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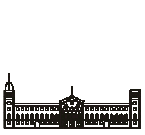
Total synthesis of [-]-anominine via target-directed organocatalysis : an asymmetric approach to the wieland-miescher ketone and analogues

Gorka Etxebarria i Jardí



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TOTAL SYNTHESIS OF (–)-ANOMININE VIA TARGET-DIRECTED ORGANOCATALYSIS: AN ASYMMETRIC APPROACH TO THE WIELAND-MIESCHER KETONE AND ANALOGUES

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Programa de Doctorat: Química Orgànica a la Indústria Quimicofarmacèutica

Bienni 2004-2006

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Memòria presentada per Gorka Etxebarria i Jardí

per a optar al títol de Doctor per la Universitat de Barcelona

Dirigida per:

Dr. Josep Bonjoch Sesé

Dr. Ben Bradshaw

Barcelona, Juliol de 2010

El treball experimental recollit en aquesta memòria es va dur a terme al Laboratori de Química Orgànica de la Facultat de Farmàcia de la Universitat de Barcelona sota la direcció del Dr. Josep Bonjoch Sesé i del Dr. Ben Bradshaw.

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TABLE OF CONTENTS

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PUBLICATIONS

1. ***Polycyclic framework synthesis of anominine and tubingensin A indole diterpenoids***. B. Bradshaw, G. Etxebarria-Jardí, J. Bonjoch. *Org. Biomol. Chem.*, **2008**, *6*, 772–778.

2. ***Efficient Solvent-Free Robinson Annulation Protocols for the Highly Enantioselective Synthesis of the Wieland–Miescher Ketone and Analogues***. B. Bradshaw, G. Etxebarría-Jardi, J. Bonjoch, S. F. Viózquez, G. Guillena, C. Nájera. *Adv. Synth. Catal.*, **2009**, *351*, 2482–2490.

3. ***Total Synthesis of (–)-Anominine***. B. Bradshaw, G. Etxebarria-Jardí, J. Bonjoch. *J. Am. Chem. Soc.*, **2010**, *132*, 5966–5967.

   This paper has been reviewed in Synfacts: ***Total Synthesis of (–)-Anominine with an Organocatalytic Key Step***. B. List, L. Ratjen. *Synfacts*, **2010**, *7*, 833.

4. ***(S_a,S)-N-[2-(4-Methylphenylsulfonamido)-1,1´-binaphthyl-2´-yl]-(S)-pyrrolidine-2-carboxamide: An Organocatalyst for the Direct Aldol Reaction***. S. F. Viózquez, G. Guillena, C. Nájera, B. Bradshaw, G. Etxebarria-Jardi, J. Bonjoch. Article submitted to *Organic Syntheses* by invitation of the editors.

5. ***Synthesis of (S)-8a-methyl-3,4,8,8a-tetrahydro-1,6-(2H,7H)-naphthalenedione via N-tosyl-(S_a)-binam-L-prolinamide Organocatalysis***. B. Bradshaw, G. Etxebarria-Jardí, S. F. Viózquez, G. Guillena, C. Nájera. Article submitted to *Organic Syntheses* by invitation of the editors.

As a part of my scientific formation a research placement was done, resulting in one publication:

6. ***Total Synthesis of the Anti-Apoptotic Agents Iso- and Bongkrekic Acids***. A. Francais, A. Leyva, G. Etxebarria-Jardi, S. V. Ley. *Org. Lett.*, **2010**, *12*, 340–343.

PERSONAL CONTRIBUTION TO CONGRESSES

1. ***Synthetic Approaches to the Diterpenoid Alkaloids Aspernomine and Anominine.*** G. Etxebarria-Jardí, B. Bradshaw, J. Bonjoch. Oral Comunication, *Workshop de Xarxa Temàtica (2005 XT 065): "Síntesi de Productes Naturals i Fàrmacs Enantiopurs"*, Barcelona, **October 2006**.

2. ***Towards the Synthesis of Aspernomine, Anominine and Tubingensin A.*** G. Etxebarria-Jardí, B. Bradshaw, J. Bonjoch. Oral Comunication, *Workshop de Xarxa Temàtica (2005 XT 065): "Síntesi de Productes Naturals i Fàrmacs Enantiopurs"*, Paris, **November 2007**.

3. ***Aproximació a la síntesi estereoselectiva de la Tubingensina A, Anominina y Aspernomina.*** G. Etxebarria-Jardí, B. Bradshaw, J. Bonjoch. Oral Comunication, *Societat Catalana de Química. V Trobada de Joves Investigadors dels Països Catalans*, Vic, **January 2008**.

4. ***Aproximación a la síntesis estereoselectiva de la Tubingensina A, Anominina y Aspernomina*.** G. Etxebarria-Jardí, B. Bradshaw, J. Bonjoch. Oral Comunication, *Sociedad Española de Química. XXII Reunión Bienal de Química Orgánica*, Tarragona, **June 2008**.

5. ***Síntesi Orgànica, Desenvolupament de Nous Fàrmacs.*** G. Etxebarria-Jardí**.** Oral Comunication, *III Jornada de Recerca a la Facultat de Farmàcia*, Barcelona. **February 2010**.

RESEARCH PLACEMENT

1. **University of Cambridge** (Cambridge, UK). Department of Chemistry, Supervisor: Prof. Dr. Steve Ley. *Total Synthesis of the Anti-Apoptotic Agents Iso- and Bongkrekic Acids*. **January-May 2009**.

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	*t*-Butoxycarbonyl
bp	boiling point
br	broad
c	concentration
^{13}C-NMR	carbon-13 nuclear magnetic resonance
calcd	calculated
Celite®	filtration agent (90% SiO_2, 4% Al_2O_3, 3.3% Na_2O and K_2O, 1.3% Fe_2O_3, 0.5% CaO)
COSY	correlation spectroscopy
CW	clockwise
d	doublet
δ	chemical shift
DIBAL-H	diisobutylaluminium hydride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
DET	diethyl tartrate
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
eq	equivalent

eq	equatorial
GC	gas chromatography
H^+	proton
[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
IR	infrared
i	iso
j	coupling constant
KHMDS	potassium bis(trimethylsilyl)azide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)azide
Lit.	literature
L-Sel	L-Selectride® (lithium tri-*sec*-butylborohydride)
M	molar
m	multiplet
m	meta
M^+	molecular ion
m/z	mass to charge ratio
m-CPBA	meta-chloroperoxybenzoic acid
mmol	millimoles
mol	moles
mp	melting point
MS	mass spectrometry
Ms	mesyl
MVK	methyl vinyl ketone
o	ortho
[O]	oxidation
Oxone®	2 $KHSO_5 \cdot K_2SO_4 \cdot KHSO_4$

p	para
p.	page
PCC	pyridinium chlorochromate
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
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
td	triplet of doublets
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMS-Cl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl
WMK	Wieland-Miescher ketone
wt	weight

PREFACE

This dissertation is divided into seven chapters. The first one consists of a general introduction to the natural products and lifecycle of fungal sclerotia. Furthermore, there are proposals for the biosynthesis of the related diterpenoids from *Aspergillus spp.* In order to put the work in context, there is a precedents part containing the attempted synthesis of one of these compounds by Danishefsky, and the previous results towards the preparation of these natural products obtained in our group.

The second chapter is focused on the publication '*Polycyclic framework synthesis of anominine and tubingensin A indole diterpenoids*' (B. Bradshaw, G. Etxebarria-Jardí, J. Bonjoch. *Org. Biomol. Chem.*, **2008**, *6*, 772–778) together with other results and detours not included in this paper.

The third chapter contains all the methodologic work for the large-scale, enantioselective preparation of the Wieland–Miescher Ketone and Analogues ('*Efficient Solvent-Free Robinson Annulation Protocols for the Highly Enantioselective Synthesis of the Wieland–Miescher Ketone and Analogues*', B. Bradshaw, G. Etxebarría-Jardi, J. Bonjoch, S. F. Viózquez, G. Guillena, C. Nájera. *Adv. Synth. & Cat.,* **2009**, *351*, 2482–2490) and its further optimisation to two Organic Syntheses Procedures submitted by invitation of the editor.

The fourth chapter is centered on the total synthesis of the diterpenoid anominine ('*Total Synthesis of (–)-Anominine'*, B. Bradshaw, G. Etxebarria-Jardí, J. Bonjoch. *J. Am. Chem. Soc.*, **2010**, *132*, 5966–5967) with all the unpublished results that allow to a more in-depth understanding of the overall synthetic strategy.

The fifth chapter contain the conclusions and outline. The sixth chapter is an experimental section with the compound preparation procedures together with the proton and carbon NMR of selected compounds. It also contains a compendium of all the publications that resulted throughout this thesis.

Finally, a summary of the work done in the doctoral placement at the laboratory of Dr. Steve Ley in Cambridge (UK) is attached. It only includes the successful results for the synthesis of iso- and bongkrekic acids (A. Francais, A. Leyva, G. Etxebarria-Jardi, S. V. Ley. *Org. Lett.*, **2010**, *12*, 340–343). The work carried by the author was on the eastern fragment, but for the sake of clarity the full synthesis is described. Moreover, it also contains the thesis summary in catalan.

CHAPTER 1.

INTRODUCTION AND OBJECTIVES

1.1 Natural Products from Fungal Sclerotia

It is generally accepted that many plants and animals produce and sequester metabolites that serve as chemical defences. By contrast, relatively little is known about chemical defence systems that have evolved among fungi. Many species of higher fungi produce specially adapted bodies called sclerotia as a means of surviving harsh climates or nutrient-poor conditions.[1]

These relatively large resting bodies can survive from several months to several years in the soil, but the factors that permit the long-term survival of sclerotia are not fully understood. Since fungi commonly thrive in competitive environments, it is often hypothesized that sclerotial metabolites prevent or reduce predation by fungivorous insects[2] make a significant contribution to sclerotial longevity, and thus, increasing their chances of survival.

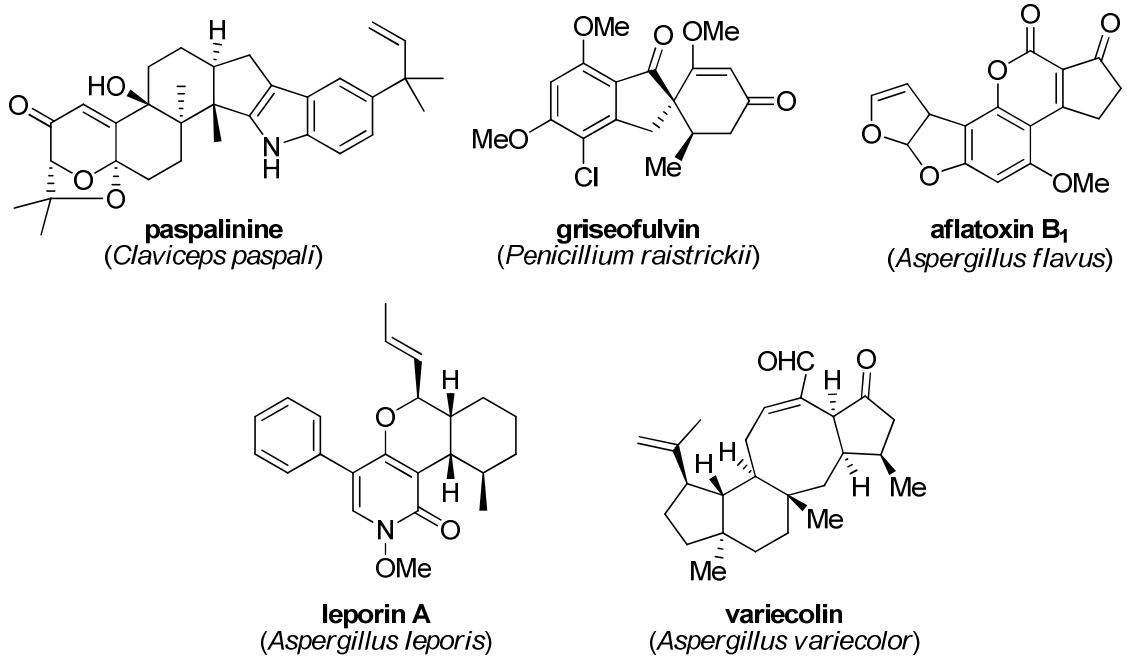
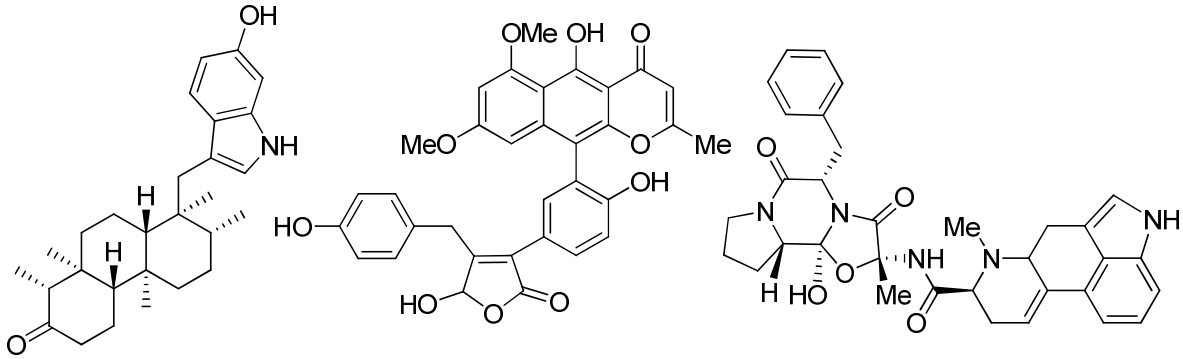


Figure 1.1 Natural Products from Fungal Sclerotia.

[1] W. B. Turner, D. C. Aldridge, *Fungal Metabolites II;* Academic Press: New York, **1983**, p. 631**.**
[2] D. T. Wicklow, In *Coevolution of Fungi with Plants and Animals;* Editors: K. A. Pirozynski, D. Hawksworth; Academic Press: New York, **1988,** p. 174–201 and references therein.

Some sclerotium-producing species of the widespread genus *Aspergillus* and *Claviceps* are known to produce significant amounts of a variety of important mycotoxins, such as aflatoxin or ergotamine. Indeed, fungal metabolites have been implicated in diseases of plants and insects, animal poisonings, biocontrol of other fungi, interspecies antagonism and eventually contamination of human and livestock food supplies. The wide extent and the extraordinary diversity of fungal species, make them a source of diverse and valuable natural products, an example of them is depicted in figure 1.1.



radarin A (*Aspergillus sulphureus*) **carbonarin A** (*Aspergillus carbonarius*) **ergotamine** (*Claviceps purpurea*)

Figure 1.1 (cont.) Natural Products from Fungal Sclerotia.

1.2 Lifecycle

Sclerotia are reproductive bodies that can lie dormant in soil for extended periods of time[3] (Figure 1.2, A). Under favourable conditions (onset of spring, rain period, etc.), sclerotia eventually germinate forming fruity bodies (B). The sexual reproductive cycle begins when sclerotia start to produce spores, which are simultaneously ejected when suitable grass hosts are flowering (C). These airborne spores cause infection when fall onto any nutrient source (*i.e.* plant leaves, flowers, fruits, D) provoking a reduction in the yield and quality of grain produced, and eventually cause disease if infected grain is fed to humans or livestock.

[3] (a) H. G. Floss, *Tetrahedron*, **1976**, 32, 873–912. (b) H. G. Floss, J. A. Anderson, In: *The Biosynthesis of mycotoxins: A Study in Secondary Metabolism,* Editor: P. S. Steyn, Academic Press, New York, **1980**, p. 17–67. (c) J. Rutschmann, P. A. Stadler, In: *Ergot Alkaloids and Related Compounds,* Editors: B. Berde, H. O. Schield, Springer-Verlag, Berlin, **1978**, p. 29–85. (d) J. Smith, J.A. Pateman. *Genetics and physiology of aspergillus*. Academic Press, New York, **1977**. (e) M. Didek-Brumec, V. Gaberc-Porekar, M. Alačević, *Critical Reviews in Biotechnology,* **1996**, *16*, p. 257–299.

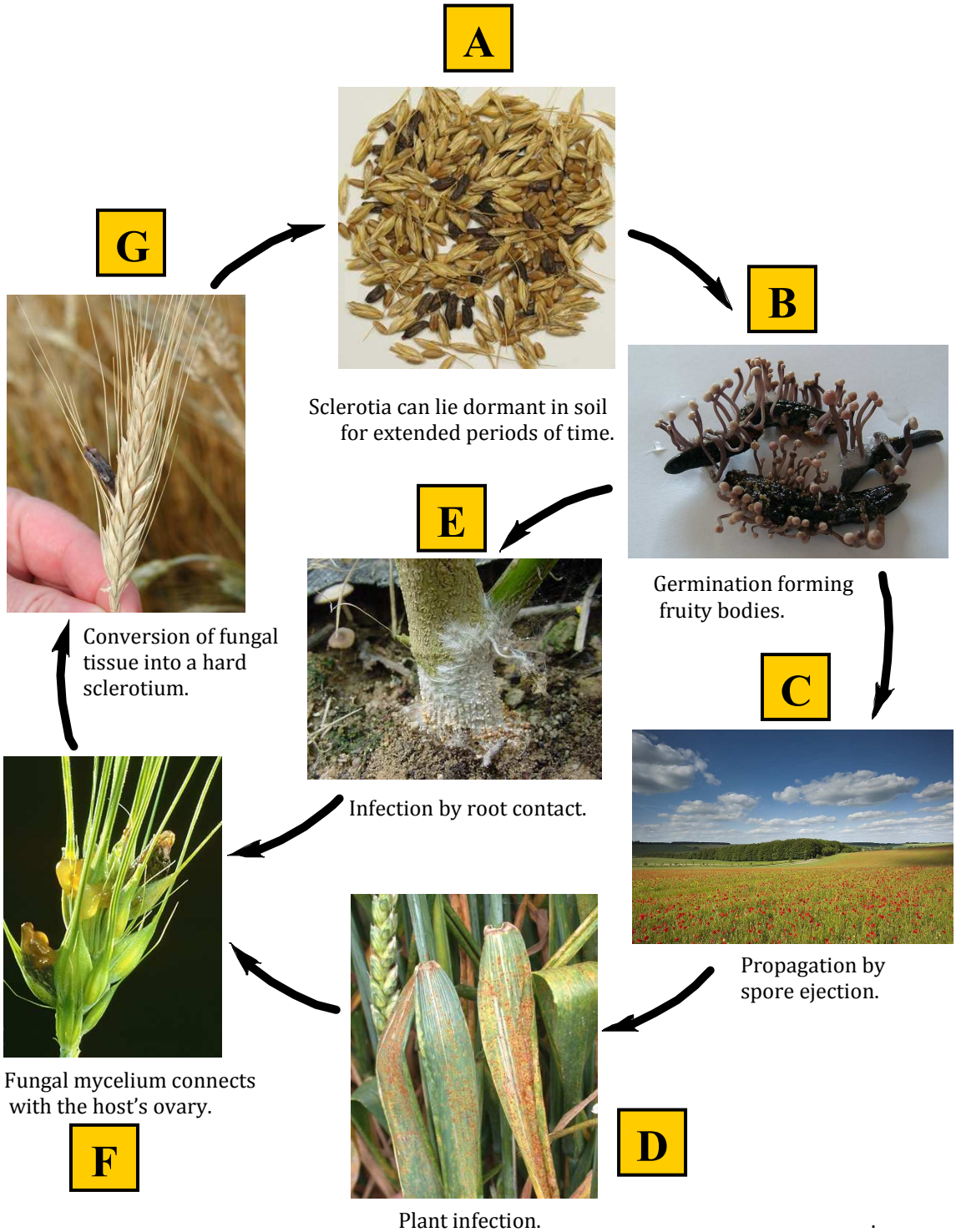


Figure 1.2 Fungal Sclerotia Lifecycle

An alternative way of asexual reproductive cycle is possible if germinating sclerotia are in contact with roots or basal stems. Sclerotium can produce mycelia, which can directly infect the plant (E). The first stage of ergot infection manifests itself as a white soft tissue which propagates throughout the plant. The proliferating parasitic fungal mycelium then connects with the host's vascular system destroying the plant ovary (F). Inside the seed container, the fungal tissue is converted into a hard dry sclerotium forming an ergot kernel (G). At this stage, terpenes, alkaloids and lipids are accumulated in the sclerotium as a source of nutrients for the next lifecycle. Finally, the sclerotium fall to the ground where it can stay dormant until favourable climatic conditions appear and the cycle repeats.

1.3 Diterpenoids from *Aspergillus spp.*

Evidence that defensive metabolites of plants are often concentrated in reproductively important plant parts[4] make them an important target of the groups that isolate natural products. A systematic study of fungal sclerotia made by Gloer's group showed that often contain unique antiinsectan metabolites that help to protect them from predation.[5] This work has been characterized by a particularly high incidence of previously undescribed natural products, an example of the products isolated from the sclerotium of *Aspergillus* species is depicted in Figure 1.3. Most compounds contain a common terpene part and therefore, it seems reasonable that they might come from a common biogenetic pathway.

[4] D. F. Rhodes, *Am. Nut.*, **1986**, *125*, 205–238.
[5] D. T. Wicklow, P. F. Dowd, J. B. Gloer, In *The Genus Aspergillus*; Editors: K. A. Powell, J. Peberdy, A. Renwick; Plenum, New York, **1994**, 93–114.

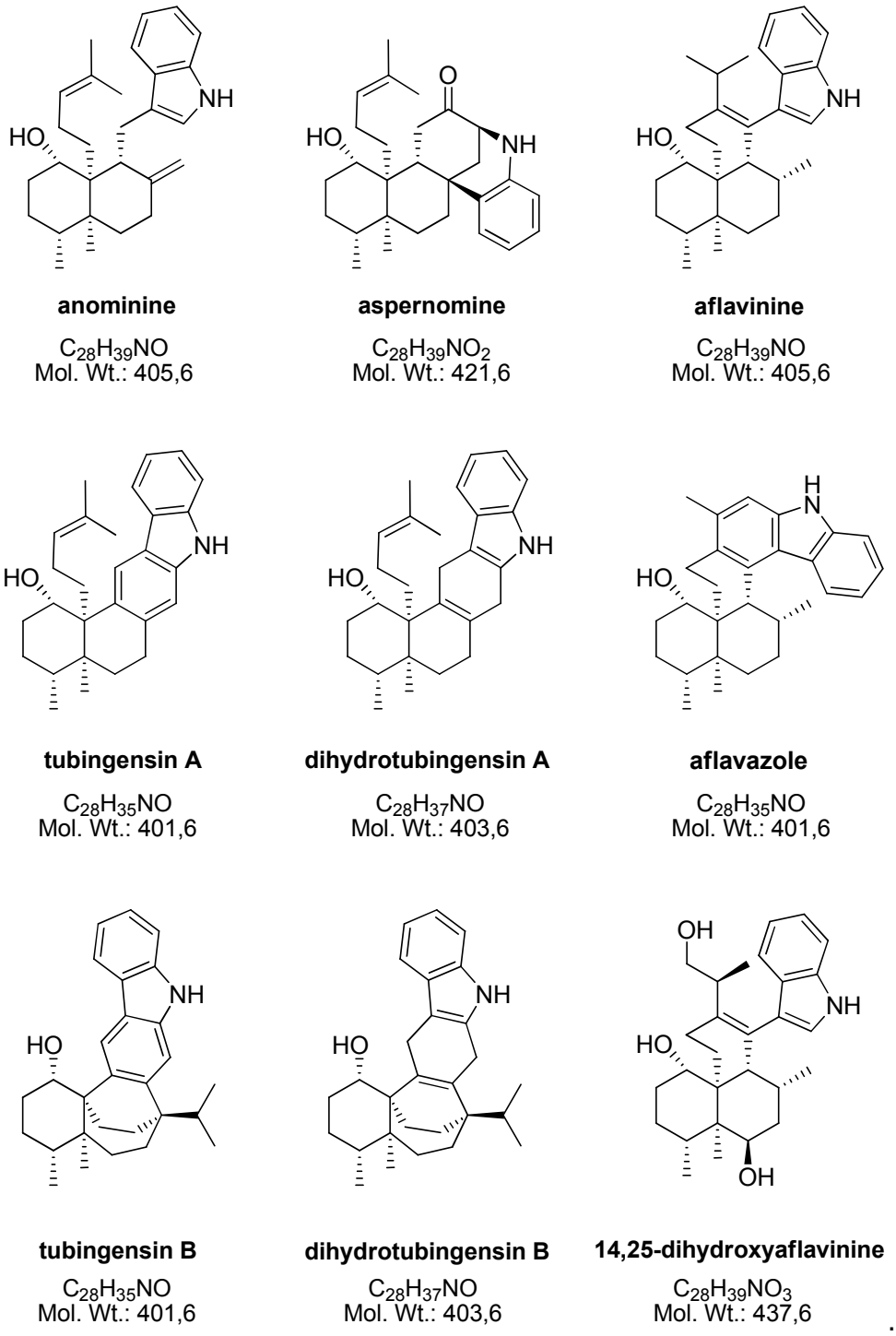


Figure 1.3 Diterpenoids from *Aspergillus spp.*

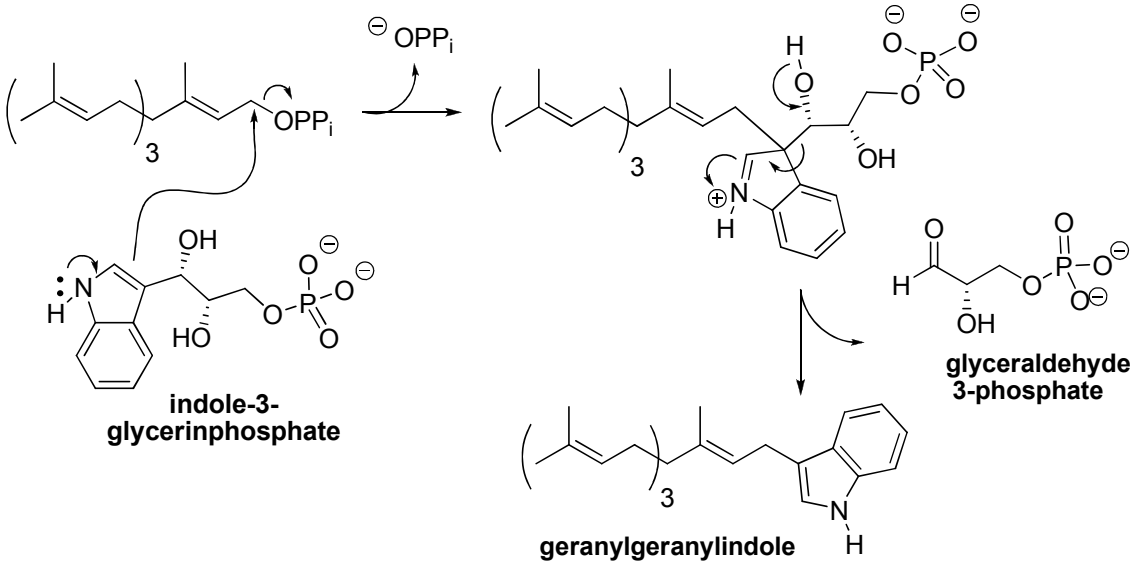
Terpenes represent one of the largest and most diverse classes of secondary metabolites, with over 55,000 members isolated to date. However, all of them derive from the same biogenetic unit, which is combined and folded to give an exotic array of chiral, carbocyclic skeletons.[6] Further oxidation and rearrangement result in an almost endless number of conceivable structures. Their ubiquity in nature often result in natural products of 'mixed' biosynthetic origins,[7] as well as the fact that they can be rearranged and highly oxidised, means that there is not a truly general strategy for their synthetic construction. Because the carbon skeleton of a terpene is often its defining structural feature, it is there that synthetic chemists usually begin their planning. Indeed, a plethora of approaches for accessing terpene ring systems are often published before an actual total synthesis. Unfortunately, significant difficulties are often encountered in attempting to translate the results of a model system to one laden with more functionality; in some cases an entirely new strategy must be devised to access the natural product.[8] This highlights the fact that subtle steric and electronic factors, as well as functional-group incompatibilities, are often difficult -or impossible- to predict at the beginning of a total synthesis endeavour.[9]

For those reasons, a chemist has to look into all sources of information (previous approaches/syntheses, conformational analysis, biosynthesis) prior to design a synthetic route. If available, biosynthetic mechanism could bring to light some reactivity and structural information that would be useful as a starting point. Since no biogenetic data was available for any of the products of the family, we decided to analyse their biosynthesis by proposing plausible pathways. Having in mind that all the family products are C_{28}, it is fairly reasonable that they come from a mixed origin, and more precisely, a diterpene condensed with an indole as the heterocyclic moiety.

[6] T. J. Maimone, P. S. Baran, *Nature Chem.*, **2007**, *3*, 396–407.
[7] P.M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*. Wiley, West Sussex, UK, **2002**.
[8] M.A. Sierra, M.C. de la Torre, *Dead Ends and Detours, Direct Ways to Successful Total Synthesis*. Wiley-VCH, Weinheim, Germany, **2004**.
[9] F.Z. Dörwald, *Side Reactions in Organic Synthesis*. Wiley-VCH, Weinheim, Germany, **2005**.

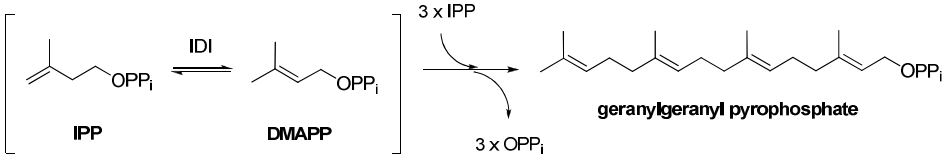
1.4 Biosynthesis

Mevalonic acid[10] is the precursor for the 5-carbon terpenic biogenetic units: dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP). Later on in the biogenetic sequence, three molecules of IPP are condensed with one of DMAPP giving geranylgeranyl pyrophosphate (GGPP, Scheme 1.1), and then is attacked by indole-3-glycerinphosphate rendering the common metabolite glyceraldehydes-3-phosphate and the precursor for the whole family: geranylgeranylindole. The differences between each compound derive from the different folding or spatial disposition when cyclising, plus differences in the Wagner-Meerwein rearrangements and different oxidation state. The following pages will be dedicated to what we believe is their biogenesis from a mechanistic and structural point of view based on literature precedents.



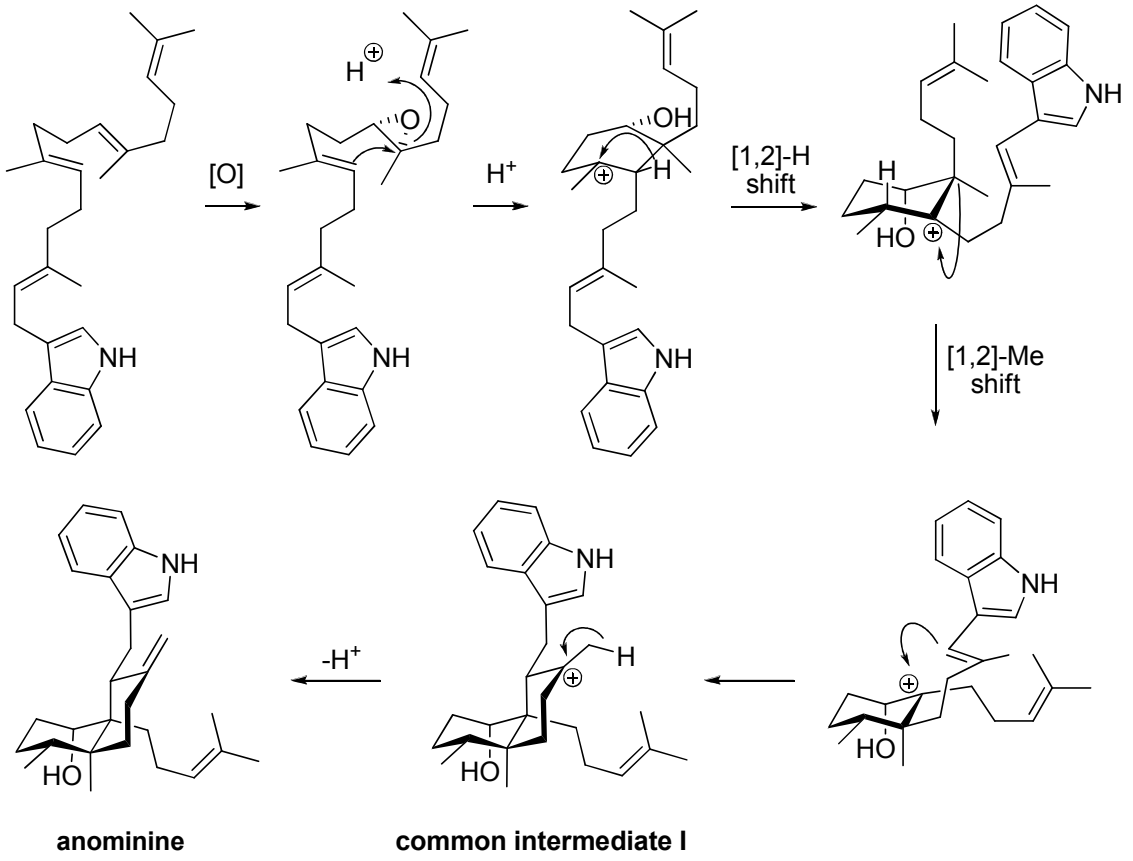
Scheme 1.1 Postulated Geranylgeranylindole Biosynthesis.

[10] The condensation of three molecules of acetyl coenzyme A (AcSCoA) gives (S)-3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which after reduction raises mevalonic acid (MVA). This, is decarboxylated and phosphorylated to render the two building blocks for the biosynthesis of terpenes, which can be isomerised *in vivo* by the IDI enzyme.



1.4.1 Anominine Biosynthesis

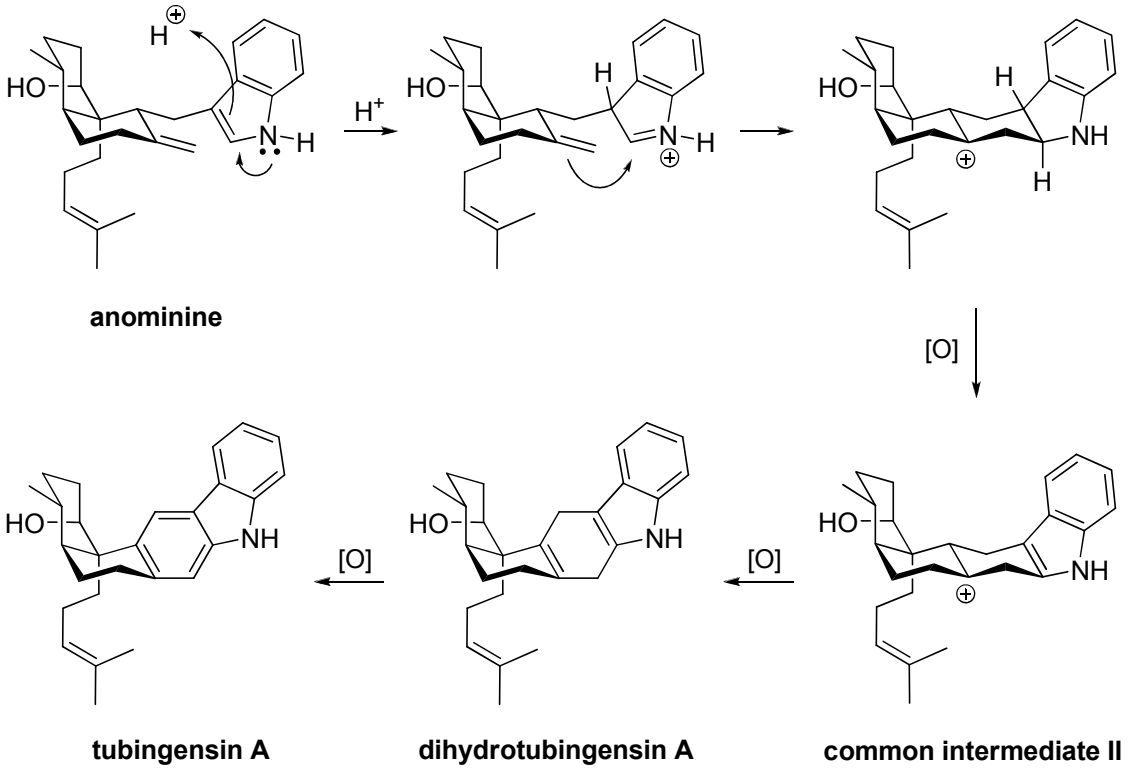
Geranylgeranylindole, the precursor for the products of the family, undergoes an enzymatic selective epoxidation to promote the cationic reaction cascade (Scheme 1.2). Nucleophilic attack of the neighbouring double bond would generate the first cyclohexane ring. 1,2 hydride shift would place the carbocation in a suitable position for a 1,2 methyl shift to occur. Then, a subsequent nucleophilic attack of closest alkene would provide the *cis*-fused decalin structure for the **common intermediate I**. Elimination of an exocyclic proton would render anominine.



Scheme 1.2 Postulated Anominine Biosynthesis.

1.4.2 Tubingensins A and B Biosynthesis

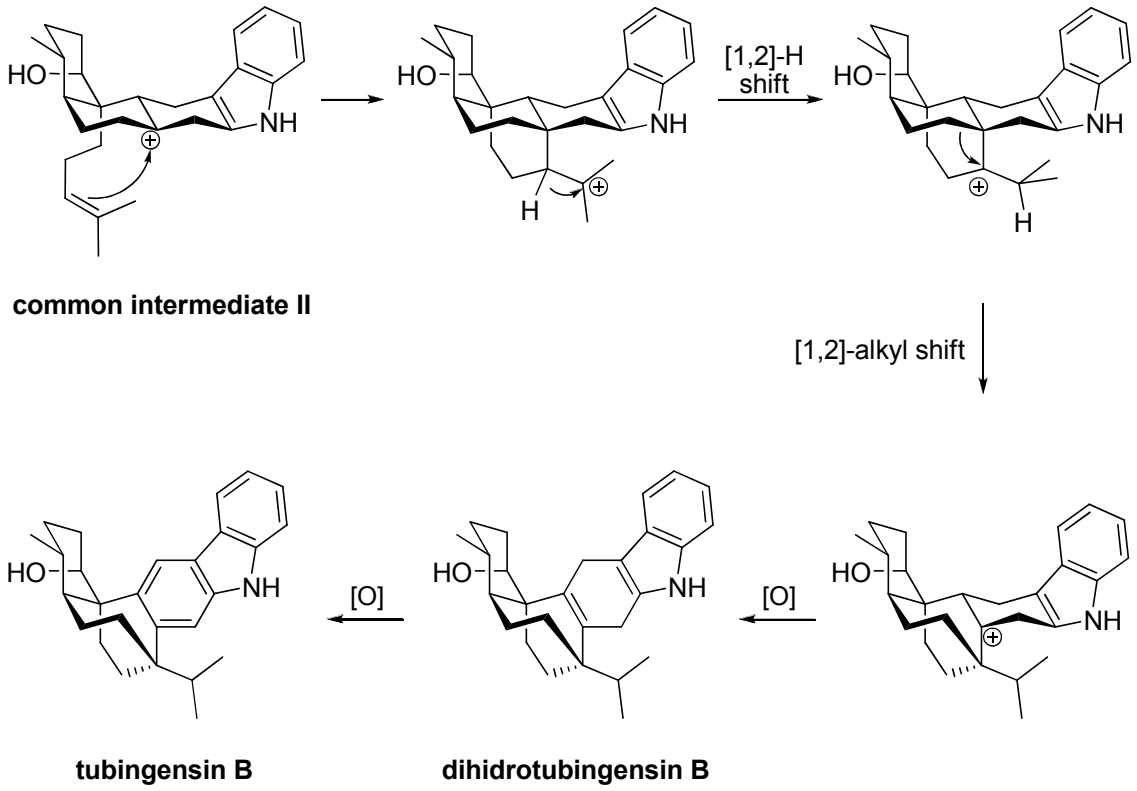
Anominine is postulated to be the precursor for the biogenesis of tubingensins and aspernomine,[11] and a plausible reaction mechanism is depicted in Scheme 1.3. Upon protonation of the indole nitrogen atom, the formed iminium ion is attacked by the proximal exocyclic double bond generating the pentacyclic backbone of the **common intermediate II**. Upon oxidation of this intermediate dihydrotubingensin A and tubingensin A are obtained.



Scheme 1.3 Postulated Dihidro- and Tubingensin A Biosynthesis.

[11] F-P. Wang, Q-H. Chen, *The Alkaloids: Chemistry and Biology*, Editor: G. A. Cordell, Elsevier Academic Press, **2008**, 176–178.

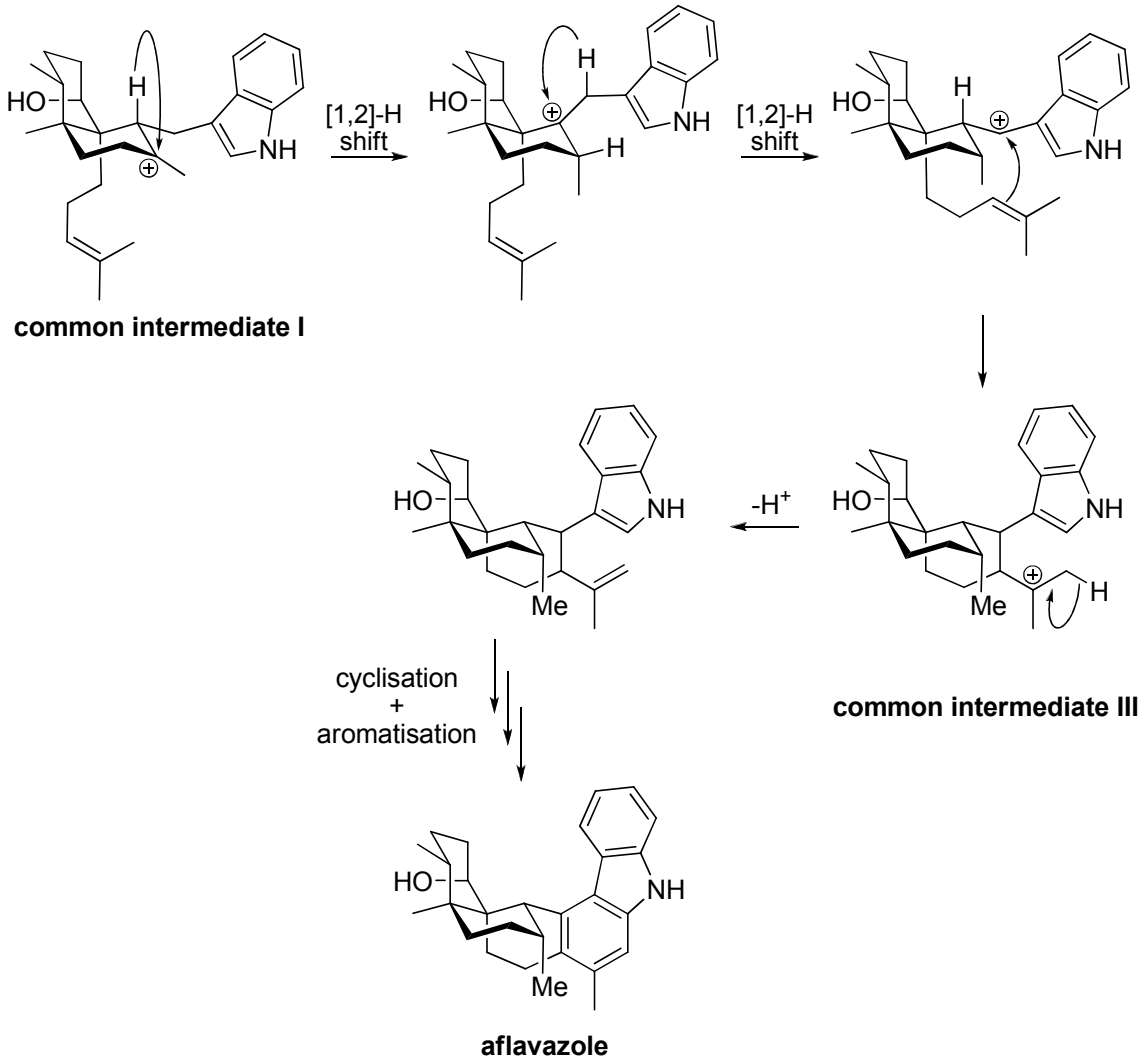
In contrast, if the carbocation of the **common intermediate II** is attacked by the side chain alkene a hexacyclic framework is obtained (Scheme 1.4). A consecutive 1,2 hydride and alkyl shifts followed by oxidations would provide the dihydrotubingensin B and tubingensin B skeletons.



Scheme 1.4 Postulated Dihydro- and Tubingensin B Biosynthesis.

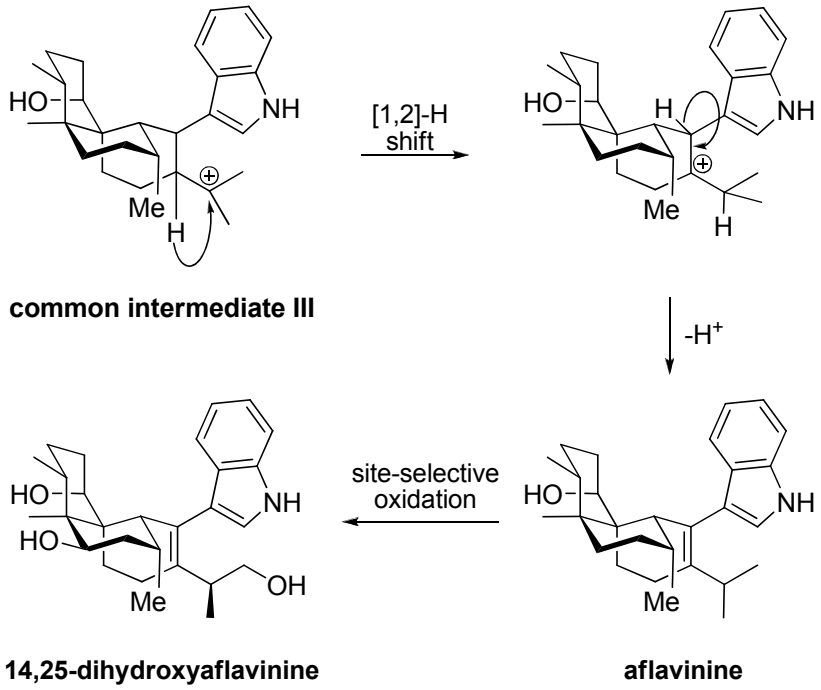
1.4.3 Aflavazole and Aflavinine Biosynthesis

For the biogenesis of aflavazole and aflavinine a diversion is taken in the biosynthetic pathway. The **common intermediate I** undergoes a series of 1,2 hydride shifts leading to a benzylic carbocation (Scheme 1.5), which is stabilised by delocalisation throughout the indole. Nucleophillic attack of the side chain double bond would furnish the fused tricyclic structure of the aflavinine-type compounds, depicted as **common intermediate III**. A proton loss would provide the isopropenyl side chain, which after cyclisation and aromatisation would give the aflavazole natural product.



Scheme 1.5 Aflavazole Biosynthesis.

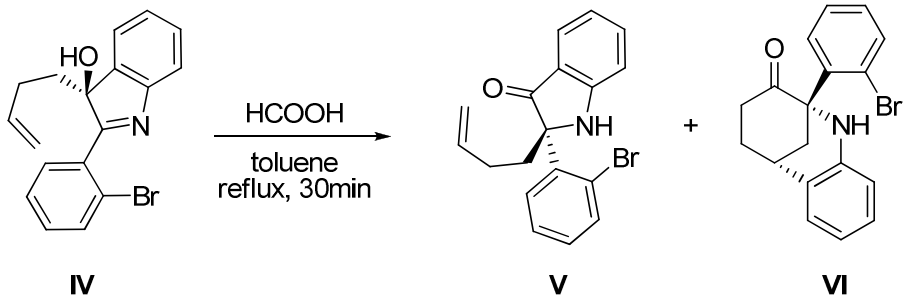
However, if **common intermediate III** undergoes a 1,2 hydride shift and a subsequent proton elimination (Scheme 1.6) the natural product aflavinine is obtained. Two site selective oxidations would give the 14,25-dihydroxy derivative.



Scheme 1.6 Aflavinine and 14,25-Dihydroxyaflavinine Biosynthesis.

1.4.4 Aspernomine Biosynthesis

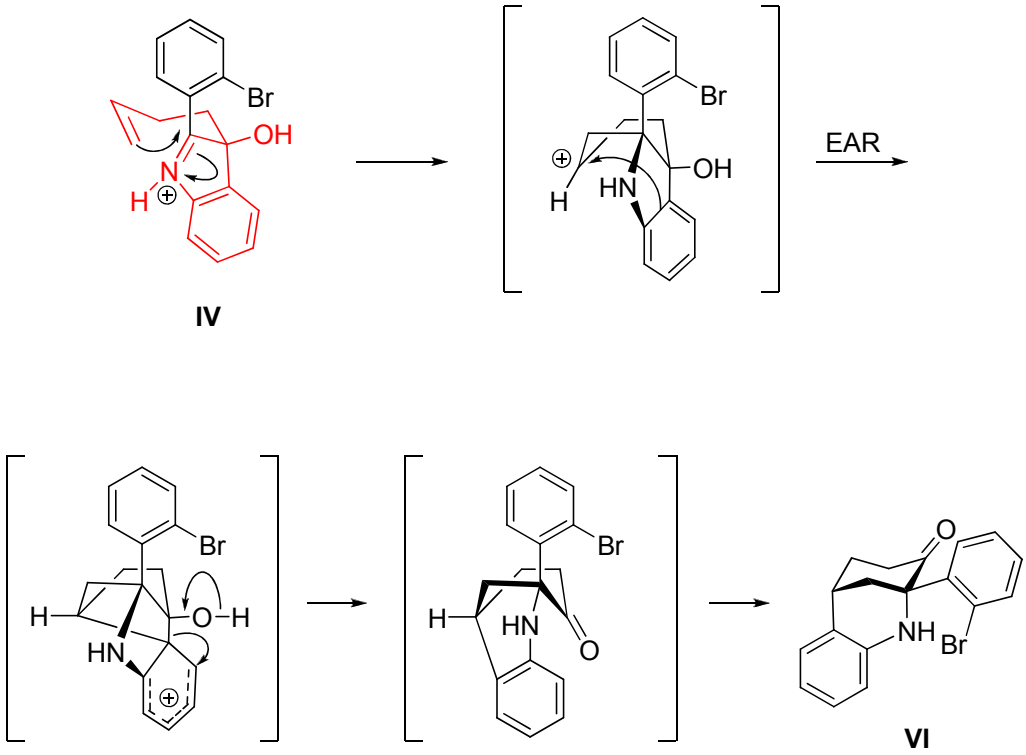
Looking carefully at the structure of anominine it is difficult to understand which biosynthetic pathway leads to the natural product aspernomine. It was initially speculated that they had a different biosynthetic pathway,[12] but after serendipitous discovery by McWorther[13] it soon became evident that a rearrangement may be involved in the aspernomine biogenesis. Attempts to convert indole **IV** to indanone **V** by treatment with formic acid at thermodynamic conditions gave a mixture of two products, the first being the expected Mannich-type product and **VI** coming from an unexpected rearrangement (Scheme 1.7).



Scheme 1.7 Unexpected Rearrangement.

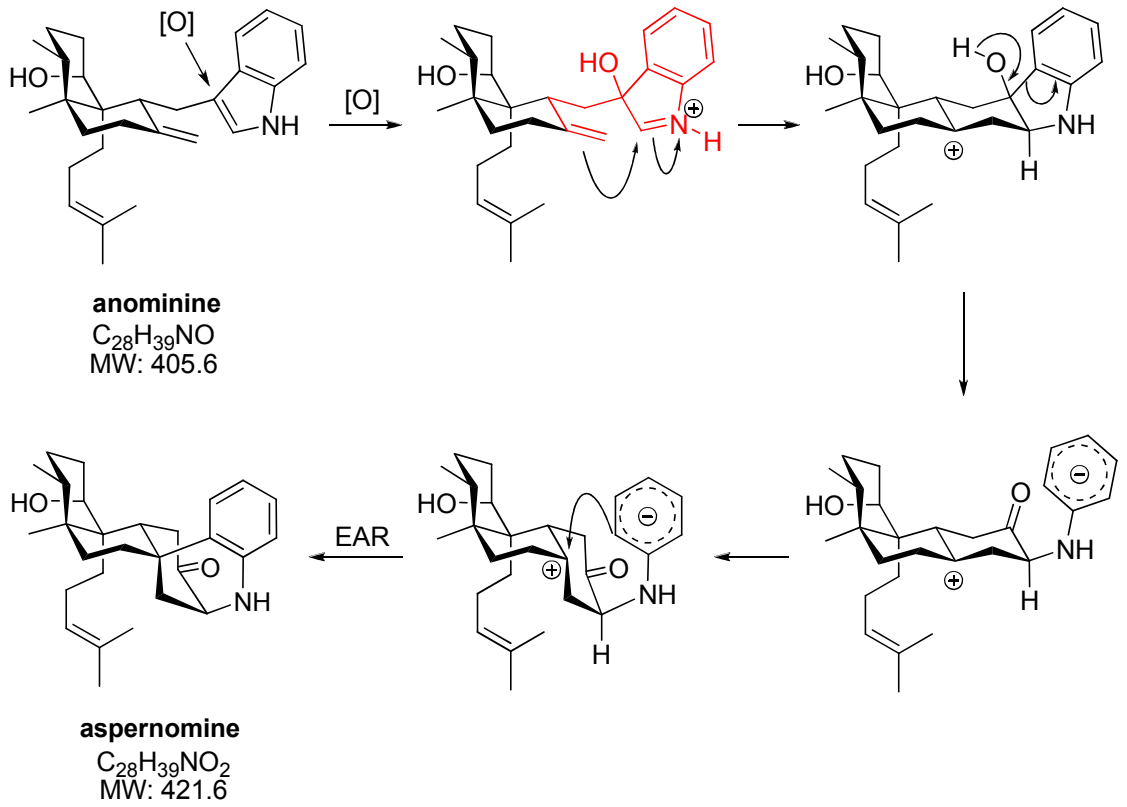
The mechanistic rationale is depicted in Scheme 1.8. Upon protonation of the indolic nitrogen the terminal double bond of the side chain (disposed in chairlike conformation) attacks the position 2 of the indole forming a cyclohexane ring. The resulting carbocation undergoes an electrophilic addition reaction (EAR) stabilising the carbocation by delocalisation throughout the phenyl ring, and collaterally changing to a boatlike conformation. Then, the highly-strained ring system releases the tension by rearranging itself forming a tetrahydroquinoline fused with the cyclohexanone.

[12] G. M. Staub, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *J. Am. Chem. Soc.*, **1992**, *114*, 1015–1017.
[13] Y. Liu, W. W. McWhorter Jr., C. E. Hadden, *Org. Lett.* **2003**, *5*, 333–335.



Scheme 1.8 Postulated Mechanism of the Unexpected Rearrangement.

Trying to extrapolate this mechanism to the structure of anominine, soon some differences appeared. The first thing is that in the model system there is an *ortho*-bromophenyl substituent in the position 2 of the indole. This different substitution pattern might have a crucial role in the reaction pathway that cannot be forgotten. However, this mechanistic proposal is translated to the anominine structure and is depicted in Scheme 1.9. Oxidation of indole 3-position combined with a protonation of the indolic nitrogen set the functionality ready to be attacked by the exocyclic alkene. Then, the pinacol-like rearrangement occurs, and the corresponding anion is stabilised by delocalisation. The conformational change (from *trans* to *cis* fusion) bring the phenyl ring closer to the carbocation making easier the EAR to finally give the pentacyclic ring system of the natural product aspernomine.



Scheme 1.9 Proposed Biosynthesis of Aspernomine (common parts are drawn in red).

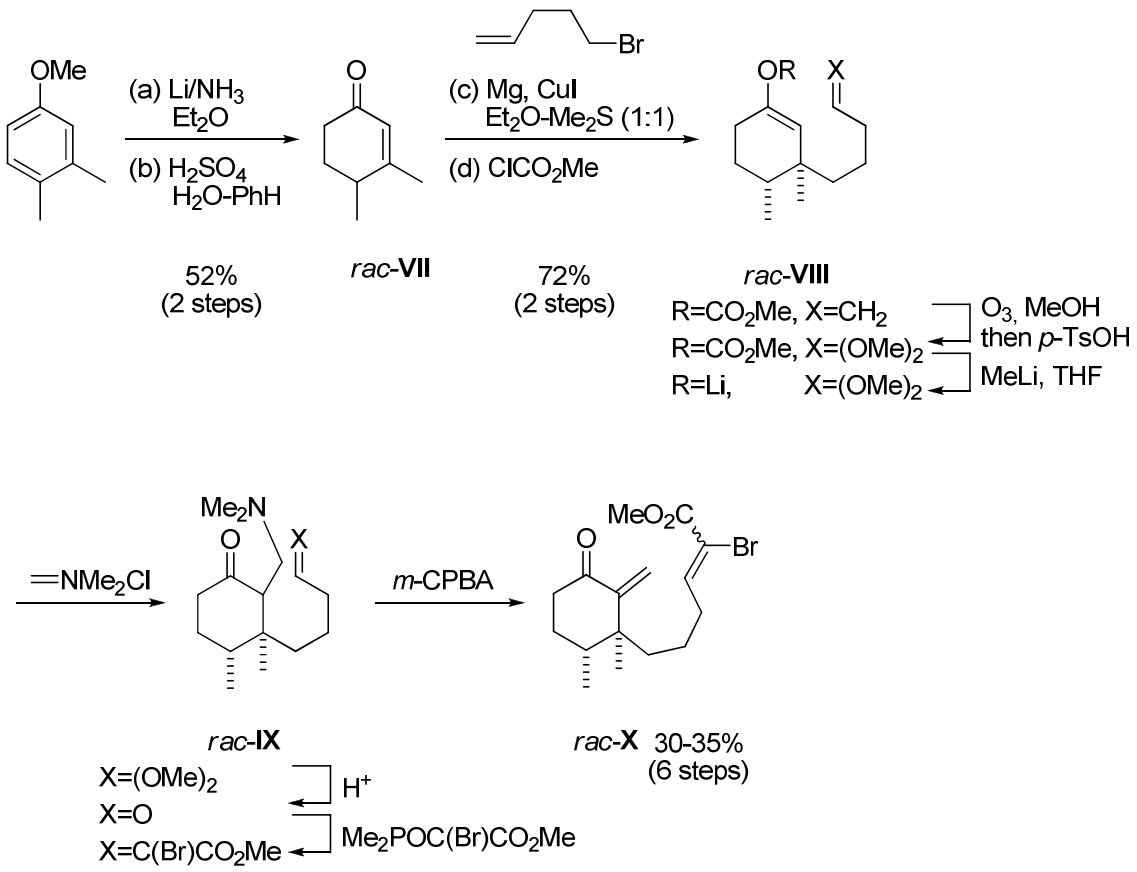
1.5 Previous Work

1.5.1 Danishefsky's Attempted Synthesis of Aflavinine

The only work done towards the total synthesis of this family of compounds is the Danishefky's attempted synthesis of aflavinine. The group developed a methodology to diastereoselectively generate the B and C rings of aflavinine in a single step which proved to be very effective when using a model lacking the methyl in C3 position. When applying the methodology to the real substrate the stereochemical course of the reaction did not follow the same pattern, and as a consequence 4-*epi*-aflavinine was obtained. A summary of the synthesis is discussed below.

To prove if it was possible they first employed a racemic model to validate the methodology. Starting from 3,4-dimethylanisole and using a known protocol[14] they obtained enone **VII** (Scheme 1.10). They based their initial strategy on the observation of Ziegler,[15] who reported that upon organocuprate addition the required *cis* relationship of the methyl groups at C13 and C14 could be established. Addition of organocuprate onto the racemic enone **VII** and subsequent trapping with methyl chloroformate generated racemic enol carbonate **VIII**. Selective ozonolysis and *in-situ* protection of the newly-formed aldehyde delivered the ester. Generation of the lithium enolate and quenching with Eschenmoser's salt provided the crude Mannich base **IX,** which after acidic treatment, homologation and oxidative unveiling of the α-methylene ketone delivered the desired biselectrophile **X** as an *E:Z* mixture. The overall yield for the ten-step conversion from commercial substrates was 11-13%.

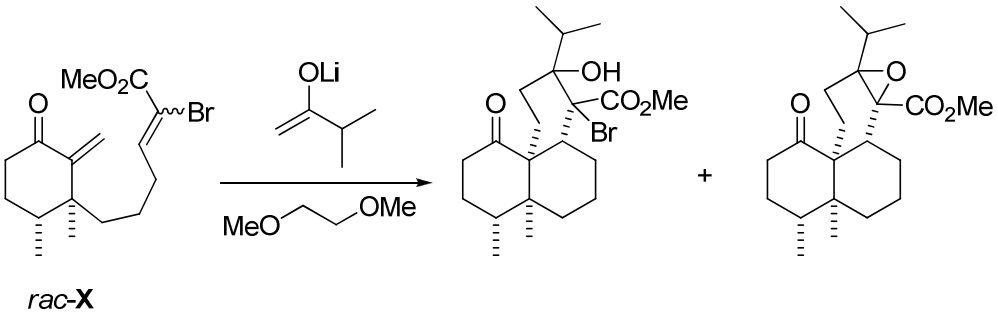
[14] W. G. Dauben, G. W. Shaffer, V. D. Vietmeyer, *J. Org. Chem.*, **1968**, *33,* 4060–4069.
[15] F. E. Ziegler, G.R. Reid, W. L. Studt, P. A. Wender, *J. Org. Chem.*, **1977**, *42,* 1991–2001.



Scheme 1.10 Preparation of Model Precursors

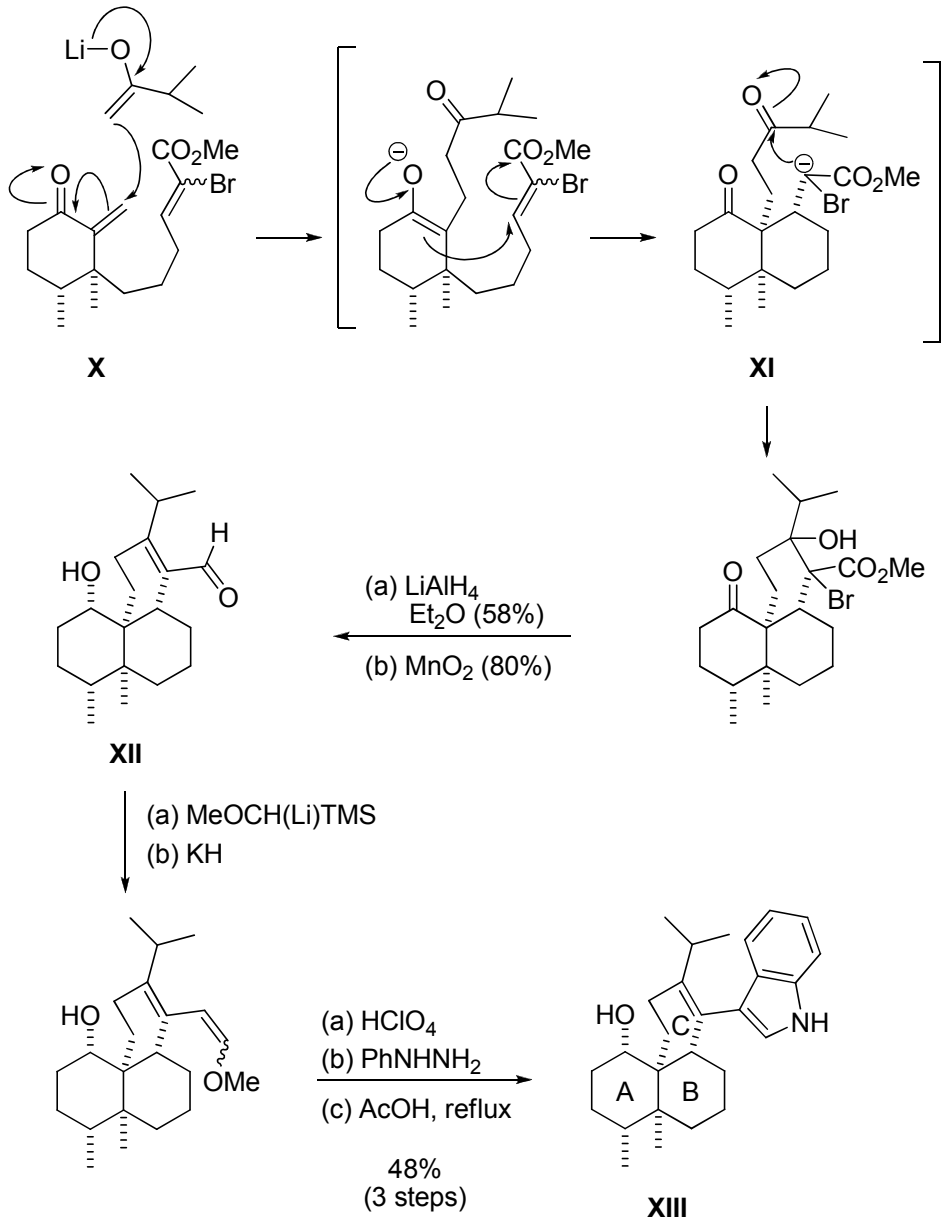
The substrate was then set for the pivotal double annulation ([2+2+2] annulation, Scheme 1.11). Addition of the kinetic lithium enolate of methyl isopropyl ketone started the anionic addition cascade which furnished the tricycle. In the first step, the enolate is added to the more reactive α,β-unsaturated ketone of **X**, followed by the addition of the corresponding enolate to the α,β-unsaturated ester. The intermediate ketone **XI** is finally attacked by the remaining enolate completing the tricyclic backbone of aflavinine in a complete diastereoselective manner. Further reduction and allylic oxidation yielded aldehyde **XII**, which after homologation and Fischer indole synthesis supplied noraflavinine **XIII**.

Equation:



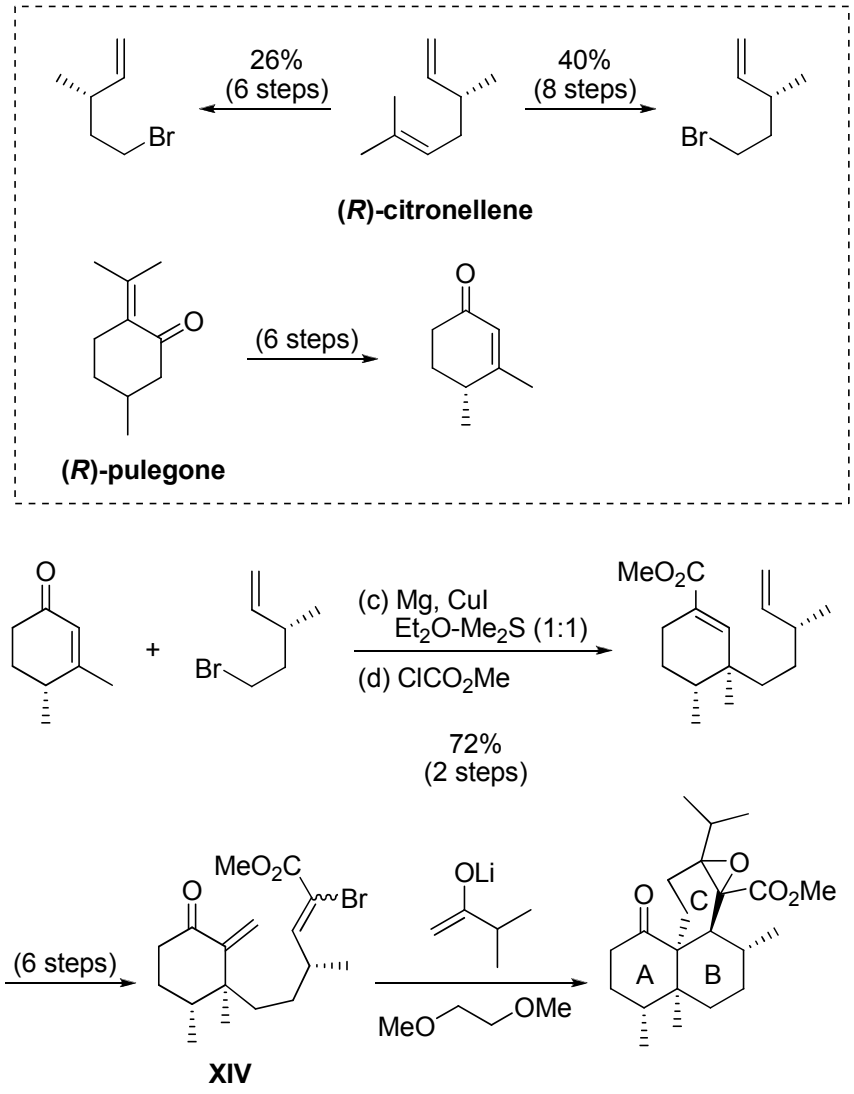
rac-**X**

Mechanism:



Scheme 1.11 Model [2+2+2] Annulation.

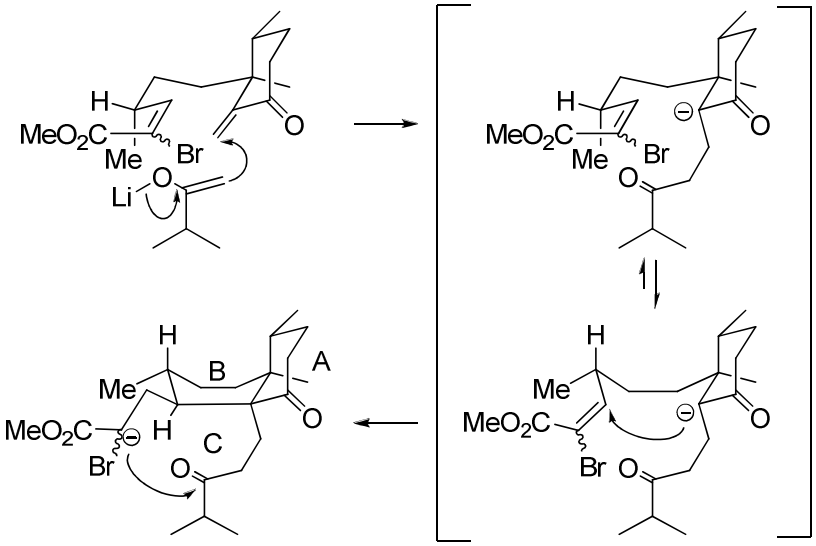
Once the conditions of the [2+2+2] annulation were established in the 3-desmethyl compound, it was the turn for the substrate leading to the natural product. The chiral building blocks were obtained from (*R*)-citronellene[16] (for the organocuprate) and from (*R*)-pulegone[17] (for the enone partner). Repetition of the same reaction sequence led to the desired chiral key intermediate **XIV**, which was submitted to the [2+2+2] conditions. Unexpectedly, the presence of the vicinal stereogenic centre affected dramatically the stereochemical outcome of the reaction obtaining the desired product but epimeric at the C4 position.



Scheme 1.12 26 steps (18 Longest Linear Sequence)

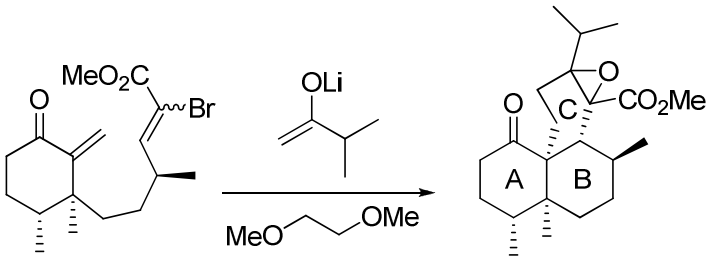
[16] E. R. Ireland, R. C. Anderson, R. Badoud, B. J. Fitzsimmons, G. J. McGarvey, S. Thaisrivongs, C. S. Wilcox, *J. Am. Chem. Soc.*, **1983**, *105*, 1988.
[17] M. G. Silvestri, *J. Org. Chem.*, **1983**, *48,* 2419.

The mechanistic rationale is depicted in Scheme 1.13. The enolate generated in the initial Michael addition should attack the α,β-unsaturated ester, disposed in a chairlike conformation. But now, the 1,3-diaxial repulsion exerted by the extra methyl group makes the molecule arrange in a boatlike disposition, in which the enolate side chain at C4 and the methyl group at C3 are related in a trans sense, thus obtaining a product with the *cis* A/B, *trans* B/C stereochemistry.



Scheme 1.13 [2+2+2] Annulation Mechanism.

The aforementioned hypothesis was confirmed by doing the same reaction but employing a C3 epimer (Scheme 1.14). This time, the equilibrium between boat- and chairlike conformation is shifted to the latter, and therefore all the ring fusion (A/B and B/C) is all-*cis*. Unfortunately, this confirmed that by employing the [2+2+2] annulation this product cannot be obtained, since the stereochemical outcome of the reaction is governed by the C3 stereocenter, but in an opposite selectivity than the desired.

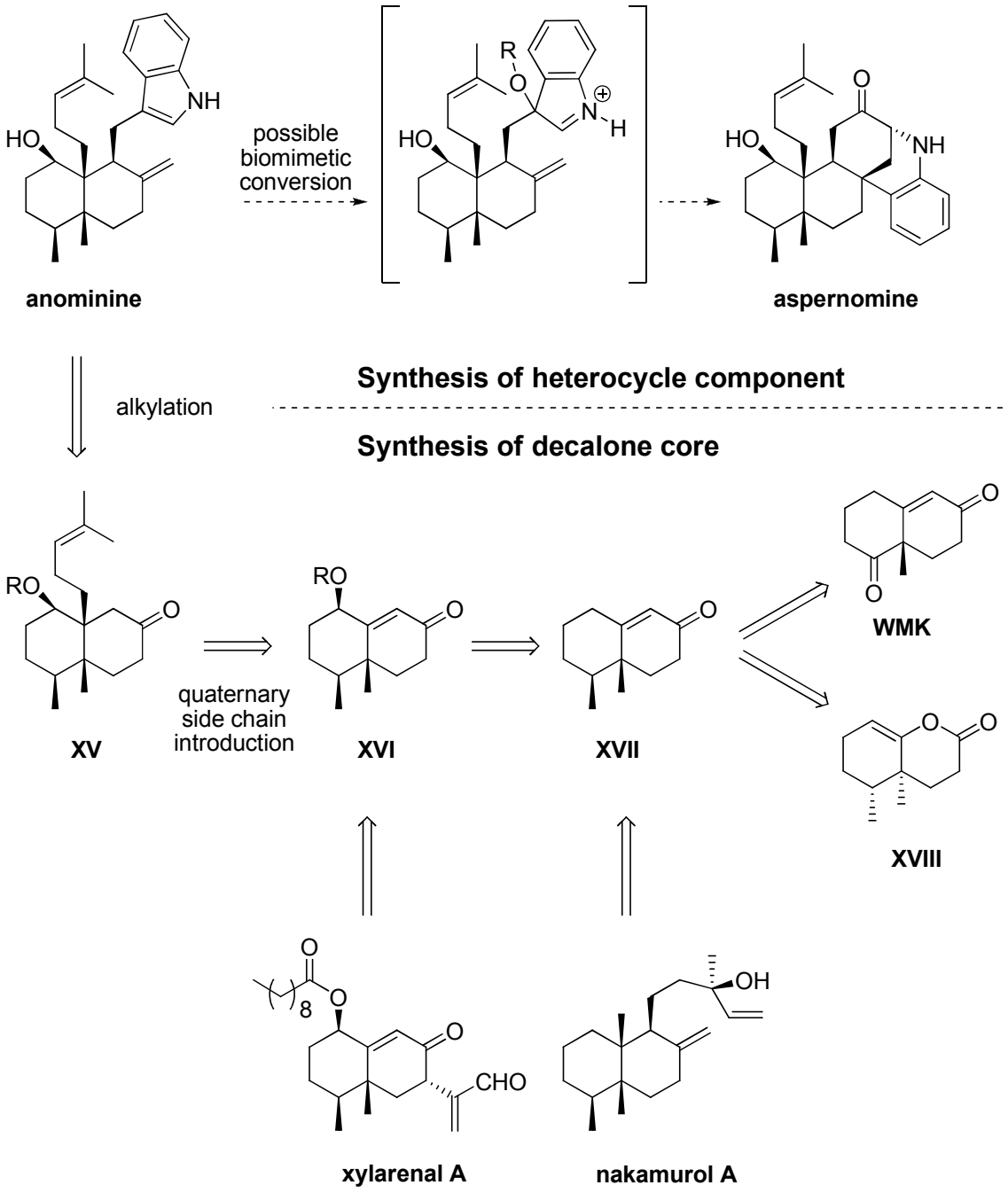


Scheme 1.14 Confirmation Experiment.

1.5.2 Initial Strategy for the Synthesis of Anominine

Our group has traditionally focused on the study and synthesis of natural products with interesting pharmacologic properties. Having in mind that little work has been done on the synthesis of the structurally interesting *Aspergillus* diterpenoids in conjunction with important biological activities made them a focus of interest for our research group. For these reasons, fifteen years ago our group embarked on a project targeting the synthesis of *Aspergillus* natural products and structurally related diterpenoids.

After considering that many of the natural products may be able to be prepared by biogenetic means from anominine as discussed in section 1.4, the main target of the project was the synthesis of the natural product anominine (Scheme 1.15). The initial strategy consisted in taking advantage of the work in the group towards the total synthesis of xylarenal A and nakamurol A. We sought to capitalise on this work by using key intermediates **XVI** and **XVII** developed during these syntheses. As a consequence, the synthesis of anominine would rely on a late introduction of the heterocyclic component on intermediate **XV**, followed by the installation of the quaternary side chain on **XVI**. This product not only serves as a precursor for anominine but also is a building block for the preparation of marine natural products, such as xylarenal A. At the same time, **XVII** has been used as a precursor for nakamurol A. Interestingly, both enantiomeric series could be prepared since **XVII** is obtained either from Wieland-Miescher ketone (WMK) or the enol lactone **XVIII**. With these intermediates being crucial to this initial strategy, now follows a brief summary into their synthesis in the context of the corresponding total synthesis.



Scheme 1.15 Initial Retrosynthetic Analysis.

1.5.3 Nakamurol A Synthesis

Marine sponges *Agelas nakamurai* have proved to be rich sources of unusual diterpenoids with interesting biological activities as well as unique structures (Figure 1.5)[18]. The structure of nakamurol A was elucidated in 1996 although neither its relative configuration at C13 nor its absolute configuration was established. The diterpenoid nakamurol A is made up of a *cis*-decalin embodying four contiguous stereogenic centres and a side chain containing an allylic tertiary alcohol. Its previously unknown skeletal arrangement[19] which has been named thelepogane due to its similarity with the alkaloid thelepoghine[20], is related to that of labdanes and clerodanes (Figure 1.4).[21]

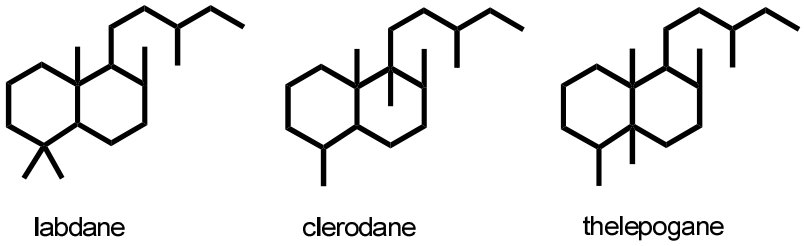


Figure 1.4 Labdane, Clerodane and Thelepogane Skeletal Types.

Interestingly, this particular backbone arrangement of the *cis*-decalin unit, which contains side chains at C4, C5, C8, C9 and C10, is the same as the products isolated from the fungus *Aspergillus* spp.,[22] the marines sponges *Agelas nakamurai* and *Cacospongia mycofijiensis*,[23] the australian grass *Thelepogon elegans*, and some compounds of the Valerianaceae family.[24]

[18] N. Shoji, A. Umeyama, M. Teranaka, S. Arihara; *J. Nat. Prod.*, **1996**, *59*, 448–450.
[19] A compound with the same bicyclic ckeleton was later isolated: T. Iwagawa, M. Kaneko, H. Okamura, M. Nakatani, R. W. M. van Soest; *J. Nat. Prod.*, **1998**, *61*, 1310–1312.
[20] W. D. Crow; *Aust. J. Chem.*, **1962**, *15*, 159–161.
[21] For reviews in this field see: (a) T. Torokoyama; *Synthesis*, **2000**, 611-633. (b) E. A. Klein Gebbink, B. J. M. Jansen, A. de Groot; *Phytochemistry*, **2002**, *61*, 737–770.
[22] J. B. Gloer; *Acc. Chem. Res.*, **1995**, *28*, 343–350.
[23] T. A. Johnson, T. Amagata, K. V. Sashidhara, A. G. Oliver, K. Tenney, T. Matainaho, K. K-H. Ang, J. H. McKerrow, P. Crews; *Org. Lett.*, **2009**, *11*, 1975–1978.
[24] A. Srikrishna, R. Viswajanani, C. Dinesh, *J. Chem. Soc. Perkin Trans. 1*, **2000**, 4321–4327, and references therein.

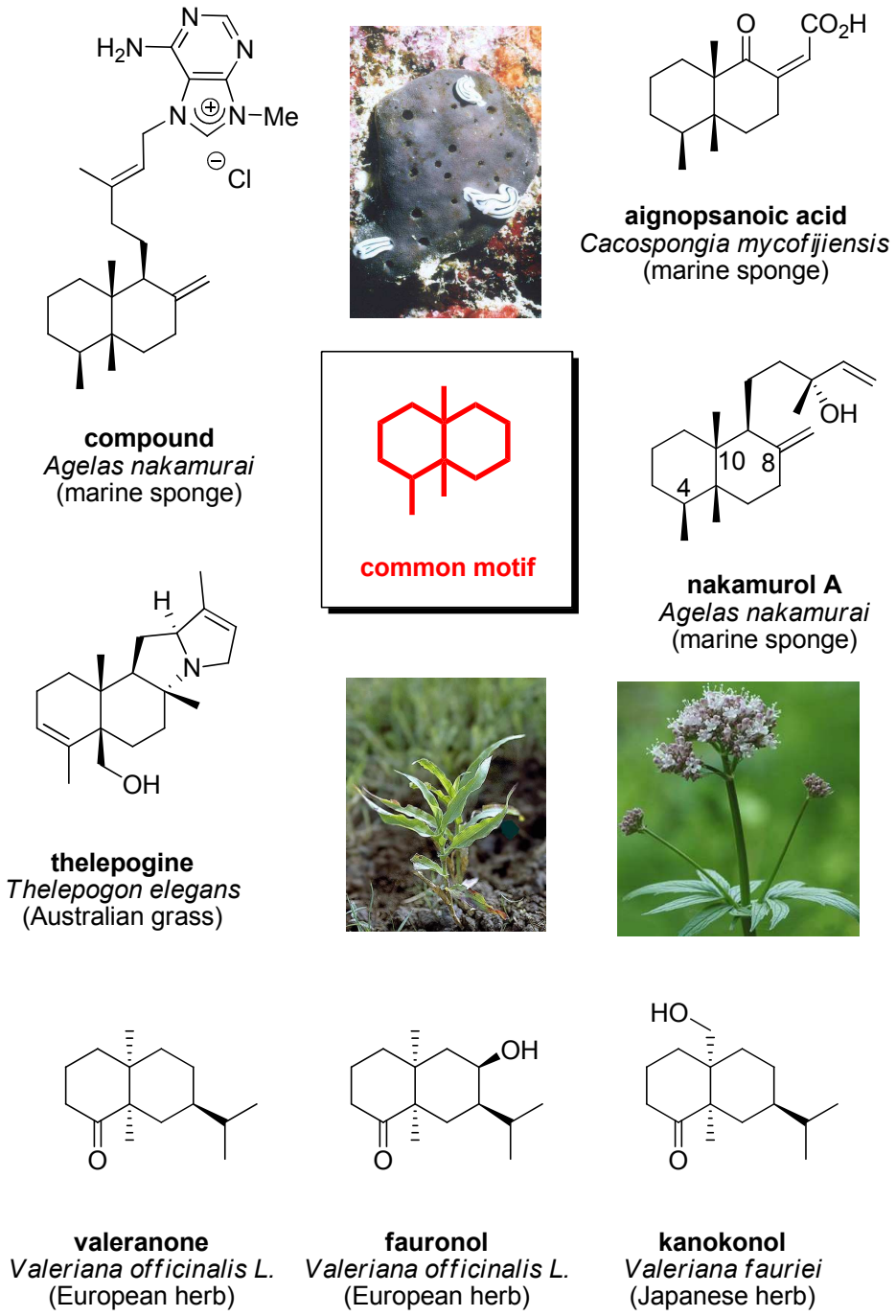
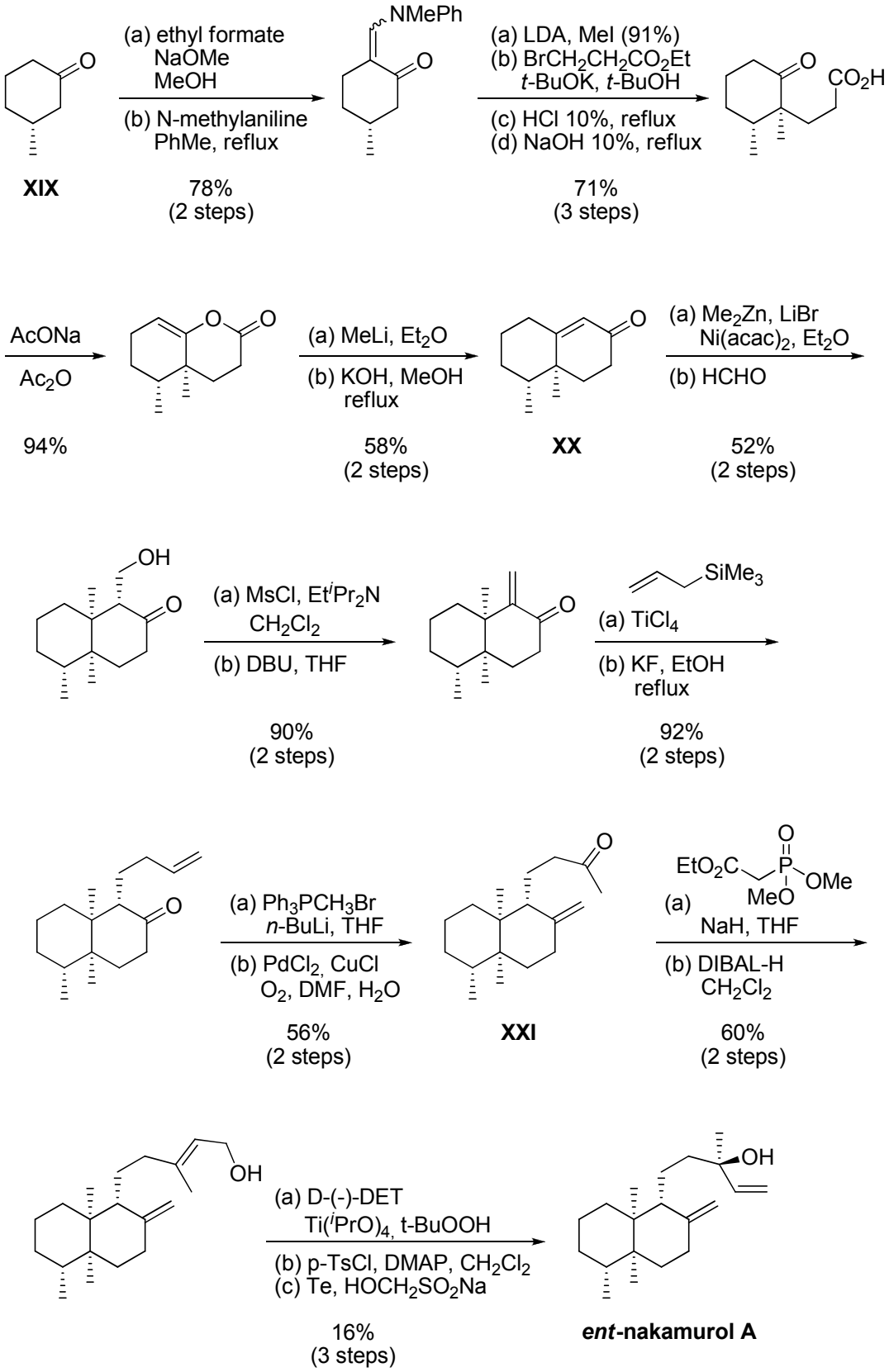


Figure 1.5 Related Diterpenoids.

These types of compounds have attracted our attention not only for the unique carbon skeleton, but also for their interesting biological activities. The synthesis and assignment of absolute configuration of nakamurol A was previously described in our research group[25] and constituted the first entry to the thelepogane skeleton (Scheme 1.16). Absolute configuration was established by commencing the synthesis with the chiral commercially available ketone **XIX**, which was converted to enantiopure **XX** via Piers's protocol[26] following our previously reported procedure[27]. Having the stereocentres at C4 and C5 in the correct relative configuration, next step was the introduction of the C9 and C10 substituents, which were introduced via conjugate addition and trapping of the enolate with formaldehyde. Three-carbon homologation by Sakurai reaction, Wittig reaction on the C8 ketone and Wacker oxidation of the side chain afforded **XXI**. Horner-Wadsworth-Emmons homologation yielded the backbone which was further reduced to the allylic alcohol. The substrate is set to introduce the stereogenic centre via Sharpless epoxidation, and the remaining alcohol was eliminated to give nakamurol A. Determination of the absolute stereochemistry for the first time revealed that the compound prepared was the nonnatural compounds, i.e. *ent*-nakamurol.

[25] (a) J. Bonjoch, J. Cuesta, S. Díaz, A. González; *Tetrahedron Lett*., **2000**, *41*, 5669-5672. (b) S. Díaz, J. Cuesta, A. González, J. Bonjoch; *J. Org. Chem.*, **2003**, *68*, 7400–7406.
[26] E. Piers, R. W. Britton, W. de Waal; *Can J. Chem.*, **1969**, *47*, 4307–4312
[27] J. Cuesta, A. González, J. Bonjoch; *Tetrahedron: Asymmetry*, **1999**, *10*, 3365–3370.

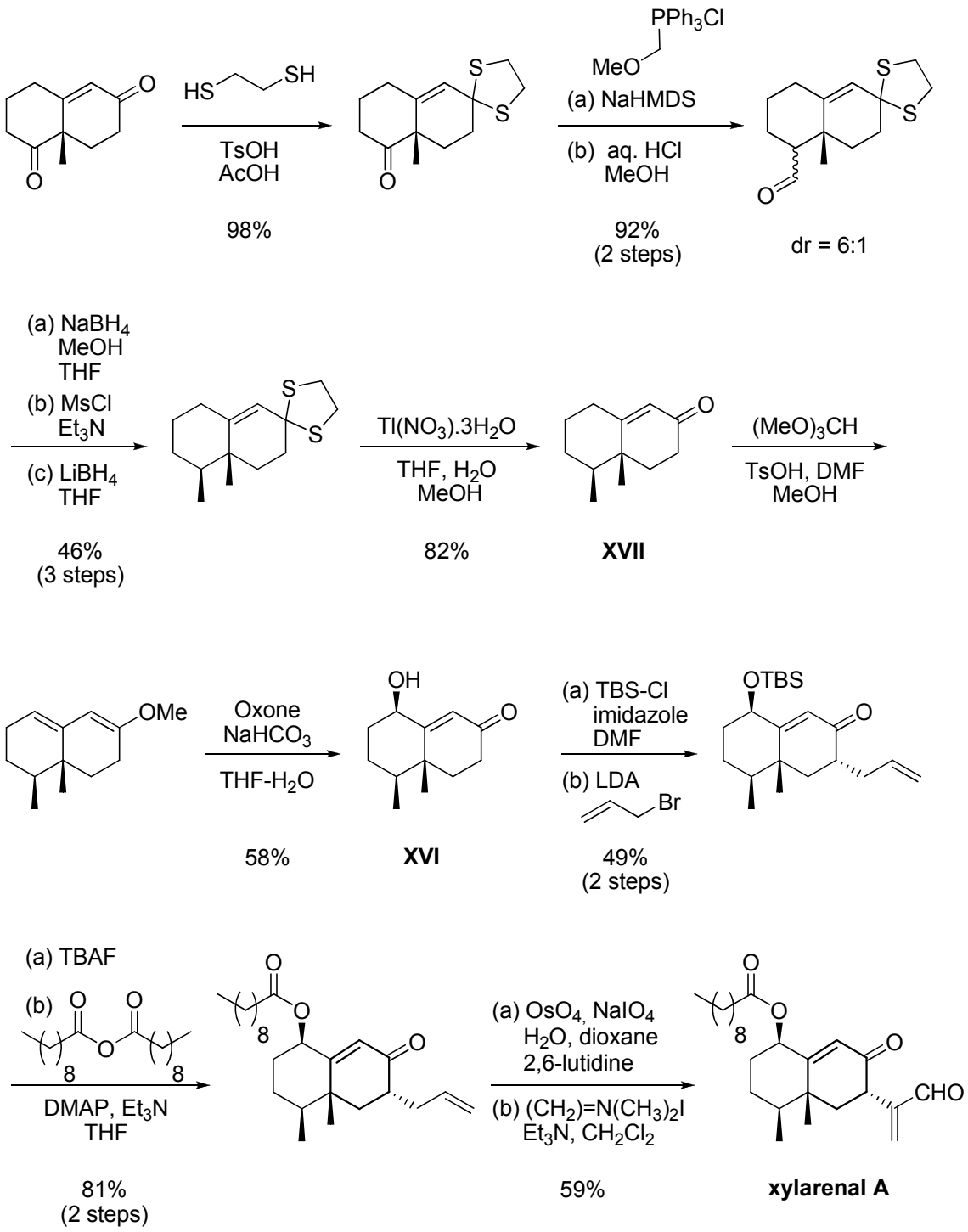


Scheme 1.16 Syntheis of *ent*-Nakamurol A.

1.5.4 Xylarenal A

After the synthesis of nakamurol A, our group embarked on a study towards the synthesis of eremophilane terpenoid xylarenal A, which shares some structural motifs to the former. Xylarenal A is a natural product isolated from the fermentation of the fungal strain *Xylaria persicaria* onto fruits of *Liquidambar styraciflua L*. Although absolute stereochemistry was not yet assigned, the relative one was determined by NMR spectroscopy. The synthetic plan towards (+)-xylarenal A was based on the use of enantiopure Wieland-Miescher ketone as the chiral precursor[28] (Scheme 1.17). Following Paquette's methodology[29] afforded **XVII**, which after δ–oxidation to render **XVIII**, introduction of the lipophillic side chain and the vinylic aldehyde furnished the aforementioned natural product. Building on this approach, the synthetic entry to the nonnatural enantiomer *ent*-xylarenal A was also achieved starting from **XX**, obtained in the synthesis of nakamurol A, and following the same protocol described for the natural one.

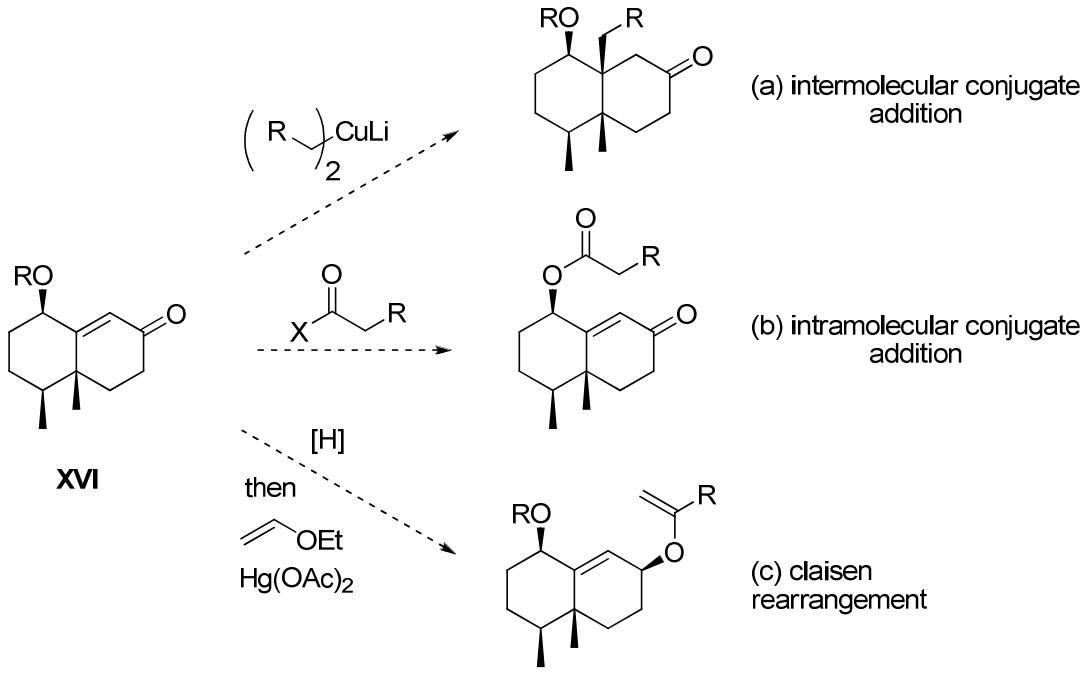
[28] S. Díaz, A. González, B. Bradshaw, J. Cuesta, J. Bonjoch; *J. Org. Chem.*, **2005**, *70*, 3749–3752.
[29] L. A. Paquette, T-Z. Wang, C. M. G. Philippo, S. Wang; *J. Am. Chem. Soc.*, **1994**, *116*, 3367–3374.



Scheme 1.17 Synthesis of Xylarenal A.

1.5.5 Attempts to Install the Quaternary Side Chain of Anominine

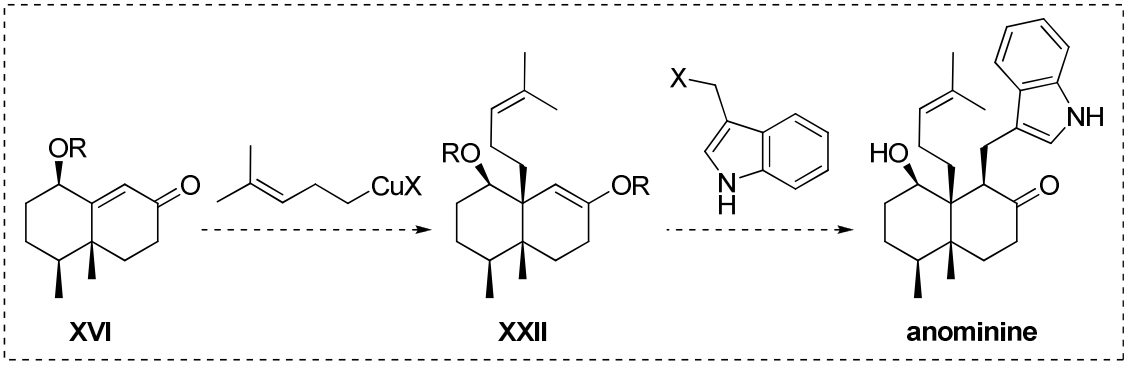
After these total syntheses and with the acquired experience in the preparation of enantiopure polysubstituted decalins our group focused the efforts towards the synthesis of the terpenoid anominine. The initial idea was to find a protocol to build on the methodology developed for the synthesis of the previous natural products. Having established a solid route to the intermediate **XVI**, the next key step would be the installation of the quaternary centre at C20 (anominine biogenetic numbering). For these crucial transformations three different options were envisaged: (a) intermolecular conjugate addition, (b) intramolecular conjugate addition, and (c) Claisen rearrangement of an allylic alcohol (Scheme 1.18).



Scheme 1.18 Methods for Introducing the Quaternary Centre at C-20.

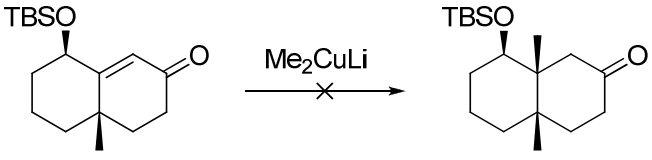
1.5.5.1 Intermolecular Conjugate Addition

The first approach was to install the side chain at C-20 via an intermolecular conjugate addition. The shortest route consisted in the introduction of the homoprenyl through by an organocopper reagent, trapping of the enolate and alkylation with halomethylindole (Scheme 1.19).



Scheme 1.19 Synthetic Plan.

Preliminary tests done by submitting **XVI** to allyltrimethylsilane and titanium(IV) tetrachloride under Sakurai conditions did not give **XXII**, either working with the protected or unprotected alcohol. Furthermore, lithium dimethylcuprate gave the same disappointing results. None of the conjugate addition products was detected, but instead the reduction product was found. One reason to explain this is the high congestion of the decalin convex face, where all substituents block the attack of the nucleophile. This low reactivity is also found in simpler systems using the smaller methylcuprate and lacking C29 methyl (Scheme 1.20).

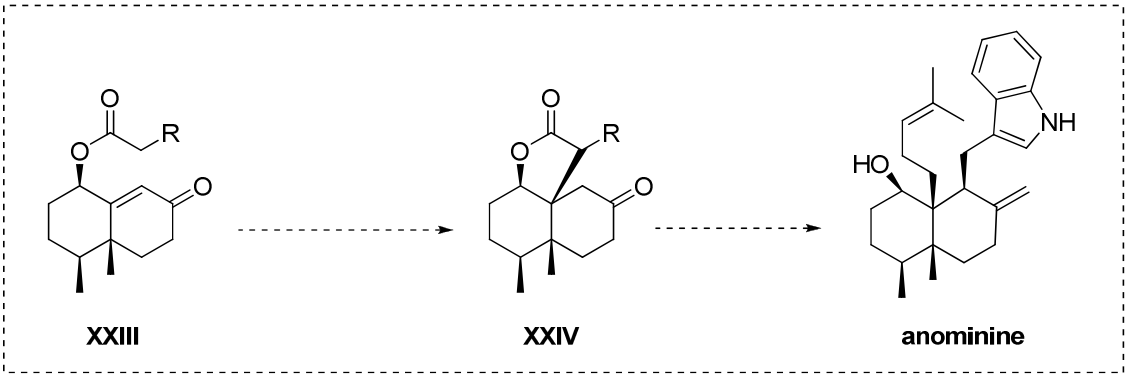


Scheme 1.20 Conjugate Addition Studies on **XXII** Model.

Since any of the experiments did give the desired product we were forced to abandon this approach and try other feasible methodologies.

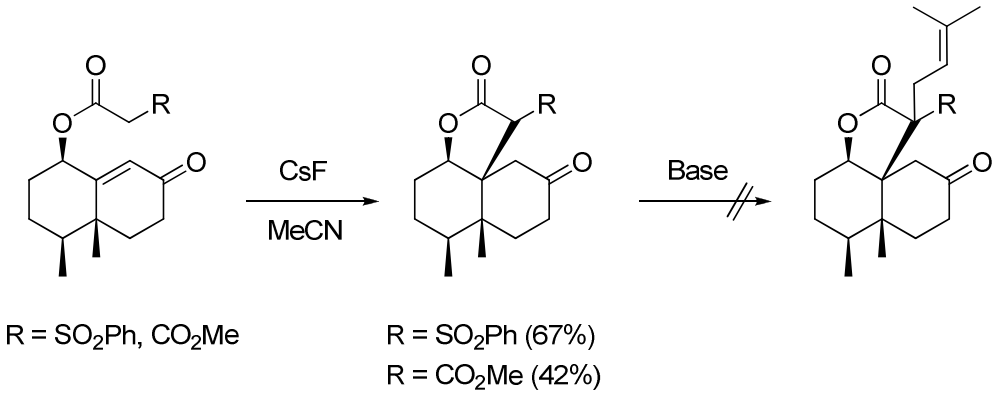
1.5.5.2 Intramolecular Conjugate Addition

In order to avoid the steric bulk, an intramolecular version was examined. The idea was to attach a substituent onto the alcohol group which would act as a protecting group and at the same time act as a tether bringing the nucleofile close to the reactive site (Scheme 1.21). For this approach there were two types of reactivity envisaged: (a) generation of a carbon-centered radical followed by its trapping of the enone; and (b) attack of an activated methylene upon the electrophillic enone moiety.



Scheme 1.21 Synthetic Plan.

A diversity of radical methodologies were explored but none of them resulted in a successful result.[30] However, in the ionic approach the side chain is added at the beta position of the enone, giving the desired bridged tricyclic structure (Scheme 1.22). The next crucial step was the elongation of the side chain, but unfortunately, none of the bases employed (K_2CO_3, NaH, Cs_2CO_3, CsF or MeONa) gave the desired product. Furthermore, attempts to work with these sterically congested compounds was unsuccessful and therefore this approach was abandoned.

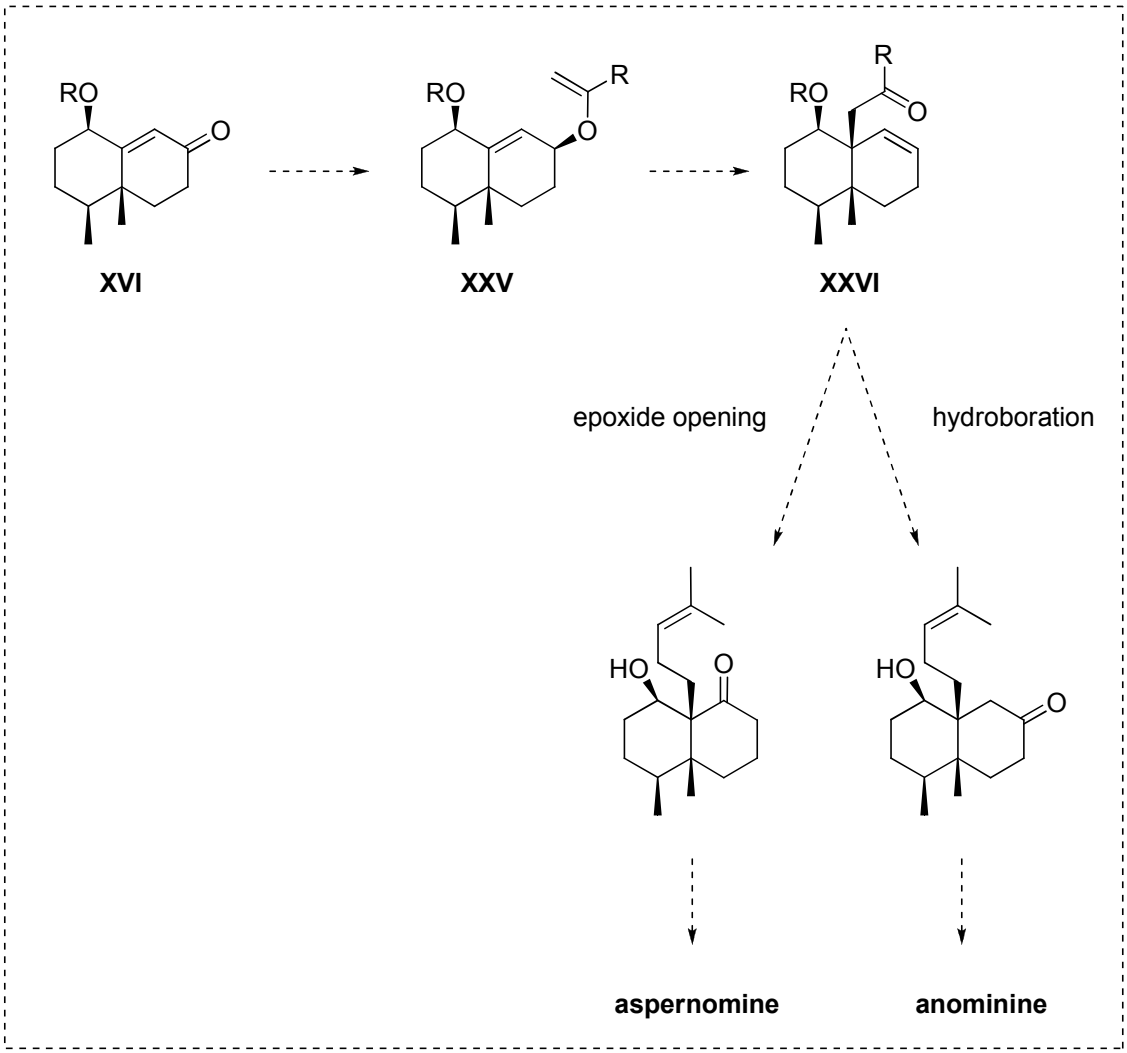


Scheme 1.22 Synthetic Plan.

[30] J. Cuesta PhD thesis, University of Barcelona, **2000**, p. 47.

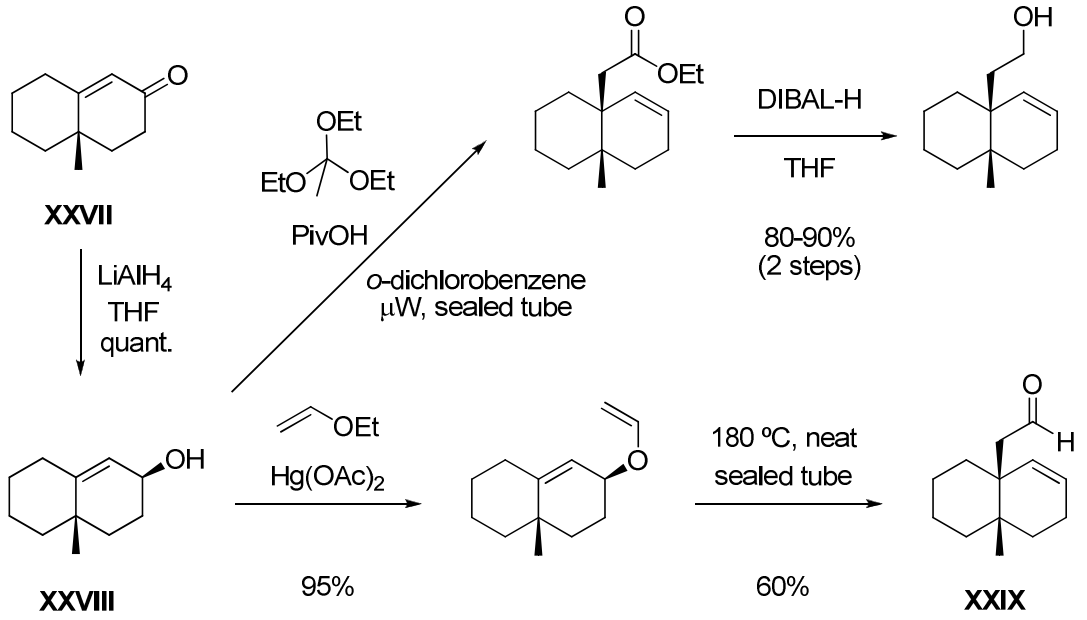
1.5.5.3 Claisen Rearrangement Process. Model Studies

The third possibility envisaged was the Claisen rearrangement of an allyl vinyl ether such as **XXV**, which would give the desired core **XXVI** with all the stereocentres in place (Scheme 1.23). The resulting alkene could be either epoxidised or hydroborated to give the aspernomine or anominine nuclei.



Scheme 1.23 Claisen Rearrangement Synthetic Plan.

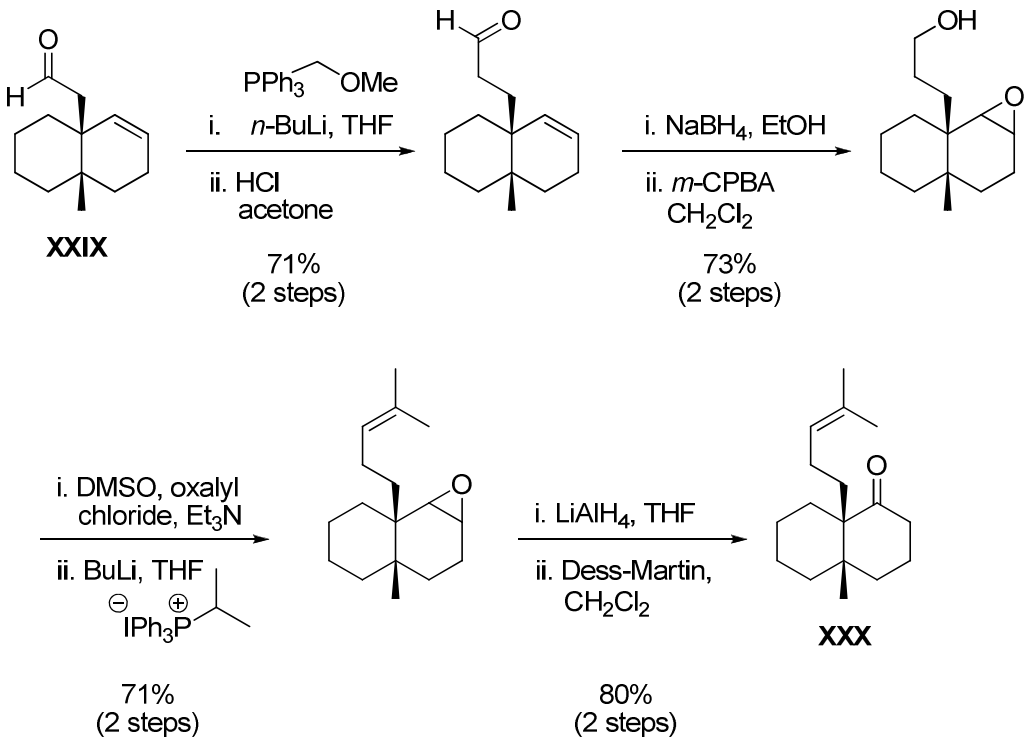
Before trying to do the rearrangement in **XXV** it was decided to develop the methodology on a simpler model which could allow us to gain experience with this reaction (Scheme 1.24). The model chosen was **XXVIII**, which was readily prepared from **XXVII** on a large scale according to a known procedure.[31] While working under thermal conditions gave poor yields,[32] the use a microwave reactor boosted the reaction efficiency. An alternative method using classical thermal Claisen conditions rendered **XXIX** in moderate yield.



Scheme 1.24 Model Claisen Rearrangement Tests.

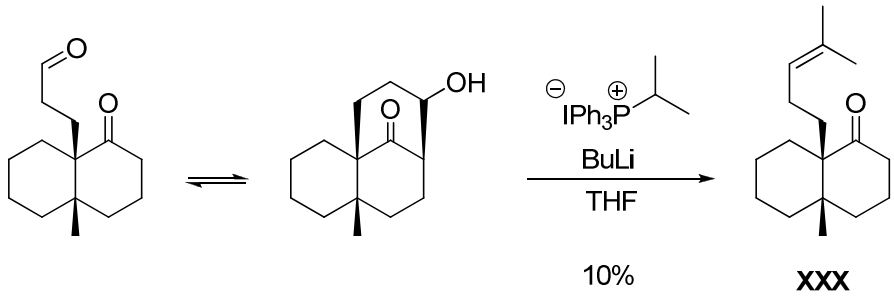
Attempts to explore the side chain elongation and functionalisation on **XXIX** were far from straightforward (Scheme 1.25). It took eight steps to elaborate the complete side chain and the nuclei functionality from the rearranged product **XXIX** to the final product **XXX**.

[31] C. H. Heathcock, J. E. Ellis, J. E. McMurry, A. Coppolino, *Tetrahedron Lett.,* **1971***, 12*, 4995–4996.
[32] **XXVIII**, triethyl orthoformate, pivalic acid at 160 °C gave 5% of the rearranged ester.



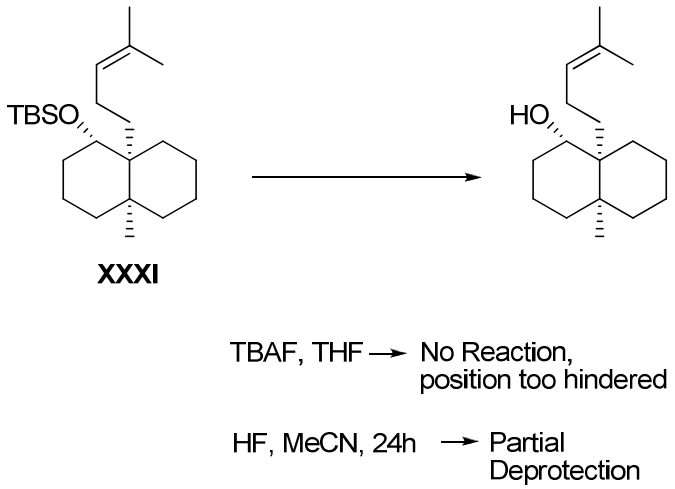
Scheme 1.25 Chain Elongation Tests.

Another drawback is the necessity to work with protected ketones and alcohols to avoid intramolecular aldols and hemiacetalisations (Scheme 1.26).



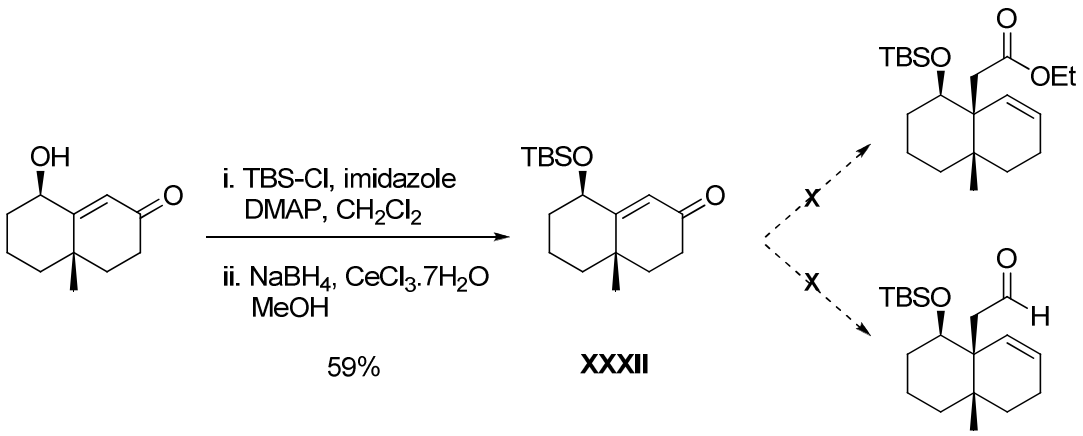
Scheme 1.26 Formation of a Hemiacetal.

Finally, some information about the choice of the alcohol protecting group was collected. During the course of this study the compound **XXXI** was prepared with a TBS ether α to a quaternary centre. Attempts to remove it proved to be very difficult (i.e. HF, 24 h), making it a bad choice due to its extreme stability (Scheme 1.27). This indicated that the less resistant triethylsilyl (TES) group might be an ideal candidate thus balancing well stability and ease of removal.



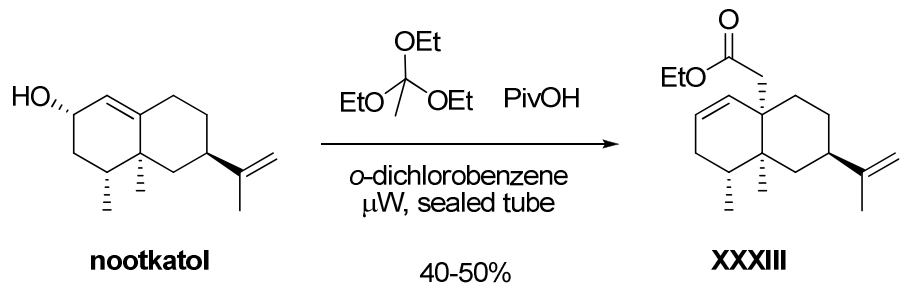
Scheme 1.27 Attempted TBS Group Removal.

