 1:1 hexane–EtOAc) as colorless solids.

43a:

CCDC number: 2217473

mp: 123-126 °C (hexane–CH_2Cl_2).

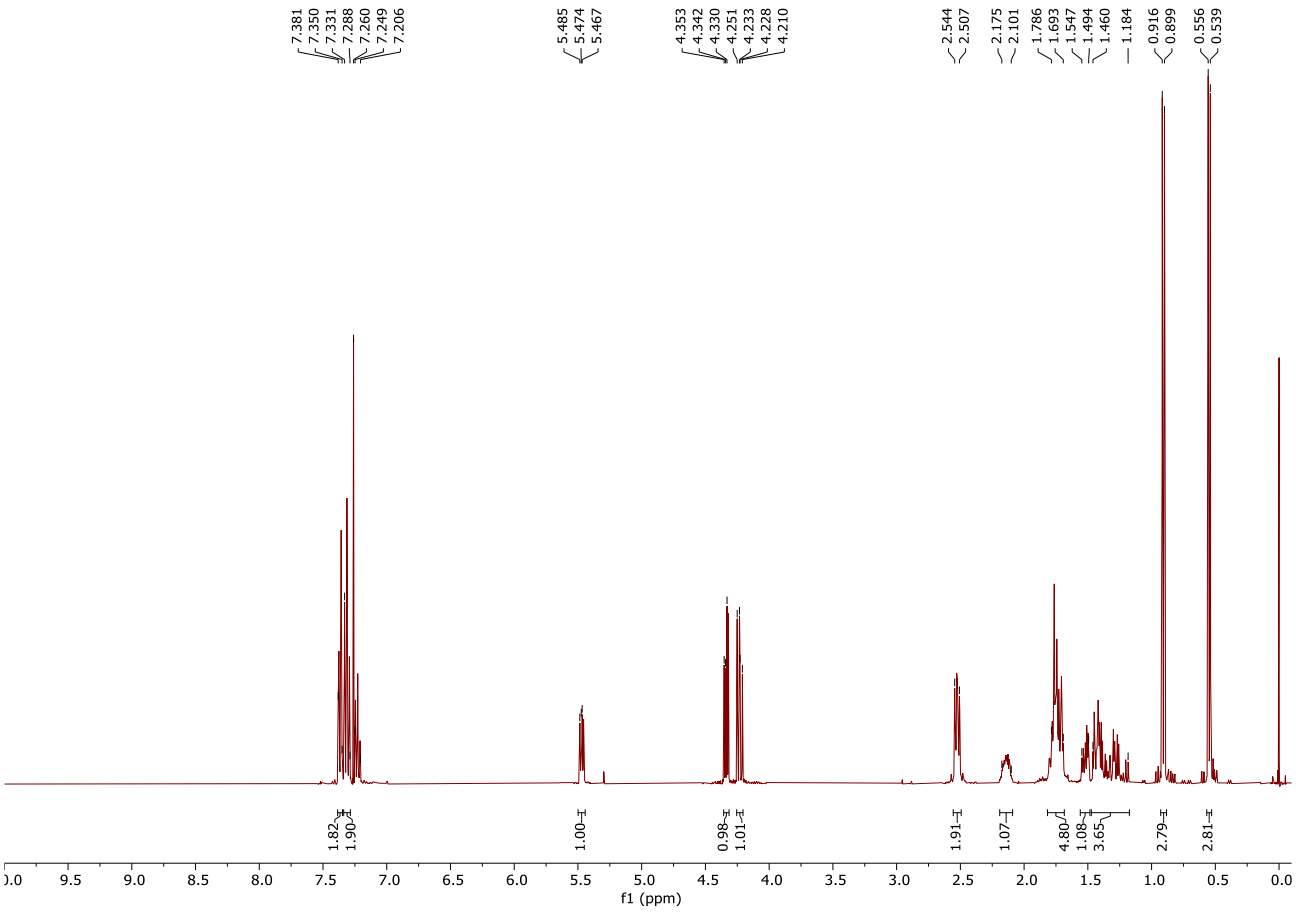
$[\alpha]^{23}_D$ – 173.2 (*c* 1.02, $CHCl_3$).

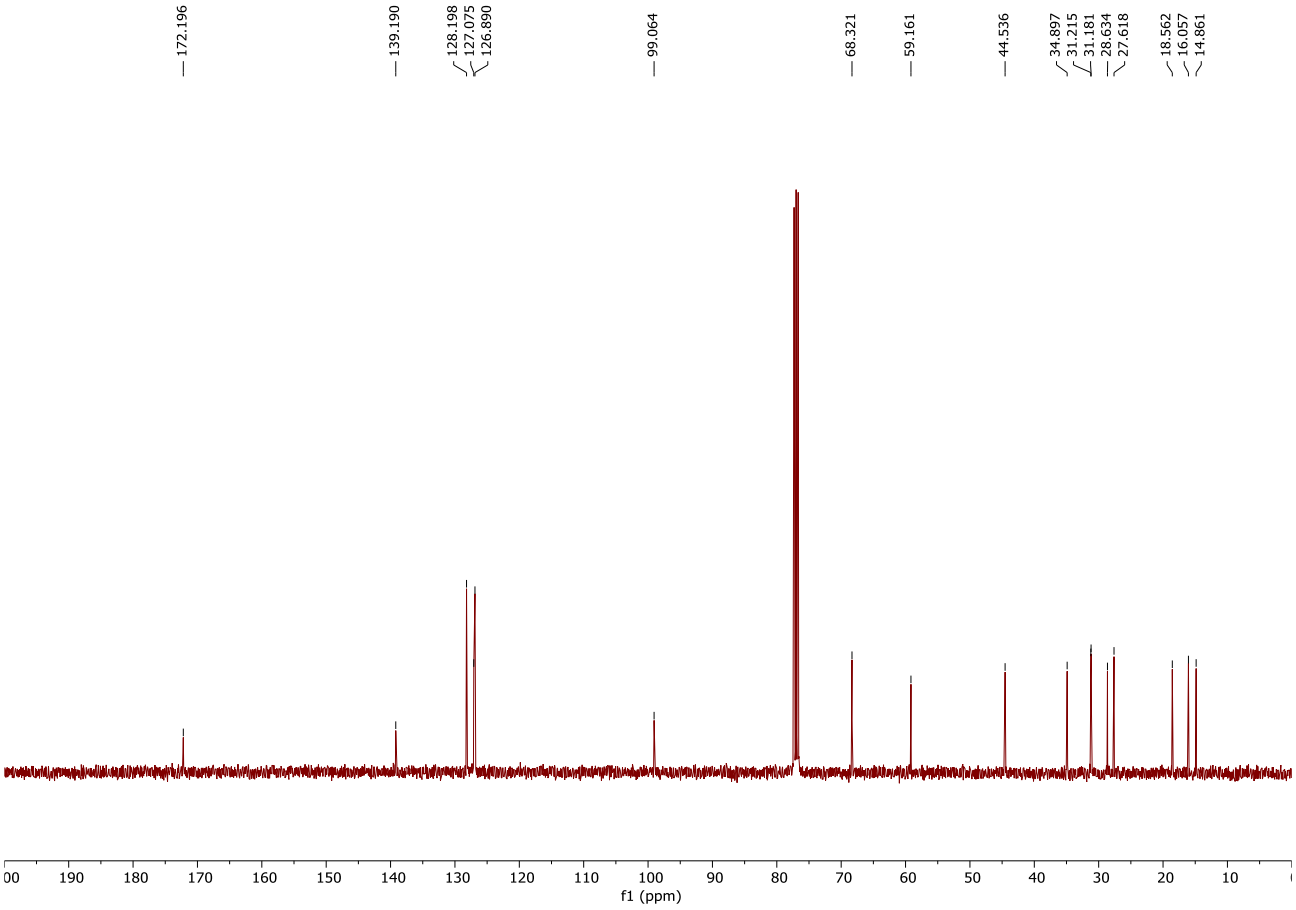
IR (NaCl): 1655 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.35-7.38 (m, 2H, ArH), 7.33-7.29 (m, 2H, ArH), 7.25-7.21 (m, 1H, ArH), 5.47 (dd, *J* = 7.2, 4.4 Hz, 1H, H-3), 4.34 (dd, *J* = 9.2, 4.4 Hz, 1H, H-2), 4.23 (dd, *J* = 9.2, 7.2 Hz, 1H, H-2), 2.54-2.51 (m, 2H, H-6), 2.17-2.10 (m, 1H, H-8), 1.79-1.69 (m, 4H, H-7, H-7a and H-11), 1.55-1.49 (m, 1H, H-9), 1.46-1.18 (m, 3H, H-9 and H-10), 0.91 (d, *J* = 6.8 Hz, 3H, CH_3C-8), 0.55 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.2 (CO), 139.2 (C-Ar), 126.9 (CH-Ar), 128.2 (CH-Ar), 127.1 (CH-Ar), 99.1 (C-11a), 68.3 (C-2), 59.2 (C-3), 44.5 (C-7a), 34.9 (C-11), 31.2 (C-9 and C-8), 28.6 (C-6), 27.6 (C-10), 18.6 (CH_3C-8), 16.1 (CH_3C-11), 14.9 (C-7).

HRMS Calcd for [$C_{19}H_{25}NO_2$ + H^+]: 300.1958; found 300.1959.


7.381
7.350
7.331
7.288
7.260
7.249
7.206
5.485
5.474
5.467
4.353
4.342
4.330
4.251
4.233
4.228
4.210
2.544
2.507
2.175
2.101
1.786
1.693
1.547
1.494
1.460
1.184
0.916
0.899
0.556
0.539
1.82
1.90
1.00
0.98
1.01
1.91
1.07
4.80
1.08
3.65
2.79
2.81
f1 (ppm)


172.196
139.190
128.198
127.075
126.890
99.064
68.321
59.161
44.536
34.897
31.215
31.181
28.634
27.618
18.562
16.057
14.861
f1 (ppm)

43b:

CCDC number: 2217479

mp: 174-177 °C (hexane–CH_2Cl_2).

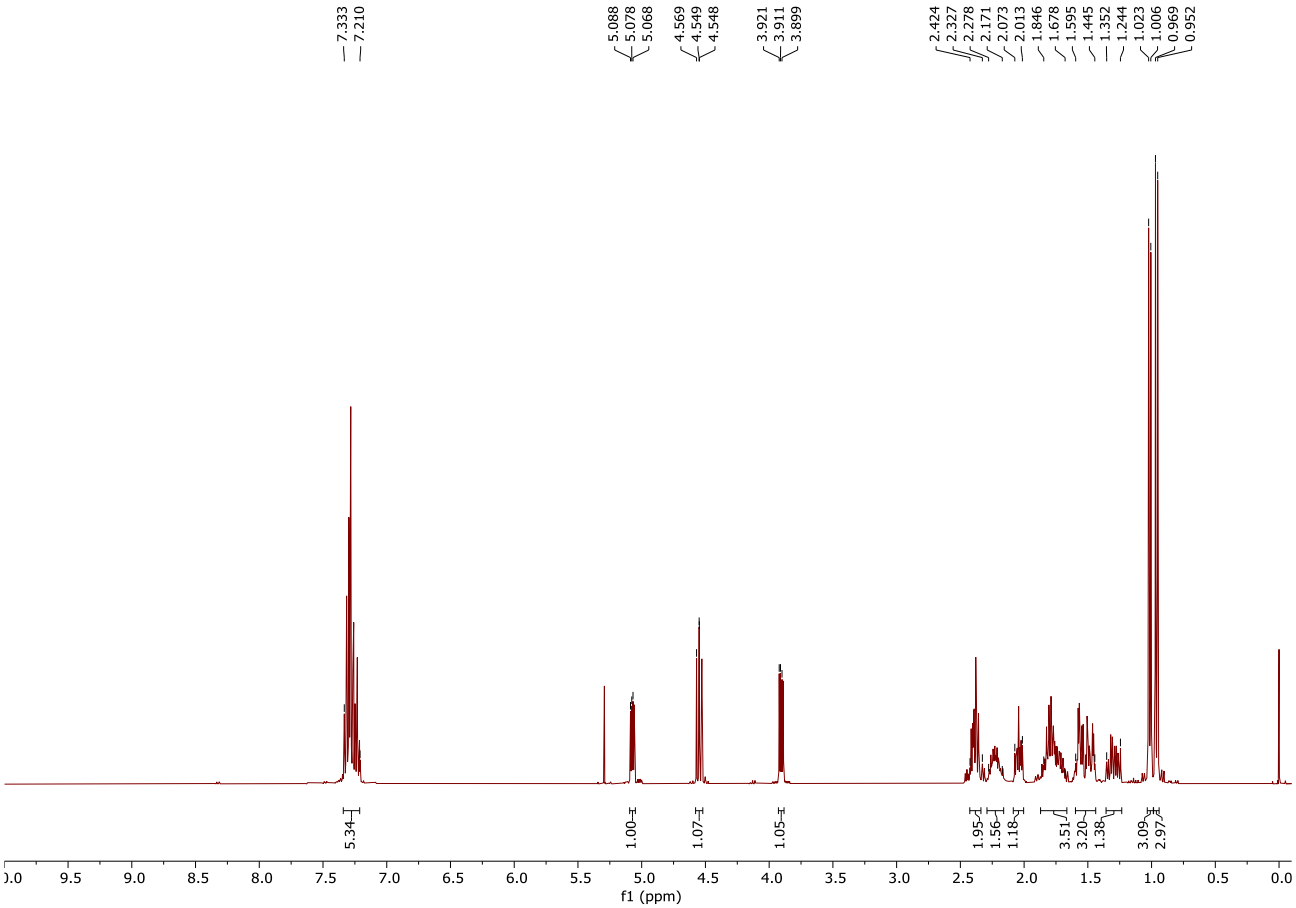
$[\alpha]^{23}_D$ + 52.6 (*c* 1.01, $CHCl_3$).

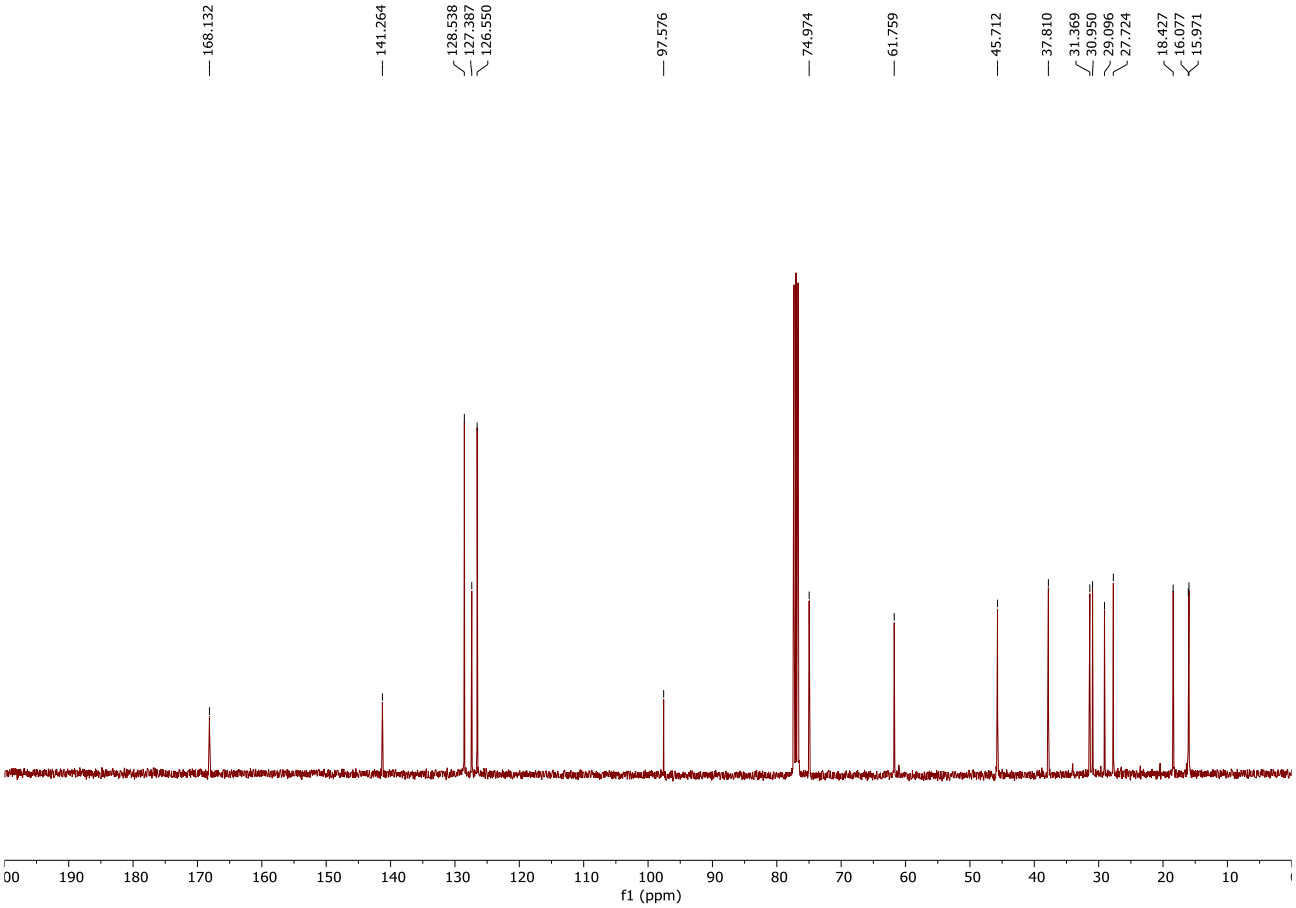
IR (NaCl): 1662 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.33-7.21 (m, 5H, ArH), 5.08 (dd, *J* = 8.0, 4.0 Hz, 1H, H-3), 4.55 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 3.90 (dd, *J* = 8.8, 4.0 Hz, 1H, H-2), 2.42-2.33 (m, 2H, H-6), 2.28-2.17 (m, 1H, H-11), 2.07-2.01 (m, 1H, H-7a), 1.85-1.68 (m, 3H, H-7 and H-8), 1.60-1.45 (m, 2H, H-9 and H-10), 1.35-1.24 (m, 1H, H-10), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3C-8), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3C-11).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.1 (CO), 141.3 (C-Ar), 127.4 (CH-Ar), 128.5 (CH-Ar), 126.6 (CH-Ar), 97.6 (C-11a), 75.0 (C-2), 61.8 (C-3), 45.7 (C-7a), 37.8 (C-8), 31.4 (C-11), 31.0 (C-9), 29.1 (C-6), 27.7 (C-10), 18.4 (*C*H_3C-11), 16.1 (*C*H_3C-8), 16.0 (C-7).

HRMS Calcd for [$C_{19}H_{25}NO_2$ + H^+]: 300.1958; found 300.1960.


7.333
7.210
5.088
5.078
5.068
4.569
4.549
4.548
3.921
3.911
3.899
2.424
2.327
2.278
2.171
2.073
2.013
1.846
1.678
1.595
1.445
1.352
1.244
1.023
1.006
0.969
0.952
5.34
1.00
1.07
1.05
1.95
1.56
1.18
3.51
3.20
1.38
3.09
2.97
f1 (ppm)


168.132
141.264
128.538
127.387
126.550
97.576
74.974
61.759
45.712
37.810
31.369
30.950
29.096
27.724
18.427
16.077
15.971
f1 (ppm)

43c:

CCDC number: 2217472

mp: 98-102 °C (hexane–CH_2Cl_2).

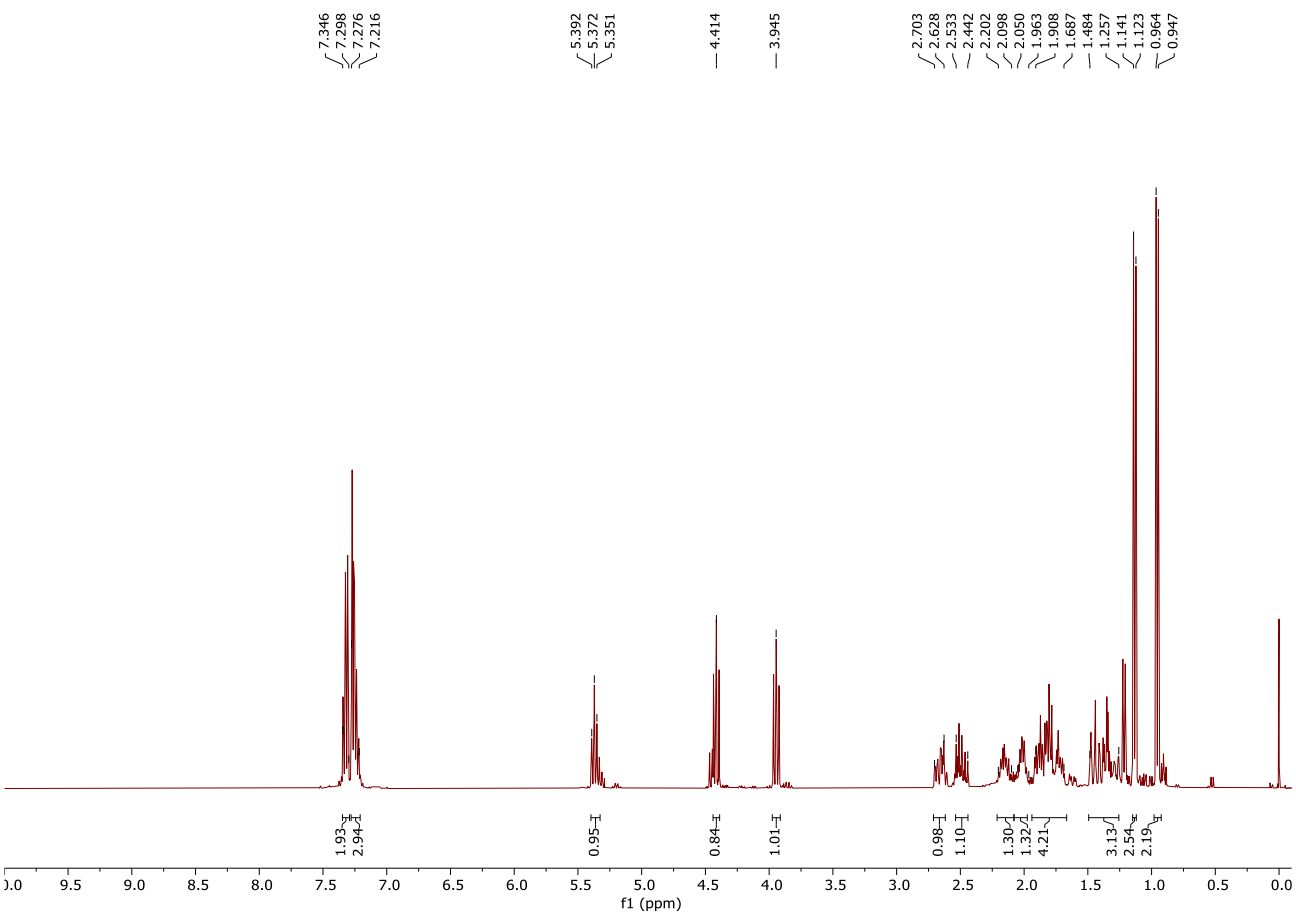
$[\alpha]^{23}_D$ – 133.8 (*c* 1.01, $CHCl_3$).

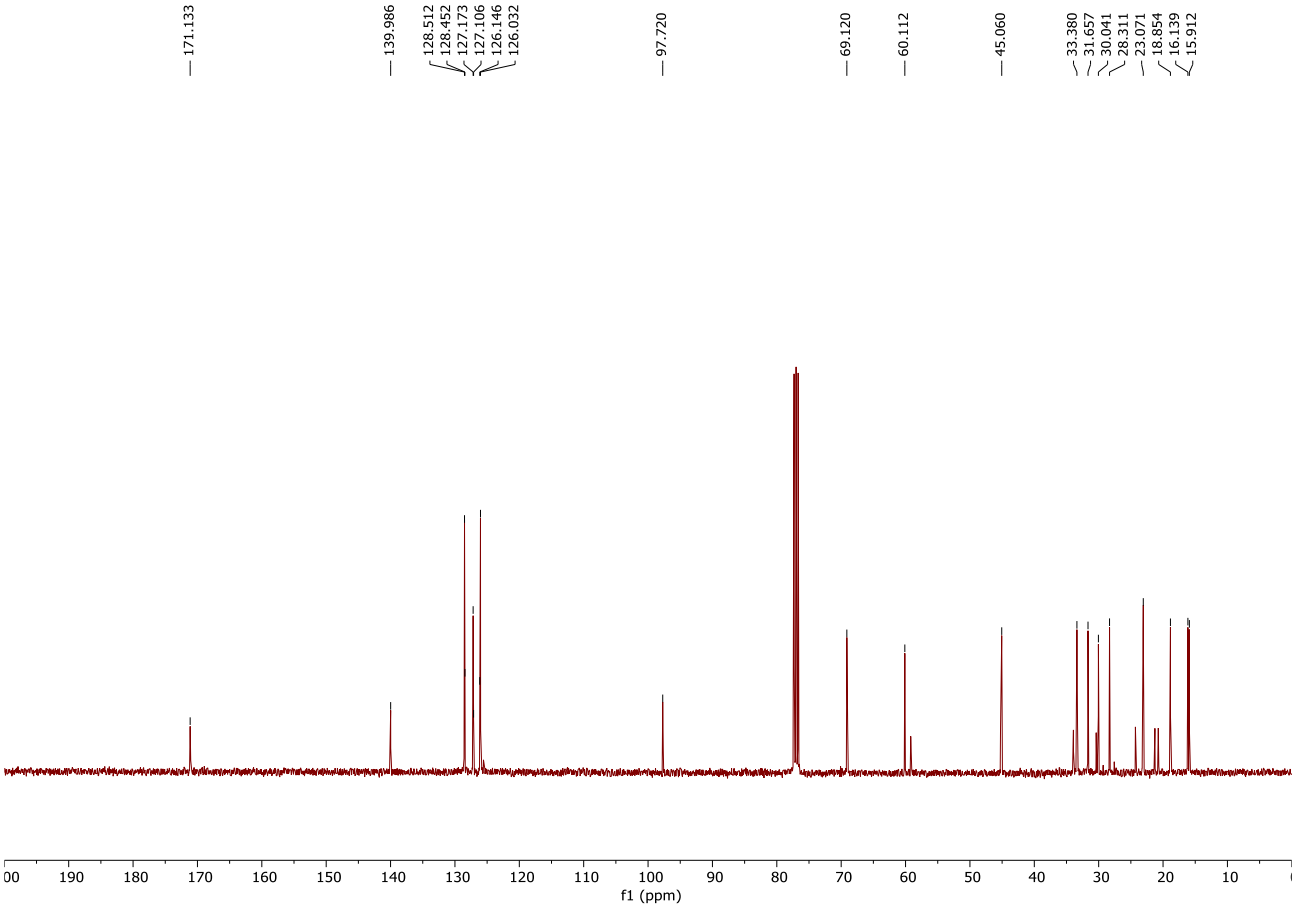
IR (NaCl): 1655 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.35-7.30 (m, 2H, ArH), 7.28-7.22 (m, 3H, ArH), 5.37 (t, *J* = 8.0 Hz, 1H, H-3), 4.41 (m, 1H, H-2), 3.95 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 2.70-2.63 (m, 1H, H-6), 2.53-2.44 (m, 1H, H-6), 2.20-2.10 (m, 1H, H-8), 2.05-1.96 (m, 1H, H-11), 1.91-1.69 (m, 4H, H-7, H-7a and H-9), 1.48-1.26 (m, 3H, H-9 and H-10), 1.13 (d, *J* = 7.2 Hz, 3H, CH_3C-11), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3C-8).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.1 (CO), 140.0 (C-Ar), 127.2 (CH-Ar), 128.5 (CH-Ar), 126.1 (CH-Ar), 97.7 (C-11a), 69.1 (C-2), 60.1 (C-3), 45.1 (C-7a), 33.4 (C-11), 31.7 (C-8), 30.0 (C-6), 28.3 (C-9), 23.1 (C-10), 18.9 (*C*H_3C-8), 16.1 (C-7), 15.9 (*C*H_3C-11).

HRMS Calcd for [$C_{19}H_{25}NO_2$ + H^+]: 300.1958; found 300.1958.


7.346
7.298
7.276
7.216
5.392
5.372
5.351
4.414
3.945
2.703
2.628
2.533
2.442
2.202
2.098
2.050
1.963
1.908
1.687
1.484
1.257
1.141
1.123
0.964
0.947
1.93
2.94
0.95
0.84
1.01
0.98
1.10
1.30
1.32
4.21
3.13
2.54
2.19
f1 (ppm)


171.133
139.986
128.512
128.452
127.173
127.106
126.146
126.032
97.720
69.120
60.112
45.060
33.380
31.657
30.041
28.311
23.071
18.854
16.139
15.912
f1 (ppm)

43d:

CCDC number: 2217481

mp: 99-103 °C (hexane–CH_2Cl_2).

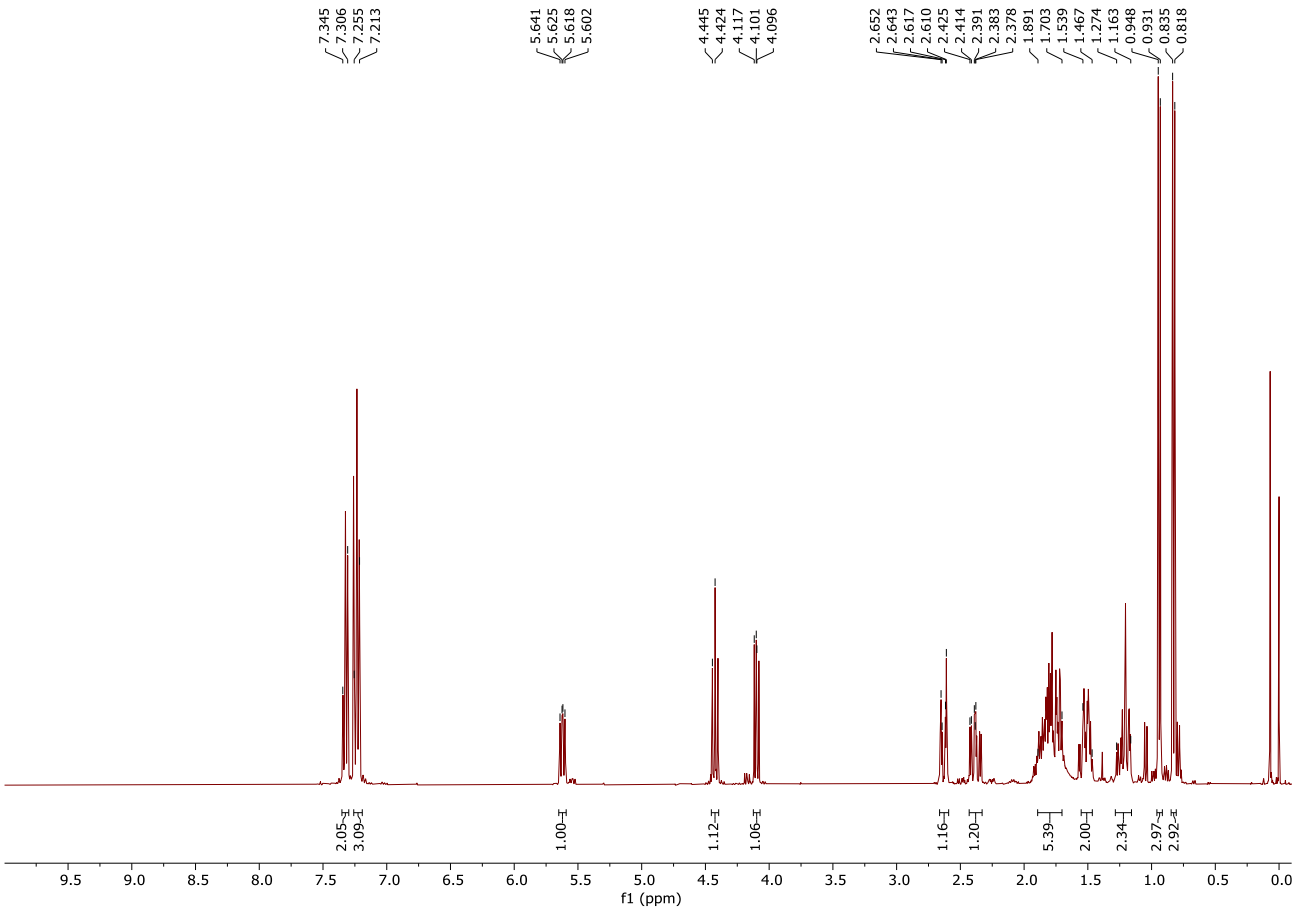
$[\alpha]^{23}_D$ – 194.4 (*c* 1.05, $CHCl_3$).

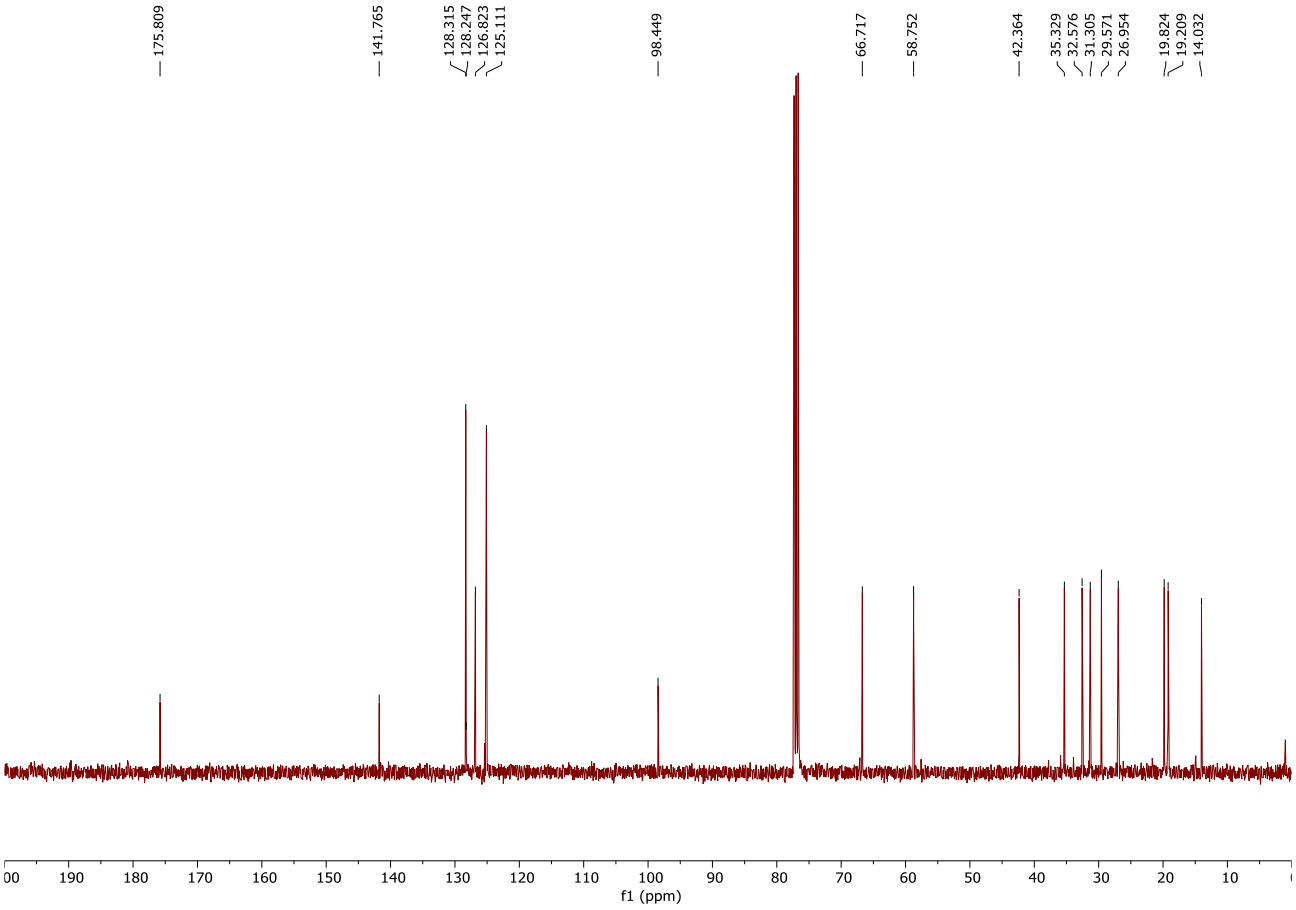
IR (NaCl): 1668 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.34-7.31 (m, 2H, ArH), 7.26-7.21 (m, 3H, ArH), 5.62 (dd, *J* = 8.4, 6.4 Hz, 1H, H-3), 4.42 (t, *J* = 8.4 Hz, 1H, H-2), 4.10 (dd, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.63 (dt, *J* = 16.8, 2.8 Hz, 1H, H-6), 2.38 (ddd, *J* = 16.8, 13.6, 4.4 Hz, 1H, H-6), 1.89-1.70 (m, 5H, H-7, H-7a, H-8, H-9 and H-11), 1.54-1.47 (m, 2H, H-7 and H-10), 1.27-1.16 (m, 2H, H-9 and H-10), 0.94 (d, *J* = 6.8 Hz, CH_3C-8), 0.83 (d, *J* = 6.8 Hz, CH_3C-11).

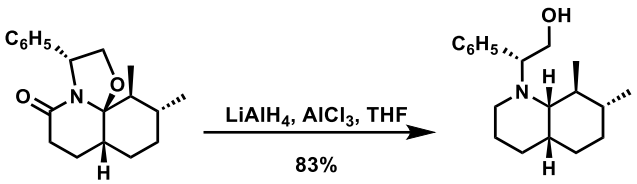
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8 (CO), 141.8 (C-Ar), 126.8 (CH-Ar), 128.3 (CH-Ar), 125.1 (CH-Ar), 98.4 (C-11a), 66.7 (C-2), 58.8 (C-3), 42.4 (C-7a), 35.3 (C-6), 32.6 (C-8), 31.3 (C-11), 29.6 (C-10), 27.0 (C-9), 19.8 (*C*H_3C-8), 19.2 (C-7), 14.0 (*C*H_3C-11).

HRMS Calcd for [$C_{19}H_{25}NO_2 + H^+$]: 300.1958; found 300.1955.


7.345
7.306
7.255
7.213
5.641
5.625
5.618
5.602
4.445
4.424
4.117
4.101
4.096
2.652
2.643
2.617
2.610
2.425
2.414
2.391
2.383
2.378
1.891
1.703
1.539
1.467
1.274
1.163
0.948
0.931
0.835
0.818
2.05
3.09
1.00
1.12
1.06
1.16
1.20
5.39
2.00
2.34
2.97
2.92
f1 (ppm)


175.809
141.765
128.315
128.247
126.823
125.111
98.449
66.717
58.752
42.364
35.329
32.576
31.305
29.571
26.954
19.824
19.209
14.032
f1 (ppm)

(4a*R*,7*R*,8*S*,8a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7,8-dimethyldecahydroquinoline (44):



42a 44

$LiAlH_4$ (13.5 mL of a 1M solution in THF, 13.5 mmol) was slowly added to a stirring suspension of $AlCl_3$ (555 mg, 4.2 mmol) in anhydrous THF (25 mL) at 0 °C. After 1 h, the mixture was cooled at –78 °C, and a solution of the lactam **42a** (623 mg, 2.1 mmol) in anhydrous THF (10 mL) was added dropwise. The stirring was continued at –78 °C for 90 min and at rt for 2 h. Cold water was slowly added until no bubbling is seen and the resulting mixture was filtered over Celite®.The filtrate was dried and concentrated. Flash chromatography (9:1 to 7:3 hexane–EtOAc) afforded decahydroquinoline **44** (498 mg, 83%) as a colorless solid:

mp: 94 –97 °C (hexane–CH_2Cl_2).

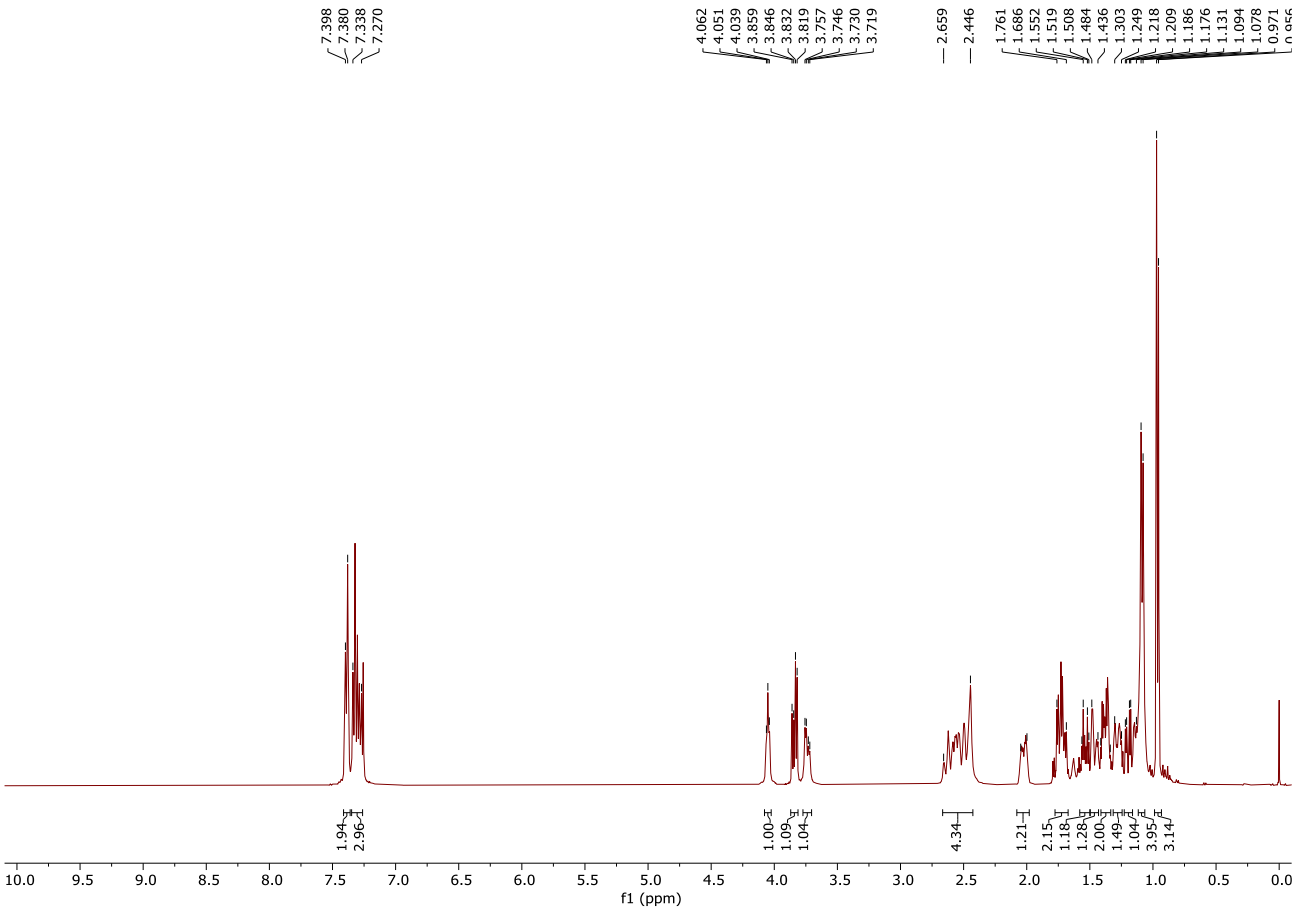
$[\alpha]^{23}_D$ – 65.8 (*c* 1.0, $CHCl_3$).

IR (NaCl): 3420 (OH) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.38- 7.40 (m, 2H, ArH), 7.27-7.34 (m, 3H, ArH), 4.05 (m, 1H, C*H*CH_2O), 3.84 (dd, *J* = 10.8, 5.2 Hz, 1H, CHC*H*$_2$O), 3.74 (dd, *J* = 10.8, 4.4 Hz, 1H, CHC*H*$_2$O), 2.45-2.66 (m, 4H, H-2, H-8a and OH), 2.00-2.05 (m, 1H, H-8), 1.69-1.76 (m, 2H, H-4 and H-4a), 1.54 (dt, *J* = 13.2, 4.4 Hz, 1H, H-6), 1.44-1.48 (m, 1H, H-6), 1.34-1.41 (m, 2H, H-3 and H-5), 1.25-1.30 (m, 1H, H-4), 1.19 (dd, *J* = 13.2, 4.0 Hz, 1H, H-5), 1.08-1.12 (m, 1H, H-3), 1.13-1.15 (m, 1H, H-7), 1.09 (d, *J* = 6.4 Hz, 3H, CH_3C-8), 0.96 (d, *J* = 6.0 Hz, 3H, CH_3C-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.0 (C-Ar), 127.5 (CH-Ar), 128.6 (CH-Ar), 128.4 (CH-Ar), 65.4 (*C*HCH$_2$O), 63.6 (CH*C*H$_2$O), 63.1 (C-8a), 40.6 (C-2), 39.2 (C-7), 35.9 (C-4a), 31.1 (C-6), 30.0 (C-5), 29.8 (C-8), 25.0 (C-4), 21.1 (C-3), 20.8 (*C*H$_3$C-8), 15.7 (*C*H$_3$C-7).

HRMS Calcd for [$C_{19}H_{29}NO + H^+$]: 288.2332; found 288.2332.


7.398
7.380
7.338
7.270
4.062
4.051
4.039
3.859
3.846
3.832
3.819
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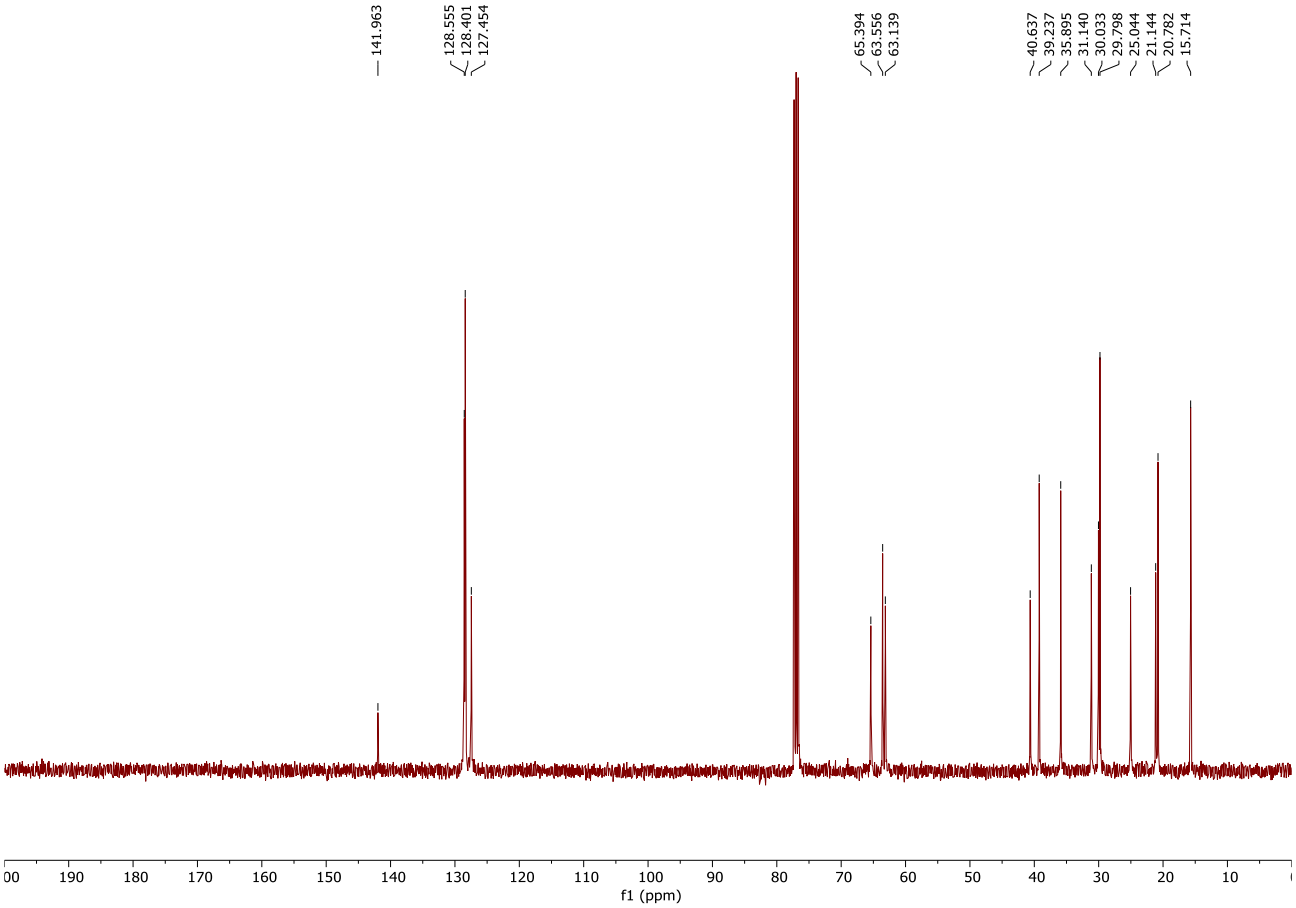
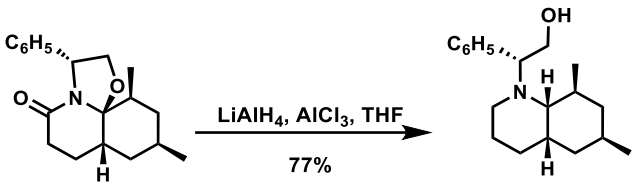
3.746
3.730
3.719
2.659
2.446
1.761
1.686
1.552
1.519
1.508
1.484
1.436
1.303
1.249
1.218
1.209
1.186
1.176
1.131
1.094
1.078
0.971
1.94
2.96
1.00
1.09
1.04
4.34
1.21
2.15
1.18
1.28
2.00
1.49
1.04
3.95
3.14
f1 (ppm)


141.963
128.555
128.401
127.454
65.394
63.556
63.139
40.637
39.237
35.895
31.140
30.033
29.798
25.044
21.144
20.782
15.714
f1 (ppm)

(4a*S*,6*R*,8*S*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,8-dimethyldecahydroquinoline (45):



24a **45**

Operating as described in the preparation of decahydroquinoline **44**, from $LiAlH_4$ (5.8 mL of a 1M solution in THF, 5.8 mmol), $AlCl_3$ (240 mg, 1.8 mmol) in anhydrous THF (12 mL), and a solution of lactam **24a** (269 mg, 0.9 mmol) in anhydrous THF (8 mL), decahydroquinoline **45** (200 mg, 77%) was obtained after flash column chromatography (9:1 hexane–EtOAc) as a colorless solid:

mp: 38-40 °C (hexane–CH_2Cl_2).

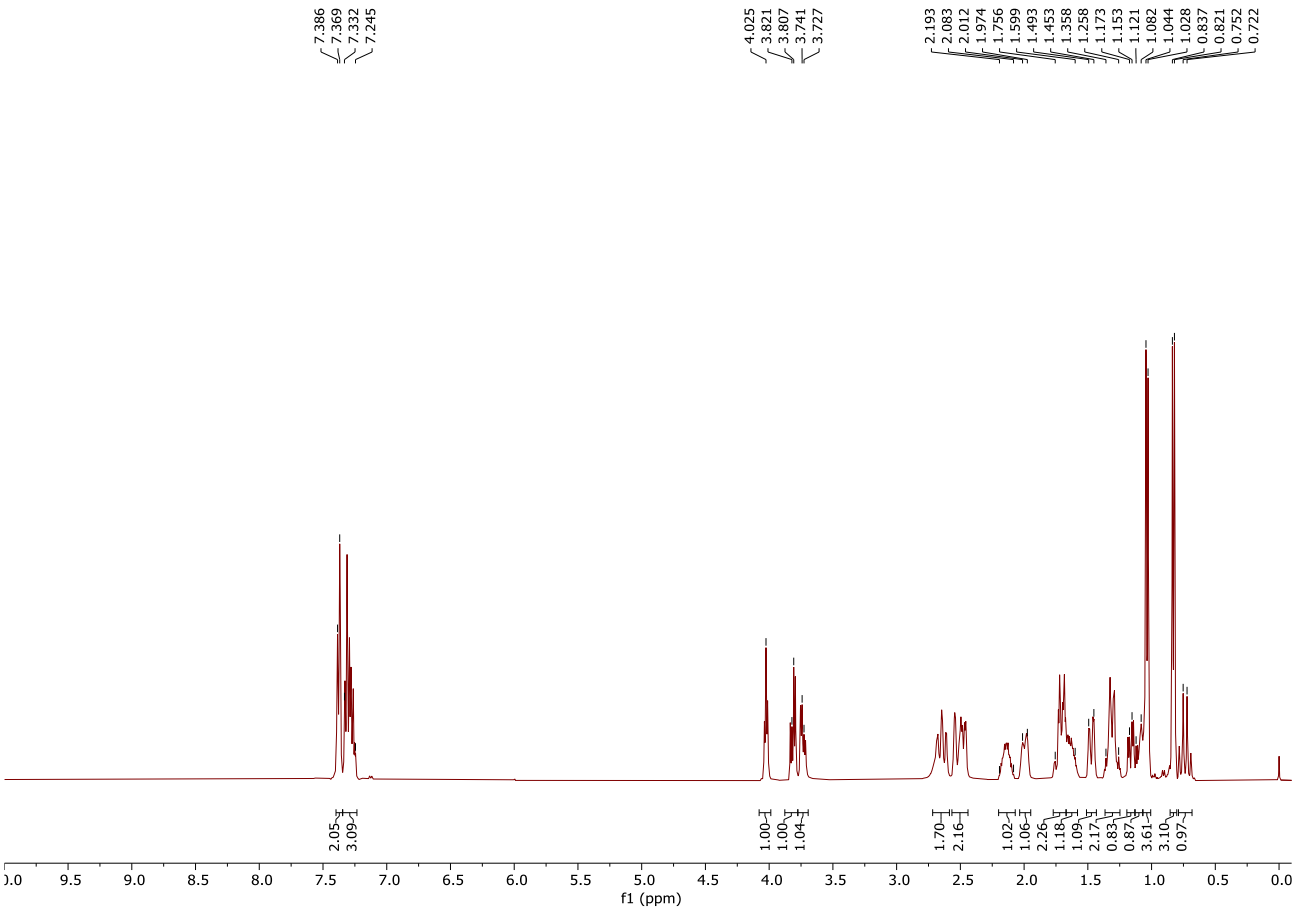
$[\alpha]^{23}_D$ – 24.7 (*c* 1.0, $CHCl_3$).

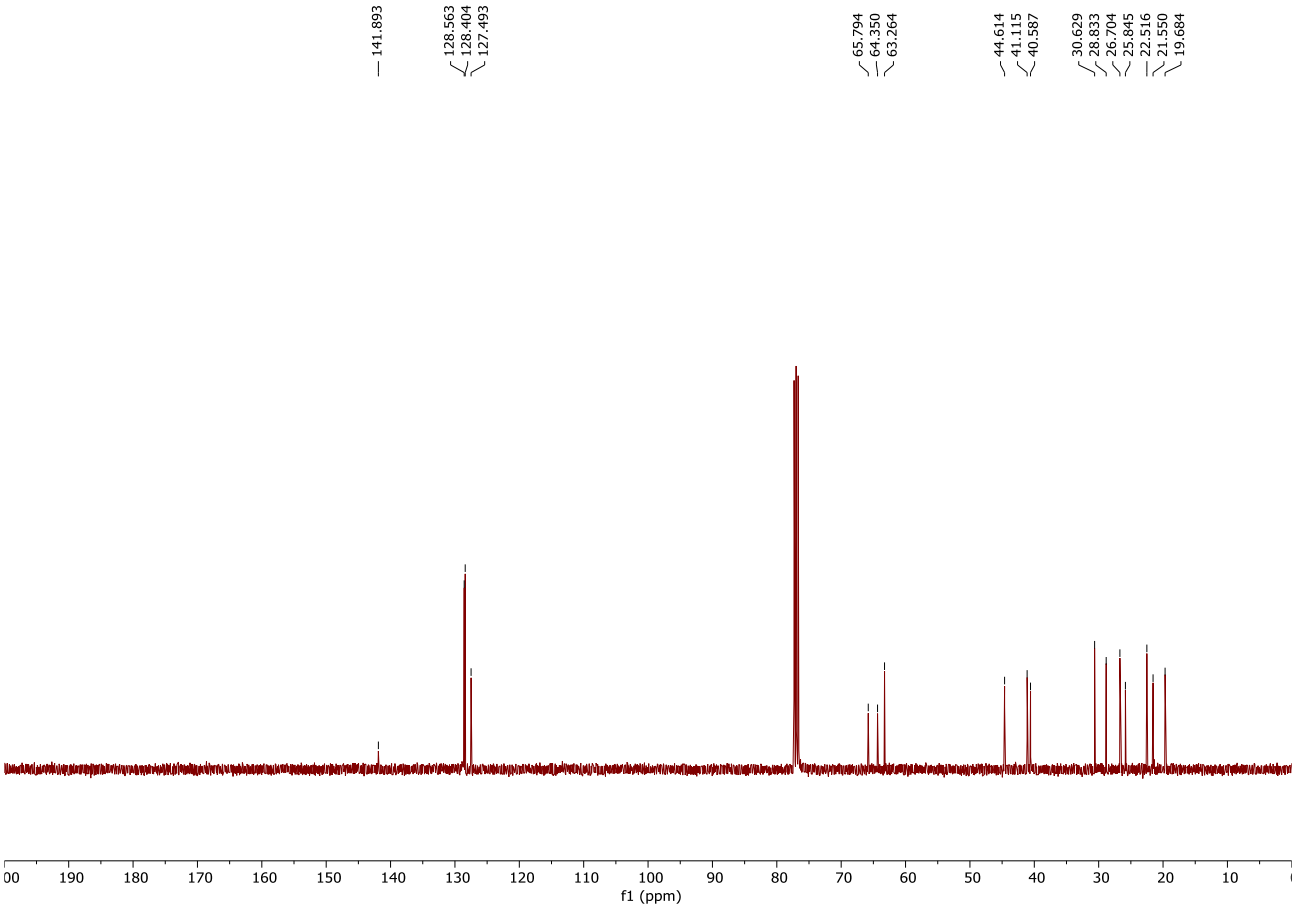
IR (NaCl): 3425 (OH) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.25-7.40 (m, 5H, ArH), 4.03 (t, *J* = 5.2 Hz, 1H, C*H*CH_2O), 3.82 (dd, *J* = 10.8, 5.2 Hz, 1H, CHC*H*$_2$O), 3.73 (dd, *J* = 10.8, 4.8 Hz, 1H, CHC*H*$_2$O), 2.61-2.69 (m, 1H, H-2), 2.51-2.55 (m, 1H, H-2), 2.47 (dd, *J* = 10.8, 4.8 Hz, 1H, H-8a), 2.09-2.19 (m, 1H, H-6), 1.96-2.03 (m, 1H, H-4a), 1.63-1.74 (m, 2H, H-5, H-7), 1.59-1.66 (m, 1H, H-8), 1.45-1.50 (m, 1H, H-4), 1.28-1.37 (m, 2H, H-3, H-5), 1.16 (dd, *J* = 12.8, 4.8 Hz, 1H, H-4), 1.06-1.12 (m, 1H, H-3), 1.03 (d, *J* = 6.4 Hz, 3H, CH_3C-6), 0.83 (d, *J* = 6.4 Hz, 3H, CH_3C-8), 0.73 (q, *J* = 12.0 Hz, 1H, H-7).

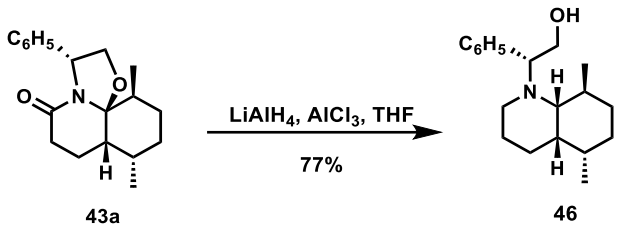
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.9 (C-Ar), 128.6 (CH-Ar), 128.4 (CH-Ar), 127.0 (CH-Ar), 65.8 (*C*HCH_2O), 64.3 (C-8a), 63.3 (CH*C*H_2O), 44.6 (C-7), 41.1 (C-4), 40.6 (C-2), 30.6 (C-4a), 28.8 (C-6), 26.7 (C-8), 25.8 (C-5), 22.5 (*C*H_3C-8), 21.6 (C-3), 19.7 (*C*H_3C-6).

HRMS Calcd for [$C_{19}H_{29}NO + H^+$]: 288.2322; found 288.2322.


7.386
7.369
7.332
7.245
4.025
3.821
3.807
3.741
3.727
2.193
2.083
2.012
1.974
1.756
1.599
1.493
1.453
1.358
1.258
1.173
1.153
1.121
1.082
1.044
1.028
0.837
0.821
0.752
0.722
2.05
3.09
1.00
1.00
1.04
1.70
2.16
1.02
1.06
2.26
1.18
1.09
2.17
0.83
0.87
3.61
3.10
0.97
f1 (ppm)


141.893
128.563
128.404
127.493
65.794
64.350
63.264
44.614
41.115
40.587
30.629
28.833
26.704
25.845
22.516
21.550
19.684
f1 (ppm)

(4a*S*,5*S*,8*S*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-5,8-dimethyldecahydroquinoline (46):



43a 46

Operating as described in the preparation of decahydroquinoline **44**, from $LiAlH_4$ (13 mL of a 1M solution in THF, 13.0 mmol), $AlCl_3$ (530 mg, 3.97 mmol) in anhydrous THF (25 mL), and a solution of lactam **43a** (595 mg, 1.99 mmol) in anhydrous THF (15 mL), decahydroquinoline **46** (441 mg, 77%) was obtained after flash column chromatography (95:5 hexane–EtOAc) as a yellowish oil:

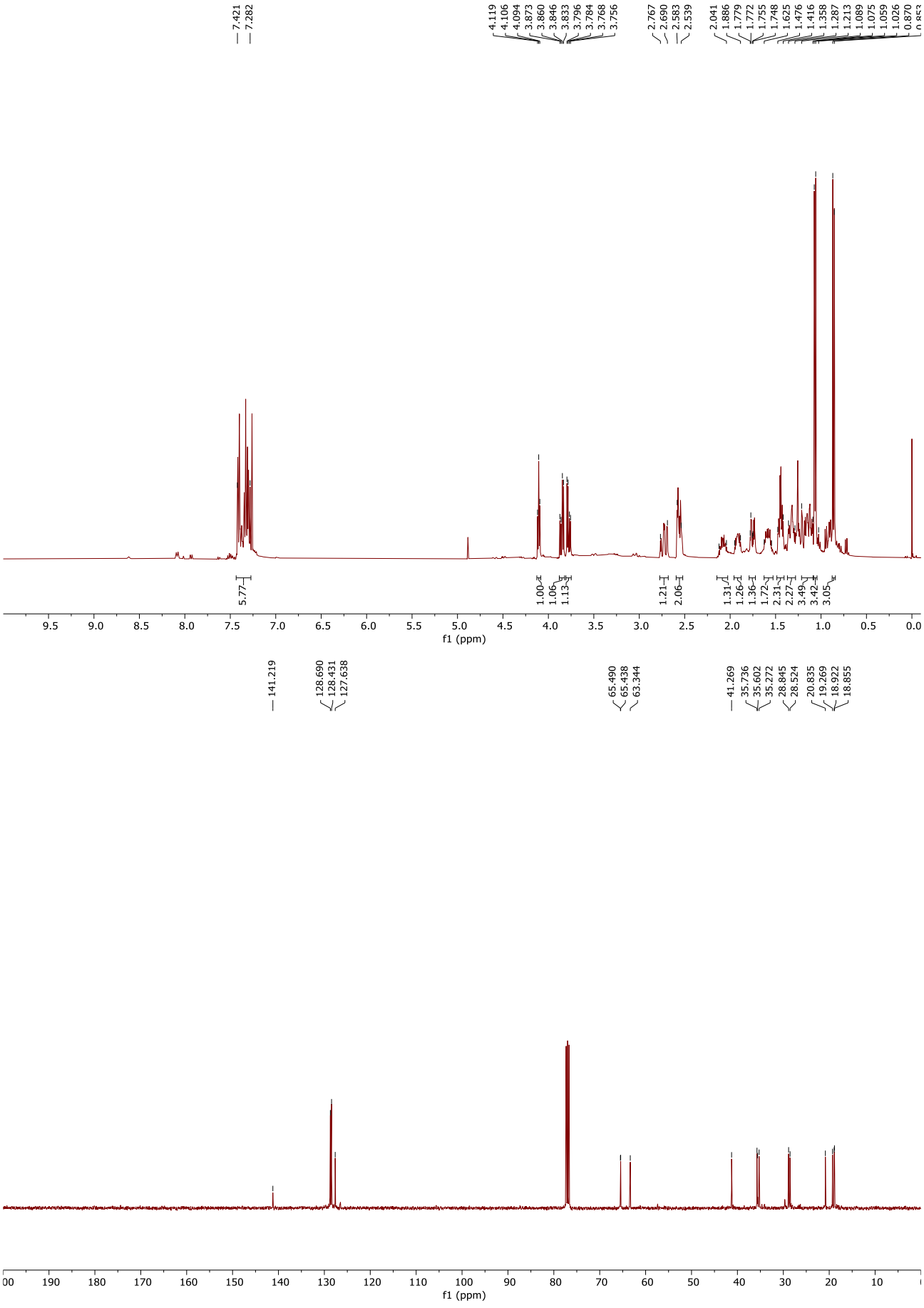
$[\alpha]^{23}_{D}$ – 33.2 (*c* 1.03, $CHCl_3$).

IR (NaCl): 3425 (OH) cm^{-1}.

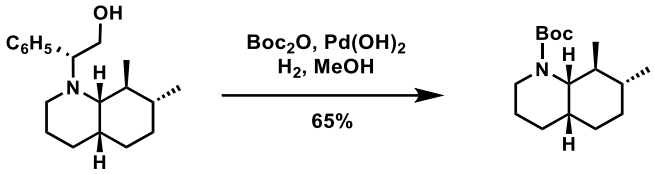
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.42-7.28 (m, 5H, ArH), 4.11 (t, *J* = 5.2 Hz, 1H, C*H*CH_2O), 3.85 (dd, *J* = 11.0, 5.2 Hz, 1H, CHC*H*$_2$O), 3.78 (dd, *J* = 11.0, 4.8 Hz, 1H, CHC*H*$_2$O), 2.77-2.69 (m, 1H, H-2), 2.58-2.54 (m, 2H, H-2 and H-8a), 2.12-2.04 (m, 1H, H-8), 1.96-1.89 (m, 1H, H-4a), 1.75 (dq, *J* = 9.6, 2.8 Hz, 1H, H-7), 1.63-1.54 (m, 1H, H-5), 1.48-1.42 (m, 2H, H-4), 1.36-1.29 (m, 2H, H-3 and H-6), 1.21-1.09 (m, 3H, H-3, H-6 and H-7), 1.08 (d, *J* = 6.4 Hz, 3H, CH_3C-8), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3C-5).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.2 (C-Ar), 128.4 (CH-Ar), 127.6 (CH-Ar), 128.7 (CH-Ar), 65.5 (*C*HCH_2O), 65.4 (C-8a), 63.3 (CH*C*H_2O), 41.3 (C-2), 35.7 (C-5), 35.6 (C-4a), 35.3 (C-7), 28.8 (C-6), 28.5 (C-8), 20.8 (C-3), 19.3 (*C*H_3C-8), 18.9 (C-4 and *C*H_3C-5).

HRMS Calcd for [$C_{19}H_{29}NO + H^+$]: 288.2332; found 288.2332.


7.421
7.282
4.119
4.106
4.094
3.873
3.860
3.846
3.833
3.796
3.784
3.768
3.756
2.767
2.690
2.583
2.539
2.041
1.886
1.779
1.772
1.755
1.748
1.625
1.476
1.416
1.358
1.287
1.213
1.089
1.075
1.059
1.026
0.870
5.77
1.00
1.06
1.13
1.21
2.06
1.31
1.26
1.36
1.72
2.31
2.27
3.49
3.42
3.05
f1 (ppm)
141.219
128.690
128.431
127.638
65.490
65.438
63.344
41.269
35.736
35.602
35.272
28.845
28.524
20.835
19.269
18.922
18.855
f1 (ppm)

(4a*R*,7*R*,8*S*,8a*S*)-1-(*tert*-Butoxycarbonyl)-7,8-dimethyldecahydroquinoline (47):



44 47

A solution of *cis*-decahydroquinoline **44** (160 mg, 0.6 mmol) and Boc_2O (330 mg, 1.5 mmol) in CH_3OH (13 mL) containing 40% $Pd(OH)_2$ (64 mg) was stirred under hydrogen at rt for 8h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash chromatography (99:1 to 95:5 hexane–Et_2O) afforded decahydroquinoline **47** (96.4 mg, 65%) as a yellowish oil:

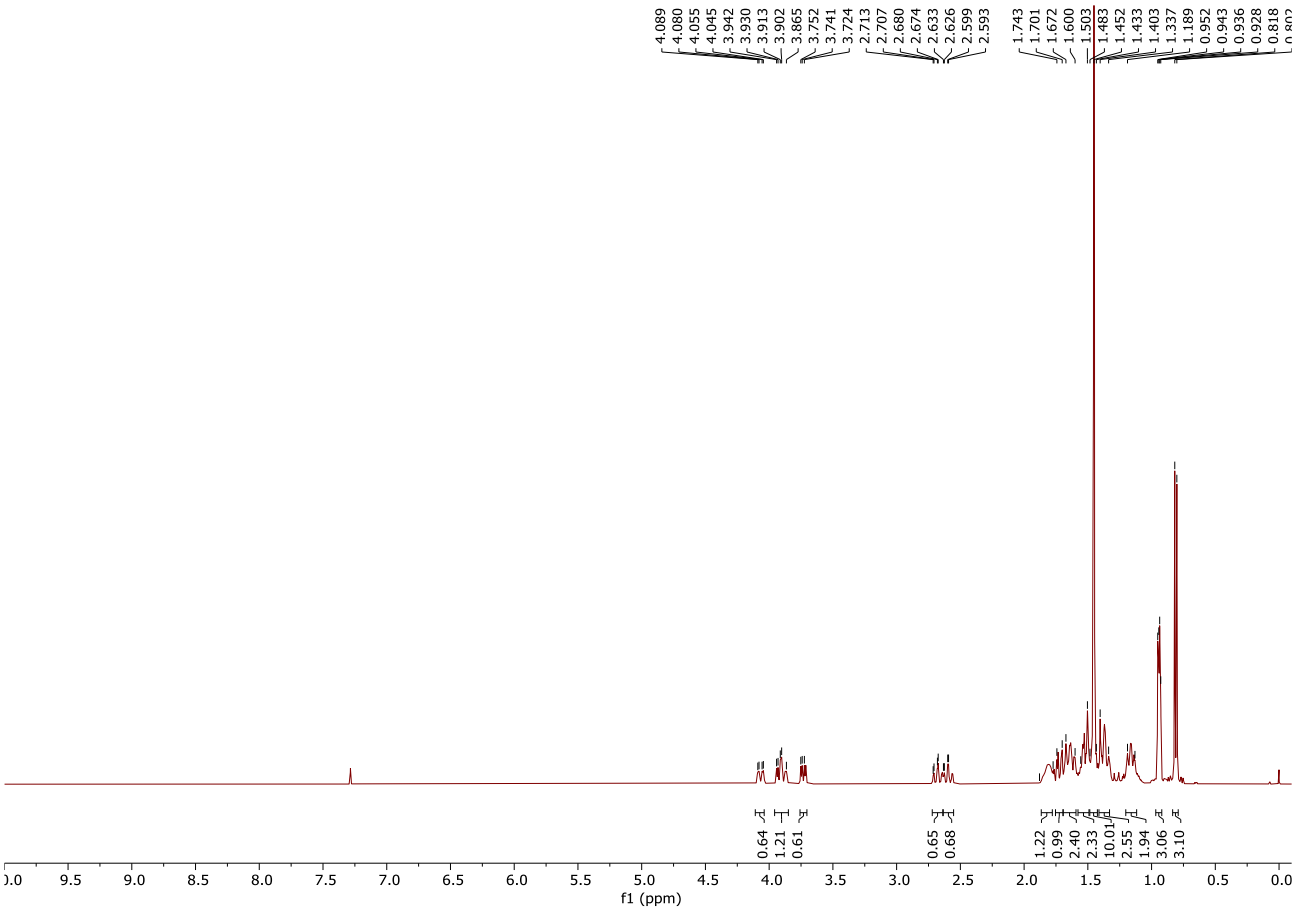
$[\alpha]^{23}_D$ – 52.0 (*c* 1.1, $CHCl_3$).

IR (NaCl): 1690 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 4.06 and 3.92 [(dd, *J* =11.6, 4.8 Hz) and (dd, *J* = 13.6, 3.6 Hz), 1H, H-2], 3.73 and 3.91-3.86 [(dd, *J* = 11.2, 4.4 Hz) and (m), 1H, H-8a], 2.68 and 2.60 [(td, *J* = 13.6, 2.8 Hz) and (td, *J* = 13.2, 2.4 Hz), 1H, H-2], 1.88-1.77 (m, 1H, H-4a), 1.74-1.70 (m, 1H), 1.67-1.60 (m, 2H), 1.56-1.50 (m, 2H), 1.45 [s, 9H, $(CH_3)_3$], 1.48-1.43 (m, 1H), 1.40-1.34 (m, 2H), 1.19-1.13 (m, 2H), 0.95-0.93 (m, 3H, CH_3C-7), 0.81 (d, *J* = 6.4 Hz, 3H, CH_3C-8).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 and 155.2 (CO), 78.9 and 78.7 [*C*$(CH_3)_3$], 59.1 and 57.6 (C-8a), 38.6 and 38.5 (CH), 38.9 and 37.6 (C-2) 35.6 and 35.3 (CH), 35.3 and 35.1 (C-4a), 30.9 and 30.7 (CH_2), 30.1and 30.0 (CH_2), 28.4 [C(*C*$H_3)_3$], 26.2 and 25.8 (C-3), 24.6 (CH_2), 20.3 (*C*H_3C-7), 14.9 and 14.4 (*C*H_3C-8).

HRMS Calcd for [$C_{16}H_{29}NO_2 + Na^+$]: 290.2091; found 290.2094.


