UNIVERSITAT DE BARCELONA

Development of a divergent strategy towards the synthesis of lycopodium alkaloids

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Programa de Doctorat: Química Orgànica Experimental i Industrial

DEVELOPMENT OF A DIVERGENT STRATEGY TOWARDS THE SYNTHESIS OF LYCOPODIUM ALKALOIDS

Memòria presentada per Gisela Saborit Villarroya

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The experimental work included in this PhD thesis was carried out in the Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona under the direction of Prof. Josep Bonjoch and Dr. Ben Bradshaw between the period of October 2012 to May 2016.

Calculations that appear in this work were performed by Carles Bo and Ruth Dorel at the Institute of Chemical Research of Catalonia (ICIQ) and Prof. Enrique Gómez-Bengoa at the University of the Basque Country.

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HPLC separation and crystal structure of (-)-**2** was carried out at CSIC-Universidad de Zaragoza by Professor Carlos Cativiela and Dr. Ana-Isabel Jiménez

El treball experimental recollit en aquesta memòria es va dur a terme al Laboratori de Química Orgànica de la Facultat de Farmàcia de la Universitat de Barcelona sota la direcció del Prof. Josep Bonjoch Sesé i del Dr. Ben Bradshaw en el període comprés entre octubre de 2012 i maig de 2016.

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I qui m'havia de dir que acabaria abandonant el transport públic per anar a compartir pis a la Riera Blanca amb tres representants del Perelló: la Neus, la Maria i la Sònia. Amb vosaltres he après a passar la granera, a prendre lo poval, a dir txeic!!!, a caçar moixons i a netejar l'escuranda. I segur que me'n deixo perquè cada dia amb vosaltres ha sigut una caixa de sorpreses.

Seria injusta si no dediqués unes línies a un grup d'amics molt divers i especial que ha sortit d'aquests 5 anys. Joves glòries, cadascú de nosaltres aporta alguna cosa que fa que quan un falta, no siguem el mateix. Mafalda, no tinguis por de dir el què penses. Ets molt intel·ligent i espabilada. Ramos, ets un exemple a seguir. No conec una persona més treballadora i amb ganes d'aprendre que tu.

La Magda, que he fet córrer per la diagonal a canvi d'un cacaolat, que he fet esperar sempre per anar a dinar i s'ha acabat convertint en una bona amiga. L'Ángel, que no ha sigut company de laboratori però és imprescindible. Fas honor al teu nom.

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Contents

PUBLICATIONS

1. ***Synthetic and DFT Studies Towards a Unified Approach to Phlegmarine Alkaloids: Aza-Michael Intramolecular Processes Leading to 5-Oxodecahydroquinolines***. B. Bradshaw, C. Luque-Corredera, G. Saborit, C. Cativiela, R. Dorel, C. Bo, J. Bonjoch. *Chem. Eur. J.* **2013**, *19*, 13881-13892.

2. ***Synthetic approaches towards the Lycopodium alkaloids***. B. Bradshaw, G. Saborit-Villarroya, C. Luque-Corredera, M. Balañà, J. Bonjoch. *Recent Advances of Pharmaceutical Sciences.* **2014**, *10*, 143-163.

3. ***Synthesis of (±)-Serralongamine A and the Revised Structure of Huperzine N***. Saborit V, G.; Bosch, C.; Parella, T.; Bradshaw, B.; Bonjoch, J. *J. Org. Chem.* **2016**, *81*, 2629−2634.

4. ***Synthesis of cis-hydrindan-2,4-diones bearing a quaternary stereocenter through a Danheiser annulation.*** Manuscript in preparation

CONTRIBUTIONS TO CONGRESSES

November 2013, Andorra. Gisela Saborit, Ben Bradshaw, Josep Bonjoch. Collective synthesis approach to the lycopodium alkaloids. Joves investigadors dels països Catalans.

June 2014, Alicante-Spain. Gisela Saborit, Ben Bradshaw, Josep Bonjoch. Towards the total synthesis of (+)-fawcettimine. XXV Reunió Bienal de Química Orgánica.

25th International Society of Heterocyclic Chemistry Congress, Santa Barbara CA. Ben Bradshaw, Caroline Bosch, Carlos Luque-Corredera, Claudio Parra, Gisela Saborit Villarroya and Josep Bonjoch. To Phlegmarines and Beyond - Strategies for Efficiency and Diversity in Natural Product Synthesis.

January 2016, **Toulouse**. Caroline Bosch, Gisela Saborit, Ben Bradshaw, Josep Bonjoch. Decahydroquinoline ring NMR patterns as a tool for the stereochemical elucidation of phlegmarine alkaloids.

ABBREVIATIONS AND ACRONYMS

$[\alpha]^{22}_{D}$	specific optical rotatory power at λ= 589 nm
aq.	aqueous
atm	atmosphere
ax	axial
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl carbonate
bp	boiling point
br	broad
c	concentration
^{13}C NMR	carbon-13 nuclear magnetic resonance
calcd	calculated
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
Celite®	filtration agent
COSY	correlation spectroscopy
$[Cu(tbs)_2]$	bis(N-tertbutylsalicylaldiminato) copper(II)
d	day(s), doublet (spectra)
δ	chemical shift
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMP	Dess-Martin periodinane
DPPA	diphenyl phosphoryl azide
DTAD	di-*tert*-butyl azodicarboxylate
dd	doublet of doublets
dm	doublet of multiplets
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
epi	epimer
equiv.	equivalent
eq	equatorial
[H]	reduction
^{1}H-NMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum correlation spectroscopy
IBX	*o*-Iodoxybenzoic acid
J	coupling constant
LDA	lithium diisopropylamide
Lit.	literature
L-Selectride®	lithium tri-*sec*-butylborohydride
M	molar
m	multiplet
M^{+}	molecular ion
m/z	mass to charge ratio
m-CPBA	meta-chloroperoxybenzoic acid
mol	moles
mp	melting point
MS	mass spectrometry
Ms	mesyl (methylsulfonyl)
n.a	not available
Ns	4-nitrobenzenesulfonyl
n.d.	not determined

[O]	oxidation
OTBS	*tert*-butyldimethylsilyl ether
OTES	triethylsilyl ether
OTMS	trimethylsilyl ether
OTPS	triphenylsilyl ether
p.	page
ppm	parts per million
quant.	quantitative
R	generalized alkyl group or substituent
R_f	retention factor
rac	racemic
ref.	reference
rt	room temperature
s	singlet
sat.	saturated
sol.	solution
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
Teoc	trimethylsilyl-ethoxycarbonyloxy
Teoc-Osu	[2-(trimethylsilyl)ethoxycarbonyloxy]succinimide
td	triplet of doublets
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl
wt	weight

1. The lycopodium alkaloids: Introduction and objectives

1.1 The lycopodium alkaloids

1.1.1 Introduction

The lycopodium alkaloids are a diverse range of structures isolated from the genus *Lycopodium*, a group of fern-like club-mosses, which are mainly found in tropical regions, in particular in areas of coniferous forests, mountainous regions and marshlands. Whilst crude extracts of these plants have been used throughout human history for their medicinal properties, it was not until Bödeker isolated lycopodine from *L. Complanatum*[1] in 1881 that serious scientific studies of the individual alkaloids components began. However, it wasn't until 1938 that its correct molecular formula was deduced by Achmatowicz and Uzieblo[2] and until 1960 that MacLean and co-workers finally elucidated its structure.[3] Since then, around 300 individual compounds have been isolated,[4] a number that continues to grow every year. Due to the vast structural diversity that this family of compounds possess, in 1995 Ayer proposed a classification system that divided these alkaloids in four distinct classes or subfamilies: the phlegmarine, the lycopodine, the lycodine and the fawcettimine class (Figure 1.1).[5]

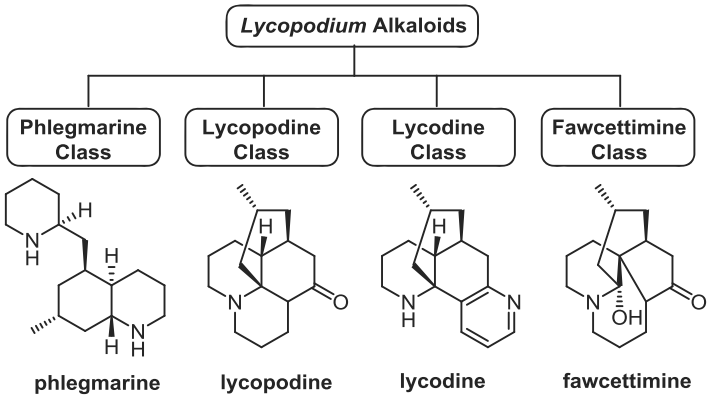


Figure 1.1. The four classes of lycopodium alkaloids.

[1] Bödeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363-367.
[2] Achmatowicz, O.; Uzieblo, W. *Roczniki Chem.* **1938**, *18*, 88-95.
[3] Harrison, W. A.; Curcumelli-Rodostamo, M.; Carson, D. F.; Barclay, L. R. C.; MacLean, D. B.; *Can. J. Chem*. **1961**, 2086-2099.
[4] Ma, X.; Gang, D.R. *Nat. Prod. Rep.* **2004**, *21*, 752-772.
[5] Ayer, W. A.; Trifonov, L. S. *The Alkaloids* (*Academic Press*), **1994**, *45*, 233-266.

1.1.2 Overview of bioactivities

Due to the wide distribution of these plants, it is not surprising that many have been used extensively in traditional folk medicine throughout history. Various plant extracts from lycopodium have been used for maladies of the eyes, skin irritations, inflammation of the liver, irritation of the intestinal tract, wound cure, pulmonary disease and their ability to induce pregnancy. Indeed, alkaloid extracts from *Lycopodium complanatum* have proved to have different biological activites such as antibacterial, antifungal and antimicrobial.[6] An in depth anaylisis of these extracts showed that the main components were lycopodine, dihydrolycopodine and lycodine. However, nowadays extracts from lycopodium are not commonly used due to the fact that their side-effects often outweigh their benefits. Furthermore, the majority of these treatments have yet to be proven through empirical scientific studies. Despite this, from the limited studies undertaken so far, it has been discovered that many of these compounds do indeed possess important biological activities that warrant further investigation and development (Figure 1.2). One highly promising potential area of these compounds is for the treatment of severe neurodegenerative diseases such as Alzheimer's. Examples include huperzine A[7] and lycoposerramine C,[8] which act as inhibitors of the enzyme acetylcholinesterase (AChE). The effect of huperzine A in the central cholinergic system also improves short and long-term memory in patients of cerebral arteriosclerosis. On the other hand, complanadine B from the lycodine class stimulates nerve growth factor (NGF) production in human glial cells.[9] Lycoposerramine Z, from the phlegmarine class, contains an unusual nitrone moiety which has been postulated to act as a radical trap, halting destructive

[6] Orhan, I.; Ozcelik, B.; Aslan, S.; Kartal, M.; Karaoglu, T.; Sener, B.; Terzioglu, S.; Iqbal Choudhary, M. *Nat. Prod. Res.* **2009**, *23*, 514–526.
[7] J. S. Liu, Y. L. Zhu, C. M. Yu, Y. Z. Zhou, Y. Y. Han, F. W.Wu, B. F. Qi, *Can. J. Chem.* **1986**, *64*, 837–839.
[8] Takayama, H.; Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 8307-8311.
[9] Morita, H.; Ishiuchi, K.; Haganuma, A.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2005**, *61*, 1955-1960.

cascades initiated by free radicals and hence also has potential application in combating neurodegenerative diseases.[10]

The other major area where the lycopodium alkaloids have been shown to possess promising activities is for the treatment of cancer. For example, complanadine A, a dimer of lycodine, was found to be cytotoxic against murine leukaemia cells (IC_{50}, 5.6 μg/ml),[11] lyconadin B, from the phlegmarine group, exhibits biological activity against brain tumors[12] and lycopodine has the ability to bring about inhibition in the growth of HeLa55 cells.[13] Serratezomine A, a fawcettimine type compound containing an unsual spiro structure, shows cytotoxicity against murine lymphoma and human epidermoid carcinoma cells.[14]

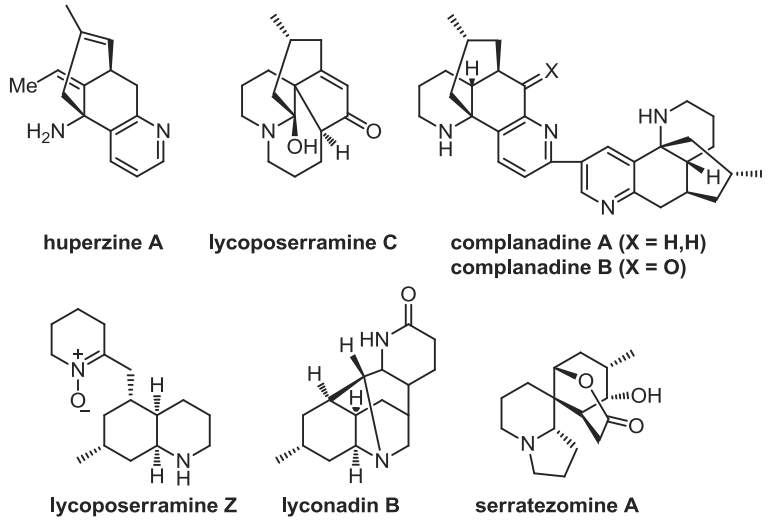


Figure 1.2. Examples of some biologically active lycopodium alkaloids.

Unfortunately, so far an extensive study of the biological activities of the lycopodium alkaloids has been hindered by the lack of material available from

[10] (a) Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223–229. (b) Sun, Y.; Yu, P.; Zhang, G.; Wang, L.; Zhong, H.; Zhai, Z.; Wang, L.; Wang, Y. *J. Neurosci. Res*. **2012**, *90*, 1667–1669.
[11] Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *Tetrahedron Lett*. **2000**, *41*, 9069–9073.
[12] Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14*, 5995-6000.
[13] Mandal, S. K.; Biswas, R.; Bhattacharyya, S. S.; Paul, S.; Dutta, S.; Pathak, S.; Khuda-Bukhsh, A. R. *Eur. J. Pharmacol.* **2010**, *626*, 115–122.
[14] Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *J. Org. Chem*. **2000**, *65*, 6241-6245.

natural sources since the wild plants are slow growing and only yield small quantities of the active products. Attempts to cultivate the plants have so far been unsuccessful due to the demanding conditions required.[4] It therefore seems likely that for the present moment total synthesis remains the only viable method to obtain sufficient quantities of material to continue to investigate the potential beneficial properties of these alkaloids.

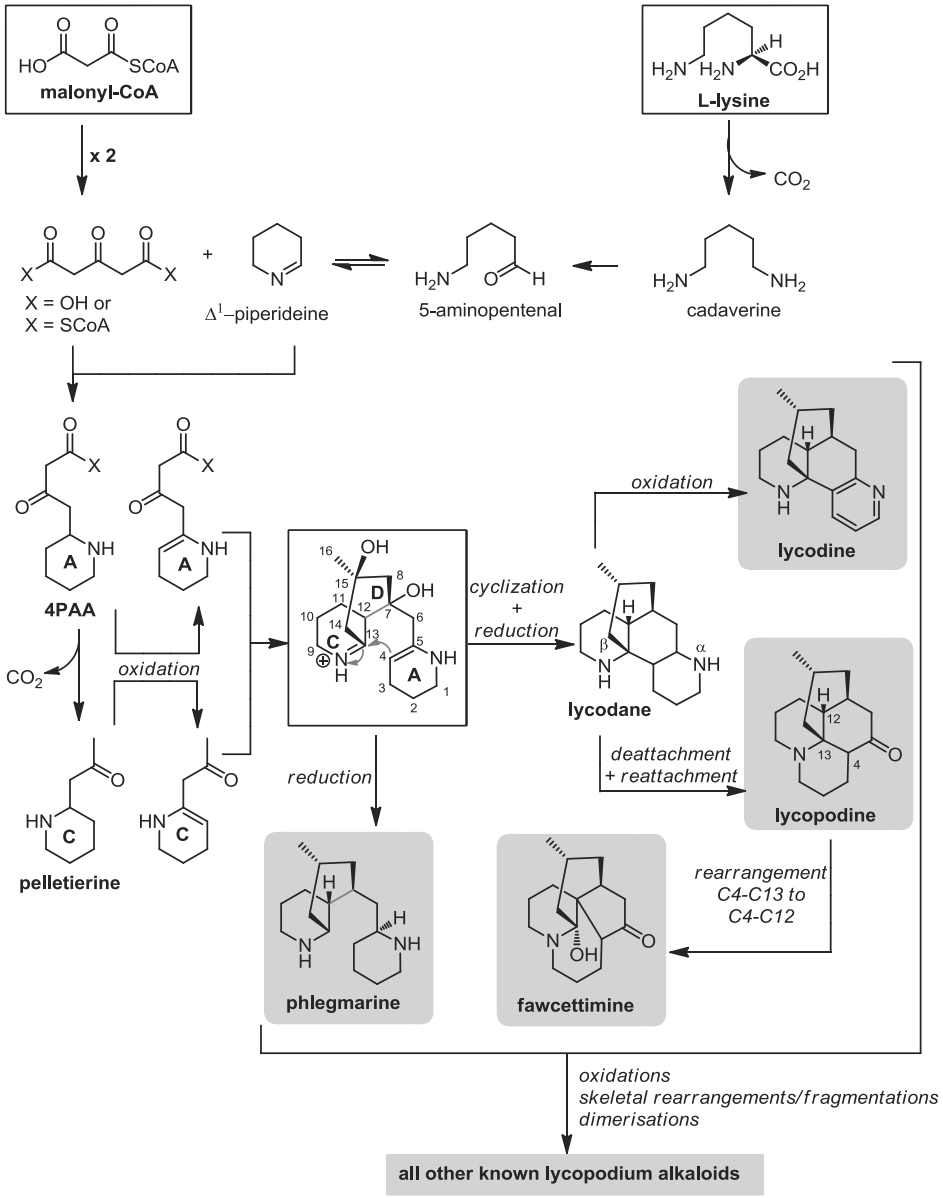
1.1.3 Biosynthesis

The biosynthetic pathway leading to all lycopodium alkaloids is still not clear, although a basic overview is outlined in Scheme 1.1 based on the present knowledge.[4] The vast structural diversity encountered among the lycopodium alkaloids is thought to derive from just two simple components, lysine and malonyl Co-A. The entry point into the pathway is through the decarboxylation of lysine to form cadaverine which is transformed to Δ^1-piperideine. At the same time, two molecules of malonyl-CoA are condensed to form acetonedicarboxylic acid, whose union with Δ^1-piperideine leads to 4-(2-piperidyl) acetoacetate (4PAA), which is then decarboxylated to form pelletierine. At this point 4PPA and pelletierine are likely oxidized to their corresponding enamines which are then coupled to form a cyclized intermediate bearing the core structure of phlegmarine. From here, the pathway likely diverges into two paths: (i) the dimeric intermediate is reduced to give phlegmarine with its all *trans* stereochemistry.[15] (ii) Alternatively, cyclisation with bond formation between C-4 and C-13 gives the lycodane skeleton. Here again, the pathway diverges into two pathways: (i) If the piperidine A ring is oxidized leads directly to lycodine. (ii) Detachment of C-1 from N_α of the lycodane skeleton and reattachment to N_β gives lycopodine whose rearrangement of the B ring via migration of the C-4 to C-13 bond to C-12 forms the 5 membered ring of fawcettimine. This reaction may go through the oxidized 12-hydroxy compound (see Section 3.1.2 for further details).

All the other lycopodium alkaloids can be traced back to these four key structures which are modified usually by oxidations, dimerisations and skeletal

[15] Other *cis* phlegmarine alkaloids and their derivatives which are commonly classed as the "miscellaneous group" likely arise at this juncture by different control in the reduction step.

fragmentations and rearrangements. Examples of compounds from each class will be discussed in more detail in the subsequent chapters dealing with each structural type.



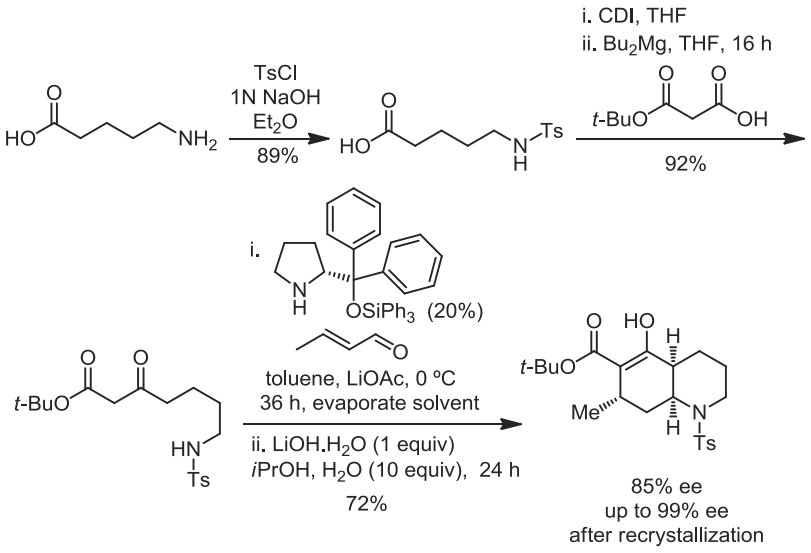
Scheme 1.1. Overview of the biosynthesis of the lycopodium alkaloids

1.2 Previous work and precedents

Extensive synthetic work has been carried out to the lycopodium alkaloids and will be discussed in detail in each of the subsequent chapters. Here we only concern ourselves with previous work in our research group that has the potential to act as a basis for a unified synthesis of the lycopodium alkaloids.

1.2.1 Organocatalyzed synthesis of decahydroquinolines

Previously, our group has developed a highly efficient route to 5-oxodecahydroquinolines by employing a tandem reaction sequence from a simple acyclic β-keto ester bearing a tosyl protected nitrogen tether.[16] Upon treatment with crotonaldehyde in the presence 1 equiv of $LiOH \cdot H_2O$ and 10 equiv of water in *i*PrOH, it underwent a tandem Robinson-annulation aza-Michael cyclization to give the decahydroquinoline ring (Scheme 1.2). An asymmetric version was then developed by using the modified Hayashi catalyst[17] to render the initial Michael addition enantioselective allowing for formation of the bicyclic product in 85% ee. Recrystallisation allowed the obtention of this material in enantiopure form (>99% ee).

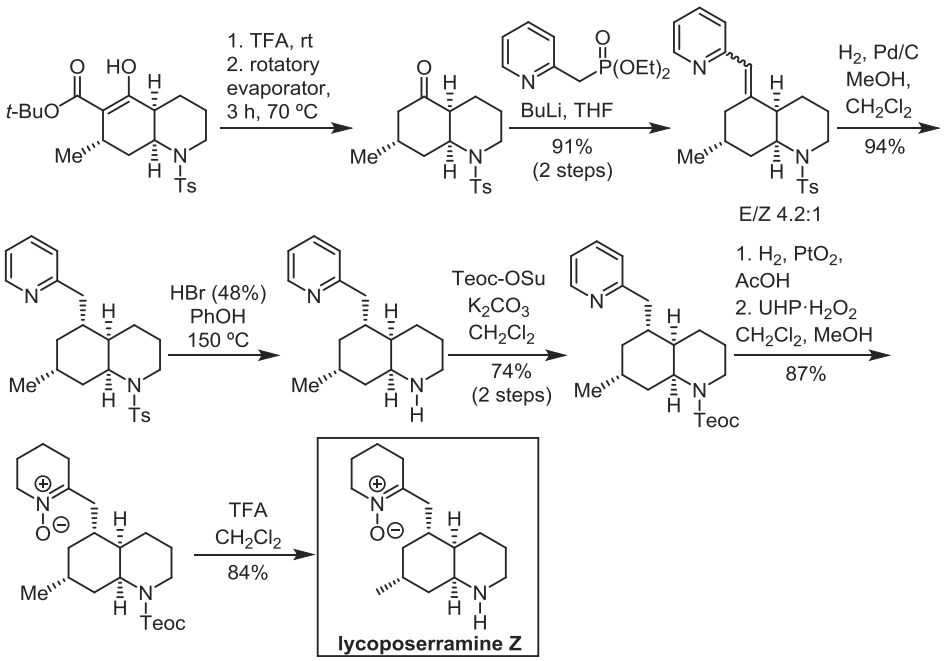


Scheme 1.2. Synthetic approach to *cis*-5-oxodecahydroquinolines.

[16] Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326–329.
[17] Wang, Y.; Li, P.; Liang, X.; Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383-1389.

1.2.2 Application to the total synthesis of lycoposerramine Z

This product contained the all *cis* type A stereochemistry[18] which ideally positioned it for a synthesis of the phlegmarine alkaloid lycoposerramine Z (Scheme 1.3).[16] After decarboxylation the decahydroquinoline building block underwent a Horner-Wadsworth-Emmons reaction with a pyridine phosphonate to install all the remaining carbon atoms. Hydrogenation of the resulting vinyl pyridine took place from the top face to install all the required stereogenic centres. Since the conditions required to remove the tosyl group were likely not compatible with the sensitive nitrone moiety it was first necessary to exchange it for the easily removable Teoc group used by Takayama in his synthesis of the same compound.[19] Hydrogenation of the pyridine ring and oxidation with urea peroxide followed by treatment with TFA[20] then furnished lycoposerramine Z in 12 steps and 20% overall yield.



Scheme 1.3. Total synthesis of (+)-lycoposerramine Z.

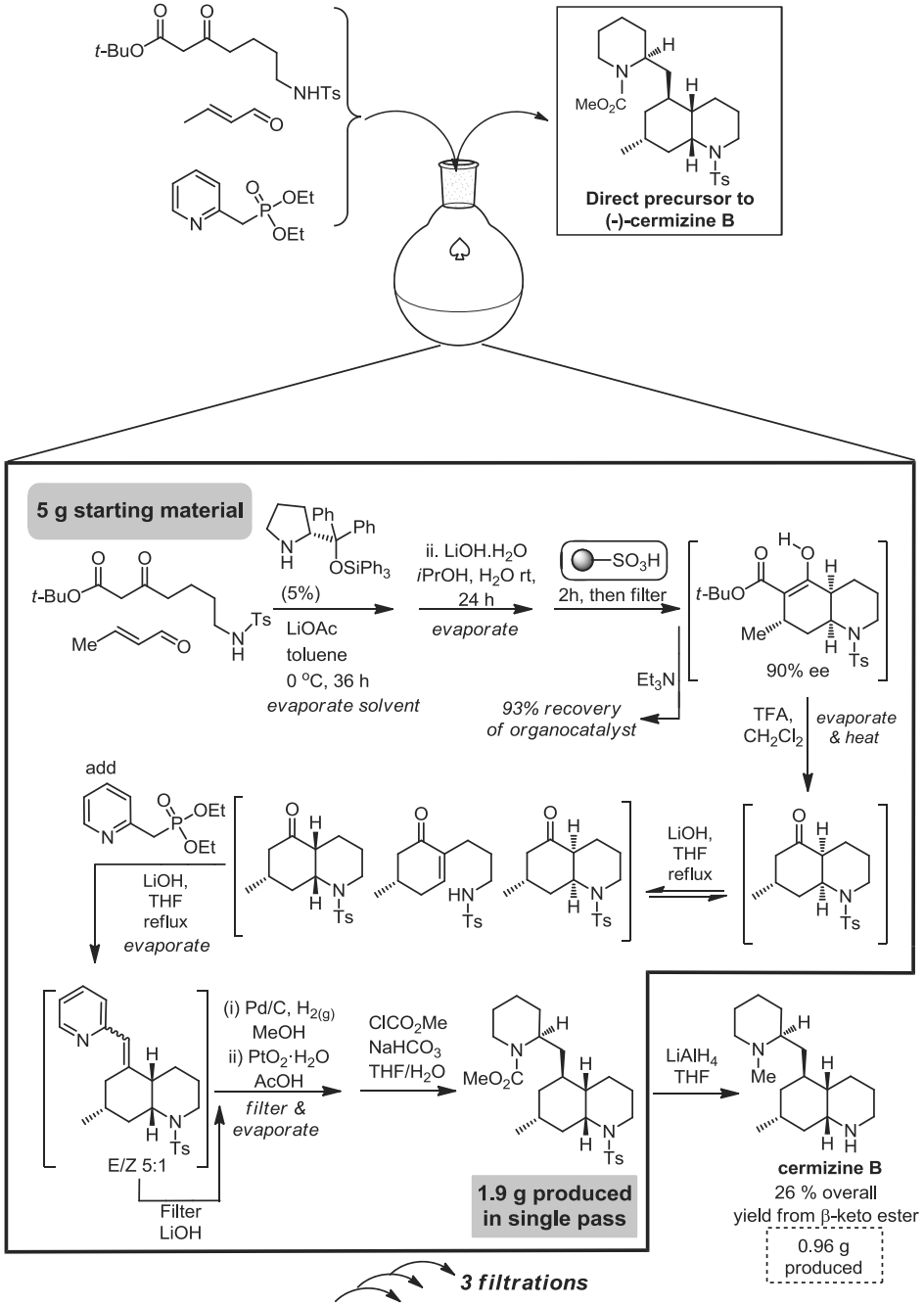
[18] For a full discussion of the relative stereochemisty classification system of the phlegmarine alkaloids see chapter 2.
[19] Tanaka, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2009**, *74*, 8675–8680.
[20] Use of TBAF or TASF according to the reference above were problematic due to the difficulties of separating the reageant from the final product.

1.2.3 Gram-scale total synthesis of cermizine B via an uninterrupted sequence

The same decahydroquinoline building block was also used in a highly efficient synthesis of cermizine B (Scheme 1.4).[21] Notably, this sequence could produce a gram of the final compound from just 5 g of the β-keto ester precursor. This was made possible by using tandem reactions, solid supported scavengers, pot-economy[22] and a synthetic design that avoided any redundant transformation in what we term "holistic synthesis".

After formation of the decahydroquinoline nucleus[23] the reaction mixture was treated with an acidic resin to scavenge the basic residues and to capture the organocatalyst which could then be recovered in 93% yield (after chromatography) by treating the resin with Et_3N. Given that the catalyst required for the synthesis is the more expensive enantiomer, the recovery of the catalyst becomes increasingly more important on a large scale. Since it was not necessary to work up or purify the reaction by column chromatography, simple evaporation allowed advancement to the subsequent step. Treatment with TFA to remove the ester followed by evaporation and refluxing with LiOH in THF allowed equilibration to the type B stereochemistry albeit as a mixture. Addition of a pyridine phosphonate allowed selective trapping of the type B intermediate and forced the equilibrium in favoured of the desired product. Finally, hydrogenation of the vinyl pyridine with Pd/C followed by addition of PtO_2 gave the piperidine which was converted to the methyl carbamate. This completed the uninterrupted sequence and allowed the undesired epimer to be removed by chromatography. Finally, reduction with $LiAlH_4$ removed the tosyl group and converted the carbamate to a methyl group to complete the synthesis, giving the desired product on a gram scale. Notably by eliminating nearly all the work-ups and column chromatography reduced the amount of time to carry out the synthesis and significantly reduced the amount of wastes produced.

[21] Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Chem. Commun.* **2014**, *50*, 7099–7102.
[22] Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green. Chem*. **2007**, *9*, 438-440.
[23] It was found that the ee of the reaction increased from 85% to 90% using recrystallized organocatalyst.



Scheme 1.4 Gram-scale synthesis of cermizine B showing all the intermediates formed in the uninterrupted sequence from β-keto ester starting material.

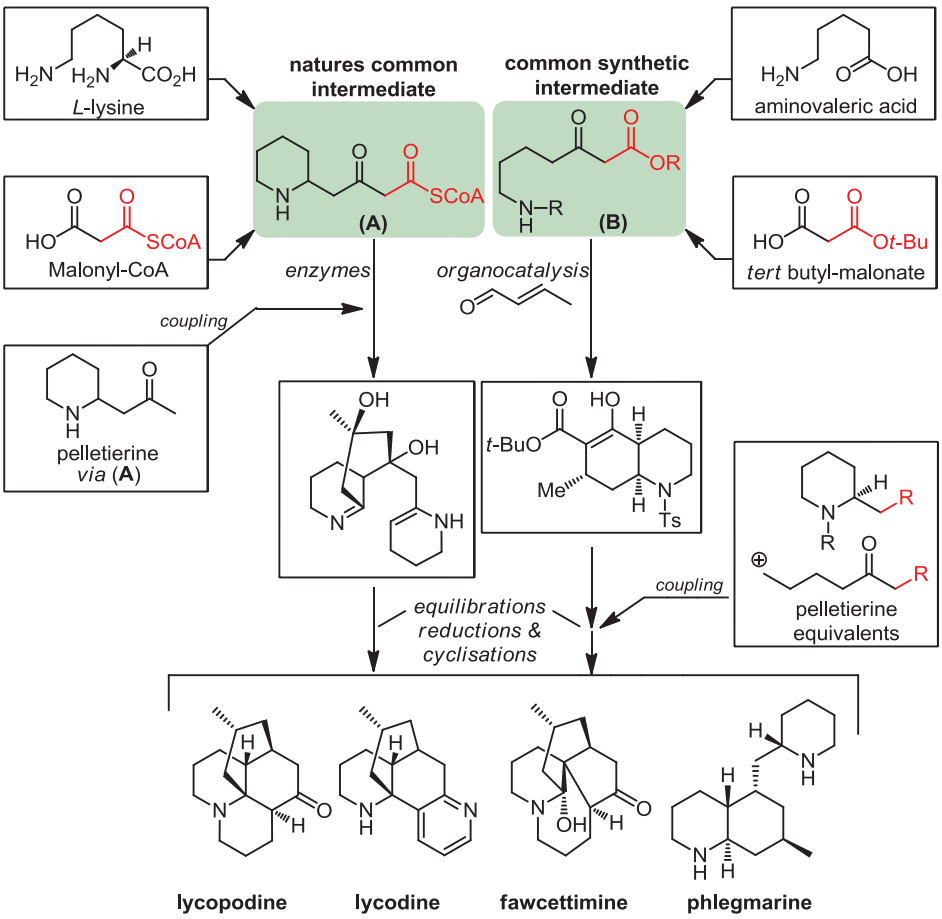
1.3 Objectives

1.3.1 Overall concept

So far the decahydroquinoline building block described in section 1.2.1 has been employed by our research group in the synthesis of two natural compounds from the lycopodium alkaloids: the *cis*-phlegmarines lycoposerrammine Z and cermizine B. We asked ourselves if the use of this building block could be extended to synthesize not only the *trans* type phlegmarines but also one of each of the other representative family members of the lycopodium alkaloids: lycopodine, lycodine and fawcettimine. Currently no unified approach to the lycopodium alkaloids has been reported[24] with all approaches focused on a single molecular target or "target-oriented synthesis" approaches.[25] Biosynthesis in nature provides an appealing alternative to this traditional 'single-target' approach to chemical synthesis in that it typically involves the construction of multiple natural product through the assembly of a common intermediate. As we have seen in the biosynthesis (Section 1.1.3) this is how nature constructs the lycopodium alkaloids using a handful of common intermediates which are then diversified into the wide variation of compounds observed. We thought it might be possible to take inspiration and mimic this conceptual approach via synthesis (Scheme 1.5). As discussed above, in nature all types of the lycopodium alkaloids derive from *L*-lysine and Malonyl CoA which form 4-(2-piperidyl) acetoacetyl-CoA (**A**). In our approach, a common nitrogen containing ketoester intermediate **B** would be used which in turn derives from analogous products to the natural biosynthetic pathway, namely aminovaleric acid as the nitrogen containing precursor equivalent of lysine and *tert*-butyl malonate as the synthetic equivalent of malonyl CoA. As in the biosynthesis, the ester group is used as an activating group which is then lost via decarboxylation. Addition of pelletierine in the biosynthetic route assembles the full carbon framework. In our modified approach, addition of a methyl piperidine or open chain compound would fulfill the same function.

[24] Whilst some attempts have been made to enable a diversity orientated synthesis to the lycopodium alkaloids so far these studies have still centered on only one of particular class. For a key example see: Zhang, J.; Wu J.; Hong, B.;Ai, W.; Wang, X.;Li, H.; Lei, W. *Nat. Comm.* **2014**, *5*, 4614-4624.

[25] Anagnostaki, E. E.; Zografos, A. L. *Chem. Soc. Rev.* **2012**, *41*, 5613–5625.



Scheme 1.5 The four parent lycopodium alkaloids derived from nature's building blocks and proposed synthetic equivalents.

The proposed conversion of **B** to each of the parent lycopodium alkaloids is outlined in the following section.

1.3.2 Synthetic Plan

Our general synthetic plan to synthesize all four of the parent lycopodium alkaloids is outlined in Scheme 1.6. The β-keto ester **i** would be converted to the corresponding decahydroquinolines **ii** and ***ent*-ii** by employing the appropriate organocatalyst enantiomer according to the method outlined in section 1.2 above.[26] The ester would be then removed to give the unstable decahydroquinoline **iii** which, upon treatment with base, would undergo a retro aza Michael reaction to **iv**. By carefully selecting of reaction conditions, the nucleophile and the nitrogen-protecting group we postulated that **iv** could be converted into each of the four lycopodium structures.

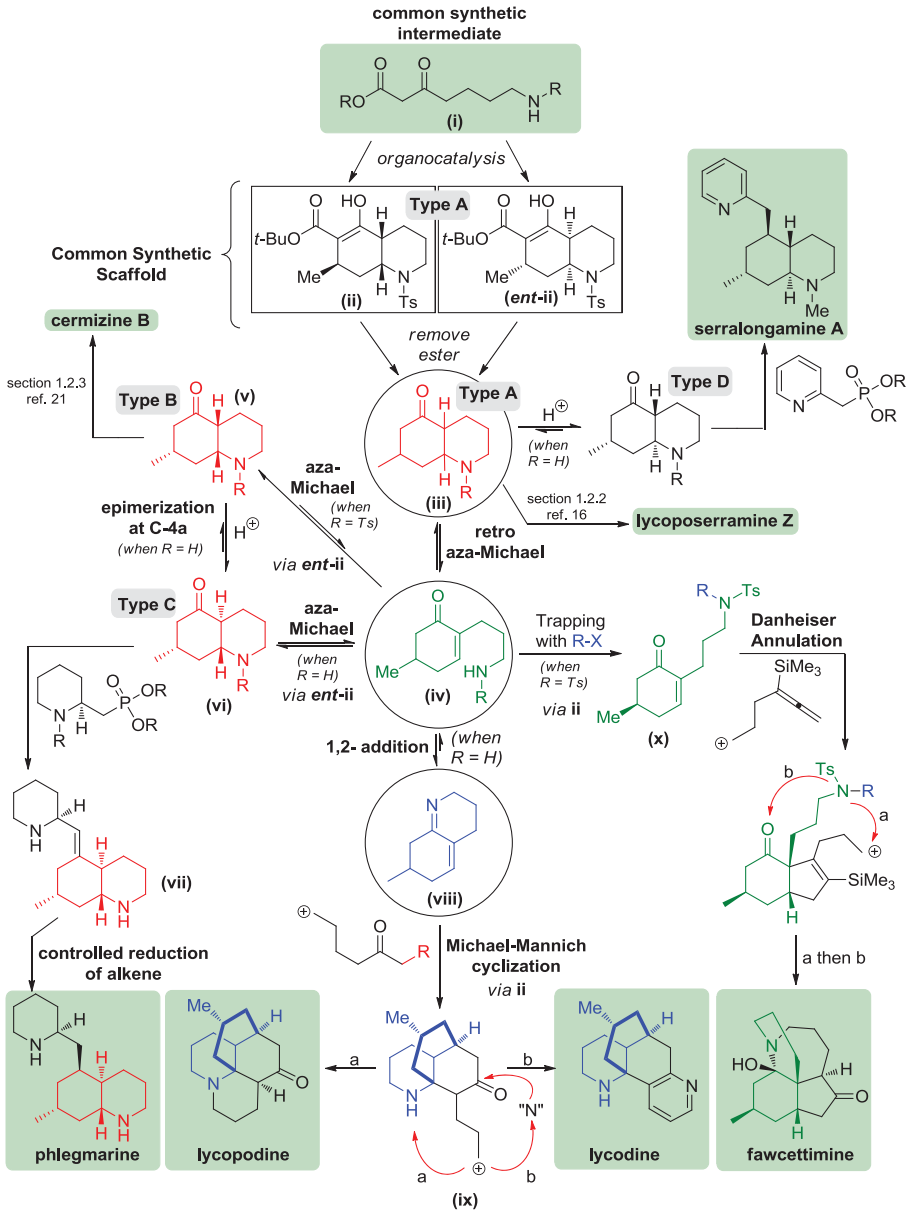
Synthesis of phlegmarine: Equilibration of **iv** (N = Ts) to type B decahydroquinoline **v** followed by removal of the tosyl group and equilibration under acid conditions should give the type C decahydroquinoline **vi** (see Section 2.3.2 for full details and calculations). Coupling of **vi** to a chiral piperidine and controlled reduction from the bottom face would furnish phlegmarine. In an analogous manner but proceeding from the type A intermediate **iii**, it should be possible to access phlegmarines of type D stereochemistry, such as serralongamine A for the first time.

Synthesis of lycodine and lycopodine: If the tosyl group on **iv** is removed, it is known that these type of compounds undergo aza-Michael reaction and could potentially give the type C nucleus (**vi**) directly. However, it is also known that these compounds also rapidly equilibrate to the 1,2 addition product **viii**.[27] For lycopodine and lycodine which share a similar ring system nucleus, a tandem Michael-Mannich cyclization was proposed to give intermediate of type **ix**, in which the pendant side chain would be used to form the pyridine ring of lycodine or cyclise on to the nitrogen atom in a biomimetic inspired manner to give lycopodine.

Synthesis of fawcettimine: Trapping the equilibrium intermediate **iv** (R = Ts) with an alkyl group (e.g benzyl) would give a cyclohexenone intermediate **x** that

[26] Since our strategy requires the 1,2-addition of the nitrogen onto the carbonyl (for lycopodine, lycodine and fawcettimine) effectively inverting the C-7 methyl centre we needed access to both enantiomers (**ii**) and (***ent*-ii**).
[27] Brosius, A.D.; Overman, L.E. *J. Org. Chem.* **1997**, *62*, 440-441.

would then be used in a Danheiser annulation reaction to install the fused cyclopentane ring system along with the required side chain bearing all the remaining carbon atoms. Formation of the 7-membered ring via a Mitsunobu process, followed by deprotection of the nitrogen and its spontaneous cyclization onto the ketone would complete the synthesis.



Scheme 1.6. Overview of synthetic plan to access each of the parent lycopodium alkaloids.

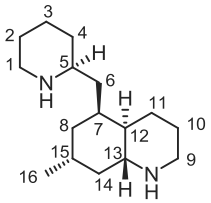
2. Towards the synthesis of (-)-phlegmarine and total synthesis of *trans*-decahydroquinoline phlegmarine-type alkaloids

Chem. Eur. J. **2013**, *19*, 13881-13892

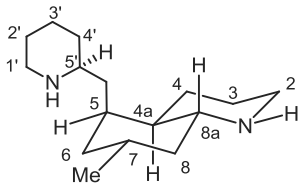
J. Org. Chem. **2016**, *81*, 2629−2634

2.1 Introduction

Phlegmarine was first isolated in 1978 by Braekman.[28] It is the parent member of the miscellaneous group of the lycopodium alkaloids and as discussed previously (Section 1.1.3) it is considered to play a key role in the biosynthesis of all the other main lycopodium alkaloids.[4]



phlegmarine
biogenetic numbering



phlegmarine
systematic numbering

When Braekman isolated phlegmarine he assigned a general structure but was unable to establish any stereochemical relationships. It was the pioneering work by MacLean[29] three years later, which established the relative configuration of the four stereogenic centers of the decahydroquinoline ring in the molecule and established that phlegmarine possess a *trans* stereochemistry ring fusion system. It was not until 1999 that Comins *et al.* carried out the first asymmetric total synthesis of the phlegmarine derivative Nα-acetyl-Nβ-methylphlegmarine and determined the absolute stereochemistry of this compound as being *R* at the methylated carbon atom and *S* at the stereogenic carbon in the piperidine ring.[30]

2.1.1 Classification of the phlegmarine alkaloids

The phlegmarine alkaloids are structurally characterized by the presence of a 5,7-disubstituted decahydroquinoline ring and a $C_{16}N_2$ skeleton. The substitution pattern, based on a methyl group at C-7 and a (2-piperidyl)methyl side chain at C-5, and the type of ring fusion (*cis* or *trans*) show a variety of stereochemical arrangements, which can be divided into four main types which we have designated A to D to facilitate their identification. Additionally, a notation α or β for the orientation of the (2-piperidyl)methyl side chain at C-5,

[28] Nyembo, L.; Goffin, A.; Hootelé, C.; Braekman, J. C. *Can. J. Chem*. **1978**, *56*, 851-865.
[29] (a) Szychowski, J.; MacLean, D. B. *Can. J. Chem*. **1979**, *57*, 1631-1637. (b) Leniewski, A.; Szychoski, J.; MacLean, D. B. *Can. J. Chem*. **1981**, *59*, 2479-2490.
[30] Comins, D.L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999,** *64,* 2184-2185.

which can be partially (as nitrone) or fully oxidized (as pyridine), has been introduced (Figure 2.1). Lycoposerramine Z[31] and serratezomine E[32] are compounds of **type A** group, where the C-7 methyl substituent and the ring fusion hydrogen atoms are all arranged in a *cis* orientation at the bottom face. In **type B** compounds, the ring fusion hydrogen atoms are in a *cis* orientation but *trans* with respect to the C-7 methyl group. Cermizines A and B[33] feature this stereochemical arrangement. **Type C** compounds are the most numerous group, in which the ring fusion is *trans* and the H-8a and the C-7 methyl are arranged in a *trans* relationship. This group includes the parent compound phlegmarine and a number of N-methylated and acetylated derivatives with a 5β disposition. Lycoposerramine X[31] and huperzines L and J[34] are alkaloids of type C(5α) showing an equatorial disposition of the side chain. With the isolation of serralongamine A[35] during the experimental period of this work, a new type of phlegmarine alkaloids was discovered, here designated as **type D**. In this group, the ring fusion hydrogens are arranged *trans* and the H-8a is *cis* with respect to the C-7 methyl. Besides containing a hereto unknown stereochemical arrangement, this compound features a pyridine instead of the usual piperidine ring. When it was isolated, serralongamine A was thought to be the first phlegmarine alkaloid to possess this stereochemical arrangement. However, our group recently completed[36] the total synthesis of the putative structure of huperzine N[37] and found that its structure was missassigned. Instead, the NMR data of natural huperzine N would be explained by the structure shown in Figure 2.1, which belong to type D group. In the same isolation paper, the authors proposed huperzine M as a new phlegmarine alkaloid. Again, analysis of its NMR data showed that this compound has identical structure to that of lycoposerramine Y.[31] Similarly, huperzine K[38] was proposed to have the same

[31] Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223-229.
[32] Kubota, T.; Yahata, H.; Yamamoto, S.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3577-3580.
[33] Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015-7023.
[34] Gao, W.; Li, Y.; Jiang, S.; Zhu, D. *Planta Med*. **2000**, *66*, 664-667.
[35] Jiang, W.-P.; Ishiuchi, K.; Wu, J.-B.; Kitanaka, S. *Heterocycles* **2014**, *89*, 747-752.
[36] Bosch, C.; Fiser, B.; Gómez-Bengoa, E.; Bradshaw, B.; Bonjoch, J. *Org. Lett.* **2015**,*17*, 5084–5087.
[37] Gao, W.-Y.; Li, Y.-M.; Jiang, S.-H.; Zhu, D.-Y. *Helv. Chim. Acta* **2008**, *91*, 1031-1035.
[38] Gao, W.; Li, Y.; Jiang, S.; Zhu, D. *Planta Med*. **2000**, *66*, 664-667.

stereochemical arrangement as lycoposerramine Y, but analysis of its NMR data suggested that it has a stereochemical pattern of type Dβ.

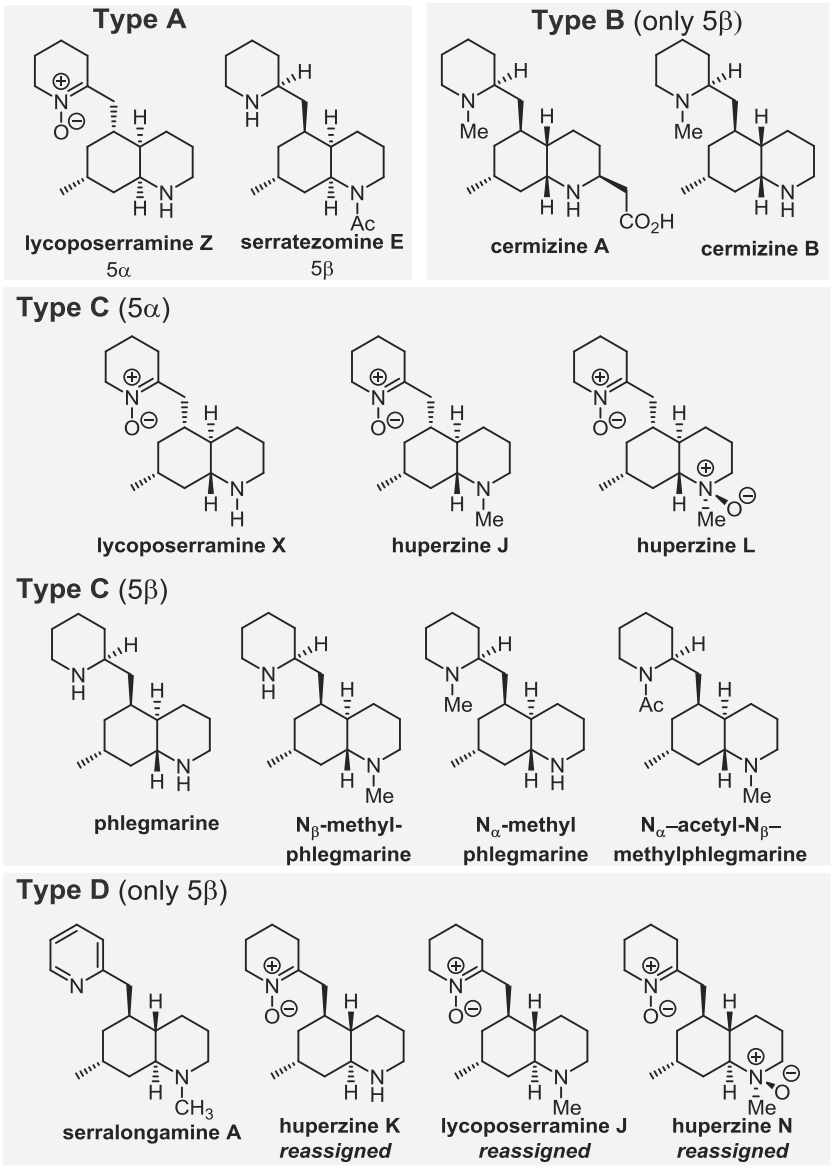


Figure 2.1. All known phlegmarine alkaloids.

2.1.2 Related *trans* decahydroquinoline containing lycopodium alkaloids

Additionally, other compounds biogenetically related to phlegmarine have been isolated (Figure 2.2). The lycobelines,[39] which have been reported during the development of this research project, are proposed to come from the cleavage of the piperidine ring of phlegmarine. The activity of these compounds against lung, colon, liver and leukemia tumorous cell lines was tested but non of them was found to be cytotoxic. Lycoperine A, a dimeric compound likely derived from two *trans* decahydroquinoline units, inhibits acetylcholinesterase.[40] Serratezomine D, isolated from the same plant as serratezomine E,[32] is a dimer that contains two type C *trans* decahydroquinoline units and also exhibits acetyl cholinesterase inhibitory activity.

The most recently phlegmarine alkaloid isolated was the $\Delta^{13,N}$,*N*α-methylphlegmarine-Nβ-oxide and is first to contain a nitrone at Nβ.[41]

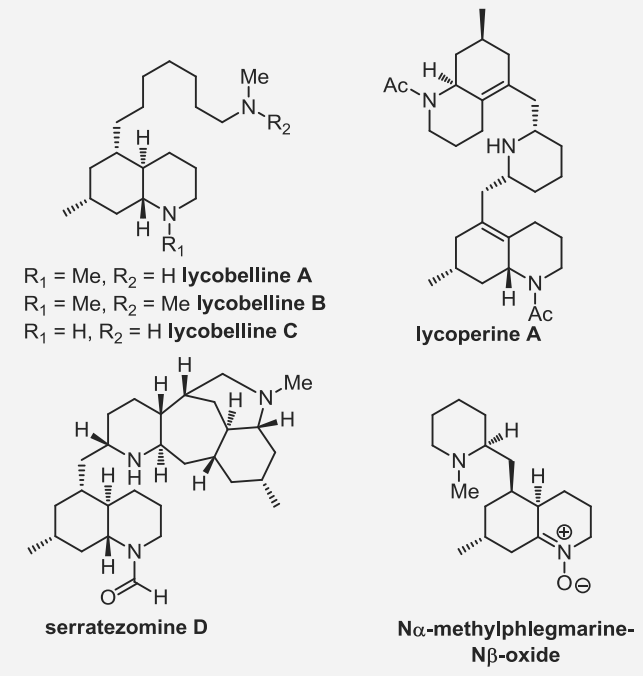


Figure 2.2. Other *trans* phlegmarine type alkaloids.

[39] Hirasawa, Y.; Matsuya, R.; Shaari, K.; Lajis, N.H.; Uchiyama, N.; Goda Y.; Morita H. *Tetrahedron Lett*. **2012**, 53, 3971–3973
[40] Hirasawa, Y.; Kobayashi, J.; Morita, H. *Org. Lett*. **2006**, *8*, 123-126.
[41] Wang, Z.; Wu, J.; Zhao, N.; Yang, Y.; Chen, Y. *Nat. Prod. Res.* **2016**, 30, 241-245.

2.1.3 Previous syntheses of phlegmarine type alkaloids

Despite the importance of this class of compounds from a biosynthetic point of view and potential to use them as biomimetic precursors to the other classes of lycopodium alkaloids, the phlegmarine type has been one of the least studied (Table 2.1), with most of the early synthetic work to the phlegmarine type alkaloids focused on those containing a *trans*-decahydroquinoline ring. After the initial pioneering work developed by MacLean,[29] it was Comins who reported the first synthesis of a phlegmarine derivative.[30] It was not until 10 years later that Takayama reported the synthesis of lycoposerramine X and Z, which have *trans* and *cis* stereochemistry, respectively. One year later, Comins expanded his original methodology to synthesize not only phlegmarine but all of the related type C (5β) derivatives.

Table 2.1. Previous syntheses of phlegmarine type lycopodium alkaloids. [42] (* denotes racemic synthesis).

Year	*Natural Product*	*Author*	*Structural type**
1979[29]	N_α-methyl-N_β-acetylphlegmarine	MacLean	Cβ
1999[30]	N_α-Acetyl-N_β-methylphlegmarine	Comins	Cβ
2009[19]	lycoposerramines X and Z	Takayama	Cα / Aα
2010[43]	phlegmarine	Comins	Cβ
2013[16]	lycoposerramine Z	Bonjoch-Bradshaw	Aα
2014[21]	cermizine B	Bonjoch-Bradshaw	Bβ
2015[36]	serratezomine E	Bonjoch-Bradshaw	Aβ
2016[44]	serralongamine A and Huperzine N*	This PhD work	Dβ / Dβ
2016[45]	lycoposerramine Z	Yao	Aα

[42] Lycoposerramines V and W with a pyridine ring have been also synthesized. (a) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. lett*. **2007**, 9, 4069-4072. (b) Zhang, L.; Zhou, T.T.; Qi, S-X.; Xi, J.; Yang, X-L.; Yao, Z.Y. *Chem. Asian*. *J.* **2014**, 9, 2740-2744.

[43] Wolfe, B.H.; Libby, A.H.; Al-awar, R.S.; Foti, C.J.; Comins D. L. *J. Org. Chem.* **2010**, *75*, 8564–8570

[44] Saborit, G. V; Bosch, C.; Parella, T.; Bradshaw, B.; Bonjoch, J. *J. Org. Chem.* **2016**, *81*, 2629−2634. (See section 2.7).

[45] Zhang, L-D.; Zhong, L-R. ; Xi, J.; Yang, X-L.; Yao, Z-J. *J. Org. Chem.*, **2016**, *81*, 1899–1904.

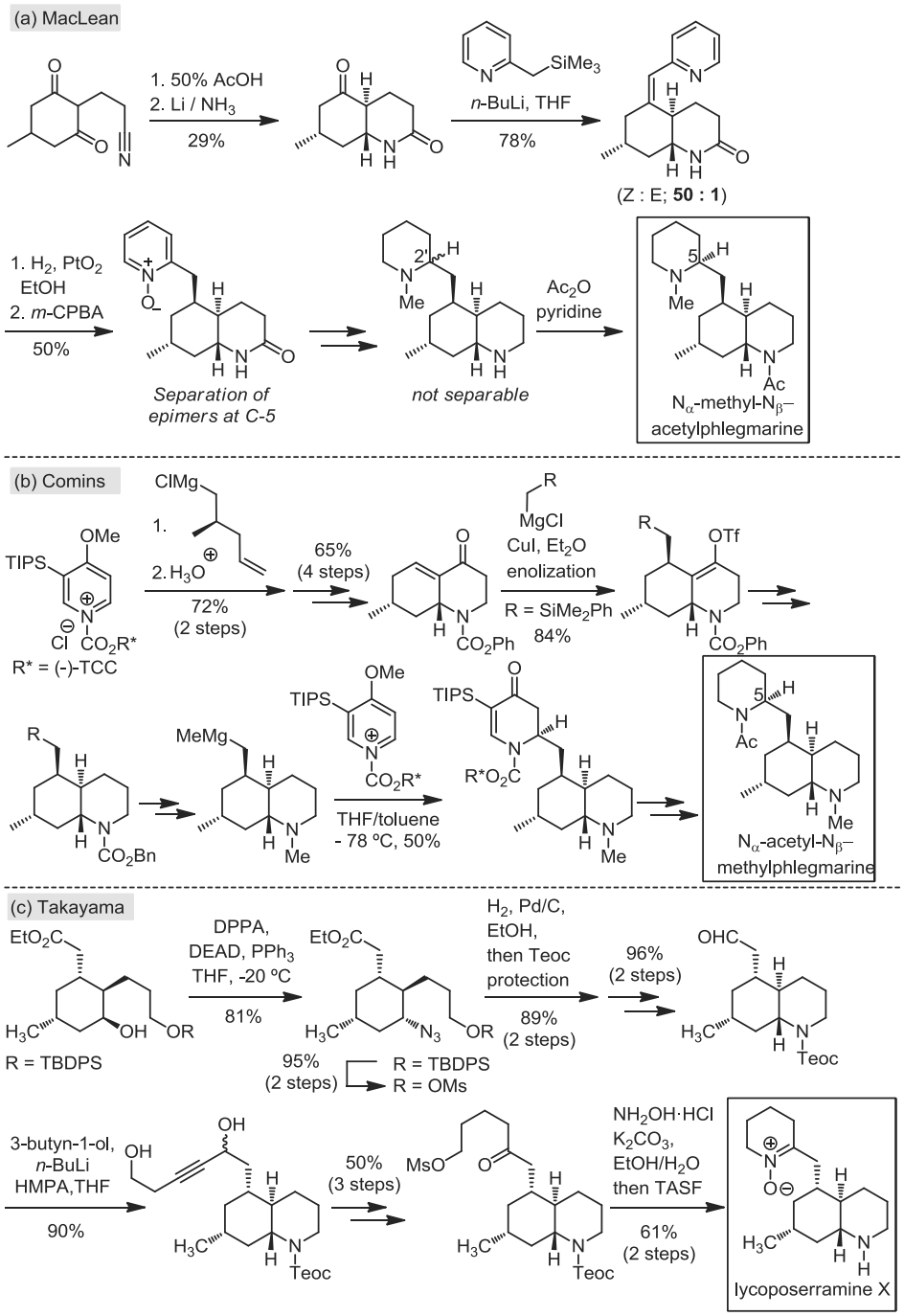
2.1.4 Overview of previous synthesis

When MacLean began the synthesis of phlegmarine, he proposed that it contained an all *cis* decahydroquinoline system (type A), based on the structure of a related compound.[29] However, after arriving to a compound with this stereochemistry, he realized that its NMR data did not match with that reported by Braekman[28] and proposed that phlegmarine contains a *trans* decahydroquinoline core. Thus, starting from 2-(2-cyanoethyl)-5-methyl-1,3-cyclohexanedione the *trans* decahydroquinoline was prepared in two steps. Peterson olefination furnished a mixture of Z/E vinyl pyridines, which upon reduction with Pt gave two epimers that were separable in its N-oxide form. Then, transformation into the methyl pyridine and hydrogenation over Pt gave a mixture of diastereomeric piperidines at C-2', which could only be separated after reduction of the amide function and acylation. However, the lack of material did not allow a determination of the stereochemistry. The synthesis of MacLean established the relative stereochemistry at four of the five stereogenic centers and showed that the stereochemistry pattern in phlegmarine is the same configuration found in lycopodine and most other lycopodium alkaloids (Scheme 2.1a).

In the first enantioselective synthesis of a naturally ocurring phlegmarine (Scheme 2.1b), Comins stablished the configuration at C-8a with the addition of the Grignard reagent of (*R*)-5-chloro-4-methylpentene to an acylpyridium salt containing (-)-TCC as the chiral auxiliary.[30] Then, conjugate addition of a silyl containing Grignard reagent took place with complete stereoselectivity, giving the correct stereochemistry at C-5. Hydrogenation of an endocyclic olefin provided the C-4a stereogenic center. Then, a second addition of the chiral auxiliary allowed the introduction of the piperidine ring with the correct stereochemistry at C-2' (Scheme 2.1b).

Takayama's synthesis of lycoposerramine X involved the transformation of (*R*)-3-methylcyclohexanone into a highly functionalized cyclohexanone (Scheme 2.1c). A Mitsunobu reaction allowed installation of both the nitrogen atom and the C-8a stereogenic center. Then, hydrogenation of the azide resulted in concomitant closure of the *trans* decahydroquinoline ring. Addition of an alkynyl

anion served to install all the carbons necessary for the nitrone ring, which was closed upon treatment with hydroxylamine.

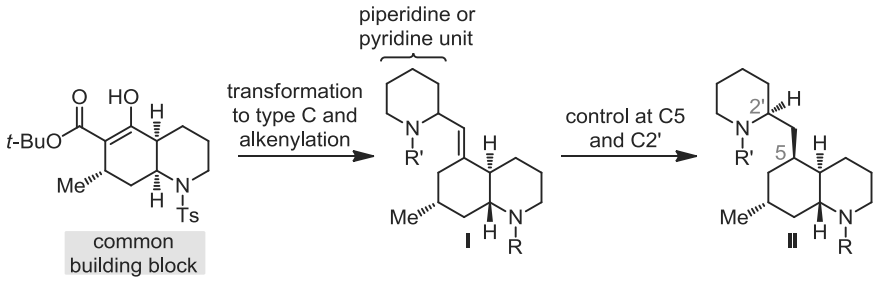


Scheme 2.1. Previous syntheses of *trans*-decahydroquinoline phlegmarines.

2.2 Objectives

2.2.1 Overview of synthetic plan

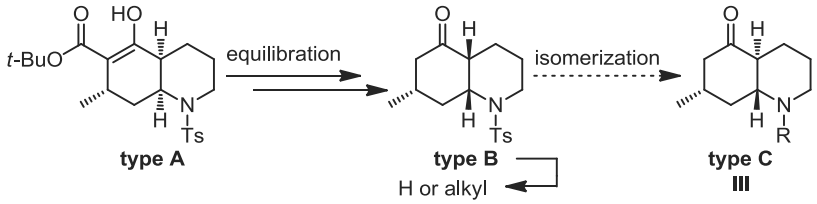
Our synthetic plan to prepare phlegmarine includes the transformation of the all *cis* stereochemistry of our common building block into the *trans* type C decahydroquinoline of phlegmarine followed by the introduction of a vinyl piperidine or pyridine ring to obtain **I**. Then, a stereoselective hydrogenation at C-5 would give an advanced precursor **II**, which would only require removal of the protecting groups to obtain phlegmarine (Scheme 2.2).



Scheme 2.2 Overview of synthetic plan to synthesize phlegmarine.

2.2.2 Proposed access to type C decahydroquinoline

To convert the decahydroquinoline building block of type A that we had successfully employed in the synthesis of *cis*-phlegmarines (Section 1.2) into the *trans* type C decahydroquinoline **III**, we propose the route outlined in Scheme 2.3.

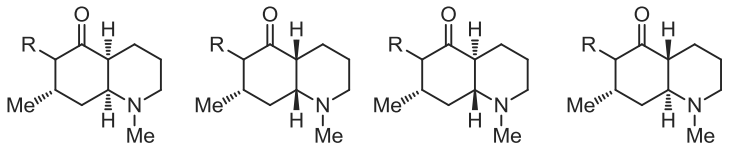


Scheme 2.3 Proposed transformation of all *cis* decahydroquinoline into *trans* phlegmarine nucleus.

As reported in the total synthesis of cermizine B[21] (Section 1.2.3) the common building block of type A lacking the *tert* butyl ester group is unstable and can enter into equilibrium with the more stable type B decahydroquinoline. Notably, when there is an electron-withdrawing group at the nitrogen atom only the *cis* decahydroquinolines structures are accessible by the aza-Michael cyclization.

However, taking into account literature precedents,[46] it seemed possible that the type C stereochemistry might be accessed by interchanging the nitrogen-substituent group. Indeed, calculations indicated that when the lone nitrogen pair was not delocalized, the relative stability was strongly affected and the *trans* isomer became the most stable diastereoisomer (Table 2.2).[47]

Table 2.2. Relative energies, ΔE, and free energies ΔG in gas phase and solution (water) for the enol tautomers of β-keto esters **Ai**-**Di** and keto tautomers of ketones **Aii**-**Dii**



A*i* R = CO_2t-Bu **B*i*** R = CO_2t-Bu **C*i*** R = CO_2t-Bu **D*i*** R = CO_2t-Bu
A*ii* R = H **B*ii*** R = H **C*ii*** R = H **D*ii*** R = H

	A*i*	**A*ii***	**B*i***	**B*ii***	**C*i***	**C*ii***	**D*i***	**D*ii***
E gas phase	2.6	4.3	1.9	3.6	1.0	0.0	0.0	1.6
G gas phase	2.7	5.4	2.3	2.7	0.9	**0.0**	0.0	**1.7**

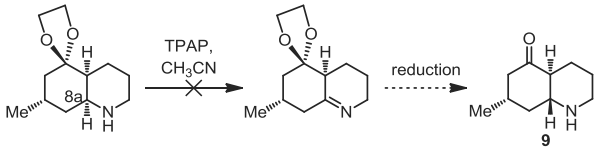
[a] All values in kcal·mol^{-1}

With this information in hand, we proposed that removal of the tosyl group from a cyclized compound of type B and a simple isomerization at C-4a via enolization should reprotonate opposite face and give the desired *trans* stereochemistry.[48]

[46] (a) Grob, C. A.; Kiefer, H. R. *Helv. Chim. Acta* **1965**, *48*, 799–807; (b) Johnson, R. A.; Murray, H. C.; Reineke, L. M.; Fonken, G. S;. *J. Org. Chem*. **1968**, 33, 3207–3217. (c) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem. Eur. J*. **2001**, *7*, 3446–3460.

[47] Bradshaw, B.; Luque-Corredera, C.; Saborit, G.; Cativiela, C.; Dorel, R.; Bo, C.; Bonjoch, J. *Chem. Eur. J.* **2013**, *19*, 13881–13892.

[48] Preliminary attempts to obtain type C by direct aza-Michael cyclization of a free amine onto a cyclohexenone led to the 1,2-addition product. Inversion of the C-8a stereocentre by oxidation/reduction sequence of the free amine is an alternative route but was ruled out when we were not able to prepare the required imine, for example using TPAP/CH_3CN (Goti, A.; Romani, M. *Tetrahedron. Lett* **1994**, *35*, 6567-6579).

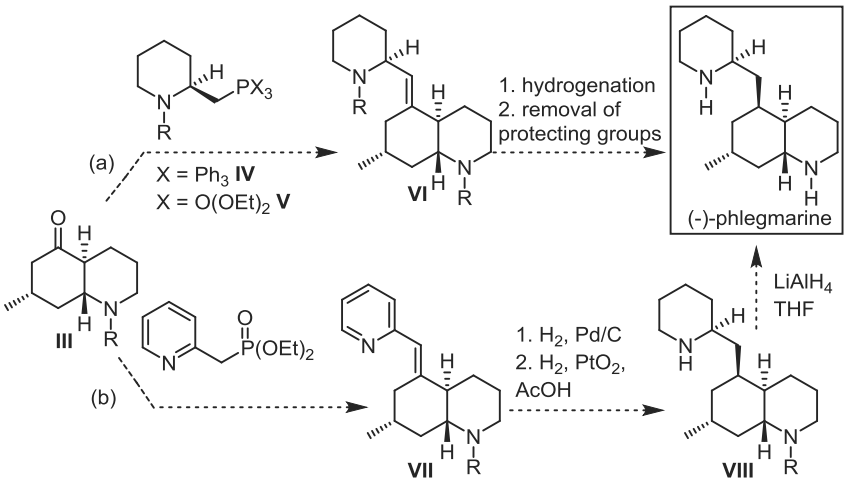


9

For other unsuccessful efforts to invert the stereochemistry at C-8a in related compound see: Comins, D.L.; Al-Awar, R.S. *J. Org. Chem.* **1995**, *60*, 711-716.

2.2.3 Proposed introduction of piperidine unit

Once we have the *trans* decahydroquinoline **III** in hand, two synthetic routes were envisaged for the introduction of the piperidine moiety (Scheme 2.4). Given the results of previous synthetic attempts by other groups[29] as well as our own[21] it would be expected that some kind of additional asymmetric control would be required to have the correct stereocenter at the C-2' of the piperidine ring. Therefore, we proposed route (a) where an enantiopure piperidine phosphonium salt **IV** or phosphonate **V** bearing the desired stereochemistry at its C-2' would be added to **III**. The synthesis would be completed by hydrogenation at the C-5 of **VI** with the chiral piperidine hopefully influencing the reduction. Alternatively, we also proposed route (b), where the piperidine group would be formed by coupling a pyridine phosphonate to give **VII**, in a similar manner as in the synthesis of lycoposerramine Z.[16] Whilst this route would be more straightforward as it follows well established precedents from our group, the stereochemical control or separation of epimers would be potentially problematic. Reduction of the pyridine ring and removal of the protecting groups of **VIII** would then complete the synthesis.

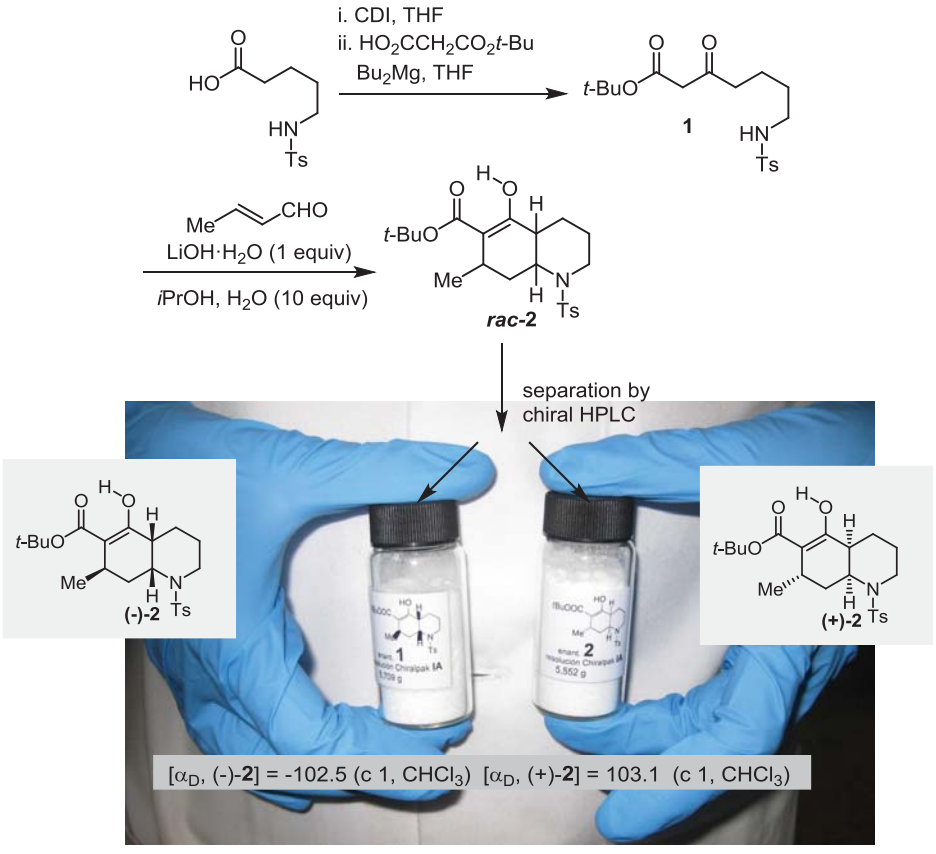


Scheme 2.4 Proposed introduction of piperidine ring and reductions to synthesize phlegmarine.

2.3 Synthesis of Type C nucleus

2.3.1 Racemic large scale preparation of type A common bulding block and separation by preparative chiral HPLC

As mentioned before, we needed access to both enantiomers of **2** since lycopodine, lycodine and fawcettimine show the opposite configuration at C-7 to that of phlegmarine. Working on a large scale from **1** and following the procedure reported in the synthesis of lycoposerramine Z,[16] β-keto ester **1** was treated with crotonaldehyde in *i*PrOH and $LiOH·H_2O$ in the presence of water. This method allowed the preparation of *rac*-**2**, on a 20 g scale and without need for purification, which was resolved on a chiral HPLC column (Scheme 2.5) in collaboration with Prof. Carlos Cativiela from the University of Zaragoza to obtain 5.5 g and 5.7 g of (-)-**2** and (+)-**2**, respectively (see experimental section for further details).



Scheme 2.5. Preparation of *rac*-**2** and separation of resulting enantiomers.

2.3.2 Crystal structure of (-)-2

From these compound, it was possible to obtain x-ray quality crystals which allowed the structure of (-)-**2** to be fullyl determined (Figure 2.3). Notably, the tosyl group is observed to lie over the plane of the molecule, which results in a CH/π interaction between both the methyl and sulphonamide group.[49]

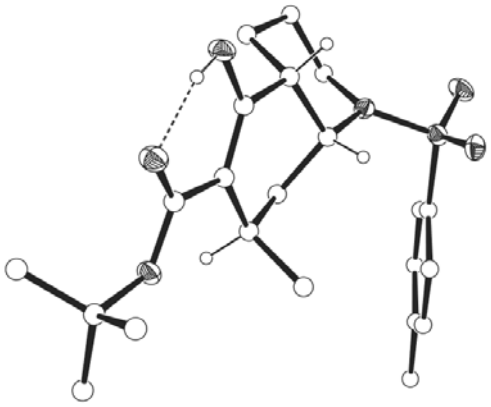
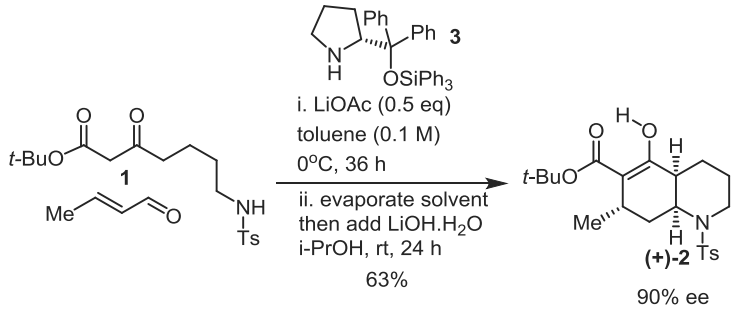


Figure 2.3 Crystal structure of (-)-**2**.

2.3.3 Preparation of common type A building block by organocatalysis

Additionally, following the procedure described in our group[21] we prepared decahydroquinoline (+)-**2** on a 5 g scale starting from **1** using the modified Hayashi catalyst **3** to promote the inital Michael addition[16] (Scheme 2.6).

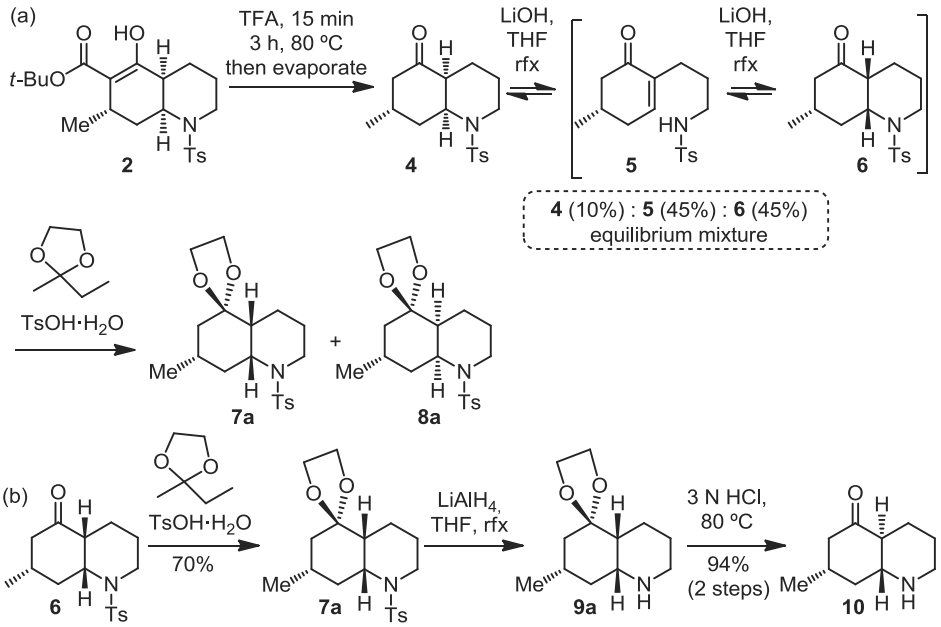


Scheme 2.6 Large scale organocatalyzed synthesis of the decahydroquinoline building block (+)-**2**.

[49] Raju, K. R.; Bloom, W.G.J.; An, Y.; Wheeler, E.S. *Chem. Phys. Chem*, **2011**, *12*, 3116-3130.

2.3.4 Conversion of type A to type C decahydroquinoline[50]

With ready access to the key building block **2**, we began evaluating its conversion to the type C decahydroquinoline system. Following our previous precedents,[21] removal of the ester by treatment with TFA followed by decarboxylation gave **4**. Equilibration with LiOH in THF at reflux for 16 h gave the known equilibrium mixture. We first thought that addition of 2-ethyl-2-methyl-1,3-dioxolane to the equilibrium mixture would selectively protect **6** - the ring opened product **5** should not be reactive under these conditions - and shift the equilibrium in favour of the formation of the type B acetal product, in a similar manner to that of the synthesis of cermizine B.[21] However, the desired **7a** was formed together with **8a** bearing the type A stereochemistry, which could not be separated (Scheme 2.7a). Alternatively, chromatography on alumina of the equilibrium mixture furnished pure **6** in 17% yield, which after protection with 2-ethyl-2-methyl-1,3-dioxolane gave **7a** in 70% yield. Removal of the tosyl group with $LiAlH_4$ and treatment with 3 N HCl at 80 ºC gratifyingly gave the target **10** bearing the type C stereochemistry, as a single compound (Scheme 2.7b).

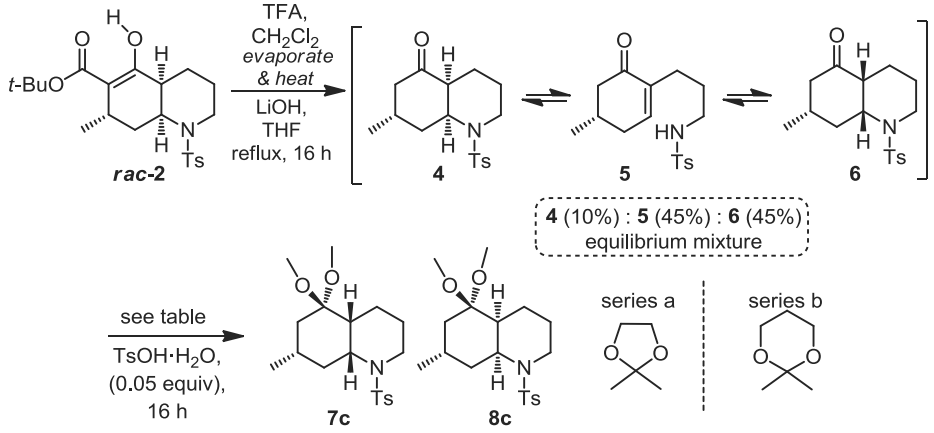


Scheme 2.7 (a) Initial attempts to selectively form **7a** from the equilibrium mixture. (b) Preparation of **10** from pure **6**.

[50] For all initial development studies *rac*-**2** was used.

However, the overall yield of this sequence was too low to be used for a total synthesis (15% over 4 steps). Calculations, as well as experimental data, indicated that the equilibrium between the type A and type B compounds was fixed at a set ratio and so it seemed that modifying the cyclisation conditions (e.g different acids or bases) would not be able to affect the equilibration ratio to our favour. We then screened other acetals that could selectively react with **6** (Table 2.3).

Table 2.3. Formation of equilibrium mixture and type B trapping with an acetal.

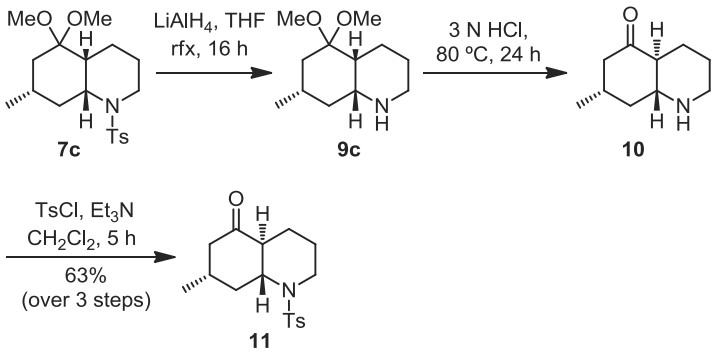


Entry	*Acetal*	*Solvent*	*Temp (ºC)*	*Yield (%)*[b]	*Ratio (7:8)*[a]
1	$(CH_2OH)_2$	toluene	reflux	n.d.	**7a**/**8a** 60:40
2[d]	$(CH_2OH)_2$	toluene	reflux	45	**7a**/**8a** 73:27[c]
3	2,2-dimethyl-1,3-propanediol	toluene	reflux	30	**7b**/**8b** 53:47
4	2-ethyl-2-methyl-1,3-dioxolane	-	rt	n.d.	**7b**/**8b** 60:40
5	$CH(OCH_3)_3$	methanol	70	60	**7c**/**8c** 86:14
6	-	methanol	70	61	**7c**/**8c** 90:10

(a) Ratio determined by ^{1}H NMR spectra of the purified reaction mixture. (b) Calculated for the three steps: decarboxylation, equilibration and acetalization. (c) Except in entry 2, in all the cases we could observe the ring opened **5** in the crude reaction mixture. (d) Reaction time increased to 48 h.

Addition of ethylene glycol resulted in the formation of an inseparable mixture of **7a** and **8a**, together with the ring opened product **5** (entry 1). Increasing the reaction time up to 48 h resulted in the consumption of the ring opened product **5** but still we could observe the acetal bearing the type A stereochemistry. Other acetals did not give a satisfactory convertion to type B and also gave the ring

opened product **5** (entries 3 and 4). To our delight, treatment of the equilibrium mixture with methanol, trimethyl orthoformate and TsOH at 70 ºC for 16 h afforded the desired type B compound in a 86:14 ratio.[51] Optimization of these conditions by omitting the trimethyl orthoformate from the reaction gave even a better proportion (entry 6).[52] Then, removal of the tosyl group and isomerisation at C-4a under the same conditions as before afforded phlegmarine nucleus **10** (Scheme 2.8). To complete the synthesis of phlegmarine it was necessary to protect the free amine **10** and following the previous synthesis reported by our group[16,21] we chose the tosyl group. Crude **10** was treated with TsCl in CH_2Cl_2 with Et_3N, which within 5 h furnished **11** in 63% yield over three steps from **7c**. It should be noted that when protected, type B stereochemistry is more stable, so the product can potentially isomerise back to the *cis* compound. Indeed, acid formed by degradation of tosyl chloride was found to induce the epimerization. This undesired process can also take place in basic conditions. When we attempted the purification of **11** with the use of the polymer supported QuadraSil® (bearing a primary amine group) to scavenge the excess tosyl chloride we could also observe the isomerization of **11** back to **6**. However, if the crude mixture was purified as soon as the reaction was completed, this unwanted side reaction could be avoided.



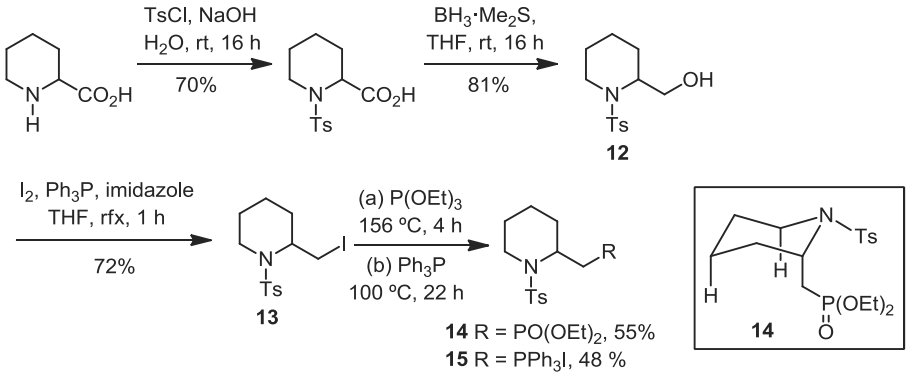
Scheme 2.8. Optimized preparation of the phlegmarine nucleus via methyl acetal.

[51] Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157–1160.
[52] Although we could also observe the ring opened product **5**, it could be separated by chromatography and reused to prepare more acetal **7c** by equilibration with LiOH in refluxing THF and acetalization under the optimized conditions.

2.4 Introduction of the piperidine ring of phlegmarine via addition of a piperidine coupling partner.

2.4.1 Preparation of tosyl protected piperidine coupling partner

With the *trans* decahydroquinoline nucleus of phlegmarine in hand, we attempted the coupling of a piperidine bearing the desired stereochemistry at the C-2' carbon. For this route we first had to prepare an N-protected piperidine phosphonium salt or phosphonate. In a first approach, we thought that a *p*-toluene sulphonamide would be a good protecting group, since it would be removed together with the tosyl group of the decahydroquinoline ring in the last step of the synthesis. Protection of racemic commercially available pipecolic acid with tosyl chloride,[53] followed by hydroboration[54] led to alcohol **12**, which was transformed into iodide **13**[55] in 30% overall yield over 3 steps. Treatment of **13** with neat triethyl phosphite at 156 ºC[56] overnight gave piperidine phosphonate **14** in 55% yield. Alternatively, **13** was treated with Ph_3P at 100 ºC overnight to give phosphonium salt **15** in 48% (Scheme 2.9).[57]



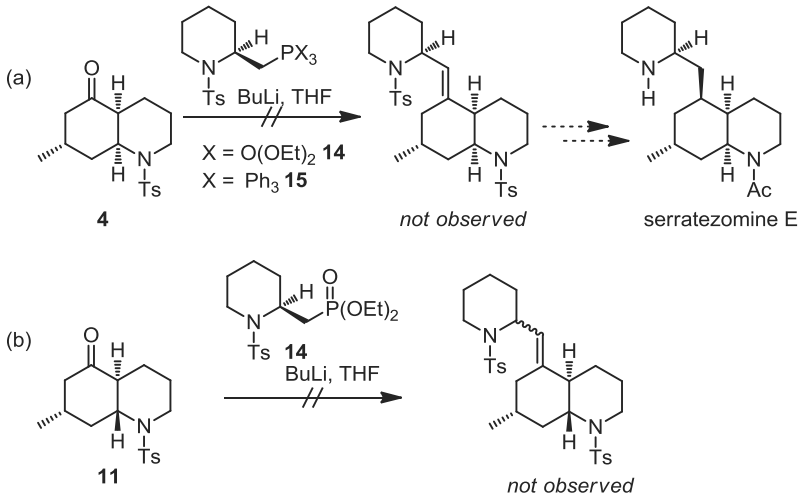
Scheme 2.9 Preparation of the piperidine coupling partner.

[53] Varray, S.; Lazaro, R.; Martinez, J.; Lamaty. F. *Eur. J. Org. Chem*. **2002**, 2308-2316
[54] Oberboersch, Stefan et al. 2008046573, 24 Apr 2008.
[55] Van den Broek, S. M. W.; Lemmers, J. G. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Biomol. Chem.* **2012**, *10*, 945–951.
[56] Gan, X.; Binyamin, I.; Rapko, B. M.; Fox, J.; Duesler, E. N.; Paine, R. T. *Inorg. Chem.* **2004**, *43*, 2443–2448.
[57] Lakanen, J. R.; Pegg, A. E.; Coward, J. K. *J. Med. Chem.* **1995**, *38*, 2714–2727.

Analysis of the ^{13}C NMR spectra of both piperidines **14** and **15** indicated that the substituent at C-2 is preferentially located in an axial disposition (large upfielding at C-4 and C-6).[58]

2.4.2 Attempted coupling of tosyl protected piperidine coupling partner

With phosphonate **14**[59] and Wittig salt **15**[60] in hand, the coupling with the more readily available *cis* decahydroquinoline **4** was tried. This was thought as a pseudo model study because the resulting compound would be en route to serratezomine E (scheme 2.10a). However, both couplings failed and we mainly observed the ring opening of the decahydroquinoline **4**. We first thought that the conformation of **4** might make it too sterically encumbered and we decided to attempt the coupling with the planar target compound **11** (Scheme 2.10b). Again, the coupling failed and a complex mixture of compounds together with the ring opened product **5** was obtained. These results suggest that the conformational behaviour of **14** and **15** might also exert an unfavorable effect.

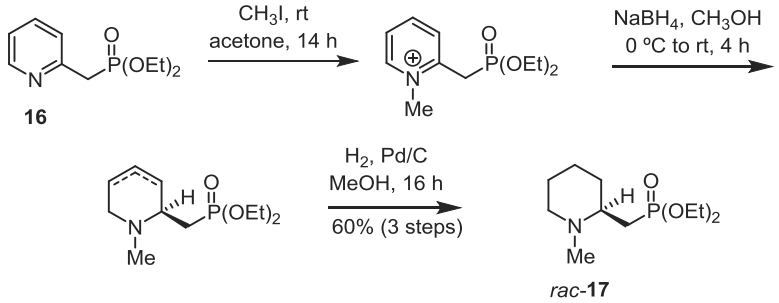


Scheme 2.10. (a) Attempted coupling of piperidines **14** and **15** with all *cis* decahydroquinoline. (b) Attempted HWE reaction of *trans* decahydroquinoline **10** with phosphonate **14**.

[58] For conformational studies of 2-alkylpiperidine with *N*-withdrawing groups, see: (a) Johnson, R.A. *J. Org. Chem.* **1968**, *33*, 3627-3632. (b) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, J. *J. Am. Chem. Soc.* **2011**, *133*, 4774-4777.
[59] Matsubara, R.; Jamison, T. F. *J Am. Chem.Soc.* **2010**, *120*, 6880–6881.
[60] Herold, P.; Mah, R.; Tschinke, V.; Stojanovic, Aleksandar; Behnke, D.; Marti, C.; Stutz, S.;J.Stjepan. EP 1958634. 2008 Aug 20.

2.4.3 Preparation of racemic *N*-methyl piperidine coupling partner

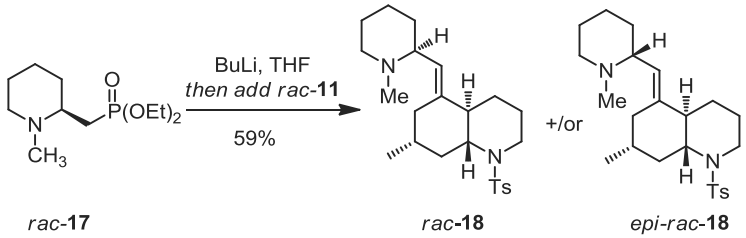
Given the disappointing results described above, we thought to replace the tosyl for a methyl group, which would be less sterically hindered, would make the H-2' proton less acidic, and would induce a different conformational behaviour of the piperidine phosphonate. In a first approach, the racemic piperidine phosphonate bearing an *N*-methyl group was prepared (Scheme 2.11). Starting from pyridine phosphonate **16**, treatment with methyl iodide gave the methylated salt, which was partially reduced with $NaBH_4$. Finally, hydrogenation with 30% Pd/C gave the piperidine in 60% overall yield over 3 steps.[61] The chemical shift of C-4 of *rac*-**17** compared to that of **14** indicated that this time the methyl phosphonate at C-2 is in an equatorial disposition.



Scheme 2.11. Preparation of racemic N-methyl piperidine phosphonate *rac*-**17**.

2.4.4 Coupling of *rac*-17 with *rac-trans* decahydroquinoline 11

With *rac*-**17** in hand, its coupling with racemic *trans*-decahydroquinoline **11** was attempted and to our delight, the Horner-Wadsworth-Emmons reaction gave the desired alkene **18** +/or *epi-rac*-**18** in 59% yield, as a single isomer at the double bond (Scheme 2.12).[62]

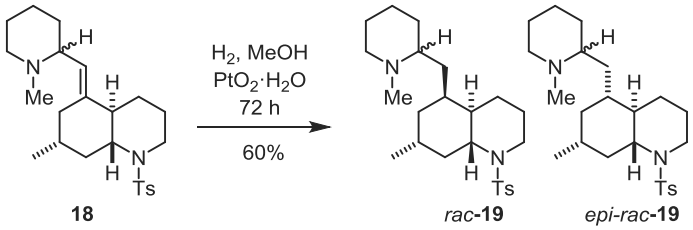


Scheme 2.12. Coupling of *rac*-**17** with *rac*-**11**.

[61] Efange, S. M. N.; Tu, Z.; Hohenberg, K. Von; Francesconi, L.; Howell, R. C.; Rampersad, M. V; Todaro, L. J.; Papke, R. L.; Kung, M. *J. Med. Chem.* **2001**, *13*, 4704–4715.
[62] It was not possible to determine the relative stereochemistry at C-2' as signals are almost identical.

2.4.5 Hydrogenation of coupled piperidine product

Although compound **18** and *epi*-**18** were racemic, to gain more information about the reactivity of the compounds under study, we attempted the hydrogenation of the vinyl piperidine. The first attempts using Pd/C resulted in a very low reaction rate (after 72 h the reaction had run until a 50%). We thought that addition of LiOH to avoid protonation of the piperidine would increase the solubility of the starting material. However, little reaction was observed upon stirring for 16 h. Fortunately, changing the catalyst to $PtO_2 \cdot H_2O$ we managed to run the reaction to completion within 72 h (Scheme 2.13). Extensive analysis of the NMR data of **19** indicated that it was the desired compound in a 3:1 ratio.



Scheme 2.13. Hydrogenation of *rac*-**18** and epi *rac*-**18**.

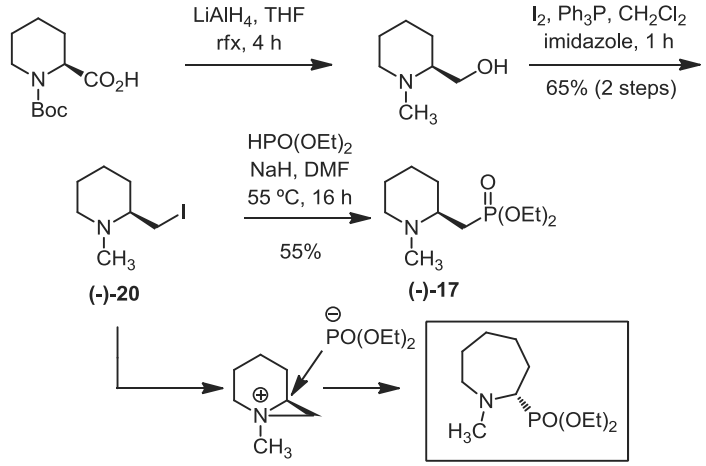
At this point, it was necessary to perform the HWE reaction with enantiomerically pure starting materials. Following the procedure developed before (see Table 2.3 and Scheme 2.8), we prepared enantiomerically pure *trans* decahydroquinoline **11** from the common building block **2**. The synthesis of enantiomerically pure **17** is described in the following section.

2.4.6 Preparation of enantiopure *N*-Me piperidine coupling partner

The synthesis of enantiomerically pure **17** was carried out in a straightforward manner from commercially available (*S*)-Boc-protected pipecolic acid.[63] Reduction with $LiAlH_4$[64] followed by conversion of the alcohol to the iodide[65] gave **20**[66] in 65% yield in two steps.

[63] Available in Sigma Aldrich: Boc-Pip-OH 5 g 168.0 €
[64] De Costa, B. R.; Dominguez, C.; He, X.; Williams, W.; Radesca, L.; Bowen, W. *J. Med. Chem.* **1992**, 4334–4343.
[65] The analogue N-benzyl-2-iodomethylpyrrolidine (Hjelmgaard, T.; Tanner, D. *Org. Biomol. Chem.* **2006**, *4*, 1796–1805) was isolated in only 38% yield and was found to be unstable.
[66] For the synthesis of the related chloro analogue of (-)-**20**, see: Deng, H.; Gifford, A.N.; Zvonok, A.M.; Cui, G.; Li, X.; Fan, P.; Deschamps, J.R.; Flippen-Anderson, J.L.; Gatley, S.J.; Makriyannis, A. *J. Med. Chem*. **2005**, *48*, 6386-6392.

In a first attempt to convert **20** to phosphonate **17**, it was treated with $P(OEt)_3$ at 156 ºC, similarly to the preparation of piperidine phosphonate **16**.[67] However, no reaction took place and the starting material decomposed. We also attempted treatment of **20** with diethyl phosphite using sodium hydride in THF, but no reaction took place due to the low solubility of the starting material. Finally, by changing the solvent to the more polar DMF, (-)-**17** was obtained in 55% (Scheme 2.14), together with a 20% of a by-product, which we presume corresponds to the structure depicted below. This compound might come from the intermediacy of an aziridium ion formed due to the highly basic conditions.[68]

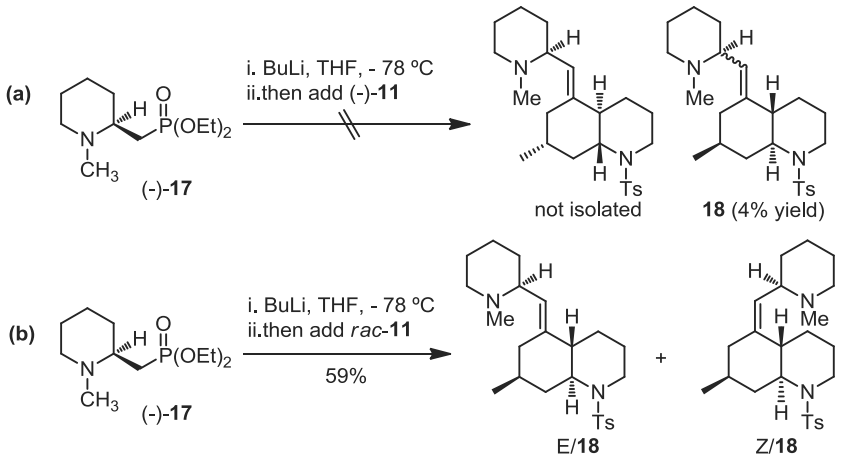


Scheme 2.14. Preparation of enantiopure N-methyl piperidine phosphonate **16**.

2.4.7 Attempted coupling of enantiopure *N*-methyl piperidine coupling partner

At this point, we attempted the coupling of (-)-**17** with (-)-**11**. Unfortunately, no reaction took place and instead, we could observe the ring opened product **5** (Scheme 2.15a). By careful purification of the reaction mixture we could isolate compound **18** in 4% yield. It should be noted that preparation of common building block (+)**-2** takes place in 90% ee, thus there remains a 5% of (-)-**2**, which may account for the formation of **18**. In order to understand the failure of this reaction, we attempted the coupling of enantiomerically pure **17** with *rac*-**11** (Scheme 2.15b). This time the reaction took place in 59% yield to give **18** as a 1:1 mixture of Z/E diastereomers.

[67] Cushman, M.; Mihalic, J. T.; Kis, K.; Bacher, A. *J. Org. Chem*. **1999**, *64*, 3838-3845.
[68] Mena, M.; Bonjoch, J.; Gómez-Pardo, D.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930-5935.



Scheme 2.15 (a) Horner Wadsworth Emmons coupling of (-)-**17** and (-)-**11**. (b) HWE reaction between (-)-**17** and *rac*-**11**.

2.4.8 Rationalization for the failed coupling in the enantiopure series

When an enantiopure substrate is employed in a reaction with an enantiopure reagent, at least one new stereogenic unit is incorporated in the product. Under these circumstances there are two separate factors that can affect the reaction course: i) the stereochemistry of the substrate (internal stereocontrol) and 2) the asymmetric features of the chiral reagent (external stereocontrol). These two factors can act either in concert, leading to a highly stereoselective process (matched) [ie. (+)-**11** with (-)-**17** and the enantiomeric pair], or be mutually opposed, leading to a poorly stereoslective process (mismatched). In some cases (as occurs here between (-)-**11** and (-)-**17**), the mismatch is so strong that the expected reaction pathway is kinetically unfavourable and entirely different products form instead. The unsuccessful coupling between enantiopure phosphonate (-)-**17** and decahydroquinoline (-)-**11** await DFT studies to understand the lack of reactivity between them. It should be noted that from our experience the stability of the decahydroquinolines is very limited, in many cases depending on the nucleophile employed. We often observed the retro aza-Michael reaction instead of the ketone coupling.

Due to these complications, we moved to the synthesis of phlegmarine via path (b) of Scheme 2.4.

2.5 Synthetic approach towards phlegmarine via addition of a pyridine phosphonate

2.5.1 Hydrogenation of type C vinylpyridine: calculations and considerations

The key step of this approach was the reduction of a vinylpyridine **XI**, which would have to position the substituent axially. Analysis of its structure showed that in this *trans* decahydroquinoline the hydrogenation seems not so controllable like in the *cis* series. The *trans* decahydroquinolines of type C shown in Figure 2.4, both the N-tosyl and N-H derivatives, with the CH_2Py in an equatorial position are 2.8 and 2.3 Kcal·mol^{-1} more stable than its respective compound with an axial substituent.

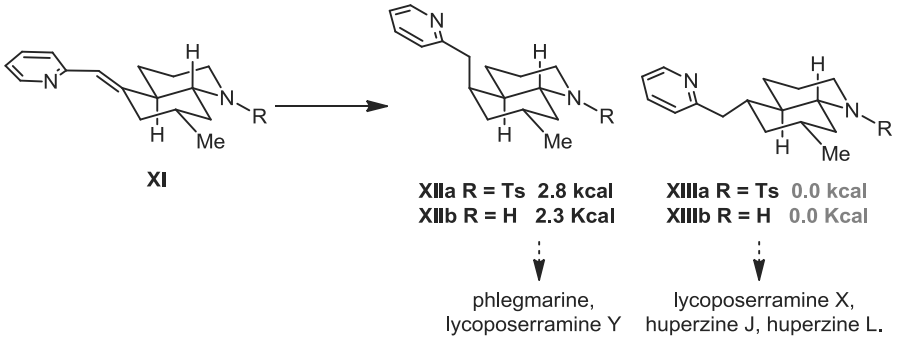
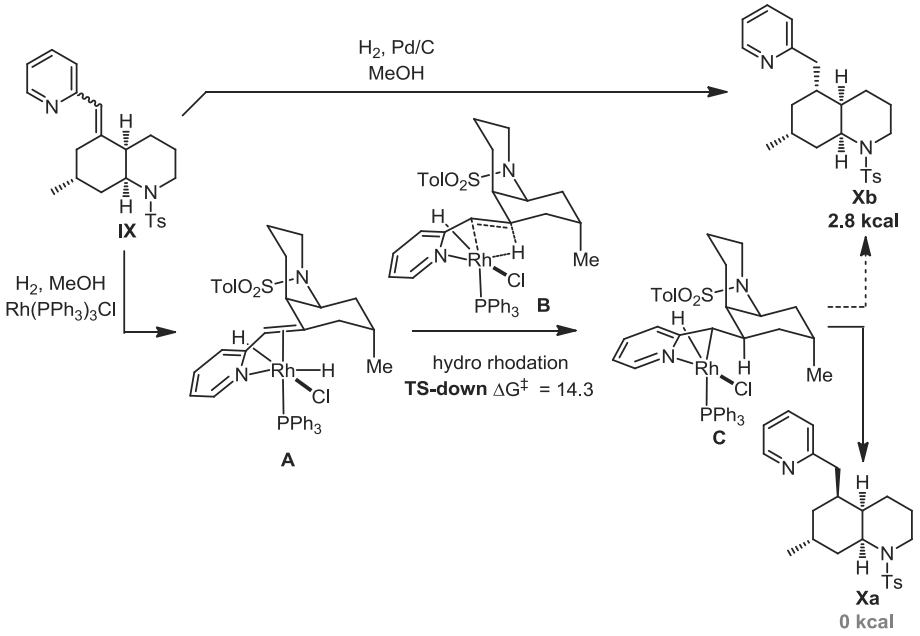


Figure 2.4 Relative stabilities of N-Ts and N-H 5-pyridin-2-yl-methyl *trans* type C decahydroquinolines in Kcal·mol^{-1}.

2.5.2 Background and precedents for the hydrogenation process of the vinylpyridines

During the elaboration of this thesis, our group simultaneously studied the hydrogenation of vinylpyridines in type A decahydroquinolines to overturn the facial selectivity and to give the more thermodynamically favoured compound **Xa**. As reported in the synthesis of lycoposerramine Z,[16] hydrogenation of **IX** using Pd/C took place from the more accessible top face to give **Xb**, since it is believed to be governed by an axially positioned methyl group, which blocks the approach from the lower face of the molecule, leading to the kinetic decahydroquinoline **Xb**. In collabroation with Prof. Gómez-Bengoa, calculations showed that **Xa** was 2.8 kcal·mol^{-1} more stable than its **Xb** epimer. After extensive screening of conditions,[36] reduction over Wilkinson's catalyst proved to successfully reverse the selectivity of the standard

hydrogenation, providing compound **Xa** in 96:4 ratio (Scheme 2.16). This compound was then used for the total synthesis of serratezomine E. Given the sterically impeded nature of the β,β disubstituted vinylpyridine and large size of Wilkinson's catalyst, it was presumed the reaction proceeded via a coordination of the catalyst.[69]



Scheme 2.16 Proposed mechanism for the Rh-catalyzed hydrogenation of **IX**.

With this information in hand we set to prepare the required *trans* decahydroquinoline containing a vinylpyridine. Of note it is that lycoposerramine X and huperzines J and L contain an equatorial piperidyl methyl substituent and could possibly be obtained by the methodology described above using Wilkinson's catalyst (Figure 2.5).

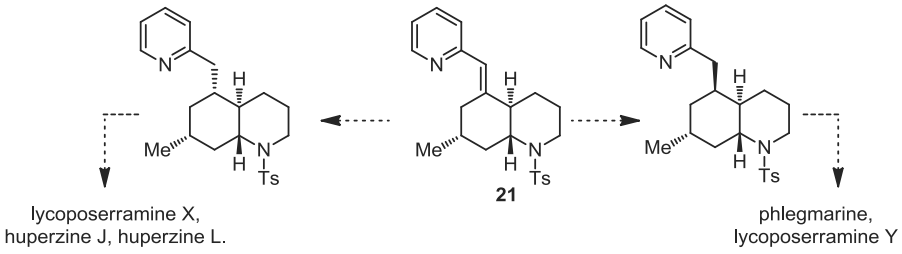
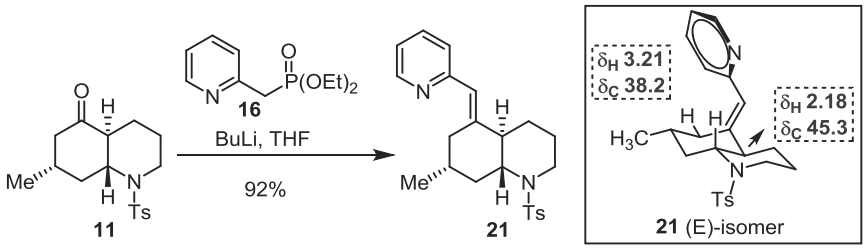


Figure 2.5. Accessible phlegmarine alkaloids from vinyl pyridine **21**.

[69] Indeed, no reduction took place with the benzene analogue of **IX** (not shown).

2.5.3 Coupling of a pyridine phosphonate

Decahydroquinoline **11** was treated with a solution of the lithium anion of phosphonate **16** to give **21** in 92% yield (Scheme 2.17). In contrast to our previous syntheses (see Schemes 1.3 and 1.4), the vinyl pyridine was obtained as a single isomer. The downfield shift of the H-6eq (δ 3.21 ppm) and the upfield shift at C-6 (δ 38.2 ppm) agree with a steric crowding of the pyridyl ring upon H-6eq associated with the E configuration of the exocyclic double bond. With **21** in hand the stage was set to try the crucial reduction.



Scheme 2.17. Coupling of **11** with phosphonate **16**.

2.5.4 Hydrogenation process of vinylpyridine 21

When the hydrogenation was performed using Pd/C as a catalyst in MeOH (Table 2.5, entry 1) the desired **22** was obtained as a 3:2 mixture of epimers. Other solvents were screened to try to increase the selectivity but they gave poorer results (entries 2-3). As yet, it is not clear what factors influence the hydrogenation of **22** but we believed that addition of a chiral acid might block the top face by coordination with the pyridine. Indeed, addition of 1.0 equiv of **24b**[70] to enantiomerically pure **21** increased the selectivity and **22** was obtained as the major isomer as a 4:1 mixture of diastereomers, quantitatively (entry 4).[71] The hydrogenation was also performed with the unsubstituted **24a** and its enantiomer **25a** (entry 5-6) and in both cases no diastereoselection was observed, proving the R substituent is crucial for the selectivity. To assess which catalyst is match and mismatched the hydrogenation was also

[70] (a) Rueping, M.; Merino, E.; Koenigs, R.M. *Adv. Synth. Catal*. **2010**, *352*, 2629 – 2634. (b) Rueping, M.; Bootwicha, T.; Sugiono, E. *Beilstein J. Org. Chem.* **2012,** *8,* 300–307. (c) Rueping, M.; Antonchick. A.P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4562 –4565.

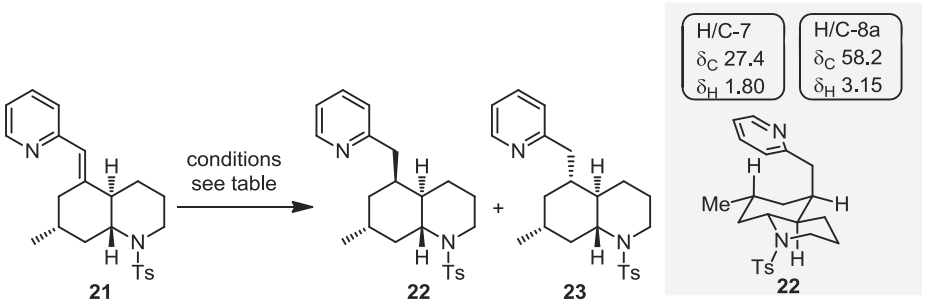
[71] For posible ways to make this reaction catalytically, see: Neel, J. A.; Milo, A.; Sigman, M.S.; Toste, F.D. *J. Am. Chem. Soc*. **2016**, *138*, 3863−3875 and references cited therein.

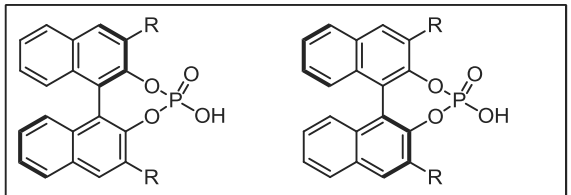
performed using the catalyst **25b** having the opposite configuration (entry 7). Surprisingly, **25b** did not have any effect on the selectivity of the hydrogenation and an almost equimolar mixture of epimers was obtained. In order to evaluate the influence of the R group on the catalyst we attempted the hydrogenation with the anthracenyl derivative **24c**. According to Rueping's group, this catalyst gives superior results in the hydrogenation of pyridines.[70c] Although the hydrogenation using **24c** took place with moderate selectivity using methanol as a solvent it was very slow and only 40% conversion was observed after 24 h (entry 8). We believe that the poor solubility of the chiral ion pair in methanol might prevent the reaction to take place. Changing the solvent to the more apolar toluene allowed us to achieve complete solubility of the reagents, but regardless no selectivity was observed (entry 9).[72]

Alternatively, the reduction was also performed using Wilkinson's catalyst, in a similar manner to that of the reduction of type A vinyl pyridines.[36] To our surprise, despite the structural difference to the type A compound, the reduction took place exclusively from the top face giving **23** as a single isomer. We also performed the reduction of the alkene under the radical conditions developed in our group (entry 10)[73] and again **23** was obtained as the main compound although in less proportion than with Wilkinson's catalyst. Although **22** and **23** were close running by TLC, we could separate the compound bearing the phlegmarine stereochemistry and perform a full characerization of **22**. Both isomers can be differentiated by the chemical shift of the C-7. Thus, in **23** the steric compression made by the axial pyridine unit pushes the electrons of the H/C-7 sigma bond off to the carbon resulting in an upfield of C-7 (4.8 ppm) and a downfield of H-7 (0.48 ppm) with respect to **23**.

[72] A more extensive screening of other commercially available chiral phosphoric acid catalyst might reveal an increased diastereoselective ratio, but was considered prohibitively expensive.
[73] Unpublished results. See also: Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300-1303.