After successfully appling the Claisen methodology on **XXVIII** it was necessary to study the rearrangement on a more complex model such as **XXXII** (Scheme 1.28). The molecule has an extra TBS ether and was only lacking one methyl from **XVI**. No rearranged product was found under the successful conditions assayed before, presumably due to the steric effect of the TBS substituent contiguous to the ring fusion, which blocks the face making disfavoured the sigmatropic rearrangement. It could be imagined that the rearrangement with the needed precursor for the total synthesis would be, at least, as difficult as with the model, and as a consequence, the Claisen rearrangement approach had to be abandoned.



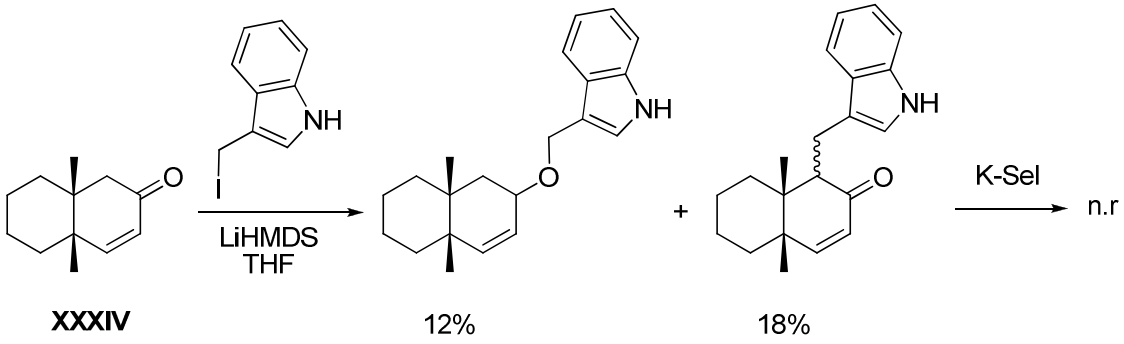
Scheme 1.28 Model Claisen Rearrangement Tests.

We also tested the methodology on a more elaborated substrate from the chiral pool (Scheme 1.29). Nootkatone, a component of grapefruit, was reduced under Luche's conditions to give nootkatol, which was subsequently submitted to our optimised microwave conditions for the Claisen rearrangement furnishing **XXXIII** in moderate yields. Despite having the core of anominine in only two steps from commercial sources and three of the five stereocentres in place, we chose not to continue with this approach for the following: (a) the elaborate sequence that would require for degrading the isopropylene unit and installing the required functionality at the B ring; (b) the unavailability of the unnatural enantiomer, making impossible to extrapolate the methodology to the other enantiomer if required; and (c) the relative expensive price (71 €/g) of the chiral starting material. However, after many setbacks this example gave a proof of concept of an idea that was becoming clear: *namely that the second quaternary stereocentre had to be introduced prior to the installation of the required alcohol at C19, which would have to be moved into place later by a transposition reaction*.



Scheme 1.29 Claisen Rearrangement Test on Nootkatol.

The introduction of the indole moiety was also studied (Scheme 1.30). By alkylating enone **XXXIV** (used as a simpler model)[33] with 3-iodomethylindole gave a mixture of the *O*-alkylation product along with the desired compound in low overall yield. The close proximity of the α-carbon to the quaternary centre makes this position quite hindered to attack the iodoindole, and consequently, the *O*-alkylation become a substantial side reaction. Subsequent 1,4-reduction with K-Selectride® resulted in no reaction indicating once again that functionalities in close proximity to the methyl quaternary centres (what effectively characterises these family of natural products) results in a reduced reactivity or complete deactivation of the group in question.

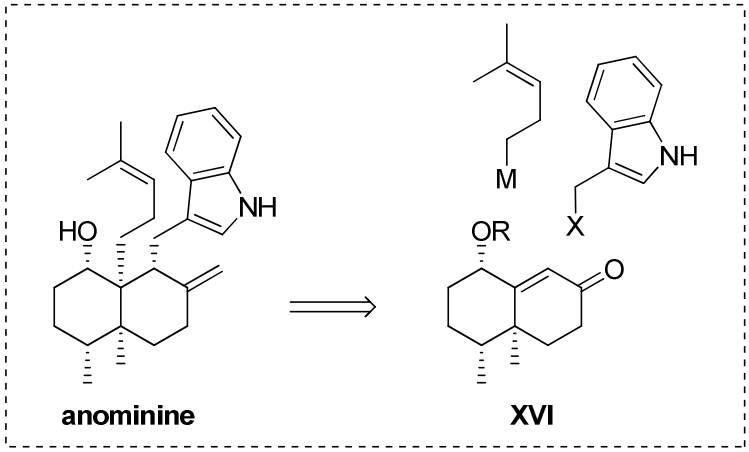


Scheme 1.30 Alkylation Test on **XXXIV**.

[33] This was prepared from **XXVII** by lithium dimethylcuprate addition followed by IBX oxidation.

1.6 State-of-the-Art and Objectives

In the last decade, our research group embarked on the synthesis of *Aspergillus* diterpenoids, beginning its study in Javier Cuesta PhD thesis. In this work, a methodology for the preparation of either (+)-**XVI** or (–)-**XVI** was developed starting from (+)-Wieland-Miescher ketone and (*R*)-3-methylcyclohexanone, respectively. Having both enantiomers of **XVI** in hand, a synthetic plan towards anominine was envisaged (Scheme 1.31), which relied on the conjugate addition of a nucleophillic isohexenyl species and trapping of the enolate with a gramine derivative.



Scheme 1.31 Retrosynthetic Plan towards Anominine.

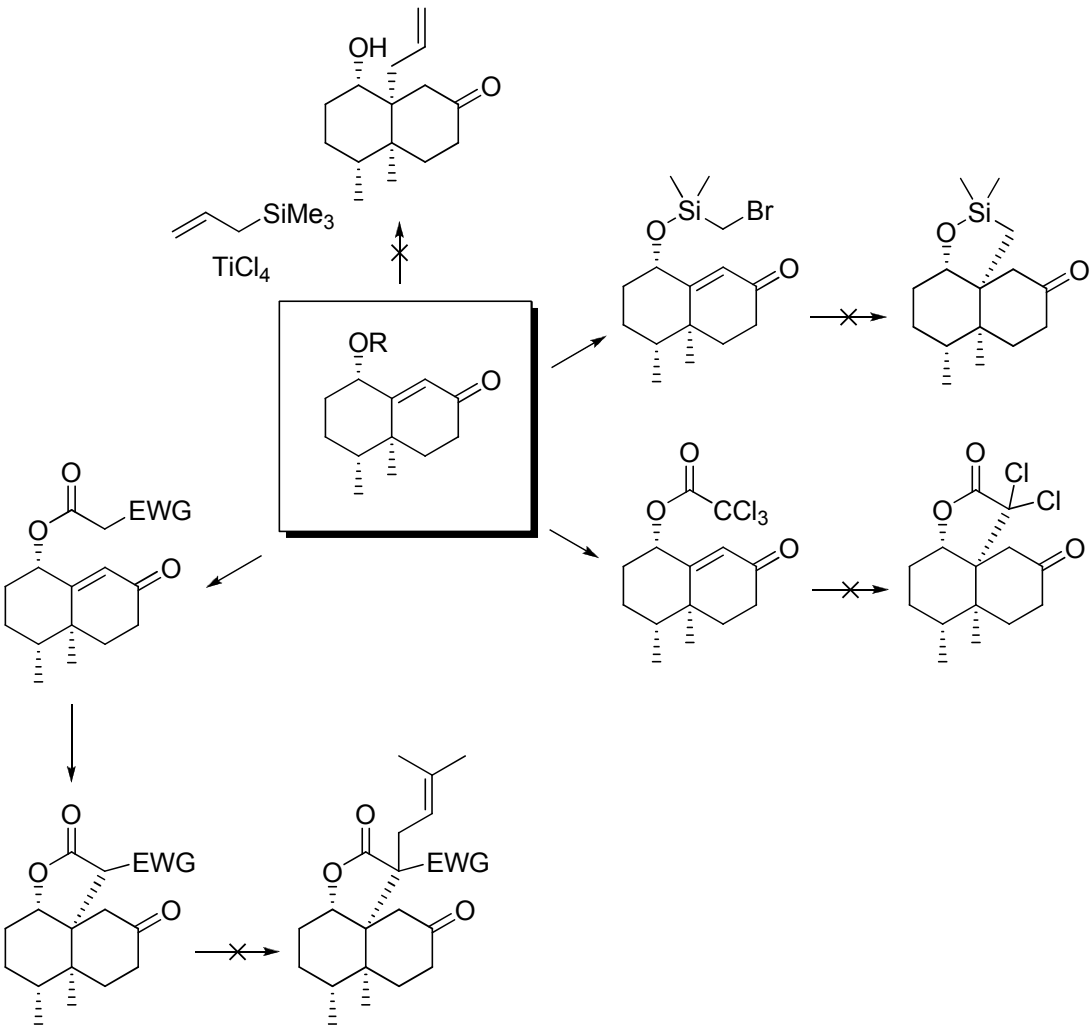
However, **VI** showed an extreme steric hindrance which avoided the introduction of a side chain in all the strategies that were employed (Scheme 1.32):

- Impossibility to introduce side chain via intermolecular conjugate addition under Sakurai conditions.

- The intramolecular version of this reaction whereas a substituent is appended onto the oxygen function (EWG = CO_2Me, SO_2Ph) gave satisfactory results but further elongation of the chain and double decarboxylation was impossible to achieve.

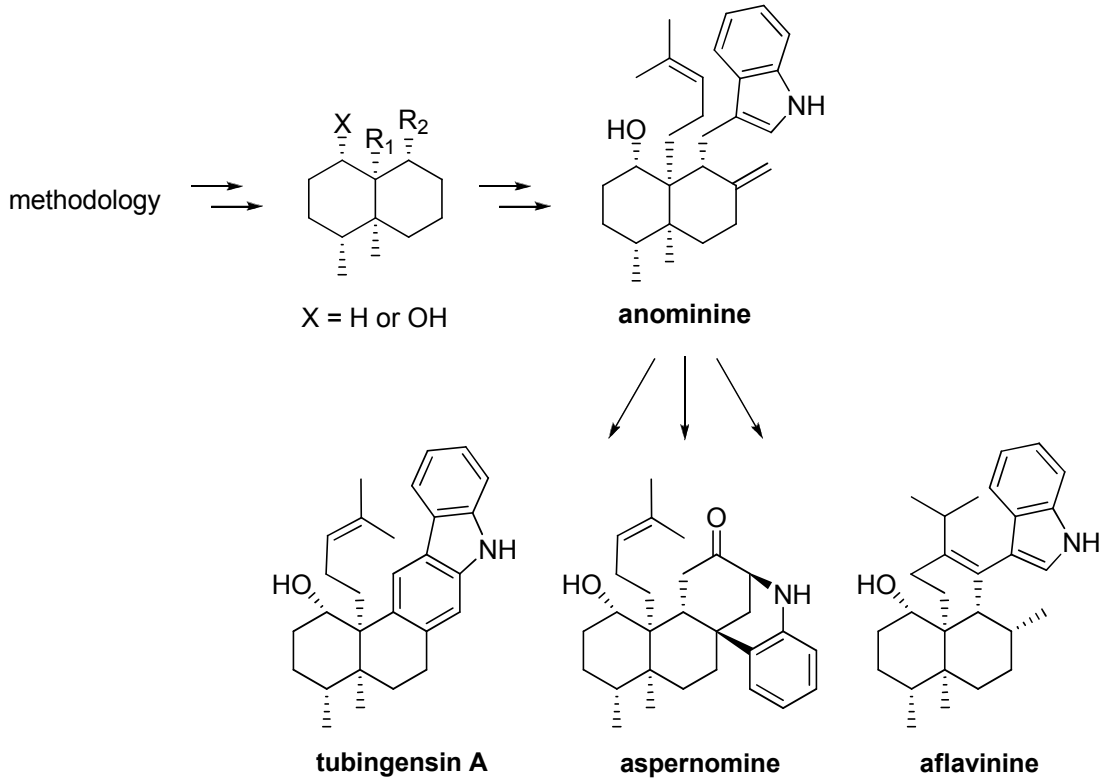
- Generation of a carbon-centred radical and its trapping by the endocyclic olefin did not result in the formation of the desired *cis*-fused decalone.

- Claisen rearrangement worked using a simpler model but failed when applied to a more elaborated substrate.



Scheme 1.32 Summary of the Attempted Routes towards Anominine.

Since the introduction of the two quaternary substituents is the principal limitation, it seems essential to install both of them prior to elaboration of the remaining functionalities in the highly-congested decalin. Therefore, in the present thesis we planned to develop a new strategy for the synthesis of enantiopure *cis*-1,4a,5,8a-polyalkylnaphthalenes that could be used to prepare the diterpenoid anominine as the principal objective. Furthermore, it was hoped that this work would lay the ground work to access to related diterpenoids isolated from the sclerotium of other species of *Aspergillus* such as tubingensin A, aspernomine and aflavinine, either by biomimetic synthesis from anominine, or *de novo* synthesis from late synthetic intermediates (Scheme 1.33).



Scheme 1.33 Main Objectives.

Since a lot of the initial work would be based on the use of simpler model substrates based around the nakamurol A bicyclic system, we hoped that these intermediates could also have a second use in total synthesis and be directed towards simpler diterpenoids isolated from *Agelas nakamurai* and *Cacospongia mycofijiensis* marine sponges, such as the products depicted in Figure 1.5.

CHAPTER 2.

MODEL STUDIES

Org. Biomol. Chem., **2008**, *6*, 772–778.

2.1 Introduction

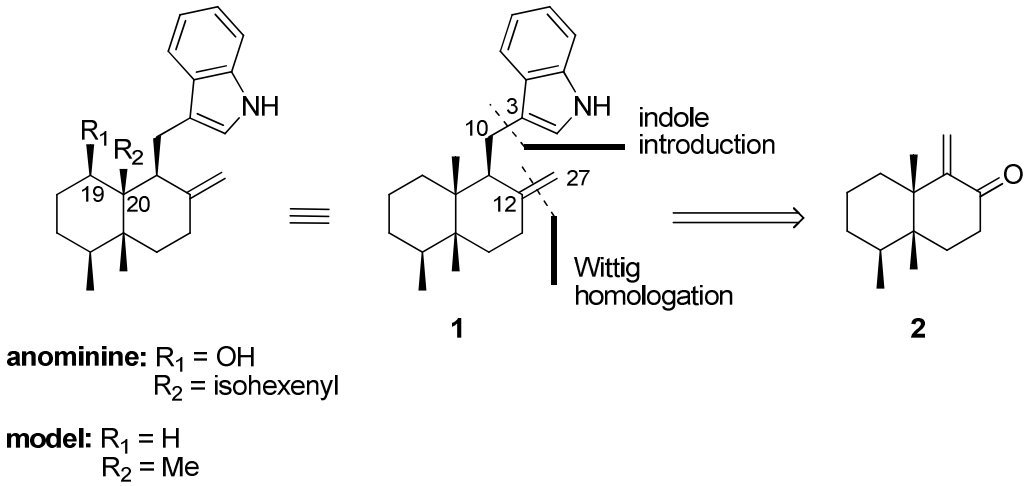
As outlined in the summary of the previous chapter, none of the methodologies tested (Claisen rearrangement, inter- and intramolecular conjugate addition) which attempted the introduction of the side chain at C20 late in the synthesis were deemed viable strategies. With this information in hand, we decided to develop a new strategy using a model of anominine, which would be focused on two key concepts:

- Early introduction of the two quaternary stereocentres.

- Inserting the adequate functionality on the skeleton to effectively introduce the heterocyclic unit.

2.2 Synthesis of Anominine Polycyclic Skeleton

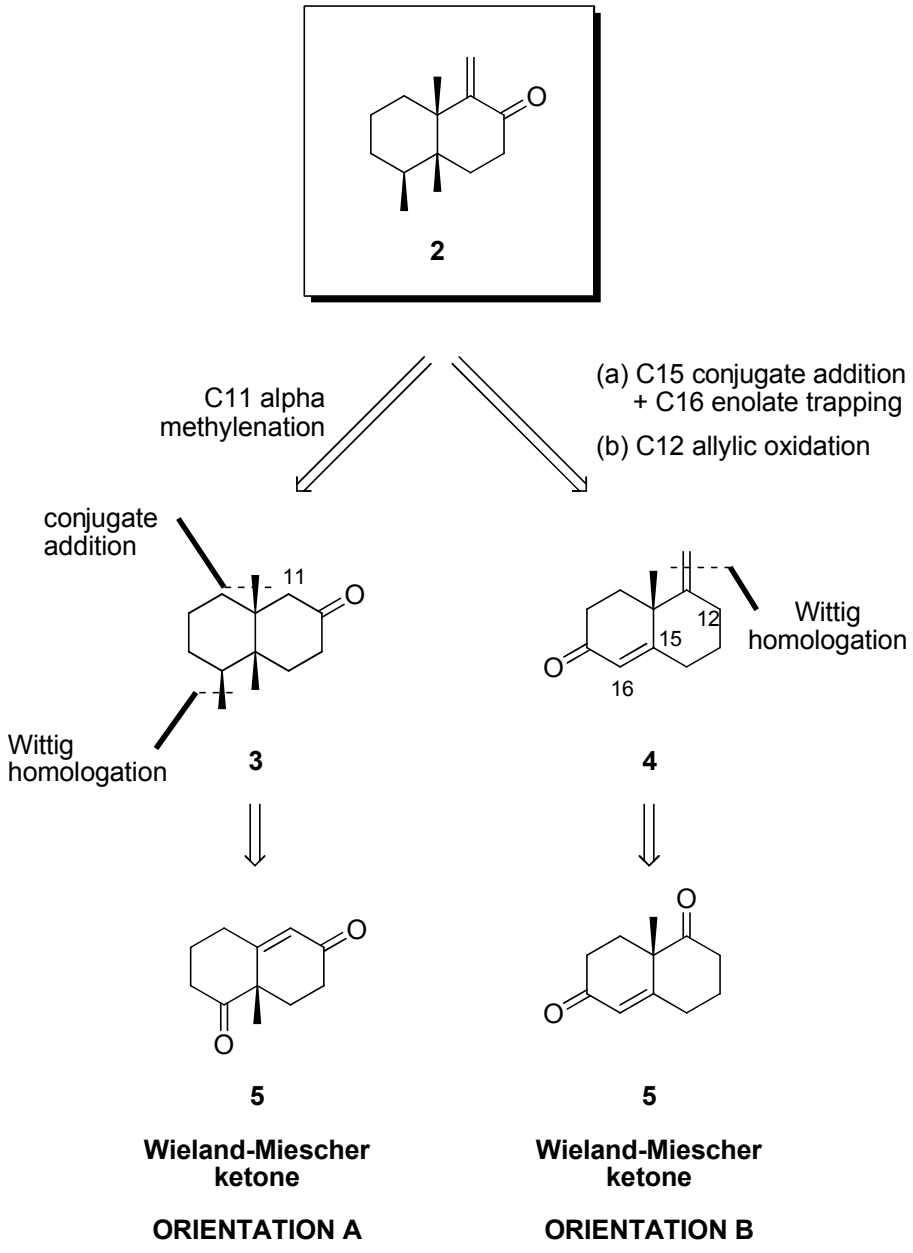
The model target would be lacking the hydroxyl group at C19 and the isohexenyl side chain at C20 (Scheme 2.1). Regarding anominine synthesis, since the indole moiety could not be introduced by alkylation with a simpler model, a conjugate addition upon an enone was envisaged. This, at the same time would have the correct functionality to install the exocyclic methylene at C12 by a standard Wittig homologation and would lead to an intermediate such as **2**, which is the key intermediate in our research group synthesis of nakamurol A. However, as stated the synthesis of **2** would differ from our previous synthesis in that the two quaternary centres would be established at the outset of the synthesis.



Scheme 2.1 Anominine Model **1** Retrosynthetic Analysis.

At this point, a potential starting material such as Wieland-Miescher ketone (WMK) was identified as a chiral retron subunit[1] of the important subgoal **2** (Scheme 2.2). However, two orientations of WMK are possible, since its functionalisation can lead to the desired subtarget via different synthetic strategies. On one hand, in orientation A **2** can be disconnected at C10-C11 bond through an alpha methylenation giving ketone **3**. Conjugate addition at C20 and Wittig homologation at C16 would provide WMK building block. On the other hand, in orientation B **2** can be retrosynthetically traced back to **4** via allylic oxidation at C12, conjugate addition and enolate trapping would install C15 and C16 methyl substituents, and ketone functional group removal at C17. Finally, Wittig olefination at C11 would provide WMK as a starting material but with a 180° rotation with respect to the other orientation. A further aim of this model synthesis was not only to gather methodological information (transformations, reagents, conditions, protecting groups) concerning the synthetic pathway, but also which orientation would be most favourable to access to the natural product anominine.

[1] E. J. Corey, X-M. Cheng. *The Logic of Chemical Synthesis*; John Wiley and. Sons, Inc., New York, **1989**, p. 33.

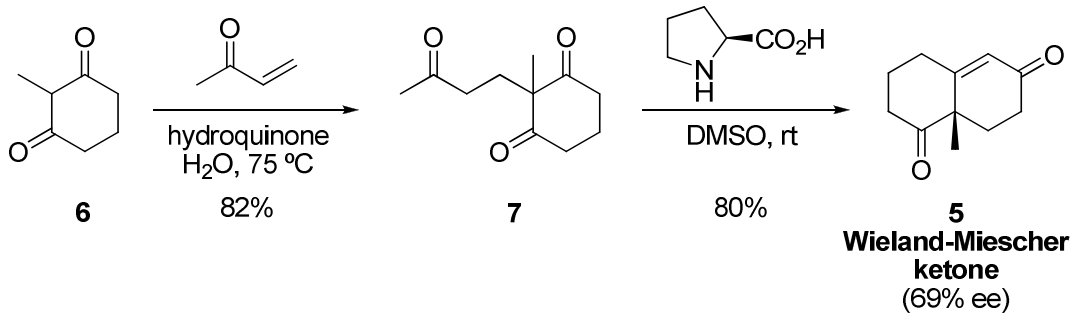


Scheme 2.2 Two Orientations of WMK in Anominine Synthesis.

Both approaches were done in parallel, chronologically at the same time, but for the sake of clarity they will be discussed separately.

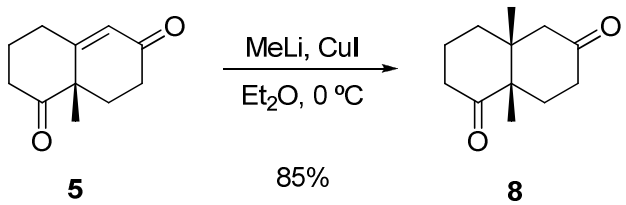
2.2.1 Orientation A

Model synthesis started from commercially available 2-methyl-1,3-cyclohexanedione (**6**), which was transformed to WMK in 66% overall yield and 69% ee following Harada's protocol[2] (Scheme 2.3). Work-up procedure for the Michael step proved to be difficult due to the use of 2 equivalents of methyl vinyl ketone (MVK), which polimerised to give a sticky oily residue. To the resulting crude material was added 10 mol% of L-Pro which after stirring at rt for 6 days furnished optically active WMK. Since we only wanted to validate the methodology towards both natural products, WMK was used in racemic form.[3]



Scheme 2.3 Preparation of Wieland-Miescher Ketone.

Addition of lithium dimethylcuprate to WMK smoothly furnished *cis*-decalin **8** in a diastereoselective manner (Scheme 2.4).

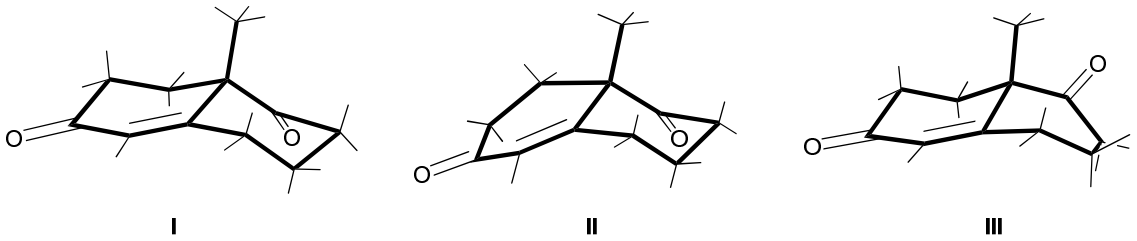


Scheme 2.4 Organocopper Addition upon WMK.

[2] N. Harada, T. Sugioka, H. Uda , T. Kuriki, *Synthesis*, **1990**, 53–56.

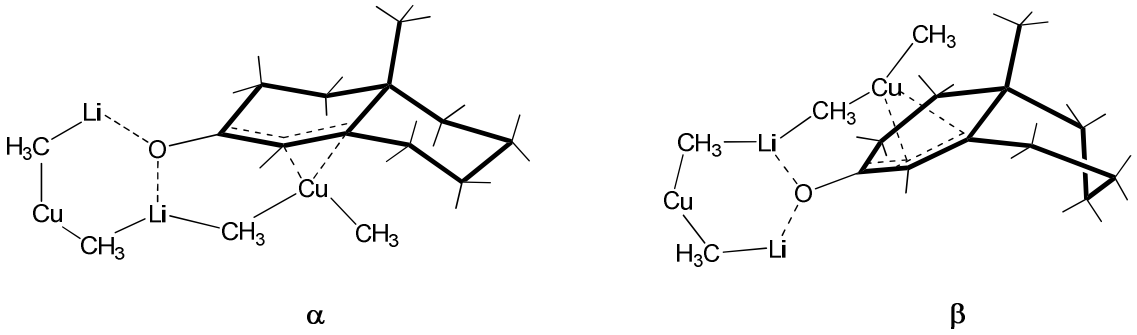
[3] Initially, several crystallisations were done to obtain enantiopure for future total synthesis projects. In order to give utility to the racemic discarded material, it was used in the model synthesis. The absolute stereochemistry is arbitrarily depicted as *S* to be homogenous with the configuration of the products of Chapter 3 and Chapter 4.

Although these empirical results are well-known,[4] its mechanistic rationalisation is yet to be fully understood. The conformation of WMK in solution is known, being **I** (relative energy 0 kcal/mol, 87% population), **II** (relative energy 1.2 kcal/mol, 11% population) and **III** (relative energy 2.1 kcal/mol, 2% population) its major conformers[5] (Scheme 2.5, proton atoms are omitted for the sake of clarity).



Scheme 2.5 Low-Energy Conformations of WMK.

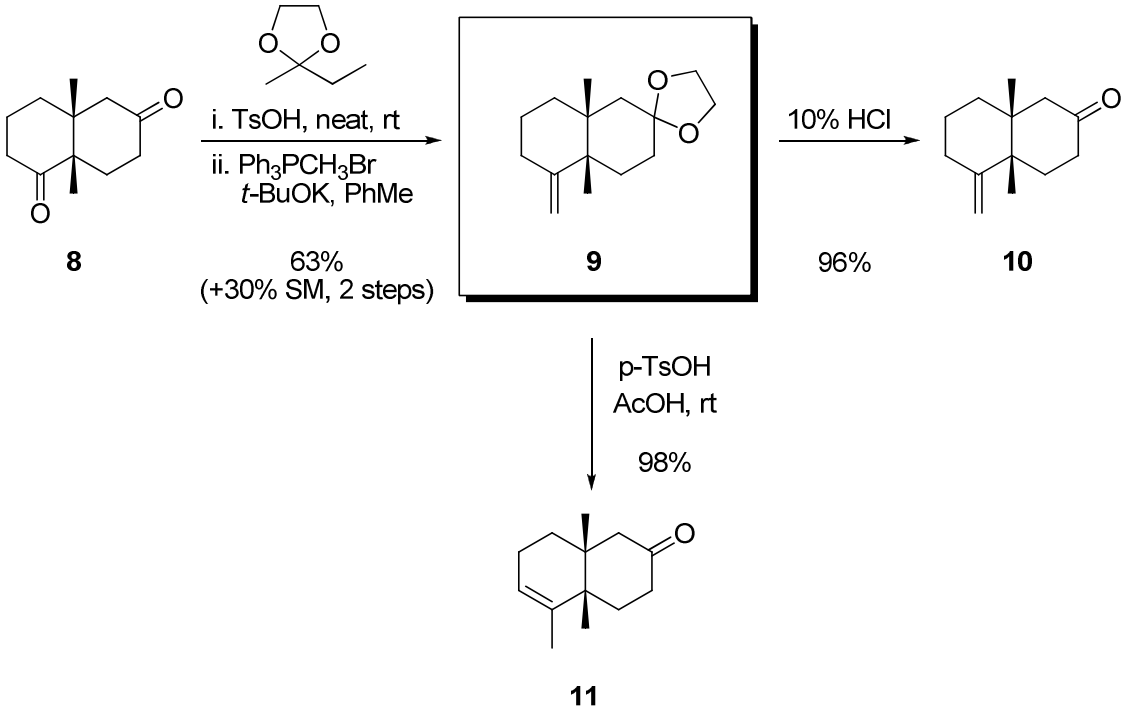
Despite the π-complex intermediates that have been identified and characterised,[6] the rationale behind the reaction mechanism is not yet fully understood. It has been proved that β-face π-intermediate is the most stable and populated species (Scheme 2.6), leading to the exclusive formation of β-methyloctalones.



Scheme 2.6 Conformations of π-complex intermediates of WMK-$(Me_2CuLi)_2$.

[4] (a) B. Breit, P. Demel, In *Modern Organocopper Chemistry*; N. Krause, Ed.; Wiley-VCH: Weinheim, 2002. (b) J. A. Marshall, W. I. Fanta, H. Roebke, *J. Org. Chem.*, **1965**, *31*, 1016–1020. (c) J. Kabbara, S. Flemming, K. Nickisch, H. Neh, J. Westermann, *Liebigs Ann.*, **1995**, 401–406.
[5] A. Aamouche, F. J. Devlin, P. J. Stephens, *J. Am. Chem. Soc.*, **2000,** *122*, 7358–7367
[6] W. Henze, T. Gärtner, R. M. Gschwind, *J. Am. Chem. Soc.*, **2008**, *130*, 13718–13726.

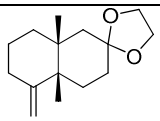
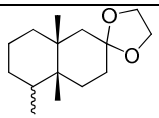
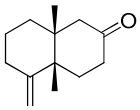
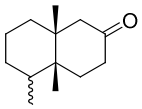
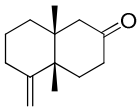
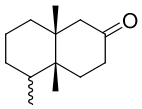
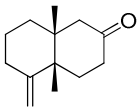
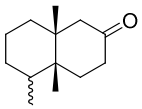
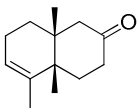
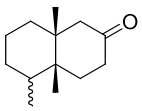
Chemoselective protection of the less hindered carbonyl of **8** was accomplished using 2-ethyl-2-methyl-1,3-dioxolane in acid medium, and subsequent Wittig methylenation of the remaining carbonyl group gave the *cis*-dimethyl decalin **9** (Scheme 2.9). The initial idea was to hydrogenate the double bond hoping that, both angular methyl substituents could do a facial discrimination allowing us to obtain exclusively the all-*cis* trimethyl-substituted scaffold of the model subtarget **2**.



Scheme 2.9 Preparation of Substrates for Hydrogenation.

Hydrogenation of **9** employing palladium on charcoal gave quantitatively the reduced product but with a 1:3 *syn–anti* diastereoselectivity (Table 2.1, Entry 1). However, a reversed selectivity was found when ketone **10**, obtained by hydrolysis of **9** (10% aqueous HCl), was used as the substrate (Entry 2). The *cis–trans* ratio was further improved by using Wilkinson's catalyst,[7] which resulted in a 2:1 ratio (Entry 3). The diastereoselectivity was improved even further by employing Adam's catalyst[8] (Entry 4), but still significant amounts of the undesired product were formed. Hoping that an endocyclic rather than exocyclic double bond might increase the selectivity further, we attempted the hydrogenation of **11**, isomerised by acid treatment of **9** using TsOH and AcOH. Unfortunately the hydrogenation failed, probably due to extreme steric hindrance. Since the reduced product could not be separated by chromatography, we decided to prepare the required intermediate **2** by an alternative route.

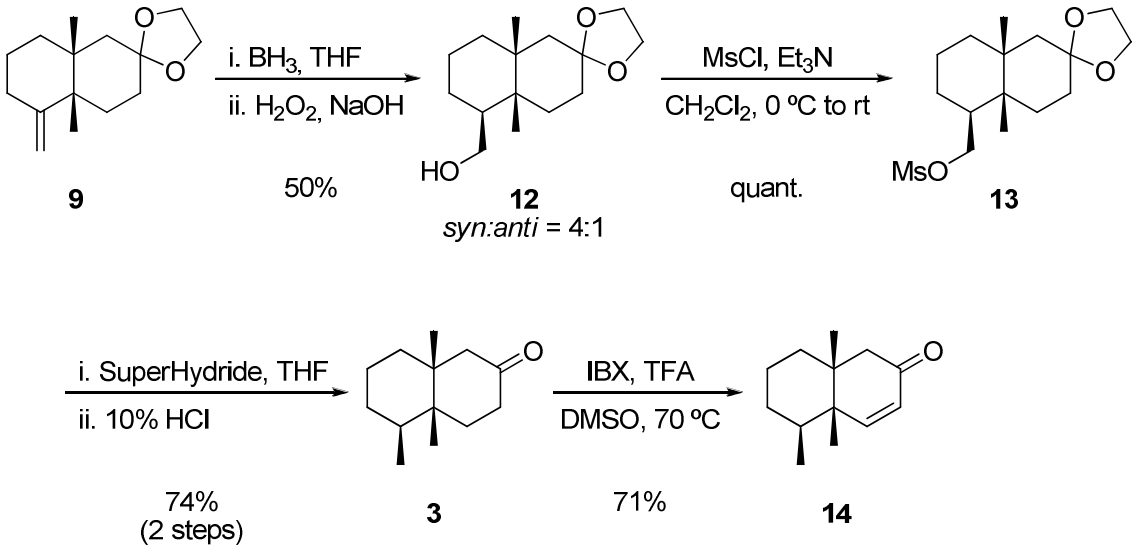
Table 2.1 Hydrogenation Studies.

Entry	Alkene	Conditions	Product	Yield	*syn*:*anti*[a]
1		Pd/C (30% in mass), H_2 (10 atm), CH_2Cl_2, rt, 1 d		quant.	1 : 3
2		Pd/C (70 mol%), H_2 (30 atm), CH_2Cl_2, rt, 1 d		quant.	1.5 : 1
3		$(Ph_3P)_3RhCl$ (1 mol%), H_2 (30 atm), PhH, rt, 3 d		quant.	2 : 1
4		PtO_2 (10 mol%), H_2 (30 atm), CH_2Cl_2, rt, 1 d		quant.	3 : 1
5		PtO_2 (10 mol%), H_2 (30 atm), CH_2Cl_2, rt, 1 d		n.r	–

[a] Determined by integration of the corresponding signals in ^{1}H-NMR.

[7] T. Ling, F. Rivas, E. A. Theodorakis, *Tetrahedron Lett.*, **2002**, *43*, 9019–9022.
[8] A. K. Cheung, R. Murelli, M. L. Snapper, *J. Org. Chem.*, **2004**, *69*, 5712–5719.

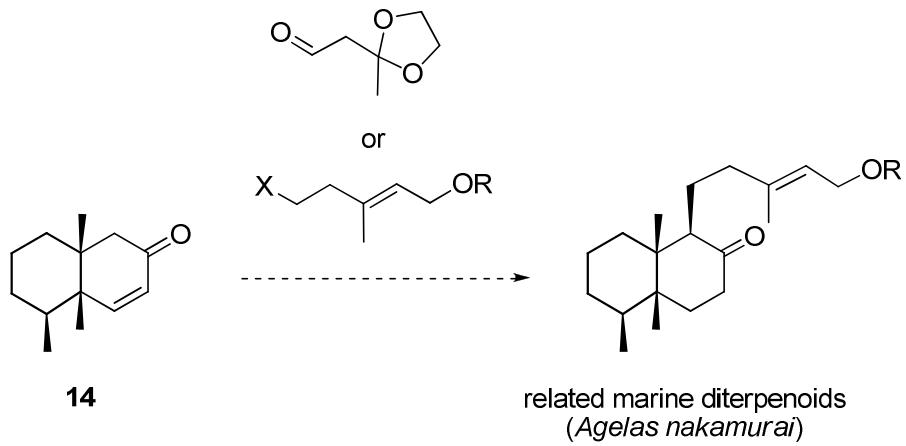
Hydroboration[9] and oxidation of **9** gave **11** in moderate yields as a 4:1 mixture of diastereoisomers (Scheme 2.10). The alcohols could be separated by column chromatography,[10] and the desired one was mesylated to furnish **13** in quantitative yield. Displacement of the mesylate by SuperHydride® (lithium triethylborohydride) and acetal cleavage by acidic quench delivered **3** in 74% overall yield. Oxidation of **3** with IBX (*o*-iodoxybenzoic acid)[11] formed the enone **13**, which effectively blocked the most accessible methylene of the ketone group of **3**.



Scheme 2.10 Preparation of **14**.

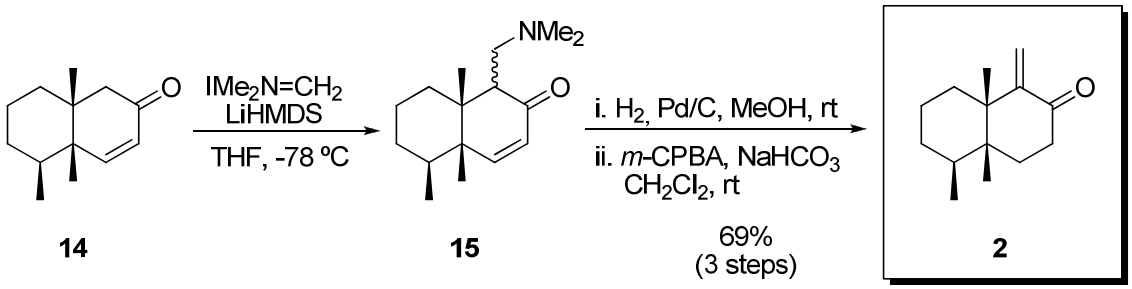
[9] Employing 9-BBN gave a dirtier crude.
[10] Alternatively, oxidation to the aldehyde worked quantitatively, but K_2CO_3/MeOH/H_2O epimerisation failed.
[11] K. C. Nicolaou, T. Montagnon, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

Initial attempts to utilise **14** for the synthesis of other related diterpenoids (Scheme 2.11) resulted unfruitful. Further attempts to alkylate the ketone α'-position (*i.e.* at C11) were problematic probably due to the extreme steric hindrance exerted by the three proximal methyl substituents, predominantly leading to *O*- rather than *C*-alkylation.



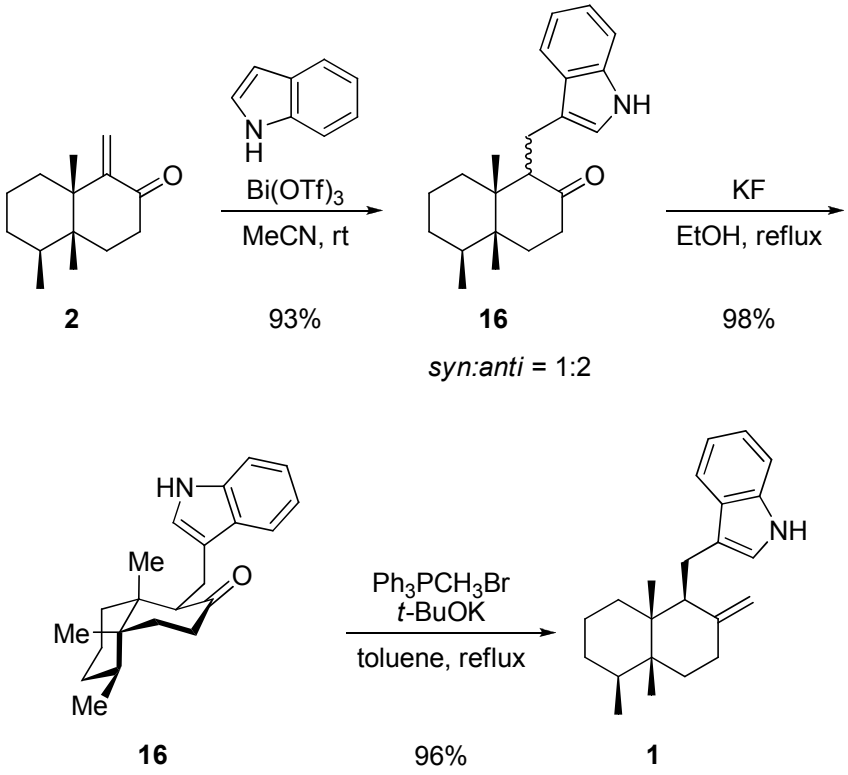
Scheme 2.11 Suggested Route to *Agelas* Diterpenoids by Alkylation of **14**.

Between all electrophiles used (3-iodomethyl indole, allyl bromide, formaldehyde, benzyl chlorormethyl ether) only Eschenmoser's salt gave the alkylated product (Scheme 2.12). Hydrogenation of the crude **15** followed by *m*-CPBA oxidation generated pivotal exocyclic enone **2** in 11 steps and 18% overall yield from WMK.



Scheme 2.12 Preparation of **2**.

Following our planned strategy, indole was installed via Lewis acid-promoted conjugate addition (Scheme 2.13). Thus, catalysis of bismuth(III) triflate promoted the addition of indole which smoothly generated **16** as a 1:2 mixture of *syn*:*anti* diastereoisomers. Isomerisation was performed by submitting the epimers to potassium fluoride in refluxing ethanol giving ketone **16** in quantitative yield. Finally, Wittig homologation effectively introduced the double bond and represented the preparation of anominine polycyclic framework **1**.[12]



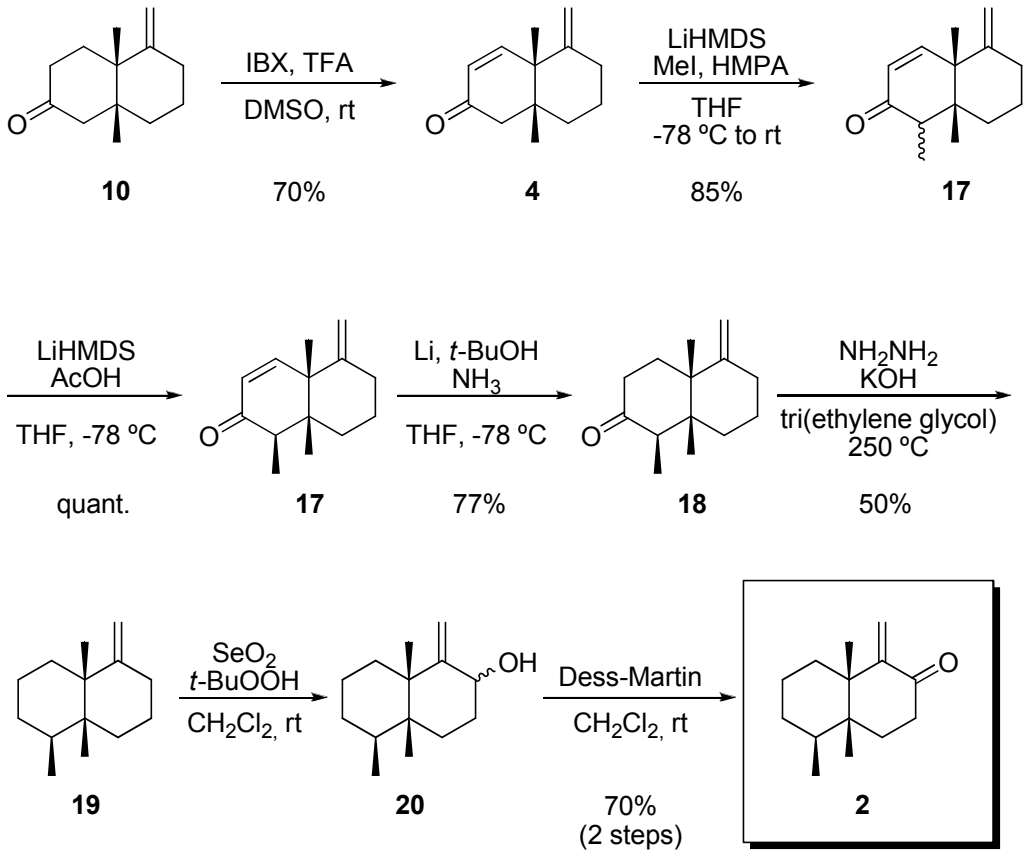
Scheme 2.13 Preparation of Anominine Framework **1**.

2.2.2 Orientation B

To complete our synthetic studies towards the synthesis of the polycyclic structures of anominine, we evaluated if a different orientation of WMK was possible. Thus, intermediate **10** was oxidised to the enone **4** under the previously

[12] This part of the work has been published in:
B. Bradshaw, G. Etxebarria-Jardí, J. Bonjoch. *Org. Biomol. Chem.*, **2008**, *6*, 772–778.

employed IBX-TFA conditions (Scheme 2.14). Alkylation at the α-position[13] furnished **17** as a mixture of epimers, which were subsequently isomerised under basic kinetic conditions.[14] Removal of the functionality was achieved with lithium in ammonia followed by Wolff-Kishner reduction.[15] The high temperatures needed for the last step resulted in a partial isomerisation of the methyl in α-position, probably due to the acidity of the proton in the hydrazone intermediate. It has to be said that this would not be a real problem in the full system since the oxygen function would have transposed instead of removed. Moreover, olefin **19** was oxidised by SeO_2/*t*-BuOOH[16] yielding the mixture of alcohols **20**. Finally, Dess-Martin oxidation completed synthesis of enone **2** in both orientations from WMK.



Scheme 2.14 Preparation of **2** via Orientation B of WMK.

[13] Employment of less toxic DMPU instead of HMPA resulted in starting material recovery.
[14] Several methods were tested: KF in refluxing EtOH (starting material decomposition), MeONa/MeOH (no reaction) and DBU/CH_2Cl_2 (no reaction).
[15] Barton-McCombie deoxygenation of the corresponding xanthate ester obtained by standard protocol did not give the desired product.
[16] A. F. Barrero, J. E. Oltra, J. M. Cuerva, A. Rosales, *J. Org. Chem.*, **2002**, *67*, 2566–2571.

Attempted Biomimetic Conversion of 1 to the Tubingensin A and Aspernomine Frameworks

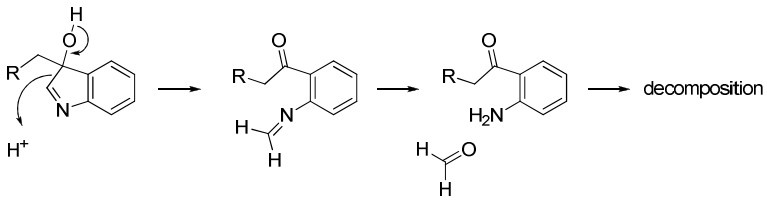
With **1** in hand, we looked to see if was feasible to convert it to both heterocyclic cores of tubingensin A and aspernomine (Scheme 2.15). Attempted oxidation of **1** with PIFA (phenyl iodofluoroacetate) or PIA (henyl iodoacetate)[17] were both unsuccessful returning only decomposed products. Attempts to oxidise using UV light in the presence of a photosensitiser met with similar disappointing results. It should be pointed out that to our knowledge there are no examples of oxidation of 2-substituted indoles without any group in the 1-position. This may be due to the fact that oxidation causes opening of the indole ring which then degrades.[18] Whilst it may be possible to carefully oxidise the indole in the natural product under controlled conditions using enzymes, it would seem that this is not a viable transformation in the laboratory.

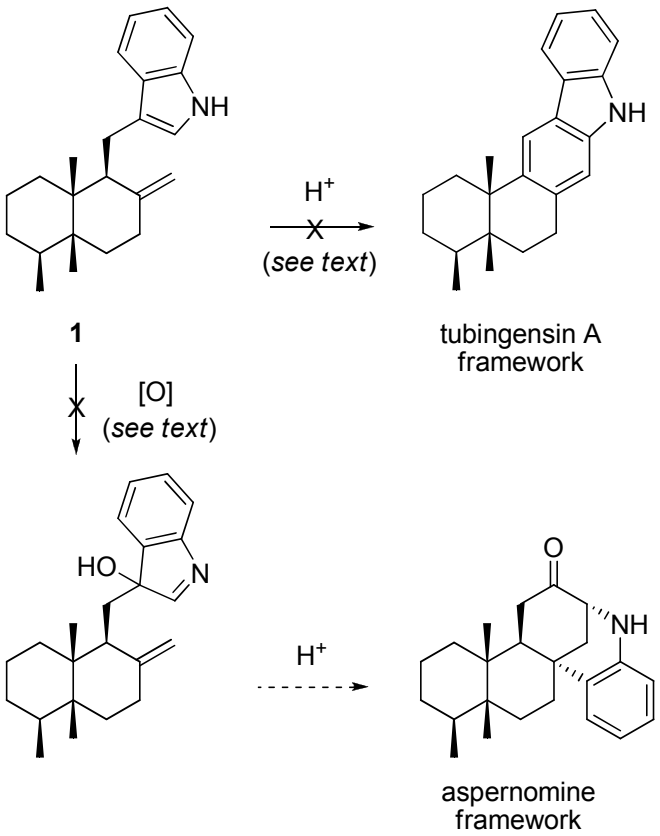
Cyclisation of anominine to tubingensin A framework attempted by treating **2x35** with various acids (TsOH, formic acid in refluxing toluene, HI). However, in all cases multiple products were obtained (degradation products) and none of all could be identified as the desired material.

Whilst it may be possible to successfully effect these transformations, it was decided that it could require a more in-depth study that was beyond the scope of this current work. Moreover, starting material **1** was in short supply and would have not allowed us to an exhaustive survey of conditions.

[17] D. V. C. Awang, A. Vincent, *Can. J. Chem.*, **1980**, *58*, 1589.

[18]

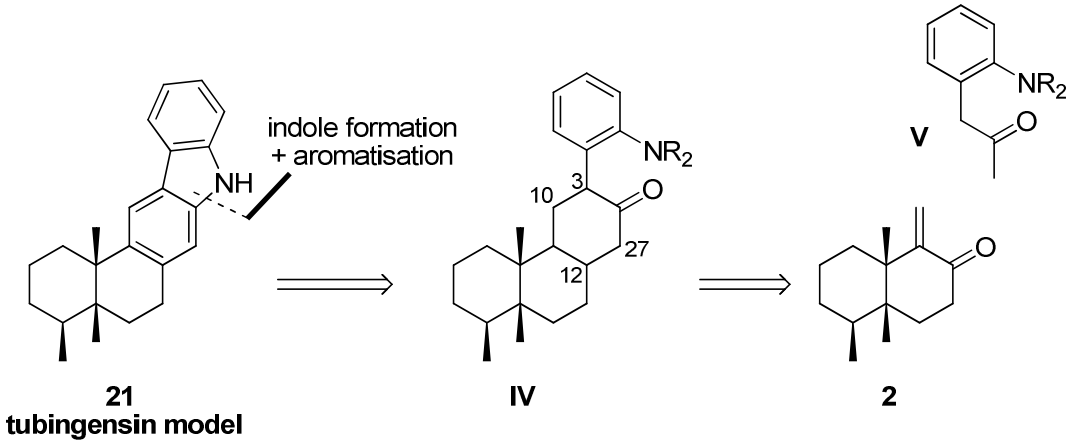




Scheme 2.15 Attempted Biomimetic Conversion of **1** to the Tubingensin A and Aspernomine Frameworks.

2.3 Synthesis of Tubingensin A Polycyclic Skeleton

Despite a possible biomimetic interconversion (*see Chapter 1*), we sought to prepare tubingensin A by synthetic means after the unsuccessful biological-inspired route. Having intermediate **2** in hand, we envisaged a straightforward synthesis for tubingensin A, a related diterpenoid from *Aspergillus spp*. Hence, tubingensin A model is disconnected at the carbazole C-N bond revealing **IV** (Scheme 2.16). This intermediate suggests its potential formation by condensation of an amine and a ketone, and a latter aromatisation of the carbocyclic ring. Further disconnection at C3-C10 and C27-C12 bonds would lead to ketone **V** and the common pivotal intermediate **2**. The enone functionality postulates that a Robinson annulation is plausible by treatment of **V** with base.

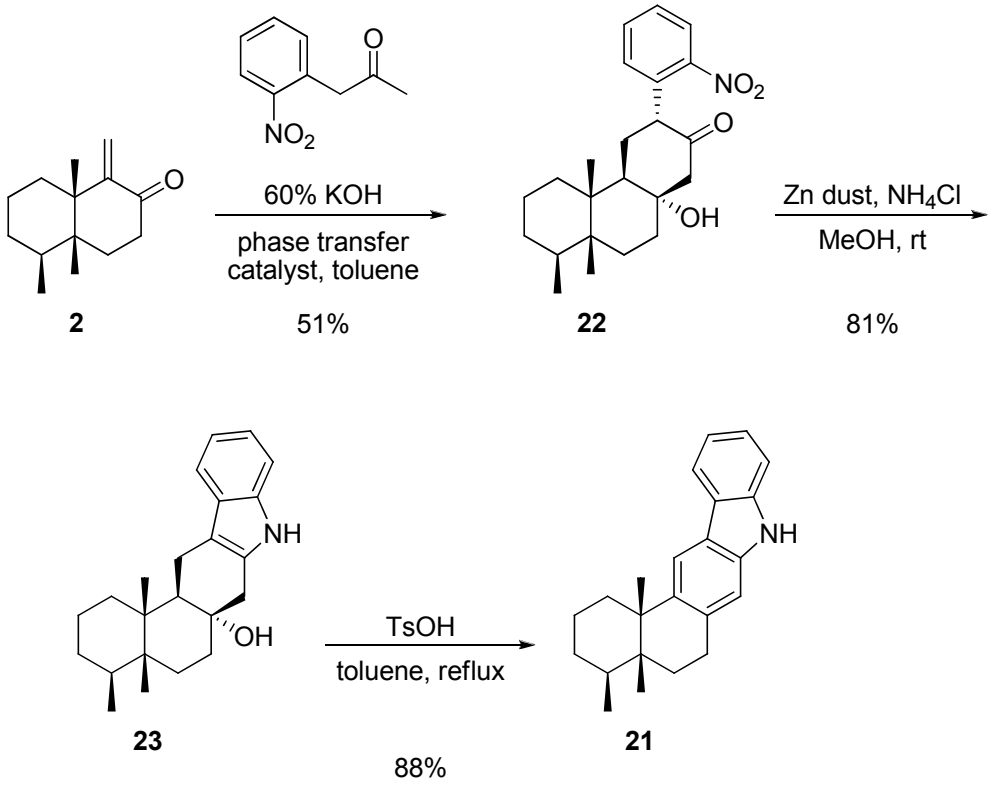


Scheme 2.16 Retrosynthetic Analysis for Tubingensin A Model (**21**).

We then focused our attention on the tubingensin skeleton using the same common key intermediate **2**. This enone reacted with 1-(2-nitrophenyl)propan-2-one[19] in a biphasic system (toluene/60% aqueous KOH) and in the presence of a chiral phase transfer catalyst under the conditions developed by Vandewalle[20] (Scheme 2.17). Initially, the reaction progressed *via* a conjugate addition followed by Robinson annulation to give the cyclohexanone ring **22** as a single diastereomer

[19] M. P. Doyle, W. J. Bryker, *J. Org. Chem.*, **1979**, *44*, 1572–1574.
[20] W. Nerinckx, M. Vandewalle, *Tetrahedron: Asymmetry*, **1990**, *1*, 265.

without elimination of the hydroxyl. We believe that the catalyst acts only as a phase transfer agent and is not solely responsible for the stereocontrol, since we isolated Michael adduct as a complex mixture of diastereomers. This suggests that it is the KOH that epimerises the mixture under thermodynamic control to produce the single stable diastereomer **22**. Reduction of the nitro group with Zn and ammonium chloride as a source of protons smoothly produced the indole **23** in 81% yield. To complete the synthesis, the tertiary alcohol was eliminated in the presence of TsOH in refluxing toluene, the dihydro intermediate formed undergoing spontaneous oxidation under the reaction conditions. We found that if the reaction was worked up too early after TLC analysis showed that no starting material remained, a mixture of **21** and dihydro derivatives analogous to 10,27-dihydrotubingensin A was isolated. Stirring this mixture overnight in chloroform, exposed to the air, was sufficient to complete the oxidation to the tubingensin A framework **21**.



Scheme 2.17 Preparation of Tubingensin A Framework **21**.

2.4 Attempts to Introduce the C20 Quaternary Centre

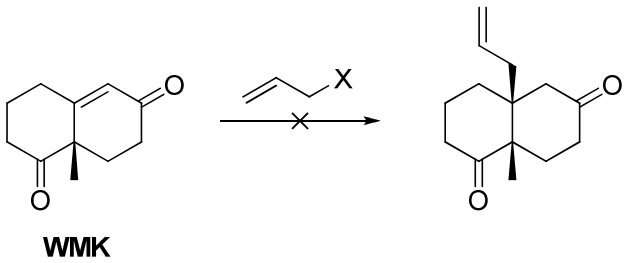
With two routes in hand using model substrates it was at first decided that the initial sequence (with the WMK in Orientation A) seemed most promising for further development. Thus, the next phase involved:

- Introduction of a substituent at the C20 quaternary centre which could be further elaborated to the complete isohexenyl side chain.

- Investigation on transposition of the C16 oxygen to C19 and installation of the C16 methyl group.

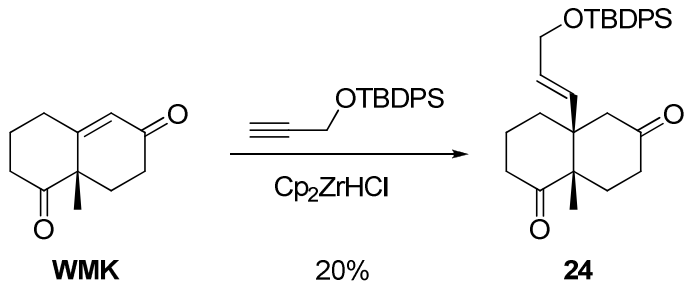
2.4.1 Installation of C20 Quaternary Centre

The addition of allyl organometallic species upon WMK was also studied (Scheme 2.18). Unfortunately, it did not work neither under standard conditions (allylmagnesium bromide, CuI, LiCl) nor Sakurai conditions (allyltrimethylsilane, $TiCl_4$). Once again, the steric hindrance seems to be the responsible of the lack of reactivity, since smaller methylcuprate is easily added to the same substrate.



Scheme 2.18 Addition of Allyl Organometallic Species upon WMK.

The only side chain larger than a methyl that could be introduced was via a hydrozirconation reaction[21] (Scheme 2.19). Although the yield was low the reaction was not optimised, and with further development it should be possible. However, these conditions are not ideal since Schwartz reagent is not particularly cheap and easy to handle, and would be needed in very large quantities at such an early part of the synthesis.



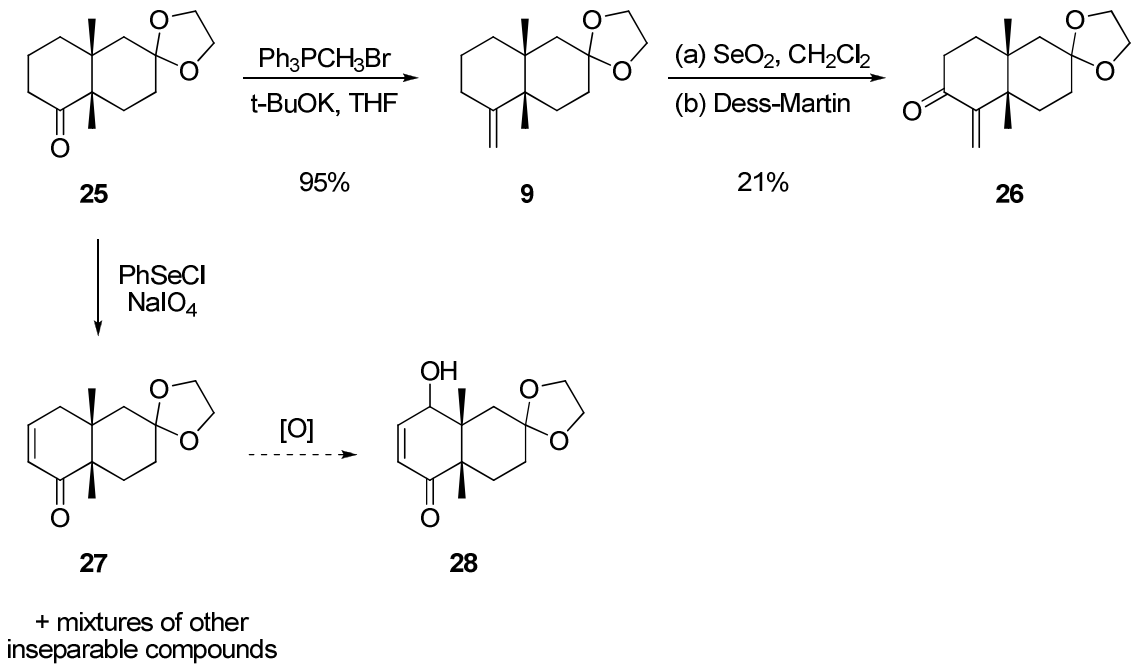
Scheme 2.19 Hydrozirconation Reaction upon WMK.

2.4.2 Transposition of Oxygen from C16 to C19 and Introduction of C16 Methyl

To transpose the oxygen **25** was first homologated to the alkene **9**, which was then oxidised in the allylic position with selenium dioxide (Scheme 2.20). Unfortunately the yield here was very low. Furthermore, to introduce C18-C19 double bond in **26** would also require PhSeCl. Thus, large amounts of toxic selenium reagent would be required and combined with low yields did not seem a viable route.

An alternative route based on oxidation/elimination of **25** with PhSeCl gave a mixture of products of which **27** was one component but could be adequately purified from other by-products. With small amounts of a mixture of **27** the oxidation to **28** analogous to Danishefsky[22] could not be tested.

[21] P. Wipf, C. Kendall, *Topics in Organometallic Chemistry, Metallocenes in Regio- and Stereoselective Synthesis*, Springer Berlin/Heidelberg, **2005**, Volume 8/2005, p. 1–25.
[22] J. G. Allen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001,** *123,* 351–352.

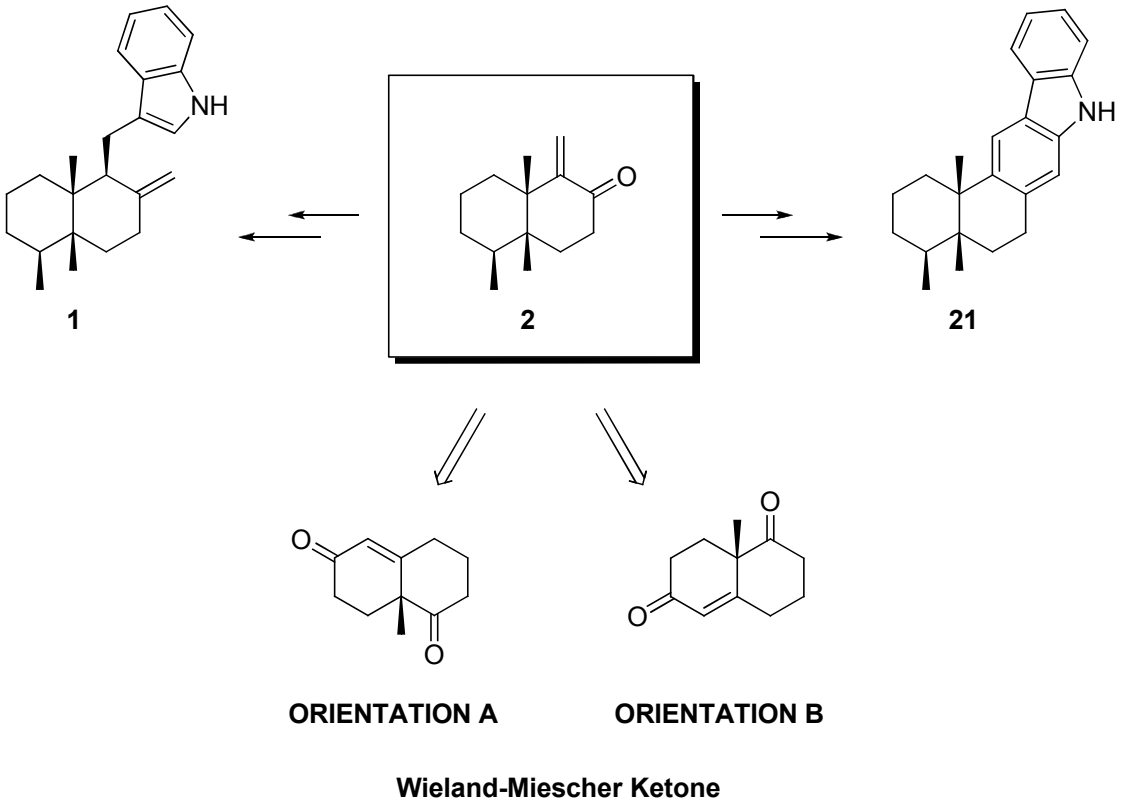


Scheme 2.20 Alternative Routes.

After these initial investigations the initial route (Orientation A) did not seem viable and so we turned to focus our attentions on Orientation B.

2.3 Summary and Conclusions

The polycyclic structures of anominine and tubingensin A have been prepared from the key intermediate **2**. The introduction of the heterocyclic moieties of both terpenoids has been assayed resulting in an efficient methodology for the introduction of the heterocycles via conjugate addition upon an enone. Furthermore, two different routes to this pivotal intermediate had been examined, both starting from the common Wieland-Miescher ketone building block but in a different orientation (Scheme 2.21).



Scheme 2.21 Synthesis of Anominine and Tubingensin A Polycyclic Structures from WMK via Key Intermediate **2**.

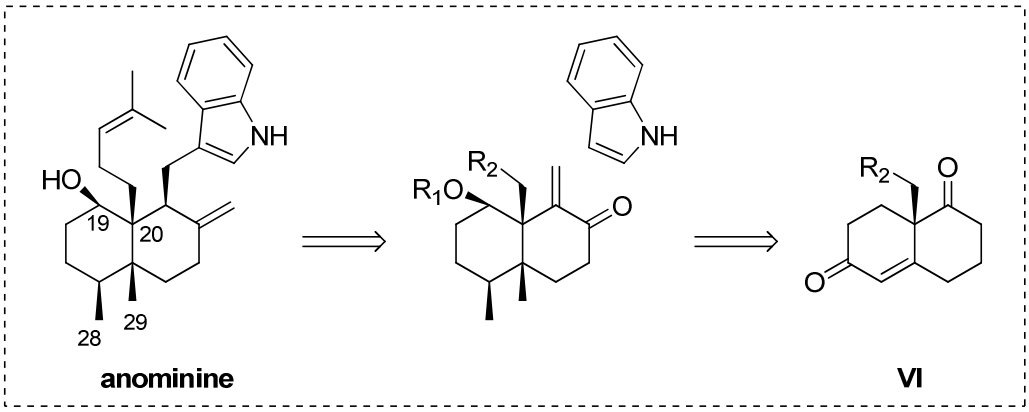
WMK orientation A has proved efficient for the preparation of the model polycyclic frameworks, as well as the related terpenoids from the marine sponge *Agelas nakamurai*. However, it seems not a viable route for the preparation of *Aspergillus spp.* products since the required side chain could not be introduced via conjugate addition.

On the other hand, the orientation B of WMK is not a good option for the model synthesis of the polycyclic structures due to the problematic removal of the oxygen function in the A-ring. In contrast, this orientation seems a good possibility for the total synthesis of anominine due to some factors:

- The oxygen functionality is in the correct place for being transposed via an allylic rearrangement.

- The angular methyl C29 could be introduced by conjugate addition in a complete stereoselective fashion on WMK.

For these reasons the orientation B was chosen for further development, and this in turn implied that a WMK derivative such as **VI** would form the chiral precursor for the synthesis (Scheme 2.22), which is adequately functionalised at R_2 to form the side chain.



Scheme 2.22 Retrosynthesis for Anominine with the Orientation B of a WMK derivative.

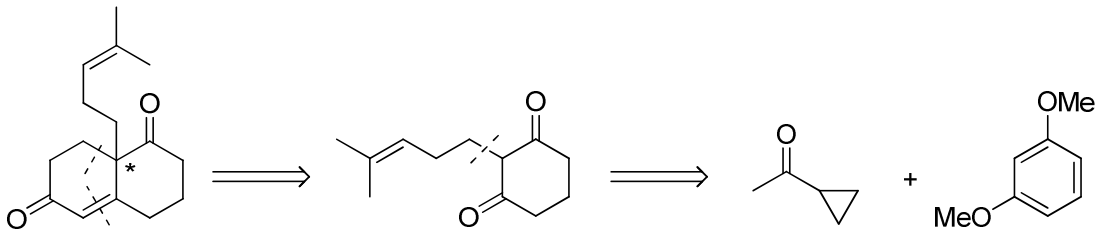
CHAPTER 3.

ENANTIOSELECTIVE SYNTHESIS OF WIELAND-MIESCHER KETONE DERIVATIVES

Adv. Synth. Catal., **2009**, *351*, 2482–2490.

3.1 Introduction

As discussed in the previous chapter, the chiral precursor for the total synthesis of anominine should be a Wieland-Miescher ketone analogue, synthesized via an intramolecular aldol condensation. Retrosynthetically, the chiral building block should incorporate the quaternary substituent from the beginning of the synthesis and ideally, should be the homoprenyl full chain (Figure 3.1). Based on problems encountered previously in the stepwise elaboration of the side chain (see section 1.5.5.3), whilst the double bond of the side chain may be incompatible with some steps it was thought that could be temporarily protected, analogously to that used by Shibasaki in his total synthesis of garsubellin A.[1] This could be disconnected back via Robinson annulation to **30** a known 1,3-dicarbonyl compound,[2] and at the same time is traced back to anisole and methyl cyclopropyl ketone.

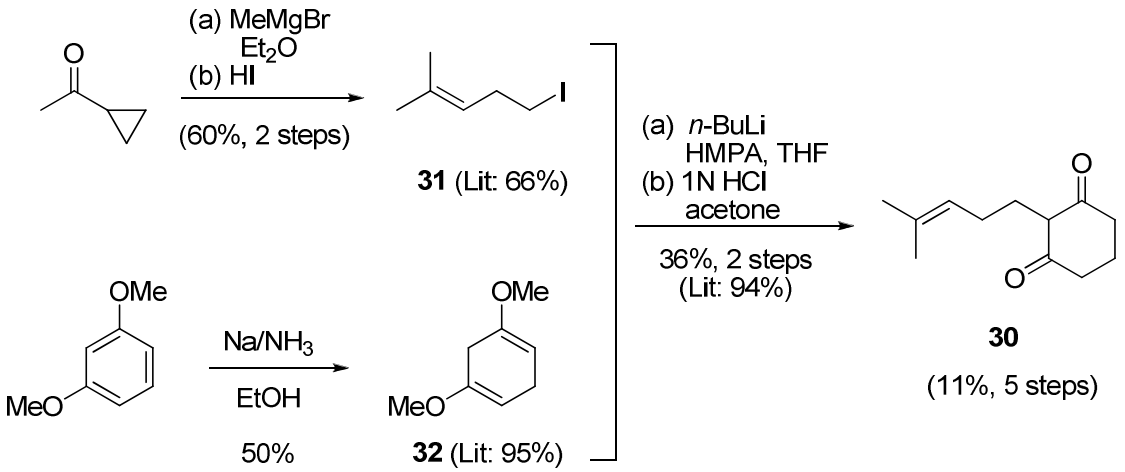


29 **30**

Figure 3.1 Retrosynthetic Analysis of **29**.

[1] A. Kuramochi, H. Usoda, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.*, **2005**, *127*, 14200–14201.
[2] E. Piers, J. R. Grierson, *J. Org. Chem.*, **1977**, *42*, 3755–3757.

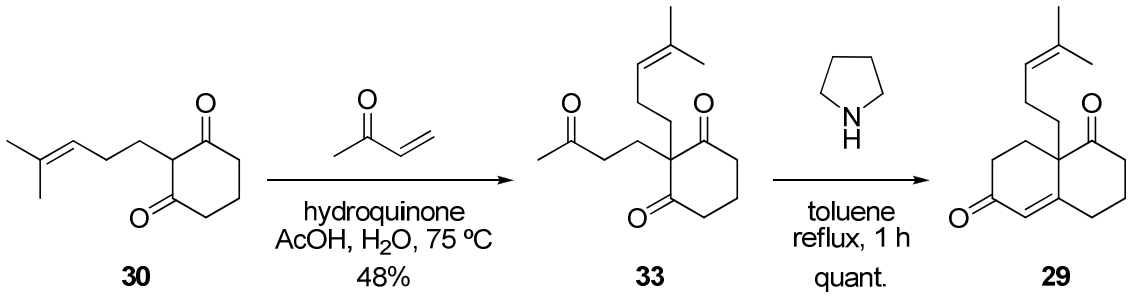
Synthetically speaking, ketone **30** has to be prepared by alkylation of 2,5-dihydroanisole with 4-bromo-2-methyl-2-pentene (Scheme 3.1), since direct alkylation of the parent 1,3-cyclohexanedione is only efficient with reactive alkylating reagents such as methyl iodide and allylic or benzylic halides. However, with less reactive alkylating agents such as 4-bromo-2-methyl-2-pentene, the reaction is generally sluggish and low yielding. Thus, side chain **31** is prepared from methyl cyclopropyl ketone via Grignard addition and acid-induced cyclopropane opening.[3] Birch reduction[4] of anisole would give the desired precursor **32** to perform the alkylation. Lithium anion of **32** was generated by *n*-BuLi/HMPA addition,[5] followed by enolate trapping with **31** and subsequent acidic quench yielded **30** in 36% for the last two steps.



Scheme 3.1 Synthesis of **30**.

[3] G. Vidari, G. Lanfranchi, F. Masciaga, J. Moriggi, *Tetrahedron: Asymmetry.,* **1996**, *7*, 3009–3020.
[4] A.J. Birch, *J. Chem. Soc.,* **1947**, 102.
[5] The described methodology used *t*-BuLi instead but we wanted to substitute it because of the danger when using it on large scale.

Introduction of methyl vinyl ketone under aqueous acidic conditions rendered **33** in moderate yield (Scheme 3.2). Initial cyclisation attempts employing 25 mol% proline were unsuccessful, and only was possible forcing the reaction with pyrrolidine in refluxing toluene. In summary, racemic Wieland-Miescher ketone analogue **29** was obtained in 7 steps and 5% overall yield from commercial sources.



Scheme 3.2 Synthesis of **29**.

Taking in mind that **29** is not obtained in enantiopure form and it would need several recrystallisations to yield optically pure material, it is quite sure that a large amount of **29** would be discarded in this enantioenrichment process. Adding to this that **29** would be a building block in the early beginning of the synthesis and therefore a long journey is still to come, seems quite inappropriate to waste such an amount of material. For this reason, we considered the possibility of preparing this building block in highly enantiopure fashion (*i.e.* removing the need for enantioenrichment) in order to save material, money and time and provide adequate amounts of this building block to launch the synthesis.

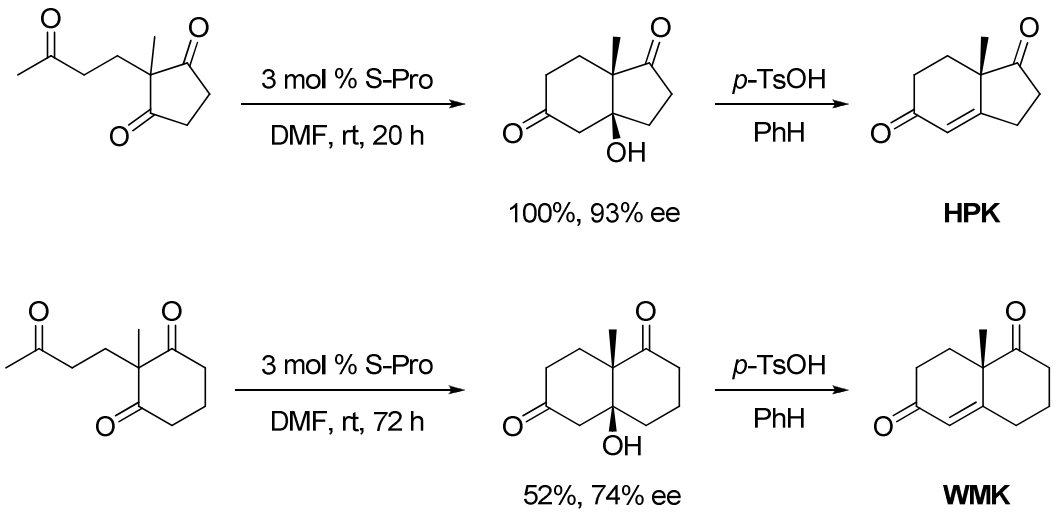
3.2 Precedents

3.2.1 Examples of WMK Preparation

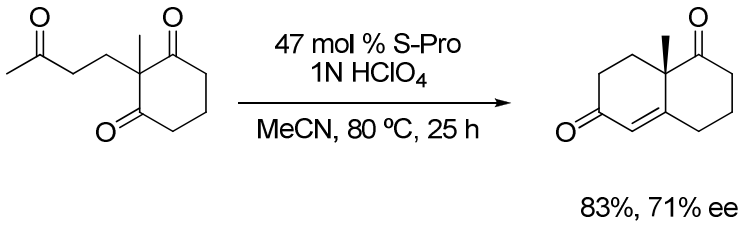
Before embarking on the study for the enantioselective preparation of **29** we looked carefully to the precedents in this area. The first example of an aminocatalytic asymmetric aldol reaction[6] is the Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 3.3 and 3.4). This was a proline-catalyzed aldolisation of di- and triketones discovered in the early 1970s. This reaction was the first example of a highly enantioselective organocatalytic process which has been broadly applied to steroid and natural product synthesis.[7] Although the chemical and optical yields are excellent for the Hajos-Parrish ketone (HPK, bicyclo[4.3.0]decaline derivative) the same reaction but for Wieland-Miescher ketone (bicyclo[4.4.0]decaline derivative) is not as outstanding.

[6] (a) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623, **1971**. (b) U. Eder, G. R. Sauer, R. Wiechert, German Patent DE 2014757, **1971**. (c) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497. (d) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

[7] (a) J. Gutzwiller, P. Buchschacher, A. Fürst, *Synthesis,* **1977**, 53. (b) S. Takano, C. Kasahara, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1981**, 635. (c) J. C. Blazejewski, *J. Fluorine Chem.* **1990**, *46*, 515. (d) S. Terashima, S. Sato, K. Koga, *Tetrahedron Lett.* **1979**, *36*, 3469. (e) A. Przézdziecka, W. Stephanenko, J. Wicha, *Tetrahedron: Asymmetry,* **1999**, *10*, 1589. (f) S. Kwiatkowska, A. Syed, C. P. Brock, D. S. Watt, *Synthesis,* **1989**, 818. (g) D. Rajagopal, R. Narayanan, S. Swaminathan, *Tetrahedron Lett.* **2001**, *42*, 4887. (h) N. Ramamurthi, S. Swaminathan, *Indian J. Chem., Sect. B,* **1990**, *29*, 401. (i) S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, M. J. D. Grandi, *J. Am. Chem. Soc.*, **1996**, *118*, 2843.



Scheme 3.3 First Organocatalised Examples by Hajos and Parrish.



Scheme 3.4 Eder, Sauer and Wiechert Synthesis of WMK.

Apart from the original method several new protocols for the Robinson annulation have been developed, the most representative ones are highlighted in Table 3.1. In the late 90's Barbas III and co-workers used an antibody to do the cyclodehydration step (intramolecular aldol) of the Robinson annulation.[8] The antibody showed an excellent stereospecificity giving only one isomer with excellent chemical and optical yields. Despite achieving an outstanding result this methodology in not synthetically useful, due to the long reaction times required to perform the transformation (10 days at room temperature), its price (in 2010: 263 € for 10 mg, average M_W = 150000), and the large dilution required in this step (50 mL for 110 mg substrate).

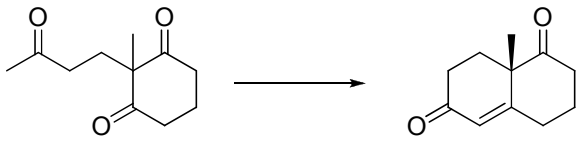
[8] G. Zhong; T. Hoffmann; R. A. Lerner; S. Danishefsky; C. F. Barbas III, *J. Am. Chem. Soc.*, **1997**, *119*, 8131–8132.

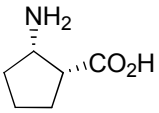
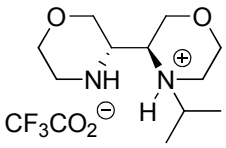
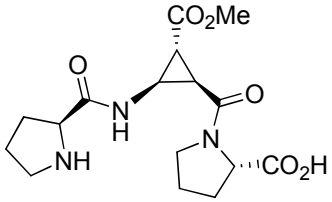
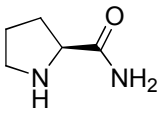
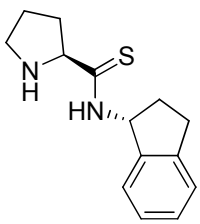
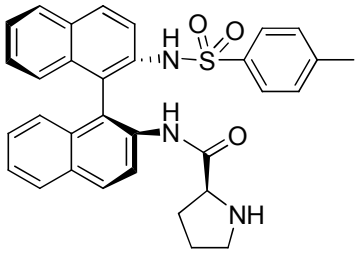
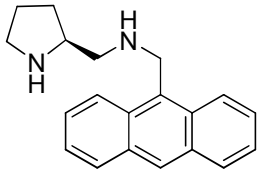
It was until 2005 that the next example was reported, when Davies and co-workers described that β-amino acid (1*R*,2*S*)-cispentacin promoted the Hajos-Parrish-Eder-Sauer-Wiechert reaction[9] and also gave Wieland-Miescher ketone in 75% and 86% ee in 5 days and with 30 mol% catalyst loading. One year later, Kanger and co-workers developed a series of bimorpholin-type catalysts and applied them to the intramolecular aldol reactions.[10] Chemical and optical yields are slightly better than the prior but the major drawback is the catalyst synthesis, which is prepared from diethyl tartrate in 8 steps.

In 2008, the Reiser group obtained similar chemical and optical yields using a tripeptide but the reaction time was shortened to one day.[11] In the same year, Zhang,[12] Nájera[13,14] and Endo[15] reported three new proline derivatives that catalysed the preparation of WMK with high enantioselectivities.

[9] a) S. G. Davies, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Chem. Commun.*, **2005**, 3802–3804; b) S. G. Davies, A. J. Russell, R. L. Sheppard, A. D: Smith, J. E. Thompson, *Org. Biomol. Chem.*, **2007**, *5*, 3190–3200.
[10] (a) T. Kanger; K. Kriis; T. Pehk; A. Müürisepp; M. Lopp, *Tetrahedron: Assymmetry.* **2002**, *13*, 857–865. (b) T. Kanger; K. Kriis; M. Laars; T. Kailas; A. Müürisepp; T. Pehk; M. Lopp, *J. Org. Chem.*, **2007**, *72*, 5168–5173.
[11] V. D'Elia, H. Zwicknagl, O. Reiser, *J. Org. Chem.*, **2008**, *73*, 3262–3265.
[12] X.-M. Zhang, M. Wang, Y.-Q. Tu, C.-A. Fan, Y.-J. Jiang, S.-Y. Zhang, F.-M. Zhang, *Synlett*, **2008**, 2831–2835.
[13] D. Almasi, D. A. Alonso, C. Nájera, *Adv. Synth. Catal.*, **2008**, *350*, 2467–2472.
[14] G. Guillena, C. Nájera, S. F. Viózquez, *Synlett*, **2008**, 3031–3035.
[15] Y. Akahane, K. Inomata, Y. Endo, *Heterocycles*, **2009**, *77*, 1065–1078.

Table 3.1 Comparison of Different Catalysts and Conditions for the Enantioselective Synthesis of Wieland-Miescher Ketone.[a]



Antibody 38C2				
94%, 96% ee 0.11 mol%, 10 d	75%, 86% ee 30 mol%, 5 d	84%, 91% ee 5 mol%, 3 d	88%, 92% ee 10 mol%, 1 d	
10 mg at 263 €	7 steps	8 steps	15 steps	
				
68%, 87% ee 30 mol%, 6 d	99%, 86% ee 5 mol%, 1 d	95%, 90% ee 5 mol%, 1 d	68%, 84% ee 30 mol%, 1 d	
1g at 74€	4 steps	3 steps	6 steps	

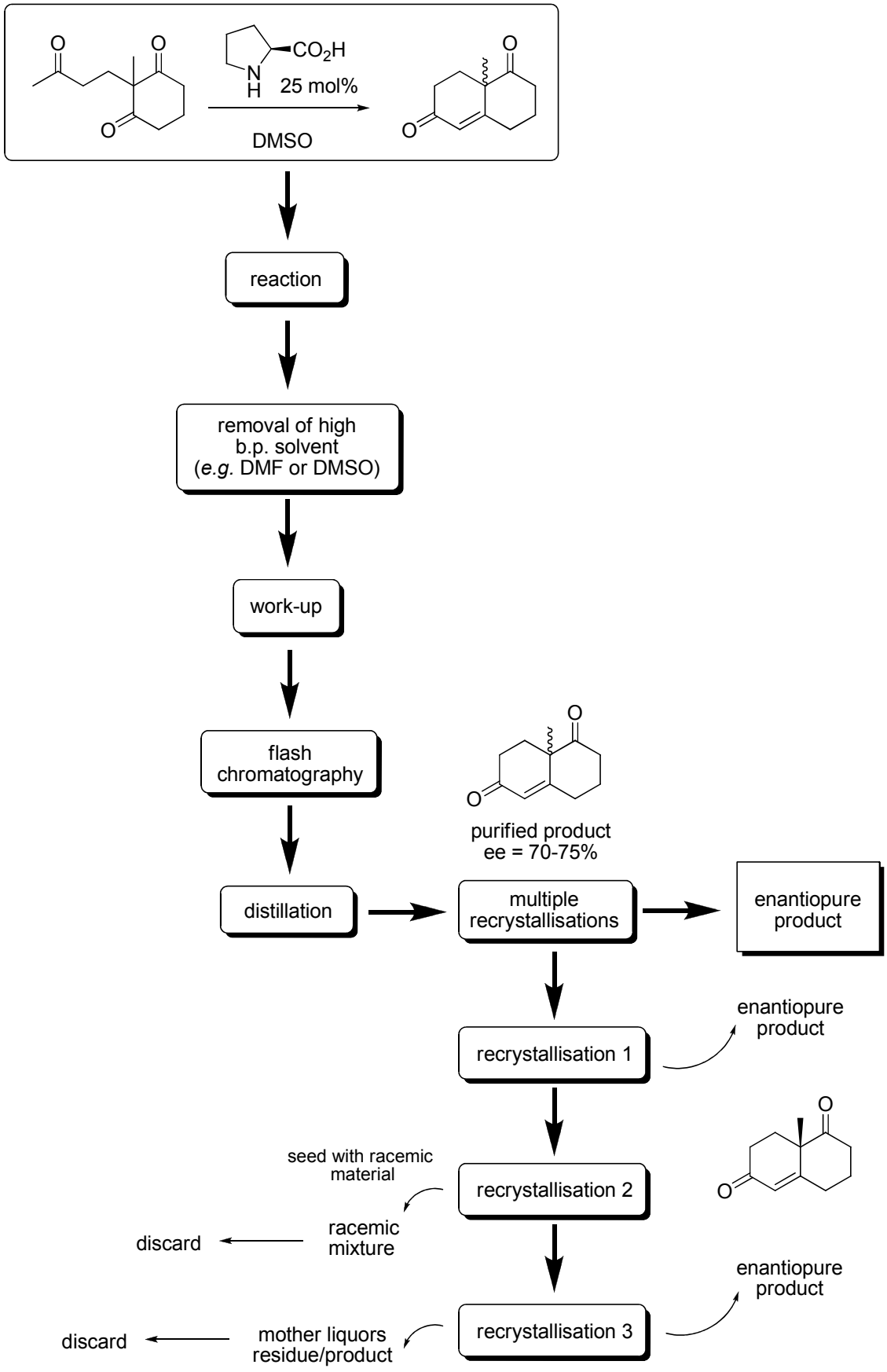
[a] Yields and enantioselectivities of WMK are reported, as well as catalyst loading, reaction time, number of steps for the catalyst preparation from commercial sources and price (if commercially available).

3.2.2 Experimental Operations

Despite being a very laborious and low yielding sequence, the method to prepare enantiopure WMK using proline has persisted for the last 30 years due in part to the relative cheapness of the starting materials and lack of viable alternative methods. As a consequence, this procedure has been employed in numerous occasions to supply building blocks for total synthesis.[16]

Experimentally speaking, high-boiling point solvent has to be removed, difficult work up has to done, and finally the purification which requires a column chromatography and a distillation (Scheme 3.5). On large scale these processes are far from trivial undertakings, since chromatography is prone to serious complications and distillation can result in material decomposition. Having obtained the product in a yield of 70% according to the literature but more realistically 50%, the product has to be enriched if it has to be used as part of an enantioselective synthesis. Several recrystallisations are needed to obtain enantiopure material and eventually the yield is halved. As we were embarking in a complex natural product total synthesis large amounts of WMK derivatives would be necessary and therefore, it was evident that we would need to significantly improve this sequence. Ideally, we would have to develop a methodology which would allow us to simplify the isolation sequence and increase the enantioselectivity to above 90% to avoid the lengthy recrystallisation sequence. Furthermore, it is very important to have a good methodology which would allow us to obtain large amounts bicyclic chiral precursor with the easiest experimental procedure possible.

[16] For Total Syntheses using the WMK up until 2007, see: G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry*, **2007**, *18*, 2249–2293 (references 242-256). For recent applications see: (a) A. B. Smith III, L. Kürti, A. H. Davulcu, Y. S. Cho, *Org. Process. Res. Dev.*, **2007**, *11*, 19–24. (b) S. Hanessian, N. Boyer, G. J. Reddy, B. Deschênes-Simard, *Org. Lett.*, **2009**, *11*, 4640–4643. (c) D. C. J. Waalboer, H. A. vanKalkeren, M. C. Schaapman, F. L. vanDelft, F. P. J. T. Rutjes, *J. Org. Chem.*, **2009**, *74*, 8878–8881. (d) K. Ma, C. Zhang, M. Liu, Y. Chu, L. Zhou, C. Hu, D. Ye, *Tetrahedron Lett.*, **2010**, 51, 1870–1872. (e) V. M. T. Carneiro, H. M. C. Ferraz, T. O. Vieira, E. E. Ishikawa, L. F. Silva Jr., *J. Org. Chem.*, **2010,** *75*, 2877–2882 (f) F. Churruca, M. Fousteris, Y. Ishikawa, M. W. Rekowski, C. Hounsou, T. Surrey, A. Giannis, *Org. Lett.*, **2010**, *12*, 2096–2099.



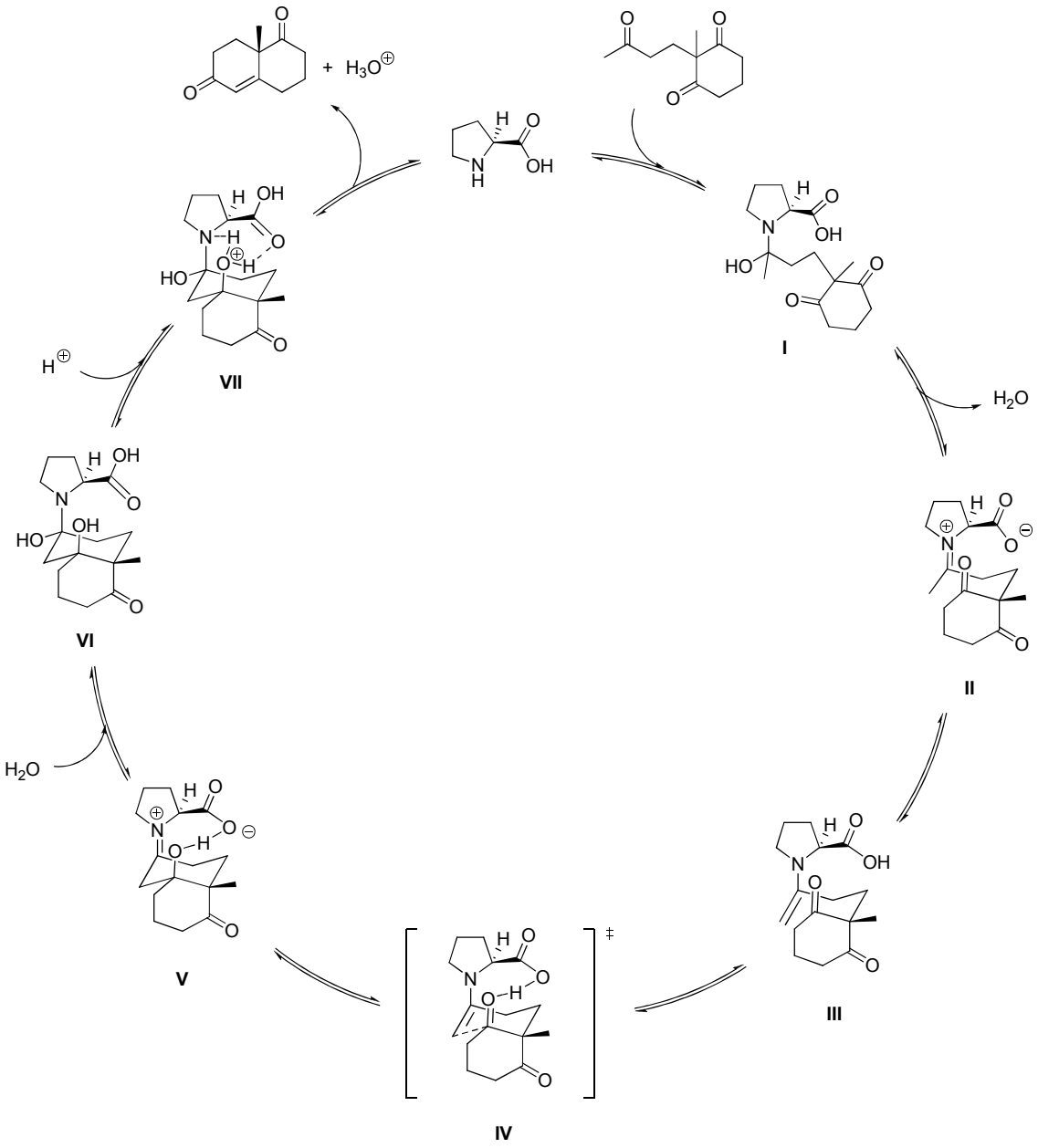
Scheme 3.5 Experimental Flowchart of Current WMK Preparation.

3.2.3 Mechanism of the Proline-Catalysed Aldol Reaction.

Aldol reactions combine a nucleophilic addition, which is acid-catalyzed, with an enolisation, which is catalyzed by both acids and bases.[17] These properties make it possible for the aldolisation to be catalyzed by both Lewis and Brønsted acids and bases.

Extensive research has been conducted by several research groups to elucidate the mechanism of proline-catalyzed aldol reactions.[18] Initially, only limited mechanistic information was available for the proline-catalyzed intermolecular aldol reaction, most of which came from a closer look at the studies of alternative catalysts in the intermolecular aldolisations.[19] A number of different models have been proposed for this intramolecular aldol reaction,[5] until quite recently Marquez and Metzger were able to intercept and characterize intermediates **I**, **III**, **V**, and **VI** for WMK (Scheme 3.6) with an ESI-MS study,[20] supporting the enamine mechanism proposed by List.[6b]

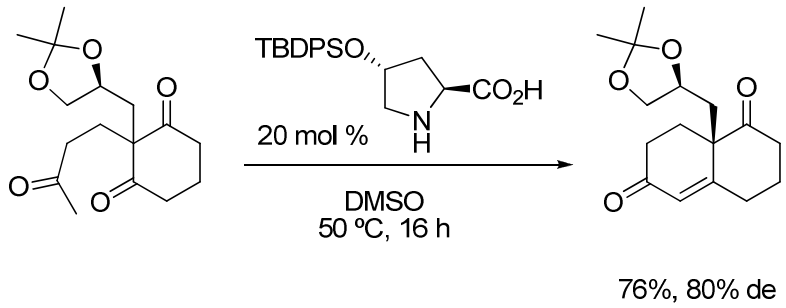
[17] (a) R. Mahrwald, *Modern Aldol Reactions*; Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2004**; Vols. 1 and 2. (b) F. Tanaka, C. F. Barbas III. In *Enantioselective Organocatalysis*; P. I. Dalko, Ed.; Wiley-VCH: Weinheim, **2007**; p. 19.
[18] (a) B. List, *Acc. Chem. Res.*, **2004**, *37*, 548. (b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.*, **1974**, *39*, 1615. (c) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.*, **1980**, *108*, 2353 (d) C. Agami, C. Puchot, *J. Mol. Catal.*, **1986**, *38*, 341. (e) C. Agami, C. Puchot, *Tetrahedron*, **1986**, *42*, 2037. (f) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.*, **2001**, *123*, 11273. (g) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.*, **2001**, *123*, 12911. (h) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.*, **2003**, *125*, 16. (i) F. R. Clemente, K. N. Houk, *Angew. Chem., Int. Ed.*, **2004**, *43*, 5766. (j) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. U.S.A.*, **2004**, *101*, 5839. (k) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.*, **2004**, *37*, 558. (l) F. R. Houk, K. N. Clemente, *J. Am. Chem. Soc.*, **2005**, *127*, 11294. (m) D. Rajagopal, M. S. Moni, S. Subramanian, S. Swaminathan, *Tetrahedron: Asymmetry,* **1999**, *10*, 1631.
[19] (a) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.*, **2001**, *123*, 5260. (b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.*, **2000**, *122*, 2395.
[20] C. Marquez, J. O. Metzger, *Chem. Commun.*, **2006**, 1539.



Scheme 3.6 Catalytic Cycle of the Proline-Catalysed Aldol Reaction Applied to the Wieland-Miescher Ketone.

3.2.4 Other Procedures of WMK Analogues Preparation

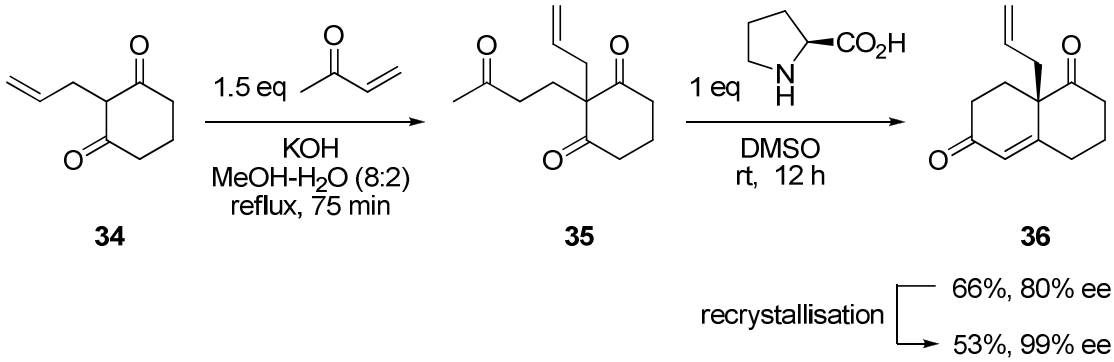
Little work has been done in the enantioselective preparation of Wieland-Miescher ketone analogues having a substituent different than a methyl. Paquette's group used a proline-based catalyst to prepare Wieland-Miescher ketone analogues bearing an elaborated side chain (Scheme 3.7).[21] They wanted to investigate if this remote stereocentre could enhance enantioselectivity in the cyclisation. However, chemical and optical yields are not good enough for a stereoselective synthesis. This material would still require substantial recrystallisations to obtain enantiopure material with subsequent reductions in yields.



Scheme 3.7 Paquette's WMK Analogue Stereoselective Synthesis.

The other method found in the literature was the preparation of the allyl derivative **36** by Hanselmann and co-workers[22] and relied upon proline to induce stereoselectivity in the cyclisation (Scheme 3.8). The drawbacks of this protocol are analogous to the methyl analogue: a) the moderate overall chemical yield; b) the relatively low optical yield which requires multiple crystallisations to have enantiopure material, and as a consequence, the low overall quantity of enantiopure material that is obtained; c) the tedious experimental manipulations required to purify the product.

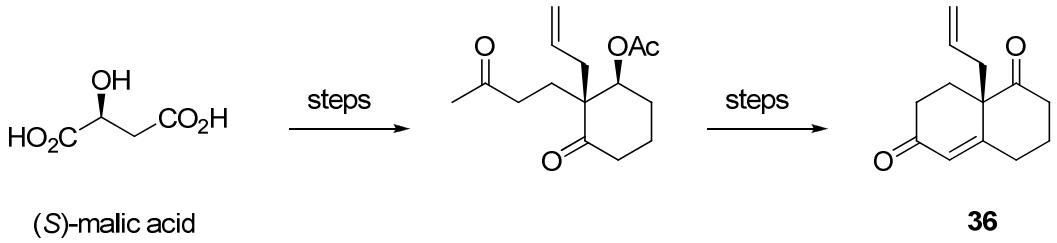
[21] T. Nagamine, K. Inomata, Y. Endo, L. A. Paquette, *J. Org. Chem.* **2007**, *72*, 123–131.
[22] R. Hanselmann, M. Benn, *Synthetic Commun.* **1996**, *26*, 945–961.



Scheme 3.8 Hanselmann's Synthesis of **36**.

Regardless of the limitations previously explained, this protocol has still been used to obtain building blocks employed in total synthesis.[23]

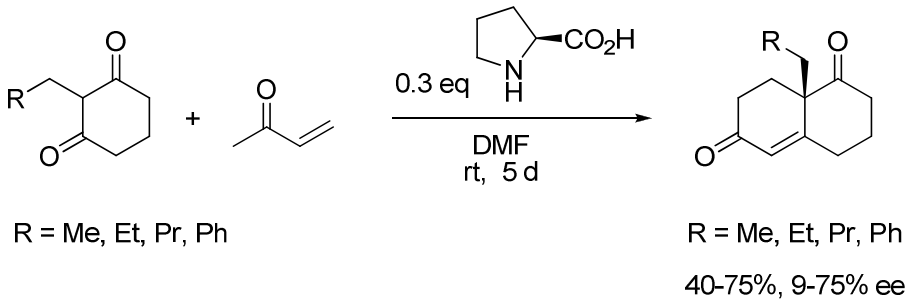
A decade later, absolute configuration of both enantiomers of allyl-WMK was confirmed by synthesizing them from the chiral pool (*S*-malic acid) and comparing the specific rotations of the resultants to that of the known compounds (Scheme 3.9).[24]



Scheme 3.9 Determination of Absolute Configuration of **36**.

[23] K. C. Nicolaou, A. J. Roecker, H. Monenschein, P. Guntupalli, M. Follmann, *Angew. Chem.,* **2003**, *42*, 3637–3642.
[24] K. Hiroya, T. Takahashi, K. Shimomae, T. Sakamoto, *Chem. Pharm. Bull.*, **2005**, *53*, 207–213.

Recently, Ramachary has developed a one-pot Robinson annulation methodology for the enantioselective synthesis of WMK analogues.[25] Even though being a conceptually nice approach to these compounds, yields and enantioselectivities are moderate.



Scheme 3.10 Ramachary's One-Pot Robinson Annulation.

Looking at these examples it seems reasonable to affirm that the large-scale preparation of WMK analogues is still an unresolved problem. Not only for the development of a general methodology which would provide access to enantiopure decalins, but also for an experimentally easy protocol which allow to obtain these building blocks in a multigram scale, since WMK is often the starting material of lengthy synthetic sequences and therefore, it must be produced in large quantities. For this reasons, we decided to develop a methodology which would allow us to secure large amounts of enantiopure material which was required for our total synthesis of anominine.

[25] (a) D. B. Ramachary, M. Kishor, *J. Org. Chem.*, **2007**, *72*, 5056–5068. (b) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.*, **2008**, *6*, 2488–2492.

3.3 Large-Scale Preparation of Wieland-Miescher Ketone Derivatives

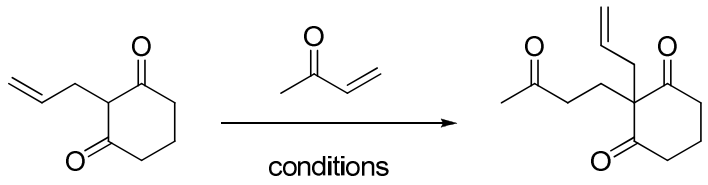
3.3.1 Optimisation of the MVK alkylation

After the initial difficulties in preparing the isohexenyl 1,3-diketone derivative **30** we focused on use of the allyl derivative as a starting point to develop the new protocol, since this known compound could be relatively easy prepared in a single step. Since we would need large amounts of the triketone **35** we focused first to improve its preparation. The described methodology for the methyl analog[26] (Table 3.2, Entry 1) was first adapted which while giving a good yield was problematic due to the excess of MVK used, which polymerised and resulted in a difficult work-up. Basic conditions employing KOH[1] (Entry 2) and Triton B[11,27] (Entry 3) resulted in the equal or lower yields, whilst omitting the base and working in water[28] (Entry 4) gave high yields but progress was too slow (10 days) to be a useful protocol. The reaction was even slower working in neat MVK probably due to the low solubility of the reagents (Entry 5). The use of Et_3N in DMF[29] (Entry 6) proved to be a good procedure. However, a large excess of MVK was required and yields were somewhat reduced by the interference of DMF in the work-up. Furthermore, while similar methods have been described using alternative solvents, such as THF,[30] acetonitrile[31] or EtOAc,[32] we decided to perform the Michael reaction under solvent-free conditions.

[26] J. Gutzwiller, P. Buchschacher, A. Fürst, *Synthesis,* **1977**, 167–168.
[27] T. Rajamannar, N. Palani, K. K. Balasubramanian, *Synth. Commun.* **1994**, *24*, 279–292.
[28] M. Scheck, M. A. Kock, H. Waldmann, *Tetrahedron*, **2008**, *64*, 4792–4802.
[29] H. Shigehisa, T. Mizutani, S. Tosaki, T. Ohshima, M. Shibasaki, *Tetrahedron*, **2005**, *61*, 5057–5065.
[30] T. Honda, F. G. Favaloro, Jr., T. Janosik, Y. Honda, N. Suh, M. B. Sporn, G. W. Gribble, *Org. Biomol. Chem.*, **2001**, *1*, 4384–4391.
[31] For organocatalyzed intermolecular reactions in water using proline derivatives, see: (a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.*, **2006**, *118*, 972–975; *Angew. Chem. Int. Ed.*, **2006**, *45*, 958–961; (b) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.*, **2006**, *128*, 734–735.
[32] S. G. Davies, A. J. Russell, R. L. Sheppard, A. D: Smith, J. E. Thompson*, Org. Biomol. Chem.*, **2007**, *5*, 3190–3200.

We were pleased to find the reaction was cleaner and proceeded more rapidly. In further refinements, the Et_3N was reduced to only 1 mol% and the MVK to only 1.1 equiv., which meant the method was extremely atom efficient. This in turn facilitated reactions on a large scale, since the majority of the MVK was incorporated into the product and did not have to be removed during the work-up. MVK is a volatile, highly toxic reagent that decomposes in the reaction mixture, so reducing the amount of MVK can be considered a very useful achievement. Using this simple protocol, the reaction reached completion in only 3 h in excellent yield (96% after column chromatography, Table 3.2, Entry 7).

Table 3.2. Different Protocols for MVK Alkylation.



34 **35**

Entry	Conditions	Yield (%)[a]
1	MVK (2.5 eq), AcOH, H_2O, hydroquinone, 75 ºC, overnight	82
2	MVK (1.5 eq), 10% KOH, 4:1 MeOH/H_2O, reflux, 75 min	82
3	MVK (1.5 eq), triton B (0.1 eq), MeOH, 60 ºC, 12 h	41
4	MVK (2 eq), H_2O, drop of EtOH, rt, 10 d	92
5	MVK (2 eq), rt, 14 d	35
6	MVK (3 eq), DMF, Et_3N (0.3 eq), overnight/12 h	87
7	MVK (1.1 eq), Et_3N (1 mol%), rt, 3 h	96

[a] Yield of isolated **35** after purification by flash chromatography.

3.3.2 Catalyst Screening

With an optimised Michael addition step in hand we focused on our main objective, the intramolecular aldol reaction. The previously described procedure by Hanselmann and Benn[5] served us as a starting point for the optimisation. By using this procedure with stoichiometric L-Pro in DMSO, compound (+)-**36** was prepared on a large scale in 72% yield and 84% ee (Table 3.3 Entry 1 and Figure 3.2). However, the cumbersome work-up and the laborious process for increasing the enantiopurity prompted us to optimize the synthesis of **36**. For this purpose, first the L-Pro catalyst loading was reduced from 100 mol% to 25 mol%, but a detrimental effect on the achieved enantioselectivity was observed (compare entries 2–3). The use of 50 mol% in entry 2 makes the reaction to proceed faster (24 h) but the enantioselectivity is moderate (64%). However, in entry 3 the reaction is slower (48 h) making it more selective and leading it to a higher ee (74%). Then, the process was studied using different proline-type organocatalysts **B–G** under various reaction conditions (Table 3.3): catalyst **B** (Entry 4) with brine,[4] **C**[33] in THF (Entry 5), or **D–F** under solvent-free conditions (Entries 6–8). Chemical yields ranged from good to excellent, but the enantiomeric excess was very poor, except for prolinamide **E**.

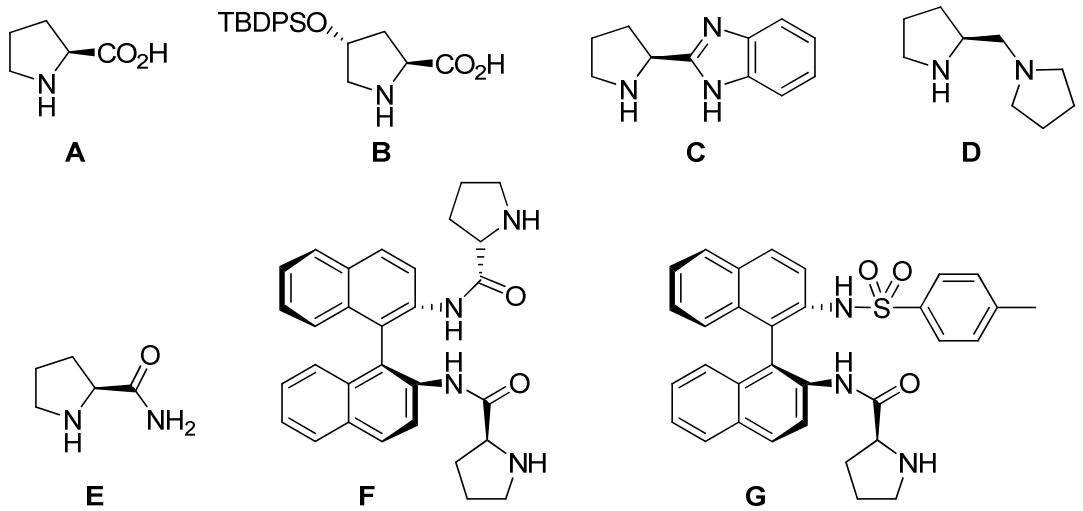
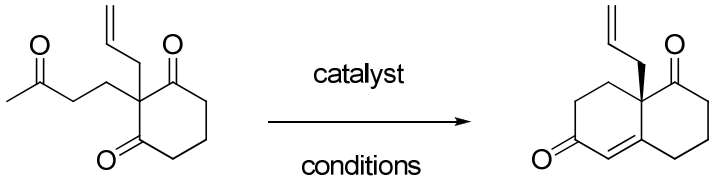


Figure 3.2 Catalysts Employed.

[33] E. Lacoste, E. Vaique, M. Berlande, I. Pianet, J.-M. Vincent, Y. Landais, *Eur. J. Org. Chem.* **2007**, 167–177.

Table 3.3 Catalyst Screening for the Intramolecular Aldol Reaction.



35 **36**

Entry	Catalyst (mol%)	Solvent	Time	Yield (%)[a]	ee (%)[b]
1	**A** (100)	DMSO	24 h	72	84
2	**A** (50)	DMSO	24 h	76	64
3	**A** (25)	DMSO	48 h	80	74
4	**B** (5)	brine	10 d	93	40
5	**C** (20)[c]	THF	24 h	90	34
6	**D** (5)[d]	free	24 h	93	8
7	**E** (5)[d]	free	24 h	96	82
8	**F** (5)[d]	free	24 h	87	32
9	**A** (5)	free	14 d	74	46
10	**G** (5)[d]	free	24 h	93	94
11	***ent*-G** (5)[d]	free	24 h	93	94[e]
12	**G** (5)[d]	brine	36 h	76	94
13	**G** (2.5)[d,f]	free	5 d	93	97
14	**G** (1)[d]	free	20 d	86	96

[a] Yield of isolated **36** after purification by flash chromatography.
[b] Determined by HPLC with a Chiralcel OD-H column.
[c] TFA (20 mol%) was added.
[d] Benzoic acid (1 mol%) was added.
[e] The opposite enantiomer was obtained.
[f] Reaction on 3-g scale of **35**.

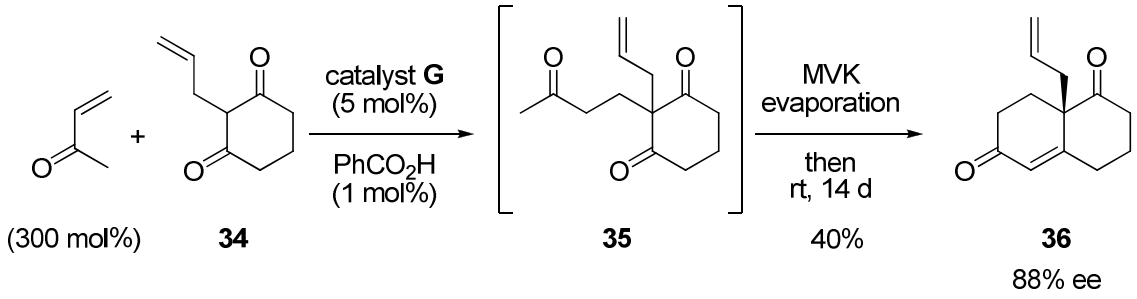
When L-Pro was used, this time working without solvent, the reaction was slow and the ee low (Entry 9). Using binam-proline-sulfonamide **G**, a recently reported catalyst for aldol processes in a solvent-free procedure,[34,35] for the synthesis of ketone **36**, a considerable improvement in the enantioselectivity (94%) was observed with an excellent 93% chemical yield (Entry 10).[36] The

[34] G. Guillena, C. Nájera, S. F. Viózquez, *Synlett*, **2008**, 3031–3035.
[35] For a pioneering solvent-free synthesis of Wieland-Miescher ketone (49%, 62.5% ee) using L-Pro (26 mol%), see: D. Rajagopal, K. Rajagopalan, S. Swaminathan, *Tetrahedron: Asymmetry*, **1996**, *7*, 2189–2190.
[36] As a result of the oral communication of the author in the "XXII Reunión Bienal de Química Orgánica" celebrated at Tarragona on June 2008, and after a chemistry discussion with Gabriela Guillena, we were asked to start a collaboration with Nájera's group hoping that their newly-developed catalyst could improve yield and enantioselectivity of our desired transformation.

process was carried out with the same efficiency using the catalyst ***ent*-G** to afford (–)-4 (Entry 11). The reaction also worked in brine, giving equally high enantioselectivity albeit with a lower chemical yield (Entry 12). The catalyst loading of **G** could be reduced to 2.5 mol% with a longer reaction time but increasing the enantioselectivity to 97% (Entry 13). The reaction even worked with only 1 mol% of catalyst (Entry 14) with similar enantiomeric excess (96%), although it required three weeks to reach completion.

3.3.3 One-Pot Asymmetric Robinson Annulation

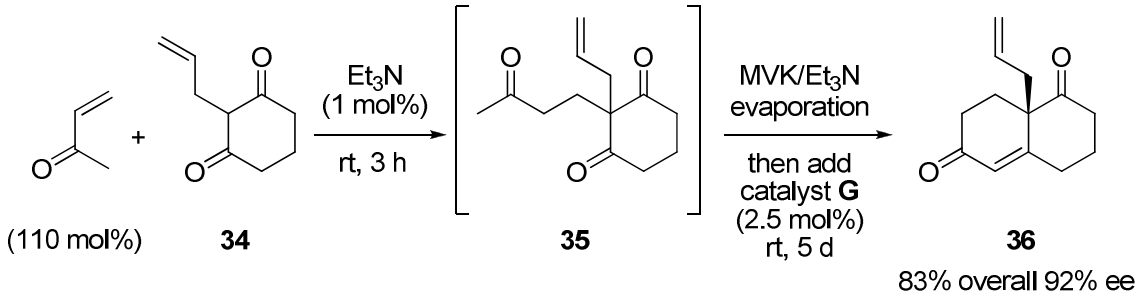
Since the catalyst could be easily separated from the product by direct chromatography of the reaction mixture, we examined its recyclability. We found that even in a large-scale reaction (3 g of **35**), the recovered catalyst (87% yield, not totally purified) could be reused to give a second batch of compound **36** in 96% yield and 94% ee. After the reaction conditions in two separate reactions for the asymmetric Robinson annulation (Michael + intramolecular aldol) of **34** to **36** were successfully established and knowing the ability of L-Pro to catalyse both reactions,[37] the one-pot process was investigated. We began by seeing if the organocatalyst binam **G** could catalyze the alkylation reaction with MVK and the cyclisation (Scheme 3.10).



Scheme 3.10 One-Pot Robinson Annulation.

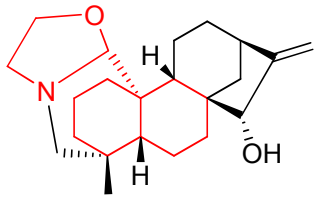
[37] T. Bui, C. F. Barbas III, *Tetrahedron Lett.*, **2000**, *41*, 6951–6954. For a recent improvement by changing the solvent DMSO for CH_3CN, see: K. E. Lazarski, A. A. Rich, C. M. Mascarenhas, *J. Chem. Educ.*, **2008**, *85*, 1531–1534.

Although catalysis took place, the reaction (5 mol% catalyst, MVK 3 equiv., 1 mol% benzoic acid) was slow and stopped at the triketone **35** stage without evolving further to the cyclised product **36** even after a prolonged reaction time (3 days). A thorough evaporation of the MVK under high vacuum allowed the reaction to progress to **36** but extremely slowly, reaching only 40% completion after 2 weeks. Moreover, when compared to the single-step process, a lower enantiomeric excess (88%) was obtained. Due to the fact that catalyst **G** allowed a clean reaction for both transformations in separated sequences, but failed in a one-pot, one-step procedure (**34**→**35**→**36**), the new solvent-free alkylation method was assayed. After the Michael process was carried out, the catalytic Et_3N and remaining MVK were evaporated (Scheme 3.11). The subsequent addition of catalyst **G** (2.5 mol%) to the crude triketone **35** gave compound **36** (92% ee) in 83% overall yield for the two steps. The slightly lower enantiomeric excess in this reduced protocol may be due to the extremely low catalyst loading, which makes the reaction more sensitive to small amounts of impurities formed in the alkylation step.

