# Asymmetric Synthesis of Decahydroquinolines via Organocatalysis: Total Synthesis of (+)-Lycoposerramine Z and (-)-Cermizine B

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Programa de Doctorat: Química Orgànica Experimental i Industrial

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Memòria presentada per Carlos Luque Corredera

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Dirigida per:

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Calculations that appear in this work were performed by Carles Bo and Ruth Dorel at the Institute of Chemical Research of Catalonia (ICIQ).

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# Contents

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## PUBLICATIONS

1. ***cis-Decahydroquinolines via Asymmetric Organocatalysis: Application to the total synthesis of Lycoposerramine Z***. B. Bradshaw, C. Luque-Corredera, J. Bonjoch. *Org.Lett.***, 2013**, *15*, 326-329.

2. ***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.

3. ***A Gram-scale route to Phlegmarine Alkaloids: Rapid Total Synthesis of (-)-Cermizine B***. B. Bradshaw, C. Luque-Corredera, J. Bonjoch. *Chem. Commun.*, **2014**, *50*, 7099-7102.

4. ***Synthetic approaches towards the Lycopodium alkaloids***. B. Bradshaw, G. Saborit-Villarroya, C. Luque-Corredera, M. Balañà, J. Bonjoch. *Recent Advances of Pharmaceutical Sciences.* **2014**. (*in press).*

5. ***A Unified approach to the cis-Phlegmarine Alkaloids.*** B. Bradshaw, C. Bosch, C. Luque-Corredera, J. Bonjoch. *(Manuscript in preparation).*

## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| $[\alpha]^{22}_{D}$ | specific optical rotatory power at λ= 589 nm |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| Anal. | elemental analysis |
| 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 |
| 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 |
| GC | gas chromatography |
| [H] | reduction |
| HMPA | hexamethylphosphoramide |
| $^{1}$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 |
| KHMDS | potassium bis(trimethylsilyl)azide |
| LDA | lithium diisopropylamide |
| LiHMDS | lithium bis(trimethylsilyl)azide |
| 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 | mol(es) |
| mp | melting point |
| MS | mass spectrometry |
| Ms | mesyl (methylsulfonyl) |
| n.a | not available |
| Ns | 4-nitrobenzenesulfonyl |
| [O] | oxidation |
| OTBS | *tert*-butyldimethylsilyl ether |
| OTES | triethylsilyl ether |
| OTMS | trimethylsilyl ether |
| OTPS | triphenylsilyl ether |

| | |
|---|---|
| p. | page |
| ppm | parts per million |
| R | generalized alkyl group or substituent |
| $R_f$ | retention factor |
| *rac* | racemic |
| ref. | reference |
| rt | room temperature |
| *s* | singlet |
| sat. | saturated |
| sol. | solution |
| Superhydride® | lithium triethylborohydride |
| t | triplet |
| TASF | tris(dimethylamino)sulfonium difluorotrimethylsilicate |
| 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. Introduction and Objectives:

## The Phlegmarine Alkaloids

## 1.1. Introduction and Objectives

### 1.1.1. The phlegmarine alkaloids

The lycopodium alkaloids,[1] 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. To date almost 300 lycopodium alkaloids have been discovered, and in order to more easily manage this vast structural diversity a classification system was established which divided these alkaloids in four distinct classes or subfamilies. These are the phlegmarine or miscellaneous class, lycopodine, lycodine and fawcettimine (figure 1.1).

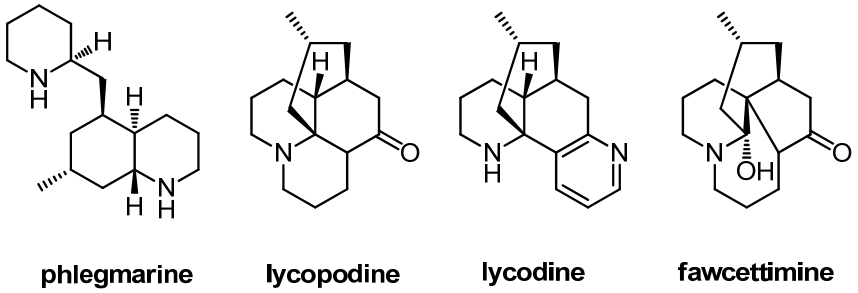



**Figure 1.1**. Classification of the lycopodium alkaloids.

Whilst many of the lycopodium alkaloids can be related to back to one of these four parent compounds and bear the same stereochemical relationship, the subsequent discovery of many products that deviated from this neat classification required the invention of a "miscellaneous class". This class groups together many phlegmarine type structures that have different stereochemical relationships to the parent compound such as a *cis* relationship at the ring fusion positions. The number of compounds that are grouped into the miscellaneous class has continued to grow significantly and rather than being anomalies, the following sections will outline the central and fundamental role the phlegmarine type compounds of all types play within the lycopodium alkaloid family.

[1]Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004***, 21,* 752-772.

### 1.1.2. Structural classification of the phlegmarine type 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 (Figure 1.2).

**Type A** compounds are those which contain the C-7 (methyl substituent) and C-4a and C-8a (ring fusion hydrogen atoms) all arranged in a *cis* orientation. Serratezomine E[2] and its epimer at C-5 lycoposerramine Z,[3] which in turn contains an unusual nitrone moiety, are the representative products for this specific type. **Type B** compounds are characterized by having the ring fusion hydrogens in *cis*, but *trans* respect the C-7 methyl group. This group includes cermizine A,[4] which is the only compound to feature an ethanoic acid appendage at C-2 of the decahydroquinoline ring, cermizine B,[4] huperzine M,[5] and huperzine N.[5]

**Type C** compounds are the most numerous group, in which the ring fusion hydrogens and the C-7 methyl are all arranged *trans* to each other. This group includes phlegmarine[6] and a number of N-methylated and acetylated derivatives, lycoposerramine Y[3] and huperzine K,[7] which posses a nitrone unit as do lycoposerramine X,[3] huperzine J,[7] and L[7] but are epimeric at C-5. Until very recently with the isolation of serralongamine A,[8] the **Type D** stereochemistry with ring fusion hydrogens arranged *trans* and the C-8a hydrogen *cis* to the C-7 methyl was unknown. This compound features a pyridine instead of the usual piperidine ring system.

[2]Kubota, T.; Yahata, H.; Yamamoto, S.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3577-3580.
[3]Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223-229.
[4]Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015-7023.
[5]Gao, W.-Y.; Li, Y.-M.; Jiang, S.-H.; Zhu, D.-Y. *Helv. Chim. Acta* **2008**, *91*, 1031-1035.
[6]Nyembo, L.; Goffin, A.; Hootelé, C.; Braekman, J.-C. *Can. J. Chem*. **1978**, *56*, 851-865.
[7]Gao, W.; Li, Y.; Jiang, S.; Zhu, D. *Planta Med*. **2000**, *66*, 664-667.
[8]Jiang, W.-P.; Ishiuchi, K.; Wu, J.-B.; Kitanaka, S. *Heterocycles* **2014**, *89*, 747-752.

The stereochemistry in the piperidine ring appendage appears always to have the *S* configuration whilst the carbon atom linked to the methyl group is *R*.[9]

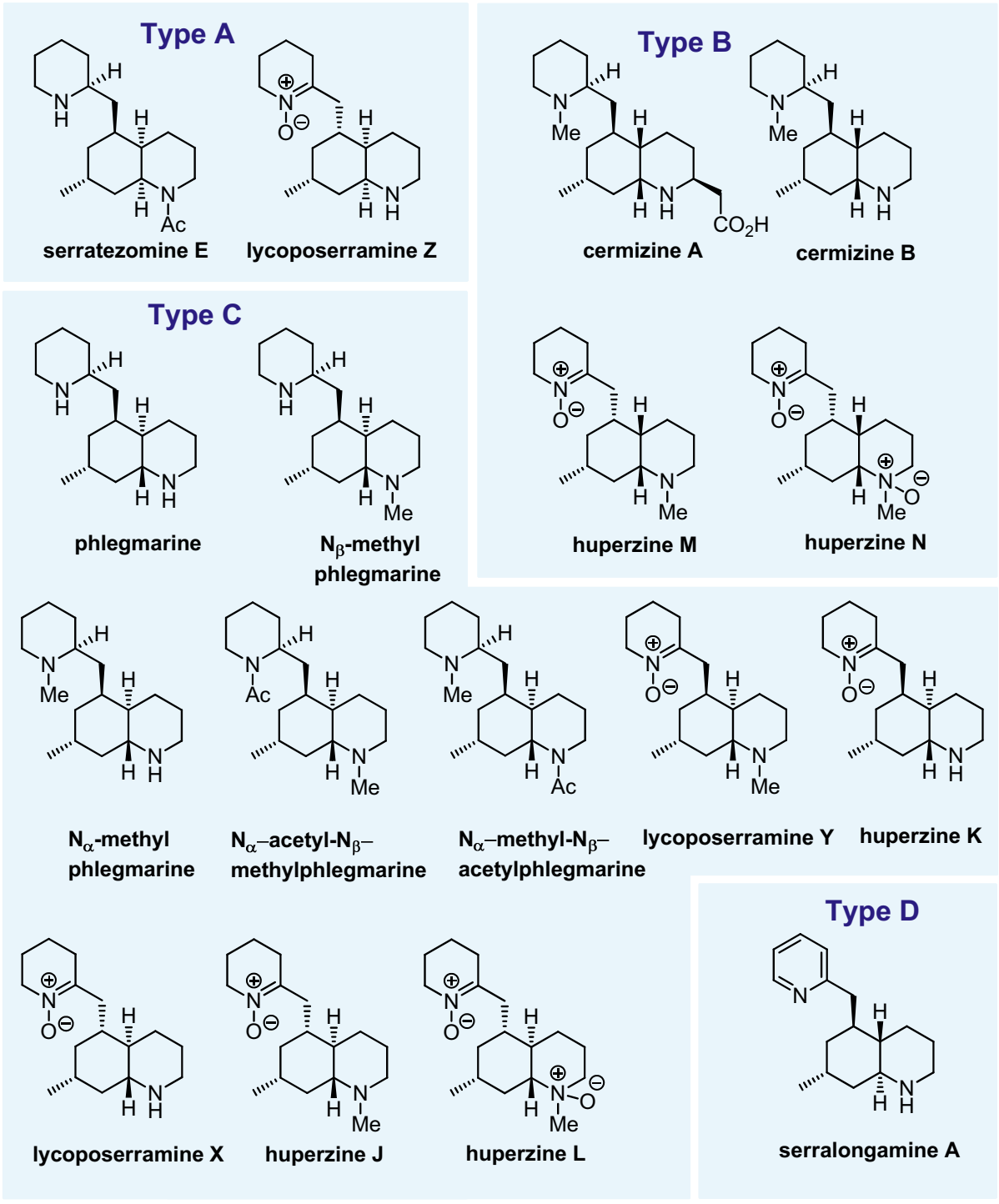
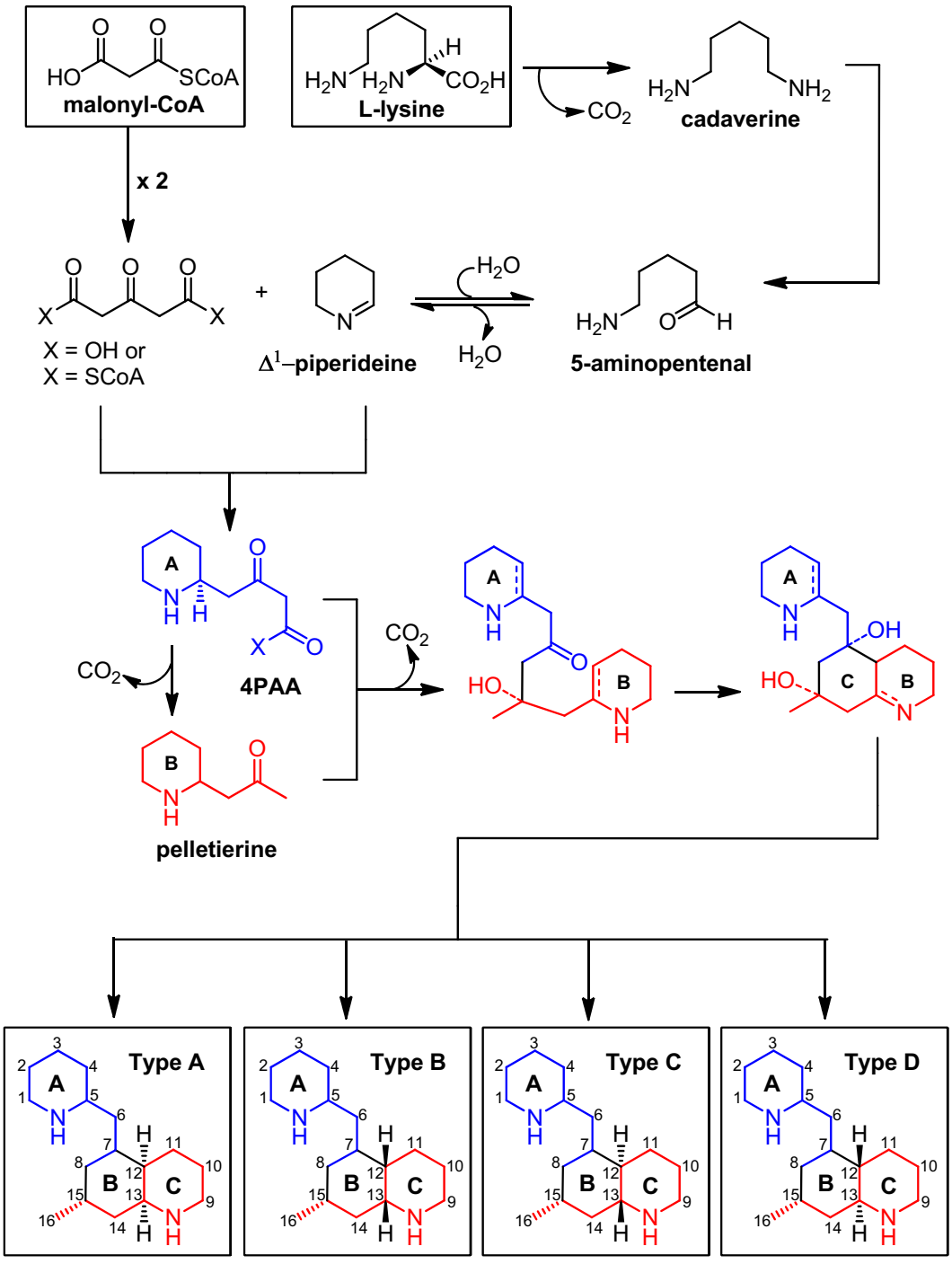



**Figure 1.2**. All known phlegmarine alkaloids grouped by core structural type.

[9] When the absolute configuration is unknown, some phlegmarine alkaloid isolation papers depict the enantiomer of the corresponding structure shown in Figure 1.2.

### 1.1.3. Biosynthesis of the phlegmarine alkaloids

A basic overview of the biosynthesis of the different phlegmarine nuclei is outlined in scheme 1.1 based on the present knowledge.[1] The entry point into the pathway is through the decarboxylation of lysine to form cadaverine which is then transformed to $\Delta^1$-piperideine. At the same time, two molecules of malonyl-CoA are condensed to form acetonedicarboxylic acid, whose union with $\Delta^1$-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 a dimeric intermediate via an aldol type coupling. Presumably at some point the piperidine ring of the pelletierine type intermediate, which forms the B ring, is oxidized to an enamine type structure which then cyclises onto the C-6 carbonyl to form the C ring. Subsequent reduction of the ring system leads to the formation of the observed stereochemical diversity present in these compounds. It is not clear if this process is tightly regulated by specific enzymes that selectively give each of the four stereochemistries observed or proceeds without control generating the compounds in a random manner. Alternatively, it may well be that only one of the four possible structures is formed (most likely the type C structure) and the others arise by epimerization of the respective stereogenic centres.




**Scheme 1.1**. Proposed biosynthesis of the phlegmarine alkaloids.

### 1.1.4. Phlegmarines: biosynthetic precursors of the lycopodium alkaloids

The biosynthetic pathway leading to all lycopodium alkaloids has long been a source of debate and is still not clear. It was Braekman, who reported the isolation of phlegmarine in 1978,[6] that first postulated that this compound may serve as a key intermediate in the biosynthesis of all the lycopodium alkaloids. So far this remains the currently accepted hypothesis (see Scheme 1.2). From each of the core phlegmarine structures further complexity and diversity is arrived at via three main modifications: oxidations, ring fragmentations and ring cross linkage.[10] Additionally, a number of dimeric compounds are known which probably arise via a parallel phlegmarine skeleton biosynthesis pathway, in which the 4PAA intermediate contains a dicarbonylic side chain at C-1 as well as the C-5 position. The type A skeleton features in a large amount of lycopodium alkaloid subsets including nankakurine B,[11] luciduline,[12] lyconadin C, A, and B,[13] dihydrolycolucine,[14] huperminone A,[15] and lycoposerramine V and W.[16] The type B phlegmarine is less prevalent featuring in the two dimeric compounds spirolucidine[17] which also features a type A nucleus and possibly lycoperine A.[18] The type C compounds are fundamental in that they are likely the key precursors to the other three main classes of lycopodium alkaloids: fawcettimine, lycopodine and lycopodine and their many subsequent derivatives. Other compounds derived from type C phlegmarine alkaloids include lycobelline A[19] via fragmentation of the piperidine ring and serratezomine D[2] a dimeric compound, which contains two type C nuclei embedded within its structure. Serralongamine A[8] presumably arises via oxidation of the A ring piperidine of a type D phlegmarine precursor.

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[10] In a number of cases where the core stereochemistry is lost via an oxidation or fragmentation reaction the resulting compound may arise from more than one possible phlegmarine precursor.
[11] Hirasawa, Y.; Morita, H.; Kobayashi, J. *Org. Lett*. **2004**, *6*, 3389–3391.
[12] Ayer, W. A.; Masaki, N.; Nkunika, D.-S. *Can. J. Chem*. **1968**, *46*, 3631-3642.
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[15] Hirasawa, Y.; Kato, Y.; Wong, C.-P. Uchiyawa, N.; Goda, Y.; Hadi, H.-A.; Morita, H. *Tetrahedron Lett*. **2013**, *54*, 1593-1595.
[16] Shigeyawa, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H.; *Org. Lett*. **2007**, *20*, 4069-4072.
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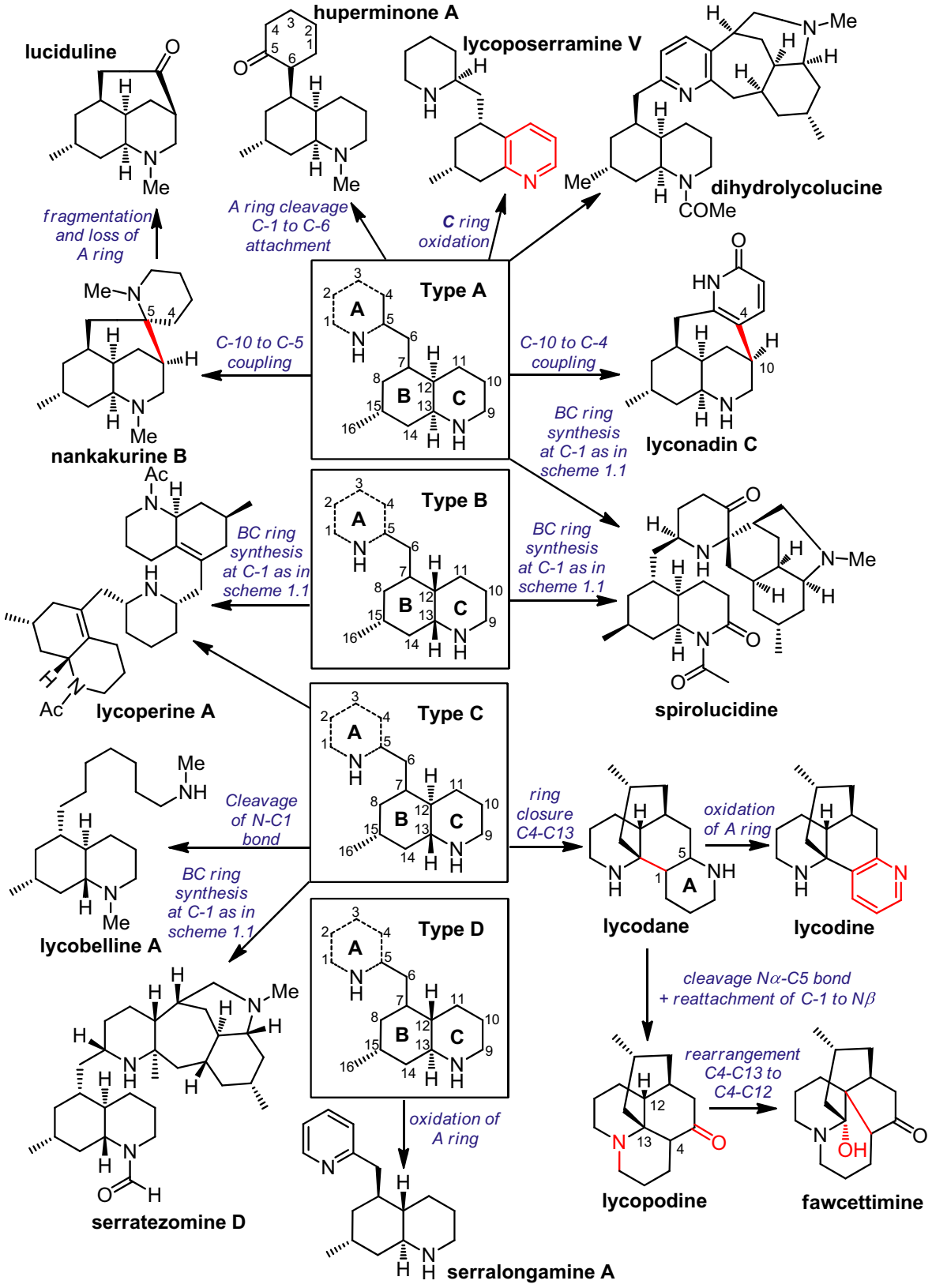



**Scheme 1.2**. Biosynthesis of miscellaneous and main class Lycopodium alkaloids from phlegmarine building blocks.

### 1.1.5. Bioactivities of the phlegmarine alkaloids

Whilst little information is known about the biological activities of the phlegmarine alkaloids they appear to have similar properties to the other classes of lycopodium alkaloids. This family of natural products have elicited major interest in recent years as potential treatments for cancer[7] and severe neurodegenerative diseases[20] such as Alzheimer's.[21] However, to date extensive biological studies have been hindered due to limited availability of material from natural sources and attempts to remedy this situation by accessing material via cultivation or fermentation have so far been unsuccessful.[1]

One of the most interesting features of the phlegmarine compounds is the presence of the nitrone moiety which may result in them having neuroprotective activity due to the ability of this functional group to act as a radical trap.[22] An outline of this process is shown in figure 1.3. Oxidative stress can lead to the formation of free radicals which left unchecked can wreck havoc on the brain tissue by an initiating a series of processes, which result in inflammation of the brain. If this process continues for sufficient time it inevitable will lead eventually to some form of neurodegenerative disease such as Alzheimer's. However, if on the other hand the radical is intercepted by a compound containing a nitrone moiety the radical can be captured as a stable spin-adduct and the radical is neutralized before it initiate the destructive cascade.

[20] Xu, J.; Lacoske, M. H.; Theodorakis, E. A. *Angew. Chem., Int. Ed*. **2014**, *53*, 956-987.
[21] Sun, Y.; Yu, P.; Zhang, G.; Wang, L.; Zhong, H.; Zhai, Z.; Wang, L.; Wang, Y. *J. Neurosci. Res*. **2012**, *90*, 1667–1669.
[22] Porcal, W.; Hernández, P.; González, M.; Ferreira, A.; Olea-Azar, C.; Cerecetto, H.; Castro, A. *J. Med. Chem.* **2008**, *51*, 6150-6159.

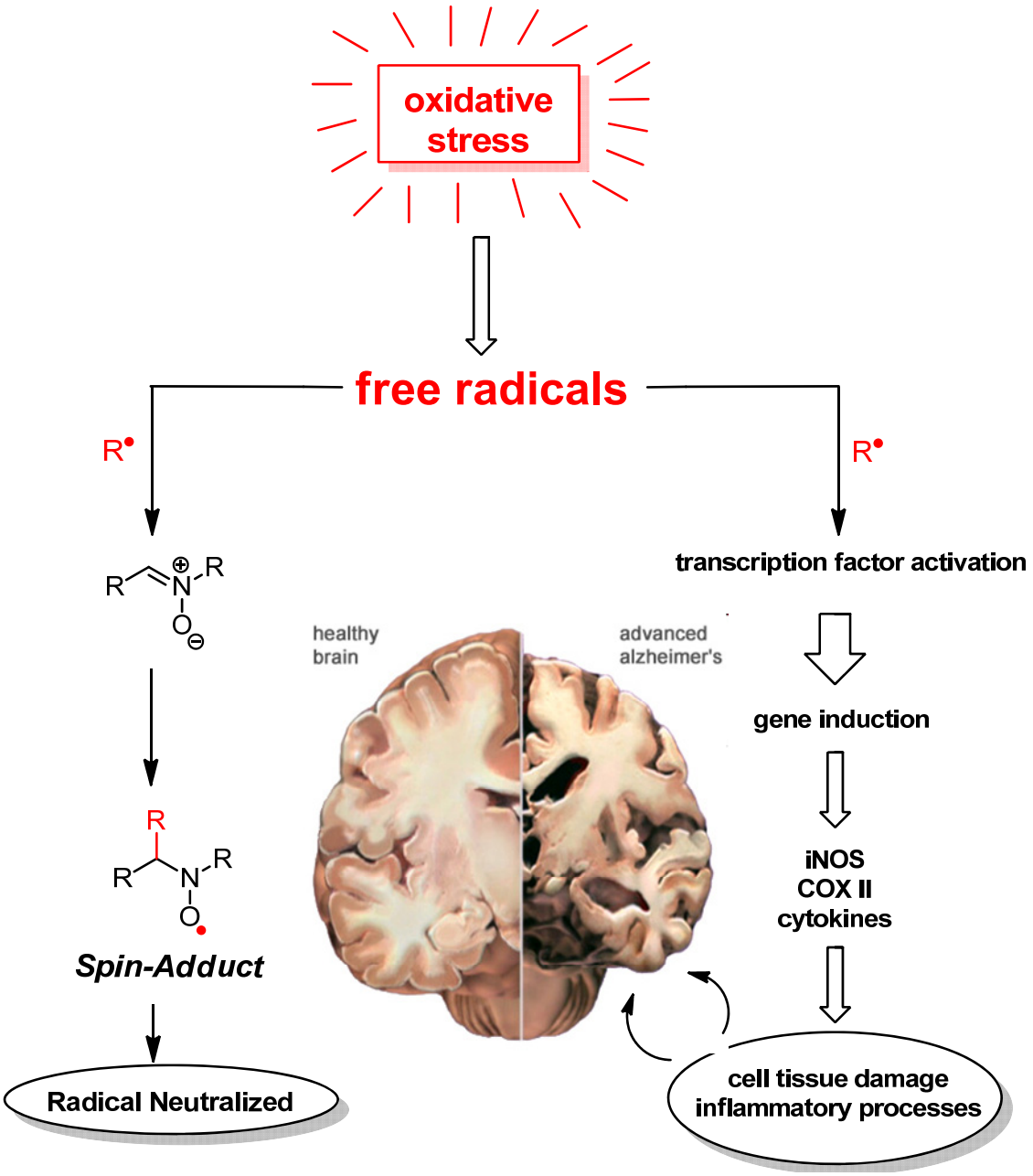



**Figure 1.3.** The nitrone moiety as a neuroprotective agent preventing destructive radical cascades.

## 1.2. Previous Synthesis of Phlegmarine Alkaloids

While there are numerous approaches towards the total synthesis of all the classes of lycopodium alkaloids,[23] the phlegmarine subclass has received less attention until relatively recently. In this section an overview of all the prior syntheses of the phlegmarine alkaloids is presented.

### 1.2.1. MacLean's approach to the *cis*-phlegmarine skeleton

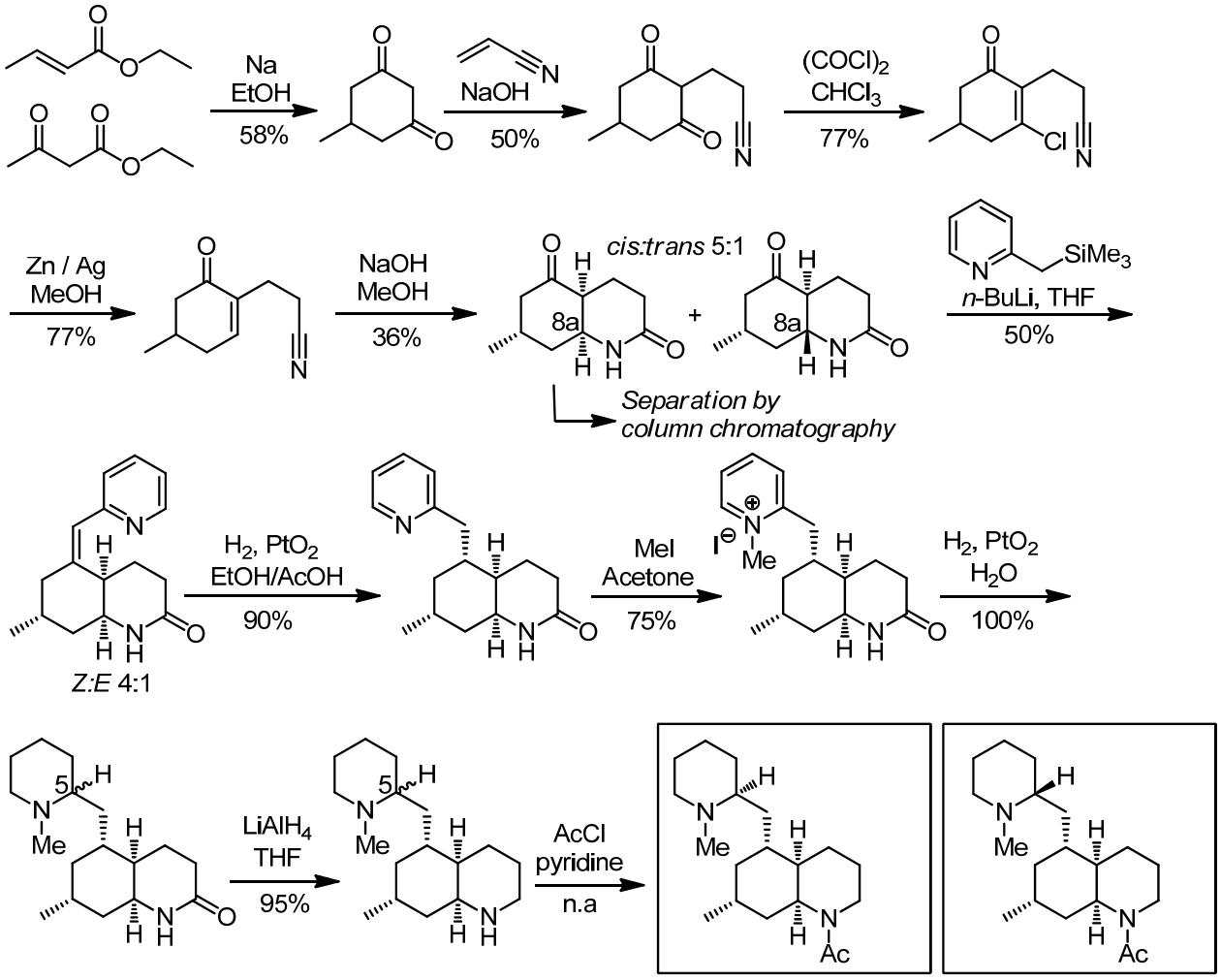
Braekman, as described in the biosynthesis section, reported the isolation of phlegmarine in 1978. He assigned a general structure but was unable to assign any stereochemical relationships. It was the pioneering work by MacLean[24] three years later, which established the relative configuration of four of the five asymmetric centers in the molecule and established that phlegmarine possessed a *trans* stereochemistry fusion ring system.

Since initially it was not known the stereochemistry pattern in phlegmarine natural product, MacLean set out to prepare a *cis* decahydroquinoline derivative to determine by comparison if this relative configuration between all the stereogenic centers matched with a sample of the natural product, (scheme 1.3).

Formation of 5-methylcyclohexane-1,3-dione followed by Michael addition with acrylonitrile and subsequent reduction of the carbonyl functionality afforded the key cyanocyclohexanone. This compound was converted to a 5:1 mixture of bicyclic ketolactams under hydrolysis conditions giving as major product the one which contains all *cis* stereochemistry. These two bicycles could be separated by column chromatography, which allowed carrying out the Peterson olefination only on the *cis* lactam, giving a 4:1 mixture of *Z*/*E* isomers respectively. The vinyl pyridine substrates (Z and E isomers) were separated and were subjected to alkene hydrogenation studies. The hydrogenation of the major Z isomer gave all *cis* stereochemistry and the minor E isomer gave a mixture 1:4 in favour of the epimer. The lactam with the four stereocenteres in *cis* orientation was converted to the quaternary salt and subsequent reduction

[23] For a extensive review focusing on the the total synthesis of the lycopodium alakoids see: P. Siengalewicz, J. Mulzer and U. Rinner,*The Alkaloids*, **2013**, vol. 72, p. 1-151.
[24] 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.

of the pyridine ring employing the Adam's catalyst gave an epimeric mixture at C-5. Reduction of the lactam and final acetylation afforded two *cis*-derivatives which unfortunately, were found to not correspond to the natural $N_{\alpha}$-methyl-$N_{\beta}$-acetylphlegmarine after NMR comparison.



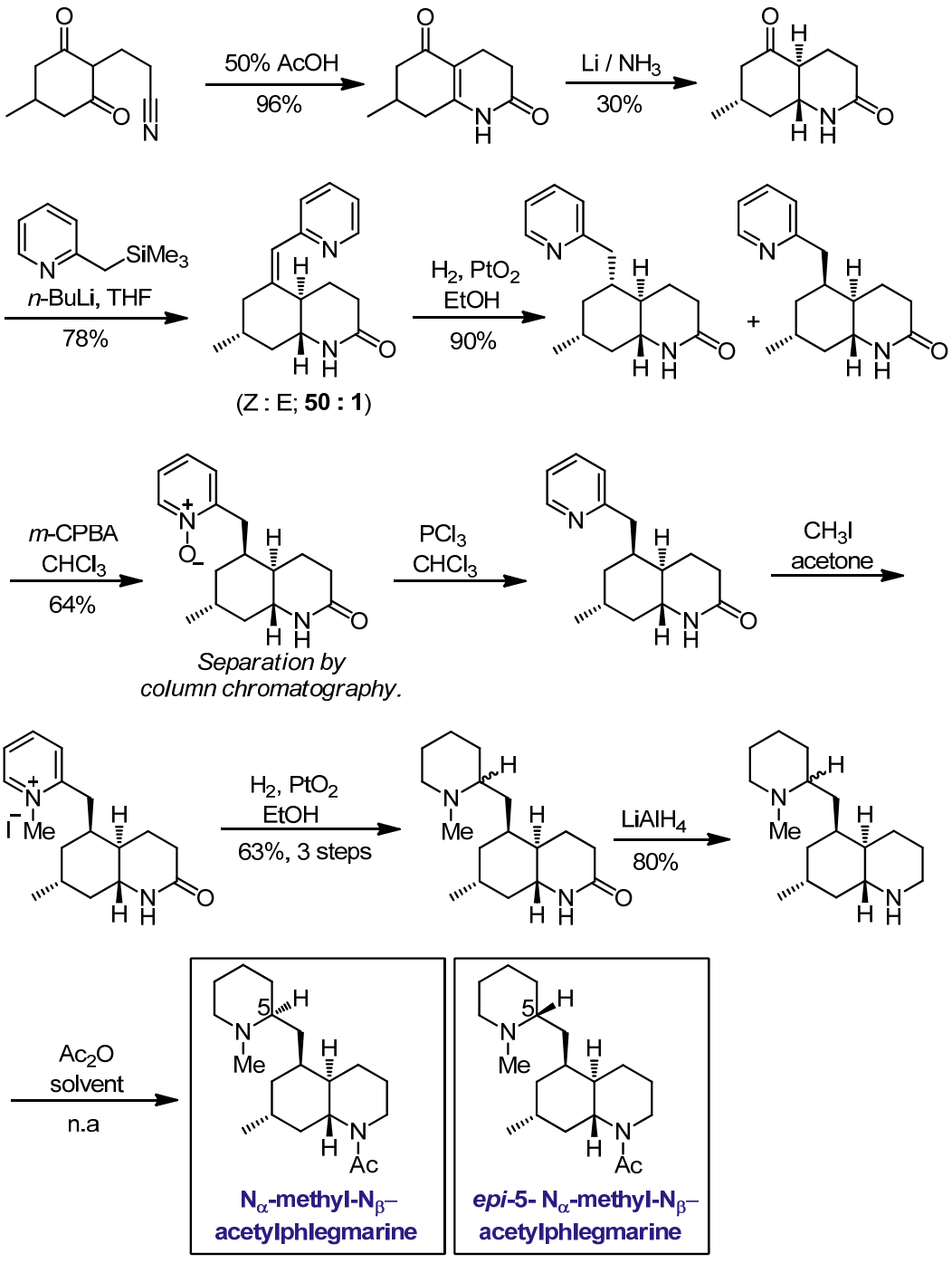

**Scheme 1.3**. MacLean's first synthesis of phlegmarine isomers (*cis*-decahydroquinolines series).

### 1.2.2. Synthesis of Nα-methyl-Nβ-acetylphlegmarine

MacLean then turned to the preparation of compounds with a *trans* fusion ring system. Whilst the *trans*-ketolactam could be prepared by the previous procedure, due to the low yield of the process and the difficulty to separate the *trans* from the *cis* compound, was divised an alternative route. If the same cyanocyclohexane-dione intermediate (prepared as in the previous synthesis) was treated with 50% acetic acid it could be converted it into a conjugated enone, which upon subsequent reduction with lithium in liquid ammonia gave the desired *trans*-lactam. This product was subjected to the same series of reactions as its *cis*-isomer in the first approach. Then, Peterson reaction with 2-trimethylsilylmethylpyridine gave a 50:1 mixture of *Z*/*E* isomers respectively. Alkene reduction of the *Z* isomer with Adam's catalyst was not selective giving a mixture of pyridylmethyl epimers. In order to separate the mixture it was necessary the convert them to the corresponding N-oxides, and once separated, these two compounds were treated with phosphorous trichloride to regenerate the pyridine ring, which was subsequently quaternerized and hydrogenated to give the corresponded amino lactams. Reduction of the lactam functionality and final acetylation of the nitrogen gave two epimers (see Scheme 1.4).

Although the stereochemistry of the last chiral center could not be assigned, one of these epimers showed to be identical in its TLC behaviour in several solvents systems with a sample of $N_\alpha$-methyl-$N_\beta$-acetylphlegmarine. Unfortunately, MacLean and co-workers did not have sufficient amounts of natural material to establish a spectroscopic comparison.

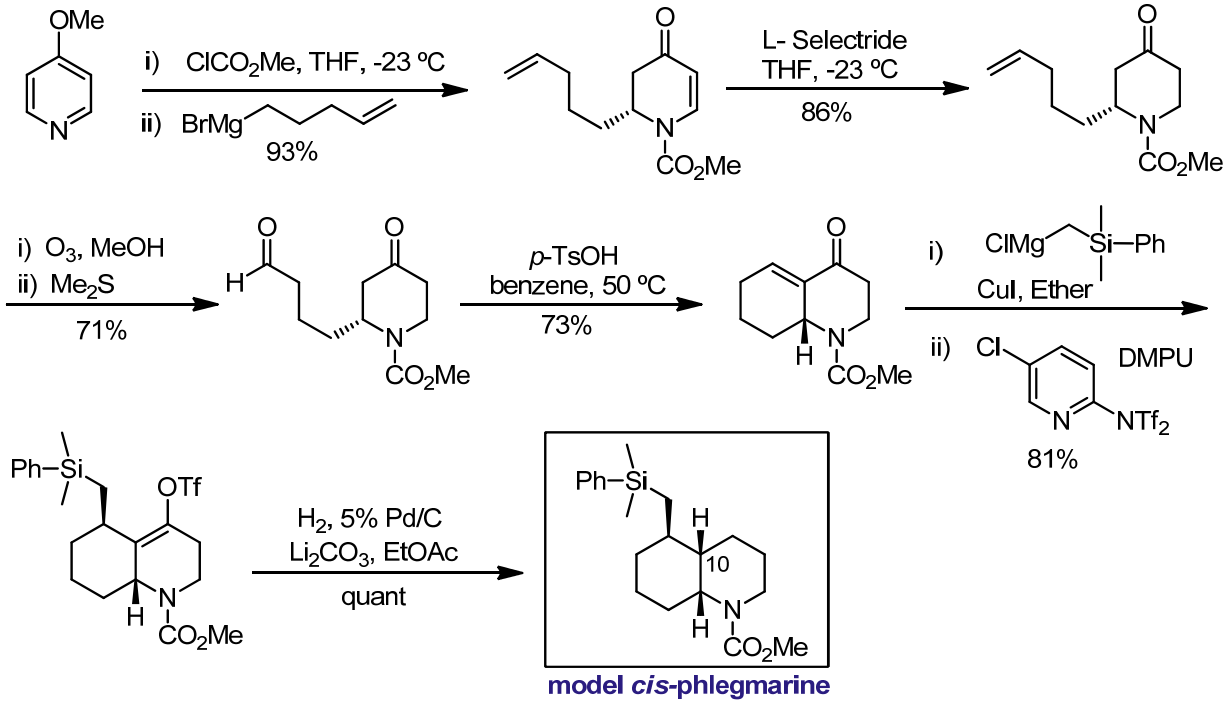
In summary, the MacLean synthesis establishes the relative stereochemistry at C-12 and C-13 (which determine the *trans* fusion ring system), C-15 (the methyl substituent), and C-7, and therefore showed that the stereochemistry pattern in phlegmarine is the same configuration found in lycopodine and most other lycopodium alkaloids.




**Scheme 1.4**. MacLean's second synthesis of phlegmarine isomers (*trans*-decahydroquinolines series).

### 1.2.3. Model Studies towards the synthesis of phlegmarine

In 1995 Comins published a general methodology for the syntheses of *cis*-decahydroquinolines and *trans*-decahydroquinolines[25] and its subsequent application to the total synthesis of phlegmarine and derivatives. Although the main objective in this paper was to develop a general methodology for the synthesis of *trans*-decahydroquinolines, the stereochemistry present in phlegmarine and its derivatives, Comins and co-workers found that the methodology could also allow access to the *cis* aza-bicycles (see Scheme 1.5).



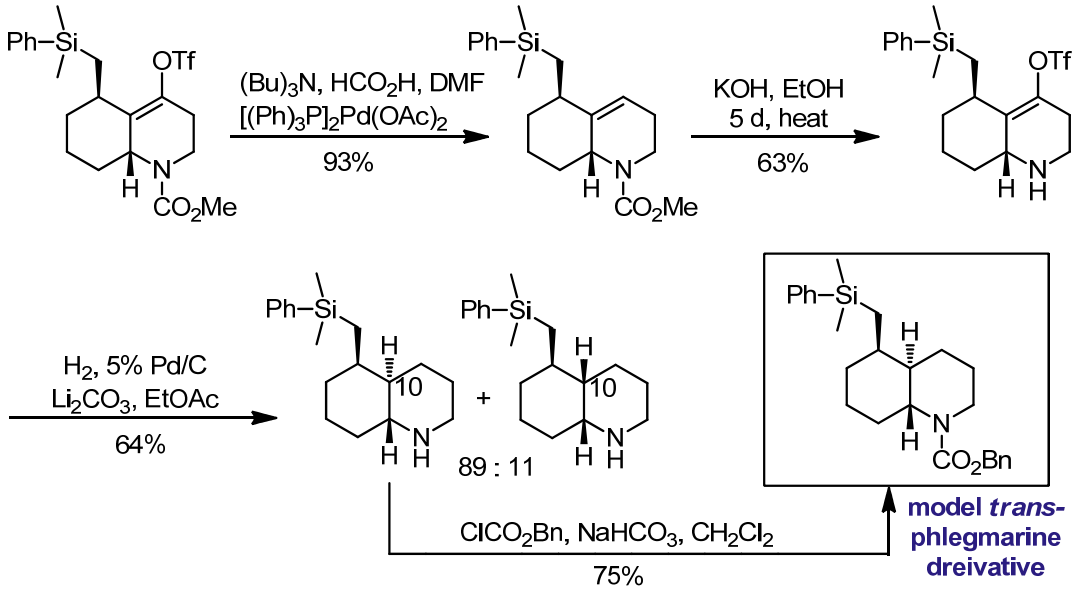

**Scheme 1.5**. Model studies towards the total synthesis of phlegmarine alkaloids: obtention of *cis*-decahydroquinoline ring system.

The synthesis started with addition of the 5-bromo-1-pentene Grignard reagent to an N-acylpyridinium salt (used repeatedly as a starting precursor in many developed methodologies by this group) followed by subsequent reduction of the resulting enone with L-Selectride to give the tetrahydropyridone. Ozonolysis and an intramolecular aldol condensation gave the bicyclic enone, which was converted to the corresponded vinyl triflate with a

[25] Comins, D. L.; Al-awar, R.; *J. Org. Chem*. **1995**, *60*, 711-716.

copper-mediated 1,4-addition of the methyl silyl Grignard reagent. Finally, catalytic hydrogenation revealed that the alkene reduction worked in a efficient stereoselective manner, obtaining the *cis*-decahydroquinoline skeleton. The authors thought that the carbamate on the nitrogen atom was creating a specific conformation and the *cis*-stereochemistry was produced because of the resulting ring strain.

This hypothesis led the authors to modify their strategy, hydrolyzing the methyl carbamate to the corresponding amine before subjecting the alkene to hydrogenation step. The process gave the *trans* and *cis* amines in an 89:11 ratio respectively. These two diastereomers were separated by chromatography, and the pure *trans* amine was protected with benzyl chloroformate to give the corresponding carbamate (see Scheme 1.6).




**Scheme 1.6**. Model studies towards the total synthesis of phlegmarine alkaloids: Obtention of *trans*-decahydroquinoline ring system.

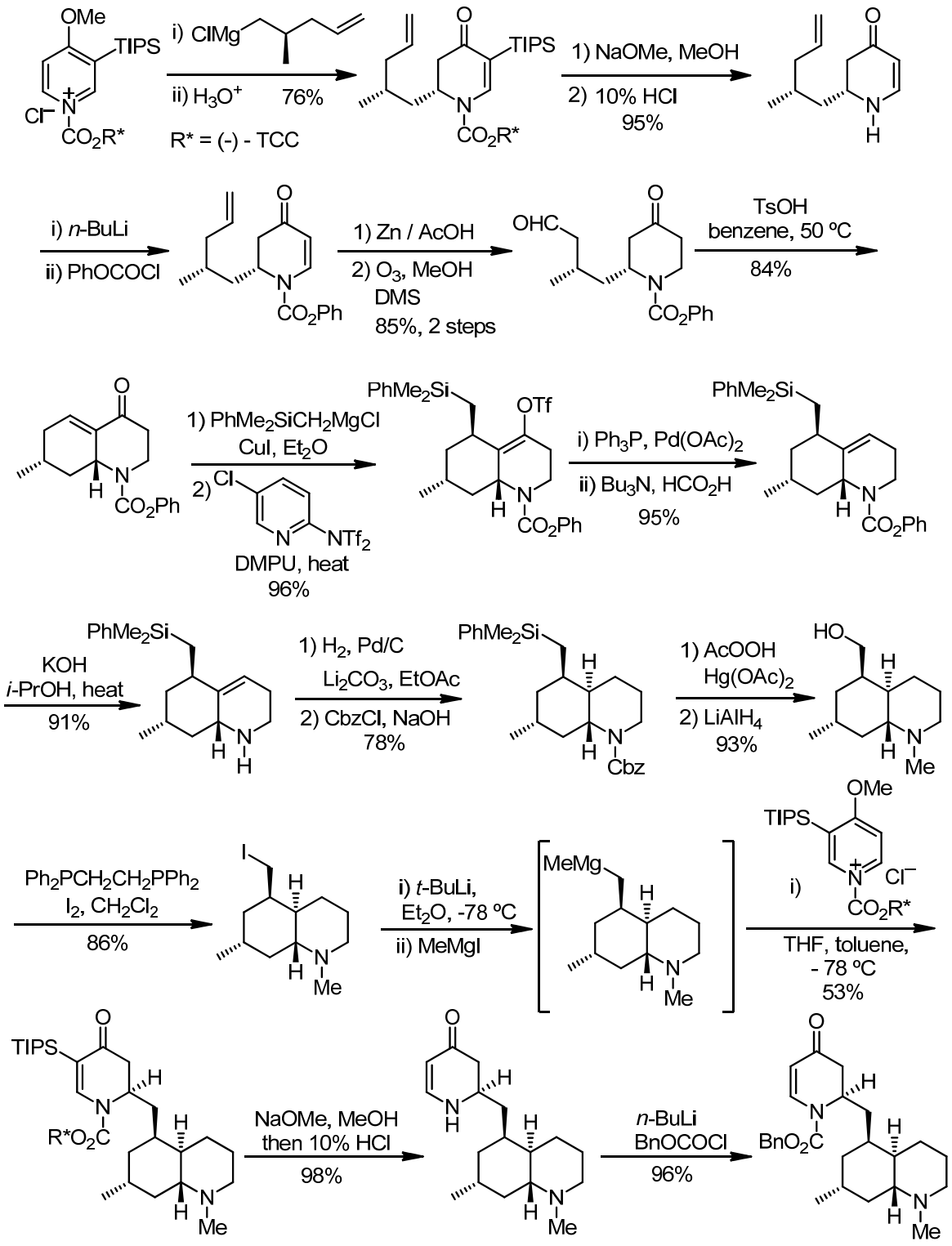
### 1.2.4. Total synthesis of phlegmarine and its derivatives

Four years later, and taking as reference the model studies described above, Comins and co-workers synthesized the phlegmarine derivative $N_\alpha$-acetyl-$N_\beta$-methylphlegmarine in asymmetric form, establishing the absolute configuration of the phlegmarines for the first time.[26] Eleven years later, the same group obtained the phlegmarine natural product and other derivatives[27] with an excellent stereocontrol using their methodology based on the use of N-acylpyridinium salt chemistry (scheme 1.7).

The synthesis began with the addition of the chiral Grignard reagent to the chiral N-acylpyridinium salt, followed by treatment with NaOMe/MeOH, then protection, removal of the double bond and ozonolysis gave an aldehyde, which was converted to the bicyclic enone via acid-mediated cyclization. Selective conjugate cooper-mediated 1,4 addition gave the vinyl triflate, which was subsequently removed and the resulting alkene was hydrogenated to give *trans*-decahydroquinoline as a major product.

Fleming oxidation and subsequent lithium aluminium hydride reduction gave the amino-alcohol. The next steps were focused to the asymmetric construction of the piperidine ring, which contains the last chiral center to complete the enantioselective synthesis of these alkaloids. Thus, the amino-alcohol was converted to Grignard reagent via the corresponding iodide and reacted with the same chiral auxiliary N-acylpyridinium salt used in the construction of the decahydroquinoline ring system. The TIPS group and TCC auxiliary were removed with NaOMe/MeOH to obtain the key intermediate, which contains the five stereocenters required and was used as the common precursor for the synthesis of the five alkaloids synthesized in this paper, whose only differ in the substituents on the $N_\alpha$ and $N_\beta$ (see Scheme 1.8).

[26] Comins, D. L.; Libby, A. H.; Al-awar, R.; Foti, C. J.; *J. Org. Chem*. **1999**, *64*, 2184-2185.
[27] Wolfe, B. H.; Libby, A. H.; Al-awar, R. S.; Foti, C. J.; Comins, D. L. *J. Org. Chem*. **2010**, *75*, 8564–8570.

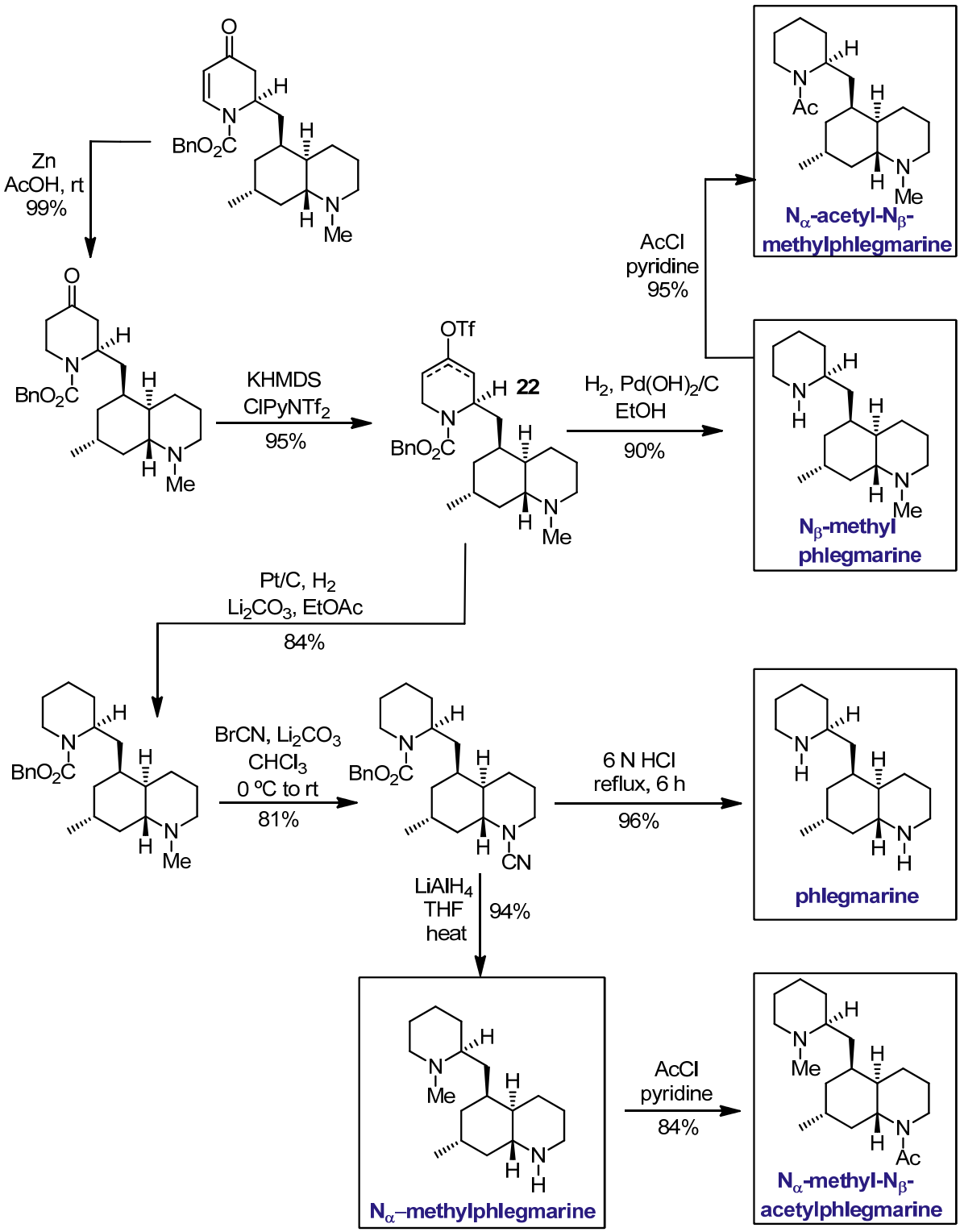



**Scheme 1.7**. Comins' synthesis of common intermediate en route to a unified approach to trans-phlegmarine alkaloids.

The building block with all stereocenters in place (prepared in Scheme 1.7) was reduced with Zn/AcOH and then converted to the corresponding enol triflate. Subjecting this compound to hydrogenation removed the triflate to give $N_\beta$-methyl- phlegmarine. After acylation of the free nitrogen $N_\alpha$-acetyl-$N_\beta$-methylphlegmarine was then obtained (scheme 1.8).

Hydrogenation of the same common triflate intermediate, also led to removal of the triflate but maintained the carbamate on the piperidinic nitrogen. Treatment with cyanogen bromide affords the cyano-decahydroquinoline, which under reflux in acid media removed the protecting groups on the nitrogen atoms affording phlegmarine.

The cyano-decahydroquinoline was also subjected to reductive conditions with lithium aluminium hydride to give $N_\alpha$-methylphlegmarine, and subsequent acylation gave the $N_\alpha$-methyl-$N_\beta$-acetylphlegmarine (unnatural derivative).



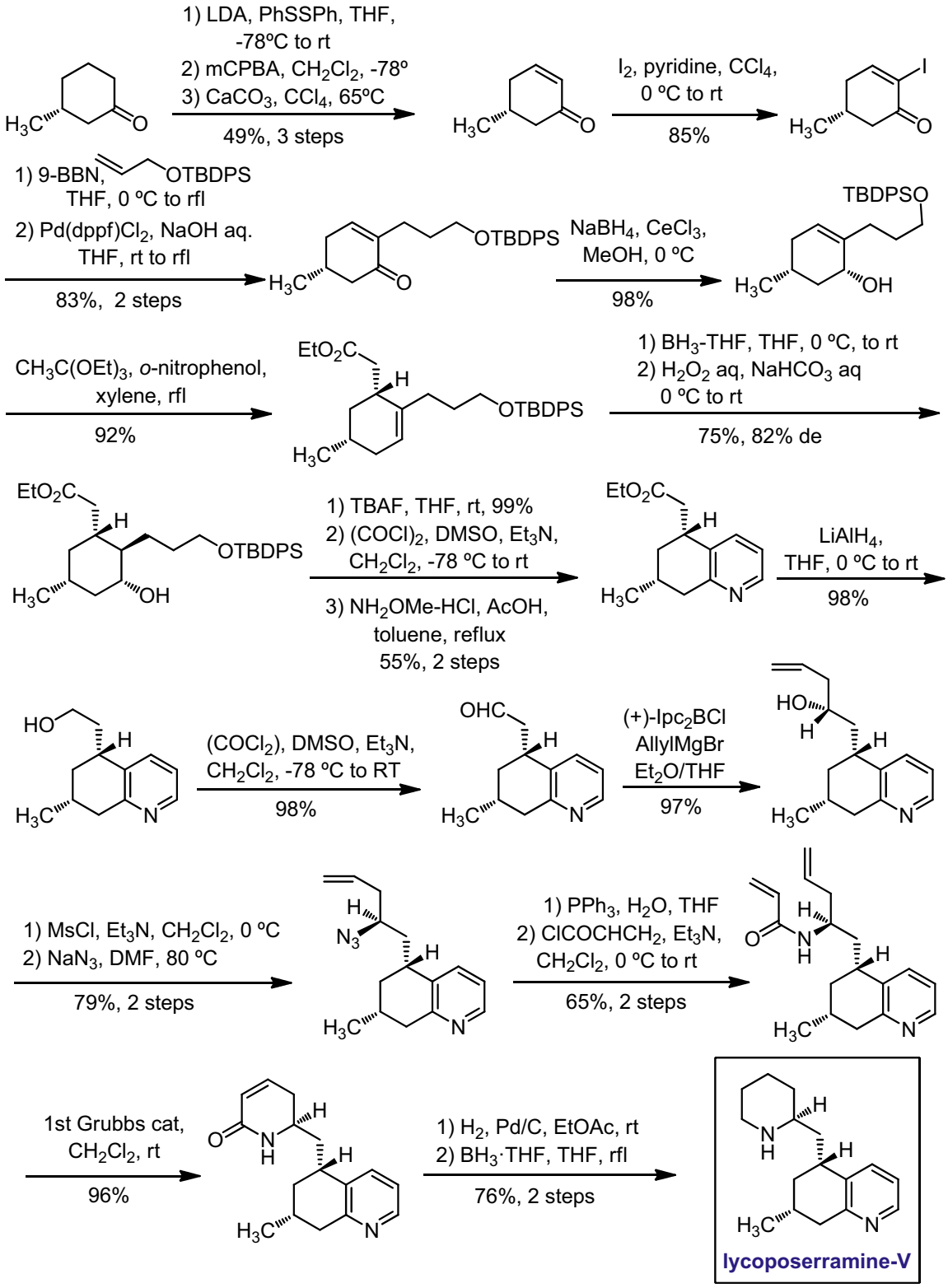

**Scheme 1.8**. Total synthesis of phlegmarine and all its related derivatives by Comins.

### 1.2.5. Total synthesis of lycoposerramines V and W

The phlegmarine alkaloids lycoposerramines W and V[16] were both isolated and synthesized for the first time by Takayama and co-workers in 2007. Starting from commercially available (*R*)-3-methylcyclohexanone, which through sulfenilation, oxidation and dehydrosulfenilation sequence was converted into the corresponded enone. The next steps were the installation of a 3-hydroxypropane sidechain under Pd-catalyzed Suzuki-Miyaura conditions, subsequent reduction of the ketone to alcohol, and a Johnson-Claisen rearrangement to obtain the cyclohexene intermediate. After further functional group manipulations, they obtained the unique 5,6,7,8-tetrahydroquinoline skeleton, which is characteristic of only these two products in the entire family of phlegmarines.

The main purpose of the remaining steps was the construction of 2-substituted piperidine appendance. The strategy employed was the formation of an allylic alcohol from the previous aldehyde and subsequent conversion to an azide. Subsequent conversion to a primary amine via a Staudinger reaction and acylation, gave a bis alkene set up for a ring closing metathesis reaction. The final steps involved closure of the piperidine ring, hydrogenation of the double bond and lactam reduction to afford the natural product lycoposerramine V (Scheme 1.9).

The route was flexible enough to complete the synthesis of the related compound lycoposerramine W, which has a hydroxyl group at C-4, from the advanced common azide intermediate synthesized via the sequence above. The key difference in the approach was the coupling of an alternate group to the nitrogen for the RCM reaction, which had functionality to allow the introduction of the required hydroxyl group at the C-4 position.




**Scheme 1.9**. Total synthesis of lycoposerramine V by Takayama.

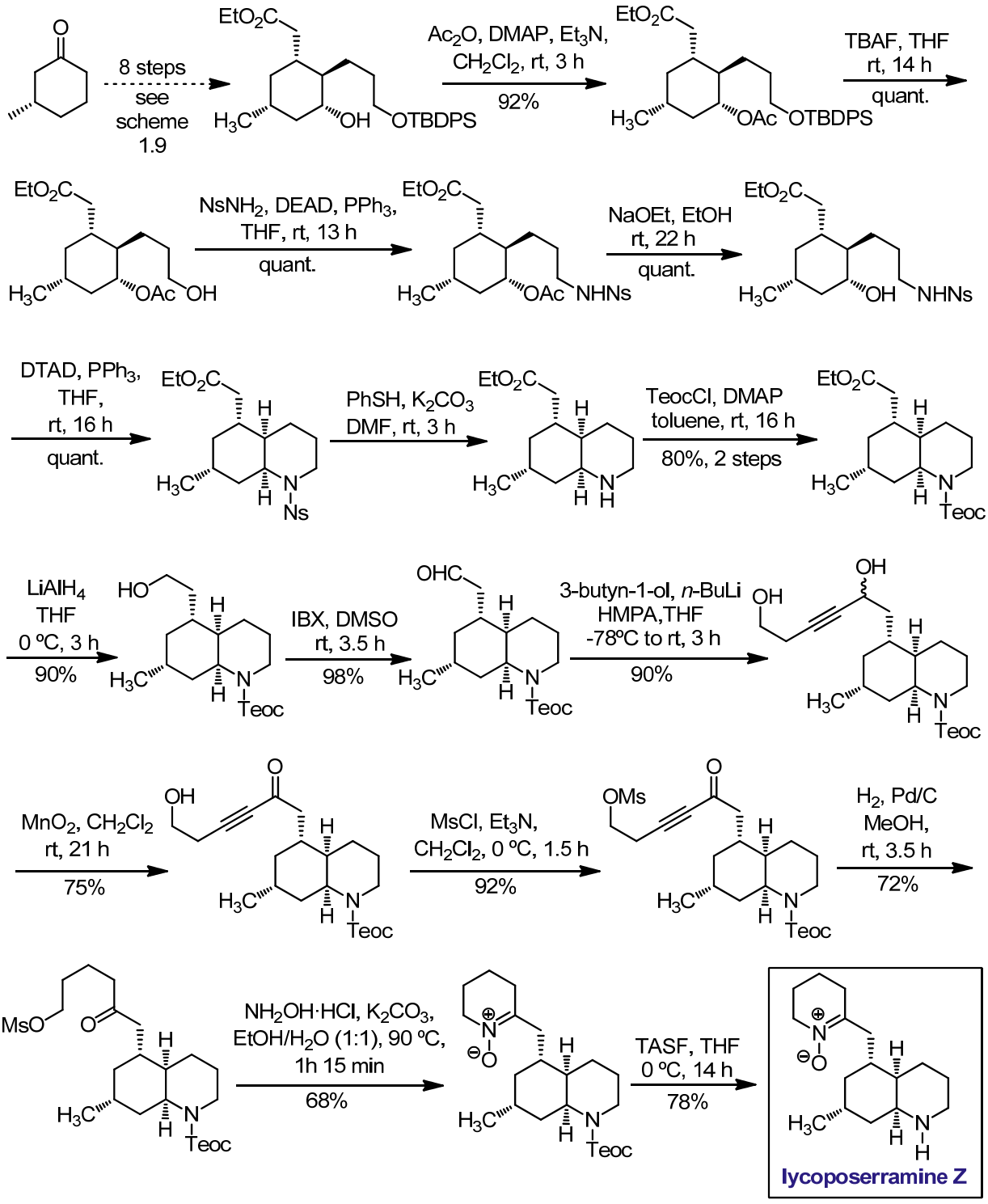
### 1.2.6. Total synthesis of lycoposerramine Z

After the successful completion of the total syntheses of the phlegmarine alkaloids lycoposerramines V and W, Takayama's group focused their attention on the synthesis of lycoposerramines X and Z.[28] These two compounds are identical with the exception that they are epimeric at C-13. Thus, lycoposerramine X is a *trans*-decahydroquinoline and lycoposerramine Z has the fusion hydrogen atoms in a *cis* orientation.

The initial steps are the same that are used in the synthesis of lycoposerramines V and W until the obtention of the polysubstituted cyclohexane ring system. After a number of protecting group manipulations on the primary and secondary alcohols, an intramolecular Mitsunobu reaction gave the *cis*-decahydroquinoline skeleton. To complete the synthesis the remaining steps focused on the construction of the nitrone containing piperidine ring. Because of the sensitive nature of the nitrone functional group, the nitrogen-protecting group was exchanged at this point to a Teoc carbamate, whose later removal would be more compatible in the presence of the nitrone group. After reduction and oxidation steps, was obtained the aldehyde, which was treated with an alkynyl anion to append the carbon chain necessary for the construction of the required nitrone ring.

After three steps for the interconversion of functional groups a keto-mesylate was obtained which was treated with $NH_2OH{\cdot}HCl$ and $K_2CO_3$ in $EtOH/H_2O$ to give the cyclic nitrone. Finally, the removal of the carbamate on the nitrogen resulted in the first asymmetric total synthesis of lycoposerramine Z, completed in 24 steps and 4.8% yield (scheme 1.10)

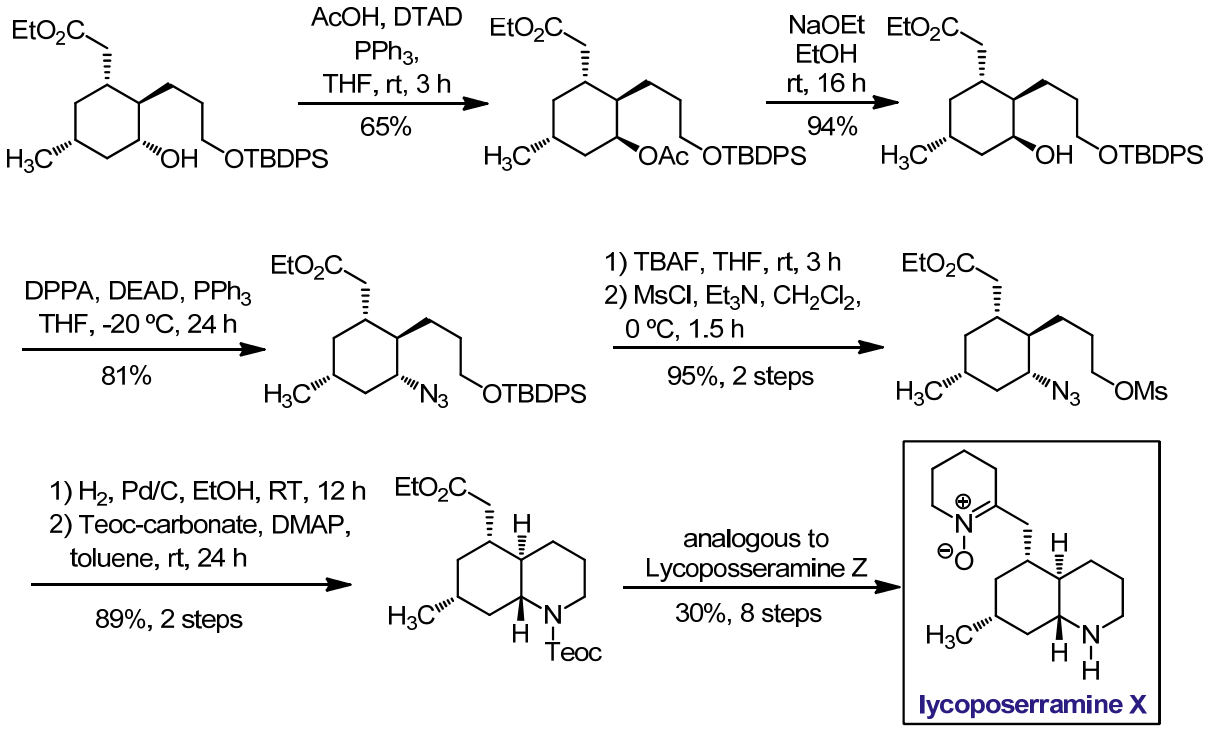
[28] Tanaka, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem*. **2009**, *74*, 8675-8680.




**Scheme 1.10**. Total synthesis of lycoposerramine Z by Takayama.

### 1.2.7. Total synthesis of lycoposerramine X

Following essentially the same route developed for lycoposerramine Z, Takayama and co-workers turned their attention to the very closely related Lycoposerramine X[28] bearing a *trans* fusion ring system (see scheme 1.11). To construct the *trans*-decahydroquinoline skeleton an additional Mitsonobu reaction was carried out (thus inverting the future C-13 centre in relation to what was prepared previously for the *cis* decahydroquinoline) via an azide. Subsequent reduction via $H_2$, Pd/C in EtOH led to the spontaneous cyclization giving the required *trans*-decahydroquinoline. The last steps of this synthesis are exactly the same transformations used for lycoposerramine Z.

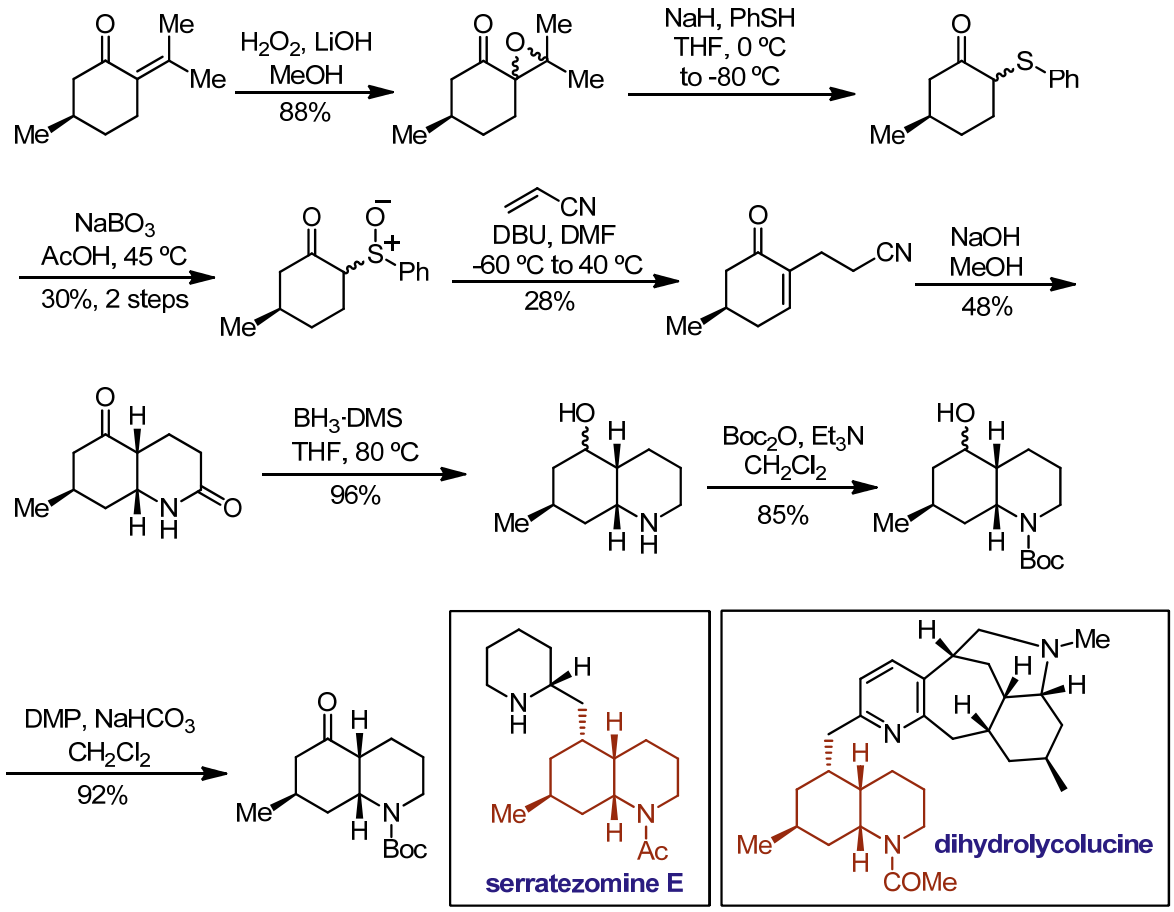



**Scheme 1.11**. Total synthesis of lycoposerramine X by Takayama.

### 1.2.8. Towards the total synthesis of dihydrolycolucine

The Sarpong group designed an approach to the highly complex dimeric compound dihydrolycolucine which comprises a northern fragment similar to the the lyconadins and a southern part similar to serratezomine E.[29]

In order to adapt their synthesis of lyconadin A[30] they required a 5-oxodecahydroquinoline fragment with type A stereochemistry. Adapting the synthetic approach developed by Maclean (see schemes 1.3 and 1.4) the route was made enantiopure by starting from (*R*)-(+)-pulegone (scheme 1.12).



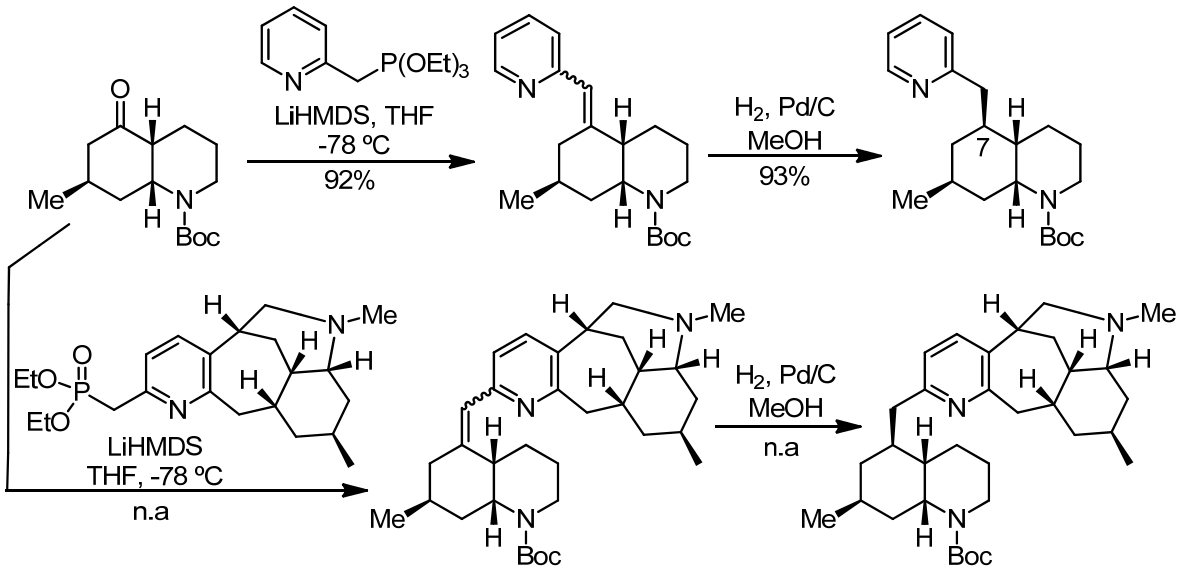

**Scheme 1.12**. Sarpong´s synthesis of Type A nucleus en route to serratezomine E and dihydrolycolucine.

This starting material was converted to the corresponding thioether, which in turn was oxidized to the sulfoxide. Conjugate addition of

[29] Sarah Elizabeth House, 2010, University of California, Berkeley.
[30] Whilst this compound bears many similiarities to the phlegmarine alkakoids the presence of the 7-membered ring led to a completely different disconnection approach: see: Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc*. **2008**, *130*, 7222-7223.

acrylonitrile with DBU followed by in situ elimination of the sulfoxide functionality, intercepted the key nitrile intermediate used by MacLean but now in enantiopure form. The next steps included the formation of the lactams and subsequent reduction with $BH_3$·DMS to obtain a diastereomeric mixture of alcohols, which were reoxidized to afford the bicyclic ketone substrate.

To test the coupling reaction they chose the simpler phlegmarine compound serratezomine E as a model target. Thus the type A building block was subjected to a Horner-Wadsworth-Emmons reaction with a pyridine methyl phosphonate unit, giving the corresponded coupled alkenes (E/Z 1.5:1) (scheme 1.13). Hydrogenation of this Boc-protected tricycle resulted in a diastereoselective alkene reduction, but unfortunately this stereochemistry was the opposite to that required for the synthesis of serratezomine E. Whilst, the authors then went on to describe the analogous sequence with the elaborated tetracyclic phosphonate unit and carry out the hydrogenation towards dihydrolycolucine - no yields are given for these steps. Presumably, the poor facial selectivity combined with lack of material didn't allow them to quantify these transformations and led them to abandon the synthesis.




**Scheme 1.13.** Sarpong's approximation to serratezomine E and dihydrolycolucine.

## 1.2.9. Overview of phlegmarine alkaloids syntheses

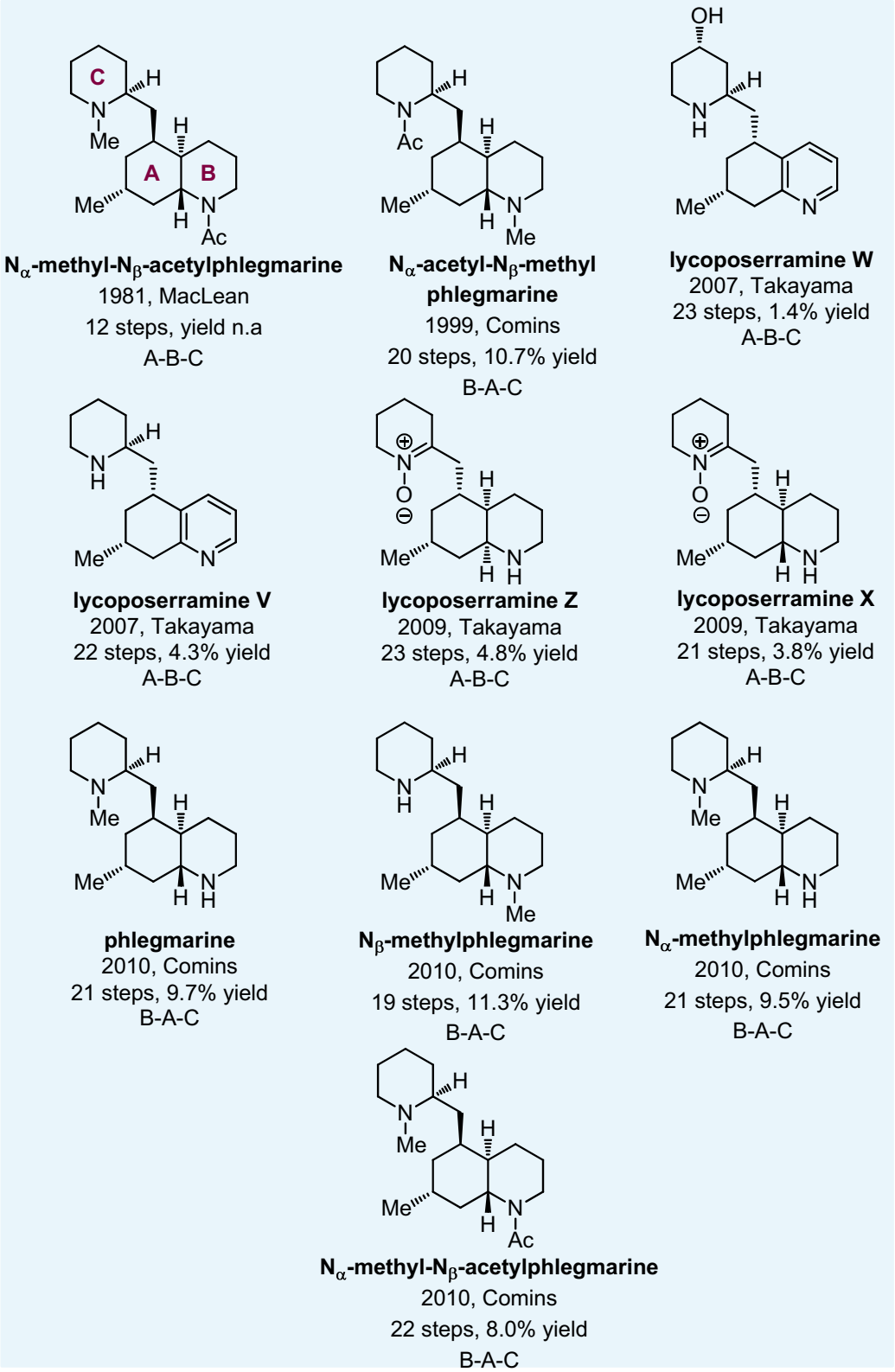


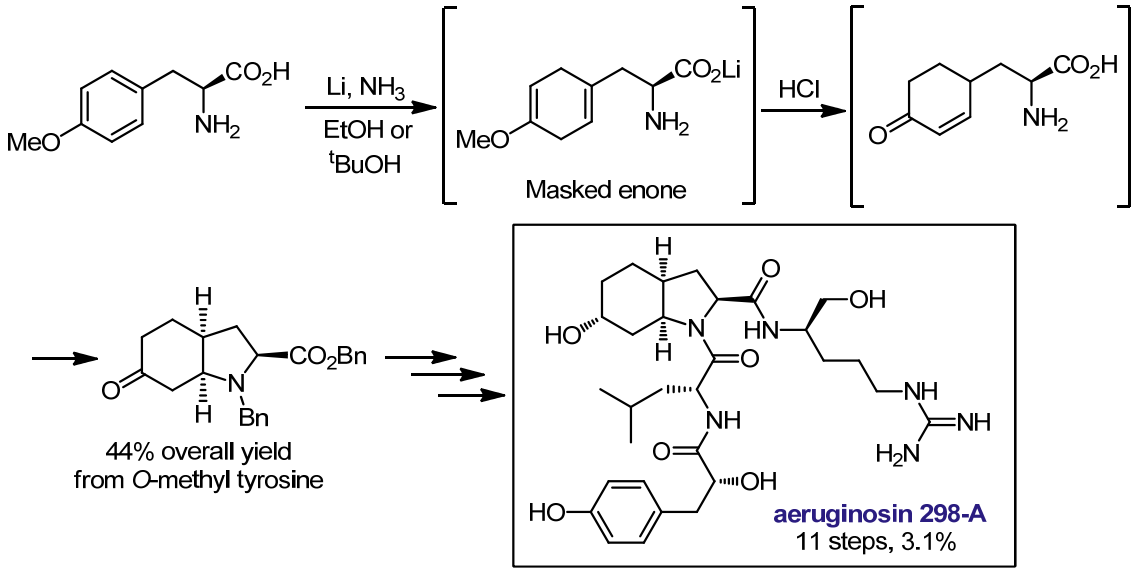

**Figure 1.4.** Overview of completed phlegmarine alkaloid total syntheses until 2010.

## 1.3. Our Own Precedents in the Synthesis of Nitrogen-containing Compounds via Intramolecular aza-Michael Processes

Previously, our research group has extensively used the intramolecular aza-Michael reaction to construct aza-bicycles for its subsequent application to the total synthesis of nitrogen-containing natural products.

### 1.3.1. Synthesis of 6-octahydroindoles: application to aeruginosin 298-A

One of the pioneering works was the first synthesis of aeruginosin,[31] a peptide of cyanobacteria type. The core 6-oxo-octrahydroindole was synthesized by Birch reduction of *O*-methyl derivative of L-tyrosine followed by treatment with acid, and aza-Michael reaction (see Scheme 1.14).



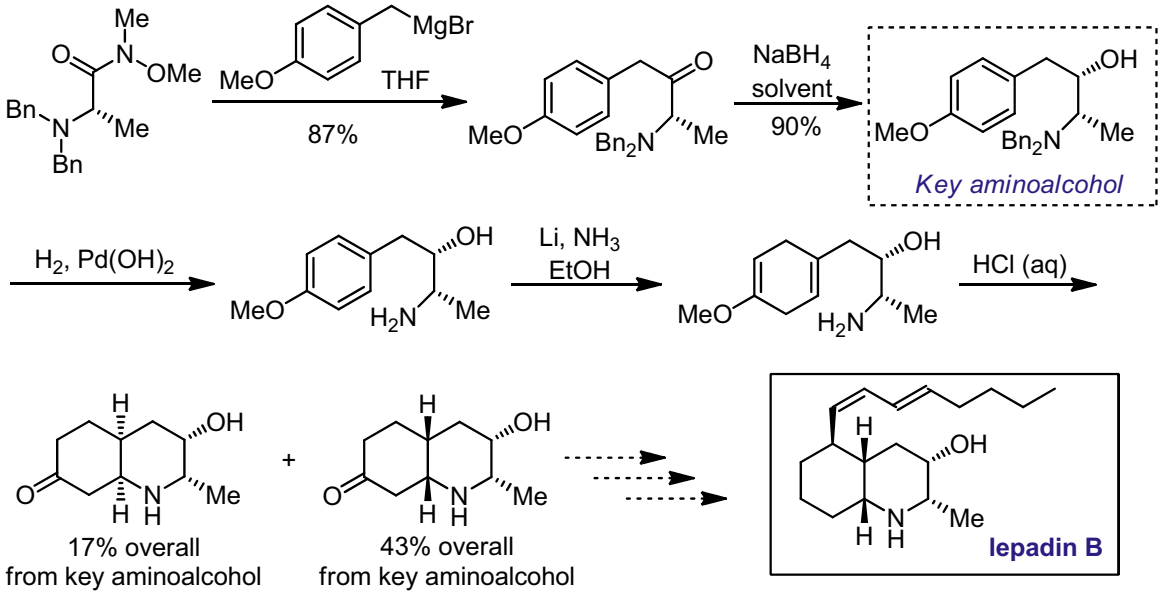

**Scheme 1.14.** Method for the octahydroindole core of aeruginosin 298-A and its total synthesis.

Elaboration of this building block then gave aeruginosin 298-A, which represented the first total synthesis of a natural product of this family.

[31] Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem. Eur. J*. **2001**, *7*, 3446-3460.

### 1.3.2. Synthesis of decahydroquinolines. Approximation to lepadin alkaloids

This methodology was then applied to the formation of decahydroquinolines,[32] although the direct adaptation of the procedure was not possible because there is no equivalent analog of L-tyrosine. Thus, the required starting material had to be prepared in a multistep process from the amino acid alanine, to which was coupled the aromatic unit via the Weinreb amide. The amino ketone underwent a diastereoselective reduction to the corresponding key amino-alcohol ready for the aminocyclization process.




**Scheme 1.15**. Application of the Birch reduction/aza-Michael methodology for the synthesis of decahydroquinolines.

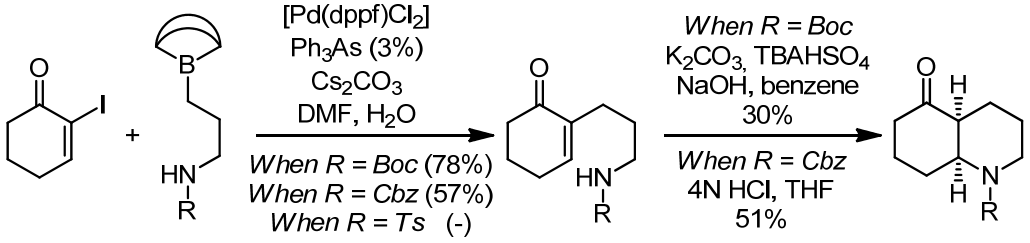
At this point, the key amino-alcohol intermediate was subjected to the Birch reduction/aminocyclization sequence developed in the previous synthesis of aeruginosin 298-A, to give two *cis*-decahydroquinolines with four stereogenic centers which have the relative configuration found in the lepadin alkaloids.[33] However, not enough material could be achieved via this route to complete the synthesis.

[32] Mena, M.; Valls, N.; Borregán, M.; Bonjoch, J. *Tetrahedron* **2006**, *62*, 9166-9173.
[33] The minor component is the enantiomer of another lepadin alkaloid.

### 1.3.3. Synthesis of 5-oxodecahydroquinolines[34]

In addition to the lengthy sequence and the limited selectivity of the aza-Michael reaction in the previous route to decahydroquinolines, which didn't allow large quantities of material, one of the main problems with the above route would be the required laborious transposition of the carbonyl group from C-7 to C-5 in order to introduce a side chain in this position. Thus, an alternative strategy was developed to access 5-oxodecahydroquinolines directly.

The required cyclic enones for the aza-Michael cyclization were synthesized via Suzuki coupling reaction between 2-iodocyclohex-2-enone and the 9-BBN alkyl derivatives (scheme 1.16). It was found that the reaction only worked in the presence of carbamates (Boc and Cbz) whilst other nitrogen protecting groups, such as the tosyl-protected derivative could not be formed under these conditions. With the substrates in hand, the aza-Michael cyclization was investigated by screening a wide range of conditions. It was found that basic conditions were favourable for the formation of Boc-protected decahydroquinoline, whilst the Cbz analog could be cyclised under acid conditions.

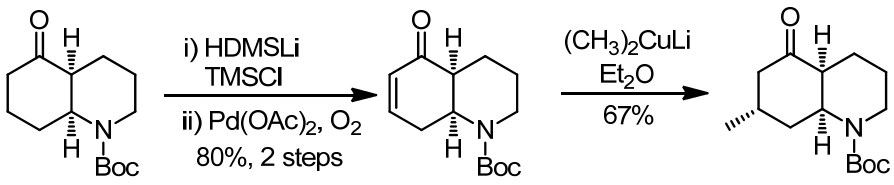



**Scheme 1.16**. Synthesis of 5-oxo-*cis*-decahydroquinolines

Unfortunately, in both cases it was observed that the resulting decahydroquinoline product was unstable, readily undergoing a retro aza-Michael reaction during the column chromatography purification. Although the yields were moderate in both cases, sufficient amounts of material was obtained to study the next steps for the obtention of 7-methyl derivatives, which would be advanced intermediates towards phlegmarine alkaloids. After the formation of the silyl enol ether, Saegusa reaction via Pd(II) gave the corresponding cyclic

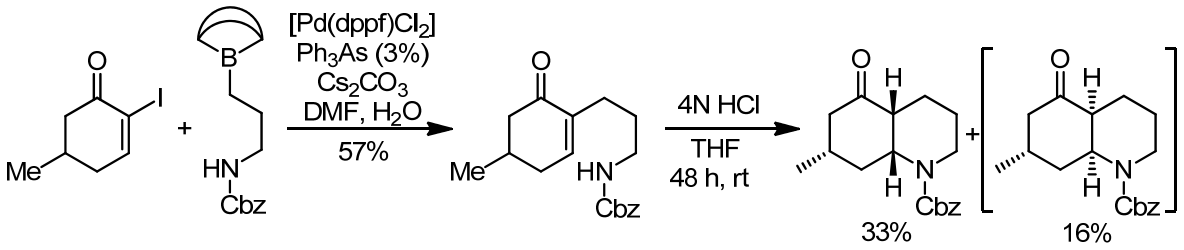
[34] For an account of this work see: Mar Borregán Prats Ph D. Thesis Universitat de Barcelona, 2009. This alternative route had the potential to access the phlegmarine as well as the lepadin alkaloids by incorporating the required substituents on the side-chain.

enone. Conjugate addition to install the methyl group at C-7 was diastereoselective, giving the methyl in a *cis*-orientation with the hydrogen fusion ring atoms[35] (type A stereochemistry) (see Scheme 1.17).




**Scheme 1.17.** Access to type A stereochemistry.

After this study, it was evaluated if the aza-Michael cyclization would work when the methyl group was incorporated into the starting enone instead of introducing it after the cyclization step. The Cbz cyclohexenone analog was prepared and after application of acid conditions to promote the aza-Michael reaction gave a mixture in which the major product contained the methyl group in *trans*-orientation with hydrogen fusion ring atoms (see Scheme 1.18). Once again, the products were unstable easily entering into equilibrium with the opened enone starting material.

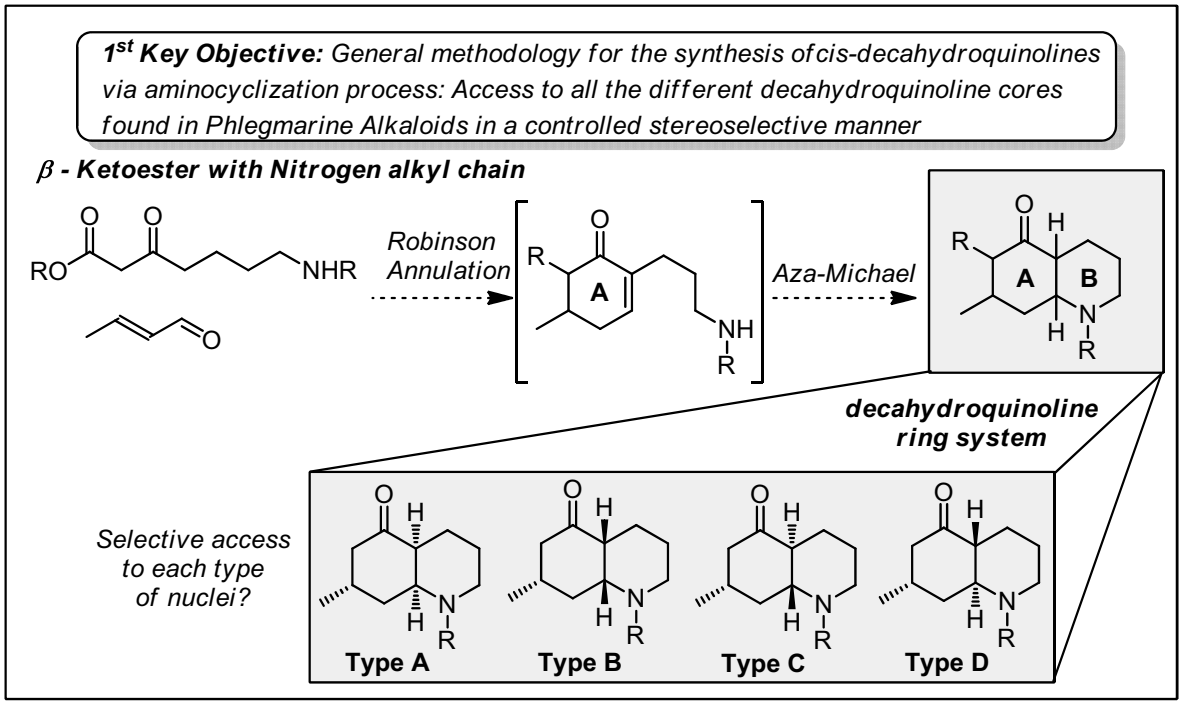



**Scheme 1.18.** Access to type B stereochemistry.

[35] Following the same reaction sequence for the N-Cbz derivative the process proved to be less diastereoselective, giving decahydroquinoline and its epimer at C-7 in a 3:1 ratio (40% overall yield). However it cannot be ruled out that the minor product (type B) occurred via a partial retro aza-Michael reaction/aza-Michael reaction after the addition was complete.

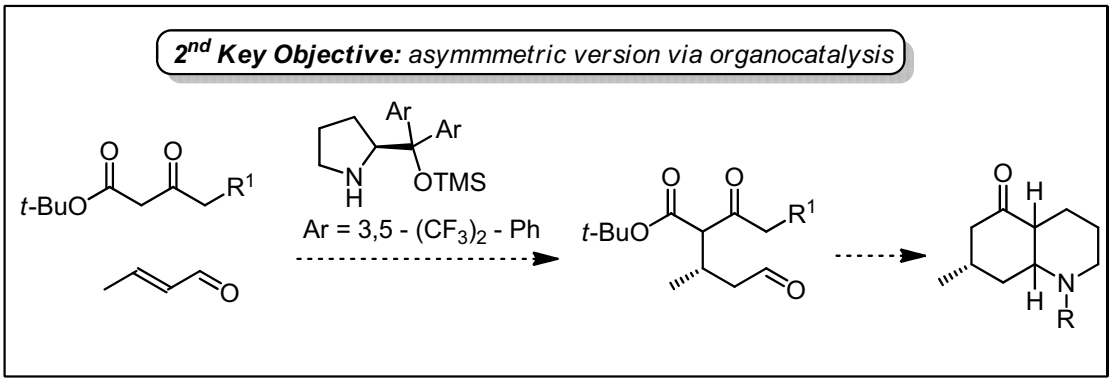
## 1.4. Summary of Objectives and Synthetic Plan

Although the previous methodology allowed access to two types of 5-oxodecahydroquinolines (types A and B), it had to be improved since the products always were obtained as a mixture of the decahydroquinolines and the starting enones. Furthermore, the method required starting materials whose preparation was laborious and did not allow more varied nitrogen protecting groups (only carbamates), which greatly reduces the possibility to carry out a study of conditions. Taking these results as the basis of this thesis, the first objective for us was to develop a more efficient method to access the decahydroquinoline ring system. We believed it might be possible to prepare the corresponding enone in a more direct way, via a Robinson annulation between a β-keto ester and an enal component. Furthermore, if the initial β-keto ester had installed a nitrogen alkyl chain, once the cyclohexenone is formed, it could be possible to carry out the aza-Michael cyclization *in-situ*, synthesizing the decahydroquinoline ring system in a single step (see Scheme 1.19). Focus would also be placed on modifying the conditions and substrates to allow the route to access each of the four stereochemistries A-D.



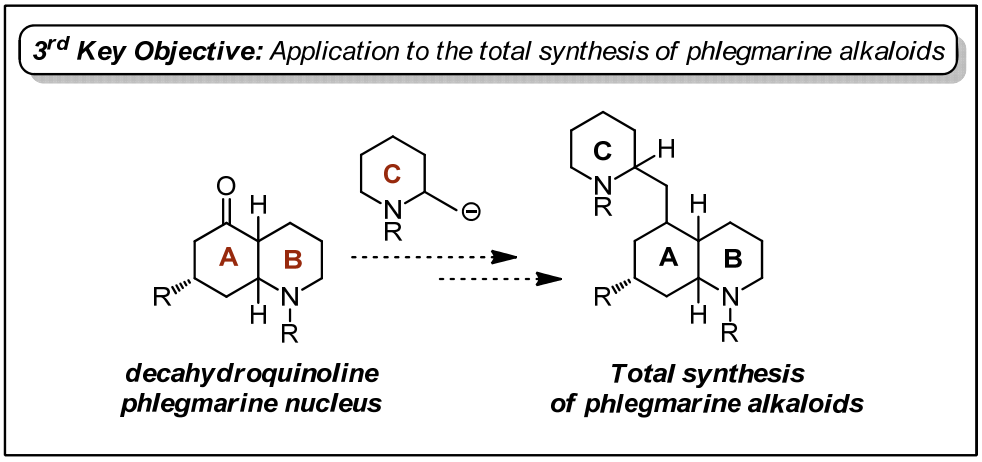

**Scheme 1.19**. Proposed one-pot tandem reaction for rapid synthesis of decahydroquinoline ring system and access to four different stereochemistries.

If such a strategy could be realised the second key objective would be to make it enantiopure via organocatalysis[36] (see Scheme 1.20).




**Scheme 1.20**. One-pot synthesis of optically pure decahydroquinolines via organocatalysis.

Once we had access to the different decahydroquinoline nuclei in an enantiopure manner, we hoped to apply these building blocks to the rapid synthesis of phlegmarine alkaloids by addition of a suitable methyl piperidine unit (Scheme 1.21).




**Scheme 1.21**. Use of 5-oxodecahydroquinolines as a platforms for the rapid synthesis of phlegmarine alkaloids.

[36] For studies to access enantiopure cyclohexenones from β-keto esters via organocatalysis see: Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun*. **2006**, 4928-4930.

## 2. A Unified Synthetic Approach to the Phlegmarine Nuclei: Stereoselective Formation of 5-Oxodecahydroquinolines

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

## 2.1. Synthetic Studies on the One-pot Robinson Annulation/ Intramolecular aza-Michael Reaction

The first key objective of this thesis was to attempt the one-pot tandem Robinson annulation/aza-Michael reaction to give rapid access to the decahydroquinoline ring system (see Figure 2.1). For this purpose we required ready access to the tethered nitrogen β-keto ester fragment. We chose the tosyl as the activating group for the nitrogen due to its improved stability and increased nucleophilicity[37] over the use of carbamate groups, which had proven to be only moderately successful in the initial studies (see section 1.3.3). For the ester we chose the *tert*-butyl group based on the precedents of Jørgensen as a requirement for the organocatalytic step,[36] and its in-situ removal under acidic conditions. Alternatively, this group would be sufficiently stable if the Robinson annulation/aza-Michael reaction was conducted under basic conditions.

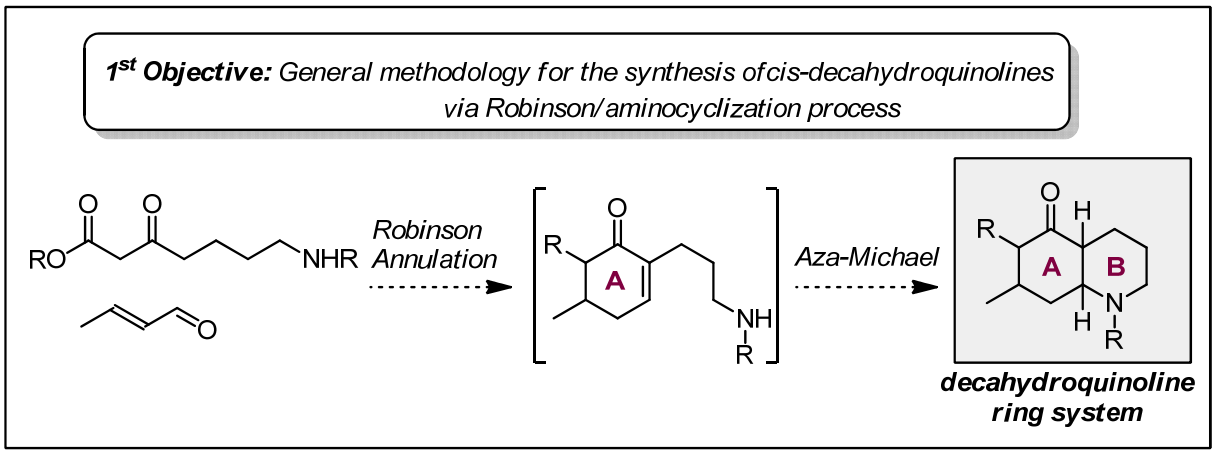
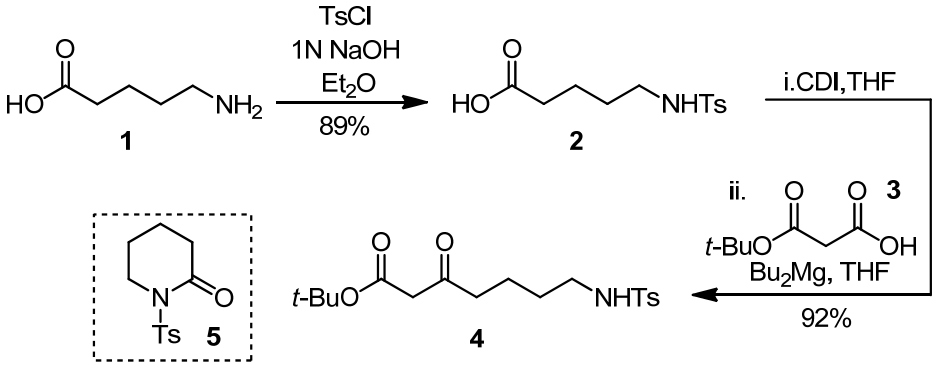



**Figure 2.1.** Key objective 1 – Overview of strategy to rapidly form the decahydroquinoline ring system present in the phlegmarine alkaloids.

[37] Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem*. **2004**, *69*, 2268-2271.

### 2.1.1. Preparation of starting material

We began with the protection[38] of commercially available 5-aminovaleric acid **1** with TsCl, and subsequent homologation[39] with 2 equiv of mono *tert*-butyl malonate[40] to synthesize the Ts-protected β-keto ester **4** (scheme 2.1). Whilst the sequence proceeded in good yield it was observed the formation of the intramolecular cyclisation product **5** from **2** during the homologation reaction. Although this compound had a slightly different $R_f$ to **4** it was difficult to remove by chromatography, appearing in most of the fractions collected. Increasing the quantity of **3** employed in the reaction to 3 equiv, effectively reduced the formation of **5** to trace quantities

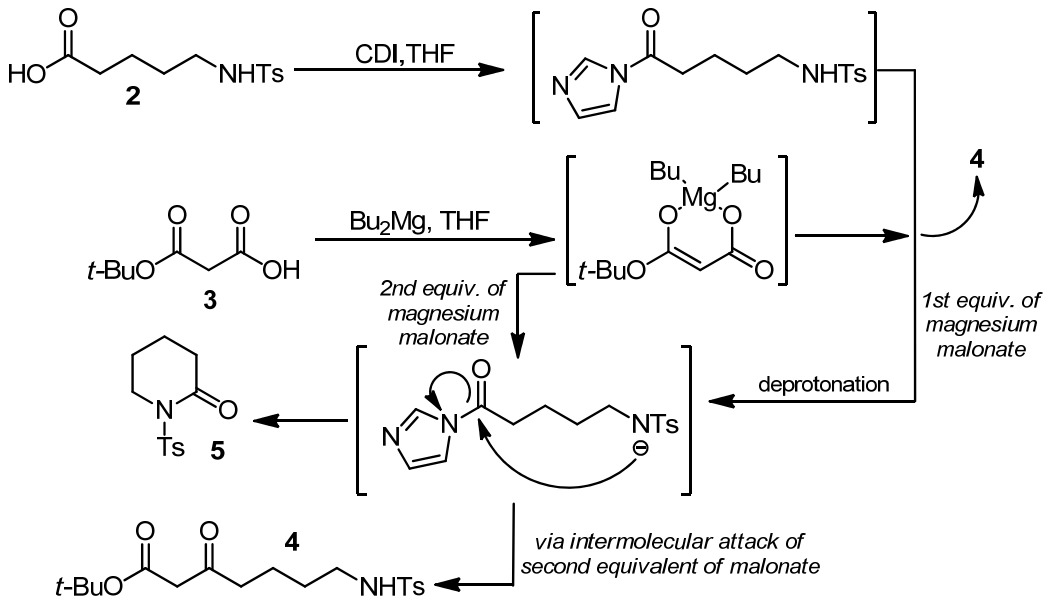



**Scheme 2.1.** Preparation of the Ts-protected β-keto ester **4**.

It should be noted that reducing the quantity of *tert*-butyl malonate **3** and $Bu_2Mg$ from two to one equivalents led to only traces of the β-keto ester product **4** being formed and with **5** as the major compound observed. A control experiment of reacting the tosyl protected valeric acid **2** with CDI and following the reaction by TLC for up to 2 h led to negligible formation of **5**. Only when the magnesium enolate of **3** was added to the flask was **5** observed (see Scheme 2.2).