4.089
4.080
4.055
4.045
3.942
3.930
3.913
3.902
3.865
3.752
3.741
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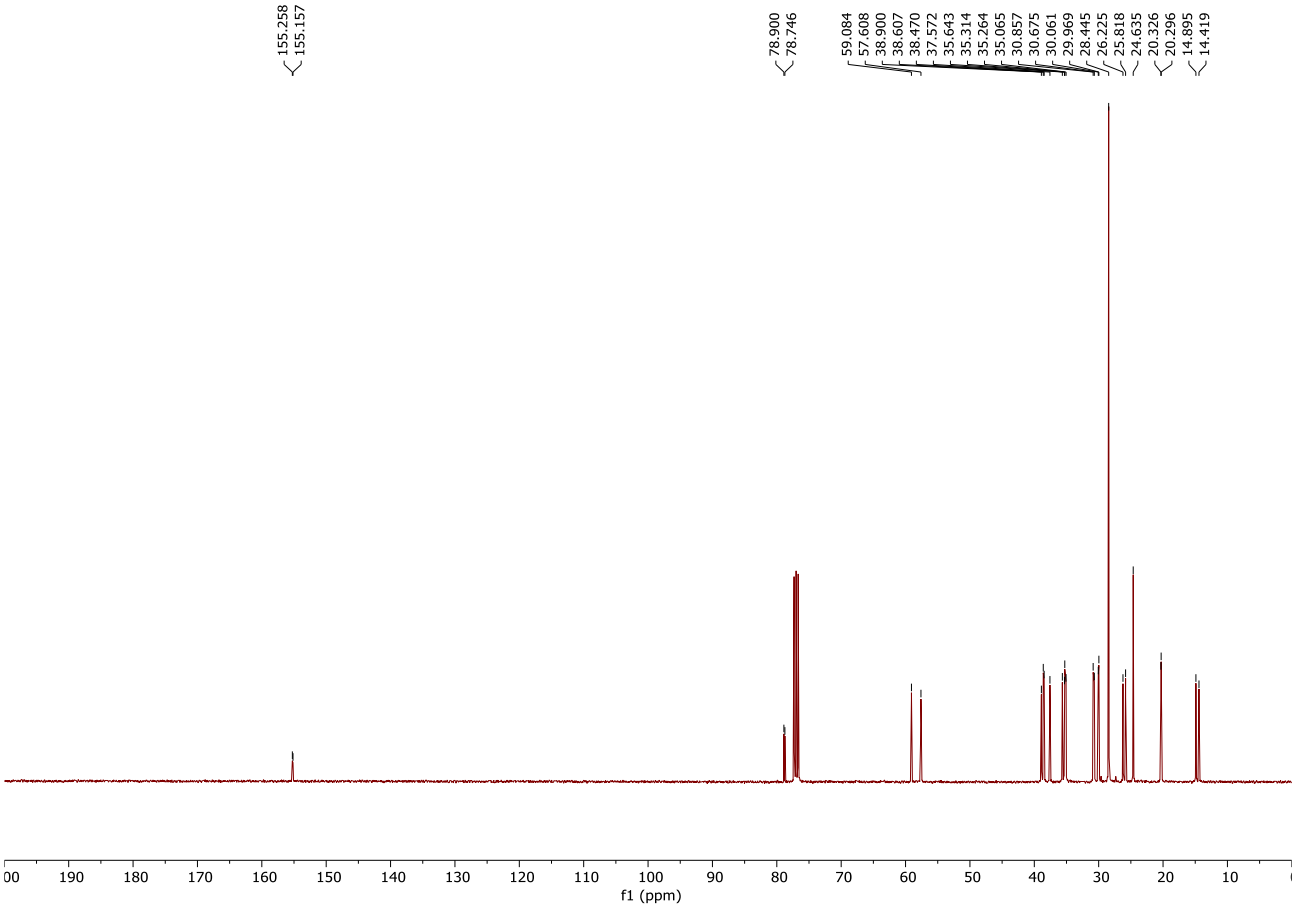
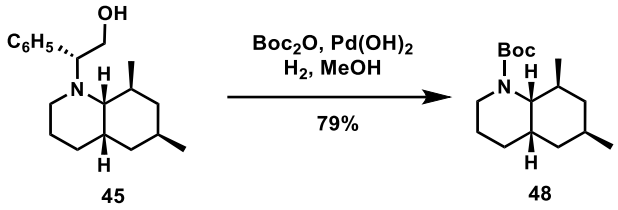
2.713
2.707
2.680
2.674
2.633
2.626
2.599
2.593
1.743
1.701
1.672
1.600
1.503
1.483
1.452
1.433
1.403
1.337
1.189
0.952
0.943
0.936
0.928
0.818
0.64
1.21
0.61
0.65
0.68
1.22
0.99
2.40
2.33
10.01
2.55
1.94
3.06
3.10
f1 (ppm)


155.258
155.157
78.900
78.746
59.084
57.608
38.900
38.607
38.470
37.572
35.643
35.314
35.264
35.065
30.857
30.675
30.061
29.969
28.445
26.225
25.818
24.635
20.326
20.296
14.895
14.419
f1 (ppm)

(4a*S*,6*R*,8*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-6,8-dimethyldecahydroquinoline (48):



Operating as in the preparation of decahydroquinoline **47**, from decahydroquinoline **45** (116 mg, 0.4 mmol), Boc_2O (106 mg, 0.5 mmol) and 40% $Pd(OH)_2$ (46 mg) in CH_3OH (9 mL), decahydroquinoline **48** (88 mg, 79%) was obtained after flash column chromatography (99:1 to 95:5 hexane–Et_2O) as a yellowish oil:

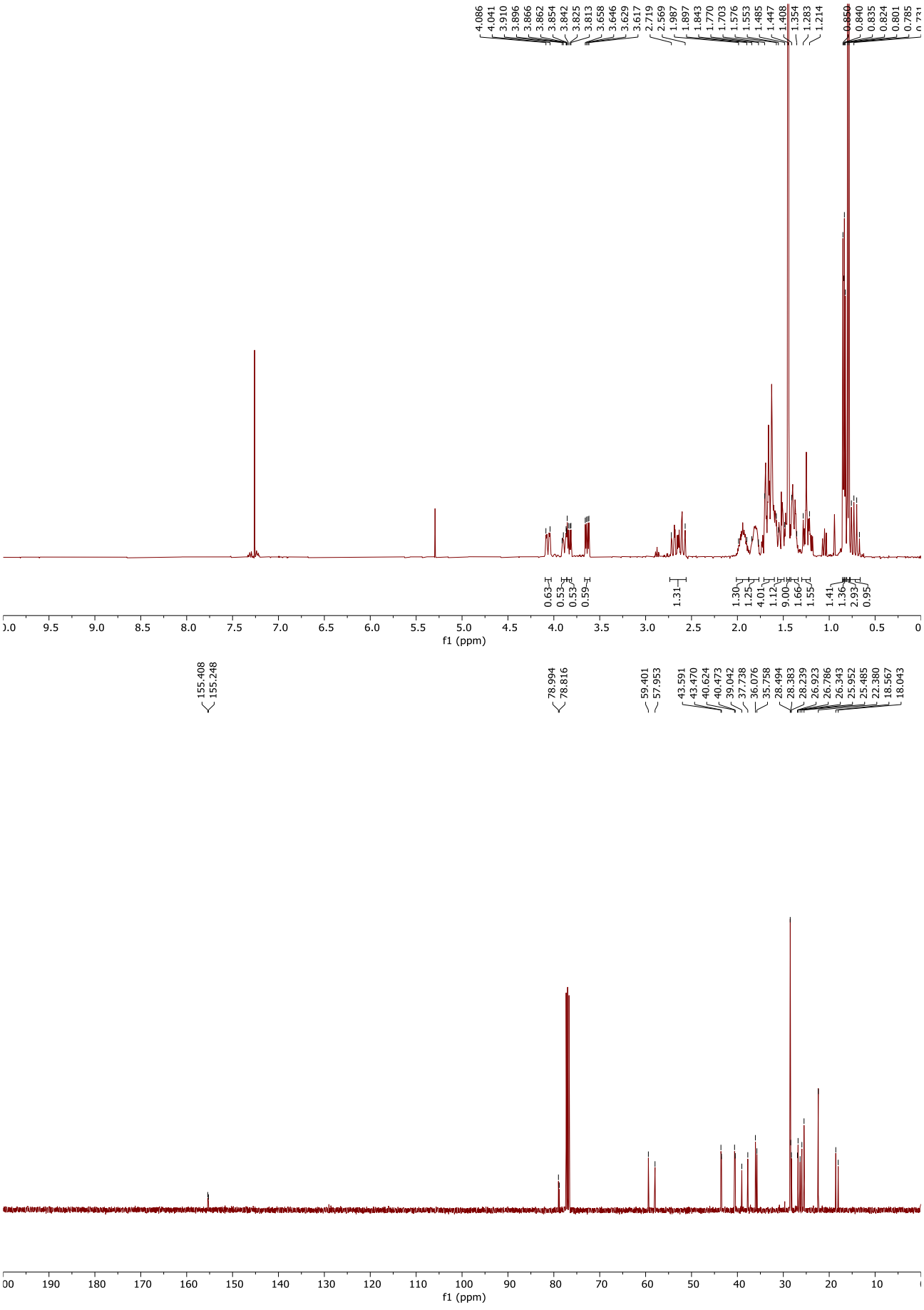
$[\alpha]^{23}_D$ – 15.5 (*c* 1.0, $CHCl_3$).

IR (NaCl): 1691 (CO) cm^{-1}.

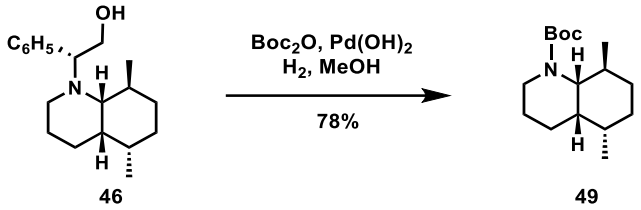
^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 4.06 and 3.88 [(m) and (dd, *J* = 13.6, 4.0 Hz), 1H, H-2_b], 3.83 and 3.63 [(dd, *J* = 11.6, 4.8 Hz) and (dd, *J* = 16.4, 4.8 Hz), 1H, H-8a], 2.68 and 2.64 [(td, *J* = 13.2, 2.8 Hz) and (td, *J* = 13.2, 2.4 Hz), 1H, H-2_a], 1.99-1.90 (m ,1H, H-8), 1.84-1.77 (m, 1H, H-4a), 1.70-1.58 (m, 4H, H-3, H-6 and H-7_b), 1.53-1.49 (m, 1H, H-5_b), 1.45 [s, 9H, $(CH_3)_3$], 1.40-1.35 (m, 2H, H-4), 1.28-1.21 (m, 1H, H-5_a), 0.85 and 0.83 (d, *J* = 4.2 Hz, 3H, CH_3C-8), 0.79 (d, *J* = 6.4 Hz, 3H, CH_3C-6), 0.72 (q, *J* = 11.6 Hz, 1H, H-7_a).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4 and 155.2 (CO), 78.9 and 78.8 [*C*$(CH_3)_3$], 59.4 and 57.9 (C-8a), 43.6 and 43.5 (C-7), 40.6 and 40.5 (C-5), 39.0 and 37.8 (C-2), 36.1 and 35.8 (C-4a), 28.5 [C(*C*$H_3)_3$], 28.4 and 28.2 (C-8), 26.9 and 26.8 (C-6), 26.3 and 25.9 (C-3) 25.5 (C-4), 22.4 (CH_3C-8), 18.6 and 18.0 (CH_3C-6).

HRMS Calcd for [$C_{16}H_{29}NO_2 + H^+$]: 268.2271; found 268.2268.


4.086
4.041
3.910
3.896
3.866
3.862
3.854
3.842
3.825
3.813
3.658
3.646
3.629
3.617
2.719
2.569
1.987
1.897
1.843
1.770
1.703
1.576
1.553
1.485
1.447
1.408
1.354
1.283
1.214
0.850
0.840
0.835
0.824
0.801
0.785
0.63
0.53
0.53
0.59
1.31
1.30
1.25
4.01
1.12
9.00
1.66
1.55
1.41
1.36
2.93
0.95
f1 (ppm)
155.408
155.248
78.994
78.816
59.401
57.953
43.591
43.470
40.624
40.473
39.042
37.738
36.076
35.758
28.494
28.383
28.239
26.923
26.786
26.343
25.952
25.485
22.380
18.567
18.043
f1 (ppm)

(4a*S*,5*S*,8*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5,8-dimethyldecahydroquinoline (49):



Operating as described in the preparation of decahydroquinoline **47**, from decahydroquinoline **46** (439 mg, 1.53 mmol), Boc_2O (900 mg, 4.12 mmol), and 40% $Pd(OH)_2$ (176 mg) in CH_3OH (35 mL), decahydroquinoline **49** (319 mg, 78%) was obtained after flash column chromatography (99:1 to 95:5 hexane–Et_2O) as a colorless liquid:

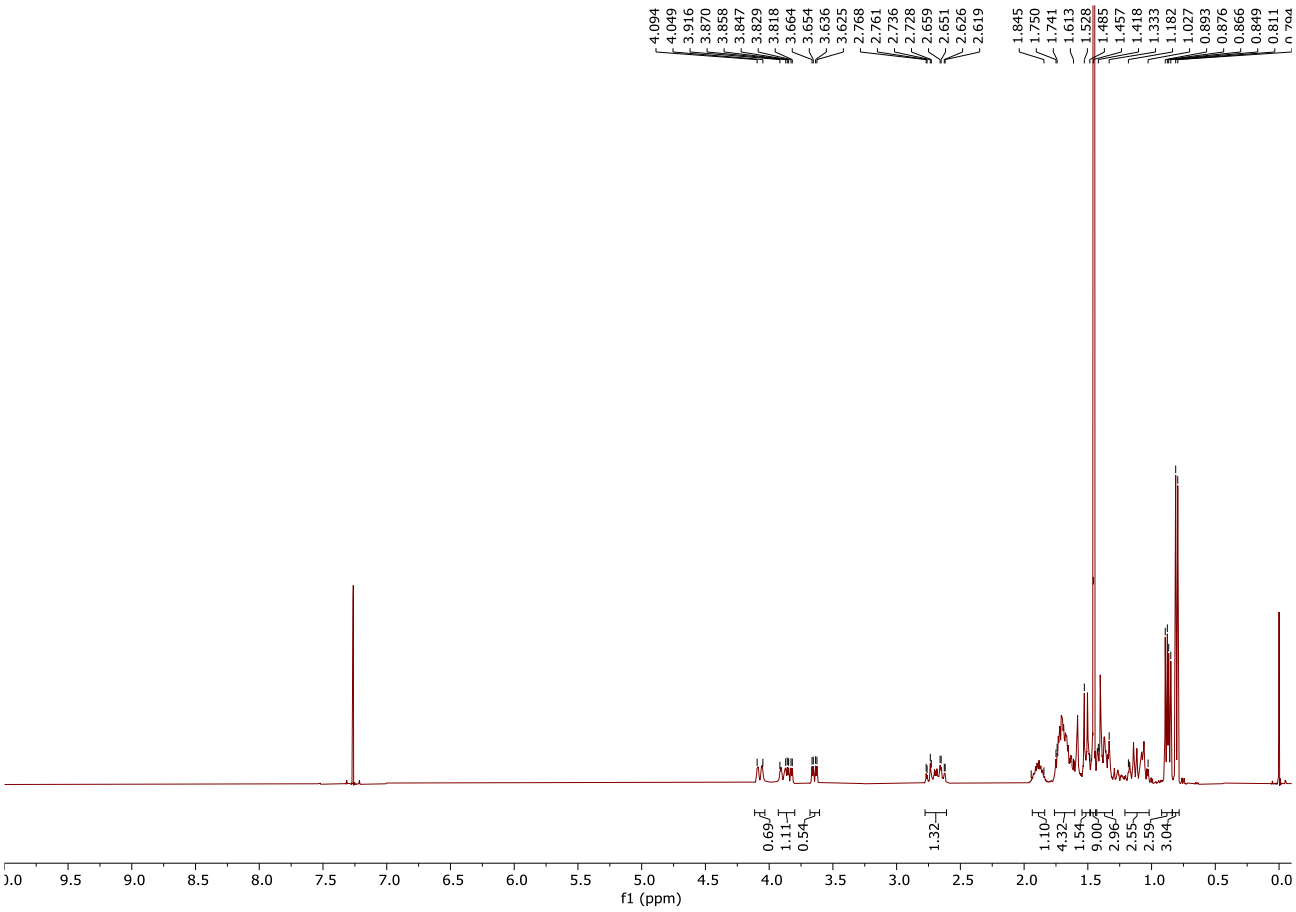
$[\alpha]^{23}_D$ – 23.8 (*c* 1.05, $CHCl_3$).

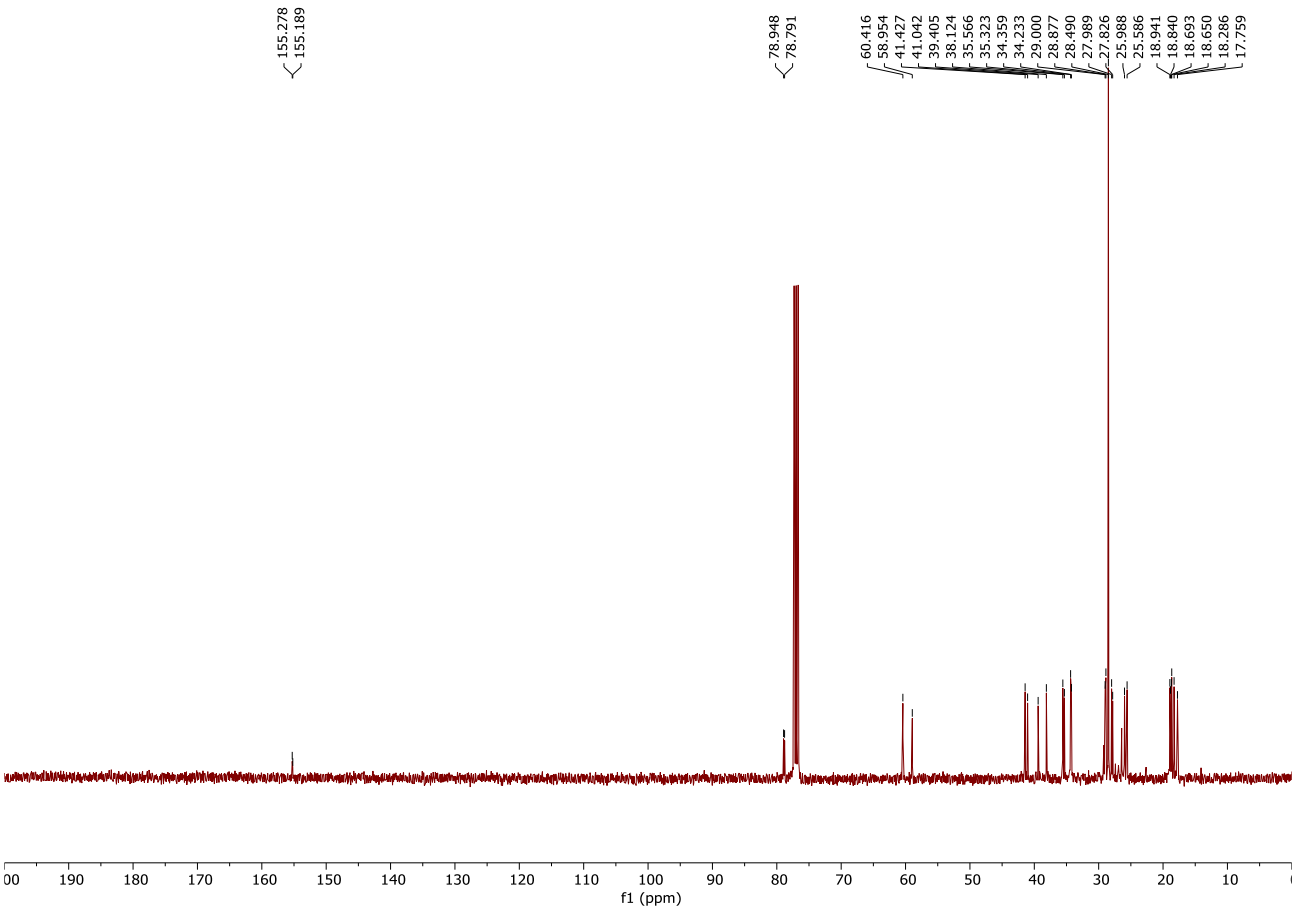
IR (NaCl): 1691 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ4.09-4.05 and 3.92-3.87 [(m) and (m), 1H, H-2], 3.84 and 3.64 [(dd, *J* = 11.2, 4.0 Hz) and (dd, *J* = 11.6, 4.4 Hz), 1H, H-8a], 2.73 and 2.68 [(td, *J* = 12.8, 2.8 Hz) and (td, *J* = 12.8, 2.8 Hz), 1H, H-2], 1.94-1.84 (m, 1H, H-8), 1.75-1.61 (m, 4H, H-3, H-4a, H-5 and H-7), 1.53-1.48 (m, 1H, H-4), 1.46 [s, 9H, $(CH_3)_3$], 1.42-1.33 (m, 3H, H-3, H-4 and H-6), 1.18-1.03 (m, 2H, H-6 and H-7), 0.88 and 0.86 [(d, *J* = 6.8 Hz) and (d, *J* = 6.8 Hz), 3H, CH_3C-5], 0.80 (d, *J* = 6.4 Hz, CH_3C-8).

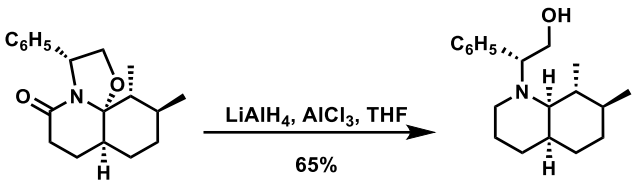
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.3 and 155.2 (CO), 78.9 and 78.8 [*C*$(CH_3)_3$], 60.4 and 59.0 (C-8a), 41.4 and 41.0 (C-5), 39.4 and 38.1 (C-2), 35.6 and 35.3 (C-4a), 34.4 and 34.2 (C-7), 29.0 and 28.9 (C-6), 28.5 [C(*C*$H_3)_3$], 28.0 and 27.8 (C-8), 26.0 and 25.6 (C-3), 18.9 and 18.8 (CH_3C-5), 18.7 and 18.6 (C-4), 18.3 and 17.8 (CH_3C-8).

HRMS Calcd for [$C_{16}H_{29}NO_2 + Na^+$]: 290.2091; found 290.2090.


4.094
4.049
3.916
3.870
3.858
3.847
3.829
3.818
3.664
3.654
3.636
3.625
2.768
2.761
2.736
2.728
2.659
2.651
2.626
2.619
1.845
1.750
1.741
1.613
1.528
1.485
1.457
1.418
1.333
1.182
1.027
0.893
0.876
0.866
0.849
0.811
0.69
1.11
0.54
1.32
1.10
4.32
1.54
9.00
2.96
2.55
2.59
3.04
f1 (ppm)


155.278
155.189
78.948
78.791
60.416
58.954
41.427
41.042
39.405
38.124
35.566
35.323
34.359
34.233
29.000
28.877
28.490
27.989
27.826
25.988
25.586
18.941
18.840
18.693
18.650
18.286
17.759
f1 (ppm)

(4a*S*,7*S*,8*R*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7,8-dimethyldecahydroquinoline (50):



42b 50

Operating as described in the preparation of decahydroquinoline **44**, from $LiAlH_4$ (14.4 mL of a 1M solution in THF, 14.4 mmol), $AlCl_3$ (590 mg, 4.43 mmol) in anhydrous THF (25 mL), and a solution of lactam **42b** (663 mg, 2.21 mmol) in anhydrous THF (10 mL), decahydroquinoline **50** (412 mg, 65%) was obtained after flash column chromatography (9:1 to 7:3 hexane–EtOAc) as a yellowish oil:

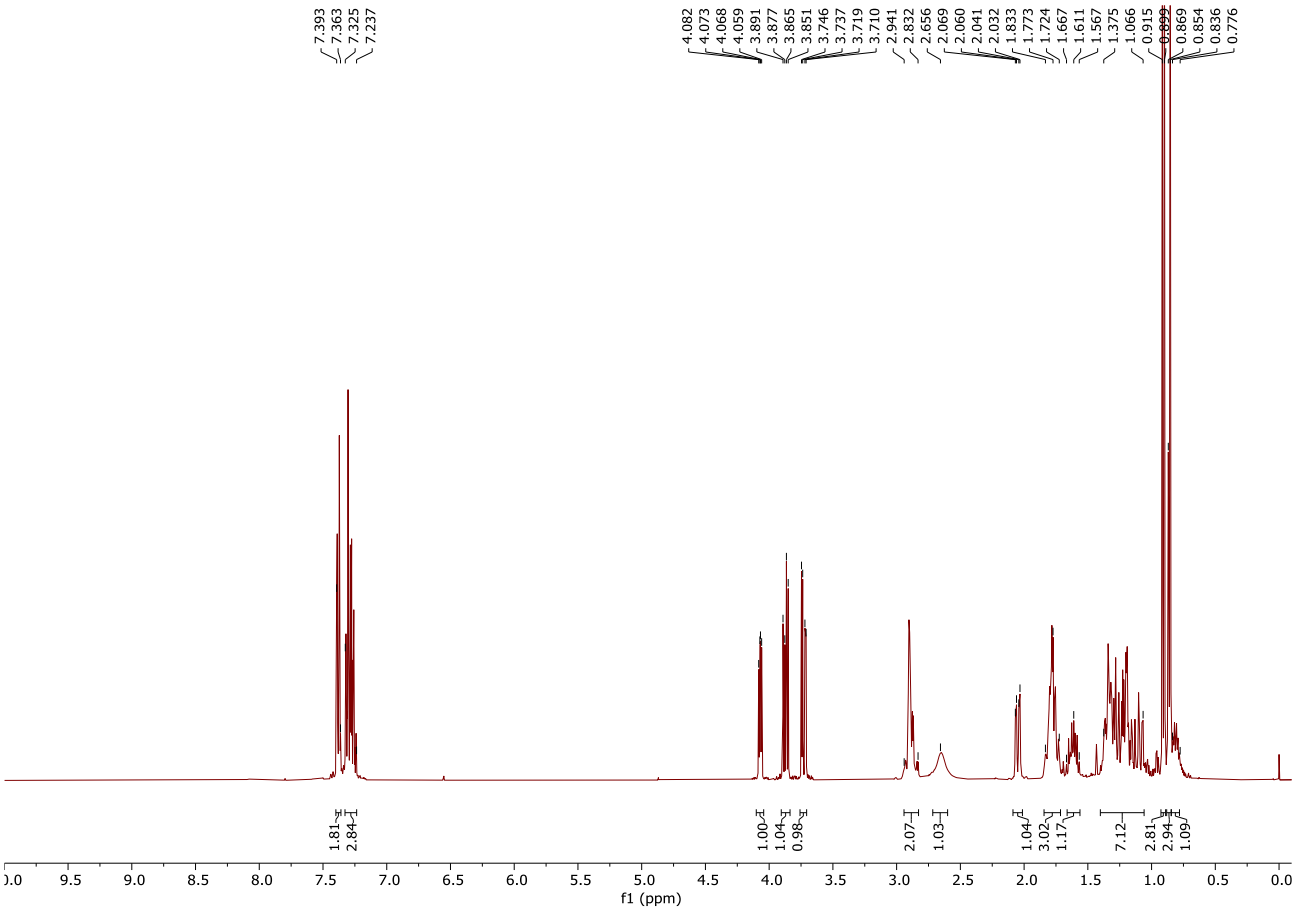
$[\alpha]^{23}_{D}$ – 42.4 (*c* 1.0, $CHCl_3$).

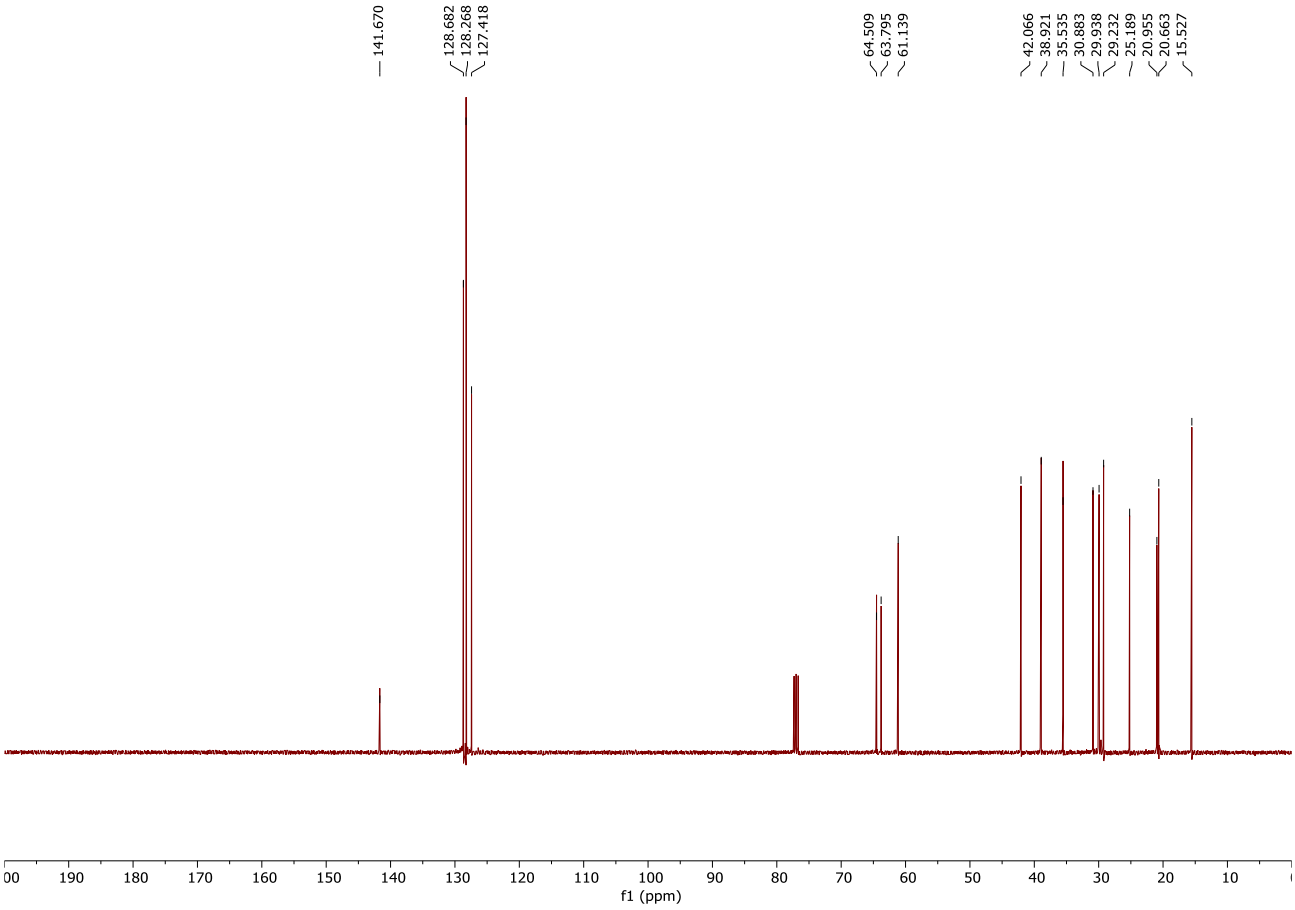
IR (NaCl): 3313 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.39-7.36 (m, 2H, ArH), 7.33-7.24 (m, 3H, ArH), 4.07 (dd, *J* = 5.6, 3.6 Hz, 1H, C*H*CH_2O), 3.87 (dd, *J* = 10.6, 5.6 Hz, 1H, CHC*H*$_2$O), 3.73 (dd, *J* = 10.6, 3.6 Hz, 1H, CHC*H*$_2$O), 2.94-2.83 (m, 2H, H-2), 2.66 (br s, 1H, OH), 2.05 (dd, *J* = 11.2, 3.6 Hz, 1H, H-8a), 1.83-1.67 (m, 3H, H-3, H-4a and H-5), 1.61-1.57 (m, 1H, H-8), 1.38-1.07 (m, 6H, H-3, H-4, H-5 and H-6), 0.91 (d, *J* = 6.4 Hz, 3H, CH_3C-7), 0.86 (d, *J* = 6 Hz, 3H, CH_3C-8), 0.84- 0.78 (m, 1H, H-7).

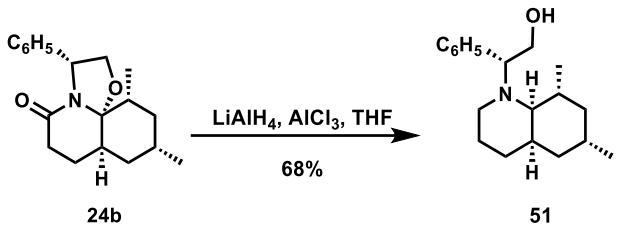
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.7 (C-Ar), 127.4 (CH-Ar), 128.3 (CH-Ar), 28.7 (CH-Ar), 64.5 (*C*HCH$_2$O), 63.8 (CH*C*H$_2$O), 61.1 (C-8a), 42.1 (C-2), 38.9 (C-7), 35.5 (C-8), 30.9 (C-6), 29.9 (C-5), 29.2 (C-4a), 25.2 (C-4), 21.0 (C-3), 20.7 (*C*H$_3$C-8), 15.5 (*C*H$_3$C-7).

HRMS Calcd for [$C_{19}H_{29}NO + H^+$]: 288.2322; found 288.2319.


7.393
7.363
7.325
7.237
4.082
4.073
4.068
4.059
3.891
3.877
3.865
3.851
3.746
3.737
3.719
3.710
2.941
2.832
2.656
2.069
2.060
2.041
2.032
1.833
1.773
1.724
1.667
1.611
1.567
1.375
1.066
0.915
0.899
0.869
0.854
0.836
0.776
1.81
2.84
1.00
1.04
0.98
2.07
1.03
1.04
3.02
1.17
7.12
2.81
2.94
1.09
f1 (ppm)


141.670
128.682
128.268
127.418
64.509
63.795
61.139
42.066
38.921
35.535
30.883
29.938
29.232
25.189
20.955
20.663
15.527
f1 (ppm)

(4a*R*,6*S*,8*R*,8a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,8-dimethyldecahydroquinoline (51):



24b **51**

Operating as described in the preparation of decahydroquinoline **44**, from $LiAlH_4$ (7.3 mL of a 1M solution in THF, 7.3 mmol), $AlCl_3$ (300 mg, 2.26 mmol) in anhydrous THF (15 mL), and a solution of lactam **24b** (338.2 mg, 1.13 mmol) in anhydrous THF (10 mL), decahydroquinoline **51** (222 mg, 68%) was obtained after flash column chromatography (9:1 to 7:3 hexane–EtOAc) as a yellowish oil:

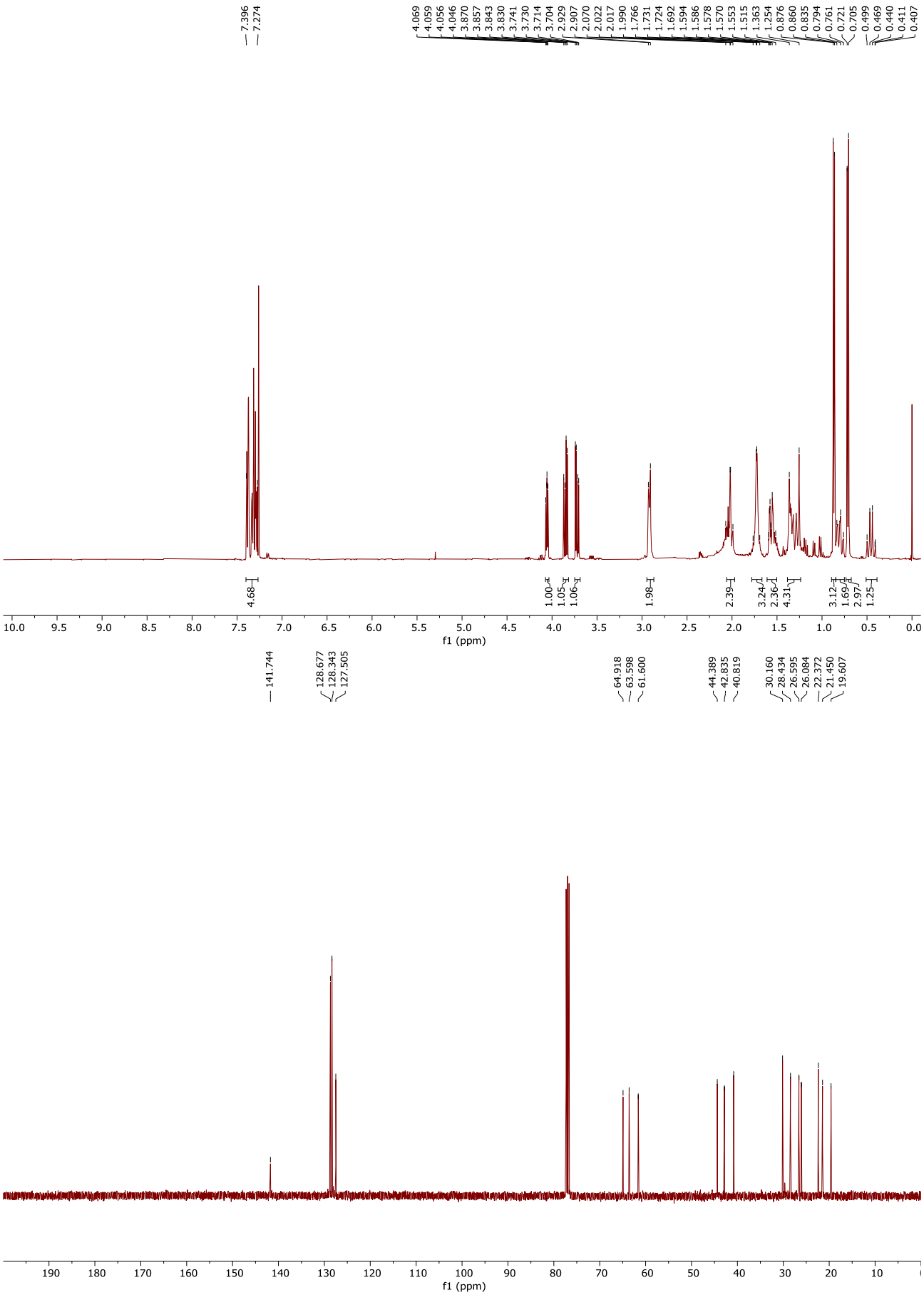
$[\alpha]^{23}_{D}$ – 65.2 (*c* 1.1, $CHCl_3$).

IR (NaCl): 3395 (OH) cm^{-1}.

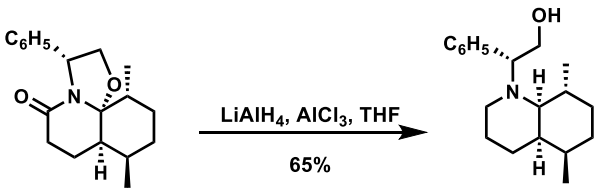
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.27-7.40 (m, 5H, ArH), 4.05 (dd, *J* = 5.2 Hz, 4.0 Hz, 1H, C*H*CH_2O), 3.85 (dd, *J* = 10.8, 5.2 Hz, 1H, CHC*H*$_2$O), 3.72 (dd, *J* = 10.8, 4.0 Hz, 1H, CHC*H*$_2$O), 2.91-2.93 (m, 2H, H-2), 1.99-2.07 (m, 2H, H-6, H-8a), 1.69-1.76 (m, 3H, H-3, H-4a, H-5), 1.51-1.59 (m, 2H, H-7, H-8), 1.25-1.36 (m, 3H, H-3, H-5, H-4), 0.87 (d, *J* = 6.4 Hz, 3H, CH_3C-6), 0.76-0.84 (m, 1H, H-4), 0.71 (d, *J* = 6.4 Hz, 3H, CH_3C-8), 0.45 (q, *J* = 12.0 Hz, 1H, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.7 (C-Ar); 127.5 (CH-Ar), 128.3 (CH-Ar), 128.7 (CH-Ar), 64.9 (*C*HCH_2O), 63.6 (CH*C*H_2O), 61.6 (C-8a), 44.4 (C-7), 42.8 (C-2), 40.8 (C-4), 30.2 (C-4a), 28.4 (C-6), 26.6 (C-8), 26.1 (C-5), 22.4 (*C*H_3C-8), 21.4 (C-3), 19.6 (*C*H_3C-6).

HRMS Calcd for [$C_{19}H_{29}NO + H^+$]: 288.2322; found 288.2322.


7.396
7.274
4.069
4.059
4.056
4.046
3.870
3.857
3.843
3.830
3.741
3.730
3.714
3.704
2.929
2.907
2.070
2.022
2.017
1.990
1.766
1.731
1.724
1.692
1.594
1.586
1.578
1.570
1.553
1.515
1.363
1.254
0.876
0.860
0.835
0.794
0.761
0.721
0.705
0.499
0.469
0.440
0.411
0.407
4.68
1.00
1.05
1.06
1.98
2.39
3.24
2.36
4.31
3.12
1.69
2.97
1.25
f1 (ppm)
141.744
128.677
128.343
127.505
64.918
63.598
61.600
44.389
42.835
40.819
30.160
28.434
26.595
26.084
22.372
21.450
19.607
f1 (ppm)

(4a*R*,5*R*,8*R*,8a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-5,8-dimethyldecahydroquinoline (52):



43b 52

Operating as described in the preparation of decahydroquinoline **44**, from $LiAlH_4$ (11.6 mL of a 1M solution in THF, 11.6 mmol), $AlCl_3$ (477 mg, 3.57 mmol) in anhydrous THF (25 mL), and a solution of lactam **43b** (535 mg, 1.79 mmol) in anhydrous THF (10 mL), decahydroquinoline **52** (412 mg, 65%) was obtained after flash column chromatography (9:1 to 7:3 hexane–EtOAc) as a yellowish oil:

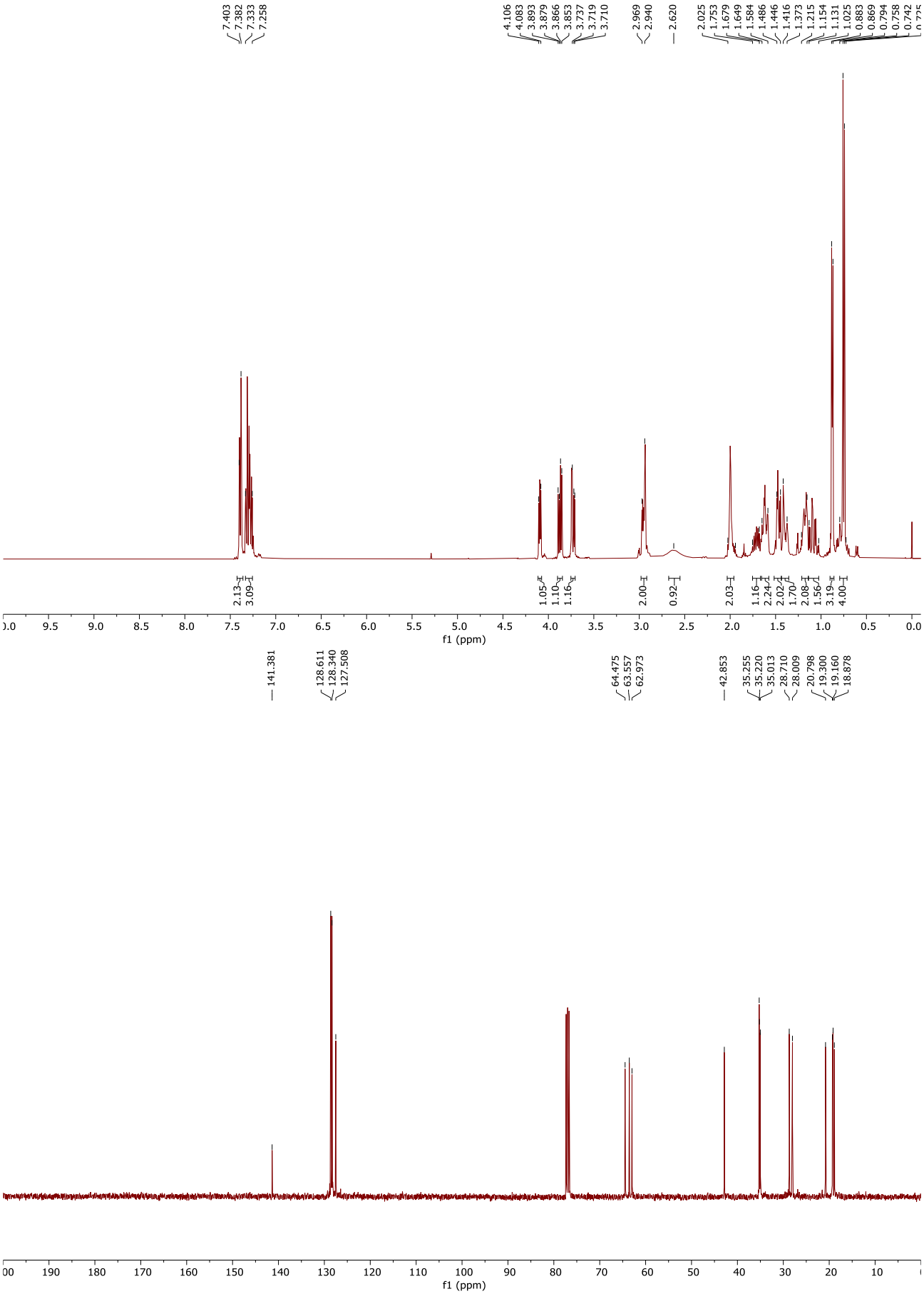
$[\alpha]^{23}_{D}$ – 42.4 (*c* 1.0, $CHCl_3$).

IR (NaCl): 3417 (OH) cm^{-1}.

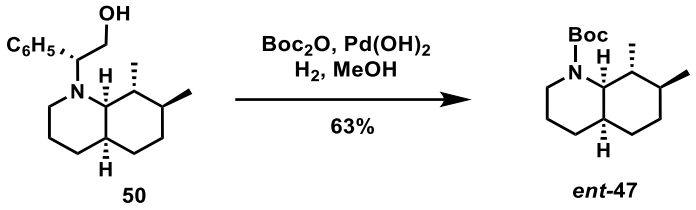
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.40-7.38 (m, 2H, ArH), 7.33-7.26 (m, 3H, ArH), 4.11-4.08 (m, 1H, C*H*CH_2O), 3.87 (dd, *J* = 10.8, 5.6 Hz, 1H, CHC*H*$_2$O), 3.73 (dd, *J* = 10.8, 3.6 Hz, 1H, CHC*H*$_2$O), 2.97-2.94 (m, 2H, H-2), 2.62 (br s, 1H, OH), 2.02-1.94 (m, 2H, H-8 and H-8a), 1.75-1.68 (m, 1H, H-3), 1.65-1.58 (m, 2H, H-5 and H-7), 1.49-1.45 (m, 2H, H-4), 1.42-1.37 (m, 1H, H-3), 1.21-1.15 (m, 2H, H-4a and H-6), 1.13-1.03 (m, 1H, H-6), 0.88 (d, *J* = 5.6 Hz, 3H, CH_3C-8), 0.75 (d, *J* = 6.4 Hz, 3H, CH_3C-5), 0.79-0.73 (m, 1H, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.4 (C-Ar), 127.5 (CH-Ar), 128.3 (CH-Ar), 128.6 (CH-Ar), 64.5 (*C*HCH_2O), 63.6 (CH*C*H_2O), 63.0 (C-8a), 42.9 (C-2), 35.3 (C-4a), 35.2 (C-5), 35.0 (C-7), 28.7 (C-6), 28.0 (C-8), 20.8 (C-3), 19.3 (*C*H_3C-8), 19.2 (C-4), 18.9 (*C*H_3C-5).

HRMS Calcd for [$C_{19}H_{29}NO + H^+$]: 288.2322; found 288.2321.


7.403
7.382
7.333
7.258
4.106
4.083
3.893
3.879
3.866
3.853
3.737
3.719
3.710
2.969
2.940
2.620
2.025
1.753
1.679
1.649
1.584
1.486
1.446
1.416
1.373
1.215
1.154
1.131
1.025
0.883
0.869
0.794
0.758
0.742
2.13
3.09
1.05
1.10
1.16
2.00
0.92
2.03
1.16
2.24
2.02
1.70
2.08
1.56
3.19
4.00
f1 (ppm)
141.381
128.611
128.340
127.508
64.475
63.557
62.973
42.853
35.255
35.220
35.013
28.710
28.009
20.798
19.300
19.160
18.878
f1 (ppm)

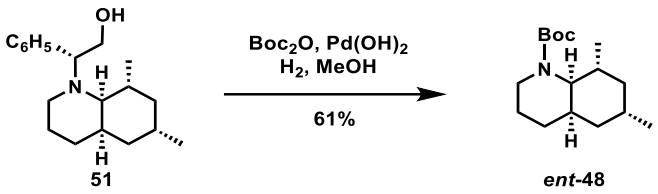
(4a*S*,7*S*,8*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-7,8-dimethyldecahydroquinoline (*ent*-47)



Operating as in the preparation of decahydroquinoline **47**, from decahydroquinoline **50** (156 mg, 0.54 mmol), Boc_2O (319 mg, 1.46 mmol) and 40% $Pd(OH)_2$ (63 mg) in CH_3OH (13 mL), decahydroquinoline ***ent*-47** (91.2 mg, 63%) was obtained after flash column chromatography (99:1 to 95:5 hexane–Et_2O) as a yellowish oil:

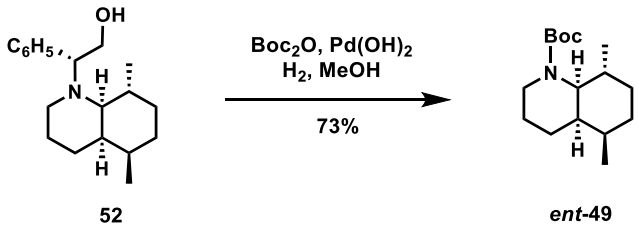
$[\alpha]^{23}_D$ + 52.5 (*c* 1.2, $CHCl_3$).

(4a*R*,6*S*,8*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-6,8-dimethyldecahydroquinoline (*ent*-48)



Operating as described in the preparation of decahydroquinoline **47**, from decahydroquinoline **51** (106 mg, 0.37 mmol), Boc_2O (97 mg, 0.44 mmol), and 40% $Pd(OH)_2$ (43 mg) in CH_3OH (8.5 mL), decahydroquinoline ***ent*-48** (64 mg, 61%) was obtained after flash column chromatography (99:1 to 95:5 hexane–Et_2O) as a yellowish oil:
$[\alpha]^{23}_D$ + 15.2 (*c* 1.0, $CHCl_3$).

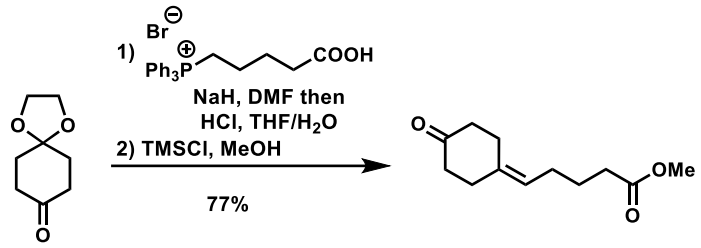
(4a*R*,5*R*,8*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-5,8-dimethyldecahydroquinoline (*ent*-49)



Operating as described in the preparation of decahydroquinoline **47**, from decahydroquinoline **52** (439 mg, 1.53 mmol), Boc_2O (900 mg, 4.12 mmol), and 40% $Pd(OH)_2$ (176 mg) in CH_3OH (35 mL), decahydroquinoline ***ent*-49** (300 mg, 73%) was obtained after flash column chromatography (99:1 to 95:5 hexane–Et_2O) as a yellowish oil:
$[\alpha]^{23}_D$ + 23.3 (*c* 1.03, $CHCl_3$).

6.5 Experimental Procedures and Spectroscopic Data – Chapter 3

Methyl 4-oxocyclohexylidene-5-pentenoate (55):



53 55

First Step: 4-(carboxybutyl)triphenylphosphonium bromide (2.95 g, 6.7 mmol, 98%) was added portionwise to a suspension of NaH (340 mg, 13.4 mmol, 95%) in anhydrous DMF (16 mL) at 0 °C, the resulting suspension was stirred at 0 °C for 10 min. 1,4-Cyclohexanedione monoethylene acetal **53** (1.00 g, 6.21 mmol, 97%) in anhydrous DMF (6 mL) was added into the reaction mixture and the stirring was continued for 10 min at 0 °C, and at room temperature for 18 h.

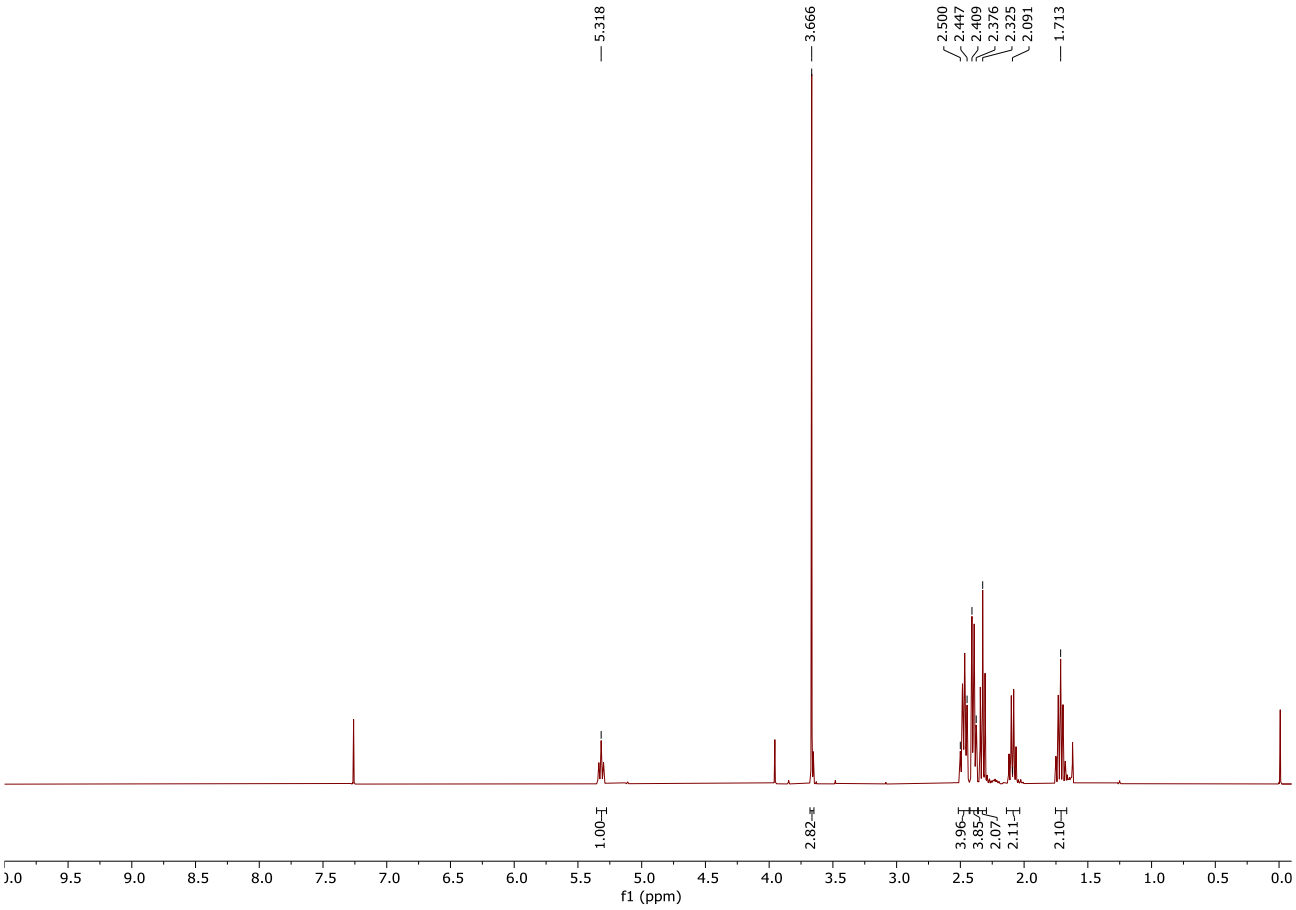
Second Step: The resulting suspension was dissolved in 2 M aqueous HCl until pH 1 and stirred at room temperature for 6 h. Then, the solution was extracted with toluene and the combined organic extracts were dried filtered and concentrated to give crude 5-(4-oxocyclohexylidene)pentanoic acid **54** (3.45 g) as a yellowish oil.

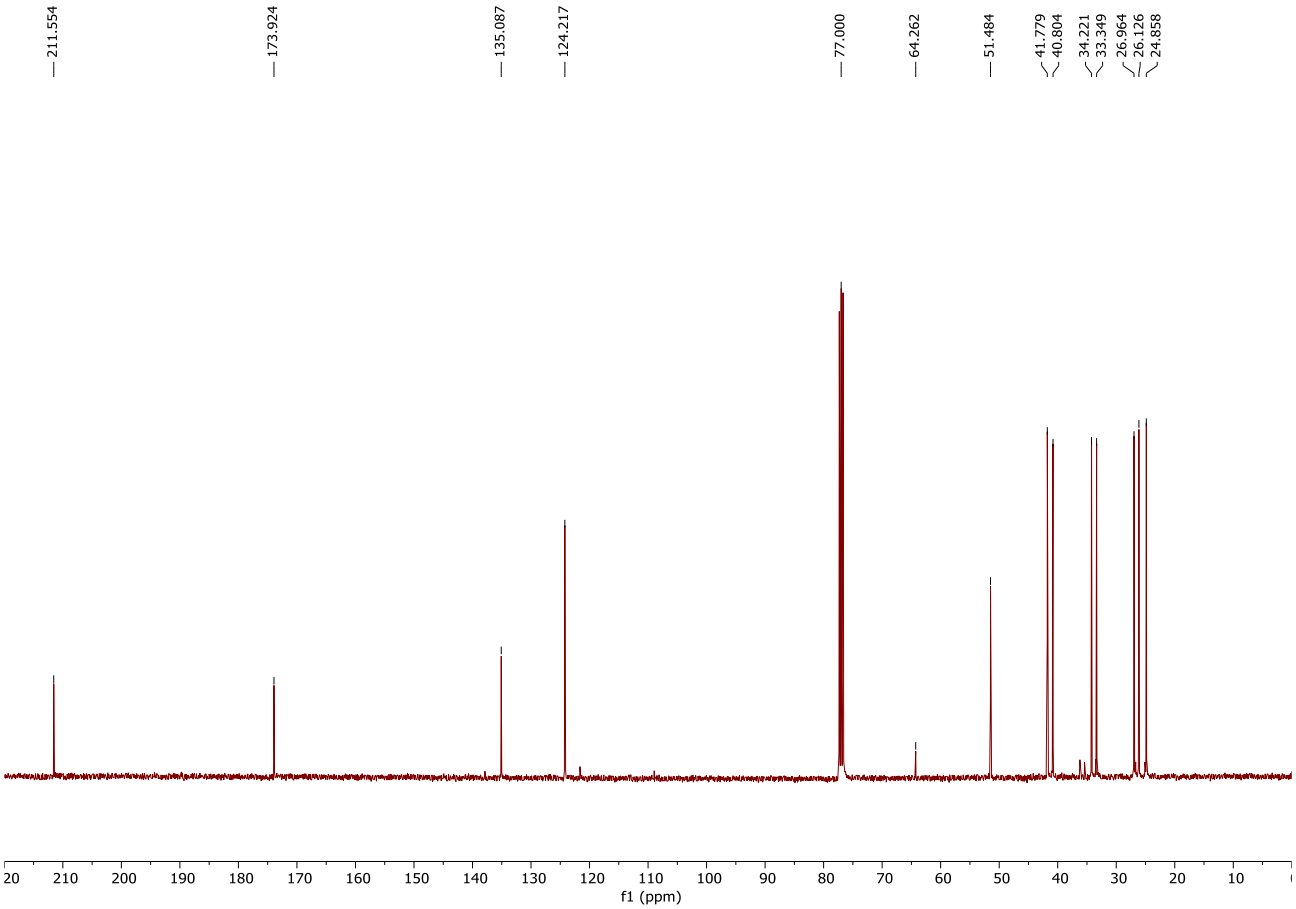
Third Step: To a solution of the above crude in anhydrous MeOH (8 mL) was added trimethylsilyl chloride (1.05 g, 9.63 mmol) under Ar atmosphere. After stirring at room temperature overnight, the reaction mixture was concentrated, and the residue was diluted with EtOAc and washed with $NaHCO_3$. The organic layer was dried, filtered, and concentrated. Flash chromatography (from 8:2 to 7:3 hexane–EtOAc) afforded methyl 5-(4-oxocyclohexylidene)pentanoate **55** (988 mg, 75 %) as a pale yellow liquid:

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 5.32 (t, *J* = 8.0 Hz, 1H, H-1), 3.67 (s, 3H, OCH_3), 2.50-2.45 (m, 4H), 2.41-2.38 (m, 4H), 2.32 (t, *J* = 8.0 Hz, 2H, H-2), 2.09 (q, *J* = 8.0 Hz, 2H, H-4), 1.71 (quint, *J* = 8.0 Hz, 2H, H-3).

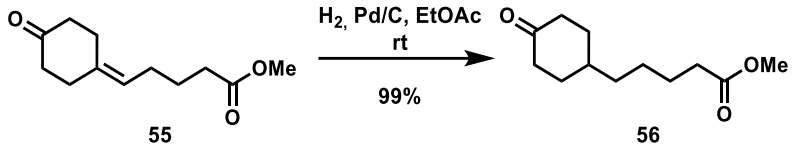
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.6 (CO), 173.9 (COO), 135.1 (=C), 124.2 (C-1), 51.5 (CH_3O), 41.8 (CH_2), 40.8 (CH_2), 34.2 (CH_2), 33.3 (C-2), 27.0 (C-4), 26.1 (CH_2), 24.9 (C-3).

HRMS Calcd for [$C_{12}H_{19}O_3 + H^+$]: 211. 1329; found 211.1332.


5.318
3.666
2.500
2.447
2.409
2.376
2.325
2.091
1.713
1.00
2.82
3.96
3.85
2.07
2.11
2.10
f1 (ppm)


211.554
173.924
135.087
124.217
77.000
64.262
51.484
41.779
40.804
34.221
33.349
26.964
26.126
24.858
f1 (ppm)

Methyl 4-oxocyclohexanepentanoate (56):

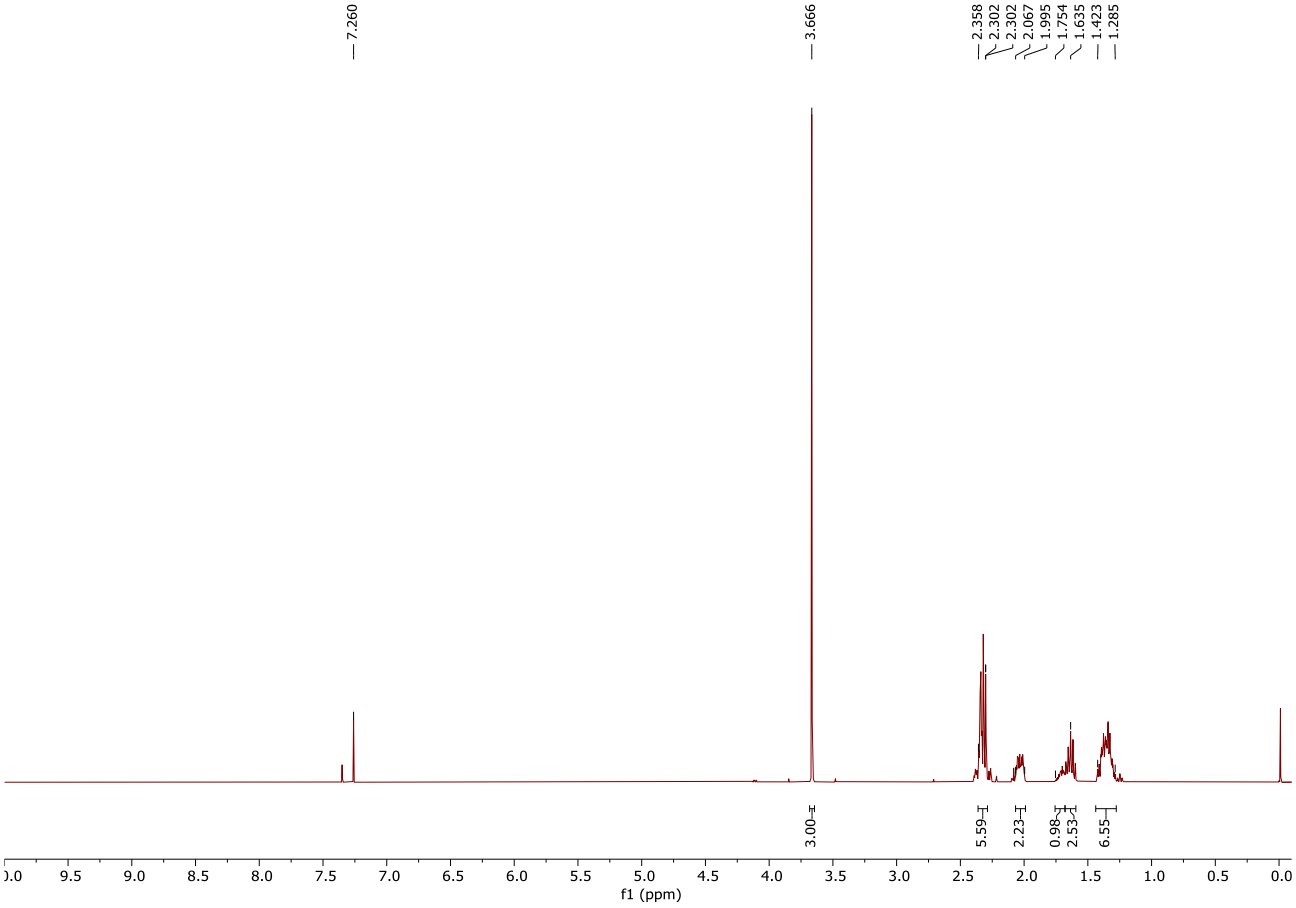


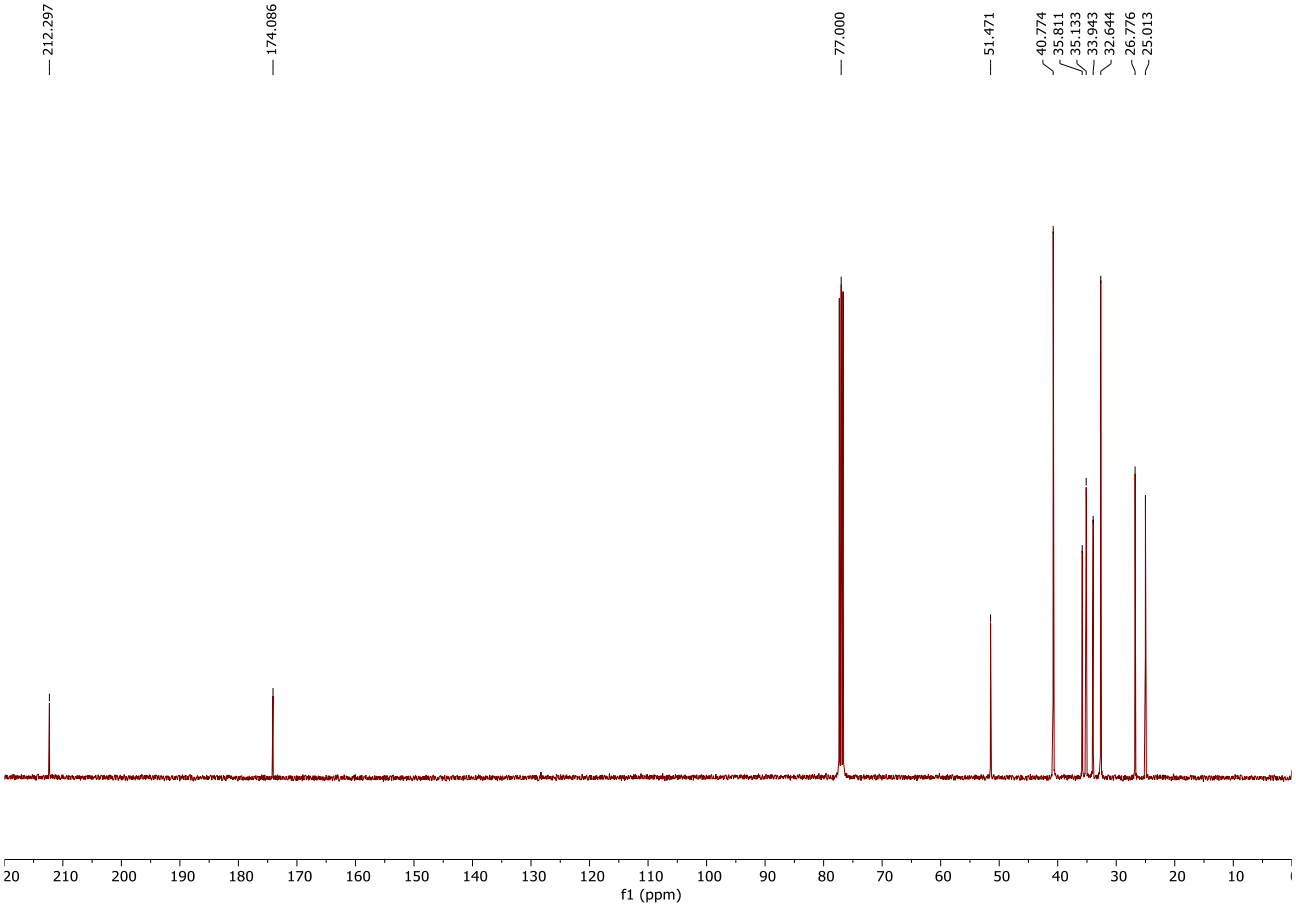
A solution of keto ester **55** (3.01 g, 14.33 mmol) and Pd/C (300 mg) in EtOAc (125 mL) was stirred under hydrogen atmosphere (1 atm) at rt for 18h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated to afford methyl 4-oxocyclohexylpentanoate **56** (3.01 g, 99 %) as a yellow liquid**:**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 3.67 (s, 3H, CH_3O), 2.36-2.30 (m, 6H), 2.07-2.00 (m, 2H), 1.75-1.68 (m, 1H, H-6), 1.63 (quint, *J* = 8 Hz, 2H, H-3), 1.42-1.29 (m, 6H).

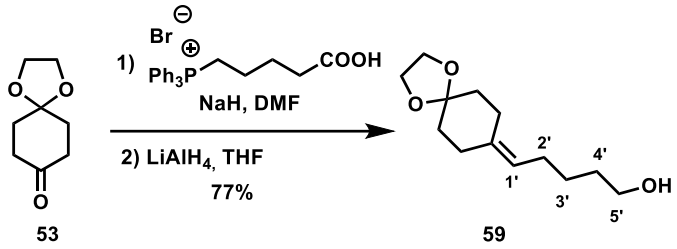
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.3 (CO), 174.1 (COO), 51.5 (CH_3O), 40.8 (CH_2), 35.8 (CH), 35.1 (CH_2), 33.9 (CH_2), 32.6 (CH_2), 26.8 (CH_2), 25.0 (CH_2).

HRMS Calcd for [$C_{12}H_{21}O_3 + H^+$]: 213.1485; found 213.1479.


7.260
3.666
2.358
2.302
2.302
2.067
1.995
1.754
1.635
1.423
1.285
3.00
5.59
2.23
0.98
2.53
6.55
f1 (ppm)


212.297
174.086
77.000
51.471
40.774
35.811
35.133
33.943
32.644
26.776
25.013
f1 (ppm)

4-(5-Hydroxypentylidene)cyclohexanone ethylene acetal (59):



53 59

First Step: 4-(carboxybutyl)triphenylphosphonium bromide (28.10 g, 63.40 mmol) was added portionwise to a suspension of NaH (3.38 g, 126.80 mmol, 90%) in anhydrous DMF (140 mL) at 0 °C, the resulting suspension was stirred at 0 °C for 10 min. 1,4-Cyclohexanedione monoethylene acetal **53** (9.72 g, 60.40 mmol) in anhydrous DMF (60 mL) was added into the reaction mixture and the stirring was continued for 10 min at 0 °C, and at room temperature for 18 h. The resulting suspension was dissolved in water and washed with CH_2Cl_2. Then, pH was adjusted to 3-4 by addition of 2 M aqueous HCl solution and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, *J* = 7.6 Hz, 1H, H-1'), 3.97 [s, 4H, $(CH_2)_2O_2$], 2.36-2.32 (m, 2H), 2.27-2.21 (m, 4H), 2.09-2.04 (m, 2H), 1.70-1.63 (m, 6H);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.8 (COO), 138.0 (Cq), 121.6 (CH), 109.0 (Cq), 64.3 (CH_2), 36.2 (CH_2), 35.4 (CH_2), 33.5 (CH_2), 33.2 (CH_2), 26.6 (CH_2), 25.0 (CH_2), 24.9 (CH_2);

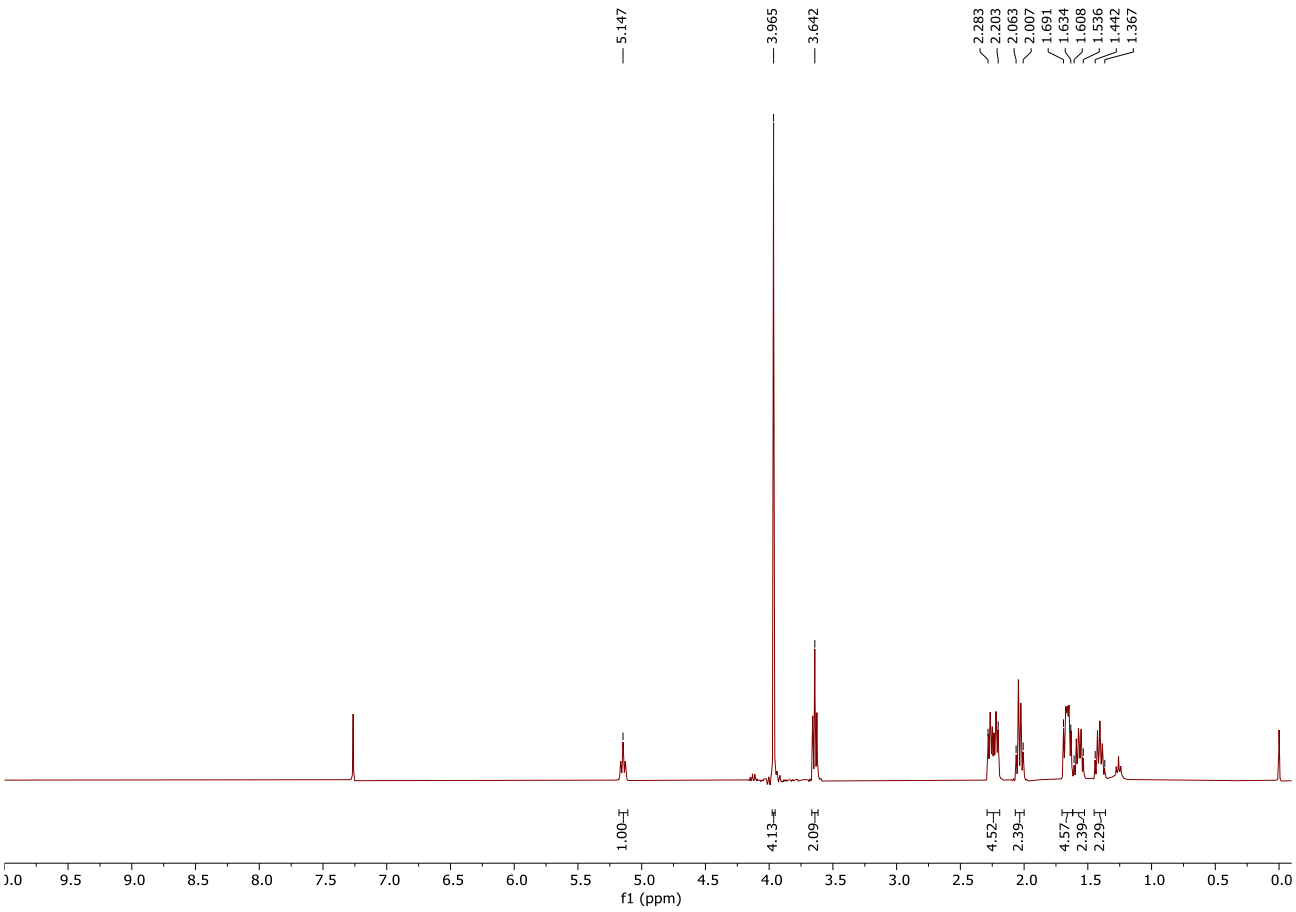
Second Step: A solution of the above crude in anhydrous THF (80 mL) was added dropwise to a cooled suspension (0 °C) of $LiAlH_4$ (11.80 g, 301.80 mmol) in anhydrous THF (300 mL), and the mixture was stirred at 0 °C for 15 min and at rt for 2 h. The reaction was poured into ice, diluted in EtOAc and filtered through Celite®. The resulting solution was extracted with EtOAc, dried and concentrated. Flash chromatography (7:3 to 1:1 hexane–EtOAc, SiO_2 previously treated with Et_3N) afforded alcohol **59** (10.11 g, 77%) as a colourless oil:

IR (NaCl): 3423 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 5.15 (t, *J* = 7.2 Hz, 1H, H-1'), 3.97 [s, 4H, $(CH_2)_2O_2$], 3.64 (t, *J* = 6.4 Hz, 2H, H-5'), 2.28-2.20 (m, 4H, H-3 and H-5), 2.06-2.01 (m, 2H, H-2'), 1.69-1.63 (m, 4H, H-2 and H-6), 1.61-1.54 (m, 2H, H-4'), 1.44-1.37 (m, 2H, H-3').