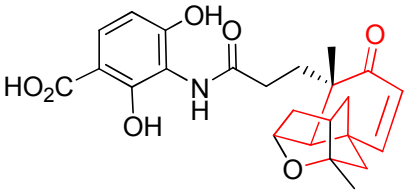


Scheme 3.11 One-Pot Stepwise MVK Alkylation Combined with Intramolecular Aldol Reaction.

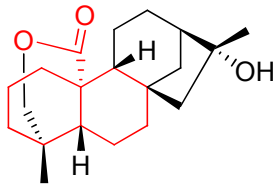
Despite the lower enantioselectivities, the simplicity of this procedure may be beneficial when working on a large scale. Considering the wide extent of angular-substituted decalins (see Figure 3.3) and the successful results obtained for the enantioenriched synthesis of ketone **36**, we decided to test its applicability to other substrates, such as a series of other Wieland–Miescher ketone analogues.



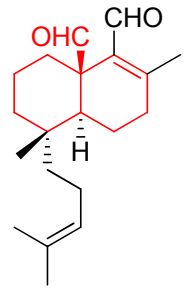
veatchine



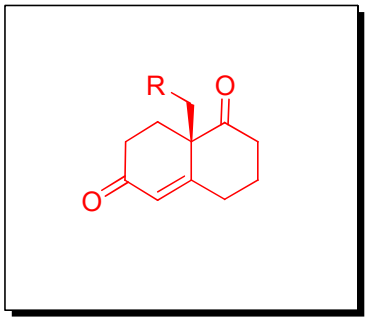
platensimycin
novel antibiotic

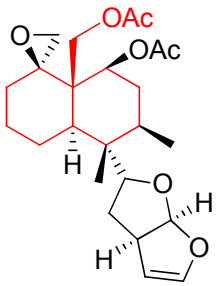


neotripterifordin
anti HIV agent

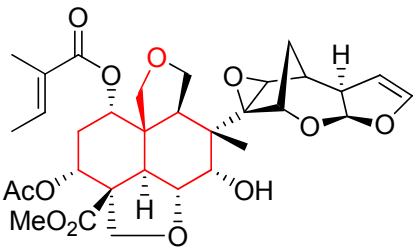


perrottetianal A
insect antifeedant

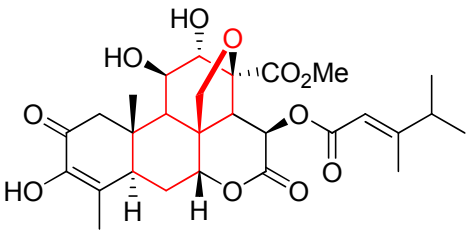




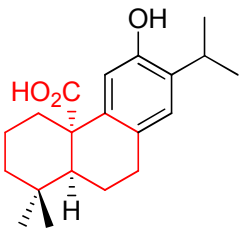
clerodin
insect antifeedant



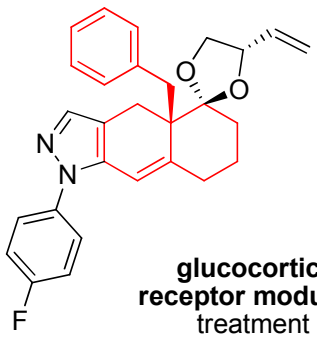
azadirachtin
insect antifeedant



bruceantin
antitumor agent



pisiferic acid
farnesyltransferase inhibitor

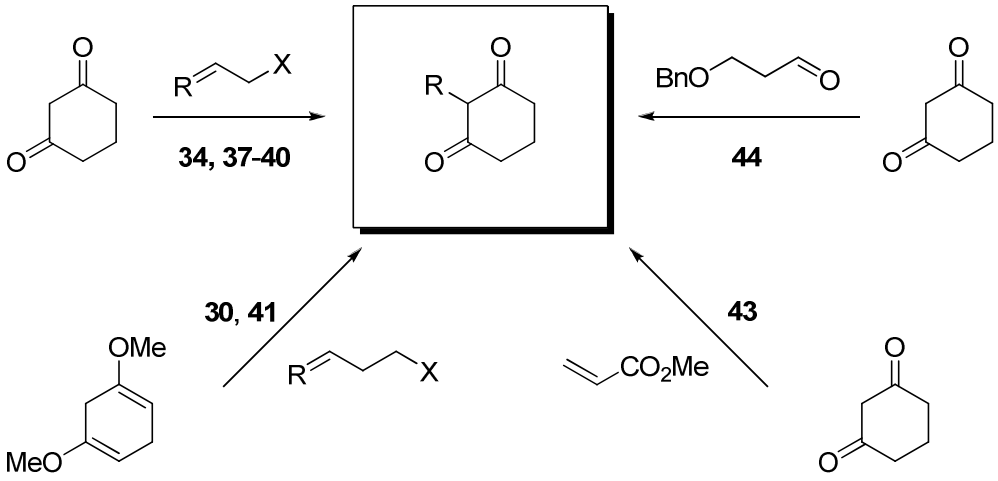


glucocorticoid receptor modulators
treatment of
autoimmune disorders

Figure 3.3 Natural Products Containing WMK-Analogue Subunits.

3.3.4 Substrate Preparation

The substrates chosen for this study were a variety of alkyl- , alkenyl- , alkynyl- and aryl-substituted 1,3-cyclohexanediones that might be useful in synthesis. Activated halides (*i.e.* allylic, benzylic and propargylic) were prepared by alkylation of 1,3-cyclohexanedione (Scheme 3.12 and Figure 3.4). For example, substrates **34** and **37** were synthesized according to our previously described procedure (*see figure and experimental section for more accurate details*), whereas substrates **38**,[38] **39**[39] and **40**[40] were prepared according to literature methodologies. However, unactivated halides (**41** and **30**) had to be prepared by alkylation of 2,5-dimethoxydihydrobenzene and further hydrolysis of enol ether.[41] Compound **42** was prepared from **30** by catalytic hydrogenation and methyl ester **43** was built up by Michael addition to methyl acrylate.[42] Finally, product **44** was generated by Knoevenagel condensation and reduction with the Hantzsch ester from the corresponding aldehyde.[43]



Scheme 3.12 Substrate Preparation.

[38] D. Lertpibulpanya, S. P. Marsden, *Org. Biomol. Chem.*, **2006**, *4*, 3498–3504.
[39] M. Fagnoni, P. Schmoldt, T. Kirschberg, J. Mattay, *Tetrahedron,* **1998**, *54*, 6427–6444.
[40] (a) T. Rajamannar, N. Palani, K. P. Balasubramanian, *Synth. Commun.*, **1993**, *23*, 3095–3108; (b) I. Shimada,K. Maeno, K. Kazuta, H. Kubota, T. Kimizuka, Y. Kimura, K. Hatanaka, Y. Naiotu, F. Wanibuchi, S. Sakamoto,S. Tsukamoto, *Bioorg. Med. Chem.*, **2008**, *16*, 1966–1982.
[41] E. Piers, J. R. Grierson, *J. Org. Chem.*, **1977**, *42*, 3755–3757.
[42] M. Scheck, M. A. Kock, H. Waldmann, *Tetrahedron*, **2008**, *64*, 4792–4802.
[43] D. B. Ramachary, M. Kishor, *J. Org. Chem.*, **2007**, *72*, 5056–5068.

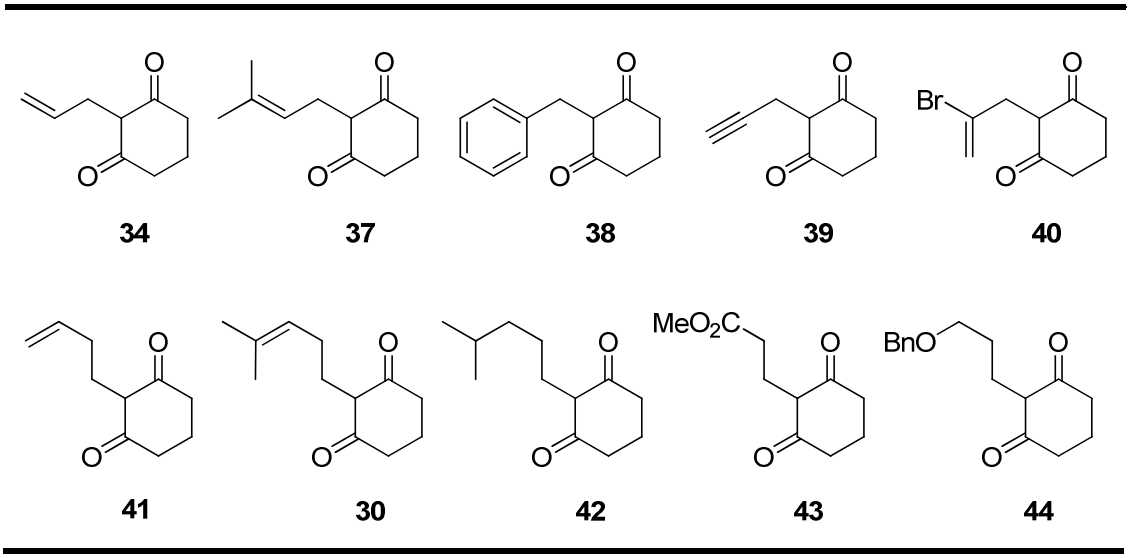
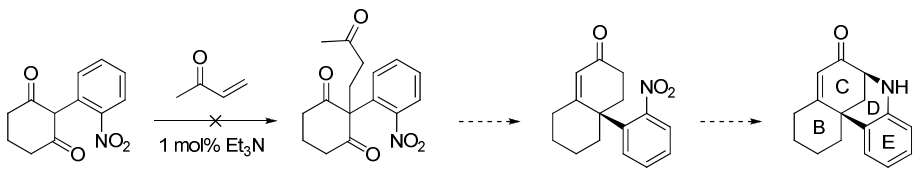


Figure 3.4 Precursors for the Robinson Annulation.

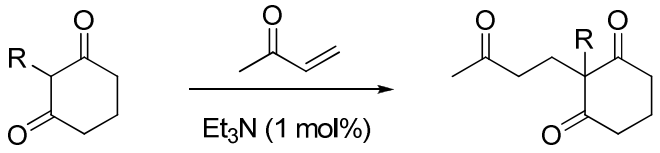
To synthesize compounds **33**, **45-52** our solvent-free methodology was used (Table 3.4).[44] The Michael addition to methyl vinyl ketone of compounds **30**, **34**, **37-44** for the preparation of the aforementioned triketones was carried out whenever possible using the solvent-free procedure developed for the optimized synthesis of **35** described above.[45] It should be noted that the success of the reaction depends on the triketone product being an oil, and thus able to act as a 'solvent', dissolving the starting material, which in all series was a solid compound. When the triketone formed was a solid (*i.e.* compounds **46** and **48**), a small amount of DMF (1–2 mL/g of starting material) was added to solubilise the reactants.

[44] The developed methodology was also tried for 2-aryl-substituted 1,3-cyclohexanedione in order to test the feasibility of constructing the BCDE ring system of aspernomine. Unfortunately, no product was detected because of the degradation of starting material.



[45] In a number of cases the quantity of MVK was increased to 2 equiv. when working on a smaller scale to ensure a complete reaction of the starting material.

Table 3.4 Preparation of 2-substituted 2-(3-oxobutyl)-1,3-cyclohexanediones **3c**–**3k**.[a]



Entry	R	Product	Yield (%)[b]
1	$CH_2CH=(CH_3)_2$	**45**	95
2	CH_2Ph	**46**	94
3	CH_2CCH	**47**	97
4	$CH_2CBr=CH_2$	**48**	88
5	$(CH_2)_2CH=CH_2$	**49**	90
6	$(CH_2)_2CH=C(CH_3)_2$	**33**	93
7	$(CH_2)_3CH(CH_3)_2$	**50**	85
8	$CH_2CH_2CO_2Me$	**51**	77
9	$(CH_2)_3OCH_2Ph$	**52**	91

[a] See Supporting Information for detailed experimental procedures. The reaction time was 24 h except for **3c** (6 h) and **3e** (4 h).
[b] Yield of isolated product after purification by column chromatography.

3.3.5 Cyclisation

The results of the asymmetric intramolecular aldol reaction of triketones **33**, **45**-**52** using the binam-prolinamide catalyst **G** are summarized in Table 3.5. In general due to the increased steric bulk of the side chain the reactions were slower than the aforementioned procedure leading to allyl derivative **36**, and varied from 4 days (**55**-**57**, **60**) to 10 days (**29**, **54**). Moreover, a catalyst loading of 5 mol% was required, which had to be increased to 10 mol% for the synthesis of **56** and **59**. The results obtained with substrates embodying the benzyl and 2-bromopropenyl appendages were better than those previously reported,[46] as well as WMK analogues **54** and **56**, which were obtained in 70% yield in each case and 94% and 96% ee, respectively. The new propargylic derivative **55** was formed in 78% yield

[46] X.-M. Zhang, M. Wang, Y.-Q. Tu, C.-A. Fan, Y.-J. Jiang, S.-Y. Zhang, F.-M. Zhang, *Synlett*, **2008**, 2831–2835.

and 90% ee. The most lipophilic compounds **29**, **57**, **58** were obtained with successful enantiodiscrimination, although in moderate yields (54–59%). The synthesis of the isohexyl derivative **58** was performed since it could be considered as a latent form[47] of the interesting homoprenyl derivative **29** for the synthesis of anominine and other related terpenes. Whereas compound **29** gave an excellent ee (96%), the effect of changing the double bond to a saturated side chain gave an unexpected result with compound **58** being obtained in only 84% ee. The products with an oxygenated side-chain **59** and **60** were isolated in 71% and 78% yield, respectively, and high ee. In summary, while yields in some cases were moderate,[48] the enantiomeric excess was uniformly excellent and superior to any obtained by other enantiocatalysts studied in Wieland–Miescher ketone synthesis.

Finally, it should be noted that while the procedure proved to have a very broad scope for the synthesis of 8a-susbstituted 3,4,8,8a-tetrahydronaphthalene-(2H,7H)-1,6-diones, a limitation was found when attempting to extend it to 5-methyl and 8a-aryl derivatives.[49]

[47] For a site-selective oxidation of isopropyl-ending alkyl side chains to the corresponding tertiary alcohol, see inter alia: a) C. Gómez-Reino, C. Vitale, M. Maestro, A. Mouriño, *Org. Lett.*, **2005**, *7*, 5885–5887; b) M. S. Chen, C. White, *Science*, **2007**, *318*, 783–787.

[48] It should be noted that the reactions on a 100-mg scale were unoptimised and we have observed that on increasing the scale generally better yields are obtained.

[49] Thus, when using catalyst **G**, the triketone obtained by the reaction of **34** with ethyl vinyl ketone did not undergo cyclisation, as well as with the 2-aryl substituted cyclohexanones.

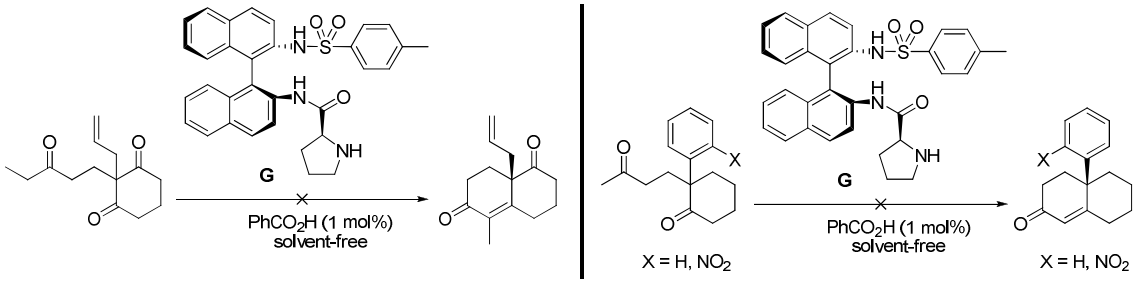
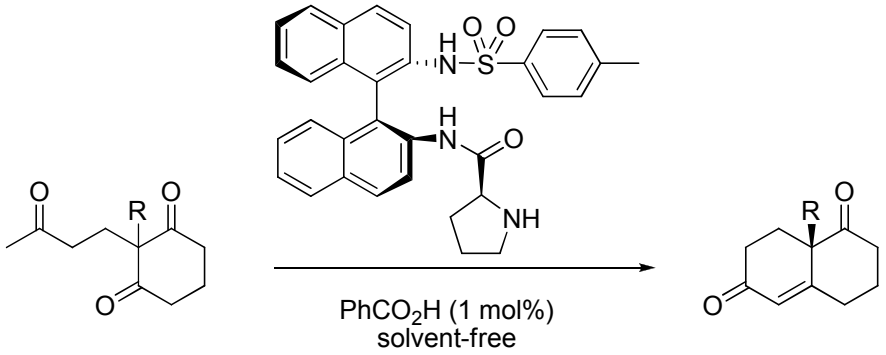
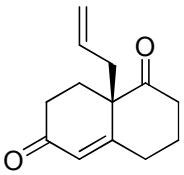
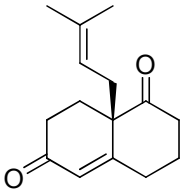
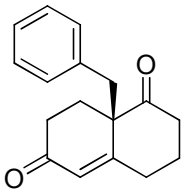
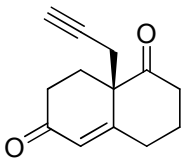
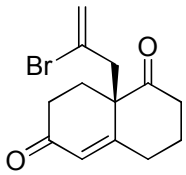
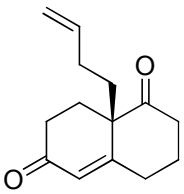
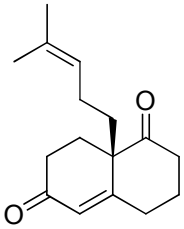
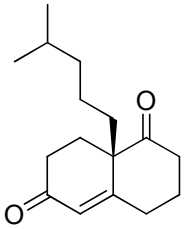
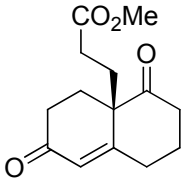
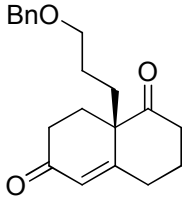


Table 3.5 Synthesis of Wieland–Miescher ketone analogues **29**, **36**, **53–60** using binam-prolinamide **G**.[a]

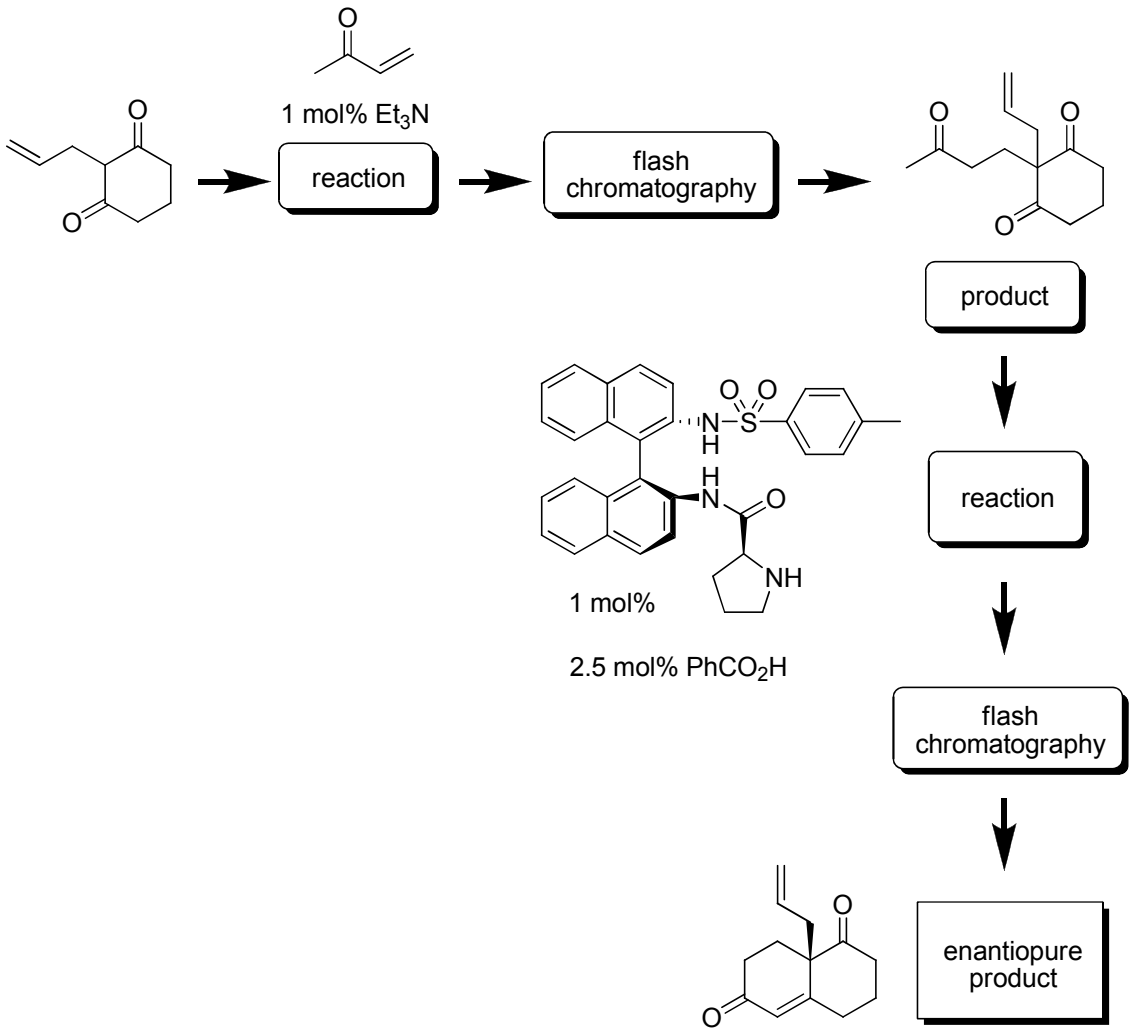


				
36	**53**	**54**	**55**	**56**
93%, 97% ee[b,d]	88%, 96% ee	70%, 94% ee[e]	78%, 90% ee	70%, 96% ee[c,f]
				
57	**29**	**58**	**59**	**60**
54%, 95% ee	59%, 96% ee	53%, 84% ee	71%, 95% ee[c,g]	78%, 94% ee

[a] All reactions carried out with 5 mol% of catalyst **G** and 1% benzoic acid unless otherwise noted. Yields reported correspond to the amount of isolated product after purification by column chromatography. Reaction times were 4 days (**55–57** and **60**), 5 days (**36** and **53**), 7 days (**58**), 8 days (**59**), and 10 days (**54** and **29**).
[b] 2.5 mol% of catalyst **G** was used.
[c] 10 mol% of catalyst **G** was used.
[d] Lit.: (56%; 85% ee);[30] (66%; 80% ee).[1]
[e] Lit.: (56%; 86% ee);[30] (50%; 72% ee).[1]
[f] Lit.: (46%; 83% ee).[30]
[g] Lit.: (65%; 87% ee).[30]

As it has been shown our methodology proved to be a general protocol for the enantioselective synthesis of Wieland-Miescher ketone analogues, and above all, the allyl derivative was obtained in the best yield and enantiomeric excess. Furthermore, the experimental operations have been reduced substantially (*compare Scheme 3.13 with Scheme 3.5*) which add extra value to this newly-developed methodology.

Initially, we had wanted to prepare the isohexenyl derivative **29**, but taking in mind the amount of steps required to synthesize its precursors combined with the low yield of the cyclisation, we evaluated the possibility to use allyl derivative **36** as a building block for the synthesis. Furthermore, whilst we initially believed the double bond would be compatible with the next steps of the synthesis, (*as it would be seen in Chapter 4*) the olefin will not be compatible with some of the oxidative operations. Having all these restrictions in mind seems that the best option is to prepare **36**, then convert the allyl to a masked group throughout the synthesis which could be easily transformed to the isohexenyl at the appropriate moment. In addition, to have a synthetically useful methodology it has to be performed in large-scale, and that was the next step to optimise.



Scheme 3.13 Experimental Flowchart of the Newly-Developed Methodology.

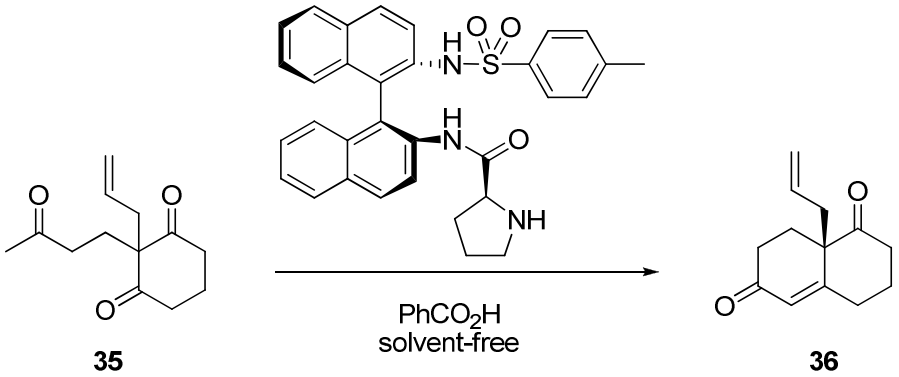
3.3.6 Large-Scale Preparation

The asymmetric cyclisation comprises two steps: i) the initial intramolecular aldol reaction, which is catalysed by the proline derivative, and ii) the dehydration of the aldol addition products, which is acid-catalysed. In the previous catalyst screening (Table 3.3) we observed that at the same acid concentration, reaction times decrease when increasing catalyst loading. Alternatively, enantiomeric excess drops when increasing catalyst loading. This is in accordance to theory,[50] which establishes that the more catalyst loading the faster the reaction is, but as a consequence, the reaction is less enantioselective. Our experiments were focused to find the optimum amounts of catalyst and acid which balanced maximum enantioexcess and minimum reaction time. The results are depicted in table 3.6. The fastest reaction was found when using 5% catalyst and 1% acid (Entry 1, ee = 94%). Moreover, the best enantioexcess was found when using 2.5% catalyst and 1% acid (Entry 2, ee = 97%). Decreasing to 1% the amount of catalyst did not drop enantioexcess but elongated reaction time (Entry 3). However, in terms of *catalyst economy* for the optimum enantioselectivity the best result is when using 1% catalyst and 2.5% acid (Entry 6). When comparing this result with entry 2 means that for almost the same enantioexcess we could do 2.5 batches of product with the same amount of catalyst.

[50] For this specific reaction: $v = (k_{\text{uncatalysed}} + k_{\text{catalysed}} [\text{catalyst}]) [\text{triketone}]$

IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (**1997**).

Table 3.6 Acid and catalyst concentration screening for the cyclisation of **3b**.

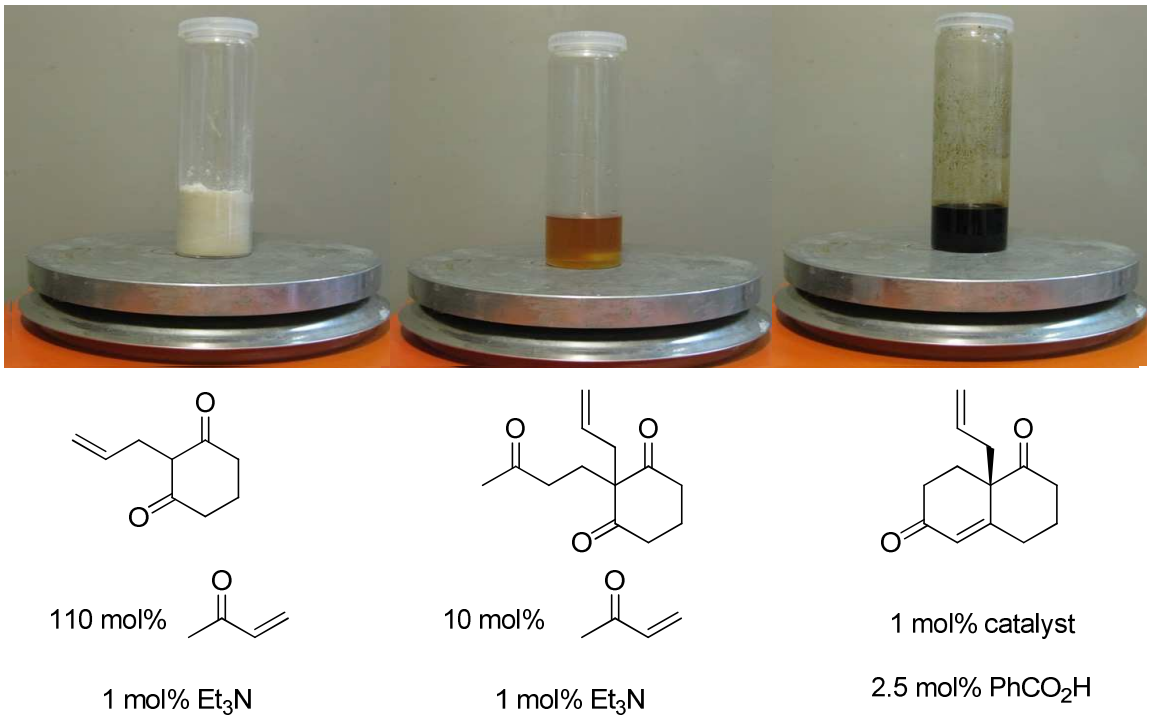


35 **36**

Entry	Catalyst (mol%)	Acid (mol%)	Time	Yield (%)[a]	ee (%)[b]
1	5	1	1 d	93	94
2	2.5	1	4 d	93	97
3	1	1	20 d	86	96
4	1	10	1.5 d	94	88
5	1	5	3 d	92	92
6	1	2.5	6 d	93	94

[a] Yield of isolated **36** after purification by flash chromatography.
[b] Determined by HPLC with a Chiralcel OD-H column.

Apart from the high chemical and optical yields, our newly-developed methodology is a great improvement in terms of experimental procedure. No special apparatus or equipment are required and the reactions should be performed in a vial in order to obtain good mixing and to remove water in the aldol cyclisation which condenses and remains on the vial wall, effectively removed from the reaction medium. Furthermore, no inert atmosphere is needed and reactions are run at room temperature. In the first step, the reagents are placed in a standard glass vial (Picture 3.1 Left) and after three hours of reaction all the initial solid 1,3-diketone is dissolved (Picture 3.1 Centre), which means that the Michael addition is finished. After removing the excess of MVK and Et_3N by thorough evaporation, binam catalyst is added making the solution turn black, and after six days of stirring at room temperature the reaction is complete (Picture 3.1 Right).



Picture 3.1 Large-Scale Preparation of **36**.

Considering the wide extent of WMK subunits in natural products and drugs (Figure 3.5), and since this methodology represents a breakthrough in the synthesis of WMK derivatives we envisaged the possibility to improve a longstanding unresolved problem in organic synthesis: the facile preparation of Wieland-Miescher ketone.

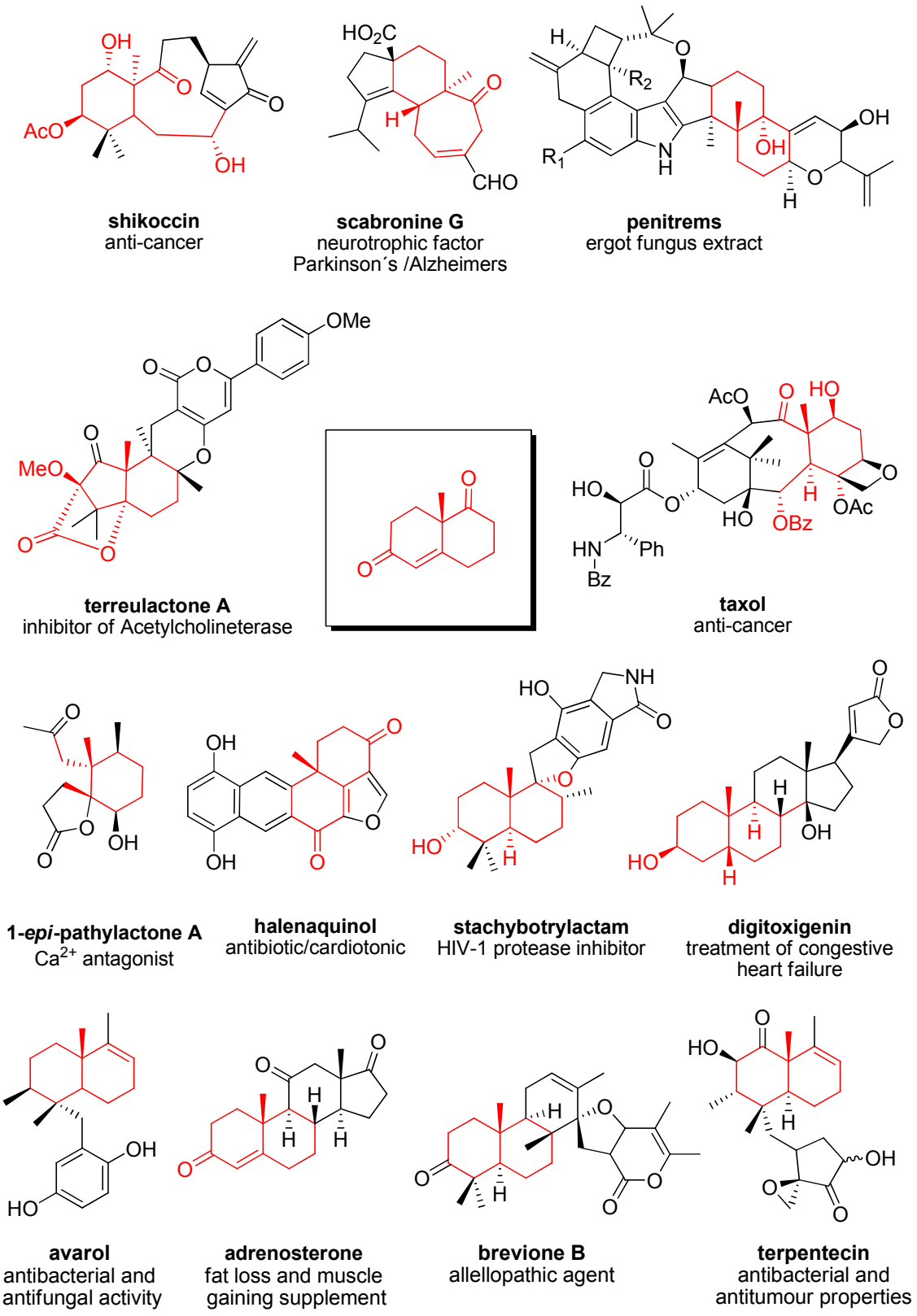


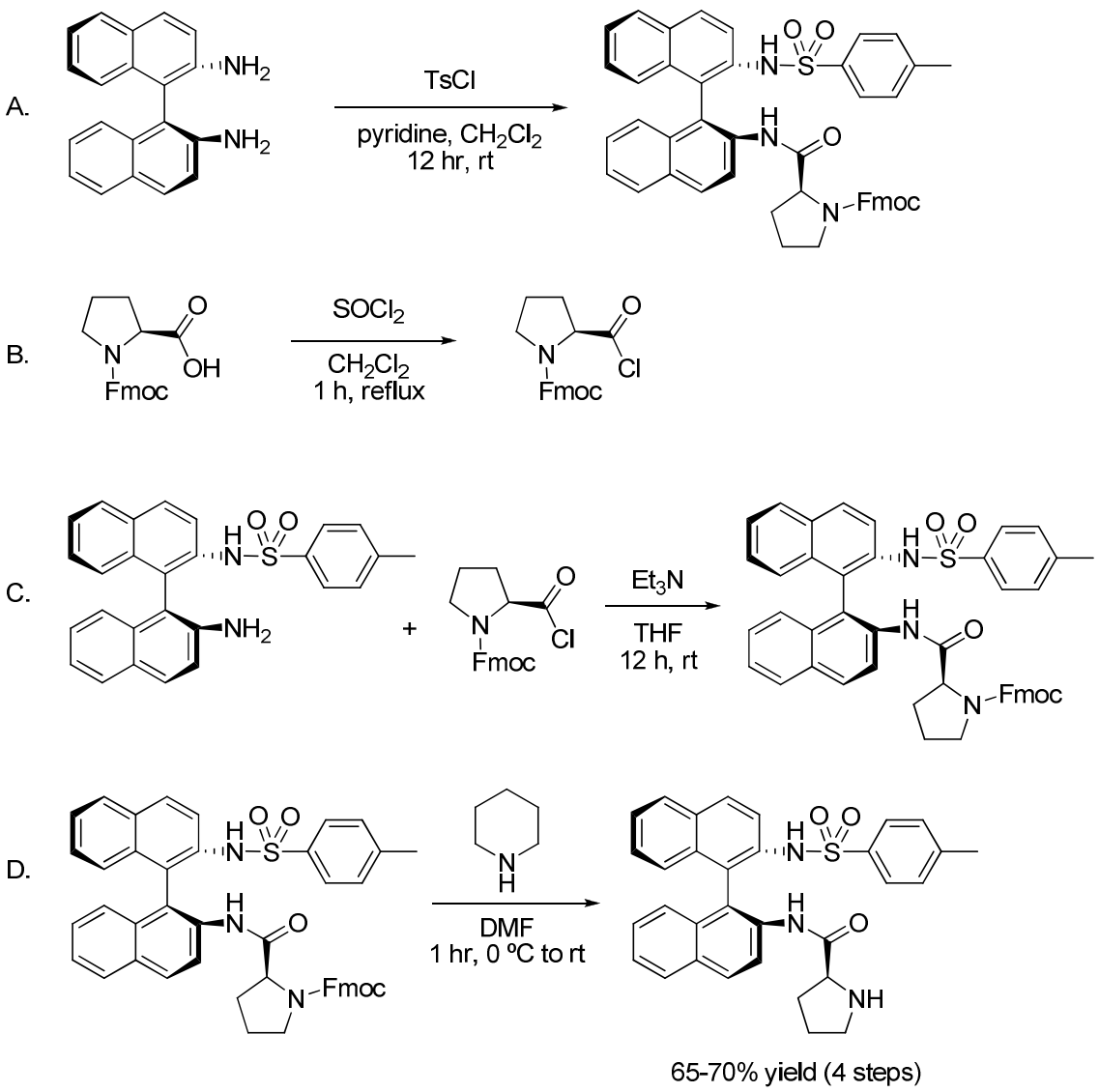
Figure 3.5 Natural Products Containing WMK Subunits.

3.3.6.1 *Organic Syntheses* Procedure

As a result of this experimentally-easy protocol we were asked to submit a proposal to submit of our methodology as an Organic Synthesis procedure. The first thing to do was to optimise for scaling-up and if possible, to shorten the catalyst synthesis.

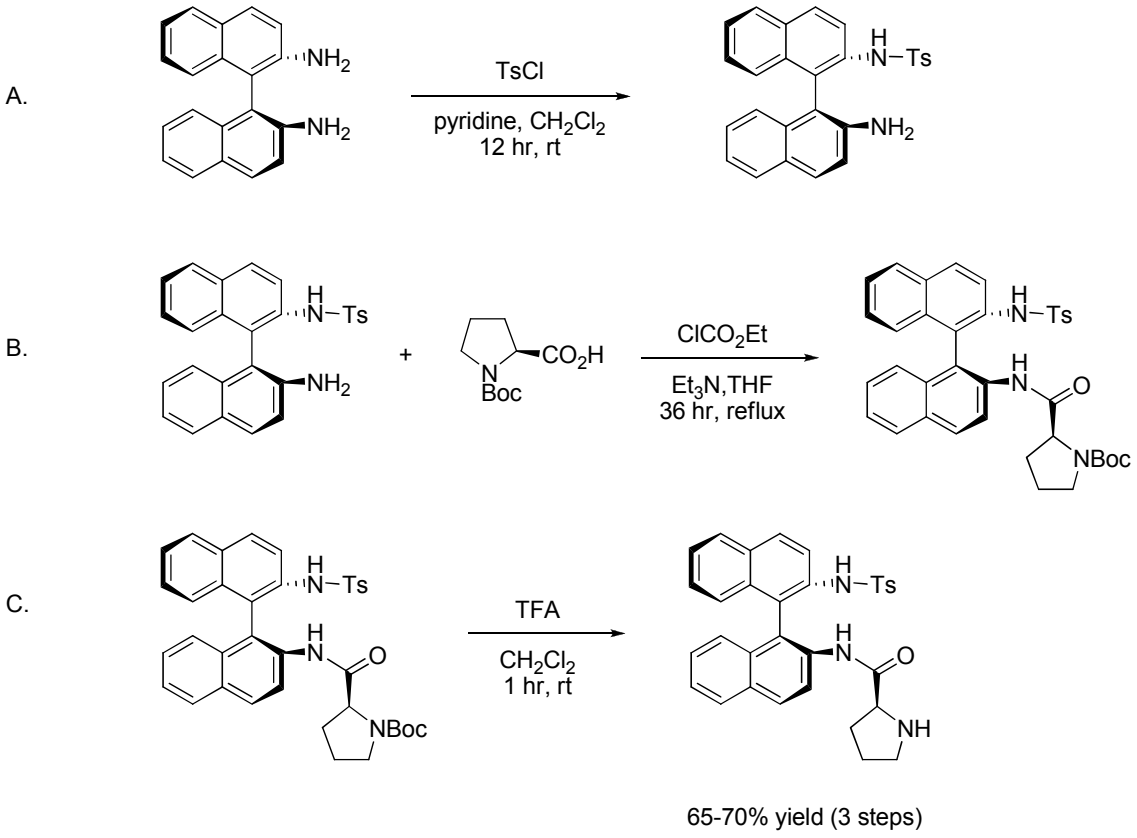
3.6.6.2 Catalyst Synthesis

The catalyst was developed by Nájera's group, and its initial synthesis showed in Scheme 3.14 required four steps and 65–70% overall yield. The main drawbacks of this methodology are the use of corrosive thionyl chloride to generate the acid chloride (Equation B) which is used in excess, and must be removed at the end of the reaction (Equation C). Moreover, the crude reaction mixture containing piperidine and fluorene complicates the purification after last step (Equation D). The overall yields after 4 steps vary from 65 to 70%.



Scheme 3.14 Initial Binam-Prolinamide Catalyst Synthesis.

The catalyst synthesis could be reduced to three steps by substituting acid chloride activation with mixed anhydride generation (Scheme 3.15, Equation B). The mixed anhydride is prepared *in-situ* and subsequently coupled with tosyl-binam present in the reaction mixture. The protecting group for the proline nitrogen is switched from FMOC to BOC, so in this manner last step reaction crude is much cleaner than before (BOC degradation products are volatile, Equation C). The overall yield is the same as in the previous preparation but with one step less and easier experimental manipulations.

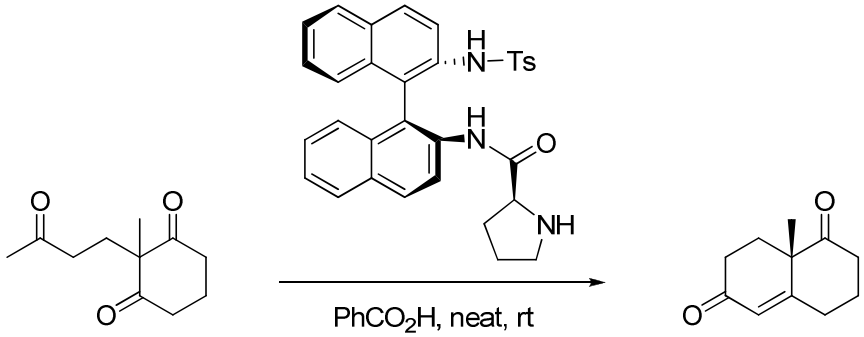


Scheme 3.15 Optimised Binam-Prolinamide Catalyst Synthesis.

3.3.6.3 Wieland-Miescher Ketone Preparation

Our experiments were focused to find the optimum amounts of catalyst and acid which balanced maximum enantioexcess and minimum reaction time. We started from the optimised version for the allyl series, and varied the amounts of catalyst and acid. The results are depicted in table 3.7. Initially, we had observed similar results with the methyl series as the allyl series. As the catalyst concentration decreases ee increases (Entries 1-3), but when 1 mol% catalyst is reached the reaction goes extremely slow and is no longer viable.

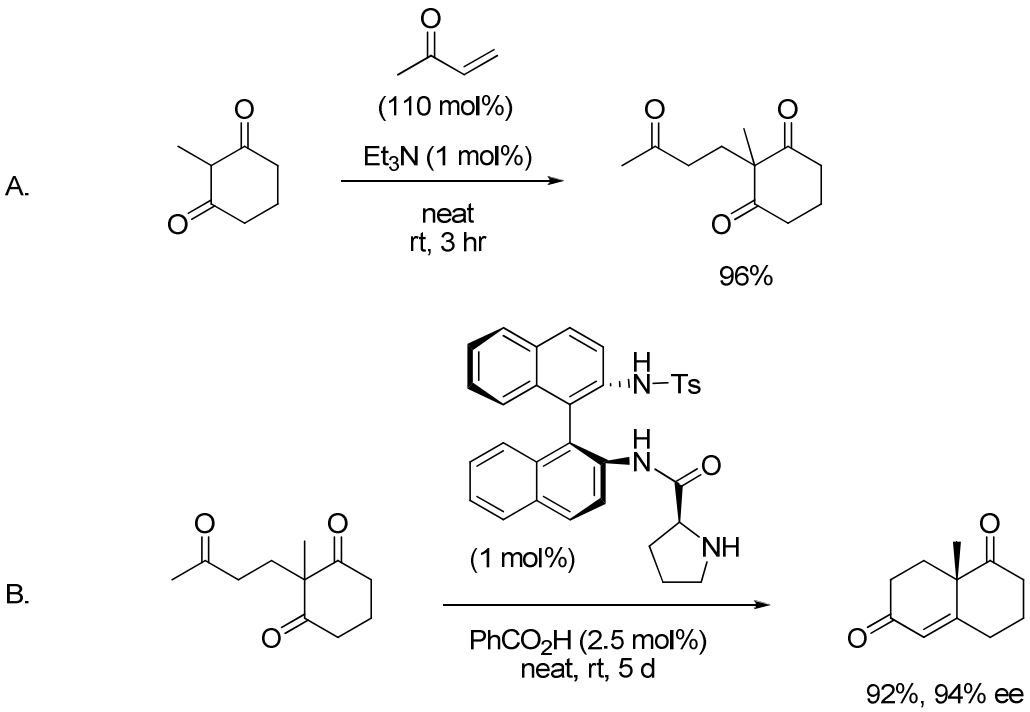
Table 3.7 Acid and Catalyst Concentration Screening for the Cyclisation of WMK.



Entry	Catalyst (mol%)	Acid (mol%)	Time	Yield (%)[a]	ee (%)[b]
1	5	1	1 d	95	90
2	2.5	1	4 d	95	92
3	1	1	slow	n.r.	n.r.
4	2	0.5	7 d	94	94
5	1	2.5	5 d	92	94
6	0.5	2.5	12 d	81	93
7	0.5	5	10 d	97	92
8	0.5	10	7 d	93	86
9	0.25	5	16 d	68[c]	90
10	0.25	10	14 d	87[c]	87
11	0.25	20	7 d	67[c]	82

[a] Yield of isolated **WMK** after purification by flash chromatography.
[b] Determined by HPLC with a Chiralcel OD-H column.
[c] Reaction stopped after reaction time.

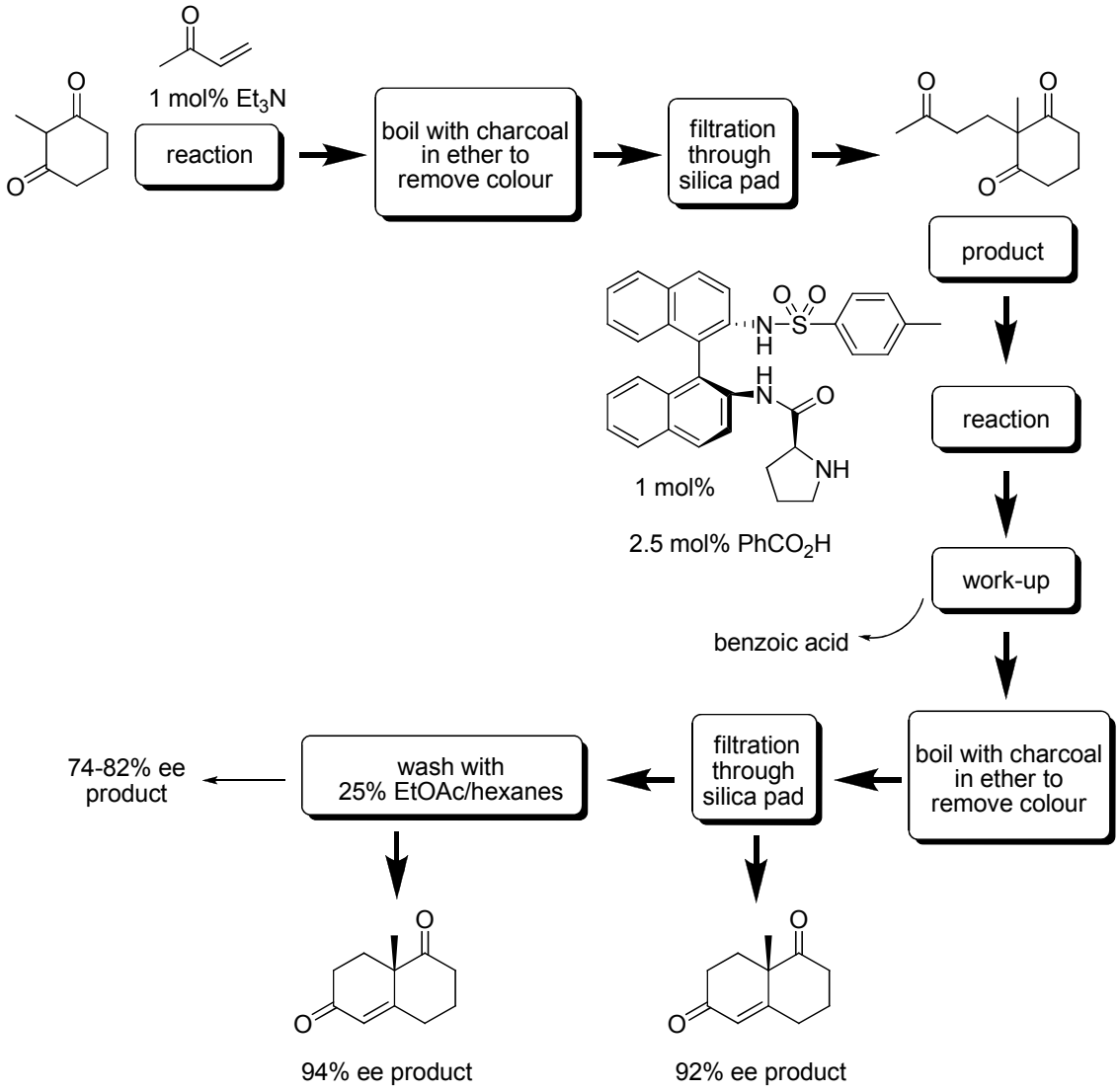
We found that increasing acid concentration also increase reaction rates but decreases ee. So we tried reducing acid to 0.5 mol% and using 2 mol% catalyst, which gave 94% ee (Entry 4). Alternatively, we looked at increasing the acid and concurrently reducing the quantity of catalyst (the most limiting reagent) and found that in analogous fashion 1% catalyst and 2.5% acid gave good results (Entry 5), practically identical as Entry 4 (2% catalyst 0.5% acid) but with the advantage of using half the catalyst. Further reductions in catalyst loading resulted in longer reaction times and slightly lower enantioselectivities (Entries 6-11), thus Entry 5 was chosen as the optimal reaction conditions.



Scheme 3.16 Optimised Preparation of Wieland-Miescher Ketone.

Our aim was to optimise even further the synthesis of Wieland–Miescher ketone in terms of experimental efficiency. Since the yields and enantioselectivities are quite high, we focused on reduce experimental manipulations in order to improve our methodology. The main goal was to reduce if possible, the purifications by column chromatography and substitute them for crystallisations or distillations.

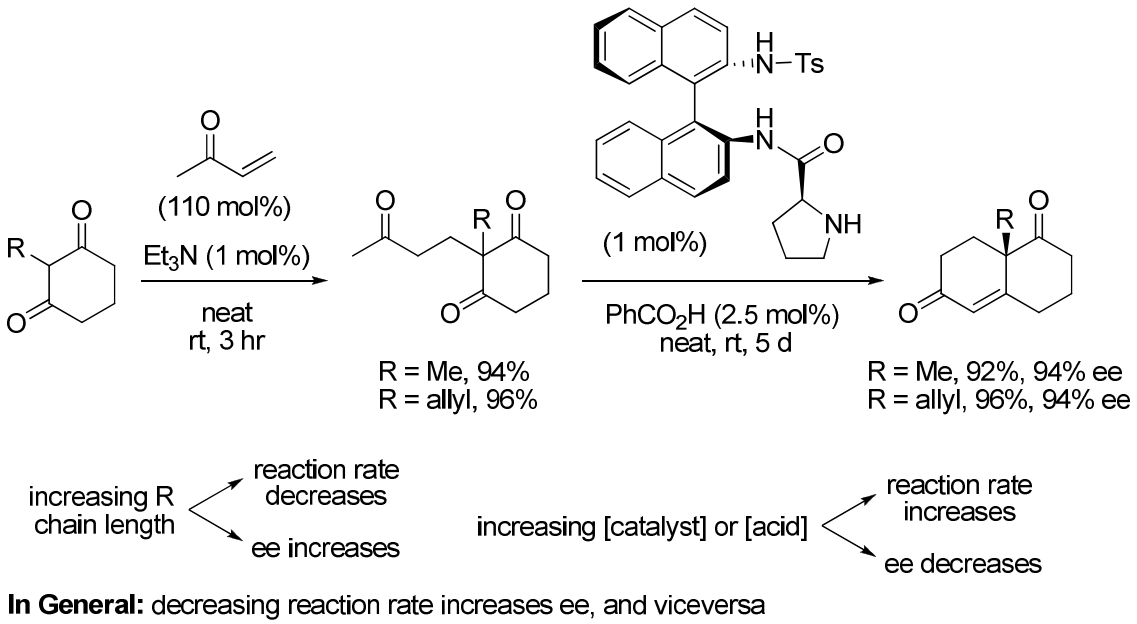
We noted that in some cases when applying the 1% catalyst protocol reaction was very slow. Purity of all reagents was investigated, methyl vinyl ketone was distilled, and finally we found that batches of 2-methyl-1,3-cyclohexandione vary in quality. The impurities were removed by recrystallising twice the substrate in water-ethanol. Since only 1 mol% catalyst is used in the second step, minor amounts of impurities can poison the catalyst and stop the reaction. After the Michael addition the reaction crude is dissolved in diethyl ether and boiled 15 minutes with activated charcoal and filtered through a short silica pad to remove impurities. Then, evaporation of the solvent along with the remaining excess of methyl vinyl ketone and triethylamine cleanly rendered Michael adduct in 96% yield. Addition of 1 mol% catalyst and 2.5 mol% of benzoic acid smoothly furnished Wieland-Miescher ketone. This crude is again dissolved in ether, boiled with charcoal and filtered through a short silica pad giving desired product in 93% chemical and 92% optical yield. If further enantioenrichment is required, the resulting solid can be slurried with 25% EtOAc/hexanes obtaining crystals with 94% ee and mother liquors ranging from 74-82%. The experimental flowchart of the optimised procedure is depicted in Scheme 3.17.



Scheme 3.17 Experimental Flowchart for the Improved Synthesis of WMK.

3.4 Summary and Conclusions

What initially started as a way to obtain an analogue of the Wieland-Miescher ketone for our synthesis of anominine turned out to be an experimentally-easy and robust methodology much wider in scope than our original plan. In general, the faster the reactions are, the lower the enantioselectivities (Scheme 3.18). Moreover, when increasing chain length reaction rates decrease, but in contrast, enantioselectivity increases. On the other hand, when increasing acid and/or catalyst concentrations reaction rates increase, thus lowering enantioselectivity. For the allyl- and methyl-substituted derivatives the catalyst loading is reduced to 1 mol% and yields are up to 90% overall and 94% ee. Both Michael addition and intramolecular aldol step are optimised resulting in a great improvement for the global Robinson annulation. No solvents are used and column chromatography purifications can be avoided thus culminating a sustainable and cheap procedure for the synthesis of substituted-decalins which should prove very useful in natural product synthesis.



Scheme 3.18 Summary of Reaction Parameters.

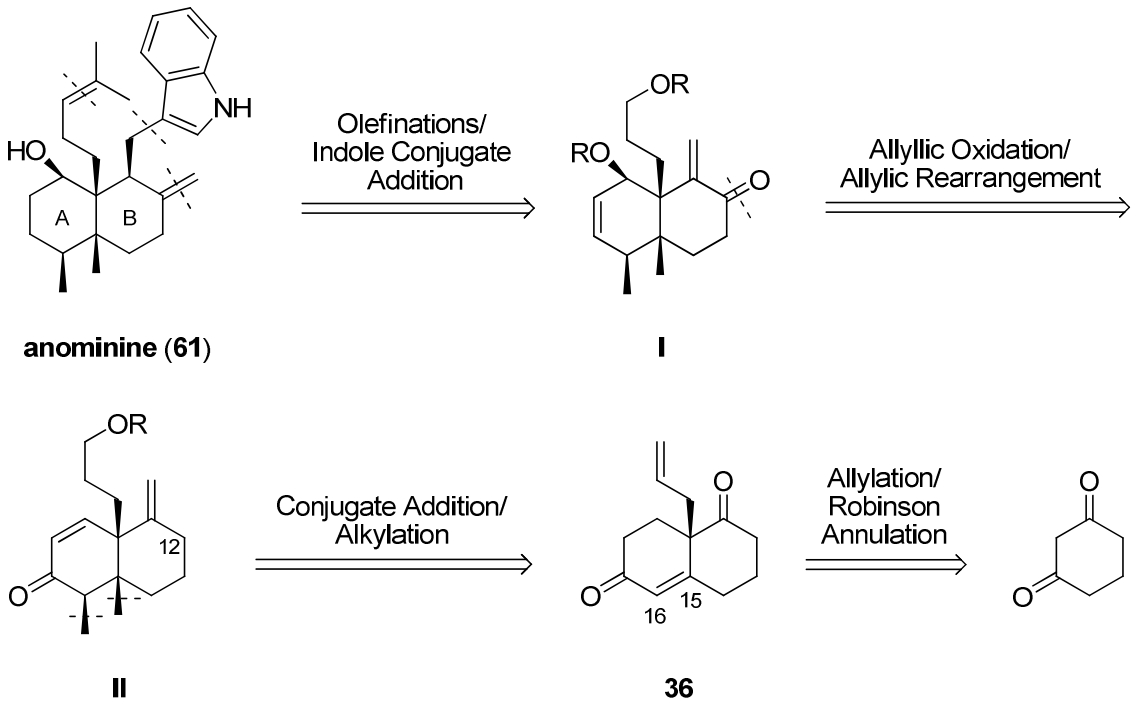
CHAPTER 4.

TOTAL SYNTHESIS OF ANOMININE

J. Am. Chem. Soc., **2010**, *132*, 5966–5967.

4.1 Retrosynthetic Analysis

So far the basic outline of synthetic plan for anominine had been established in Chapter 2. With the development of an effective large-scale WMK analogue synthesis in hand (Chapter 3), it was now the time to combine these two results into one coherent strategy. The retrosynthetic analysis that guided our efforts to prepare anominine is depicted in Scheme 4.1. In our previous model studies we planned to introduce the heterocyclic moiety via an indole conjugate addition to an enone. The olefins would be introduced in a late stage of the synthesis giving compound **I**. This intermediate would potentially come through an allylic oxidation at C12 position combined with an allylic-oxygen rearrangement of enone **II**. The key quaternary stereocentre at C12 would be installed by a methyl conjugate addition and the vicinal C16 methyl could be introduced in asymmetric fashion taking advantage of the geometry of the molecule. In the end, Wieland-Miescher derivative **36** would be generated by allylation of 1,3-cyclohexanedione and subsequent Robinson annulation methodology developed in the previous chapter.



Scheme 4.1 Retrosynthetic Analysis.

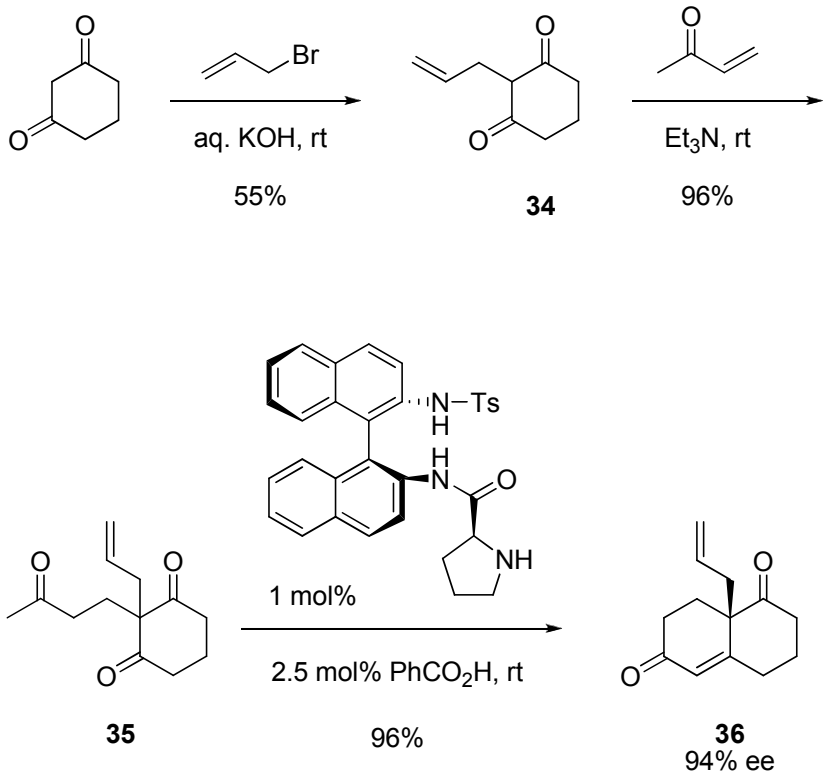
4.2 Large-Scale Preparation of 62

The first part of the synthesis relied upon a fast-throughput material processing, thus ensuring multigram-amounts of enone **II** could be obtained. Our aim was to develop a methodology which allowed us to avoid as many chromatography purifications, and if possible, couple as many transformations to telescope a reaction sequence thus ensuring brevity of execution.[1]

The journey started from commercially available 1,3-cyclohexanedione (Scheme 4.2) which was subjected to allylation in a biphasic fashion using aqueous potassium hydroxide. The low yield obtained is due to the difficulties to avoid double allylation or *O*-allylation since both methylene protons are quite acidic. However, the double allylated and *O*-allylated by-products are oils and were easily removed by washings the crude product with hexanes. On the contrary, starting material was difficult to separate from desired product, making preferable to add a slight excess of allyl bromide in order to consume all 1,3-cyclohexanedione. Although in this manner more by-products are generated and consequently lower yields are obtained, the purification is much easier making this procedure more time and effort efficient. Further tests adding copper[2] as an additive gave similar results and attempts to crystallise this material resulted in aromatisation of the carbocycle. Attempts to improve this step using Triton B (benzyltrimethylammonium hydroxide)[3] gave similar yields, but with a complicated work-up due to the amphiphilicity of the ammonium salt.

[1] T. Hudlický, J. W. Reed, *The Way of Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2004**.
[2] C. Prakash, A. K. Mohanakrishnan, *Eur. J. Org. Chem.*, **2008**, 1535–1543.
[3] T. Rajamannar, N. Palani, K. Balasubramanian, *Synth. Commun.*, **1993**, *23*, 3095.

Our recently-developed solvent-free methodology[4] (*see Chapter 3*) was applied smoothly furnishing Wieland-Miescher derivative **36** in 92% yield and 94% ee over the two steps.



Scheme 4.2 Large-Scale Preparation of **36**.

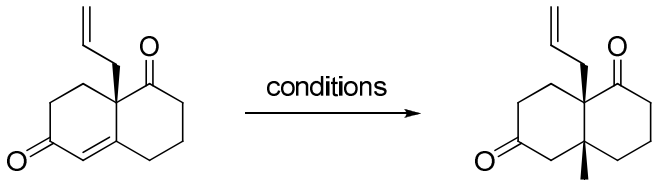
[4] B. Bradshaw, G. Etxebarria-Jardí, J. Bonjoch, S. Viózquez, G. Guillena, C. Nájera. *Adv. Synth. Catal.,* **2009**, *351*, 2482–2490.

The next key step was the diastereoselective introduction of angular methyl substituent which followed our methodology developed in Chapter 2 for the model synthesis (Table 4.1). Compound **62** was obtained in 61% yield using a known methodology[5] where a premixed solution of methylithium and copper iodide is added to the cold enone (Entry 1). Attempts to reduce the amount of methyllithium to 2.5 or 4 equivalents resulted in low conversions (Entry 2, 3). By increasing the amount of copper iodide to 3 eq and thus ensuring that no excess methyllithium remained which could effect 1,2 additions, the yield reached 79% (Entry 4). During the course of this thesis writing an extensive study of the lithiumdimethylcuprate conjugate addition to the same substrate was found in a PhD thesis.[6] Although competitive formation of 1,2-addition products during Gilman addition reaction on sterically demanding systems is a recognised problem,[7] it has been unresolved in a general manner. While 1,2-addition usually constitutes about 30-50% yield, addition of propanal dramatically decreases it to minute amounts (*ca.* 2%) making 1,4-addition product being obtained to up to 96%. It seems that propanal addition disrupts a cuprate species which is highly-reactive towards 1,2-addition, a similar effect to that obtained by water addition.[8] By adding 1.5 eq. of propanal prior to enone addition (Entry 5), similar yields were obtained. It should be noted that in the described method[6] HMPA was used as an additive (95% yield in small scale). However, the large amounts of this highly toxic reagent that would have been required ruled out its use. Therefore, the formation of 1,2-addition products might be a consequence of the difficulty to attack the strerically demanding substrate more than the presence of a highly-reactive cuprate species.

[5] R. A. Smith, D.J. Hannah. *Tetrahedron*, **1979**, *35*, 1183–1189.
[6] Roger Hanselmann PhD thesis, University of Calgary, **1996**, p. 25: https://dspace.ucalgary.ca/bitstream/1880/29331/1/20740Hanselmann.pdf
[7] (a) E. J. Corey, N. W. Boaz. *Tetrahedron Lett.*, **1985**, *26*, 6015-6022. (b) R. A. J. Smith, S. H. Bertz. *Tetrahedron*, **1990**, *46*, 4091.
[8] E. J. Corey, F. J. Hannon, N. W. Boaz. *Tetrahedron*, **1989**, *45*, 545–555.

The stereochemical outcome rationale for the formation of the *cis*-fused naphthalendione is the same as discussed in Chapter 2 for the corresponding methyl derivative and hence, it will not be discussed here.

Table 4.1 Preparation of **62**.



36
(94% ee)

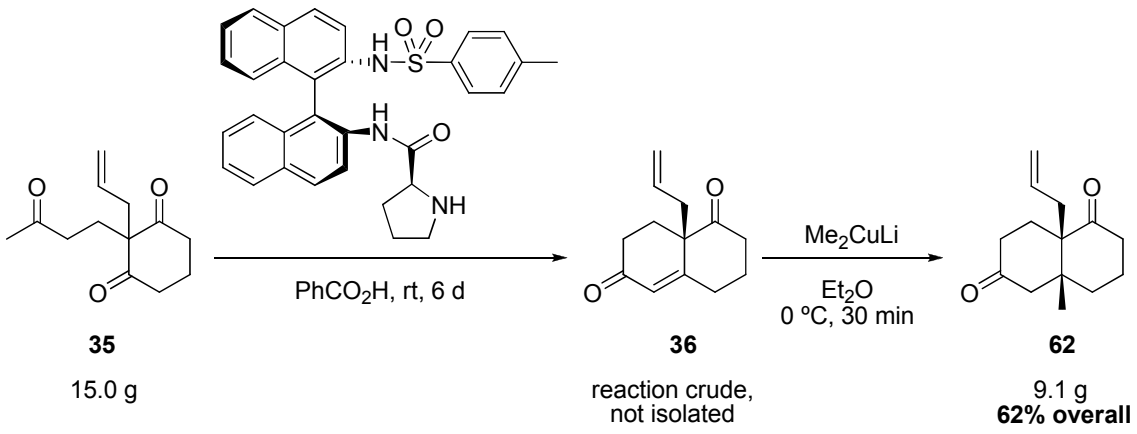
62

Entry	**Conditions**	**Yield**[a]
1	MeLi (5 eq), CuI (2.5 eq), Et_2O, 0 °C, 1h	61%
2	MeLi (2.5 eq), CuI (1.25 eq), Et_2O, 0 °C, 1h	20%
3	MeLi (4 eq), CuI (2 eq), Et_2O, 0 °C, 1h	57%
4	MeLi (5 eq), CuI (3 eq), Et_2O, 0 °C, 1h	79%
5	MeLi (6 eq), CuI (3 eq), propanal, Et_2O, 0 °C, 1h	70%

[a] Yield of isolated **62** after purification by column chromatography.

4.2.1 Consecutive Aldol and Conjugate Addition

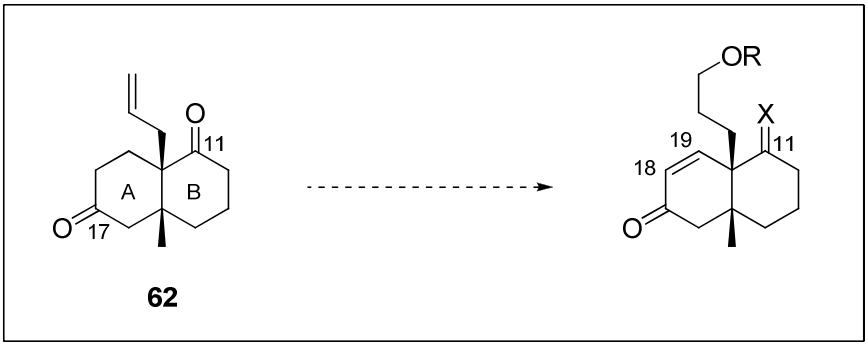
Since our aim was to couple as many transformations to obtain synthesis brevity, we focused on developing a protocol which allowed us to perform the aldol and conjugate addition reactions in a consecutive fashion. In this manner, stirring **35** in standard glass vial together with the binamprolinamide catalyst and benzoic acid for 6 days gave **36** (Scheme 4.3). The enone was diluted with Et_2O, dried over $MgSO_4$ and added via syringe to a solution of lithium dimethylcuprate to give **62** in 62% for the 2 steps. Although the yield is lower than doing the sequence stepwise (76%), it might be beneficial when working on large-scale and a fast-throughput of material is required. It should be noted that using the original WMK methodology (1 eq of L-Pro in DMSO) such an operation would be impossible to carry out.



Scheme 4.3 Consecutive Aldol and Conjugate Addition Reactions.

4.3 Differentiation of the Carbonyl Groups in 62

Next steps were the differentiation of the carbonyl groups in **62** (Scheme 4.4) in order to install the double bond on the A-ring required for the regioselective introduction of C16 methyl and the allylic transposition of the oxygen functionality, as well as the suitable functionality for the C11 position which could be carried through all these transformations.



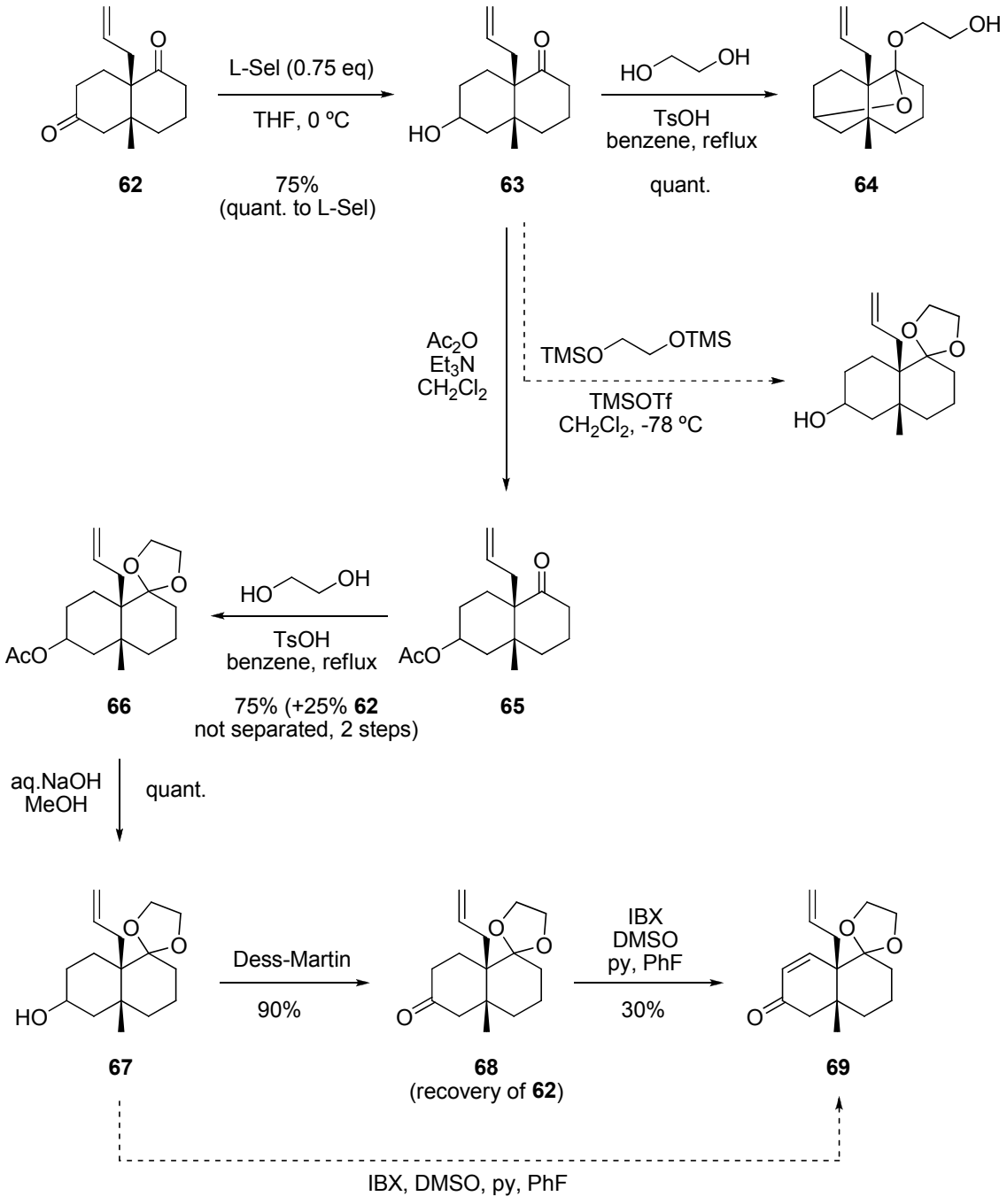
Scheme 4.4 Differentiation of the Carbonyl Groups at C11 and C17.

4.3.1 Via Selective Reduction at C17

Compound **62** was selectively reduced at the C17 position using 0.75 eq of L-Selectride (Scheme 4.5). Atempts to protect C11 ketone as ethylidene acetal resulted in the obtention of product **64** when standard methodology was used, and no reaction proceeded when using Noyori's protocol[9] with *bis*(TMS)ethylene glycol. Since no direct acetalisation could be done on **63**, we had to protect C17 alcohol as an acetate and then protect the ketone under standard procedure to yield **66**. Deprotection in aqueous methanolic sodium hydroxide rendered alcohol **67**. Since no double oxidation using Nicolaou's hipervalent iodine reagent IBX[10] could be done, we had to do it stepwise by first submitting alcohol **67** to Dess-Martin reagent (75% yield from **62** and recovery of 25% of **62**) and then oxidising with IBX. Attempts to epoxidise **69** either with H_2O_2 in 10% NaOH or ^{t}BuOOH/Triton B in toluene resulted in no reaction.

This sequence seems to be acceptable in terms of yield but long (6 steps), as a consequence, other pathways were explored.

[9] T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett.,* **1980**, *21*, 1357.
[10] K. C. Nicolaou, T. Montagnon, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

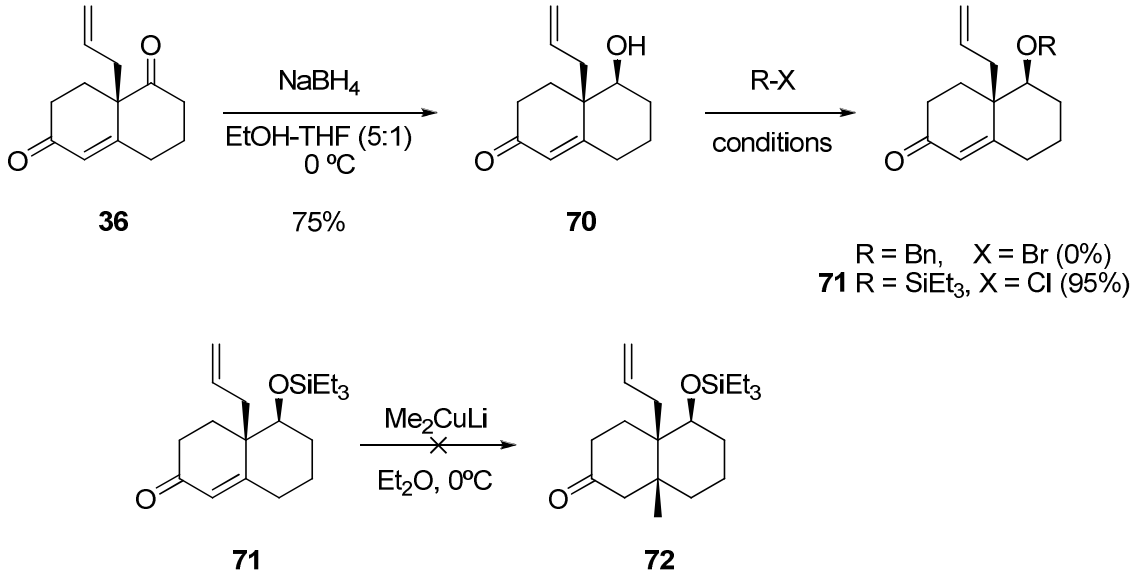


62 **63** **64** **65** **66** **67** **68** **69**

Scheme 4.5 Preparation of **69**.

4.3.2 Via Selective Reduction at C11

Addition of sodium borohydride to **36** gave **70** as a single isomer in 75% yield (Scheme 4.6). Initial attempts to protect the resulting alcohol as a benzyl ether failed in all conditions tried (2 eq NaH/1.5 eq BnBr/0.1 eq Bu_4NI/DMF, 1.5 eq Ag_2O/2 eq BnBr/0.1 eq KI/CH_2Cl_2, 12 eq Et^iPr_2N/6 eq BnBr/0.1 eq DMAP/0.1 eq Bu_4NI/THF). Then, alcohol **70** could be protected as a triethylsilyl ether employing 1.1 eq Et_3Si-Cl and 2 eq imidazole in CH_2Cl_2 furnishing **71** in 95% yield. However, it did not react under the aforementioned conjugate addition conditions, an unfortunate result with some literature precedent.[11]

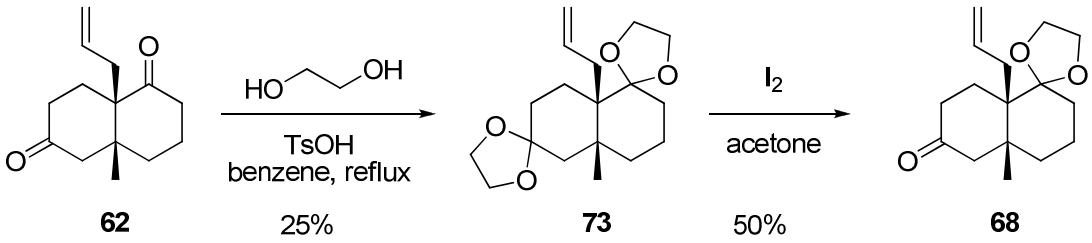


Scheme 4.6 Preparation of **72**.

[11] A. S. Vellekoop, R. A. J. Smith, *Tetrahedron*, **1998**, *54*, 11971–11994

4.3.3 Via Selective Acetal Cleavage at C17

Dione **62** was protected under standard conditions to give diacetal **73** (Scheme 4.7) along with some polar products, probably a mixture of the corresponding hemiacetals. Submitting this compound to iodine in acetone[12] surprisingly gave **68** as a single product. This result shows the big difference in reactivity of the same group but under different environment. The adjacent quaternary centre shields the acetal avoiding the approach of the bulky iodine and thus preventing the deprotection of the acetal. Therefore, it might be possible to protect selectively at C17 and modify the carbonyl group at C11. This sequence proved to be shorter (3 steps to **69** counting the corresponding IBX oxidation) compared with the previous one, but overall was low yielding.

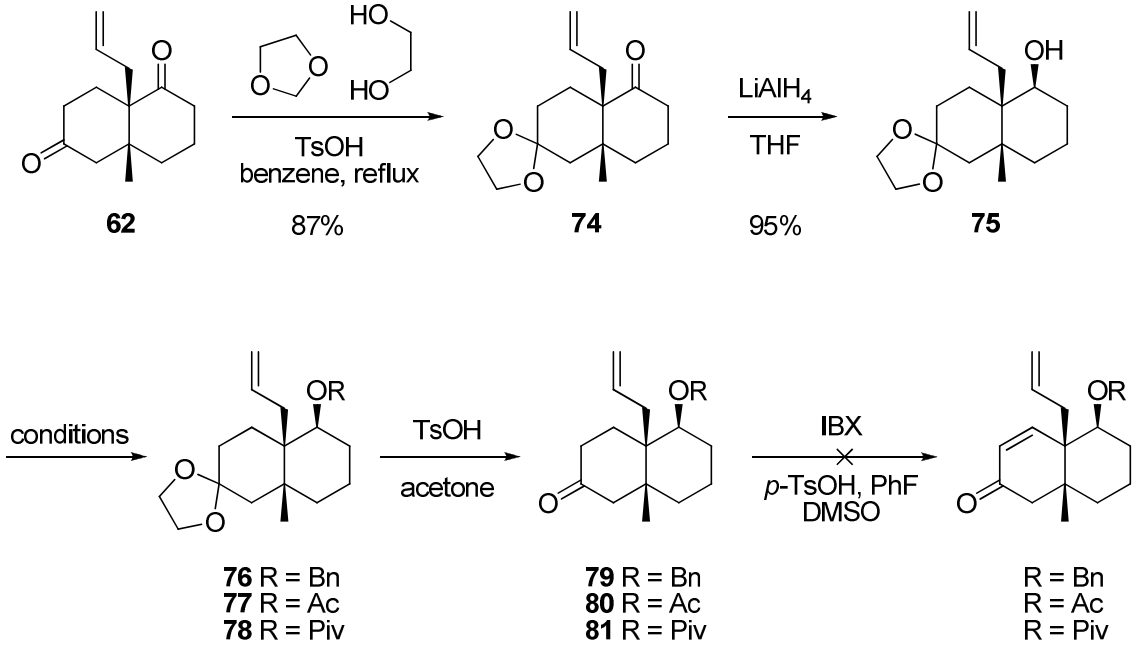


Scheme 4.7 Preparation of **68**.

[12] J. Sun, Y. Dong, L. Cao, X. Wang, S. Wang, Y. Hu, *J. Org. Chem.* **2004**, *69*, 8932–8934.

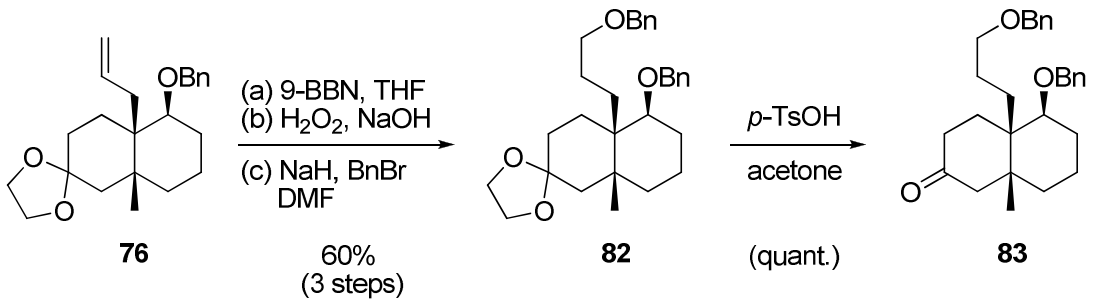
4.3.4 Via Selective Acetalisation at C17 and Reduction at C11

Since we observed a reactivity difference between the two carbonyl groups we subjected dione **62** under mild acetalisation conditions and satisfactorily, **74** was obtained in 87% yield (Scheme 4.8). Reduction of the remaining ketone with sodium borohydride required a large excess of reductant (*i.e.* 8 eq $NaBH_4$ for 25% conversion). By employing lithium aluminium hydride was quantitatively obtained alcohol **75**, which was protected as a benzyl ether (NaH/BnBr/*n*-Bu_4NI/DMF), acetate (Ac_2O/DMAP/py/CH_2Cl_2) and pivaloate (Piv-Cl). Removal of the acetal was then accomplished by transacetalisation in the presence of a large excess of acetone. However, IBX oxidation resulted in cleavage of the hydroxyl protecting group in all cases studied.



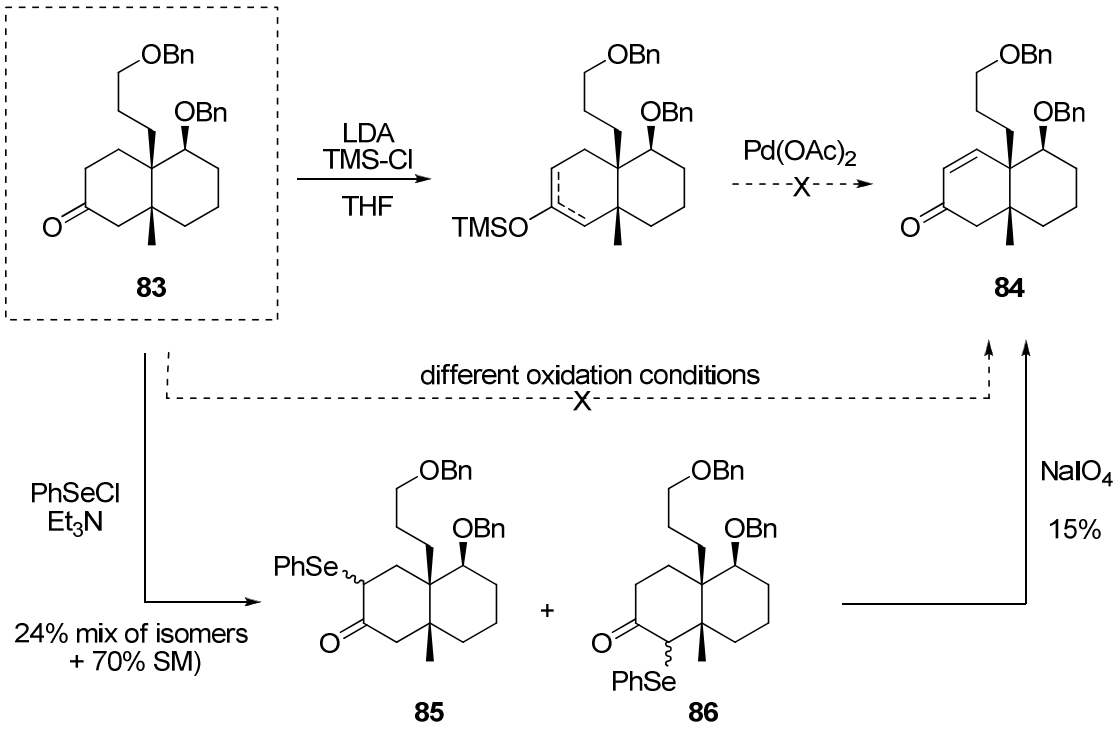
Scheme 4.8 Preparation of **79–81**.

An alternative route depicted in Scheme 4.9 was studied. Olefin **76** was hydroborated and the remaining alcohol was protected as benzyl ether followed by acetal removal under transacetalisation conditions.



Scheme 4.9 Preparation of **83**.

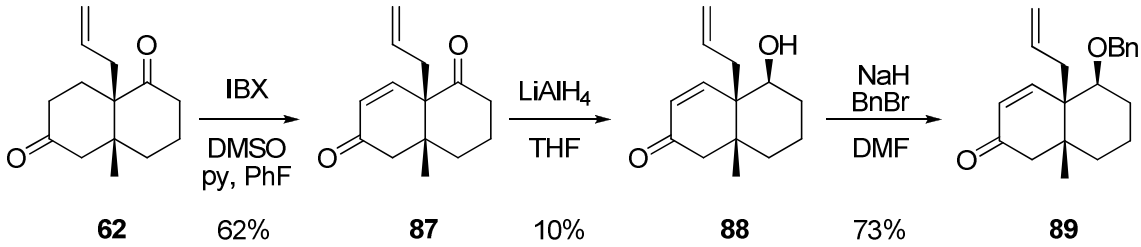
To introduce the double bond to allow methyl regioselective alkylation several methods were tested (Scheme 4.10). None of the oxidations tested (IBX/*p*-TsOH/DMSO/PhF; IBX/pyridine *N*-oxide/DMSO; Br_2/HBr/py and Saegusa oxidation) gave the desired enone **84**. Enolate generation of **83** was found to be not regiospecific since trapping with either TMS-Cl or PhSeCl gave a mixture of regioisomers. Attempts to convert **85** into **84** by oxidation gave very low overall yields, an unacceptable result giving as well the toxicity of using selenium reagents.



Scheme 4.10 Preparation of **84**.

4.3.5 Via Selective IBX Oxidation

The initial idea was to oxidise dione **62** to the dienone, and afterwards selectively reduce C12-C13 double bond by conjugate reduction taking advantage of the molecular geometry. Surprisingly, when **62** was submitted to IBX oxidation conditions it gave mainly enone **87** along with minute amounts (*ca.* 9%) of the dioxidised product (Scheme 4.11). Reduction of **87** with lithium aluminium hydride furnished alcohol **88** which was subsequently protected as a benzyl ether in 73% yield.



Scheme 4.11 Preparation of **89**.

We balanced advantages and disadvantages of these different ways of differentiating the two carbonyl groups, and the conclusions are the following:

- Protecting the C11 carbonyl (as ethylidene acetal, benzyl ether, silicon ether, acetate or pivaloate) not only adds two or more extra steps to the reaction sequence, but also brings incompatibility problems with the next steps.

- The most easy and efficient way is the selective acetalisation at C17, which keeps the other carbonyl free to work with it.

As a consequence of both observations we decided to mask the C11 carbonyl as a double bond, which at the same time has the required functionality to install the exocyclic enone to incorporate the heterocyclic moiety. In this manner we save some unnecessary steps of reduction, protection and deprotection.

4.3.6 Via Selective Acetalisation and Wittig

We had initially focused on protecting the C11 position to avoid problems in differentiating of multiple double late in the synthesis. However, after setbacks due to the incompatibility of many protecting groups with the reaction conditions (i.e. the IBX step) we decided that direct introduction of the double bond from the start would:

- Avoid problems with protecting group. It should be compatible to the IBX oxidation conditions.

- The required functionality for the allylic oxidation would be in place and would therefore reduce considerably the number of steps in the synthesis.

However, it should be noted that whilst this approach had a great number of advantages, it was deemed a very high risk strategy due to the need to differentiate several double bonds towards the end of the synthesis.

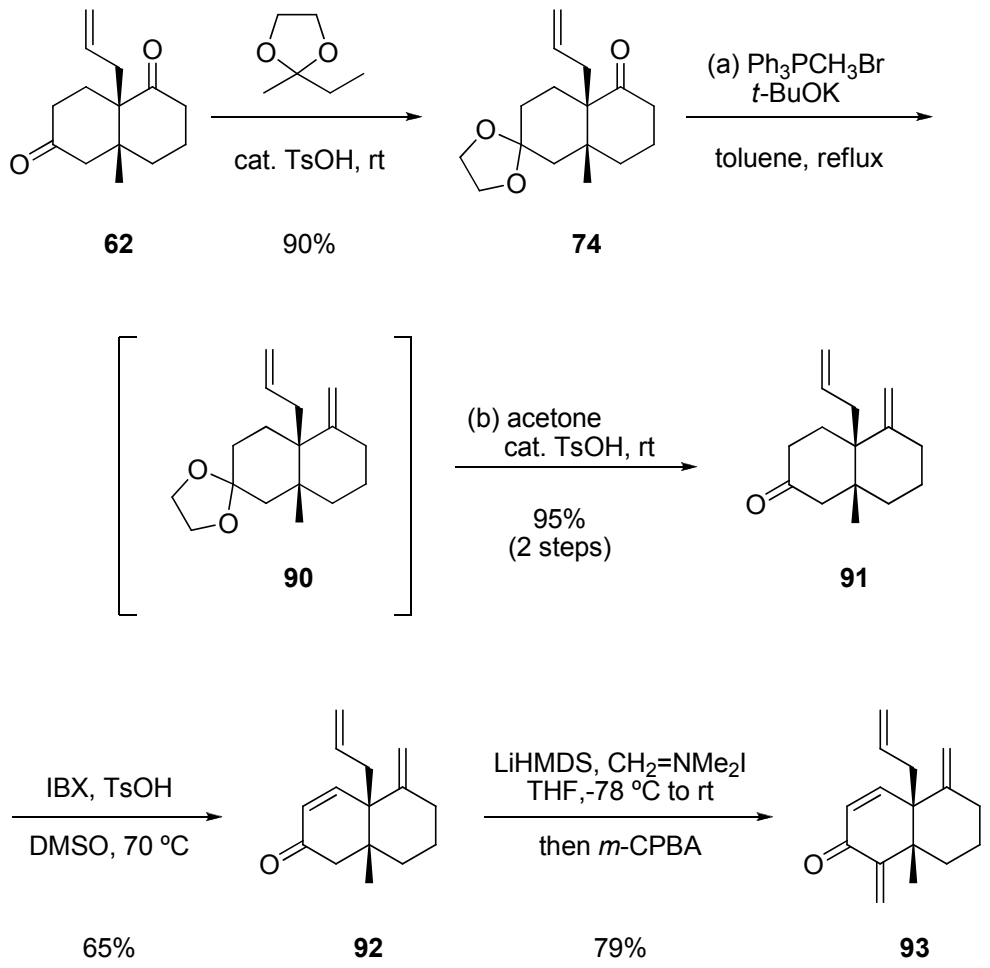
Regioselective olefination was achieved using a relay procedure similar to that developed for the trimethyl model analogue (Chapter 2). Selective protection of the less-hindered carbonyl by transacetalisation using 2-ethyl-2-methyl-1,3-dioxolane furnished **74** in 90% yield (Scheme 4.12). Exposure of this crude product to Wittig olefination and acidic quench rendered olefin **91** in excellent yield and multigram scale. An alternative acetalisation methodology using ethilenglicol/TsOH in benzene[13] proved to be less efficient.

[13] P. J. Sammes, L. J. Street, R. J. Whitby. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 281–289.

The necessary enone functionality was introduced by oxidation with IBX. Several oxidant loadings and different acids (TFA, TsOH)[14] were tested but ultimately moderate yields were achieved for the key synthetic enone intermediate, which not only ensured the regioselectivity for the next alkylation step but also provided the necessary functionality for the rearrangement required to install the oxygen atom at C19.

Initial attempts to introduce the C28 methyl either with LiHMDS/MeI or LDA/MeI/HMPA alkylation failed by the predominance of *O*-alkylated product, and plans to move the oxygen from C17 to C19 by a Wharton transposition were also thwarted by the unreactive nature of the internal double bond towards epoxidation. This reactivity handicap is explained by the shielding effect of the contiguous quaternary carbons, which make that many attempted trivial transformations failed, particularly when the reactive site was adjacent to one of the quaternary centres. LDA deprotonation of enone **92** and trapping of the enolate by benzotriazole-formaldehyde complex[15] led to incomplete reactions (*ca.* 50-60%), even though adding an excess of aldehyde.[16] Best results were obtained when using an other telescoped protocol, LiHMDS/Eschenmoser's salt[17] gave dimethylamine derivative, which was subsequently eliminated to render desired compound **93**.

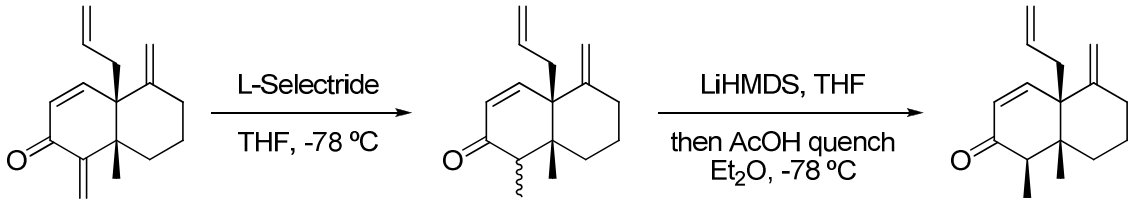
[14] Similar yields were obtained using both acid additives, but reaction time was longer when using TFA (4–5 days) than when employing TsOH (overnight).
[15] G. Deguest, L. Bischoff, C. Fruit, F. Marsais. *Org. Lett*. **2007**, *9*, 1165–1167.
[16] Alternatively, the use of solid paraformaldehyde in DMF or aqueous formaldehyde/NaOH resulted in no reaction.
[17] M. Mandal, H. Yun, G. B. Dudley, S. Lin, D. S. Tan, S. J. Danishefsky, *J. Org. Chem.* **2005**, *70*, 10619–10637.



Scheme 4.12 Preparation of **93**.

4.4 Preparation of Selenide 99

Exocyclic enone was chemoselectively reduced with L-Selectride® (lithium tri-*sec*-butylborohydride) at low temperature to furnish **93** as a mixture of diastereoisomers (*syn*:*anti* 3:2, Scheme 4.13). Other alternatives to perform the 1,4 reduction such as K-Selectride® (potassium tri-*sec*-butylborohydride) in THF resulted in incomplete reactions, whilst $ZnCl_2/Pd(PPh_3)_4/Ph_2SiH_2/CHCl_3$ [18] gave complete reduction with an improved diastereoselective ratio (*syn*:*anti* 4:1). However, since it still would be needed to epimerise the mixture, this protocol was discarded due to the expense of the reagents and the difficult purification (large amounts of additives are obtained in the crude reaction mixture). To epimerise the C16 methyl group many conditions were tried (KF/EtOH, DBU/CH_2Cl_2, EtONa/EtOH). It was found that the ratio worsened leading us to conclude that the product was under kinetic control. Treating **94** with LiHMDS and quenching with AcOH in Et_2O at –78 °C gave **94** exclusively.[19]



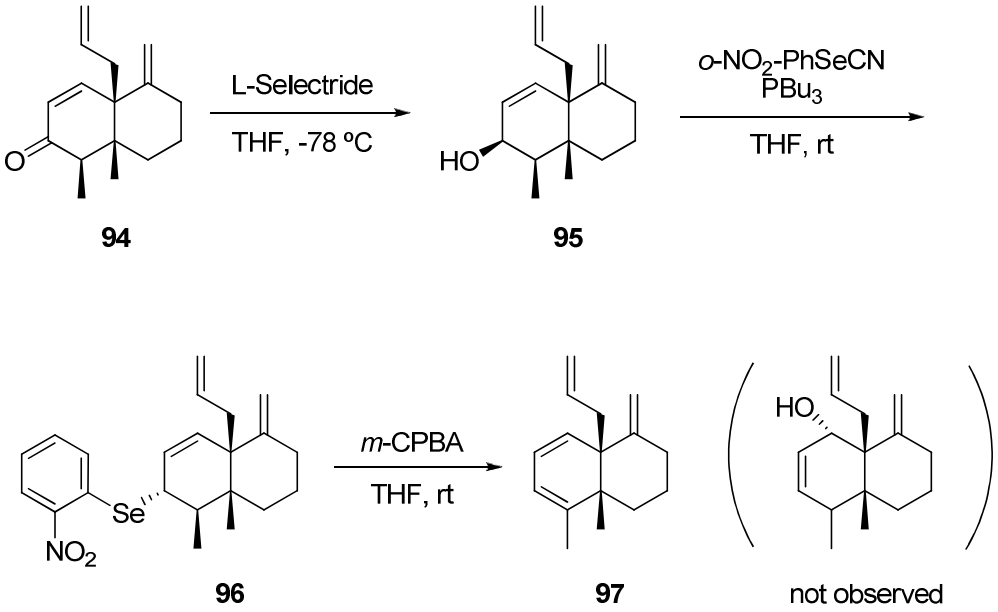
93 91% **94** 89% **94**

Scheme 4.13 Preparation of **94.**

Reduction of **94** with L-Selectride® gave *syn*-alcohol **95** as a single product (Scheme 4.14). Reduction with the smaller $NaBH_4$ gave a *ca.* 1.5:1 mixture of the *syn*:*anti* , which indicated that the desired *anti* isomer was not favoured. We thus pressed on with the *syn* isomer which was subjected to Grieco conditions[20] to furnish **96**, which under oxidation gave elimination product **97**. Unfortunately the

[18] E. Keinan, N. Greenspoon. *J. Am. Chem. Soc.* **1986**, *108*, 7314–7325.
[19] It was found that if quench temperature was rose to 0 °C there was an unexpected material loss.
[20] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485–1486.

rearrangement of *anti*-selenoxide proceeds slower than the elimination pathway, resulting in the obtention of **97**. However, no overoxidised products were found,[21] in which a selenoperoxide species (formed by overoxidation of the selenoxide) could attack any double bonds in the substrate. With the need to perform the sigmatropic rearrangement but using *syn*-selenide, the *anti*-alcohol was required. We therefore went back to see if we could obtain *anti*-**95** in good yield.



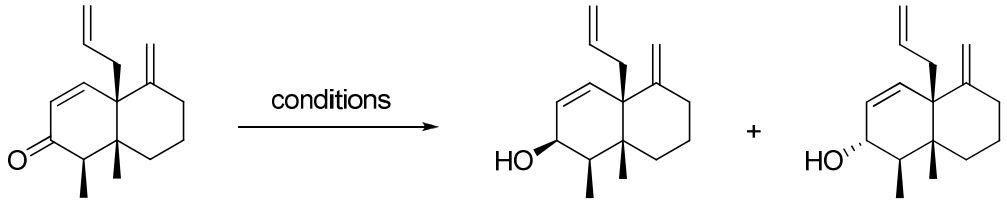
Scheme 4.14 Attempted Rearrangement of **96**.

Since we already had access to **95** effectively from reduction from **94**, we began by attempting a Mitsunobu inversion of this compound. However, due to the sterically encumbered environment of the alcohol, combined with the deactivation caused by being allylic, no reaction was observed. Attempts to activate the alcohol as a mesylate (MsCl, Et_3N) led once again to the elimination product **97** by base-promoted *anti* elimination.

[21] (a) T. Hori,K. B. Sharpless, *J. Org. Chem.*, **1978**, *43*, 1689–1697. (b) V. N. Zhabinskii, A. J. Minnaard, J. B. P. A. Wijnberg, A. de Groot, *J. Org. Chem.*, **1996**, *61*, 4022–4027. (c) P. A. Zoretic, R. J. Chambers, G. Marbury, A. A. Riebiro, *J. Org. Chem.*, **1985**, *50*, 2981–2987.

As stated before, reduction with 2 eq. of sodium borohydride at room temperature gave a 1.5:1 mixture of diastereoisomers (Table 4.2, Entry 1). By lowering the temperature to 0 °C and adding cerium(III) chloride a 1:1 mixture was obtained, but reaction was incomplete (Entry 2). By lowering the temperature to –78 °C and slowly warming to room temperature the selectivity could be increased to 1:1.5 in favour of the *anti* isomer (Entry 3). Further reduction of the temperature to –100 °C did not increase the diastereoselectivity (Entry 4).

Table 4.2. Reduction of **94**.

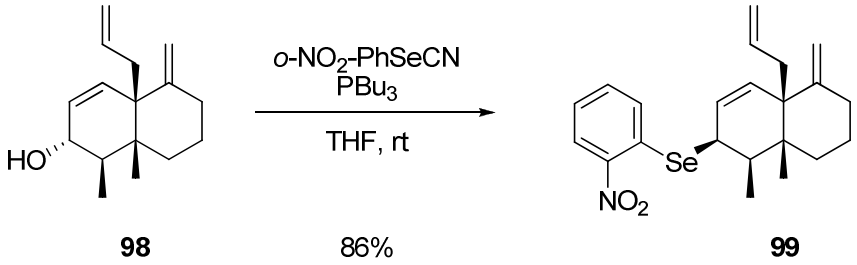


94 ***95*** ***98***

Entry	Conditions	*syn*[a]	*anti*[a]
1	$NaBH_4$ (2 eq), EtOH, rt, 4 h	55%	31%
2	$NaBH_4$ (1.2 eq), $CeCl_3 \cdot 7H_2O$ (1.2 eq), THF, 0 °C, 4 h	20%[b]	20%[b]
3	$NaBH_4$ (2 eq), $CeCl_3 \cdot 7H_2O$ (1.5 eq), MeOH, –78 °C to rt, 16 h	33%	52%
4	$NaBH_4$ (2 eq), $CeCl_3 \cdot 7H_2O$ (1.5 eq), MeOH, –100 °C to rt,16 h	30%	50%

[a] Determined by integration of the ^{1}H-NMR signals.
[b] 60% of starting material was recovered.

The 1.5:1 *anti*:*syn* mixture of diastereoisomers resulting from Luche's reduction could be separated by flash chromatography.[22] In order to recover material for the synthesis, undesired epimer could be recycled by an oxidation and reduction sequence.[23] Finally, a*nti* alcohol was smoothly converted to the allylic selenide **4x26** set up to undergo the key sigmatropic rearrangement (Scheme 4.15).



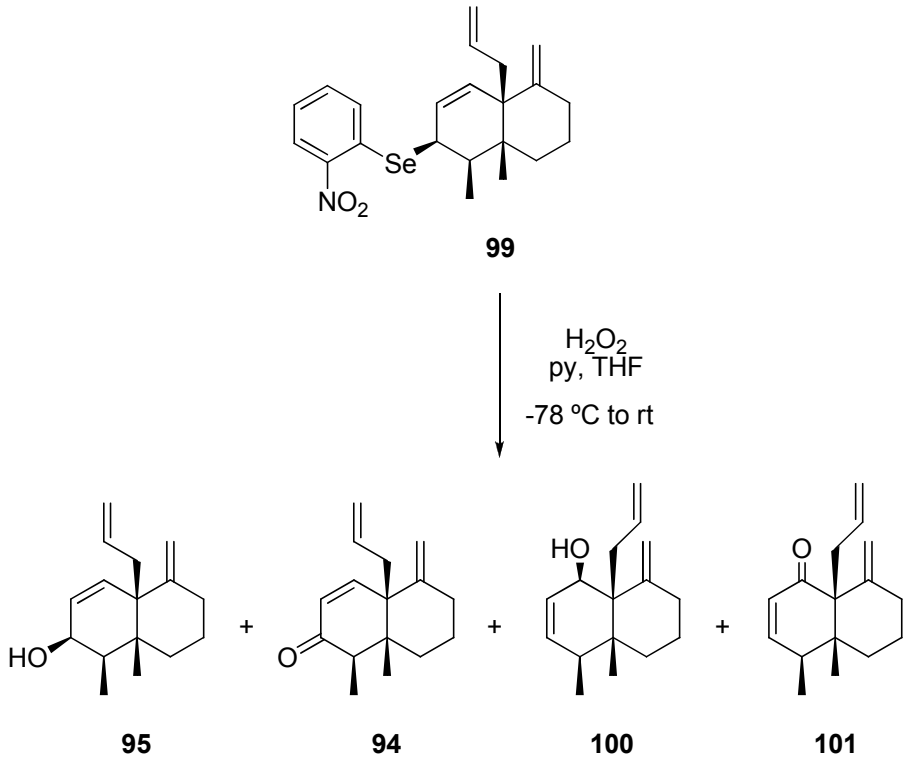
Scheme 4.15 Preparation of **99**.

[22] Unfortunately, both isomers had almost identical R_f and could not be completely separated by usual column chromatography. Thus, initially **95** and **98** were processed together as a mixture which upon oxidation of the corresponding selenides, the undesired **96** formed **97**, and could be easily separated. Later, it was found that the compounds **95** and **98** could be completely separated using Biotage® chromatography.

[23] Oxidation was performed by Dess-Martin periodinane in CH_2Cl_2 and reduction was done by using the optimised Luche aforementioned conditions.

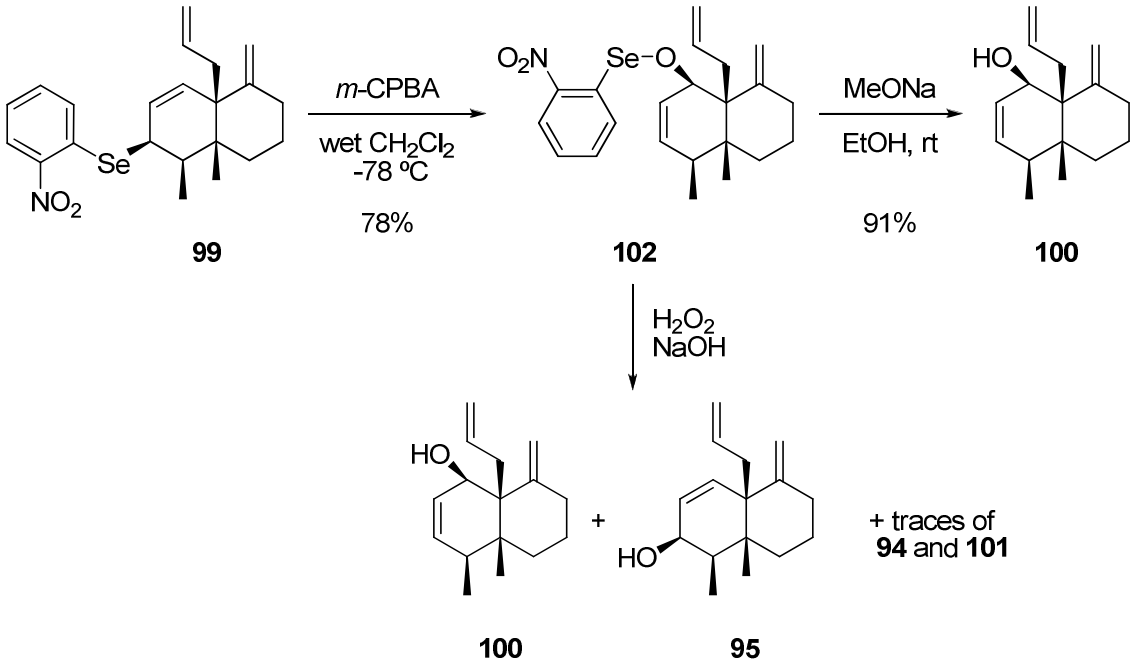
4.5 [2,3]-Sigmatropic Rearrangement

Selenide **99** was submitted to oxidation by hydrogen peroxide to give a mixture of products (Scheme 4.16), being **94** and **95** the major ones and only detecting trace amounts of **100** and **101**. This disappointing result forced us to try other oxidants such as *t*-butyl hydroperoxide but similar results were obtained. After screening numerous oxidants, *m*-CPBA was selected as the best candidate to move forward and refine the conditions.



Scheme 4.16 Attempted Rearrangement of **99**.

Since *m*-CPBA is commercially available as a *ca.* 70% with water, initial attempts were carried out under non-anhydrous conditions. Adding 1 eq (not precisely controlled) of *m*-CPBA gave mainly **100** plus the other observed compounds. Slowly adding 1 eq of *m*-CPBA and reducing the temperature to –78 °C led to the isolation of a bright yellow compound which was identified as **102** (Scheme 4.17). In sharp contrast, when working in anhydrous medium[24] a mixture of **94** and **95** was obtained. The stable selenenate **102** was cleaved by treatment with sodium ethoxide, which underwent a clean conversion to the desired alcohol **100**. It was essential that only one equivalent of oxidant was added since initial attempts to cleave selenenate **102** by oxidation with H_2O_2 resulted in a retro 2,3-rearrangement giving seleninate **III** (depicted in Scheme 4.18) and **95** upon hydrolysis.

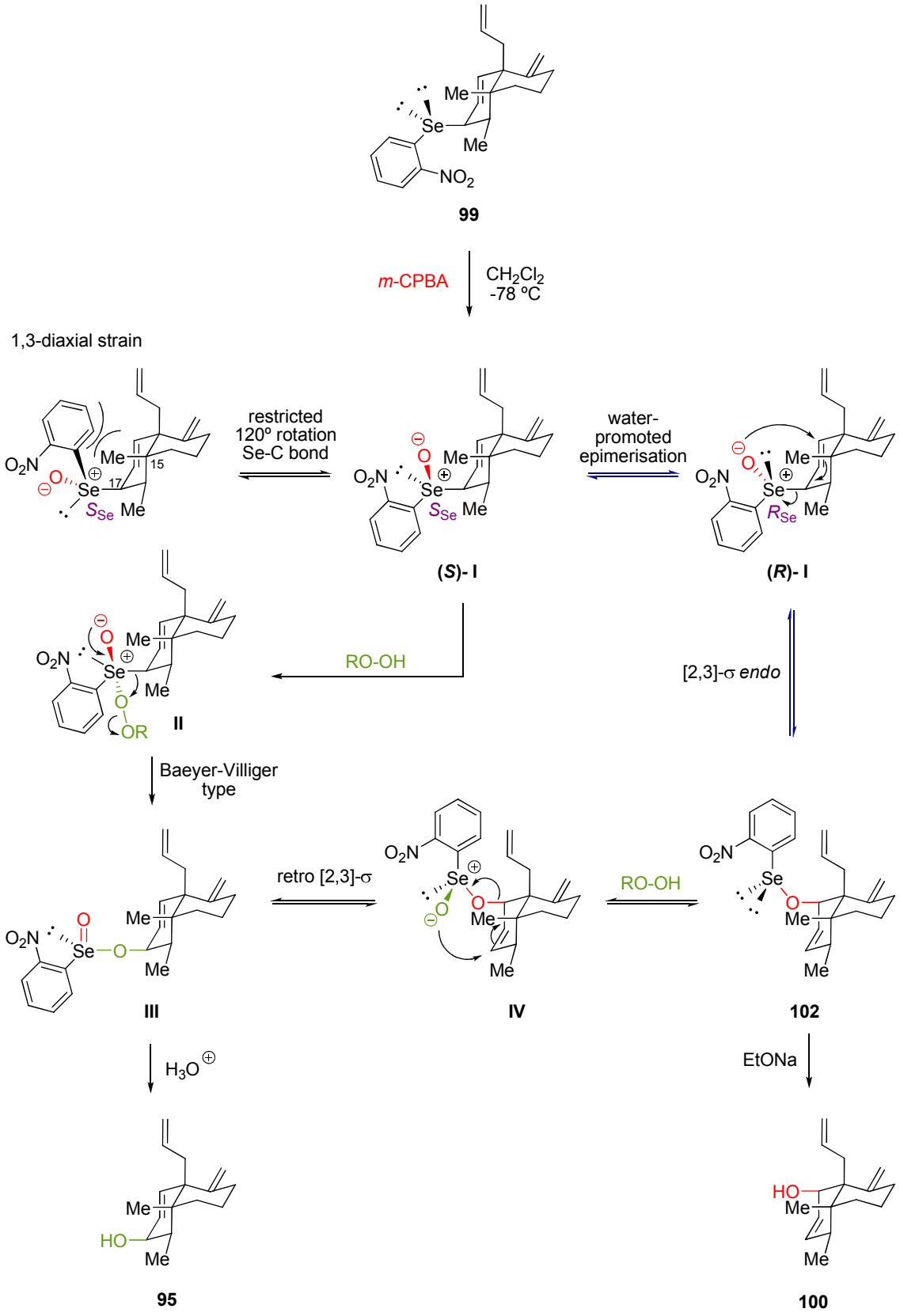


Scheme 4.17 Preparation of **100**.

[24] Using dry solvents and adding a $MgSO_4$ pre-dried CH_2Cl_2 solution of *m*-CPBA as well as 4Å molecular sieves in the reaction set up.

Chiral selenoxides[25] can be obtained either by enantioselective oxidation[26] of the corresponding selenides or by diastereoselective oxidation[27] of selenides bearing a chiral moiety. It had been shown that the formation of an achiral hydrate accounts for the fast racemisation of selenoxides in the presence of acid and water.[28,29] Furthermore, rearrangement of the allylic selenoxides proceeds much faster than that of the corresponding sulfoxides, via an *endo* transition state and detailed kinetic and thermodynamic studies have been carried out.[30] Taking these aspects in mind and trying to rationalise this experimental results a mechanism is proposed in Scheme 4.18. Arrows of the anhydrous reaction path are depicted in black while the ones of the aqueous mechanism are depicted in blue. Presumably, the (*S*)-selenoxide **I** cannot adopt the required conformation for the rearrangement process because of steric hindrance around the C17-Se bond, which is due to the bulkiness of the *o*-nitrophenyl group and the methyl group at C15. However, water-induced epimerization at the Se stereogenic center led to the (*R*)-selenoxide **I**, which could evolve to selenenate **102** through the [2,3]-sigmatropic rearrangement, and eventually to **100**. Furthermore, if an excess of oxidizing agent was used two by-product pathways are possible. First of all, **102** could be oxidised to seleninate **IV** and this at the same time, could give **III** via a retro 2,3-rearrangement. And secondly, (*S*)-selenoxide **I** could evolve through a Baeyer-Villiger-like process to the corresponding seleninate **III**, which under *in-situ* hydrolysis could give the alcohol **95**.