Table 2.5. Study of hydrogenation at C-5.





Entry	*Catalyst*[a]	*H source*	*Solvent*	*Chiral acid*	*dr 22:23* [(b)]
1	Pd/C	H_2	MeOH	-	60:40
2	Pd/C	H_2	CH_2Cl_2	-	55:45
3	Pd/C	H_2	Benzene	-	56:44
4[c]	Pd/C	H_2	MeOH	**24b**	80:20
5[c]	Pd/C	H_2	MeOH	**24a**	65:35
6[c]	Pd/C	H_2	MeOH	**25a**	63:37
7[c]	Pd/C	H_2	MeOH	**25b**	65:35
8[c]	Pd/C	H_2	MeOH	**24c**	70:30
9[c]	Pd/C	H_2	toluene	**24c**	65:35
10[d]	$Rh(PPh_3)_3Cl$	H_2	MeOH	-	1:99
11	$Mn(dpm)_3$	$PhSiH_3$	dichloroethane	-	12:88

[a] *Reaction conditions*: 50% mol catalyst loading. Reaction were performed in 5-15 mg scale. [b] Determined by ^1H NMR analysis of the crude. [c] enantiopure starting material. Reaction performed with 1.0 equiv of chiral phosphoric acid [d] 15% mol catalyst loading

2.5.5 Rationalization of the facial selectivity of the hydrogenations reactions

We believe that the facial selectivity observed for the reduction of **21** using a chiral acid was due to the protonation of the pyridine. Molecular models of **21** with **24b** indicated that the R group (R = 3,5$(CF_3)_2C_6H_3$) might clash with the C-7 methyl, making the anion of **24b** position itself over the top face of the molecule and thus favouring reduction from the bottom face.

This steric interaction was not observed with the enantiomer **25b**. For the hydrogenation with Wilkinson's catalyst we propose a transition state (Figure 2.6), where the pyridine is coordinated to the Rh atom as a possible explanation for the high stereoselectivity of the reaction.

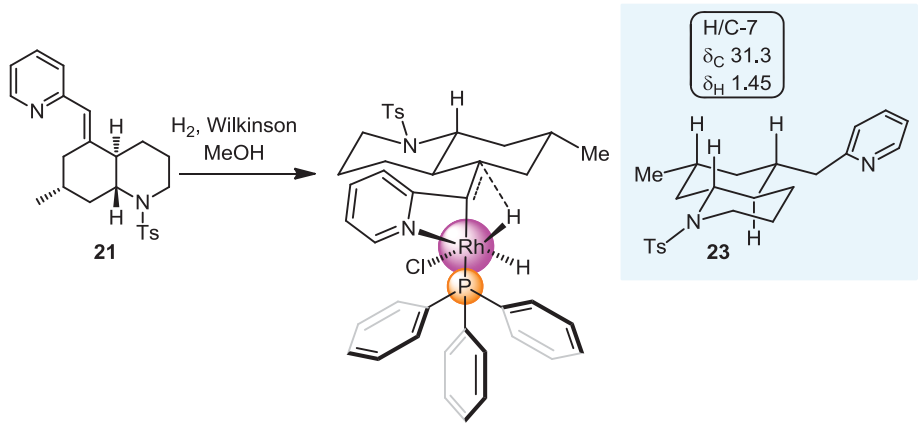
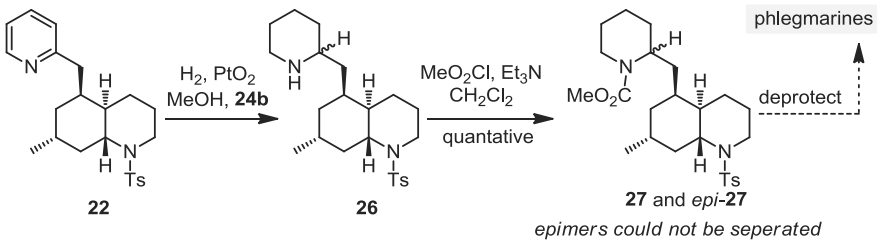


Figure 2.6. Proposed transition state leading to **23** and its NMR data.

2.5.6 Attempted diastereoselective reduction of the piperidine ring using a chiral phosphoric acid

Having found a method for the reduction of vinyl pyridine **21**, we set about attempting to complete the total synthesis of phlegmarine. We wondered if the reduction of the pyridine could be also performed diastereoselectively by adding a chiral phosphoric acid. To evaluate the reaction, we treated **22** with 1 equiv of chiral phosphoric acid **24a** (see Table 2.5 entry 5). We then added PtO_2 to the reaction mixture. After 16 h under an H_2 atmosphere, were pleased to observe that the piperidine was fully reduced within 24 h to obtain **26**. Repetition of the reaction with the chiral phosphoric acid **24b** was then carried out and, whilst the pyridine ring was reduced in an analogous manner, no evident diastereoselectivity was observed, according to the GC-MS analysis (Scheme 2.18). Protection of the free amine by treatment of the crude with methyl chloroformate was undertaken to see if we could, in an analogous manner to our synthesis of cermizine B,[21] separate the resulting epimers by column chromatagraphy. Unfortunately, no separation could be obtained.

At this point, due to the low amount of material available we could not perform a full characterization of the epimeric mixture of carbamates **27** and *epi*-**27**.



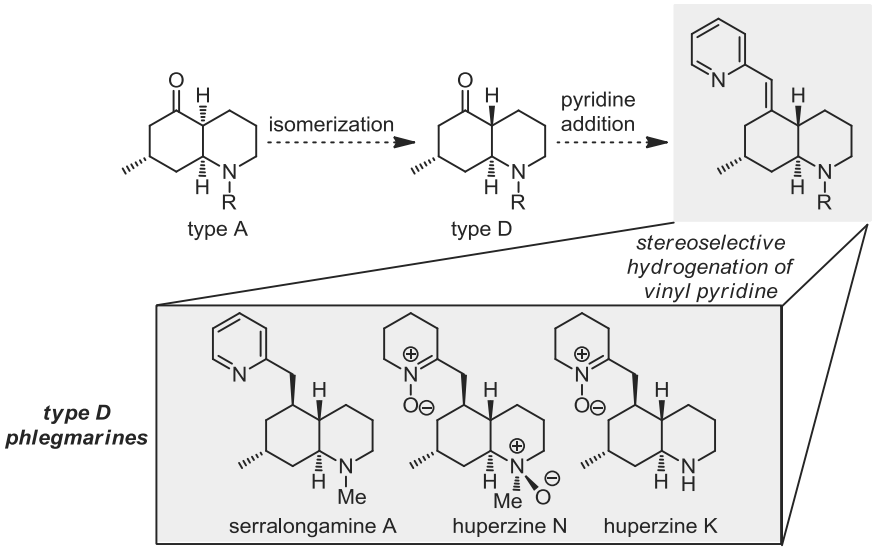
Scheme 2.18 Attempted diastereoselective reduction of pyridine **22**.

2.6. Access to phlegmarine alkaloids of type D

In parallel to the work detailed above, we also investigated an analogous route to the type D phlegmarine alkaloids.

2.6.1 Overview of strategy

Given that the above process (see section 2.4.4) allowed the interconversion of type B compounds to type C, we expected the same reaction sequence would transform type A compounds to type D, which is found in serralongamine A[35] and Huperzines N[37] and K[38] (Scheme 2.19).

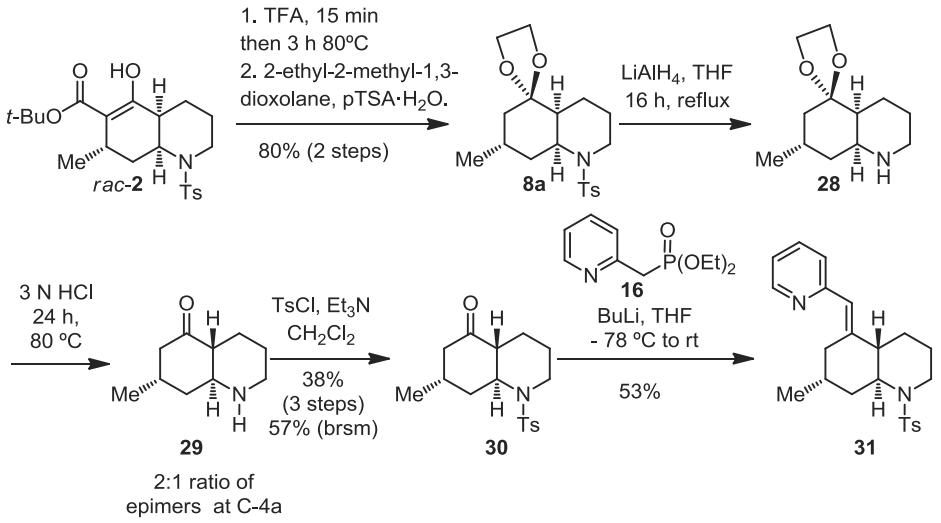


Scheme 2.19. Access to type D decahydroquinolines and natural products containing this stereochemical arrangement.

It should be noted that the C-5 methyl substituent is positioned equatorially and therefore should be readily accessible with the use of the Wilkinson's catalyst.

2.6.2 Conversion of type A decahydroquinoline to type D

Following a similar experimental to that described in section 2.4.4, all *cis* decahydroquinoline **2** was treated with TFA and subsequently protected with 2-ethyl-2-methyl-1,3-dioxolane in TsOH to give acetal **8a** in 80% yield after 2 steps. Treatment of **8a** with $LiAlH_4$ and acid induced epimerization at C-4a gave the corresponding secondary amine **29** as a 2:1 mixture of epimers. As shown in Table 2.2, the difference in stability of the methyl analogues **Aii** and **Dii** is about 2.7 kcal/mol while for **Cii** and **Bii** is 3.6 kcal/mol, which might explain why isomerization at type B takes places completely and in this case only partially. Nevertheless, both epimers could be separated after tosylation of the mixture to furnish the required decahydroquinoline **30** with a *trans* type D ring fusion in 38% yield after three steps.[74] This ketone reacted with a solution of the lithium anion of phosphonate **16** to give vinylpyridine derivative **31** in 53% yield, diastereoselectively providing the *E* isomer (Scheme 2.20).[75]

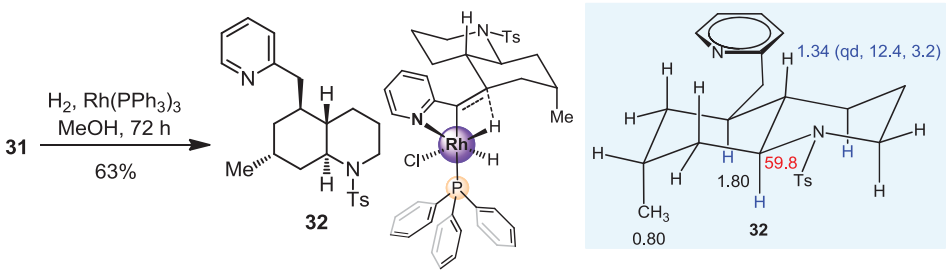


Scheme 2.20. Synthesis of the phlegmarine type D stereochemistry.

[74] The type A material could be recovered and recycled.
[75] The downfield shift of the H-6eq (δ 3.07) and the upfield shift at C-6 (δ35.2) agree with a steric crowding of the pyridyl ring upon H-6eq associated with the E configuration of the exocyclic double bond.

2.6.3 Hydrogenation of vinylpyridine 31

Hydrogenation of vinylpyridine **31** using Wilkinson's catalyst allowed the hydrogen to be delivered exclusively from the bottom face. Thus, a pyridine directed hydrogenation provided access to the valuable intermediate **32** with a contra-steric selectivity (Scheme 2.21)



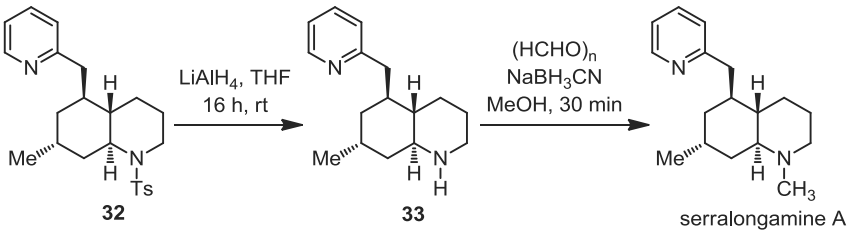
Scheme 2.21 Reduction of vinyl pyridine **31** with Wilkinson's catalyst. Transition State Leading to **32** and its representative NMR Data

The stereoselectively-formed decahydroquinoline **32** showed the same relative configuration in its four stereogenic centers as serralongamine A and Huperzine N. The configuration at C-5 was ascertained considering the multiplicity of the signal corresponding to H-4a, which implies a *trans* relationship between H-4a and H-5, both in an axial disposition. Moreover, the chemical shift for C-8a (δ 59.8) did not differ from that observed in the precursors **30** (δ 60.3) and **31** (δ 60.6), indicating that the pyridylmethyl side chain is not axially located.[76] Hydrogenation with Pd/C in methanol was also attempted to confirm the selectivity was not determined solely by the substrate itself. Indeed, we obtained **32** as a minor product (2:1 ratio) together with the C-5 epimer (not shown).

2.6.4 Total synthesis of serralongamine A and huperzine N

Removal of the tosyl group in **32** using $LiAlH_4$ followed by reductive *N*-methylation of **33** gave serralongamine A in 76% yield for the two steps, which constitutes the first synthetic entry to a phlegmarine alkaloid embodying a type D decahydroquinoline (Scheme 2.22).

[76] For the influence of the steric compression effect on NMR chemical shifts, see: (a) Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223-229. (b) Kolocouris, A. *Tetrahedron Lett.* **2007**, *48*, 2117-2122.



Scheme 2.22 Completion of the total synthesis of serralongamine A

It is noteworthy that the NMR data of our synthetic serralongamine A were clearly different from those reported for the isolated serralongamine A in CD_3OD. Since basic nitrogen atoms readily protonate, we were able to reproducibly obtain ^{1}H and ^{13}C NMR spectra of the free base forms of serralongamine A in CD_3OD containing $NaOCD_3$.[77] We surmised that the natural isolate corresponded to its ditrifluoroacetate salt. Thus, the NMR spectrum of synthetic serralongamine A was examined by titrating a sample of the free base with TFA and this time the NMR data of the synthetic sample was identical to that of the isolated compound (for a comparison of NMR data for natural and synthetic serralongamine A as the double TFA salt see experimental part).

2.6.5 Structural reassignment of huperzine N

Initially, the structure proposed for huperzine N contained a type B decahydroquinoline (Figure 2.7a). However, after describing the total synthesis of the putative structure of huperzine N[36] and analysis of the ^{13}C NMR data of the natural product we found out that its structure was missassigned. The putative and natural huperzine N are clearly differentiated by their ^{13}C NMR data: (i) the chemical shifts of C(2) and C(4) are more deshielded (8 and 11 ppm, respectively) in the natural product. These data suggest that huperzine N has a *trans*-decahydroquinoline ring core instead of the *cis*-ring fusion originally reported; (ii) the chemical shift of the methyl group at C(7), which resonates at δ 19.0 in huperzine N, but at δ 22.2 in the putative compound, indicates an axial disposition, which is only possible in a *trans*-decahydroquinoline with a

[77] For a similar NMR protocol to measure the free base and its TFA salt spectra in alkaloid synthesis, see: (a) Altman, R. A.; Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M.; Taupin, V. *J. Org. Chem*. **2010**, *75*, 7519−7534. (b) Lee, A. S.; Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2014**, *136*, 13442−13452.

stereoparent of type D. Consequently, the NMR reported for huperzine N can be explained by the structure shown below (Figure 2.7b).

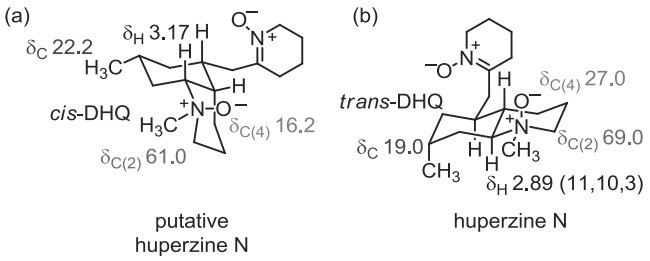
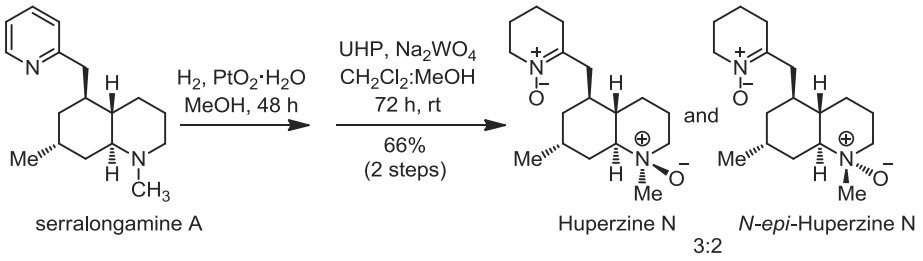


Figure 2.7. Differential NMR trends between putative (a) and natural huperzine N (b).

2.6.6 Total synthesis of huperzine N

With serralongamine A in hand, there only remained two steps to complete the synthesis of the new structure proposed for huperzine N. Reduction of the pyridine ring of serralongamine A gave the corresponding piperidine as an inconsequential mixture of epimers at C-2', which after prolonged oxidation with Na_2WO_4/ urea·H_2O_2 (UHP) led to huperzine N by formation of both the amine *N*-oxide and nitrone functionalities (Scheme 2.23).



Scheme 2.23 Synthesis of huperzine N from serralongamine A

The spectroscopic data of the synthetic sample were identical in all respects to those reported for the natural product,[37] although a side product purified together with huperzine N was also formed. Two-dimensional NMR spectroscopy of the mixture identified the minor product as the *N*-oxide epimer of huperzine N. Although the oxidation of cyclic tertiary amines normally takes place axially,[78] the presence of an equatorial substituent increases the

[78] Shvo, Y.; Kaufman, E. D. *J. Org. Chem*. **1981**, *46*, 2148−2152.

equatorial oxidation,[79] as occurred in our substrate (C8-C8a bond). Thus, the reaction did not work diastereoselectively and N-*epi*-huperzine N was also formed. The stereostructure and the complete ^{1}H, ^{13}C, and ^{15}N chemical shifts assignment of both epimers (Figure 2.8) and also their protonated forms[80] (see chapter 6 for details) were performed from the analysis of COSY, ROESY,[81] HSQC, HMBC, and TOCSY correlation spectra of the mixture.

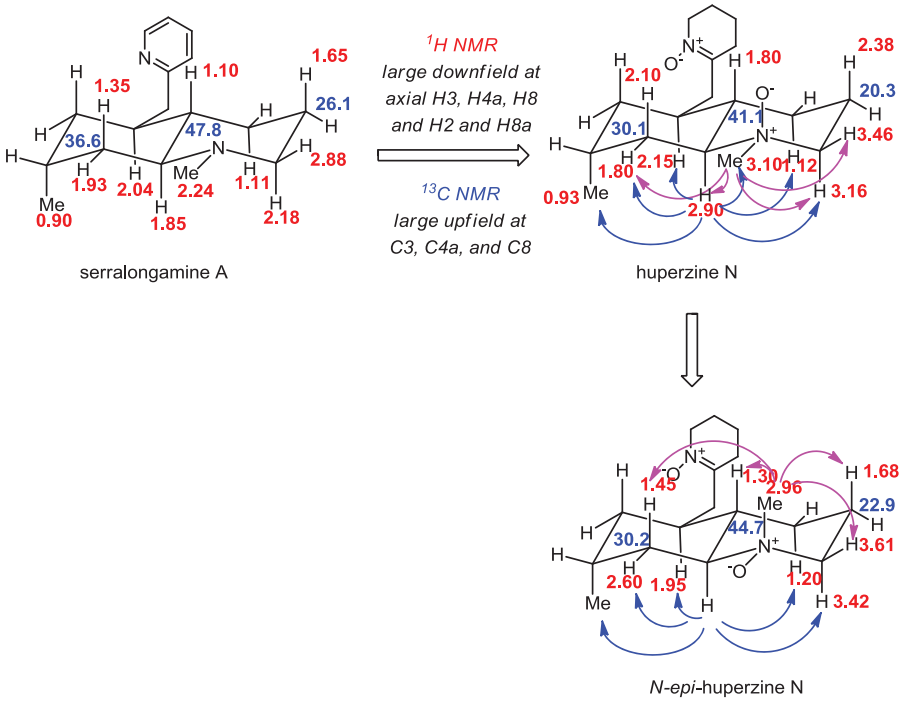


Figure 2.8. Characteristic NMR data and selected NOEs of huperzine N, *N-epi*-huperzine N and serralongamine A

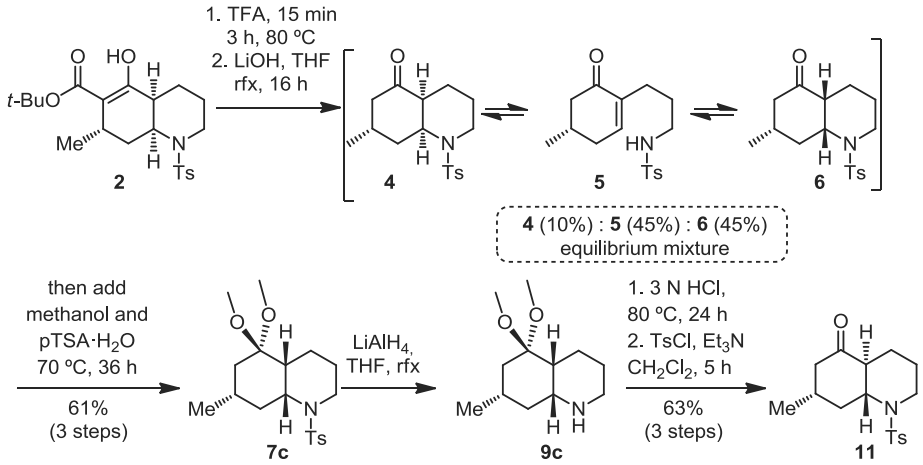
[79] Kawazoe, Y.; Tsuda, M. *Chem. Pharm. Bull.* **1967**, *15*, 1405−1410.

[80] In huperzine N and *N-epi*-huperzine N, the protonation of the *N*-oxide function leads to a deshielding of the α-hydrogens. It should be noted that the protons in a 1,3-diaxial relationship with the N-oxide function are not affected or even slightly shielded upon protonation (e.g., H-10, H-12, and H-14 in huperzine N). For NMR studies in this field, see: Lebrun, B.; Braekman, J. C.; Daloze, D. *Magn. Reson. Chem.* **1999**, *37*, 60−64.

[81] When huperzine N was originally isolated, NOE correlations were established between the putative H-12 proton and signals at *N*-Me and H-13. However, according to our ROESY NMR, which allowed the revised *trans* configuration to be established, these cross-peaks were due to H-14eq. This error is attributed to the ^{1}H chemical shift degeneracy between H-12 and H-14eq. This observation is fully confirmed by the NOE contacts observed in the related epimer and protoned N-oxide derivatives, as well as of the characteristic multiplet J pattern of H-12 and H-13.

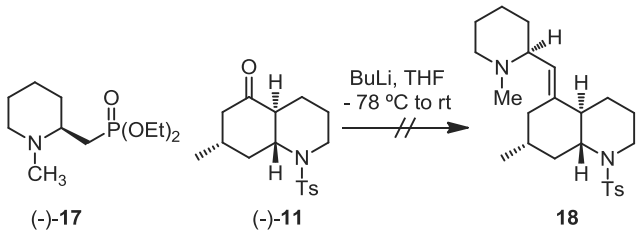
2.7 Summary and conclusions

The *trans*-decahydroquinoline nucleus of phlegmarine has been obtained by adding an acetal to the equilibrium mixture to trap the type B stereochemistry and a complete epimerization at the C-4a (Scheme 2.24).



Scheme 2.24 Access to *trans* type C nucleus of phlegmarine

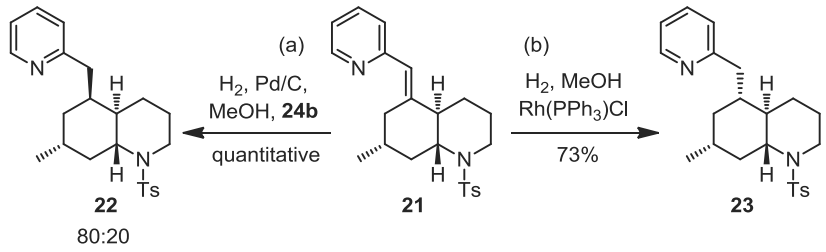
A N-methyl piperidine phosphonate **17** has been used to introduce the piperidine ring of phlegmarine (Scheme 2.25). This reaction works well when *rac*-**11** is treated with a solution of the lithium anion of methyl piperidine phoshonate *rac*-**17** and (-)-**17**. However, no reaction takes places with both enantiomerically pure starting materials, which indicates that this process is mismatched.



Scheme 2.25. HWE between a methyl piperidine phosphonate **17** and *trans*-decahydroquinoline **11**.

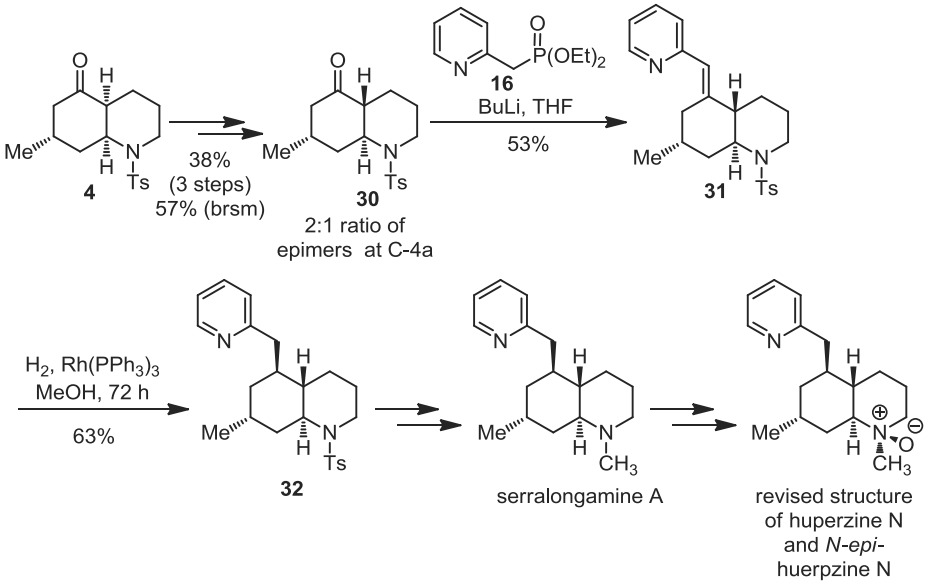
However, an alternative pathway were the vinyl pyridine **22** is reduced in the presence of chiral phosphoric acid **24b** to give **23** as a 4:1 mixture of diasteroemers has been developed (Scheme 2.26). When this reduction is

carried out with the Wilkinson's catalyst we obtained **23** having the opposite configuration of **22** at C-5 as a single isomer, opening the way to access the phlegmarine alkaloids lycoposerramine X and huperzines J and L.



Scheme 2.26. Reduction of vinyl pyridine **21** under different conditions.

The total synthesis of (±)-serralongamine A has been achieved via partial epimerization at C-4a of **4** and complete stereoselective hydrogenation of vinyl pyridine **31** with Wilkinson's catalyst. From this compound we have also been able to obtain huperzine N and demostrated that when it was isolated its structure was missassigned (Scheme 2.27). Of note it is that formation of the N-methyl-N-oxide is not diastereoselective and *N-epi*-huperzine N was also obtained.



Scheme 2.27. Synthesis of serralongamine A and the revised structure of huperzine N.

3. Synthetic approaches towards the synthesis of (+)-fawcettimine

3.1 Introduction

3.1.1 Isolation and structure of fawcettimine

Fawcettimine was first isolated from *Lycopodium fawcetti* by Burnell in 1959 as its perchlorate salt.[82] However, it was not until 1967 that Inubushi[83] stablished that its structure possesses a *cis* fused 6,5-carbocyclic framework with an all-carbon quaternary center and an azonane ring. In the same paper, Inubushi proposed that, in solution, fawcettimine exists mainly as the carbinolamine form (Figure 3.1), but could not stablish the configuration at the C-4. With his synthesis of fawcettimine, Heathcock determined this stereocenter to be *S* and also stablished that the structure of fawcettimine from a synthetic perspective can be simplified to the construction of the 6,5-bicyclic core and the azonane rings since the keto amine form spontaneously cyclizes to the carbinolamine form.[84]

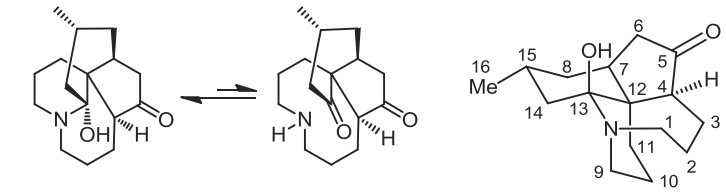


Figure 3.1 Structure of fawcettimine.

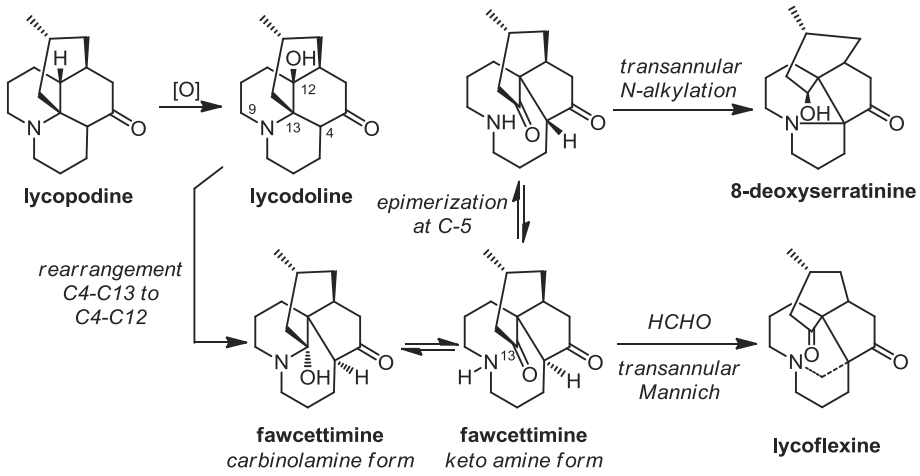
Since the discovery of fawettimine many other fawcettimine-type alkaloids have been isolated, with this class now comprising of around 80 of the 300 known lycopodium alkaloids (Figure 3.2). These compound are formed via several main pathways namely oxidations, migrations, rearrangements, cross-linking and dimerization.

[82] (a) Burnell, R. H. *J. Chem. Soc.* **1959**, 3091-3093. (b) Burnell, R.H.; Mootoo, B.S.; *Can. J. Chem.* **1961**, 1090-1093.
[83] Inubushi, Y.; Ishii, H.; Harayama, T.; Burnell, R.H.; Ayer, W.A.; Altenkirk, B. *Tetrahedron Lett.* **1967**, 1069-1072.
[84] (a) Heathcock, C.H.; Smith, K. M.; Blumenkopf, T. A. *J. Am. Chem. Soc*. **1986**, *108*, 5022-5024. (b) Heathcock, C.H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548-1562.

3.1.2 Fawcettimine and related compounds

According to Inubushi, the 5-membered ring of fawcettimine arises from the cleavage of the C4-C13 bond of lycodoline (the 12-hydroxyl derivative of lycopodine) and formation of a C4-C12 bond.

As commented, fawcettimine also exists in a ring opened form which can then undergo various reactions to generate a diverse range of structures. For example, the serratinine type alkaloids form via transannular alkylation of this opened form. Alternatively, lycoflexine is proposed to be formed after condensation of the free amine with formaldehyde and a subsequent transannular Mannich reaction (Scheme 3.1).



Scheme 3.1 Biogenesis of fawcettimine type compounds.

Other fawcettimine derivatives (Figure 3.2) form by oxidations at different positions, dehydrations or oxidative couplings to generate dimeric species, for example phlegmariurine B. From all the known fawcettimine type alkaloids, lycopoclavamine A is the only one that possesses the opposite configuration at the C-15 methyl group. Huperzine Q and its N-oxide derivative might be generated by an intramolecular reaction of the hydroxyl group of fawcettimine with the C-16 methyl group. Alternatively, oxidation of the free amine and intramolecular attack of the C-9 to the resulting imine might result in the formation of the tetracyclic structure of lycojaponicumin C. This compound has been found to have potential anti-inflammatory activity in *in vitro* studies using

macrophages.[85] Despite its major structural variation, serratezomine A[14] also belongs to the fawcettimine class, and is proposed to originate from serratinine through a Polonovski type reaction.[86]

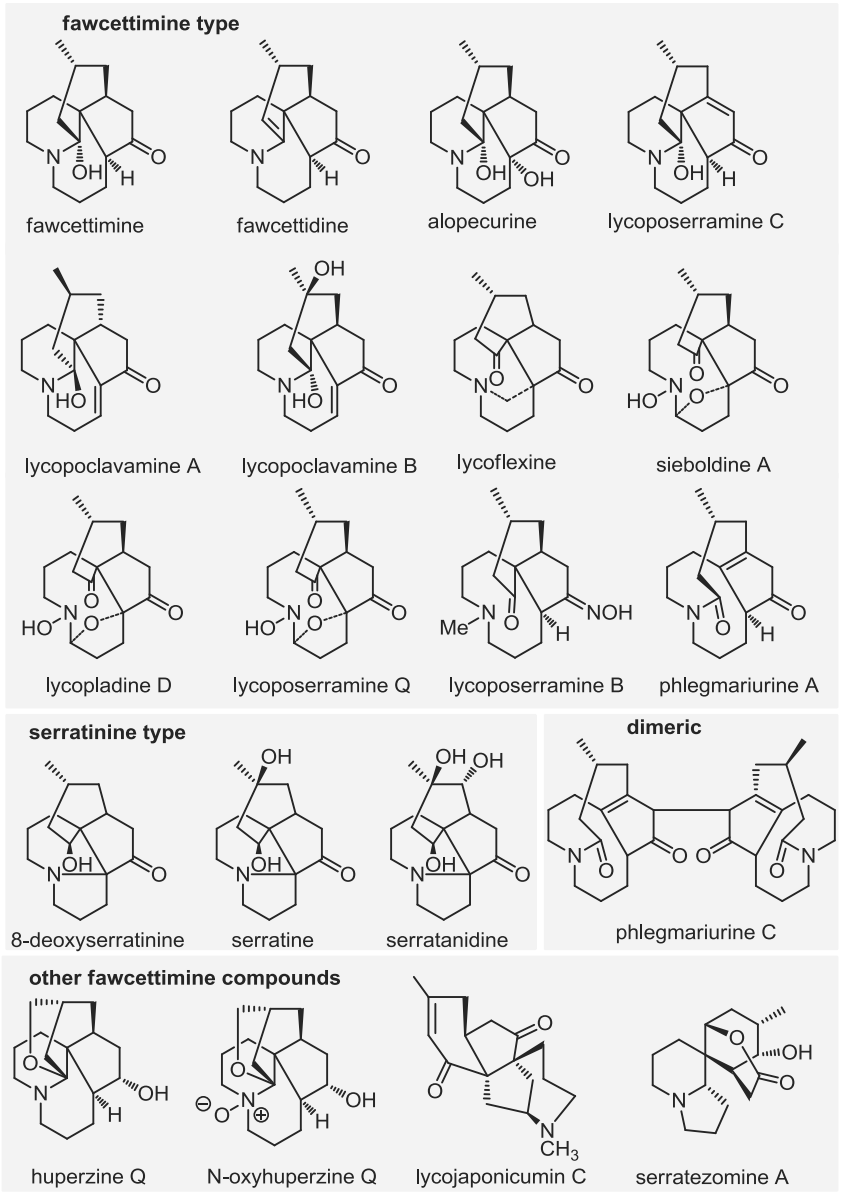


Figure 3.2 Representative compounds of the fawcettimine class.

[85] Wang, X.; Zhang, G.; Zhuang, P.; Zhang, Y.; Yu, S.; Bao, X.; Zhang, D.; Yuan, Y.; Chen, N.; Ma, S.; Qu, J.; Li, Y. *Org. Lett.* **2012**, *14*, 289–292.
[86] Morita, H.; Kobayashi, J. *J. Org. Chem.* **2002**, 67, 5378-5381.

3.2 Previous synthesis of (+)-fawcettimine

Amongst all the lycopodium alkaloids, the fawcettimine type has been the subject of extensive synthetic research with the vast majority of the syntheses being reported from 2007 onwards (see Table 3.1).[87] As a consequence, most of the syntheses carried out are enantioselective with (*R*)-3-methyl cyclohexenone used as the most popular source of chirality. Since the C ring forms spontaneously by cyclization of the free amine onto the C-13 carbonyl, the structure of fawcettimine can be simplified into the keto amine shown in Figure 3.3. The key defining feature of each strategy is generally based on the method used to assemble the 5-membered B ring, which can be loosely grouped into four types: (i) B to D, (ii) simultaneous B and D ring formation via Pauson Khand reaction, (iii) D→A+C→B, which has been employed in a few cases, and finally (iv) D→B→A+C,[88] which represents the most common employed strategy and involves a conjugate addition to a cyclohexenone D ring, followed by cyclisation to form the B ring.

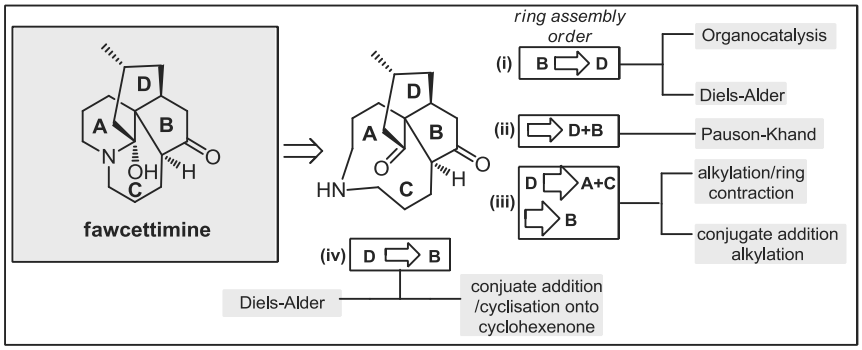


Figure 3.3 Overview of strategies to assemble fawcettimine type compounds

[87] For a more in depth review of methods to form fawcettimine type products see: Wang, X.; Li, H.; Lei, X.; *Synlett*, **2013**, *24*, 1032-1043

[88] In some cases the B ring is constructed first then the D ring.

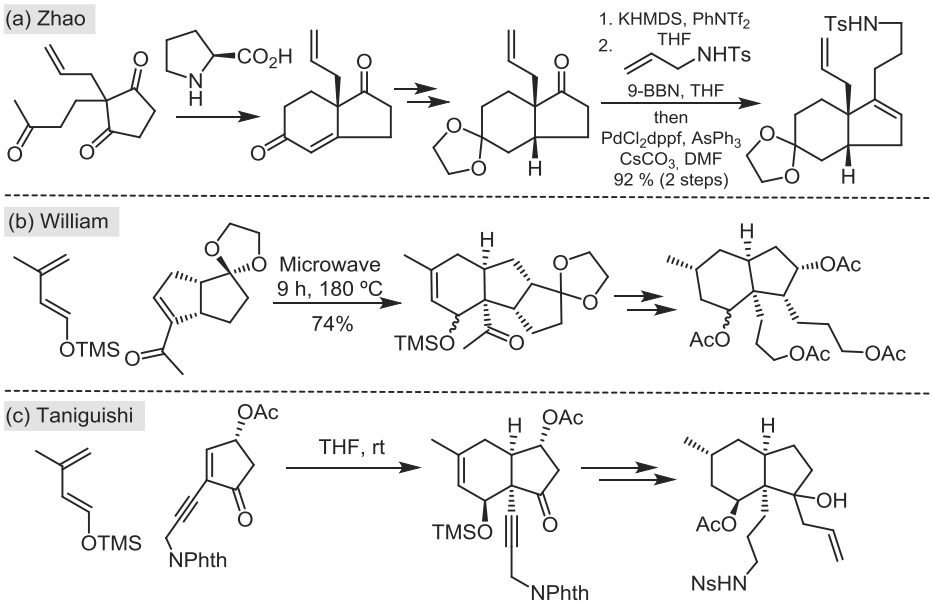
Table 3.1. Previous synthesis of fawcettimine and related compounds (* denotes asymmetric synthesis)

Year	*Natural Product(s)*	*Author*	*Strategy**
1979	fawcettimine	Inubushi	D→B→A+C
1986	fawcettimine	Heathcock	D→B→A+C
2007	fawcettimine	Toste	D→B→A+C*
2008	fawcettidine	Dake	D→C→B→A*
2010	fawcettimine	Jung	D→B→A+C*
2010	fawcettimine + lycoposerramine B	Mukai	acyclic→DB→A+C*
2011	fawcettimine +lycoflexine	Wei	D→B→A+C*
2010	lycoflexine + (fawcettimine)	Mulzer	D→BA→C*
2011	alopecuridine + (sieboldine A)	Meng	D→A+C→B*
2012	fawcettimine	William	D→A→B→C*
2012	fawcettimine (8-deoxyserratinine)	Lei	D→A+C→B*
2012	fawcettimine + fawcettidine	Takayama	acyclic→DB→A+C*
2013	lycojaponicumin C (fawcettimine, fawcettidine, 8-deoxyserratinine)	Tu-Wang	D→B→A+C*
2013	lycopladine D, fawcettidine, lycoposerramine Q	Zhao	D→B→A+C*
2014	fawcettimine, lycoflexine	Zhai	D→B→A+C
2014	8-deoxyserratinine, fawcettimine, lycopoclavamine-A, serratine, lycopoclavamine-B, serratanidine	Taniguchi	D→B→A+C*
2015	fawcettimine, fawcettidine, lycoflexine, huperzine Q, Lycoposerramine Q, N-oxyhuperzine Q	Zhao	D→B→A+C*

(i) B→D ring assembly

Zhao took advantage of the 6,5 ring system of the Hajos-Parish ketone for his synthesis of fawcettimine and related compounds (Scheme 3.2a).[89] After reduction of the enone, the side-chain to construct the A+C rings was appended via a Suzuki coupling of the corresponding triflate. Alternatively, William[90] and Tanigushi[91] used the Diels-Alder cycloaddition to construct the 6-membered D ring by coupling a diene with a preformed 5-membered ring dienophile (Scheme 3.2b and c, respectively).

[89] (a) Zeng, C.; Zheng, C.; Zhao, J.; Zhao, G. *Org. Lett.* **2013**, *15*, 2002–2005. (b) Zeng, C.; Zhao, J.; Zhao, G. *Tetrahedron* **2015**, *71*, 64–69.
[90] Pan, G.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 4801-4811.
[91] Zaimoku, H.; Taniguchi, T. *Chem. Eur. J.* **2014**, *20*, 9613–9619.

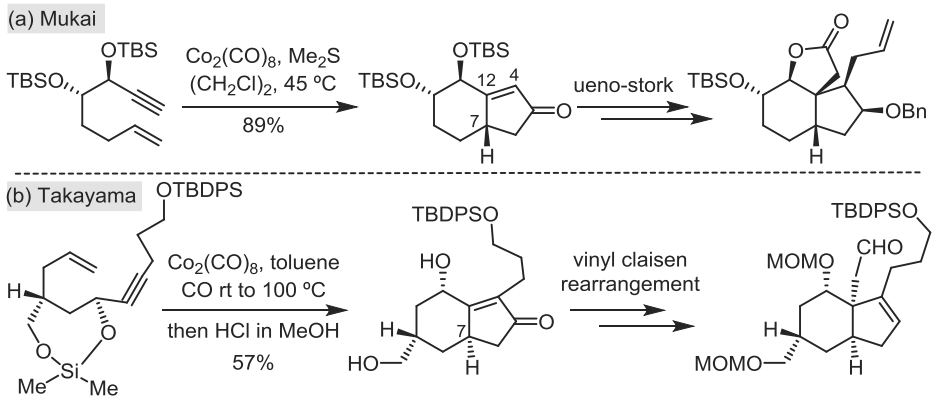


Scheme 3.2. B→D ring assembly via organocatalysis or the Diels-Alder reaction

(ii) Simultaneous D+B ring assembly

The Pauson-Khand reaction is a classic method for the formation of 5 membered rings, so therefore it is not surprising that it has been used to access the 6,5-nucleus of fawcettimine. Mukai employed a stereoselective Pauson-Khand reaction of a silyl protected enyne (scheme 3.3a) which allowed the simultaneous formation of the D-B ring system and introduction of the correct stereochemistry at C-7.[92] A Ueno-Stork reaction was then used to install both the C-4 and the quaternary carbon at C-12 stereocenters. Takayama developed an alternative approach using a 7-membered silyl-tethered compound as the starting material for his Pauson-Khand reaction (scheme 3.3b).[93] Of note is that without the use of a cyclic silyl enol ether, the reaction takes places to give the C-7 epimer as the major product. A vinyl Claisen rearrangement then was used to introduce the quaternary centre and set up the functionality required to assemble the 9-membered ring.

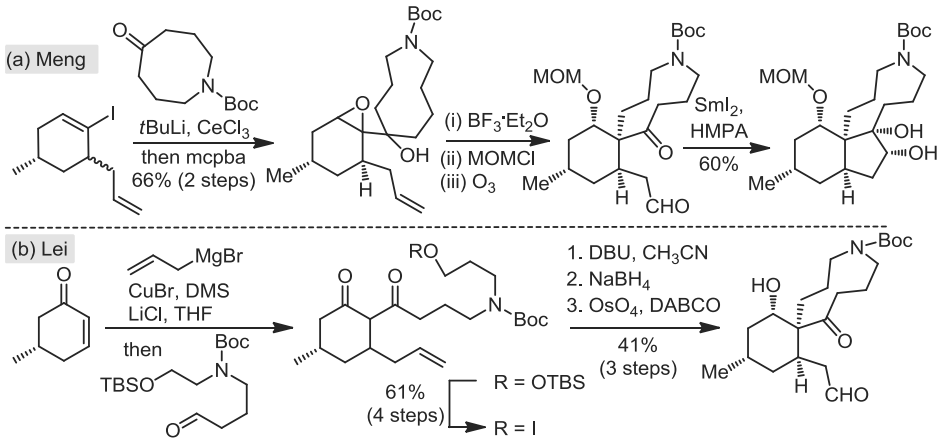
[92] Otsuka, Y.; Inagaki, F.; Mukai, C. *J. Org. Chem*. **2010**, *75*, 3420–3426.
[93] Nakayama, A.; Kitajima, M.; Takayama, H. *Synlett* **2012**, *23*, 2014-2024.



Scheme 3.3 Strategies involving the Pauson-Khand reaction.

(iii) D→A+C→B ring assembly

Meng and co-workers used the vinyl iodide derived from 2-iodo-5-methyl cyclohexenone and coupled it to a 9-membered ring fragment. Subsequent semi-pinacol rearrangement led to ring expansion and formation of the azononane ring structure. Pinacol coupling was then used to construct the B ring of sieboldine A (Scheme 3.4a).[94] Lei used a similar strategy to Meng but forming the azonane ring by conjugate addition/trapping strategy followed by an intramolecular alkylation. A SmI_2 mediated pinacol coupling of a keto-aldehyde was then performed in analogous manner shown before to construct the 5 membered ring (Scheme 3.4b).[95]



Scheme 3.4. Strategies involving a Pinacol reaction to close the B ring.

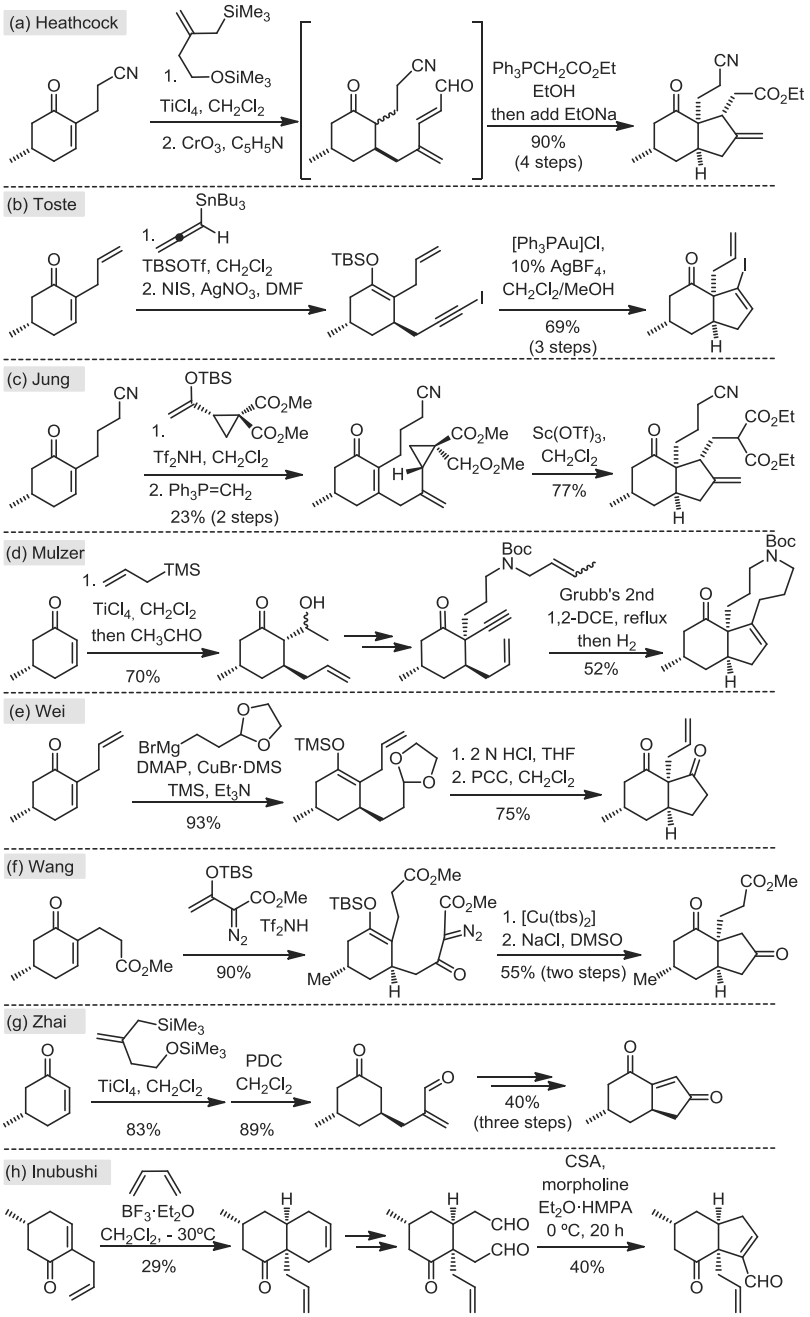
[94] Zhang, X.M.; Tu,Y-Q.;Zhang,F-M.;Shao,H.;Meng,X.*Angew.Chem.Int.Ed*.**2011**,*50*,3916–3919
[95] Li, H.; Wang, X.; Lei, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 491-495.

(iv) D→B ring assembly

The vast majority of methods to construct fawcettimine involve a conjugate addition onto a cyclohexenone followed by cyclization. Heathcock was the first to adopt this strategy using a diastereoselective Sakurai allylation and an intramolecular 1,4-Michael addition reaction (Scheme 3.5a).[84] In the first enantioselective synthesis of fawcettimine by Toste,[96] an allenyl stannane was used as the conjugate addition partner and a gold(I)-catalyzed cyclization of a terminal alkyene iodide was used to close the five membered ring (Scheme 3.5b). Jung developed a diastereospecific intramolecular attack of a silyl enol ether of a cyclopropane-1,1-diester which, upon treatment with a Lewis acid, opened with subsequent formation of the 5-membered ring to give an intermediate analogous to Heathcock (Scheme 3.5c).[97] Mulzer used a conjugate addition-enolate trapping strategy (Scheme 3.5d). Oxidation to the diketone allowed alkylation to form the quaternary centre. Finally, conversion of the ketone to an alkyne set up the key intermediate which underwent an enynene ring closing metathesis reaction to form both the 9 and the 5 membered rings of fawcettimine in a single step.[98] Wei employed addition of the Grignard of 2-(2-bromoethyl)-1,3-dioxolane followed by acid promoted Helquist annulation via desilylation, acetal removal and aldol condensation to close the hydrindanone core of fawcettimine (Scheme 3.5e).[99] Wang[100] made use of a Mukayama-Michael addition-carbene addition cyclization to construct a common intermediate that allowed the first enantioselective total synthesis of lycojaponicumin C (Scheme 3.5f). Zhai employed a Sakurai allylation via an elaborated allyl silane which after oxidation allowed the formation of the 5-membered B ring via an aldol reaction (Scheme 3.5g).[101] Finally, in the very first synthesis of fawcettimine, Inubushi used the Diels-Alder reaction to form a

[96] Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673.
[97] Jung, M. E.; Change, J. J. *Org. Lett*. **2010**, *12*, 2962-2965.
[98] Ramharter, J..; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc*. **2010**, *132*, 14338–14339.
[99] Yang, Y-R.; Shen, L.; Huang, J-Z.; Xu, T.; Wei, K. *J. Org. Chem*. **2011**, *76*, 3684–3690.
[100] Hou, S.-H.; Tu, Y.-Q.; Liu, L.; Zhang, F.-M.; Wang, S.-H.; Zhang, X-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11373–11376.
[101] Xu, K.; Cheng, B.; Li, Y.; Xu, T.; Yu, C.; Zhang, J.; Ma, Z.; Zhai, H. *Org. Lett*. **2014**,*16*, 196-199.

decalone which was then cleaved followed by a diastereoselective aldol reaction to form the 6,5-bicyclic nucleus (Scheme 3.5h).[102]



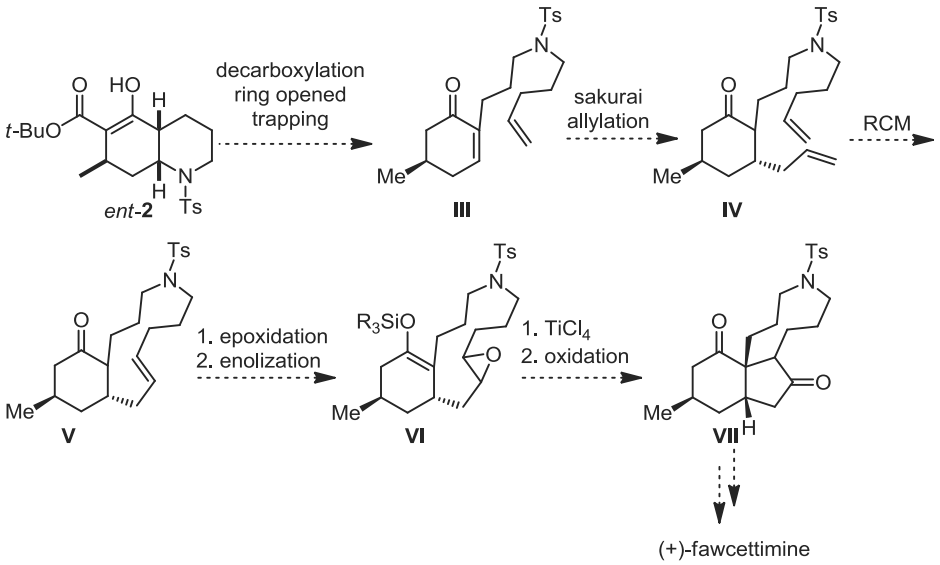
Scheme 3.5 Strategies involving a conjugate addition-cyclization.

[102] Harayama, T.; Takatani, M.; Inubushi, Y. *Tetrahedron Lett.* **1979**, *20*, 4307-4310.

3.3 Previous synthetic studies towards fawcettimine via transannular ring closure.

3.3.1 Synthetic plan

Initial attempts to construct fawcettimine from our common building block starting material were based on the proposed strategy shown in scheme 3.6.[103] Decarboxylation of *ent*-**2** and treatment under basic conditions to trap the cyclohexenone by alkylation with 4-bromopentene would give **III**. Then, Sakurai allylation to **IV** and ring closing methatesis would furnish the key precursor **V**. At this point, both the 5 and the 9 membered rings would be formed by a transannular ring closure that involves epoxidation to **VI**, thermodynamic enolization and treatment with $TiCl_4$ to induce an enol ether attack to the epoxide and furnish compound **VII**.[104] This would represent and advanced intermediate and only removal of the tosyl protecting group and reoxidation would be needed to complete the synthesis of fawcettimine.

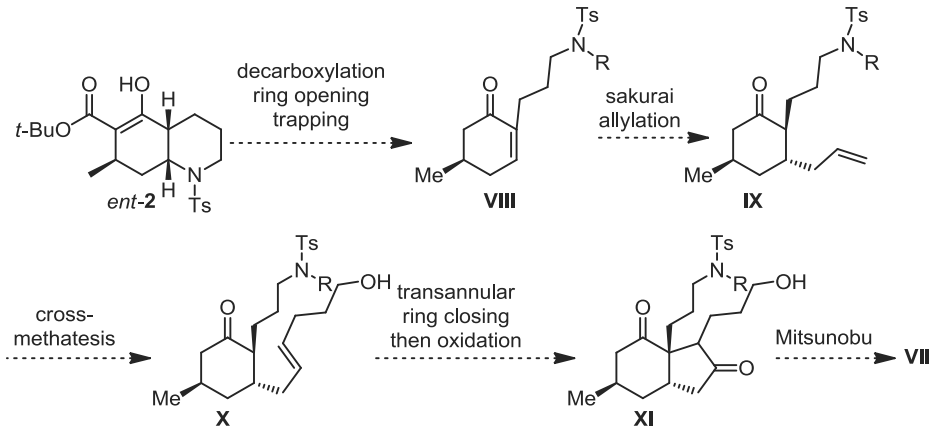


Scheme 3.6 Proposed synthesis of fawcettimine from *ent*-**2**.

Considering that the macrocycle might prevent the transannular ring closure to take place, we proposed an alternative route (Scheme 3.7). After Sakurai allylation at the ring opened product **VIII** to give **IX**, cross methatesis would be used to join the remaining carbon atoms, providing compound **X**. At this point,

[103] Gisela Saborit Masters thesis University of Barcelona, **2013**.
[104] Chen, P.; Carroll, P.J.; Sieburth, Scott S.M. *Org. Lett.* **2010**, *12*, 4510-4512.

the transannular ring closure would be used in an acyclic system. Then, an intramolecular Mitsunobu reaction of compound **XI** would furnish the same intermediate **VII** obtained before.



Scheme 3.7 Alternative retrosynthetic analysis of fawcettimine.

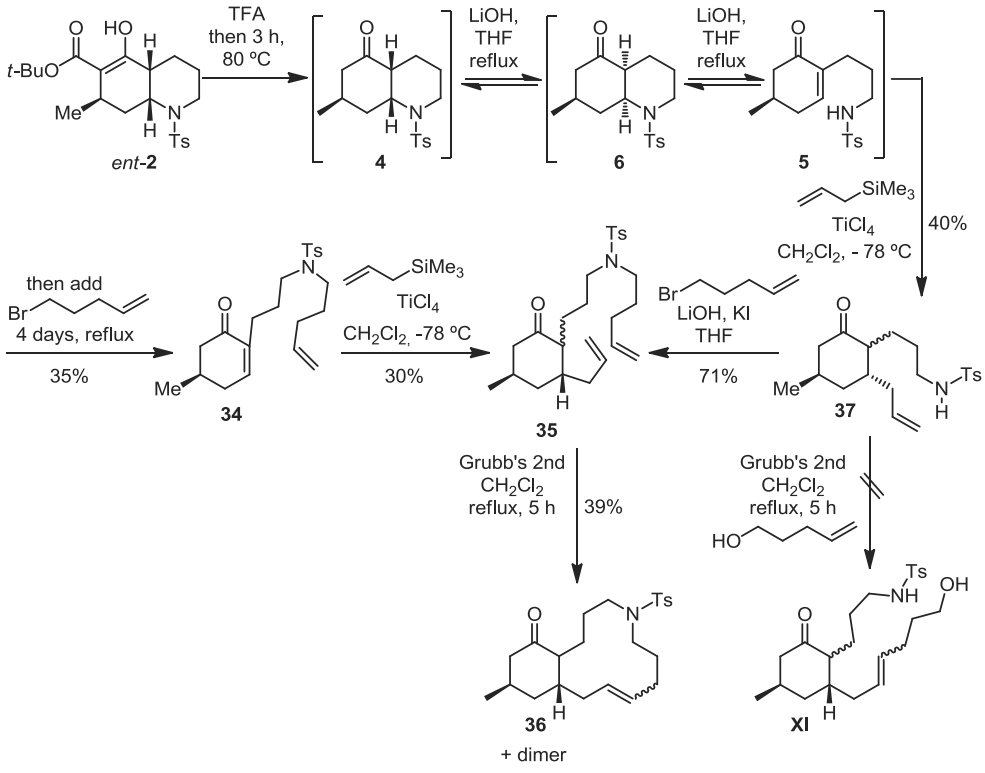
3.3.2 First generation synthesis – preliminary investigation

After decarboxylation of compound *ent*-**2**, treatment with LiOH in refluxing THF gave a mixture of compounds **4**, **5** and **6** (Scheme 3.8). Addition of 5-bromopentene allowed alkylation of the free sulfonamide of **5** to give **34** in 35% yield.[105] Sakurai allylation to the α,β-unsaturated cyclohexenone took place to furnish **35** albeit in 30% yield. Notably was that the stereochemistry at the newly formed C-C bond was in accordance to that of the natural product.[106] Although **35** was obtained as a mixture of epimers at C-2, this is inconsequential for the total synthesis since later on this center epimerizes.[84] Then, ring closing methatesis employing a protocol used within our research group[107] presumably gave the desired compound **36** but in moderate yield (39%) and accompanied by significant amounts of a dimeric compound. Due to the low material available and the resulting compound being a complex mixture of epimers at C-2 and E/Z diastereomers we could not perform a full characterization of **36**. However, analysis using HRMS indicated that we had

[105] The same equilibrium occurs when treating **4** with K_2CO_3 in refluxing acetonitrile. For alkylation of free sulfonamides with 5-bromopentene see: Sambasivarao K.; Kuldeep, S. *Eur. J. Org. Chem.* **2007**, *35*, 5909-5916.
[106] Blumenkopf, T.A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354–2358.
[107] Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernández, I.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 568–571.

obtained the cyclized product. An alternative pathway for the preparation of **35** was also investigated. Cyclohexanone **5** was isolated in 15% yield by chromatography on alumina of the equilibrium mixture. Then, a Sakurai allylation gave **37** in 40% yield followed by subsequent alkylation of the free sulfonamide with 5-bromopentene to furnish **35** in 71% yield. Note that this time, the yield of the alkylation step was higher due to the presence of KI in the reaction mixture. Although both the Sakurai allylation and the alkylation step took place in higher yields than before, the purification of the equilibrium mixture led to a low overall yield for the preparation of **35** (4% in three steps).

A brief investigation of the path b by the cross metathesis of allyl **37** with pentenol was discouraging leading to a complicated mixture of chiefly dimeric products.

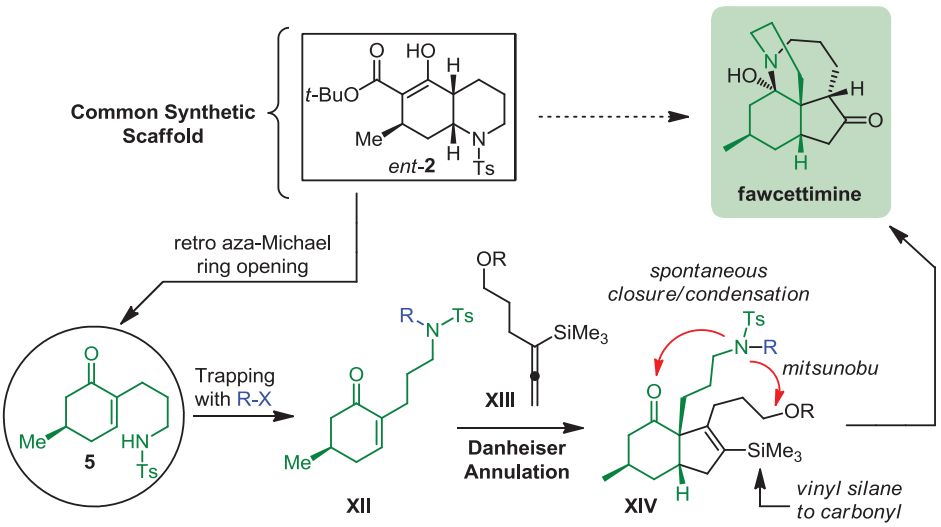


Scheme 3.8. Preliminary results to obtain (+)-fawcettimine.

After careful consideration of the problems presented by this approach, this route was not pursued further and we moved to an alternative approach to prepare fawcettimine.

3.4 Objectives

As seen in section 3.2, the defining feature of the syntheses of most of the fawcettimine-type compounds is the construction of the 5 membered ring. There then follows a number of steps to elaborate the side chain, adjust the oxidation state of the molecule, accompanied by the use of several protecting group steps, which often results in lengthy synthetic sequences. Ideally, the best strategy would be one where the coupling of two fragments assembles the complete carbon skeleton without the need for chain elongation to assemble the azonane ring. We proposed that the use of the Danheiser cyclopentene annulation reaction of cyclohexenone **XII** (formed by trapping the retro Michael equilibrium mixture with a suitable electrophile such as BnBr or PMBBr) and an allene bearing an oxygen surrogate, such as **XIII**, could furnish compound **XIV** containing the 6,5-nucleus of fawcettimine. This advanced intermediate with all the carbons in place would then only require transformation of the vinyl silane moiety into the C-5 carbonyl and closure of the 9-membered ring via a Mitsunobu coupling (Scheme 3.9)



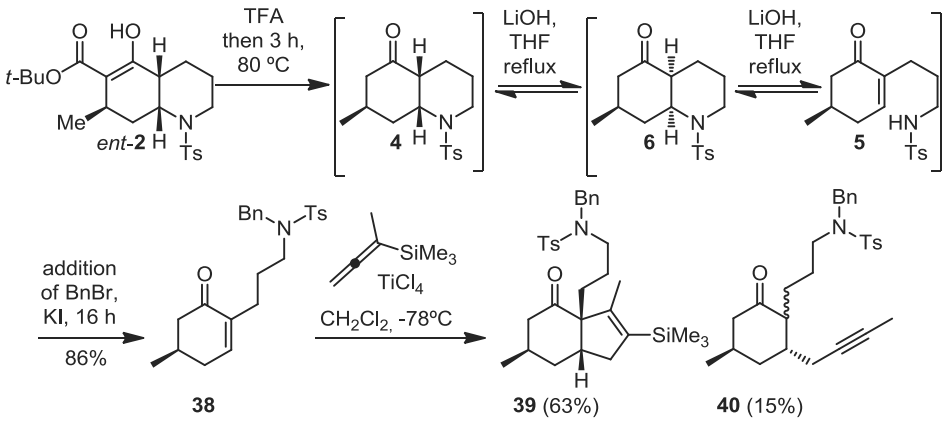
Scheme 3.9. Proposed synthetic route to fawcettimine using a Danheiser cyclopentene annulation reaction as the key step.

3.5 Synthetic approach towards fawcettimine via a Danheiser annulation strategy – Model Studies

Before preparing an allene containing all the carbons necessary for the synthesis of fawcettimine, we evaluated the viability of the Danheiser annulation with an allene that was commercially available.

3.5.1 Initial model studies - coupling with trimethylsilyl-1,2-butadiene

Again, for this route we needed to trap the ring opened cyclohexenone **5** with an electrophile. In this case, decarboxylation followed by treatment with LiOH, KI, and trapping with BnBr in refluxing THF for 16 h gave cyclohexenone **38** in 86% yield. Treatment of **38** with commercially available 3-trimethylsilyl-1,2-butadiene in the presence of $TiCl_4$ afforded the *cis*-6,5-bicylic core **39** in 63% yield as a single diastereomer (Scheme 3.10).[108] We also isolated the alkyne **40** as a mixture of diastereomers at C-2 in 15% yield.



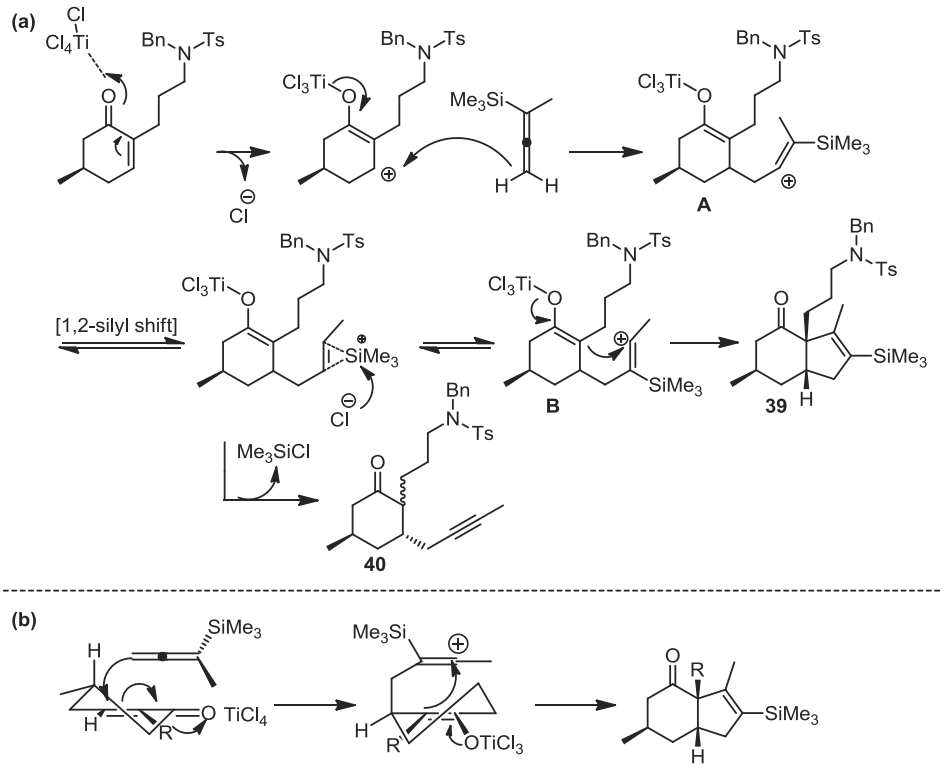
Scheme 3.10. Model Danheiser annulation of **38** and 3-trimethylsilyl-1,2-butadiene.

3.5.2 Mechanism of the Danheiser annulation

To account for the stereochemical outcome of the reaction and the formation of the byproduct **40** the mechanism of the reaction is shown below (scheme 3.11a). Initally, titanium tetrachloride coordinates to the carbonyl of the enone to give a titanium enolate bearing a carbocation at the β position. Then, the C3 carbon of the allene attacks the allylic carbocation to give **A**, which is

[108] Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604–1606.

stabilized by the adjacent C-Si bond. A [1,2]-shift of this group gives vinyl carbocation **B**, that is then trapped by the initially formed titanium enolate to produce a 5-membered ring. Formation of compound **40** is due to the interception of the trimethyl silyl cationic species via addition of chloride ion to form TMSCl. As mentioned in the previous section, compound **39** was obtained as a single isomer. The high stereoselectivity of this reaction can be explained by *suprafacial* addition to the double bond of the *α*,*β*-unsaturated compound (scheme 3.11b). [109]



Scheme 3.11. (a) Proposed mechanism for the Danhseiser annulation and (b) explanation of stereoselectivity of the reaction.

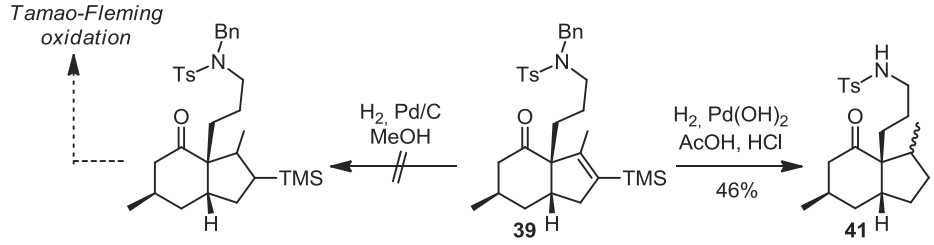
With the initial success of the reaction to rapidly assembly the D-B core of fawcettimine, we set about the next two objectives (i) conversion of the vinyl silane moiety to the C-5 carbonyl and (ii) evaluation of fully elaborated allenes

[109] Danheiser, L.R.; Takahashi, T.; Bértok, B.; Dixon, R. B. *Tetrahedron Lett.* **1993**, *34*, 3845-3848.

containing all the carbon atoms required to close the 9-membered A-C ring precursor.

3.5.3 Conversion of the vinyl silane moiety to a ketone

Initial attempts to convert the vinyl silane group to a carbonyl were focused using a Tamao-Fleming oxidation. We thought that **39** could be converted to bis ketone analogous to fawcettimine by hydrogenation to remove both benzyl and the double bond followed by Tamao-Fleming oxidation to convert the trimethyl silyl moiety to a carbonyl. However, removal of both double bond and benzyl group proved to be troublesome. Hydrogenation under neutral conditions with Pd/C only resulted in the recovery of starting material, with the double bond being surprisingly resistant to reduction. Switching to $Pd(OH)_2$ in the presence of acetic acid and HCl[110] removed both benzyl and the double bond but unfortunately also the trimethylsilyl group providing **41** in 46% yield (Scheme 3.12)

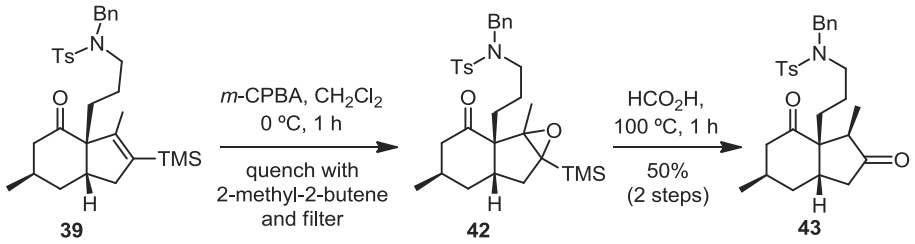


Scheme 3.12. Attempted transformation of the vinyl silane group into a carbonyl.

Eventually, the transformation of the vinylsilane moiety in **39** to the corresponding carbonyl group characteristic of fawcettimine was performed through an alternative two-step procedure (Scheme 3.13). Epoxidation of **39** with *m*-CPBA gave **42** as a mixture of diastereomers. After purification of the crude mixture the yield was quite low (21%), which made us think that the epoxide might not be stable either upon chromatography or work-up. Thus, we thought to add 2-methyl-2-butene as a scavenger to mop up any excess of *m*-CPBA and directly perform the next steps without purification of the crude epoxide.

[110] Rabasso, N.; Fadel, A. *Tetrahedron Lett*. **2010**, *51*, 60-63.

Indeed, treatment with formic acid at reflux furnished ketone **43** as 3.5:1 mixture of epimers at C(9) in 50% for 2 steps.[111]



Scheme 3.13. Transformation of the cyclic vinyl silane group into a carbonyl.

The relative configuration of the major epimer of **43** was established on the basis of the cross-peak in the NOESY spectrum that correlated the methyl group at C(9) with the methylene protons adjacent to the quaternary carbon of the side chain at C(1') (Figure 3.4). Again, the configuration at the C(9) is not relevant for the success of the approach since this stereogenic center is epimerizable, as shown by Heathcock.[84]

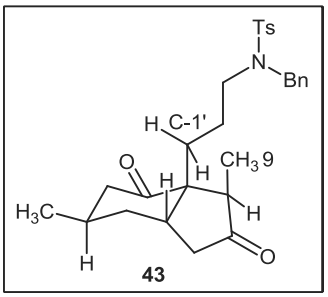
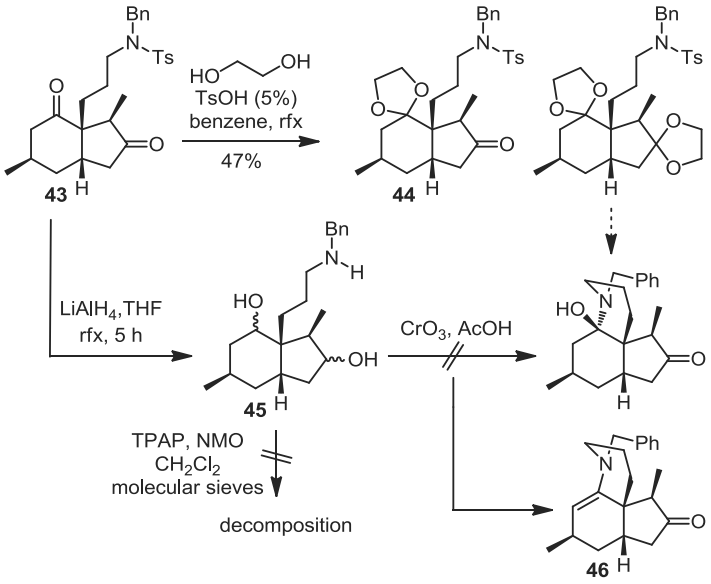


Figure 3.4. Confirmation of the stereochemistry at C-9 by NOESY correlation.

[111] a) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am .Chem. Soc*, **2011**, *133*, 736-739; b) Patil, S.G.; Nagendrappa, G. *Indian. J. Chem.* **2002**, *41B*, 1019-1024.

3.5.4 Attempted formation of the C ring using the model substrate

To further elaborate intermediate **43** we also attempted the formation of the C ring by condensation of a secondary amine onto the C-2 carbonyl (Scheme 3.14). According to Heathcock's synthesis, removal of the tosyl group with HBr was expected to give decomposition of the starting material.[84] However, in our previous work,[16,21] proposed $LiAlH_4$ as an altenative reagent to remove the tosyl group in milder conditions, but protection of both carbonyl was necessary. However, after treatment with ethylene glycol in refluxing benzene only the C-2 underwent the acetalization to give **44** since the C-8 was too encumbered.[112] Alternatively, **43** was treated with $LiAlH_4$ in THF at reflux for 5 h to give **45** as an inconsequential mixture of diastereomers. According to the synthesis of Heathcock, **45** was treated with CrO_3 in AcOH.[84] However, no hemiaminal product was detected and alkene **46** was obtained instead, although the small amount of material we had did not allow us the carry out a full characterization. We surmised that the 7-membered ring in the natural product prevents the dehydration to take place. The use of TPAP to oxidise the alcohols was not successful and a complicated mixture of products was obtained.

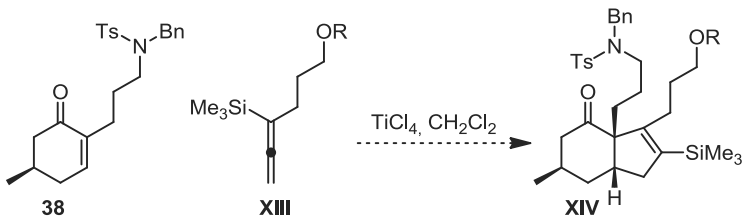


Scheme 3.14 Attempts to close the C ring.

[112] These same conditions applied to a similar substrate to **43** resulted in protection of both carbonyls. See ref. 101

3.6 Attempted total synthesis of fawcettimine

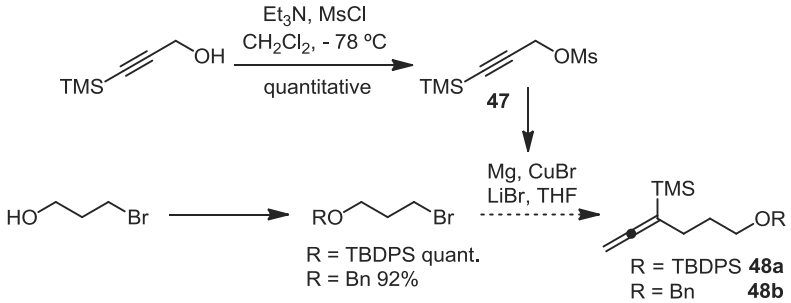
Considering the good results obtained in the model studies, we then focused on the preparation of allenes such as **XIII**, that contain all the carbons required for the synthesis of fawcettimine and a protected oxygen functionality (scheme 3.15).



Scheme 3.15. Construction of fawcettimine skeleton.

3.6.1 Preparation of fully elaborated allenes

The most direct method for the synthesis of allenes was developed by Vermeer and Westmijze,[113] which is based on the reaction of trimethylsilyl propynyl sulfonic esters, such as **47**, with organocuprates (scheme 3.16). However, all the attempts to prepare allenes **48a** and **48b** using the aforementioned procedure failed. We presume the problem arised in the formation of the organocuprate reagent.

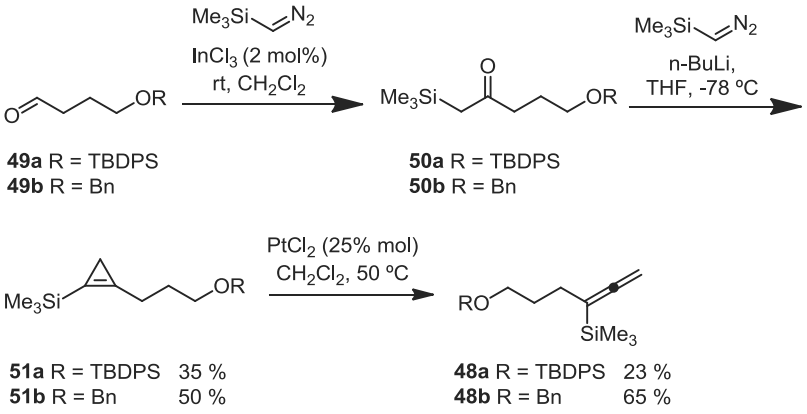


Scheme 3.16 Vermeer-Westmijze preparation of allenes.

To prepare the desired compounds we turned to the methodology of Lee *et al*.[114] which have reported the convertion of α-TMS ketones to silylated

[113] Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390-392
[114] (a) Sun C.; Li, J.; Demerzhan, S.; Lee D. ARKIVOC, **2011**, *iv*, 17-25. (b) Sun C.; Li, J.; Lee D. *J. Am. Chem. Soc.* **2010**, *132*, 6640-6641. (c) Sun C.; Li, J.; Demerzhan, S.; Lee D. *J. Am. Chem. Soc.* **2011**, *133*, 12964-12967.

cyclopropenes and then the transformation to the desired allenes via a $PtCl_2$ catalyzed rearrangement.[115] Thus, we prepared aldehydes **49a**[116] and **49b**, [117] from 1,4-butanediol which were then homologated with TMS diazomethane to furnish unstable α-TMS ketones **50a** and **50b**, respectively. These compounds were directly used in the next step due to their tendency to undergo rearrangement to silyl enol ethers or protodesilylation. Finally, cyclopropenation using TMS diazomethane furnished the silylated cylopropenes **51a** and **51b** in 35% and 50% yield, respectively (Scheme 3.17). Rearrangement of the silylated cyclopropenes to allenes was more difficult than expected and required more catalyst loading than reported. Nevertheless, allenes **48a** and **48b** were prepared in 23% and 65% yield, respectively.



Scheme 3.17 Preparation of allenes **48a** and **48b**.

3.6.2 Screening of fully elaborated allenes

With allenes **48a** and **48b** in hand, the Danheiser annulation with cyclohexenone **38** was first evaluated with silyl protected allene **48a** (Scheme 3.18a). However, after stirring for 1 h at – 78 ºC TLC and NMR analysis of the

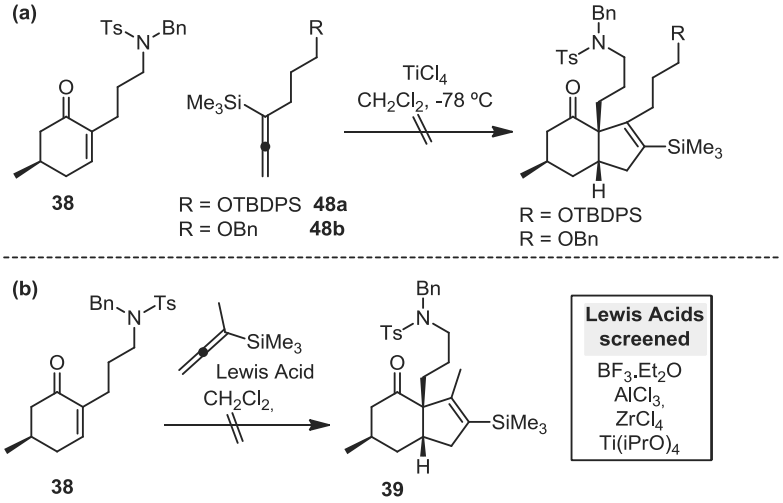
[115] A TBS analogue of allene **47a** could be also prepared more directly by the method of Evans but in our hand we could not reproduce this metohd. Evans, D. A.; Sweeney, Z. K.; Rovis, T. Tedrow, Jason S. *J. Am. Chem. Soc*. **2001**, *123*, 12095-12096.

[116] (a) Prepared in 57% yield within two steps: Logan, A.W.J.; Parker, J. S.; Hallside, M. S.; Burton J. W.; *Org. Lett*. **2012**, *14*, 2490-2424 (for the protection step) (b) Luo, J.; Li, H.; Wu, J.; Xing, X.; Dai, W-M. *Tetrahedron* **2009**, *65*, 6828–6833 (for the oxidation step).

[117] Prepared in 54% yield within two steps: See: (a) Crimmins, M.T.; DeBaillie, A.C. *J. Am. Chem. Soc.* **2006**, *128*, 4936-4937 (for the protection step) (b). Nielsen, L.; Lindsay, K.B.; Faber, J.; Nielsen, N.C.; Skrydstrup,T. *J. Org. Chem.* **2007**, *72*, 10035-10044. (for the oxidation step)

crude did not show any coupled product but decomposition of the allene. We believed that the strong Lewis acid conditions of the reaction might remove the silicon protecting group. Thus, we switched to the more robust benzyl group containing allene **48b** but this too underwent decomposition and no corresponding product could be detected. To rule out increased steric hindrance due to the amino propyl side chain or the stability of the allenes upon exposure to $TiCl_4$ being a problem we tried the Danheiser annulation using commercially available 2-cyclohexen-1-one and allene **48b**. Again, the reaction failed, which suggested that the presence of a Lewis donor interferes in the reaction mechanism.

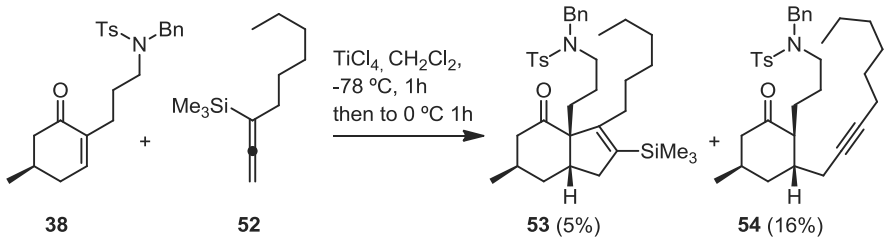
To the best of our knowledge, the Danheiser reaction has only been carried out with $TiCl_4$.[118] We wondered if the use of other Lewis acids might be possible, being both milder and having better selectivity for the desired product. From the range of Lewis acids attempted, we could only observe the formation of the desired compound with $AlCl_3$ and $BF_3{\cdot}Et_2O$ but only in small amounts and, therefore, this optimisation was not carried on further (Scheme 3.18b).



Scheme 3.18. (a) Attempt to perform the Danheiser annulation using oxygen containing allenes and (b) Evaluation of other Lewis acids in the Danheiser coupling reaction.

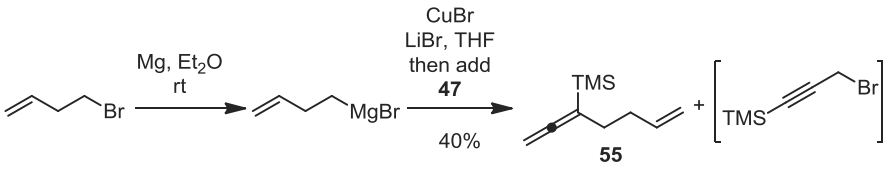
[118] The Sakurai allylation, which usually requires $TiCl_4$ as the Lewis acid, has been reported to work also with $BF_3{\cdot}Et_2O$, $AlCl_3$ and $InCl_3$/TMSCl. See: Lee, K.; Sung, S.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8648-8649.

Nevertheless, we were also intrigued if the reaction was sensitive to steric constraint. Thus, we prepared allene **52** bearing a hexyl substituent (using the method of Westmijze and Vermeer, from commercially available hexyl magnesium bromide) and treated it with cyclohexenone **38**. However, no reaction was observed after 1 h at - 78 ºC but this time the allene seemed to be stable under the reaction conditions. The reaction had to be warmed to rt and we were delighted to see that the desired 6,5-membered ring **53** was formed albeit in low yield (5%) along with increased relative proportion of the alkyne side product **54** (16%). (Scheme 3.19).



Scheme 3.19. Evaluation of the Danheiser annulation with an allene containing a non heteroatom functionalized side chain.

Encouraged by this result, we decided to try and optimise the reaction with an allene bearing alternative functionality that could be used in the total synthesis of fawcettimine. It was thought that either a trialkyl silyl group or a double bond might serve as oxygen surrogates. Given the more lengthy procedures to construct an allene with a terminal silyl group, we focused on the latter compound. Thus, allene bearing a 1-butenyl **55** was prepared using the method of Vermeer and Westmijze in 40% yield.

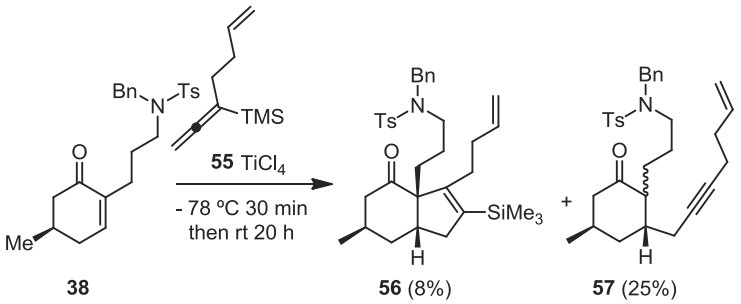


Scheme 3.20. Preparation of alternative allenes and Danheiser annulation.

A by-product was also obtained for which the structure depicted in scheme 3.20 was proposed and which could account for the moderate yield. It should be noted that these allenes were very apolar eluting with pentane alone from a

column, thus making separation by chromatography from similar compounds difficult. Moreover, these compounds were relatively volatile and care had to be taken to evaporate them under controlled conditions using only low boiling point solvent such as pentane.

With **55** in hand, we treated it with cyclohexenone **38** and $TiCl_4$ (Scheme 3.21). Again, no reaction took place at – 78 ºC and the reaction was warmed to rt and stirred overnight. However, after stirring overnight all the starting material had not been consumed but the desired bycyclic compound **56** was obtained, again in a low 8% yield. This time, the yield of the by-product **57** was increased up to 25%.



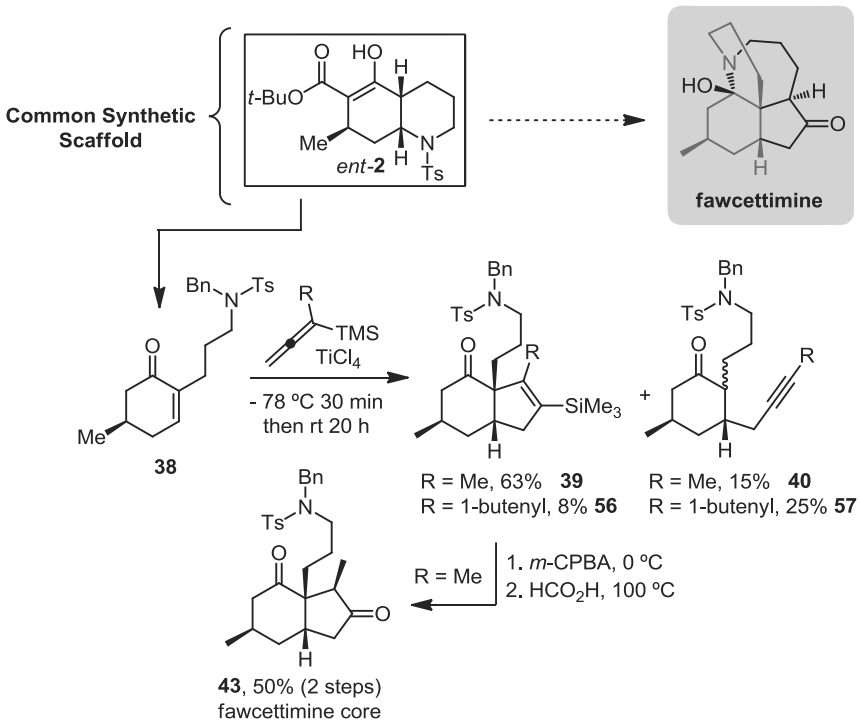
38 **56** (8%) **57** (25%)

Scheme 3.21. Evaluation of an allene containing a non-lewis acidic group.

It appears that the increase in the steric bulk of the full side chain prevents the reaction at – 78 ºC and it only goes at higher temperatures. Unfortunately, the competing undesired trapping of the $SiMe_3$ by the chloride anion is increased, in addition to degradation of the allene side chain.

3.7 Conclusions and future work

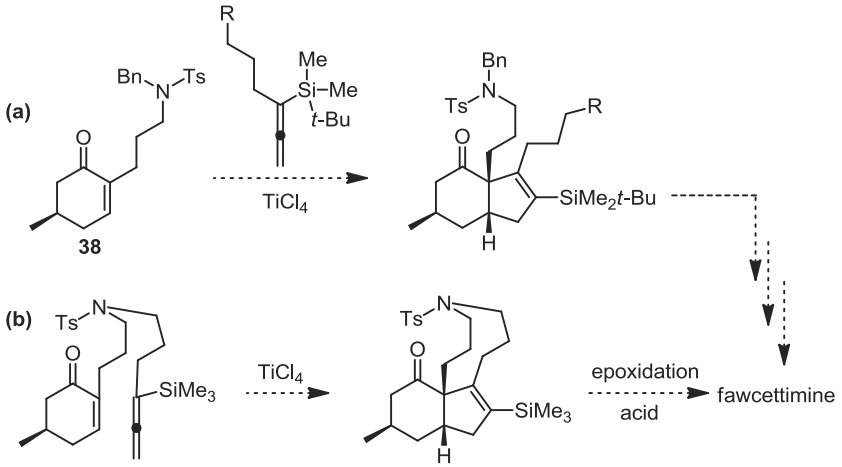
A new strategy for the construction of the 5-membered ring of fawcettimine has been developed by the use of the Danheiser cyclopentene annulation reaction. This reaction has proved to work reasonably well with the less substituted 3-trimethylsilyl-1,2-butadiene. However, addition of a fully substituted allene bearing an oxygen protected group failed to give the desired cyclopentene annulation product. The use of an oxygen surrogate such as a double bond gave the desired product, albeit in very low yield and in this case the product coming from desilylation was obtained as the major compound (Scheme 3.22).



Scheme 3.22. Summary of the Danheiser cyclopentene annulation

If the yield of the Danheiser annulation could be increased to a reasonable yield then it would open the way for one of the shortest syntheses of the fawcettimine

alkaloids thus far. The addition of an acid scavenger[119] might intercept the HCl and prevent the desilylation of the reaction intermediate. On the other hand, we propose two alternative pathways (i) changing the silyl group on the allene coupling partner by adding a *tert*-butyl substituent[119] which may stabilise the reactive intermediate enough to limit the formation of the alkyne by-product group (scheme 3.23a). (ii) Alternatively, carrying out the reaction in an intramolecular sense might increase the reactivity of the allene and would also eliminate the need for subsequent manipulations as well as protecting groups. It would be possible from this intermediate to achieve fawcettimine in just 2 steps via epoxiation, acid treatment to open the epoxide and simultaneous deprotection of the tosyl group (scheme 3.23b). The key obstacle to overcome here would be how to couple the side chain with a reactive allene unit or to form it after coupling with cyclohexenone **5**.

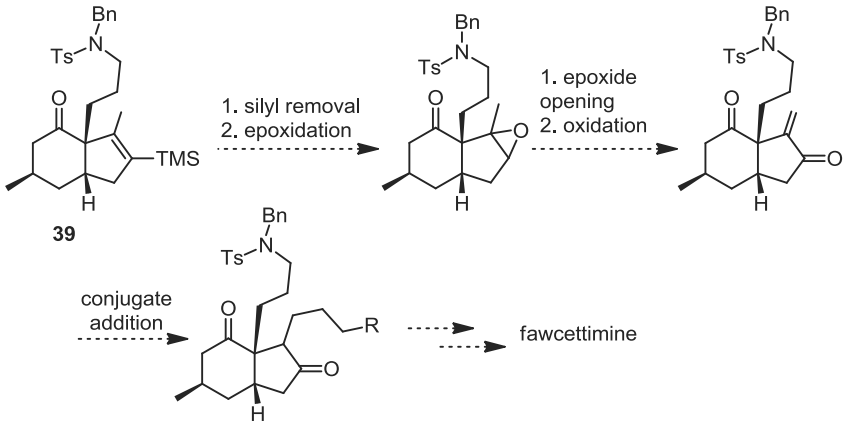


Scheme 3.23. Proposed future work to synthesize fawcettimine (a) via modified silyl group on the allene (b) intramolecular Danheiser annulation.

Finally, given the problems of increasing the length of the side chain on the allene coupling partner we considered the possibility of revisiting the model compound **39** and trying to functionalise the methyl group in some manner to allow elaboration of the side chain. Since TFA has been reported as a reagent to remove the TMS group[120] we reasoned that subsequent epoxidation and ring

[119] Becker D.A.; Danheiser R. L. *J. Am. Chem. Soc*. **1989**, *111*, 389-391.
[120] Deng, R.; Sun, L.; Li, Z. *Org. Lett*. **2007**, *9*, 5207-5210.

opening would furnish an allyl alcohol which would be oxidized to an enone and used to add the remaining carbon side chain (scheme 3.24).



Scheme 3.24 Conversion of model compound into fawcettimine.

4. Synthetic approaches towards the syntheses of (-)-lycodine and (-)-lycopodine

4.1 Introduction

Lycopodine and lycodine are the representative compounds of the lycopodine and lycodine class of the lycopodium alkaloids, respectively. Of the 300 known lycopodium alkaloids, the lycopodine class represents the most numerous group with around 100 known compounds. On the other hand, the lycodine group only comprises the 10% of these natural products with around 30 members. As commented in section 1.1.3, these compounds are derived from lycodane, which is formed by a cascade cyclization of a phlegmarine like skeleton.

Structurally, these two compounds are highly related sharing the same BCD ring system with the key difference occurring in the A ring (Figure 4.1), which in lycodine is in the form of a pyridine and in lycopodine it is attached to the β-nitrogen to form a quinolizidine system with the C ring. Due to this structural communality, many synthetic approaches towards these two classes of compounds often overlap. For this same reason, we discuss our results to assemble these structures together in this chapter.

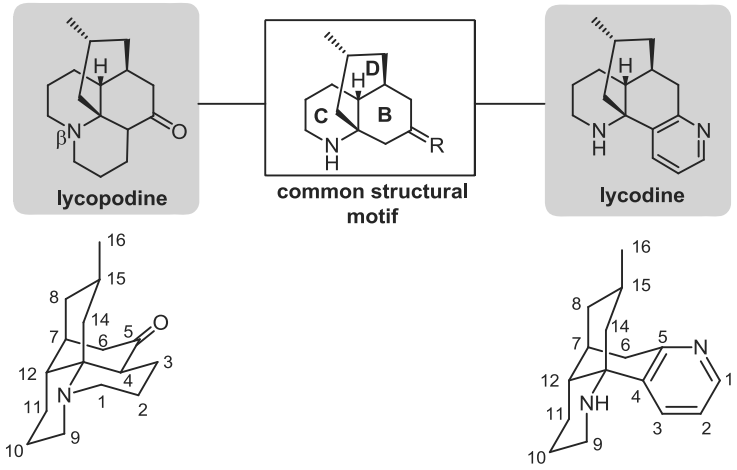


Figure 4.1. Lycopodine and lycodine and common structural motif shared by both compounds.

4.2 Classification and biological activities

Lycopodine and related compounds: The parent compound lycopodine has been found to bring about inhibition in the growth of HeLa cells[121] and also to inhibit the proliferation of prostate cancer cells.[122] Investigations indicated that lycopodine might be used for the treatment of chronic fatigue as well.[123] Analogues of lycopodine (Figure 4.2a) are formed by oxidation at different positions of the parent structure, such as in clavolonine and the lycoposerramines G and I. The carbonyl group can be also in the form of an enamide as in flabelline (via cleavage of the piperidine ring without loss of nitrogen), or esterified as in the case of lycoposerramine O. Other more complicated lycopodine structures can be formed by breaking the D ring between the C-8 and C-15 positions, as in the case of annotidine or connecting the C-4 and C-10 carbons, like in lycopecurine.

Lycodine and related compounds: Whilst not as numerous as the lycopodine group, the lycodine class are the lycopodium alkaloids which show the most promising biological activities (Figure 3.2b). Huperzine A, formed by the fragmentation of the C ring of lycodine, and huperzine B are, to date, the most outstanding compounds belonging to the lycodine group due to their ability to inhibit acetylcholinesterase (AChE) and hence can be used for the treatment of neurodegenerative diseases.[124] Huperzine A is also notable for its antioxidant and insecticidal activities.[125] Other compounds belonging to this class are flabellidine, which is closely related to flabelline, and hydroxypropyllycodine, the first lycopodium alkaloid found to possess a 19-carbon skeleton. Interestingly, in both lycopodine and lycodine class the D and the C ring are in a *trans*

[121] Mandal, S. K.; Biswas, R.; Bhattacharyya, S. S.; Paul, S.; Dutta, S.; Pathak, S.; Khuda-Bukhsh, A. R. *Eur. J. Pharmacol*. **2010**, *626*, 115–122.
[122] Bishayee, K.; Chakraborty, D.; Ghosh, S.; Boujedaini, N. *Eur. J. Pharmacol.* **2013**, *698*, 110–121.
[123] Banerjee, J.; Biswas, S.; Madhu, N. R.; Karmakar, S. R.; Biswas, S. J. *J. Pharmacogn Phytochem*. **2014**, *3*, 207-210.
[124] Liu, J. S.; Zhu, Y. L.; Yu C. M.; Zhou, Y. Z.; Han,Y. Y.; Wu, F. W.; Qi, B. F. *Can. J. Chem*. **1986**, *64*, 837–839. Despite the high activity of this compound compared to others currently on the market to treat Alzheimers, it has not been pursued because of it being in the common domain and therefore being non patentable.
[125] Banerjee, J.; Biswas, S.; Madhu, N. R.; Karmakar, S. R.; Biswas, S. J. *J. Pharmacogn Phytochem*. **2014**, *3*, 207–210.

configuration. However, in sauroxine these rings are arranged *cis*.[126] Other notable compounds of this group are complanadines A and B, which are two unsymmetrical dimers of lycodine.[127] These compounds have been found to be potential leads for the treatment of Alzheimer's disease due to its ability to enhance nerve growth factor activity.

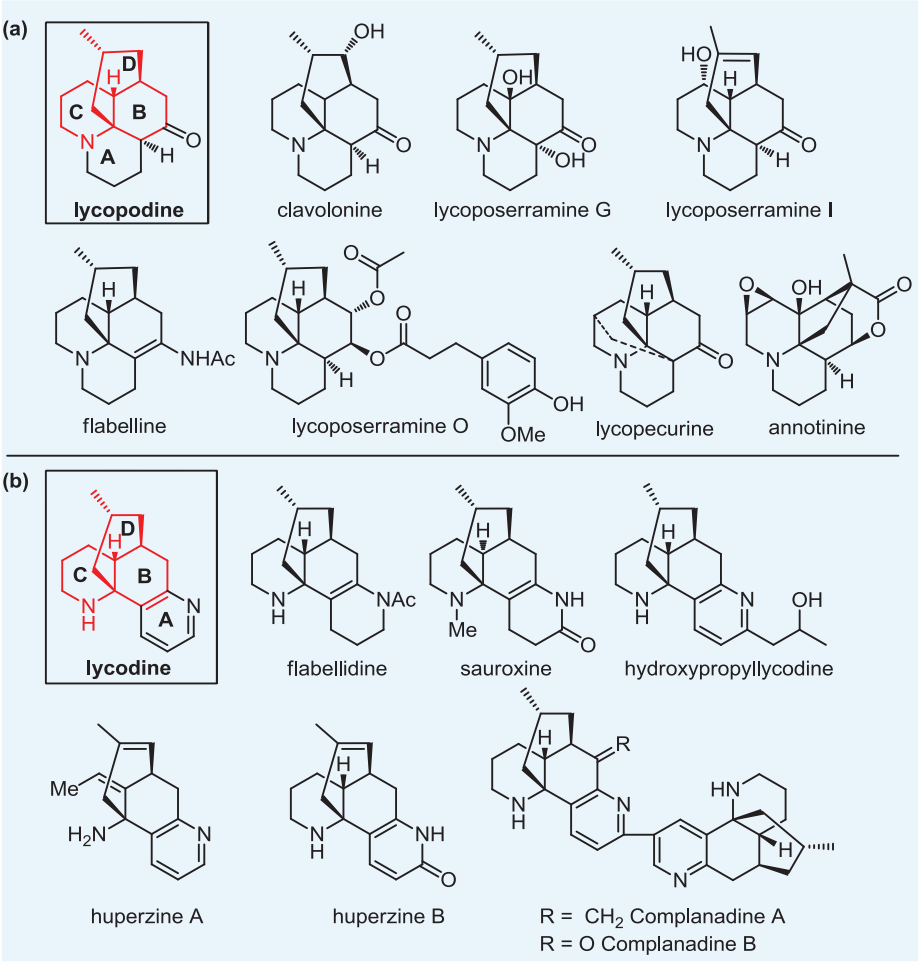


Figure 4.2 Representative compounds of the (a) lycopodine and (b) lycodine class.

[126] (a) Deulofeu, V.; De Langhe, J. *J. Am. Chem. Soc.* **1942**, *64,* 968-969. (b) Ayer, W.A.; Habgood, T. E. *Tetrahedron* **1965**, *21,* 2169-2172.
[127] (a) Complanadine A: Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *Tetrahedron Lett.* **2000**, *41*, 9069–9073. (b) Complanadine B: Morita, H.; Ishiuchi, K.; Haganuma, A.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2005**, *61*, 1955–1960.

4.3 Previous synthesis of lycodine and related compounds

Along with the phlegmarine group, the synthesis of the lycodine class has been the least studied (Table 4.1). In the late 80's, Heathcock and Schumann reported the first racemic syntheses of lycodine. The first actual enantioselective synthesis of lycodine was only recently reported by Siegel, en route to complanadine A, who used pulegone as the source of chirality.[128] Hirama also obtained enantiopure lycodine by resolution on a chiral column of a synthetic intermediate and also stablished its absolute configuration. Recently, Takayama completed the syntheses of both lycodine and flabellidine starting from an enantiopure oxazolidinone as the source of chirality. In all, 3 racemic and 5 enantioselective total synthesis of lycodine and its derivatives have been described.

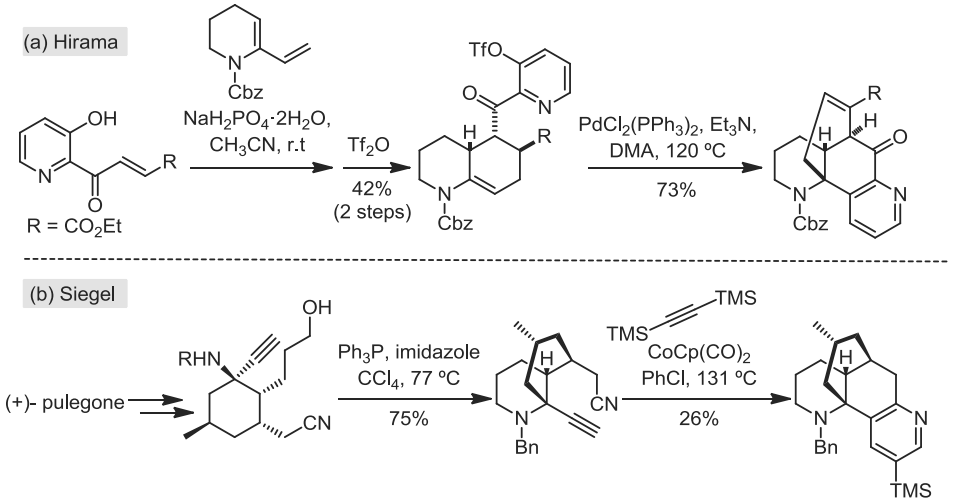
Table 4.1. Previous syntheses of lycodine type lycopodium alkaloids.

Year	*natural product*	*Author*	*ring assembly strategy*	*Racemic/ Enantiopure*
1982[129]	lycodine	Heathcock	D→C→B→A	Racemic
1983[130]	lycodine	Schumann	CD→A→B	Racemic
2010[131]	lycodine	Hirama	A→C→B→D	Racemic
2010[132]	complanadine A	Sarpong	CD→A→B	Enantiopure
2013[133]	lycodine & complanadine A	Siegel	D→C→BA	Enantiopure
2013[134]	complanadine B	Sarpong	DC→A→B	Enantiopure
2013[135]	complanadines A and B	Hirama	A→C→B→D	Enantiopure
2014[136]	flabellidine & lycodine	Takayama	acyclic→CA→BD	Enantiopure

[128] In 2010 Sarpong prepared Boc protected lycodine in enantiopure form en route to the total synthesis of complanadine A (also using pulegone as the source of chirality) although it should be noted that this intermediate was never converted to lycodine.
[129] Heathcock, C. H.; Kleinman, E.; Binkley, E.S. *J. Am. Chem. Soc*. **1982**, *104*, 1054-1068.
[130] Schumann, D.; Naumann, A. *Liebigs. Ann. Chem.* **1983**, 220–225.
[131] Tsukano, C.; Zhao, L.; Takemoto, Y.; Hirama, M. *Eur. J. Org. Chem.* **2010**, 4198-4200.
[132] Fischer D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926-5927.
[133] Siegel, D.; Yuan, C.; Chang, C-T.; Axelrod. A. *J. Org. Chem.* **2013**, *78*, 5647-5668.
[134] Newton, J. N.; Fischer, D. F.; Sarpong, R. *Angew. Chem. Int. Ed*. **2013**, *52*, 1726 –1730.
[135] Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirama, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 1722–1725.
[136] Azuma, M.; Yoshikawa, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Am. Chem. Soc.* **2014**, *136*, 11618–11621.

(i) Via cycloaddition reactions

Hirama's synthesis of lycodine involves a Diels-Alder cycloaddition of a picolinate derived α,β-unsaturated ester with an amino diene to furnish the CB skeleton. Then, an intramolecular Mizoroki-Heck reaction is used to close the B ring. These reactions allowed the construction of the full skeleton of lycodine and the remaining steps served to introduce the C-15 methyl group (Scheme 4.1a).[131] Elaboration of (+)-pulegone to the cyano alcohol shown in Scheme 4.1b was used by Siegel to then close the decahydroquinoline core of lycodine. The key reaction to form the BA rings of lycodine was a highly regioselective [2+2+2] cycloaddition of an alkyne nitrile and 1,2-bis(trimethylsilyl)ethyne.[132]

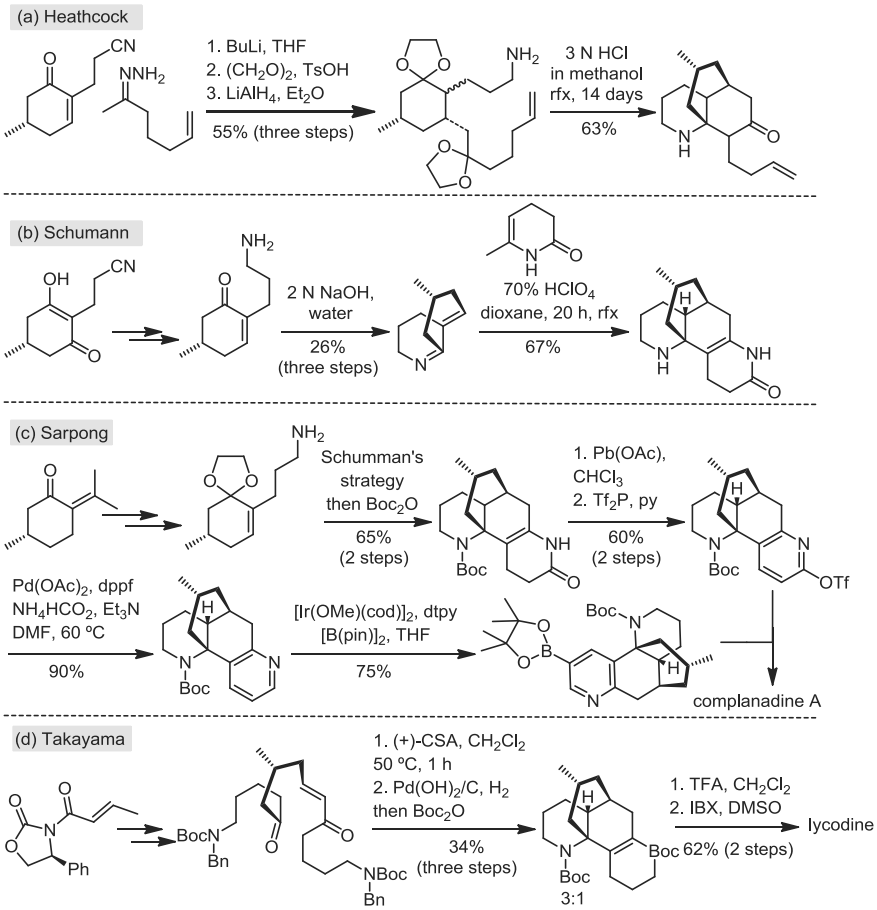


Scheme 4.1 Strategies involving cycloaddition reactions to construct the skeleton of lycodine.