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.8 (C-4), 122.6 (C-1'), 109.0 (C-1), 64.1 [$(CH_2)_2O_2$)], 62.6 (C-5'), 36.1 (CH_2), 35.3 (CH_2), 33.4 (CH_2), 32.1 (C-4'), 27.0 (C-2'), 26.0 (C-3'), 24.9 (CH_2).

HRMS Calcd for [$C_{13}H_{22}O_3 + H^+$]: 227.1642; found 227.1631.


5.147
3.965
3.642
2.283
2.203
2.063
2.007
1.691
1.634
1.608
1.536
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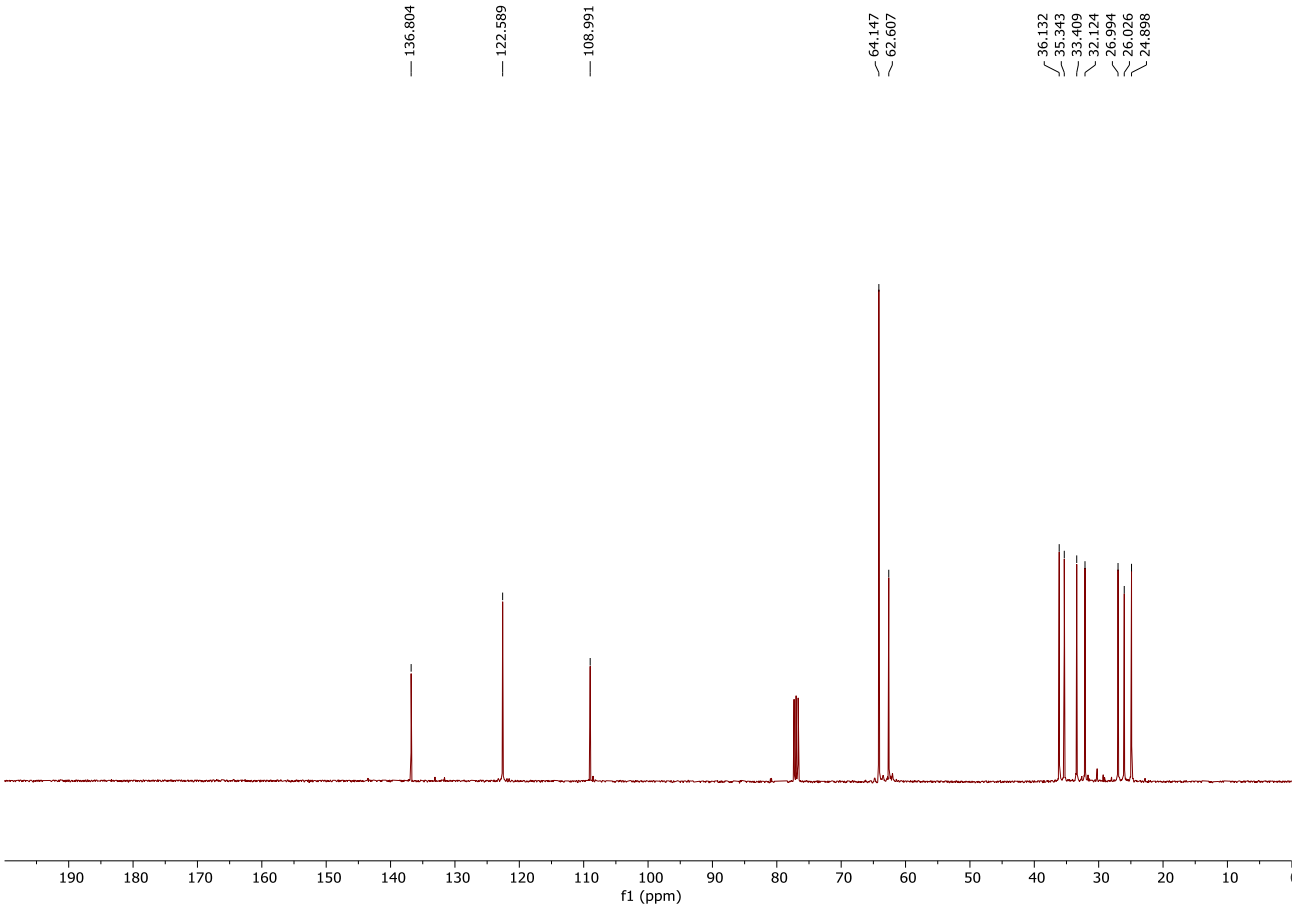
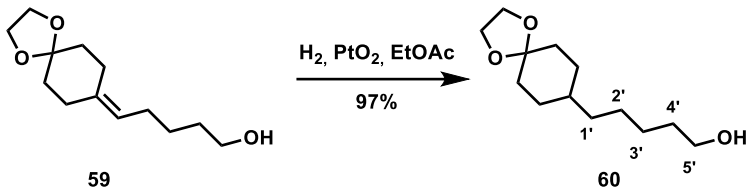
2.09
4.52
2.39
4.57
2.39
2.29
f1 (ppm)


136.804
122.589
108.991
64.147
62.607
36.132
35.343
33.409
32.124
26.994
26.026
24.898
f1 (ppm)

4-(5-Hydroxypentyl)cyclohexanone ethylene acetal (60):



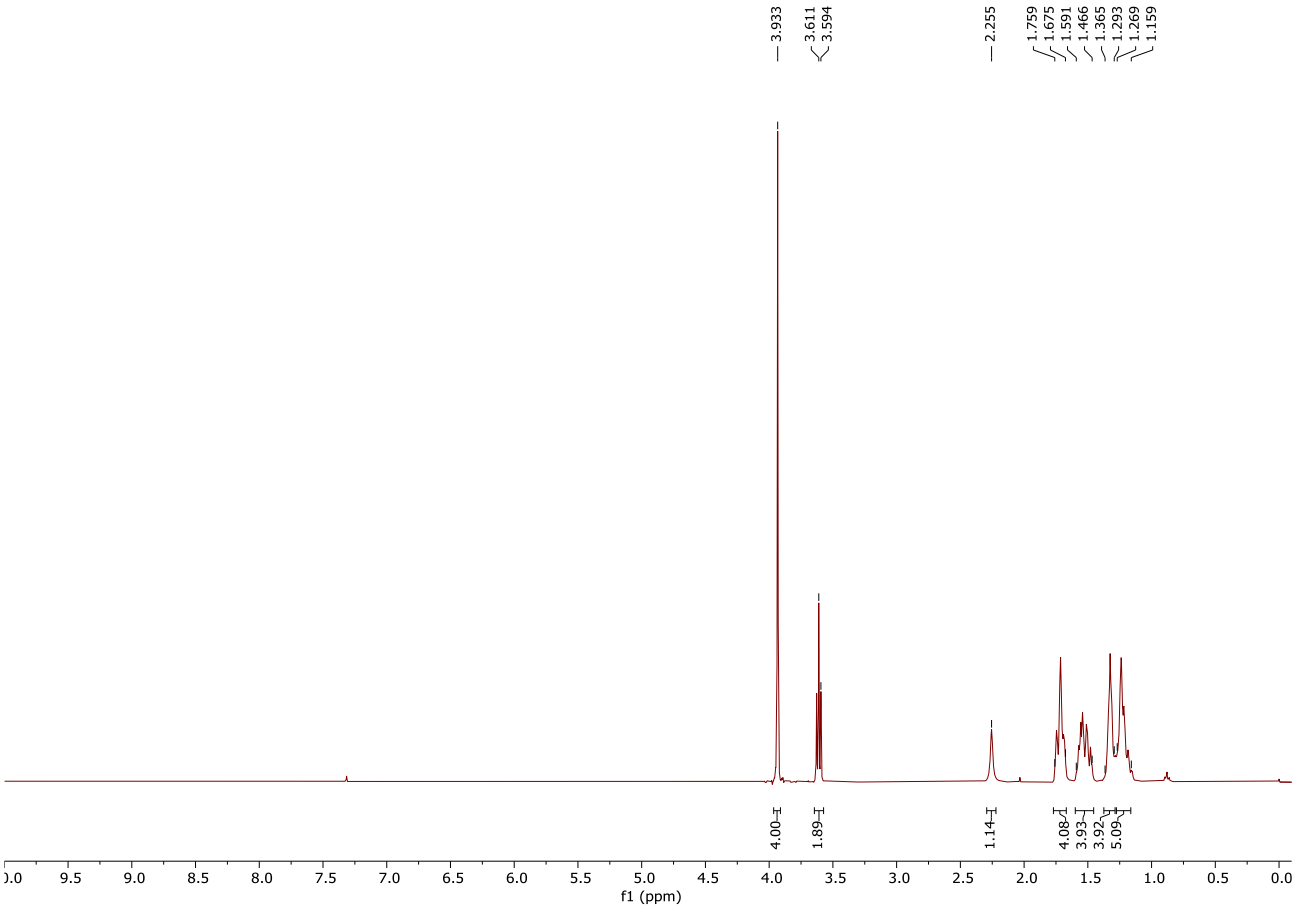
A solution of alcohol **59** (10.05 g, 44.19 mmol) in EtOAc (350 mL) containing PtO_2 (1.00 g) was stirred under hydrogen atmosphere (1 atm) at rt for 18 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated to afford alcohol **60** (10.09 g, 97%) as a colorless oil:

IR (NaCl): 3425 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 3.93 [s, 4H, $(CH_2)_2O_2$], 3.61 (t, *J* = 6.8 Hz, 2H, H-5'), 2.27 (brs, OH), 1.76-1.68 (m, 4H, H-2 and H-3), 1.60-1.47 (m, 4H, H-3 and H-4'), 1.36-1.29 (m, 5H, H-4, H-2' and H-3'), 1.27-1.16 (m, 4H, H-2 and H-2').

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 109.1 (C-1), 64.1 and 64.0 [$(CH_2)_2O_2$)], 62.7 (C-5'), 36.1 (C-4 and C-2'), 34.4 (C-3), 32.6 (C-4'), 30.1 (C-2), 26.9 (C-1'), 25.9 (C-2').

HRMS Calcd for [$C_{13}H_{24}O_3 + H^+$]: 229.1798; found 229.1801.


3.933
3.611
3.594
2.255
1.759
1.675
1.591
1.466
1.365
1.293
1.269
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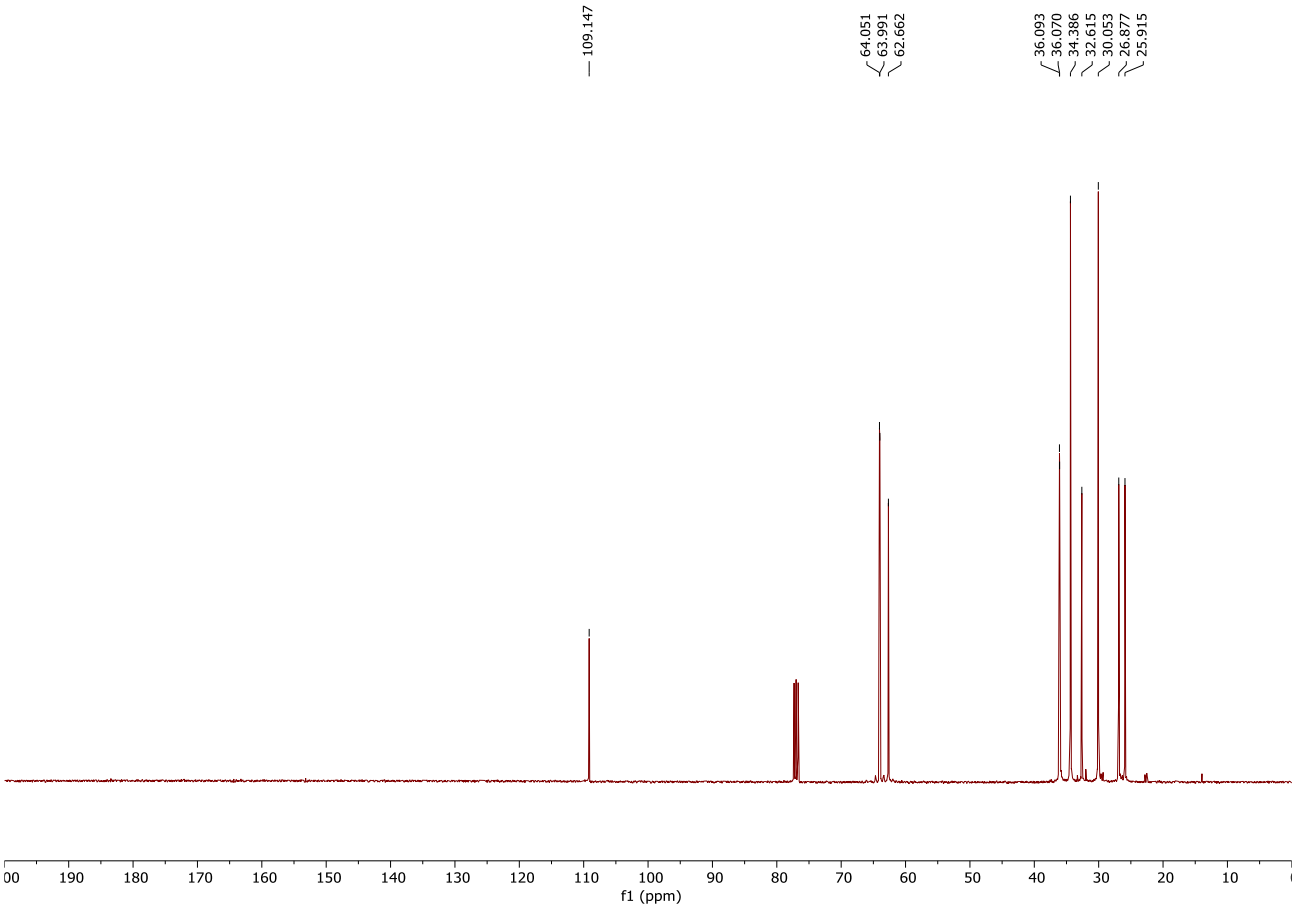
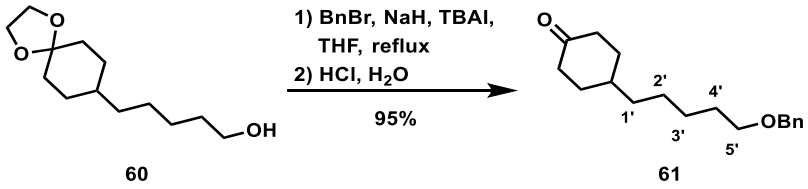
4.00
1.89
1.14
4.08
3.93
3.92
5.09
f1 (ppm)


109.147
64.051
63.991
62.662
36.093
36.070
34.386
32.615
30.053
26.877
25.915
f1 (ppm)

4-(5-Benziloxypentyl)cyclohexanone (61):



60 61

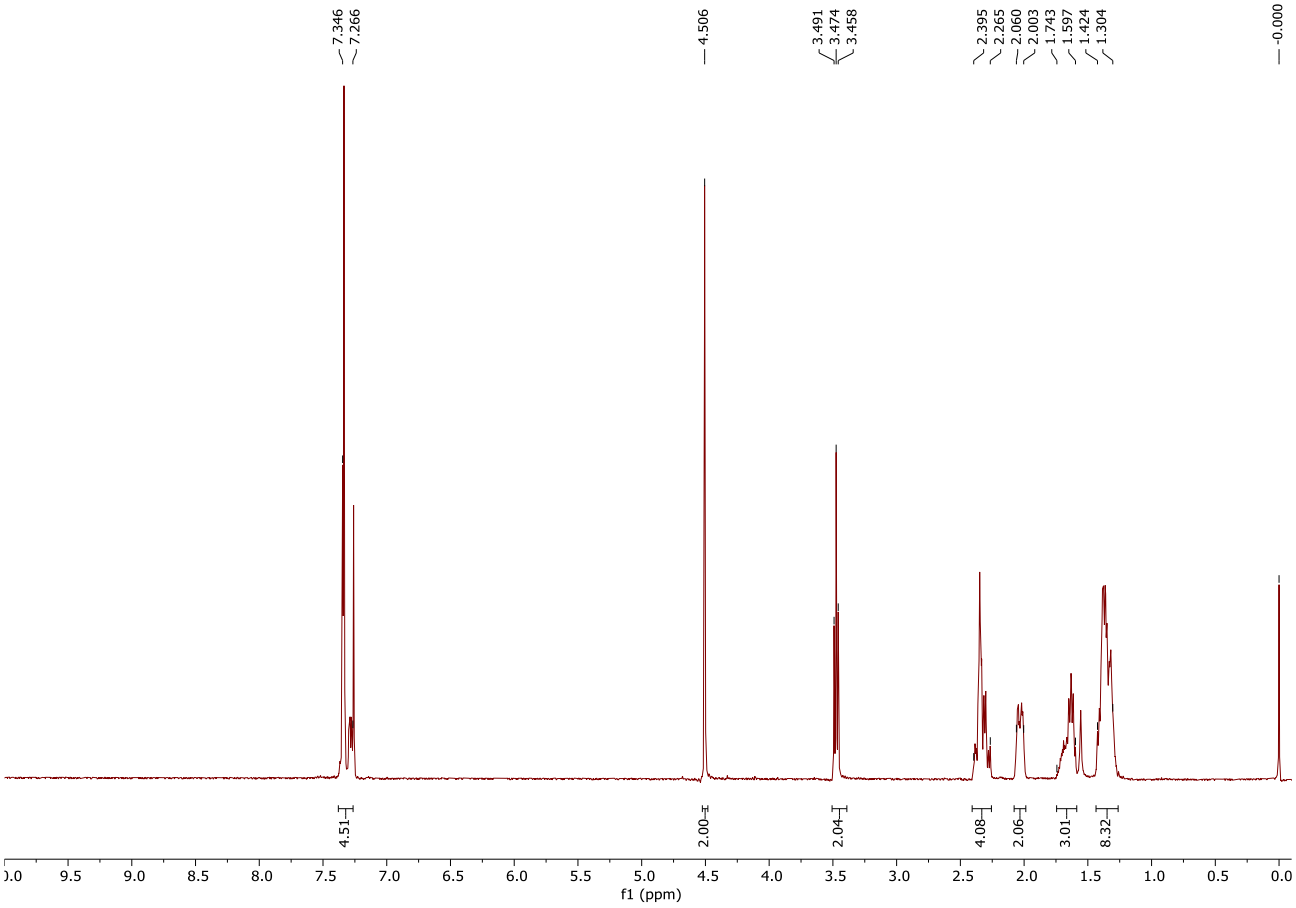
NaH (2.89 g, 108.40 mmol, 90%) was added to a solution of alcohol **60** (9.91 g, 43.36 mmol) in anhydrous THF (163 mL) and the mixture was stirred at 0 °C for 20 min. Then BnBr (6.30 mL, 52.03 mmol) and TBAI (490 mg, 1.30 mmol) were sequentially added and the mixture was heated to reflux for 24 h. Water was added to the resulting suspension and the mixture was acidified to pH 1 by addition of 6 M aqueous HCl and stirred 18 h at room temperature. The resulting mixture was extracted with Et_2O, dried and concentrated. Flash column chromatography (9:1 hexane–EtOAc) afforded ketone **61** (11.26 g, 95%) as a colourless oil:

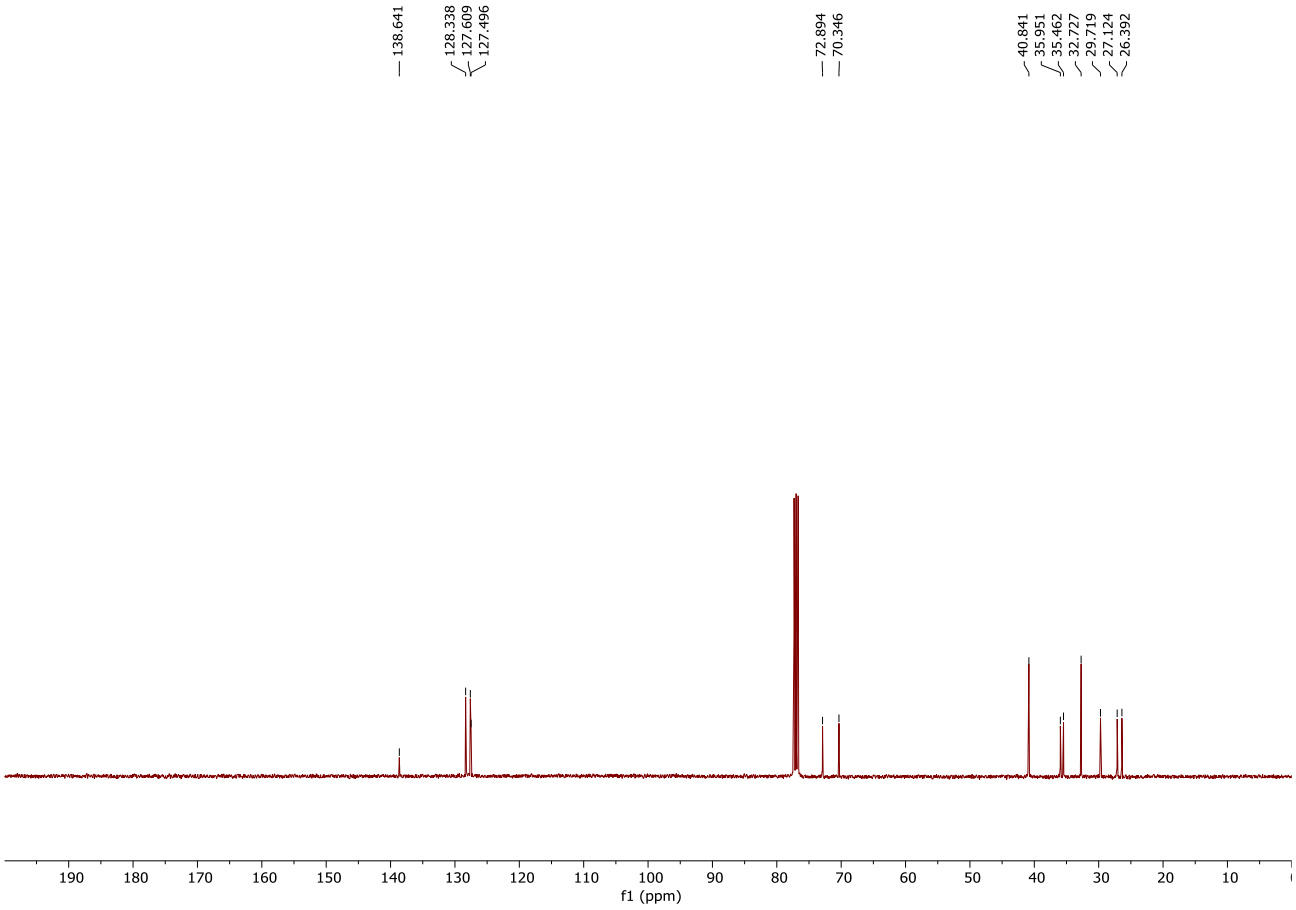
IR (NaCl): 1715 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.35-7.27 (m, 5H, ArH), 4.51 (s, 2H, CH_2Ph), 3.47 (t, *J* = 6.8 Hz, 2H, H-5'), 2.40-2.27 (m, 4H, H-2), 2.06-2.00 (m, 2H, H-3$_b$), 1.74-1.60 (m, 3H, H-4 and H-4'), 1.42-1.30 (m, 8H, H-3$_a$, H-1', H-2' and H-3').

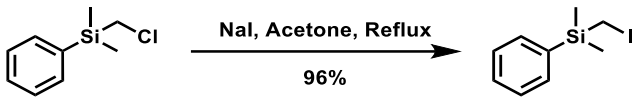
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.5 (CO), 138.6 (C-*i*), 128.3 (C-*m*), 127.6 (C-*p*), 127.5 (C-*o*), 72.9 (CH_2Ph), 70.3 (C-5'), 40.8 (C-2), 36.0 (C-4), 35.5 (C-3'), 32.7 (C-3), 29.7 (C-4'), 27.1 (C-1'), 26.4 (C-2').

HRMS Calcd for [$C_{18}H_{26}O_2$ + H^+]: 275.2006; found 275.2009.


7.346
7.266
4.506
3.491
3.474
3.458
2.395
2.265
2.060
2.003
1.743
1.597
1.424
1.304
-0.000
4.51
2.00
2.04
4.08
2.06
3.01
8.32
f1 (ppm)

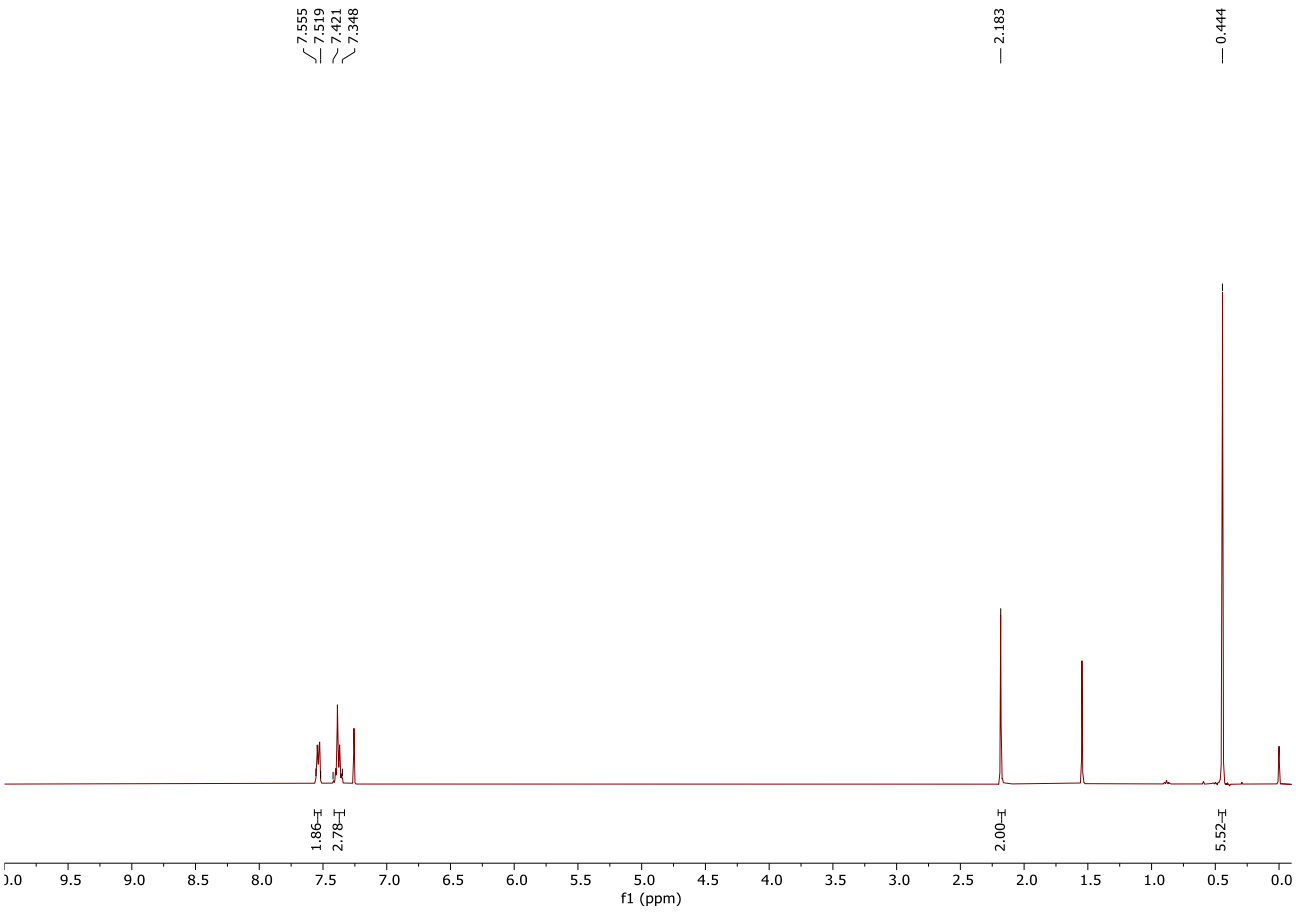

138.641
128.338
127.609
127.496
72.894
70.346
40.841
35.951
35.462
32.727
29.719
27.124
26.392
f1 (ppm)

(Iodomethyl)dimethyl(phenyl)silane:

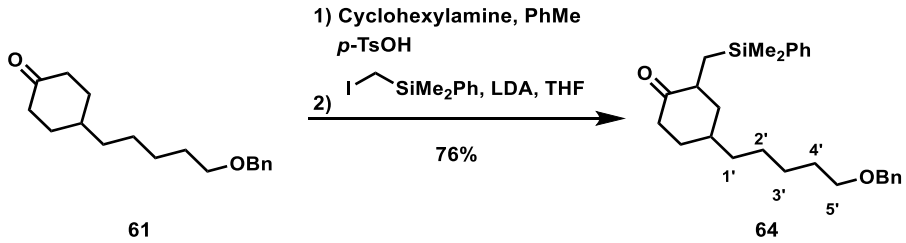


Sodium iodide (3.79 g, 25.3 mmol) was added to a solution of (chloromethyl)dimethyl(phenyl)silane (4.31 g, 22.9 mmol, 98%) in acetone (22 mL) and the mixture was heated to reflux for 24 h. Then, the mixture was cooled down and the solvent evaporated. The resulting slurry was resuspended in pentane and filtered through Celite®. The filtrate was dried and concentrated to give the corresponding iodosilane **x** (6.16 g, 96%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 2H, ArH), 7.42-7.35 (m, 3H, ArH), 2.18 (s, 2H, CH_2Si), 0.44 (s, 6H, CH_3Si).


7.555
7.519
7.421
7.348
2.183
0.444
1.86
2.78
2.00
5.52
f1 (ppm)

4-(5-Benzyloxypentyl)-2-[(dimethylphenylsilyl)methyl]cyclohexanone (64):



61 64

First Step: A mixture of ketone **61** (10.54 g, 38.44 mmol), cyclohexylamine (8.90 mL, 76.88 mmol) and *p*-TsOH (742 mg, 3.84 mmol) in anhydrous toluene (180 mL) was heated at reflux under Dean Stark conditions for 16 h. After cooling at room temperature, Et_3N was added and the resulting solution was washed with 2 M aqueous KOH, dried and concentrated. The imine was unstable and was immediately used without further purification:

Second Step: LDA (26.6 mL of a 1.59 M solution in THF/heptane/ethylbenzene, 42.28 mmol) was added dropwise to a solution of the above crude imine in anhydrous THF (32 mL) at 0 °C, and the resulting mixture was stirred at this temperature for 1 h. Then, (iodomethyl)dimethylphenylsilane (11.67 g, 42.28 mmol) was added dropwise to the mixture, and the stirring was continued for an additional 1 h. Buffer solution (50 mL; AcOH/H_2O/NaOAc 25 mL: 25 mL: 12.5 g) was added and the resulting mixture was stirred for 10 min. The separated organic layer was sequentially washed with brine and saturated aqueous $NaHCO_3$, dried, and concentrated. Flash column chromatography (95:5 hexane/EtOAc) afforded silane **64** (11.66 g, 76%, *cis:trans* mixture) as a yellowish oil.

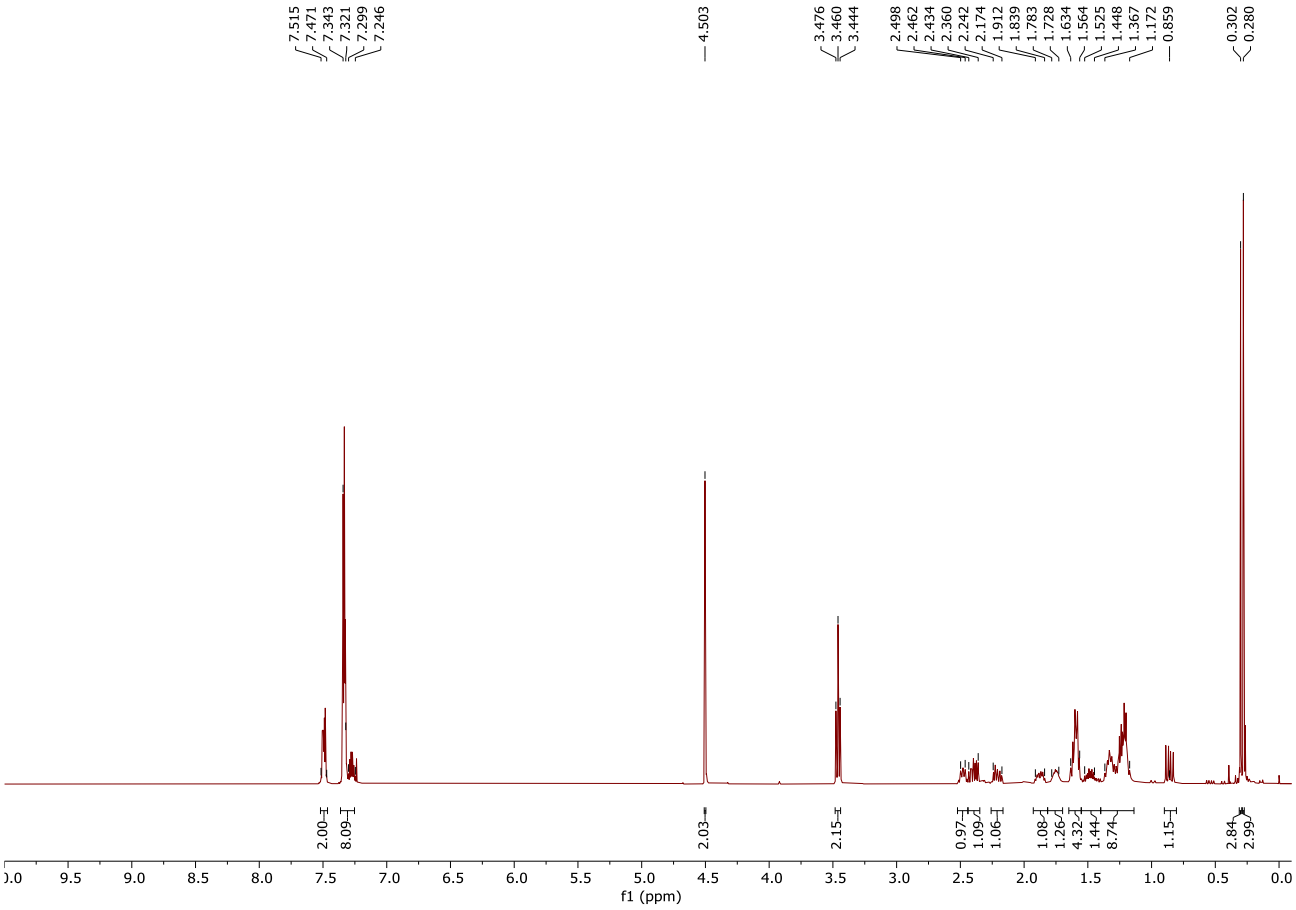
Data for the major isomer:

IR (NaCl): 1711 (CO) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.52-7.47 (m, 2H, ArH), 7.34-7.25 (m, 8H, ArH), 4.50 (s, 2H, CH_2Ph), 3.46 (t, *J* = 6.4 Hz, 2H, C-5'), 2.50-2.46 (m, 1H, H-2), 2.43-2.36 (m, 1H, H-6), 2.24-2.17 (m, 1H, H-6), 1.91-1.84 (m, 1H, H-5), 1.78-1.73 (m, 1H, H-4), 1.63-1.56 (m, 4H, C-3' and C-4'), 1.52-1.45 (m, 1H, H-5), 1.37-1.17 (m, 7H, $CH_{2a}Si$, H-3, H-2' and H-1'), 0.86 (dd, *J* = 14.8, 8.4 Hz, 1H, $CH_{2b}Si$), 0.30, 0.28 (s, 3H, CH_3Si);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.0 (CO), 138.6 and 133.5 (C-*i*), 128.9 and 128.3 (C-*m*), 127.8 (C-*p*), 127.5 and 127.4 (C-*m*), 72.8 (CH_2Ph), 70.3 (C-5'), 44.0 (C-2), 39.8 (C-3'), 37.3 (C-6), 33.9 (C-3), 32.2 (C-5), 31.3 (C-4), 29.7 (C-4'), 27.3 (C-1'), 26.3 (C-2'), 17.3 (CH_2Si), -2.2 (CH_3Si), -2.8 (CH_3Si);

HRMS Calcd for [$C_{27}H_{38}O_2Si + NH_4^+$]: 440.2979; found 440.2967.


7.515
7.471
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7.321
7.299
7.246
4.503
3.476
3.460
3.444
2.498
2.462
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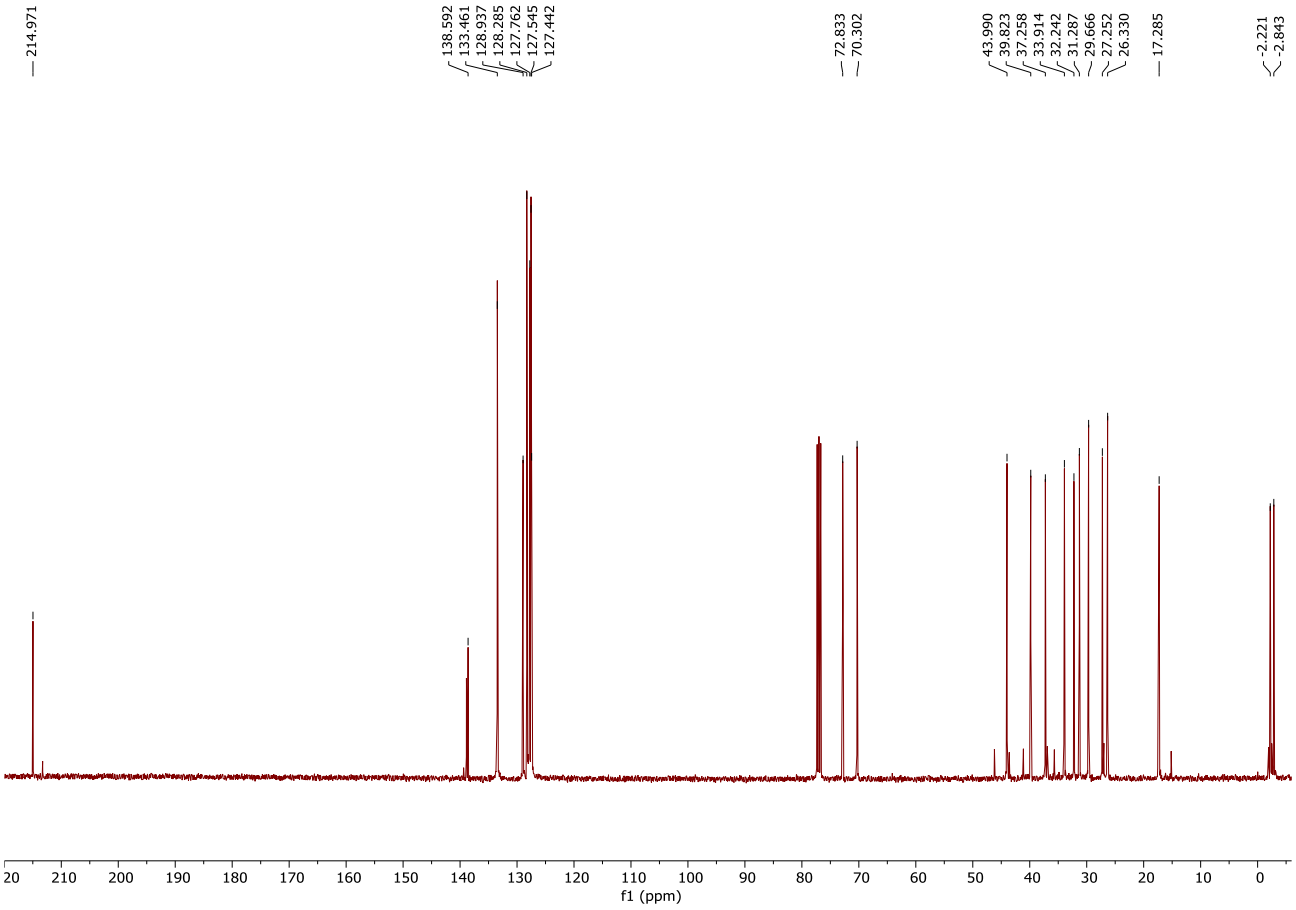
2.360
2.242
2.174
1.912
1.839
1.783
1.728
1.634
1.564
1.525
1.448
1.367
1.172
0.859
0.302
0.280
2.00
8.09
2.03
2.15
0.97
1.09
1.06
1.08
1.26
4.32
1.44
8.74
1.15
2.84
2.99
f1 (ppm)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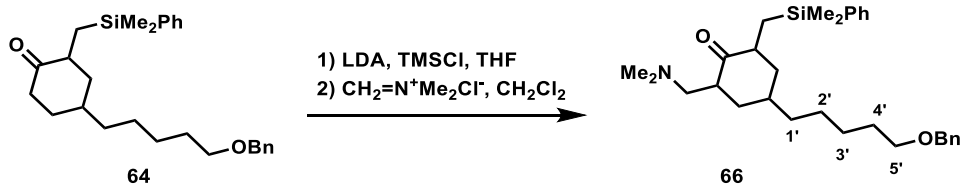
128.285
127.762
127.545
127.442
72.833
70.302
43.990
39.823
37.258
33.914
32.242
31.287
29.666
27.252
26.330
17.285
-2.221
-2.843
f1 (ppm)

4-(5-Benzyloxypentyl)-2-(*N*,*N*-dimethylaminomethyl)-6[(dimethylphenylsilyl)methyl]cyclo-hexanone (66):



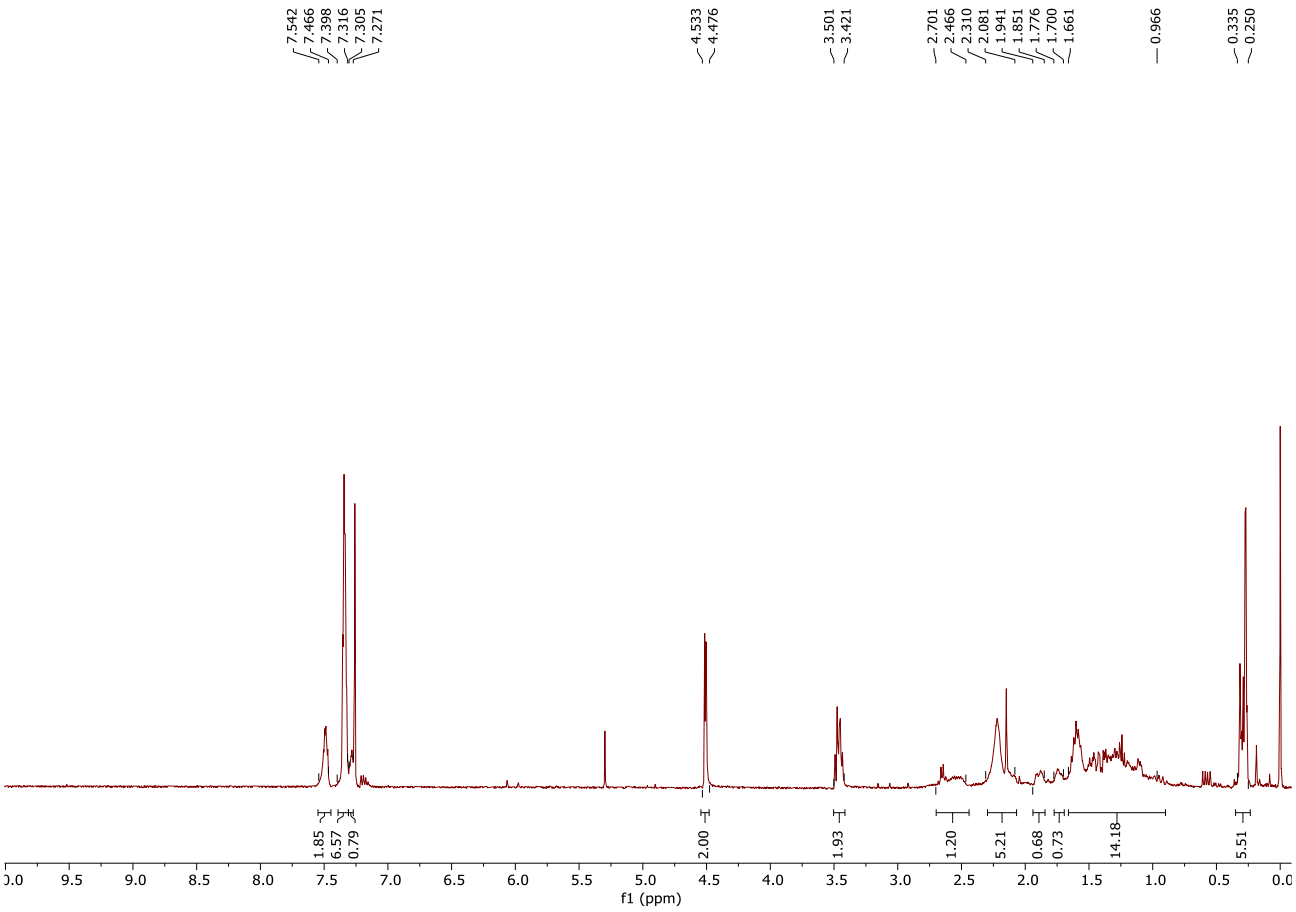
First Step: A solution of LDA (16.61 mL, 1.59 M in THF/heptane/ethylbenzene, 26.41 mmol) was added dropwise to a solution of silane **64** (11.16 g, 26.41 mmol) in anhydrous THF (23 mL) at –78 °C, and the mixture was stirred at –78 °C for 1 h. TMSCl (4.00 mL, 31.69 mmol) was added dropwise to the cold mixture, and the stirring was continued at –78 °C for 15 min and at rt for 1 h. The resulting mixture was diluted in hexane, filtered over Celite,® and concentrated to afford the crude silane **65**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 2H), 7.36-7.32 (m, 6H), 7.31-7.27 (m, 1H), 7.22-7.16 (m, 1H), 4.69-4.65 (m, 1H), 4.50 (s, 2H), 3.45 (t, *J* = 6.8 Hz, 2H), 2.12-1.95 (m, 1H), 1.63-1.48 (m, 6H), 1.31-1.09 (m, 8H), 0.78 (dd, *J* = 14.8, 10.8 Hz, 1H), 0.30 (s, 3H), 0.29 (s, 3H), 0.15 (s, 9H).

Second Step: N,*N*-Dimethylmethyleneiminium chloride (2.47 g, 26.41 mmol) was added to a solution of the above crude silane in CH_2Cl_2 (30 mL) and the mixture was stirred at room temperature until the complete dissolution of the salt (16 h). 2 M aqueous HCl was added until pH 4, and the stirring was continued for an additional 1 h. Saturated aqueous $NaHCO_3$ was added until basic pH and the stirring was continued for 15 min. The biphasic mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated to afford crude amine **66** as a mixture of diastereomers.

Data for the major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.47 (m, 2H), 7.40-7.32 (m, 7H), 7.30-7.27 (m, 1H), 4.53-4.48 (m, 2H), 3.50-3.42 (m, 2H), 2.70-2.47 (m, 2H), 2.31-2.08 (m, 6H), 1.94-1.85 (m, 1H), 1.78- 1.70 (m, 1H), 1.66-0.97 (m, 15H), 0.34-0.25 (m, 6H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 216.2, 141.6, 141.0, 135.9, 131.2, 130.7, 130.1, 130.0, 129.9, 75.2, 72.8, 61.2, 48.1, 46.4, 45.1, 44.2, 40.0, 34.9, 34.2, 32.1, 30.3, 28.7, 17.2, 0.5, 0.0.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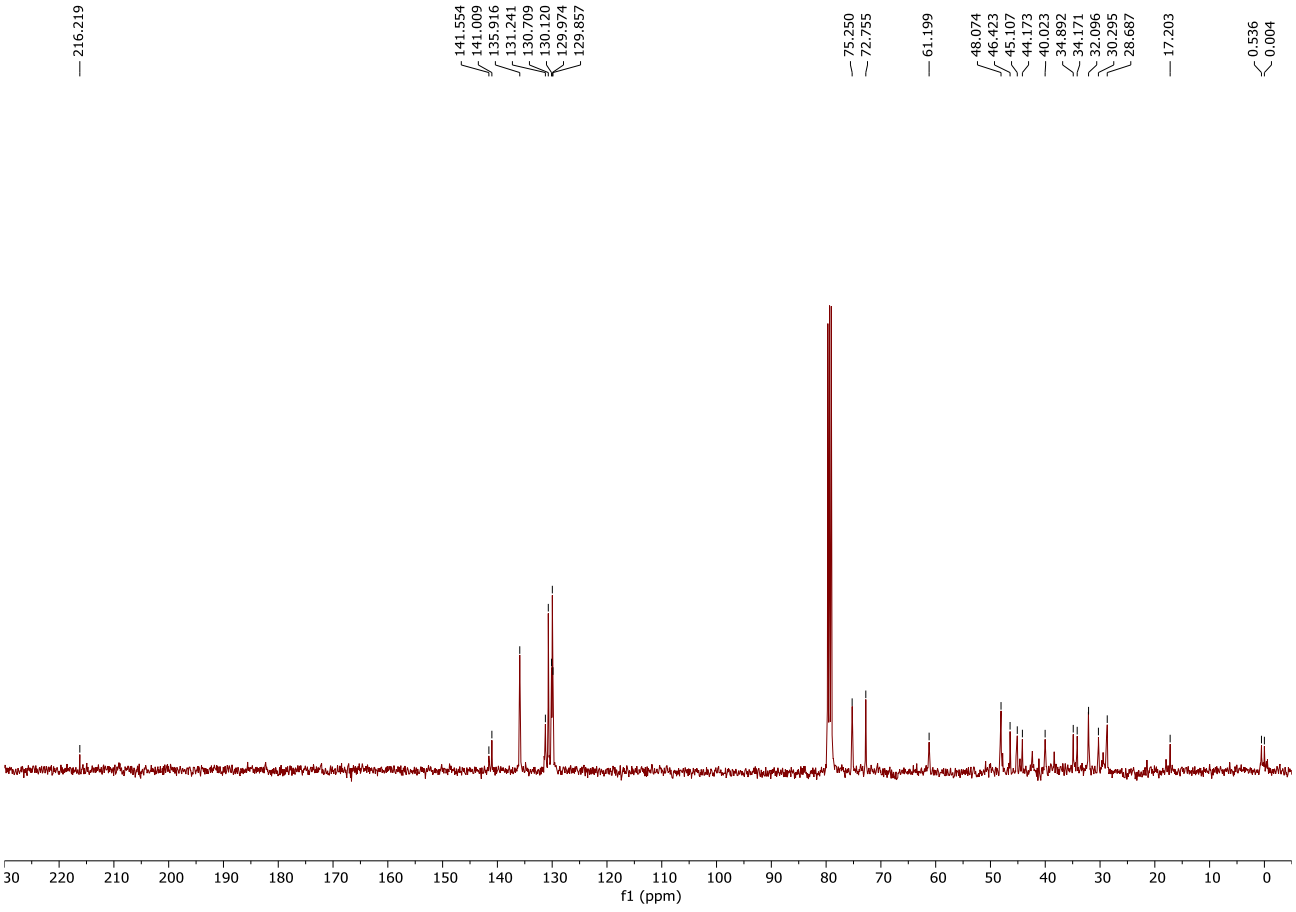
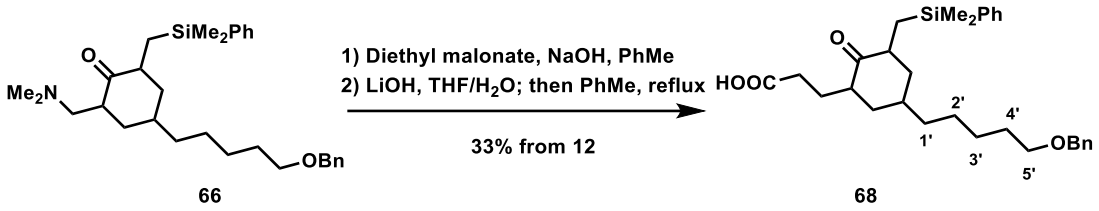
7.398
7.316
7.305
7.271
4.533
4.476
3.501
3.421
2.701
2.466
2.310
2.081
1.941
1.851
1.776
1.700
1.661
0.966
0.335
0.250
1.85
6.57
0.79
2.00
1.93
1.20
5.21
0.68
0.73
14.18
5.51
f1 (ppm)


216.219
141.554
141.009
135.916
131.241
130.709
130.120
129.974
129.857
75.250
72.755
61.199
48.074
46.423
45.107
44.173
40.023
34.892
34.171
32.096
30.295
28.687
17.203
0.536
0.004
f1 (ppm)

5-(Benzyloxypentyl)-3-[(dimethylphenylsilyl)methyl]-2-oxocyclohexanepropionic acid (68):



First Step: NaOH (422 mg, 10.56 mmol) and diethyl malonate (4.23 g, 26.41 mmol) were added to a solution of the above amine **66** in anhydrous toluene (20 mL) and the mixture was heated to reflux temperature for 24 h. Then, the mixture was cooled down and the solvent was evaporated.

Second Step: $LiOH \cdot H_2O$ (10.43 g, 211.28 mmol) was added to a solution of the above crude in THF/H_2O (1:3, 200 mL), and the mixture was stirred at room temperature for 16 h. Then, pH was adjusted to 2-3 by addition of 4 M aqueous HCl, and the mixture was extracted with CH_2Cl_2. The extracts were dried and concentrated, and the resulting residue was resuspended in toluene (100 mL). The mixture was heated to reflux for 2 h, cooled, and concentrated. Flash column chromatography (9:1 to 6:4 hexane/EtOAc) afforded a diastereoisomeric mixture of ketoacids **68** (4.29 g, 33% from **64**) as a yellowish oil.

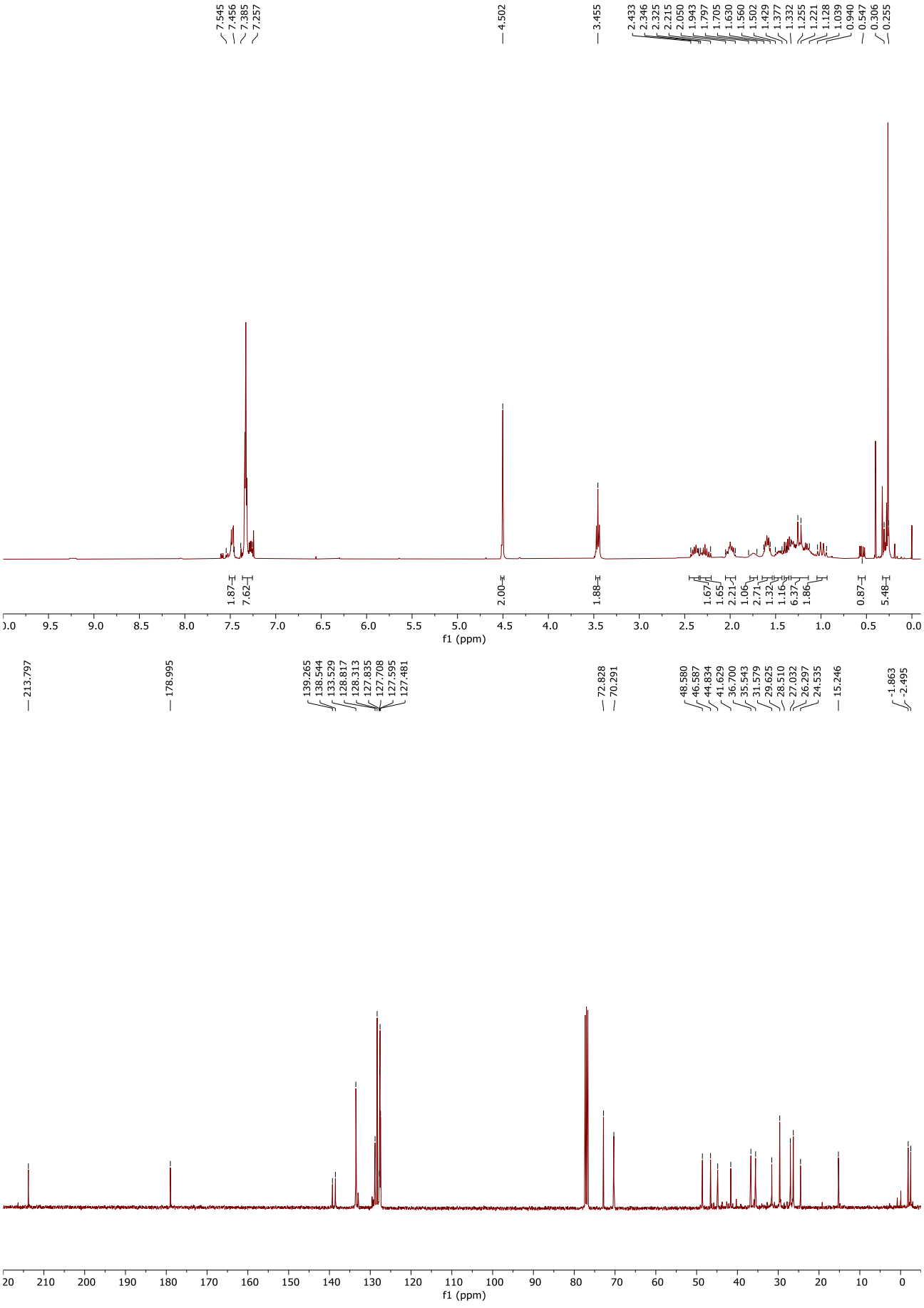
Data for the major isomer:

IR (NaCl): 1710 (CO) cm^{-1};

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.55-7.46 (m, 2H, ArH), 7.39-7.26 (m, 8H, ArH), 4.50 (s, 2H, CH_2Ph), 3.45 (t, *J* = 6.4 Hz, 2H, H-5'), 2.43-2.35 (m, 2H, $CH_2CH_{2a}CO_2H$ and H-3), 2.33-2.16 (m, 2H, $CH_2CH_{2b}CO_2H$ and H-1), 2.05-1.94 (m, 3H, $CH_{2a}CH_2CO_2H$, H-4_a and H-6_a), 1.80-1.71 (m, 1H, H-5), 1.63-1.56 (m, 2H, H-4'), 1.50-1.43 (m, 1H, H-4_b), 1.38 (dd, *J* = 15.2, 6.8 Hz, 1H, $CH_{2a}Si$), 1.33-1.29 (m, 6H, H-1', H-2' and H-3'), 1.04-0.94 (m, 2H, $CH_{2b}CH_2CO_2H$ and H-6_b), 0.55 (dd, *J* = 15.2, 6.4 Hz, 1H, $CH_{2b}Si$), 0.26-0.31 [m, 6H, $(CH_3)_2Si$];

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.8 (CO), 179.0 (CO_2H), 139.3 (Cq-Ar), 138.5 (Cq-Ar), 133.5 (CH-Ar), 128.8 (CH-Ar), 128.3 (CH-Ar), 127.8 (CH-Ar), 127.7 (CH-Ar), 127.6 (CH-Ar), 127.5 (CH-Ar), 72.8 (CH_2Ph), 70.3 (C-5'), 48.6 (C-1), 46.6 (C-3), 44.8 (C-6), 41.6 ($CH_2CH_2CO_2H$), 36.7 (C-5), 35.5 (C-3'), 31.6 ($CH_2CH_2CO_2H$), 29.6 (C-4'), 27.0 (C-1'), 26.3 (C-2'), 24.5 (C-4), 15.2 (CH_2Si), –1.9 (CH_3Si), –2.5 (CH_3Si);

HRMS Calcd for [$C_{30}H_{42}O_4Si - H^+$]: 493.2780; found 493.2781.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7.385
7.257
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3.455
2.433
2.346
2.325
2.215
2.050
1.943
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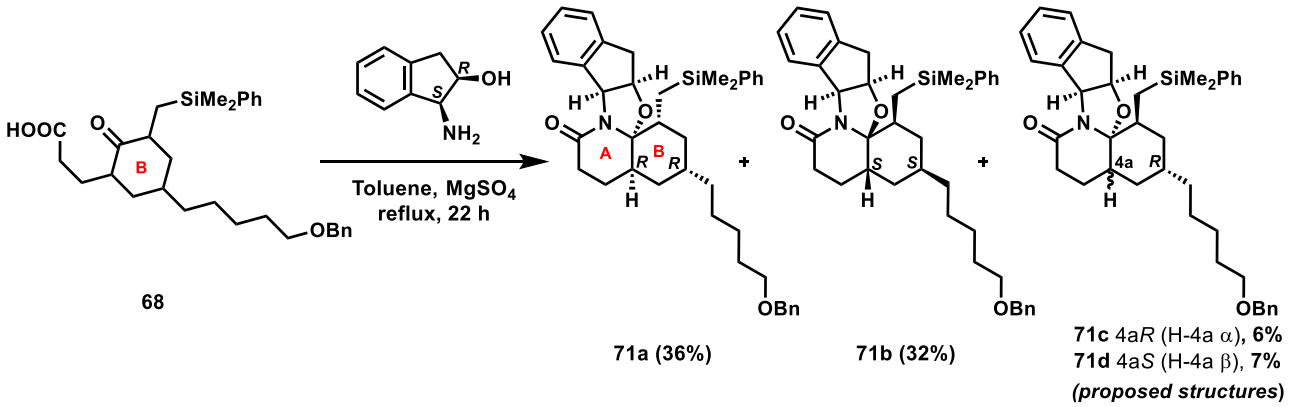
1.705
1.630
1.560
1.502
1.429
1.377
1.332
1.255
1.221
1.128
1.039
0.940
0.547
0.306
0.255
1.87
7.62
2.00
1.88
1.67
1.65
2.21
1.06
2.71
1.32
1.16
6.37
1.86
0.87
5.48
f1 (ppm)
213.797
178.995
139.265
138.544
133.529
128.817
128.313
127.835
127.708
127.595
127.481
72.828
70.291
48.580
46.587
44.834
41.629
36.700
35.543
31.579
29.625
28.510
27.032
26.297
24.535
15.246
1.863
2.495
f1 (ppm)

(1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)- and (1*S*,3*S*,4a*S*,8a*S*,13a*R*,14a*S*)-3-(5-Benzyloxypentyl)-1-[(dimethyl-phenylsilyl)methyl]-7-oxoperhydroindeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (71a and 71b):



(1*S*,2*R*)-(–)-*cis*-1-Amino-2-indanol (1.09 g, 7.02 mmol) and anhydrous $MgSO_4$ (1.18 g) were added to a solution of ketoacid **68** (2.32 g, 4.68 mmol) in anhydrous toluene (54 mL). The mixture was heated at reflux for 16 h. After cooling, the solvent was evaporated and the residue was resuspended in EtOAc and washed with saturated aqueous $NaHCO_3$. The organic phase was dried and concentrated. Flash column chromatography (9:1 to 7:3 hexane/EtOAc) afforded lactams **71a** (1.00 g, 36%), **71b** (897 mg, 32%), **71c** (167 mg, 6%), and **71d** (198 mg, 7%) as yellowish oils.

71a:

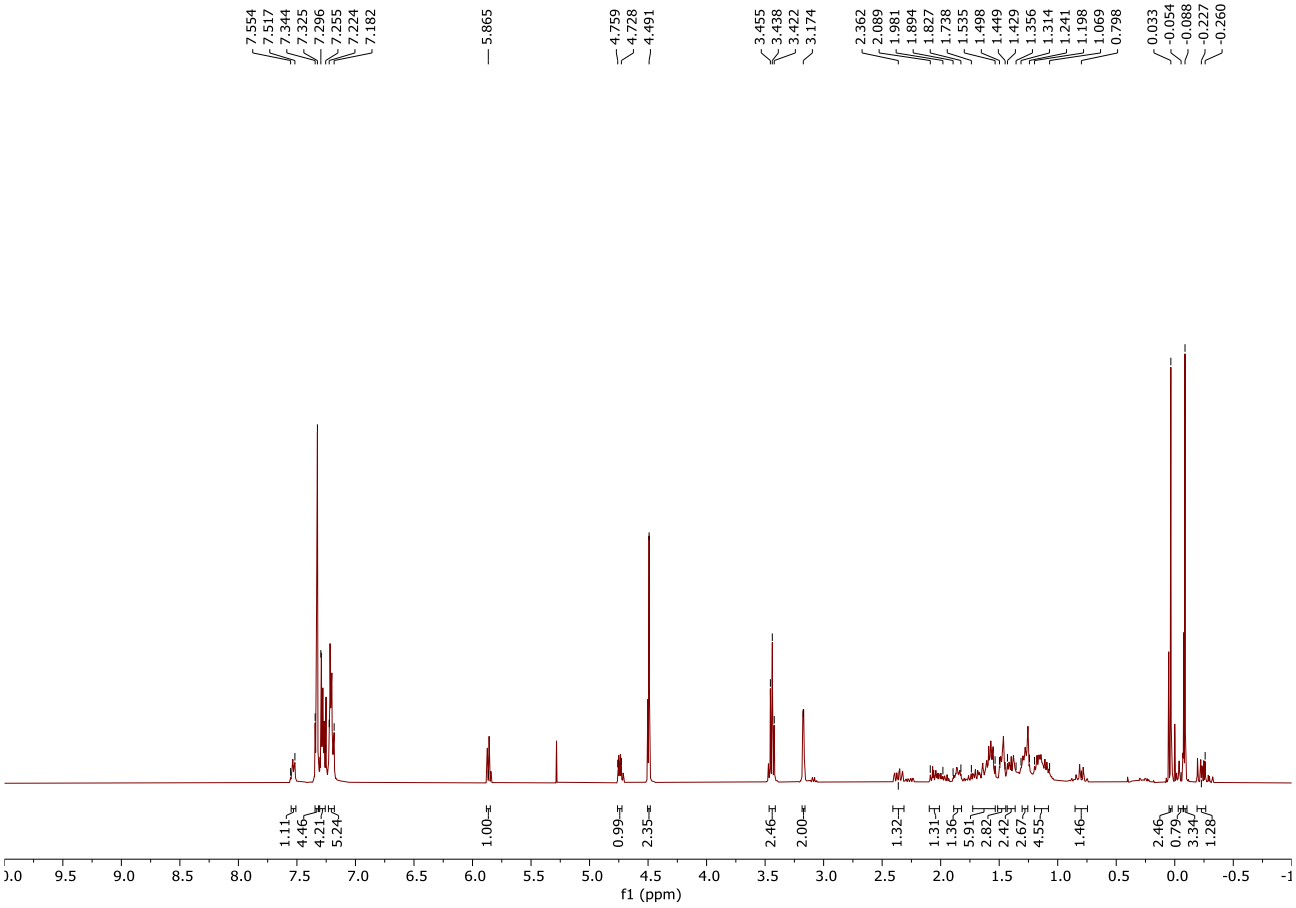
$[\alpha]^{23}_D$ + 90.3 (*c* 1.1, $CHCl_3$).

IR (NaCl): 1651 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.55-7.52 (m, 1H, ArH), 7.34-7.33 (m, 4H, ArH), 7.30-7.25 (m, 4H, ArH), 7.22-7.18 (m, 5H, ArH), 5.87 (d, *J* = 6.4 Hz, 1H, H-8a), 4.76-4.73 (m, 1H, H-13a), 4.49 (s, 2H, CH_2Ph), 3.44 (t, *J* = 6.8 Hz, 2H, H-5'), 3.17 (m, 2H, H-13), 2.36 (ddd, *J* = 17.2, 9.6 and 2.8 Hz, 1H, H-6_a), 2.09-1.98 (m, 1H, H-6_b), 1.89-1.83 (m, 1H, H-4a), 1.74-1.54 (m, 4H, H-4' and H-5), 1.50-1.45 (m, 3H, H-3 and H-4), 1.43-1.36 (m, 2H, H-1 and H-2_{ec}), 1.31-1.24 (m, 2H, H-2'), 1.20-1.07 (m, 4H, H-1' and H-3'), 0.80 (q, *J* = 13.6 Hz, 1H, H-2_{ax}), 0.03 (s, 3H, CH_3Si), –0.05 (dd, *J* = 15.2, 2.0 Hz, 1H, $CH_{2a}Si$), –0.09 (s, 3H, CH_3Si), –0.23 (dd, *J* = 15.2, 11.2 Hz, 1H, $CH_{2b}Si$).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.2 (CO), 141.7 (C-Ar), 141.0 (C-Ar), 133.3 (CH-Ar), 128.7 (CH-Ar), 128.3 (CH-Ar), 128.3 (CH-Ar), 127.6 (CH-Ar), 127.6 (CH-Ar), 127.4 (CH-Ar), 127.4 (CH-Ar), 126.4 (CH-Ar), 124.9 (CH-Ar), 99.4 (C-14a), 77.7 (C-13a), 72.8 (CH_2Ph), 70.4 (C-5'), 66.1 (C-8a), 38.7 (C-4a), 38.1 (C-13), 37.1 (C-2), 36.3 (C-3'), 35.8 (C-3), 33.6 (C-4), 30.8 (C-1), 29.7 (C-4'), 28.3 (C-6), 26.8 (C-1'), 26.3 (C-2'), 19.7 (C-5), 14.2 (CH_2Si), –2.3 (CH_3Si), –2.6 (CH_3Si).