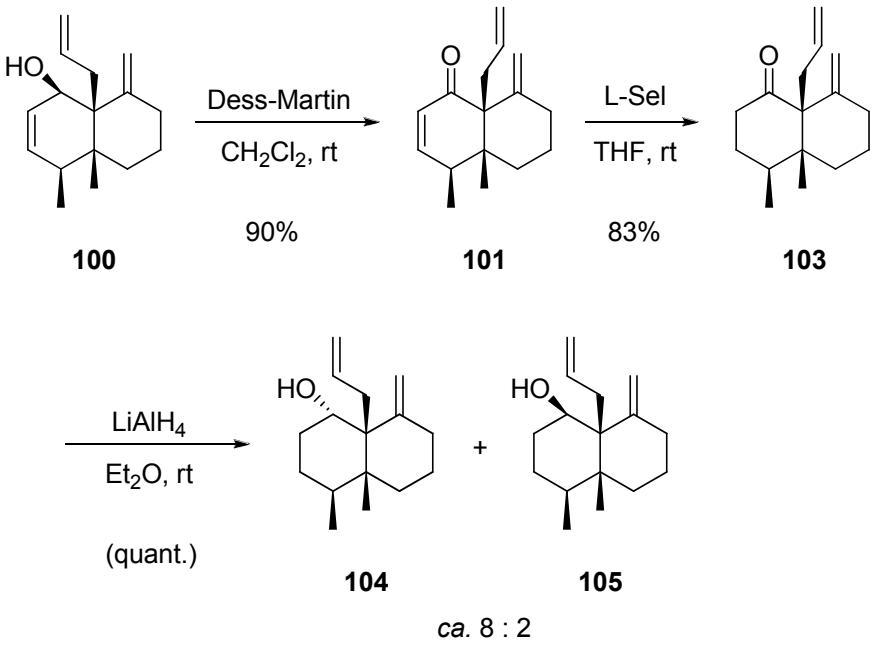
[25] Y. Nishibayashi, S. Uemura, *Topics in Current Chemistry, Organoselenium Chemistry*, Springer Berlin / Heidelberg, **2000**, Volume 208/2000, pages 201–233.
[26] F. A. Davis, R. T. Reddy, *J. Org. Chem.* **1992**, *57*, 2599–2606.
[27] H. J. Reich, K. E. Yelm, *J. Org. Chem.* **1991**, *56*, 5672–5679.
[28] F. A. Davis, O. D. Stringer, J. P. McCauley, *Tetrahedron* **1985**, *41*, 4747–4757.
[29] Y. Nakashima, T. Shimizu, K. Hirabayashi, F. Iwasaki, M. Yamasaki, N. Kamigata, *J. Org. Chem.* **2005**, *70*, 5020–5027.
[30] H. J. Reich, K. E. Yelm, S. Wollowitz, *J. Am. Chem. Soc.* **1983**, *105*, 2503–2504.



Scheme 4.18 Proposed Mechanism of the [2,3]-Sigmatropic Rearrangement.

4.6 Core Functionalisation

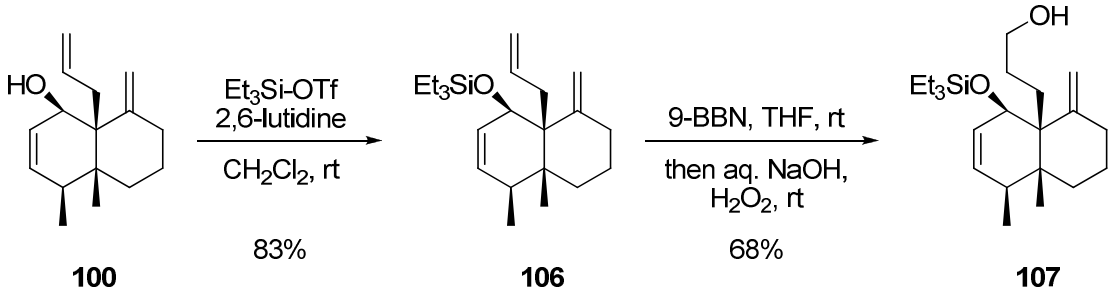
Once the oxygen functionality was installed in the correct place next crucial steps to achieve were the side chain elaboration and the introduction of the heterocyclic moiety. Initial approach to remove the endocyclic double bond relied upon a sequence of allylic alcohol oxidation with Dess-Martin periodinane and 1,4 reduction with K-Selectride® at low temperature giving desired ketone **103** in 75% overall yield (Scheme 4.19). Further 1,2 reduction with lithium aluminium hydride in ether[31] was quantitative but gave mainly the wrong configuration of the alcohol. Attempts to solve this setback were explored by submitting **103** to K-Selectride® but no reaction occurred, probably due to the bulkiness of the reductant. Reducing with Li/MeOH resulted in the formation of an unidentified side-product. ^{1}H-NMR of the crude showed no allyl proton signals, but no further characterisation was done.



Scheme 4.19 Preparation of **104**.

[31] S. Danishefsky, S. Chackalamannil, P. Harrison, M. Silvestri. *J. Am. Chem. Soc*. **1985**, *107*, 2474–2484.

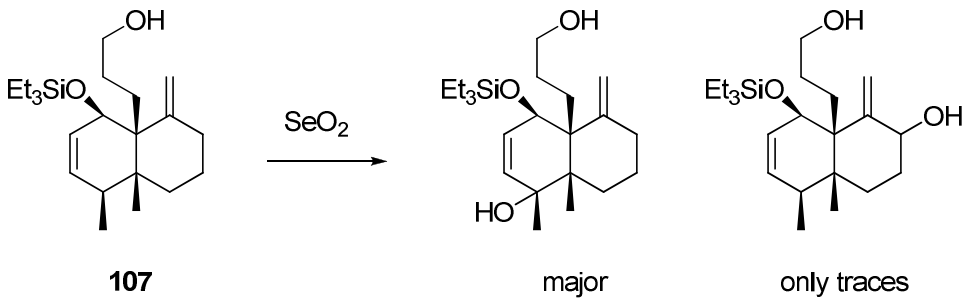
Believing it may be possible to remove the C17-C18 double bond later in the sequence we decided to protect the alcohol group in **100** and press on with the synthesis. Based on our earlier observations on the stability of silicon protecting groups in this position (*see Chapter 2*) we chose to protect it as a triethylsilyl (TES) ether. Initial attempts to protect the alcohol with TES-Cl/imidazole in dichloromethane were unsuccessful, probably due to the proximity of two quaternary centres.[32] Since a stronger electrophile was required, the combination of TES triflate/2,6-lutidine effected the desired transformation in 83% yield (Scheme 4.20). Selective hydroboration at the allyl side chain with 9-BBN furnished **107** in 68% yield. However, careful addition of 1 eq was required since the other double bonds were prone to hydroboration under longer reaction times and with more equivalents of reductant.



Scheme 4.20 Preparation of **1072**.

Presuming that internal double bond would be much more hindered, we tried to generate the required enone by oxidising with selenium dioxide. Unfortunately, endocyclic double bond was more accessible and C16 position was mainly oxidised, with just traces of the desired product being found (Scheme 4.21).

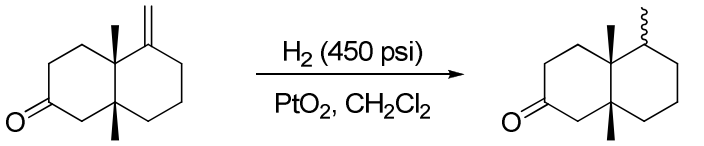
[32] We thought that a smaller silyl group might be easier to introduce and therefore we introduced trimethylsilyl under classical conditions. However, during concentration of the crude reaction mixture the protecting group was cleaved and the acid generated by the hydrolysis isomerised the C10-C11 double bond mainly to the more stable endocyclic one.



107 major only traces

Scheme 4.21 Attempted Selective Oxidation at C12.

Here, the synthetic strategy was again evaluated and, based on the observation that the exocyclic methylene was considerably less reactive than the endocyclic double bond, an alternative route was envisaged. Based on our earlier work with **10** being resistant to hydrogenation under standard conditions (450 psi hydrogen pressure needed) we thought it should be possible to selectively hydrogenate C17-C18 rather than the exocyclic double bond.



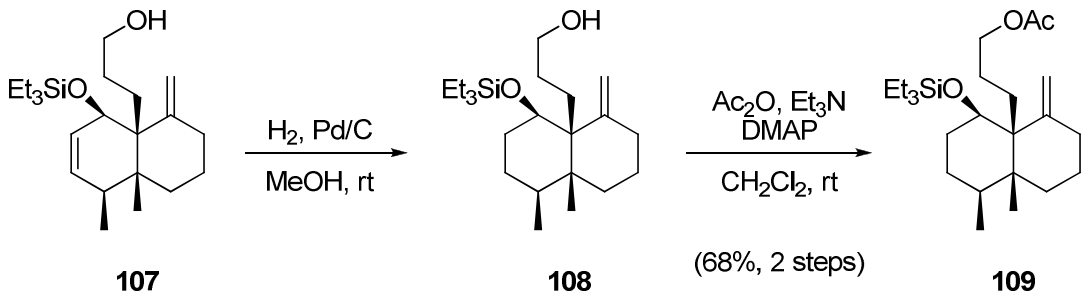
10 quant. **3**

syn:anti = 3 : 1

Scheme 4.22 Hydrogenation of **10**.

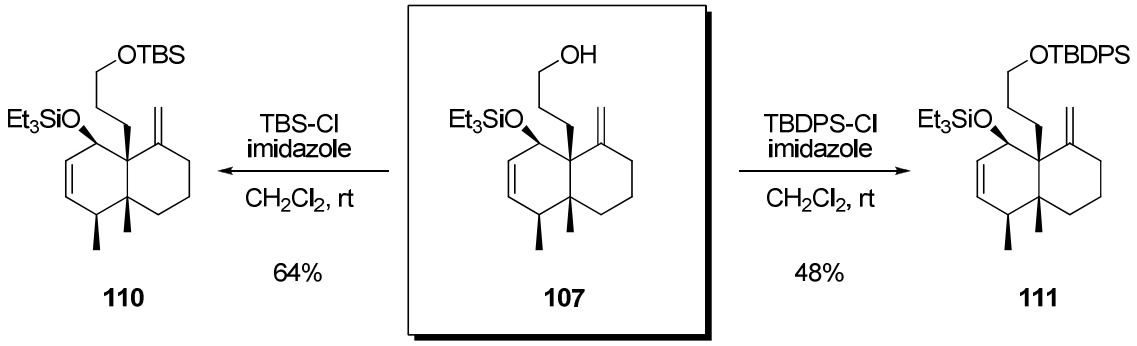
After causing so many setbacks, the steric hindrance of the molecule now worked to our favour, as we could chemoselectively hydrogenate[33] internal alkene in **107** keeping the exocyclic one mainly intact (10-20% reduction, Scheme 4.23). Protection of C23 alcohol as an acetal furnished **109** in 68% overall yield.

[33] Hydrogenation was performed at atmospheric pressure.



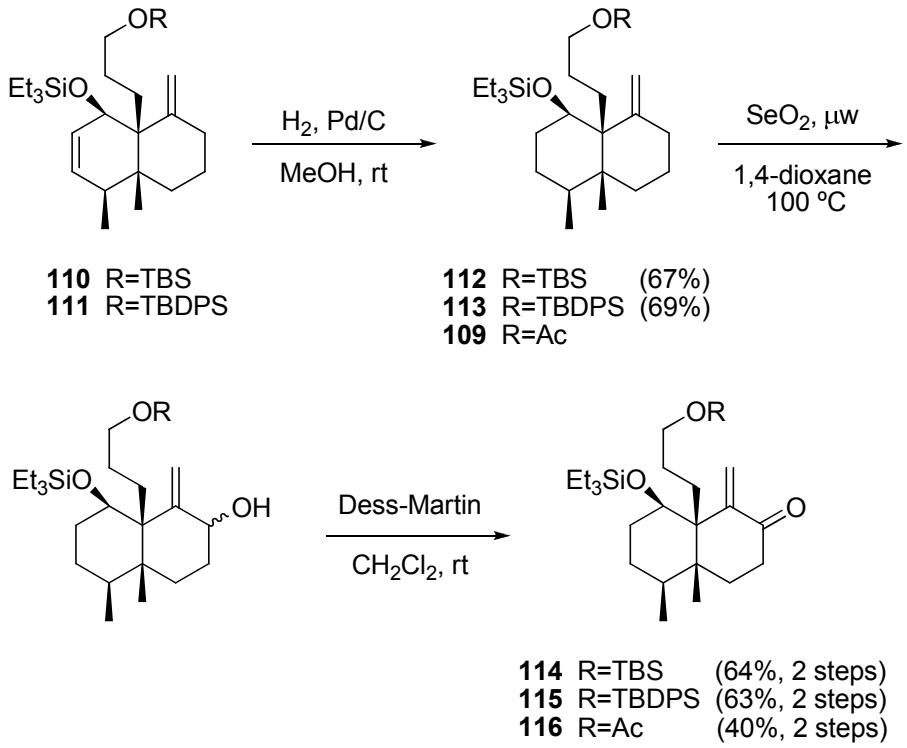
Scheme 4.23 Selective Hydrogenation of **107**.

In parallel, alcohol **107** was protected as a *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (TBDPS) ether (Scheme 4.24).



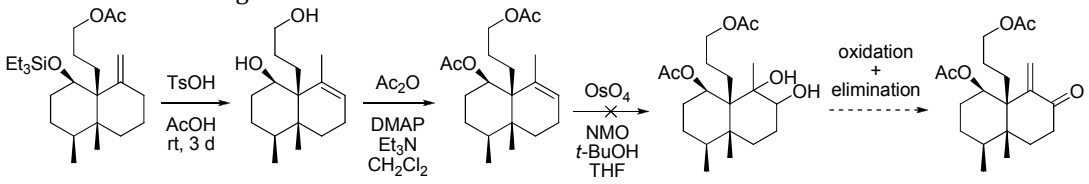
Scheme 4.24 Protection of C23 alcohol of **107**.

At this point the three series of TBS-, TBDPS- and acetate-protected alcohols were moved forward in the synthesis to test which protecting group was better for the key indole conjugate addition (Scheme 4.25). Therefore, **110** and **111** were hydrogenated using the conditions optimised before. The corresponding enones were obtained by selenium-mediated allylic oxidation and Dess-Martin oxidation. Since the yields obtained were not satisfactory enough an alternative sequence was tested,[34] but found unsuitable so we pressed ahead.



Scheme 4.25 Preparation of **114**–**116**.

[34] Isomerisation of the double bond to the more substituted one was achieved by TsOH/AcOH along with concomitant alcohol deprotection. Diol was masked as a diacetate ready to perform the dihydroxylation. Unfortunately, the impeded nature of the internal double bond prevented any reaction from occurring.

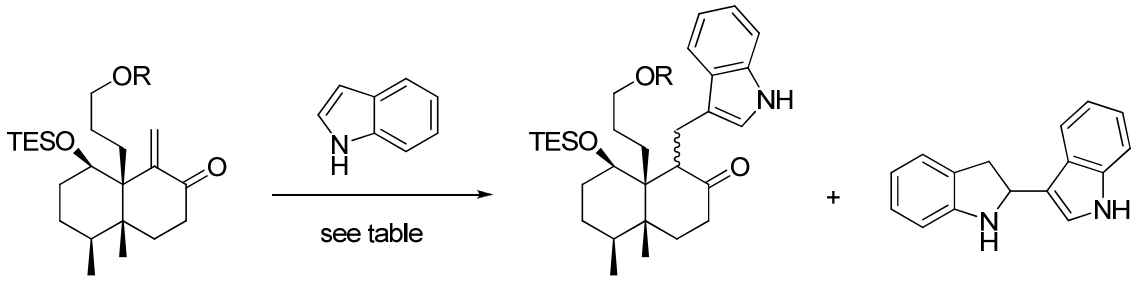


4.7 Indole Conjugate Addition

Attempts to apply our previously developed methodology of indole conjugate addition[35] (Table 4.3) did not give the desired product and resulted in decomposition of starting material to unidentified by-products (cleavage and subsequent addition of the alcohol to the enone, Entries 1-3). Presumably, the ether oxygen atom coordinates to the Lewis acid thus facilitating the cleavage of the Si-O bond, and at the same time, the free alcohol is added to the activated enone. Expecting that a stronger and larger protecting group would prevent its cleavage, *tert*-butyldiphenylsilyl was used instead but the same disappointing results were obtained. Apparently, the principal problem was the known instability of sililoxy derivatives with Lewis acids such as $BiBr_3$,[36] $InCl_3$,[37] $ZnCl_2$,[38] but contradictory references showing the silyl ethers stability to Lewis acids were also found.[39] When no protecting was employed same results were obtained (Entry 4). However, switching protecting group to acetate did not result in decomposition of the starting material but an indolic dimer by-product was obtained[40] (Entries 5-6). An alternative protocol using iodine in methanol[41] did not give any reaction (Entry 7). This means that acetate group is stable under Lewis acid conditions but on the other hand, that bismuth(III) triflate, unlike in the model system (*see Chapter 2*), was not able to catalyse the indole conjugate addition.

[35] A. V. Reddy, K. Ravinder, T. V. Goud, P. Krishnaiah, T. V. Raju and Y. Venkateswarlu, *Tetrahedron Lett.* **2003**, *44*, 6257.
[36] J. S. Bajwa, J. Vivelo, J. Slade, O. Repic, T. Blacklock, *Tetrahedron Lett.*, **2000**, *41*, 6021–6024.
[37] J. S. Yadav, B. V. S. Reddy, C. Madan, *New J. Chem.*, **2000**, *24*, 853–854.
[38] R. D. Crouch, J. M. Polizzi, R. A. Cleiman, J. Yi, C. A. Romany, *Tetrahedron Lett.*, **2002**, *43*, 7151–7153.
[39] M. D. Carrigan, D. Sarapa, R. C. Smith, L. C. Wieland, R. S. Mohan, *J. Org. Chem.*, **2002**, *67*,1027–1030.
[40] S. Aburatani, J. Uenishi, *Heterocycles*, **2008**, *75*, 1407–1416.
[41] S. Y. Wang, S. J. Ji, T. P. Loh, *Synlett*, **2003**, *15,* 2377–2379.

Table 4.3 Indole Conjugate Addition.



Entry	R	Conditions	Yield[a]
1	TBS	I[b] (1 eq), $Bi(OTf)_3$ (0.03 eq), MeCN, rt, 1 h	decomposition
2	TBS	I[b] (1.5 eq), $Bi(OTf)_3$ (0.05 eq), MeCN, rt, 1 h	decomposition
3	TBDPS	I[b] (1.5 eq), $Bi(OTf)_3$ (0.05 eq), MeCN, rt, 1 h	decomposition
4	H	I[b] (1 eq), $Bi(OTf)_3$ (0.1 eq), MeCN, rt, 2 h	decomposition
5	Ac	I[b] (1.1 eq), $Bi(OTf)_3$ (0.05 eq), MeCN, rt, 3 h	n.r + by-product
6	Ac	I[b] (1.1 eq), $Bi(OTf)_3$ (1.1 eq), MeCN, rt, 3 h	n.r + by-product
7	Ac	I[b] (1 eq), I_2 (0.1 eq), MeOH, rt, 16 h	n.r

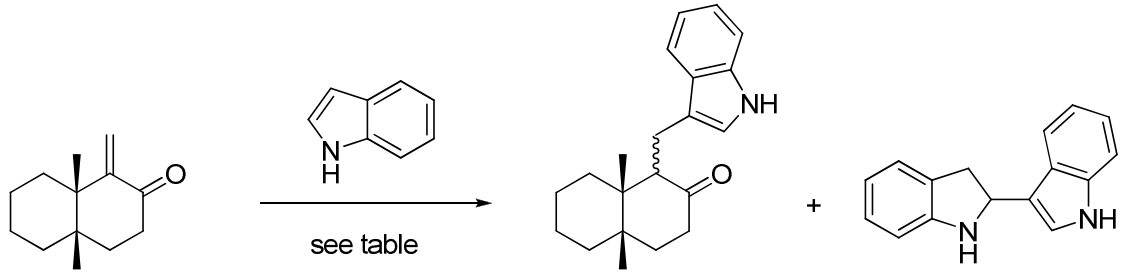
[a] As analysed by thin layer chromatography and crude NMR spectra.
[b] Indole.

Due to limitations in the quantity of enone **116** available we decided to do a screening of different Lewis acids on a simpler model such as **117** (Table 4.4). Employing Lewis acids known for their catalytic activity in Friedel-Crafts alkylation such as Selectfluor®,[42] or iron(II) tetrafluoroborate[43] gave recovery of all starting material (Entries 1-2). Brønsted 2,5-dinitrosulfonic acid[44] and bismuth(III) triflate gave the desired product along with the known by-product (Entries 3-5), yet adding Proton-Sponge® (*N*,*N*,*N*',*N*'-tetramethylnaphthalene-1,8-diamine) cleanly gave **118**, although it needed three days to complete the reaction

[42] J. S. Yadav, B. V. Subba Reddy, A. Raju, K. Ravindar, G. Baishya, *Chemistry Letters* **2007**, *36*, 1056–1057.
[43] T. Itoh, H. Uehara, K. Ogiso, S. Nomura, S. Hayase, M. Kawatsura, *Chemistry Letters* **2007**, *36*, 50–51.
[44] G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.*, **2007**, *9*, 1403–1405.

(Entry 6). In contrast, iodine in methanol smoothly gave the addition product in only 30 min (Entry 7), whereas indium(III) bromide[45] needed four days (Entry 8). Finally, zirconium(IV) chloride[46] furnished **118** in quantitative yield and only in thirty minutes time (Entry 9), being one of the best candidates for the test in the substrate required for the total synthesis.

Table 4.4 Qualitative screening of Lewis acid for the indole conjugate addition of model **117**.



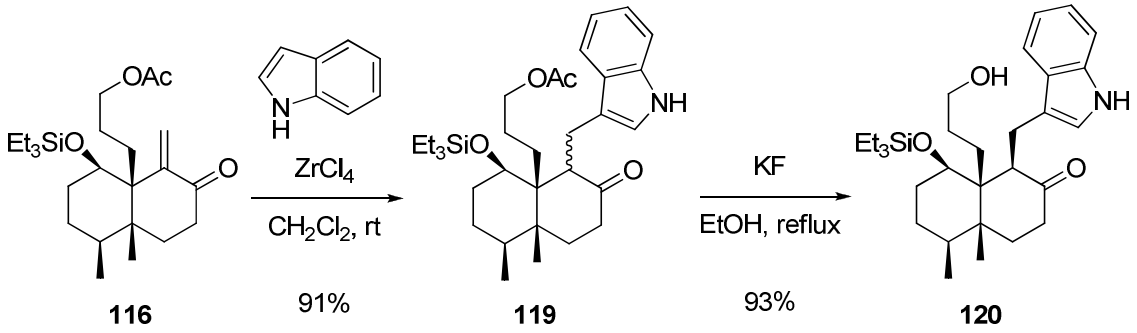
117 **118**

Entry	Conditions	Yield[a]
1	I[b] (1 eq), Selectfluor®[c] (0.1 eq), MeCN, rt, 24 h	n.r
2	I[b] (1 eq), $Fe(BF_4)_2 \cdot 6\ H_2O$, MeCN, 4 d	n.r
3	I[b] (1 eq), 2,5-dinitrosulfonic acid (0.05 eq), MeCN	prod+byprod
4	I[b] (2 eq), $Bi(OTf)_3$ (0.05 eq), MeCN	prod+byprod
5	I[b] (1 eq), $Bi(OTf)_3$ (0.03 eq), K_2CO_3 (0.15 eq), MeCN, rt, 3 d	prod+byprod
6	I[b] (1 eq), $Bi(OTf)_3$ (0.03 eq), P-S[d] (0.06 eq), MeCN, rt, 3 d	quant.
7	I[b] (1 eq), I_2 (0.1 eq), MeOH, rt, 30 min	quant.
8	I[b] (1.3 eq), $InBr_3$ (0.1 eq), CH_2Cl_2, rt, 4 d	quant.
9	I[b] (1 eq), $ZrCl_4$ (0.08 eq), CH_2Cl_2, rt, 30 min	quant.

[a] As analysed by thin layer chromatography and crude NMR spectra.
[b] Indole.
[c] 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).
[d] Proton-sponge®: *N*,*N*,*N*',*N*'-tetramethylnaphthalene-1,8-diamine.

[45] M. Dorbec , J-C. de Florent, C. Monneret, M-N. Rager, C. Fosse, E. Bertounesque, *Eur. J. Org. Chem.* **2008**, 1723–1731.
[46] V. Kumar, S. Kaur, S. Kumar, *Tetrahedron Lett.* **2006**, *47*, 7001–7005.

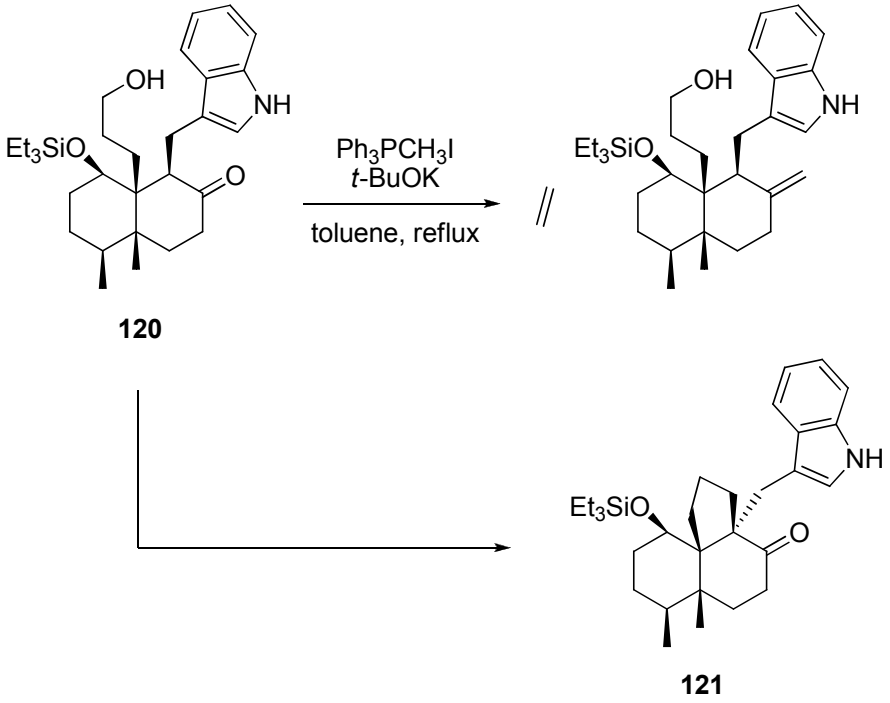
When the above optimised conditions were applied to the synthetic material **119** was smoothly obtained as a mixture of diastereoisomers (Scheme 4.26), along with significant amounts of the homocoupled indole by-product which could not be separated by column chromatography. Epimerisation of α-position with potassium fluoride in refluxing ethanol gave the desired configuration, as well as concurrent acetate removal allowing the indole by-product to be easily separated.



Scheme 4.26 Preparation of **120**.

4.8 Completion of the Synthesis

Wittig olefination was attempted onto the unprotected alcohol **120** obtaining tricyclic system **121**, which may come from an enolate attack either on to the activated phosphine oxide or an iodide formed by the excess of Wittig's salt (Scheme 4.27).

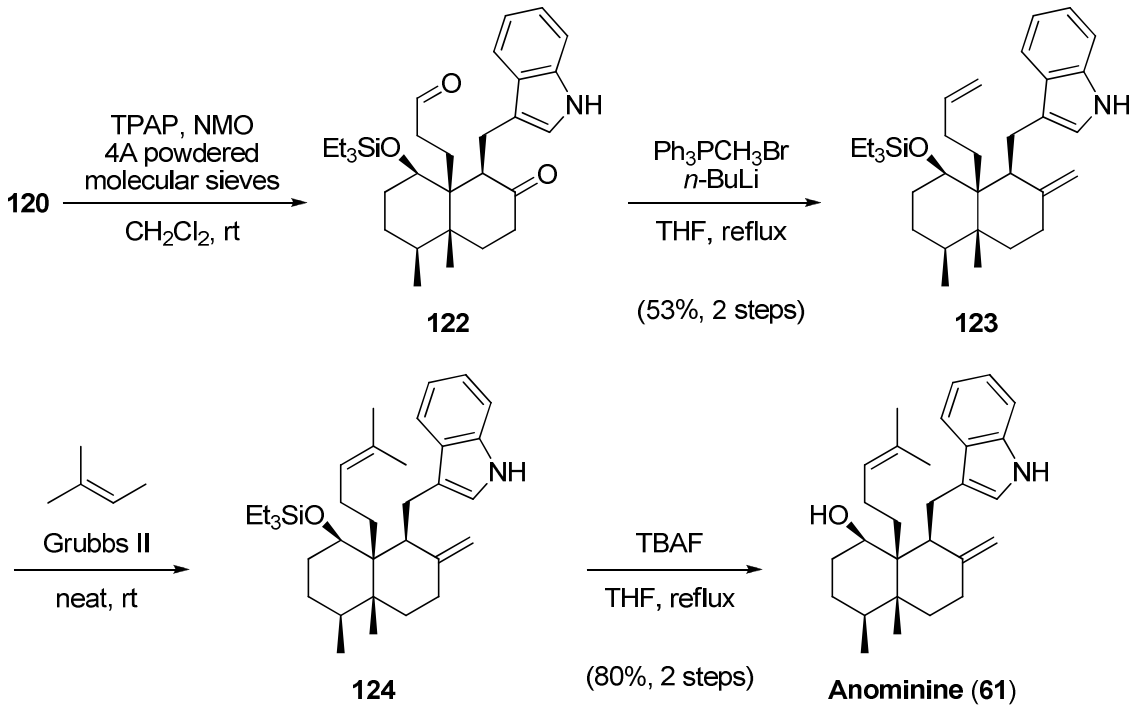


Scheme 4.27 Unexpected formation of **121**.

Alcohol was submitted to oxidation using Dess-Martin reagent[47] but unfortunately, other side-products were obtained, probably due to the oxidation of the indole.[48] An alternative protocol using Parikh-Doering[49] oxidation was assayed obtaining the desired aldehyde but this method was deemed unsuitable due to the need to remove the excess of reagents by chromatography. Finally, Ley's perruthenate oxidation[50] cleanly yielded aldehyde **122** (Scheme 4.28). Potentially unstable aldehyde was not purified and used directly in the next step. Our initial

[47] D. B. Dess, J. C. Martin, *J. Org. Chem.,* **1983**, *48*, 4155–4156.
[48] T. Dohi, K. Morimoto, A. Maruyama, Y. Kita, *Org. Lett.*, **2006**, *8*, 2007–2010
[49] J. R. Parikh, W. von E. Doering, *J. Am. Chem. Soc.*, **1967**, *89*, 5505–5507.
[50] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis*, **1994**, 639–666.

workplan was to elaborate the side chain by selectively reacting isopropyl triphenylphosphonium amide THF solution with the aldehyde, and later on generate the exocyclic methylene group by Wittig olefination. Unfortunately, no product was isolated from the reaction mixture and we had to reformulate the our strategy. Submitting both carbonyl groups to olefination by a more activated ylide we could obtain the diene, and maybe perform a selective cross metathesis with the side chain olefin. In this manner we might prevent the possible side reactions derived from collateral aldol reactions. Addition of the crude aldehyde to a preformed solution of ylide and its further reflux for 12 hours furnished diene product in 53% yield from alcohol **120**.



Scheme 4.28 Completion of the Synthesis.

Having diene **123** in hand, the next step was to selectively react the external double bond with 2-methyl-2-butene by means of a cross metathesis. Thus, stirring diene **123** with second-generation Grubbs catalyst[1] in neat 2-methyl-2-butene at room temperature for two days smoothly rendered compound **124**. Removal of the silicon protecting group was effected by submitting **124** to tetra-*n*-butylammonium fluoride (TBAF) in refluxing THF. Purification of the product by column chromatography afforded Anominine in 80% yield from diene **123**, showing identical ^{1}H and ^{13}C NMR spectroscopic data to those reported for the natural product.

Next thing to establish was the absolute stereochemistry of natural anominine by correlating the optical rotation of the synthetic anominine. The data obtained, $[\alpha]_D$ –21.0 (*c* 0.3, MeOH) for **61** resulted in the assignment of the *ent*-anominine for **61** and the shown absolute configuration depicted in Figure 4.1 for the natural (+)-anominine[2] (Lit: $[\alpha]_D$ +23.6 (*c* 0.85, CH_3OH).

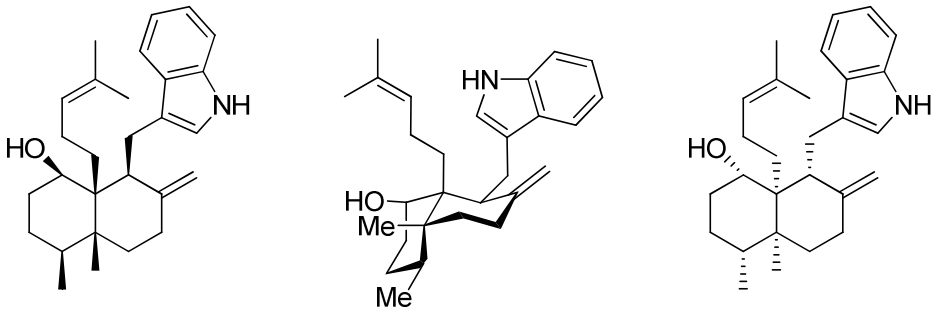


Figure 4.1 3D Representation of Synthetic Anominine.

[1] A. K. Chatterjee, T. L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
[2] Systematic name: (1*S*,4*R*,4a*S*,8*R*,8a*S*)-8-[(1*H*-indol-3-yl)methyl]-4,4adimethyl-7-methylene-8a-(4-methylpent-3-enyl)decahydronaphthalen-1-ol. Diterpenoid **61** was named nominine when it was isolated, but in 1982 the same name had been given to a hetisine-type aconite alkaloid. After consultation with Prof. Gloer (University of Iowa), it was decided to change the name of the indole diterpenoid **61** to anominine. Gloer, J. B.; Rinderknecht, B. L.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 2530–2532.

4.9 Summary and Conclusions

In summary, (–)-anominine (**61**) was constructed in 27 steps from 1,3-cyclohexanedione, and represents the first total synthesis of this natural product. The development of a new, experimentally-easy, highly-efficient methodology for the synthesis of Wieland-Miescher ketone derivatives gives access to enantiopure material in large amounts, which can eventually find a wide application in natural product synthesis. Anominine's absolute stereochemistry is established by a stereoselective intramolecular aldol catalysed by 1 mol % of proline derivative. Since generation of the subsequent stereocenters are governed by the initial one, synthesizing natural anominine could be done by using the enantiomer of the binamprolinamide catalyst, which had been done previously in Chapter 3.

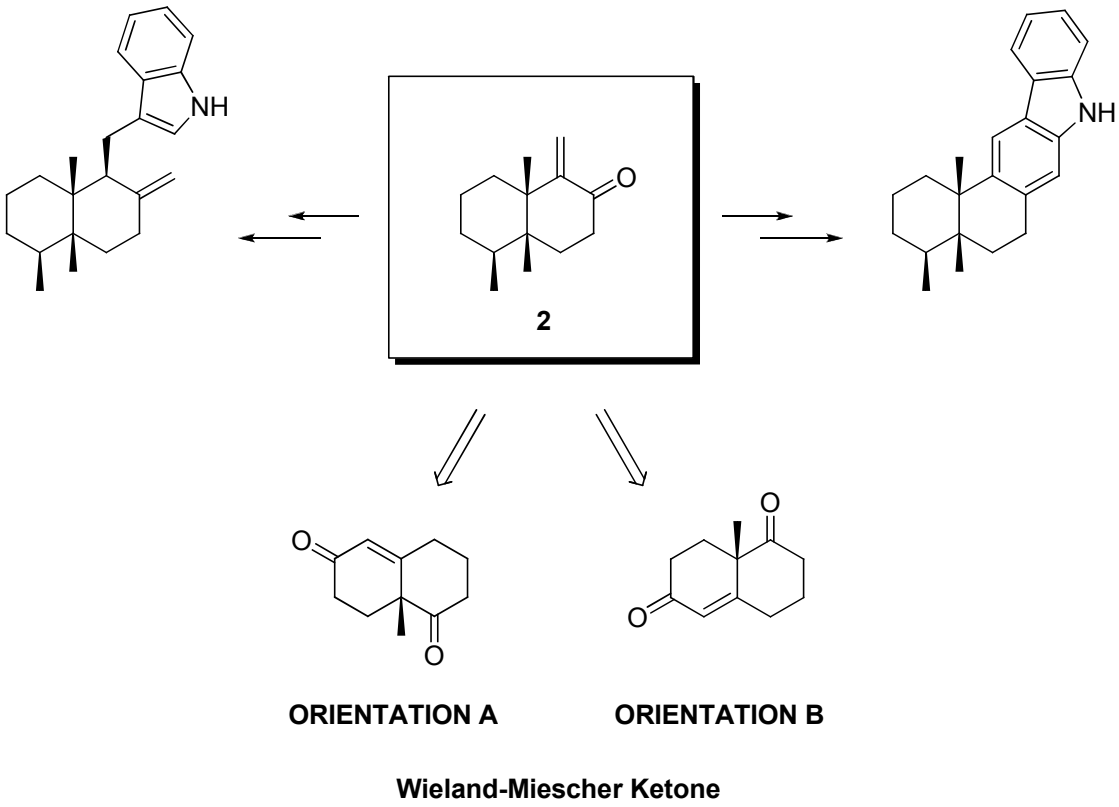
The unusual and highly congested terpene skeleton presented us with many challenges and revisions of our initial synthetic planning but in return deepened our understanding of this family of natural products. The unsuccessful results of presumably straightforward transformations demonstrate the extreme steric hindrance of the molecule, and explain the difficulty to achieve trivial reactions on such a congested decalin. Taking advantage of these unreactive pockets we could use several chemoselective transformations, such as protections, oxidations, hydrogenations, hydroborations and cross-metathesis, all controlled by the structurally congested nature of the bicyclic core. An unusual [2,3]-sigmatropic rearrangement was used to transport oxygen functionality through the decalin and to set the alcohol configuration. Finally, a zirconium(IV)-catalysed indole conjugate addition is also highlighted. In conclusion, this synthesis opens the way to access other related natural products from *Aspergillus* spp. either via biomimetic processes or synthetic routes.

CHAPTER 5.

CONCLUSIONS

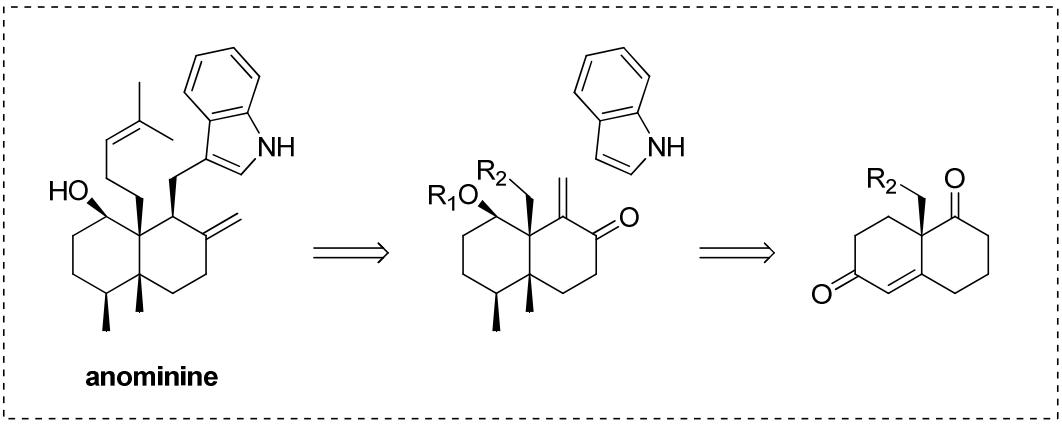
Conclusions

The model studies for the synthesis of anominine brought to the light some restrictions and therefore, gave us information of how to design a viable synthetic plan towards anominine (Scheme 5.1).



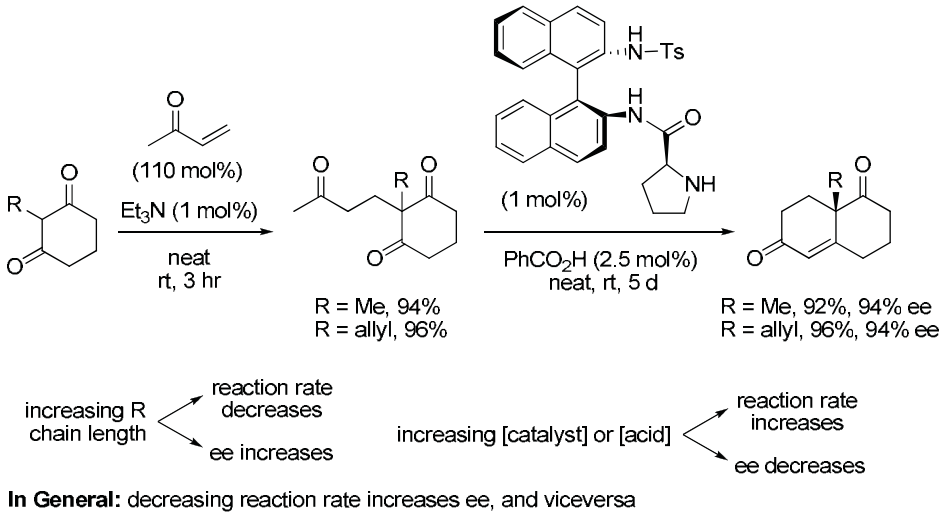
Scheme 5.1 Synthetic Routes towards Anominine and Tubingensin A Models.

With these restrictions in mind and the results obtained in the model synthesis, a new synthetic route was designed (Scheme 5.2). For this new approach a chiral Wieland-Miescher ketone derivative would be required, and employed in this particular orientation. As a consequence, large amounts of enantiopure bicyclic precursor would be needed, and therefore, a methodology for the preparation of this type of compounds had to be developed.



Scheme 5.2 Synthetic Routes towards Anominine.

An experimentally-easy, robust methodology for the synthesis of Wieland-Miescher ketone derivatives was developed for a broad variety of compounds. In general, the faster the reactions are, the lower the enantioselectivities (Scheme 5.3). Moreover, when increasing chain length reaction rates decrease, but in contrast, enantioselectivity increases. For the other hand, when increasing acid and/or catalyst concentrations reaction rates increase, thus lowering enantioselectivity. For the allyl- and methyl-substituted derivatives the catalyst loading was reduced to 1 mol% and yields of up to 90% overall and 94% ee were obtained. Both the Michael addition and intramolecular aldol step were optimised resulting in a great improvement for the global Robinson annulation. No solvents are used and column chromatography purifications are avoided thus culminating a sustainable and cheap procedure for the synthesis of substituted-decalins that might be very useful in natural product synthesis.



Scheme 5.3 Newly-Developed Robinson Annulation Methodology.

(–)-Anominine was constructed in 27 steps from 1,3-cyclohexanedione and represents the first total synthesis of this natural product and confirms the absolute stereochemistry of the natural product (Figure 5.1 and Scheme 5.5). Anominine's absolute stereochemistry is established by a stereoselective intramolecular aldol catalysed by 1 mol % of proline derivative. Since generation of the next stereocenters is governed by the initial one, synthesizing natural anominine could be done by using the alternative enantiomer of the binamprolinamide catalyst. Furthermore, its unusual and highly congested terpene skeleton presented us with many challenges and revisions of our initial synthetic planning but in return deepened our understanding of this family of natural products. The unsuccessful results of pressumably-easy transformations demonstrate the extreme steric hindrance of the molecule, and explain the difficulty to achieve trivial reactions on such a congested decalin. Taking advantage of these unreactive pockets several chemoselective transformations could be used, such as protections, oxidations, hydrogenations, hydroborations and cross-metathesis, all controlled by the structurally congested nature of the bicyclic core. An unusual [2,3]-sigmatropic rearrangement was used to transport oxygen functionality through the decalin and to set the alcohol configuration. Despite developing effective conditions of the indole conjugate addition using a model

system [$Bi(OTf)_3$ in acetonitrile], this methodology was completely ineffective for the actual substrate. Careful screening of Lewis acid and judicious selection of protecting group identified $ZrCl_4$ as the only Lewis acid that effectively carried out the key coupling reaction.

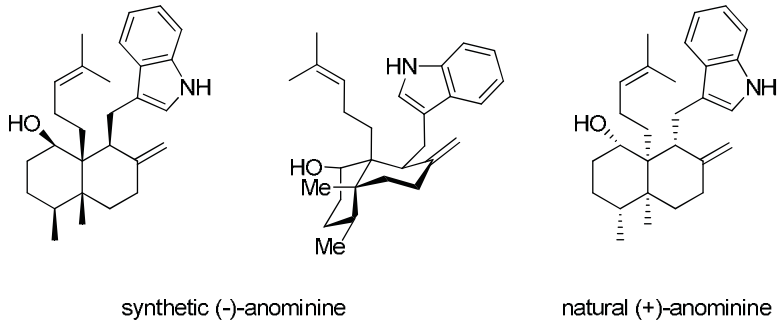
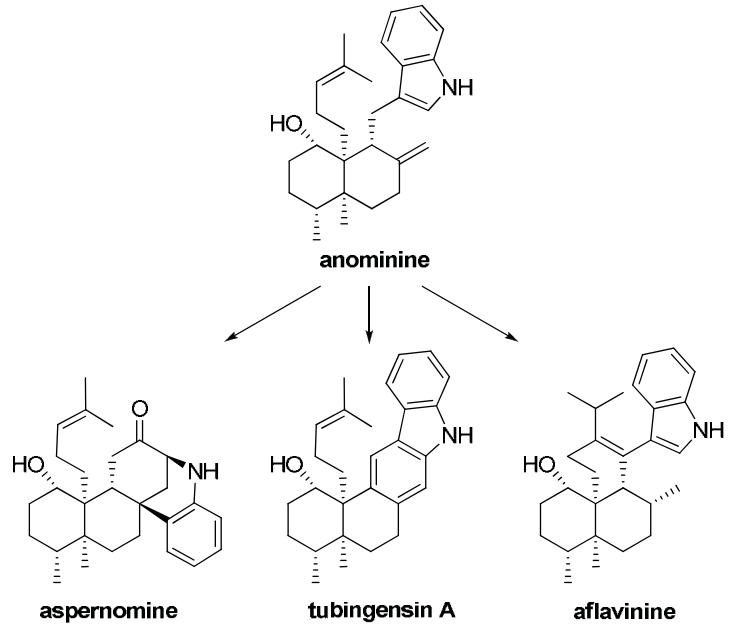
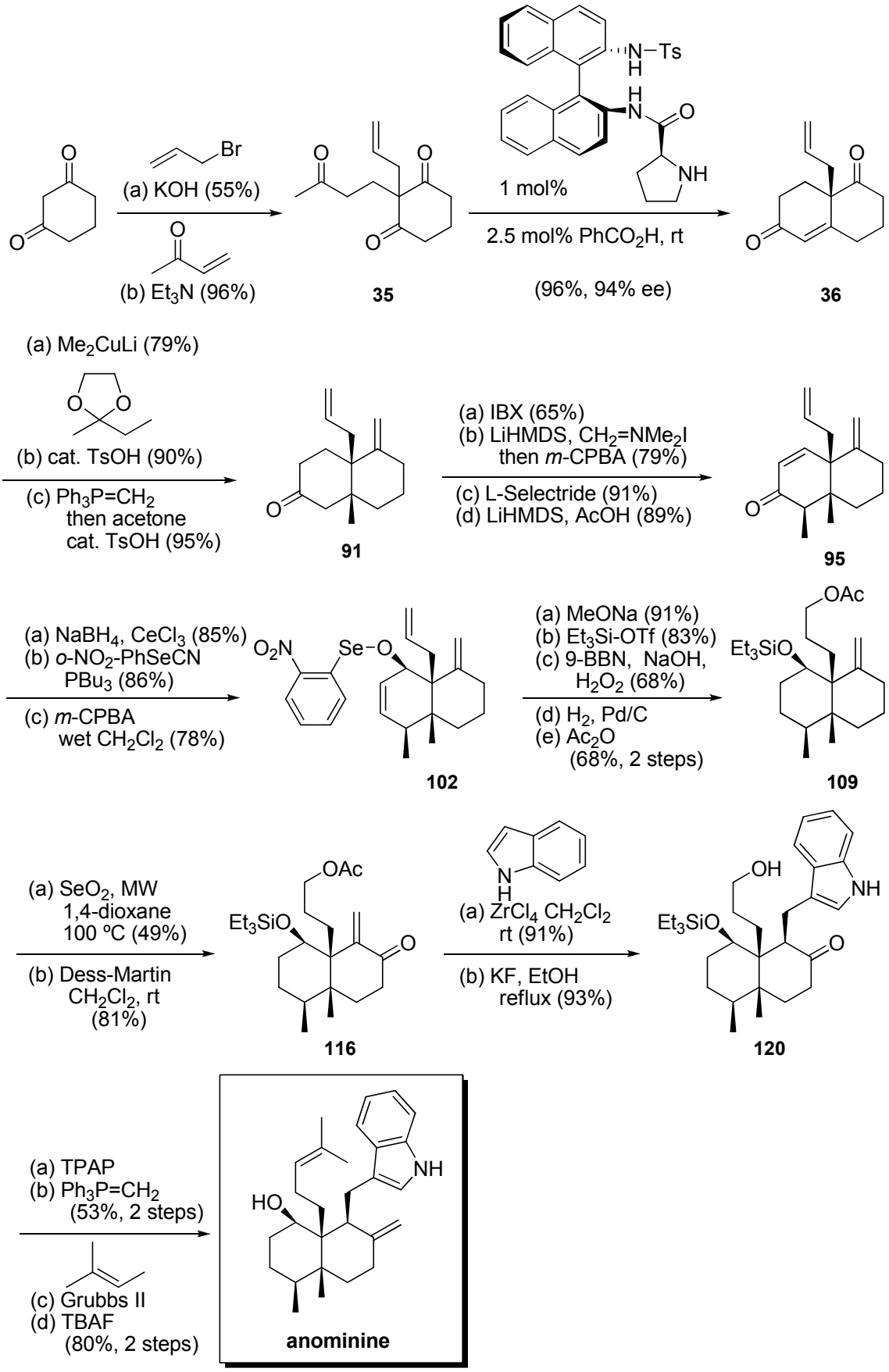


Figure 5.1 Comparison between Natural- and Unnatural Anominine.

The results reported in this work opens the way to access other related heterocyclic diterpenoids from *Aspergillus* spp. either via biomimetic processes or *de novo* synthetic routes (Scheme 5.4).



Scheme 5.4 Possible Obtention of the Other Related Diterpenoids.



Scheme 5.5 Synthesis of Anominine.

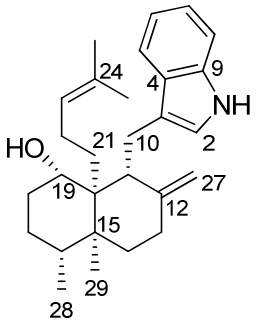
CHAPTER 6.

EXPERIMENTAL SECTION AND SPECTRA

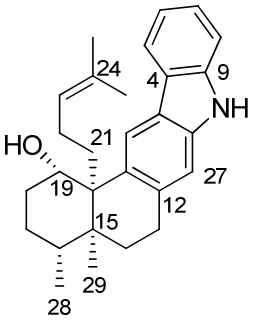
Experimental Section

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 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 $MgSO_4$ except where stated otherwise. Evaporation of solvent was accomplished with a rotatory evaporator. NMR spectra were recorded in $CDCl_3$ (unless otherwise specified) on a Varian Gemini 300 or Varian VNMRS 400. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. Specific optical rotatory power was recorded in a Perkin-Elmer 241 polarimeter using a Na continue lamp.

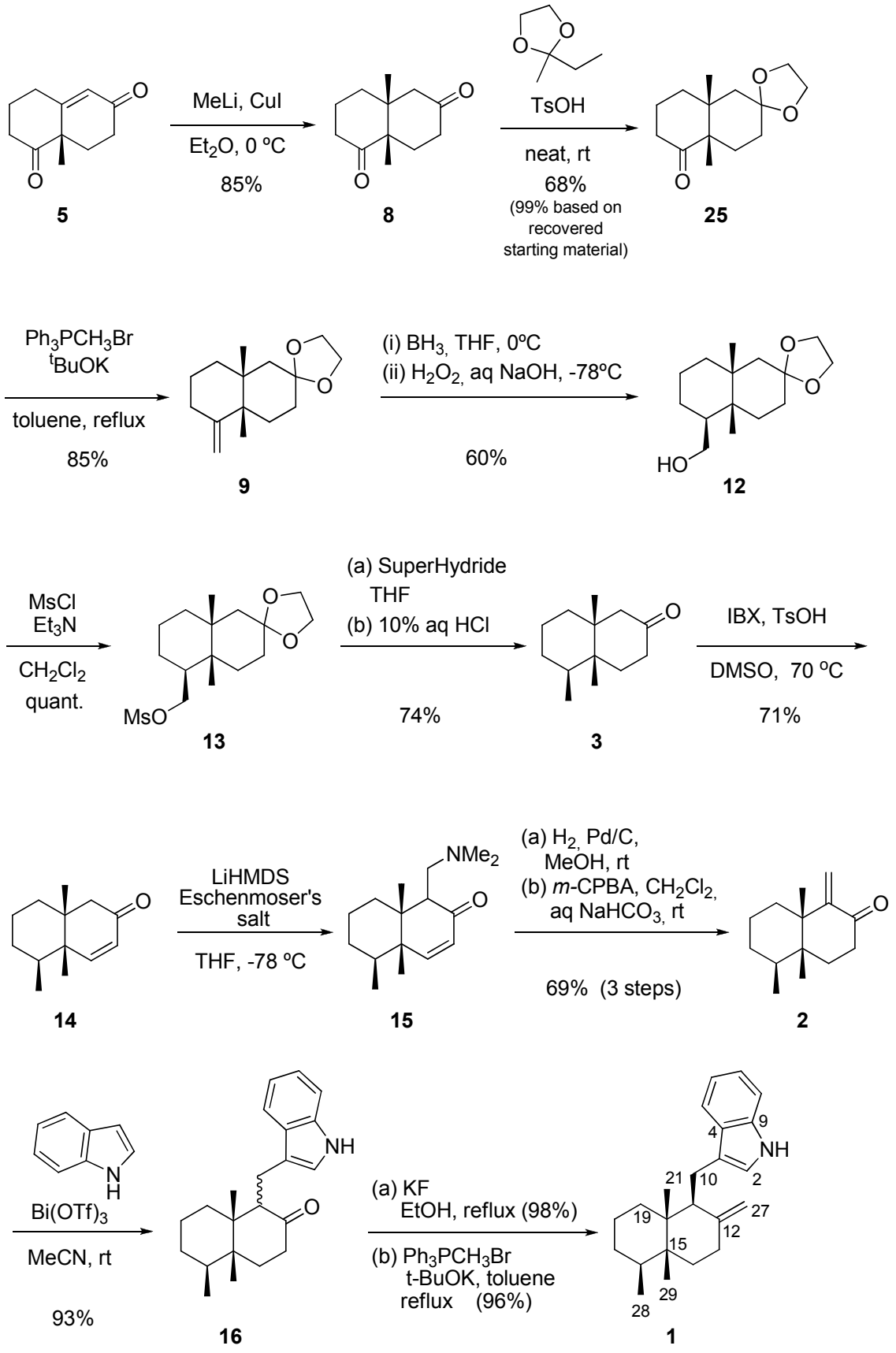
Terpene biogenetic numbering was used in the NMR assignation of all compounds, and the IUPAC nomenclature is followed in the headings



anominine



tubingensin A



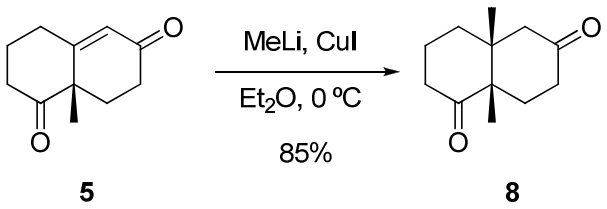
Scheme 6.1 Synthesis of Racemic Anominine Polycyclic Framework.

Table 1. ^{13}C NMR Chemical Shifts of Compounds towards Anominine Polycyclic Framework.[a]

Prod	5	8	25	9	12	3	14	2	16	1	(+)-61[b]
C2	-	-	-	-	-	-	-	-	123.5	121.7	121.2
C3	-	-	-	-	-	-	-	-	115.9	116.7	117.1
C4	-	-	-	-	-	-	-	-	127.5	128.0	127.7
C5	-	-	-	-	-	-	-	-	118.5	118.7	118.5
C6	-	-	-	-	-	-	-	-	119.1	119.0	119.1
C7	-	-	-	-	-	-	-	-	121.6	121.7	121.8
C8	-	-	-	-	-	-	-	-	111.0	111.0	111.0
C9	-	-	-	-	-	-	-	-	135.9	135.9	136.0
C10	-	-	-	-	-	-	-	120.5	17.4	19.9	21.4
C11	125.8	50.8	43.6	41.8	40.6	49.0	46.1	152.4	53.6	42.5	45.9
C12	198.3	214.9	109.6	108.1	110.0	213.4	200.2	203.2	213.6	149.5	149.8
C13	33.6	38.8	34.8	35.8	37.0	37.6	126.3	35.3	39.6	32.9	33.5
C14	29.6	31.5	31.6	31.2	29.5	32.2	159.4	32.2	32.5	33.9	34.4
C15	50.6	51.8	51.9	32.3	37.4	37.9	39.3	38.3	38.7	39.7	40.9
C16	211.0	211.7	216.2	132.1	39.2	31.0	37.8	32.6	30.9	30.5	31.1
C17	37.6	37.1	37.7	32.9	30.3	30.4	30.1	30.4	30.6	31.1	25.4
C18	22.9	21.9	21.7	22.5	21.3	21.9	21.7	21.7	21.9	21.6	28.8
C19	31.7	34.5	30.0	27.3	25.2	35.9	35.4	28.9	33.5	32.1	70.0
C20	165.8	44.8	41.0	38.3	37.0	41.8	42.1	44.8	47.0	42.8	47.9
C21	-	23.3	24.8	23.2	25.0	24.6	24.9	27.2	18.8	18.3	29.2
C27	-	-	-	-	-	-	-	-	-	107.7	107.7
C28	-	-	-	107.9	64.2	15.3	16.9	15.7	16.0	16.5	14.7
C29	23.3	21.2	20.5	20.1	17.1	16.1	15.3	15.7	16.3	16.3	18.3

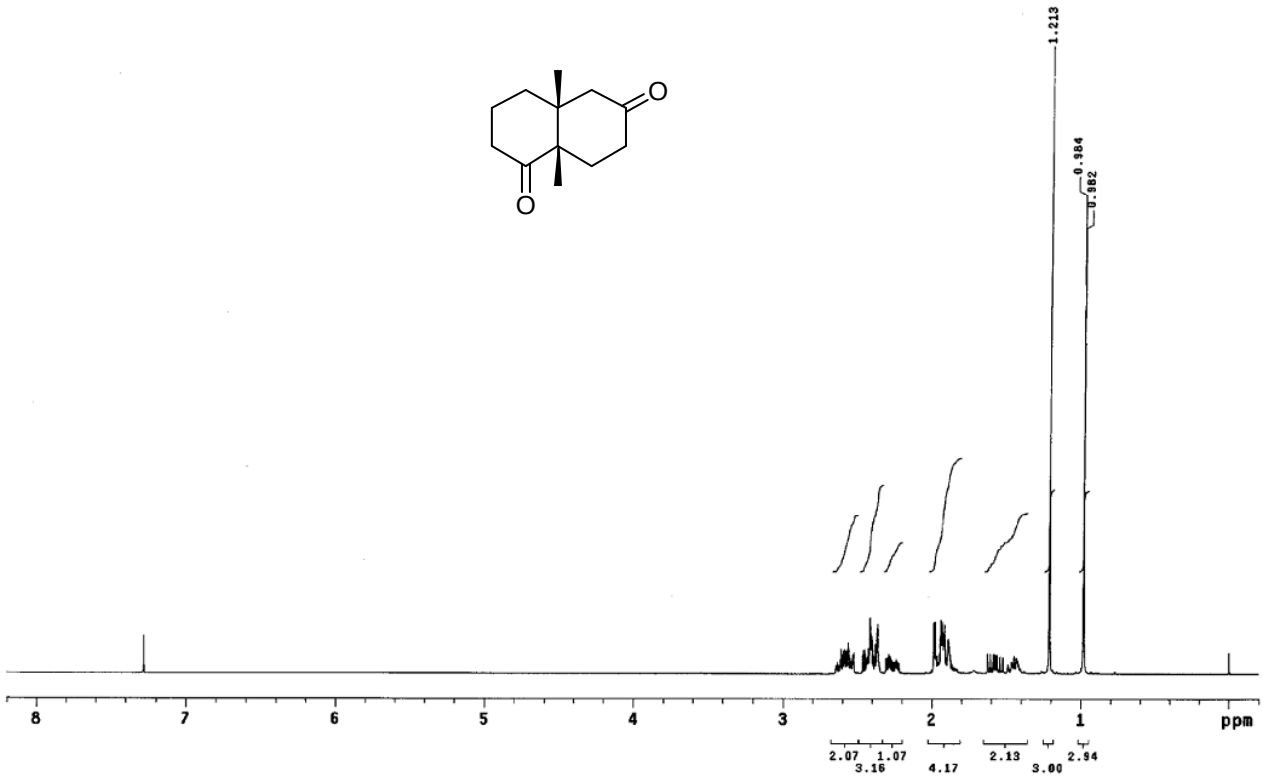
[a]Diterpene biogenetic numbering is used in this table. Assignments were aided by gCOSY and HMQC spectra.
[b]Natural anominine.

(4a*RS*,8a*SR*)-4a,8a-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*,7*H*-naphthalene-1,6-dione (8)



5 **8**

To a dispersion of copper iodide (32 g, 0.168 mol) in Et_2O (700 mL) at 0 °C was added MeLi (1.6 M in Et_2O, 175 mL, 0.280 mol), and the mixture was stirred for 1 h. A solution of enone **5** (10 g, 0.056 mol) in Et_2O (100 mL) was added, and the reaction was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution and stirred for 2 h, the aqueous layer was separated and extracted with EtOAc (5 × 100 mL), the combined organic layers were washed with NH_4Cl, brine, dried and concentrated. Purification of the residue by chromatography (10% EtOAc/hexane) gave diketone **8** (9.15 g, 85%) as a white solid; mp 129-131 °C; ^{1}H NMR (300 MHz, COSY) δ 0.98 (s, 3H, Me-29), 1.21 (s, 3H, Me-21), 1.45 (ddd, *J* = 11.0, 11.0, 5.0 Hz 1H, H-19$_{ax}$), 1.55 (ddd, *J* = 13.7, 11.1, 5.6 Hz, 1H, H-14$_{ax}$), 1.85-1.95 (m, 3H, 2H-18, H-19$_{eq}$), 1.97 (dd, *J* = 14.5, 2.1 Hz, 1H, H-11$_{eq}$), 2.26 (dddd, *J* = 15.2, 7.2, 5.6, 3.2 Hz, 1H, H-13$_{eq}$), 2.39 (d, *J* = 14.5 Hz, 1H, H-11$_{ax}$), 2.40 (dm, *J* = 14.0 Hz, 1H, H-17$_{eq}$), 2.42 (dm, *J* = 13.5 Hz, 1H, H-14$_{eq}$), 2.57 (dddd, *J* = 14.4, 11.0, 6.6, 1.5 Hz, 1H, H-13$_{ax}$), 2.58 (m, 1H, H-17$_{ax}$); ^{13}C NMR (75 MHz, DEPT, HSQC) δ 21.2 (C-29), 21.9 (C-18), 23.3 (C-21), 31.5 (C-14), 34.5 (C-19), 37.1 (C-17), 38.8 (C-13), 44.8 (C-20), 50.8 (C-11), 51.8 (C-15), 211.7 (C-16), 214.9 (C-12); HRMS Calcd for $C_{12}H_{19}O_2$ (MH^+) 195.1379, found 195.1381.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0.982
8
7
6
5
4
3
2
1
ppm
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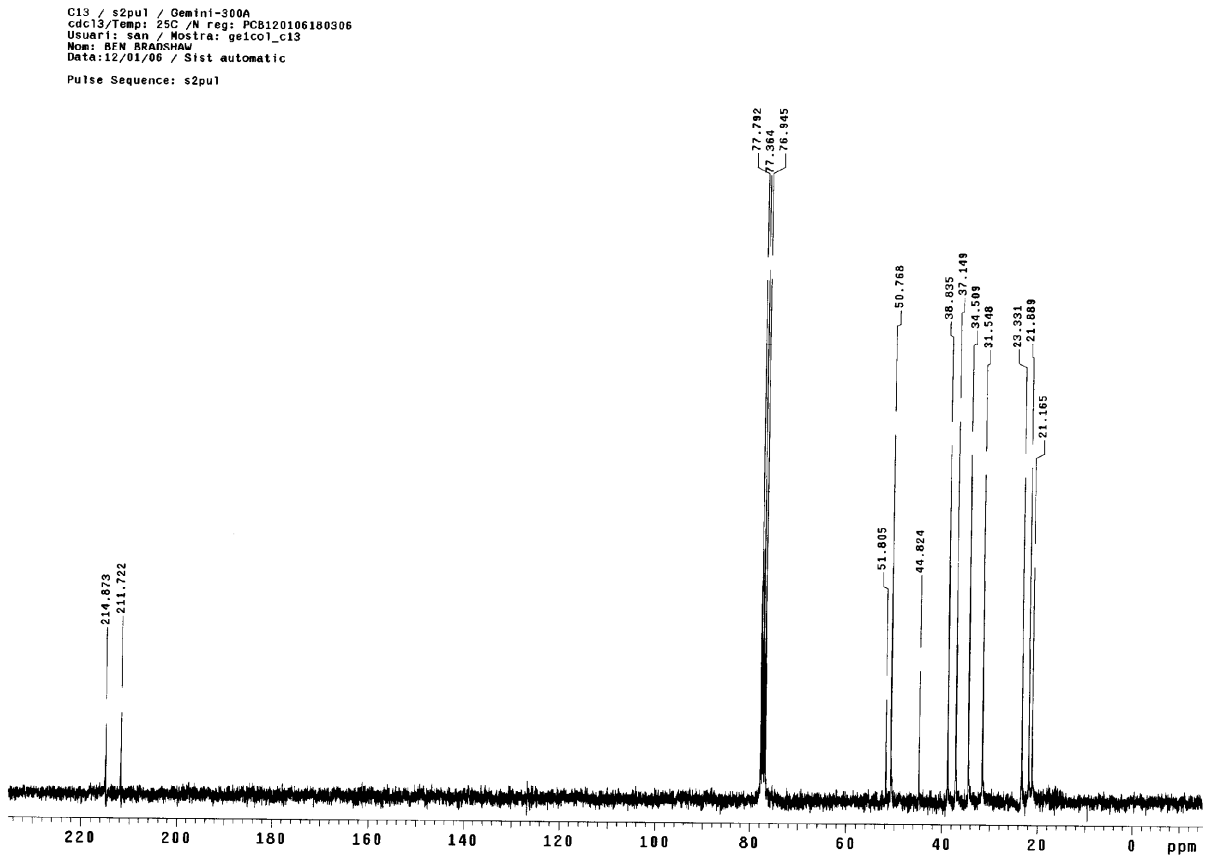
1.07
3.16
4.17
2.13
3.00
2.94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Data:12/01/06 / Sist automatic
Pulse Sequence: s2pul
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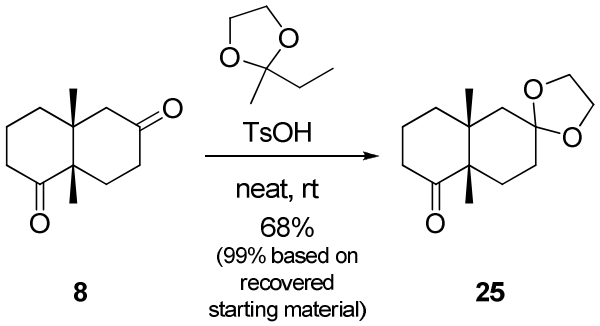
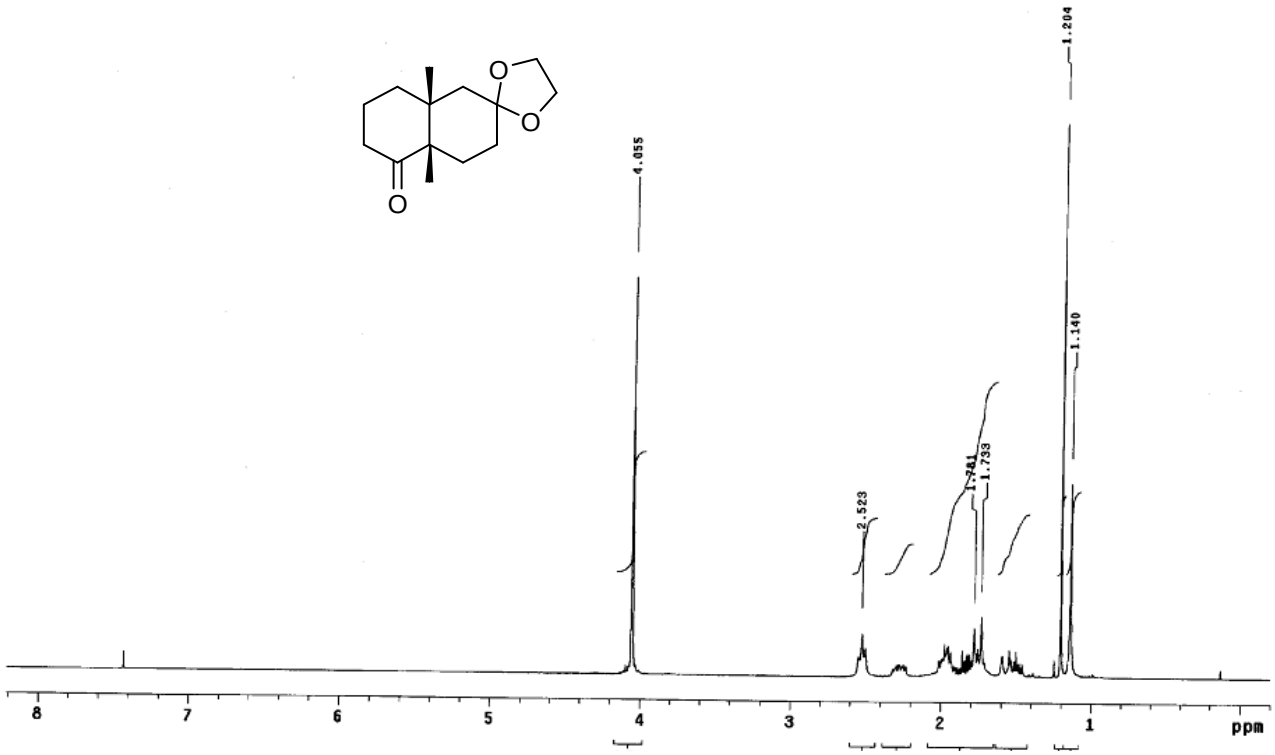
77.792
77.364
76.945
51.805
50.768
44.824
38.835
37.149
34.509
31.548
23.331
21.889
21.165
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(4a*RS*,8a*SR*)-4a,8a-Dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*,7*H*-naphthalene-1,6-dione 6-monoethylene acetal (25)



8 **25**

A solution of diketone **8** (3.3 g, 16.99 mmol) and *p*-toluenesulfonic acid monohydrate (162 mg, 0.85 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (10.6 mL, 85 mmol) was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 100 mL), the combined organic layers were washed with brine, dried and concentrated. Purification of the residue by chromatography (5% EtOAc) gave **25** (2.7 g, 68%) followed by recovered starting material **8** (1.05 g): overall yield 99% based on recovered starting material: ^{1}H NMR (300 MHz, COSY) δ 0.97 (s, 3H), 1.03 (s, 3H), 1.35-1.45 (m, 2H), 1.50-1.70 (m, 5H), 1.75-1.85 (m, 2H), 2.10 (m, 1H), 2.35 (m, 2H), 3.88 (s, 4H); ^{13}C NMR (75 MHz, DEPT, HSQC) δ 20.5 (C-29), 21.7 (C-18), 24.8 (C-21), 30.0 (C-19), 31.6 (C-14), 34.8 (C-13), 37.7 (C-17), 41.0 (C-20), 43.6 (C-11), 51.9 (C-15), 64.2 and 64.4 (OCH_2), 109.6 (C-12), 216.2 (C-16); HRMS Calcd for $C_{14}H_{23}O_3$ (MH^+) 239.1641, found 239.1642.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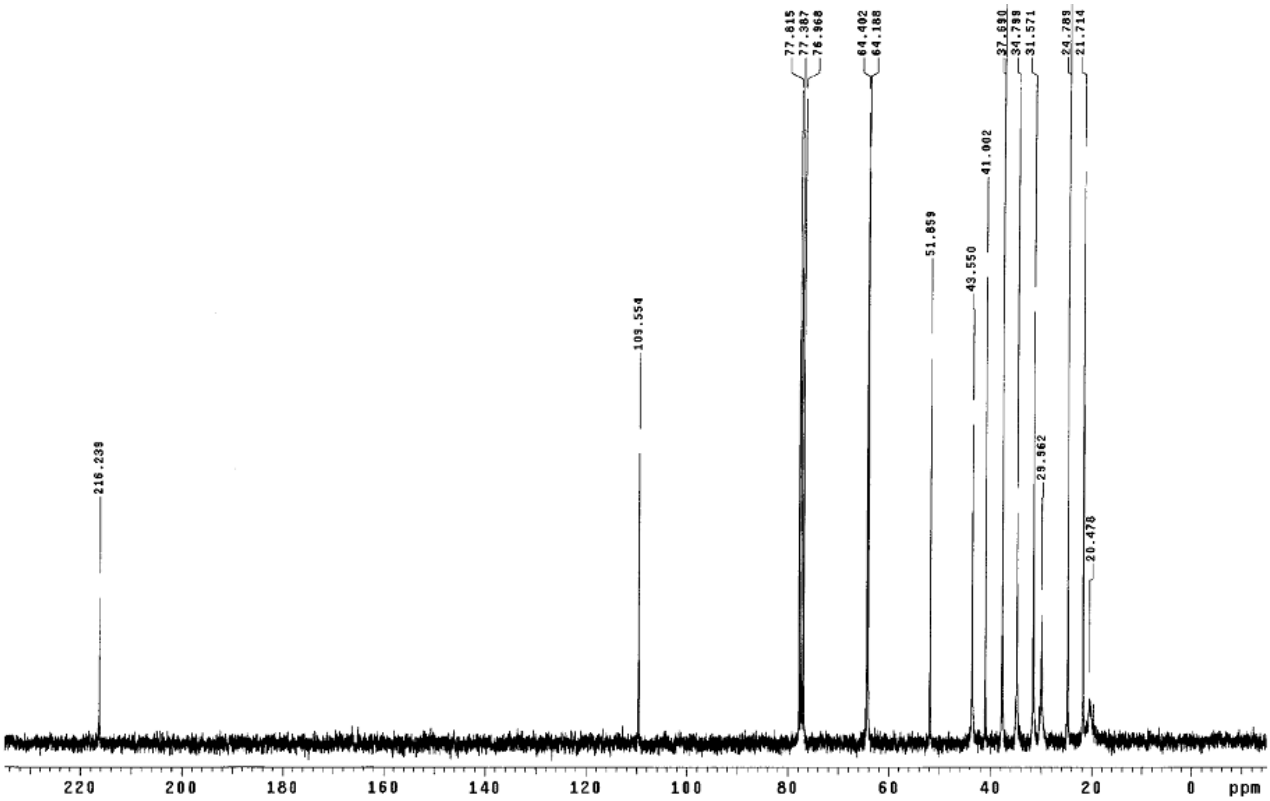
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20.478
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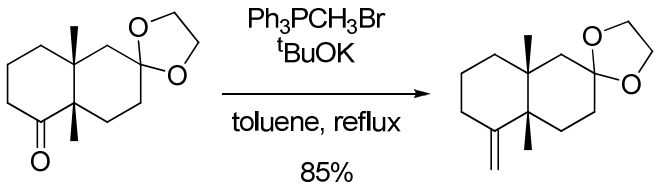
200
180
160
140
120
100
80
60
40
20
0
ppm

(4a*RS*,8a*SR*)-4a,8a-Dimethyl-5-methylene-3,4,4a,5,6,7,8,8a-octahydro-1*H*-naphthalen-2-one ethylene acetal (9)



25 **9**

A solution of methyltriphenylphosphonium bromide (20.0 g, 56.5 mmol) and potassium *tert*-butoxide (6.3 g, 56.5 mmol) in toluene (120 mL) was stirred at reflux for 1 h. Ketone **25** in toluene (40 mL) and was then added dropwise to the above solution and the resulting mixture was stirred at reflux for 4 h. The reaction was quenched by the addition of acetone (3 mL), stirring at 100 °C for 30 min and then by the addition of water (100 mL). The reaction mixture was extracted with Et_2O (3 × 200 mL), the combined organic layers were washed with brine, dried and concentrated. Purification of the residue by chromatography (1% EtOAc/hexane) gave alkene **9** (2.5 g, 94%) as a clear oil: ^{1}H NMR (300 MHz, COSY)[1] δ 0.90 (br s, 3H), 1.08 (s, 3H), 1.43-1.84 (m, 8H), 2.12-2.37 (m, 4H), 3.83-4.06 (m, 4H), 4.73 and 4.78 (2 s, 1H each); ^{13}C NMR (75 MHz, DEPT, HSQC) δ 20.1 (Me), 22.5 (C-18), 23.2 (Me), 27.3 (C-19), 31.2 (C-14), 32.3 (C-15), 32.9 (C-17), 35.8 (C-13), 38.3 (C-20), 41.8 (C-11), 63.5 and 63.7 (OCH_2), 107.9 (C-28), 108.1 (C-12), 132.1 (C-16); HRMS Calcd for $C_{15}H_{25}O_2$ (MH^+) 237.1849, found 237.1853.

[1] Broad signals due to the conformational inversion of the decalin ring.

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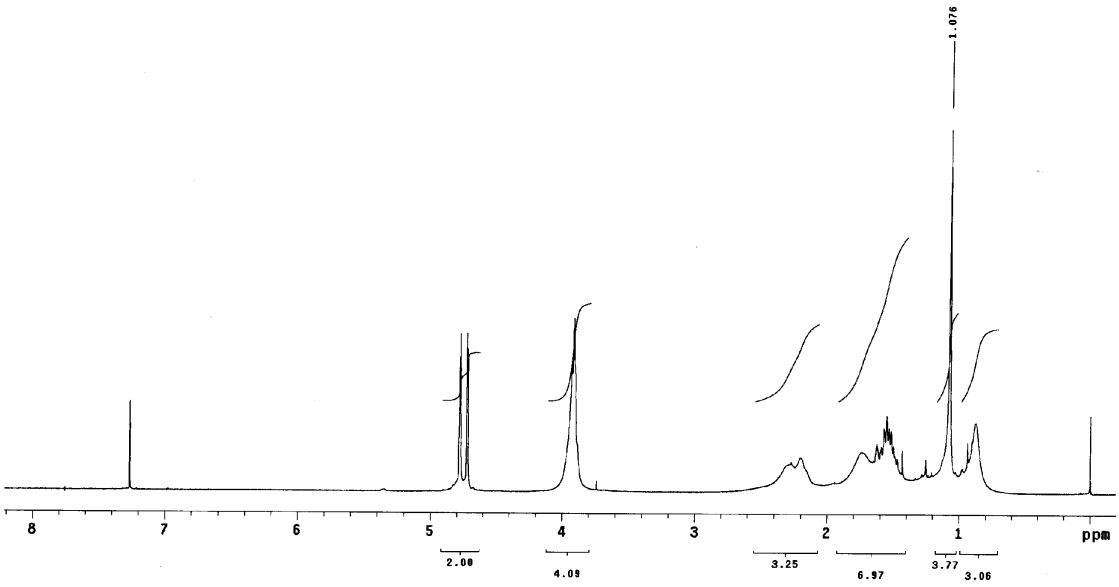
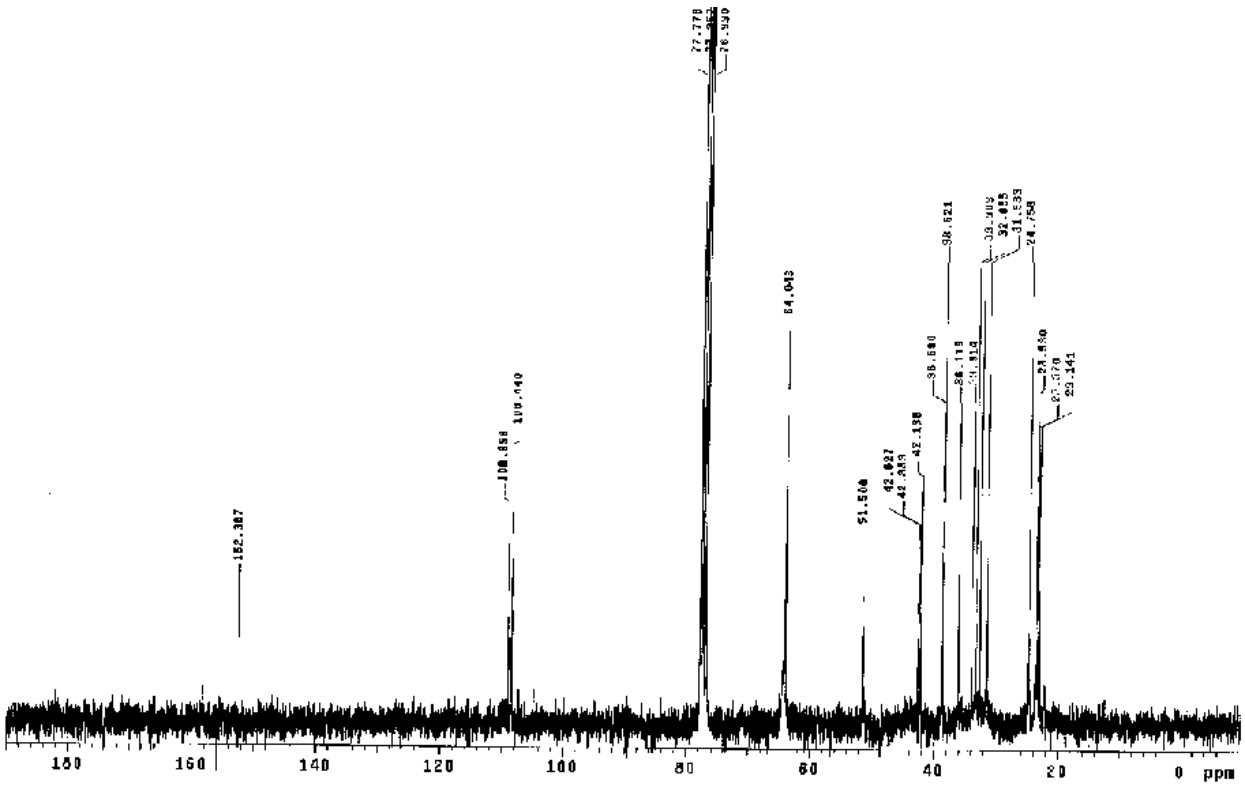
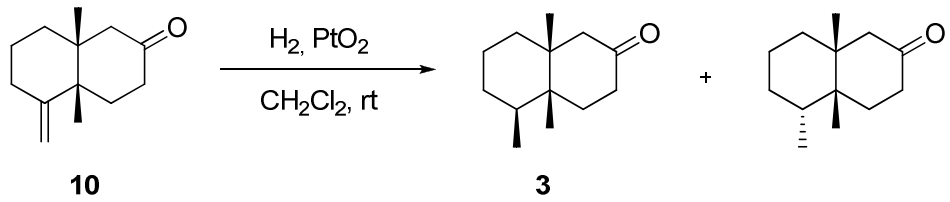
Data:11/04/07 / Sist automatic

Pulse Sequence: s2pul





Hydrogenation of 10



10 **3**

A solution of ketone **10** (100 mg, 0.57 mmol), platinum (IV) oxide hydrate (20 mg, 0.06 mmol) and hydrogen (450 psi) in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 h. The mixture was filtrated through Celite, dried and concentrated to give ~100 mg of material. The composition of the mixture was 3:1 in favour of the all-*syn* epimer as found by ^{1}H NMR spectroscopy. The products had identical R_f values were not separable by chromatography.

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SERVEIS CIENTIFICO-TECNICS

UNITAT DE RMN D ALT CAMP

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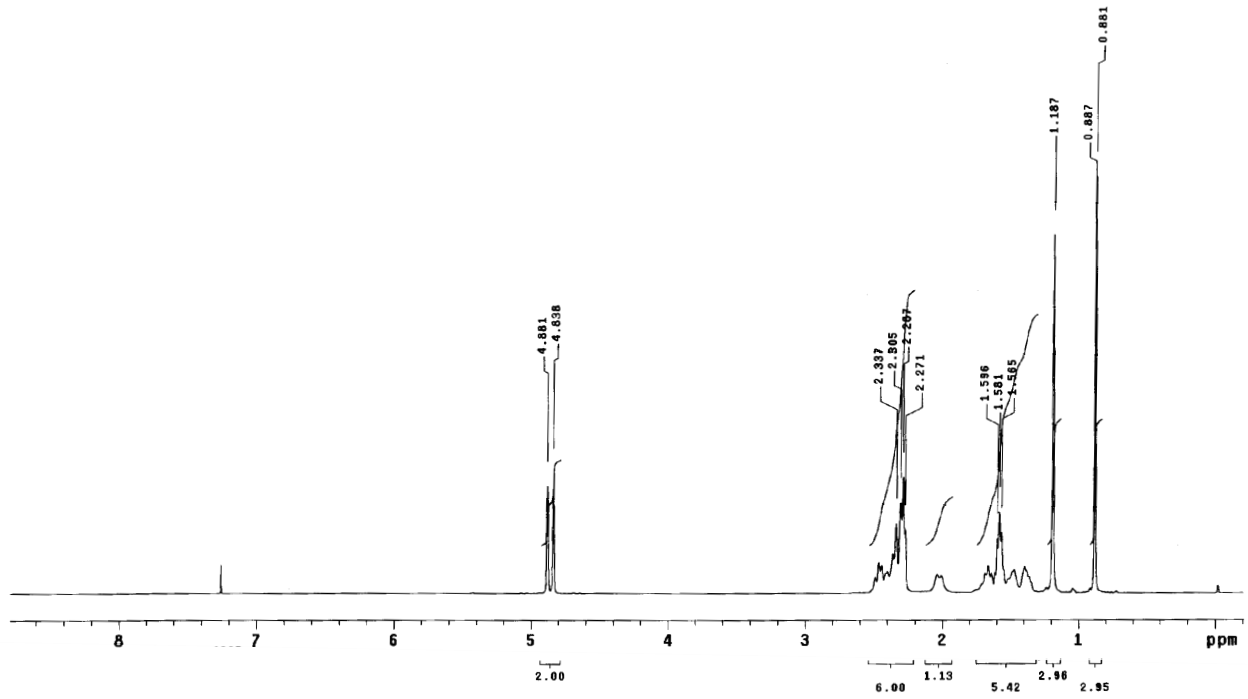
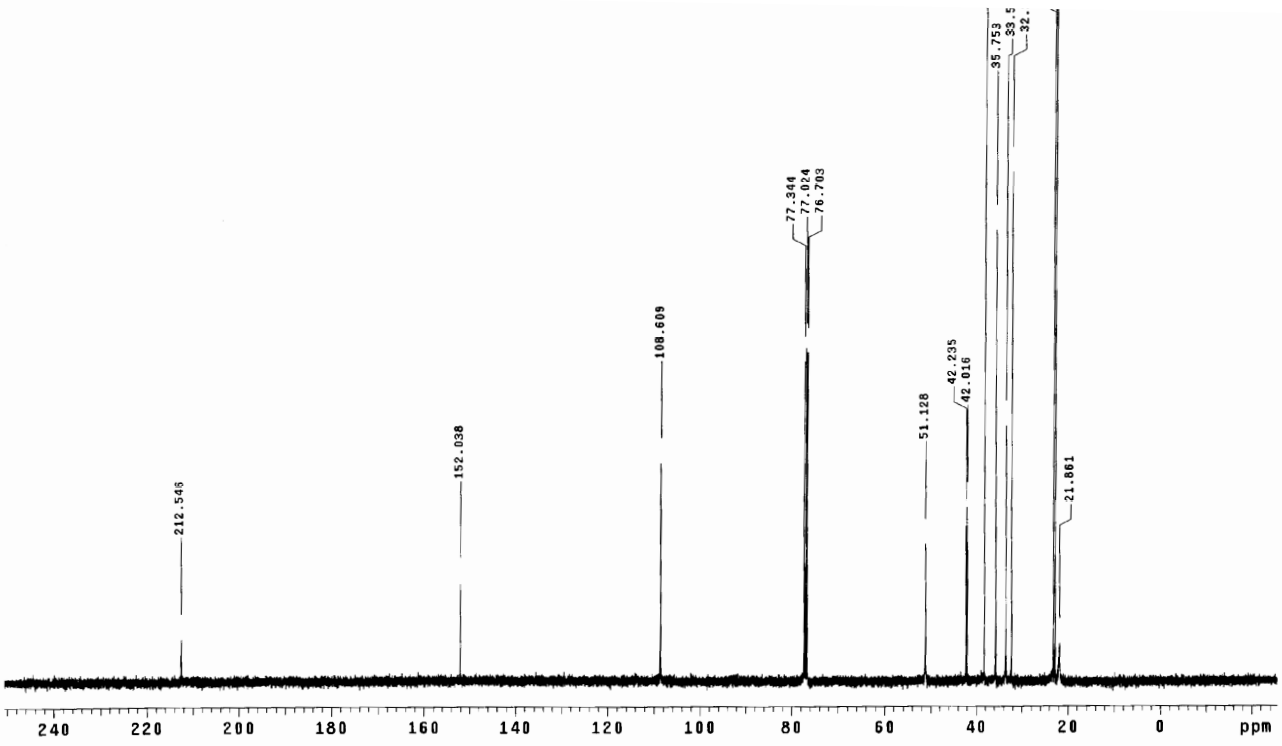
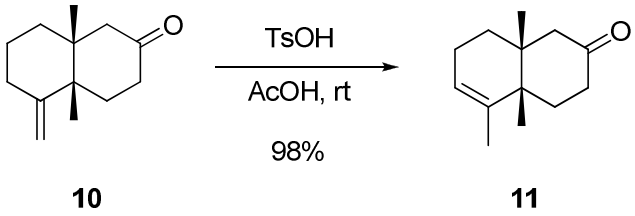
Data: 10/04/07 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



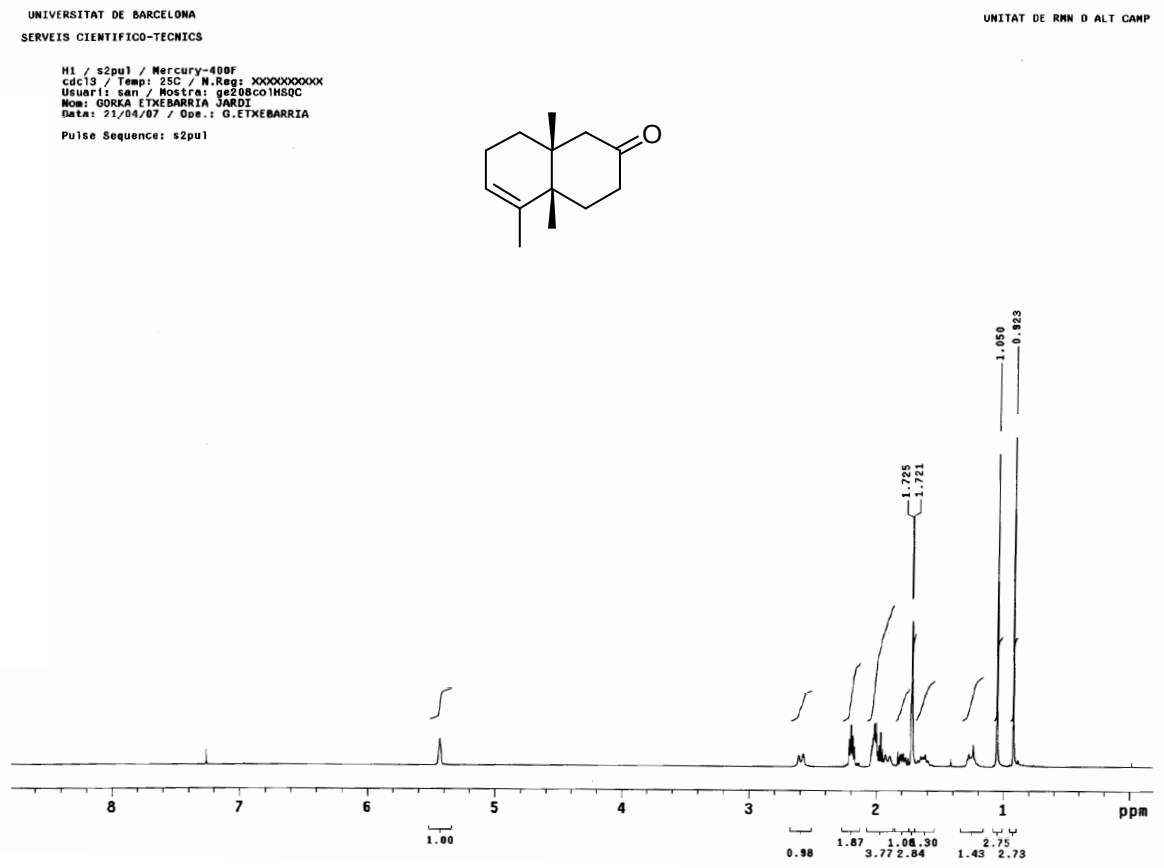


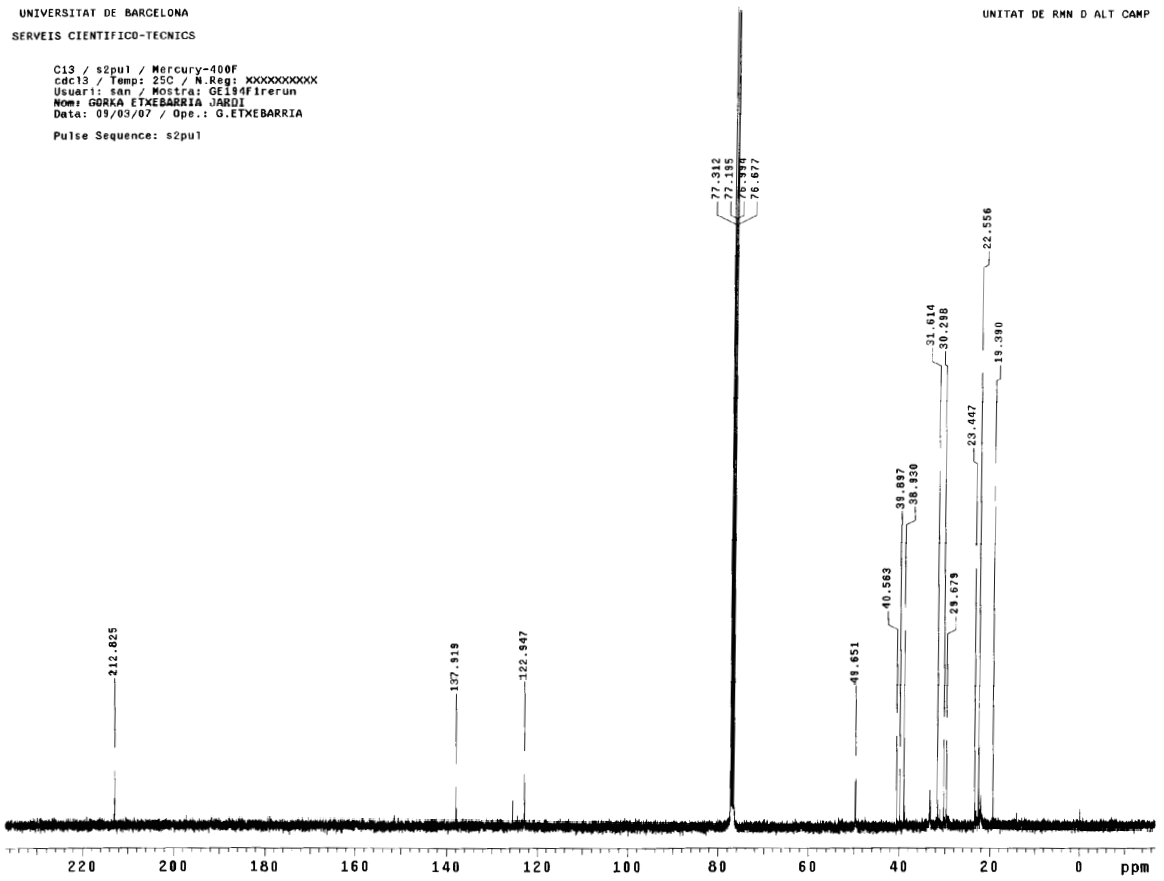
(4a*RS*,8a*SR*)-Trimethyl-3,4,4a,7,8,8a-hexahydro-1*H*-naphthalen-2-one (11)



10 **11**

p-Toluenesulfonic acid monohydrate (149 mg, 0.78 mmol) was added to a solution of **10** (100 mg, 0.52 mmol) in AcOH (2 mL) and the resulting mixture was stirred at room temperature for 48 h. The reaction was quenched with water, and extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried and concentrated. Purification of the residue by chromatography (10% EtOAc/hexane) gave **11** (98 mg, 98%) as a colourless oil: ^{1}H NMR (400 MHz, COSY) δ 0.92 (s, 3H, Me), 1.05 (s, 3H, Me), 1.25 (m, 1H, H-19), 1.65 (m, 1H, H-19), 1.73 (s, 3H, Me-28), 1.80 (m, 1H, H-14), 1.91 (d, J = 13.0 Hz, 1H, H-11), 1.95-2.05 (m, 3H, 2 H-18 and H-14), 2.20 (m, 2H, 2 H-13), 2.59 (d, *J* = 13.4 Hz, 1H, H-11), 5.43 (s, 1H, H-17); ^{13}C NMR (100 MHz, DEPT, HSQC) δ 19.4 (Me-29), 22.1 (br Me-28), 22.6 (C-18), 23.4 (C-21), 31.6 (C-19), 33.2 (br C-14), 38.9 (C-13), 39.9 (br C-15), 40.6 (C-20), 49.6 (C-11), 122.9 (C-17), 137.9 (C-16), 212.8 (C-12); HRMS Calcd for $C_{13}H_{21}O$ (MH^+) 193.1592, found 193.1592.


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge208co1HSQC
Nom: GORKA ETXEBARRIA JARDI
Data: 21/04/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
O
1.050
0.923
1.725
1.721
8
7
6
5
4
3
2
1
ppm
1.00
0.98
1.87
3.77
2.84
2.75
1.43
2.73


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: GE194firerun
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Data: 09/03/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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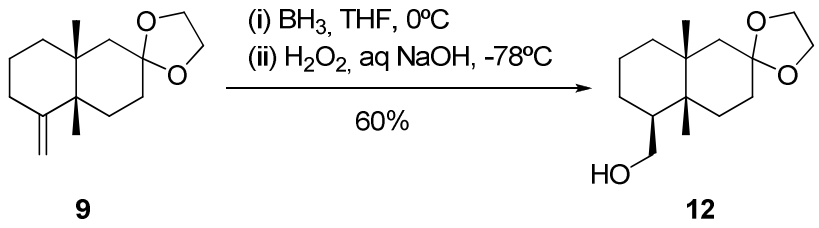
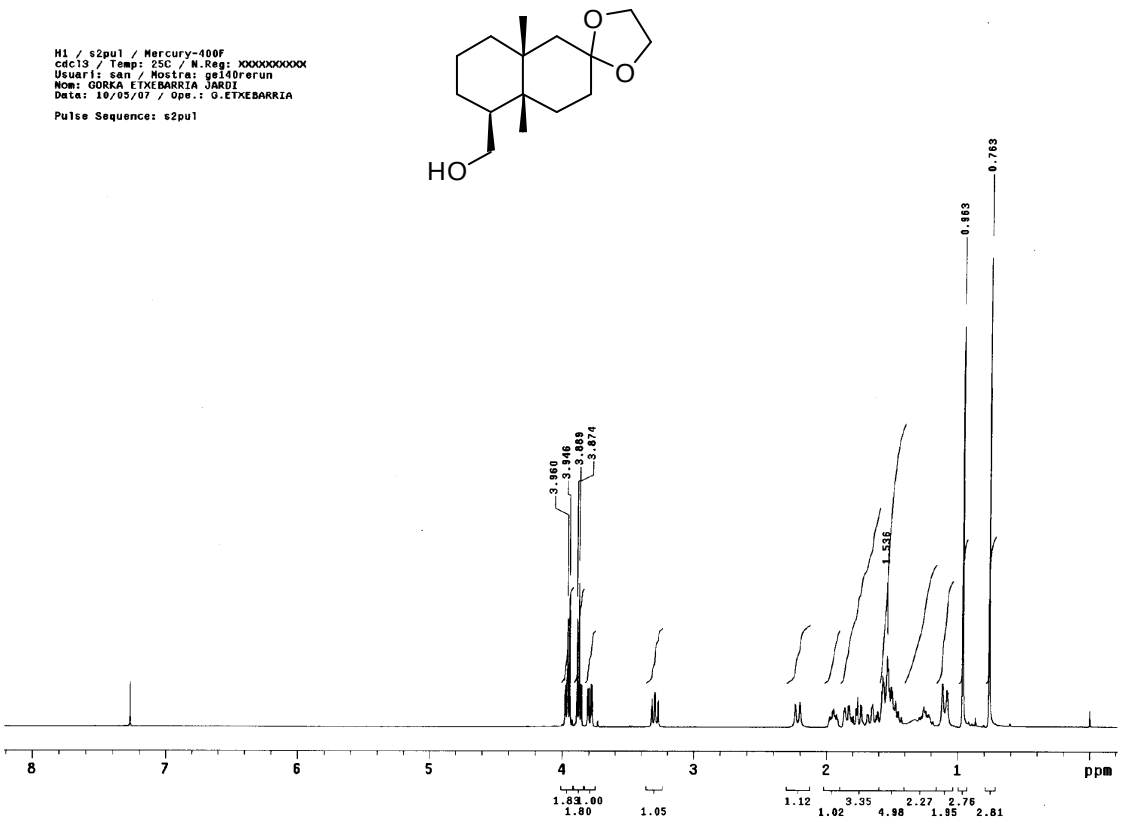
77.195
76.994
76.677
212.825
137.919
122.947
49.651
40.583
39.897
38.930
31.614
30.288
29.679
23.447
22.556
19.390
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(4a*RS*,5*SR*,8a*RS*)-5-Hydroxymethyl-4a,8a-dimethyloctahydronaphthalen-2-one ethylene acetal (12)



9 **12**

BH_3 (1 M in THF, 25.4 mL, 25.4 mmol) was added dropwise to a cooled (0 °C) solution of alkene **9** (2.0 g, 8.5 mmol) in THF (10 mL). The resulting mixture was warmed to room temperature, stirred for 2 h. The mixture was then cooled to −78 °C, and a premixed solution of 4 mL of 30% aqueous H_2O_2 and 4 mL of 3 M NaOH was added. After stirring the mixture overnight at room temperature, the aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried and concentrated in vacuo. Purification by chromatography (25% EtOAc/hexane) gave the alcohol **12** (1.1 g, 60%, +12% of epimer) as a clear oil: ^{1}H NMR (400 MHz, COSY) δ 0.76 (s, 3H, Me-29), 0.96 (s, 3H, Me-21), 1.10 (dd, *J* = 14.0, 2.0 Hz, 2H, H-11$_{ax}$, H-13$_{eq}$), 1.15 (m, 1H, H-19$_{ax}$), 1.42-1.60 (m, 5H, H-13$_{ax}$, H-17$_{eq}$, H-14$_{eq}$, 2 H-18), 1.65 (td, *J* = 13.8, 2.8 Hz, 1H, H-14$_{ax}$), 1.75 (m, 1H, H-17$_{ax}$), 1.83 (dm, *J* = 11.9 Hz, 1H, H-19$_{eq}$), 1.95 (dddd, *J* = 12.0, 7.7, 4.0, 3.3 Hz, 1H, H-16$_{ax}$), 2.22 (d, *J* = 14.0 Hz, 1H, H-11$_{eq}$), 3.30 (dd, *J* = 10.4, 8.8 Hz, 1H, H-28), 3.79 (dd, *J* = 10.4, 3.3 Hz, 1H, H-28), 3.87-3.96 (m, 4H, OCH_2); ^{13}C NMR (100 MHz, DEPT, HSQC) δ 17.1 (C-29), 21.3 (C-18), 25.0 (C-21), 25.2 (C-19), 29.5 (C-14), 30.3 (C-17), 37.0 (C-13), 37.0 (C-20), 37.5 (C-15), 39.2 (C-16), 40.6 (C-11), 63.4 (OCH_2), 64.2 (C-28), 64.3 (OCH_2), 110.0 (C-12); HRMS Calcd for $C_{15}H_{27}O_3$ (MH^+) 255.1960, found 255.1954.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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gel40rerun
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Data: 10/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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3.869
3.874
1.538
0.983
0.763
8
7
6
5
4
3
2
1
ppm
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1.05
1.12
3.35
2.27
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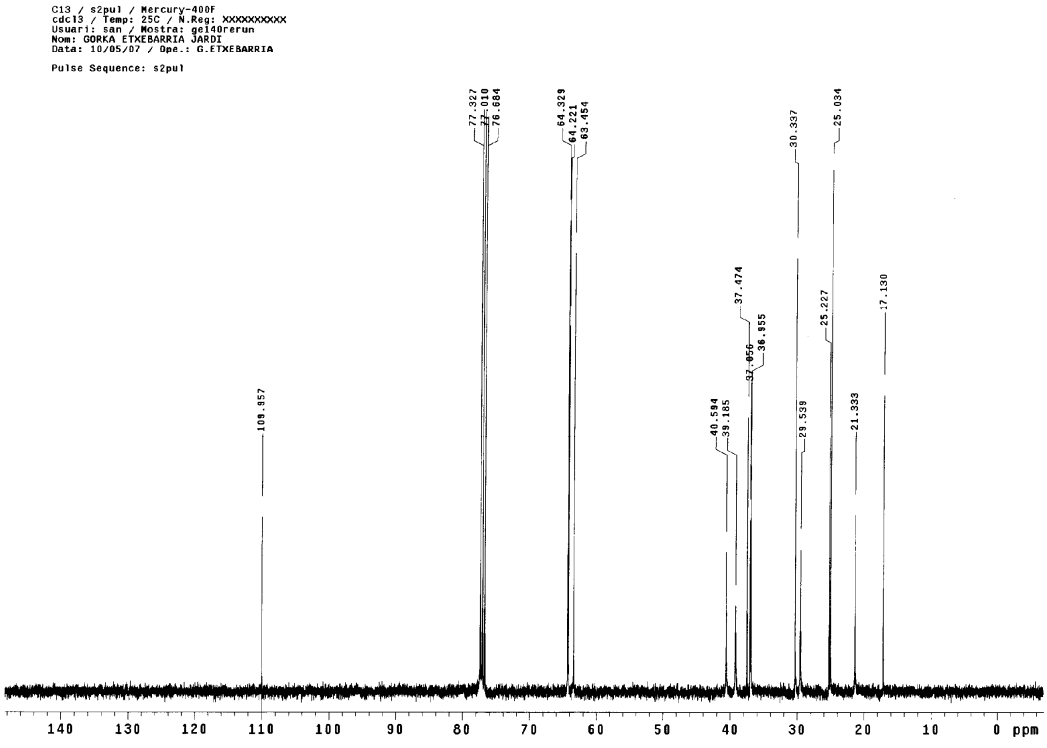
4.98
1.95
2.81


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gel40rerun
Nom: GORKA ETXEBARRIA JARDI
Data: 10/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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76.684
64.329
64.221
63.454
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40.584
39.185
37.474
36.955
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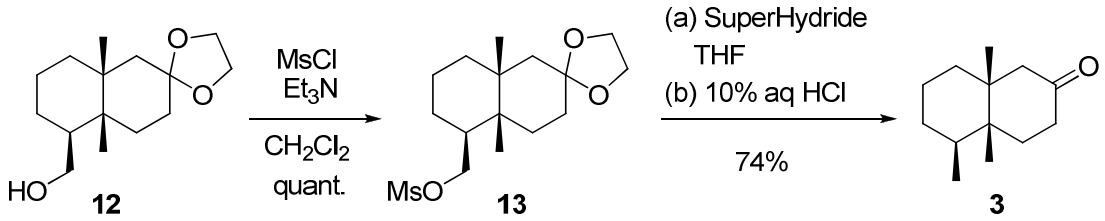
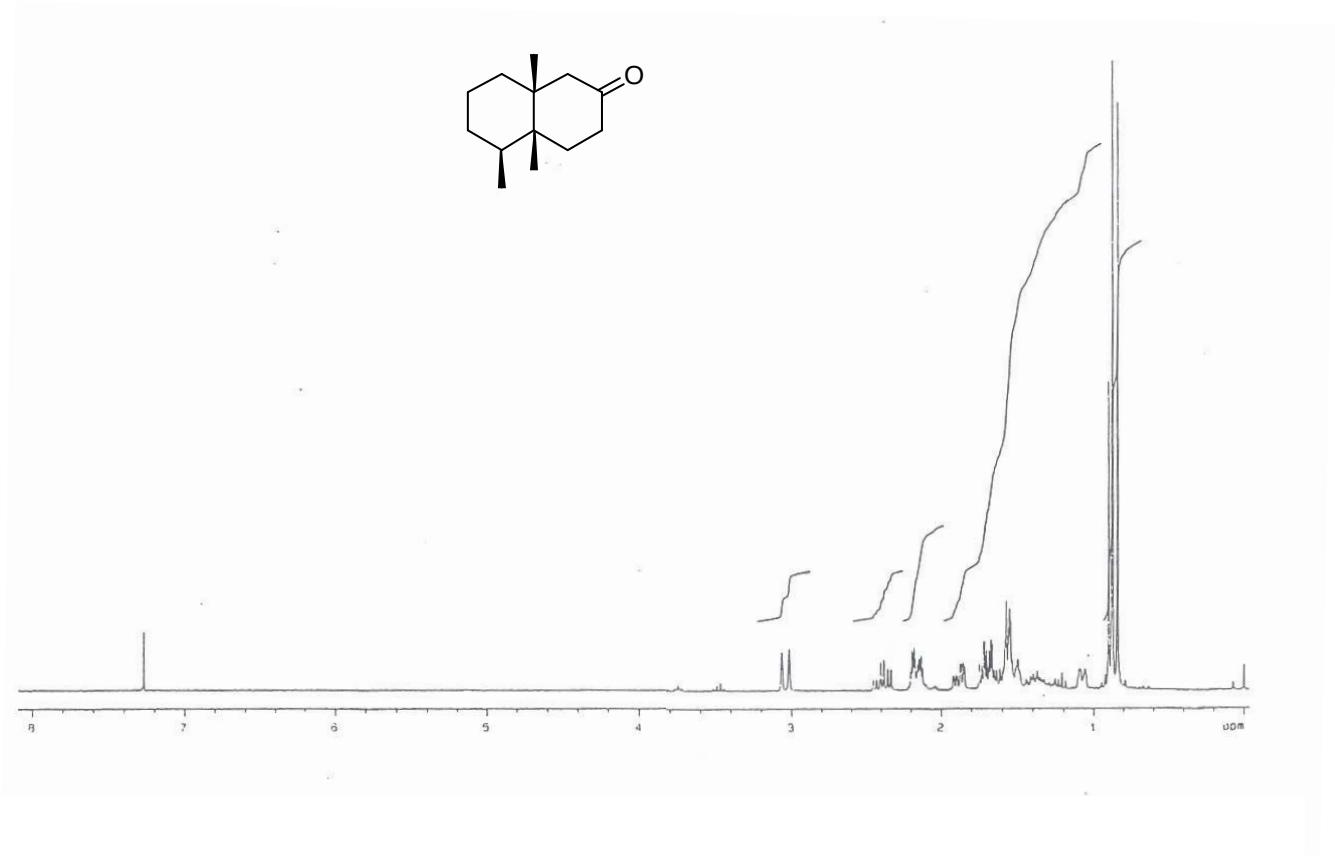
29.539
25.034
25.227
21.333
17.130
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

(4a*RS*,5*SR*,8a*RS*)-4a,5,8a-Trimethyl-3,4,4a,5,6,7,8,8a-octahydro-1*H*-naphthalen-2-one (3)



A cooled (0 °C) solution of alcohol **12** (800 mg, 3.14 mmol) in CH_2Cl_2 (25 mL) was treated sequentially with Et_3N (0.95 mL, 6.57 mmol) and methanesulfonyl chloride (270 mL, 3.46 mmol). After being stirred at room temperature for 1.5 h, the mixture was diluted with CH_2Cl_2 and washed with H_2O (15 mL), brine (2 × 5 ml), dried, and concentrated to give the mesylate, which was used in the next step without additional purification: ^{1}H NMR (300 MHz, COSY) δ 0.80 (s, 3H, Me-21), 0.98 (s, 3H, Me-29), 1.12 (dd, *J* = 14.2, 2.2 Hz, 2H, H-11$_{eq}$, H-13$_{eq}$), 1.24-1.40 (m, 1H, H-18$_{eq}$), 1.41-1.62 (m, 5H, H-13$_{ax}$, H-17$_{eq}$, H-14$_{eq}$, H-19$_{eq,ax}$), 1.63-1.86 (m, 3H, H-14$_{ax,}$ H-17$_{ax,}$ H-18$_{ax}$), 2.09-2.32 (m, 2H, H-11$_{ax,}$ H-16), 2.99 (s, 3H,-O$_3$S*Me*), 3.78-4.06 (m, 5H, H-28, OC*H*$_2$), 4.35 (dd, *J* = 9.52, 3.65 Hz, 1H, H-28). A solution of the mesylate **13** in THF (12 mL) was treated with SuperHydride® (1 M in THF, 9.42 mL, 9.42 mmol) and the resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with 10% aqueous HCl (20 mL), stirred for 2 h and then extracted with Et_2O (3 × 20 mL), dried and concentrated. Purification by chromatography (10% EtOAc/hexane) gave **3** (450 mg, 74% from alcohol **12**) as a white solid. All data were in accordance/identical to those previously reported.[2] ^{1}H NMR (500 MHz, COSY) δ 0.84 and 0.88 (2s, 3H, Me-21 and Me-29), 0.89 (d, *J* = 6.5 Hz, 3H, Me-28), 1.07 (dm, *J* = 10.5 Hz, 1H, H-19$_{eq}$), 1.30-1.40 (m, 1H, H-17), 1.50-1.60 (m, 4H, H-17, H-18$_{eq,ax}$, H-19$_{ax}$), 1.68 (td, *J* = 14.5, 5.0 Hz, 1H, H-14$_{ax}$), 1.69 (dd, *J* = 14.5, 2.1 Hz, H-10$_{eq}$), 1.89 (ddd, *J* = 14.5, 6.5, 2.1 Hz, 1H, H-14$_{eq}$), 2.14 (m, 1H, H-13$_{eq}$), 2.39 (td, *J* = 14.5, 5.0 Hz, 1H, H-13$_{ax}$), 3.04 (d, *J* = 14.5 Hz, 1H, H-10$_{ax}$); ^{13}C NMR (50 MHz, DEPT, HSQC) δ 15.3 (Me-28), 16.1 (Me-29), 21.9 (C-18), 24.6 (Me-21), 30.4 (C-17), 31.0 (C-16), 32.2 (C-14), 35.9 (C-19), 37.6 (C-13), 37.9 (C-15), 41.8 (C-20), 49.0 (C-10), 213.4 (C-12).