(ii) D→CB ring assembly using intramolecular Mannich cyclization

All the syntheses included in this strategy use the intramolecular Mannich cyclization to close the DCB ring system of lycodine and then a final elaboration to furnish the A ring (Scheme 4.2). Of note is that all of them use a 5-methyl substituted cyclohexanone as the starting material. Heathcock was the first to develop this strategy using a conjugate addition of a hydrazone to the cyano enone shown below (Scheme 4.2a) and following treatment with a methanolic solution of HCl.[129] In his synthesis, Schumann closed the four rings of lycodine using a 1,3-annulation of an α,β-unsaturated imine and a pyridone.[130] This was prepared by reduction of a cyano enone and oxidation with PDC. Then, a base

promoted 1,2-addition of the amine onto the carbonyl afforded the key α,β-unsaturated imine (Scheme 4.2b).130 The strategy used by Sarpong to furnish the lycodine fragments of complanadine A was essentially the same as Schumann, although it was performed in enantiopure form starting from (+)-pulegone. Triflation at the C-2 position of the pyridine set the first coupling partner. Then, an iridium catalyzed functionalization at the C-3 position of the pyridine ring served to introduce the boronic ester group (Scheme 4.2c).[132] Finally, Suzuki cross coupling of both moieties gave complanadine A. Recently, the synthetic approach of Takayama to complete the synthesis of lycodine and flabellidine relied on a biogenetic inspired cascade cyclization of a chiral linear precursor derived from an oxazolidinone.[135] Oxidation with IBX of the A ring furnished lycodine (Scheme 4.2d).



Scheme 4.2 Strategies involving a Mannich cyclization

4.4 Previous syntheses of lycopodine and related compounds

Lycopodine has been the target of a number of synthetic investigations. The first syntheses of lycopodine were completed simultaneously by Stork and Ayer in 1968, although Wiesner had reported the synthesis of 12-*epi*-lycopodine one year earlier. In all, 9 racemic and 1 enantiopure total synthesis have been reported to date, with the D→C→B→A order being the most prevalent ring construction strategy (Table 4.2).

Table 4.2. Summary of the most relevant previous synthesis of lycopodine and its derivatives.

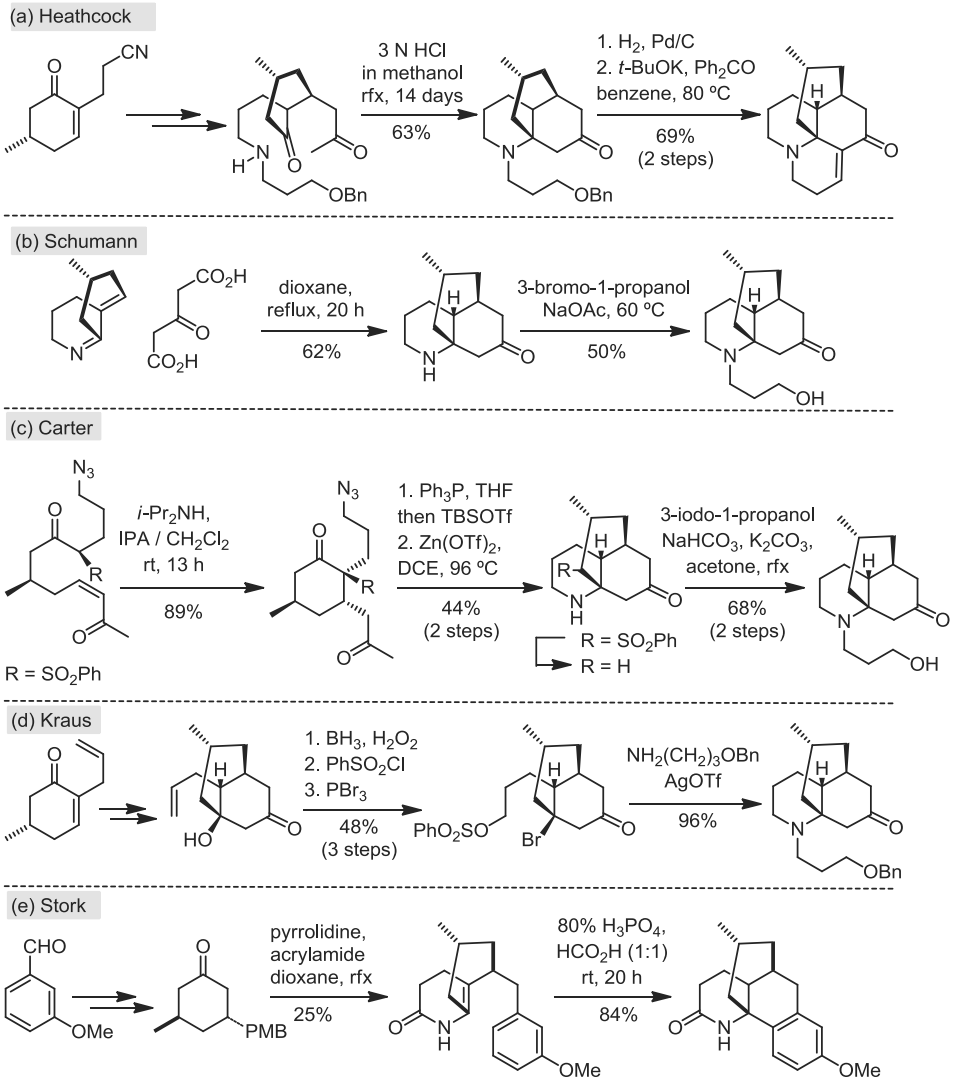
Year	*Natural Product*	*Author*	*Ring Construction Strategy*	*Racemic/ enantiopoure*
1967[137]	12-*epi*-lycopodine	Wiesner	D→C→B→A	racemic
1968[138]	lycopodine	Stork	D→C→B→A	racemic
1968[139]	lycopodine	Ayer	B→A→C→D	racemic
1978[129]	lycopodine	Heathcock	D→C→B→A	racemic
1982[140]	lycopodine	Schumann	D→C→B→A	racemic
1984[141]	lycopodine	Wenkert	C→A→B→D	racemic
1985[142]	lycopodine	Kraus	D→B→C→A	racemic
1998[143]	lycopodine	Grieco	B→A→D→C	racemic
1998[144]	lycopodine	Mori	D→C→B→A	racemic
1997[145]	lycopodine	Padwa	acyclic→CD→B→A	racemic
2005[146]	Clavolonine	Evans	acyclic→DC→B→A	enantiopure
2008[147]	lycopodine	Carter	D→C→B→A	enantiopure
2011[148]	7-hydroxylycopodine	Snider	D→C→B→A	racemic

[137] (a) Dugas, H.; Hazenberg, M E.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett*. **1967**, 4931-4936. (b) Dugas, H.; Hazenberg, M E.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett*. **1968**, 5643-5646.
[138] Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648.
[139] Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. *J. Am. Chem. Soc.* **1968**, *90*, 1648–1650.
[140] Schumann, D.; Mueller, H. J.; Naumann, A. *Liebigs Ann. Chem.* **1982**, 1700–1705.
[141] Wenkert E.; Broka, C. A.; *J. Chem. Soc. Chem. Commun*. **1984**, 714-715.
[142] Kraus, G. A.; Hon, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 4341-4342.
[143] Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128–5129.
[144] Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem. In. Ed* **1998**, 636–637.
[145] Padwa, A.; Brodney, M. A.; Marino, J. P.; Jr., Sheehan, S. M. *J. Org. Chem*. **1997**, *62*, 78-87.
[146] D. A. Evans. ; Scheerer, J. R. *Angew. Chem. Int. Ed*. **2005**, *44*, 6038-6042
[147] Yang, H.; Carter, R.G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238–9239.
[148] Lin, H-Y.; Snider, B. B. *Org. Lett*. **2011**, *13*, 1234-1237.

(i) DCB→A ring assembly strategy

As commented above, of all the syntheses of lycopodine reported so far, the main strategy that dominates is first assembly of the DCB skeleton and then closure of the A ring. The most commonly used strategy to construct the DCB skeleton of lycopodine is a Mannich cyclization, which was first developed by Heathcock (Scheme 4.3a) and involved a cyclohexanone bearing a benzyloxy propyl appendage.[129] Schumann also took advantage of his 1,3-annulation strategy using 1,3-acetone dicarboxylic acid as the nucleophile (Scheme 4.3b).[130] At this point, alkylation of the free amine with 3-bromo-1-propanol gave the same intermediate reported by Heathcock. The first enantioselective synthesis of a lycopodine related compound was that of clavolonine A by Evans and which also used a similar Mannich strategy (not shown). However, instead of starting from a racemic D ring building block like Heathcock, a chiral auxiliary strategy was used to form an acyclic chain which was then cyclised to form the D ring in enantiopure form.[146] A few years later, Carter achieved the first enantioselective synthesis of lycopodine using a Michael addition of a keto sulfone to form the D ring followed by a Staudinger reaction and a Mannich cyclization to close the C and the B rings (Scheme 4.3c).[147] In his synthesis of lycopodine, Kraus (Scheme 4.3d) also first closed the DBC system although he made use of a bridgehead carbocation to close the C ring onto a preassembled DB system.[142] Finally, Snider closed the DCB skeleton of 7-hydroxylycopodine using a Prins reaction of an alkyne onto a silyl enol ether.[148] In each of these approaches the A ring of lycopodine was closed by an Oppenauer oxidation-aldol reaction sequence. The last step of these syntheses involves a hydrogenation of the resulting enone.

An alternative approach to construct the DCB skeleton was described by Stork (Scheme 4.3e).[138] Preparation of the 5-methyl cyclohexenone shown in Scheme 4.3e was effected in 4 steps from *m*-methoxybenzaldehyde. Then, the C ring was added by treatment with pyrrolidine and acrylamide. The key reaction of this synthesis was a Pictet-Spengler cyclization of the aromatic ring onto an iminium group. The aromatic ring was then fragmented and used to form the required carbon atoms of the A ring.

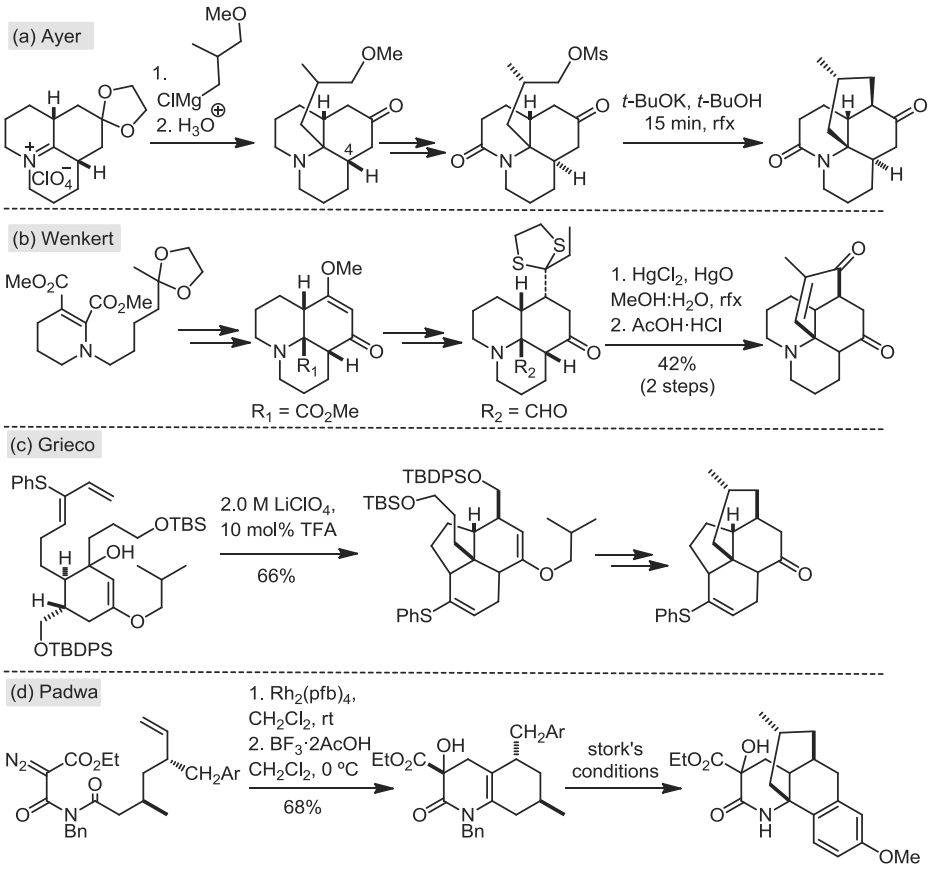


Scheme 4.3 Strategies involving the construction of the DCB ring system.

(ii) Miscellaneous strategies

Different ring construction strategies which do not follow the same disconnection logic include the synthesis of the hexahydrojulolidine by Wenkert and Ayer followed by the closure of the D ring. Ayer began with the functionalization of 6-methoxytetrahydroquinoline and then Birch reduction to furnish an iminium salt.[139] After treatment with an organometallic chain to add all the carbons necessary for the construction of the D ring, an isomerisation at C-4 was required. The D ring was closed by treatment with the mesylate with *t*-

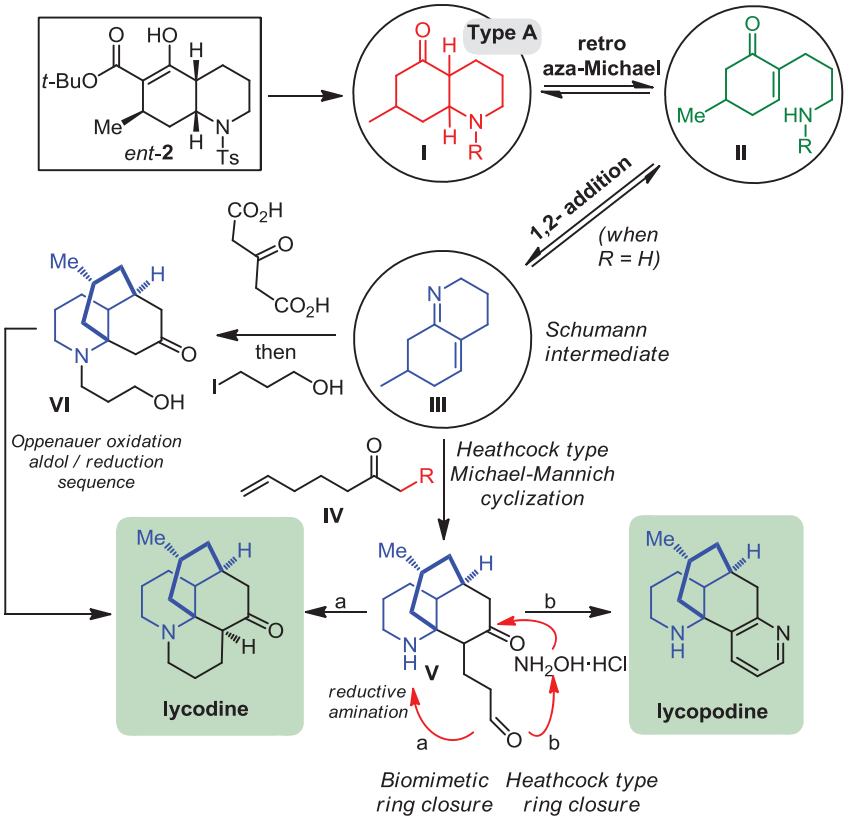
BuOK in *t*-BuOH (Scheme 4.4a). On the other hand, Wenkert constructed the ABC skeleton from an acid-induced followed by a base catalysed cyclization onto a dimethyl piperidine.[141] Again, the D ring was added via an organometallic chain followed by an aldol reaction (Scheme 4.4b). Grieco used a [4+2] cycloaddition of an oxygen stabilized allyl cation to form the BA system followed by a radical cyclization that served to install the methyl group and close the D ring.[143] Finally, the synthesis ended by a Stieglitz rearrangement (Scheme 4.4c). Padwa arrived at the same intermediate as Stork using a cycloaddition reaction of an isomünchnone promoted by rhodium (II) perfluorobutyrate and subsequent treatment with BF_3·AcOH (Scheme 4.4d).[145] Closure of the B ring was affected under the same conditions described by Stork.



Scheme 4.4 Miscellaneous ring construction strategies.

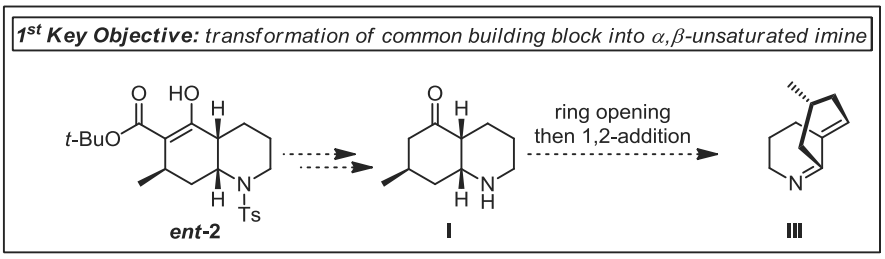
4.4 Objectives and Synthetic Plan

As described in section 1.3.2 we envisioned that the synthesis of lycopodine and lycodine could be achieved by preparing Heathcock's late stage intermediate **V**, but using our building block *ent*-**2**, to prepare imine **III** via the ring opened product **II**,[27] and a β-keto ester **IV** bearing all the carbons necessary to complete the synthesis (Scheme 4.5). In this approach, the A ring of lycopodine would be closed by a reductive amination, whereas lycodine would be formed by adding hydroxylamine hydrochloride.[129] Alternatively, a 1,3-annulation of **III** with acetone dicarboxylic acid, according to Schumann's synthesis,[130] followed by alkylation would render intermediate **VI**, from which it would be possible to close the A ring using an Oppenauer-aldol cyclization and hydrogenation of the resulting enone.



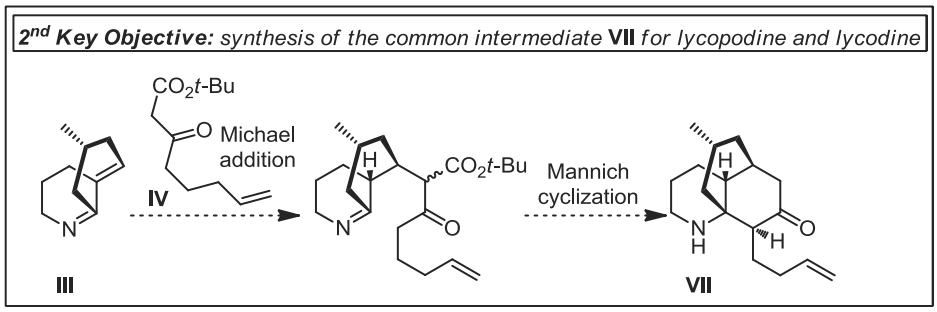
Scheme 4.5 Proposed strategy to construct lycodine and lycopodine from *ent*-**2**.

Thus, we had three key objectives. The first would be the preparation of α,β-unsaturated imine **III** in enantiopure manner from common building block *ent*-**2** (Scheme 4.6). As also discussed in section 1.3.2, we required the use of the enantiomer of the common building block employed in the phlegmarine series. We envisioned that secondary amine **I** should undergo 1,2-addition onto the carbonyl, according to previous studies carried out by Overmann, [27] to give **III**.



Scheme 4.6 Gram scale preparation of α,β-unsaturated imine **III**.

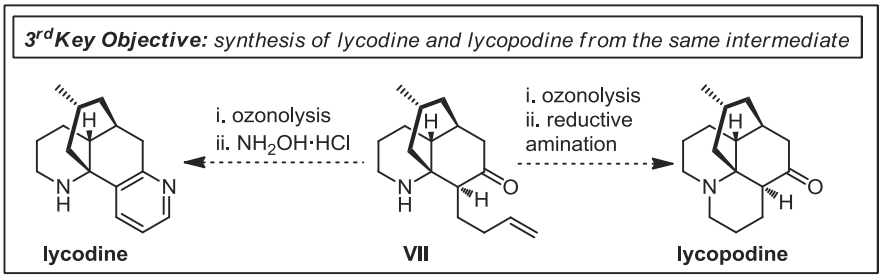
With this compound in hand, the second key objective would be the study of a tandem Mannich-Michael reaction that would lead to tricyclic amino ketone **VII**, in a similar manner to that of the syntheses of Schumann[140] and Heathcock.[129] In our case, we would use β-keto ester **IV** to add all the carbons necessary for the synthesis of both compounds (Scheme 4.7).



Scheme 4.7 Preparation of the common intermediate **VII**.

The final objective for the completion of the synthesis of both natural products would be performed from key intermediate **VII**. Using the same procedure reported by Heathcock, ozonolysis followed by treatment with hydroxylamine hydrochloride would furnish lycodine.[129]

However, we propose that reductive amination after ozonolysis of intermediate **VII** would lead to lycopodine (Scheme 4.8).



Scheme 4.8 Proposed transformation of Heathcock's intermediate into lycodine and lycopodine.

4.5 Preparation of α,β-unsaturated imine III

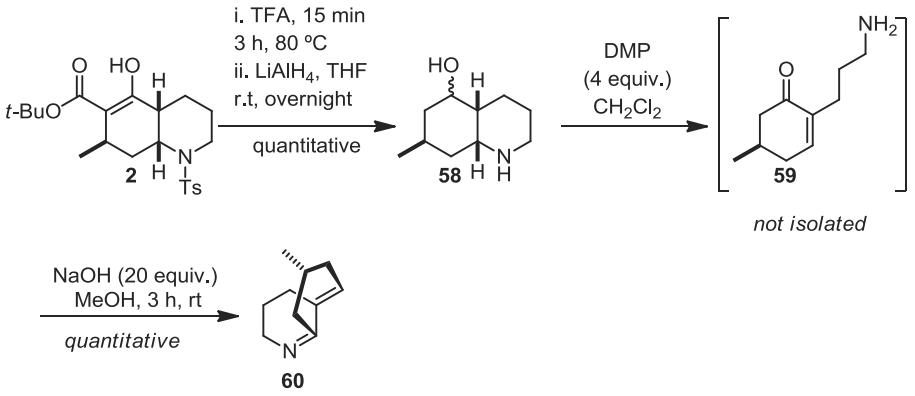
The first key objective was an effective preparation of imine **III** from common intermediate *ent*-**2**.

4.5.1 Method A: Via Oxidation/reduction sequence

Treatment of common building block *ent*-**2** with TFA followed by $LiAlH_4$ gave amino alcohol **58** quantitatively as an inconsequential mixture of 3:1 diastereomers (Scheme 4.9). Attempted oxidation of **58** with PDC[130] according to the precedent of Schumann in his synthesis of the analogous ring opened product was unsuccessful. However, changing to the milder Dess-Martin periodinane reagent, the oxidation took place although the reaction was not completed with 2 equiv of reagent. Furthermore, the decahydroquinoline compound was never observed with the oxidised compound undergoing spontaneous ring opening to cyclohexenone **59**. Initially, the requirement for such a large excess of oxidant was attributed to the high polarity of amino alcohol **58** which was only partially soluble in dichloromethane.[149] Addition of other cosolvents such as MeCN or THF increased the solubility slightly but the reaction still did not go to completion with just 2 equiv of oxidant. Similarly, the addition of water[150] to both solubilise and increase the efficiency of the Dess Martin reagent was also unsuccsseful. Finally, it was found that with the use of 4 equiv of Dess Martin the reaction was completed in 3 h. Quenching with

[149] When left to stand compound **58** formed a clear biphase when CH_2Cl_2 was added and the mixture allowed to settle.
[150] Meyer. D.S.; Schreiber, S. L. *J. Org. Chem*. **1994**,*59*, 7549-7552

isopropanol followed by stirring in methanolic hydroxide solution caused the cyclohexeneone **59** to be converted to imine **60** in 3 h. Additionally, the Dess Martin reagent was removed completely via aqueous work-up at this stage.

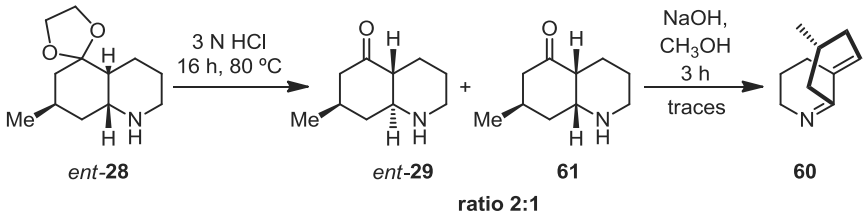


Scheme 4.9. Oxidation/Reduction sequence to access **60**.

It was not possible to determine the purified yield of **60** due to the unstable nature of this compound, which underwent decomposition by column chromatography.[151]

4.5.2 Method B: Via Acetal *ent*-28

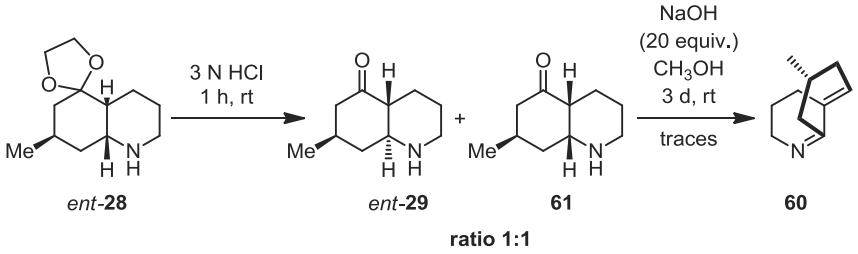
Alternatively, we thought to use the route developed in section 2.7.2 for the synthesis of *trans* decahydroquinolines (Scheme 4.10). We envisioned that exposure of the mixture of type A and type D decahydroquinolines to a methanolic solution of NaOH[27] would induce ring opening and 1,2-addition of both isomers. However, only trace quantities of the desired compound **60** were obtained after stirring for 3 h, which suggested that *ent*-**29** is too stable to undergo the ring opening reaction and that the *cis* decahydroquinoline **61** only partially underwent the reaction.



Scheme 4.10. Access to imine **60** from *ent*-**29**

[151] In his synthesis of lycopodine, Schumann (ref 140) purifies this compound by distillation but in our hands it underwent decomposition.

Attempts to minimse the amount of *trans* compound ent-**29** by deprotecting under milder acidic conditions were briefly investigated such as the use of TsOH (1.1 eq) in acetone and 1 N HCl (all at room temperature), but were unsuccessful in removing the acetal. Finally, the use of 3 N HCl for 1 h at room temperature[152] was found to remove the acetal but gave a 1:1 mixture of *ent*-**29** and **61**. Finally, it was found that if the mixture of *ent*-**29** and **61** was stirred under basic conditions for 3 d, then complete conversion to the imine **60** could be obtained (Scheme 4.11).



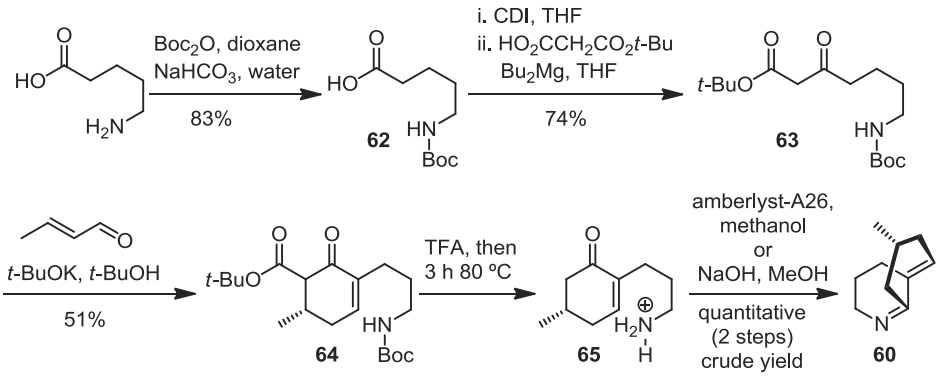
Scheme 4.11. Modified approach to **60** from *ent*-**29**.

4.5.3 Method C: Via Boc protected β-keto ester 64

A third route was examined using a Boc protected keto β-ester **64**, which had been evaluated in the original methodology towards the common building block **2**.[47] Thus, protection of 5-aminovaleric acid and subsequent homologation[153] gave **63**, that was cyclised by treatment with crotonaldehyde and *t*-BuOK in refluxing *t*-BuOH to give **64** in 51% yield.[154] We believe that the more moderate yield might be due to decomposition of the Michael adduct intermediate (not shown) under the more aggressive cyclisation conditions. Nevertheless, treatment with TFA and subsequent heating allowed removal of the *tert*-butyl ester and Boc groups to form the protonated form of **65**.[155]

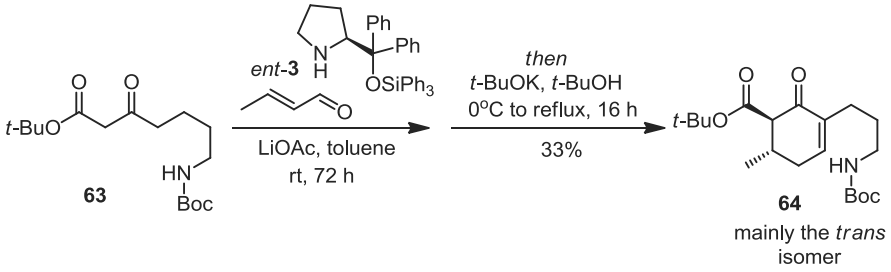
[152] After 30 minutes, traces of the acetal still remained with a 1:1 ratio. Another experiment running the reaction for 3 h gave complete deprotection and the same 1:1 ratio.
[153] Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem. Int. Ed.* **1979**, *18*, 72-73.
[154] From previous studies, we knew that the Boc group prevented the aza-Michael cyclisation to the decahydroquinoline. The reaction needed more forcing conditions to access the cyclohexenone since the reaction was now not driven to completion by the aza-Michael reaction.
[155] No aza-Michael or 1,2 addition products were observed.

Treatment of **65** with NaOH/MeOH as before or with amberlyst A-26 in methanol[156] gave key imine **60** (Scheme 4.12).[157] The formation of imine **60** was quantitative by NMR.



Scheme 4.12. Alternative preparation of imine **60**.

In order to see if we could carry out the above synthesis in an asymmetric manner we employed organocatalyst *ent*-**3** in the initial Michael step, in a similar fashion to the tosyl analog (Scheme 4.13). Unfortunately, unlike the tosyl series, the coupling did not proceed as efficiently indicating that the protecting group even though it is remote from the reactive centre, may influence the reaction in some way. After cyclisation, the yield for the synthesis of cyclohexenone **64** was a moderate 33%.



Scheme 4.13 Asymmetric synthesis of **64** via organocatalysis

[156] We examined the use of a solid supported base with the later intention of removing all work-ups from this sequence to enable the synthesis of lycopodine, in a one-pot or pot economy manner analogous to our synthesis of cermizine B (Section 1.2.3)

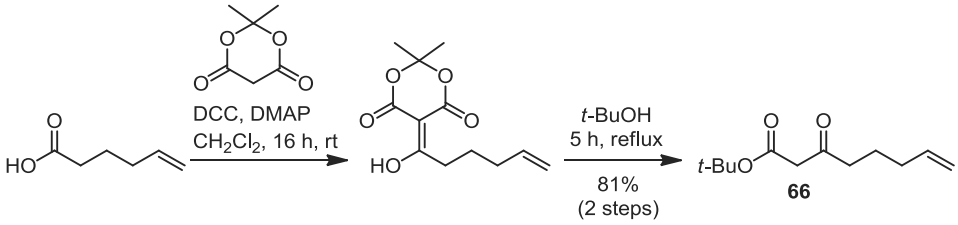
[157] Of note it is that the 1,2-addition could be also performed using LiOH in *i*PrOH or a methanolic solution of NaOH but we chose amberlyst A-26 because it can be removed by simple filtration and minimised the manipulations required for the unstable α,β-unsaturated imine **60**.

Unfortunately, after examining a number of solvent systems, we could not separate this compound by chiral HPLC to determine the enantiomeric excess of the reaction. However, given that we could access imine **60** in enantiopure form via the previous two methods, the optimisation of this approach was not developed further.

4.6 Study of the tandem Michael-Mannich cyclization to assemble the B ring

4.6.1 Preparation of β-keto ester coupling partner

In order to study the tandem Mannich-Michael reaction we needed to prepare the β-keto ester **66**. This was prepared in 81% yield from commercially available 5-hexenoic acid using Meldrum's acid followed by treatment with *t*-BuOH (scheme 4.14). [158]



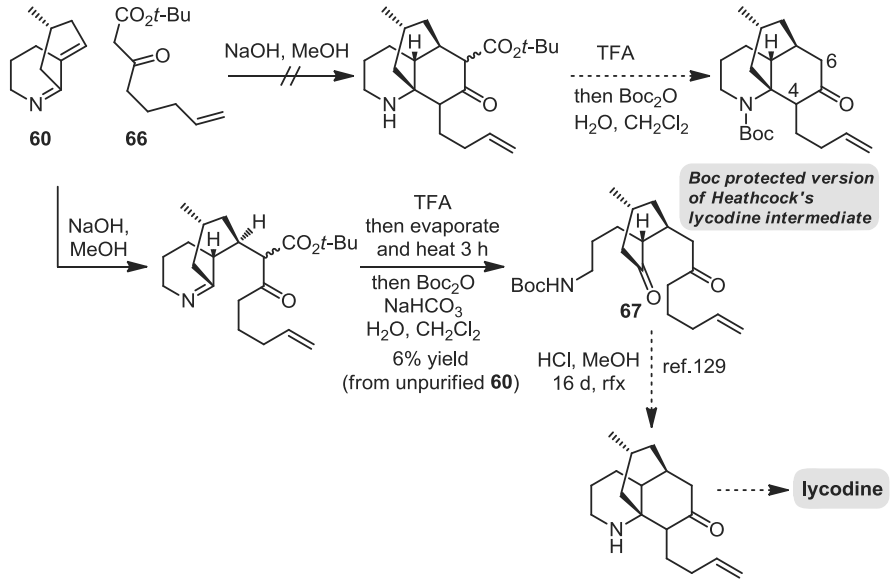
Scheme 4.14. Preparation of β-keto ester **66**

4.6.2 Coupling of β-keto ester 66

Initial studies towards the key Mannich-Michael cyclization (Scheme 4.15) were carried out using the same conditions employed to cyclise **65** to imine **60** using a methanolic solution of sodium hydroxide (20 equiv). After treatment overnight at rt, work-up revealed that the two fragments had coupled in a significant proportion as evidenced by the expected loss of the alkene peak at 5.68 ppm. The spectrum was difficult to interpret due to the presence of, what we believe, were epimers at C-6 and C-4, which is inconsequential for the completion of the synthesis as both centres are lost. The resulting amine, being difficult to purify due to its high polarity was treated with TFA and then protected with Boc_2O, which we first thought it would render a compound similar to that of Heathcock's synthesis (as outlined in Scheme 4.2a). However, instead we

[158] Kralj, D.; Friedrich, M.; Grošelj, U.; Kiraly-Potpara, S.; Mede, A.; Wagger, J.; Dahmann, G.; Stanovnik, B.; Svete, J. *Tetrahedron* **2009**, *65*, 7151-7182.

isolated a compound in 6% overall yield (over three steps from **60**), [159] which turned out to be **67**. As shown in Scheme 4.15, this compound could arise from a Michael reaction at C-5 promoted by NaOH but without the desired Mannich cyclisation step. Subsequent treatment with TFA led to decarboxylation and a free amine via equilibration from the imine, which was trapped by protection with Boc_2O.[160]



Scheme 4.15. Initial attempts to affect cyclization

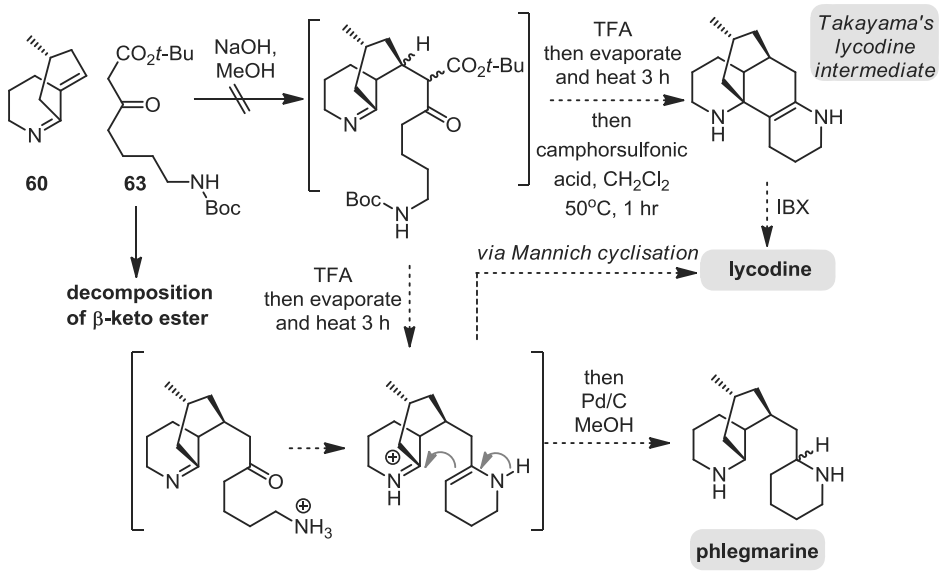
Other intermediates were also isolated but not in sufficient quantity and purity to be characterized. Compound **67** is a Boc protected version of Heathcock's cyclisation intermediate which, when heated in a methanolic solution of HCl for a prolonged time (14 d), should undergo the Mannich reaction to give the lycodine skeleton. Whilst this effectively constitutes a formal synthesis of lycodine from *ent*-**2**, we decided not pursue the completion of the synthesis of the natural product. Given the small amount of material we had in hand and the

[159] The low yield can be accounted for by the fact that much of the material remained in the imine form and was not protected. This form was likely unstable and could not be isolated by chromatography.
[160] HRMS revealed the presence of a hydroxyl group. Considering that the NMR data agrees with the structure depicted, it would be proposed an N-Boc-hydroxyl amine structure as an alternative.

lengthy cyclisation process along with similiarity to the Heathcock process we decided to try and find an alternative method to form the ring system.[161]

4.6.3 Attempted coupling of *β*-keto ester 63 en route to lycodine and phlegmarine

Given the failure of the above planned method to effect both the Michael reaction and the Mannich reaction simultaneously we began evaluating alternative approaches. During the course of this thesis Takayama published his synthesis of lycodine,[136] where the core structure was assembled rapidly (1 h reaction time) due to the presence of an enamine which greatly accelerated the Mannich cyclisation reaction.[162] We therefore tried to couple β-keto ester **63**, which we had in hand from the synthesis of imine **60** (section 4.5.3). Furthermore, it should be noted that even if the Mannich reaction failed, hydrogenation of the coupled intermediate (after treatment with acid) could give the phlegmarine skeleton in a very direct manner (Scheme 4.16).



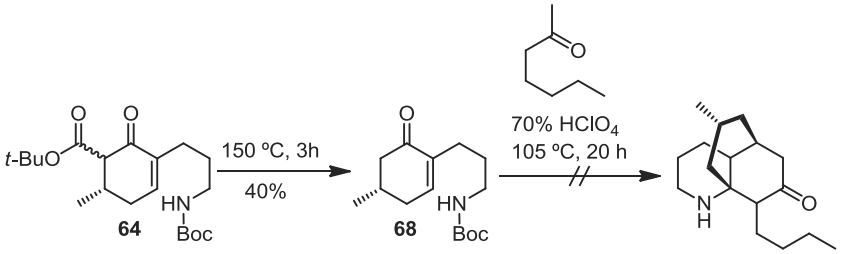
Scheme 4.16. Attempted coupling of β-keto ester **63** en route to lycodine and phlegmarine

[161] The cyclization reaction was also tried under acidic conditions with TsOH at rfx dioxane, but only decarboxylation of β-keto ester **66** back to the initial 1-hexenoic acid was observed.
[162] A similiar acceleration effect was observed in Sarpong's synthesis of complanadine A (see ref. 132)

Unfortunately, conditions which were successful for the coupling of the β-keto ester **66** bearing a simple alkene side chain, led to the rapid decomposition of **63**.[163] It should be noted that evaluation of milder conditions to effect the coupling of **60** and **66** such as LiOH or amberlyst 26 (1-3 equivalents) in *i*PrOH or MeOH led to no coupled product being observed.

4.6.4 Alternative approaches to the BCD ring system using acidic medium

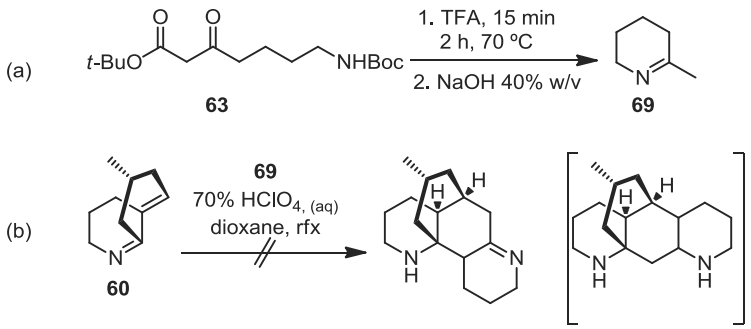
According to an adapted approach of Schumann to lycodine,[130] cyclohexenone **68** (which we prepared by heating cyclohexenone **64** at 150 ºC) and 2-heptanone[164] were treated in 70% aqueous $HClO_4$ in dioxane (Scheme 4.17). However, in our hands no reaction took place an only formation of imine **60** was observed.[165]



Scheme 4.17. Alternative construction of the BCD skeleton.

We also attempted to use other nucleophiles. Similar to Schumman's synthesis of acetylflabelline,[166] we used β-keto ester **63** to prepare the required imine **69** as a nucleophile containing a nitrogen atom (Scheme 4.18a). According to Schumann's precedent, a mixture of two isomers is formed when treating imine **60** with **69** in 70% $HClO_4$ in refluxing dioxane (Scheme 4.18b). However, no reaction took place and only decomposition of **69** was observed.

[163] It was observed by NMR that when **63** was treated with NaOH in deuterated MeOH it rapidly underwent conversion to a new product which could not be readily identified.
[164] 2-heptanone was used as cheap commercially available alternative to the required alkene product accessible by removing the ester from **66**.
[165] In his synthesis of complanadine A (Ref.132), Sarpong reported that a similar compound to **68** *in situ* undergoes a 1,2-addition under $HClO_4$ in refluxing dioxane to give α,β-unsaturated imine **60**.
[166] Schumann, D.; Müller, H-J.; Naumann, A. *Liebigs. Ann. Chem*. **1982**, 2057 -2061



Scheme 4.18 (a) Preparation of cyclic imine **69**. (b) Attempted coupling with imine **69** with **60**.

After these initial investigations we had determined that it was possible to convert our enantiopure building block *ent*-**2** into the same late stage intermediate **67** used by Heathcock in his total synthesis of racemic lycodine. The other approaches outlined in section 4.6.3 would seem the most promising for further investigation. However, time and material in hand at the end of this thesis did not allow for a more detailed investigation of the conditions to couple **60** and an analogous nitrogen containing β-keto ester coupling partner to **63**.

4.7 Formal synthesis of lycopodine

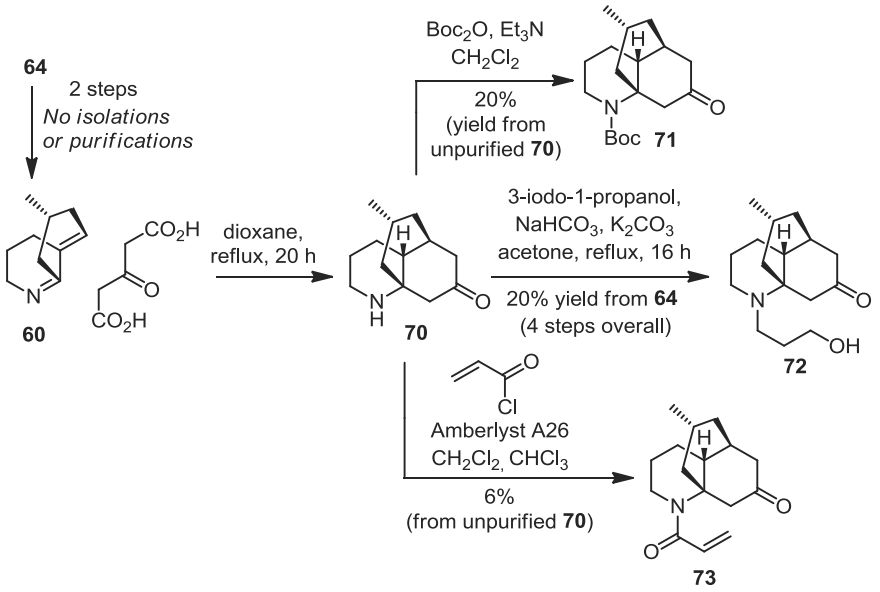
In parallel to our studies to assemble lycodine from decahydroquinoline *ent*-**2** (via imine **60**) we also sought a route to access the total synthesis of lycopodine.

4.7.1 Formation of lycopodine nucleus via coupling of 1,3-acetone dicarboxylic acid

α,β-unsaturated imine **60** is the same intermediate used by Schumann in his synthesis of lycopodine.[140] Application of his conditions - addition of 1,3-acetone dicarboxylic acid and refluxing for 20 h in dioxane- gave amino ketone **70** as a single compound (Scheme 4.19). However, it could not be readily isolated by chromatography since it underwent decomposition on purification.[167] Thus, it was protected as its Boc amine **71** in order to determine the desired structure had been formed. Having indeed determined that the core structure of

[167] The same phenonemon was observed by Carter, whose synthesis also intersected the same intermediate (see ref. 147)

lycodine and lycopodine could be readily formed, we alkylated the nitrogen of the crude product **70** with two different groups that could be used to form the final A ring of the molecule. Thus, alkylation with 3-iodo-1-propanol[147] furnished **72** in 20% yield from **64**, the same intermediate used by Schumann, Heathcock and Carter. Alternatively, acylation[168] of **70** with acryloyl chloride and Amberlyst A-26 gave acrylamide **73**, the same intermediate employed by Wiesner, in 6% yield from unpurified **70**. It should be noted that, whilst the yield of both sequences is relatively low, involved a total of 4 steps from **64** (since none of the intermediates were stable enough to isolate by chromatography), were done on a small scale and were not optimized. Despite this, the overall yield per step was around 65%, indicating that the scalability of these routes was promising and, as well, they would be suitable to enable a potential pot economy or "one-pot" approach to lycopodine, in an analogous manner as we had developed for cermizine B.[21]

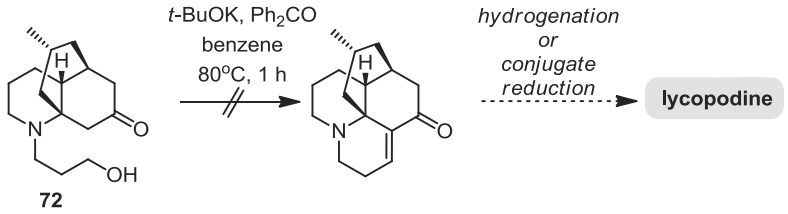


Scheme 4.19 Synthesis of lycopodine BCD skeleton.

[168]Allen, C. E.; Curran, P.R.; Brearley, A. S.; Boissel, V.; Sviridenko, L.; Press, N. J.; Stonehouse, S. P.; Armstrong, A. *Org. Lett*. **2015**, *17*, 458−460.

4.7.2 Attempted closure of the A ring of lycopodine

With two substrates in hand that had been shown by others to complete the synthesis of lycopodine, we set about trying to form the remaining A ring. The established procedure to close the remaining ring starting from pure alcohol **72** involves an Oppenauer oxidation to form an aldehyde which, due to the basic conditions of the reaction, undergoes an aldol reaction *in situ*. However, when treating **72** in a sealed tube for 1 h in benzene at 110 ºC, according to Carter's methodology,[147] we could only observe decomposition of the starting material. Alternatively, we also attempted the conditions described by Heathcock (2 h, benzene, reflux) but no reaction took place (Scheme 4.20).[129]



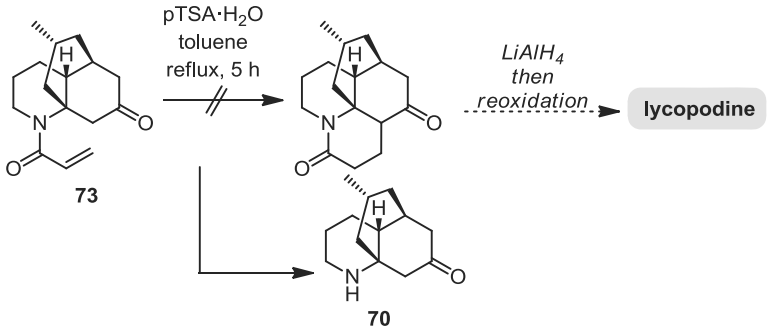
Scheme 4.20 Attempted closure of the A ring via Oppenhauer/Aldol sequence.

It should be noted that this procedure seems far from robust, with each group which tries to follow the established procedure having to modify it in order to get it to work.[169] It would seem that one of the chief problems is the retro Michael reaction of the formed aldehyde intermediate to form acrolein, which is likely decomposed rapidly under the reaction conditions before it can reform the product via a Michael reaction.[170] Having exhausted our supply of **72**, as well as examining all the known published protocols, we put this route on hold and examined if the use of the amide **73** according to Weisner would be more fruitful.

In the first synthesis of a lycopodine compound, Wiesner closed the A ring of 12-*epi*-lycopodine by an acid induced Michael addition of **73** using TsOH.[137] Unfortunately, in the published work there was not experimental detail on how to perform the reaction or NMR spectras. We therefore began trying to affect

[169] See the synthesis of 7-hydroxylycopodine (ref. 148) for detailed discussion of the problems of this reaction.
[170] Recently, Carter reported a unified synthesis of 10-oxygenated lycopodium alkaloids, where the Oppenauer-aldol reaction is performed with the use of freshly prepared *t*-BuOK. Alternative methods to close the A ring through the addition of acrolein falied. DOI:10.1021/acs.joc.6b00900

the cyclization of **73** with a catalytic amount of TsOH. However, no reaction was observed. Increasing the amount of acid until 1.0 equiv did not afford any product, even after 16 h at reflux. When the amount of TsOH was increased to 5.0 equiv, all the starting material was consumed and a new compound was observed. However, after careful chromatography, only small amount of tricycle **70** could be identified, indicating that the amide had been hydrolyzed under these rather forcing coditions (Scheme 4.21). [171]

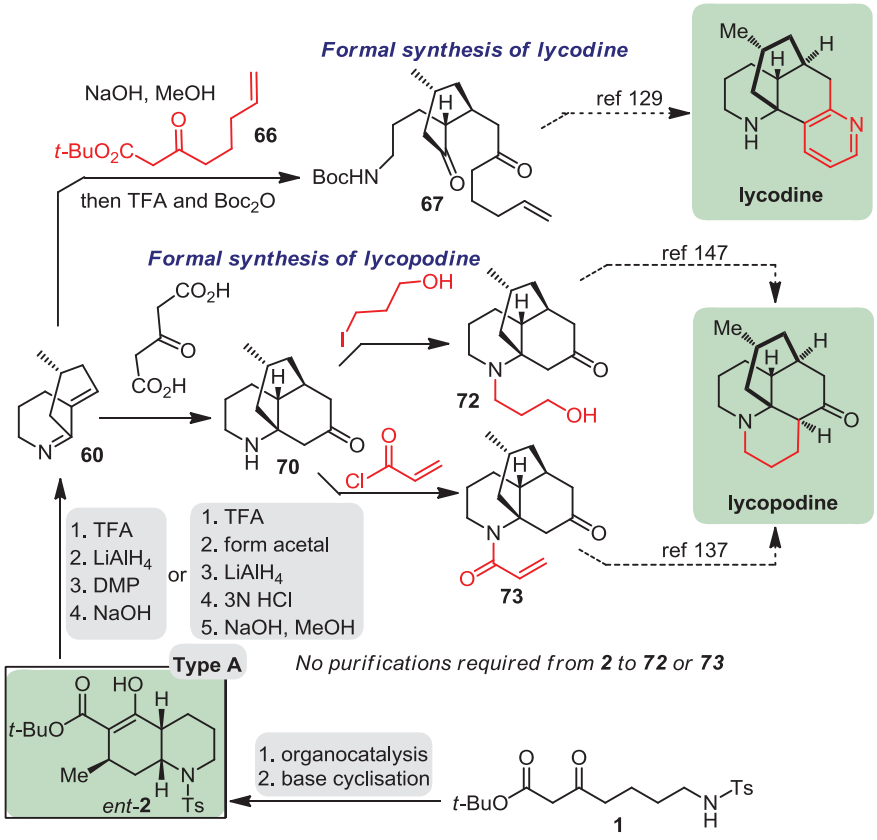


Scheme 4.21 Attempted closure of the A ring via Michael addition.

[171] See: Kim, S-W.: Bando, Y.; Horii, Z. *Tetrahedron Lett*. **1978**, *19*, 2293-2294, for closure of the A ring of anhydrolycodoline using catalytic NaOEt, dicyclohexyl-18-crown-6 in boiling DMF.

4.8 Conclusions

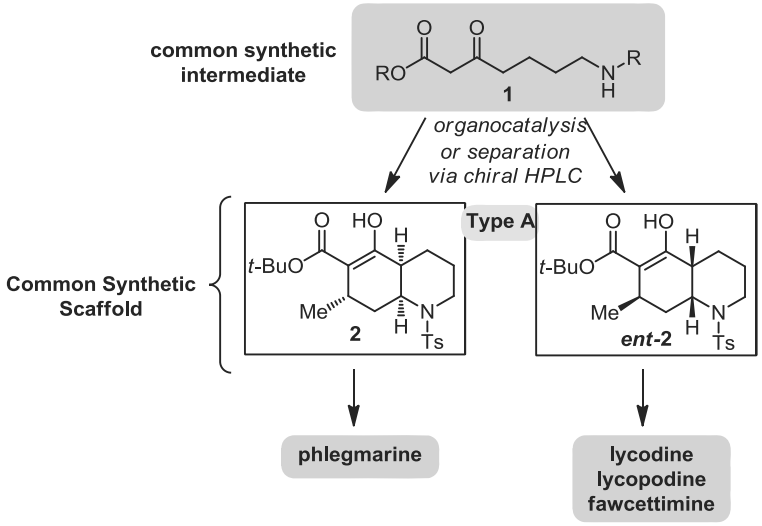
We have shown it is possible to transform decahydroquinoline *ent*-**2**, used initially in the synthesis of members of the phlegmarine group, into a common building block for the lycopodine and lycodine alkaloids (scheme 4.22). Whilst we were able to intercept key advanced intermediates of previously reported syntheses to affect formal syntheses of lycopodine and lycodine, we found difficulties in reproducing the final cyclisation. No doubt with development of optimised routes to these compounds followed by extensive investigation of the final cyclisation conditions, it should be possible to obtain routes to both lycodine and lycopodine that allow these compounds to be assembled rapidly on a large scale in a one–pot manner (Scheme 4.22).



Scheme 4.22 Transformation of decahydroquinoline *ent* -**2** into imine **60** and formal synthesis of lycodine and lycopodine.

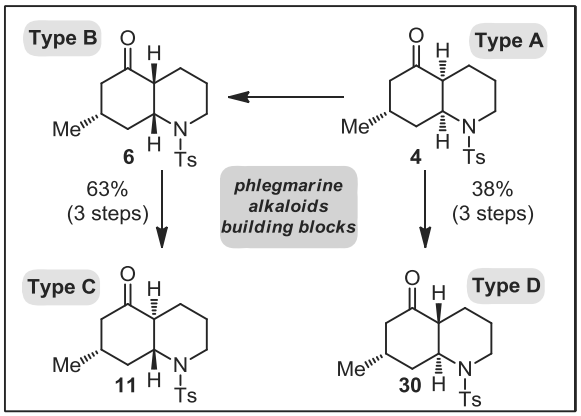
5. Conclusions

1) Both enantiomers of the decahydroquinoline building block **2** required for the synthesis of all the lycopodium alkaloids can be obtained either from organocatalysis or via large scale racemic synthesis followed by separation by preparative chiral HPLC (Scheme 5.1).



Scheme 5.1 Synthesis of decahydroquinoline building blocks for all the lycopodium alkaloids.

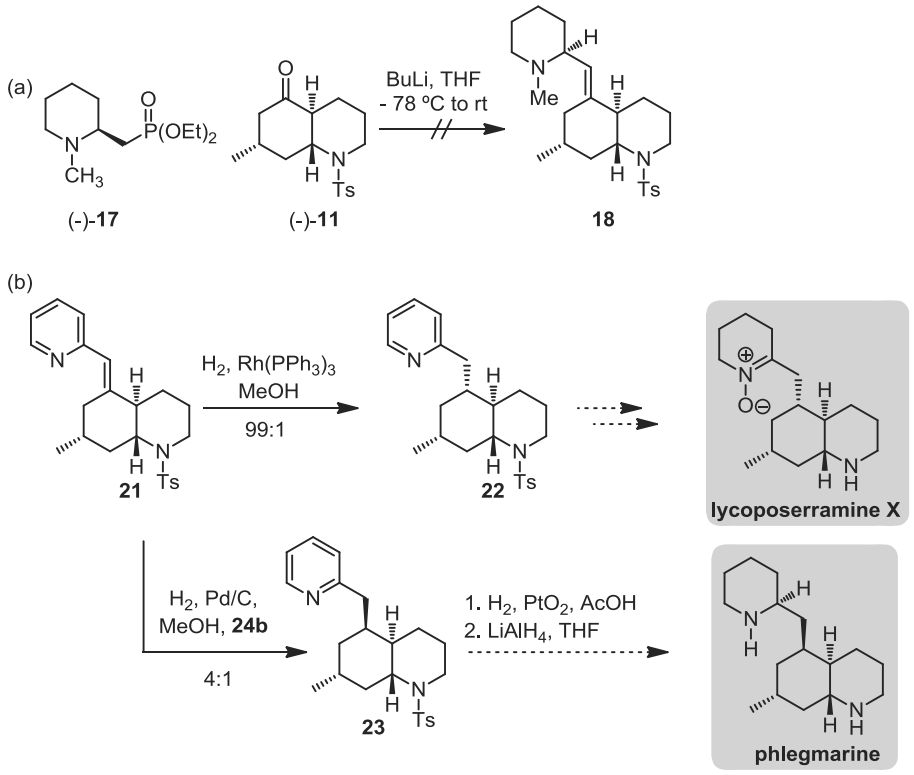
2) The four stereochemistries found in the phlegmarine alkaloid decahydroquinoline ring system were obtained from a common building block **4**, (available from **2** in one-step), through a series of equilibrations and isomerizations.



Scheme 5.2. Conversion of **2** into the four different phlegmarine stereochemical patterns A-D.

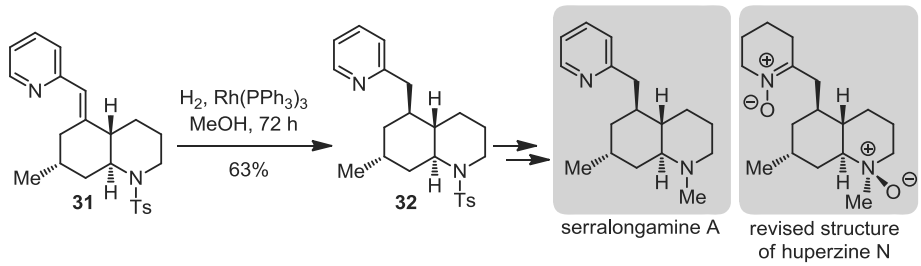
3) The N-methyl piperidine phosphonate (±)-**17** has been used to introduce in ketone (±)-**11** the piperidine ring of phlegmarine in racemic form (Scheme 5.3a). However, no reaction takes place with both enantiomerically pure starting materials, which indicates that this process is mismatched.

In a different approach towards the synthesis of phlegmarine (Scheme 5.3b), the type C intermediate **11** was coupled with a pyridine phosphonate to give **21** in 92% yield, which could be reduced in a divergent manner depending on the conditions used. Reduction with Wilkinson's catalyst gave compound **22** with almost perfect selectivity giving the stereochemistry in the phlegmarine alkaloid lycoposerramine X. On the other hand, reduction with Pd/C in the presence of the chiral phosphoric acid **24b** gave the opposite stereochemistry which is found in the natural product phlegmarine.



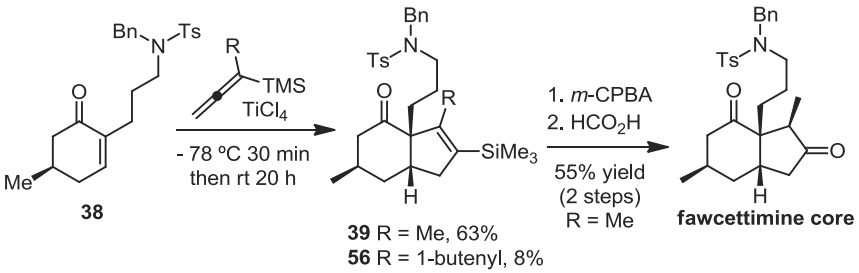
Scheme 5.3. (a) Attempted synthesis of phlegmarine via addition of a piperidine coupling partner. (b) Divergent reduction strategies of vinyl pyridine **21**.

4) Hydrogenation of vinyl pyridine **31** with Wilkinson's catalyst gave **32**, in complete diastereoselectivity. Subsequent interchange of the tosyl group for a methyl allowed for the first total synthesis of (±)-serralongamine A. Subsequent oxidation then allowed the synthesis of the revised structure of (±)- huperzine N (Scheme 5.4).



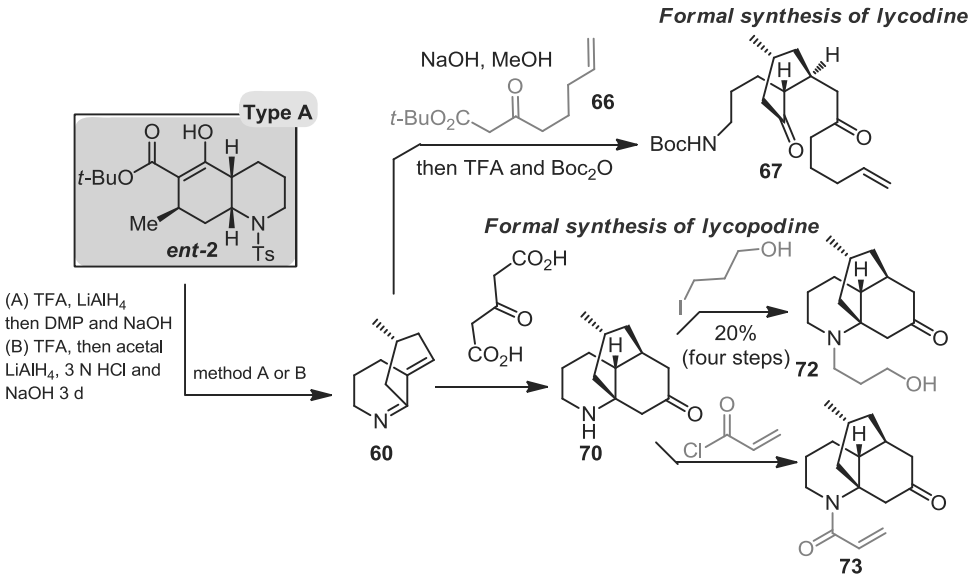
Scheme 5.4 First total synthesis of serralongamine A and the revised structure of huperzine N.

5) A new strategy for the construction of the 5-membered ring of fawcettimine also developed by the use of the Danheiser cyclopentene annulation reaction. Ring opening of the common building block *ent*-**2** and trapping the nitrogen gave cyclohexenone **38**, which upon reaction with 3-trimethylsilyl-1,2-butadiene gave **39**. Subsequent epoxidation and acid treatment allowed conversion of the vinyl silyl moiety to the substituted cyclopentanone ring system found in the natural product. Whilst the Danheiser reaction worked reasonably well with the less substituted 3-trimethylsilyl-1,2-butadiene, unfortunately addition of a fully substituted allene bearing an oxygen protected group failed to give the desired cyclopentene annulation product. The use of an oxygen surrogate such as a double bond gave the desired product, albeit in very low yield, and in this case the product coming from desilylation was obtained as the major compound (Scheme 5.5).



Scheme 5.5 Summary of the Danheiser cyclopentene annulation.

6) It was possible to transform the enantiomeric decahydroquinoline *ent*-**2** into a common intermediate **60** for lycopodine and lycodine using two different methods (scheme 5.6). By performing a Michael addition of β–keto ester **66** to α,β-unsaturated imine **60**, the same common intermediate **67** used by Heathcock to perform the key intramolecular Mannich cyclization was obtained. Alternatively, if **60** was reacted with a keto diacid followed by alkylation or acylation of the nitrogen, then it was possible to obtain the two intermediates **72** and **73**, which have both served as advanced intermediates to lycopodine.

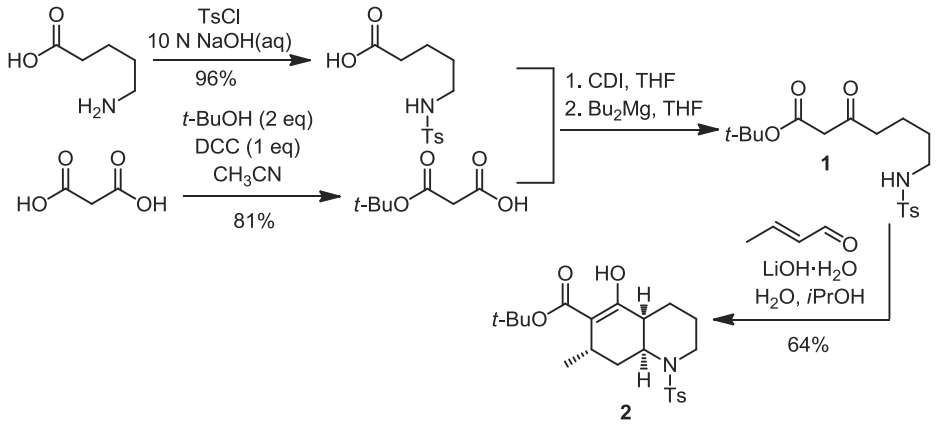


Scheme 5.6. Transformation of decahydroquinoline *ent*-**2** into α,β-unsaturated imine **60**. Formal syntheses of lycodine and lycopodine.

6. Experimental section and spectra

General: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical thin-layer chromatography was performed on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located with 1% aqueous $KMnO_4$ or hexachloroplatinate. Chromatography refers to flash chromatography and was carried out on SiO_2 (SDS silica gel 60 ACC, 35-75 µm, 230-240 mesh ASTM) or Al_2O_3 (Aluminium oxide neutral, 63 – 200 µm). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvent was accomplished with a rotatory evaporator. NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Varian VNMRS 400. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR data assignments are supported by gCOSY and gHSQC experiments. The preparative HPLC separation of compound **2** was performed with a Chiralpak® IA column, using Hexane/*i*-PrOH / $CHCl_3$ (90:5:5). Flow rate = 0.9 mL/min, λ = 254 nm.

Preparation of *rac*-2 and (+)-2



5-(4-Methylphenylsulfonamido)pentanoic acid

To a solution of 5-aminovaleric acid (12.0 g, 0.10 mol) in water (132 mL), was added a solution of 10 N NaOH (24 mL) followed by tosyl chloride (19.51 g, 0.10 mol) in 3 portions over 15 min. The reaction mixture was heated at 120 ºC for 3 h. After cooling to rt, the reaction mixture was extracted with Et_2O (2 × 100 mL) and the aqueous phase acidified to pH = 1 with 4 N HCl. The acidic phase was extracted with EtOAc (3 × 100 mL), dried, and concentrated to give the title product (26.45 g, 96%) as a white solid, which was used in the next step without purification.

Mono-tert-*butylmalonate*

In a 2 L 3-necked round bottom flask charged with malonic acid (25.80 g, 0.25 mol), *t*-BuOH (47 mL, 0.50 mol) and acetonitrile (740 mL) was added DCC (56.3 g, 1.1 eq) dissolved in acetonitrile (500 mL) through an addition funnel at 0 ºC under argon. The mixture was kept at that temperature for 90 min, filtrated through celite and concentrated. The residue was dissolved in Et_2O (250 mL) and extracted with saturated aq $NaHCO_3$ solution (2 x 250 mL). The aqueous was cautiously acidified until pH = 1 with 4 N HCl and extracted with EtOAc (2 x 300 mL). The organics were dried, filtered and concentrated to give mono-*tert*-butylmalonate (32.1 g, 81%).

tert-Butyl 7-(4-Methylphenylsulfonamido)-3-oxoheptanoate (1)

Dibutyl magnesium (Aldrich, 1 M in heptanes, 74 mL, 74 mmol) was added to a solution of mono-*tert*-butylmalonate (35.6 g, 0.22 mol) in THF (640 mL) in a 2 L flask. The mixture was stirred for 15 min at -78 ºC, warmed to rt and stirred for 1 h. Concurrently, in a 1 L flask carbonyldiimidazole (CDI) (18.02 g, 0.111 mol) was added to a solution of 5-(4-Methylphenylsulfonamido)pentanoic acid (20 g, 73.7 mmol) in THF (640 mL). The mixture was stirred for 15 min at 0 ºC, warmed to room temperature and stirred for 45 minutes before being added dropwise to the magnesium malonate solution via canula. The resulting mixture was stirred overnight at room temperature and part of the solvent was evaporated. The solution was then quenched with 10% citric acid (200 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ solution (150 mL), brine (100 mL), dried and concentrated to give crude **1**,[172] which was used in the next step without further purification.

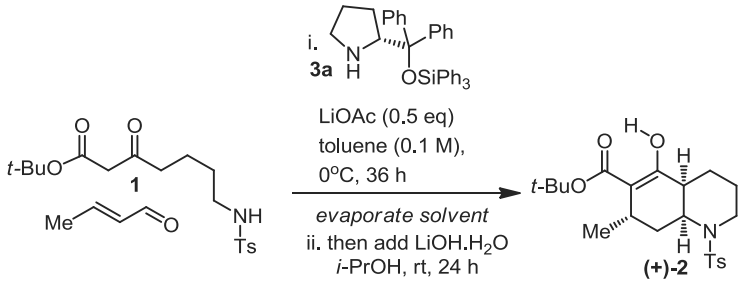
(4a*RS*,7*RS*,8a*RS*)-*tert*-Butyl 7-Methyl-1-(4-methylphenylsulfonyl)-5-oxo-decahydroquinoline-6-carboxylate (*rac*-2)

To a cooled (0 ºC) solution of the previous crude in *i*PrOH (245 mL) and H_2O (13.4 mL, 0.741 mol, 10 equiv) was added crotonaldehyde (5.71 g, 81.5 mmol, 6.8 mL, 1.1 equiv) followed by $LiOH{\cdot}H_2O$ (3.11 g, 74.1 mmol, 1.0 equiv). The reaction mixture was allowed to come to rt and stirred for 36 h, quenched with saturated aq NH_4Cl solution (50 mL), and the layers were separated. The aqueous was extracted with EtOAc (3 x 200 mL) and the organics were combined, dried, and concentrated. The crude material was filtered through a pad of silica which was washed with 25% EtOAc/hexanes (1.0 L first fraction 17.1 g, 1.0 L second fraction 5.5 g and 1 L third fraction 2 g) and 100% EtOAc fourth fraction (1 L, 5 g). Fraction three (2 g) contained a mixture of ring opened-ring closed products, which was reacted with $LiOH{\cdot}H_2O$ (200 mg, 4.74 mmol, 1 equiv), H_2O (0.85 mL, 47.4 mmol, 10 equiv) and *i*PrOH (15.8 mL) at rt overnight. Fraction four (5 g) belongs to the ring opened non-dehydrated product, which was reacted in the same conditions as described before ($LiOH{\cdot}H_2O$ (474 mg, 11.3 mmol, 1.0 equiv), H_2O (2.03 mL, 0.113 mol, 10 equiv)

[172] For NMR data see, ref. 16

and *i*PrOH (38 mL). Both crude extracts were purified by chromatography (2.5→5→10→25% EtOAc in hexanes) to give ***rac*-2** (5,24 g). The overall yield for ***rac*-2** was 64 % (20.1 g).[173]

(4a*S*,7*S*,8a*S*)-*tert*-Butyl 7-Methyl-1-(4-methylphenylsulfonyl) -5-oxodecahydro quinoline-6-carboxylate (+)-2

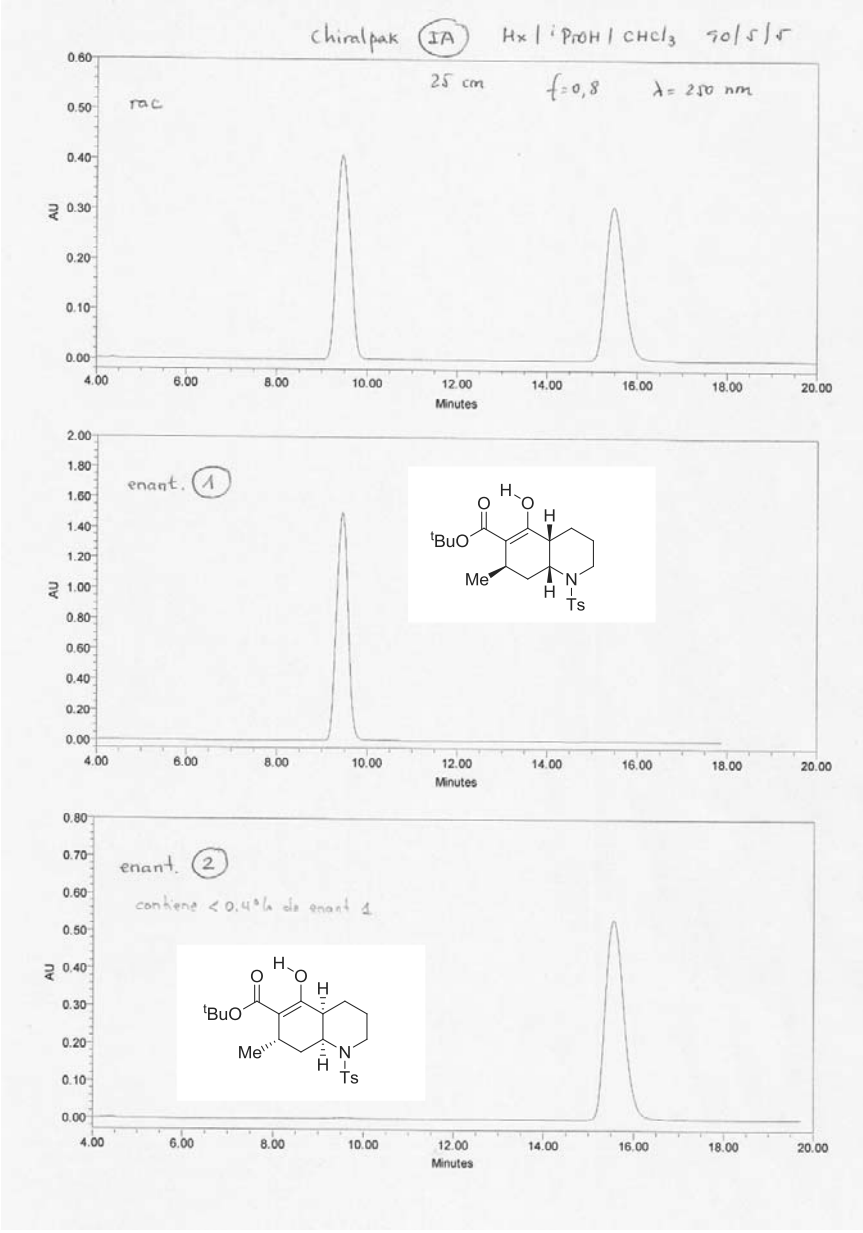


To a solution of **1** (5.00 g, 13.5 mmol) in toluene (125 mL) at 0 ºC was added crotonaldehyde (1.04 g, 1.23 mL, 14.9 mmol, 1.1 equiv), triphenylsilyl ether **3a** (346 mg, 0.67 mmol, 0.05 equiv), LiOAc (445 mg, 6.76 mmol, 0.5 equiv) and the resulting mixture was stirred for 48 h at 0 ºC. Excess crotonaldehyde and toluene were removed by evaporation before addition of *i*PrOH (12.5 mL), $LiOH \cdot H_2O$ (567 mg, 13.5 mmol, 1.0 equiv) and H_2O (2.4 mL, 0.135 mol, 10 equiv) at 0 ºC and the resulting solution stirred for 24 h at rt. The solvent was removed and the crude mixture was purified by chromatography (5→10→25→50→100% EtOAc/hexane) to give (+)-**2** (3.9 g, 65%) in 90% ee.[174]

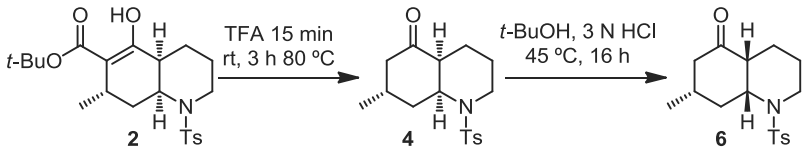
[173] Working on a 5 g scale from **1**, *rac*-**2** was obtained in 79% yield.
[174] For NMR data, see ref. 16

Chromatography resolution of *rac*-2

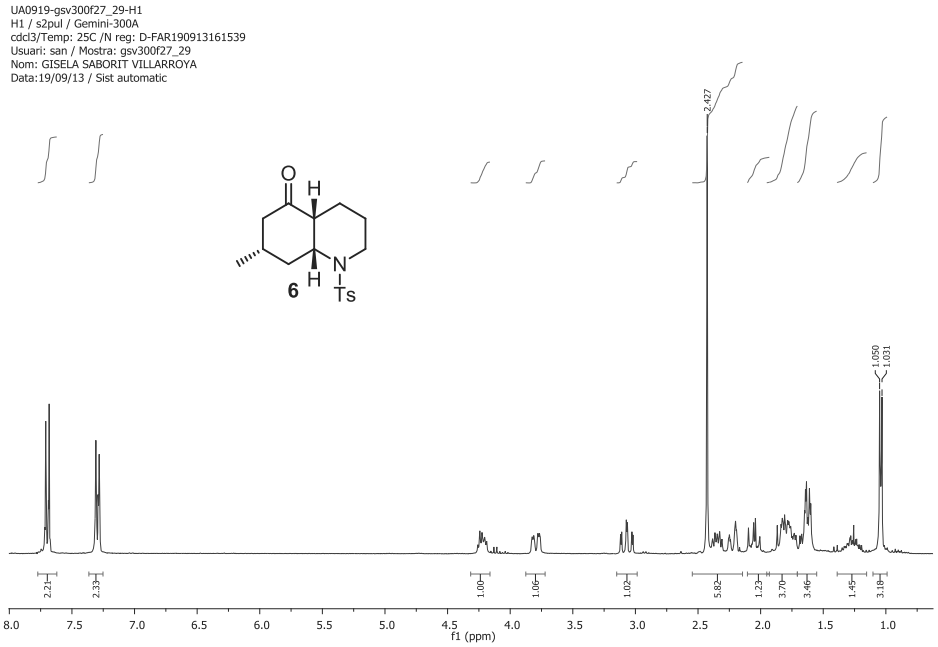
HPLC separation of ***rac*-2** was performed in a Chiralpak® IA column, using Hexane / *i*PrOH / $CHCl_3$ (90:5:5). Flow rate = 0.8 mL/ min, λ = 250 nm; enantiomer (-)-**2** t = 9.0 min, enantiomer (+)-**2** t = 15.5 min.

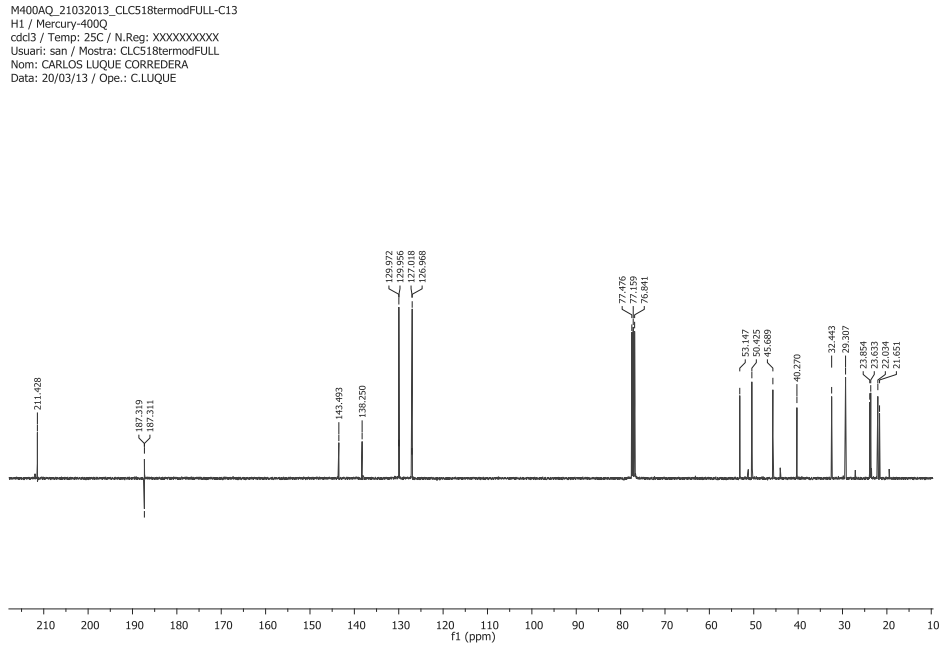


(4a*RS*,7*SR*,8a*RS*)-7-Methyl-1-(4-methylphenylsufonamido)-5-oxodeca-hydroquinoline (6). Method A.

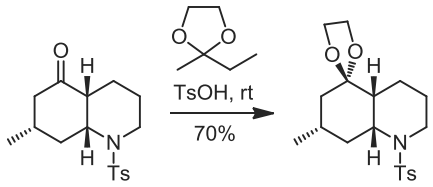


Decahydroquinoline **2** (2.4 g, 5.7 mmol) was dissolved in TFA (5.7 mL) and stirred for 15 min at rt. The solvent was evaporated under reduced pressure, the last traces of TFA were removed by azeotroping with toluene (3 x 10 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 70 ºC for 3 h to give the crude decahydroquinoline **4**. To a solution of crude **4** in *t*-BuOH (33 ml) was added 3 N HCl (53 mL) and the resulting mixture was stirred for 16 h at 45 ºC. The reaction was quenched with 1 N NaOH (21 mL) and extracted with EtOAc (3 x 35 mL). The combined organic layers were washed with brine (100 mL), dried and concentrated. Purification by chromatography (Al_2O_3, 5→10→25→50% EtOAc in hexane) gave **6** (311 mg, 17%) as a yellow oil followed by a 1:1 mixture of **4** and **6** (1.02 g) and the ring opened product **7** (507 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 1.04 (d, *J* = 6.0 Hz, 3H, Me), 1.30 (m, 1H, H-3ax), 1.62 (m, 1H, H-3eq), 1.65 (m, 2H, H-4), 1.81 (m, 2H, H-8), 2.05 (1H, H-7ax), 2.20 (1H, H-6eq), 2.35 (1H, H-4a), 2.55 (1H, H-6ax), 3.06 (td, *J* = 13.2, 2.4 Hz, 1H, H-2ax), 3.78 (dd, *J* = 13.2, 3.6 Hz, 1H, H-2eq), 4.22 (1H, H-8a), 7.28 (d, *J* = 6.3 Hz, 2H, *m*-Ts), 7.70 (d, *J* = 6.3 Hz, 2H, *o*-Ts); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 21.9 (Me), 23.3 (C-4), 23.7 (C-3), 29.2 (C-8), 32.3 (C-7), 40.1(C-2), 45.5 (C-6), 50.2 (C-8a), 53.0 (C-4a), 126.9 (*o*-Ts), 129.8 *(m*-Ts), 138.1 (*p*-Ts), 143.4 (*o*-Ts), 211.4 (C-5). HRMS calcd for $C_{17}H_{24}NO_3S$ ($M+H^+$) 322.1471, found 322.1470.


UA0919-gsv300f27_29-H1
H1 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: D-FAR190913161539
Usuari: san / Mostra: gsv300f27_29
Nom: GISELA SABORIT VILLARROYA
Data:19/09/13 / Sist automatic
O
H
N
H
Ts
6
2.427
1.050
1.031
2.21
2.33
1.00
1.06
1.02
5.82
1.23
3.70
3.46
1.45
3.18
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
f1 (ppm)

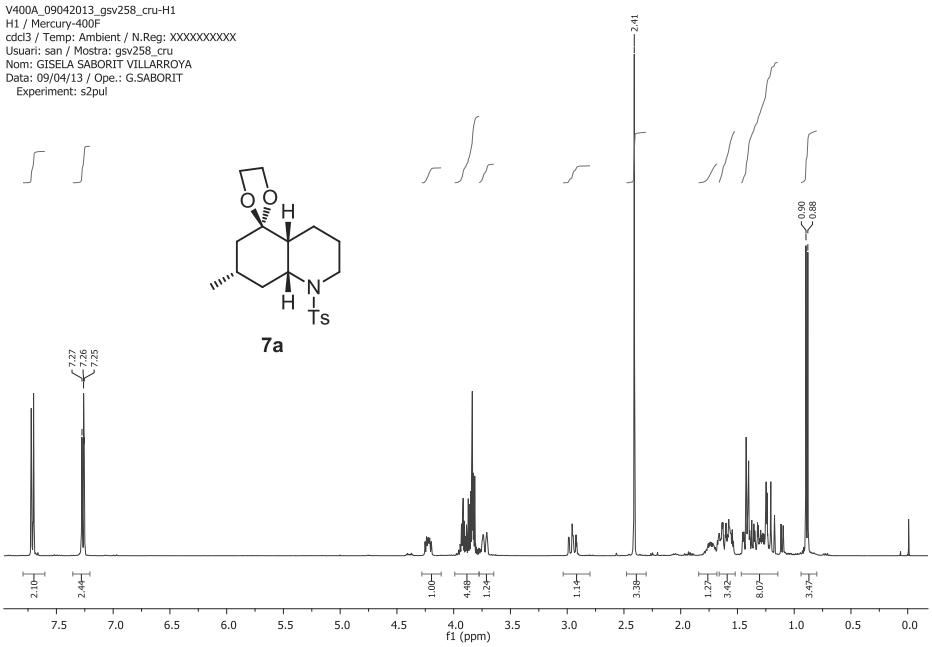

M400AQ_21032013_CLC518termodFULL-C13
H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC518termodFULL
Nom: CARLOS LUQUE CORREDERA
Data: 20/03/13 / Ope.: C.LUQUE
211.428
187.319
187.311
143.493
138.250
129.972
129.956
127.018
126.968
77.476
77.159
76.841
53.147
50.425
45.889
40.270
32.443
29.307
23.854
23.633
22.034
21.651
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

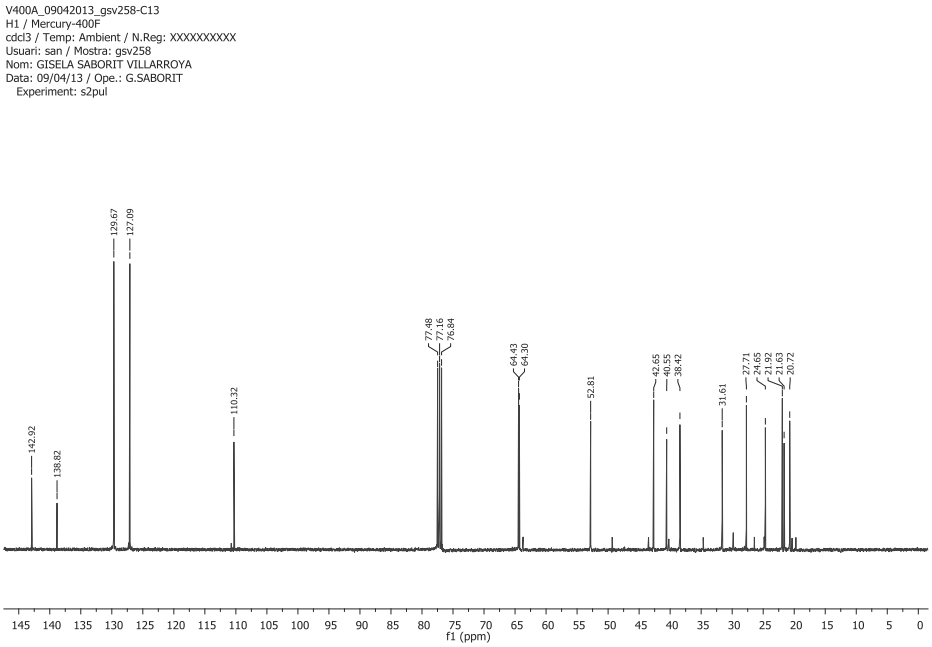
(4a*RS*,7*SR*,8a*RS*)-7-Methyl-1-(4-methylsulfonyl)-5-oxodecahydroquinoline ethylene acetal (7a)



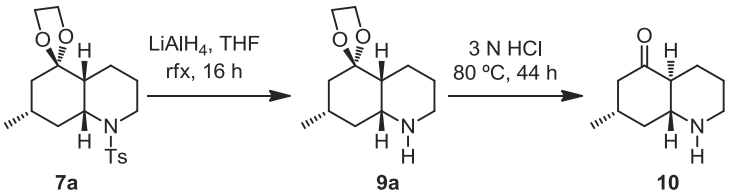
6 **7a**

To a solution of **6** (244 mg, 0.76 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (0.95 mL, 10 equiv) was added TsOH (7.5 mg, 0.038 mmol) and the mixture was stirred for 16 h at rt. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried and concentrated. The resulting material, after heating at the rotary evaporator at 70 ºC for 2 h to remove excess 2-ethyl-2-methyl-1,3-dioxolane, gave **7a** (186 mg, 70%) as a white solid; ^{1}H NMR (400 MHz, COSY) 0.89 (d, J = 7.0 Hz, 3H, Me), 1.21 (t, *J* = 12.8 Hz, 1H, H-6ax), 1.30 (m, 1H, H-3), 1.35 (dm, *J* = 12.5 Hz, H-4eq), 1.38-1.45 (m, 3H, H-8, H-6eq), 1.55 (m, 2H, H-3, H-4a), 1.60 (m, 1H, H-3), 1.65 (tm, *J* = 12.5 Hz, H-4ax), 1.75 (m, 1H, H- 7ax), 2.42 (s, 3H, $ArCH_3$) 2.96 (td, *J* = 13.0, 2.6 Hz, 1H, H-2ax), 3.74 (dm, *J* = 13.0 Hz, 1H, H-2eq), 3.82-3.94 (m, 4H, OCH_2), 4.23 (dt, *J* = 11.2, 5.2 Hz, 1H, H-8a), 7.27 (d, *J* =8.4 Hz, 2H, m-Ts), 7.72 (d, *J* = 8.4 Hz, 2H, o-Ts); ^{13}C NMR (400 MHz, HSQC) 20.6 (C-4), 21.5(ArCH3), 21.7 (CH3), 24.5 (C-3), 27.5 (C-7), 31.4 (C-8), 38.3 (C-6), 40.4 (C-2), 42.5(C-4a), 52.6 (H-8a), 64.1 and 64.2 (OCH_2), 110.2 (C-5), 126.9 (*o*-Ts), 129.5 (*m*-Ts), 138.7 (*p*-Ts), 142.8 (*ipso*-Ts). HRMS calcd for $C_{19}H_{28}NO_4S$ $(M+H)^+$ 366.1739, found 366.1736.


V400A_09042013_gsv258_cru-H1
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv258_cru
Nom: GISELA SABORIT VILLARROYA
Data: 09/04/13 / Ope.: G.SABORIT
Experiment: s2pul
7a
f1 (ppm)

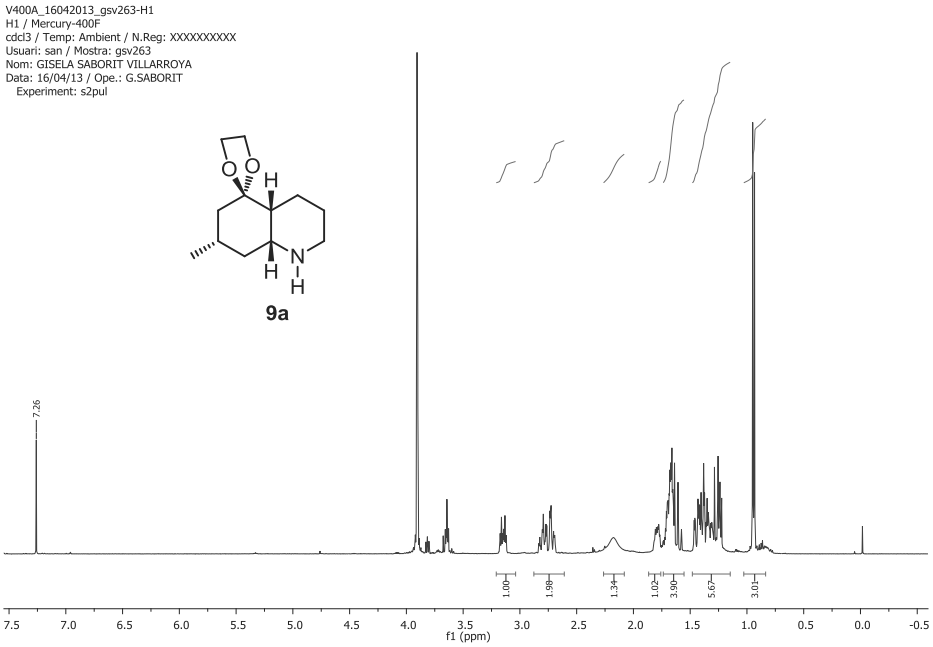

V400A_09042013_gsv258-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv258
Nom: GISELA SABORIT VILLARROYA
Data: 09/04/13 / Ope.: G.SABORIT
Experiment: s2pul
f1 (ppm)

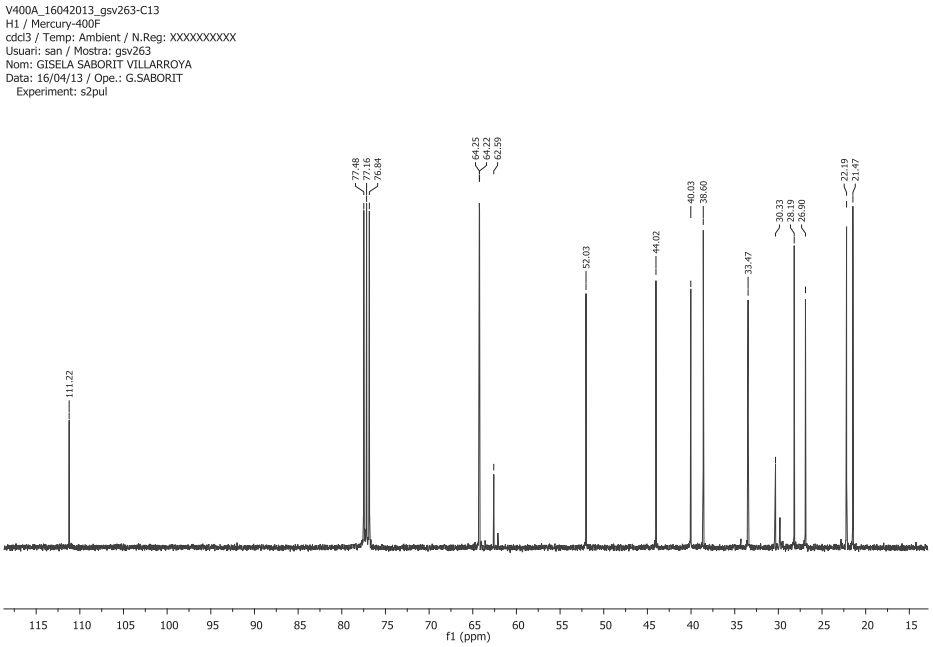
(4a*RS*,7*RS*,8a*SR*)-7-Methyl-5-oxodecahydroquinoline ethylene acetal (9a) and (4a*S*,7*S*,8a*S*)-7-Methyl-5-oxodecahydroquinoline (10)



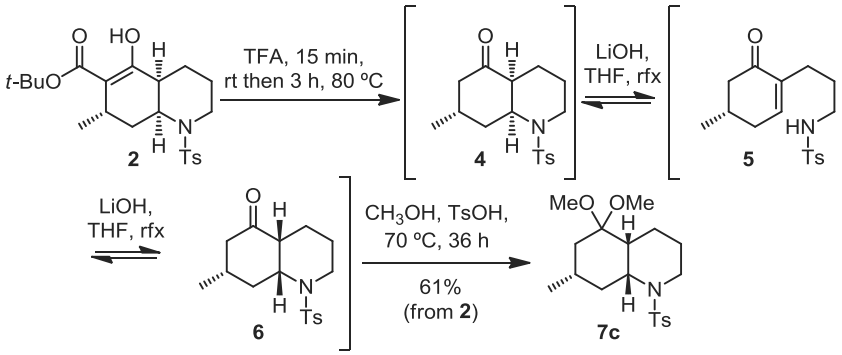
7a **9a** **10**

To a solution of $LiAlH_4$ (191 mg, 5.04 mmol) in THF (19 mL) at 0 ºC was added dropwise a solution of **7a** (185 mg, 0.504 mmol) in THF (10 mL + 5 mL rinse). The resulting mixture was allowed to reach rt and then refluxed for 16 h. The reaction was cooled to 0 ºC and quenched by careful dropwise addition of water (0.20 mL), 15% aq NaOH (0.20 mL) and water (0.6 mL). The mixture was diluted with diethyl ether (7 mL), and then Na_2SO_4 was added. After stirring for 15 min, the mixture was filtered through a pad of celite and concentrated to give the crude amino acetal **9a**. ^{1}H NMR (400 MHz, COSY) 0.89 (d, *J* = 6.8 Hz, 3H, Me), 1.27 (m, 1H, H-6), 1.30-1.40 (m, 3H, H-3, H-4, H-8), 1.45 (ddd, *J* = 11.6, 4.4, 2.4 Hz, 1H, H-6eq), 1.65-1.72 (m, 4H, H-3, H-4, H 8, H-7), 1.79 (m, 1H, H-4a), 2.20 (br, NH), 2.71 (dm, *J* = 12.6 Hz, 1H, H-2eq), 2.80 (td, *J* =12.8, 2.6 Hz, 1H, H-2ax), 3.15 (dt, *J* = 12.4, 4.4 Hz, 1H, H-8a), 3.90 (s, 4H, OCH_2). ^{13}C NMR (400 MHz, HSQC) 21.3 (C-4), 22.0 (CH_3), 26.7 (C-3), 28.0 (C-7), 33.3 (C-8), 38.4 (C-6), 39.9 (C-2), 43.9 (C-4a), 51.9 (C-8a), 64.1 (OCH_2), 111.1 (C-5). HRMS calcd for $C_{12}H_{22}NO_2$ $(M+H)^+$ 212.1645, found 212.1649. The above acetal **9a** was dissolved in 3 N HCl (13 mL) and heated at 80 ºC for 44 h. The mixture was basified with Na_2CO_3 (pH = 11), extracted with CH_2Cl_2 (3 × 40 mL) and dried. Concentration gave amine **10** (79 mg) as a clear yellow oil. For NMR data of **10** see p. 134.


V400A_16042013_gsv263-H1
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv263
Nom: GISELA SABORIT VILLARROYA
Data: 16/04/13 / Ope.: G.SABORIT
Experiment: s2pul
9a
7.26
1.00
1.98
1.34
1.02
3.90
5.67
3.01
f1 (ppm)

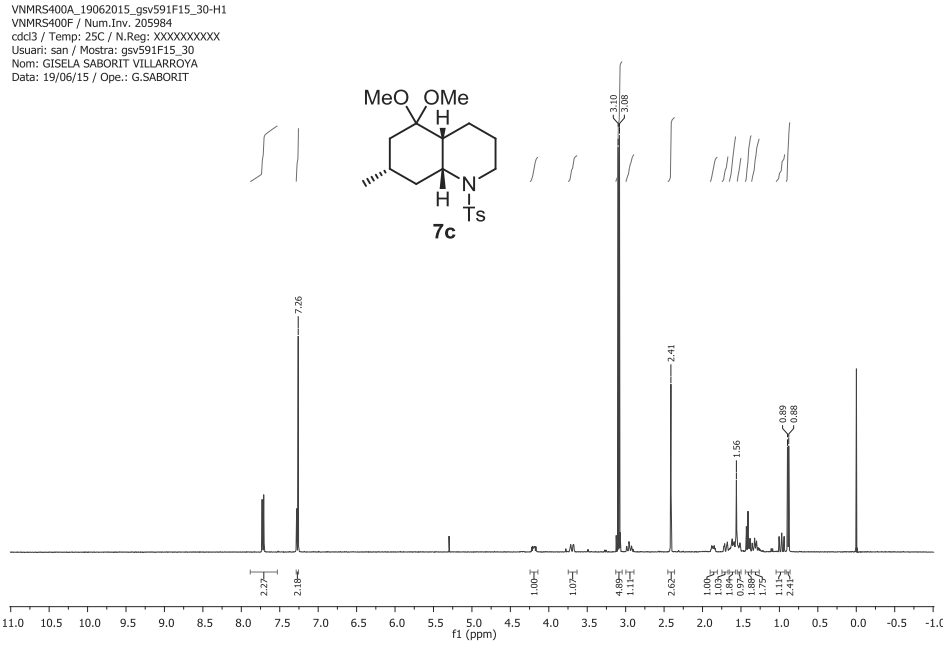

V400A_16042013_gsv263-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv263
Nom: GISELA SABORIT VILLARROYA
Data: 16/04/13 / Ope.: G.SABORIT
Experiment: s2pul
111.22
77.48
77.16
76.84
64.25
64.22
62.59
52.03
44.02
40.03
38.60
33.47
30.33
28.19
26.90
22.19
21.47
f1 (ppm)

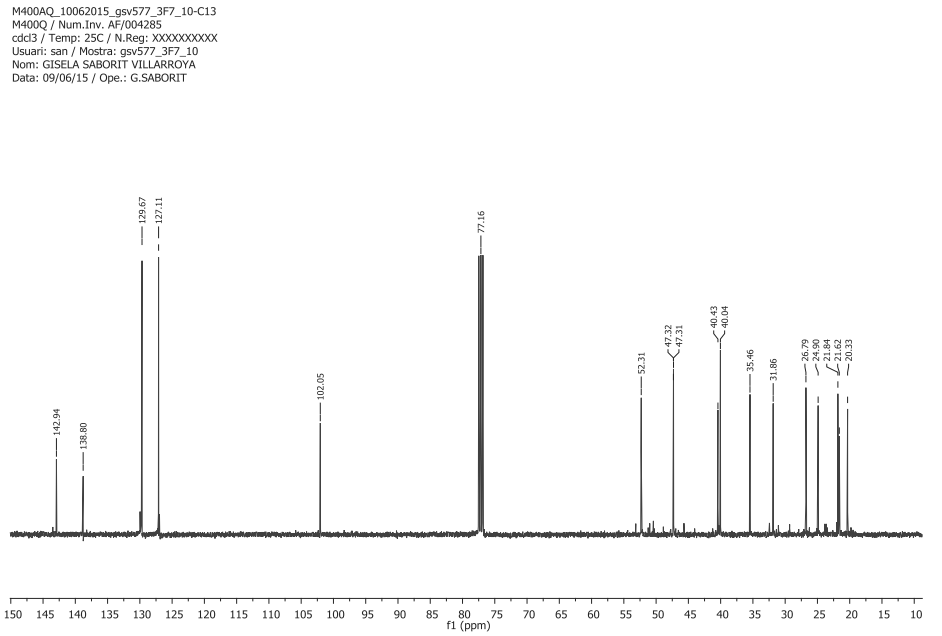
(4a*R*,7*S*,8a*R*)-7-Methyl-1-(4-methylsulfonyl)-5,5-dimethoxydecahydro quinoline (7c). Method B.



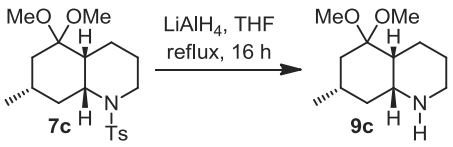
Decahydroquinoline **2** (1.91 g, 4.53 mmol) was dissolved in TFA (3.2 mL) and stirred under nitrogen for 15 min at rt. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 15 mL). The reaction flask was maintained on the rotatory evaporator under vacuum at 80 ºC for 3 h to give **4** as a brown oil. The crude decahydroquinoline **4** was dissolved in THF (18 mL), LiOH (507 mg, 21.2 mmol) was added and the resulting mixture was refluxed for 16 h. After cooling to rt the solvent was removed and the crude dissolved in EtOAc (25 mL). The organics were washed with saturated aqueous NH_4Cl (25 mL) and the aqueous was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (25 mL), dried, and concentrated. The resulting crude was dissolved in methanol (42 mL) and $TsOH{\cdot}H_2O$ (40 mg, 0.212 mmol) was added. After heating for 36 h at 70 ºC the mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL), the methanol removed by evaporation and the aqueous extracted with Et_2O (2 x 80 mL). The organics were combined and washed with brine (20 mL), dried, filtered and concentrated. The crude was purified by chromatography (5→10, 100% EtOAc/hexane). Firstly eluted the acetal (-)-**7c** protected product (805 mg, 52%) as a white solid. (mp 134 ºC. Rf 0.75 (50% EtOAc / hexanes), $[\alpha]_D$ -42.2, c 1, $CHCl_3$) and then the ring opened product **5** (400 mg), which was treated under the same equilibration conditions and then with MeOH and TsOH to give another 140 mg of **7c** (61% overall yield). ^{1}H NMR (400 MHz, COSY) 0.89 δ (d, J = 6.8 Hz, 3H, Me), 0.97 (t, *J* = 13.0 Hz, 1H, H-6ax), 1.31 (td, *J* = 13.6, 2.3 Hz, 1H, H-3ax), 1.32 (td, *J* = 13.6, 2.3 Hz, 1H, H-4ax), 1.40 (m, 2H, H-8), 1.53 (m, 1H, H-4eq), 1.61 (m, 2H, H-3eq, H-7), 1.69 (dm, *J* = 12.4 Hz, 1H, H-6eq), 1.86 (m, 1H, H-4a), 2.40 (s, 3H, $ArCH_3$), 2.94 (td, *J* = 13.0, 2.9 Hz, 1H, H-2ax), 3.07 and 3.09 (2s, 3H each), 3.69 (dm, *J* = 15.2 Hz, 1H, H-2eq), 4.19 (m, 1H, H-8a), 7.27 (d, *J* = 8.4 Hz, 2H, *m*-Ts), 7.71 (d, *J* = 8.4 Hz, 2H, *o*-Ts).

^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 20.3 (C-4), 21.6 (CH_3Ar), 21.8 (CH_3), 24.9 (C-3), 26.8 (C-7), 31.9 (C-8), 35.5 (C-6), 40.0 (C-2), 40.4 (C-4a), 47.3 ($2CH_3O$), 52.3 (C-8a), 102.3 (C-5), 127.1 (*o*-Ts), 129.7 (*m*-Ts), 138.8 (*p*-Ts), 142.9 (*ipso*-Ts). HRMS calcd for $C_{19}H_{30}NO_4S$ $(M+H)^+$ 368.1890, found 368.1895.

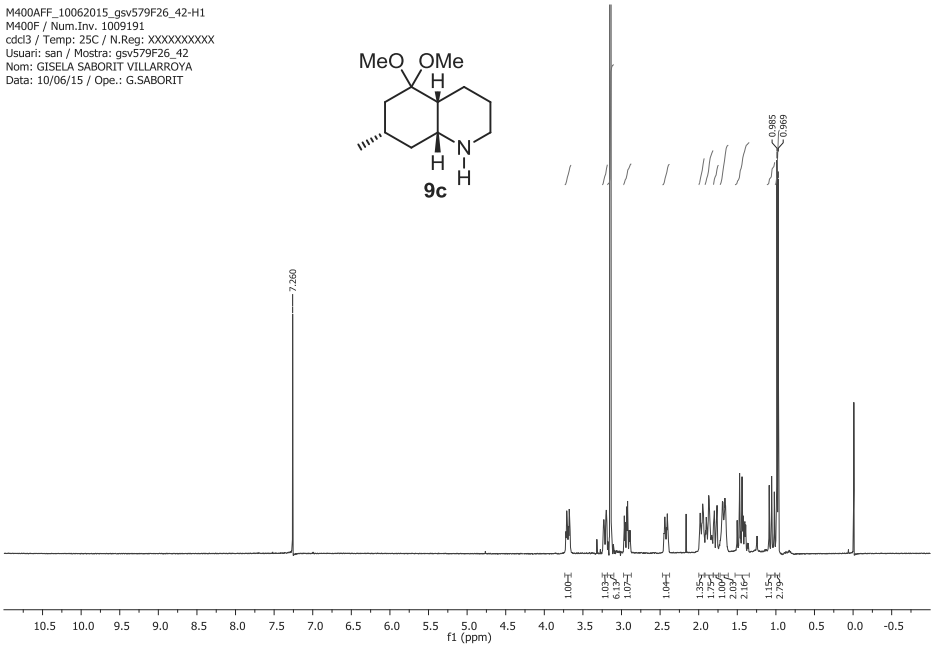


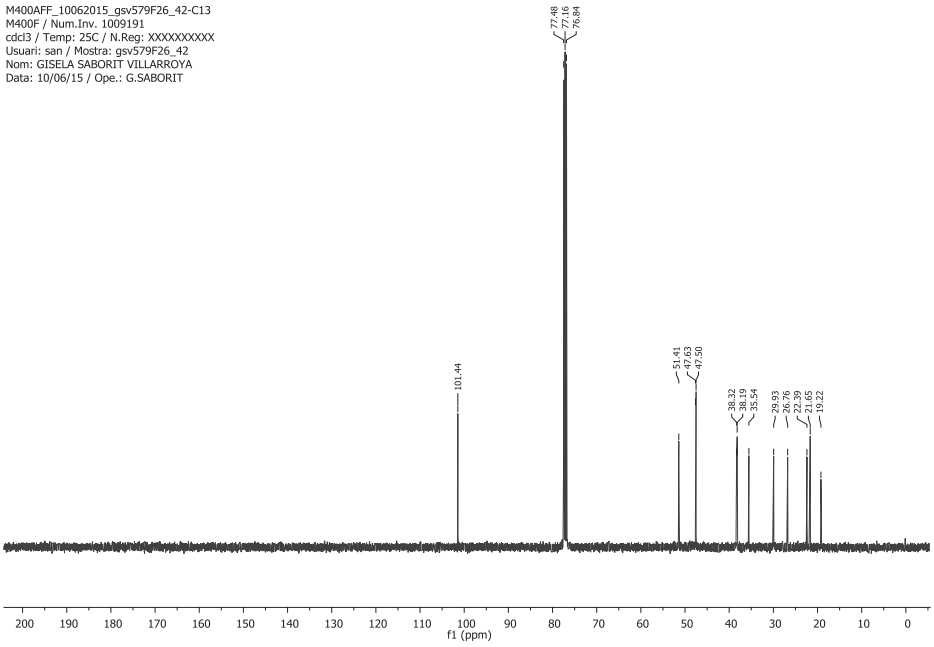


(4a*R*,7*S*,8a*R*)-5,5-Dimethoxy-7-methyldecahydroquinoline (9c)

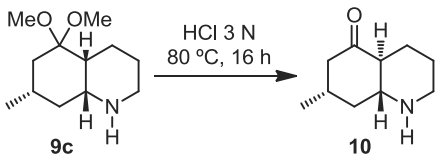


To a flame dried round bottom flask equipped with a magnetic stirrer was added $LiAlH_4$ (975 mg, 25.7 mmol) and THF (16 mL) at 0 ºC under argon. A solution of **7c** (944 mg, 2.57 mmol) in THF (82 mL) was added dropwise and the mixture was allowed to come to room temperature, stirred for 1 h and then refluxed overnight. After cooling to room temperature the reaction was quenched with the dropwise addition of water (1.0 mL), 15% aq NaOH (1.0 mL) and water (3.0 mL) at 0 ºC. The mixture was diluted with ether (30 mL), Na_2SO_4 was added and the mixture stirred for another 15 minutes. Filtration through a pad of celite and concentration gave **9c** (462 mg). The crude product was essentially pure and was used in the next step without further purification. An analytical sample was prepared by chromatography on alumina (1.0→2.5→5→10% CH_2Cl_2/MeOH) to give **9c**. Rf 0.38 (10% CH_2Cl_2/MeOH); $[\alpha]_D$ +7.33 (c 1, $CHCl_3$);. ^{1}H NMR (400 MHz, COSY) 0.98 (d, *J* = 6.4 Hz, 3H, CH_3), 1.04 (t, *J* = 12.8 Hz, 1H, H-6ax), 1.40 (m, 1H, H-4), 1.47 (m, 1H, H-8ax), 1.67 (m, 2H, H-4, H-7), 1.78 (dm, *J* = 14.0 Hz, 1H, H-6eq), 1.88 (m, 2H, H-3), 1.96 (dt, *J* = 13.0, 4.0 Hz, 1H, H-8), 2.42 (td, *J* = 16.8, 3.8 Hz, 1H, H-4a), 2.93 (td, *J* = 13.0, 4.1 Hz, 1H, H-2ax), 3.14 (s, 6H, CH_3O), 3.19 (dm, *J* = 12.8 Hz, 1H, H-2eq), 3.69 (td, *J* = 13.2, 4.3 Hz, 1H, H-8a). ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.2 (C-4), 21.6 (CH_3), 22.4 (C-3), 26.8 (C-7), 29.9 (C-8), 35.5 (C-6), 38.2 (C-4a), 38.3 (C-2), 47.5 (CH_3O), 47.6 (CH_3O), 51.4 (C-8a), 101.4 (C-5). HRMS calcd for $C_{12}H_{24}NO_2$ $(M+H)^+$ 214.1802, found 214.1807.