Thus, we believe the first equivalent deprotonates the NHTs and the use of excess reagents is essential to compete with the slow intramolecular cyclization.

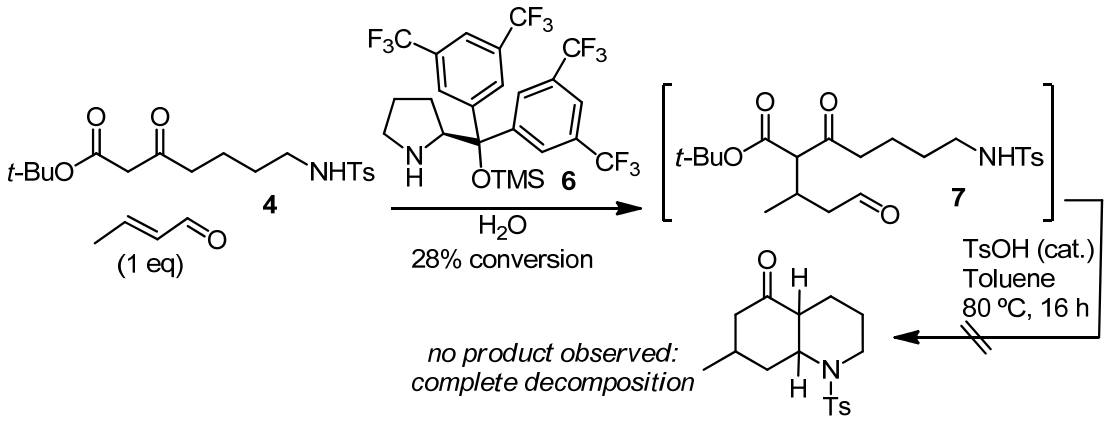
[38] Kokotos, C.; Aggarwal, V. *Chem. Commun*. **2006**, 2156-2158.
[39] Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 72-73.
[40] *tert*-Butyl malonate **3** is commercially available but is moderately expensive. However it can be readily prepared on a large in a single step according to the following procedure: Erixon, K. M.; Dabalos, C. L.; Leeper, F. J. *Org. Biomol. Chem*. **2008**, *6*, 3561-3572.




**Scheme 2.2.** Formation of byproduct **5**.

### 2.1.2. Initial attempts to effect the one-pot tandem reaction.

Once the synthesis of β-keto ester **4** was optimized we applied the conditions described by Jørgensen for the synthesis of simple cyclohexenones via organocatalysis[36] (see Scheme 2.3). Unfortunately, coupling of **4** with crotonaldehyde resulted in only a low amount of the coupled product **7**. The subsequent cyclisation was complicated by the fact that **7** could not be purified as it was not stable to column chromatography.




**Scheme 2.3.** Initial unsuccessful attempt to synthesize decahydroquinoline nucleus in a "one-pot" manner using Jørgensen's conditions.

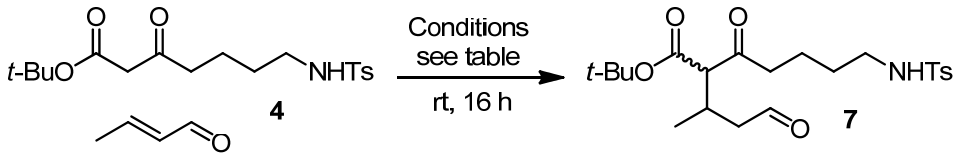
Thus the complete crude mixture was treated with TsOH in toluene to remove the ester, form the cyclohexenone and effect the aza-Michael reaction.

However, this resulted in a complete decomposition of the starting material and no product could be identified from the reaction mixture.

### 2.1.3. Screening of conditions for the Michael Addition reaction

After the initial problems of coupling the enal under the described organocatalyzed conditions we looked for other methods to effect the Michael reaction, even under non-asymmetric conditions (see Table 2.1).

**Table 2.1** Screening of conditions for the Michael addition.



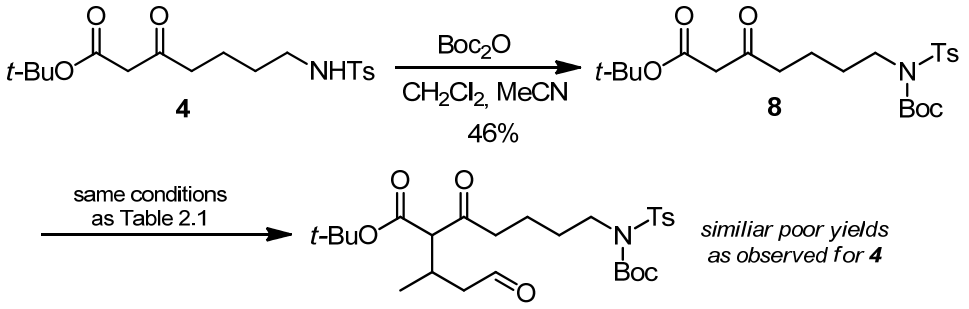

| *Entry* | *Reagent* | *Crotonaldehyde (eq.)* | *Solvent* | *yield (%)* |
|---|---|---|---|---|
| 1 | MS 3Å | 2.5 | DMF | No reaction |
| 2 | $CeCl_3$ / NaI | 1.1 | - | 28% (+ SM) |
| 3 | $Al_2O_3$ | 1.0 | - | 10% (+ SM) |
| 4 | $Et_3N$ (1%) | 1.0 | - | Unknown product |
| 5 | **6** (0.1 eq) | 1.5 | $H_2O$ | 28% (+ SM) |
| 6 | **6** (0.1 eq) | 1.5 | - | 10% (+ SM) |

Examining numerous catalysts such as, 3Å molecular sieves,[41] $CeCl_3$/NaI,[42] $Al_2O_3$,[43] and $Et_3N$[44] resulted in disappointing results, again with only low conversion to the Michael adduct in some cases (entries 2, 3). Attempts to increase the yield of the coupled product with the Jørgensen catalyst **6** (entries 5 and 6) by using excess crotonaldehyde or by switching to solvent free conditions (entry 6) led to equally disappointing results.

Believing the problem may arise from the interaction of the NHTosyl group with the crotonaldehyde via an intermolecular aza-Michael addition[45] we

[41] Villano, R.; Scettri, A. *Synthesis* **2005**, 757 –760.
[42] Bartoli, G.; Bosco, M.; Bellucci, M. C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem*. **1999**, 617–620.
[43] Noël, R.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.; Lhommet, G. *J. Org. Chem*. **2005**, *70*, 9044–9047.
[44] Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *J. Am. Chem. Soc*. **2010**, *132*, 5966-5967.
[45] Yoshitomi, Y.; Arai, H.; Makino, K.; Hamada, Y.; *Tetrahedron* **2008**, *64*, 11568-11579. For asymmetric aza-Michael reactions in alkaloid synthesis, see: Amara, Z.; Caron, J.; Joseph, D. *Nat. Prod. Rep.* **2013**, *30*, 1211-1225. See also, Reyes, E.; Fernández, M.; Uría, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Curr. Org. Chem*. **2012**, *16*, 521-546.

blocked the free N-H via preparation of the NTs-Boc derivative (see Scheme 2.4). Our thinking was that if the aza-Michael reaction was carried out under acidic conditions, in-situ deprotection would liberate the NH functionality to take part in the aza-Michael reaction without requiring a separate deprotection step in the tandem reaction. However, application of the same conditions to **8** described in Table 2.1 resulted in similar outcomes and in no case could we obtain satisfactory quantities of the corresponding Michael addition product.

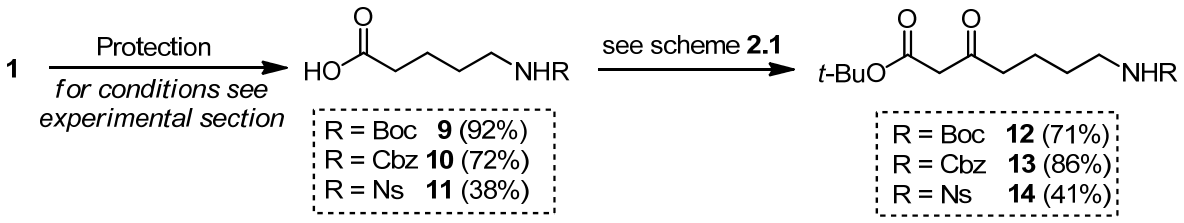



**Scheme 2.4.** Preparation of the diprotected keto ester **8,** and its attempted Michael coupling with crotonaldehyde.

After these initial disappointing results we decided to attempt the tandem reaction directly instead of trying to optimize the component steps of the reaction.

### 2.1.4. Preparation of alternative β-keto ester starting materials.

Unsure whether the tosyl group was the optimum nitrogen activating group we prepared other β-keto esters bearing alternative groups (Boc **12**, Cbz **13** and Nosyl **14**) to screen the reaction conditions (see Scheme 2.5).



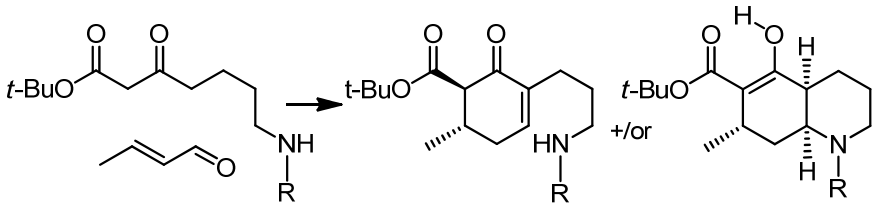

**Scheme 2.5.** Preparation of alternative *N*-protected β-keto esters.

### 2.1.5. Screening of conditions for the tandem reaction

We decided to focus on the use of basic conditions, which could in theory effect the Michael reaction, the Robinson and the aza-Michael reaction in a consecutive manner. Indeed, after treatment of the β-keto esters **12** and **13** with KO*t*Bu in *t*BuOH[46] in the presence of crotonaldehyde we were pleased to observe the formation of the Robinson cyclization products **15** and **16**, respectively, although the corresponding aza-Michael cyclized products **19** and **20** were not detected at all (Table 2.2, entries 1 and 2). Satisfyingly, treatment of the corresponding tosyl analog **4** under the same conditions not only gave the Robinson annulation product **17**, but also moderate amounts of the ester-bearing aza-Michael product **21** (entry 3). Notably, this product bore *cis* stereochemistry (type A) (see section 2.1.7 for structure determination), and moreover, in contrast with the approach developed before this thesis, the decahydroquinoline obtained was completely stable during silica chromatography, with no retro aza-Michael product being observed, even on prolonged standing. A comparable result was obtained using the nosyl derivative **14** (entry 4). Other conditions were then screened to see if we could drive the reaction to completion and exclusively obtain the cyclized product **21**. The use of 10% LiOH in *i*PrOH[47] (entry 5) predominantly gave an undehydrated Robinson aldol product. However, increasing the quantity of LiOH to 2 equiv led to an improved formation of **21** at room temperature (entry 6). Under these new conditions, we studied the cyclization of keto esters **12**, **13**, and **14**, bearing Boc, Cbz and Ns activating groups respectively (entries 7-9). However, all performed significantly worse than the tosyl-bearing keto ester **4**. Notably, the carbamate protected substrates Cbz and Boc, in line with the previously employed conditions using KO*t*Bu, gave only the Robinson adduct and significant quantities of the undehydrated Robinson aldol product. The use of *n*$Bu_4$NOH/KOH[48] or *n*$Bu_4$NOH/LiOH also gave good results, although once again significant quantities of the ring-opened product were obtained (entries 10, 11).

[46] Chong, B.; Ji, Y.; Oh, S.; Yang, J.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323-9325.
[47] Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738-4744.
[48] Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc. Perkin Trans. 1* **2002**, 895-900.

**Table 2.2.** Screening of conditions for the one-pot Robinson aza-Michael reaction.




| | | |
|---|---|---|
| R = Boc | **12** | **15** | **19** |
| R = Cbz | **13** | **16** | **20** |
| R = Ts | **4** | **17** | **21** |
| R = Ns | **12** | **18** | **22** |

| ***Entry***[(a)] | ***R*** | ***Reagents (equiv)*** | ***Solvent*** | ***Product (Yield [%])***[(b)] |
|---|---|---|---|---|
| 1 | Boc | KO*t*Bu (0.3) | *t*BuOH | **15** (55) |
| 2 | Cbz | KO*t*Bu (0.3) | *t*BuOH | **16** (63) |
| 3 | Ts | KO*t*Bu (0.3) | *t*BuOH | **17** (50), **21** (34) |
| 4 | Ns | KO*t*Bu (0.3) | *t*BuOH | **18** (29), **22** (41) |
| 5 | Ts | $LiOH \cdot H_2O$ (0.1) | *i*PrOH | n.d. |
| 6 | Ts | $LiOH \cdot H_2O$ (2) | *i*PrOH | **17** (5), **21** (57) |
| 7 | Boc | $LiOH \cdot H_2O$ (2) | *i*PrOH | **15** (18) |
| 8 | Cbz | $LiOH \cdot H_2O$ (2) | *i*PrOH | **16** (21) |
| 9 | Ns | $LiOH \cdot H_2O$ (2) | *i*PrOH | **18** (19), **22** (27) |
| 10 | Ts | TBAH (0.4)[(c)] / $KOH_{aq}$ | $Et_2O$ / THF | **17** (20), **21** (65) |
| 11 | Ts | TBAH (0.4)[(c)] / $LiOH_{aq}$ | $Et_2O$ / THF | **17** (12), **21** (71) |

**[a]** All reactions were carried out at room temperature for 24 h with 1.1 equiv. of crotonaldehyde **[b]** yield refers to the products isolated by flash chromatography; **[c]** TBAH refers to 40% $n Bu_4NOH$ in $H_2O$.

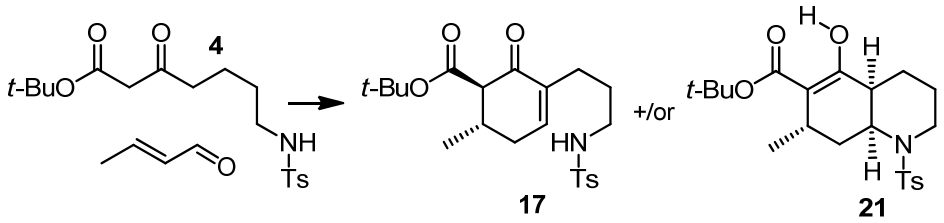
We chose to optimize the LiOH procedure, since it was simpler to carry out and gave a pure product on work-up, unlike the use of $n Bu_4NOH$ which had to be removed by chromatography.[49]

[49] The result in Table 2.2, entry 11, was obtained after optimization of the LiOH procedure carried out in Table 2.3.

### 2.1.6. Optimization of conditions for the tandem reaction

While switching to anhydrous LiOH produced a slightly better yield (Table 2.3, entry 1), subsequent increases and decreases in the base gave inferior results (entries 2 and 3). The importance of the quantity of base was also observed when returning to the use of $LiOH.H_2O$ with only one equivalent (entry 4). The quantity of crotonaldehyde was also found to be important, with increases detrimental to the reaction (entry 5). In contrast, the further addition of water to the reaction medium (10 equiv) proved extremely beneficial and resulted in less ring-opened product and consequently an increased yield of **21** to 78% (entry 6).

**Table 2.3.** Optimization of conditions for the one-pot Robinson aza-Michael reaction.




| *Entry*[(a)] | *R* | *Reagents ( equiv )* | *Solvent* | *Product ( Yield [%])*[(b)] |
|---|---|---|---|---|
| 1 | Ts | LiOH (2) | *i*PrOH | **17** (10), **21** (60) |
| 2 | Ts | LiOH (5) | *i*PrOH | **17** (16), **21** (38) |
| 3 | Ts | LiOH (1) | *i*PrOH | **17** (10), **21** (44) |
| 4 | Ts | $LiOH{\cdot}H_2O$ (1) | *i*PrOH | **17** (8), **21** (60) |
| 5 | Ts | $LiOH{\cdot}H_2O$ (1)[(c)] | *i*PrOH | **17** (6), **21** (46) |
| 6 | Ts | $LiOH{\cdot}H_2O$ (1)[(d)] | *i*PrOH | **21** (78) |

**[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]** crotonaldehyde (2 equiv) was used; **[d]** $H_2O$ (10 equiv) was added.

### 2.1.7. Determination of type A stereochemistry via NMR

The relative stereochemistry of the synthesized azabicyclic compound was elucidated by 2D NMR spectra (COSY, HSQC). It is well known that for *cis*-decahydroquinolines, when the nitrogen atom is embedded in a carbamate, carboxamide or sulfonamide group, it shows a preferred conformation in which the nitrogen lone-pair is outside with respect to the carbocyclic ring to avoid the allylic strain with the C8-C8a bond. Thus, the twin chair conformation with the nitrogen equatorially substituting the carbocyclic ring should be the lowest energy conformation for this compound if a *cis*-decahydroquinoline was formed (see Figure 2.2).

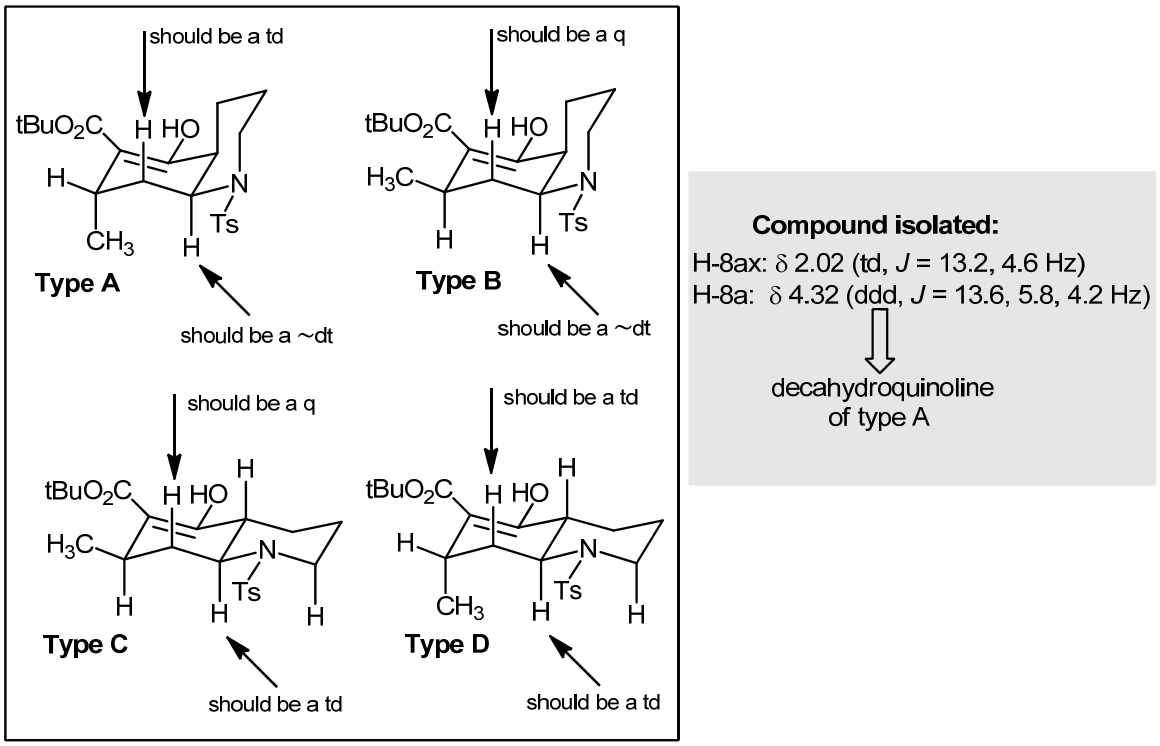



**Figure 2.2.** Determination of all *cis*-stereochemistry via NMR of decahydroquinoline **21**.

Between the two possible *cis*-decahydroquinolines (A or B), the key evidence for discarding B was found in the $^{1}H$ NMR coupling pattern for the H-8ax, which appears as triplet of doublets. This coupling pattern only is compatible with a location of the methyl group at C-7 in an axial disposition. However, this argument doesn't allow discernment between compound type A and a configuration of type D, in which there is a trans-ring fusion. In this case,

the diagnostic signal is the coupling constant pattern of H-8a. The axial proton H-8a is strongly coupled only with one adjacent axial proton. Hence, its resonance signal appears as a deceptively doublet ($J$ = 13.4 Hz) of other doublets ($J$ = 5.8, 4.2 Hz) (see Figure 2.2).

A wide range of lycopodium alkaloids are potentially accessible from building block **21** and are presented below in figure 2.3.

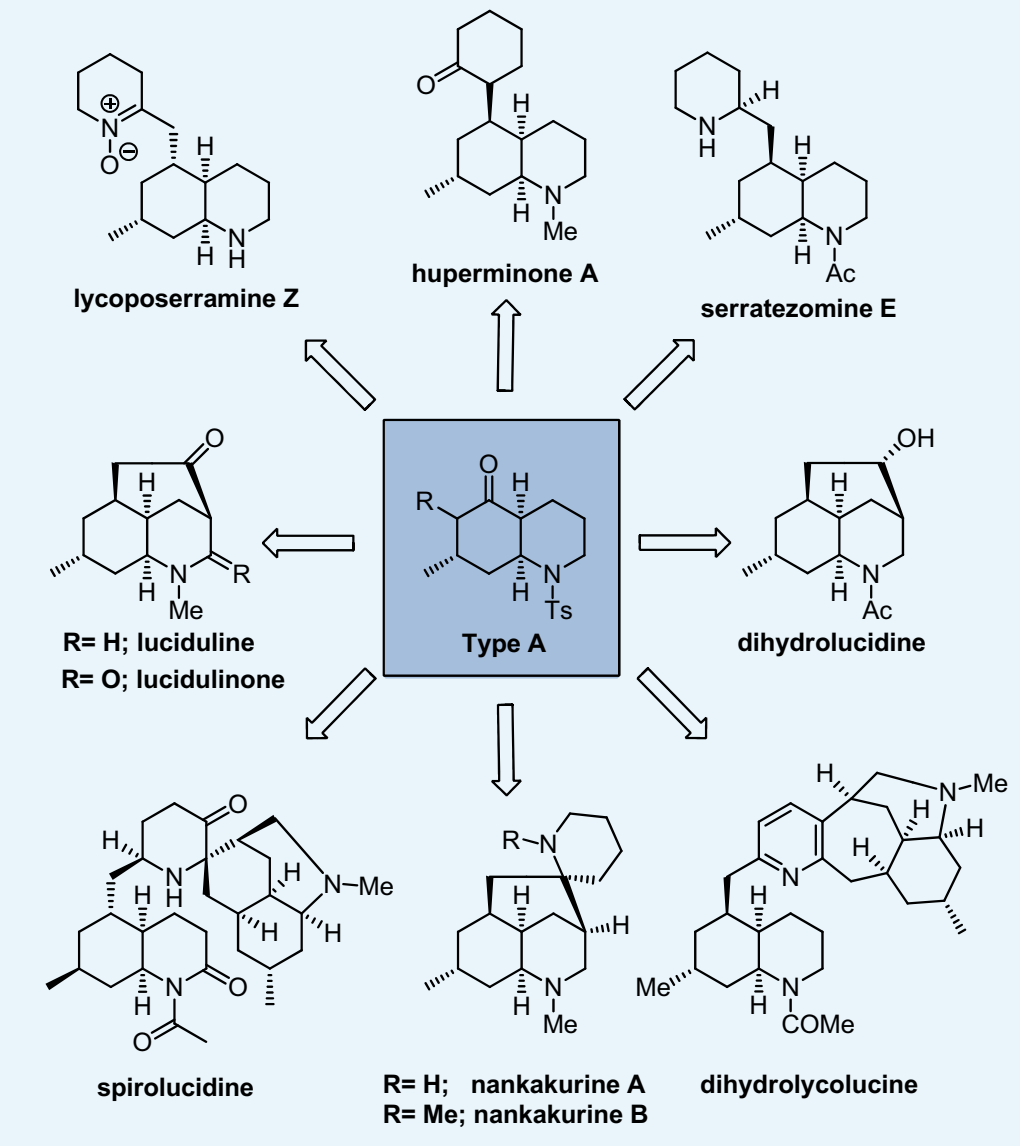


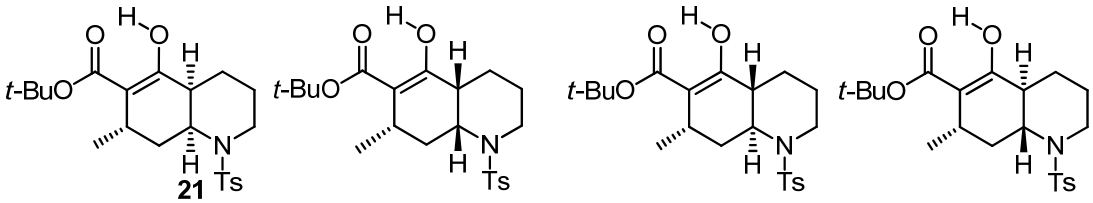

**Figure 2.3.** Lycopodium alkaloids with type A stereochemistry potentially accessible via building block **21**.

## 2.2. Mechanism of the Tandem Reaction Based on DFT Modelling Studies

### 2.2.1. Relative stability of the diastereoisomers. Access to type A stereochemistry

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 in the gas phase but also 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 for the four possible diastereoisomers and their tautomers were optimized, and their relative energies (see Table 2.4) fully justified the reactivity observed, the most stable being the one detected experimentally (β-keto ester **21**). As can be seen, **21** in its keto form was the least stable of the possible structures, but in enolic form it was the most stable compound. Notably, the β-keto ester **21** with the axial methyl group at C-7 was thermodynamically more stable than the absent epimer with the methyl substituent equatorially located.

**Table 2.4.** Relative energies and free energies in gas and in solution (water) for the keto and enol tautomers of the four possible stereoisomers A,B,C and D.

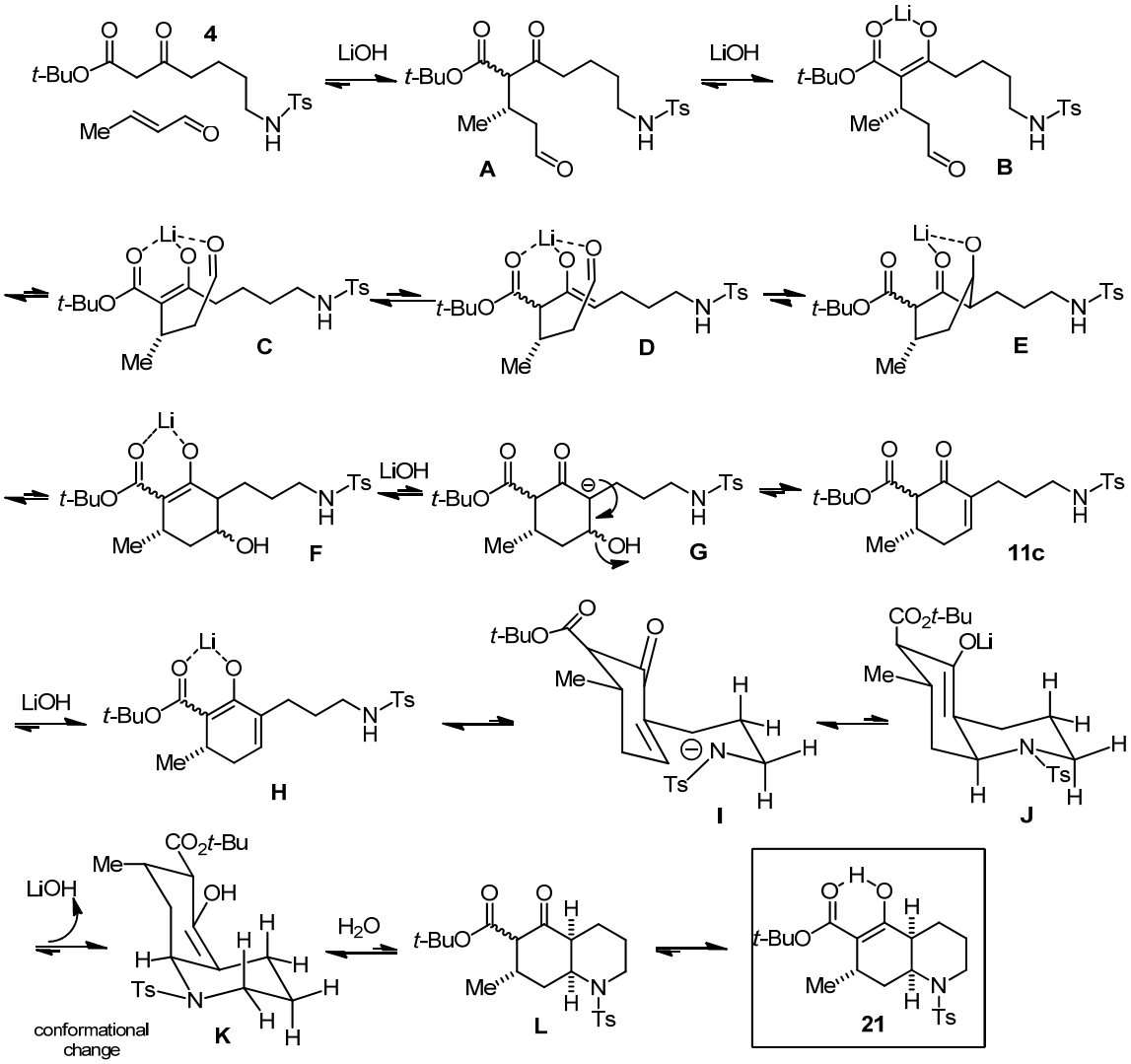



| | ***A-keto*** | ***A-enol*** | ***B-keto*** | ***B-enol*** | ***C-keto*** | ***C-enol*** | ***D-keto*** | ***D-enol*** |
|---|---|---|---|---|---|---|---|---|
| *E* (gas phase) | 12.9 | 0.0 | 12.1 | 1.2 | 6.8 | 4.9 | 9.3 | 2.3 |
| *G* (gas phase) | 11.2 | 0.0 | 10.2 | 1.0 | 5.5 | 4.4 | 7.3 | 2.9 |
| *E* (sp solv) | 8.2 | 0.0 | 8.2 | 1.7 | 2.6 | 4.6 | 5.6 | 2.6 |
| *G* (solv) | 5.4 | 0.0 | 5.7 | 1.4 | 1.4 | 4.0 | 3.5 | 2.7 |

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 in the cyclization process.

### 2.2.2. Proposed mechanism of the tandem biscyclization

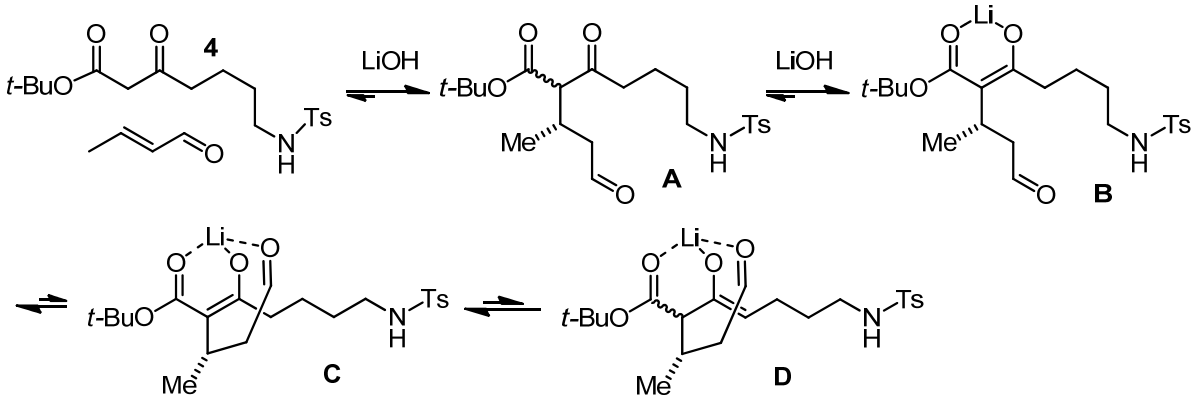
In order to understand the mechanism of the reaction and fully determine its scope for accessing other stereochemistries, extensive DFT based studies were carried out. Firstly, based on the experimental results, we propose a plausible mechanism (see Scheme 2.6) and then discuss the constituent parts.




**Scheme 2.6.** Overview of the biscyclization process mechanism leading to 5-oxodecahydroquinolines (based on experimental DFT modelling studies).

**(a) Formation of the correct enolate:** a Michael reaction between the keto ester **4** and crotonaldehyde gave the coupled product (**A**), which was further deprotonated to furnish the lithium enolate species (**B**), effectively preventing the Robinson annulation 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 (Scheme 2.7).




**Scheme 2.7.** Formation of unfavoured enolate prior to the aldol reaction.

However, it was thought that the carbonyl 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 (Figure 2.4). 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.[50]

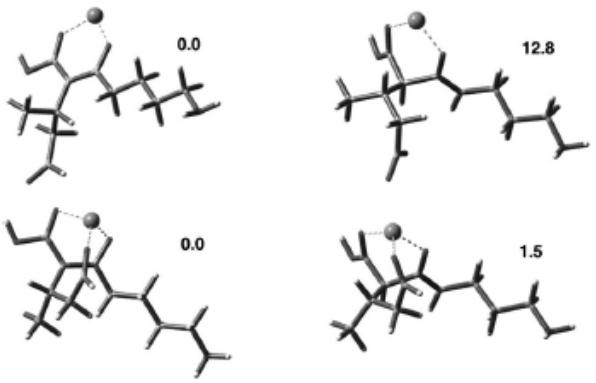
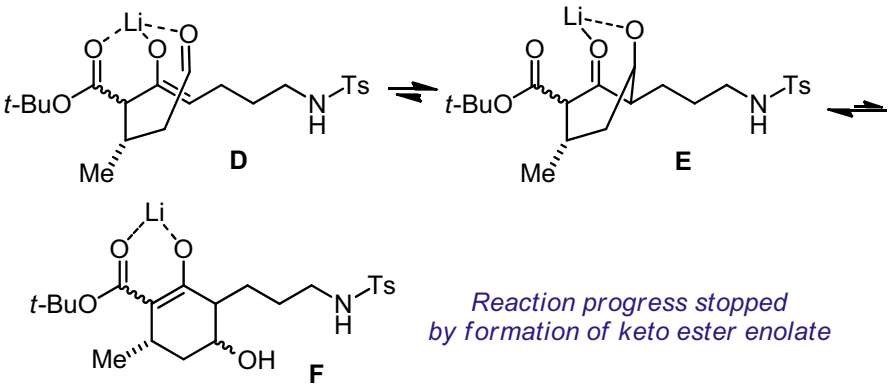



**Figure 2.4** Optimized structures and relative free energies (Kcal mol $^{-1}$) including solvent effects (*i*PrOH) for the two possible enolates, with two or three carbonyl groups coordinated to $Li^+$.

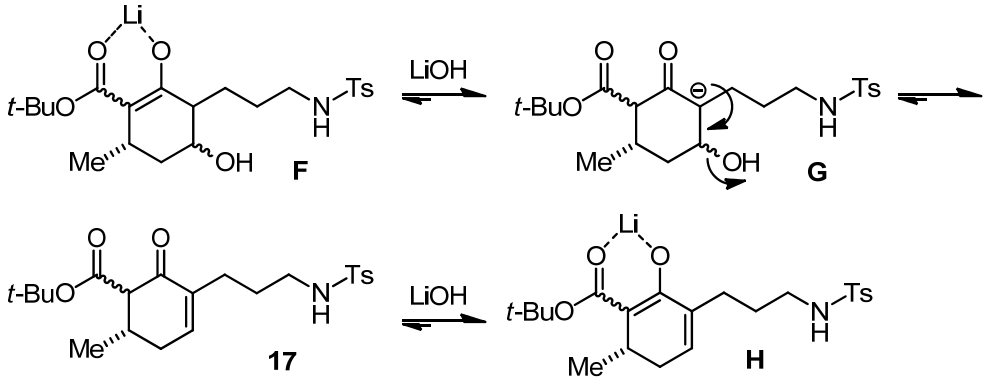
[50] The enolate at the most acidic position has its negative charge distributed along the two carbonyl groups, whereas the enolate at the less acidic position has this charge concentrated around one of the two carbonyl groups. Therefore, placing one lithium cation between the two carbonyl groups results in a greater stabilization of the most favorable enolate.

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



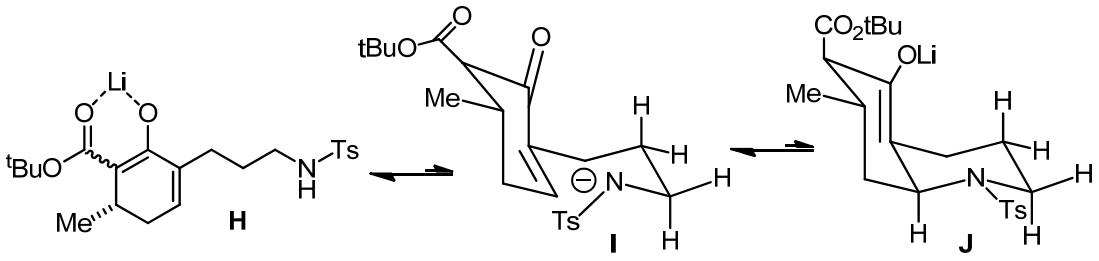

**Scheme 2.8.** Aldol reaction via less stable lithium enolate.

**(c) Elimination to cyclohexenone 17:** A small quantity of the least stable enolate (**G**) present at equilibrium undergoes dehydration to give the enone **17**. Deprotonation of the keto ester again prevents the reaction from progressing by forming the more stable enolate.




**Scheme 2.9.** Aldol dehydration step.

**(d) Aza-Michael Reaction:** A small amount of the enone **I** present at equilibrium is attacked from the top face to give aza-Michael addition product intermediate **J**.




**Scheme 2.10.** Aza-Michael cyclization step.

The configuration of the C4a and C8a stereocenters is determined in subsequent steps, namely the second cyclization (**17**→**K**) for C4a, and tautomerization (**K**→**L**) for C8b. As depicted in Scheme 2.6, the second cyclization appears to evolve through a series of intermediates (**H**, **I**, **J**), in which LiOH plays a crucial role in the formation of lithium enolate species and deprotonation of the tosylamide moiety. Modelling 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 the nucleophilic attack of the amine on the alkene C atom. These structures are collected in Figure 2.5, 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 C8a, the transition state corresponding to the attack on the opposite face of the alkene being 3.7 kcal.mol$^{-1}$ higher in energy.

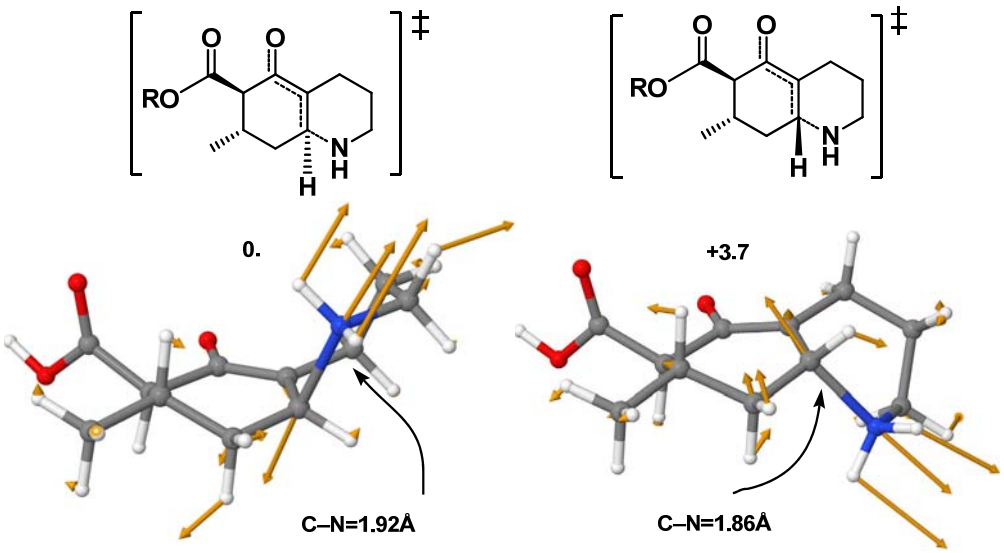
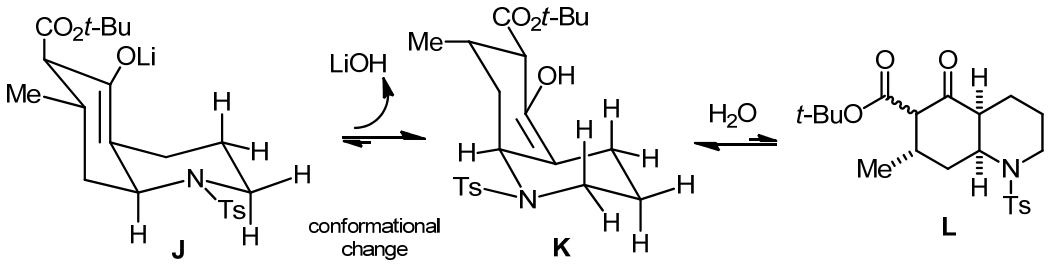



**Figure 2.5.** Molecular structures for models (R=H) of the transition states of the two possible pathways of the cyclization step in which the bicyclic system is formed, generating the C8a stereocenter. Relative free energy in Kcal $mol^{-1}$.

**(e) Protonation of the Aza-Michael Reaction Product:** Once the bicycle ring system is formed the molecule immediately undergoes a 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 favours the formation of **L** by providing a ready source of protons to trap intermediate **K** before it can revert back to the ring opened product **17** via a retro aza-Michael reaction.




**Scheme 2.11.** Protonation of lithium enolate to give the *cis*-decahydroquinoline.

The generation of the second stereogenic center C4a via the tautomerization **K** → **L** also occurs diastereoselectively. We studied this elementary proton transfer in detail, as well as the subsequent tautomerization **K** → **21**. 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.$mol^{-1}$). The need for water is in accordance with the experimental

observation of an increased reaction rate in the presence of water. As shown in Figure 2.6, 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 2.6 indicate that path *a* is preferred, both kinetically and thermodynamically, and leads to the most stable product **21**. 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 since the differences in the transition states are negligible, the free energy barrier also becomes lower.

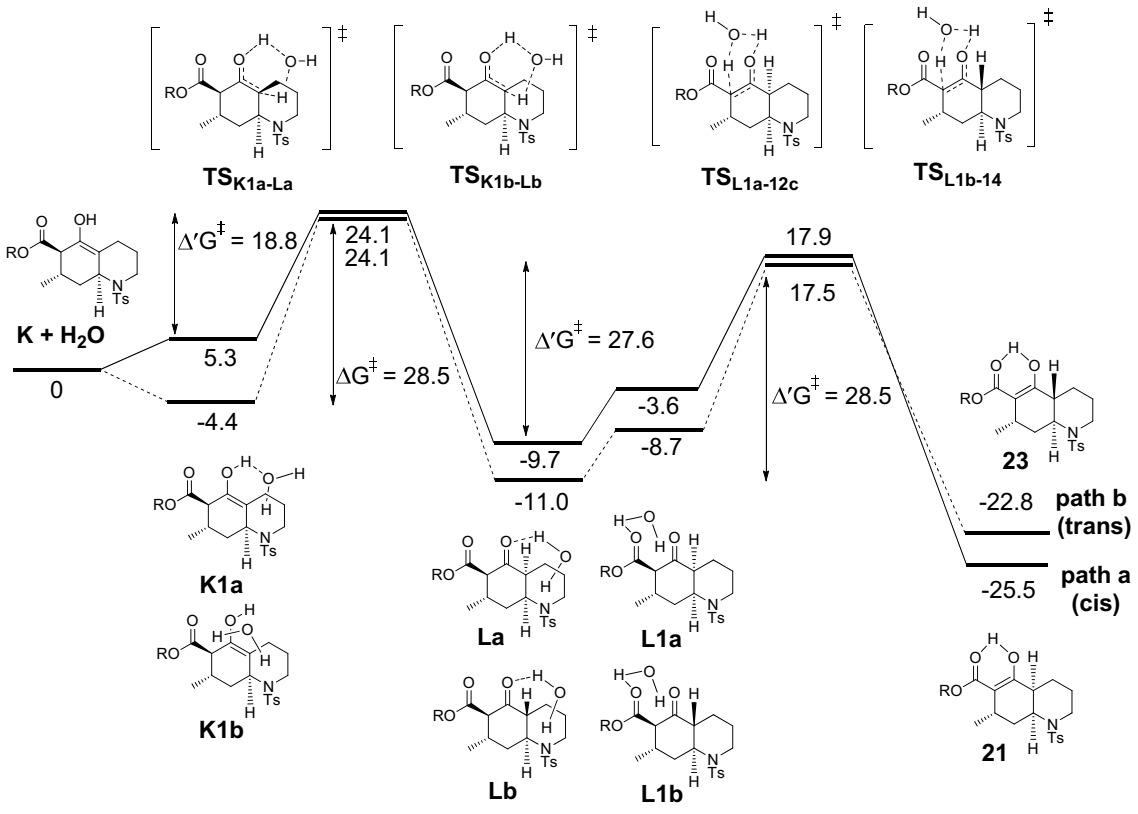
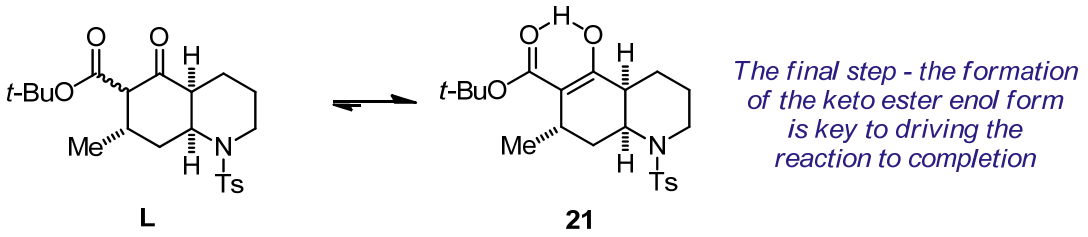



**Figure 2.6.** Reaction free energy profile for the water-assisted proton transfer steps from *K* to **21**, for R=H. All values in Kcal mol$^{-1}$.

**(f) 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 **21** (see Scheme 2.12).




**Scheme 2.12.** Tautomerisation of β-keto ester to more stable enol form.

Thus, the tandem reaction would appear to be a series of sequential equilibria, the vast majority of which are unfavourable. Only the last step in which the enol of **21** is formed is favourable, and indeed crucial, since it pushes the equilibrium over to the completion of the reaction. This overall mechanism would explain why the reactions using carbamate derivatives (**12** and **13**), which do not undergo the intermolecular aza-Michael reaction, are mostly halted at step (**b**), giving intermediates analogous to **F**. Only when the unfavourable equilibrium is overcome by using KO*t*Bu under forcing reflux conditions is the cyclohexenone (**15** and **16**) obtained. However, the poor nucleophilicity of the carbamate is not sufficient to overcome the **H**→**J** step leading to the decahydroquinoline ring.

## 2.3. Access to 5-oxodecahydroquinolines of type B

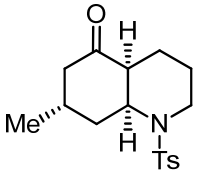
Having designed an effective strategy to achieve decahydroquinolines with the 'type A' relative stereochemistry we turned our attention to generating 'type B' products.

### 2.3.1. Relative stability of tosyl containing 5-oxodecahydroquinolines.

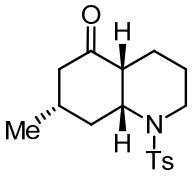
The thermodynamic stability of the *N*-tosyl-5-oxodecahydroquinolines lacking the ester group was also determined. Table 2.5 shows the relative and free energies of *cis* compounds **24** (type A) and **25** (type B), and the *trans* isomers, with the four relative configurations, as well as those of their corresponding tautomers. These calculations confirmed that, the corresponding *N*-tosyldecahydroquinoline **25**, lacking the ester group and with a "type B" stereochemistry, was now 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.

Since the calculations and initial preliminary work (see scheme 1.18) had found that this is the more stable compound then we would expect a retro aza-Michael reaction followed by reclosure of the ring would lead to the type B stereochemistry found in compounds such as huperzine M and Cermizine B (see Figure 2.7).

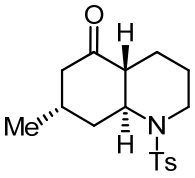
**Table 2.5.** Relative energies and free energies in gas and in solution (water) for the keto and enol tautomers of the four possible stereoisomers.



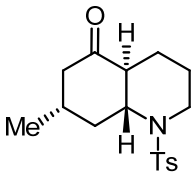

**24** (type A)




**25** (type B)




(type D)




(type C)

| | ***A-keto*** | ***A-enol*** | ***B-keto*** | ***B-enol*** | ***C-keto*** | ***C-enol*** | ***D-keto*** | ***D-enol*** |
|---|---|---|---|---|---|---|---|---|
| *E* (gas phase) | 0.8 | 9.9 | 0.0 | 9.5 | 5.6 | 13.5 | 3.6 | 14.4 |
| *G* (gas phase) | 0.5 | 9.2 | 0.0 | 8.9 | 5.2 | 12.8 | 2.9 | 13.4 |
| *E* (sp solv) | 0.8 | 10.6 | 0.0 | 10.5 | 4.6 | 14.0 | 3.6 | 14.6 |
| (*G* solv) | 0.9 | 11.0 | 0.0 | 10.8 | 4.4 | 13.3 | 2.8 | 14.2 |

A large number of natural products are potentially accessible from gaining access to a type B decahydroquinoline building block and are illustrated below (figure 2.7)

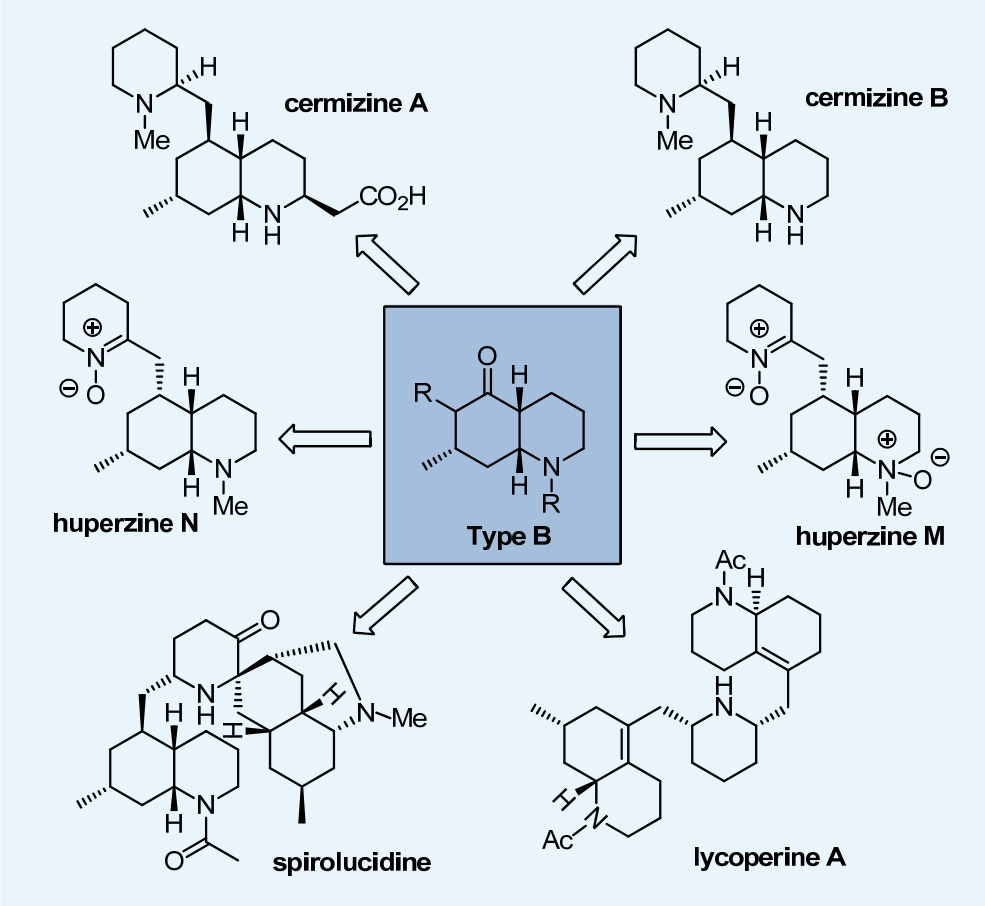


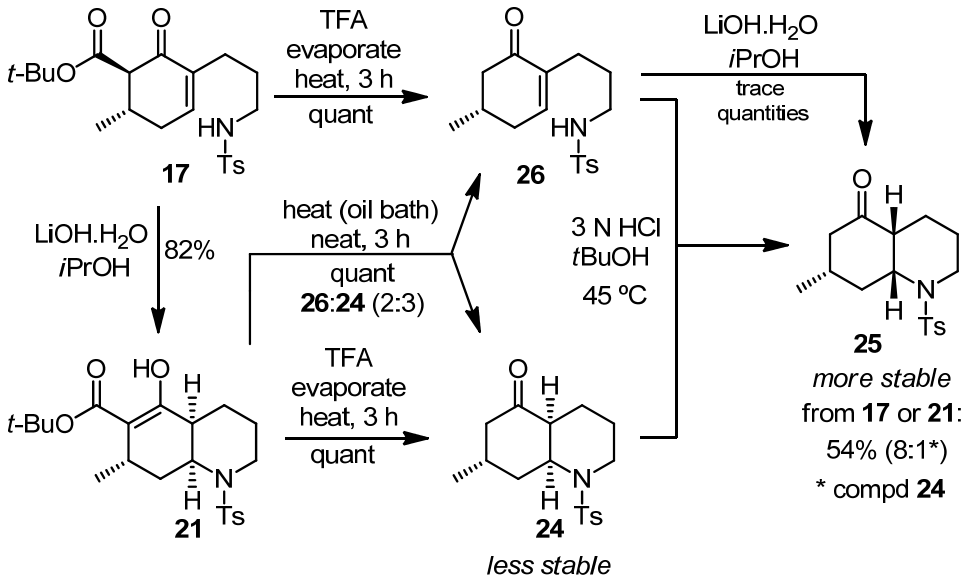

**Figure 2.7.** Lycopodium alkaloids potentially accessible from a type B 5-oxodecahydroquinoline building block.

### 2.3.2. Synthetic access to type B stereochemistry

Two routes were investigated for the formation of decahydroquinoline **25**. Treatment of β-keto ester **17** (see table 2.2, entry 3 for preparation) with neat TFA quantitatively provided the tosylamine-tethered cyclohexenone **26**. Acid treatment gave the cyclized compound **25**, corresponding to the thermodynamic compound, along with small quantities of **24** and recovered starting material. In fact, according to our calculations, the difference in energy between **24**, **25**, and **26** favours **25** by only a few kcal.mol$^{-1}$, although if we take into account the

internal degrees of freedom, in free energy terms **26** becomes the most stable species due to the formation of an intermolecular hydrogen bond between the ketone and the sulfonamide hydrogen. Alternatively, treatment of β-keto ester **21** with neat TFA followed by evaporation, azeotroping with toluene and heating quantitatively provided decahydroquinoline **24**, which, although thermodynamically less stable than **25**, was sufficiently stable to be isolated without undergoing isomerization in the process. The ester group could also be removed by heating **21** neat in an oil bath (150 °C), however this led to the formation of significant amount of the ring opened product **26**.

Interestingly, as expected, the developed domino reaction conditions ($LiOH.H_2O$, *i*PrOH, Table 2.3, entry 6) applied to cyclohexenone **17** gave **21**, but when applied to enone **26** only traces of the intramolecular aza-Michael product **25** were obtained.




**Scheme 2.13.** Access to type B relative stereochemistry.

### 2.3.3. Determination of type A and B stereochemistries by NMR

Figure 2.8 depicts the structures (relative configuration and preferred conformation) of the synthesized diastereomeric *cis*-decahydroquinolines **24** (type A) and **25** (type B), 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-Ts substituted *cis*-decahydroquinolines; in this conformation the axial 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 δ 4.40 and 4.22 for **24** and **25**, 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 **24**, which promotes a compression, deshielding the chemical shift of H-8a. Additionally, **24** and **25** are clearly differentiated by two NMR features: i) the $^{1}$H NMR chemical shift of H-$8_{ax}$, which appears more deshielded (δ 2.26) in **24** than in **25** (δ 1.81), due to its antiperiplanar location with respect to the axially located methyl group, and ii) the $^{13}$C NMR chemical shift of the Me group, which is shifted more upfield (δ 19.3) in **24** than in **25** (δ 21.9), an effect that is also observed in C-8a (δ 50.1 and 53.0, respectively).

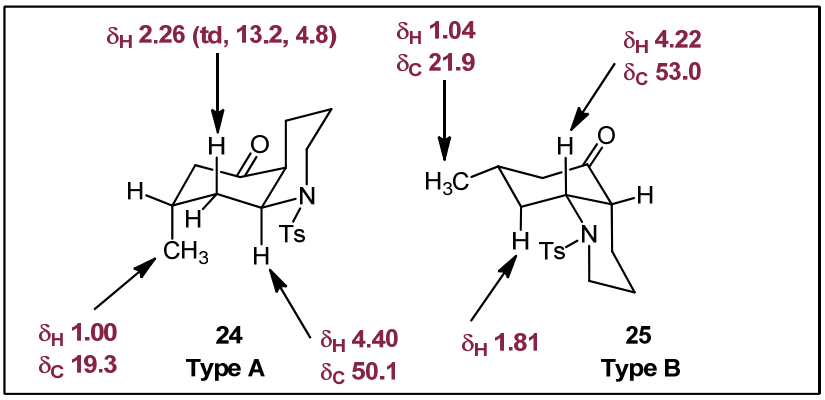



**Figure 2.8.** Conformational preference of decahydroquinolines **24** and **25** determined on the basis of NMR spectroscopic data, showing type A and B stereochemistries.

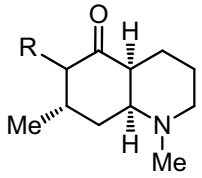
## 2.4. Access to 5-oxodecahydroquinolines of type C and type D

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 sulfonamide group. Thus, "type C" compounds with a *trans* stereochemistry at the ring junction (corresponding to the natural products, such as phlegmarine and huperzine Z, see Figure 2.9) would not be accessible via aza-Michael cyclization of compounds with an electron-withdrawing group in the nitrogen atom. However, taking into consideration literature precedents[51] and our own studies on related compounds and octahydroindoles[31] it seemed possible that structures with a *trans* ring fusion might be accessed by interchanging the nitrogen-substituent group.

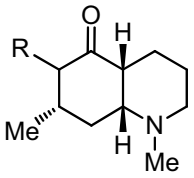
### 2.4.1. Stability of decahydroquinolines bearing non electron withdrawing groups.

To test this supposition, the thermodynamic stability of the different possible diastereoisomers 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 2.6).

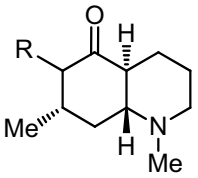
**Table 2.6.** Relative energies and free energies in gas and in solution (water) for the keto and enol tautomers of the four stereoisomers.



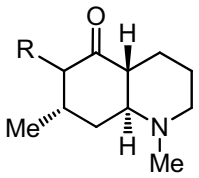
**A-1** (R = $CO_2t$Bu)
**A-2** (R = H)



**B-1** (R = $CO_2t$Bu)
**B-2** (R = H)



**C-1** (R = $CO_2t$Bu)
**C-2** (R = H)



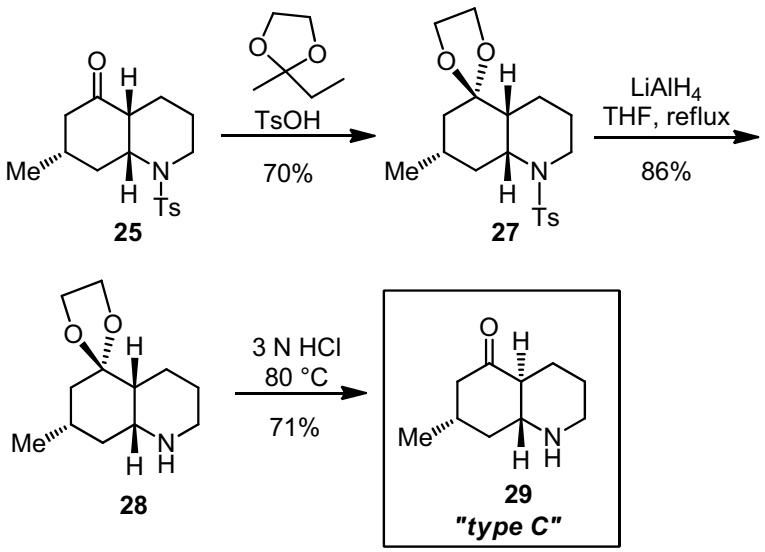
**D-1** (R = $CO_2t$Bu)
**D-2** (R = H)

| | ***A-1*** | ***A-2*** | ***B-1*** | ***B-2*** | ***C-1*** | ***C-2*** | ***D-1*** | ***D-2*** |
|---|---|---|---|---|---|---|---|---|
| *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 |

[51] For early work in this field, in which conversion of *cis*-5-oxodecahydroline into the *trans* derivatives was observed when the nitrogen atom was unsubstituted or alkyl substituted see: 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.

### 2.4.2. Synthetic access to 5-oxodecahydroquinolines of type C

Charged with this insight as proof of concept, our efforts then turned toward the experimental realization of *trans*-5-oxodecahydroquinoline synthesis.[52] Due to the propensity of 2-(3-aminopropyl)cyclohex-2-enones to undergo 1,2-addition rather than 1,4-addition,[53] 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 **25** under acetalization reaction conditions[44] gave acetal **27** (Scheme 2.14). Removal of the tosyl group with $LiAlH_4$ and treatment of the resulting aminoacetal **28** under aqueous acidic conditions gratifyingly led to removal of the acetal and epimerization at the α-carbonyl to give the target **29**.




**Scheme 2.14.** Synthesis of a decahydroquinoline with phlegmarine type C stereochemistry.

[52] The experimental work to obtain the type C and D compounds was carried out by laboratory coworker Gisela Saborit Villarroya.

[53] For the use of the 1,2-cyclization strategy in the synthesis of other lycopodium alkaloids, see: a) Schumann, D.; Müller, H.-J.; Naumann, A. *Liebigs Ann. Chem*. **1982**, 1700-1705; b) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc*. **2010**, *132*, 5926 –5927.

An overview of some of the lycopodium alkaloids with type C stereochemistry which are potentially accessible via the building block **29** are illustrated in figure 2.9.

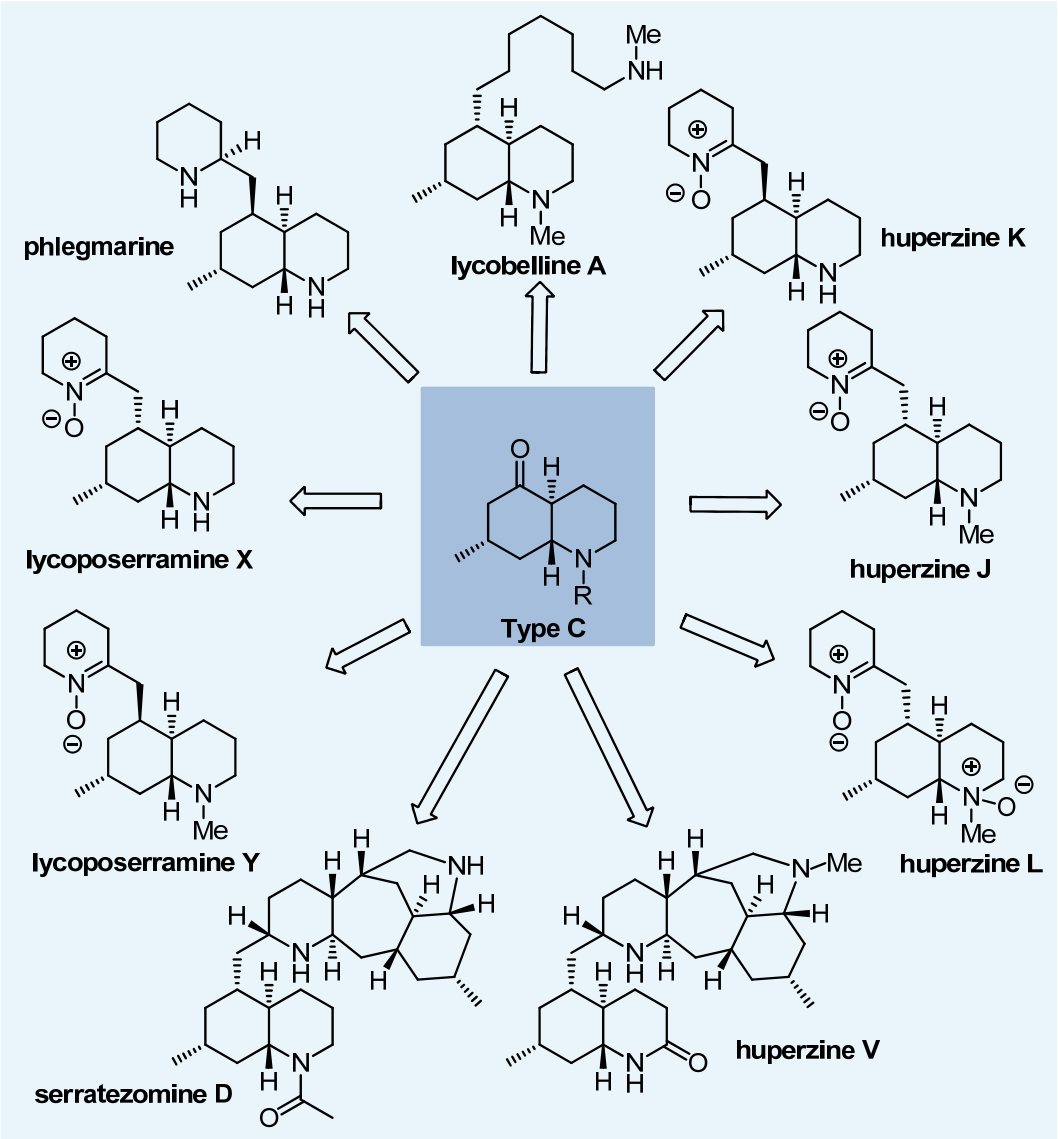



**Figure 2.9.** All phlegmarine alkaloids with type C stereochemistry potentially accessible via the building block **29**.

### 2.4.3. Synthetic access to 5-oxodecahydroquinolines of type D

The remaining possible stereochemistry ("type D") for the three centers of the decahydroquinoline core was the only one not previously found in any of the phlegmarine alkaloids at the time of our initial studies. However, during the writing of this thesis a new phlegmarine alkaloid with type D stereochemistry was isolated, serralongamine A.[8] (See Figure 2.10).

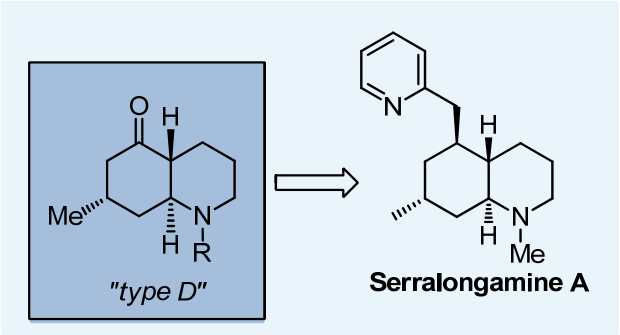
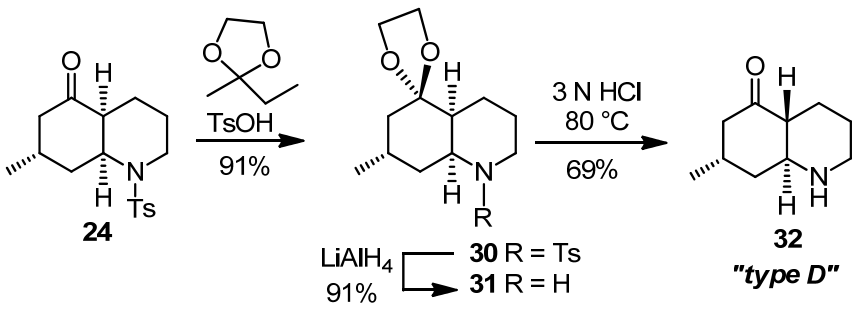



**Figure 2.10.** The only example of a type D stereochemistry found among phlegmarine alkaloids.

Given that the above process (scheme 2.14) allowed the interconversion *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 **29**, ketone **24** was protected as an acetal to give **30** (Scheme 2.15), followed by treatment with $LiAlH_4$ to remove the tosyl group. Subjecting the product **31** to the same acidic conditions as above gave the *trans* compound **32**, but in this series the isomerization was partial giving **32** along with its C-4a epimer **33** in a 2:1 ratio.




**Scheme 2.15.** Synthesis of a decahydroquinoline with phlegmarine type D stereochemistry.

### 2.4.4. Comparitive NMR analysis of type A-D 5-oxodecahydrohydrolines

The four relative stereochemistries for the 7-methyl-5-oxodecahydroquinolines (*N*-unsubstituted derivatives **33**, **34**, **29** and **32**) are depicted in Figure 2.11, which shows the diagnostic NMR signals in each case. The *cis* **(33** and **34**) and *trans* decahydroquinolines (**29** and **32**) are clearly differentiated by two NMR features: (i) the $^{1}$H NMR chemical shift of H-8a, which appears more deshielded $\delta$ = 3.2-3.6) in the *cis*- than in the trans-derivatives ($\delta$ = 2.5); (ii) the $^{13}$C chemical shift of C(4a), which is more deshielded ($\delta$ = 4–5 ppm) in the *trans* than in the *cis* derivatives. According to the multiplicity of the H-8a in the 1H NMR spectra, the preferred conformation of the *cis* decahydroquinoline **33** has the H-8a axial with respect to the N-containing ring (*N*-endo conformer), while a *N*-exo conformation with an equatorial H-8a configuration with respect to that ring is preferred for **34**, since it places the methyl substituent at C-7 in an equatorial orientation.

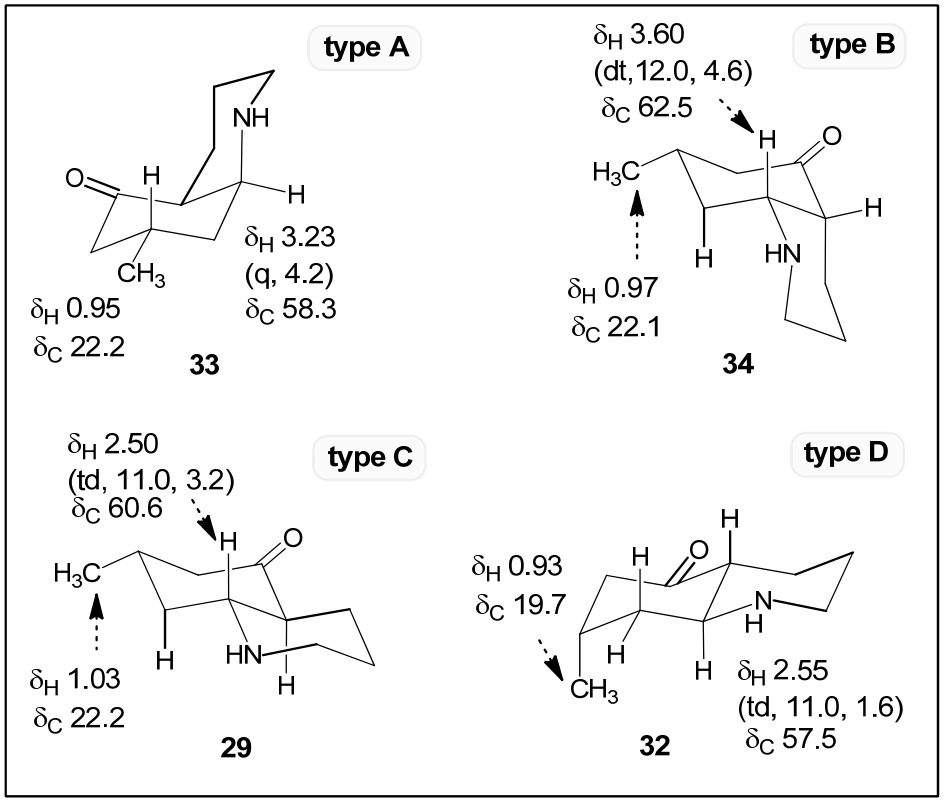
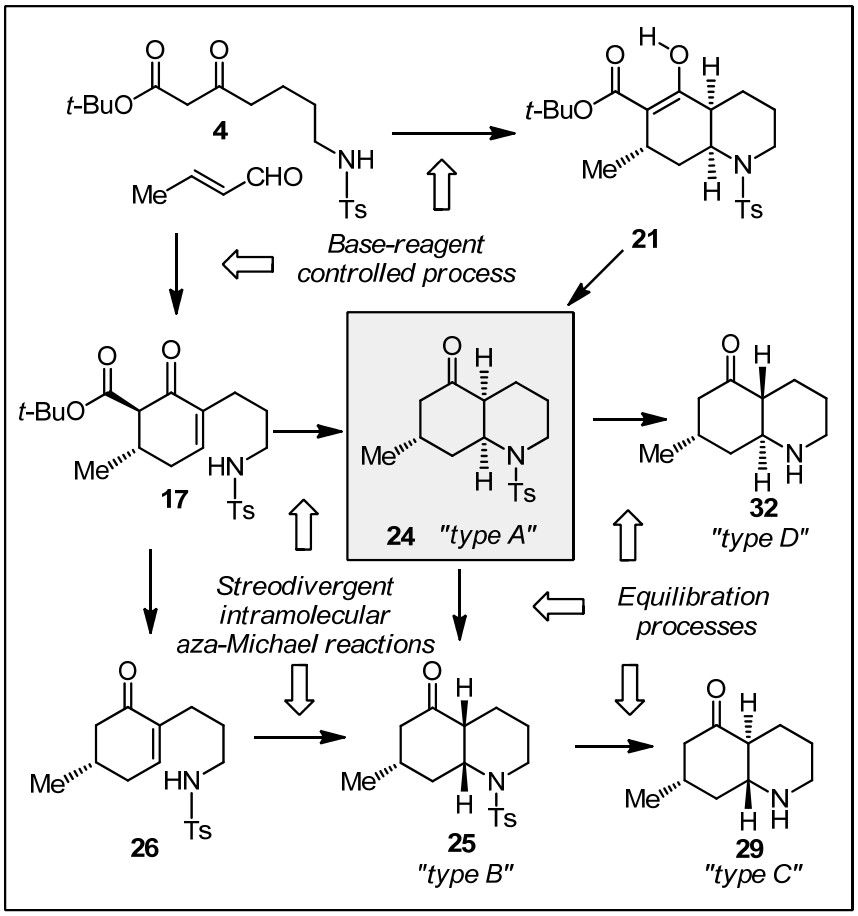



**Figure 2.11.** NMR conformational analysis of the 4 decahydroquinoline ring structures.

### 2.4.5. Overview of methods to access type A-D 5-oxodecahydroquinolines

The four relative stereochemistries of 7-methyl-5-oxodecahydroquinolines were obtained corresponding to the four main types of phlegmarine alkaloids ("types A-D") from a common simple acyclic β-keto ester intermediate **4**. This was accomplished by the development of a cascade Robinson and aza-Michael intramolecular process leading to β-keto ester **21** through a biscyclization, followed by a dealkoxycarbonylation step and a series of configurationally controlled equilibration processes (see Scheme 2.16).




**Scheme 2.16.** Overview of stereocontrolled processes leading to all stereochemistries of 7-methyl-5-oxodecahydroquinolines.

## 3. Total Synthesis of (+)-Lycoposerramine Z

*Org. Lett*. **2013**, *15*, 326-329

## 3.1. Total Synthesis of *cis*-Phlegmarine Alkaloids from a Common Intermediate

With access to all nuclei possible from the common intermediate **21** we set about evaluating their conversion to the corresponding phlegmarine alkaloids. Due to the large amount of possible compounds possible from these 4 building blocks we decided to focus our attention only on the *cis*-phlegmarine alkaloids, in particular the type A containing structures lycoposerramine Z, serratezomine E and the type B containing structures cermizine B and huperzine M (see figure 3.1). This chapter outlines the work towards the type A derivatives whilst chapter 4 deals with the respective type B derived compounds.

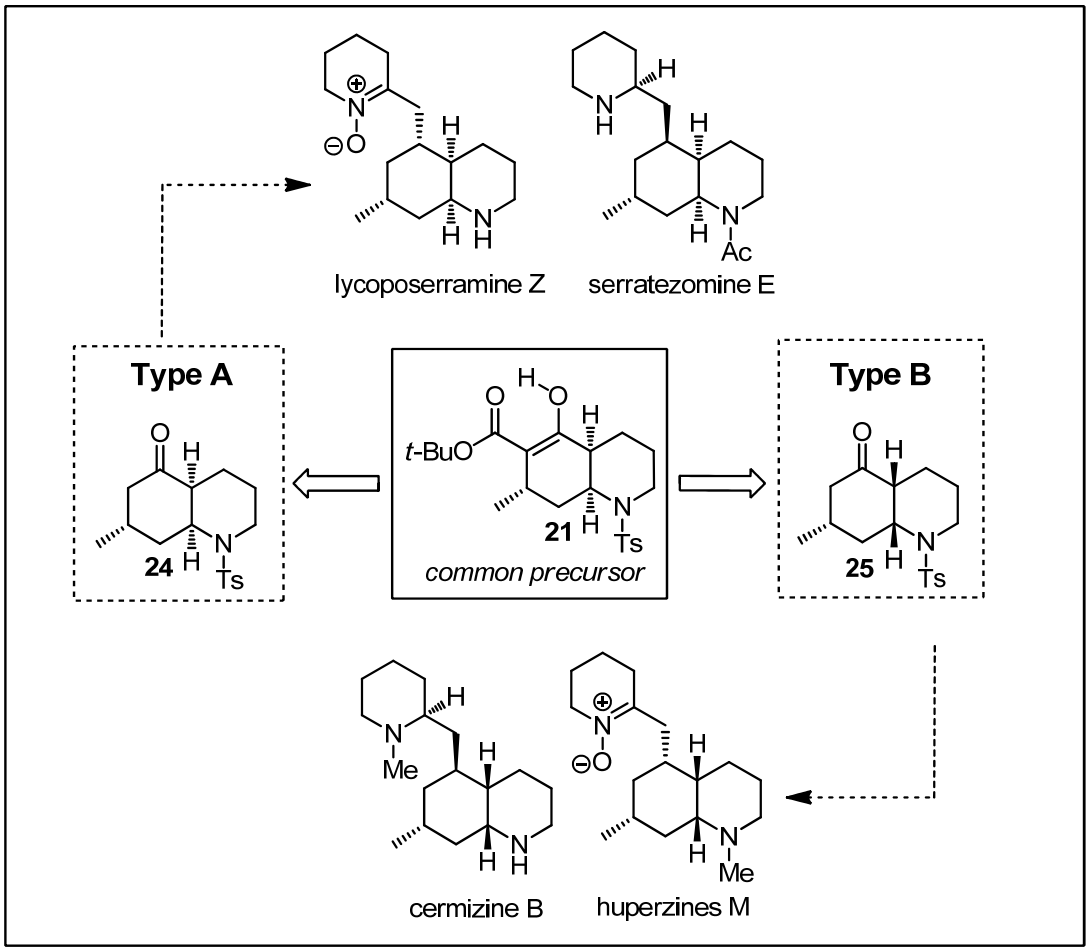



**Figure 3.1.** Total synthesis objectives from the common decahydroquinoline precursor **21**.

## 3.2. Enantioselective Version of the Tandem Reaction via Organocatalysis

In order to carry out the total syntheses of the outlined phlegmarine alkaloids we required access to sufficient quantities of the decahydroquinoline building block **21** in enantiopure form. Thus, the first key objective was to render the initial Michael addition step in the tandem Robinson/aza-Michael reaction enantioselective using organocatalysis based on the precedents set out by Jørgensen.[36]

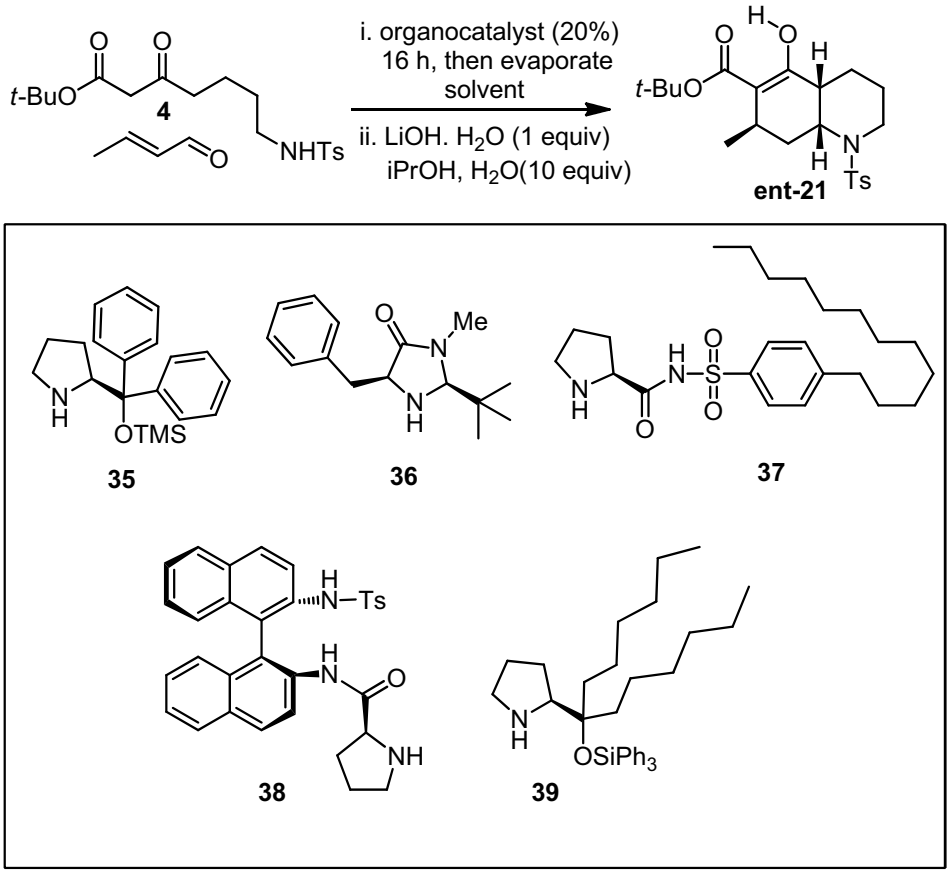
### 3.2.1. Catalyst screening for the organocatalytic step

After our initial attempts to couple β-keto ester **4** with crotonaldehyde were relatively disappointing leading to only a small amount of coupled product (see section 2.1.2) we began by examining a range of diverse catalysts[54] to promote the initial organocatalyzed Michael addition after which the tandem cyclization conditions (LiOH) were applied. These included the Hayashi catalyst **35**,[55] MacMillan catalyst **36**,[56] prolinamide **37**,[57] BINAM derivative **38**[58] and the bishexyl Hayashi type catalyst **39** introduced by Palomo. [59] It should be noted that whilst the natural product targets required the *R* enantiomer of the catalyst, all these initial studies were conducted with the more readily available *S* enantiomers.

It was found that coupled product was only obtained with the prolinol silyl ether type catalysts albeit again in poor conversion for the Michael step (≈25%). Regardless, the material was cyclized to obtain the decahydroquinoline product and the Hayashi catalyst **35** gave the best enantiomeric excess (70% ee, table 3.1 entry 1). This catalyst was therefore chosen for further studies.

[54] Catalysts **35** and **36** were commercially available, whilst **37**, **38** and **39** were prepared according to the published methods.
[55] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.
[56] Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79-87.
[57] Yang, H.; Carter, G. R. *Synlett* **2010**, *19*, 2827-2838.
[58] Bradshaw, B.; Etxebarría-Jardi, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C.; *Adv. Synth. Catal.* **2009**, *351*, 2482-2490.
[59] Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem. Int. Ed*. **2007**. *46*, 8431-8435.

**Table 3.1.** Catalyst screening for the organocatalytic Michael step.




| *Entry* | *Solvent* | *Catalyst* | *e.r.* | *ee* |
|---|---|---|---|---|
| 1 | Solvent free | **35** | 85 : 15 | 70% |
| 2 | Toluene | **36** | - | - |
| 3 | Solvent free | **37** | - | - |
| 4 | $CH_2Cl_2$ | **37** | - | - |
| 5 | Solvent free | **38** | - | - |
| 6 | $CH_2Cl_2$ | **38** | - | - |
| 7 | $H_2O$ | **39** | 80 : 20 | 60% |
| 8 | Toluene | **39** | 82 : 18 | 64% |

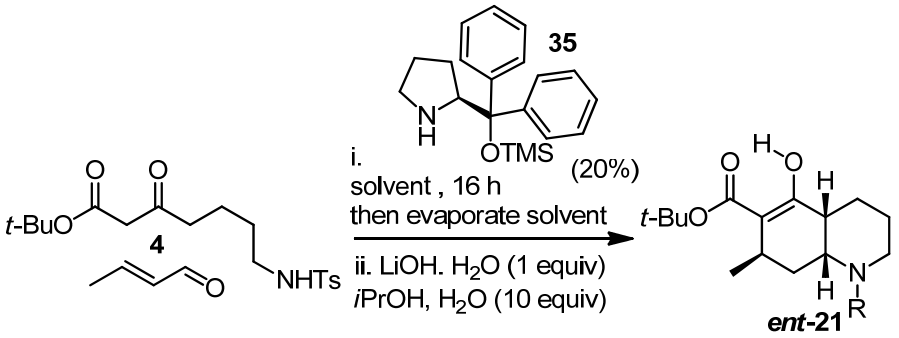
### 3.2.2. Solvent screening for the organocatalytic step

After the initial poor results using solvent free conditions or water as solvent we began studying the effect of various organic solvents to see whether the yield of coupled product could be improved.

Indeed, changing to organic solvent gave greatly improved coupling – quantitative in most cases – with the best result when the initial Michael reaction

was carried out in toluene (entry 4). In addition to the standard repertoire of solvents, a number of unusual solvent systems with potentially beneficial effects in organocatalytic reactions were investigated. These included pyridine[60] (entry 12) a pyridine/toluene mixture[60] (entry 13) and hexafluorobenzene[61] (entry 14) but were found to give no improvement over toluene.

**Table 3.2.** Solvent screening for the organocatalytic step.




| *Entry* | *Solvent* | *e.r.* | *ee* |
|---|---|---|---|
| 1 | Solvent free | 85 : 15 | 70% |
| 2 | $H_2O$ | 86.5 : 13.5 | 73% |
| 3 | $CH_2Cl_2$ | 86.5 : 13.5 | 73% |
| 4 | Toluene | 89.5 : 10.5 | 79% |
| 5 | MeOH | 84 : 16 | 68% |
| 6 | *i*-PrOH | 85.5 : 14.5 | 71% |
| 7 | MeCN | 79 : 21 | 58% |
| 8 | THF | 85.5 : 14.5 | 71% |
| 9 | Benzene | 87.5 : 12.5 | 75% |
| 10 | Hexane | 85.5 : 14.5 | 71% |
| 11 | 1,4 dioxan | - | - |
| 12 | Pyridine | - | - |
| 13 | Tol/pyridine | - | - |
| 14 | Hexafluorobenzene | 86 : 14 | 72% |

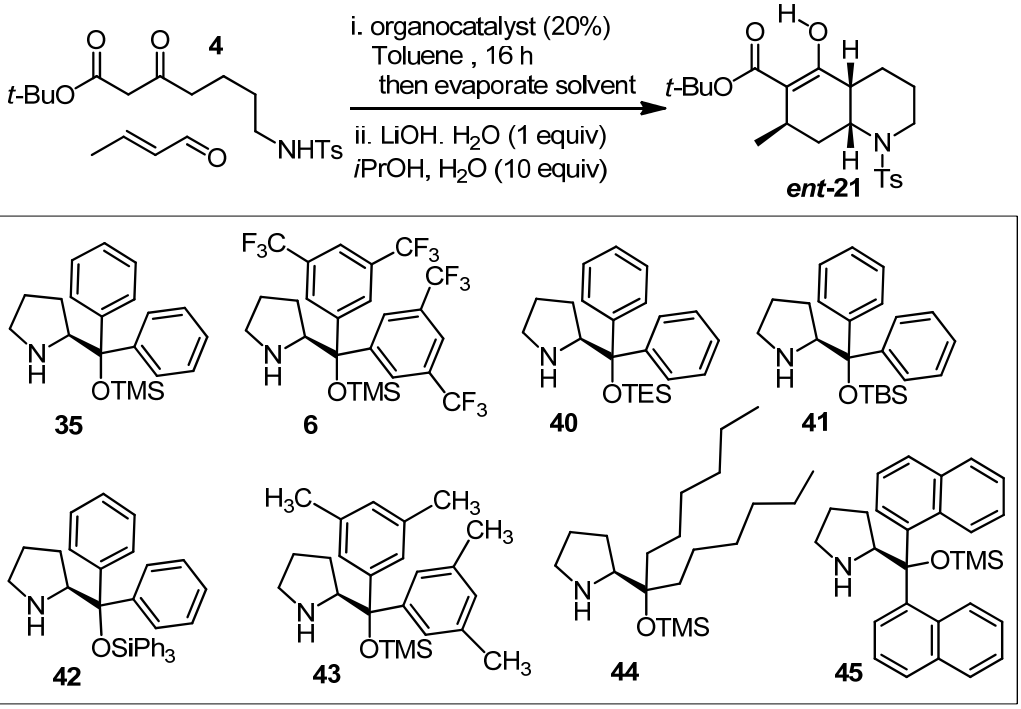
All yields were ≈50% except for entries 1 and 2, which were ≈20%.

[60] For the beneficial use of pyridine as cosolvent see: Li, L.; Seidel, D. *Org. Lett*. **2010**, *12*, 5064-5067.
[61] For the use of hexafluorobenzene as solvent see: Lattanzi, A.; De Fusco, C.; Russo, A.; Poater, A.; Cavallo, L. *Chem. Commun*. **2012**, *48*, 1650-1652.

### 3.2.3. Catalyst optimization for the organocatalytic step

Several other prolinol silyl ethers[62] were then screened (table 3.3) and the slight superiority of triphenylsilyl derivative **42**[63] led to its selection (entry 5).[64] Surprisingly, the bulky naphtyl catalyst **45** gave no coupling, and Jørgensen's catalyst **6** gave a more moderate ee despite the increased size of the substituents under the same conditions.

**Table 3.3.** Solvent screening and catalyst screening for the organocatalytic step.




| *Entry* | *Catalyst* | *e.r.* | *ee* |
|---|---|---|---|
| 1 | **35** | 89.5 : 10.5 | 79% |
| 2 | **6** | 88 : 12 | 76% |
| 3 | **40** | 85 : 15 | 70% |
| 4 | **41** | 86 : 14 | 72% |
| 5 | **42** | 90 : 10 | 80% |
| 6 | **43** | 88 : 12 | 76% |
| 7 | **44** | 85 : 15 | 70% |
| 8 | **45** | - | - |

[62] Catalysts **35**, **6**, **43** and **45** are commercially available and were obtained directly from Aldrich chemical company. **40**, **41** and **42** were prepared form commercially available (*S*)-α,α-Diphenyl-2-pyrrolidinemethanol, using the corresponding silyl ether for the alcohol protection. **44** was prepared according to the method described in reference 59.

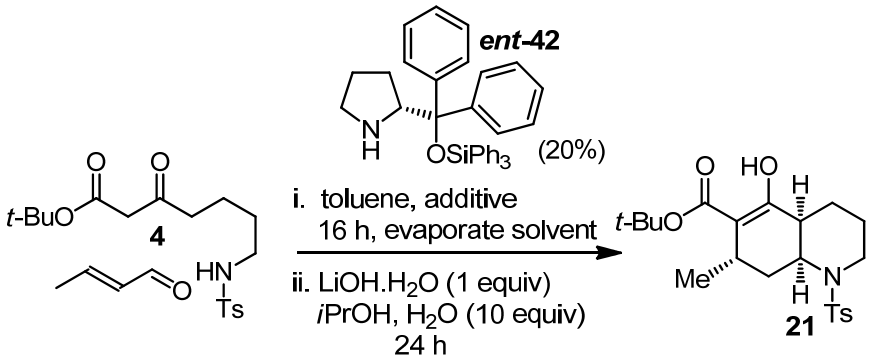
[63] For the first reported use of this catalyst, see: Wang, Y.; Li, P.; Liang, X.; Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383-1389. For its preparation and subsequent application, see: Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci.* **2011**, *2*, 353-357.

[64] While the ee was only slightly better than the Hayashi catalyst **35**, repeated runs with **42** gave more consistent and reliable results, whereas **35** sometimes gave lower than 79% ee.

### 3.2.4. Temperature and additives screening for the organocatalytic step

The reaction was further refined by lowering the temperature (table 3.4, entries 2 and 3) and the use of additives was investigated (entries 4-9). The addition of LiOAc (entry 5) was essential for obtaining a good conversion yield (72% for three bond-forming reactions) and enantiomeric ratio (>92:8). It is worth mentioning that the combination of LiOAc and another good additive, water (entry 4), were not synergistic, giving inferior results (entry 8) to their individual use.

**Table 3.4.** Temperature and additives screening for the organocatalytic step



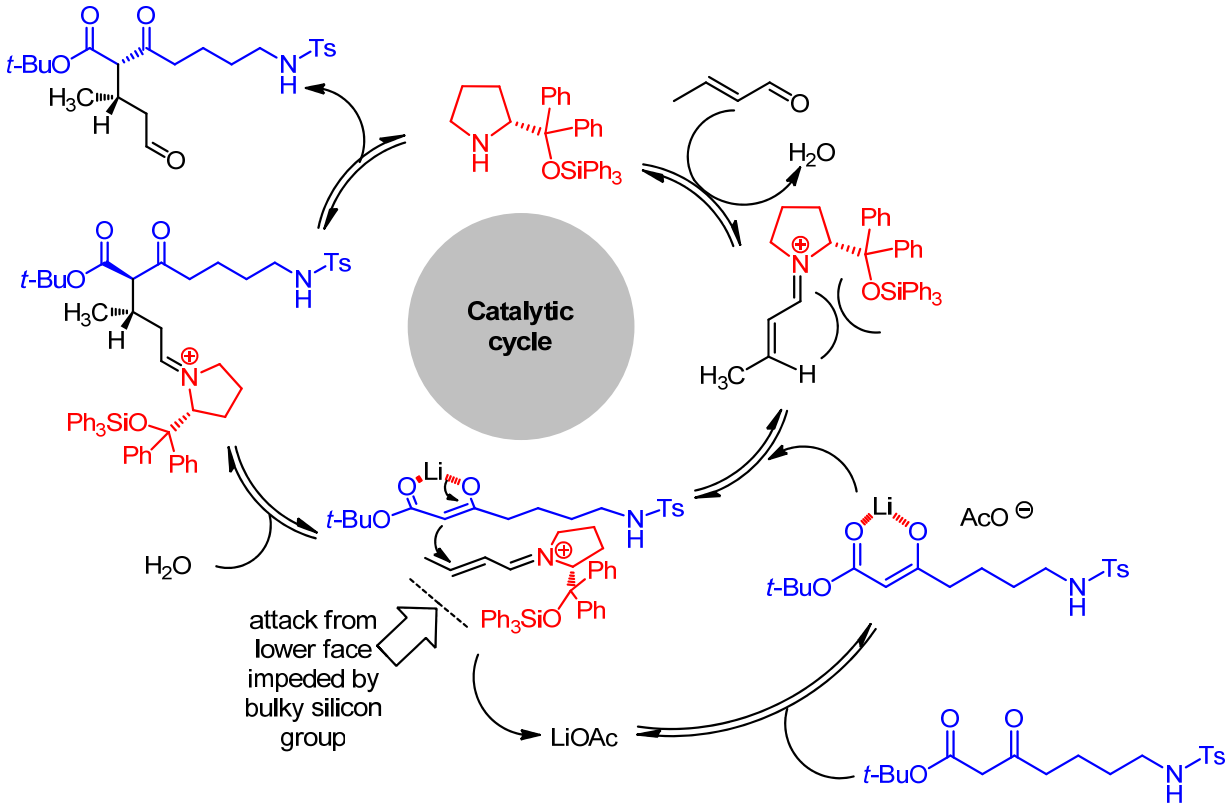

| *Entry* | *Additive (equiv)* | *Temp ( ºC )* | *yield* | *ee* |
|---|---|---|---|---|
| 1 | none | rt | 57% | 80% |
| 2 | none | 0 ºC | 57% | 82% |
| 3 | none | -20 ºC | 49% | 82% |
| 4 | $H_2O$ (10) | 0 ºC | 69% | 84% |
| 5 | LiOAc (0.5) | 0 ºC | 72% | 85% |
| 6 | KOAc (0.5) | 0 ºC | 58% | 83% |
| 7 | BzOH (0.5) | 0 ºC | 43% | 80% |
| 8 | $H_2O$ (10 ) / LiOAc (0.5) | 0 ºC | 63% | 80% |
| 9 | LiOAc (1) | 0 ºC | 66% | 82% |

### 3.2.5. Mechanism of the organocatalytic step

The mechanism for the organocatalytic part of the reaction is outlined below in scheme 3.1. The catalyst couples with crotonaldehyde to given an imine intermediate with the methyl orientated away from the bulky *O*-silyl substituent. Since this step sets the enantioselectivity of the reaction, the small size of the methyl group is responsible for the moderate enantioselectivity (in our case 84-85% ee) compared to using Michael acceptors with more bulky substituents such as phenyl.

The function of LiOAc presumably helps to activate the β-keto ester and make it more nucleophillic by helping to form the enolate.[65] This leads to increased coupling which is then reflected in the increased yield. Additionally, it may interact with the coupled product to form the tricoordinate species predicted in the previous chapter (see section 2.2.2). This would remove the free aldehyde from the equilibrium, freeing the organocatalyst to re-enter the catalytic cycle.

It is not clear what role the free NH-Ts side chain may play in the reaction e.g if it is folded back over the keto ester and interacts in the transition state via the formation of hydrogen bonds. It is clear that it must play more than just a passive role in the reaction mechanism due to the significant differences we have observed in the organocatalytic step compared to those observed by Jørgensen using simple β-keto esters.

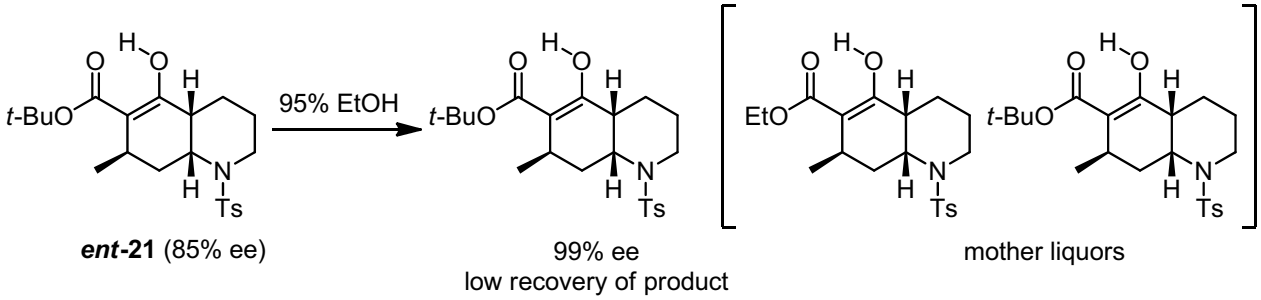



**Scheme 3.1.** Organocatalytic cycle for the formation of the Michael adduct.

[65] For an interesting study on the effect of LiOAc in organocatalyzed Michael reactions, see: Duce, S.; Mateo, A.; Alonso, I.; García Ruano, J. L.; Cid, M. B. *Chem. Commun.* **2012**, *48*, 5184-5186.

### 3.2.6. Enrichment of decahydroquinoline 21 and X-ray crystal structure

To arrive at completely enantiomerically pure decahydroquinoline **21** we screened a range common solvents to find a suitable candidiate for preparative scale recrystallization.[66] Of all the solvents tested only alcohol solvents had the right profile and 95% EtOH was chosen. However, whilst we were able to enrich the product to 99% ee, the recuperation of material was poor. We observed that the mother liquors contained an impurity we identified as the corresponding ethyl transesterification product (see Scheme 3.2).




***ent*-21** (85% ee) 99% ee low recovery of product mother liquors

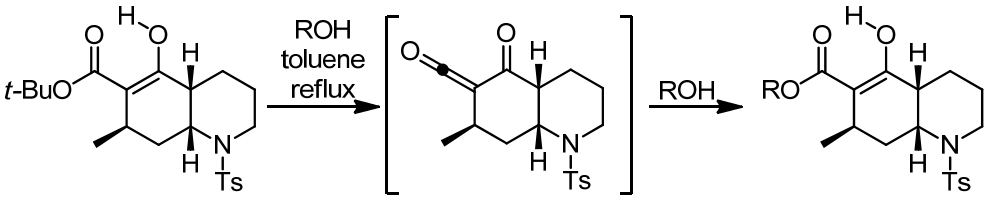
**Scheme 3.2.** Recrystallization of ***ent*-21** with EtOH. Formation of the ethyl transesterification product.

The formation of the transesterification product can be accounted by the formation of the loss of the *t*-butyl group under thermal conditions of heating the solution, leading to the ketene like intermediate which is then trapped by the alcohol solvent back to the ester.[67] (Scheme 3.3).

Whilst the use of *t*-BuOH should avoid this problem, it did not give satisfactory results. However, we were able to access ***ent*-21** in enantiopure form by recrystallization from MeOH, without the formation of any transesterification product. This provided the product in >99% ee (first crop, 65% recovery).

[66] These initial studies were carried out with the significant quantities of ***ent*-21** accumulated during the screening phase.
[67] For related phenomena see: Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713-1718.

Indeed, even if ***ent*-21** was refluxed in MeOH overnight no methyl transesterification product was observed, presumably as the temperature is not sufficiently high enough to enable the loss of the *t*-butyl group and allow formation of the ketene like intermediate.




*Note: when R = Me no transesterification product was observed even after 16 h at reflux.*

**Scheme 3.3**. Mechanism for transesterification reaction.

The crystals obtained were analyzed by X-ray diffraction and shown to have the structure shown in Figure 3.2. Surprisingly the tosyl group was located over the molecule rather orientated away to minimize steric repulsion as might be expected. We believe this phenomenon may play a key part for later observations regarding the hydrogenation of these molecules in determining facial selectivity of reduction (see section 3.3.5).

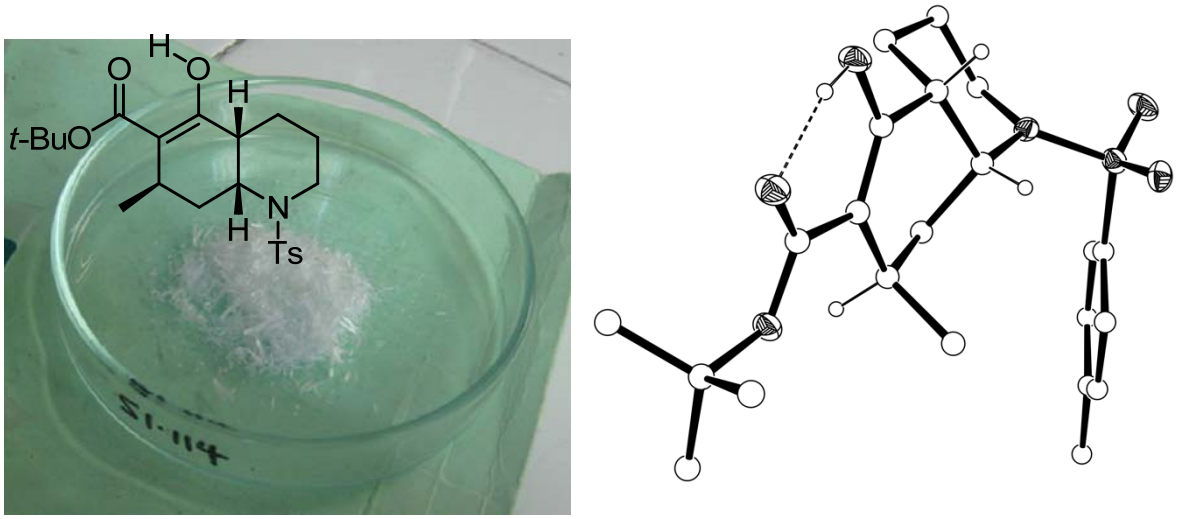



**Figure 3.2.** X-Ray analysis of the crystalline enantiopure decahydroquinoline.

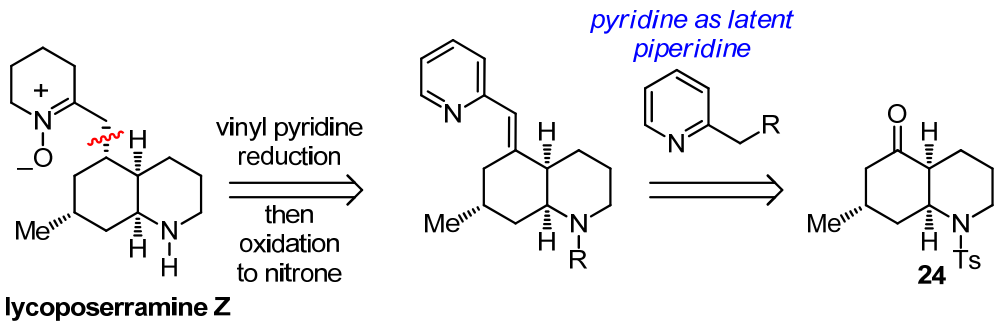
The recrystallization of the correct enantiomer proceeded in an analogous manner and good quantities of enantiopure **21** could be secured to continue the synthesis.

## 3.3. Application to the total synthesis of lycoposerramine Z

We began our synthetic studies focusing on the total synthesis of lycoposerramine Z, of which at the time there had only been one synthesis published to date (see section 1.2.6). The close similarity of the decahydroquinoline building block **21** to the final product made this an ideal choice to demonstrate the tandem cyclisation methodology to facilitate a quick and efficient synthesis of this product.

### 3.3.1 Retrosynthetic analysis

We envisaged the use of a methyl pyridine as a readily available convenient piperidine surrogate (Scheme 3.4). *A priori* we expected the hydrogenation to take place from the top face of the molecule with the axially positioned methyl blocking entry to bottom face of the molecule (see sections 3.3.4 and 3.3.5 for full discussion) to give the remaining stereocentre of the molecule. It should be noted that the alternative stereochemistry where hydrogenation takes place from the bottom face, would give access to the stereochemistry of serratezomine E. Thus, the key focus would be on obtaining clear facial selectivity and avoiding mixtures. The ideal scenario would be to access both faces in a stereoselectively controlled manner.