HRMS Calcd for [$C_{39}H_{49}NO_3Si$ + H^+]: 608.3554; found 608.3546.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3.455
3.438
3.422
3.174
2.362
2.089
1.981
1.894
1.827
1.738
1.535
1.498
1.449
1.429
1.356
1.314
1.241
1.198
1.069
0.798
0.033
-0.054
-0.088
-0.227
-0.260
1.11
4.46
4.21
5.24
1.00
0.99
2.35
2.46
2.00
1.32
1.31
1.36
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2.42
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2.46
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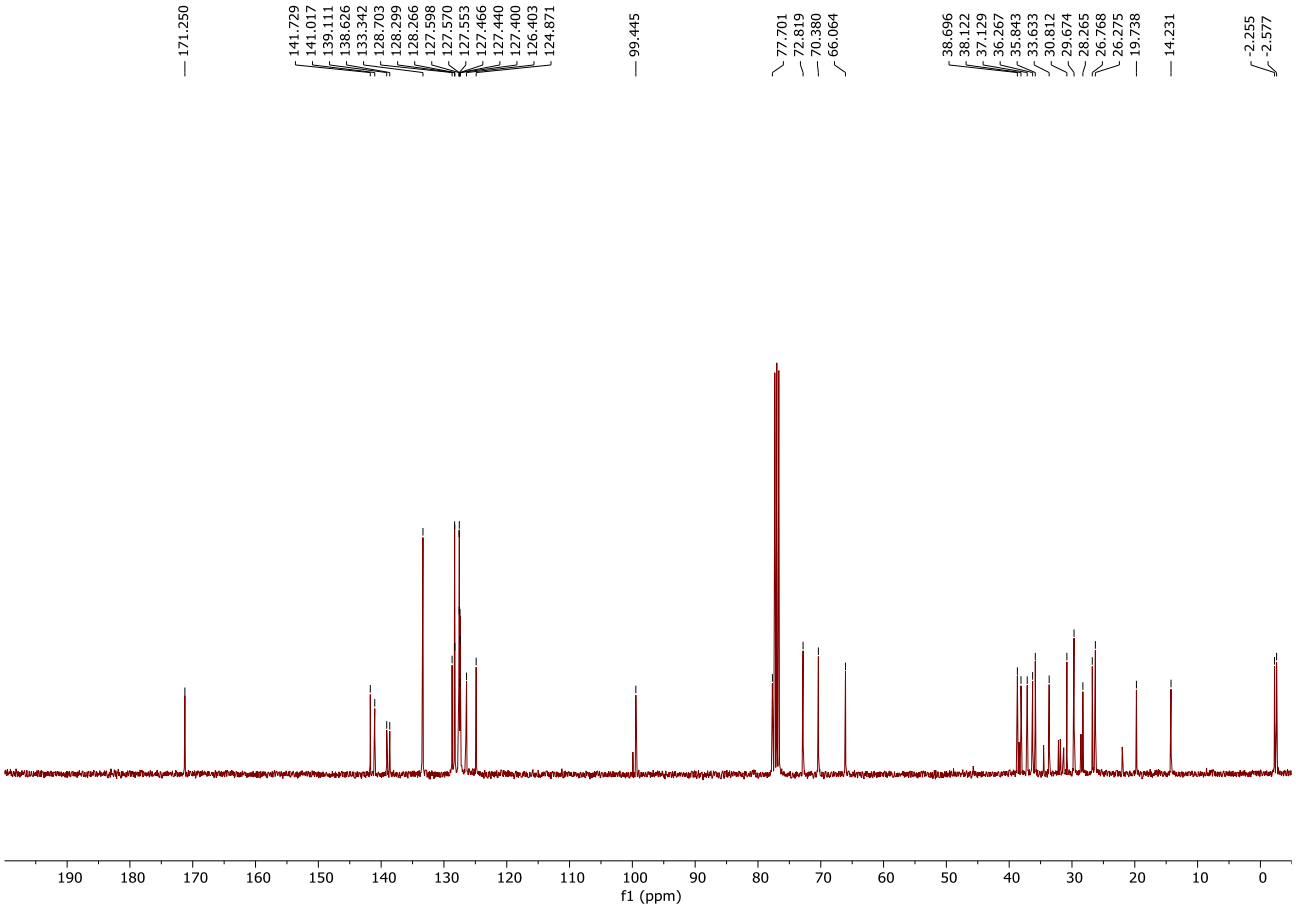
3.34
1.28
f1 (ppm)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126.403
124.871
99.445
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72.819
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38.696
38.122
37.129
36.267
35.843
33.633
30.812
29.674
28.265
26.768
26.275
19.738
14.231
-2.255
-2.577
f1 (ppm)

71b:

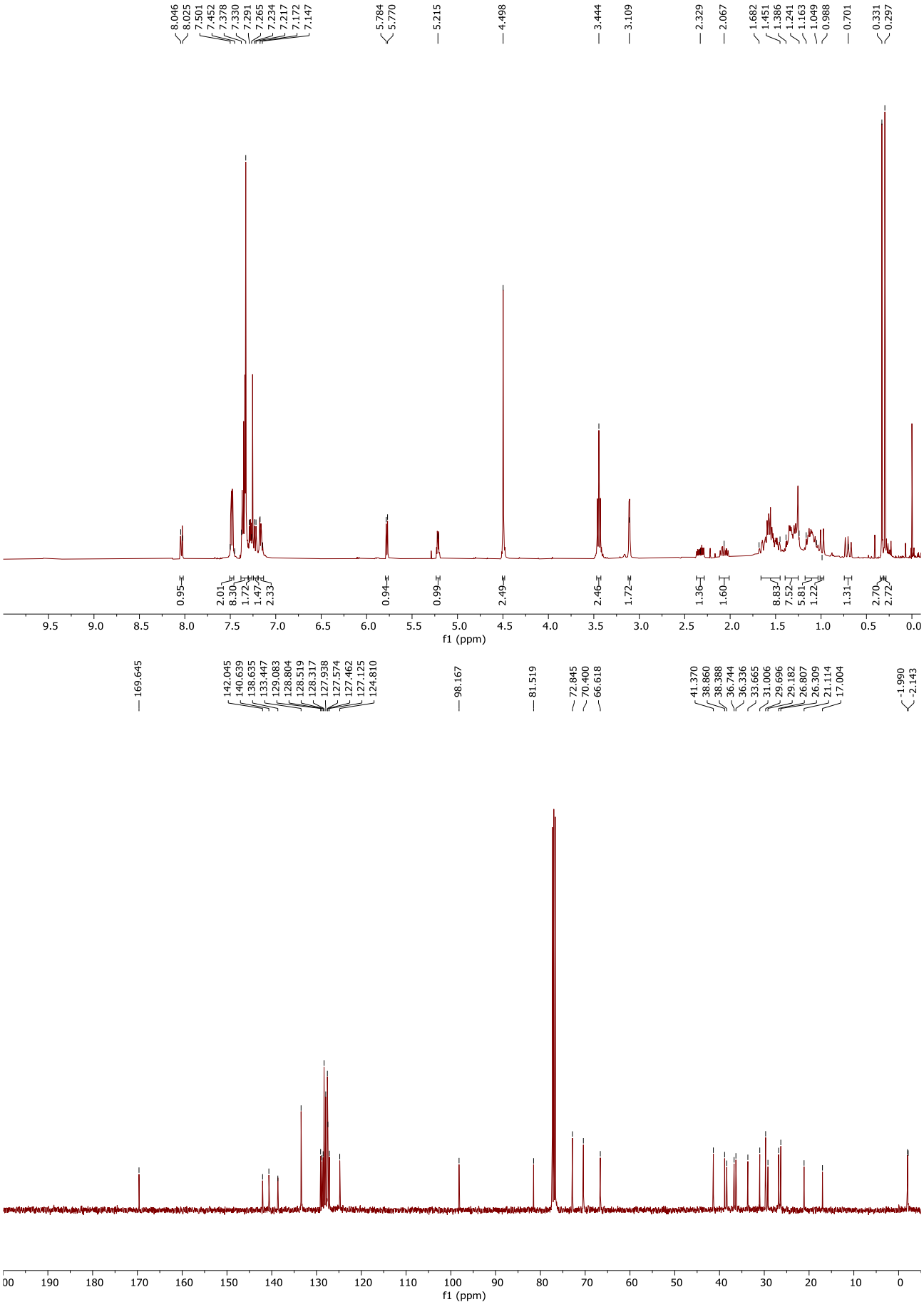
$[\alpha]^{23}_{D}$ + 38.0 (*c* 0.6, $CHCl_3$).

IR (NaCl): 1658 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 8.04 (d, *J* = 8.4 Hz, 1H, ArH), 7.50-7.47 (m, 2H, ArH), 7.38-7.33 (m, 7H, ArH), 7.29-7.27 (m, 1H, ArH), 7.24-7.21 (m, 1H, ArH), 7.18-7.14 (m, 2H, ArH), 5.78 (d, *J* = 5.8 Hz, 1H, H-8a), 5.22 (dt, *J* = 5.8, 3.4 Hz, 1H, H-13a), 4.50 (s, 2H, CH_2Ph), 3.44 (t, *J* = 6.8 Hz, 2H, CH_2OBn), 3.11 (d, *J* = 3.4 Hz, 2H, H-13), 2.33 (ddd, *J* = 18.0, 9.2, 4.4 Hz, 1H, H-6_a), 2.07 (ddd, *J* = 18.0, 10.0, 6.4 Hz, 1H, H-6_b), 1.68-1.45 (m, 7H, H-1, H-2_a, H-4', H-4a and H-5), 1.39-1.24 (m, 5H, H-2', H-3 and H-4), 1.16-1.05 (m, 5H, H-1', H-2_b, and H-3'), 0.99 (dd, *J* = 14.0, 1.6 Hz, 1H, CH_{2a}Si), 0.7 (dd, *J* = 14.0, 12.4 Hz, 1H, CH_{2b}Si), 0.33 (s, 3H, CH_3Si), 0.30 (s, 3H, CH_3Si).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.6 (CO), 142.0, 140.6 (C-Ar), 138.6 (C-Ar), 133.4 (CH-Ar), 129.1 (CH-Ar), 128.8 (CH-Ar), 128.5 (CH-Ar), 128.3 (CH-Ar), 127.9 (CH-Ar), 127.6 (CH-Ar), 127.5 (CH-Ar), 127.1 (CH-Ar), 124.8 (CH-Ar), 98.2 (C-14a), 81.5 (C-13a), 72.8 (CH_2Ph), 70.4 (C-5'), 66.6 (C-8a), 41.4 (C-4a), 38.9 (C-1), 38.4 (C-13), 36.7 (C-2), 36.3 (C-3'), 33.7 (C-4), 31.0 (C-3), 29.7 (C-4'), 29.2 (C-6), 26.8 (C-1'), 26.3 (C-2'), 21.1 (C-5), 17.0 (CH_2Si), –2.0 (CH_3Si), –2.1 (CH_3Si).

HRMS Calcd for [$C_{39}H_{49}NO_3Si + H^+$]: 608.3554; found 608.3531.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7.172
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5.770
5.215
4.498
3.444
3.109
2.329
2.067
1.682
1.451
1.386
1.241
1.163
1.049
0.988
0.701
0.331
0.297
0.95
2.01
8.30
1.72
1.47
2.33
0.94
0.99
2.49
2.46
1.72
1.36
1.60
8.83
7.52
5.81
1.22
1.31
2.70
2.72
f1 (ppm)
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142.045
140.639
138.635
133.447
129.083
128.804
128.519
128.317
127.938
127.574
127.462
127.125
124.810
98.167
81.519
72.845
70.400
66.618
41.370
38.860
38.388
36.744
36.336
33.665
31.006
29.696
29.182
26.807
26.309
21.114
17.004
-1.990
-2.143
f1 (ppm)

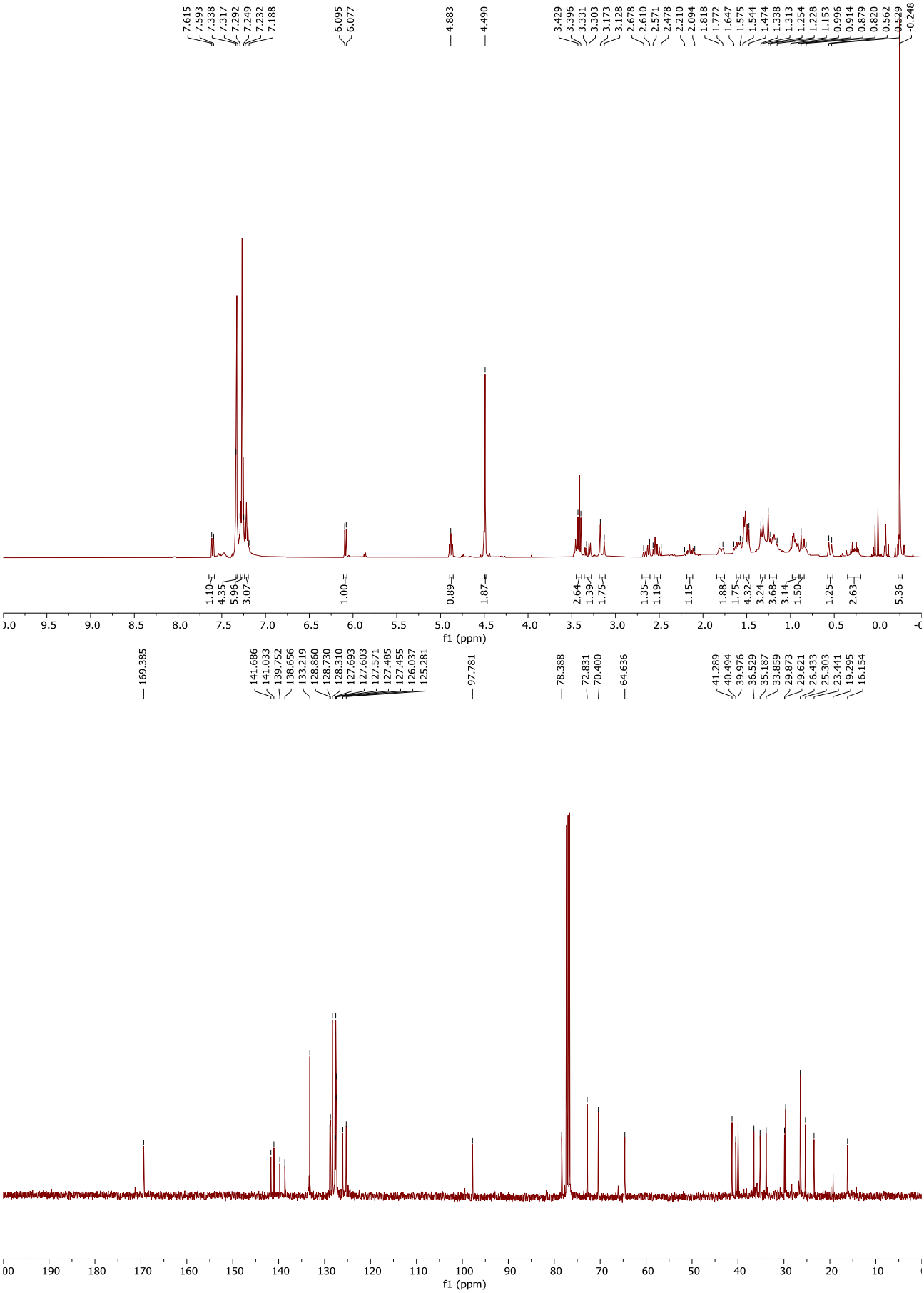
71d:

IR (NaCl): 1645 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.60 (d, *J* = 7.2 Hz, 1H, ArH), 7.32-7.34 (m, 4H, ArH), 7.25-7.29 (m, 6H, ArH), 7.20-7.23 (m, 3H, ArH), 6.08 (d, *J* = 6.8 Hz, 1H, H-8a), 4.88 (td, *J* = 6.8, 1.6 Hz, 1H, H-13a), 4.49 (s, 2H, CH_2Ph), 3.41 (t, *J* = 6.4 Hz, 2H, H-5'), 3.32 (dd, *J* = 18.0, 6.8 Hz, 1H, H-13_b), 3.13-3.17 (m, 1H, H-13_a), 2.65 (dd, *J* = 18.8, 8.8 Hz, 1H, H-6_b), 2.48-2.57 (m, 1H, H-6_a), 2.09-2.21 (m, 1H, H-5_b), 1.76-1.82 (m, 1H, C-4a), 1.58-1.65 (m, 1H, H-5_a), 1.46-1.54 (m, 5H, H-3, H-3', H-4'), 1.15-1.39 (m, 5H, H-1, H-2' and H-4), 0.91-0.98 (m, 4H, C-1' and C-2), 0.85 (d, *J* = 13.6 Hz, 1H, $CH_{2b}Si$), 0.54 (d, *J* = 13.6 Hz, 1H, $CH_{2a}Si$), –0.25 [s, 6H, $(CH_3)_2Si$].

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.4 (CO), 141.7 (C-Ar), 141.0 (C-Ar), 139.8 (C-Ar), 138.7 (C-Ar), 133.2 (CH-Ar), 128.9 (CH-Ar), 128.7 (CH-Ar), 128.3 (CH-Ar), 127.7 (CH-Ar), 127.6 (CH-Ar), 127.6 (CH-Ar), 127.5 (CH-Ar), 127.5 (CH-Ar), 126.0 (CH-Ar), 125.3 (CH-Ar), 97.8 (C-14a), 78.4 (C-13a), 72.8 (CH_2Ph), 70.4 (C-5'), 64.6 (C-8a), 41.3 (C-1), 40.5 (C-13), 40.0 (C-4a), 36.5 (C-2), 35.2 (C-3'), 33.9 (C-4), 29.9 (C-6), 29.6 (C-4'), 26.4 (C-1' and C-2'), 23.4 (C-5), 19.3 (C-3), 16.2 (CH_2Si), –2.4 (CH_3Si), –4.3 (CH_3Si).

HRMS calcd for [$C_{39}H_{49}NO_3Si + H^+$] 608.3554; found 608.3573.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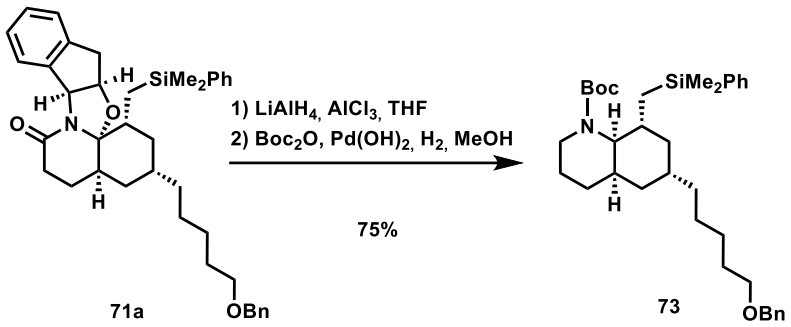
3.396
3.331
3.303
3.173
3.128
2.678
2.610
2.571
2.478
2.210
2.094
1.818
1.772
1.647
1.575
1.544
1.474
1.338
1.313
1.254
1.228
1.153
0.996
0.914
0.879
0.820
0.562
0.529
-0.248
1.10
4.35
5.96
3.07
1.00
0.89
1.87
2.64
1.39
1.75
1.35
1.19
1.15
1.88
1.75
4.32
3.24
3.68
3.14
1.50
1.25
2.63
5.36
f1 (ppm)
169.385
141.686
141.033
139.752
138.656
133.219
128.860
128.730
128.310
127.693
127.603
127.571
127.485
127.455
126.037
125.281
97.781
78.388
72.831
70.400
64.636
41.289
40.494
39.976
36.529
35.187
33.859
29.873
29.621
26.433
25.303
23.441
19.295
16.154
f1 (ppm)

(4a*R*,6*R*,8*R*,8a*R*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-(dimethylphenylsilyl) methyldecahydroquinoline (73):



First step: $LiAlH_4$ (14.00 mL of a 1M solution in THF, 14.0 mmol) was slowly added to a stirring suspension of $AlCl_3$ (572 mg, 4.29 mmol) in anhydrous THF (20 mL) at 0 °C. After 1 h, the mixture was cooled at –78 °C, and a solution of lactam **71a (**1.30 g, 2.15 mmol) in anhydrous THF (16 mL) was added dropwise. The stirring was continued at –78 °C for 90 min and at rt for 24 h. Cold water was slowly added until no bubbling and the resulting mixture was filtered over Celite®, dried and concentrated.

Second step: A solution of the above crude and Boc_2O (1.265 g, 5.80 mmol) in MeOH (50 mL) containing 40% $Pd(OH)_2$ (0.52 g) was stirred under hydrogen at rt for 24 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash chromatography (98:2 hexane/Et_2O) afforded decahydroquinoline **73** (900 mg, 75%) as a colorless oil:

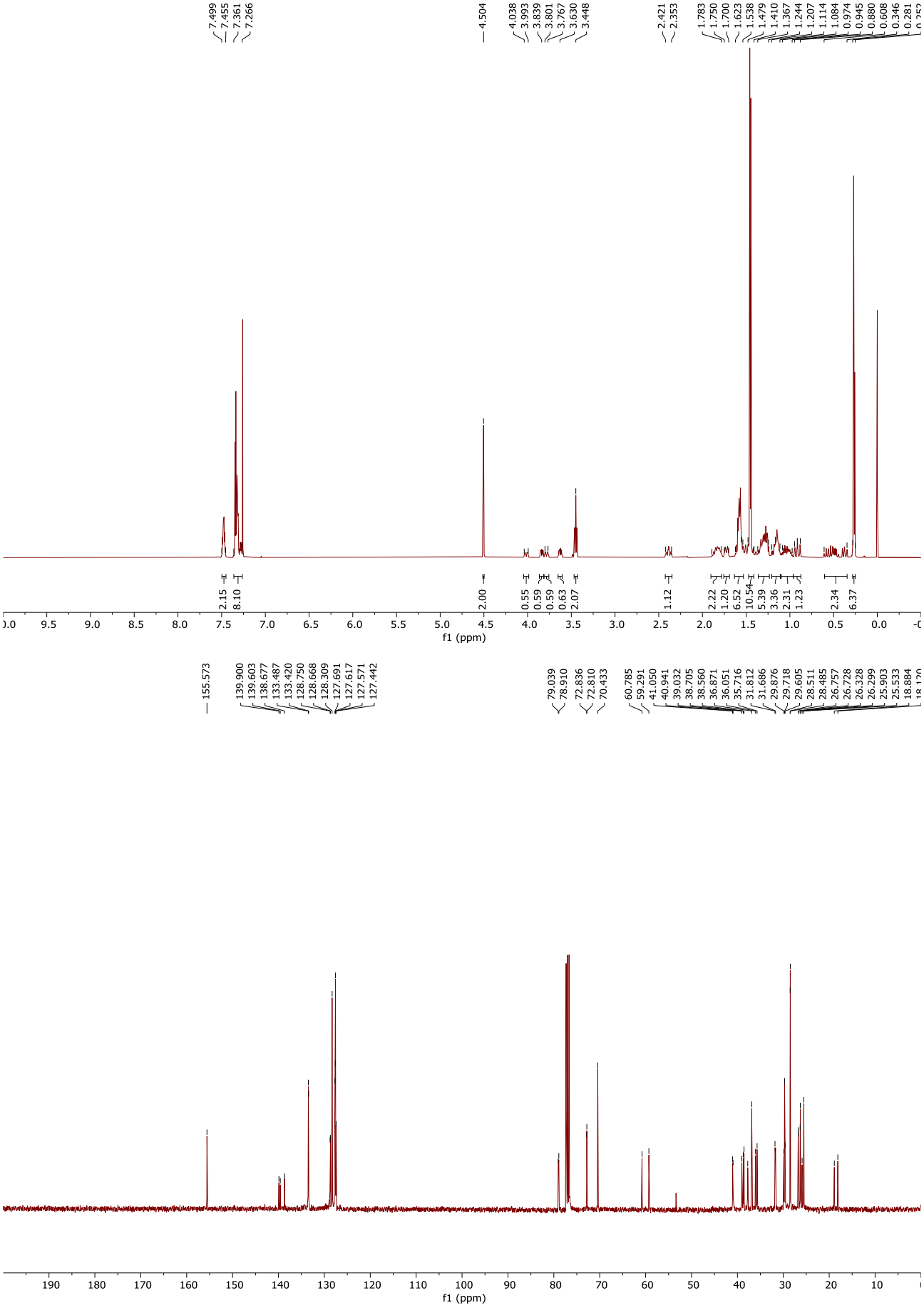
$[\alpha]^{23}_D$ + 7.4 (*c* 0.8, $CHCl_3$).

IR (NaCl): 1688 (CO).

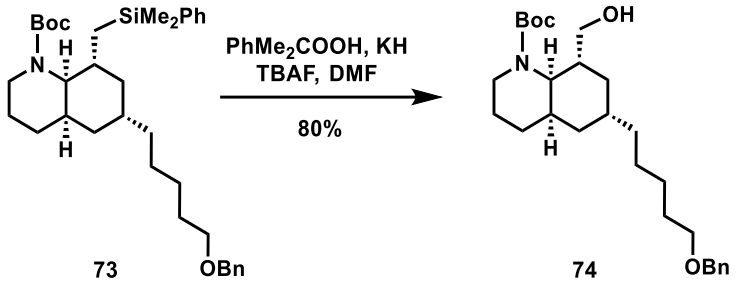
^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 7.50-7.45 (m, 2H, ArH), 7.36-7.27 (m, 8H, ArH), 4.50 (s, 2H, CH_2Ph), 3.84 and 3.63 [(dd, *J* = 11.2, 5.2 Hz) and (dd, *J* = 10.4, 4.8 Hz), 1H, H-8a], 3.45 (t, *J* = 6.8 Hz, 2H, CH_2OBn), 4.04-3.99 and 3.80-3.77 and 2.42-2.35 [(m) and (m) and (m), 2H, H-2], 1.89-1.78 (m, 2H, H-4a and H-8), 1.75-1.70 (m, 1H, H-7_b), 1.62-1.54 (m, 5H), 1.48-1.41 (m, 10H), 1.37-1.24 (m, 5H), 1.21-1.11 (m, 3H), 1.08-0.97 (m, 1H), 0.95-0.88 (m, 1H, $CH_{2a}Si$), 0.61-0.35 (m, 2H, $CH_{2b}Si$ and H-7_a), 0.28-0.25 [m, 6H, $Si(CH_3)_2$].

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (CO), 139.9 and 139.6 (C-*i*), 138.7 (C-*i*), 133.5 (CH-Ar), 133.4 (CH-Ar), 128.8 (CH-Ar), 128.7 (CH-Ar), 128.3 (CH-Ar), 127.7 (CH-Ar), 127.6 (2 CH-Ar), 127.4 (CH-Ar), 79.1 and 78.9 (Cq), 72.8 (CH_2Ph), 70.4 (CH_2OBn), 60.8 and 59.3 (C-8a), 41.0 and 40.9 (C-7), 38.7 and 38.6 (CH_2), 39.0 and 37.8 (C-2), 36.9 (CH_2), 36.0 and 35.7 (C-4a), 31.8 and 31.7 (C-6), 29.7 (CH_2), 29.9 and 29.6 (C-8), 28.5 [3 $(CH_3)_3$ and CH_2], 26.7 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 18.9 and 18.1 (CH_2Si), –1.8 and –2.0 and –2.1 and –2.2 (2 CH_3Si).

HRMS Calcd for [$C_{35}H_{53}NO_3Si + H^+$]: 564.3867; found 564.3865.



(4a*R*,6*R*,8*R*,8a*R*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-(hydroxymethyl)decahydroquinoli-ne (74):



Cumene hydroperoxide (1.27 mL, 6.86 mmol) was added dropwise to a stirred suspension of potassium hydride (1.21 mg, 8.57 mmol) in anhydrous DMF (12 mL), and the resulting mixture was stirred during 25 min. Then, a solution of decahydroquinoline **73** (967 mg, 1.71 mmol) in anhydrous DMF (12 mL) and 1.77 mL of a 1 M solution of TBAF in THF were added. After 24h, saturated aqueous $Na_2S_2O_3$ was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried and evaporated. Flash column chromatography (9:1 to 7:3 hexane–EtOAc) afforded decahydroquinoline **74** (611 mg, 80%) as a colourless oil.

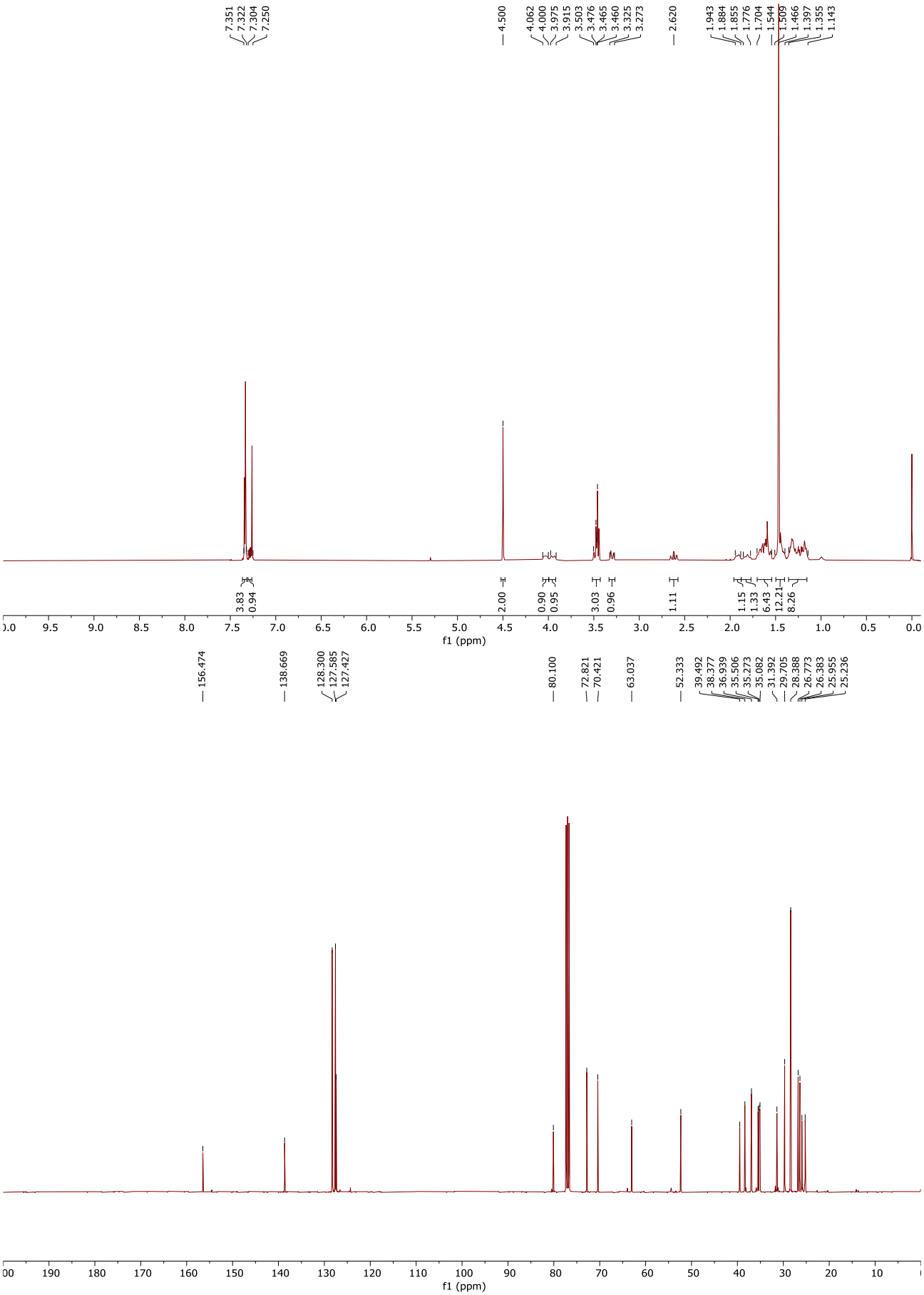
$[\alpha]^{23}_D$ + 39.1 (*c* 1.1, $CHCl_3$).

IR (NaCl): 3446 (OH), 1686, 1656 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.35-7.32 (m, 4H, ArH), 7.30-7.25 (m, 1H, ArH), 4.50 (s, 2H, CH_2Ph), 4.07-4.00 (m, 1H, H-8a), 3.98-3.91 (m, 1H, H-2), 3.50-3.47 (m, 1H, CH_2OH), 3.46 (t, *J* = 6.4 Hz, 2H, CH_2OBn), 3.32-3.27 (m, 1H, CH_2OH), 2.62 (td, *J* = 12.8, 2.6 Hz, 1H, H-2), 1.94-1.88 (m, 1H), 1.86-1.76 (m, 1H), 1.70-1.54 (m, 6H), 1.51-1.40 (m, 3H), 1.47 [s, 9H, $C(CH_3)_3$], 1.35-1.14 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (CO), 138.7 (C-Ar), 128.3 (CH-Ar), 127.6 (CH-Ar), 127.4 (CH-Ar), 80.1 [*C*$(CH_3)_3$], 72.8 (CH_2Ph), 70.4 (CH_2OBn), 63.0 (CH_2OH), 52.3 (C-8a), 39.5 (C-2), 38.4 (CH_2), 37.9 (CH_2), 35.5 (CH), 35.3 (CH_2), 35.1 (CH), 31.4 (CH), 29.7 (CH_2), 28.4 [C(*C*$H_3)_3$], 26.8 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 25.2 (CH_2).

HRMS Calcd for [$C_{27}H_{43}NO_4$ + H^+]: 446.3265; found 446.3269.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7.322
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7.250
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4.062
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3.975
3.915
3.503
3.476
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3.325
3.273
2.620
1.943
1.884
1.855
1.776
1.704
1.544
1.509
1.466
1.397
1.355
1.143
3.83
0.94
2.00
0.90
0.95
3.03
0.96
1.11
1.15
1.33
6.43
12.21
8.26
f1 (ppm)
156.474
138.669
128.300
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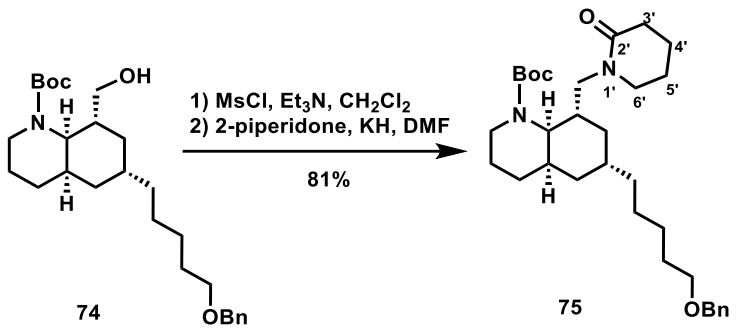
36.939
35.506
35.273
35.082
31.392
29.705
28.388
26.773
26.383
25.955
25.236
f1 (ppm)

(4a*R*,6*R*,8*S*,8a*R*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxy-carbonyl)-8-[(2-oxo-1-piperidyl)methyl]deca-hydroquinoline (75):



First step: Triethylamine (39 μL, 0.51 mmol) and MsCl (0.10 mL, 0.71 mmol) were added dropwise under inert atmosphere at 0 °C to a stirring solution of decahydroquinoline **74** (227 mg, 0.51 mmol) in anhydrous CH_2Cl_2 (2 mL). The mixture was allowed to heat to room temperature and stirred for additional 3 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and evaporated.

Second step: Freshly distilled 2-piperidone (0.18 mL, 2.04 mmol) was added to a stirred suspension of potassium hydride (293 mg, 2.08 mmol) in DMF (1 mL) at 0 °C and the stirring was continued at the same temperature for 10 min. A solution of the above crude in anhydrous DMF (3 mL) was added dropwise at 0 °C and the reaction mixture was allowed to heat to room temperature and stirred for an additional 48 h. The reaction solution was cooled to 0 °C and ice water was added, then the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, filtered and evaporated. Flash column chromatography (1:1 hexane–EtOAc then EtOAc) afforded decahydroquinoline **75** (217 mg, 81%) as a colourless oil.

$[\alpha]^{23}_D$ + 2.1 (*c* 0.7, $CHCl_3$);

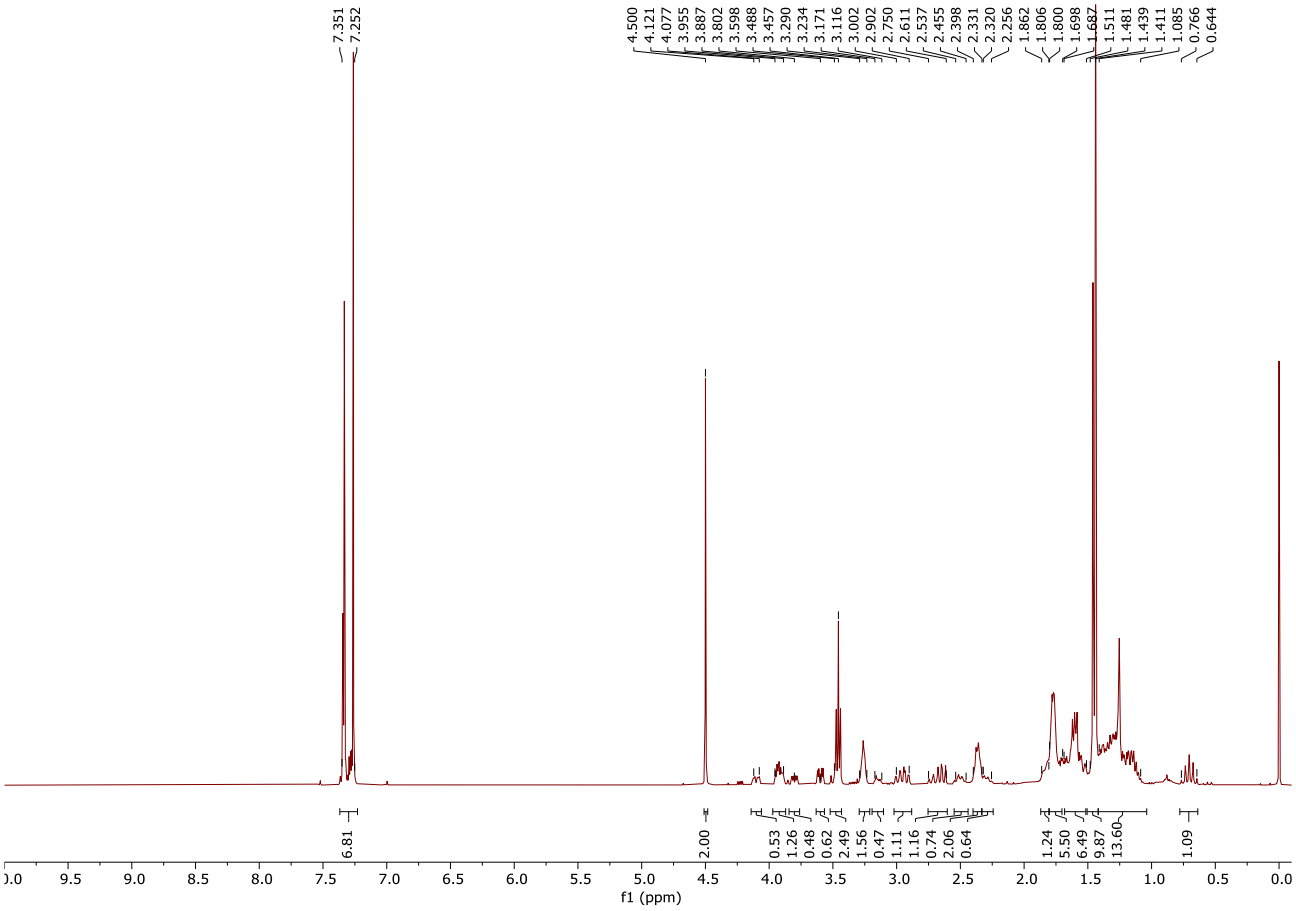
IR (NaCl): 1686 (NCOO), 1641 (CO) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.35-7.25 (m, 5H, ArH), 4.50 (s, 2H, CH_2Ph), 3.95-3.88 and 3.80 [(m) and (dd, *J* = 11.2, 4.4 Hz), 1H, H-8a], 3.46 (t, *J* = 6.4 Hz, 2H, CH_2OBn), 3.29-3.23 and 3.17-3.12 (m, 2H, C-6'), 4.12-4.08 and 3.95-3.89 and 3.00-2.90 and 2.75-2.61 [(m) and (m) and (m) and (m), 2H, H-2], 3.60 and 3.49-3.46 and 3.00-2.90 and 2.75-2.61 [(dd, *J* = 13.6, 4.0 Hz) and (m) and (m) and (m), 1H, CHC*H*$_2$N)], 2.40-2.33 (m, 2H, H-3'), 2.54-2.46 and 2.32-2.26 [(m) and (m), 1H, H-4a], 1.86-1.81 (m, 1H, H-8), 1.80-1.70 (m, 5H), 1.69-1.51 (m, 6H), 1.48-1.44 [m, 9H, $C(CH_3)_3$], 1.41-1.09 and 0.77-0.64 [(m) and (m), 11H];

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (CO), 155.2 (NCOO), 138.7 (C-Ar), 128.3 (CH-Ar), 127.6 (CH-Ar), 127.5 (CH-Ar), 79.2 [*C*$(CH_3)_3$], 72.8 (CH_2Ph), 70.4 (CH_2OBn), 57.2 and 55.9 (C-8a), 51.0

(C-6’), 52.2 and 49.0 (CH_2N), 39.2 and 38.1 and 38.0 (C-2), 37.1 and 36.8 and 36.9 (CH_2), 35.7 (C-8), 32.2 and 32.1 and 32.0 (C-3’), 31.7 and 31.4 (C-4a), 31.2 (C-6), 29.8 and 29.7 (CH_2), 28.5 (CH_2), 28.4 [$C(CH_3)_3$], 26.8 (CH_2), 26.4 ($2CH_2$), 26.3 and 26.1 (CH_2), 25.7 and 25.4 (CH_2), 23.3 (C-5’), 21.2 and 21.1 (C-4’);

HRMS Calcd for [$C_{32}H_{50}N_2O_4 + H^+$]: 527.3843; found 528.3847.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7.252
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4.121
4.077
3.955
3.887
3.802
3.598
3.488
3.457
3.290
3.234
3.171
3.116
3.002
2.902
2.750
2.611
2.537
2.455
2.398
2.331
2.320
2.256
1.862
1.806
1.800
1.698
1.687
1.511
1.481
1.439
1.411
1.085
0.766
0.644
6.81
2.00
0.53
1.26
0.48
0.62
2.49
1.56
0.47
1.11
1.16
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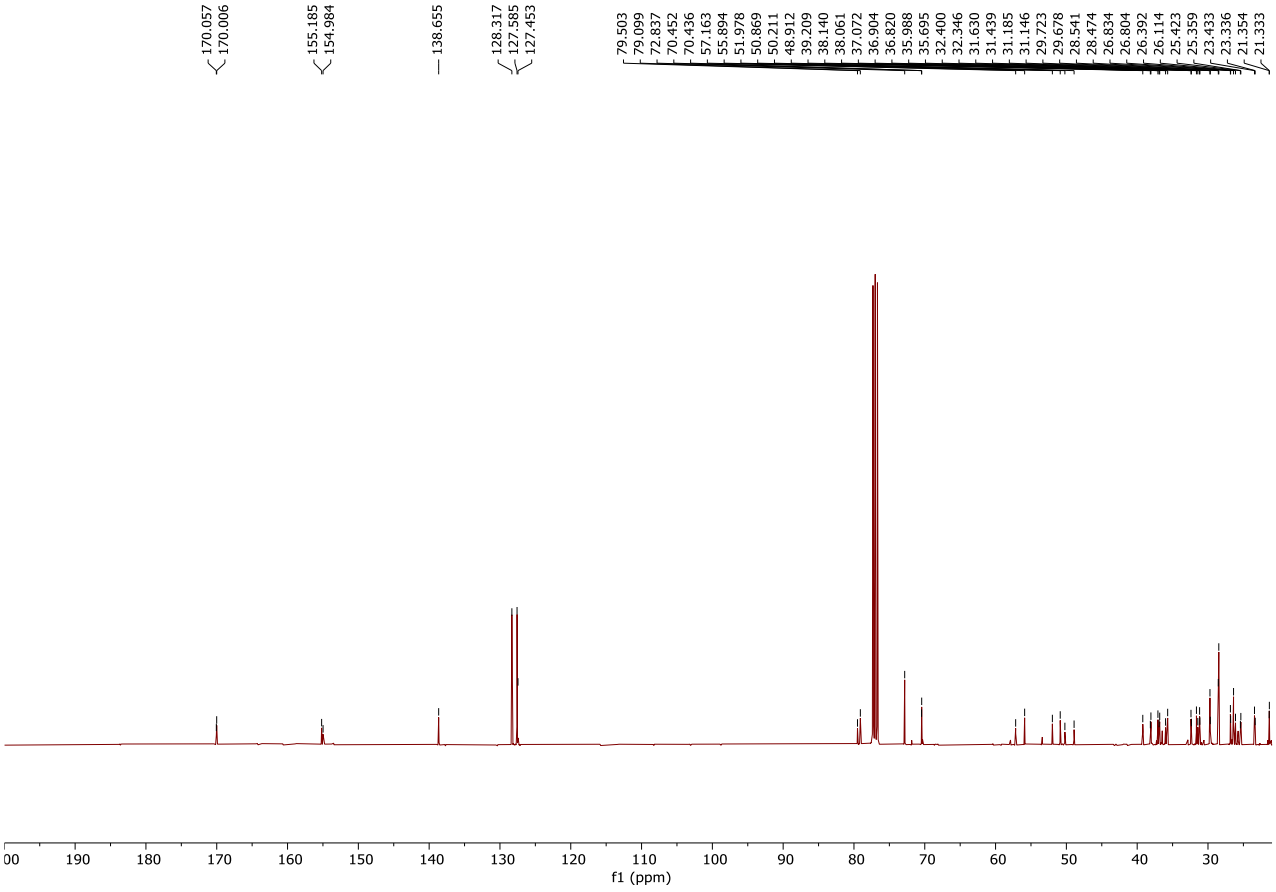
2.06
0.64
1.24
5.50
6.49
9.87
13.60
1.09
f1 (ppm)


170.057
170.006
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154.984
138.655
128.317
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127.453
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79.099
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57.163
55.894
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50.869
50.211
48.912
39.209
38.140
38.061
37.072
36.904
36.820
35.988
35.695
32.400
32.346
31.630
31.439
31.185
31.146
29.723
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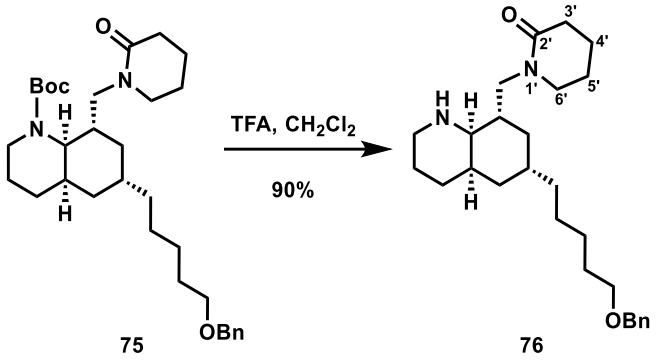
28.474
26.834
26.804
26.392
26.114
25.423
25.359
23.433
23.336
21.354
21.333
f1 (ppm)

(4a*R*,6*R*,8*S*,8a*R*)-6-(5-Benzyloxypentyl)-8-[(2-oxo-1-piperidyl)methyl]decahydroquinoline (76):



TFA (0.28 mL, 3.77 mmol) was slowly added to a solution of decahydroquinoline **75** (32 mg, 0.06 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched by addition of 2 M aqueous solution of KOH and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered and evaporated to afford decahydroquinoline **76** (23.2 mg, 90%) as a yellowish oil.

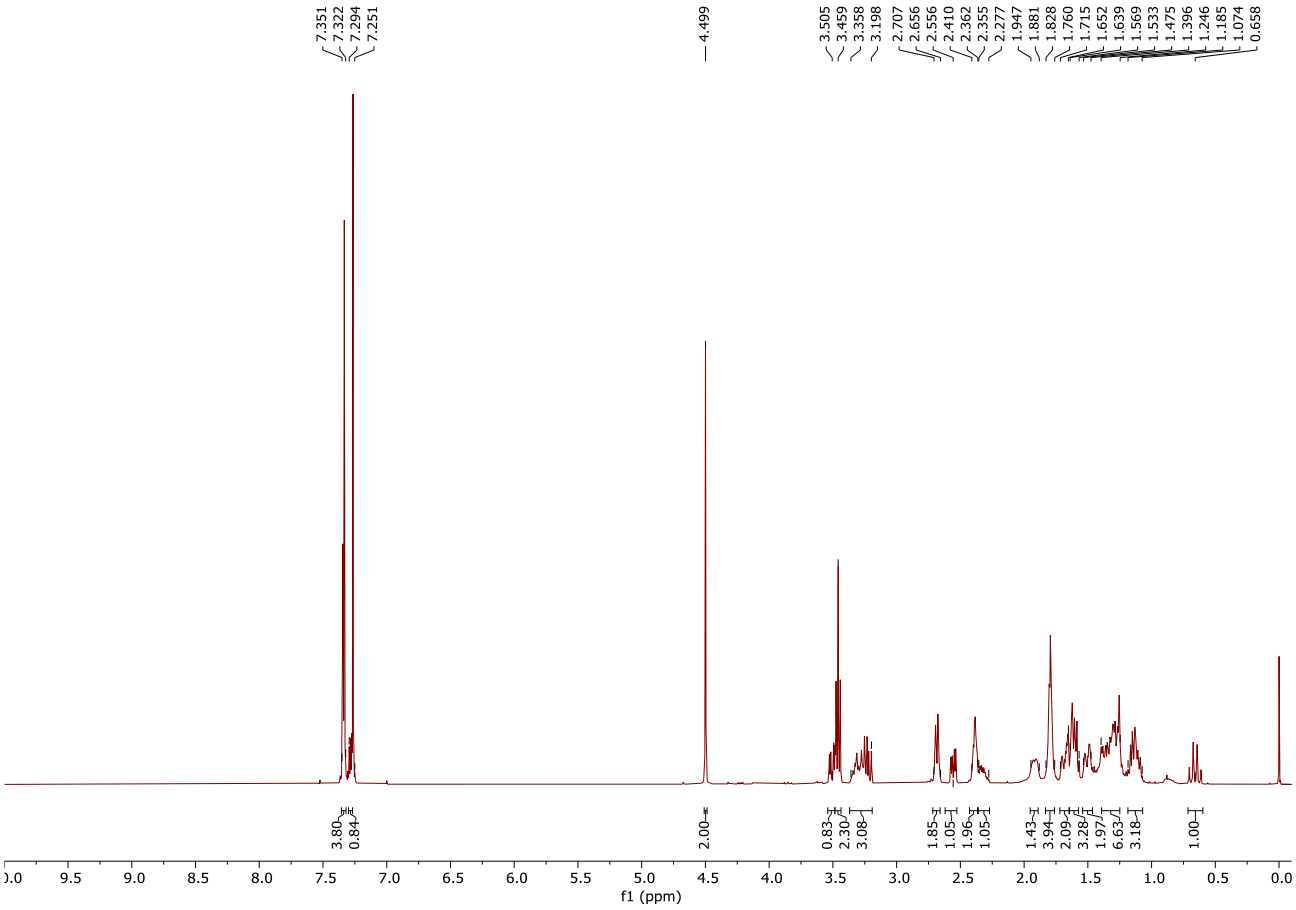
$[\alpha]^{23}_D$ – 13.3 (*c* 1.0, $CHCl_3$).

IR (NaCl): 1686 (NCOO), 1641 (NCO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 7.35-7.32 (m, 4H, ArH), 7.29-7.25 (m, 1H, ArH), 4.50 (s, 2H, CH_2Ph), 3.51 (dd, *J* = 13.6, 4.4 Hz, 1H, H-9), 3.46 (t, *J* = 6.4 Hz, 2H, CH_2OBn), 3.36-3.24 (m, 2H, H-6'), 3.22 (dd, *J* = 13.6, 8.4 Hz, 1H, H-9), 2.71-2.66 (m, 2H, H-2), 2.56 (dd, *J* = 11.2, 4.4 Hz, 1H, H-8a), 2.41-2.36 (m, 2H, H-3'), 2.36-2.28 (m, 1H, H-8), 1.95-1.88 (m, 1H, H-4a), 1.83-1.76 (m, 4H, H-4' and H-5'), 1.72-1.65 (m, 2H), 1.64-1.57 (m, 3H), 1.53-1.48 (m, 2H), 1.40-1.25 (m, 6H), 1.19-1.07 (m, 3H), 0.66 (q, *J* = 12.8 Hz, 1H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (CO), 138.7 (C-*i*), 128.3 (C-*m*), 127.6 (C-*p*), 127.4 (C-*o*), 72.8 (CH_2Ph), 70.5 (CH_2OBn), 58.2 (C-8a), 51.0 (C-9), 49.2 (C-6'), 39.6 (C-2), 38.7 (CH_2), 37.3 (CH_2), 37.1 (C-7), 36.9 (C-4a), 32.3 (C-3'), 31.5 (C-6), 30.9 (C-8), 29.7 (CH_2), 27.5 (C-3), 26.9 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 23.4 (C-5'), 21.4 (C-4').

HRMS Calcd for $[C_{27}H_{42}N_2O_2 + H^+]$: 427.3319; found 427.3322.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1.828
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1.715
1.652
1.639
1.569
1.533
1.475
1.396
1.246
1.185
1.074
0.658
3.80
0.84
2.00
0.83
2.30
3.08
1.85
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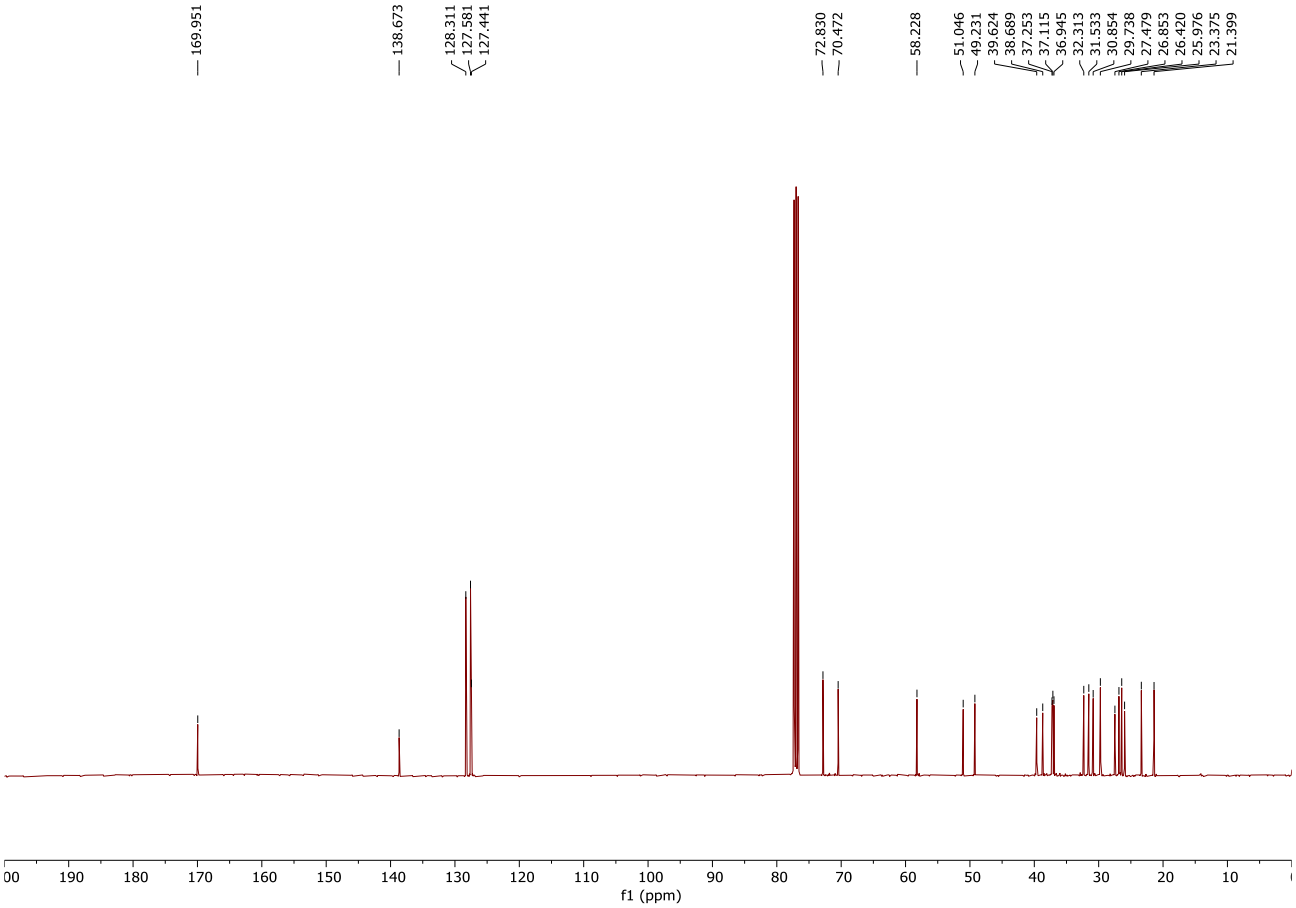
3.18
1.00
f1 (ppm)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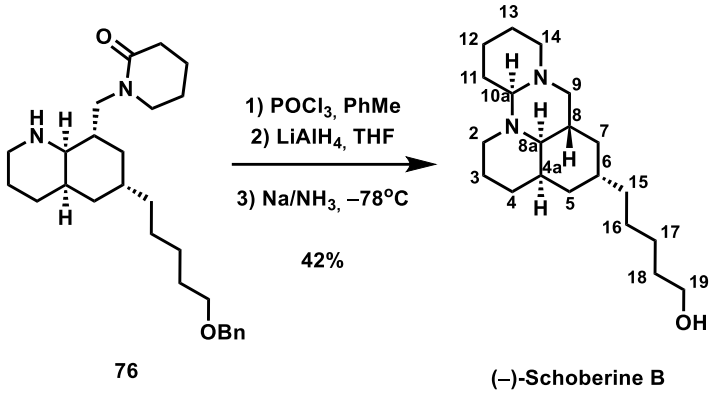
127.581
127.441
72.830
70.472
58.228
51.046
49.231
39.624
38.689
37.253
37.115
36.945
32.313
31.533
30.854
29.738
27.479
26.853
26.420
25.976
23.375
21.399
f1 (ppm)

(–)-Schoberine B:



76 (–)-Schoberine B

First Step: $POCl_3$ (16.5 μL, 0.17 mmol) was added to a solution of decahydroquinoline **x** (74.3 mg, 0.17 mmol) in anhydrous toluene (4 mL) and the mixture was heated at reflux for 3 h. The solvent was evaporated and the residue was purified by flash chromatography (NH–SiO_2, 100% CH_2Cl_2 to 8:2 CH_2Cl_2:MeOH) to afford a mixture of the product and a chlorinated byproduct.

Second Step: $LiAlH_4$ (0.27 mL of a 1M solution in THF, 0.27 mmol) was added to a stirring solution of the above mixture (58.7 mg, 0.13 mmol) in anhydrous THF (2.6 mL) at 0 °C. After 30 min, the mixture was allowed to warm to room temperature and stirred for additional 12 h. Cold water was slowly added until no bubbling and the resulting mixture was dried and concentrated. The residue was purified by flash chromatography (NH–SiO_2, 100% CH_2Cl_2) to afford a mixture of the product and a chlorinated byproduct.

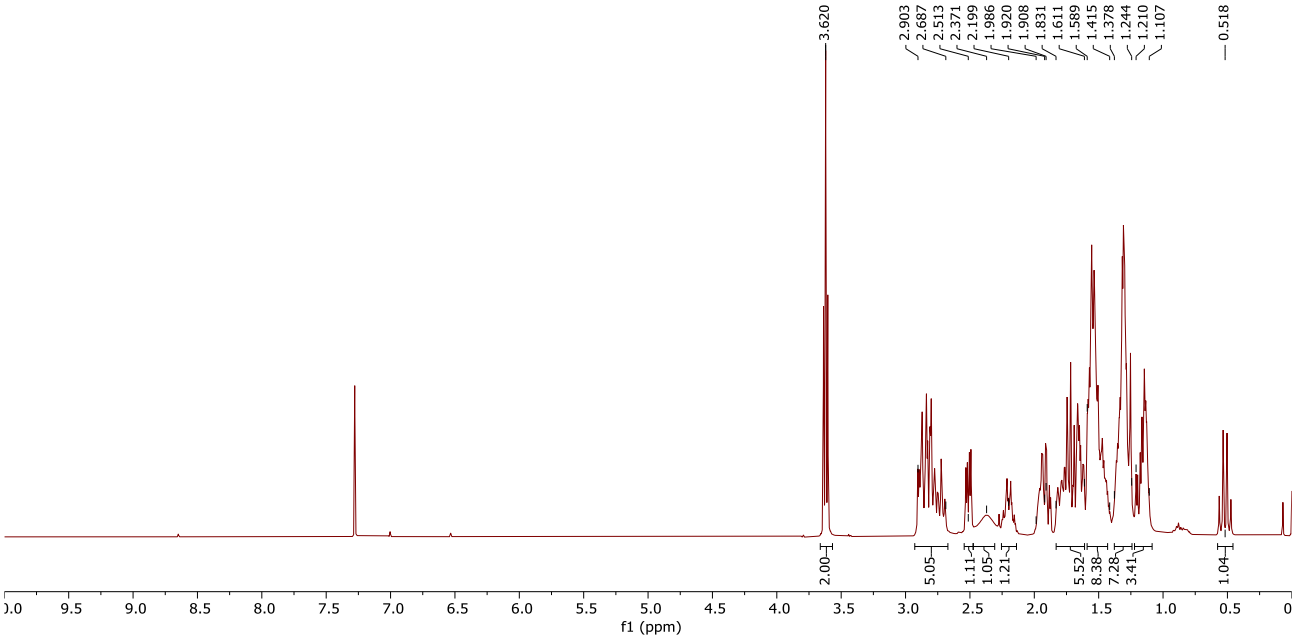
Third step: A solution of the above mixture (36 mg, 0.09 mmol) in anhydrous THF (3 mL) was added to a solution of liquid ammonia at –78 °C under argon atmosphere. Sodium was added until a persistent blue colour appeared, and the mixture was stirred for 10 min at –78 °C, then saturated aqueous NH_4Cl was added. The mixture was warmed up to room temperature, extracted with CH_2Cl_2, dried and evaporated. Flash chromatography (NH–SiO_2, 100% CH_2Cl_2 to 9:1 CH_2Cl_2:MeOH) afforded (–)-schoberine B (23.5 mg, 42%) as a colorless gum.

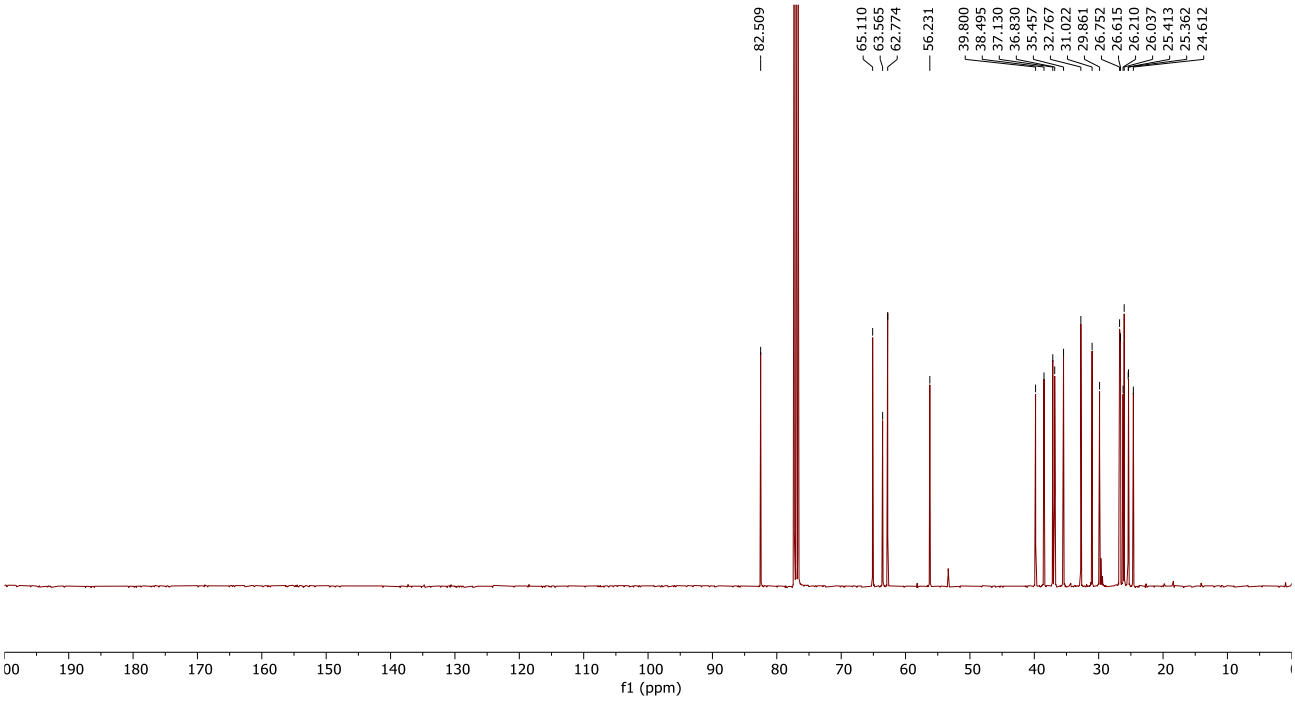
$[\alpha]^{23}_D$ – 10.7 (*c* 0.3, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K, COSY, g-HSQC) δ 3.62 (t, *J* = 6.8 Hz, 2H, CH_2OH), 2.90-2.69 (m, 5H, H-2, H-9, H-10a and H-14), 2.51 (dd, *J* = 11.2, 4.8 Hz, 1H, H-8a), 2.37 (brs, 1H, OH), 2.20 (qt, *J* = 11.2, 3.6 Hz, 1H, H-8), 1.99-1.92 (m, 1H, H-4a), 1.91 (td, *J* = 12.0, 3.6 Hz, 1H, H-14), 1.83-1.61 (m, 5H), 1.59-1.41 (m, 8H), 1.38-1.24 (m, 7H), 1.21-1.11 (m, 3H), 0.52 (q, *J* = 12.0 Hz, 1H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 82.5 (C-10a), 65.1 (C-8a), 63.6 (C-9), 62.8 (C-19), 56.2 (C-14), 39.8 (C-2), 38.5 (C-5), 37.1 (C-15), 36.8 (C-7), 35.5 (C-4a), 32.8 (C-18), 31.0 (C-6), 29.9 (C-11), 26.8 (C-16), 26.6 (C-8), 26.2 (C-3), 26.0 (C-17), 25.4 (C-13), 25.4 (C-4), 24.6 (C-12).

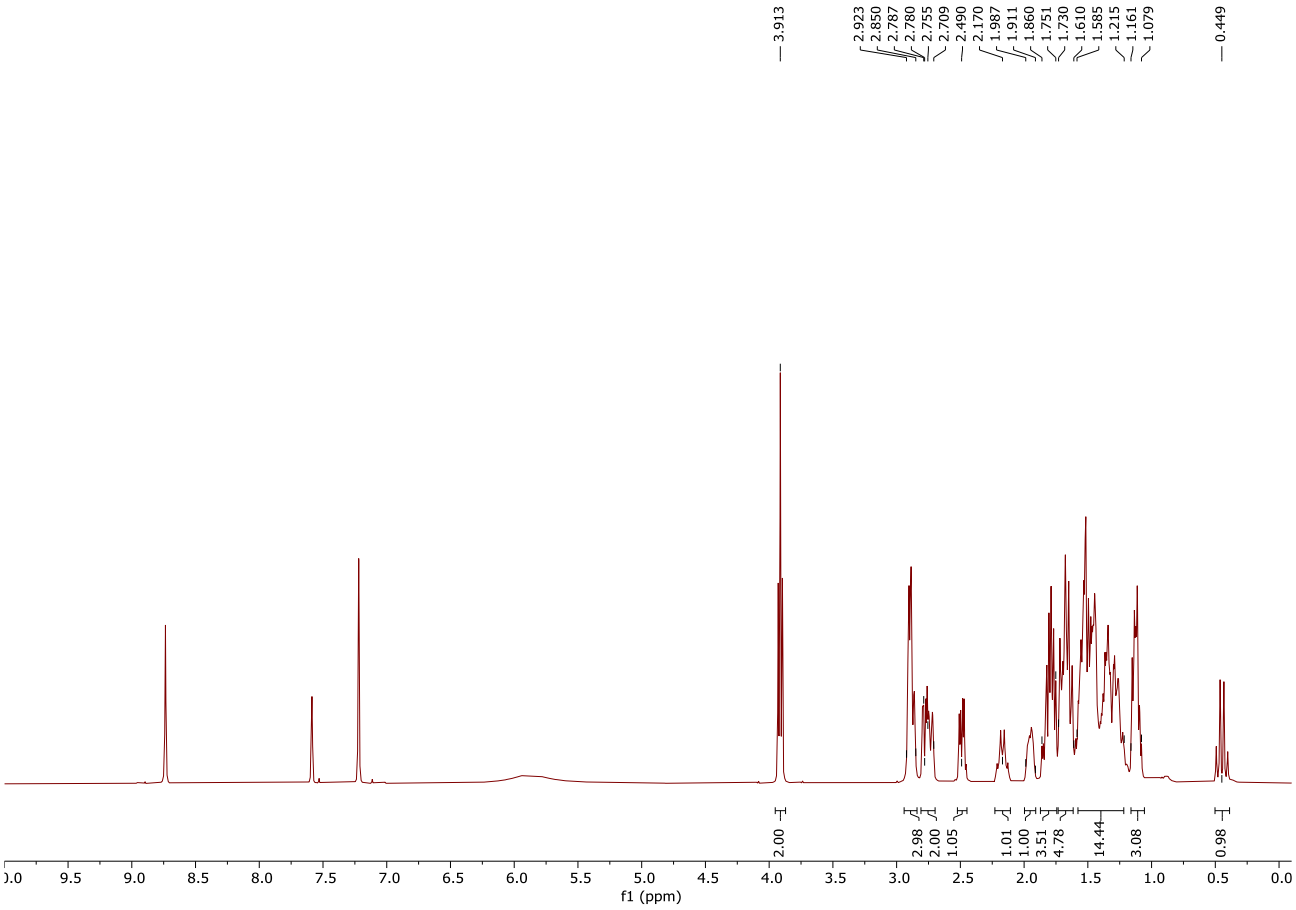
HRMS Calcd for [$C_{20}H_{36}N_2O$ + H^+]: 321.2900; found 321.2901.

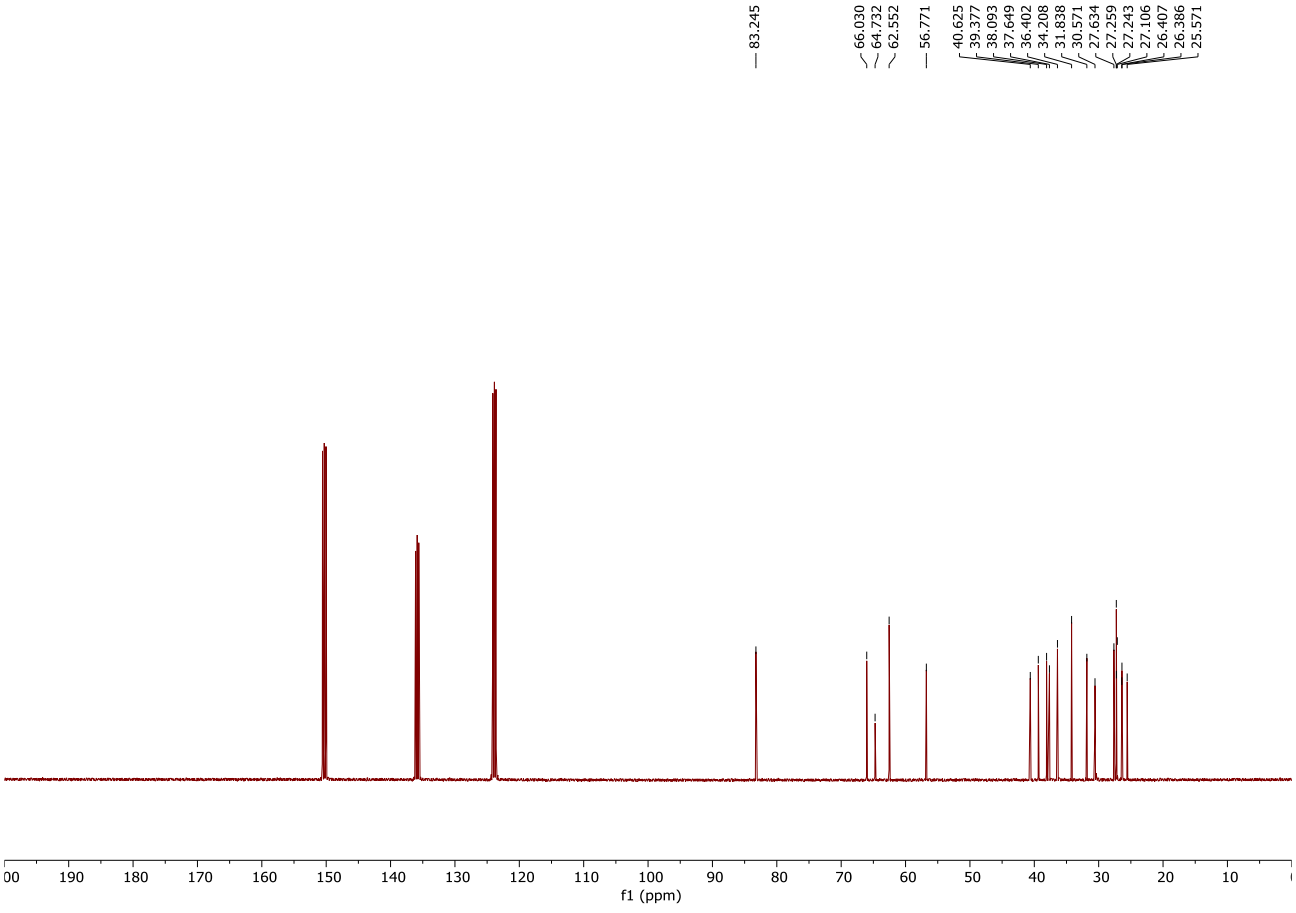




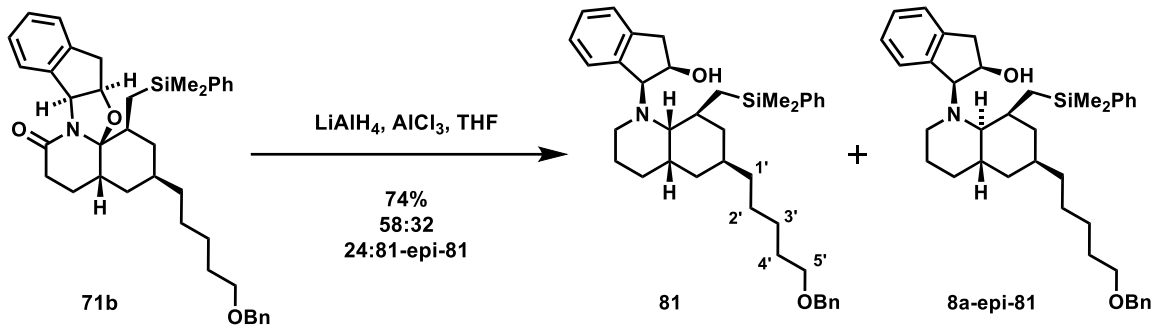
^{1}H NMR (400 MHz, Pyr-d_5, 298 K) δ 3.91 (t, *J* = 6.4 Hz, 2H, H-19), 2.92-2.85 (m, 3H, H-2, H-10a), 2.78 (dd, *J* = 12.8, 4.0 Hz, 1H, H-9), 2.76-2.71 (m, 1H, H-14), 2.49 (dd, *J* = 10.8, 4.8 Hz, 1H, H-8a), 2.17 (qt, *J* = 11.6, 4.0 Hz, 1H, H-8), 1.99-1.91 (m, 1H, H-4a), 1.86-1.75 (m, 3H), 1.73-1.61 (m, 5H), 1.59-1.22 (m, 14H), 1.16-1.08 (m, 3H), 0.45 (t, *J* = 12.0 Hz, 1H, H-7).

^{13}C NMR (101 MHz, Pyr-d_5, 313 K) δ 83.2 (C-10a), 66.0 (C-8a), 64.7 (C-9), 62.6 (C-19), 56.8 (C-14), 40.6 (C-2), 39.4 (C-5), 38.1 (C-15), 37.6 (C-7), 36.4 (C-4a), 34.2 (C-18), 31.8 (C-6), 30.6 (C-11), 27.6 (C-16), 27.3 (C-17), 27.2 (C-3), 27.1 (C-8), 26.4 (C-13), 26.4 (C-4), 25.6 (C-12).


3.913
2.923
2.850
2.787
2.780
2.755
2.709
2.490
2.170
1.987
1.911
1.860
1.751
1.730
1.610
1.585
1.215
1.161
1.079
0.449
2.00
2.98
2.00
1.05
1.01
1.00
3.51
4.78
14.44
3.08
0.98
f1 (ppm)


83.245
66.030
64.732
62.552
56.771
40.625
39.377
38.093
37.649
36.402
34.208
31.838
30.571
27.634
27.259
27.243
27.106
26.407
26.386
25.571
f1 (ppm)

(4a*S*,6*S*,8*S*,8a*S*)- and (4a*S*,6*S*,8*S*,8a*R*)-6-(5-Benzyloxypentyl)-8-(dimethylphenylsilyl)methyl -1-[(1*S*,2*R*)-2-hydroxy-1-indanyl]decahydroquinoline (81 and 8a-epi-81):



$LiAlH_4$ (7.3 mL of a 1 M solution in THF, 7.3 mmol) was slowly added to a stirring suspension of $AlCl_3$ (304 mg, 2.26 mmol) in anhydrous THF (14 mL) at 0 °C. After 1 h, the mixture was cooled at –78 °C, and a solution of lactam **71b** (671 mg, 1.13 mmol) in anhydrous THF (8.5 mL) was added dropwise. The stirring was continued at –78 °C for 90 min and at rt for 24 h. Cold water was slowly added until no bubbling, and the resulting mixture was filtered over Celite®, dried, and concentrated. Flash chromatography (9:1 hexane–EtOAc) afforded decahydroquinolines **81a** (288 mg, 43%) and **8a-epi-81** (211 mg, 31%) as yellowish oils.