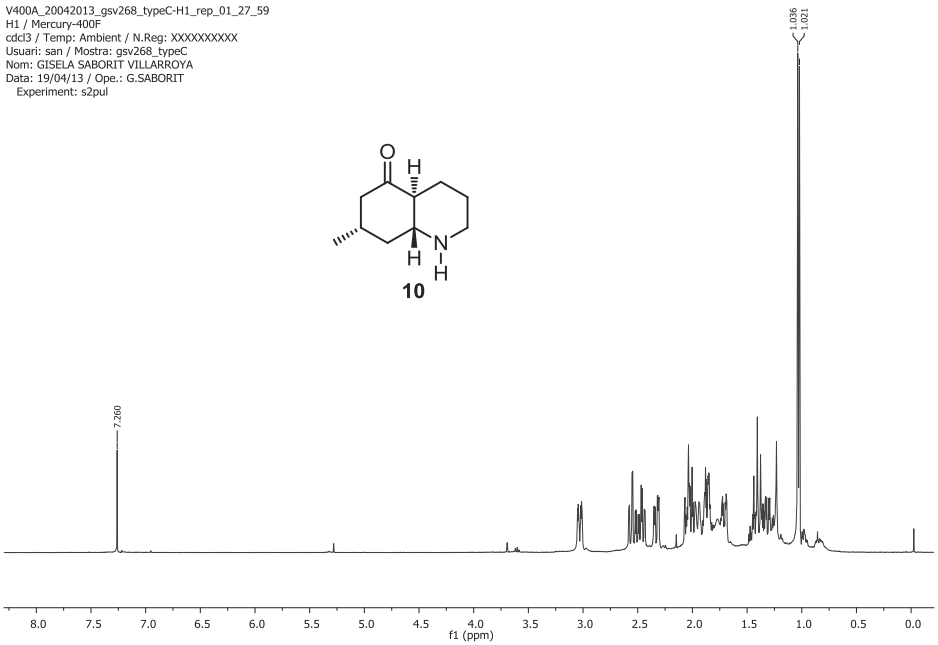

M400AFF_10062015_gsv579F26_42-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv579F26_42
Nom: GISELA SABORIT VILLARROYA
Data: 10/06/15 / Ope.: G.SABORIT
MeO
OMe
H
N
H
H
9c
7.260
0.985
0.969
1.00
1.03
6.13
1.07
1.04
1.35
1.75
1.69
2.03
2.16
1.15
2.79
10.5 10.0 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 -0.5
f1 (ppm)


M400AFF_10062015_gsv579F26_42-C13
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv579F26_42
Nom: GISELA SABORIT VILLARROYA
Data: 10/06/15 / Ope.: G.SABORIT
77.48
77.16
76.84
101.44
51.41
47.63
47.50
38.32
38.19
35.54
29.93
26.76
22.39
21.65
19.22
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

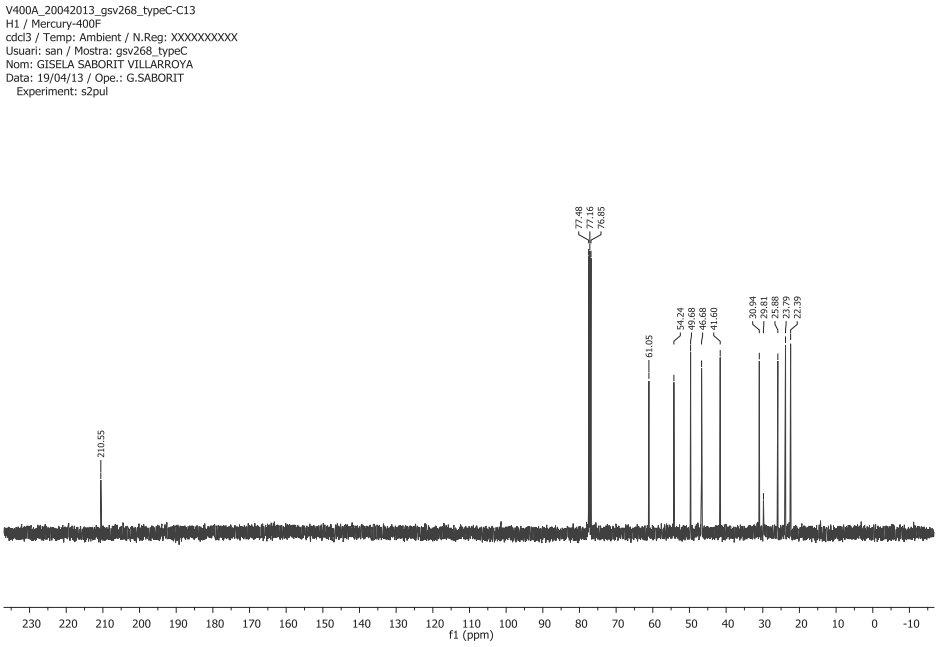
(4a*S*,7*S*,8a*S*)-7-Methyl-5-oxodecahydroquinoline (10)



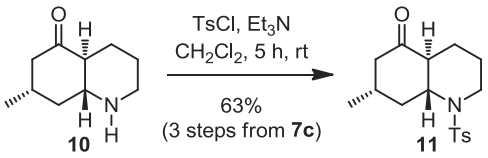
A solution of **9c** (395 mg, 0.85 mmol) in 3 N HCl (aq) (44 mL) was stirred for 16 h at 80 ºC. After cooling to rt, the mixture was carefully basified with solid Na_2CO_3 until pH = 11 at 0 ºC. The aqueous was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (3 x 50 mL), dried, filtered and concentrated to give the crude *trans*-decahydroquinoline **10**, which could be used in the next step without further purification. ^{1}H NMR (400 MHz, COSY) 1.03 (d, *J* = 6.8 Hz, 3H, Me), 1.25 (m, 1H, H-4ax), 1.34 (qm, *J* = 12.4 Hz, 1H, H-3ax), 1.46 (q, *J* = 12.4 Hz, 1H, H-8ax), 1.73 (dm, *J* = 12.4 Hz, 1H, H-3eq), 1.85 (m, 2H, H-7ax, H-8eq), 1.95 (dm, *J* = 12,0 Hz, 1H, H-4eq), 2.05 (t, *J* = 12.8 Hz, 1H, H-6ax), 2.10 (td, *J* = 11.0, 2.1 Hz, 1H, H-4a), 2.34 (ddd, *J* = 12.8, 4.0, 2.0 Hz, 1H, H-6eq), 2.46 (td, *J* = 11.0, 3.2 Hz, 1H, H-8a), 2.55 (td, *J* = 12.4, 2.8 Hz, 1H, H-2ax), 3.03 (dddd, *J* = 12.0, 4.0. 2.0, 2.0, Hz, H-2eq); ^{13}C NMR (400 MHz, HSQC) 22.2 (Me), 23.6 (C-4), 25.7 (C-3), 30.8 (C-7), 41.4 (C-8), 46.5 (C-2), 49.5 (C-6), 54.1 (C-4a), 60.9 (C-8a), 210.4 (C-5). HRMS calcd for $C_{10}H_{18}NO$ $(M+H)^+$ 168.1388, found 168.1384.


V400A_20042013_gsv268_typeC-H1_rep_01_27_59
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv268_typeC
Nom: GISELA SABORIT VILLARROYA
Data: 19/04/13 / Ope.: G.SABORIT
Experiment: s2pul
1.036
1.021
7.260
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)

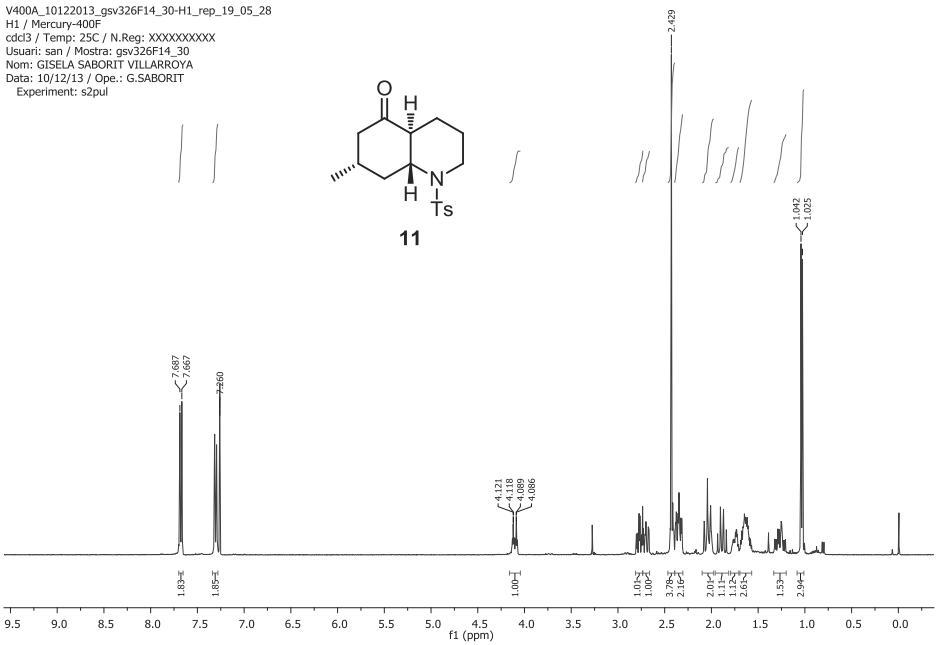
10

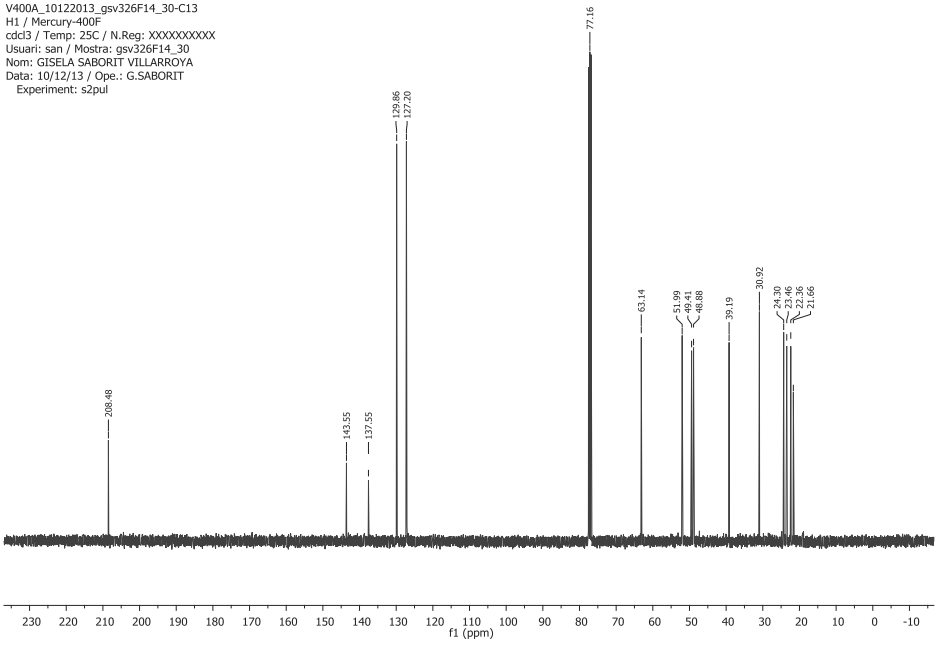

V400A_20042013_gsv268_typeC-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv268_typeC
Nom: GISELA SABORIT VILLARROYA
Data: 19/04/13 / Ope.: G.SABORIT
Experiment: s2pul
77.48
77.16
76.85
210.55
61.05
54.24
49.68
46.68
41.60
30.94
29.91
25.88
23.79
22.39
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(4a*S*,7*S*,8a*S*)-7-Methyl-1-(4-methylsulfonyl)-5-oxodecahydroquinoline (11)



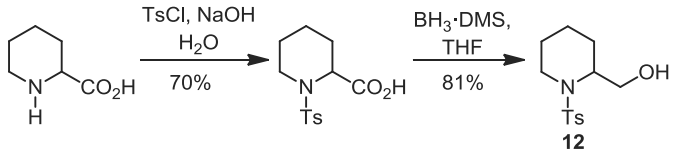
To a cooled (0 ºC) solution of the crude **10** in CH_2Cl_2 (6 mL) was added Et_3N (0.31 mL, 1.09 mmol, 1.3 equiv) followed by a solution of TsCl (370 mg, 1.94 mmol, 1.05 equiv) in CH_2Cl_2 (6 mL) dropwise. The resulting mixture was stirred at room temperature for 5 h and washed with brine (2 x 2 mL). The organics were dried, filtered and concentrated. Purification by chromatography (2.5→5→10→25% EtOAc/hexane) gave **11** (374 mg, 63% overall yield from **7c** in three steps) as a white solid. R_f 0.53 (50% hexanes/EtOAc), mp 133 ºC. $[\alpha]_D$ -68.46 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 1.03 (d, *J* = 6.8 Hz, 3H, Me), 1.26 (qd, *J* = 13.0, 6.0 Hz, 1H, H-4ax), 1.65 (m, 2H, H-3ax, H-7ax), 1.74 (dm, *J* = 13.0 Hz, 1H, H-3eq), 1.89 (q, *J* = 12 Hz, 1H, H-8ax), 2.04 (td, *J* = 12.8, 1.2 Hz, 1H, H-6ax), 2.33 (ddd, *J* = 12.8, 4.0, 1.2 Hz, 1H, H-6eq), 2.35 (dm, *J* = 12.0 Hz, 1H, H-8eq), 2.43 (s, 3H, $ArCH_3$), 2.43 (masked, 1H, H-4a), 2.70 (td, *J* = 12.4, 3.2 Hz, 1H, H-2ax), 2.77 (td, *J* = 11.2, 3.2 Hz, 1H, H-8a), 4.10 (dtd, *J* = 12.8, 4.0, 1.2 Hz, 1H, H-2eq), 7.30 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.68 (d, *J* = 8.0 Hz, 2H, *o*-Ts). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 21.7 ($ArCH_3$), 22.4 (7-CH_3), 23.5 (C-4), 24.3 (C-3), 30.7 (C-7), 39.2 (C-8), 48.9 (C-2), 49.4 (C-6), 52.0 (C-4a), 63.1 (C-8a), 127.2 (*o*-Ts), 129.9 (*m*-Ts), 137.6 (*p*-Ts), 143.5 (*ipso*-Ts), 208.5 (C-5). HRMS calcd for $C_{17}H_{24}NO_3S$ $(M+H)^+$ 332.1471, found 332.1463.


V400A_10122013_gsv326F14_30-H1_rep_19_05_28
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv326F14_30
Nom: GISELA SABORIT VILLARROYA
Data: 10/12/13 / Ope.: G.SABORIT
Experiment: s2pul
O
H
N
H
Ts
11
2.429
1.042
1.025
7.687
7.667
7.660
4.121
4.118
4.089
4.086
1.83
1.85
1.00
1.01
1.00
3.78
2.16
2.01
1.13
2.61
1.53
2.94
f1 (ppm)


V400A_10122013_gsv326F14_30-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv326F14_30
Nom: GISELA SABORIT VILLARROYA
Data: 10/12/13 / Ope.: G.SABORIT
Experiment: s2pul
77.16
129.86
127.20
208.48
143.55
137.55
63.14
51.99
49.41
48.88
39.19
30.92
24.30
23.46
22.36
21.66
f1 (ppm)

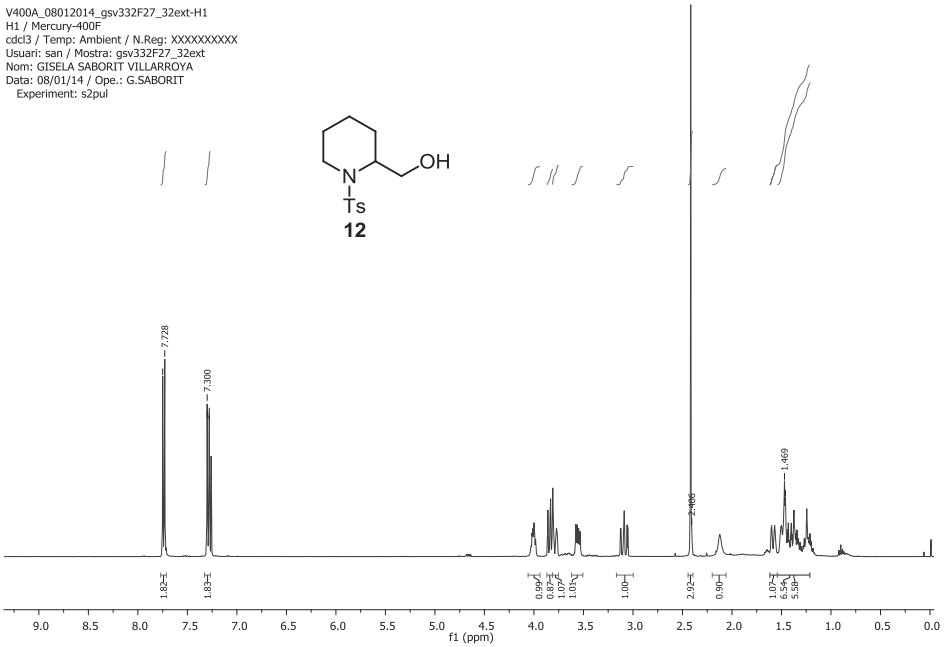
Preparation of phosphonate and wittig salts

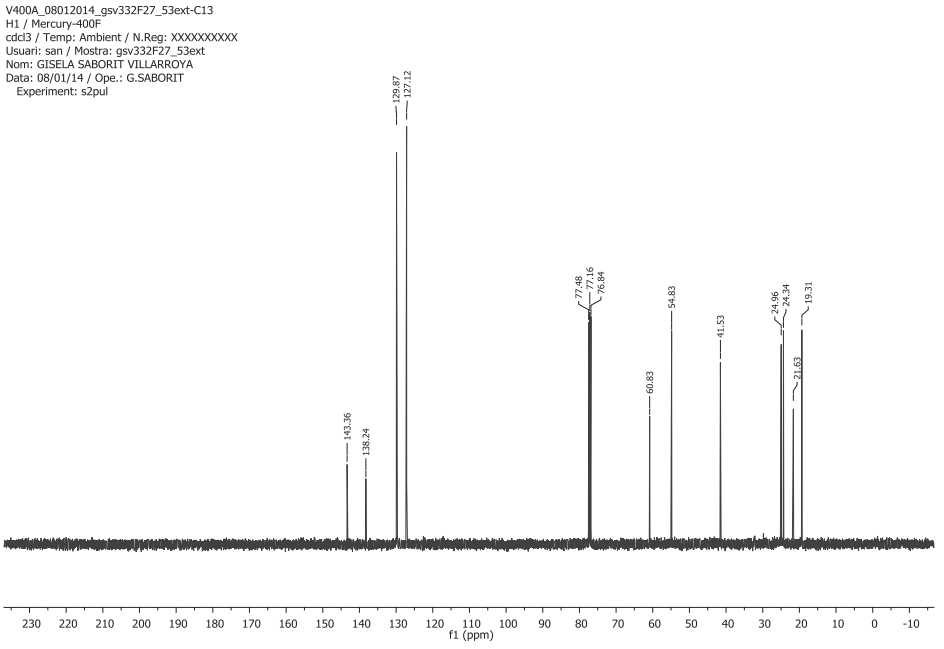
2-Hydroxymethyl-1-(4-methylphenylsulfonyl)piperidine (12)



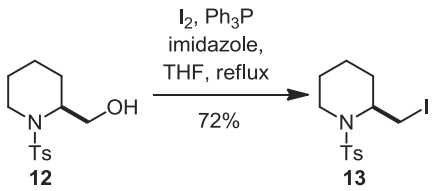
To a stirred solution of pipecolic acid (5.00 g, 38.71 mmol) in water (1.3 L) was added 1 N NaOH (62 mL, 3 eq) and TsCl (2.21 g, 11.63 mmol, 1.5 eq). After 5 h 6.5 mL of 2 N NaOH and TsCl (2.21 g, 11.59 mmol, 0.3 eq) were added and stirring was continued for a further 16 h. The reaction mixture was diluted with 2 N NaOH (50 mL) and extracted with Et_2O (3 x 200 mL). The aqueous was acidified with HCl 1N until pH 1 and extracted with CH_2Cl_2 (3 x 300 mL). Drying and evaporation gave the N-tosyl protected pipecolic acid (7.65 g, 70%), which was used in the next step without further purification.

BH_3·DMS (34 mL, 67.5 mmol, 2.5 eq) was added dropwise to a stirred solution of (1-tosylpiperidin-2-yl)methanol (7.65 g, 27.02 mmol) in THF (210 mL) at 0 ºC. After 30 minutes at this temperature the mixture was allowed to come to room temperature and stirring was continued overnight. The mixture was cooled to 0 ºC and methanol was added dropwise until no more gas was released (ca. 18 mL). The solvent was evaporated and the resulting residue was dissolved in CH_2Cl_2 (300 mL). The organics were washed with 1 N NaOH (2 x 150 mL), dried, filtered and concentrated to afford **12** (5.90 g, 81%) as a solid. The compound was pure enough to be used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 1.42 (m, 5H, H-3ax, H-4, H-5), 1.58 (dm, *J* = 14.4 Hz, H-3eq), 2.10 (br, 1H, OH), 2.41 (s, 3H, CH_3Ar), 3.09 (td, *J* = 11.0, 2.6 Hz, H-6ax), 3.56 (dd, *J* = 12.4, 5.6 Hz, 1H, CH_2OH), 3.77 (m, H-6eq), 3.82 (dd, *J* = 11.2, 8.8 Hz, 1H, CH_2OH), 4.01 (ddd, *J* = 2.4, 5.6, 11.2 Hz, 1H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 19.3 (C-4), 21.6 (CH_3Ar), 24.3 (C-5), 25.0 (C-3), 41.5 (C-6), 54.8 (C-2), 60.8 (CH_2OH), 127.1 (*o*-Ts), 129.9 (*m*-Ts), 138.2 (*p*-Ts), 143.4 (*ipso*-Ts). HRMS calcd for $C_{13}H_{20}NO_3S$ $(M+H)^+$ 270.1158, found 270.1159.

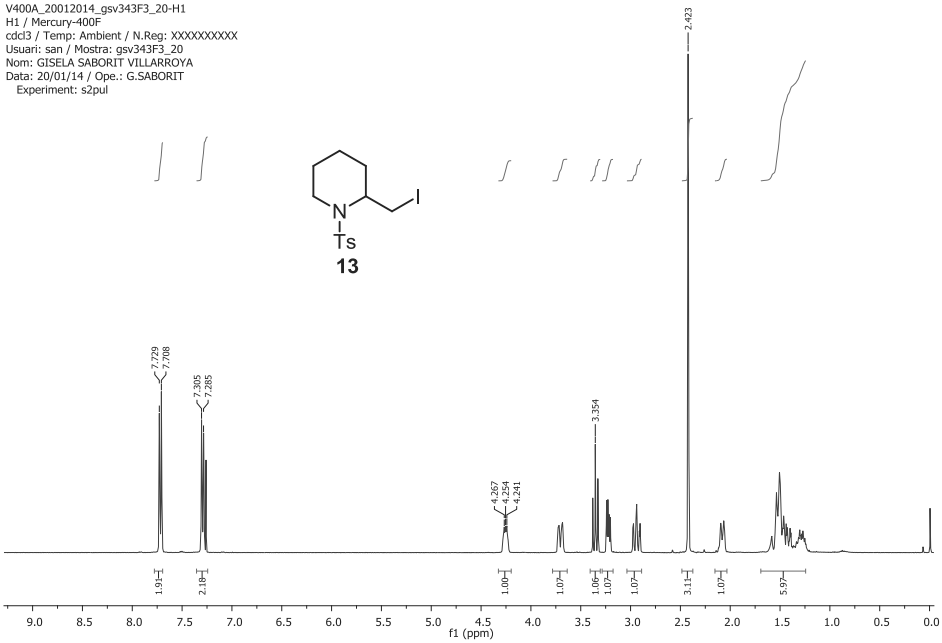

V400A_08012014_gsv332F27_32ext-H1
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv332F27_32ext
Nom: GISELA SABORIT VILLARROYA
Data: 08/01/14 / Ope.: G.SABORIT
Experiment: s2pul
OH
N
Ts
12
7.728
7.300
2.405
1.469
1.82
1.83
0.99
0.87
1.07
1.01
1.00
2.92
0.90
1.07
6.54
5.58
f1 (ppm)

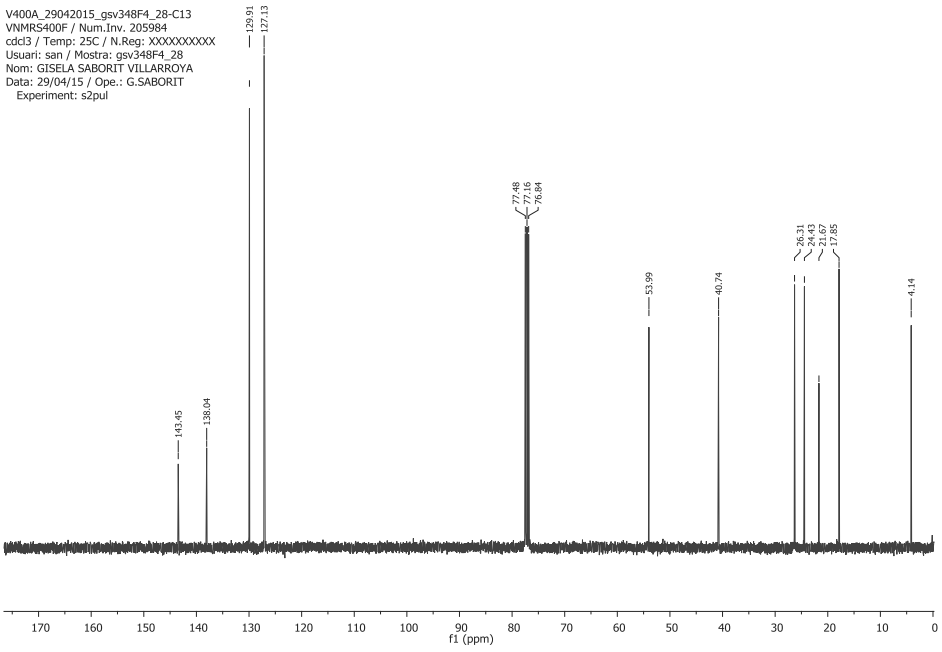

V400A_08012014_gsv332F27_53ext-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv332F27_53ext
Nom: GISELA SABORIT VILLARROYA
Data: 08/01/14 / Ope.: G.SABORIT
Experiment: s2pul
129.87
127.12
143.36
138.24
77.48
77.16
76.84
60.83
54.83
41.53
24.96
24.34
21.63
19.31
f1 (ppm)

2-Iodomethyl-1(4-methylphenylsulfonyl)piperidine (13)

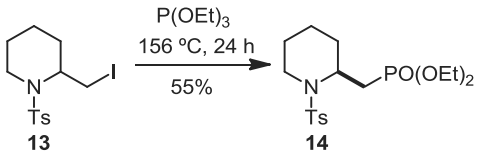


To a solution of **12** (1.78 g, 6.62 mmol) in THF (70 mL) were added Ph_3P (3.82 g, 14.55 mmol, 2.2 eq), imidazole (1.06 g, 16.53 mmol, 2.5 eq) and I_2 (3.69 g, 15.55 mmol, 2.2 eq). The resulting dark solution was stirred at 70 ºC for 45 min and concentrated. The residue was purified by chromatography (2.5→5 EtOAc/hexane) to afford **13** (1.81 g, 72%) as a yellowish oil R_f 0.64 (50% EtOAc/hexanes) ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 1.30 (m, 1H, H-5), 1.46-1.60 (m, 4H), 2.09 (dm, *J* = 12 Hz, 1H, H-3eq), 2.42 (s, 3H, CH_3Ar), 2.94 (td, *J* = 13.3, 2.3Hz, H-6ax), 3.22 (dd, *J* = 10.2, 5.2 Hz, 1H, CH_2I), 3.35 (t, *J* = 10.2 Hz, 1H, CH_2I), 3.70 (dd, *J* = 14.6, 3.6 Hz, 1H, H-6eq), 4.25 (m, 1H, H-1), 7.29 (d, *J* = 8.4 Hz, 2H, *m*-Ts), 7.72 (d, *J* = 8.4 Hz, 2H, *o*-Ts). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 4.1 (CH_2I), 17.9 (C-4), 21.7 (CH_3Ar), 24.4 (C-5), 26.3 (C-3), 40.7 (C-6), 54.0 (C-1), 127.1 (*o*-Ts), 129.9 (*m*-Ts), 138.0 (*p*-Ts), 143.5 (*ipso*-Ts). HRMS calcd for $C_{13}H_{19}INO_2S$ $(M+H)^+$ 380.0176, found 380.0176.

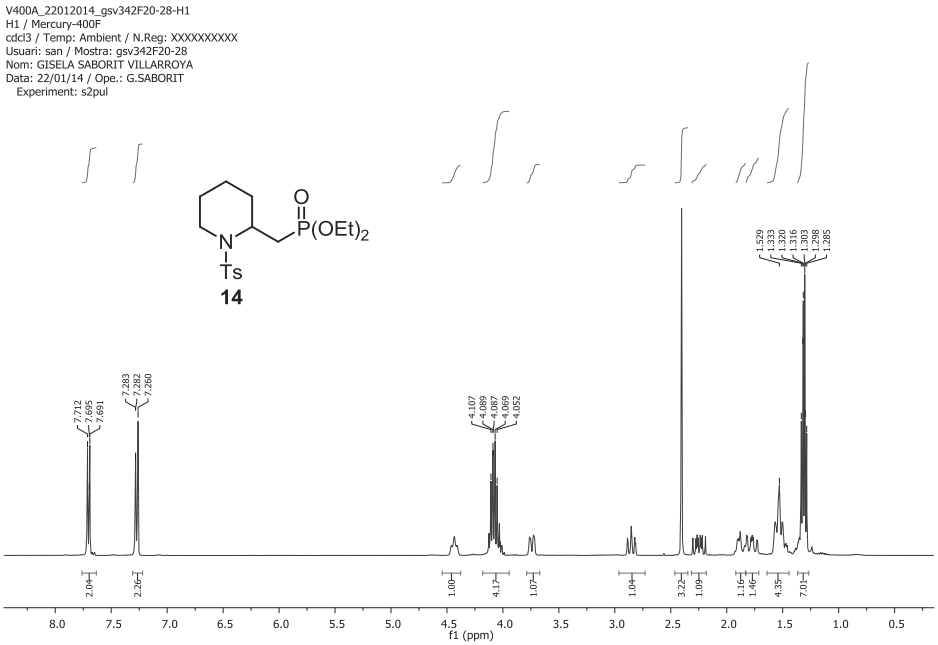

V400A_20012014_gsv343F3_20-H1
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv343F3_20
Nom: GISELA SABORIT VILLARROYA
Data: 20/01/14 / Ope.: G.SABORIT
Experiment: s2pul
N
Ts
I
13
7.729
7.708
7.305
7.285
4.267
4.254
4.241
3.354
2.423
1.91
2.18
1.00
1.07
1.06
1.07
1.07
3.11
1.07
5.97
f1 (ppm)

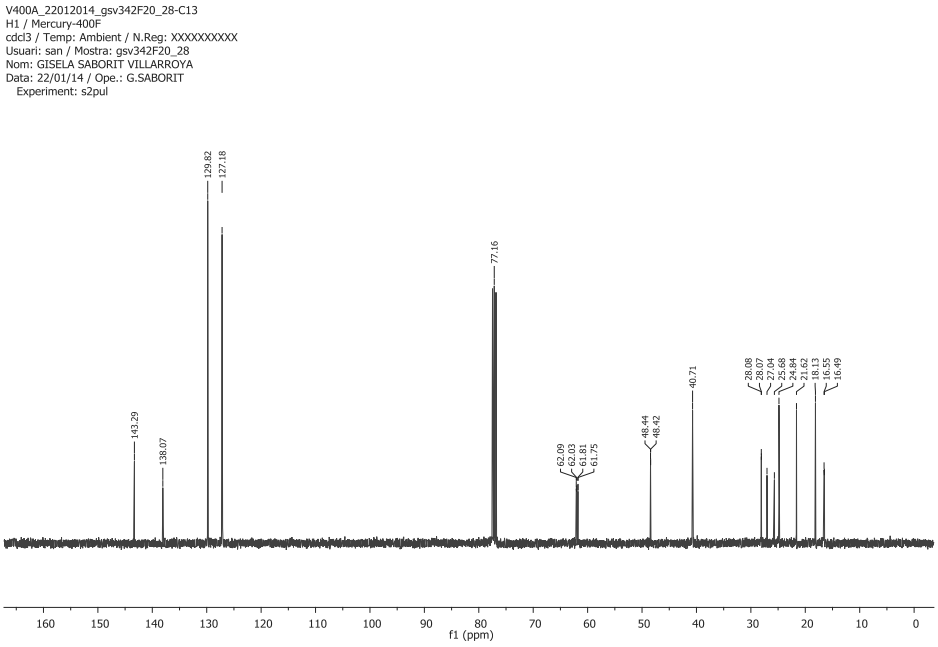

V400A_29042015_gsv348F4_28-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv348F4_28
Nom: GISELA SABORIT VILLARROYA
Data: 29/04/15 / Ope.: G.SABORIT
Experiment: s2pul
129.91
127.13
77.48
77.16
76.84
53.99
40.74
26.31
24.43
21.67
17.65
4.14
143.45
138.04
f1 (ppm)

Diethyl 1-[(4-methylphenyl)sulfonyl)-2-yl)methyl] phosphonate (14)

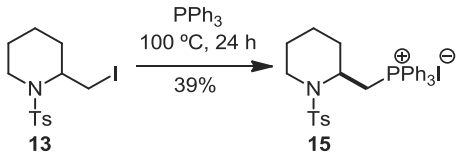


A mixture of iodide **13** (840 mg, 2.21 mmol) and triethyl phosphite (4 mL, 23.3 mmol, 10 equiv) were stirred at 156 ºC for 24 h. The volatiles were removed in a dry ice rotary evaporator and the residue was purified by chromatography (25→100% EtOAc/hexane) to give **14** (471 mg, 55%) as an oil. R_f 0.17 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.32 (m, 7H, CH_3, H-5), 1.49-1.57 (m, 4H, 2H-4, H-3, H-5), 1.77 (ddd, $^2J_{H,P}$ = 22.4 Hz; 15.2, 2.8 Hz, 1H, CH_2P), 1.88 (m, 1H, H-3), 2.25 (ddd, $^2J_{H,P}$ = 22.4 Hz; 15.2, 10.8 Hz, 1H, CH_2P), 2.40 (s, 3H, CH_3Ar), 2.85 (td, *J* = 13.0, 2.4 Hz, 1H, H-6ax), 3.74 (dd, *J* = 13.4, 3.2 Hz, 1H, H-6eq), 4.08 (m, 4H, OCH_2), 4.43 (apparent t, *J* = 10.8, 3.0, 2.8, 2.8 Hz, 1H, H-2eq), 7.26 (d, *J* = 9.2 Hz, 2H, m-Ts), 7.69 (d, *J* = 8.4 Hz, 2H, o-Ts). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 16.5 (2d, $^3J_{C,P}$ = 1.4 Hz, CH_3), 18.1 (C-4), 21.6 ($ArCH_3$), 24.8 (C-5), 26.3 (d, $^1J_{C,P}$ = 264 Hz, CH_2P), 28.1 (C-3), 40.7 (C-6), 48.4 (C-2), 61.8 and 62.0 (2d, $^2J_{C,P}$ = 6.5 Hz, OCH_2), 127.2 (*o*-Ts), 129.8 (*m*-Ts), 138.1 (*p*-Ts), 143.3 (*ipso*-Ts). HRMS calcd for $C_{17}H_{29}NO_5PS$ $(M+H)^+$ 390.1499, found 390.1501.

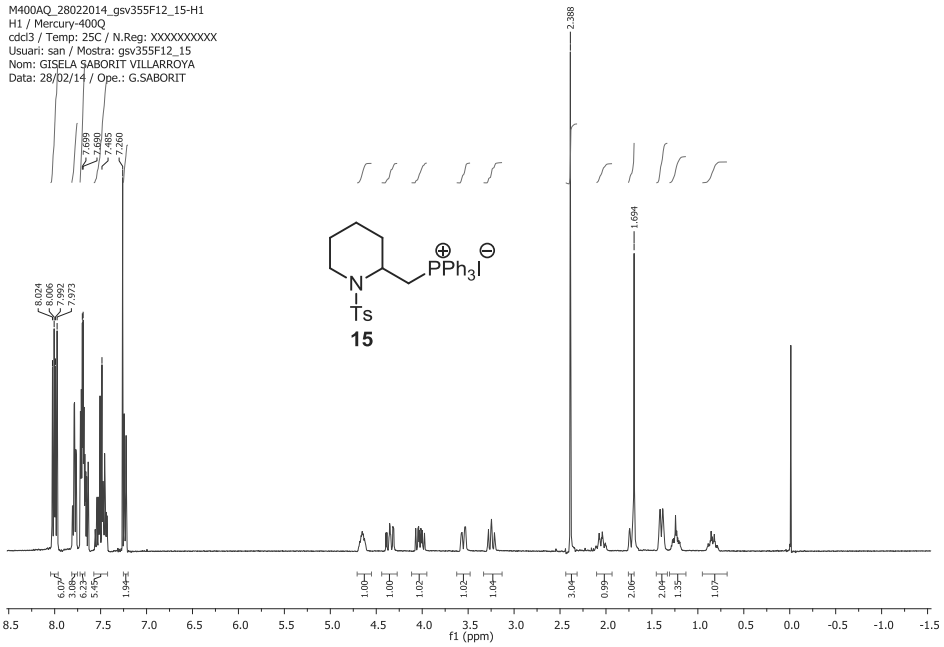

V400A_22012014_gsv342F20-28-H1
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv342F20-28
Nom: GISELA SABORIT VILLARROYA
Data: 22/01/14 / Ope.: G.SABORIT
Experiment: s2pul
O
P(OEt)2
N
Ts
14
7.712
7.695
7.691
7.283
7.282
7.280
4.107
4.098
4.087
4.069
4.052
1.529
1.333
1.320
1.316
1.303
1.298
1.285
2.04
2.26
1.00
4.17
1.07
1.04
3.22
1.09
1.16
1.40
4.35
7.01
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
f1 (ppm)

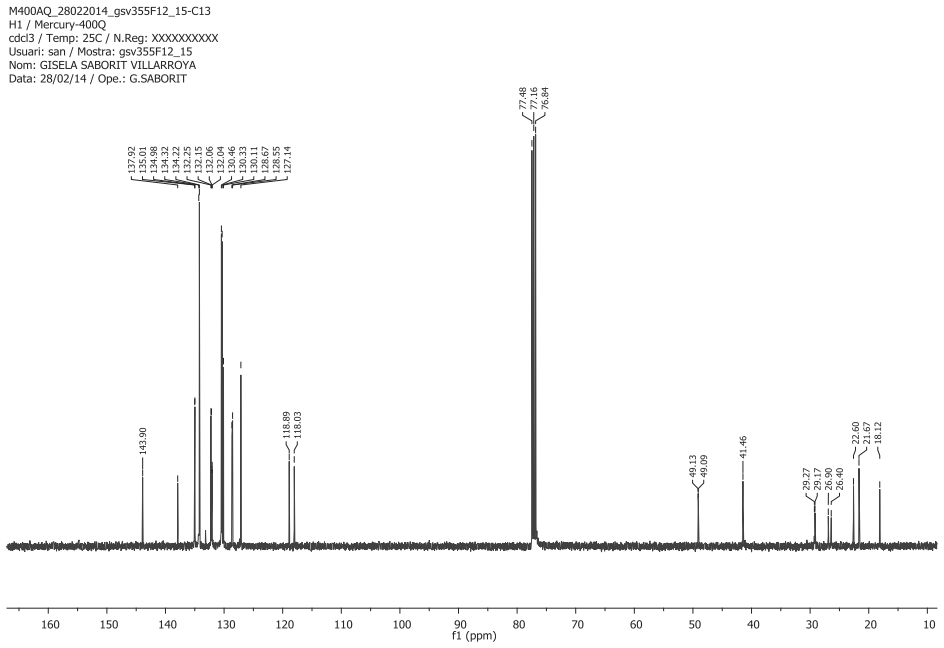

V400A_22012014_gsv342F20_28-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv342F20_28
Nom: GISELA SABORIT VILLARROYA
Data: 22/01/14 / Ope.: G.SABORIT
Experiment: s2pul
129.82
127.18
77.16
143.29
138.07
62.09
62.03
61.81
61.75
48.44
48.42
40.71
28.08
28.07
27.04
25.68
24.84
24.62
18.13
16.55
16.49
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Phosphonium-1-[(4-methylphenyl)sulfonyl]-2-piperidinyl]methyl triphenyl phosphonium iodide (15)

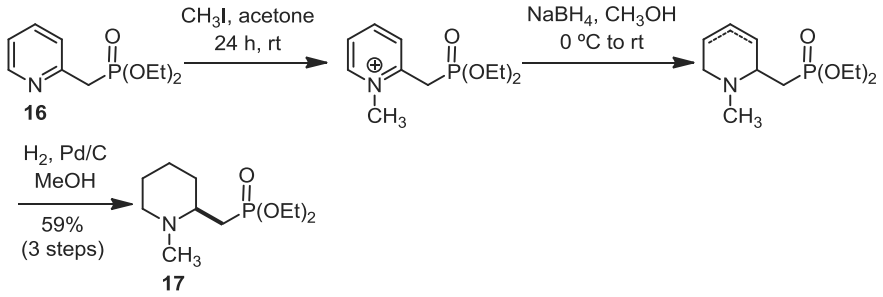


A mixture of **13** (506 mg, 1.33 mmol) and triphenylphosphine (2.8 g, 10.67 mmol, 8.0 equiv) was stirred at 100 ºC for 22 h. The reaction mixture was cooled and purified by chromatography (25→50% EtOAc / hexane followed by 10 % MeOH/CH_2Cl_2) to give 332 mg (39%) of **15**. R_f 0.5 (10% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.84 (m, 1H, H-5), 1.24 (m, 1H, H-3), 1.40 (d, *J* = 11.4 Hz, 2H, H-4, H-5), 1.72 (d, *J* = 14.0 Hz, 2H, H-3), 2.05 (m, 1H, H-4), 2.39 (s, 3H, CH_3Ar), 3.25 (td, *J* = 13.6, 2.4 Hz, 1H, H-6eq), 3.55 (dd, *J* = 15.6, 3.8 Hz, 1H, H-6ax), 4.02 (ddd, *J* = 9.2, 3.6 Hz, 1H, CH_2P), 4.35 (ddd, *J* = 14.8, 4.4, 2.0 Hz, 1H, CH_2P), 4.64 (m, 1H, H-1), 7.23 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.50 (m, 5H, Ph), 7.67 (m, 8H, Ph, *o*-Ts), 7.79 (m, 3H, *p*-Ph), 8.00 (m, 6H, Ph). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.1 (C-4), 21.7 (CH_3Ar), 22.6 (C-5), 26.4 (CH_2P), 29.7 (C-3), 41.5 (C-6), 49.1 (C-2), 118.0 (*ipso*-Ph), 118.9 (*ipso*-Ph), 127.1 (*o*-Ts), 128.6 (Ph), 128.7 (Ph), 130.1 (Ph), 130.3 (*m*-Ts), 130.5 (Ph), 132.0 (Ph), 132.1 (Ph), 132.2 (Ph), 134.2 (d, $J_{C\text{-}P}$ = 40 Hz, Ph), 135.0 (d, $J_{C\text{-}P}$ = 12.0 Hz, Ph), 137.9 (*p*-Ts), 143.9 (*ipso*-Ts). HRMS calcd for $C_{31}H_{33}NO_2SP$ $(M)^+$ 514.1964, found 514.1953


M400AQ_28022014_gsv355F12_15-H1
H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv355F12_15
Nom: GISELA SABORIT VILLARROYA
Data: 28/02/14 / Ope.: G.SABORIT
8.024
8.006
7.992
7.973
7.699
7.680
7.495
7.266
2.388
1.694
PPh3I
N
Ts
15
6.07
3.08
6.23
5.45
1.94
1.00
1.00
1.02
1.02
1.04
3.04
0.99
2.06
2.04
1.35
1.07
f1 (ppm)

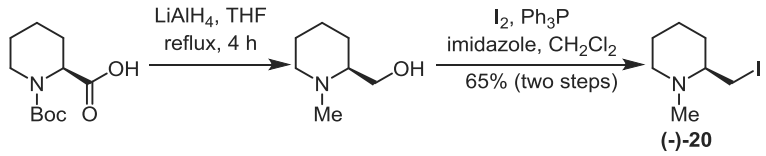

M400AQ_28022014_gsv355F12_15-C13
H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv355F12_15
Nom: GISELA SABORIT VILLARROYA
Data: 28/02/14 / Ope.: G.SABORIT
77.48
77.16
76.84
137.92
135.01
134.98
134.32
134.22
132.25
132.15
132.06
131.94
130.46
130.33
130.11
128.67
128.55
127.14
143.90
118.89
118.03
49.13
49.09
41.46
29.27
29.17
26.90
26.40
22.60
21.67
18.12
f1 (ppm)

(*RS*)-diethyl ((1-methylpiperidin-2-yl)methyl)phosphonate (*rac*-17)



A solution of pyridine phosphonate **16** (1.9 g, 8.48 mmol) and methyl iodide (7.22 g, 50.86 mmol, 6 equiv) in acetone (15 mL) was stirred at rt for 16 h. The solvent was removed and the resulting residue was used in the next step without further purification. Sodium borohydride (1.6 g, 42.38 mmol, 5.0 equiv) was added portionwise over 30 min to a cooled (0 ºC) stirred solution of the methiodide in methanol (27 mL). The reaction mixture was allowed to slowly come to room temperature, and stirring was continued overnight. The solvent was concentrated and the resulting residue was partitioned between EtOAc (20 mL) and water (15 mL). The aqueous was extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried, filtered and concentrated. Finally, to a solution of the previous crude in methanol (11 mL) was added Pd/C 10% w/w (580 mg, 0.3 equiv) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 overnight. The mixture was filtered through a pad of celite, washed through with CH_2Cl_2 and the filtrate was concentrated. Purification by chromatography (2.5→5→10% MeOH/CH_2Cl_2) afforded methyl piperidine (±)-**17** (1.24 g, 59% three steps) as a yellow oil. R_f 0.39 (10% MeOH/CH_2Cl_2) For ^{1}H NMR, ^{13}C, ^{31}P NMR, and HRMS data for **17**, see the section below describing the synthesis of enantiopure **17**.

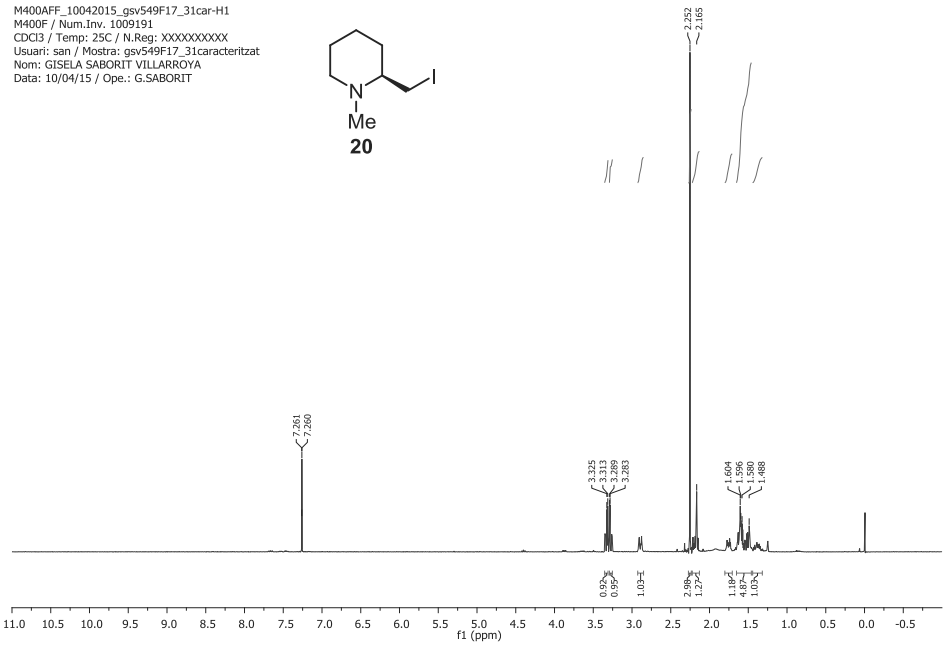
(*S*)-1-Methyl-2-iodomethylpiperidine (20)

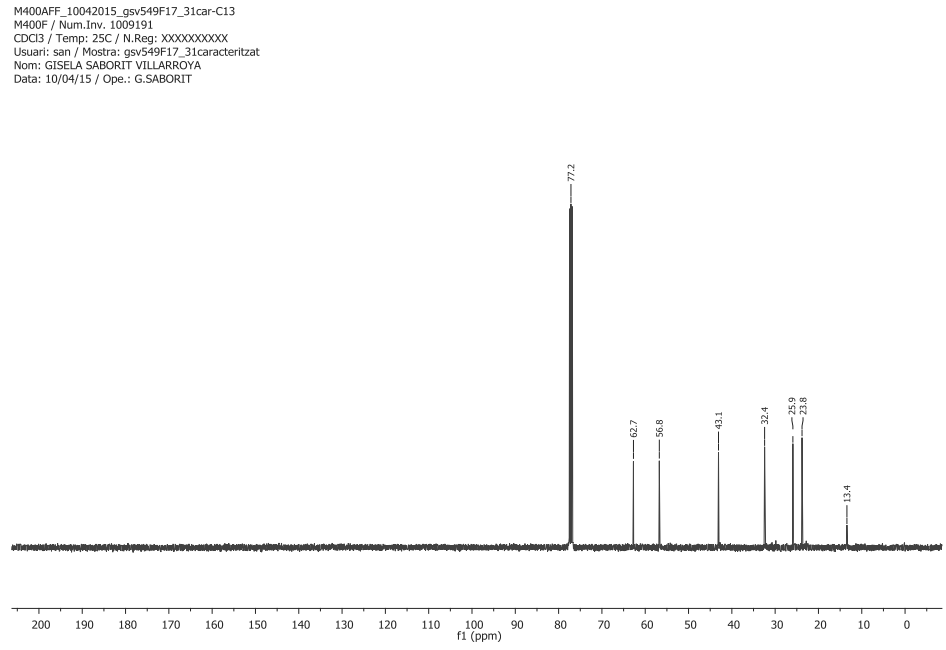


(-)-20

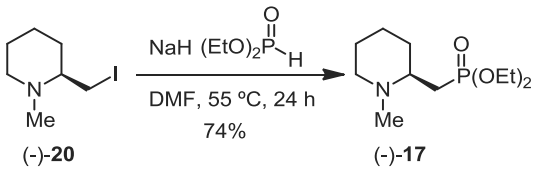
A solution of (S)-(-)-1-(*tert*-butyloxycarbonyl)-2-piperidine carboxylic acid (2.50 g, 10.9 mmol) in THF (45 mL) was added dropwise to a cooled (0 ºC) solution of $LiAlH_4$ (1.32 g, 34.9 mmol, 3.2 equiv) in THF (35 mL) under argon. The resulting mixture was refluxed for 4 h, cooled to 0 ºC and quenched by the dropwise addition of 1.3 mL of H_2O, 1.3 mL of aqueous 15% NaOH and 4.0 mL of H_2O. It was then diluted with Et_2O (50 mL), dried and filtered through a pad of celite. After it was washed through with CH_2Cl_2 the solvent was removed to give 1-methyl-2-piperidinemethanol[175] (1.13 g) pure enough to be used in the next step without further purification. To a suspension of imidazole (1.12 g, 17.49 mmol) and Ph_3P (3.44 g, 13.12 mmol, 1.5 equiv) in dry CH_2Cl_2 (21 mL) at 0 ºC was added I_2 (3.33 g, 13.12 mmol) in three portions over 30 minutes under argon. After stirring for an additional 10 min at rt, a solution of (S)-(-)-1-methyl-2-piperidinemethanol (1.13 mg, 8.75 mmol) in CH_2Cl_2 (22 mL) was added and the resulting mixture was stirred for 1 h at rt. The reaction mixture was concentrated and purified by chromatography (50→100% hexane/EtOAc, 0→0.5→1% CH_2Cl_2/ MeOH) to give 1.9 g of (-)-**20** (90% purity, 65% yield over 2 steps)[176] as a yellow solid: Rf = 0.57 (10% MeOH/CH_2Cl_2); $[\alpha]_D$ -8.22 (*c* 1, $CHCl_3$); mp 174 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 1.38 (m, 1H, H-4ax), 1.49 (m, 1H, H-2ax), 1.50-1.64 (m, 4H, H-5, H-3), 1.75 (dtd, *J* = 12.8, 3.6, 1.6 Hz, 1H, H-4eq), 2.18 (m, 1H, H-6ax), 2.25 (s, 3H, N-CH_3), 2.89 (dtd, *J* = 11.6, 2.6, 1.6 Hz, 1H, H-6eq), 3.27 (dd, *J* = 10.6, 2.2 Hz, 1H, CH_2I), 3.35 (dd, *J* = 10.4, 4.8 Hz, 1H, CH_2I). ^{13}C NMR (400 MHz, $CDCl_3$, HSQC) 13.4 (CH_2I), 23.8 (C-4), 25.9 (C-5), 32.4 (C-3), 43.1 (CH_3N), 56.8 (C-6), 62.7 (C-2). HRMS calcd for $C_7H_{14}NI$ $(M+H)^+$ 240.0244, found 240.0233.

[175] For NMR data, see Alvarez-Ibarra, C.; Luján, J. F. C.; Quiroga-Feijóo, M. L. *Tetrahedron: Asymmetry.* **2010**, *21*, 2334-2345.
[176] Compound (-)-**20** is contaminated with Ph_3PO; a simple acid-base wash allows pure (-)-**17** to be obtained. However, the iodide being very polar was partially lost in the process. Nevertheless, the remaining Ph_3PO does not affect the next step.


M400AFF_10042015_gsv549F17_31car-H1
M400F / Num.Inv. 1009191
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv549F17_31caracteritzat
Nom: GISELA SABORIT VILLARROYA
Data: 10/04/15 / Ope.: G.SABORIT
Me
20
2.252
2.165
7.261
7.260
3.315
3.313
3.289
3.283
1.604
1.596
1.580
1.488
0.92
0.95
1.03
2.98
1.27
1.00
4.87
1.03
1
f1 (ppm)

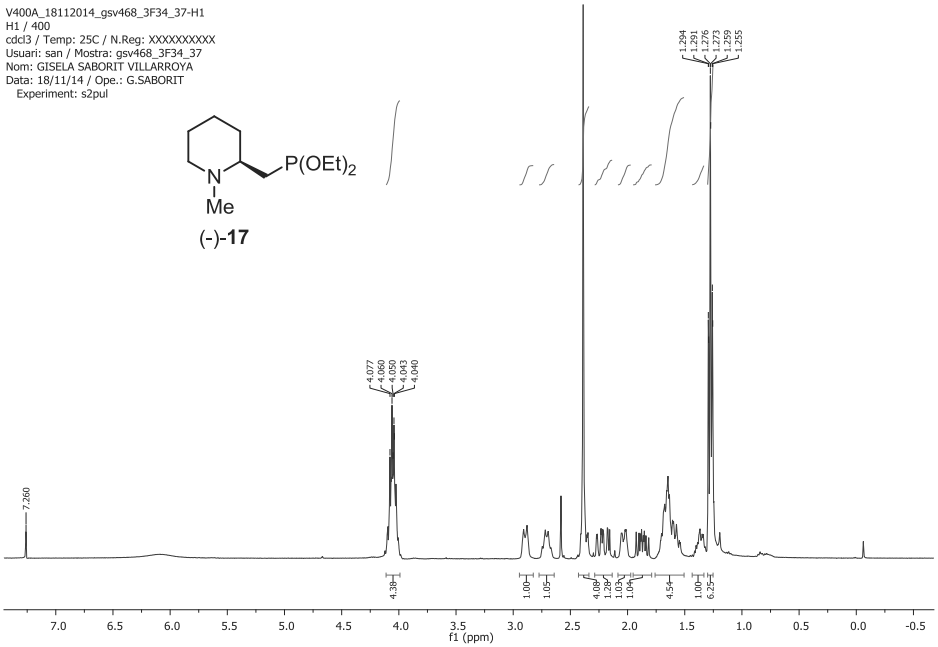

M400AFF_10042015_gsv549F17_31car-C13
M400F / Num.Inv. 1009191
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv549F17_31caracteritzat
Nom: GISELA SABORIT VILLARROYA
Data: 10/04/15 / Ope.: G.SABORIT
77.2
62.7
56.8
43.1
32.4
25.9
23.8
13.4
f1 (ppm)

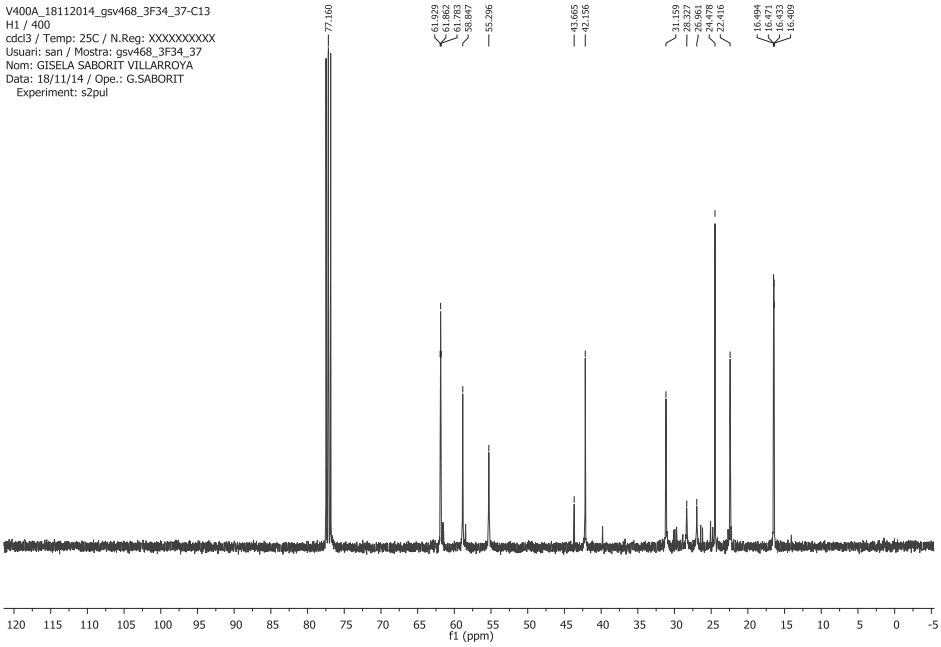
(*S*)-diethyl (1-methylpiperidine-2-yl)methylphosphonate (17)

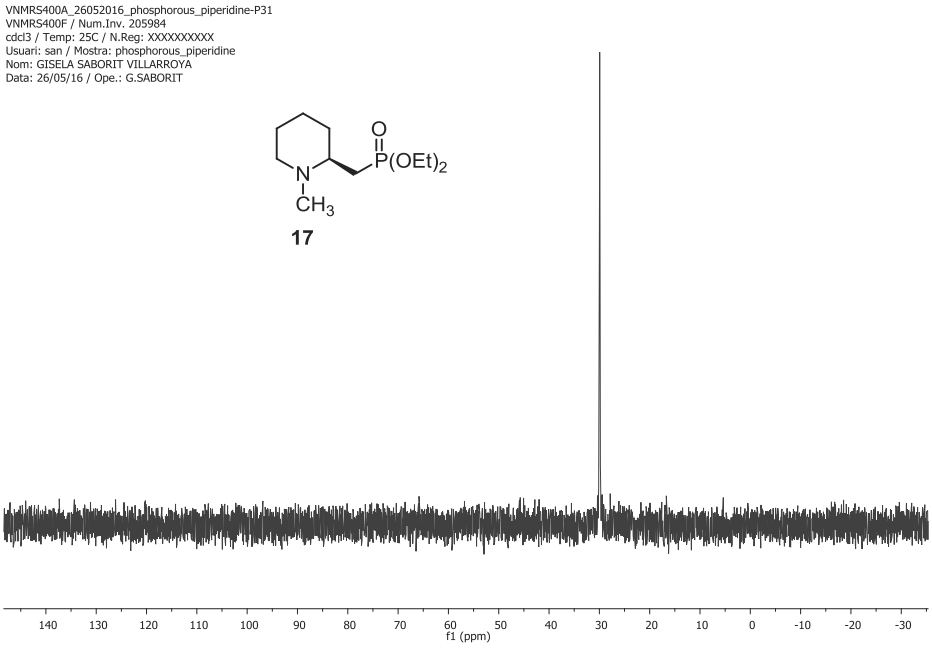


To a stirred suspension of NaH (953 mg, 23.84 mmol) in DMF (16 mL) under argon is carefully added diethyl phosphite (3.1 mL, 23.84 mmol) at 0 ºC. The mixture was stirred at rt for 45 min before a solution of (-)-**20** (1.9 g, 7.95 mmol) in dry DMF (15 mL) was added dropwise. The reaction was stirred at 55 ºC for 16 h and the solvent removed on a dry ice rotary evaporator. Chromatography (1%→2.5→5→10 % CH_2Cl_2/ MeOH) afforded (-)-**17** (1.1 g, 55%) as an oil: *Rf* 0.31 (10% MeOH/CH_2Cl_2); $[\alpha]_D$ -18.7 (c 1, $CHCl_3$);[177] ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) δ 1.27 (td, 6H, *J* = 7.2, 1.5 Hz, C*H*$_3$), 1.38 (m, 1H, H-4), 1.54-1.70 (m, 4H, H-3, H-4, 2H-5), 1.87 (ddd, $^2J_{H,P}$ = 20.0; 15.2, 9.6 Hz, 1H, CH_2P), 2.03 (br d, *J* = 12.0 Hz, 1H, H-3eq), 2.21 (ddd, $^2J_{H,P}$ = 20.0; 15.2, 3.6 Hz, 1H, CH_2P), 2.39 (s, 3H, NCH_3), 2.43 (masked, 1H, H-6eq), 2.71 (dddd, *J* = 12.2, 9.6, 5.2, 3.4 Hz, 1H, H-2ax), 2.96 (br d, *J* = 12 Hz, 1H, H-6eq), 4.06 (m, 4H, OC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) δ 16.4 and 16.5 (2d, $^3J_{CP}$ = 2.3, *C*H_3), 22.4 (C-4), 24.4 (C-5), 27.7 (br d, $^1J_{C,P}$ = 137.0 Hz, CH_2-P), 30.9 (C-3), 42.2 (NCH_3), 55.3 (C-6), 58.9 (C-2), 61.9 (t, $^2J_{C,P}$ = 7.3 Hz, O*C*H_2); ^{31}P (162 MHz, $CDCl_3$) δ 29.9. HRMS calcd for $C_{11}H_{25}NO_3P$ $(M+H)^+$ 250.1567, found 250.1575.

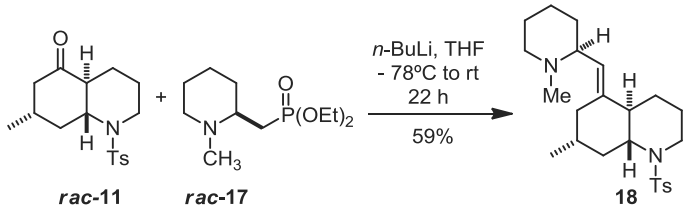
[177] The sample was slightly impurified


V400A_18112014_gsv468_3F34_37-H1
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv468_3F34_37
Nom: GISELA SABORIT VILLARROYA
Data: 18/11/14 / Ope.: G.SABORIT
Experiment: s2pul
P(OEt)2
N
Me
(-)-17
f1 (ppm)


V400A_18112014_gsv468_3F34_37-C13
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv468_3F34_37
Nom: GISELA SABORIT VILLARROYA
Data: 18/11/14 / Ope.: G.SABORIT
Experiment: s2pul
f1 (ppm)

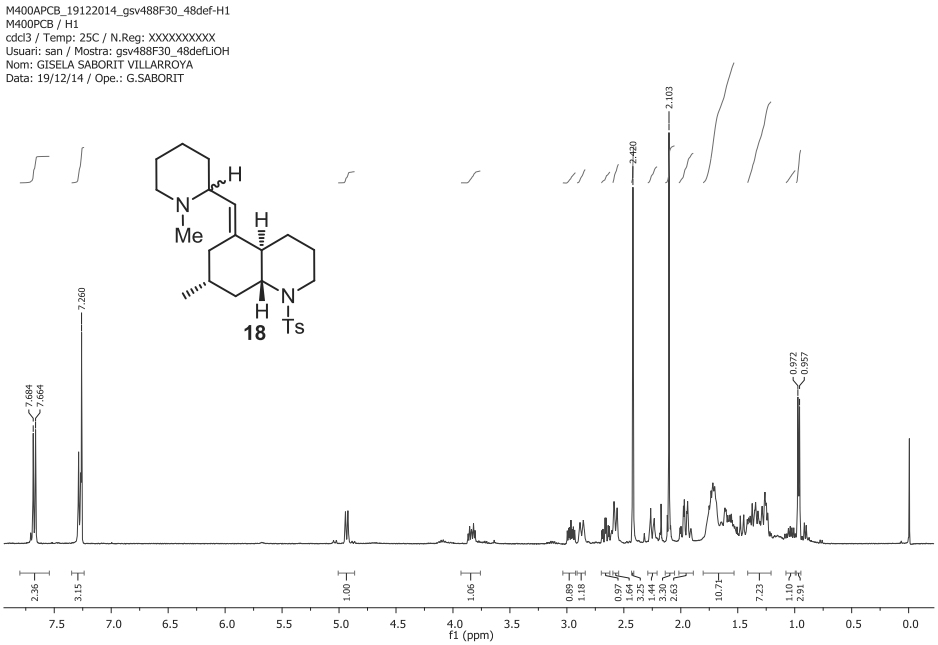

VNMRS400A_26052016_phosphorous_piperidine-P31
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: phosphorous_piperidine
Nom: GISELA SABORIT VILLARROYA
Data: 26/05/16 / Ope.: G.SABORIT
O
P(OEt)2
N
CH3
17
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

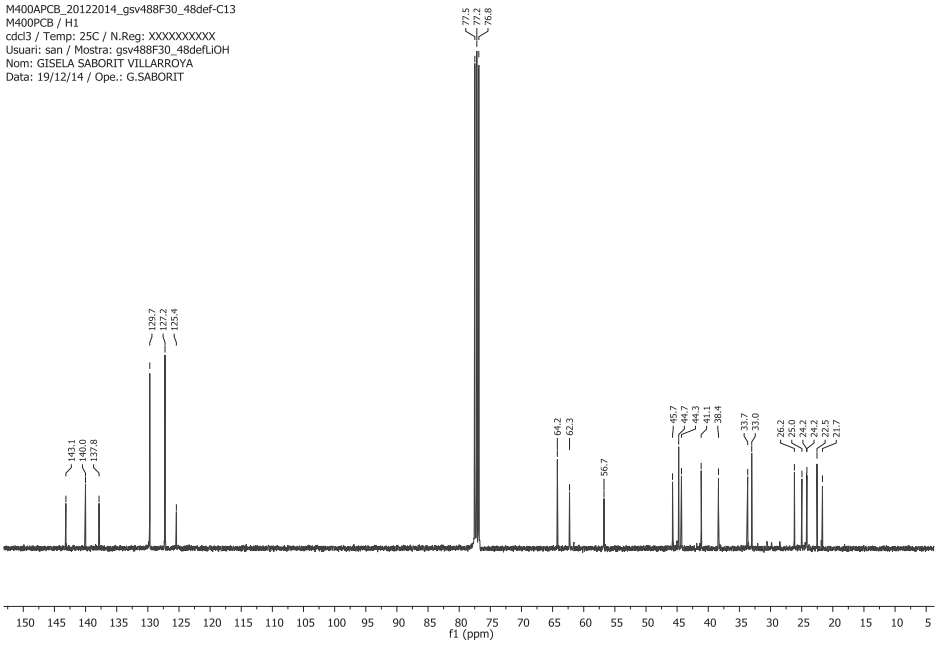
(4a*RS*,7*RS*,8a*RS*)-5-[(*SR*)-(1-methyl)-2-piperidylmethyl)]-7-methyl-1-(4-methylsulfonyl)decahydroquinoline (18)



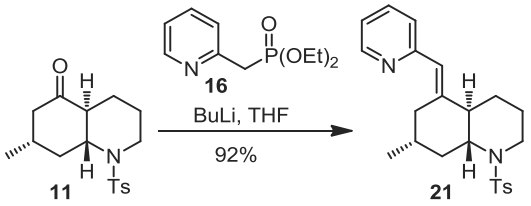
***rac*-11** ***rac*-17** **18**

Both the piperidine phosphonate and the decahydroquinoline were previously dried by azeotroping with benzene. To a stirred solution of *rac*-**17** (126 mg, 0.508 mmol, 3.5 equiv) in THF (2 mL) was added n-BuLi (1.6 M in hexane solution, 0.34 mL, 3.5 equiv) at – 78 ºC. The reaction mixture was stirred for 10 min at -78 °C, then a solution of decahydroquinoline *rac*-**11** (50 mg, 0.156 mmol, 1.0 equiv) in THF (1 mL) was added and the mixture stirred for 5 min at – 78 ºC. Finally, the reaction mixture was allowed to warm to rt and stirred for 22 h at rt. Concentration of the reaction mixture, followed by purification by chromatography (5→10% MeOH/CH_2Cl_2 followed by 1:2:0.1 MeOH/CH_2Cl_2/concd NH_4OH) afforded **18** (38 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 0.97 (d, 3H, *J* = 6.0 Hz, 3H), 1.24 (m, 1H, H-6ax), 1.25-1.30 (m, 2H, H-7, H-3'), 1.46 (m, 1H, H-8ax), 1.50-1.80 (m, 8H, 2H-3, 2H-4, 2H-4', 2H-5'), 1.92 (td, *J* = 11.6, 3.2 Hz, 1H, H-4a), 1.96 (td, *J* = 11.6, 3.2 Hz, 1H, H-6'ax), 2.11 (s, 3H, N-CH_3), 2.26 (d, *J* = 12.4 Hz, 1H, H-8eq), 2.56 (d, 1H, *J* = 10.8 Hz, H-2'), 2.55 (masked, 1H, H-6eq), 2.66 (td, *J* = 11.2, 3.6 Hz, H-8a), 2.87 (dt, *J* = 11.2, 4.0 Hz, 1H, H-6'eq), 2.96 (ddd, *J* = 12.8, 10.4, 4.8 Hz, 1H, H-2ax), 3.83 (dt, *J* = 12.8, 5.6 Hz, 1H, H-2eq), 4.90 (d, 1H, *J* = 8.8 Hz, =CH), 7.28 (d, *J* = 8.0 Hz, 2H, *o*-Ts), 7.67 (d, *J* = 8.0 Hz, 2H, *m*-Ts); ^{13}C NMR (400 MHz, $CDCl_3$, HSQC) δ 21.7 (ArCH_3), 22.5 (7-CH_3), 24.1 (C-3), 24.2 (C-4'), 25.0 (C-4), 26.1 (C-5'), 33.0 (C-7), 33.7 (C-3'), 38.4 (C-6), 41.2 (C-8), 44.3 (N CH_3), 44.8 (C-4a), 45.8 (C-2), 56.8 (C-6'), 62.2 (C-2'), 64.1 (C-8a), 125.6 (=CH), 127.9 (*o*-Ts), 130.2 (*m*-Ts), 137.8 (*p*-Ts), 140.2 (C-5), 143.4 (*ipso*-Ts). HRMS calcd for $C_{24}H_{37}N_2O_2S$ $(M+H)^+$ 417.2570, found 417.2587

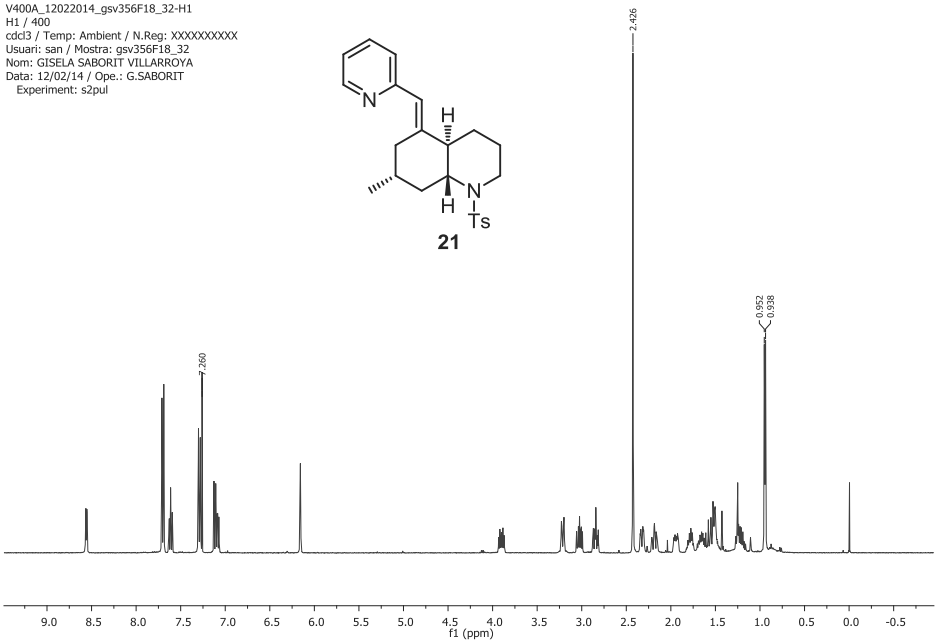

M400APCB_19122014_gsv488F30_48def-H1
M400PCB / H1
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv488F30_48defLiOH
Nom: GISELA SABORIT VILLARROYA
Data: 19/12/14 / Ope.: G.SABORIT
Me
H
N
H
N
Ts
18
7.684
7.664
7.260
2.420
2.103
0.977
0.957
f1 (ppm)


M400APCB_20122014_gsv488F30_48def-C13
M400PCB / H1
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv488F30_48defLiOH
Nom: GISELA SABORIT VILLARROYA
Data: 19/12/14 / Ope.: G.SABORIT
77.5
77.2
76.8
143.1
140.0
137.8
129.7
127.2
125.4
64.2
62.3
56.7
45.7
44.7
44.3
41.1
38.4
33.7
33.0
26.2
25.0
24.2
24.2
22.5
21.7
f1 (ppm)

(*E*)-(4a*R*,7*R*,8aR)-7-Methyl-1-(4-methylsulfonyl)-5-(pyridin-2-ylmethylene)decahydroquinoline (21)



Both the pyridine phosphonate and decahydroquinoline (-)-**11** were previously dried by azeotroping with benzene. To a stirred solution of phosphonate **16** (264 mg, 1.15 mmol) in THF (3.3 mL) at -78 ºC was added n-BuLi (1.6 M in hexanes, 0.72 mL, 1.15 mmol). The resulting red solution was stirred for 30 min at rt before a solution of decahydroquinoline (-)-**11** (75 mg, 0.23 mmol) in THF (1.5 mL) was added dropwise via syringe at -78 ºC. The reaction mixture was stirred for 30 min at -78 ºC, 1 h at -30 ºC and 1 h at 0 ºC before it was quenched with sat. aq. NH_4Cl (6.0 mL). The mixture was extracted with EtOAc (2 × 6 mL) and the combined organic extracts were dried, filtered, concentrated and purified by chromatography (5→10→25% EtOAc/hexane) to give **21** (84 mg, 92%) as a white solid. R_f 0.45 (50% hexanes/EtOAc); mp = 122 ºC. $[\alpha]_D$ +51.98 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 0.94 (d, *J* = 5.6 Hz, 3H, CH_3), 1.22 (qd, *J* = 12.4, 6.4 Hz, 1H, H-4ax), 1.45-1.60 (m, 3H, H-6ax, H-7ax, H-8ax), 1.65 and 1.78 (2m, 1H each, 2H, 2H-3), 1.95 (dm, *J* = 12.8 Hz 1H, H-4eq), 2.18 (tm, *J* = 12.0 Hz, 1H, H-4a), 2.32 (dm, *J* = 12.4 Hz, H-8eq), 2.42 (s, 3H, $ArCH_3$), 2.85 (td, *J* = 10.8, 3.6 Hz, 1H, H-8a), 3.02 (td, *J* = 11.6, 2.8, 4.4 Hz, 1H, H-2ax), 3.21 (dd, *J* = 9.8, 1.8 Hz, 1H, H-6eq), 3.90 (dt, *J* = 11.6, 5.8 Hz, 1H, H-2eq), 6.16 (s, 1H, C=CH), 7.08 (m, 1H, H-5 py), 7.11 (d, *J* = 8.0 Hz, 1H, H-3 py), 7.28 (d, *J* = 8.0 Hz, 2H, *o*-Ts), 7.60 (td, *J* = 7.6, 2.0 Hz, 1H, H-4 py), 7.70 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 8.54 (dm, *J* = 4.8 Hz, 1H, H-6 py). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 21.7 (CH_3Ar), 22.4 (7-CH_3), 24.1 (C-3), 25.2 (C-4), 32.6 (C-7), 38.2 (C-6), 41.1 (C-8), 45.3 (C-4a), 45.8 (C-2), 63.9 (C-8a), 121.1 (C-5 py), 121.8 (=CH), 124.2 (C-3, py), 127.3 (*o*-Ts), 129.7 (*m*-Ts), 136.1 (C-4 py), 137.3 (*p*-Ts), 143.2 (*ipso*-Ts), 146.5 (C-5), 149.4 (C-6 py), 157.2 (C-2 py). HRMS calcd for $C_{23}H_{29}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.1956.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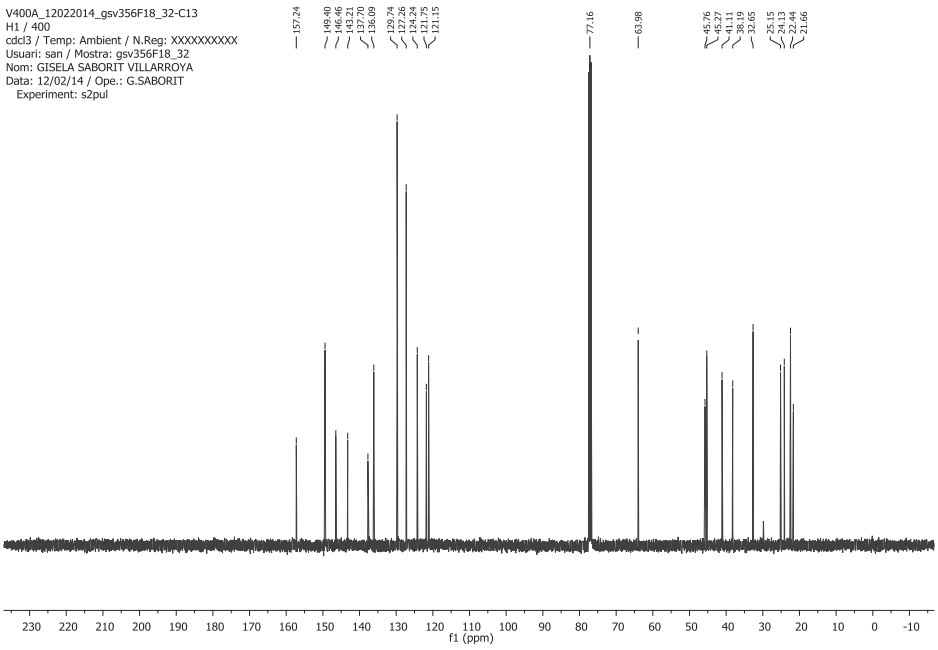
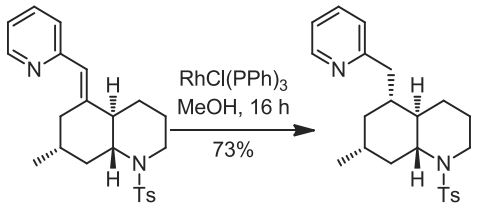
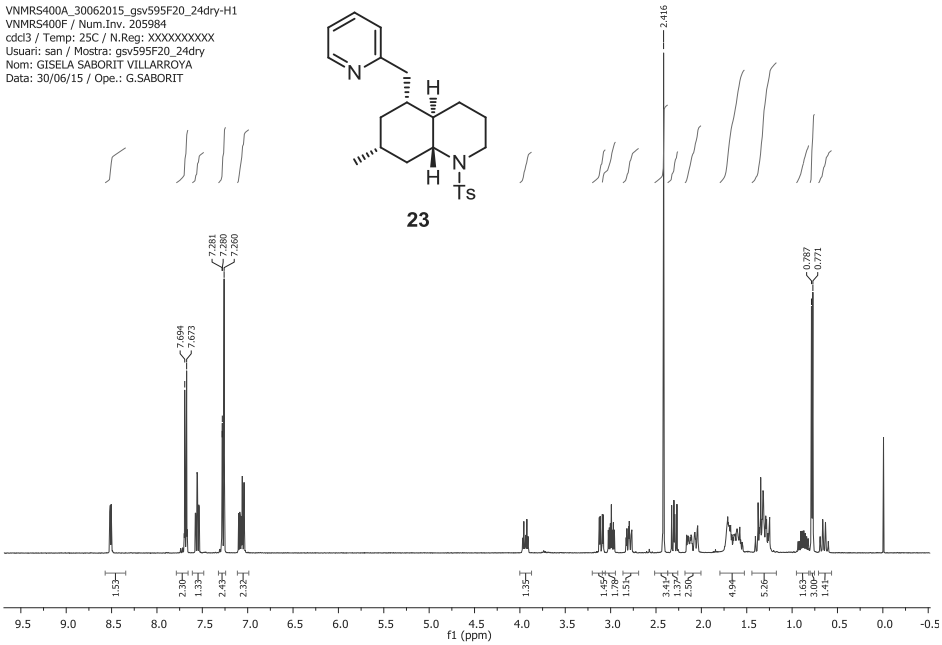
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv356F18_32
Nom: GISELA SABORIT VILLARROYA
Data: 12/02/14 / Ope.: G.SABORIT
Experiment: s2pul
N
H
H
N
Ts
21
2.426
7.260
0.952
0.938
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


V400A_12022014_gsv356F18_32-C13
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv356F18_32
Nom: GISELA SABORIT VILLARROYA
Data: 12/02/14 / Ope.: G.SABORIT
Experiment: s2pul
157.24
149.40
146.46
143.21
137.70
136.09
129.74
127.26
124.34
121.75
121.15
77.16
63.98
45.76
45.27
41.11
38.19
32.65
25.15
24.13
23.44
21.66
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(4aR,5S,7R,8aR)-7-methyl-5-(pyridin-2-ylmethyl)-1-tosyldecahydro quinoline (23)



Alkene **22** (8.0 mg, 0.03 mmol) was hydrogenated overnight in the presence of Wilkinson's catalyst (0.15 eq) in methanol (2.61 mL, 0.01 M). The reaction mixture was concentrated and the residual oil was subjected to chromatography (5→10→25→40% EtOAc/hexane) to give **23** (16 mg, 73%) as a single isomer. R_f 0.38 (50% hexanes/EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.65 (q, *J* = 12.0 Hz, 1H, H-6ax), 0.78 (d, *J* = 6.0 Hz, 3H, CH_3), 0.88 (qd, *J* = 12.0, 6.4 Hz, 1H, H-4ax), 1.32 (m, 3H, H-7, H-6, H-4a), 1.61 (m, 3H, H-3, H-5), 2.06 (dm, *J* = 10.4 Hz, 1H, H-8), 2.13 (qd, *J* = 9.6, 2.8 Hz, 1H, H-4eq), 2.30 (dd, *J* = 13.2, 10.0 Hz, 1H, CH_2Py), 2.42 (s, 3H, $ArCH_3$), 2.80 (td, *J* = 10.4, 3.2 Hz, 1H, H-8a), 2.99 (ddd, *J* = 13.2, 8.8, 4.4 Hz, 1H, H-2ax), 3.10 (dd, *J* = 13.2, 4.0 Hz, 1H, CH_2Py), 3.94 (dt, *J* = 13.2, 5.2 Hz, 1H, H-2eq), 7.05 (d, *J* = 8.0 Hz, 1H, H-3 Py), 7.09 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H, H-5 Py), 7.27 (d, *J* = 8 Hz, 2H, *m*-Ts), 7.56 (td, *J* = 7.6, 2.0 Hz, 1H, H-4 Py), 7.68 (d, *J* = 8.0 Hz, 2H, *o*-Ts), 8.51 (dm, *J* = 4.8 Hz, 1H, H-6 Py). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.6 ($ArCH_3$), 22.4 (CH_3), 24.9 (C-3), 27.4 (C-4), 31.3 (C-7), 40.1 (C-6), 40.3 (C-8), 42.2 (C-5), 42.2 (CH_2Py), 44.4 (C-4a), 47.0 (C-2), 64.3 (C-8a), 121.1 (C-5 Py), 124.1 (C-3 Py), 127.1 (*o*-Ts), 129.6 (*m*-Ts), 136.1 (C-4 Py), 138.8 (*p*-Ts), 142.9 (*ipso*-Ts), 149.5 (C-6 Py), 161.1 (C-2 Py). HRMS calcd for $C_{23}H_{31}N_2O_2S$ $(M+H)^+$ 399.2101, found 399.2096.


VNMRS400A_30062015_gsv595F20_24dry-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv595F20_24dry
Nom: GISELA SABORIT VILLARROYA
Data: 30/06/15 / Ope.: G.SABORIT
N
H
H
N
Ts
23
2.416
7.281
7.280
7.260
7.694
7.673
0.797
0.771
1.53
2.30
1.33
2.43
2.32
1.35
1.45
1.78
1.55
3.47
1.37
2.50
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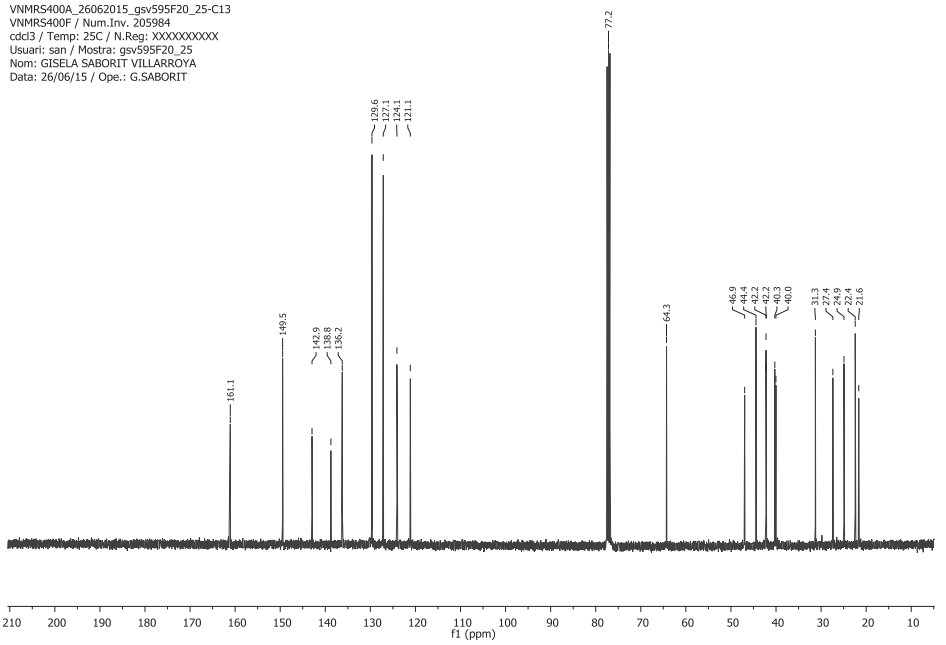
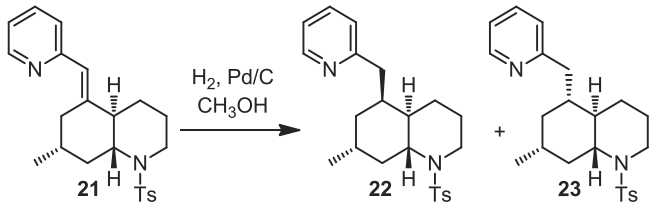
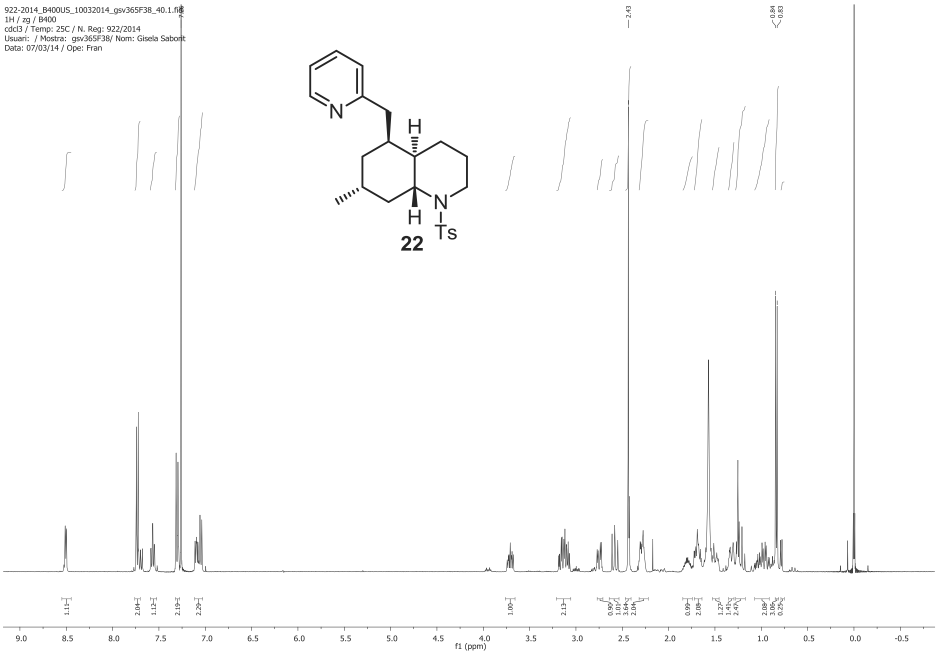
5.26
1.63
3.00
1.41
f1 (ppm)


VNMRS400A_26062015_gsv595F20_25-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv595F20_25
Nom: GISELA SABORIT VILLARROYA
Data: 26/06/15 / Ope.: G.SABORIT
77.2
129.6
127.1
124.1
121.1
161.1
149.5
142.9
138.8
136.2
64.3
46.9
44.4
43.2
42.2
40.3
40.0
31.3
27.4
26.9
22.4
21.6
f1 (ppm)

(4aR,5S,7R,8aR)-7-methyl-5-(pyridin-2-ylmethyl)-1-tosyldecahydroquinoline (22)



To a stirred solution of **21** (30 mg, 0.081 mmol) in MeOH (0.8 mL) was added Pd/C (10% w/w, 15 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 for 5 h. The mixture was diluted with CH_2Cl_2, filtered through a pad of celite, washed through with CH_2Cl_2 and the filtrate was concentrated. An analytical sample of **22** was obtained by chromatography (2.5→5→10→20→30% EtOAc/hexane). NMR data for the phlegmarine type **22**: R_f 0.45 (50% hexanes/EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 0.94 (d, *J* = 6.8 Hz, 3H, CH_3), 1.00 (m, 2H, H-4, H-6), 1.23 (q, *J* = 12.4 Hz, 1H, H-8), 1.32 (dm, *J* = 13.6 Hz, 1H, H-4ax), 1.49 (m, 1H, H-6), 1.69 (m, 2H, C-3, C-5eq), 1.80 (m, 1H, C-7), 2.29 (m, 2H, H-8, H-4a), 2.43 (s, CH_3Ar), 2.58 (dd, *J* = 16.0, 13.2 Hz, 1H, CH_2Py), 2.75 (dd, *J* = 13.2, 4.0 Hz, 1H, CH_2Py), 3.08 (ddd, *J* =3.6 Hz, 1H, H-2ax), 3.15 (m, 1H, C-8a), 3.71 (t, *J* = 13.8 Hz, 1H, C-2ax), 7.05 (d, *J* = 8.0 Hz, 1H, H-5py), 7.08 (dd, *J* = 7.2, 5.6 , H-3 Py), 7.28 (d, *J* = 8.4 Hz, 2H, *o*-Ts), 7.37 (td, *J* = 7.6, 2.0 Hz, H-4 Py), 7.73 (d, *J* = 8.4 Hz, 2H, *m*-Ts), 8.5 (dm, *J* = 4.8 Hz, 1H, H-6 Py). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 21.7 ($ArCH_3$), 22.4 (CH_3), 24.1 (C-3), 26.2 (C-6), 26.5 (C-7), 35.9 (CH_2Py), 37.4 (C-4), 39.7 (C-4a), 41.9 (C-8), 42.8 (C-5), 44.1 (C-2), 58.2 (C-8a), 121.2 (C-5 Py), 123.6 (C-3 Py), 127.2 (*o*-Ts), 129.6 (*m*-Ts), 136.4 (C-4 py), 137.7 (*p*-Ts), 143.2 (*ipso*-Ts), 149.5 (C-6 Py), 161.5 (C-2 Py). HRMS calcd for $C_{23}H_{31}N_2O_2S$ $(M + H)^+$, 399..2101 found 399.2095.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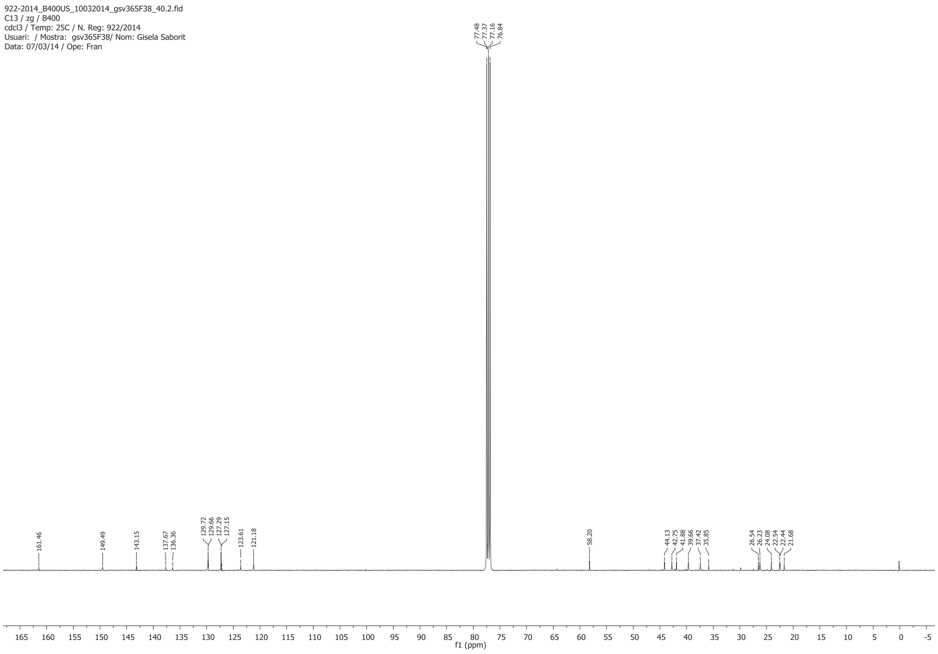
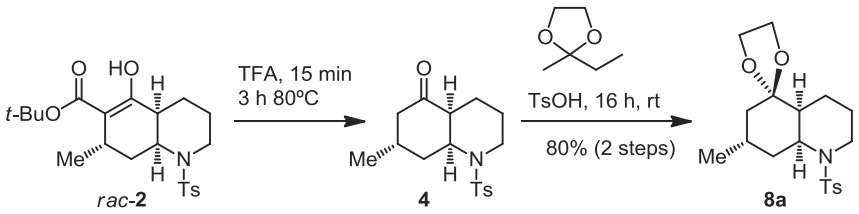
1H / zg / B400
cdcl3 / Temp: 25C / N. Reg: 922/2014
Usuari: / Mostra: gsv365F38/ Nom: Gisela Saborit
Data: 07/03/14 / Ope: Fran
22
Ts
f1 (ppm)

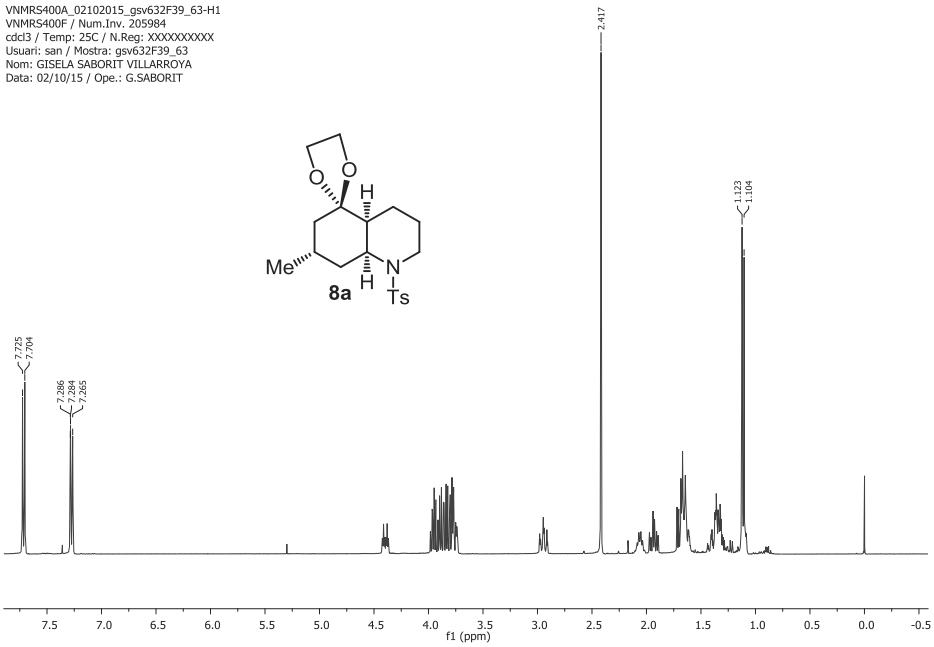

922-2014_B400US_10032014_gsv365F38_40.2.fid
C13 / zg / B400
cdcl3 / Temp: 25C / N. Reg: 922/2014
Usuari: / Mostra: gsv365F38/ Nom: Gisela Saborit
Data: 07/03/14 / Ope: Fran
f1 (ppm)

(4a*RS*,7*RS*,8a*SR*)-7-Methyl-1-(4-methylsulfonyl)-5-oxodecahydroquinoline ethylene acetal (8a)



A solution of *rac*-**2**[178] (536 mg, 1.27 mmol, 1 equiv) in TFA (1.27 mL) was stirred for 15 min at rt. The solvent was evaporated under reduced pressure, the last traces of TFA were removed by azeotroping with toluene (3 × 2 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 70 ºC for 3 h to give the crude decahydroquinoline **4**. 2-ethyl-2-methyl-1,3-dioxolane (1.6 mL, 12.73 mmol, 10 equiv) was added followed by TsOH (12 mg, 0.064 mmol, 0.05 equiv) and the mixture was stirred for 16 h at room temperature. The reaction was then diluted with Et_2O (15 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous was extracted with of Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (7 mL), dried, and concentrated. Purification by chromatography (5→10→25% EtOAc/hexane) gave **8a** (373 mg, 80%) as a white solid: *Rf* = 0.71 (1:1 EtOAc/hexanes); mp 100 °C.; ^{1}H NMR (400 MHz, COSY) 1.09 (dm, *J* = 13.2 Hz, 1H, H-8eq), 1.11 (d, *J* = 7.2 Hz, 3H, Me), 1.28-1.38 (m, 2H, H-4, H-6), 1.41 (dm, *J* = 12.5 Hz, 1H, H-3eq), 1.60-1.65 (m, 2H, H-3, H-4), 1.66 (m, 1H, H-4a), 1.69 (dd, *J* = 14.0, 6.4 Hz, 1H, H-6), 1.93 (td, *J* = 13.2, 5.6 Hz, 1H, H-8ax), 2.05 (m,1H, H-7eq), 2.41(s, 3H, $ArCH_3$) 2.96 (td, *J* = 13.2, 3.0 Hz, 1H, H-2ax), 3.75 (dm, *J* = 13.2 Hz, 1H, H-2eq), 3.78-3.98 (m, 4H, OCH_2), 4.39 (dt, *J* = 13.2, 4.4 Hz, 1H, H-8a), 7.71 (d, *J* = 8.4 Hz, 2H, *m*-Ts), 7.27 (d, *J* = 8.0 Hz, 2H, *o*-Ts); ^{13}C NMR (400 MHz, HSQC) 19.5 (CH_3), 20.0 (C-3), 21.3 ($ArCH_3$), 24.5 (C-4), 26.1 (C-7), 27.4 (C-8), 34.4 (C-6), 39.9 (C-2), 43.2 (C-4a), 49.0 (C-8a), 63.4 and 64.2 (OCH_2), 110.5 (C-5), 126.8 (*o*-Ts), 129.4 (*m*-Ts), 138.5 (*p*-Ts), 142.7 (*ipso*-Ts). HRMS calcd for $C_{19}H_{28}NO_4S$ $(M+H)^+$ 366.1734, found 366.1733.

[178] *Rac*-**2** was previously crystallized in methanol to remove traces of the keto form of this compound. If this is not done, when treated with TFA the keto form spontaneously opens to give **5**, which then forms the type B decahydroquinoline **6**.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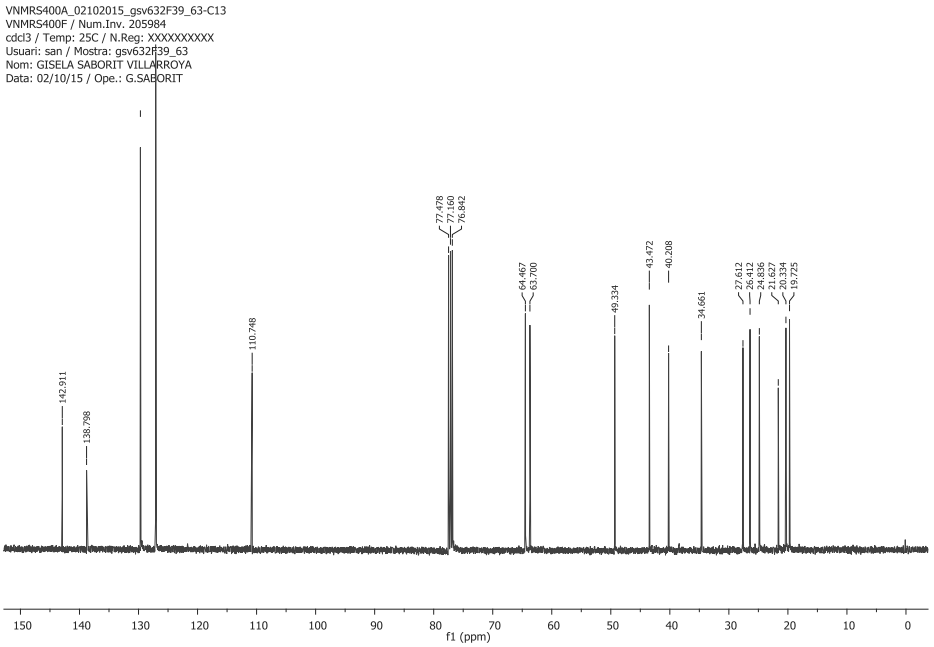
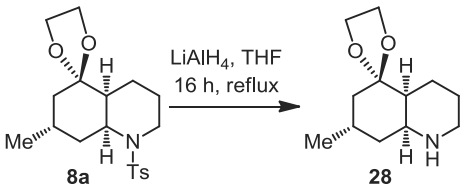
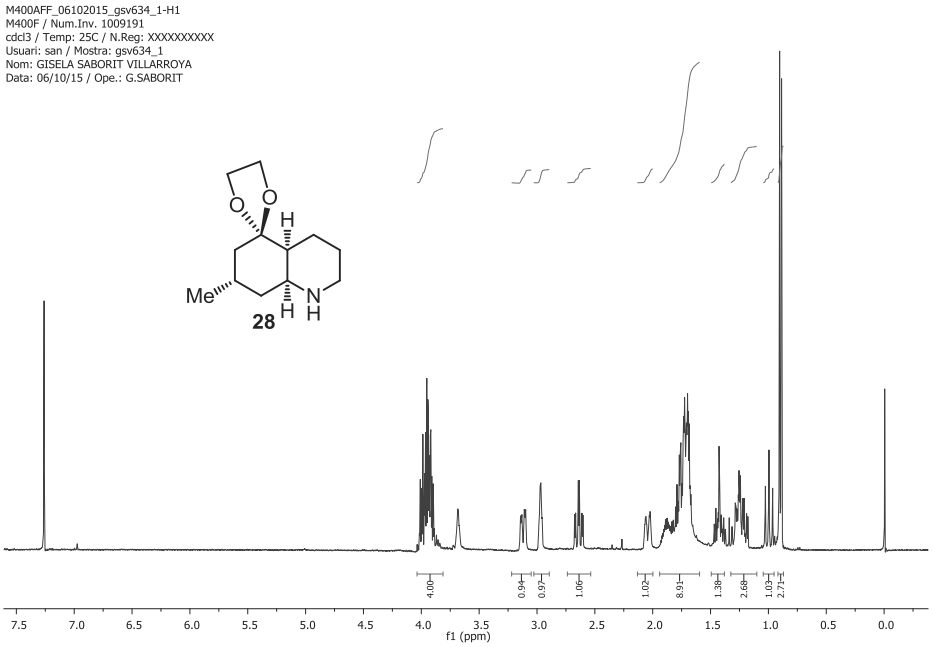
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv632F39_63
Nom: GISELA SABORIT VILLARROYA
Data: 02/10/15 / Ope.: G.SABORIT
2.417
1.123
1.104
7.725
7.704
7.286
7.284
7.265
Me
H
H
N
Ts
8a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

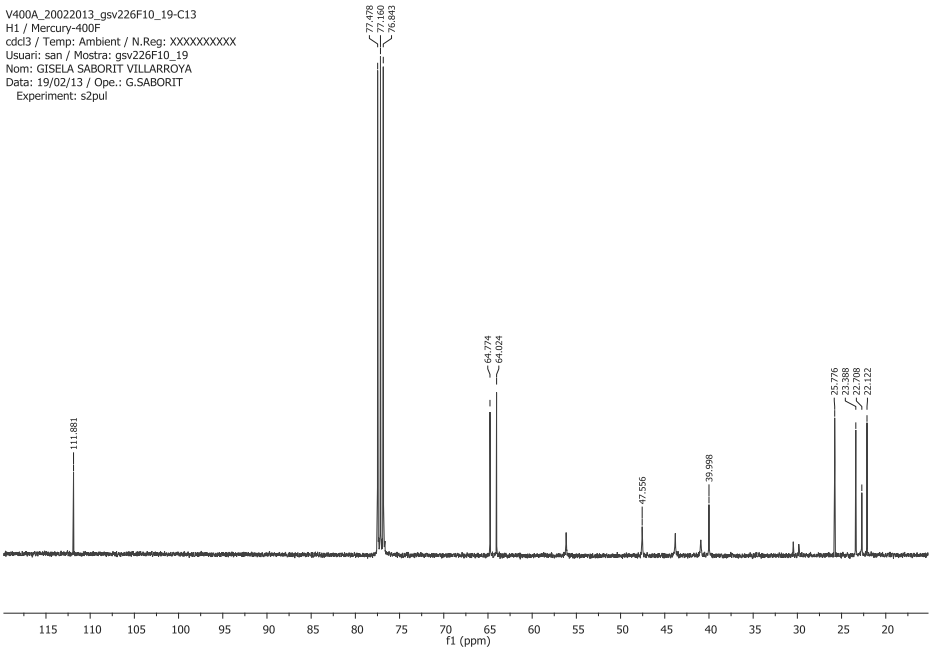

VNMRS400A_02102015_gsv632F39_63-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv632F39_63
Nom: GISELA SABORIT VILLARROYA
Data: 02/10/15 / Ope.: G.SABORIT
142.911
138.798
110.748
77.478
77.160
76.842
64.467
63.700
49.334
43.472
40.208
34.661
27.612
24.873
24.836
21.627
20.334
19.725
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(4a*RS*,7*RS*,8a*SR*)-7-Methyl-5-oxodecahydroquinoline ethylene acetal (28)

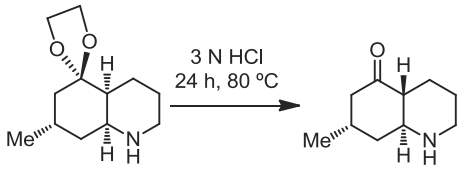


To a solution of $LiAlH_4$ (388 mg, 10.21 mmol, 10 equiv) in THF (6 mL) at 0 ºC was added dropwise a solution of **8a** (373 mg, 1.02 mmol) in THF (32 mL). The resulting mixture was allowed to warm to room temperature and then refluxed for 16 h. The reaction was cooled to 0 ºC and quenched by careful dropwise addition of water (0.4 mL), 2 N NaOH (0.4 mL), and water (1.2 mL). The mixture was diluted with diethyl ether (12 mL), dried and stirred for 15 minutes. Filtration through a pad of celite and concentration gave amine **28** (184 mg) as a light yellow oil. The compound was used in the next step without further purification. An analytical sample for analysis was obtained by chromatography (5→10% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, COSY) 0.89 (d, *J* = 6.8 Hz, 3H, Me), 0.99 (t, *J* = 12.4 Hz, 1H, H-6ax), 1.18-1.29 (m, 2H, H-3, H-8), 1.38-1.45 (m, 1H, H-4ax), 1.7-1.8 (m, 4H, H-3, H-4a, H-6eq, H-8), 1.85 (m, 1H, H-7ax), 2.04 (ddd, *J* = 11.6, 4.4, 2.4 Hz, 1H, H-4eq), 2.64 (td, *J* = 12.8, 3.6 Hz, 1H, H-2ax), 2.97 (q, *J* = 3.2 Hz, 1H, H-8a), 3.13 (dt, *J* = 12.4, 2.4 Hz, 1H, H-2eq), 3.89-4.01 (m, 4H, OCH_2); ^{13}C NMR (400 MHz, HSQC) 22.0 (CH_3), 22.5 (C-3), 23.2 (C-4), 25.6 (C-7), 39.8 (C-4a), 40.8 (C-8), 43.6 (C-6), 47.4 (C-2), 56.0 (C-8a), 63.9 and 64.6 (OCH_2), 111.7 (C-5). HRMS calcd for $C_{12}H_{22}NO_2$ (M+H)+ 212.1645, found 121.1644.


M400AFF_06102015_gsv634_1-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv634_1
Nom: GISELA SABORIT VILLARROYA
Data: 06/10/15 / Ope.: G.SABORIT
Me
H
N
H
28
4.00
0.94
0.97
1.06
1.02
8.91
1.38
2.60
1.03
2.71
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)

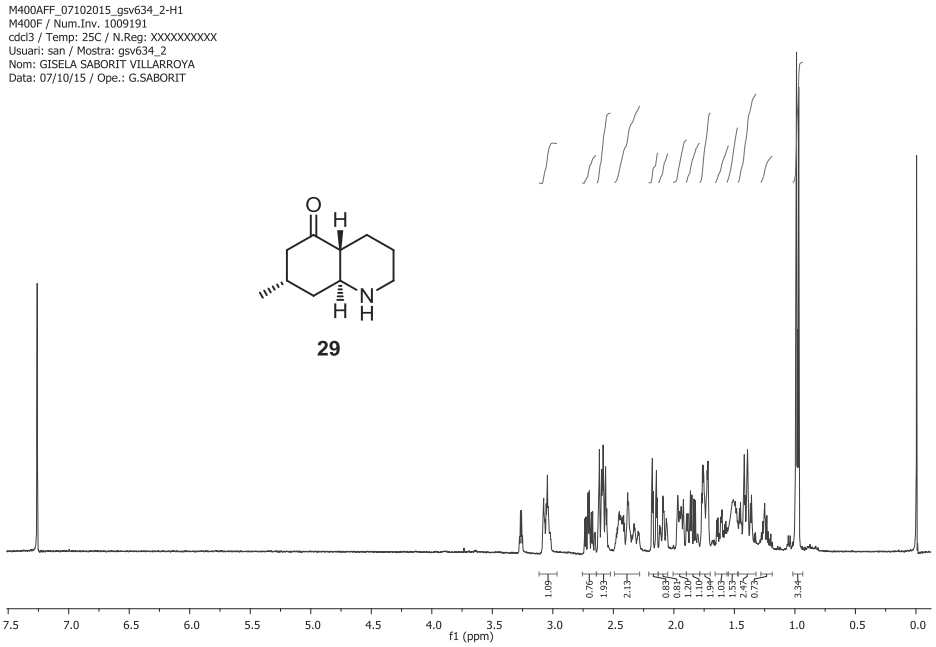

V400A_20022013_gsv226F10_19-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv226F10_19
Nom: GISELA SABORIT VILLARROYA
Data: 19/02/13 / Ope.: G.SABORIT
Experiment: s2pul
77.478
77.160
76.843
64.774
64.024
111.881
47.556
39.998
35.776
23.588
22.708
22.122
115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

(4a*RS*,7*SR*,8a*SR*)-7-Methyl-5-oxodecahydroquinoline (29)

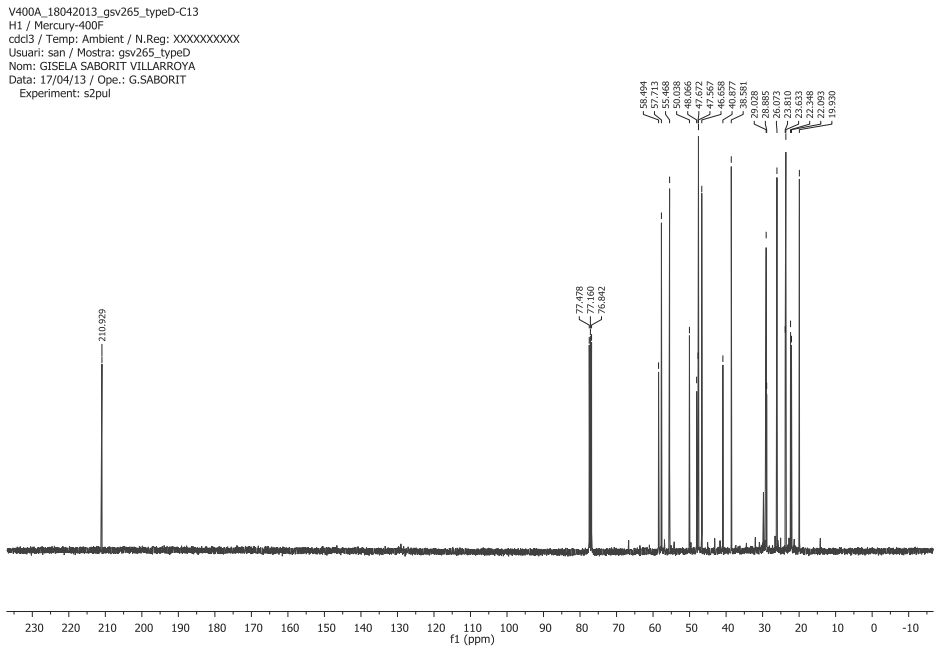


28 **29**

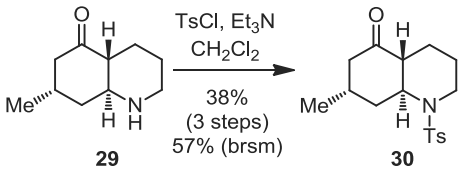
Acetal **28** obtained above (184 mg) was dissolved in 3 N HCl (25 mL) and heated to 80 ºC for 24 h. The mixture was basified with Na_2CO_3 (pH = 11) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried and concentrated to give a **29** as a 2:1 mixture of epimers. NMR data for **29**: ^{1}H NMR (400 MHz, COSY) 0.94 (d, *J* = 7.2 Hz, 3H, Me), 1.37 (qt, *J* = 12.0, 1.6 Hz, H-4ax), 1.70 (m, 1H, H-4eq), 1.74 (m, 1H, H-8eq), 1.83 (td, *J* = 12.0, 4.8 Hz, H-8ax), 1.92 (m, H-3), 2.05 (td, *J* = 12.0, 4.8 Hz, 1H, H-4a), 2.12 (dt, *J* = 13.6 Hz, 2.0 Hz, 1H, H-6eq), 2.25 (m, 1H, H-3), 2.40 (m, 1H, H-7), 2.55 (tm, *J* = 12.5 Hz, 1H, H-2ax), 2.58 (td, *J* = 13.6, 2.8 Hz, H-6), 2.66 (td, *J* = 10.8, 4.4 Hz, 1H, H-8a), 3.02 (dm, *J* = 12.5 Hz, 1H, H-2eq); ^{13}C NMR (400 MHz, HSQC) 19.8 (Me), 23.5 (C-3), 25.9 (C-4), 28.9 (C-7), 38.4 (C-8), 46.5 (C-2), 47.4 (C-6), 55.3 (C-4a), 57.6 (C-8a), 210.8 (C-5). HRMS calcd for $C_{10}H_{18}NO$ $(M+H)^+$ 168.1388, found 168.1380.