[2] Díaz, S.: Cuesta, J.; González, A.; Bonjoch, J. *J. Org. Chem*. **2003**, *68*, 7400-7406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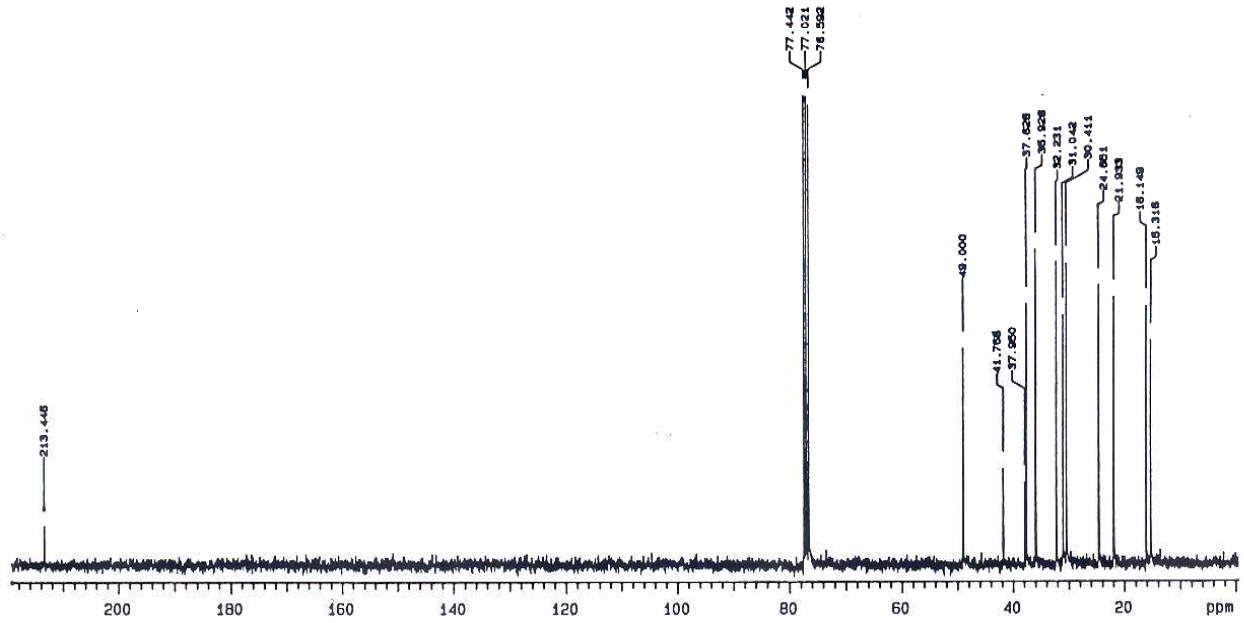
6
5
4
3
2
1
0pm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76.592
49.000
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37.628
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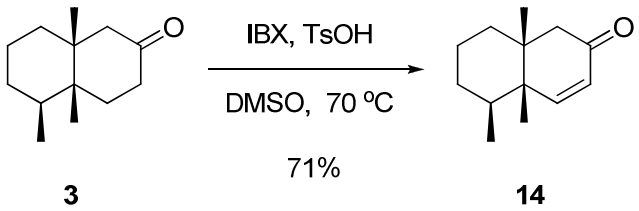
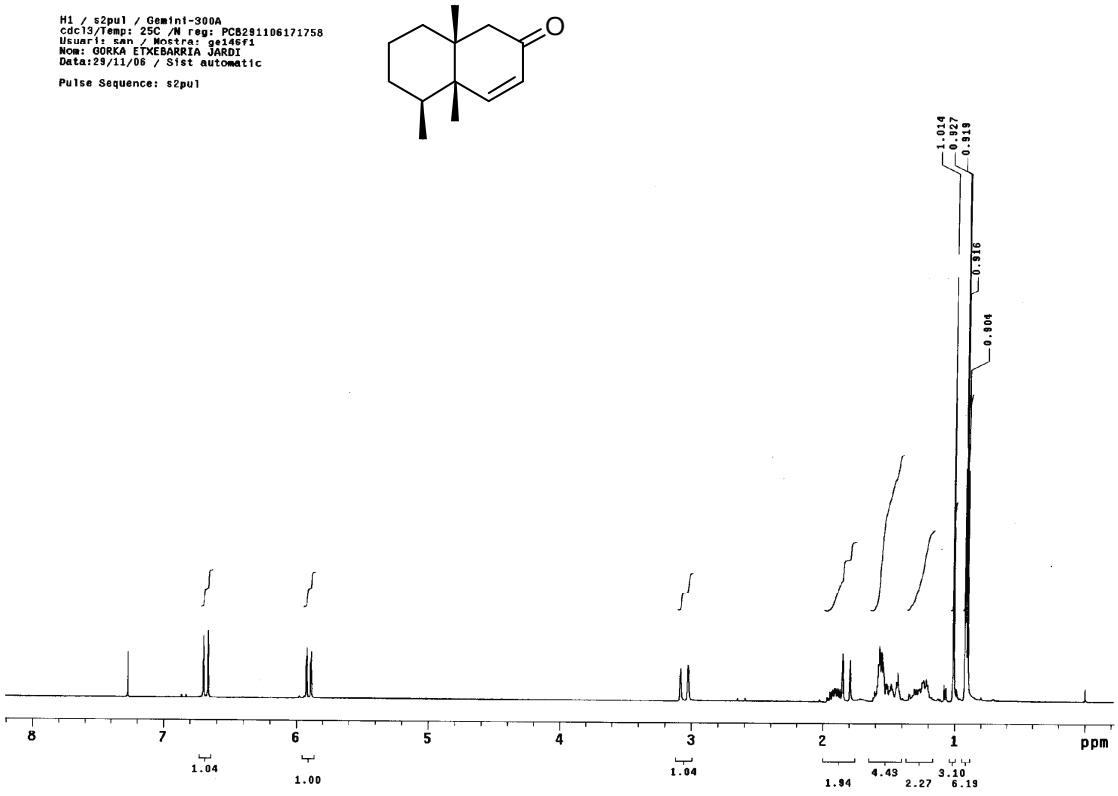
32.231
31.042
30.411
24.861
21.933
18.149
15.316
200
180
160
140
120
100
80
60
40
20
ppm

(4a*RS*,5*RS*,8a*SR*)-Trimethyl-4a,5,6,7,8,8a-hexahydro-1*H*-naphthalen-2-one (14)



3 **14**

To a solution of ketone **3** (400 mg, 2.06 mmol) in DMSO (6 mL) was added *o*-iodoxybenzoic acid (IBX, 1.44 g, 5.15 mmol) and *p*-toluenesulfonic acid monohydrate (118 mg, 0.62 mmol), and the mixture was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature and partitioned between EtOAc (40 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with EtOAc (5 × 40 mL), the combined organic layers were washed with saturated $NaHCO_3$, saturated sodium thiosulfate solution, brine, dried and concentrated. Purification by chromatography (10% EtOAc/hexane) gave **14** (281 mg, 71%) as a colourless oil: ^{1}H NMR (300 MHz) δ 0.91 (d, *J* = 6.8 Hz, 3H, Me-28), 0.92 and 1.01 (2s, 3H each, Me-29 and Me-21), 1.15 (m, 2H), 1.40-1.64 (m, 4H), 1.82 (d, *J* = 16.9 Hz, 1H, H-11), 1.91 (ddd, *J* = 12.3, 6.7, 3.5 Hz, 1H, H-16), 3.06 (d, *J* = 16.9 Hz, 1H, H-11), 5.91 (d, *J* = 10.2 Hz, 1H, H-13), 6.68 (d, *J* = 10.2 Hz, 1H, H-14); ^{13}C NMR (75 MHz, DEPT) δ 13.3 (Me), 16.9 (C-28), 21.7 (C-18), 24.9 (Me), 30.1 (C-17), 35.4 (C-19), 37.8 (C-16), 39.3 (C-15), 42.1 (C-20), 46.1 (C-11), 126.3 (C-13), 159.4 (C-14), 200.2 (C-12); HRMS Calcd for $C_{13}H_{21}O$ (MH^+) 193.1592, found 193.1601.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Data:29/11/06 / Sist automatic
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0.516
0.304
8
7
6
5
4
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2
1
ppm
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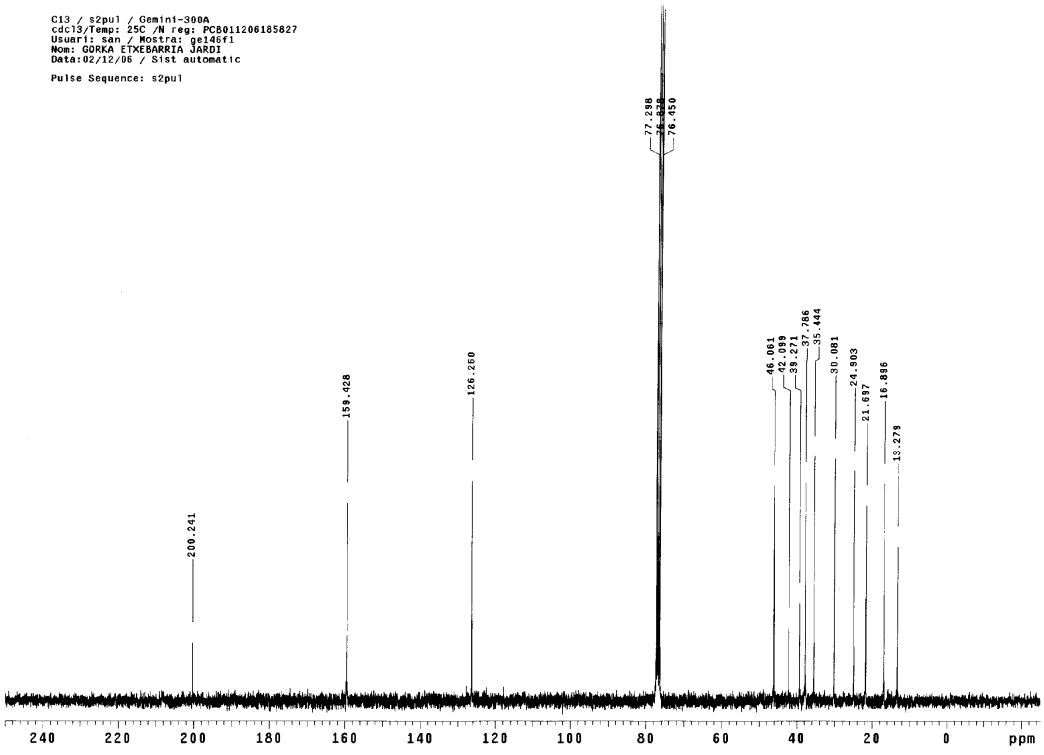
1.00
1.04
1.94
4.43
2.27
3.10
6.19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Usuari: san / Mostra: ge146f1
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Data:02/12/06 / Sist automatic
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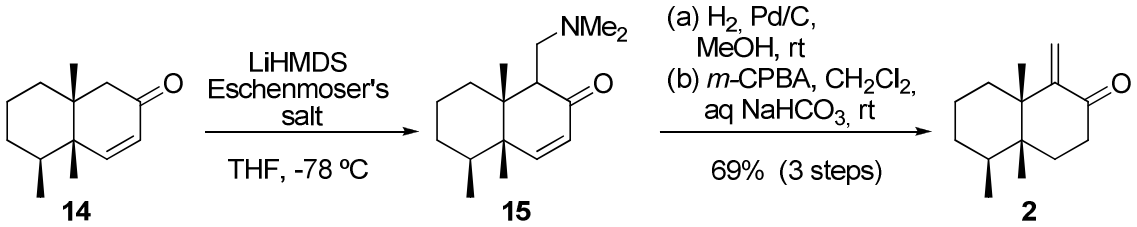
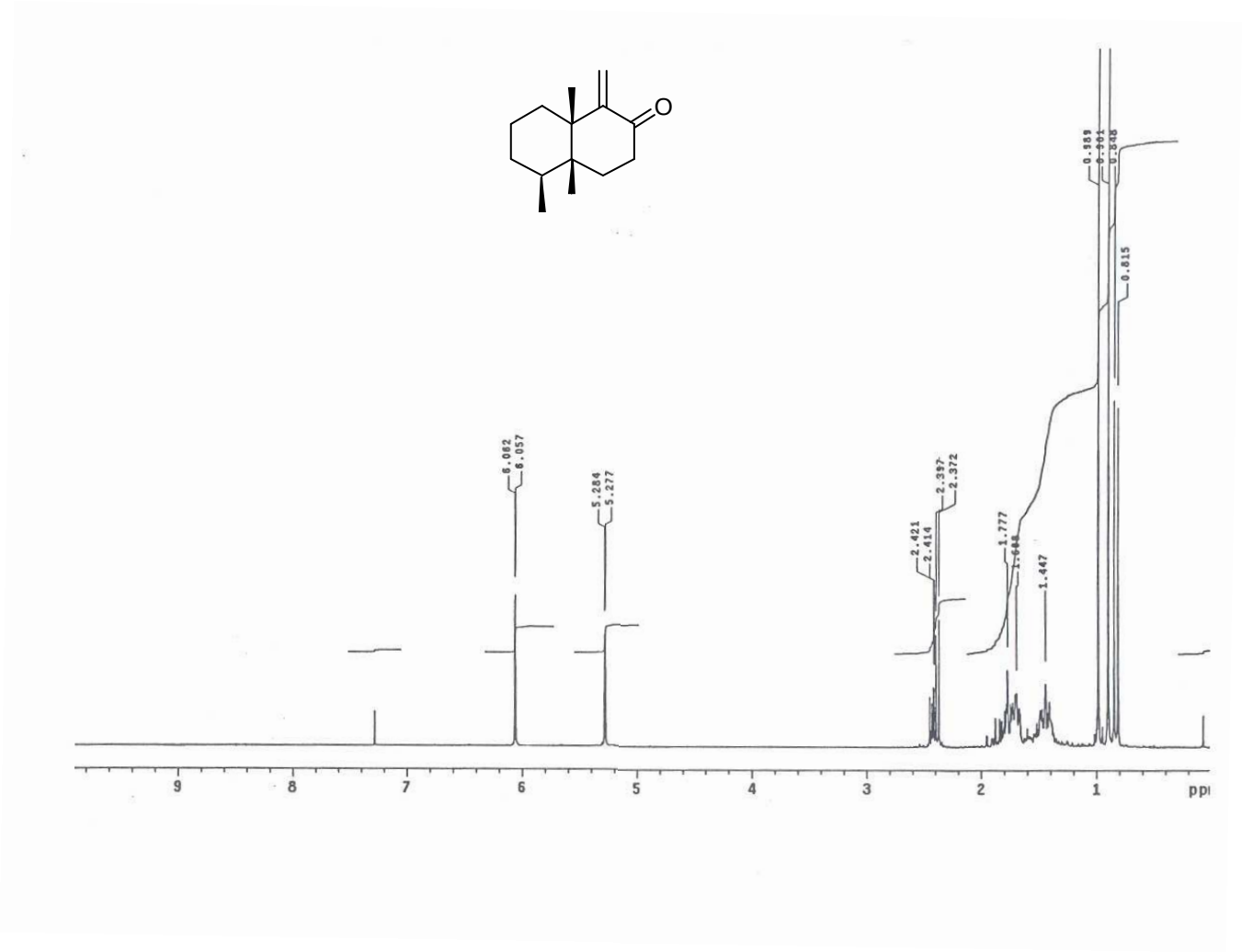
200
180
160
140
120
100
80
60
40
20
0
ppm

(4a*RS*,5*SR*,8a*SR*)- 4a,5,8a-Trimethyl-1-methylene-3,4,4a,5,6,7,8,8a-octahydro-1*H*-naphthalen-2-one (2)



Enone **14** (506 mg, 2.64 mmol) in THF (10 mL) was added dropwise to a cooled (−78 °C) solution of LiHMDS (1 M in THF, 5.27 mL, 5.27 mmol) in THF (7.5 mL). The resulting solution was was stirred for 5 min at –78 °C, warmed to 0 °C, stirred for 1 h, recooled to −78 °C then transferred via cannula over 15 min to a stirred suspension of Eschenmoser's salt (1.47 g, 7.92 mmol,) in 15 mL of THF at –78 °C. The resulting mixture was stirred for 10 min at –78 °C, then for 10 min in a r water bath, and then transferred to a separatory funnel with ether (50 mL) and saturated $NaHCO_3$ solution (10 mL). The aqueous layer was separated, diluted with 50 mL of water, and extracted with 50 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to give a yellow/orange oil **15**. The residue was dissolved in MeOH (50 mL), Pd/C (100 mg) was added, and the mixture was stirred under hydrogen (1 atm) for 16 h. The mixture was filtered through Celite, dried and concentrated. This crude material was partitioned between CH_2Cl_2 (25 mL) and saturated $NaHCO_3$ solution (12.5 mL), and *m*-CPBA (Aldrich, 57–86%, 911 mg, 5.28 mmol, 1.5–2.3 equiv) was added in one portion. The resulting mixture was stirred vigorously for 20 min, then transferred to a separatory funnel and separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure *at room temperature* to avoid undesired polimerisation. Purification by chromatography (5% EtOAc/hexane) gave **2** as clear oil (350 mg, 71%). All spectroscopic data was identical to that previously reported.[2] ^{1}H NMR (300 MHz, COSY) δ 0.83 (d, *J* = 6.9 Hz, 3H, Me-28), 0.90 and 0.99 (2s, 3H each, Me-21 and Me-29), 1.40-1.53 (m, 4H), 1.67-1.87 (m, 5H), 2.41 (m, 2H, H-13$_{eq,ax}$), 5.28 (d, *J* = 1.5 Hz, 1H), 6.06 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, DEPT, HSQC) δ 15.7 (Me-28 and Me-29), 21.5 (C-18), 27.2 (Me-21), 28.9 (C-19), 30.4 (C-17), 32.2 (C-14), 32.6 (C-16), 35.3 (C-13), 38.3 (C-15), 44.8 (C-20), 120.5 (C-10), 152.4 (C-11), 203.2 (C-12).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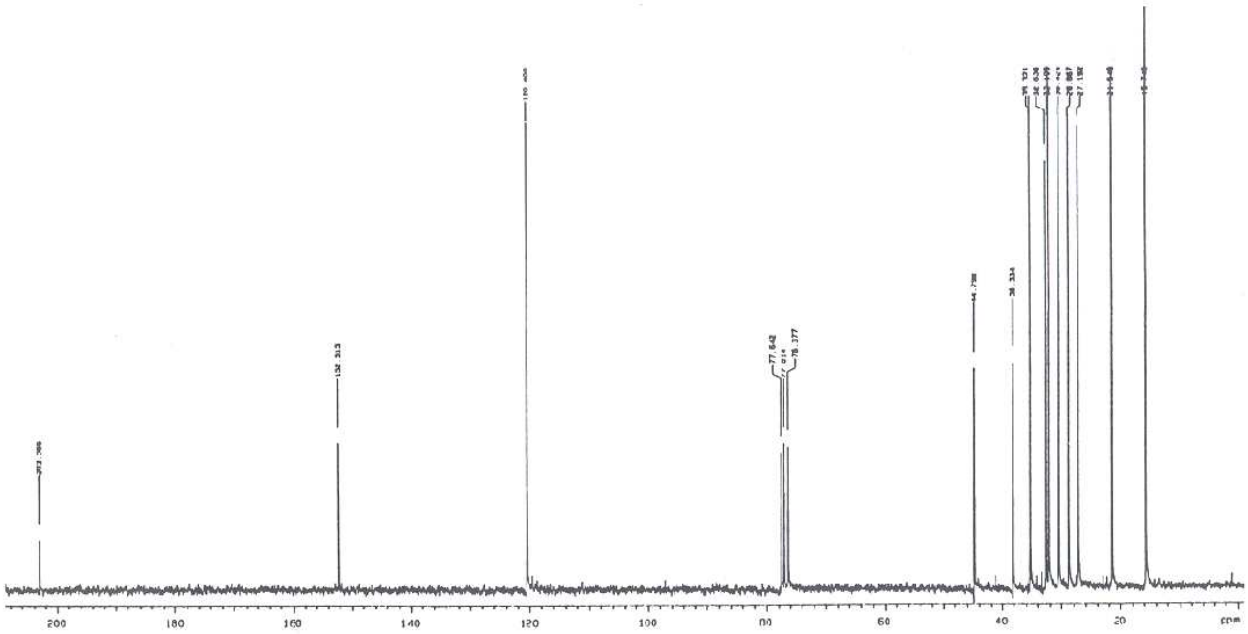
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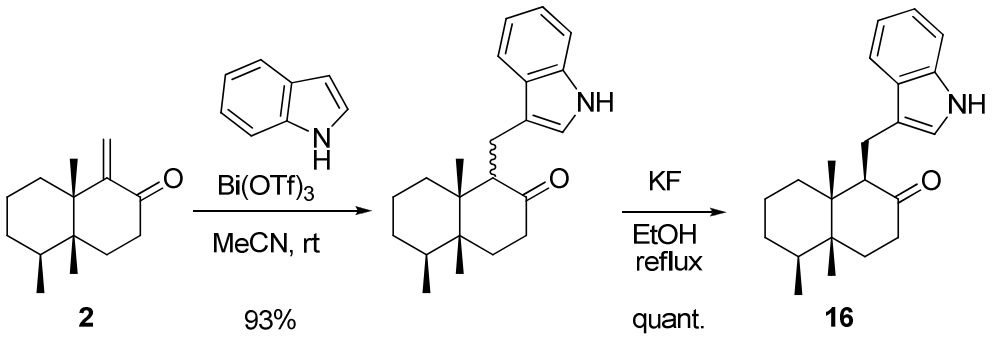
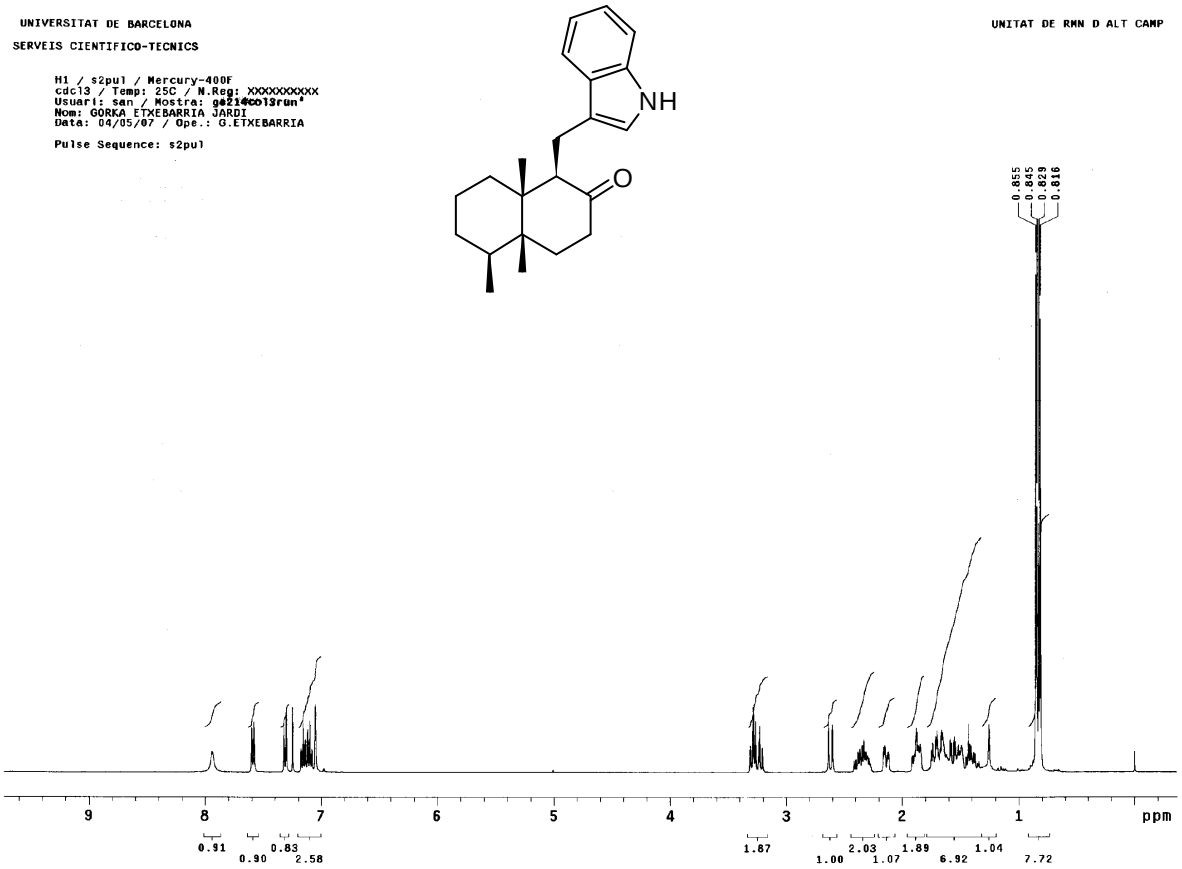
60
40
20
ppm

(1*RS*,4a*RS*,5*SR*,8a*RS*)-1-(1*H*-Indol-3-ylmethyl)-4a,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-1*H*-naphthalen-2-one (16)



To a solution of indole (37 mg, 0.32 mmol), and the enone **2** (65 mg, 0.32 mmol) in CH_3CN (1 ml) was added bismuth triflate (6 mg, 0.01 mmol, 3 mol%) and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 and absorbed onto silica. Purification by column chromatography (5% EtOAc/hexane) gave ketoindole (95 mg, 93%) as a mixture of epimers. The mixture was dissolved in EtOH (10 mL), potassium fluoride (255 mg, 4.40 mmol) was added, and the resulting mixture was heated at reflux for 48 h. After the reaction was cooled to room temperature, the mixture was partitioned between water and CH_2Cl_2, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by chromatography (25% EtOAc/hexane) gave **16** (93 mg, 98%) as a white solid. ^{1}H NMR (400 MHz, COSY) δ 0.82 (s, 3H, Me), 0.83 (d, *J* = 6.8 Hz, 3H, Me-28), 0.86 (s, 3H, Me), 1.40 (qd, *J* = 12.8, 4.8 Hz, 1H, H-17$_{ax}$), 1.51 (dm, *J* = 12.5 Hz, 1H, H-17$_{eq}$), 1.55-1-70 (m, 3H, H-14$_{ax}$, 2 H-18), 1.71 (td, *J* = 14.0, 4,5 Hz, 1H, H-19$_{ax}$), 1.87 (dm, *J* = 14.0 Hz, 1H, H-14$_{eq}$), 1.90 (ddd, *J* = 14.0, 6.0, 2.4 Hz, 1H, H-19$_{eq}$), 2.14 (ddd, *J* = 12.9, 4.4, 2.4 Hz, 1H, H-13$_{eq}$), 2.31 (m, 1H, H-16$_{ax}$), 2.37 (td, *J* = 14.0, 6.0 Hz, 1H, H-13$_{ax}$), 2.62 (d, *J* = 13.5 Hz, 1H, H-10), 3.25 (dd, *J* = 13.5, 9.5 Hz, 1H, H-10), 3.30 (d, *J* = 9.5 Hz, 1H, H-11), 7.05 (d, *J* = 2.2 Hz, 1H, H-2), 7.10 (t, *J* = 7.8 Hz, 1H, H-6), 7.16 (t, *J* = 7.8 Hz, 1H, H-7), 7.31 (d, *J* = 8.0 Hz, 1H, H-8), 7.59 (d, *J* = 7.8 Hz, 1H, H-5), 7.94 (br s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) δ 16.0 (C-28), 16.3 (C-29), 17.4 (C-10), 18.8 (C-21), 21.9 (C-18), 30.6 (C-17), 30.9 (C-16), 32.5 (C-14), 33.5 (C-13), 38.7 (C-15), 39.6 (C-19), 47.0 (C-20), 53.6 (C-11), 111.0 (C-8), 115.9 (C-3), 118.5 (C-5), 119.1 (C-6), 121.6 (C-7), 123.5 (C-2), 127.5 (C-4), 135.9 (C-9), 213.6 (C-12); HRMS Calcd for $C_{22}H_{29}NO$ (M^+) 323.2249, found 323.2260.


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: ge214col3run'
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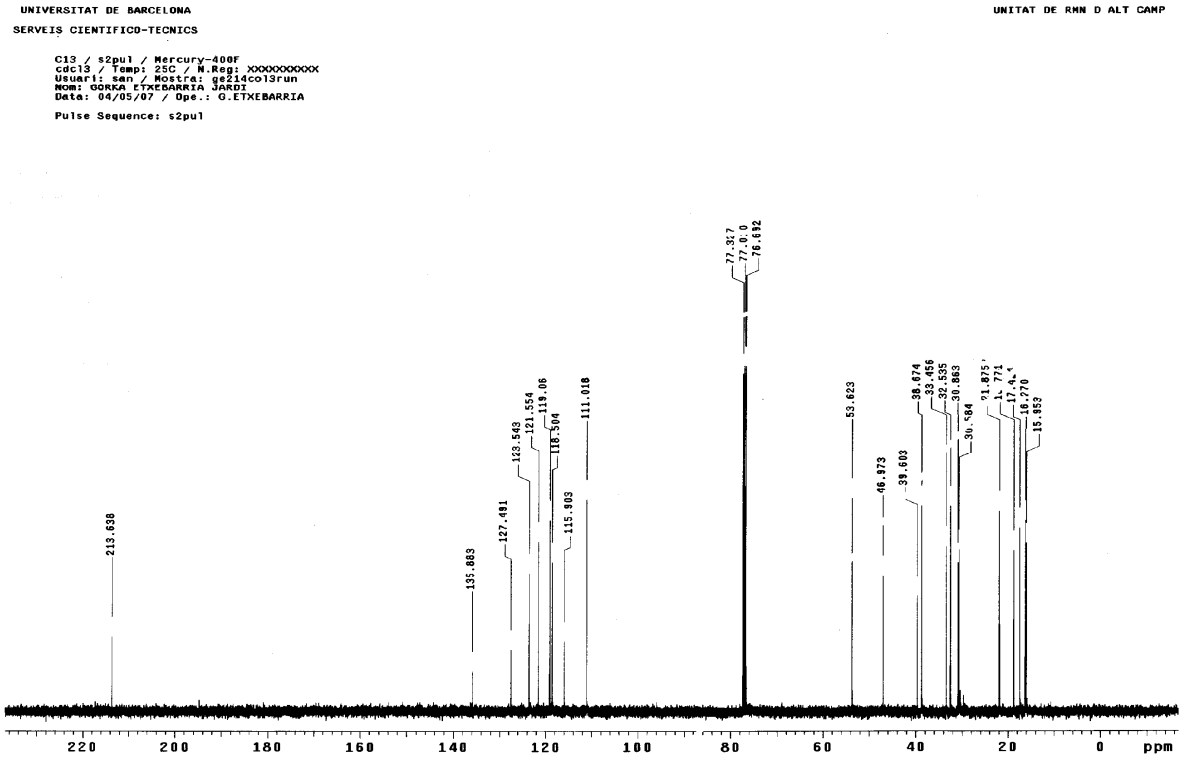
Data: 04/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
NH
O
0.855
0.845
0.829
0.816
9
8
7
6
5
4
3
2
1
ppm
0.91
0.90
0.83
2.58
1.87
1.00
2.03
1.07
1.89
6.92
1.04
7.72


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: ge214col3run
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Data: 04/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
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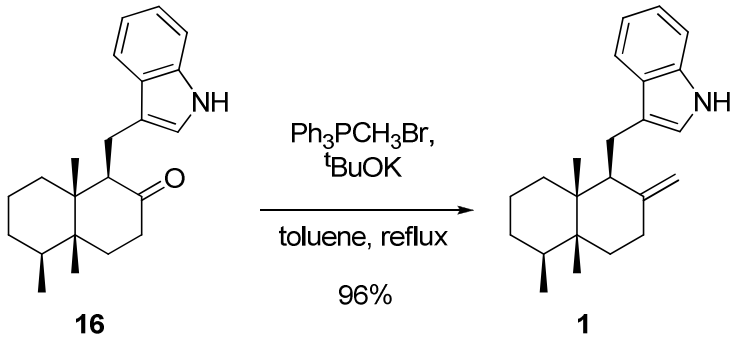
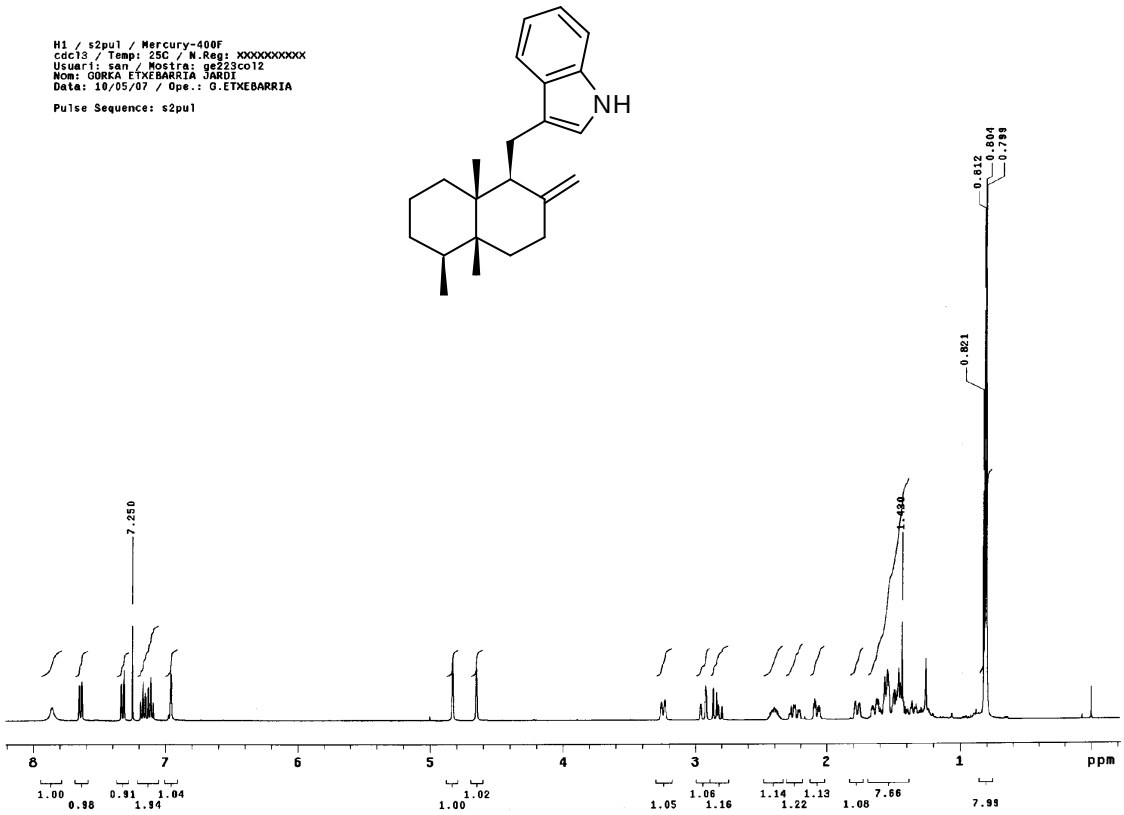
135.883
127.491
123.543
121.554
119.06
118.504
115.903
111.018
77.317
77.0 0
76.692
53.623
46.973
39.603
38.674
33.456
32.535
30.863
30.584
21.875
21.771
17.274
16.770
15.652
220
200
180
160
140
120
100
80
60
40
20
0
ppm

3-[(1*RS*,4a*SR*,5*RS*,8a*SR*)-4a,5,8a-Trimethyl-2-methylenedecahydronaphthalen-1-ylmethyl]-1*H*-indole (1)



16 **1**

A solution of methyltriphenylphosphonium bromide (200 mg, 0.56 mmol) and potassium *tert*-butoxide (55 mg, 0.49 mmol) in toluene (5 mL) was stirred at 90 ºC for 30 min. A solution of ketone **16** (40 mg, 0.12 mmol) in toluene (3 mL) was added, and the reaction was heated at 90 °C for 2 h. After the mixture was cooled to room temperature, the reaction was quenched with water, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by column chromatography (2.5% EtOAc/hexane) gave **1** (38 mg, 96%) as a white solid: ^{1}H NMR (400 MHz, COSY) δ 0.80 and 0.81 (2 s, 3H each, Me-21, Me-29), 0.81 (d, *J* = 6.8 Hz, 3H, Me-28) 1.20-1.55 (m, 6H, 2 H-18, 2 H-17, H-14$_{ax}$, H-19$_{ax}$), 1.64 (dm, *J* = 14.0 Hz, 1H, H-14$_{eq}$), 1.77 (dm, *J* = 12.0 Hz, 1H, H-19$_{eq}$), 2.08 (ddd, *J* = 13.9, 4.4, 2.6 Hz, 1H, H-13$_{eq}$), 2.25 (dt, *J* = 13.9, 13.7, 5.2 Hz, 1H, H-13$_{ax}$), 2.40 (ddd, *J* = 10.8, 6.5, 3.9 Hz, 1H, H-16), 2.83 (dd, *J* = 16.0, 10.3 Hz, 1H, H-10), 2.94 (d, *J* = 16.0 Hz, 1H, H-10), 3.24 (d, *J* = 10.3 Hz, 1H, H-11), 4.65 (d, 1H, H-27), 4.83 (d, *J* = 1.6 Hz, 1H, H-27), 6.96 (s, 1H, H-2), 7.11 (ddd, *J* = 7.6, 7.2, 1.1 Hz, 1H, H-6), 7.17 (t, *J* = 7.6 Hz, 1H, H-7), 7.33 (d, *J* = 8.0 Hz, 1H, H-8), 7.65 (d, *J* = 7.9 Hz, 1H, H-5), 7.86 (br s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) δ 16.3 (C-29), 16.5 (C-28), 18.3 (C-21), 19.9 (C-10), 21.6 (C-18), 30.5 (C-16), 31.1 (C-17), 32.1 (C-19), 32.9 (C-13), 33.9 (C-14), 39.7 (C-15), 42.5 (C-11), 42.8 (C-20), 107.7 (C-27), 111.0 (C-8), 116.7 (C-3), 118.7 (C-5), 119.0 (C-6), 121.5 (C-7), 121.7 (C-2), 128.0 (C-4), 135.9 (C-9), 149.5 (C-12); HRMS Calcd for $C_{23}H_{31}N$ (M^+) 321.2456, found 321.2457.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Usuari: san / Mostra: ge223co12
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Data: 10/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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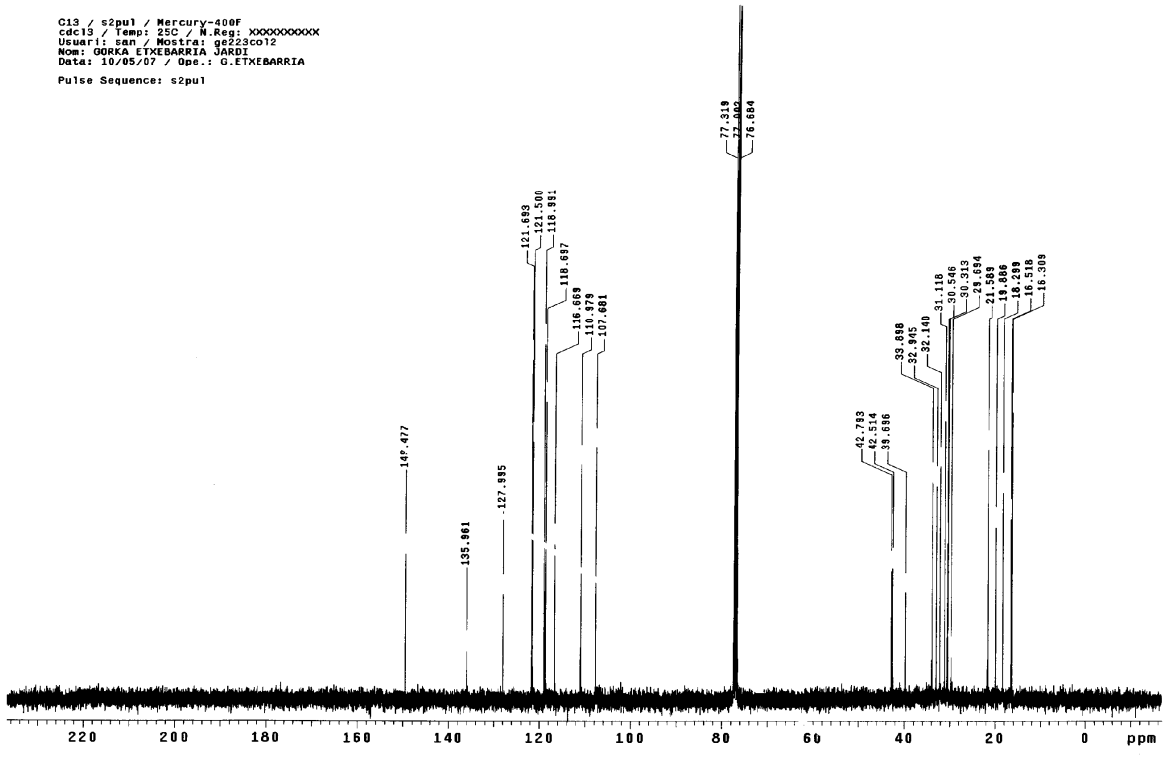
1.430
0.821
0.812
0.804
0.799
ppm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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge223co12
Nom: GORKA ETXEBARRIA JARDI
Data: 10/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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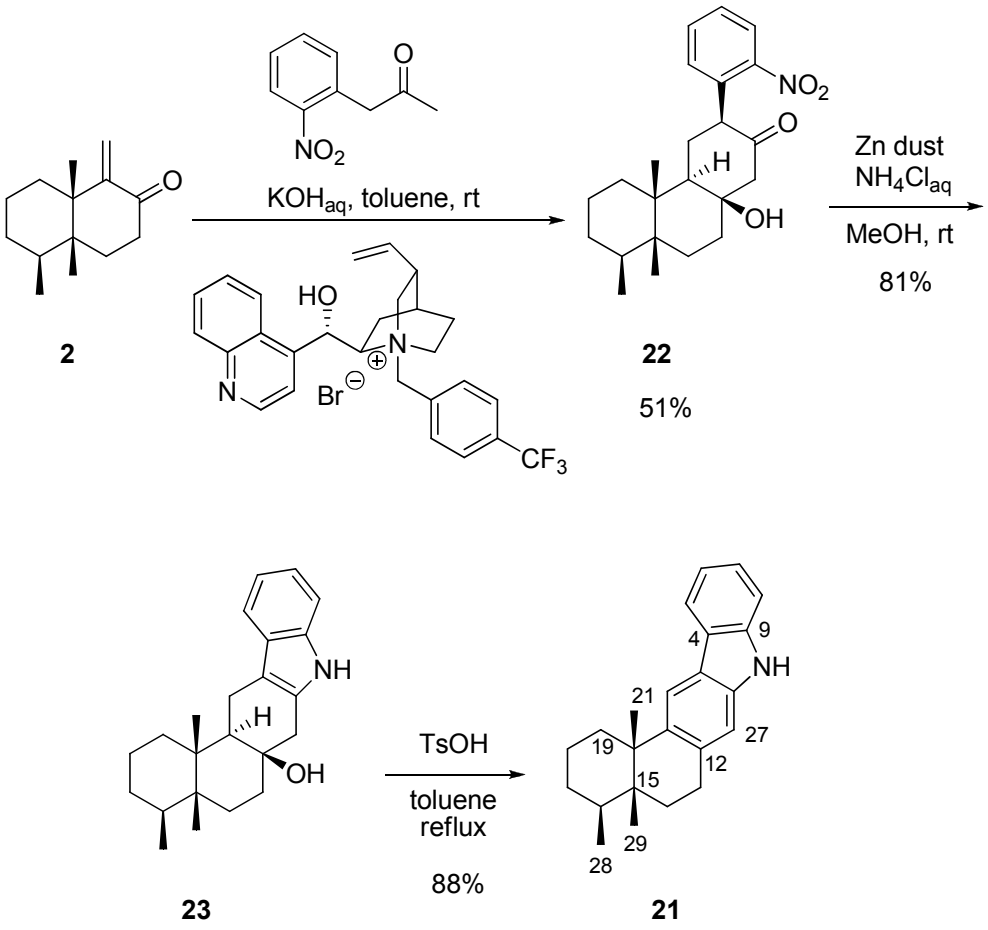
77.002
76.684
121.693
121.500
118.991
118.697
116.669
110.379
107.861
149.477
135.961
127.985
42.783
42.514
39.696
33.698
32.945
32.140
31.118
30.156
30.313
28.684
21.589
19.886
18.299
16.518
16.309
ppm



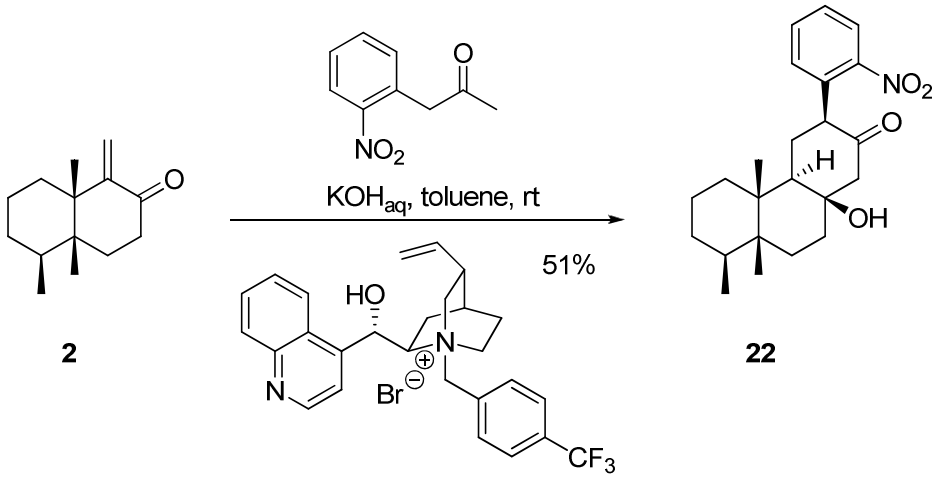
Scheme 6.2 Synthesis of Racemic Tubingensin A Polycyclic Framework.

Table 1. ^{13}C NMR Chemical Shifts of Compounds towards Tubingensin A Polycyclic Framework.[a]

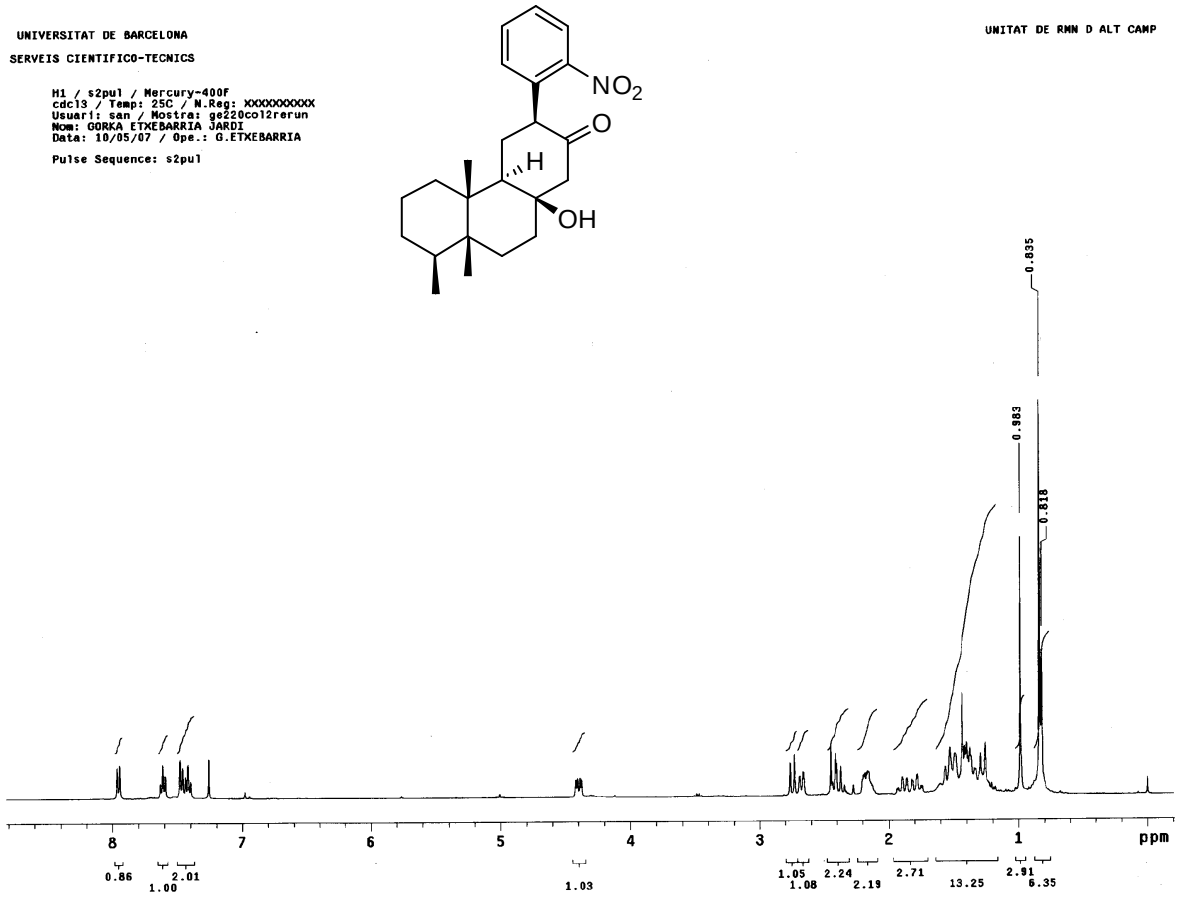
Prod	2	22	23	21	Tubingensin A[b]
C2	-	206.4	127.6	137.7	137.8
C3	-	52.8	108.9	122.4	121.3
C4	-	133.7	130.9	123.7	123.8
C5	-	132.9	117.9	119.9	119.8
C6	-	130.6	121.4	119.0	119.1
C7	-	127.7	119.3	125.2	125.3
C8	-	124.6	110.6	110.1	110.4
C9	-	149.5	136.4	140.0	140.0
C10	120.5	29.9	17.5	117.5	118.5
C11	152.4	41.4	38.1	135.0	132.4
C12	203.2	76.4	71.8	136.2	135.1
C13	35.3	35.0	33.9	26.6	27.1
C14	32.2	27.0	27.3	28.6	29.4
C15	38.3	39.1	39.1	37.8	38.8
C16	32.6	30.2	30.0	32.0	32.6
C17	30.4	30.7	30.6	29.7	25.4
C18	21.7	21.6	21.5	22.7	29.6
C19	28.9	33.1	32.6	33.6	71.3
C20	44.8	39.2	39.2	42.1	47.2
C21	27.2	20.6	20.0	30.7	34.9
C27	-	57.7	41.4	110.3	110.7
C28	15.7	16.0	15.9	16.3	16.2
C29	15.7	16.3	16.6	16.3	18.4

[a]Diterpene biogenetic numbering is used in this table. Assignments were aided by gCOSY and gHMQC spectra.
[b]Natural tubingensin A.

(3*RS*,4a*SR*,8*RS*,8a*SR*,10a*SR*)-10a-Hydroxy-4b,8,8a-trimethyl-3-(2-nitrophenyl)dodecahydro-1*H*-phenanthren-2-one (22)



To a solution of 1-(2-nitrophenyl)propan-2-one (93 mg, 0.52 mmol), *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (27 mg, 0.05 mmol) and 60% (w/v) KOH (0.25 mL) in toluene (2 mL) was added enone **2** (100 mg, 0.52 mmol) in toluene (3 mL) and the mixture was stirred at room temperature for 48 h. The mixture was partitioned between water and CH_2Cl_2, and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by column chromatography (20% EtOAc/hexane) gave **22** (94 mg, 51%) as a bright yellow solid: ^{1}H NMR (400 MHz, COSY) δ 0.83 (d, *J* = 6.4 Hz, 6H, Me-28, Me-29), 0.98 (s, 3H, Me-21), 1.20-1.40 (m, 5H, H-13$_{eq}$, H-14$_{eq}$, H-17, H-19), 1.45-1.60 (m, 4H, H-17, 2 H-18, H-19), 1.78 (td, *J* = 14.0, 4.0 Hz, 1H, H-13$_{ax}$), 1.90 (td, *J* = 14.0, 4.0 Hz, 1H, H-14$_{ax}$), 2.15 (m, 2H, H-10$_{eq}$, H-16), 2.39 (q, *J* = 12.5 Hz, 1H, H-10$_{ax}$), 2.43 (d, *J* = 14.0 Hz, 1H, H-27$_{eq}$), 2.68 (dd, *J* = 11.9, 2.4 Hz, 1H, H-11), 2.75 (d, 1H, H-27$_{ax}$), 4.40 (dd, *J* = 12.4, 5.3 Hz, 1H, H-3$_{ax}$), 7.42 (t, *J* = 7.7 Hz, 1H, H-7), 7.47 (d, *J* = 7.7 Hz, 1H, H-5), 7.61 (t, *J* = 7.7 Hz, 1H, H-6), 7.95 (d, *J* = 7.7 Hz, 1H, H-8); ^{13}C NMR (100 MHz, DEPT, HSQC) δ 16.0 (C-28), 16.3 (C-29), 20.5 (C-21), 21.6 (C-18), 27.0 (C-14), 29.9 (C-10), 30.2 (C-16), 30.7 (C-17), 33.1 (C-19), 35.0 (C-13), 39.1 (C-15), 39.2 (C-20), 41.4 (C-11), 52.8 (C-3), 57.7 (C-27), 76.4 (C-12), 124.6 (C-8), 127.7 (C-7), 130.6 (C-6), 132.9 (C-5), 133.6 (C-4), 149.5 (C-9), 206.4 (C-2); HRMS Calcd for $C_{23}H_{32}NO_4$ (MH^+) 386.2331, found 386.2330.


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
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Data: 10/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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O
H
OH
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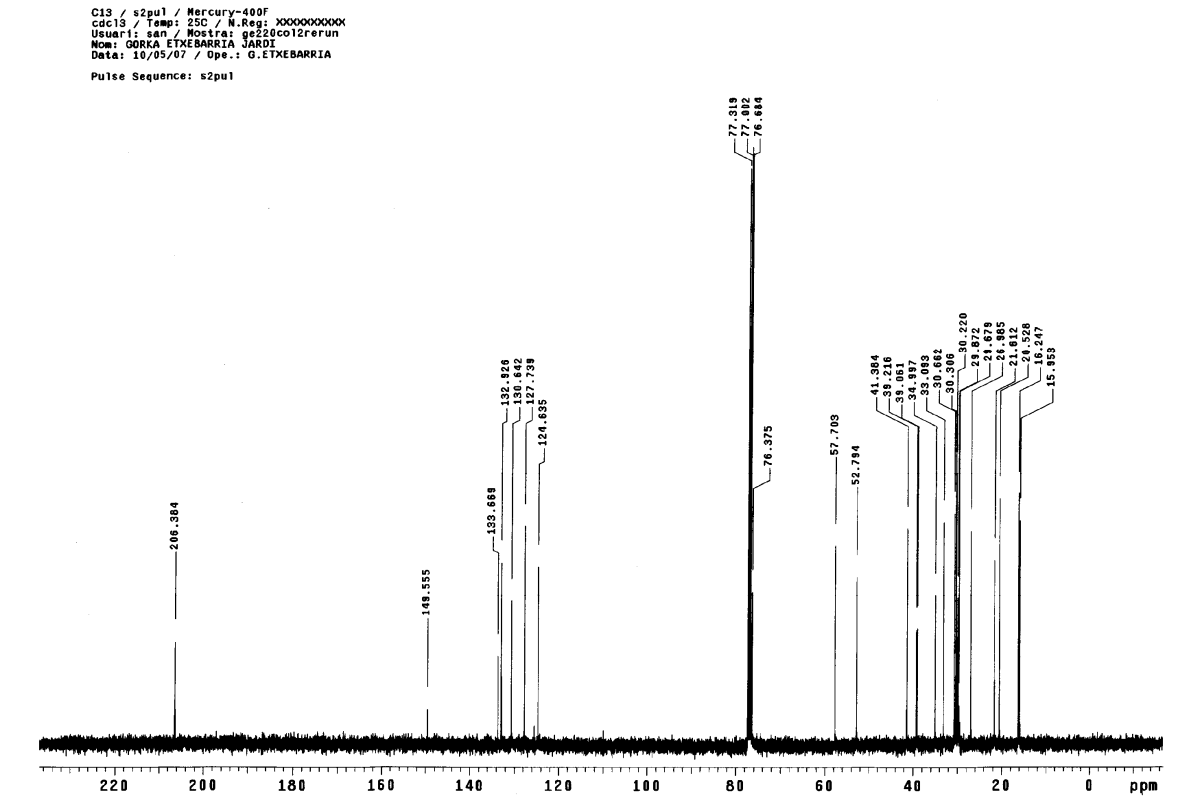
0.983
0.818
8
7
6
5
4
3
2
1
ppm
0.86
2.01
1.00
1.03
1.05
1.08
2.24
2.19
2.71
13.25
2.91
6.35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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge220col2rerun
Nom: GORKA ETXEBARRIA JARDI
Data: 10/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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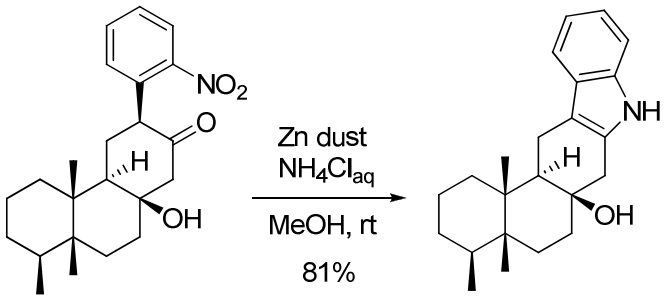
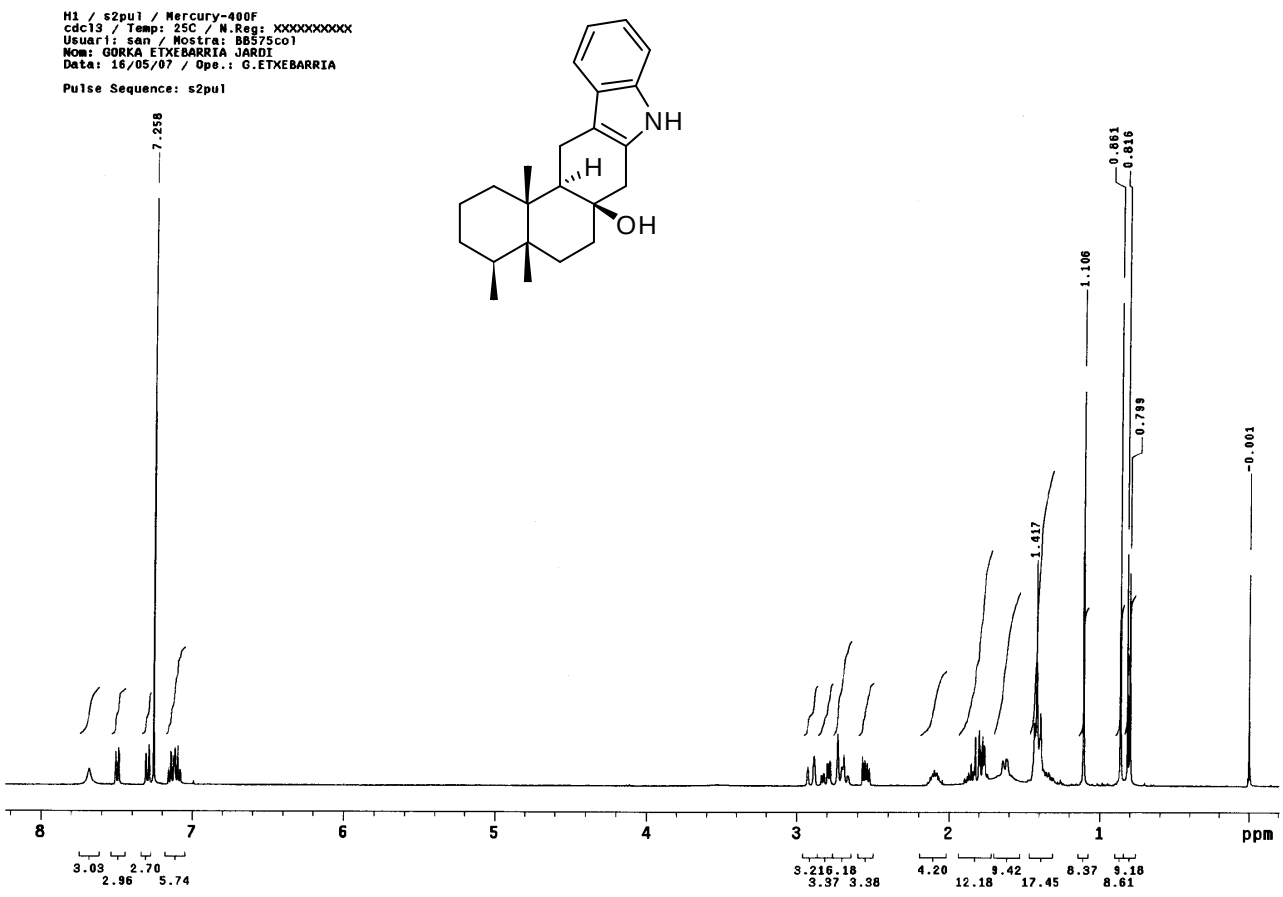
132.826
130.442
127.738
124.635
77.319
77.002
76.684
76.375
57.703
52.794
41.384
39.216
39.061
34.997
33.083
30.662
30.386
30.220
29.872
21.679
21.985
21.612
21.528
16.247
15.953
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(4*RS*,4a*RS*,6a*RS*,13a*RS*,13b*RS*)-4,4a,13b-Trimethyl-2,3,4,4a,5,6,6a,7,8,13,13a,13b-dodecahydro-1*H*-naptho[2,1-*b*]carbazol-6a-ol (23)



22 **23**

To a solution of **22** (27 mg, 0.07 mmol) in MeOH (2 mL) were added sequentially sat. aq. NH_4Cl (0.7 mL), Zn dust (460 mg, 7.0 mmol) and the mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, filtered through Celite and washed with EtOAc. The combined organic layers were washed with $NaHCO_3$, brine, dried and concentrated. Purification of the residue by chromatography (20% EtOAc/hexane) gave alkene **23** (19 mg, 81%) as a light yellow solid: ^{1}H NMR (400 MHz, COSY) δ 0.81 (d, *J* = 6.8 Hz, Me-28), 0.86 (s, 3H, Me-29), 1.11 (s, 3H, Me-21), 1.26-1.48 (m, 7H, 2 H-14, 2 H-17, 2 H-18, H-19$_{ax}$), 1.60 (dm, *J* = 12.0 Hz, 1H, H-19$_{eq}$), 1.72-1.92 (m, 2H, 2 H-13), 2.10 (m, 1H, H-16), 2.55 (dd, *J* = 12.0, 5.5 Hz, 1H, H-11$_{ax}$), 2.70 (dd, *J* = 14.5, 13.0 Hz, 1H, H-10$_{ax}$), 2..71 (d, *J* = 16.0 Hz, 1H, H-27), 2.81 (dd, *J* = 14.5, 6.0 Hz, 1H, H-10$_{eq}$), 2.91 (d, *J* = 16.0 Hz, 1H, H-27), 7.11 (ddd, *J* = 7.7, 7.5, 1.2 Hz, 1H, H-7), 7.13 (ddd, *J* = 7.7, 7.1, 1.3 Hz 1H, H-6), 7.30 (d, *J* = 7.5 Hz, 1H, H-8), 7.50 (d, *J* = 7.5 Hz, 1H, H-5), 7.68 (s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) δ 15.9 (C-28), 16.6 (C-29), 17.5 (C-10), 20.0 (C-21), 21.5 (C-18), 27.3 (C-14), 30.0 (C-16), 30.6 (C-17), 32.6 (C-19), 33.9 (C-13), 38.1 (C-11), 39.1 (C-15), 39.2 (C-20), 41.4 (C-27), 71.8 (C-12), 108.9 (C-3), 110.6 (C-8), 117.9 (C-5), 119.3 (C-7), 121.4 (C-6), 127.6 (C-2), 130.9 (C-4), 136.4 (C-9); HRMS Calcd for $C_{23}H_{31}NO$ (M^+) 337.2406, found 337.2408.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1.106
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0.816
0.799
0.001
1.417
8
7
6
5
4
3
2
1
ppm
3.03
2.70
2.96
5.74
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3.37
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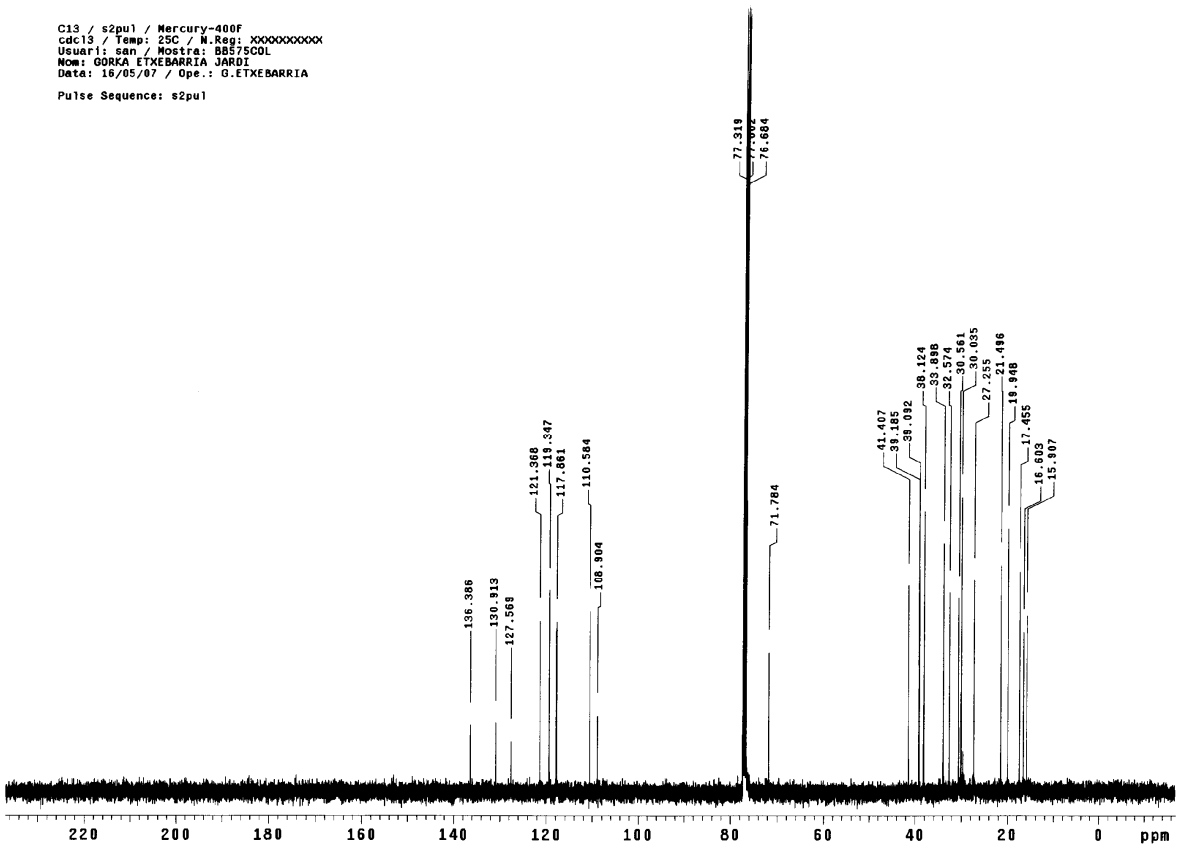
12.18
9.42
17.45
8.37
9.18
8.61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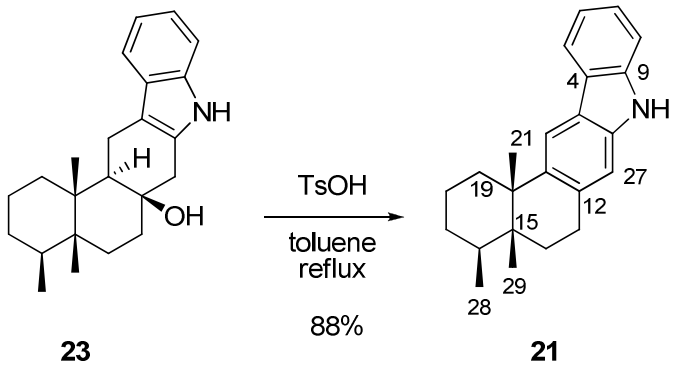
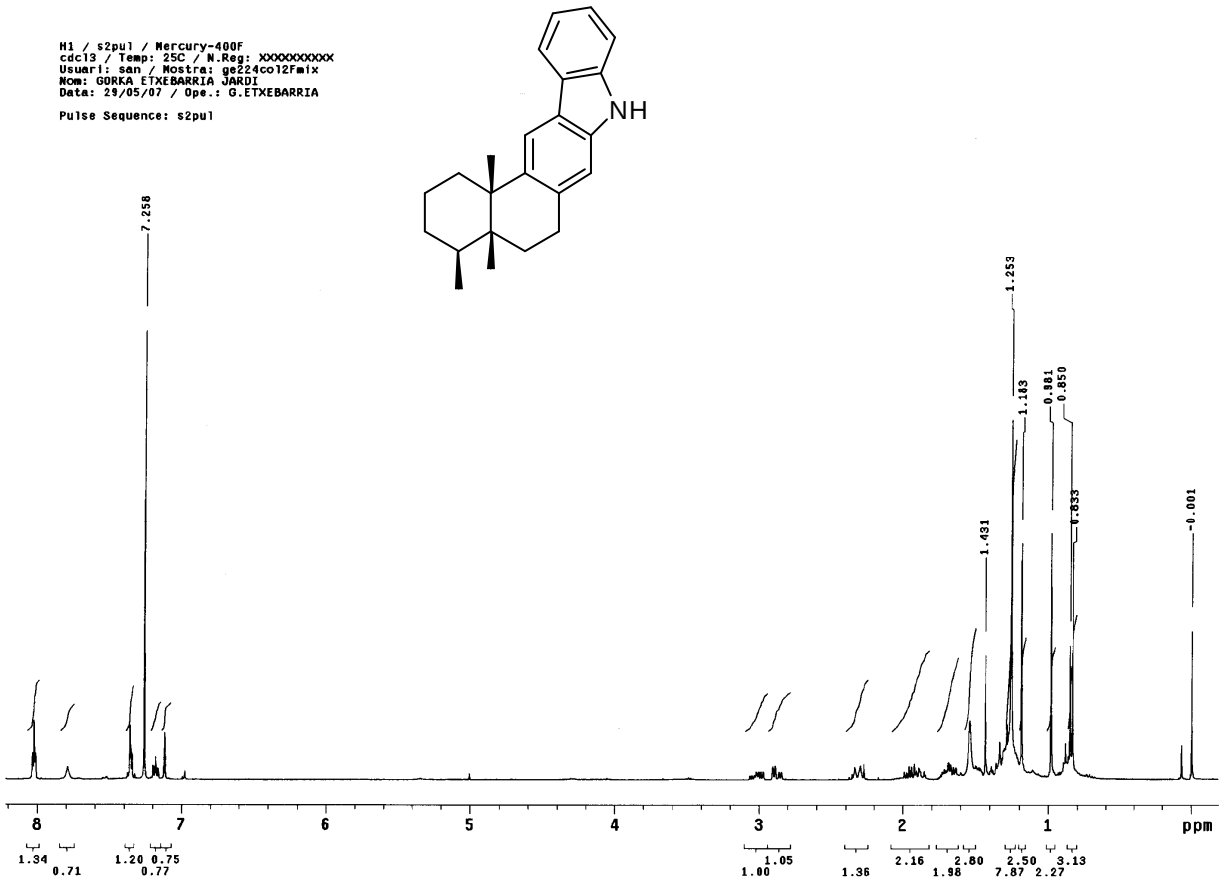
Usuari: san / Mostra: BB575COL
Nom: GORKA ETXEBARRIA JARDI
Data: 16/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
77.319
76.684
136.386
130.913
127.568
121.368
119.347
117.861
110.584
108.904
71.784
41.407
39.185
38.092
38.124
33.886
32.574
30.561
30.035
27.235
21.496
19.948
17.455
16.603
15.907
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(4*RS*,4a*SR*,13b*RS*)-4,4a,13b-Trimethyl-2,3,4,4a,5,6,8,13b-octahydro-1*H*-naptho[2,1-*b*]carbazole (21)



23 **21**

To a solution of **23** (12 mg, 0.04 mmol) in toluene (10 mL) was added *p*-toluenesulfonic acid (7 mg, 0.04 mmol) and the mixture was stirred at reflux for 3 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with sat. aq. $NaHCO_3$, H_2O, brine, dried and concentrated. Purification of the residue by column chromatography (5% EtOAc/hexane) gave carbazole **21** (10 mg, 88%) as a light yellow solid: ^{1}H NMR (400 MHz, COSY) δ 0.84 (d, *J* = 6.8 Hz, 3H, Me-28), 0.98 (s, 3H, Me-29), 1.18 (s, 3H, Me-21), 1.22-1.28 (m, 1H), 1.45-1.57 (m, 2H), 1.61-1.77 (m, 3H), 1.79-2.11 (m, 2H), 2.25 (m, 1H), 2.87 (dd, *J* = 17.5, 6.4 Hz, 1H, H-13$_{eq}$), 3.02 (ddd, *J* = 17.5, 13.0, 7.3 Hz, 1H, H-13$_{ax}$), 7.12 (s, 1H, H-27), 7.18 (ddd, *J* = 8.0, 5.7, 2.5 Hz, 1H, H-6), 7.35 (m, Hz, 2H, H-7, H-8), 7.79 (br s, 1H, NH), 8.02 (s, 1H, H-10), 8.02 (d, *J* = 7.6 Hz, 1H, H-5); ^{13}C NMR (100 MHz, DEPT, HSQC) δ 16.3 (C-28 and C-29), 22.7 (C-18), 26.6 (C-13), 28.6 (C-14), 29.7 (C-17), 30.9 (C-21), 32.1 (C-16), 33.6 (C-19), 37.8 (C-15), 42.1 (C-20), 110.1 (C-8), 110.3 (C-27), 117.5 (C-10), 119.0 (C-6), 119.9 (C-5), 122.4 (C-3), 123.7 (C-4), 125.2 (C-7), 135.0 (C-11), 136.2 (C-12), 137.7 (C-2), 140.0 (C-9).


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge224col2fmix
Nom: GORKA ETXEBARRIA JARDI
Data: 29/05/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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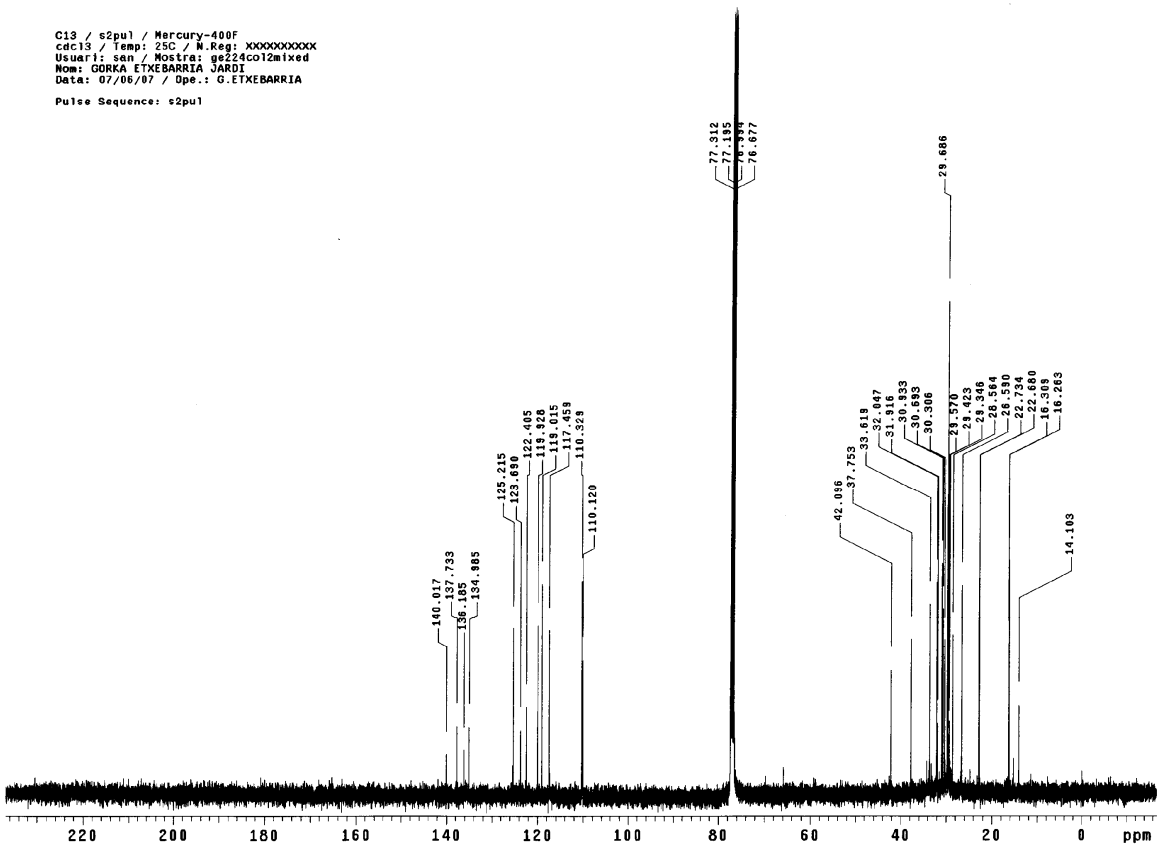
7.258
1.253
1.183
0.861
0.850
1.431
0.833
-0.001
8
7
6
5
4
3
2
1
ppm
1.34
0.71
1.20
0.75
0.77
1.05
1.00
1.36
2.16
2.80
1.98
2.50
7.87
3.13
2.27


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge224col2mixed
Nom: GORKA ETXEBARRIA JARDI
Data: 07/06/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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77.195
76.934
76.677
29.686
140.017
137.733
136.185
134.985
125.215
123.630
122.405
119.920
119.015
117.459
110.329
110.120
42.056
37.753
33.619
32.047
31.916
30.933
30.693
30.306
29.570
29.423
28.346
28.564
28.590
22.734
22.680
16.309
16.263
14.103
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Table 1. ^{13}C NMR Chemical Shifts of Compounds towards Anominine.[a]

Prod	35	36	62	91	92	93	94	95	98	99	102
C2	-	-	-	-	-	-	-	-	-	-	-
C3	-	-	-	-	-	-	-	-	-	-	-
C4	-	-	-	-	-	-	-	-	-	-	-
C5	-	-	-	-	-	-	-	-	-	-	-
C6	-	-	-	-	-	-	-	-	-	-	-
C7	-	-	-	-	-	-	-	-	-	-	-
C8	-	-	-	-	-	-	-	-	-	-	-
C9	-	-	-	-	-	-	-	-	-	-	-
C10	-	-	-	110.9	112.6	111.7	112.9	112.3	113.4	113.2	109.1
C11	209.7	209.1	211.5	147.8	148.8	149.3	148.4	150.9	151.6	151.5	149.1
C12	16.9	38.4	38.2	32.8	32.2	33.4	32.5	32.6	33.1	32.7	32.5
C13	16.9[b]	23.3	21.8	22.6	23.2	23.5	22.6	22.6	22.3	22.8	22.9
C14	38.9	31.9	34.0	35.8	35.4	34.8	31.7	31.5	31.7	31.2	30.5
C15	209.7[b]	164.9	45.4	45.1	41.1	46.2	44.6	38.6	41.2	39.1	39.1
C16	29.9	126.5	50.4	50.5	47.4	150.2	44.8	34.3	35.8	33.7	32.6
C17	207.5	198.2	213.1	213.2	200.7	188.3	202.4	69.2	72.7	48.6	134.3
C18	38.4	33.3	38.3	37.9	127.7	128.1	127.4	127.4	128.1	127.1	125.3
C19	27.9	26.2	28.3	30.0	153.0	155.4	150.8	133.5	133.1	131.9	67.4
C20	67.7	54.7	55.0	43.0	49.1	49.6	50.2	49.4	48.9	48.9	49.8
C21	40.1	39.9	39.1	38.7	35.5	37.9	35.6	36.1	38.7	36.1	32.7
C22	132.0	131.6	132.3	134.6	133.5	137.7	135.6	134.8	134.8	34.6	136.1
C23	119.5	119.5	118.5	116.7	118.3	118.4	118.2	117.0	116.9	117.1	116.5
C24	-	-	-	-	-	-	-	-	-	-	-
C25	-	-	-	-	-	-	-	-	-	-	-
C26	-	-	-	-	-	-	-	-	-	-	-
C27	-	-	-	-	-	-	-	-	-	-	-
C28	-	-	-	-	-	119.8	6.4	10.5	10.1	15.1	14.7
C29	-	-	23.0	23.1	23.1	21.0	17.0	18.4	16.8	18.8	18.3

[a]Diterpene biogenetic numbering is used in this table. Assignments were aided by gCOSY and gHMQC spectra

[b]These carbons have the same shift as C-11 and C-12 due to the fact that the molecule has C2-symmetry.

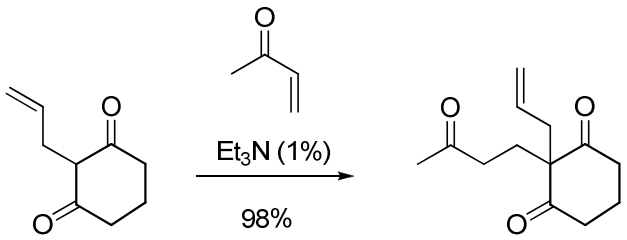
Table 1. ^{13}C NMR Chemical Shifts of Compounds towards Anominine.[a]

Prod	100	106	107	109	109a	116	120	122	123	(–)-61[b]	(+)-61[c]
C2	-	-	-	-	-	-	123.1	123.1	121.1	121.2	121.2
C3	-	-	-	-	-	-	116.4	116.1	117.3	117.1	117.1
C4	-	-	-	-	-	-	127.1	127.0	127.7	127.7	127.7
C5	-	-	-	-	-	-	118.4	118.3	118.6	118.6	118.5
C6	-	-	-	-	-	-	119.2	119.3	119.1	119.1	119.1
C7	-	-	-	-	-	-	121.7	121.8	121.8	121.8	121.8
C8	-	-	-	-	-	-	111.1	111.1	111.0	111.0	111.0
C9	-	-	-	-	-	-	135.9	136.0	135.9	135.9	136.0
C10	109.1	108.3	108.5	111.7	118.2	121.5	18.9	18.9	21.4	21.4	21.4
C11	149.1	149.8	149.9	149.8	150.1	150.2	55.2	55.1	45.5	45.8	45.9
C12	32.5	32.7	32.9	34.9	75.8	203.5	213.0	212.6	149.3	148.9	149.8
C13	22.9	23.1	23.0	23.0	25.5	35.5	38.6	38.7	33.7	33.5	33.5
C14	30.5	30.6	30.4	33.0	27.4	30.1	29.1	29.3	34.6	34.4	34.4
C15	39.1	39.2	39.4	40.7	40.5	39.6	40.7	40.4	41.0	40.8	40.9
C16	32.6	32.8	32.7	32.7	32.8	33.2	31.8	31.8	31.1	31.1	31.1
C17	134.3	133.0	133.1	26.5	26.0	26.0	27.4	25.2	25.6	25.4	25.4
C18	125.3	125.8	125.7	29.9	27.4	26.4	29.5	29.7	29.0	28.7	28.8
C19	67.4	67.6	67.3	70.0	70.0	69.6	71.9	71.3	70.7	70.0	70.0
C20	49.8	50.2	49.7	50.3	49.7	51.0	51.9	51.5	48.4	47.9	47.9
C21	32.7	32.2	23.5	24.5	29.6	29.1	34.2	34.3	29.5	29.2	29.2
C22	136.1	135.7	27.0	21.3	23.5	22.6	25.3	41.0	29.7	23.8	23.9
C23	116.5	115.5	64.0	65.6	65.6	65.0	64.4	201.8	140.5	125.8	125.8
C24	-	-	-	-	-	-	-	-	113.6	131.2	131.2
C25	-	-	-	-	-	-	-	-	-	17.8	17.8
C26	-	-	-	-	-	-	-	-	-	25.7	25.8
C27	-	-	-	-	-	-	-	-	106.9	107.7	107.7
C28	14.6	14.7	14.7	15.7	15.6	15.7	16.5	16.6	16.8	16.6	16.6
C29	17.6	17.7	17.5	17.4	17.4	17.2	18.0	18.0	18.5	18.7	18.7

[a]Diterpene biogenetic numbering is used in this table. Assignments were aided by gCOSY and gHMQC spectra.
[b]Synthetic anominine.
[c]Natural anominine.

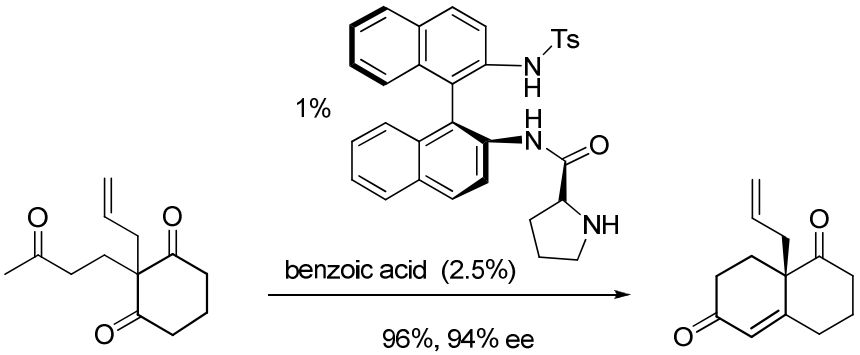
(*R*)-8a-Allyl-3,4,8,8a-tetrahydronaphthalene-1,6-(2*H*,7*H*)-dione (36)

Stepwise



34 **35**

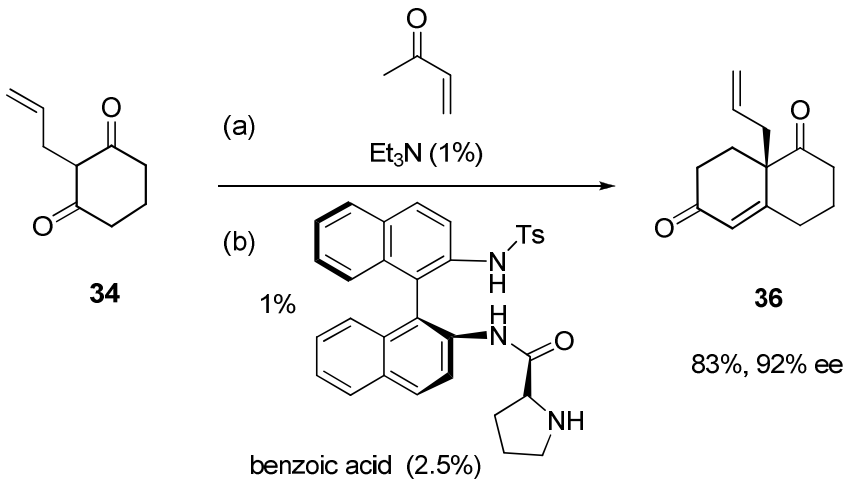
Part 1: To diketone **34** (11.28 g, 74.12 mmol) in a standard laboratory glass vial (10 × 3 cm, V = 50 mL) with stirrer bar was added methyl vinyl ketone (6.68 mL, 81.53 mmol) followed by Et_3N (103 mL, 0.74 mmol). The initial thick suspension slowly became more fluid as the solid gradually dissolved to give a yellow/orange solution. After 4 h the mixture was absorbed onto silica and purified by column chromatography (0→10→25% EtOAc/hexane) to give **35** (16.35 g, 98%) as a clear light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, IUPAC nomenclature is used): δ 1.97 (quint, *J* = 6.6 Hz, 2H, H-5), 2.04 (t, *J* = 7.2 Hz, 2H,CH_2-C2), 2.10 (s, 3H, CH_3), 2.33 (t, *J* = 7.2 Hz, 2H, CH_2CO), 2.49 (d, *J* = 7.6 Hz, 2H, CH_2 allyl), 2.54-2.70 (m, 4H, C-4 and C-6), 5.04 (m, 2H, =CH_2), 5.50-5.60 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9 (C-5), 27.9 (CH_2-C2), 29.9 (CH_3), 38.4 (CH_2), 38.9 (C-4 and C-6), 40.1 (CH_2 allyl), 67.7 (C-2), 119.5 (=CH_2), 132.0 (=CH), 207.5 (CO), 209.7 (C-1 and C-3). HRMS (ESI) Calcd for $C_{13}H_{19}O_3$ 223.1328 (MH^+), found 223.1321.



35 **36**

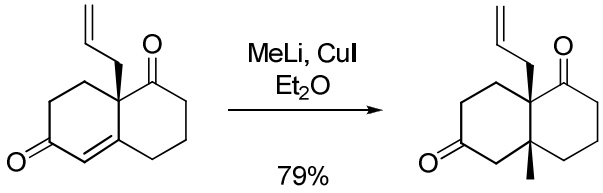
Part 2: In a standard laboratory glass vial (10 × 3 cm, V = 50 mL) with stirrer bar was added **35** (14.0 g, 63.0 mmol) followed by the binamprolinamide catalyst (337 mg, 0.63 mmol) and benzoic acid (193 mg, 1.58 mmol). The resulting mixture darkened (dark brown/black) and was stirred for 6 days. The mixture was absorbed onto silica and purified by column chromatography (0→5→10→25% EtOAc/hexane) to give the cyclised product **36** (12.37 g, 96%) as a clear yellow oil. $[\alpha]_D^{22}$: +86 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY, IUPAC nomenclature is used) δ 1.71 (qt, *J* = 13.2, 4.0 Hz, 1H, H-3$_{ax}$), 2.08 (dt, *J* = 14.0, 9.6 Hz, 1H, H-8$_{ax}$), 2.17 (dm, *J* = 13 Hz, H-3$_{eq}$), 2.23 (dt, *J* = 14.4, 4.6 Hz, 1H, H-8$_{eq}$), 2.42 (dd, *J* = 9.6, 4.6 Hz, 2H, H-7), 2.51 (dm, *J* = 14.4 Hz, 2H, H-2$_{eq}$, H-4$_{eq}$), 2.57 (d, *J* = 7.2 Hz, CH_2), 2.62-2.70 (m, 2H, H-2$_{ax}$ and CH_2), 2.78 (td, *J* = 14.0, 5.2 Hz, 1H, H-4$_{ax}$), 5.10 (d, *J* = 8.5 Hz, 1H, =CH_2), 5.14 (d, *J* = 16 Hz, 1H, =CH_2), 5.60 (m, 1H, =CH), 5.89 (s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 23.3 (C-3), 26.2 (C-8), 31.9 (C-4), 33.3(C-7), 38.4 (C-2), 39.9 (CH_2), 54.7 (C-8a), 119.5 (=CH_2), 126.5 (C-5), 131.6 (=CH), 164.9 (C-4a), 198.2 (C-6), 209.1 (C-1). HRMS (ESI) calcd for $C_{13}H_{17}O_2$ 205.1223 (MH^+), found 205.1219.

One-Pot Two-Step Robinson Annulation of 34 to 36



To dione **34** (500 mg, 3.28 mmol) in a standard glass vial with stirrer bar was added methyl vinyl ketone (0.297 mL, 3.62 mmol) followed by Et_3N (0.005 mL, 0.034 mmol). The initial thick suspension slowly became more fluid as the solid slowly dissolved to give a yellow/orange solution/oil. After 3 h the mixture was concentrated on a rotary evaporator and then kept under high vacuum with stirring for 3 h. Catalyst **G** (44 mg, 0.082 mmol) and benzoic acid (4 mg, 0.033 mmol) were added and the resulting mixture was stirred for 4 days. The mixture was absorbed onto silica gel and purified by column chromatography (gradient of hexane-EtOAc, 100:0 to 75:25) to give **36** (533mg, 83%, 92% ee) as a clear yellow oil.

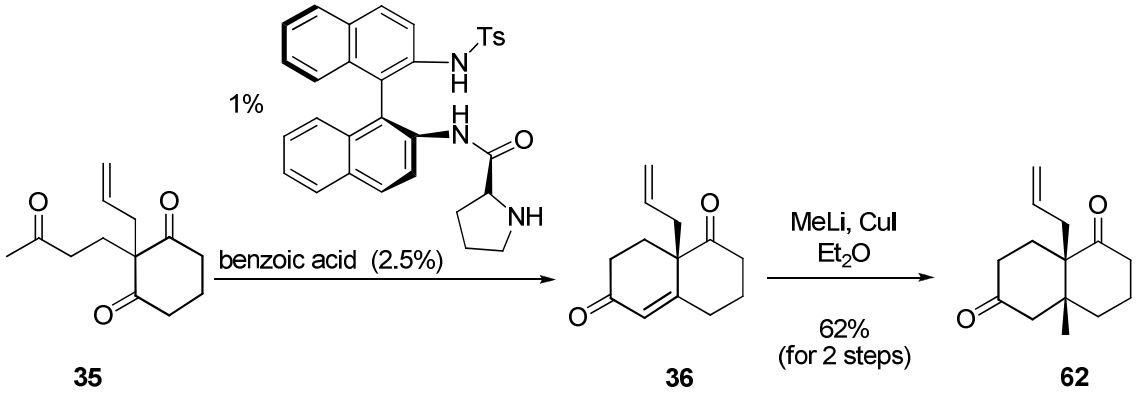
(4a*R*,8a*R*)-8a-Allyl-4a-methylhexahydronaphthalene-1,6-(2*H*,7*H*)-dione (62)



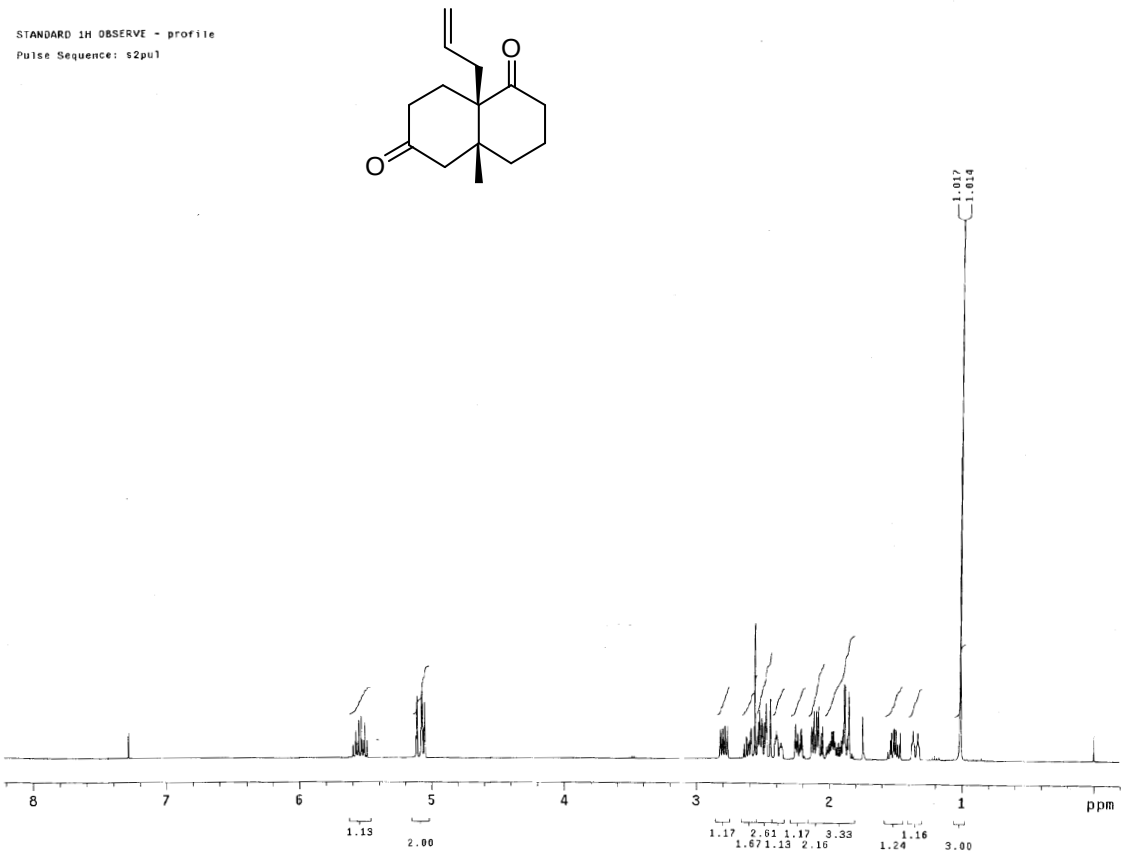
36 **62**

To a dispersion of copper iodide (23.4 g, 123.0 mmol) in anhydrous Et_2O (620 mL) at 0 °C was added MeLi (1.6 M in Et_2O, 128 mL, 205.0 mmol), and the mixture was stirred for 1 h. A solution of enone **36** (8.38 g, 41.0 mmol) in Et_2O (80 mL) was added dropwise, and the reaction was stirred at 0 °C for 30 min. The reaction was very carefully quenched with saturated aqueous NH_4Cl solution and then stirred for 2 h at rt. The aqueous layer was separated and extracted with EtOAc (3 × 200 mL), the combined organic layers were washed with NH_3/NH_4Cl, brine, dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography (0→5→10→25% EtOAc/hexane) gave diketone **62** (7.12 g, 79%) as a white solid. mp 58-62 °C; R_f 0.2 (25% EtOAc/hexanes); $[\alpha]_D$ –67 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 1.00 (s, 3H, H-29), 1.35 (dm, *J* = 14.4 Hz, 1H, H-14), 1.51 (m, 1H, H-19$_{ax}$), 1.87 (dd, *J* = 13.6, 2.4 Hz, 1H, H-16), 1.85-2.00 (m, 3H, 2H-13, H-14), 2.10 (m, 1H, H-21), 2.25 (dm, *J* = 14.5 Hz, H-18), 2.38 (dm, *J* = 14.0 Hz, H-12), 2.46 (d, *J* = 13.2 Hz, 1H, H-16), 2.48-2.53 (m, 2H, H-18, H-19), 2.62 (ddm, *J* = 14.5, 6.7 Hz, 1H, H-12), 2.79 (dd, *J* = 14.0, 7.2 Hz, 1H, H-21), 5.05 (m, 2H, 2H-23), 5.55 (m, 1H, H-22); ^{13}C NMR (100 MHz, HSQC) δ 21.8 (C-13), 23.0 (C-29), 28.3 (C-19), 34.0 (C-14), 38.2 (C-12), 38.3 (C-18), 39.1 (C-21), 45.4 (C-15), 50.4 (C-16), 55.0 (C-20), 118.5 (C-23), 132.3 (C-22), 211.5 (C-11), 213.1 (C-17); HRMS calcd for $C_{14}H_{20}O_2$ (MH^+) 221.1536, found 221.1534.

Consecutive Cyclisation and Conjugate Addition of 35 to 62



In a standard laboratory glass vial (10 × 3 cm, V = 50 mL) with stirrer bar was added **35** (15.0 g, 67.0 mmol) followed by the binamprolinamide catalyst (35 mg, 6.3 mmol) and benzoic acid (193 mg, 1.58 mmol). The resulting mixture darkened (dark brown/black) and was stirred for 6 days. The mixture was diluted with Et_2O (40 mL) $MgSO_4$ (15 g) was added and the resulting mixture was stirred for 30 min. The agitation was stopped and the supernatant was added via syringe to a solution of methylcuprate prepared according to the method above [MeLi (209 mL, 335 mmol), CuI (38.28 g, 201 mmol), Et_2O (700 mL)] to give **62** (9.1 g, 62%).


STANDARD 1H OBSERVE - profile
Pulse Sequence: s2pul
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O
1.017
1.014
8
7
6
5
4
3
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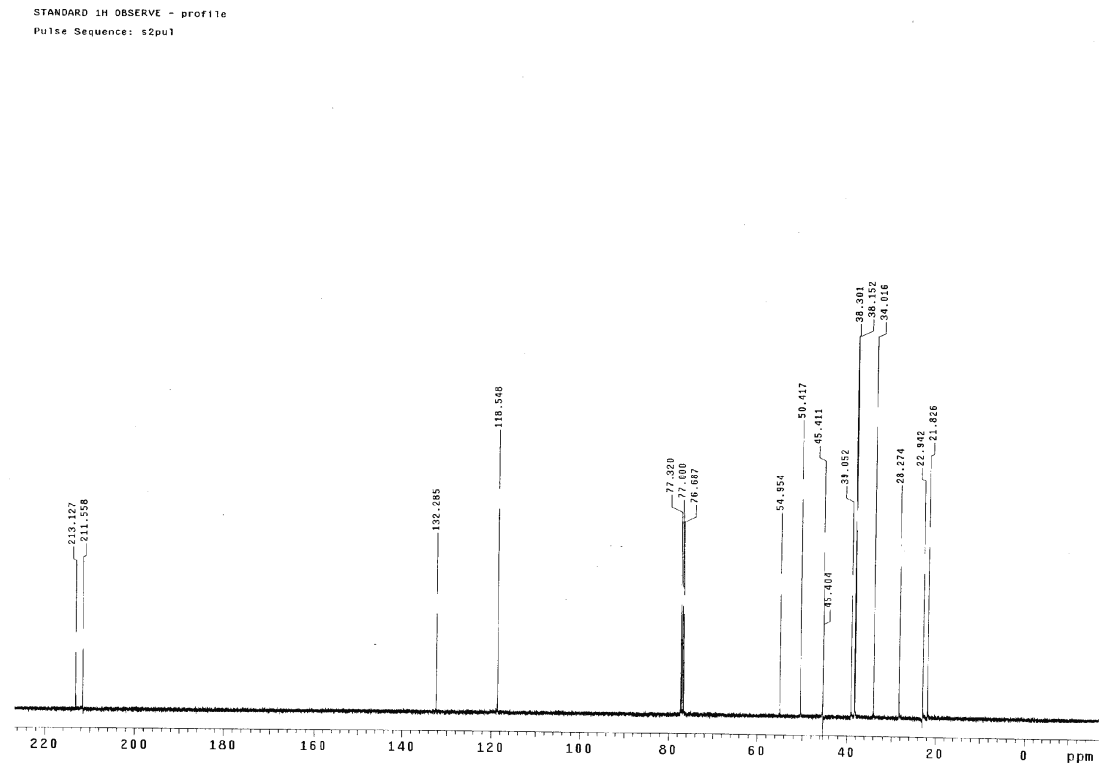
1.17
2.16
3.33
1.24
1.16
3.00


STANDARD 1H OBSERVE - profile
Pulse Sequence: s2pul
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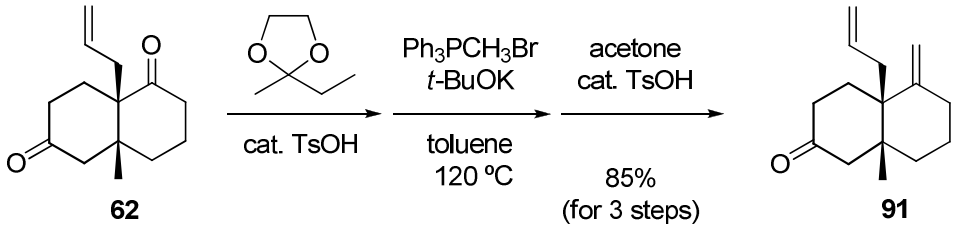
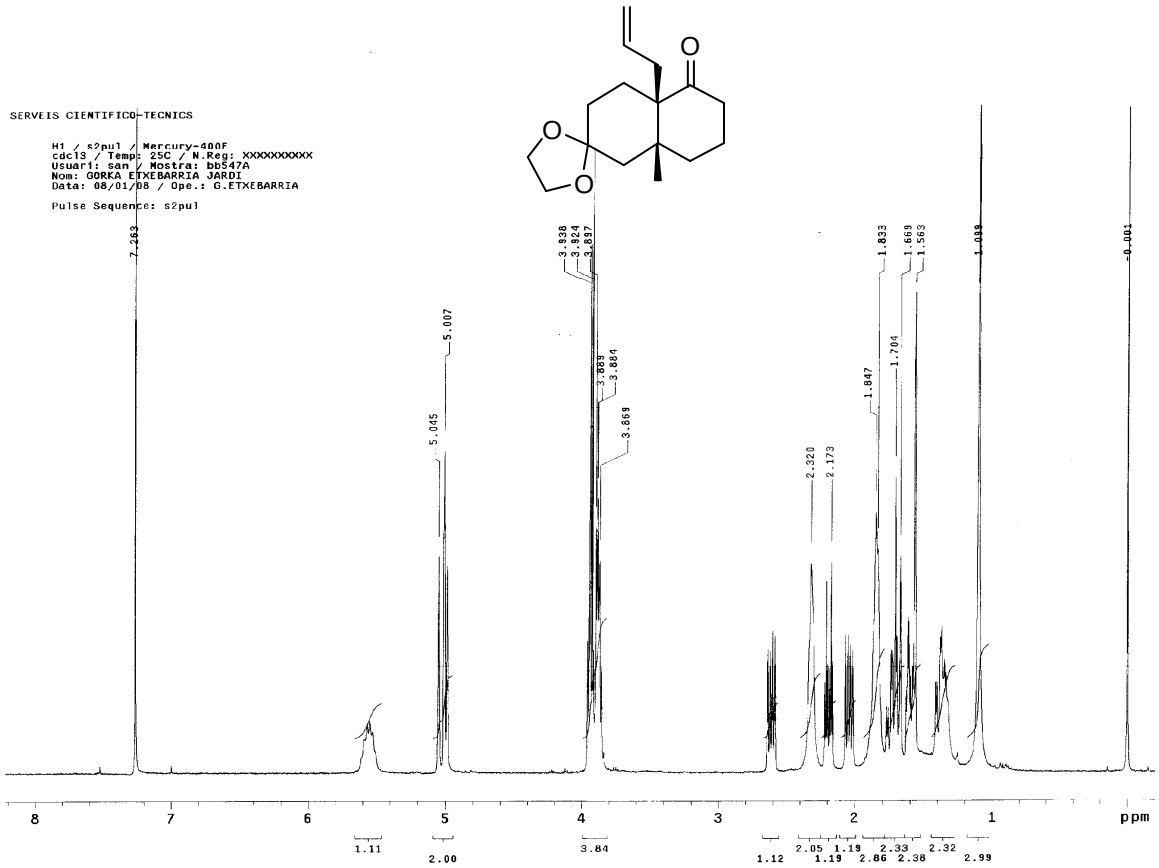
211.558
132.285
118.548
77.320
77.000
76.687
54.554
50.417
45.411
45.404
31.052
38.301
30.152
34.016
28.274
22.942
21.826
220
200
180
160
140
120
100
80
60
40
20
0
ppm

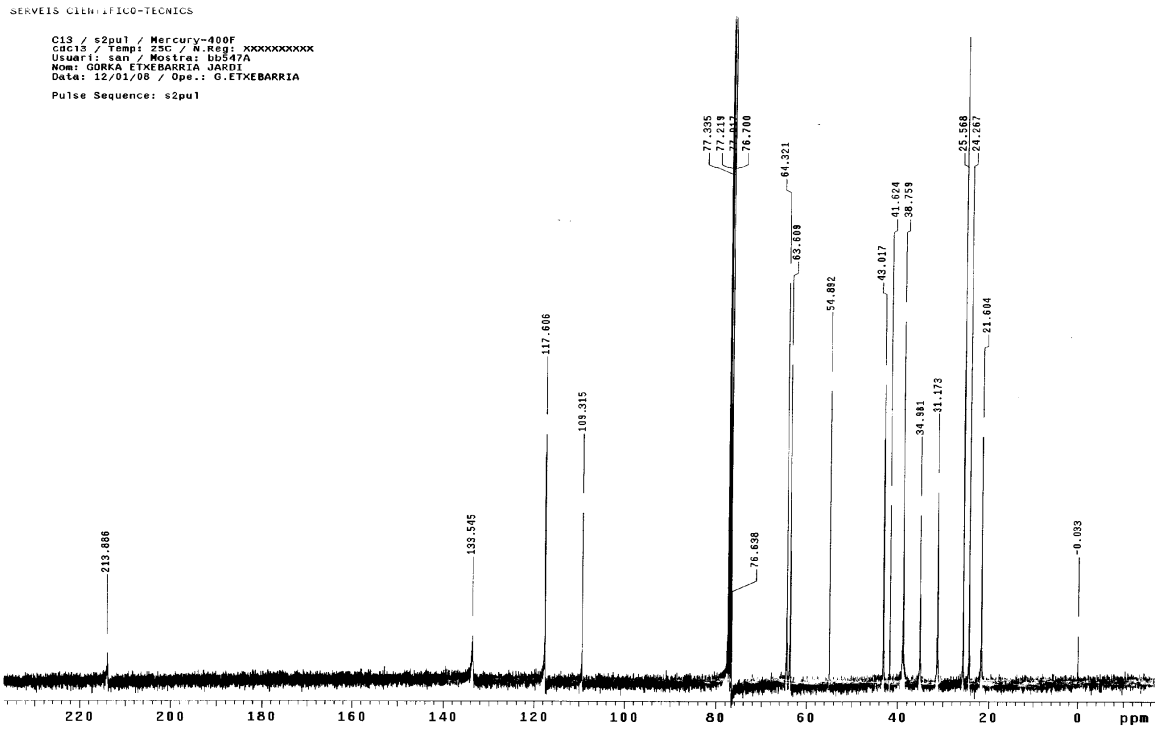
(4a*S*,8a*R*)-4a-Allyl-8a-methyl-5-methyleneoctahydronaphthalen-2-(1*H*)-one (91)

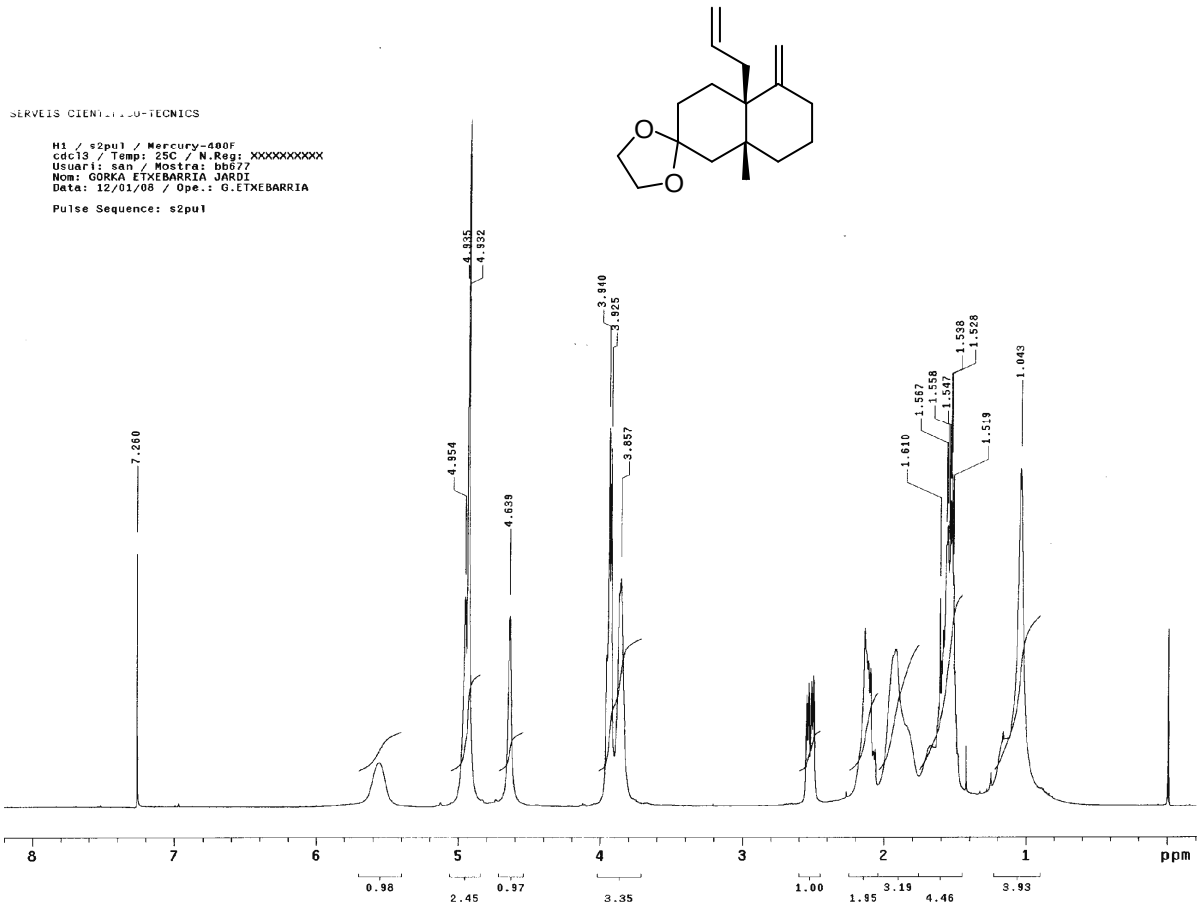


A solution of methyltriphenylphosphonium bromide (98.52 g, 0.28 mol) and potassium *tert*-butoxide (30.95 g, 0.28 mol) in toluene (700 mL) was stirred at reflux for 1 h. Concurrently, a solution of diketone **62** (15.19 g, 0.069 mol) and *p*-toluenesulfonic acid (656 mg, 3.45 mmol) in 2-ethyl-2-methyl-[1,3]-dioxolane (34.5 mL, 0.28 mol) was stirred at rt for 1 h. The 2-butanone formed was evaporated on a rotary evaporator and the resulting solution was stirred for a further 15 min before being added to the Wittig solution via syringe. The flask was rinsed with dry toluene (2 × 20 mL) and the resulting mixture was refluxed for 16 h, cooled and the quenched by the addition of acetone (30 mL) and then refluxed for a further 30 min. After cooling to rt the mixture was diluted with hexane (600 mL) and filtered through a pad of silica (12 × 6 cm deep). The pad was washed with 10% EtOAc/hexane until no more product was detected by TLC of the eluent. The combined washings were concentrated and then dissolved in acetone (700 mL). TsOH (656 mg, 3.45 mmol) was added and the resulting mixture stirred for 16 h. The mixture was quenched with $NaHCO_3$ (aq) (100 mL) and concentrated *in vacuo* to remove the acetone. The mixture was extracted with Et_2O (3 × 400 mL), the combined organic extracts dried and concentrated. Purification of the residue by column chromatography (0→1→2.5→5% EtOAc/hexane) gave ketoalkene **91** (12.78 g, 85%) as a white solid. mp 74-76 °C; R_f 0.4 (25% EtOAc/hexanes); $[\alpha]_D$ –82 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.93 (s, 3H, H-29), 1.19 (dm, *J*=14.5 Hz, 1H, H-14), 1.60-1.80 (m, 5H, H-16, H-14, H-19, 2H-13), 1.90 (m, 1H, H-21), 2.18-2.31 (m, 4H, H-19, 2H-12, H-18), 2.54 (td, *J*=14.0, 6.8 Hz, H-18$_{ax}$), 2.69 (dd, *J*=14.0, 6.0 Hz, 1H, H-21), 2.78 (dm, *J*=13.2 Hz, 1H, H-16), 4.82 and 4.98 (2s, 1H each, 2H-10), 5.04 (m, 2H, H-23), 5.60 (m, 1H, H-22); ^{13}C NMR (100 MHz, HSQC) δ 22.6 (C-13), 23.1 (C-29), 30.0 (C-19), 32.8 (C-12), 35.8 (C-14), 37.9 (C-18), 38.7 (C-21), 43.0 (C-20), 45.1 (C-15), 50.5 (C-16), 110.9 (C-10), 116.7 (C-23), 134.6 (C-22),

147.8 (C-11), 213.2 (C-17); HRMS calcd for $C_{15}H_{22}O$ (MH^+) 219.1743, found 219.1742.