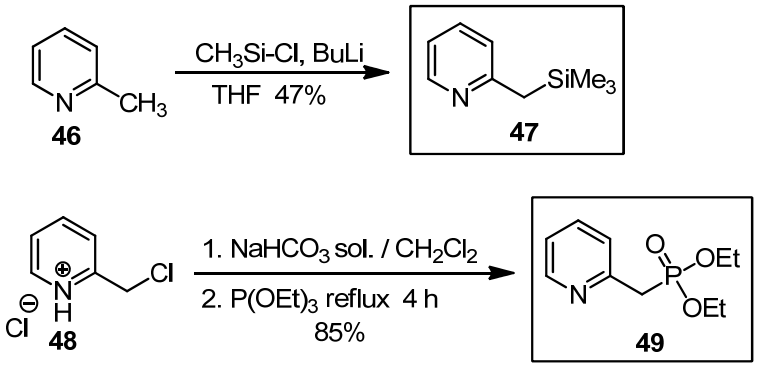

**Scheme 3.4.** Retrosynthesis of lycoposerramine Z.

### 3.3.2. Preparation of pyridine coupling partners

To couple the methyl pyridine, two methods were investigated, a Peterson reaction analogous to that used by McClean in his synthesis of phlegmarines (see sections 1.2.1 and 1.2.2) and a Horner-Wadsworth-Emmons type reaction with a methyl pyridine phosphonate.[68]

The preparation of the trimethylsilyl derivative **47** for the Peterson reaction was accomplished from commercially available 2-picoline **46**, employing *n*-BuLi and trimethylsilyl chloride.[69] However, in our hands the reaction led to the formation of subproducts, which could only be separated via careful distillation, with the overall yield of the process being quite low as a result. This problem was exacerbated on a large scale such that large amounts of the desired TMS pyridine could not be easily secured although enough material was obtained to evaluate the Peterson reaction.

On the other hand, the procedure to prepare the methyl pyridine phosphonate **49** for the Horner Wadsworth Emmons reaction was significantly more straightforward. Starting from the commercially available 2-(chloromethyl) pyridine hydrochloride **48**, conversion to the free base and subsequent Arbuzov reaction with triethylphosphite gave the phosphonate **49** in high yield.[70] (Scheme 3.5).

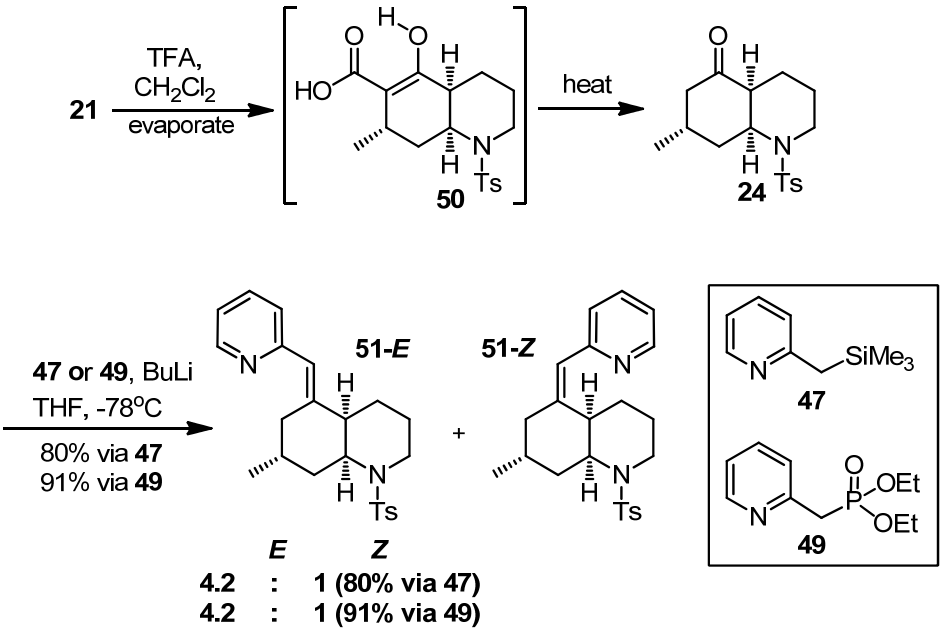



**Scheme 3.5.** Preparation of different activated methyl pyridine coupling reagents.

[68] This is the same strategy used by Sarpong in his previous work torwards the total synthesis of dihydrolycolucine (see section 1.2.8 and reference 29). However, we only became aware of this work during the writing of this thesis.
[69] Musker, W.-K.; Scholl, R.-L.; *J. Organomet. Chem*. **1971**, *27*, 37-43.
[70] Gan, X.; Binyamin, I.; Rapko, B. M.; Fox, J.; Duesler, E. N.; Paine, R. T. *Inorg. Chem.* **2004**, *43*, 2443-2448.

### 3.3.3. Formation of vinylpyridine fragment at C-5

Starting from enantiopure decahydroquinoline **21,** the *t*-butyl ester-locking group was removed with TFA to give ketoacid **50**, which, upon azeotropical removal of TFA with toluene and heating, underwent decarboxylation to ketone **24**. Addition of this material directly to a solution of the lithium anion of 2-(trimethylsilyl)methylpyridine **47** or of phosphonate **49** gave the vinylpyridine derivative **51** in excellent yield as a mixture of *Z*/*E* isomers (~1:4.2)[71] which could be separated by chromatography (Scheme 3.6). However, this turned out to be inconsequential since hydrogenation of the mixture or each isolated isomer gave the same product.




**Scheme 3.6.** Coupling of the methylpyridine fragment

[71] Interestingly, this diastereoselectivity is the reverse of that observed in the related 2,5-dioxodecahydroquinoline system: see reference 24 (sections 1.2.1 and 1.2.2).

The comparison of the $^{13}C$ NMR data of **51-*E*** and **51-*Z*** allowed the assignment of the alkene configuration.[72] Thus, in the *E* major isomer a crowding interaction is found between the pyridyl group and H-6eq, which results in an upfield shift (8.7 ppm) of C-6 with respect to the *Z* isomer. A similar interaction between the pyridyl group and H-4a appears in the *Z*-isomer of **51**, causing an upfield (9.3 ppm) of C-4a as compared with **51-*E***. Furthermore, both isomers could be differentiated by $^{1}H$ NMR by considering the deshielding effect exerted by the pyridyl group upon the H-4a in the Z isomer (δ 3.55; compare with δ 2.40 in **51-*E***) and upon the H-6eq methine proton in the *E* isomer (δ 3.14; compare with δ 2.57 in the *Z* isomer).

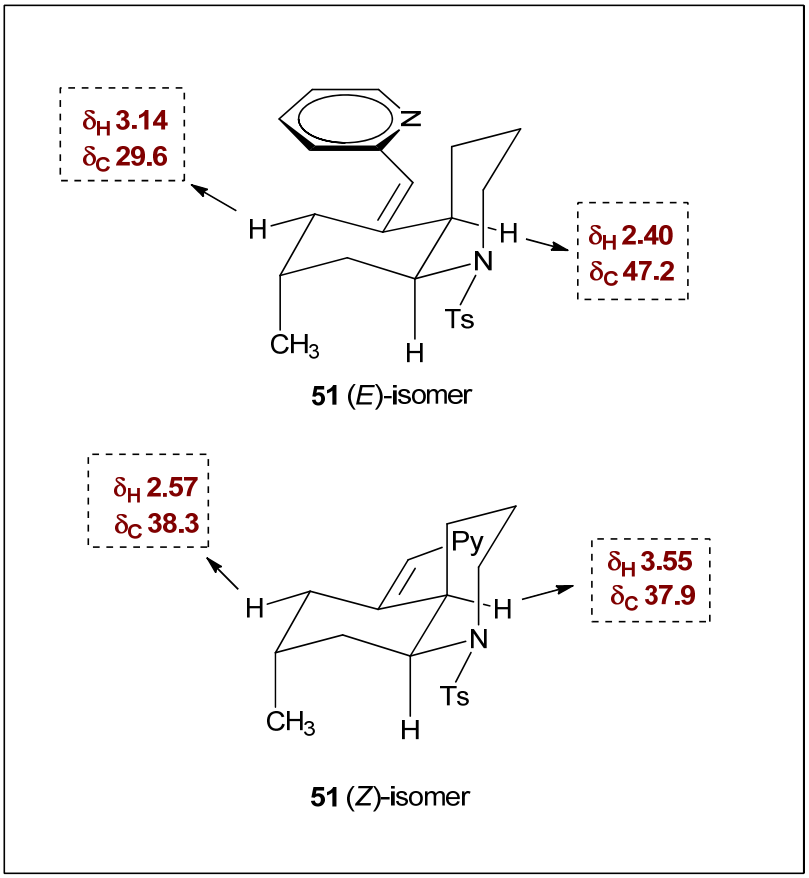
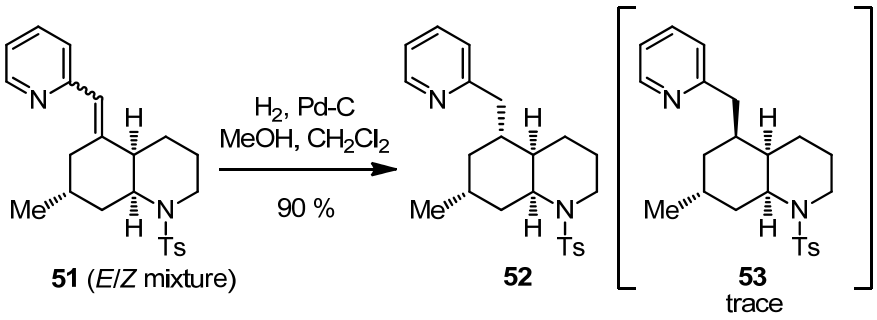



**Figure 3.3.** Assignment of the alkene **51** E/Z configurations by NMR.

[72] For a discussion about the assignment of the *Z*/*E* stereochemistry in hexocyclic double bonds using NMR data, see: a) Van Binst, G.; Tourwe, D. *Org. Magn. Reson.* **1972**, *4*, 625-631. b) Bennasar, M.-L-: Bosch, J. *Tetrahedron* **1986**, *42*, 637-647. c) Solé, D. García-Rubio, S.; Bosch, J.; Bonjoch, J. *Heterocycles* **1996**, *43*, 2415-2424.

### 3.3.4. Diastereoselective hydrogenation of alkene

Hydrogenation of the mixture or each isolated isomer gave the same *all-cis*-product **52** in which the hydrogen was delivered from the top face (see Scheme 3.7). The epimer **53** was observed but in very minor trace quantities (~9.5:1). Dichloromethane was used as a co-solvent for the hydrogenation when it was observed that **51** (*E*/*Z* mixture) was completely insoluble in MeOH.[73]




**Scheme 3.7.** Diastereoselective hydrogenation of the alkene **51 (***E*/*Z* mixture**)**.

### 3.3.5. Rationalization of Hydrogenation facial selectivity

Analysis of the $^{1}H$ and $^{13}C$ NMR spectra of both *E*/*Z* isomers of the starting material (**51*E*** and **51*Z***) allowed us to establish that the preferred conformation of these compounds accommodates axial positioning of the methyl group, which avoids the allylic 1,3-strain[74] both for the exocyclic double bond (with the C(4)-C(4a) bond) and the *N*-tosyl group (with the C(8)-C(8a) bond).[75] This preferred conformation impedes hydrogenation from the bottom face leading exclusively to decahydroquinoline **52**, in which the substituents at C(5) and C(7) are axially located according to NMR data. Thus, the crucial role of the axial methyl group in the process was clearly established, as it sterically impedes hydrogenation from the bottom face (see Figure 3.4).

[73] However, later studies regarding cermizine B (Chapter 4, see section 4.4 for full discussion) revealed that the addition of dichloromethane caused less selectivity. Indeed on evaluating the reaction in MeOH, the minor quantities of the epimer **53** were completely eliminated. Whilst the substrate wasn't initially soluble it did dissolve over the course of the reaction.
[74] Hoffmann, R. W. *Chem. Rev.* **1989**, *89,* 1841-1873.
[75] Booth, H.; Bostock, A. H. *J. Chem. Soc. Perkin Trans 2* **1972**, 615-621.

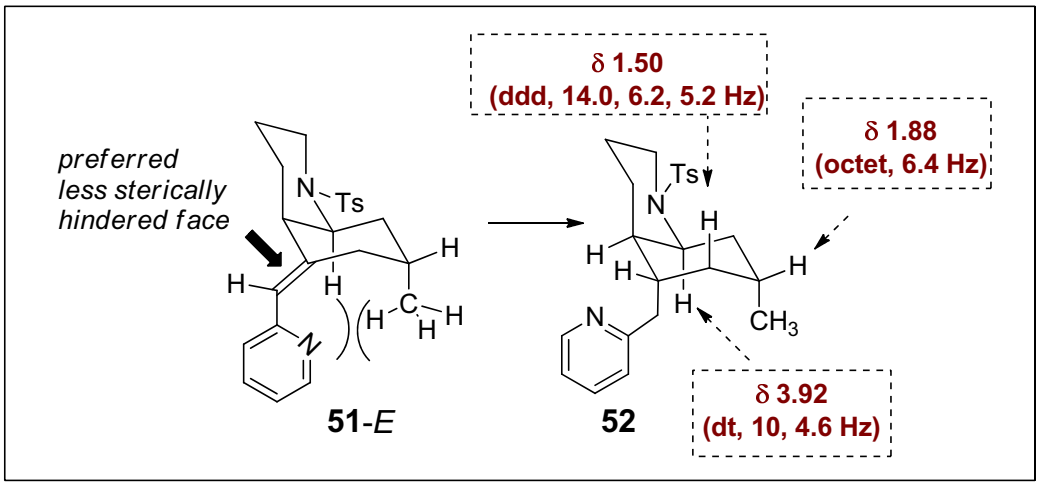



**Figure 3.4.** Rationalization for hydrogenation from the top face and assignment of resulting product.

Initially, whilst we believed that the methyl group played the defining role in the hydrogenation, later results (see section 4.4.3) revealed the important effect of the tosyl group on the diastereoselectivity of the reaction. Probably, the sulphonamide ring also covers the bottom face of the molecule in a similar manner to that seen in the X-ray structure of compound **21** (p.77).

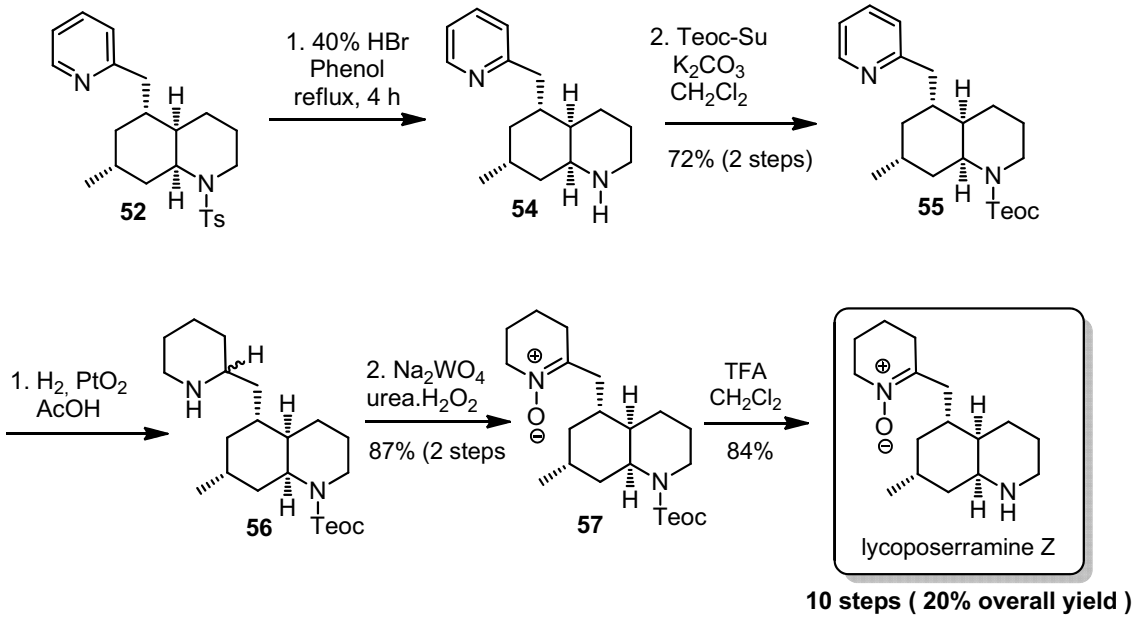
### 3.3.6. Completion of the synthesis of (+)-lycoposerramine Z

With **52** in hand bearing all the required stereocentres in place for lycoposseramine Z, the tosyl group was replaced by a Teoc group prior to the installation of the sensitive nitrone moiety, which had been shown to be readily removable in the presence of the nitrone functionality in the previous synthesis of lycoposerramine Z by Takayama (see section 1.2.6).

A number of conditions for the tosyl deprotection were studied including MeOH/Mg,[76] (no reaction) and Na/Naphtalene[77] in THF (decomposition) without success. Finally, treatment with HBr in the presence of phenol as additive,[78] despite being rather harsh conditions, resulted in clean formation of the corresponding amine product **54** in high yield (Scheme 3.8). Reprotection with the more readily labile Teoc group gave **55.** Then, with the Teoc-carbamate in

[76] Coeffard, V.; Thobie-Gautier, C.; Beaudet, I.; Le Grognec, E.; Quintard, J.-P. *Eur. J. Org. Chem*. **2008**, 398-391.
[77] Hong, S.; Yang, J.; Weinreb, S.-M. *J. Org. Chem*. **2006**, *71*, 2078-2089.
[78] Calvisi, G.; Dell'Uomo, N.; De Angelis, F.; Dejas, R.; Giannessi, F.; Tinti, M.-O. *Eur. J. Org. Chem*. **2003**, 4501-4505.

hand, we focused the next steps to synthesize the nitrone from the present pyridine functionality. Reduction of the pyridine ring with $PtO_2$/AcOH gave the piperidine **56** as an inconsequential mixture of epimers. For the subsequent oxidation to the nitrone were tested three different catalytic systems: $SeO_2$ with $H_2O_2$ as co-catalyst,[79] $Na_2WO_4 \cdot 2H_2O$[80] and $Na_2MoO_4$,[81] both with UHP (Urea-Hydrogen-Peroxide) as co-catalyst in MeOH media. All the three catalysts oxidized the piperidine to the nitrone with good yields, but $Na_2WO_4 \cdot 2H_2O$ was faster and cleaner than $Na_2MoO_4$ and its manipulation was easier than toxic $SeO_2$. Under these conditions the nitrone **57** was obtained in high yield and the spectroscopic data was identical with those reported by Takayama in his previous synthesis (see section 1.2.6).




**Scheme 3.8.** Completion of the total synthesis of lycoposerramine Z.

Whilst the synthesis of **57** constitutes a formal synthesis of lycoposerramine Z, for the sake of a complete enantioselective total synthesis of the natural product, the Teoc group removal was first attempted according to the reported conditions using TBAF. However, whilst the reaction was

[79] Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett*. **1987**, *28*, 2383-2386.
[80] Ohtake, H.; Imada, Y.; Murahashi, S. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 2737–2754.
[81] Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett*. **1995**, *36*, 3561–3562.

successful it was extremely difficult to remove the residues of the tetrabutylammonium salt, which contaminated the product. Finally we found that the Teoc group could be readily removed by stirring with TFA for 2 h[82] without effecting the sensitive nitrone group. Moreover, the reagent could readily be removed by evaporation to leave the corresponding salt, which was dissolved in $CH_2Cl_2$ and neutralized by the small amount of sat. aq. $NaHCO_3$ solution. Drying of the solution with sodium sulphate enabled isolation of the pure product.[83] The total synthesis of (+)-lycoposerramine Z was completed in 10 experimental steps with a 20% overall yield. The resulting (+)-lycoposerramine Z showed identical NMR spectroscopic data[84] and the same specific rotation value to those reported for the natural product.

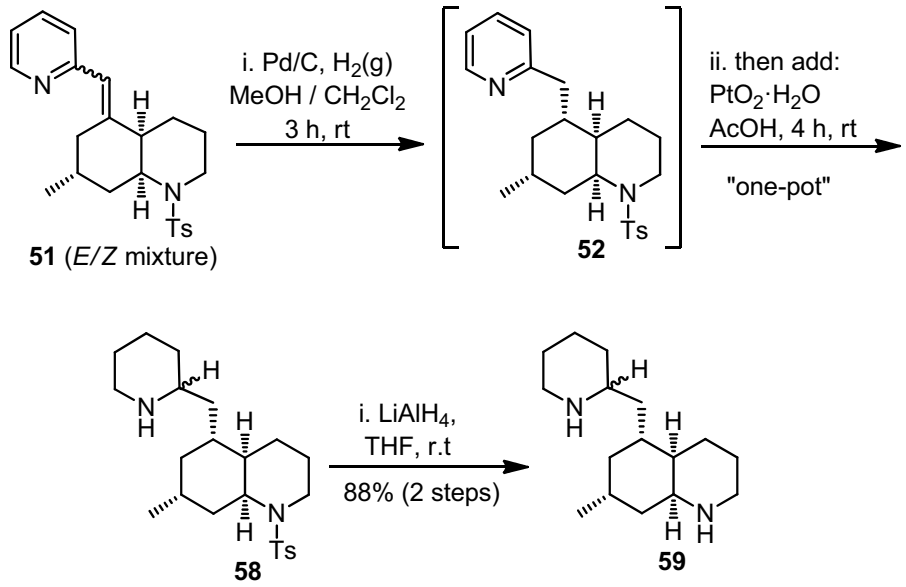
### 3.3.7. Attempted chemoselective oxidation approach to lycoposerramine Z

Whilst the above synthesis is significantly shorter than the previously reported route, eliminating the requirement for the interconversion of the protecting groups would make it even more efficient. To this end we believed that if a selective oxidation of the piperidine ring could be accomplished over oxidation of the slightly more hindered decahydroquinoline ring system, then the protecting group interchange could be eliminated. Additionally, the hydrogenation steps to reduce the vinyl pyridine moiety could be carried out in a single operation streamlining the synthesis even further. Whilst there is no literature precedent for this type of selective oxidation, a similar strategy is used by nature to arrive at these compounds.

[82] a) For deprotection of N-Teoc carbamates with TFA, see: Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc. Chem. Comm*. **1978**, 358–350. b) For the stability of a nitrone moiety to TFA, see: Medina, S. I.; Wu, J.; Bode, J. W. *Org. Biomol. Chem*. **2010**, *8*, 3405–3417.

[83] Given the advantages of using TFA in the last step it is clear that a Boc group would be a more convenient option for the protection of the nitrogen group.

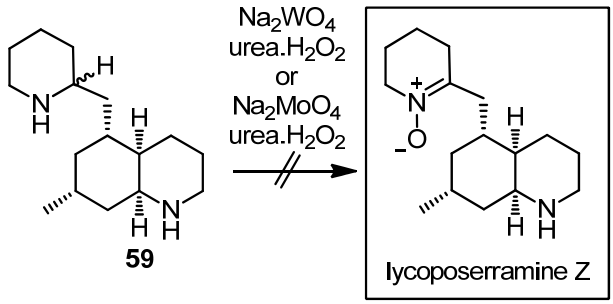
[84] The product readily protonated leading to broad signals. Addition of a small amount of ground solid NaOH to the NMR tube avoided this problem. See Overman's synthesis of Nankakurine A for similar example: Nilsson, B.-L.; Overman, L.-E.; Read de Alaniz, J.; Rohde, J.-M. *J. Am. Chem. Soc*. **2008**, *130*, 11297-11299.




**Scheme 3.9.** Synthesize of diamine starting material for selective oxidation test.

Thus, **51** was reduced with Pd/C to reduce the alkene[85] followed by addition of $PtO_2$ and AcOH to effect the reduction of the pyridine ring to give **58** (scheme 3.9). It should be noted that whilst the $PtO_2$ in AcOH could also be used to reduce the alkene at the same time, the facial selectivity was not as good as using Pd/C in MeOH.[86]

With the diamine **59** in hand, we examined the selective oxidation employing $Na_2WO_4 \cdot 2H_2O$ and $Na_2MoO_4$ (see scheme 3.10).




**Scheme 3.10.** Attempted selective oxidation of diamine **59**

[85] Note dichloromethane was used as a cosolvent since it was unknown at this time the slight counter-effect it had on the selectivity of the hydrogenation.
[86] This was confirmed by an experiment in which the vinylpyridine fragment was reduced using $PtO_2 \cdot H_2O$, and were obtained significant quantities of the C-7 epimer (detected by NMR), demonstrating less diastereoselectivity in the hydrogenation process.

However, the extreme polarity of all the products involved, combined with the small amounts of material we had at this stage, complicated significantly the purification of the reaction. Therefore this did not allow us to conclusively determine the outcome of the oxidation.

## 4. Gram-scale total synthesis of Cermizine B via an *uninterrupted sequence*

*Chem. Commun.* **2014***, 50,* 7099-7102.

## 4.1. Efficiency in the total synthesis of the natural products

The syntheses of numerous highly complex natural products, once viewed as impossible, have now been successfully achieved, as advances in the synthetic methodologies developed within the previous decades have come to maturity. However, as yet most of these syntheses are not efficient from a practical point of view. The "next" direction for this field is not the synthesis of complex natural products as an end unto itself, but rather the procurement of tangible and meaningful quantities of these structures.[87] The following quote from Paul Wender distinctly sums up the situation: "*The challenge now in synthesis is therefore increasingly, not whether a molecule can be made, but whether it can be made in practical fashion, in sufficient quantities for the needs of research and/or society, and in a way that is environmentally friendly if not ideal*." [88]

### 4.1.1. The phlegmarine alkaloids: benefits of rapid large scale access

Having access to highly efficient synthetic routes to the phlegmarine alkaloids that are modular, highly flexible and can produce them in quantity would enable a full study of the biosynthesis of all the lycopodium alkaloids. In turn this may allow for a unified synthesis of these compounds based on biomimetic principals. Such studies may be key to one day developing the lycopodium alkaloids into new medicines for the treatment of diseases for which as yet there are no effective cures such as cancer and Alzheimer's disease (see figure 4.1).

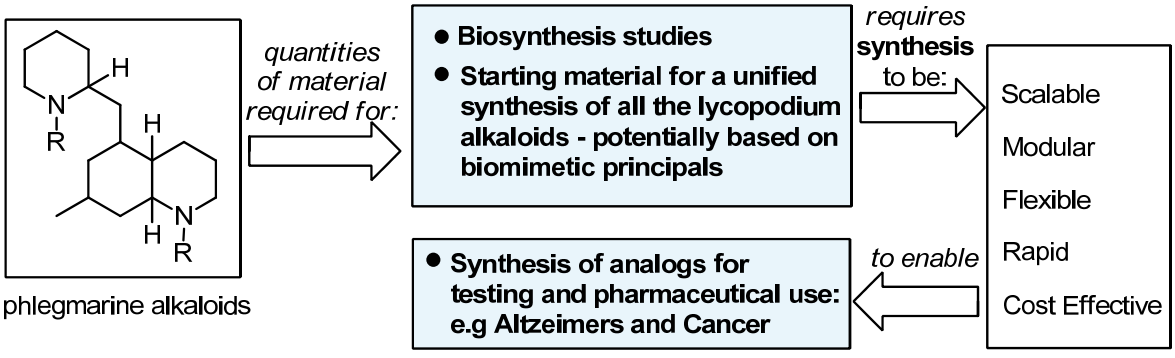



**Figure 4.1.** Potential benefits for rapid large scale access to the phlegmarine alkaloid template.

[87] Kuttruff, C. A.; Eastgate, M. D.; Baran, P. S. *Nat. Prod. Rep*. **2014**, *31*, 419-432.
[88] Quote from Paul Wender see: Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197-201.

### 4.1.2. Standard synthesis using the "*stop-and-go"* procedure

One of the main impediments to accessing viable quantities of complex natural products in a timely and cost-effective manner is the 'stop-and-go' approach,[89] in which syntheses are built on sequences of individual chemical transformations after each of which the sequence is stopped whilst a purification step is carried out prior to continuation. This "purification phase" undoubtedly involves the greatest investment of time and materials in any total synthesis endeavour and is a major source of waste generation (see figure 4.2). These manipulations also inevitably lead to losses of material at each phase of the process and ultimately a lowering of the overall yield.[90] The fact that undesired compounds can be separated at each phase means that inefficient and none selective reactions can be tolerated within the complete scheme.

Additionally, an analysis of a typical synthetic sequence will typically reveal that the majority of steps can be classed as "unproductive". These include functional group interconversions (FGIs) such as adjustments of the oxidation state of the molecule, protection-deprotection steps, functional group transpositions and the introduction and removal of chiral auxiliaries.

Thus much of the work carried out and waste produced is a direct result of transformations that effectively do not forward the construction of the target molecule. The costs incurred in the synthesis by these additional steps inevitably make it prohibitively expensive to produce anything more than only very small quantities of material with a typical laboratory synthesis finishing with less than 10 mg of the final product.

[89] Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477-1489.
[90] Even if each step of the process is 100% efficient, some quantities of material will be lost at each phase of the purification process see: Wernerova, M.; Hudlicky, T. *Synlett* **2010**, 2701–2707.

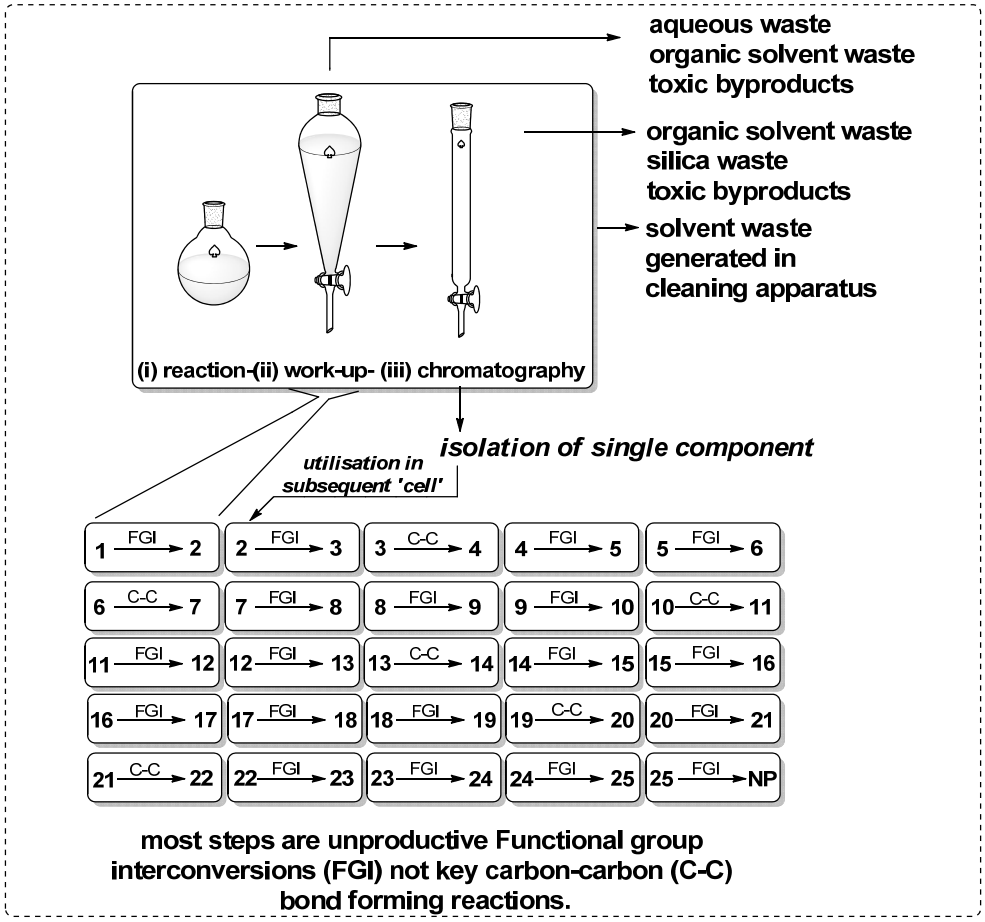



**Figure 4.2.** Typical synthesis of a moderately complex natural product **(**~25 steps) using the classical *stop-and-go* procedure.

As summarised in section 1.4 of the introduction, a number of syntheses of the phlegmarine alkaloids have been successfully realised, however they each on average require around 25 steps for their realization and have only been able to procure milligram quantities of material. It is of note that all of these products were synthesized by using the 'stop-and-go' procedure and generally feature a number of "unproductive" steps.

### 4.1.3. "Holistic based synthesis": an alternative to "*stop-and-go"*

Having established that one of the main impediments to synthetic efficiency is closely linked with the classical "*stop-and-go"* procedure used in conjunction with a large number of non-productive functional group transformations, an alternative strategy called "holistic synthesis" is proposed. Here a carefully planned series of series of tandem reactions[91] in combination with 'pot-economy'[92] would offer a potent solution to the problem of how to obtain more efficient synthetic sequences. By eliminating the need for work-up and product isolation between successive synthetic steps, it may become possible to complete an entire multi-step sequence in a single pot,[93] a process that approaches Wender's definition of an 'ideal synthesis,[88,94] (see Figure 4.3). Rather than seeing a synthesis as a series of discreet reactions, it is now viewed as a "single reaction process" with every reaction connected into one long synthetic step. Whilst essentially an "ideal", this alternative way at looking at a synthesis opens new perspectives for innovation. For example, the design for new efficient reaction processes which construct multiple C-C bonds under non demanding conditions. To implement such a strategy there are two complimentary factors to consider:

**(i) Synthetic Design element:** the design of the synthesis of the target molecule needs to be undertaken to arrive at a synthetic route with the minimal amount of steps possible. This is best achieved by dividing the route up into series of tandem reactions as well as employing as much as possible protecting group-free[95] and redox-free strategies[96] to avoid any unnecessary steps.

**(ii) Practical Design element:** Once a short highly efficient route is arrived at, the next step is to find strategies to link the tandem reactions together. In order to link together the above reactions without resorting to work-ups or chromatography, a number of solutions could be explored based on

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[91] a) Enders, D.; Grondal, C.; Hüttl, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 1570-1581. b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136. c) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chem*. **2010**, *2*, 167-178. d) Ambrosini, L. M.; Lambert, T. H. *ChemCatChem*. **2010**, *2*, 1373-1380. e) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev*. **2014**, *114*, 2390-2431.
[92] Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem*. **2007**, *9*, 438-440.
[93] Vaxelaire, C.; Winter, P.; Christmann, M. Angew. *Chem. Int. Ed*. **2011**, *50*, 3605-3607. (see also section **4.1.4**).
[94] a) Wender, P. A. *Tetrahedron* **2013**, *69*, 7529-7550. b) Wender, P. A. *Nat. Prod. Rep*. **2014**, *31*, 433-440.
[95] Young, I. S.; Baran, P. S. *Nature Chem.* **2009**, *1*, 193-205.
[96] Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657-4673.

uninterrupted synthesis,[93] principals where volatile reagents are used which can then be removed by evaporation. In the case where this is not possible the use of scavengers/solid-supported reagents[97] preferably employed in propylene "tea-bags" that can be introduced into the reaction and then easily removed. Alternatively, simple filtration could be employed. As much as possible these captured solvents[98] and reagents could be recycled. Ideally, if the route is sufficiently short it should be feasible to not have to remove any small quantities of secondary products that are formed from the main product at each step.

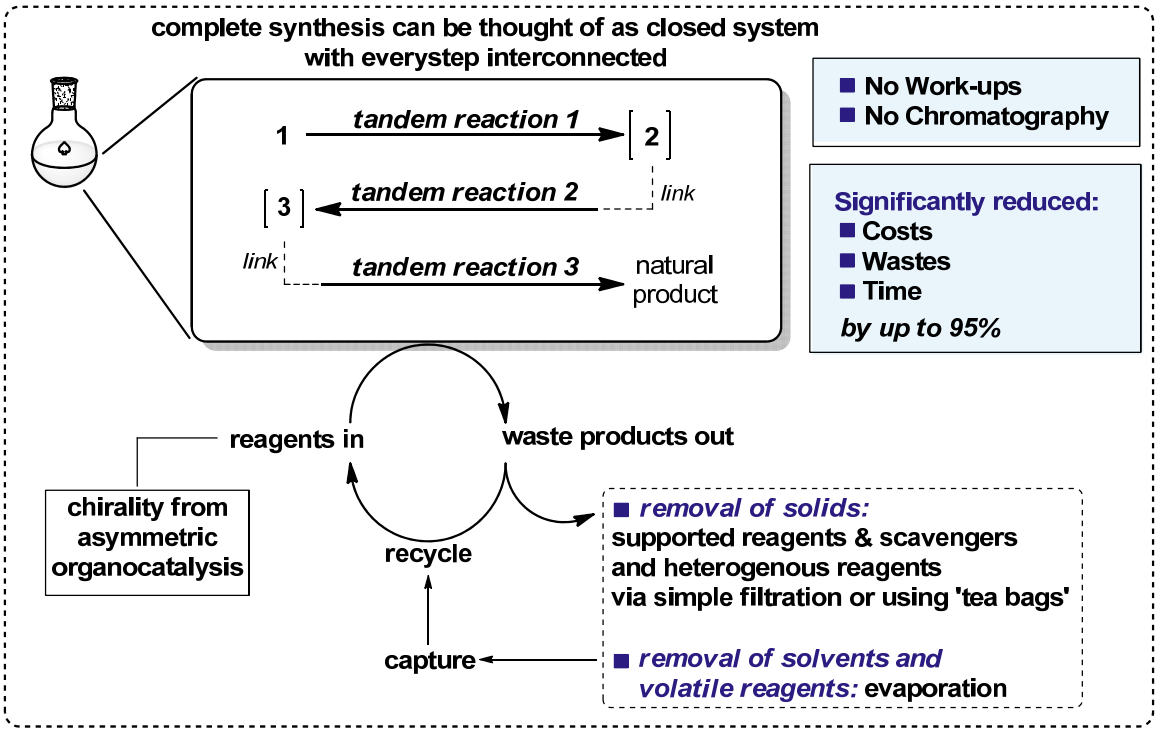



**Figure 4.3.** Proposed construction of a natural product in a single flask without resorting to work-ups and purifications using a self-contained series of carefully orchestrated of tandem reactions.

[97] Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem. Int. Ed*. **2002**, *41*, 2194-2197.
[98] a) Drueckhammer, D. G.; Gao, S. Q.; Liang, X.; Liao, J. *ACS Sustainable Chem. Eng*. **2013**, *1*, 87−90. b) Seyler, C.; Capello, C.; Hellweg, S.; Bruder, C.; Bayne, D.; Huwiler, A.; Hungerbühler, K. *Ind. Eng. Chem. Res*. **2006**, *45*, 7700-7709.

### 4.1.4. Efficiency in action: Hayashi's One-pot synthesis of (-)-Oseltamivir (tamiflu)

An illustrative example of the viability of many of these concepts is the one-pot gram-scale synthesis of the important antiviral agent (-)-Oseltamivir (tamiflu) by the Hayashi group (Figure 4.4).

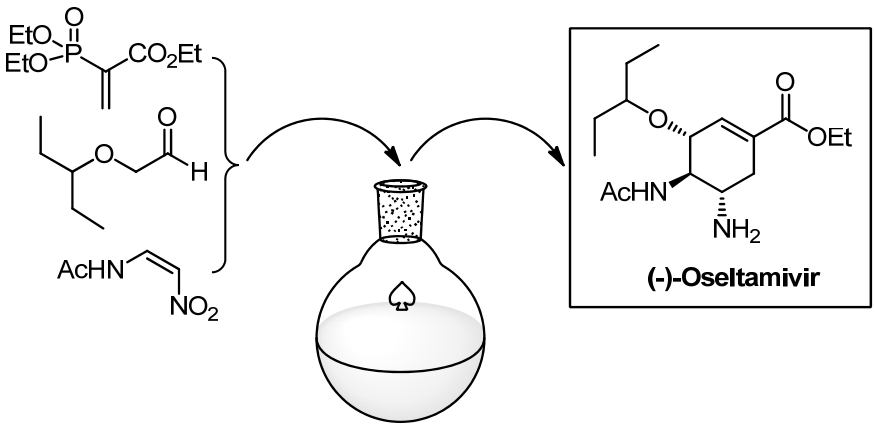


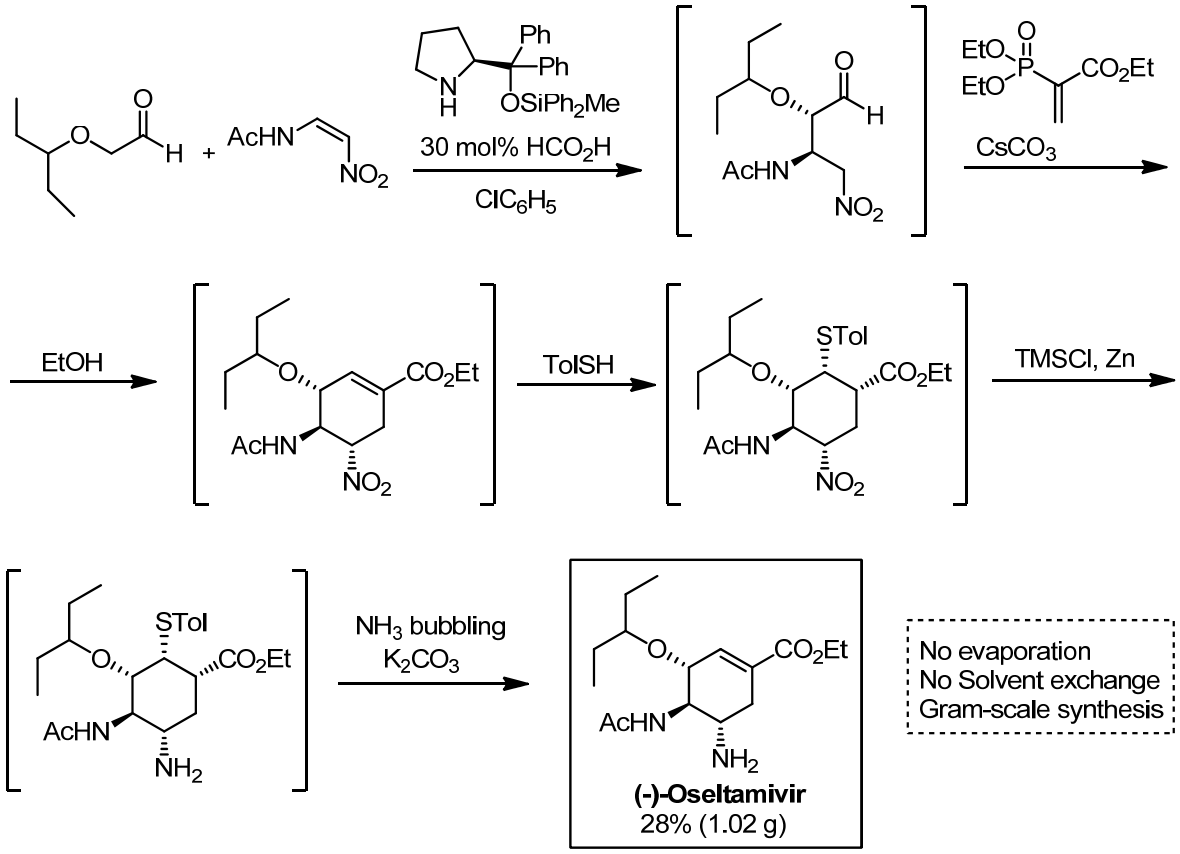

**Figure 4.4.** One-pot synthesis of (-)-Oseltamivir on a gram scale.

In 2009 Hayashi and co-workers were able to complete the total synthesis of (-)-Oseltamivir employing an easy, rapid and effective procedure based on only three one-pot operations.[99] The key to the synthesis was the deployment of a tandem organocatalytic reaction to rapidly construct the core structure in a single step. They subsequently proceeded to optimize the process to shorten the synthesis to only two one-pot reaction sequences[100] and then finally carrying out the complete sequence in a single flask without even the need for solvent exchange (Scheme 4.1).[101]

The optimized sequence synthesis began with an organocatalyzed Michael reaction of β-alkoxyaldehyde and *cis*-nitroalkene promoted by (*S*)-diphenylprolinol silyl ether, which proceeded with good yield and enantioselectivity in the presence of an acid additive. The resulting nitroalkane

[99] Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed*. **2009**, *48*, 1304-1307.
[100] Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem. Eur. J*., **2010**, *16*, 12616-12626.
[101] Mukaiyama, T.; Ishikawa, H.; Koshino, H.; Hayashi, Y. *Chem. Eur. J*. **2013**, *19*, 17789-17800.

reacted with the vinylphosphonate via an intramolecular Horner-Wadsworth-Emmons reaction to give the cyclohexenecarboxylate. Treatment with *p*-toluenethiol led to the Michael adduct, which effectively protected the double bond through the remaining steps. Reduction of the nitro group to an amine and final retro-Michael reaction of the thiol moiety gave the final product in good yield.




**Scheme 4.1.** One-pot total synthesis of (-)-Oseltamivir on a gram scale by Hayashi

The Hayashi group has used the same design principals in their synthesis of ABT-341[102] and the prostaglandins.[103] The above sequence is testament to the power of using tandem organocatalyzed reactions and pot economy in unison.

[102] Ishikawa, H.; Honma, M.; Hayashi, Y. *Angew. Chem. Int. Ed*. **2011**, *50*, 2824-2827.
[103] Hayashi, Y.; Umemiya, S. *Angew. Chem. Int. Ed*. **2013**, *52*, 3450-3452.

## 4.2. Gram-scale total synthesis of cermizine B via uninterrupted sequence

Having developed a strategy to Type A containing phlegmarine natural products we now turned our attention to products with a type B nucleus embedded in their structure – notably cermizine B.

### 4.2.1. Conceptual Design of the synthesis

Given the development of the tandem reaction to the core decahydroquinoline building block as well as the possibility to carry out a one-pot hydrogenation of the vinyl pyridine unit (sections 3.3.4 and 3.3.5) we believed it could be possible to construct cermizine B in a global one pot process (see figure 4.5) using the holistic strategy outlined in section 4.1.3.

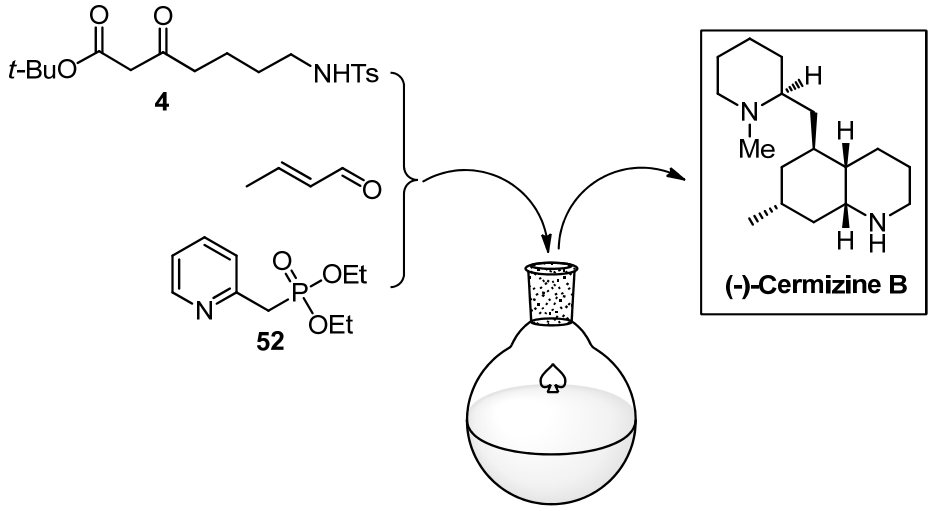
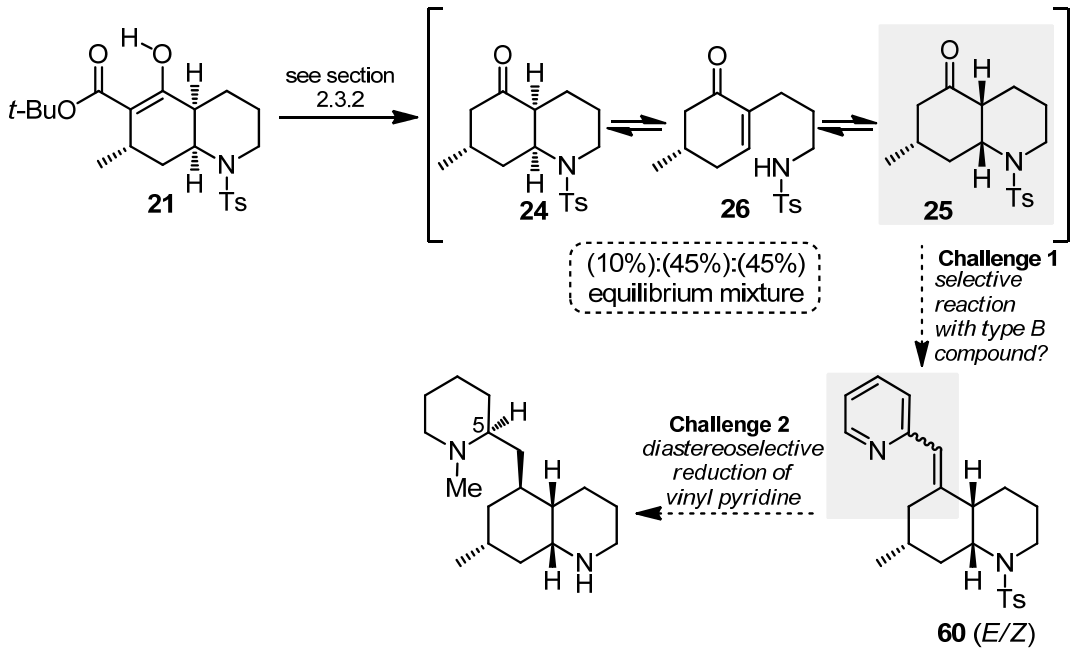



**Figure 4.5.** Conceptual strategy for the one-pot synthesis of (-)-cermizine B employing an uninterrupted sequence of reactions in a single flask.

We envisaged the synthesis composing of three tandem reactions (i) an organocatalyzed tandem Robinson Aza-Michael reaction developed in chapter 3 (ii) equilibration of the type A to type B stereochemistry (see chapter 2) and coupling of the vinyl pyridine unit and finally (iii) reduction of the vinyl pyridine unit. Once optimized as individual sequences the proposal was to “stitch” them together to enable one continuous process that could be carried out in one-pot.

In chapter 2 we described the formation of the type B stereochemistry of the decahydroquinoline ring system under both basic and acidic conditions. However, whilst studies showed this to be the dominant decahydroquinoline isomer, it was found it existed with an equal amount of the ring-opened product. Whilst this mixture could be separated by careful chromatography - **24** and **25** have almost identical $R_f$ values it could not be considered a viable method to this compound. A key challenge would be to find a way to obtain the type B core **25** in significant quanties and free from other compounds.

An additional challenge would be the selective reduction of the vinyl pyridine unit. Given the above results in our synthesis of lycoposseramine Z (chapter 3) the double bond could be reduced by substrate control. However given the results of previous synthetic attempts by other groups it would be expected that some kind of additional asymmetirc control would be required to control the C-5 stereocentre of the piperidine ring.




**Scheme 4.2.** Challenges for the synthesis of (-)-cermizine B using decahydroquinoline building block **21**.

### 4.2.2. Sequence 1: Optimization of decahydroquinoline formation

Whilst the first one-pot synthesis of the decahydroquinoline building block worked well and could be considered "ideal" from a design perspective, we were interested in improving the process from a practical point of view, notably reduction in the quantity of the organocatalyst (20% loading in the initial method). The cost of organocatalysts can be relatively expensive on scale up so it is important not only to reduce the catalytic loadings as much as possible without detriment to the reaction time and enantioselectivity, but also to try to recycle the catalyst used. Furthermore, we hoped that some minor adjustments could improve the enantioselectivity of the reaction since we wanted to carry the material forward without purifications, which would also include eliminating the recrystallization step to enrich the material purity.

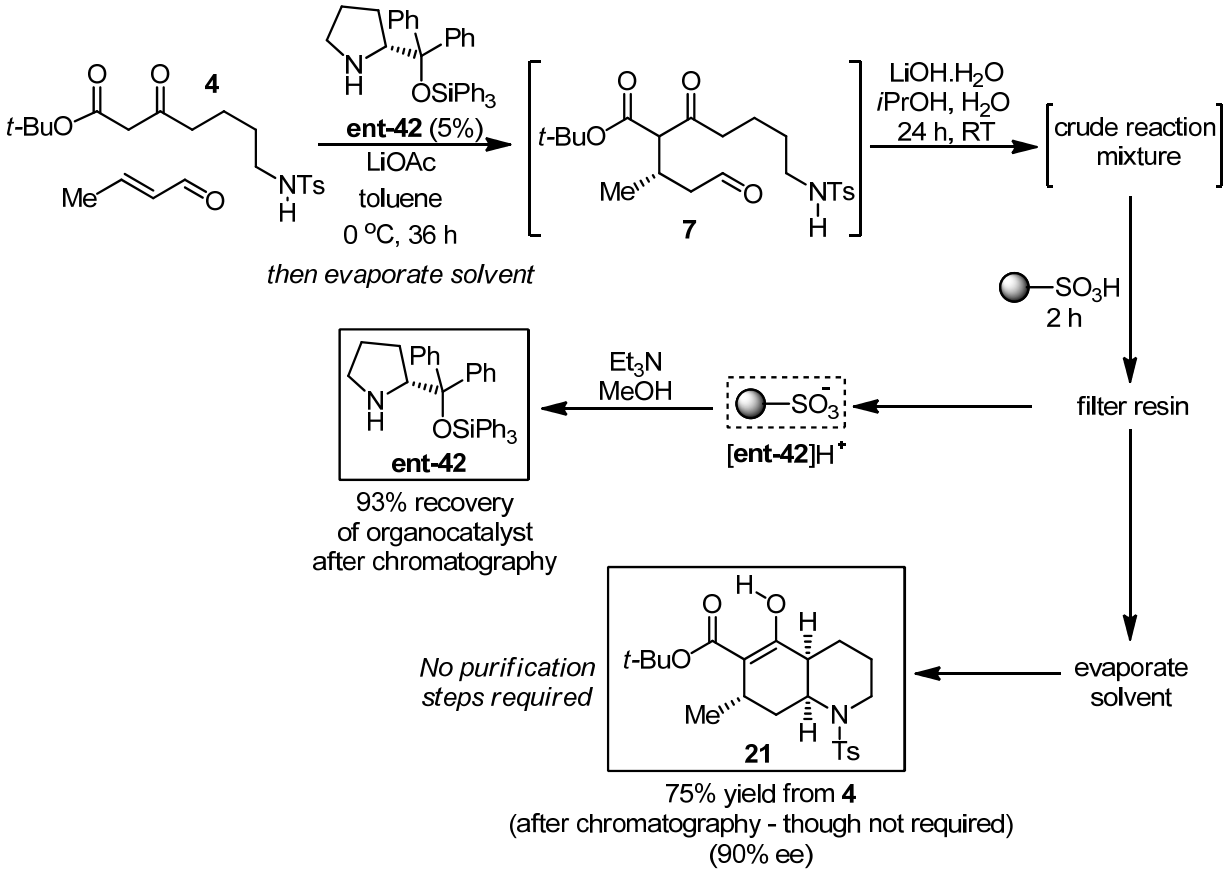
The first one-pot operation was carried out with reduced loadings (5 and 10%) of the modified Hayashi catalyst ***ent*-42** and found to increase the ee of the reaction to 86% ee albeit with an extension of the reaction time from 24 to 36 h. Finally, we were pleased to observe the ee of the reaction could be further increased to 90% by using recrystallized catalyst ***ent*-42**[104] under the same conditions. Removal of the solvent and treatment of **7** with LiOH in the presence of *i*PrOH and water, led to the tandem aldol condensation/intramolecular aza-Michael reaction, which delivered *cis*-decahydroquinoline **21**. With the aim of minimizing waste and preventing downstream accumulation in the eventual uninterrupted sequence, the reaction mixture was treated with a sulfonic acid resin which after stirring in the reaction mixture for 2 h was filtered.[105] This process eliminated the need for any work-up procedure to remove the basic residues and also allowed the capture and recuperation of the organocatalyst in excellent yield. This solution is a simple alternative to recycling the catalyst via immobilization on solid support.[106] It

[104] Our initial studies had employed commercially available (R)-(+)-$\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol. Initially we did not prepare significant quantities of the catalyst to enable its purification via recrystallization.

[105] Alternatively, instead of filtering the resin it could also be encapsulated in a tea-bag, allowed to infuse in the reaction mixture and then removed without the need for the filtration step to adhere to a stricter "one-pot" reaction definition.

[106] Of course this method does not allow the catalyst to be used in flow chemistry processes but has the advantage that standard "of the shelf" catalysts can be used and their activities are not modified by the presence of being attached to the resin.

should be noted that not only did the modified catalyst (triphenylsilyl instead of trimethylsilyl diphenylprolinol ether) improve the enantiomeric excess but it's significantly more robust nature also proved essential for its recovery with the acidic resin at the end of the reaction. Using this one-pot procedure decahydroquinoline **21** was isolated in 75% overall yield from keto ester **4**. Notably, along with decahydroquinoline **21**, small amounts of non-cyclized product (i. e. **17**) and material with the β-keto ester in the keto rather than enol form were also isolated. While the presence of these products reduced the yield of **21**, they pose no problem in the complete uninterrupted sequence since they would too be converted to the final product if chromatography was avoided, thereby effectively increasing the yield of the first sequence and highlighting one of the ancillary benefits of avoiding the "stop and go" strategy.



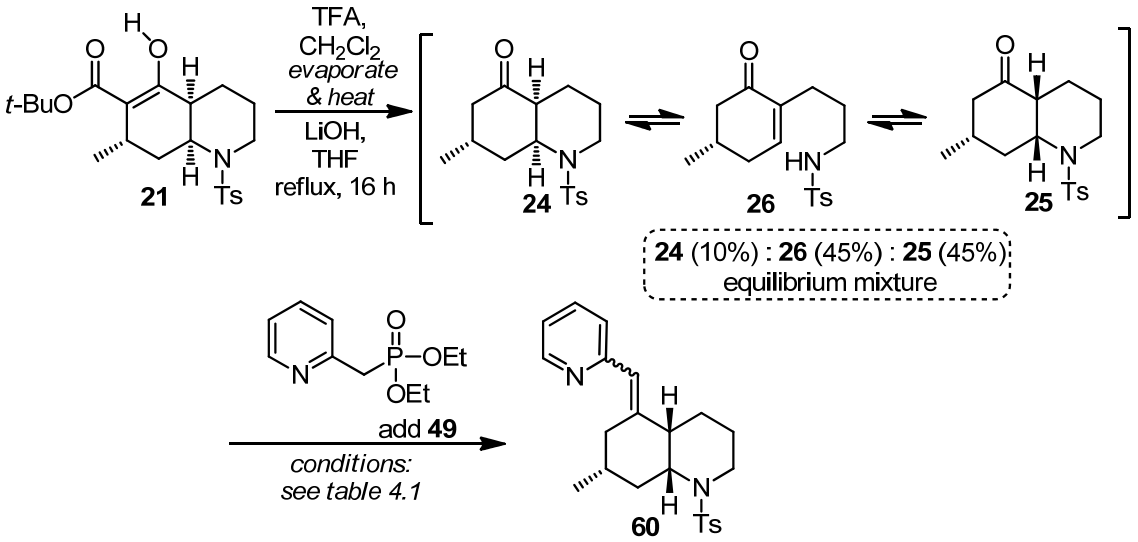

**Scheme 4.3.** Optimization of first one-pot sequence – removal of the basic residues and capture of the organocatalyst by using an acidic resin.

### 4.2.3. Sequence 2: Studies on the HWE reaction to couple the methylpyridine unit

Calculations as well as experimental data indicated that the equilibrium 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 in our favour. We postulated that if the reaction was carried out under basic conditions (giving the same ratio of products) but then the phosphonate **49** was added to the equilibrium mixture, it could undergo a Horner-Wadsworth-Emmons type coupling with **25** - the ring-opened product **26** should be not reactive under these conditions - and shift the equilibrium in favour of the formation of the coupled product.

To try out this theory, the ester **21** was treated with TFA and equilibrated with LiOH according to the standard conditions to give a mixture of **24**, **26** and **25** (see scheme 4.4).

Indeed, it was found that direct addition of phosphonate **49** to the refluxing equilibration mixture led to a chemoselective reaction with **25**, and by means of a shift in the equilibrium, vinylpyridine **60** was formed as an inconsequential mixture of *Z*/*E* isomers (1:5 ratio)[107] albeit in moderate yield (table 4.1, entry 1).[108]




**Scheme 4.4** Horner-Wadsworth-Emmons reaction applied to introduce the methylpyridine fragment in the 5-oxodecahydroquinoline of type B stereochemistry.

[107] As before in the synthesis of lycoposerramine Z the hydrogenation of each isomer gave the same result, obviating the need to separate them.
[108] The remaining mass balance was unreacted starting material.

Surprisingly, while we expected that the phosphonate **49** should react preferentially with the type B decahydroquinoline **25** (as it was the most abundant reactive species in the mixture) it would still be expected that some quantity of the corresponding type A compound **51** should be formed via **24**. However, none was observed we therefore speculate that the ketone in **25** is significantly more accessible than in **24**.

Attempts to increase the yield included the addition of water (entry 2),[109] and the use of microwave heating (entry 3), but both were unsuccessful. A breakthrough happened when we noted the coupling reaction proceeded to completion with excellent yield if carried out under solvent-free conditions using an excess of the phosphonate (entry 4) and 48 h to give the coupled product **60** in an excellent yield (89%) over the entire sequence from **21**. Subsequent modifications included attempting to reduce the quantity of phosphonate **49** employed, but this led to incomplete reaction (entry 5). We believed that one of the requirements for the large excess of **49** was that it also acted as the reaction "solvent", thus if the equivalents were reduced it led to inferior mixing. Attempt to account for this by adding a small amount of pyridine as a readily available and removable methylpyridine surrogate (entry 6) was unsuccessful. We therefore decided to apply the conditions described in the entry 4 to progress with the synthesis.

**Table 4.1** Screening of conditions for the Horner-Wadsworth-Emmons reaction.

| ***Entry*** | **49** | ***LiOH*** | ***Solvent*** | ***Temp*** | ***Time*** | ***Yield*** |
|---|---|---|---|---|---|---|
| 1 | 1.5 | 5 eq | THF | reflux | 24 h | 53% |
| 2 | 1.5 | 5 eq | THF/$H_2O$ | reflux | 24 h | SM |
| 3 | 1.5 | 5 eq | $H_2O$ | MW (75 ºC) | 30 min | SM |
| 4 | 3 | 5 eq | - | rt | 24 h | 89% |
| 5 | 1.1 | 5 eq | - | rt | 48 h | 72% |
| 6 | 1.5 | 3 eq | pyridine (1.5eq) | rt | 72 h | 70% |

[109] The use of water in these couplings is well documented and was employed to dissolve the base which was not readily soluble in THF.

### 4.2.4. Stereochemical assignment of the coupled products 60 *E*/*Z* by NMR

The comparison of the $^{13}C$ NMR data of **60*E*** and **60*Z*** allowed the assignment of the alkene configuration (Figure 4.6). In the minor isomer **60*Z*** a crowding interaction is found between the pyridyl group and H-4a, which results in an upfield shift (9.3 ppm) of C-4a with respect to the isomer **60*E***. A similar interaction between the pyridyl group and H-6eq appears in the *E*-isomer **60*E***, causing an upfield (8.5 ppm) of C-6 as compared with **60*Z***.

Furthermore, both isomers could be differentiated by $^{1}H$ NMR by considering the deshielding effect exerted by the pyridyl group upon the H-4a in the *Z* isomer ($\delta$ 3.44); compare with $\delta$ 2.35 in **60*E*** and upon the H-6eq methine proton in the *E*-isomer ($\delta$ 3.22); compare with $\delta$ 2.09 in **60*Z***.

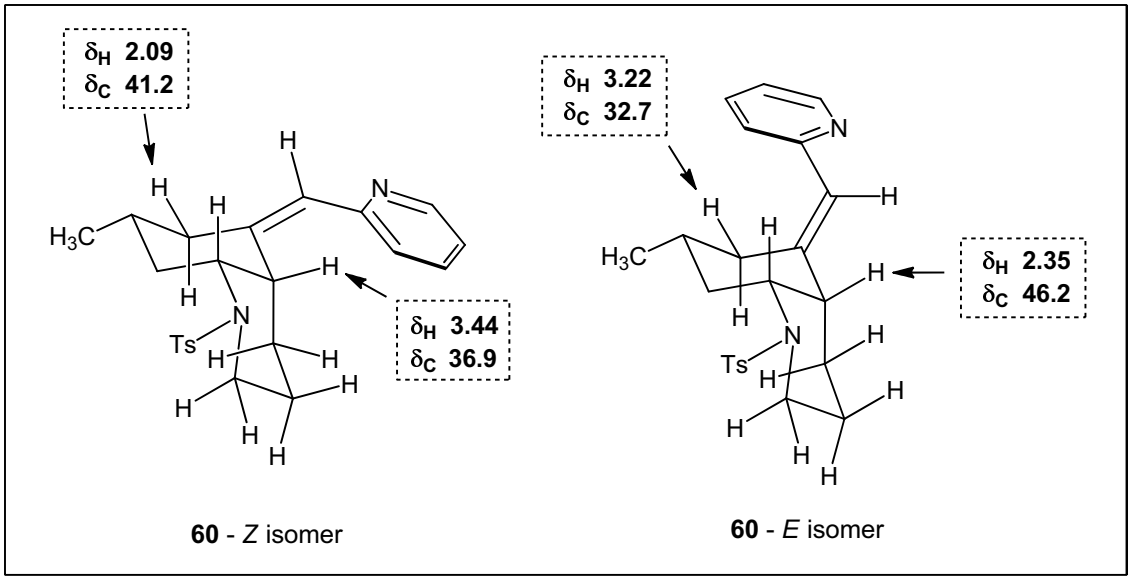


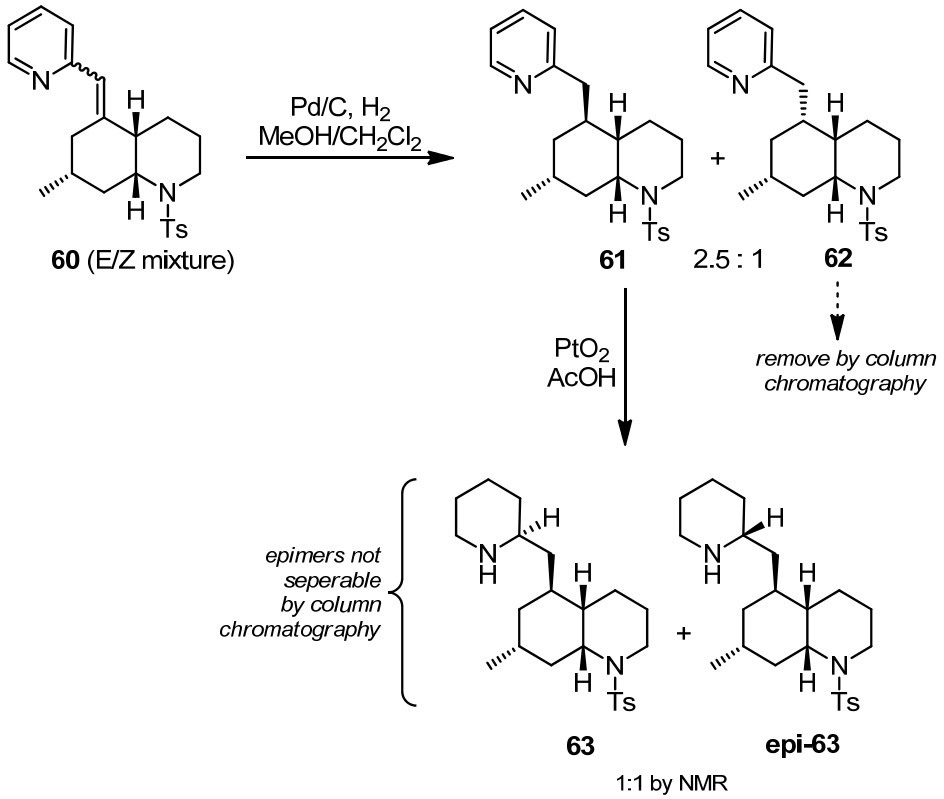

**Figure 4.6.** Assignment of the alkene **60** configuration by comparison of the $^{1}H$ and $^{13}C$ NMR's.

### 4.2.5. Initial evaluation of the reduction of the vinyl pyridine unit of 60

With **60** now in hand we found that hydrogenation in $MeOH/CH_2Cl_2$[110] took place preferentially from the bottom face of the molecule albeit with moderate selectivity. Whilst the products **61** and **62** were close running by TLC they could be separated by careful column chromatography. With **61** available

[110] Once again the addition of $CH_2Cl_2$ was necessary since **60** was completely insoluble in MeOH alone.

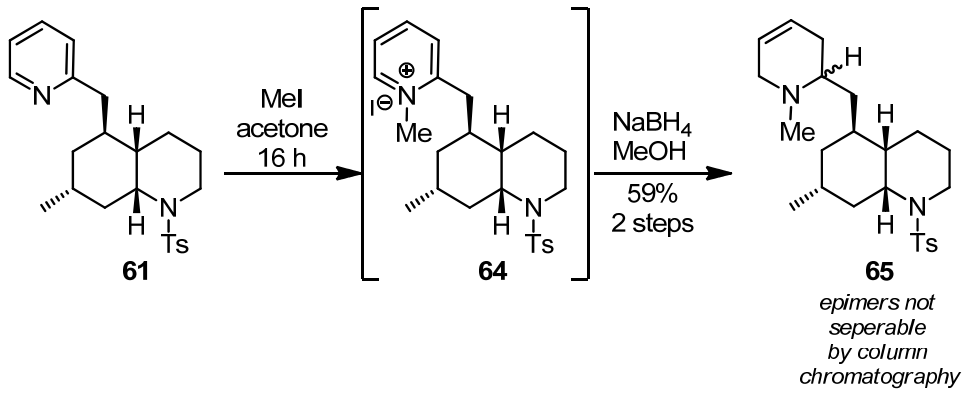
in pure form, we found that subsequent pyridine reduction in the presence of $PtO_2 \cdot H_2O$ in AcOH resulted in an epimeric mixture (**63** and ***epi*-63**) at the piperidinic C-5 (see Scheme 4.5). Whilst this was not altogether unexpected we found that we could not separate them by chromatography to characterize each compound and to continue to complete the synthesis of cermizine B.




**Scheme 4.5** Initial studies to reduce vinyl pyridine moiety and determine the diastereoselectivity.

After the unsuccessful attempts to separate the epimers of **63**, we sought an alternative route for the reduction of the pyridine moiety via the formation of the pyridinium salt (Scheme 4.6). Treatment of pyridine **61** with MeI in acetone led to the precipitation of the quaternary amine salt **64**, albeit along with a small amount of another product which could not be identified. Regardless, this crude product was then reduced with $NaBH_4$ giving the alkene **65**. The resulting

product, as in the hydrogenation, gave a mixture of epimers which could not be separated.[111]




**Scheme 4.6.** Reduction of the pyridine ring via formation of a quaternary pyridinium salt.

Given these problems, we evaluated the possibility of introducing an asymmetric reaction into the sequence to define the stereochemistry of the vinyl pyridine unit rather than relying on substrate control. We revised the literature to find a possible solution.

[111] Because of additional impurities, the non seperable nature of the epimers and the small ammount of material produced, compound **65** could not be fully characterized.

## 4.3. Diastereoselective hydrogenation of alkylpyridines

### 4.3.1. Literature precedents.

The formation of alkyl pyridines via reduction of pyridines is still an area without a straightforward solution.[112] One of the main problems is the stability of the aromatic system of the pyridine ring compared to other ring systems (such as quinolines for example), which necessitates the use of powerful reducing conditions or the placement of activating groups on the pyridine ring.

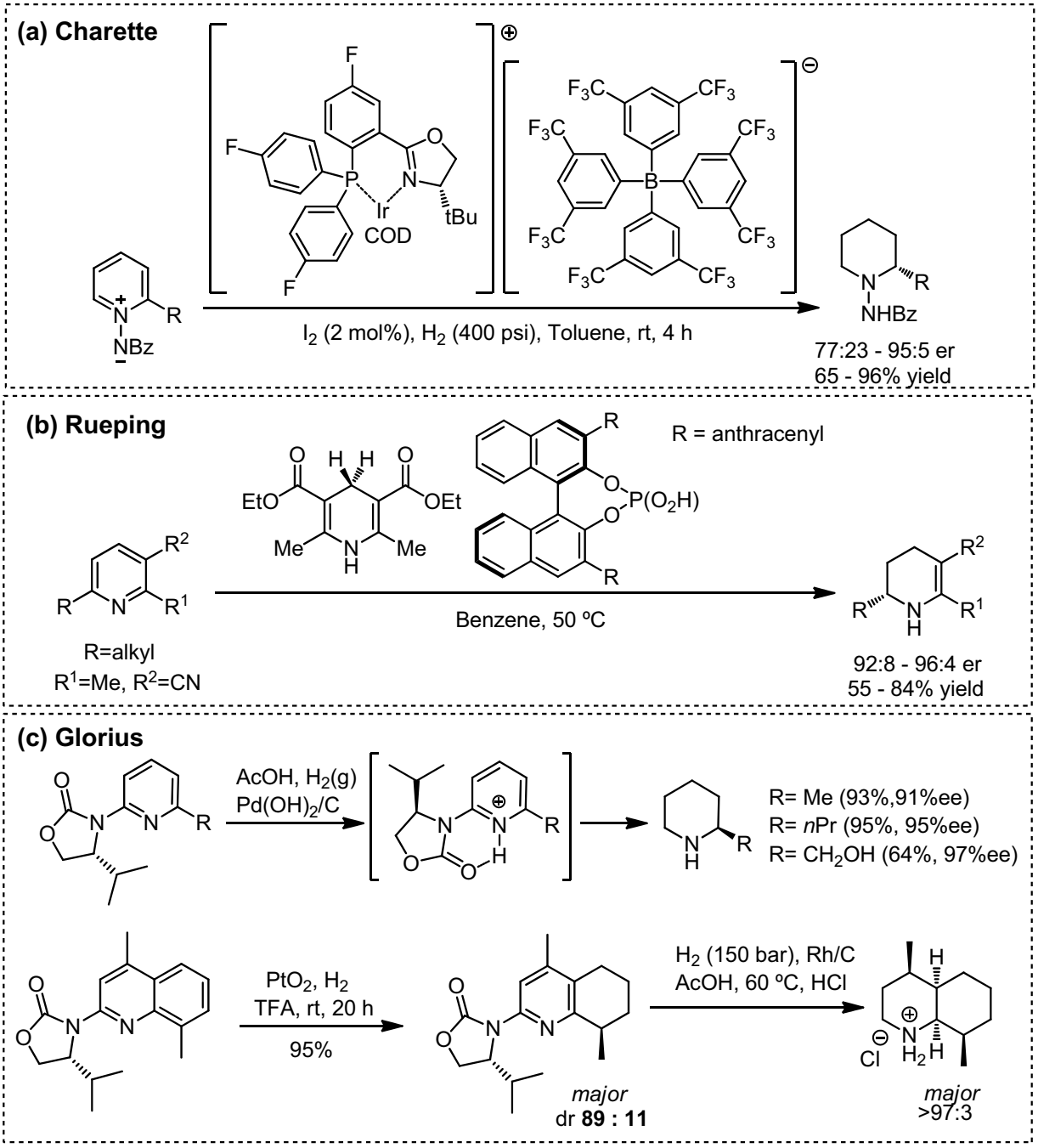
Charette and co-workers developed an asymmetric hydrogenation of pyridine derivatives using an Ir-phosphinooxazoline complex, an achiral auxiliary and *N*-benzoyliminopyridinium ylides (Scheme 4.7.a).[113] The benzoylimino moiety serves as both an activator of substrates and a secondary coordinating group for the catalyst.

Organocatalysts have also been shown to be active for asymmetric hydrogenation of pyridines (Scheme 4.7.b). Rueping and co-workers reported an enantioselective reduction of pyridines in the presence of a BINOL phosphate Brønsted acid catalyst using Hantzsch dihydropyridine as the hydride source.[114] However, the substrate scope is limited by the requirement for the incorporation of electron withdrawing groups on the pyridine ring.

Glorius and co-workers reported a highly efficient method for the asymmetric hydrogenation of chiral *N*-(2-pyridyl)-oxazolidinones (Scheme 4.7.c).[115] Reductions of highly substituted pyridines are possible in good yield and high diastereoselectivities creating multiple stereocenters in a single step. The high diastereoselectivity is ascribed to strong hydrogen bonding between the pyridinium and oxazolidinone moiety via the use of acetic acid as the solvent. By forming a rigid intermediate, the isopropyl group on the oxazolidinone shields the top face leaving the bottom face accessible. Glorius later reported an extension of this methodology to the reduction of quinolines in

[112] Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171-4175.
[113] Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc*. **2005**, *127*, 8966-8967.
[114] Rueping, M.; Antonchick, A. P.; *Angew. Chem. Int. Ed*. **2007**, *46*, 4562-4565.
[115] Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehman, C. W. *Angew. Chem. Int. Ed*. **2004**, *43*, 2850-2852.

which the non heteroatom containing ring was reduced allowing for selectivity at sites remote from the auxiliary.[116]




**Scheme 4.7**. Methods for the asymmetric hydrogenation of pyridines via (a) catalytic asymmetric hydrogenation (b) organocatalysis (c) chiral auxillary approach employing oxazolidinones.

[116] Heitbaum, M.; Fröhlich, R.; Glorius, F. *Adv. Synth. Catal*. **2010**, *352*, 357-362.

### 4.3.2. Retrosynthetic Design

After evaluating the possible options we decided to employ Glorius's oxadazolidone methodology, principally because of its potential to direct the hydrogenation to the back face of the molecule and to possibly augment the observed selectivity of the double bond hydrogenation since we also required that it also take place from the lower face of the molecule. We hoped that this remote effect in combination with the diastereoselective control imparted by the decahydroquinoline ring system would make the whole reductive process highly selective (see figure 4.7). An additional benefit of this approach would be the possibility to form the required N-methyl group in the same reaction via addition of formaldehyde to the reaction mixture to effect a reductive amination.

We figured that the best way to introduce the auxiliary would be by incorporating it onto the phosphonate in order to maintain maximum convergence in the synthetic sequence.

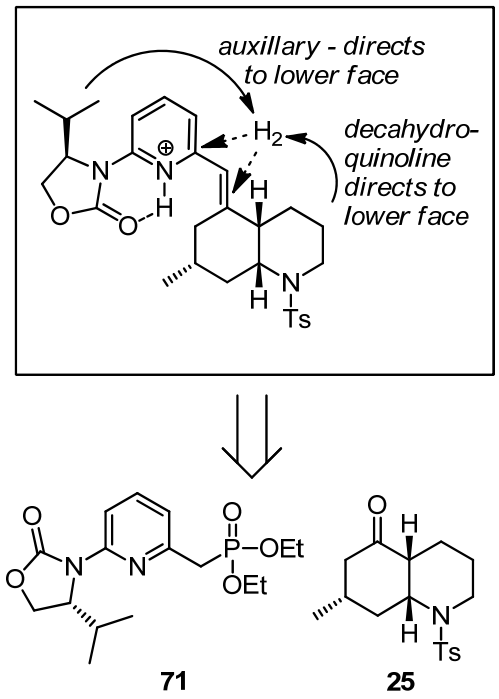
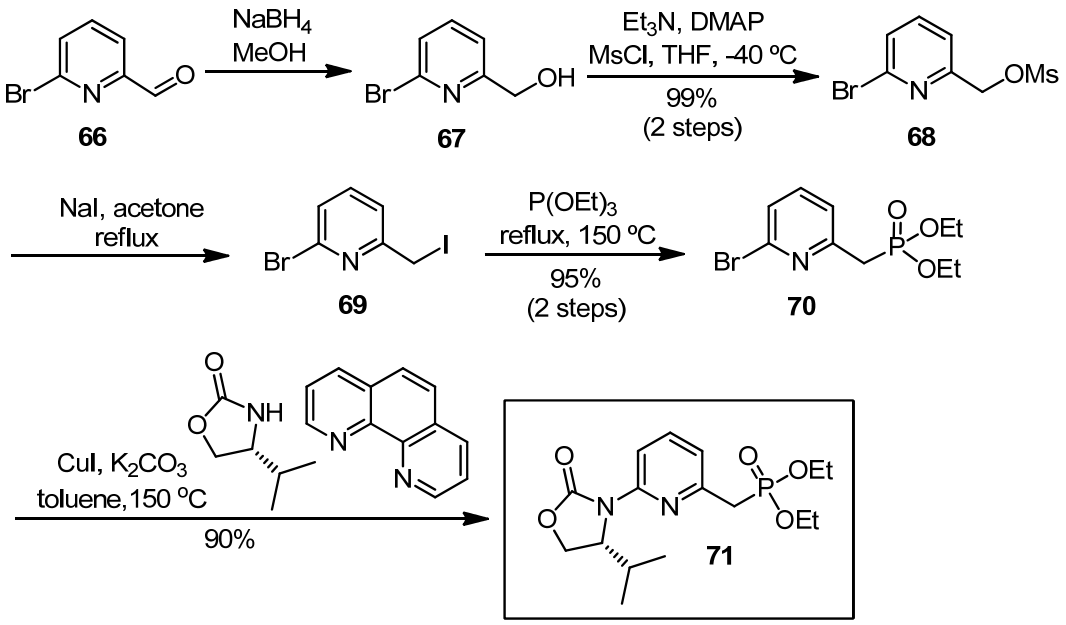



**Figure 4.7.** Proposed stereochemical control of both chiral centres by the use of an oxazolidinone derived chiral auxiliary in combination with diastereoselective control imparted by the decahydroquinoline ring system.

### 4.3.3. Preparation of pyridine methyl phosphonate coupling partner

For the preparation of the bromopyridine phosphonate required to couple to the oxazolidinone auxiliary, we took advantage of a synthesis which had previously been reported in the literature.[117] Thus, commercially available bromopyridine aldehyde **66** was reduced to the alcohol **67** with $NaBH_4$ in MeOH, the resulting crude material was then mesylated to give **68** in 99% yield over the two steps from **66**. Displacement of the mesyl group gave iodide **69** which was then converted to the known phosphonate **70** via an Arbuzov reaction in the presence of triethylphosphite in 95% overall yield over the two steps. The bromopyridine **70** was coupled to auxiliary using copper catalysis[118] in the presence of phenanthroline as the ligand to give **71** in 90% yield.[119] (Scheme 4.8)



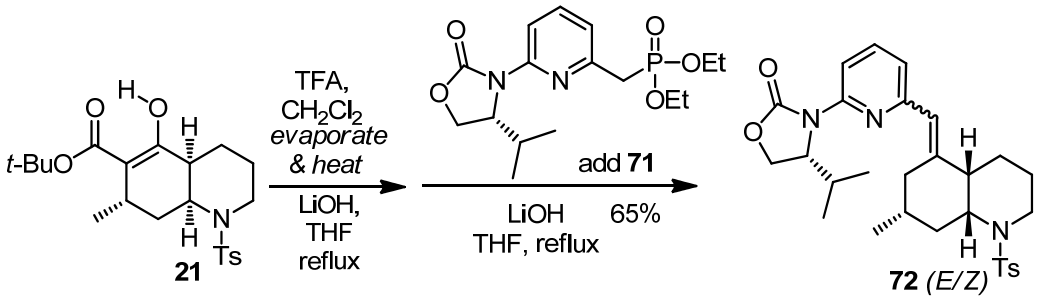

**Scheme 4.8.** Synthesis of oxazolidinone containing phosphonate **71**.

[117] Kawano, T.; Kato, T.; Du, C.; Ueda, I. *Bull. Chem. Soc. Jpn.* **2003**, *76,* 709-719.
[118] These conditions are slightly different to those published by the authors. We thank Professor Glorius (personal communication) for providing us with these improved conditions.
[119] We initially evaluated an alternative route in which we first performed the coupling of the auxiliary, since we were unsure if the auxiliary coupling would be compatible with the phosphonate moiety. However, we chose the route outlined in scheme 4.8 since the precious auxiliary was only introduced in the last step and the resulting final product was easier to purify.

### 4.3.4. Study of the coupling reaction with phosphonate 71

With phosphonate **71** in hand, decahydroquinoline **21** was decarboxylated and isomerised with LiOH in THF according to the standard conditions. However, when we applied the optimum conditions developed for the coupling of the simple phosphonate **49** using no solvent (table 4.1, entry 4) we observed practically no coupled product and significant degradation of the auxiliary phosphonate starting material **71**.

Fortunately, when the reaction was performed with solvent (THF, reflux, 48 h) the coupled product was formed in moderate yield as a mixture of *E/Z* isomers (Scheme 4.9). Brief attempts to optimise the reaction by increasing the reaction time and equivalents of base and phosphonate were unfruitful in driving the reaction to completion.[120] However, since sufficient material could be obtained by this route we proceeded to examine the key hydrogenation step.




**Scheme 4.9.** Coupling of auxiliary phosphonate under equilibrating conditions.

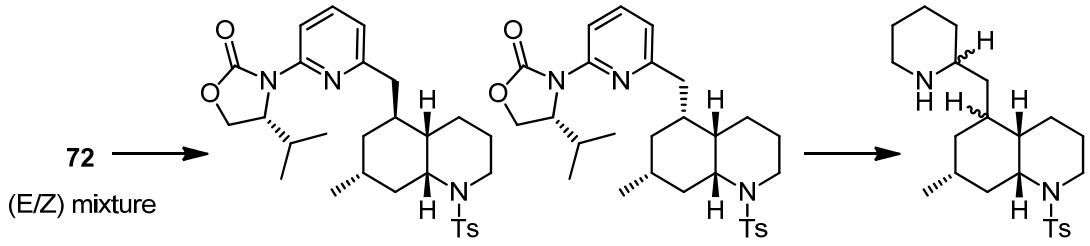
### 4.3.5. Study of hydrogenation of pyridine auxiliary 72

Hydrogenation of **72** was examined under a series of conditions (see table 4.2). The described conditions by Glorius required the use of high pressures, however we began by hydrogenating with $PtO_2$ in AcOH (entry 1), the same conditions we had used previously. Whilst after 24 h we observed the reaction was not complete extending the reaction time to 48 h gave the piperidine product **74** with complete loss of the auxiliary as we expected. However, the resulting product was isolated as a mixture of diastereoisomers.

[120] The remaining mass balance was recovered as starting material.

Suspecting that the culprit was the non selective reduction of the alkene, we conducted the hydrogenation with Pd/C in AcOH, so that only the alkene was reduced to determine the diastereoselectivity of this step. Indeed, under these conditions the facial selectivity was poor giving just a 2.3:1 ratio of **73** and *epi*-**73** respectively (entry 2). Unfortunately, unlike in the non auxiliary series these compounds could not be separated column chromatography. Carrying out the reaction in MeOH gave as expected a reversal of selectivity (entry 3), since the auxiliary would be expected to be blocking the bottom face in absence of acid. Surprisingly, the use of TFA as solvent also gave a complete reversal in the selectivity giving 1:2.5 ratio for **73** and epi-**73** (entry 4).

**Table 4.2.** Conditions tested for the hydrogenation in the presence of pyridine auxiliary




| *Entry* | *Catalyst*[a] | *Solvent* | *Product* |
|---|---|---|---|
| 1 | $PtO_2 \cdot H_2O$ | AcOH | **74**[b] |
| 2 | Pd/C | MeOH | **73**/epi-**73** (1:2.2) |
| 3 | Pd/C | AcOH | **73**/epi-**73** (2.3 : 1) |
| 4 | Pd/C | TFA | **73**/epi-**73** (1 : 2.5) |

[a]20% by mass [b]isolated as a mixture of epimers at C-5 and C-7 which could not be determined.

Given the low selectivity and the polarity of the resulting piperidine compounds we were not able to determine the selectivity of the reduction of the C-5 stereocentre of the pyridine. Due to these complications we returned to investigate the reduction of the simpler vinyl pyridine system **60** to see if we could shed some light on the selectivity of the alkene reduction and how to improve it. We then hoped that with this information we could return to the **72** and re-evaluate the reduction.

## 4.4. Diastereoselective Hydrogenation of Type B Vinylpyridines

### 4.4.1. Hydrogenation of Type B compounds with a tosyl group

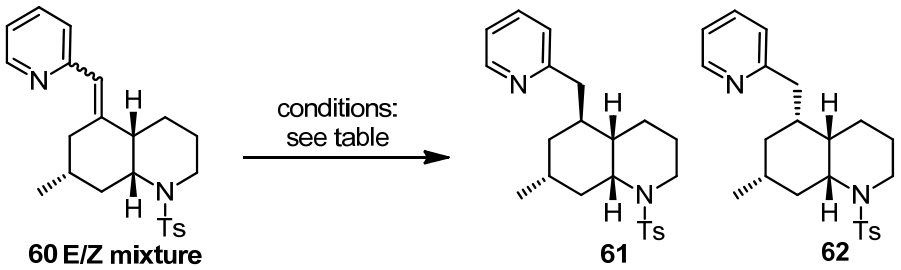
We began by looking at the hydrogenation of **60** in different solvents to see what effect this would have on the course of the reaction. As stated before reduction with MeOH/$CH_2Cl_2$ gave a 2.5:1 ratio (table 4.3, entry 1). The alkene **60** was completely insoluble in MeOH thus necessitating the presence of the cosolvent. However, when the reaction was conducted in MeOH, the reaction did reach completion with a surprising increase in selectivity to 5:1 (entry 2). Indeed if the reaction was carried out in $CH_2Cl_2$ alone the ratio dropped to 1.5:1 (entry 3) indicating a very strong solvent effect on the reaction and perhaps explaining the poor selectivity for the reduction of **72**.

Encouraged by these results we screened a large range of possible solvents but MeOH remained the solvent of choice. Notably the use of AcOH gave a very poor selectivity (1.8:1) indicating that whilst the use of the auxiliary fared better (2.3:1) giving a slight increase in selectivity via remote induction it was not sufficient to overcome this very sensitive solvent dependability of the hydrogenation reaction. Given the preference of polar protic solvents the use of water (entry 7) was tried as an additive but gave the same result as MeOH used alone.

Additionally, the brief evaluation of other palladium catalyst $Pd(OH)_2$ and $PtO_2$ gave even less selectivity (entries 9 and 10 respectively). The use of $Et_3SiH$ as an alternative hydrogenation gave a similar but slight inferior result with a ratio of 4:1 (entry 11).

These results would indicate that the reduction step is potentially dominated by the isoelectric effect of the solvent and a discussion as why this might be the case is outlined in section 4.4.2.

**Table 4.3.** Selectivity of the hydrogenation of the C-5 alkene.

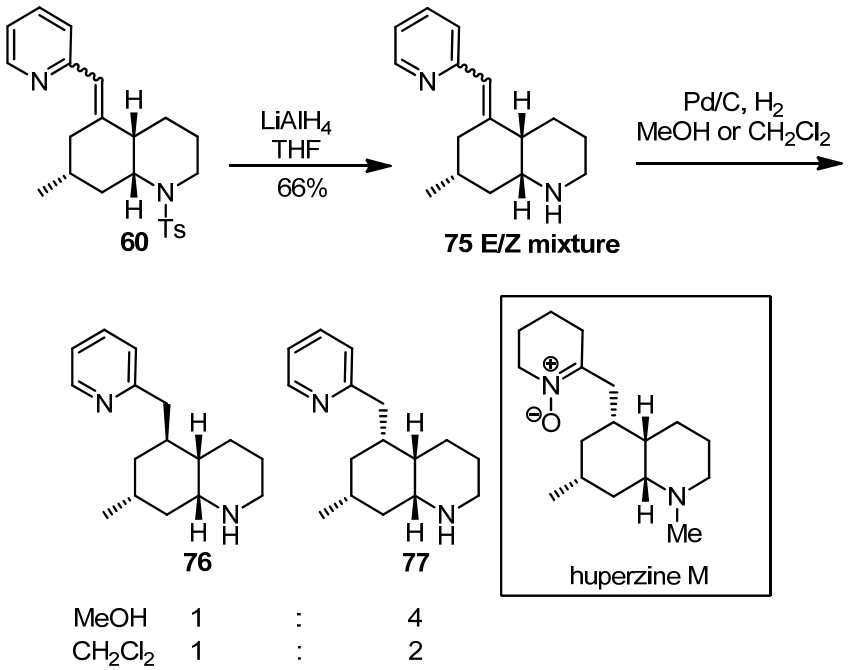



| *Entry* | *Catalyst*[a] | *H source* | *Solvent*[b] | *Ratio (61 : 62)* |
|---|---|---|---|---|
| 1 | Pd/C | $H_2$ | $MeOH/CH_2Cl_2$[c] | 2.5 : 1 |
| 2 | Pd/C | $H_2$ | MeOH | 5 : 1 |
| 3 | Pd/C | $H_2$ | $CH_2Cl_2$ | 1.5 : 1 |
| 4 | Pd/C | $H_2$ | EtOAc | 3 : 1 |
| 5 | Pd/C | $H_2$ | toluene | 2.2 : 1 |
| 6 | Pd/C | $H_2$ | AcOH | 1.8 : 1 |
| 7 | Pd/C | $H_2$ | $MeOH/H_2O$[d] | 5 : 1 |
| 8 | Pd/C | $H_2$ | *t*-BuOH | 3.5 : 1 |
| 9 | $Pd(OH)_2$ | $H_2$ | MeOH | 1.8 : 1 |
| 10 | $PtO_2$ | $H_2$ | MeOH | 1 : 1[e] |
| 11 | Pd/C | $Et_3Si$-H | MeOH | 4 : 1 |

[a]The catalyst was used with 20% loading by weight. [b]concentration=8 mL/mmol. [c]1:1 by volume. [d] 10% by volume [e] other impurities isolated along with product.

### 4.4.2. Hydrogenation of Type B compounds without a tosyl group

Removal of the tosyl group with $LiAlH_4$ gave the free amine compound **75**. Hydrogenation of this compound was found to lead a reversal in the selectivity to give more selective reduction from the top face of the molecule to give the opposite stereochemistry in approximately 4:1 ratio. Notably, this provides the stereochemical arrangement of another phlegmarine alkaloid huperzine M.[17] Given that the use of $CH_2Cl_2$ significantly increased the quantity of the huperzine M type stereochemistry in the tosyl series (see table 4.3, entry 3) we also carried out the reduction in this solvent. However, it was observed that once the tosyl group is removed, this effect is not additive and the selectivity for the huperzine M type stereochemistry dropped to just 2:1 (Scheme 4.10).




**Scheme 4.10.** Deprotection of tosyl group to give free amine compound **75.** Selectivity of the hydrogenation of the alkene. Access to huperzine M stereochemistry.

### 4.4.3. Rationalization of the hydrogenation facial selectivity

We believe that the facial selectivity for the reduction of **60** was primarily influenced by the tosyl group, which effectively blocked the top face of the molecule. To explain the sensitivity of the reaction to solvent we believe **75** to be highly lipophilic hence its poor solubility in MeOH. This solvent forces the aromatic rings together via a stacking effect which locks the tosyl group over the top face of the molecule. When a solvent such as $CH_2Cl_2$ is used which readily

solubilises **75** then this effect is less important and therefore the tosyl group does not shield the top face so effectively. The use of AcOH, which protonates the pyridine ring also reduces the stacking effect and accounts for the low ratio in this solvent as well.

Removal of the tosyl group prior to the hydrogenation led to the selective reduction from the top face of the molecule to give the opposite stereochemistry (i.e **77**) since now the facial selectivity is dominated by the piperidine ring which blocks the lower face (Figure 4.8).

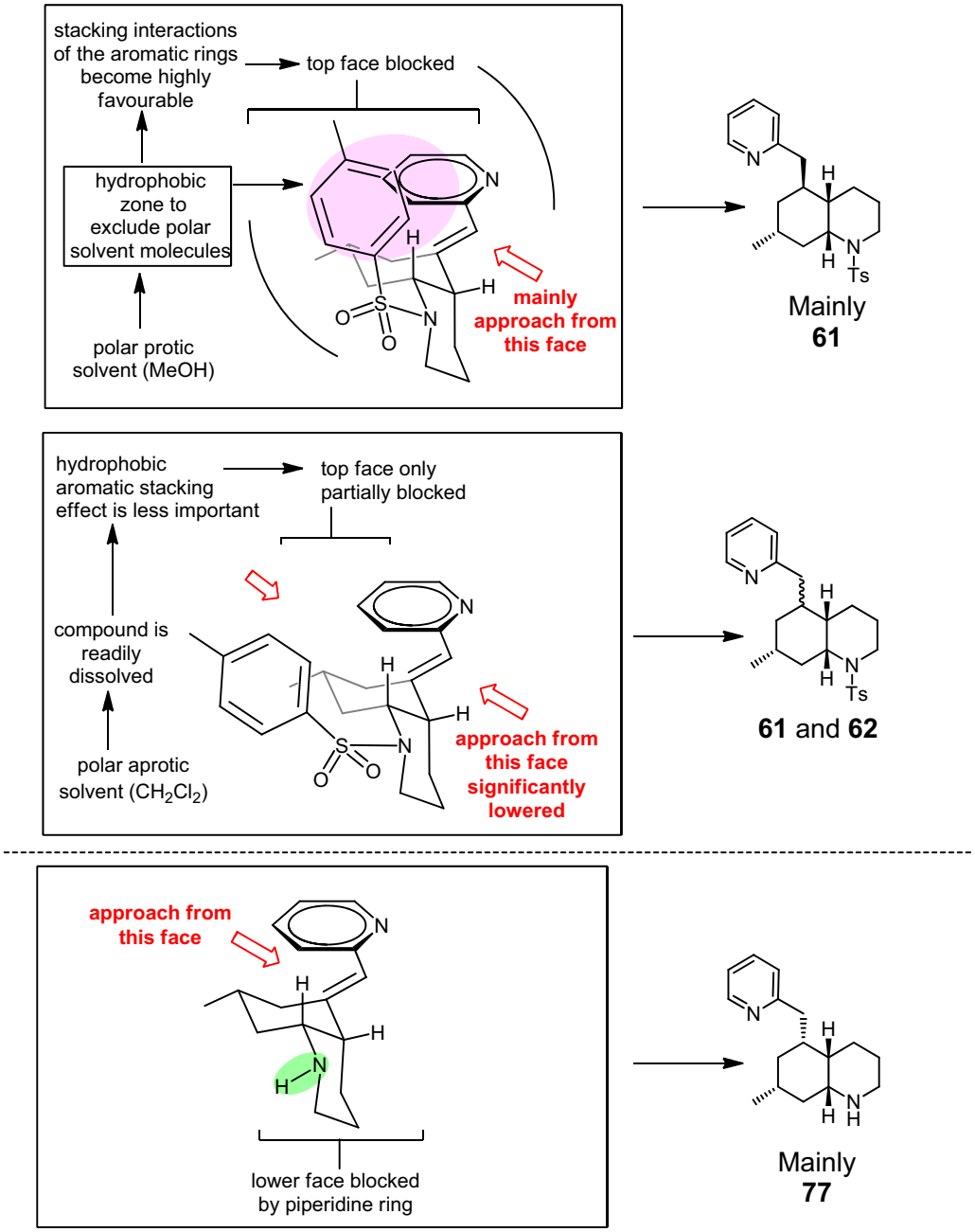
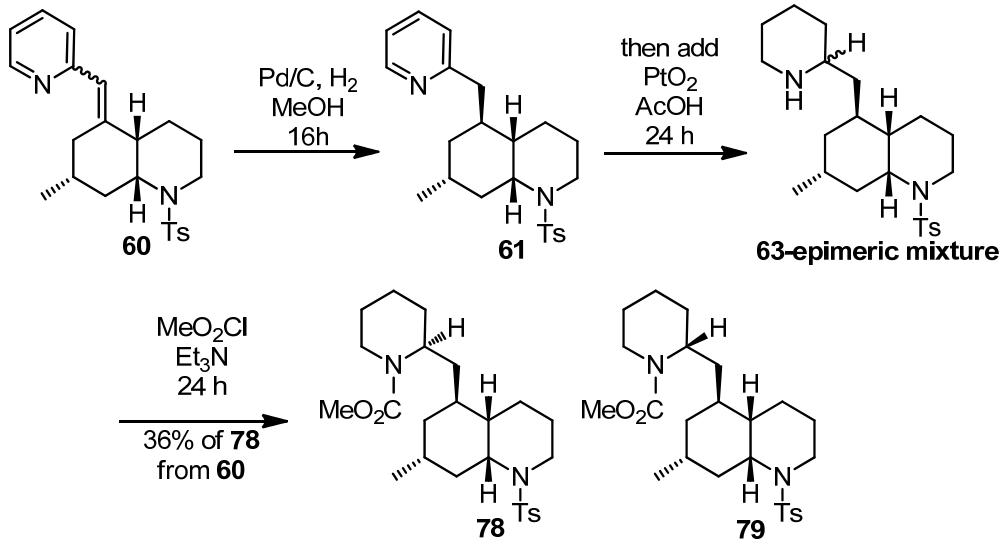



**Figure 4.8.** 3D explanation about the selectivity of the hydrogenation depending on the solvent and the tosyl group.

### 4.4.4. Completion of the total synthesis of cermizine B

Reduction of the alkene **60** with the optimised conditions to **61** followed by reduction of the pyridine ring with $PtO_2$ gave a highly polar mixture of epimers at C-5 which could not be separated. Fortunately, treatment of this mixture with methyl chloroformate gave the corresponding carbamates **78** and **79** which were now readily separable in approximately 1:1 ratio (Scheme 4.11). These two compounds were markedly different: the proton NMR spectra of **79** gave clean defined signals whilst the spectra of the desired epimer **78** were broad due to the restricted rotation of the carbamate. Secondly, upon standing **78** existed as a white solid whereas **79** was a clear yellow oil and could not be induced to crystallize (see figure 4.9).




**Scheme 4.11.** Reduction of the vinyl pyridine ring and carbamation.

Subsequent reduction of both compounds with $LiAlH_4$ smoothly converted the carbamate into the required methyl as well as removed the tosyl group. Whilst until this point the assignation of the epimers **78** and **79** had been speculative, comparison of both products with data for the natural product proved our assignation had been correct. The compound obtained from **78** showed NMR spectroscopic data identical to those reported for the natural product and the optical rotation obtained: $[\alpha]_D$ = -3.1 (c 0.7, MeOH), was very close to the literature value for (-)-cermizine B {lit[11] $[\alpha]_D$ -2.0 (c 0.6, MeOH)} thus also confirming the absolute configuration of the natural product. Furthermore,

the epimer **79** whilst giving a similar NMR spectrum had a vastly different rotation in both size and value (scheme 4.12).

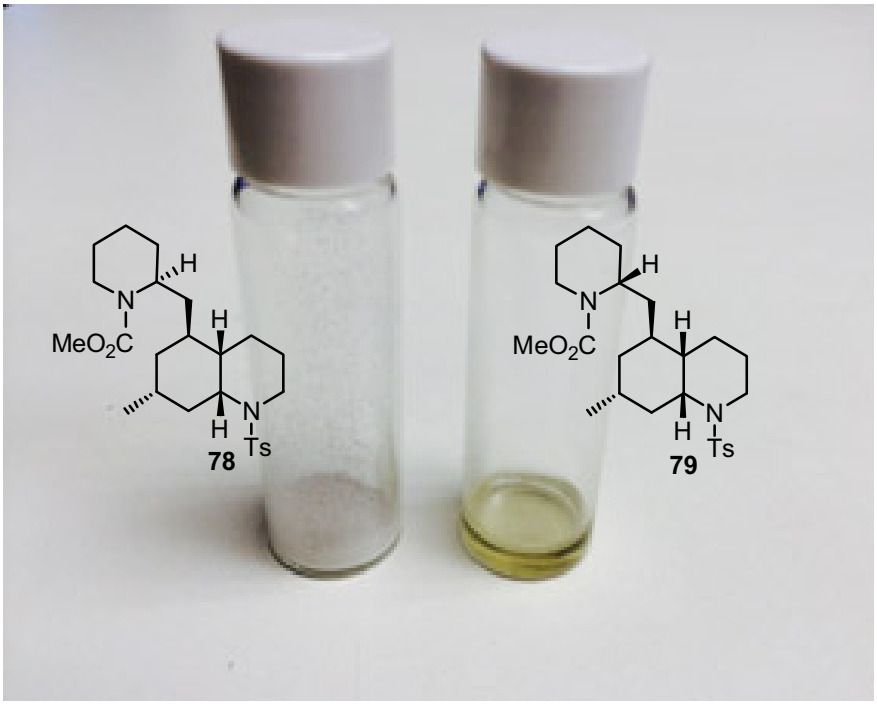
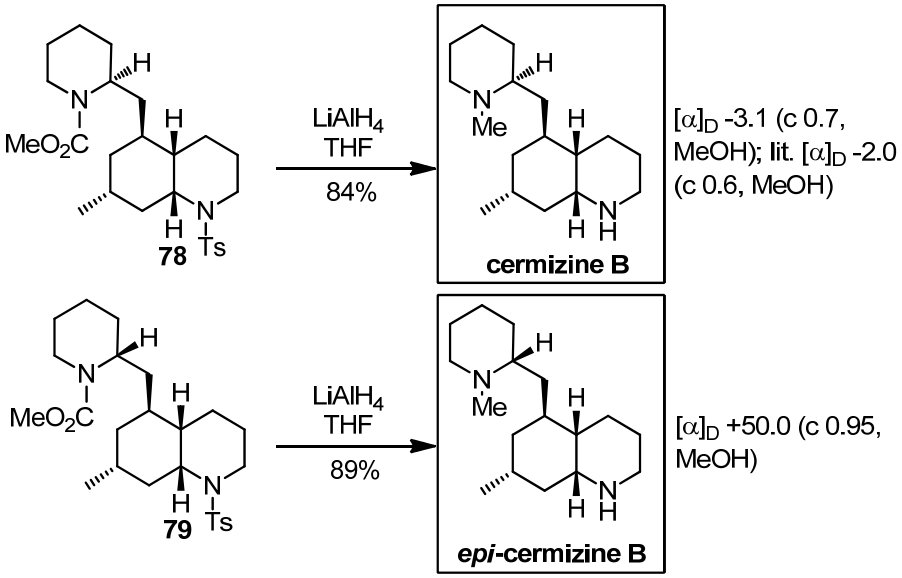



**Figure 4.9.** Difference in physical properties of the carbamate epimers **78** and **79**.

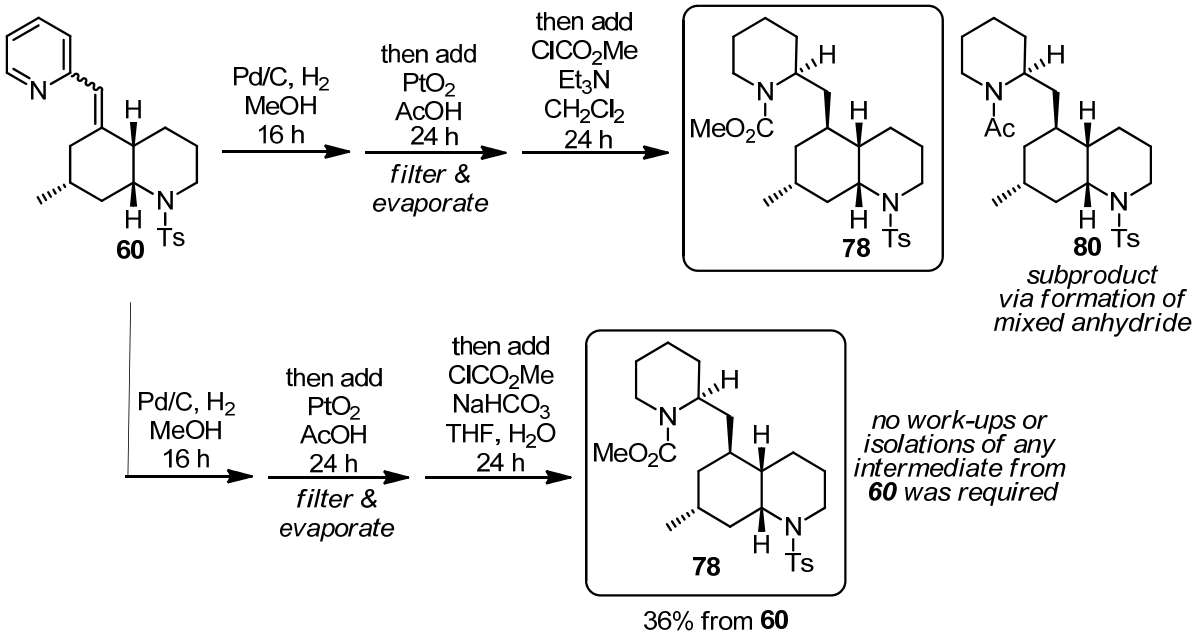



**Scheme 4.12.** Reduction of carbamates **78** and **79** and comparison to cermizine B.

### 4.4.5. Optimization of sequence 3

With the steps to access cermizine B now completed we set about trying to convert these reactions into one-pot sequence. Thus, alkene **60** was hydrogenated in the presence of Pd/C in MeOH. Subsequent hydrogenation of the pyridine ring was then accomplished by direct addition of $PtO_2$ and AcOH to the reaction mixture. Filtration of the catalysts and evaporation of the AcOH acid gave the epimeric amines which were directly converted to the corresponding carbamates. However, now we observed the formation of an additional compound in significant quantities (~45% of the total mass) which was determined to be the acetamide **80**, presumably formed by the traces of AcOH in the reaction mixture which in the presence of methyl chloroformate gave a mixed anhydride responsible for the acylation.