M400AFF_07102015_gsv634_2-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv634_2
Nom: GISELA SABORIT VILLARROYA
Data: 07/10/15 / Ope.: G.SABORIT
O
H
H
N
H
1.09
0.76
1.93
2.19
0.83
0.81
1.20
1.10
1.94
1.03
1.53
2.47
0.71
3.34
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)

29

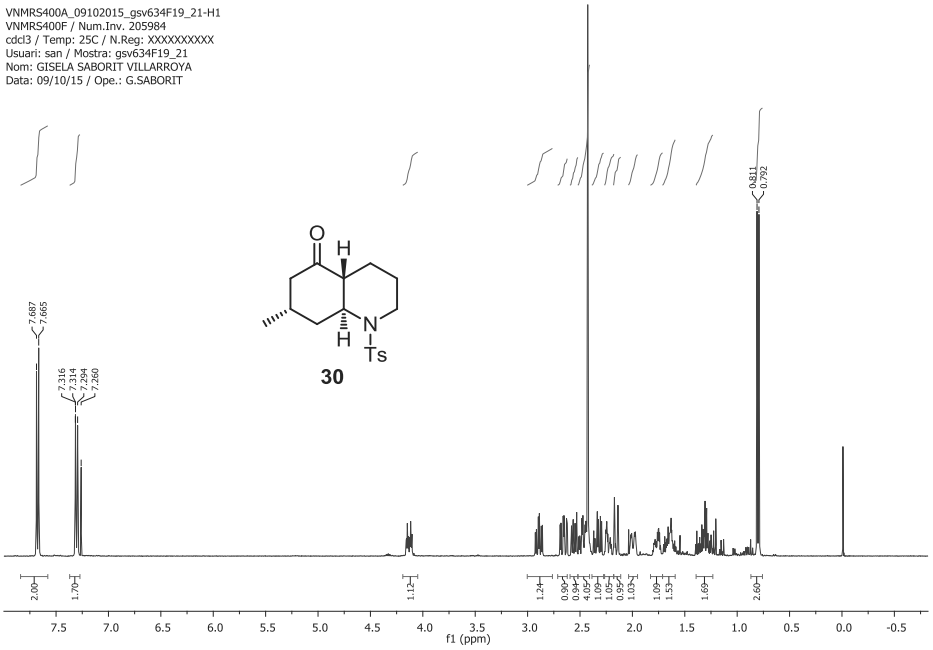

V400A_18042013_gsv265_typeD-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv265_typeD
Nom: GISELA SABORIT VILLARROYA
Data: 17/04/13 / Ope.: G.SABORIT
Experiment: s2pul
58.494
57.713
55.468
50.038
48.066
47.672
47.366
46.658
40.877
38.581
29.028
28.885
26.073
23.810
23.633
22.348
22.043
19.930
210.929
77.478
77.160
76.842
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(4a*RS*,5*S*,7*R*,8a*R*)-5-(*S*)-(1-Methyl)-2-piperidylmethyl)]-7-methyl-1-(4-methylsulfonyl)decahydroquinoline (30)



29 **30**

To a cooled (0 °C) stirred solution of the above mixture of **29** and its epimer (110 mg) in CH_2Cl_2 (8 mL) was added a solution of TsCl (214 mg, 1.12 mmol, 1.1 equiv) in CH_2Cl_2 (4 mL), followed by Et_3N (0.17 mL, 1.23 mmol, 1.2 equiv). The mixture was stirred at rt for 6 h and diluted with CH_2Cl_2 (20 mL). The organics were washed with brine (2 × 5 mL), dried, concentrated, and purified by chromatography (5→10→25% EtOAc in hexanes) to yield successively **30** (59 mg) and **4** (121 mg, 38% in three steps, 57% brsm) as a white solid: Rf = 0.35 (25% EtOAc/hexanes); mp 108 °C; ^{1}H NMR (400 MHz, COSY) δ 0.81 (d, *J* = 7.2 Hz, 3H, CH_3), 1.32 (m, 1H, H- 4ax), 1.64 (m, 1H, H-3ax), 1.76 (m, 1H, H-3eq), 2.00 (dd, *J* = 12.8, 3.6 Hz, 1H, H-4eq), 2.15 (dt, *J* = 13.6, 2.4 Hz, 1H, H-6ax), 2.23 (dm, *J* = 12.4 Hz, 1H, H-8eq), 2.33 (td, *J* = 13.6, 4.6 Hz, 1H, H-8ax), 2.40 (masked, H- 7), 2.42 (s, 3H, CH_3Ar), 2.46 (qd, 1H, *J* = 11.4, 3.2 Hz, H-4a), 2.56 (dd, *J* = 11.6, 4.0 Hz, 1H, H-6eq), 2.66 (td, *J* = 11.2, 3.2, 1.6 Hz, 1H, H-2ax), 2.89 (td, *J* = 11.4, 4.0 Hz, 1H, H-8a), 4.13 (dtd, *J* = 12.8, 4.0, 1.2 Hz, 1H, H-2eq), 7.30 (d, *J* = 8.4 Hz, 2H, o-Ts), 7.68 (d, *J* = 8.4 Hz, 2H, m-Ts); ^{13}C NMR (100 MHz, HSQC) δ 18.9 (CH_3), 21.6 (ArCH_3), 23.5 (C-4), 24.4 (C-3), 28.5 (C-7), 36.1 (C-8), 47.3 (C-6), 49.3 (C-2), 53.1 (C-4a), 60.3 (C-8a), 127.3 (m-Ts), 129.8 (o-Ts), 137.1 (ipso-Ts), 143.6 (p-Ts), 209.1 (C-5). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{24}NO_3S$ 322.1471, found 322.1464.


VNMRS400A_09102015_gsv634F19_21-H1
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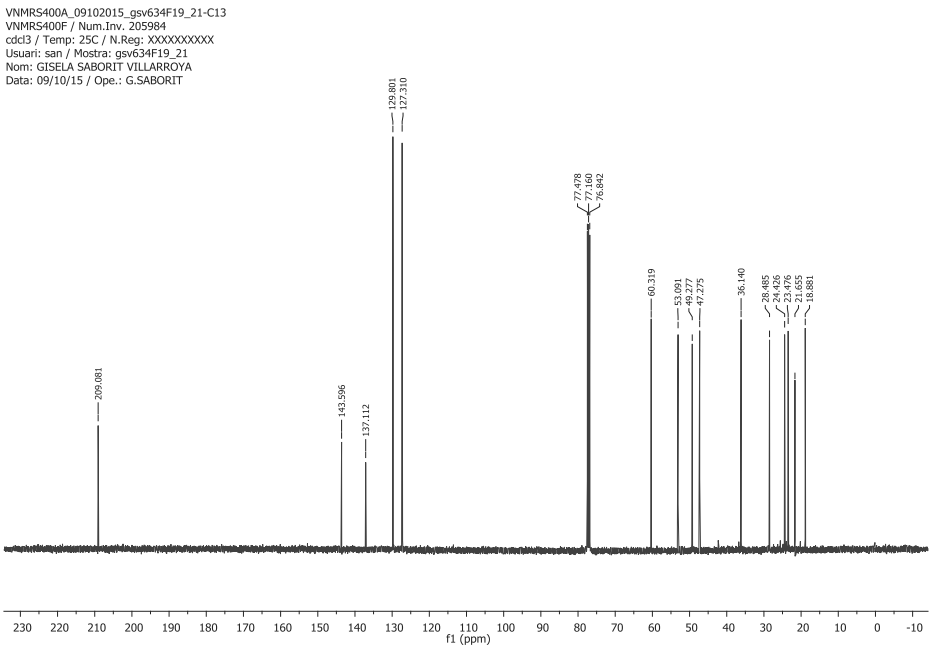
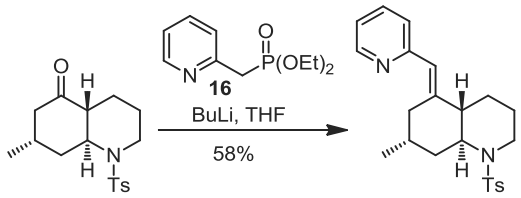
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv634F19_21
Nom: GISELA SABORIT VILLARROYA
Data: 09/10/15 / Ope.: G.SABORIT
7.687
7.665
7.316
7.314
7.294
7.260
0.811
0.792
2.00
1.70
1.12
1.24
0.90
0.94
4.05
1.05
1.00
0.95
1.03
1.09
1.55
1.69
2.60
f1 (ppm)

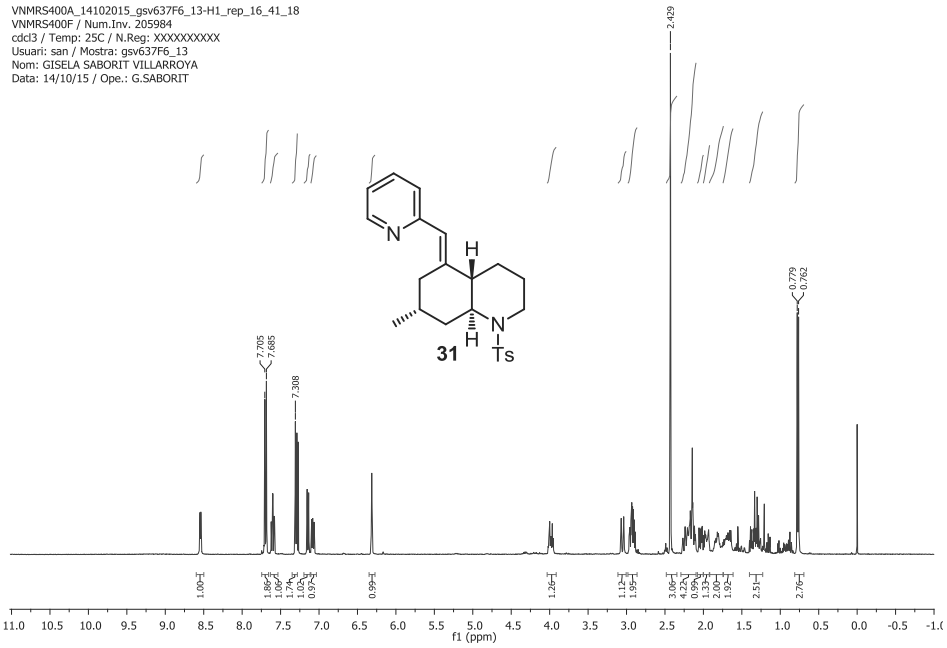
30


VNMRS400A_09102015_gsv634F19_21-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv634F19_21
Nom: GISELA SABORIT VILLARROYA
Data: 09/10/15 / Ope.: G.SABORIT
209.081
143.596
137.112
129.801
127.310
77.478
77.160
76.842
60.319
53.091
49.277
47.275
36.140
28.485
24.476
23.476
21.655
18.881
f1 (ppm)

(*E*)-(4a*S*,7*R*,8a*S*)-7-methyl-1-(4-methylsulfonyl)-5-(pyridin-2-ylmethylene) decahydroquinoline (31)



Both the pyridine phosphonate and decahydroquinoline **30** were previously dried by azeotroping with benzene. To a stirred solution of phosphonate **16** (190 mg, 0.84 mmol) in THF (2.4 mL) at -78 ºC was added n-BuLi (1.6 M in hexanes, 0.52 mL, 0.84 mmol). The resulting red solution was stirred for 30 min at room temperature before a solution of **30** (54 mg, 0.168 mmol) in THF (1 mL) was added dropwise via syringe at -78 ºC. The reaction mixture was stirred for 30 min at -78 ºC, 1 h at -30 ºC and 1 h at 0 ºC before it was quenched with sat. aq. NH_4Cl (4 mL). The mixture was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were dried, filtered, concentrated and purified by chromatography (5→10→25% EtOAc/hexane) to give **31** (38 mg, 58%) as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 0.77 (d, *J* = 7.2 Hz, 3H, CH_3), 1.31 (qd, 1H, *J* = 18.0, 5.9 Hz, H-4ax), 1.50-1.74 (m, 3H, H-3), 1.82 (m, 1H, H-3), 1.95 (dm, *J* = 13.2 Hz, 1H, H-4eq), 2.03 (dd, *J* = 12.6, 4.2 Hz, 1H, H-6), 2.12 (m, 1H, H-8), 2.17 (m, 4H, H-6), 2.42 (s, 3H, $ArCH_3$), 2.92 (td, 1H, *J* = 8.8, 4.4 Hz, H-2eq), 2.95 (q, 1H, *J* = 4.4 Hz, H-8a), 3.07 (td, *J* = 13.1, 2.1 Hz, 1H, H-8ax), 3.97 (dt, *J* = 12.8, 5.6 Hz, 1H, H-2ax), 6.31 (s, 1H, C=CH), 7.07 (ddd, *J* = 7.2, 4.8, 0.8 Hz, 1H, H-5 py), 7.13 (d, *J* = 8.0 Hz, 1H, H-3 py), 7.28 (d, *J* = 8.4 Hz, 2H, *o*-Ts), 7.59 (td, *J* = 7.6, 2.0 Hz, 1H, H-4 py), 7.69 (d, *J* = 8.4 Hz, 2H, *m*-Ts), 8.54 (dm, *J* = 4.8 Hz, 1H, H-6 py). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 18.2 (CH_3), 21.7 (CH_3Ar), 24.5 (C-3), 25.8 (C-4), 29.3 (C-7), 35.2 (C-8), 38.1 (C-6), 46.3 (C-4a), 46.8 (C-2), 60.6 (C-8a), 121.2 (C-5 py), 124.0 (C-3 Py), 124.1 (=CH), 127.3 (*o*-Ts), 129.7 (*m*-Ts), 136.0 (C-4 Py), 137.3 (*p*-Ts), 143.3 (*ipso*-Ts), 144.7 (C-5), 149.3 (C-6 Py), 157.3 (C-2 Py). HRMS calcd for $C_{23}H_{29}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.1956.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VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv637F6_13
Nom: GISELA SABORIT VILLARROYA
Data: 14/10/15 / Ope.: G.SABORIT
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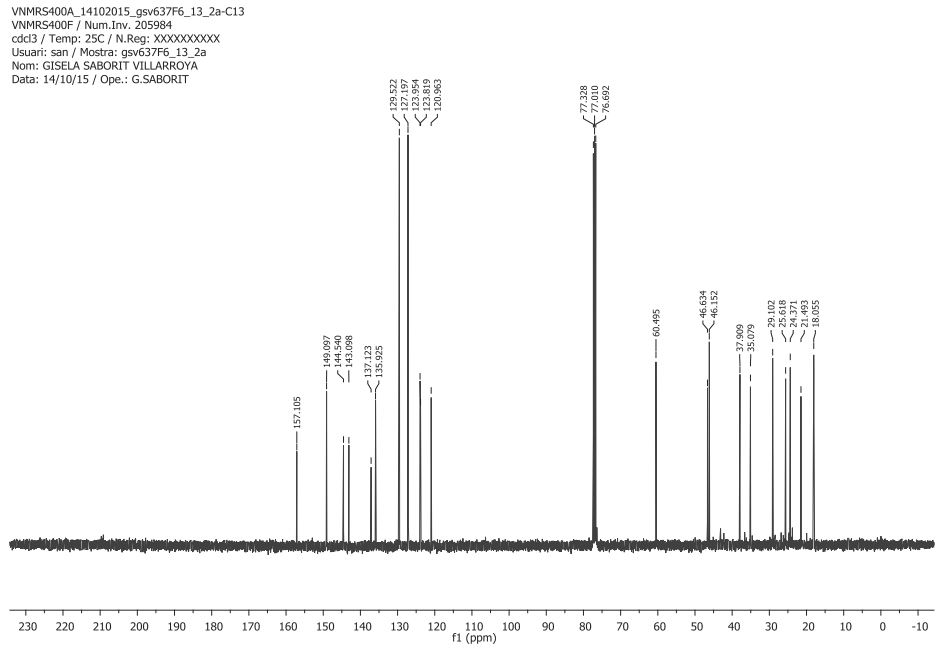
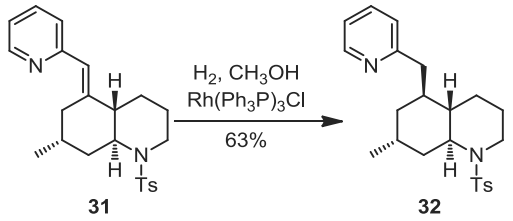
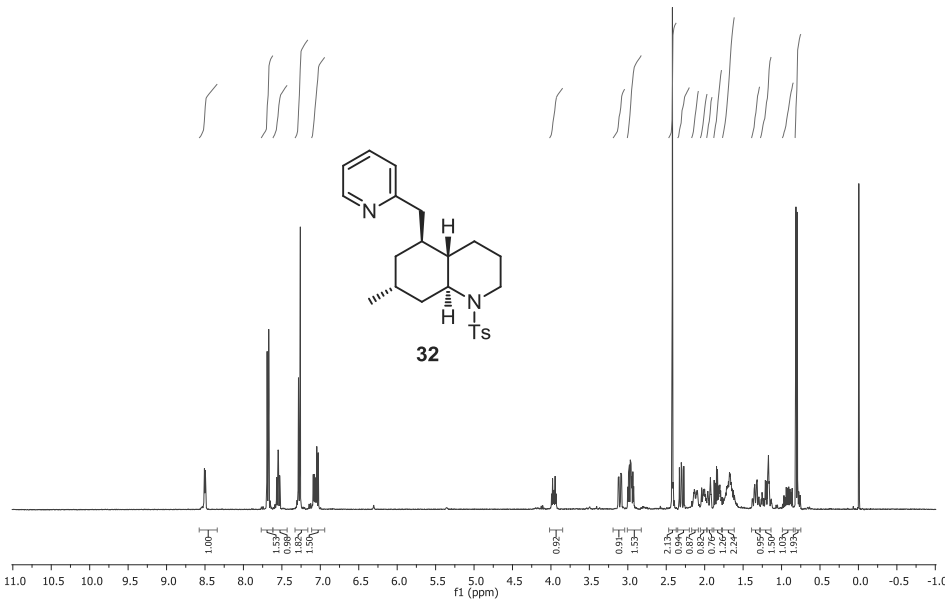
7.705
7.685
7.308
0.779
0.762
31
f1 (ppm)

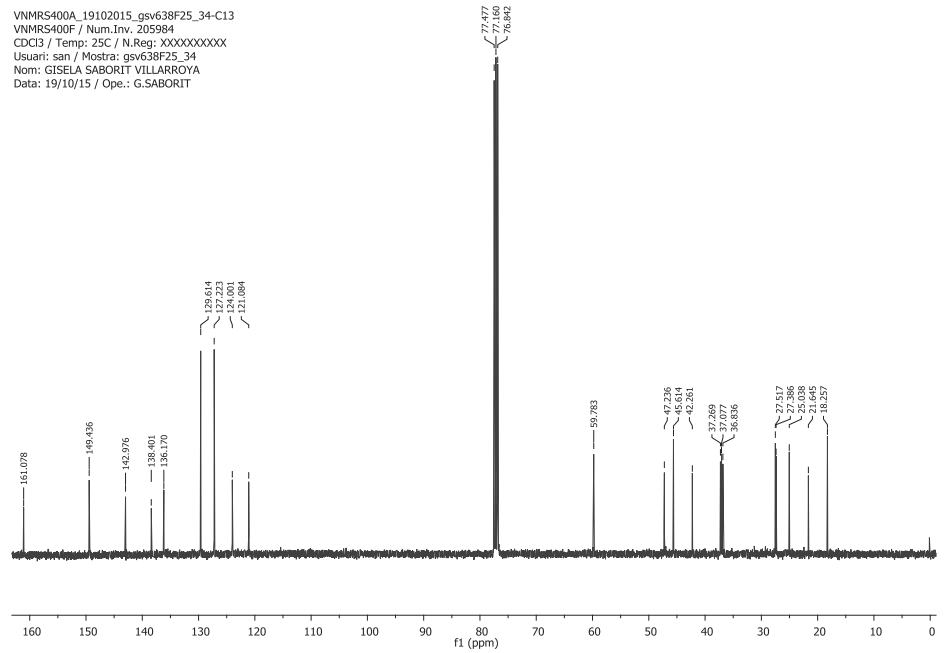

VNMRS400A_14102015_gsv637F6_13_2a-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv637F6_13_2a
Nom: GISELA SABORIT VILLARROYA
Data: 14/10/15 / Ope.: G.SABORIT
129.572
127.197
123.954
123.819
120.963
77.328
77.010
76.692
157.105
149.097
144.540
140.098
137.123
135.925
60.495
46.634
46.152
37.909
35.079
29.102
25.618
24.371
21.493
18.055
f1 (ppm)

(4aS,5S,7R,8aS)-7-methyl-5-(pyridin-2-ylmethyl)-1-tosyldecahydroquinoline (32)



To a stirred solution of **31** (27 mg, 0.068 mmol) in MeOH (7 mL) was added Wilkinson's catalyst $RhCl(PPh_3)_3$ (16 mg, 0.017 mmol, 25 mol %) at rt. The resulting mixture was rapidly evacuated and backfilled with H_2 three times and then stirred under an atmosphere of H_2 for 72 h. The mixture was concentrated, and purified by chromatography (5→10→25% EtOAc in cyclohexane) to give **32** (17 mg, 63%): Rf = 0.5 (1:1 EtOAc/ cyclohexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, *J* = 7.2 Hz, 3H, CH_3), 0.91 (qd, *J* = 12.4, 6.2 Hz, 1H, H-4ax), 1.20 (m, 2H, H-6), 1.34 (qd, *J* = 12.4, 3.2, 1H, H-4a), 1.65 (m, 2H, H-3), 1.80 (m, 1H, H-5), 1.86 (td, *J* = 12.4, 4.8 Hz, 1H, H-8ax), 1.94 (dm, *J* = 12.4 Hz, 1H, H-8eq), 2.00 (m, 1H, H-7), 2.12 (dm, *J* = 12.0 Hz, 1H, H-4eq), 2.30 (dd, *J* = 13.4, 8.8 Hz, 1H, CH_2Py), 2.42 (s, 3H, $ArCH_3$), 2.94−3.00 (m, 2H, H-2ax, H-8a), 3.11 (dd, *J* = 13.4, 4.0 Hz, 1H, CH_2Py), 3.97 (dt, *J* = 13.2, 5.6 Hz, 1H, H-2eq), 7.04 (d, *J* = 8.0 Hz, 1H, H-3 Py), 7.08 (m, 1H, H-5 Py), 7.28 (d, *J* = 8.4 Hz, 2H, o-Ts), 7.55 (td, *J* = 7.6, 1.6 Hz, 1H, H-4 Py), 7.68 (d, *J* = 8.0 Hz, 2H, m-Ts), 8.50 (dm, *J* = 4.0 Hz, 1H, H-6 Py); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 18.3 (CH_3), 21.6 ($ArCH_3$), 25.1 (C-3), 27.4 (C-4), 27.5 (C-7), 36.8 (C-6), 37.1 (C-8), 37.3 (C-5), 42.3 (CH2Py), 45.6 (C-4a), 47.3 (C-2), 59.8 (C-8a), 121.1 (C-5 Py), 124.0 (C-3 Py), 127.2 (o-Ts), 129.7 (m-Ts), 136.2 (C-4 Py), 138.4 (p-Ts), 143.0 (ipso-Ts), 149.4 (C-6 Py), 161.1 (C-2 Py). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{31}N_2O_2S$ 399.2101, found 399.2116.


N
H
H
N
Ts
32
1.00
1.53
0.98
1.82
1.50
0.92
0.91
1.53
2.13
0.94
0.83
0.82
0.76
1.26
2.24
0.99
1.56
1.03
1.93
11.0 10.5 10.0 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 -0.5
f1 (ppm)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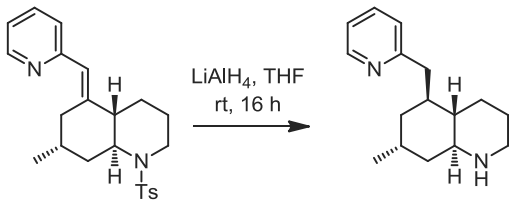
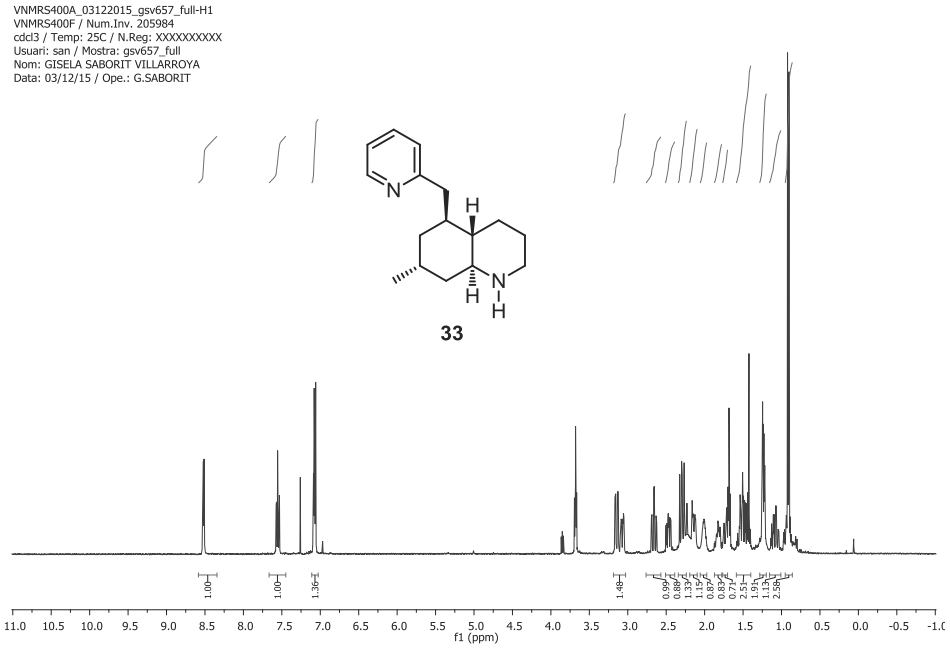
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv638F25_34
Nom: GISELA SABORIT VILLARROYA
Data: 19/10/15 / Ope.: G.SABORIT
77.477
77.160
76.842
161.078
149.436
142.976
138.401
136.170
129.614
127.223
124.001
121.084
59.783
47.236
45.614
42.261
37.269
37.077
36.836
27.517
27.386
25.038
23.645
18.257
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(4aRS,5RS,7SR,8aRS)-7-Methyl-5-(pyridin-2-ylmethyl)-decahydroquinoline (33)



32 **33**

A solution of sulfonamide **32** (17 mg, 0.043 mmol) in THF (1 mL) was added to a stirred suspension of $LiAlH_4$ (16 mg, 0.43 mmol) in THF (1 mL) at 0 °C. The reaction was stirred overnight at rt and quenched by addition of one drop of water, another of aqueous 15% NaOH, and three drops of water. The mixture was diluted with CH_2Cl_2, filtered through a pad of Celite, and washed thoroughly with CH_2Cl_2. Evaporation of the solvent gave **33**, which was pure enough to be used in the following step. An analytical sample of secondary amine **33** was obtained by chromatography on alumina (1−5% MeOH in CH_2Cl_2): Rf = 0.22 (5:95 MeOH: CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7.2 Hz, 3H, CH3), 0.92 (qd, *J* = 12.0, 3.2 Hz, 1H, H-4a), 1.09 (qd, *J* = 12.0, 4.0 Hz, 1H, H-4ax), 1.20− 1.25 (m, 2H, 2H-6), 1.44 (td, *J* = 12.0, 4.2 Hz, 1H, H-8ax), 1.52 (dt, *J* = 12.4, 2.0 Hz, 1H, H-8eq), 1.53 (m, 1H, H-3eq), 1.71 (tt, *J* = 13.2, 3.2 Hz, 1H, H-3ax), 1.82 (m, 1H, H-5), 2.01 (m, 1H, H-7eq), 2.14 (dd, *J* = 13.0, 3.0 Hz, 1H, H-4eq), 2.30 (dd, *J* = 13.2, 10.0 Hz, 1H, CH_2Py), 2.47 (ddd, 1H, *J* = 11.2, 10.0, 4.0 Hz, H-8a), 2.66 (td, 1H, *J* = 12.2, 3.0 Hz, H-2ax), 3.07 (dm, *J* = 12.0 Hz, 1H, H-2eq), 3.14 (dd, *J* = 13.2, 4.0 Hz, 1H, CH_2Py), 7.06−7.09 (m, 2H, H-3 Py, H-5 Py), 7.55 (td, J = 8.0, 1.6 Hz, 1H, H-4 Py), 8.52 (dd, J = 5.2, 2.0 Hz, 1H, H-6 Py); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2 (CH_3), 27.2 (C-3), 27.5 (C-7), 28.8 (C-4), 36.4 (C-5), 37.6 (C-6), 39.4 (C-8), 41.9 (CH_2Py), 47.0 (C-2), 48.4 (C-4a), 56.2 (H-8a), 120.9 (C-5 Py), 123.9 (C-3 Py), 136.1 (C-4 Py), 149.4 (C- 6 Py), 161.8 (C-2 Py). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{24}N_2$ 245.2012, found 245.2009.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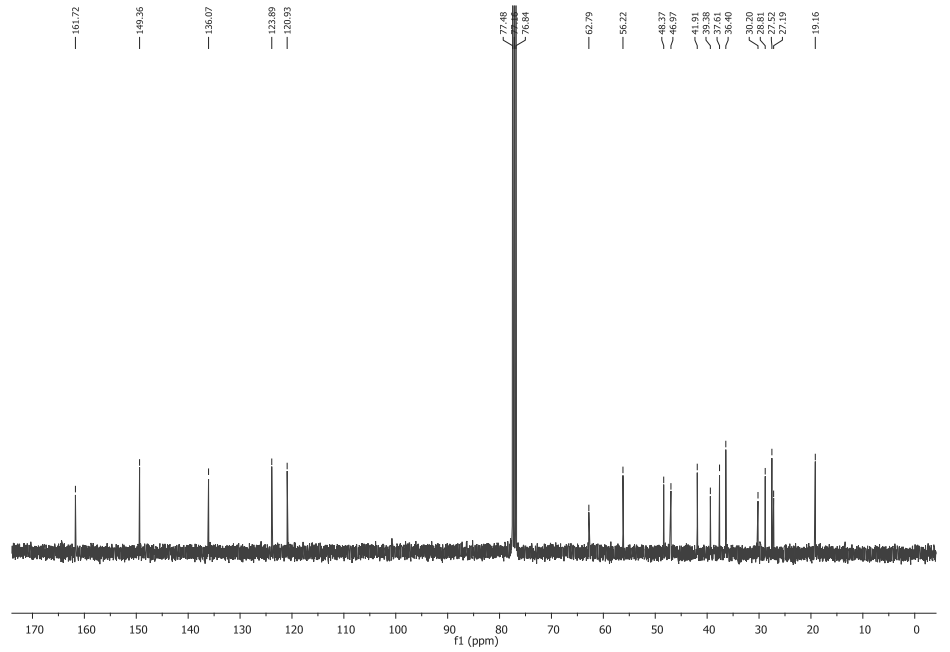
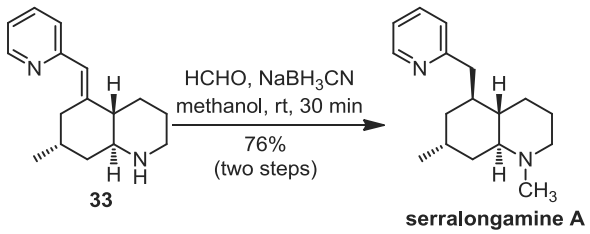
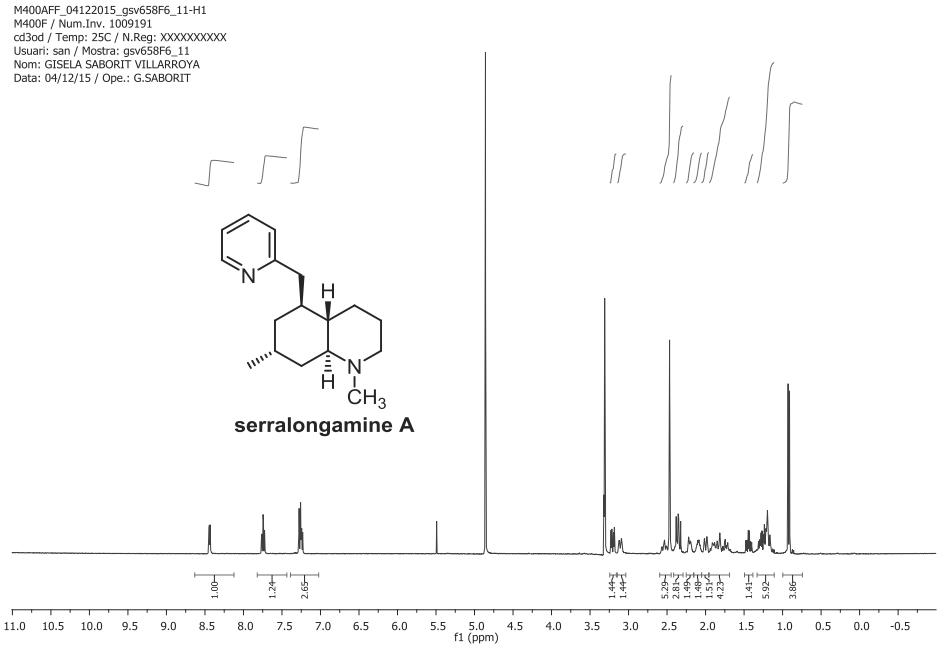
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv657_full
Nom: GISELA SABORIT VILLARROYA
Data: 03/12/15 / Ope.: G.SABORIT
33
f1 (ppm)


161.72
149.36
136.07
123.89
120.93
77.48
77.16
76.84
62.79
56.22
48.37
46.97
41.91
39.38
37.61
36.40
30.20
28.81
27.52
27.19
19.16
f1 (ppm)

(4a*RS*,5*RS*,7*SR*,8a*RS*)-1,7-Dimethyl-5-(pyridin-2-ylmethyl)-decahydroquinoline (rac-Serralongamine A)



To a solution of the above crude amine **33** (10 mg, 0.043 mmol) in MeOH (2.3 mL) was added 37% aqueous formaldehyde (24 mL, 0.328 mmol) and $NaBH_3CN$ (18 mg, 0.287 mmol) at 0 °C, and the mixture was stirred at rt for 30 min. The volatiles were evaporated, and the crude was purified on neutral alumina (CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to give serralongamine A (8.4 mg, 76% over two steps from **32**): Rf = 0.70 (5% CH_3OH in CH_2Cl_2). This sample was dissolved in CD_3OD, and $NaOCD_3$ (0.1Min CD_3OD) was added. ^1H and ^{13}C NMR spectra of the free base were obtained: ^1H NMR (400 MHz, CD_3OD, $NaOCD_3$) δ 0.90 (d, *J* = 7.6 Hz, 3H, CH_3), 1.10−1.15 (masked, 1H, H-4a), 1.11 (br q, *J* = 12.0 Hz, 1H, H-4ax), 1.15 (br d, *J* = 12 Hz, 1H, H-6eq), 1.25 (td, *J* = 12.4, 4.4 Hz, 1H, H-6ax), 1.35 (td, *J* = 12.4, 4.8 Hz, 1H, H-8ax), 1.65−1−75 (m, 2H, 2H-3), 1.80−1.92 (m, 2H, H-5 and H-8a), 1.93 (dm, *J* = 12.0 Hz, 1H, H-8eq), 2.03 (m, 1H, H-7), 2.16 (dm, *J* = 11.8 Hz, 1H, H-4eq), 2.18 (td, *J* = 12.8, 3.2 Hz, 1H, H-2ax), 2.24 (s, 3H, CH_3), 2.30 (dd, *J* = 13.2, 10.4 Hz, 1H, CH_2Py), 2.88 (dm, *J* = 12.0 Hz, 1H, H-2eq), 3.19 (dd, *J* = 13.2, 4.0 Hz, 1H, CH_2Py), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1H, H-5 Py), 7.25 (t, *J* = 7.4 Hz, 1H, H-3 Py), 7.73 (tt, *J* = 7.6, 1.6 Hz, 1H, H-4 Py), 8.42 (dm, *J* = 4.8, 1H, H-6 Py). ^{13}C NMR (100 MHz, CD_3OD, $NaOCD_3$) δ 19.5 (CH_3), 26.1 (C-3), 28.5 (C-7), 29.6 (C-4), 36.6 (C-8), 37.8 (C-5), 38.0 (C-6), 42.6 (CH_2Py), 43.1 (NCH_3), 47.8 (C-4a), 58.5 (C-2), 64.8 (C-8a), 122.7 (C-3 Py), 125.7 (C-5 Py), 138.4 (C-4 Py), 149.5 (C-6 Py), 162.6 (C-2 Py). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{27}N_2$ 259.2168, found 259.2169.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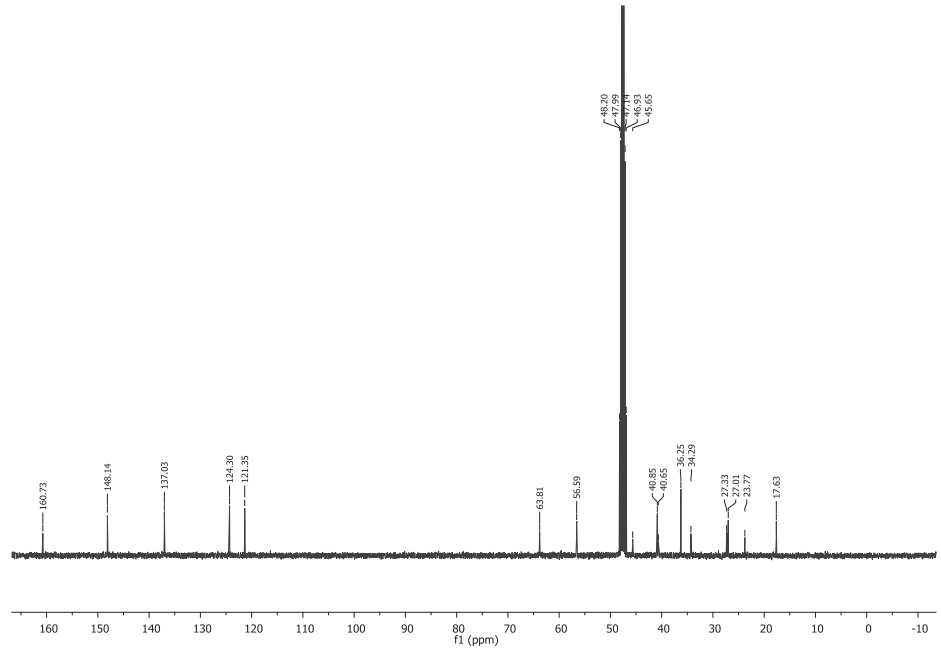
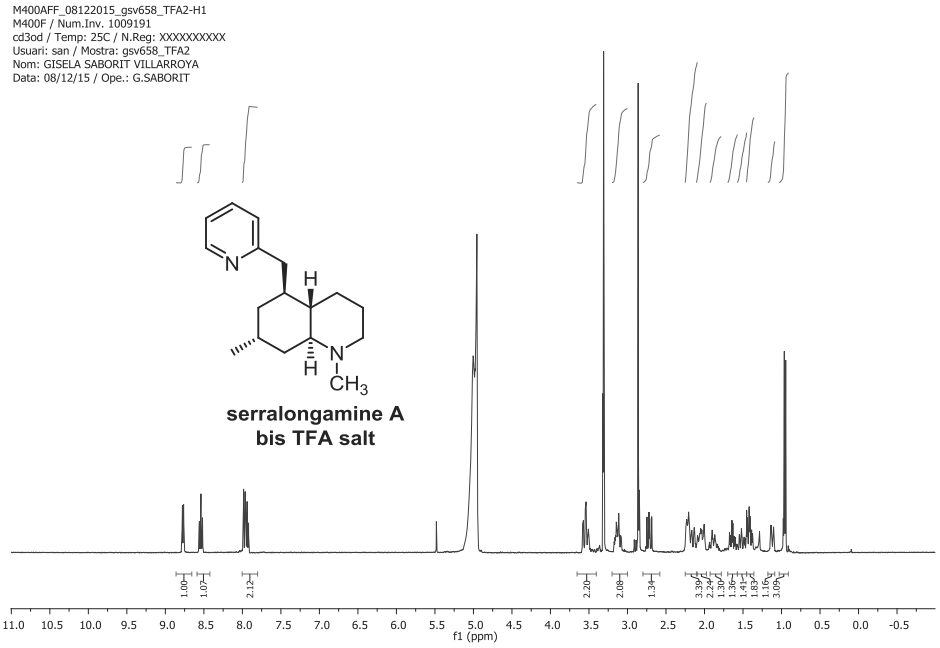
M400F / Num.Inv. 1009191
cd3od / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv658F6_11
Nom: GISELA SABORIT VILLARROYA
Data: 04/12/15 / Ope.: G.SABORIT
serralongamine A
f1 (ppm)


160.73
148.14
137.03
124.30
121.35
63.81
56.59
48.20
47.99
47.16
46.93
45.65
40.85
40.65
36.25
34.29
27.33
27.01
23.77
17.63
f1 (ppm)

Spectra matching the reported spectra of (−)-**serralongamine A** were obtained after the addition of TFA in CD_3OD. ^1H (400 MHz, CD_3OD, TFA) δ 0.95 (d, *J* = 7.6 Hz, 3H, CH_3), 1.15 (br d, *J* = 13.2 Hz, 1H, H-6eq), 1.41 (td, *J* = 12.8, 4.8 Hz, 1H, H-6ax), 1.44 (td, *J* = 12.4, 4.4 Hz, 1H, H-4ax), 1.53 (qd, *J* = 12.0, 2.8 Hz, 1H, H-4a), 1.64 (td, *J* = 12.4, 4.8 Hz, 1H, H-8ax), 1.88 (qt, *J* = 12.4, 4.0 Hz, 1H, H-3ax), 2.00−2.09 (m, 2H, H-3eq, H-5ax), 2.15 (br d, *J* = 12.4 Hz, 1H, H-8eq), 2.22 (br d, *J* = 12.0 Hz, 1H, H-7eq), 2.24 (m, 1H, H-4eq), 2.72 (dd, *J* = 14.4, 10.4 Hz, 1H, CH_2Py), 2.86 (s, 3H, NCH_3), 3.12 (td, *J* = 13.0, 3.2 Hz, 1H, H-2ax), 3.15 (td, *J* = 12.2, 4.0 Hz, 1H, H-8a), 3.52 (br, *J* = 13.0 Hz, 1H, H-2eq), 3.56 (dd, *J* = 14.4, 4.0 Hz, 1H, CH_2Py), 7.85 (ddd, *J* = 7.2, 5.6, 0.8 Hz, 1H, H-5 Py), 7.88 (d, *J* = 8.0 Hz, 1H, H-3 Py), 8.54 (td, J = 8.0, 1.6 Hz, 1H, H-4 Py), 8.77 (d, *J* = 5.6 Hz, 1H, H-6 Py); ^{13}C NMR (100 MHz, CD_3OD, TFA) δ 18.3 (CH_3), 24.0 (C-3), 27.1 (C-4), 28.1 (C-7), 33.8 (C-8), 36.8 (C-6), 37.5 (C-5), 37.9 (CH_2Py), 41.4 (NCH_3), 46.3 (C-4a), 57.4 (C-2), 66.0 (C-8a), 126.3 (C-5 Py), 129.4 (C-3 Py), 142.8 (C-6 Py), 147.8 (C-4 Py), 157.7 (C-2 Py).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M400F / Num.Inv. 1009191
cd3od / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv658_TFA2
Nom: GISELA SABORIT VILLARROYA
Data: 08/12/15 / Ope.: G.SABORIT
serralongamine A
bis TFA salt
f1 (ppm)

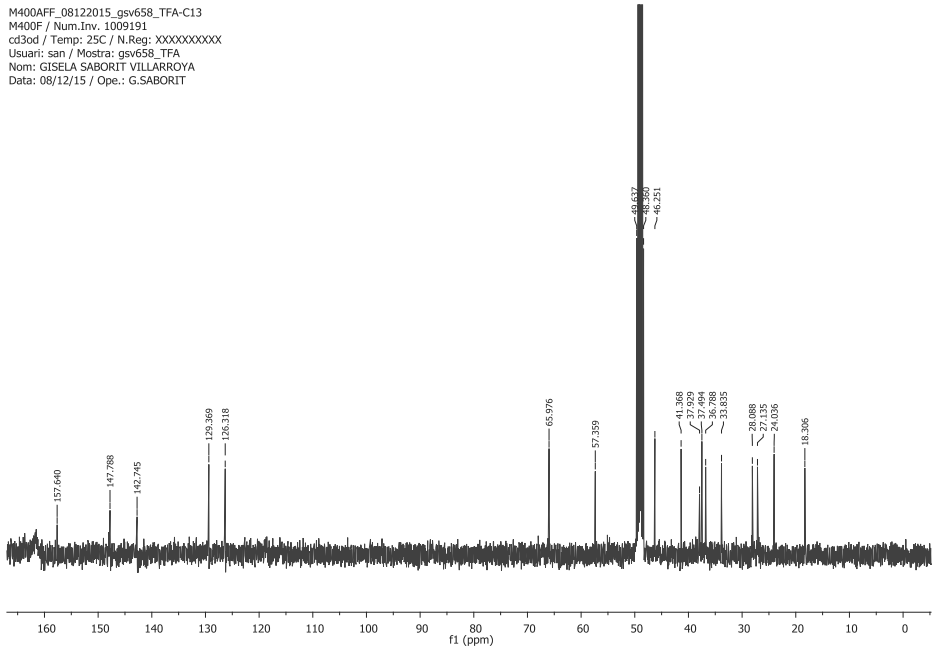
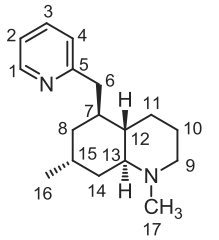

M400AFF_08122015_gsv658_TFA-C13
M400F / Num.Inv. 1009191
cd3od / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv658_TFA
Nom: GISELA SABORIT VILLARROYA
Data: 08/12/15 / Ope.: G.SABORIT
157.640
147.768
142.745
129.369
126.318
65.976
57.359
49.637
48.360
46.251
41.368
37.929
37.494
36.788
33.855
28.088
27.135
24.036
18.306
f1 (ppm)

Table 6.1. ^{1}H NMR data for serralogamine A in CD_3OD

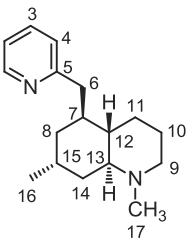


Serralongamine A

	Synthetic free base [179]	bis-TFA salt[179]	Isolated serralongamine A[35]
	δ ^{1}H	δ ^{1}H	δ ^{1}H
1	8.42 (dm, 4.8 Hz)	8.77 (d 5.6 Hz)	8.73 (d 5.7 Hz)
2	7.24 (dd, 7.6, 4.8 Hz)	7.94 (m)	7.85 (dd, 6.9, 5.7 Hz)
3	7.73 (tt, 7.6, 1.6 Hz)	8.54 (td, 8.0, 1.6 Hz)	8.44 (dd, 8.0, 6.9 Hz)
4	7.25 (t, 7.4 Hz)	7.97 (d, 8.0 Hz)	7.88 (d, 8.0 Hz)
6a	2.30 (dd, 13.2, 10.4 Hz)	3.51 (m)	3.51 (dd, 13.6, 4.2 Hz)
6b	3.19 (dd, 13.2, 4.0 Hz)	2.71 (dd 14.0, 10.4 Hz)	2.66 (dd, 13.6, 10.9 Hz)
7	1.80-1.92 (m)	2.04 (m)	2.04 (m)
8a	1.15 (br d, 12.0 Hz)	1.39 (m)	1.38 (m)
8b	1.25 (td, 12.4, 4.4 Hz)	1.14 (brd 14.8 Hz)	1.15 (brd 13.4 Hz)
9a	2.88 (dm, 12.0 Hz)	3.56 (m)	3.54 (m)
9b	2.18 (td, 12.8, 3.2 Hz)	3.09 (m)	3.12 (ddd, 13.4, 13.4, 2.4 Hz)
10a	1.65 (m)	2.04 (m)	2.04 (m)
10b	1.65 (m)	1.88 (m)	1.86 (m)
11a	2.16 (dm, 11.8 Hz)	2.23 (m)	2.24 (m)
11b	1.11 (br, 12.0 Hz)	1.45 (m)	1.41 (m)
12	1.10-1.15 (masked)	1.50 (m)	1.48 (m)
13	1.80-1.92 (m)	3.16 (m)	3.15 (m)
14a	1.93 (dm, 12.0 Hz)	2.15 (brd 12.4 Hz)	2.16 (brd 12.8 Hz)
14b	1.35 (td, 12.4, 4.8 Hz)	1.60 (td 12.4, 4.8 Hz)	1.60 (ddd 12.8, 12.8, 4.6 Hz)
15	2.03 (m)	2.20 (m)	2.22 (1H, m)
16	0.90 (d, 7.6 Hz)	0.96 (d 7.6 Hz)	0.96 (d 6.9 Hz)
17	2.24 (s)	2.86 (s)	2.87 (s)

[179] ^{1}H NMR recorded at 400 MHz. Assignments were aided by gCOSY and gHSQCAD spectra.

Table 6.2. ^{13}C NMR data for serrolangamine A in CD_3OD



Serralongamine A

	Synthetic free base[180]	bis-TFA salt[35]	Isolated serralongamine A[35]
	δ ^{13}C	δ ^{13}C	δ ^{13}C
1	149.5	142.8	143.8
2	125.7	126.3	125.9
3	138.4	147.8	146.6
4	122.7	129.4	128.8
5	162.6	157.7	158.1
6	42.6	37.9	38.5
7	37.8	37.5	37.5
8	38.0	36.8	36.8
9	58.5	57.4	57.4
10	26.1	24.0	24.1
11	29.6	27.1	27.2
12	47.8	46.3	46.4
13	64.8	66.0	66.0
14	36.6	33.8	33.9
15	28.5	28.1	28.1
16	19.5	18.3	18.3
17	43.1	41.4	41.4

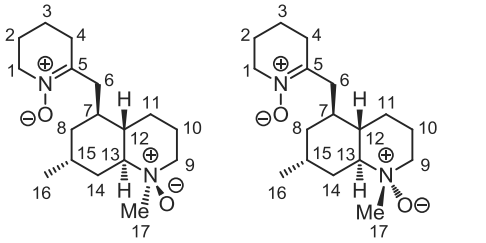
[180] ^{13}C NMR recorded at 100 MHz. Assignments were aided by gCOSY and gHSQCAD spectra.

(1RS,4aSR,5SR,7RS,8aSR)-1,7-Dimethyl-5-(2,3,4,5-tetrahydropyridine1-oxide) decahydroquinoline N-Oxide (huperzine N)

To a stirred solution of **serralongamine A** (8 mg, 0.031 mmol) in AcOH (0.25 mL) was added PtO_2 (20% w/w, 2 mg) at rt. The resulting mixture was evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 for 16 h. The mixture was diluted with CH_2Cl_2 (2 mL) before it was filtered through a pad of Celite and washed through with CH_2Cl_2. The filtered solution was washed with 1N NaOH, dried, and concentrated. To a solution of the above crude diamine in MeOH/CH_2Cl_2 (1:1; 0.2 mL) were added in one portion UHP (30 mg, 0.31 mmol) and $Na_2WO_4 \cdot 2H_2O$ (2 mg, 0.006 mmol), and the mixture was stirred at rt for 72 h. After concentration, CH_2Cl_2 was added and the reaction mixture was filtered, concentrated, and purified by chromatography (2.5−10% MeOH in CH_2Cl_2 and then 85/15/1.5 $CHCl_3$/ MeOH/NH_3) to give **huperzine N** and ***N-epi*-huperzine N** (6 mg, 66%, 3:2 ratio) as a colorless oil, which solidified on standing: Rf = 0.20 (80/20/2 $CHCl_3$/MeOH/NH_3). Data for huperzine N. ^{1}H NMR(400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 7.2 Hz, 3H, CH_3), 1.12 (qd, *J* = 12.0, 3.0 Hz, 1H, H-4ax), 1.28 (masked, 1H, H-6eq), 1.40 (td, *J* = 12.0, 4.0 Hz, 1H, H-6ax), 1.58 (br d, *J* = 13.0 Hz, 1H, H-3eq), 1.68 (m, 2H, H-4′), 1.80 (m, 2H, H-4a, H-8ax), 1.88 (m, 2H, H-5′), 1.88 (masked, 1H, CH_2Py), 2.05 (m, 1H, H-4eq), 2.10 (1H, m, H-8eq), 2.21 (m, 1H, H-5), 2.38 (masked, 1H, H-3ax), 2.40 (t, *J* = 6.0 Hz, 2H, H-3′), 2.98 (dd, *J* = 12.0, 3.0 Hz, 1H, CH_2Py), 2.90 (td, J = 11.5, 3.2 Hz, 1H, H-8a), 3.10 (s, 3H, NCH_3), 3.14 (ddd, *J* = 12.0, 11.0, 3.0 Hz, 1H, H-2ax), 3.46 (br d, *J* = 12.0 Hz, 1H, H-2eq), 3.75 (t, *J* = 6.4 Hz, 2H, H-6′); ^{13}C NMR (100 MHz, HSQC) δ 18.9 (C-4′), 19.0 (CH_3), 20.3 (C-3), 23.3 (C-5′), 27.0 (C-4), 27.1 (C-7), 29.9 (C-3′), 30.1 (C-8), 32.4 (C-5), 36.7 (CH_2Py), 36.8 (C-6), 41.1 (C-4a), 57.6 (NCH_3), 58.5 (C-6′), 69.1 (C-2), 73.8 (C-8a), 148.0 (C-2′); ^{15}N (50 MHz, deduced from ^{1}H−^{15}N HMBC correlations) δ 114.7 (N-oxide), 271.7 (nitrone). HRMS (ESI-TOF) m/z: [M + H]+ calcd for $C_{17}H_{31}N_2O_2$ 295.2380; found 295.2374. Data for *N-epi*-huperzine N. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 7.2 Hz, 3H, CH_3), 1.20 (masked, 1H, H-4ax), 1.30 (m, 1H, H-4a), 1.35 (m, 1H, H-6), 1.40 (m, 1H, H-6), 1.45 (td, *J* = 12.0, 3.0 Hz, 1H, H-8ax), 1.68 (m, 1H, H-3eq), 1.68 (m, 2H, H-4′), 1.87 (m, 2H, H-5′), 1.87 (masked, 1H, H-3ax), 1.95 (m, 1H, H-5), 2.05 (m, 1H, H-4eq), 2.35 (masked, 1H, CH_2Py), 2.40 (t, J = 6.0 Hz, 2H, H-2′), 2.60 (1H, m, H-8eq), 2.70 (m, 1H, CH_2Py), 2.96 (s, 3H, NCH_3), 3.21 (br t, *J* = 12.0 Hz, 1H, H-8a), 3.42 (td, J = 12.0, 3.0 Hz, 1H, H-2ax), 3.61 (br d, *J* =12.0 Hz, 1H, H-2eq), 3.72 (t, *J* = 6.4 Hz, 2H, H-6′); ^{13}C NMR (100 MHz, HSQC) δ 18.2 (CH_3), 19.2 (C-4′), 22.9 (C-3), 23.3 (C-5′), 27.1 (C-4), 27.2 (C-7), 29.9 (C-3′), 30.2 (C-8), 34.6 (C-5), 35.5 (CH2py), 37.5 (C- 6), 44.7 (C-4a), 48.0 (NCH3), 58.6 (C-6′), 71.1 (C-2), 75.9 (C-8a), 147.2 (C-2′); ^{15}N (50

MHz, deduced from $^{1}H–^{15}N$ HMBC correlations) δ 113.8 (N-oxide), 271.0 (nitrone). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{31}N_2O_2$ 295.2380; found 295.2374.

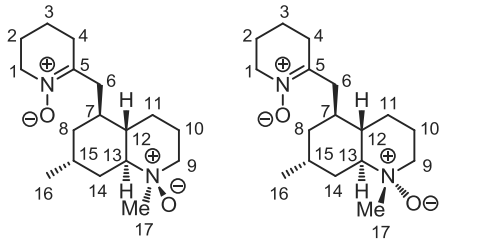
Table 6.3. Comparison of ^{1}H NMR data for synthetic huperzine N, *N-epi*-huperzine N, and natural huperzine N in $CDCl_3$



	Synthetic huperzine N[181]	*N-epi*-huperzine N[1]	Huperzine N[182]
	δ ^{1}H	δ ^{1}H	δ ^{1}H
1	3.75 (t, 6.4)	3.72 (t, 6.4)	3.75 (t, 6.0)
2	1.87 (m)	1.87 (m)	1.84-1.92 (m)
3	1.68 (m)	1.68 (m)	1.64-1.69 (m)
4	2.40 (t, 6.0)	2.40	2.34 (t, 6.0)
6	2.98 (dd, 12.0, 3.0)	2.70	2.96 (dd, 12, 3)
	1.88 (masked)	2.35	1.91 (d, 12)
7	2.15 (m)	1.95 (m)	2.10-2.17 (m)
8	1.40 (td, 12.0, 4.0)	1.40 (m)	1.34 (ddd, 12, 8, 4)
	1.28 (masked)	1.35 (m)	1.29 (br d, 12)
9	3.46 (br d, 12.0)	3.61 (br d, 12.0)	3.35 (br d, 12)
	3.16 (ddd, 12.0, 11.0, 3.0)	3.42 (td, 12.0, 3.0)	3.14 (ddd, 12, 11, 3)
10	1.58 (br d, 13.0)	1.68	1.57 (br d, 14)
	2.38 (masked)	1.87	1.34-43 (m)
11	2.05 (m)	2.05 (m)	2.01-2.06 (m)
	1.12 (qd, 12.0, 3.0)	1.20 (masked)	1.08-1.13 (m)
12	1.80 (m)	1.30 (m)	1.78-1.83 (m)
13	2.90 (td, 11.5, 3.2)	3.21 (br t, 12.0)	2.89 (ddd, 11, 10, 3)
14	2.10 (m)	2.60	2.06-2.17 (m)
	1.80 (m)	1.45 (td, 12.0, 3.0)	1.67-1.72 (m)
15	2.21 (m)	2.23 (m)	2.16-2.25 (m)
16	0.93 (d, 7.2)	0.99 (d, 7.2)	0.93 (d, 7)
17	3.10 (s)	2.96 (s)	3.04 (s)

[181] Recorded at 400 MHz. Assignments were aided by gCOSY and gHSQCAD spectra.
[182] Recorded at 400 MHz (See ref.37).

Table 6.4. Comparison of ^{13}C NMR data data for synthetic huperzine N, *N-epi*-huperzine N, and natural huperzine N in $CDCl_3$

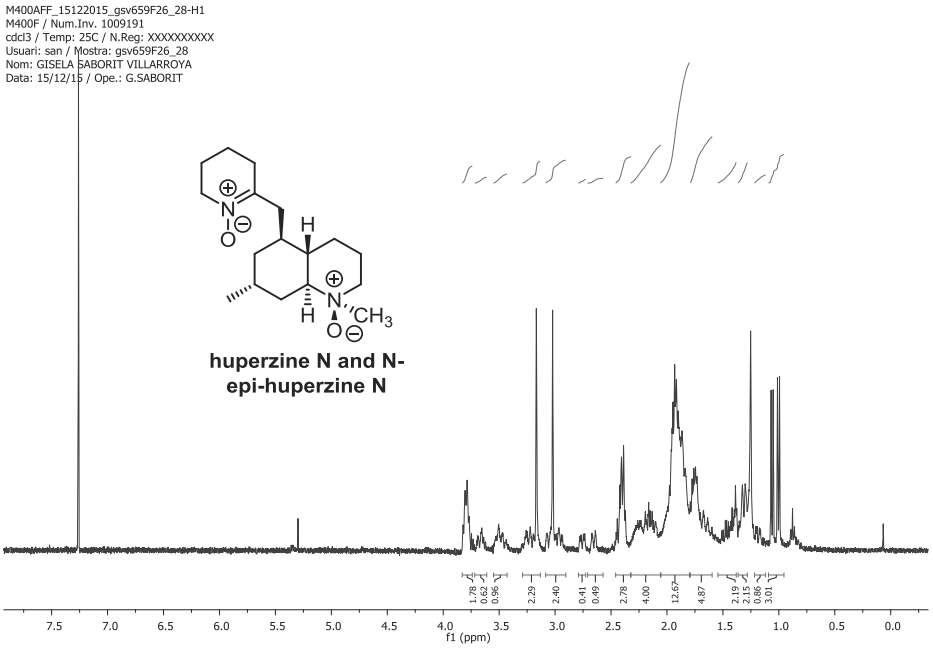


huperzine N **N-*epi*-huperzine N**

biogenetic numbering

	Synthetic huperzine N[183]	*N-epi*-huperzine N	Huperzine N[182]
	δ ^{13}C	δ ^{13}C	δ ^{13}C
1	58.5	58.6	58.2
2	23.3	23.3	23.1
3	18.9	19.2	18.8
4	29.9	29.9	30.0
5	147.9	147.2	148.0
6	36.7	35.5	36.4
7	32.4	34.6	32.3
8	36.8	37.5	36.6
9	69.1	71.1	69.0
10	20.3	22.9	20.1
11	27.0	27.1	27.0
12	41.1	44.7	40.8
13	73.8	75.9	73.4
14	30.1	30.2	30.0
15	27.1	27.2	26.8
16	19.0	18.2	19.0
17	57.6	48.0	57.6

[183] Recorded at 100 MHz. Assignments were aided by gCOSY and gHSQCAD spectra.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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv659F26_28
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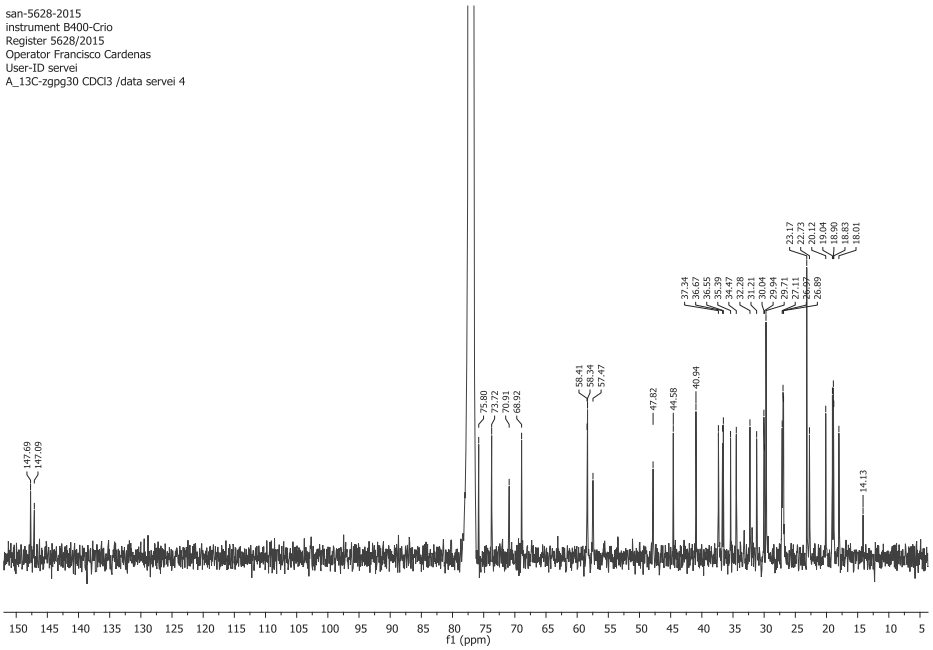
Data: 15/12/15 / Ope.: G.SABORIT
huperzine N and N-epi-huperzine N
f1 (ppm)


san-5628-2015
instrument B400-Crio
Register 5628/2015
Operator Francisco Cardenas
User-ID servei
A_13C-zgpg30 CDCl3 /data servei 4
f1 (ppm)

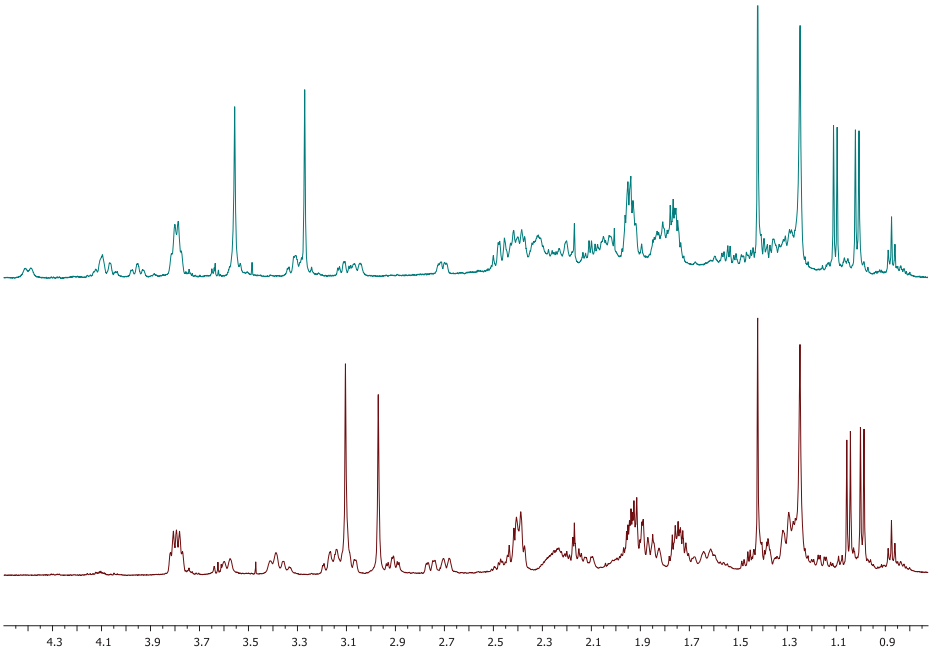


Figure 6.1 ^{1}H NMR spectra (500 MHz, $CDCl_3$) of the N-oxide compounds N-*epi*-huperzine N and huperzine N (bottom) and their protonated derivatives (top). Note the strong downshield effect on all proton resonances near to the protonated N-oxide functionality.

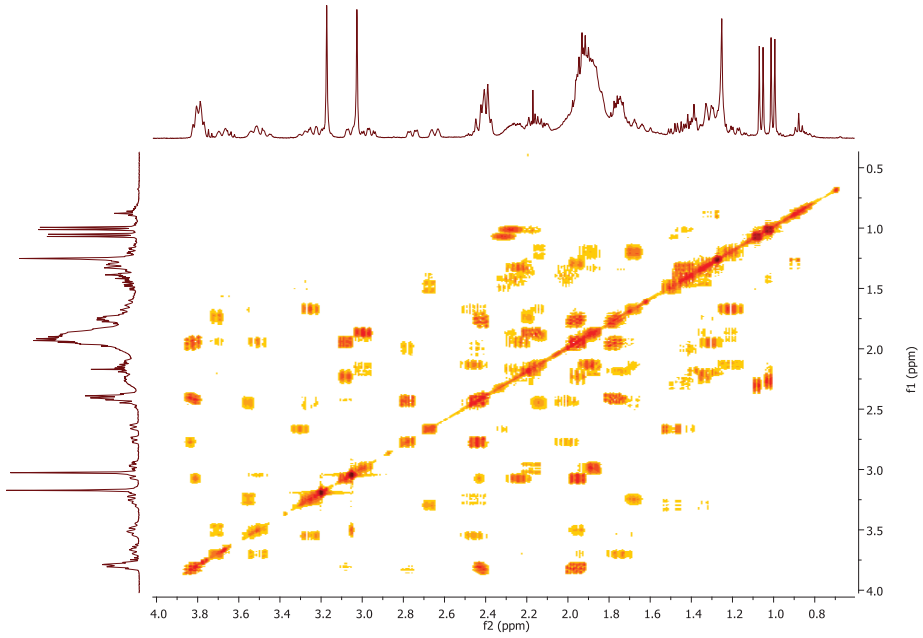


Figure 6.2. ^{1} H- ^{1}H COSY spectrum of the mixture containing the two N-oxide derivatives.

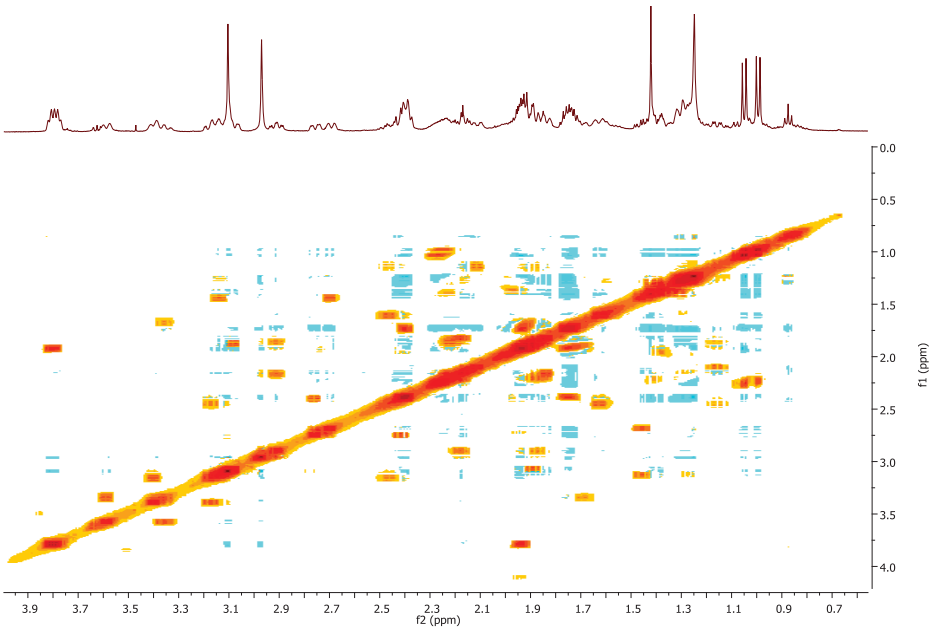


Figure 6.3. 2D ^{1}H- ^{1}H TOCSY spectrum (mixing time of 60 ms) of the mixture containing the two N-oxide derivatives.

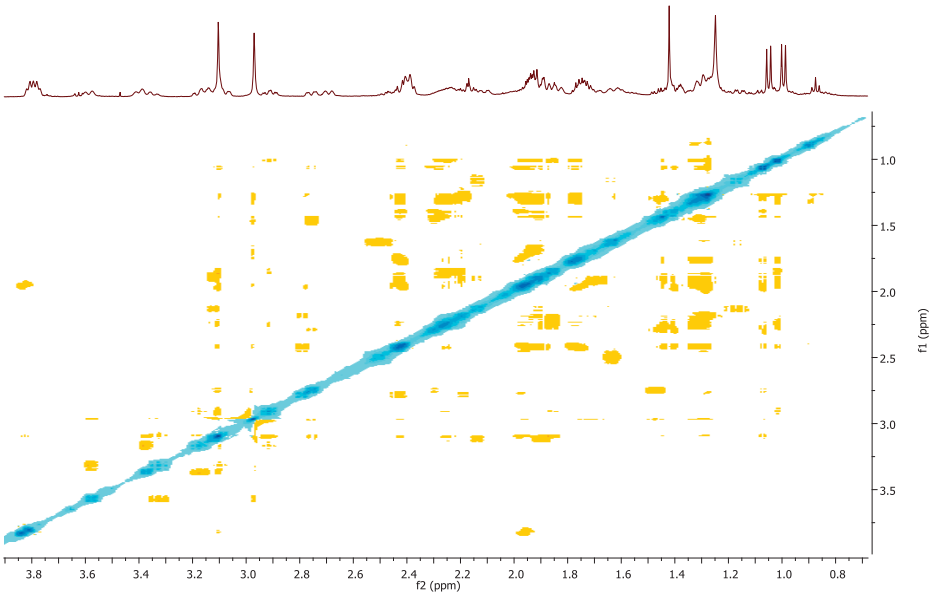


Figure 6.4. 2D ^{1}H- ^{1}H ROESY spectrum (mixing time of 500 ms) of the mixture containing the two N-oxide derivatives.

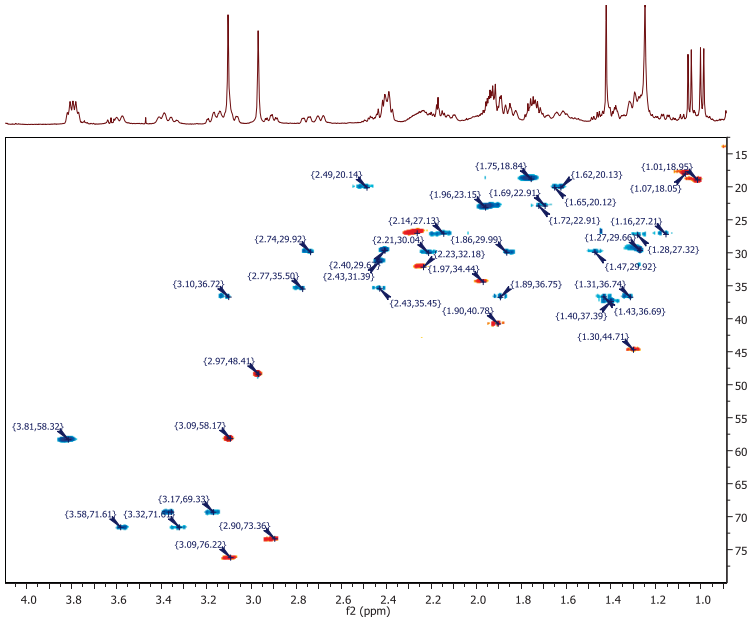


Figure 6.5. ^{1}H- ^{13}C multiplicity-edited HSQC

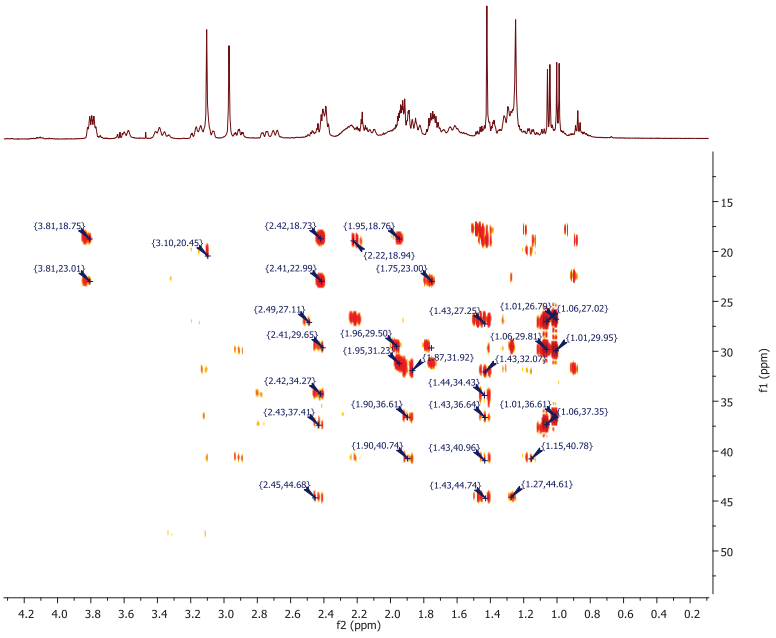


Figure 6.6. ^{1}H- ^{13}C HMBC spectrum (optimized to 8 Hz)

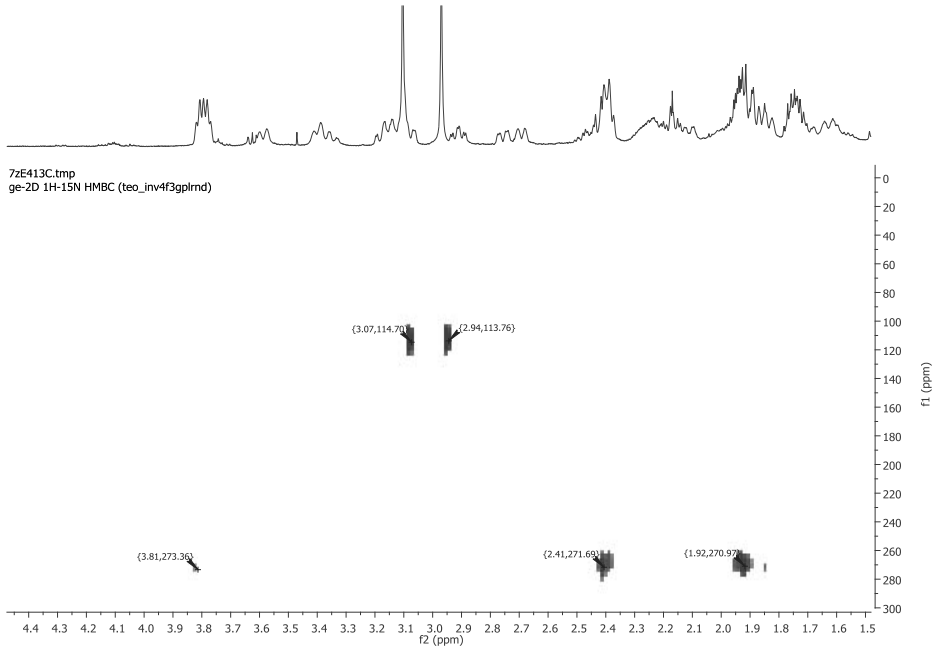
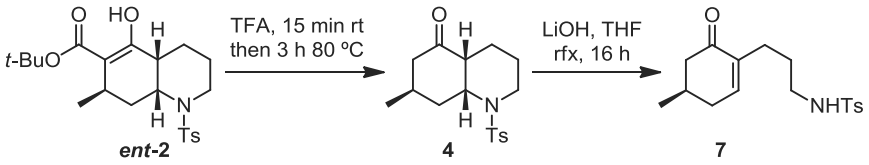


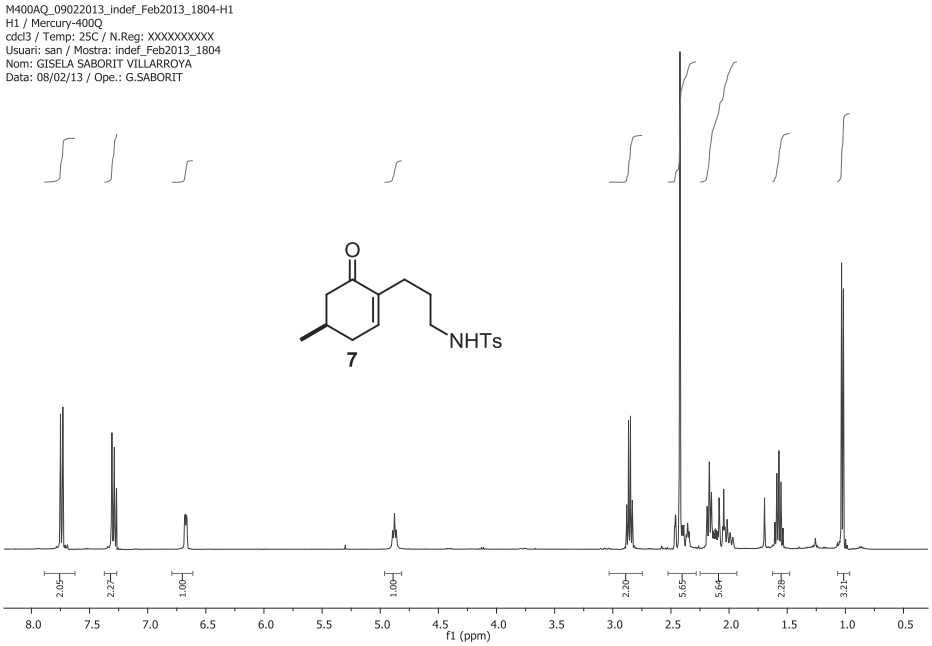
Figure 6.7 ^{1}H- ^{15}N HMBC (optimized to 8 Hz).

5-Methyl-2-[3-(4-methylsufanamido)propyl]cyclohex-2-enone (7)



ent-**2** **4** **7**

A solution of *ent*-**2** (1.6 g, 2.9 mmol) in TFA (3 mL) was stirred for 15 min. The solvent was evaporated under reduced pressure, the last traces of TFA were removed by azeotroping with toluene (3 x 5 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 70 ºC for 3 h to give the crude decahydroquinoline **4**. A solution of crude **4** in THF (17 mL) and LiOH (355 mg, 14.83 mmol) was stirred for 16 h at reflux, filtered through celite and purified by chromatography (2.5→5→10%→25% EtOAc/hexane) to give **7** (182 mg, 15%).^{1}H NMR (400 MHz, COSY) δ 1.02 (d, *J* = 6.4 Hz, 3H, CH_3), 1.57 (quint, *J* = 6.5 Hz, 2H, H-2´) 2.01-2.18 (m, 2H, H-6, H-4), 2.17 (t, *J* = 6.5 Hz, 2H, H-1´), 2.35-2.46 (m, 3H, H-4, H-5, H-6), 2.42 (s, 3H, CH_3), 2.85 (q, *J* = 6.5 Hz, 2H, H-3´), 4.87 (t, *J* = 6.5 Hz, 1H, NH), 6.67 (m, 1H, H-3), 7.29 (d, *J* = 8 Hz, 2H, *m*-Ts), 7.73 (d, *J*= 8 Hz, 2H, *o*-Ts). ^{13}C NMR (400 MHz, HSQC) δ 21.1 (CH_3), 21.5 ($ArCH_3$), 26.0 (C-5), 28.9 (C-2´), 30.5 (C-1´), 34.3 (C-4), 42.2 (C-3´), 46.4 (C-6), 127.9 (*o*-Ts), 129.6 (*m*-Ts), 137.0 (*p*-Ts), 138.1 (*ipso*-Ts), 143.2 (C-2), 146.1 (C-3), 199.9 (C-1). HRMS calcd for $C_{17}H_{24}NO_3S$ ($M+H^+$) 322.1471, found 322.1469.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Data: 08/02/13 / Ope.: G.SABORIT
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NHTs
7
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2.27
1.00
1.00
2.20
5.65
5.64
2.28
3.21
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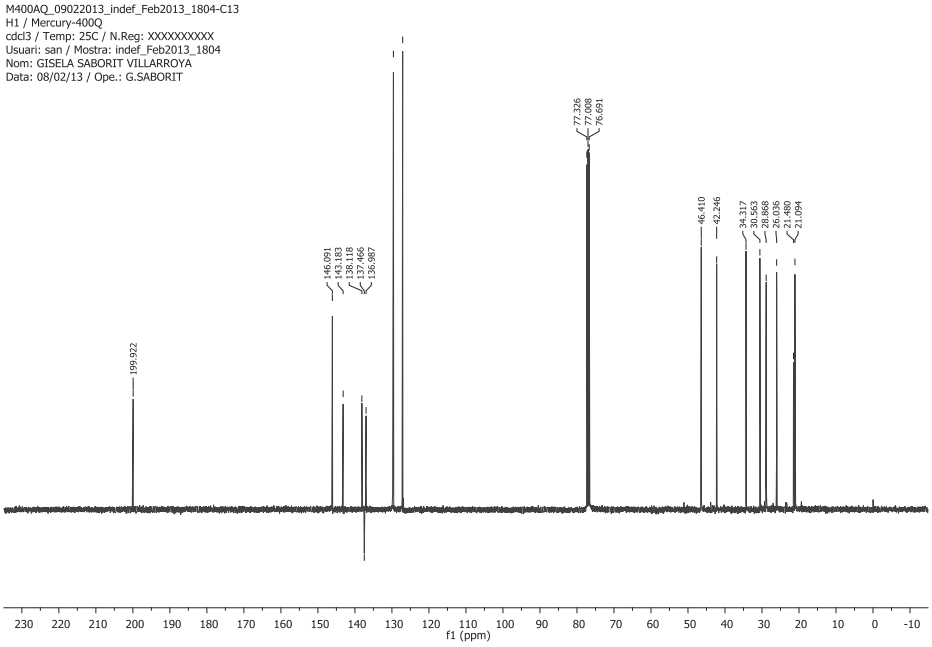
f1 (ppm)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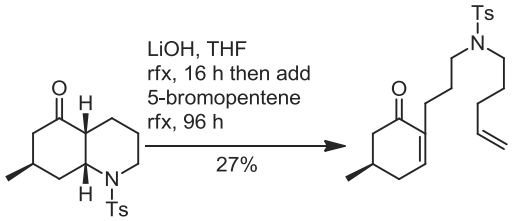
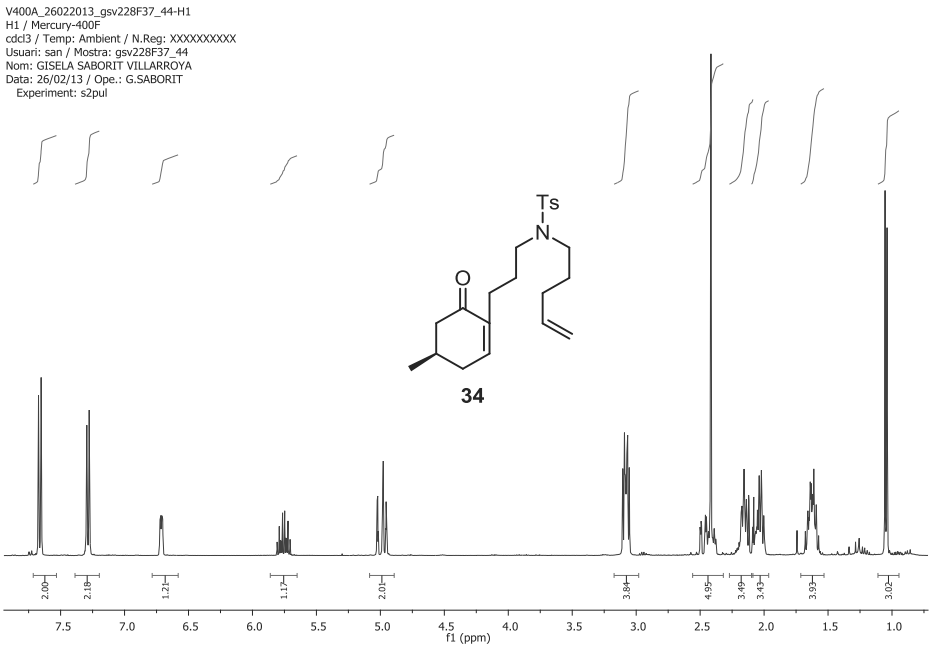
137.466
136.987
77.326
77.008
76.691
46.410
42.246
34.317
30.563
28.868
26.656
21.480
21.094
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5-Methyl-2-[3-(4-methylsufanamido)-*N*-(pent-4-en-1-yl)-propyl]cyclohex-2-enone (34)



4 **34**

To a solution of **4** (287 mg, 0.89 mmol) in THF (4 mL) was added LiOH (81 mg, 3.40 mmol) and the mixture was stirred overnight at reflux. Then, 5-bromopentene was added (0.4 mL, 3.40 mmol) and stirring was continued for further 96 h. The mixture was filtered through celite and purified by chromatography (SiO_2, 5→10→25%→50% EtOAc/hexane) to give **34** (93 mg, 27%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.3 Hz, 3H, CH_3), 1.63 (m, 4H, H-2', H-2''), 2.00-2.17 (m, 7H, H-6, H-5, H-4, H-3'', H-1'), 2.41 (s, 3H, CH_3), 2.45 (m, 2H, H-6, H-4), 3.08 (ddd, *J* = 9.4, 7.6, 5.2 Hz, 4H, H-3', H-1''), 4.98 (m, 2H, H-5''), 5.76 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, H-4''), 6.71 (m, 1H, H-3), 7.29 (d, *J* = 8 Hz, 2H, *m*-Ts), 7.66 (d, *J*= 8 Hz, 2H, *o*-Ts). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.3 (CH_3), 21.6 ($ArCH_3$), 26.8 (C-5), 27.7 (C-2'), 27.9 (C-2''), 30.7 (C-1'), 30.9 (C-3''), 34.4 (C-4), 46.7 (C-6), 47.9 (C-3'), 48.2 (C-1''), 115.3 (C-5''), 127.2 (*o*-Ts), 129.7 (*m*-Ts), 136.9 (*p*-Ts), 137.6 (C-4''), 138.4 (*ipso*-Ts), 143.1 (C-2), 145.4 (C-3), 199.6 (C-1). HRMS calcd for $C_{22}H_{32}NO_3S$ $(M+H)^+$ 390.2097, found 390.2097.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Data: 26/02/13 / Ope.: G.SABORIT
Experiment: s2pul
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N
O
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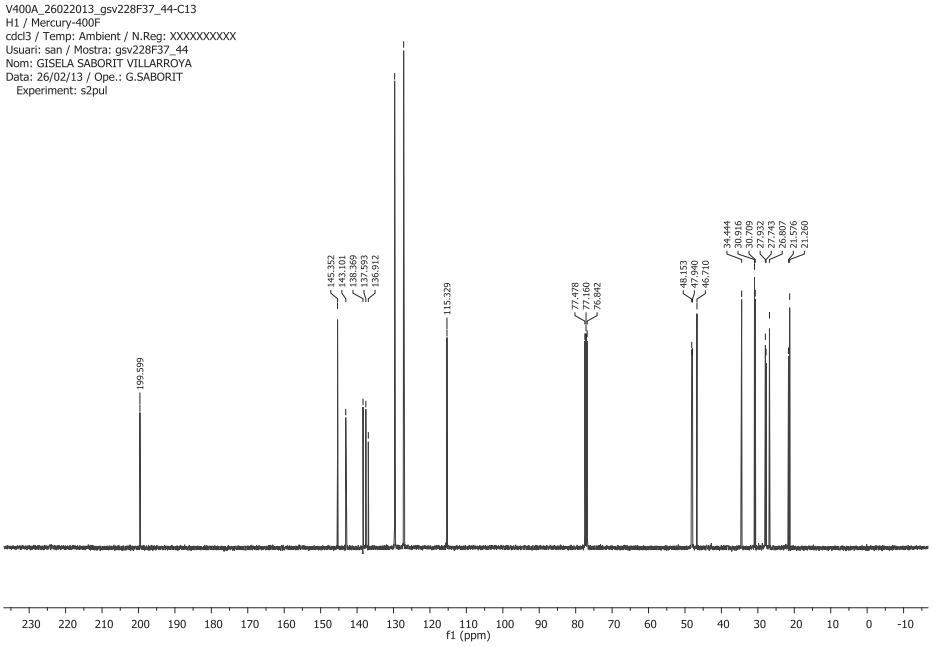
2.18
1.21
1.17
2.01
3.84
4.95
3.49
3.43
3.93
3.02
f1 (ppm)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cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv228F37_44
Nom: GISELA SABORIT VILLARROYA
Data: 26/02/13 / Ope.: G.SABORIT
Experiment: s2pul
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143.101
138.369
137.593
136.912
115.329
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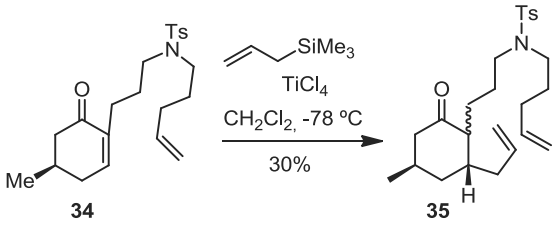
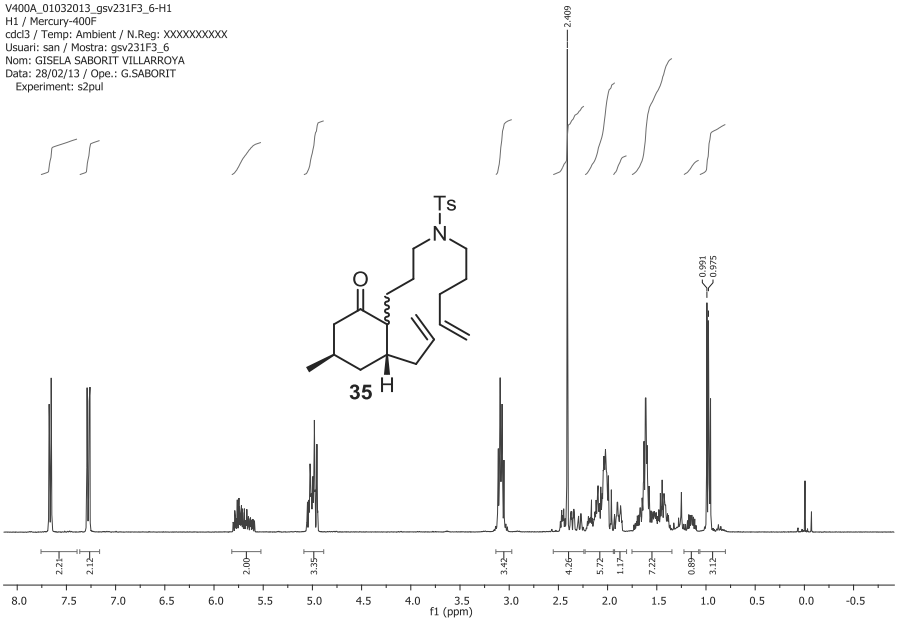
77.160
76.842
48.153
47.940
46.710
34.444
30.916
30.709
27.932
22.743
26.807
21.576
21.260
f1 (ppm)

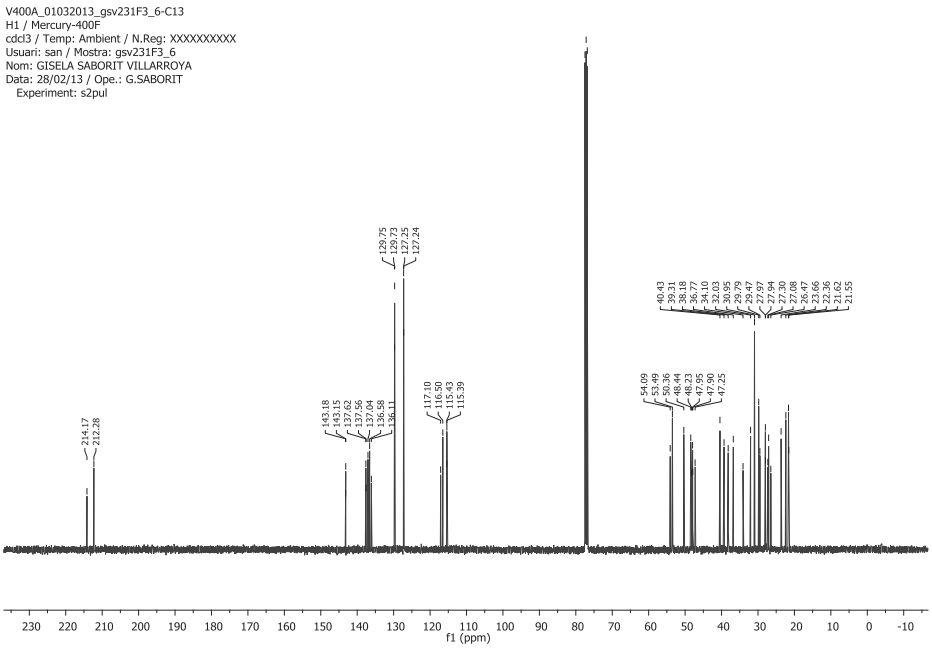
(2*RS*, 3*RS*, 5*SR*) and (2*RS*, 3*SR*, 5*SR*)-3-Allyl-5-Methyl-2-[(4-aza-4methylphenylsulfonyl)-9-nonenyl] cyclohexanone (35)



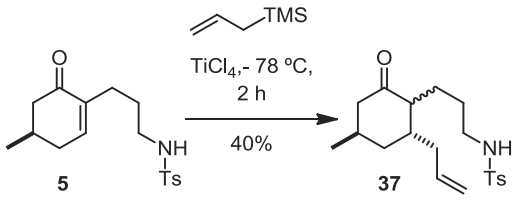
A solution of **34** (87 mg, 0.22 mmol) in CH_2Cl_2 (0.34 mL) was cooled to -78 °C and $TiCl_4$ (0.07 mL, 0.54 mmol, 2.4 equiv) was added. After 5 min, allyltrimethylsilane (0.05 mL, 0.67 mmol, 3 equiv) was added and the resultant solution was stirred for 2 h at -78 °C, until TLC indicated the disappearance of starting material. A solution of Et_3N (0.30 mL, 2.14 mmol, 9.6 equiv) in MeOH (1 mL, 2.14 mmol, 9.6 equiv) was added dropwise. After 5 min, the mixture was kept at -78 ºC and diluted with Et_2O (2 mL). The organics were washed with aqueous 10% HCl (2 mL), saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL), dried and concentrated. The crude extract was purified by chromatography 2.5→5→10% EtOAc/hexane) to give **35** (29 mg, 30% yield) as a 1:1 mixture of diastereomers. HRMS calcd for $C_{25}H_{38}NO_3S$ $(M + H)^+$ 432.2567, found 432.2563. Compound **35**: ^{1}H NMR (400 MHz, COSY) δ 0.96 (d, *J* = 6.0 Hz, 3H, CH_3), 1.49-1.72 (m, 6H, 3-CH_2, CH_2), 1.90-2.24 (m, 5H, H-6ax, H-5, H-3, 3-CH_2), 2.31 (dm, *J* = 12.6 Hz, H-6eq), 2.40 (masked, 1H, H-2ax), 2.42 (s, 3H, ArCH_3), 3.12-3.18 (m, 4H, CH_2N, H-3'), 4.98 (m, 4H, =CH_2), 5.64 (m, 2H, =CH), 7.30 (d, *J* = 8 Hz, 2H, *m*-Ts), 7.75 (d, *J* = 8 Hz, 2H, *o*-Ts). ^{13}C NMR (100 MHz, HSQC) δ 21.6 (*Ar*CH_3), 22.4 (CH_3), 23.7 (C-5), 27.1 and 28.0 (CH_2), 29.8 (C-5), 31.0 and 32.0 (CH_2C=), 36.8 (C-4), 40.4 (C-3), 48.0 and 48.4 (NCH_2), 50.4 (C-6), 53.5 (C-2), 115.4 and 116.5 (=CH_2), 127.2 (*o*-Ts), 129.7, (*m*-Ts), 136.1 and 137.7 (=CH), 136.7 (*p*-Ts), 143.2 (*ipso*-Ts), 212.3 (C-1). HRMS calcd for $C_{25}H_{38}NO_3S$ $(M + H)^+$ 432.2567, found 432.2563. Compound *epi*-**35**: ^{1}H NMR (400 MHz, COSY) –selected signals- δ 0.92 (d, *J* = 6.4 Hz, 3H, CH_3), 2.05 (masked, H-2ax), 2.10 (masked, H-6ax), 2.25 (dd, 1H, H-6eq); ^{13}C NMR (100 MHz, HSQC) δ 21.2 (CH_3), 21.6 (*Ar*CH_3), 23.4, 27.3, 27.8 (CH_2), 29.5 (C-5), 34.2 (3-CH_2), 36.7 (C-4), 38.1, 39.0 (C-3), 47.9 and 48.2 (NCH_2), 47.3 (C-6),

54.1 (C-2), 116.1 and 117.1 (=CH_2), 127.2 (*o*-Ts), 129.8 (*m*-Ts), 136.1 and 137.7 (=CH), 136.7 (*p*-Ts), 143.2 (*ipso*-Ts), 214.3 (C-1).

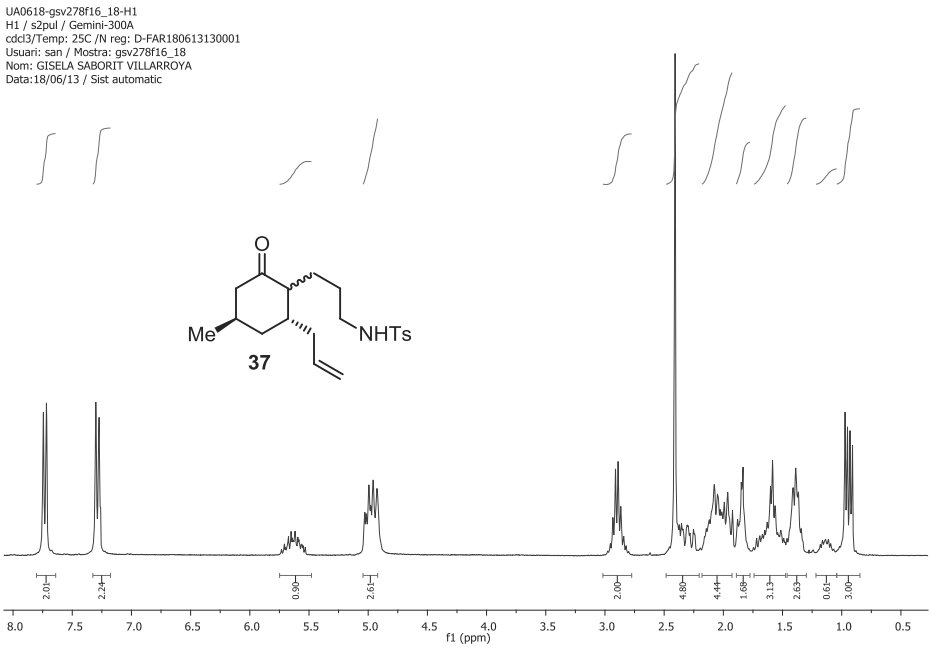


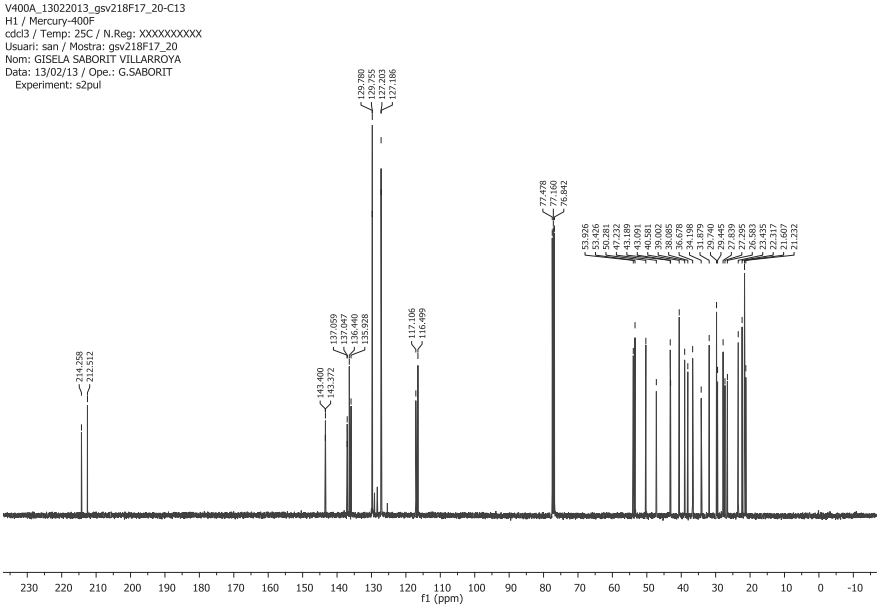


(2*RS*, 3*RS*, 5*SR*) and (2*RS*, 3*SR*, 5*SR*)-3-Allyl-5-Methyl-2-[(N-4methylphenylsulfonyl)-3-aminopropyl] cyclohexanone (37)

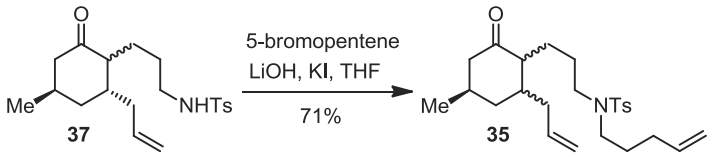


To a stirred solution of **5** (171 mg, 0.53 mmol) in CH_2Cl_2 (0.8 mL) at -78 °C was added $TiCl_4$ (0.18 mL, 1.28 mmol, 2.4 equiv). After 5 min, a solution of allyltrimethylsilane (0.08 mL, 1.04 mmol, 3 equiv) in CH_2Cl_2 (0.54 mL) was added dropwise. The resultant solution was stirred for 2 h at -78 °C, until TLC indicated the disappearance of starting material. A solution of Et_3N (0.47 mL, 3.34 mmol, 9.6 equiv) in MeOH (0.14 mL, 3.34 mmol, 9.6 equiv) was added dropwise. After 5 min, the mixture was kept at -78 ºC and diluted with Et_2O (6 mL). The organics were washed with aqueous 10% HCl (8 mL), saturated aqueous $NaHCO_3$ (8 mL) and brine (8 mL), dried and concentrated. Chromatography (2.5→5→10%→25% EtOAc/hexane) provided **50** as a 1:1 diastereomeric ratio (78 mg, 40%). **Compound 37**. Selected signals: ^{1}H NMR (400 MHz, COSY) δ 0.98 (d, *J* = 4 Hz, 3H, CH_3), 1.10-1.19 (m, 2H, 1-CH_2), 1.40 (m, 2H, 2-CH_2, H-4), 1.52-1.72 (m, 3H, 2-CH_2, C*H*$_2$-CH=CH_2), 1.89-2.13 (m, 5H, C*H*$_2$-CH=CH_2, H-6, H-4, H-5), 2.26-2.39 (m, 2H, H-2, H-6), 2.42 (s, 3H, ArCH_3), 2.91 (m, 2H, 3-CH_2), 4.99 (m, 2H,), 5.63 (m, 1H, C*H*=CH_2), 7.29 (d, *J* = 8 Hz, 2H, *m*-Ts), 7.75 (d, *J* = 8.0 Hz, 2H, *o*-Ts). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (*Ar*CH_3), 22.3 (CH_3), 23.4 (1-CH_2), 26.6 (2-CH_2), 27.3, 27.8, 29.6 (C-5), 31.9 (C*H*$_2$-CH=CH_2), 38.1 (C-4), 40.6 (C-3), 43.2 (3-CH_2), 50.3 (C-6), 53.4 (C-2), 116.1 (CH=C*H*$_2$), 127.2 (*o*-Ts), 129.8 (*m*-Ts), 135.9 (C*H*=CH_2), 137.1 (*p*-Ts), 143.4 (*ipso*-Ts) 212.5 (C-1). HRMS calcd for $C_{20}H_{30}NO_3S$ (M + H) $^+$ 364.1939, found 364.1939.


UA0618-gsv278f16_18-H1
H1 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: D-FAR180613130001
Usuari: san / Mostra: gsv278f16_18
Nom: GISELA SABORIT VILLARROYA
Data:18/06/13 / Sist automatic
O
Me
NHTs
37
2.01
2.24
0.90
2.61
2.00
4.80
4.44
1.68
3.13
2.63
0.61
3.00
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
f1 (ppm)

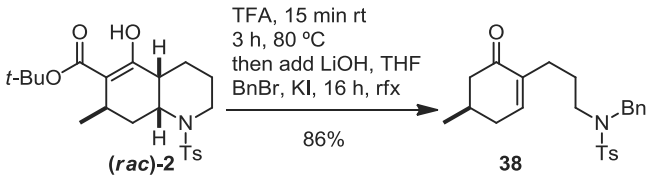

V400A_13022013_gsv218F17_20-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv218F17_20
Nom: GISELA SABORIT VILLARROYA
Data: 13/02/13 / Ope.: G.SABORIT
Experiment: s2pul
214.268
213.512
143.400
143.372
137.659
137.447
136.440
135.928
129.780
129.355
127.203
127.186
117.106
116.499
77.478
77.160
76.842
53.926
53.496
50.281
47.232
43.189
41.901
40.581
39.002
38.085
36.678
34.198
31.879
29.740
29.445
27.839
27.295
26.583
24.455
22.317
21.607
21.232
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(2*RS*, 3*RS*, 5*SR*) and (2*RS*, 3*SR*, 5*SR*)-3-Allyl-5-Methyl-2-[(4-aza-4methylphenylsulfonyl)-9-nonenyl] cyclohexanone (35)



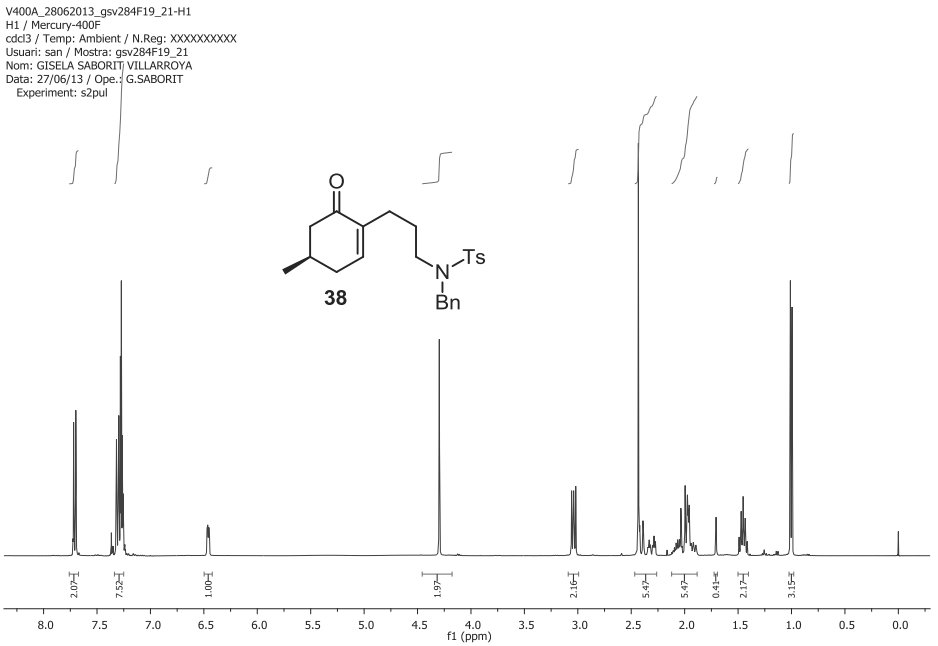
A solution of **37** (56 mg, 0.154 mmol), LiOH (18 mg, 0.77 mmol, 5.0 equiv), KI (128 mg, 0.77 mmol, 5.0 equiv) and 5-bromopentene (0.1 mL, 0.77 mmol, 5.0 equiv) in THF (2 mL) was stirred for 48 h at reflux. After cooling to room temperature the mixture was filtered off and the filter cake was washed with CH_2Cl_2. The solvent was evaporated and the crude extract was purified by chromatography (2.5→5→10→25% EtOAc/hexane) to give **35** (47 mg, 71%). For NMR data see p. 188).