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Usuari: san / Mostra: bb677
Nom: GORKA ETXEBARRIA JARDI
Data: 12/01/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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4.935
4.932
4.639
3.940
3.925
3.857
1.610
1.567
1.558
1.547
1.538
1.528
1.519
1.043
8
7
6
5
4
3
2
1
ppm
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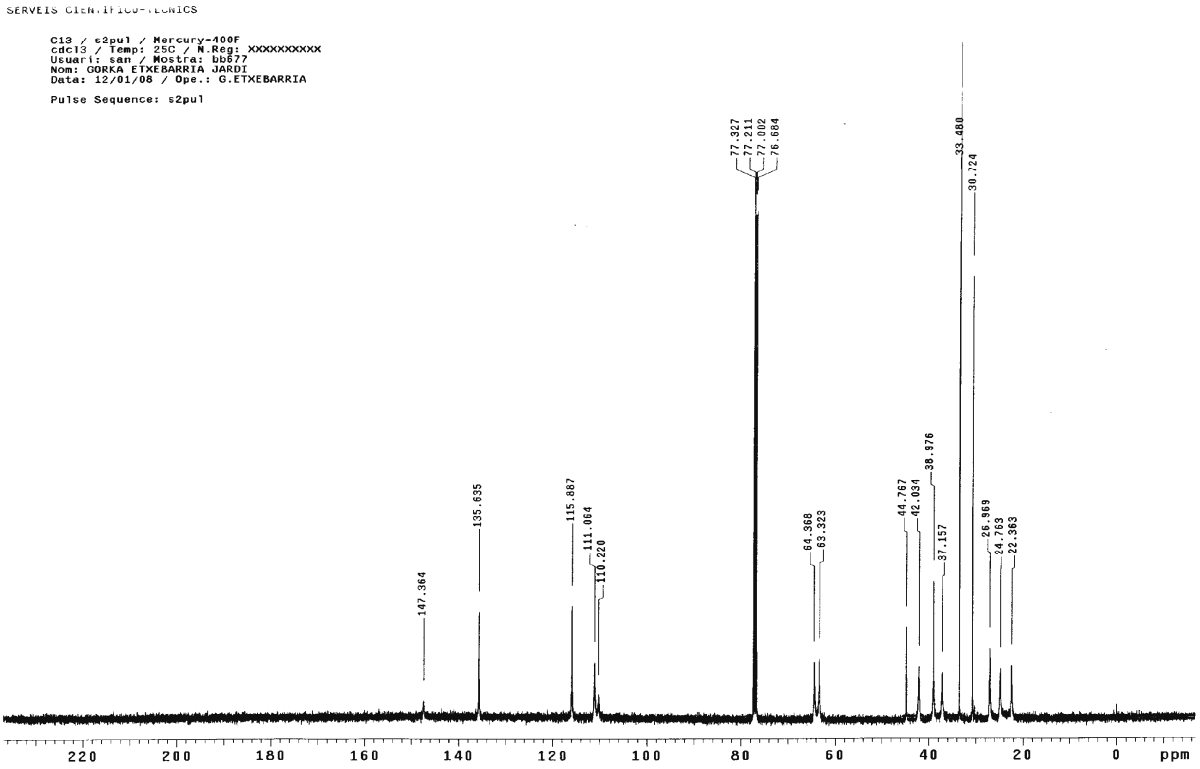
2.45
0.97
3.35
1.00
1.85
3.19
4.46
3.93


SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb677
Nom: GORKA ETXEBARRIA JARDI
Data: 12/01/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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115.887
111.064
110.220
77.327
77.211
77.002
76.684
64.368
63.323
44.767
42.034
38.876
37.157
33.480
30.124
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140
120
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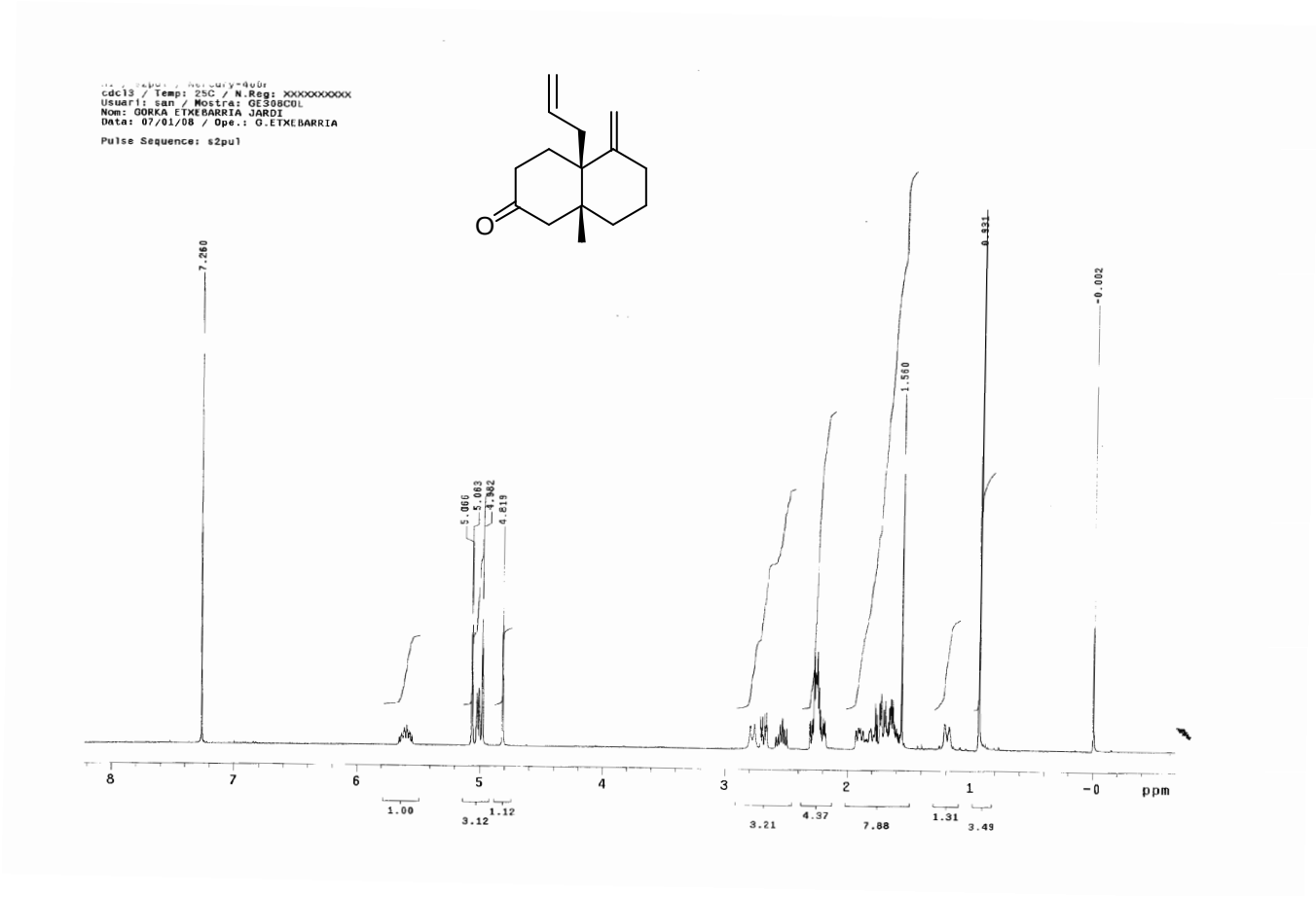
80
60
40
20
0
ppm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Data: 07/01/08 / Ope.: G.ETXEBARRIA
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8
7
6
5
4
3
2
1
-0
ppm
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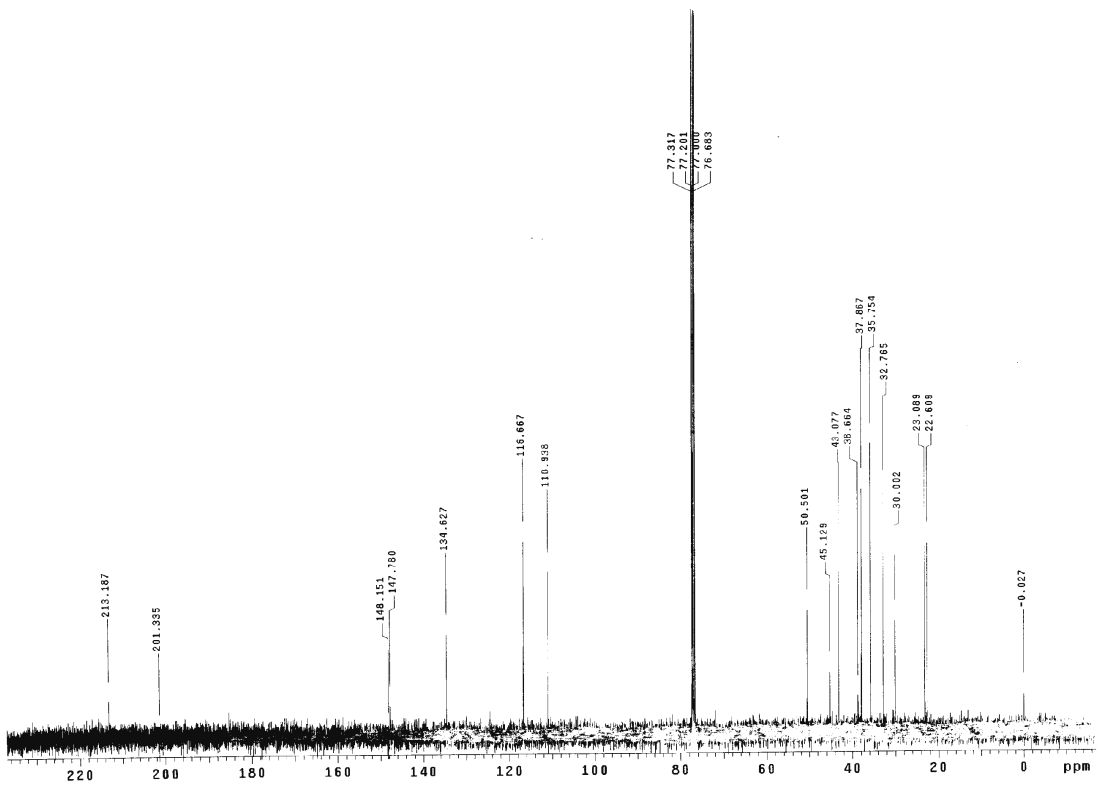
3.12
1.12
3.21
4.37
7.88
1.31
3.49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77.201
77.000
76.683
213.187
201.335
148.151
147.780
134.627
116.667
110.938
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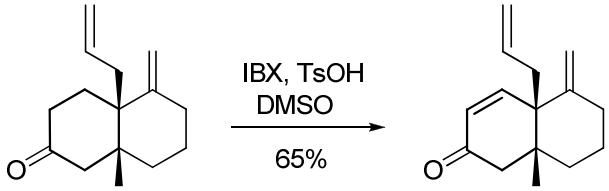
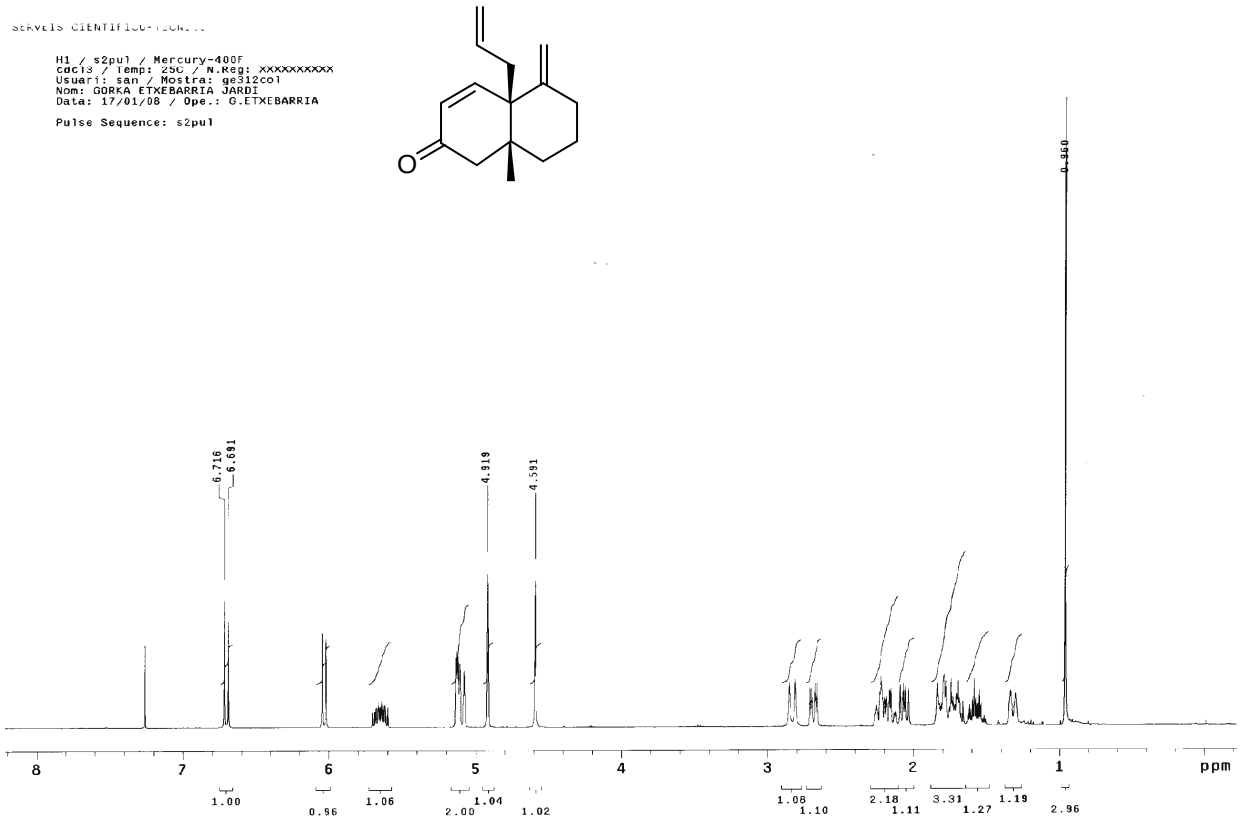
45.129
43.077
38.664
37.867
35.754
32.765
30.002
23.089
22.608
-0.027
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(4a*R*,8a*R*)-4a-Allyl-8a-methyl-5-methylene-4a,5,6,7,8,8a-hexahydronapthlalen-2(1*H*)-one (92)



91 **92**

To a solution of ketone **91** (3.61 g, 16.5 mmol) in DMSO (130 mL) was added IBX (11.58 g, 41.0 mmol) and TsOH (0.94 g, 4.55 mmol) and the mixture was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (100 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with EtOAc (5 × 50 mL), the combined organic layers were washed with saturated $NaHCO_3$, brine, dried and concentrated. Purification by chromatography (0→5% EtOAc in hexanes) gave **92** (2.31 g, 65%) as a colourless oil/foam: mp 72-74 °C; R_f 0.4 (25% EtOAc/hexanes); $[\alpha]_D$ –50 (*c* 0.9, $CHCl_3$); 1H NMR (400 MHz, COSY) δ 0.96 (s, 3H, H-29), 1.32 (dm, *J* = 14.4 Hz, 1H, H-14), 1.58 (qt, *J* = 12.8, 4.6Hz, 1H, H-13$_{ax}$), 1.70 (m, 1H, H-13$_{eq}$), 1.75 (m, 1H, H-14), 1.81 (d, *J* = 16 Hz, 1H, H-16), 2.10 (dd, *J* = 14.0, 9.2 Hz, 1H, H-21), 2.18 (td, *J* = 13.2, 4.4 Hz, H-12$_{ax}$), 2.23 (dm, *J* = 13.2 Hz, H-12$_{eq}$), 2.68 (dd, *J* = 14.0, 5.6 Hz, 1H, H-21), 2.83 (d, *J* = 16 Hz, 1H, H-16), 4.59 (s, 1H, H-10), 4.92 (s, 1H, H-10), 5.09 (m, 2H, H-23), 5.66 (m, 1H, H-22), 6.03 (dd, *J* = 6.0, 1.2 Hz, H-18), 6.70 (d, *J* = 6 Hz, 1H, H-19); ^{13}C NMR (100 MHz, HSQC) δ 23.1 (C-29), 23.2 (C-13), 32.2 (C-12), 35.4 (C-14), 35.5 (C-21), 41.1 (C-15), 47.4 (C-16), 49.1 (C-20), 112.6 (C-10), 118.3 (C-23), 127.7 (C-18), 133.5 (C-22), 148.8 (C-11), 153.0 (C-19), 200.7 (C-17); HRMS calcd for $C_{15}H_{20}O$ (MH^+) 217.1586, found 217.1585.


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge312col
Nom: GORKA ETXEBARRIA JARDI
Data: 17/01/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
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4.591
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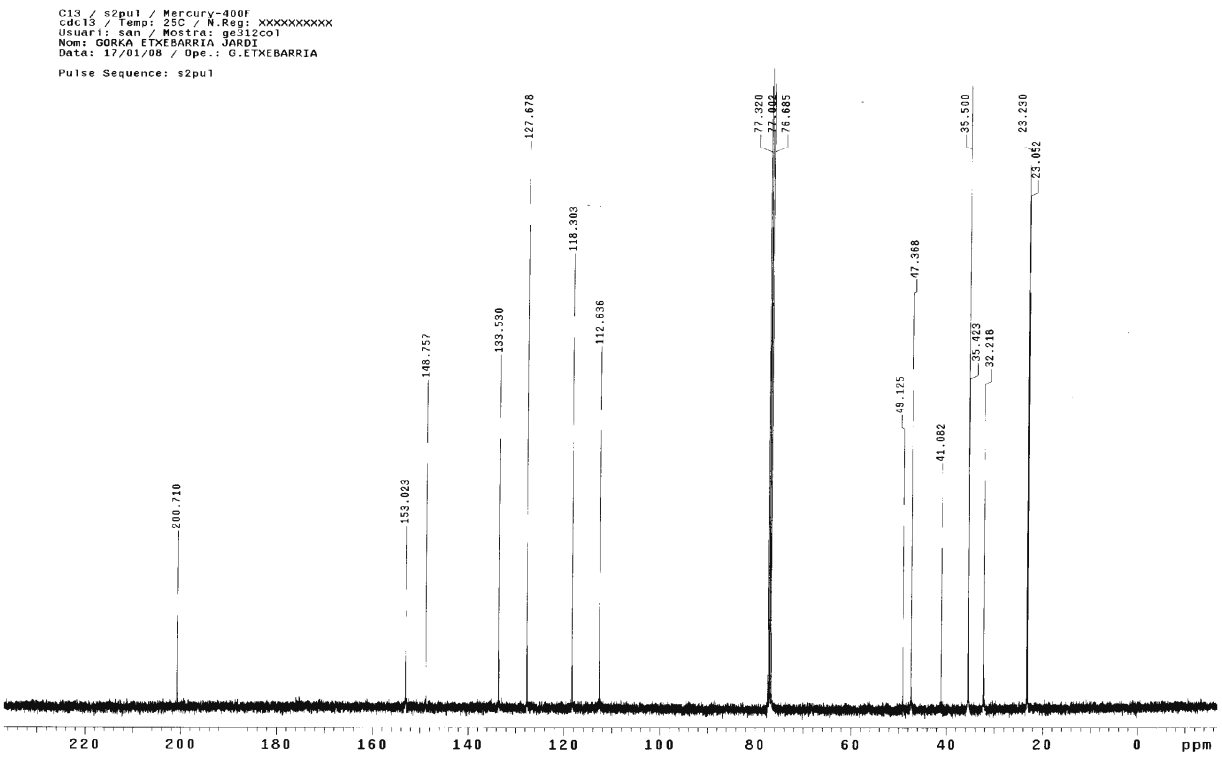
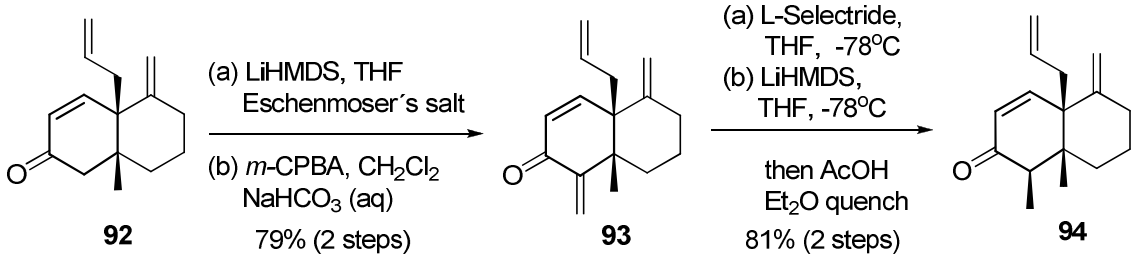
8
7
6
5
4
3
2
1
ppm
1.00
0.96
1.06
2.00
1.04
1.02
1.08
1.10
2.18
1.11
3.31
1.27
1.19
2.96

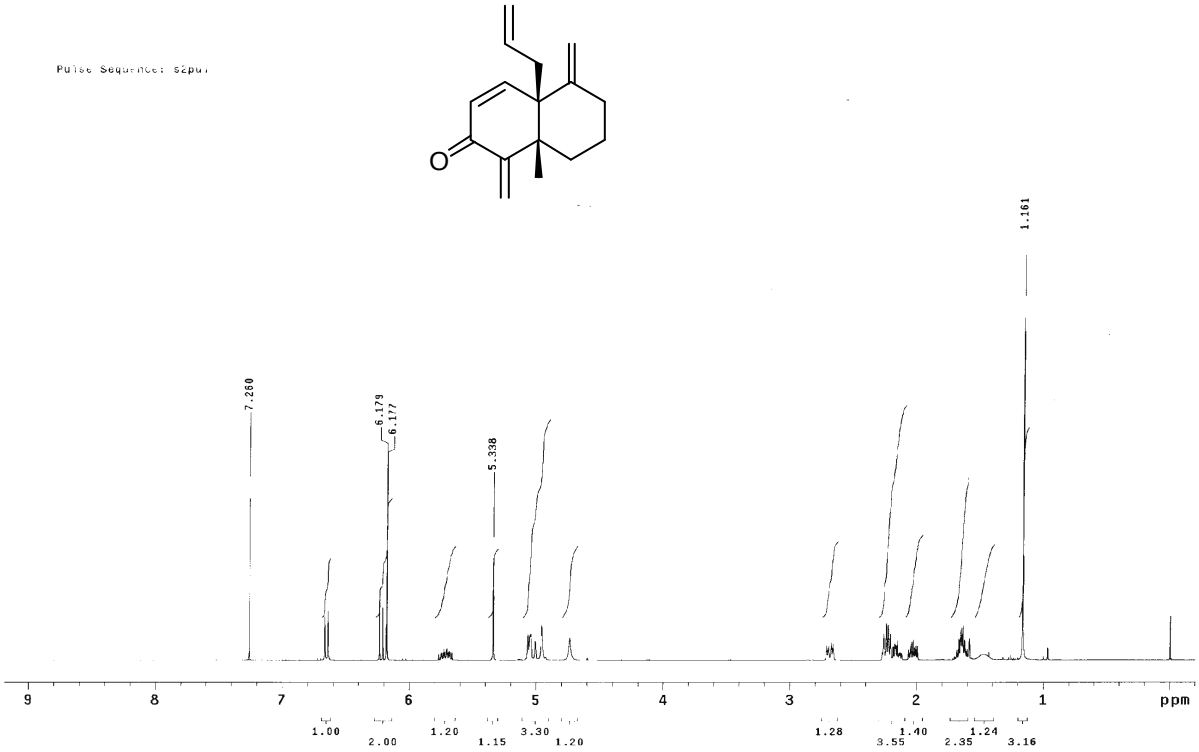

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge312col
Nom: GORKA ETXEBARRIA JARDI
Data: 17/01/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
200.710
153.023
148.757
133.530
127.678
118.303
112.636
77.320
77.002
76.685
69.125
47.368
41.082
35.423
35.500
32.218
23.230
23.052
220
200
180
160
140
120
100
80
60
40
20
0
ppm

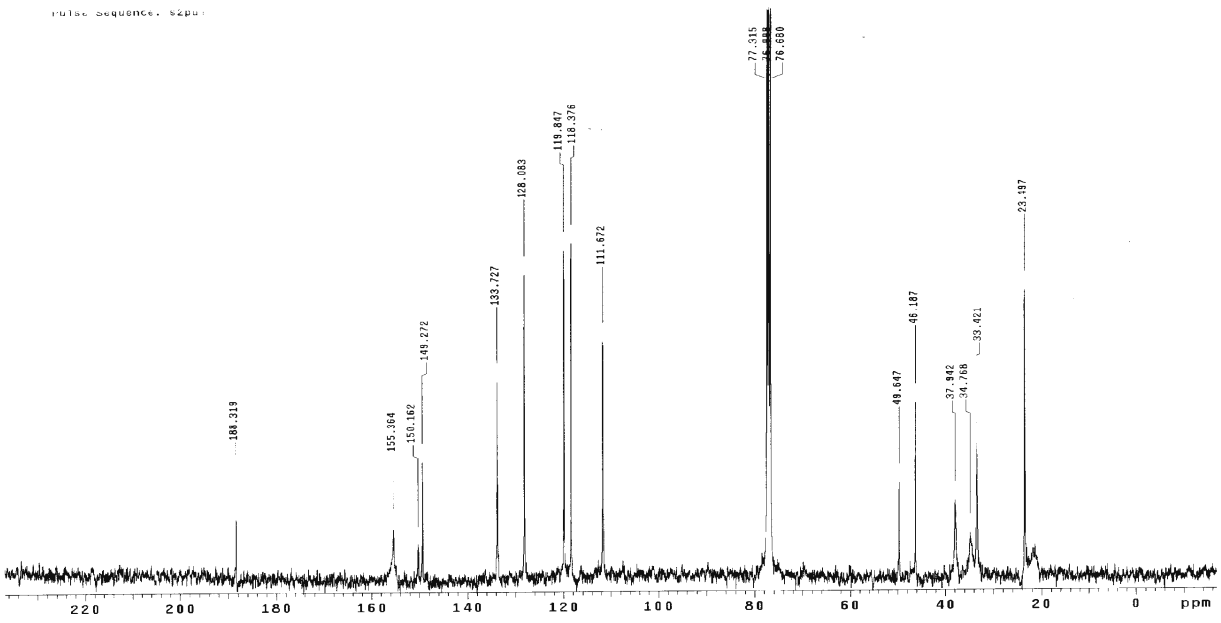
(1*R*,4a*R*,8a*R*)-4a-Allyl-1,8a-dimethyl-5-methylene-4a,5,6,7,8,8a-hexahydronapthlalen-2(1*H*)-one (94)



Enone **92** (4.67 g, 21.59 mmol) in THF (80 mL) was added dropwise to a cooled (–78 °C) solution of LiHMDS (1 M in THF, 43.2 mL, 43.18 mmol) in THF (50 mL). The resulting solution was stirred for 5 min at –78 °C, warmed to 0 °C, stirred for 1 h, recooled to –78 °C then transferred via cannula over 15 min to a stirred suspension of freshly opened Eschenmoser's salt (11.98 g, 64.77 mmol,) in 120 mL of THF at –78 °C. The resulting mixture was stirred for 30 min at –78 °C, then for 30 min in a room temperature water bath, and then transferred to a separatory funnel with Et_2O (500 mL) and saturated $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with 2 × 500 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to give a yellow/orange oil. The crude material was dissolved in CH_2Cl_2 (280 mL) and sat. aq. $NaHCO_3$ (140 mL). *m*-CPBA (9.68 g, 43.18 mmol) was added under vigorous stirring. After 10 min the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated *in vacuo* without heating. Purification by column chromatography (EtOAc in hexanes, 0→1→2.5% for **93** and then 5→10% for **92**) gave **93** (3.9 g, 79%) as a light yellow oil and **6** (300 mg, 7%) as an off-white solid. **Data for 93**: R_f 0.5 (25% EtOAc/hexanes); $[\alpha]_D$ –16 (*c* 0.8, $CHCl_3$); 1H NMR (400 MHz, COSY) δ 1.16 (s, 3H, H-29), 1.60 (m, 2H, H-13), 2.03 (m, 2H, H-12), 2.16 (m, 2H, H-14), 2.24 (m, 1H, H-21), 2.68 (dd, *J* = 14, 6 Hz, 1H, H-21), 4.73 (br s, 1H, H-10), 4.96 (br s, 1H, H-10), 5.00-5.06 (m, 2H, H-23), 5.34 (dd, *J* = 1.2, 0.8 Hz, 1H, H-28), 5.72 (m, 1H, H-22), 6.18 (d, *J* = 0.8 Hz, 1H, H-28), 6.22 (dd, *J* = 6.0, 0.8 Hz, 1H, H-18), 6.65 (d, *J* = 10 Hz, 1H, H-19); ^{13}C NMR (100 MHz, HSQC) δ 21.0 (C-29), 23.5 (C-13), 33.4 (C-12), 34.8^{br} (C-14), 37.9 (C-21), 46.2 (C-15), 49.6 (C-20), 111.7 (C-10), 118.4 (C-23), 119.8 (C-28); 128.1 (C-18), 137.7

(C-22); 149.3 (C-11), 150.2 (C-16), 155.4 (C-19), 188.3 (C-17); HRMS calcd for $C_{16}H_{21}O$ (MH^+) 229.1586, found 229.1582.

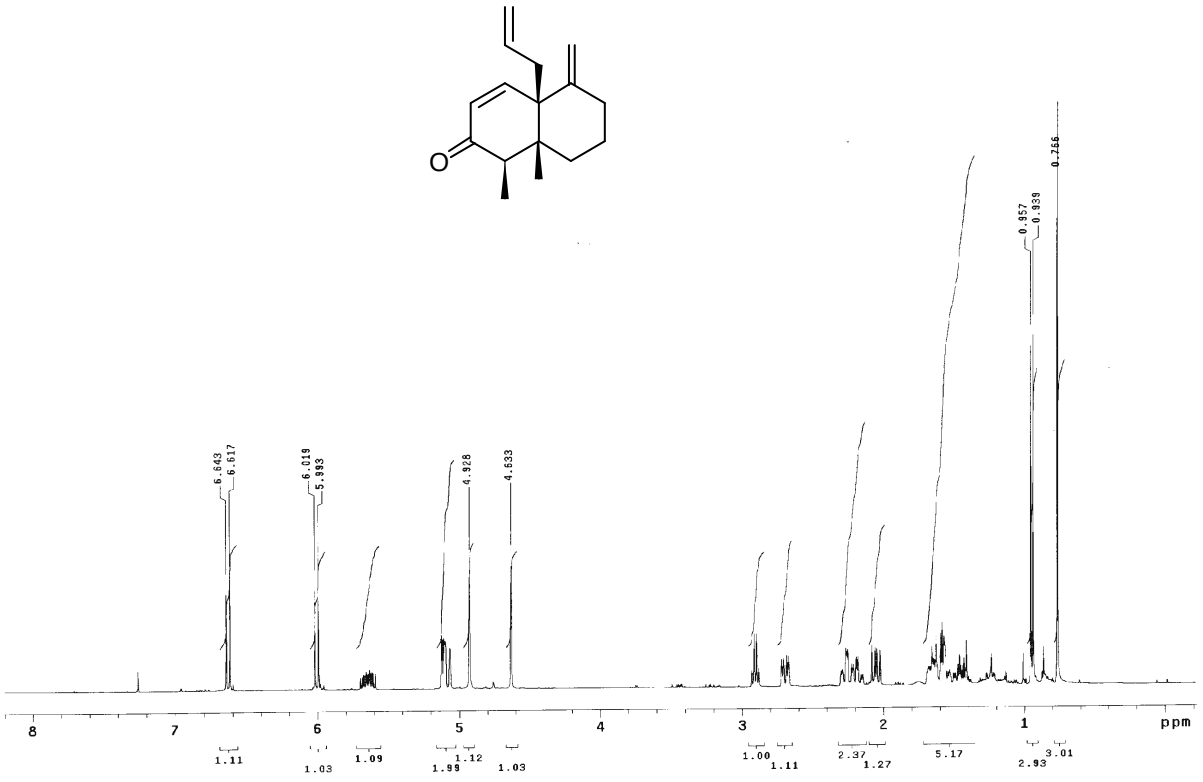




Conversion of 93 to 94

Part 1: To a solution of dienone **93** (3.48 g, 15.24 mmol) in THF (140 mL) at –78 °C was added L-Selectride (1 M in THF, 30.5 mL, 30.5 mmol). The resulting mixture was stirred for 1 h at –78 °C and then quenched by the sequential addition of 2M NaOH (60 mL) and H_2O_2 30 % wt sol (30 mL). The resulting mixture stirred for 2 h and extracted with Et_2O (3 × 200 mL), the combined organic layers were washed with sat. aq. $NaHCO_3$, brine, dried and concentrated. Purification by chromatography (0→1→2.5→5% EtOAc/hexane) gave the reduced enone (3.2 g, 91%) as a mixture of epimers.

Part 2: To a solution LiHMDS (1 M in THF, 30.4 mL, 30.4 mmol) in THF (100 mL) at –78 °C was added a solution of the reduced enone (2.8 g, 12.16 mmol) in THF (20 mL + 10 mL wash). The resulting mixture was stirred for 15 min at –78 °C, warmed to –15°C, stirred for 20 min and then recooled to –78 °C. AcOH (3.48 mL, 60.8 mmol) in Et_2O (~8 mL) was added and after 15 min water (10 mL) was added. The mixture was warmed to room temperature and sat. aq. $NaHCO_3$ (100 mL) was added. The aqueous layer was separated and extracted with Et_2O (3 × 100 mL), the combined organic layers were washed with sat. aq. $NaHCO_3$ solution, brine, dried and concentrated. Purification by chromatography (0→2.5→5% EtOAc/hexanes chromatography gave **94** (2.5 g, 89%) as a white solid. mp 54-58 °C; R_f 0.65 ((25% EtOAc/hexanes); $[\alpha]_D$ –57 (*c* 1.1, $CHCl_3$); 1H NMR (400 MHz, COSY) δ 0.77 (s, 3H, H-29), 0.95 (d, *J* = 7.2 Hz, 3H, H-28), 1.44 (dt, *J* = 12.4, 4.8 Hz, 1H, H-13$_{ax}$),1.53-1.69 (m, 3H, 2H-14, H-13$_{eq}$), 2.05 (dd, *J* = 14.0, 8.8 Hz, 1H, H-21), 2.18 (td, *J* = 13.2, 4.8 Hz, 1H, H-12$_{ax}$), 2.27 (dm, *J* = 13 Hz, H-12$_{eq}$), 2.69 (dd, *J* = 14.0, 5.4 Hz, 1H, H-21), 2.90 (q, *J* = 7.2, 1H, H-16), 4.63 (s, 1H, H-10), 4.93 (s, 1H, H-10), 5.10 (m, 2H, H-23), 5.64 (m, 1H, H-22), 6.01 (d, *J* = 10 Hz, 1H, H-18), 6.63 (d, *J* = 10 Hz, 1H, H-19); ^{13}C NMR (100 MHz, HSQC) δ 6.4 (C-28), 17.0 (C-29), 22.6 (C-13), 31.7 (C-14), 32.5 (C-12), 35.6 (C-21), 44.6 (C-15), 44.8 (C-16), 50.2 (C-20), 112.9 (C-10), 118.2 (C-23), 127.4 (C-18), 135.6 (C-22), 148.4 (C-11), 150.8 (C-19), 202.4 (C-17); HRMS calcd for $C_{16}H_{22}O$ (MH^+) 231.1743, found 231.1743.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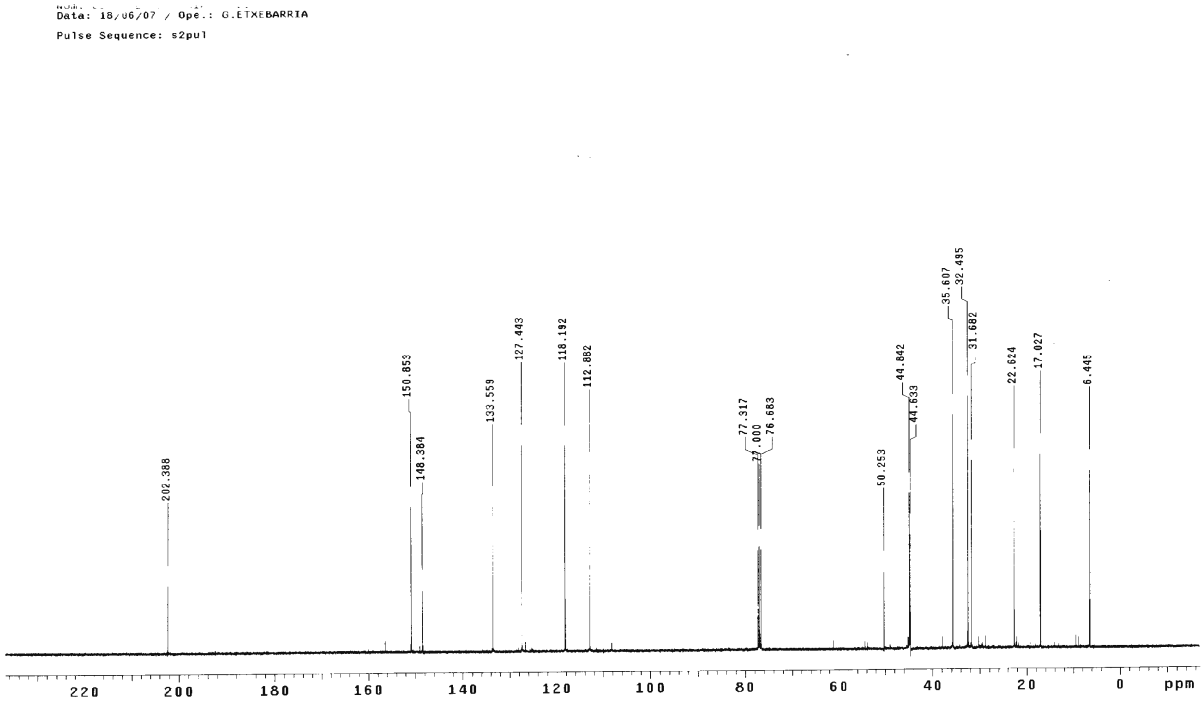
5.17
2.93
3.01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200
180
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140
120
100
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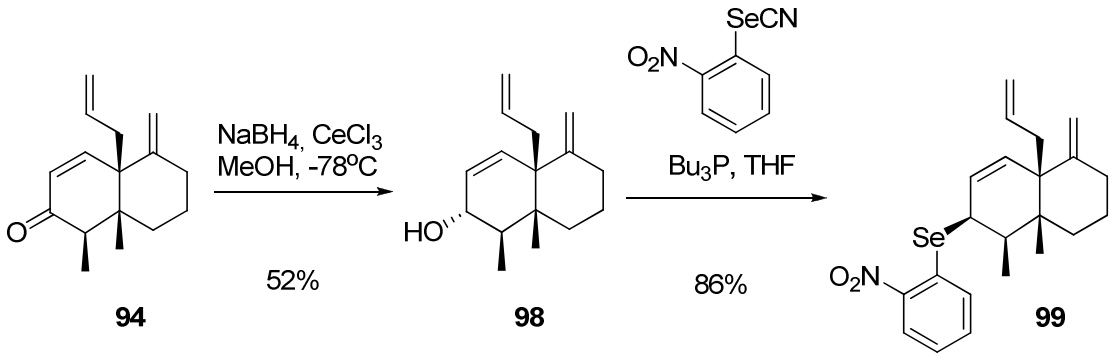
60
40
20
0
ppm

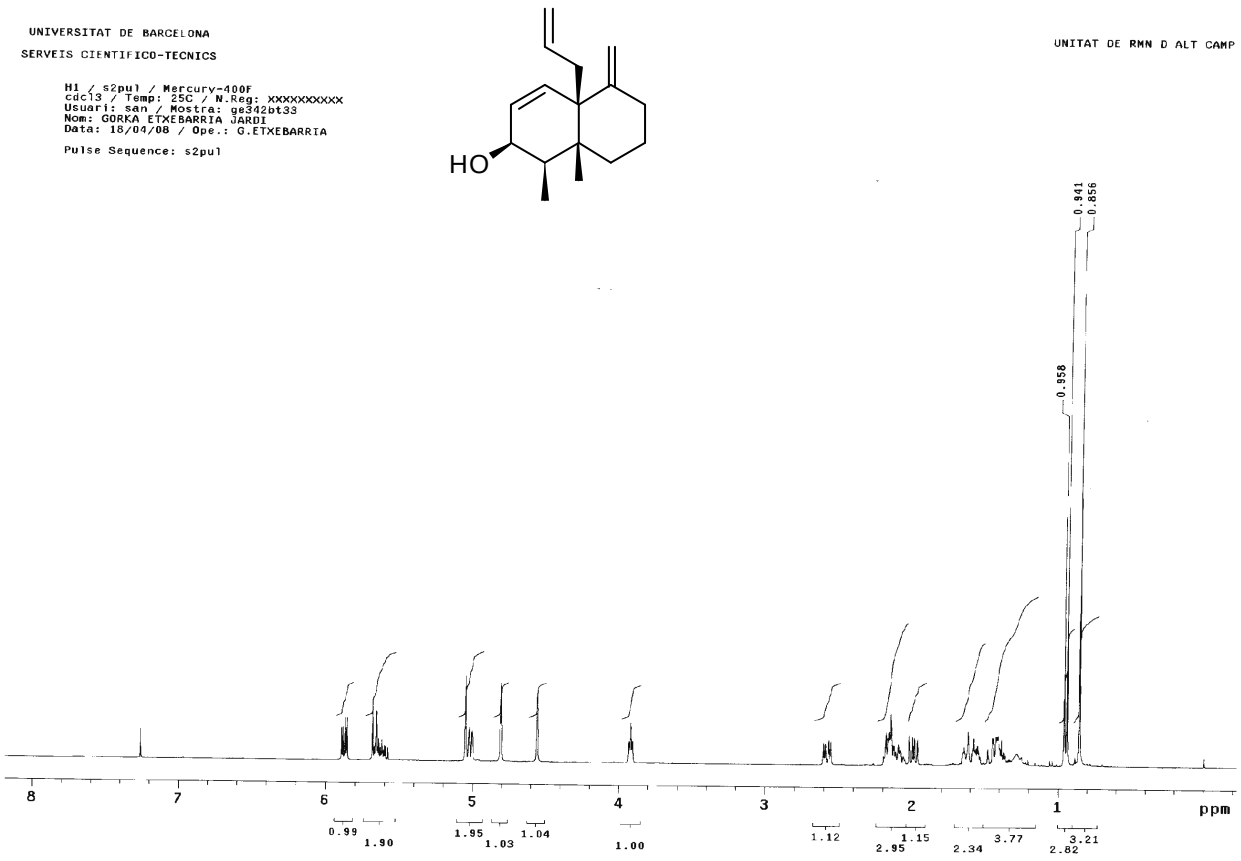
4a-Allyl-1,8a-dimethyl-5-methylene-2-(2-nitrophenylselanyl)-1,2,3,4,4a,5,6,8a-octahydronaphthalene (99)

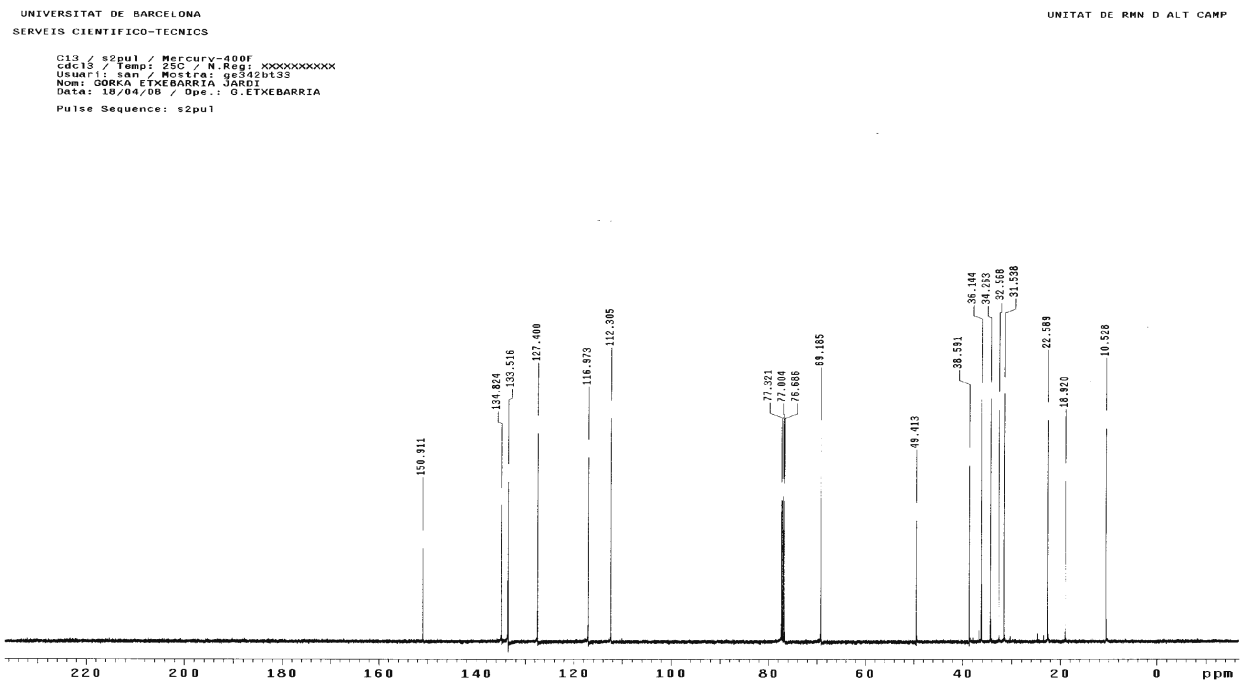


Part 1: To a solution of enone **94** (2.15 g, 9.33 mmol) and $CeCl_3 \cdot 7H_20$ (5.21 g, 14.00 mmol) in MeOH (233 mL) at –78 °C was added $NaBH_4$ (706 mg, 18.67 mmol) in one portion. The resulting mixture was stirred for 1 h at –78 °C and slowly warmed up to room temperature overnight. The reaction was quenched by addition of 15 mL of acetone and then 15 mL of H_2O. The solvent was evaporated *in vacuo* and the residue partitioned between Et_2O (200 mL) and H_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by Biotage® column chromatography (CH_2Cl_2 in hexanes, 0→10→20→30→40% for **95** and then 60% for **98**) gave **95**[3] (720 mg, 33%) as a white solid followed by **98** (1.13 g, 52%) as a white solid. **Data for 95**: mp 48-50 °C; R_f 0.25 (2 × 10% EtOAc/hexanes) $[\alpha]_D$ +19 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.86 (s, 3H , H-29), 0.96 (d, *J* = 7.2 Hz, 3H, H-28), 1.29 (br s, 1H, OH), 1.42 (m, 2H, H-13, H14$_{ax}$), 1.56 (m, 1H, H-13), 1.64 (dm, *J* = 12.0 Hz, 1H, H-21), 2.00 (dd, *J* = 13.6, 8.0 Hz, 1H, H-21), 2.14 (m, 3H, H-16, 2H-12), 2.58 (dd, *J* = 14.0, 6.0 Hz, 1H, H-21), 3.92 (t, *J* = 4.4 Hz, 1H, H-17), 4.56 and 4.82 (2s, 2H, 2H-10), 5.03 (m, 2H, 2H-23), 5.63 (m, 1H, H-22), 5.67 (d, *J* = 10 Hz, 1H, H-19), 5.88 (dd, *J* = 10.0, 3.6 Hz, 1H, H-18); ^{13}C NMR (100 MHz, HSQC) δ 10.5 (C-28), 18.9 (C-29), 22.6 (C-13), 31.5 (C-14), 32.6 (C-12), 34.3 (C-16), 36.1 (C-21), 38.6 (C-15), 49.4 (C-20), 69.2 (C-17), 112.3 (C-10), 117.0 (C-23), 127.4 (C-18),

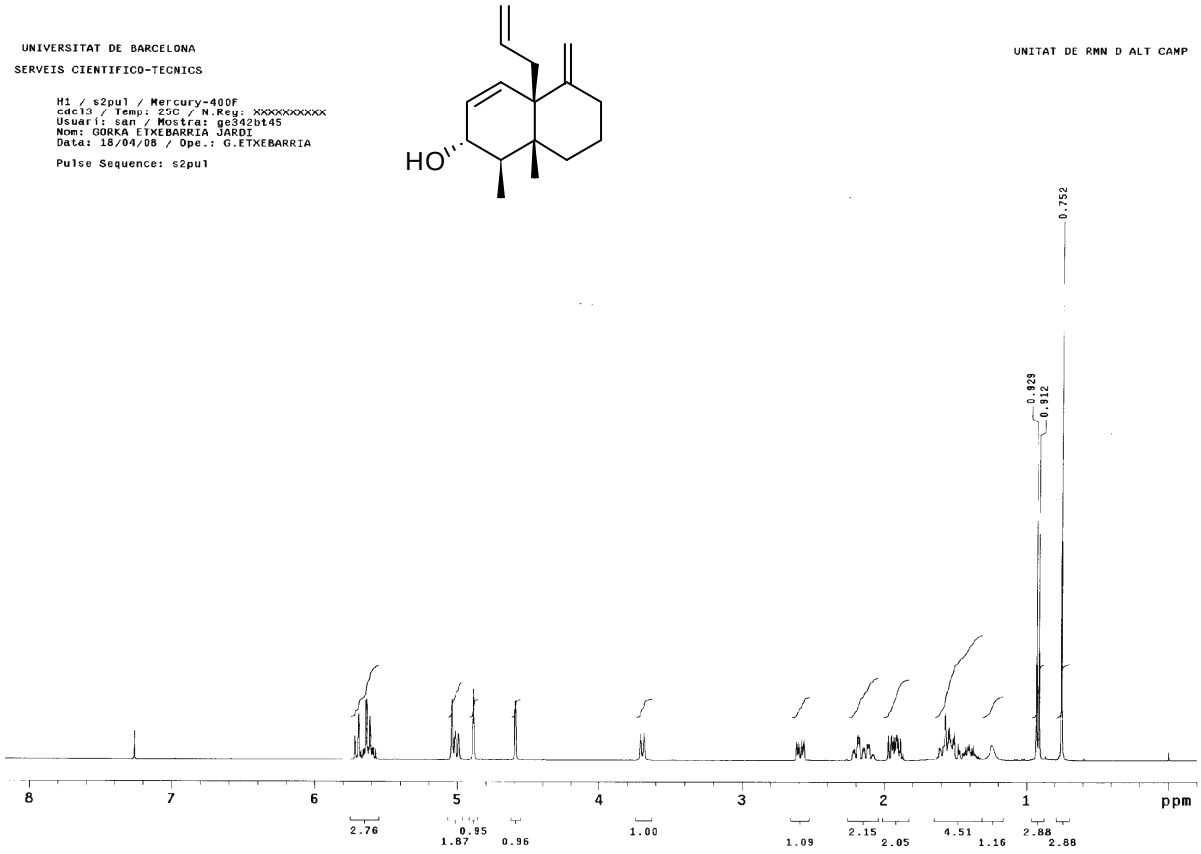
[3] **95** was recycled to **94** by Dess-Martin oxidation. To a solution of alcohol **95** (1.7 g, 7.32 mmol) in non anhydrous CH_2Cl_2 (105 mL) at rt was added Dess-Martin periodinane (3.41 g, 8.05 mmol) portionwise. The resulting mixture was stirred for 15 min and then quenched by addition of sat. aq. $NaHCO_3$ (20 mL). The crude mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and absorbed onto silica gel for purification by column chromatography (2.5→5→10% EtOAc/hexanes) to give ketone **94** (1.57 g, 93%) as an off-white solid.

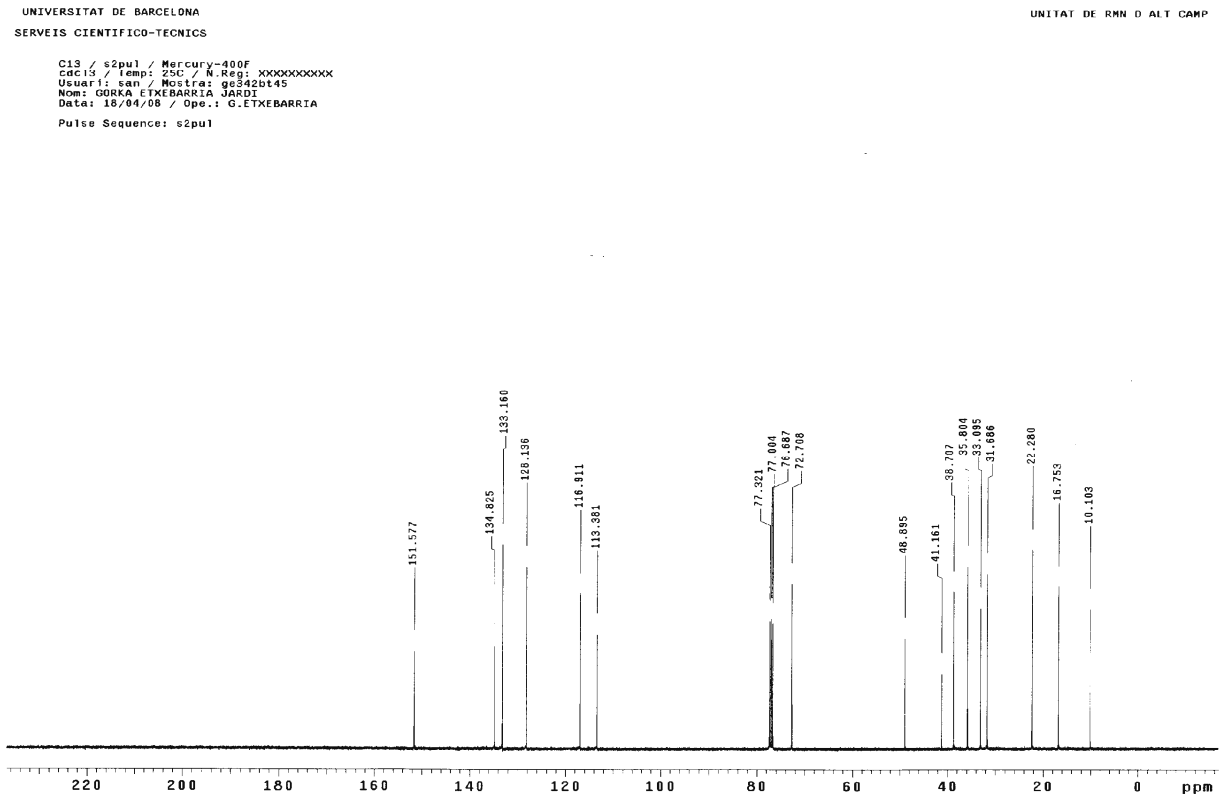
133.5 (C-19), 134.8 (C-22), 150.9 (C-11); HRMS calcd for $C_{16}H_{23}$ (MH^+-H_2O) 215.1794, found 215.1802.





Data for 7A: mp 92-94 °C; R_f 0.2 (2 × 10% EtOAc/hexanes); $[\alpha]_D$ –96 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, COSY) δ 0.76 (s, 3H , H-29), 0.92 (d, *J* = 6.8 Hz, 3H, H-28), 1.24 (br s, 1H, OH), 1.40 (m, 1H, H-13), 1.55 (m, 3H, 2H-14, H-13), 1.92 (m, 2H, H-16, H-21), 2.11 (td, , *J* = 10.3, 6.0 Hz, 1H, H-12$_{ax}$), 2.19 (dm, *J* = 10.3 Hz, 1H, H-12$_{eq}$), 2.59 (dd, *J* = 13.6, 6.0 Hz, 1H, H-21), 3.75 (dt, *J* = 10.0, 1.6 Hz, 1H, H-17), 4.59 (d, *J* = 1.2 Hz, 1H, H-10), 4.89 (t, *J* = 2.0 Hz, 1H, H-10), 5.00 (m, 2H, 2H-23), 5.62 (m, 2H, H-22, H-19), 5.70 (dd, *J* = 10, 2.4 Hz, 1H, H-18), ^{13}C NMR (100 MHz, HSQC) δ 10.1 (C-28), 16.8 (C-29), 22.3 (C-13), 31.7 (C-14), 33.1 (C-12), 35.8 (C-16), 38.7 (C-21), 41.2 (C-15), 48.9 (C-20), 72.7 (C-17), 113.4 (C-10), 116.9 (C-23), 128.1 (C-18), 133.1 (C-19), 134.8 (C-22), 151.6 (C-11); HRMS calcd for $C_{16}H_{24}ONa$ ($M+Na^+$) 255.1719, found 255.1721.


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge342bt45
Nom: GORKA ETXEBARRIA JARDI
Data: 18/04/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
HO
0.752
0.929
0.912
8
7
6
5
4
3
2
1
ppm
2.76
0.95
1.87
0.96
1.00
1.09
2.15
2.05
4.51
1.16
2.88
2.88

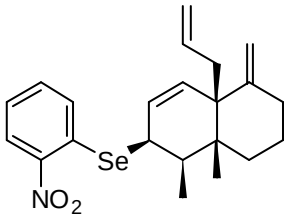

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge342bt45
Nom: GORKA ETXEBARRIA JARDI
Data: 18/04/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
151.577
134.825
133.160
128.136
116.911
113.381
77.321
77.004
76.687
72.708
48.885
41.161
38.707
35.804
33.095
31.686
22.280
16.753
10.103
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Part 2: To a solution of alcohol **98** (1.34 g, 5.31 mmol) and *o*-nitrophenyl selenocyanate (2.41 g, 10.62 mmol) in anhydrous THF (55 mL) was added tri-*n*-butylphosphine (2.9 mL, 11.68 mmol) dropwise. The resulting mixture was stirred at rt for 16 h and then absorbed onto silica gel for purification by column chromatography (0→0.5→1→2.5% EtOAc in hexanes) to give selenide **99** (1.9 g, 86%) as an bright yellow solid. mp 82-84 °C; R_f 0.7 (25% EtOAc/hexanes); $[\alpha]_D$ +310 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.87 (s, 3H , H-29), 1.0 (d, *J* = 7.2 Hz, 3H, H-28), 1.40 (m, 1H, H-13), 1.57 (m, 3H, 2 × H-14, H-13), 2.01 (dd, *J* = 14.4, 8.8 Hz, H-21), 2.13 (td, *J* = 13.6, 4.4 Hz, H-21$_{ax}$), 2.19 (dm, *J* = 13.6, 8.8 Hz, H-12$_{eq}$), 2.60 (dd, *J* = 14.0, 5.6 Hz, 1H, H-21), 2.68 (q, *J* = 6.8Hz, 1H, H-16$_{eq}$), 4.06 (t, *J* = 4.8 Hz, 1H, H-17), 4.58 (s, 1H, H-10), 4.85 (s, 1H, H-10), 5.02 (m, 2H, H-23), 5.58 (d, 1H, *J* = 10.8 Hz, H-19), 5.62 (m, 1H, H-22), 5.98 (dd, *J* = 10.4, 4.0 Hz, 1H, H-18), 7.29 (qd, *J*= 8.4. 0.8 Hz, Ar-H-4'), 7.51 (td, *J*= 8.4, 0.8 Hz, Ar-H-5'), 7.72 (d, *J*= 8.4 Hz, Ar-H6'), 8.14 (dd, *J*= 8.4, 1.2 Hz, Ar-H-3'); ^{13}C NMR (100 MHz, HSQC) δ 15.1 (C-28), 18.8 (C-29), 22.8 (C-13), 31.2 (C-14), 32.7 (C-12), 33.7 (C-16), 36.1 (C-21), 39.1 (C-15), 48.6 (C-17), 48.9 (C-20), 113.2 (C-10), 117.1 (C-23), 125.6 (C-3' Ar), 126.0 (C-4' Ar), 127.1 (C-18), 130.1 (C-6' Ar), 131.9 (C-19), 133.2 (C-5' Ar), 133.6 (C-1' Ar), 134.6 (C-22), 148.5 (C-2' Ar), 151.5 (C-11); HRMS calcd for $C_{22}H_{31}N_2O_2Se$ ($M+NH_4^+$) 435.1545, found 435.1550.

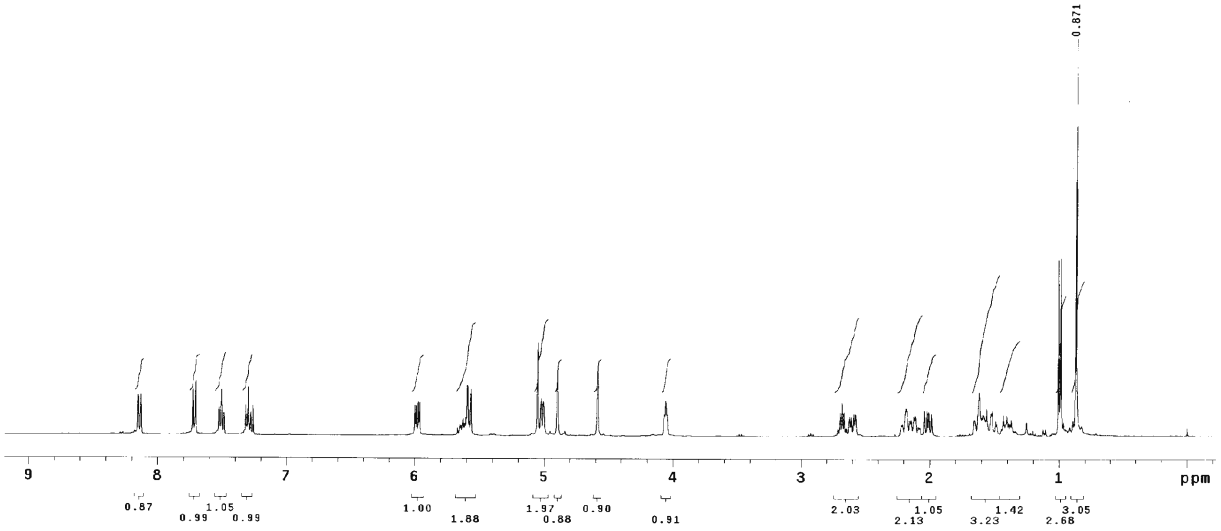
UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge343col
Nom: GORKA ETXEBARRIA JARDI
Data: 21/04/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



UNITAT DE RMN D ALT CAMP

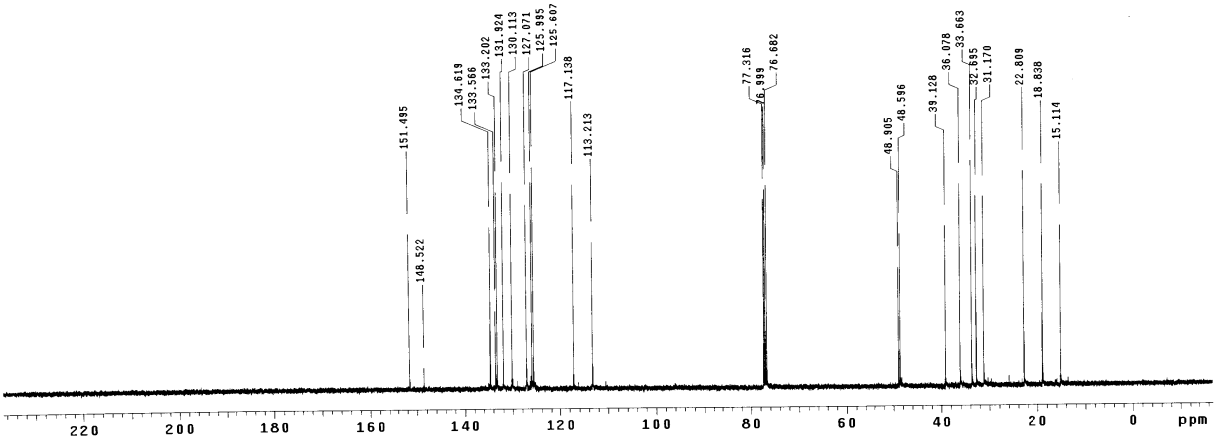


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS

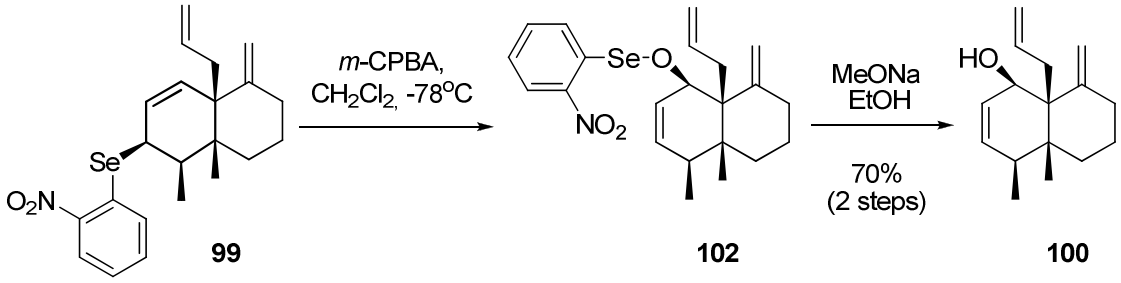
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge343col
Nom: GORKA ETXEBARRIA JARDI
Data: 21/04/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul

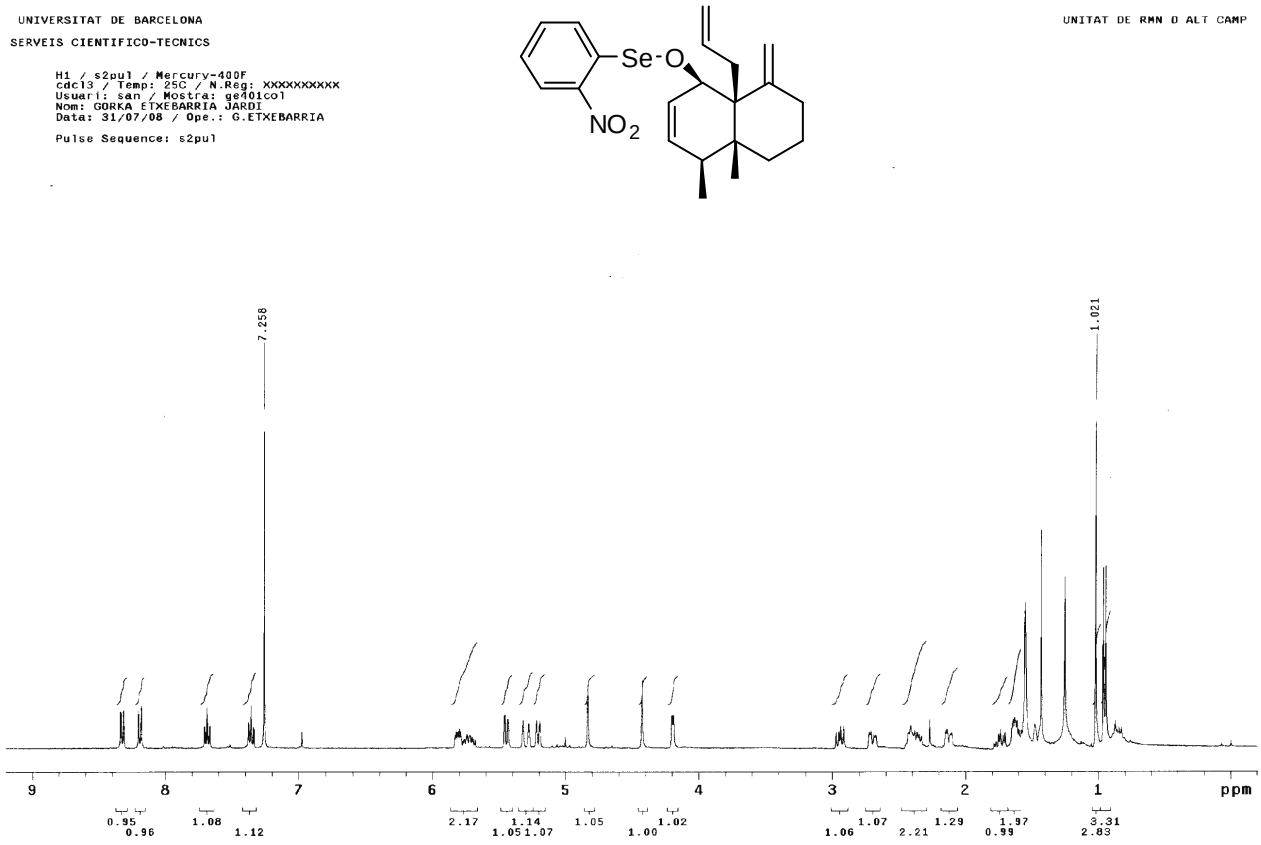
UNITAT DE RMN D ALT CAMP

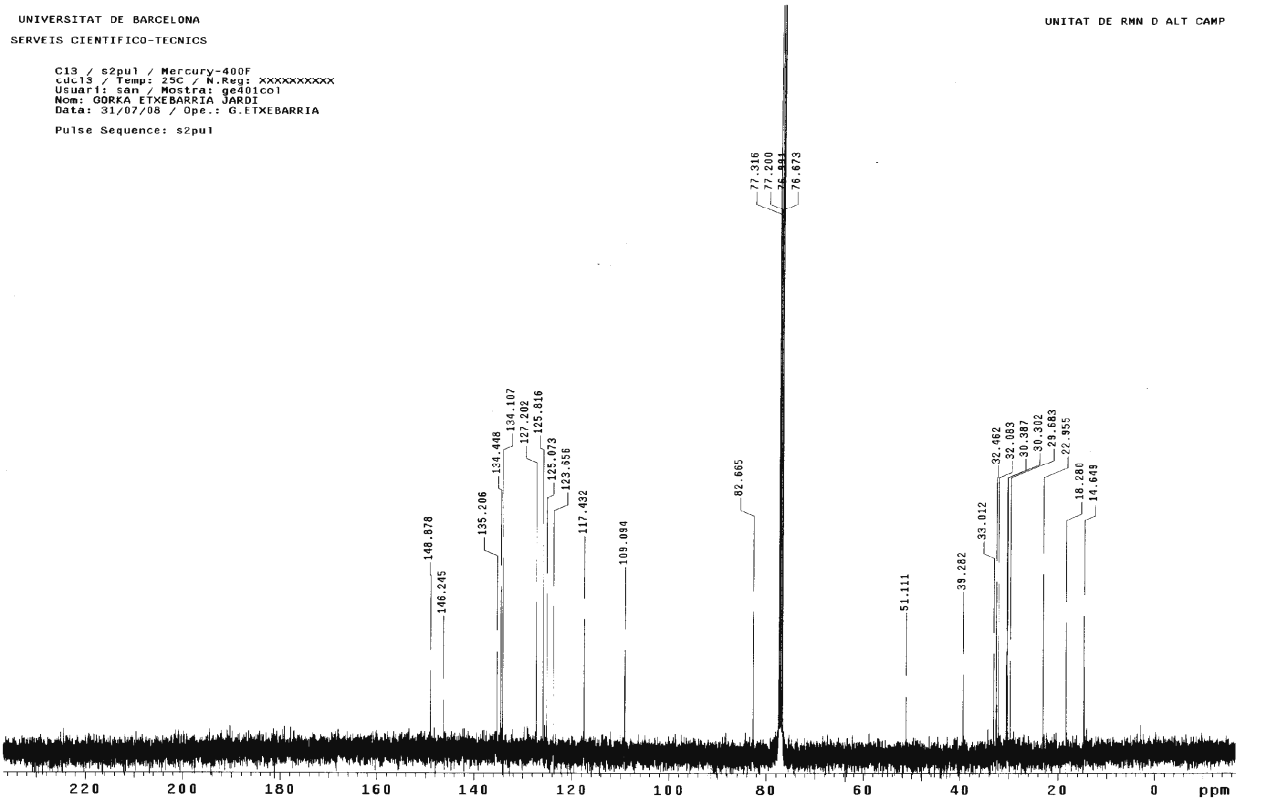


(1*R*,4*S*,4a*R*,8a*R*)-8a-Allyl-4,4a-dimethyl-8-methylene-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ol (100)

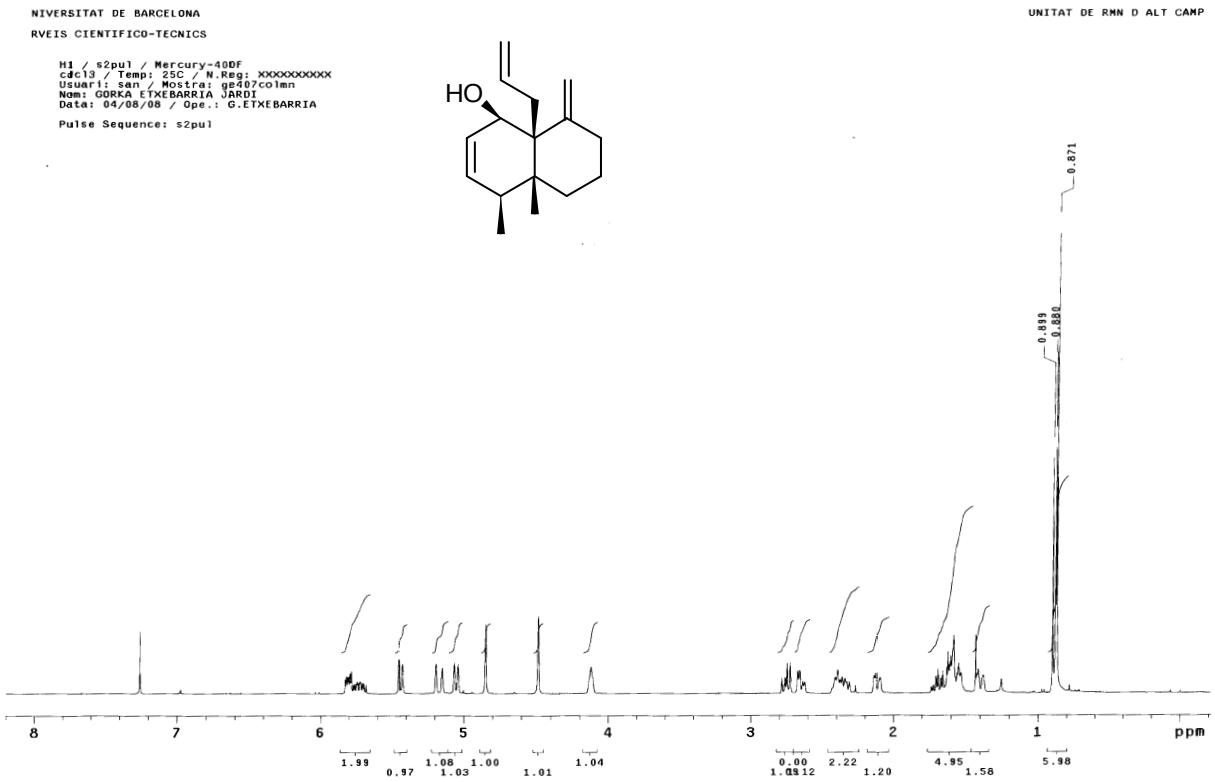


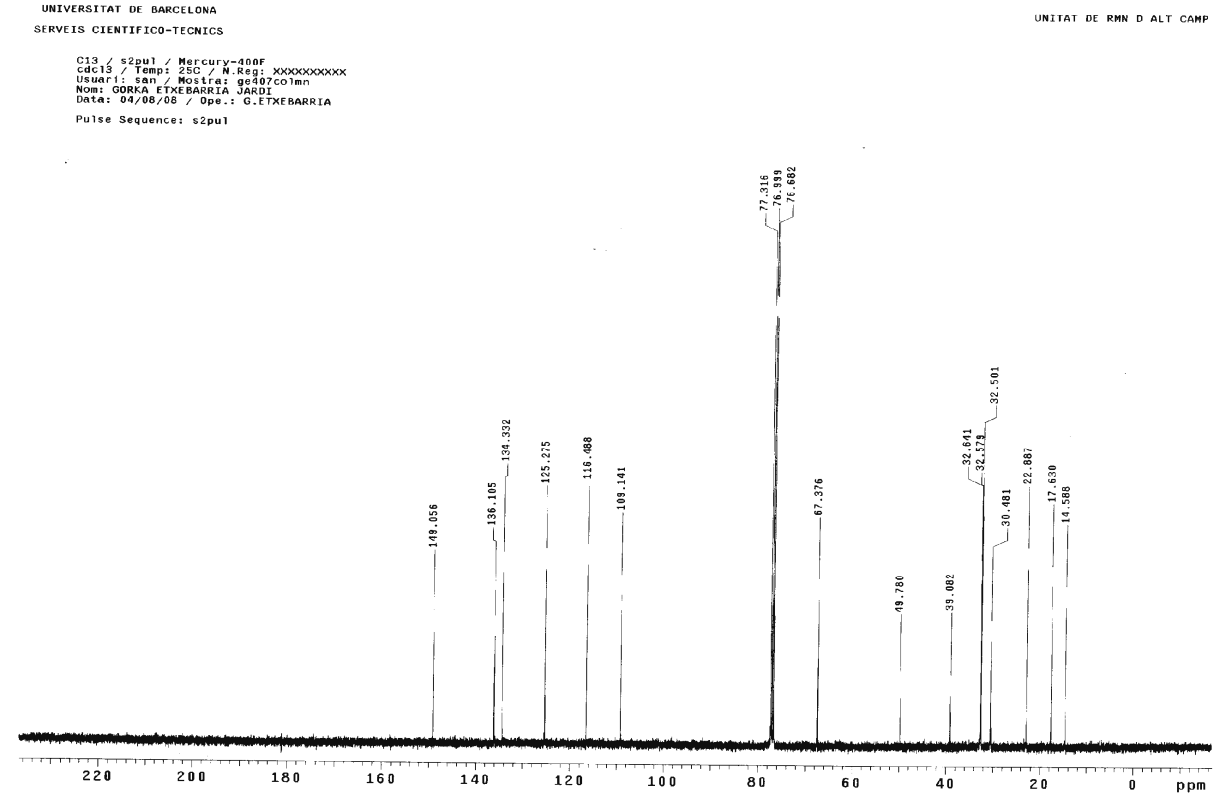
Part 1: To a solution of selenide **99** (1.9 g, 4.56 mmol) in non anhydrous CH_2Cl_2 (180 mL) at –78 °C was added dropwise (via syringe pump) a solution 77% *m*-CPBA (1.23 g, 5.48 mmol) in CH_2Cl_2 over 5 h. The reaction was quenched with 60 mL of sat. aq. $NaHCO_3$ and diluted with 200 mL of CH_2Cl_2. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, concentrated and the resultant crude material was used directly the next step. In order to obtain a pure sample for analysis the reaction mixture was purified by chromatography (0→0.5→1→2.5% EtOAc/hexanes) to give **102** as bright orange solid: mp 109-113 °C; R_f 0.5 (10% EtOAc/hexanes) $[\alpha]_D$ –119 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.96 (d, *J* = 7.6 Hz, 3H, H-28), 1.02 (s, 3H , H-29), 1.5-1.6 (m, 3H, 2H-14, H-13), 1.74 (qd, 3H, *J* = 14.0, 5.0 Hz, 1H, H-13$_{ax}$), 2.12 (dd, *J* = 13.5 Hz, 1H, H-12$_{eq}$), 2.35 (m, 1H, H-12), 2.41 (m, 1H, H-16), 2.71 (dd, *J* = 10.4, 8.4 Hz, 1H, H-21), 2.94 (dd, *J* = 14.0, 8.4 Hz, 1H, H-21), 4.19 (d, *J* = 4.4 Hz, 1H, H-19), 4.43 (s, 1H, H-10), 4.84 (s, 1H, H-10), 5.21 (d, , *J* = 10.4 Hz, 1H, H-23), 5.30 (d, *J* = 16.8 Hz, 1H, H-23), 5.45 (d, *J* = 10.0, 1H, H-17), 5.73 (m, 1H, H-22), 5.81 (m, 1H, H-18), 7.36 (td, *J* = 8.0, 1.0 Hz, 1H, H-4'Ar),7.69 (td, *J* = 8.0, 1.0 Hz, 1H, H-5'Ar),8.19 (d, *J* = 8.0 Hz, 1H, H-6'Ar), 8.33 (dd, *J* = 8.4, 1.2 Hz, 1H, H-3'Ar); ^{13}C NMR (100 MHz, HSQC) δ 14.7 (C-28), 18.3 (C-29), 23.0 (C-13), 30.4 (C-14), 32.1 (C-21), 32.5 (C-12), 33.0 (C-16), 39.3 (C-15), 51.1 (C-20), 82.7 (C-19), 109.1 (C-10), 117.4 (C-23), 125.3 (C-18), 134.3 (C-17), 135.2 (C-22), 148.9 (C-11); HRMS calcd for $C_{22}H_{27}NO_3NaSe$ ($M+Na^+$) 456.1048, found 456.1046.


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge401col
Nom: GORKA ETXEBARRIA JARDI
Data: 31/07/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
Se-O
NO2
7.258
1.021
9
8
7
6
5
4
3
2
1
ppm
0.95
0.96
1.08
1.12
2.17
1.14
1.05
1.07
1.05
1.00
1.02
1.06
1.07
2.21
1.29
1.97
0.99
3.31
2.83

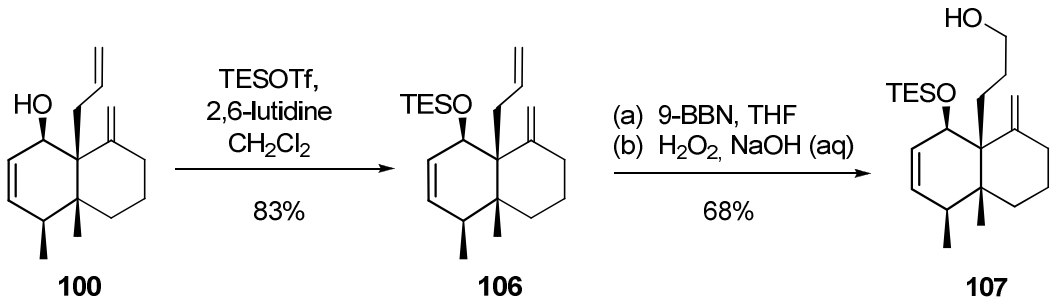

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge401col
Nom: GORKA ETXEBARRIA JARDI
Data: 31/07/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
77.316
77.200
76.831
76.673
148.878
146.245
135.206
134.448
134.107
127.202
125.816
125.673
123.456
117.432
109.094
82.665
51.111
39.282
33.012
32.462
32.083
30.387
30.302
29.683
22.955
18.280
14.649
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Part 2: To a stirred solution of the crude selenate ether **102** (1.97 g, 4.56 mmol) in EtOH (160 mL) at 0 °C was added sodium methoxide (370 mg, 6.84 mmol) in one portion. The bright orange solution immediately darkened and was allowed to stir for 30 min at rt. The solvent was evaporated *in vacuo* and the residue partitioned between Et_2O (400 mL) and H_2O (60 mL). The layers were separated and the aqueous layer was extracted with Et_2O (150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (0→0.5→1→2.5% EtOAc/hexanes) gave alcohol **100** (740 mg, 70% over 2 steps) as a light yellow oil. R_f 0.3 (10% EtOAc/hexanes); $[\alpha]_D$ –139 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.88 (s, 3H, H-29), 0.89 (d, *J* = 7.2 Hz, 3H, H-28), 1.40 (dm, *J* = 13.5 Hz, 1H, H-14$_{eq}$), 1.60 (m, 2H, H-13), 1.69 (td, *J* = 13.6, 5.6 Hz, 1H, H-14$_{ax}$), 2.10 (m, 1H, H-12), 2.36 (m, 2H, H-12 , H-16), 2.65 (dd, *J* = 14.0, 5.2 Hz, 1H, H-21), 2.75 (dd, *J* = 14.0, 8.4 Hz, 1H, H-21), 4.12 (br s, 1H, H-19), 4.49 (s, 1H, H-10), 4.85 (s, 1H, H-10), 5.05 (d, *J* = 10.4 Hz, 1H, H-23), 5.17 (dd, *J* = 17.2, 0.8 Hz, 1H, H-23), 5.44 (d, *J* = 10.0 Hz, 1H, H-17), 5.74 (m, 1H, H-22), 5.81 (dm, *J* = 10.0 Hz,1H, H-18); ^{13}C NMR (100 MHz, HSQC) δ 14.6 (C-28), 17.6 (C-29), 22.9 (C-13), 30.5 (C-14), 32.5 (C-12), 32.6 (C-16), 32.7 (C-21), 39.1 (C-15), 49.8 (C-20), 67.4 (C-19), 109.1 (C-10), 116.5 (C-23), 125.3 (C-18), 134.3 (C-17), 136.1 (C-22), 149.1 (C-11); HRMS calcd for $C_{16}H_{23}$ (MH^+–H_2O) 215.1794, found 215.1797.

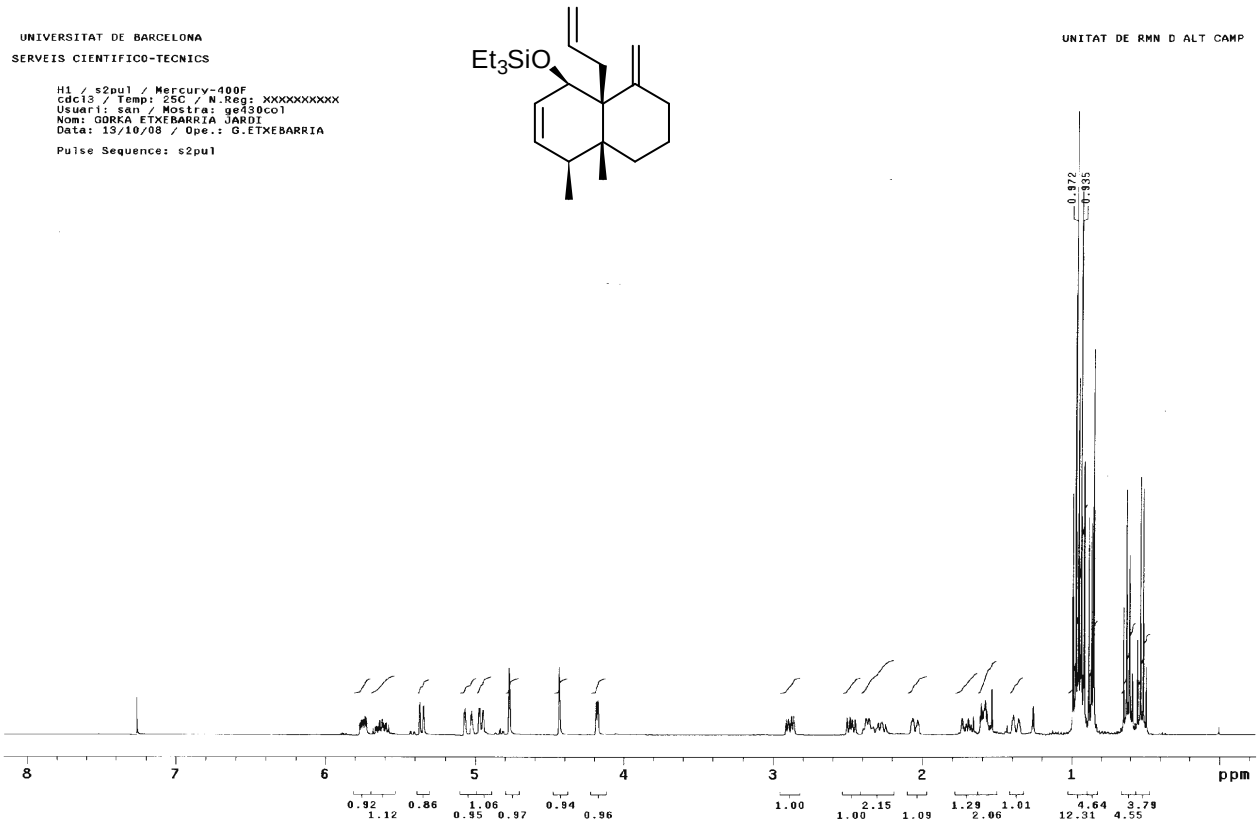

NIVERSITAT DE BARCELONA
RVEIS CIENTIFICO-TECNICS
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge407colmn
Nom: GORKA ETXEBARRIA JARDI
Data: 04/08/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
HO
0.871
0.899
0.880
8
7
6
5
4
3
2
1
ppm
1.99
0.97
1.08
1.03
1.00
1.01
1.04
0.00
2.22
1.20
4.95
1.58
5.98

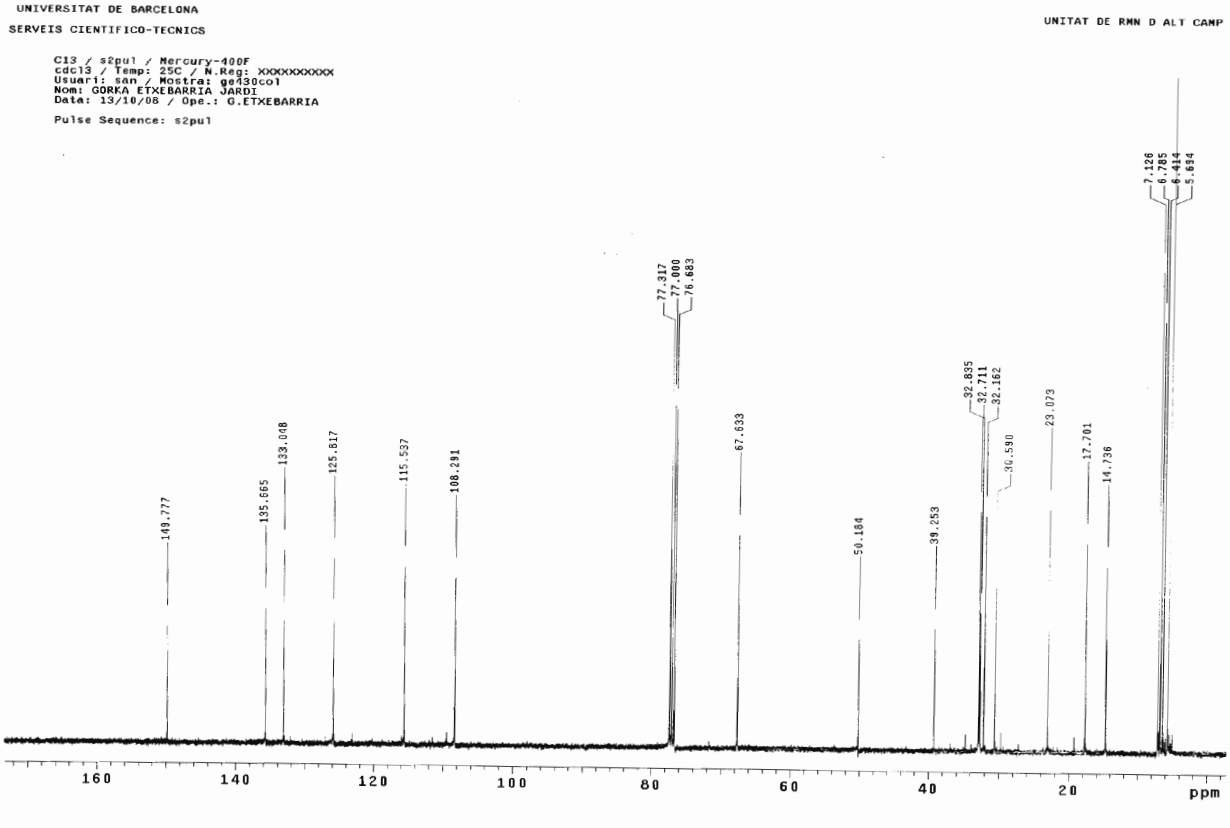

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge407colmn
Nom: GORKA ETXEBARRIA JARDI
Data: 04/08/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
149.056
136.105
134.332
125.275
116.488
109.141
77.316
76.999
76.682
67.376
49.786
39.082
32.641
32.578
32.501
30.481
22.887
17.630
14.588
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(1*R*,4*S*,4a*R*,8a*R*)-8a-(3-Hydroxypropyl)-4,4a-dimethyl-8-methylene-1-triethylsilyloxy-1,4,4a,5,6,7,8,8a-octahydronaphthalene (107)

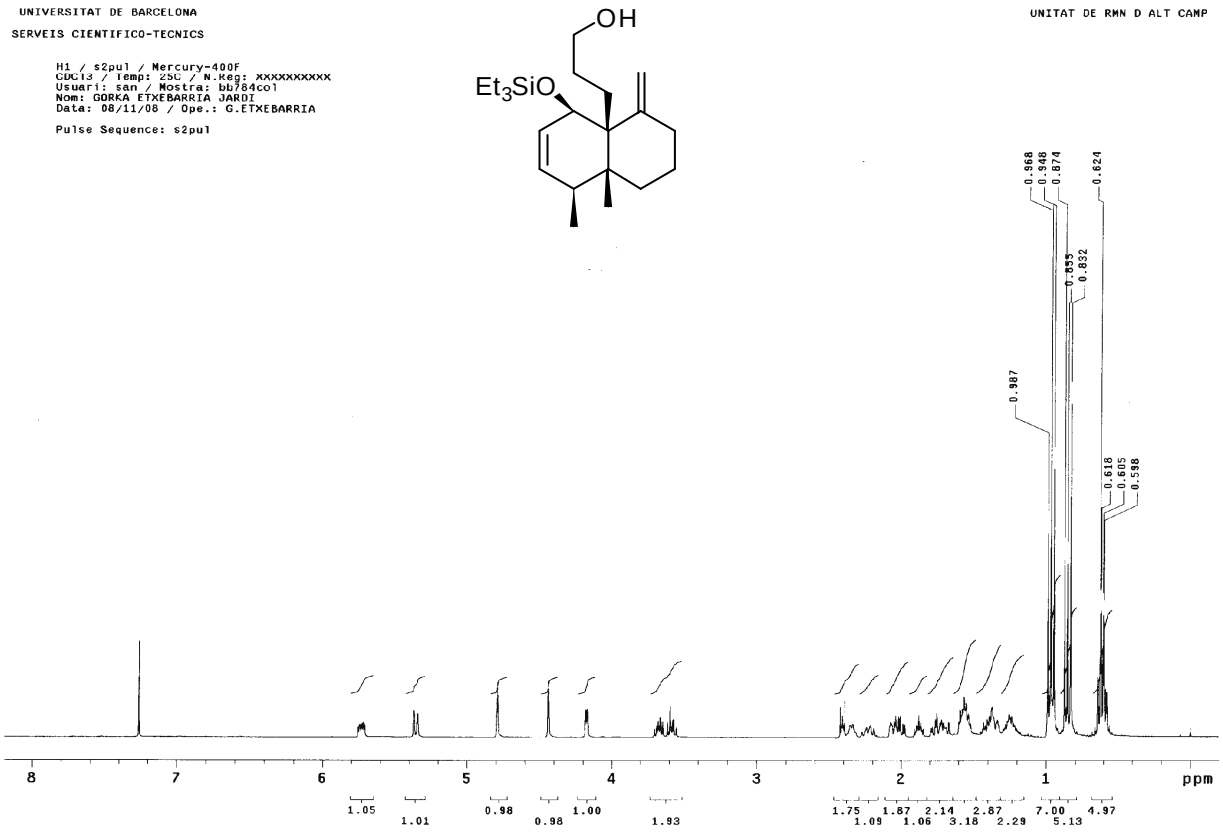


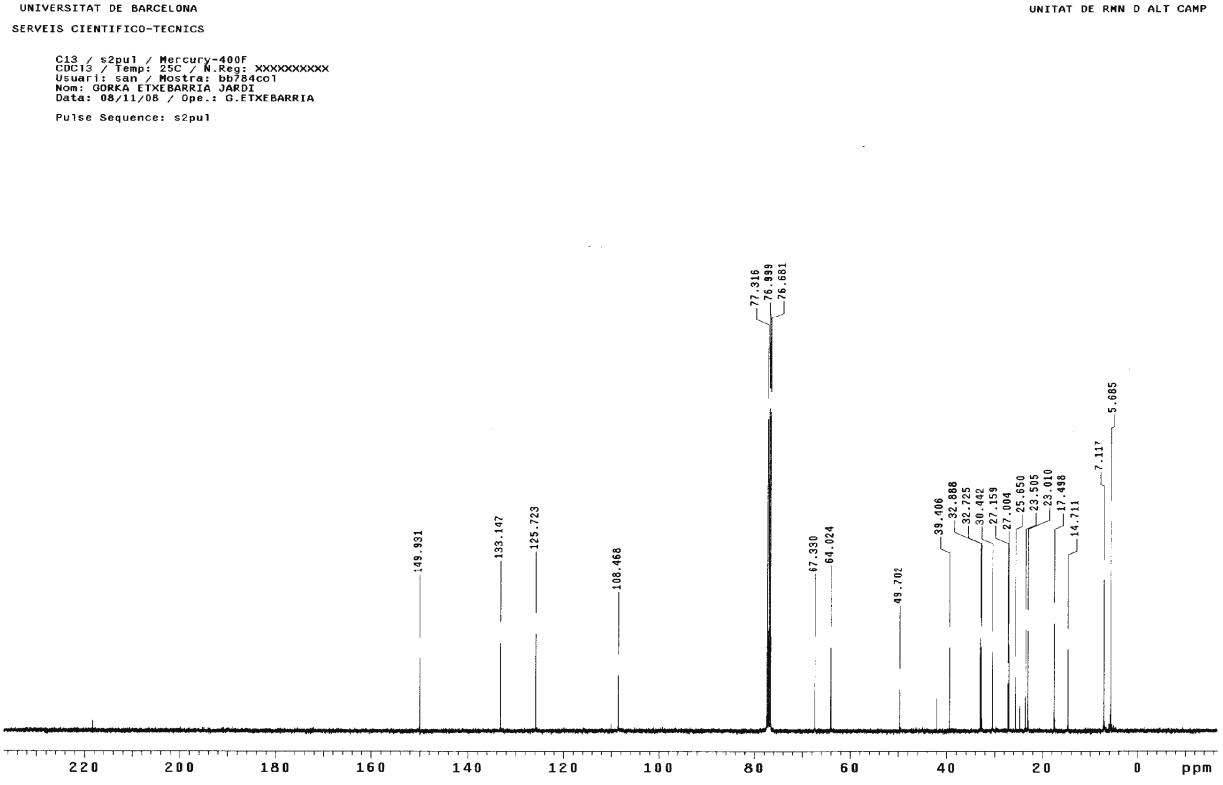
Part 1: Triethylsilyltrifluoromethanesulfonate (755 µL, 3.34 mmol) was added to a solution of the alcohol **100** (740 mg, 3.18 mmol) and 2,6-lutidine (924 µL, 7.96 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min and then quenched by the addition of sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (hexanes) gave **106** (910 mg, 83%) as a colourless oil. R_f 0.8 (10% EtOAc/hexanes); $[\alpha]_D$ +155 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.52 and 0.62 (2q, *J* = 7.6 Hz, 6H, Si($\underline{CH_2}CH_3)_3$), 0.85 (s, 3H , H-29), 0.87 (d, *J* = 7.2 Hz, 3H, H-28), 0.94 and 0.97 (2t, *J* = 7.6 Hz, 9H, Si($CH_2\underline{CH_3})_3$), 1.38 (dm, *J* = 13.5 Hz, 1H, H-14$_{ax}$), 1.58 (m, 2H, H-13), 1.70 (m, 1H, H-14), 2.05 (dm, *J* = 13.0 Hz, 1H, H-12$_{eq}$), 2.27 (t, *J* = 13.0 Hz, 1H, H-12$_{ax}$), 2.36 (q, *J* = 7.2 Hz, 1H, H-16$_{ax}$), 2.48 (dd, *J* = 13.6, 8.0 Hz, 1H, H-21), 2.88 (dd, *J* = 14.4, 6.4 Hz, 1H, H-21), 4.18 (d, *J* = 4.0 Hz, 1H, H-19), 4.44 and 4.77 (2s, 1H each, 2H-10), 4.96 (dm, *J* = 10.4 Hz, 1H, H-23), 5.05 (dm, *J* = 17.2 Hz, 1H, H-23), 5.36 (dd, *J* = 10.0, 1.6 Hz, 1H, H-17), 5.62 (m, 1H, H-22), 5.74 (m, 1H, H-18); ^{13}C NMR (100 MHz, HSQC) δ 5.7 and 6.4 (Si($\underline{CH_2}CH_3)_3$), 6.8 and 7.1 (Si($CH_2\underline{CH_3})_3$), 14.7 (C-28), 17.7 (C-29), 23.1 (C-13), 30.6 (C-14), 32.2 (C-21), 32.7 (C-12), 32.8 (C-16), 39.2 (C-15), 50.2 (C-20), 67.6 (C-19), 108.3 (C-10), 115.5 (C-23), 125.8 (C-18), 133.0 (C-17), 135.7 (C-22), 149.8 (C-11).


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge430col
Nom: GORKA ETXEBARRIA JARDI
Data: 13/10/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
Et3SiO
0.972
0.935
8
7
6
5
4
3
2
1
ppm
0.92
1.12
0.86
1.06
0.95
0.97
0.94
0.96
1.00
2.15
1.00
1.09
1.29
2.06
1.01
4.64
12.31
3.79
4.55

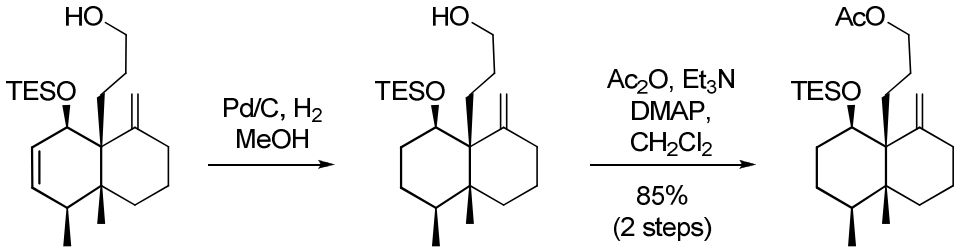

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge430col
Nom: GORKA ETXEBARRIA JARDI
Data: 13/10/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
149.777
135.665
133.048
125.817
115.537
108.291
77.317
77.000
76.683
67.633
50.184
39.253
32.835
32.711
32.162
30.590
23.073
17.701
14.736
7.126
6.785
6.414
5.694
160
140
120
100
80
60
40
20
ppm

Part 2: To a solution of triene **106** (277 mg, 0.80 mmol) in THF (14 mL) was added a solution of 9-BBN 0.5 M in THF (2.4 mL, 1.2 mmol) and stirred for 1 h at room temperature. Aqueous 2M NaOH (0.7 mL) and H_20_2 30% wt solution (0.7 mL) were added and the resulting mixture stirred for 2 h. The reaction mixture was extracted with Et_2O (3 × 20 mL), the combined organic layers were washed with sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, brine, dried and concentrated. Purification by chromatography (0→2.5→5→10% EtOAc/hexanes) gave **107** (172 mg, 68%) as a white waxy solid; R_f 0.4 (25% EtOAc/hexanes); $[\alpha]_D$ –129 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.59 (m, 6H, Si($\underline{CH_2}CH_3)_3$), 0.83 (s, 3H, H-29), 0.86 (d, *J* = 7.6 Hz, 3H, H-28), 0.97 (m, 9H, Si($CH_2\underline{CH_3})_3$), 1.25 (m, 1H, H-22), 1.38 (m, 2H, H-14, H-22), 1.56 (m, 2H, H-13), 1.73 (m, 2H, H-14, H-21), 2.02 (m, 2H, H-12, H-21), 2.22 (m, 1H, H-16), 2.34 (dm, *J* = 12.5 Hz, 1H, H-12), 3.57 and 3.67 (2m, 1H each, 2H-23), 4.18 (d, *J* = 4.4 Hz, 1H, H-19), 4.44 and 4.79 (2s, 1H each, 2H-10), 5.35 (dd, *J* = 9.6, 1.6 Hz, 1H, H-17), 5.73 (m, 1H, H-18); ^{13}C NMR (100 MHz, HSQC) δ 5.7 (Si($\underline{CH_2}CH_3)_3$), 7.1 (Si($CH_2\underline{CH_3})_3$), 14.7 (C-28), 17.5 (C-29), 23.0 (C-13), 23.5 (C-21), 27.0 (C-22), 30.4 (C-14), 32.7 (C-16), 32.9 (C-12), 39.4 (C-15), 49.7 (C-20), 64.0 (C-23), 67.3 (C-19), 108.5 (C-10), 125.7 (C-18), 133.1 (C-17), 149.9 (C-11); HRMS calcd for $C_{22}H_{40}O_2SiNa$ ($M+Na^+$) 387.2695, found 387.2686.


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb784col
Nom: GORKA ETXEBARRIA JARDI
Data: 08/11/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
OH
Et3SiO
0.968
0.948
0.874
0.624
0.833
0.832
0.987
0.618
0.605
0.598
8
7
6
5
4
3
2
1
ppm
1.05
1.01
0.98
0.98
1.00
1.93
1.75
1.09
1.87
1.06
2.14
3.18
2.87
2.29
7.00
5.13
4.97

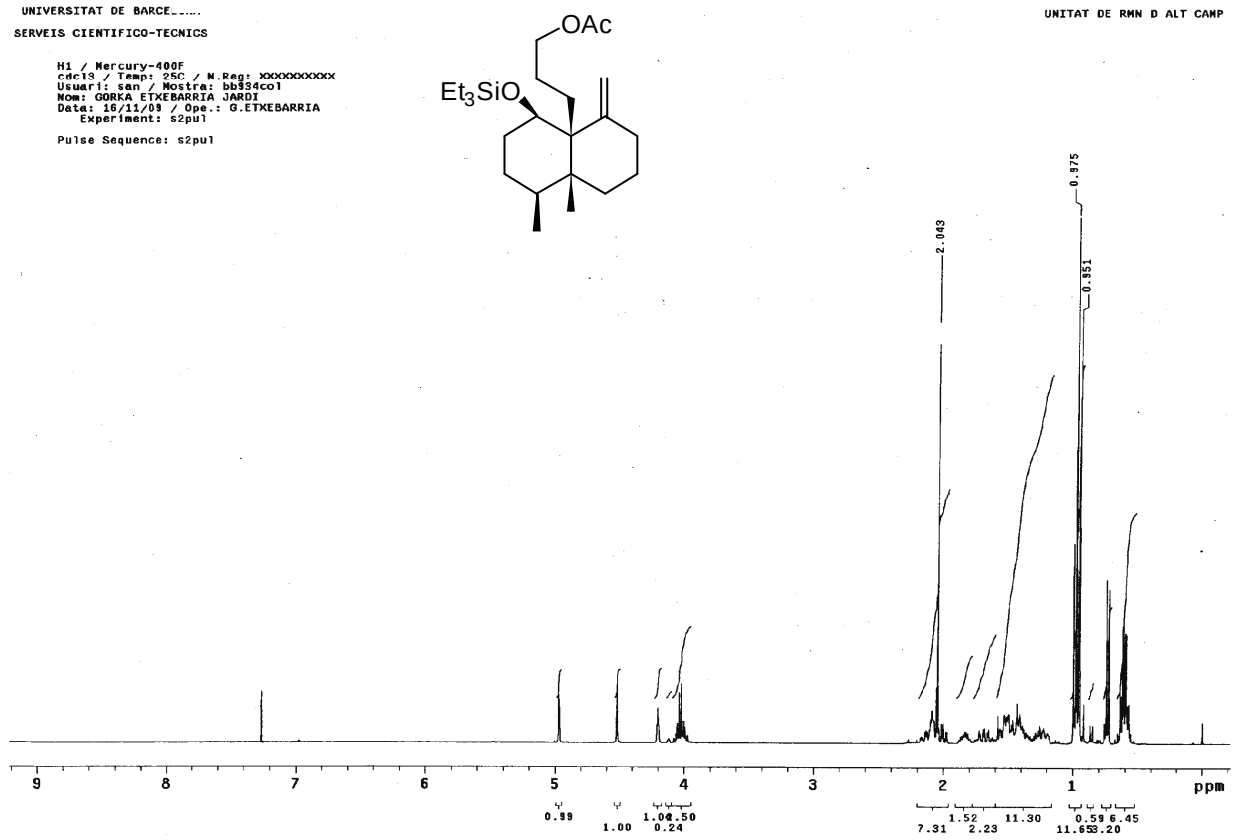

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb784col
Nom: GORKA ETXEBARRIA JARDI
Data: 08/11/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
77.316
76.998
76.681
149.931
133.147
125.723
108.468
67.330
64.024
49.702
39.408
32.888
32.725
30.442
27.153
27.004
25.650
23.505
23.010
17.498
14.711
7.117
5.685
220
200
180
160
140
120
100
80
60
40
20
0
ppm

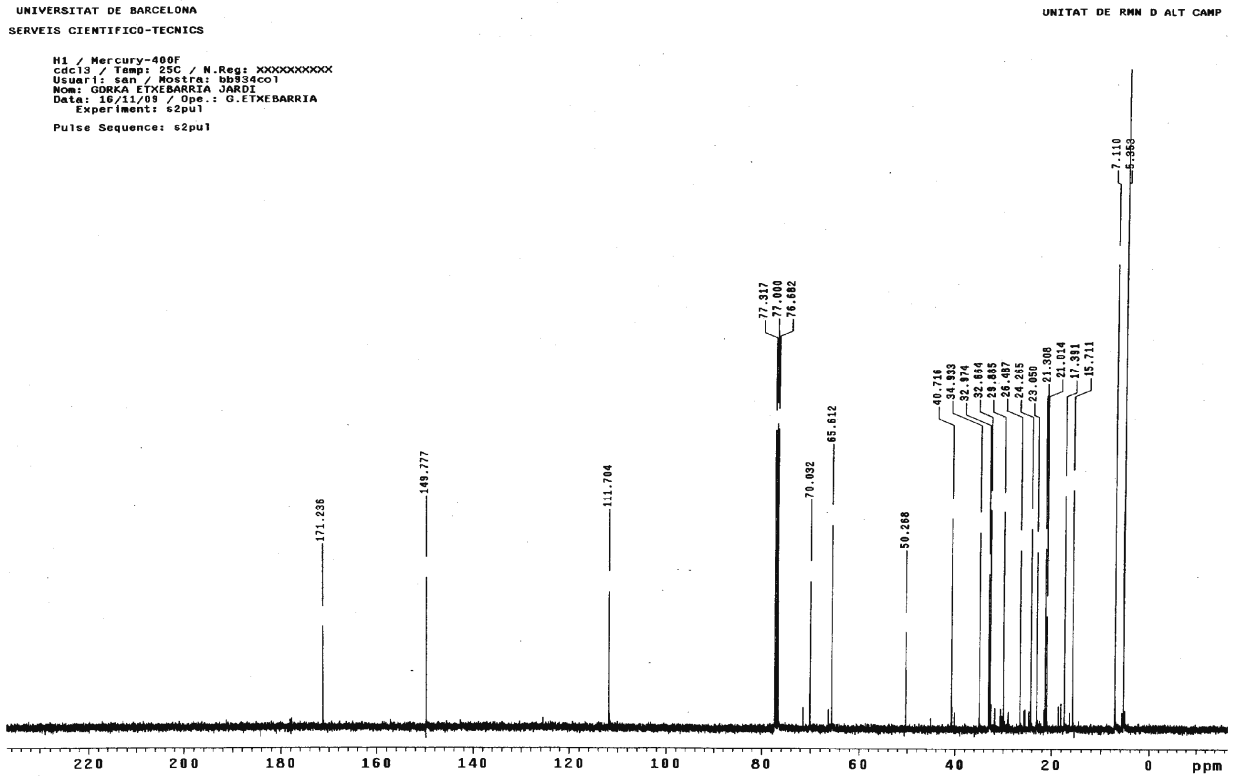
(1*S*,4*R*,4a*R*,8a*R*)-4a-(3-Acetoxypropyl)-1,8a-dimethyl-5-methylene-4-(triethylsilyloxy)decahydronaphthalene (109)



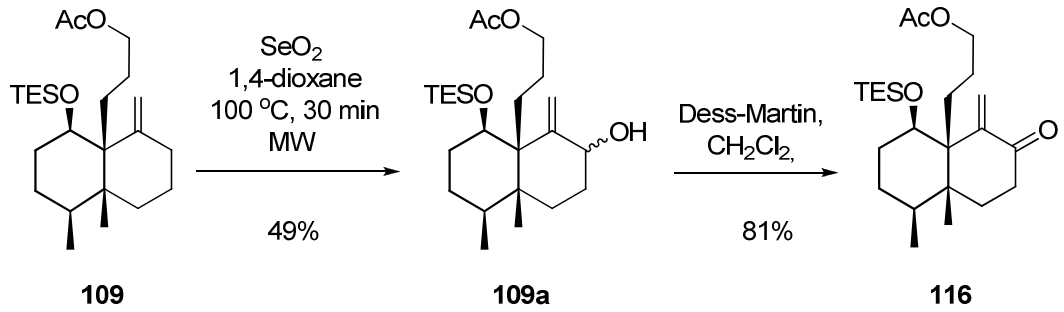
107 **108** **109**

To a stirred solution of **107** (103 mg, 0.282 mmol) in MeOH (13.5 mL) was added Pd/C (10% w/w, 21 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen and then stirred under an atmosphere of H_2 for 10 min. 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 Filtrate was concentrated *in vacuo* to give **108** as a light yellow oil (~100 mg). To the above mixture (~0.282 mmol) dissolved in CH_2Cl_2 (5 mL) was added Et_3N (0.59 mL, 4.23 mmol), DMAP (7 mg, 0.0564 mmol) and then Ac_2O (0.266 mL, 2.82 mmol). The resulting mixture was stirred for 2 h and then diluted with CH_2Cl_2 (50 mL) quenched by the addition of sat. aq. $NaHCO_3$ (2 × 10 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were dried and concentrated. Purification by chromatography (0→1→2.5% EtOAc/hexanes) gave **109** (98 mg, 85%) as a colourless oil. which comprised of ~20% of material in which the exocyclic double was also reduced. R_f 0.6 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.59 (m, 6H , Si($\underline{CH_2}CH_3)_3$), 0.83 (s, 3H , H-29), 0.86 (d, *J* = 7.6 Hz, 3H, H-28), 0.97 (m, 9H , Si($CH_2\underline{CH_3})_3$), 1.20-1.30 (m, 2H, H-13, H-17), 1.40-1.55 (m, 6H, 2H-14, H-13, H-18, 2H-22), 1.70 (m, 1H, H-17), 1.80 (m, 1H, H-16), 1.99 (dd, *J* = 13.2, 4.8 Hz, 1H, H-21), 2.10 (m, 2H, 2H-12), 2.15 (ddd, *J* = 14.0, 4.8, 2.84 Hz, 1H, H-18$_{eq}$), 4.02 (m, 2H, 2H-23), 4.20 (t, *J* = 2.8 Hz, 1H, H-19), 4.52 and 4.97 (2s, 1H each, 2H-10); ^{13}C NMR (100 MHz, HSQC) δ 5.4 (Si$\underline{CH_2}CH_3$), 7.1 ($SiCH_2\underline{CH_3}$), 15.7 (C-28), 17.4 (C-29), 21.0 (OAc), 21.3 (C-22), 23.0 (C-13), 24.5 (C-21), 26.5 (C-17), 29.9 (C-18), 32.7 (C-16), 33.0 (C-14), 34.9 (C-12), 40.7 (C-15), 50.3 (C-20), 65.6 (C-23), 70.0 (C-19), 111.7 (C-10), 149.8 (C-11), 171.2 (CO). HRMS calcd for $C_{24}H_{45}O_3Si$ (MH^+) 409.3132, found 409.3132.


UNIVERSITAT DE BARCE_____
SERVEIS CIENTIFICO-TECNICS
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb834col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/11/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
OAc
Et3SiO
2.043
0.875
0.851
9
8
7
6
5
4
3
2
1
ppm
0.99
1.00
1.04
0.24
4.50
7.31
1.52
2.23
11.30
0.59
11.65
6.45
3.20

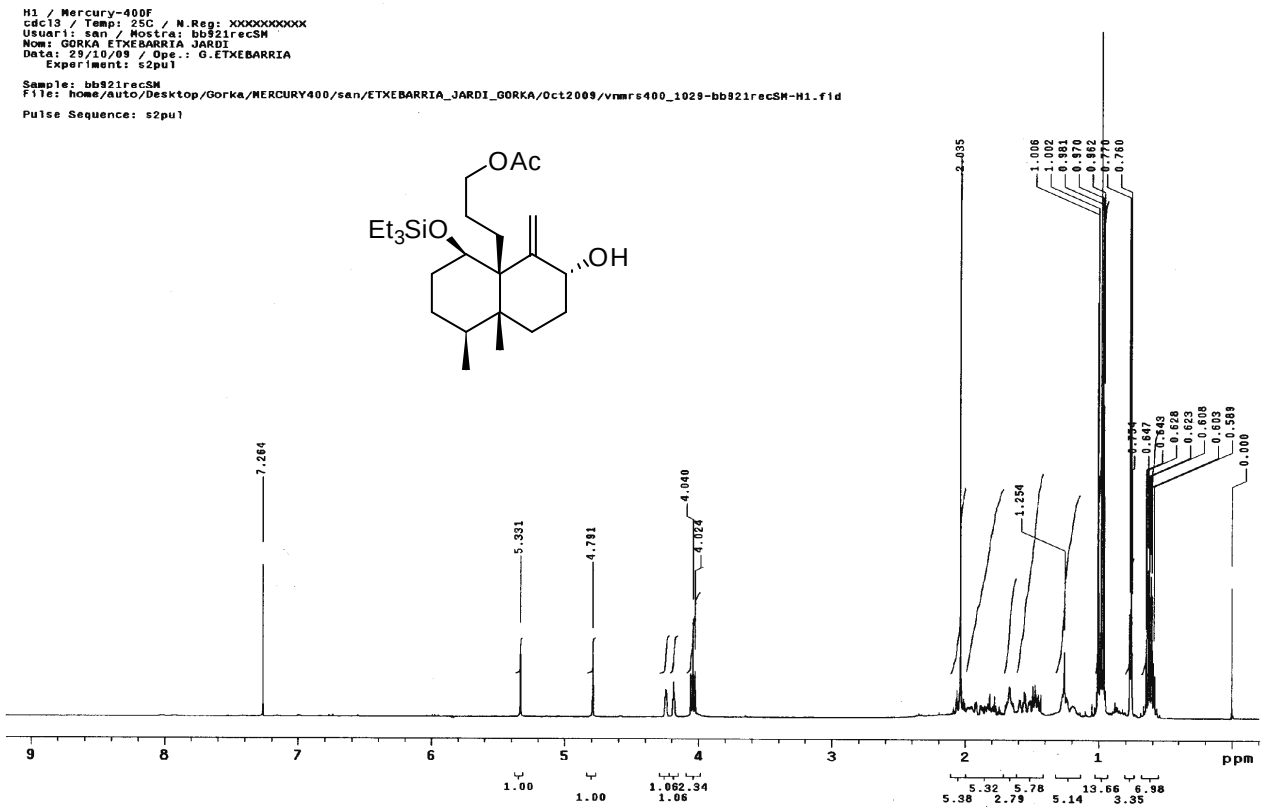

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb834col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/11/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
171.238
149.777
111.704
77.317
77.000
76.682
70.032
65.612
50.268
40.718
34.933
32.974
32.054
29.865
28.487
24.255
23.050
21.308
21.014
17.491
15.711
7.110
6.868
220
200
180
160
140
120
100
80
60
40
20
0
ppm

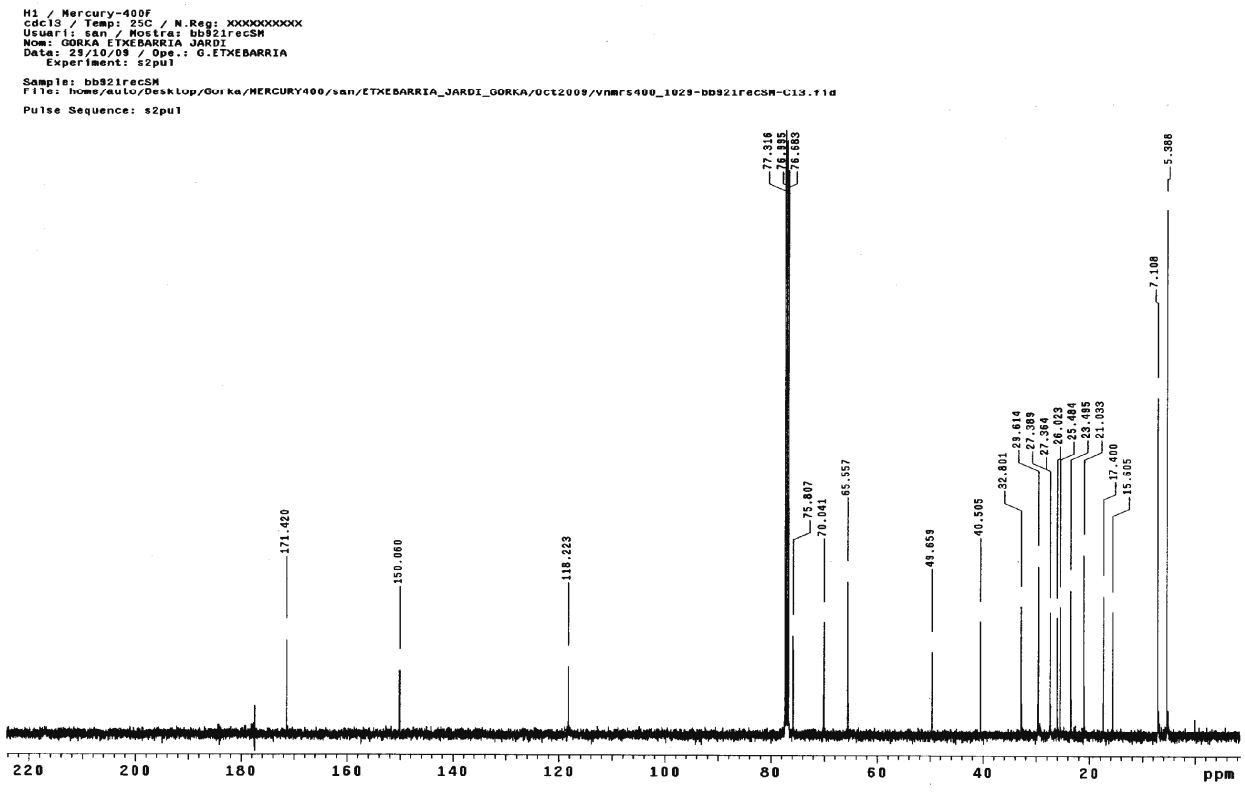
(4a*R*,5*S*,8*R*,8a*S*)-8a-(3-Acetoxypropyl)-4a-5-dimethyl-1-methylene-8-Triethylsilyloxyoctahydronaphthalen-2(1*H*)-one (116)



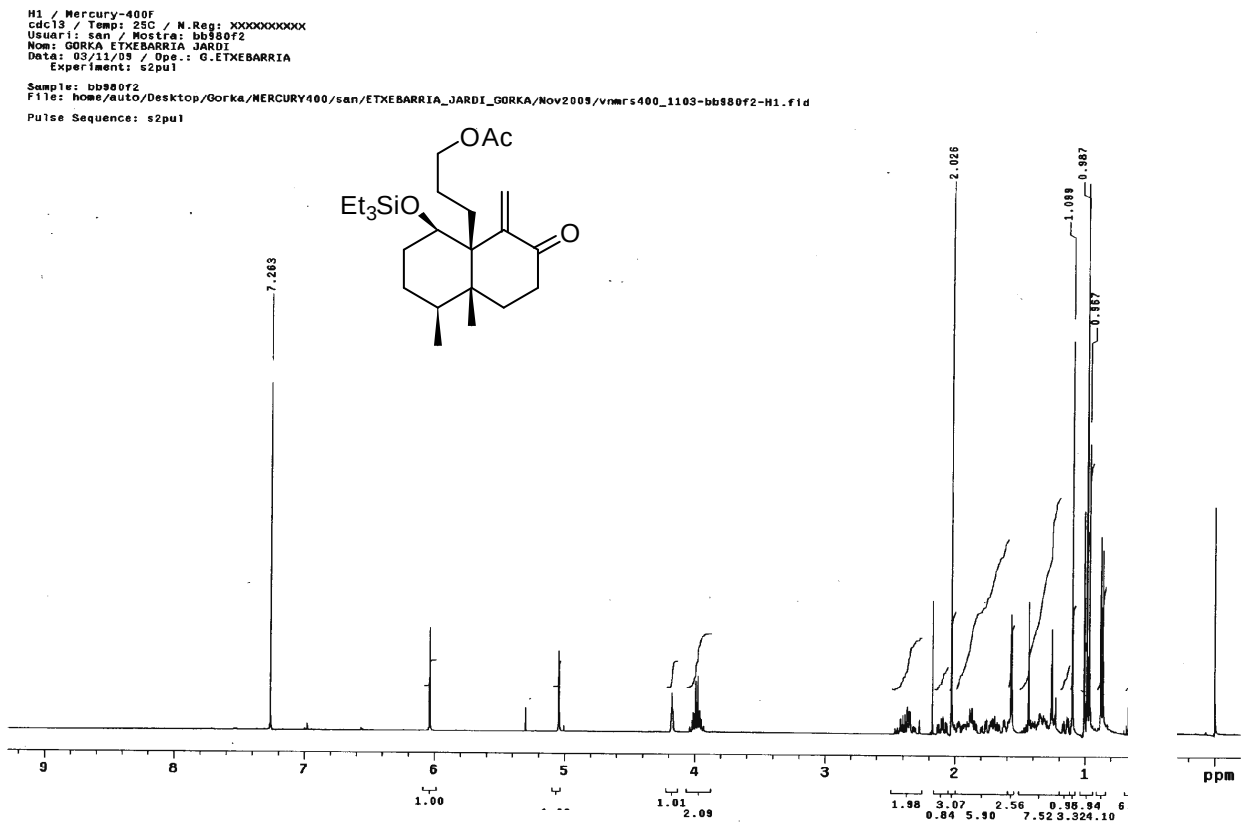
109 **109a** **116**

Part 1: A mixture of alkene **109** (100 mg, 0.195 mmol), SeO_2 (35 mg, 0.312 mmol) and dioxane (3 mL) in a sealed vessel was heated to 100 °C (external temperature monitoring) for 3 cycles of 10 min (at 30 s intervals) at 30 psi in a CEM Discover Labmate® microwave reactor. The solution was diluted with CH_2Cl_2 (10 mL) filtered through Celite and washed through with CH_2Cl_2. Concentration of the filtrate *in vacuo* and purification by chromatography (0→1→2.5→5→10→25% EtOAc/hexanes) gave recovered **109** (47 mg of which ~40% is the reduced compound) followed by **109a** as a mixture of diastereoisomers (41 mg, 49%) as a light yellow oil. **Data for the main diastereoisomer:** R_f 0.2 (25% EtOAc/hexanes); $[\alpha]_D$ –19 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.62 (qd, *J* = 8.0, 2.0 Hz, 6H, Si($\underline{CH_2}CH_3)_3$), 0.76 (d, *J* = 6.4, 3H, H-28), 0.98 (t, *J* = 7.6 Hz, 9H, Si($CH_2\underline{CH_3})_3$), 1.00 (s, 3H, H-29), 1.20-1.30 (m, 2H, H-17, H-18), 1.40-1.55 (m, 4H, H-18, H-21, 2H-22), 1.67 (m, 1H, H-16), 1.78 (tt, *J*= 14.0, 4.0 Hz, 1H, H-14$_{ax}$), 1.82 (m, 1H, H-13), 1.85 (m, 1H, H-14$_{eq}$), 1.90 (m, 1H, H-21), 2.04 (s, 3H, OAc), 2.08 (m, 1H, H-13), 4.04 (t, *J* = 6.4 Hz, 2H, H-23), 4.19 (dd, *J* = 2.8, 2.4 Hz, 1H, H-19$_{eq}$), 4.25 (br s, 1H, H-12$_{eq}$), 4.79 and 5.33 (2s, 1H each, 2H-10); ^{13}C NMR (100 MHz, HSQC) δ 5.4 (Si($\underline{CH_2}CH_3)_3$), 7.1 (Si($CH_2\underline{CH_3})_3$), 15.6 (C-28), 17.4 (C-29), 21.0 (OAc), 23.5 (C-22), 25.5 (C-13), 26.0 (C-17), 27.4 (C-18), 27.4 (C-14), 27.4 (C-18), 29.6 (C-21), 32.8 (C-16), 40.5 (C-15), 49.7 (C-20), 65.6 (C-23), 70.0 (C-19), 75.8 (C-12), 118.2 (C-10), 150.1 (C-11), 171.4 (CO); HRMS calcd for $C_{24}H_{48}NO_4Si$ ($M+NH_4^+$) 442.3347, found 442.3344.