81:

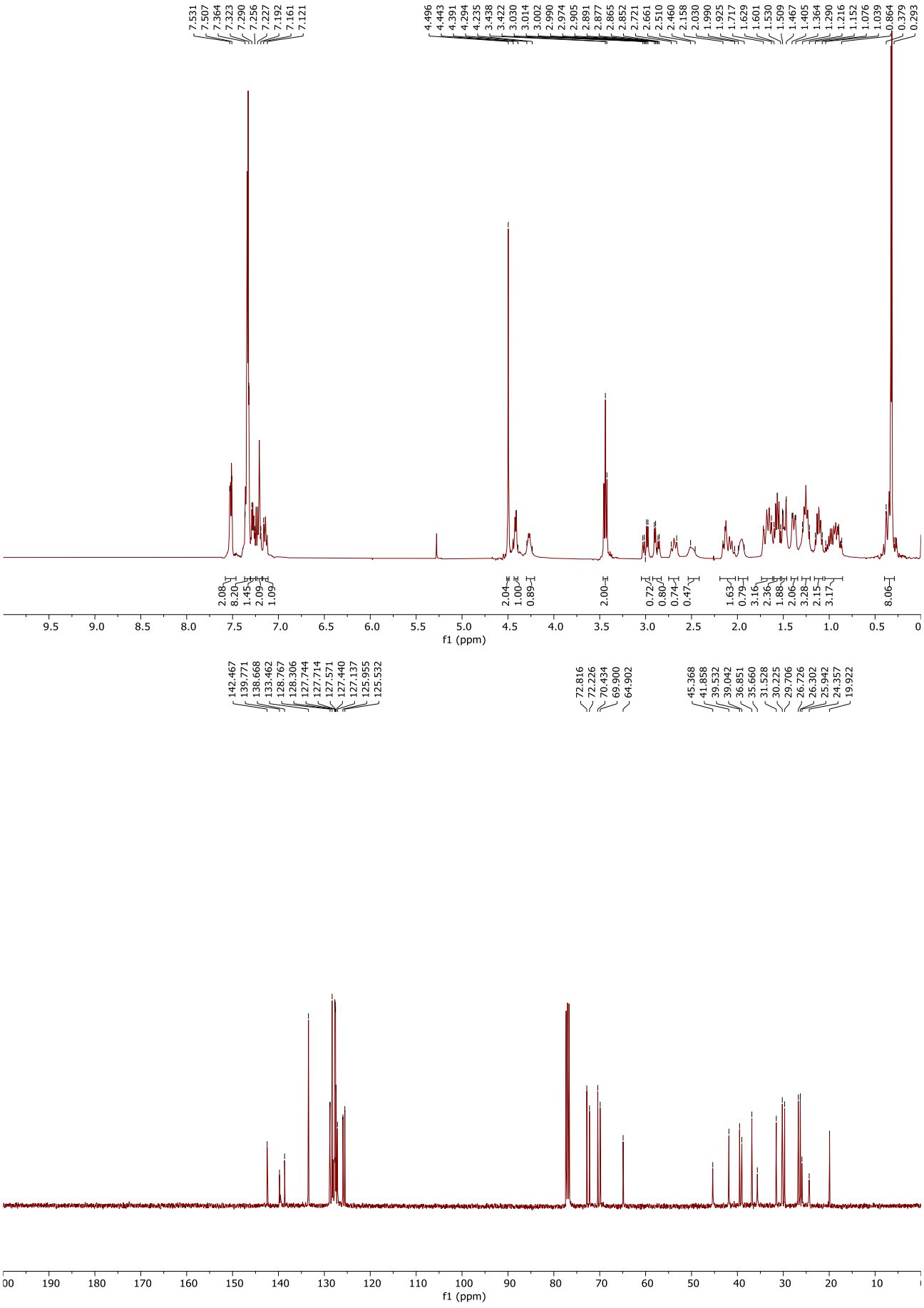
$[\alpha]^{23}_D$ + 26.6 (*c* 1.1, $CHCl_3$).

IR (NaCl): 3156 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 7.53-7.51 (m, 2H, ArH), 7.36-7.32 (m, 8H, ArH), 7.29-7.26 (m, 1H, ArH), 7.23-7.19 (m, 2H, ArH), 7.16-7.12 (m, 1H, ArH), 4.50 (m, 2H, CH_2Ph), 4.44-4.39 (m, 1H, CHN), 4.29-4.23 (m, 1H, C*H*OH), 3.44 (t, *J* = 6.4 Hz, 2H, H-5'), 3.00 (dd, *J* = 16.0, 6.4 Hz, 1H, CH_{2a}CHOH), 2.88 (dd, *J* = 16.0, 5.6 Hz, 1H, CH_{2b}CHOH), 2.72-2.66 (m, 1H, H-2_a), 2.51-2.46 (m, 1H, H-2_b), 2.16-2.03 (m, 2H, H-8 and H-8a), 1.99-1.93 (m, 1H, H-4a), 1.72-1.63 (m, 3H, H-3_a, H-4_a and H-5_a), 1.60-1.53 (m, 2H, H-4'), 1.51-1.47 (m, 2H, CH_{2a}Si and H-3_b), 1.40-1.36 (m, 2H, H-5_b and H-7_a), 1.29-1.22 (m, 3H, H-2' and H-6), 1.15-1.08 (m, 2H, H-1'), 1.04-0.86 (m, 3H, H-3' and H-7_b), 0.38-0.29 (m, 2H, CH_{2b}Si, H-4_b), 0.33 (s, 3H, CH_3Si), 0.32 (s, 3H, CH_3Si).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 139.8, and 138.7 (C-*i*), 133.5 (CH-Ar), 128.8 (CH-Ar), 128.3 (CH-Ar), 127.7 (2 CH-Ar), 127.6 (CH-Ar), 127.4 (CH-Ar), 127.1 (CH-Ar), 126.0 (CH-Ar), 125.5 (CH-Ar), 72.8 (CH_2Ph), 72.2 (C*H*OH), 70.4 (C-5'), 69.9 (CHN), 64.9 (C-8a), 45.4 (C-2), 41.9 (C-4), 39.5 (*C*H_2CHOH), 39.0 (C-7), 36.9 (C-3'), 35.7 (C-4a), 31.5 (C-6), 30.2 (C-8), 29.7 (C-4'), 26.7 (C-1'), 26.3 (C-2'), 25.9 (C-5), 24.4 (C-3), 19.9 (CH_2Si), –1.9 (2 CH_3Si).

HRMS Calcd for [$C_{39}H_{53}NO_2Si + H^+$]: 596.3918; found 596.3920.



8a-epi-81:

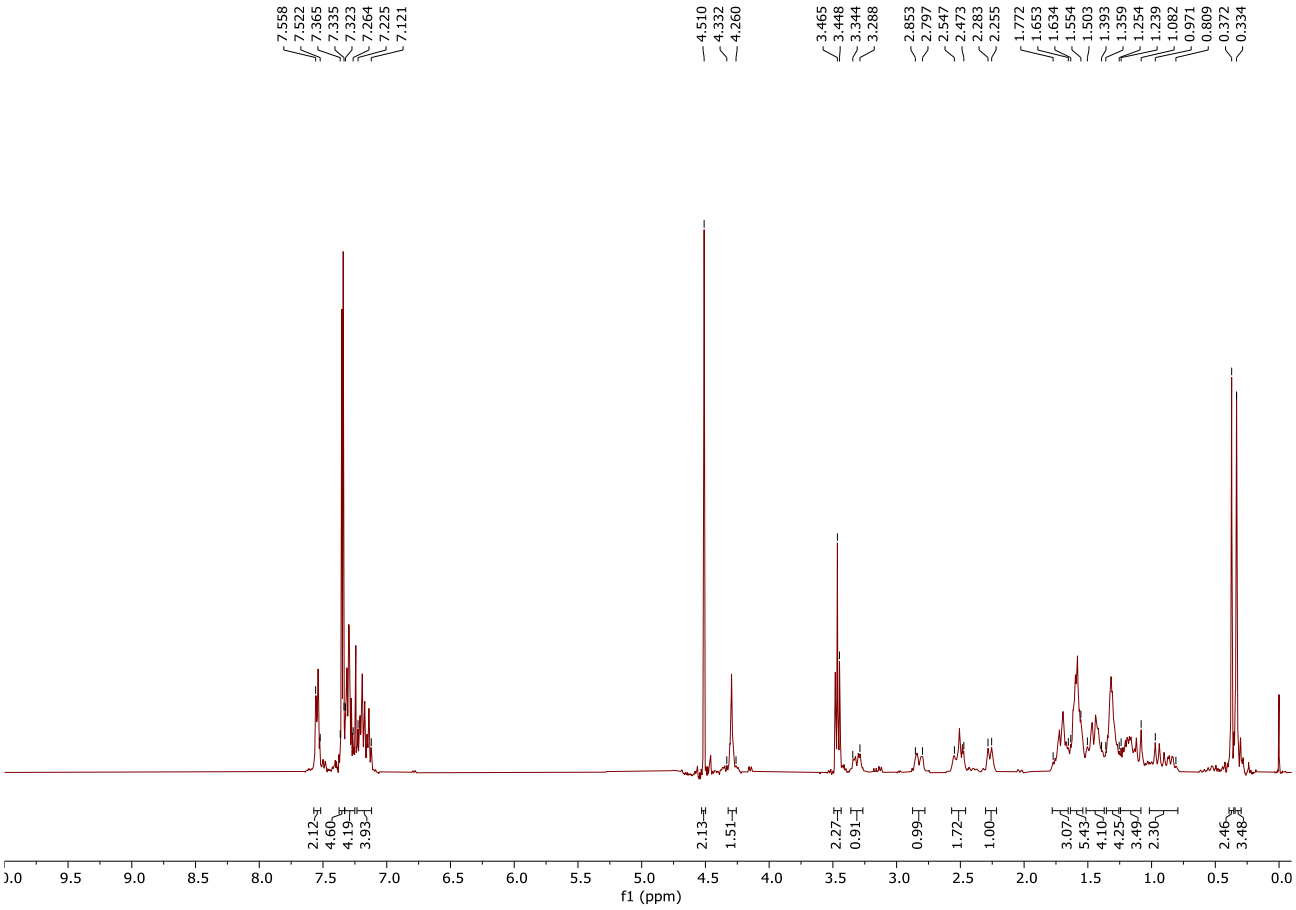
$[\alpha]^{23}_{D}$ + 48.1 (*c* 1.0, $CHCl_3$).

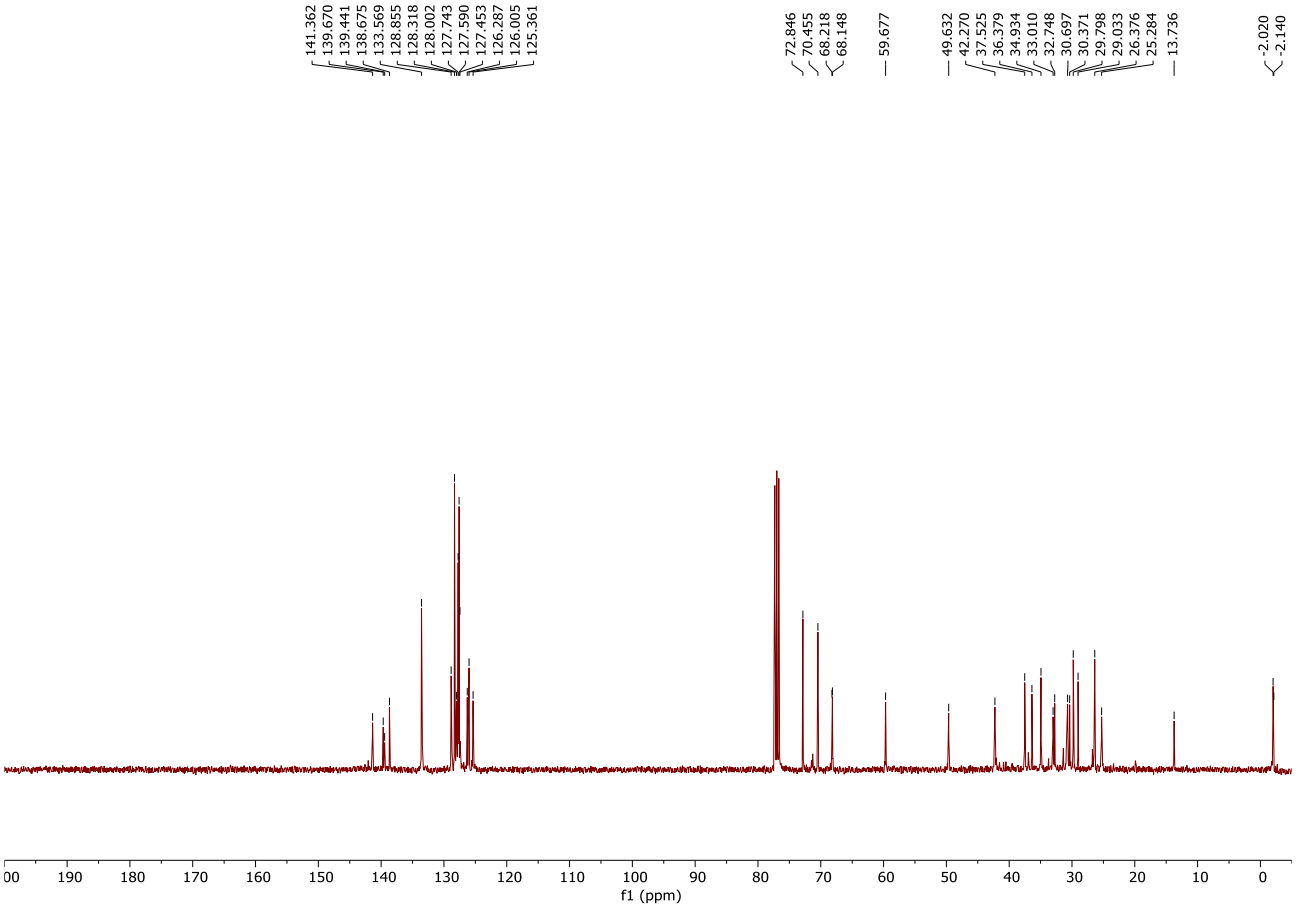
IR (NaCl): 3205 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, g-HSQC) δ 7.56-7.52 (m, 2H, ArH), 7.36-7.34 (m, 4H, ArH), 7.32-7.26 (m, 4H, ArH), 7.23-7.12 (m, 4H, ArH), 4.51 (m, 2H, CH_2Ph), 4.33-4.26 (m, 2H, C*H*OH and CHN), 3.46 (t, *J* = 6.8 Hz, 2H, H-5'), 3.34-3.29 (m, 1H, CH_{2a}CHOH), 2.85-2.80 (m, 1H, CH_{2b}CHOH), 2.55-2.47 (m, 2H, H-8 and H-8a), 2.28-2.25 (m, 1H, H-2_a), 1.77-1.65 (m, 3H, H-2_b and H-3), 1.63-1.55 (m, 5H, H-4_a, H-4a, H-4' and H-6), 1.50-1.39 (m, 4H, H-3_a', H-5 and H-7_a), 1.36-1.25 (m, 4H, H-1_a', H-2' and H-3_b'), 1.24-1.08 (m, 3H, CH_{2a}Si, H-1_b' and H-7_b), 0.97-0.81 (m, 2H, CH_{2b}Si and H-4_b), 0.37 (s, 3H, CH_3Si), 0.33 (s, 3H, CH_3Si).

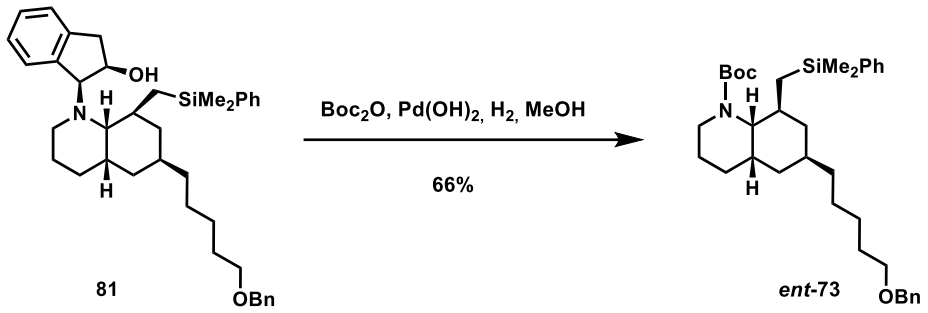
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 139.7, 139.4, and 138.7 (C-Ar), 133.6 (CH-Ar), 128.9 (CH-Ar), 128.3 (CH-Ar), 128.0 (CH-Ar), 127.7 (CH-Ar), 127.6 (CH-Ar), 127.5 (CH-Ar), 126.3 (CH-Ar), 126.0 (CH-Ar), 125.4 (CH-Ar), 72.8 (CH_2Ph), 70.5 (CH_2OBn), 68.2 (C*H*OH), 68.1 (C-8a), 59.7 (CHN), 49.6 (C-2), 42.3 (*C*H_2CHOH), 37.5 (C-7), 36.4 (C-3'), 34.9 (C-3), 33.0 (C-4), 32.7 (C-4a), 30.7 (C-8), 30.4 (C-6), 29.8 (C-4'), 29.0 (C-1'), 26.4 (C-2'), 25.3 (C-5), 13.7 (CH_2Si), –2.0 (CH_3Si), –2.1 (CH_3Si).

HRMS Calcd for [$C_{39}H_{53}NO_2Si + H^+$]: 596.3918; found 596.3919.


7.558
7.522
7.365
7.335
7.323
7.264
7.225
7.121
4.510
4.332
4.260
3.465
3.448
3.344
3.288
2.853
2.797
2.547
2.473
2.283
2.255
1.772
1.653
1.634
1.554
1.503
1.393
1.359
1.254
1.239
1.082
0.971
0.809
0.372
0.334
2.12
4.60
4.19
3.93
2.13
1.51
2.27
0.91
0.99
1.72
1.00
3.07
5.43
4.10
4.25
3.49
2.30
2.46
3.48
f1 (ppm)


141.362
139.670
139.441
138.675
133.569
128.855
128.318
128.002
127.743
127.590
127.453
126.287
126.005
125.361
72.846
70.455
68.218
68.148
59.677
49.632
42.270
37.525
36.379
34.934
33.010
32.748
30.697
30.371
29.798
29.033
26.376
25.284
13.736
-2.020
-2.140
f1 (ppm)

(4a*S*,6*S*,8*S*,8a*S*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-(dimethylphenylsilyl) methyldecahydroquinoline (*ent*-73):

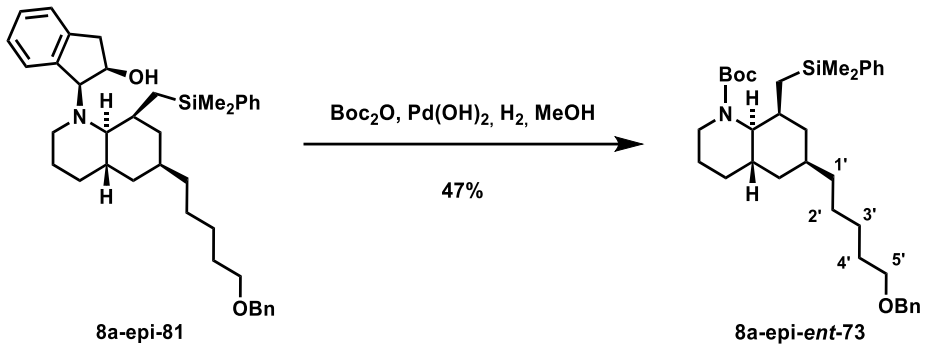


A solution decahydroquinoline **81** (218 mg, 0.37 mmol) and Boc_2O (220 mg, 1.01 mmol) in MeOH (50 mL) containing 40% $Pd(OH)_2$ (520 mg) was stirred under hydrogen at rt for 3 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash chromatography (98:2 to 9:1 hexane–Et_2O) afforded decahydroquinoline ***ent*-73** (137 mg, 66%) as a colourless oil:

$[\alpha]^{23}_D$ – 7.7 (*c* 1.3, $CHCl_3$).

HRMS Calcd for [$C_{35}H_{53}NO_3Si + H^+$]: 564.3867; found 564.3858.

(4a*S*,6*S*,8*S*,8a*R*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-(dimethylphenylsilyl)methyldeca-hydroquinoline (8a-epi-*ent*-73):



Operating as described in the preparation of decahydroquinoline **9**, from decahydroquinoline **8a-epi-81** (169 mg, 0.28 mmol), Boc_2O (171 mg, 0.78 mmol), and 40% $Pd(OH)_2$ (68 mg) in MeOH (7 mL), decahydroquinoline **8a-epi-*ent*-73** (80 mg, 47%) was obtained after flash column chromatography (98:1 to 9:1 hexane–Et_2O) as a colourless oil:

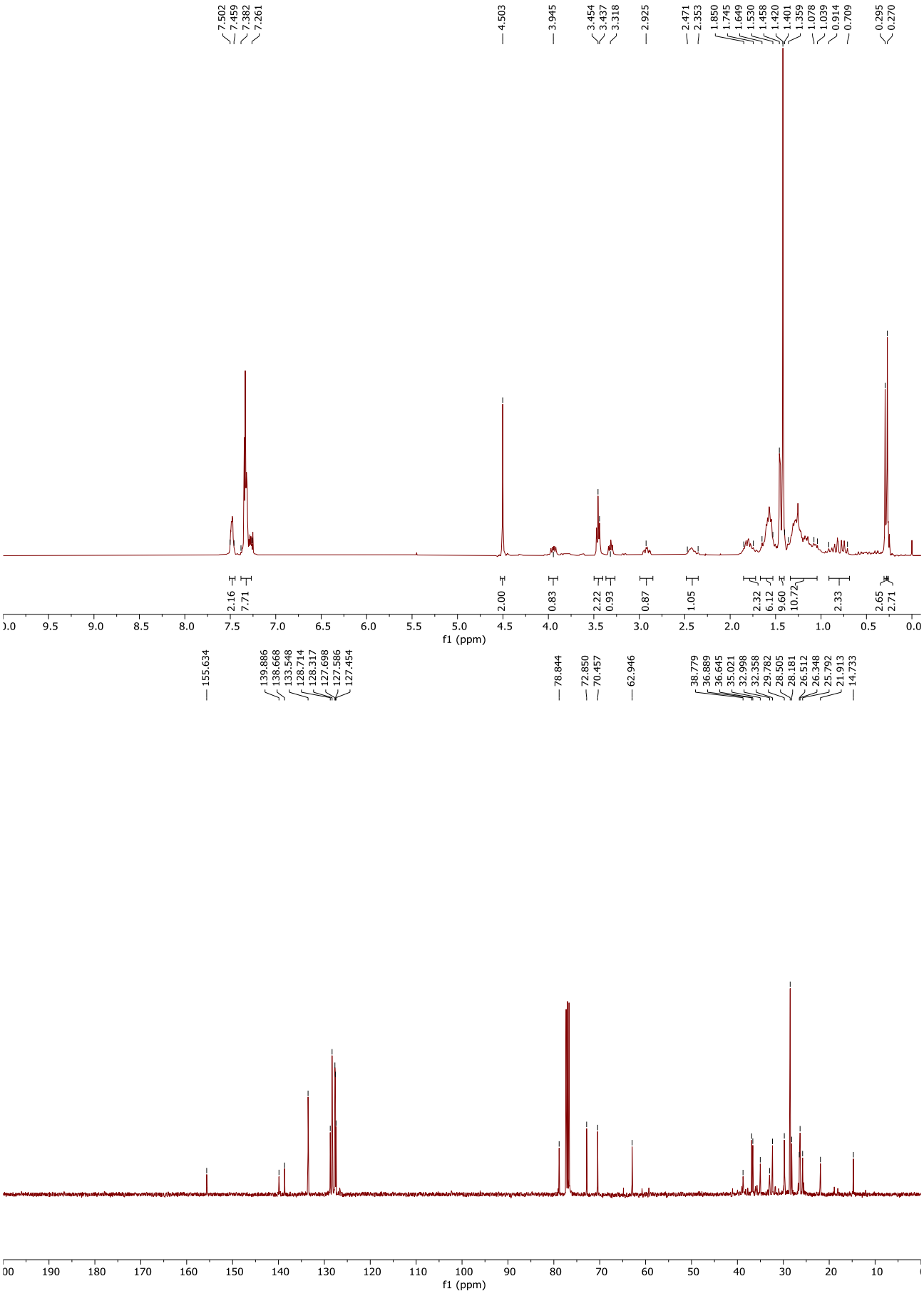
$[\alpha]^{23}_D$ + 83.3 (*c* 0.7, $CHCl_3$).

IR (NaCl): 1689 (CO) cm^{-1}.

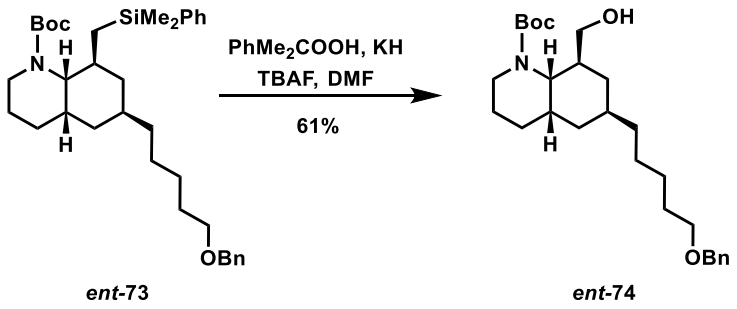
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.50-7.46 (m, 2H, ArH), 7.38-7.26 (m, 8H, ArH), 4.50 (m, 2H, CH_2Ph), 3.95 (dd, *J* = 14.0, 7.6 Hz, 1H, H-2$_a$), 3.45 (t, *J* = 6.8 Hz, 2H, H-5'), 3.32 (dd, *J* = 12.0, 5.2 Hz, 1H, H-8a), 2.96-2.88 (m, 1H, H-2$_b$), 2.47-2.35 (m, 1H, H-8a), 1.85-1.74 (m, 2H, H-3 and H-4a), 1.65-1.53 (m, 6H), 1.45-1.40 [m, 9H, $(CH_3)_3$], 1.36-1.04 (m, 10H), 0.91-0.71 (m, 2H, CH_2Si), 0.29 (s, 3H, CH_3Si), 0.27 (s, 3H, CH_3Si).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (CO), 139.9 (C-*i*), 138.7 (C-*i*), 133.5 (CH-Ar), 128.7 (CH-Ar), 128.3 (CH-Ar), 127.7 (CH-Ar), 127.6 (CH-Ar), 127.5 (CH-Ar), 78.8 [*C*$(CH_3)_3$], 72.8 (CH_2Ph), 70.5 (C-5'), 62.9 (C-8a), 38.8 (C-2), 36.9 (CH_2), 36.6 (CH_2), 35.0 (C-7), 33.0 (C-8), 32.4 (C-6), 29.8 (C-4), 28.5 [C(*C*$H_3)_3$], 28.2 (CH_2), 26.5 (C-1'), 26.3 (C-2'), 25.8 (C-4a), 21.9 (C-3), 14.7 (CH_2Si), –2.0 (CH_3Si), –2.1 (CH_3Si).

HRMS Calcd for [$C_{35}H_{53}NO_3Si + H^+$]: 564.3867; found 564.3862.



(4a*S*,6*S*,8*S*,8a*S*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-(hydroxymethyl)decahydroquinoline (*ent*-74):



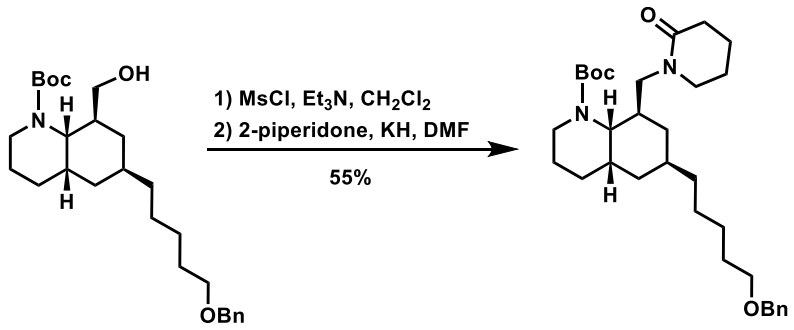
ent-73 *ent*-74

Operating as described in the preparation of compound **74**, from decahydroquinoline ***ent*-73** (314.1 mg, 0.56 mmol) in anhydrous DMF (4.8 mL) and KH (391 mg, 2.79 mmol), cumene hydroperoxide (0.42 mL, 2.23 mmol) and TBAF (1.11 mL, 1.11 mmol) in anhydrous DMF (3.9 mL), decahydroquinoline ***ent*-74** (152 mg, 61%) was obtained as a colourless oil:

$[\alpha]^{23}_{D}$ – 39.1 (*c* 1.4, $CHCl_3$).

HRMS Calcd for [$C_{27}H_{43}NO_4$ + H^+]: 446.3265; found 446.3271.

(4a*S*,6*S*,8*R*,8a*S*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-[(2-oxo-1-piperidyl)methyl]deca-hydroquinoline (*ent*-75):



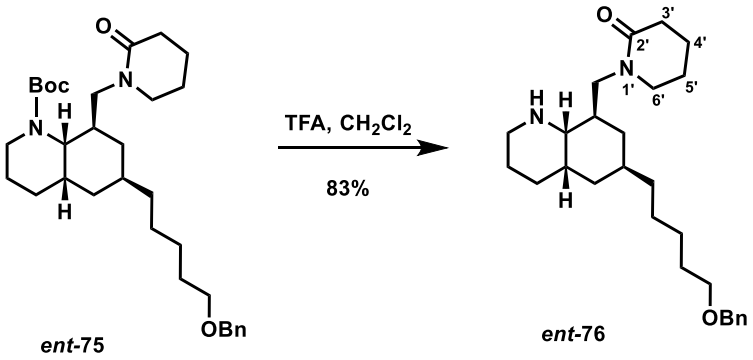
ent-74 *ent*-75

Operating as described in the preparation of compound **75**, from decahydroquinoline ***ent*-74** (160 mg, 0.36 mmol), MsCl (28 µL, 0.36 mmol) and Et_3N (70 µL, 0.50 mmol) in anhydrous CH_2Cl_2 (1.4 mL) followed by 2-piperidone (0.13 mL, 1.44 mmol) and KH (207 mg, 1.44 mmol) in anhydrous DMF (3.00 mL) afforded decahydroquinoline ***ent*-75** (104.3 mg, 55%) as a colourless oil:

$[\alpha]^{23}_{D}$ – 2.5 (*c* 0.9, $CHCl_3$).

HRMS Calcd for [$C_{32}H_{50}N_2O_4$ + H^+]: 527.3843; found 528.3850.

(4a*S*,6*S*,8*R*,8a*S*)-6-(5-Benzyloxypentyl)-8-[(2-oxo-1-piperidyl)methyl]decahydroquinoline (*ent*-76):



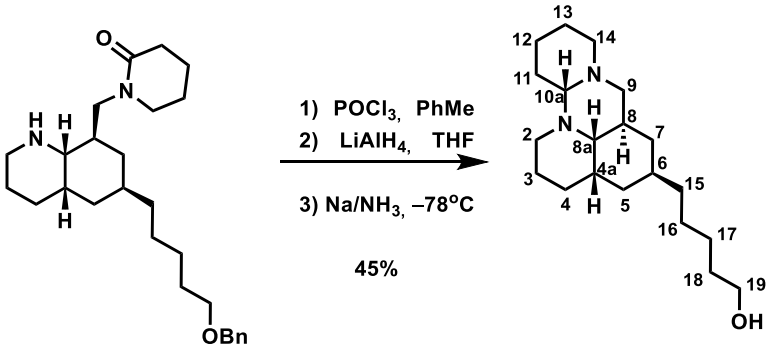
ent-75 *ent*-76

Operating as described in the preparation of decahydroquinoline **76**, from decahydroquinoline ***ent*-75** (104.3 mg, 0.20 mmol) and TFA (0.91 mL, 12.26 mmol) in anhydrous CH_2Cl_2 (9 mL) afforded decahydroquinoline ***ent*-76** (70 mg, 83%) as a yellowish oil:

$[\alpha]^{23}_D$ + 15.2 (*c* 1.1, $CHCl_3$).

HRMS Calcd for [$C_{27}H_{42}N_2O_2$ + H^+]: 427.3319; found 427.3324.

(+)-Schoberine B:



ent-76 (+)-Schoberine B

Operating as described in the preparation of **(–)-schoberine B**, from decahydroquinoline ***ent*-76** (70 mg, 0.164 mmol), $POCl_3$ (15.5 µL, 0.164 mmol), $LiAlH_4$ (0.22 mL of a 1 M solution in THF, 0.22 mmol) and Na/NH_3 mixture, afforded **(+)-schoberine B** (23.7 mg, 45%) as a colorless solid:

CCDC number: 2294529

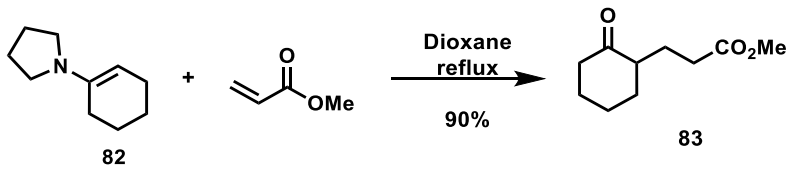
mp: 105-107 °C (hexane/CH_2Cl_2).

$[\alpha]^{23}_D$ + 11.9 (*c* 0.4, MeOH).

HRMS Calcd for [$C_{20}H_{36}N_2O$ + H^+]: 321.2900; found 321.290

6.6 Experimental Procedures and Spectroscopic Data – Chapter 4

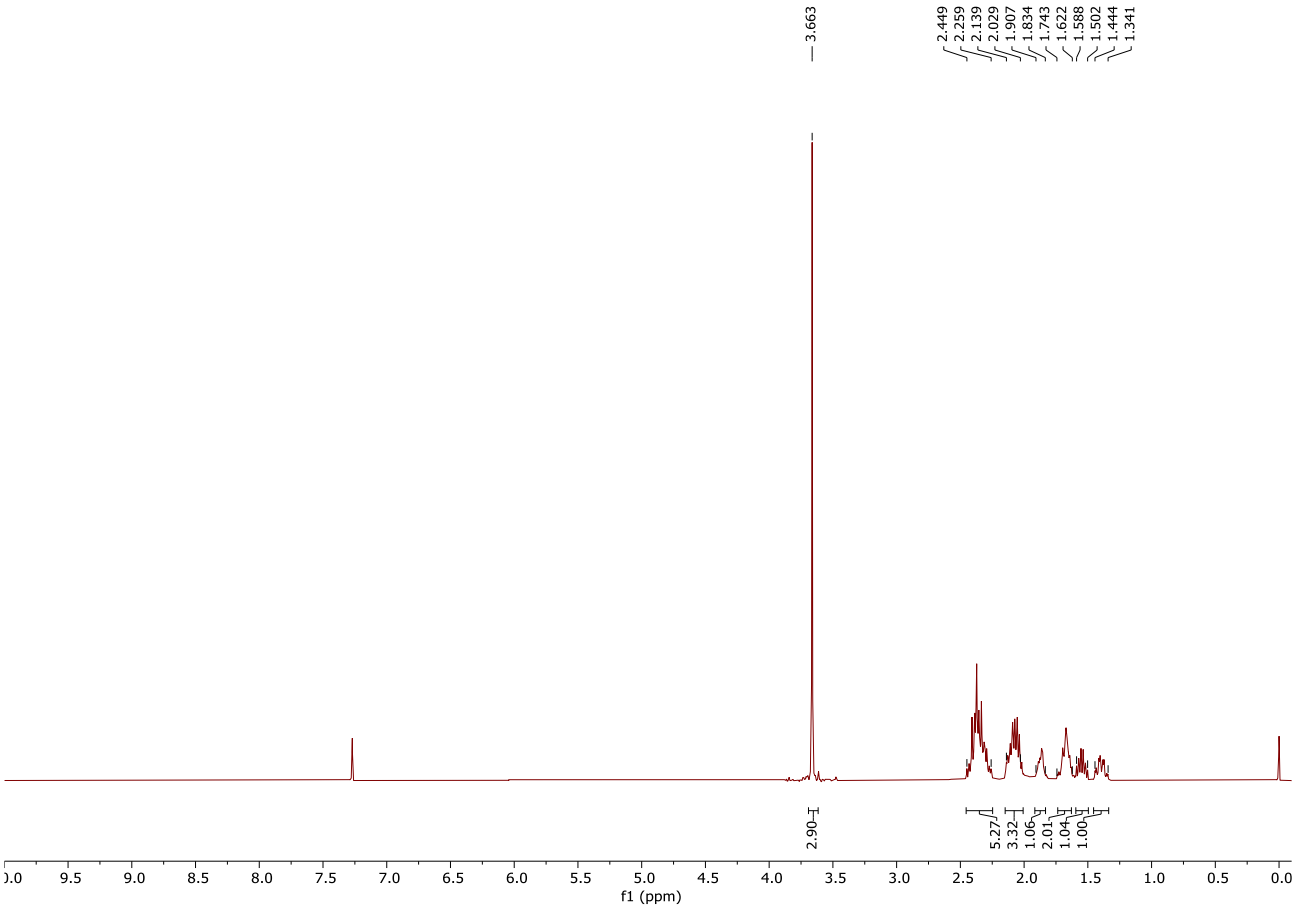
Methyl 2-oxocyclohexanepropionate (83):



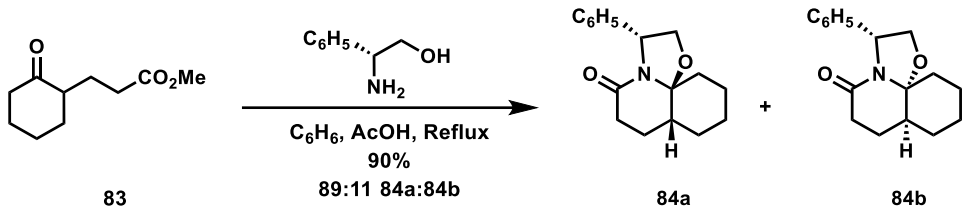
82 83

Methyl acrylate (3.44 mL, 0.04 mol) was added to a solution of 1-pyrrolidino-1-cyclohexene **82** (6.0 mL, 0.04 mol, 97%) in anhydrous dioxane (13.8 mL) and the mixture was heated at reflux. After 3 h, a buffer solution (10 mL, AcOH–H_2O–NaOAc, 10 mL:10 mL:5 g) was added and the mixture was stirred at reflux temperature for 1 h. Then, Et_2O was added to the cooled mixture, and the resulting solution was washed with 2M aqueous HCl and brine. The organic extracts were dried and concentrated to afford ketoester **83** as a yellow oil (6.05 g, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H, CH_3), 2.26-2.45 (m, 5H), 2.02-2.14 (m, 3H), 1.83-1.91 (m, 1H), 1.62-1.74 (m, 2H), 1.50-1.59 (m, 1H), 1.34-1.44 (m, 1H).


3.663
2.449
2.259
2.139
2.029
1.907
1.834
1.743
1.622
1.588
1.502
1.444
1.341
2.90
5.27
3.32
1.06
2.01
1.04
1.00
f1 (ppm)

(3*R*,7a*R*,11a*S*)- and (3*R*,7a*S*,11a*R*)-5-Oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (84a and 84b):



83 84a 84b

AcOH (2.3 mL, 0.04 mol) was added to a solution of ketoester **83** (4.96 g, 0.03 mol) and (*R*)-phenylglycinol (5.54 g, 0.04 mol) in benzene (207 mL). The mixture was heated at reflux for 24 h with azeotropic elimination of water by a Dean-Stark system. After cooling to room temperature, the solvent was evaporated. Flash column chromatography (from 9:1 to 7:3 hexane–EtOAc) affording tricyclic lactam **84a** as a colorless solid (6.55 g, 80%) and lactam **84b** as a yellow oil (835 mg, 10%).

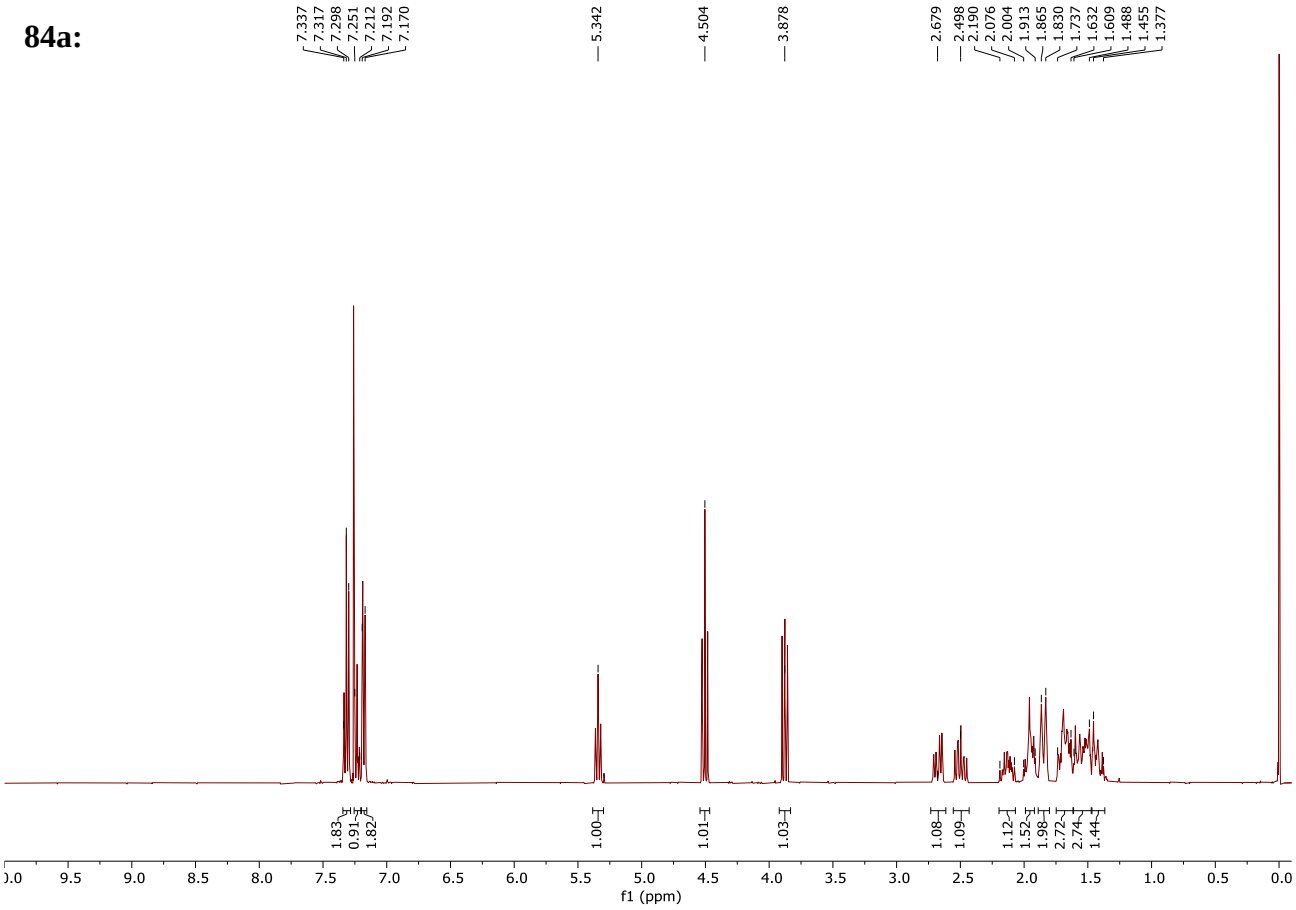
84a:

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2H, ArH), 7.25-7.21 (m, 1H, ArH), 7.19-7.17 (m, 2H, ArH) 5.34 (t, *J* = 8.4 Hz, 1H, H-3), 4.50 (t, *J* = 8.8 Hz, 1H, H-2), 3.89 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 2.68 (dd, *J* = 18.5 and 7.5 Hz, 1H, H-6), 2.50 (ddd, *J* = 18.6, 10.3 and 8.4 Hz, 1H, H-6), 2.19-2.08 (m, 1H), 2.00-1.91 (m, 1H), 1.86-1.83 (m, 2H), 1.74-1.63 (m, 3H), 1.61-1.49 (m, 3H), 1.46-1.38 (m, 1H).

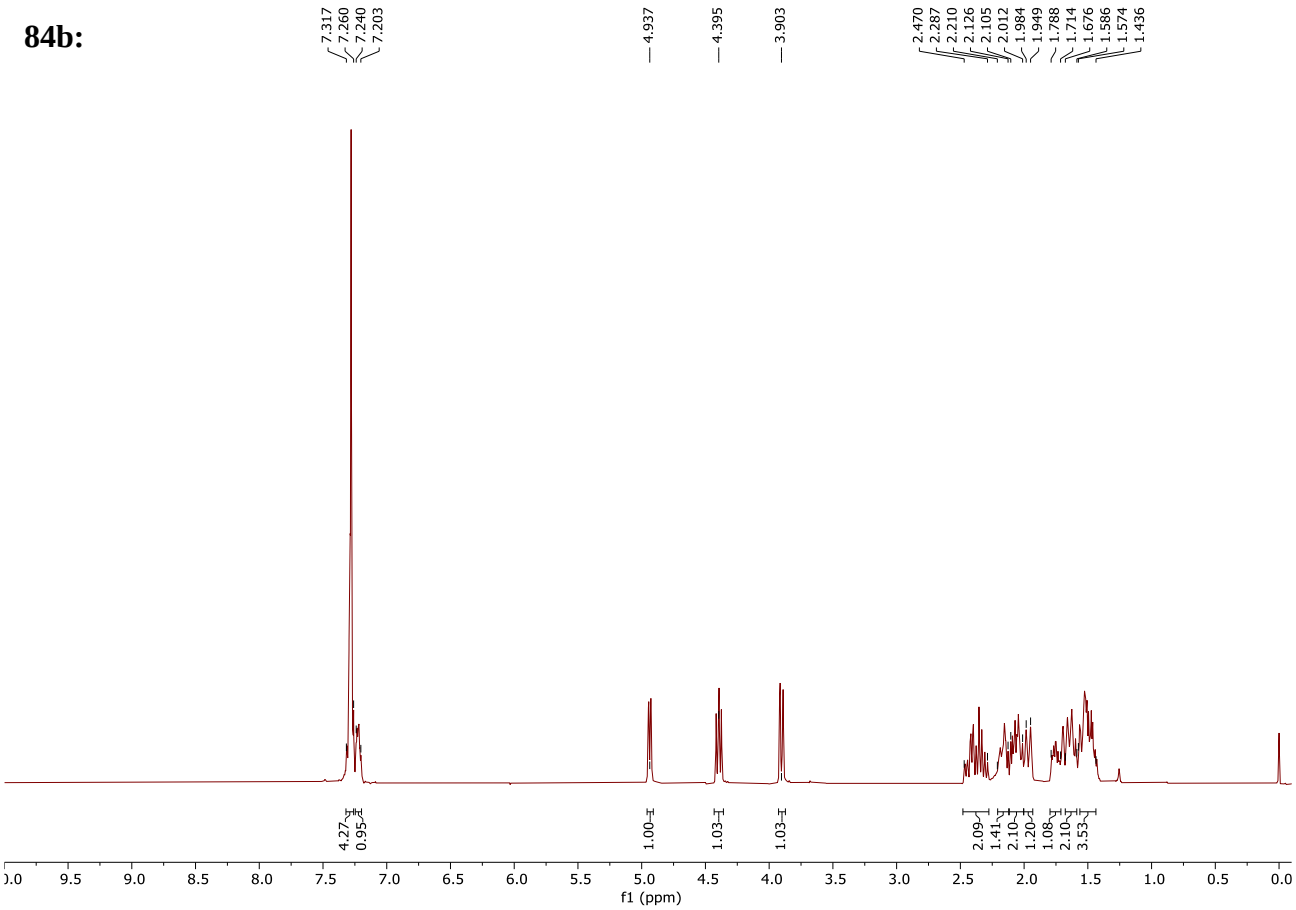
84b:

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H, ArH), 7.24-7.20 (m, 1H, H-Ar), 4.94 (d, *J* = 7.2 Hz, 1H, H-3), 4.40 (dd, *J* = 7.2, 9.2 Hz, 1H, H-2), 3.90 (dd, *J* = 1.8, 8.8 Hz, 1H, H-2), 2.47-2.29 (m, 2H, H-6), 2.21-2.13 (m, 1H), 2.11-2.01 (m, 2H), 1.98-1.95 (m, 1H), 1.71-1.79 (m, 1H), 1.58-1.67 (m, 2H), 1.44-1.58 (m, 3H).

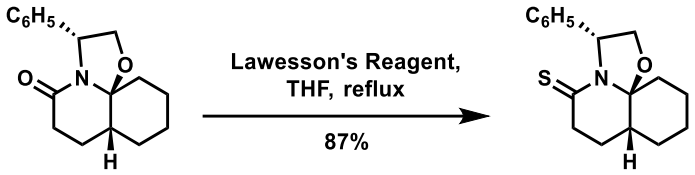
84a:


7.337
7.317
7.298
7.251
7.212
7.192
7.170
5.342
4.504
3.878
2.679
2.498
2.190
2.076
2.004
1.913
1.865
1.830
1.737
1.632
1.609
1.488
1.455
1.377
1.83
0.91
1.82
1.00
1.01
1.03
1.08
1.09
1.12
1.52
1.98
2.72
2.74
1.44
f1 (ppm)

84b:


7.317
7.260
7.240
7.203
4.937
4.395
3.903
2.470
2.287
2.210
2.126
2.105
2.012
1.984
1.949
1.788
1.714
1.676
1.586
1.574
1.436
4.27
0.95
1.00
1.03
1.03
2.09
1.41
2.10
1.20
1.08
2.10
3.53
f1 (ppm)

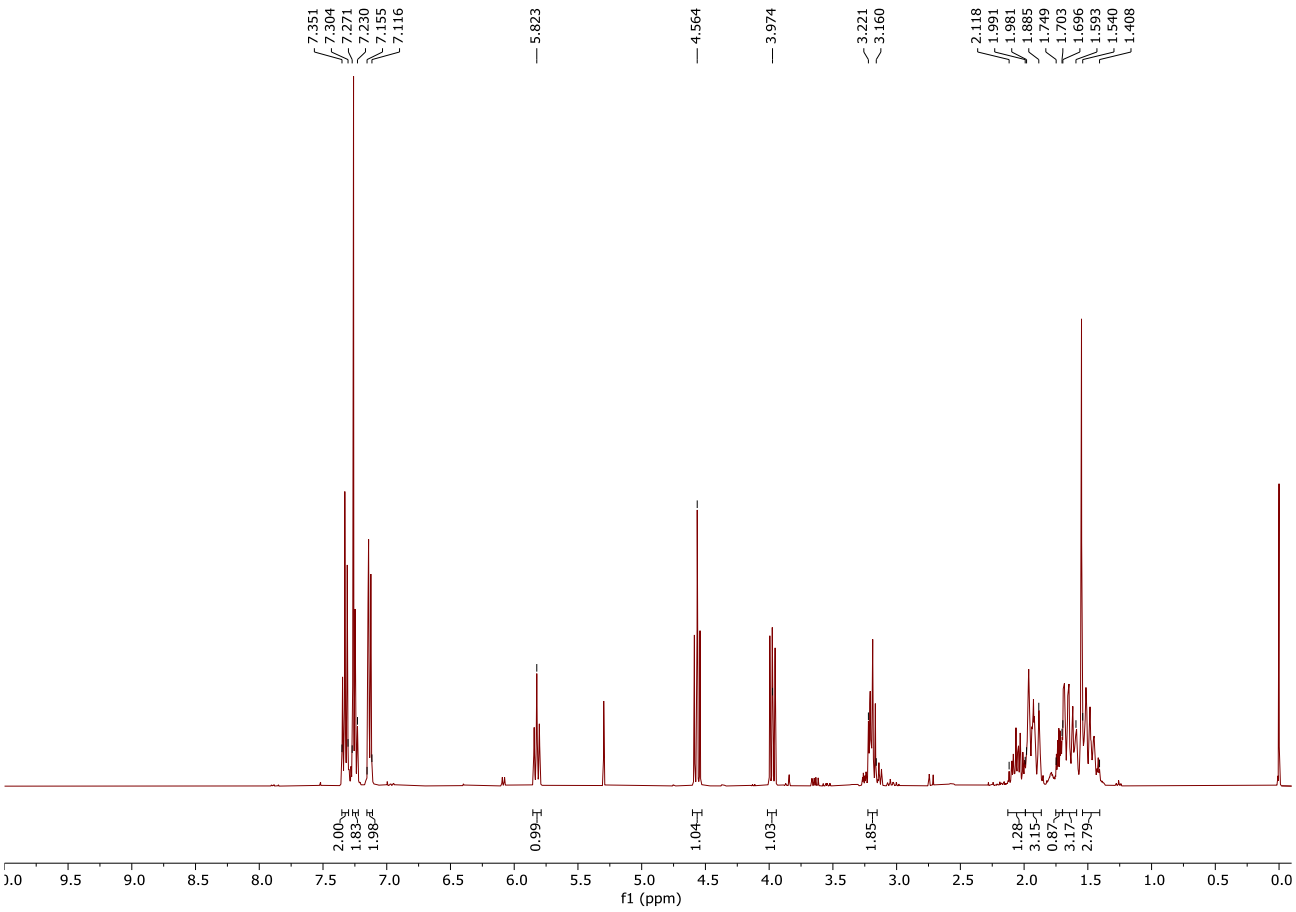
(3*R*,7a*R*,11a*S*)-3-Phenyl-5-thioperhydrooxazolo[2,3-*j*]quinoline (85):



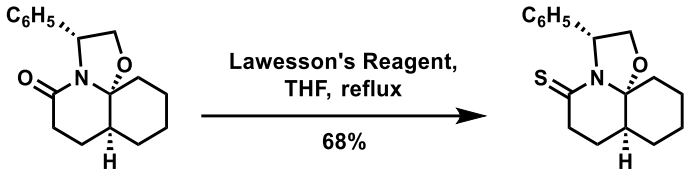
84a **85**

Lawesson's reagent (15.00 g, 55 mmol, 99%) was added to a stirring solution of tricyclic lactam **84a** (9.15 g, 33.7 mmol) in anhydrous THF (330 mL). The resulting mixture was heated at reflux temperature for 2 h, cooled, and concentrated. Flash chromatography (98:2 to 9:1 hexane–EtOAc) afforded thiolactam **85** as a white solid (8.48 g, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H, ArH), 7.27-7.23 (m, 1H, ArH), 7.15-7.12 (m, 2H, ArH), 5.82 (t, *J* = 8 Hz, 1H, H-3), 4.56 (t, *J* = 9.2 Hz, 1H, H-2), 3.97 (dd, *J* = 9.2, 7.6 Hz, 1H, H-2), 3.22-3.17 (m, 2H, H-6), 2.12-1.99 (m, 1H), 1.98-1.88 (m, 3H), 1.74-1.70 (m, 1H), 1.69-1.59 (m, 3H), 1.55-1.45 (m, 3H).


7.351
7.304
7.271
7.230
7.155
7.116
5.823
4.564
3.974
3.221
3.160
2.118
1.991
1.981
1.885
1.749
1.703
1.696
1.593
1.540
1.408
2.00
1.83
1.98
0.99
1.04
1.03
1.85
1.28
3.15
0.87
3.17
2.79
f1 (ppm)

(3*R*,7a*S*,11a*R*)-3-Phenyl-5-thioperhydrooxazolo[2,3-*j*]quinoline (3-epi-*ent*-85)



84b 3-epi-*ent*-85

Operating as described in the preparation of thiolactam **85**, from **84b** (9.29 g, 34.2 mmol), Lawesson's reagent (15.23 g, 37.7 mmol) in anhydrous THF (312 mL), thiolactam **3-epi-*ent*-85** (6.66 g, 68%) was obtained after flash column chromatography (9:1 hexane–EtOAc) as a pale-yellow solid.

mp: 158-160 °C (hexane–CH_2Cl_2).

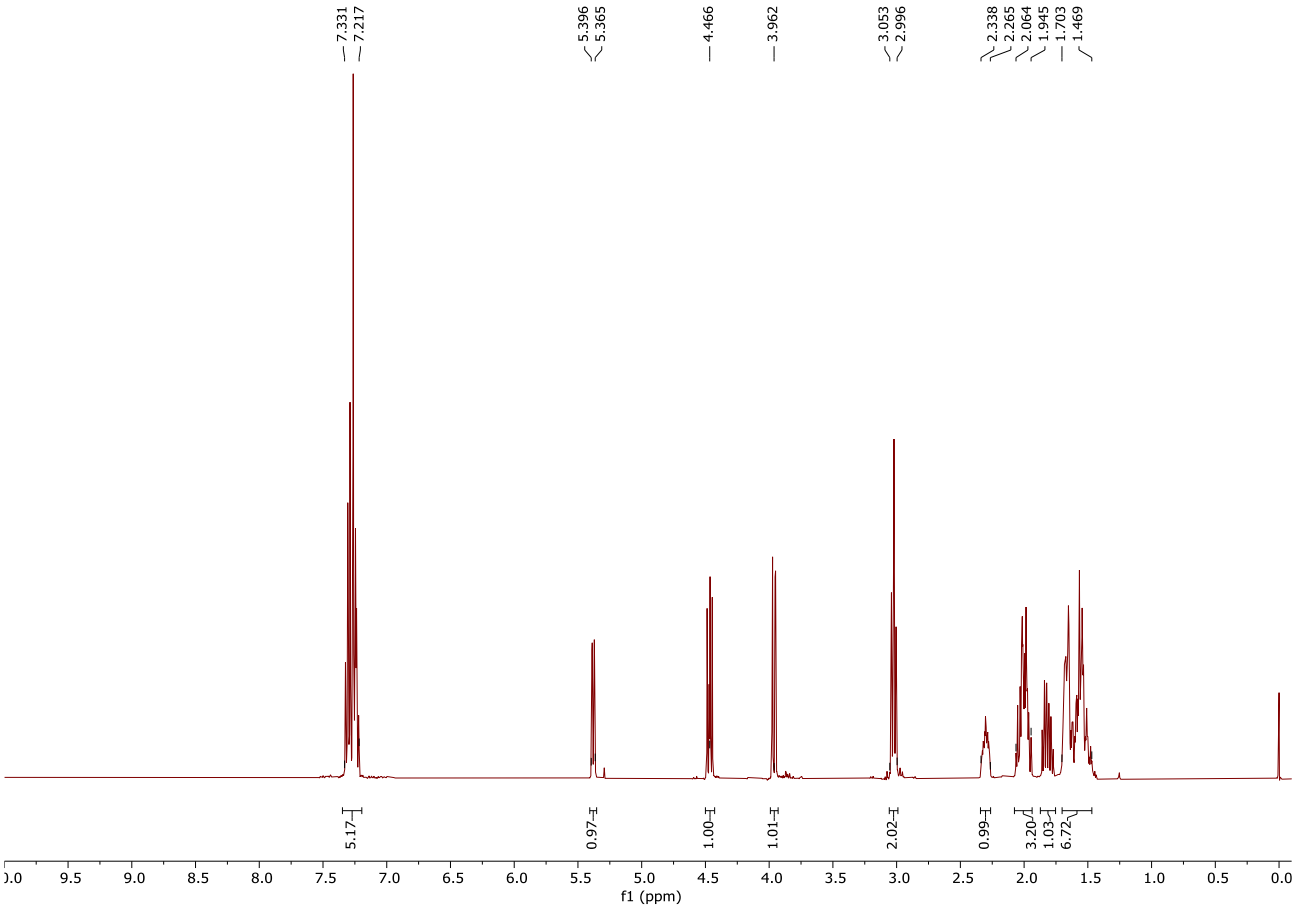
$[\alpha]^{23}_D$ + 258.3 (*c* 1.0, $CHCl_3$).

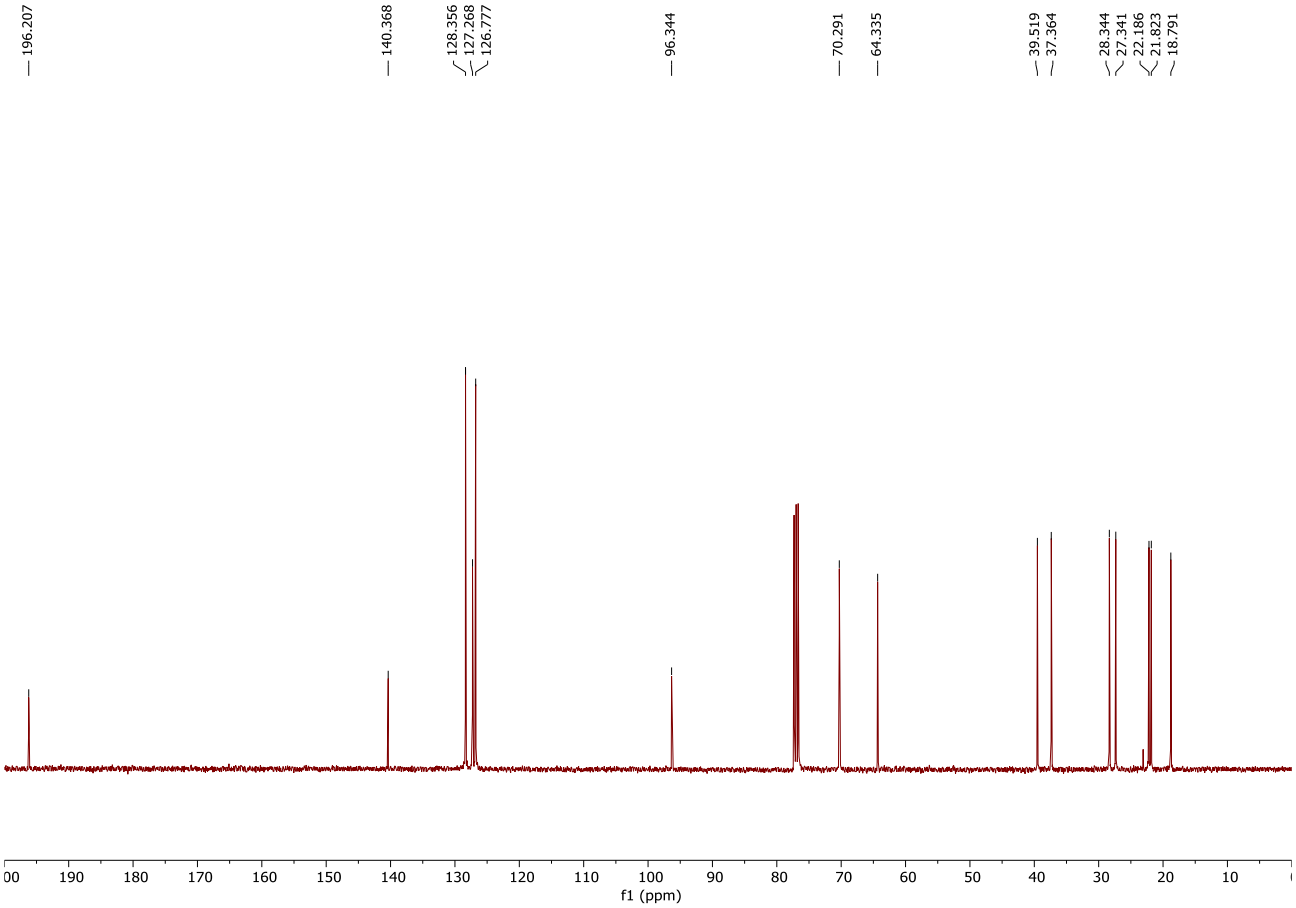
IR (NaCl): 1153 (CS) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H, ArH), 5.39-5.37 (m, 1H, H-3), 4.47 (dd, *J* = 9.2, 6.8 Hz, 1H, H-2), 3.96 (dd, *J* = 9.2, 1.6 Hz, 1H, H-2), 3.06-3.00 (m, 2H, H-6), 2.34-2.26 (m, 1H, H-7a), 2.06-1.95 (m, 3H, H-7, H-8, H-11), 1.86-1.77 (m, 1H, H-7), 1.70-1.47 (m, 6H, H-8, H-9, H-10, H-11).

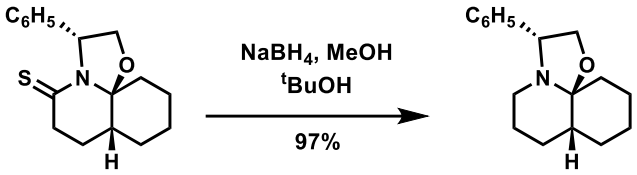
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.2 (CS), 140.4 (C-Ar), 128.4 (CH-Ar), 127.3 (CH-Ar), 126.8 (CH-Ar), 96.3 (C-11a), 70.3 (C-2), 64.3 (C-3), 39.5 (C-6), 37.4 (C-7a), 28.3 (C-11), 27.3 (C-8), 22.2 (CH_2), 21.8 (C-7), 18.8 (CH_2).

HRMS Calcd for [$C_{17}H_{21}NOS + H^+$]: 288.1417; found 288.1417.


7.331
7.217
5.396
5.365
4.466
3.962
3.053
2.996
2.338
2.265
2.064
1.945
1.703
1.469
5.17
0.97
1.00
1.01
2.02
0.99
3.20
1.03
6.72
f1 (ppm)


196.207
140.368
128.356
127.268
126.777
96.344
70.291
64.335
39.519
37.364
28.344
27.341
22.186
21.823
18.791
f1 (ppm)

(3*R*,7a*R*,11a*S*)-3-Phenylperhydrooxazolo[2,3-*j*]quinoline (86):



85 **86**

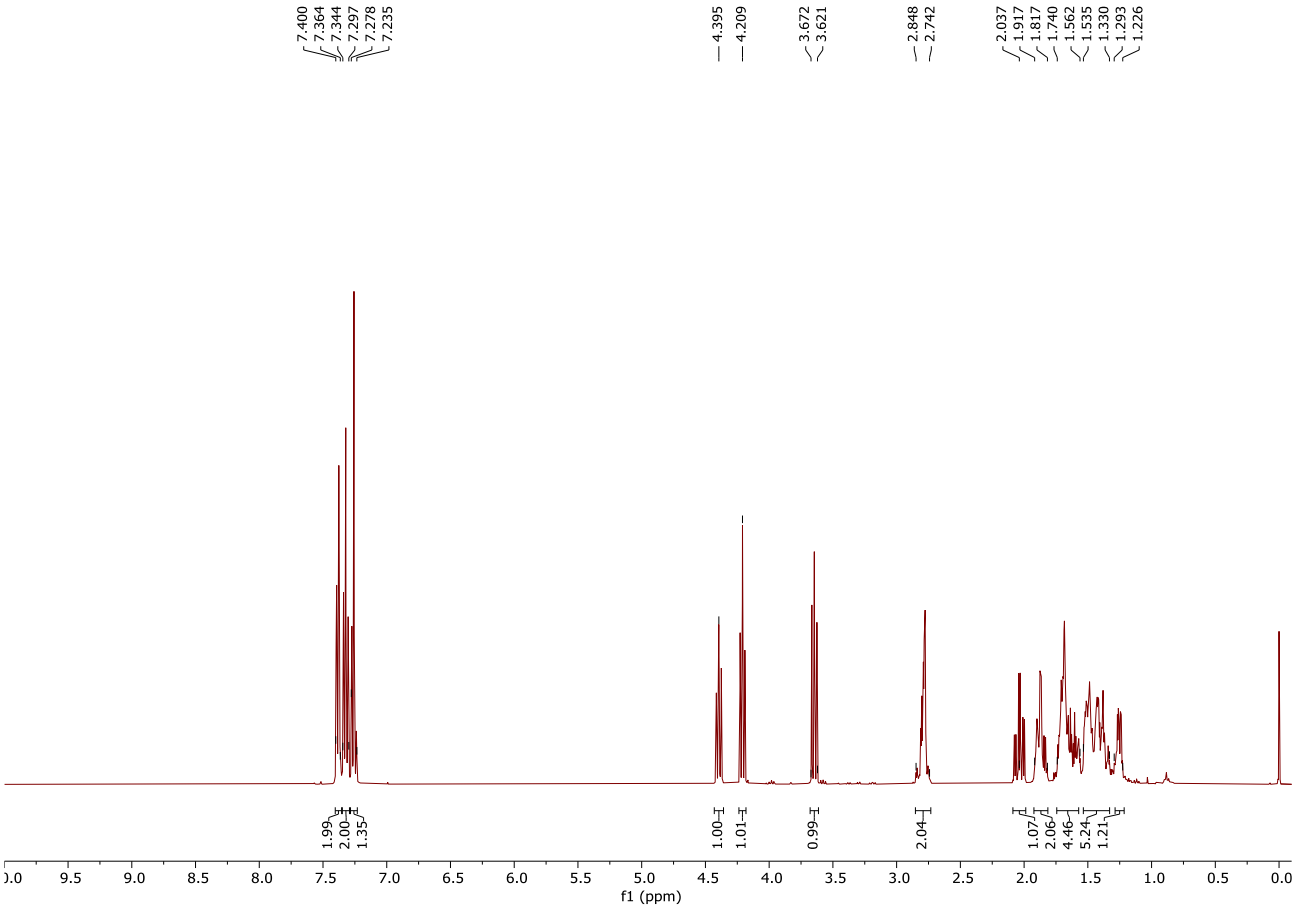
Methanol (12 mL, 295.7 mmol) was added dropwise via a syringe pump over a period of 6 h to a refluxing solution of thiolactam **85** (1.04 g, 3.61 mmol) and $NaBH_4$ (2.18 g, 55.6 mmol) in *t*-BuOH (28 mL). Water was added to the cooled mixture and the resulting solution was extracted with CH_2Cl_2. The combined organic phases were dried, filtrated, and concentrated. Flash column chromatography (95:5 hexane–EtOAc, SiO_2 treated with Et_3N) afforded hemiaminal **86** (904 mg, 97%) as a colorless oil.

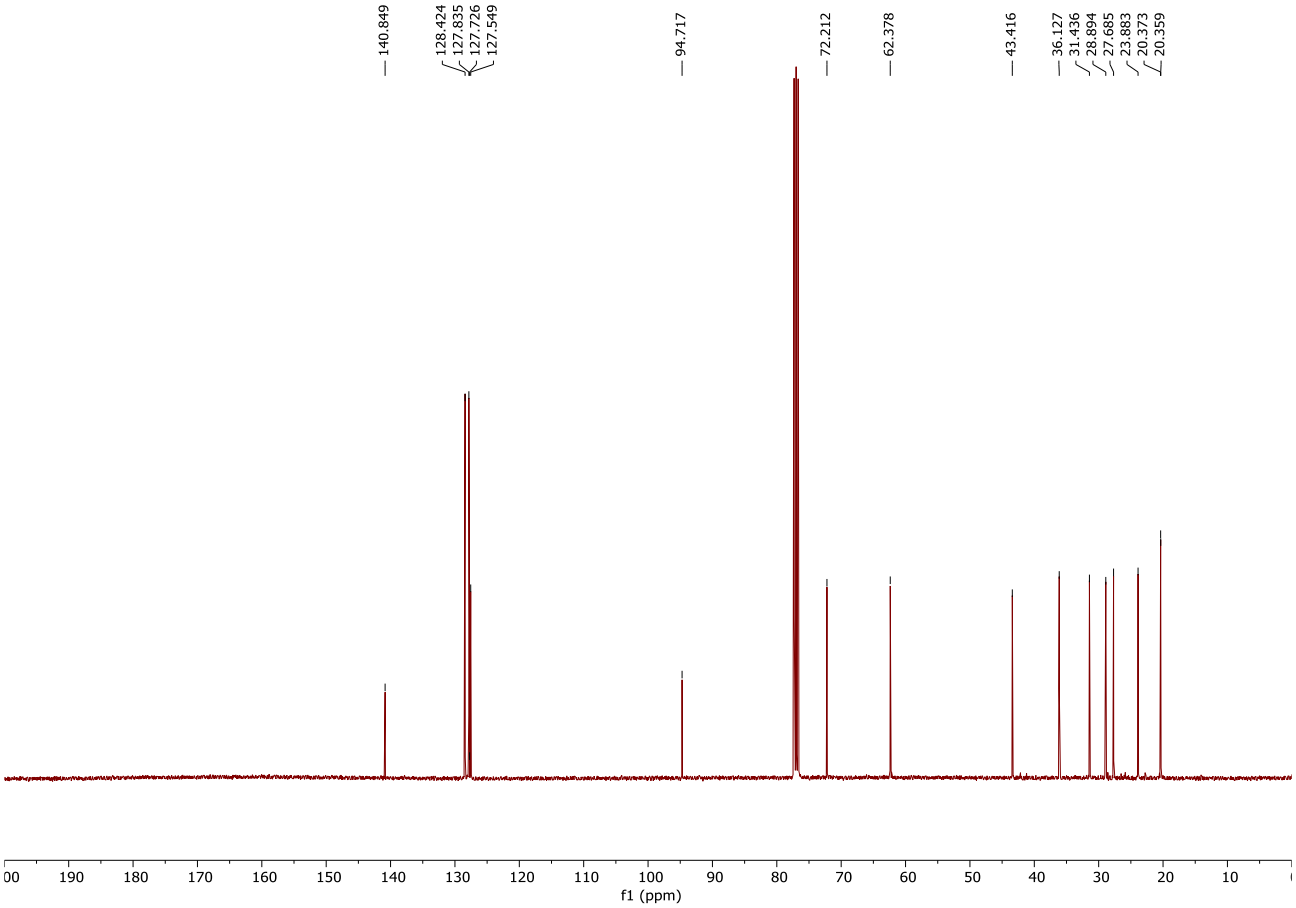
$[\alpha]^{23}_D$ + 258.3 (*c* 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H, ArH), 7.34-7.30 (m, 2H, ArH), 7.28-7.23 (m, 1H, ArH), 4.39 (t, *J* = 7.6 Hz, 1H, H-3), 4.21 (t, *J* = 7.6 Hz, 1H, H-2), 3.67-3.62 (m, 1H, H-2), 2.85-2.74 (m, 2H, H-5), 2.04 (td, *J* = 13.2, 4.8 Hz, 1H, H-11), 1.92-1.82 (m, 2H), 1.74-1.56 (m, 4H), 1.53-1.33 (m, 5H), 1.29-1.23 (m, 1H).

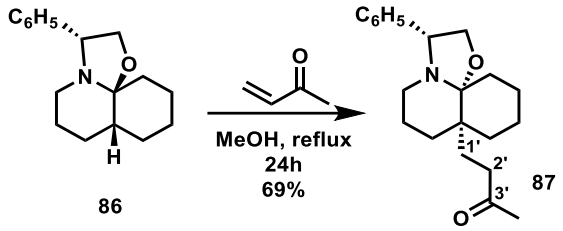
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.8 (C-Ar), 128.4 (CH-Ar), 127.8 (CH-Ar), 127.7 (CH-Ar), 127.5 (CH-Ar), 94.7 (C-11a), 72.2 (C-2), 62.4 (C-3), 43.4 (C-5), 36.1 (C-7a), 31.4 (C-11), 28.9 (CH_2), 27.7 (CH_2), 23.9 (CH_2), 20.4 ($2CH_2$).