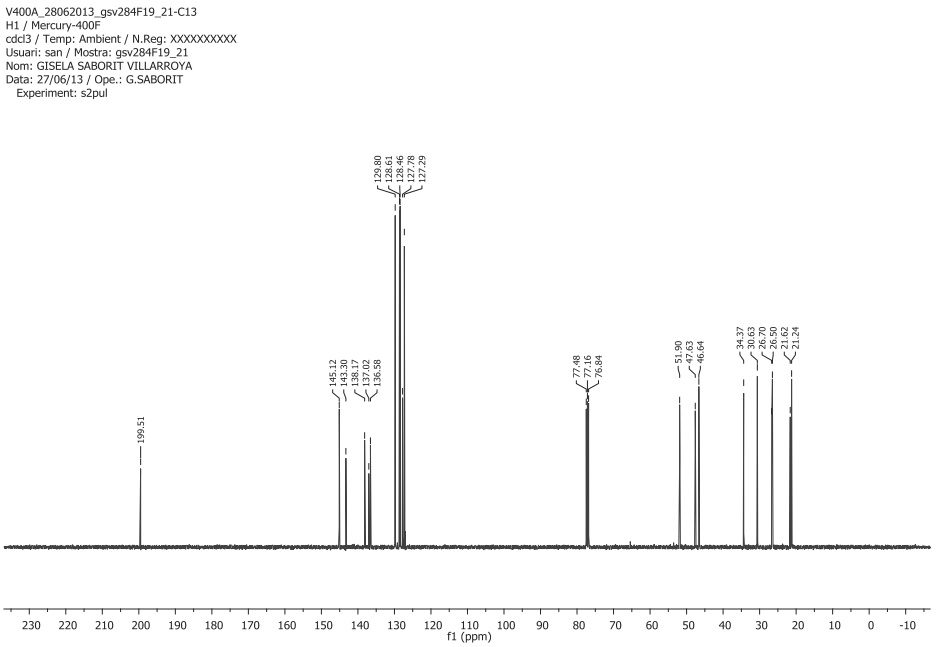
(*RS*)-5-Methyl-2-[3-(N-benzyl-N-(4methylphenylsulfonyl))aminopropyl] cyclohex-2-enone (38)



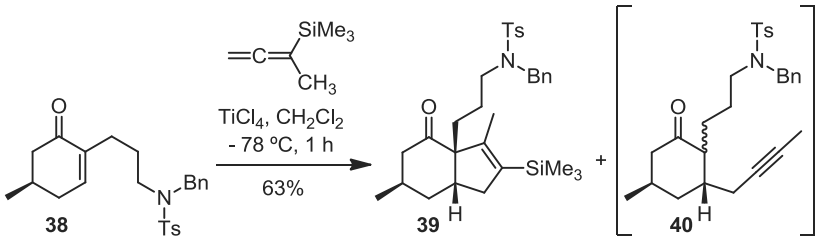
Compound ***rac*-2** (2.0 g, 4.75 mmol) was treated with TFA (3.3 mL) for 15 min at rt, the solvent was removed, and the last traces of TFA were removed by azeotroping with toluene (2 × 10 mL). The reaction flask was maintained on the rotatory evaporator at 70 ºC for 3 h. To a solution of the above ketone in THF (21 mL) were added succesively LiOH (568 mg, 23.74 mmol, 5.0 equiv), KI (2.36 g, 14.24 mmol, 3.0 equiv) and benzyl bromide (1.7 mL, 14.24 mmol, 3.0 equiv), and the mixture was stirred at reflux overnight. The mixture was allowed to reach rt, filtered through a pad of celite and the filter cake was thoroughly washed with DCM. The volatiles were removed and the crude was purified by chromatography (2.5→5→10% EtOAc/hexane) to give **38** (1.7 g, 86%); R_f = 0.42 (25% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (d, *J* = 6.2 Hz, 3H, CH_3), 1.46 (quint, *J* = 7.7 Hz, 2H, H-2'), 1.90-2.06 (m, 4H, H-4, H-6, H-1'), 2.27-2.43 (m, 5H, H-4, H-6, $ArCH_3$), 3.03 (m, 2H, H-3'), 4.30 (CH_2Ph), 6.46 (m, 1H, H-3), 7.28 (m, 7H, *o*-Ts, Ph), 7.71 (d, *J* = 8.3 Hz, 2H, *m*-Ts); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2 (CH_3), 21.6 ($ArCH_3$), 26.5 (C-5), 26.7 (C-2'), 30.6 (C-1'), 34.4 (C-4), 46.6 (C-6), 47.6 (C-3'), 51.9 (CH_2Ph), 127.3 (*o*-Ts), 127.8 (*p*-Bn), 128.6 (*o*-Bn), 129.8 (*m*-Ts),

136.6 (*ipso*-Bn), 137.0 (*p*-Ts), 138.2 (*ipso*-Ts), 143.3 (C-2), 145.1 (C-3), 199.5 (C-1). HRMS Calcd for $C_{24}H_{30}NO_3S$ $(M + H)^+$ 412.1941, found 412.1938.

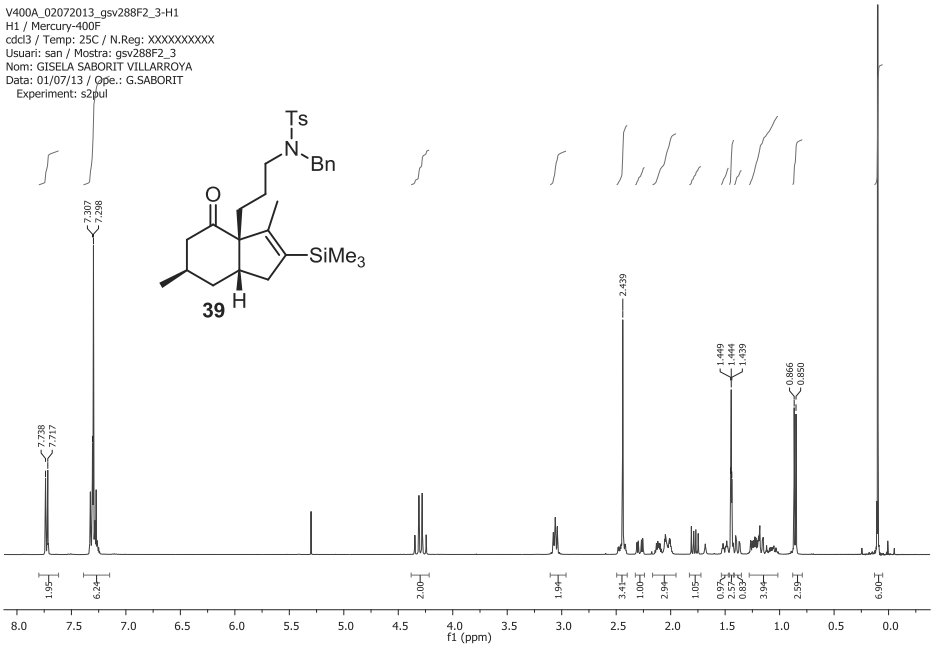


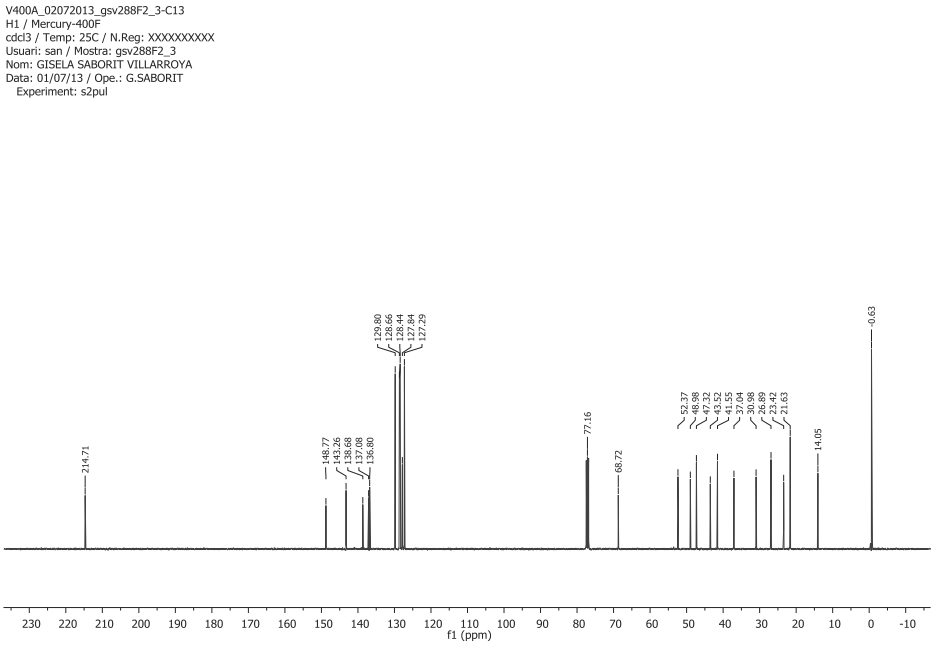


(1*RS*,4*SR*,6*RS*)-1-[*N*-Benzyl-N-(4-methylphenylsulfonyl)-3-aminopropyl]-4,9-dimethyl-8-trimethylsilylbicyclo[4.3.0]non-8-en-2-one (39)

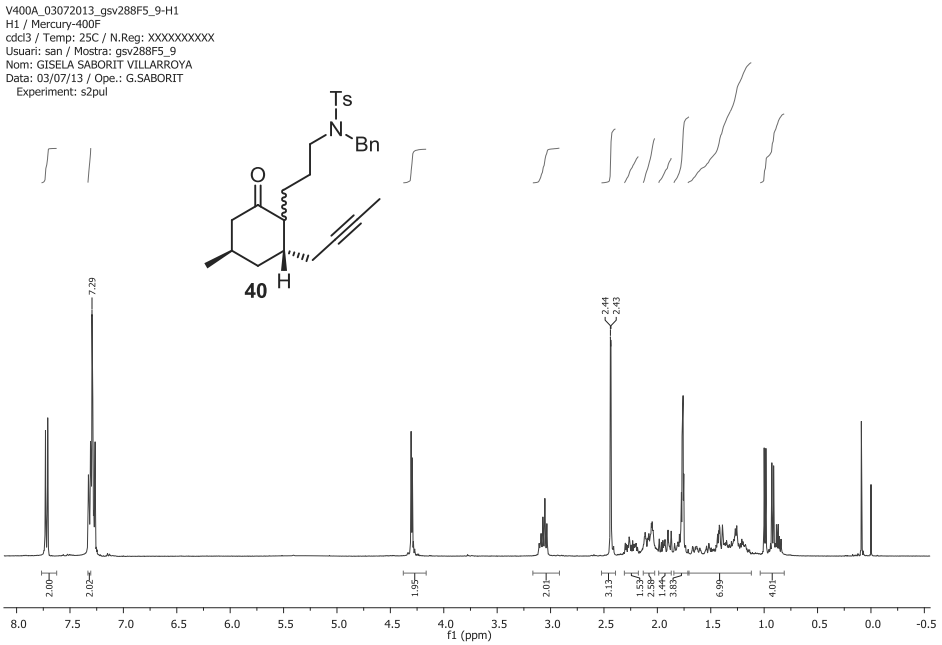


To stirred solution of **38** (470 mg, 0.98 mmol) and 1-methyl-1-(trimethylsilyl) allene (0.32 mL, 1.94 mmol, 1.7 equiv) in CH_2Cl_2 (6 mL) at – 78ºC was added dropwise $TiCl_4$ (0.21 mL, 1.7 mmol). The resulting dark red solution was stirred at – 78 ºC for 1 h and then poured into a separating funnel containing a mixture of water (25 mL) and diethyl ether (25 mL). The aqueous was extracted with diethyl ether (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried, filtered and concentrated. The crude product was purified by chromatography (2.5→5→10% EtOAc/hexane) to give **39** (385 mg, 63 %). ^{1}H NMR (400 MHz, COSY) 0.09 (s, 9H, $(CH_3)_3Si$), 0.85 (d, *J* = 6.8 Hz, 3H, CH_3), 1.15-1.25 (m, 4H, H-5, H-1', 2H-2'), 1.39 (td, *J* = 12.4, 3.3 Hz, 1H, H-5ax), 1.44 (t, *J* = 2.1 Hz, 3H, 9-CH_3), 1.50 (dm, *J* = 13.6 Hz, 1H, H-1'), 1.77 (dd, *J* = 16.0, 8.5 Hz, 1H, H-3ax), 1.99-2.05 (m, 2H, H-4, H-7), 2.11 (dddd, *J* = 10, 5, 5, 5 Hz, 1H, H-6), 2.27 (ddd, *J* = 16.0, 5.6, 1.4 Hz, 1H, H-3eq), 2.43 (s, 3H, $ArCH_3$), 2.44 (ddq, *J* = 11.0, 5.5, 2.1 Hz, 1H, H-7), 3.06 (t, *J* = 7.4 Hz, 2H, H-3'), 4.30 (2d, *J* = 14.8 Hz, 2H, CH_2Ph), 7.30-7.35 (m, 6H, *o*-Ts, Ph), 7.73 (d, *J* = 8.3 Hz, 2H, *m*-Ts); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.6 ($(CH_3)_3Si$), 14.0 (9-CH_3), 21.6 (CH_3), 21.6 ($ArCH_3$), 23.4 (C-2'), 26.9 (C-4), 31.0 (C-5), 37.0 (C-1'), 41.6 (C-6), 43.5 (C-7), 47.3 (C-3), 49.0 (C-3'), 52.4 (NCH_2Ar), 68.7 (C-1), 127.3 (*o*-Ts), 127.8 (Ph), 128.4 (Ph), 128.7 (Ph), 129.8 (*m*-Ts), 136.8 (*ipso*-Ph), 137.1 (*p*-Ts), 138.7 (*ipso*-Ts), 143.3 (C-8), 148.8 (C-9), 214.7 (C-2). HRMS calcd for $C_{31}H_{44}NO_3SSi$ $(M + H)^+$ 538.2806, found 538.2798.


V400A_02072013_gsv288F2_3-H1
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv288F2_3
Nom: GISELA SABORIT VILLARROYA
Data: 01/07/13 / Ope.: G.SABORIT
Experiment: s2pul
Ts
N
Bn
O
SiMe3
H
39
7.738
7.717
7.307
7.298
2.439
1.449
1.444
1.439
0.866
0.850
f1 (ppm)


V400A_02072013_gsv288F2_3-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv288F2_3
Nom: GISELA SABORIT VILLARROYA
Data: 01/07/13 / Ope.: G.SABORIT
Experiment: s2pul
214.71
148.77
143.26
138.68
137.08
136.80
129.80
128.66
128.44
127.84
127.29
77.16
68.72
52.37
48.98
48.22
43.52
41.55
37.04
30.98
26.88
23.42
21.63
14.05
0.63
f1 (ppm)

The product coming from desilylation **40** was also obtained as a mixture of diastereomers at C-2 (68 mg, 15%). **3-(2-Butynyl)-5-methyl-2-[(*N*-benzyl-*N*-(4-methylphenylsulfonyl)-3-aminopropyl] cyclohexanone**: R_f = 0.39 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, major isomer) δ 0.99 (d, J = 6.8 Hz, 5-CH_3), 1.14-1.54 (m, 4H, H-1' 2H-2', H-4), 1.63 (2dd, J = 11.0, 2.6 Hz, 1H, H-1'), 1.75 (t, J = 2.4 Hz, CH_3), 1.93 (m, 1H, H- 1''), 2.07 (m, 3H, H-1', H-4, H-5), 2.26 (m, 2H, H-3, H-6, H-2), 2.43 (s, $ArCH_3$), 3.06 (m, 2H, H-3'), 4.23 (s, 2H, CH_2Ph), 7.29 (m, 5H, Ph, *m*-Ts), 7.71 (d, J = 8.0 Hz, 2H *o*-Ts). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.6 (CH_3), 18.0 (C-1´´), 21.6 (CH_3Ts), 22.4 (5-CH_3), 23.2 (C-1´), 26.1 (C-2´), 29.8 (C-5), 38.7 (C-4), 40.2 (C-3), 47.6 (C-3´), 50.2 (C-6), 51.4 (NCH_2Ar), 52.6 (C-2), 76.5 (C-3´´), 77.8 (C-2´´), 127.3 (*o*-Ts), 127.8 (*p*-Bn), 128.5 (*m*-Bn), 128.6 (*o*-Bn), 129.8 (*m*-Ts), 136.6 (*ipso*-Bn), 136.7 (*p*-Ts), 137.1 (*ipso*-Ts), 143.3 (*p*-Ts), 211.8 (C-1). HRMS Calcd for $C_{28}H_{36}NO_3S$ $(M + H)^+$ 466.2410, found 466.2415.


V400A_03072013_gsv288F5_9-H1
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv288F5_9
Nom: GISELA SABORIT VILLARROYA
Data: 03/07/13 / Ope.: G.SABORIT
Experiment: s2pul
Ts
N
Bn
O
H
40
7.29
2.44
2.43
2.00
2.02
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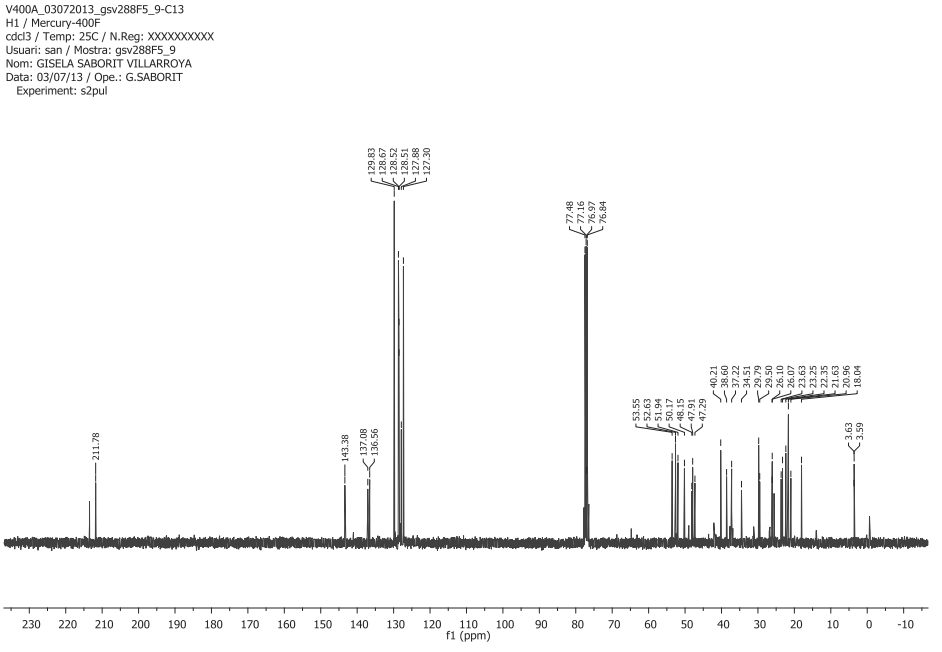
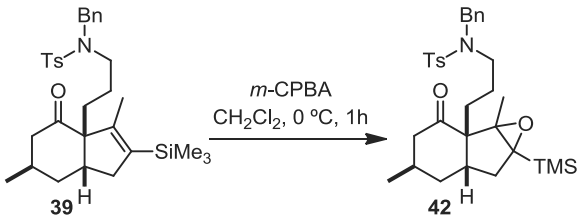
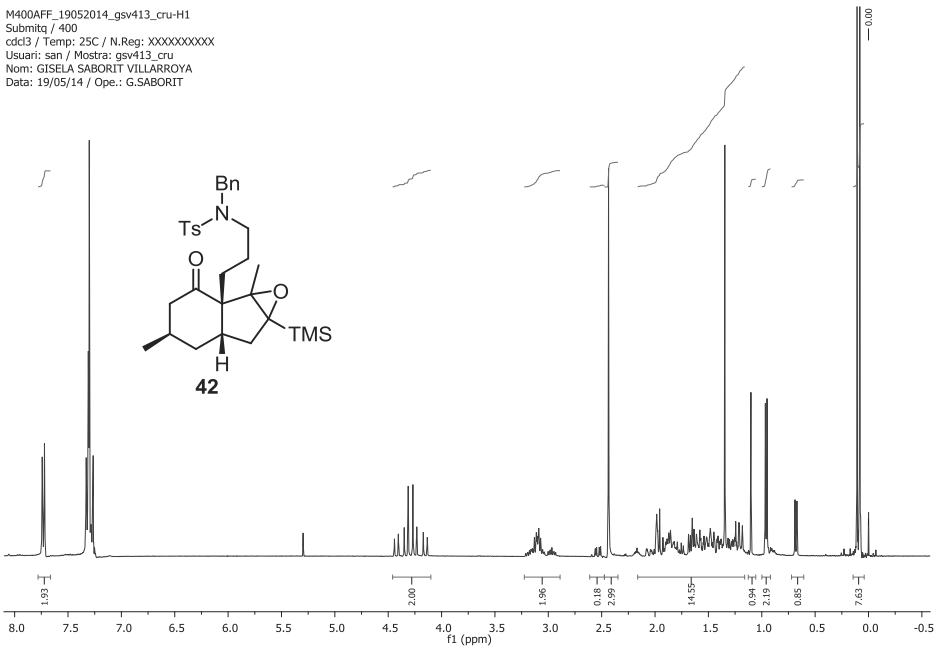
2.01
3.13
1.58
2.94
1.44
3.83
6.99
4.01
f1 (ppm)

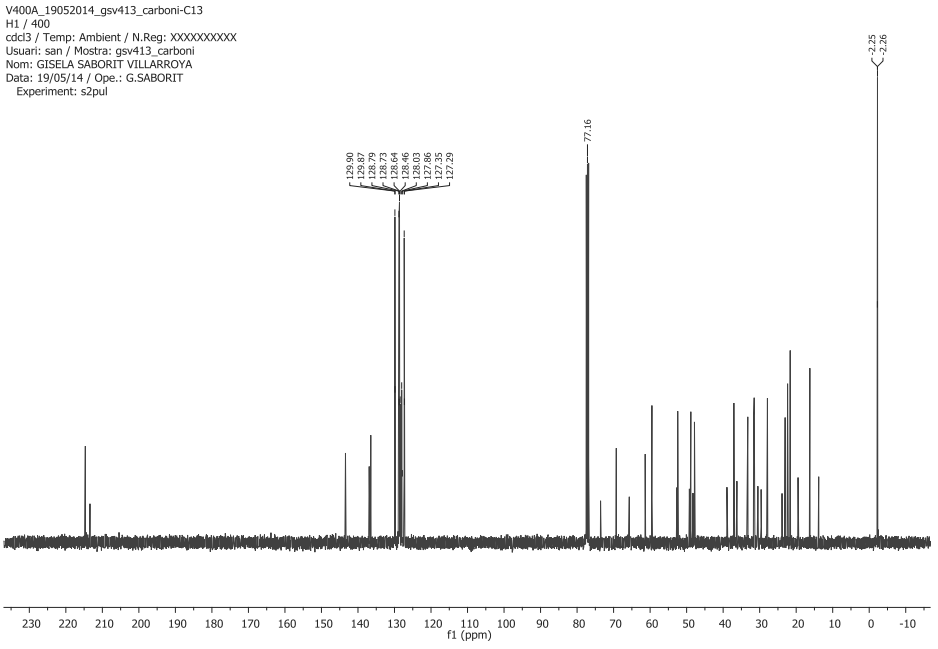

V400A_03072013_gsv288F5_9-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv288F5_9
Nom: GISELA SABORIT VILLARROYA
Data: 03/07/13 / Ope.: G.SABORIT
Experiment: s2pul
129.83
128.67
128.52
128.51
127.88
127.30
77.48
77.16
76.97
76.84
211.78
143.38
137.08
136.56
53.55
52.63
51.94
50.17
48.45
47.91
47.29
40.21
38.60
37.22
34.51
29.79
29.50
26.10
24.07
23.63
23.25
22.35
21.63
20.96
18.04
3.63
3.59
f1 (ppm)

(1*RS*,4*SR*,6*RS*,8*SR*,9*SR*)-1-[*N*-Benzyl-*N*-(4-methylphenylsulfonyl)-2-oxo-3-aminopropyl]-4,9-dimethyl-8-trimethylsilylbicyclo[4.3.0]-8,9-oxirane (42)

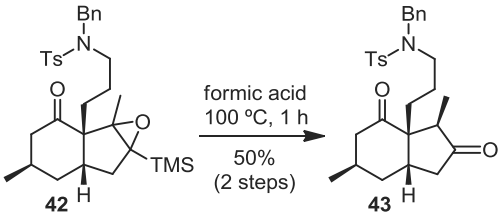


To a solution of **39** (30 mg, 0.056 mmol) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (9 mg, 0.112 mmols) followed by *m*-CPBA (12 mg, 0.053 mmol) at 0 ºC. After stirring for 1 h at 0 ºC, 2-methyl-2-butene (0.12 mL) was added to quench the last traces of *m*-CPBA and the mixture was allowed to stir for 10 min at 0 ºC. Filtration and concentration afforded a 3:1 mixture of diastereomeric epoxy silanes **42**, which was directly used in the following step without further purification. An analytical sample of **42** was obtained by chromatography (5→10→25% EtOAc in hexanes): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 9H, $(CH_3)_3Si$), 0.95 (d, *J* = 6.4 Hz, 3H, CH_3), 1.24 (m, 2H, H-1', H-5), 1.35 (s, 3H, 9-CH_3), 1.38-1.67 (m, 6H, 2H-2', 2H-7, H-5, H-1'), 1.84 (m, 2H, H-4, H-6), 1.95 (m, 2H, H-3), 3.06 (m, 2H, H-3'), 4.25 and 4.33 (2d, *J* = 14.8 Hz, 1H each, CH_2Ph), 7.32 (m, 7H, *o*-Ts, Ph), 7.73 (d, 2H, *J* = 8.0 Hz, *m*-Ts); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ -2.3 ($(CH_3)_3Si$), 16.2 (9-CH_3), 21.6 ($ArCH_3$), 22.4 (CH_3), 23.0 (C-2'), 28.0 (C-7), 31.4 (C-6), 31.6 (C-5), 33.3 (C-1'), 37.1 (C-4), 47.9 (C-3), 48.9 (C-3'), 52.4 (CH_2Ph), 59.5 (C-1), 61.4 (C-9), 69.3 (C-8), 127.3 (*o*-Ts), 127.9 (*p*-Bn), 128.7 (*m*-Bn), 128.8 (*o*-Bn), 129.9 (*m*-Ts), 136.5 (*ipso*-Bn), 137.0 (*p*-Ts), 143.4 (*ipso*-Ts), 214.7 (C-2), 217.8 (C-9). HRMS Calcd for $C_{31}H_{44}NO_4SSi$ $(M + H)^+$ 554.2755, found 554.2744.

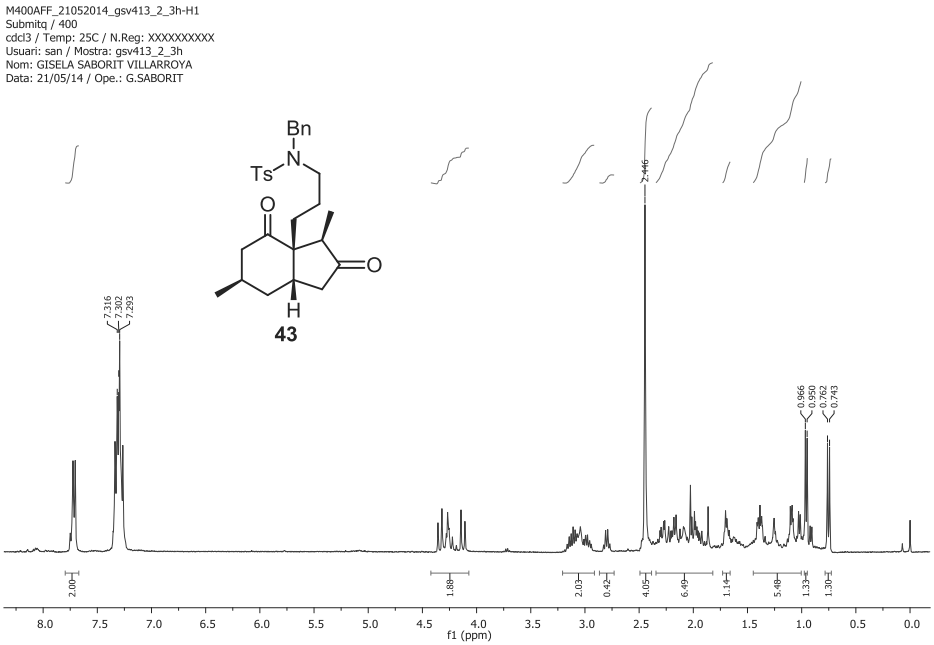

M400AFF_19052014_gsv413_cru-H1
Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv413_cru
Nom: GISELA SABORIT VILLARROYA
Data: 19/05/14 / Ope.: G.SABORIT
Bn
N
Ts
O
O
TMS
H
42
0.00
1.93
2.00
1.96
0.18
2.99
14.55
0.94
2.19
0.85
7.63
f1 (ppm)


V400A_19052014_gsv413_carboni-C13
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv413_carboni
Nom: GISELA SABORIT VILLARROYA
Data: 19/05/14 / Ope.: G.SABORIT
Experiment: s2pul
129.90
129.87
128.79
128.73
128.64
128.46
128.03
127.86
127.35
127.29
77.16
2.25
2.26
f1 (ppm)

(1*RS*,4*SR*,6*RS*,9*SR*)-1-[*N*-Benzyl-*N*-(4-methylphenylsulfonyl)-3-aminopropyl]-4,9-dimethylbicyclo[4.3.0]non-2,8-dione (43)



A solution of the crude epoxide **42** in formic acid (1.0 mL) was heated at reflux for 1 h, cooled, concentrated, and purified by chromatography (5→10→25% EtOAc in hexanes) to afford diketone **43** as a 3.5:1 mixture of diastereomers (15 mg, 55% yield, over 2 steps). Data for the major diastereomer: R_f = 0.23 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75 (d, *J* = 7.6 Hz, 3H, 9-CH_3), 0.97 (d, *J* = 6.4 Hz, 3H, 4-CH_3), 0.99 (m, 1H, H-2'), 1.04 (dd, *J* = 6.8, 4.0 Hz, 1H, H-2'), 1.36 (m, 2H, H-1'), 1.63-1.71 (m, 2H, H-5), 1.91-2.01 (m, 2H, H-7eq, H-3ax), 2.11 (m, 1H, H-4), 2.17 (m, 1H, H-7ax), 2.29 (dd, *J* = 13.6, 4.0 Hz, 2H, H-3eq), 2.45 (masked, 1H, H-6), 2.77 (q, *J* = 7.6 Hz, 1H, H-9), 2.97 (m, 1H, H-3'), 3.09 (q, *J* = 7.2 Hz, 1H, H-3'), 4.12-4.33 (2d, *J* = 14.8 Hz, 2H, CH_2Ph), 7.30-7.35 (m, 6H, *m*-Ts, Ph), 7.73 (d, *J* = 8.3 Hz, 2H, *o*-Ts); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.9 (9-CH_3), 21.1 (4-CH_3), 21.7 (CH_3Ar), 23.8 (C-2'), 28.0 (C-1'), 29.9 (C-4), 32.5 (C-5), 38.6 (C-6), 40.7 (C-7), 45.5 (C-3), 46.5 (C-9), 49.0 (C-3'), 53.0 (NCH_2Ar), 58.1 (C-1), 127.3 (*o*-Ts), 128.2 (Ph), 128.7 (Ph), 128.8 (Ph), 129.9 (*m*-Ts), 136.5 (*ipso*-Ph), 136.6 (*p*-Ts), 143.6 (*ipso*-Ts), 212.6 (C-8), 217.8 (C-2). HRMS Calcd for $C_{28}H_{36}NO_4S$ $(M + H)^+$ 482.2360, found 482.2359.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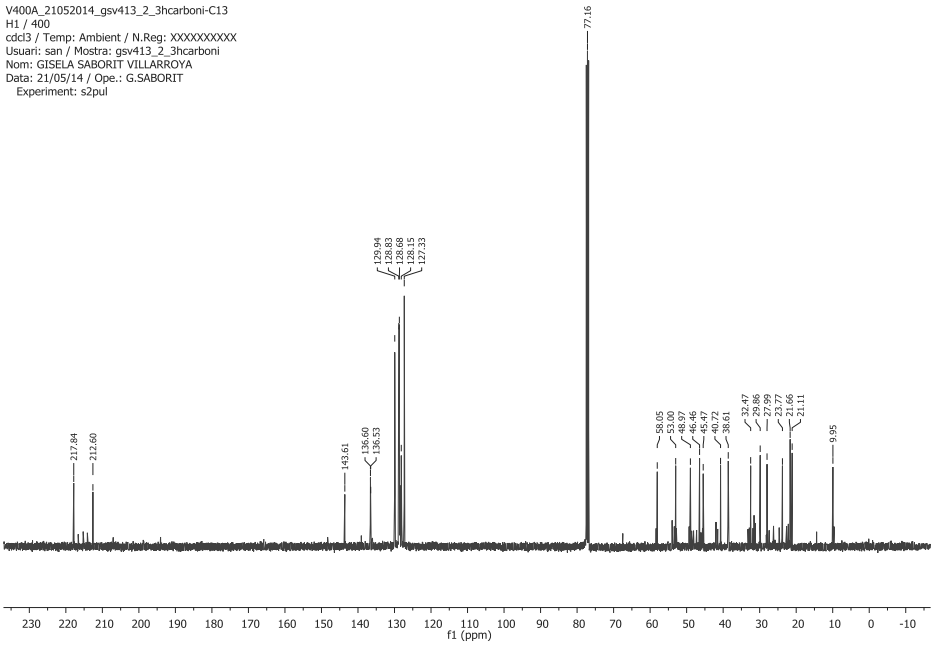
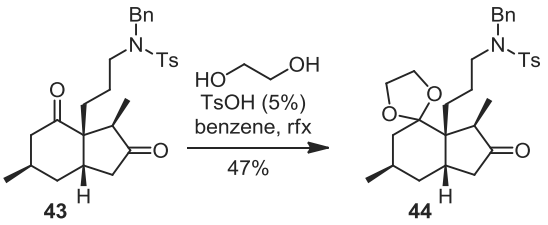
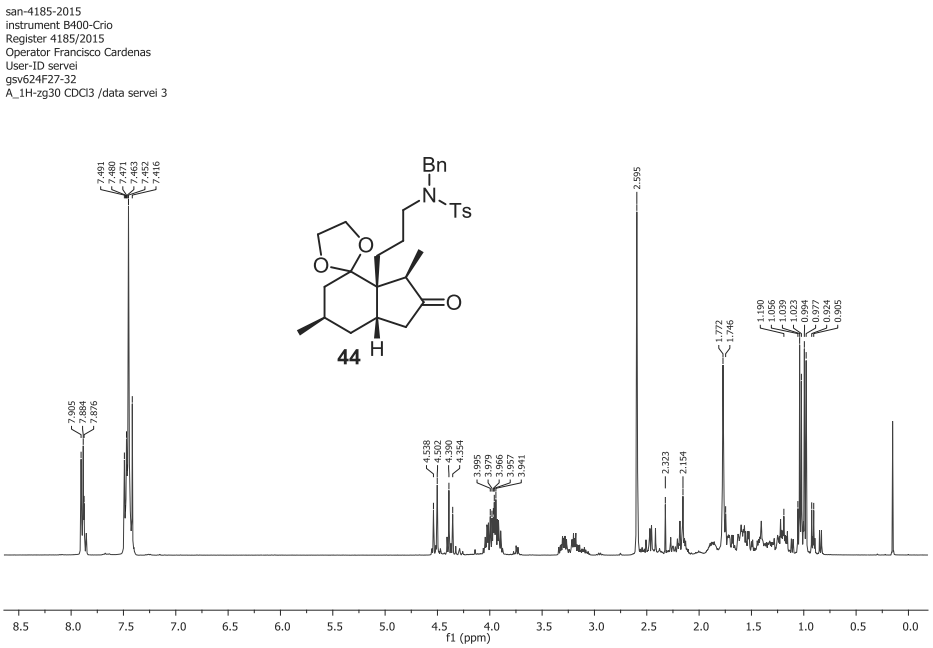
Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv413_2_3h
Nom: GISELA SABORIT VILLARROYA
Data: 21/05/14 / Ope.: G.SABORIT
Bn
N
Ts
O
O
H
43
7.316
7.302
7.293
2.446
0.966
0.950
0.762
0.743
2.00
1.88
2.03
0.42
4.05
6.49
1.14
5.40
1.33
1.30
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

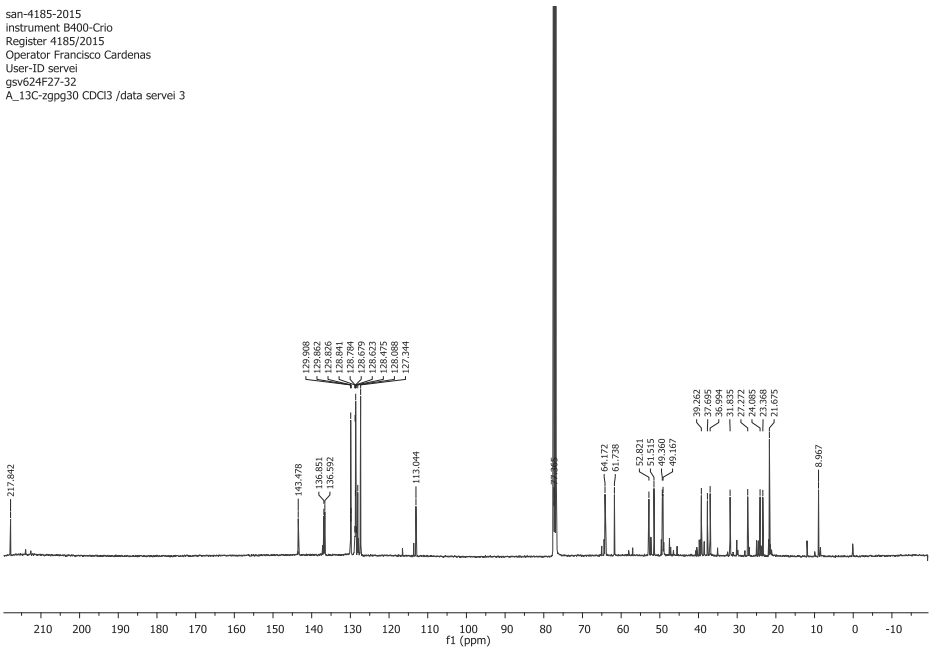

V400A_21052014_gsv413_2_3hcarboni-C13
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv413_2_3hcarboni
Nom: GISELA SABORIT VILLARROYA
Data: 21/05/14 / Ope.: G.SABORIT
Experiment: s2pul
77.16
129.94
128.83
128.68
128.15
127.33
217.84
212.60
143.61
136.60
136.53
58.05
53.00
48.97
46.46
45.47
40.72
38.61
32.47
29.86
27.99
23.77
21.66
21.11
9.95
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(1*SR*,4*RS*,6SR,9*RS*)-1-[*N*-Benzyl-N-(4-methylphenylsulfonyl)-3-aminopropyl]-4,9-dimethyl-2,8-dione-bicyclo[4.3.0]non-2,8-ethylene acetal (44)

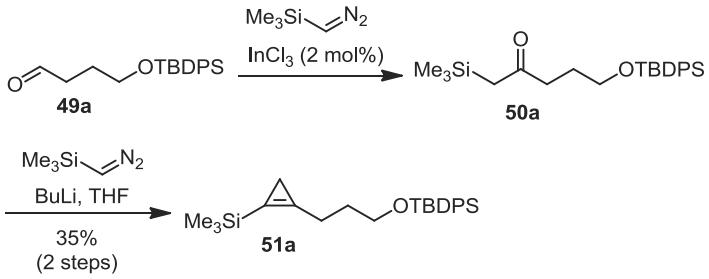


To a solution of dienone **43** (35 mg, 0.073 mmol) and ethylene glycol (113 mg, 1.82 mmol, 0.1 mL, 25.0 equiv) in benzene (2.5 mL) was added *p*-TSA (14 mg, 0.073 mmol, 1.0 equiv). The reaction was refluxed for 24 h, cooled and diluted with Et_2O (4 mL). The organics were washed with sat. $NaHCO_3$, H_2O, brine, dried with Na_2SO_4. The crude was purified by chromatography (2.5→5→10% EtOAc/hexane) to give **44** (18 mg, 47%): ^{1}H NMR (400 MHz, gCOSY) δ 0.82 (d, *J* = 6.4 Hz, 3H, 4-CH_3), 0.88 (d, *J* = 6.8 Hz, 3H, 9-CH_3), 1.03 (m, 2H), 1.21 (m, 2H), 1.40 (m, 3H), 1.72 (m, 1H), 2.06 (m, 1H), 2.32 (dd, *J* = 21.2, 15.2 Hz, 1H), 2.44 (s, 3H, ArCH_3), 3.02 (m, 2H), 3.81 (m, 3H), 4.22-4.36 (2d, *J* = 14.8 Hz, 2H, CH_2Ph), 7.30-7.35 (m, 6H, *m*-Ts, Ph), 7.73 (d, *J* = 8.3 Hz, 2H, *o*-Ts); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (4-CH_3), 23.4 (C-2'), 24.1 (C-4), 27.3 (C-7), 31.8 (C-1'), 37.0 (C-6), 37.7 (C-5), 39.3 (C-3), 49.1 (C-1), 49.4 (C-3'), 51.5 (C-9), 52.8 (NCH_2Ar), 61.7 (CH_2O), 64.2 (CH_2O), 113.0 (C-2), 127.3 (*o*-Ts), 128.2 (*m*-Ph), 128.7 (*o*-Ph), 128.8 (*p*-Ph), 129.9 (*m*-Ts), 136.6 (*ipso*-Ph), 136.9 (*p*-Ts), 143.6 (*ipso*-Ts), 217.9 (C-2). HRMS calcd for $C_{30}H_{40}NO_5S$ (M + H^+) 526.2622, found 526.2640.


san-4185-2015
instrument B400-Crio
Register 4185/2015
Operator Francisco Cardenas
User-ID servei
gsv624F27-32
A_1H-zg30 CDCl3 /data servei 3
Bn
N
Ts
O
O
O
H
44
7.491
7.480
7.471
7.463
7.452
7.416
7.905
7.884
7.876
4.538
4.502
4.390
4.354
3.995
3.979
3.966
3.957
3.941
2.595
2.323
2.154
1.772
1.746
1.190
1.056
1.039
1.023
1.004
0.977
0.924
0.905
f1 (ppm)

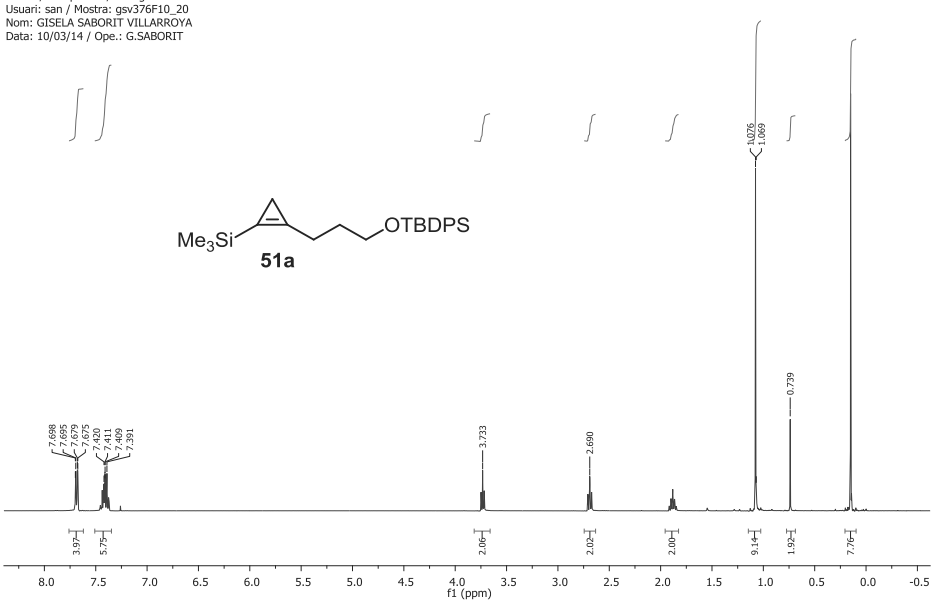

san-4185-2015
instrument B400-Crio
Register 4185/2015
Operator Francisco Cardenas
User-ID servei
gsv624F27-32
A_13C-zgpg30 CDCl3 /data servei 3
217.842
143.478
136.851
136.592
129.908
129.862
129.806
128.841
128.784
128.679
128.623
128.475
128.088
127.344
113.044
77.315
64.172
61.738
52.821
51.515
49.360
49.167
39.262
29.565
26.994
31.835
27.272
24.085
23.368
21.675
8.867
f1 (ppm)

Preparation of cyclopropene 51a

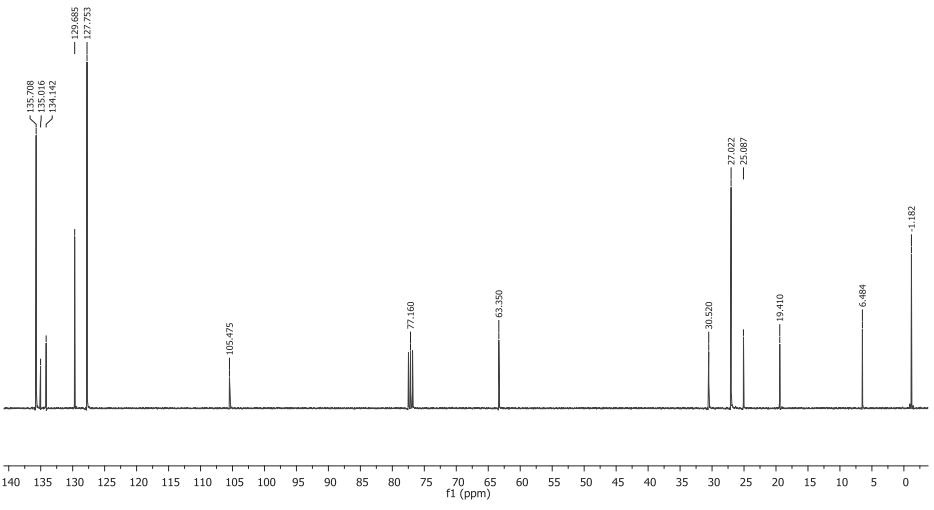


To a stirred solution of aldehyde **49a** (140 mg, 0.43 mmol) and trimethylsilyl diazomethane (2.0 M in diethyl ether, 0.26 mL, 0.51 mmol, 1.2 equiv) in CH_2Cl_2 (3.4 mL) was added $InCl_3$ at once (2 mg, 8.6 µmol), 0.02 equiv). Vigorous bubbling was observed and the mixture was stirred at rt in the air for 30 minutes. The volatiles were evaporated and the resulting crude α-TMS ketone **50a** was subjected to the next step without purification. To a cooled (- 78 °C) solution of TMS diazomethane (2.0 M in diethyl ether, 0.26 mL, 0.51 mmol, 1.2 equiv) in THF (0.9 mL) was added *n*-BuLi (1.6 M in hexane, 0.56 mL, 1.3 equiv) dropwise. After the mixture was stirred at −78 °C for 30 minutes, a solution of the crude α-TMS ketone **50a** in THF (0.4 mL) was carefully added into the mixture. Then the reaction was stirred at -78 ºC for 40 minutes. The reaction mixture was warmed to room temperature and quenched by adding 1 mL of an aqueous saturated NH_4Cl solution. The mixture was dried, filtered through a short pad of silica gel and concentrated to afford the crude trimethylsilyl cyclopropene. Purification by chromatography (0.5→1→2.5→5% EtOAc/hexane) furnished **51a** (63 mg, 35 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 0.15 (s, 9H, $SiMe_3$), 0.74 (s, 2H, H-3), 1.07 (s, 9H, $(CH_3)_3C$), 1.88 (q, *J* = 13.6 Hz, 2H, H-2'), 2.69 (t, *J* = 7.2 Hz, 2H, H-1'), 3.73 (t, *J* = 6.4 Hz, 2H, H-3'), 7.40-7.42 (m, 6H), 7.69 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.2 (Me_3Si), 6.5 (C-3), 19.4 ($C(CH_3)_3$), 25.1 (C-1'), 27.0 ($C(CH_3)_3$), 30.5 (C-2'), 63.4 (C-3'), 105.5 (C-2), 127.8 (*m*-Ph), 129.7 (*p*-Ph), 134.1 (*ipso*-Ph), 135.0 (C-1), 135.7 (*o*-Ph). HRMS calcd for $C_{16}H_{25}OSi$ $(M+H)^+$ 261.1669, found 261.1673.

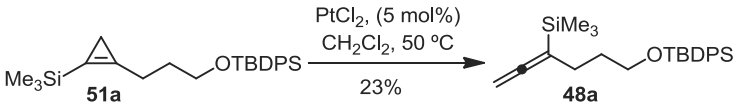
M400AFF_10032014_gsv376F10_20-H1
Submitq / 400
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv376F10_20
Nom: GISELA SABORIT VILLARROYA
Data: 10/03/14 / Ope.: G.SABORIT



M400AFF_10032014_gsv376F10_20-C13
Submitq / 400
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv376F10_20
Nom: GISELA SABORIT VILLARROYA
Data: 10/03/14 / Ope.: G.SABORIT

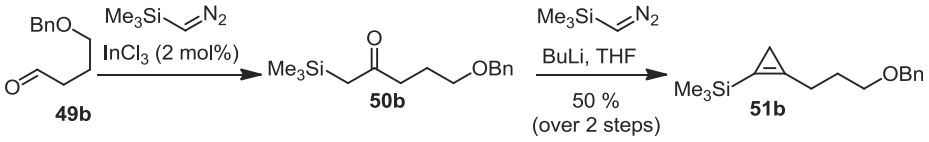


Preparation of allene 48a



To a solution of **51a** (57 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added $PtCl_2$[184] (73% Pt, 10 mg, 0.038 mmol, 0.25 equiv) and the mixture was stirred in a sealed vial at 50 ºC (sand bath) for 72 h. The crude was filtered through a pad of silica and purified by chromatography (0.25→0.5% EtOAc/hexane) to furnished **48a** (13 mg, 23 % over two steps).[185]

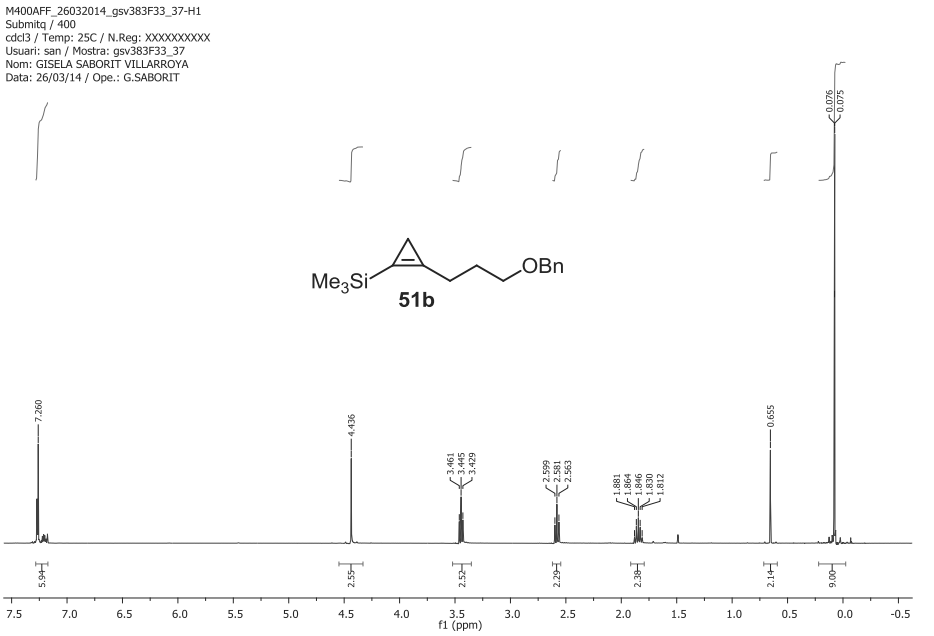
Preparation of cyclopropane 51b

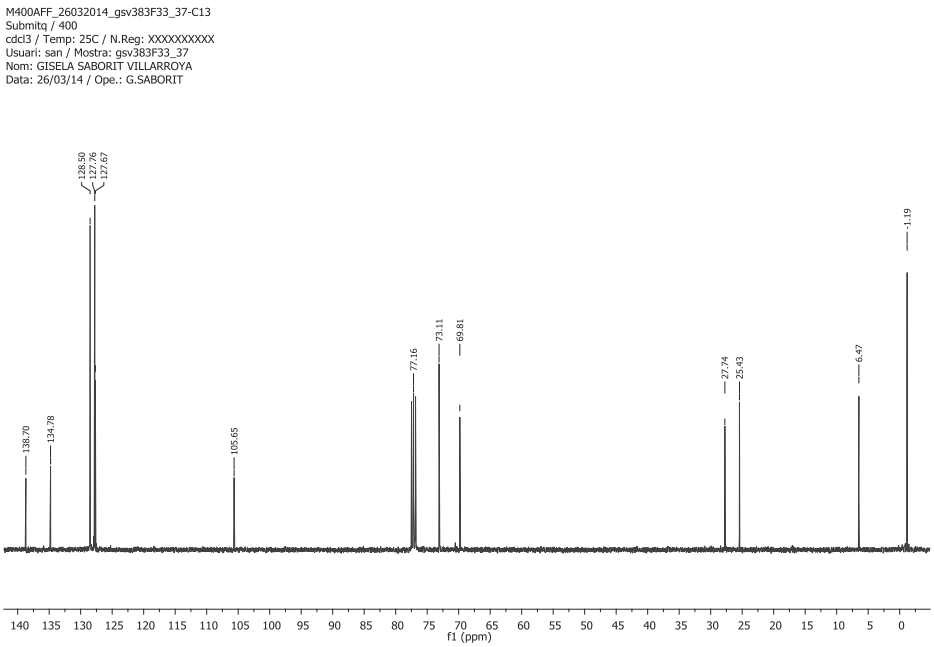


To a stirred solution of aldehyde **49b** (1.7 g, 9.54 mmol) in CH_2Cl_2 (10 mL) was added trimethylsilyl diazomethane (2.0 M in diethyl ether, 5.7 mL, 11.45 mmol, 1.2 equiv) followed by careful addition of $InCl_3$ (42 mg, 0.19 mmol, 0.02 equiv). Vigorous bubbling was observed and the mixture was stirred at room temperature in the air for 20 minutes. The volatiles were evaporated and the resulting crude α-TMS ketone **50b** was used in the next step without purification. To a cooled (- 78 °C) solution of TMS diazomethane (2.0 M in diethyl ether, 5.7 mL, 11.4 mmol, 1.2 equiv) in THF (20 mL) was added *n*-BuLi (1.6 M in hexane, 7.8 mL, 1.3 equiv) dropwise. After the mixture was stirred at -78 °C for 30 minutes, a solution of the crude α-TMS ketone **50b** in THF (10 mL) was added into the mixture dropwise. Then the reaction was stirred at -78 ^{o}C for 40 minutes. The reaction mixture was warmed up to room temperature and quenched by adding 1 mL of an aqueous saturated NH_4Cl solution. The mixture was dried, filtered through a short pad of silica gel and concentrated to afford the crude trimethylsilyl cyclopropene. Purification by chromatography (0.5→1→2.5→5% EtOAc/hexane) furnished **51b** (1.55 g, 63 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 0.08 (s, 9H, Me_3Si), 0.65 (s, 2H, H-3), 1.84 (m, 2H, H-2'), 2.55 (t, *J* = 7.2 Hz, 2H, H-1'), 3.45 (t, *J* = 6.4 Hz, 2H, H-3'), 4.44

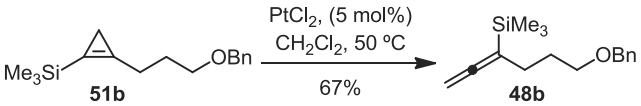
[184] Purchased in sigma aldrich (98% purity)
[185] See ref.115 for NMR data.

(s, 2H, CH_2Ph), 7.20-7.27 (m, 5H, Bn). ^{13}C NMR (100 MHz, gHSQC) δ -1.2 (Me_3Si), 6.5 (C-3), 25.4 (C-1'), 27.7 (C-2'), 69.8 (C-3'), 73.1 (CH_2Ph), 105.7 (C-2), 127.7 (*o*-Bn), 127.8 (*p*-Bn), 128.5 (*m*-Bn), 134.8 (*ipso*-Bn), 138.7 (C-1). HRMS calcd for $C_{16}H_{25}OSi$ $(M+H)^+$ 261.1669, found 261.1673.

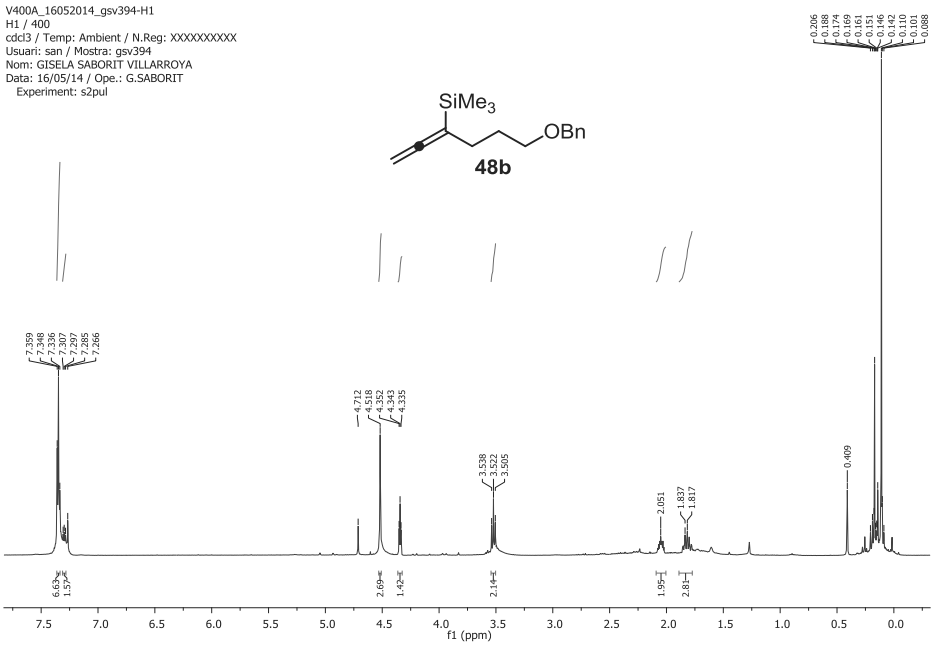


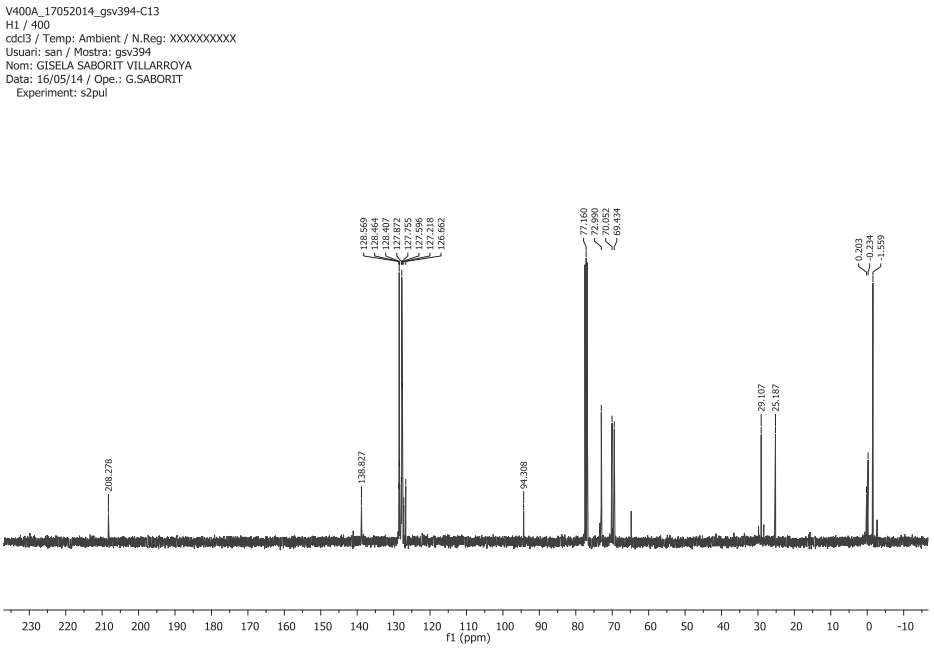


Preparation of allene (48b)

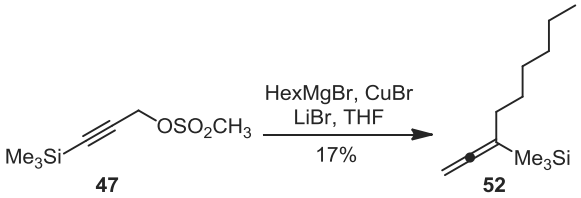


To a flame dried sealed tube was added $PtCl_2$ (36 mg, 0.14 mmol, 0.25 equiv) and a solution of cyclopropene **51b** (150 mg, 0.58 mmol) in CH_2Cl_2 (1.6 mL). The resulting suspension was stirred at 50 ºC (oil bath) overnight and filtered through a pad of celite. The filter cake was washed thouroughly with CH_2Cl_2 and the solvent removed to give 100 mg of the desired allene **48b** (67% yield), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 0.11 (s, 9H, Me_3Si), 1.82 (m, 2H, H-5), 2.05 (m, 2H, H-4), 3.52 (t, *J* = 6.4 Hz, 2H, H-6), 4.34 (t, *J* = 3.4 Hz, 2H, CH_2Ph), 4.52 (s, 2H, CH_2Ph), 7.37 (m, 5H, Bn). ^{13}C NMR (100 MHz, gHSQC) δ -1.6 (Me_3Si), 25.2 (C-4), 29.1 (C-5), 69.4 (CH_2Ph), 70.1 (C-6), 73.0 (C-1), 94.3 (C-3), 126.7 (*o*-Bn), 127.8 (*p*-Bn), 128.6 (*m*-Bn), 138.8 (*ipso*-Bn), 208.3 (C-2). HRMS calcd for $C_{16}H_{25}OSi$ $(M+H)^+$ 261.1669, found 261.1669.


V400A_16052014_gsv394-H1
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv394
Nom: GISELA SABORIT VILLARROYA
Data: 16/05/14 / Ope.: G.SABORIT
Experiment: s2pul
SiMe3
OBn
48b
f1 (ppm)


V400A_17052014_gsv394-C13
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv394
Nom: GISELA SABORIT VILLARROYA
Data: 16/05/14 / Ope.: G.SABORIT
Experiment: s2pul
f1 (ppm)

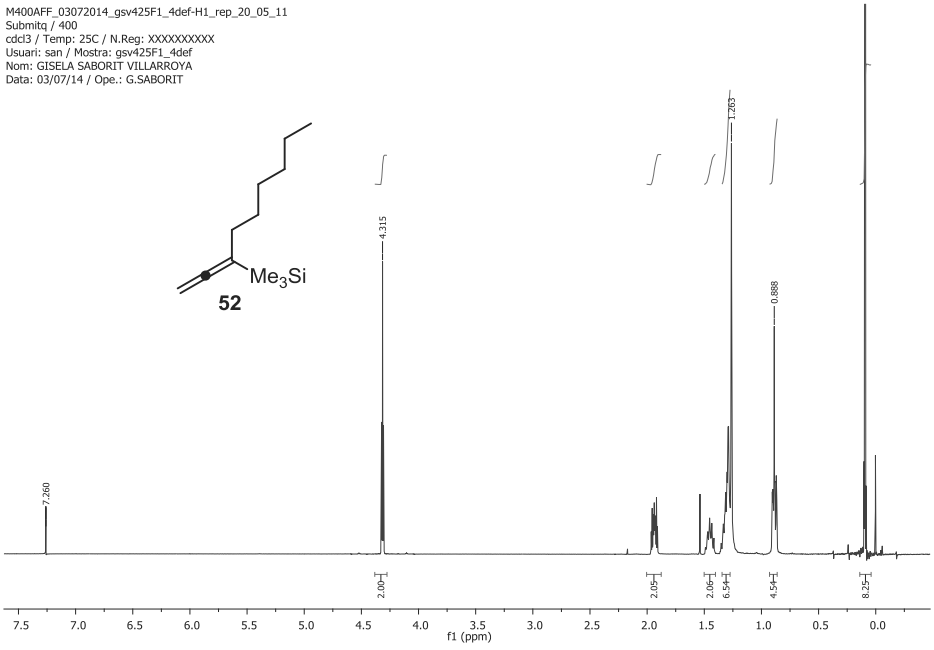
3-trimethylsilyl-1,2-nonadiene (52)

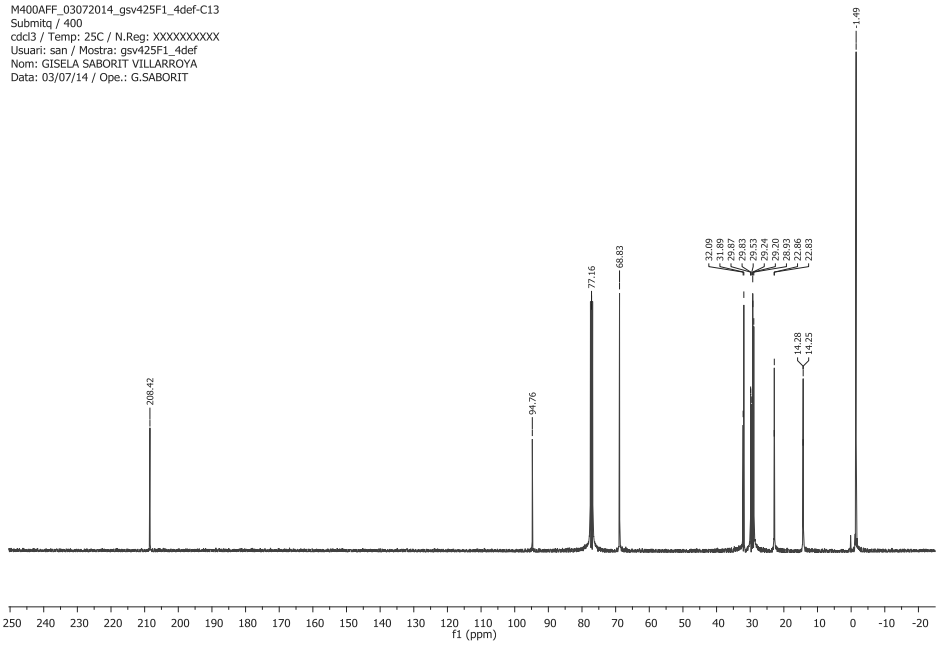


3-(Trimethylsilyl)prop-2-yn-1-ol (865 mg, 6.74 mmol) was dissolved in CH_2Cl_2 (20 mL) under argon. The solution was cooled to -78 °C, followed by addition of Et_3N (1.9 mL, 13.49 mmol). $MeSO_2Cl$ (0.52 mL, 6.74 mmol) was added over a period of 10 min, leading to the formation of a white precipitate. After stirring at -78 °C for 1 h, the reaction mixture was washed with 0.5 M aq. HCl (8 mL), saturated aqueous $NaHCO_3$ (11 mL), and brine (11 mL). After extraction of the aqueous layers with CH_2Cl_2 (2 × 30 mL), the combined organic layers were dried and the solvent was removed to give **47** (1.29 g) as a pale yellow liquid, which was used without further purification. To a 2-necked flame-dried 50 mL flask were introduced LiBr [previously activated by keeping at 86 ºC overnight] (237 mg, 2.72 mmol, 1.1 equiv), THF (6.3 mL) and CuBr (391 mg, 2.72 mmol, 1.1 equiv) at -10 °C. n-HexMgBr (1.36 mL of a 2.0 M solution in Et_2O, 2.72 mmol, 1.1 equiv.) was added via syringe pump over 1.5 h. The resulting suspension was stirred at -10 °C for 1 h, cooled to - 60 °C and a solution of **47** (511 mg, 2.48 mmol) in THF (1.6 mL) was added via syringe pump over 30 min. After being stirred for additional 30 min at - 60 °C, the mixture was allowed to warm to rt over 1 h, kept at that temperature for an additional 90 min and then poured into aq. saturated NH_4Cl solution (8 mL, adjusted to pH 8 using NH_4OH). The organic layer was separated and the aqueous extracted with pentane (3 x 8 mL). The organics were washed with sat. pH 8 NH_4Cl solution (8 mL), brine (8 mL) dried, filtered, and concentrated. The residue was purified by chromatography (100% pentane) to provide allene **52** (85 mg, 28%) as an oil.[186] δ ^{1}H NMR (400 MHz, gCOSY) 0.09 (s, 9H, Me_3Si), 0.88 (td, *J* = 7.2, 2.0 Hz, 3H, H-9), 1.30 (m, 6H, H-5, H-6, H-7), 1.45 (m, 2H, H-5), 1.94 (m, 2H, H-4), 4.32 (t, 2H, *J* = 3.2 Hz, H-1). ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.49 (Me_3Si), 14.3 (C-9),

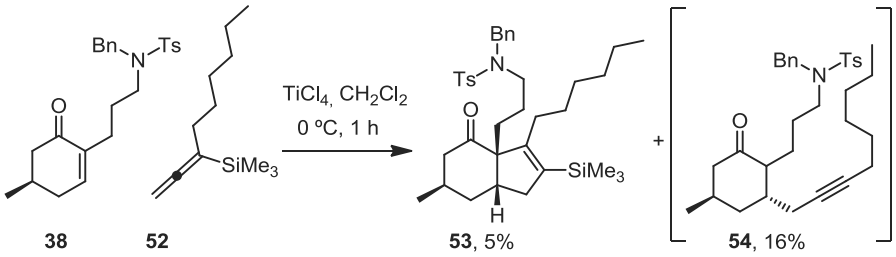
[186] The exact mass of this compound could not be determined by ESI-HRMS due to its instability.

22.8 (C-8), 28.9 (C-6), 29.2 (C-5), 29.8 (C-4), 31.9 (C-7), 68.9 (C-1), 94.5 (C-3), 208.4 (C-2).



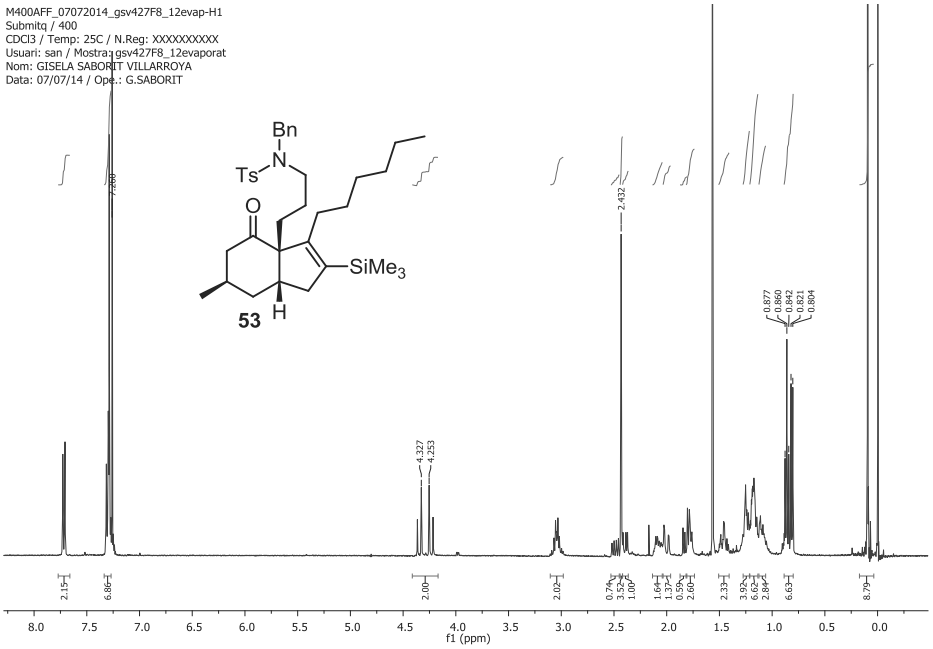


(1*RS*,4*SR*,6*RS*)-1-[*N*-Benzyl-N-(4-methylphenylsulfonyl)-3-aminopropyl]-9-hexyl-4-methyl-8-trimethylsilylbicyclo[4.3.0]non-8-en-2-one (53)



38 **52** **53**, 5% **54**, 16%

To a cooled (- 78 ºC) solution of **38** (98 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) was added allene **52** (71 mg, 0.36 mmol, 1.7 equiv) in CH_2Cl_2 (1 + 1mL). $TiCl_4$ (0.04 mL, 1.7 mmol) was added dropwise and the resulting dark red mixture was stirred at - 78 ºC for 1 h. After this time, TLC showed no reaction, thus the mixture was warmed to 0 ºC and then stirred for another 1 h at rt. Then the reaction mixture was quenched by the addition of water (5 mL) and the aqueous extracted with Et_2O (2 x 5 mL). The combined organic layers were dried, filtered, concentrated and the crude was purified by chromatography (2.5→5→10→25% EtOAc/hexane) to give **53** (7.0 mg, 5%) together with 20 mg of **54** (20 mg, 16%) and recovered starting material (64 mg). Data for **53**. ^{1}H NMR (400 MHz, COSY) 0.09 (s, 9H, $(CH_3)_3Si$), 0.81 (d, *J* = 6.8 Hz, 3H, CH_3), 0.86 (t, 3H, *J* = 6.4 Hz, H-6''), 1.09-1.27 (m, 13H, 2H-2', H-1', H-5, 2H-2'', 2H-3'', 2H-4'', 2H-5''), 1.42-1.51 (m, 2H, H-5, H-1'), 1.78 (dd, *J* = 8.0, 16.0 Hz, 2H, H-1''), 1.84 (d, *J* = 6.8 Hz, 1H, H-3), 2.00 (dd, *J* = 16.8, 2.8 Hz, 1H, H-7), 2.09 (m, 2H, H-4, H-6), 2.40 (dd, *J* = 7.2, 5.2 Hz, 1H, H-3), 2.43 (s, 3H, CH_3Ar), 2.49 (dd, *J* = 16.8, 8.0 Hz, 1H, H-7), 3.04 (q, *J* = 6.0 Hz, 2H, H-3'), 4.29 (2d, *J* = 15.2 Hz, 2H, CH_2Ph), 7.30-7.35 (m, 7H, *o*-Ts, Ph), 7.73 (d, *J* = 8.4 Hz, 2H, *m*-Ts). ^{13}C NMR (101 MHz, $CDCl_3$) δ -0.5 ($(CH_3)_3Si$), 14.2 (C-6''), 21.2 (CH_3), 21.7 ($ArCH_3$), 22.8 (C-5''), 23.6 (C-2'), 27.0 (C-4), 28.8 (C-1''), 30.2 (C-5), 31.4 (C-2''), 31.7 (C-4''), 32.1 (C-3''), 37.5 (C-1'), 41.1 (C-6), 44.2 (C-7), 47.7 (C-3), 49.0 (C-3'), 52.3 (NCH_2Ph), 69.4 (C-1), 127.3 (*o*-Ts), 127.8 (Ph), 128.4 (Ph), 128.7 (Ph), 129.8 (*m*-Ts), 136.9 (*ipso*-Ph), 137.2 (*p*-Ts), 139.4 (C-8), 143.2 (*ipso*-Ts), 154.1 (C-9), 214.6 (C-2). HRMS calcd for $C_{36}H_{54}NO_3SSi$ $(M + H)^+$ 608.3588, found 608.3591.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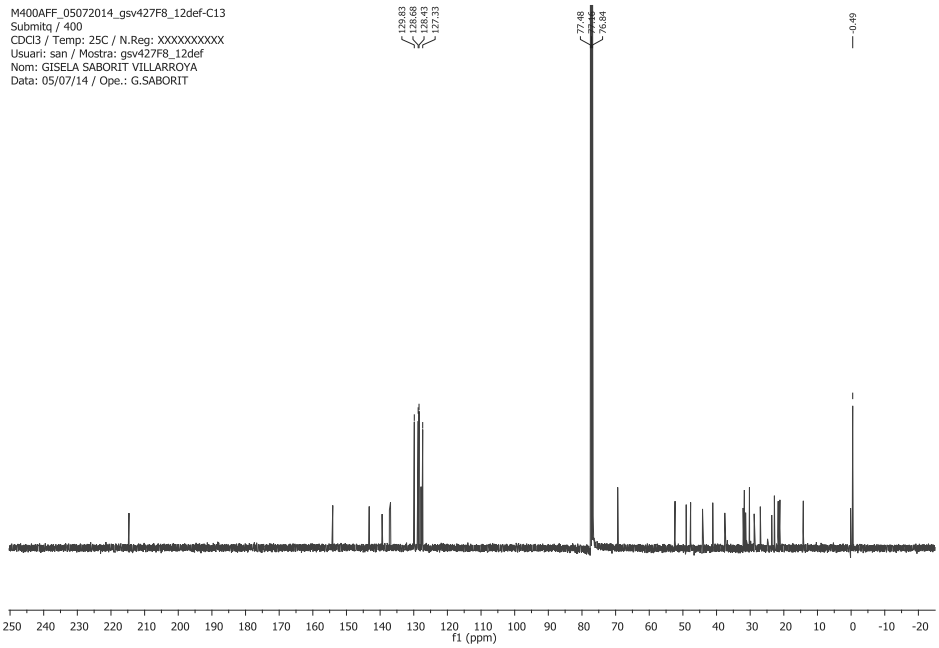
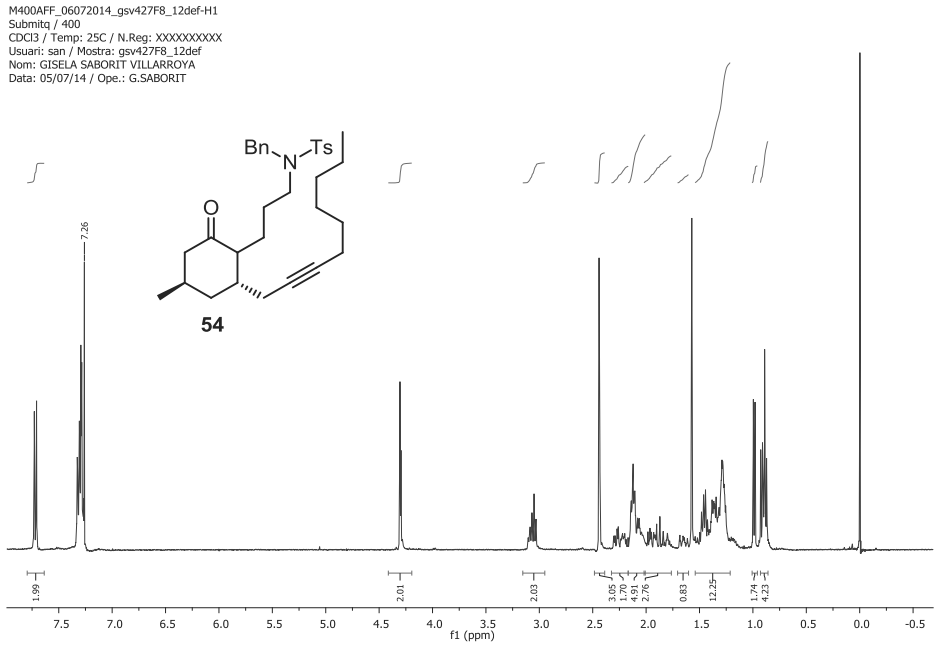
Usuari: san / Mostra: gsv427F8_12evaporat
Nom: GISELA SABORIT VILLARROYA
Data: 07/07/14 / Ope.: G.SABORIT
Bn
N
Ts
O
SiMe3
H
53
7.266
4.327
4.253
2.432
0.877
0.860
0.842
0.821
0.804
2.15
6.86
2.00
2.02
0.74
3.52
1.00
1.64
1.37
0.95
2.60
2.33
3.92
6.62
2.84
6.63
8.79
f1 (ppm)


M400AFF_05072014_gsv427F8_12def-C13
Submitq / 400
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv427F8_12def
Nom: GISELA SABORIT VILLARROYA
Data: 05/07/14 / Ope.: G.SABORIT
129.83
128.68
128.43
127.33
77.48
77.16
76.84
-0.49
f1 (ppm)

Characterization data for the product coming from desilylation. **3-(2-nonyl)-5-methyl-2-[(*N*-benzyl-*N*-(4-methylphenylsulfonyl)-3-aminopropyl] cyclo hexanone (54)**: ^{1}H NMR (400 MHz, COSY) δ 0.88 (d, *J* = 6.8 Hz, CH_3), 0.88 (masked, 1H, H-1'), 0.99 (d, *J* = 6.4 Hz, 3H, 5-CH_3) 1.23-1.54 (m, 12H, H-1', H-4, 2H-2', 2H-5'', 2H-4'', 2H-7'', 2H-8''), 1.63 (dtd, *J* = 14.0, 11.0, 2.6 Hz, 1H, H-1''), 1.89 (m, 3H, H-6, H-3, H-4), 2.06 (m, 5H, H-5, H-3, H-1''), 2.20 (m, 1H, H-2), 2.28 (dd, *J* = 12.8, 1.6 Hz, 1H, H-6), 2.43 (s, CH_3Ts), 3.06 (m, 2H, 2H-3'), 4.23 (s, 2H, CH_2Ph), 7.29 (m, 7H, Ph, *m*-Ts), 7.71 (d, *J* = 8.0 Hz, 2H *o*-Ts). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (C-9''), 18.9 (C-1''), 22.4 (C-8''), 22.7 (C-4''), 23.3 (C-1'), 26.1 (C-2'), 28.7, 29.1 (C-6''), 29.2 (C-5''), 29.8 (C-5), 31.5 (C-7''), 38.6 (C-4), 40.2 (C-3), 47.9 (C-3'), 50.3 (C-6), 52.0 (NCH_2Ph), 52.7 (C-2), 76.8 (C-3''), 82.2 (C-2''), 127.3 (*o*-Ts), 127.8 (Ph), 128.4 (Ph), 128.7 (Ph), 129.8 (*m*-Ts), 136.9 (*ipso*-Ph), 137.2 (*p*-Ts), 139.4 (C-8), 143.2 (*ipso*-Ts), 211.8 (C-1). HRMS calcd for $C_{33}H_{46}NO_3S$ $(M + H)^+$ 536.3193, found 536.3191.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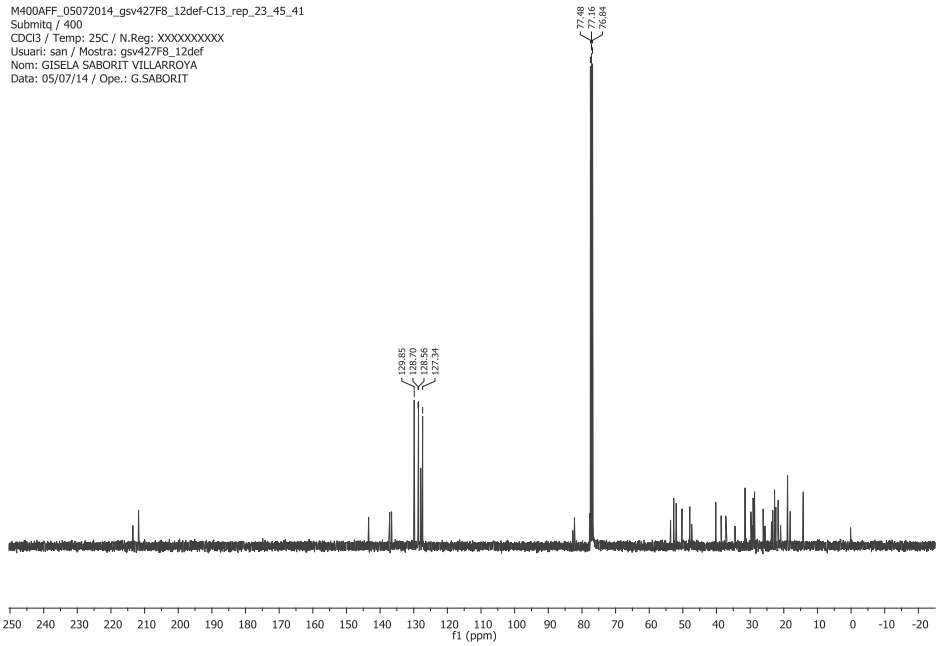
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv427F8_12def
Nom: GISELA SABORIT VILLARROYA
Data: 05/07/14 / Ope.: G.SABORIT
Bn
N
Ts
O
54
7.26
1.99
2.01
2.03
3.05
1.70
4.91
2.76
0.83
12.25
1.74
4.23
f1 (ppm)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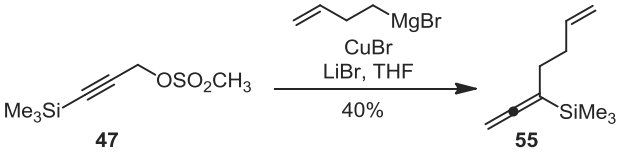
Submitq / 400
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv427F8_12def
Nom: GISELA SABORIT VILLARROYA
Data: 05/07/14 / Ope.: G.SABORIT
77.48
77.16
76.84
129.85
128.70
128.56
127.34
f1 (ppm)

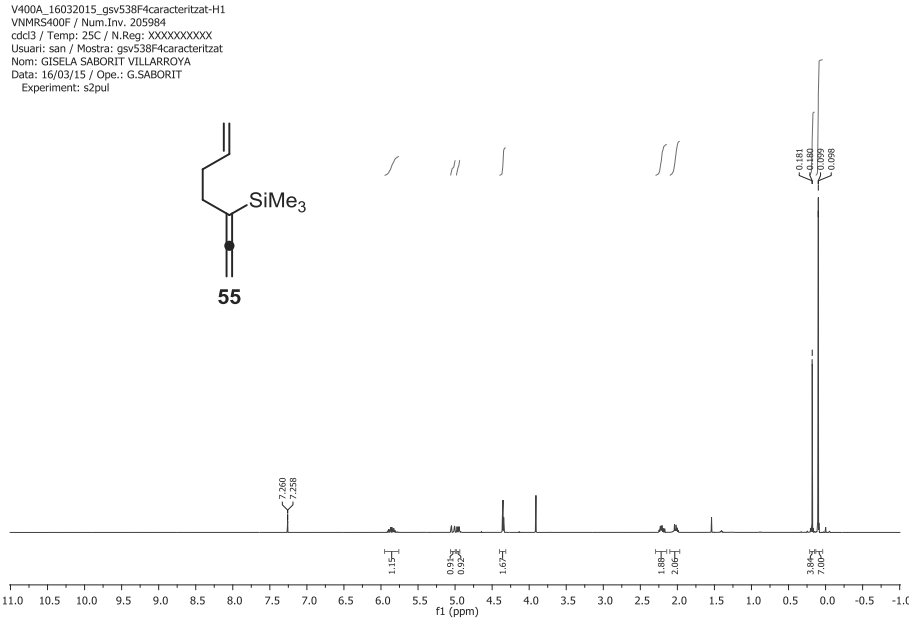
3-trimethylsilyl-1,2,6-heptatriene (55)



47 **55**

To a flame dried three-neck 100 mL round bottom flask fitted with septums and a reflux condenser under an argon atmosphere was added powdered magnesium (900 mg, 37.0 mmol, 2.5 equiv) followed by THF (15 mL). 4-bromobutene (1.5 mL, 14.8 mmol, 1.0 equiv) was added at a rate of 10 mL/hr with a syringe pump. The solution refluxed gently during addition and was allowed to stir at room temperature for 16 h. To a flame dried 50 mL two necked flask was added LiBr (236 mg, 2.7 mmol, 1.1 equiv) and it was evacuated and backfilled with argon three times. Then, CuBr (390 mg, 2.71 mmol, 1.1 equiv) was added followed by THF (6.0 mL) and the green mixture was stirred at rt for 10 min before being cooled to – 20 ºC. Then, the Grignard reagent prepared above (2.7 mL) was added dropwise over 10 min and the resulting dark solution was stirred for 1 h at this temperature. After cooling to – 60 ºC, a solution of **47**[187] (500 mg, 2.42 mmol) in THF (1.5 mL) was added via syringe pump over 30 min and the mixture was stirred for additional 30 min at - 60 °C. The mixture was allowed to warm to 23 °C over 1 h, kept at 23 °C for an additional 1 h, and then quenched by addition of aq. saturated NH_4Cl solution (5 mL). The organic layer was separated and the aqueous extracted with pentane (3 x 10 mL). The combined organic layers were washed with NH_4Cl (5 mL), brine (5 mL), dried, filtered, and concentrated. The residue was purified by chromatography (100% pentane) to provide allene **55** (157 mg, 40%) as an oil. ^{1}H NMR (400 MHz, gCOSY) 0.10 (s, 9H, Me_3Si), 2.02 (tt, *J* = 8.8, 3.2 Hz, 2H, H-4), 2.18 (qm, *J* = 7.3 Hz, 2H, H-5), 4.35 (td, *J* = 3.4, 0.4 Hz, 2H, H-1), 4.96 (qd, *J* = 16.8, 1.6, 1H, H-7), 5.03 (dq, *J* = 9.6, 1.2 Hz, 1H, H-7), 5.85 (m, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.6 (Me_3Si), 28.1 (C-4), 33.3 (C-5), 69.5 (C-1), 94.3 (C-3), 114.7 (C 7), 138.1 (C-6), 208.4 (C-2). $[M + H]^+$ Calcd for $C_{10}H_{19}Si$ 167.1256, found 167.0146.[188]

[187] Prepared as described before for compound **52**.
[188] The HRMS Found value differs from the expected (Calcd) value by more than 0.003 m/z unit, which might be attributed to the low stability of this compound.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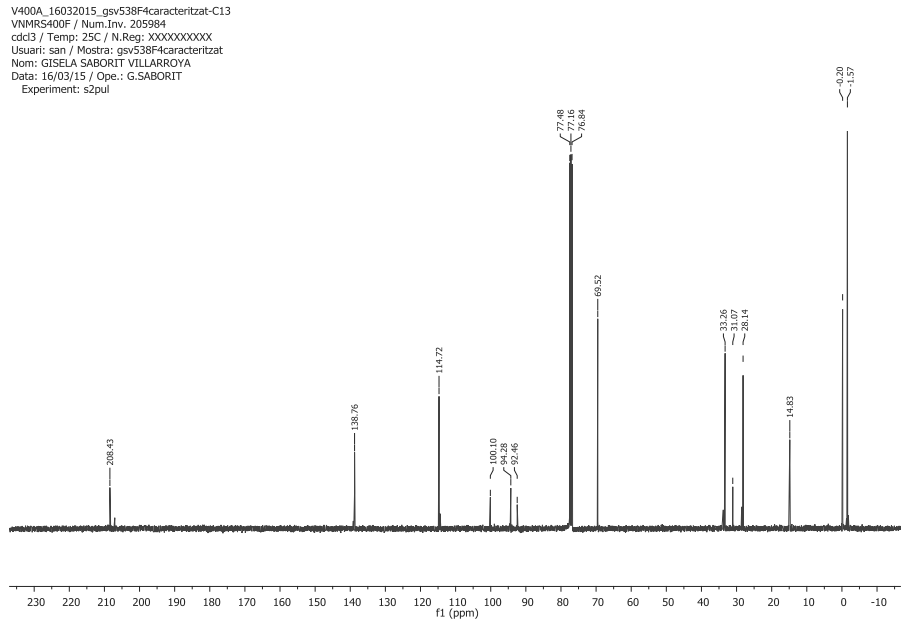
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv538F4caracteritzat
Nom: GISELA SABORIT VILLARROYA
Data: 16/03/15 / Ope.: G.SABORIT
Experiment: s2pul
SiMe3
55
7.260
7.258
0.161
0.160
0.099
0.098
1.15
0.91
0.92
1.67
1.89
2.06
3.84
7.00
f1 (ppm)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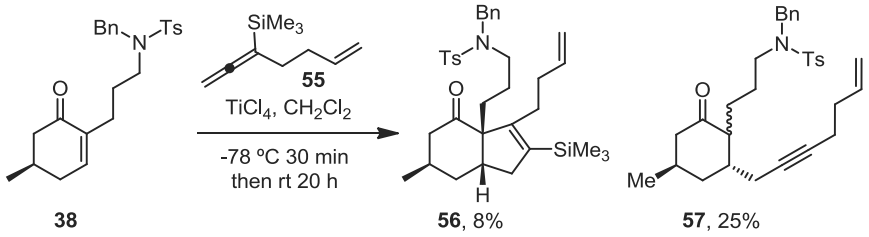
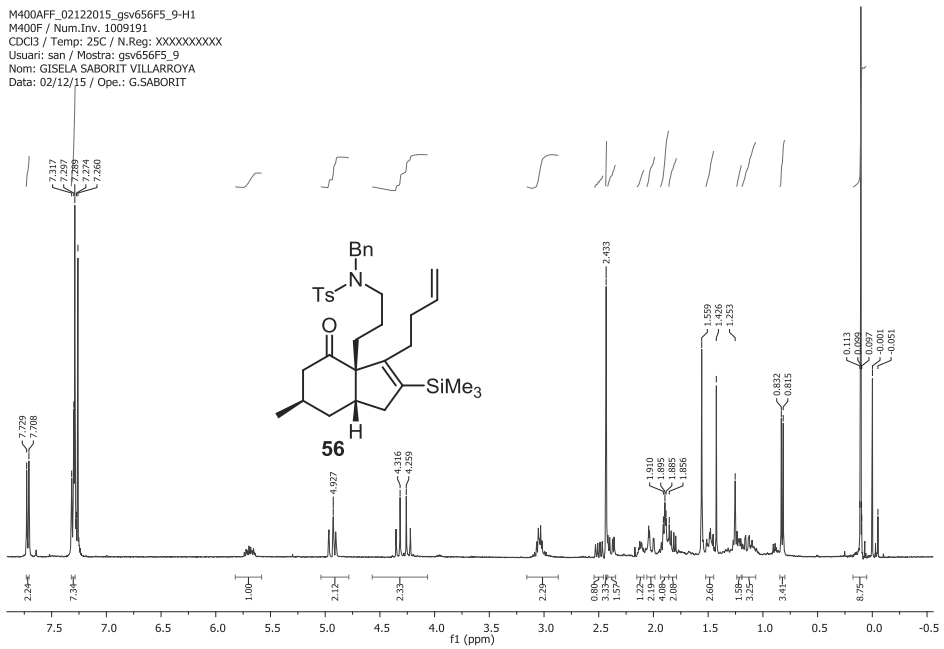
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv538F4caracteritzat
Nom: GISELA SABORIT VILLARROYA
Data: 16/03/15 / Ope.: G.SABORIT
Experiment: s2pul
208.43
138.76
114.72
100.10
94.38
92.46
77.48
77.16
76.84
69.52
33.26
31.07
26.14
14.83
-0.20
-1.57
f1 (ppm)

(1*RS*,4*SR*,6*RS*)-1-[N-Benzyl-N-(4-methylphenylsulfonyl)-3-aminopropyl]-9-(3-butenyl)-4-methyl-8-(trimethylsilyl)bicyclo[4.3.0]non-8-en-2-one (56)



38 **56**, 8% **57**, 25%

To a cooled (- 78 ºC) solution of **38** (173 mg, 0.421 mmol) in CH_2Cl_2 (1 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 0.42 mL, 1.0 equiv) and the resulting dark red solution was stirred at – 78 ºC for 5 min before allene **55** (70 mg, 0.421 mmol, 1.0 equiv) was added dropwise in CH_2Cl_2 (1 mL). The reaction mixture was kept at – 78 ºC for 30 min and slowly warmed to rt. After stirring for 20 h the reaction was transferred to a mixture of water (10 mL) and Et_2O (10 mL). The aqueous was separated and extracted with Et_2O (2 x 10 mL). The organics were combined, dried, filtered and concentrated. The crude was purified by chromatography (2.5→5→10% EtOAc/hexane) to give **56** (20 mg, 8%) followed by the product coming from desilylation **57**, as an epimeric mixture (53 mg, 25%) and recovered starting material (78 mg). R*f* 0.54 (25% EtOAc/hexanes). ^{1}H NMR (400 MHz, COSY) δ 0.09 (s, 9H, $(CH_3)_3Si$), 0.82 (d, *J* = 6.8 Hz, 3H, CH_3), 1.13 (m, 3H, 2H-2', H-5), 1.21 (m, 1H, H-1'), 1.49 (m, 2H, H-1', H-5), 1.83 (dd, *J* = 16.4, 7.2 Hz, 1H, H-7), 1.90 (m, 4H, H-1'', H-2''), 2.02 (m, 2H, H-3, H-6), 2.11 (m, 1H, H-4), 2.39 (dd, *J* = 16.8, 6.0 Hz, 1H, H-7), 2.43 (s, 3H, $ArCH_3$), 2.50 (dd, *J* = 16.4, 8.2 Hz, 1H, H-3), 3.04 (m, 2H, H-3'), 4.24 and 4.33 (2d, *J* = 14.8 Hz, 1H each, CH_2Ph), 4.91 (d, *J* = 10.8, 1.6 Hz, 1H, $=CH_2$), 4.95 (d, *J* = 15.6, 1.6 Hz, 1H, $=CH_2$), 5.68 (m, 1H, =CH), 7.30-7.35 (m, 7H, *o*-Ts, Ph), 7.73 (d, *J* = 8.3 Hz, 2H, *m*-Ts); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -0.5 ($(CH_3)_3Si$), 21.2 (CH_3), 21.7 ($ArCH_3$), 23.7 (C-2'), 27.0 (C-4), 27.9 (C-2''), 32.1 (C-5), 35.2 (C-1''), 37.4 (C-1'), 41.2 (C-6), 44.0 (C-3), 47.7 (C-7), 49.0 (C-3'), 52.4 (NCH_2Ar), 69.3 (C-1), 114.7 ($=CH_2$), 127.3 (*o*-Ts), 127.8 (Ph), 128.4 (Ph), 128.7 (Ph), 129.9 (*m*-Ts), 136.9 (*ipso*-Ph), 137.1 (*p*-Ts), 138.2 (=CH), 140.4 (*ipso*-Ts), 143.3 (C-8), 153.0 (C-9), 214.6 (C-2). HRMS Calcd for $C_{34}H_{48}NO_3SSi$ $(M + H)^+$ 578.3119, found 578.3119.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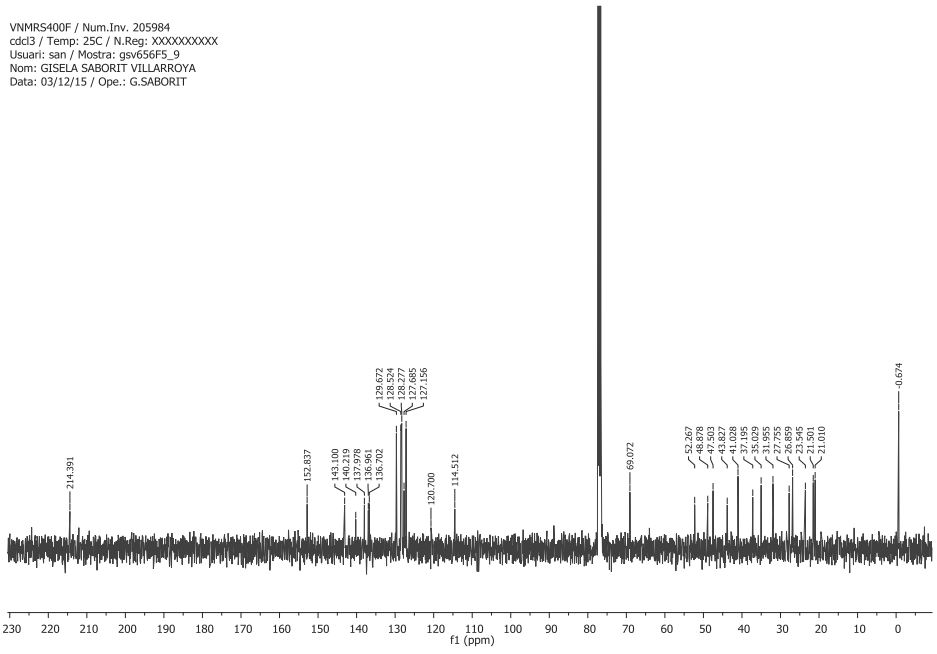
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv656F5_9
Nom: GISELA SABORIT VILLARROYA
Data: 02/12/15 / Ope.: G.SABORIT
Bn
N
Ts
O
SiMe3
H
56
f1 (ppm)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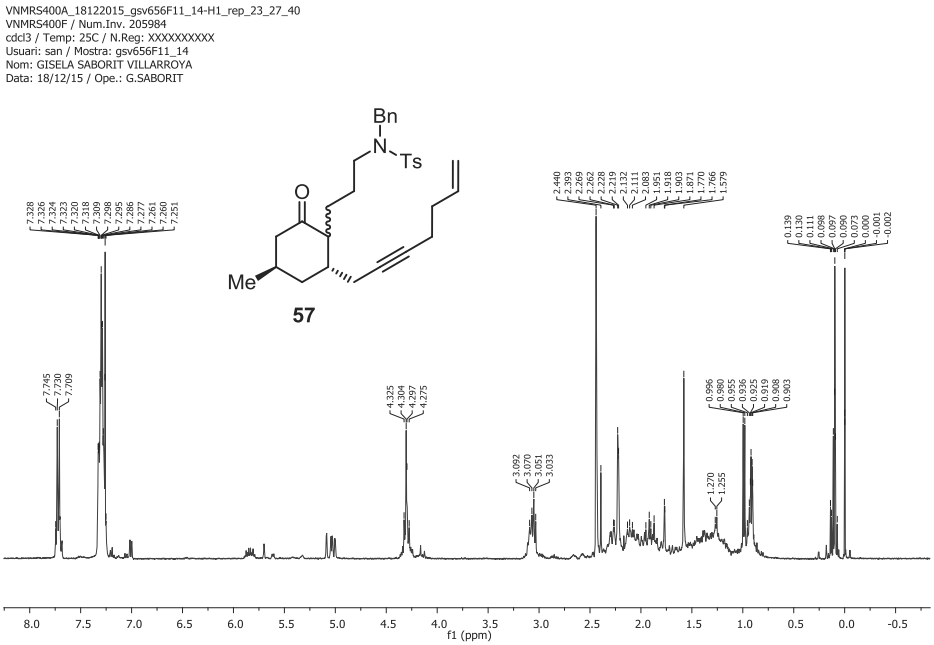
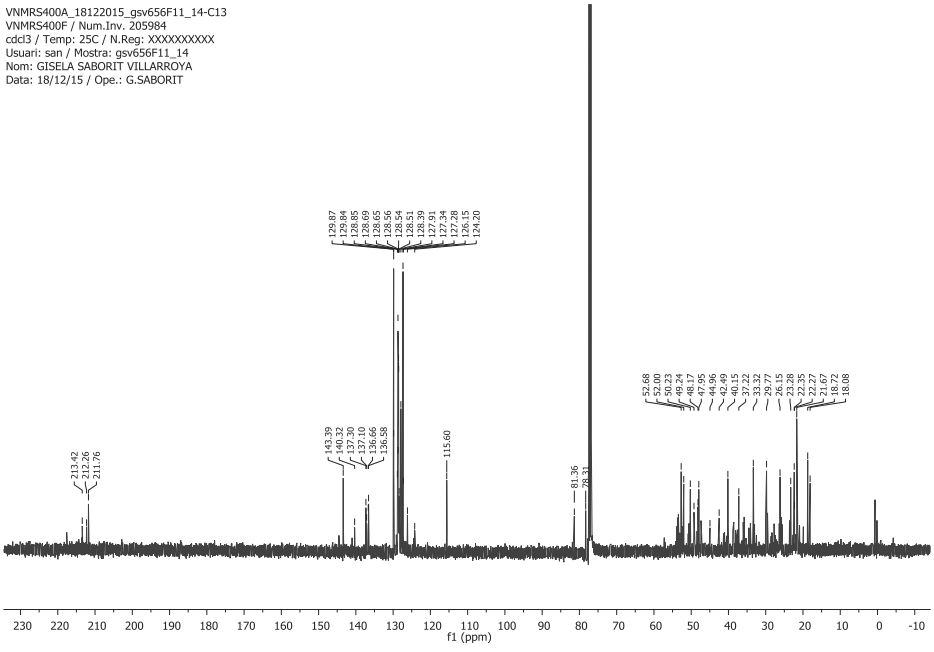
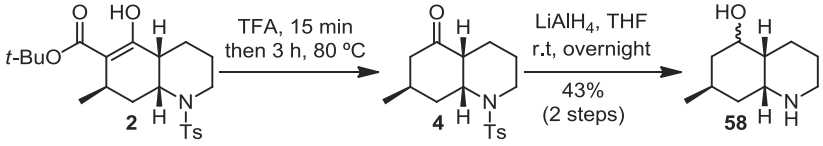
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv656F5_9
Nom: GISELA SABORIT VILLARROYA
Data: 03/12/15 / Ope.: G.SABORIT
f1 (ppm)

Characterization data for the product coming from desilylation. **3-(7-heptene-3-yne)-5-methyl-2-[(N-benzyl-N-(4-methylphenylsulfonyl)-3 aminopropyl] cyclohexanone 57** ^{1}H NMR (400 MHz, COSY). δ 0.97 (d, *J* = 6.4 Hz, 3H, CH_3), 1.15-1.47 (m, 11H, 2H-4, H-5, 2H-1', 2H-2', 2H-4'', 2H-5''), 1.67 (m, 1H, H-1''), 1.86-2.12 (m, 5H, H-3, H-6, H-1''), 2.29 (m, 1H, H-6), 2.44 (s, 3H, CH_3Ar), 3.07 (m, 2H, H-3'), 4.30 (m, 2H, CH_2Ph), 5.04 (2dd, *J* = 17.2, 3.6 Hz, 2H, H-7''), 5.84 (m, 1H, H-6''), 7.29 (m, 7H, Ph, *m*-Ts), 7.71 (d, *J* = 8.0 Hz, 2H *o*-Ts). ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.7 (C-1´´), 21.6 (CH_3Ts), 22.4 (5-CH_3), 23.4 (C-1´), 26.2 (C-2´), 29.8 (C-5), 33.3 (C-3''), 37.0 (C-4), 40.1 (C-3), 48.1 (C-3´), 50.3 (C-6), 52.1 (NCH_2Ar), 52.7 (C-2), 78.6 (C-3´´), 81.4 (C-2´´), 115.5 (C-7''), 127.4 (*o*-Ts), 128.0 (*p*-Bn), 128.5 (*m*-Bn), 128.7 (*o*-Bn), 129.9 (*m*-Ts), 136.6 (*ipso*-Bn), 136.7 (*p*-Ts), 137.1 (C-2''), 137.3 (*ipso*-Ts), 143.5 (*p*-Ts), 211.8 (C-1). HRMS calcd for $C_{31}H_{40}NO_3S$ $(M + H)^+$ 506.2723, found 506.2720.


VNMRS400A_18122015_gsv656F11_14-H1_rep_23_27_40
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv656F11_14
Nom: GISELA SABORIT VILLARROYA
Data: 18/12/15 / Ope.: G.SABORIT
Bn
N
Ts
O
Me
57
f1 (ppm)

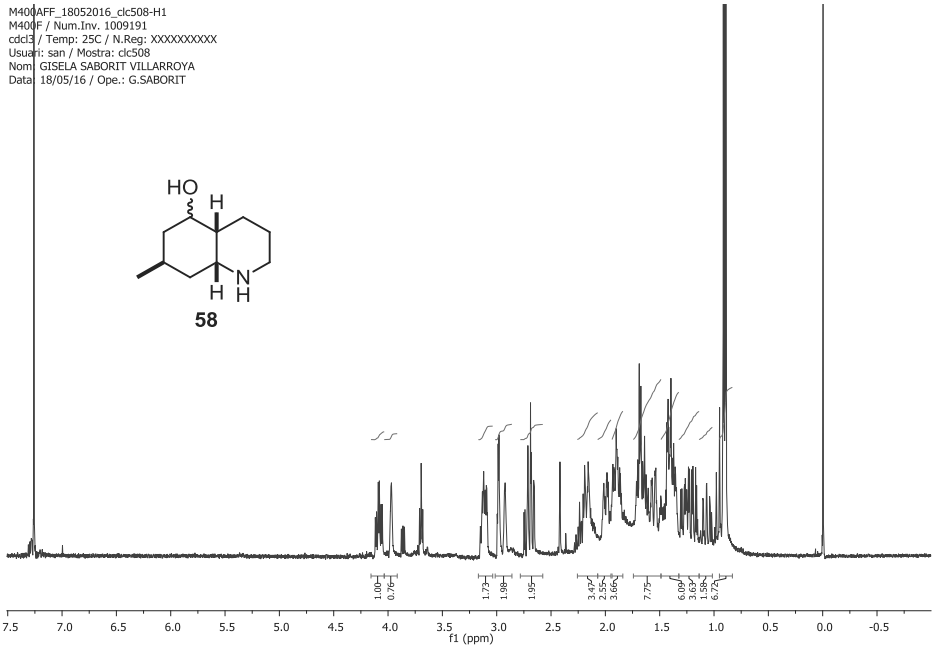

VNMRS400A_18122015_gsv656F11_14-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv656F11_14
Nom: GISELA SABORIT VILLARROYA
Data: 18/12/15 / Ope.: G.SABORIT
f1 (ppm)

(4a*RS*,5*RS*,7*RS*,8a*RS*)-7-Methyl-5-hydroxydecahydroquinoline (58)



Rac-**2** (4.0 g, 9.5 mmol) was treated with TFA (7.5 mL) at rt for 15 minutes. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 2 mL). The reaction flask was maintained on the rotatory evaporator at 70 ºC for 3 h. The crude **4** was dissolved in THF (40 mL) and was added to a flame dried flask containing $LiAlH_4$ (3.5 g, 91.4 mmol, 10 equiv) and THF (500 mL) at 0 ºC. The reaction was allowed to warm to rt, stirred overnight at quenched by the dropwise addition of H_2O (3.5 mL), 15% aqueous NaOH (3.5 mL) and H_2O (10 mL) at 0 ºC. The reaction was filtered through celite and concentrated. The crude was purified by chromatography on alumina (1→2.5%→5% CH_3OH:CH_2Cl_2) to give **58** as a 3:1 epimeric mixture (741 mg, 46%). Compound **58eq**:[189] ^{1}H NMR (400 MHz, COSY) δ 0.90 (d, *J* = 6.8 Hz, 3H, CH_3), 0.94 (q, *J* = 12.4 Hz, 1H, H-6ax), 1.19 (td, *J* = 12.4, 4.0 Hz, H-8ax), 1.30-1.45 (m, 4H, 2H-3, H-4ax, H-4a), 1.53 (dm, *J* = 12.4 Hz, 1H, H-8eq), 1.65 (qt, *J* = 12, 4 Hz, 1H, H3-ax), 1.90 (m, 1H, H-7ax), 1.99 (dm, J = 12.0 Hz, 1H, H-6eq), 2.17 (dm, J = 12.0 Hz, 1H, H-4eq), 2.68 (td, *J* = 12.4, 3.2 Hz, 1H, H-2ax), 2.96 (q, *J* = 3.2 Hz, 1H, H-8a), 3.09 (dddd, *J* = 12.4, 5, 2.5, 2.5 Hz, 1H, H-2eq), 4.09 (td, *J* = 10.7, 4.4 Hz, 1H, H-5ax); ^{13}C NMR (100 MHz, HSQC) δ 21.4 (C-3), 22.3 (CH3), 25.1 (C.4), 26.7 (C.7), 41.8 (C-8), 43.3 (C-6), 45.1 (C-4a), 48.2 (C-2), 57.0 (C-8a), 67.1 (C-5). HRMS calcd for $C_{10}H_{20}NO$ ($M+H^+$) 170.1539, found 170.1540.