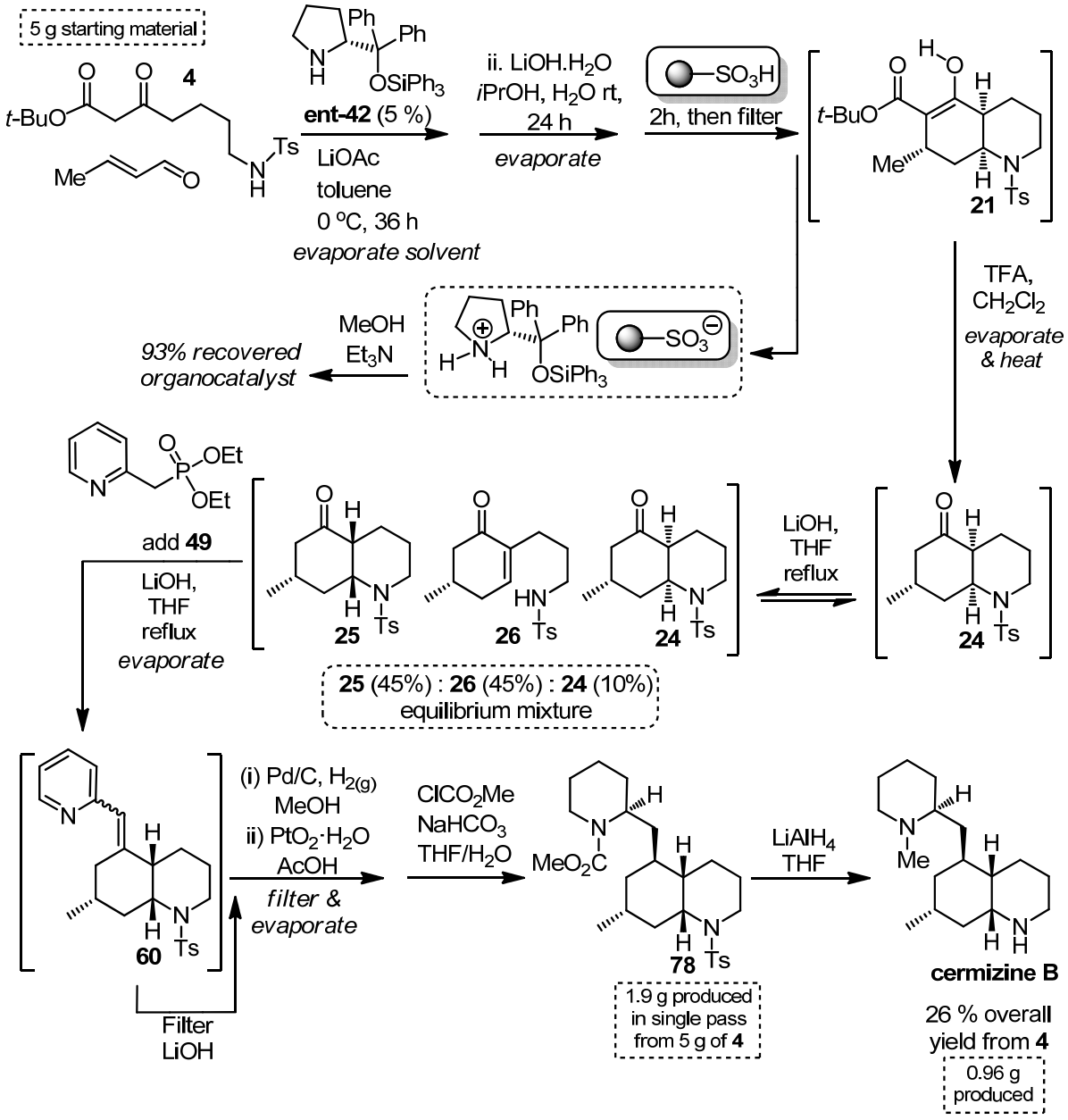
Fortunately, we found that if the steps were repeated as above but the carbamation step was carried out under Schotten-Baumann type conditions (methyl chloroformate in THF and aqueous $NaHCO_3$) the side product **80** was not observed (Scheme 4.13).




**Scheme 4.13.** Optimization of the third one-pot sequence.

### 4.5. Gram-scale total synthesis of cermizine B via *uninterrupted* sequence

After the successful completion of the synthesis via a sequence involving 3 one-pot reactions, we sought to eliminate the remaining purification steps until carbamate **78**, which would render the whole process even more efficient (Scheme 4.14).



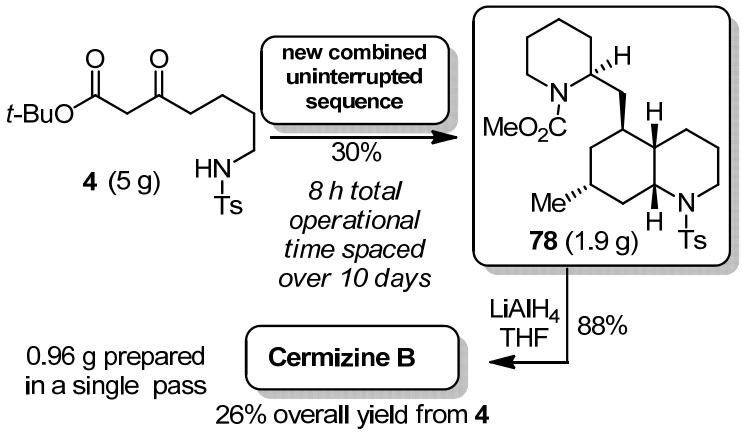

**Scheme 4.14.** Gram-scale synthesis of cermizine B and all the intermediates formed in the uninterrupted sequence from β-keto ester **4**.

Thus, after treatment with the resin at the end of the first one-pot sequence, the solvent was removed by evaporation and the resulting material

was fed directly into the second set of tandem reactions, and then, after subsequent removal of the LiOH by filtration, into the third set. Reduction of this enantioenriched material **78** (after a single purification step to remove **79**), with $LiAlH_4$ then took place in 88% yield to give 0.96 g of the target cermizine B from just 5 g of the starting β-keto ester **4**. By eliminating the aforementioned purification procedures, the overall yield for the new integrated sequence was increased to 26%.

### 4.5.1. Analysis of cermizine B synthesis according to Jørgensen's classification

The complete synthesis was then analysed according to the one-pot classification system of Jørgensen.[121] The most striking feature of the uninterrupted sequence from the starting material **4** to the precursor of cermizine B **78**, is that it consists of eight consecutive reactions for eight manual operations (nmo) and only one final purification. For the total synthesis of cermizine B, which required an additional step and purification, the values of $Y_{PBF}$ (76% yield per bond formed) and $Y_{PMO}$ (86% yield per manual operation) indicate that each step in this synthesis proceeded in high yield. The very high value of the purification factor ($P_f$ = 6) is also noteworthy (Scheme 4.15).




| nmo | $Y_{PBF}$ [%] | $Y_{PMO}$ [%] | $P_f$ |
|---|---|---|---|
| 9 | 76 | 86 | 6 |

**Scheme 4.15.** Analysis of cermizine B synthesis according to Jørgensen's classification.

[121] Albrecht, L.; Jiang, H.; Jørgensen, K.A. *Angew. Chem. Int. Ed*. **2011**, *50*, 8492-8509.

### 4.5.2. Analysis of cermizine B synthesis according to economy

The route was also evaluated from an economy perspective, calculating the time and total resources used in the synthesis (see table 4.4).

From the β-keto ester **4** until the obtention of carbamate **78** a total of approximately just 7 L of solvent was required. To put this in perspective this equals the amount of solvent that is often used in the purification of a single compound from a single chemical transformation on a moderate scale.

Evaluating the sequence from a time economy perspective it can be seen only that only about 8-12 h of operational time (i.e equal to one full work day) (spaced over a period of 10 days) was required with a daily average of just 15-30 minutes. It should be noted that the majority of the total time was required for the completion of the two chromatographic purifications. Further optimization to remove one or both of these purifications would not only decrease the total time drastically but would also reduce significantly the solvent required.

**Table 4.4.** Analysis of cermizine B synthesis according to economy principles.

| ***Operation*** | ***Solvent used*** | ***T. reaction*** | ***T. operator*** |
|---|---|---|---|
| Organocatalysis | 100 mL Toluene | 36 h | 10 min |
| Tandem reaction | 100mL *i*-PrOH | 24 h | 10 min |
| Scavenger + filtration | 15 mL $CH_2Cl_2$ | 5 h | 20 min |
| Decarboxylation + Azeotrope | 15 mL TFA + 45 mL Tol. | 3.5 h | 10 min |
| Equilibration | 40 mL THF | 24 h | 20 min |
| HWE + quick filtration | 1 L $CH_2Cl_2$ | 72 h | 60 min |
| Pd (alkene reduction) | 100 mL MeOH | 16 h | 10 min |
| $PtO_2 \cdot H_2O$ (py reduction) + Filtr. | 100 mL AcOH | 24 h | 60 min |
| Carbamation | 50 mL THF + 50 mL $H_2O$ | 24 h | 30 min |
| Column chromatography | 3L Hex / EtOAc[a] | - | 4 h |
| **8** manual operations[b] | **6.8 L** SOLVENT | **10 days** | **8 h** |
| $LiAlH_4$ (carbamate reduction) | 100 mL THF | 24 h | 30 min |
| Final column chromatography | 3 L $CH_2Cl_2$ / MeOH[c] | - | 4 h |

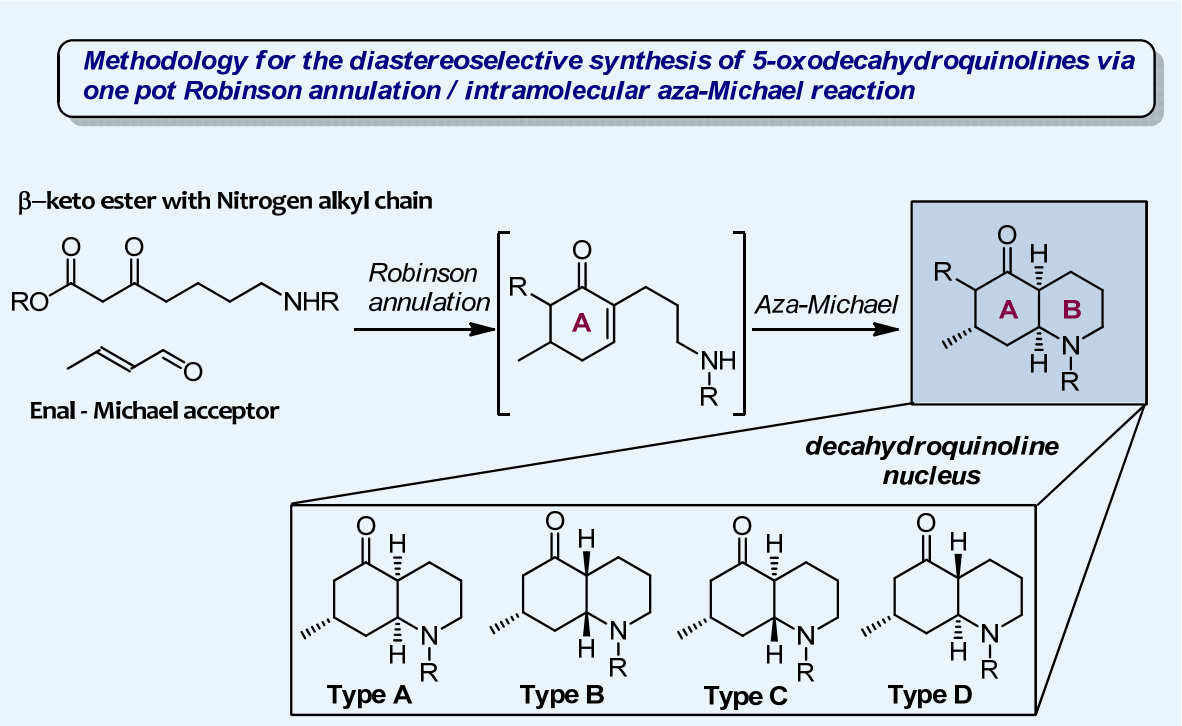
[a] 1.5 L of 5% EtOAc / Hex and 1.5 L of 10% EtOAc / Hex [b] 8 manual operations considering organocatalysis and tandem reaction together as one operation, [c] 1L of 1%, followed by 1L of 2.5% $CH_2Cl_2$ / MeOH, and finally 1L of $CH_2Cl_2$/MeOH/$NH_3$.

For example it might be possible to separate **78** from its epimer taking advantage of the difference in physical properties of these two compounds. Recycling of the wrong epimer would also increase the overall efficiency of the process quite significantly. It should be pointed out that the above synthesis as a single entity has not been fully optimised and we believe there still remains plenty of potential to make further improvements.

The considerable difference in the number of required steps compared with previous approaches to phlegmarine-type alkaloids underlines the efficiency and simplicity offered by asymmetric organocatalytic one-pot cascades.

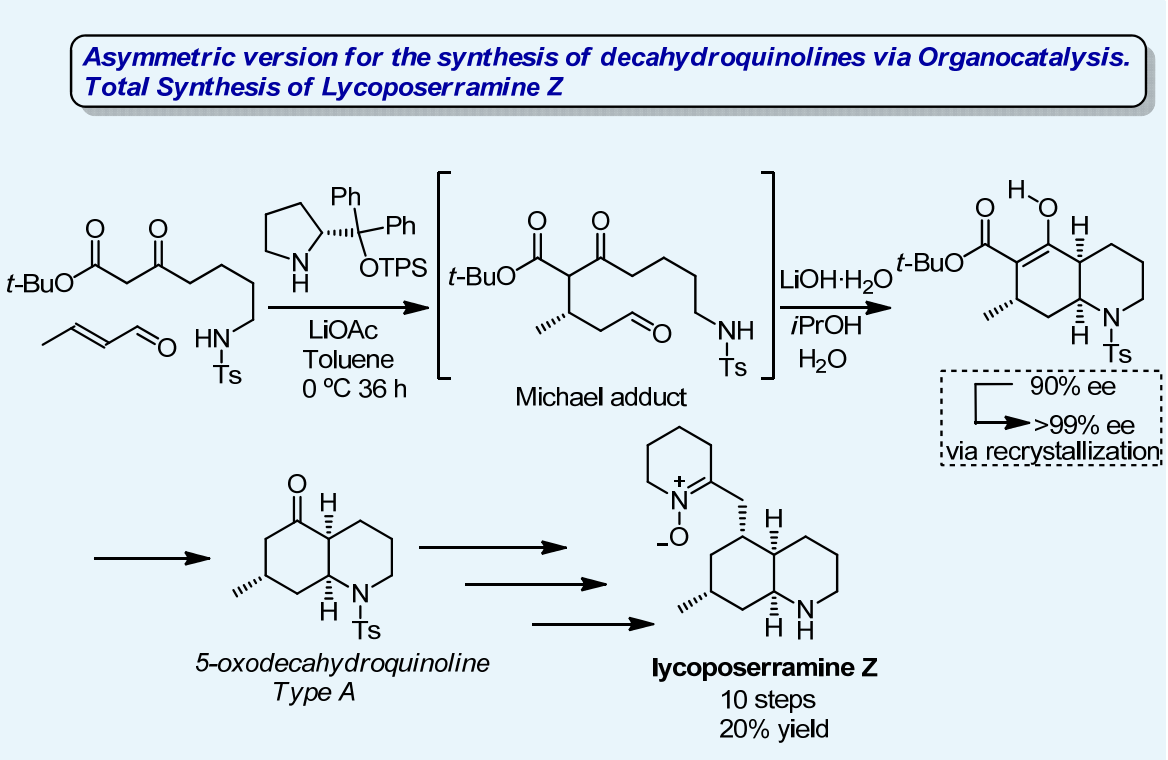
# 5. Conclusions

**1)** The treatment of a *tert*-butyl β-keto ester tethered to an ω-amino monoprotected group with crotonaldehyde using LiOH as the base, furnishes domino reactions involving the consecutive formation of two C-C bonds and one C-N bond in a sequence that comprises an intermolecular Michael process, followed by intramolecular aldol and aza-Michael reactions. This general methodology for the diastereoselective synthesis of 5-oxodecahydroquinolines implies a biscyclization and the formation of three stereocontrolled stereogenic centres in a single operational step. The resulting *cis*-decahydroquinoline of type A (arising from the dealkoxycarbonylation reaction) allows, through thermodynamic controlled processes, access to all other relative stereochemistries, providing a set of valuable building blocks (decahydroquinolines of Type B, C, and D) (Scheme 5.1).



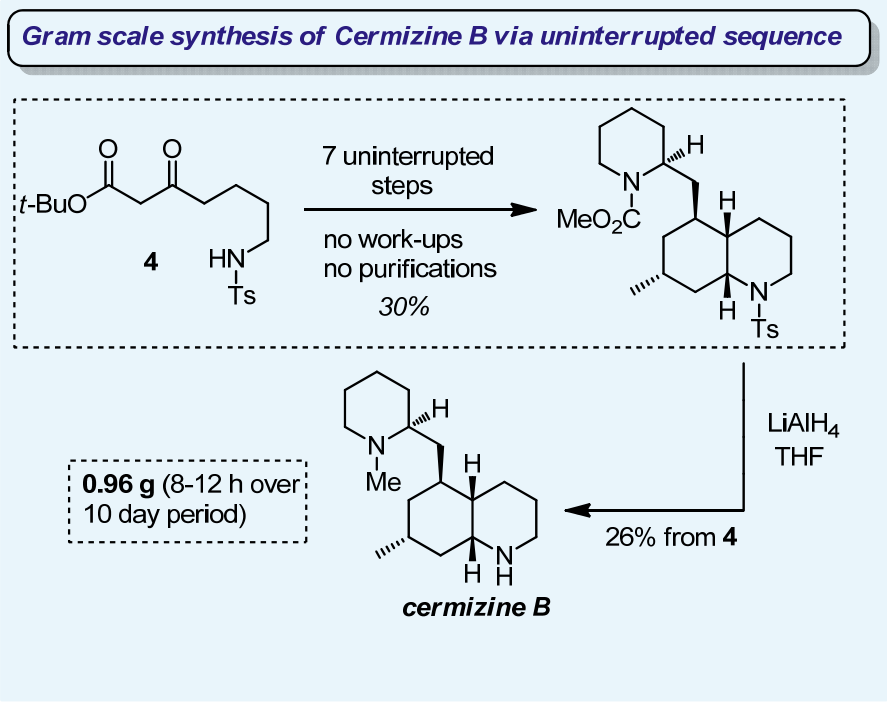

**Scheme 5.1.** Tandem reaction for the diastereoselective synthesis of 5-oxodecahydroquinolines.

**2)** The asymmetric Robinson annulation / intramolecular aza-Michael reaction leading to decahydroquinolines in a single step, from an achiral and acyclic simple β-keto ester, is not feasible using the classical reaction conditions developed by Jørgensen to synthesize cyclohexenones. After the initial organocatalyzed Michael addition, treatment with acid to promote the dealkoxycarbonylation and intramolecular aldol reaction failed, probably due to the presence of the nucleophilic nitrogen atom in the structure. In contrast, if LiOH is added after the organocatalysis step, the Robinson annulation and the following azacyclization take place in very good yield. The method has been optimized after screenings for the solvent, temperature, additives and catalysts. The resulting decahydroquinoline building block has been used in the total synthesis of the phlegmarine alkaloid lycoposerramine Z, which has been efficiently synthesized: 10 steps and 20% overall yield (see Scheme 5.2).




**Scheme 5.2.** Synthesis of decahydroquinolines via organocatalysis and its application to the total synthesis of lycoposerramine Z.

**3)** A potent solution for the problematic stop-and-go procedure, in which it is necessary to stop the synthesis after each operational step to carry out the work-up and purification of intermediates, is the combination of *pot economy* strategy and tandem reactions. Following this alternative strategy, we have developed an efficient synthesis of the alkaloid cermizine B via an uninterrupted sequence of 7 reactions, which allowed 1 gram of the natural product to be synthesized, employing 8-12 h of operational time over 10 days.

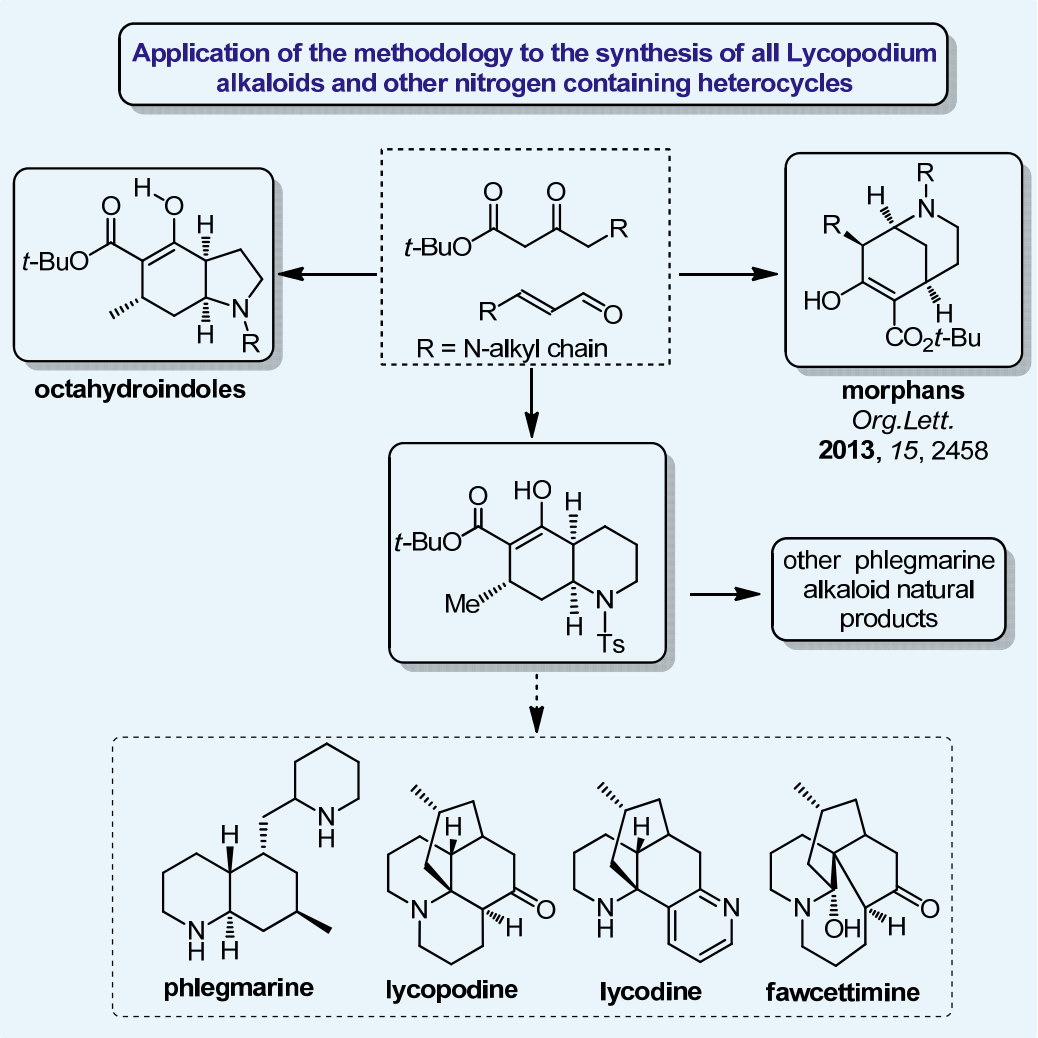



**Scheme 5.3.** Gram scale synthesis of cermizine B via uninterrupted sequence.

**4)** The scope of the strategy developed in the experimental studies carried out in the present PhD Thesis has been extended and applied to other research projects. Thus, the described methodology is not only applicable to the decahydroquinoline nucleus for the total synthesis of phlegmarine alkaloids, but can also be potentially applied to the synthesis of other members of the Lycopodium family. Furthermore, the method can also provide access to other nitrogen-containing heterocycles such as morphans[122] or octahydroindoles with some

[122] Bradshaw, B.; Parra, C.; Bonjoch, J. *Org Lett.* **2013**, *15*, 2458-2462.

structural changes in the starting materials (such as the number of carbon atoms in the initial β-keto ester or the installation of the nitrogen atom in the Michael acceptor or in the donor) (see Scheme 5.4).

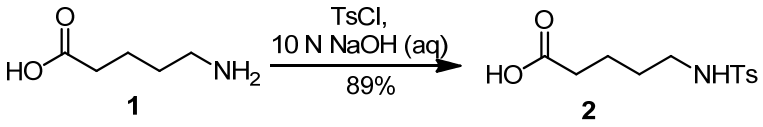



**Scheme 5.4.** Application of the methodology developed in this thesis to other nitrogen containing nuclei and natural product systems.

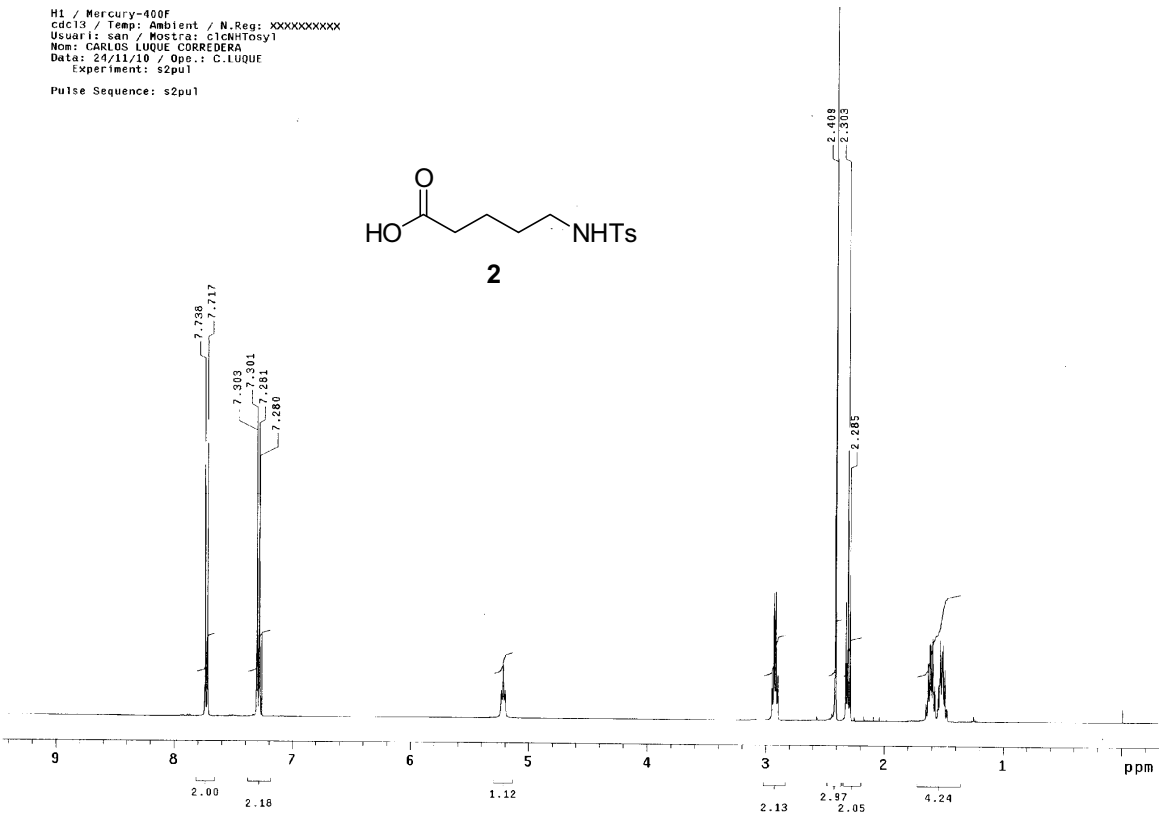
# 6. Experimental Section and Spectra

**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 2% ethanolic anysaldehyde. Chromatography refers to flash chromatography and was carried out on $SiO_2$ (SDS silica gel 60 ACC, 35-75 μm, 230-240 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous $MgSO_4$. Evaporation of solvent was accomplished with a rotatory evaporator. NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 300 or Varian VNMRS 400. Chemical shifts of $^1H$ and $^{13}C$ NMR spectra are reported in ppm downfield ($\delta$) from $Me_4Si$. HPLC analyses for the determination of enantiomeric excess were carried out using a DAICEL CHIRALPAK IC column (250×4.6 mm I.D., 5 μm; Chiral Technologies Europe) on a Waters model 2487 Dual Absorbance Detector and set at the wavelength of 254 nm. The chromatographic resolution of compound **21** was achieved using hexane/*i*PrOH 80: 20 as the mobile phase in an isocratic run.

**5-(4-Methylphenylsulfonamido)pentanoic acid (2)**




To a solution of 5-aminovaleric acid **1** (10.0 g, 85.4 mmol) in water (110 mL), was added 10 N NaOH (20 mL) followed by tosyl chloride (16.3 g, 85.4 mmol) into 3 portions over 15 min. The reaction mixture was then heated at reflux temperature for 3 h. After cooling to rt, the reaction mixture was extracted with $Et_2O$ (2 × 50 mL) and acidified to pH = 1 with 4 N HCl. The acidic phase was extracted with EtOAc (3 × 100 mL), dried and concentrated *in vacuo* to give **2** (20.6 g, 89%) as a white solid, which was used in the next step without purification. $R_f$ 0.50 (EtOAc); $^1$H NMR (400 MHz, COSY) $\delta$ 1.52 (m, 2H, H-4), 1.62 (m, 2H, H-3), 2.30 (t, *J* = 7.2 Hz, 2H, H-2), 2.41 (s, 3H, $CH_3$), 2.92 (q, *J* = 6.4 Hz, 2H, H-5), 5.22 (t, *J* = 6.4 Hz, 1H, NH), 7.29 (d, *J* = 8.4 Hz, 2H, *m*-Ts) 7.73 (d, *J* = 8.2 Hz, 2H, *o*-Ts); $^{13}$C NMR (100 MHz, HSQC) 21.5 (C-3), 28.8 (C-4), 33.2 (C-2), 42.6 (C-5), 127.0 (*o*-Ts), 129.7 (*m*-Ts), 136.7 (*p*-Ts), 143.5 (*ipso*-Ts), 178.8 (CO) HRMS calcd for $C_{12}H_{17}NO_4S$ $(M - H)^-$ 270.0806, found 270.0806.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cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: clcNHTosyl
Nom: CARLOS LUQUE CORREDERA
Data: 24/11/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
O
HO
NHTs
2
7.738
7.717
7.303
7.301
7.281
7.280
2.409
2.303
2.285
9
8
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6
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2
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ppm
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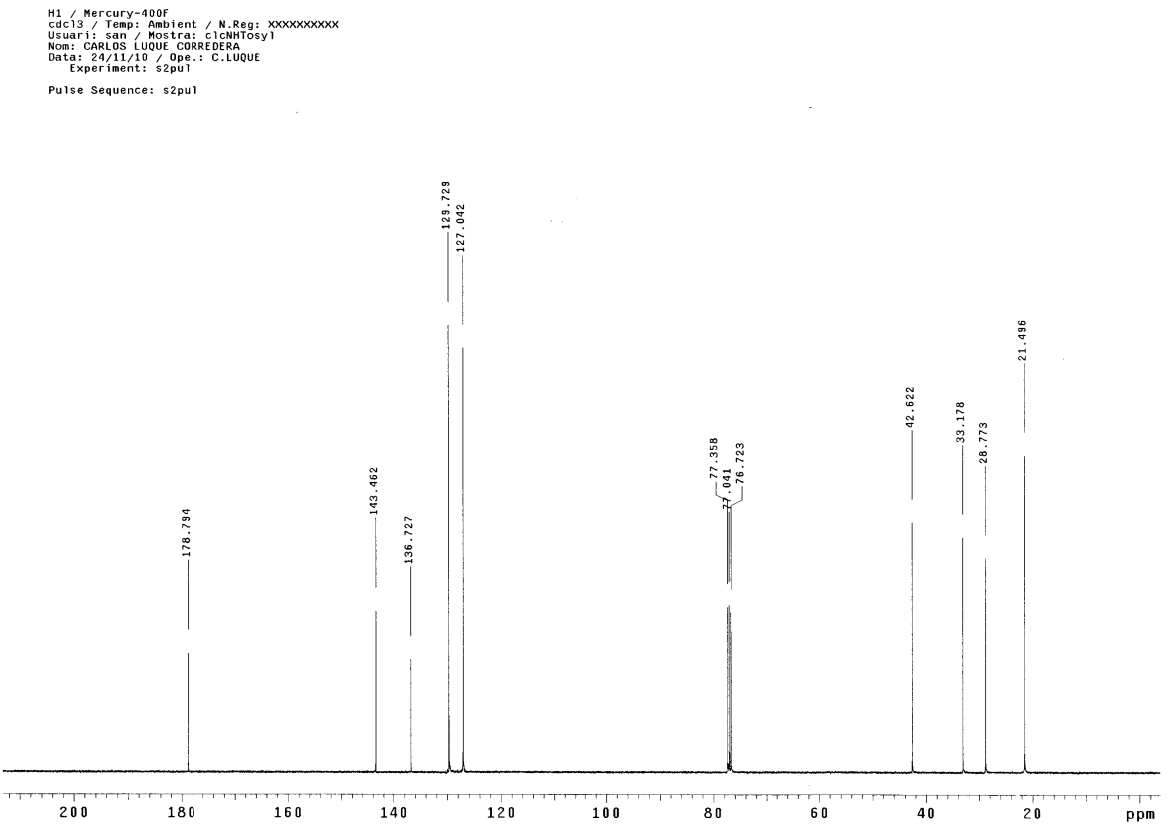
2.18
1.12
2.13
2.97
2.05
4.24


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: clcNHTosyl
Nom: CARLOS LUQUE CORREDERA
Data: 24/11/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
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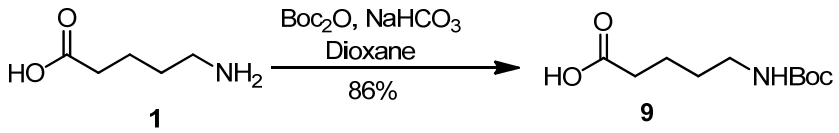
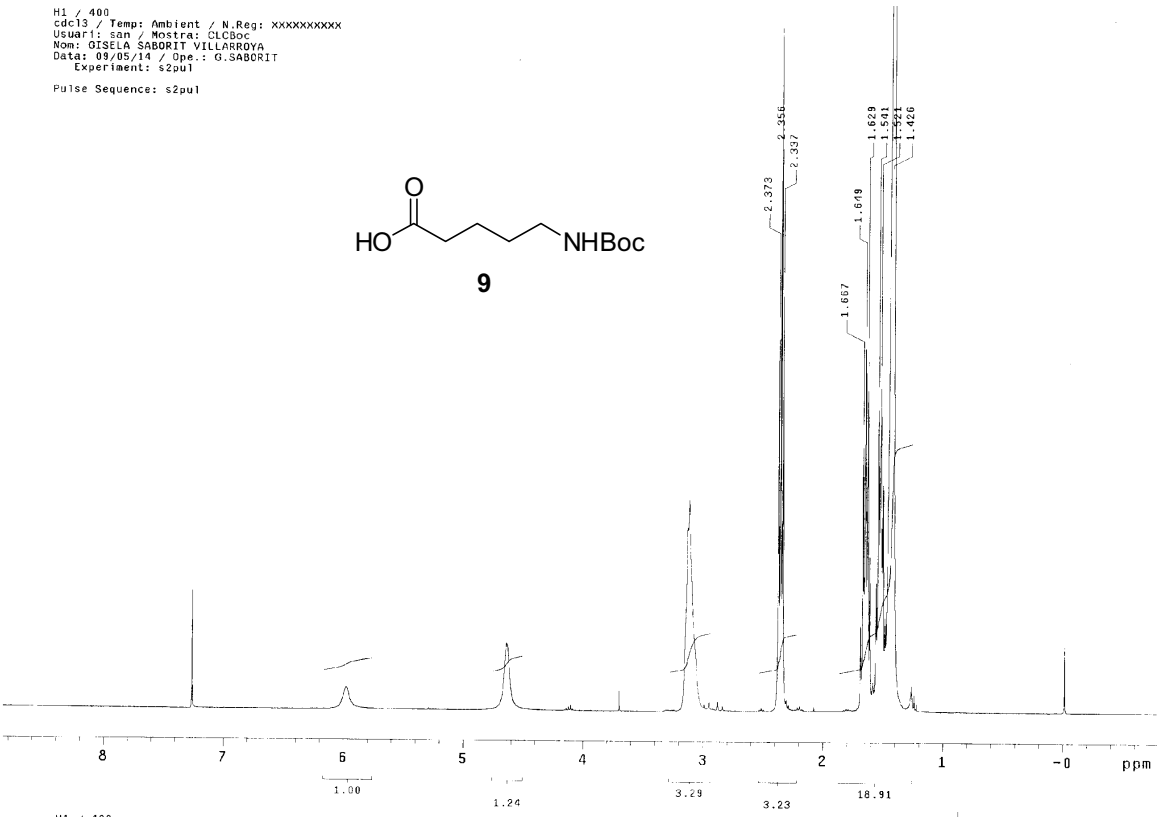
143.462
136.727
129.729
127.042
77.358
77.041
76.723
42.622
33.178
28.773
21.496
200
180
160
140
120
100
80
60
40
20
ppm

**5-(*tert*-Butoxycarbonyl)aminopentanoic acid (9)**




**1** **9**

To a solution of $Boc_2O$ (8.4 g, 38.4 mmol) in dioxane (30 mL) at 0 ºC was added a solution of 5-aminovaleric acid **1** (3.0 g, 25.6 mmol) and $NaHCO_3$ (4.30 g, 51.2 mmol) in water (72 mL) at 5 ºC. The resulting mixture was stirred at 0 ºC for 1 h, then at rt overnight. After TLC control to confirm the reaction was finished, the reaction was quenched by the addition of water (50 mL), and the aqueous layer was extracted twice with EtOAc (2 × 30 mL). The combined aqueous phase was acidified to pH = 1 with 4 N HCl and the acidic phase was extracted with EtOAc (3 × 100 mL), dried and concentrated *in vacuo* to give **9** (5.0 g, 86%) as a white solid. $R_f$ 0.50 (EtOAc); $^1$H NMR (400 MHz, COSY) $\delta$ 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) 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.


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
Pulse Sequence: s2pul
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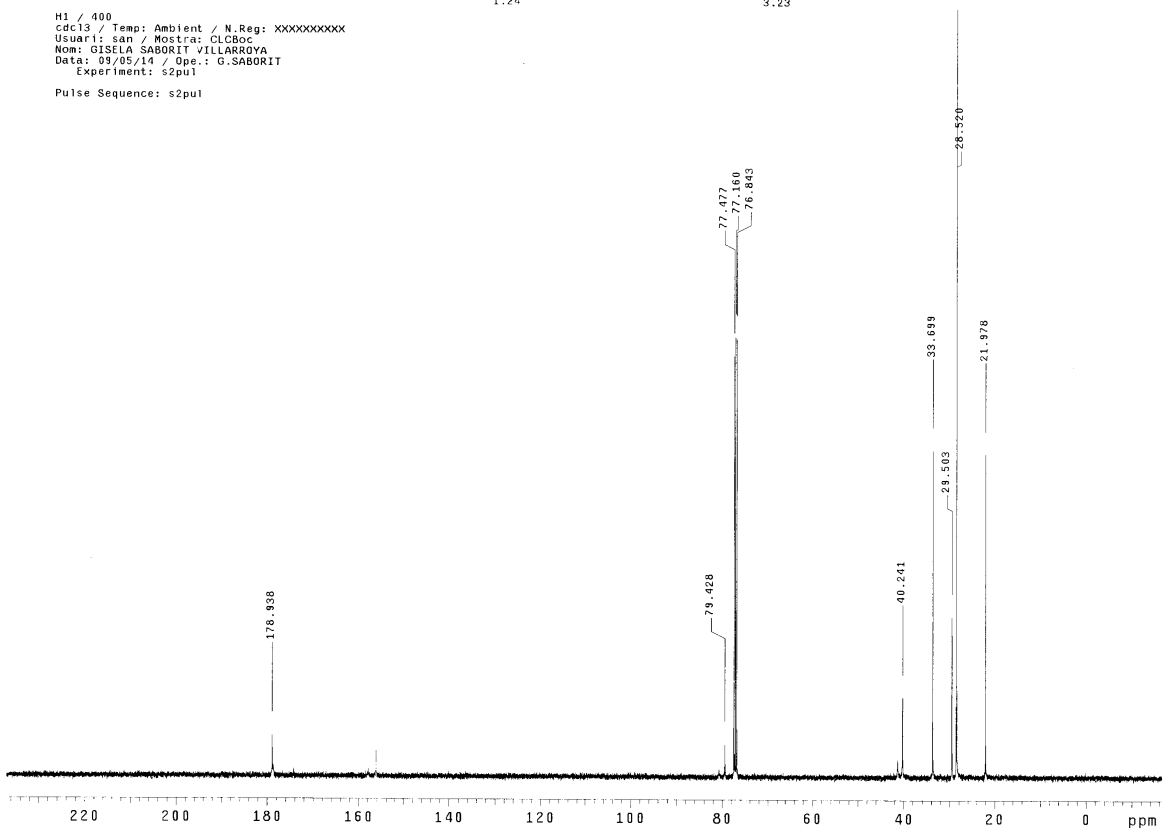
2.337
2.373
1.649
1.667
1.628
1.541
1.521
1.426
8
7
6
5
4
3
2
1
-0
ppm
1.00
1.24
3.29
3.23
18.91

HO NHBoc

O

**9**


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
Pulse Sequence: s2pul
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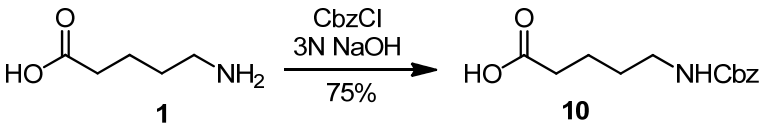
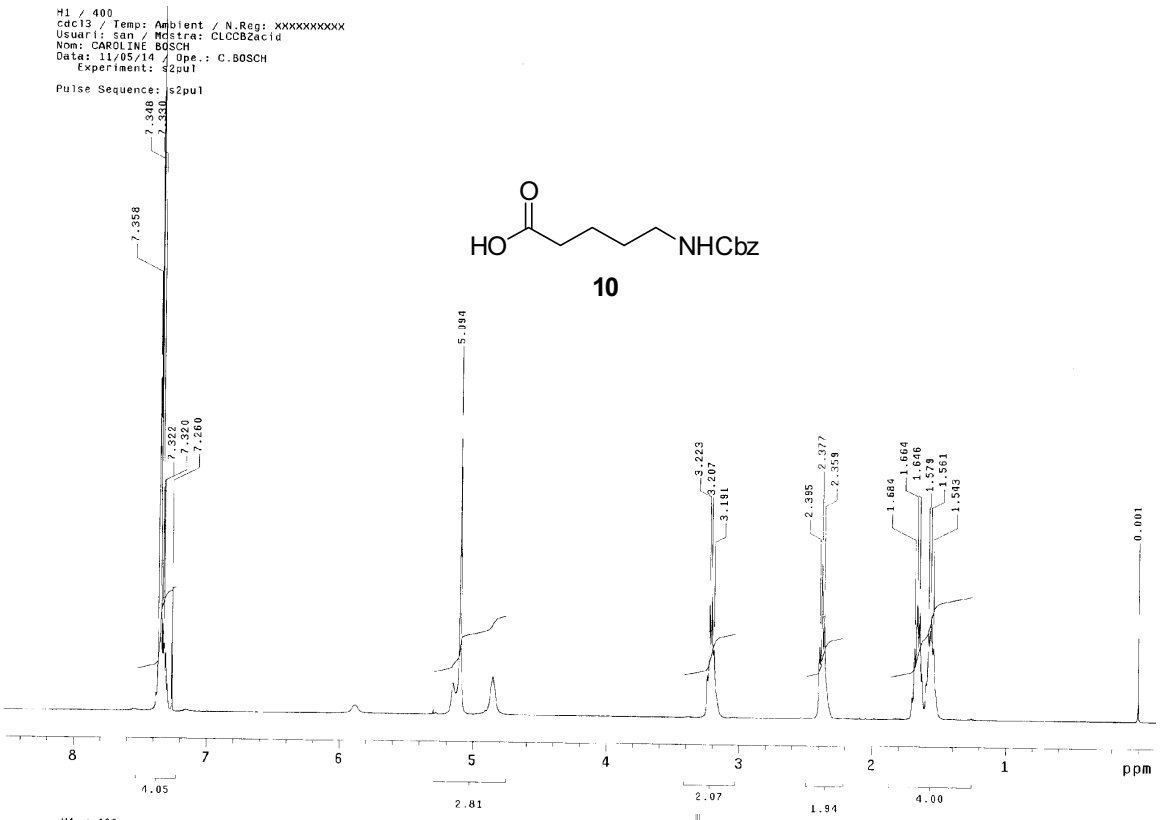
79.428
77.477
77.160
76.843
40.241
33.699
29.503
28.520
21.978
220
200
180
160
140
120
100
80
60
40
20
0
ppm

**5-(Benzyloxycarbonylamino)pentanoic acid (10)**




To a solution of 5-aminovaleric acid **1** (5.0 g, 42.7 mmol) in 3 N NaOH (85 mL) was added CbzCl (6.4 mL, 42.7 mmol) dropwise at 0 ºC. The solution was stirred for 3 h at rt, then the reaction mixture was washed with Et2O (3 × 20 mL), and the aqueous layer was acidified to pH = 1 with 3 N HCl and extracted with EtOAc (3 × 100 mL), dried with Na2SO4 and concentrated in vacuo to give **10** (8.04 g, 75%) as a white powder. $R_f$ 0.50 (EtOAc); $^1$H NMR (400 MHz, COSY) $\delta$ 1.52-1.68 (m, 4H, H-3, H-4), 2.38 (t, $J$ = 7.2 Hz, 2H, H-2), 3.20 (q, $J$ = 6.3 Hz, 2H, H-5), 4.98 (br s, 1H, NH), 5.10 (s, 2H, Ar$CH_2$), 7.33-7.36 (m, 5H, Ar); $^{13}$C NMR (100 MHz, HSQC) 21.8 (C-3), 29.4 (C-4), 33.5 (C-2), 40.7 (C-5), 66.8 (*C*$H_2$Ar), 128.2 (Ar), 128.6 (Ar), 136.7 (Ar), 156.6 (Ar), 178.8 (CO) HRMS calcd for $C_{12}H_{17}NO_4S$ $(M + H)^+$ 252.1238, found 252.1243.


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCCBZacid
Nom: CAROLINE BOSCH
Data: 11/05/14 / Ope.: C.BOSCH
Experiment: s2pul
Pulse Sequence: s2pul
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7.330
7.358
7.322
7.320
7.260
5.094
3.223
3.207
3.191
2.395
2.377
2.359
1.684
1.664
1.646
1.578
1.561
1.543
0.001
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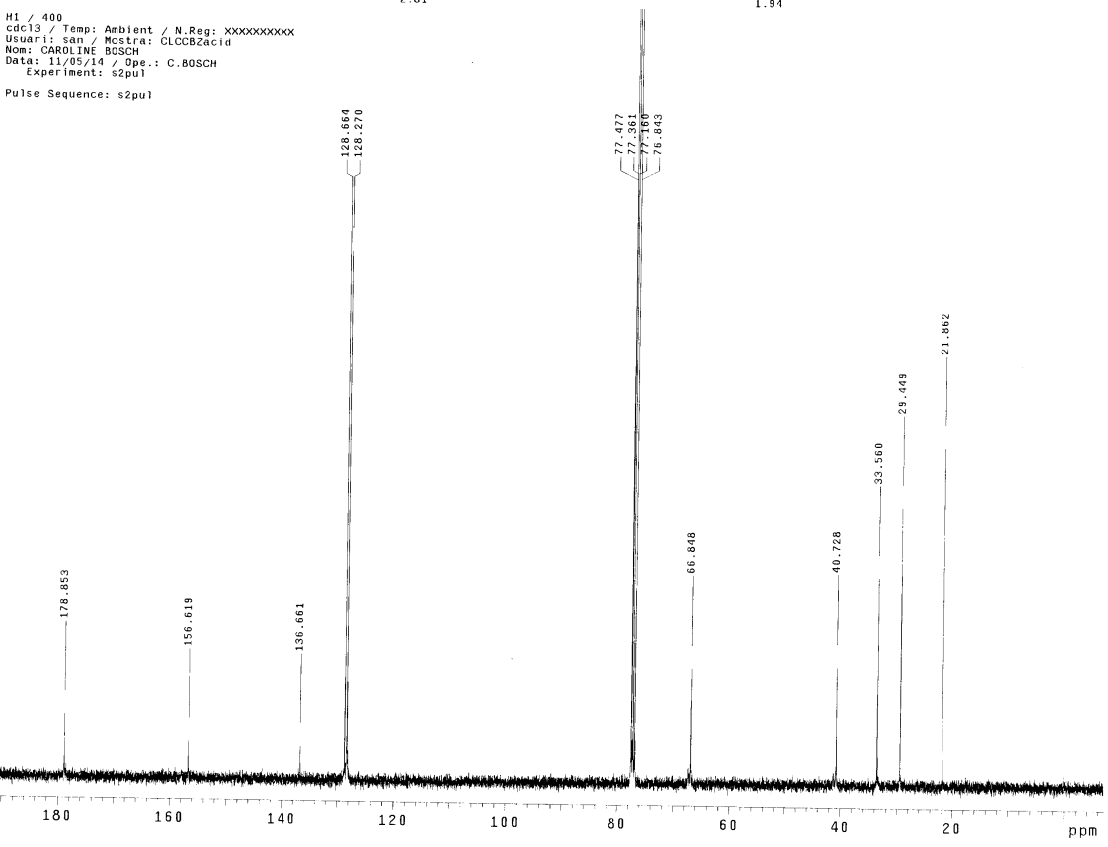
7
6
5
4
3
2
1
ppm
4.05
2.81
2.07
1.94
4.00


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCCBZacid
Nom: CAROLINE BOSCH
Data: 11/05/14 / Ope.: C.BOSCH
Experiment: s2pul
Pulse Sequence: s2pul
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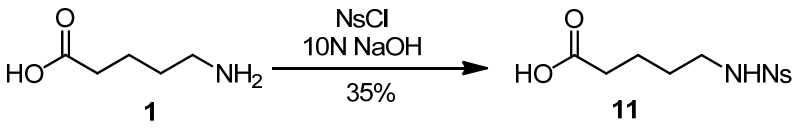
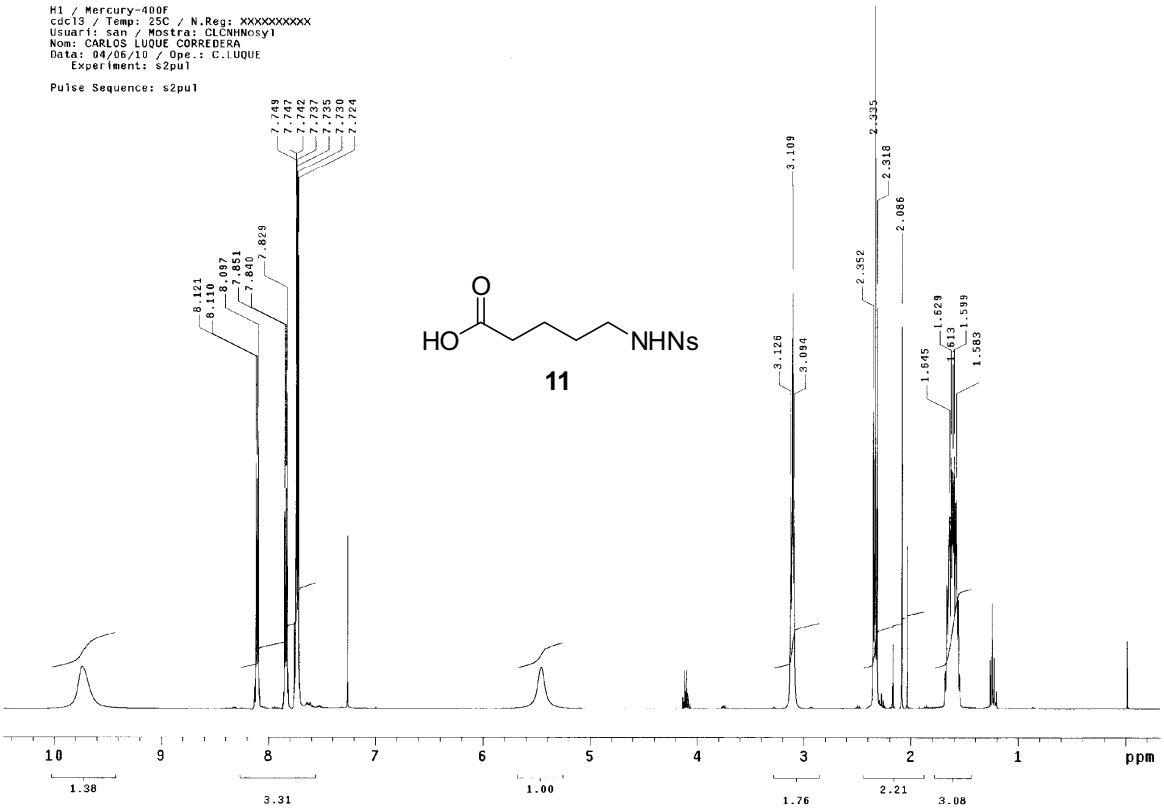
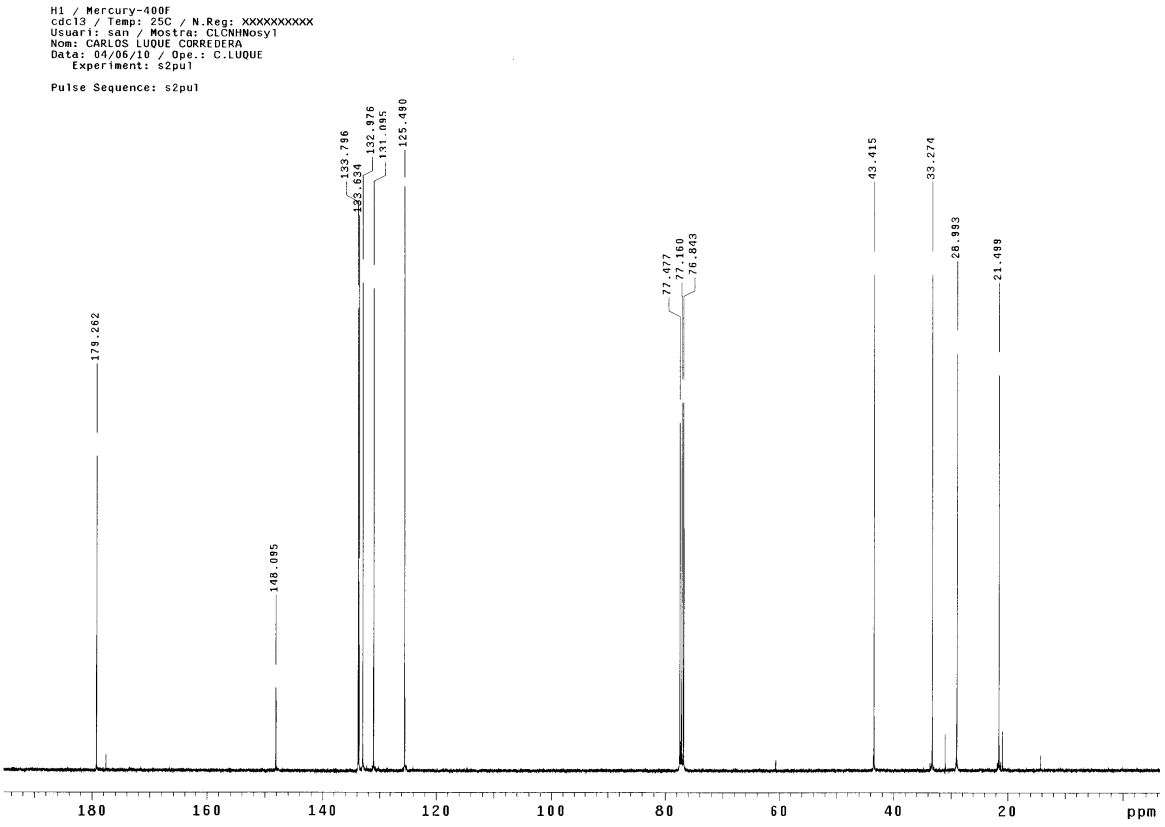
136.661
128.664
128.270
77.477
77.361
77.160
76.843
66.848
40.728
33.560
29.449
21.362
180
160
140
120
100
80
60
40
20
ppm

**5-[(2-Nitrophenyl)sulfonylamino]pentanoic acid (11)**

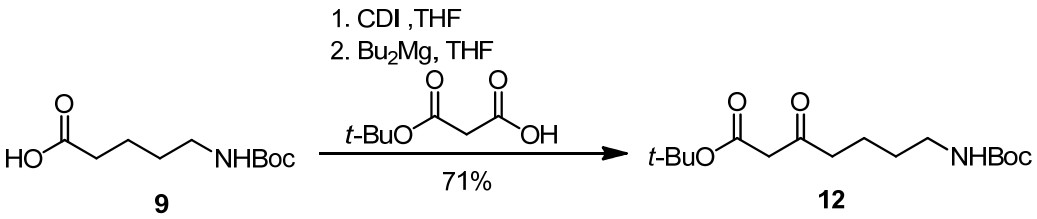



To a solution of 5-aminovaleric acid **1** (2.0 g, 17.1 mmol) in 1 N NaOH (85 mL) at 0 ºC was added a solution of NsCl (8.14 g, 36.7 mmol) in $Et_2O$ (435 mL) dropwise during 30 minutes. The resulting mixture was stirred at rt for 24 h, then the aqueous and the organic layers were separated. The aqueous phase was washed with $Et_2O$ (2 × 30 mL) and acidified to pH = 1 with 2 N HCl. The acidic phase was extracted with EtOAc (3 × 100 mL), dried with $Na_2SO_4$ and concentrated in vacuo to give **11** (1.8 g, 35%) as a brown solid. The crude of the reaction was pure enough and it can be employed in the next step without further purification. $R_f$ 0.50 (EtOAc); $^1$H NMR (400 MHz, COSY) $\delta$ 1.61-1.68 (m, 4H, H-3, H-4), 2.36 (t, $J$ = 6.9 Hz, 2H, H-2), 3.12 (q, $J$ = 6.3 Hz, 2H, H-5), 5.38 (m, 1 H, NH), 7.73-7.76 (m, 2H, Ar), 7.85-7.88 (m, 1H, Ar), 8.12-8.15 (m, 1H, Ar); $^{13}$C NMR (100 MHz, HSQC) 21.5 (C-3), 29.0 (C-4), 33.2 (C-2), 43.4 (C-5), 125.5 (3-Ns), 131.1 (6-Ns), 132.9 (4-Ns), 133.6 (1-Ns), 133.8 (5-Ns), 148.1 (2-Ns), 179.2 (CO) HRMS calcd for $C_{11}H_{15}N_2O_6S$ $(M + H)^+$ 303.0654, found 303.0652.


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCNHNosyl
Nom: CARLOS LUQUE CORREDERA
Data: 04/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.749
7.747
7.742
7.737
7.735
7.730
7.724
8.121
8.110
8.097
7.851
7.840
7.829
3.109
3.126
3.094
2.335
2.318
2.086
2.352
1.629
1.613
1.599
1.583
1.645
O
HO
NHNs
11
10
9
8
7
6
5
4
3
2
1
ppm
1.38
3.31
1.00
1.76
2.21
3.08

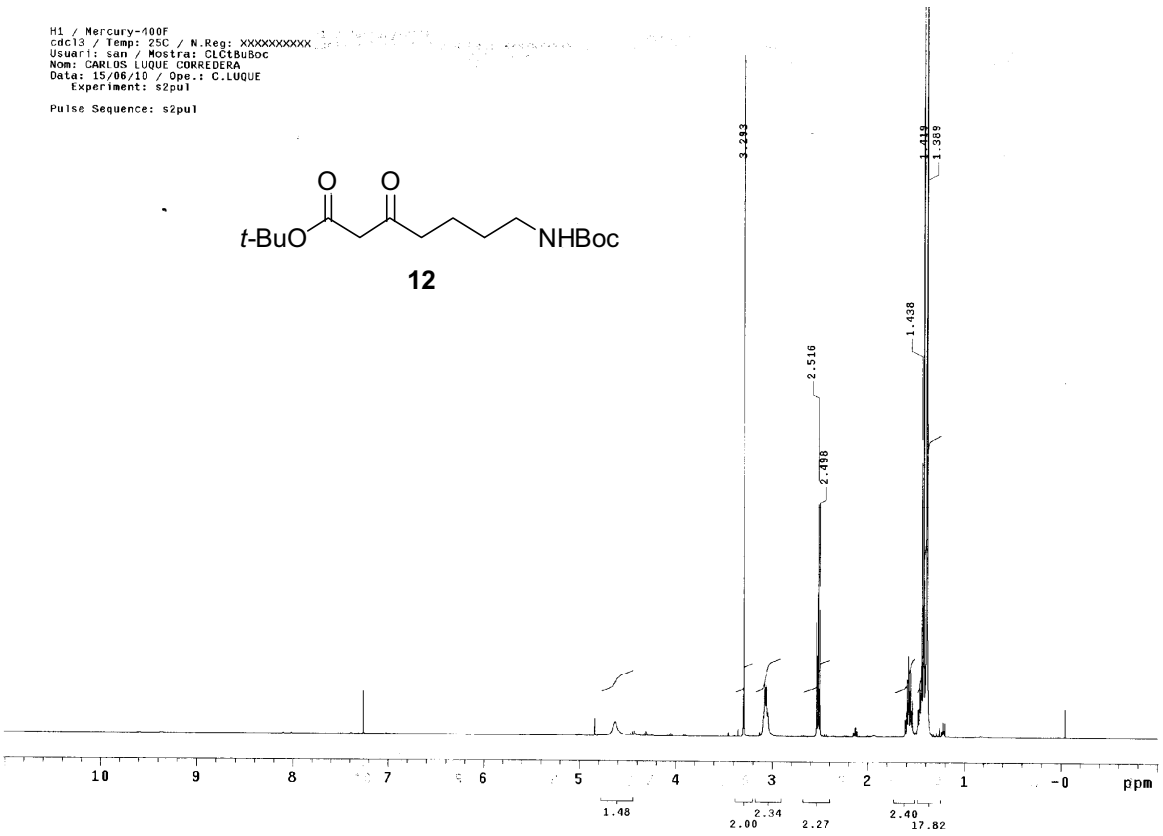

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCNHNosyl
Nom: CARLOS LUQUE CORREDERA
Data: 04/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
179.262
148.095
133.786
133.634
132.976
131.095
125.490
77.477
77.160
76.843
43.415
33.274
28.993
21.499
180
160
140
120
100
80
60
40
20
ppm

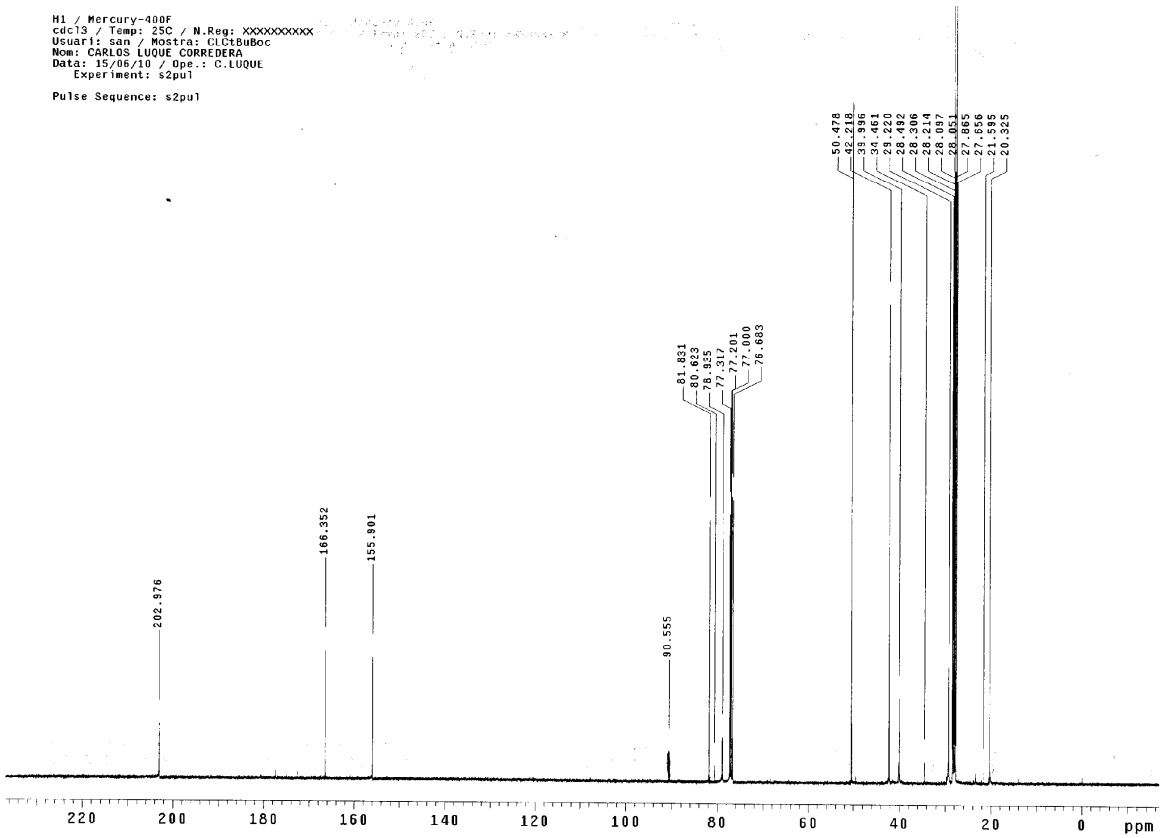
***tert*-Butyl 7-[(*tert*-Butoxycarbonyl)amino]-3-oxoheptanoate (12)**



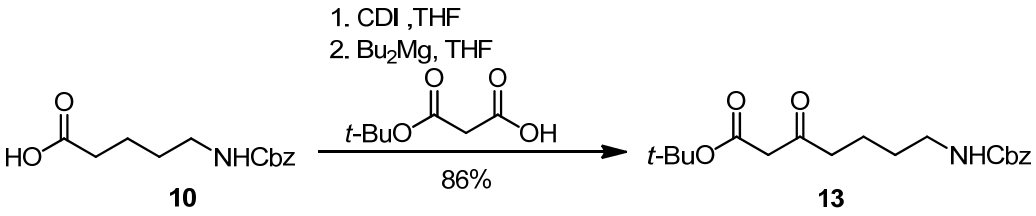

**9** **12**

Dibutyl magnesium (Aldrich, 1 M in hexane, 6.26 mL, 6.26 mmol) was added to a solution of mono-*tert*-butylmalonate (2.01 g, 12.5 mmol) in THF (50 mL). The mixture was stirred for 15 min at -78 ºC, warmed to room temperature and stirred for 1 h. Concurrently, in a separate flask carbonyldiimidazole (CDI) (1.11 g, 6.83 mmol) was added to a solution of 5-((tert-butyloxycarbonyl)amino)pentanoic acid **9** (1.24 g, 5.69 mmol) in THF (50 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. The resulting mixture was stirred overnight at room temperature, quenched with 10% citric acid solution (8.5 mL/mmol substrate), the layers were separated and the aqueous phase was extracted twice with $Et_2O$ (3 × 3 mL/mmol of substrate). The combined organic extracts were washed with saturated aq $NaHCO_3$ solution, brine, dried and concentrated *in vacuo*. Purification by column chromatography (5→10→25% EtOAc in hexanes) gave **12** (1.22 g, 71%); $^1$H NMR (400 MHz, COSY, $CDCl_3$) δ 1.39 (s, 9H, $CH_3$), 1.42 (s, 9H, $CH_3$), 1.45 (masked, 2H, H-6), 1.56 (m, 2H, 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 ($CH_3$), 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.


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
Pulse Sequence: s2pul
t-BuO
NHBoc
12
3.243
2.516
2.498
1.438
1.419
1.389
1.48
2.34
2.00
2.27
2.40
17.82
ppm

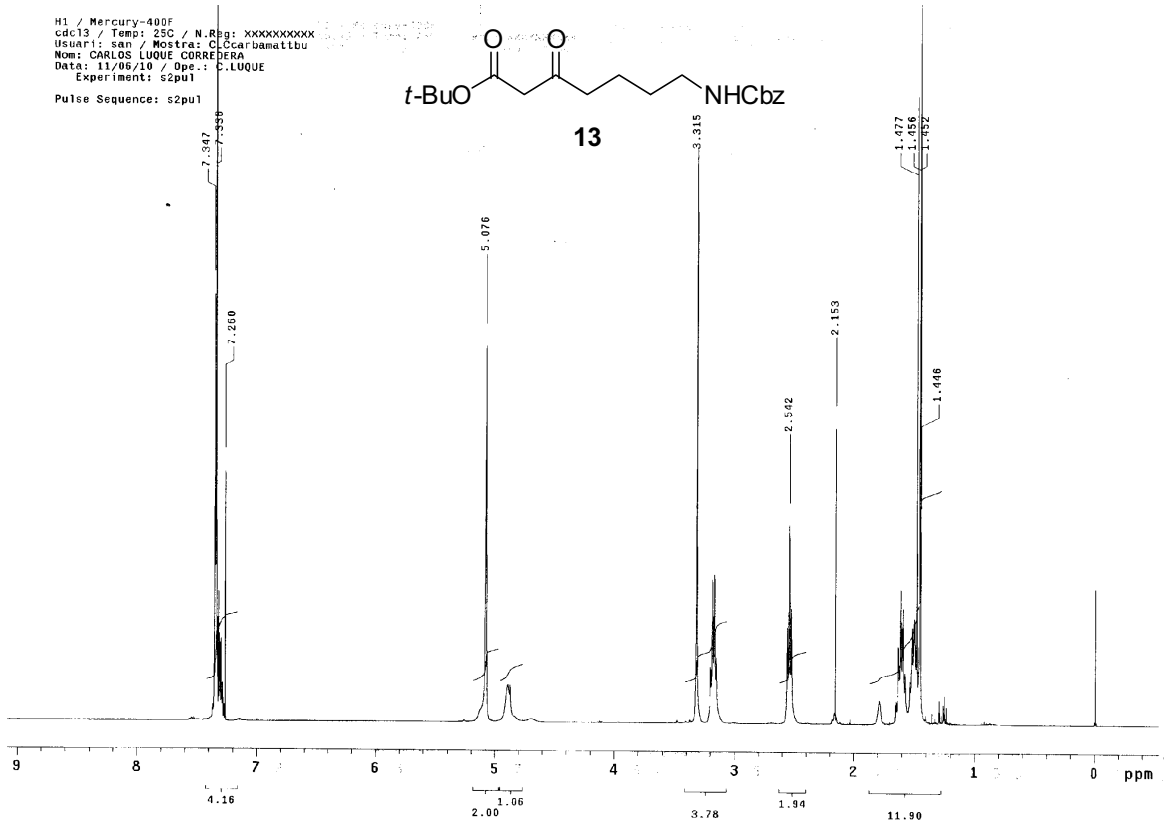

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCtBuBoc
Nom: CARLOS LUQUE CORREDERA
Data: 15/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
202.976
166.352
155.801
90.555
81.831
80.623
78.855
77.317
77.201
77.000
76.683
50.478
42.218
38.886
34.461
29.220
28.492
28.306
28.214
28.097
28.051
27.865
27.656
21.595
20.325
ppm

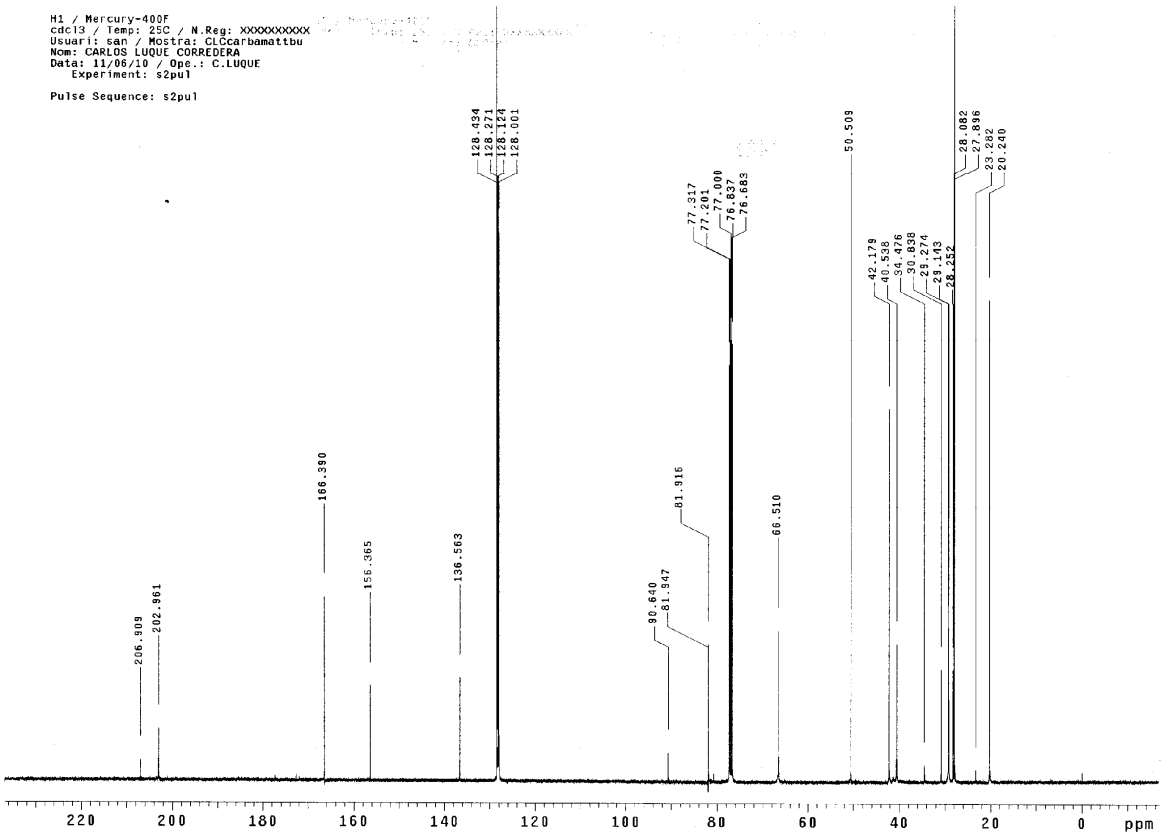
***tert*-Butyl 7-[(Benzyloxycarbonyl)amino]-3-oxoheptanoate (13)**



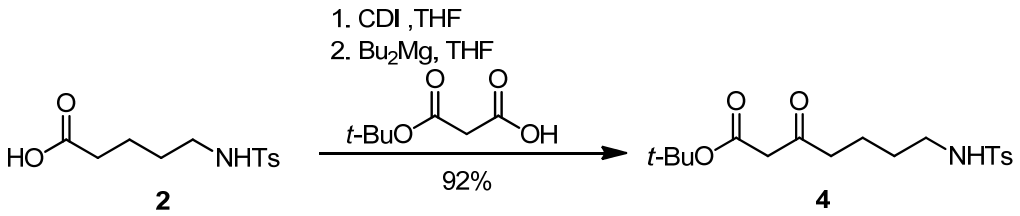

**10** **13**

Dibutyl magnesium (Aldrich, 1 M in heptane, 8 mL, 8 mmol) was added to a solution of mono-*tert*-butylmalonate (2.52 g, 15.73 mmol) in THF (35 mL). The mixture was stirred for 15 min at -78 ºC, warmed to room temperature and stirred for 1 h. Concurrently, in a separate flask carbonyldiimidazole (CDI) (1.39 g, 8.58 mmol) was added to a solution of 5-[(benzyloxycarbonyl)amino]pentanoic acid **10** (1.8 g, 7.16 mmol) in THF (35 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. The resulting mixture was stirred overnight at room temperature, quenched with 10% citric acid solution (8.5 mL/mmol substrate), the layers were separated and the aqueous phase was extracted twice with $Et_2O$ (3 × 3 mL/mmol of substrate). The combined organic extracts were washed with saturated aq $NaHCO_3$ solution, brine, dried and concentrated *in vacuo*. Purification by column chromatography (5→10→25% EtOAc in hexanes) gave **13** (2.15g, 86%); $^1$H NMR (400 MHz, COSY, $CDCl_3$) $\delta$ 1.46 (s, 9H, ($CH_3$)$_3$C), 1.50 (quint, *J* = 7.6 Hz, 2H, H-6), 1.61 (quint, *J* = 7.6 Hz, 2H, H-5), 2.55 (t, *J* = 6.8 Hz, 2H, H-4), 3.19 (q, *J* = 6.4 Hz, 2H, H-7), 3.32 (s, 2H, H-2), 4.85 (s, 1H, NH), 5.08 (s, 2H, $CH_2$Ar), 7.28-7.37 (m, 5H, Ar); $^{13}$C NMR (100 MHz, HSQC) δ 20.3 (C-5), 27.9 ($CH_3$), 29.2 (C-6), 40.6 (C-7), 42.2 (C-4), 50.6 (C-2), 66.6 ($CH_2$Ar), 82.0 (C), 128.0 (Ar), 128.2 (Ar), 128.5 (Ar), 136.6 (Ar), 156.4 (CO), 166.4 (C-1), 203.0 (C-3). HRMS calcd for $C_{19}H_{28}NO_5$ ($MH^+$) 350.1971.


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCcarbamattbu
Nom: CARLOS LUQUE CORREDERA
Data: 11/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
t-BuO
NHCbz
13
7.347
7.330
7.260
5.076
3.315
2.542
2.153
1.477
1.456
1.452
1.446
4.16
2.00
1.06
3.78
1.94
11.90
ppm


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCcarbamattbu
Nom: CARLOS LUQUE CORREDERA
Data: 11/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
206.909
202.961
166.380
156.365
136.563
128.434
128.271
128.124
128.001
90.640
81.947
81.916
77.317
77.201
77.000
76.837
76.683
66.510
50.509
42.179
40.536
40.276
34.838
29.274
28.143
28.252
28.082
27.896
23.202
20.240
ppm

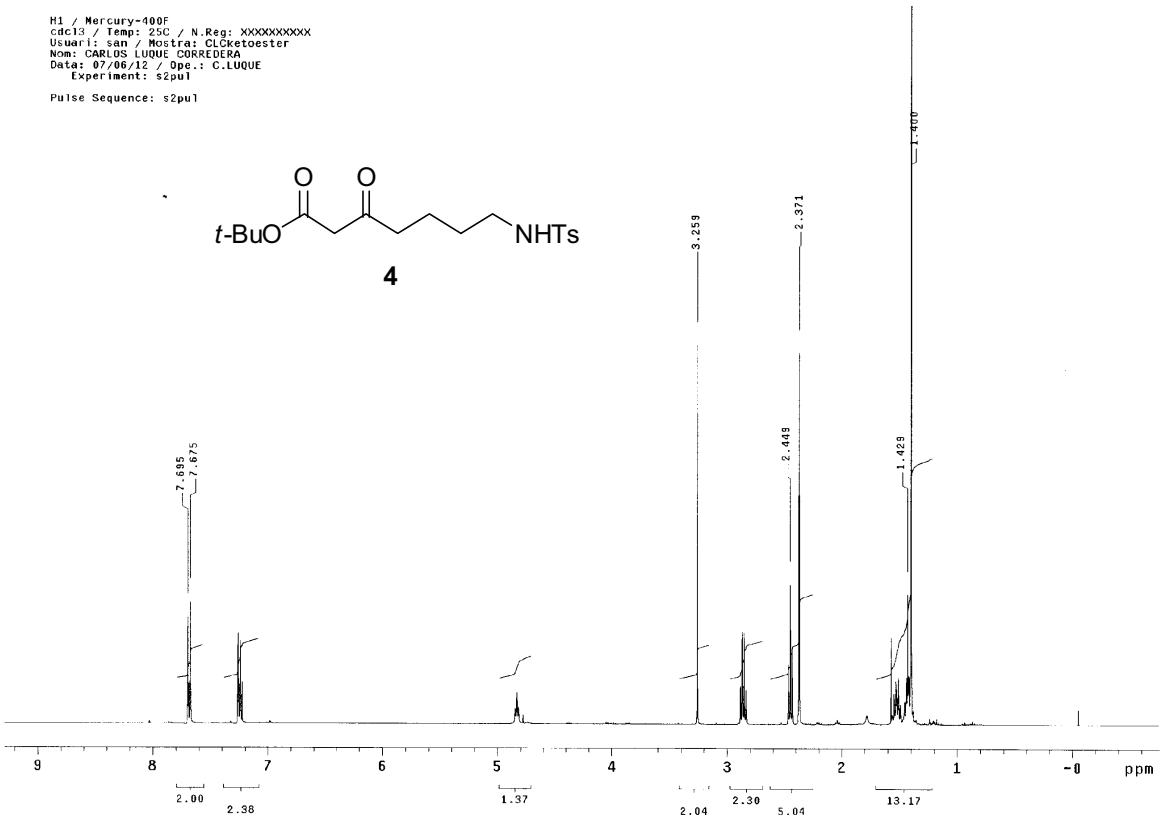
***tert*-Butyl 7-(4-Methylphenylsulfonamido)-3-oxoheptanoate (4)**

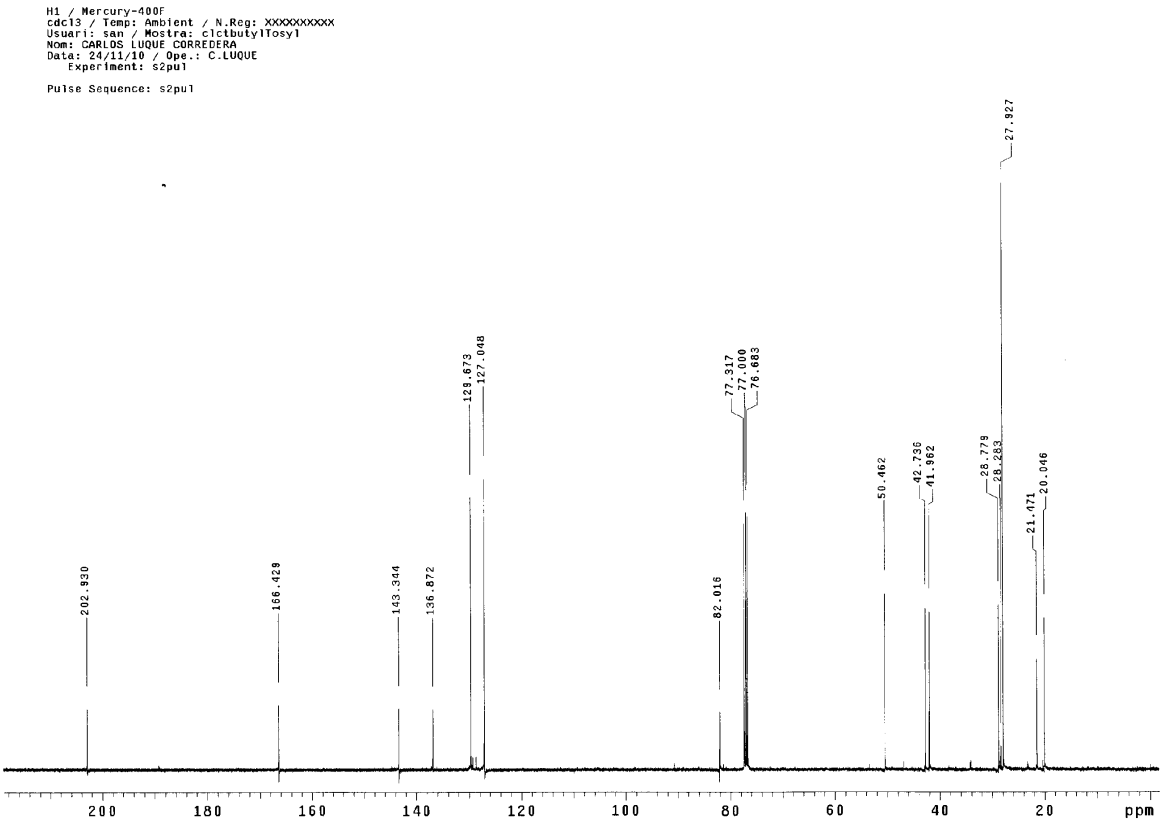



**2** **4**

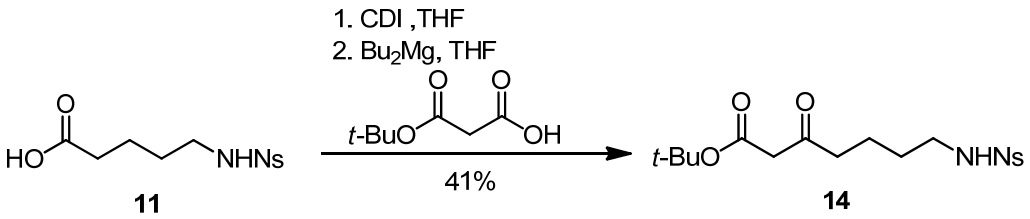
Dibutyl magnesium (Aldrich, 1 M in heptane, 18.5 mL, 18.5 mmol) was added to a solution of mono-*tert*-butylmalonate (8.2 mL, 55.5 mmol, 3 equiv[123]) in THF (160 mL). The mixture was stirred for 15 min at -78 ºC, warmed to room temperature and stirred for 1 h. Concurrently, in a separate flask carbonyldiimidazole (CDI) (4.5 g, 27.7 mmol) was added to a solution of 5-(4-methylphenylsulfonamido)pentanoic acid **2** (5.0 g, 18.5 mmol) in THF (160 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. The resulting mixture was stirred overnight at room temperature, quenched with 10% citric acid solution (8.5 mL/mmol substrate), the layers were separated and the aqueous phase was extracted twice with $Et_2O$ (3 × 3 mL/mmol of substrate). The combined organic extracts were washed with saturated aq. $NaHCO_3$ solution, brine, dried and concentrated *in vacuo*. Purification by column chromatography (5→10→25% EtOAc in hexanes) gave **4** (6.3 g, 92%); $^1$H NMR (400 MHz, COSY) $\delta$ 1.45 (s, 9H, $C(CH_3)_3$), 1.48 (m, 2H, H-5), 1.58 (m, 2H, H-6), 2.42 (s, 3H, $CH_3$), 2.50 (t, *J* = 7.0 Hz, 2H, H-4), 2.91 (q, *J* = 6.4 Hz, 2H, H-7), 3.30 (s, 2H, H-2), 4.70 (t, *J* = 6.4 Hz, 1H, NH), 7.31 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.73 (d, *J* = 8.0 Hz, 2H, *o*-Ts); $^{13}$C NMR (400 MHz, HSQC) δ 20.1 (C-6), 21.5 ($ArCH_3$), 28.0 ($CH_3$), 28.8 (C-5), 42.0 (C-4), 42.8 (C-7), 50.5 (C-2), 82.0 (C), 127.0 (*o*-Ts), 129.7 (*m*-Ts), 136.9 (*p*-Ts), 143.4 (*ipso*-Ts), 166.4 (C-1), 202.9 (C-3).

[123] 2 equivalents of *tert*-butyl malonate were used. In optimization studies it was observed that better results for the tosyl protected substrate were achieved with 3 equiv.


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCketoester
Nom: CARLOS LUQUE CORREDERA
Data: 07/06/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
O
O
t-BuO
NHTs
4
7.695
7.675
3.259
2.449
2.371
1.429
1.400
9
8
7
6
5
4
3
2
1
-0
ppm
2.00
2.38
1.37
2.04
2.30
5.04
13.17

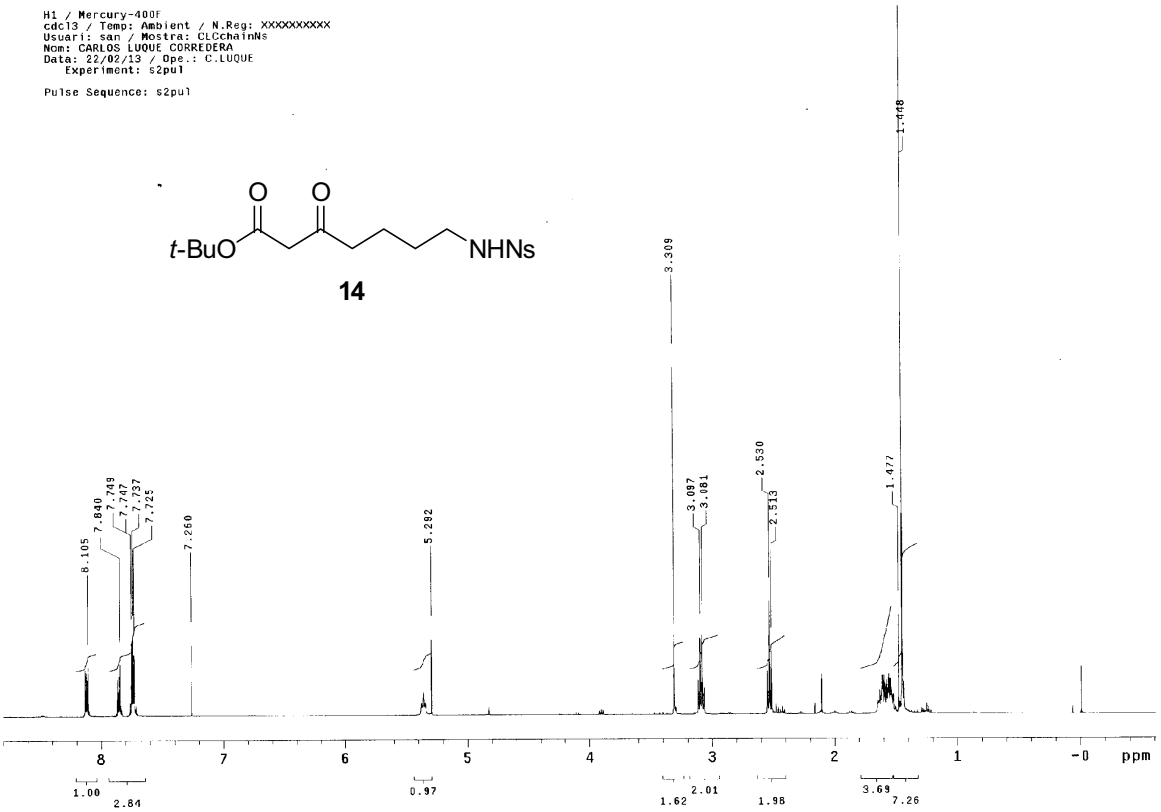

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: clctbutylTosyl
Nom: CARLOS LUQUE CORREDERA
Data: 24/11/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
202.930
166.428
143.344
136.872
129.673
127.048
82.016
77.317
77.000
76.683
50.462
42.736
41.962
28.779
28.283
27.927
21.171
20.046
200
180
160
140
120
100
80
60
40
20
ppm

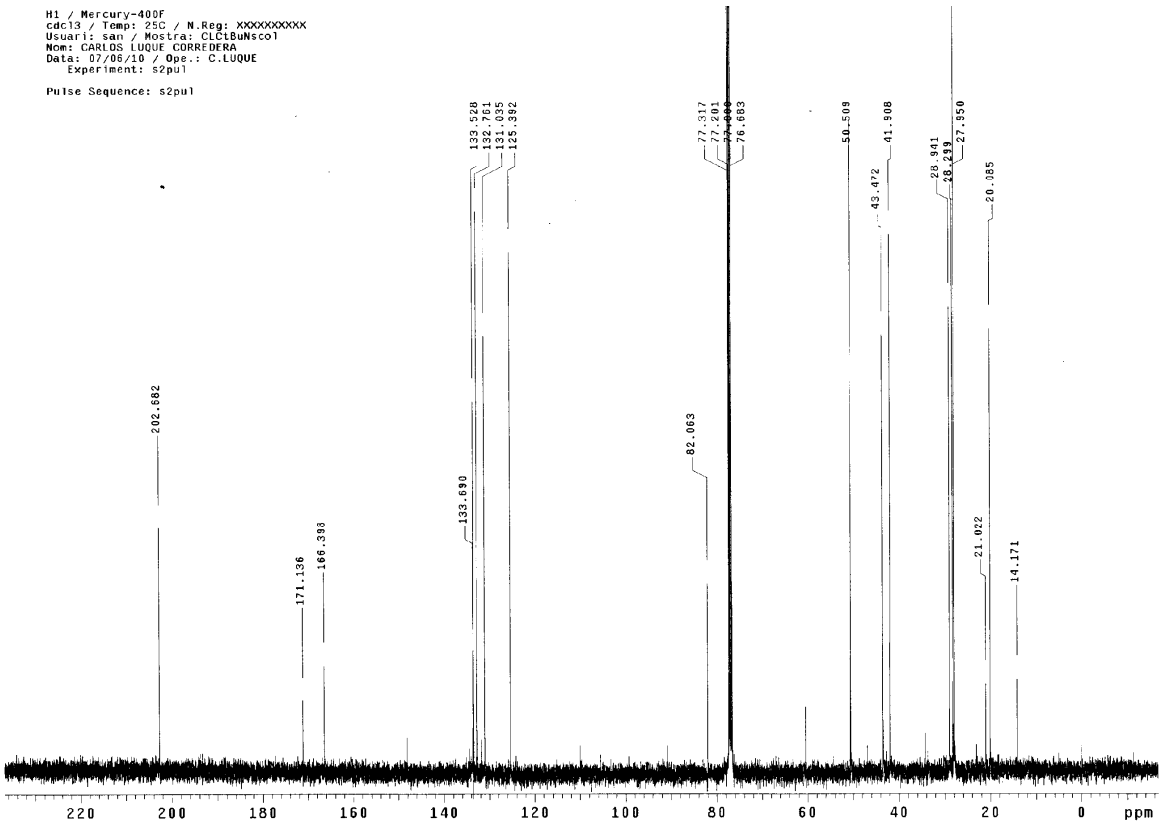
***tert*-Butyl 7-(2-Nitrophenylsulfonamido)-3-oxoheptanoate (14)**



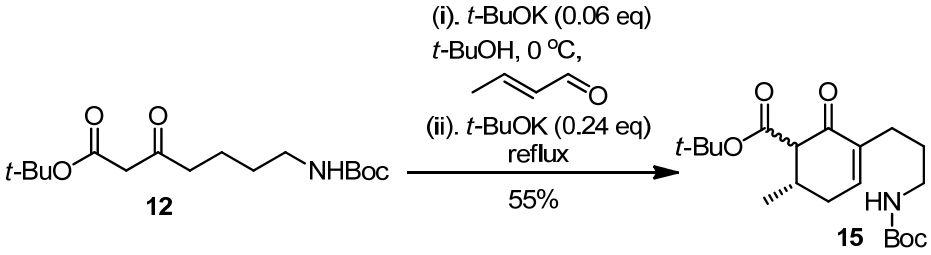

**11** **14**

Dibutyl magnesium (Aldrich, 1 M in heptane, 3.4 mL, 3.4 mmol) was added to a solution of mono-*tert*-butylmalonate (1.0 mL, 6.8 mmol) in THF (30 mL). The mixture was stirred for 15 min at -78 ºC, warmed to room temperature and stirred for 1 h. Concurrently, in a separate flask carbonyldiimidazole (CDI) (551 mg, 3.4 mmol) was added to a solution of 5-(2-nitrophenylsulfonamido)pentanoic acid **11** (974 mg, 3.4 mmol) in THF (30 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. The resulting mixture was stirred overnight at room temperature, quenched with 10% citric acid solution (8.5 mL/mmol substrate), the layers were separated and the aqueous phase was extracted twice with $Et_2O$ (3 × 3 mL/mmol of substrate). The combined organic extracts were washed with saturated aq $NaHCO_3$ solution, brine, dried and concentrated *in vacuo*. Purification by column chromatography (5→10→25% EtOAc in hexanes) gave **14** (537 mg, 41%); $^1$H NMR (400 MHz, COSY) $\delta$ 1.45 (s, 9H, $C(CH_3)_3$), 1.6 (m, 4H, H-5, H-6), 2.53 (t, *J* =6.8 Hz, 2H, H-4), 3.09 (q, *J* = 6.4 Hz, 2H, H-7), 3.31 (s, 2H, H-2), 5.34 (t, *J* = 6.4 Hz, 1H, NH), 7.74 (m, 2H), 7.86 (m, 1H), 8.12 (m, 1H). $^{13}$C NMR (400 MHz, HSQC) δ 20.1 (C-6), 28.0 ($CH_3$), 28.9 (C-5), 42.0 (C-4), 43.5 (C-7), 50.5 (C-2), 82.1 (C), 125.4 (3-Ns), 131.0 (6-Ns), 132.8 (4-Ns), 133.5 (5-Ns),133.7(1-Ns), 148.0 (2-Ns), 166.4 (C-1), 202.7 (C-3). HRMS calcd for $C_{17}H_{28}N_3O_7S$ (M + $NH_4^+$) 418.1642, found 418.1643.

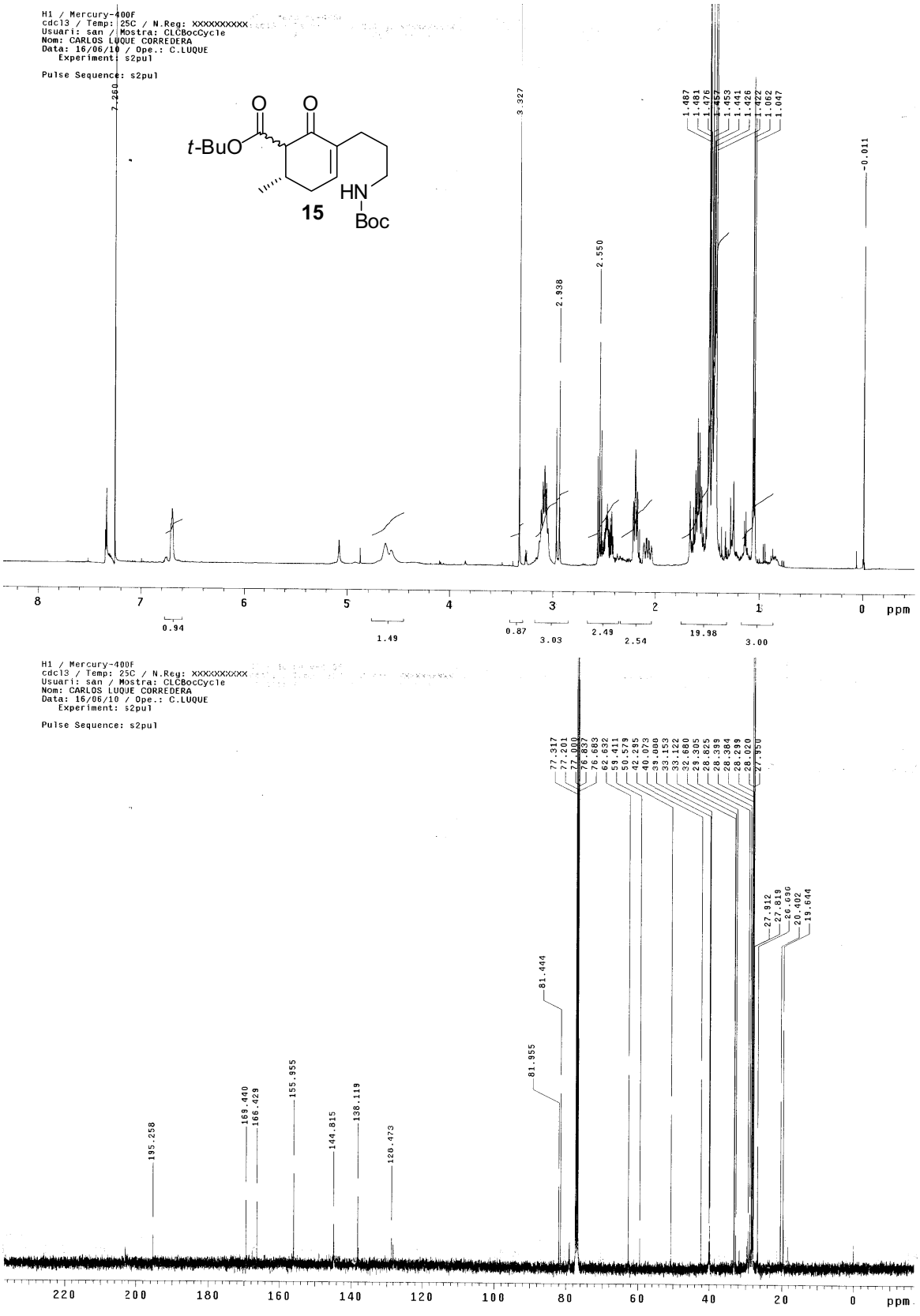

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCchainNs
Nom: CARLOS LUQUE CORREDERA
Data: 22/02/13 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
O
O
t-BuO
NHNs
14
8.105
7.840
7.749
7.747
7.737
7.725
7.260
5.282
3.309
3.097
3.081
2.530
2.513
1.477
1.448
ppm
1.00
2.84
0.97
1.62
2.01
1.98
3.69
7.26


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCtBuNscol
Nom: CARLOS LUQUE CORREDERA
Data: 07/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
202.682
171.136
166.398
133.690
133.528
132.761
131.035
125.392
82.063
77.317
77.201
76.683
50.509
43.472
41.908
28.941
28.249
27.950
20.985
21.022
14.171
ppm

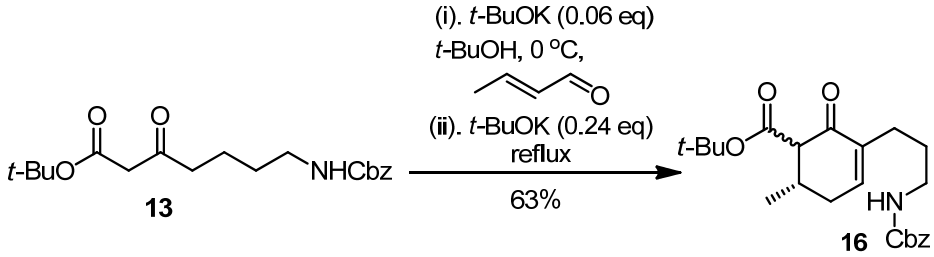
***tert*-Butyl-3-[3-(tert-Butoxycarbonylamino)propyl]-6-methyl-2-oxocyclohex-3-enecarboxylate (15)**



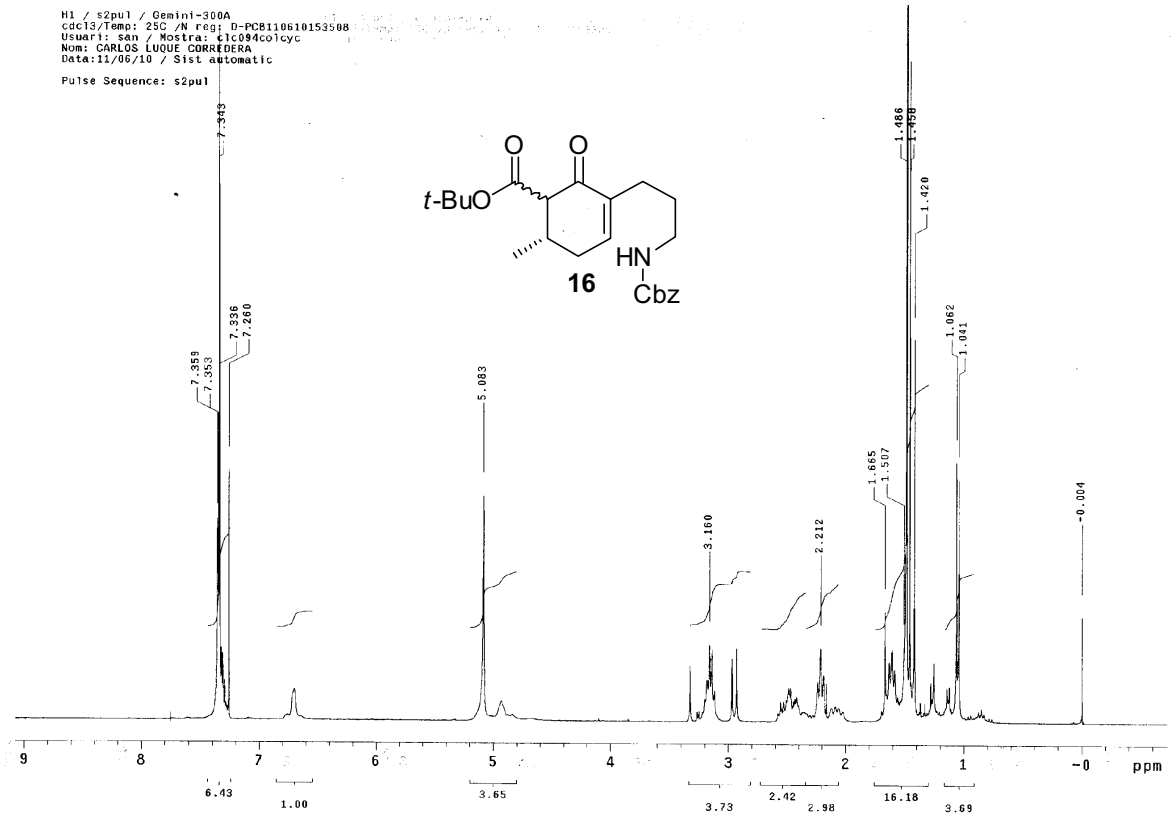

To a solution of β-keto ester **12** (304 mg, 1 mmol) in *tert*-butanol (1 mL) was added crotonaldehyde (77 mg, 1.10 mmol). After stirring for 5 min at room temperature the solution was cooled to 0 ºC and potassium *tert*-butoxide (6.7 mg, 0.06 equiv) were added. The reaction was stirred for 30 min at room temperature and a further portion of potassium *tert*-butoxide (27 mg, 0.24 equiv) was added. The reaction mixture was heated to reflux for 24 h, cooled to room temperature and quenched by the addition of sat $NH_4Cl$ (aq) (1.5 mL/mmol), diluted with $Et_2O$ (8.6 mL/mmol) and the phases separated, brine (2 x 3 mL/mmol), dried and concentrated *in vacuo*. Purificacion by column chromatography ($SiO_2$, 5→25% EtOAc in hexane) gave **15** (204 mg, 55%); $^1H$ NMR (400 MHz, COSY) $\delta$ 1.04 (d, $J$ = 6.4 Hz, 3H, $CH_3$), 1.41 (s, 9H, ($CH_3$), 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.