HRMS Calcd for [$C_{17}H_{23}NO + H^+$]: 258.1852; found 258.1853.


7.400
7.364
7.344
7.297
7.278
7.235
4.395
4.209
3.672
3.621
2.848
2.742
2.037
1.917
1.817
1.740
1.562
1.535
1.330
1.293
1.226
1.99
2.00
1.35
1.00
1.01
0.99
2.04
1.07
2.06
4.46
5.24
1.21
f1 (ppm)


140.849
128.424
127.835
127.726
127.549
94.717
72.212
62.378
43.416
36.127
31.436
28.894
27.685
23.883
20.373
20.359
f1 (ppm)

(3*R*,7a*S*,11a*R*)-7a-(3-Oxobutyl)-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (87):



Methylvinylketone (0.16 mL, 1.95 mmol) was added to a stirring solution of amine **86** (100 mg) in methanol (2.0 mL), and the resulting mixture was stirred at reflux temperature for 24 h. After cooling at room temperature, the solvent was evaporated. Flash chromatography (98:2 to 85:15 hexane–EtOAc) afforded compound **87** (100 mg, 69%) as a colorless gum.

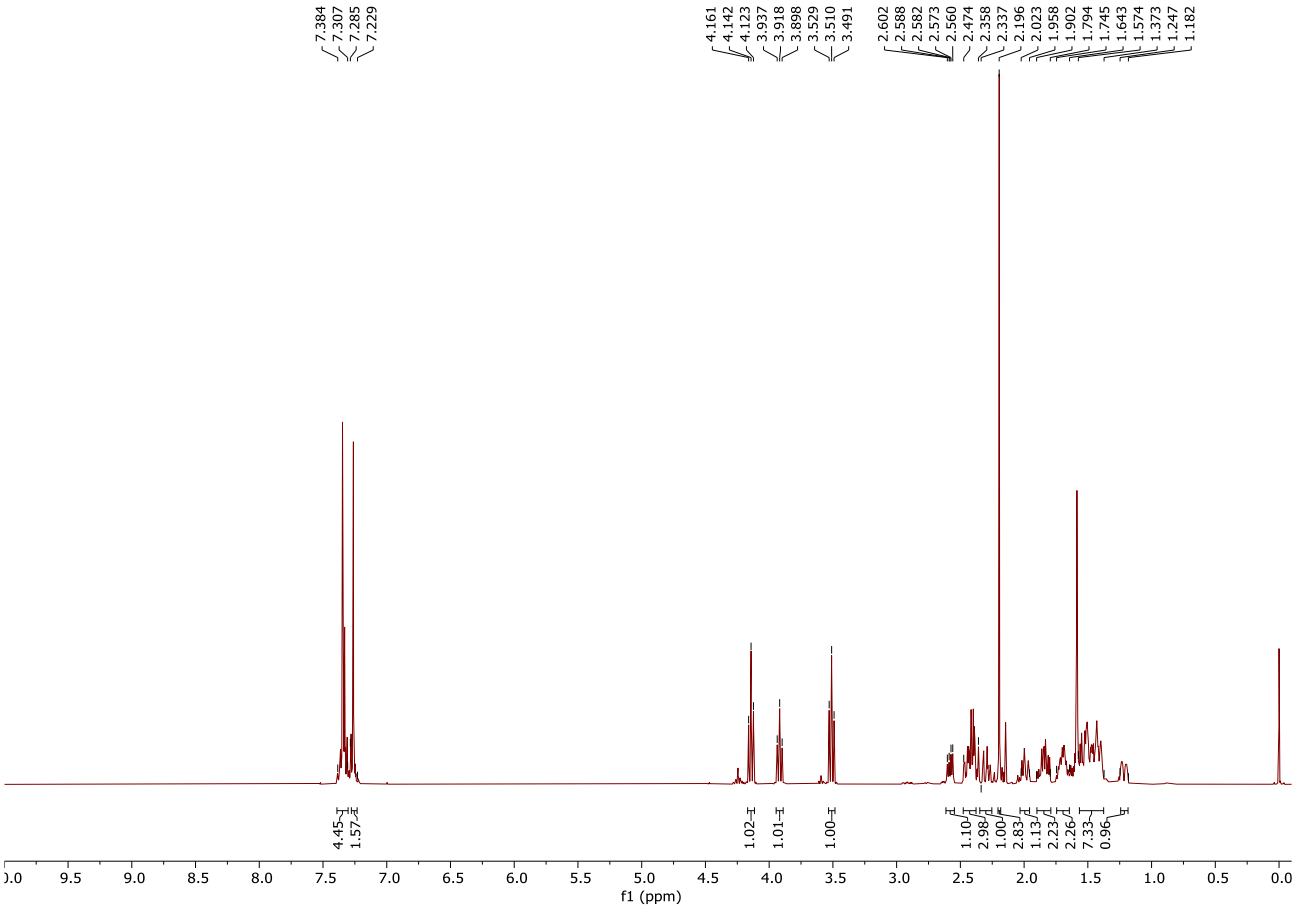
$[\alpha]^{23}_{D}$ –84.1 (c 1.0, $CHCl_3$).

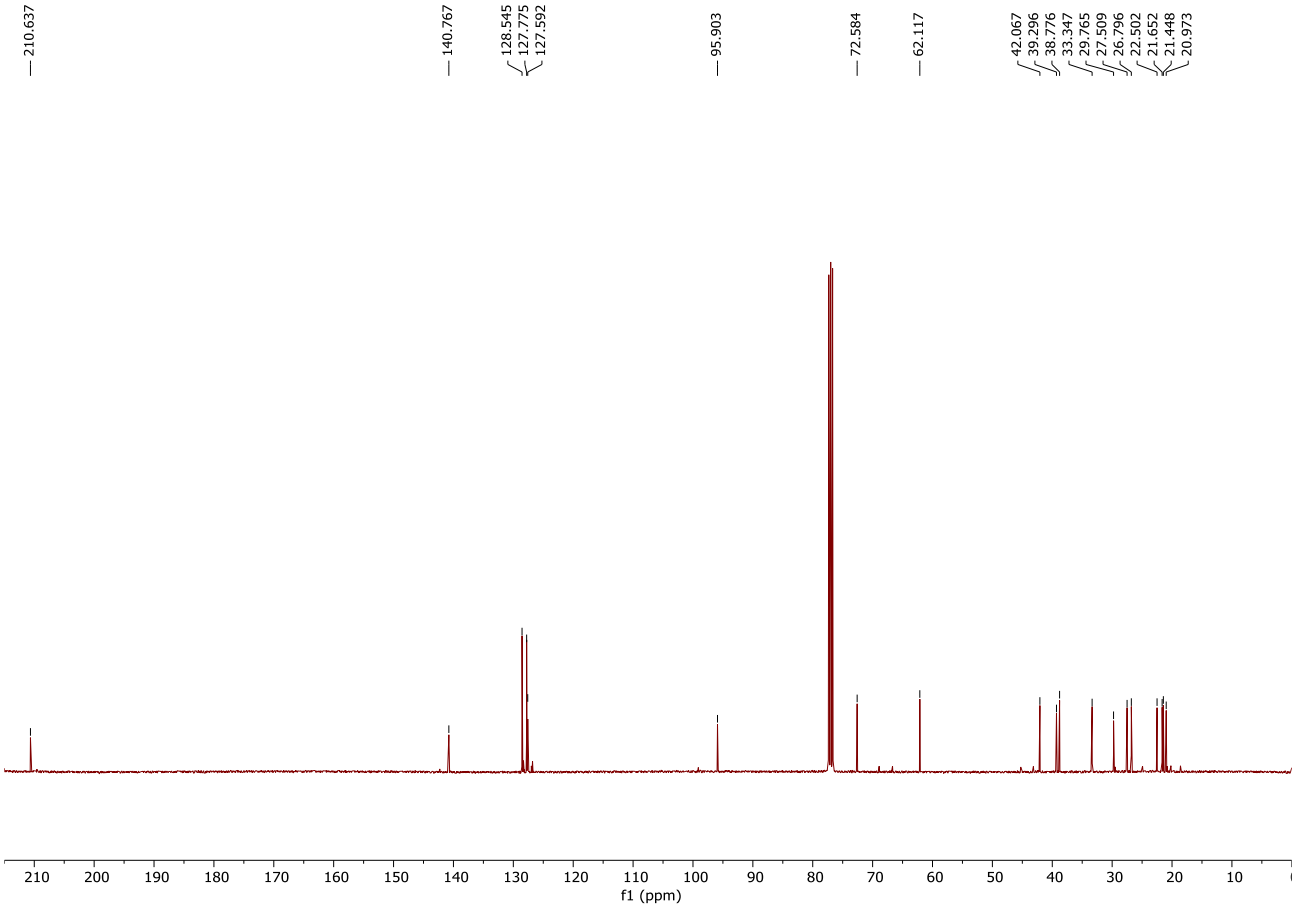
IR (NaCl): 1713 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.38-7.31 (m, 4H, ArH), 7.29-7.23 (m, 1H, ArH), 4.14 (t, *J* = 7.6 Hz, 1H, H-2), 3.92 (t, *J* = 7.6 Hz, 1H, H-3), 3.51 (t, *J* = 7.6 Hz, 1H, H-2), 2.58 (dd, *J* = 11.6, 5.6 Hz, 1H, H-5), 2.47-2.36 (m, 3H, H-2', H-5 and H-6) , 2.34-2.25 (m, 1H, H-2'), 2.20 (s, 3H, CH_3), 2.02-1.96 (m, 1H, H-6), 1.90-1.79 (m, 2H), 1.75-1.64 (m, 2H), 1.57-1.37 (m, 7H), 1.25-1.18 (m, 1H).

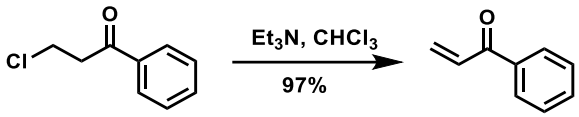
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.6 (CO), 140.8 (C-Ar), 128.5 (CH-Ar), 127.8 (CH-Ar), 127.6 (CH-Ar), 95.9 (C-11a), 72.6 (C-2), 62.1 (C-3), 42.1 (C-5), 39.3 (C-7a), 38.8 (C-2'), 33.3 (CH_2), 29.8 (CH_3), 27.5 (CH_2), 26.8 (C-6), 22.5 (CH_2), 21.7 (CH_2), 21.4 (CH_2), 21.0 (CH_2).

HRMS Calcd for [$C_{21}H_{29}NO_2 + H^+$]: 328.2271; found 328.2275.


7.384
7.307
7.285
7.229
4.161
4.142
4.123
3.937
3.918
3.898
3.529
3.510
3.491
2.602
2.588
2.582
2.573
2.560
2.474
2.358
2.337
2.196
2.023
1.958
1.902
1.794
1.745
1.643
1.574
1.373
1.247
1.182
4.45
1.57
1.02
1.01
1.00
1.10
2.98
1.00
2.83
1.13
2.23
2.26
7.33
0.96
f1 (ppm)


210.637
140.767
128.545
127.775
127.592
95.903
72.584
62.117
42.067
39.296
38.776
33.347
29.765
27.509
26.796
22.502
21.652
21.448
20.973
f1 (ppm)

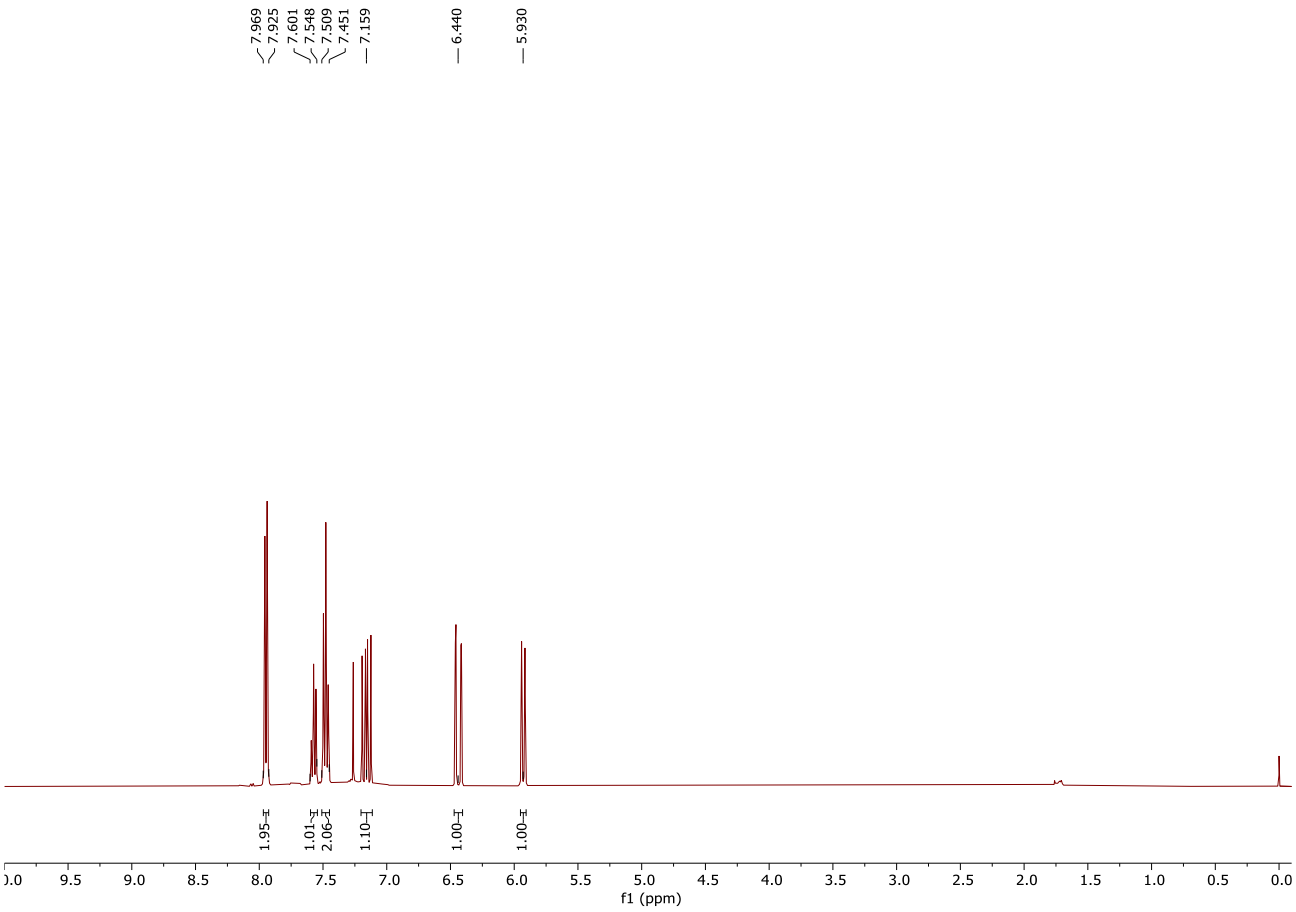
Phenyl vinyl ketone:[99]



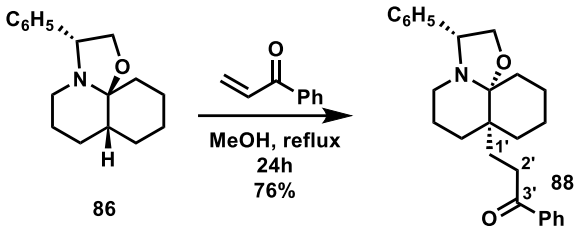
To a stirred solution of 3-chloropropiophenone (5.0 g, 29.65 mmol) in $CHCl_3$ (66 mL) was added Et_3N (9.9 mL, 71.2 mmol) and stirred for 18 h. The mixture was washed with 2 M HCl, water, and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford phenyl vinyl ketone (3.80 g, 97%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.92 (m, 2H, ArH), 7.60-7.55 (m, 1H, ArH), 7.51-7.45 (m, 2H, ArH), 7.16 (dd, *J* = 16.8, 10.4 Hz, 1H, H-2), 6.44 (dd, *J* = 16.8, 1.8 Hz, 1H, H-3), 5.93 (dd, *J* = 10.4, 1.8 Hz, 1H, H-3).

[99] Dimirjian, C.A.; Castiñeira Reis, M.; Balmond, E.I.; Turman, N. C.; Rodriguez, E.P.; Di Maso, M.J.; Fettinger, J.C.; Tantillo D.J.; Shaw, J. T. *Org. Lett.* **2019**, *21*, 7209-7212.


7.969
7.925
7.601
7.548
7.509
7.451
7.159
6.440
5.930
1.95
1.01
2.06
1.10
1.00
1.00
f1 (ppm)

(3*R*,7a*S*,11a*R*)-7a-(3-oxo-3-phenylpropyl)-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (88):



Operating as described in the preparation of compound **87**, from **86** (78.1 mg, 0.30 mmol) and phenyl vinyl ketone (200 mg, 1.52 mmol) in MeOH (2 mL), compound **88** (90 mg, 76 %) was obtained after flash column chromatography (99:1 to 95:5 hexane–EtOAc) as a yellowish oil.

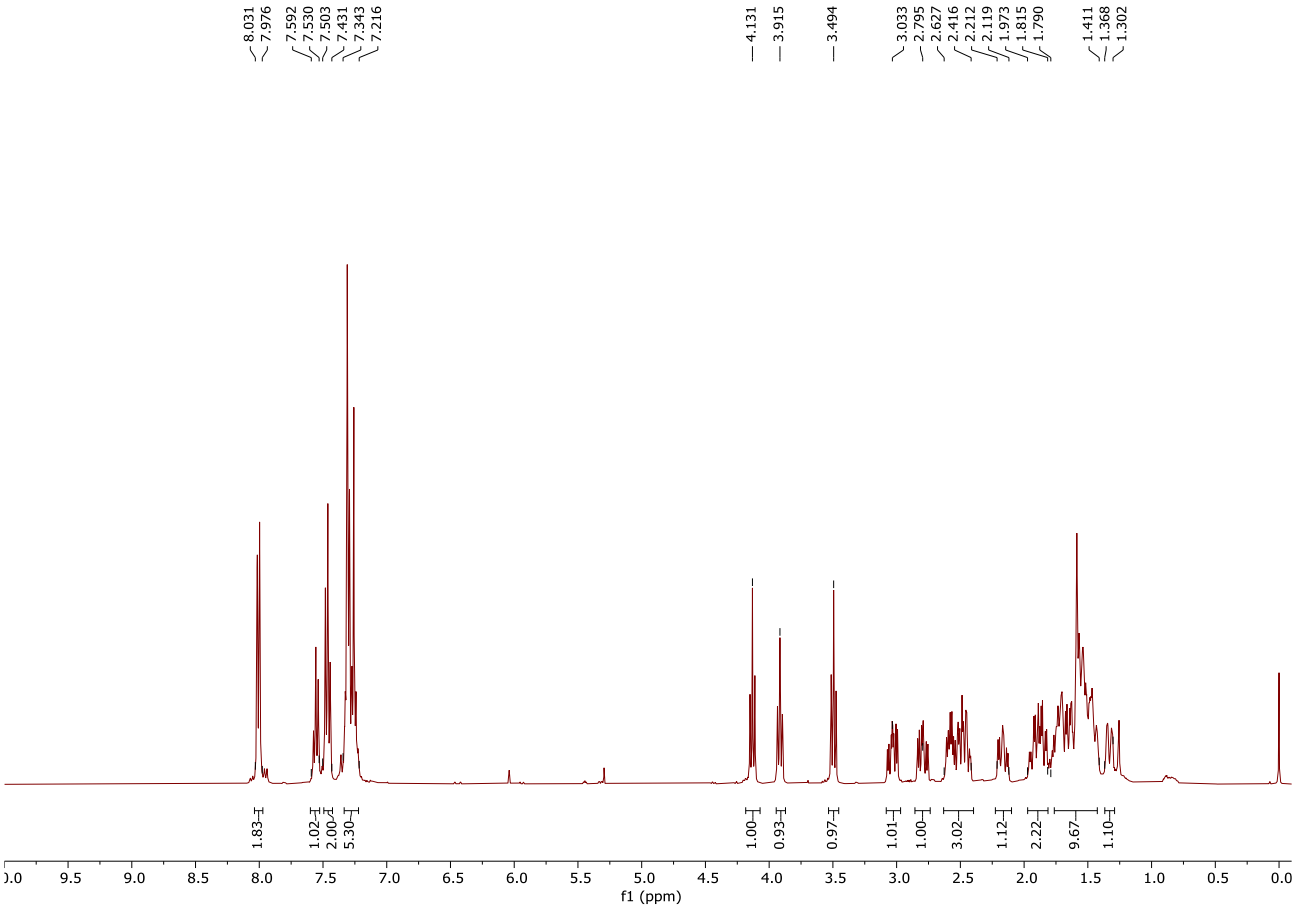
$[\alpha]^{23}_{D}$ – 29.6 (*c* 1.0, $CHCl_3$).

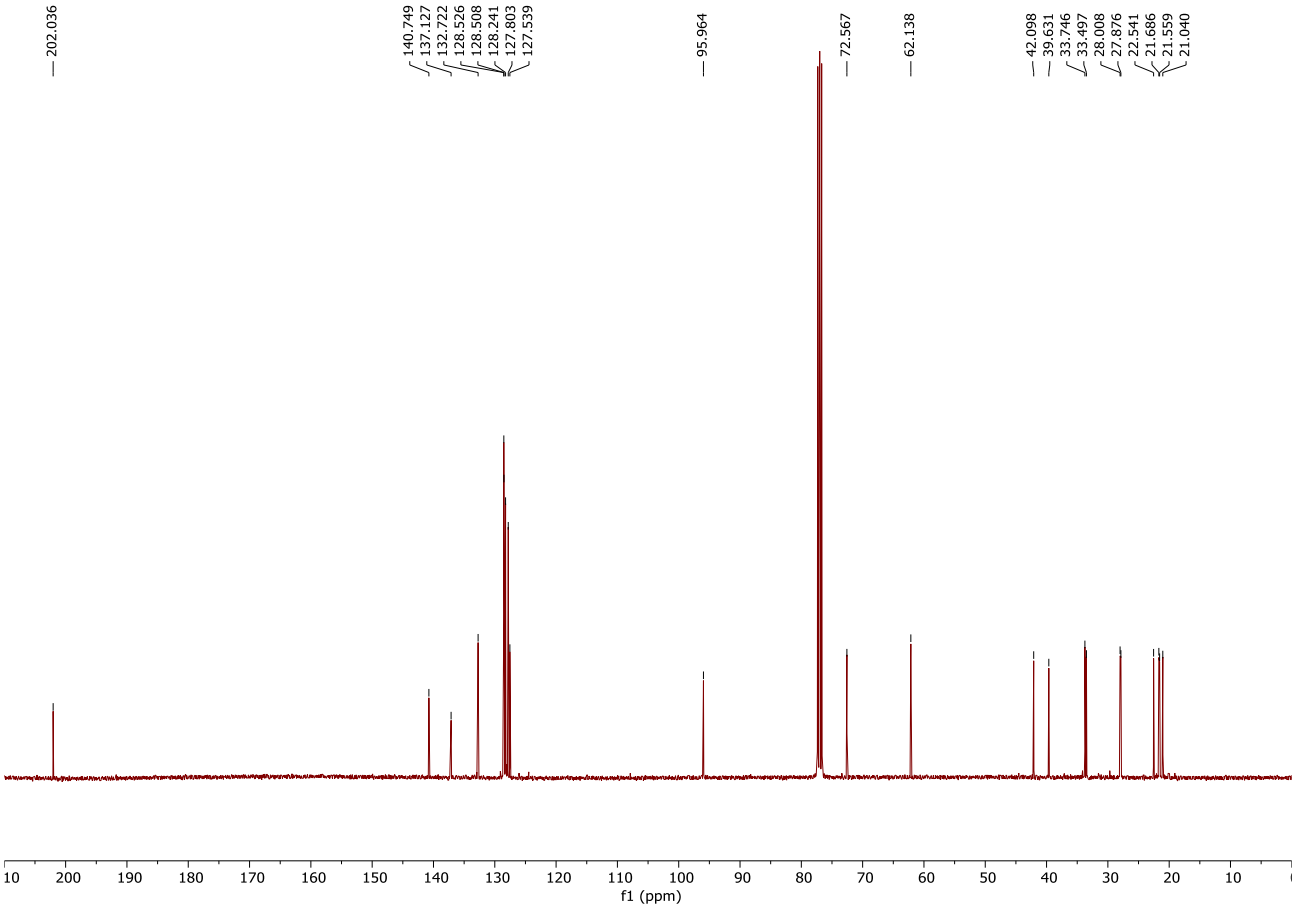
IR (NaCl): 1685 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 8.03-7.98 (m, 2H, ArH), 7.59-7.53 (m, 1H, ArH), 7.50-7.43 (m, 2H, ArH), 7.34-7.22 (m, 5H, ArH), 4.13 (t, *J* = 7.6 Hz, 1H, H-2), 3.92 (t, *J* = 7.6 Hz, 1H, H-3), 3.49 (t, *J* = 7.6 Hz, 1H, H-2), 3.03 (ddd, *J* = 14.8, 12.0, 4.8 Hz, 1H, H-2'), 2.80 (ddd, *J* = 14.8, 12.0, 5.2 Hz, 1H, H-2'), 2.63-2.42 (m, 3H, H-5 and H-1'), 2.21-2.12 (m, 1H, H-1'), 1.97-1.82 (m, 2H), 1.79-1.41 (m, 9H), 1.37-1.30 (m, 1H).

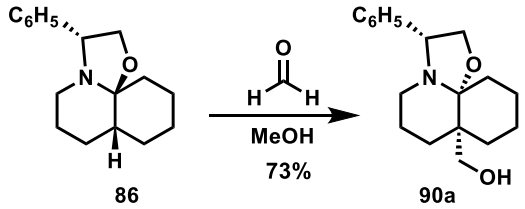
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.0 (CO), 140.7 (C-Ar), 137.1 (C-Ar), 132.7 (CH-Ar), 128.5 (CH-Ar), 128.5 (CH-Ar), 128.2 (CH-Ar), 127.8 (CH-Ar), 127.5 (CH-Ar), 96.0 (C-11a), 72.6 (C-2), 62.1 (C-3), 42.1 (C-5), 39.6 (C-7a), 33.7 (C-2'), 33.5 (CH_2), 28.0 (C-1'), 27.9 (CH_2), 22.5 (CH_2), 21.7 (CH_2), 21.6 (CH_2), 21.0 (CH_2).

HRMS Calcd for [$C_{26}H_{31}NO_2 + H^+$]: 390.2428; found 390.2426.


8.031
7.976
7.592
7.530
7.503
7.431
7.343
7.216
4.131
3.915
3.494
3.033
2.795
2.627
2.416
2.212
2.119
1.973
1.815
1.790
1.411
1.368
1.302
1.83
1.02
2.00
5.30
1.00
0.93
0.97
1.01
1.00
3.02
1.12
2.22
9.67
1.10
f1 (ppm)


202.036
140.749
137.127
132.722
128.526
128.508
128.241
127.803
127.539
95.964
72.567
62.138
42.098
39.631
33.746
33.497
28.008
27.876
22.541
21.686
21.559
21.040
f1 (ppm)

(3*R*,7a*S*,11a*R*)-7a-(Hydroxymethyl)-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (90a):



Formalin (0.09 mL of a 37% w/w in H_2O solution, 1.21 mmol) was added to a stirring solution of hemiaminal **86** (62.5 mg, 0.24 mmol) in MeOH (1.2 mL) and the resulting mixture was stirred at room temperature for 21 h. Then, the solvent was evaporated. Flash chromatography (95:5 to 8:2 hexane–EtOAc) afforded **90a** (51 mg, 73%) as a colorless oil.

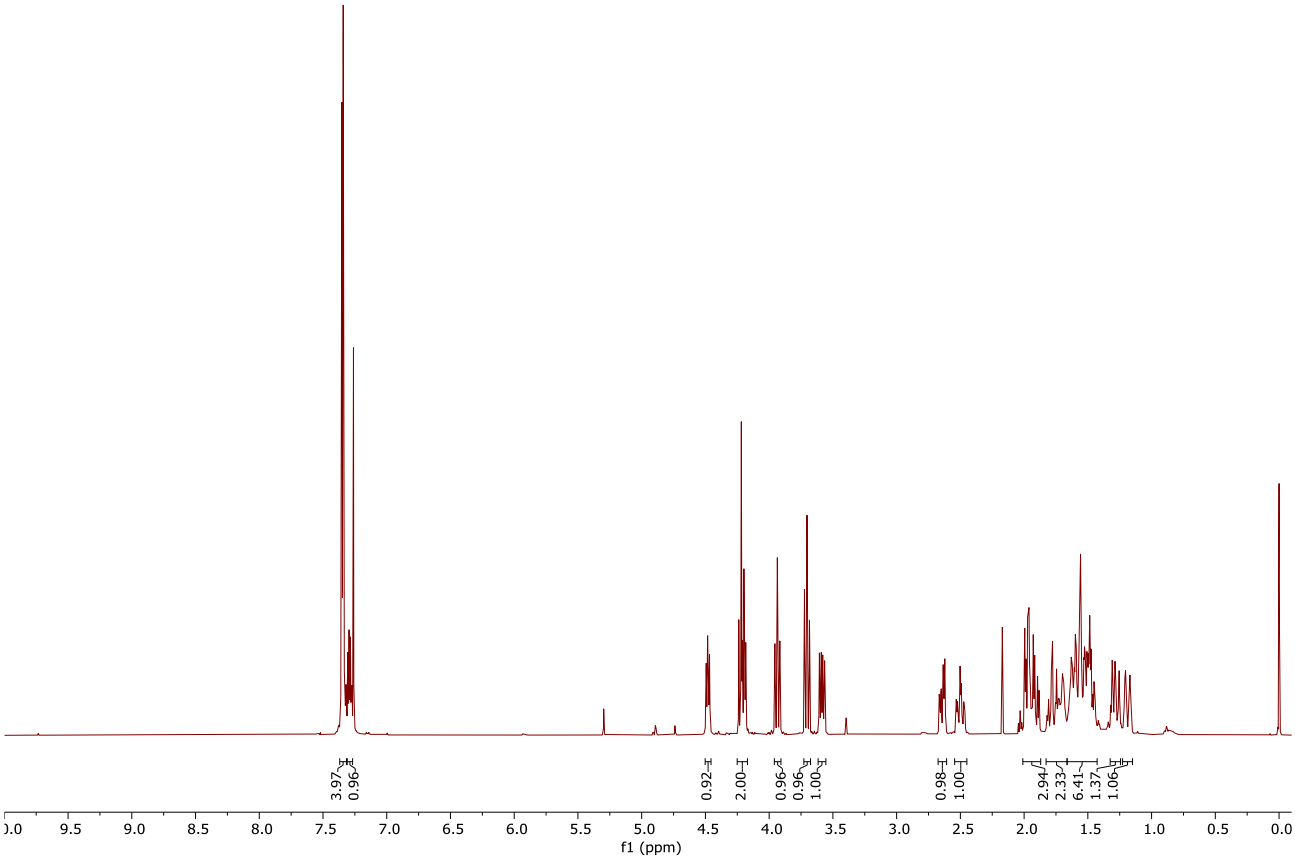
$[\alpha]^{23}_D$ –73.2 (*c* 0.8, $CHCl_3$).

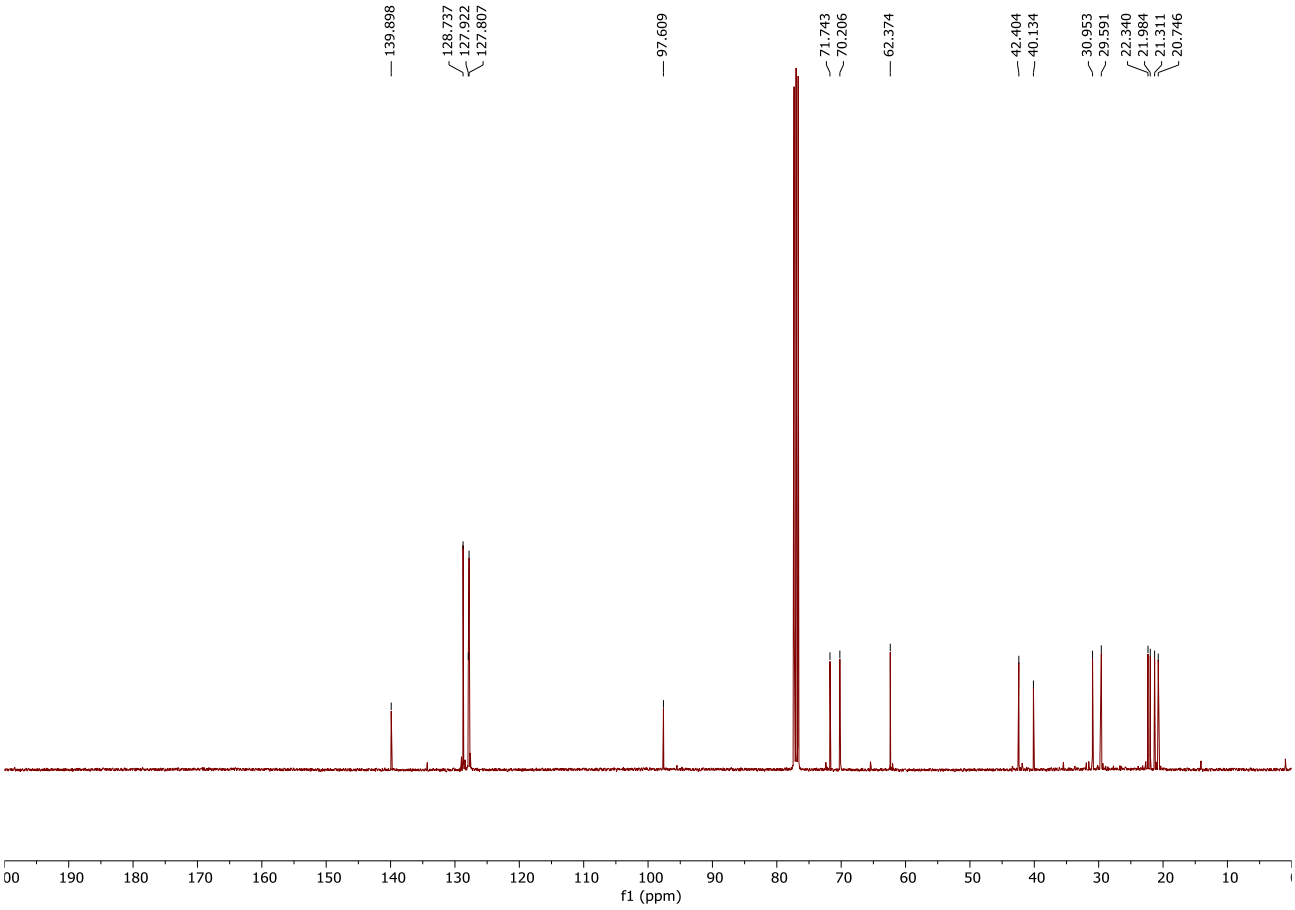
IR (NaCl): 3500 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.32-7.37 (m, 4H, ArH), 7.27-7.31 (m ,1H, ArH), 4.47-4.49 (m, 1H, OH), 4.17-4.25 (m, 2H, H-2 and H-1'), 3.94 (t, *J* = 8.0 Hz, 1H, H-3), 3.70 (t, *J* = 8.0 Hz, 1H, H-2), 3.59 (dd, *J* = 10.4, 6.0 Hz, 1H, H-1'), 2.61-2.67 (m, 1H, H-5), 2.46-2.54 (m, 1H, H-5), 1.87-2.00 (m, 3H), 1.67-1.82 (m, 2H), 1.43-1.66 (m, 5H), 1.24-1.32 (m ,1H), 1.16-1.21 (m, 1H).

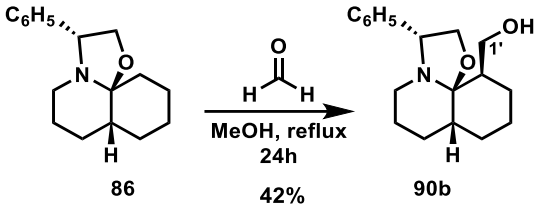
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.9 (C-Ar), 128.7 (CH-Ar), 127.9 (CH-Ar), 127.8 (CH-Ar), 97.6 (C-11a), 71.7 (C-2), 70.2 (C-1'), 62.4 (C-3), 42.4 (C-5), 40.1 (C-7a), 31.0 (CH_2), 29.6 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 21.3 (CH_2), 20.7 (CH_2).

HRMS Calcd for [$C_{18}H_{25}NO_2 + H^+$]: 288.1958; found 288.1964.


3.97
0.96
0.92
2.00
0.96
0.96
1.00
0.98
1.00
2.94
2.33
6.41
1.37
1.06
f1 (ppm)


139.898
128.737
127.922
127.807
97.609
71.743
70.206
62.374
42.404
40.134
30.953
29.591
22.340
21.984
21.311
20.746
f1 (ppm)

(3*R*,7a*R*, 11*R*, 11a*R*)-11-(Hydroxymethyl)-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (90b):



Operating as described in the preparation of compound **87**, from **86** (545 mg, 2.11 mmol) and formalin (0.8 mL of a 37% w/w in H_2O solution, 10.6 mmol) in MeOH (10.6 mL), compound **90b** (258 mg, 42%) was obtained after flash column chromatography (95:5 to 8:2 hexane–EtOAc) as a white solid.

mp = 76-78 °C (hexane/CH_2Cl_2).

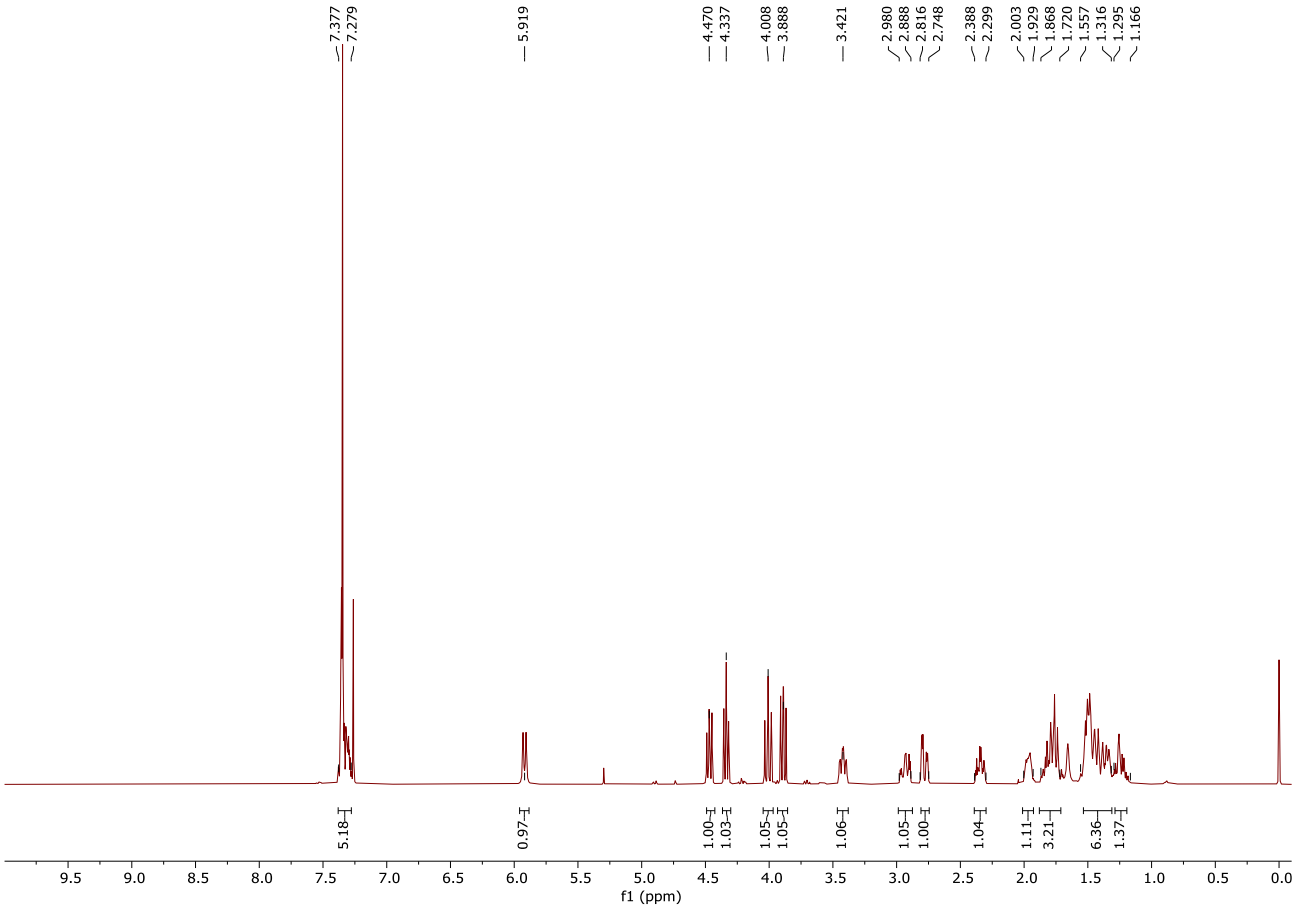
$[\alpha]^{23}_D$ –77.1 (*c* 0.9, $CHCl_3$).

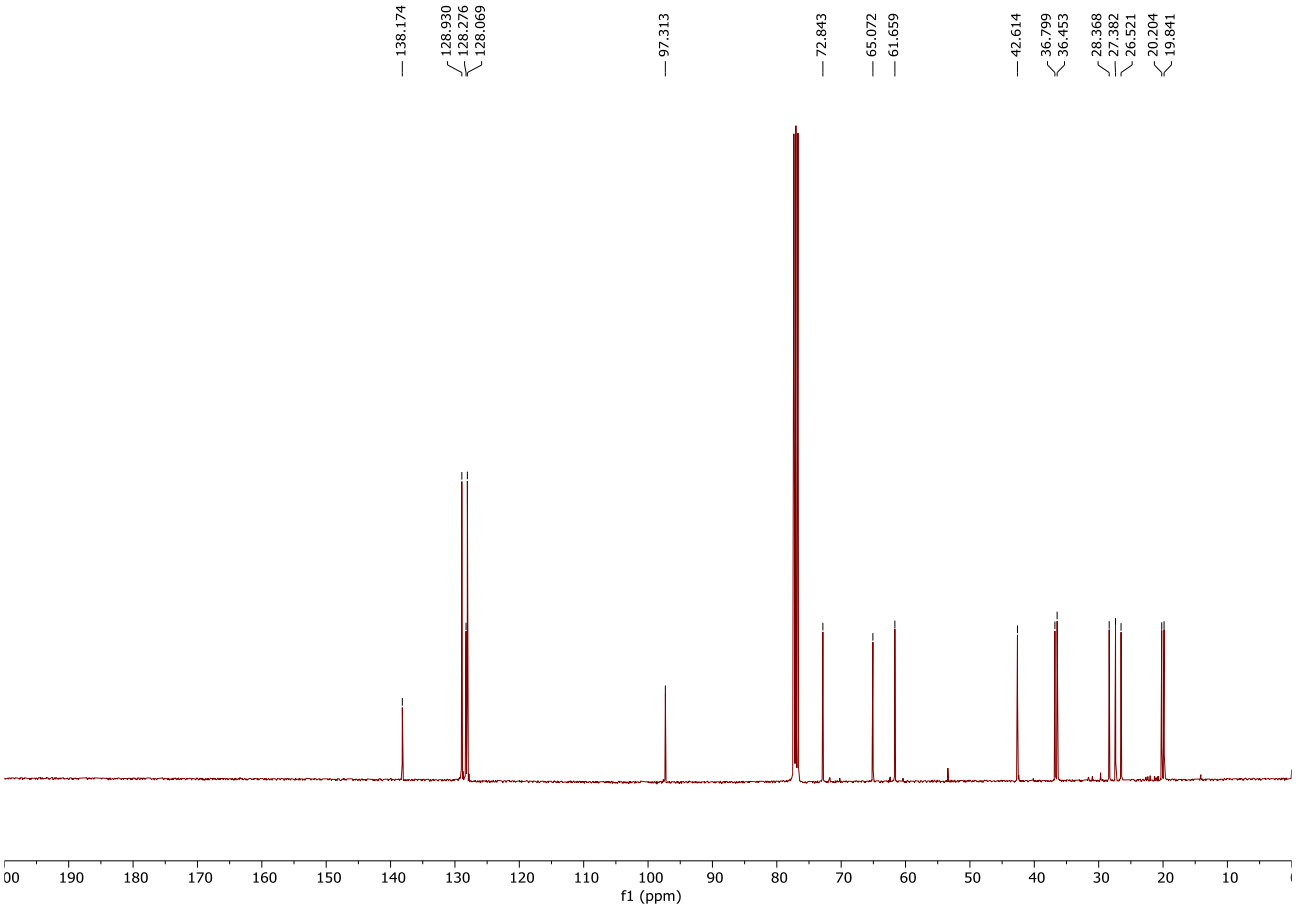
IR (NaCl): 3284 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.38-7.28 (m, 5H, ArH), 5.92 (d, *J* = 9.6 Hz, 1H, OH), 4.47 (dd, *J* = 8.8, 7.2 Hz, 1H, H-3), 4.34 (t, *J* = 7.6 Hz, 1H, H-2), 4.01 (t, *J* = 10.4 Hz, 1H, H-1'), 3.89 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 3.42 (td, *J* = 10.4, 3.2 Hz, 1H, H-1'), 2.98-2.89 (m, 1H, H-5), 2.82-2.75 (m, 1H, H-5), 2.39-2.30 (m, 1H, H-11), 2.00-1.93 (H-7a), 1.87-1.72 (m, 3H), 1.56-1.32 (m, 6H), 1.29-1.17 (m, 1H).

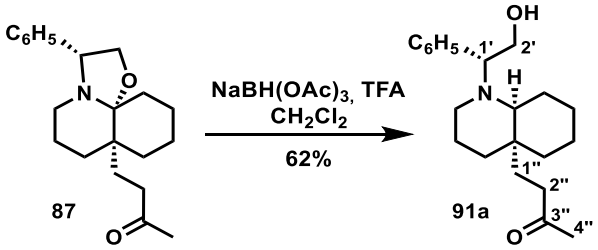
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.2 (C-Ar), 128.9 (CH-Ar), 128.3 (CH-Ar), 128.1 (CH-Ar), 97.3 (C-11a), 72.8 (C-3), 65.1 (C-1'), 61.7 (C-2), 42.6 (C-5), 36.8 (C-11), 36.5 (C-7a), 28.4 (CH_2), 27.4 (CH_2), 26.5 (CH_2), 20.2 (CH_2), 19.8 (CH_2).

HRMS Calcd for [$C_{18}H_{25}NO_2$ + H^+]: 288.1958; found 288.1962.


7.377
7.279
5.919
4.470
4.337
4.008
3.888
3.421
2.980
2.888
2.816
2.748
2.388
2.299
2.003
1.929
1.868
1.720
1.557
1.316
1.295
1.166
5.18
0.97
1.00
1.03
1.05
1.05
1.06
1.05
1.00
1.04
1.11
3.21
6.36
1.37
f1 (ppm)


138.174
128.930
128.276
128.069
97.313
72.843
65.072
61.659
42.614
36.799
36.453
28.368
27.382
26.521
20.204
19.841
f1 (ppm)

(4a*S*,8a*S*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-4a-(3-oxobutyl)decahydroquinoline (91a):



Trifluoroacetic acid (23 μL, 0.31 mmol) and $NaBH(OAc)_3$ (646 mg, 3.05 mmol) were sequentially added to a stirring solution of **87** (201 mg, 0.61 mmol) in dry CH_2Cl_2 (7.8 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 5 h. Then, water was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (from 9:1 to 1:1 hexane–EtOAc) afforded **91a** (128 mg, 62%) as a viscous colorless liquid.

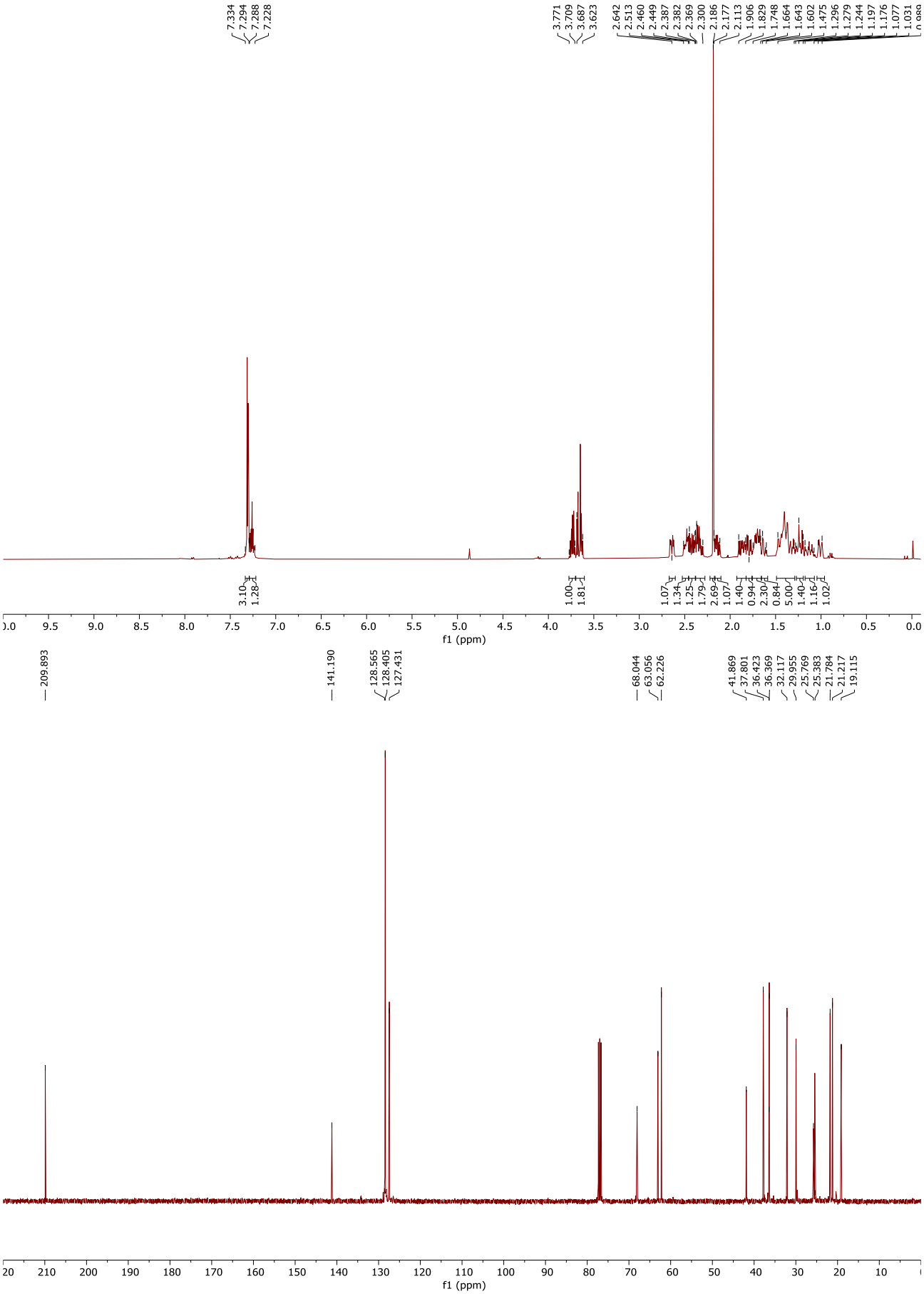
$[\alpha]^{23}_D$ + 5.2 (*c* 1.0, $CHCl_3$);

IR (NaCl): 1712 (CO), 3454 (OH) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.33-7.29 (m, 3H, ArH), 7.23-7.29 (m, 2H, ArH), 3.70-3.77 (m, 1H, H-1'), 3.62-3.69 (m, 2H, H-1' and H-2'), 2.64 (dd, *J* = 11.6, 3.6 Hz, 1H, H-8a), 2.51-2.46 (m, 1H), 2.45-2.39 (m, 1H), 2.37-2.30 (m, 2H), 2.19 (s, 3H, H-4''), 2.17-2.11 (m, 1H), 1.91-1.83 (m, 1H), 1.79 (dd, *J* = 16.6, 4.4 Hz, 1H), 1.75-1.66 (m, 2H), 1.64-1.60 (m, 1H), 1.48-1.30 (m, 5H), 1.28-1.20 (m, 1H), 1.18-1.08 (m, 1H), 1.03-0.99 (m, 1H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.9 (CO), 141.2 (C-Ar), 128.6 (CH-Ar), 128.4 (CH-Ar), 127.4 (CH-Ar), 68.0 (C-1'), 63.1 (C-2'), 62.2 (C-8a), 41.9 (CH_2), 37.8 (CH_2), 36.4 (C-4a), 36.4 (CH_2), 32.1 (CH_2), 30.0 (C-4''), 25.6 (CH_2), 25.3 (CH_2), 21.8 (CH_2), 21.2 (CH_2), 19.1 (CH_2).

HRMS Calcd for $[C_{21}H_{31}NO_2 + H^+]$: 330.2428; found 330.2428.


7.334
7.294
7.288
7.228
3.771
3.709
3.687
3.623
2.642
2.513
2.460
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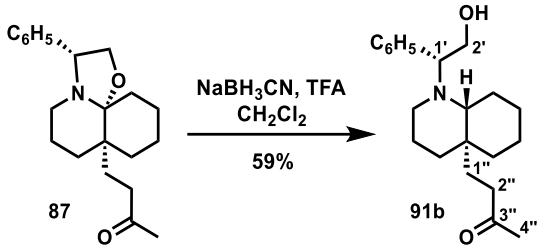
2.387
2.382
2.369
2.300
2.186
2.177
2.113
1.906
1.829
1.748
1.664
1.643
1.602
1.475
1.296
1.279
1.244
1.197
1.176
1.077
1.031
3.10
1.28
1.00
1.81
1.07
1.34
1.25
1.79
2.69
1.07
1.40
0.94
2.30
0.84
5.00
1.40
1.16
1.02
f1 (ppm)
209.893
141.190
128.565
128.405
127.431
68.044
63.056
62.226
41.869
37.801
36.423
36.369
32.117
29.955
25.769
25.383
21.784
21.217
19.115
f1 (ppm)

(4a*S*,8a*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-4a-(3-oxobutyl)decahydroquinoline (91b):



Trifluoroacetic acid (20 μL, 0.26 mmol) and $NaBH_3CN$ (166 mg, 2.64 mmol) were sequentially added to a stirring solution of **87** (173 mg, 0.53 mmol) in dry CH_2Cl_2 (6.4 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 24 h. Then water was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (from 9:1 to 5:5 hexane–EtOAc) afforded **91b** (103 mg, 59%) as a viscous colorless liquid.

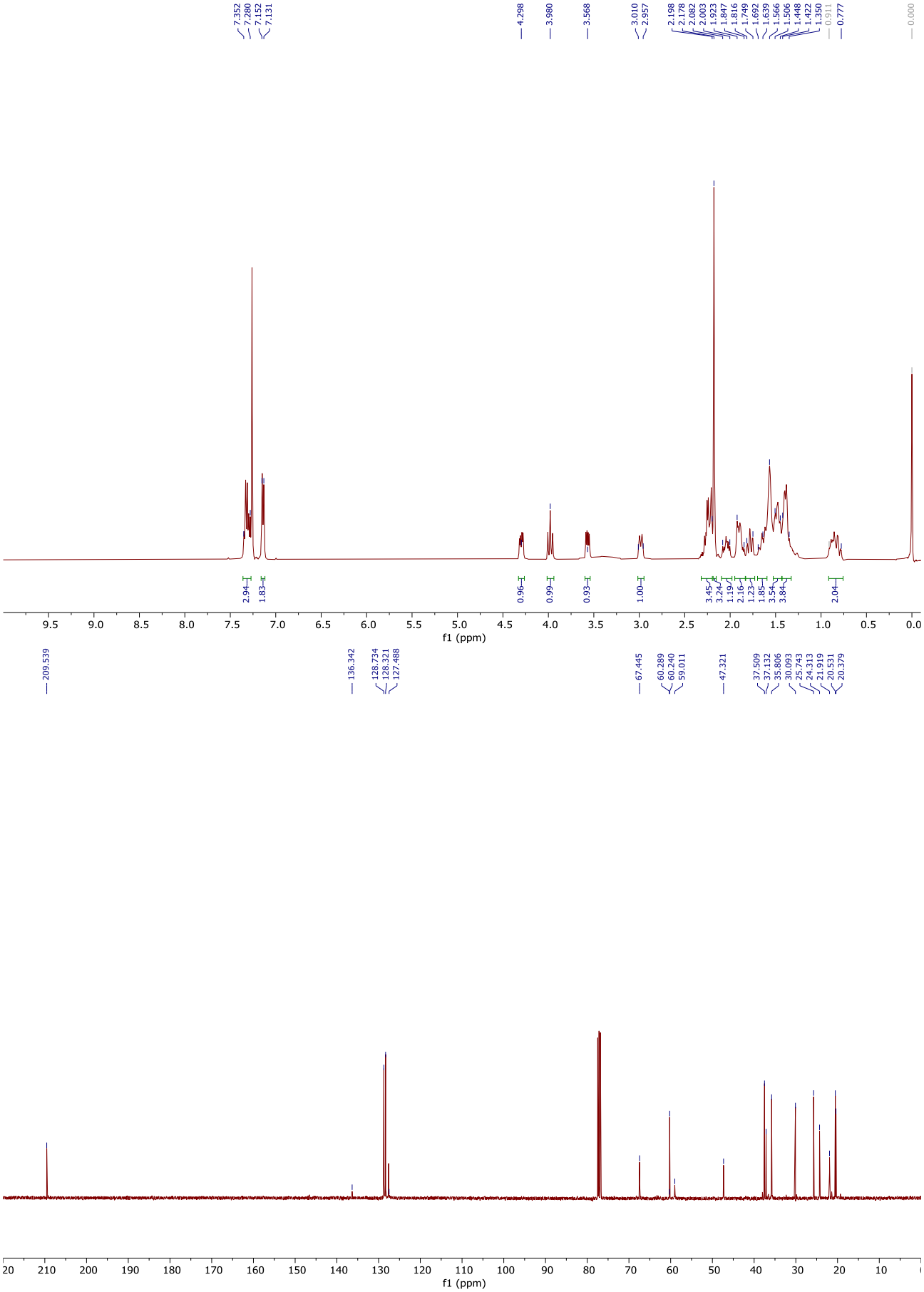
$[\alpha]^{23}_D$ –55.6 (*c* 1.0, $CHCl_3$).

IR (NaCl): 1713 (CO), 3446 (OH) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.28-7.35 (m, 3H, ArH), 7.13-7.15 (m, 2H, ArH), 4.30 (dd, *J* = 5.0, 10.9 Hz, 1H), 3.98 (t, *J* = 10.5 Hz, 1H, H-2'), 3.57 (dd, *J* = 5.0, 10.2 Hz, 1H, H-2'), 2.98 (d, *J* = 11.24 Hz, 1H, H-2), 2.20-2.32 (m, 4H), 2.18 (s, 4H, H-3''/H-8a), 2.00-2.08 (m, 1H), 1.85-1.92 (m, 2H), 1.77 (dt, *J* = 2.8, 12.0 Hz, 1H, H-2), 1.59-1.68 (m, 1H), 1.45-1.51 (m, 3H), 1.35-1.40 (m, 4H), 0.78-0.91 (m, 2H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.5 (CO), 136.3 (C-Ar) 128.7 (CH-Ar), 128.3 (CH-Ar), 127.5 (CH-Ar), 67.4 (C-8a), 60.2 (CH_2), 59.0 (C-1'), 47.3 (CH_2), 37.5 (CH_2), 37.1 (C-4a), 37.1 (CH_2), 35.8 (CH_2), 30.1 (C-3''), 25.7 (CH_2), 24.3 (CH_2), 21.9 (CH_2), 20.5 (CH_2), 20.4 (CH_2).

HRMS Calcd for [$C_{21}H_{31}NO_2 + H^+$]: 330.2428; found 330.2426.


7.352
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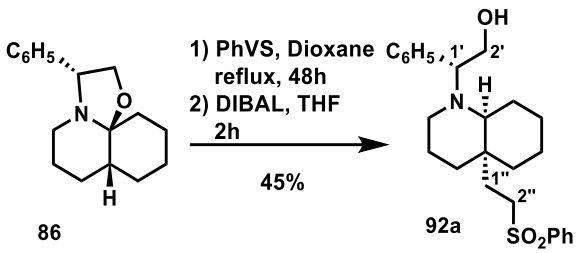
7.131
4.298
3.980
3.568
3.010
2.957
2.198
2.178
2.082
2.003
1.923
1.847
1.816
1.749
1.692
1.639
1.566
1.506
1.448
1.422
1.350
0.911
0.777
0.000
2.94
1.83
0.96
0.99
0.93
1.00
3.45
3.24
1.19
2.16
1.23
1.85
3.54
3.84
2.04
f1 (ppm)
209.539
136.342
128.734
128.321
127.488
67.445
60.289
60.240
59.011
47.321
37.509
37.132
35.806
30.093
25.743
24.313
21.919
20.531
20.379
f1 (ppm)

(4a*S*,8a*S*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-4a-[2-(phenylsulfonyl)ethyl]decahydroquinoline (92a):



First Step: Phenyl vinyl sulfone (2 g, 11.91 mmol) was added to a stirring solution of amine **86** (613 mg, 2.38 mmol) in dioxane (12 mL), and the resulting mixture was stirred at reflux temperature for 48 h. After cooling at room temperature, the solvent was evaporated to give an inseparable mixture of **89** (513 mg, 51% - Yield calculated by ^{1}H NMR) and PhVS

Second Step: DIBAL (12.1 mL of a 1M solution in THF, 12.1 mmol) was added to a stirring solution of the above crude in anhydrous THF (13.4 mL), and the stirring was continued at room temperature for 2 h. After that, ~~a~~ 2M solution of NaOH was added, and the mixture was extracted with CH_2Cl_2, dried and evaporated. Flash column chromatography (from 9:1 to 7:3 hexane–EtOAc) afforded decahydroquinoline **92a** (453 mg, 88%, 45% from **86**) as a white solid.

mp = 152-153 °C (hexane/CH_2Cl_2).

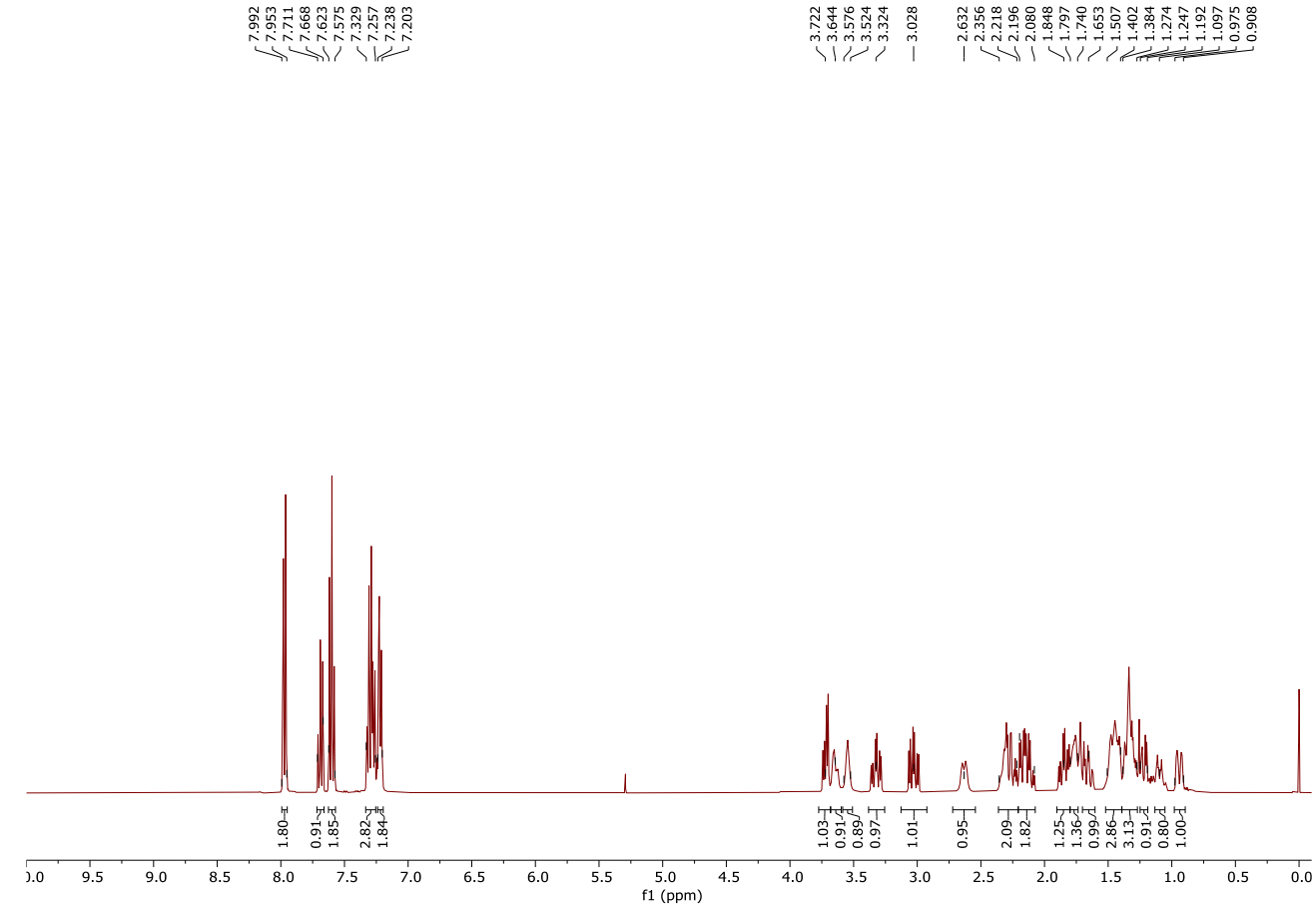
$[\alpha]^{23}_{D}$ +10.0 (*c* 1.0, $CHCl_3$).

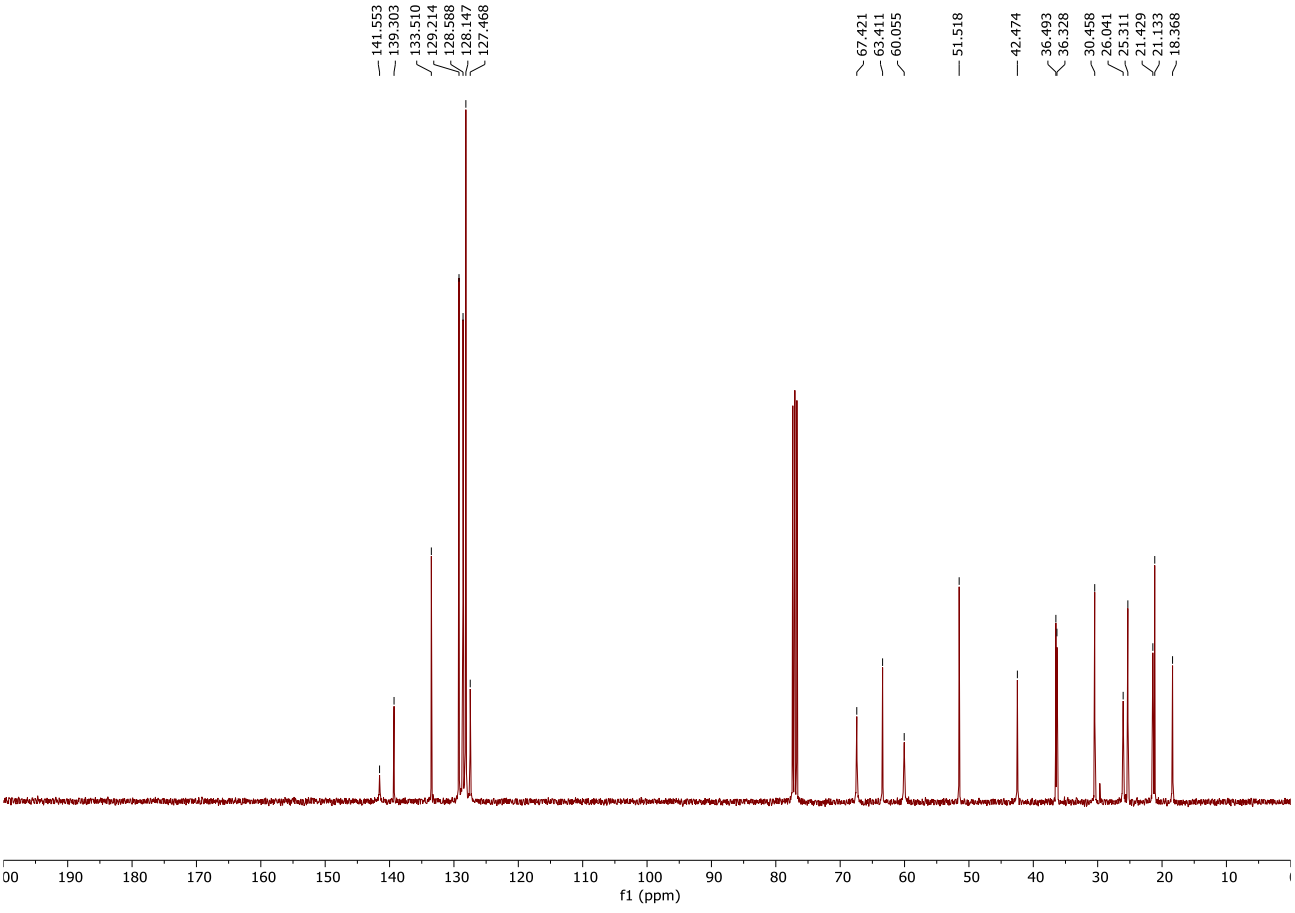
IR (NaCl): 3500 (OH), 1146, 1306 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 8.00-7.95 (m, 2H, ArH), 7.71-7.67 (m, 1H, ArH), 7.62-7.58 (m, 2H, ArH), 7.33-7.26 (m, 3H, ArH), 7.24-7.20 (m, 2H ArH), 3.72 (dd, *J* = 11.4, 4.7 Hz, 1H, H-2'), 3.64 (dd, *J* = 11.6, 4.7 Hz, 1H, H-2'), 3.58-3.52 (m, 1H, H-1'), 3.32 (td, *J* = 13.0, 4.8 Hz, 1H, H-2''), 3.02 (td, *J* = 13, 4.8 Hz, 1H, H-2''), 2.63 (d, *J* = 10.3 Hz, 1H, H-8a), 2.36-2.21 (m, 2H, H-2), 2.20-2.08 (m, 2H, H-1''), 1.85 (td, *J* = 14, 5.1 Hz, 1H, H-4), 1.80-1.74 (m, 1H, OH), 1.73-1.71 (m, 1H, H-6), 1.65 (td, *J* = 12.6, 3.6, 1H, H-8), 1.51-1.40 (m, 3H, H-3, H-7, H-8), 1.38-1.27 (m, 3H, H-3, H-5, H-7), 1.24-1.29 (m, 1H, H-5), 1.10 (dt, *J* = 12.6, 3.7 Hz, 1H, H-6), 0.98-0.91 (m, 1H, H-4).

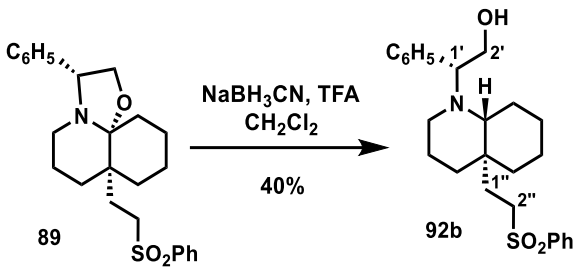
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.6 (C-Ar), 139.3 (C-Ar), 133.5 (CH-Ar), 129.2 (CH-Ar), 128.6 (CH-Ar), 128.1 (CH-Ar), 127.5 (CH-Ar), 67.4 (C-1'), 63.4 (C-2'), 60.1 (C-8a), 51.5 (C-2''), 42.5 (C-2), 36.5 (C-4a), 36.3 (C-5), 30.5 (C-1''), 26.0 (C-4), 25.3 (C-6), 21.4 (C-3), 21.1 (C-7), 18.4 (C-8).

HRMS Calcd for [$C_{25}H_{33}NO_3S$ + H^+]: 428.2254; found 428.2245.


7.992
7.953
7.711
7.668
7.623
7.575
7.329
7.257
7.238
7.203
3.722
3.644
3.576
3.524
3.324
3.028
2.632
2.356
2.218
2.196
2.080
1.848
1.797
1.740
1.653
1.507
1.402
1.384
1.274
1.247
1.192
1.097
0.975
0.908
1.80
0.91
1.85
2.82
1.84
1.03
0.91
0.89
0.97
1.01
0.95
2.09
1.82
1.25
1.36
0.99
2.86
3.13
0.91
0.80
1.00
f1 (ppm)


141.553
139.303
133.510
129.214
128.588
128.147
127.468
67.421
63.411
60.055
51.518
42.474
36.493
36.328
30.458
26.041
25.311
21.429
21.133
18.368
f1 (ppm)

(4a*S*,8a*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-4a-[2-(phenylsulfonyl)ethyl]decahydroquinoline (92b):



Trifluoroacetic acid (21 μL, 0.28 mmol) and $NaBH_3CN$ (174 mg, 2.75 mmol) were added to a stirring solution of **89** (235 mg, 0.55 mmol) in dry CH_2Cl_2 (5.3 mL) at 0 ˚C, and the stirring was continued at room temperature for 72 h. Then, water was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (SiO_2, from 9:1 to 5:5 hexane-EtOAc) afforded **92b** (95.4 mg, 40%) as a viscous liquid.