[189] Minor signals were observed at δ 3.97 (br, H-5eq), 2.92 (br q, *J* = Hz, H-8a) and 0.91 (d, *J* = 6.8 Hz, CH_3) in the ^{1}H NMR spectrum and at δ 73.0, 58.0 and 38.0 for the methine at C-5, C-8a and C-4a, respectively in the ^{13}C NMR spectrum.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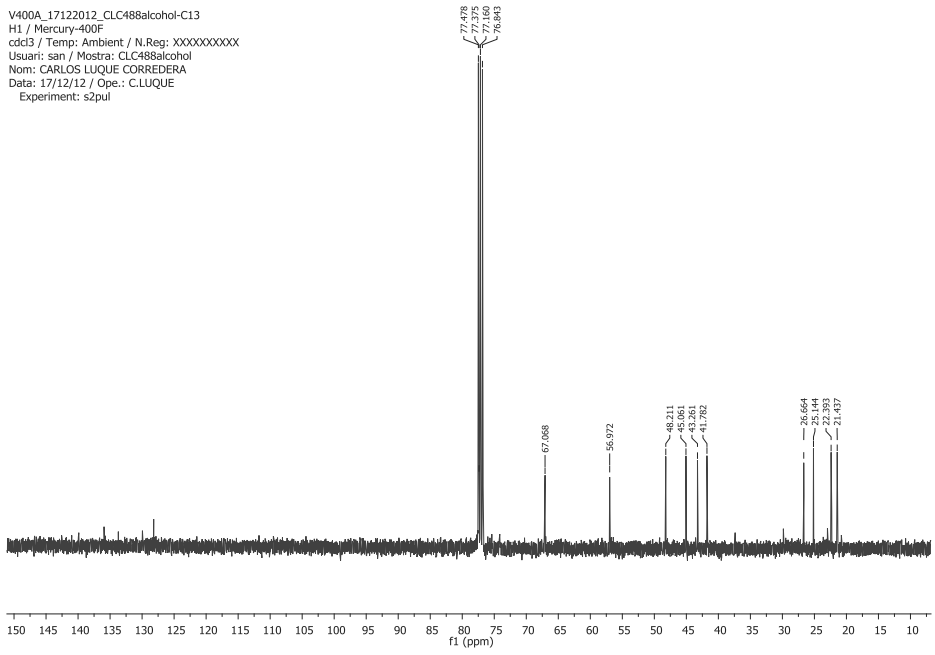
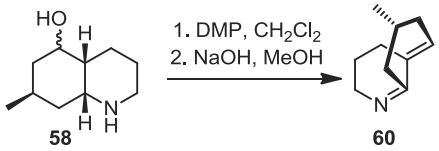
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: clc508
Nom: GISELA SABORIT VILLARROYA
Data: 18/05/16 / Ope.: G.SABORIT
HO
H
H
N
H
58
1.00
0.76
1.79
1.98
1.95
3.47
2.55
3.66
7.75
6.09
3.63
1.58
6.72
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


V400A_17122012_CLC488alcohol-C13
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC488alcohol
Nom: CARLOS LUQUE CORREDERA
Data: 17/12/12 / Ope.: C.LUQUE
Experiment: s2pul
77.478
77.375
77.160
76.843
67.068
56.972
49.211
45.061
43.261
41.782
26.664
25.144
22.393
21.437
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

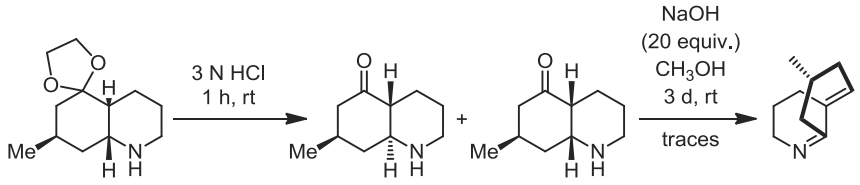
(4a*RS*,5*RS*,7*RS*,8a*RS*)-7-Methyl-5-hydroxydecahydroquinoline (60)



58 **60**

To a stirred solution of crude amino alcohol **58** (23 mg, 0.136 mmol) in CH_2Cl_2 (1.2 mL) was added DMP (230 mg, 0.54 mmol, 4.0 equiv) and the resulting mixture was stirred for 3 h at rt. Addition of 0.03 mL of *i*PrOH was performed to quench excess reagent. The solvent was removed and the crude dissolved in 2 mL of a 2 N methanolic solution of NaOH. After 2 h at rt the solvent was removed, the residue diluted with CH_2Cl_2 (6 mL) and washed with brine (3 mL). The aqueous was extracted with CH_2Cl_2 (2 x 6 mL), the organics combined, dried, filtered and concentrated to give crude imine **60** (11 mg, 55%).[190]

Alternatively, **60** was prepared as shown below:

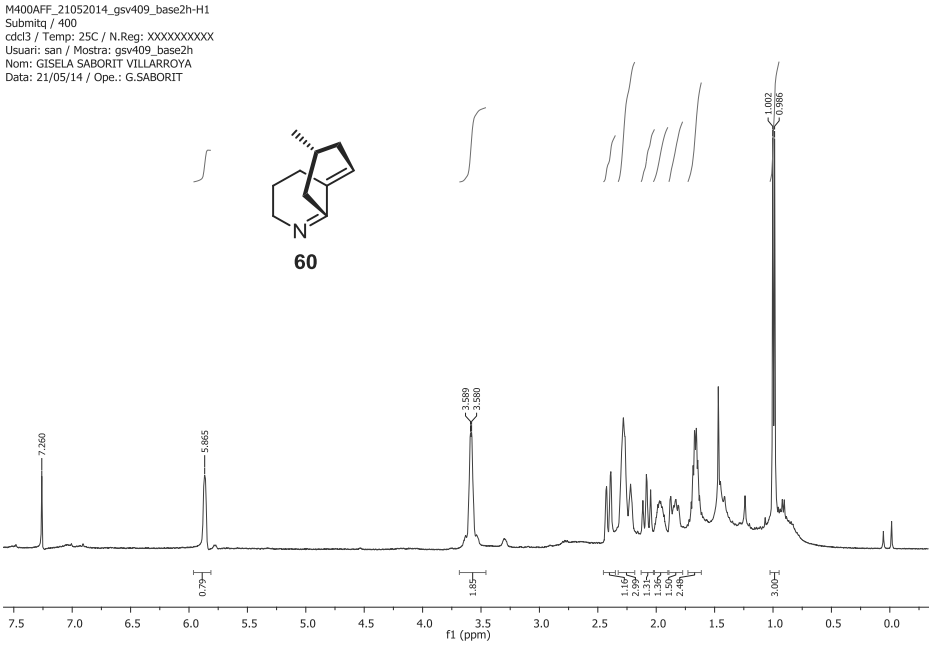


ent-**28** *ent*-**29** **61** **60**

ratio 1:1

A solution of *ent*-**28** (50 mg, 0.23 mmol) in 3 N HCl (6 mL) was stirred for 1 h, quenched by the addition of NaOH until pH > 11 and extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were dried, filtered and concentrated to give *ent*-**29** and **61** as a 1:1 mixture of epimers. The crude mixture was dissolved in methanol and cooled to 0 ºC. NaOH (184 mg, 4.6 mmol, 20 equiv) was added, the mixture was warmed to rt and stirred for 3 d. The solvent was removed and the residue diluted with brine (6 mL). The aqueous was extracted with CH_2Cl_2 (3 x 6 mL) and the combined organic layers dried, filtered and concentrated to give **60** (35 mg, 80%).

[190] Attempts to purify imine **60** either by chromatography or distillation failed.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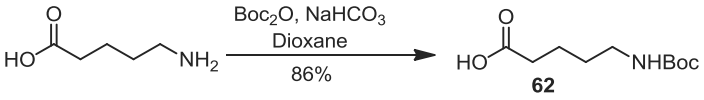
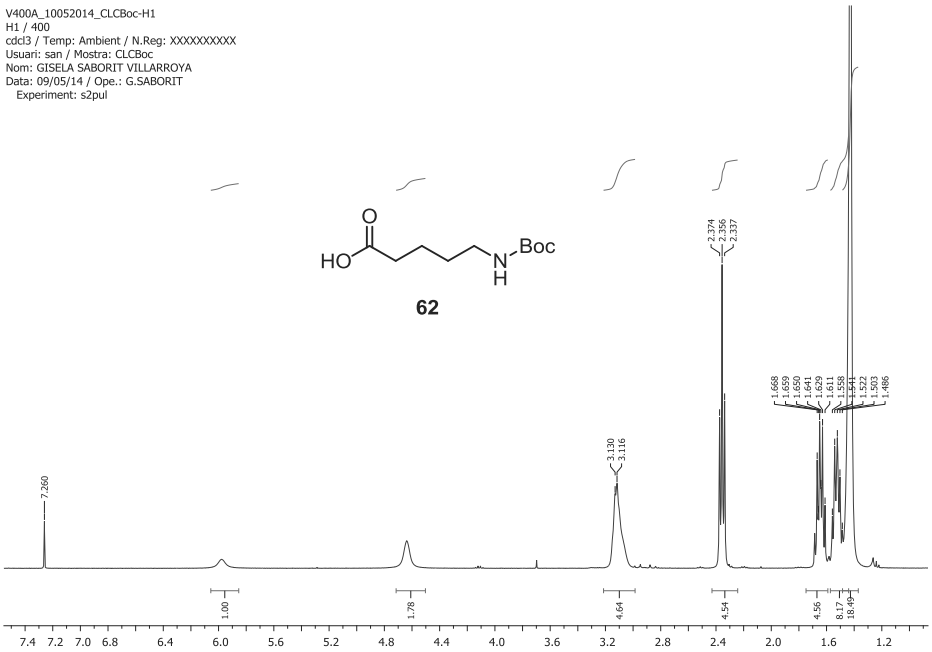
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv409_base2h
Nom: GISELA SABORIT VILLARROYA
Data: 21/05/14 / Ope.: G.SABORIT
60
7.260
5.865
3.589
3.580
1.002
0.986
0.79
1.85
1.16
2.99
1.31
1.36
1.50
2.46
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

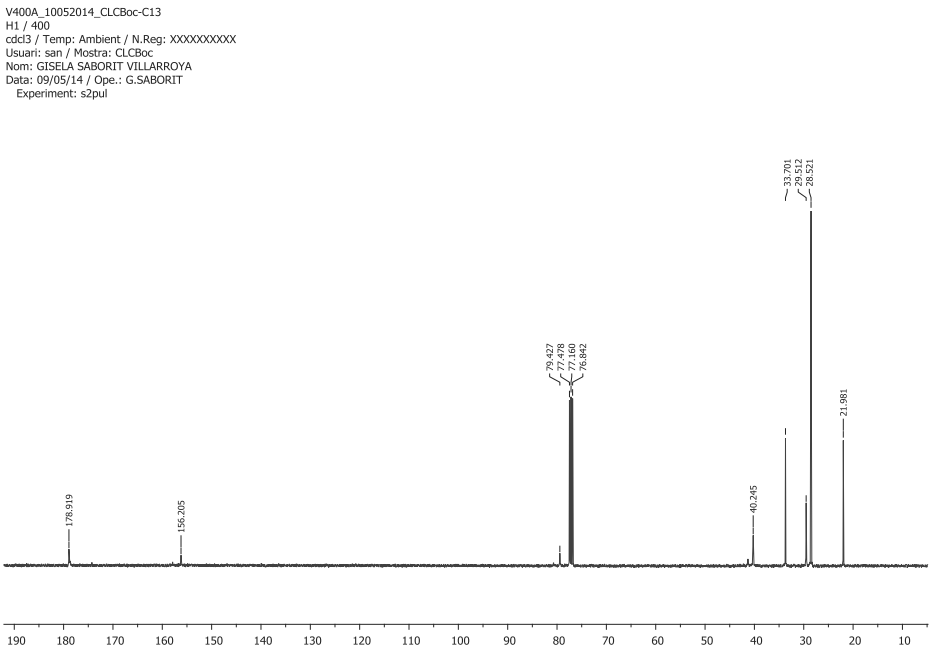
5-(*tert*-Butoxycarbonyl)aminopentanoic acid (62)



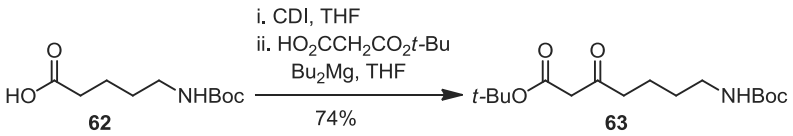
62

To a solution of Boc_2O (17.8 g, 81.5 mmol) in dioxane (64 mL) at 0 ºC was added a solution of 5-aminovaleric acid (6.37 g, 54.4 mmol) and $NaHCO_3$ (9.14 g, 0.109 mol) in water (153 mL) at 5 ºC. The resulting mixture was stirred at 0 ºC for 1 h, then at rt overnight. The reaction was quenched by the addition of water (100 mL), and the aqueous layer was extracted twice with EtOAc (2 × 180 mL). The combined aqueous phase was acidified to pH = 1 with 4 N HCl and the acidic phase was extracted with EtOAc (3 × 250 mL), dried and concentrated. The crude was crystallized from pentane:Et_2O (3:1) to give **62** (9.8 g, 83%) as a white solid. R_f 0.50 (EtOAc); ^{1}H NMR (400 MHz, COSY) δ 1.43 (s, 9H), 1.54 (m, 2H, H-4), 1.65 (m, 2H, H-3), 2.36 (t, J = 7.2 Hz, 2H, H-2), 2.92 (br, 2H, H-5), 4.60 (br, 1H, NH); ^{13}C NMR (100 MHz, HSQC) δ 21.8 (C-3), 28.4 (CH_3), 29.4 (C-4), 33.5 (C-2), 40.1 (C-5), 79.3 (C), 178.8 (CO) HRMS calcd for $C_{12}H_{17}NO_4S$ $(M - H)^-$ 270.0806, found 270.0806.

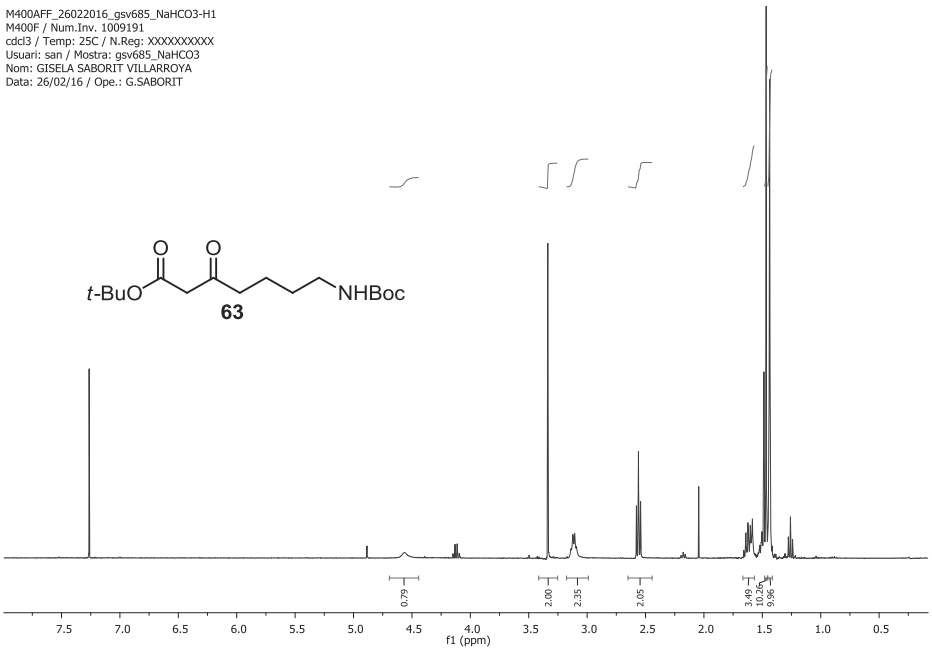

V400A_10052014_CLCBoc-H1
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCBoc
Nom: GISELA SABORIT VILLARROYA
Data: 09/05/14 / Ope.: G.SABORIT
Experiment: s2pul
HO
O
N
H
Boc
62
7.260
3.130
3.116
2.374
2.356
2.337
1.668
1.659
1.650
1.641
1.630
1.611
1.558
1.541
1.522
1.503
1.486
1.00
1.78
4.64
4.54
4.56
8.17
18.49
7.4 7.2 7.0 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2

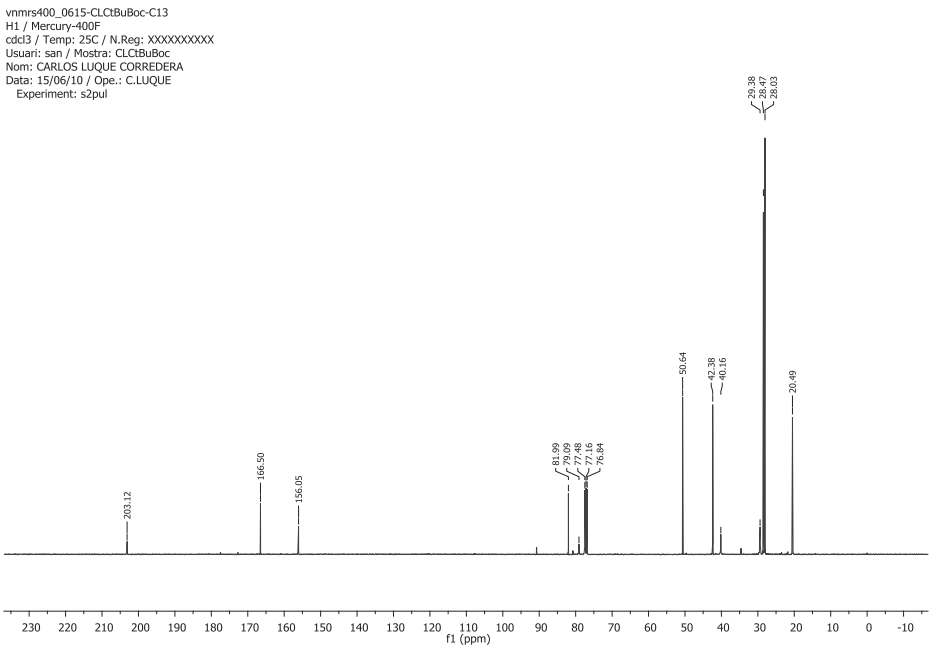

V400A_10052014_CLCBoc-C13
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCBoc
Nom: GISELA SABORIT VILLARROYA
Data: 09/05/14 / Ope.: G.SABORIT
Experiment: s2pul
178.919
156.205
79.427
77.478
77.160
76.842
40.245
33.701
29.512
28.521
21.981
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

tert-Butyl 7-[(_tert_-Butoxycarbonyl)amino]-3-oxoheptanoate (63)

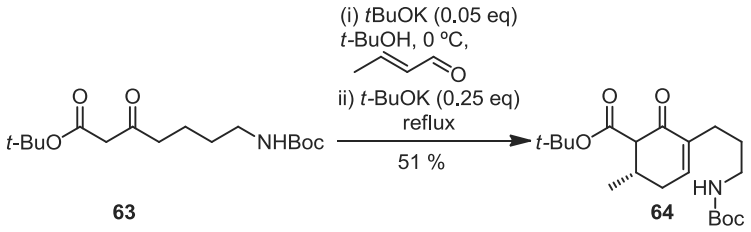


Dibutyl magnesium (Aldrich, 1 M in heptane, 15.2 mL, 1.1 equiv) was added to a solution of mono-*tert*-butylmalonate (4.6 g, 29.0 mmol, 2.1 equiv) in THF (120 mL). The mixture was stirred for 15 min at -78 ºC, warmed to rt and stirred for 1 h. Concurrently, in a separate flask carbonyldiimidazole (CDI) (2.69 g, 16.57 mmol, 1.2 equiv) was added to a solution of **62** (3.0 g, 13.8 mmol, 1 equiv) in THF (120 mL). The mixture was stirred for 15 min at 0 ºC, warmed to room temperature and stirred for 1 h before being added to the magnesium malonate solution via canula. The resulting mixture was stirred overnight at room temperature, quenched with 10% citric acid solution (100 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ solution (40 mL), brine (40 mL), dried and concentrated. Purification by chromatography (2.5→5→10→25% EtOAc/hexane) gave **63** (3.1 g, 74%). (^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ 1.39 (s, 9H, CH_3), 1.42 (s, 9H, CH_3), 1.51 (masked, 2H, H-6), 1.62 (q, *J* = 6.8 Hz, 3H, H-5), 2.52 (t, *J* = 6.8 Hz, 2H, H-4), 3.06 (q, *J* = 6.4 Hz, 2H, H-7), 3.29 (s, 2H, H-2), 4.63 (br, 1H, NH); ^{13}C NMR (100 MHz, HSQC) δ 20.3 (C-5), 27.9 (CH3), 28.3 (CH_3), 29.2 (C-6), 40.0 (C-7), 42.2 (C-4), 50.5 (C-2), 78.9 (C), 81.8 (C), 155.9 (CO), 166.4 (C-1), 203.0 (C-3). HRMS calcd for $C_{16}H_{30}NO_5$ ($M + H^+$) 316.2115, found 316.2118.


M400AFF_26022016_gsv685_NaHCO3-H1
M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv685_NaHCO3
Nom: GISELA SABORIT VILLARROYA
Data: 26/02/16 / Ope.: G.SABORIT
t-BuO
NHBoc
63
0.79
2.00
2.35
2.05
3.49
10.26
9.96
f1 (ppm)

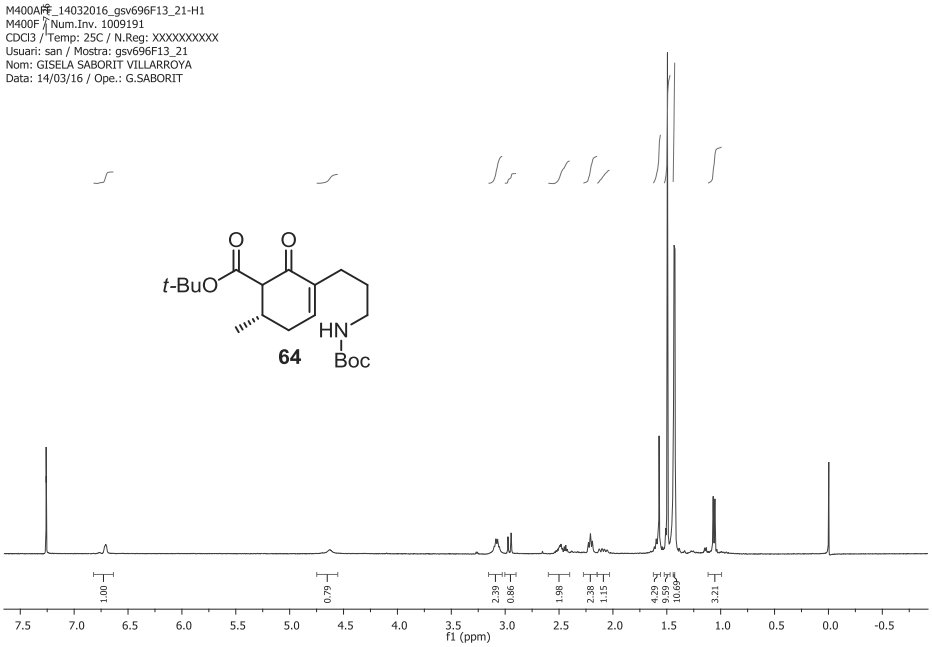

vnmrs400_0615-CLCtBuBoc-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCtBuBoc
Nom: CARLOS LUQUE CORREDERA
Data: 15/06/10 / Ope.: C.LUQUE
Experiment: s2pul
203.12
166.50
156.05
81.99
79.98
77.48
77.16
76.84
50.64
42.38
40.16
29.38
28.47
28.03
20.49
f1 (ppm)

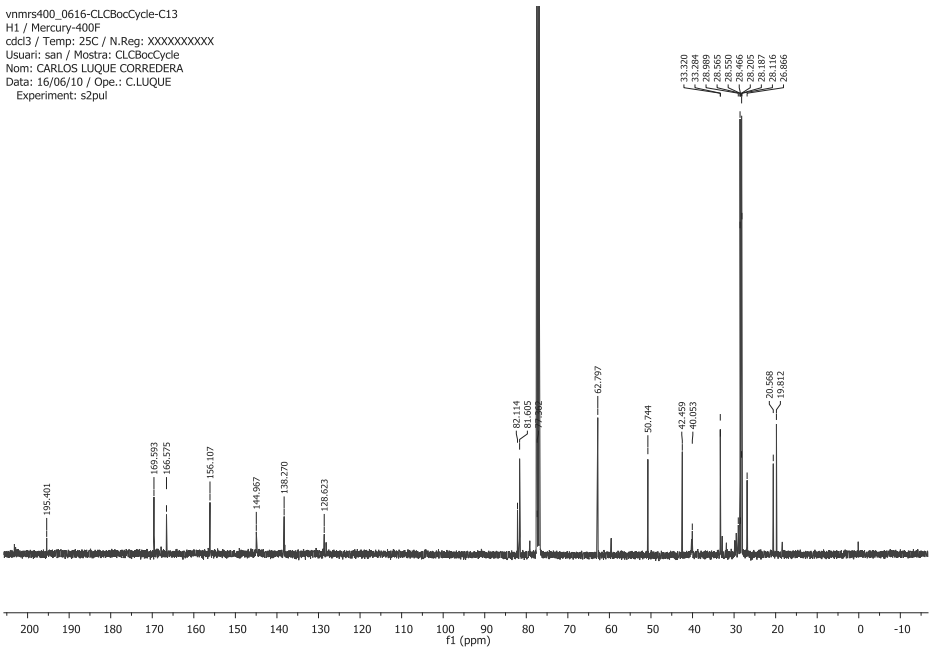
tert-Butyl 3-[3-(tert-Butoxycarbonylamino)propyl]-6-methyl-2-oxocyclohex-3-enecarboxylate (64)



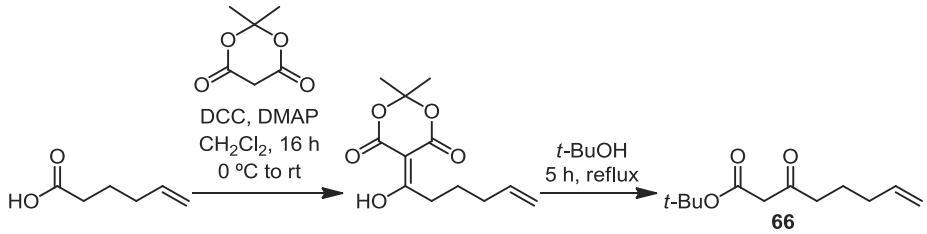
63 **64**

To a stirred solution of β-keto ester **63** (303 mg, 1 mmol) and crotonaldehyde (0.1 mL, 1.1 equiv) in *t*-BuOH (1 mL) was added a catalytic amount of *t*-BuOK (6 mg, 0.05 equiv) at 0 °C. After stirring for 30 min at that temperature *t*-BuOK (22 mg, 0.2 equiv) was added again and the mixture was refluxed for 20 h. Upon cooling to room temperature, the mixture was quenched with 1.5 mL of aqueous saturated NH_4Cl (1.5 mL) and diluted ether (9 mL). The aqueous was extracted with Et_2O (2 x 9 mL) and the combined organic layers were dried, filtered and concentrated. The crude product was purified by chromatography (5→10→25% EtOAc in hexanes) to give **64** (187 mg, 51%) as a yellow oil. ^{1}H NMR (400 MHz, COSY) 1.04 (d, *J* = 6.4 Hz, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)$), 1.47 (s, 9H, (CH_3), 1.56 (quint, *J* = 7.4 Hz, 2H, H-2´), 2.07 (ddq, *J* = 15.8, 12.0, 2.8 Hz, 1H, H-5ax), 2.19 (t, *J* = 7.2 Hz, 2H, H-1´), 2.47 (dt, *J* = 15.8, 5.2 Hz, 1H, H-5eq), 2.50 (m, 1H, H-6ax), 2.94 (d, *J* = 12 Hz, 1H, H-1ax), 3.06 (q, *J* = 6.4 Hz, 2H, H-3´), 4.65 (br, 1H, NH), 6.70 (dd, *J* = 5.2, 2.8 Hz, 1H, H-4); ^{13}C NMR (400 MHz, HSQC) 19.6 (CH_3), 26.7 (C-1´), 28.0 ((CH_3)$_3$C), 28.4((CH_3)$_3$C), 28.8 (C-2´), 33.0 (C-5), 33.1 (C-6), 39.9 (C-3'), 62.6 (C-1), 81.4 (C), 138.1 (C-3), 144.8 (C-4), 155.9 (NH*C*O), 169.4 (CO_2*t*Bu), 195.2 (C-2). HRMS calcd for $C_{20}H_{34}NO_5$ ($M+H^+$) 368.2431, found 368.2430.


M400A羊_14032016_gsv696F13_21-H1
M400F 犬Num.Inv. 1009191
CDCl3 /Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv696F13_21
Nom: GISELA SABORIT VILLARROYA
Data: 14/03/16 / Ope.: G.SABORIT
O
O
t-BuO
HN
Boc
64
1.00
0.79
2.39
0.86
1.98
2.38
1.15
4.29
5.97
10.69
3.21
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 -0.5
f1 (ppm)

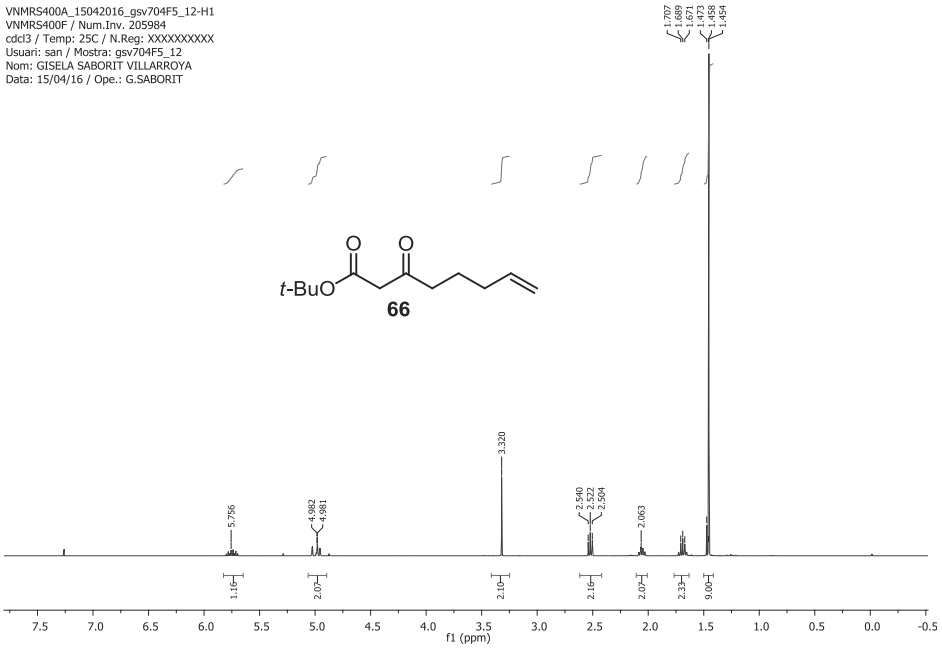

vnmrs400_0616-CLCBocCycle-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCBocCycle
Nom: CARLOS LUQUE CORREDERA
Data: 16/06/10 / Ope.: C.LUQUE
Experiment: s2pul
33.320
33.284
28.888
28.565
28.550
28.466
28.305
28.107
28.116
26.866
195.401
169.593
166.575
156.107
144.967
138.270
128.623
82.114
81.605
77.000
62.797
50.744
42.459
40.653
20.568
19.812
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

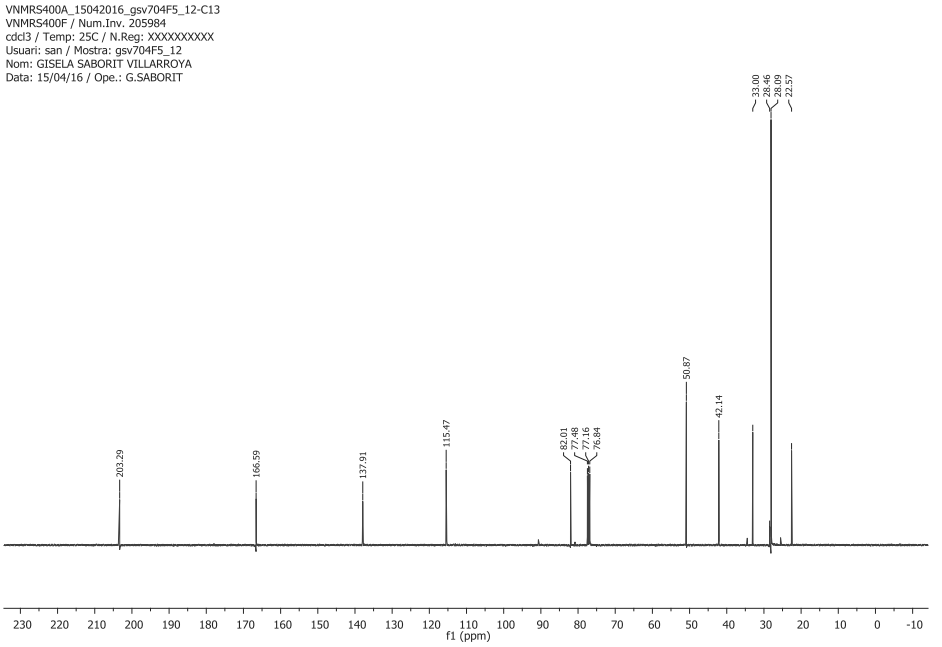
tert-butyl 3-oxo-7-octenoate (66)



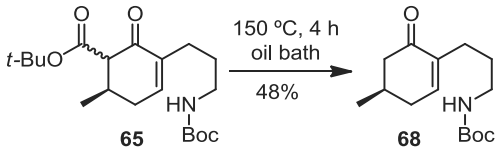
66

A solution of DCC (994 mg, 4.82 mmol, 1.1 equiv) in CH_2Cl_2 (4.4 ml) was slowly added to a stirred solution of Meldrum's acid (630 mg, 4.38 mmol, 1.0 equiv), 1-hexenoic acid (0.52 mL, 4.38 mmol, 1.0 equiv), and DMAP (590 mg, 4.82 mmol, 1.1 equiv) in CH_2Cl_2 at 0 ºC (ice-bath). The reaction mixture was stirred at rt for 16 h and the precipitated solid was removed by filtration and washed thoroughly with CH_2Cl_2. The filtrate was subsequently washed with 1 M aq $NaHSO_4$ (2 x 30 mL), brine (30 mL), dried, filtered, and concentrated. The residue was immediately dissolved in *tert*-butanol (28 mL) and the solution was refluxed under argon for 5 h. The volatiles were removed and the residue purified by chromatography (1→2.5→5% hexane/EtOAc) to give **66** (750 mg, 81%). ^{1}H NMR (400 MHz, COSY) 1.45 (s, 9H, $(CH_3)_3$), 1.69 (quint, *J* = 7.3 Hz, 2H, H-5), 2.06 (qt, *J* = 6.8, 1.6 Hz, 2H, H-6), 2.52 (t, *J* = 7.2 Hz, 2H, H-4), 3.32 (s, 2H, H-2), 4.98 (m, 2H, H-8), 5.76 (m, 1H, H-7); ^{13}C NMR (400 MHz, HSQC) 22.6 (C-5), 28.1 $(CH_3)_3$), 33.0 (C-6), 42.1 (C-4), 50.9 (C-2), 82.0 (C), 115.5 (C-8), 137.9 (C-7), 166.6 (C-1), 203.3 (C-3). HRMS calcd for $C_{12}H_{21}O_3$ ($M+H^+$) 213.1485, found 213.1484.

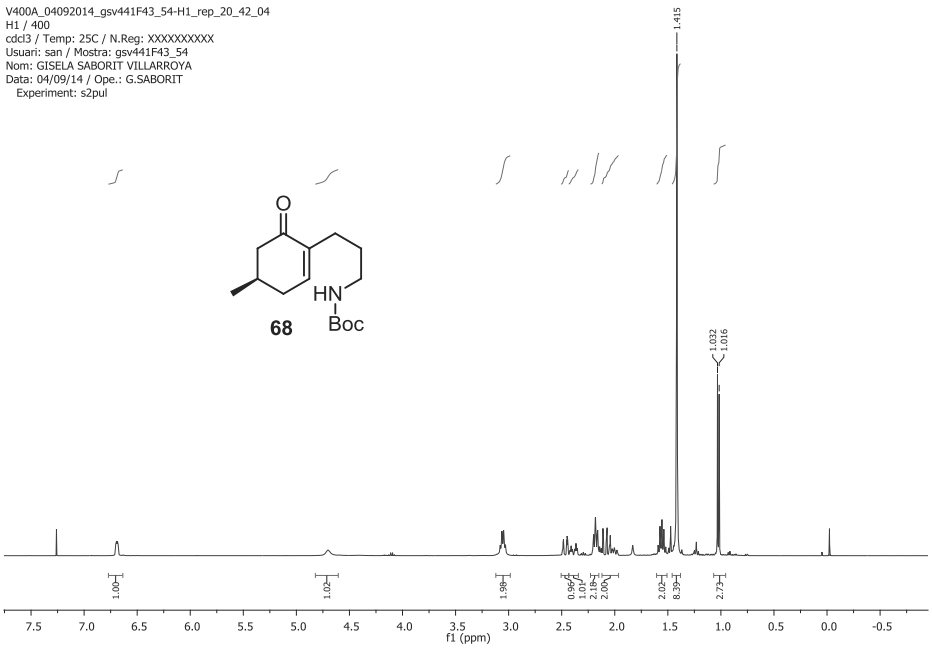

VNMRS400A_15042016_gsv704F5_12-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv704F5_12
Nom: GISELA SABORIT VILLARROYA
Data: 15/04/16 / Ope.: G.SABORIT
t-BuO
66
f1 (ppm)

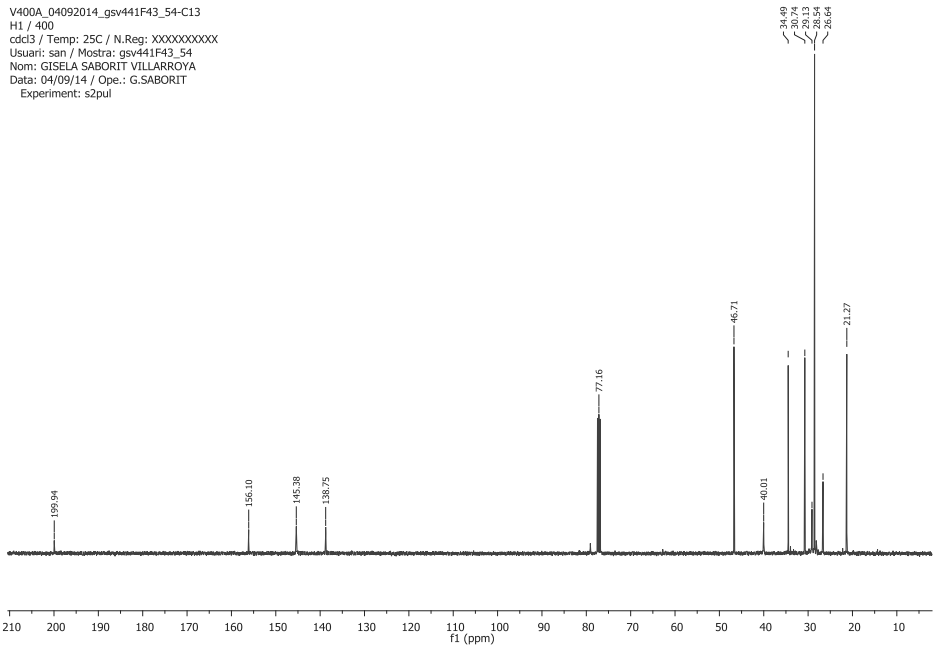

VNMRS400A_15042016_gsv704F5_12-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv704F5_12
Nom: GISELA SABORIT VILLARROYA
Data: 15/04/16 / Ope.: G.SABORIT
f1 (ppm)

(*SR*)-5-Methyl-2-[3-(*tert*-Butoxycarbonylamino)-propyl]cyclohex-2-enone (68)

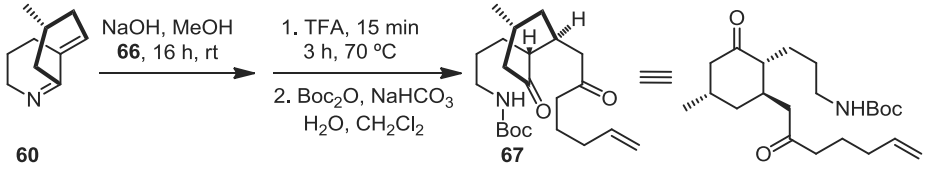


A flask containing **65** (700 mg, 1.93 mmol) was heated for 4 h at 150 ºC in an oil bath. The crude was purified by chromatography (5→10→25% EtOAc in hexanes) to give **68** (250 mg, 48%) as an oil. ^{1}H NMR (400 MHz, COSY) 1.02 (d, *J* = 6.4 Hz, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)$), 1.56 (quint, *J* = 7.3 Hz, 2H, H-2'), 2.00 (m, 1H, H-4eq), 2.08 (m, 1H, H-6eq), 2.13 (m, 1H, H-5), 2.18 (t, *J* = 6.8 Hz, 2H, H-1'), 2.38 (dtd, *J* = 18.4, 4.4, 1.0 Hz, 1H, H-4ax), 2.47 (ddd, *J* = 15.2, 3.2, 1.6 Hz, 1H, H-6ax), 3.06 (q, *J* = 6.8 Hz, 2H, H-3'), 6.69 (m, 1H, H-3). ^{13}C NMR (400 MHz, HSQC) 21.3 (CH_3), 26.6 (C-1´), 28.5 ((CH_3)$_3$C), 29.1 (C-2´), 30.7 (C-5), 34.4 (C-4), 40.0 (C-3'), 46.7 (C-6), 79.1 (C), 138.5 (C-3), 145.4 (C-2), 156.1 (NH*C*O), 199.9 (C-1). HRMS calcd for $C_{15}H_{26}NO_3$ ($M+H^+$) 268.1907, found 268.1909.


V400A_04092014_gsv441F43_54-H1_rep_20_42_04
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv441F43_54
Nom: GISELA SABORIT VILLARROYA
Data: 04/09/14 / Ope.: G.SABORIT
Experiment: s2pul
1.415
1.032
1.016
O
HN
Boc
68
1.00
1.02
1.98
0.90
0.97
2.18
2.00
2.04
8.39
2.79
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 -0.5
f1 (ppm)

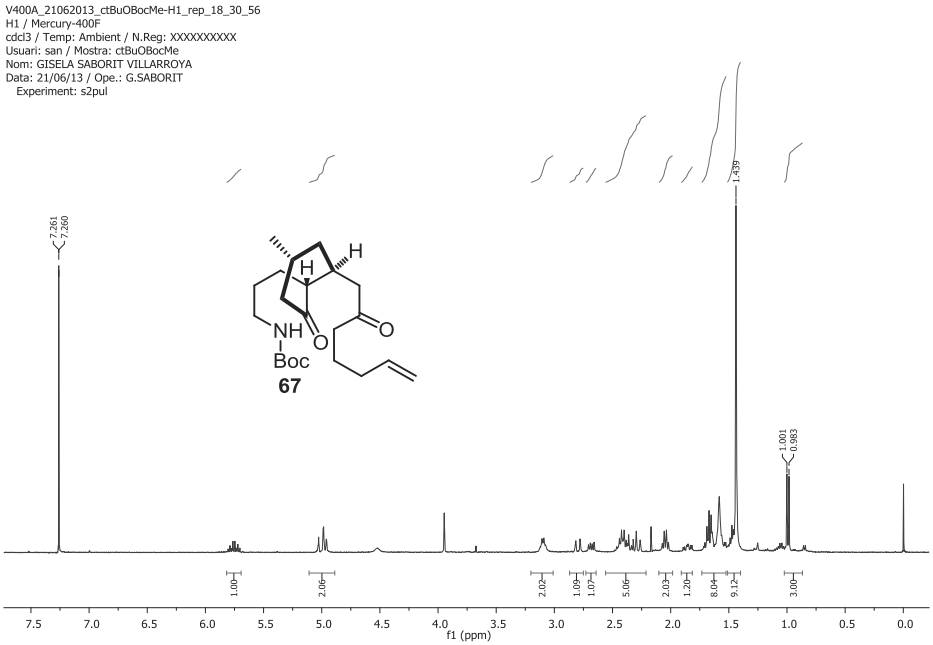

V400A_04092014_gsv441F43_54-C13
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv441F43_54
Nom: GISELA SABORIT VILLARROYA
Data: 04/09/14 / Ope.: G.SABORIT
Experiment: s2pul
34.49
30.74
29.13
28.54
26.64
46.71
21.27
77.16
40.01
199.94
156.10
145.38
138.75
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

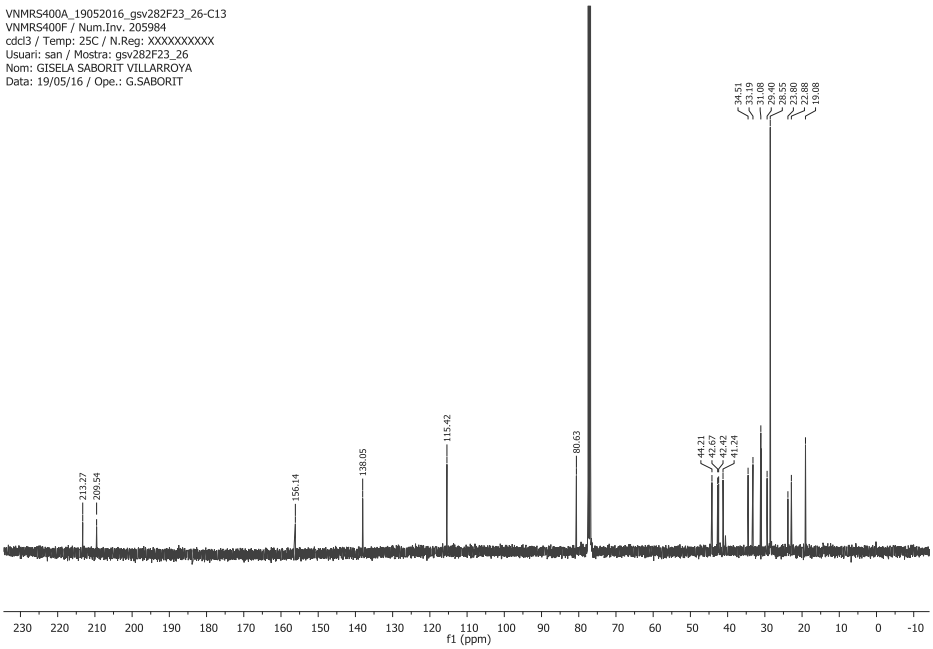
(2*RS*,3*RS*,5*SR)*-2-[3-(*N*-*tert*-butoxycarbonyl)-3-aminopropyl]-5-methyl-3-(2-oxo-6-heptenyl)cyclohexanone (67)



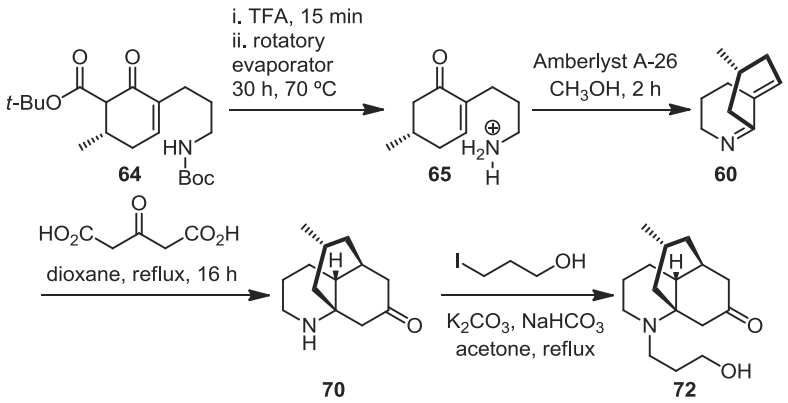
The crude mixture **60** (43 mg, 0.26 mmol, 1.0 equiv) and **66** (118 mg, 0.527 mmol, 2.0 equiv) were treated with NaOH (186 mg, 4.65 mmol, 18 equiv) in MeOH (2.6 mL) for 16 h at rt. The solvent was removed and 5 mL of saturated aqueous NH_4Cl was added. The aqueous was extracted with CH_2Cl_2 (3 x 10 mL) and the organics combined, washed with brine (6 mL), dried and concentrated. The crude was treated with TFA (0.52 mL) for 15 min, the solvent was removed, and the last traces of TFA were removed by azeotroping with toluene (2 × 2 mL). The reaction flask was maintained on the rotatory evaporator at 70 ºC for 3 h. To the crude was added $CHCl_3$ (1 mL), H_2O (1 mL) and a solution of Boc_2O (73 mg, 0.34 mmol, 1.1 equiv) in $CHCl_3$ (0.2 mL) followed by $NaHCO_3$ (55 mg, 2.2 equiv, 0.65 mmol). After stirring for 16 h at rt the reaction mixture was diluted with CH_2Cl_2 and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried, filtered and concentrated. The crude was purified by chromatography (5→10→25% EtOAc in cyclohexane) to give **67** (7 mg, 6% from unpurified **60**). ^{1}H NMR (400 MHz, COSY) δ 0.99 (d, *J* = 7.2 Hz, 3H, Me), 1.06 (m, 1H, H-2'), 1.44 (s, 9H, $C(CH_3)$), 1.46 (masked, 1H, H-2'), 1.50 (m, 2H, H-5, H-1'), 1.67 (m, 4H, 2H-4, 2H-4''), 1.86 (td, *J* = 12.0, 4.0 Hz, 1H, H-1'), 2.05 (q, *J* = 6.8 Hz, 2H, H-5''), 2.30 (m, 2H, H-1'',H-3''), 2.40 (m, 4H, H-3, H-2, 2H-1''), 2.68 (dd, *J* = 14, 8 Hz, 1H, H-6), 2.80 (d, *J* = 14.4 Hz, 1H, H-3''), 3.10 (q, *J* = 6.4 Hz, 2H, H-3'), 4.52 (br, 1H, NH), 5.00 (m, 2H, CH_2=CH), 5.75 (m, 1H, CH_2=*CH*). ^{13}C NMR (400 MHz, HSQC) 19.1 (CH_3), 22.8 (C-4), 23.8 (C-2'), 28.5 ((CH_3)$_3$C, C-5), 29.4 (C-1'), 31.1 (C-3), 33.2 (C-5''), 34.5 (C-4''), 40.7 (C-3'), 41.2 (C-2), 42.4 (C-1''), 42.7 (C-3''), 44.2 (C-6), 80.6 (C), 115.4 (=CH_2), 138.1 (=CH), 156.1 (NH*C*O), 209.5 (CO), 213.3 (C-1). HRMS calcd for $C_{22}H_{38}NO_5$ ($M+H^+$) 396.2744, found 396.2737.[191]

[191] See ref. 160


V400A_21062013_ctBuOBocMe-H1_rep_18_30_56
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ctBuOBocMe
Nom: GISELA SABORIT VILLARROYA
Data: 21/06/13 / Ope.: G.SABORIT
Experiment: s2pul
7.261
7.260
1.439
1.001
0.983
NH
Boc
O
O
H
H
67
1.00
2.06
2.02
1.09
1.07
5.06
2.03
1.20
8.04
9.12
3.00
f1 (ppm)


VNMRS400A_19052016_gsv282F23_26-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv282F23_26
Nom: GISELA SABORIT VILLARROYA
Data: 19/05/16 / Ope.: G.SABORIT
34.51
33.19
31.08
29.40
28.55
23.80
22.88
19.08
213.27
209.54
156.14
138.05
115.42
80.63
44.21
42.67
42.42
41.24
f1 (ppm)

Formal synthesis of lycopodine

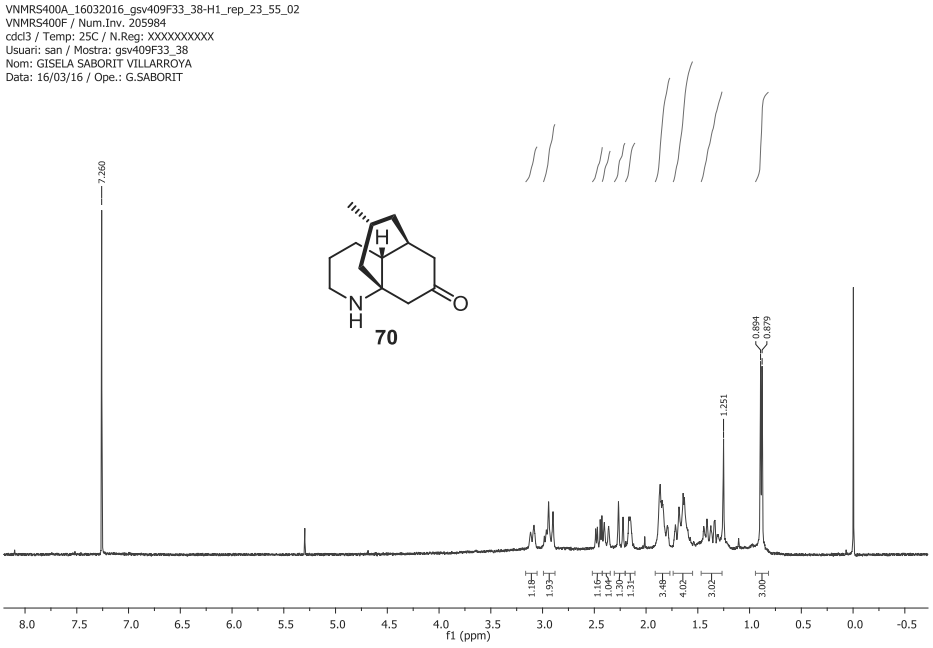


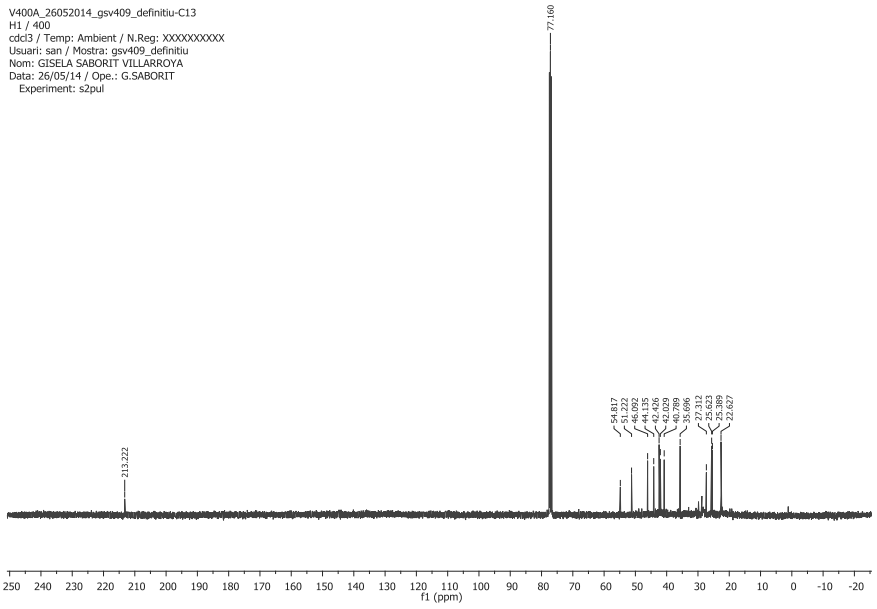
Cyclohexenone **64** (165 mg, 0.46 mmol) was treated with TFA (0.5 mL) at rt for 15 minutes. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 2 mL). The reaction flask was maintained on the rotatory evaporator at 70 ºC for 3 h to give **65** as its trifluoroacetate salt. This was dissolved in methanol (4.0 mL), Amberlyst A-26 (670 mg, 1.7 equiv) was added at 0 ºC and the mixture was stirred at rt for 2 h. Na_2SO_4 was added and the mixture was filtered and concentrated to give **60** as a red oil.

(4aRS,5SR ,8aSR, 10RS)- 10-Methylhexahydro-1H-5,8a-propanoquinolin-7(8H)-one (70)

Crude **60** was dissolved in dioxane (1.0 mL), acetone dicarboxylic acid (134 mg, 0.92 mmol, 2.0 equiv) was added and the mixture was refluxed overnight under argon. The solvent was removed and the crude was used in the next step without further purification. An analytical sample was prepared by chromatography (1→2.5→5.0→10% MeOH in CH_2Cl_2).^{1}H NMR (400 MHz, COSY) δ ^{1}H 0.87 (d, *J* = 6.0 Hz, 3H, CH_3), 1.32 (td, *J* = 13.2, 4.0 Hz, 1H, H-9ax), 1.41 (br d, *J* = 12.8 Hz, 1H, H-11), 1.64-1.68 (m, 4H, 2H-4, H-10, H-9eq), 1.79-1.89 (m, 4H, 2H-3, H-11, H-4a), 2.16 (m, 1H, H-5), 2.23 (d, *J* = 18.0 Hz, 1H, H-9ax), 2.38 (d, *J* = 17.0 Hz, 1H, H-8ax), 2.46 (dd, *J* = 18.4, 7.2 Hz, 1H, H-6ax), 2.91 (d, *J* = 17.0 Hz, 1H, H-8eq), 2.97 (br t, *J* = 12.4 Hz, 1H, H-2ax), 3.10 (br d, *J* = 12.4 Hz, 1H, H-2eq). ^{13}C NMR (400 MHz, HSQC) 22.7 (CH_3), 24.4 (C-4), 24.9 (C-3), 25.9 (C-10), 35.3 (C-5), 39.9 (C-2), 41.8 (C-9), 41.9 (C-6), 42.4

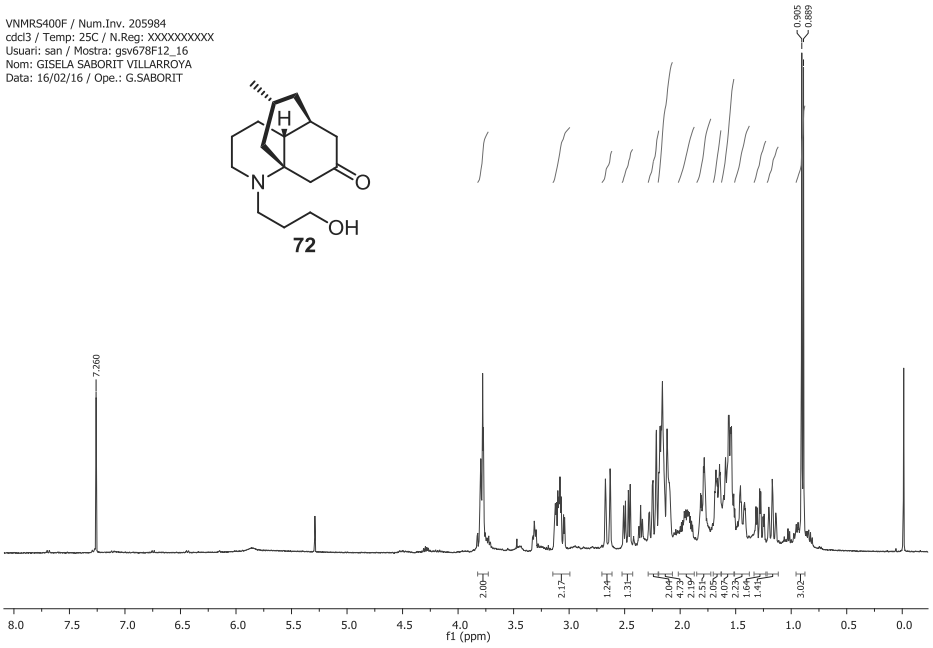
(C-4a), 44.5 (C-8), 48.6 (C-11), 56.5 (C-8a), 210.0 (C-7). HRMS calcd for $C_{13}H_{22}NO$ $(M+H)^+$ 208.1696, found 208.1699.





(4a*RS*,5*SR*,8a*SR*,10*RS*)- 1- (3-Hydroxypropyl)- 10-methylhexahydro1*H*-5,8a-propanoquinolin-7(8H)-one (72)

To the crude amine **70** in acetone (4.8 mL) was added K_2CO_3 (134 mg, 0.97 mmol, 2.12 equiv), $NaHCO_3$ (134 mg, 1.59 mmol, 3.5 equiv) followed by 3-iodo-1-propanol (71 mg, 65 µL, 0.384 mmol, 1.5 equiv) and the reaction mixture was heated at reflux overnight. After cooling to rt the solvent was removed and the crude was purified by chromatography (1→2.5→5.0→10% MeOH in CH_2Cl_2) to give known **72** (23 mg, 20%, over 4 steps) as a light yellow liquid. ^{1}H NMR (400 MHz, COSY) δ ^{1}H 0.87 (d, *J* = 6.0 Hz, 3H, CH_3), 1.19 (t, *J* = 12.4, 1.6 Hz, 1H, H-11ax), 1.29 (td, *J* = 12.0, 4.0 Hz, 1H, H-9ax), 1.45 (m, 1H, H-10), 1.55 (m, 3H, H-3), 1.65 (m, 3H, H-4a), 1.67 (masked, 1H, H-9eq), 1.80 (dt, *J* = 12.8, 2.8 Hz, 1H, H-3eq), 1.90-2.00 (m, 2H, H-4ax, 2CH_2), 2.11 (m, 1H, H-5), 2.15 (masked, 1H, H-11 eq), 2.16 (d, *J* = 16.6 Hz, 1H, H-8ax), 2.20 (masked, 1H, H-6), 2.26 (td, *J* = 12.0, 3.0 Hz, 1H, H-2ax), 2.48 (dd, *J* = 17.2, 2.4 Hz, 1H, H-6), 2.64 (dd, *J* = 16.6, 1.2 Hz, 1H, H-8eq), 3.10 (dm, *J* = 12.0 Hz, H-2eq), 3.15 (m, 2H, CH_2N), 3.78 (dd, *J* = 8.4, 2.8 Hz, 2H, CH_2OH). ^{13}C NMR (400 MHz, HSQC) 22.7 (CH_3), 25.5 (C-10), 25.8 (C-3), 25.9 (C-4), 27.9 (CH_2), 36.0 (C-5), 39.3 (C-8), 41.8 (C-9), 42.5 (C-6), 44.0 (C-4a), 46.7 (C-2), 46.8 (C-11), 48.6 (NCH_2), 59.8 (C-8a), 64.4 (CH_2OH), 212.3 (C-7). HRMS calcd for $C_{16}H_{28}NO_2$ $(M+H)^+$ 266.2115, found 266.2117.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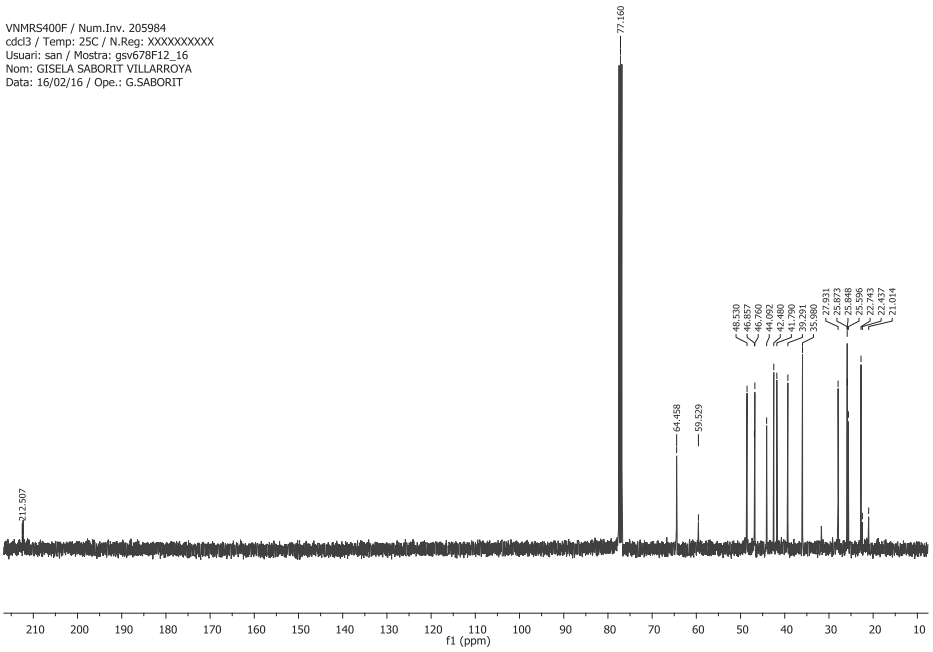
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv678F12_16
Nom: GISELA SABORIT VILLARROYA
Data: 16/02/16 / Ope.: G.SABORIT
H
N
O
OH
72
0.905
0.889
7.260
2.00
2.17
1.24
1.31
2.09
2.27
2.19
2.51
2.05
4.07
2.23
1.64
1.41
3.02
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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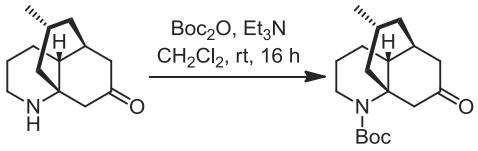
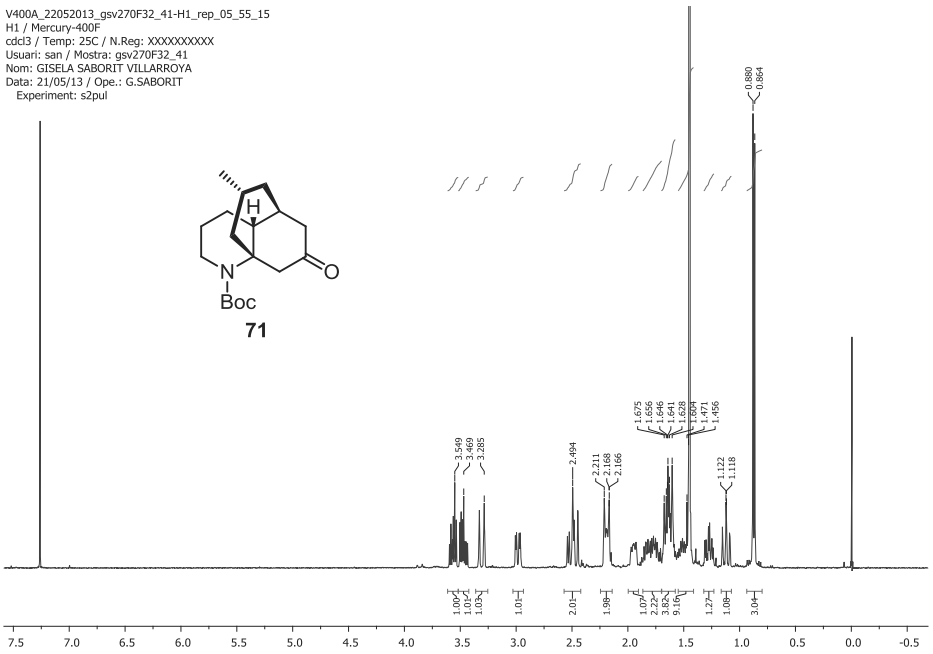
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv678F12_16
Nom: GISELA SABORIT VILLARROYA
Data: 16/02/16 / Ope.: G.SABORIT
77.160
48.530
46.857
46.760
44.092
42.480
41.700
39.291
35.980
27.931
25.873
25.668
25.596
22.743
22.437
21.014
64.458
59.529
212.507
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

(4a*RS*,5*SR*,8a*SR*,10*RS*)-1-*tert*-butyloxycarbonyl-10-methylhexahydro-1*H*-5,8a-propanoquinolin-7(8H)-one (71)



70 **71**

To a stirred solution of unpurified **70** (82 mg, 0.39 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) was added Et_3N (0.17 mL, 1.18 mmol, 3.0 equiv) followed by Boc_2O (0.13 mL, 0.552 mmol, 1.4 equiv) at 0 ºC. The resulting mixture was allowed to come to rt and stirred overnight. The solvent was removed and the crude residue was purified by chromatography (2.5→5→10% EtOAc/hexanes) to give **71** (25 mg, 20%). ^{1}H NMR (400 MHz, COSY) δ 0.88 (d, *J* = 6.4 Hz, 3H, Me), 1.12 (td, *J* = 12.6, 1.6 Hz, 1H, H-11ax), 1.28 (td, *J* = 12.8, 4.0 Hz, 1H, H-6ax), 1.45 (s, 9H, CH_3), 1.45 (masked, 1H, H-7), 1.60-1.70 (m, 3H, H-4, H-6), 1.75-1.85 (m, 2H, H-3), 1.95 (m, 1H, H-4a), 2.20 (m, 2H, H-8ax, H-5), 2.47 (d, *J* = 17.6 Hz, 1H, H-9ax), 2.51 (dd, *J* = 17.6, 5.6 Hz, 1H, H-8eq), 2.99 (ddd, 1H, *J* = 12.6, 4.0, 1.6 Hz, H-11eq), 3.31 (d, *J* = 17.6 Hz, H-9eq), 3.48 (ddd, *J* = 13.6, 9.0, 4.4 Hz, 1H, H-2ax), 3.57 (dt, J = 13.6, 5.2 Hz, 1H, H-2eq); ^{13}C NMR (100 MHz, HSQC) δ 22.6 (Me), 22.9 (C-4), 23.0 (C-3), 26.1 (C-7), 28.7 (C(*CH*$_3$)), 35.4 (C-5), 40.2 (C-2), 41.0 (C-4a), 41.9 (C-8), 42.2 (C-6), 45.9 (C-11), 46.5 (C-9), 59.8 (C-8a), 80.1 (*C*(CH_3), 155.6 (*C*ON), 211.3 (CO). HRMS calcd for $C_{18}H_{30}NO_3$ $(M+H)^+$ 308.2220, found 308.2218.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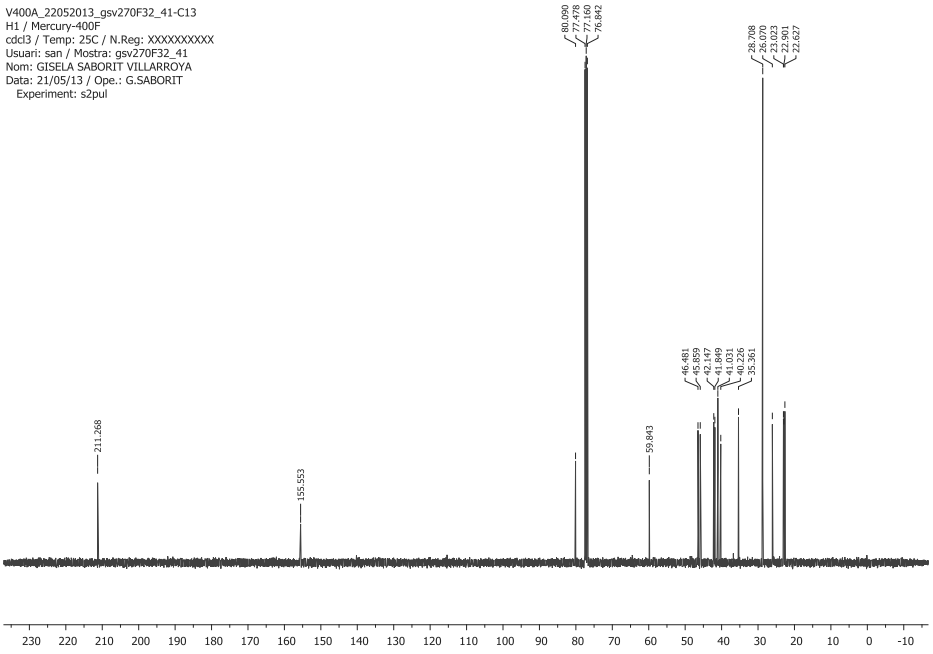
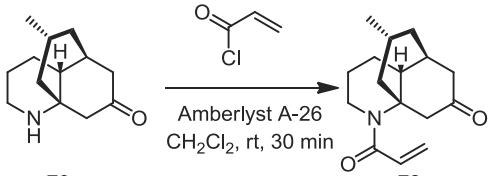
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv270F32_41
Nom: GISELA SABORIT VILLARROYA
Data: 21/05/13 / Ope.: G.SABORIT
Experiment: s2pul
H
N
Boc
O
71
0.880
0.864
3.549
3.468
3.285
2.494
2.211
2.168
2.166
1.675
1.656
1.646
1.641
1.628
1.471
1.456
1.122
1.118
1.00
1.07
1.03
1.01
2.01
1.98
1.07
2.22
2.82
9.16
1.27
1.08
3.04
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
-0.5

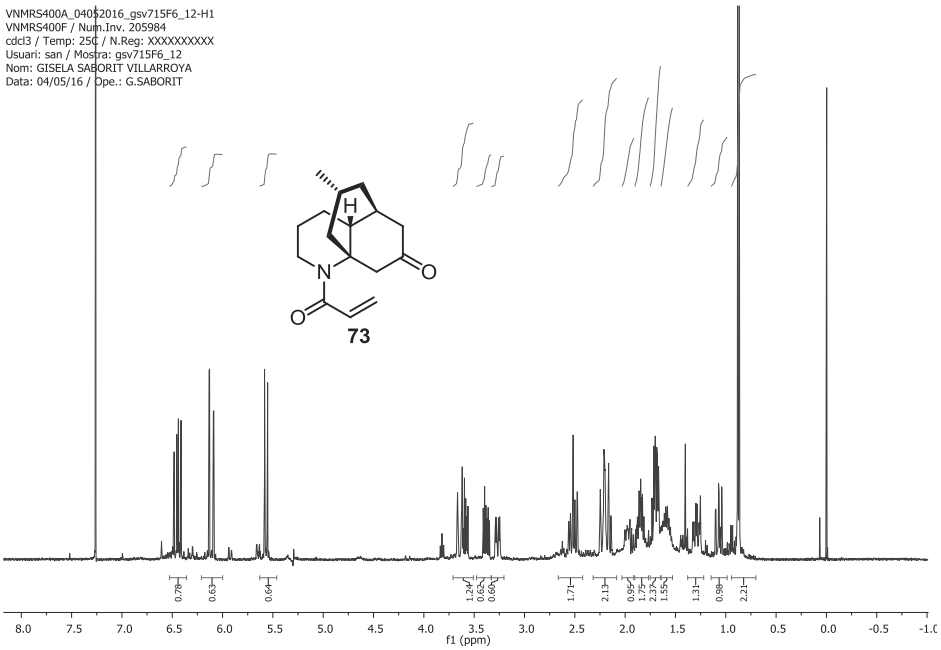

V400A_22052013_gsv270F32_41-C13
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv270F32_41
Nom: GISELA SABORIT VILLARROYA
Data: 21/05/13 / Ope.: G.SABORIT
Experiment: s2pul
80.090
77.478
77.160
76.842
28.708
26.700
23.023
22.901
22.627
46.481
45.859
43.647
41.849
41.031
40.226
35.361
211.268
155.553
59.843
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

(4a*RS*,5*SR*,8a*SR*,10*RS*)-1-acryloyl-10-methylhexahydro1*H*-5,8a propanoquinolin-7(8H)-one (73)



70 **73**

To a stirred solution of unpurified amine **70** (30 mg, 0.145 mmol) in $CHCl_3$ (0.4 mL) was added acryloyl chloride (52 mg, 47 μl, 4.0 equiv, 3 mM in CH_2Cl_2) at 0 ºC and the mixture was stirred at rt for 5 min. Subsequently, Amberlyst A26 (OH-form) (40 mg) was added and the mixture stirred for another 20 min. The resin was removed by filtration and subsequently washed with CH_2Cl_2, concentrated and purified by chromatography (CH_2Cl_2 / MeOH 0.5→1%) to give **73** (5 mg, 6% over from unpurified **70**). ^{1}H NMR (400 MHz, COSY) δ 0.88 (d, *J* = 6.0 Hz, 3H, Me), 1.05 (td, *J* = 12.4, 2.0 Hz, 1H, H-2ax), 1.29 (td, *J* = 12.0, 4.0 Hz, 1H, H-11ax), 1.56-1.65 (m, 1H, H-10), 1.65-1.75 (m, 3H, 2H-3, H-11eq), 1.85 (masked, qd, *J* = 13.0, 6.0 Hz, 2H-4), 1.95-2.00 (m, 1H, H-4a), 2.21 (br d, *J* = 17.6 Hz, 1H, H-6ax), 2.51 (dd, *J* = 17.2, 1.6 Hz, 1H, H-8ax), 3.27 (ddd, *J* = 12.6, 4.0, 1.6 Hz, 1H, H-2eq), 3.38 (dt, *J* = 14.0, 5.2 Hz, 1H, H-9ax), 3.59 (dd, *J* = 8.4 ,4.0 Hz, 1H, H-9eq), 3.64 (dt, *J* = 17.2, 4.0 Hz, 1H, H-8eq), 5.56 (dd, *J* = 10.6, 1.8 Hz, 1H, CH=C*H*$_2$), 6.13 (dd, *J* = 16.8, 1.8 Hz, CH=C*H*$_2$), 6.43 (dd, *J* = 16.8, 10.4 Hz, 1H, C*H*=CH$_2$). ^{13}C NMR (100 MHz, HSQC) δ 22.5 (CH_3), 22.7 (C-3), 23.3 (C-4), 26.1 (C-10), 35.3 (C-5), 40.9 (C-4a), 41.9 (C-9), 42.0 (C-6), 42.2 (C-11), 44.5 (C-2), 45.5 (C-8), 61.2 (C-8a), 126.3 (CH=*C*H$_2$), 132.0 (*C*H=CH$_2$), 168.3 (N*C*O), 210.7 (C-7). HRMS calcd for $C_{16}H_{24}NO_2$ $(M+H)^+$ 262.1802, found 262.1809.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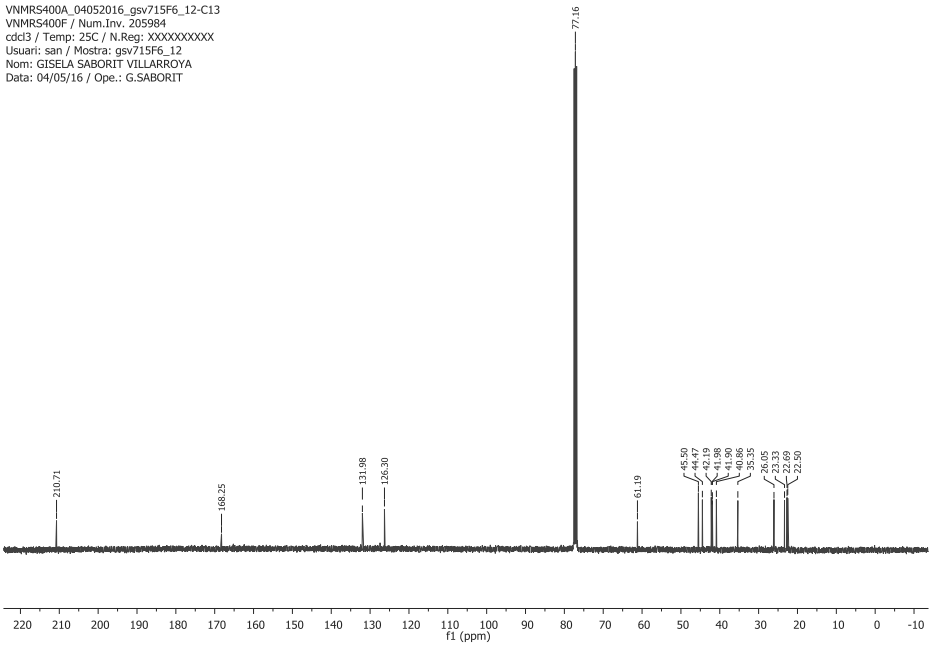
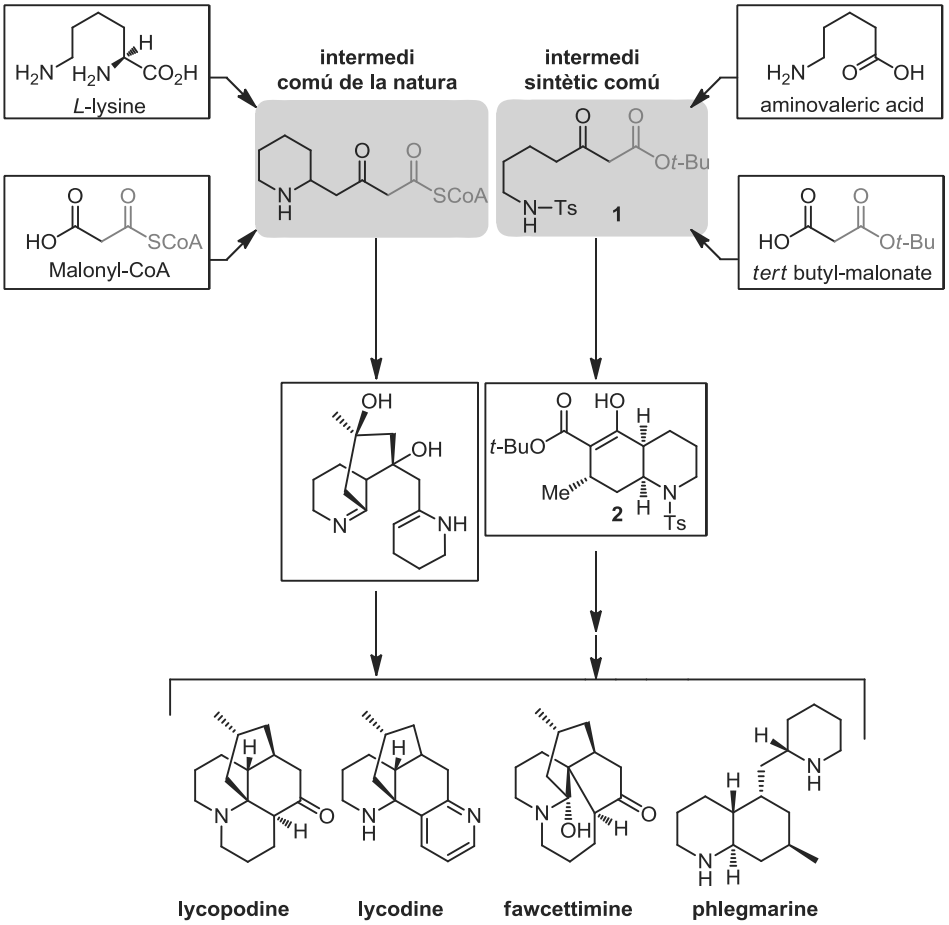
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv715F6_12
Nom: GISELA SABORIT VILLARROYA
Data: 04/05/16 / Ope.: G.SABORIT
H
N
O
O
73
0.78
0.63
0.64
1.24
0.63
0.60
1.71
2.13
0.95
1.75
2.37
1.55
1.31
0.98
2.21
f1 (ppm)


VNMRS400A_04052016_gsv715F6_12-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv715F6_12
Nom: GISELA SABORIT VILLARROYA
Data: 04/05/16 / Ope.: G.SABORIT
77.16
210.71
168.25
131.98
126.30
61.19
45.50
44.47
42.19
41.98
41.90
40.86
35.35
28.55
23.31
22.69
22.50
f1 (ppm)

Annex I: Resum en català

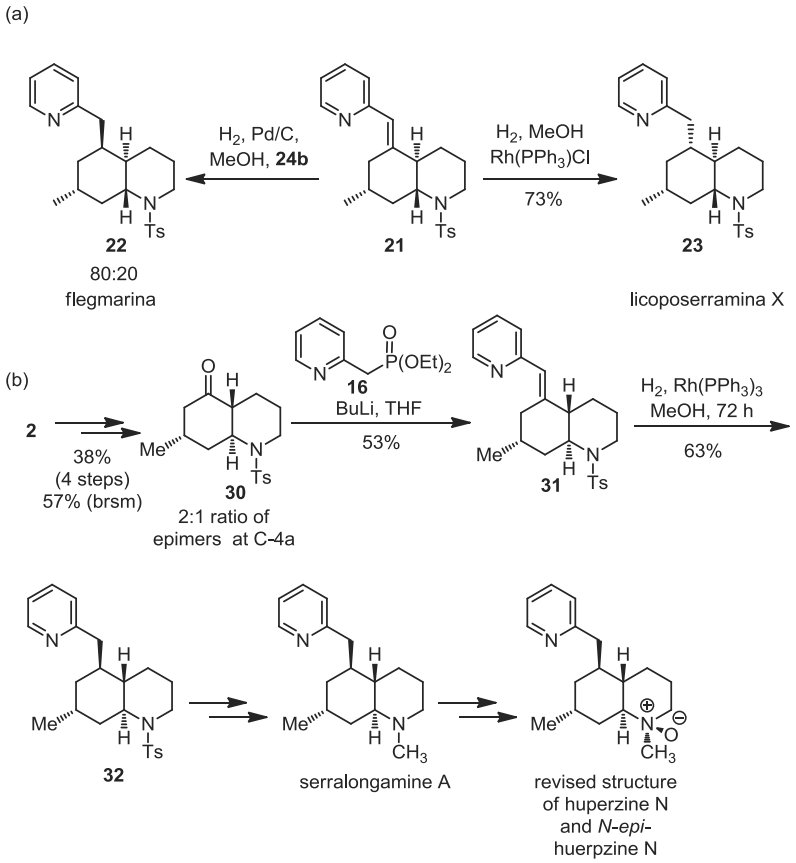
En la present tesi doctoral s'ha desenvolupat una estratègia per obtenir els esquelets dels quatre alcaloides licopodium representatius a partir d'un mateix intermedi sintètic comú **1**, de manera semblant al procés que té lloc a la natura (Esquema 1). Com que tant la licopodina, la licodina com la fawcettimina tenen una configuració diferent al C-7 de la que presenta la flegmarina s'han preparat 20 grams del compost **2** de forma racèmica i s'ha dut a terme la separació dels dos enantiòmers per HPLC preparatiu.



Esquema 1. Quatre alcaloides licopodium representatius

Per a la síntesi de la flegmarina ha sigut necessari transformar l'estructura de *cis*-decahidroquinolina de **2** en la *trans* decahidroquinolina de la flegmarina. A continuació s'ha addicionat un fosfonat de piridina i s'ha procedit a la hidrogenació de la vinil piridina en dues condicions diferents (Esquema 2a).

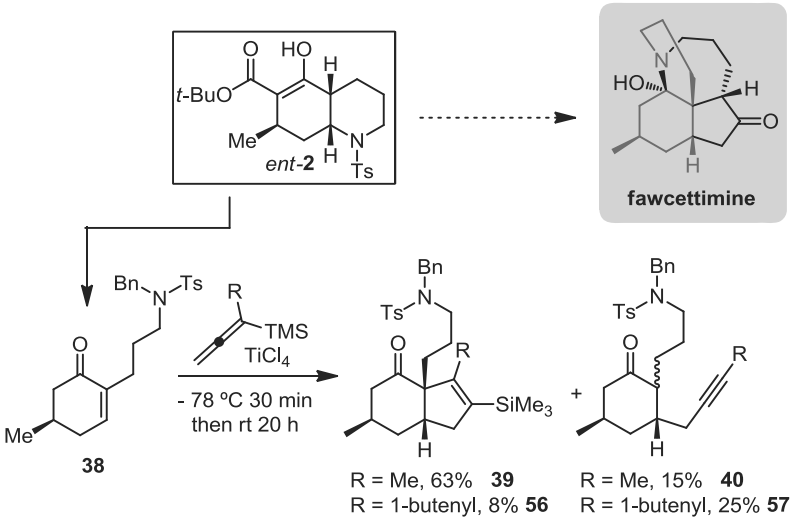
Fent servir Pd/C com a catalitzador la hidrogenació té lloc amb una diastereoselectivitat 1:1, mentre que l'addició d'un àcid fosfòric quiral provoca un augment de la diastereoselectivitat de fins a 4:1, a favor del producte de tipus flegmarina. Per contra, si la hidrogenació es fa amb el catalitzador de Wilkinson, s'obté el diastereòmer de tipus licoposerramina X amb una proporció de 1:99. Per altra banda, també s'ha pogut transformar la decahidroquinolina de tipus *cis* en el nucli de la serralongamina A i l'huperzina N.[192] La hidrogenació de la vinil piridina **31** amb el catalitzador de Wilkinson dona l'esquelet dels dos alcaloides esmentats de manera totalment diastereoselectiva. (Esquema 2b)



Esquema 2. Hidrogenació de la vinil piridina **21** en dues condicions diferents. (b) Síntesi de la serralongamina A i de la Huperzina N.

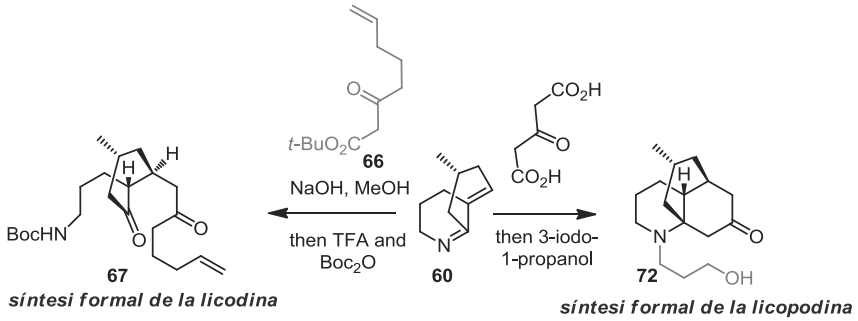
[192] (a) Saborit V, G.; Bosch, C.; Parella, T.; Bradshaw, B.; Bonjoch, J. *J. Org. Chem.* ***2016***, *81*, 2629−2634. (b) B. Bradshaw, C. Luque-Corredera, G. Saborit, C. Cativiela, R. Dorel, C. Bo, J. Bonjoch. *Chem. Eur. J.* **2013**, *19*, 13881-13892.

L'esquelet de la fawcettimina s'ha pogut preparar a partir de la reacció d'anelació de Danheiser. Tot i que l'estudi model amb un al·lè senzill va donar l'anell 6,5 amb un rendiment del 65%, l'addició d'un al·lè amb una cadena elaborada va donar l'adducte desitjat amb un rendiment del 8% (Esquema 3).



Esquema 3. Annelació de Danheiser per a la preparació del nucli 6,5 de la fawcettimina.

Finalment, s'ha arribat a una síntesi formal tant de la licopodina com de la licodina. En els dos casos s'ha aconseguit transformar l'intermedi sintètic comú en una imina α,β insaturada, necessària per a la síntesi dels dos alcaloides. Si aquesta imina es tracta amb l'àcid dicarboxílic de l'acetona seguit d'alquilació amb 3-iodo-1-propanol s'obté un precursor **72** que conté tots els àtoms de carboni de la licopodina. Alternativament, si aquest precursor es tracta amb un β-ceto ester que conté una cadena d'1-butenil **66** s'obté un intermedi sintètic **67** usat prèviament per Heathcock en la síntesi de la licodina (Esquema 4).



Esquema 4. Síntesi formal de la licopodina i de la licodina.

Annex II: Publications

CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201301715

Synthetic and DFT Studies Towards a Unified Approach to Phlegmarine Alkaloids: Aza-Michael Intramolecular Processes Leading to 5-Oxodecahydroquinolines

Ben Bradshaw,*[a] Carlos Luque-Corredera,[a] Gisela Saborit,[a, b] Carlos Cativiela,[b] Ruth Dorel,[c] Carles Bo,*[c, d] and Josep Bonjoch*[a]

Abstract: A diastereoselective synthesis of *cis*-5-oxodecahydroquinolines is described in which three stereocenters are generated in a one-pot reaction. The reaction involves a lithium hydroxide-promoted Robinson annulation/intramolecular aza-Michael domino process from an achiral acyclic tosylamine-tethered β-keto ester. The development and scope of this reaction was facilitated through the use of DFT-based mechanistic studies, which enabled the observed diastereodivergent course of the azacyclization to be rationalized. The varying stereochemistry and stability of the resulting decahydroquinolines was found to depend on whether a β-keto ester or ketone were embedded in the substrates undergoing aminocyclization. This synthetic approach gave access not only to both diastereomeric *cis*-decahydroquinolines from the same precursor, but also to the corresponding *trans* isomers, through an epimerization processes of the corresponding N-unsubstituted *cis*-5-oxodecahydroquinolines. The described methodology provides advanced building-blocks with the three relative stereochemistries required for the total synthesis of phlegmarine alkaloids.

Keywords: alkaloids · aza-Michael reaction · density functional calculations · nitrogen heterocycles · stereoselective synthesis

Introduction

Phlegmarine alkaloids, belonging to one of the four classes of *lycopodium* alkaloids,[1] are structurally characterized by the presence of a 5,7-disubstituted decahydroquinoline ring and a $C_{16}N_2$ skeleton. The substitution pattern, based on a methyl group at C(7) and a (2-piperidyl)methyl side chain at C(5), and the type of ring fusion (*trans*[2] or *cis*[3]) show a variety of stereochemical arrangements, as depicted in Figure 1. This basic phlegmarine nucleus provides the biogenetic template for all *lycopodium* alkaloids, including those of the three main classes (lycopodine, lycodine, and fawcettimine; Figure 2a), as well as others that retain the decahydroquinoline nucleus (Figure 2b).[4] In common with most *lycopodium* alkaloids, those of the phlegmarine type have wide-ranging biological activities, with particular potential for the treatment of neurogenerative diseases.[5]

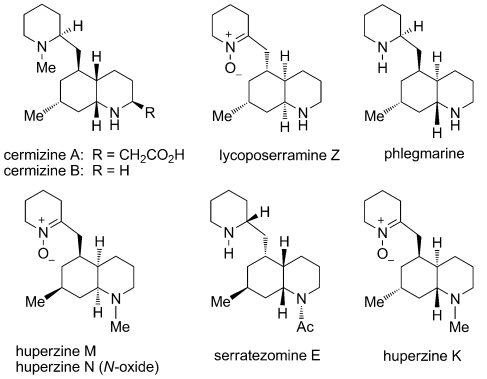


Figure 1. Phlegmarine alkaloids with a *cis*-decahydroquinoline core and two examples bearing a *trans*-decahydroquinoline.

In this full report, we disclose our synthetic studies towards 5-oxodecahydroquinolines[6–8] in which our aim was to develop a unified approach to the phlegmarine alkaloids.

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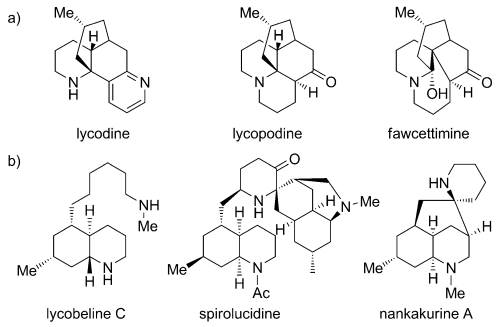
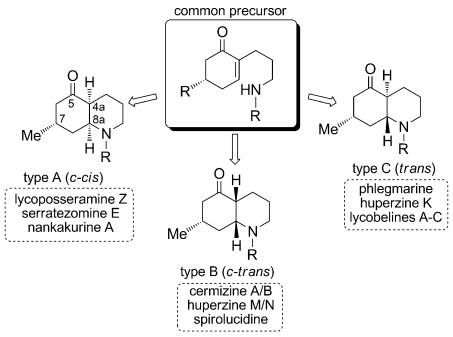


Figure 2. a) The main *Lycopodium* alkaloid groups biogenetically derived from *trans* phlegmarines. b) *Lycopodium* alkaloids derived from phlegmarines with retention of the decahydroquinoline ring system.

Theoretical data obtained by DFT-based calculations shed light on the stereochemical processes and allowed us to propose reaction mechanisms that explain the experimental results.

The highly diverse phlegmarine alkaloids can be divided into three main types, which we have designated A–C[9] based on the relative orientation of the 7-methyl group and the ring fusion hydrogen atoms (Scheme 1). We planned to

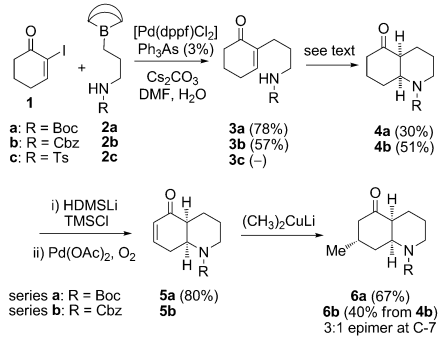


Scheme 1. Postulated unified approach to the various 5-oxodecahydroquinoline nuclei from a common intermediate through an aza-Michael reaction.

use a monoprotected amine-tethered cyclohexenone[10,11] as the common precursor, which would give access to the three types of relative configuration between C(4a), C(7), and C(8a) through control of an intramolecular aza-Michael reaction[12] or subsequent isomerization of the resulting products. Moreover, a conformationally controlled process would also provide access to both configurations at the stereogenic center at C(5).[13]

Results and Discussion

Preliminary approach: We initially studied the formation of the target *cis*-5-oxodecahydroquinoline through an aminocyclization process from an N-protected 2-(3-aminopropyl)-cyclohex-2-enone lacking the methyl group in the carbocyclic ring. We hoped to use this achiral substrate to generate the product in enantiopure form through an asymmetric organocatalyzed reaction.[14] Subsequent dehydrogenation and conjugate addition upon the resulting enone would then introduce the required methyl substituent at C(7) (Scheme 2).



Scheme 2. Synthesis of 7-methyl-5-oxodecahydroquinolines (type A).

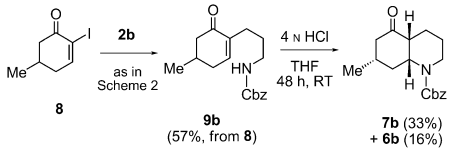
The required enone starting materials for the study were prepared by using a Suzuki coupling under Trost reaction conditions[15] between 2-iodocyclohex-2-enone (**1**)[16] and the 9-borabicyclo[3.3.1]nonane (9-BBN) alkyl derivatives **2**, formed from the corresponding N-protected allylamines.[17] The 2-substituted cyclohex-2-enones **3a** and **3b** were formed in 78 and 57% yield, respectively,[18] but the tosyl-protected enone **3c** was not formed under these conditions. With the substrates in hand, the aza-Michael cyclization was investigated. Exposure of **3a** to a wide range of conditions known to promote aza-Michael reactions[19] proved unfruitful (see the Supporting Information, Table S1). A moderate amount of cyclized product was obtained by using a phase transfer process (K_2CO_3, $TBAHSO_4$, NaOH, benzene),[20] with *cis*-decahydroquinoline **4a** being isolated in 30% yield. However, it was observed that the resulting product was unstable, readily undergoing a retro aza-Michael reaction upon silica chromatography.

A variety of conditions were also investigated for the analogous Cbz-protected derivative **3b** with equally disappointing results. Although no cyclized product was observed under several basic or acidic conditions,[21] exposure of **3b** to a 4 N HCl solution in THF at room temperature for 48 h gave azabicyclic compound **4b** in 51% yield. Again, the cyclized product was unstable, although it was separable from the ring-opened product by rapid chromatography on alumina.

In an endeavor to develop an asymmetric version of the process, cyclization of Boc-protected derivative **3a** was attempted with a wide range of organocatalysts, including primary and secondary amines, chiral phosphoric acids, and phase-transfer catalysts. However, in no case was any cyclized product observed.

Despite the poor yields, we had sufficient amounts of substrates to study the stereochemical course of the process that leads to a 7-methyl substituted derivative. Regioselective conversion of ketone **4a** into its less substituted silylenol ether (not depicted), followed by its oxidative conversion by a catalytic Pd^{II}-based Saegusa reaction,[22] gave α,β-unsaturated ketone **5a** (Scheme 2). The conjugate addition to install the methyl group at C-7 was diastereoselective, with **6a** being isolated in 67% yield in a kinetically substrate-controlled reaction. The resulting ketone **6a**[23] showed a "type A" stereochemistry, corresponding to that found in lycoposerramine Z. Following the same reaction sequence for the N-Cbz derivative **4b**, the process proved to be less diastereoselective, giving decahydroquinoline **6b** and its epimer at C-7 (**7b**) in a 3:1 ratio (40% overall yield).[24]

To evaluate the aza-Michael cyclization process with starting material bearing the methyl group, we prepared compound **9b**[10] from 2-iodo-5-methylcyclohex-2-enone (**8**) by a cross-coupling reaction analogous to that described above (Scheme 3). Exposing **9b** to the same acid conditions as the



Scheme 3. Aza-Michael cyclization of cyclohexenone **9b**. Access to type B stereochemistry.

desmethyl analogue **3b** gave decahydroquinoline **7b** as the main product, the relative stereochemistry ("type B") of which differed from that previously observed when the methyl group was installed after the cyclization step.

Once again, cyclized compound **7b** proved to be relatively unstable, and easily entered into equilibrium with the open-chain enone derivative. These initial synthetic studies enabled us to determine the NMR pattern for the two types of *cis*-decahydroquinolines (A and B) bearing an electron-withdrawing substituent on the nitrogen atom, which facilitated the determination of the diastereomer ratio in the reaction mixtures. Figure 3 depicts the structures (relative configuration and preferred conformation) of the synthesized diastereomeric *cis*-decahydroquinolines **6b** and **7b**, with their stereochemistry elucidated on the basis of 2D NMR spectra (COSY, HSQC).

The twin chair conformation with the nitrogen substituent occupying an equatorial position on the carbocyclic ring is the lowest energy conformation for these *N*-Cbz substituted *cis*-decahydroquinolines; in this conformation the axial

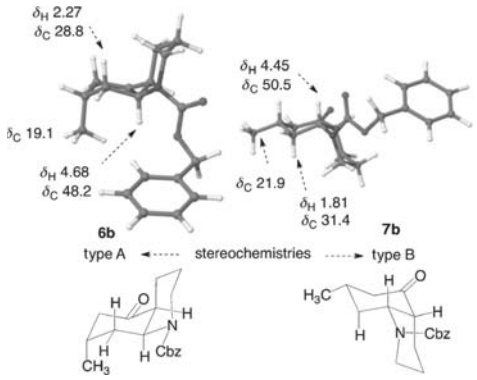


Figure 3. Conformational preference of decahydroquinolines **6b** and **7b** determined on the basis of NMR spectroscopic data, showing type A and type B stereochemistries.

proton H-8a is strongly coupled to axial H-8. Hence, its resonance signal appears as a deceptively simple doublet ($J=13.0$ Hz) of triplets ($J=5.2$ Hz), centered at $\delta=4.68$ and 4.45 ppm for **6b** and **7b**, respectively. At the same time, this multiplicity ensures the *cis* ring fusion in both isomers and also corresponds to a *cis* 1,3-relationship between H-8a and the axial methyl group at C-7 in **6b**, which promotes a compression, deshielding the chemical shift of H-8a. Additionally, **6b** and **7b** are clearly differentiated by two NMR features: 1) the ^{1}H NMR chemical shift of H-8_{ax}, which appears more deshielded ($\delta=2.27$ ppm) in **6b** than in **7b** ($\delta=1.81$ ppm), due to its antiperiplanar location with respect to the axially located methyl group, and 2) the ^{13}C NMR chemical shift of the Me group, which is shifted more upfield ($\delta=19.1$ ppm) in **6b** than in **7b** ($\delta=21.9$ ppm), an effect that is also observed in C-8a ($\delta=48.2$ and 50.5 ppm, respectively).

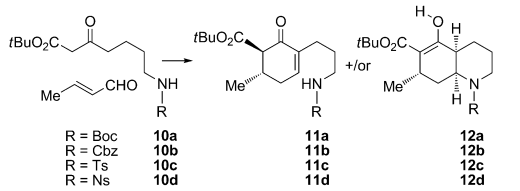
Although these initial studies allowed access to two of the desired stereochemistries of the phlegmarine alkaloids, the low yields and unstable nature of the intermediates made us consider a modified synthetic strategy.

Revised synthetic approach: access to type A 5-oxodecahydroquinolines: We believed it might be possible to prepare the required substrate for cyclization directly through a Robinson annulation procedure from a suitable keto ester bearing a nitrogen-protected tether (i.e., **10**). We also hoped that such a method would facilitate access to compounds such as **11**, bearing more varied nitrogen protecting groups, some of which are not available by palladium cross-coupling. Furthermore, because the Robinson annulation can be carried out in either basic or acidic media, it opened the possibility of forming the cyclohexenone and decahydroquinoline in a single step.

We began by synthesizing a range of β-keto ester intermediates **10a–d** by protection of 5-aminovaleric acid and subsequent homologation with *tert*-butyl malonates (see the Supporting Information). Michael addition of the carbamate- and sulfonamide-tethered β-keto esters **10a–d** to cro-

tonaldehyde under a range of conditions[25] gave low yields of the corresponding Michael adduct (not shown). Moreover, subsequent cyclization under acid conditions (TsOH, toluene)[26] resulted in complete decomposition of the starting materials. However, upon treatment of keto esters **10a** and **10b** with KO*t*Bu in *t*BuOH,[27] in the presence of crotonaldehyde, we were pleased to observe the formation of the Robinson cyclization products **11a** and **11b**, respectively, although the corresponding aza-Michael cyclized products **12a** and **12b** were not detected at all (Table 1, entries 1 and 2). Satisfyingly, treatment of the corresponding tosyl analogue **10c** under the same conditions not only gave the Robinson annulation product **11c**, but also moderate amounts of the ester-bearing aza-Michael product **12c** (entry 3). Most notably, this product bore the same relative *cis* stereochemistry as **6a** (type A) and opposite to that formed under the equilibrating thermodynamic conditions used for **7b** above. Moreover, unlike the analogous 5-oxodecahydroquinolines **6b** and **7b**, the product was completely stable during silica chromatography, with no retro aza-Michael product being observed, even on prolonged standing. Other conditions were screened to examine whether the reaction could be driven to completion and exclusively achieve the cyclized product **11c**. A comparable result was obtained by using the nosyl derivative **10d** (entry 4). The use of 10% LiOH in *i*PrOH[28] (entry 5) gave predominantly the undehydrated Robinson aldol product. However, increasing the quantity of LiOH to two equivalents led to improved formation of **12c** at room temperature (entry 6). Under these new conditions, we studied the cyclization of keto esters **10a**, **10b**, and **10d**, bearing Boc, Cbz and Ns activating groups, respectively (entries 7–9). However, all performed significantly worse than the tosyl-bearing keto ester **10c**. Notably, carbamate-protected substrates Cbz and Boc, in line with the previously employed conditions using KO*t*Bu, gave only the Robinson adduct, albeit in low yields and accompanied by significant quantities of the undehydrated Robinson aldol product.

Table 1. Screening conditions for one-pot Robinson aza-Michael reaction.[a]

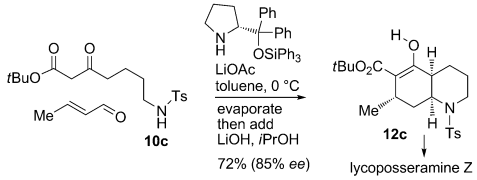


R = Boc **10a** **11a** **12a**
R = Cbz **10b** **11b** **12b**
R = Ts **10c** **11c** **12c**
R = Ns **10d** **11d** **12d**

Entry	R	Reagents ([equiv])	Solvent	Product (yield [%])[b]
1	Boc	KO*t*Bu (0.3)	*t*BuOH	**11a** (55)
2	Cbz	KO*t*Bu (0.3)	*t*BuOH	**11b** (63)
3	Ts	KO*t*Bu (0.3)	*t*BuOH	**11c** (50), **12c** (34)
4	Ns	KO*t*Bu (0.3)	*t*BuOH	**11d** (29), **12d** (41)
5	Ts	LiOH·H_2O (0.1)	*i*PrOH	n.d.[g]
6	Ts	LiOH·H_2O (2)	*i*PrOH	**11c** (5), **12c** (57)
7	Boc	LiOH·H_2O (2)	*i*PrOH	**11a** (18)
8	Cbz	LiOH·H_2O (2)	*i*PrOH	**11b** (21)
9	Ns	LiOH·H_2O (2)	*i*PrOH	**11d** (19), **12d** (27)
10	Ts	TBAH[c](0.4)/KOH_{aq}	Et_2O/THF	**11c** (20), **12c** (65)
11	Ts	TBAH[c] (0.4)/$LiOH_{aq}$	Et_2O/THF	**11c** (12), **12c** (71)
12	Ts	LiOH (2)	*i*PrOH	**11c** (10), **12c** (60)
13	Ts	LiOH (5)	*i*PrOH	**11c** (16), **12c** (38)
14	Ts	LiOH (1)	*i*PrOH	**11c** (10), **12c** (44)
15	Ts	LiOH·H_2O (1)	*i*PrOH	**11c** (8), **12c** (60)
16	Ts	LiOH·H_2O (1)[d]	*i*PrOH	**11c** (6), **12c** (46)
17	Ts	LiOH·H_2O (1)[e]	*i*PrOH	**12c** (78)
18	Ns	LiOH·H_2O (1)[e]	*i*PrOH	**12d** (47)
19[f]	Ts	LiOH·H_2O (1)[e]	*i*PrOH	**12c** (72)

[a] All reactions were carried out at room temperature for 24 h with 1.1 equiv of crotonaldehyde unless otherwise stated; [b] yield refers to the products isolated by flash chromatography; [c] TBAH refers to 40% nBu_4NOH in H_2O; [d] crotonaldehyde (2 equiv) was used; [e] H_2O (10 equiv) was added; [f] using an organocatalyst, see Scheme 4; [g] n.d. = not determined.

Finally, with the optimized conditions in hand, we found that using an appropriate organocatalyst for the initial Michael step rendered the process asymmetric (Table 1, entry 19 and Scheme 4). From enantiopure decahydroquinoline **12c**, we have recently reported the total synthesis of phlegmarine alkaloid lycoposerramine Z.[6a]



Scheme 4. Formation of **12c** in asymmetric form using organocatalysis.

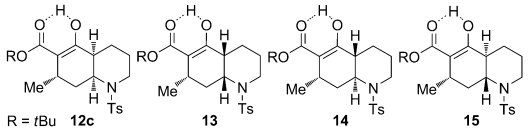
As can be seen from these results, when the ester was present, the aza-Michael intramolecular reaction gave exclusively compounds with a *cis* (type A) stereochemistry. This was the reverse of the stereochemical result obtained

when the cyclohexenone moiety underwent an intramolecular aza-Michael process, which led predominantly to type B compounds.

A number of key questions remained to be answered: 1) Why did the ester reverse the stereochemistry of the ring fusion hydrogen atoms? 2) Compared with the initial studies, for example, **9b**→**7b**, why did the carbamates not cyclize in the presence of the ester? 3) Why did the carbamates give very low yields of the Robinson cyclization product (the process stopped at the aldol stage) using conditions that gave excellent results for the tosylamides?

Relative stability of the diastereomers: To shed light on the diastereoselectivity of the intramolecular aza-Michael processes, calculations were undertaken to examine the role played by the β-keto ester group in these cyclizations. The calculations were done not only on molecules in the gas phase but also by using an implicit solvent model, and we found that the inclusion of solvent effects did not significantly change the order of relative energies. The structures of the four possible diastereomers (**12c** and **13**–**15**) and their tautomers were optimized and their relative energies (see Table 2) fully justified the reactivity observed, the most stable being the one detected experimentally (i.e., β-keto ester **12c**). As can be seen, **12c** in its keto form, was the least stable of the possible structures, but in enolic form it was the most stable compound. Notably, β-keto ester **12c**, with the axial methyl group at C-7, was thermodynamically more stable than the absent epimer with the methyl substituent located equatorially. We postulated that the bulky *tert*-butoxycarbonyl group located on the same plane as the equatorial methyl substituent at C-7 would result in steric crowding, thereby precluding the formation of its epimer at C-7 (i.e., **13** in Table 2) in the cyclization process.

Table 2. Relative and free energies in the gas phase and in solution (water) for the keto and enol tautomers of the four stereoisomers **12c** and **13**–**15** (R = *t*Bu).[a]

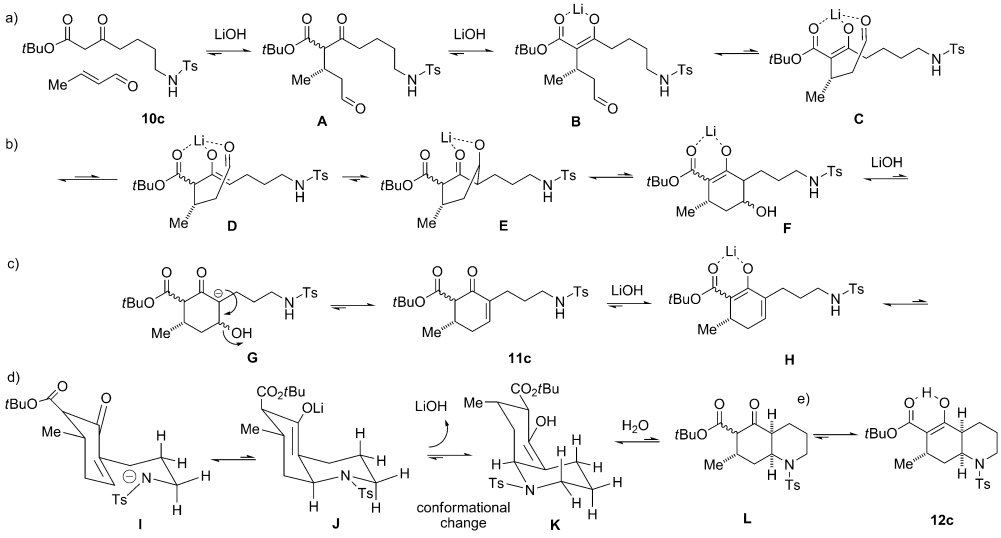


	12c		13		14		15	
	keto	enol	keto	enol	keto	enol	keto	enol
E (gas phase)	12.9	0.0	12.1	1.2	9.3	2.3	6.8	4.9
G (gas phase)	11.2	0.0	10.2	1.0	7.3	2.9	5.5	4.4
E (sp solv)	8.2	0.0	8.2	1.7	5.6	2.6	2.6	4.6
G (solv)	5.4	0.0	5.7	1.4	3.5	2.7	1.4	4.0

[a] All values in kcal mol^{-1}.

Understanding the reaction mechanism: To understand the mechanism of the reaction and fully determine its scope for accessing other stereochemistries, extensive DFT-based studies were carried out. Based on the experimental results, we proposed a plausible mechanism for the reaction **10c** to **12c**, which was then refined and corroborated by DFT modeling studies (Scheme 5).

Formation of the correct enolate: Michael reaction between keto ester **10c** and crotonaldehyde gave coupled product **A**, which was further deprotonated to furnish lithium enolate species **B**, effectively preventing the Robinson annulation



Scheme 5. Overview of the Michael reaction, intramolelcular aldol, and intramolecular aza-Michael cascade biscyclization process leading to 5-oxodecahydroquinolines based on experimental and DFT modeling studies.

from progressing. Indeed, the relative stability of the two possible lithium enolates, in which the two carbonyl groups coordinate to the cation, indicated that the enolate in the most acidic position is the most stable species by 12.8 kcal mol^{-1} and thus the required enolate would not be formed (Figure 4, top).

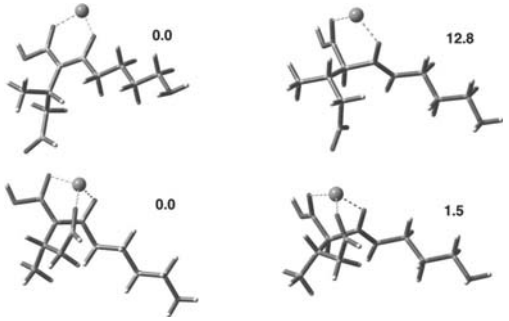


Figure 4. Optimized structures and relative free energies (kcal mol^{-1}) including solvent effects (*i*PrOH) for the two possible enolates, with two or three carbonyl groups coordinated to Li^+.

However, it was thought that the carbonyl group on the side chain could play a role in facilitating the formation of the target enolate. To check this hypothesis, we considered the structures of the two possible enolates, which had three carbonyl groups coordinated to the lithium cation, and determined their relative free energies; these are depicted in Figure 4 (bottom). The enolate in the most acidic position becomes less stable, and the difference in stability between the two possible lithium enolates was only 1.5 kcal mol^{-1}. This would account for the formation of the enolate at the less acidic position, which would allow the proposed mechanism to take place.[30]

Aldol reaction: Once the required regiospecific enolate is formed, the aldol reaction can take place to give the alkoxide species **E**. However, proton transfer to the alkoxide from the keto ester reforms the more stable enolate **F**, effectively halting the reaction once again.

*Elimination to cyclohexenone **11c***: A small quantity of the least stable enolate (**G**) present at equilibrium undergoes dehydration to give enone **11c**. Deprotonation of the keto ester again prevents the reaction from progressing by forming the more stable enolate **H**.

Aza-Michael reaction and protonation: A small amount of enone **I** present at equilibrium is attacked from the top face to give aza-Michael addition product intermediate **J**, which immediately undergoes protonation and a ring flip to form **K**. In the changed conformation the methyl group is located in the axial position. The presence of water favors the formation of **L** by providing a ready source of protons to trap intermediate **K** before the retro aza-Michael product can revert back to the ring-opened product **11c**.

Formation of the enol tautomer: Finally, formation of the hydrogen bond between the enol form and the ester group effectively locks the molecule, driving the reaction to completion and ensuring the stability of **12c**.