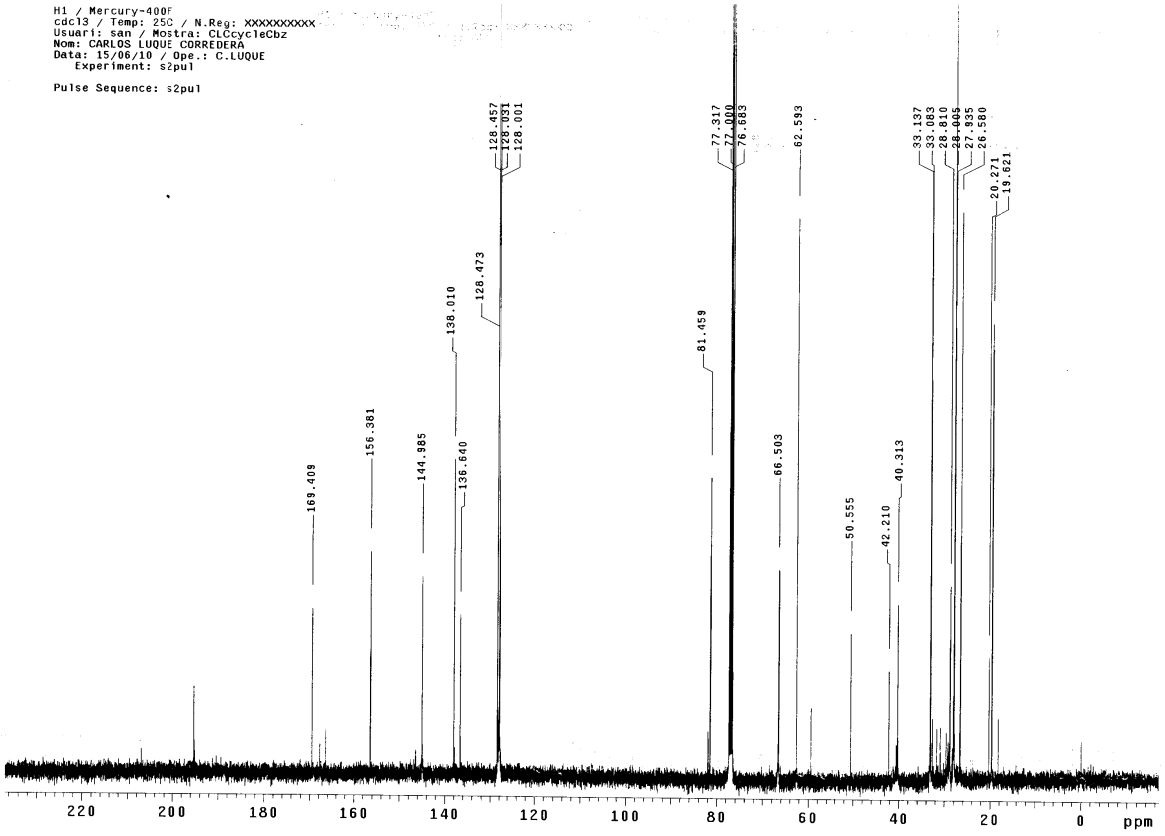

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCBocCycle
Nom: CARLOS LUQUE CORREDERA
Data: 16/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
t-BuO
O
O
HN
Boc
15
7.260
3.327
2.938
2.550
1.487
1.481
1.476
1.457
1.453
1.441
1.426
1.422
1.062
1.047
-0.011
0.94
1.49
0.87
3.03
2.49
2.54
19.98
3.00
ppm
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
Pulse Sequence: s2pul
77.317
77.201
77.000
76.837
76.683
62.632
59.411
50.579
42.295
40.073
33.080
33.155
33.122
32.680
28.305
28.825
28.399
28.384
28.299
28.020
27.950
27.912
27.819
20.402
19.644
81.444
81.955
195.258
169.440
166.429
155.955
144.815
138.119
120.473
ppm

**_tert_-Butyl-3-[3-(Benzyloxycarbonylamino)propyl]-6-methyl-2-oxocyclohex-3-enecarboxylate (16)**

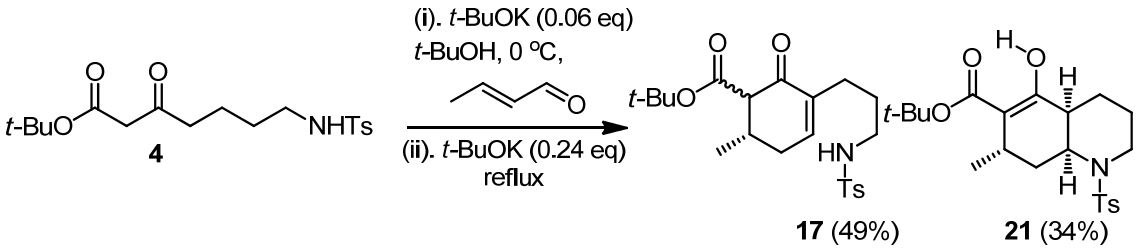



To a solution of β-keto ester **13** (200 mg, 0.525 mmol) in *tert*-butanol (5 mL) was added crotonaldehyde (41 mg, 0.58 mmol). After stirring for 5 min at room temperature the solution was cooled to 0 ºC and potassium *tert*-butoxide (3.5 mg, 0.06 equiv) were added. The reaction was stirred for 30 min at room temperature and a further portion of potassium *tert*-butoxide (14 mg, 0.24 equiv) was added. The reaction mixture was heated to reflux for 24 h, cooled to room temperature and quenched by the addition of sat $NH_4Cl$ (aq) (1.5 mL/mmol), diluted with $Et_2O$ (8.6 mL/mmol) and the phases separated, brine (2 x 3 mL/mmol), dried and concentrated *in vacuo*. Purificacion by column chromatography ($SiO_2$, 5→25% EtOAc in hexane) gave **16** (132 mg, 63%) as a yellow oil; $^1H$ RMN (300 MHz, COSY) $\delta$ 1.05 (d, *J* = 6.3 Hz, 3H, $CH_3$), 1.48 (s, 9H, $CH_3$), 1.60 (quint, *J* = 7.5 Hz, 2H, H-2´), 2.08 (ddm, *J* = 15.8 12.0 Hz, 1H, H-5ax), 2.21 (t, *J* = 7.5 Hz, 2H, H-1´), 2.48 (dt, *J* = 14.8 Hz, *J* = 6 Hz, 1H, H-5eq), 2.95 (d, *J* = 11.7 Hz, 1H, H-1ax), 3.16 (q, *J* = 7.5 Hz, 2H, H-3´), 4.93 (br, 1H, NH), 5.08 (s, 2H, $CH_2Ph$), 6.70 (br s, 1H, H-4), 7.30-7,35 (m, 5H, Ph); $^{13}C$ NMR (400 MHz, HSQC) 19.6 ($CH_3$), 26.6 (C-1´), 28.0 (($CH_3$)$_3$C), 28.8 (C-2´), 33.0 (C-5), 33.1 (C-6), 40.3 (C-3´), 62.6 (C-1), 66.5 ($CH_2Ph$), 81.4 (C), 128.0, 128.1, 128.5, 136.6 ($CH_2Ph$), 138.0 (C-3), 144.9 (C-4), 156.3 (NH*C*O), 169.4 ($CO_2$*t*Bu), 195.2 (C-2). HRMS calcd for $C_{23}H_{32}NO_5$ (M + $H^+$) 402.2266, found 402.2275.


H1 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: D-PCB110610153508
Usuari: san / Mostra: clc094colcyc
Nom: CARLOS LUQUE CORREDERA
Data:11/06/10 / Sist automatic
Pulse Sequence: s2pul
t-BuO
HN
Cbz
16
7.343
7.336
7.260
7.359
7.353
5.083
3.160
2.212
1.665
1.507
1.486
1.458
1.420
1.062
1.041
-0.004
6.43
1.00
3.65
3.73
2.42
2.98
16.18
3.69
ppm


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCcycleCbz
Nom: CARLOS LUQUE CORREDERA
Data: 15/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
169.409
156.381
144.985
138.010
136.640
128.473
128.457
128.031
128.001
81.459
77.317
77.000
76.683
66.503
62.593
50.555
42.210
40.313
33.137
33.083
28.810
28.005
27.835
26.580
20.271
19.621
ppm

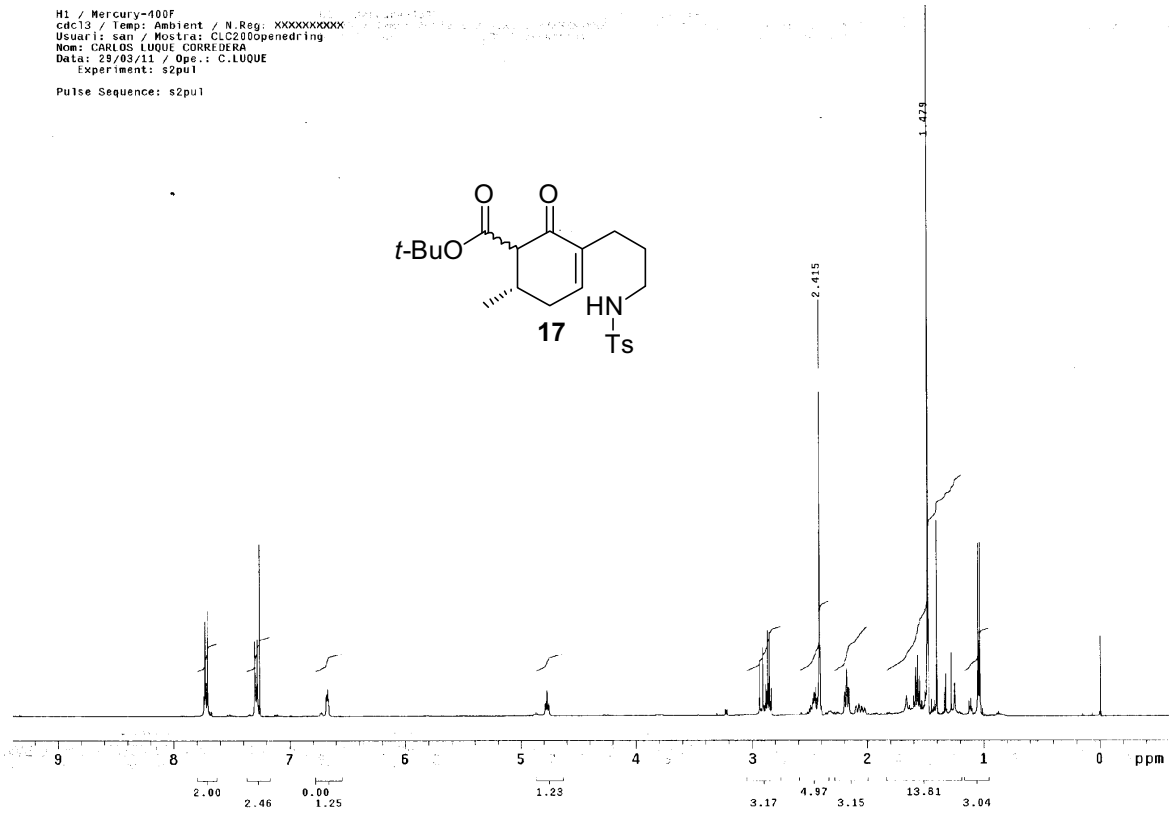
**_tert_-Butyl 6-Methyl-3-(3-(4-methylphenylsulfonamido)propyl)-2-oxocyclohex-3-enecarboxylate (17) and _tert_-butyl _(4aRS,7RS,8aRS)_-7-methyl-1-(4-methylphenylsulfonyl)-5-oxodecahydroquinoline-6-carboxylate (21)**

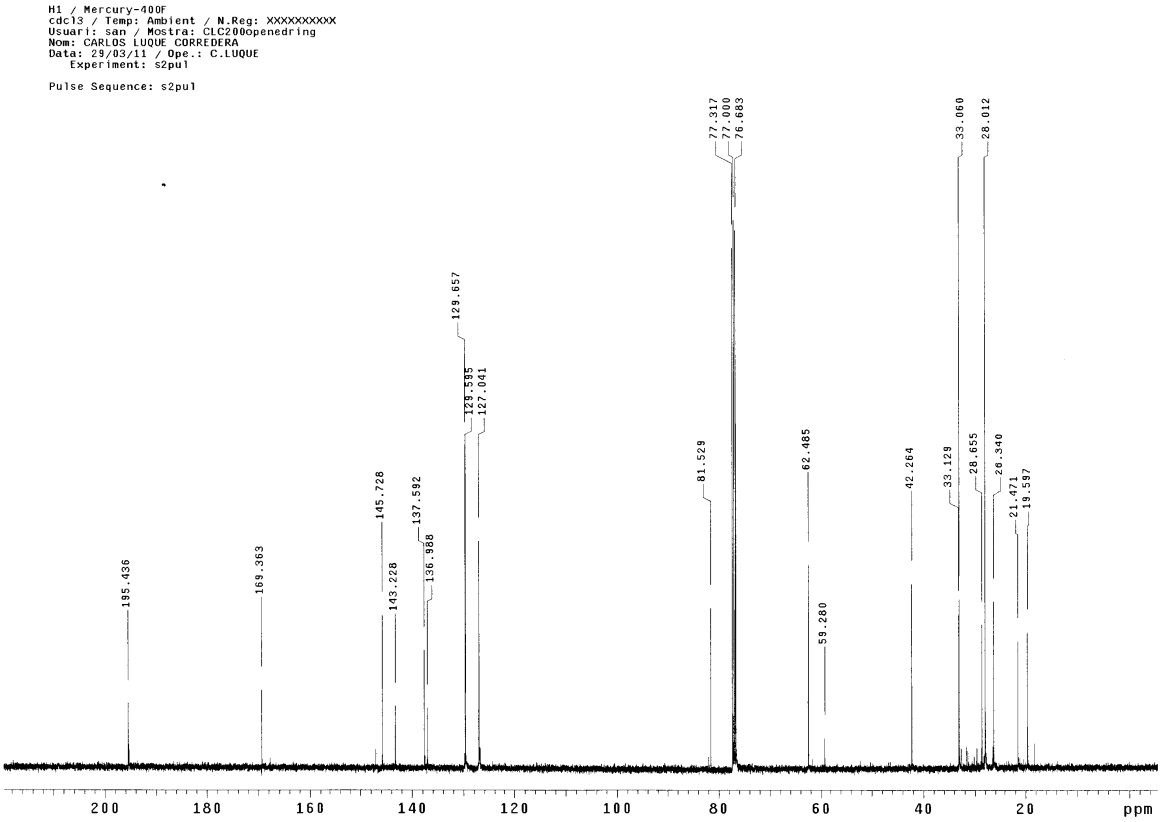



To a solution of β-keto ester **4** (200 mg, 0.541 mmol) in *tert*-butanol (5.5 mL) was added crotonaldehyde (42 mg, 0.595 mmol). After stirring for 5 min at room temperature the solution was cooled to 0 ºC and potassium *tert*-butoxide (3.6 mg, 0.06 equiv) were added. The reaction was stirred for 30 min at room temperature and a further portion of potassium *tert*-butoxide (14.6 mg, 0.24 equiv) was added. The reaction mixture was heated to reflux for 24 h, cooled to room temperature and quenched by the addition of sat $NH_4Cl$ (aq) (1.5 mL/mmol), diluted with $Et_2O$ (8.6 mL/mmol) and the phases separated, brine (2 x 3 mL/mmol), dried and concentrated *in vacuo*. Purificacion by column chromatography ($SiO_2$, 5→25% EtOAc in hexane) gave **21** (78 mg, 34%) and cyclohexenone **17** (113 mg, 49%).

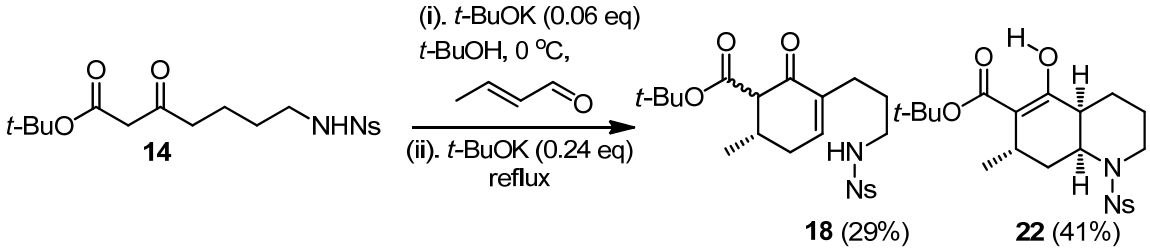
**Data for 17:** $^1$H NMR (400 MHz, COSY) $\delta$ 1.04 (d, *J* = 6.4 Hz, 3H, $CH_3$), 1.48 (s, 9H, ($CH_3$), 1.56 (quint, *J* = 6.8 Hz, 2H, H-2´), 2.07 (ddq, *J* = 16.0, 12, 2.8 Hz, 1H, H-6ax), 2.18 (t, *J* = 7.2 Hz, 2H, H-1´), 2.40-2.45 (masked, 2H, H-5, H-6), 2.41 (s, 3H, $CH_3$Ar), 2.85 (q, *J* = 6.4 Hz, 2H, H-3´), 2.91 (d, *J* = 11.6 Hz, 1H, H-1ax), 4.77 (t, *J* = 6.4 Hz, 1H, NH), 6.67 (br, 1H, H-4), 7.28 (d, *J* = 7.6 Hz, 2H, *m*-Ts), 7.71 (d, *J* = 8.4 Hz, 2H, *o*-Ts). $^{13}$C NMR (400 MHz, HSQC) 19.6 ($CH_3$), 21.5 (Ar$CH_3$) 26.3 (C-1´), 28.0 ($CH_3$), 28.6 (C-2´), 33.0 (C-5), 33.1 (C-6), 42.2 (C-3´), 62.5 (C-1), 81.5 (C), 127.0 (*o*-Ts), 129.6 (*m*-Ts), 136.9 (*p*-Ts), 137.5 (C-3), 143.2 (*ipso*-Ts), 145.7 (C-4), 169.3 (CO), 195.4 (C-2). HRMS calcd for $C_{22}H_{35}N_2O_5S$ (M + $NH_4^+$) 439.2261, found 439.2261.

For NMR data of **21**, see below when it was prepared using $LiOH{\cdot}H_2O$ as base and *i*-PrOH as solvent.


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC200penedring
Nom: CARLOS LUQUE CORREDERA
Data: 29/03/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
t-BuO
O
O
HN
Ts
17
1.429
2.415
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.46
0.00
1.25
1.23
3.17
4.97
3.15
13.81
3.04


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC200penedring
Nom: CARLOS LUQUE CORREDERA
Data: 29/03/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
195.436
169.363
145.728
143.228
137.592
136.988
129.657
129.595
127.041
81.529
77.317
77.000
76.683
62.485
59.280
42.264
33.129
33.060
28.655
28.340
28.012
21.471
19.537
200
180
160
140
120
100
80
60
40
20
ppm

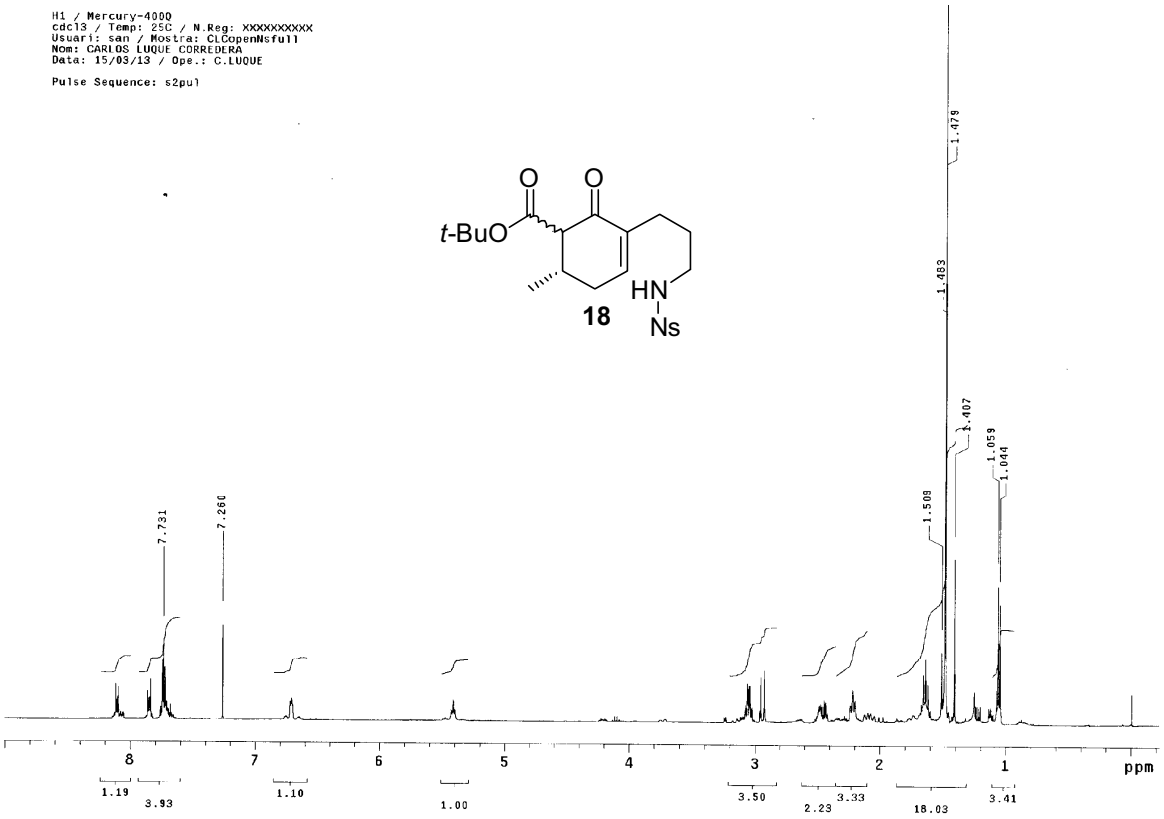
**_tert_-Butyl 6-Methyl-3-[3-(2-nitrophenylsulfonamido)propyl]-2-oxocyclohex-3-enecarboxylate and (18) and _tert_-butyl _(4aRS,7RS,8aRS)_-7-methyl-1-(2-nitrophenylsulfonyl)-5-oxodecahydroquinoline-6-carboxylate (22)**




To a solution of β-keto ester **14** (125 mg, 0.312 mmol) in *tert*-butanol (3.2 mL) was added crotonaldehyde (24 mg, 0.343 mmol). After stirring for 5 min at room temperature the solution was cooled to 0 ºC and potassium *tert*-butoxide (2.1 mg, 0.06 equiv) were added. The reaction was stirred for 30 min at room temperature and a further portion of potassium *tert*-butoxide (8.4 mg, 0.24 equiv) was added. The reaction mixture was heated to reflux for 24 h, cooled to room temperature and quenched by the addition of sat $NH_4Cl$ (aq) (1.5 mL/mmol), diluted with $Et_2O$ (8.6 mL/mmol) and the phases separated, brine (2 x 3 mL/mmol), dried and concentrated *in vacuo*. Purificacion by column chromatography ($SiO_2$, 5→25% EtOAc in hexane) gave **22** (47 mg, 41%) and cyclohexenone **18** (33 mg, 29%).

**Data for 18:** $^1$H NMR (400 MHz, COSY) $\delta$ 1.04 (d, *J* = 6 Hz, 3H, $CH_3$), 1.48 (s, 9H, ($CH_3$), 1.63 (quint, *J* = 6.8 Hz, 2H, H-2´), 2.07 (ddm, *J* = 13.2 Hz, J = 11.0 Hz, 1H, H-5ax), 2.21 (t, *J* = 7.2 Hz, 2H, H-1´), 2.45 (m 2H, H-5, H-6ax), 2.50 (m, 1H, H-2.93 (d, *J* = 11.2 Hz, 1H, H-1ax), 3.05 (q, *J* = 6.8 Hz, 2H, H-3´), 5.42 (t, *J* = 6.0 Hz, 1H, NH), 6.70 (dd, *J* = 5.6 Hz, *J* = 2.8 Hz, 1H, H-4), 7.73 (m, 2H, NsH), 7.84 (m, 1H, NsH), 8.10 (m, 1H, NsH): $^{13}$C NMR (400 MHz, HSQC) 19.6 ($CH_3$), 26.6 (C-1´), 28.0 ($CH_3$), 28.6 (C-2´), 33.0 (C-5), 33.1 (C-6), 43.1 (C-3´), 62.5 (C-1), 81.5 (C), 125.3, 131.0, 132.7, 133.5, 133.8 (Ns), 137.4 (C-3), 145.6 (C-4), 147.0 (C-2´Ns), 169.3 (CO), 195.2 (C-2). HRMS calcd for $C_{17}H_{21}N_2O_7S$ ($M+H^+$ -*t*Bu) 397.1064, found 397.1073.

For NMR data of **22**, see below when it was prepared using $LiOH{\cdot}H_2O$ as base and *i*-PrOH as solvent.


H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCopenNsfull
Nom: CARLOS LUQUE CORREDERA
Data: 15/03/13 / Ope.: C.LUQUE
Pulse Sequence: s2pul
t-BuO
O
O
HN
Ns
18
7.731
7.260
1.509
1.479
1.483
1.407
1.059
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1.19
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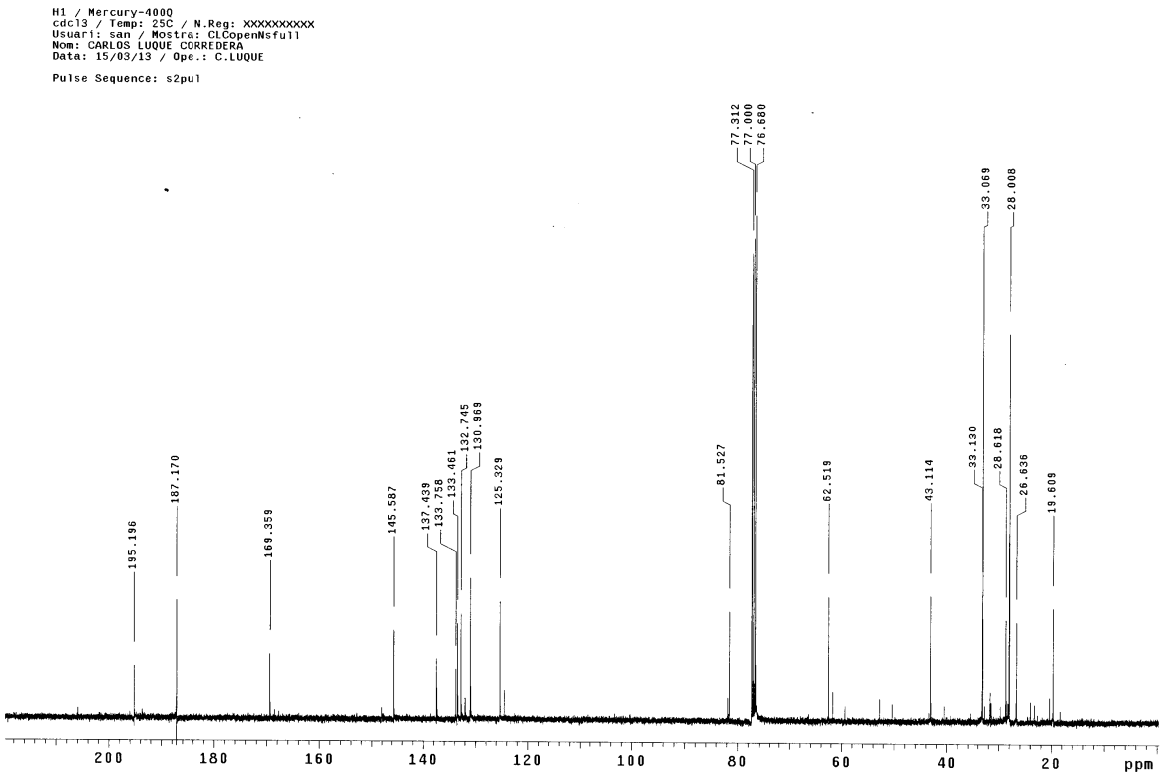
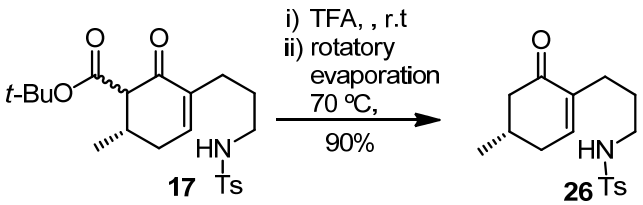
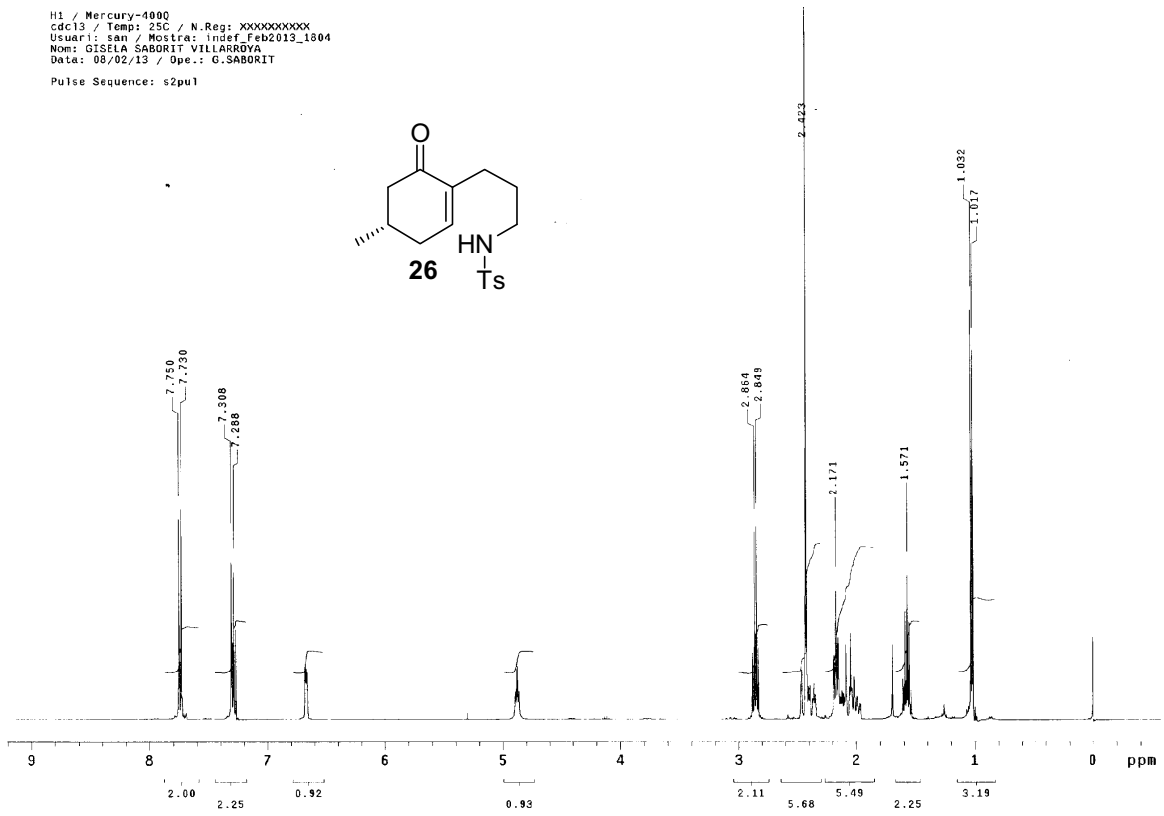
3.50
2.23
3.33
18.03
3.41
ppm

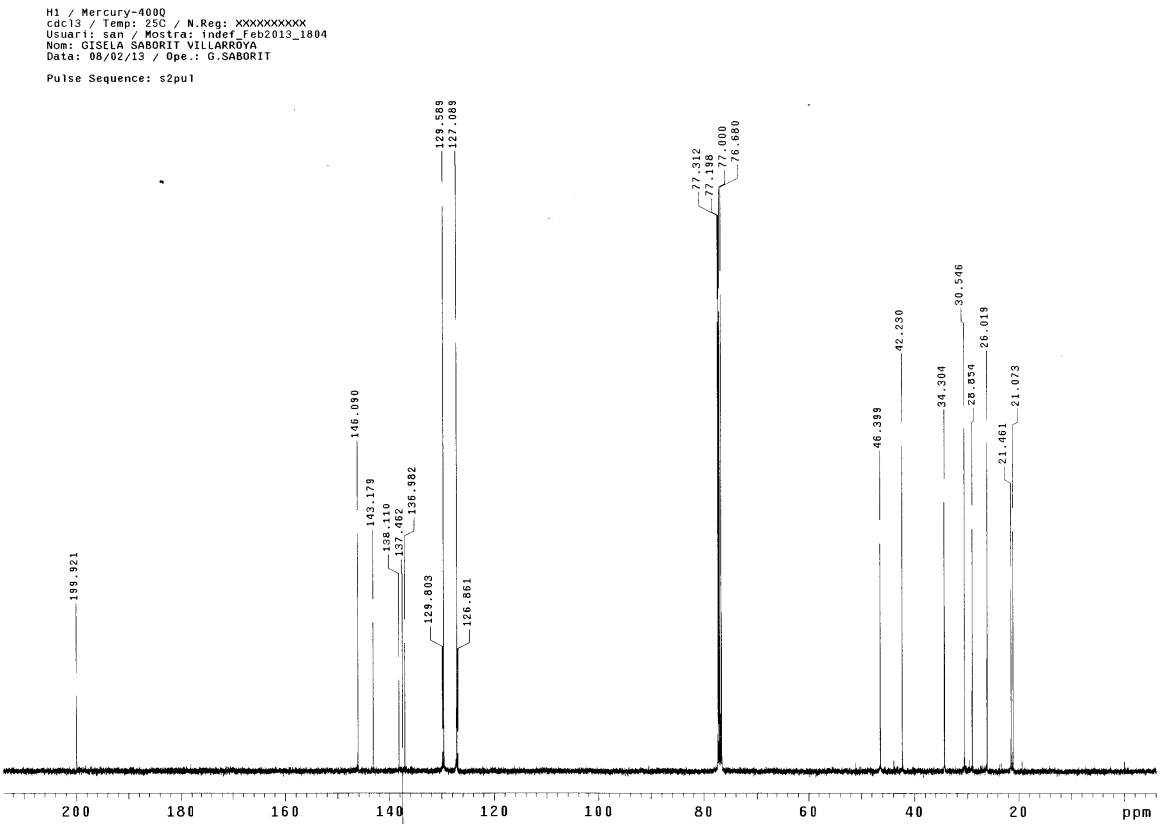

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCopenNsfull
Nom: CARLOS LUQUE CORREDERA
Data: 15/03/13 / Ope.: C.LUQUE
Pulse Sequence: s2pul
195.196
187.170
169.359
145.587
137.439
133.758
133.461
132.745
130.969
125.329
81.527
77.312
77.000
76.680
62.519
43.114
33.130
33.069
28.618
28.008
26.636
19.609
ppm

**5-Methyl-2-[3-(4-methylsufanamido)propyl]cyclohex-2-enone (26)**

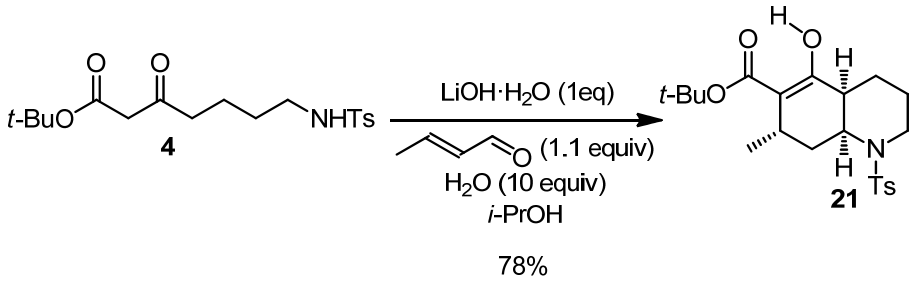



β-keto ester **17** (41 mg, 0.1 mmol) was dissolved in TFA (0.1 mL) and stirred for 15 min at room temperature. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 2 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 70 ºC for 3 h. Purification by column chromatography (5→10→25% EtOAc/hexane) gave **26** (28 mg, 90%) as a yellow oil: $^{1}$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 (H-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.

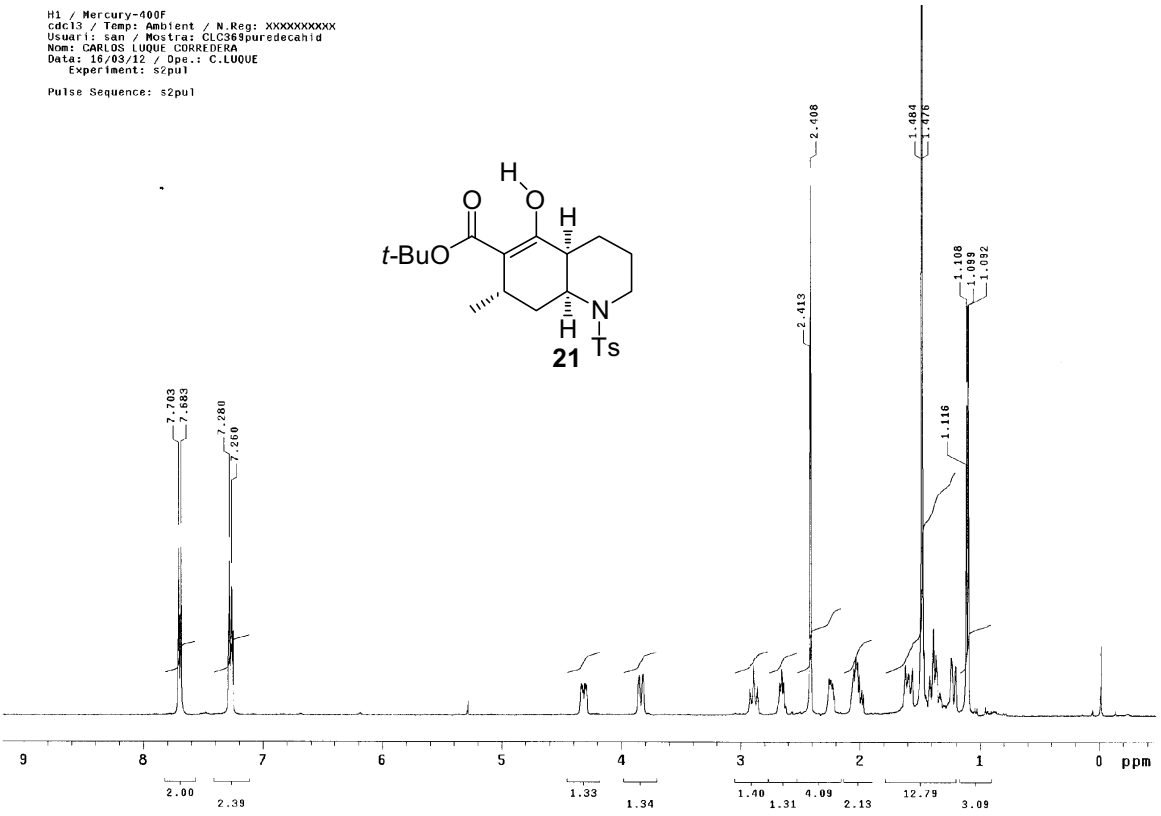

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: indef_Feb2013_1804
Nom: GISELA SABORIT VILLARROYA
Data: 08/02/13 / Ope.: G.SABORIT
Pulse Sequence: s2pul
O
HN
Ts
26
7.750
7.730
7.308
7.288
2.864
2.849
2.423
2.171
1.571
1.032
1.017
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.25
0.92
0.93
2.11
5.68
5.49
2.25
3.19


H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: indef_Feb2013_1804
Nom: GISELA SABORIT VILLARROYA
Data: 08/02/13 / Ope.: G.SABORIT
Pulse Sequence: s2pul
199.921
146.090
143.179
138.110
137.462
136.982
129.803
129.589
127.089
126.861
77.312
77.198
77.000
76.680
46.389
42.230
34.304
30.546
28.854
26.019
21.461
21.073
200
180
160
140
120
100
80
60
40
20
ppm

***(4aR*,7R*,8aR*)*-tert-Butyl7-Methyl-1-(4-methylphenylsulfonyl)-5-oxodecahydro-quinoline-6-carboxylate (21). Racemic version.**




To a solution of keto ester **4** (237 mg, 0.64 mmol) in *i*PrOH (2.2 mL) and $H_2O$ (0.115 mL, 6.4 mmol) was added crotonaldehyde (49 mg, 0.70 mmol) followed by $LiOH{\cdot}H_2O$ (27 mg, 0.64 mmol). The reaction mixture was stirred for 24 h, quenched with saturated aq $NH_4Cl$ solution (2.5 mL), and the product was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried, and concentrated in vacuo, and the crude material was purified by column chromatography (5→10→25% EtOAc/hexane) to give the keto ester **21** (212 mg, 78%) as a light yellow solid: mp 120 ºC. $^1$H NMR (400 MHz, COSY) δ 1.10 (d, *J* = 6.8 Hz, 3H, $CH_3$ax), 1.22 (dm, *J* = 12.4 Hz, H-8eq), 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-8ax), 2.06 (1H, H-4), 2.26 (q, *J* = 5.2 Hz, 1H, H-4a), 2.42 (s, 3H, $ArCH_3$), 2.66 (quint d, *J* = 6.4, 1.6 Hz, 1H, H-7eq), 2.90 (td, *J* = 12.8, 2.4 Hz, 1H, H-2ax), 3.86 (dm, *J* = 12.4 Hz, 1H, H-2eq), 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 (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 (3 $CH_3$), 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 (C-5); HRMS calcd for $C_{22}H_{32}NO_5S$ $(M+H)^+$ 422.1996, found 422.1986.


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC369puredecahid
Nom: CARLOS LUQUE CORREDERA
Data: 16/03/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
t-BuO
21
Ts
7.703
7.683
7.280
7.260
2.408
2.413
1.484
1.476
1.116
1.108
1.099
1.092
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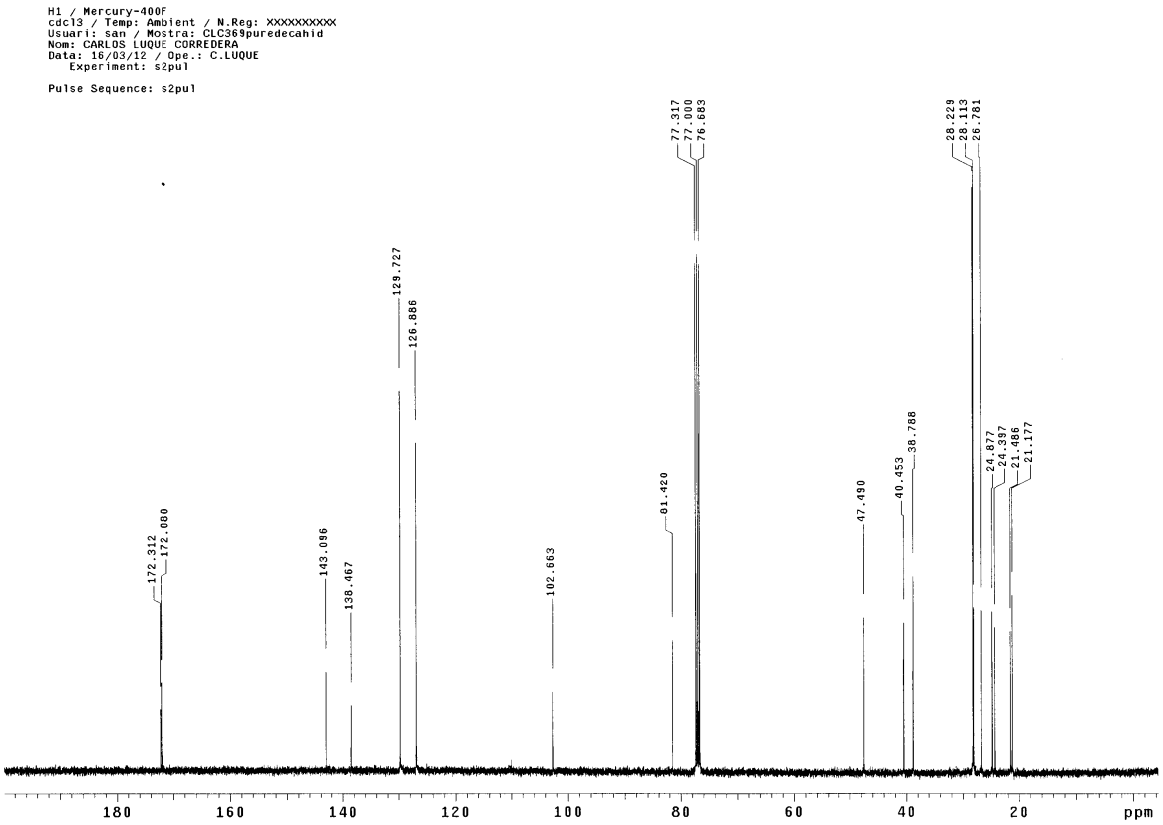
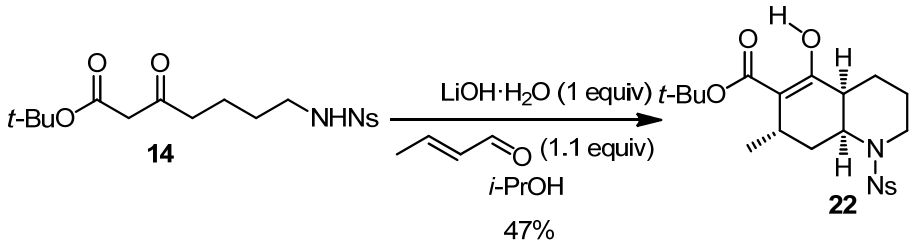
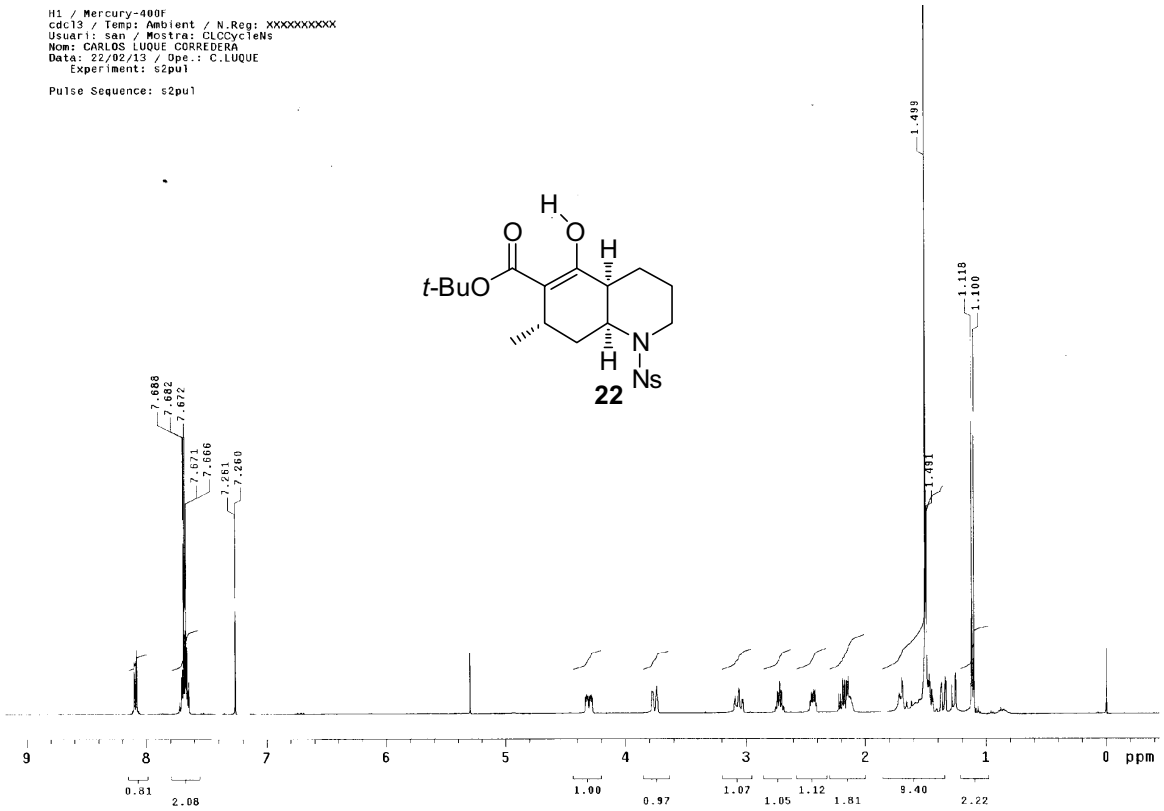
1.34
1.40
1.31
4.09
2.13
12.79
3.09

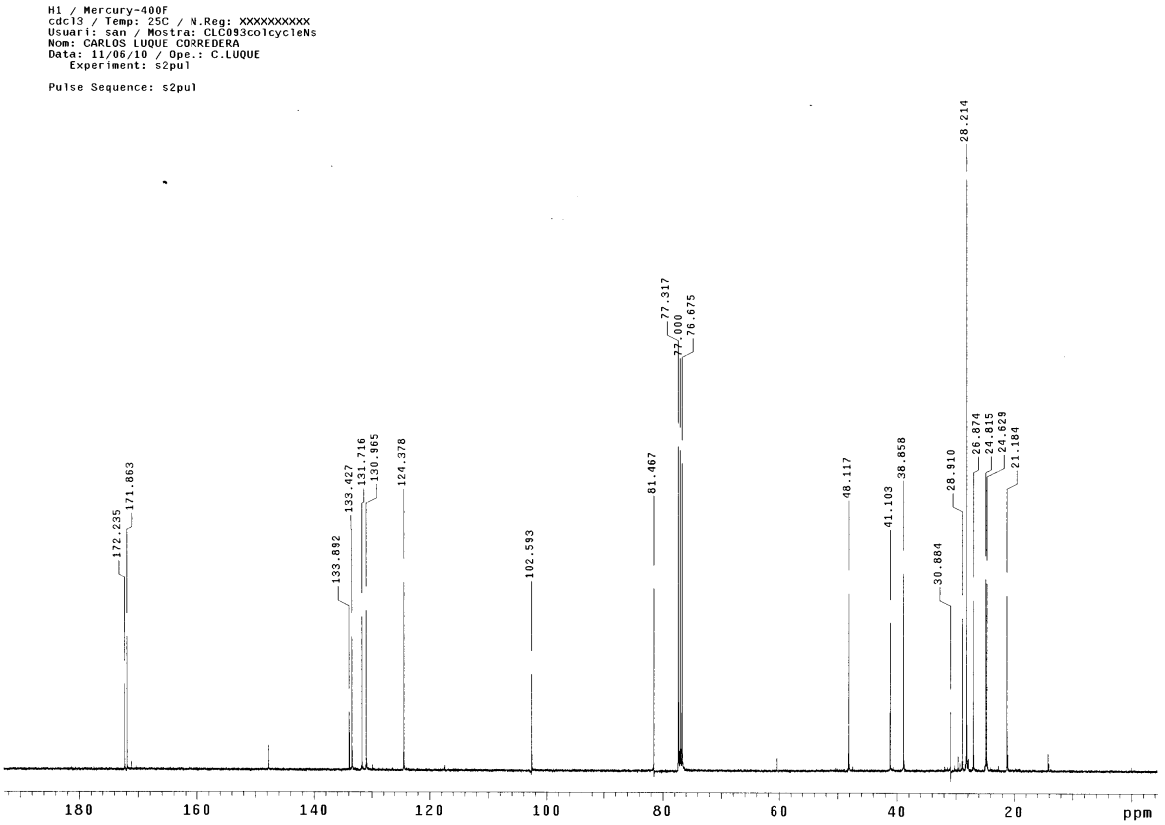

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC369puredecahid
Nom: CARLOS LUQUE CORREDERA
Data: 16/03/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
77.317
77.000
76.683
28.229
28.113
26.781
129.727
126.886
172.312
172.080
143.096
138.467
102.663
01.420
47.490
40.453
38.788
24.877
24.587
21.486
21.177
ppm

***tert*-Butyl *(4aRS,7RS,8aRS)*-7-Methyl-1-(2-nitrophenylsulfonyl)-5-oxodecahydroquinoline-6-carboxylate (22)**

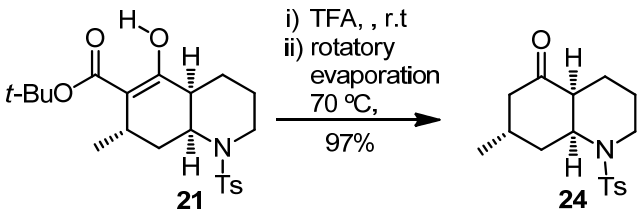



To a solution of β-keto ester **14** (100 mg, 0.250 mmol) in *i*PrOH (1 mL) and $H_2O$ (0.05 mL, 2.5 mmol) was added crotonaldehyde (19 mg, 0.275 mmol) followed by $LiOH \cdot H_2O$ (11 mg, 0.250 mmol). The reaction mixture was stirred for 24 h, quenched with saturated aq $NH_4Cl$ solution (2 mL), and the product was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried, and concentrated in vacuo, and the crude material was purified by column chromatography (5→10→25% EtOAc/hexane) to give **22** (53 mg, 47%) as a yellow solid; $^1$H NMR (400 MHz, COSY) δ 1.10 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.35 (dm, *J* = 12.4 Hz, 1H, H-8eq), 1.45-1.50 (m, 2H, H-3, H-4) 1.50 (s, 9H, $CH_3$), 1.7 (m, 1H, H-3), 2.12 (m, 1H, H-4), 2.17 (td, J = 13.2, 5.6 Hz, H-8ax), 2.43 (dt, *J* = 10.4, 5.2 Hz, 1H, H-4a), 2.71 (quint, *J* = 6.8, 1.2 Hz, 1H, H-7eq), 3.06 (td, *J* = 13.2, 2.4 Hz, 1H, H-2ax), 3.76 (dm, *J* = 13.2 Hz, 1H, H-2eq), 4.29 (ddd, *J* = 13.6, 5.6, 3.2 Hz, 1H, H-8a), 7.64-7.75 (m, 3H, NsH), 8.09 (dd, *J* = 6.8, 2.4 Hx, 1H, H-3´Ns); $^{13}$C NMR (400 MHz, HSQC) δ 21.2 ($CH_3$), 24.6 (C-3), 24.8 (C-4), 26.8 (C-7), 28.2 ($CH_3$), 28.9 (C-8), 38.8 (C-4a), 41.1 (C-2), 48.1 (C-8a), 81.4 (C), 102.6 (C-6), 124.4 (C-Ns), 130.9 (C-Ns), 131.7 (C-Ns), 133.4 (C-Ns), 133.8 (C-1´Ns) 147.5 (C-2´Ns), 171.8 ($CO_2R$), 172.2 (C-5). HRMS calcd for $C_{21}H_{32}N_3O_7S$ (M + $NH_4^+$) 470.1955, found 470.1947.

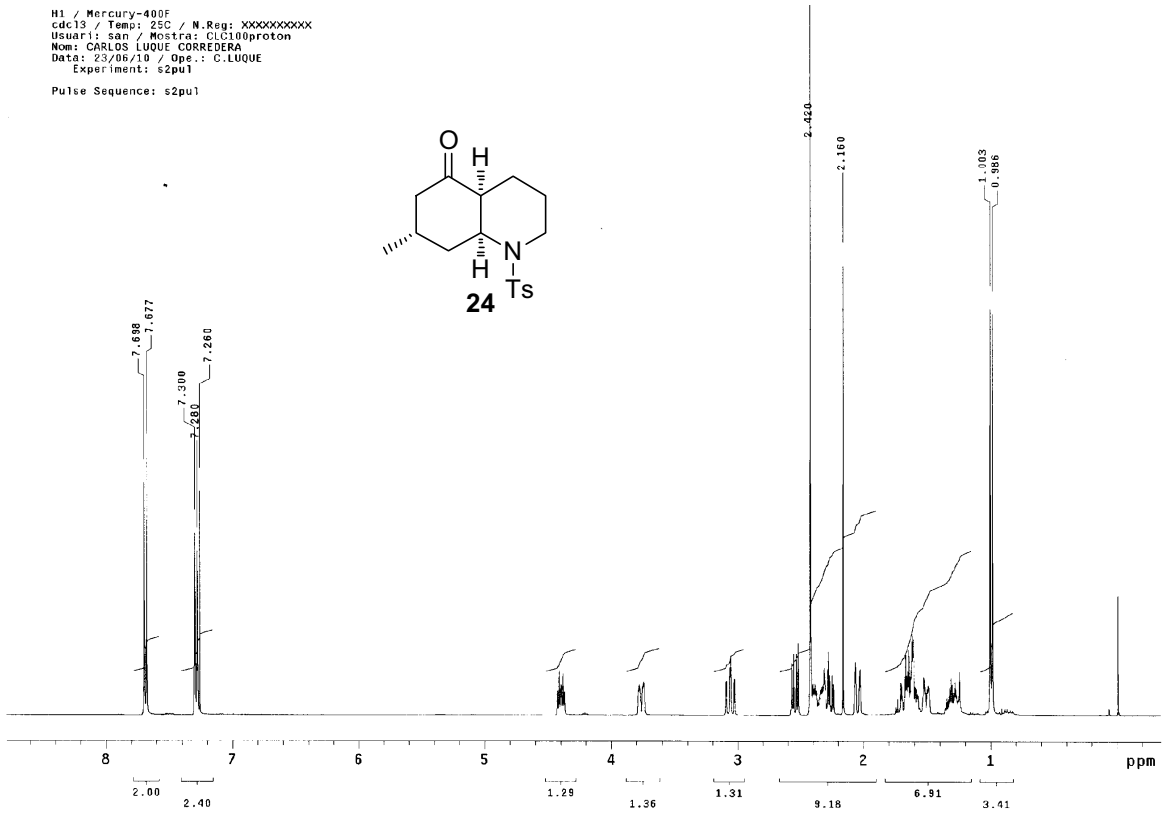

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCCycleNs
Nom: CARLOS LUQUE CORREDERA
Data: 22/02/13 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
t-BuO
Ns
22
7.688
7.682
7.672
7.671
7.666
7.261
7.260
1.499
1.491
1.118
1.100
ppm
0.81
2.08
1.00
0.97
1.07
1.05
1.12
1.81
9.40
2.22

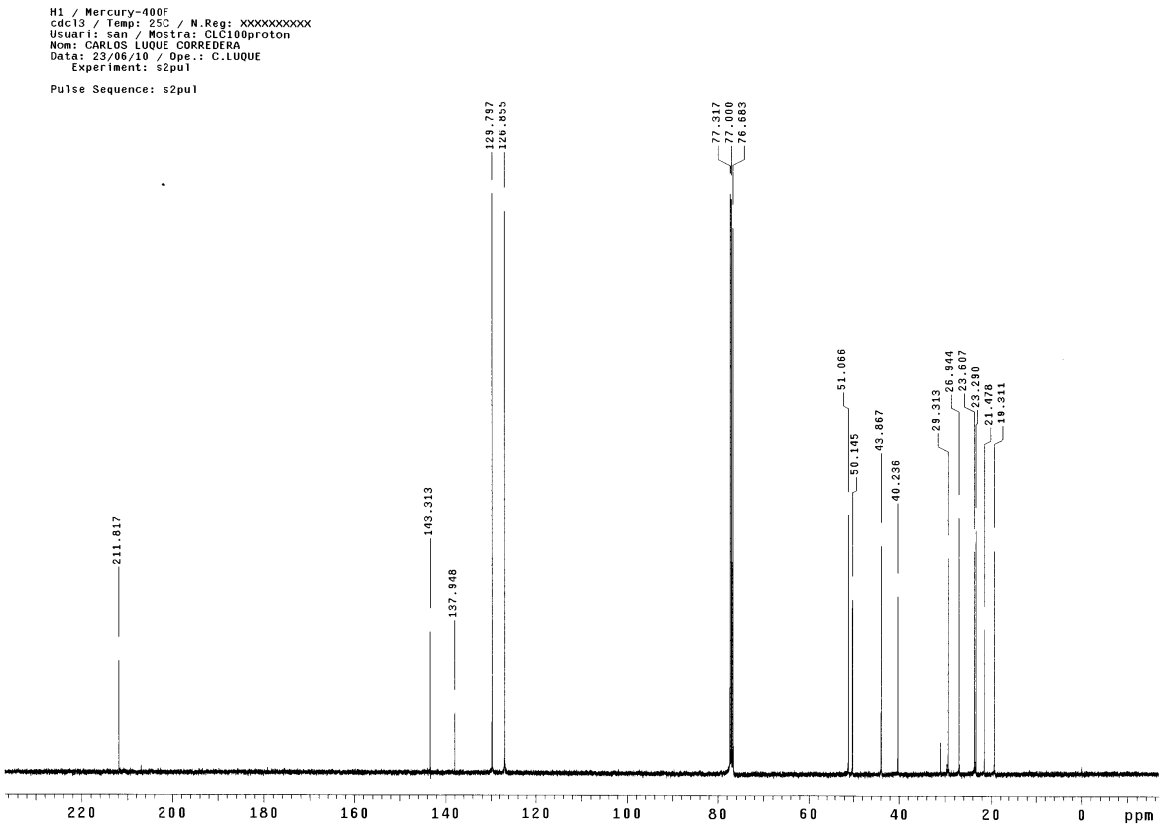

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC093colcycleNs
Nom: CARLOS LUQUE CORREDERA
Data: 11/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
172.235
171.863
133.892
133.427
131.716
130.965
124.378
102.593
81.467
77.317
77.000
76.675
48.117
41.103
38.858
30.884
28.910
28.214
26.874
24.815
24.629
21.184
ppm

***(4aRS,7RS,8aSR)*-7-Methyl-1-(4-methylsulfonyl)-5-oxodecahydroquinoline (24) (Type A)**

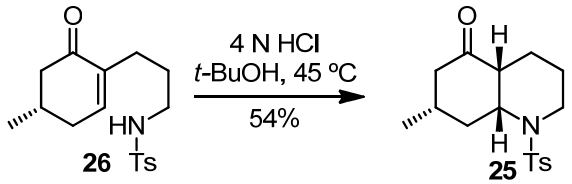



Keto ester **21** (415 mg, 0.984 mmol) was dissolved in TFA (1.65 mL) and stirred for 5 min at room temperature. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 2 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 70 ºC for 3 h to give the crude decahydroquinoline **24** (306 mg, 97%) as a brown oil. $^{1}$H NMR (400 MHz, COSY) $\delta$ 1.00 (d, *J* = 7.2 Hz, 3H, Me), 1.25 (qt, *J* = 13.0, 4.0 Hz, 1H, H-3ax), 1.50 (dm, *J* = 13.0 Hz, H-8eq), 1.60-1.70 (m, 3H, 2H-4, H-3eq), 2.05 (dm, *J* = 14.6 Hz, 1H, H-6eq), 2.26 (td, *J* = 13.2, 4.8 Hz, 1H, H-8ax), 2.30 (m, 1H, H-7), 2.40 (m, 1H, H-4a), 2.42 (s, 3H, $ArCH_3$), 2.55 (dd, *J* = 14.4, 6.0 Hz, 1H, H-6ax), 3.06 (td, *J* = 13.2, 2.4 Hz, 1H, H-2ax), 3.76 (dm, *J* = 13.2 Hz, 1H, H-2eq), 4.40 (dt, *J* = 13.0, 5.2 Hz, 1H, H-8a), 7.29 (d, *J* = 8.4 Hz, 2H, *m*-Ts), 7.69 (d, *J* = 8.4 Hz, 2H, *o*-Ts); $^{13}$C NMR (400 MHz, HSQC) δ 19.3 (Me), 21.5 (Ar*C*$H_3$), 23.3 (C-4), 23.6 (C-3), 26.9 (C-7), 29.3 (C-8), 40.2 (C-2), 43.8 (C-6), 50.1 (C-8a), 51.1 (C-4a), 126.9 (*o*-Ts), 129.7 (*m*-Ts), 138.4 (*p*-Ts), 143.3 (*ipso*-Ts), 211.8 (C-5).


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC100proton
Nom: CARLOS LUQUE CORREDERA
Data: 23/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
O
H
N
H
Ts
24
7.698
7.677
7.300
7.280
7.260
2.420
2.160
1.003
0.986
8
7
6
5
4
3
2
1
ppm
2.00
2.40
1.29
1.36
1.31
9.18
6.91
3.41

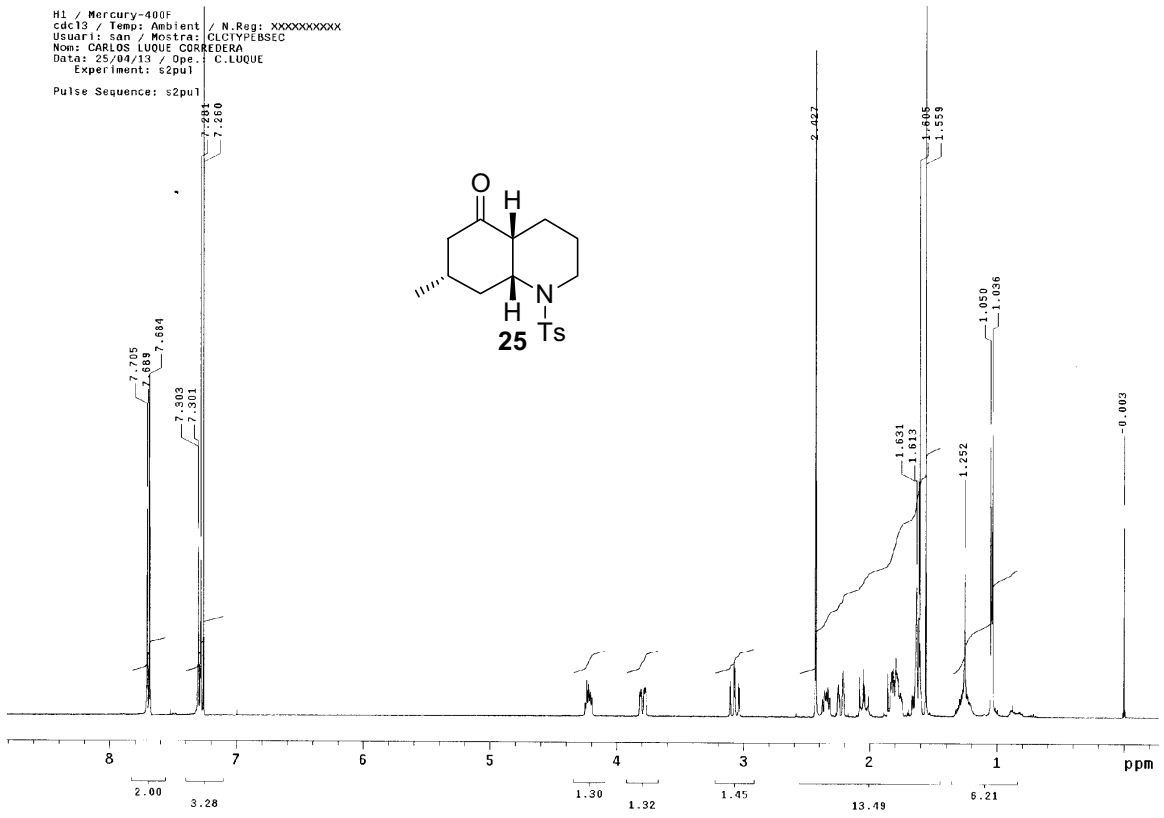

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC100proton
Nom: CARLOS LUQUE CORREDERA
Data: 23/06/10 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
211.817
143.313
137.948
129.787
126.855
77.317
77.000
76.683
51.066
50.145
43.867
40.236
29.313
26.944
23.607
23.290
21.478
19.311
220
200
180
160
140
120
100
80
60
40
20
0
ppm

***(4aRS,7SR,8aRS)*-7-Methyl-1-(4-methylphenylsufonamido)-5-oxodecahydroquinoline (25) (Type B)**




To a solution of **26** (450 mg, 1.40 mmol) in *t*-BuOH (8 ml) was added 3 N HCl (13 ml) and the resulting mixture was stiired for 14 h at 45 ºC. The reaction was quenched with NaOH 1 N (5 ml) and extracted with EtOAc (2 x 8 ml), the combined organic layers were washed with brine, dried and concentrated *in vacuo*. Purification by column chromatography ($Al_2O_3$, 5→50% EtOAc in hexane) gave **25** (228 mg, 54%) as an 8:1 mixture of **21** as a yellow oil followed by the ring-opened product **26** (170 mg, 40%). $^1$H NMR (400 MHz, $CDCl_3$, COSY) $\delta$ 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.

Identical results were obtained starting from decahydroquinoline **24** providing the *type-B stereochemistry by isomerization of type-A stereochemistry*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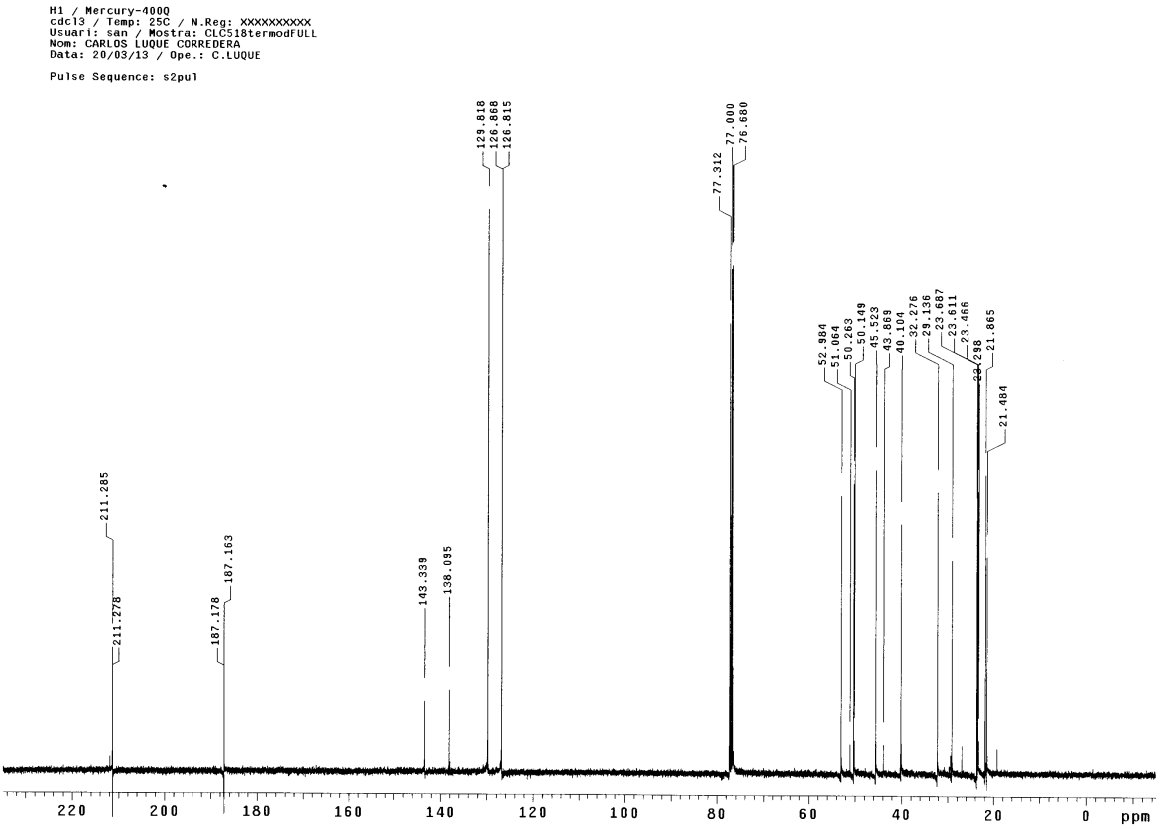
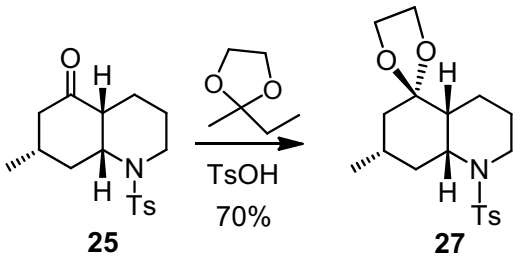
Usuari: san / Mostra: CLCITYPEBSEC
Nom: CARLOS LUQUE CORREDERA
Data: 25/04/13 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.705
7.689
7.684
7.303
7.301
7.264
7.260
2.427
1.631
1.613
1.605
1.559
1.252
1.050
1.036
-0.003
O
H
N
H
Ts
25
ppm
2.00
3.28
1.30
1.32
1.45
13.49
6.21

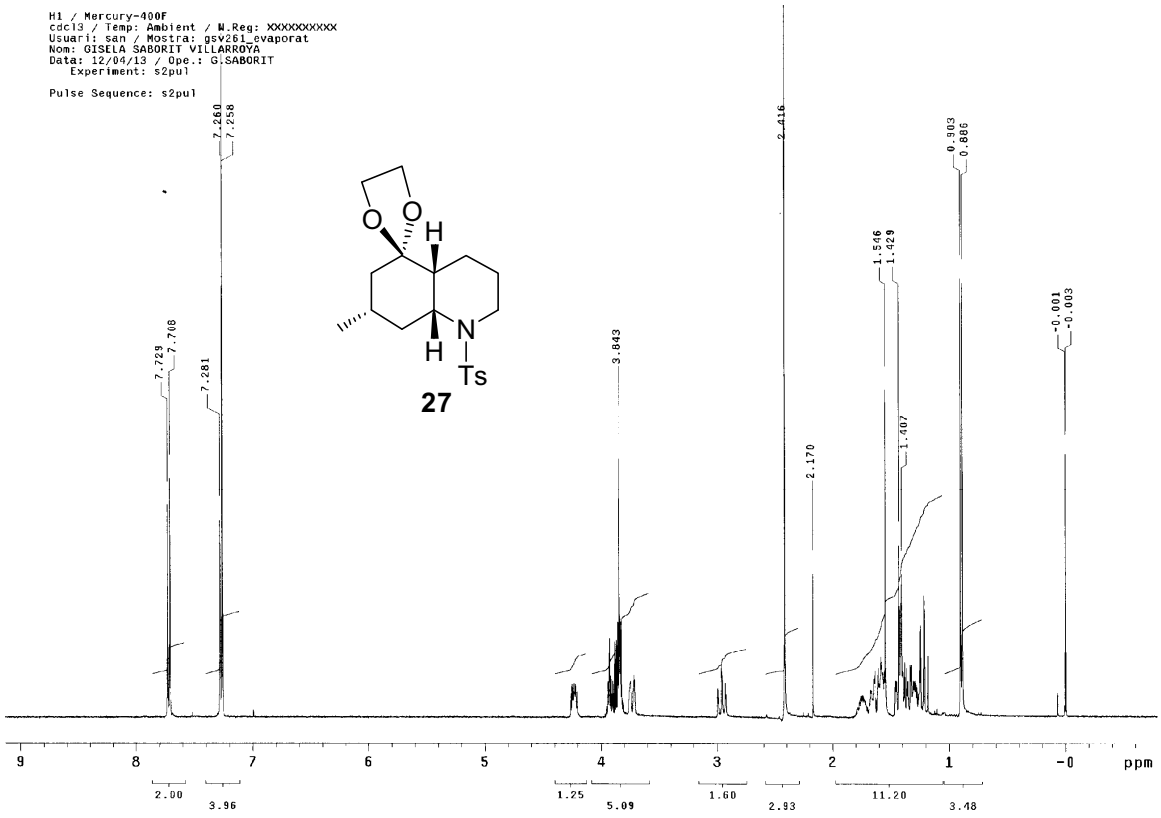

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC518termodFULL
Nom: CARLOS LUQUE CORREDERA
Data: 20/03/13 / Ope.: C.LUQUE
Pulse Sequence: s2pul
211.285
211.278
187.178
187.163
143.339
138.095
129.818
126.868
126.815
77.312
77.000
76.680
52.984
52.484
52.083
50.149
45.523
43.869
40.104
32.276
29.136
23.687
23.611
23.466
23.298
21.865
21.484
ppm

***(4aRS,7SR,8aRS)*-7-Methyl-1-(4-methylphenylsufonamido)-5-oxodecahydroquinoline ethylene acetal (27)**




**25** **27**

To a solution of **25** (244 mg, 0.76 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (0.95 mL, 10 equiv) was added *p*-toluenesulfonic acid (7.5 mg, 0.038 mmol) and the mixture was stirred for 16 h at room temperature. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with of $Et_2O$ (3 × 25 mL). The combined organic extracts were and washed with brine (25 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting material, after heating at the rotary evaporator under vacuum at 70 ºC for 2 h to remove excess 2-ethyl-2-methyl-1,3-dioxolane, give **27** (186 mg, 70 %) as a white solid; $^1$H NMR (400 MHz, COSY) $\delta$ 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($ArCH_3$), 21.7 ($CH_3$), 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.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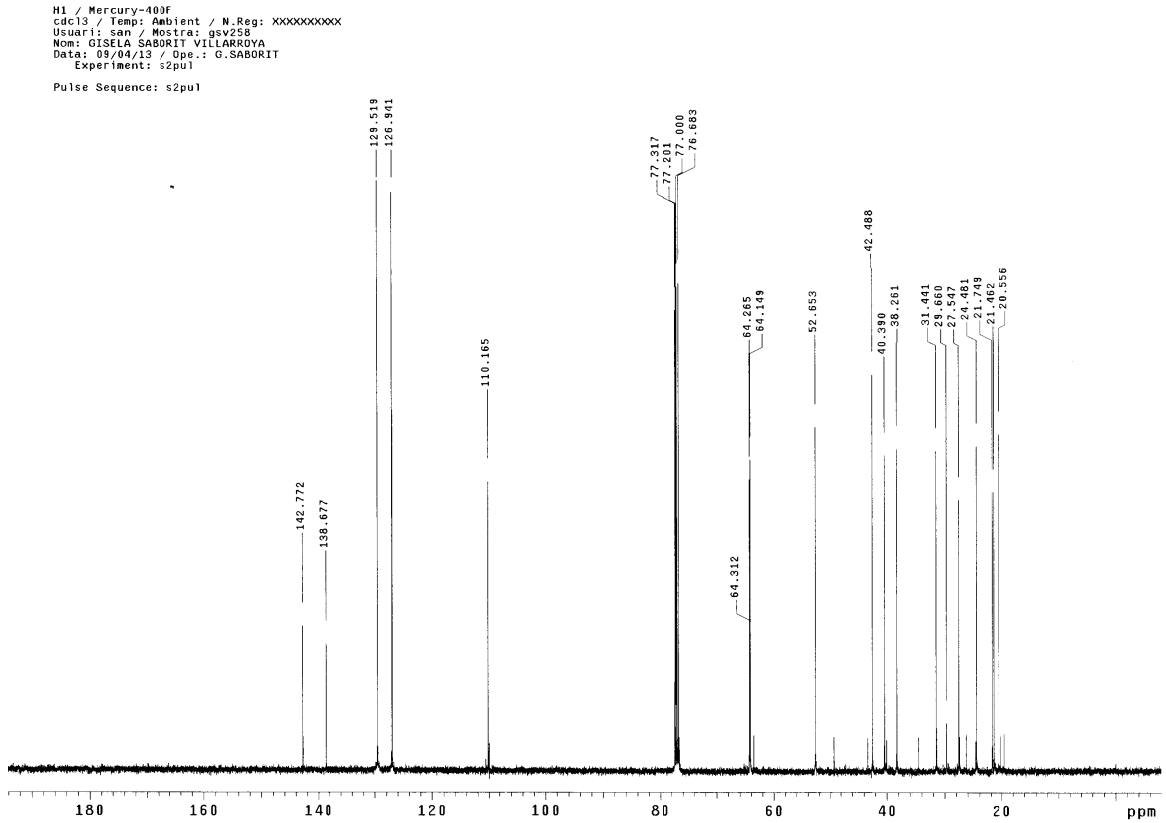
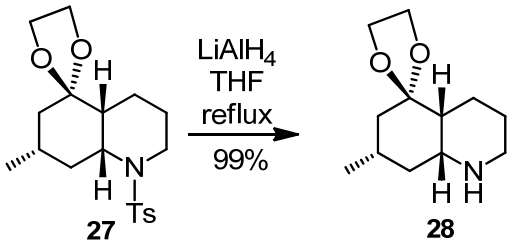
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv261_evaporat
Nom: GISELA SABORIT VILLARROYA
Data: 12/04/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
7.260
7.258
7.729
7.708
7.281
3.843
2.416
2.170
1.546
1.429
1.407
0.903
0.886
-0.001
-0.003
O
O
H
H
N
Ts
27
9
8
7
6
5
4
3
2
1
-0
ppm
2.00
3.96
1.25
5.09
1.60
2.93
11.20
3.48

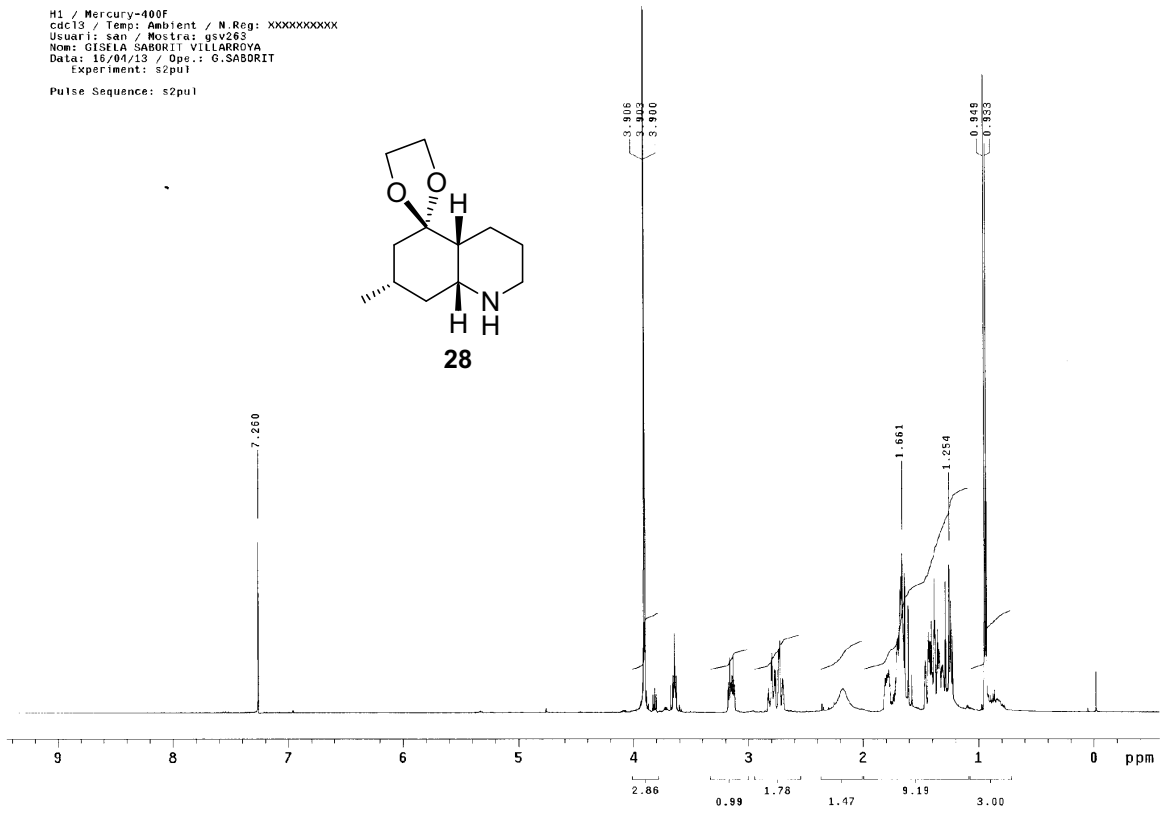

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv258
Nom: GISELA SABORIT VILLARROYA
Data: 09/04/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
129.519
126.941
77.317
77.201
77.000
76.683
142.772
138.677
110.165
64.265
64.149
64.312
52.653
42.488
40.390
38.261
31.441
29.660
27.547
24.481
21.749
21.462
20.556
180
160
140
120
100
80
60
40
20
ppm

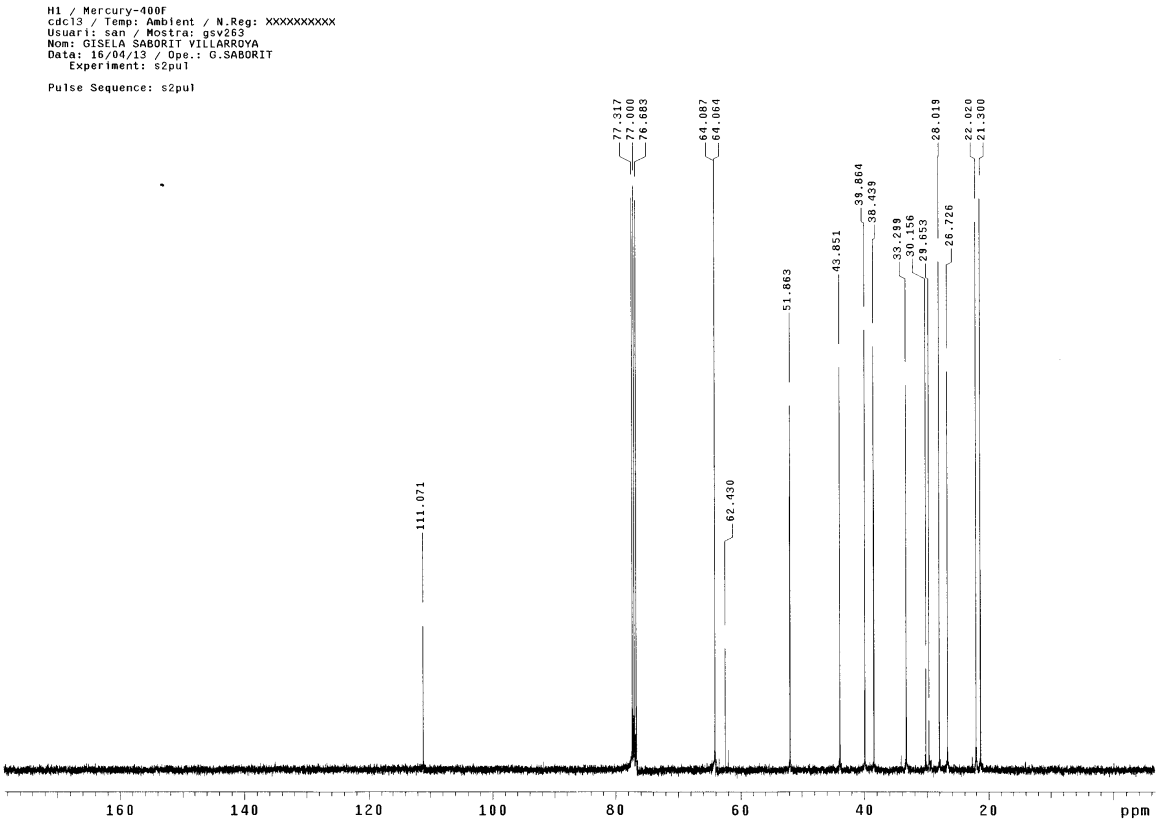
***(4aRS,7RS,8aSR)*-7-Methyl-5-oxodecahydroquinoline ethylene acetal (28)**



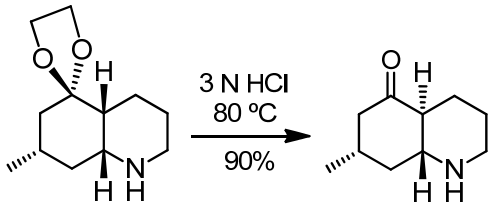

**27** **28**

To a solution of $LiAlH_4$ (191 mg, 5.04 mmol) in THF (19 mL) at 0 ºC was added dropwise a solution of **27** (185 mg, 0.504 mmol) in THF (10 mL + 5 mL rinse). The resulting mixture was allowed to reach to room temperature and then refluxed for 16 h. The reaction was re cooled to 0 ºC and quenched by careful dropwise addition of water (0.20 mL), 2 N NaOH (0.20 mL) and water (0.6 mL). The mixture was diluted with diethyl ether (7 mL), dried ($Na_2SO_4$) and stirred for 15 min. Filtration through a pad of celite and concentration *in vacuo* gave amino acetal **28** (106 mg, 99%) as a light yellow oil, which was used in the next step without further purification; $^1$H NMR (400 MHz, COSY) $\delta$ 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-3 or 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 (two signals, $OCH_2$), 111.1 (C-5). HRMS calcd for $C_{17}H_{24}NO_3S$ ($M+H^+$) 322.1471, found 322.1470.


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
Pulse Sequence: s2pul
28
7.260
3.906
3.903
3.900
1.661
1.254
0.949
0.933
9
8
7
6
5
4
3
2
1
0
ppm
2.86
0.99
1.78
1.47
9.19
3.00

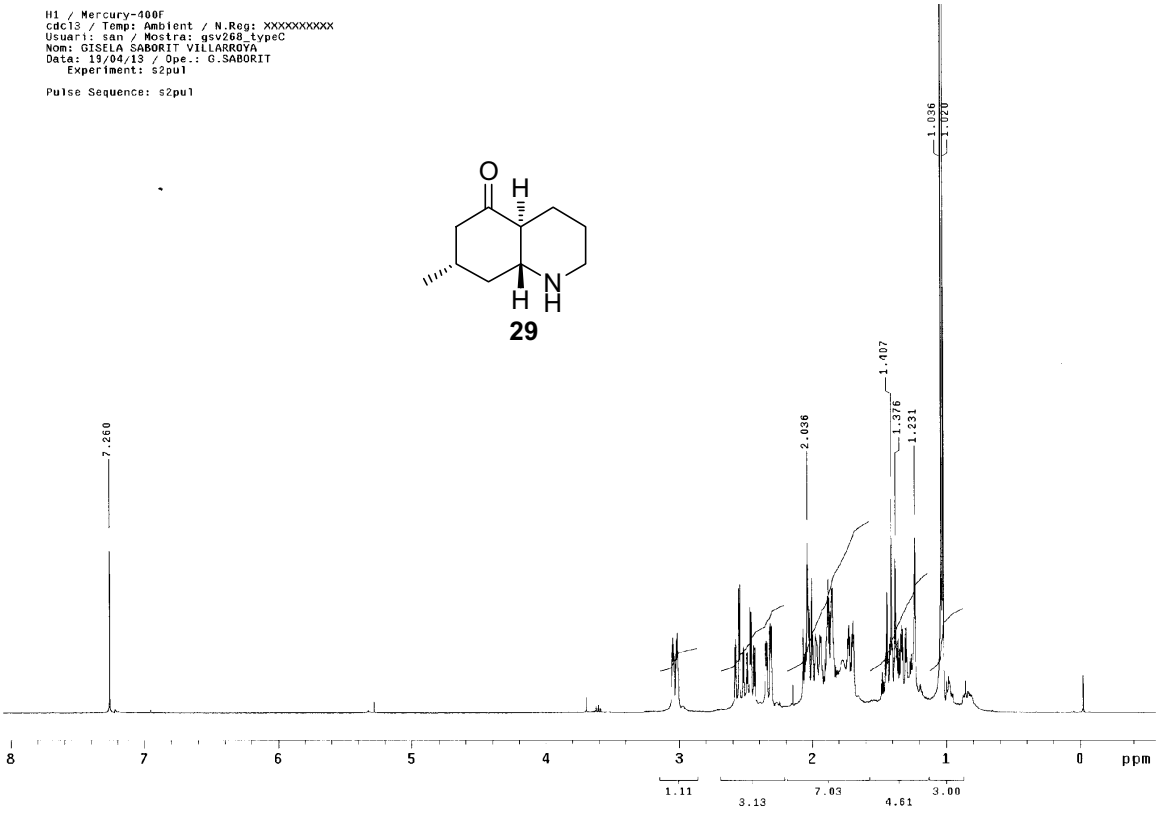

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv263
Nom: GISELA SABORIT VILLARROYA
Data: 16/04/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
77.317
77.000
76.683
64.087
64.064
62.430
111.071
51.863
43.851
39.864
38.439
33.299
30.156
29.653
28.019
26.726
22.020
21.300
160
140
120
100
80
60
40
20
ppm

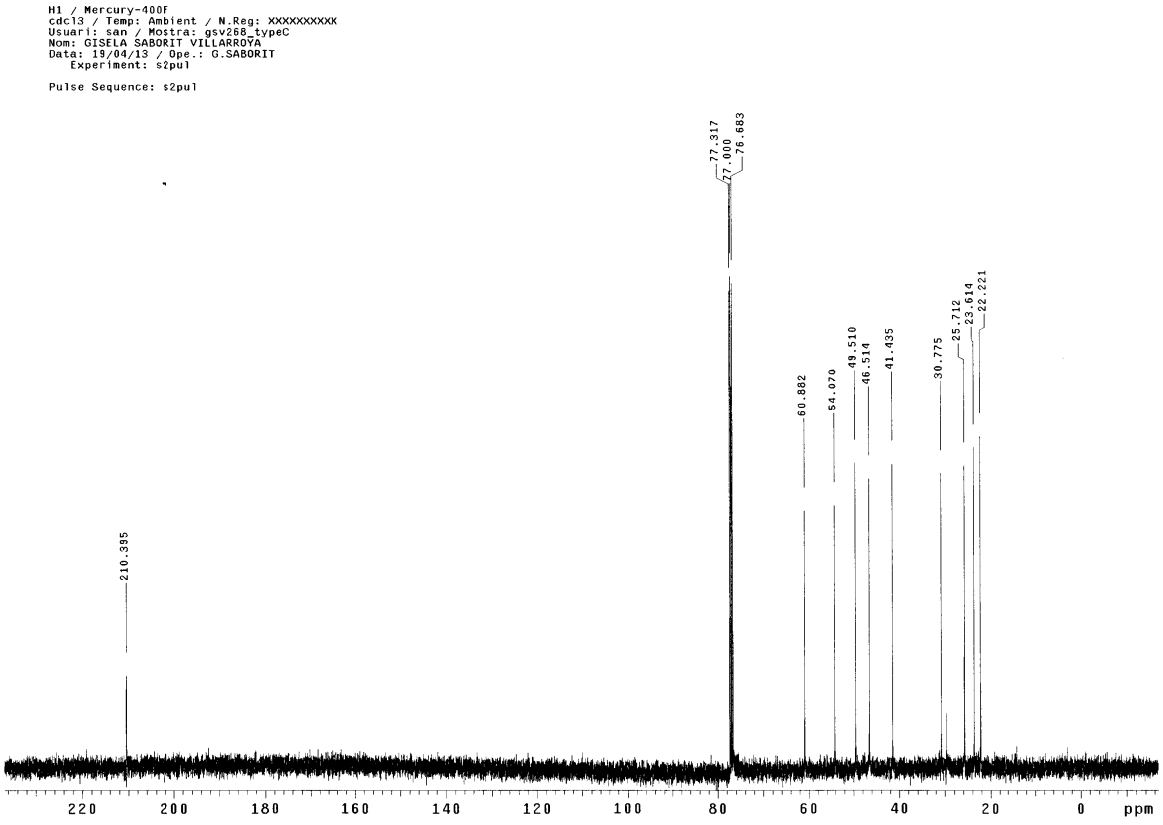
***(4aRS,7RS,8aSR)*-7-Methyl-5-oxodecahydroquinoline (29) (Type C)**



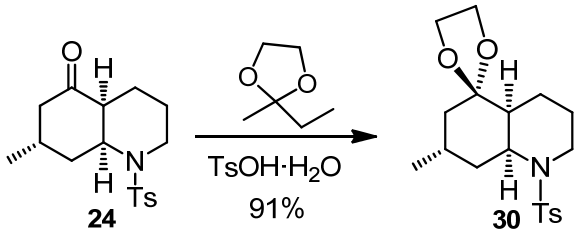

**28** **29**

Amino acetal **28** (111 mg, 0.53 mmol) was dissolved in 3 N HCl (13 mL) and heated to 80 ºC 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 **29** (79 mg, 90%) as a clear yellow oil; $^1$H NMR (400 MHz, COSY) $\delta$ 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.