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb921recSM
Nom: GORKA ETXEBARRIA JARDI
Data: 29/10/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Sample: bb921recSM
File: home/auto/Desktop/Gorka/MERCURY400/san/ETXEBARRIA_JARDI_GORKA/Oct2009/vnmrs400_1029-bb921recSM-H1.fid
Pulse Sequence: s2pul
OAc
Et3SiO
OH
7.264
5.331
4.791
4.040
4.024
2.035
1.254
1.006
1.002
0.981
0.970
0.962
0.770
0.760
0.000
ppm


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb921recSM
Nom: GORKA ETXEBARRIA JARDI
Data: 29/10/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Sample: bb921recSM
File: home/auto/Desktop/Gorka/MERCURY400/san/ETXEBARRIA_JARDI_GORKA/Oct2009/vnmrs400_1029-bb921recSM-C13.fid
Pulse Sequence: s2pul
171.420
150.060
118.223
77.316
76.683
75.807
70.041
65.557
49.659
40.505
32.801
28.614
27.388
27.364
26.023
25.484
23.495
21.033
17.400
15.605
7.108
5.388
ppm

Part 2: To a stirred solution of alcohol **109a** (127 mg, 0.298 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (253 mg, 0.596 mmol) at rt. The reaction mixture was stirred for 30 min before it was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried and concentrated in *vacuo*. Purification by chromatography (0→5→10→25% EtOAc/hexanes) gave **116** (102 mg, 81%) as a colourless oil. R_f 0.6 (25% EtOAc/hexanes); $[\alpha]_D$ −12.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.61 (qd, *J* = 8.0, 2.0 Hz, 6H, Si($\underline{CH_2}CH_3)_3$), 0.76 (d, *J* = 6.4, 3H, H-28), 0.98 (t, *J* = 7.6 Hz, 9H, Si($CH_2\underline{CH_3})_3$), 1.00 (s, 3H, H-29), 1.15 (dm, *J*= 12.8 Hz, 1H, H-18$_{eq}$), 1.25-1.45 (m, 3H, H-22, H-17), 1.60 (m, 1H, H-21), 1.69 (ddd, *J*= 14, 7.2, 2.0 Hz, 1H, H-14), 1.76 (td, *J* = 12.8, 3.6 Hz, 1H, H-17$_{ax}$), 1.90 (m, 2H, H-14, H-16), 1.99 (m, 1H, H-21), 2.03 (s, 1H, OAc), 2.10 (td, *J* = 12.8, 5.2 Hz, 1H, H-18$_{ax}$), 2.33 (ddd, *J* = 16.8, 6.0, 2.4 Hz, 1H, H-13$_{eq}$), 2.40 (ddd, *J* = 16.8, 13.6. 5.2 Hz, 1H, H-13$_{ax}$), 3.95 and 4.01 (2dt, *J* = 10.8, 6.8 Hz, 2H, 2H-23), 4.17 (t, *J* = 2.4 Hz, 1H, H-19), 5.02 and 6.03 (2s, 1H each, 2H-10); ^{13}C NMR (100 MHz, HSQC) δ 5.3 (Si($\underline{CH_2}CH_3)_3$), 7.1 (Si($CH_2\underline{CH_3})_3$), 15.7 (C-28), 17.2 (C-29), 20.9 (OAc), 22.6 (C-22), 26.0 (C-17), 26.4 (C-18), 29.1 (C-21), 30.1 (C-14), 33.2 (C-16), 35.5 (C-13), 39.6 (C-15), 51.0 (C-20), 65.0 (C-23), 69.6 (C-19), 121.5 (C-10), 150.2 (C-11), 171.2 (CO), 203.5 (C-12); HRMS calcd for $C_{24}H_{48}NO_4Si$ ($M+NH_4^+$) 440.3191, found 440.3198.


H1 / Mercury-400F
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Usuari: san / Mostra: bb980f2
Nom: GORKA ETXEBARRIA JARDI
Data: 03/11/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Sample: bb980f2
File: home/auto/Desktop/Gorka/MERCURY400/san/ETXEBARRIA_JARDI_GORKA/Nov2009/vnmrs400_1103-bb980f2-H1.fid
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O
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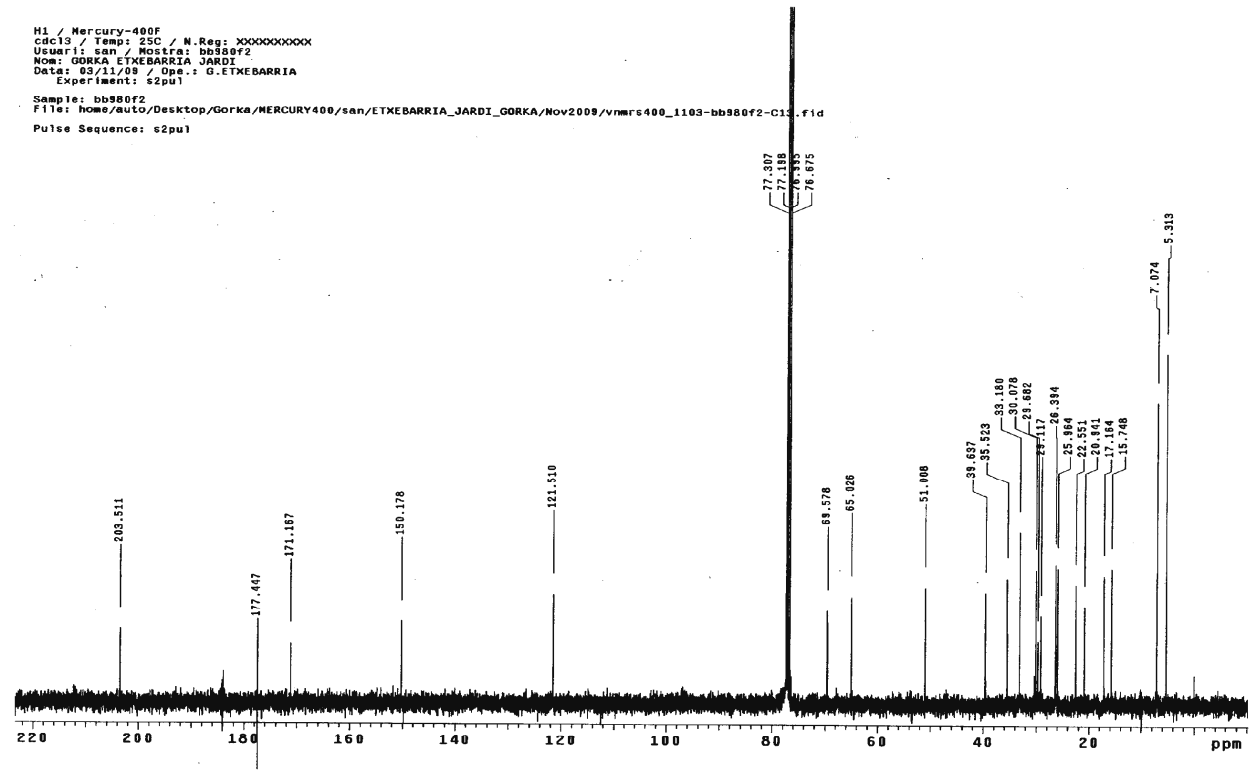
2.026
1.089
0.987
0.867
ppm


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb980f2
Nom: GORKA ETXEBARRIA JARDI
Data: 03/11/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Sample: bb980f2
File: home/auto/Desktop/Gorka/MERCURY400/san/ETXEBARRIA_JARDI_GORKA/Nov2009/vnmrs400_1103-bb980f2-C13.fid
Pulse Sequence: s2pul
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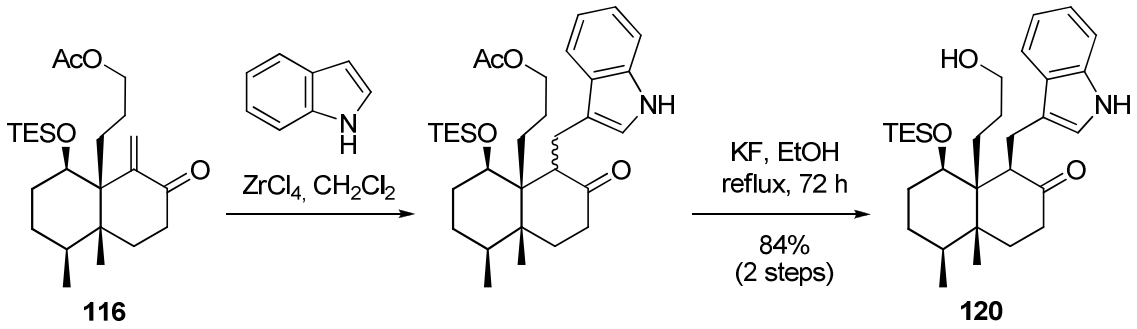
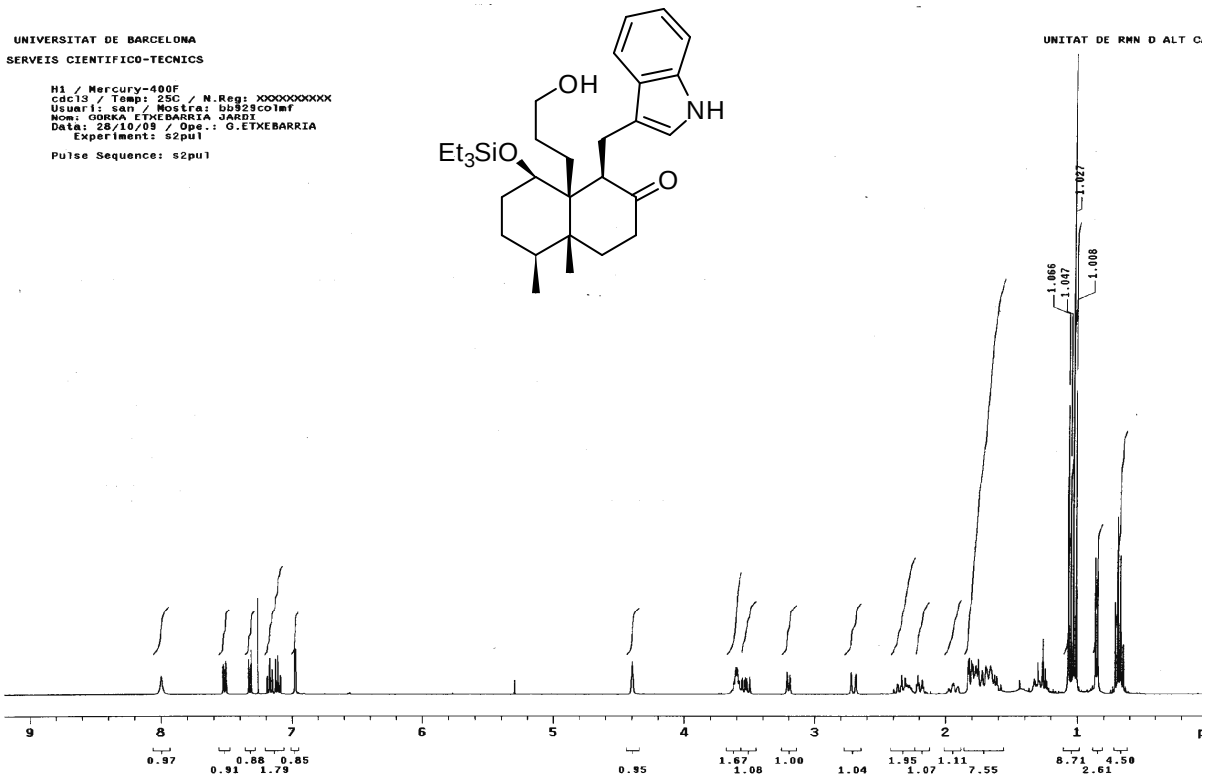
77.188
76.675
203.511
177.447
171.187
150.178
121.510
69.578
65.026
51.008
39.637
35.523
33.180
30.078
29.682
26.394
25.964
22.551
20.841
17.184
15.748
7.074
5.313
ppm

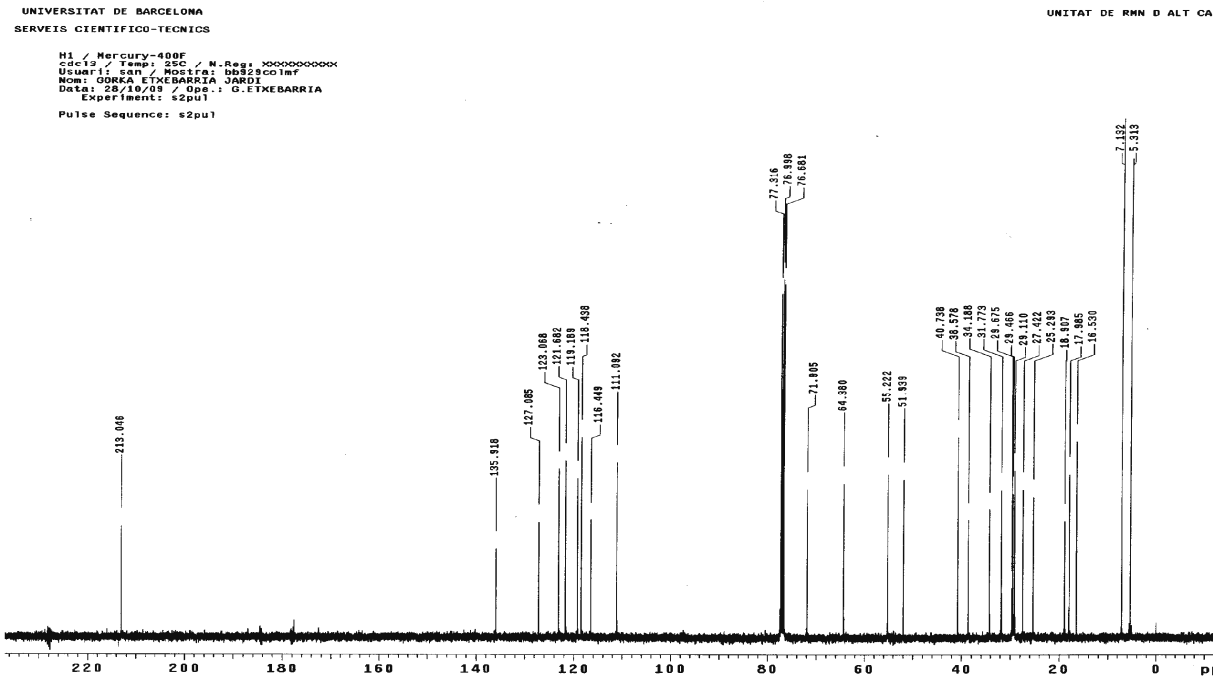
(1*R*,4a*R*,5*S*,8a*R*)-1-[(1*H*-Indol-3-yl)methyl]-8a-(3-hydroxypropyl)-4a,5-dimethyl-8-(triethylsilyloxy)octahydro-1*H*-naphthalen-2-one (120)



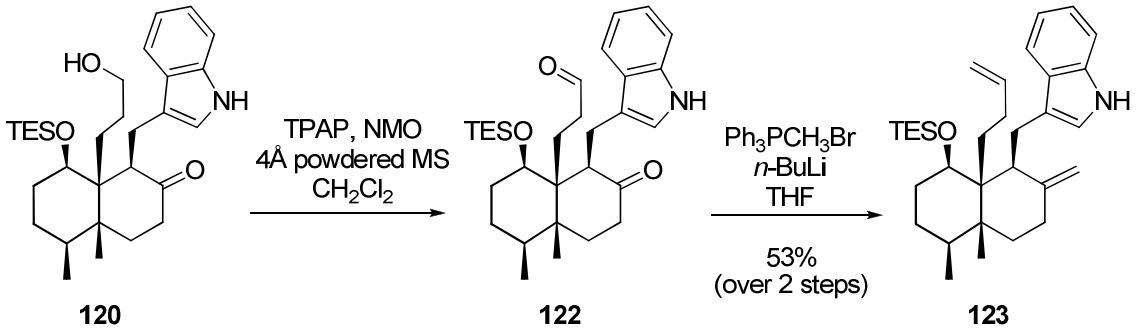
Part 1: To a solution of indole (53 mg, 0.454 mmol), and the enone **12** (64 mg, 0.151 mmol) in CH_2Cl_2 (1.5 mL) was added $ZrCl_4$ (7 mg, 0.03 mmol, 20 mol%) and the mixture was stirred at rt for 30 min. A further equivalent of indole (18 mg, 0.151 mmol) was added followed by further $ZrCl_4$ (7 mg, 0.03 mmol, 20 mol %) and stirred for 30 min. The mixture was added to a separating funnel along with ethyl acetate (25 mL) and washed with water (2 × 5 mL), dried (Na_2SO_4) and concentrated. Purification of the residue by chromatography (0→2.5→5→10→ 25% EtOAc/hexanes) gave **120** as a mixture of epimers as a turquoise oil. **Part 2:** The mixture of **120** was dissolved in EtOH (6.5 mL), potassium fluoride (132 mg, 2.27 mmol, 15 eq) was added, and the resulting mixture was heated at reflux for 72 h. After the reaction was cooled to room temperature, the mixture was partitioned between water and CH_2Cl_2 (20 mL), and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by chromatography (0→10→25→50% EtOAc/hexanes) gave **120** (63 mg, 84% for 2 steps) as a light yellow oil. R_f 0.4 (50% EtOAc/hexanes); $[\alpha]_D$ −26.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.68 (q, *J* = 7.6 Hz, 6H, Si$\underline{CH_2}CH_3)_3$), 0.85 (d, *J* = 6.8 Hz, 3H, H-28), 1.03 (t, *J* = 7.6 Hz, 9H, Si($CH_2\underline{CH_3})_3$), 1.07 (s, 3H, H-29), 1.2-1.4 (m, 2H, 1H-22, H-18$_{eq}$), 1.60-1.75 (m, 5H, 2H-14, 2H-17, 1H-22), 1.80 (m, 2H, H-21), 1.95 (tm, *J* = 13 Hz, 1H H-18$_{ax}$), 2.19 (dt, *J* = 13.2, 3.6 Hz, 1H, H-13$_{eq}$), 2.27 (m, 1H, H-16), 2.35 (dd, *J* = 13.2, 10.4 Hz, 1H, H-13$_{ax}$), 2.70 (d, *J* = 14 Hz, 1H, H-10), 3.20 (d, *J* = 8.8 Hz, 1H, H-11), 3.53 (dd, *J* = 14.5, 8.8 Hz, 1H, H-10), 3.60 (q, *J* = 5.2 Hz, 2H, H-23), 4.39 (s, 1H, H-19), 6.97 (d, *J* = 2.4 Hz, 1H, H-2), 7.11 (td, *J* = 8, 1.2 Hz, 1H, H-7), 7.17 (td, *J* = 8, 1.2 Hz, 1H, H-6), 7.32 (d, *J* = 8 Hz, 1H, H-8), 7.51 (d, *J* = 8 Hz, 1H, H-5), 8.00 (br s, 1H, NH); ^{13}C NMR (100 MHz, HSQC) δ 5.3 (Si($\underline{CH_2}CH_3)_3$, 7.1 (Si($CH_2\underline{CH_3})_3$, 16.5 (C-28), 18.0 (C-29), 18.9 (C-

10), 25.3 (C-22), 27.4 (C-17), 29.1 (C-14), 29.5 (C-18), 31.8 (C-16), 34.2 (C-21), 38.6 (C-13), 40.7 (C-15), 51.9 (C-20), 55.2 (C-11), 64.4 (C-23), 71.9 (C-19), 111.1 (C-8), 116.4 (C-2), 118.4 (C-3), 119.2 (C-4), 121.7 (C-5), 123.1 (C-6), 213.0 (C-12); HRMS calcd for $C_{30}H_{48}NO_3Si$ (MH^+) 498.3398, found 498.3379.



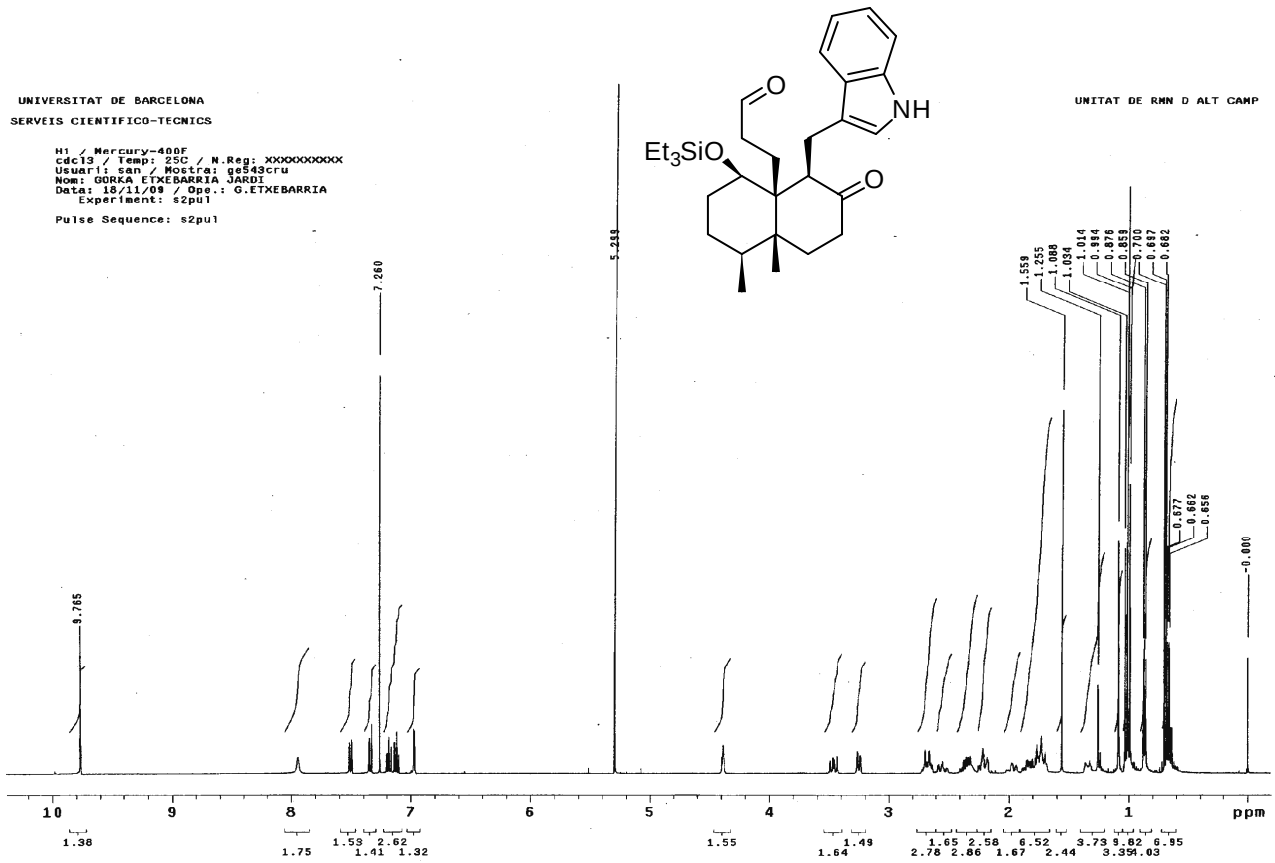


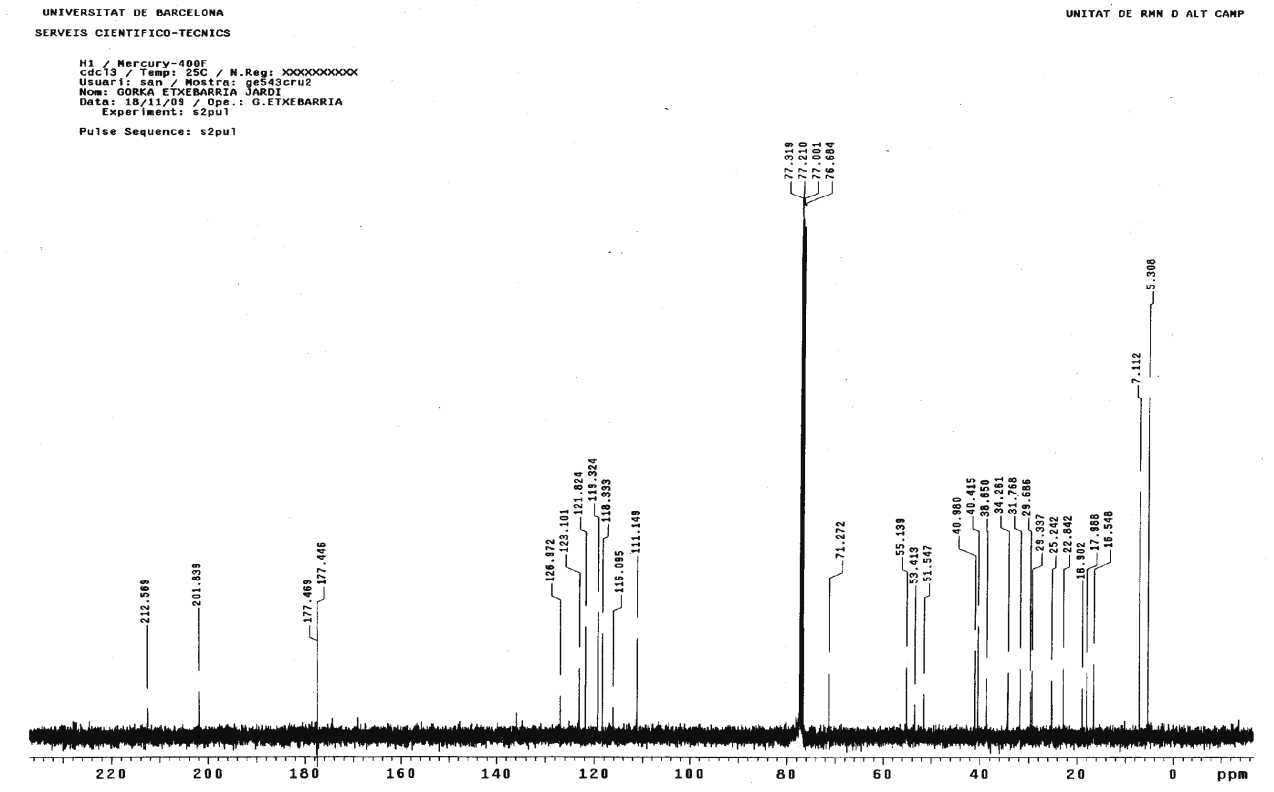
3-{[(1*S*,4a*R*,5*S*,8*R*,8a*R*)-8a-(But-3-enyl)-4a,5-dimethyl-2-methylene-8-(triethylsilyloxy)decahydronaphthalen-1-yl]methyl}-1*H*-indole (123)



120 **122** **123**

Part 1: To a solution of alcohol **120** (26 mg, 0.052 mmol) in CH_2Cl_2 (4 mL) was added 4Å powdered molecular sieves (60 mg), NMO (12 mg, 0.104 mmol). TPAP (2 mg, 0.005 mmol) was added in one portion and the resulting mixture was stirred for 15 min at rt. The dark solution was then filtered through a short pad of silica using CH_2Cl_2 as eluent. Evaporation of the solvent gave **122** as an off-white foam which was used directly in the next step. **Data for 122:** R_f 0.5 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.67 (qd, *J* = 7.6, 1.2 Hz, 9H, Si($CH_2\underline{CH_3}$)$_3$), 0.87 (d, *J* = 6.8 Hz, 3H, H-28), 1.01 (t, *J* = 8.0 Hz, 6H, Si($\underline{CH_2}CH_3$)$_3$), 1.09 (s, 3H, H-29), 1.20-1.40 (m, 2H, H-22, H-18$_{eq}$), 1.60-1.75 (m, 5H, 2H-14, 2H-17, H-22), 1.78 (m, 2H, 2H-21), 1.97 (tm, *J* = 13.0 Hz, 1H, H-18$_{ax}$), 2.20 (m, 1H, H-16), 2.33 (dd, *J* = 13.2, 10.4 Hz, 1H, H-13$_{ax}$), 2.67 (d, J = 14.0 Hz, 1H, H-11), 3.25 (d, J = 9.6 Hz, 1H, H-10), 3.46 (dd, J = 14.4, 9.6 Hz, 1H, H-10), 4.39 (br s, 1H, H-19), 6.97 (d, *J* = 2.4 Hz, 1H, H-2), 7.11 (td, *J* = 8.0, 1.2 Hz, 1H, H-7), 7.16 (td, *J* = 8.0, 1.2 Hz, 1H, H-6), 7.34 (d, *J* = 8.0 Hz, 1H, H-8), 7.50 (d, *J* = 8.0 Hz, 1H, H-5), 7.94 (br s, 1H, NH), 9.77 (t, *J* = 1.2 Hz, 1H, H-23); ^{13}C NMR (100 MHz, HSQC) δ 5.3 (Si($\underline{CH_2}CH_3$)$_3$), 7.1 (Si($CH_2\underline{CH_3}$)$_3$), 16.6 (C-28), 18.0 (C-29), 18.9 (C-10), 25.2 (C-17), 29.3 (C-14), 29.7 (C-18), 31.8 (C-16), 34.3 (C-21), 38.7 (C-13), 40.4 (C-15), 41.0 (C-22), 51.5 (C-20), 55.1 (C-11), 71.3 (C-19), 111.1 (C-8), 116.1 (C-3), 118.3 (C-5), 119.3 (C-6), 121.8 (C-7), 123.1 (C-2), 127.0 (C-4), 136.0 (C-9), 201.8 (C-23), 212.6 (C-12).


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge543cru
Nom: GORKA ETXEBARRIA JARDI
Data: 18/11/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
Et3SiO
O
NH
O
9.765
7.260
5.288
1.559
1.255
1.088
1.034
1.014
0.984
0.876
0.859
0.700
0.687
0.682
0.677
0.662
0.656
-0.000
10
9
8
7
6
5
4
3
2
1
ppm
1.38
1.75
1.53
1.41
2.62
1.32
1.55
1.64
1.49
1.65
2.78
2.58
2.86
6.52
1.67
3.73
2.44
9.82
3.35
6.95
4.03


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge543cru2
Nom: GORKA ETXEBARRIA JARDI
Data: 18/11/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
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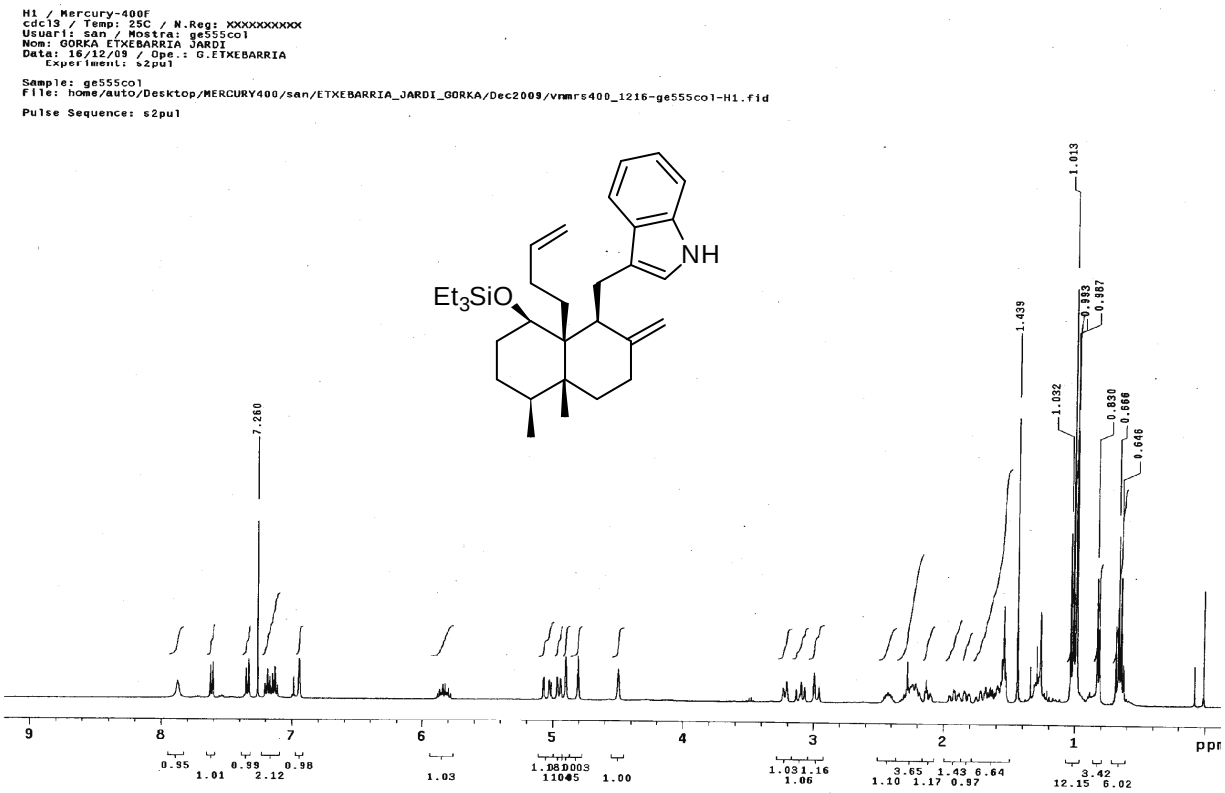
77.210
77.001
76.684
5.308
7.112
212.568
201.939
177.469
177.446
128.872
123.101
121.824
119.324
118.333
115.095
111.149
71.272
55.139
53.413
51.547
40.980
40.415
38.850
34.281
31.768
29.686
28.337
25.242
22.842
18.902
17.988
16.548
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Part 2: To a stirred solution of methyltriphenylphosphonium bromide (315 mg, 0.882 mmol) in THF (3 mL) at −78 °C was added n-BuLi (1.6 M in hexanes, 0.49 mL, 0.780 mmol). The resulting solution was stirred for 1 h at 0 °C before a solution of the dicarbonyl compound **122** (25 mg, 0.050 mmol) was added dropwise via syringe at −78 °C. After allowing the mixture to warm up to rt, it was heated to reflux for 16 h and then quenched by the addition of wet Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography (0→2.5% EtOAc in hexanes) gave **123** (15 mg, 53% over the 2 steps) as clear oil. **Data for 123:** R_f 0.3 (25% EtOAc/hexanes); $[\alpha]_D$ −5.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, COSY) δ 0.66 (q, *J* = 8.0 Hz, 9H, Si($CH_2\underline{CH_3}$)$_3$), 0.82 (d, *J* = 6.8, 3H, H-28), 0.99 (s, 3H, H-29), 1.01 (t, *J* = 7.6 Hz, 6H, Si($\underline{CH_2}CH_3$)$_3$), 1.24-1.35 (m, 2H, H-17, H-21), 1.50-1.70 (m, 3H, H-18, 2H-14), 1.72 (td, *J* = 12.8 Hz, 1H, H-17), 1.84 (tm, *J* = 13.6 Hz, 1H, H-21), 1.92 (tm, *J* = 13.2 Hz, 1H, H-18), 2.12 (ddd, *J* = 12.8, 3.6, 3.2 Hz, 1H, H-13), 2.16-2.34 (m, 3H, H-13, 2H-22), 2.43 (m, 1H, H-16), 2.98 (d, J = 15.4 Hz, H-10), 3.10 (dd, J = 15.4, 10.0 Hz, H-10), 3.22 (d, J = 10.4 Hz, 1H, H-11), 4.50 (s, 1H, H-19), 4.90 and 4.81 (2s, 1H each, 2H-27), 4.95 (d, *J* = 10.4 Hz, 1H, H-24), 5.05 (dd, *J* = 16.8, 1.6 Hz, 1H, H-24), 5.17 (dm, *J* = 16.8 Hz, 1H, H-23), 6.94 (d, *J* = 2.0 Hz, 1H, H-2), 7.13 (dd, *J* = 7.6, 6.8 Hz, 1H, H-6), 7.19 (dd, *J* = 8.0, 6.8 Hz, 1H, H-7), 7.34 (d, *J* = 8.0 Hz, 1H, H-8), 7.61 (d, *J* = 7.6 Hz, 1H, H-5), 7.88 (br s, 1H, H-1); ^{13}C NMR (100 MHz, HSQC) δ 5.4 (Si($\underline{CH_2}CH_3$)$_3$), 7.2 (Si($CH_2\underline{CH_3}$)$_3$), 16.8 (C-28), 18.5 (C-29), 21.4 (C-10), 25.6 (C-17), 29.0 (C-18), 29.5 (C-21), 29.7 (C-22), 30.3 (C-18), 31.1 (C-16), 33.7 (C-13), 34.6 (C-14), 41.0 (C-15), 45.5 (C-11), 48.4 (C-20), 70.7 (C-19), 106.9 (C-27), 111.0 (C-8), 113.6 (C-24), 117.3 (C-3), 118.6 (C-5), 119.1 (C-6), 121.1 (C-2), 121.8 (C-7), 127.7 (C-4), 135.9 (C-9), 140.5 (C-23), 149.3 (C-12); HRMS calcd for $C_{32}H_{48}NOSi$ ($M-H^+$) 490.3511, found 490.3505.


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge555col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/12/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Sample: ge555col
File: home/auto/Desktop/MERCURY400/san/ETXEBARRIA_JARDI_GORKA/Dec2009/vnmrs400_1216-ge555col-H1.fid
Pulse Sequence: s2pul
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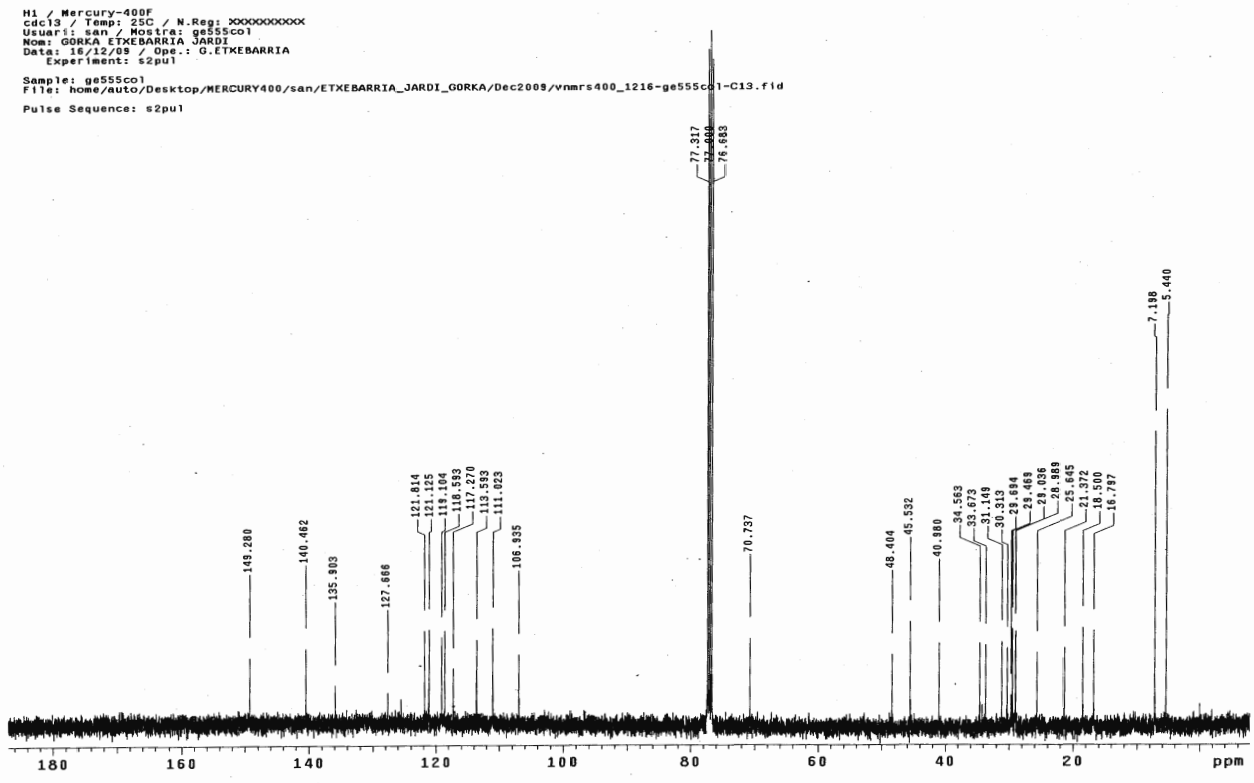
1.439
1.032
1.013
0.993
0.987
0.830
0.666
0.646
ppm


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge555col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/12/09 / Ope.: G.ETXEBARRIA
Experiment: s2pul
Sample: ge555col
File: home/auto/Desktop/MERCURY400/san/ETXEBARRIA_JARDI_GORKA/Dec2009/vnmrs400_1216-ge555col-C13.fid
Pulse Sequence: s2pul
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76.683
149.280
140.462
135.903
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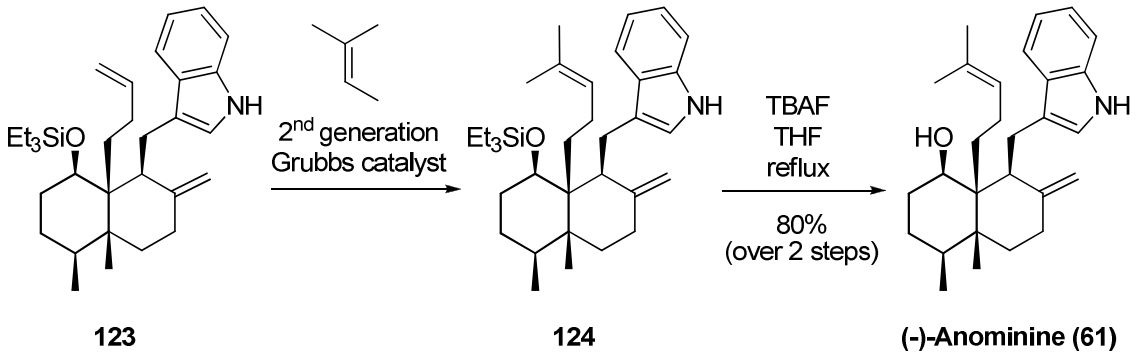
119.104
118.593
117.270
113.593
111.023
106.335
70.737
48.404
45.532
40.380
34.563
33.673
31.149
30.313
29.694
29.466
29.036
28.389
25.645
21.372
18.500
16.797
7.198
5.440
ppm

(1*R*,4*S*,4a*R*,8*S*,8a*R*)-8-[(1*H*-indol-3yl)methyl]-4,4a-dimethyl-7-methylene-8a-(4-methylpent-3-enyl)decahydronaphthalen-1-ol

Anominine (61)

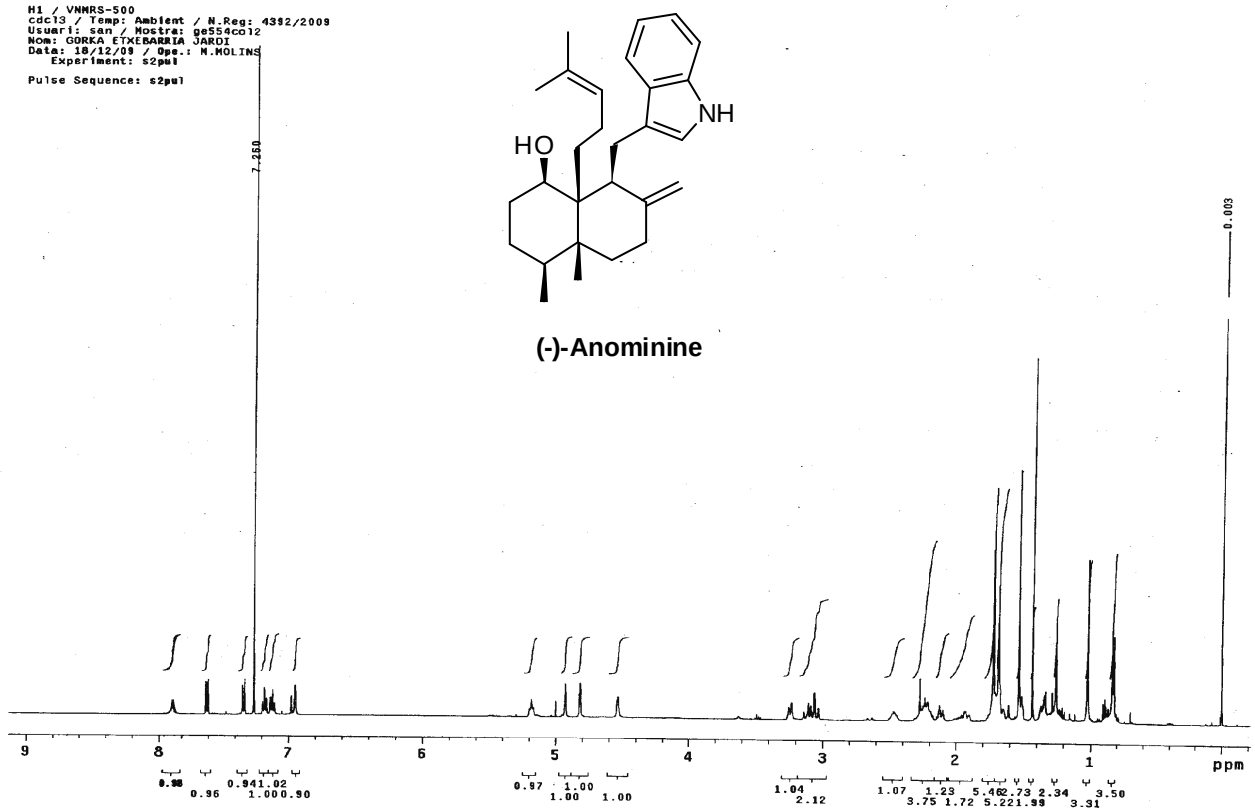


123 **124** **(-)-Anominine (61)**

Part 1: To a solution of alkene **123** (11 mg, 0.022 mmol) in 2-methyl-2-butene (0.1 mL) in a screw-top vial was added Grubbs 2nd generation catalyst (2 mg, 0.002 mmol). The vial was flushed with argon, sealed with parafilm and stirred at rt for 2 days. The resulting solution was filtered through a short pad of silica eluting with CH_2Cl_2 and the solvent was evaporated under reduced pressure to give 10 mg of **124** which was used directly in the next step.

Part 2: To a solution of silyl ether **124** in THF (5 mL) was added TBAF (1 M in THF, 0.1 mL) and the resulting mixture was refluxed for 16 h. After the mixture was cooled to room temperature, the reaction was quenched with water and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography (2.5% EtOAc in hexanes) gave **61** (7 mg, 80%) as a clear oil.

R_f 0.4 (25% EtOAc/hexanes); $[\alpha]_D$ −21.0 (*c* 0.3, MeOH), Lit: $[\alpha]_D$ +23.6 (*c* 0.85, MeOH); ^{1}H NMR (400 MHz, COSY) δ 0.83 (d, *J* = 6.5, 3H, H-28), 1.03 (s, 3H, H-29), 1.24-1.38 (m, 2H, H-17, H-21), 1.48-1.54 (m, 1H, H-14), 1.62-1.76 (m, 4H, H-14, H-17, H-18, H-21), 1.69 (s, 3H, H-25), 1.72 (s, 3H, H-26), 1.93 (m, 1H, H-18), 2.11 (ddd, *J* = 13.0, 3.5, 3.0 Hz, 1H, H-13), 2.23 (m, 3H, H-13, 2H-22), 2.47 (m, 1H, H-16), 3.05 (d, J = 11.2 Hz, H-10), 3.10 (dd, J = 11.2, 7.6 Hz, H-10), 3.24 (br d, J = 7.6 Hz, 1H, H-11), 4.54 (s, 1H, H-19), 4.82 (s, 1H, H-27), 4.93 (s, 1H, H-27), 5.19 (dd, *J* = 7.5, 7.0 Hz, 1H, H-23), 6.95 (br s, 1H, H-2), 7.12 (dd, *J* = 7.5, 7.0 Hz, 1H, H-6), 7.18 (dd, *J* = 7.5, 6.5 Hz, 1H, H-7), 7.34 (d, *J* = 8.0 Hz, 1H, H-8), 7.61 (d, *J* = 7.5 Hz, 1H, H-5), 7.88 (br s, 1H, H-1); ^{13}C NMR (100 MHz, HSQC) δ 16.6 (C-28), 17.8 (C-25), 18.7 (C-29), 21.4 (C-10), 23.8 (C-22), 25.4 (C-17), 25.7 (C-26), 28.7 (C-18), 29.2 (C-21), 31.1 (C-16), 33.5 (C-13), 34.4 (C-14), 40.8 (C-15), 45.8 (C-11), 47.9 (C-20), 70.0 (C-19), 107.7 (C-27), 111.0 (C-8), 117.1 (C-3), 118.6 (C-5), 119.1 (C-6), 121.2 (C-2), 121.8 (C-7), 125.8 (C-23), 127.7 (C-4), 131.2 (C-24), 135.9 (C-9), 148.9 (C-12); HRMS calcd for $C_{28}H_{38}NO$ ($M-H^+$) 404.2959, found 404.2952.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Experiment: s2pul
Pulse Sequence: s2pul
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HO
NH
(-)-Anominine
9
8
7
6
5
4
3
2
1
ppm
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0.941.02
1.000.90
0.97
1.00
1.00
1.00
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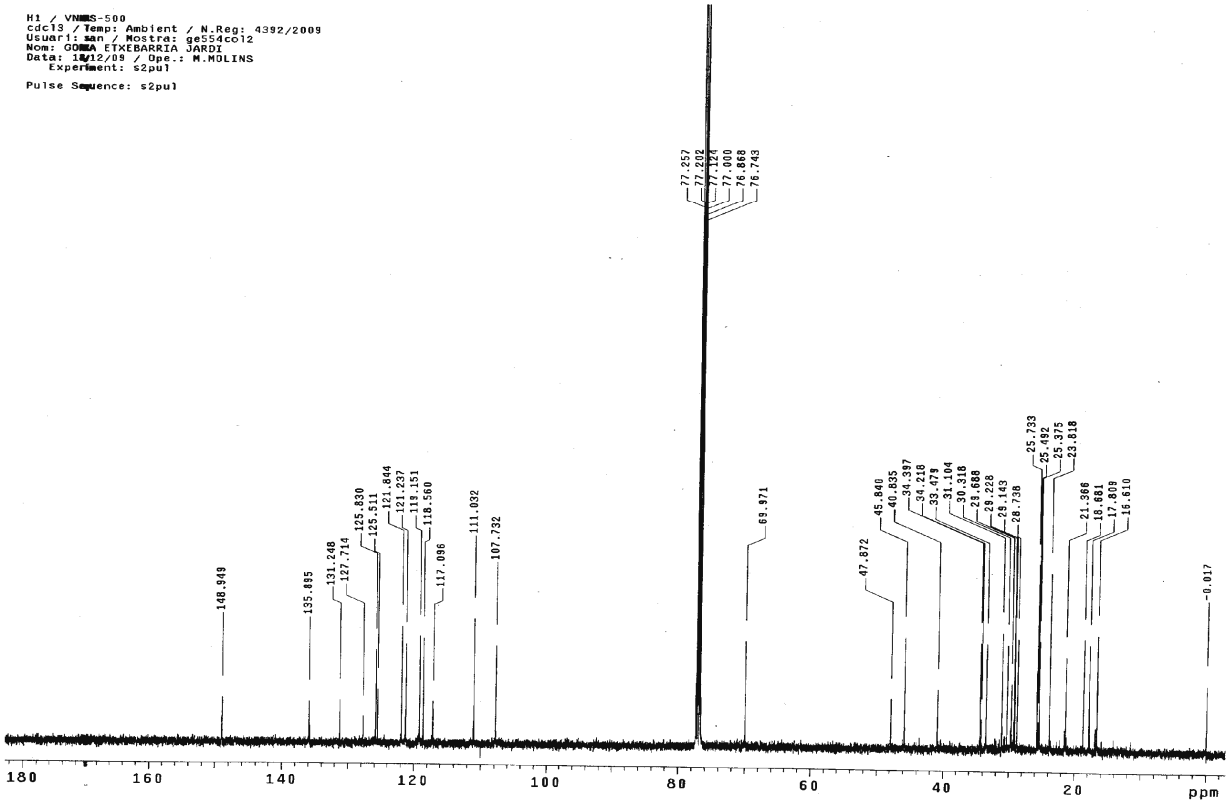
3.31
3.50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Pulse Sequence: s2pul
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119.151
118.560
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47.872
45.840
40.835
34.397
34.218
33.479
31.104
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29.143
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25.492
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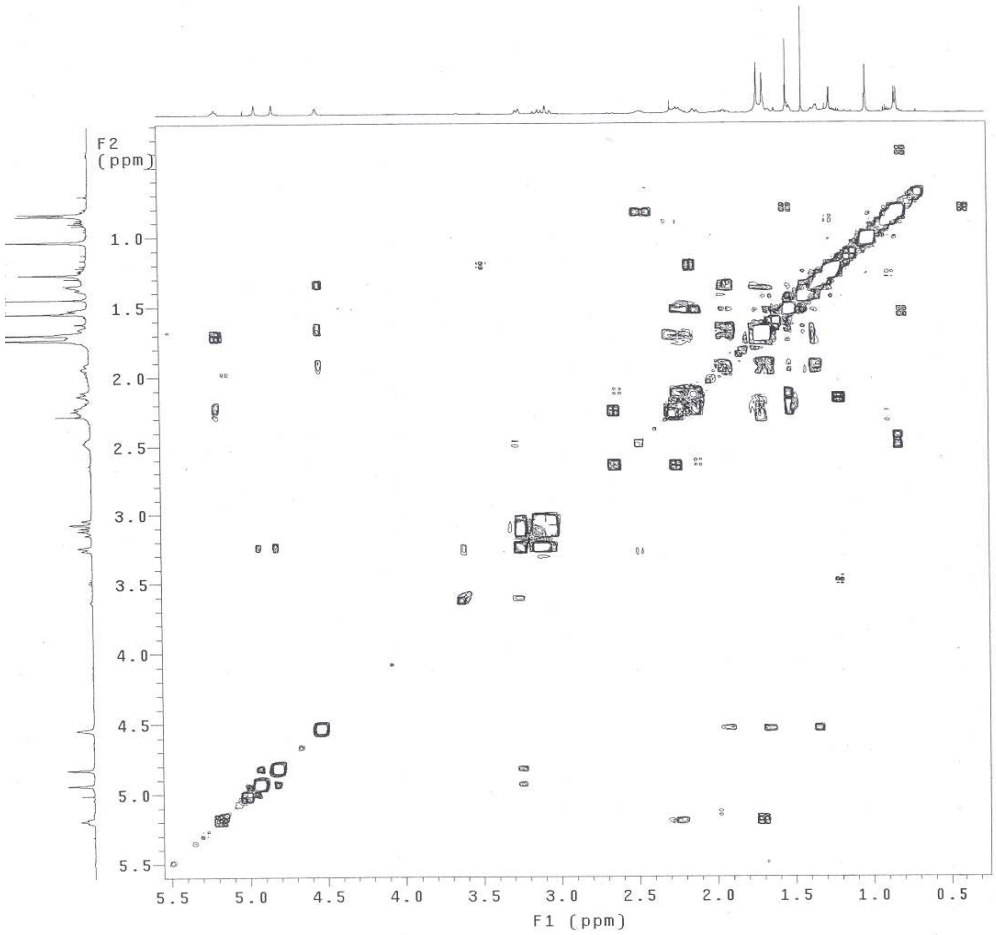
ppm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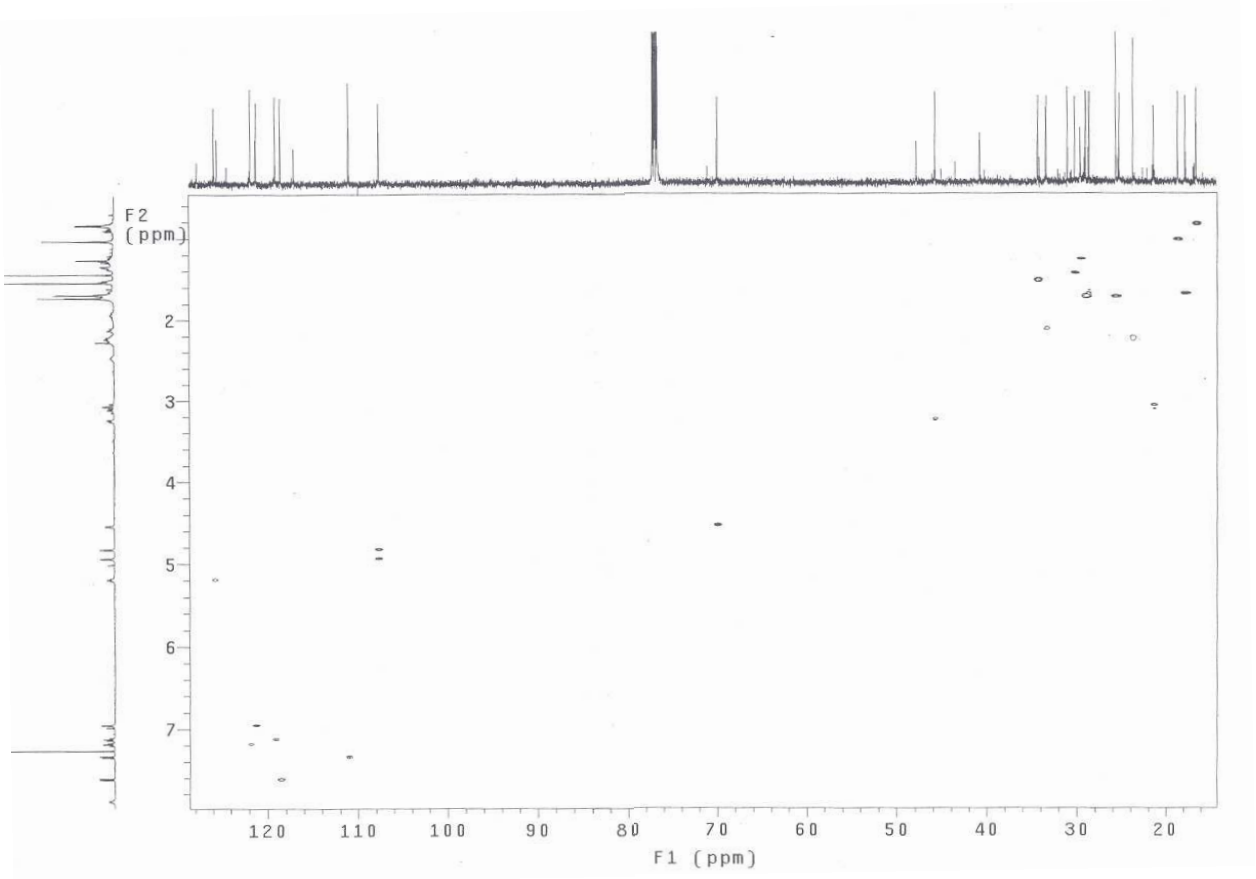
F1 (ppm)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(ppm)
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6
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F1 (ppm)

CHAPTER 7.

COMPENDIUM OF PUBLICATIONS

Polycyclic framework synthesis of anominine and tubingensin A indole diterpenoids†

Ben Bradshaw, Gorka Etxebarria-Jardí and Josep Bonjoch*

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A highly congested decalin embodying an α-methylene ketone is synthesized in 11 steps from the Wieland–Miescher ketone and efficiently converted to the polycyclic frameworks of anominine and tubingensin A, which constitutes the first approach to the skeleton of these indole diterpenoids.

Introduction

Fungal sclerotia often contain unique antiinsectan metabolites that can offer protection against predation.[1] Among them, anominine (**1**),‡[2,3] isolated from *Aspergillus nomius*, shows potent activity against the crop pest *Helicoverpa zea*, and tubingensin A (**2**),[4] isolated from *A. tubingensis*, displays *in vitro* antiviral activity against the herpes simplex virus type 1 (Fig. 1). Structurally, **1** is made up of a *cis*-decalin embodying five stereogenic centres, two of which are contiguous quaternary carbons, and **2** shows a unique

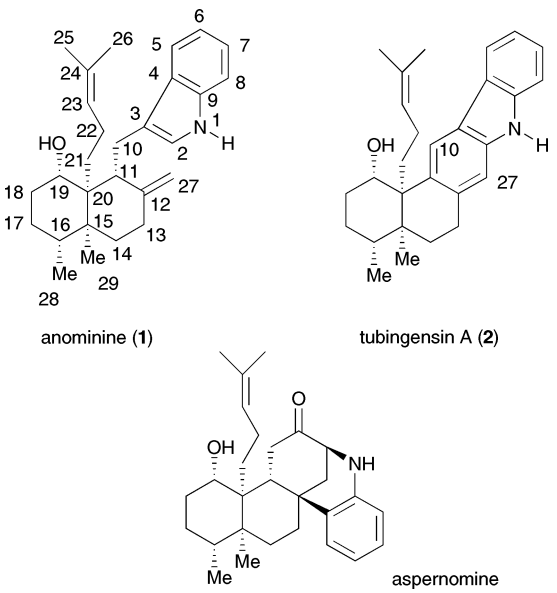
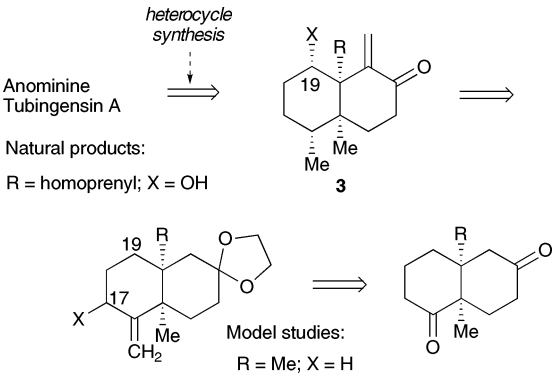


Fig. 1 Heterocyclic diterpenoids from *Aspergillus* sp.

9*H*-octahydronaphtho[2,1-*b*]carbazole ring system.[5] The related compound aspernomine,[6] also isolated from *Aspergillus nomius*, contains the same decalin motif but features a novel bridged tetrahydroquinoline ring system, which may arise biogenetically from a rearrangement of an oxidized form of anominine.[7] Like anominine it is an antiinsectan metabolite and in addition exhibits significant cytotoxicity towards three human solid tumour cell lines.

Given the biological activities and the novel and synthetically challenging structures of these indole diterpenoids, possessing a prenylated sesquiterpenoid carbon skeleton, together with no previously reported approaches,[8] we embarked on a program of research to evaluate their total synthesis.

Based on our experience in the synthesis of unusual terpenoids such as nakamurol A[9] and xylarenal A,[10] we identified enone **3** (Scheme 1) as a key synthetic intermediate. We planned to explore the usefulness of its exocyclic α-methylene ketone unit for incorporating the heterocyclic ring fragment linked or fused to the decalin core of **1** and **2**.



Scheme 1 Outline of a possible synthesis of anominine and tubingensin A.

We have previously reported[9] the synthesis of **3** (R = Me, X = H) *via* a four step sequence (48%) from intermediate **A**, which in turn was prepared from (*R*)-3-methylcyclohexanone (8 steps, 30% overall yield).[11] However, our first generation synthesis of **3** did not allow the introduction of a hydroxyl group at C-19, which precluded its extension to the total synthesis of anominine and related diterpenoids. Moreover, an analogous approach (**A** → **B** → **3** R = Me, X = OH) did not allow the introduction of the quaternary centre. The installation of a hydroxyl group at

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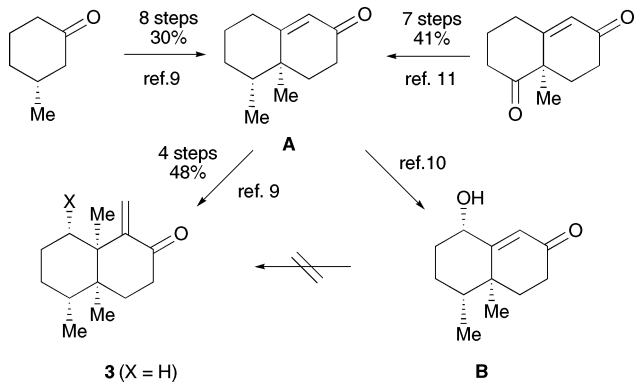
† Electronic supplementary information (ESI) available: ^{13}C NMR chemical shifts of all compounds (Table 1) and copies of selected ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b718280e

‡ Diterpenoid **1** was named nominine when isolated in 1989. However, in 1982 the same name had been given to another natural product isolated in 1956, the hetisine-type aconite alkaloid nominine (ref. 3*a*). Furthermore, the original nominine has recently been synthesized (ref. 3*b*). After consulting Prof. Gloer (Iowa University) it was decided to change the name of the indole diterpenoid **1** to anominine. We have used Gloer's numbering of the anominine skeleton (ref. 2) throughout the discussion.

C(19) from **A** to give **B** has been previously reported by us (Scheme 2), but initial attempts to add various organometallics upon a hydroxyl-protected derivative of **B** did not result in any 1,4-addition. This was not altogether surprising given the type of compounds involved and the known effects of even remote oxygen atoms from the reactive site.[12]



Scheme 2 Previous results.

We therefore sought to design a second-generation synthesis of enone **3** to incorporate a degree of flexibility that would enable us to introduce later the C-19 hydroxyl and homoprenyl group.[13,14] In this paper we disclose our overall synthetic strategy and its successful application to the synthesis of the polycyclic frameworks of anominine and tubingensin A.

Results and discussion

A second generation synthesis of enone 3

The new synthesis of enone **3** (Scheme 3) starts from Wieland–Miescher ketone (**4**),[15] the quaternary centre at C-20 being introduced by conjugate addition of methyl cuprate.[16] Chemoselective protection of the less hindered carbonyl of **5** was accomplished using 2-ethyl-2-methyl-1,3-dioxolane in acid medium. Wittig methylenation of the remaining carbonyl group in **6** gave the *cis*-dimethyl decalin **7**. The diastereoselectivity observed in the initial hydrogenation (H_2, Pd-C, solvent) of **7** was the opposite of what was desired, the *trans* derivative **8a** being the main compound formed (Fig. 2). However, a reversed selectivity was found when ketone **9**, obtained by hydrolysis of **7** (10% HCl aq), was used as the substrate. The *cis*–*trans* ratio was further improved by changing the catalyst from Pd to Pt and using CH_2Cl_2 as the solvent, which resulted in a 3 : 1 ratio of decalones **10** and **8b**, respectively, in quantitative yield. Hoping that an endocyclic rather than exocyclic double bond might increase the selectivity further, we attempted the hydrogenation of **11**,[17] however this failed, probably due to extreme steric hindrance. Since compounds **10** and **8b** could not be separated by chromatography, we decided to prepare the required

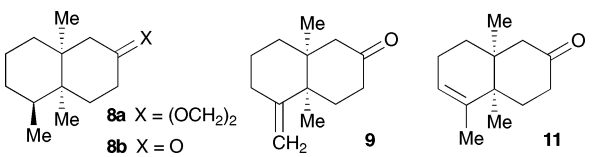
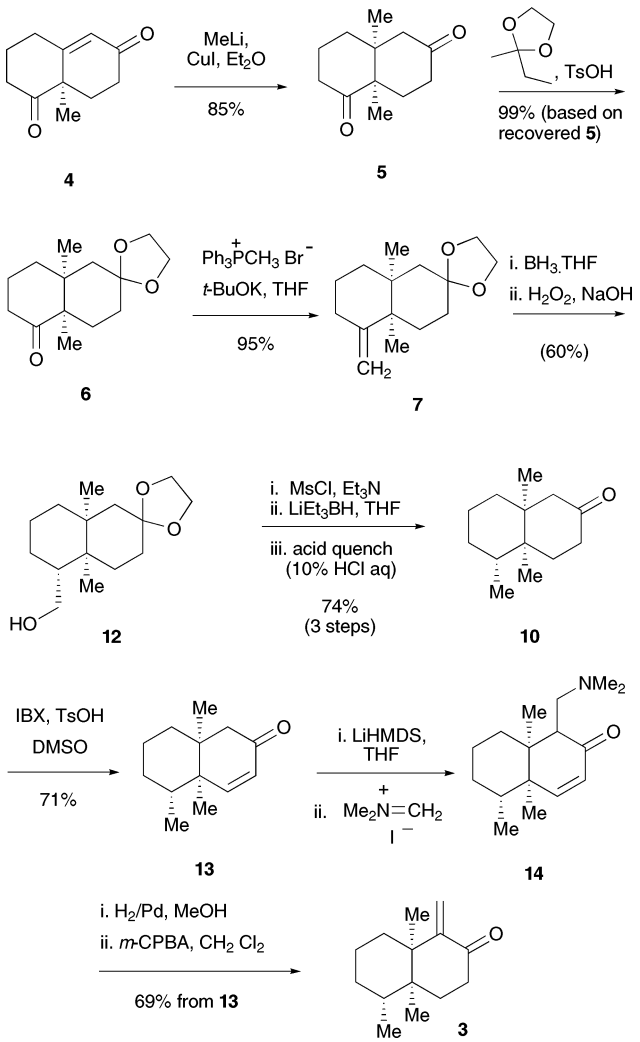


Fig. 2



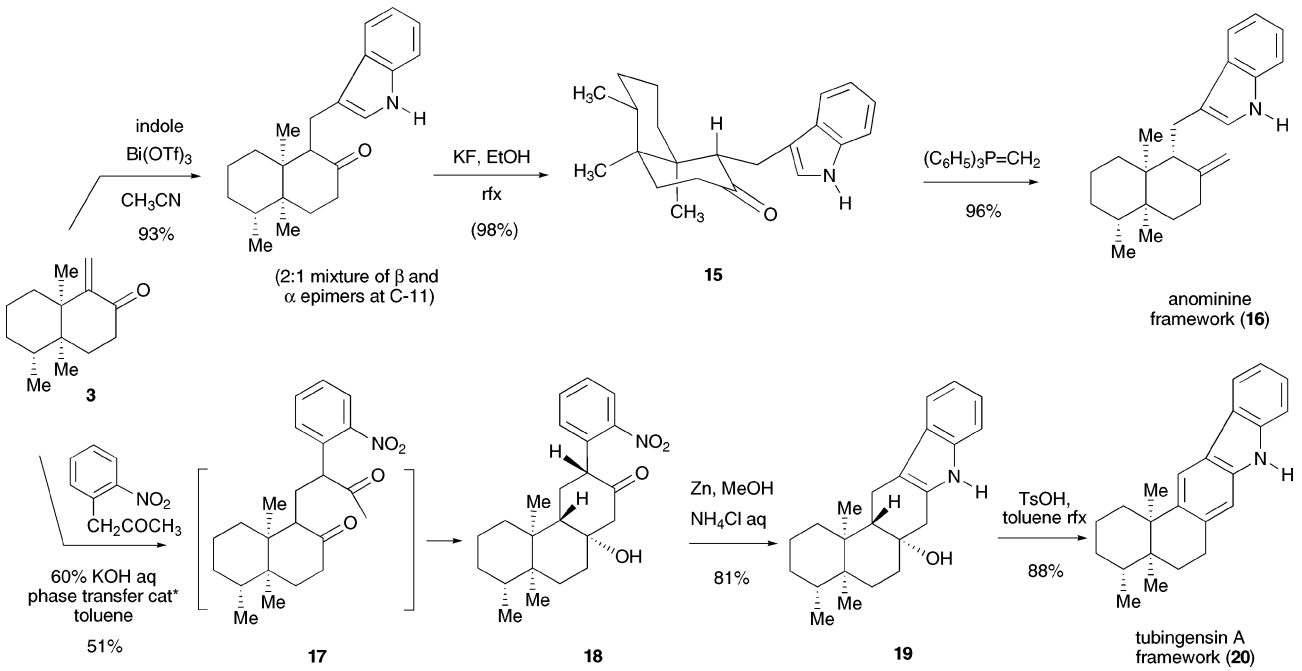
Scheme 3 A second-generation synthesis of enone **3**.

intermediate **10** by hydroboration of **7** followed by reduction of the corresponding alcohol. This gave an easily separated 4 : 1 mixture of alcohols **12** and its epimer (not shown) in 75% overall yield. Removal of the hydroxyl group was carried out efficiently by mesylation, Superhydride reduction and acid quench to give the stereochemically pure ketone **10**.

Oxidation of **10** with IBX (*o*-iodoxybenzoic acid)[18] formed the enone **13**, which effectively blocked the most accessible methylene of the ketone group of **10**. Attempts to alkylate the α′-position of the ketone (*i.e.* at C-11) was problematic probably due to the extreme steric hindrance exerted by the three proximal methyl substituents, predominantly leading to *O*- rather than *C*-alkylation. Fortunately, reaction of the lithium enolate of **13** with Eschenmoser's salt, hydrogenation of the crude polar amine **14** followed by *m*-CPBA oxidation generated the exocyclic enone **3**. We were thus able to synthesize the key intermediate **3** in 11 steps and 18% overall yield from the Wieland–Miescher ketone.

Synthesis of anonimine and tubingensin A polycyclic skeletons

The remaining challenge was to elaborate the heterocyclic rings to access the polycyclic skeletons of anominine and tubingensin A. Conjugate addition of indole to enone **3** in the presence of



Scheme 4 Synthesis of anominine and tubingensin A polycyclic skeletons.

bismuth triflate[19] smoothly generated the coupled product **15** in excellent yield as a 1 : 2 mixture of diastereomers favouring the undesired stereosiomer (Scheme 4). Isomerisation of the epimeric mixture with KF in refluxing EtOH provided the all *cis* diastereomer in quantitative yield. Wittig homologation completed the synthesis of the anominine model **16**.

We then focused our attention on the tubingensin skeleton using the same common enone **3** intermediate. This enone reacted with 1-(2-nitrophenyl)propan-2-one[20] in a biphasic system (toluene/60% KOH aq) with the addition of a chiral phase transfer catalyst§ under the conditions developed by Vandewalle and Nerinckx.[21] Initially, the reaction progressed *via* a conjugate addition (*i.e.* **17**) followed by Robinson annulation to give the cyclohexanone ring as a single diastereomer **18** without elimination of the hydroxyl to form the enone. We believe that the catalyst acts only as a phase transfer agent and is not solely responsible for the stereocontrol, since we isolated intermediate **17** as a complex mixture of diastereomers. This suggests that it is the KOH that epimerises the mixture under thermodynamic control to produce the single stable diastereomer **18**. While the stereogenic centres formed in this reaction are not relevant to the synthesis of the tubingensin A framework, it should be noted that the stereochemistry at C-11 is the same as that of aspernomine. This would suggest that this ring structure could also be accessed by modifying this methodology. Reduction of **18** with Zn smoothly produced the indole **19** in 81% yield. Finally, to complete the synthesis, the tertiary alcohol was eliminated in the presence of TsOH in refluxing toluene, the dihydro intermediate formed undergoing spontaneous oxidation under the reaction conditions. We found that if the reaction was worked up too early after tlc analysis showed that no starting material remained, a mixture of **20** and dihydro derivatives analogous to 10,27-dihydrotubingensin A[5] was isolated. Stirring this mixture overnight in chloroform, exposed to the air, was sufficient to complete the oxidation.

§ *N*-(4-trifluoromethylbenzyl)cinchoninium bromide

Summary and conclusions

In summary, we have completed a synthesis of the polycyclic frameworks of anominine and tubingensin A. As a prelude to working on their total synthesis, we have demonstrated the viability of exocyclic enones as ideal molecular scaffolds for the incorporation of the heterocyclic fragments of these natural products. We have also reported a modified synthesis of the highly congested decalin **3**, which should allow the incorporation of the functionality required for the common component of these terpenoid natural products. Application of this methodology to the total synthesis of these indole diterpenoids is currently in progress and the results will be reported in due course.

Experimental section

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 anisaldehyde. Chromatography refers to flash chromatography 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 $MgSO_4$, except where stated otherwise. 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 (δ) from Me_4Si.

Terpene biogenetic numbering was used in the NMR assignation of all compounds and the IUPAC nomenclature is followed in the headings. Table 1 with all ^{13}C NMR data is found in the ESI.†

(4*aRS*,8*aSR*)-4*a*,8*a*-Dimethyl-3,4,4*a*,5,8,8*a*-hexahydro-2*H*,7*H*-naphthalene-1,6-dione 5

To a dispersion of copper iodide (32 g, 0.168 mol) in Et_2O (700 mL) at 0 °C was added MeLi (1.6 M in Et_2O, 175 mL, 0.280 mol), and the mixture was stirred for 1 h. A solution of enone **4** (10 g, 0.056 mol) in Et_2O (100 mL) was added, and the reaction was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution and stirred for 2 h, the aqueous layer was separated and extracted with EtOAc (5 × 100 mL), the combined organic layers were washed with saturated aqueous NH_4Cl in 20% aqueous NH_3 (5 : 1) and brine, dried, and concentrated. Purification of the residue by chromatography (10% EtOAc–hexane) gave diketone **5** (9.15 g, 85%) as a white solid; mp 129–131 °C; ^1H NMR (300 MHz, COSY) 0.98 (s, 3H, Me-29), 1.21 (s, 3H, Me-21), 1.45 (ddd, $J = 11.0, 11.0, 5.0$ Hz, 1H, H-19$_{ax}$), 1.55 (ddd, $J = 13.7, 11.1, 5.6$ Hz, 1H, H-14$_{ax}$), 1.85–1.95 (m, 3H, 2H-18, H-19$_{eq}$), 1.97 (dd, $J = 14.5, 2.1$ Hz, 1H, H-11$_{eq}$), 2.26 (dddd, $J = 15.2, 7.2, 5.6, 3.2$ Hz, 1H, H-13$_{eq}$), 2.39 (d, $J = 14.5$ Hz, 1H, H-11$_{ax}$), 2.40 (dm, $J = 14.0$ Hz, 1H, H-17$_{eq}$), 2.42 (dm, $J = 13.5$ Hz, 1H, H-14$_{eq}$), 2.57 (dddd, $J = 14.4, 11.0, 6.6, 1.5$ Hz, 1H, H-13$_{ax}$), 2.58 (m, 1H, H-17$_{ax}$); ^{13}C NMR (75 MHz, DEPT, HSQC) 21.2 (C-29), 21.9 (C-18), 23.3 (C-21), 31.5 (C-14), 34.5 (C-19), 37.1 (C-17), 38.8 (C-13), 44.8 (C-20), 50.8 (C-11), 51.8 (C-15), 211.7 (C-16), 214.9 (C-12); HRMS calcd for $C_{12}H_{19}O_2$ (MH^+) 195.1379, found 195.1381.

(4*aRS*,8*aSR*)-4*a*,8*a*-Dimethyl-3,4,4*a*,5,8,8*a*-hexahydro-2*H*,7*H*-naphthalene-1,6-dione 6-monoethylene acetal 6

A solution of diketone **5** (3.3 g, 16.99 mmol) and *p*-toluenesulfonic acid monohydrate (162 mg, 0.85 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (10.6 mL, 85 mmol) was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 100 mL), the combined organic layers were washed with brine, dried and concentrated. Purification of the residue by chromatography (5% EtOAc) gave **6** (2.7 g, 68%) as a clear oil, followed by recovered starting material **5** (1.05 g): overall yield 99% based on recovered starting material: ^1H NMR (300 MHz) 0.97 (s, 3H), 1.03 (s, 3H), 1.35–1.45 (m, 2H), 1.50–1.70 (m, 5H), 1.75–1.85 (m, 2H), 2.10 (m, 1H), 2.35 (m, 2H), 3.88 (s, 4H); ^{13}C NMR (75 MHz, DEPT) 20.5 (C-29), 21.7 (C-18), 24.8 (C-21), 30.0 (C-19), 31.6 (C-14), 34.8 (C-13), 37.7 (C-17), 41.0 (C-20), 43.6 (C-11), 51.9 (C-15), 64.2 and 64.4 (OCH_2), 109.6 (C-12), 216.2 (C-16); HRMS calcd for $C_{14}H_{23}O_3$ (MH^+) 239.1641, found 239.1642.

(4*aRS*,8*aSR*)-4*a*,8*a*-Dimethyl-5-methylene-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one ethylene acetal 7

A solution of methyltriphenylphosphonium bromide (20.0 g, 56.5 mmol) and potassium *tert*-butoxide (6.3 g, 56.5 mmol) in toluene (120 mL) was stirred at reflux for 1 h. Ketone **6** (2.7 g, 11.25 mmol) in toluene (40 mL) and was then added dropwise to the above solution and the resulting mixture was stirred at reflux for 4 h. The reaction was quenched by the addition of acetone (3 mL), stirring at 100 °C for 30 min and then by the addition of water (100 mL). The reaction mixture was extracted with Et_2O (3 × 200 mL), the combined organic layers were washed with brine, dried and concentrated. Purification of the residue by chromatography (1% EtOAc–hexane) gave alkene **7** (2.5 g, 95%) as a clear oil: ^1H NMR (300 MHz)¶ 0.90 (br s, 3H), 1.08 (s, 3H), 1.43–1.84 (m, 8H), 2.12–2.37 (m, 4H), 3.83–4.06 (m, 4H), 4.73 and 4.78 (2 s, 1H each); ^{13}C NMR (75 MHz, DEPT) 20.1 (Me), 22.5 (C-18), 23.2 (Me), 27.3 (C-19), 31.2 (C-14), 32.3 (C-15), 32.9 (C-17), 35.8 (C-13), 38.3 (C-20), 41.8 (C-11), 63.5 and 63.7 (OCH_2), 107.9 (C-28), 108.1 (C-12), 132.1 (C-16); HRMS calcd for $C_{15}H_{25}O_2$ (MH^+) 237.1849, found 237.1853.

Hydrogenation of 9

Platinum(IV) oxide hydrate (20 mg, 0.06 mmol) was added to a stirred solution of ketone **9** (100 mg, 0.57 mmol) in CH_2Cl_2 (10 mL). The mixture was flushed with hydrogen and stirred under pressure (450 psi) in a sealed apparatus at room temperature for 16 h. The mixture was filtered through Celite, dried and concentrated to give ~100 mg of material. The composition of the mixture was 3 : 1 in favour of the all-*syn* epimer as found by ^1H NMR spectroscopy. The products had identical R_f values and were not separable by chromatography.

(4*aRS*,8*aSR*)-Trimethyl-3,4,4*a*,7,8,8*a*-hexahydro-1*H*-naphthalen-2-one 11

p-Toluenesulfonic acid monohydrate (149 mg, 0.78 mmol) was added to a solution of **9** (100 mg, 0.52 mmol) in AcOH (2 mL) and the resulting mixture was stirred at room temperature for 48 h. The reaction was quenched with water, and extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried and concentrated. Purification of the residue by chromatography (10% EtOAc–hexane) gave **11** (98 mg, 98%) as a colourless oil: ^1H NMR (400 MHz) 0.92 (s, 3H, Me), 1.05 (s, 3H, Me), 1.25 (m, 1H, H-19), 1.65 (m, 1H, H-19), 1.73 (s, 3H, Me-28), 1.80 (m, 1H, H-14), 1.91 (d, $J = 13.0$ Hz, 1H, H-11), 1.95–2.05 (m, 3H, 2 H-18 and H-14), 2.20 (m, 2H, 2 H-13), 2.59 (d, $J = 13.4$ Hz, 1H, H-11), 5.43 (s, 1H, H-17); ^{13}C NMR (100 MHz, DEPT, HSQC) 19.4 (Me), 22.1 (br Me), 22.6 (C-18), 23.4 (C-21), 31.6 (C-19), 33.2 (br C-14), 38.9 (C-13), 39.9 (br C-15), 40.6 (C-20), 49.6 (C-11), 122.9 (C-17), 137.9 (C-16), 212.8 (C-12); HRMS calcd for $C_{13}H_{21}O$ (MH^+) 193.1592, found 193.1592.

(4*aRS*,5*SR*,8*aRS*)-5-Hydroxymethyl-4*a*,8*a*-dimethyloctahydronaphthalen-2-one ethylene acetal 12

BH_3 (1 M in THF, 25.4 mL, 25.4 mmol) was added dropwise to a cooled (0 °C) solution of alkene **7** (2.0 g, 8.5 mmol) in THF (10 mL). The resulting mixture was warmed to room temperature, stirred for 2 h. The mixture was then cooled to −78 °C, and a premixed solution of 4 mL of 30% aqueous H_2O_2 and 4 mL of 3 M NaOH was added. After stirring the mixture overnight at room temperature, the aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed

¶ Broad signals due to the conformational inversion of the decalin ring.

with saturated aqueous $NaHCO_3$, brine, dried and concentrated *in vacuo*. Purification by chromatography (25% EtOAc–hexane) gave the alcohol **12** (1.1 g, 60%) followed by its epimer (220 mg, 12%) as clear oils: ^{1}H NMR (400 MHz, COSY) 0.76 (s, 3H, Me-29), 0.96 (s, 3H, Me-21), 1.10 (dd, J = 14.0, 2.0 Hz, 2H, H-11$_{ax}$, H-13$_{eq}$), 1.15 (m, 1H, H-19$_{ax}$), 1.42–1.60 (m, 5H, H-13$_{ax}$, H-17$_{eq}$, H-14$_{eq}$, 2 H-18), 1.65 (td, J = 13.8, 2.8 Hz, 1H, H-14$_{ax}$), 1.75 (m, 1H, H-17$_{ax}$), 1.83 (dm, J = 11.9 Hz, 1H, H-19$_{eq}$), 1.95 (dddd, J = 12.0, 7.7, 4.0, 3.3 Hz, 1H, H-16$_{ax}$), 2.22 (d, J = 14.0 Hz, 1H, H-11$_{eq}$), 3.30 (dd, J = 10.4, 8.8 Hz, 1H, H-28), 3.79 (dd, J = 10.4, 3.3 Hz, 1H, H-28), 3.87–3.96 (m, 4H, OCH_2); ^{13}C NMR (100 MHz, DEPT, HSQC) 17.1 (C-29), 21.3 (C-18), 25.0 (C-21), 25.2 (C-19), 29.5 (C-14), 30.3 (C-17), 37.0 (C-13), 37.0 (C-20), 37.5 (C-15), 39.2 (C-16), 40.6 (C-11), 63.4 (OCH_2), 64.2 (C-28), 64.3 (OCH_2), 110.0 (C-12); HRMS calcd for $C_{15}H_{27}O_3$ (MH^+) 255.1960, found 255.1954.

(4*aRS*,5*SR*,8*aRS*)-4*a*,5,8*a*-Trimethyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one 10

A cooled (0 °C) solution of alcohol **12** (800 mg, 3.14 mmol) in CH_2Cl_2 (25 mL) was treated sequentially with Et_3N (0.95 mL, 6.57 mmol) and methanesulfonyl chloride (270 mL, 3.46 mmol). After being stirred at room temperature for 1.5 h, the mixture was diluted with CH_2Cl_2 and washed with H_2O (15 mL), brine (2 × 5 mL), dried, and concentrated to give the mesylate, which was used in the next step without additional purification: ^{1}H NMR (300 MHz) 0.80 (s, 3H, Me-21), 0.98 (s, 3H, Me-29), 1.12 (dd, J = 14.2, 2.2 Hz, 2H, H-11$_{eq}$, H-13$_{eq}$), 1.24–1.40 (m, 1H, H-18$_{eq}$), 1.41–1.62 (m, 5H, H-13$_{ax}$, H-17$_{eq}$, H-14$_{eq}$, H-19$_{eq,ax}$), 1.63–1.86 (m, 3H, H-14$_{ax,}$ H-17$_{ax,}$ H-18$_{ax}$), 2.09–2.32 (m, 2H, H-11$_{ax,}$ H-16), 2.99 (s, 3H, –O_3S*Me*), 3.78–4.06 (m, 5H, H-28, O*C*H_2), 4.35 (dd, J = 9.52, 3.65 Hz, 1H, H-28). A solution of the above mesylate in THF (12 mL) was treated with Superhydride (1 M in THF, 9.42 mL, 9.42 mmol) and the resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with 10% aqueous HCl (20 mL), stirred for 2 h and then extracted with Et_2O (3 × 20 mL), dried and concentrated. Purification by chromatography (10% EtOAc–hexane) gave **10** (450 mg, 74% from alcohol **12**) as a white solid. All data were in accordance to those previously reported.[9] For ^{13}C NMR data, see Table 1 in the ESI.†

(4*aRS*,5*RS*,8*aSR*)-Trimethyl-4*a*,5,6,7,8,8*a*-hexahydro-1*H*-naphthalen-2-one 13

To a solution of ketone **10** (400 mg, 2.06 mmol) in DMSO (6 mL) was added *o*-iodoxybenzoic acid (IBX, 1.44 g, 5.15 mmol) and *p*-toluenesulfonic acid monohydrate (118 mg, 0.62 mmol), and the mixture was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature and partitioned between EtOAc (40 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with EtOAc (5 × 40 mL), the combined organic layers were washed with saturated $NaHCO_3$, saturated sodium thiosulfate solution, brine, dried and concentrated. Purification by chromatography (10% EtOAc–hexane) gave **13** (281 mg, 71%) as a colourless oil: ^{1}H NMR (300 MHz) 0.91 (d, J = 6.8 Hz, 3H, Me-28), 0.92 and 1.01 (s, 3H each, Me-29 and Me-21), 1.15 (m, 2H), 1.40–1.64 (m, 4H), 1.82 (d, J = 16.9 Hz, 1H, H-11), 1.91 (ddd, J = 12.3, 6.7, 3.5 Hz, 1H, H-16), 3.06 (d, J = 16.9 Hz, 1H, H-11), 5.91 (d, J = 10.2 Hz, 1H, H-13), 6.68 (d, J = 10.2 Hz, 1H, H-14); ^{13}C NMR (75 MHz, DEPT) 13.3 (Me), 16.9 (C-28), 21.7 (C-18), 24.9 (Me), 30.1 (C-17), 35.4 (C-19), 37.8 (C-16), 39.3 (C-15), 42.1 (C-20), 46.1 (C-11), 126.3 (C-13), 159.4 (C-14), 200.2 (C-12); HRMS calcd for $C_{13}H_{21}O$ (MH^+) 193.1592, found 193.1601.

(4*aRS*,5*SR*,8*aSR*)- 4*a*,5,8*a*-Trimethyl-1-methylene-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one 3

Enone **13** (506 mg, 2.64 mmol) in THF (10 mL) was added dropwise to a cooled (−78 °C) solution of LiHMDS (1 M in THF, 5.27 mL, 5.27 mmol) in THF (7.5 mL). The resulting solution was stirred for 5 min at −78 °C, warmed to 0 °C, stirred for 1 h, recooled to −78 °C then transferred *via* cannula over 15 min to a stirred suspension of Eschenmoser's salt (1.47 g, 7.92 mmol,) in 15 mL of THF at −78 °C. The resulting mixture was stirred for 10 min at −78 °C, then for 10 min in a room temperature water bath, and then transferred to a separatory funnel with ether (50 mL) and saturated $NaHCO_3$ solution (10 mL). The aqueous layer was separated, diluted with 50 mL of water, and extracted with 50 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to give a yellow-orange oil **14**. The residue was dissolved in MeOH (50 mL), Pd/C (100 mg) was added, and the mixture was stirred under hydrogen (1 atm) for 16 h. The mixture was filtered through Celite, dried and concentrated. This crude material was partitioned between CH_2Cl_2 (25 mL) and saturated $NaHCO_3$ solution (12.5 mL), and *m*-CPBA (Aldrich, 57–86%, 911 mg, 5.28 mmol, 1.5–2.3 equiv) was added in one portion. The resulting mixture was stirred vigorously for 20 min, then transferred to a separatory funnel and separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure *at room temperature* to avoid undesired polymerisation. Purification by chromatography (5% EtOAc–hexane) gave **3** as a clear oil (350 mg, 69%). All spectroscopic data were identical to that previously reported.[9] For ^{13}C NMR data, see Table 1 in the ESI.†

(1*RS*,4*aRS*,5*SR*,8*aRS*)-1-(1*H*-Indol-3-ylmethyl)-4*a*,5,8*a*-trimethyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one 15

To a solution of indole (37 mg, 0.32 mmol), and the enone **3** (65 mg, 0.32 mmol) in CH_3CN (1 ml) was added bismuth triflate (6 mg, 0.01 mmol, 3 mol%) and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 and absorbed onto silica. Purification by column chromatography (5% EtOAc–hexane) gave ketoindole (95 mg, 93%) as a mixture of epimers. The mixture was dissolved in EtOH (10 mL), potassium fluoride (255 mg, 4.40 mmol) was added, and the resulting mixture was heated at reflux for 48 h. After the reaction was cooled to room temperature, the mixture was partitioned between water and CH_2Cl_2, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by chromatography (25% EtOAc–hexane) gave **15** (93 mg, 98%) as a white solid: mp 173–175 °C; ^{1}H NMR (400 MHz, COSY) 0.82 (s, 3H, Me), 0.83 (d, J = 6.8 Hz, 3H, Me-28), 0.86 (s, 3H, Me), 1.40 (qd, J = 12.8, 4.8 Hz, 1H, H-17$_{ax}$), 1.51 (dm, J = 12.5 Hz, 1H, H-17$_{eq}$), 1.55-1–70 (m, 3H, H-14$_{ax}$, 2 H-18), 1.71 (td, J = 14.0, 4,5 Hz, 1H, H-19$_{ax}$), 1.87 (dm, J = 14.0 Hz, 1H, H-14$_{eq}$), 1.90 (ddd, J = 14.0, 6.0, 2.4 Hz,

1H, H-19$_{eq}$), 2.14 (ddd, J = 12.9, 4.4, 2.4 Hz, 1H, H-13$_{eq}$), 2.31 (m, 1H, H-16$_{ax}$), 2.37 (td, J = 14.0, 6.0 Hz, 1H, H-13$_{ax}$), 2.62 (d, J = 13.5 Hz, 1H, H-10), 3.25 (dd, J = 13.5, 9.5 Hz, 1H, H-10), 3.30 (d, J = 9.5 Hz, 1H, H-11), 7.05 (d, J = 2.2 Hz, 1H, H-2), 7.10 (t, J = 7.8 Hz, 1H, H-6), 7.16 (t, J = 7.8 Hz, 1H, H-7), 7.31 (d, J = 8.0 Hz, 1H, H-8), 7.59 (d, J = 7.8 Hz, 1H, H-5), 7.94 (br s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) 16.0 (C-28), 16.3 (C-29), 17.4 (C-10), 18.8 (C-21), 21.9 (C-18), 30.6 (C-17), 30.9 (C-16), 32.5 (C-14), 33.5 (C-13), 38.7 (C-15), 39.6 (C-19), 47.0 (C-20), 53.6 (C-11), 111.0 (C-8), 115.9 (C-3), 118.5 (C-5), 119.1 (C-6), 121.6 (C-7), 123.5 (C-2), 127.5 (C-4), 135.9 (C-9), 213.6 (C-12); HRMS calcd for $C_{22}H_{29}NO$ (M^+) 323.2249, found 323.2260.

3-[(1*RS*,4*aSR*,5*RS*,8*aSR*)-4*a*,5,8*a*-Trimethyl-2-methylenedecahydronaphthalen-1-ylmethyl]-1*H*-indole 16

A solution of methyltriphenylphosphonium bromide (200 mg, 0.56 mmol) and potassium *tert*-butoxide (55 mg, 0.49 mmol) in toluene (5 mL) was stirred at 90 °C for 30 min. A solution of ketone **15** (40 mg, 0.12 mmol) in toluene (3 mL) was added, and the reaction was heated at 90 °C for 2 h. After the mixture was cooled to room temperature, the reaction was quenched with water, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by column chromatography (2.5% EtOAc–hexane) gave **16** (38 mg, 96%) as a white solid: mp 83–85 °C; ^{1}H NMR (400 MHz, COSY) 0.80 and 0.81 (2 s, 3H each, Me-21, Me-29), 0.81 (d, J = 6.8 Hz, 3H, Me-28), 1.20–1.55 (m, 6H, 2 H-18, 2 H-17, H-14$_{ax}$, H-19$_{ax}$), 1.64 (dm, J = 14.0 Hz, 1H, H-14$_{eq}$), 1.77 (dm, J = 12.0 Hz, 1H, H-19$_{eq}$), 2.08 (ddd, J = 13.9, 4.4, 2.6 Hz, 1H, H-13$_{eq}$), 2.25 (dt, J = 13.9, 13.7, 5.2 Hz, 1H, H-13$_{ax}$), 2.40 (ddd, J = 10.8, 6.5, 3.9 Hz, 1H, H-16), 2.83 (dd, J = 16.0, 10.3 Hz, 1H, H-10), 2.94 (d, J = 16.0 Hz, 1H, H-10), 3.24 (d, J = 10.3 Hz, 1H, H-11), 4.65 (d, 1H, H-27), 4.83 (d, J = 1.6 Hz, 1H, H-27), 6.96 (s, 1H, H-2), 7.11 (ddd, J = 7.6, 7.2, 1.1 Hz, 1H, H-6), 7.17 (t, J = 7.6 Hz, 1H, H-7), 7.33 (d, J = 8.0 Hz, 1H, H-8), 7.65 (d, J = 7.9 Hz, 1H, H-5), 7.86 (br s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) 16.3 (C-29), 16.5 (C-28), 18.3 (C-21), 19.9 (C-10), 21.6 (C-18), 30.5 (C-16), 31.1 (C-17), 32.1 (C-19), 32.9 (C-13), 33.9 (C-14), 39.7 (C-15), 42.5 (C-11), 42.8 (C-20), 107.7 (C-27), 111.0 (C-8), 116.7 (C-3), 118.7 (C-5), 119.0 (C-6), 121.5 (C-7), 121.7 (C-2), 128.0 (C-4), 135.9 (C-9), 149.5 (C-12); HRMS calcd for $C_{23}H_{31}N$ (M^+) 321.2456, found 321.2457.

(3*RS*,4*aSR*,8*RS*,8*aSR*,10*aSR*)-10*a*-Hydroxy-4*b*,8,8*a*-trimethyl-3-(2-nitrophenyl)dodecahydro-1*H*-phenanthren-2-one 18

To a solution of 1-(2-nitrophenyl)propan-2-one (93 mg, 0.52 mmol), *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (27 mg, 0.05 mmol) and 60% (w/v) KOH (0.25 mL) in toluene (2 mL) was added enone **3** (100 mg, 0.52 mmol) in toluene (3 mL) and the mixture was stirred at room temperature for 48 h. The mixture was partitioned between water and CH_2Cl_2, and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by column chromatography (20% EtOAc–hexane) gave **18** (94 mg, 51%) as a bright yellow solid: 166–168 °C; ^{1}H NMR (400 MHz, COSY) 0.83 (d, J = 6.4 Hz, 6H, Me-28, Me-29), 0.98 (s, 3H, Me-21), 1.20–1.40 (m, 5H, H-13$_{eq}$, H-14$_{eq}$, H-17, H-19), 1.45–1.60 (m, 4H, H-17, 2 H-18, H-19), 1.78 (td, J = 14.0, 4.0 Hz, 1H, H-13$_{ax}$), 1.90 (td, J = 14.0, 4.0 Hz, 1H, H-14$_{ax}$), 2.15 (m, 2H, H-10$_{eq}$, H-16), 2.39 (q, J = 12.5 Hz, 1H, H-10$_{ax}$), 2.43 (d, J = 14.0 Hz, 1H, H-27$_{eq}$), 2.68 (dd, J = 11.9, 2.4 Hz, 1H, H-11), 2.75 (d, 1H, H-27$_{ax}$), 4.40 (dd, J = 12.4, 5.3 Hz, 1H, H-3$_{ax}$), 7.42 (t, J = 7.7 Hz, 1H, H-7), 7.47 (d, J = 7.7 Hz, 1H, H-5), 7.61 (t, J = 7.7 Hz, 1H, H-6), 7.95 (d, J = 7.7 Hz, 1H, H-8); ^{13}C NMR (100 MHz, DEPT, HSQC) 16.0 (C-28), 16.3 (C-29), 20.5 (C-21), 21.6 (C-18), 27.0 (C-14), 29.9 (C-10), 30.2 (C-16), 30.7 (C-17), 33.1 (C-19), 35.0 (C-13), 39.1 (C-15), 39.2 (C-20), 41.4 (C-11), 52.8 (C-3), 57.7 (C-27), 76.4 (C-12), 124.6 (C-8), 127.7 (C-7), 130.6 (C-6), 132.9 (C-5), 133.6 (C-4), 149.5 (C-9), 206.4 (C-2); HRMS calcd for $C_{23}H_{32}NO_4$ (MH^+) 386.2331, found 386.2330.

(4*RS*,4*aRS*,6*aRS*,13*aRS*,13*bRS*)-4,4*a*,13*b*-Trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,13,13*a*,13*b*-dodecahydro-1*H*-naptho[2,1-*b*]carbazol-6*a*-ol 19

To a solution of **18** (27 mg, 0.07 mmol) in MeOH (2 mL) were added sequentially sat. aq. NH_4Cl (0.7 mL), Zn dust (460 mg, 7.0 mmol) and the mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, filtered through Celite and washed with EtOAc. The combined organic layers were washed with $NaHCO_3$, brine, dried and concentrated. Purification of the residue by chromatography (20% EtOAc–hexane) gave alkene **19** (19 mg, 81%) as a light yellow solid: mp >220 °C; ^{1}H NMR (400 MHz, COSY) 0.81 (d, J = 6.8 Hz, 3H, Me-28), 0.86 (s, 3H, Me-29), 1.11 (s, 3H, Me-21), 1.26–1.48 (m, 7H, 2 H-14, 2 H-17, 2 H-18, H-19$_{ax}$), 1.60 (dm, J = 12.0 Hz, 1H, H-19$_{eq}$), 1.72–1.92 (m, 2H, 2 H-13), 2.10 (m, 1H, H-16), 2.55 (dd, J = 12.0, 5.5 Hz, 1H, H-11$_{ax}$), 2.70 (dd, J = 14.5, 13.0 Hz, 1H, H-10$_{ax}$), 2.71 (d, J = 16.0 Hz, 1H, H-27), 2.81 (dd, J = 14.5, 6.0 Hz, 1H, H-10$_{eq}$), 2.91 (d, J = 16.0 Hz, 1H, H-27), 7.11 (ddd, J = 7.7, 7.5, 1.2 Hz, 1H, H-7), 7.13 (ddd, J = 7.7, 7.1, 1.3 Hz 1H, H-6), 7.30 (d, J = 7.5 Hz, 1H, H-8), 7.50 (d, J = 7.5 Hz, 1H, H-5), 7.68 (s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) 15.9 (C-28), 16.6 (C-29), 17.5 (C-10), 20.0 (C-21), 21.5 (C-18), 27.3 (C-14), 30.0 (C-16), 30.6 (C-17), 32.6 (C-19), 33.9 (C-13), 38.1 (C-11), 39.1 (C-15), 39.2 (C-20), 41.4 (C-27), 71.8 (C-12), 108.9 (C-3), 110.6 (C-8), 117.9 (C-5), 119.3 (C-7), 121.4 (C-6), 127.6 (C-2), 130.9 (C-4), 136.4 (C-9); HRMS calcd for $C_{23}H_{31}NO$ (M^+) 337.2406, found 337.2408.

(4*RS*,4*aSR*,13*bRS*)-4,4*a*,13*b*-Trimethyl-2,3,4,4*a*,5,6,8,13*b*-octahydro-1*H*-naptho[2,1-*b*]carbazole 20

To a solution of **19** (12 mg, 0.04 mmol) in toluene (10 mL) was added *p*-toluenesulfonic acid (7 mg, 0.04 mmol) and the mixture was stirred at reflux for 3 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with sat. aq. $NaHCO_3$, H_2O, brine, dried and concentrated. Purification of the residue by column chromatography (5% EtOAc–hexane) gave carbazole **20** (10 mg, 88%) as a light yellow gum: ^{1}H NMR (400 MHz) 0.84 (d, J = 6.8 Hz, 3H, Me-28), 0.98 (s, 3H, Me-29), 1.18 (s, 3H, Me-21), 1.22–1.28 (m, 1H), 1.45–1.57 (m, 2H), 1.61–1.77 (m, 3H), 1.79–2.11 (m, 2H), 2.25 (m, 1H), 2.87 (dd, J = 17.5, 6.4 Hz, 1H, H-13$_{eq}$), 3.02 (ddd, J = 17.5, 13.0, 7.3 Hz, 1H, H-13$_{ax}$), 7.12 (s, 1H, H-27), 7.18 (ddd, J = 8.0, 5.7, 2.5 Hz, 1H, H-6), 7.35 (m, Hz, 2H, H-7, H-8), 7.79 (br s, 1H, NH), 8.02 (s, 1H, H-10), 8.02 (d, J = 7.6 Hz, 1H,

H-5); ^{13}C NMR (100 MHz, DEPT) 16.3 (C-28 and C-29), 22.7 (C-18), 26.6 (C-13), 28.6 (C-14), 29.7 (C-17), 30.9 (C-21), 32.1 (C-16), 33.6 (C-19), 37.8 (C-15), 42.1 (C-20), 110.1 (C-8), 110.3 (C-27), 117.5 (C-10), 119.0 (C-6), 119.9 (C-5), 122.4 (C-3), 123.7 (C-4), 125.2 (C-7), 135.0 (C-11), 136.2 (C-12), 137.7 (C-2), 140.0 (C-9).

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Efficient Solvent-Free Robinson Annulation Protocols for the Highly Enantioselective Synthesis of the Wieland–Miescher Ketone and Analogues

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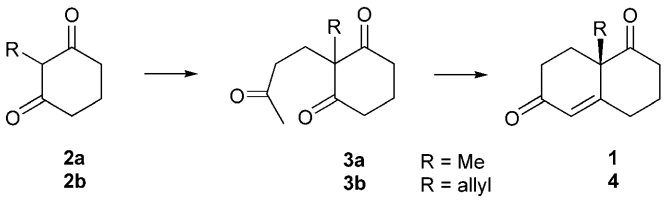
Abstract: A highly efficient (93% overall yield) and enantioselective (94% *ee*) synthesis of the Wieland–Miescher ketone (10-g scale) through a solvent-free Robinson annulation procedure is reported. The process involves only 1 mol% triethylamine as the base in the initial Michael process and the organocatalyst *N*-tosyl-(S_a)-binam-L-prolinamide (2 mol%) and benzoic acid (0.5 mol%) for the intramolecular aldol process. This green protocol is applied to a wide range of valuable building block analogues of the Wieland–Miescher ketone (10 examples). Among these, a noteworthy compound for terpene synthesis is the 8a-allyl derivative, which is prepared in 93% yield and 97% *ee* in a process allowing the recovery and reutilization of the organocatalyst. Furthermore, a one-pot, two-step process has also been developed.

Keywords: asymmetric synthesis; carbocycles; organocatalysis; solvent-free reactions; terpenoids

Introduction

The enantiopure Wieland–Miescher (W-M) ketone (**1**) has been used extensively in the synthesis of a wide variety of terpenoids and steroids.[1] The Robinson annulation of 2-methyl-1,3-cyclohexanedione (**2a**) to give **1** through an L-proline-promoted aldolization of dione **3a** (Scheme 1) was reported in 1971,[2] but the low enantioselectivity of the reaction (about 70% *ee*) involved recrystallization steps to achieve the enantiomerically pure **1** with a subsequent drop in overall yield.[3]



Scheme 1. The Wieland–Miescher ketone synthesis.

The renaissance of organocatalysis[4] and the advent of a plethora of new catalysts for aldol reactions[5] have allowed the preparation of **1** to be re-evaluated and improved. In the pioneering work of Barbas, who studied the one-step Robinson annulation of **2a** by testing a series of secondary amines, the synthesis of **1** was achieved in a one-pot reaction (35 mol% of L-Pro, 89 h, 49%, 76% *ee*).[6] The Wieland–Miescher ketone (**1**) has been subsequently prepared with higher enantiomeric excess, notably using the following catalysts: the cyclic β-amino acid (1*R*,2*S*)-cispentacin (30 mol%, 108 h, 75%, 86% *ee*);[7] (3*S*,3′*S*)-4-isopropyl-3,3′-bimorpholine·TfOH (5 mol%, 70 h, 84%, 91% *ee*);[8] the tripeptide Pro-▲-Pro (10 mol%, 24 h, 88%, 92% *ee*);[9] a prolinethioamide from L-Pro and (*R*)-1-aminoindane (5 mol%, 24 h, 99%, 86% *ee*);[10] *N*-tosyl-(S_a)-binam-L-prolinamide (5 mol%, 27 h, 95%, 90% *ee*);[11] and L-prolinamide (30 mol%, 144 h, 68%, 87% *ee*).[12]

Despite this success, the development of protocols for an efficient synthesis of Wieland–Miescher ketone and analogues is still a challenge and has become a much attempted research endeavour.[13–15] We have re-

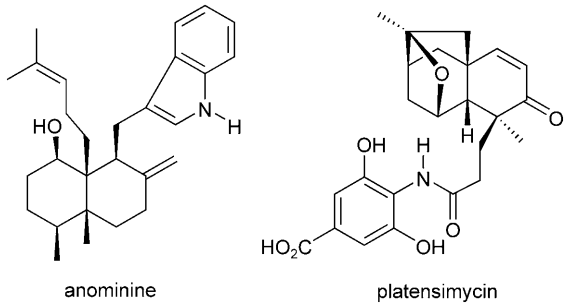


Figure 1.

cently reported that (S_a)- and (R_a)-binam-derived L-prolinamides[16] as well as *N*-tosyl-(S_a)-binam-L-prolinamide[11,17] are highly efficient bifunctional organocatalysts for the enantioselective aldol reactions. The good results obtained in the preparation of the W-M ketone (**1**)[11] prompted us to renew our synthetic studies of W-M ketone analogue **4**, a potential building block[18] for the total synthesis of diterpenoid alkaloids isolated from *Aspergillus* spp. (e.g., anominine, Figure 1).[19,20] Other related bicyclic enones (**5**–**13**) were also targeted to evaluate the scope of the protocol and to obtain advanced synthetic intermediates for future natural product synthesis (e.g., platensimycin, Figure 1).[21] Moreover, studies were also carried out to improve the synthesis of the Wieland–Miescher ketone itself.

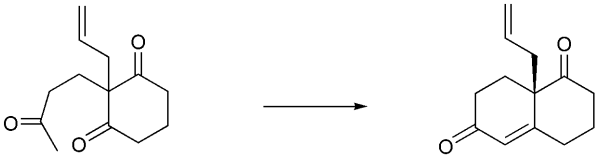
Results and Discussion

Synthesis of the 8a-Allyl W-M Ketone Analogue

When we first became interested in compound **4**, there were two reported syntheses: one using L-Pro (100 mol%, DMSO, 1 d)[22] and another involving a long sequence with (*S*)-malic acid as the starting material.[23] Using Hanselman's procedure,[22] with L-Pro in DMSO, compound (+)-**4** was prepared on a large scale in 72% yield and 84% *ee* (Table 1, entry 1). However, the cumbersome work-up and the laborious process for increasing the enantiopurity prompted us to optimize the synthesis of **4**. For this purpose, first the L-Pro catalyst loading was reduced from 100 mol% to 25 mol%, but a detrimental effect on the achieved enantioselectivity was observed (Table 1, compare entries 1–3).

Then, the process was studied using different proline-type organocatalysts **B**–**G** under various reaction conditions (Table 1 and Figure 2): catalyst **B** (Table 1, entry 4) with brine,[24] **C**[25] in THF (entry 5), or **D**–**F** under solvent-free conditions (entries 6–8). Chemical yields ranged from good to excellent, but the enantiomeric excess was very poor, except for prolinamide **E**.

Table 1. Synthesis of the allyl W-M ketone analogue **4**.[a]



Entry	Catalyst (mol%)	Solvent	Time	Yield [%][b]	*ee* [%][c]
1	**A** (100)	DMSO	24 h	72	84
2	**A** (50)	DMSO	24 h	76	64
3	**A** (25)	DMSO	48 h	80	74
4	**B** (5)	brine	10 d	93	40
5	**C** (20)[d]	THF	24 h	90	34
6	**D** (5)[e]	free	24 h	93	8
7	**E** (5)[e]	free	24 h	96	82
8	**F** (5)[e]	free	24 h	87	32
9	**A** (5)	free	14 d	74	46
10	**G** (5)[e]	free	24 h	93	94
11	*ent*-**G** (5)[e]	free	24 h	93	94[f]
12	**G** (5)[e]	brine	36 h	76	94
13	**G (2.5)**[e,g]	**free**	**5 d**	**93**	**97**
14	**G** (1)[e]	free	20 d	86	96

[a] Unless otherwise noted, the reaction was carried out with 100 mg of triketone **3b**.
[b] Yield of isolated **4** after flash chromatography.
[c] Determined by HPLC with a Chiralcel OD-H column.
[d] TFA (20 mol%) was added.
[e] Benzoic acid (1 mol%) was added.
[f] The opposite enantiomer was obtained
[g] Reaction on 3-g scale of **3b**.

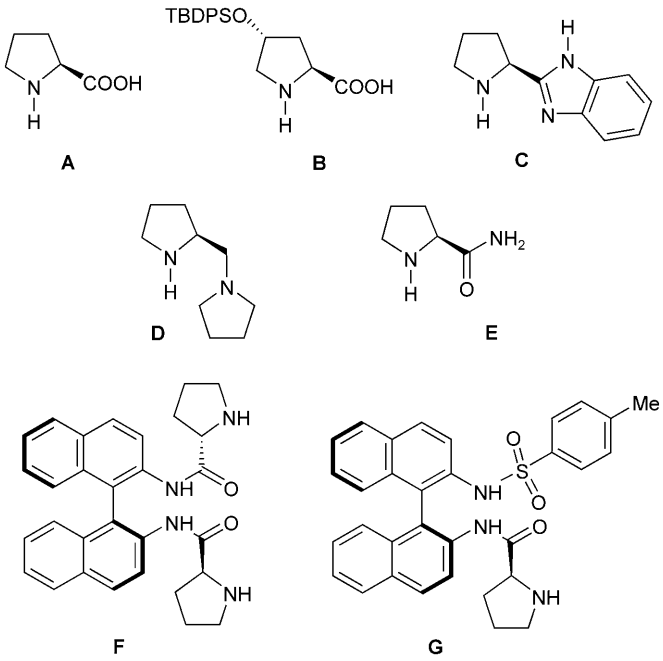


Figure 2. Organocatalysts used.

When L-Pro was used, this time working without solvent, the reaction was slow and the *ee* low (entry 9).

Using binam-proline-sulfonamide **G**, a recently reported catalyst for aldol processes in a solvent-free procedure,[11,26] for the synthesis of ketone **4**, a considerable improvement in the enantioselectivity (94%) was observed with an excellent 93% chemical yield (Table 1, entry 10). The process was carried out with the same efficiency using the catalyst *ent*-**G** to afford (−)-**4** (entry 11). The reaction also worked in brine, giving equally high enantioselectivity albeit with a lower chemical yield (entry 12).

The catalyst loading of **G** could be reduced to 2.5 mol% without a fall in reactivity and increasing the enantioselectivity to 97% (Table 1, entry 13). The reaction even worked with only 1 mol% of catalyst (entry 14) with similar *ee* (96%), although it required three weeks to reach completion.

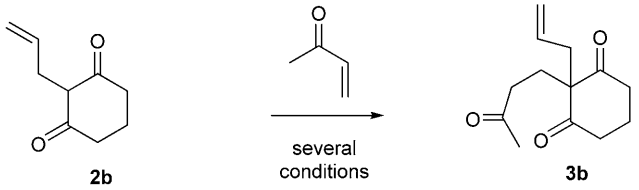
Since the catalyst could be easily separated from the product by direct chromatography of the reaction mixture, we examined its recyclability. We found that even in a large-scale reaction (3 g of **3b**), the recovered catalyst (87% yield) could be reused to give a second batch of compound **4** in 96% yield and 94% *ee*. Then, the optimization of the synthesis of the required starting material **3b** was attempted (see below), in order to improve the overall synthesis of compound **4**.

A New Protocol for the Synthesis of 2-Substituted 2-(3-Oxobutyl)-1,3-cyclohexanediones

In order to prepare the triketone intermediates (i.e., **3b**) required for the asymmetric synthesis of the Wieland–Miescher ketone and its analogues, we initially relied on an adaption of Gutzwiller's method[3a] for the Michael addition of **2b** to MVK[27] (Table 2, entry 1). However, although efficient on a large scale, the reaction gave inferior results when was used to prepare less than 0.5–1 g.[28]

Other conditions such as using KOH[22] (Table 2, entry 2) or Triton B[14,29] (entry 3) as the base, did not improve the results and required the use of high temperatures. Omitting the base and working in water[30] (entry 4) gave high yields but progress was too slow (10 d) to be a useful protocol. The reaction was even slower working in neat MVK probably due to the low solubility of the reagents (entry 5). The use of Et_3N in DMF[31] (entry 6) was a good procedure and, most importantly, proved to be amenable for small-scale reactions. However, a large excess of MVK was required and yields were somewhat reduced by the interference of DMF in the work-up. While similar methods have been described using alternative solvents, such as THF,[32] acetonitrile[24] or EtOAc,[7b] we decided to perform the Michael reaction under solvent-free conditions. We were pleased to find the reaction was cleaner and proceeded more rapidly. In further refinements, the Et_3N was reduced to only 1 mol% and the MVK to only 1.1 equiv., which meant the method was extremely atom efficient. This in turn facilitated reactions on a large scale, since the majority of the MVK was incorporated into the product and did not have to be removed during the work-up. Using this simple protocol, the reaction reached completion in only 3 h in excellent yield (96% after column chromatography, Table 2, entry 7).

Table 2. Conjugate addition of MVK to **2b**.



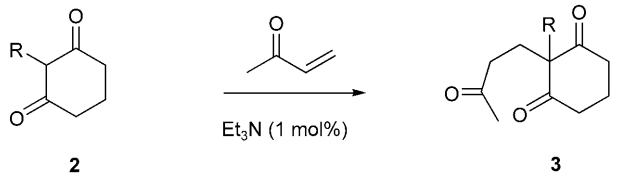
Method	Conditions	Yield
1	MVK (2.5 equiv.), AcOH, H_2O, hydroquinone, 75 °C, overnight	82%
2	MVK (1.5 equiv.), 10% KOH, 4:1 MeOH/H_2O, reflux, 75 min	82%
3	MVK (1.5 equiv.), triton B (0.1 equiv.), MeOH, 60 °C, 12 h	41%
4	MVK (2 equiv.), H_2O, drop of EtOH, r.t., 10 d	92%
5	MVK (2 equiv.), r.t., 14 d	35%
6	MVK (3 equiv.), DMF, Et_3N (0.3 equiv.), overnight/12 h	87%
7	**MVK (1.1 equiv.), Et_3N (1 mol%), r.t., 3 h**	**96%**

The other 2-(2-oxobutyl)-2-substituted-1,3-cyclohexanediones (**3**) employed in this study were prepared following the procedure depicted in Table 3.