Thus, the tandem reaction would appear to be a series of sequential equilibria, the vast majority of which are unfavorable. Only the last step, in which the enol of **12c** is formed (see Figure 6), is favorable, and indeed crucial, because it pushes the equilibrium over to the completion of the reaction.

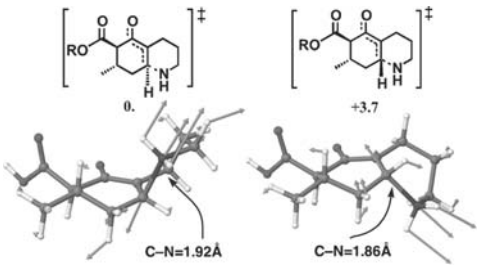


Figure 5. Molecular structures for models (R = H) of the transition states of the two possible pathways of the cyclization step in which the bicyclic system is formed, generating the C4a stereocenter. Relative free energy in kcal mol^{-1}.

This overall mechanism would explain why the reactions using carbamate derivatives (i.e., **10a** or **10b**), which do not undergo the intermolecular aza-Michael reaction, are mostly halted at step (b), giving intermediates analogous to **F**. Only when the unfavorable equilibrium is overcome by using KO*t*Bu under forcing reflux conditions is the cyclohexenone (i.e., **11a** or **11b**) obtained. However, the poor nucleophilicity of the carbamate is not sufficient to overcome the **H**→**J** step leading to the decahydroquinoline ring.

Determination of stereochemistry at C4a and C8a by DFT calculations: The configuration of the C4a and C8a stereocenters is determined in subsequent steps, namely the second cyclization (**11c**→**K**) for C4a, and tautomerization (**K**→**L**) for C8b. As depicted in Scheme 5, the second cyclization appears to evolve through a series of intermediates (**H**, **I**, and **J**), in which LiOH plays a crucial role in the formation of lithium enolate species and deprotonation of the tosylamide moiety. Modeling such a complex process would require explicitly taking into account some water molecules, thus increasing the degrees of freedom of the system. Instead of wasting efforts trying to define a more realistic model that would be more difficult to handle, we decided to simplify the problem and study this step with $-NH_2$ instead of NHTs. We determined the structure and relative stability of the two possible transition states corresponding to nucleophilic attack of the amine on the alkene C atom. These

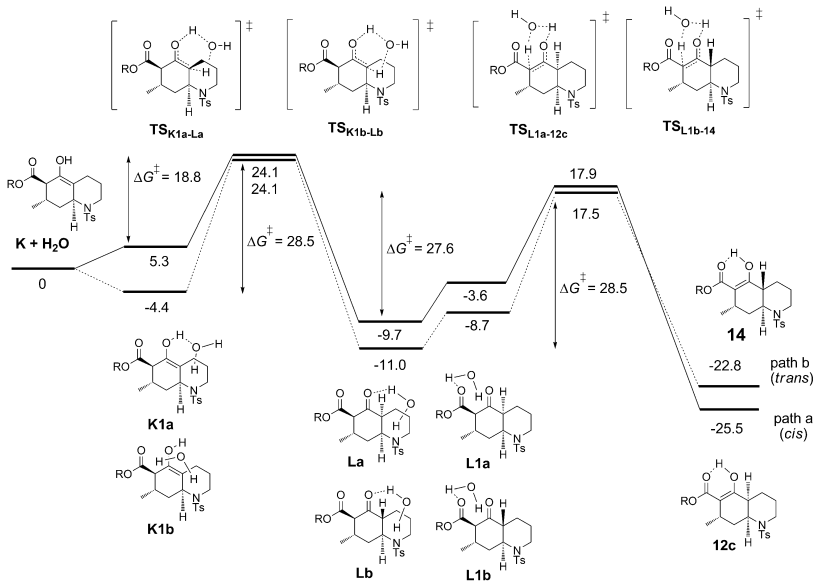


Figure 6. Reaction free energy profile for the water-assisted proton transfer steps from **K** to **12c**, for R = H. All values in kcal mol^{-1}.

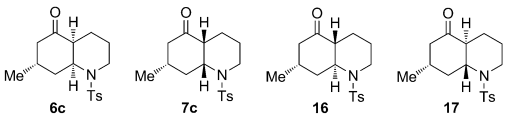
structures are collected in Figure 5, together with the relative free energy, and with arrows on each atom contributing to the unique imaginary vibrational normal mode. Note that major contributions arise from the NH_2 and C atom involved in the C–N bond-forming process. The most stable transition state corresponds precisely to the product with the stereochemistry observed at C4a, the transition state corresponding to the attack on the opposite face of the alkene being 3.7 kcal mol^{-1} higher in energy.

The generation of the second stereogenic center C8a through **K**→**L** tautomerization also takes place diastereoselectively. We studied this elementary proton transfer in detail, as well as the subsequent **K**→**12c** tautomerization. Interestingly, we found that at least one water molecule had to be present to assist proton transfer, otherwise the computed energy barriers were too high (+65 kcal mol^{-1}; see Figure S2 in the Supporting Information).[31]

The requirement for water is in accordance with the experimental observation of an increased reaction rate in the presence of water. As shown in Figure 6, path *a*, which leads to the experimentally observed *cis* product, requires the assisting water molecule to lie below the molecular plane, whereas in path *b* the proton transfer occurs at the top face of the enol double bond. The results shown in Figure 6 indicate that path *a* is preferred, both kinetically and thermodynamically, and this leads to the most stable product **12c**. Starting at **K**, in both reaction paths, an adduct with water (**K1a**/**K1b**) is formed first, the adduct from path *b* being more stable. The first transition states, TSK-L, lie at the same energy level, thus the barrier for path *a* is lower. The same occurs in the second step. Intermediates in path *b* are more stable than those in path *a* and, because the differences in the transition states are negligible, the free energy barrier also becomes lower.

Access to 5-oxodecahydroquinolines of type B: Having designed an effective strategy to achieve decahydroquinolines with the type A relative stereochemistry (Scheme 1), we turned our attention to generating type B products. The formation of type B stereochemistry had already proven feasible through an aza-Michael cyclization of a precursor lacking an ester group in the Cbz series (**9b**→**7b**; Scheme 3). To show that this trend continued across the tosylamine series, the thermodynamic stability of *N*-tosyl-5-oxodecahydroquinolines lacking the ester group was also determined. Table 3[32] shows the relative and free energies of *cis* com-

Table 3. Relative energies and free energies in gas phase and in solution (water) for the keto and enoltautomers of the four stereoisomers **6c**, **7c**, **16**, and **17**.

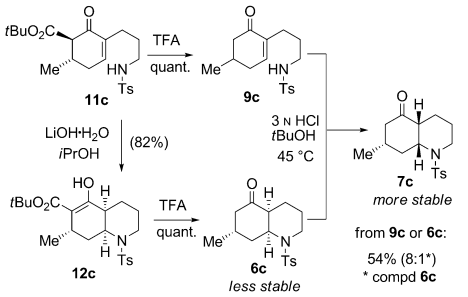


	6c		**7c**		**16**		**17**	
	keto	enol	keto	enol	keto	enol	keto	enol
E (gas phase)	0.8	9.9	0.0	9.5	3.6	14.4	5.6	13.5
G (gas phase)	0.5	9.2	0.0	8.9	2.9	13.4	5.2	12.8
E (sp solv)	0.8	10.6	0.0	10.5	3.6	14.6	4.6	14.0
G (solv)	0.9	11.0	0.0	10.8	2.8	14.2	4.4	13.3

[a] All values in kcal mol^{-1}.

pounds **6c** and **7c**, and the *trans* isomers **16** and **17**, with the four relative configurations, as well as those of their corresponding tautomers. These calculations confirmed that, in line with the cyclization of the Cbz analogue **9b** leading to **7b**, the corresponding *N*-tosyldecahydroquinoline **7c**, lacking the ester group and with a type B stereochemistry, becomes the most thermodynamically stable compound. Moreover, these data reinforce the key role played by the ester in favoring the type A stereochemistry, which has been experimentally observed.

Synthetic studies: Two routes were investigated for the formation of decahydroquinoline **7c**. Treatment of β-keto ester **11c** (Table 1, entry 3) with neat trifluoroacetic acid (TFA) quantitatively provided tosylamine-tethered cyclohexenone **9c** (Scheme 6). Acid treatment of **9c** gave the cyclized compound **7c**, corresponding to the thermodynamic compound, along with small quantities of **6c** and recovered starting material. The optimized structures for **6c** and **7c** are shown in Figure 7. In fact, according to our calculations, the difference in energy between **7c**, **6c**, and **9c** favors **7c** by only a few kcal mol^{-1}, although when the internal degrees of freedom are taken into consideration, in free energy terms, **9c** becomes the most stable species due to the formation of an intermolecular hydrogen bond between the ketone and the sulfonamide hydrogen (see Table S2 and Figure S3 in the Supporting Information).



Scheme 6. Aza-Michael cyclization of enone **9c**, obtained either from **11c** or **6c**, to decahydroquinoline **7c**. Access to type B relative stereochemistry.

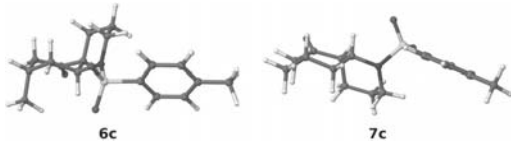


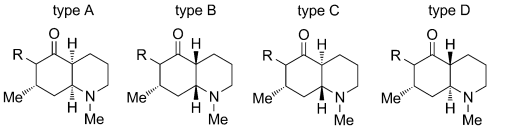
Figure 7. DFT optimized structures for *cis*-decahydroquinolines **6c** (left) and **7c** (right).

Alternatively, treatment of β-keto ester **12c** (Table 1, entry 17) with neat TFA quantitatively provided decahydroquinoline **6c**, which, although thermodynamically less stable than **7c**, was sufficiently stable to be isolated without undergoing isomerization in the process.

Interestingly, as expected, the developed domino reaction conditions (LiOH·H_2O, *i*PrOH, Table 1, entry 17) applied to cyclohexenone **11c** gave **12c**, but when applied to enone **9c** only trace amounts of the intramolecular aza-Michael product **7c** were obtained.

Access to 5-oxodecahydroquinolines of type C: After the exhaustive synthetic and mechanistic studies on the diastereoselectivity of the process, only the *cis* decahydroquinoline structures were observed, both experimentally and by calculations, in compounds bearing a carbamate or sulfonamide group. Thus, type C compounds with a *trans* stereochemistry at the ring junction (corresponding to natural products such as phlegmarine/huperzine Z) would not be accessible through aza-Michael cyclization of compounds with an electron-withdrawing group on the nitrogen atom (i.e., **9** or **11**). However, taking into consideration literature precedents[33] and our own studies on related compounds and octahydroindoles,[34] it seemed possible that this third group of structures with a *trans* ring fusion might be accessed by interchanging the nitrogen-substituent group. To test this supposition, the thermodynamic stability of the different possible diastereomers bearing a methyl group was studied. Indeed, it was found that when the lone nitrogen pair was not delocalized, the relative stability was strongly affected and the *trans* isomer became the most stable diastereoisomer (see Table 4).

Table 4. Relative energies ΔE and free energies ΔG in the gas phase and solution (water) for the enol tautomers of β-keto esters **18**–**21** and keto tautomers of ketones **22**–**25** (amine nitrogen in all cases).

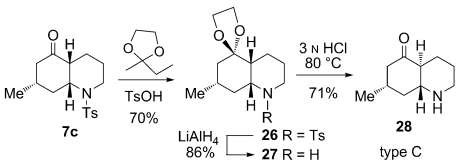


18 R = CO_2tBu
22 R = H
19 R = CO_2tBu
23 R = H
20 R = CO_2tBu
24 R = H
21 R = CO_2tBu
25 R = H

	18	**22**	**19**	**23**	**20**	**24**	**21**	**25**
E (gas phase)	2.6	4.3	1.9	3.6	1.0	0.0	0.0	1.6
G (gas phase)	2.7	5.4	2.3	2.7	0.9	0.0	0.0	1.7

[a] All values in kcal mol^{-1}.

Charged with this insight as proof of concept, we then focused on an experimental realization of *trans*-5-oxodecahydroquinoline synthesis. Due to the propensity of 2-(3-aminopropyl)cyclohex-2-enones to undergo 1,2- rather than 1,4-addition,[35] we proposed that removal of the tosyl group from a cyclized compound and a simple isomerization at C-4a would be the most effective way to access the desired *trans* stereochemistry. Thus, ketone **7c** under acetalization reac-

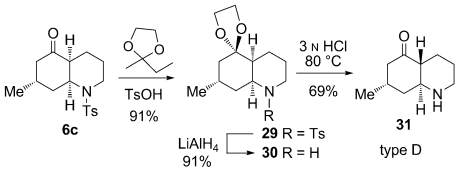


Scheme 7. Synthesis of a decahydroquinoline with phlegmarine type C stereochemistry.

tion conditions[36] gave acetal **26** (Scheme 7). Removal of the tosyl group with $LiAlH_4$ under mild conditions[37] and treatment of the resulting aminoacetal **27** under aqueous acidic conditions gratifyingly gave the target **28**,[38] indicating that epimerization at the α-carbonyl group had occurred.

Access to type D 5-oxodecahydroquinolines: The remaining possible stereochemistry (type D) for the three centers of the decahydroquinoline is the only one not previously found in any of the phlegmarine alkaloids. Given that the above process allowed the interconversion of *cis* to *trans* compounds, we expected the same reaction sequence would give the type D stereochemistry from the corresponding type A decahydroquinoline.

Thus, in an analogous manner to **7c**, ketone **6c** was protected as an acetal (i.e., **29**; Scheme 8) followed by treat-



Scheme 8. Synthesis of **31** with the unnatural phlegmarine type D stereochemistry.

ment with $LiAlH_4$ to remove the tosyl group. Subjecting **30** to the same acidic conditions to those described above gave *trans* compound **31**, but in this series the isomerization was partial and its C-4a epimer **32** (Figure 8) was also isolated in a 2:1 ratio.

The four relative stereochemistries for the 7-methyl-5-oxodecahydroquinolines (N-unsubstituted derivatives **28**, and **31**–**33**)[39] are depicted in Figure 8, which shows the diagnostic NMR signals in each case.[40] The *cis* (**32** and **33**) and *trans* (**28** and **31**) decahydroquinolines are clearly differentiated by two NMR features: 1) the ^1H NMR chemical shift of H-8a appears more deshielded ($\delta = 3.2$–3.6 ppm) in the *cis*- than in the *trans*-derivatives ($\delta = 2.5$ ppm); 2) the ^{13}C chemical shift of C(4a) is more deshielded ($\delta = 4$–5 ppm) in the *trans* than in the *cis* derivatives. According to the multiplicity of H-8a in the ^1H NMR spectra, the preferred conformation of *cis*-decahydroquinoline **32** has H-8a axial with respect to the N-containing ring (*N*-endo conformer), whereas

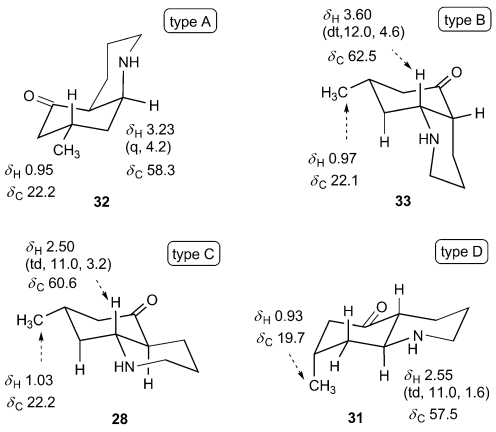
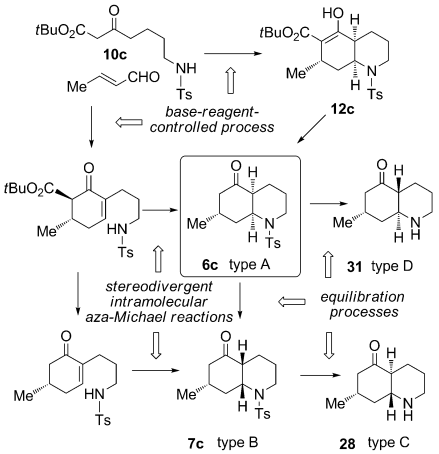


Figure 8. Conformational preference of N-unsubstituted decahydroquinolines determined on the basis of NMR spectroscopic data, showing type A–D stereochemistries.

an *N*-exo conformation with an equatorial H-8a configuration with respect to that ring is preferred for **33** because it places the methyl substituent at C-7 in an equatorial orientation.

Conclusion

Straightforward synthetic access to 7-methyl-5-oxodecahydroquinolines corresponding to the three main types of phlegmarine alkaloids (types A–C) as well as the unnatural type D , has been achieved from a common simple acyclic β-keto ester (i.e., **10c**; Scheme 9). The four relative stereochemistries of 7-methyl-5-oxodecahydroquinolines were ob-



Scheme 9. Overview of stereocontrolled processes leading to all stereochemistries of 7-methyl-5-oxodecahydroquinolines.

tained from common intermediate **6c**. This was accomplished by the development of a cascade Robinson and aza-Michael intramolecular process leading to β-keto ester **12c** through biscyclization, followed by a dealkoxycarbonylation step, and a series of configurationally controlled equilibration processes. DFT studies were used to rationalize the observed experimental results and shed light on the reaction mechanisms. Application of this methodology to a unified synthesis of the phlegmarine and other *lycopodium* alkaloids is in progress.

Experimental Section

Type A stereochemistry

*tert-Butyl (4aRS,7RS,8aRS)-7-methyl-1-(4-methylphenylsulfonyl)-5-oxodecahydroquinoline-6-carboxylate (**12c**)*: Crotonaldehyde (50 mg, 0.70 mmol) followed by $LiOH{\cdot}H_2O$ (26.8 mg, 0.64 mmol) were added to a solution of keto ester **10c** (237 mg, 0.64 mmol) in *i*PrOH (2.2 mL) and the reaction mixture was stirred for 24 h, quenched by the addition of saturated aqueous NH_4Cl (2.5 mL), and the product was extracted with EtOAc (3×10 mL). The combined organic layers were dried and concentrated in vacuo, and the crude material was purified by column chromatography (EtOAc/hexane, 5→10→25%) to give keto ester **12** (212 mg, 78%) as a solid. M.p. 124°C (MeOH); R_f= 0.34 (EtOAc/hexanes, 50%); ^{1}H NMR (400 MHz, COSY): δ=1.10 (d, J=6.8 Hz, 3H; CH_3), 1.22 (dm, J=12.4 Hz, 1H; H-8$_{eq}$), 1.40 (m, 2H; H-3, H-4), 1.5 (s, 9H; $C(CH_3)_3$), 1.6 (m, 1H; H-3), 2.02 (td, J=13.2, 6.4 Hz, 1H; H-7$_{ax}$), 2.06 (m, 1H; H-4), 2.26 (dt, J=10.4, 5.2 Hz, 1H; H-4a), 2.42 (s, 3H; $ArCH_3$), 2.66 (quint d, J=6.4, 1.6 Hz, 1H; H-7$_{eq}$), 2.90 (td, J=12.8, 2.4 Hz, 1H; H-2$_{ax}$), 3.86 (dm, J=12.4 Hz, 1H; H-2$_{eq}$), 4.32 (ddd, J=13.6, 5.8, 4.2 Hz, 1H; H-8a), 7.28 (d, J=8 Hz, 2H; *m*-Ts), 7.71 ppm (d, J=7.6 Hz, 2H; *o*-Ts); ^{13}C NMR (400 MHz, HSQC): δ=21.2 (CH_3), 21.5 ($ArCH_3$), 24.4 (C-3), 24.8 (C-4), 26.8 (C-7), 28.1 (C-8), 28.2 (CH_3), 38.8 (C-4a), 40.5 (C-2), 47.5 (C-8a), 81.4 ($C(CH_3)_3$), 102.6 (C-6), 126.9 (*o*-Ts), 129.7 (*m*-Ts), 138.4 (*p*-Ts), 143.1 (*ipso*-Ts), 172.1 (CO_2R), 172.3 ppm (C-5); HRMS: *m*/*z* calcd for $C_{22}H_{32}NO_5S$: 422.1996 $[M+H]^+$; found: 422.1986.

Type B stereochemistry

*(4aRS,7SR,8aRS)-7-Methyl-1-(4-metylphenylsulfonyl)-5-oxodecahidroquinoline (**7c**)*: HCl (3 N; 13 mL) was added to a solution of **9c** (450 mg, 1.40 mmol) in *t*BuOH (8 mL) and the resulting mixture was stirred for 14 h at 45°C. The reaction was quenched by the addition of NaOH (1 N, 5 mL) and extracted with EtOAc (2×8 mL), the combined organic layers were washed with brine, dried, and concentrated in vacuo. Purification by column chromatography (Al_2O_3; EtOAc/hexane, 5→50%) gave **7c** (228 mg, 54%) as an 8:1 mixture of **6c** as a yellow oil, followed by the ring-opened product **9c** (170 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ=1.04 (d, J=6.0 Hz, 3H; Me), 1.30 (m, 1H; H-3$_{ax}$), 1.62 (m, 1H; H-3$_{eq}$), 1.65 (m, 3H; H-4, H-7$_{ax}$), 1.81 (m, 2H; H-8), 2.05 (dd, J=14.5, 12 Hz, 1H; H-6$_{ax}$), 2.20 (dm, J=14.5 Hz, 1H; H-6$_{eq}$), 2.35 (m, 1H; H-4a), 2.43 (s, 3H; $ArCH_3$), 3.06 (td, J=13.2, 2.4 Hz, 1H; H-2$_{ax}$), 3.78 (dd, J=13.2, 3.6 Hz, 1H; H-2$_{eq}$), 4.22 (m, 1H; H-8a), 7.28 (d, J=6.3 Hz, 2H; *m*-Ts), 7.70 ppm (d, J=6.3 Hz, 2H; *o*-Ts); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC): δ=21.9 (Me), 23.3 (C-4), 23.7 (C-3), 29.2 (C-8), 32.3 (C-7), 40.1(C-2), 45.5 (C-6), 50.2 (C-8a), 53.0 (C-4a), 126.9 (*o*-Ts), 129.8 (*m*-Ts), 138.1 (*p*-Ts), 143.4 (*o*-Ts), 211.4 ppm (C-5); HRMS: *m*/*z* calcd for $C_{17}H_{24}NO_3S$: 322.1471 $[M+H]^+$; found: 322.1470.

Identical results were obtained by starting from decahydroquinoline **6c**, providing the type B stereochemistry by isomerization of type A stereochemistry.

Type C stereochemistry by isomerization of type B stereochemistry

*(4aRS,7RS,8aSR)-7-Methyl-5-oxodecahydroquinoline (**28**)*: Amino acetal **27** (111 mg, 0.53 mmol) was dissolved in 3 N HCl (13 mL) and heated to 80°C for 44 h. The mixture was basified with Na_2CO_3 (pH 11) and extracted with CH_2Cl_2 (3×40 mL). The dried organic extract was concentrated to give the pure amine **28** (79 mg, 90%) as a clear yellow oil; ^{1}H NMR (400 MHz, COSY): δ=1.03 (d, J=6.8 Hz, 3H; Me), 1.25 (m, 1H; H-4$_{ax}$), 1.34 (qm, J=12.4 Hz, 1H; H-3$_{ax}$), 1.46 (q, J=12.4 Hz, 1H; H-8$_{ax}$), 1.73 (dm, J=12.4 Hz, 1H; H-3$_{eq}$), 1.85 (m, 2H; H-7$_{ax}$, H-8$_{eq}$), 1.95 (dm, J=12,0 Hz, 1H; H-4$_{eq}$), 2.05 (t, J=12.8 Hz, 1H; H-6$_{ax}$), 2.10 (td, J=11.0, 2.1 Hz, 1H; H-4a), 2.34 (ddd, J=12.8, 4.0, 2.0 Hz, 1H; H-6$_{eq}$), 2.46 (td, J=11.0, 3.2 Hz, 1H; H-8a), 2.55 (td, J=12.4, 2.8 Hz, 1H; H-2$_{ax}$), 3.03 ppm (dddd, J=12.0, 4.0. 2.0, 2.0 Hz, 1H, H-2eq); ^{13}C NMR (400 MHz, HSQC): δ=22.2 (Me), 23.6 (C-4), 25.7 (C-3), 30.8 (C-7), 41.4 (C-8), 46.5 (C-2), 49.5 (C-6), 54.1 (C-4a), 60.9 (C-8a), 210.4 ppm (C-5); HRMS: *m*/*z* calcd for $C_{10}H_{18}NO$: 168.1388 $[M+H]^+$; found: 168.1384.

Calculations: DFT calculations were performed by applying the BVP86 functional and using the 6–311++G(d,p) basis. Molecular structures for all the species were optimized without constraints by using Density Functional Theory (DFT) based methods as implemented in Gaussian 09,[41] Revision A.02. For geometry optimizations, we used the local VWN correlation potential[42] together with the Becke's exchange[43] and the Perdew's correlation[44,45] (BVP86) generalized gradient corrections with the 6–311++G(d,p) basis set.[45] Stationary points in the potential energy hypersurface were characterized either as minima or transition states by means of harmonic vibrational frequencies calculations. Standard corrections to Gibbs free energy at 298 K were also evaluated. To estimate the free energies in 2-propanol as solvent, the SMD[46] solvation energies were computed consistently at the same level.

Acknowledgements

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[31] The conclusion was that proton transfers had to be assisted by a water molecule and also, as predicted by the previous thermodynamic studies, that changing the substituent on N changes the relative stability between diastereomers.

[32] As before, the calculations were performed not only in the gas phase but also by using an implicit solvent model, and we found

that the inclusion of solvent effects did not significantly change the order of relative energies.

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10. Synthetic approaches towards the *Lycopodium* alkaloids

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Abstract. The *Lycopodium* alkaloids are a structurally diverse group of natural products isolated from *Lycopodium* with important biological effects for the potential treatment of cancer and severe neurodegenerative diseases. To date, full biological studies have been hampered by lack of material from natural sources. Total synthesis represents a possible solution to meet this demand as well as the most effective way to design new compounds to determine structural activity relationships and obtain more potent compounds. The aim of this chapter is to summarise the work carried out in this field so far by presenting an overview of the synthetic strategies used to access each of the four key *Lycopodium* alkaloid types. Particular emphasis has been placed on methods that rapidly construct each nucleus utilizing tandem reactions.

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1. Introduction

The *Lycopodium* alkaloids, isolated from the *Lycopodium* genus of clubmosses belonging to the family of Lycopodiaceae, represent a diverse group of structures with important, wide-ranging biological effects. These compounds show great potential for the treatment of severe neurodegenerative diseases and cancers but to date biological studies have been hindered due to limited availability of material from natural sources. Attempts to access material via cultivation or fermentation have so far been unsuccessful [1] leaving total synthesis as the most promising way to access quantities of material for further biological testing. In addition, synthesis has the advantage that it easily enables structural modifications to be carried out to determine activity relationships and as a consequence design more potent analogues with improved biological profiles. The aim of this minireview is to give an overview of the synthetic strategies used to access each type of key Lycopodium alkaloids with particular emphasis on those synthetic approaches that feature tandem reactions enabling a rapid synthesis of each nucleus. Whilst a brief overview of the structures, biological properties and biosynthesis will be presented for contextual purposes, the authors direct the reader to the excellent review by Ma [1] for a more detailed coverage of these aspects.

1.1. Classification of the *Lycopodium* alkaloids

At the moment of writing this report almost 300 *Lycopodium* alkaloids have been discovered [2] which can be divided into four structural classes [3,4] based on the parent compound: phlegmarine (**1**), lycopodine (**2**), lycodine (**3**) and fawcettimine (**4**) (Fig. 1).

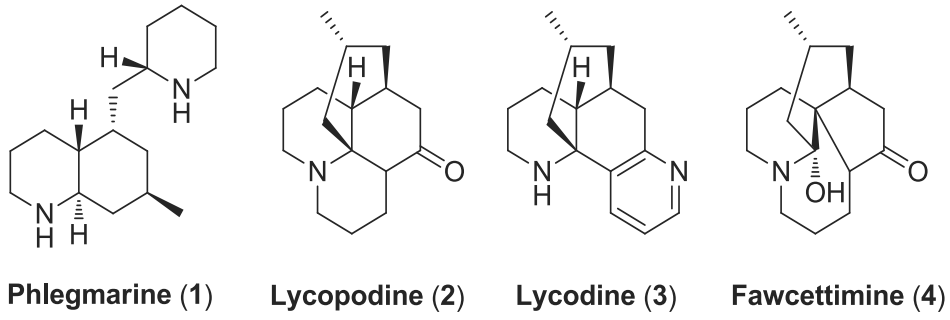


Figure 1. Representative examples of the four *Lycopodium* alkaloid classes.

1.2 . Bioactivities

An extensive biological investigation of the *Lycopodium* alkaloids has as yet not been carried out. However, from the limited studies undertaken so far it has been discovered that many of these compounds possess important biological activities that warrant further investigation and development. One key area of potential of these compounds is for the treatment of severe neurodegenerative diseases such as Alzheimer's. Examples include huperzine A [5] and lycoposerramine C [6], which act as inhibitors of the enzyme acetylcholinesterase (AChE), while lycodine-type complanadine B stimulates nerve growth factor (NGF) production in human glial cells [7]. Lycoposerramine Z from the phlegmarine structural class may potentially have neuroprotective properties due to the presence of the nitrone moiety, which can act as a free radical trap [8] helping prevent destructive cascades leading to brain deterioration (Fig. 2).

The *Lycopodium* alkaloids have also been shown to possess anticancer activities. For example, complanadine A was found to be cytotoxic against leukaemia cells in mice [9]. Lyconadine B, from the phlegmarine group exhibits biological activity against brain tumors [10] and lycopodine has the ability to bring about inhibition in the growth of HeLa55 cells [11].

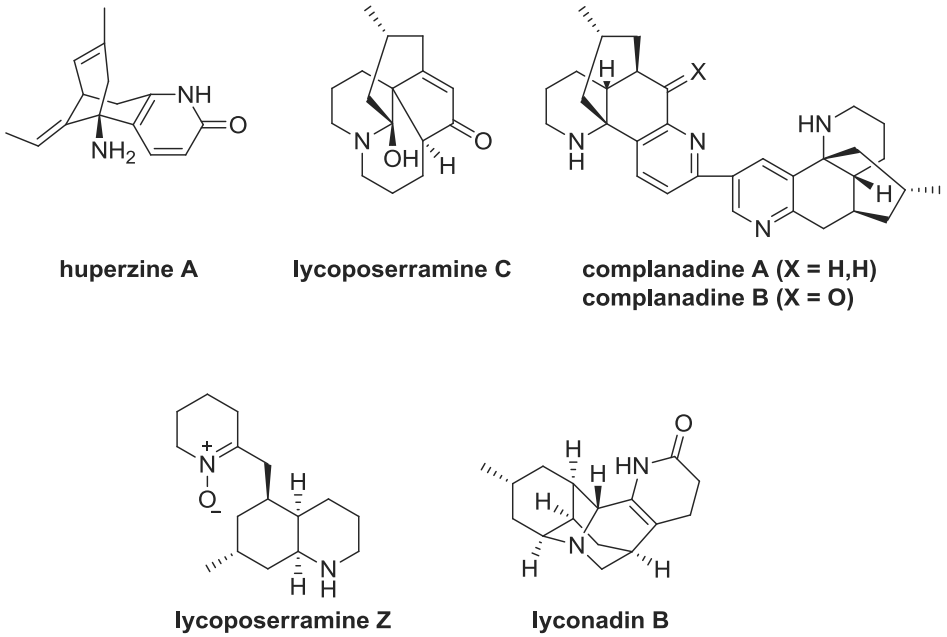
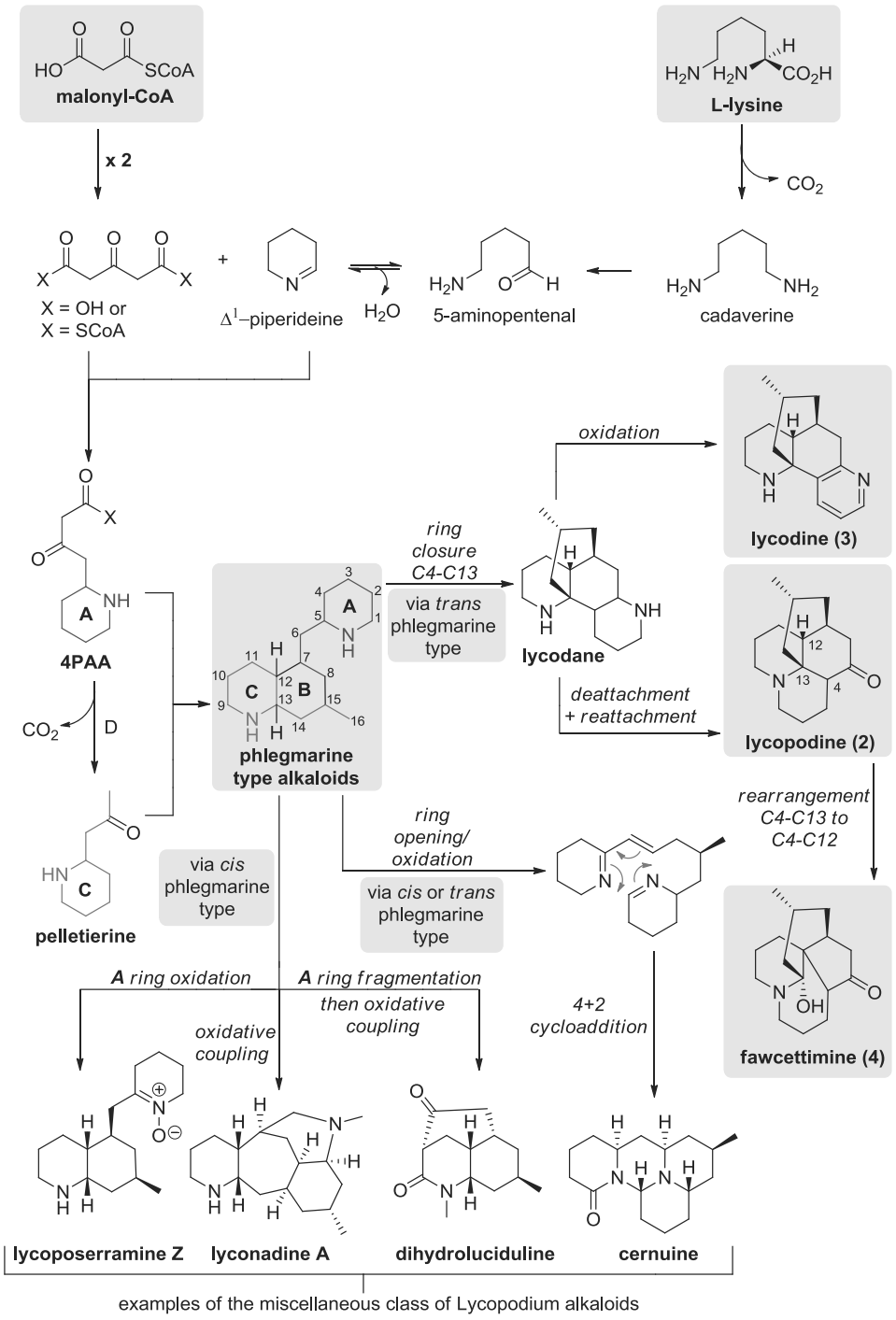


Figure 2. Some biologically active *Lycopodium* alkaloids.

1.3. Biosynthesis of the *Lycopodium* alkaloids

The biosynthetic pathway leading to all *Lycopodium* alkaloids is still not clear, although a basic overview is outlined in Scheme 1 based on the present knowledge [1]. The vast structural diversity encountered among the *Lycopodium* alkaloids is thought to derive from just two simple components, lysine and malonyl Co-A. The entry point into the pathway is through the decarboxylation of lysine to form cadaverine which is transformed to Δ^1-piperideine. At the same time, two molecules of malonyl-CoA are condensed to form acetonedicarboxylic acid, whose union with Δ^1-piperideine leads to 4-(2-piperidyl) acetoacetate (4PAA). This is then decarboxylated to form pelletierine, which is coupled to another molecule of 4PAA to form the phlegmarine-type *Lycopodium* alkaloids. These compounds are formed with multiple stereochemistries that can be separated into two main classes depending on whether the hydrogens at the ring fusion are arranged *cis* or *trans* (see section 2). It is assumed that on dimerisation slightly different pathways exist with different methods of control thus leading to the diverse range of stereochemistries observed. Phlegmarine (**1**) which is characterized by a *trans* fusion at the ring junction is considered to be the key intermediate from which the other three classes (**2**-**4**) of *Lycopodium* alkaloids are derived. Bond formation between C-4 and C-13 gives the lycodane skeleton, which after oxidation of the piperidine ring leads to lycodine (**3**). Detachment of C-1 from N_α of the lycodane skeleton and reattachment to N_β then gives lycopodine (**2**). Rearrangement of (**2**) via migration of the C-4 to C-13 bond to C-12 forms the 5-membered ring of fawcettimine (**4**). Further complexity within each of these groups is arrived at by a series of modifications of these basic ring structures such as oxidations, ring fragmentations, dimerisations and additional skeletal rearrangements.

The *cis*-fused phlegmarine alkaloids comprise the entry point to the miscellaneous class of the lycopodium alkaloids, including compounds such as lyconadine A or dihydroluciduline which maintain the same *cis* stereochemistry relationship as the parent compound. Cernuine and related quinazoline *Lycopodium* alkaloids are speculated to arise from an opening of the B ring of the phlegmarine skeleton, additional oxidation, followed by a 4+2 cycloaddition reaction. Due to the loss of the fusion stereochemistry, these compounds may arise via the *trans* or *cis* phlegmarine group intermediates.



Scheme 1. Overview of the biosynthesis of the *Lycopodium* alkaloids.

2. Phlegmarine class

Phlegmarine is the parent member of the miscellaneous group of the *Lycopodium* alkaloids and as mentioned above, is considered to play a key role in the biosynthesis of all the lycopodium alkaloids. While phlegmarine (**1**) is characterized by a *trans* substitution pattern at the ring fusion carbons, other compounds belonging to this group feature a *cis* relationship between the ring fusion hydrogens (e.g lycoposerramine Z and cermizine B). In addition to the wide variety of stereochemistries observed, other key variations are the oxidation of the nitrogen containing rings leading to pyridines (lycoposerramine V and W), nitrones (huperzine M and lycoposerramine Z) or N-oxides (huperzine N) (Fig. 3).

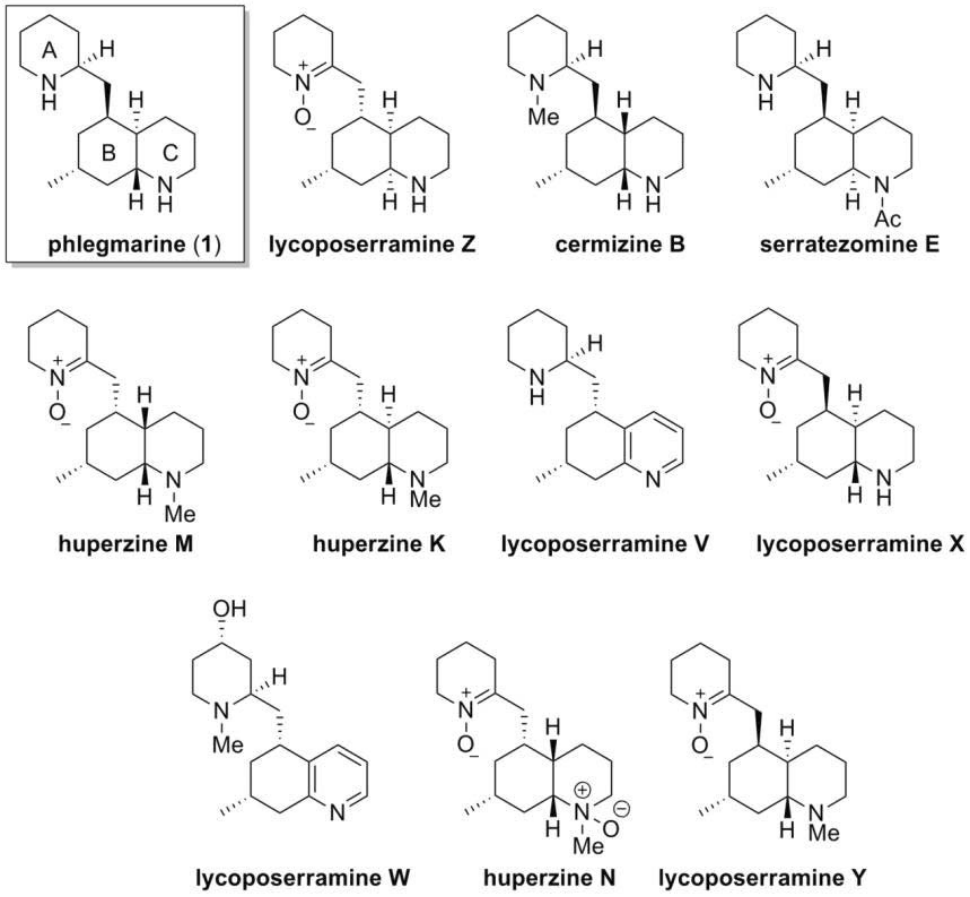


Figure 3. Representative compounds of the miscellaneous class based on the phlegmarine skeleton.

2.1. Previous synthesis of Phlegmarine type alkaloids

Despite the importance of this class of compounds from a biosynthetic point of view and their potential for use as biomimetic precursors of the other classes of *Lycopodium* alkaloids, the phlegmarine type has been one of the least studied (Table 1). Although the relative configuration of phlegmarine was established in 1981 [12] the absolute configuration of a phlegmarine derivative was not determined until 1999 [13] when Comins *et al* carried out the first asymmetric total synthesis of N_{α}-acetyl-N_{β}-methylphlegmarine using a pyridine auxiliary for the construction of both the C and A nitrogen-containing rings. Takayama's enantioselective syntheses of lycoposerramines V, W [14], X and Z [15] were accomplished using (5*R*)-methyl-2-cyclohexenone as the source of chirality. Comins then completed the synthesis of phlegmarine in 2010 [16] based on his original methodology and finally, the Bonjoch group utilized organocatalysis to form the decahydroquinoline ring system as the key step.[17]

Table 1. Previous synthesis of some Phlegmarine-type *Lycopodium* alkaloids (*denotes enantioselective synthesis).

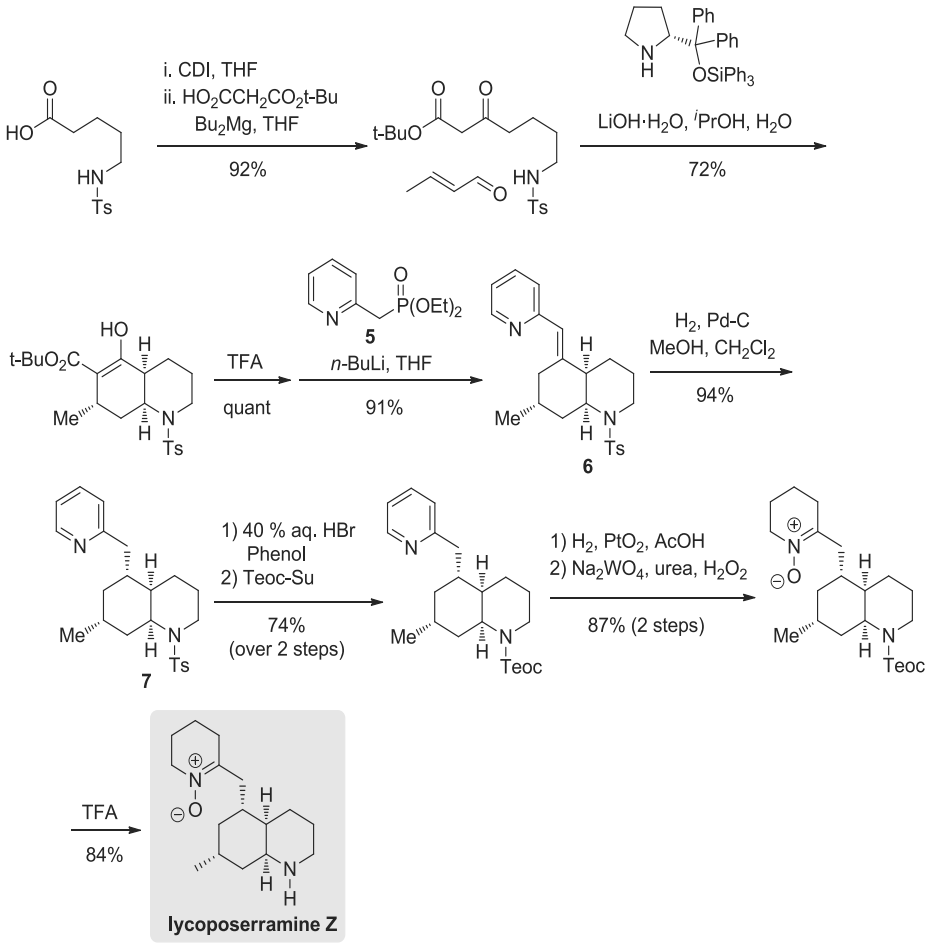
Year	*Natural Product*	*Author*	*Ring Construction Strategy*
1981 [12]	N_{α}-methyl-N_{β}-acetylphlegmarine	Maclean	B→C→A
1999 [13]	N_{α}-acetyl-N_{β}-methylphlegmarine	Comins	C→B→A*
2007 [14]	Lycoposerramine-V +(Lycoposerramine W)	Takayama	B→C→A*
2009 [15]	Lycoposerramine-X +(Lycoposerramine Z)	Takayama	B→C→A*
2010 [16]	(–)-Phlegmarine and derivatives	Comins	C→B→A*
2013 [17]	Lycoposerramine-Z	Bonjoch	acyclic→BC→A*

2.2. Bonjoch's synthesis of Lycoposerramine Z [17]

Bonjoch's group developed an asymmetric synthesis of lycoposerramine Z, where the decahydroquinoline core was assembled via an organocatalyzed diastereo and enantioselective one-pot tandem procedure (Scheme 2). Removal of the *tert* butyl ester group with TFA and coupling with pyridine phosphonate **5** assembled the complete carbon

skeleton in a rapid manner. Hydrogenation of alkene **6** took place exclusively from the top face leading to **7**, which has all the stereocentres required for lycoposerramine Z in place. The sensitive nature of the nitrone unit necessitated exchange of the tosyl group for the more readily labile Teoc group (trimethylsilylethylcarbonate), which was previously used in Takayama's synthesis of the same compound. Finally reduction of the pyridine ring followed by oxidation with Na_2WO_4 in the presence of urea peroxide installed the nitrone unit. Treatment with TFA smoothly removed the Teoc group to complete the synthesis.

It was also later shown that this method can be adapted to access all the different core decahydroquinoline stereochemistries present in the phlegmarine group via a series of controlled equilibration reactions [18].



Scheme 2. Bonjoch's total synthesis of Lycoposerramine Z.

3. Lycodine class

The lycodine (**3**) group comprises around 30 of the 300 known *Lycopodium* alkaloids. Some examples are shown in Fig. 4. Complanadine A is a dimer of two lycodine units. Hydroxypropyllycodine is the first *Lycopodium* alkaloid found to possess a 19-carbon skeleton [19]. In some compounds such as huperzines A and B the D ring is unsaturated whilst in the former the C ring has been cleaved. Casuaririne I features an unprecedented 5-membered tetrahydropyrrole ring and is believed to derive from huperzine A [20].

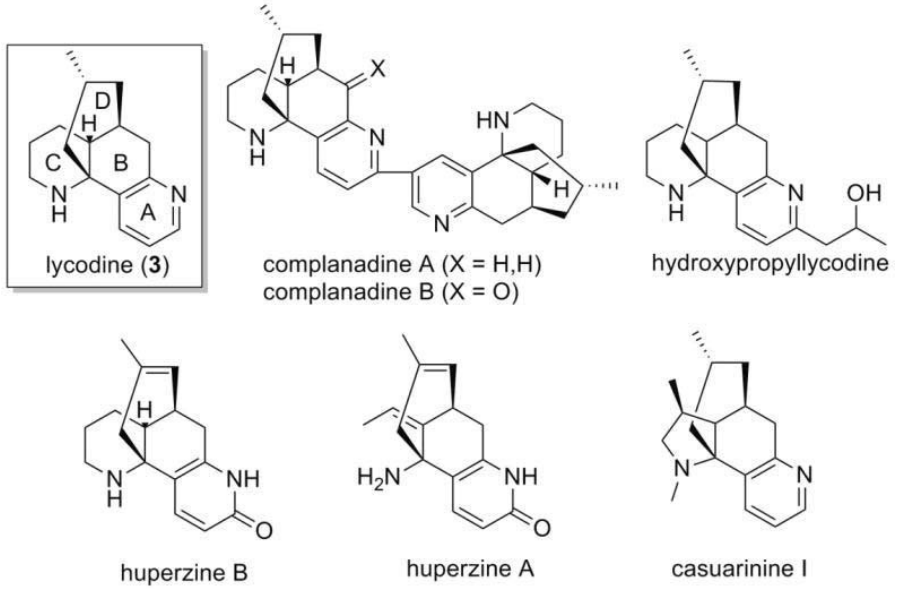


Figure 4. Representative compounds of the Lycodine group.

3.1. Previous synthesis of Lycodine and related compounds

Along with the phlegmarine group, the synthesis of the lycodine class has been the least studied. The D→C→B→A ring strategy is the most commonly used to construct the lycodine nucleus. The first synthesis of (±)-lycodine was performed by Heathcock [21], who closed the DCB skeleton in a one-pot diastereoselective Mannich condensation. Another racemic synthesis of lycodine was developed by Hirama [22] and involved a Diels-Alder cycloaddition followed by an intramolecular Mizoroki-Heck reaction to furnish the complete skeleton. In Sarpong's complanadine A synthesis [23] Boc-protected lycodine was prepared as a key intermediate en route to the

Table 2. Previous syntheses of Lycodine and its dimer's Complanadine A and B. (* denotes enantioselective synthesis).

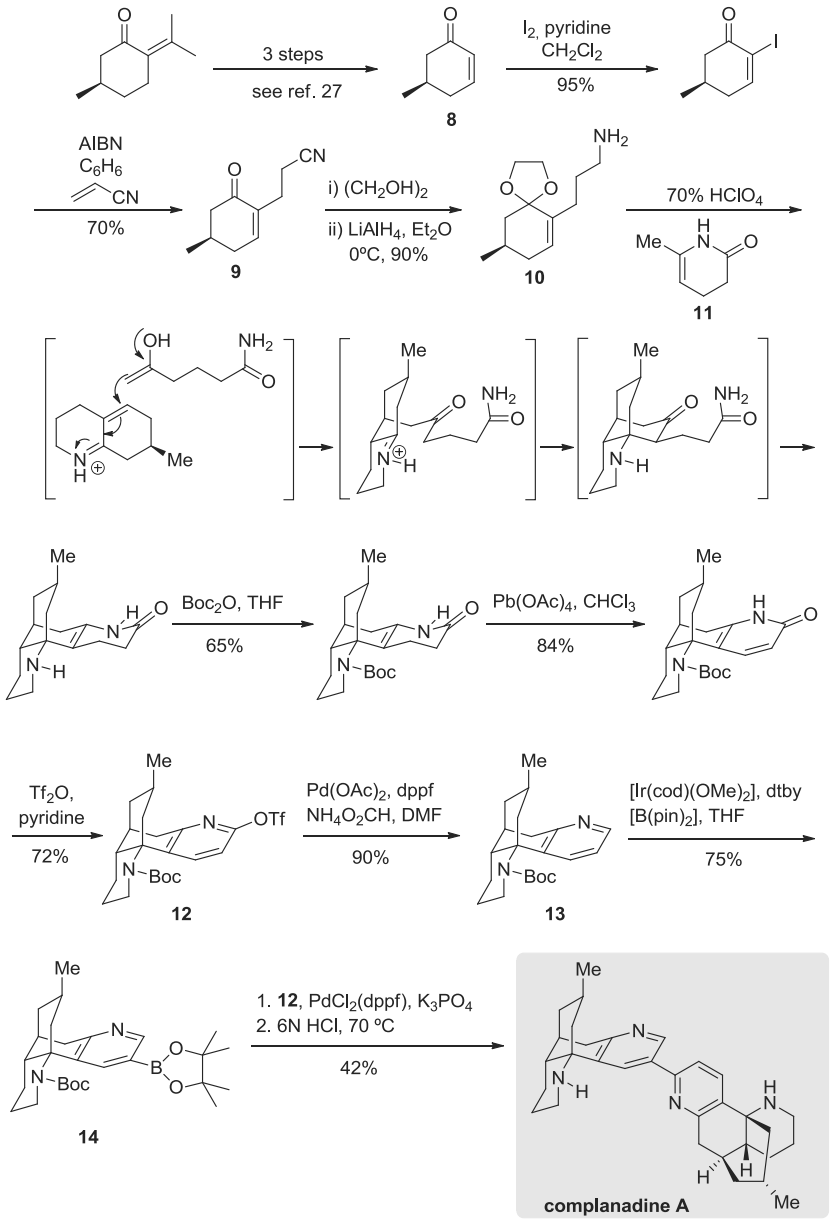
Year	*Natural Product*	*Author Strategy*	*Ring Construction*
1982 [21]	Lycodine	Heathcock	D→C→B→A
2010 [22]	Lycodine	Hirama	acyclic→CD→BA
2010 [23]	Complanadine A	Sarpong	D→DCBA*
2010 [25]	Complanadine A	Siegel	D→C→B→A*
2013 [24]	Complanadine B	Sarpong	D→DCBA
2013 [26]	Complanadines A/B	Hirama	acyclic→CD→BA

final product in enantiopure form (see Scheme 3). This same key intermediate was later used in his synthesis of complanadine B [24]. Seigel [25] made use of two Co-mediated [2+2+2] cycloaddition reactions to furnish complanadine B starting from a thioether derivative of (5*R*)-methyl-2-cyclohexenone. While as yet no enantioselective synthesis of lycodine has been described, recently Hirama [26] and co-workers reported the synthesis of Complanadines A and B starting from enantiopure (–)-lycodine, which was obtained by chiral HPLC separation.

3.2. Sarpong's synthesis of complanadine A [23]

Sarpongs´s synthesis of complanadine A takes advantage of the symmetry of the product to construct the dimer from two lycodine units via a palladium-based coupling reaction as the key step. Preparation of the (5*R*)-methyl-2-cyclohexenone starting material **8** was accomplished in 3 steps from *R*-(+)-pulegone using a reported procedure [27]. Iodination and radical addition to acrylonitrile gave **9** which after acetalization and reduction of the nitrile gave **10** the key material for the subsequent tandem cyclisation reaction. Treatment of this compound with perchloric acid led to an intermediate that was trapped with an enamide **11** via a Michael-Mannich tandem procedure to furnish the DCB core [28] followed by condensation of the amide to the carbonyl formed the A ring giving a rapid synthesis of the complete lycodine skeleton (Scheme 3). Protection of the resulting compound followed by oxidation with lead tetraacetate and triflation of the pyridone ring provided **12**. Removal of the triflate group gave Boc-protected lycodine

13 to which was introduced a boronic ester with an iridium-catalyzed functionalization at the 3 position to give **14**. Finally, Suzuki cross-coupling of **12** and **14** followed by cleavage of the Boc protecting groups completed the synthesis.



Scheme 3. Sarpong's total synthesis of complanadine A.

4. Lycopodine class

Lycopodine (Fig. 5), the first isolated *Lycopodium* alkaloid [29], is the most widespread and can be found in several different *Lycopodium* species. Out of the 300 known *Lycopodium* alkaloids discovered so far, 100 belong to the lycopodine class.

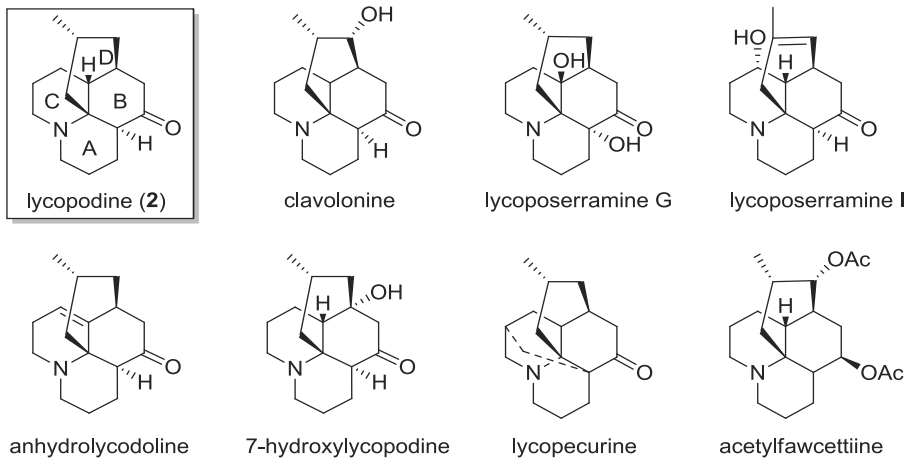


Figure 5. Some representative alkaloids belonging to the Lycopodine class.

4.1. Previous synthesis of Lycopodine and related compounds

Along with the Fawcettimine nucleus, the synthesis of lycopodine has been one of the most intensively studied, with most of the approaches reported to date relying on a common D→C→B→A ring construction strategy. The key ring-forming step usually involves the manner of formation of the B ring, which can be divided into two main approaches. The first, described by Stork, involves an intramolecular Pictet-Spengler cyclization onto an iminium group located between the D and C rings. The aromatic ring is then fragmented and used to form the required carbon atoms of the A ring. Padwa and Mori later arrived at the same key intermediate precursor in their synthetic approaches albeit by very different methods. The other key strategy to form the B ring involves an intramolecular diastereoselective Mannich cyclization approach which was first reported by Heathcock (see Scheme 4). This strategy, and variations thereof, has been the most commonly employed in subsequent synthetic approaches. The first enantioselective synthesis of a lycopodine related compound, clavolonine A was described by Evans and used a similar Mannich strategy. However, instead of following Heathcock and starting from a racemic D ring building block, a chiral auxiliary strategy

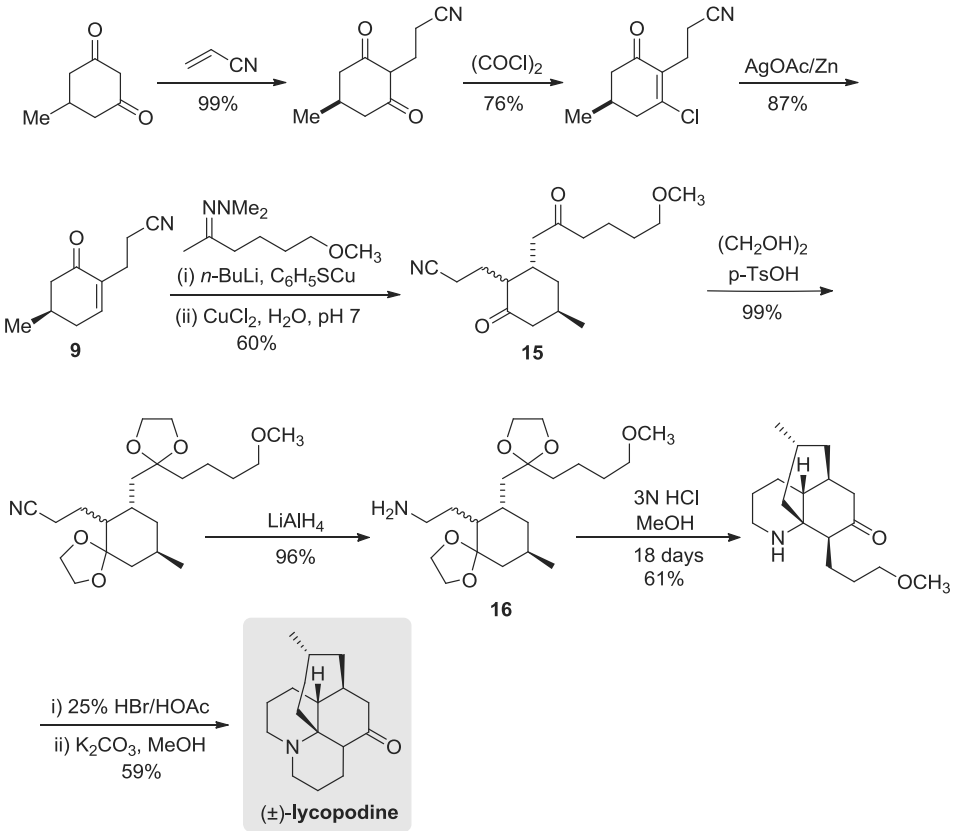
was used to form an acyclic chain which was then cyclised to form the D ring in enantiopure form. A few years later, Carter achieved the first enantioselective synthesis of lycopodine using an analogous approach to Evans employing a chiral auxiliary and a Mannich cyclisation as the key steps. Whilst a number of strategies do not fall into the categories described above, the methods employed have usually required a significant amount of additional functional group manipulation steps and consequently these strategies have not been exploited in further synthetic approaches.

Table 3. Summary of the most relevant previous syntheses of Lycopodine and its derivatives. (* denotes enantioselective synthesis).

Year	*Natural Product*	*Author*	*Ring Construction Strategy*
1967 [30]	12-epi-Lycopodine	Weisner	D→C→B→A
1968 [31]	12-epi-Lycopodine	Weisner	D→C→A→B
1968 [32]	Lycopodine	Stork	D→C→B→A
1968 [33]	Lycopodine	Ayer	BC→A→D
1978 [34]	Lycopodine	Heathcock	D→C→B→A
1978 [35]	Lycopodine	Kim	D→B→C→A
1982 [28]	Lycopodine	Schumann	D→C→B→A
1982 [21]	Lycopodine	Heathcock	D→C→B→A
1984 [36]	Lycopodine	Wenkert	C→A→B→D
1985 [37]	Lycopodine	Kraus	D→B→C→A
1998 [38]	Lycopodine	Mori	D→B→C→A
1998 [39]	Lycopodine	Grieco	B→D→CA
1997 [40]	Lycopodine	Padwa	acyclic→CD→B→A
2005 [41]	Clavolonine	Evans	acyclic→D→C→B→A*
2008 [42]	Lycopodine	Carter	acyclic→D→C→B→A*
2010 [43]	Acetylfawcettiine	Breit	D→C→B→A*
2011 [44]	Clavolonine	Fujioka	D→C→B→A*
2012 [45]	7-hydroxylycopodine	Snider	D→C→B→A

4.2. Heathcock's synthesis of Lycopodine [21]

Key to Heathcock's synthesis is an equilibrating Mannich cyclisation reaction which assembles the DCB tricyclic in a single step. The requisite material required for the cyclisation was prepared from 5-methylcyclohexane-1,3-dione, which underwent Michael addition to acrylonitrile followed by formation of the cyclohexenone. Conjugate addition of a tosyl hydrazine to **9** followed by hydrolysis of the hydrazone gave **15**. Protection of the ketone moieties as acetals then allowed the nitrile to be reduced to the primary amine. Treatment of **16** with strong acid over an extended period resulted in a diastereoselective Mannich cyclization to forming the DCB tricyclic system via equilibration to the most stable structure. Removal of the methoxyether group with HBr resulted in subsequent formation of the primary alkyl bromide, which was then cyclised onto the nitrogen under basic conditions giving lycopodine.



Scheme 4. Heathcock's total synthesis of Lycopodine.

5. Fawcettimine class

About a third of all the known lycopodium alkaloids are of the fawcettimine type. Key structural variations to the parent structure include skeletal oxidations as well as the formation of dimeric products. The fawcettimine nucleus can be simplified to the three-ring DBA system since the C ring forms spontaneously via the free amine condensing with the carbonyl to form the hemiaminal unit.

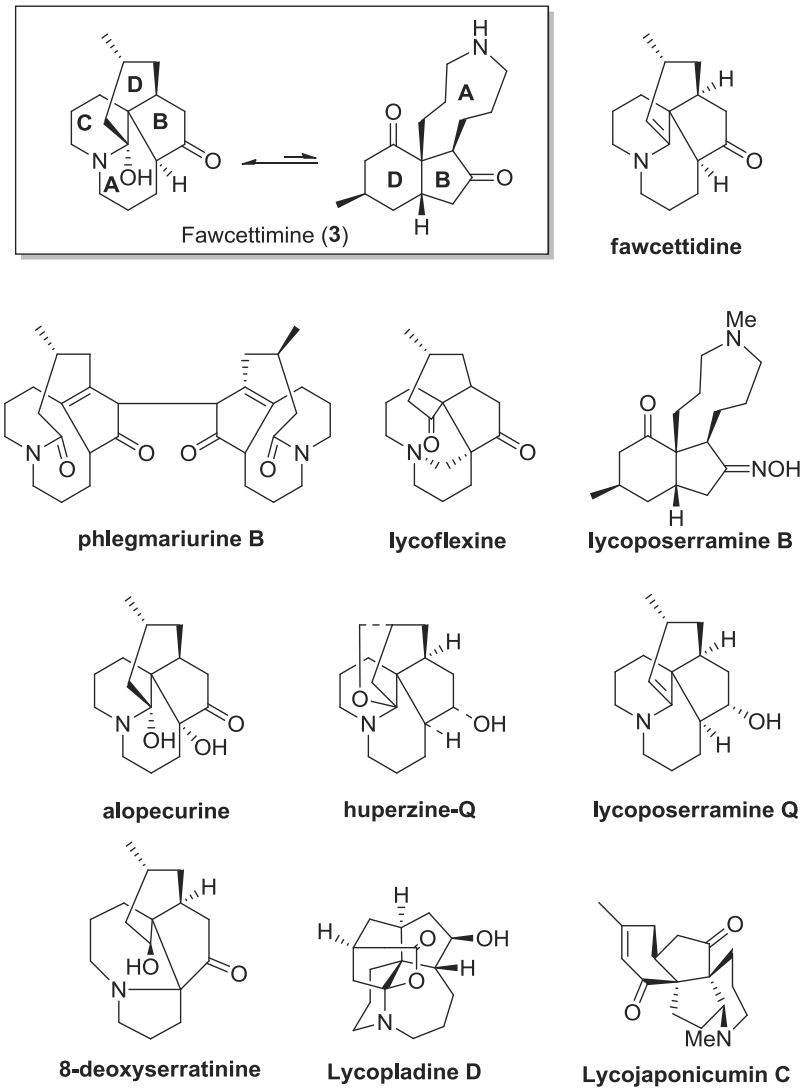


Figure 6. Representative compounds of the Fawcettimine class.

5.1. Previous synthesis of Fawcettimine and related compounds

Fawcettimine-type products have been the area of most intensive synthetic research in the field of *Lycopodium* alkaloids, with the vast majority of syntheses being reported from 2007 onwards [46].

Table 4. Previous synthesis of Fawcettimine and related compounds. (* denotes enantioselective synthesis).

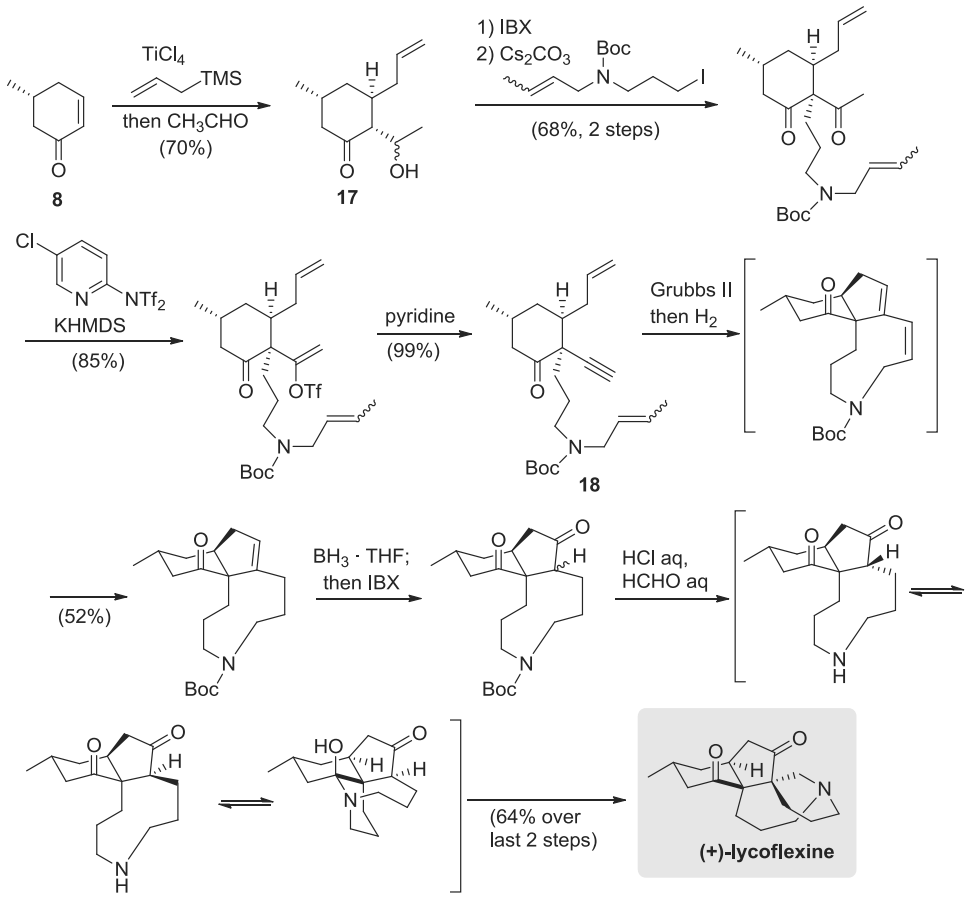
Year	*Natural Product*	*Author*	*Ring Construction Strategy*
1979 [47]	Fawcettimine	Inubushi	D→B→A→C
1986 [48]	Fawcettimine	Heathcock	D→B→A→C
1989 [49]	Fawcettimine	Heathcock	D→B→A→C
2002 [50]	Magellanine	Liao	BC→ A→D
2007 [51]	Fawcettimine	Toste	D→B→A→C*
2008 [52]	Fawcettidine	Dake	D→C→B→A*
2010 [53]	Fawcettimine (Fawcettidine)	Takayama	acyclic→DB→A→C*
2010 [54]	Fawcettimine	Jung	D→B→A→C*
2010 [55]	Fawcettimine (Lycoposerramine-B)	Mukai	acyclic→DB→A→C*
2010 [56]	Fawcettimine +(Lycoflexine)	Yang	D→B→A→C*
2010 [57]	Lycoflexine (Fawcettimine)	Mulzer	D→BA→C*
2011 [58]	Huperzine-Q	Takayama	acyclic→DB→A→C*
2010 [59]	Alopecuridine	Meng	D→A→B→C
2012 [60]	Fawcettimine	Willliam	D→A→B→C*
2012 [61]	Fawcettimine (Fawcettidine and Deoxyserratinine)	Lei	D→A→B→C*
2013 [62]	Lycojaponicumin C 8-Deoxyserratinine Fawcettimine Fawcettidine	Zhao	D→B→A→C*
2013 [63]	Lycopladine D, Fawcettidine Lycoposerramine Q	Tu	DB→A→C*

As a consequence most of the syntheses carried out are enantioselective with 3-methyl cyclohexenone **8** (derived from pulgeone) as the most popular source of chirality. As in all the previous syntheses of the *Lycopodium* alkaloids one strategy dominates for the construction of the fawcettimine skeleton. Most methods employ the D→B→A→C order (see Table 4) with the key differences in strategy centring on the assembly of the 5-membered B ring. This usually involves a conjugate addition onto a suitably substituted cyclohexenone followed by a subsequent trapping of the nucleophile via the formed carbonyl enolate. In a number of cases the order is reversed, with the 6-membered D ring being appended onto a 5-membered B ring starting material precursor, for example, using a Diels-Alder [60] or a Robinson annulation reaction [62] Alternatively, the 6,5-bicycle (D-B) core has been constructed in a single step from an acyclic precursor using a Pauson-Khand reaction [53,55].

Subsequent closure of the 9-membered A ring usually involves a Mitsunobu-type reaction. Finally, deprotection of the nitrogen yields the free amine, which then spontaneously cyclises via the hemiaminal to close the C ring.

5.2. The Mulzer synthesis of Lycoflexine and Fawcettimine

Mulzer and co-workers [57] have reported an efficient route to construct the 6,5,9-tricylic framework of fawcettimine which features an enyne ring-closing-metathesis to construct the B and A rings in a single step. Like many *Lycopodium* syntheses it utilises 3-methylcyclohexenone **8** as the starting material and source of chirality. A Sakurai-aldol sequence gave substituted cyclohexanone **17** which after oxidation with IBX was alkylated with a nitrogen-containing side chain. Conversion of the methyl ketone to an alkyne prepared the starting material **18** for the tandem cyclization reaction. Treatment with Grubbs II catalyst initiated the enyne ring-closing-metathesis first forming the five-membered B ring followed by the 9-membered A ring. The resulting diene was hydrogenated in-situ to selectively remove the less substituted alkene. The remaining alkene then underwent a hydroboration-oxidation sequence using IBX as the oxidant to directly introduce the desired ketone in the cyclopentane ring system. Deprotection of the Boc group liberated the secondary amine which underwent spontaneous cyclisation to fawcettimine. The addition of formaldehyde precipitated a Mannich reaction to give lycoflexine.



Scheme 5. Mulzer's total synthesis of (+)-lycoflexine.

6. Conclusions

An overview of the synthetic approaches used to construct the four core structural types of the *Lycopodium* alkaloids has been presented. As can be seen, for each nucleus type one ring construction strategy tends to dominate for each nucleus type and there exists significant similarity between the starting materials and intermediates employed across the range of different approaches. There are now efficient procedures for the rapid construction of each nucleus type, using tandem reactions that construct many of the rings in a single step. It is hoped that continuing work within this field will lead to new and more efficient approaches to the *Lycopodium* alkaloids and their analogs that will enable a full investigation of their important biological activities for the treatment of serious diseases such as Alzheimer's or cancer.

Acknowledgement

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4. Traditionally, the phlegmarine-type alkaloids have been grouped together into the "miscellaneous group" with all other lycopodium alkaloids that do not fall neatly in the lycopodine, lycodine or fawcettimine groups. However, the phlegmarine group represents a key structural group in its own right, particularly in light of it's pivotal importance in the biosynthesis of all the other compounds. Therefore, for the purpose of this minireview we treat it as the "phlegmarine class" and all other derivatives that do not fall into the four groups as the miscellaneous class.
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Synthesis of (±)-Serralongamine A and the Revised Structure of Huperzine N

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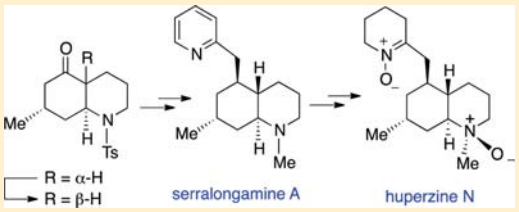
Supporting Information

ABSTRACT: A revised structure for the *Lycopodium* alkaloid huperzine N is proposed and confirmed by synthesis. The key synthetic steps involve an epimerization of a *cis*-5-oxodecahydroquinoline to the corresponding trans isomer and a coupling, followed by a diastereoselective hydrogenation using Wilkinson's catalyst to incorporate the pyridylmethyl moiety. This route allowed the alkaloid serralongamine A to be synthesized for the first time, and two additional steps led to the revised structure of huperzine N, both products bearing an unusual decahydroquinoline stereostructure.



The phlegmarine alkaloids are structurally characterized by a 5,7-disubstituted decahydroquinoline ring and a $C_{16}N_2$ skeleton.[1] They can be classified in four types, designated here as A–D,[2] according to the relationship of the ring fusion hydrogens (H-4a and H-8a) with the H-7 in the decahydroquinoline ring (DHQ) (Figure 1).[3] Moreover, the phlegmarine substitution pattern involves a (2-piperidyl)methyl side chain at C-5, which can be partially (as in nitrone) or fully oxidized (as in pyridine), thus increasing the stereochemical variation.

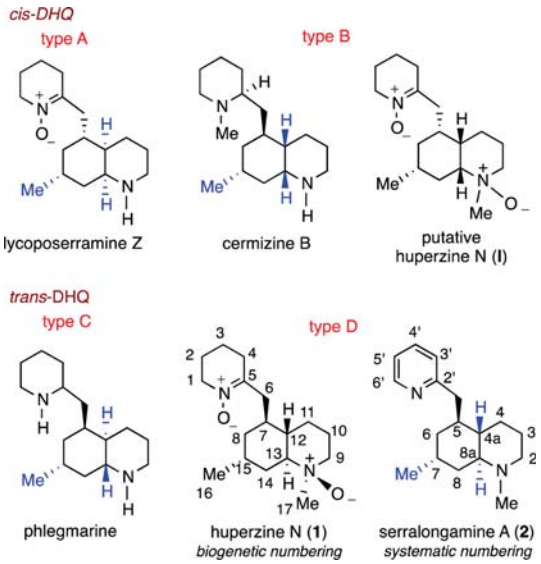


Figure 1. Phlegmarine alkaloids showing the four different stereoparents.

After recently describing the total synthesis of **I**, the proposed structure of huperzine N,[4] we revealed its misassignment. We here suggest an alternative structure for this natural product[5,6] (i.e., **1**) and confirm it by a total synthesis. Moreover, the synthesis of serralongamine A (**2**),[7] featuring a pyridine instead of the usual piperidine ring system, is also reported.

The putative (**I**) and natural huperzine (**1**) are clearly differentiated by their ^{13}C NMR data: (i) The chemical shifts of C(2) and C(4) are more deshielded (8 and 11 ppm, respectively) in **1** (Figure 2). These data suggest that huperzine

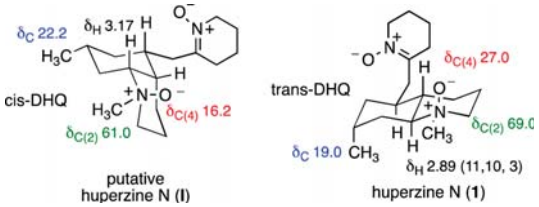


Figure 2. Differential NMR trends between putative and natural huperzine N.

N has a *trans*-decahydroquinoline ring core instead of the cis-ring fusion originally reported. (ii) The chemical shift of the methyl group at C(7), which resonates at δ 19.0 in huperzine N, but at δ 22.2 in **I**, indicates an axial disposition, which is only possible in a *trans*-decahydroquinoline with a stereoparent of type D (see Figures 1 and 2). Consequently, the NMR data reported for

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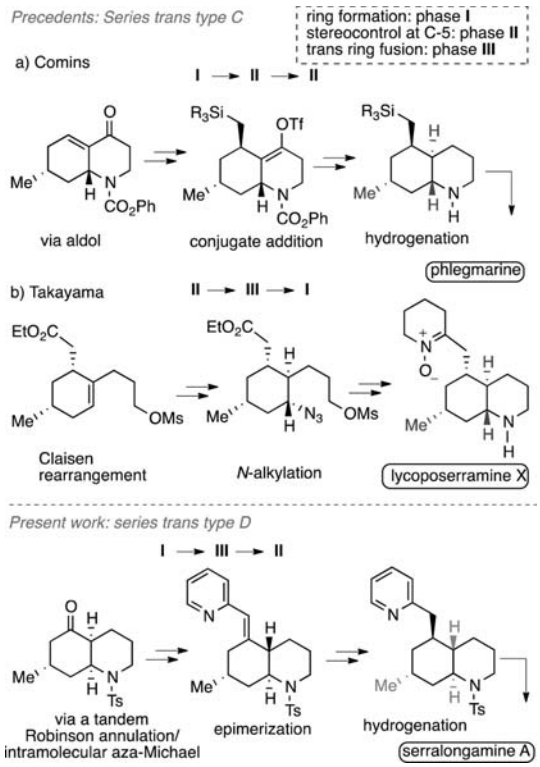
Scheme 1. Synthesis of Phlegmarines with a *trans*-Decahydroquinoline Core

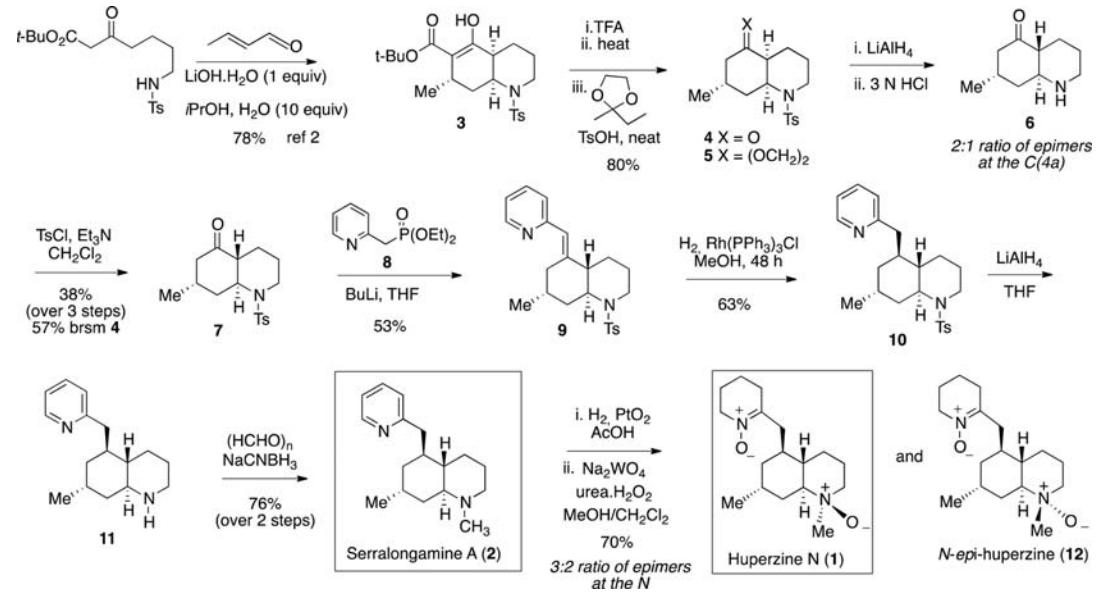


huperzine N can be explained by structure **1**. Building on this point of view, we synthesized **1** to confirm the new structural assignment.

Previous *trans*-phlegmarine syntheses have targeted alkaloids with the type C stereoparent. The synthesis of phlegmarine itself was completed by Comins,[8] who also reported the synthesis of three related alkaloids bearing different substituents at the two nitrogen atoms, while Takayama[9] achieved lycoposerramine X. The key challenges in the synthesis of these alkaloids are the generation of the *trans*-decahydroquinoline core and the stereocontrol in the genesis of the stereocenter at C-5 where the pyridylmethyl backbone is attached (Scheme 1). The two different approaches to construct the *trans*-decahydroquinoline ring with the required stereochemistry in the four stereogenic centers are summarized in Scheme 1. Comins, applying his methodolgy based on pyridinium salts, prepared a polysubstituted piperidine that furnished the bicyclic ring by an aldol reaction. Stereoselective conjugated addition, followed by a hydrogenation process, allowed a stereochemical control at C-5 and in the ring fusion, respectively. In contrast, the Takayama approach involved the elaboration of a polyfunctionalized cyclohexane compound in which the four stereogenic centers were established before the cyclization, leading to the decahydroquinoline ring.

Our approach differs from the aforementioned in both its synthetic strategy and the targeted compounds, which have a decahydroquinoline core with a type D stereoparent.[10] The synthetic plan involved the same building block used in our previous synthesis of *cis*-phlegmarines and the epimerization of the stereogenic center at C-4a to achieve a ketone with a *trans*-decahydroquinoline ring, which would allow access to phlegmarine alkaloids with a new stereochemical pattern. Control of the stereochemistry at C5 through a substrate-directable hydrogenation process would be crucial in this synthetic proposal (Scheme 2).

Scheme 2. Synthesis of (±)-Serralongamine A (2) and (±)-Huperzine N (1)



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J. Org. Chem. 2016, 81, 2629−2634

Commencing the synthesis from the easily available ketone **4**,[11] our original protocol[2] allowed the ring fusion to be changed from cis to trans, via the conversion of acetal **5** to the corresponding secondary amine and acid-induced epimerization at C(4a). Tosylation of the resulting 2:1 mixture of ketones **6** and its C4a-epimer furnished the required decahydroquinoline **7** with a trans ring fusion[12] as a single isomer after chromatographic separation. This ketone reacted with a solution of the lithium anion of phosphonate **8**[13] to give vinylpyridine derivative **9** in 53% yield, diastereoselectively providing the *E* isomer.[14] Hydrogenation of vinylpyridine **9** using Wilkinson's catalyst allowed the hydrogen to be delivered exclusively from the bottom face. Thus, a pyridine-directed hydrogenation provided access to the valuable intermediate **10** with a contrasteric selectivity (Figure 3).

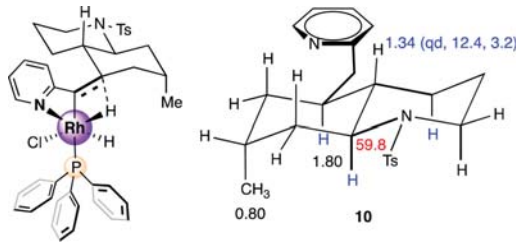

Figure 3. Transition state leading to **10** and its representative NMR data.

The stereoselectively formed decahydroquinoline **10** showed the same relative configuration in its four stereogenic centers as the target **1** and serralongamine A (**2**). The configuration at C-5 was ascertained considering the multiplicity of the signal corresponding to H-4a, which implies a trans relationship between H-4a and H-5, both in an axial disposition. Moreover, the chemical shift for C-8a (δ 59.8) did not differ from that observed in the precursors **7** (δ 60.3) and **9** (δ 60.6), indicating that the pyridylmethyl side chain is not axially located (Figure 3).[15]

Removal of the tosyl group in **10** using $LiAlH_4$, followed by reductive *N*-methylation of **11**, gave serralongamine A (**2**) in 76% yield for the two steps, which constitutes the first synthetic entry to a phlegmarine alkaloid embodying its decahydroquinoline stereoparent. The *trans*-decahydroquinoline serralongamine A differs from phlegmarine itself in the stereochemical relationship between the configuration at C7 and the trans ring fusion carbons, C4a and C8a (Figure 1).

It is noteworthy that the NMR data of our synthetic **2** were clearly different from those reported for the isolated serralongamine A in CD_3OD. Since basic nitrogen atoms readily protonate, we were able to reproducibly obtain ^1H and ^{13}C NMR spectra of the free base forms of serralongamine A in CD_3OD containing $NaOCD_3$.[16] We surmised that the natural isolate corresponded to its ditrifluoroacetate salt. Thus, the NMR spectra of synthetic serralongamine A was examined by titrating a sample of the free base with TFA. For a comparison of NMR data for natural and synthetic serralongamine A (**2**) as the double TFA salt, see the Supporting Information. As reproduced in Figure S1, NMR spectra identical to those reported for the natural product were obtained.

Having achieved **2**, we were two steps from completing the new structure proposed for huperzine N (**1**). Toward this end, reduction of the pyridine ring in B gave the corresponding piperidine, which, after oxidation with Na_2WO_4/urea·H_2O_2(UHP),[3] led to **1** by formation of both the amine *N*-oxide and nitrone functionalities, which were further confirmed by ^{15}N chemical shift NMR data. The spectroscopic data of the synthetic sample were identical in all respects to those reported for the natural product,[5] although a side product purified together with huperzine N was also formed. Two-dimensional NMR spectroscopy of the mixture identified the minor product as the *N*-oxide epimer of huperzine N. Although the oxidation of cyclic tertiary amines normally takes place axially,[17] the presence of an equatorial substituent increases the equatorial oxidation,[18] as occurred in our substrate (C8−C8a bond). Thus, the reaction did not work diastereoselectively and epimeric *N*-oxide **12** was also formed. The stereostructure and the complete ^1H, ^{13}C, and ^{15}N chemical shifts assignment of both epimers **1** and **12** (Figure 4) and also their protonated forms[19] (see the Supporting Information for details) were performed from the analysis of COSY, ROESY,[20] HSQC, HMBC, and TOCSY correlation spectra of the mixture.

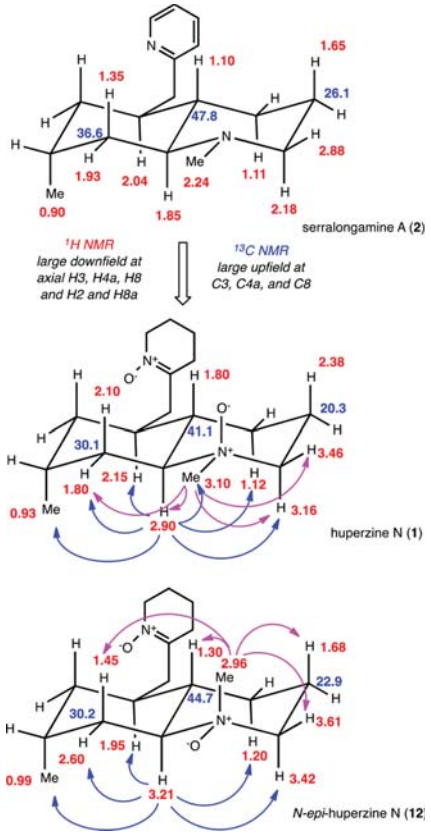

Figure 4. Characteristic NMR data and selected NOEs of huperzine N (**1**), *N-epi*-huperzine N (**12**), and serralongamine A (**2**).

The configuration of the new stereogenic center at the nitrogen atom in huperzine N was corroborated as *R*, on the basis of ^1H and ^{13}C chemical shift NMR analysis of **1** and its *N*-epimer **12**. Thus, a clear upfield shift for C(3), C(4a), and C(8) was

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observed, due to the 1,3-cis relationship between the N→O bond and the axial C−H bond of these carbon atoms (Figure 4), compared with either the free amine base nucleus (e.g., in **2**) or the *N*-epimeric *N*-oxide with the oxygen atom in an equatorial disposition (i.e., **12**).[21] The NMR data of synthetic huperzine N matched those described for the natural product, thus establishing its configuration as 1*R*,4a*S*,5*S*,7*R*,8a*S*. Although we have reported the racemic form, the phlegmarine alkaloids have always shown an *R* absolute configuration in the carbon bonded to the methyl group in the decahydroquinoline ring. Thus, the relative configuration allowed the absolute configuration to be proposed.

In summary, in this work on the phlegmarine subset of *Lycopodium* alkaloids, the first total synthesis of serralongamine A and the revised structure of huperzine N have been accomplished. The absolute configuration of the huperzine N was established, and the NMR data of the serralongamine A in its free base form are reported for the first time.

EXPERIMENTAL SECTION

General. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. All product mixtures were analyzed by thin-layer chromatography using TLC silica gel plates with a fluorescent indicator (λ = 254 nm). Analytical thin-layer chromatography was performed on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located by UV light and/or a 1% $KMnO_4$ aqueous solution or hexachloroplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60 ACC, 230−240 mesh). Drying of organic extracts during the reaction workup was performed over anhydrous Na_2SO_4. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR data assignments are supported by gCOSY and gHSQC experiments.

(4a*RS*,7*RS*,8a*RS*)-7-Methyl-1-(4-methylphenylsulfonyl)-5-oxodecahydroquinoline Ethylene Acetal (5). From crystallized keto ester **3** (536 mg, 1.27 mmol), following the procedure previously described,[11] ketone **4** was obtained and used in the next step without purification. After acetalization[2] of **4** and the purification step by chromatography (5% to 25% EtOAc in hexanes), **5** (373 g, 80%) was obtained as a white solid: R_f = 0.71 (1:1 EtOAc/hexanes); mp 100 °C. For NMR data, see ref 2.

(4a*RS*,7*SR*,8a*SR*)-7-Methyl-5-oxodecahydroquinoline (6). Operating as previously described,[2] starting from **5** (373 mg, 1.02 mmol), **6**, a 2:1 mixture of epimers at C(4a), was obtained (110 mg) as a colorless oil, which was used directly in the next step. For NMR data, see ref 2.

(4a*RS*,7*SR*,8a*SR*)-7-Methyl-5-oxo-1-(4-methylphenylsulfonyl)decahydroquinoline (7). To a cooled (0 °C) stirred solution of the above mixture of **6** and its epimer (110 mg) in CH_2Cl_2 (8 mL) was added a solution of TsCl (214 mg, 1.12 mmol, 1.1 equiv) in CH_2Cl_2 (4 mL), followed by Et_3N (0.17 mL, 1.23 mmol, 1.2 equiv). The mixture was stirred at rt for 6 h and diluted with CH_2Cl_2 (20 mL). The organics were washed with brine (2 × 5 mL), dried, concentrated, and purified by chromatography (5−25% EtOAc in hexanes) to yield successively **4** (59 mg) and **7** (121 mg, 38% in three steps, 57% brsm) as a white solid: R_f = 0.35 (25% EtOAc/hexanes); mp 108 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (d, J = 7.2 Hz, 3H, CH_3), 1.32 (m, 1H, H-4ax), 1.64 (m, 1H, H-3ax), 1.76 (m, 1H, H-3eq), 2.00 (dd, J = 12.8, 3.6 Hz, 1H, H-4eq), 2.15 (dt, J = 13.6, 2.4 Hz, 1H, H-6ax), 2.23 (dm, J = 12.4 Hz, 1H, H-8eq), 2.33 (td, J = 13.6, 4.6 Hz, 1H, H-8ax), 2.40 (masked, H-7), 2.42 (s, 3H, CH_3Ar), 2.46 (qd, 1H, J = 11.4, 3.2 Hz, H-4a), 2.56 (dd, J = 11.6, 4.0 Hz, 1H, H-6eq), 2.66 (td, J = 11.2, 3.2, 1.6 Hz, 1H, H-2ax), 2.89 (td, J = 11.4, 4.0 Hz, 1H, H-8a), 4.13 (dtd, J = 12.8, 4.0, 1.2 Hz, 1H, H-2eq), 7.30 (d, J = 8.4 Hz, 2H, *o*-Ts), 7.68 (d, J = 8.4 Hz, 2H, *m*-Ts); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9 (CH_3), 21.6 ($ArCH_3$), 23.5 (C-4), 24.4 (C-3), 28.5 (C-7), 36.1 (C-8), 47.3 (C-6), 49.3 (C-2), 53.1 (C-4a), 60.3 (C-8a), 127.3 (*m*-Ts), 129.8 (*o*-Ts), 137.1 (*ipso*-Ts), 143.6 (*p*-Ts), 209.1 (C-5). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{24}NO_3S$ 322.1471, found 322.1464.

(*E*)-(4a*RS*,7*SR*,8a*RS*)-7-Methyl-1-(4-methylphenylsulfonyl)-5-(pyridin-2-ylmethylene)decahydroquinoline (9). Both the pyridine phosphonate **8** and decahydroquinoline **7** were previously dried by azeotroping with benzene. To a stirred solution of phosphonate **8** (227 mg, 1 mmol, 5 equiv) in THF (3 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 0.52 mL, 0.84 mmol, 4.5 equiv). The resulting dark red solution was stirred for 30 min at rt before a solution of the decahydroquinoline **7** (60 mg, 0.187 mmol) in THF (1.2 mL) was added dropwise via syringe at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, 1 h at −30 °C, and 6 h at 0 °C, and quenched with sat. aq. NH_4Cl (1 mL) and water (1 mL). The mixture was extracted with EtOAc (2 × 3 mL), and the combined organic extracts were dried, concentrated, and purified by chromatography (5−40% EtOAc in hexanes) to give **9** (39 mg, 53%) as a white solid: R_f = 0.49 (50% hexane/EtOAc); mp 128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J = 7.2 Hz, 3H, CH_3), 1.31 (qd, 1H, J = 12.4, 2.0 Hz, H-4ax), 1.68 (m, 1H, H-3), 1.82 (m, 1H, H-3), 1.95 (dm, J = 13.2 Hz, 1H, H-4eq), 2.03 (dd, J = 12.6, 4.4 Hz, 1H, H-8eq), 2.12 (m, 1H, H-6ax), 2.15 (m, 1H, H-7), 2.19 (m, 1H, H-8ax), 2.24 (brt, J = 12.0 Hz, 1H, H-4a), 2.42 (s, 3H, $ArCH_3$), 2.91 (ddd, J = 13.2, 8.8, 4.4 Hz, 1H, H-8a), 2.94 (td, 1H, J = 12.8, 5.2 Hz, H-2ax), 3.07 (dt, J = 13.2, 2.0 Hz, 1H, H-6eq), 3.97 (dt, J = 12.8, 5.2 Hz, 1H, H-2eq), 6.31 (s, 1H, C═CH), 7.07 (dd, J = 7.6, 4.8 Hz, 1H, H-5 py), 7.13 (d, J = 8.0 Hz, 1H, H-3 py), 7.28 (d, J = 8.4 Hz, 2H, *o*-Ts), 7.59 (td, J = 7.6, 2.0 Hz, 1H, H-4 py), 7.69 (d, J = 8.4 Hz, 2H, *m*-Ts), 8.54 (dm, J = 4.8 Hz, 1H, H-6 py); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 18.2 (CH_3), 21.7 (CH_3Ar), 24.5 (C-3), 25.8 (C-4), 29.3 (C-7), 35.2 (C-6), 38.1 (C-8), 46.3 (C-4a), 46.8 (C-2), 60.6 (C-8a), 121.2 (C-5 py), 124.0 (C-3 Py), 124.1 (═CH), 127.3 (*o*-Ts), 129.7 (*m*-Ts), 136.0 (C-4 Py), 137.3 (*p*-Ts), 143.3 (*ipso*-Ts), 144.7 (C-5), 149.3 (C-6 Py), 157.3 (C-2 Py). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_2S$ 397.1944, found 397.1953.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-7-Methyl-5-(pyridin-2-ylmethyl)-1-(4-methylphenylsulfonyl)decahydroquinoline (10). To a stirred solution of **9** (27 mg, 0.068 mmol) in MeOH (7 mL) was added Wilkinson's catalyst $RhCl(PPh_3)_3$ (16 mg, 0.017 mmol, 25 mol %) at rt. The resulting mixture was rapidly evacuated and backfilled with H_2 three times and then stirred under an atmosphere of H_2 for 72 h. The mixture was concentrated, and purified by chromatography (5−25% EtOAc in cyclohexane) to give **10** (17 mg, 63%): R_f = 0.5 (1:1 EtOAc/cyclohexane): ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, J = 7.2 Hz, 3H, CH_3), 0.91 (qd, J = 12.4, 6.2 Hz, 1H, H-4ax), 1.20 (m, 2H, H-6), 1.34 (qd, J = 12.4, 3.2, 1H, H-4a), 1.65 (m, 2H, H-3), 1.80 (m, 1H, H-5), 1.86 (td, J = 12.4, 4.8 Hz, 1H, H-8ax), 1.94 (dm, J = 12.4 Hz, 1H, H-8eq), 2.00 (m, 1H, H-7), 2.12 (dm, J = 12.0 Hz, 1H, H-4eq), 2.30 (dd, J = 13.4, 8.8 Hz, 1H, CH_2Py), 2.42 (s, 3H, $ArCH_3$), 2.94−3.00 (m, 2H, H-2ax, H-8a), 3.11 (dd, J = 13.4, 4.0 Hz, 1H, CH_2Py), 3.97 (dt, J = 13.2, 5.6 Hz, 1H, H-2eq), 7.04 (d, J = 8.0 Hz, 1H, H-3 Py), 7.08 (m, 1H, H-5 Py), 7.28 (d, J = 8.4 Hz, 2H, *o*-Ts), 7.55 (td, J = 7.6, 1.6 Hz, 1H, H-4 Py), 7.68 (d, J = 8.0 Hz, 2H, *m*-Ts), 8.50 (dm, J = 4.0 Hz, 1H, H-6 Py); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 18.3 (CH_3), 21.6 ($ArCH_3$), 25.1 (C-3), 27.4 (C-4), 27.5 (C-7), 36.8 (C-6), 37.1 (C-8), 37.3 (C-5), 42.3 (CH_2Py), 45.6 (C-4a), 47.3 (C-2), 59.8 (C-8a), 121.1 (C-5 Py), 124.0 (C-3 Py), 127.2 (*o*-Ts), 129.7 (*m*-Ts), 136.2 (C-4 Py), 138.4 (*p*-Ts), 143.0 (*ipso*-Ts), 149.4 (C-6 Py), 161.1 (C-2 Py). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{31}N_2O_2S$ 399.2101, found 399.2116.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-7-Methyl-5-(pyridin-2-ylmethyl)-decahydroquinoline (11). A solution of sulfonamide **10** (17 mg, 0.043 mmol) in anhydrous THF (1 mL) was added to a stirred suspension of $LiAlH_4$ (16 mg, 0.43 mmol) in THF (1 mL) at 0 °C. The reaction was stirred overnight at rt and quenched by addition of one drop of water, another of aqueous 15% NaOH, and three drops of water. The mixture was diluted with CH_2Cl_2, filtered through a pad of Celite, and washed thoroughly with CH_2Cl_2. Evaporation of the solvent gave **11**, which was pure enough to be used in the following step. An analytical sample of secondary amine **11** was obtained by chromatography on alumina (1−5% MeOH in CH_2Cl_2): R_f = 0.22 (5:95 MeOH:CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 7.2 Hz, 3H, CH_3), 0.92 (qd, J = 12.0, 3.2 Hz, 1H, H-4a), 1.09 (qd, J = 12.0, 4.0 Hz, 1H, H-4ax), 1.20−1.25 (m, 2H, 2H-6), 1.44 (td, J = 12.0, 4.2 Hz, 1H, H-8ax), 1.52 (dt, J = 12.4, 2.0 Hz, 1H, H-8eq), 1.53 (m, 1H, H-3eq), 1.71 (tt, J = 13.2, 3.2 Hz,

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J. Org. Chem. 2016, 81, 2629−2634

1H, H-3ax), 1.82 (m, 1H, H-5), 2.01 (m, 1H, H-7eq), 2.14 (dd, J = 13.0, 3.0 Hz, 1H, H-4eq), 2.30 (dd, J = 13.2, 10.0 Hz, 1H, CH_2Py), 2.47 (ddd, 1H, J = 11.2, 10.0, 4.0 Hz, H-8a), 2.66 (td, 1H, J = 12.2, 3.0 Hz, H-2ax), 3.07 (dm, J = 12.0 Hz, 1H, H-2eq), 3.14 (dd, J = 13.2, 4.0 Hz, 1H, CH_2Py), 7.06−7.09 (m, 2H, H-3 Py, H-5 Py), 7.55 (td, J = 8.0, 1.6 Hz, 1H, H-4 Py), 8.52 (dd, J = 5.2, 2.0 Hz, 1H, H-6 Py); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2 (CH_3), 27.2 (C-3), 27.5 (C-7), 28.8 (C-4), 36.4 (C-5), 37.6 (C-6), 39.4 (C-8), 41.9 (CH_2Py), 47.0 (C-2), 48.4 (C-4a), 56.2 (H-8a), 120.9 (C-5 Py), 123.9 (C-3 Py), 136.1 (C-4 Py), 149.4 (C-6 Py), 161.8 (C-2 Py). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{24}N_2$ 245.2012, found 245.2009.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-1,7-Dimethyl-5-(pyridin-2-ylmethyl)-decahydroquinoline (*rac*-Serralongamine A, 2). To a solution of the above crude amine **11** (10 mg, 0.043 mmol) in MeOH (2.3 mL) was added 37% aqueous formaldehyde (24 mL, 0.328 mmol) and $NaBH_3CN$ (18 mg, 0.287 mmol) at 0 °C, and the mixture was stirred at rt for 30 min. The volatiles were evaporated, and the crude was purified on neutral alumina (CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to give **2** (8.4 mg, 76% over two steps from **10**): R_f = 0.70 (5% CH_3OH in CH_2Cl_2). This sample was dissolved in CD_3OD, and $NaOCD_3$ (0.1 M in CD_3OD) was added. ^{1}H and ^{13}C NMR spectra of the free base were obtained: ^{1}H NMR (400 MHz, CD_3OD, $NaOCD_3$) δ 0.90 (d, J = 7.6 Hz, 3H, CH_3), 1.10−1.15 (masked, 1H, H-4a), 1.11 (br q, J = 12.0 Hz, 1H, H-4ax), 1.15 (br d, J = 12 Hz, 1H, H-6eq), 1.25 (td, J = 12.4, 4.4 Hz, 1H, H-6ax), 1.35 (td, J = 12.4, 4.8 Hz, 1H, H-8ax), 1.65−1−75 (m, 2H, 2H-3), 1.80−1.92 (m, 2H, H-5 and H-8a), 1.93 (dm, J = 12.0 Hz, 1H, H-8eq), 2.03 (m, 1H, H-7), 2.16 (dm, J = 11.8 Hz, 1H, H-4eq), 2.18 (td, J = 12.8, 3.2 Hz, 1H, H-2ax), 2.24 (s, 3H, CH_3), 2.30 (dd, J = 13.2, 10.4 Hz, 1H, CH_2py), 2.88 (dm, J = 12.0 Hz, 1H, H-2eq), 3.19 (dd, J = 13.2, 4.0 Hz, 1H, CH_2py), 7.24 (dd, J = 7.6, 4.8 Hz, 1H, H-5 py), 7.25 (t, J = 7.4 Hz, 1H, H-3 py), 7.73 (tt, J = 7.6, 1.6 Hz, 1H, H-4 py), 8.42 (dm, J = 4.8, 1H, H-6 py). ^{13}C NMR (100 MHz, CD_3OD, $NaOCD_3$) δ 19.5 (CH_3), 26.1 (C-3), 28.5 (C-7), 29.6 (C-4), 36.6 (C-8), 37.8 (C-5), 38.0 (C-6), 42.6 (CH_2py), 43.1 (NCH_3), 47.8 (C-4a), 58.5 (C-2), 64.8 (C-8a), 122.7 (C-3 py), 125.7 (C-5 py), 138.4 (C-4 py), 149.5 (C-6 py), 162.6 (C-2 py). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{27}N_2$ 259.2168, found 259.2169.

Spectra matching the reported spectra of (−)-serralongamine A[6] were obtained after the addition of TFA in CD_3OD to the above sample of **2**: ^{1}H (400 MHz, CD_3OD, TFA) δ 0.95 (d, J = 7.6 Hz, 3H, CH_3), 1.15 (br d, J = 13.2 Hz, 1H, H-6eq), 1.41 (td, J = 12.8, 4.8 Hz, 1H, H-6ax), 1.44 (td, J = 12.4, 4.4 Hz, 1H, H-4ax), 1.53 (qd, J = 12.0, 2.8 Hz, 1H, H-4a), 1.64 (td, J = 12.4, 4.8 Hz, 1H, H-8ax), 1.88 (qt, J = 12.4, 4.0 Hz, 1H, H-3ax), 2.00−2.09 (m, 2H, H-3eq, H-5ax), 2.15 (br d, J = 12.4 Hz, 1H, H-8eq), 2.22 (br d, J = 12.0 Hz, 1H, H-7eq), 2.24 (m, 1H, H-4eq), 2.72 (dd, J = 14.4, 10.4 Hz, 1H, CH_2py), 2.86 (s, 3H, NCH_3), 3.12 (td, J = 13.0, 3.2 Hz, 1H, H-2ax), 3.15 (td, J = 12.2, 4.0 Hz, 1H, H-8a), 3.52 (br, J = 13.0 Hz, 1H, H-2eq), 3.56 (dd, J = 14.4, 4.0 Hz, 1H, CH_2py), 7.85 (ddd, J = 7.2, 5.6,0.8 Hz, 1H, H-5py), 7.88 (d, J = 8.0 Hz, 1H, H-3py), 8.54 (td, J = 8.0, 1.6 Hz, 1H, H-4py), 8.77 (d, J = 5.6 Hz, 1H, H-6py); ^{1}C NMR (100 MHz, CD_3OD, TFA) δ 18.3 (CH_3), 24.0 (C-3), 27.1(C-4), 28.1 (C-7), 33.8 (C-8), 36.8 (C-6), 37.5 (C-5), 37.9 (CH_2py), 41.4 (NCH_3), 46.3 (C-4a), 57.4 (C-2), 66.0 (C-8a), 126.3(C-5py), 129.4 (C-3py), 142.8 (C-6py), 147.8 (C-4py), 157.7 (C-2py).

(1*RS*,4a*SR*,5*SR*,7*RS*,8a*SR*)-1,7-Dimethyl-5-(2,3,4,5-tetrahydropyridine 1-oxide)decahydroquinoline *N*-Oxide (Huperzine N, 1). To a stirred solution of **2** (8 mg, 0.031 mmol) in AcOH (0.25 mL) was added PtO_2 (20% w/w, 2 mg) at rt. The resulting mixture was evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 for 16 h. The mixture was diluted with CH_2Cl_2 (2 mL) before it was filtered through a pad of Celite and washed through with CH_2Cl_2. The filtered solution was washed with 1 N NaOH, dried, and concentrated. To a solution of the above crude diamine in $MeOH/CH_2Cl_2$ (1:1; 0.2 mL) were added in one portion UHP (30 mg, 0.31 mmol) and $Na_2WO_4{\cdot}2H_2O$ (2 mg, 0.006 mmol), and the mixture was stirred at rt for 72 h. After concentration, CH_2Cl_2 was added and the reaction mixture was filtered, concentrated, and purified by chromatography (2.5−10% MeOH in CH_2Cl_2 and then 85/15/1.5 $CHCl_3$/$MeOH/NH_3$) to give **1** and its epimer **12** (6 mg, 66%, 3:2 ratio) as a colorless oil, which solidified on standing: R_f = 0.20 (80/20/2 $CHCl_3$/$MeOH/NH_3$).

Data for Huperzine N (1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 7.2 Hz, 3H, CH_3), 1.12 (qd, J = 12.0, 3.0 Hz, 1H, H-4ax), 1.28 (masked, 1H, H-6eq), 1.40 (td, J = 12.0, 4.0 Hz, 1H, H-6ax), 1.58 (br d, J = 13.0 Hz, 1H, H-3eq), 1.68 (m, 2H, H-4′), 1.80 (m, 2H, H-4a, H-8ax), 1.88 (m, 2H, H-5′), 1.88 (masked, 1H, CH_2py), 2.05 (m, 1H, H-4eq), 2.10 (1H, m, H-8eq), 2.21 (m, 1H, H-5), 2.38 (masked, 1H, H-3ax), 2.40 (t, J = 6.0 Hz, 2H, H-3′), 2.98 (dd, J = 12.0, 3.0 Hz, 1H, CH_2py), 2.90 (td, J = 11.5, 3.2 Hz, 1H, H-8a), 3.10 (s, 3H, NCH_3), 3.14 (ddd, J = 12.0, 11.0, 3.0 Hz, 1H, H-2ax), 3.46 (br d, J = 12.0 Hz, 1H, H-2eq), 3.75 (t, J = 6.4 Hz, 2H, H-6′); ^{13}C NMR (100 MHz, HSQC) δ 18.9 (C-4′), 19.0 (CH_3), 20.3 (C-3), 23.3 (C-5′), 27.0 (C-4), 27.1 (C-7), 29.9 (C-3′), 30.1 (C-8), 32.4 (C-5), 36.7 (CH_2py), 36.8 (C-6), 41.1 (C-4a), 57.6 (NCH_3), 58.5 (C-6′), 69.1 (C-2), 73.8 (C-8a), 148.0 (C-2′); ^{15}N (50 MHz, deduced from ^{1}H−^{15}N HMBC correlations) δ 114.7 (*N*-oxide), 271.7 (nitrone). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{31}N_2O_2$ 295.2380; found 295.2374.

Data for N-epi-Huperzine N (12). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 7.2 Hz, 3H, CH_3), 1.20 (masked, 1H, H-4ax), 1.30 (m, 1H, H-4a), 1.35 (m, 1H, H-6), 1.40 (m, 1H, H-6), 1.45 (td, J = 12.0, 3.0 Hz, 1H, H-8ax), 1.68 (m, 1H, H-3eq), 1.68 (m, 2H, H-4′), 1.87 (m, 2H, H-5′), 1.87 (masked, 1H, H-3ax), 1.95 (m, 1H, H-5), 2.05 (m, 1H, H-4eq), 2.35 (masked, 1H, CH_2py), 2.40 (t, J = 6.0 Hz, 2H, H-2′), 2.60 (1H, m, H-8eq), 2.70 (m, 1H, CH_2py), 2.96 (s, 3H, NCH_3), 3.21 (br t, J = 12.0 Hz, 1H, H-8a), 3.42 (td, J = 12.0, 3.0 Hz, 1H, H-2ax), 3.61 (br d, J = 12.0 Hz, 1H, H-2eq), 3.72 (t, J = 6.4 Hz, 2H, H-6′); ^{13}C NMR (100 MHz, HSQC) δ 18.2 (CH_3), 19.2 (C-4′), 22.9 (C-3), 23.3 (C-5′), 27.1 (C-4), 27.2 (C-7), 29.9 (C-3′), 30.2 (C-8), 34.6 (C-5), 35.5 (CH_2py), 37.5 (C-6), 44.7 (C-4a), 48.0 (NCH_3), 58.6 (C-6′), 71.1 (C-2), 75.9 (C-8a), 147.2 (C-2′); ^{15}N (50 MHz, deduced from ^{1}H−^{15}N HMBC correlations) δ 113.8 (*N*-oxide), 271.0 (nitrone). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{31}N_2O_2$ 295.2380; found 295.2374.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00025.

Tables for ^{1}H and ^{13}C NMR data of synthetic serralongamine A (**2**, free base and diprotonated sample) and huperzine N (**1**) as well as NMR data of isolated alkaloids; copies of ^{1}H and ^{13}C NMR spectra of new compounds; COSY, TOCSY, ROESY, HSQC, HMBC, and ^{1}H−^{15}N HMBC spectra of huperzine N (**1**) and its epimer **12** (PDF)

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Notes

The authors declare no competing financial interest.

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J. Org. Chem. 2016, 81, 2629−2634

(3) Systematic numbering is used throughout this paper. In the Supporting Information, the biogenetic numbering is included in all tables to facilitate the comparison of the NMR data reported for phlegmarine alkaloids with those recorded from a synthetic source (compounds **1** and **2**).
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J. Org. Chem. 2016, 81, 2629−2634