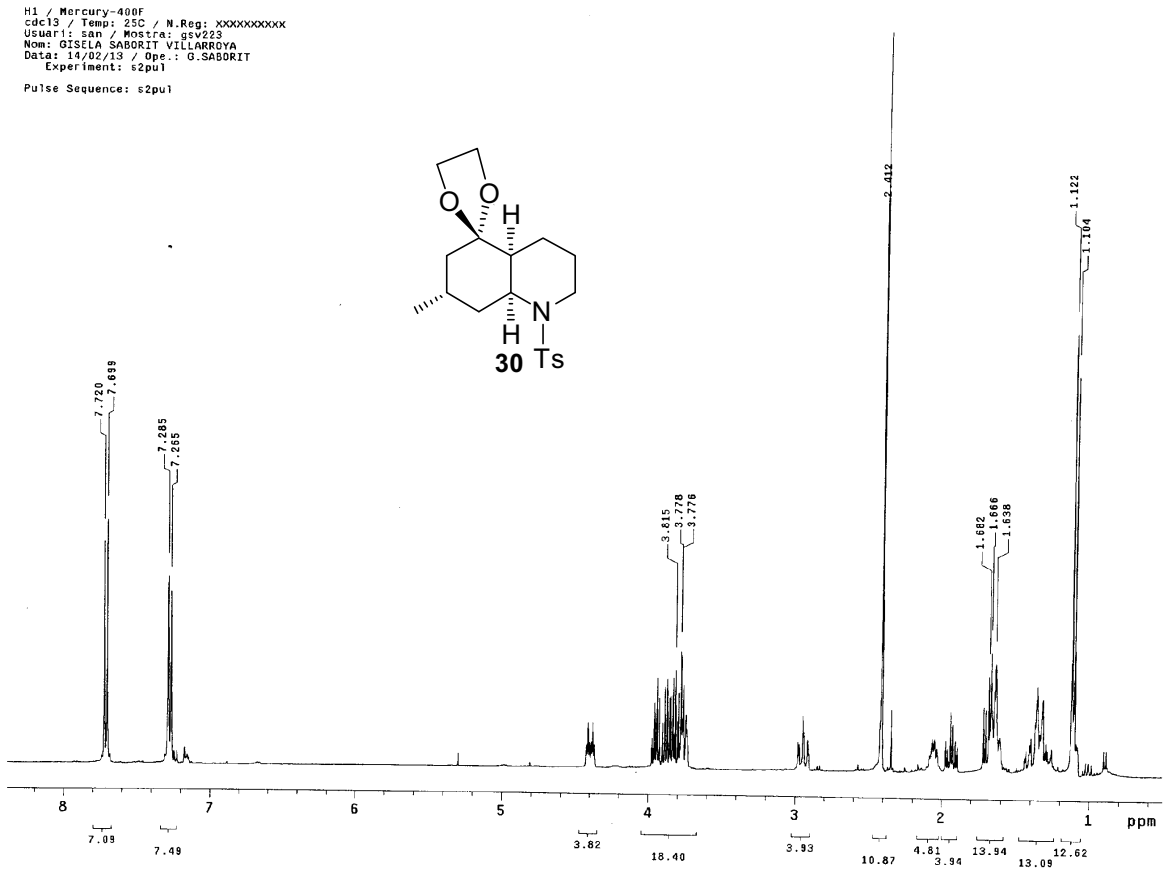

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv268_typeC
Nom: GISELA SABORIT VILLARROYA
Data: 19/04/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
O
H
H
N
H
29
7.260
2.036
1.407
1.376
1.231
1.036
1.020
8
7
6
5
4
3
2
1
0
ppm
1.11
3.13
7.03
4.61
3.00


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
Pulse Sequence: s2pul
210.395
77.317
77.000
76.683
60.882
54.070
49.510
46.514
41.435
30.775
25.712
23.614
22.221
220
200
180
160
140
120
100
80
60
40
20
0
ppm

***(4aRS,7RS,8aSR)*-7-Methyl-1-(4-methylsulfonyl)-5-oxodecahydroquinoline ethylene acetal (30)**




To a solution of compound **24** (1.03 g, 3.19 mmol, 1 equiv) in 2-ethyl-2-methyl-1,3-dioxolane (3 mL, 24.3 mmol, 7.6 equiv) was added *p*-toluenesulfonic acid (23 mg, 0.12 mmol, 0.04 equiv) and the mixture was stirred for 16 h at room temperature. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) . The organic layer was separated and the aqueous layer was extracted with of $Et_2O$ (3 × 25 mL). The combined organic extracts were and washed with brine (25 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting material was azeotroped with toluene and then maintained on the rotary evaporator under vacuum at 70 ºC for 3 h to remove excess 2-ethyl-2-methyl-1,3-dioxolane to give compound **30** (1.17 g, 91%) in essentially pure form which was used in the next step without further purification; $^1$H NMR (400 MHz, COSY) $\delta$ 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.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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv223
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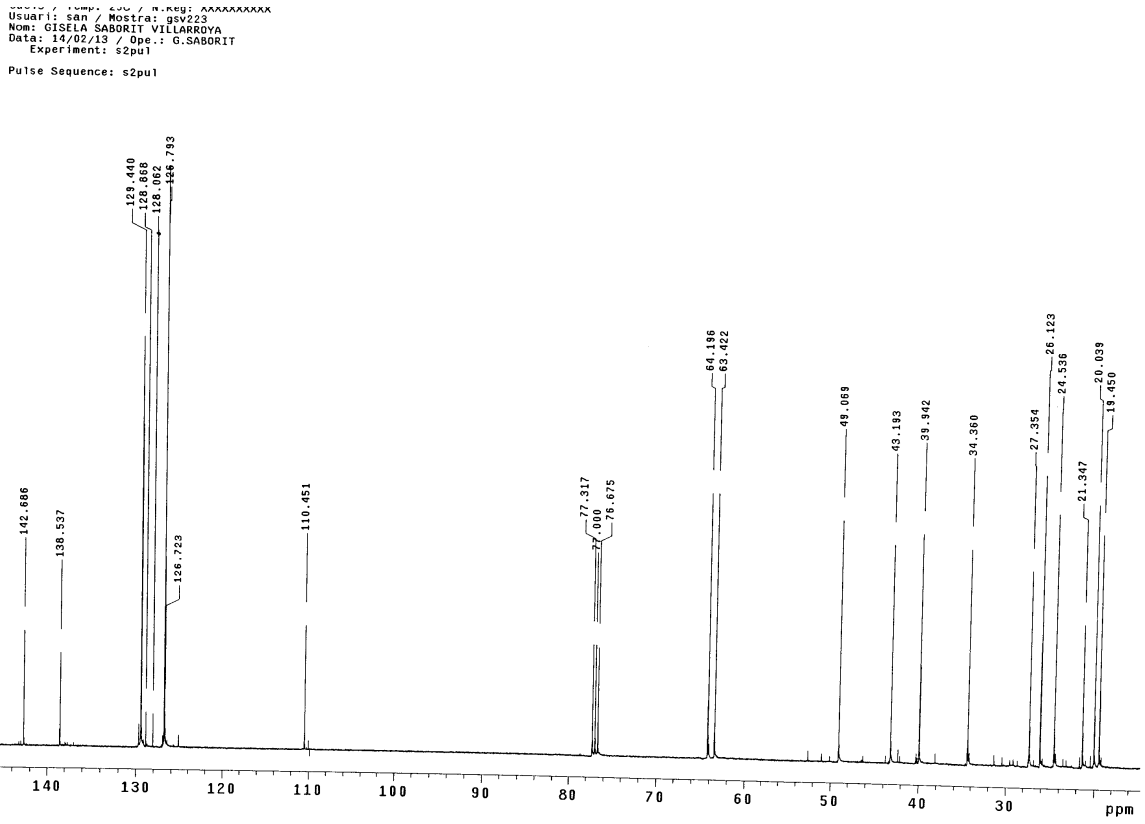
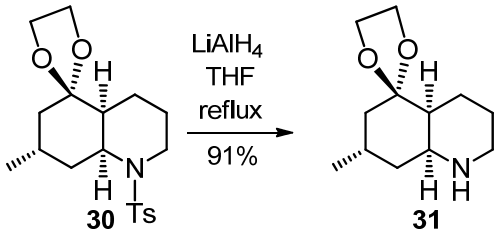
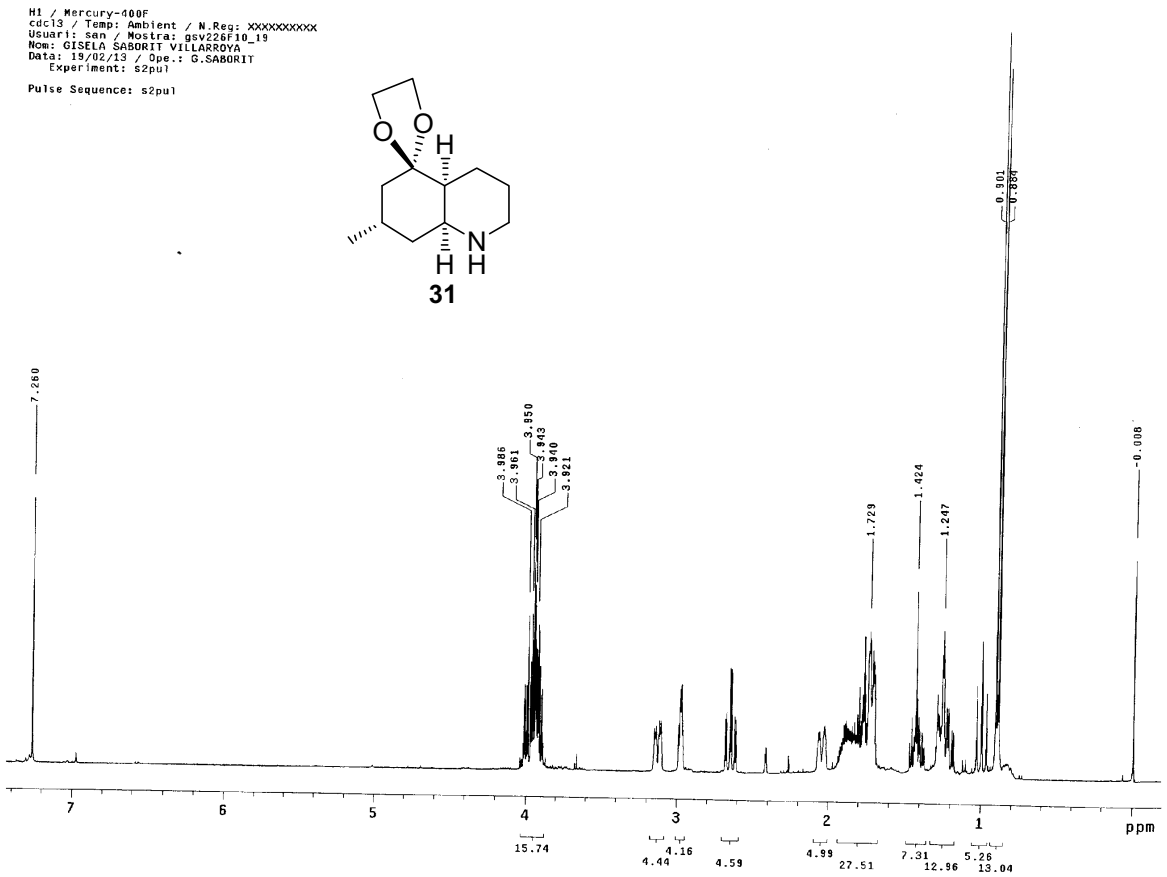
Data: 14/02/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
30
Ts
7.720
7.699
7.285
7.265
3.815
3.778
3.776
2.412
1.682
1.666
1.638
1.122
1.104
ppm
7.09
7.49
3.82
18.40
3.93
10.87
4.81
3.94
13.94
13.09
12.62


Usuari: san / Mostra: gsv223
Nom: GISELA SABORIT VILLARROYA
Data: 14/02/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
142.686
138.537
129.440
128.868
128.062
126.793
126.723
110.451
77.317
77.000
76.675
64.196
63.422
49.069
43.193
39.942
34.360
27.354
26.123
24.536
21.347
20.039
13.450
ppm

***(4aRS,7RS,8aSR)*-7-Methyl-5-oxodecahydroquinoline ethylene acetal (31)**




To a solution of $LiAlH_4$ (406 mg, 10.73 mmol) in THF (15 mL) at 0 ºC was added dropwise a solution of **30** (394 mg, 1.07 mmol) in THF (15 mL + 10 mL rinse). The resulting mixture was allowed to warm to room temperature and then refluxed for 16 h. The reaction was re 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 (15 mL), dried ($Na_2SO_4$) and stirred for 15 minutes. Filtration through a pad of celite and concentration *in vacuo* gave amine **31** (208 mg, 91%) as a light yellow oil. The compound was used in the next step without further purification. A small sample for analysis was obtained by column chromatography (5→10% MeOH in $CH_2Cl_2$); $^1$H NMR (400 MHz, COSY) $\delta$ 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.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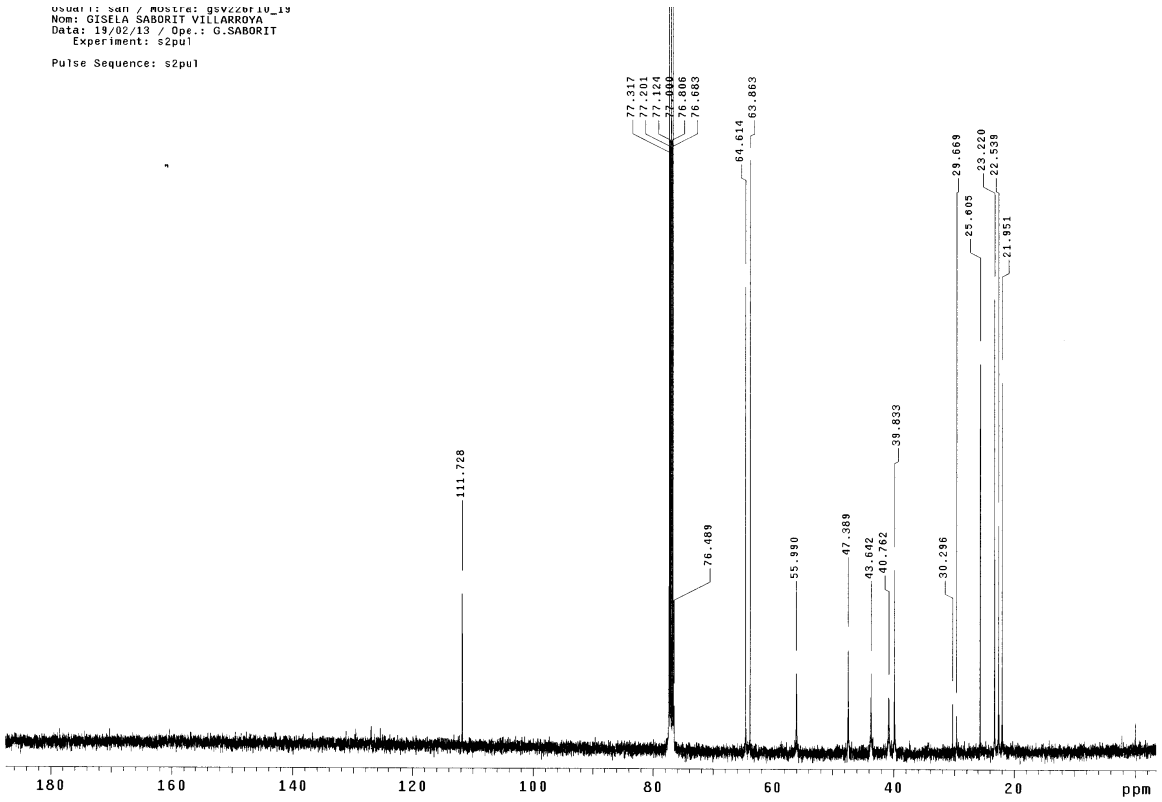
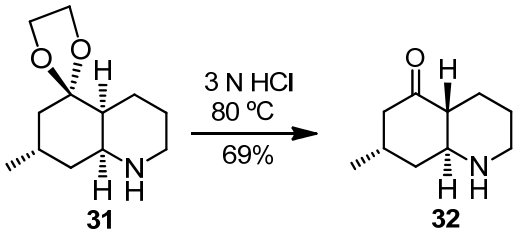
Nom: GISELA SABORIT VILLARROYA
Data: 19/02/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
O
O
H
N
H H
31
7.260
3.986
3.961
3.950
3.943
3.940
3.921
1.729
1.424
1.247
0.901
0.884
0.008
7
6
5
4
3
2
1
ppm
15.74
4.44
4.16
4.59
4.99
27.51
7.31
12.96
5.26
13.04


Usuari: San / Mostra: gsv226F10_19
Nom: GISELA SABORIT VILLARROYA
Data: 19/02/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
77.317
77.201
77.124
77.000
76.806
76.683
64.614
63.863
111.728
76.489
55.990
47.389
43.642
40.762
39.833
30.286
29.669
25.605
23.220
22.538
21.951
180
160
140
120
100
80
60
40
20
ppm

***(4aRS,7SR,8aSR)*-7-Methyl-5-oxodecahydroquinoline (32) (Type D)**

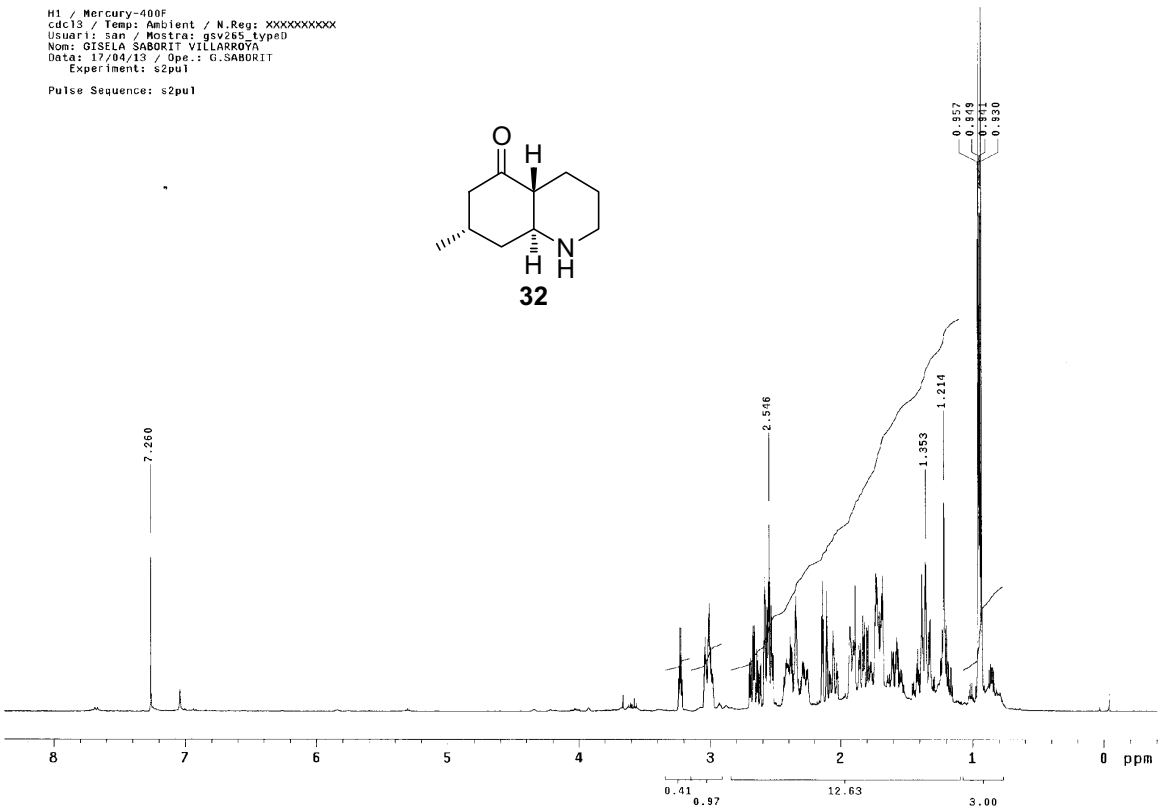



**31** **32**

Acetal **31** (138 mg, 0.65 mmol) was dissolved in 3 N HCl (16 mL) and heated to 80 ºC for 48 h. The mixture was basified with $Na_2CO_3$ (pH = 11) and extracted with $CH_2Cl_2$ (3 × 30 mL). The dried extract ($Na_2SO_4$) was concentrated to give a mixture of amines **32** and **29** in a 2:1 ratio (79 mg, 72% combined yield) as a clear yellow oil.[124]

NMR data for **32**: $^1$H NMR (400 MHz, COSY) $\delta$ 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

[124] Attempts to purify the product by column chromatography led to unidentified mixtures of compounds.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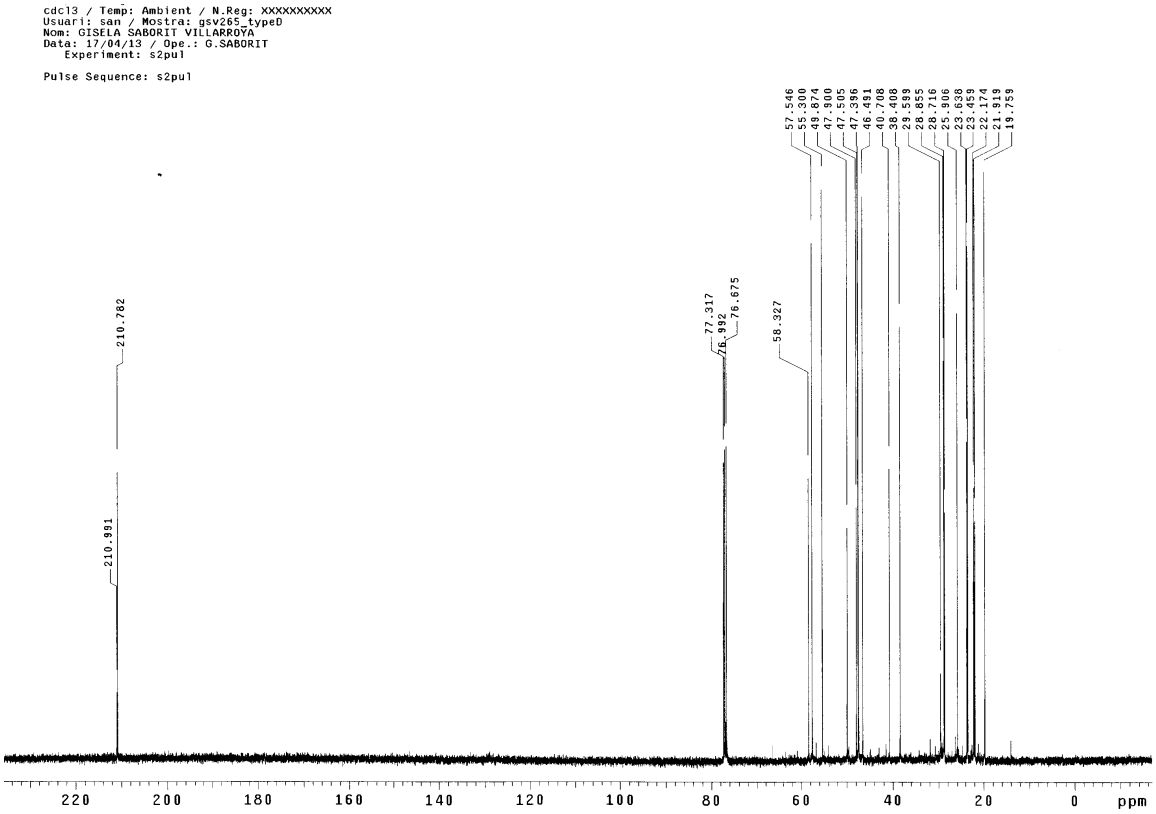
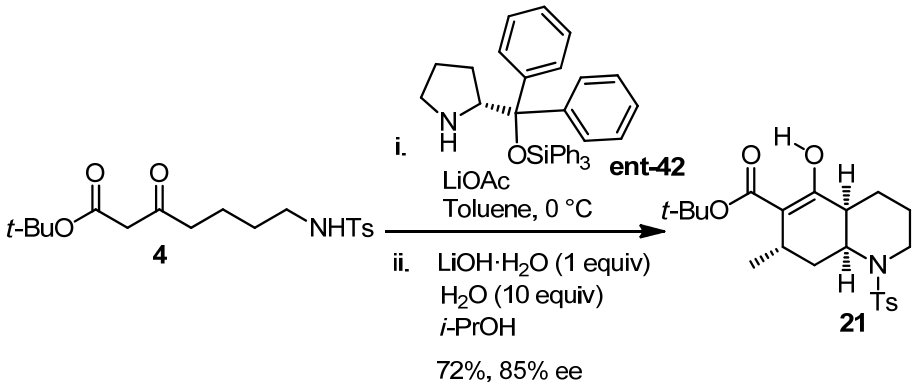
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv265_typeD
Nom: GISELA SABORIT VILLARROYA
Data: 17/04/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
O
H
H
N
H
32
7.260
2.546
1.353
1.214
0.857
0.849
0.841
0.830
8
7
6
5
4
3
2
1
0 ppm
0.41
0.97
12.63
3.00

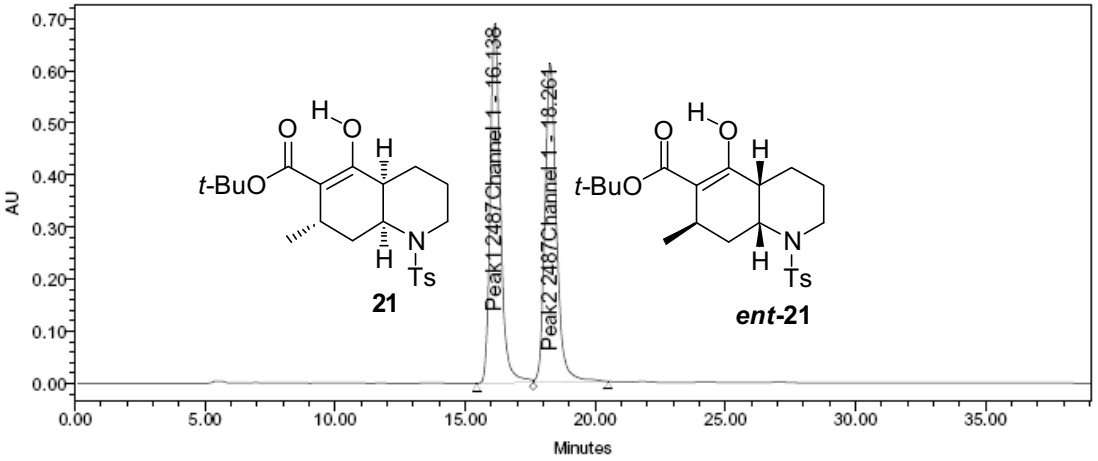

cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gsv265_typeD
Nom: GISELA SABORIT VILLARROYA
Data: 17/04/13 / Ope.: G.SABORIT
Experiment: s2pul
Pulse Sequence: s2pul
210.782
210.991
77.317
76.992
76.675
58.327
57.546
55.300
49.874
47.800
47.505
47.396
46.481
40.708
38.408
29.599
28.855
28.716
25.906
23.638
23.459
22.174
21.918
19.759
220
200
180
160
140
120
100
80
60
40
20
0
ppm

***(4aS,7S,8aS)-tert*-Butyl 7-Methyl-1-(4-methylphenylsulfonyl)-5-oxodecahydro-quinoline-6-carboxylate (21). Enantiopure version.**




To a solution of keto ester **4** (264 mg, 0.714 mmol) in toluene (6.6 mL) at 0 ºC was added crotonaldehyde (55 mg, 0.786 mmol), organocatalyst **ent-42** (73 mg, 0.143 mmol), LiOAc (24 mg, 0.357 mmol) and the resulting mixture was stirred for 16 h at 0 ºC. The mixture was concentrated on a rotary evaporator to dryness and *i*-PrOH (6.6 mL), $H_2O$ (0.13 mL, 7.14 mmol), and $LiOH{\cdot}H_2O$ (30 mg, 0.714 mmol) were added, the resulting solution being stirred for 24 h. The mixture was quenched with saturated aq $NH_4Cl$ solution (10 mL) and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and concentrated in vacuo. Purification by column chromatography (5→10→25% EtOAc/hexane) gave the enantiopure keto ester **21** (217 mg, 72%, 85% ee) as a white solid upon standing. Recrystallization from MeOH gave **21** in enantiopure form (>99% ee); mp 124 °C; $[\alpha]_D$ +103.3 (*c* 1, $CHCl_3$); HPLC (Daicel Chiralpak IC, Hexane/i-PrOH 80:20, 1 mL $min^{-1}$, l = 254 nm; minor isomer t = 18.7 min, major isomer t = 16.4 min). $R_f$ 0.34 (50% EtOAc/hexanes).

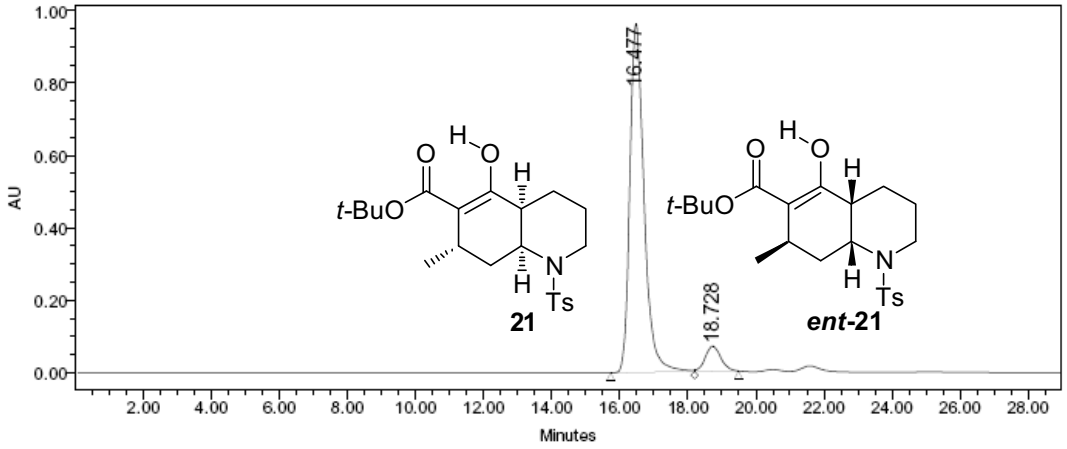
## HPLC of Racemic reaction mixture




**Processed Channel Descr.:**

| | Peak Name | RT | Area | % Area | Height |
|---|---|---|---|---|---|
| 1 | Peak1 2487Channel 1 | 16.138 | 18765073 | 49.79 | 689910 |
| 2 | Peak2 2487Channel 1 | 18.261 | 18925099 | 50.21 | 611225 |

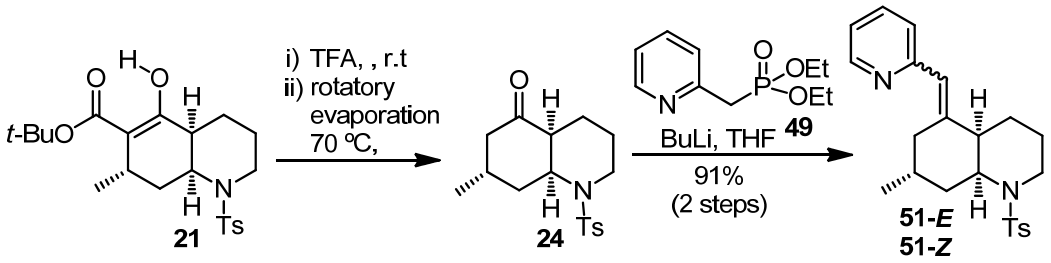
## HPLC of organocatalysed reaction mixture



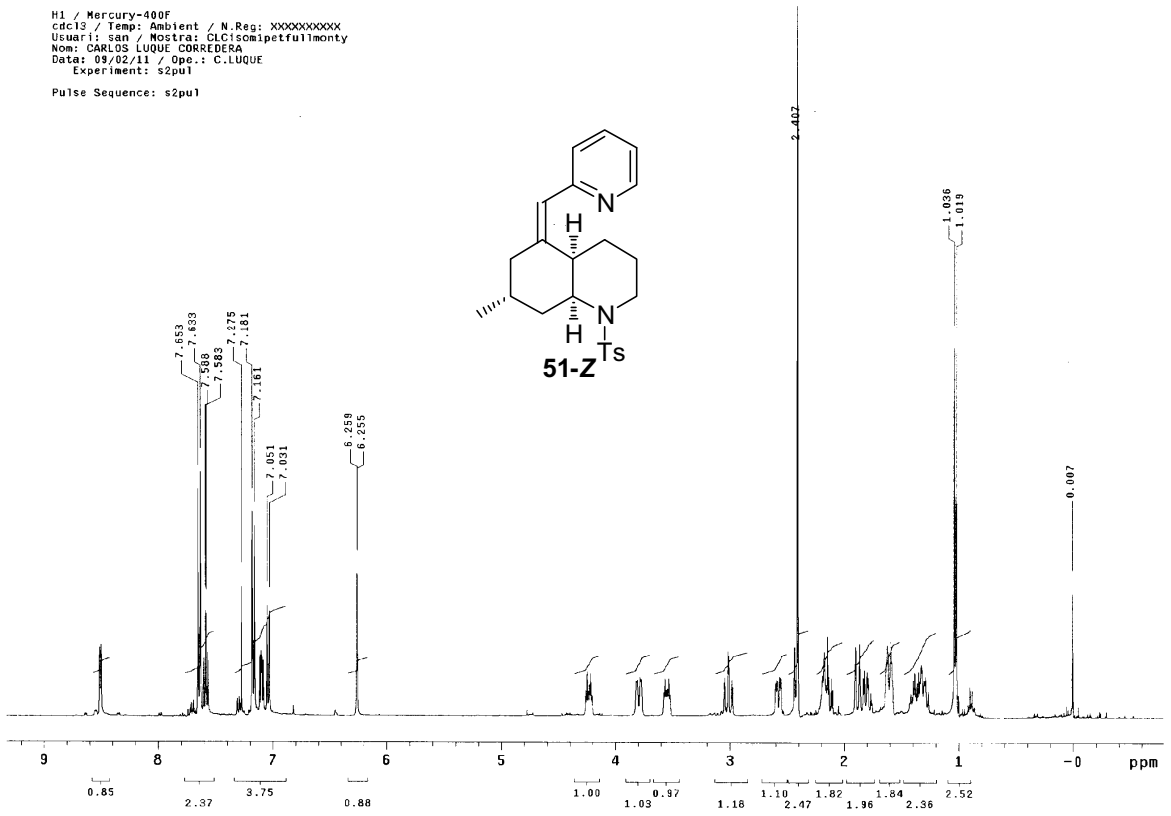

**Processed Channel Descr.:**

| | RT | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 16.477 | 27879535 | 92.68 | 963296 |
| 2 | 18.728 | 2202537 | 7.32 | 69579 |

***(4aR,7R,8aS)*-7-methyl-1-(4-methylsulfonyl)-5-(pyridin-2-ylmethylene)decahydroquinoline (51-*E* and 51-*Z*)**




**Part 1:** see previous experimental for the obtention of 5-oxodecahydroquinoline *Type A*
**Part 2:** To a stirred solution of phosphonate **49** (1.13 g, 4.92 mmol) in THF (14.3 mL) at -78 ºC was added *n*-BuLi (1.6 M in hexanes, 3.08 mL, 4.92 mmol). The resulting solution was stirred for 30 min at room temperature before a solution of the crude decahydroquinoline **24** (306 mg, 0.772 mmol) in THF (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.$NH_4Cl$ (20 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried, filtered, concentrated in vacuo, and purified by chromatography (2.5→5→10→25% EtOAc/hexane). Firstly eluted 22 mg of **51-*Z***, then 147 mg of a mixture of **51-*Z*** and **51-*E***, and finally 186 mg of **51-*E*** as a white solid. The overall yield was 94% yield of a 1:4.2 mixture of Z/E isomers **51-*Z*** and **51-*E***. Data for **51-*Z*:** $R_f$ 0.63 (50% EtOAc/hexanes); $[\alpha]_D$ +10.9 (*c* 1, $CHCl_3$); $^1$H NMR (400 MHz, COSY) δ 1.03 (d, *J* = 6.8 Hz, 3H, Me), 1.35 (m, 1H, H-8), 1.39 (m, 1H, H-3ax), 1.61 (m, 2H, H-3eq, H-4eq), 1.82 (qd, *J* = 13.0, 4.0 Hz, 1H, H-4ax), 1.89 (brd, *J* = 14.0 Hz, 1H, H-6ax), 2.13 (td, J = 13.2, 4.0 Hz, H-8ax), 2.17 (m, 1H, H-7eq), 2.41 (s, 3H, $ArCH_3$), 2.57 (ddd, *J* = 12.4, 5.0, 2.0 Hz, 1H, H-6eq), 3.01 (td, 1H, *J* = 13.2, 2.4 Hz H-2ax), 3.55 (dt, *J* = 12.8, 4.4 Hz, 1H, H-4a), 3.80 (dm, *J* = 13.2 Hz, 1H, H-2eq), 4.23 (dt, *J* = 12.8, 4.8 Hz, 1H, H-8a), 6.26 (d, *J* = 1.6 Hz, 1H, C=CH), 7.04 (d, *J* = 8.0 Hz 1H, H-3 Py), 7.10 (dd, *J* = 8.0, 4.5 Hz, 1H, H-5 Py), 7.17 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.59 (td, *J* = 7.6, 1.6 Hz, 1H, H-4 Py), 7.64 (d, *J* = 8.0 Hz, 2H, *o*-Ts), 8.51 (dm, *J* = 4.5 Hz, 1H, H-6 Py); $^{13}$C NMR (400 MHz, HSQC) δ 18.0 ($CH_3$), 21.5 ($ArCH_3$), 23.6 (C-4), 24.4 (C-3), 28.3 (C-7), 29.3 (C-8), 38.3 (C-6), 37.9 (C-4a), 40.1 (C-2), 50.4 (C-8a), 120.8 (C-5 Py), 123.5 (C-3 Py), 126.3 (=CH) 126.8 (*o*-Ts), 129.5 (*m*-Ts), 135.9 (C-4 Py), 138.8 (*p*-Ts), 142.5 (*ipso*-Ts), 145.5 (C-5), 149.3 (C-6 Py), 156.3 (C-2 Py); HRMS calcd for $C_{23}H_{28}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.194.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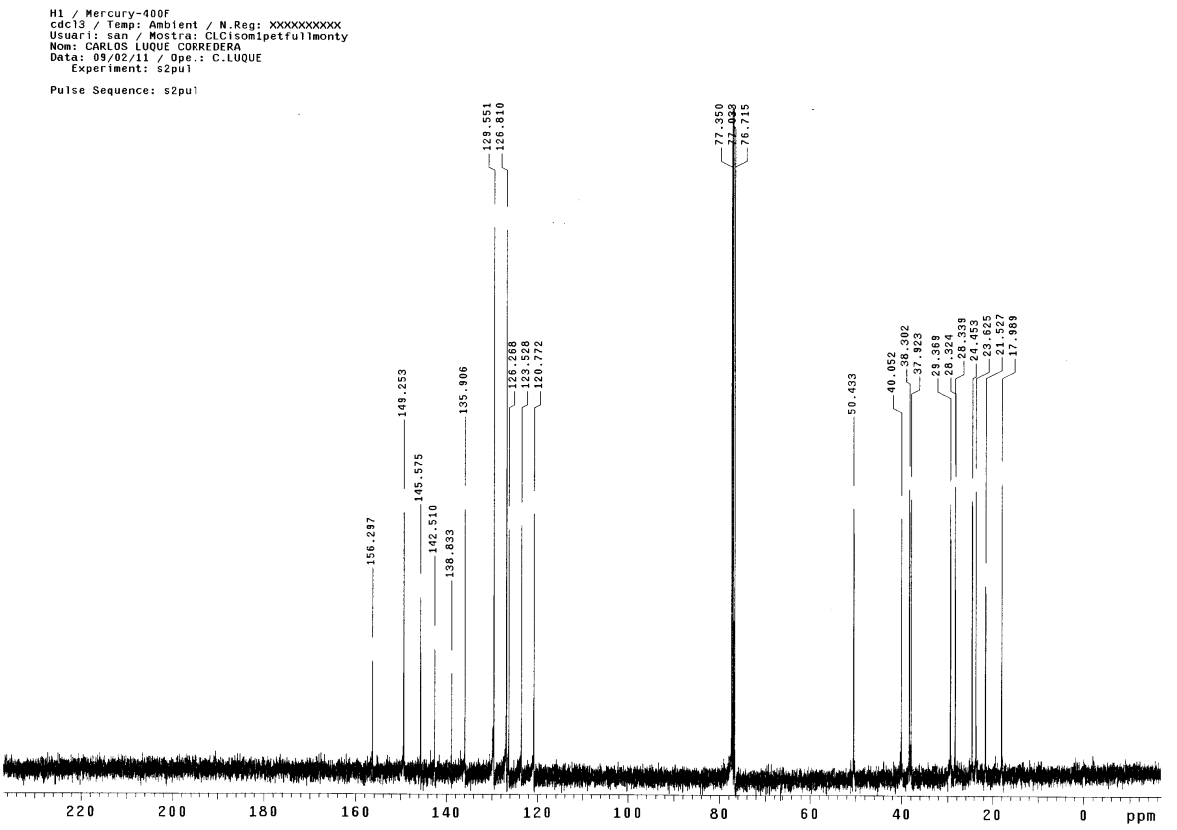
Usuari: san / Mostra: CLCisomipetfullmonty
Nom: CARLOS LUQUE CORREDERA
Data: 09/02/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
51-Z
ppm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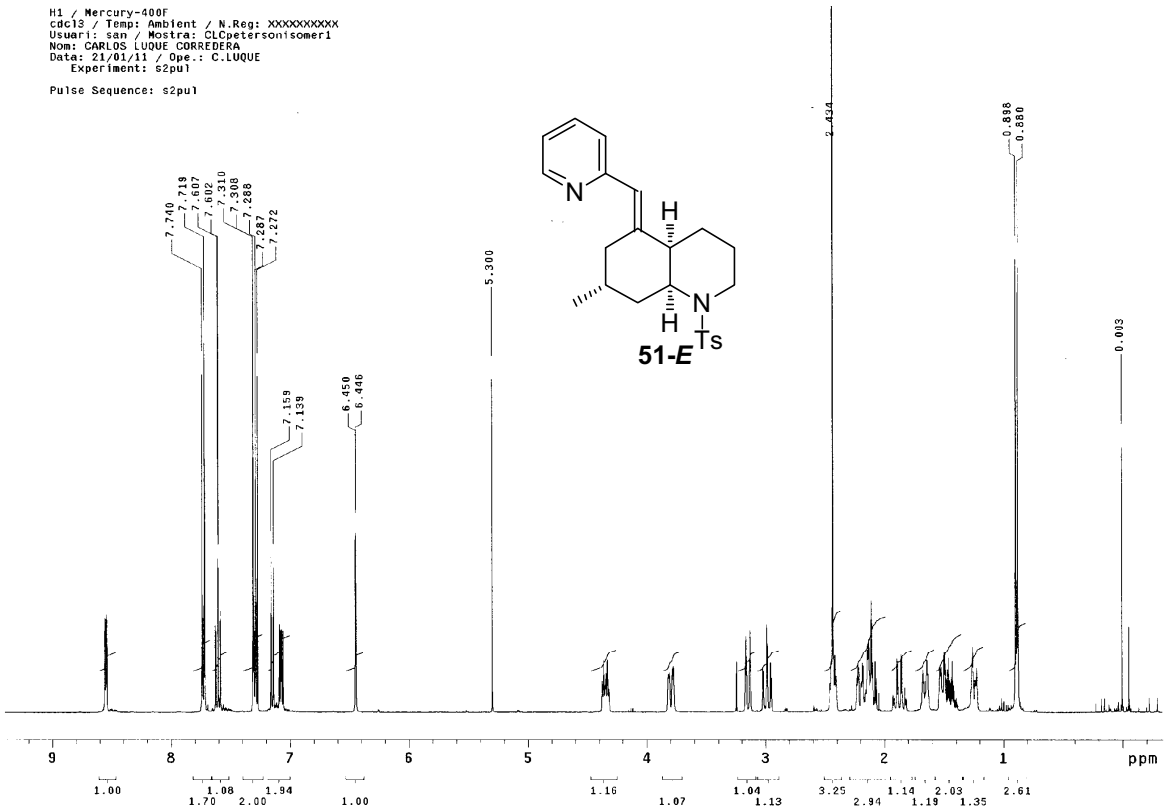
Usuari: san / Mostra: CLCisomipetfullmonty
Nom: CARLOS LUQUE CORREDERA
Data: 09/02/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
ppm

**51-*E* isomer:** mp 103 ºC; $R_f$ 0.55 (50% EtOAc/hexanes); $[\alpha]_D$ +68 (*c* 1, $CHCl_3$); $^1H$ NMR (400 MHz, COSY) $\delta$ 0.88 (d, *J* = 7.2 Hz, 3H, Me), 1.24 (m, 1H, H-8), 1.44 (m, 1H, H-4ax), 1.50 (dm, *J* = 13 Hz, 1H, H-4eq), 1.64 (dm, *J* = 13 Hz, 1H, H-3eq), 1.86 (qd, *J* = 13, 3 Hz, 1H, H-3ax), 2.08 (m, 2H, H-7, H-8), 2.20 (m, 1H, H-6), 2.40 (masked, H-4a), 2.42 (s, 3H, $ArCH_3$), 2.97 (td, *J* = 13.2, 2.8 Hz, 1H, H-2ax), 3.14 (d, *J* = 14 Hz, 1H, H-6), 3.78 (dm, *J* = 12.8 Hz, 1H, H-2eq), 4.33 (dt, *J* = 12.8, 4.8 Hz, 1H, H-8a), 6.43 (d, *J* = 1.6, Hz, 1H, C=CH), 7.06 (m, 1H, H-5 Py), 7.15 (d, *J* = 8.0 Hz, 1H, H-3 Py), 7.29 (dd, *J* = 8.8, 0.8 Hz, 2H, *m*-Ts), 7.59 (td, *J* = 8.0, 2.0 Hz, 1H, H-4 Py), 7.72 (d, *J* = 8 Hz, 2H, *o*-Ts), 8.54 (dm, *J* = 4.5 Hz, 1H, H-6 Py); $^{13}C$ NMR (400 MHz, HSQC) δ 18.0 ($CH_3$), 21.5 ($ArCH_3$), 24.9 (C-3), 25.1 (C-4), 28.5 (C-7), 29.2 (C-8), 29.6 (C-6), 39.8 (C-2), 47.2 (C-4a), 51.0 (C-8a), 120.9 (C-5 Py), 124.1 (C-3 Py), 126.5 (=CH), 126.9 (*o*-Ts), 129.7 (*m*-Ts), 136.0 (C-4 Py), 138.7 (*p*-Ts), 142.9 (*ipso*-Ts), 146.1 (C-5), 149.1 (C-6 Py), 156.7 (C-2 Py); HRMS calcd for $C_{23}H_{28}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.1937.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Usuari: san / Mostra: CLCpetersonisomer1
Nom: CARLOS LUQUE CORREDERA
Data: 21/01/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
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7.602
7.310
7.308
7.288
7.287
7.272
7.159
7.139
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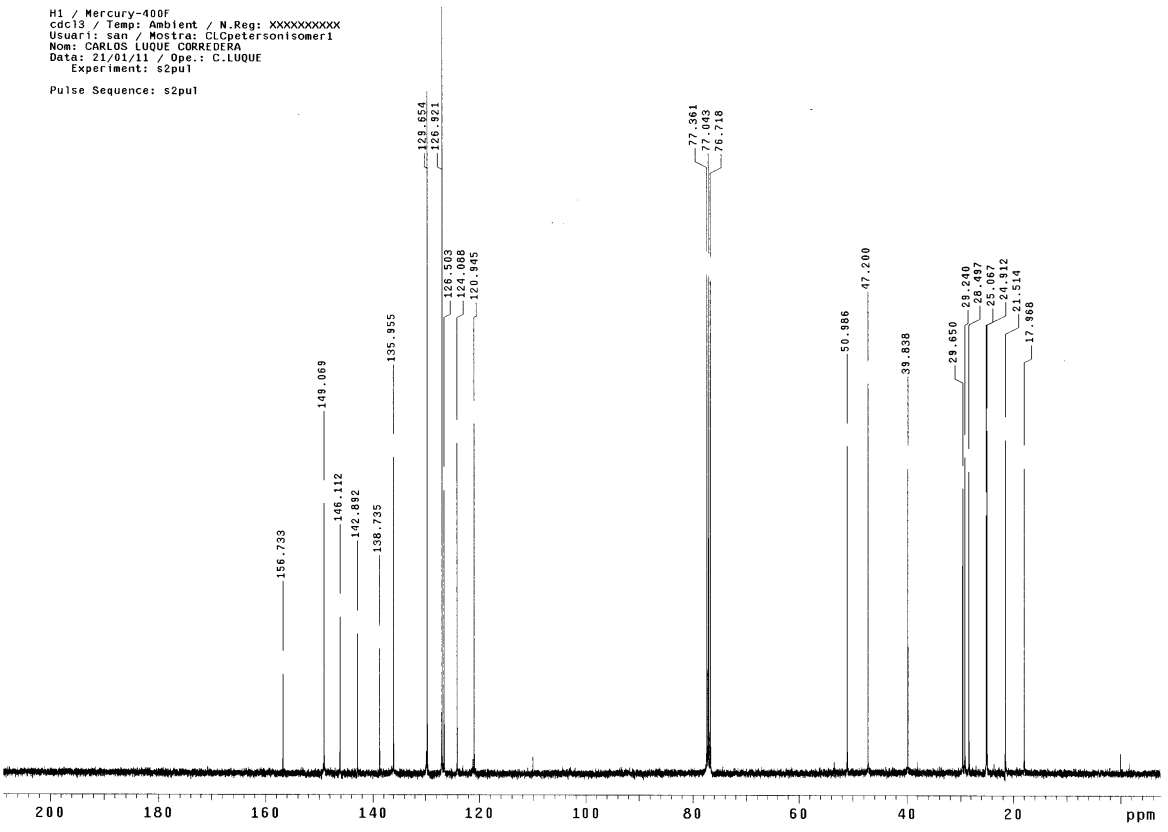
6.446
5.300
2.434
0.898
0.880
0.003
ppm
1.00
1.08
1.70
1.94
2.00
1.00
1.16
1.07
1.04
1.13
3.25
2.94
1.14
1.19
2.03
1.35
2.61

**51-*E***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cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCpetersonisomer1
Nom: CARLOS LUQUE CORREDERA
Data: 21/01/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
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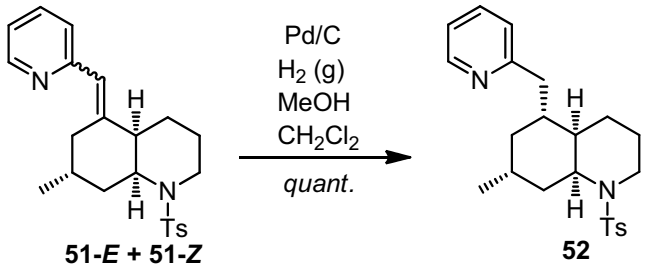
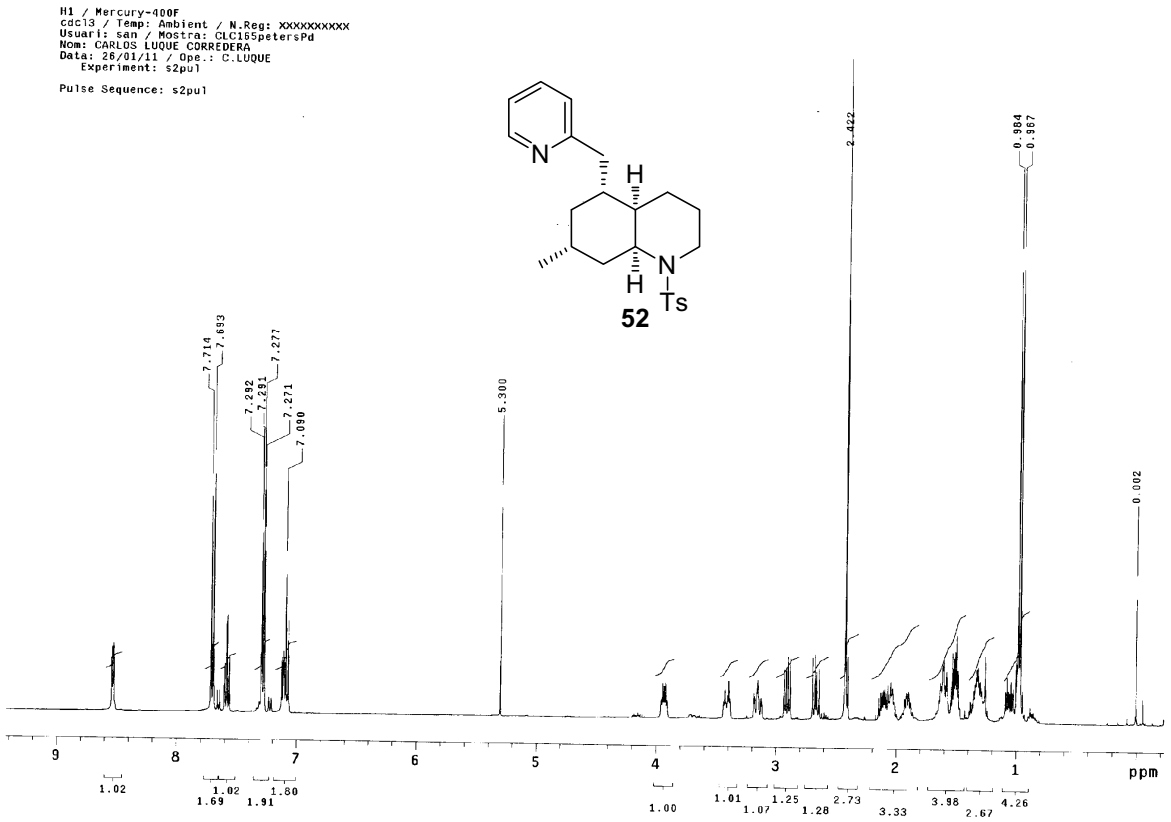
146.112
142.892
138.735
135.955
129.654
126.921
126.503
124.088
120.945
77.361
77.043
76.718
50.986
47.200
39.838
29.650
29.240
28.497
25.067
24.912
21.514
17.968
ppm

***(4aR,5R,7R,8aS)*-7-methyl-5-(pyridine-2-ylmethyl)-1-tosyldecahydroquinoline (52)**




**51-*E* + 51-*Z*** **52**

To a stirred solution of the mixture of **51-*E*** and **51-*Z*** (341 mg, 0.86 mmol) in MeOH/$CH_2Cl_2$ 1:1 (14 mL) was added Pd/C (10% w/w, 34 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 3 h. The mixture was diluted with $CH_2Cl_2$ ( ≈ 30 mL), filtered through a pad of celite, washed through with $CH_2Cl_2$ and the filtrate was concentrated in *vacuo*. The crude product **52** was essentially pure and was used in the next step without further purification. An analytical sample was prepared by flash silica gel chromatography (5→10→25% EtOAc/hexane) to give **52** as a colourless oil: $R_f$ 0.37 (50% EtOAc/hexanes); $[\alpha]_D$ +16.3 (*c* 1, $CHCl_3$); $^1$H NMR (400 MHz, COSY) δ 0.96 (d, *J* = 6.8 Hz, 3H, $CH_3$), 0.99 (dt, *J* = 14.0, 5.2 Hz 1H, H-6eq), 1.04 (dt, *J* = 13.2, 5.5 Hz, 1H, H-8eq), 1.30 (m, 2H, H-3, H-4), 1.50 (ddd, *J* =14.0, 6.2 5.2 Hz 1H, H-6ax), 1.50 (masked, 1H, H-5eq), 1.58 (m, 2H, H-3, H-4), 1.88 (octet, *J* = 6.4 Hz, H-7eq), 2.03 (m, 1H, H-4a), 2.10 (ddd, *J* = 13.0, 10.0, 6.4 Hz, 1H, H-8ax), 2.41 (s, 3H, $ArCH_3$), 2.65 (dd, *J* = 13.2, 8.0 Hz, 1H, $CH_2Py$), 2.94 (dd, *J* = 13.2, 6.4 Hz, 1H, $CH_2Py$), 3.14 (td, *J* = 11.6, 3.2 Hz, 1H, H-2ax), 3.40 (dt, *J* = 12.4, 4.0 Hz, 1H, H-2eq), 3.92 (dt, *J* = 10.0, 4.6 Hz, 1H, H-8a), 7.05 (d, *J* = 8.0 Hz, 1H, H-3 Py), 7.12 (m, 1H, H-5 Py), 7.28 (d, *J* = 8.4 Hz, 2H, *m*-Ts), 7.58 (td, *J* = 7.8, 1.6 Hz, 1H, H-4 Py), 7.70 (d, *J* = 8.4 Hz, 2H, *o*-Ts), 8.53 (dm, *J* = 4.8 Hz, 1H, H-6 Py); $^{13}$C NMR (100 MHz, HSQC) δ 21.5 ($ArC\underline{H}_3$), 22.2($CH_3$), 24.0 (C-4), 26.2 (C-3), 27.2 (C-7), 31.1(C-8), 34.0 (C-6), 39.4 (C-4a), 39.7 (C-5), 42.5 (C-2), 44.2 ($CH_2Py$), 51.4 (C-8a), 121.0 (C-5 Py), 123.7 (C- 3 Py), 126.8 (*o*-Ts), 129.5 (*m*-Ts), 136.1 (C-4 Py), 137.5 (*p*-Ts), 142.8 (*ipso*-Ts), 149.3 (C-6 Py), 160.8 (C-2 Py); HRMS calcd for $C_{23}H_{30}N_2O_2S$ $(M+H)^+$ 399.2101, found 399.2097.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Data: 26/01/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
N
H
H
N
Ts
52
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7.693
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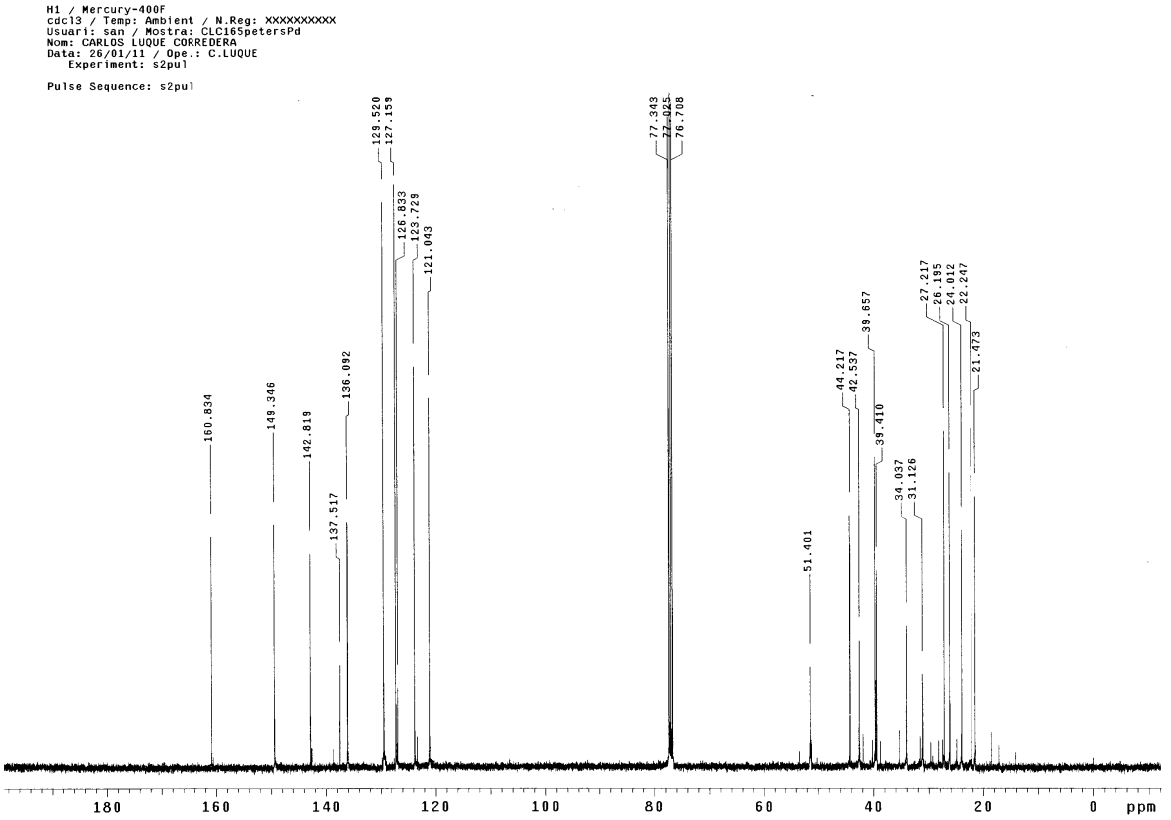
7.281
7.277
7.271
7.090
5.300
2.422
0.984
0.967
0.002
ppm


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC165petersPd
Nom: CARLOS LUQUE CORREDERA
Data: 26/01/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
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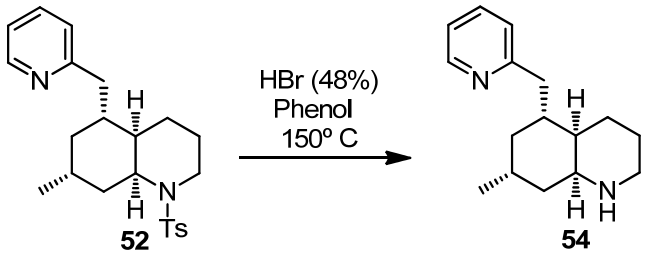
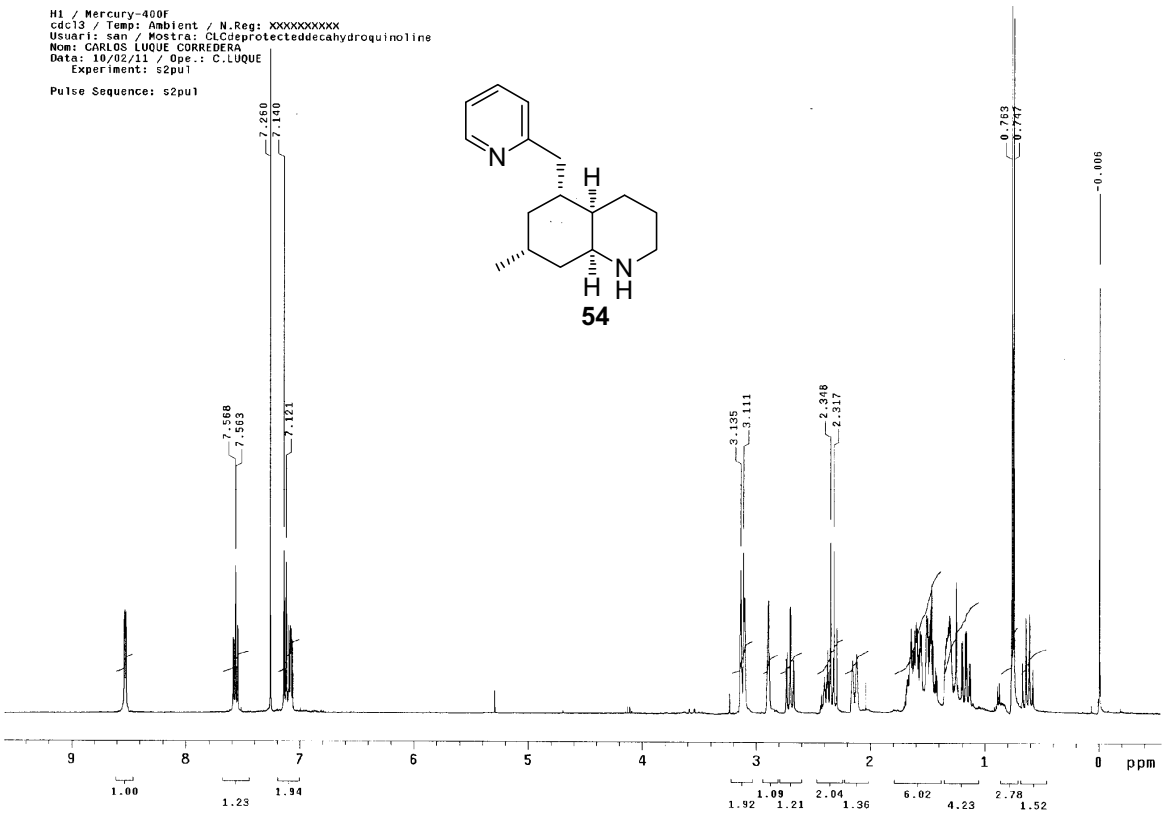
149.346
142.819
137.517
136.092
129.520
127.159
126.833
123.728
121.043
77.343
77.025
76.708
51.401
44.217
42.537
39.657
39.410
34.037
31.126
27.217
26.195
24.012
22.247
21.473
ppm

***(4aR,5R,7R,8aS)*-7-methyl-5-(pyridine-2ylmethyl)decahydroquinoline (54)**




**52** **54**

A solution of **52** (~0.86 mmol)) and phenol (283 mg, 3.01 mmol) in HBr 48% (4.0 mL) was stirred at reflux for 4 h. The reaction was quenched by addition of $H_2O$ (5 mL) and diluted with EtOAc (5 mL). The organic layer was separated, and the aqueous layer was basified with sat. aq. NaOH and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated and the resulting crude material **54** (150 mg) was essentially pure and was used directly in the next step. An analytical sample was prepared by flash chromatography on alumina (2.5→5→10% MeOH/$CH_2Cl_2$): $R_f$ 0.33 (10% MeOH/$CH_2Cl_2$); $^1$H NMR (400 MHz, COSY) δ 0.62 (q, *J* = 11.6 Hz, 1H, H-6ax), 0.75 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.16 (td, *J* = 12.8, 3.6 Hz, 1H, H-8ax), 1.30 (s, 1H, NH), 1.34 (m, 2H, H-5ax, H-3), 1.42-1.52 (m, 2H, H-4ax, H-6eq), 1.56-1.68 (m, 3H, H-3, H-4a, H-8eq), 2.11 (dm, *J* = 13.2 Hz, 1H, H-4eq), 2.33 (t, *J* = 12.8 Hz, 1H, $CH_2$Py), 2.40 (m, 1H, H-7ax), 2.70 (td, *J* = 12.0, 3.0 Hz, 1H, H-2ax), 2.90 (q, *J* = 3.0 Hz, 1H, H-8a), 3.12 (dd, *J* = 12.8, 3.2 Hz, 1H, $CH_2$Py), 3.12 (dm, *J* = 12.4 Hz, 1H, H-2eq), 7.08 (m, 1H, H-5 Py), 7.13 (d, *J* = 8.0 Hz, 1H, H-3 Py), 7.56 (td, *J* = 7.8, 1.6 Hz, 1H, H-4 Py), 8.52 (dm, *J* = 4.8 Hz, 1H, H-6 Py); $^{13}$C NMR (100 MHz, HSQC) δ 21.4 (C-3), 22.6 ($CH_3$), 26.7 (C-4a), 27.0 (C-4), 33.5 (C-7), 40.8 (C-5), 40.9 (C-6), 42.0 (C-8), 42.7 ($CH_2$Py), 48.1 (C-2), 56.7 (C-8a), 120.7 (C-5 Py), 123.6 (C-3 Py), 135.9 (C-4 Py), 149.1 (C-6 Py), 161.8 (C-2 Py); HRMS calcd for $C_{16}H_{24}N_2$ $(M+H)^+$ 245.2012, found 245.2009.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Usuari: san / Mostra: CLCdeprotecteddecahydroquinoline
Nom: CARLOS LUQUE CORREDERA
Data: 10/02/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
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7.568
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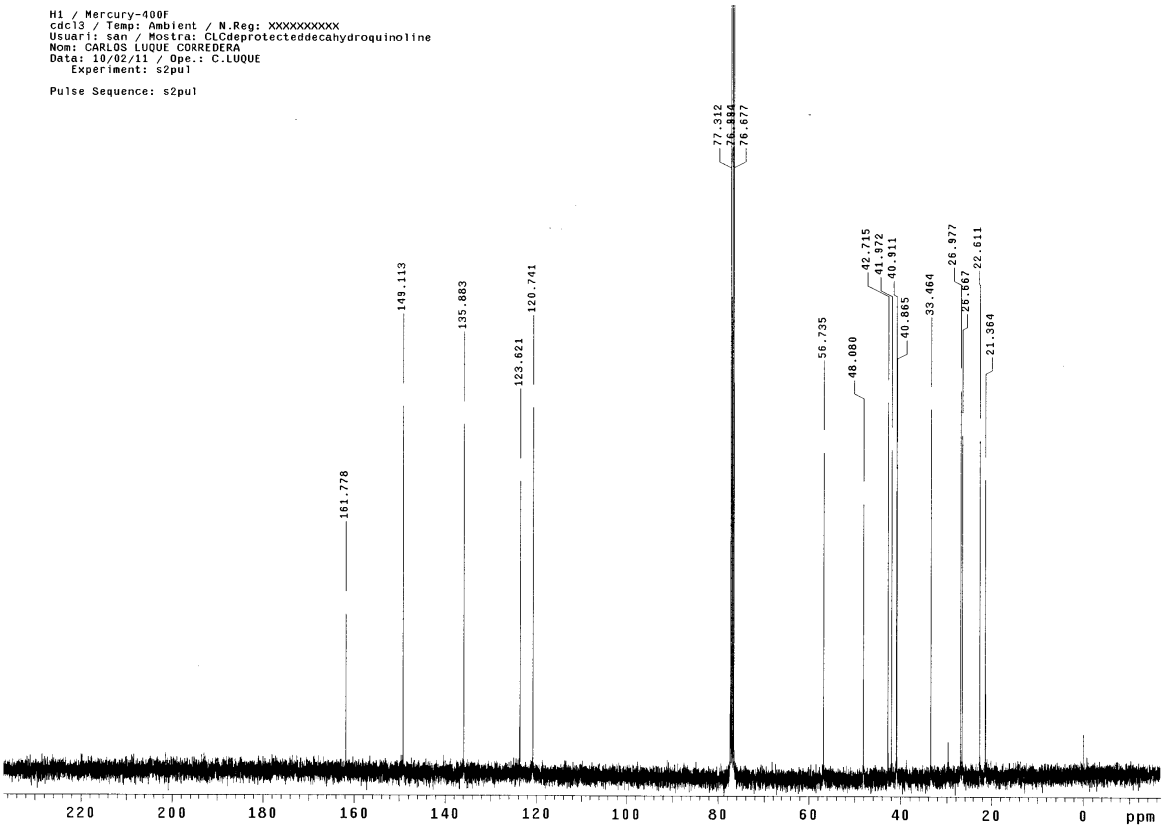
7.121
3.135
3.111
2.346
2.317
0.763
0.747
-0.006
1.00
1.23
1.94
1.92
1.09
1.21
2.04
1.36
6.02
4.23
2.78
1.52
ppm

54


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCdeprotecteddecahydroquinoline
Nom: CARLOS LUQUE CORREDERA
Data: 10/02/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
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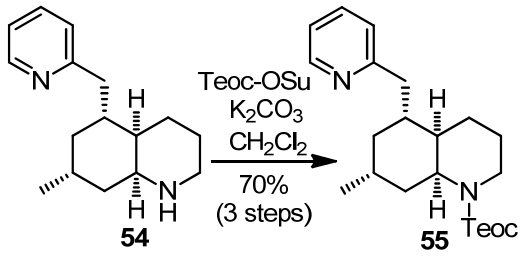
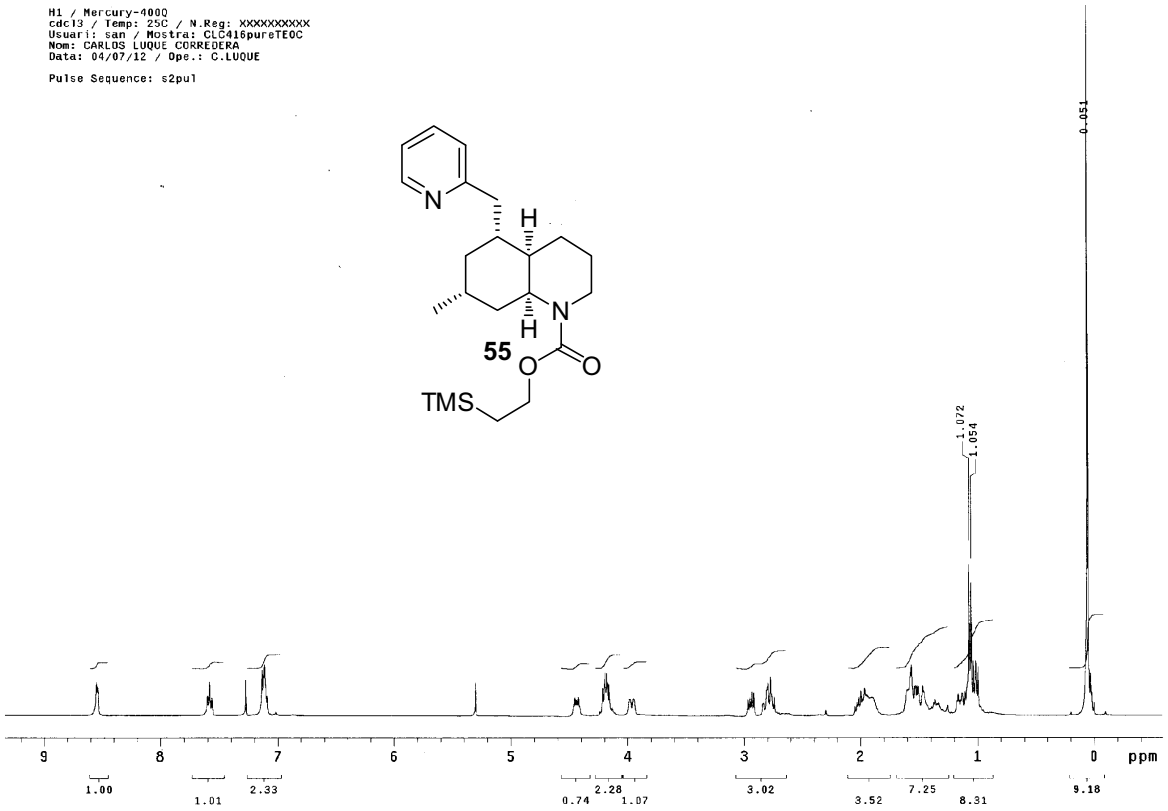
76.677
161.778
149.113
135.883
123.621
120.741
56.735
48.080
42.715
41.972
40.911
40.665
33.464
26.977
26.667
22.611
21.364
ppm

**(4*aR*,5*R*,7*R*,8*aS*)-2-(Trimethylsilyl)ethyl-7-Methyl-5-(pyridin-2-ylmethyl) octahydroquinoline-1(2H)-carboxylate (55)**




To a stirred solution of deprotected decahydroquinoline **54** (~0.86 mmol) in dry $CH_2Cl_2$ (3.7 mL) were added $K_2CO_3$ (297 mg, 2.15 mmol) and Teoc-OSu[125] (446 mg, 1.72 mmol) at room temperature under argon atmosphere. After stirring for 24 h at room temperature, the reaction mixture was poured into $H_2O$ and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with sat.aq.$NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude was dissolved in $Et_2O$ (15 mL) and was acidified to pH=1 with 2 N HCl. The acidic phase was extracted with $Et_2O$ (2 × 5 mL), carefully basified with sat.aq. $NaHCO_3$, extracted with $CH_2Cl_2$ (3 × 10 mL), dried and concentrated in vacuo to give **55** (168 mg, 70%) as an oil: $R_f$ 0.51 (50% EtOAc/hexanes); $[\alpha]_D$ -10.1 (*c* 1, $CHCl_3$); $^1$H NMR (400 MHz, COSY) $\delta$ 0.05 (s, 9H, $SiMe_3$), 1.02 (m, 2H, $CH_2Si$), 1.06 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.10 (masked, 1H, H-6), 1.15(m, 1H, H-8eq), 1.30-1.45 (m, 2H, H-3, H-4), 1.50-1.60 (m, 4H, H-3, H-4, H-6, H-4a), 1.90-2.05 (m, 3H, H-7eq, H-8ax, H-5), 2.77 (masked 1H, $CH_2Py$), 2.80 (td, *J* = 12.8, 3.0 Hz, 1H, H-2ax), 2.94 (dd, *J* = 13.0, 7.2 Hz, 1H, $CH_2Py$), 3.95 (dm, *J* = 12.8 Hz, 1H, H-2eq), 4.18 (m, 2H, $CO_2CH_2$), 4.44 (dt, *J* = 12.0, 4.8 Hz, 1H, H-8a), 7.10 (m, 2H, H-3 and H-5 Py), 7.58 (td, *J* = 8.0, 2.0 Hz, 1H, H-4 Py), 8.54 (d, *J* = 4.2 Hz, 1H, H-6 Py); $^{13}$C NMR (100 MHz, HSQC) δ -1.4 ($SiMe_3$), 17.8 ($CH_2Si$), 22.4 ($CH_3$), 25.2 (C-4), 26.4 (C-3), 27.4 (C-7), 29.1 (C-8), 32.7 (C-6), 38.7 (C-5), 39.0 (C-2), 41.0 (C-4a), 45.0 ($CH_2Py$), 46.9 (C-8a), 63.2 ($CO_2CH_2$), 121.0 (C-5 Py), 123.7 (C- 3 Py), 136.1 (C-4 Py), 149.4 (C-6 Py), 155.9 (CO), 161.1 (C-2 Py).

[125] Teoc-OSu = 1-[2-(trimethylsilyl)ehtoxycarbonyloxy]pyrrolidin-2,5-dione.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Usuari: san / Mostra: CLC416pureTEOC
Nom: CARLOS LUQUE CORREDERA
Data: 04/07/12 / Ope.: C.LUQUE
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TMS
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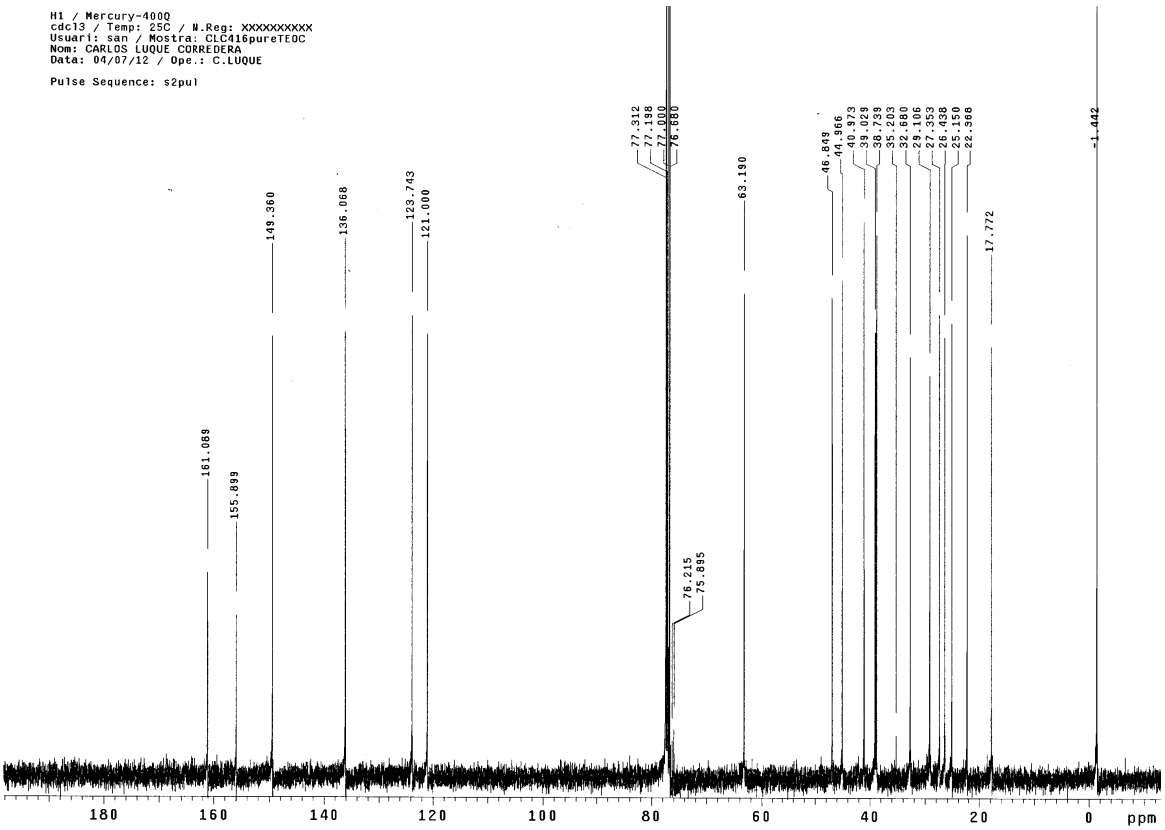
1.01
2.33
0.74
2.28
1.07
3.02
3.52
7.25
8.31
9.18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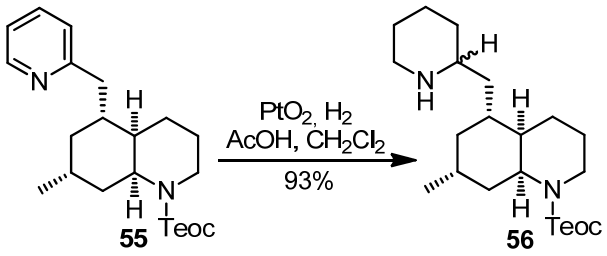
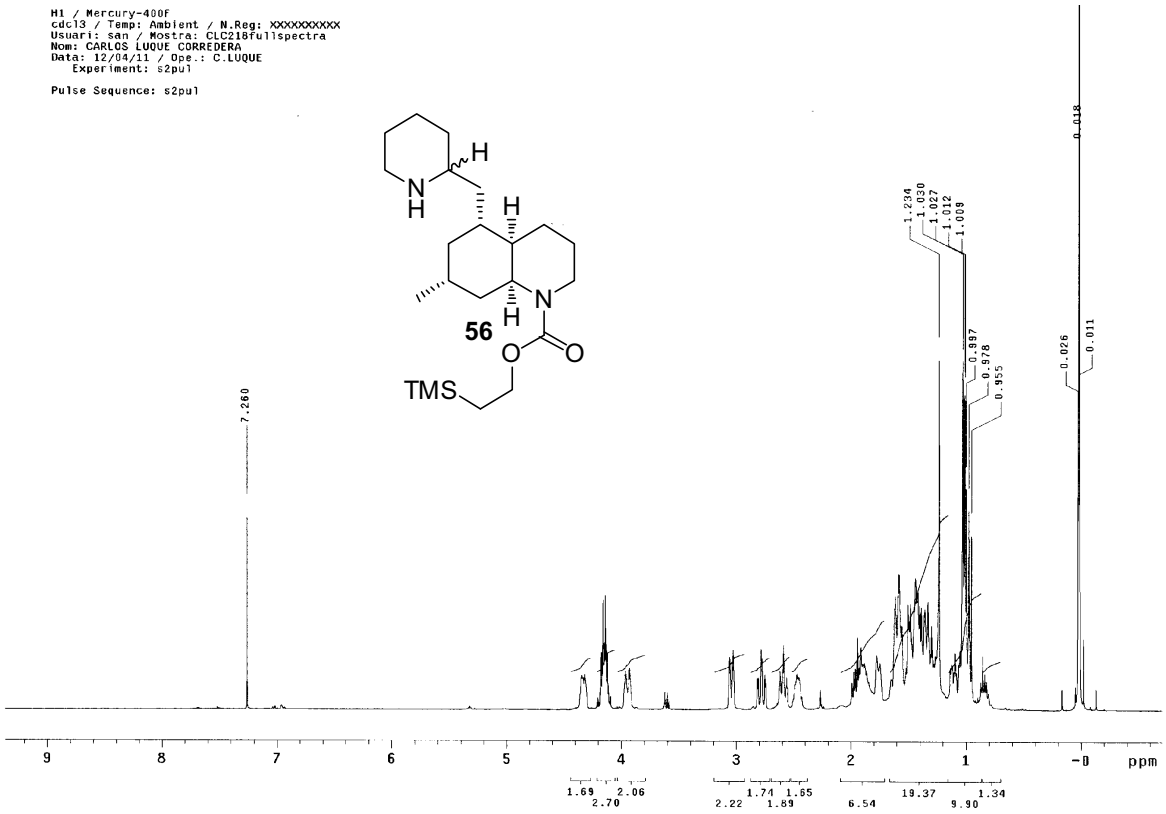
Usuari: san / Mostra: CLC416pureTEOC
Nom: CARLOS LUQUE CORREDERA
Data: 04/07/12 / Ope.: C.LUQUE
Pulse Sequence: s2pul
ppm

***(4aR,5R,7R,8aS)*-2-(trimethylsilyl)ethyl-7-methyl-5-(piperidin-2-ylmethyl)octahydroquinoline-1(*2H*)-carboxylate (56)**




**55** **56**

To a stirred solution of **55** (153 mg, 0.394 mmol) in AcOH (3 mL) was added $PtO_2$ (20% w/w, 31 mg) at room temperature. 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 $CH_2Cl_2$ ( ≈ 20 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 *in vacuo* to give the epimeric mixture **56** (144 mg, 93%) as a colourless oil; $^1$H NMR (400 MHz, COSY) δ 0.02 (s, 9H, $SiMe_3$), 1.02 (m, 2H, $CH_2Si$), 1.02 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.10 (masked, 1H, H-6), 1.15 (m, 1H, H-8eq), 1.25-1.50 (m, 9H), 1.60 (m, 4H), 1,75 (m, 2H), 1.85-2.00 (m, 3H, H-7eq, H-8ax), 2.47 (m, 1H, H-2´ax), 2.59 (td, *J* = 12.8, 3.0 Hz, 1H, H-6´ax), 2.78 (td, *J* = 12.8, 3.0 Hz, 1H, H-2ax), 3.04 (dm, *J* = 12 Hz, 1H, H-6´eq), 3.94 (dm, *J* = 13.6 Hz, 1H, H-2eq), 4.14 and 4.17 (2 m, 1H each, $CO_2CH_2$), 4.33 (dm, *J* = 12.0 Hz, 1H, H-8a); $^{13}$C NMR (100 MHz, HSQC) δ -1.5 ($SiMe_3$), 17.7 ($CH_2Si$), 22.1 ($CH_3$), 24.8/24.9 (C-4´), 25.3 (C-4), 26.5/26.6 (C-3), 26.7(C-5´) 27.4/27.5 (C-7), 29.1/29.2 (C-8), 32.5/33.1 (C-3´), 36.3/36.7 (C-6), 39.0 (C-5), 39.4 (C-2), 39.9 (C-4a), 44.5/44.6 ($CH_2$), 46.6 and 46.7 (C-6´), 47.1 (C-8a), 54.5 and 54.9 (C-2´), 63.1 ($CO_2CH_2$), 155.9 (CO); HRMS calcd for $C_{22}H_{42}N_2O_2Si$ $(M+H)^+$ 395.3088, found 395.3088.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Data: 12/04/11 / Ope.: C.LUQUE
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Pulse Sequence: s2pul
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1.027
1.012
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0.978
0.955
0.026
0.011
0.018
9
8
7
6
5
4
3
2
1
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ppm
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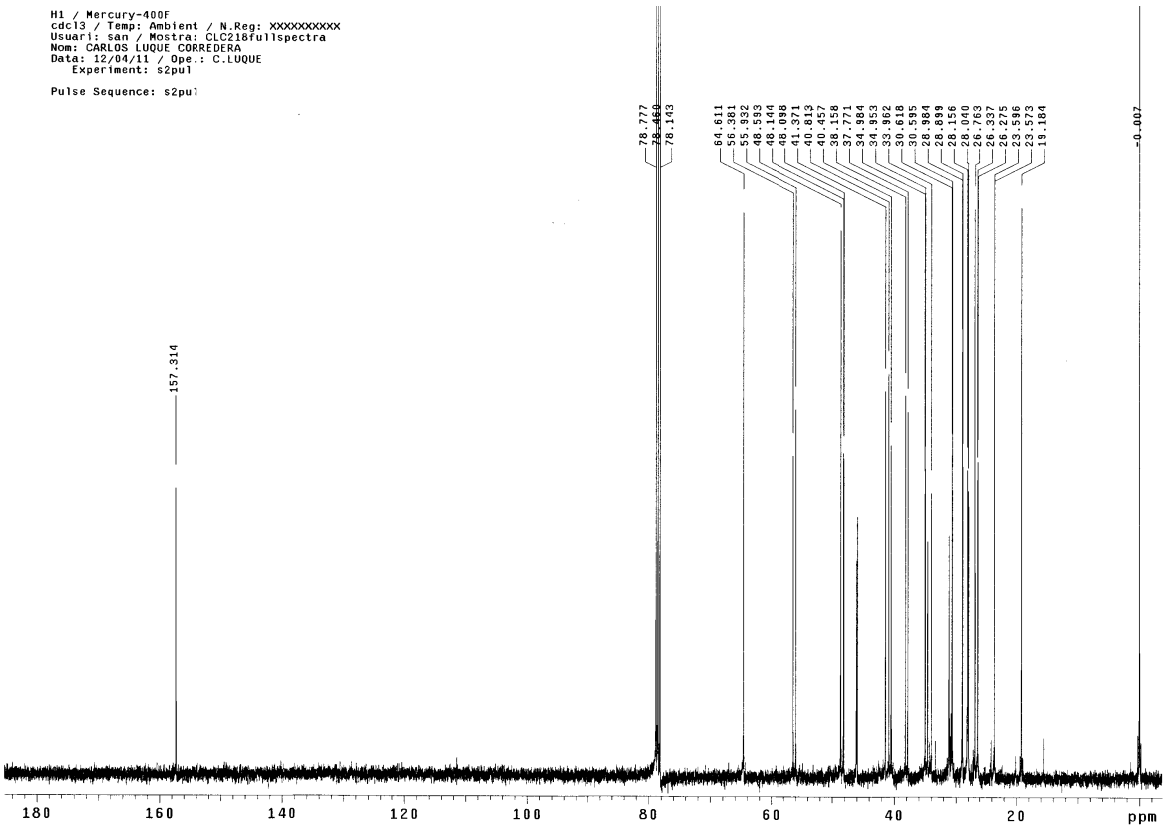
2.22
1.74
1.85
6.54
19.37
9.90
1.34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cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC218fullspectra
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Data: 12/04/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
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78.460
78.143
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48.593
48.144
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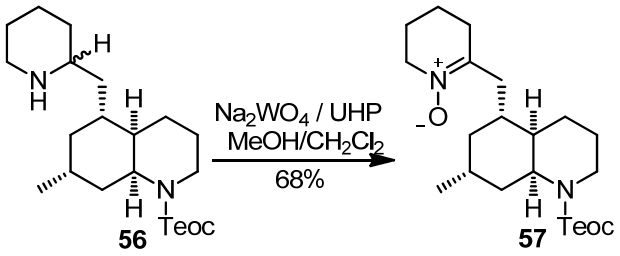
38.158
37.771
34.984
34.953
33.962
30.618
30.595
28.984
28.699
28.156
28.000
26.763
26.337
26.275
23.596
23.573
19.184
-0.007
180
160
140
120
100
80
60
40
20
ppm

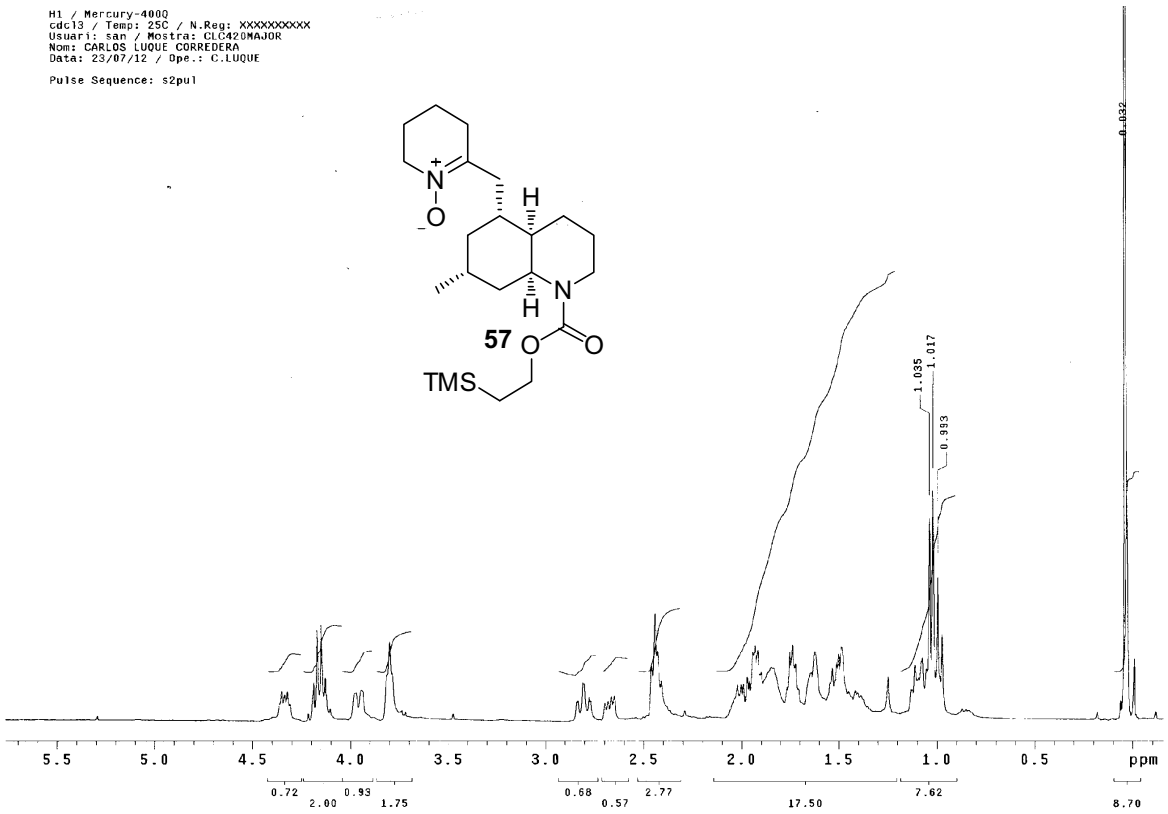
**6-[(4*aR*,5*R*,7*R*,8*aS*)-7-Methyl-1-[[2-(trimethylsilyl)ethoxycarbonyl)decahydro-quinolin-5-ylmethyl)]-2,3,4,5-tetrahydropyridine 1-oxide (57)**




56 57

To a solution of mixture **56** (50 mg, 0.127 mmol) in MeOH/ $CH_2Cl_2$ 1:1 (0.6 mL) were added in one portion UHP[126] (47.8 mg, 0.508 mmol) and $Na_2WO_4 \cdot 2H_2O$ (2.1 mg, 0.006 mmol) and the mixture was stirred at room temperature for 6 h (until no more starting material was detected by TLC control). The reaction mixture was concentrated *in vacuo* to remove the solvent, and then the residue was dissolved in $CH_2Cl_2$ and filtered to separate the UHP traces. The filtrate was concentrated in vacuo and purified by column chromatography (1→2.5→5% MeOH/$CH_2Cl_2$) to gave the cyclic nitrone **57** (35 mg, 68%) as a colourless oil which had identical spectral data that the previous reported. $R_f$ 0.4 (10% MeOH/$CH_2Cl_2$); $[\alpha]_D$ +0.9 (*c* 1, $CHCl_3$), lit: $[\alpha]_D$ -17.2 (*c* 0.19, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz, COSY) $\delta$ 0.03 (s, 9H, $SiMe_3$), 0.99 (t, *J* = 8.6 Hz, 2H, $CH_2Si$), 1.03 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.10 (m, 2H, H-6, H-8), 1.40 (m, 1H, H-3), 1.48**-**1.54 (m, 3H, H-4a, H-6, H-4), 1.62**-**1.64 (m, 2H, H-3, H-4), 1.75 (m, 2H, H-4´), 1.85 (m, 1H, H-7), 1.94 (m, 2H, H-3´), 1.98 (m, H-8), 2.00 (m, 1H, H-5), 2.44 (m, 3H, $CH_2$, 2H-5´), 2.67 (dd, *J* =13.0, 6.2 Hz, 1H, $CH_2$), 2.80 (1H, td, *J* =12.8, 2.4 Hz, 1H, H-2ax), 3.80 (m, 2H, H-2´), 3.96 (br d, *J* =13.2 Hz, 1H, H-2eq), 4.15 and 4.17 (2 dt, *J* = 15.0 and 8.5 Hz, 1H each, $CO_2CH_2$), 4.34 (dt, *J* =12.0, 4.5 Hz, 1H, H-8a); $^{13}$C NMR ($CDCl_3$, 100 MHz, gHSQC) **-**1.5 ($SiMe_3$), 17.8 ($CH_2Si$), 18.9 (C-4´), 22.5 ($CH_3$), 23.1 (C-3´), 24.8 (C-3), 26.4 (C-4), 27.2 (C-7), 29.5 (C-8), 30.8 (C-5´), 34.0 (C-6), 36.3(C-5), 38.8 ($CH_2$), 39.1 (C-4a), 39.5 (C-2), 47.3 (C-8a), 58.2 (C-2´), 63.2 ($CO_2CH_2$), 148.3 (C-6´), 155.9 ($CO_2R$). HRMS calcd for $C_{22}H_{40}N_2O_3Si$ $(M+H)^+$ 409.2881, found 409.2877.

[126] UHP = Urea-Hydrogen-Peroxide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Usuari: san / Mostra: CLC420MAJOR
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Pulse Sequence: s2pul
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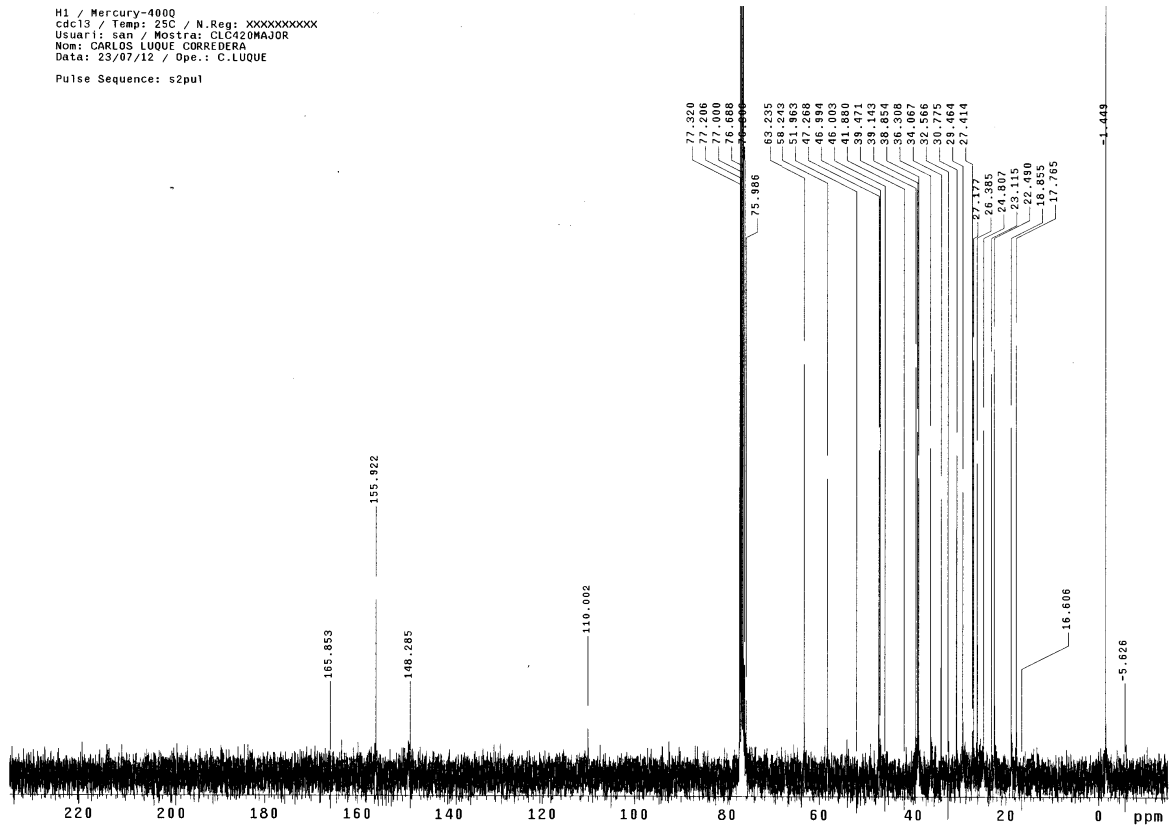
TMS
ppm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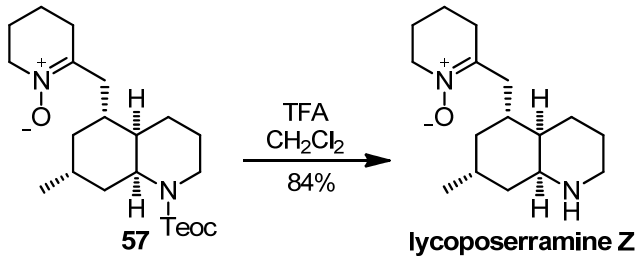
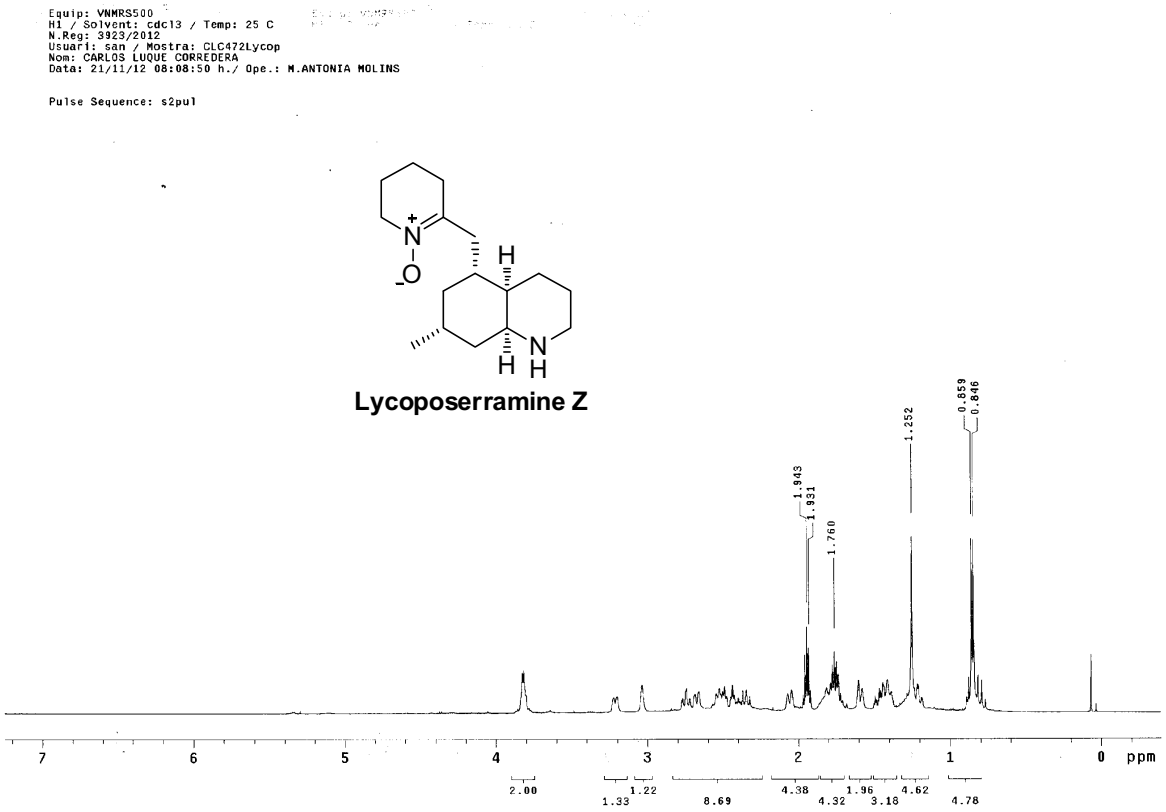
Usuari: san / Mostra: CLC420MAJOR
Nom: CARLOS LUQUE CORREDERA
Data: 23/07/12 / Ope.: C.LUQUE
Pulse Sequence: s2pul
ppm

**6-[(4*aR*,5*R*,7*R*,8*aS*)-(7-Methyldecahydroquinolin-5-yl)methyl]-2,3,4,5-tetrahydro-pyridine 1-oxide . [lycoposerramine-Z]**

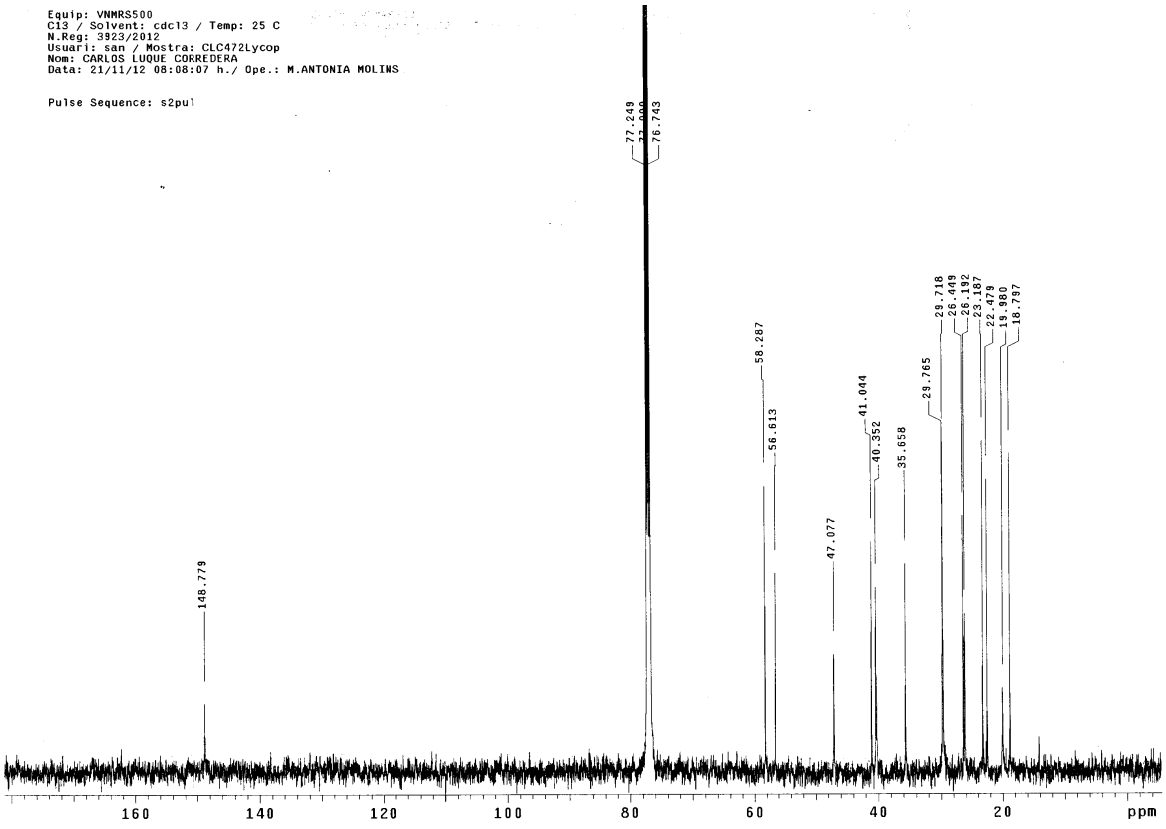



**57** **lycoposerramine Z**

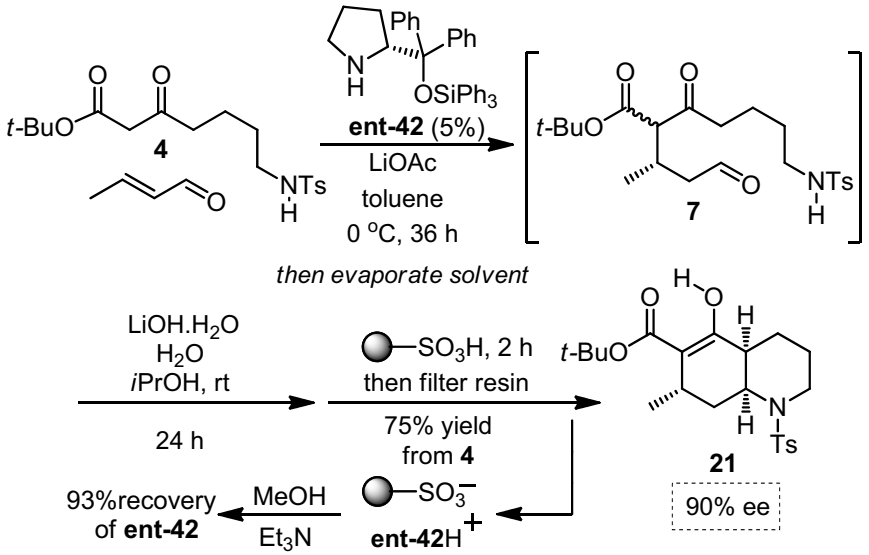
To a stirred solution of **57** (15 mg, 0.037 mmol) in dry $CH_2Cl_2$ (5.0 mL), was added TFA (1.0 mL) and the reaction mixture was stirred for 3 h at rt before being concentrated to dryness under reduced pressure. To the crude mixture was added water (65 µL), MeOH (200 µL) and $CH_2Cl_2$ (7.5 mL) followed by solid $NaHCO_3$ (300 mg) and the resulting mixture was stirred for 5 min. $Na_2SO_4$ (~1 g), was added, the mixture stirred for a further 5 min and then filtered, the filter cake washed with 5% MeOH/$CH_2Cl_2$ and the filtrate concentrated under reduced pressure. The resulting crude material was purified by silica column chromatography (2.5→5% MeOH/$CH_2Cl_2$ followed by 1:2:0.1 MeOH/$CH_2Cl_2$/concd $NH_4OH$) to give lycoposerramine Z (8.1 mg, 84%) as a colourless oil with spectral data identical to those previously reported for the natural product: $R_f$ 0.15 (MeOH/$CH_2Cl_2$/concd $NH_4OH$=1:2:0.1); $[\alpha]_D$ +10.6 (*c* 0.5, MeOH); lit: $[\alpha]_D$ +9.6 (*c* 0.34, MeOH); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 0.80 (q, *J* = 12.5 Hz, 1H, H-6ax), 0.85 (d, *J* = 6.5 Hz, 3H, $CH_3$), 1.21 (td, *J* = 13.4, 3.7 Hz, 1H, H-8ax), 1.25-1.36 (2H, m, 2H, H-3, H-4a), 1.44 (1H, tt, *J* =13.7, 4.3 Hz, 1H, H-4ax), 1.55 (br d, *J* = 12.8 Hz, 1H, H-6eq), 1.65 (m, 2H, H-3, H-8eq), 1.75 (m, 3H, 2H-4´, H-7ax), 1.95 (m, 2H, 2H-3´), 2.03 (br d, *J* = 13.4 Hz, 1H, H-4eq), 2.34 (dd, *J* =13.0, 11.0 Hz, 1H, $CH_2$), 2.45 (m, 3H, 2H-3´, H-5ax), 2.66 (brd, *J* = 13.5 Hz, 1H, $CH_2$) 2.74 (td, 1H, *J* = 12.5, 2.0 Hz, 1H, H-2ax), 3.03 (br s, 1H, H-8a), 3.20 (br d, *J* = 12.5 Hz, 1H, H-2eq), 3.82 (br t, *J* = 5.8 Hz, 2H, H-2´); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 18.8 (C-4´), 20.0 (C-3), 22.5 ($CH_3$), 23.2 (C-3), 26.5 (C-7), 26.2 (C-4), 29.7 (C-5), 29.8 (C-5), 35.7 ($CH_2$), 40.4 (C-4a), 41.0 (C-6), 40.4 (C-8), 47.1 (C-2), 56.6 (C-8a), 58.3 (C-2´), 148.8 (C-6´).




**Lycoposerramine Z**



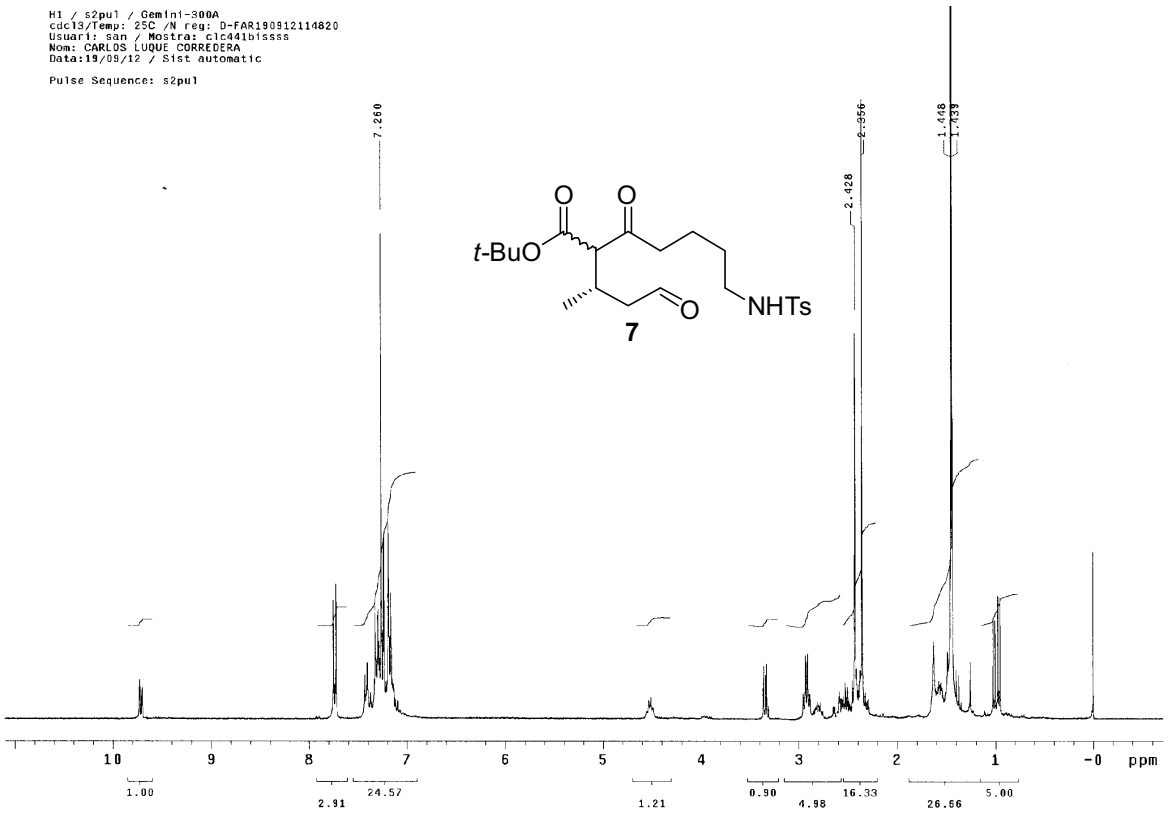
***(4aS,7S,8aS)*-t*ert*-Butyl 7-Methyl-1-(4-methylphenylsulfonyl)-5-oxodecahydro-quinoline-6-carboxylate (21). 1st One-pot sequence**

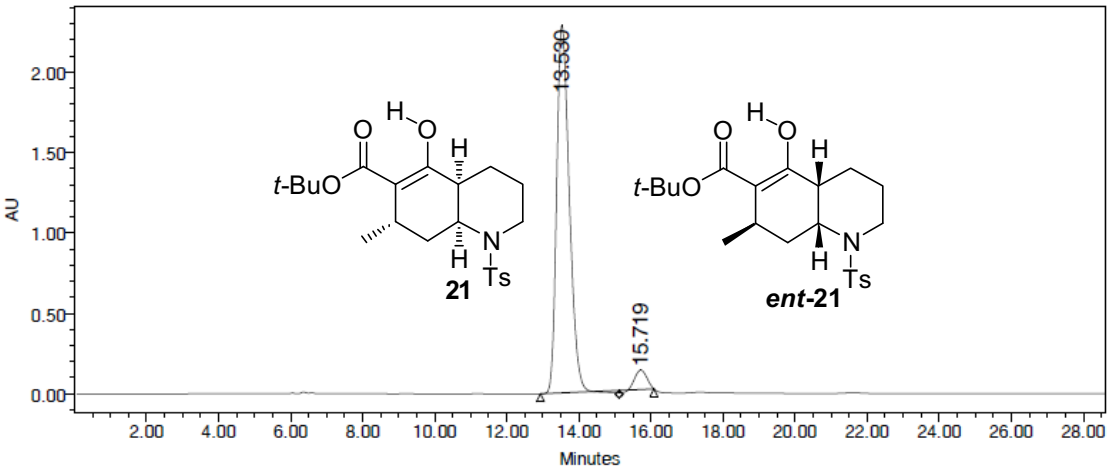



To a solution of keto ester **4** (500 mg, 1.35 mmol) in toluene (12.5 mL) at 0 ºC was added crotonaldehyde (104 mg, 1.49 mmol), triphenylsilyl ether **ent-42**[127] (35 mg, 0.07 mmol), LiOAc (45 mg, 0.7 mmol) and the resulting mixture was stirred for 36 h at 0 ºC. Excess crotonaldehyde was removed on a rotary evaporator before addition[128] of *i*PrOH (12.5 mL), LiOH·$H_2O$ (57 mg, 1.35 mmol) and $H_2O$ (0.24 mL, 13.5 mmol), and the resulting solution stirred for 24 h. To this flask was added the polymer support (*PS*) of *p*-toluenesulfonic acid (2.1 g) and the mixture was stirred for 2 h. The solid support was filtered, and the filtrate was concentrated *in vacuo*, and the crude was purified by chromatography (0→5→10→25% EtOAc/hexane) to give the enantioenriched keto ester **21** (427 mg, 75%, 90% ee by HPLC) as a white solid upon standing. *Recovery of the organocatalyst*: The solid support was stirred for 2 h with a mixture of 10% triethylamine in methanol (20 mL), filtered and the solvent removed *in vacuo*. Purification by column chromatography (2.5→5% MeOH/$CH_2Cl_2$) gave the recovered catalyst **ent-42** (33 mg, 93%).

[127] Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci* **2011**, *2*, 353-357. If the catalyst was used without recrystallization the enantiomeric excess of **21** decreased to 85% ee.