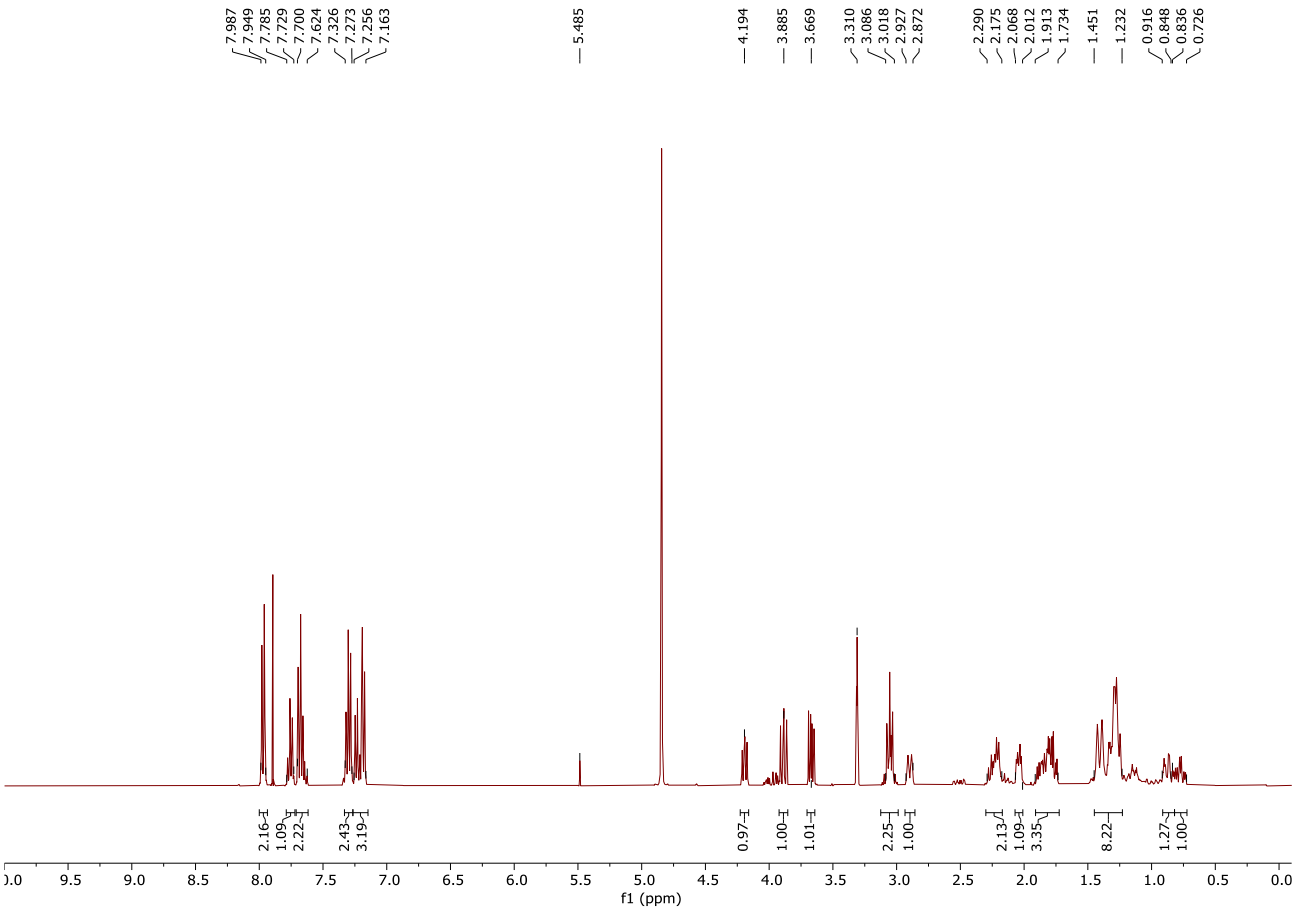
$[\alpha]^{23}_D$ –92.0 (*c* 1.0, $CHCl_3$);

IR (NaCl): 3503 (OH), 1146, 1306 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD, COSY, *g*-HSQC) δ 8.00-7.94 (m, 2H, ArH), 7.79-7.72 (m, 1H, ArH), 7.71-7.62 (m, 2H, ArH), 7.33-7.27 (m, 2H, ArH), 7.27-7.15 (m, 3H, ArH), 4.19 (dd, *J* = 8.6, 6.6 Hz, 1H, H-1'), 3.89 (dd, *J* = 10.6, 8.6 Hz, 1H, H-2'), 3.67 (dd, *J* = 10.6, 6.6 Hz, 1H, H-2'), 3.05 (tt, *J* = 9.2, 8.0 Hz, 2H, H-2''), 2.93-2.86 (dm, *J* = 8.4 Hz, 1H, H-2), 2.30-2.17 (m, 2H, H-1'', H-8), 2.07-2.01 (m, 1H, H-8a), 1.91-1.72 (m, 3H, H-1', H-2, H-5), 1.45-1.23 (m, 7H), 1.19-1.09 (m, 1H, H-1''), 0.90-0.86 (m, 1H, H-4), 0.83-0.73 (m, 1H, H-4).

^{13}C NMR (100.6 MHz, CD_3OD) δ 140.1 (C-Ar), 138.0 (C-Ar), 135.0 (CH-Ar), 130.6 (CH-Ar), 129.8 (CH-Ar), 129.3 (CH-Ar), 129.1 (CH-Ar), 128.2 (CH-Ar), 68.6 (C-8a), 62.6 (C-2''), 61.0 (C-1'), 51.8 (C-2''), 49.4 (C-2), 38.1 (C-4a), 36.7 (C-4), 36.3 (C-3), 26.5 (C-5), 25.4 (C-8), 22.8 (C-6), 21.2 (C-7), 21.0 (C-1'').

HRMS Calcd for [$C_{25}H_{33}NO_3S$+ H^+]: 428.2254; found 428.2254.


7.987
7.949
7.785
7.729
7.700
7.624
7.326
7.273
7.256
7.163
5.485
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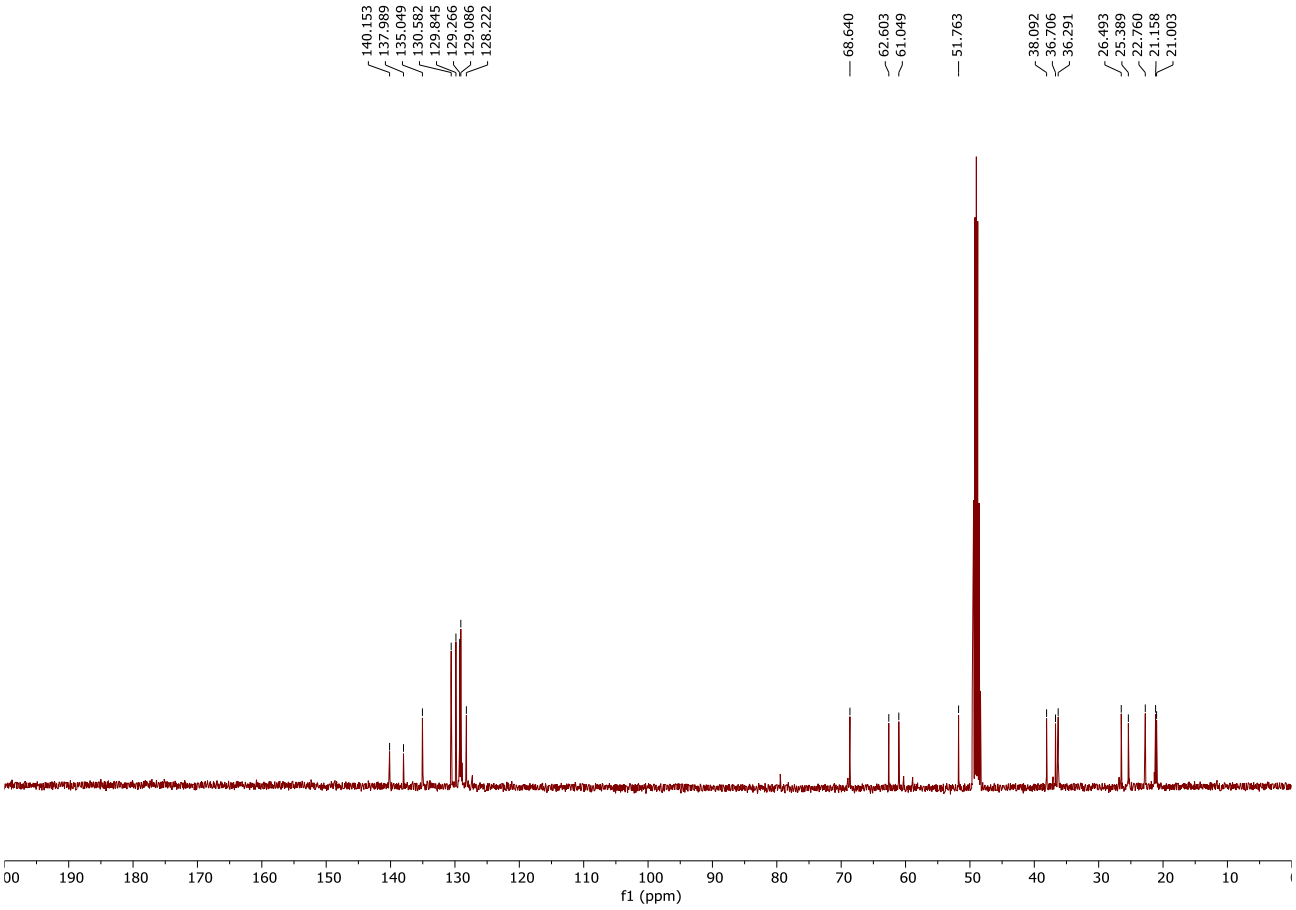
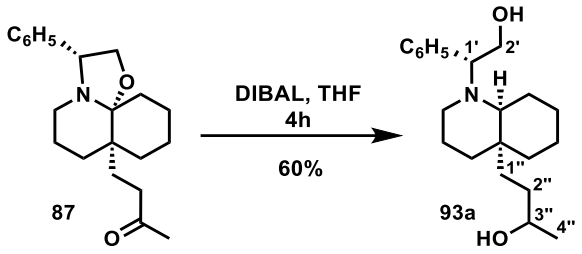
3.885
3.669
3.310
3.086
3.018
2.927
2.872
2.290
2.175
2.068
2.012
1.913
1.734
1.451
1.232
0.916
0.848
0.836
0.726
2.16
1.09
2.22
2.43
3.19
0.97
1.00
1.01
2.25
1.00
2.13
1.09
3.35
8.22
1.27
1.00
f1 (ppm)


140.153
137.989
135.049
130.582
129.845
129.266
129.086
128.222
68.640
62.603
61.049
51.763
38.092
36.706
36.291
26.493
25.389
22.760
21.158
21.003
f1 (ppm)

(4a*S*,8a*S*)-4a-(3-Hydroxybutyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]decahydroquinoline (93a):



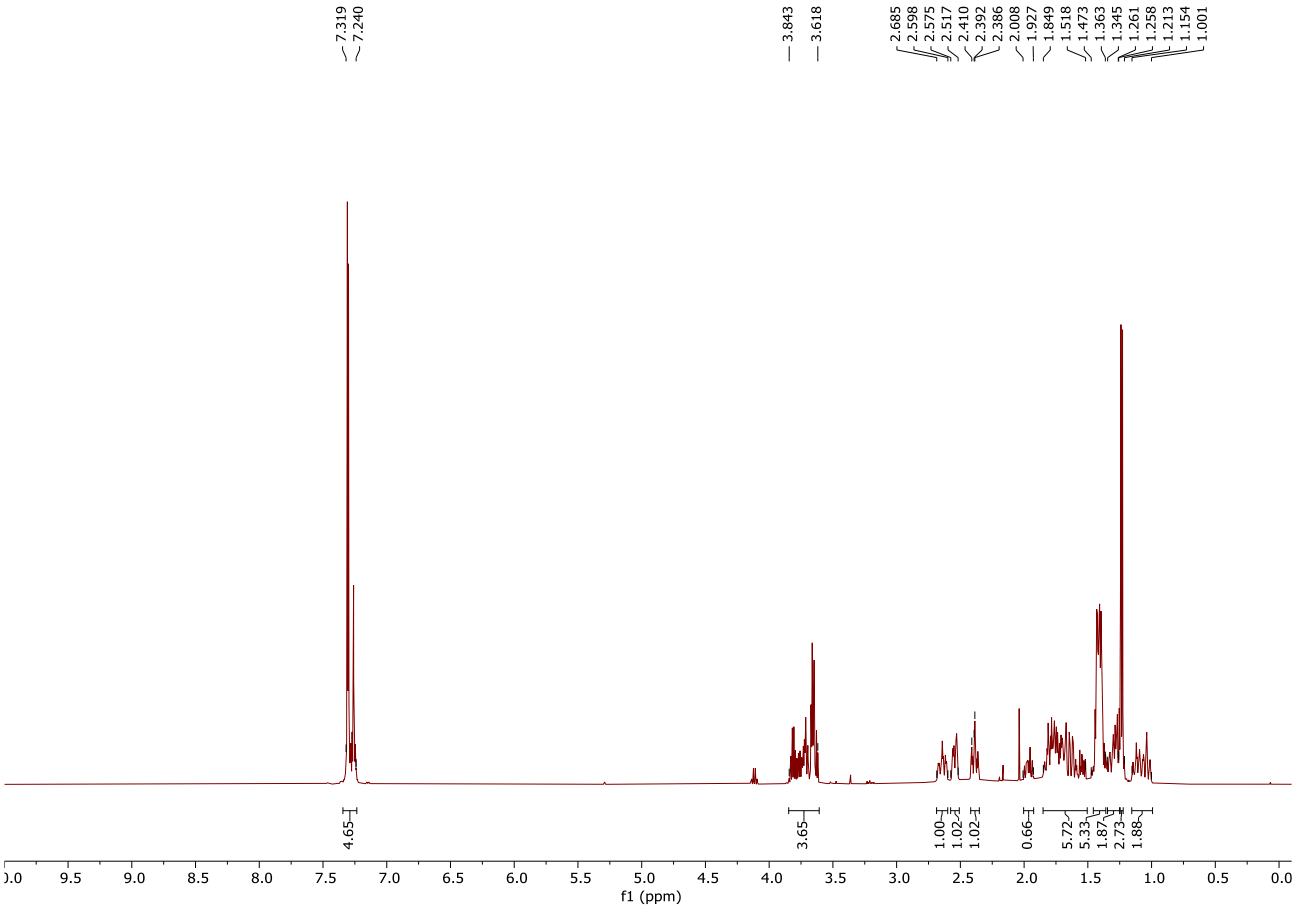
DIBAL (0.85 mL of a 1M solution in THF, 0.85 mmol) was added to a stirring solution of hemiaminal **87** (55.6 mg, 0.17 mmol) in anhydrous THF (1.9 mL) at room temperature. After 4h, 2 M solution of NaOH was added and the mixture was extracted with CH_2Cl_2, dried and evaporated. Flash column chromatography (8:2 to 1:1 hexane–EtOAc) afforded decahydroquinoline **93a** (34 mg, 60%) as a colorless liquid.

IR (NaCl): 3384 (OH) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.32-7.24 (m, 5H, ArH), 3.84-3.62 (m, 4H, H-1' and H-2' and H-3''), 2.69-2.60 (m, 1H, H-8a), 2.58-2.52 (m, 1H, H-2), 2.39 (td, J = 9.6, 2.4 Hz, 1H), 2.01-1.93 and 1.85-1.52 [(m) and (m), 7H], 1.47-1.36 (m, 5H), 1.34-1.26 (m, 2H), 1.26-1.21 (m, 3H, H-4''), 1.15-1.00 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1 (C-Ar), 128.6 (CH-Ar), 128.3 (CH-Ar), 127.4 (CH-Ar), 68.8 (C-3''), 68.3 (C-1'), 63.2 and 62.8 (C-8a), 62.7 (C-2'), 41.4 (C-2), 36.6 (C-4a and CH_2), 34.3 and 34.0 (CH_2), 32.7 and 32.4 (CH_2), 26.2 and 25.9 (CH_2), 25.6 (CH_2), 23.8 and 23.4 (C-4''), 21.9 (CH_2), 21.3 (CH_2), 19.6 and 19.5 (CH_2).

HRMS Calcd for [$C_{21}H_{33}NO_2 + H^+$]: 332.2584; found 332.2580.


7.319
7.240
3.843
3.618
2.685
2.598
2.575
2.517
2.410
2.392
2.386
2.008
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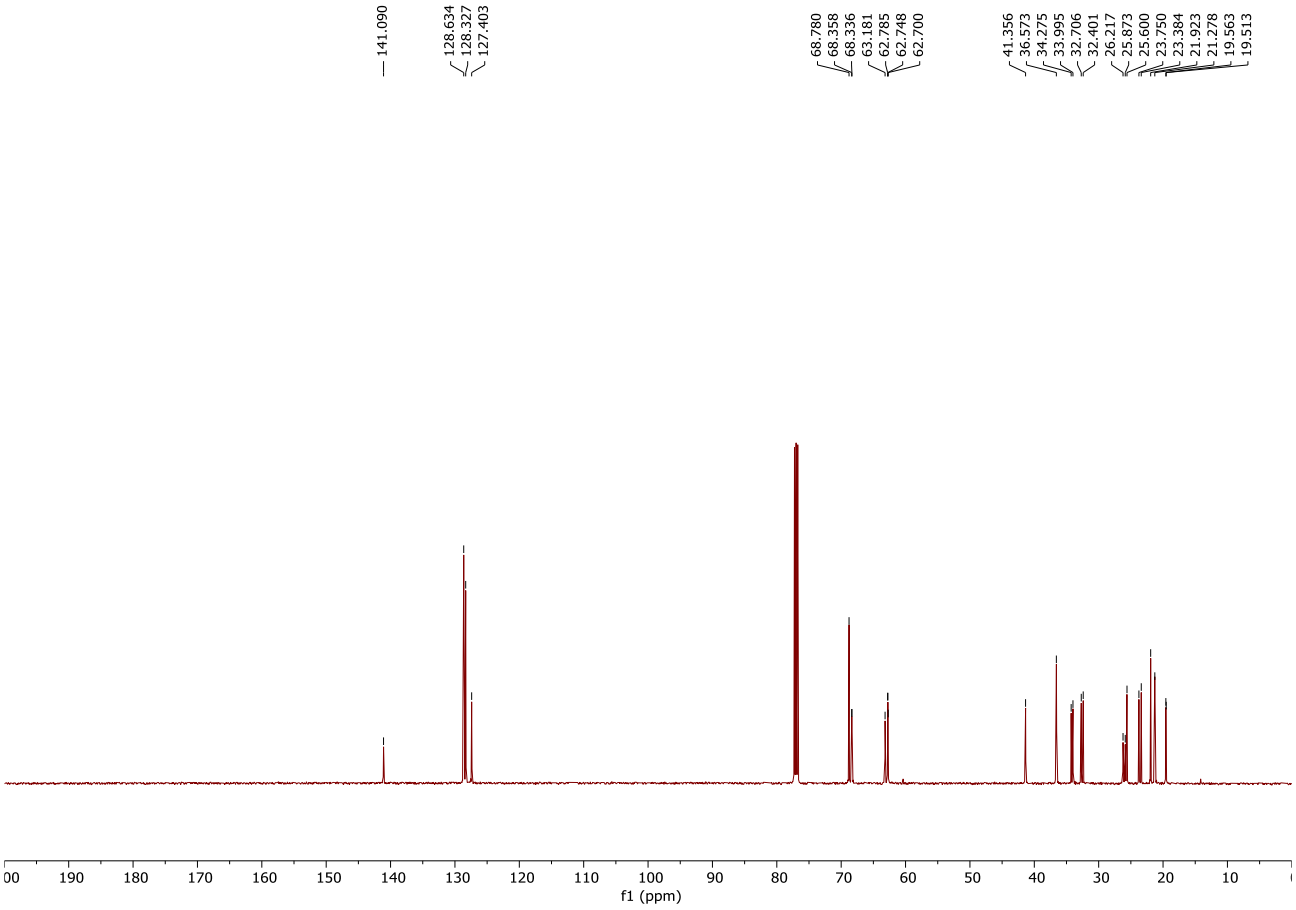
1.849
1.518
1.473
1.363
1.345
1.261
1.258
1.213
1.154
1.001
4.65
3.65
1.00
1.02
1.02
0.66
5.72
5.33
1.87
2.73
1.88
f1 (ppm)


141.090
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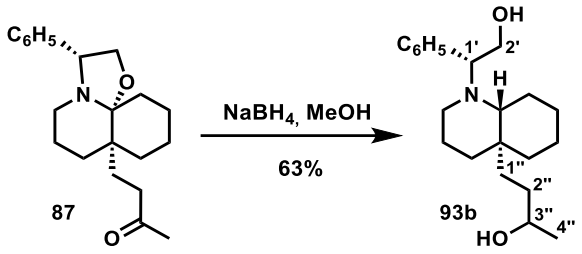
127.403
68.780
68.358
68.336
63.181
62.785
62.748
62.700
41.356
36.573
34.275
33.995
32.706
32.401
26.217
25.873
25.600
23.750
23.384
21.923
21.278
19.563
19.513
f1 (ppm)

(4a*S*,8a*R*)-4a-(3-Hydroxybutyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]decahydroquinoline (93b):



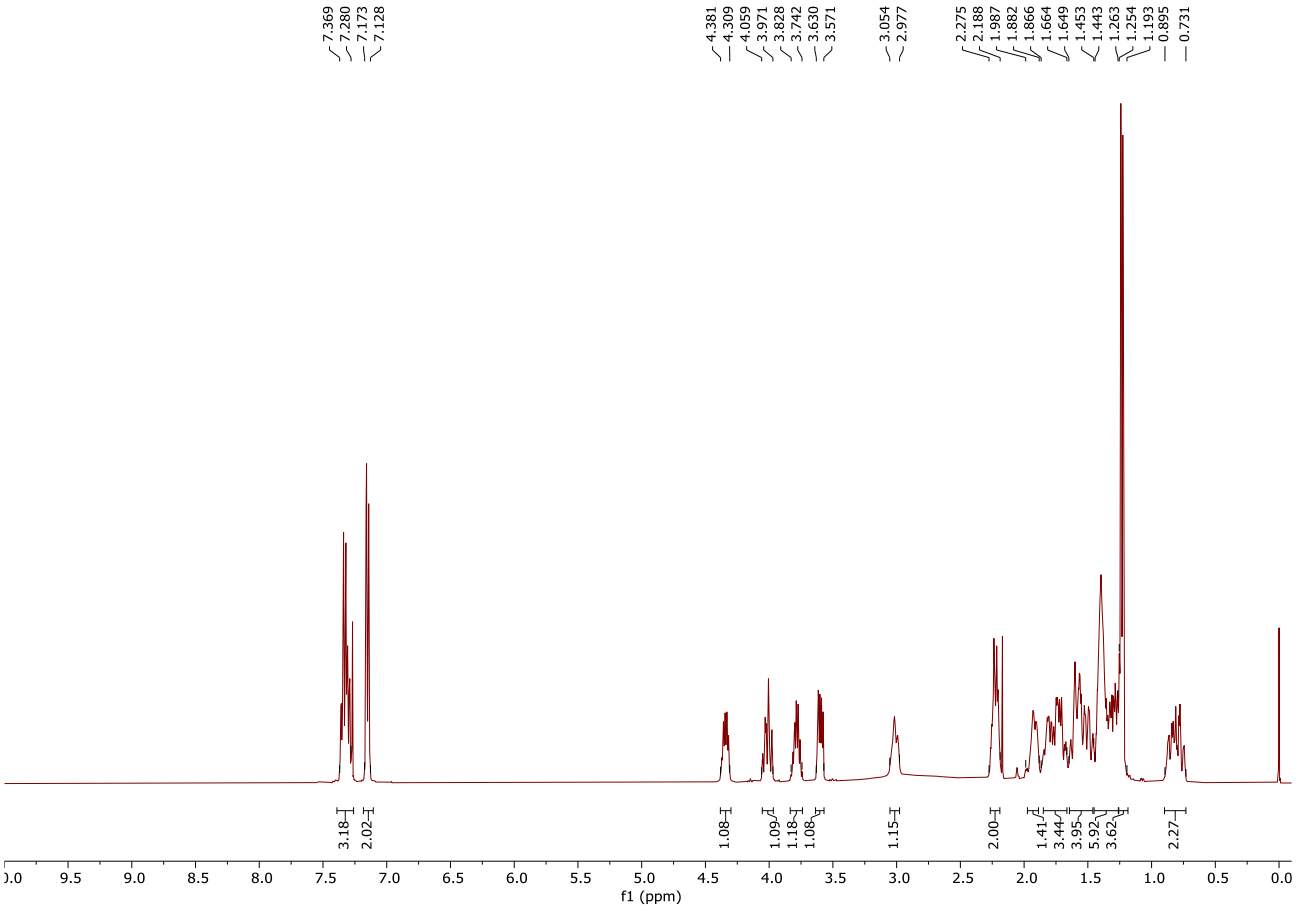
$NaBH_4$ (367 mg, 9.71 mmol) was added to a solution of **87** (636 mg, 1.94 mmol) in methanol (21.6 mL) and the mixture was stirred for 1h. After that, water was added and the mixture was extracted with CH_2Cl_2, dried and evaporated. Flash column chromatography (8:2 to 1:1 hexane–EtOAc) afforded decahydroquinoline **93b** (408 mg, 63%) as a colorless liquid.

IR (NaCl): 3390 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.37-7.28 (m, 3H, ArH), 7.17-7.13 (m, 2H, ArH), 4.38-4.31 (m, 1H, H-1'), 4.06-3.97 (m, 1H, H-2'), 3.83-3.74 (m, 1H, H-3''), 3.63-3.57 (m, 1H, H-2'), 3.05-2.98 (m, 1H), 2.28-2.19 (m, 2H), 1.99-1.88 (m, 1H), 1.87-1.66 (m, 3H), 1.65-1.45 (m, 4H), 1.44-1.26 (m, 6H), 1.25-1.19 (m, 4H), 0.90-0.73 (m, 2H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.3 (C-Ar), 128.5 (CH-Ar), 128.2 (CH-Ar), 127.4 (CH-Ar), 68.9 (C-1'), 67.4 (C-8a), 59.9 (C-2'), 58.5 (C-3''), 47.1 (C-2), 37.2 (C-4a), 35.8 (CH_2), 35.7 (CH_2), 32.1 (C-2''), 25.7 (CH_2), 24.2 (CH_2), 23.8 (C-4''), 23.5 (CH_2), 22.2 (CH_2), 20.2 (CH_2).

HRMS Calcd for [$C_{21}H_{33}NO_2 + H^+$]: 332.2584; found 332.2588.


7.369
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3.971
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3.630
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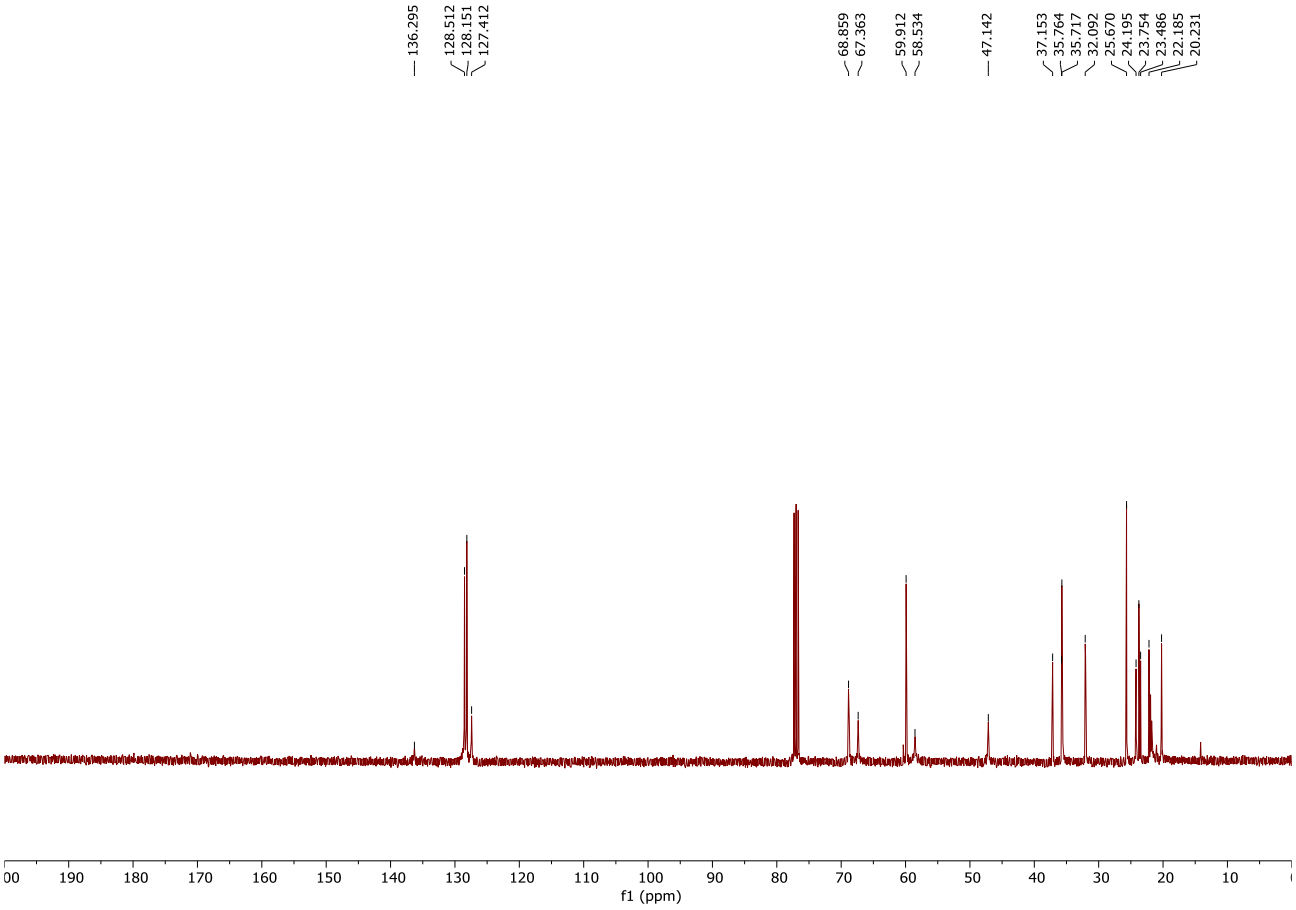
3.054
2.977
2.275
2.188
1.987
1.882
1.866
1.664
1.649
1.453
1.443
1.263
1.254
1.193
0.895
0.731
3.18
2.02
1.08
1.09
1.18
1.08
1.15
2.00
1.41
3.44
3.95
5.92
3.62
2.27
f1 (ppm)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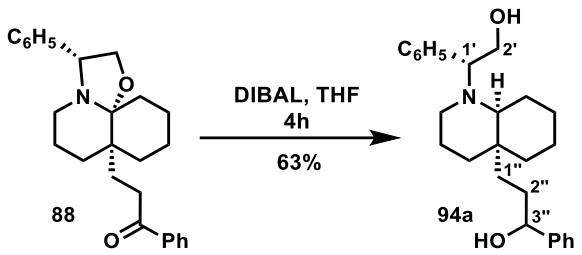
127.412
68.859
67.363
59.912
58.534
47.142
37.153
35.764
35.717
32.092
25.670
24.195
23.754
23.486
22.185
20.231
f1 (ppm)

(4a*S*,8a*S*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-4a-[3-hydroxy-3-phenylpropyl]decahydroquinoline (94a):



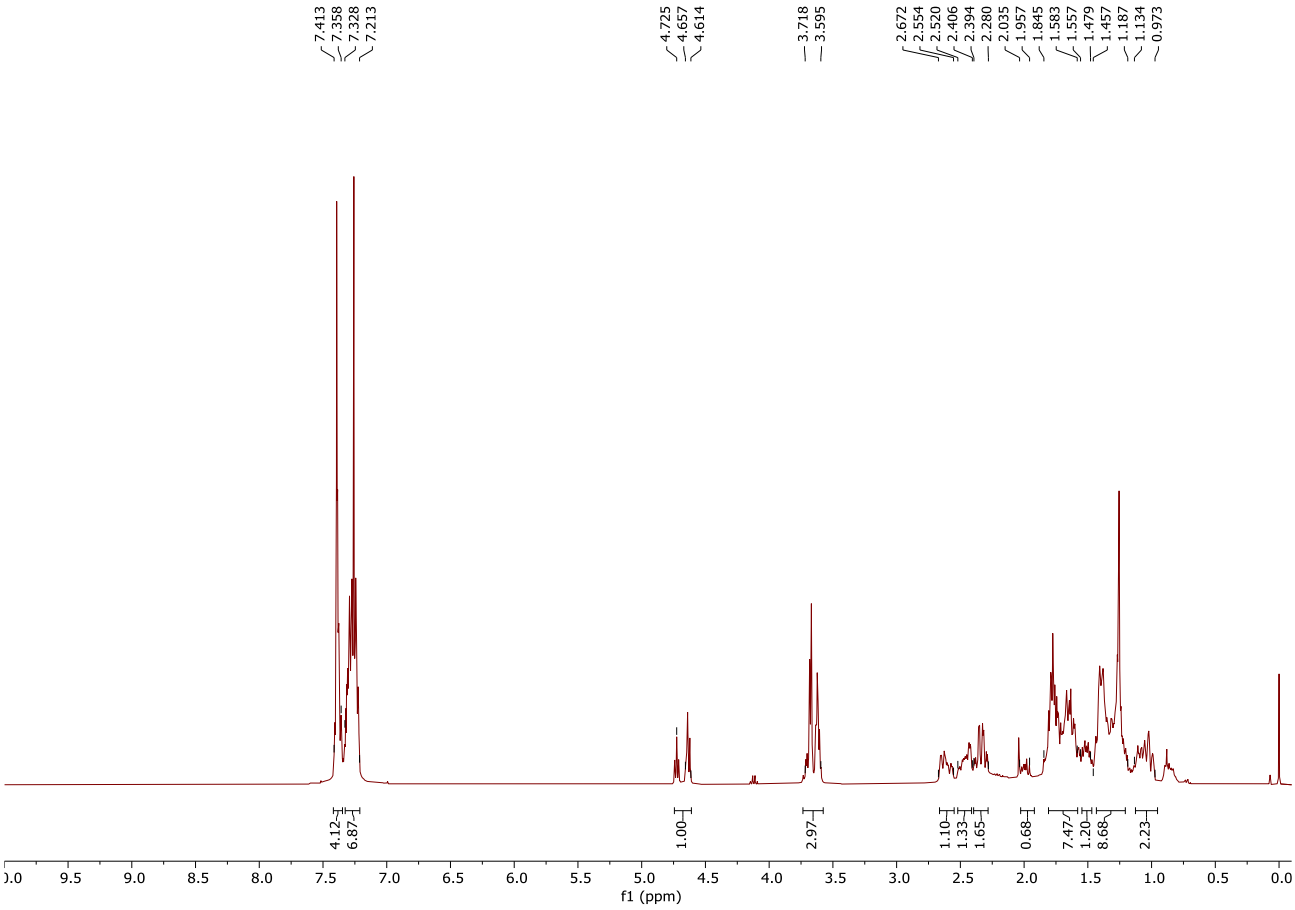
Operating as described in the preparation of decahydroquinoline **93a**, from DIBAL (3.7 mL of a 1M solution in THF, 3.7 mmol) and hemiaminal **88** (115 mg, 0.37 mmol) in anhydrous THF (4.1 mL), decahydroquinoline **94a** (72.7 mg, 63%) was obtained after flash column chromatography (95:5 to 8:2 hexane–EtOAc) as a colorless oil:

IR (NaCl): 3418 (OH) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.41-7.36 (m, 4H, ArH), 7.33-7.22 (m, 6H, ArH), 4.73 and 4.66-4.62 [(t, *J* = 6.4 Hz) and (m), 1H, H-3''], 3.73-3.59 (m, 3H, H-1' and H-2'), 2.67-2.56 (m, 1H, H-8a), 2.53-2.41 (m, 1H, H-2), 2.40-2.28 (m, 1H, H-2), 1.86-1.59 (m, 7H), 1.59-1.47 (m, 1H), 1.45-1.19 (m, 8H), 1.14-0.97 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2 and 144.9 (C-Ar), 141.3 (C-Ar), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 127.5 (CH-Ar), 127.4 (CH-Ar), 127.3 (CH-Ar), 125.9 (CH-Ar), 75.4 and 75.3 (C-3'), 68.2 and 68.1 (C-1'), 62.9 (C-2'), 62.4 (C-8a), 41.6 and 41.4 (CH_2), 36.7 and 36.6 (C-4a and CH_2), 34.5 and 34.0 (CH_2), 32.8 and 32.5 (CH_2), 29.7 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 21.9 and 21.8 (CH_2), 21.3 (CH_2), 19.4 and 19.3 (CH_2).

HRMS Calcd for [$C_{26}H_{35}NO_2 + H^+$]: 394.2741; found 394.2745.


7.413
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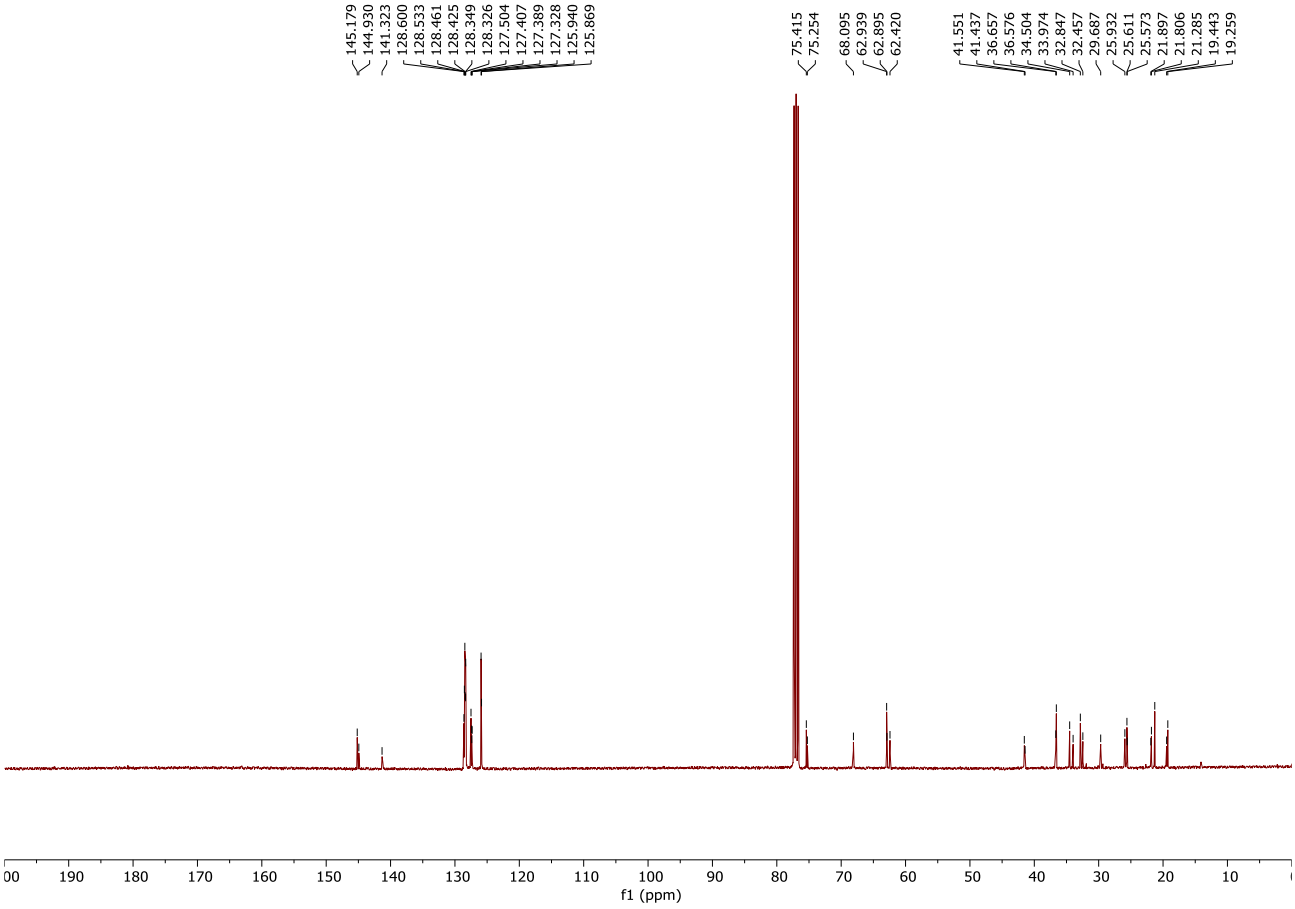
4.657
4.614
3.718
3.595
2.672
2.554
2.520
2.406
2.394
2.280
2.035
1.957
1.845
1.583
1.557
1.479
1.457
1.187
1.134
0.973
4.12
6.87
1.00
2.97
1.10
1.33
1.65
0.68
7.47
1.20
8.68
2.23
f1 (ppm)


145.179
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128.533
128.461
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128.349
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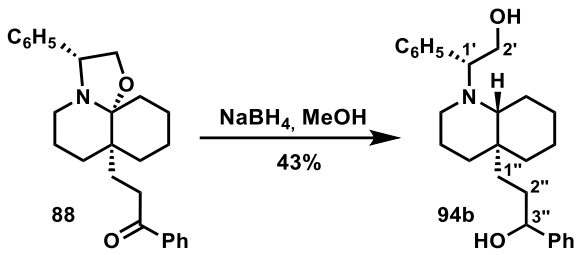
127.504
127.407
127.389
127.328
125.940
125.869
75.415
75.254
68.095
62.939
62.895
62.420
41.551
41.437
36.657
36.576
34.504
33.974
32.847
32.457
29.687
25.932
25.611
25.573
21.897
21.806
21.285
19.443
19.259
f1 (ppm)

(4a*S*,8a*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-4a-[3-hydroxy-3-phenylpropyl]decahydroquinoline (94b):



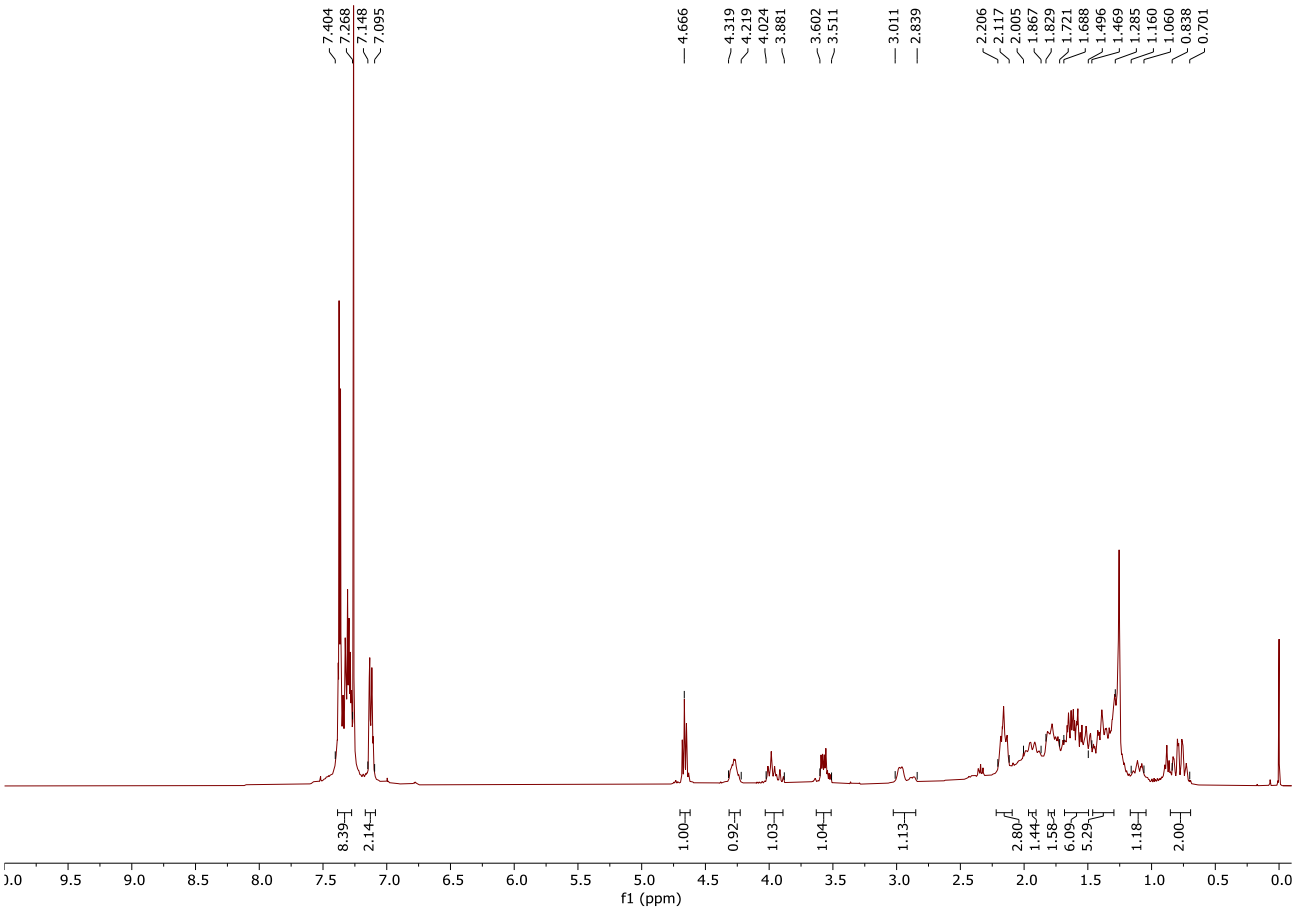
Operating as described in the preparation of decahydroquinoline **93b**, from $NaBH_4$ (24 mg, 0.63 mmol) and hemiaminal **88** (40 mg, 0.13 mmol) in methanol (1.4 mL), decahydroquinoline **94b** (17.5 mg, 43%) was obtained after flash column chromatography (9:1 to 7:3 hexane–EtOAc) as a yellowish oil.

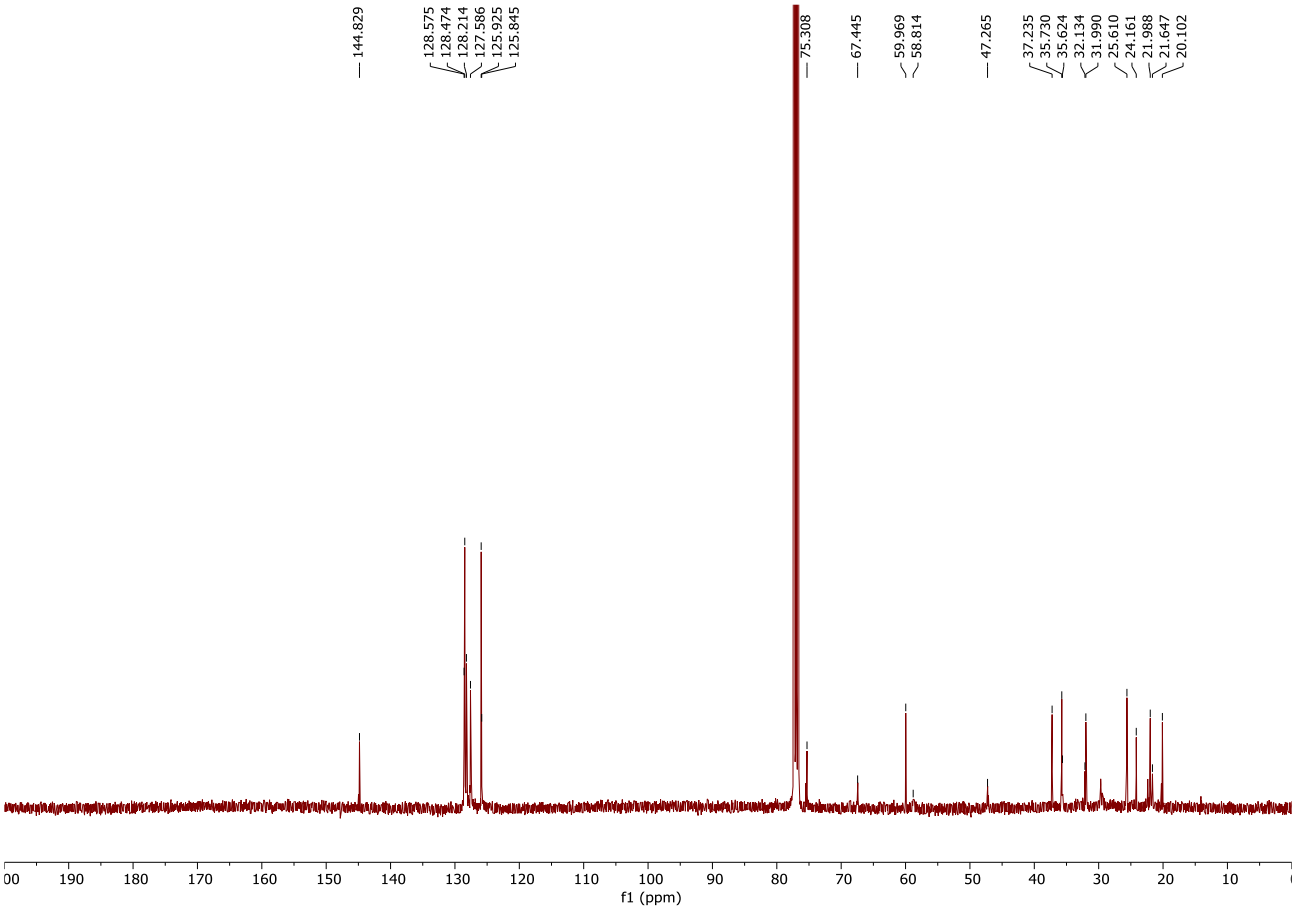
IR (NaCl): 3435 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.40-7.27 (m, 8H, ArH), 7.15-7.10 (m, 2H, ArH), 4.67 (t, *J* = 6.0 Hz, 1H, H-3''), 4.32-4.22 (m, 1H, H-1'), 4.02-3.88 (m, 1H, H-2'), 3.60-3.51 (m, 1H, H-2'), 3.01-2.84 (m, 1H, H-2), 2.21-2.12 (m, 3H), 2.00-1.87 (m, 1H), 1.83-1.72 (m, 1H), 1.69-1.50 (m, 6H), 1.47-1.28 (m, 5H), 1.16-1.06 (m, 1H), 0.84-0.70 (m, 2H).

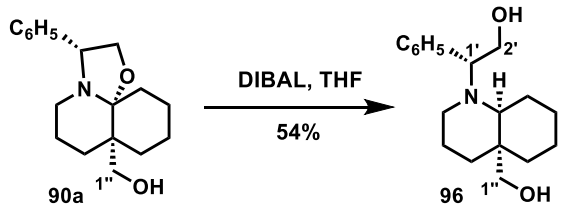
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.8 (C-Ar), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.2 (CH-Ar), 127.6 (CH-Ar), 125.9 (CH-Ar), 125.8 (CH-Ar), 75.3 (C-3''), 67.4 (C-8a), 60.0 (C-2'), 58.8 (C-1'), 47.3 (C-2), 37.2 (C-4a), 35.7 (CH_2), 35.6 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 25.6 (CH_2), 24.2 (CH_2), 22.0 (CH_2), 21.6 (CH_2), 20.1 (CH_2).

HRMS Calcd for [$C_{26}H_{35}NO_2 + H^+$]: 394.2741; found 394.2746.


7.404
7.268
7.148
7.095
4.666
4.319
4.219
4.024
3.881
3.602
3.511
3.011
2.839
2.206
2.117
2.005
1.867
1.829
1.721
1.688
1.496
1.469
1.285
1.160
1.060
0.838
0.701
8.39
2.14
1.00
0.92
1.03
1.04
1.13
2.80
1.44
1.58
6.09
5.29
1.18
2.00
f1 (ppm)


144.829
128.575
128.474
128.214
127.586
125.925
125.845
75.308
67.445
59.969
58.814
47.265
37.235
35.730
35.624
32.134
31.990
25.610
24.161
21.988
21.647
20.102
f1 (ppm)

(4a*R*,8a*S*)-4a-(Hydroxymethyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]decahydroquinoline (96):



Operating as described in the preparation of decahydroquinoline **93a**, from DIBAL (1.74 mL of a 1M solution in THF, 1.74 mmol) and amine **90a** (50 mg, 0.17 mmol) in anhydrous THF (1.93 mL), decahydroquinoline **96** (27.2 mg, 54%) was obtained after flash column chromatography (7:3 hexane–EtOAc to 100% EtOAc) as a colorless solid:

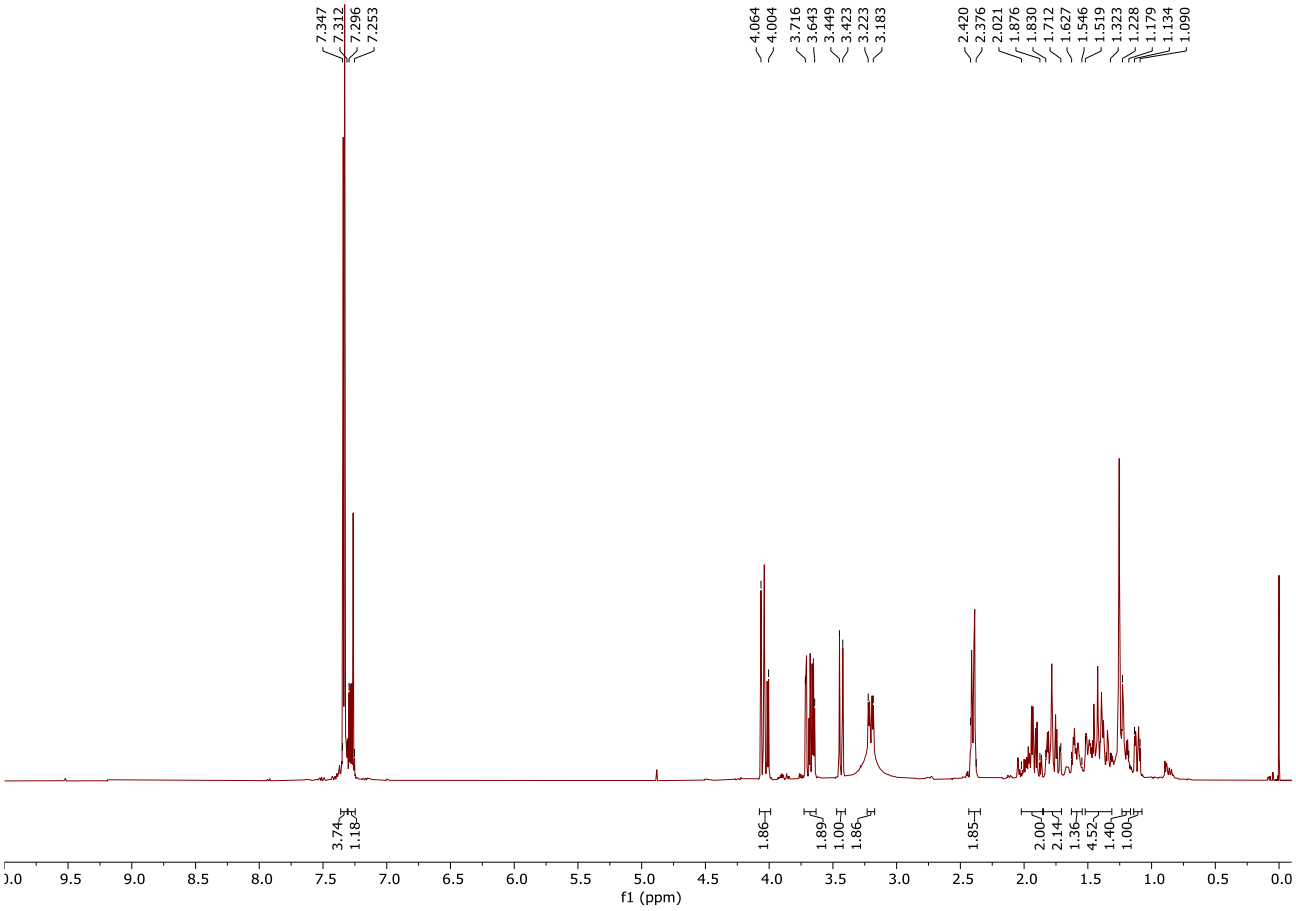
$[\alpha]^{23}_{D}$ –22.6 (*c* 1.0, $CHCl_3$).

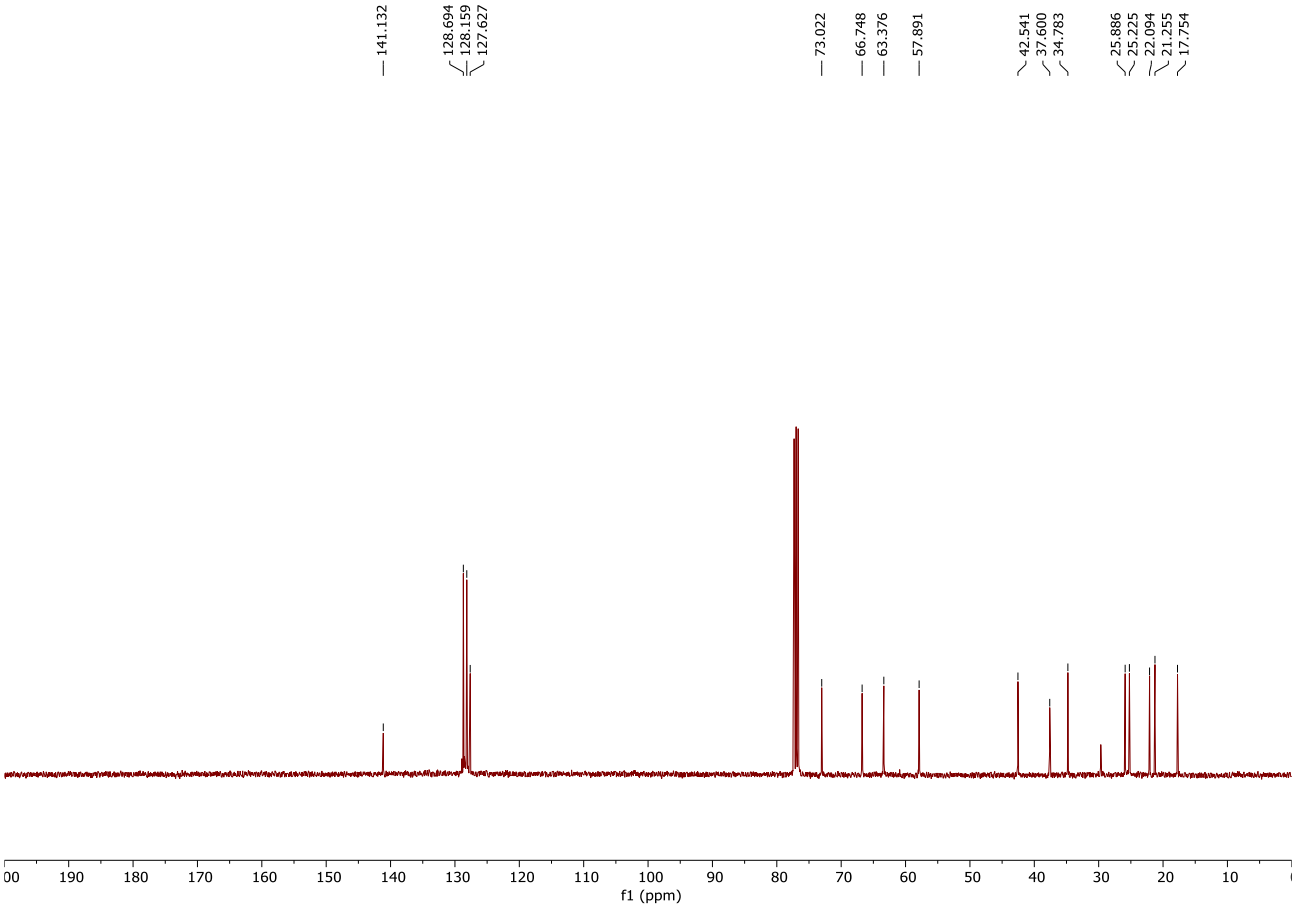
IR (NaCl): 3382 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.34 (d, *J* = 4.4 Hz, 4H, ArH), 7.32-7.23 (m, 1H, ArH), 4.10-3.98 (m, 2H, H-2' and H-1''), 3.75-3.62 (m, 2H, H-1' and H-2'), 3.44 (d, *J* = 10.5 Hz, 1H, H-1''), 3.20 (dd, *J* = 11.8, 4.2 Hz, 1H, H-8a), 2.44-2.36 (m, 2H, H-2), 2.03-1.84 (m, 2H), 1.86-1.69 (m, 2H), 1.65-1.52 (m, 1H), 1.55-1.30 (m, 4H), 1.22-1.15 (m, 2H), 1.16-1.07 (m, 1H).

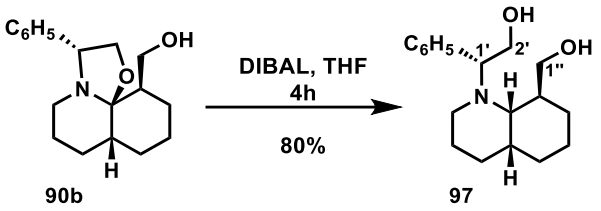
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.1 (C-Ar), 128.7 (CH-Ar), 128.2 (CH-Ar), 127.6 (CH-Ar), 73.0 (C-1''), 66.7 (C1'), 63.4 (C-2'), 57.9 (C-8a), 42.5 (C-2), 37.6 (C-4a), 34.8 (CH_2), 25.9 (CH_2), 25.2 (CH_2), 22.1 (CH_2), 21.3 (CH_2), 17.8 (CH_2).

HRMS Calcd for [$C_{18}H_{27}NO_2$ + H^+]: 290.2115; found 290.2112.


7.347
7.312
7.296
7.253
4.064
4.004
3.716
3.643
3.449
3.423
3.223
3.183
2.420
2.376
2.021
1.876
1.830
1.712
1.627
1.546
1.519
1.323
1.228
1.179
1.134
1.090
3.74
1.18
1.86
1.89
1.00
1.86
1.85
2.00
2.14
1.36
4.52
1.40
1.00
f1 (ppm)


141.132
128.694
128.159
127.627
73.022
66.748
63.376
57.891
42.541
37.600
34.783
25.886
25.225
22.094
21.255
17.754
f1 (ppm)

(4a*R*, 8*S*, 8a*S*)-8-(Hydroxymethyl)-1-[(*R*)-2-hydroxy-1-phenylethyl]decahydroquinoline (97):



Operating as described in the preparation of decahydroquinoline **93a**, from DIBAL (9.5 mL of a 1M solution in THF, 9.5 mmol) and amine **90b** (272 mg, 0.95 mmol) in anhydrous THF (10.5 mL), decahydroquinoline **97** (219 mg, 80%) was obtained after flash column chromatography (7:3 hexane–EtOAc to 100% EtOAc) as a colorless solid:

mp = 101–106 °C (hexane/CH_2Cl_2).

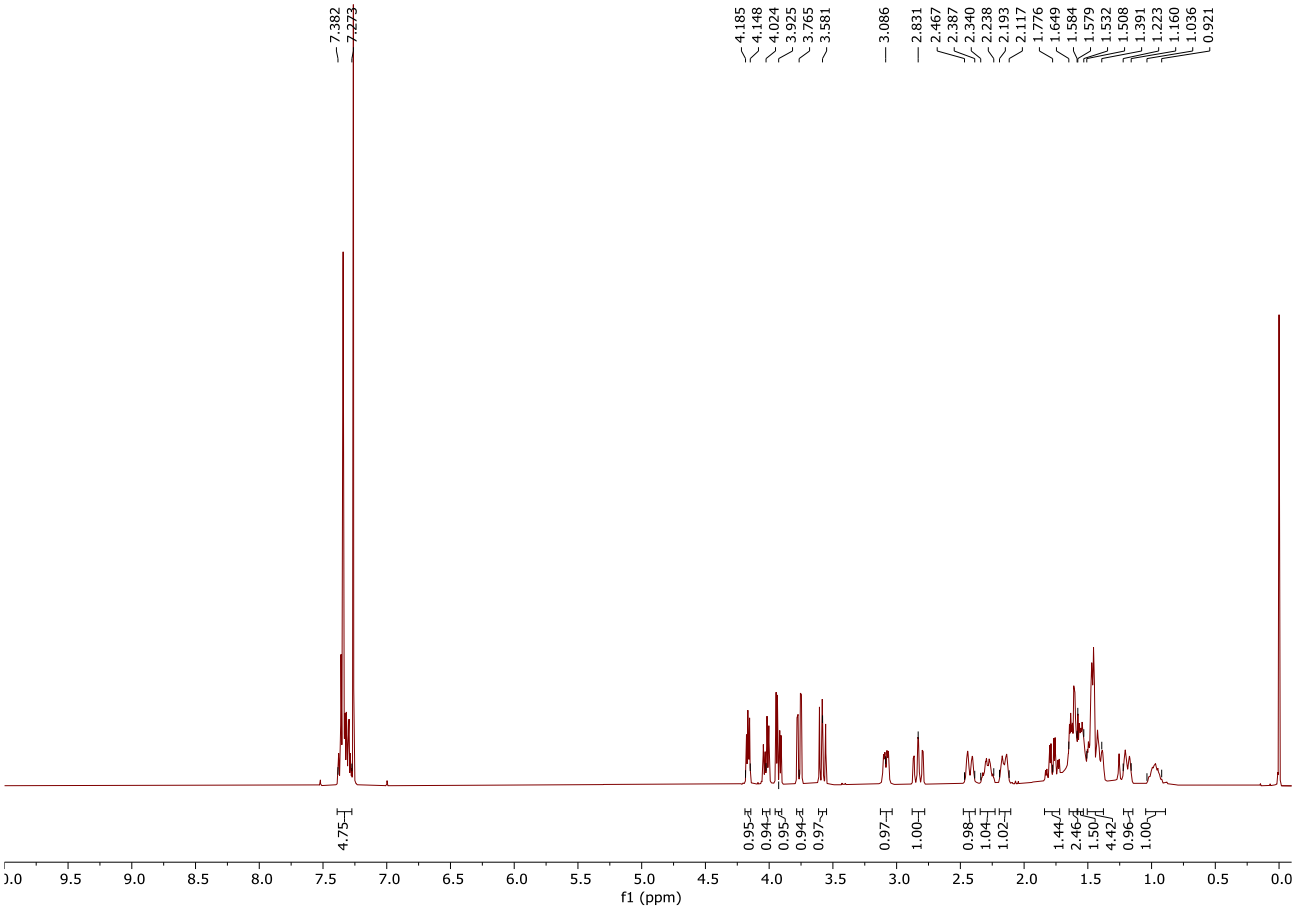
$[\alpha]^{23}_D$ –7.4 (*c* 1.0, $CHCl_3$).

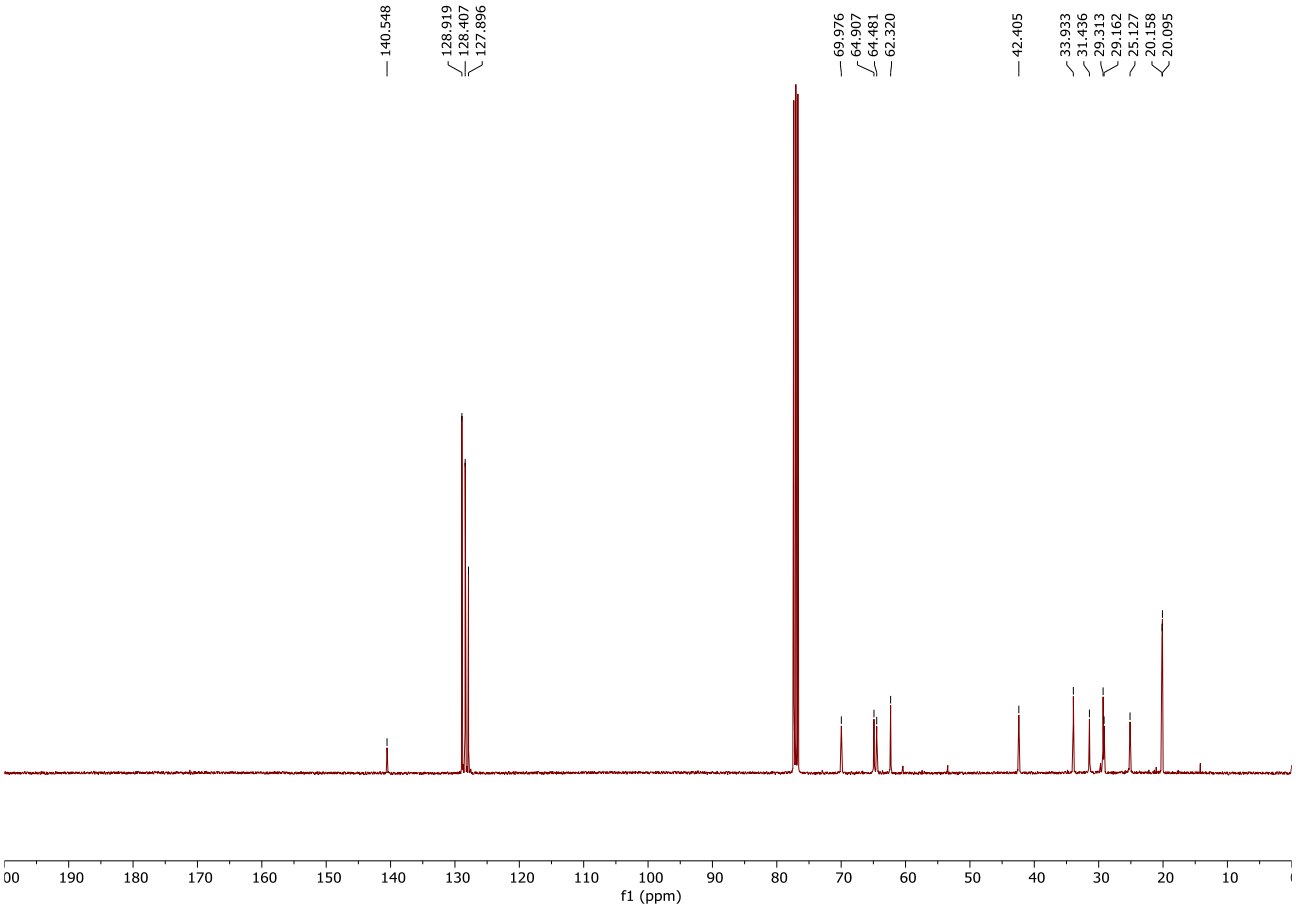
IR (NaCl): 3356 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.38-7.27 (m, 5H, ArH), 4.19-4.15 (m, 1H, H-1'), 4.02 (dd, *J* = 11.6, 6.0 Hz, 1H, H-2'), 3.93 (dd, *J* = 11.6, 4.4 Hz, 1H, H-2'), 3.76 (dd, *J* = 10.4, 3.6 Hz, 1H, H-1''), 3.58 (dd, *J* = 10.4, 8.4 Hz, 1H, H-1''), 3.09 (dd, *J* = 6.8, 4.4 Hz, 1H, H-8a), 2.83 (td, *J* = 14.8, 3.2 Hz, 1H, H-2), 2.47-2.39 (m, 1H, H-2), 2.34-2.24 (m, 1H, H-8), 2.19-2.12 (m, 1H, H-4a), 1.78 (qd, *J* = 13.2, 4.0 Hz, 1H), 1.65-1.58 (m, 2H), 1.58-1.53 (m, 1H), 1.51-1.39 (m, 4H), 1.22-1.16 (m, 1H), 1.04-0.92 (m, 1H).

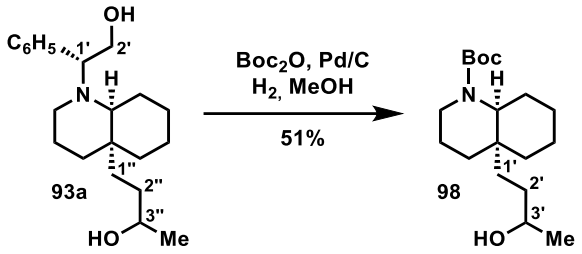
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.5 (C-Ar), 128.9 (CH-Ar), 128.4 (CH-Ar), 127.9 (CH-Ar), 70.0 (C-1''), 64.9 (C-2'), 64.5 (C-1'), 62.3 (C-8a), 42.4 (C-2), 33.9 (C-8), 31.4 (CH_2), 29.3 (C-4a), 29.2 (CH_2), 25.1 (CH_2), 20.2 (CH_2), 20.1 (CH_2).

HRMS Calcd for [$C_{18}H_{27}NO_2 + H^+$]: 290.2115; found 290.2111.