[128] At this time compound **7** can be checked by $^1$H NMR and shows to be an epimeric mixture at the β-keto ester methine carbon: $^1$H NMR (300 MHz) 0.96 and 1.01 (2d, *J* = 6.6 Hz, $CH_3$), 1.44 and 1.45 (2s, $C(CH_3)_3$), 2.36 and 2.43 (2s, ArMe), 2.81 (br quint, *J* = 6.6 Hz, CHMe), 2.92 (q, *J* = 6.6 Hz, $CH_2N$), 3.35 (dd, *J* = 6.4, 2.8 Hz, CH), 4.51 and 4.53 (2t, *J* = 6.4 Hz,NHTs), 9.70 and 9.73 (2t, *J* = 1.5 Hz, CHO).




Channel: 2487Channel 1; Processed Channel: ; Result Id: 4151; Processing Method: a

**Processed Channel Descr.:**

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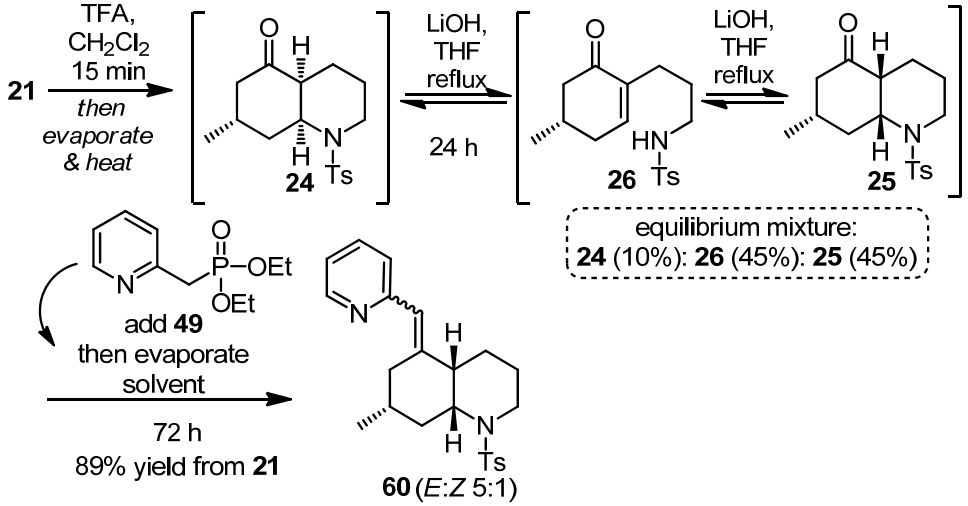
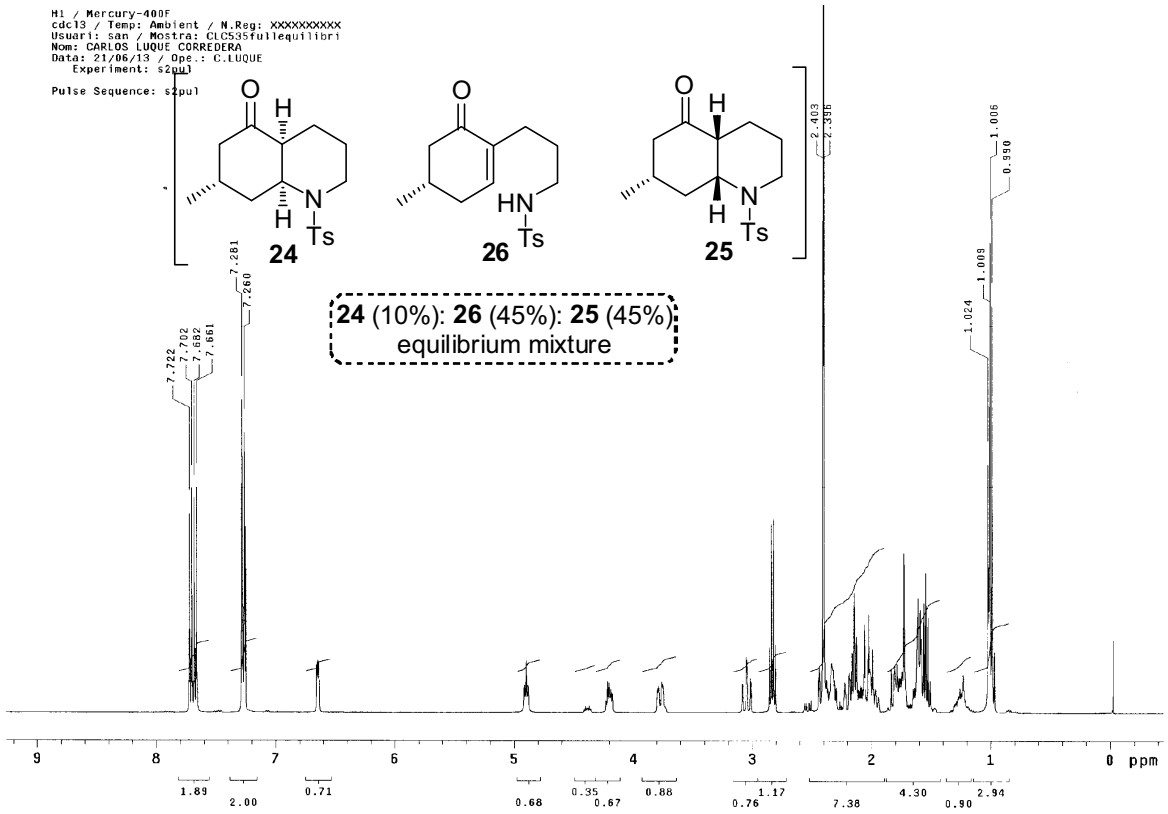
| 2 | 15.719 | 2965265 | 5.04 | 121234 |

***(4aS,7R,8aR)*-7-Methyl-1-(4-methylsulfonyl)-5-(pyridin-2-ylmethylene) decahydroquinoline (60-*E* and 60-*Z*). 2nd one-pot sequence**

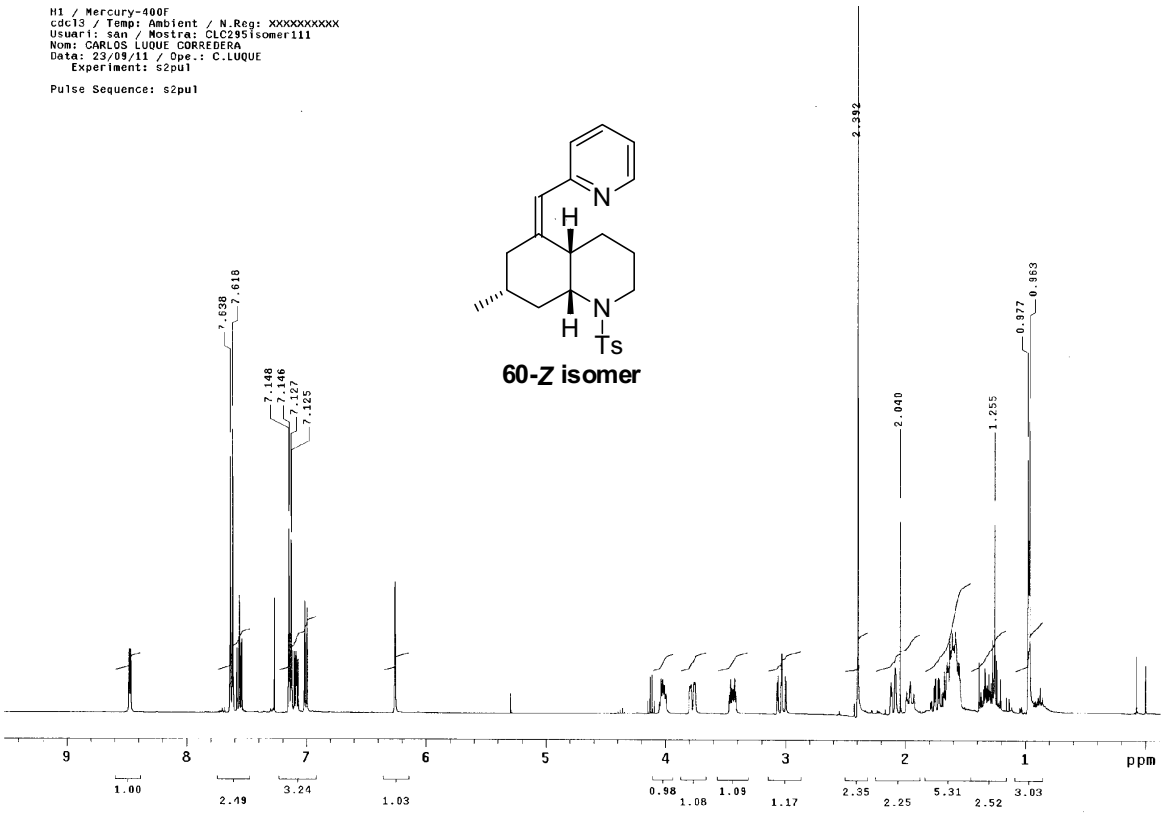



Keto ester **21** (582 mg, 1.4 mmol) was dissolved in TFA (1.4 mL) and stirred under nitrogen for 15 min at room temperature. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 15 mL). The reaction flask was maintained on the rotatory evaporator under vacuum at 80 ºC for 3 h to give the crude decahydroquinoline **24** as brown oil. The crude decahydroquinoline **24** was dissolved in THF (4.8 mL) and LiOH (67 mg, 2.8 mmol) was added and the resulting mixture was refluxed for 24 h. After cooling to room temperature, phosphonate **49** (963 mg, 4.2 mmol) was added in one portion followed by further portions of LiOH (168 mg, 7.0 mmol), and the solvent was evaporated. The mixture was stirred without solvent at room temperature for 3 days. The crude was dissolved in $Et_2O$ (5 mL) and was acidified to pH = 1 with 2 N HCl (15 mL). The layers were separated and the acidic phase was carefully basified with sat. aq. $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 20 mL), dried and concentrated *in vacuo*. The crude material was purified by chromatography (2.5→5→5→10% EtOAc/hexane) to give the pure coupled product **60** (485 mg, 89%) as a white solid and as a 5:1 mixture of *E*/*Z* isomers.[129]

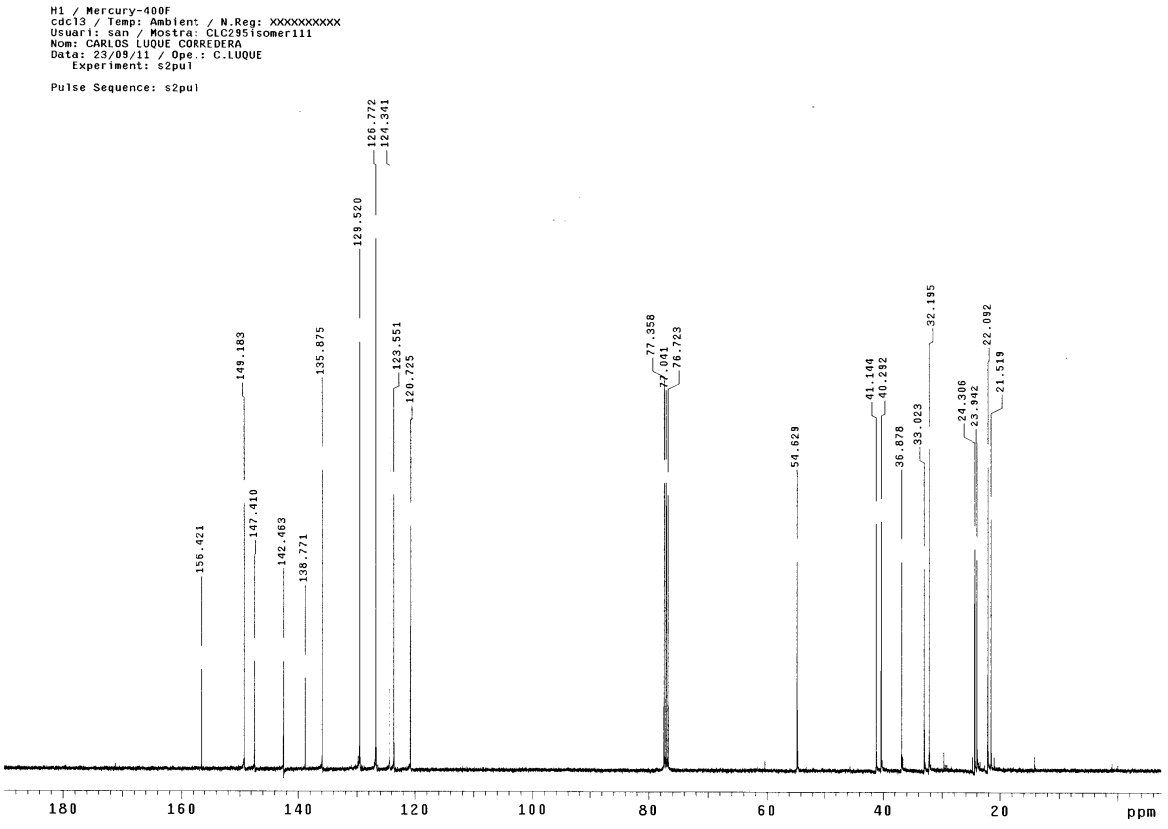
[129] Pure samples of **60-*E*** and **60-*Z*** were obtained if the crude material was purified by chromatography (2.5→5→10% EtOAc/hexane). Firstly eluted was the minor *Z* isomer, followed by the major *E* isomer.


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Uswari: san / Mostra: CLC535fullequilibri
Nom: CARLOS LUQUE CORREDERA
Data: 21/06/13 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
24
26
25
24 (10%): 26 (45%): 25 (45%)
equilibrium mixture
ppm

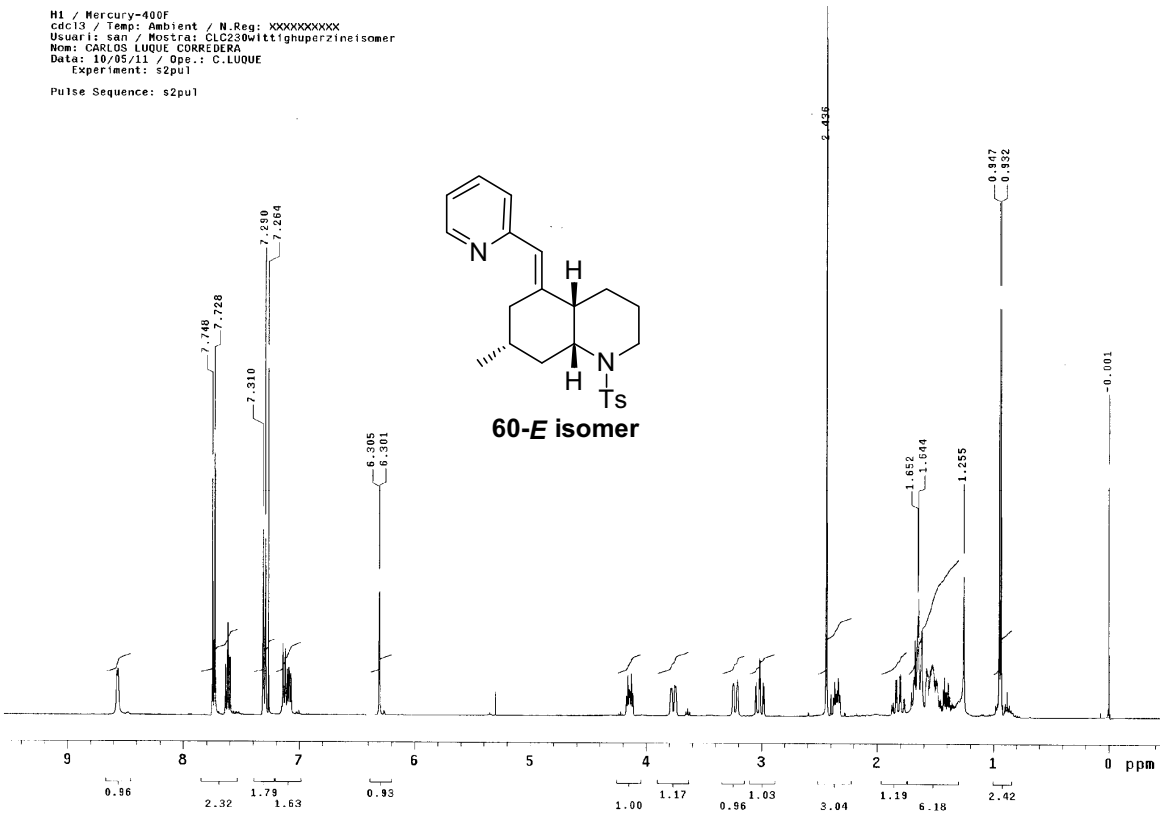
**60-*Z* isomer:** $[\alpha]_D$ -12.2 (*c* 1, $CHCl_3$); $R_f$ 0.56 (50% EtOAc/hexanes); $^1H$ NMR (400 MHz, COSY) $\delta$ 0.97 (d, *J* = 5.6 Hz, Me), 1.32 (qt, *J* = 12.8, 4.4 Hz, H-3ax), 1.55-1.65 (m, 5H, H-3eq, H-4eq, H-7ax, 2H-8), 1.72 (qd, *J* = 13.2, 4.0 Hz, H-4ax), 1.96 (td, *J* = 12, 1.6 Hz, H-6ax), 2.08 (dm, *J* = 12 Hz, H-6eq), 2.39 (s, 3H, $ArCH_3$), 3.02 (td, *J* = 13.6, 2.8 Hz, H-2ax), 3.44 (dt, *J* = 12.8, 4.6 Hz, H-4a), 3.77 (dm, *J* = 13.6 Hz, H-2eq), 4.02 (ddd, *J* = 10.8, 5.6, 4.4 Hz, H-8a), 6.26 (d, *J* = 1.6 Hz, =CH), 7.00 (d, *J* = 8 Hz, H-3 Py), 7.09 (ddd, *J* = 8.0, 4.4, 0.8 Hz, H-5 Py), 7.13 and 7.63 (2d, *J* = 8 Hz, 2 H each, ArH), 7.56 (td, *J* = 8.0, 2 Hz, H-4 Py), 8.47 (d, *J* = 4.4 Hz, H-6 Py); $^{13}C$ NMR (100 MHz, HSQC) 21.5 ($CH_3Ar$), 22.1 (7-$CH_3$), 23.9 (C-4), 24.3 (C-3), 32.2 (C-8), 33.0 (C-7), 36.9 (C-4a), 40.3 (C-2), 41.1 (C-6), 54.6 (C-8a), 120.7 (C-5 Py), 123.6 (C-3 Py), 124.3 (=CH), 126.7 (*o*-Ts), 129.5 (*m*-Ts), 135.9 (C-4 Py), 138.8 (*p*-Ts), 142.5 (*ipso*-Ts), 147.4 (C-5), 149.2 (C-6 Py), 156.4 (C-2 Py). HRMS calcd for $C_{23}H_{29}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.1946.


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC295isomer111
Nom: CARLOS LUQUE CORREDERA
Data: 23/09/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.638
7.618
7.148
7.146
7.127
7.125
2.392
2.040
1.255
0.977
0.963
ppm
1.00
2.49
3.24
1.03
0.98
1.08
1.09
1.17
2.35
2.25
5.31
2.52
3.03

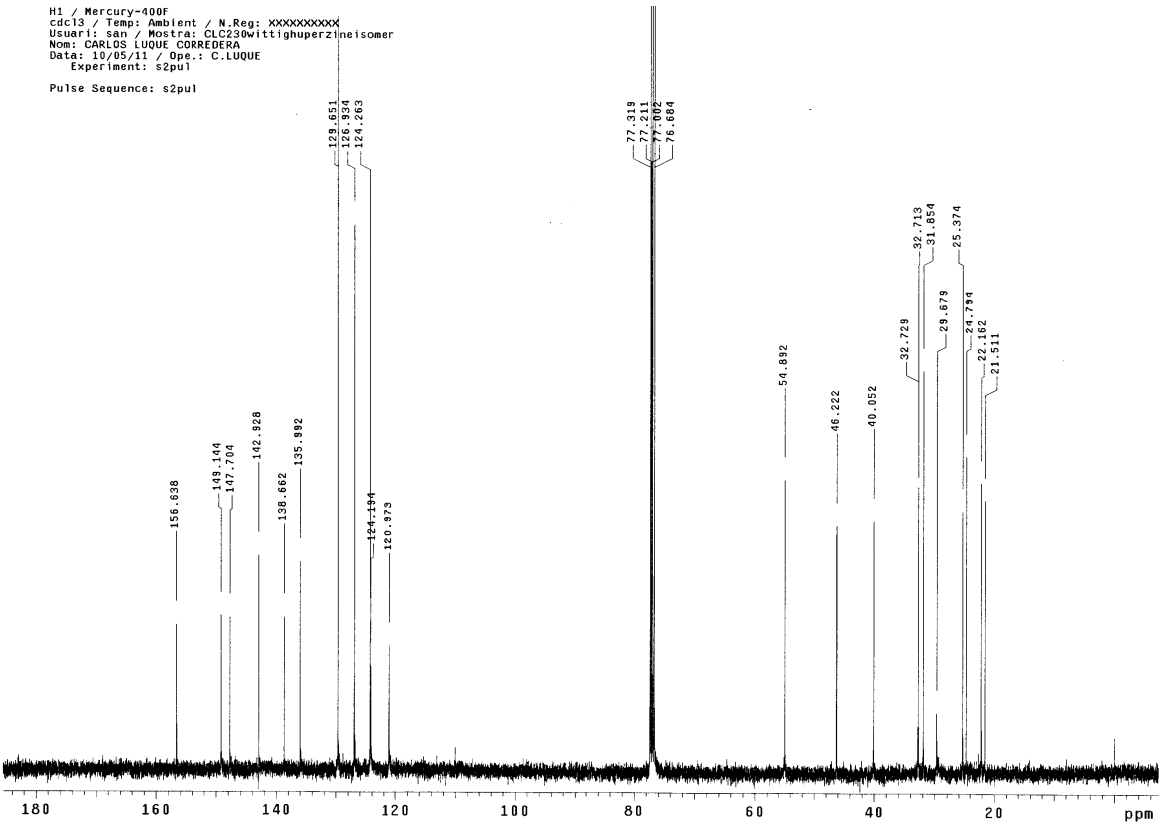
**60-*Z* isomer**


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC295isomer111
Nom: CARLOS LUQUE CORREDERA
Data: 23/09/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
156.421
149.183
147.410
142.463
138.771
135.875
129.520
126.772
124.341
123.551
120.725
77.358
77.041
76.723
54.629
41.144
40.232
36.878
33.023
32.195
24.306
23.942
22.092
21.519
ppm

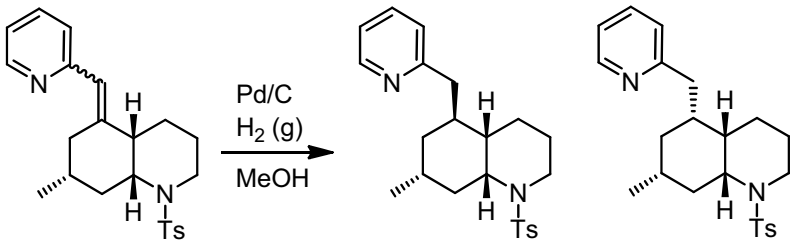
**60-*E* isomer:** $[\alpha]_D$ -61.9 (c 1, $CHCl_3$); $R_f$ 0.49 (50% EtOAc/hexanes); $^1H$ NMR (400 MHz, COSY) $\delta$ 0.94 (d, *J* = 6.0 Hz, $CH_3$), 1.42 (qt, 12.8, 4.4 Hz, H-3ax), 1.48-1.58 (m, H-4, H-7, 2H-8), 1.60-1.70 (masked, H-3), 1.65 (td, *J* = 13, 1.6 Hz, H-6ax), 1.81 (qd, *J* = 13.2, 4.0 Hz, H-4ax), 2.35 (dt, *J* = 12.8, 4.6 Hz, H-4a), 2.44 (s, $ArCH_3$), 3.01 (td, *J* = 13.2, 2.8 Hz, H-2ax), 3.22 (dd, *J* = 13.2, 2.0 Hz, H-6eq), 3.76 (dm, *J* = 13.2 Hz, H-2eq), 4.14 (dt, *J* = 12.0, 4.8 Hz, H-8a), 6.30 (d, *J* = 1.6 Hz, =CH), 7.09 (dd, *J* = 8.0, 4.4 Hz, H-5 Py), 7.13 (d, *J* = 8 Hz, H-3 Py), 7.30 and 7.74 (2d, *J* = 8 Hz, 2 H each, Ts), 7.61 (td, *J* = 8.0, 2 Hz, H-4 Py), 8.57 (d, *J* = 4.4 Hz, H-6 Py); $^{13}C$ NMR (100 MHz, HSQC ) 21.5 ($CH_3Ar$), 22.1 ($CH_3$), 24.8 (C-4) , 25.4 (C-3), 31.9 (C-8), 32.7 (C-6), 32.7 (C-7), 40.1 (C-2), 46.2(C-4a), 54.9 (C-8a), 121.0 (C-5 Py), 124.2 (C-3 Py), 124.2 (=CH), 126.9 (*o*-Ts), 129.6 (*m*-Ts), 136.0 (C-4 Py), 138.7 (*p*-Ts), 142.9 (*ipso*-Ts), 147.7 (C-5), 149.1 (C-6 Py), 156.6 (C-2 Py). HRMS calcd for $C_{23}H_{29}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.1945.


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC230wittighuperzineisomer
Nom: CARLOS LUQUE CORREDERA
Data: 10/05/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.748
7.728
7.310
7.290
7.264
6.305
6.301
2.436
1.652
1.644
1.255
0.947
0.932
0.001
0.96
2.32
1.79
1.63
0.93
1.00
1.17
0.96
1.03
3.04
1.19
6.18
2.42
ppm

**60-*E* isomer**


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC230wittighuperzineisomer
Nom: CARLOS LUQUE CORREDERA
Data: 10/05/11 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
129.651
128.934
124.263
77.319
77.211
77.002
76.684
156.638
149.144
147.704
142.928
138.662
135.992
124.194
120.973
54.892
46.222
40.052
32.729
32.713
31.854
29.679
25.374
24.794
22.162
21.511
ppm

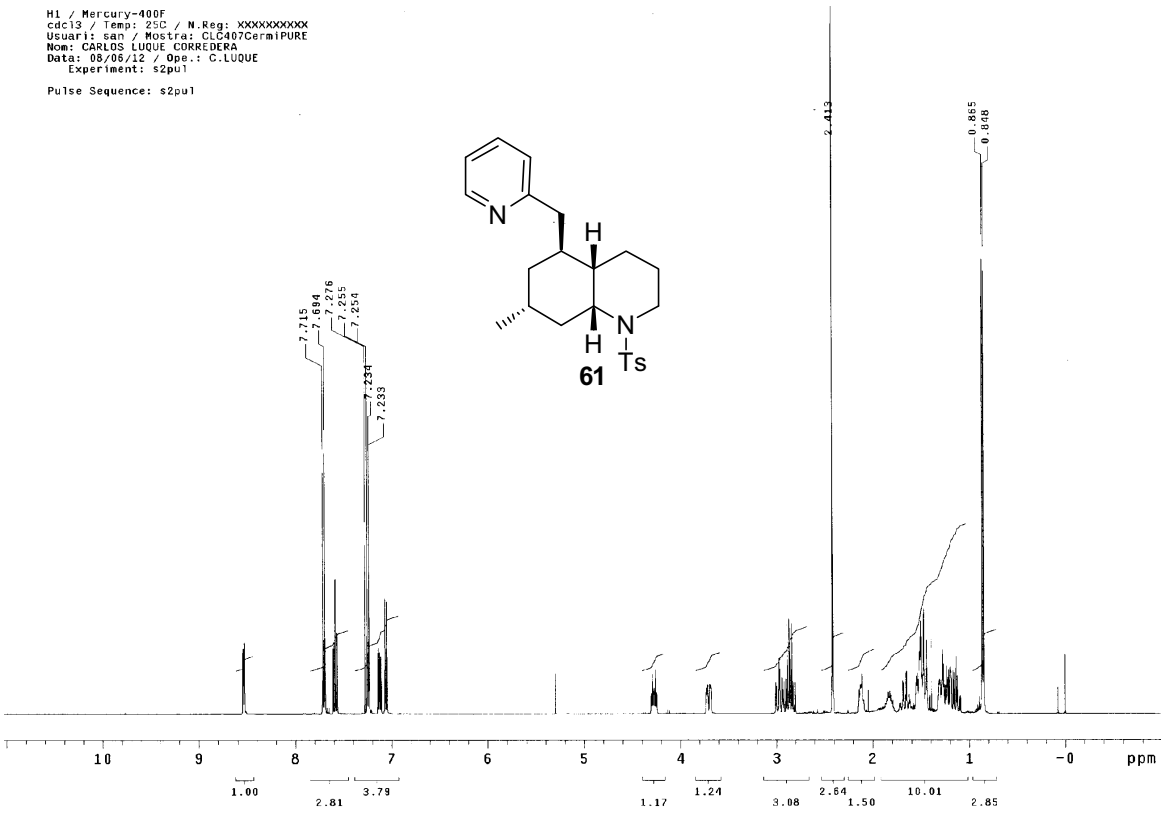
***(4aS,5S,7R,8aR)*-7-Methyl-1-(4-methylsulfonyl)-5-(pyridin-2-ylmethyl)decahydroquinoline (61 and 62)**

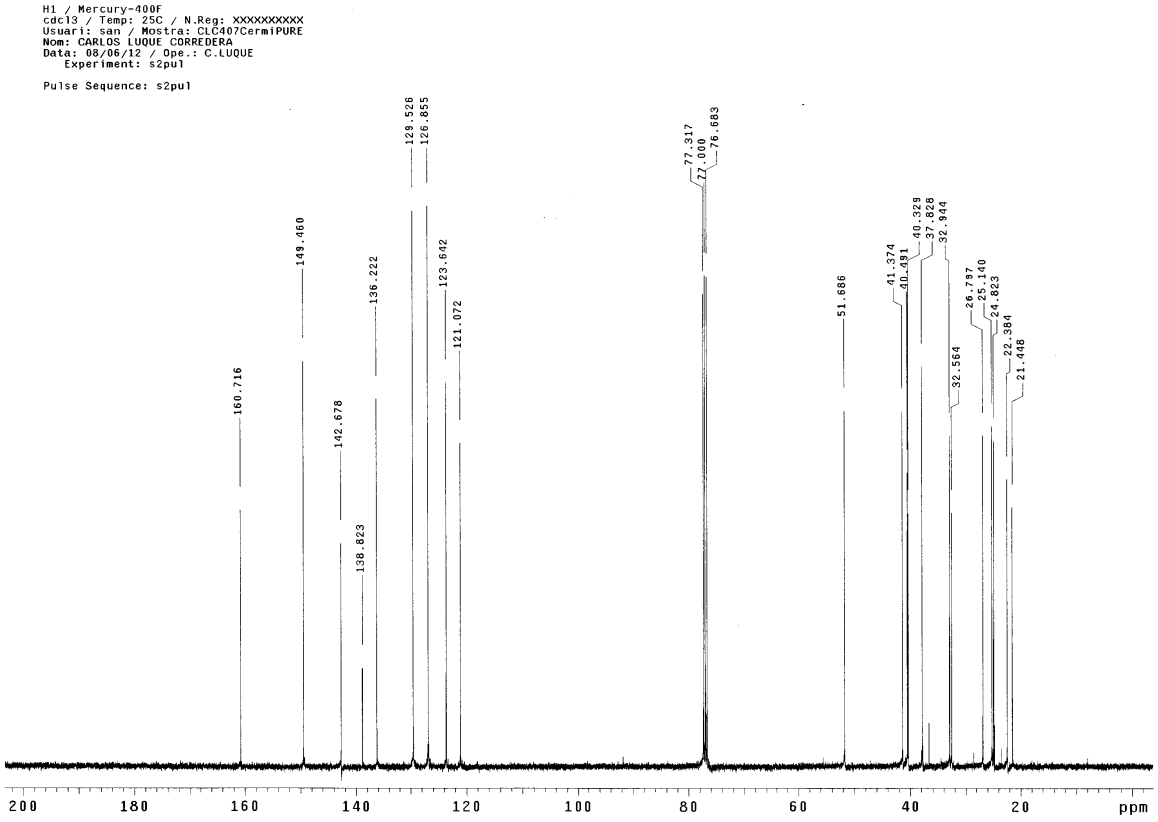



**60 (*E*/*Z* mixture)** **61 (75%)** **62 (15%)**

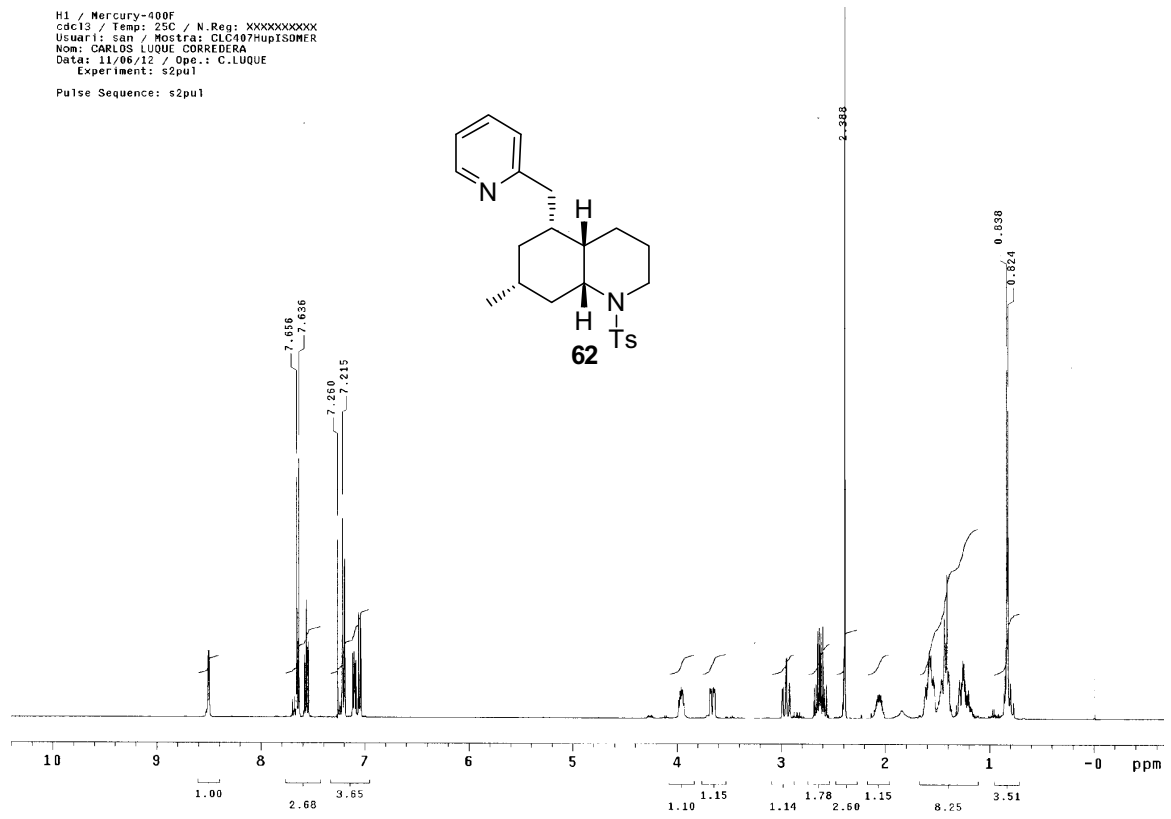
To a stirred solution of **60** (909 mg, 2.3 mmol) in MeOH (18 mL) was added Pd/C (20% w/w, 182 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of $H_2$ overnight. The mixture was diluted with $CH_2Cl_2$ (≈ 20 mL) before it was filtered through a pad of celite, washed through with $CH_2Cl_2$ and the filtrate was concentrated *in vacuo*. Purification by chromatography (5→10→25% EtOAc/hexane) gave **61** (627 mg, 67%) as a colorless oil, followed by a mixture of **61** and **62** (126 mg, 16%), and finally **62** (75 mg, 8%) was obtained as a white solid. Overall yield 90% (5:1 ratio for **61**/**62**).

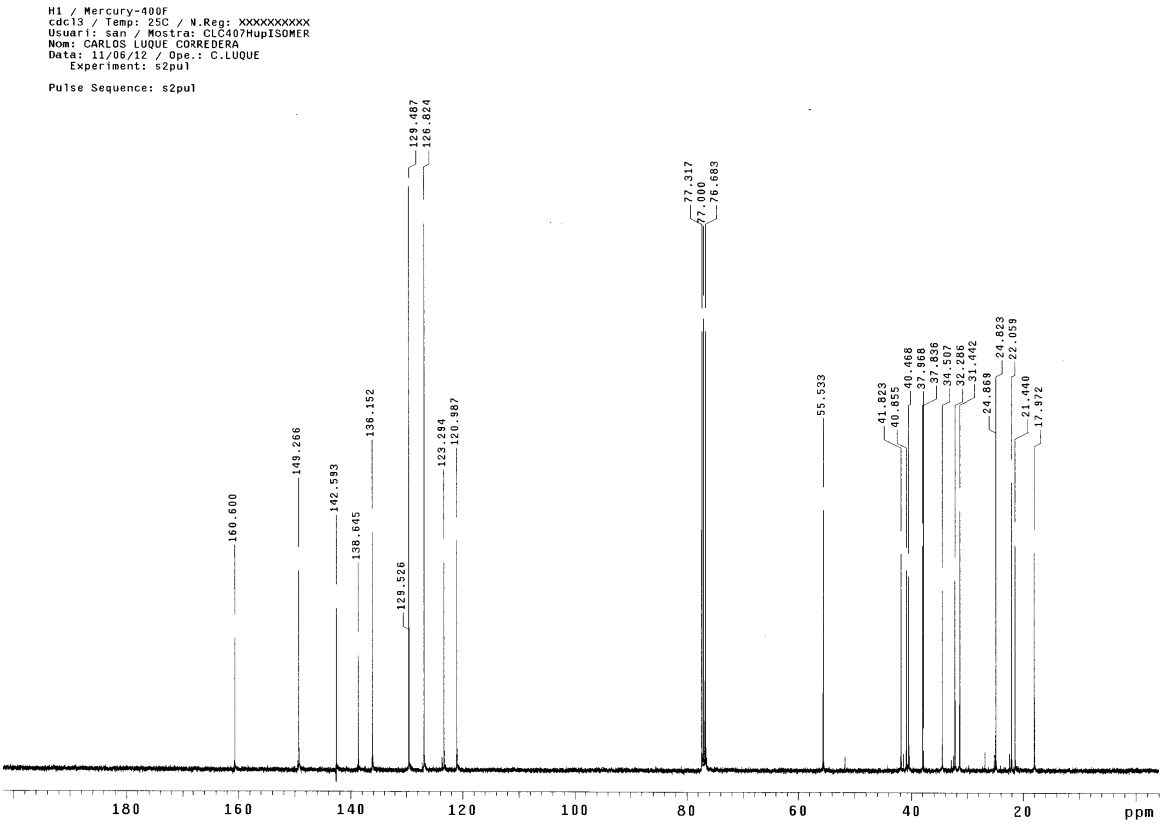
**Data for 61**: $[\alpha]_D$ -15.1 (*c* 1, $CHCl_3$); $R_f$ 0.65 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, COSY) $\delta$ 0.86 (d, *J* = 6.8 Hz, $CH_3$), 1.16 (td, 13.6, 4.8 Hz, H-6ax), 1.20-1.31 (m, 3H, H-3, H-4, H-6eq), 1.40-1.60 (m, 4 H, H-4a, H-3eq, 2H-8) 1.65 (qd, *J* = 12.8, 4.0 Hz, 1H, H-4ax), 1.83 (m, H-7ax), 2.12 (m, H-5eq), 2.41 (s, 3H, $ArCH_3$), 2.82 (dd, *J* = 13.6, 7.6 Hz, $CH_2Py$), 2.89 (dd, *J* = 13.6, 8.0 Hz, $CH_2Py$ ), 2.97 (td, *J* = 13.6, 3.2 Hz, H-2ax), 3.71 (dm, *J* = 13.6, H-2eq) 2.0 Hz, H-6eq), 4.27 (dt, *J* = 12, 4.8 Hz, H-8a), 7.05 (dt, *J* = 8.0, 1.0 Hz, H-3 Py), 7.12 (ddd, *J* = 8.0, 4.8, 1.2 Hz, H-5 Py), 7.24 and 7.70 (2d, *J* = 8 Hz, 2H each, Ts), 7.59 (td, *J* = 8.0, 2 Hz, H-4 Py), 8.53 (d, *J* = 4.8 Hz, H-6 Py). $^{13}$C NMR (100 MHz, HSQC) 21.5 ($CH_3Ar$), 22.4 (7-$CH_3$), 24.8 (C-4), 25.1 (C-3), 26.8 (C-7), 32.5 (C-6), 32.9 (C-8), 37.8 (C-4a), 40.3 (C-5), 40.5 (C-2), 41.4 ($CH_2Py$), 51.7 (C-8a), 121.1 (C-5 Py), 123.6 (C-3 Py), 126.9 (*o*-Ts), 129.5 (*m*-Ts), 136.2 (C-4 Py), 138.8 (*p*-Ts), 142.7 (*ipso*-Ts), 149.5 (C-6 Py), 160.7 (C-2 Py). HRMS calcd for $C_{23}H_{31}N_2O_2S$ $(M + H)^+$ 399.2101, found 399.2104.


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC407CermiPURE
Nom: CARLOS LUQUE CORREDERA
Data: 08/06/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.715
7.694
7.276
7.255
7.254
7.234
7.233
2.413
0.865
0.848
N
H
H
N
Ts
61
10
9
8
7
6
5
4
3
2
1
-0
ppm
1.00
2.81
3.79
1.17
1.24
3.08
2.64
1.50
10.01
2.85

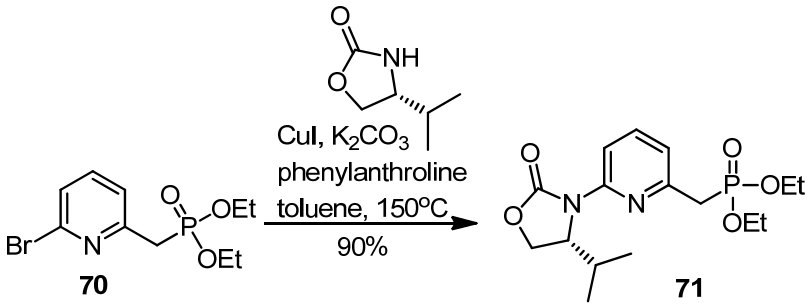

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC407CermiPURE
Nom: CARLOS LUQUE CORREDERA
Data: 08/06/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
160.716
149.460
142.678
138.823
136.222
128.526
126.855
123.642
121.072
77.317
77.000
76.683
51.686
41.374
40.491
40.329
37.828
32.944
32.564
26.797
25.140
24.823
22.384
21.448
200
180
160
140
120
100
80
60
40
20
ppm

**Data for 62**: $[\alpha]_D$ -39.1 (*c* 1, $CHCl_3$); $R_f$ 0.59 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, COSY) $\delta$ 0.83 (d, *J* = 5.6 Hz, $CH_3$), 0.84 (q, *J* = 12.4 Hz, 1H, H-6ax), 1.18-1.30 (m, 2H, H-3, H-6eq), 1.38-1.48 (m, 4H, H-4, H-8, H-7ax), 1.50-1.62 (m, 3H, H-4, H-3, H-4a) 2.02 (m, 1H, H-5ax), 2.39 (s, 3H, $ArCH_3$), 2.59 (dd, *J* = 13.2, 8.4 Hz, 1H, $CH_2$Py), 2.66 (dd, *J* = 13.2, 7.2 Hz, 1H, $CH_2$Py), 2.95 (td, *J* = 13.6, 2.4 Hz, 1H, H-2ax), 3.64 (ddd, *J* = 13.2, 4.4, 3.2 Hz, H-2eq), 3.96 (ddd, *J* = 10.4, 5.2, 5.2 Hz, 1H, H-8a), 7.05 (dd, *J* = 8.4, 1.2 Hz, H-3 Py), 7.12 (ddd, *J* = 8.4, 4.8, 1.2 Hz, 1H, H-5 Py), 7.20 and 7.64 (2d, *J* = 8.4 Hz, 2 H each, *m*- and *o*-Ts), 7.56 (td, *J* = 7.6, 2 Hz, H-4 Py), 8.50 (dm, *J* = 4.8 Hz, H-6 Py); $^{13}$C NMR (100 MHz, HSQC) 18.0 (C-4), 21.4 ($ArCH_3$), 22.1 ($CH_3$), 24.9 (C-3), 31.4 (C-8), 32.3 (C-7), 34.5 (C-6), 38.0 (C-4a), 40.5 (C-2), 40.9 (C-5), 41.8 ($CH_2$Py), 55.5 (C-8a), 121.0 (C-5 Py), 123.3 (C-3 Py), 126.8 (*o*-Ts), 129.5 (*m*-Ts), 136.2 (C-4 Py), 138.6 (*p*-Ts), 142.6 (*ipso*-Ts), 149.3 (C-6 Py), 160.6 (C-2 Py). HRMS calcd for $C_{23}H_{31}N_2O_2S$ $(M+H)^+$ 399.2101, found 399.2116.

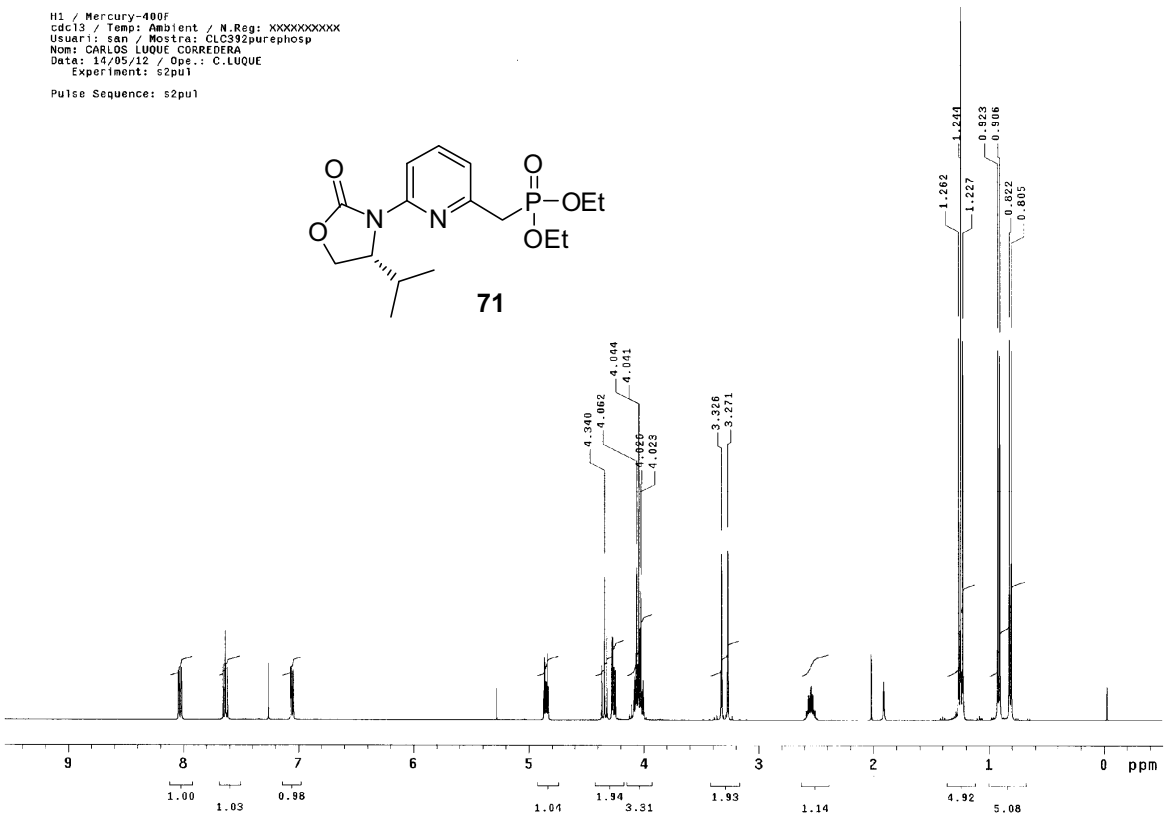

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC407HupISOMER
Nom: CARLOS LUQUE CORREDERA
Data: 11/06/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.656
7.636
7.260
7.215
2.388
0.838
0.824
62
ppm

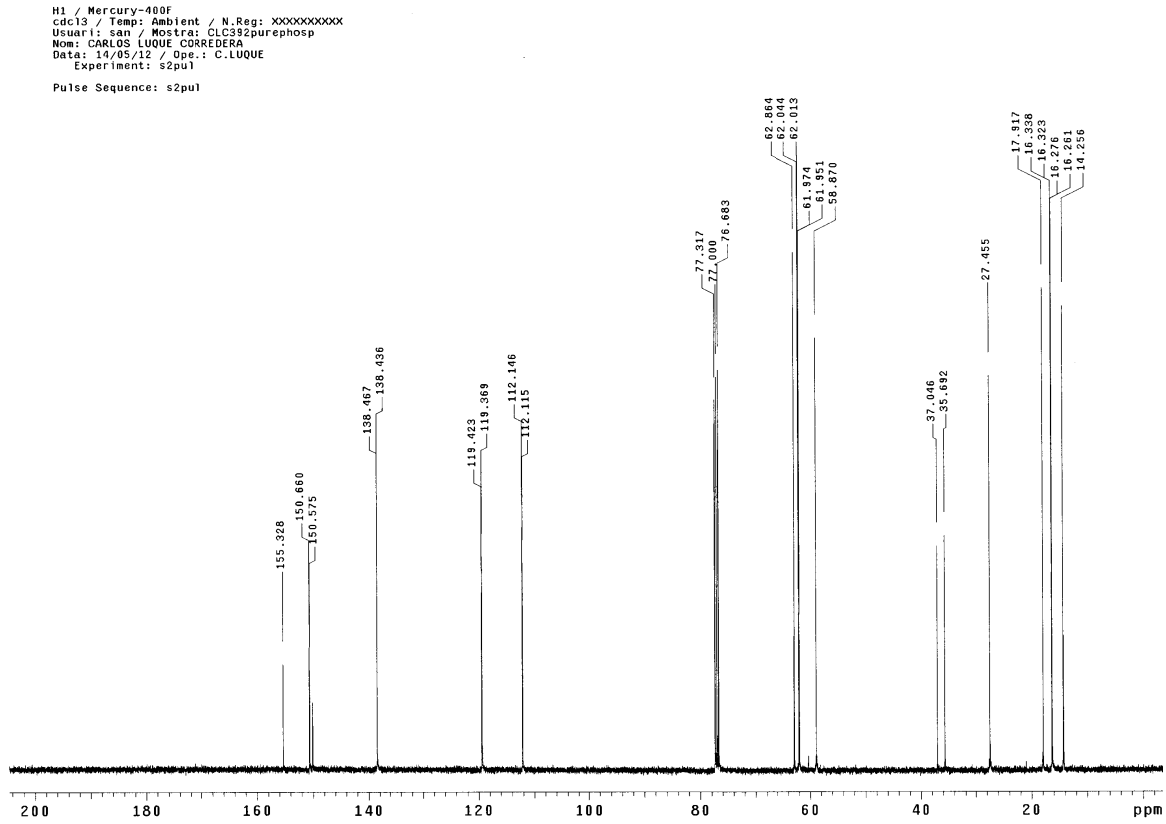

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC407HupISOMER
Nom: CARLOS LUQUE CORREDERA
Data: 11/06/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
129.487
126.824
77.317
77.000
76.683
160.600
149.266
142.593
138.645
136.152
129.526
123.284
120.987
55.533
41.823
40.855
40.468
37.968
37.836
34.507
32.305
31.402
24.869
24.823
22.059
21.440
17.972
ppm

**_(R)_-diethyl ((6-(4-Isopropyl-2-oxazolidin-3-yl)pyridin-2-yl)methyl)phosphonate (71)**

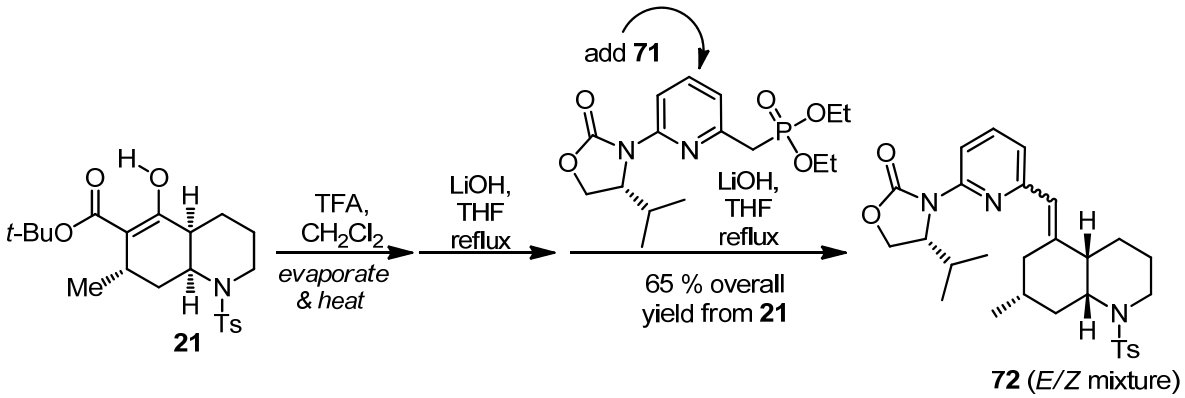



To a solution of diethyl ((6-bromopyridin-2-yl)methyl)phosphonate **70** (2.0 g, 6.5 mmol) in dry toluene (15 mL) was added (*R*)-(+)-4-isopropyl-2-oxazolidine (924 mg, 7.15 mmol), copper iodide 99.9% (124 mg, 0.65 mmol), potassium carbonate (1.8 g, 13 mmol) and phenanthroline (117 mg, 0.65 mmol) under argon atmosphere. The resulting mixture was heated at reflux for 24 h. After the reaction was cooled to room temperature, the mixture was diluted with AcOEt (≈15 mL) and it was filtered through a pad of Celite and washed through AcOEt. The filtrate was concentrated *in vacuo*, and the resulting crude was purified by column chromatography (10→25→50→100% EtOAc/hexane) to give the coupled product **71** (2.09 g, 90%) as a pale yellow oil. $R_f$ 0.44 (100% EtOAc); $[\alpha]_D$ -32.4 (c 1, $CHCl_3$); $^1$H NMR (400 MHz, COSY) $\delta$ 0.80 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 0.90 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.25 (t, 6 H, $CH_2CH_3$), 2.55 (heptet pf doublets, J = 6.8, 4.0 Hz, 1H, $CH_3CHCH_3$), 3.30 (d, *J* = 22 Hz, 2H, $CH_2PO(OEt)_2$), 4.00-4.10 (m, 4H, $OCH_2$), 4.24-4.27 (dd, *J* = 8.8, 4 Hz, 1H, $OCH_2$), 4.34 (t, *J* = 8.8 Hz, 1H, $OCH_2$), 4.84 and 4.86-4.87 (dt, J = 8.8, 4.0 Hz, 1H, NCH), 7.06 (dd, *J* = 7.6, 2.4 Hz, 1H, 3-Py), 7.63 (t, *J* = 8 Hz, 1H, 4-Py), 8.02 (dd, *J* = 8.4, 2.4 Hz, 1H, 5-Py); $^{13}$C NMR (400 MHz, HSQC) $\delta$ 14.3 ($CH_3$), 16.3 ($OCH_2CH_3$), 17.9 ($CH_3$), 27.5 (CH), 36.4 (d, $CH_2P(O)$), 58.9 (NCH), 61.9 (d, $OCH_2$), 112.1 (5-Py), 119.4 (3-Py), 138.4 (4-Py), 150.6 (6-Py), 150.6 (2-Py), 155.3 (NCO); HRMS calcd for $C_{16}H_{26}N_2O_5P$ $(M+H)^+$ 357.1574, found 357.1577.

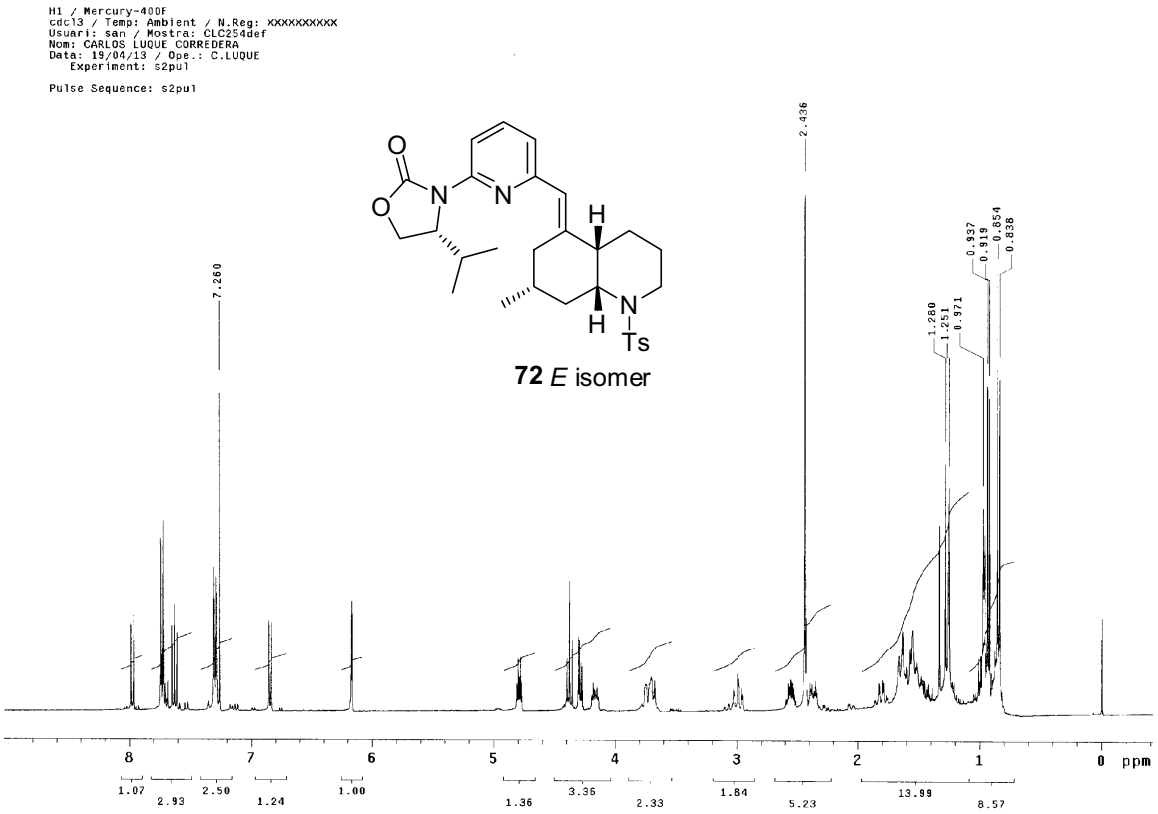

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC392purephosp
Nom: CARLOS LUQUE CORREDERA
Data: 14/05/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
71
4.340
4.062
4.044
4.041
4.026
4.023
3.326
3.271
1.262
1.227
0.923
0.906
0.822
0.805
ppm
1.00
1.03
0.98
1.01
1.94
3.31
1.93
1.14
4.92
5.08


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC392purephosp
Nom: CARLOS LUQUE CORREDERA
Data: 14/05/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
155.328
150.660
150.575
138.467
138.436
119.423
119.369
112.146
112.115
77.317
77.000
76.683
62.864
62.004
62.013
61.974
61.951
58.870
37.046
35.692
27.455
17.917
16.338
16.323
16.276
16.261
14.256
ppm

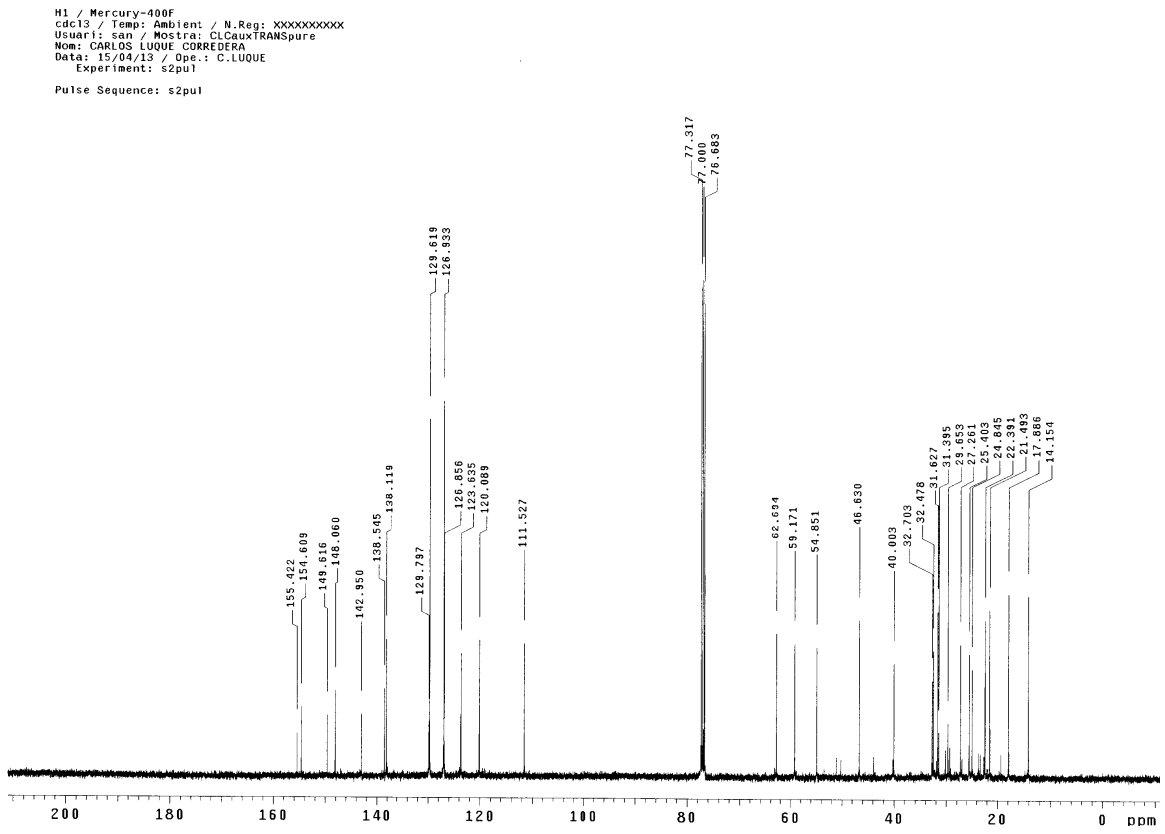
**(*R*)-4-Isopropyl-3-(6-((*E*)-((4*aS*,7*R*,8*aR*)-7-methyl-1-tosyloctahydroquinolin-5(*1H*)-ylidene)methyl)pyridin-2-yl)oxazolidin-2-one (72)**



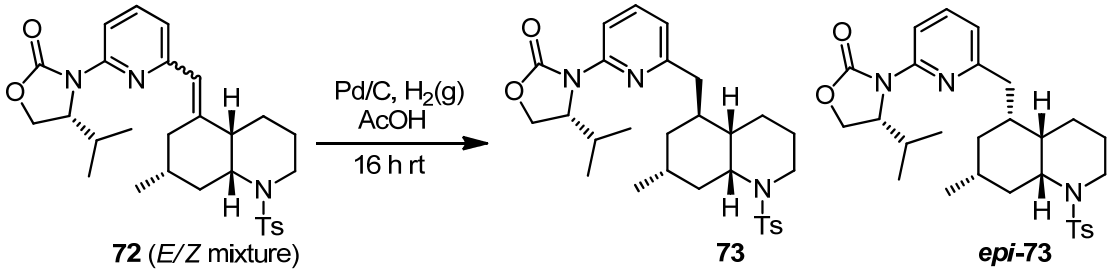

Keto ester **21** (1.26 g, 2.99 mmol) was dissolved in TFA (2.9 mL) and stirred under nitrogen for 15 min at room temperature. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 10 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 80 ºC for 3 h to give the crude decahydroquinoline **24** as a brown oil. The above product **24** was dissolved in THF (10 mL) and LiOH (143 mg, 5.98 mmol) was added and the resulting mixture was refluxed for 24 h to give the equilibration mixture with traces of **24**, **25** and opened enone **28**. Phosphonate **71** (1.6 g, 4.49 mmol) was added in one portion followed by further portions of LiOH (215 mg, 8.97 mmol). The mixture was refluxed for a further 24 h before being cooled to room temperature and the solvent was concentrated *in vacuo*. The crude material was purified by column chromatography (2.5→5→10% EtOAc/hexane) to give **72** (1.024 g, 65%) as a colourless oil as a mixture of (~4.4:1) E/Z isomers. ***E* isomer:** $[\alpha]_D$ -87.2 (c 1, $CHCl_3$); $R_f$ 0.58 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, COSY) δ 0.85 and 0.93 (2d, *J* = 6.8 Hz, 3H each, $CH_3$), 0.97 (d, *J* = 5.2 Hz, 7-$CH_3$), 1.40 (m, H-3ax), 1.50-1.60 (m, H-4, H-7, 2H-8), 1.60-1.70 (m, 2H H-3eq, H-6ax), 1.80 (qd, *J* = 13.2, 4.0 Hz, H-4ax), 2.36 (dt, *J* = 12.8, 4.6 Hz, H-4a), 2.44 (s, 3H, Ar*CH*$_3$), 2.56 (m, CH), 2.99 (td, J = 13.2, 2.8 Hz, H-2ax), 3.70 (masked, H-6eq), 3.74 (dm, *J* = 13.2 Hz, H-2eq), 4.14 (dt, *J* = 12.0, 4.8 Hz, H-8a), 4.29 (dd, *J* = 7,2, 4.0 Hz, 1H, $NCH_2$), 4.38 ( t, *J* = 7.2 Hz, 1H, $NCH_2$), 4.80 (dt, *J* = 7.2, 4.0 Hz, OCH), 6.18 (s, =CH), 6.85 (d, *J* = 8.0 Hz, H-5 Py), 7.30 and 7.74 (2d, *J* = 8 Hz, 2H each, ArH), 7.64 (t, *J* = 8.0 Hz, H-4 Py), 7.98 (d, *J* = 8 Hz, H-3 Py). $^{13}$C NMR (100 MHz, HSQC) 14.1 and 17.9 ($CH_3$ aux), 21.5 ($CH_3$ Ar), 22.4 (7-$CH_3$), 24.8 (C-3) , 25.4 (C-4), 27.2 (CH aux), 31.6 (C-7), 32.5 (C-8), 32.7 (C-6), 40.0 (C-2), 46.6 (C-4a), 54.8 (C-8a), 59.2 (OCH), 62.7 ($NCH_2$), 111.5 (C-5 Py), 120.1 (C-3 Py), 123.6 (=CH), 126.9 (*o*-Ts), 129.8 (*m*-Ts), 138.1 (C-4 Py), 138.5 (*p*-Ts), 142.9 (=C), 148.0 (C Ar), 149.6 (C-2 Py), 154.6 (C-6 Py), 155.4 (NCO); HRMS calcd for $C_{29}H_{38}N_3O_4S$ $(M+H)^+$ 524.2578, found 524.2573.


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC254def
Nom: CARLOS LUQUE CORREDERA
Data: 19/04/13 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.260
2.436
1.280
1.251
0.971
0.937
0.919
0.854
0.838
8
7
6
5
4
3
2
1
0 ppm
1.07
2.93
2.50
1.24
1.00
1.36
3.36
2.33
1.84
5.23
13.99
8.57

**72** *E* isomer


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLCauxTRANSpure
Nom: CARLOS LUQUE CORREDERA
Data: 15/04/13 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
77.317
77.000
76.683
129.619
126.933
126.856
123.635
120.089
111.527
155.422
154.609
149.616
148.060
142.950
138.545
138.119
129.797
62.694
59.171
54.851
46.630
40.003
32.703
32.478
31.627
31.395
29.653
27.261
25.463
24.865
22.391
21.493
17.886
14.154
200
180
160
140
120
100
80
60
40
20
0 ppm

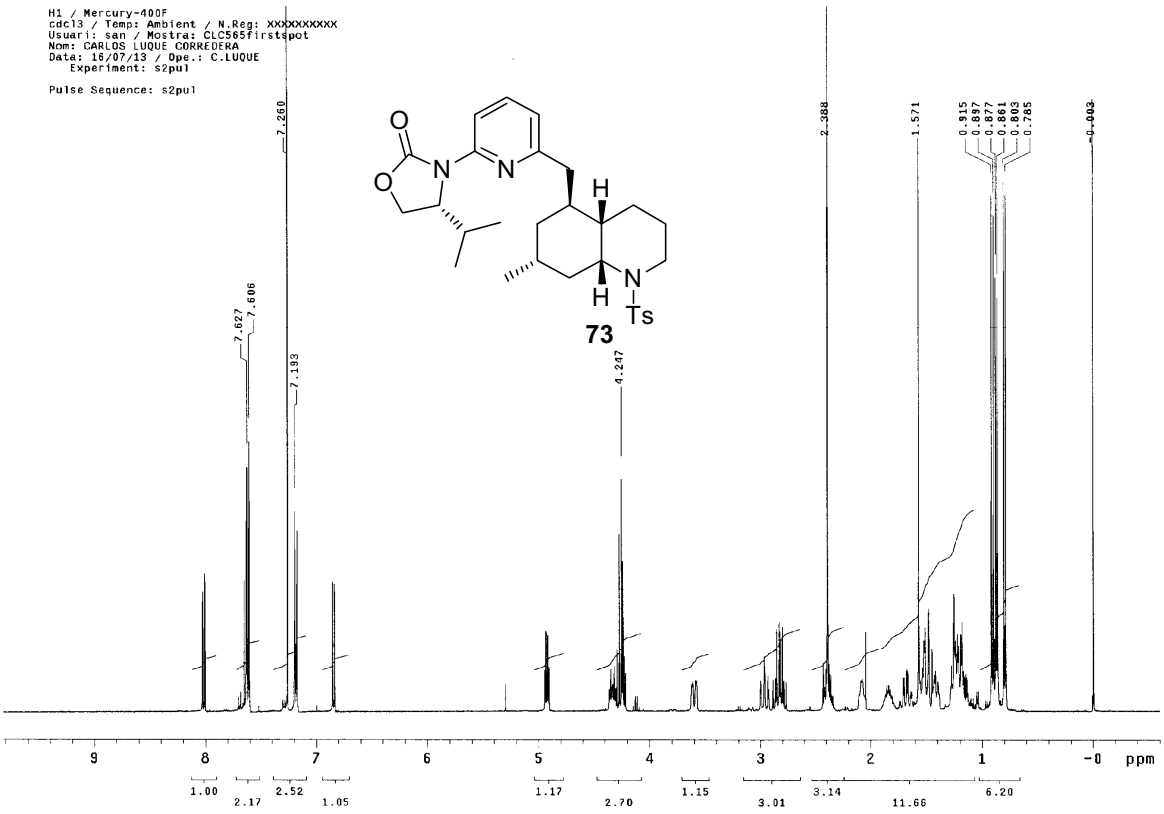
***(R)*-4-Isopropyl-3-(6-(((4*aS*,5*S*,7*R*,8*aR*)-7-methyl-1-tosyldecahydroquinolin-5-yl)methyl)pyridin-2-yl)oxazolidin-2-one (73)**

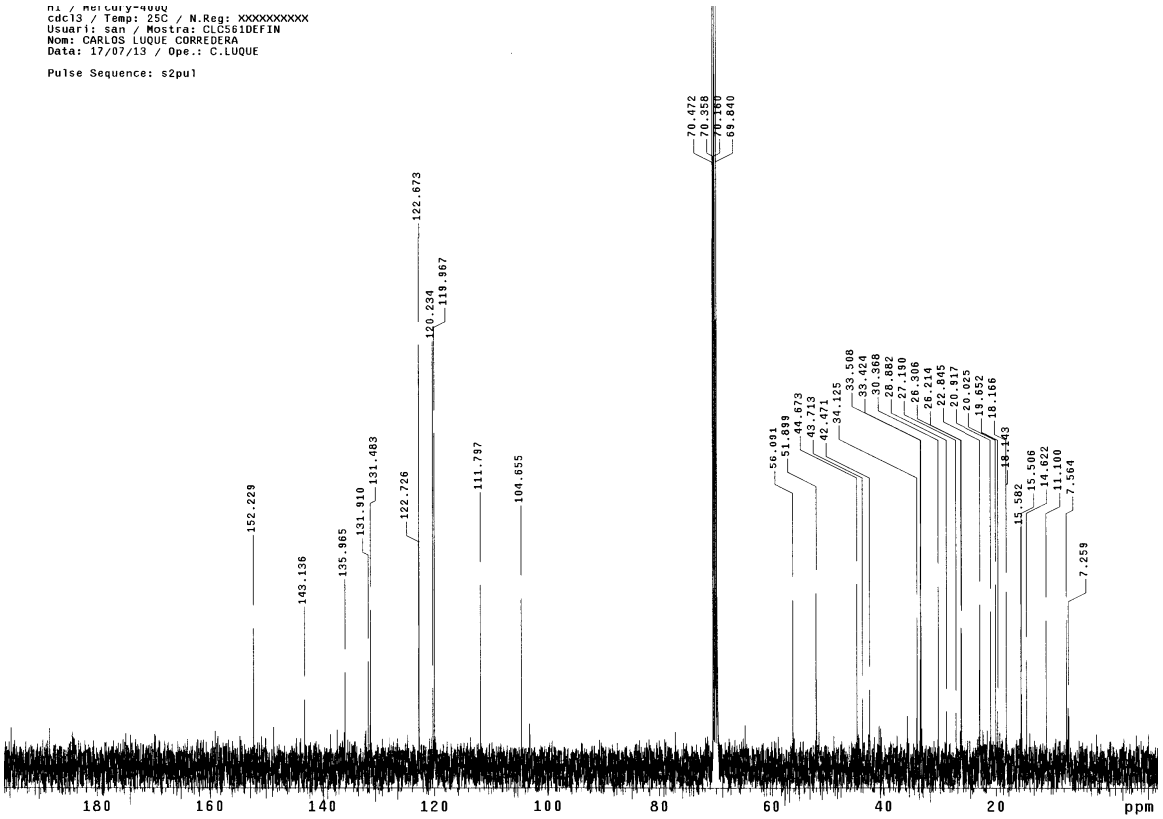



**72** (*E/Z* mixture) **73** ***epi*-73**

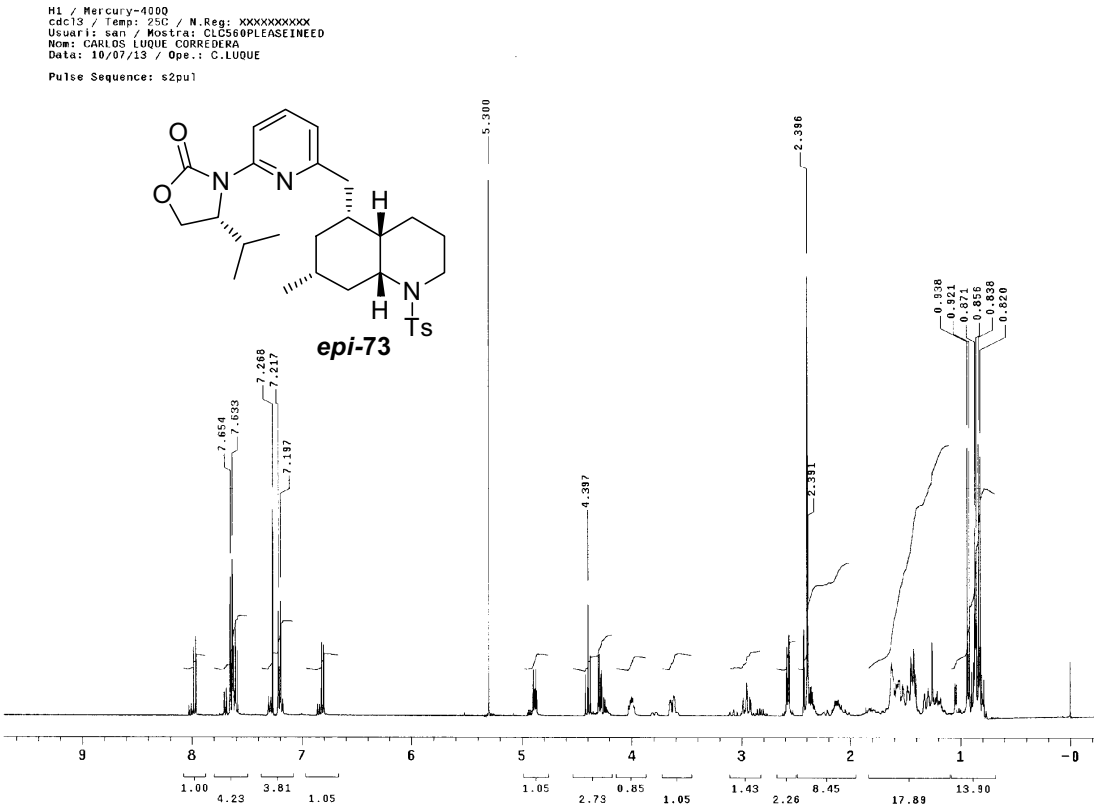
To a stirred solution of **72** (50 mg, 0.095 mmol) in AcOH (0.7 mL) was added Pd/C (20% w/w, 182 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of $H_2$ overnight. The mixture was diluted with $CH_2Cl_2$ (≈10 mL) before it was filtered through a pad of celite, washed through with $CH_2Cl_2$ and the filtrate was concentrated in *vacuo*. Purification by column chromatography (2.5→5→10→25% EtOAc/hexane) gave **73** (12 mg, 24%) as a colourless oil, followed by a mixture of **73** and ***epi*-73** (27 mg, 54%) as a colourless oil, and finally was obtained ***epi*-73** (8 mg, 16%) as a white solid. 94% combined yield. The ratio is 2.3:1 **73** / ***epi*-73**, determined by NMR.

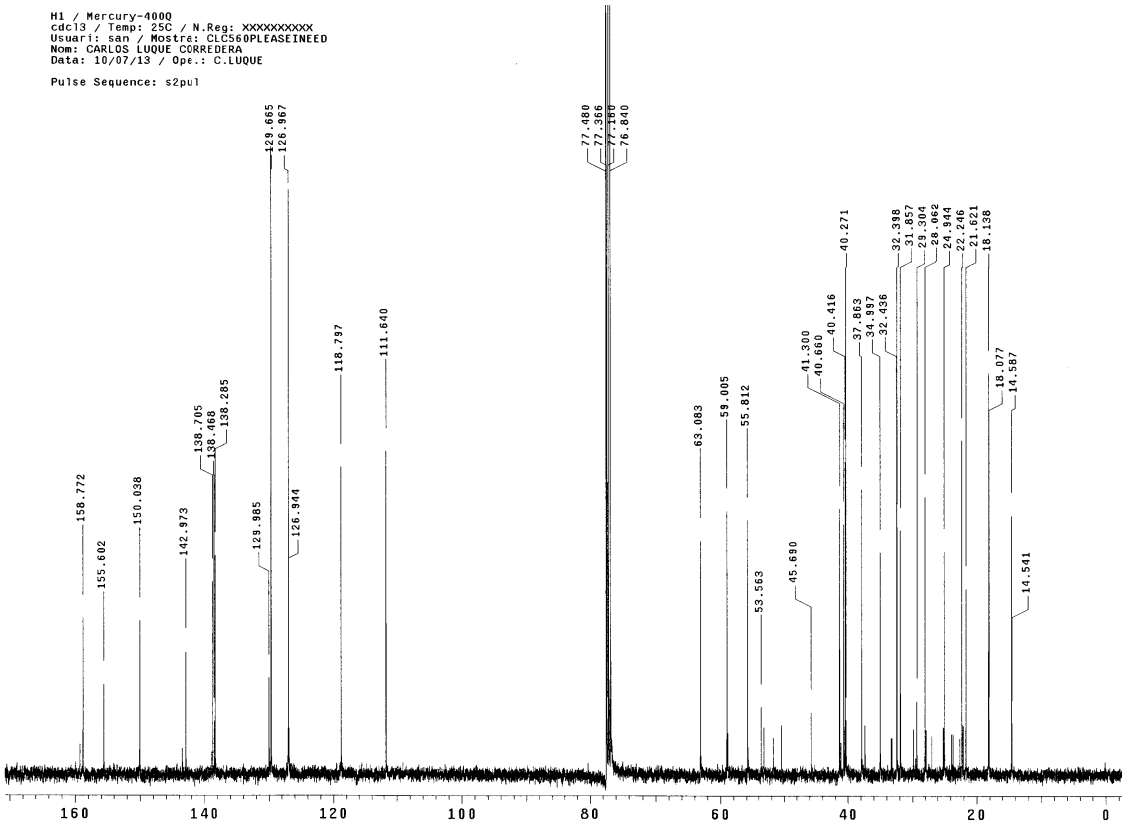
**Data for 73**: $[\alpha]_D$ -22.1 (c 1, $CHCl_3$); $R_f$ 0.44 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, COSY) δ 0.78 and 0.86 (2d, *J* = 7.2 Hz, 3H each, $CH_3$), 0.90 (d, *J* = 7.2 Hz, 7-$CH_3$), 1.12-1.27 (m), 1.39-1.54 (m, H-4, H-7, 2H-8), 1.63-1.71 (m), 1.81 (qd, *J* = 13.2, 4.0 Hz, H-4ax), 2.1 (m, 1H, H-x), 2.34 (dt, *J* = 12.8, 4.6 Hz, H-4a), 2.39 (s, 3H, Ar*CH*$_3$), 2.76 (td, *J* = xx Hz, H-x), 2.93 (dt, J = 13.2, 2.8 Hz, H-2ax), 3.58 (masked, H-6eq), 3.58 (dm, *J* = 14 Hz, H-2eq), 4.21 (dd, *J* = 7.2, 4.0 Hz, 1H, $NCH_2$), 4.32 (dt, *J* = 12.0, 4.8 Hz, H-8a), 4.90 (dt, *J* = 8.4, 4.4 Hz, OCH), 6.83 (d, *J* = 7.2 Hz, H-5 Py), 7.17 and 7.60 (2d, *J* = 8 Hz, 2H each, ArH), 7.63 (t, *J* = 8.0 Hz, H-4 Py), 8.0 (d, *J* = 8 Hz, H-3 Py). $^{13}$C NMR (100 MHz, HSQC) 14.6 and 18.1 ($CH_3$), 20.9 (Ar$CH_3$), 22.8 (7-$CH_3$), 26.2 (C-3), 26.3 (C-4), 27.2 (CH aux), 30.3 (C-7), 33.4 (C-8), 33.5 (C-6), 44.6 (C-2), 51.9 (C-4a), 56.0 (C-8a), 59.2 (OCH), 62.7 ($NCH_2$), 111.7 (C-5 Py), 119.9 (C-3 Py), 122.6 (*o*-Ts), 122.7 (*m*-Ts), 131.4 (C-4 Py), 135.9 (*p*-Ts), 143.1 (*ipso*-Ts), 149.6 (C-2 Py), 154.6 (C-6 Py), 155.4 (NCO); HRMS calcd for $C_{29}H_{40}N_3O_4S$ $(M + H)^+$ 526.2734, found 526.2722.


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC565firstspot
Nom: CARLOS LUQUE CORREDERA
Data: 16/07/13 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
7.260
7.627
7.606
7.193
4.247
2.388
1.571
0.915
0.897
0.877
0.861
0.803
0.785
0.003
73
9
8
7
6
5
4
3
2
1
-0
ppm
1.00
2.17
2.52
1.05
1.17
2.70
1.15
3.01
3.14
11.66
6.20

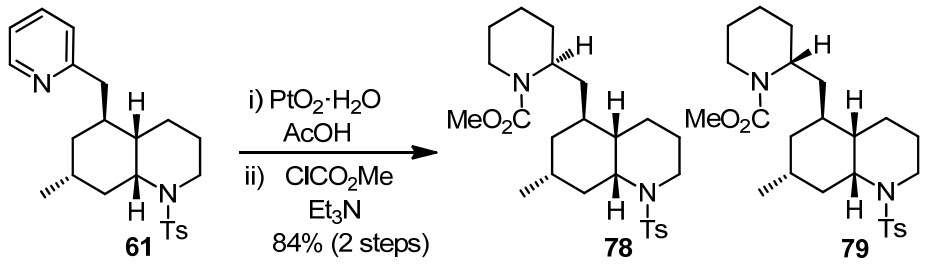

cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC561DEFIN
Nom: CARLOS LUQUE CORREDERA
Data: 17/07/13 / Ope.: C.LUQUE
Pulse Sequence: s2pul
70.472
70.358
70.160
69.840
152.229
143.136
135.965
131.910
131.483
122.726
122.673
120.234
119.967
111.797
104.655
56.091
51.839
44.673
43.713
42.471
34.125
33.508
33.424
30.368
28.882
27.190
26.306
26.214
22.845
20.417
20.025
19.652
18.166
18.143
15.582
15.506
14.622
11.100
7.564
7.259
180
160
140
120
100
80
60
40
20
ppm

**Data for *epi*-73**: $[\alpha]_D$ -51.0 (c 1, $CHCl_3$); $R_f$ 0.39 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, COSY) $\delta$ 0.82 and 0.86 (2d, *J* = 6.8 Hz, 3H each, $CH_3$), 0.92 (d, *J* = 6.8 Hz, 7-$CH_3$), 1.18-1.33 (m, H-3ax), 1.41-1.45 (m, H-4, H-7, 2H-8), 1.47-1.63 (m, 2H H-3eq, H-6ax), 2.11 (qd, *J* = 13.2, 4.0 Hz, H-4ax), 2.34 (dt, *J* = 12.8, 4.6 Hz, H-4a), 2.39 (s, 3H, Ar*CH*$_3$), 2.56 (m, CH), 2.92 (td, J = 13.2, 2.8 Hz, H-2ax), 3.61 (masked, H-6eq), 3.98 (dm, *J* = 13.2 Hz, H-2eq), 4.22 (dt, *J* = 12.0, 4.8 Hz, H-8a), 4.27 (dd, *J* = 9.2, 3.6 Hz, 1H, $NCH_2$), 4.37 (t, *J* = 8.8 Hz, 1H, $NCH_2$), 4.86 (dt, *J* = 7.2, 4.0 Hz, OCH), 6.80 (d, *J* = 8.0 Hz, H-5 Py), 7.20 and 7.64 (2d, *J* = 8 Hz, 2H each, ArH), 7.58 (t, *J* = 8.0 Hz, H-4 Py), 7.97 (d, *J* = 8 Hz, H-3 Py). $^{13}$C NMR (100 MHz, HSQC) 14.5 and 18.0 ($CH_3$ aux), 21.6 ($CH_3$ Ar), 22.2 (7-$CH_3$), 24.9 (C-3), 28.0 (C-4), 29.3 (CH aux), 31.8 (C-7), 32.3 (C-8), 32.4 (C-6), 34.9 (C-4a), 37.8 (C-5), 40.2 (C-2), 45.7 (C-4a), 55.8 (C-8a), 59.0 (OCH), 63.0 ($NCH_2$), 111.6 (C-5 Py), 118.8.1 (C-3 Py), 126.9 (*o*-Ts), 129.6 (*m*-Ts), 138.3 (C-4 Py), 138.5 (*p*-Ts), 142.9 (*ipso*-Ts), 150.0 (C-2 Py), 155.6 (C-6 Py), 158.7 (NCO); HRMS calcd for $C_{29}H_{40}N_3O_4S$ $(M+H)^+$ 526.2734, found 526.2724.


H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: sam / Mostra: CLC560PLEASEINEED
Nom: CARLOS LUQUE CORREDERA
Data: 10/07/13 / Ope.: C.LUQUE
Pulse Sequence: s2pul
epi-73
5.300
2.396
2.391
4.397
7.654
7.633
7.268
7.217
7.197
0.938
0.921
0.871
0.855
0.838
0.820
1.00
4.23
3.81
1.05
1.05
2.73
0.85
1.05
1.43
2.26
8.45
17.89
13.90

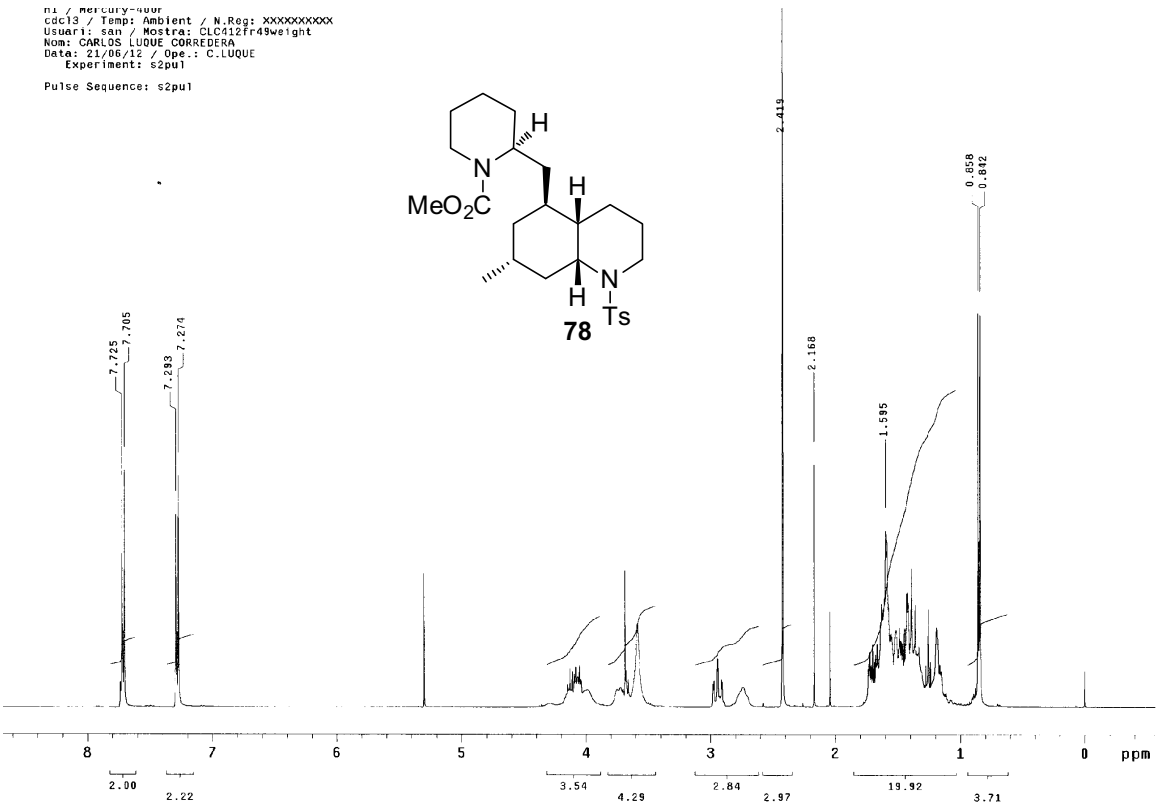

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: sam / Mostra: CLC560PLEASEINEED
Nom: CARLOS LUQUE CORREDERA
Data: 10/07/13 / Ope.: C.LUQUE
Pulse Sequence: s2pul
77.480
77.366
77.160
76.840
129.665
126.967
158.772
155.602
150.038
142.973
138.705
138.468
138.285
129.985
126.944
118.797
111.640
63.083
59.005
55.812
53.563
45.690
41.300
40.660
40.416
40.271
37.863
34.937
32.438
32.398
31.857
29.304
28.062
24.944
22.246
21.621
18.138
18.077
14.587
14.541

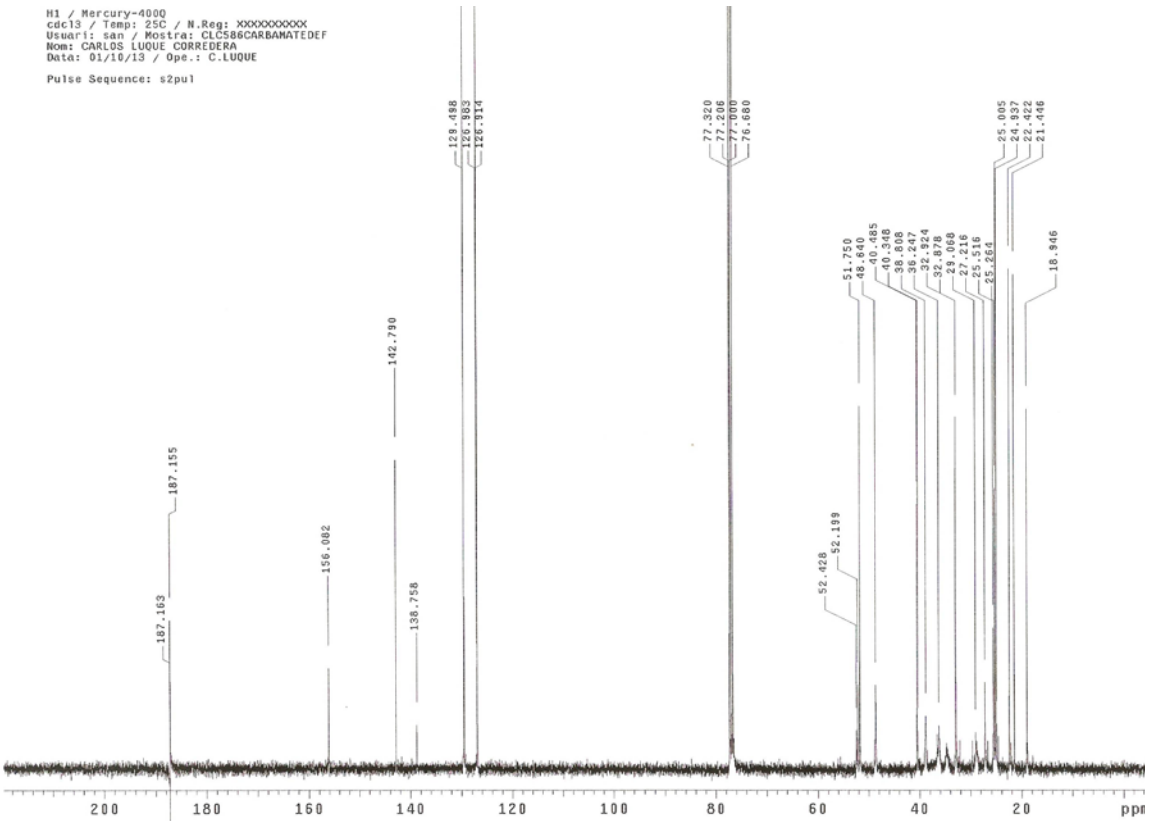
***(4aS,5S,7R,8aR)*-5-[(*S*)-(1-Methoxycarbonyl)-2-piperidylmethyl)]-7-methyl-1-(4-methylsulfonyl)decahydroquinoline (78)**



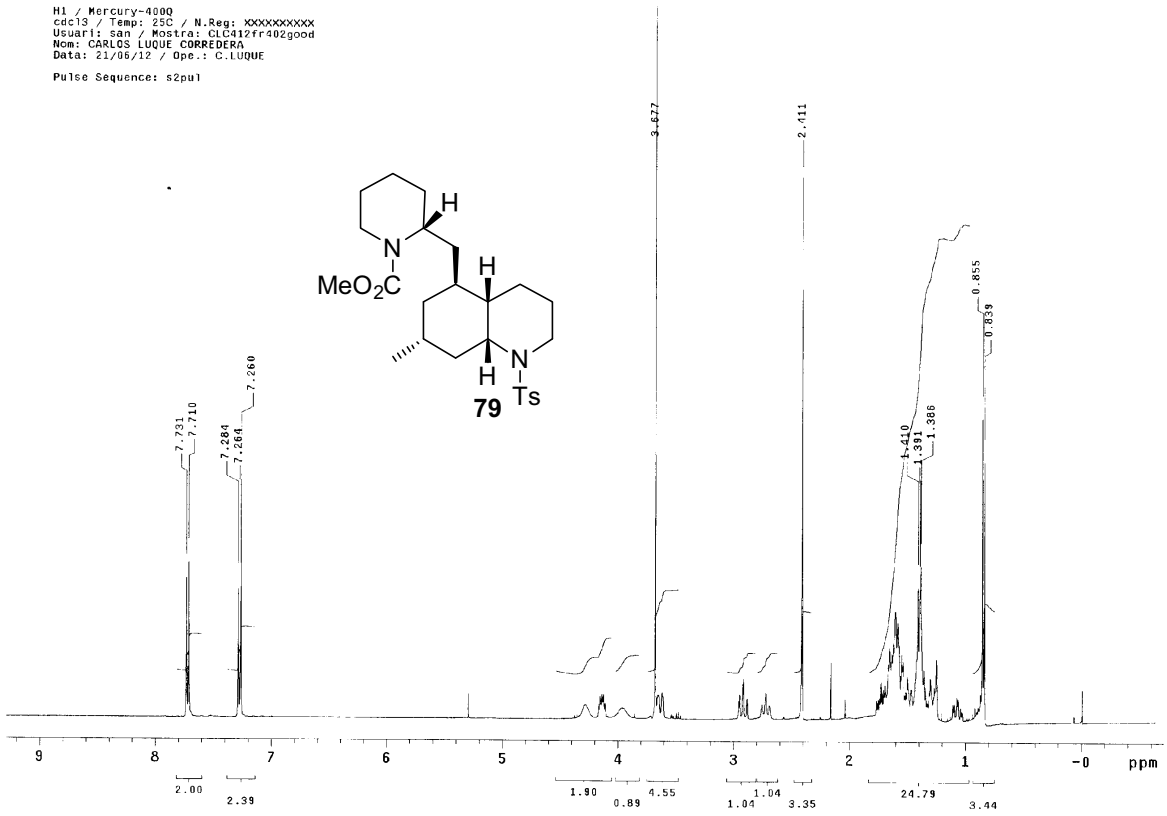

61 78 79

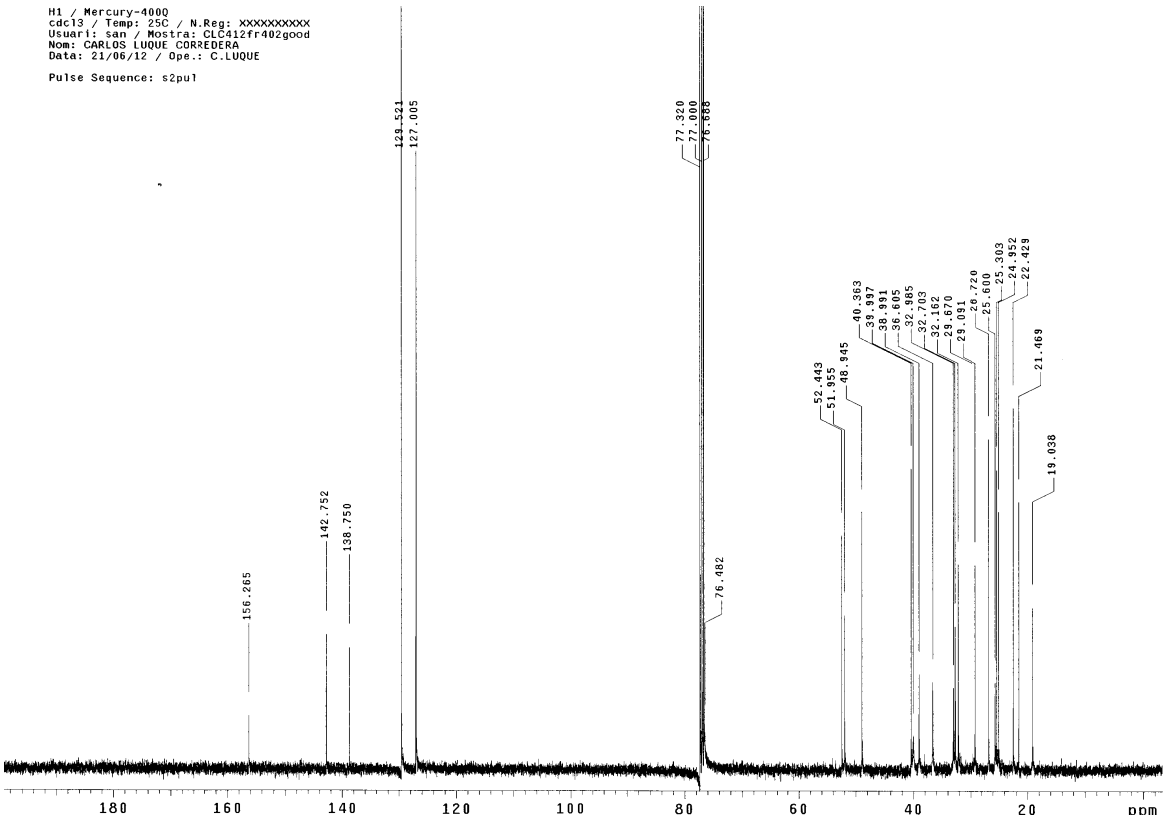
To a stirred solution of **61** (500 mg, 1.25 mmol) in AcOH (9.4 mL) was added $PtO_2$ (20% w/w, 100 mg) at rt. The resulting mixture was evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of $H_2$ for 16 h. The mixture was diluted with $CH_2Cl_2$ ( ≈ 15 mL) before it 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 *in vacuo* to give the epimeric mixture of piperidines **63** (not shown) as a colorless oil which was used in the next step wihout further purification. To a stirred solution of the above mixture (1.25 mmol) in $CH_2Cl_2$ (6.2 mL) was added triethylamine (0.87 mL, 6.25 mmol) followed by methyl chloroformate (0.29 mL, 3.75 mmol). After 24 h the reaction was quenched by the addition of 3 N HCl (2 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification by chromatography (2.5→5→10→25% EtOAc/hexane) gave **79** (206 mg, 35%) as a colorless oil, followed by a mixture of **79** and **78** (61 mg, 11%), and finally the product **78** (204 mg, 35%) eluted. **Data for 78**: white solid, mp 115 ºC; $[\alpha]_D$ -18.8 (*c* 1, $CHCl_3$); $R_f$ 0.48 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, COSY) $\delta$ 0.83 (d, *J* = 6 Hz, $CH_3$), 1.15 (m, 2 H), 1.30-1.60 (m, 16 H), 1.69 (m, 1 H, 5-$CH_2$), 2.41 (s, Ar$CH_3$), 2.73 (br, H-6´ax), 2.90 (td, *J* = 13.2, 2.8 Hz, H-2ax), 3.57 (br s, OMe), 3.72 (br d, *J* =12.0 Hz, H-2eq), 3.98 (br, H-6´eq), 4.05 (dt, *J* = 12.0, 4.8 Hz, H-8a), 4.12 (br, H-2´), 7.26 (d, *J* = 8.4 Hz, *m*-Ts), 7.70 (d, *J* = 8.4 Hz, 2 H, *o*-Ts). $^{13}$C NMR (100 MHz, HSQC) 19.1 (C-4´), 21.6 ($CH_3$Ar), 22.6 ($CH_3$), 25.2 (C-4), 25.4 (C-3), 25.7 (C-5´), 27.4 (C-7), 29.2 (br, C-3´), 33.0 (C-8), 33.1 (5-$CH_2$), 34.8 (br, C-6), 36.4 (br, C-4a) 39.0 (br, C-6´), 40.5 (br, C-5), 40.6 (C-2), 48.8 (br, C-2´), 51.9 (C-8a), 52.4 (br, OMe), 127.1 (*o*-Ts), 129.7 (*m*-Ts), 138.9 (*p*-Ts), 143.0 (*ipso*-Ts), 156.2 ($CO_2$Me); HRMS calcd for $C_{25}H_{39}N_2O_4S$ $(M+H)^+$ 463.2625, found 463.262.


cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC412fr49weight
Nom: CARLOS LUQUE CORREDERA
Data: 21/06/12 / Ope.: C.LUQUE
Experiment: s2pul
Pulse Sequence: s2pul
MeO2C
Ts
78
7.725
7.705
7.293
7.274
2.419
2.168
1.595
0.858
0.842
ppm
2.00
2.22
3.54
4.29
2.84
2.97
19.92
3.71

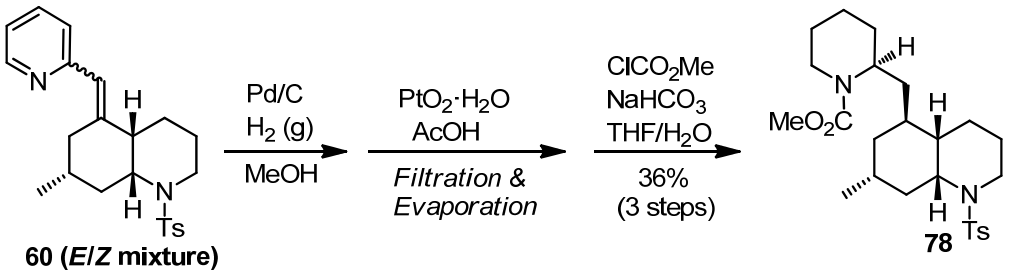

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC586CARBAMATEDEF
Nom: CARLOS LUQUE CORREDERA
Data: 01/10/13 / Ope.: C.LUQUE
Pulse Sequence: s2pul
187.155
187.163
156.082
142.790
138.758
129.488
126.983
126.914
77.320
77.206
77.000
76.680
52.428
52.199
51.750
48.640
40.485
40.348
38.808
38.247
32.924
32.878
29.068
27.216
25.516
25.264
25.005
24.937
22.422
21.446
18.946
ppm

**Data for 79**: $[\alpha]_D$ -0.9 (*c* 1, $CHCl_3$); $R_f$ 0.52 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, COSY) $\delta$ 0.85 (d, *J* = 6.4 Hz, $CH_3$), 1.07 (td, *J* = 12.4, 4.8 Hz, 1H, H-8ax), 1.25-1.44 (m, 7H, H-5, H-4a, 2H-3´, H-3, H-4, H-8eq), 1.45-1.80 (m, 9H, 5-$CH_2$, 2H-5´,H-3, H-4, 2H-4´, H-7), 2.41 (s, 3H, $ArCH_3$), 2.72 (t, *J* = 13.2 Hz, 1H, H-6´ax), 2.91 (td, *J* = 13.2, 2.8 Hz, 1H, H-2ax), 3.63 (dm, *J* = 13.2 Hz, H-2eq), 3.68 (s, 3H, OMe), 3.96 (br, 1H, H-6´eq), 4.14 (dt, *J* = 12.0, 4.2 Hz, 1H, H-8a), 4.28 (br, 1H, H-2´eq), 7.27 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.71 (d, *J* = 8.0 Hz, 2H, *o*-Ts); $^{13}$C NMR (100 MHz, HSQC) 19.0 (C-4´), 21.5 ($ArCH_3$), 22.4 ($CH_3$), 24.9 (C-4), 25.3 (C-3), 25.6 (br, C-5´), 26.7 (C-7), 29.1 (C-3´), 32.2 (C-8), 32.7 (C-6), 33.0 (br, 5-$CH_2$), 36.6 (C-4a), 39.0 (C-6´), 40.0 (br, C-5), 40.4 (C-2), 48.9 (C-2´), 52.0 (C-8a), 52.4 (OMe), 127.0 (*o*-Ts), 129.5 (*m*-Ts), 138.8 (*p*-Ts), 142.8 (*ipso*-Ts), 156.3 ($CO_2Me$); HRMS calcd for $C_{25}H_{39}N_2O_4S$ $(M+H)^+$ 463.2625, found 463.2622.


H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC412fr402good
Nom: CARLOS LUQUE CORREDERA
Data: 21/06/12 / Ope.: C.LUQUE
Pulse Sequence: s2pul
MeO2C
N
H
H
H
N
Ts
79
3.627
2.111
0.855
0.839
1.410
1.391
1.386
7.731
7.710
7.284
7.264
7.260
ppm
2.00
2.39
1.90
0.89
4.55
1.04
1.04
3.35
24.79
3.44


H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CLC412fr402good
Nom: CARLOS LUQUE CORREDERA
Data: 21/06/12 / Ope.: C.LUQUE
Pulse Sequence: s2pul
129.521
127.005
77.320
77.000
76.688
76.482
156.265
142.752
138.750
52.443
51.955
48.945
40.363
39.997
38.991
36.605
32.985
32.703
32.162
29.670
29.091
26.720
25.600
25.303
24.952
22.429
21.469
19.038
ppm

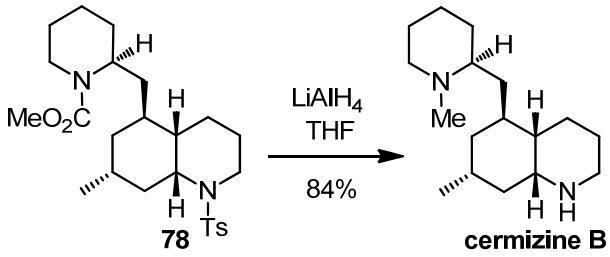
***(4aS,5S,7R,8aR)*-5-[(*S*)-(1-Methoxycarbonyl)-2-piperidylmethyl)]-7-methyl-1-(4-methylsulfonyl)decahydroquinoline (78) 3rd One-pot Sequence**




To a stirred solution of **60** (519 mg, 1.31 mmol) in MeOH (10 mL) was added Pd/C (20% w/w, 104 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of $H_2$ overnight. To the same flask was added $PtO_2 \cdot H_2O$ (20% w/w, 104 mg) and AcOH (10 mL), then the hydrogen purging operation was repeated, and the resulting mixture stirred overnight. The mixture was diluted with $CH_2Cl_2$ (≈ 20 mL) before it was filtered through a pad of celite and washed through with $CH_2Cl_2$. The filtered solution was concentrated *in vacuo.* The resulting product was dissolved in a 1:1 mixture of THF/$H_2O$ (42 mL in total), $NaHCO_3$(s) (2.2 g, 26.2 mmol) was added and the mixture cooled at 0 ºC. Methyl chloroformate (0.51 mL, 6.6 mmol) was added and the reaction was allowed to warm to rt. After 24 h the THF was evaporated and the mixture was diluted with $CH_2Cl_2$ (≈ 20 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic extracts were dried and concentrated in vacuo. Purification by chromatography (2.5→5→10→25% EtOAc/hexane) gave **79** (237 mg, 39%) as a colorless oil, followed by a diastereomeric mixture (77 mg)[130], and finally **78** (218 mg, 36%) eluted as a white solid. For compounds **78** and **79** the combined overall yield from **60** was 85%.

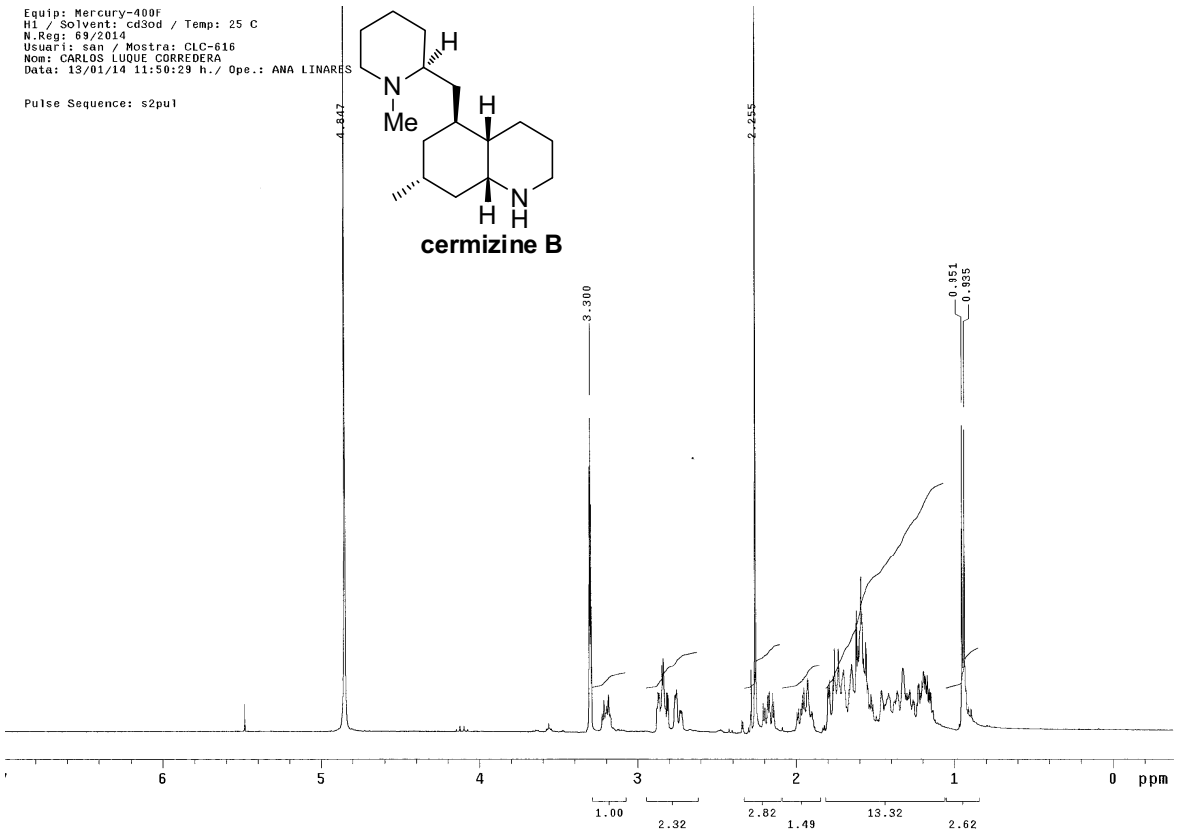
[130] This sample was contaminated with minor quantities of **62** coming from the initial hydrogenation of the double bond.

***(4aS,5S,7R,8aR)*-7-Methyl-5-[(*S*)-(1-methylpiperidin-2-yl)methyl]decahydroquinoline [cermizine B]**

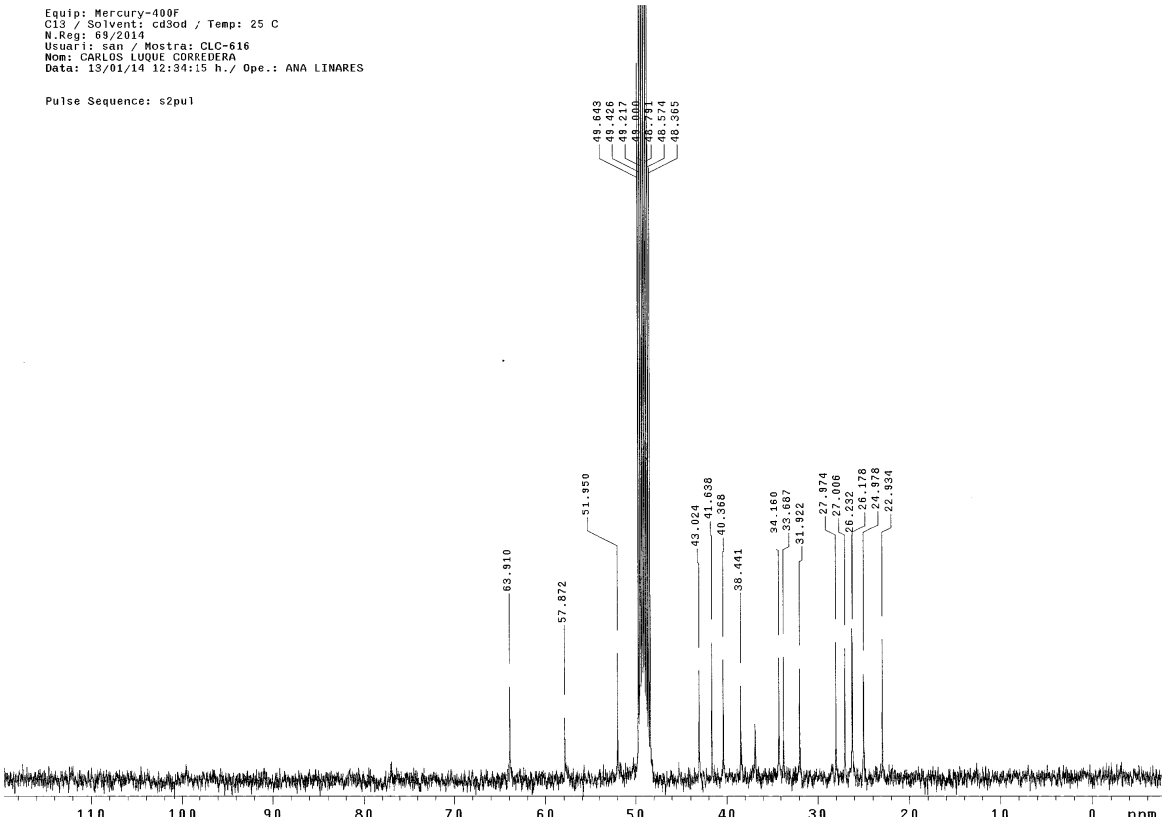



To a stirred solution of the carbamate **78** (50 mg, 0.108 mmol) in THF (10 mL) was added $LiAlH_4$ (47.1 mg, 1.08 mmol) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by the careful addition of water (0.05 mL), 15% aq. NaOH (0.05 mL) and a second portion of water (0.15 mL). The mixture was then diluted with $CH_2Cl_2$ before it was filtered through a pad of celite, and washed through with $CH_2Cl_2$. The filtrate was concentrated *in vacuo* and the product was purified by column chromatography (2.5→5% MeOH/$CH_2Cl_2$ followed by 1:2:0.1 MeOH/$CH_2Cl_2$/concd $NH_4OH$) to give cermizine B (24 mg, 84%) as a colourless oil with spectral data identical to those previously reported for the isolated natural product. $R_f$ 0.2 (MeOH/$CH_2Cl_2$/concd $NH_4OH$=1:2:0.1); $[\alpha]_D$ -3.1 (*c* 0.7, MeOH); lit[131] : $[\alpha]_D$ -2 (*c* 0.6, MeOH); $^1$H NMR (400 MHz, COSY) $\delta$ 0.94 (d, *J* = 6.4 Hz, $CH_3$), 1.15 (m, 1H, H-8), 1.18 (m, 1H, H-6), 1.22 (m, 1H, H-4), 1.30 (m, 1H, H-3), 1.32 (m, 1H, H-8), 1.38 (m, 1H, H-11), 1.40 (m, 2H, H-14, H-2), 1.55 (m, 1H, H-10), 1.56 (m, 1H, H- 7), 1.60 (m, 2H, H-2, H-14), 1.64 (m, 1H, H-12), 1.65 (m, 1H, H-15), 1.70 (m, 2H, H-3, H-10), 1.75 (m, 1H, H-11) 1.78 (m, 1H, H-4), 1.90 (m, 1H, H-5), 1.95 (m, 1H, H-6), 2.17 (td, *J* = 11.6, 3.2 Hz, 1H, H-1ax), 2.25 (s, 3H, H-19), 2.72 (br d, *J* = 12.4 Hz, 1H, H-9), 2.82 (td, *J* = 12.4, 2.8 Hz, 1H, H-9), 2.85 (br d, *J* = 11.6 Hz, 1H, H-1eq), 3.19 (dt, *J* = 12.0, 4.4 Hz, 1H, H-13). $^{13}$C NMR (100 MHz, HSQC) 22.9 (C-16), 25.0 (C-3), 26.2 (C-11), 26.2 (C-2), 27.0 (C-10), 28.0 (C-15), 31.9 (C-4), 33.7 (C-8), 34.2 (C-14), 36.9 (C-6), 38.4 (C-7), 40.4 (C-9), 41.6 (C-12), 43.0 (C-19), 52.0 (C-13), 57.9 (C-1), 63.9 (C-5). HRMS calcd for $C_{17}H_{33}N_2$ $(M+H)^+$ 265.2638, found 265.2635.

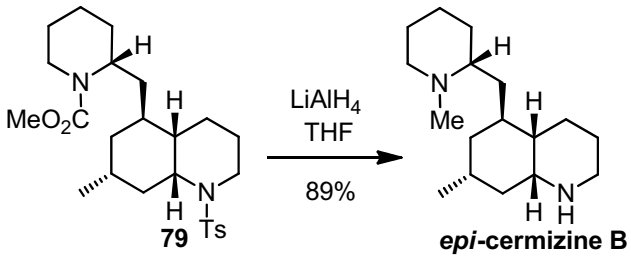
[131] Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015.


Equip: Mercury-400F
H1 / Solvent: cd3od / Temp: 25 C
N.Reg: 69/2014
Usuari: san / Mostra: CLC-616
Nom: CARLOS LUQUE CORREDERA
Data: 13/01/14 11:50:29 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
4.847
3.300
2.255
0.951
0.935
6
5
4
3
2
1
0 ppm
1.00
2.32
2.82
1.49
13.32
2.62

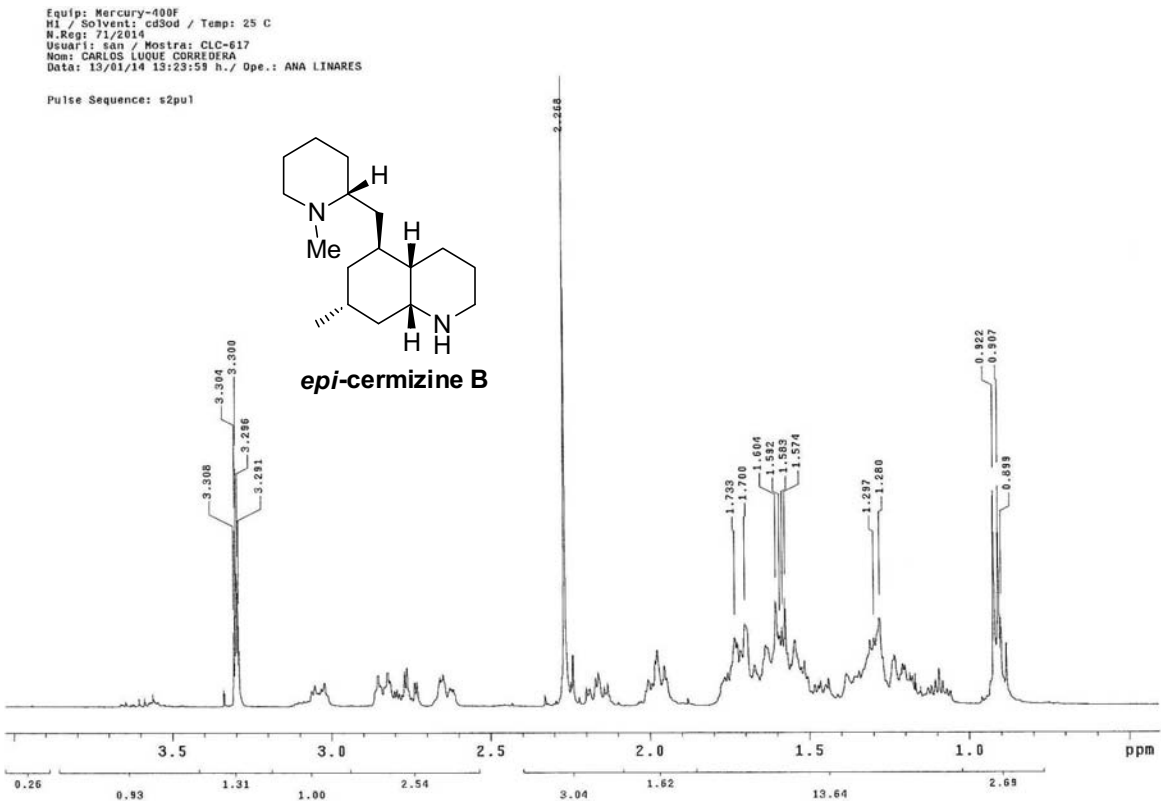
cermizine B


Equip: Mercury-400F
C13 / Solvent: cd3od / Temp: 25 C
N.Reg: 69/2014
Usuari: san / Mostra: CLC-616
Nom: CARLOS LUQUE CORREDERA
Data: 13/01/14 12:34:15 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
49.643
49.426
49.217
49.000
48.791
48.574
48.365
63.910
57.872
51.950
43.024
41.638
40.368
38.441
34.169
33.667
31.922
27.974
27.006
26.232
26.178
24.978
22.934
110
100
90
80
70
60
50
40
30
20
10
0 ppm

***(4aS,5S,7R,8aR)*-7-Methyl-5-[(*R*)-(1-methylpiperidin-2-yl)methyl]decahydro-quinoline [*epi*-cermizine B]**




To a stirred solution of the carbamate **79** (69 mg, 0.149 mmol) in THF (13 mL) was added $LiAlH_4$ (57 mg, 1.49 mmol) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by the careful addition of water (0.07 mL), 15% aq. NaOH (0.07 mL) and a second portion of water (0.21 mL). The mixture was then diluted with $CH_2Cl_2$ before it was filtered through a pad of celite, and washed through with $CH_2Cl_2$. The filtrate was concentrated *in vacuo* and the product was purified by column chromatography (2.5→5% MeOH/$CH_2Cl_2$ followed by 1:2:0.1 MeOH/$CH_2Cl_2$/concd $NH_4OH$) to give ***epi*-cermizine B** (35 mg, 89%) as a colourless oil with spectral data identical to those previously reported for the isolation of the natural product. $R_f$ 0.2 (MeOH/$CH_2Cl_2$/concd $NH_4OH$=1:2:0.1); $[\alpha]_D$ +50.0 (*c* 0.95, MeOH); $^1$H NMR (400 MHz, COSY) $\delta$ 0.91 (d, *J* = 6 Hz, $CH_3$), 1.05 (ddd, *J* = 14.2, 9.2, 4.4 Hz, 1H, H-6), 1.20 (m, 2H, H-4, H-8), 1.30 (m, 1H, H-8), 1.35 (m, 1H, H-14), 1.25-1.40 (m, 3H, H-3, H-2, H-11), 1.45 (m, 1H, H-15), 1.50 (m, 1H, H-7), 1.60 (m, 1H, H-14), 1.50-1.65 (m, 10H, H-2, 2H-10, H-11, 1.60-1.80 (m, 4H, H-3, H-4, H-12, H-14), 1.95 (m, 1H, H-5), 2.00 (m, 1H, H-6), 2.17 (td, *J* = 12.0, 4.0 Hz, 1H, H-1), 2.27 (s, 3H, H-19), 2.64 (brd, *J* = 12.4 Hz, 1H, H-9), 2.76 (ddd, *J* = 13.2, 12.4, 3.2 Hz, 1H, H-9), 2.84 (brd, *J* = 12.2 Hz, 1H, H-1), 3.03 (dt, *J* = 12.2, 4.4 Hz, 1H, H-13). $^{13}$C NMR (100 MHz, HSQC) 23.1 (C-16), 25.0 (C-3), 26.3 (C-11), 26.9 (C-2), 27.9 (C-10), 28.4 (C-15), 32.0 (C-4), 34.8 (C-14), 36.7 (C-8), 36.9 (C-6), 38.6 (C-7), 39.3 (C-12), 40.5 (C-9), 43.1 (C-19), 51.4 (C-13), 57.9 (C-1), 64.1 (C-5); HRMS calcd for $C_{17}H_{33}N_2$ $(M+H)^+$ 265.2638, found 265.2634.







***epi*-cermizine B**

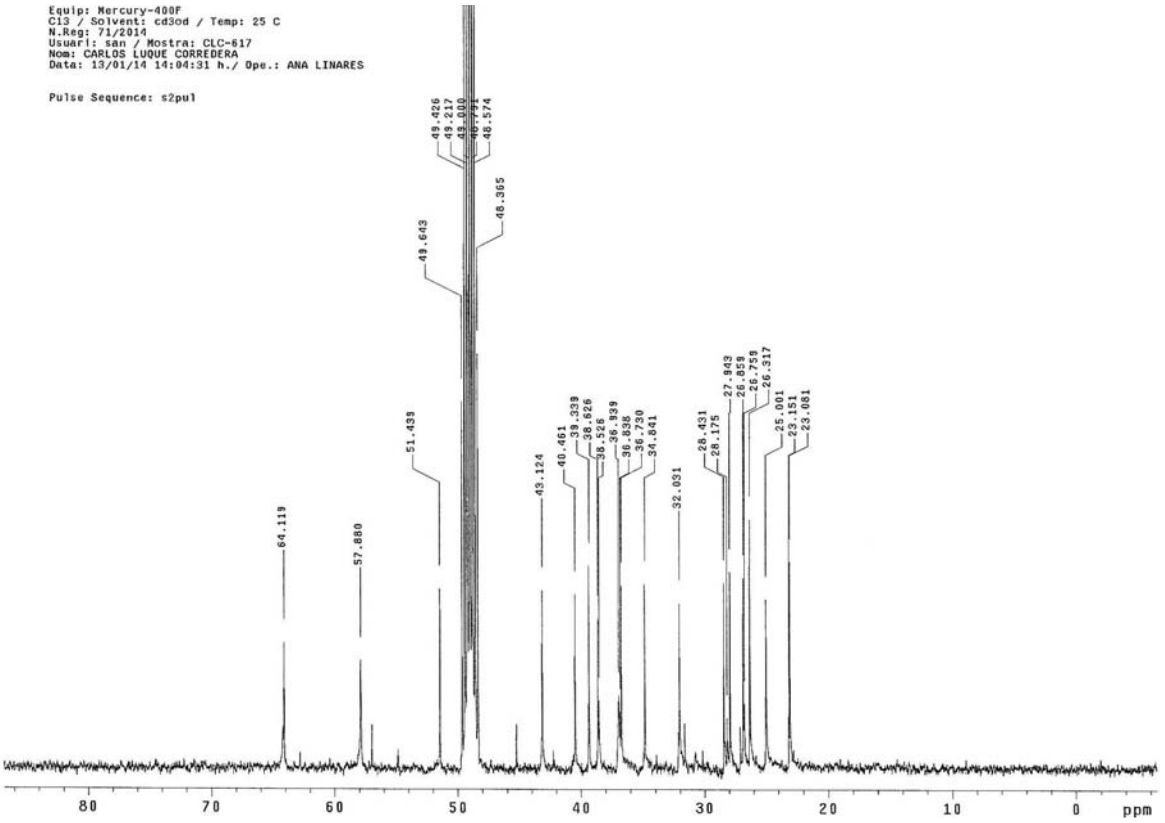
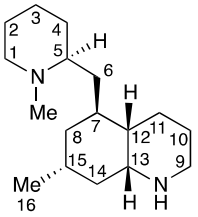


**Table S1**. Comparison of $^1$H NMR data for (-) **cermizine B** and ***epi*-cermizine B** in $CD_3OD$

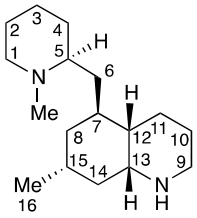



cermizine B

| | Natural **cermizine B**[1] | Synthetic **cermizine B**[2] | Synthetic ***epi*-cermizine B**[2] |
|---|---|---|---|
| **1** | 2.84 (br d, 11.1) | 2.85 (br d, 11.6) | 2.84 (br d, 12.2) |
| | 2.17 (td, 11.1, 3.6) | 2.17 (td, 11.6, 3.2) | 2.17 (td, 12.0, 4.0) |
| **2** | 1.60 (m) | 1.60 (m) | 1.50-1.70 (m) |
| | 1.41 (m) | 1.40 (m) | 1.25-1.40 (m) |
| **3** | 1.73 (m) | 1.70 (m) | 1.60-1.80 (m) |
| | 1.32 (m) | 1.30 (m) | 1.25-1.40 (m) |
| **4** | 1.78 (m) | 1.78 (m) | 1.75 (m) |
| | 1.24 (m) | 1.22 (m) | 1.15-1.25 (m) |
| **5** | 1.92 (m) | 1.90 (m) | 1.95 (m) |
| **6** | 1.97 (m) | 1.95 (m) | 2.00 (m) |
| | 1.19 (m) | 1.18 (m) | 1.05 (ddd, 14.2, 9.2, 4.4) |
| **7** | 1.56 (m) | 1.56 (m) | 1.50 (m) |
| **8** | 1.32 (m) | 1.32 (m) | 1.30 (m) |
| | 1.18 (m) | 1.15 (m) | 1.20 (m) |
| **9** | 2.78 (td, 12.6, 2.9) | 2.82 (td, 12.4, 2.8) | 2.76 (ddd, 13.2, 12.4, 3.2) |
| | 2.67 (br d, 12.6) | 2.72 (br d, 12.4) | 2.64 (br d, 12.4) |
| **10** | 1.66 (m) | 1.70 (m) | 1.50-1.65 (m) |
| | 1.52 (m) | 1.55 (m) | 1.50-1.65 (m) |
| **11** | 1.76 (m) | 1.70-1.80 (m) | 1.50-1.65 (m) |
| | 1.38 (m) | 1.38 (m) | 1.25-1.40 (m) |
| **12** | 1.61 (m) | 1.64 (m) | 1.70 (m) |
| **13** | 3.09 (dt, 12.1, 4.5) | 3.19 (dt, 12.0, 4.4) | 3.03 (dt, 12.2, 4.4) |
| **14** | 1.61 (m) | 1.60 (m) | 1.60 (m) |
| | 1.41 (m) | 1.40 (m) | 1.35 (m) |
| **15** | 1.63 (m) | 1.65 (m) | 1.45 (m) |
| **16** | 0.94 (d, 6.2) | 0.94 (d, 6.4) | 0.91 (d, 6.0) |
| **19** | 2.26 (s) | 2.25 (s) | 2.27 (s) |

[1] Recorded at 500 MHz (*Tetrahedron* 2004, **60**, 7015-7023). [2] Recorded at 400 MHz. Assignments were aided by gCOSY and gHSQCAD spectra.

**Table S2**. Comparison of $^{13}C$ NMR data for (-) **cermizine B**, and ***epi*-cermizine B** in $CD_3OD$

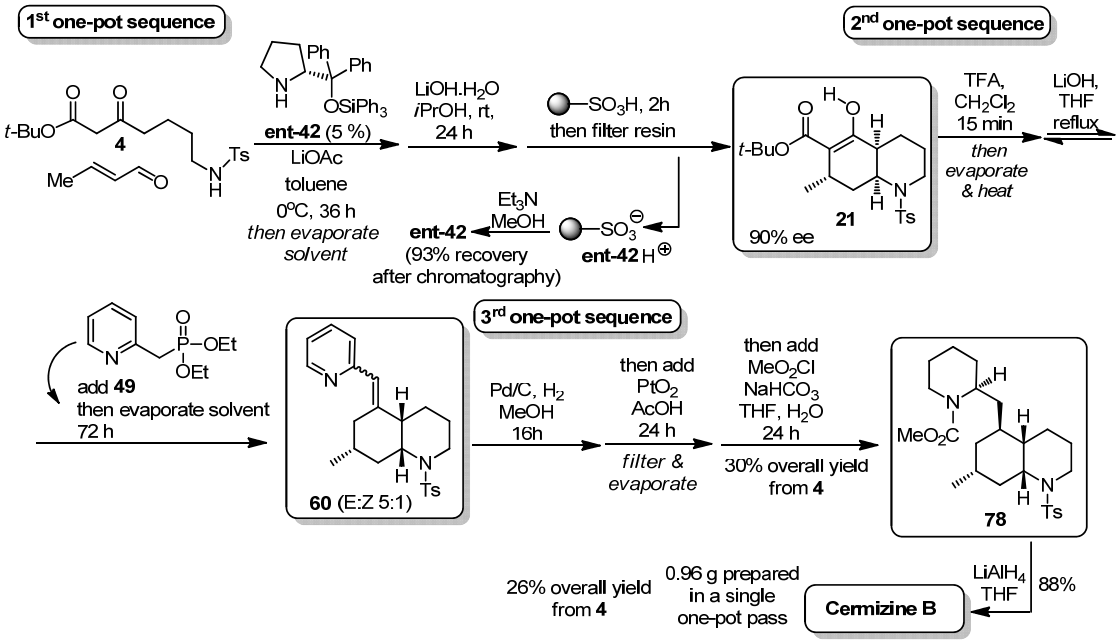



cermizine B

| carbon | cermizine B[1] | Synthetic **cerm.B**[2] | Synthetic *epi*-**cerm.B**[2] |
|---|---|---|---|
| **1** | 57.9 | 57.9 | 57.9 |
| **2** | 26.7 | 26.2 | 26.8 |
| **3** | 25.0 | 25.0 | 25.0 |
| **4** | 32.0 | 31.9 | 32.0 |
| **5** | 64.0 | 63.9 | 64.1 |
| **6** | 37.0 | 36.9 | 36.9 |
| **7** | 38.6 | 38.4 | 38.6 |
| **8** | 33.9 | 33.7 | 36.7 |
| **9** | 40.5 | 40.4 | 40.5 |
| **10** | 27.7 | 27.0 | 27.9 |
| **11** | 26.3 | 26.2 | 26.3 |
| **12** | 42.1 | 41.6 | 39.3 |
| **13** | 51.7 | 52.0 | 51.4 |
| **14** | 34.8 | 34.2 | 34.8 |
| **15** | 28.1 | 28.0 | 28.4 |
| **16** | 23.0 | 22.9 | 23.1 |
| **19** | 43.1 | 43.0 | 43.1 |

[1] Recorded at 125 MHz (*Tetrahedron* 2004, **60**, 7015-7023). [2] Recorded at 100 MHz. Assignments were aided by gHSQCAD spectra.

**Gram-scale total synthesis of cermizine B via uninterrupted sequence**




To a solution of keto ester **4** (5 g, 13.5 mmol) in toluene (126 mL) at 0 ºC was added crotonaldehyde (1.23 mL, 14.9 mmol), triphenylsilyl ether **ent-42** (346 mg, 0.68 mmol), and LiOAc (445 mg, 6.75 mmol), and the resulting mixture was stirred for 36 h at 0 ºC. Excess crotonaldehyde and toluene were removed on a rotary evaporator before addition of *i*PrOH (125 mL) and LiOH·$H_2O$ (567 mg, 13.5 mmol) was added, and the resulting solution was stirred for 24 h. To this flask was added the polymer-bound of *p*-toluenesulfonic acid (21.0 g, 30-60 mesh, Aldrich) and the mixture was stirred for 2 h. The solid support was filtered[132] and the filtrate was concentrated in vacuo to give the enantioenriched keto ester **21** (90% ee by HPLC). The crude material was dissolved in TFA (13.5 mL) and stirred under nitrogen for 15 min at room temperature. The solvent was evaporated under reduced pressure, the last traces of TFA were removed by azeotroping with toluene (3 × 50 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 80 ºC for 3 h to give decahydroquinoline **24** as a brown oil. The crude reaction product was dissolved in THF (46 mL), LiOH (647 mg, 27 mmol) was added, and the resulting mixture was refluxed for 24 h before addition of the phosphonate **49** (9.4 g, 40.5 mmol) at room temperature, followed by further portions of LiOH (1.62 g, 67.5 mmol). The solvent was removed *in vacuo* and the resulting mixture was stirred at room temperature for 3 days before being dissolved in $CH_2Cl_2$ (250 mL).

[132] Recovery of the catalyst according to the method outlined before gave 321 mg, (93%) of **ent-42**.

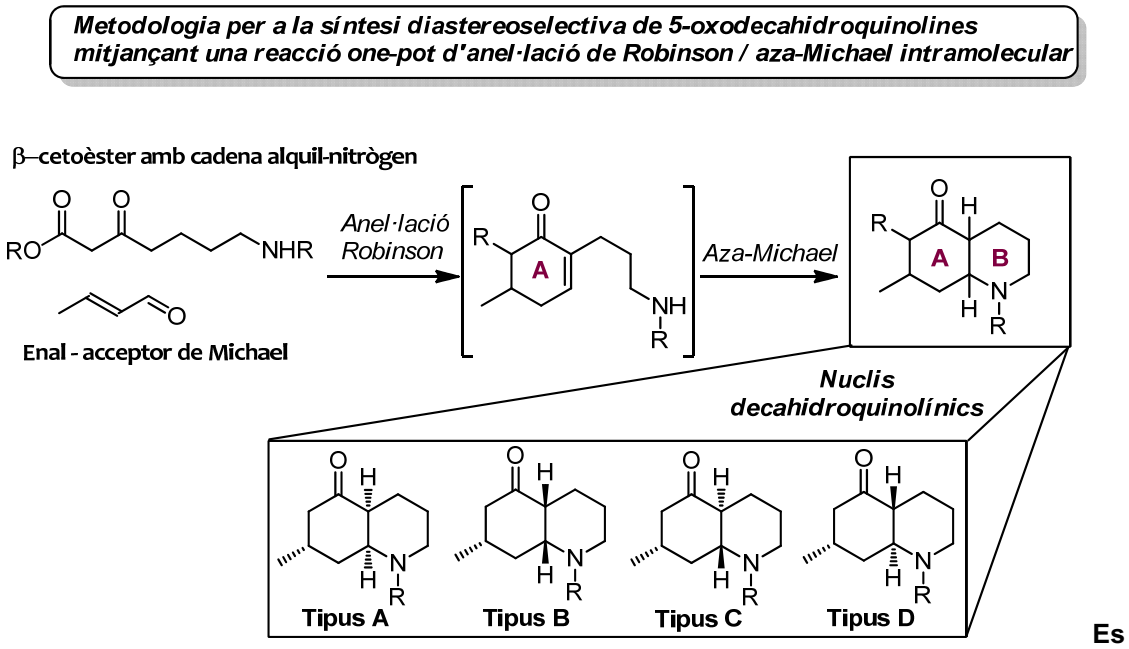
The precipitate of LiOH was removed by simple filtration[133], washed through with $CH_2Cl_2$ (1 L), concentrated *in vacuo* into the filtrate the original flask. The crude mixture was dissolved in MeOH (100 mL) and Pd/C (5% w/w, 270 mg) was added at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of $H_2$ for 16 h. The reaction was purged with argon before AcOH (100 mL) was added to the mixture, followed by $PtO_2 \cdot H_2O$ (5% w/w, 270 mg), at room temperature. The flask was purged with hydrogen as described above and the reaction was stirred for 24 h at rt. After purging the mixture with argon, it was diluted with $CH_2Cl_2$ (≈ 20 mL) and the heterogenous catalysts (Pd and $PtO_2 \cdot H_2O$) were removed by filtration through a pad of celite and the cake was washed through with $CH_2Cl_2$. The solvents were concentrated *in vacuo* to give a brown oil. This crude material was dissolved in a 1:1 mixture of THF/$H_2O$ (430 mL), $NaHCO_3$ (22.7 g, 270 mmol) was added and the mixture cooled to 0 ºC. Methyl chloroformate (5.21 mL, 67.5 mmol) was added dropwise and the mixture allowed to warm rt. After 24 h the THF was evaporated and the mixture was diluted with $CH_2Cl_2$ (≈ 100 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification by chromatography (2.5→5→10→25% EtOAc/hexane) gave **79** as colorless oil, followed by **78** (1.90 g, 30% from **4**).[134] To a stirred solution of carbamate **78** (1.90 g, 4.1 mmol) in THF (350 mL) was added $LiAlH_4$ (1.6 g, 41 mmol) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by the careful addition of water (1.6 mL), 15% aq. NaOH (1.6 mL) and a second portion of water (4.8 mL). The mixture was then diluted with $CH_2Cl_2$ before it was filtered through a pad of celite, and washed through with $CH_2Cl_2$. The filtrate was concentrated *in vacuo* and the product was purified by column chromatography (2.5→5% MeOH/$CH_2Cl_2$ followed by 1:2:0.1 MeOH/$CH_2Cl_2$/concd $NH_4OH$) to give **cermizine B** (960 mg, 88%) as a colorless oil.

[133] The mixture was filtered through a short pad (0.5 cm) of silica. This served to not only remove the precipitated LiOH but also retain the unreacted excess phosphonate **49**).

[134] The specific rotation value of this sample: $[\alpha]_D$ -19.0 (*c* 1, $CHCl_3$) agrees with the sample of **78** synthesized from enantiopure **21.**

**Annex I (Resum en català)**

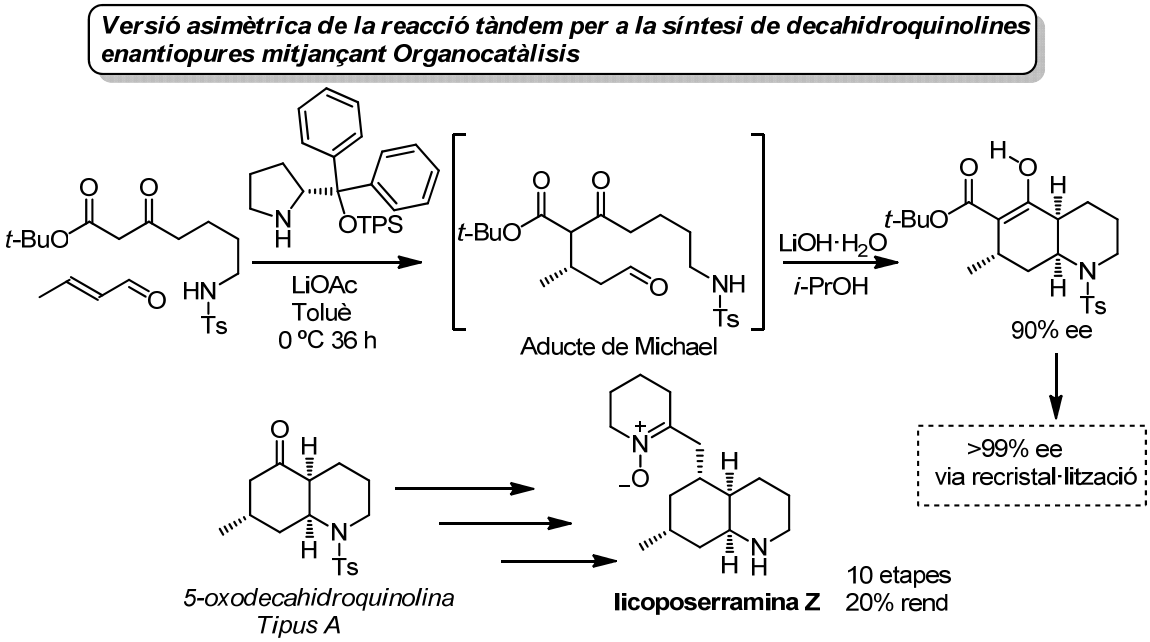
**1)** En primer lloc s'ha desenvolupat una metodologia general per a la síntesi diastereoselectiva de 5-oxodecahidroquinolines mitjançant una reacció *one-pot* d'anel·lació de Robinson / reacció aza-Michael intramolecular, que permet obtenir el nucli de decahidroquinolina en un sol pas des d'un β-cetoèster aquiral i acíclic. Aquesta metodologia, no només permet la formació de *cis*-decahidroquinolines (tipus A i B), sinó que també dóna accés als corresponents isòmers *trans*-decahidroquinolínics (tipus C i D) (veure Esquema 1).




**Es**

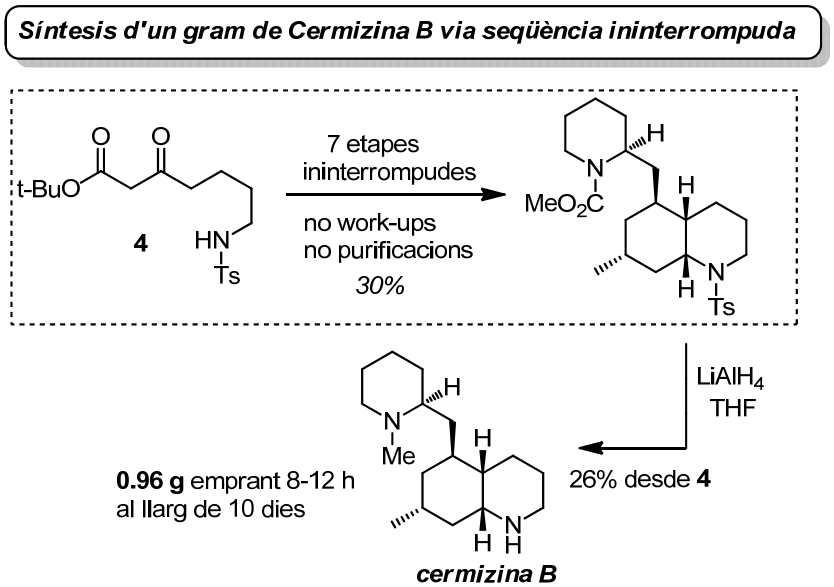
**quema 1.** Reacció tàndem per a la síntesi diastereoselectiva de 5-oxodecahidroquinolines.

**2)** S'ha dissenyat una versió asimètrica de la metodologia desenvolupada per així tenir accés als diferents nuclis decahidroquinolínics enantiopurs per mitjà de organocatàlisis. El mètode ha estat optimitzat després de realitzar estudis de dissolvents, temperatures i catalitzadors. Aquest building block ha estat aplicat a la síntesis total de l'alcaloide licoposerramina Z, el qual s'ha sintetitzat de forma ràpida i eficient (10 etapes, 20% rendiment global) (veure Esquema 2).




**Esquema 2.** Síntesis de decahidroquinolines via organocatàlisis. Síntesis total de licoposerramina Z.

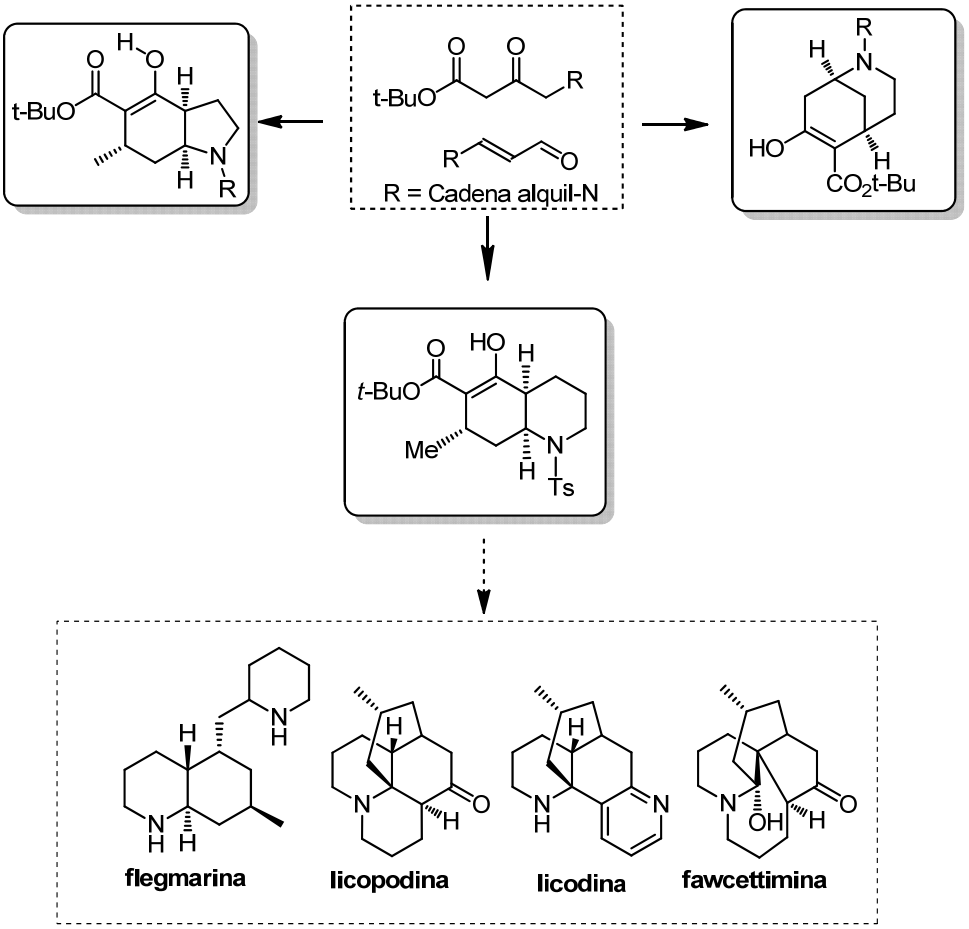
**3)** L'aplicació de l'estratègia coneguda com "*pot economy*" a una síntesis formada per una sèrie de reaccions tàndem pot ser una solució en quant eficiència dels processos i economització de recursos i temps. S'ha realitzat la primera síntesi de l'alcaloide cermizina B de manera eficient i obtenint un gram de producte natural emprant un total de 8 hores treballades en el transcurs de 10 dies naturals.




**Esquema 3.** Síntesis de cermizina B emprant l'estratègia *pot economy* i reaccions tàndem.

**4)** La metodologia descrita no només és aplicable als nuclis decahidroquinolínics conduents a la síntesi d'alcaloides flegmarina, sinó que també pot conduir als altres alcaloides de la familia Lycopodium, completant així una síntesi biomimètica de tots aquests compostos de forma anàloga de com ho fa la natura.

A més, la metodologia es pot extrapol·lar a altres tipus de nuclis (morfans o octahidroindols) emprant petites variacions en els materials de partida (així com variacions de número de carbonis en els materials de partida, o l' instal·lació del nitrògen en el donador o acceptor de Michael) (veure Esquema 5.4).




**Esquema 4.** Potencialitat de la metodologia per a la síntesis de tots els alcaloides Lycopodium i extrapol·lació a la síntesi *one-pot* d'altres heterocicles nitrogenats.

**Annex II (Publications)**

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# *cis*-Decahydroquinolines via Asymmetric Organocatalysis: Application to the Total Synthesis of Lycoposerramine Z

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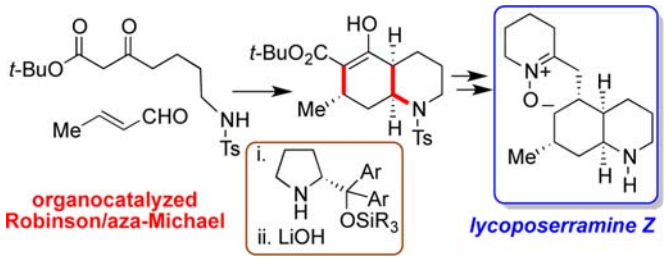
**ABSTRACT**




**A concise synthesis of the *Lycopodium* alkaloid lycoposerramine Z is reported. Key to the strategy is a one-pot organocatalyzed Michael reaction followed by a domino Robinson annulation/intramolecular aza-Michael reaction promoted by LiOH, leading to enantiopure *cis*-decahydroquinolines.**

Lycoposerramine Z (**1**), isolated by Takayama in 2006,[1] belongs to a small class of phlegmarine-type *Lycopodium* alkaloids (Figure 1) that serve as biogenetic intermediates between pelletierine and all other alkaloids of this complex family with around 250 congeners.[2] Interestingly, **1** incorporates an unusual nitrone moiety,[3] which has been postulated to act as a radical trap, halting destructive cascades initiated by free radicals, and hence has potential application in neurodegenerative diseases.[4] In 2009, starting from the chiral pool, Takayama's group completed the first total synthesis of **1**,[5] which remains to date the only synthesis of a phlegmarine alkaloid with a *cis*-ring fused decahydroquinoline unit.[6]

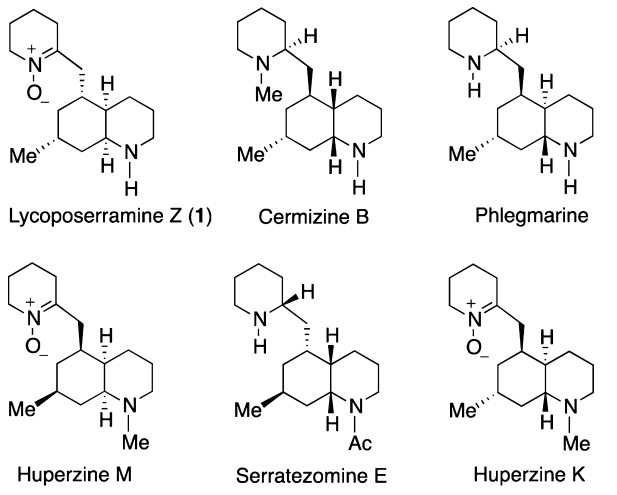


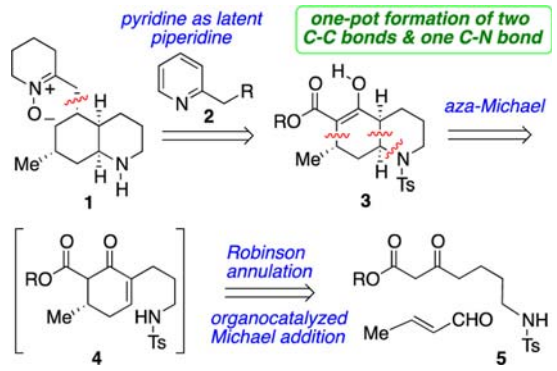

**Figure 1.** Phlegmarine-type *Lycopodium* alkaloids.

We herein report a concise, enantioselective synthesis of lycoposerramine Z (**1**). The cornerstone of our synthetic

(1) Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223–229.
(2) (a) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772. (b) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729.
(3) The nitrone group was later found in related compounds: Gao, W.; Li, Y.; Jiang, S.; Zhu, D. *Helv. Chim. Acta* **2008**, *91*, 1031–1035.
(4) Sun, Y.; Yu, P.; Zhang, G.; Wang, L.; Zhong, H.; Zhai, Z.; Wang, L.; Wang, Y. *J. Neurosci. Res.* **2012**, *90*, 1667–1669.
(5) Tanaka, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2009**, *74*, 8675–8680.
(6) For the synthesis of related phlegmarines embodying the most usual trans-ring fusion in the decahydroquinoline ring, see: (a) Leniewski, A.; Szychowski, J.; MacLean, D. B. *Can. J. Chem.* **1981**, *59*, 2479–2490. (b) Comins, D. L.; Libby, A. H.; Al-awar, R.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184–2185. (c) Wolfe, B. H.; Libby, A. H.; Al-awar, R.; Foti, C. J.; Comins, D. L. *J. Org. Chem.* **2010**, *75*, 8564–8570. (d) Reference 5.

10.1021/ol303257y 
**Published on Web 12/27/2012**

**Scheme 1.** Retrosynthesis of Lycoposerramine Z

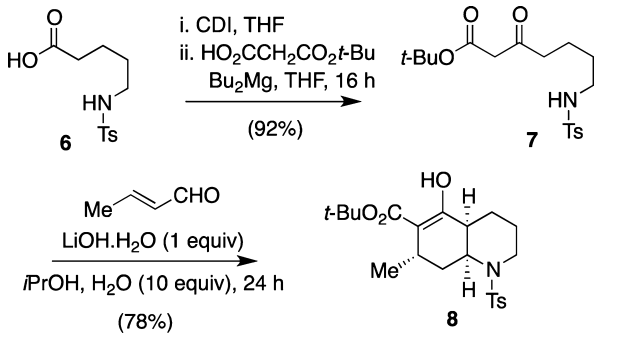



approach is a rapid asymmetric assembly of the azabicyclic core by a novel organocatalyzed diastereo- and enantioselective one-pot tandem synthesis of decahydroquinolines. In this process two C–C bonds and one C–N bond (Scheme 1) and three stereogenic centers are created in a single step.[7,8]

As outlined in Scheme 1, we envisaged that the piperidine appendage could be introduced by the coupling of a methylpyridine **2** with a 5-oxodecahydroquinoline. The $\beta$-keto ester **3** precursor of the latter would be formed via a Robinson annulation of the simple acyclic keto ester **5** through an initial organocatalyzed Michael addition, followed by an in situ intramolecular aza-Michael reaction of the generated cyclohexenone **4**. We speculated that the retention of the ester group in **3** would be essential for the success of our strategy, helping to stabilize the $\beta$-amino ketone moiety and prevent side reactions.[9,10]

The synthesis of **1** began with the *N*-tosylation of the commercially available 5-aminopentanoic acid, and the resulting acid **6** was subjected to a homologation with mono-*tert*-butylmalonate under Masamune-type conditions[11] to give **7** (77% over two steps, Scheme 2). The reaction conditions for the key Robinson annulation/intramolecular aza-Michael biscyclization process to achieve decahydroquinoline **8** from **7** and crotonaldehyde were first examined in a nonasymmetric version. After considerable experimention[12] we found that the decahydroquinoline ring could be generated in a straighforward one-pot reaction using $LiOH \cdot H_2O$ (1 equiv) in *i*PrOH[13] in the presence of water (10 equiv).[14] We were delighted to find that under these conditions decahydroquinoline *rac*-**8** was delivered in only one step and as a single diastereoisomer. As predicted, the retention of the ester group stabilized the compound by forming the enolic tautomer, which effectively acts as a locking group, preventing the ring opening by a retro aza-Michael reaction in the basic reaction medium or in the purification step (silica gel chromatography).

**Scheme 2.** Synthesis of *rac*-**8**




To carry out the reaction in asymmetric form, the Hayashi catalyst[15] was chosen to promote the initial organocatalyzed Michael addition, after which the tandem cyclization conditions (LiOH) were applied.[16,17] A screening of solvents indicated that toluene was the optimal choice. Several other catalysts,[18] mainly diaryl-prolinol silyl ethers,[19] were then screened, and the slight superiority of triphenylsilyl derivative **9**[20] led to its selection (Table 1, entry 1).

The reaction was further refined by lowering the temperature (entries 2 and 3) and the use of additives was

(7) For organocatalytic cascade reactions in total synthesis, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178. (b) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188. (c) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278–1293.

(8) For recent enantioselective synthesis of *cis*-decahydroquinolines, see: (a) Ito, T.; Overman, L. E.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 3272–3273. (b) Kagugawa, K.; Nemoto, T.; Kohno, Y.; Yamada, Y. *Synthesis* **2011**, 2540–2548. (c) Amat, M.; Navio, L.; Llor, N.; Molins, E.; Bosch, J. *Org. Lett.* **2012**, *14*, 210–213. (d) Gärtner, M.; Qu, J.; Helmchen, G. *J. Org. Chem.* **2012**, *77*, 1186–1190.

(9) We have observed that direct azacyclization upon an enone to give 5-oxodecahydroquinolines is troublesome since the cyclized compound is in equilibrium with the ring-opened $\alpha,\beta$-unsaturated ketone: Borregan, M. Ph.D. Thesis, University of Barcelona, Spain, 2009.

(10) No intramolecular aza-Michael process leading to 5-oxodecahydroquinolines has been described so far. For interesting results related to this field, see: (a) Brosius, A. D.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 440–441. (b) Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem.* **2004**, *69*, 2268–2271.

(11) (a) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72–73. (b) Hodgson, D. M.; Labande, A. L.; Pierard, Y. T. M.; Castro, M. A. E. *J. Org. Chem.* **2003**, *68*, 6153–6159.

(12) For instance, *t*-BuOK in *t*-BuOH was not sufficiently effective, despite its frequent use in Robinson reactions: Chong, B.; Ji, Y.; Oh, S.; Yang, J.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323–9325.

(13) These reaction conditions were adapted from those used by Baran (LiOH (0.1 equiv), *i*PrOH, rt, 24 h) in the synthesis of cryptone: Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738–4744. It should be noted that these previously published conditions were unsuccessful when applied to **3** and crotonaldehyde.

(14) Water was necessary to drive the aza-Michael reaction to completion. In its absence significant amounts of the ring-opened Robinson annulation product were obtained (20–30%).

(15) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

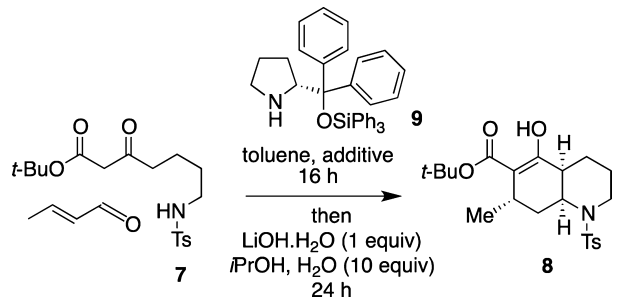
(16) The classical procedure to achieve cyclohexenones developed by Jorgensen using an initial organocatalyzed Michael addition followed by treatment with TsOH was unsuccessful when starting from **3**: Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928–4930.

(17) For an organocatalytic initial Michael reaction and Robinson annulation that retains the ester group, see: Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479.

(18) The results of the initial screening of solvents and catalysts are summarized in the Supporting Information.

(19) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264.

**Table 1.** Screening Conditions for the Organocatalyzed Robinson Annulation/aza-Michael Reaction[a]



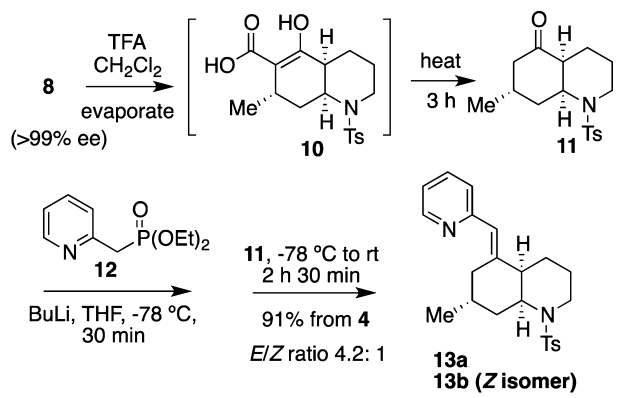

| entry | additive (equiv) | temp (°C) | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | none | rt | 57 | 80 |
| 2 | none | 0 | 57 | 82 |
| 3 | none | −20 | 49 | 82 |
| 4 | $H_2O$ (10) | 0 | 69 | 84 |
| 5 | LiOAc (0.5) | 0 | 72 | 85 |
| 6 | KOAc (0.5) | 0 | 58 | 83 |
| 7 | BzOH (0.5) | 0 | 43 | 80 |
| 8 | $H_2O$ (10)/LiOAc (0.5) | 0 | 63 | 80 |
| 9 | LiOAc (1) | 0 | 66 | 82 |

[a] 20% catalyst loading of **5** was used in a 0.1 M solution of **3**. Toluene was evaporated before proceeding with the tandem biscyclization.

investigated (entries 4−10). The addition of LiOAc[21] (entry 5) was essential for obtaining a good conversion yield (72% for three bond-forming reactions) and enantiomeric ratio (>92:8). It is worth mentioning that the combination of LiOAc and another good additive, water (entry 4), were not synergistic, giving results (entry 8) inferior to those with their individual use.

In general, in comparison with bulkier groups, the small size of the methyl group sets a limit to the maximum enantioselectivity (in our case 84−85% ee) in organocatalyzed Michael additions.[16] However, we were able to access (+)-**8** in enantiopure form by recrystallization of **8** from MeOH,[22] which provided the product in >99% ee (first crop, 65% recovery).

**Scheme 3.** Coupling of the Methylpyridine Fragment




With enantiopure decahydroquinoline (+)-**8** in hand, we set about converting it into the natural product lycoposerramine Z. Removal of the *tert*-butyl ester locking group with TFA gave ketoacid **10**, which upon azeotropical removal of TFA with toluene by heating underwent decarboxylation to ketone **11** (Scheme 3). The material was used immediately in the next step without any purification[23] and added directly to a solution of the lithium anion of phosphonate **12**[24] to give vinylpyridine derivatives **13** in excellent yield (91%). A mixture of *Z*/*E* isomers (~1:4.2) was observed,[25,26] which were separated by chromatography. However, this turned out to be inconsequential since hydrogenation of the mixture or each isolated isomer gave the same all-*cis*-product **14** in which the hydrogen was delivered from the top face (see Scheme 4, which depicts the major isomer **13a**). Analysis of the $^1$H and $^{13}$C NMR spectra of both *Z*/*E* diastereomers of the starting material (**13a** and **13b**) allowed us to establish that the preferred conformation of these compounds accommodates axial positioning of the methyl group, which avoids the allylic 1,3-strain[27] both for the exocyclic double bond (with the C(4)−C(4a) bond) and the *N*-tosyl group (with the C(8)−C(8a) bond).[28] This preferred conformation is involved in steric interactions that influence the diastereoselectivity of the hydrogenation process. The reduction led exclusively to decahydroquinoline **14**, in which the substituents at C(5) and C(7) are axially located according to NMR data. Thus, the crucial role of the axial methyl group in the process was clearly established, as it sterically impedes hydrogenation from the bottom face.

With all four introduced stereogenic centers now in place, the tosyl group was replaced by a Teoc group prior to the installation of the sensitive nitrone moiety.[29,30] Thus, the tosyl group was removed (HBr, phenol) to give **15**, which was converted into the Teoc carbamate **16** (Scheme 5). Reduction of the pyridine ring with $PtO_2$/AcOH gave the piperidine **17** as an inconsequential mixture of epimers

(20) For the first reported use of this catalyst, see: Wang, Y.; Li, P.; Liang, X.; Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383–1389. For its preparation and subsequent application, see: Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci* **2011**, *2*, 353–357.

(21) For an interesting study on the effect of LiOAc in organocatalyzed Michael reactions, see: Duce, S.; Mateo, A.; Alonso, I.; García Ruano, J. L.; Cid, M. B. *Chem. Commun.* **2012**, *48*, 5184–5186.

(22) The use of EtOH gave a certain amount of transesterification products. For related phenomena, see: Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713–1718.

(23) Fortunately, under the reaction conditions the product did not undergo a retro aza-Michael reaction. However, it should be noted that upon prolonged manipulation (e.g., silica gel chromatography, etc.) the ring-opened product began to be observed.

(24) Gan, X.; Binyamin, I.; Rapko, B. M.; Fox, J.; Duesler, E. N.; Paine, R. T. *Inorg. Chem.* **2004**, *43*, 2443–2448.

(25) Using the lithium anion of 2-(trimethylsilyl)methylpyridine (ref 6a) in a Peterson reaction, compounds **13** were isolated in the same ratio but with a slightly lower yield (80%).

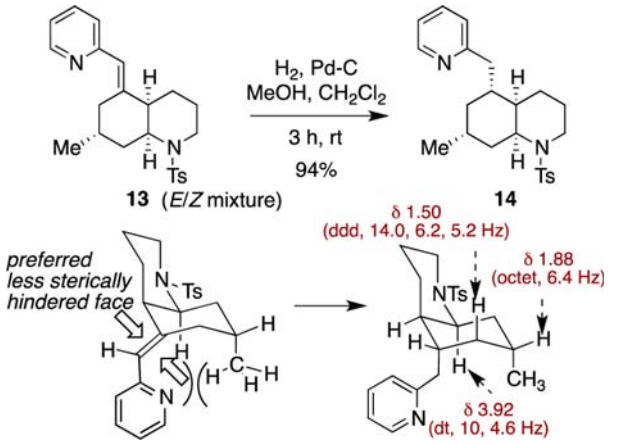
(26) Interestingly, this diastereoselectivity is the reverse of that observed in the related 2,5-dioxodecahydroquinoline system: see ref 6a.

(27) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1873.

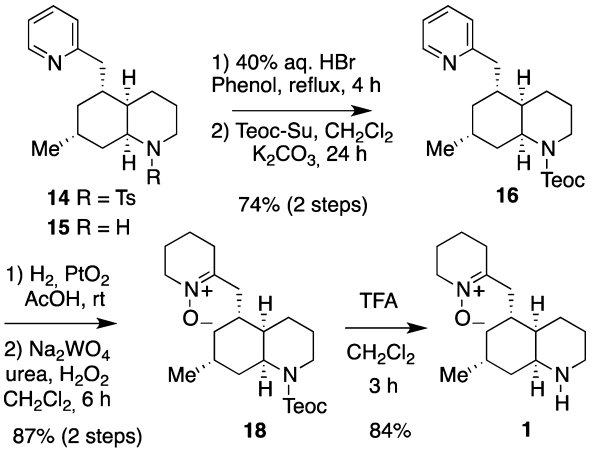
(28) Booth, H.; Bostock, A. H. *J. Chem. Soc., Perkin Trans 2* **1972**, 615–621.

(29) This protecting group was used by Takayama in his synthesis of **1**, where it was shown that it could be removed in the presence of the sensitive nitrone moiety.

**Scheme 4.** Diasteroselective Reduction of Alkene **13**




**Scheme 5.** Completion of the synthesis of lycoposerramine Z



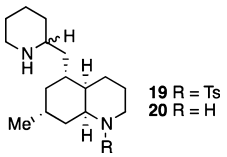

(not shown). This was oxidized with $Na_2WO_4$/urea peroxide[31] to give nitrone **18**, which was identical to the final intermediate in Takayama's synthesis.[5] Although the deprotection of **18** to lycoposerramine Z has already been reported, for the sake of a complete enantioselective total synthesis of **1**, the Teoc group was removed using TFA.[32,33] The resulting (+)-lycoposerramine Z showed identical NMR spectroscopic data to those reported for the natural product,[1] as well as the same specific rotation value as synthetic **1**.[5]

In summary, we have described a short synthesis of lycoposerramine Z, which was completed in only 10 steps (20% overall yield)[34] from commercially available 5-aminopentanoic acid. Key to the success of the synthesis was a one-pot tandem organocatalyzed formation of decahydroquinolines, which allowed a rapid enantio- and diastereoselective assembly of the alkaloid core structure. We believe that the methodology presented here not only has the potential to provide access to numerous other *Lycopodium* alkaloids but also should prove applicable in the asymmetric synthesis of other important nitrogen-containing heterocyclic structures. Research in this direction is now underway.

**Acknowledgment.** Support of this research was provided by the Spanish Ministry of Economy and Competitiveness (Project CTQ2010-14846/BQU).

**Supporting Information Available.** Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(30) Attempts to avoid the exchange of the protecting groups via a biomimetic chemoselective oxidation of diamine **20** were unsuccessful. Diamine **20** was prepared via a one-pot hydrogenation of the vinylpyridine moiety of **13** to give piperidine **19**, from which the tosyl group was removed by treatment with $LiAlH_4$ (88% over two steps). Unfortunately, we were unable to chemoselectively oxidize the latter with $Na_2MoO_4$[31] (0.5−1 equiv) to directly deliver lycoposerramine Z (**1**).




(31) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett.* **1995**, *36*, 3561–3562. See also: Ohtake, H.; Imada, Y.; Murahashi, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2737–2754.

(32) (a) For deprotection of *N*-Teoc carbamates with TFA, see: Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc. Chem. Comm* **1978**, 358–350. (b) For the stability of a nitrone moiety to TFA, see: Medina, S. I.; Wu, J.; Bode, J. W. *Org. Biomol. Chem.* **2010**, *8*, 3405–3417.

(33) This protocol greatly simplified the isolation procedure, avoiding the use of TASF or TBAF for the *N*-Teoc cleavage in **18**.

(34) This compares favorably with the 24 steps reported in the first synthesis of lycoposerramine Z (ref 5).

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

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**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]

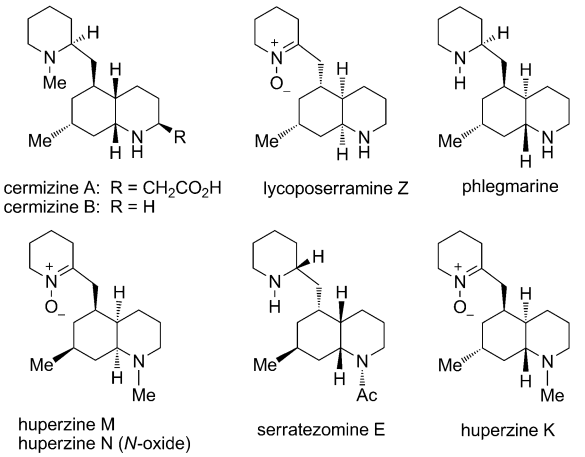


Figure 1. Phlegmarine alkaloids with a *cis*-decahydroquinoline core and two examples bearing a *trans*-decahydroquinoline.

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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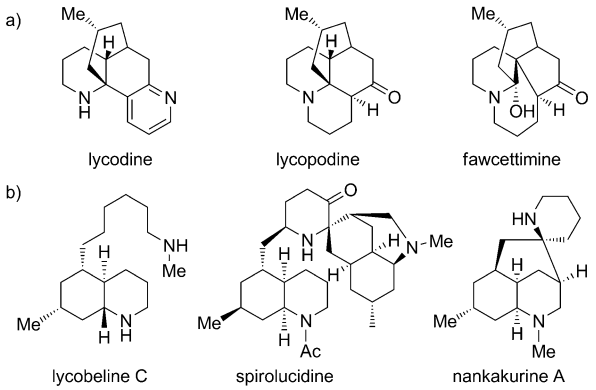
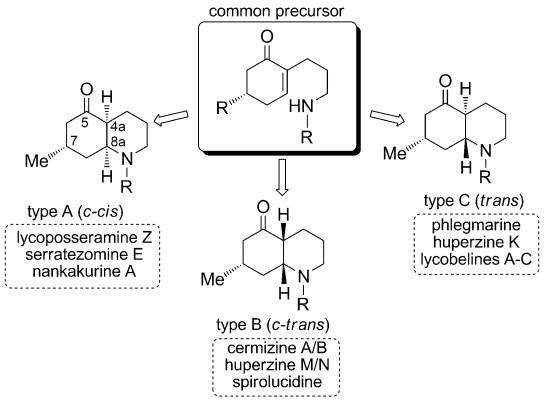



Figure 2. a) The main *Lycopodium* alkaloid groups biogenetically derived from *trans* phlegmarines. b) *Lycopodium* alkaloids derived from phlegmarines with retention of the decahydroquinoline ring system.

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

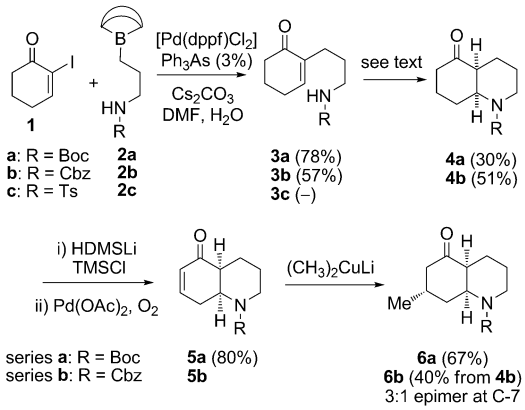



Scheme 1. Postulated unified approach to the various 5-oxodecahydroquinoline nuclei from a common intermediate through an aza-Michael reaction.

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.

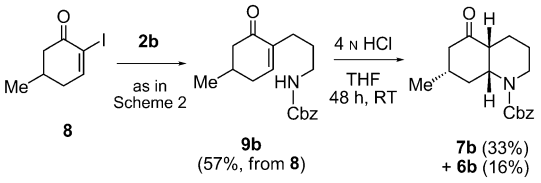
A variety of conditions were also investigated for the analogous Cbz-protected derivative **3b** with equally disappointing results. Although no cyclized product was observed under several basic or acidic conditions,[21] exposure of **3b** to a 4 N HCl solution in THF at room temperature for 48 h gave 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

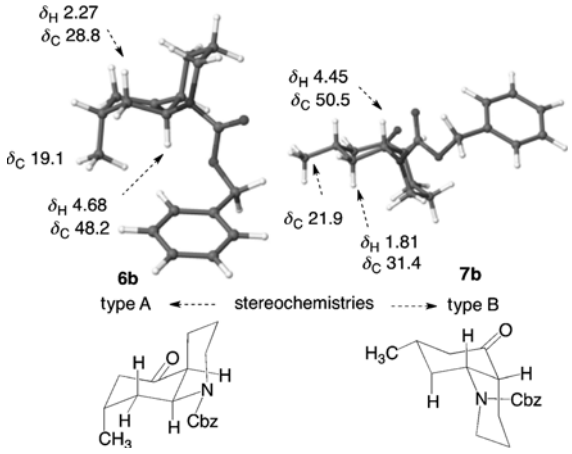



Figure 3. Conformational preference of decahydroquinolines **6b** and **7b** determined on the basis of NMR spectroscopic data, showing type A and type B stereochemistries.

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.

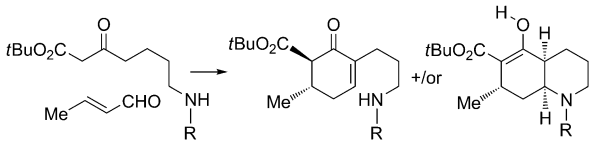
**Revised synthetic approach: access to type A 5-oxodecahydroquinolines**: We believed it might be possible to prepare the required substrate for cyclization directly through a Robinson annulation procedure from a suitable keto ester bearing a nitrogen-protected tether (i.e., **10**). We also hoped that 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]

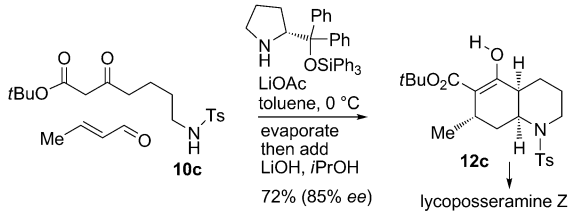



R = Boc **10a** **11a** **12a**
R = Cbz **10b** **11b** **12b**
R = Ts **10c** **11c** **12c**
R = Ns **10d** **11d** **12d**

| 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 | $LiOH{\cdot}H_2O$ (0.1) | *i*PrOH | n.d.[g] |
| 6 | Ts | $LiOH{\cdot}H_2O$ (2) | *i*PrOH | **11c** (5), **12c** (57) |
| 7 | Boc | $LiOH{\cdot}H_2O$ (2) | *i*PrOH | **11a** (18) |
| 8 | Cbz | $LiOH{\cdot}H_2O$ (2) | *i*PrOH | **11b** (21) |
| 9 | Ns | $LiOH{\cdot}H_2O$ (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 | $LiOH{\cdot}H_2O$ (1) | *i*PrOH | **11c** (8), **12c** (60) |
| 16 | Ts | $LiOH{\cdot}H_2O$ (1)[d] | *i*PrOH | **11c** (6), **12c** (46) |
| 17 | Ts | $LiOH{\cdot}H_2O$ (1)[e] | *i*PrOH | **12c** (78) |
| 18 | Ns | $LiOH{\cdot}H_2O$ (1)[e] | *i*PrOH | **12d** (47) |
| 19[f] | Ts | $LiOH{\cdot}H_2O$ (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

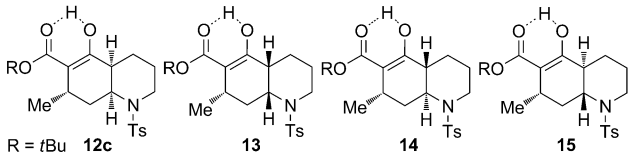
  

when the cyclohexenone moiety underwent an intramolecular aza-Michael process, which led predominantly to type B compounds.

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]

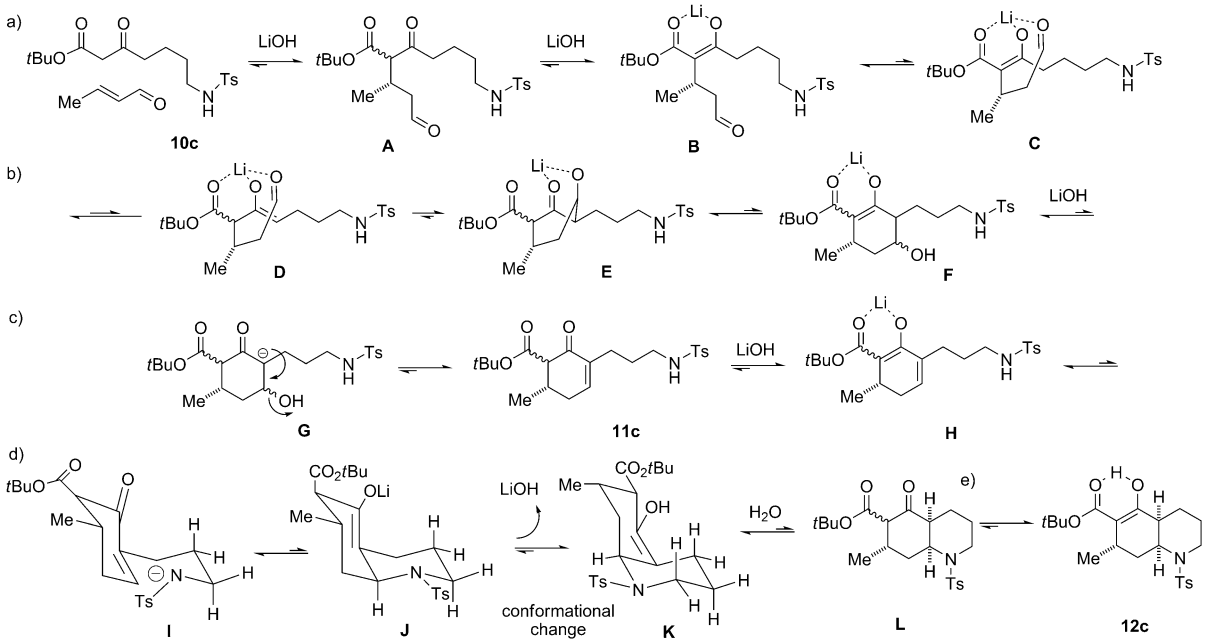



| | **12c** | | **13** | | **14** | | **15** | |
|---|---|---|---|---|---|---|---|---|
| | keto | enol | keto | enol | keto | enol | keto | enol |
| *E* (gas phase) | 12.9 | 0.0 | 12.1 | 1.2 | 9.3 | 2.3 | 6.8 | 4.9 |
| *G* (gas phase) | 11.2 | 0.0 | 10.2 | 1.0 | 7.3 | 2.9 | 5.5 | 4.4 |
| *E* (sp solv) | 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).

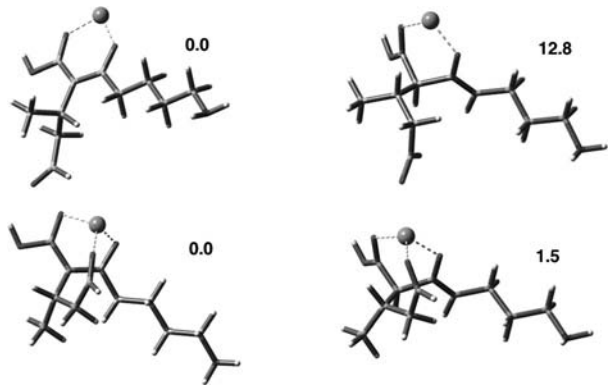



Figure 4. Optimized structures and relative free energies (kcal mol$^{-1}$) including solvent effects (*i*PrOH) for the two possible enolates, with two or three carbonyl groups coordinated to $Li^+$.

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.

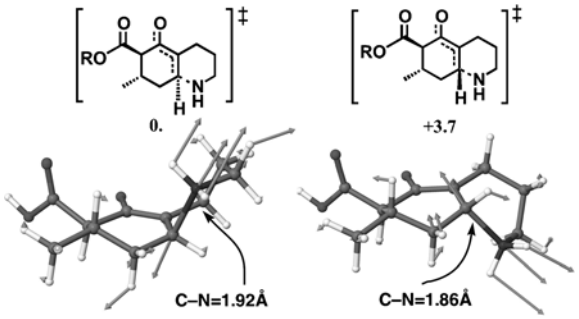



Figure 5. Molecular structures for models (R = H) of the transition states of the two possible pathways of the cyclization step in which the bicyclic system is formed, generating the C4a stereocenter. Relative free energy in kcal mol$^{-1}$.

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

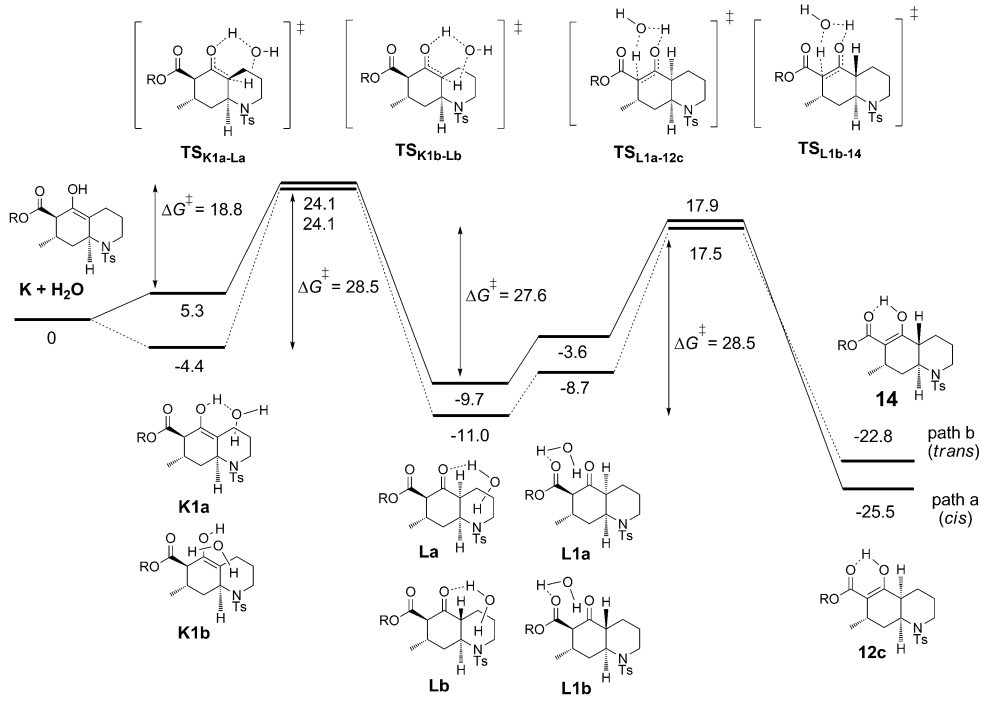



Figure 6. Reaction free energy profile for the water-assisted proton transfer steps from **K** to **12c**, for R = H. All values in kcal mol$^{-1}$.

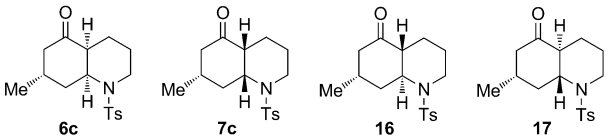
structures are collected in Figure 5, together with the relative free energy, and with arrows on each atom contributing to the unique imaginary vibrational normal mode. Note that major contributions arise from the $NH_2$ and C atom involved in the C–N bond-forming process. The most stable transition 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**.



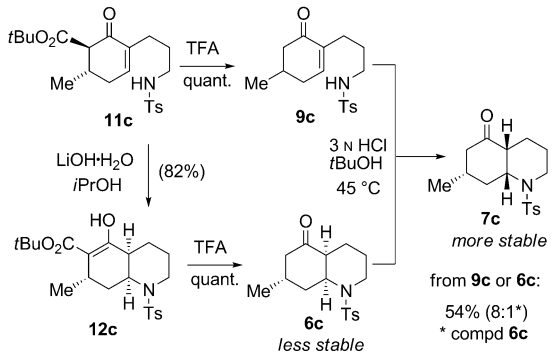

| | **6c** | | **7c** | | **16** | | **17** | |
|---|---|---|---|---|---|---|---|---|
| | keto | enol | keto | enol | keto | enol | keto | enol |
| *E* (gas phase) | 0.8 | 9.9 | 0.0 | 9.5 | 3.6 | 14.4 | 5.6 | 13.5 |
| *G* (gas phase) | 0.5 | 9.2 | 0.0 | 8.9 | 2.9 | 13.4 | 5.2 | 12.8 |
| *E* (sp solv) | 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.

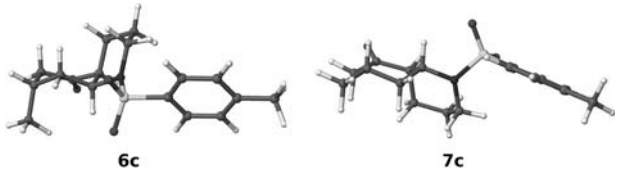


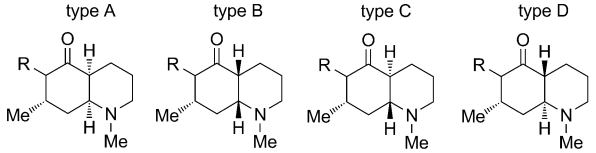

Figure 7. DFT optimized structures for *cis*-decahydroquinolines **6c** (left) and **7c** (right).

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 Δ*E* and free energies Δ*G* 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).



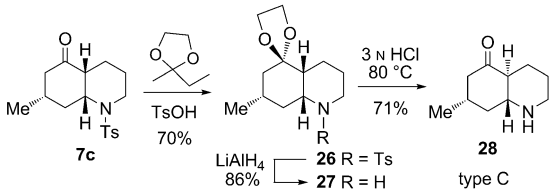

**18** R = $CO_2t$Bu, **22** R = H
**19** R = $CO_2t$Bu, **23** R = H
**20** R = $CO_2t$Bu, **24** R = H
**21** R = $CO_2t$Bu, **25** R = H

| | **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-

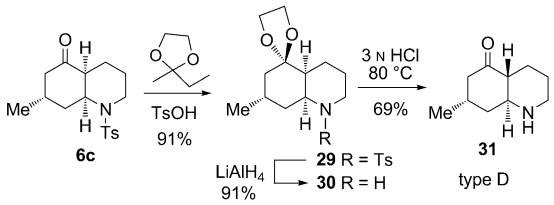



Scheme 7. Synthesis of a decahydroquinoline with phlegmarine type C stereochemistry.

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

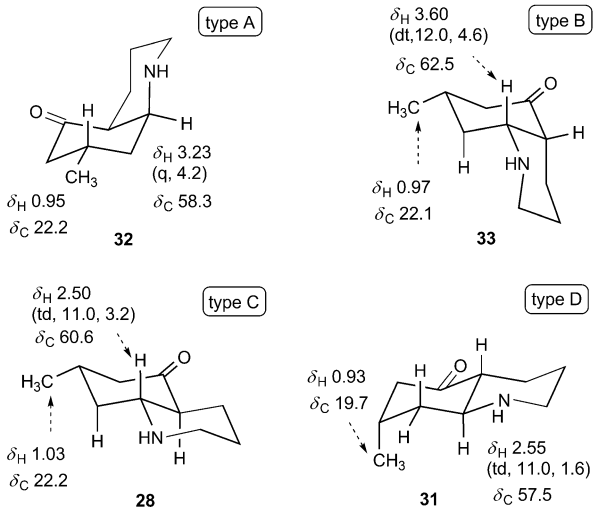
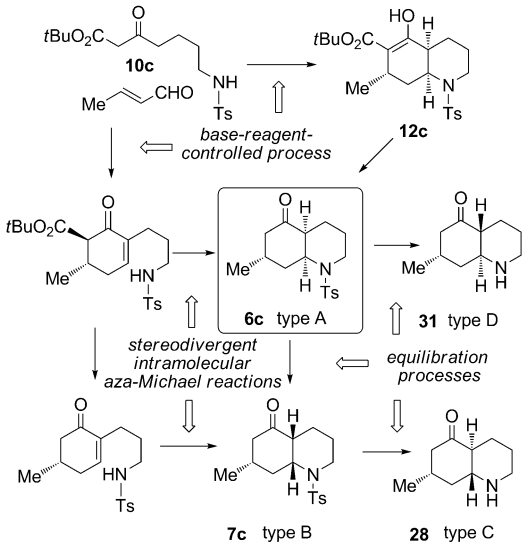



Figure 8. Conformational preference of N-unsubstituted decahydroquinolines determined on the basis of NMR spectroscopic data, showing type A–D stereochemistries.

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): $\delta$=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): $\delta$=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): $\delta$=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): $\delta$=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): $\delta$=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): $\delta$=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.

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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

  

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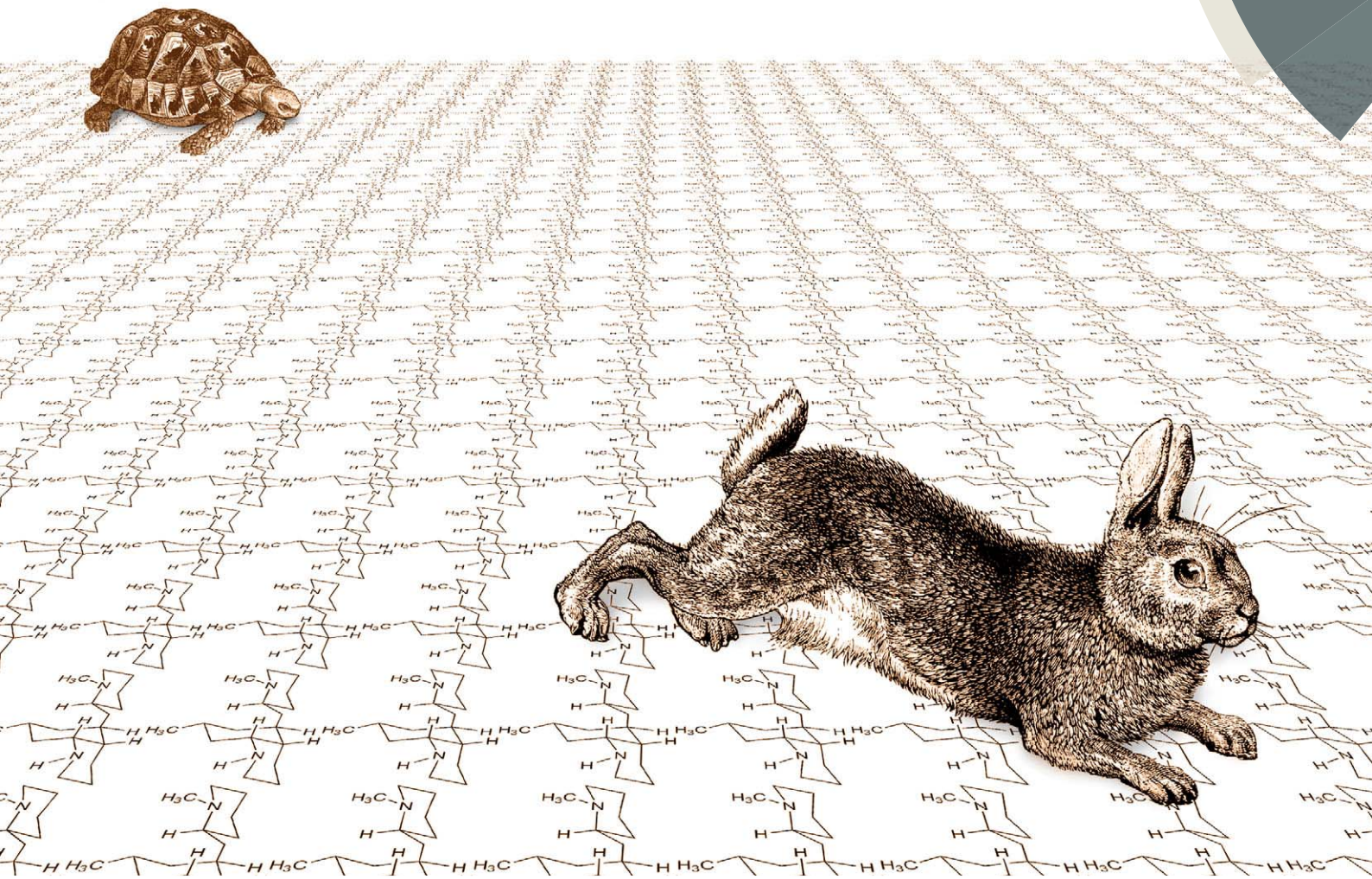

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A gram-scale route to phlegmarine alkaloids: rapid total synthesis of (–)-cermizine B

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# A gram-scale route to phlegmarine alkaloids: rapid total synthesis of (−)-cermizine B†

Ben Bradshaw,* Carlos Luque-Corredera and Josep Bonjoch*

**The synthesis of the *Lycopodium* alkaloid (−)-cermizine B (1), which establishes its absolute configuration, is achieved by combining asymmetric organocatalysis and an uninterrupted eight-step reaction sequence, followed by a final reduction step. This "pot-economy" strategy provides access to the *cis*-phlegmarine stereoparent embedded in 1 for the first time, rapidly and on a gram-scale.**

One of the main impediments to accessing viable quantities of complex natural products in a timely and cost-effective manner is the 'stop-and-go' approach,[1] which requires a purification step after each synthetic operation. This undoubtedly involves the greatest investment of time and materials in any total synthesis endeavour and is a major source of waste generation. An alternative strategy involving a series of tandem reactions[2] in combination with 'pot-economy'[3] offers a potent solution to this problem. By eliminating the need for work-up and product isolation between successive synthetic steps, it becomes possible to complete an entire multi-step sequence in a single pot,[4] a process that approaches Wender's definition of an 'ideal synthesis'.[5]

With this aim in mind, and based on our recent work on asymmetric synthesis of decahydroquinolines using organocatalysis,[6] we decided to apply the aforementioned "one-pot" operational approach in the field of *Lycopodium* alkaloids[7] (Fig. 1). This group of structurally diverse compounds have elicited major interest in recent years for their potential use in the treatment of severe neurodegenerative diseases.[7d,8] A great number of approaches to the main classes of *Lycopodium* alkaloids,[9] namely lycopodine, lycodine, and fawcettimine, have been developed, but there are limited synthetic entries to their biogenetic precursors, the phlegmarine alkaloids. To date, the synthesis of *cis*-phlegmarine alkaloids has been limited to lycoposerramine Z,[6a,10] whereas synthetic efforts towards *trans*-phlegmarines include the pioneering studies of MacLean,[11] the attainment of lycoposerramine X by Takayama[10,12] and the comprehensive phlegmarine synthesis reported by Comins.[13] Considering that all the previous syntheses, apart from our recent work,[6a] have required more than twenty steps, a more efficient entry to the phlegmarine alkaloids would not only be a desirable goal in itself, but could also be used as a platform to access members of the other classes of *Lycopodium* alkaloids.

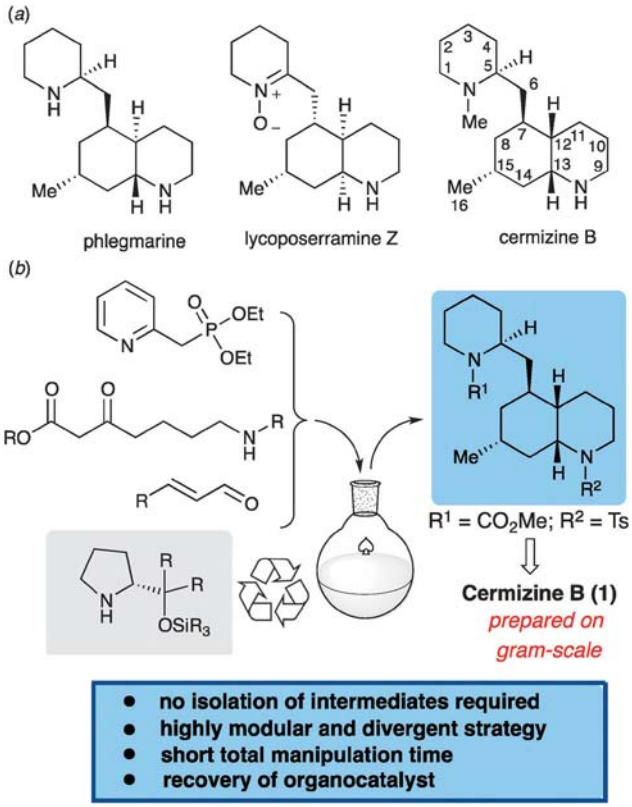


Fig. 1 (a) Structures of phlegmarine alkaloids (the three stereoparents), including the biogenetic numbering. (b) Strategy for synthesis of cermizine B.

We herein report a highly efficient synthesis and the absolute configuration of the *cis* phlegmarane-type alkaloid cermizine B (**1**),[14]

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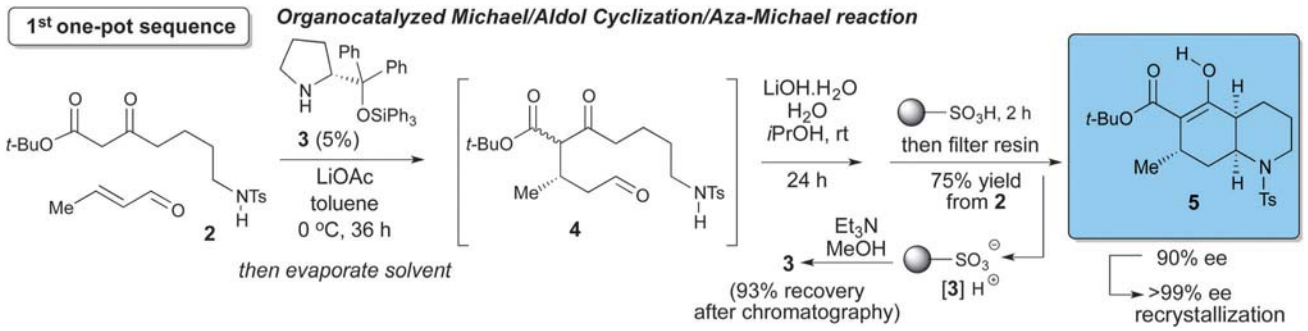



Scheme 1 Optimized synthesis of *cis*-decahydroquinoline **5**.

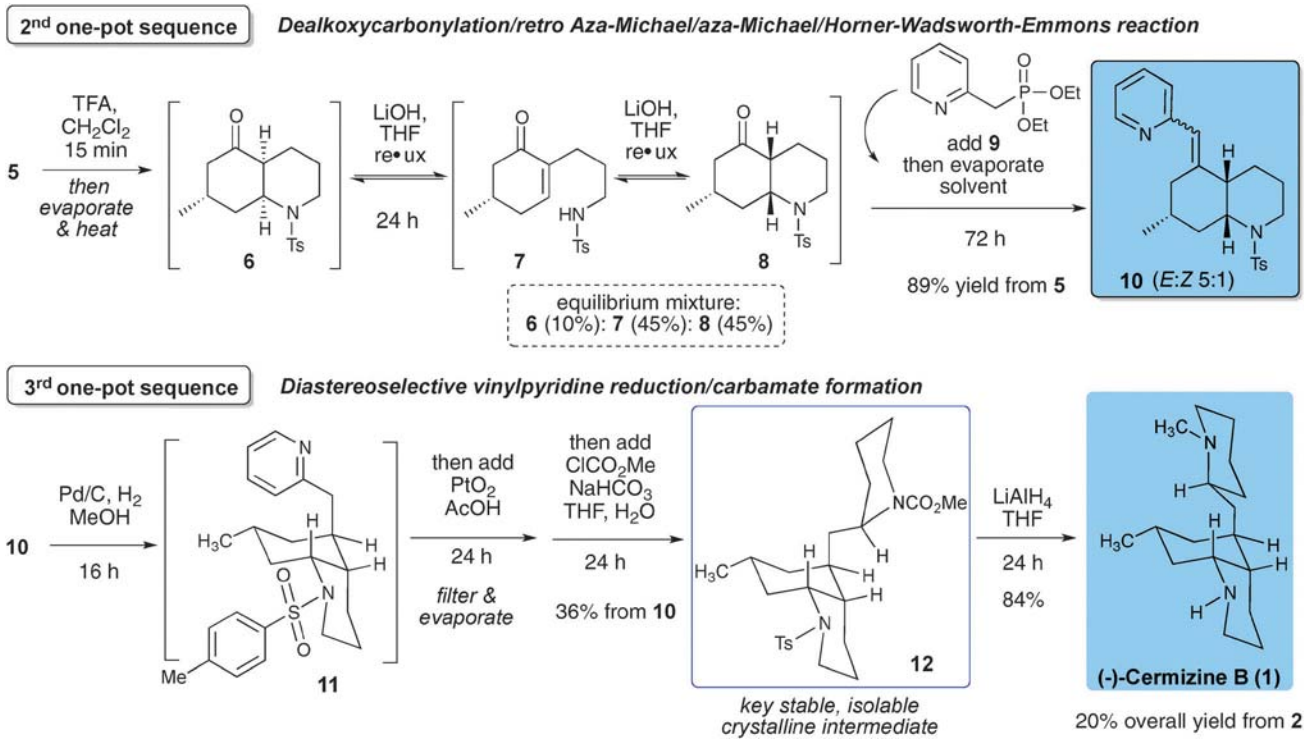
the first of a member of the *cis*-phlegmarine subset with an anti stereochemical relationship between the ring-fusion hydrogens and the prototypical methyl substituent (C-16) in the decahydroquinoline ring.

The overall process was initially developed by dividing the synthesis into three sets of tandem reactions (Scheme 1), which were subsequently fused into a single sequence. The first one-pot operation began with β-keto ester **2**, which underwent an organocatalyzed Michael reaction in the presence of just 5% loading of the modified Hayashi catalyst **3**,[15] improving our preliminary published results.[6a] Removal of the solvent and treatment of **4** with LiOH in the presence of iPrOH and water led to the tandem aldol condensation–intramolecular aza-Michael reaction, which delivered *cis*-decahydroquinoline **5**. With the aim of minimizing waste and preventing downstream accumulation in the eventual uninterrupted sequence, the reaction mixture was treated with a sulfonic acid resin, eliminating the need for any work-up procedure by removing the basic residues and also allowing the capture and recuperation of the organocatalyst in excellent yield. We believe that this solution is a simple alternative to recycling the catalyst *via* immobilization on a solid support. It should be noted that not only did the modified catalyst (triphenylsilyl instead of trimethylsilyl diphenylprolinol ether) improve the enantiomeric excess but its significantly more robust nature also proved essential for its recovery with the acidic resin at the end of the reaction. Decahydroquinoline **5** was isolated in 75% overall yield[16] from keto ester **2** with 90% ee.

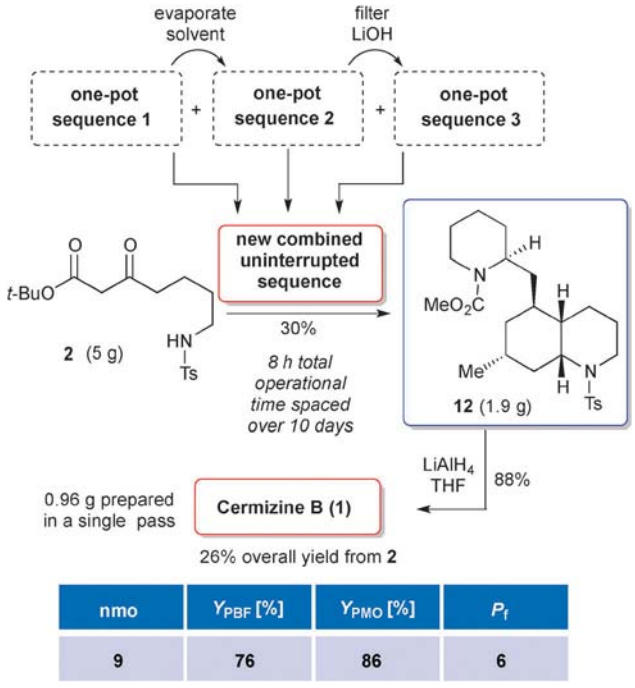
The second one-pot sequence (Scheme 2) commenced with treatment of **5** with TFA, followed by evaporation and heating to effect the complete decarboxylation of the resulting keto acid moiety. Direct addition of LiOH and THF to the reaction pot, followed by refluxing overnight resulted in the retro aza-Michael ring opening of **6** to **7**, and subsequent partial closure to the more stable decahydroquinoline **8**,[6b] with the required stereochemistry present in cermizine B. Although the closure did not go to completion, giving an equilibrium mixture of **6**:**7**:**8** (1:4.5:4.5, respectively), it was found that direct addition of phosphonate **9** led to a chemoselective reaction with **8**, and by means of a shift in the equilibrium, vinylpyridine **10** was formed exclusively as an inconsequential mixture of *Z*/*E* isomers (1:5 ratio). Hydrogenation (see below) of each isomer gave the same result, obviating the need to separate them. Furthermore, we noted that this coupling reaction performed better if carried out under solvent-free conditions, giving **10** in an excellent yield of 89% over the entire sequence from **5**. For the final one-pot sequence, alkene **10** was hydrogenated in the presence of Pd/C in MeOH, which delivered the hydrogen selectively from the bottom face of the molecule in a 5:1 ratio to give **11**. We believe that the facial selectivity was primarily influenced by the tosyl group, which effectively blocked the top face of **10**. Removal of the tosyl group prior to the hydrogenation led to the selective reduction from the top face of the molecule to give the opposite stereochemistry. Notably, this provides the stereochemical arrangement of another phlegmarine alkaloid (huperzine M).[17] Hydrogenation of the pyridine ring was then accomplished by direct addition of $PtO_2$ and AcOH to the reaction mixture containing **11**.[18] Filtration, evaporation and carbamation with methyl chloroformate gave **12** as a stable, readily purified epimeric mixture. Finally, treatment with $LiAlH_4$ converted the carbamate into the required methyl group and smoothly removed the tosyl group to give cermizine B (**1**), which showed NMR spectroscopic data identical to those reported for the natural product (see ESI†). The overall yield of the complete sequence was 20%. The data obtained for **1** $[\alpha]_D$ = −3.1 (*c* 0.7, MeOH) also confirmed that the absolute configuration depicted in Fig. 1 corresponds to that of the natural product (−)-cermizine B {lit[14] $[\alpha]_D$ −2.0 (*c* 0.6, MeOH)}.[19]

After the successful completion of the synthesis *via* a sequence involving 3 one-pot reactions, we sought to eliminate the remaining purification steps until carbamate **12**, which would render the whole process even more efficient (Scheme 3). Thus, after treatment with the resin at the end of the first one-pot sequence, the solvent was removed by evaporation and the resulting material was fed directly into the second set of tandem reactions, and then, after subsequent removal of the LiOH by filtration, into the third set. Reduction of this enantioenriched material, *i.e.* **12** (after a single purification step to remove *epi*-**12**), with $LiAlH_4$ then took place in 88% yield to give 0.96 g of the target cermizine B (**1**) from just 5 g of the starting β-keto ester **2**. By eliminating the aforementioned purification procedures, the overall yield for the new integrated sequence was increased to 26%, and could be completed in only 8 h of operational time, spaced over 10 days. To evaluate the overall efficiency of the process we applied the notation introduced by Jørgensen for one-pot reactions[4c] (see Scheme 3). The most striking feature of the uninterrupted sequence from the starting material to the precursor of cermizine B is that it consists of eight consecutive reactions for eight manual operations (nmo) and only one final purification. For the total synthesis of cermizine B, which required an additional step and purification, the values of $Y_{PBF}$ (76% yield per bond formed) and




Scheme 2 Total synthesis of (−)-cermizine B (**1**).




| nmo | $Y_{PBF}$ [%] | $Y_{PMO}$ [%] | $P_f$ |
|---|---|---|---|
| 9 | 76 | 86 | 6 |

Scheme 3 Pot-economy synthesis of cermizine B on a gram-scale and summary of the process according to Jørgensen's notation (ref. 4c).

$Y_{PMO}$ (86% yield per manual operation) indicate that each step in this synthesis proceeded in high yield. The very high value of the purification factor ($P_f$ = 6), which denotes the number of purifications avoided, is also noteworthy. The considerable difference in the number of required steps compared with previous approaches to phlegmarane-type alkaloids underlines the efficiency and simplicity offered by asymmetric organocatalytic one-pot cascades.

In summary, a highly efficient, enantioselective total synthesis of cermizine B (**1**) was completed using a carefully orchestrated series of tandem reactions and the principles of pot economy. Our route to cermizine B constitutes the first synthesis of this type of *cis*-phlegmarine alkaloids. The convergent decahydroquinoline synthetic entry was key to the successful development of this concise, sustainable eight-step procedure that has allowed a gram scale synthesis of the natural product.[20] Considering the flexible, highly convergent and modular nature of this methodology, it could also be used to access the other phlegmarine alkaloids by changing stereomotifs in the decahydroquinoline core. Furthermore, it should enable the rapid synthesis of other *Lycopodium* alkaloids and analogs for the development of a comprehensive structure–activity relationship of this important class of compounds.

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