7.382
7.273
4.185
4.148
4.024
3.925
3.765
3.581
3.086
2.831
2.467
2.387
2.340
2.238
2.193
2.117
1.776
1.649
1.584
1.579
1.532
1.508
1.391
1.223
1.160
1.036
0.921
4.75
0.95
0.94
0.95
0.94
0.97
0.97
1.00
0.98
1.04
1.02
1.44
2.46
1.50
4.42
0.96
1.00
f1 (ppm)


140.548
128.919
128.407
127.896
69.976
64.907
64.481
62.320
42.405
33.933
31.436
29.313
29.162
25.127
20.158
20.095
f1 (ppm)

(4a*S*,8a*S*)-1-(*tert*-Butoxycarbonyl)-4a-(3-hydroxybutyl)decahydroquinoline (98):



A solution of decahydroquinoline **93a** (54.4 mg, 0.17 mmol) and Boc_2O (44 mg, 0.20 mmol) in MeOH (3.5 mL) containing 40% Pd/C (22 mg) was stirred under hydrogen at rt for 16 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash column chromatography (9:1 to 85:15 hexane–EtOAc) afforded decahydroquinoline **98** (26.1 mg, 51%) as a colorless oil:

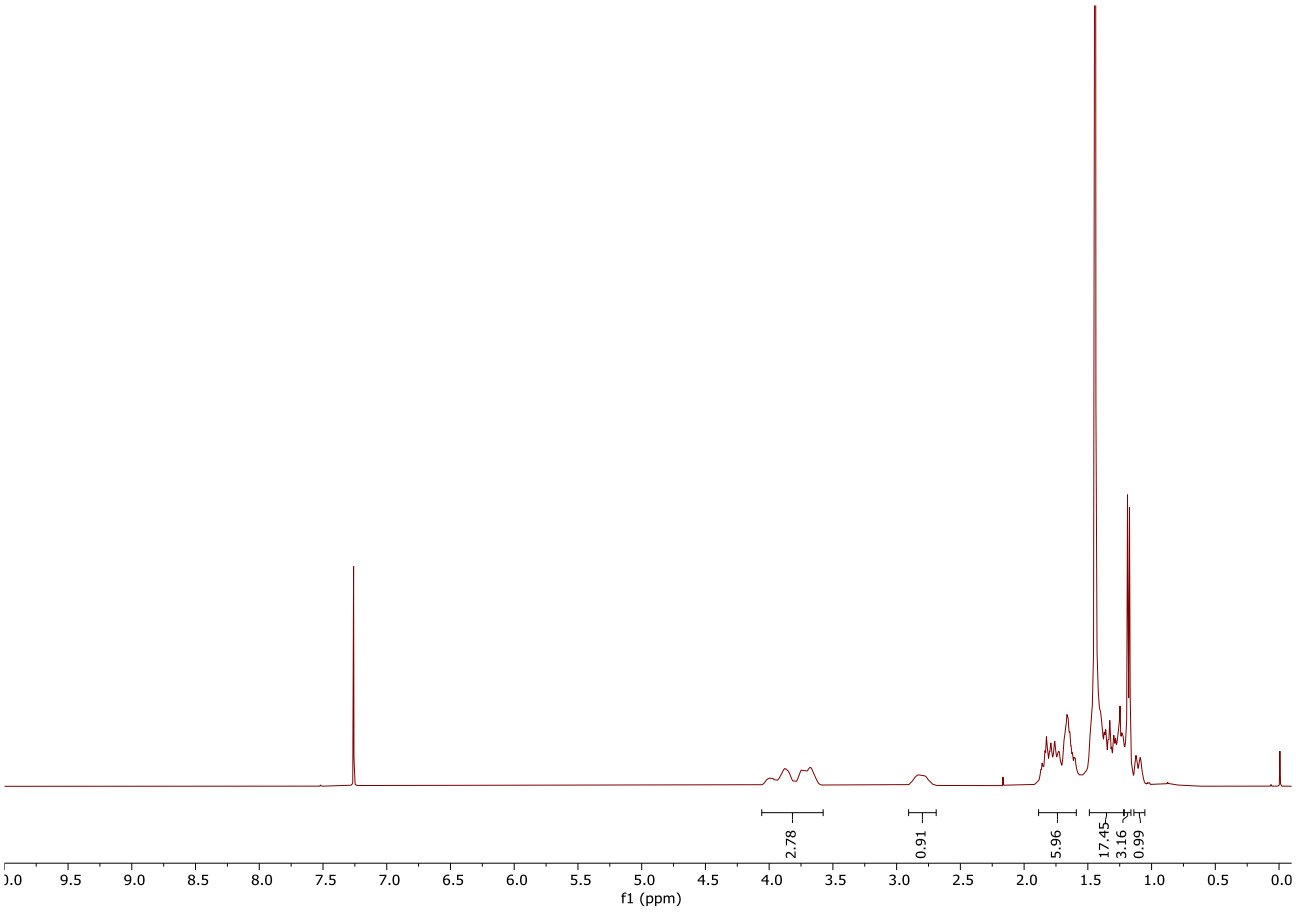
Several of the signals in the ^{1}H and ^{13}C NMR spectrum of **98** at 25 ºC were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

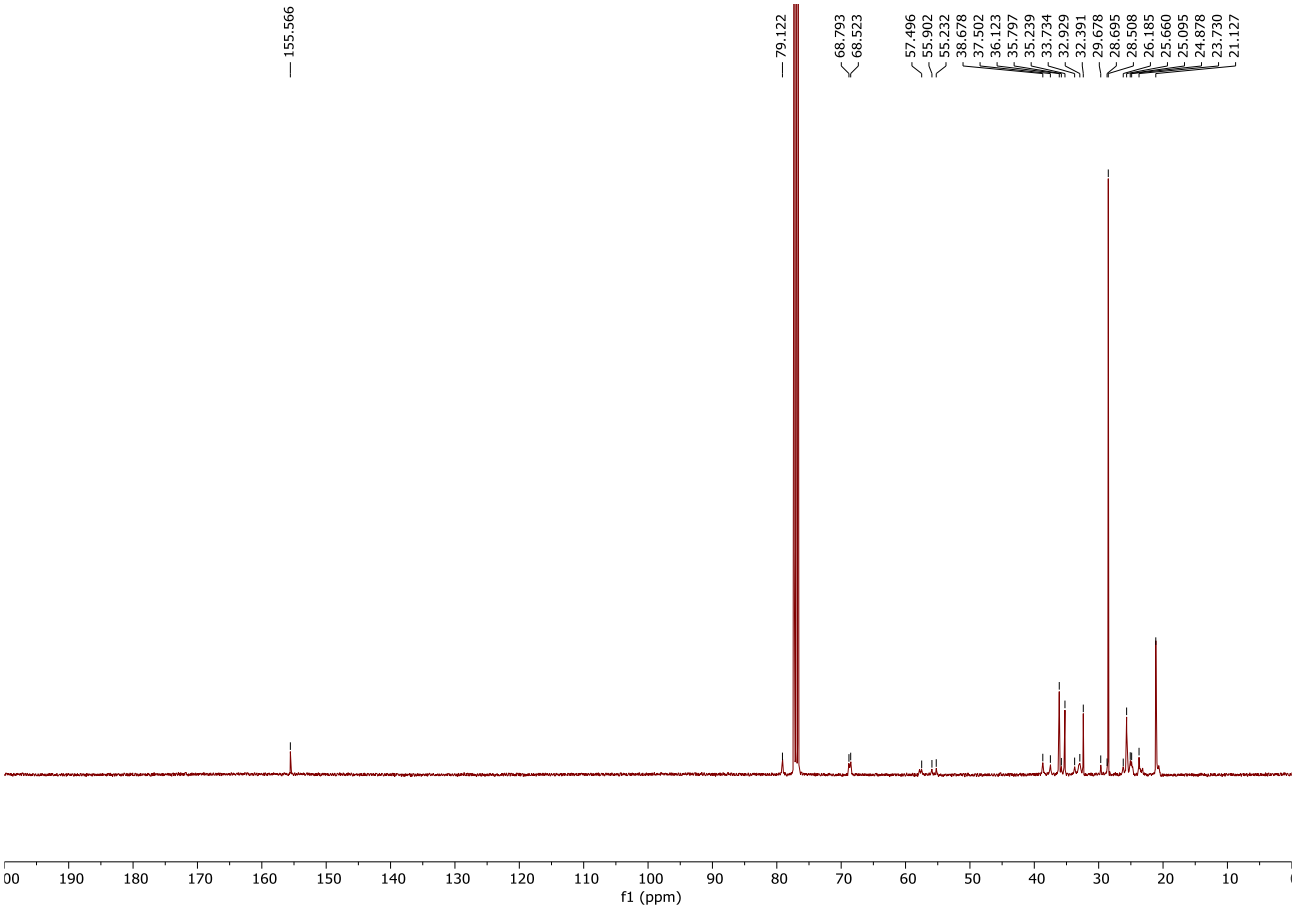
IR (NaCl): 3446 (OH), 1689, 1668 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 4.05-3.62 (m, 3H, H-2, H-8a and H-3'), 2.90- 2.73 (m, 1H, H-2), 1.89-1.58 (m, 6H), 1.54-1.22 (m, 18H), 1.18 (d, J = 6.4 Hz, 3H, CH_3), 1.14- 1.06 (m, 1H).

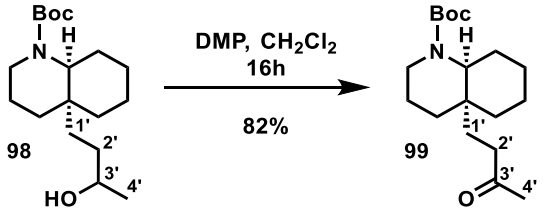
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (CO), 79.1 [$C(CH_3)_3$], 68.8 and 68.5 (C-3'), 57.9, 57.5, 55.9 and 55.2 (C-8a), 38.7 and 37.5 (C-2), 36.1 (CH_2), 35.2 (C-4a), 33.7 and 32.9 (CH_2), 32.4 (CH_2), 28.5 [$C(CH_3)_3$], 25.7 (2 CH_2), 25.1 and 24.9 (CH_2), 23.7 (CH_3), 21.1 (CH_2), 20.7 (CH_2).

HRMS Calcd for [$C_{18}H_{33}NO_3 + H^+$]: 312.2533; found 312.2525.


2.78
0.91
5.96
17.45
3.16
0.99
f1 (ppm)


155.566
79.122
68.793
68.523
57.496
55.902
55.232
38.678
37.502
36.123
35.797
35.239
33.734
32.929
32.391
29.678
28.695
28.508
26.185
25.660
25.095
24.878
23.730
21.127
f1 (ppm)

(4a*S*,8a*S*)-1-(*tert*-Butoxycarbonyl)-4a-(3-oxobutyl)decahydroquinoline (99):



Dess-Martin periodinane (40 mg, 0.09 mmol) was added to a stirring solution of the amine **98** (20.9 mg, 0.07 mmol) in dry CH_2Cl_2 (0.5 mL) at room temperature. After 16 h, 10% aqueous NaOH was added and the resulting mixture was extracted with CH_2Cl_2, dried and concentrated. Flash column chromatography (8:2 hexane–EtOAc) afforded decahydroquinoline **99** (17 mg, 82%) as a colorless oil.

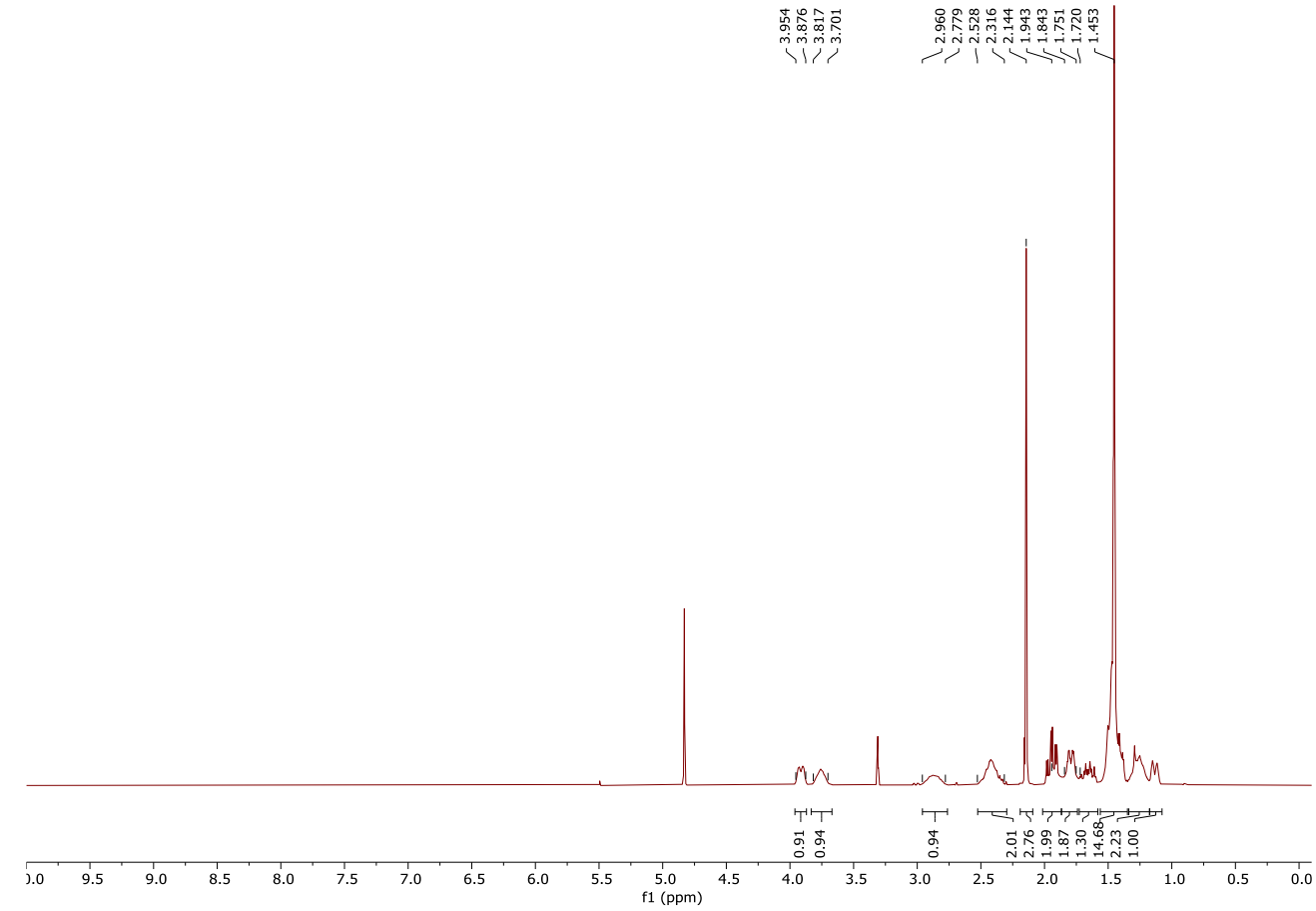
$[\alpha]^{23}_D$ +12.0 (*c* 1.0, $CHCl_3$).

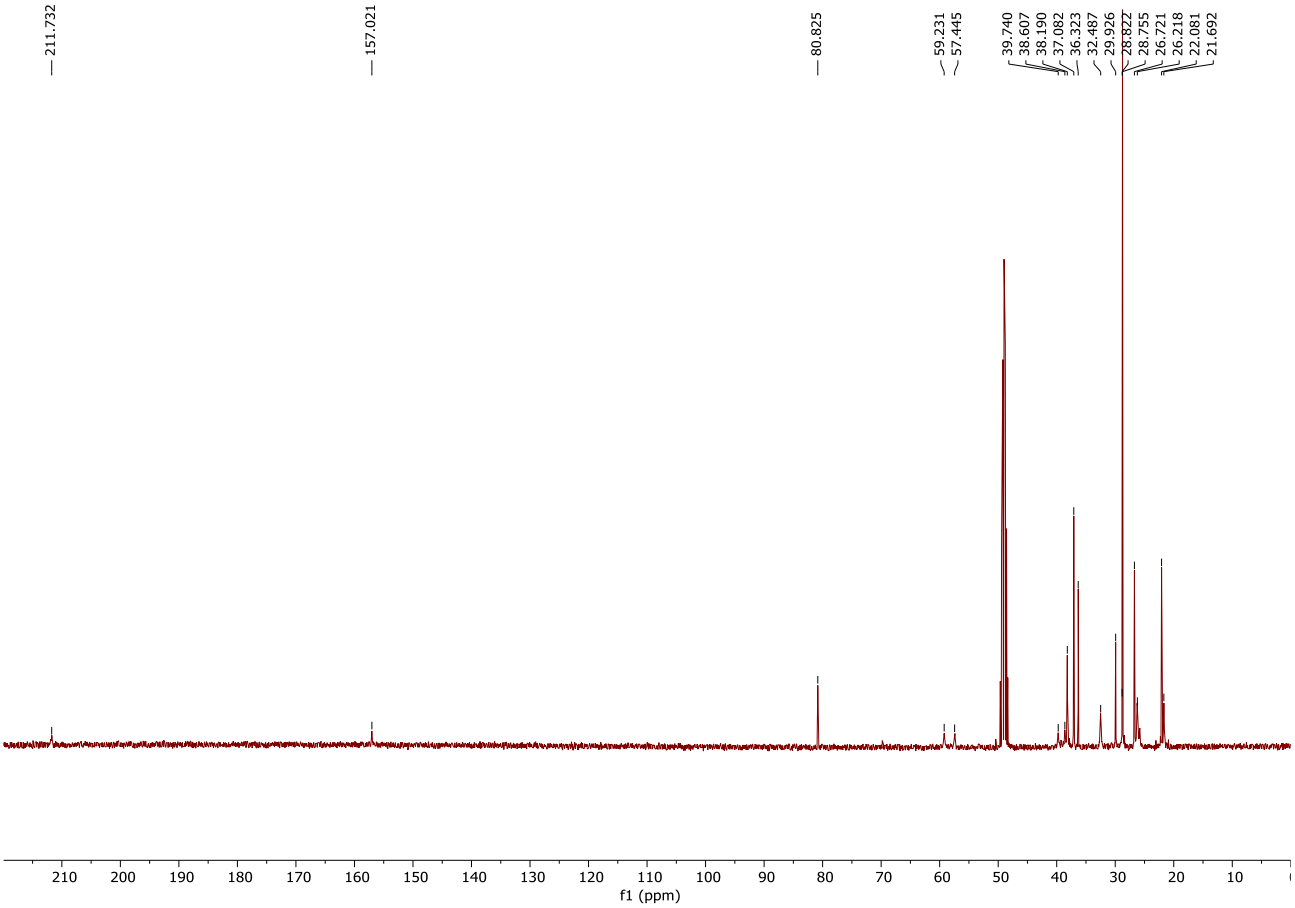
IR (NaCl): 1715 and 1676 (CO) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD, COSY, *g*-HSQC) δ 3.95-3.88 (m, 1H, H-2), 3.82-3.70 (m, 1H, H-8a), 2.96-2.78 (m, 1H, H-2), 2.53-2.32 (m, 2H, H-2'), 2.14 (s, 3H, H-4'), 1.94 (td, *J* = 13.8, 4.6 Hz, 2H, H-3, H-4), 1.84-1.75 (m, 2H, H-5, H-7), 1.72-1.59 (m, 1H, H-3), 1.45 [s, 9H, $C(CH_3)_3$], 1.50-1.36 (m, 6H, H-6, H-7, H-8, H-1'), 1.33-1.19 (m, 2H, H-5, H-6), 1.17-1.09 (m, 1H, H-4).

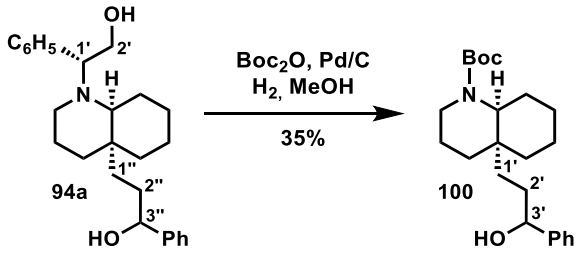
^{13}C NMR (101 MHz, CD_3OD) δ 211.7 (C-3'), 157.0 (CO), 80.8 [*C*$(CH_3)_3$], 59.2 and 57.5 (C-8a), 39.7 and 38.6 (C-2), 38.2 (C-2'), 37.1 (C-6), 36.3 (C-4a), 32.5 (C-7), 29.9 (C-4'), 28.8 [C(*C*$H_3)_3$], 26.7 (C-5), 26.2 (C-4), 25.8 (C-8), 22.1 (C-1'), 21.7 (C-3).

HRMS Calcd for [$C_{18}H_{31}NO_3 + H^+$]: 310.2377; found 310.2372.


3.954
3.876
3.817
3.701
2.960
2.779
2.528
2.316
2.144
1.943
1.843
1.751
1.720
1.453
0.91
0.94
0.94
2.01
2.76
1.99
1.87
1.30
14.68
2.23
1.00
f1 (ppm)


211.732
157.021
80.825
59.231
57.445
39.740
38.607
38.190
37.082
36.323
32.487
29.926
28.822
28.755
26.721
26.218
22.081
21.692
f1 (ppm)

(4a*S*,8a*S*)-1-(*tert*-Butoxycarbonyl)-4a-(3-hydroxy-3-phenylpropyl)decahydroquinoline (100):



Operating as in the preparation of decahydroquinoline **98**, from decahydroquinoline **94a** (72.7 mg, 0.19 mmol), Boc_2O (48.3 mg, 0.22 mmol) and 40% Pd/C (29 mg) in MeOH (3.8 mL), decahydroquinoline **100** (24.1 mg, 35%) was obtained after flash column chromatography (95:5 to 8:2 hexane–EtOAc) as a yellowish oil:

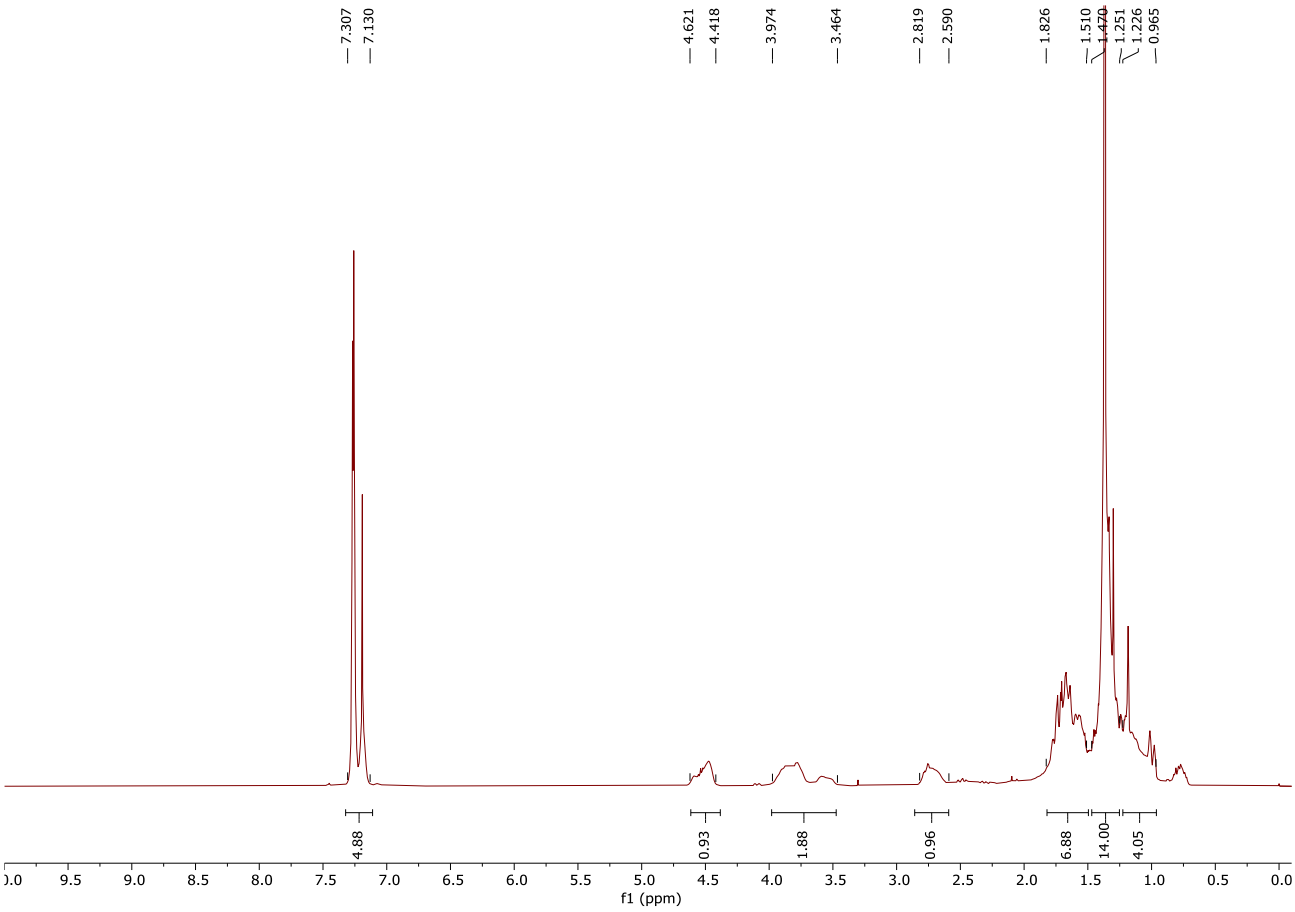
Several of the signals in the ^{1}H and ^{13}C NMR spectrum of **100** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

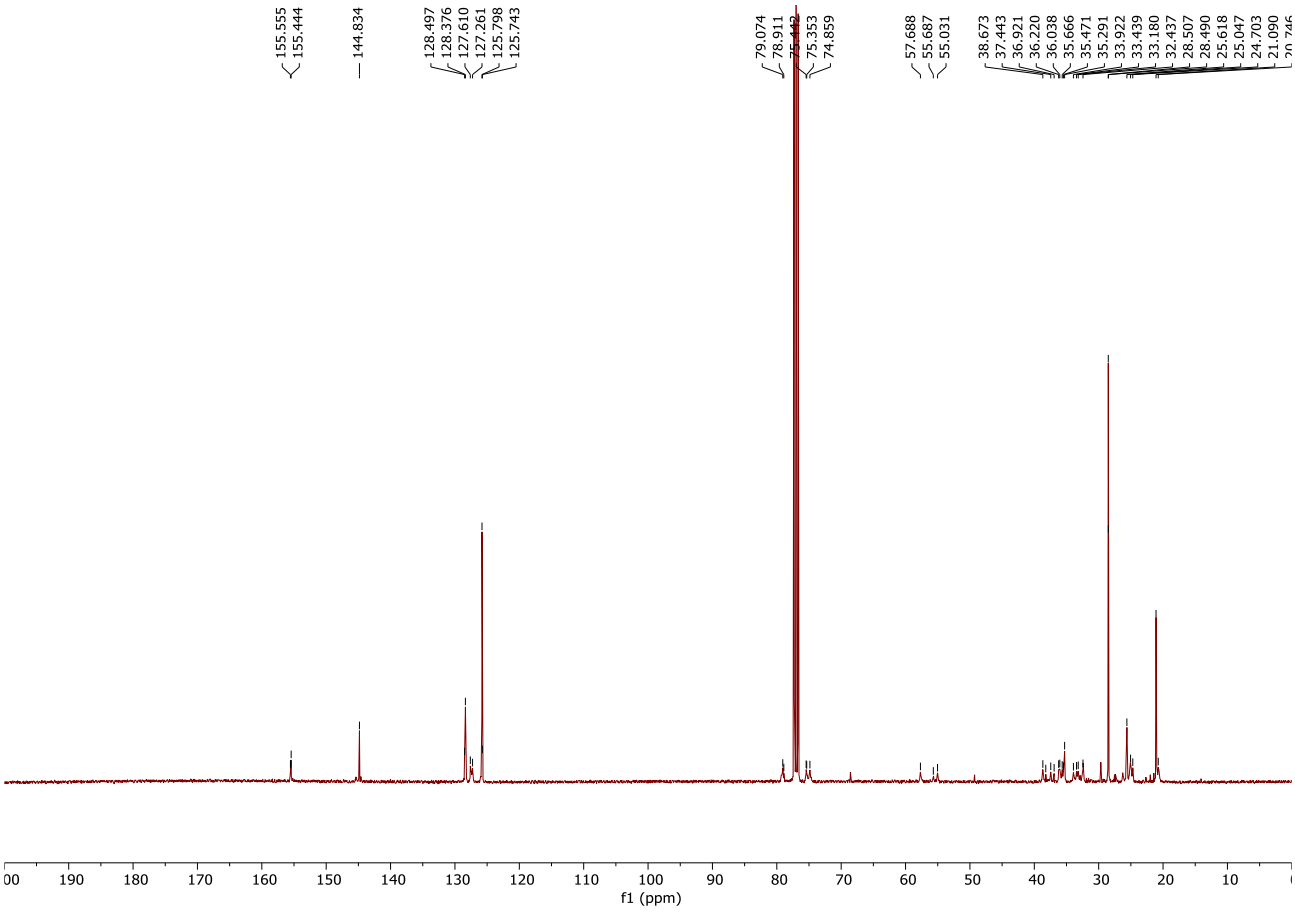
IR (NaCl): 3444 (OH), 1687, 1667 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.31-7.13 (m, 5H, ArH), 4.62-4.42 (m, 1H, H-3'), 3.97-3.46 (m, 2H, H-2 and H-8a), 2.82-2.59 (m, 1H, H-2), 1.83-1.51 (m, 7H), 1.47-1.25 (m, 14H), 1.23-0.97 (m, 4H).

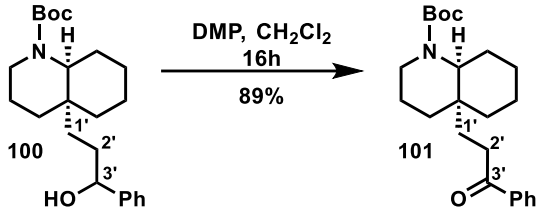
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 and 155.4 (CO), 144.8 (C-Ar), 128.5 and 128.4 (CH-Ar), 127.6 and 127.3 (CH-Ar), 125.8 and 125.7 (CH-Ar), 79.1 and 78.9 [*C*$(CH_3)_3$], 75.4, 75.4 and 74.9 (C-3'), 57.7 and 55.0 (C-8a), 38.7 and 38.2 and 37.4 and 36.9 (C-2), 36.2 and 36.0 (C-4a), 35.7 and 35.5 (CH_2), 35.3 (CH_2), 33.9 and 33.4 (CH_2), 33.2 and 32.4 (CH_2), 28.5 [C(*C*H_3)], 25.6 (CH_2), 25.0 and 24.7 (CH_2), 21.1 (CH_2), 20.7 (CH_2).

HRMS Calcd for [$C_{23}H_{35}NO_3 + H^+$]: 374.2690; found 374.2691.


7.307
7.130
4.621
4.418
3.974
3.464
2.819
2.590
1.826
1.510
1.470
1.251
1.226
0.965
4.88
0.93
1.88
0.96
6.88
14.00
4.05
f1 (ppm)


155.555
155.444
144.834
128.497
128.376
127.610
127.261
125.798
125.743
79.074
78.911
75.442
75.353
74.859
57.688
55.687
55.031
38.673
37.443
36.921
36.220
36.038
35.666
35.471
35.291
33.922
33.439
33.180
32.437
28.507
28.490
25.618
25.047
24.703
21.090
f1 (ppm)

(4a*S*,8a*S*)-1-(*tert*-Butoxycarbonyl)-4a-(3-oxo-3-phenylpropyl)-decahydroquinoline (101):



Operating as in the preparation of decahydroquinoline **99**, from decahydroquinoline **100** (19.7 mg, 0.053 mmol) and DMP (31.3 mg, 0.05 mmol) in CH_2Cl_2 (0.4 mL), decahydroquinoline **101** (17.5 mg, 89%) was obtained after flash column chromatography (8:2 hexane–EtOAc) as a yellowish oil:

Several of the signals in the ^1H and ^{13}C NMR spectrum of **101** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

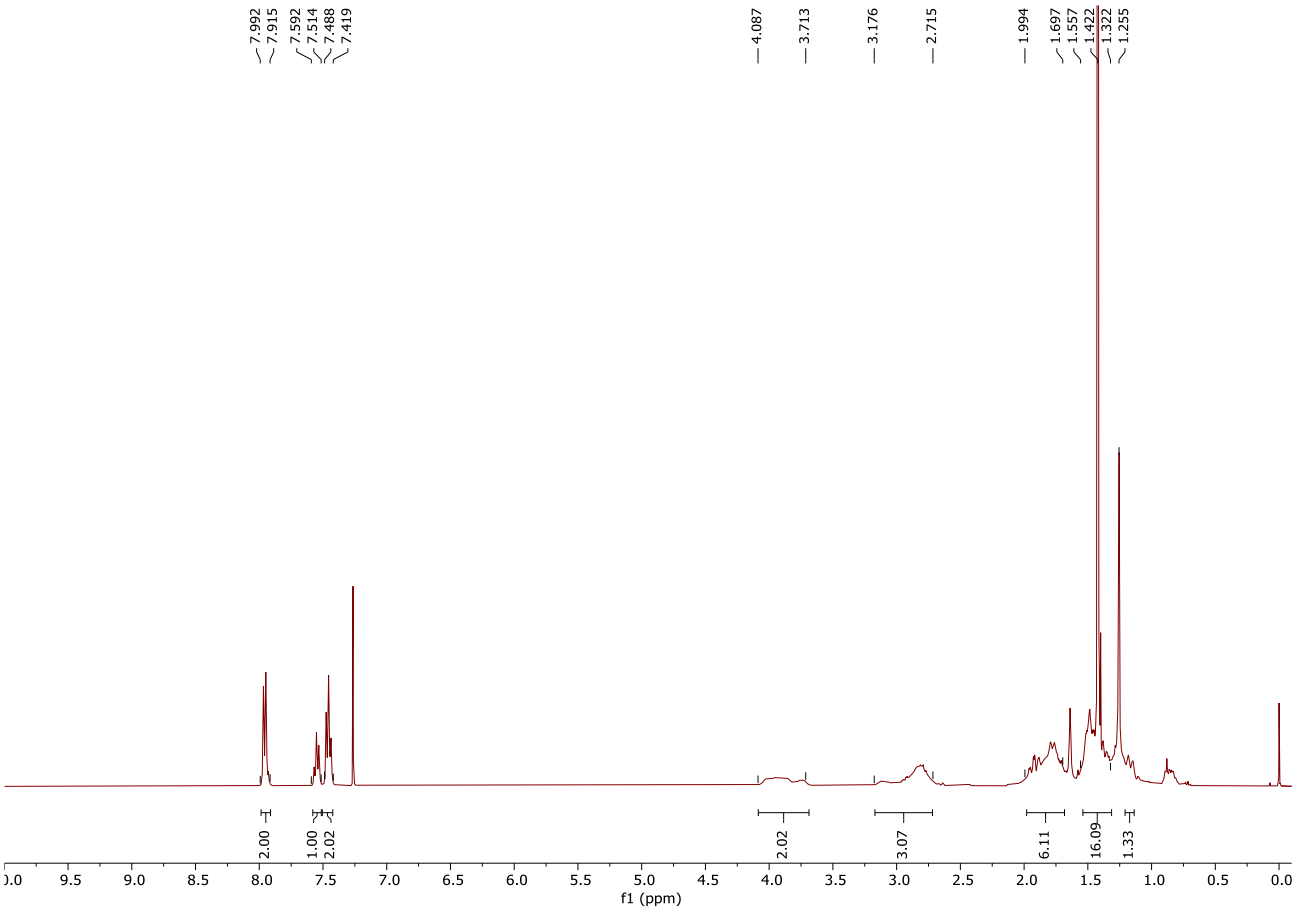
$[\alpha]^{23}_D$ + 17.6 (*c* 0.7, $CHCl_3$).

IR (NaCl): 1686 (CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.98-7.93 (m, 2H, ArH), 7.58-7.52 (m, 1H, ArH), 7.49-7.42 (m, 2H, ArH), 4.09-3.68 (m, 2H, H-2 and H-8a), 3.18-2.69 (m, 3H, H-2 and H-2'), 2.03-1.68 (m, 6H), 1.58-1.34 (m, 16H), 1.23-1.13 (m, 1H).

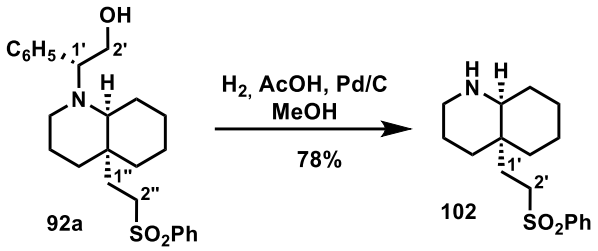
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.2 and 200.7 (CO), 155.4 and 155.2 (NCO), 137.0 (C-Ar), 132.9 (CH-Ar), 128.4 (CH-Ar), 128.1 (CH-Ar), 79.2 [*C*$(CH_3)_3$], 57.5 and 55.3 (C-8a), 38.5 and 37.4 (C-2), 36.1 (CH_2), 35.4 (C-4a), 32.5 (CH_2), 32.2 (CH_2), 28.4 [C(*C*$H_3)_3$], 25.8 (CH_2), 25.6 (CH_2), 25.1 and 24.7 (CH_2), 22.6 (CH_2), 21.1 and 20.7 (CH_2).

HRMS Calcd for [$C_{23}H_{33}NO_2$ + H^+]: 372.2533; found 372.2529.


7.992
7.915
7.592
7.514
7.488
7.419
4.087
3.713
3.176
2.715
1.994
1.697
1.557
1.422
1.322
1.255
2.00
1.00
2.02
2.02
3.07
6.11
16.09
1.33
f1 (ppm)

X

(4a*S*,8a*S*)-4a-[2-(Phenylsulfonyl)ethyl]decahydroquinoline (102):



A solution of decahydroquinoline **92a** (58 mg, 0.136 mmol) and AcOH (0.53 mL, 9.38 mmol) in MeOH (3 mL) containing 40% Pd/C (23 mg) was stirred under hydrogen at rt for 16 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash column chromatography (1:1 hexane–EtOAc to 100% EtOAc then 9:1 EtOAc:Et_3N) afforded decahydroquinoline **102** (32 mg, 78%) as a yellowish oil:

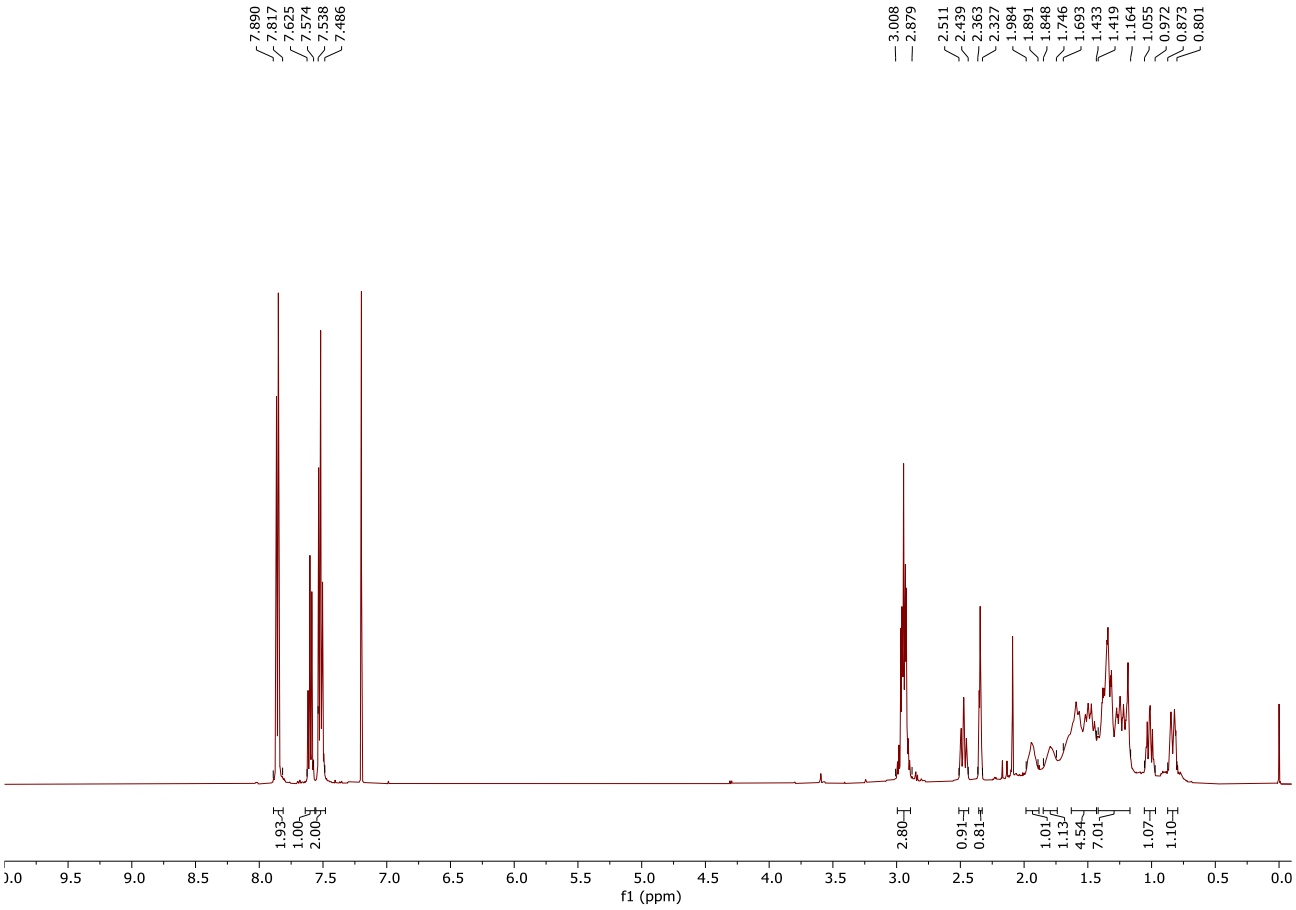
$[\alpha]^{23}_D$ –5.8 (*c* 1.4, $CHCl_3$).

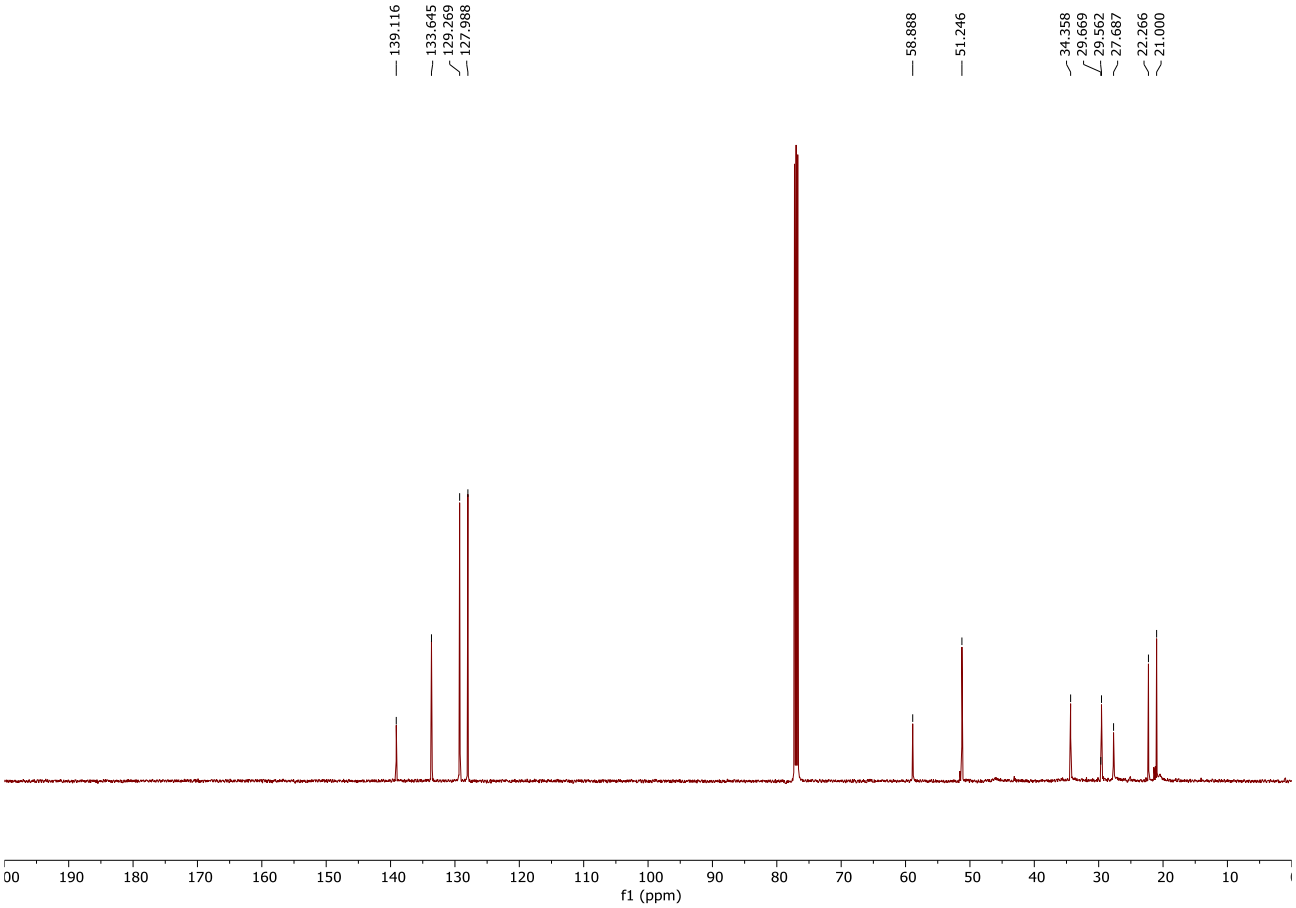
IR (NaCl): 3334 (NH), 1146, 1306 (SO_2) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.89-7.82 (m, 2H, ArH), 7.63-7.57 (m, 1H, ArH), 7.54-7.49 (m, 2H, ArH), 3.01-2.88 (m, 3H, H-2 and H-2'), 2.51-2.44 (m, 1H, H-2), 2.36-2.33 (m, 1H, H-8a), 1.98-1.89 (m, 1H), 1.85-1.75 (m, 1H), 1.69-1.43 (m, 4H), 1.42-1.16 (m, 7H), 1.06- 0.97 (m, 1H), 0.87-0.80 (m, 1H).

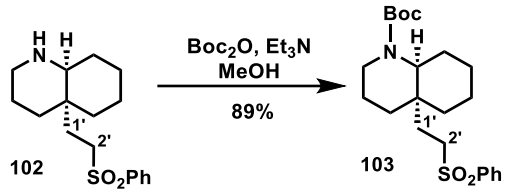
^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (C-Ar), 133.6 (CH-Ar), 129.3 (CH-Ar), 128.0 (CH-Ar), 58.9 (C-8a), 51.2 (C-2'), 34.4 (C-4a), 29.7 (CH_2), 29.6 ($2CH_2$), 27.7 (CH_2), 22.3 ($2CH_2$), 21.0 ($2CH_2$).

HRMS Calcd for [$C_{17}H_{25}NO_2S + H^+$]: 308.1679; found 308.1687.


7.890
7.817
7.625
7.574
7.538
7.486
3.008
2.879
2.511
2.439
2.363
2.327
1.984
1.891
1.848
1.746
1.693
1.433
1.419
1.164
1.055
0.972
0.873
0.801
1.93
1.00
2.00
2.80
0.91
0.81
1.01
1.13
4.54
7.01
1.07
1.10
f1 (ppm)


139.116
133.645
129.269
127.988
58.888
51.246
34.358
29.669
29.562
27.687
22.266
21.000
f1 (ppm)

(4a*S*,8a*S*)-1-(*tert*-Butoxycarbonyl)-4a-[2-(phenylsulfonyl)ethyl]decahydroquinoline (103):



Boc_2O (10.6 mg, 0.05 mmol) and Et_3N (9 μL, 0.06 mmol) were added to a solution of amine **102** (14 mg, 0.05 mmol) in CH_2Cl_2 (1.3 mL) and stirred for 16 h at room temperature. After that, the mixture was washed with saturated aqueous $NaHCO_3$, dried, filtered, and concentrated. Flash column chromatography (9:1 to 1:1 hexane–EtOAc) afforded amine **103** (16.5, 89%) as a yellowish oil.

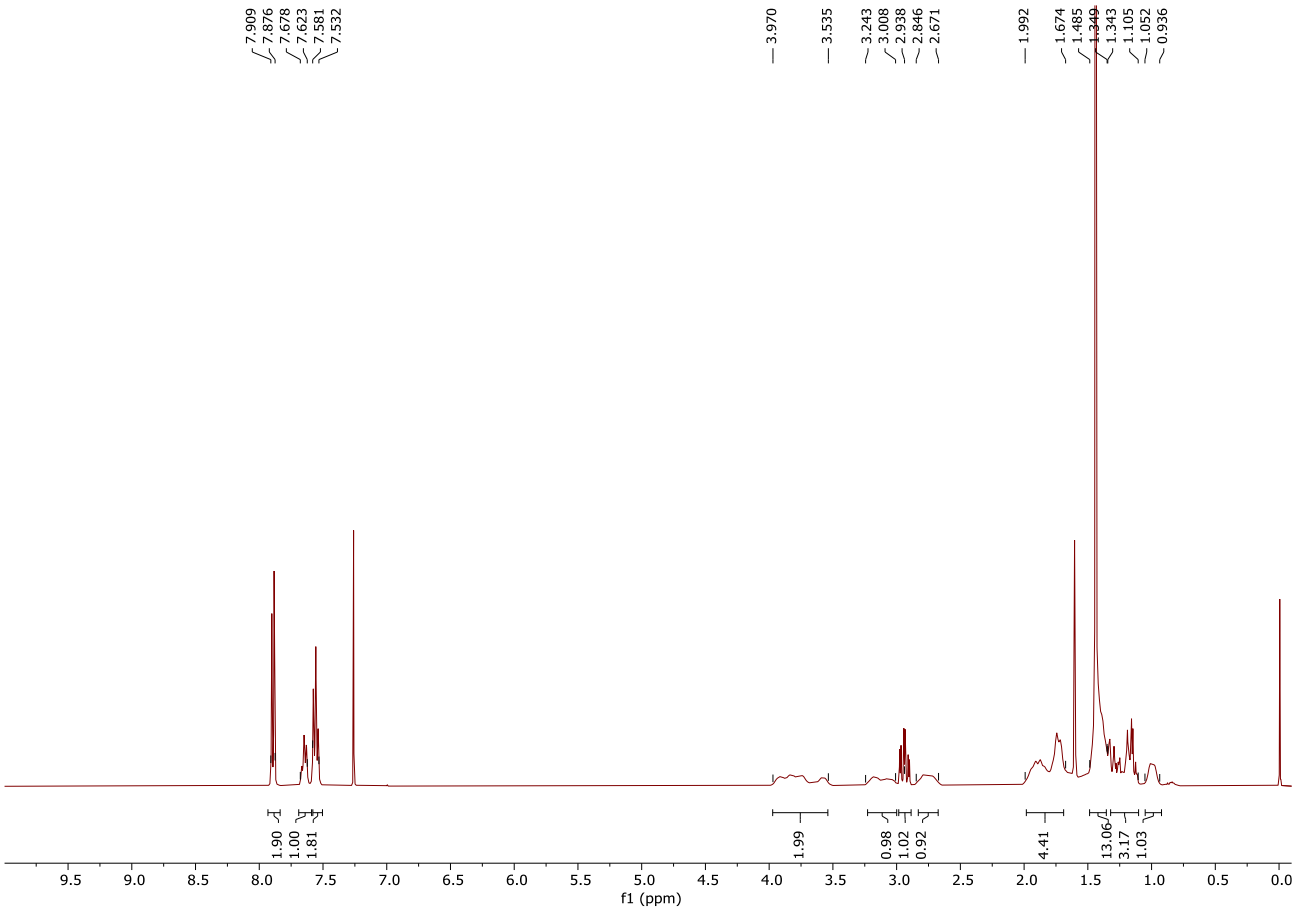
$[\alpha]^{23}_D$ +11.0 (*c* 0.8, $CHCl_3$).

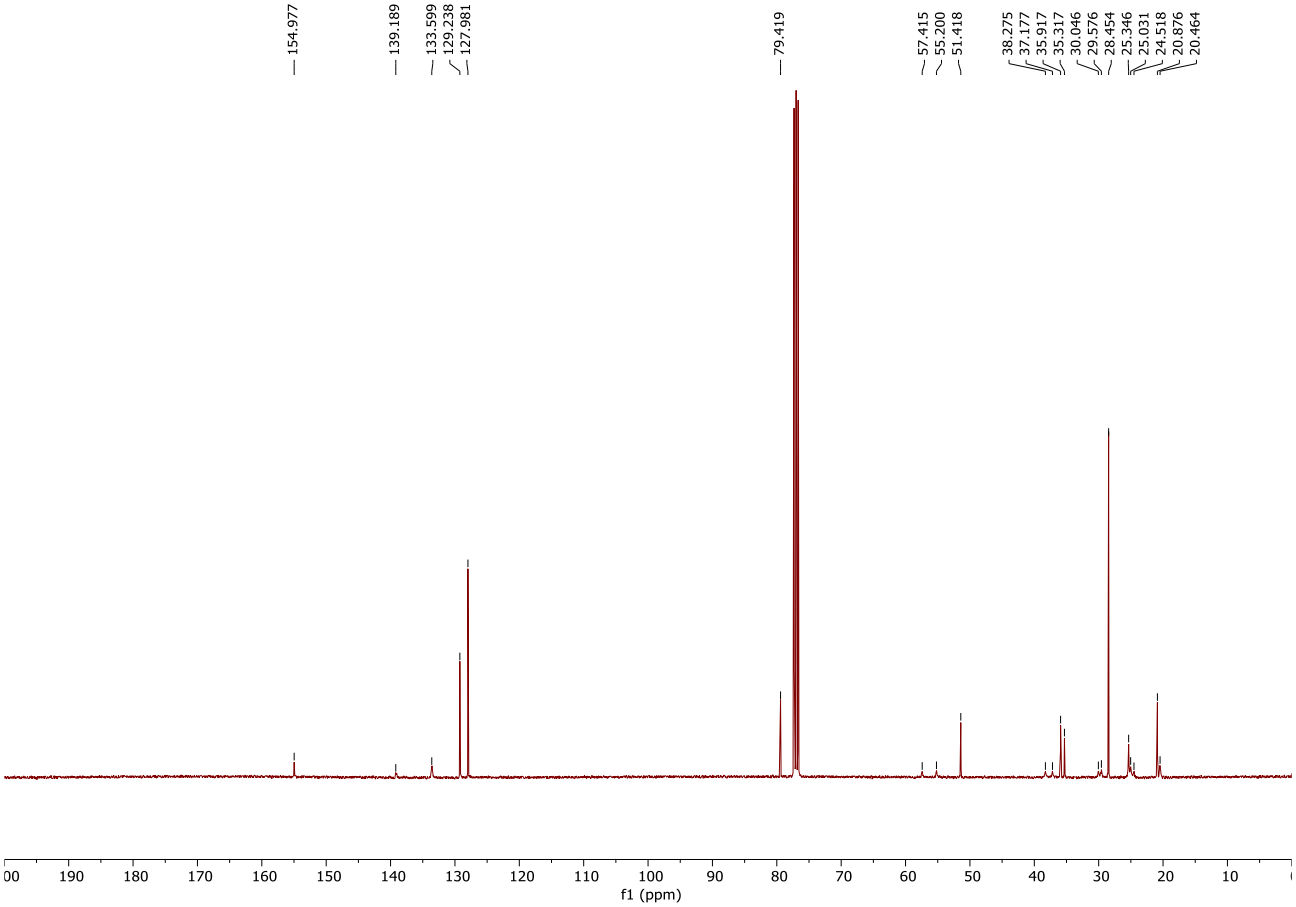
IR (NaCl): 1685 (CO), 1146 (SO_2) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 7.91-7.88 (m, 2H, ArH), 7.68-7.62 (m, 1H, ArH), 7.58-7.53 (m, 2H, ArH), 3.97-3.54 (m, 2H, H-2 and H-8a), 3.24-3.01 (m, 1H, H-2'), 2.94 (td, *J* = 12.8, 4.0 Hz, 1H, H-2'), 2.85-2.67 (m ,1H, H-2), 1.99-1.67 (m, 4H), 1.48-1.35 (m, 13H), 1.34-1.10 (m, 3H), 1.05-0.94 (m, 1H).

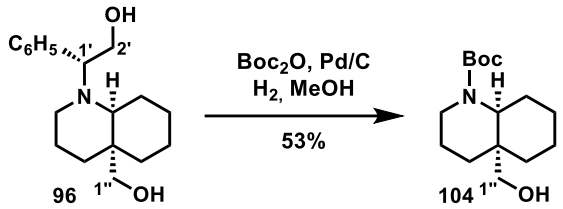
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0 (CO), 139.2 (C-Ar), 133.6 (CH-Ar), 129.2 (CH-Ar), 128.0 (CH-Ar), 79.4 [*C*$(CH_3)_3$], 57.4 and 55.2 (C-8a), 51.4 (C-2'), 38.3 and 37.2 (C-2), 35.9 (CH_2), 35.3 (C-4a), 30.0 and 29.6 (CH_2), 28.5 [C(*C*$H_3)_3$], 25.3 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 20.9 (CH_2), 20.5 (CH_2).

HRMS Calcd for [$C_{22}H_{33}NO_4S + H^+$]: 408.2203; found 408.2196.


7.909
7.876
7.678
7.623
7.581
7.532
3.970
3.535
3.243
3.008
2.938
2.846
2.671
1.992
1.674
1.485
1.349
1.343
1.105
1.052
0.936
1.90
1.00
1.81
1.99
0.98
1.02
0.92
4.41
13.06
3.17
1.03
f1 (ppm)


154.977
139.189
133.599
129.238
127.981
79.419
57.415
55.200
51.418
38.275
37.177
35.917
35.317
30.046
29.576
28.454
25.346
25.031
24.518
20.876
20.464
f1 (ppm)

(4a*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-4a-(hydroxymethyl)decahydroquinoline (104):



Operating as in the preparation of decahydroquinoline **98**, from decahydroquinoline **96** (27.2 mg, 0.09 mmol), Boc_2O (30 mg, 0.14 mmol) and 40% Pd/C (11 mg) in MeOH (1.9 mL), decahydroquinoline **104** (13.3 mg, 53%) was obtained after flash column chromatography (95:5 to 8:2 hexane–EtOAc) as a yellowish oil:

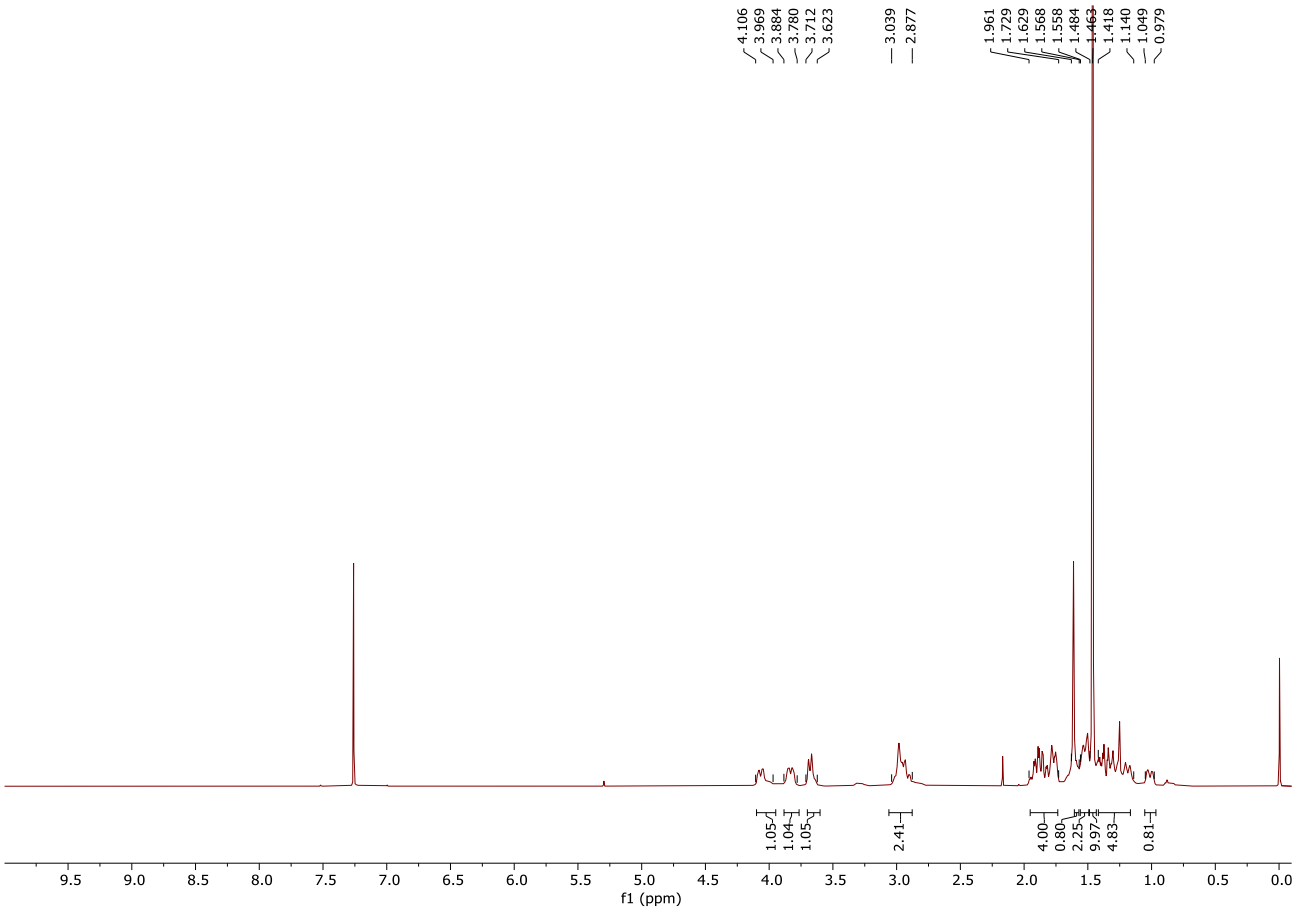
$[\alpha]^{23}_D$ –10.6 (*c* 0.7, $CHCl_3$).

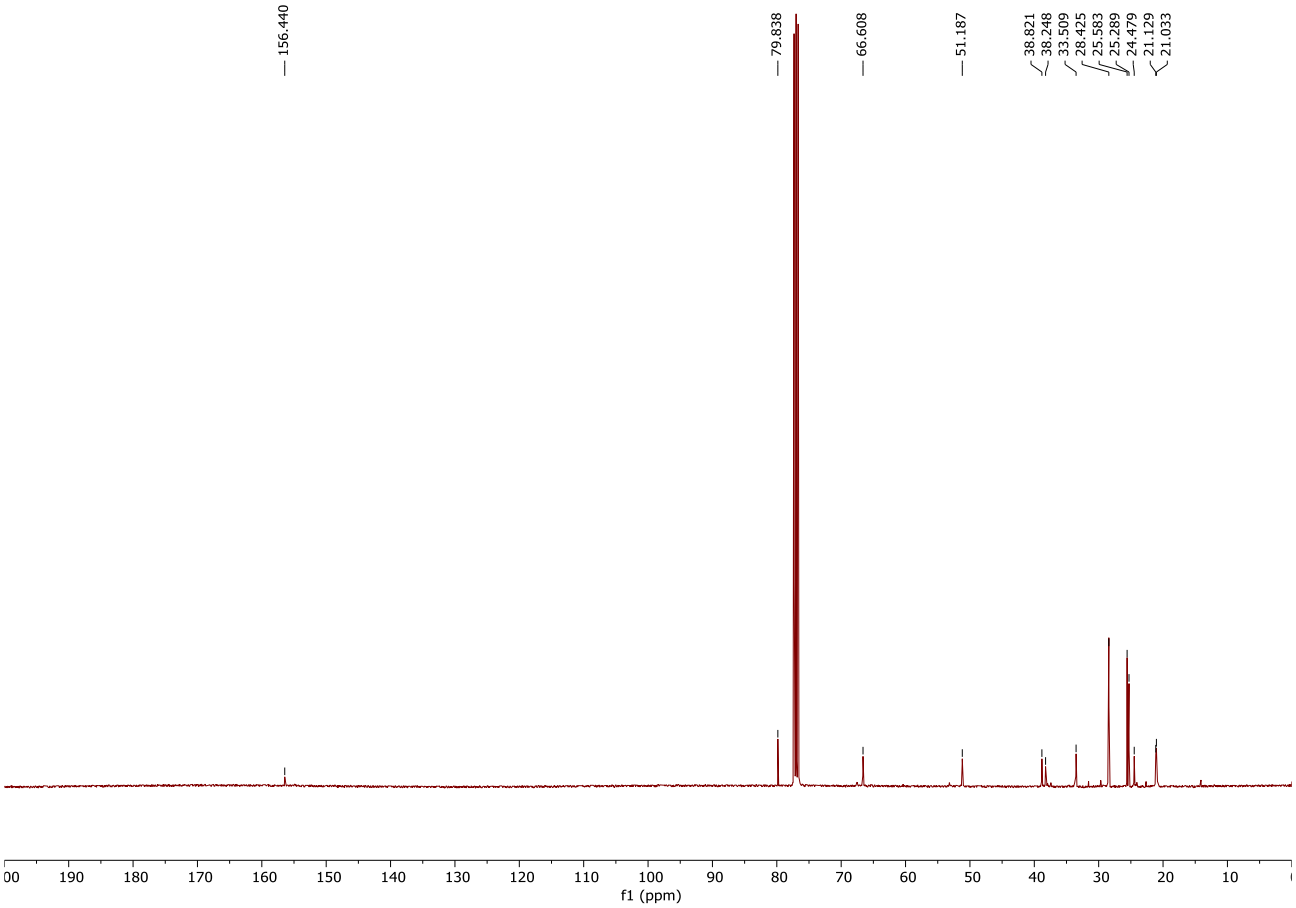
IR (NaCl): 1666, 1688 (CO), 3449 (OH) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 3.97-4.11 (m, 1H, H-8a), 3.78-3.88 (m, 1H, H-2), 3.62-3.71 (m, 1H, H-1'), 2.88-3.04 (m, 2H, H-1' and H-2), 1.73-1.96 (m, 4H), 1.57-1.63 (m, 1H), 1.48-1.56 (m, 2H), 1.46 [s, 9H, $(CH_3)_3$], 1.14-1.42 (m, 4H), 0.98-1.05 (m, 1H).

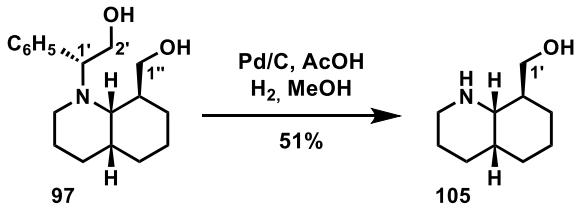
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.4 (CO), 79.8 [*C*$(CH_3)_3$], 66.6 (C-1'), 51.2 (C-8a), 38.8 (C-2), 38.2 (Cq), 33.5 (CH_2), 28.4 [C(*C*$H_3)_3$], 25.6 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 21.1 (CH_2), 21.0 (CH_2).

HRMS Calcd for [$C_{15}H_{27}NO_3$ + H^+]: 270.2064; found 270.2068.


4.106
3.969
3.884
3.780
3.712
3.623
3.039
2.877
1.961
1.729
1.629
1.568
1.558
1.484
1.463
1.418
1.140
1.049
0.979
1.05
1.04
1.05
2.41
4.00
0.80
2.25
9.97
4.83
0.81
f1 (ppm)


156.440
79.838
66.608
51.187
38.821
38.248
33.509
28.425
25.583
25.289
24.479
21.129
21.033
f1 (ppm)

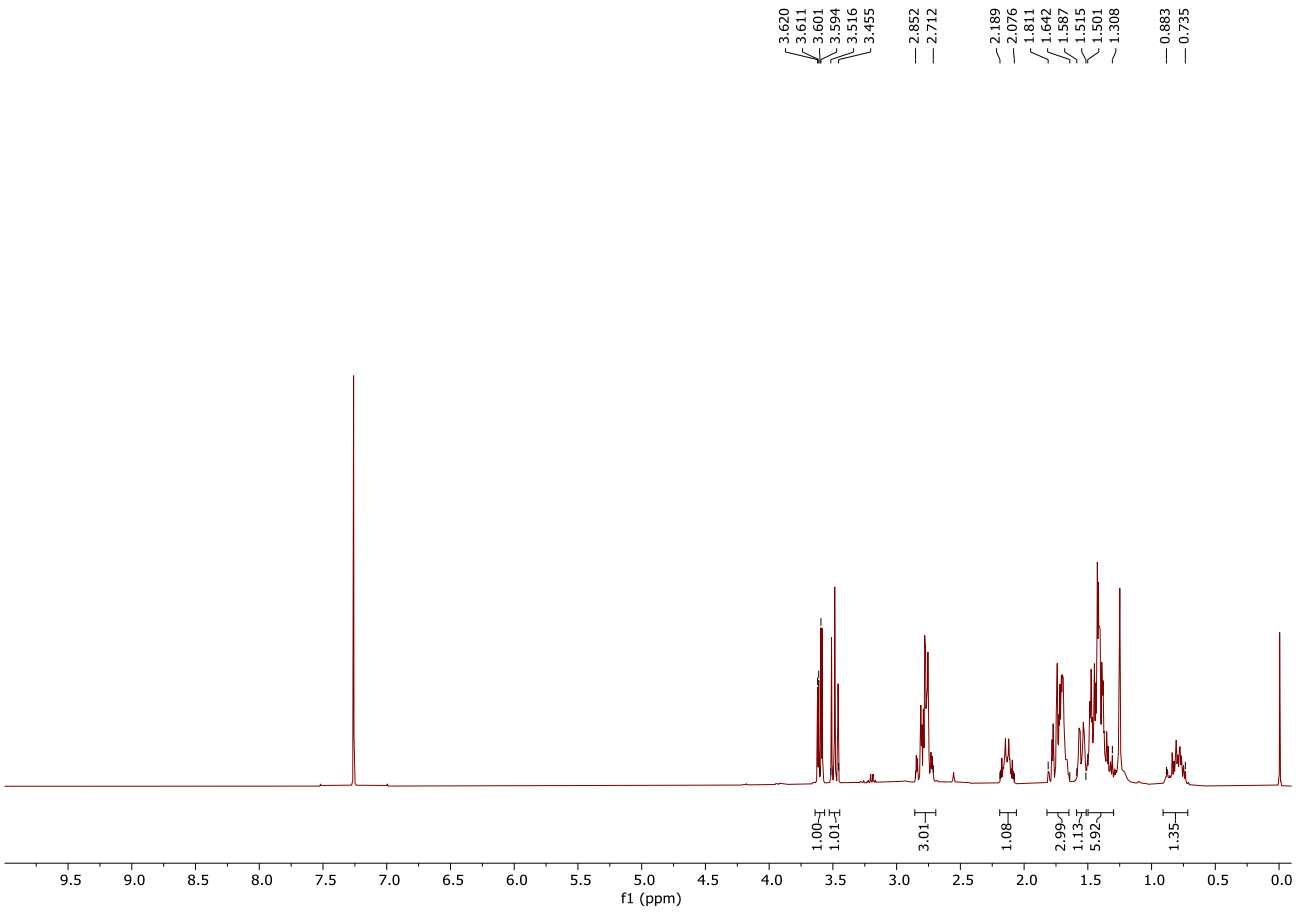
(4a*R*,8*S*,8a*S*)-8-(Hydroxymethyl)decahydroquinoline (105):



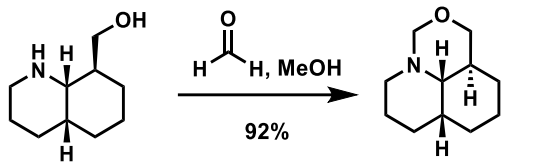
A solution of decahydroquinoline **97** (219 mg, 0.76 mmol), and AcOH (2.99 mL, 52.21 mmol) in MeOH (15 mL) containing 40% Pd/C (87 mg) was stirred under hydrogen at rt for 16 h. The catalyst was removed by filtration over Celite®, and the filtrate was basified with a 2M solution of NaOH, extracted CH_2Cl_2, dried and concentrated. Flash chromatography (100% CH_2Cl_2 then 8:2:0.1 to 8:2:0.25 CH_2Cl_2–MeOH–NH_4OH) afforded decahydroquinoline **105** (26.1 mg, 51%) as a colorless solid:

$[\alpha]^{23}_D$ +2.8 (*c* 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 3.60 (dd, *J* = 7.6, 3.6 Hz, 1H), 3.52-3.46 (m, 1H), 2.85-2.71 (m, 3H), 2.19-2.08 (m, 1H), 1.81-1.64 (m, 3H), 1.59-1.52 (m, 1H), 1.50-1.31 (m, 6H), 0.88-0.74 (m, 1H).


3.620
3.611
3.601
3.594
3.516
3.455
2.852
2.712
2.189
2.076
1.811
1.642
1.587
1.515
1.501
1.308
0.883
0.735
1.00
1.01
3.01
1.08
2.99
1.13
5.92
1.35
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

(+)-Myriozaxine A:

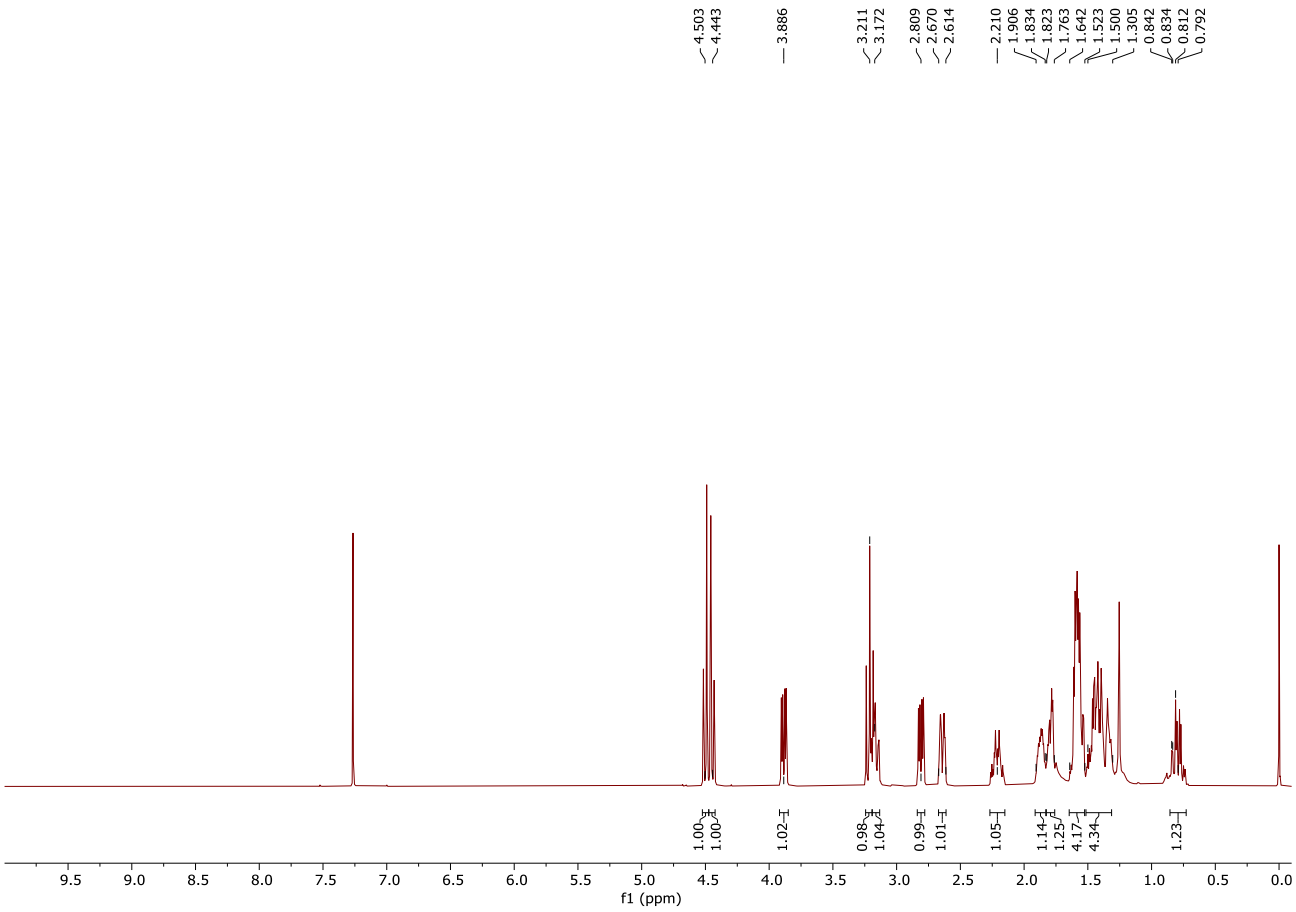


105 **(+)-Myrioxazine A**

Formalin (1 mL of a 37% w/w in H_2O solution, 13 mmol) was added to a solution of aminoalcohol **105** (108.8 mg, 0.64 mmol) in MeOH (2 mL). After 2 h, 2M aqueous solution of NaOH was added and the mixture was extracted with CH_2Cl_2, dried, filtered, and evaporated. Flash column chromatography (1:1 to 3:7 hexane–EtOAc) afforded **(+)-myrioxazine A** (106.8 mg, 92%) as a colorless oil.

$[\alpha]^{23}_D$ – 24.4 (*c* 1.2, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, *J* = 10.4 Hz, 1H), 4.44 (d, *J* = 10.4 Hz, 1H), 3.89 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.21 (t, *J* = 10.8 Hz, 1H), 3.17 (td, *J* = 12.0, 3.2 Hz, 1H), 2.81 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.67-2.61 (m, 1H), 2.21 (qt, *J* = 11.2, 4.0 Hz, 1H), 1.91-1.83 (m, 1H), 1.82-1.76 (m, 1H), 1.64-1.52 (m, 4H), 1.50-1.31 (m, 4H), 0.79 (qd, *J* = 12.0, 3.2 Hz, 1H).


4.503
4.443
3.886
3.211
3.172
2.809
2.670
2.614
2.210
1.906
1.834
1.823
1.763
1.642
1.523
1.500
1.305
0.842
0.834
0.812
0.792
1.00
1.00
1.02
0.98
1.04
0.99
1.01
1.05
1.14
1.25
4.17
4.34
1.23
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)