The required 2-substituted-1,3-cyclohexanediones **2c**,[33] **2d**,[34] **2e**,[35] and **2f**[36] were prepared by alkylation of 1,3-cyclohexanedione. For the synthesis of **2g** and **2h** Piers' procedure[37] was used, involving an alkylation of the 2,5-dimethoxydihydrobenzene. The other starting materials were prepared from cyclohexanedione by Michael addition using methyl acrylate to give **2j**[30] and Knoevenagel condensation with 3-benxyloxypropanal followed by a reduction with the Hantzsch ester, according to the protocol of Ramachary,[13] to give **2k**.

The Michael addition to methyl vinyl ketone of compounds **2** for the preparation of triketones **3c**–**3k** was carried out whenever possible using the solvent-free procedure developed for the optimized synthesis of **3b** described above.[38] It should be noted that the success of the reaction depends on the triketone product being an oil, and thus able to act as a "solvent", dissolving starting material **2**, which in all series was a

Table 3. Preparation of 2-substituted 2-(3-oxobutyl)-1,3-cyclohexanediones **3c**–**3k**.[a]



2 **3**

Entry	R	Compound	Yield [%][b]
1	$CH_2CH{=}C(CH_3)_2$	**3c**	95
2	$CH_2C_6H_5$	**3d**	94
3	$CH_2C{\equiv}CH$	**3e**	97
4	$CH_2CBr{=}CH_2$	**3f**	88
5	$(CH_2)_2CH{=}CH_2$	**3g**	90
6	$(CH_2)_2CH{=}C(CH_3)_2$	**3h**	93
7	$(CH_2)_3CH(CH_3)_2$	**3i**	85[c]
8	$(CH_2CH_2CO_2Me$	**3j**	77
9	$(CH_2)_3OCH_2C_6H_5$	**3k**	91

[a] See Supporting Information for detailed experimental procedures. The reaction time was 24 h, except for **3c** (6 h) and **3e** (4 h).
[b] Yield of isolated product after column chromatography.
[c] Prepared from **3h** by catalytic hydrogenation.

solid compound. When the triketone formed was a solid (i.e., compounds **3d** and **3f**), a small amount of DMF (1–2 mL g $^{-1}$of starting material) was added to solubilize the reactants.

Synthesis of Other 8a-Substituted Analogues of the Wieland–Miescher Ketone

The optimized Robinson annulation procedure for the synthesis of **4** both in the initial Michael reaction on **2b** and in the following asymmetric intramolecular aldolization of **3b**, could also be applied for the enantioselective synthesis of a series of other Wieland–Miescher ketone analogues (**5**–**13**). The results of the asymmetric intramolecular aldol reaction of triketones **3c**–**3k** using the binam-prolinamide catalyst **G** are summarized in Table 4. In general due to the increased steric bulk of the side chain the reactions were slower than the aforementioned procedure leading to allyl derivative **4**. Moreover, a catalyst loading of 5 mol% was required, which had to be increased to 10 mol% for the synthesis of **8** and **12**.

The prenyl-substituted product **5** was obtained in 88% yield and 96% *ee*. The results obtained with substrates embodying the benzyl and 2-bromopropenyl appendages were better than those previously reported,[12,13] W-M ketone analogues **6** and **8** being obtained in 70% yield in each case and 94% and 96% *ee*, respectively. The new propargylic derivative **7** was formed in 78% yield and 90% *ee*. The most lipophilic compounds **9**–**11** were obtained with successful enantio-discrimination, although in moderate yields (54–59%). The synthesis of the isohexyl derivative **11** was performed since it could be considered as a latent form[39] of the interesting homoprenyl derivative **10** for the synthesis of anominine and other related terpenes. Whereas compound **10** gave an excellent *ee* (96%), the effect of changing the double bond to a saturated side chain gave an unexpected result with compound **11** being obtained in only 84% *ee*. The products with an oxygenated side-chain **12** and **13** were isolated in 71% and 78% yield, respectively, and high *ee*. In summary, while yields in some cases were moderate,[40] the enantiomeric excess was uniformly excellent and superior to any obtained by other enantiocatalysts studied in Wieland–Miescher ketone synthesis.

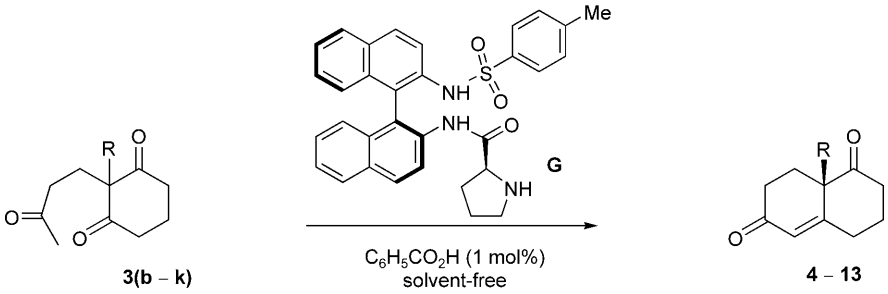
Finally, it should be noted that while the procedure proved to have a very broad scope for the synthesis of 8a-susbstituted 3,4,8,8a-tetrahydronaphthalene-(2*H*,7*H*)-1,6-diones, a limitation was found when attempting to extend it to 5-methyl derivatives.[41]

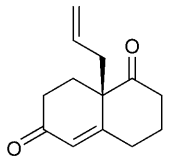
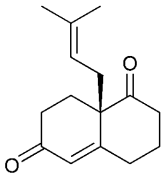
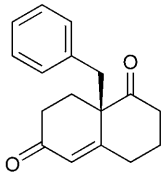
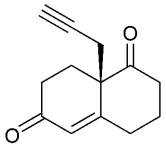
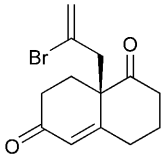
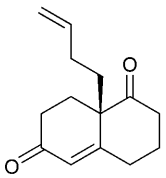
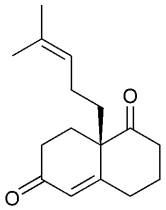
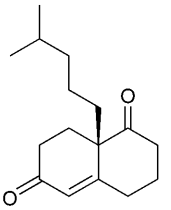
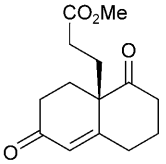
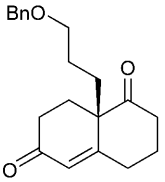
A One-Pot Asymmetric Robinson Annulation

After the reaction conditions in two separate reactions for the asymmetric Robinson annulation of **2b** to **4** were successfully established (Scheme 1, Table 1 and Table 2), the one-pot process was investigated. We began by seeing if the organocatalyst binam **G** could catalyze the alkylation reaction with MVK.[6] Although catalysis took place, the reaction (5 mol% catalyst, MVK 3 equiv., 1 mol% benzoic acid) was slow and stopped at the triketone **3b** stage without evolving further to the cyclized product **4** even after a prolonged reaction time (3 d). A thorough evaporation of the MVK under high vacuum allowed the reaction to progress to **4** but extremely slowly, reaching only 40% completion after 2 weeks. Moreover, when compared to the single-step process, a lower *ee* (88%) was obtained.

Due to the fact that catalyst **G** allowed a clean reaction for both transformations in separated sequences, but failed in a one-pot, one-step procedure (**2b**→**3b**→**4**), the new solvent-free alkylation method was assayed. After the Michael process was carried out, the catalytic Et_3N and remaining MVK were evaporated. The subsequent addition of catalyst **G** (2.5 mol%) to the crude triketone **3b** gave compound **4** (92% *ee*) in 83% overall yield for the two steps. The slightly lower enantiomeric excess in this reduced protocol may be due to the extremely low catalyst loading, which makes the reaction more sensitive to small amounts of impurities formed in the alkylation step. Despite the lower *ee*, the simplicity of this procedure may be beneficial when working on a large scale.

Table 4. Synthesis of Wieland–Miescher ketone analogues **4**–**13** using binam-prolinamide **G**.[a]



 **4**[d]	 **5**	 **6**[e]	 **7**	 **8**[f]
93% yield[b] 97% *ee*	88% yield 96% *ee*	70% yield 94% *ee*	78% yield 90% *ee*	70% yield[c] 96% *ee*
 **9**	 **10**	 **11**	 **12**[g]	 **13**
54% yield 95% *ee*	59% yield 96% *ee*	53% yield 84% *ee*	71% yield[c] 95% *ee*	78% yield 94% *ee*

[a] All reactions carried out with 5 mol% of catalyst **G** and 1% benzoic acid unless otherwise noted. Reaction times were 4 days (**7**–**9** and **13**), 5 days (**4** and **5**), 7 days (**11**), 8 days (**12**), and 10 days (**6** and **10**).
[b] 2.5 mol% of catalyst **G** was used.
[c] 10 mol% of catalyst **G** was used.
[d] Lit.: (56%; 85% *ee*);[12] (66%; 80% *ee*).[22]
[e] Lit.: (56%; 86% *ee*);[12] (50%; 72% *ee*).[22]
[f] Lit.: (46%; 83% *ee*).[12]
[g] Lit.: (65%; 87% *ee*).[12]

Synthesis of the Wieland–Miescher Ketone (1)

Given our success in the allyl and other 8a-substituted W-M ketone analogues, we hoped to apply this method to improve the synthesis of the W-M ketone itself and provide both an efficient and economical method. Previous work[11] has described the use of 5 mol% binam-prolinamide catalyst **G** to give the desired Wieland-Miescher ketone target **1** in 95% yield and 90% *ee* but only in a 100-mg scale and we were interested in preparing **1** in synthetically useful quantities for use as a building block in natural product synthesis.

For a new protocol to be viable, it would have to meet the challenge of preparing significant quantities of the enantiopure product in a short reaction time, thus ensuring a high throughput of material. Important factors to be considered were: i) a lower catalyst

loading, ii) a high *ee*, iii) a streamlined protocol not requiring a high investment of time, reagents, solvents, and iv) minimal purifications.

The first improvement was achieved in the initial alkylation with MVK to prepare the required triketone **3a**. Using the above developed protocol under solvent free conditions, **3a** was isolated in 97% yield after purification. To enhance the enantioselectivity in the aldol reaction (**3a**→**1**) the catalyst loading was lowered to 2.5 mol% and we were pleased to see a slight increase in *ee* (92%). When the catalyst further reduced to 1 mol%, the reaction was very slow (after 1 week only a quarter of the starting material had reacted). After some experimentation, it was found that, working on a 1-g scale, the catalyst loading could be reduced to 2 mol% and only a 0.5 mol% of benzoic acid was needed under the solvent-free method. Thus, the Wieland–Miescher ketone **1** was obtained in up to 94% isolated yield and with 94% *ee*. The reaction was then scaled up to 10 g of starting material **3a** without affecting the reaction performance. Thus, target **1** was isolated with 93% overall yield from 2-methyl-1,3-cyclohexanedione and in 94% *ee* (the process is illustrated in Figure 3).[42]

Conclusions

A general organocatalytic enantioselective procedure for the synthesis of the Wieland–Miescher ketone (**1**) and its analogues incorporating several side-chains at C-8a has been developed. Among the organocatalysts assayed *N*-tosyl-(S_a)-binam-prolinamide (catalyst **G**) gave the best performance. High enantioselectivities of up to 97% were obtained under solvent-free conditions with low catalyst loadings. Furthermore, the procedure was operationally simple and **G** was found to be the most efficient and stereoselective proline enantiocatalyst reported to date for this annulation process that leads to valuable building blocks for natural product synthesis. A one-pot, two-step process for the Robinson annulation of **2b** to the valuable 8a-allyl derivative **4** was also developed.

Experimental Section

General Procedure for the Michael Addition of 2-Substituted 1,3-Cyclohexanediones (2) to MVK: Preparation of 2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (3a)

To 1,3-cyclohexadione **2a** (7.5 g, 0.059 mol) in a standard glass vial (10 cm × 3 cm)[43] with stirrer bar was added methyl vinyl ketone (5.36 mL, 0.065 mol) followed by Et_3N (82 μL, 0.59 mmol). The initial thick suspension slowly became more fluid as the solid slowly dissolved to a give a yellow/orange solution/oil. After 4.5 h the mixture was absorbed onto silica and purified by column chromatography (0→5→10→25% EtOAc/hexane) to give the triketone **3a** as a clear oil; yield: 11.36 g (97%). The NMR data obtained for **3a** are identical to those previously reported.[25]

2-Allyl-2-(3-oxobutyl)-1,3-cyclohexanedione (3b)

In accordance with the general procedure, dione **2b** (4.0 g, 0.026 mol) MVK (2.37 mL, 0.029 mol) and Et_3N (36 mL, 0.26 mmol) were stirred together for 3 h. Column chromatography gave **3b** as a pale yellow oil; yield: 5.56 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.97 (quint, J = 6.6 Hz, 2H, H-4), 2.04 (t, J = 7.2 Hz, 2H,CH_2-C2), 2.10 (s, 3H, CH_3), 2.33 (t, J = 7.2 Hz, 2H, CH_2CO), 2.49 (d, J = 7.6 Hz, 2H, CH_2 allyl), 2.54–2.70 (m, 4H, C-3 and C-5), 5.04

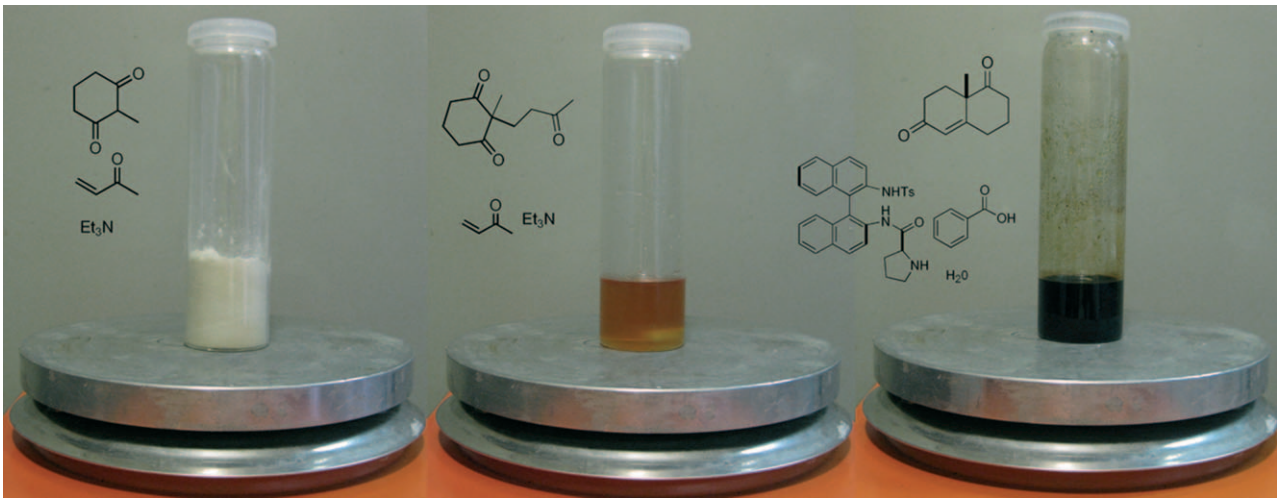


Figure 3. Robinson annulation of 2-methyl-1,3-cyclohexanedione (**2a**) under solvent-free conditions to give the Wieland–Miescher ketone (**1**) on a 10-g scale: (i) cyclohexanedione **2a**, MVK (1.1 equiv.), Et_3N (0.01 equiv.), t = 0 h (*left*); (ii) triketone **3a**, MVK (0.1 equiv.), Et_3N (0.01 equiv.), t = 4.5 h (*center*); (iii) enantiocatalytic aldol cyclization with catalyst **G** (0.02 equiv.) and benzoic acid (0.5 mol%) after 7 d (*right*).

(m, 2H, $=CH_2$), 5.50–5.60 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 (C-4), 27.9 (CH_2-C2), 29.9 (CH_3), 38.4 (CH_2), 38.9 (C-3 and C-5), 40.1 (CH_2 allyl), 67.7 (C-2), 119.5 ($=CH_2$), 132.0 (=CH), 207.5 (CO), 209.7 (C-1 and C-3); HR-MS (ESI): *m/z* = 223.1321, calcd. for $C_{13}H_{19}O_3$: 223.1328 ($M^+ + 1$).

See Supporting Information for the synthesis and spectroscopic data of triketones **3c–3k**.

(*S*)-8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (1)

In a standard glass vial (10 cm × 3 cm)[43,44] with stirrer bar was added triketone **3a** (10.0 g, 50.96 mmol) followed by the catalyst **G**[11] (546 mg, 1.02 mmol) and benzoic acid (31 mg, 0.255 mmol). The resulting mixture darkened and was stirred for 7 d. The mixture was absorbed onto silica and purified by column chromatography (0→5→10→25% EtOAc/hexane) to give the Wieland-Miescher ketone (**1**) as a clear oil which solidified on standing to give a white crystalline solid; yield: 8.57 g (94%, 94% *ee*); $[\alpha]_D^{22}$: +96 (*c* 1.1, C_6H_6); The NMR data obtained for **1** are identical to those previously reported.[7b]

(*R*)-8a-Allyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (4)[45]

Operating as above, **3b** (3.0 g, 13.5 mmol), catalyst **G** (182 mg, 0.34 mmol) and benzoic acid (17 mg, 0.13 mmol) were stirred together for 5 d. Column chromatography gave **4** as a yellow oil; yield: 2.53 g (93%, 97% *ee*); $[\alpha]_D^{22}$: +86 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.71 (qt, *J* = 13.2, 4.0 Hz, 1H, H-3ax), 2.08 (dt, *J* = 14.0, 9.6 Hz, 1H, H-8ax), 2.17 (dm, *J* = 13 Hz, H-3eq), 2.23 (dt, *J* = 14.4, 4.6 Hz, 1H, H-8eq), 2.42 (dd, *J* = 9.6, 4.6 Hz, 2H, H-7), 2.51 (dm, *J* = 14.4 Hz, 2H, H- 2eq, H-4eq), 2.57 (d, *J* = 7.2 Hz, CH2), 2.62–2.70 (m, 2H, H-2ax and CH_2), 2.78 (td, *J* = 14.0, 5.2 Hz, 1H, H-4ax), 5.10 (d, *J* = 8.5 Hz, 1H, $=CH_2$), 5.14 (d, *J* = 16 Hz, 1H, $=CH_2$), 5.60 (m, 1H, =CH), 5.89 (s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.3 (C-3), 26.2 (C-8), 31.9 (C-4), 33.3(C-7), 38.4 (C-2), 39.9 (CH_2), 54.7 (C-8a), 119.5 ($=CH_2$), 126.5 (C-5), 131.6 (=CH), 164.9 (C-4a), 198.2 (C-6), 209.1 (C-1); HR-MS (ESI): *m/z* = 205.1219, calcd. for $C_{13}H_{17}O_2$: 205.1223 ($M^+ + 1$).

See Supporting Information for the synthesis and spectroscopic data of Wieland-Miescher ketone analogues **5–13**.

One-Pot, Two-Step Robinson annulation of 2b to 4

To dione **2b** (500 mg, 3.28 mmol) in a standard glass vial with stirrer bar was added methyl vinyl ketone (0.297 mL, 3.62 mmol) followed by Et_3N (0.005 mL, 0.034 mmol). The initial thick suspension slowly became more fluid as the solid slowly dissolved to give a yellow/orange solution/oil. After 3 h the mixture was concentrated on a rotary evaporator and then kept under high vacuum with stirring for 3 h. Catalyst **G** (44 mg, 0.082 mmol) and benzoic acid (4 mg, 0.033 mmol) were added and the resulting mixture was stirred for 4 days. The mixture was absorbed onto silica gel and purified by column chromatography (gradient of hexane-EtOAc, 100:0–75:25) to give **4** as a clear yellow oil; yield: 533 mg (83%, 92% *ee*).

Acknowledgements

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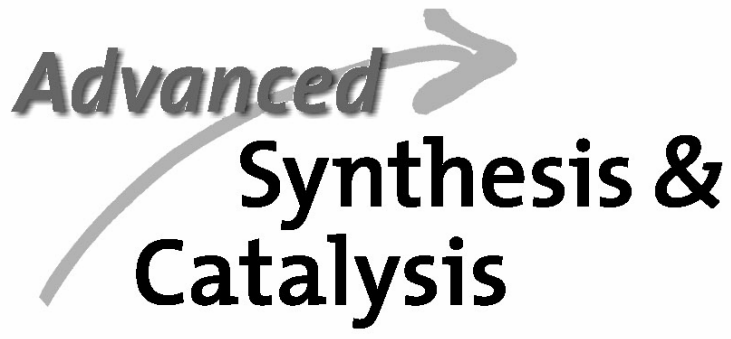
[41] Thus, when using catalyst **G**, the triketone obtained by the reaction of **2b** with ethyl vinyl ketone did not undergo cyclization.
[42] For a schematic diagram illustrating the time consuming and elaborate purification procedures required for the large scale preparation of enantiopure Wieland–Miescher ketone using L-Pro catalyst, see Supporting Information. In comparison, the use of binam-prolinamide catalyst **G** is operationally simple and easy to carry out.
[43] The reaction should be performed in a vial to obtain good mixing.
[44] Water in the aldol cyclization only forms on day 6, not before. A tall vial might be instrumental in removing the water, which condenses and remains on the vial wall, effectively removed from the reaction medium (Figure 2).
[45] The NMR data obtained for **4**,[12,22,23] **6**,[12,13] **8**,[12,29] and **12**[12] are identical to those previously reported. Values were assigned on the basis of gCOSY and gHSQC spectra.



Supporting Information

Supporting Information

Efficient Solvent-Free Robinson Annulation Protocols for the Highly Enantioselective Synthesis of the Wieland-Miescher Ketone and Analogs

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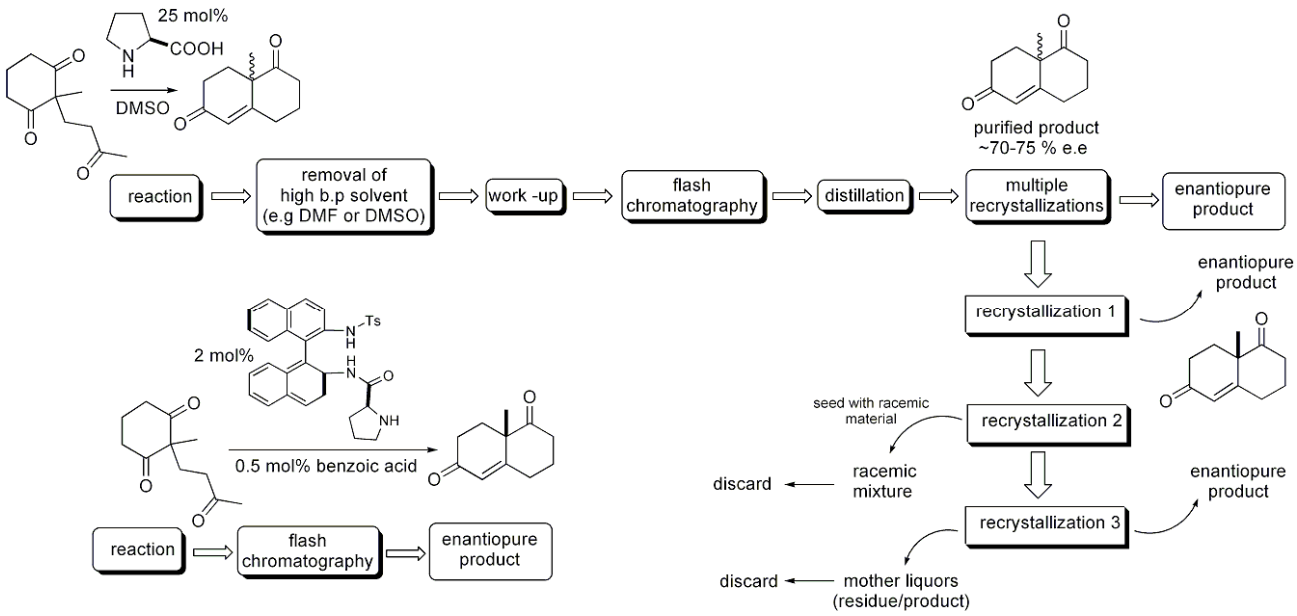


Schematic diagram illustrating the time consuming and elaborate purification procedures required for the large-scale preparation of enantiopure Wieland-Miescher ketone. In comparison the use of binam-prolinamide catalyst is operationally simple and easy to carry out.

Contents

2-(3-Methylbut-2-enyl)-2-(3-oxobutyl)-1,3-cyclohexanedione (3c)

In accordance with the general procedure, dione **2c** (300 mg, 1.66 mmol) MVK (152 μL, 1.83 mmol) and Et_3N (2 μL, 0.017 mmol) were stirred together for 6 h. Column chromatography (0→5→10→25% EtOAc/hexane) gave **3c** (395 mg, 95%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 and 1.64 (2s, 3H each), 1.90 (m, 1H), 1.96 (t, J = 6.2 Hz, 1H), 2.02 (t, J = 7.2 Hz, 2H), 2.07 (s, 3H), 2.26 (t, J = 7.6 Hz, 2H), 2.42 (d, J = 8 Hz, 2H), 2.56-2.65 (m, 4H), 4.83 (tm, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0, 17.9, 25.9, 27.5, 29.8, 36.0, 38.8, 39.0, 67.8, 117.5, 136.2, 207.8, 210.3. HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ 273.1461 (M^+ + Na), found 273.1462.

2-Benzyl-2-(3-oxobutyl)-1,3-cyclohexanedione (3d)

In accordance with the general procedure, dione **2d** (1.0 g, 4.94 mmol), MVK (453 μL, 5.44 mmol), DMF (2 mL) and Et_3N (7 μl, 0.049 mmol) were stirred together for 24 h. The mixture was dissolved in EtOAc (50 mL) and washed with brine (3 × 10 mL), dried and concentrated *in vacuo*. Column chromatography gave **3d** (1.27 g, 94%) as as a light beige solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (m, 1H), 1.72 (m, 1H), 2.08 (s, 3H), 2.11-2-19 (m, 4H), 2.28 (d, J = 7.4 Hz, 2H), 2.45 and 2.49 (2dd, J = 17.0, 7.6, 4.8 Hz,1H each), 3.06 (s, 2H), 7.00 (m, 2H), 7.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 29.7, 30.5, 38.8, 40.2, 44.1, 68.1, 127.1, 128.5, 129.9, 136.1, 207.2, 211.4. HRMS (ESI) calcd for $C_{17}H_{20}NaO_3$ 295.1305 (M^+ + Na), found 295.1308.

2-(3-Oxobutyl)-2-propargyl-1,3-cyclohexanedione (3e)

In accordance with the general procedure, dione **2e** (500 mg, 3.33 mmol) MVK (546 μL, 6.66 mmol) and Et_3N (5 μL, 0.033 mmol) were stirred together for 4 h. Column chromatography gave **3e** (711 mg, 97%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (qd, J = 13.2, 4.4 Hz, 1H), 1.95 (t, J = 2.4 Hz, 1H) 2.04 (t, J = 7.2 Hz, 2H), 2.09 (s, 3H, CH_3), 2.35 (t, J = 7.2 Hz, 2H), 2.59 (dd, J = 4.8, 2 Hz, 1H), 2.63 (m, 1H), 2.76 (ddd, J = 16.4, 9.6, 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 22.6, 29.1, 29.9, 37.7, 38.7, 66.8, 70.8, 80.2, 206.6, 208.6. HRMS (ESI) calcd for $C_{13}H_{16}NaO_3$ 243.0992 (M^+ + Na), found 243.0997.

2-(2-Bromo-2-propenyl)-2-(3-oxobutyl)-1,3-cyclohexanedione (3f)

In accordance with the general procedure, dione **2f** (200 mg, 0.865 mmol), MVK (144 μL, 1.73 mmol), DMF (200 μL) and Et_3N (6 μl, 0.043 mmol) were stirred together for 24 h. The mixture was dissolved in EtOAc (20 mL) and washed with brine (3 × 5 mL), dried and concentrated *in vacuo*. Column chromatography gave **3f** (230 mg, 88%) as as a light beige solid. The NMR data obtained for **3f** are identical to those reported previously reported.[29]

2-(But-3-enyl)-2-(3-oxobuyl)-1,3-cyclohexanedione (3g)

In accordance with the general procedure, dione **2g** (250 mg, 1.50 mmol), MVK (247 μL, 3.01 mmol) and Et_3N (11 μL, 0.075 mmol) were stirred together for 24 h. Column chromatography gave **3g** (320 mg, 90%,) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (m, 4H), 1.95 (quint, J = 6.6 Hz, 2H), 2.00 (t, J = 7.2 Hz, 2H), 2.08 (s, 3H), 2.33 (t, J = 7.2 Hz, 2H), 2.54-2.70 (m, 4H), 4.92 (d, J = 10.8 Hz, 1H), 4.96 (dd, J = 17.6, 1.2 Hz, 1H), 5.60-5.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 28.0, 28.9, 29.9, 34.4, 38.3, 38.6, 67.5, 115.4, 137.3, 207,5, 209.9. HRMS (ESI) calcd for $C_{14}H_{20}NaO_3$ 259.1305 (M^+ + Na), found 259.1302.

2-(4-Methylpent-3-enyl)-2-(3-oxobuyl)-1,3-cyclohexanedione (3h)

In accordance with the general procedure, dione **2h** (770 mg, 3.96 mmol) MVK (0.65 mL, 7.92 mmol) and Et_3N (6 μL, 0.040 mmol) were stirred together for 24 h. Column chromatography gave **3h** (0.97 g, 93%) as a pale yellow oil;^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (s, 3H), 1.64 (s, 3H), 1.76 (m, 4H), 1.95 (quint, J = 6.6 Hz, 2H), 2.01 (t, J = 7.2 Hz, 2H), 2.09 (s, 3H), 2.33 (t, J = 7.2 Hz, 2H), 2.63 (td, J = 6.8, 1.2 Hz, 4H), 4.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 17.6, 23.3, 25.6, 27.6, 29.9, 35.8, 38.5, 38.6, 67.8, 122.9, 133.0, 207.7, 210.0. HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ 287.1618 (M^+ + Na), found 287.1615.

2-(5-Methyl)pentyl-2-(3-oxobuyl)-1,3-cyclohexanedione (3i)

A suspension of **3h** (150 mg, 0.57 mmol) and Pd/C (10% w/w, 15 mg) in MeOH (10 mL) was stirred for 4 h under hydrogen. The catalyst was removed by filtration through celite and the solvent evaporated to give a residue, which was purified by flash chromatography ((0→10→25% EtOAc/hexane)) to give **3i** (128 mg, 85%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, J = 6.8 Hz, 6H), 1.10 (m, 4H), 1.45 (m, 1H), 1.76 (m, 2H), 1.95 (m, 2H), 2.01 (t, J = 7.2 Hz, 2H), 2.09 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 2.63 (t, J = 6.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 22.4, 22.5, 27.3, 27.7, 29.0, 29.9, 36.6, 38.7, 39.1, 68.2, 207.8, 210.2. HRMS (ESI) calcd for $C_{16}H_{26}NaO_3$ 289.1774 (M^+ + Na), found 289.1774.

2-[2-(Methoxycarbonyl)ethyl]-2-(3-oxobutyl)-1,3-cyclohexanedione (3j)

In accordance with the general procedure, dione **2j** (550 mg, 2.77 mmol) MVK (461 μL, 5.54 mmol) and Et_3N (4 μL, 0.028 mmol) were stirred together for 24 h. Column chromatography gave **3j** (572 mg, 77%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, J = 6.8 Hz, 6H), 1.10 (m, 4H), 1.45 (m, 1H), 1.76 (m, 2H), 1.95 (m, 2H), 2.01 (t, J = 7.2 Hz, 2H), 2.09 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 2.63 (t, J = 6.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 22.4, 22.5, 27.3, 27.7, 29.0, 29.9, 36.6, 38.7, 39.1, 68.2, 207.8, 210.2. HRMS (ESI) calcd for $C_{14}H_{20}NaO_5$ 291.1203 (M^+ + Na), found 291.1207.

2-[2-(Benzyloxy)ethyl]-2-(3-oxobutyl)-1,3-cyclohexanedione (3k)

In accordance with the general procedure, dione **2k** (846 mg, 3.25 mmol) MVK (0.53 mL, 6.5 mmol) and Et_3N (4 μL, 0.033 mmol) were stirred together for 24 h. Column chromatography gave **3k** (974 mg, 91%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (m, 1H), 1.84 (m, 1H), 1.94 (t, J = 7.2 Hz, 2H), 1.99 (t, J = 7.2 Hz, 2H), 2.09 (s, 3H), 2.33 (t, J = 7.2 Hz, 2H), 2.62 (t, J = 6.8 Hz, 4H), 3.39 (t, J = 6.4 Hz, 2H), 4.46 (s, 2H), 7.25-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 24.8, 27.5, 28.9, 32.1, 38.4, 67.7, 69.7, 72.7, 127.5, 127.6, 128.3, 138.3, 207.6, 209.9. HRMS (ESI) calcd for $C_{20}H_{26}NaO_4$ 353.1723 (M^+ + Na), found 353.1727.

(*R*)-8a-(3-Methylbut-2-enyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (5)

Following the procedure as given for the synthesis of **1**, triketone **3c** (100 mg, 0.40 mmol), catalyst **G** (11 mg, 0.02 mmol), and benzoic acid (0.5 mg, 0.004 mmol) were stirred together for 5 d. Flash chromatography (0→5→10→25% EtOAc/hexane) gave **5** (82 mg, 88%, 96% ee) as a yellow oil; $[\alpha]_D^{22}$: +93 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.61 and 1.69 (2s, 3H each, CH_3), 1.68 (qt, *J* = 14.0, 4.4 Hz, 1H, H-3ax), 2.05 (m, 1H, H-8ax), 2.13-2.19 (m, 2H, H-3eq, H-8eq), 2.38 (m, 2H, H-7), 2.45-2.54 (m, 2H, H-2eq, H-4eq), 2.50 (dd, *J* = 10.5, 7.5 Hz, 1H, CH_2), 2.62 (dd, *J* = 10.8, 7 Hz, 1H, CH_2), 2.66 (td, *J* = 14.0, 6.0 Hz, 1H, H-2ax), 2.78 (tdd, *J* = 13.5, 5.6, 2 Hz, H-4ax), 4.90 (tt, *J* = 7.4, 1.5 Hz, Hz, 1H, =CH), 5.88 (d, *J* = 1.2 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 18.0 (CH_3), 23.5 (C-3), 25.9 (CH_3), 26.4 (C-8), 32.1 (C-4), 33.7 (C-7), 34.4 (CH_2), 38.3 (C-2), 55.1 (C-8a), 117.3 (=CH), 126.4 (C-5), 136.2 (=C), 165.5 (C-4a), 198.4 (C-6), 209.9 (C-1). HRMS (ESI) calcd for $C_{15}H_{20}NaO_2$ 255.1356 (M^+ + Na), found 255.1352.

(*R*)-8a-Benzyl-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (6)[45]

Operating as above, **3d** (137 mg, 0.48 mmol), catalyst **G** (13 mg, 0.023 mmol), benzoic acid (0.6 mg, 0.005 mmol) and MeCN (0.08 mL) were stirred together for 10 d. Flash chromatography gave **6** (90 mg, 70%, 94% ee) as a yellow oil; $[\alpha]_D^{22}$: +113 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.70 (qt, *J* = 13.6, 4.4 Hz, 1H, H-3ax), 2.02 (td, *J* = 14.0, 4.4 Hz, 1H, H-8ax), 2.08-2.18 (m, 2H, H-3eq, H-8eq), 2.31 (ddd, *J* = 17.5, 14.0, 4.8 Hz, 2H, H-7ax), 2.39 (ddd, *J* = 17.5, 6.0, 3.2 Hz, 1H, H-7eq), 2.55 (dm, *J* = 14 Hz, 1H, H-4eq), 2.58 (dm, *J* = 14 Hz, 1H, H-2eq), 2.60-2.75 (m, 2H, H-2ax, H-4ax), 3.15 and 3.21 (2d, *J* = 13.6 Hz, CH_2), 5.96 (d, *J* = 1.2 Hz, 1H, H-5), 7.03-7.05 (m, 2H, ArH), 7.26-7.28 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.0 (C-3), 27.5 (C-8), 32.6 (C-4), 33.6 (C-7), 39.1 (C-2), 42.6 (CH_2), 55.8 (C-8a), 127.5 (C-5), 126.9, 128.6, 129.5, 135.5 (C_6H_5), 165.0 (C-4a), 198.2 (C-6), 209.9 (C-1). HRMS (ESI) calcd for $C_{17}H_{18}NaO_2$ 277.1199 (M^+ + Na), found 277.1195.

(*R*)-8a-(Prop-2-ynyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (7)

Operating as above, **3e** (207 mg, 0.94 mmol), catalyst **G** (13 mg, 0.023 mmol) and benzoic acid (1 mg, 0.009 mmol) were stirred together for 4 d. Flash chromatography gave **7** (149 mg, 78%, 90% ee) as a yellow oil; $[\alpha]_D^{22}$: +30 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.72 (qt, *J* = 13.4, 4.4 Hz, 1H, H-3ax), 2.13 (t, *J* = 2.8 Hz, 1H, CH), 2.10-2.20 (m, 2H, H-3eq, H-8ax), 2.35 (dt, *J* = 14.4, 4.6 Hz, 1H, H-8eq), 2.45-2.58 (m, 4H, 2H-7, H-4, and H-2), 2.66-2.82 (m, 4H, CH_2, H-2, and H-4), 5.92 (d, *J* = 1.6 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.2 (C-3), 26.1 (CH_2), 27.3 (C-8), 31.9 (C-4), 33.5 (C-7), 38.1 (C-2), 53.5 (C-8a), 73.3 (CH), 78.0 (C), 127.3 (C-5), 163.0 (C-4a), 197.8 (C-6), 208.0 (C-1). HRMS (ESI) calcd for $C_{13}H_{14}NaO_2$ 225.0886 (M^+ + Na), found 225.0891.

(*R*)-8a-(2-Bromo-2-propenyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (8)[45]

Operating as above, **3f** (115 mg. 0.38 mmol), catalyst **G** (20 mg, 0.04 mmol) and benzoic acid (0.5 mg, 0.004 mmol) were stirred together for 4 d. Flash chromatography gave **8** (76 mg, 70%, 96% ee) as a yellow oil; $[\alpha]_D^{22}$: +44 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.72 (qt, *J* = 13.6, 4.4 Hz, 1H, H-3ax), 2.15-2.22 (m, 2H, H-3eq, H-8ax), 2.36 (dt, *J* = 14.4, 4.6 Hz, 1H, H-8eq), 2.46 (dd, *J* = 10.8, 4.4 Hz, 2H, H-7), 2.52 (dm, *J* = 14 Hz, 1H, H-4eq), 2.59 (dm, *J* = 14 Hz, 1H, H-2eq), 2.80 (tdd, *J* = 14.5, 5.6, 2.0 Hz, H-4ax), 2.87 (td, *J* = 14.0, 6.0 Hz, 1H, H-2ax), 3.00 and 3.16 (2d, *J* = 15 Hz, CH_2), 5.62 (s, 2H, =CH_2), 5.91 (d, *J* = 2.0 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.8 (C-3), 26.1 (C-8), 32.2 (C-4), 33.5 (C-7), 39.0 (C-2), 46.6 (CH_2), 54.7 (C-8a), 122.3 (=CH_2), 126.4 (C), 127.2 (C-5), 163.9 (C-4a), 197.7 (C-6), 208.9 (C-1). HRMS (ESI) calcd for $C_{13}H_{15}BrNaO_2$ 305.0148 (M^+ + Na), found 305.0150.

(*S*)-8a-(But-3-enyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (9)

Operating as above, **3g** (113 mg, 0.48 mmol), catalyst **G** (13 mg, 0.024 mmol) and benzoic acid (0.6 mg, 0.005 mmol) were stirred together for 4 d. Flash chromatography gave **9** (56 mg, 54%, 95% ee) as a yellow oil; $[\alpha]_D^{22}$: +76 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.70 (qt, *J* = 13.6, 4.2 Hz, 1H, H-3ax), 1.85 (m, 2H, CH_2), 2.02 (m, 2H, CH_2), 2.07 (td, *J* = 14.4, 6.0 Hz, 1H, H-8ax), 2.15 (m, H-3eq), 2.24 (dt, *J* = 14.4, 4.4 Hz, 1H, H-8eq), 2.37 (m, 1H, H-7), 2.42 (m, 1H, H-7), 2.49 (dm, *J* = 14 Hz, 2H, H-2eq, H-4eq), 2.17 (dm, *J* = 13 Hz, H-3eq), 2.67 (td, *J* = 14.4, 6.4 Hz, 1H, H-2ax), 2.80 (tdd, *J*

= 14.0, 5.2, 1.6 Hz, 1H, H-4ax), 4.99 (d, *J* = 8.8 Hz, 1H, =CH_2), 5.04 (d, *J* = 16 Hz, 1H, =CH_2), 5.76 (m, 1H, =CH), 5.88 (d, *J* = 1.5 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.5 (C-3), 25.5 (C-8), 28.5 (CH_2), 31.8 (C-4), 33.5(C-7), 34.4 (CH_2), 38.4 (C-2), 54.6 (C-8a), 115.8 (=CH_2), 126.3 (C-5), 136.7 (=CH), 165.6 (C-4a), 198.1 (C-6), 210.0 (C-1). HRMS (ESI) calcd for $C_{14}H_{18}NaO_2$ 241.1199 (M^+ + Na), found 241.1201.

(*S*)-8a-(4-Methylpent-3-enyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (10)

Operating as above, **3h** (127 mg, 0.48 mmol), catalyst **G** (13 mg, 0.024 mmol) and benzoic acid (0.6 mg, 0.005 mmol) were stirred together for 10 d. Flash chromatography gave **10** (70 mg, 59%, 96% ee) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.57 and 1.66 (2s, 3H each, CH_3), 1.65-1.80 (m, 3H, H-3ax, CH_2), 1.90 (m, 2H, CH_2), 2.08 (dt, *J* = 14.0, 6.5 Hz, 1H, H-8ax), 2.10-2.20 (m, 2H), 2.20-2.50 (m, 4H), 2.66 (m, 1H, H-2ax), 2.79 (td, *J* = 14.0, 5.6 Hz, 1H, H-4ax), 5.08 (t, *J* = 2 Hz, 1H, =CH), 5.85 (d, *J* = 1.2 Hz, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 17.7 (CH_3), 23.5 (C-3), 25.5 (C-8), 26.4 (CH_3), 28.5 (CH_2), 31.8 (C-4), 33.5(C-7), 35.2 (CH_2), 38.3 (C-2), 54.9 (C-8a), 122.3 (=CH), 126.1 (C-5), 133.3 (=C), 166.0 (C-4a), 198.3 (C-6), 210.1 (C-1). HRMS (ESI) calcd for $C_{16}H_{22}NaO_2$ 269.1517 (M^+ + Na), found 269.1516.

(*S*)-8a-(3-Methylpentyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (11)

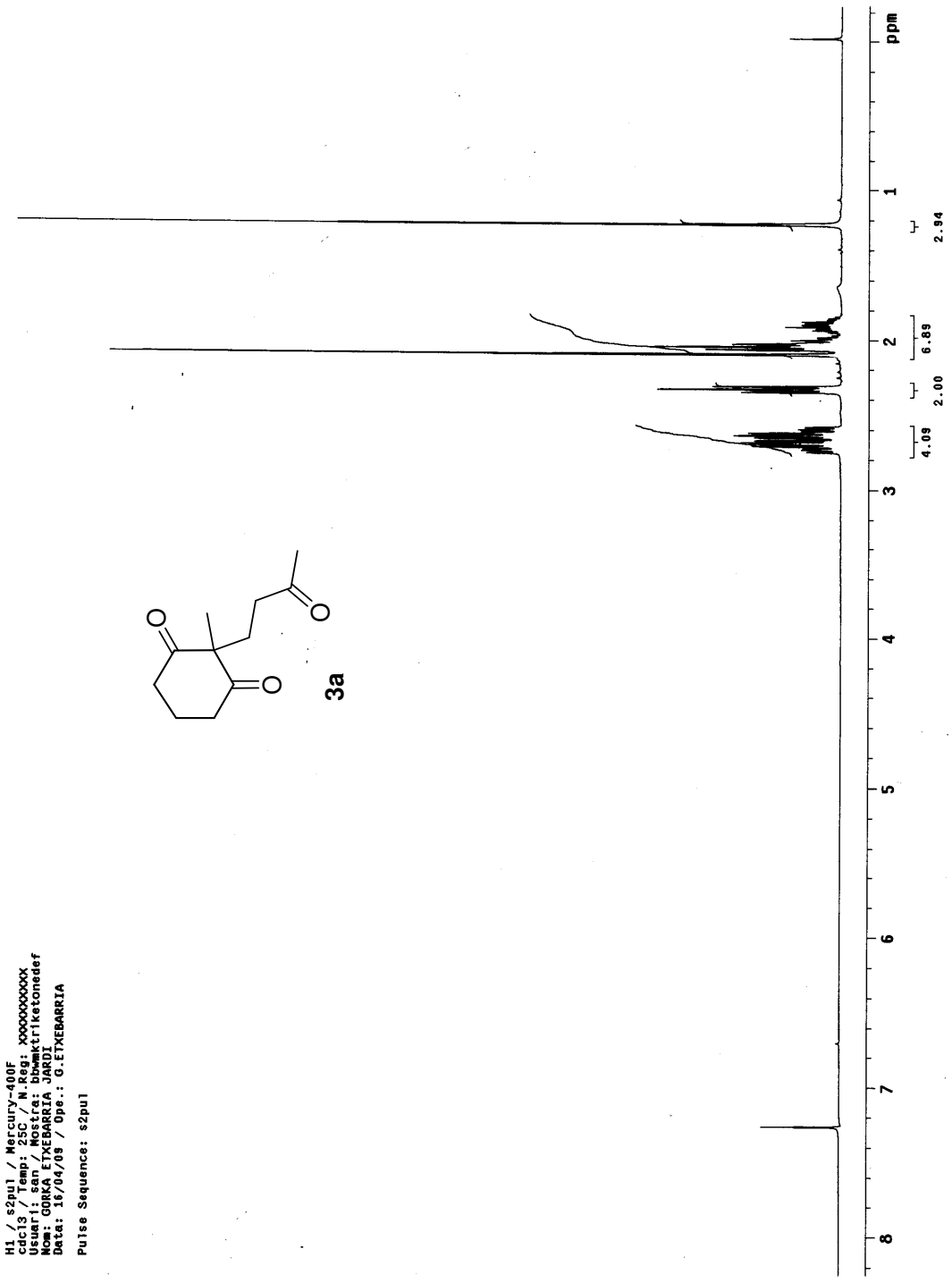
Operating as above, **3i** (67 mg, 0.25 mmol), catalyst **G** (7 mg, 0.013 mmol) and benzoic acid (0.4 mg, 0.003 mmol) were stirred together for 7 d. Flash chromatography gave **11** (33 mg, 53%, 84% ee) was isolated as a yellow oil; $[\alpha]_D^{22}$: +45 (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 0.85 (d, *J* = 6.8 Hz, 6H, CH_3), 1.00-1.35 (m, 4H, CH_2), 1.52 (m, 1H, CH), 1.63-1.78 (m, 2H, H-3ax, CH_2), 1.88 (td, *J* = 12.8, 4.0 Hz, 1H, CH_2), 2.05 (td, *J* = 14.0, 5.6 Hz, 1H, H-8ax), 2.15 (m, 1H, H-3eq), 2.24 (dt, *J* = 14.4, 4.4 Hz, 1H, H-8eq), 2.31-2.42 (m, 2H, H-7), 2.48 (dm, *J* = 14, 2H, H-2eq, H-4eq), 2.65 (td, *J* = 14.0, 6.4 Hz, 1H, H-2ax), 2.79 (td, *J* = 13.6, 5.2 Hz, 1H, H-4ax), 5.86 (s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 22.1 (CH_2), 22.5 ($2CH_3$), 23.5 (C-3), 25.6 (C-8), 27.7 (CH), 31.9 (C-4), 33.6 (C-7), 35.6 (CH_2), 38.4 (C-2), 39.1 (CH_2), 55.0 (C-8a), 126.1 (C-5), 166.2 (C-4a), 198.3 (C-6), 210.2 (C-1). HRMS (ESI) calcd for $C_{16}H_{24}NaO_2$ 271.1669 (M^+ + Na), found 271.1696.

(*R*)-8a-[(3-Methoxycarbonyl)ethyl]-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (12)[45]

Operating as above, **3j** (100 mg, 0.37 mmol), catalyst **G** (10 mg, 0.02 mmol) and benzoic acid (0.5 mg, 0.004 mmol) were stirred together for 8 d. Flash chromatography gave **12** (65 mg, 71%, 95% ee) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.69 (qt, *J* = 13.6, 4.4 Hz, 1H, H-3ax), 1.99-2.23 (m, 5H, H-3, H-8, CH_2), 2.29-2.52 (m, 6H, H-4, H-2, H-7, and CH_2), 2.72 (td, *J* = 13.6, 6.4 Hz, H-2ax), 2.81 (tdd, *J* = 14.0, 5.2, 1.6 Hz, 1H, H-4ax), 3.66 (s, 3H, OMe), 5.89 (s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.2 (C-3), 25.5 (C-8), 28.8 and 29.5 (CH_2), 31.8 (C-4), 33.3 (C-7), 38.3 (C-2), 51.9 (OMe), 53.7 (C-8a), 126.6 (C-5), 165.0 (C-4a), 172.7 (CO_2Me), 197.8 (C-6), 209.9 (C-1). HRMS (ESI) calcd for $C_{14}H_{18}NaO_4$ 273.1097 (M^+ + Na), found 273.1098.

(*S*)-8a-[(3-Benzyloxy]propyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione (13)

Operating as above, **3k** (200 mg, 0.61 mmol), catalyst **G** (16 mg, 0.03 mmol) and benzoic acid (0.74 mg, 0.006 mmol) were stirred together for 4 d. Flash chromatography gave **13** (148 mg, 78%, 94% ee) as a yellow oil; $[\alpha]_D^{22}$: +67 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY): δ = 1.40 and 1.60 (2m, 1H each, CH_2), 1.68 (qt, J = 14.0, 4.0 Hz, 1H, H-3ax), 1.88 (td, *J* = 12.4, 4.8 Hz, 1H, 1CH_2), 2.00-2.16 (m, 4H, H-3, 2H-8, CH_2), 2.20 (dt, *J* = 14.4, 4.6 Hz, H-8eq), 2.38 (m, 2H, H-7), 2.45 (dm, *J* = 13.5 Hz, 1 H, H-2eq), 2.46 (dm, *J* = 13.5 Hz, 1 H, H-4eq), 2.66 (td, *J* = 13.6, 6.4 Hz, H-2ax), 2.80 (tdd, *J* = 13.4, 5.0, 1.6 Hz, 1H, H-4ax), 3.44 (t, *J* = 6.5 Hz, 2H, OCH_2), 4.47 (s, 2H, OBn), 5.86 (d, *J* = 1.6 Hz, 1H, H-5), 7.26-7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.5 (C-3), 24.7 (CH_2), 25.5 (C-8), 31.8 (C-4), 32.0 (CH_2), 33.5 (C-7), 38.3 (C-2), 54.6 (C-8a), 69.4 (OCH_2), 73.0 (OBn), 126.2 (C-5), 127.6, 127.7, 128.4 (Ar), 138.2 (*ipso*-Ar), 165.9 (C-4a), 198.3 (C-6), 210.2 (C-1). HRMS (ESI) calcd for $C_{20}H_{24}NaO_3$ 335.1618 (M^+ + Na), found 335.1624.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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: sam / Nostre: bbwaktriketonedef
Nom: GORKA ETXEBARRIA JARDI
Data: 16/04/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
3a
ppm
1
2
3
4
5
6
7
8
4.09
2.00
6.89
2.94

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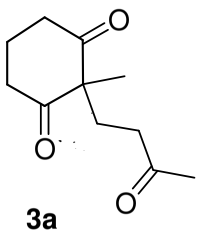
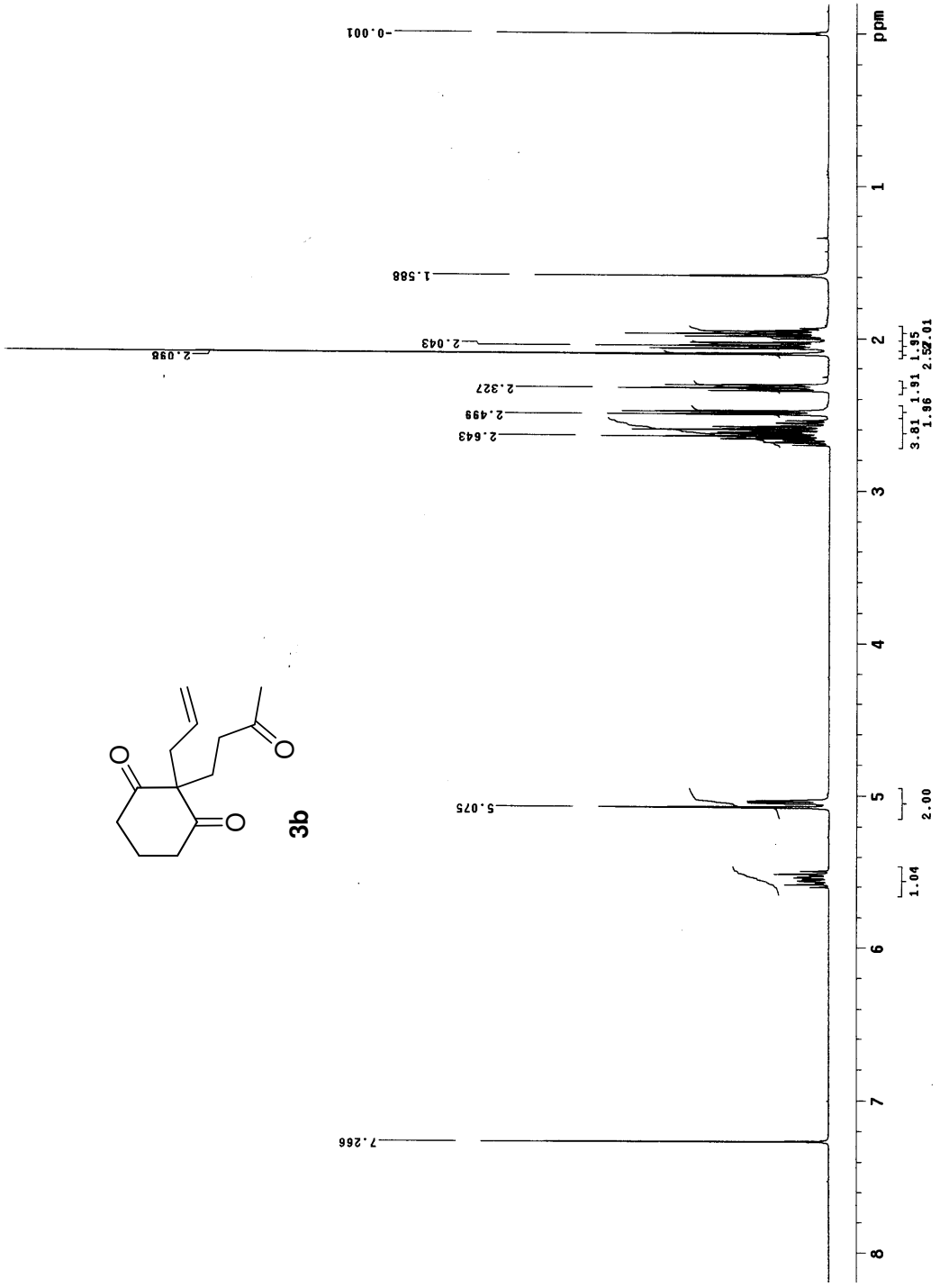
UNITAT DE RMN D ALT CAMP

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bbwmktriketonedef
Nom: GORKA ETXEBARRIA JARDI
Data: 16/04/09 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



3a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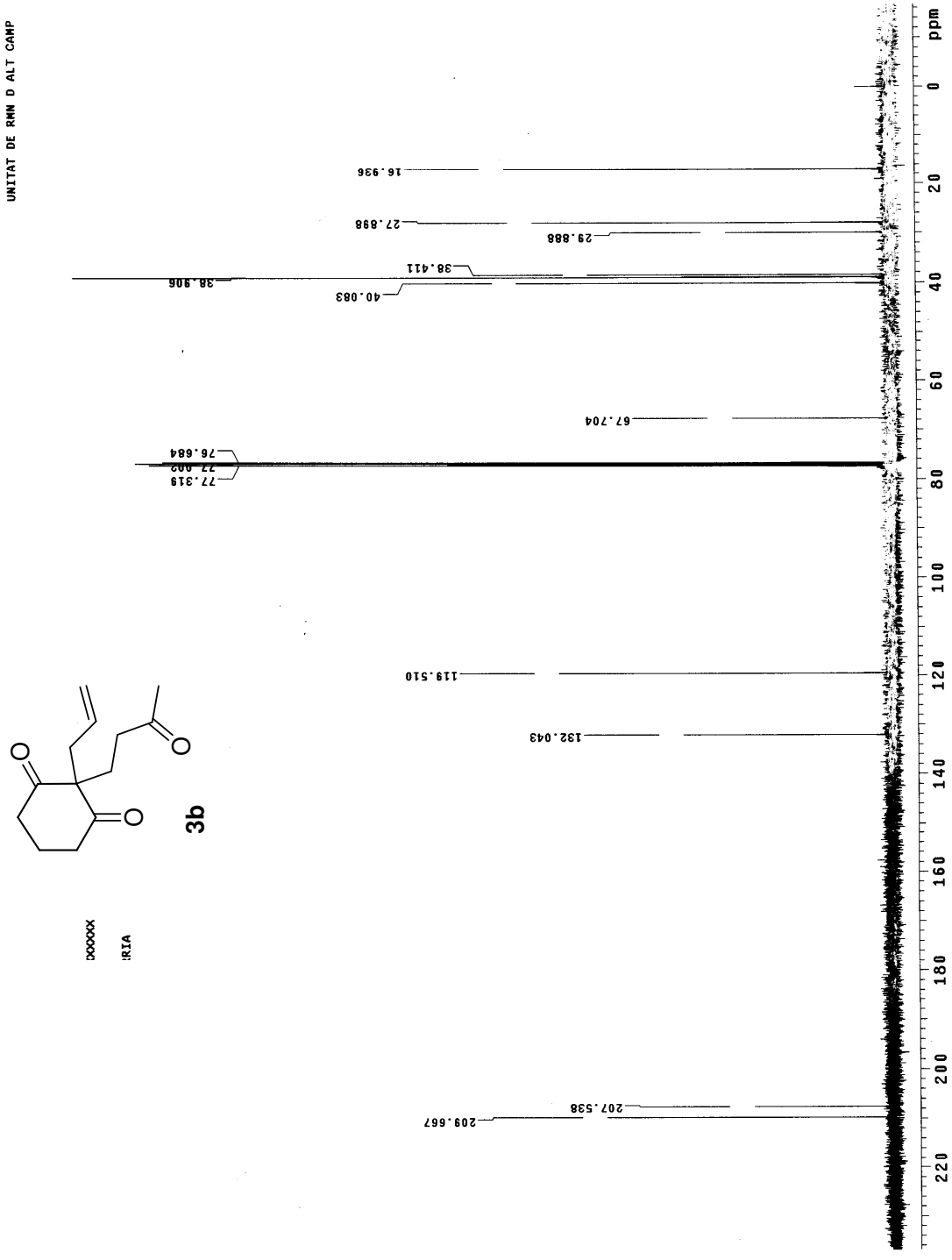
2.643
2.499
2.327
2.043
2.098
1.588
0.001
ppm
1
2
3
4
5
6
7
8
1.04
2.00
3.81
1.91
1.96
1.95
2.02.01
3b


UNITAT DE RMN D ALT CAMP
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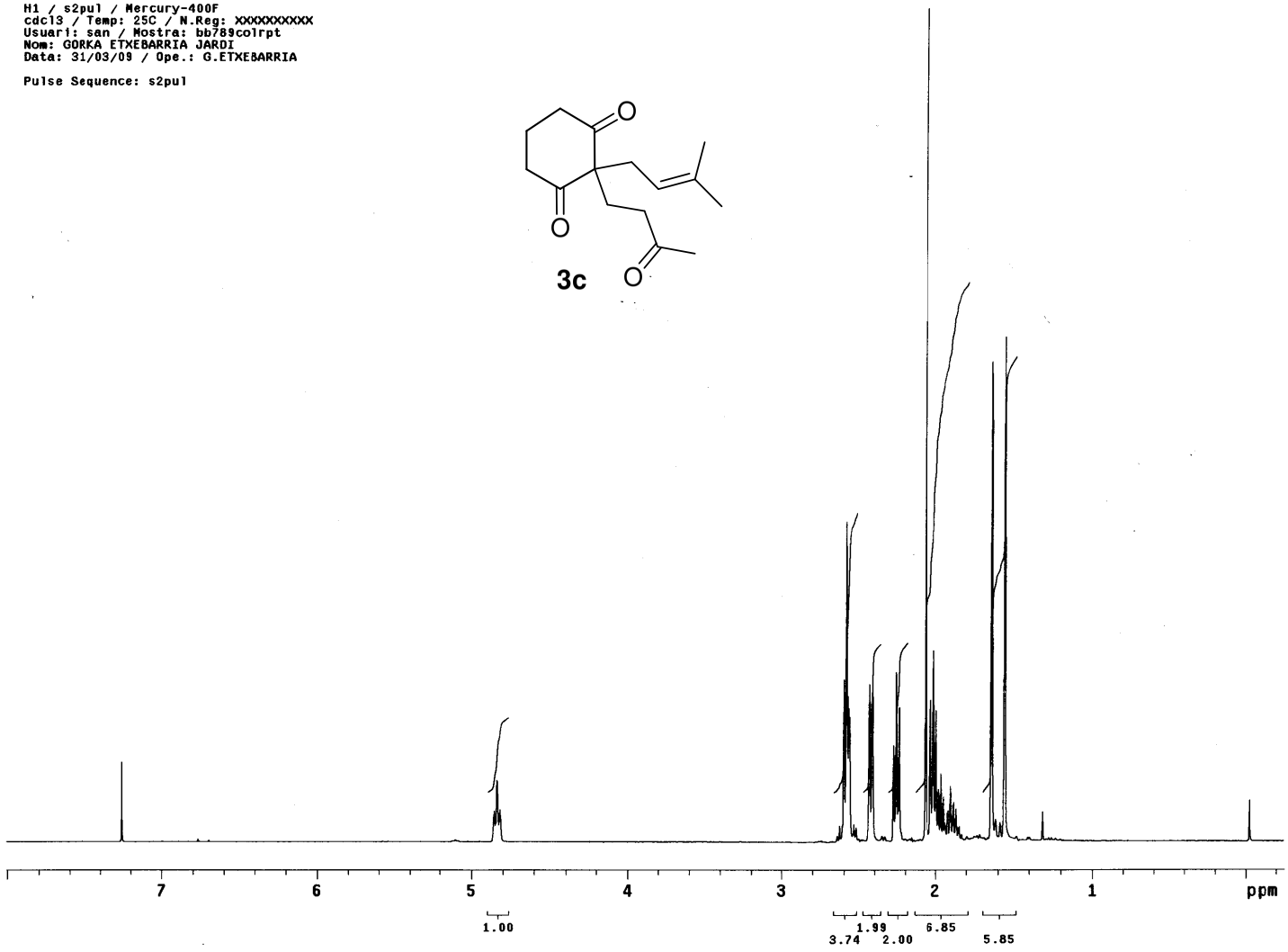
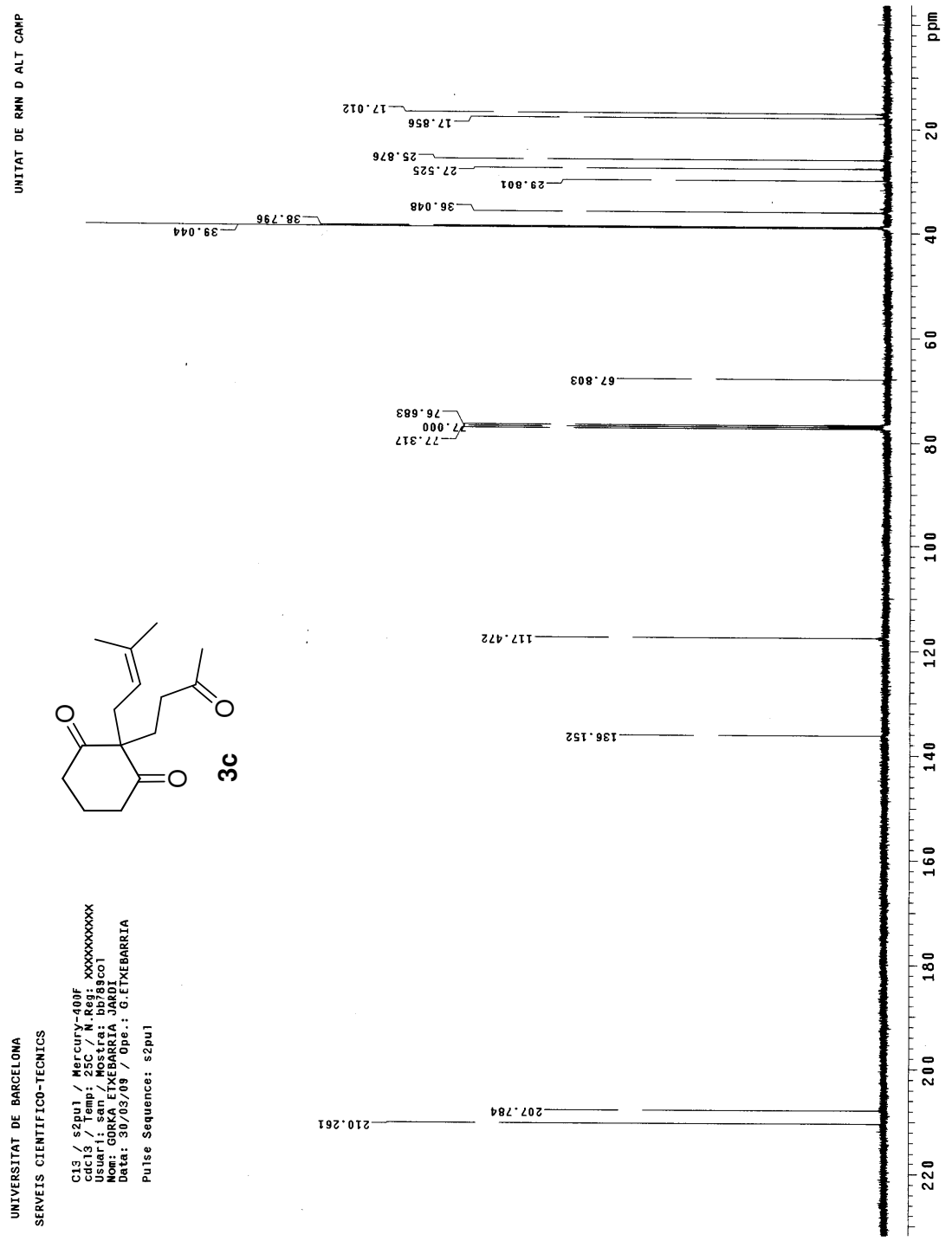
132.043
119.510
77.319
77.002
76.684
67.704
40.083
38.906
38.411
29.888
27.898
16.936
ppm
0
20
40
60
80
100
120
140
160
180
200
220
3b


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb789colrpt
Nom: GORKA ETXEBARRIA JARDI
Data: 31/03/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
O
O
O
3c
7
6
5
4
3
2
1
ppm
1.00
3.74
1.99
2.00
6.85
5.85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UNITAT DE RMN D ALT CAMP
C13 / s2pul / Mercury-400F
Cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: bb789col
Nom: GORKA ETXEBARRIA JARDI
Data: 30/03/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
3c
210.261
207.784
136.152
117.472
77.317
77.000
76.683
67.803
39.044
38.796
36.048
29.801
27.525
25.876
17.856
17.012
ppm

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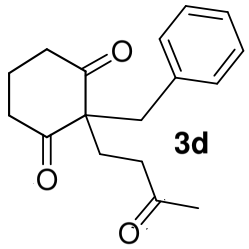
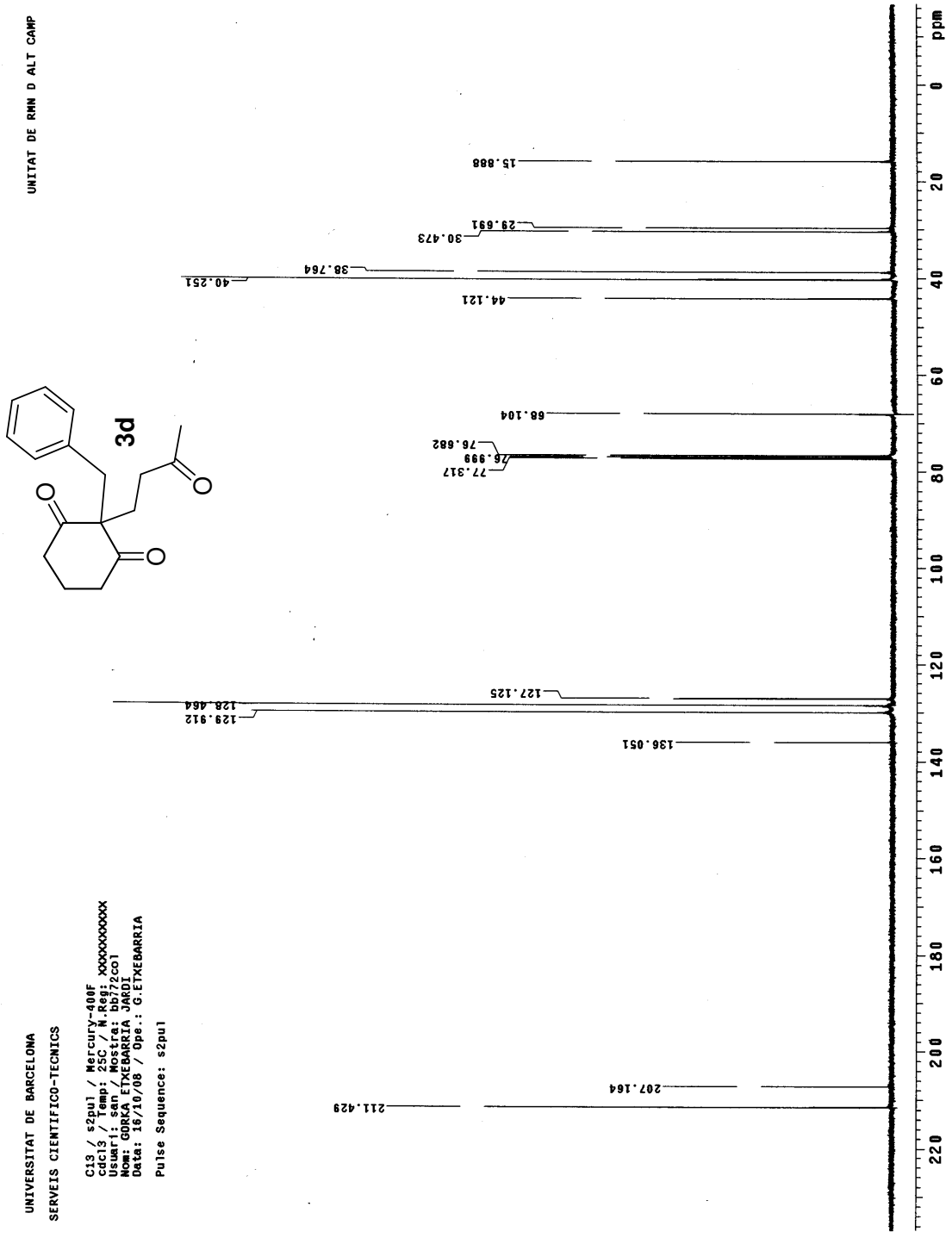
UNITAT DE RMN D ALT CAMP

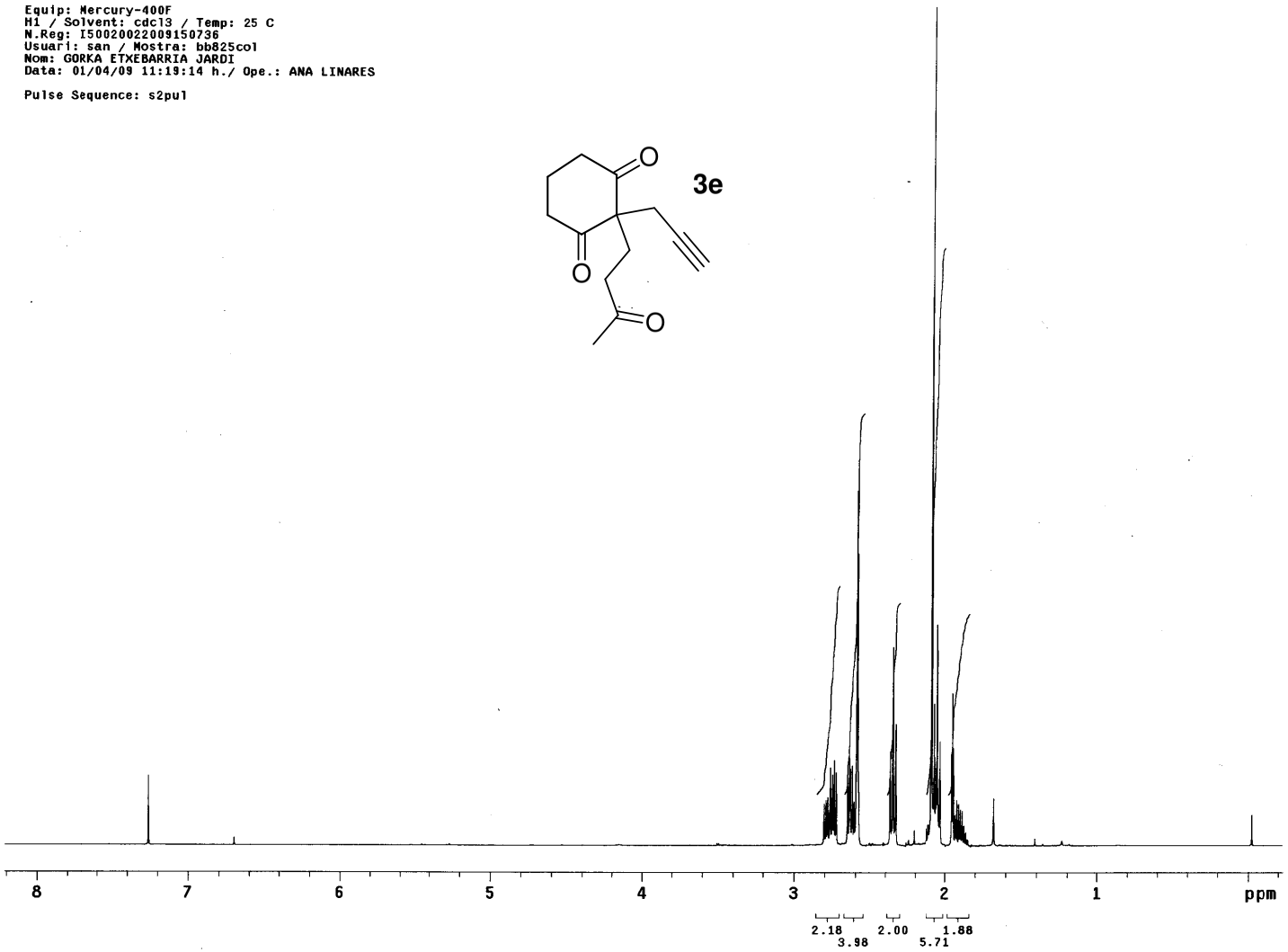
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb772col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/10/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



3d


UNITAT DE RMN D ALT CAMP
UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
CdCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb772co1
Nom: GORKA ETXEBARRIA JARDI
Data: 16/10/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
3d
15.888
29.691
30.473
38.764
40.251
44.121
68.104
76.682
76.999
77.317
127.125
128.464
129.912
136.051
207.164
211.429
ppm


Equip: Mercury-400F
H1 / Solvent: cdcl3 / Temp: 25 C
N.Reg: I50020022009150736
Usuari: san / Mostra: bb825col
Nom: GORKA ETXEBARRIA JARDI
Data: 01/04/09 11:19:14 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
3e
8
7
6
5
4
3
2
1
ppm
2.18
3.98
2.00
5.71
1.88

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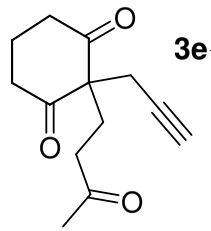
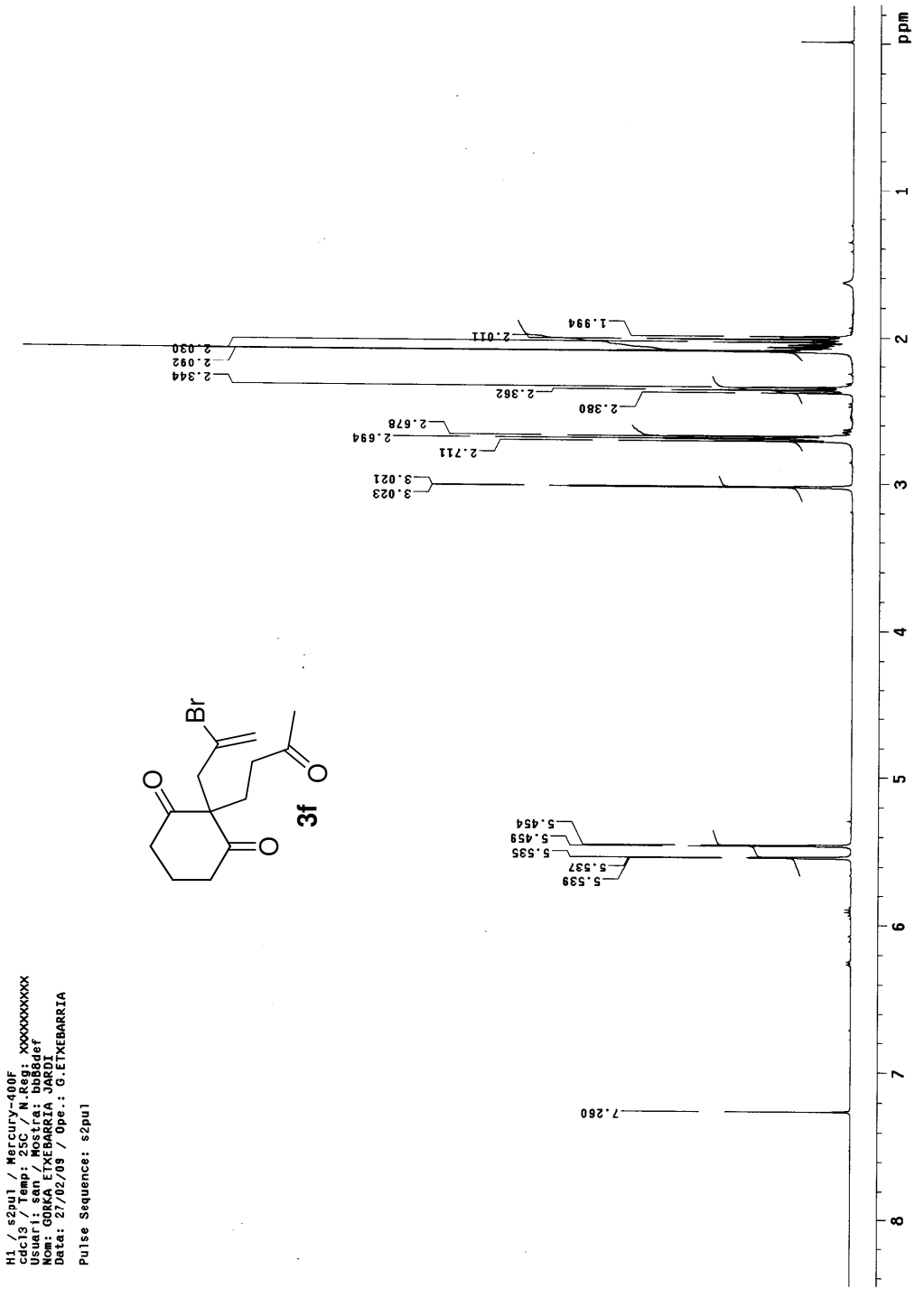
UNITAT DE RMN D ALT CAMP

Equip: Mercury-400F
C13 / Solvent: cdcl3 / Temp: 25 C
N.Reg: I500200220091507 36
Usuari: san / Mostra: bb825col
Nom: GORKA ETXEBARRIA JARDI
Data: 01/04/09 11:18:42 h./ Ope.: ANA LINARES

Pulse Sequence: s2pul



3e


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: sam Mostra: bbBBdef
Nom: GORKA ETXEBARRIA JARDI
Data: 27/02/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
Br
O
O
O
3f
7.260
5.539
5.537
5.535
5.459
5.454
3.023
3.021
2.711
2.694
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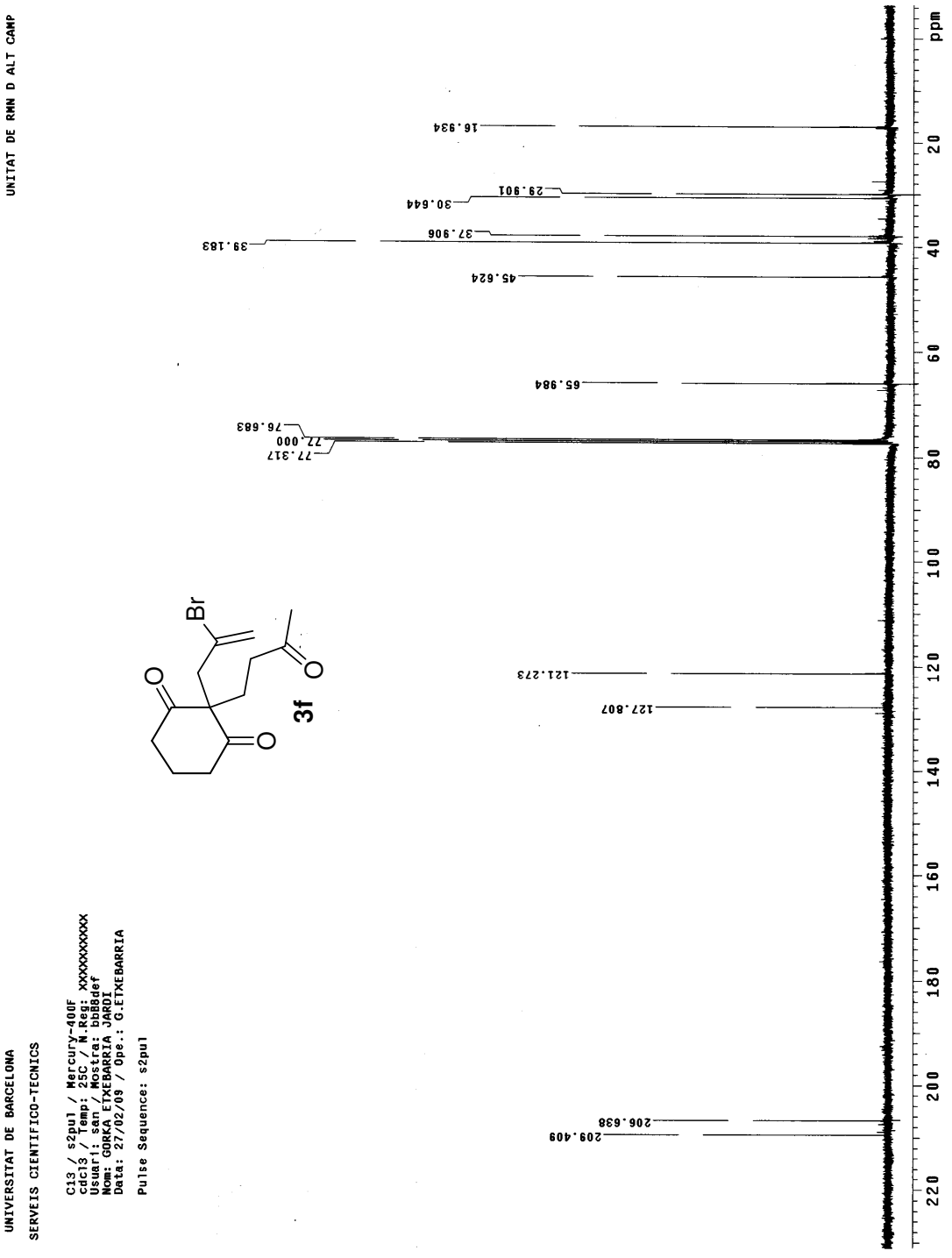
2.344
2.092
2.030
2.011
1.994
ppm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SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Rag: XXXXXXXXXX
Usuari: sam / Mostra: bbBBdef
Nom: GORKA EITXEBARRIA JARDI
Data: 27/02/09 / Ope.: G.EITXEBARRIA
Pulse Sequence: s2pul
Br
O
O
O
3f
16.934
29.901
30.644
37.906
39.183
45.624
65.984
76.683
77.000
77.317
121.273
127.807
206.638
209.409
ppm

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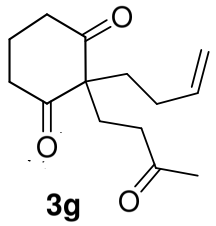
UNITAT DE RMN D ALT CAMP

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge782col
Nom: GORKA ETXEBARRIA JARDI
Data: 15/10/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



3g

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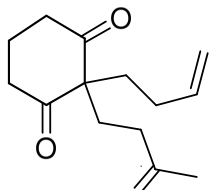
SERVEIS CIENTIFICO-TECNICS

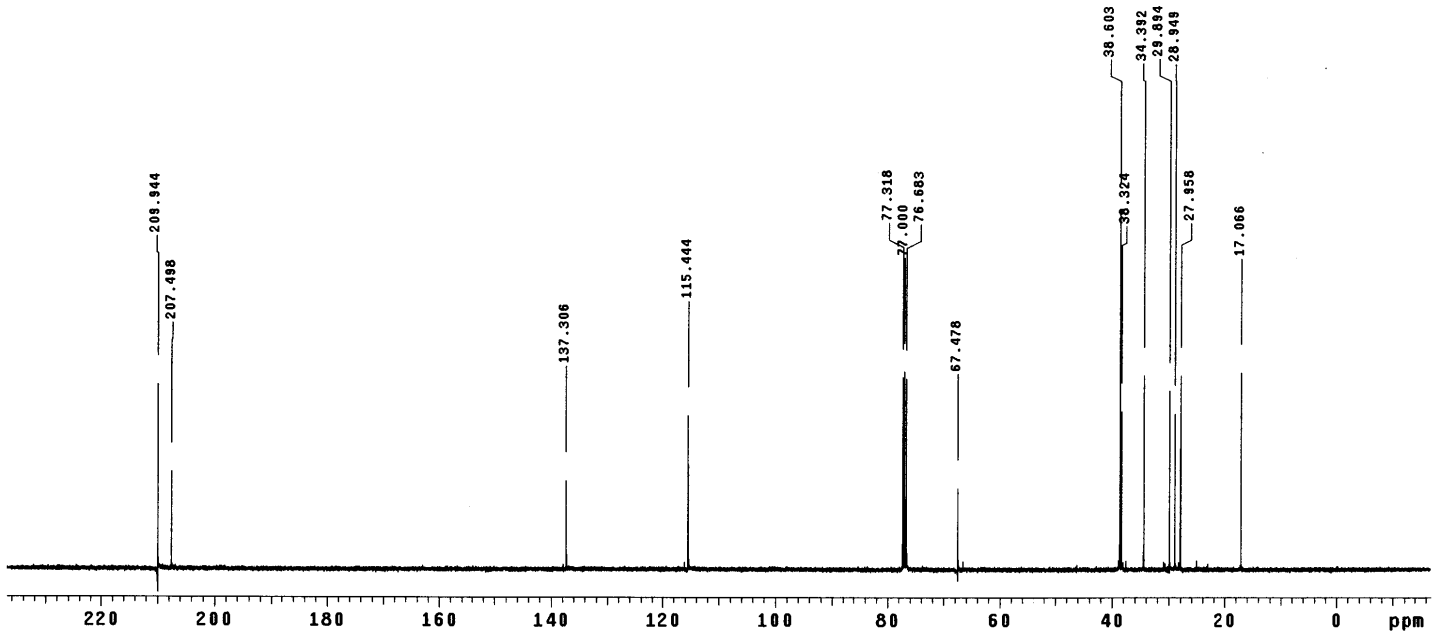
UNITAT DE RMN D ALT CAMP

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge782col
Nom: GORKA ETXEBARRIA JARDI
Data: 15/10/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



3g



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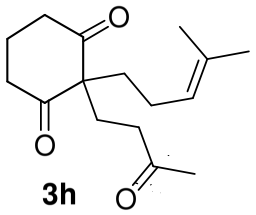
SERVEIS CIENTIFICO-TECNICS

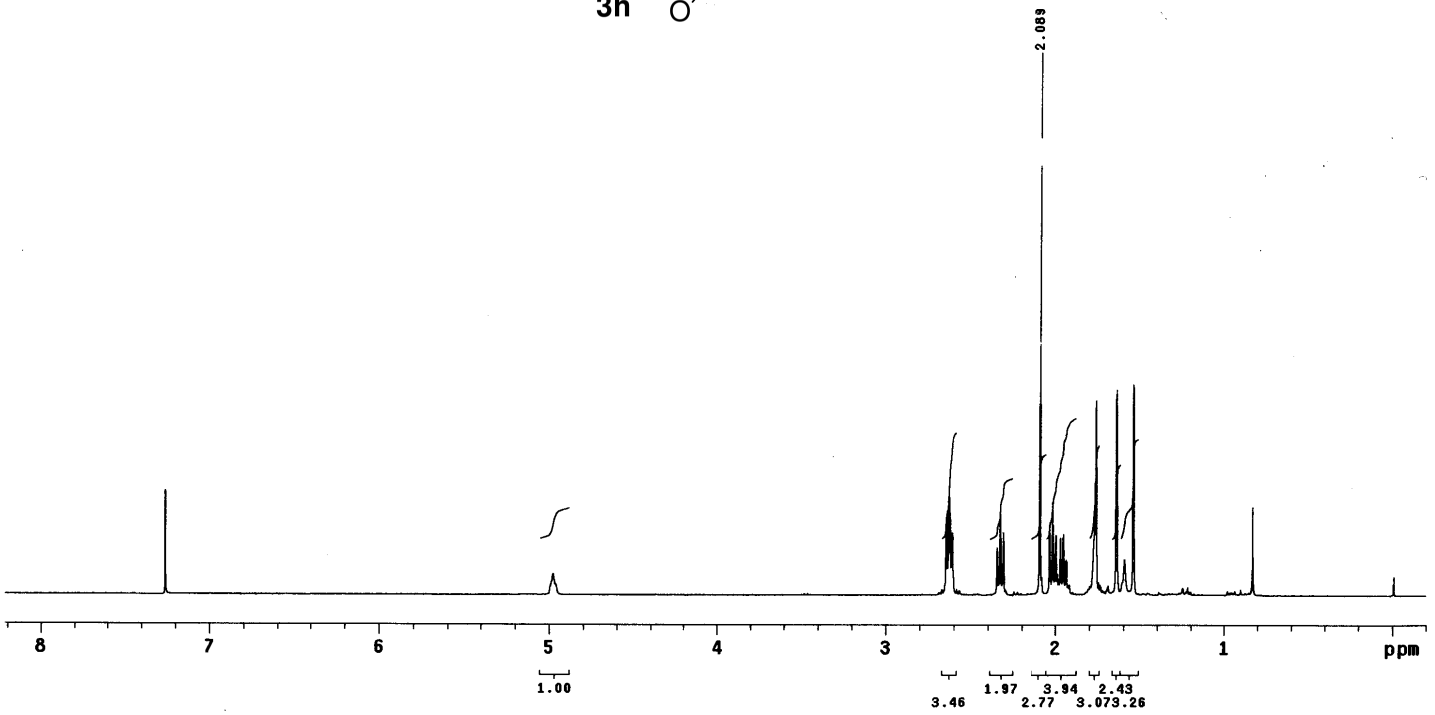
UNITAT DE RMN D ALT CAMP

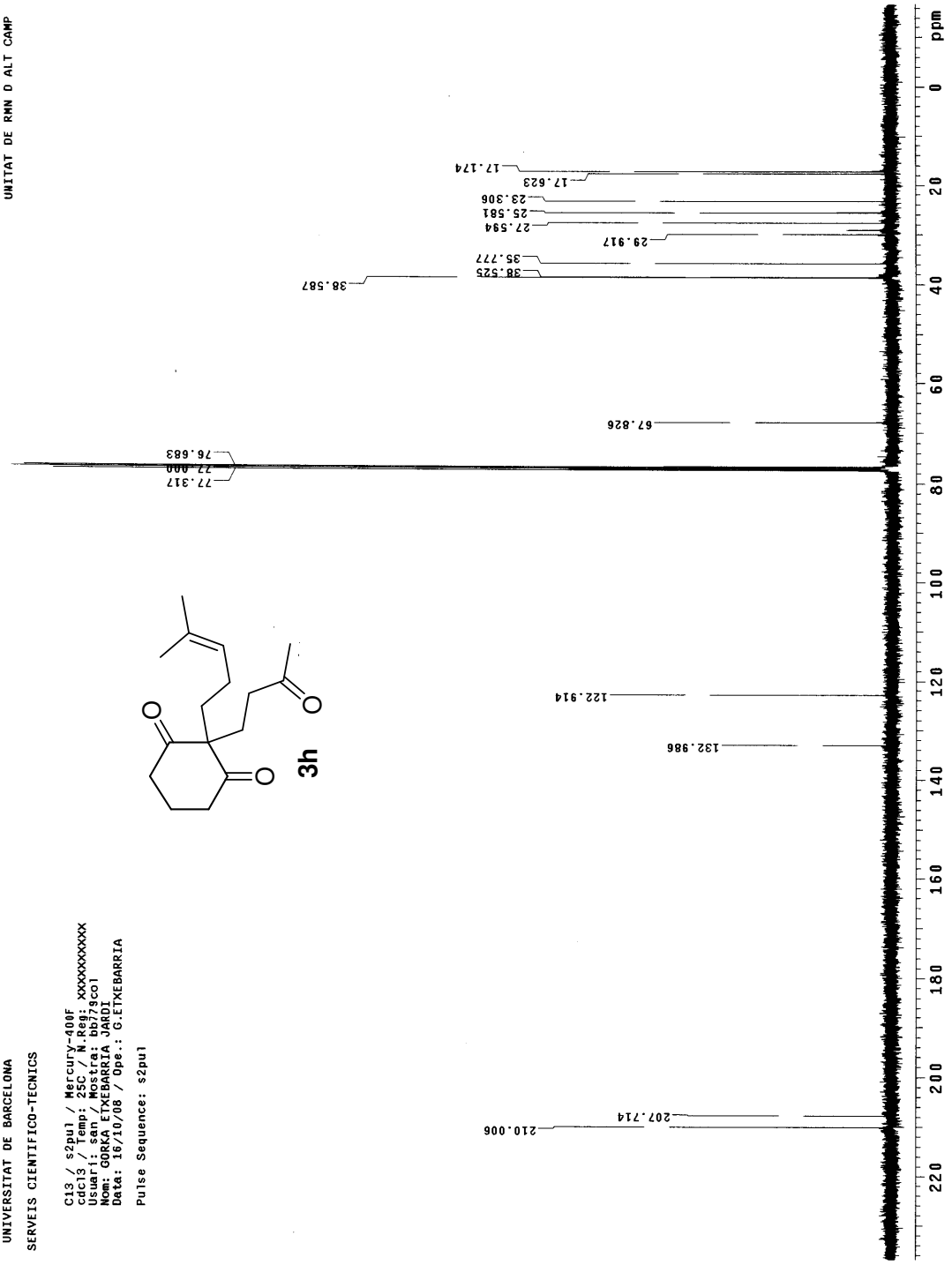
H1 / s2pul / Mercury-400f
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb779col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/10/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



3h




UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb779col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/10/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
3h
210.006
207.714
132.986
122.914
77.317
77.000
76.683
67.826
38.587
38.525
35.777
29.917
27.594
25.581
23.306
17.623
17.174
ppm

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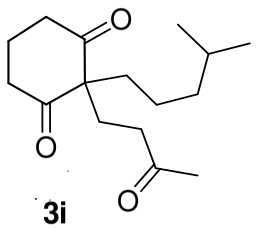
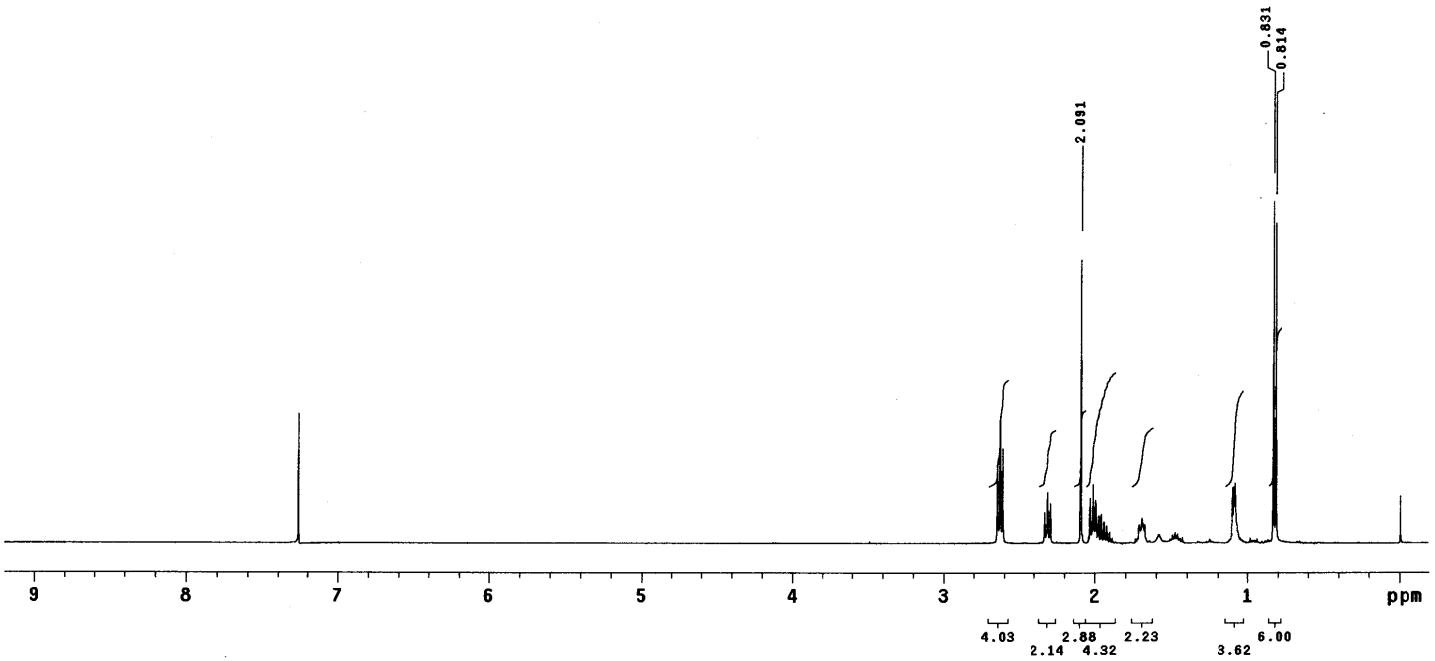
UNITAT DE RMN D ALT CAMP

H1 / s2pul / Mercury-400f
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge349col
Nom: GORKA ETXEBARRIA JARDI
Data: 06/11/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



3i



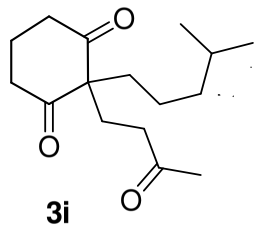
UNIVERSITAT DE BARCELONA

SERVEIS CIENTIFICO-TECNICS

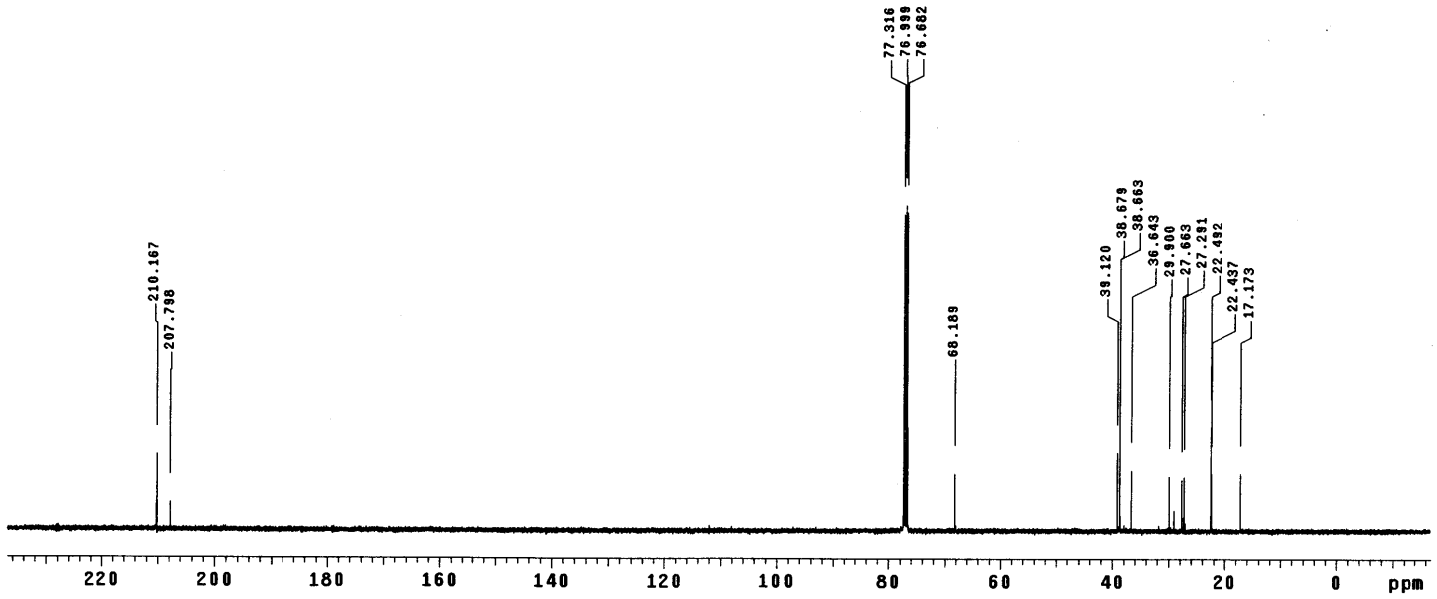
UNITAT DE RMN D ALT CAMP

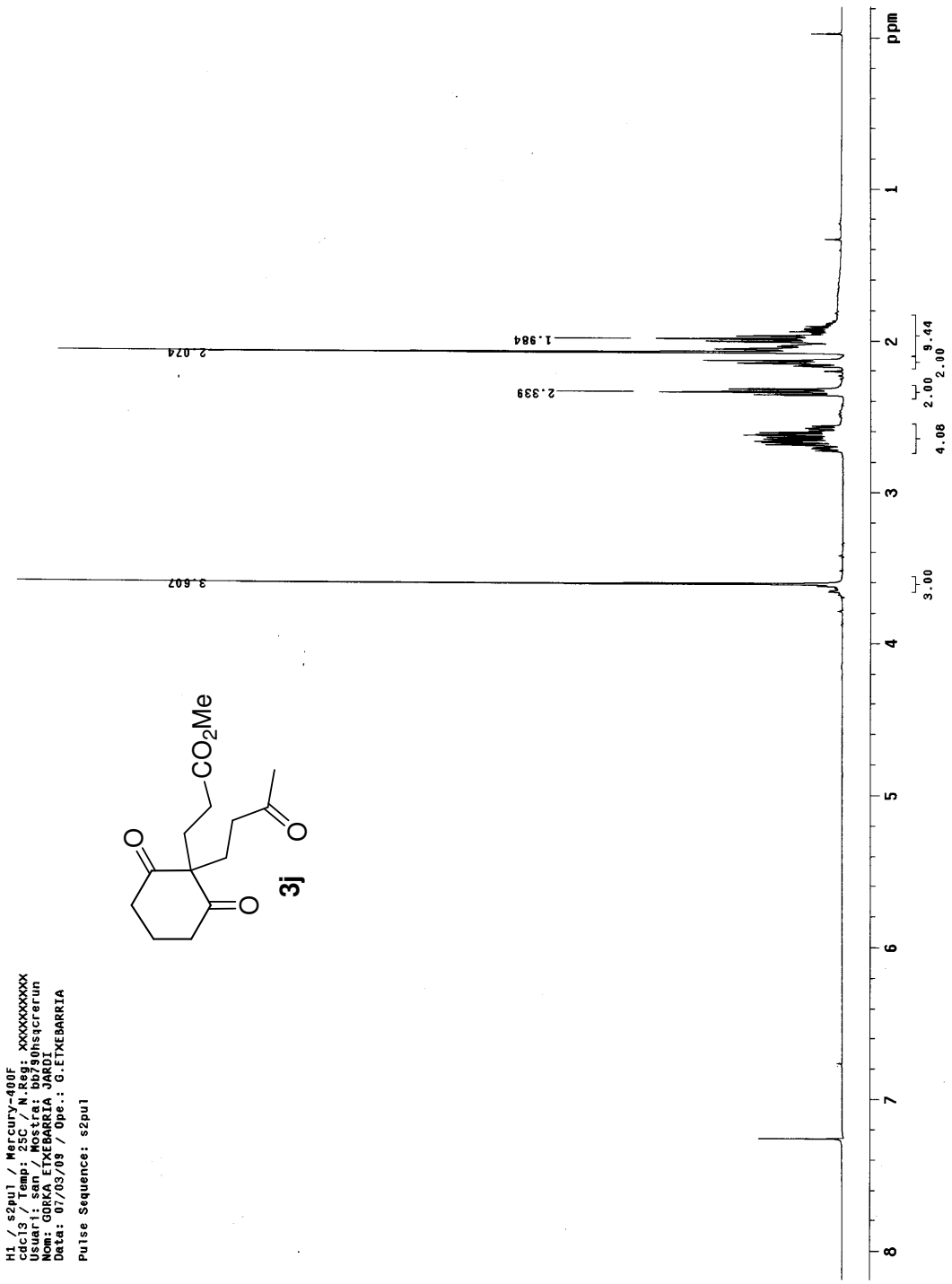
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gs349col
Nom: GORKA ETXEBARRIA JARDI
Data: 06/11/08 / Ope.: G.ETXEBARRIA

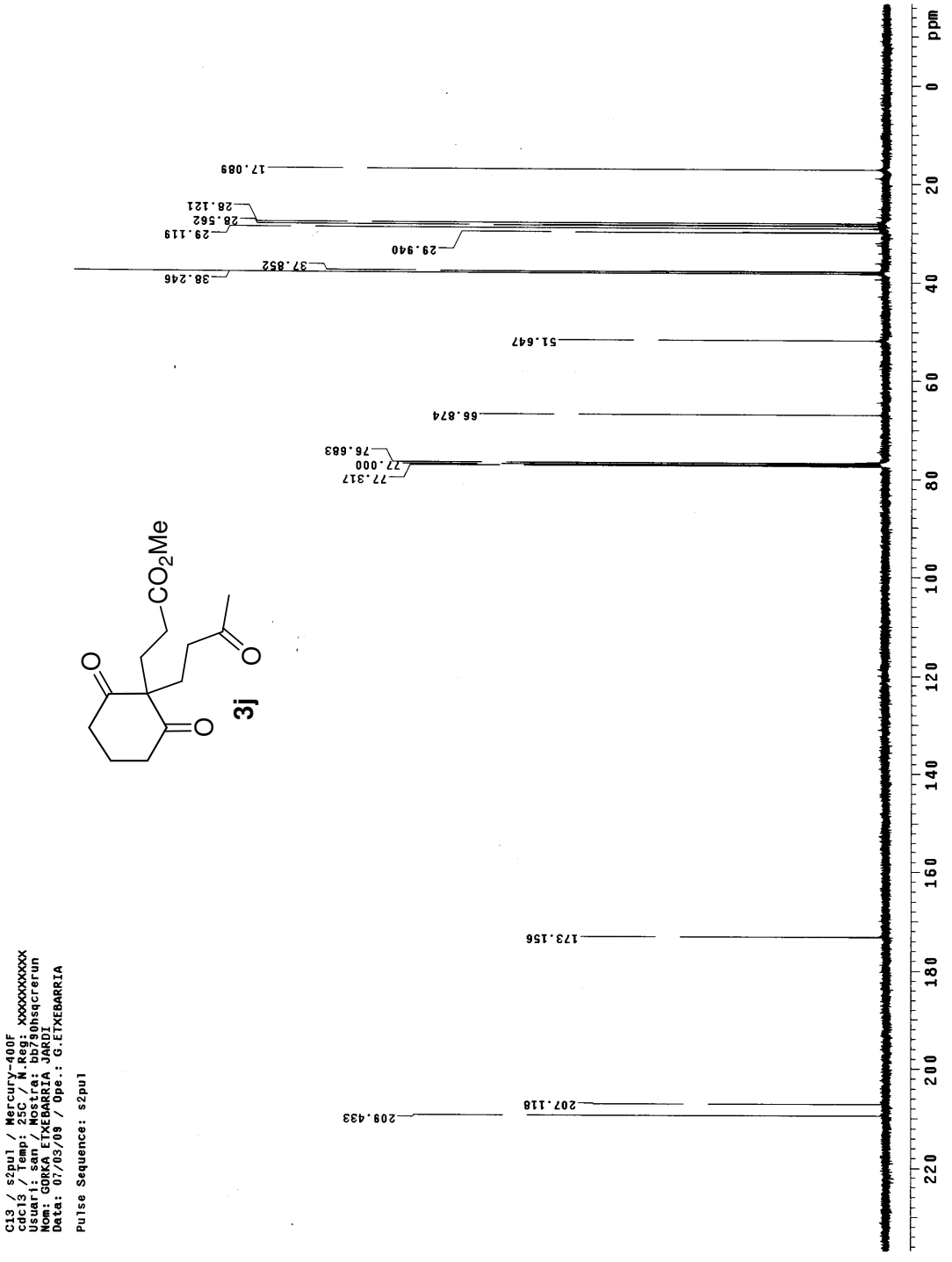
Pulse Sequence: s2pul

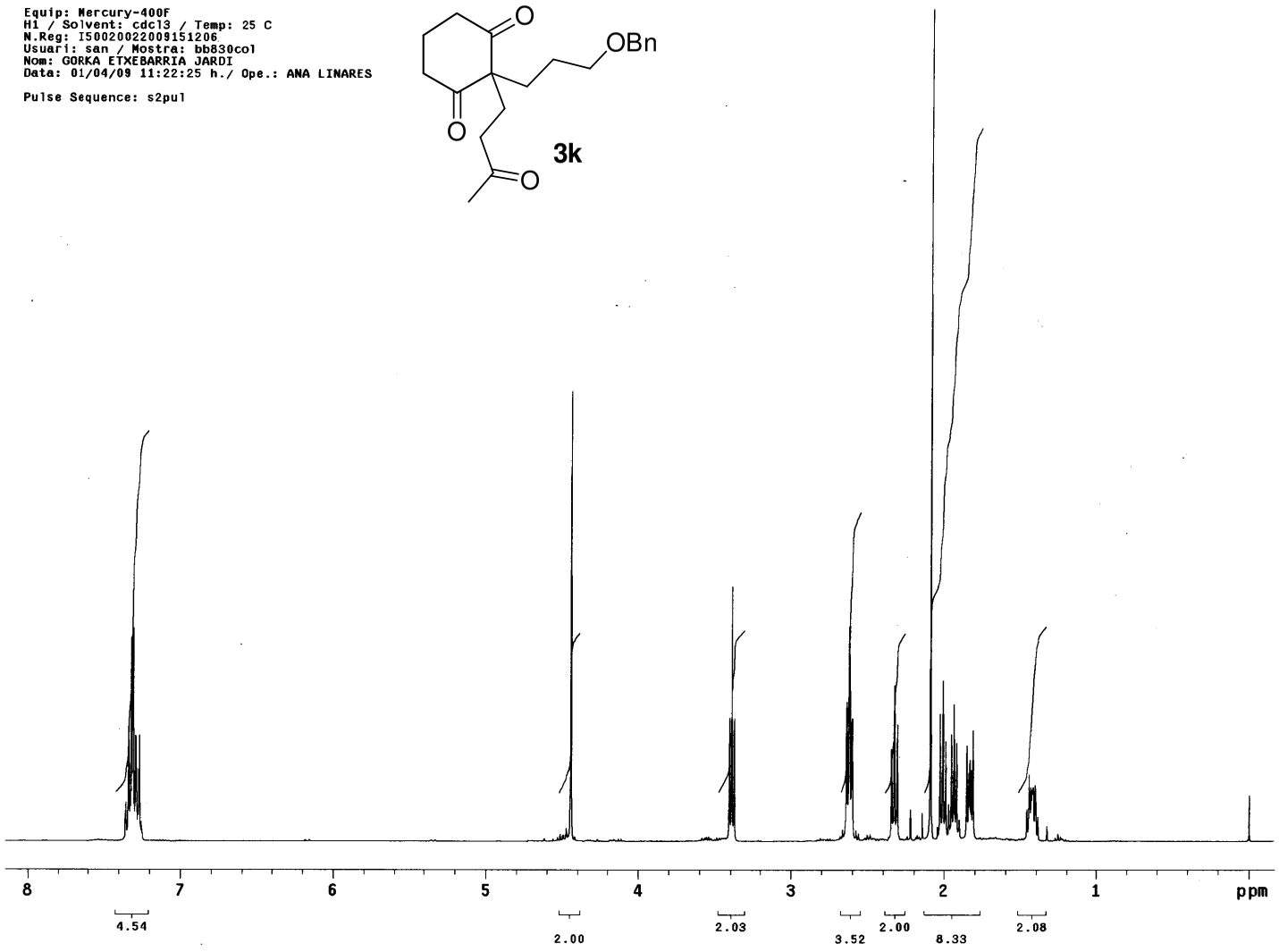


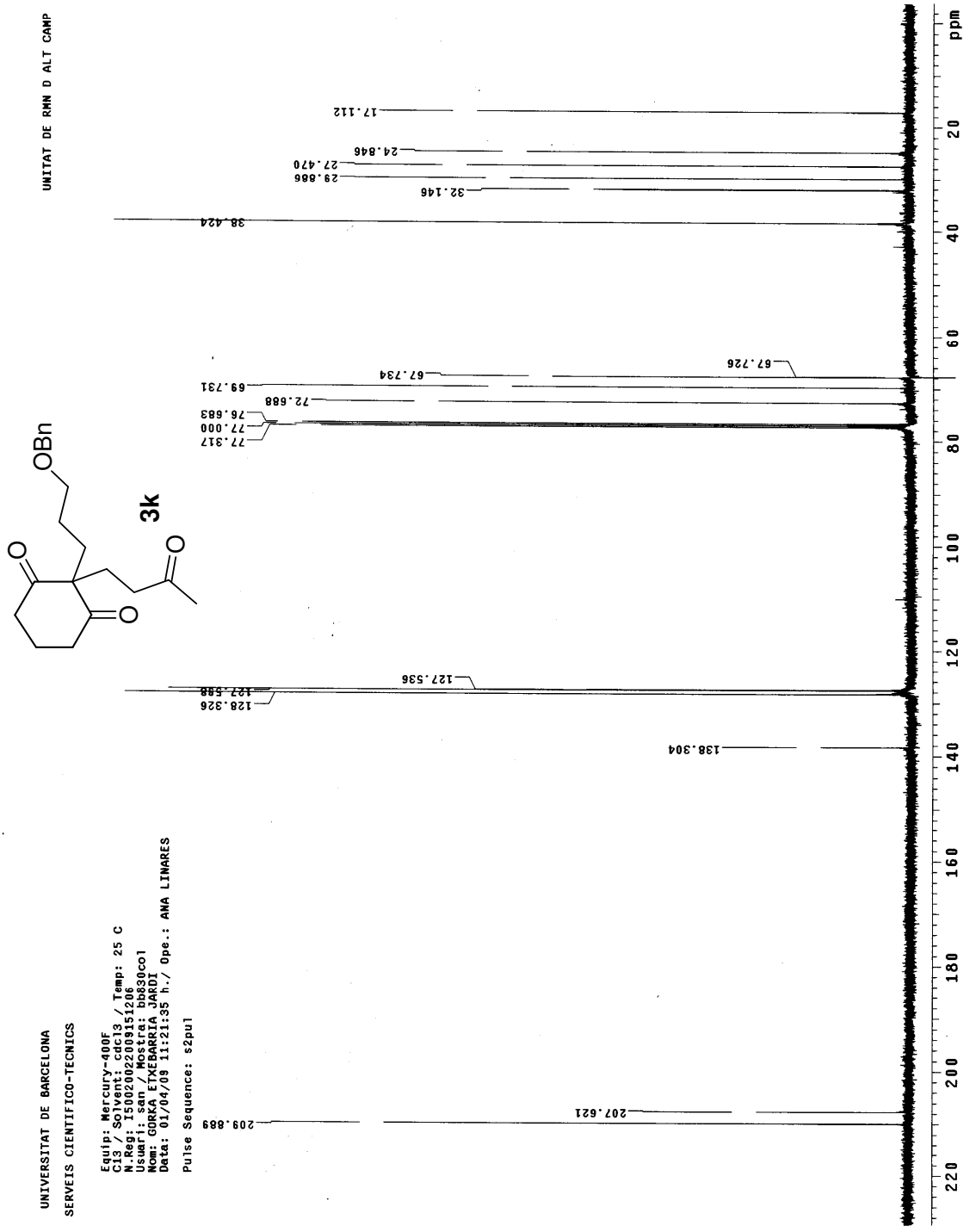
3i




H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: bb790hsqcrerun
Nom: GORKA ETXEBARRIA JARDI
Data: 07/03/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
3.807
2.074
1.984
2.339
3.00
2.00
9.44
2.00
4.08
ppm
1
2
3
4
5
6
7
8
CO2Me
O
O
O
3j

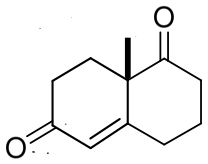

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb790hsqcrerun
Nom: GORKA ETXEBARRIA JARDI
Data: 07/03/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
17.089
28.121
28.562
29.119
29.940
37.852
38.246
51.647
66.874
76.683
77.000
77.317
173.156
207.118
209.433
ppm
0
20
40
60
80
100
120
140
160
180
200
220
CO2Me
O
O
O
3j


Equip: Mercury-400F
H1 / Solvent: cdcl3 / Temp: 25 C
N.Reg: I50020022009151206
Usuari: san / Mostra: bb830col
Nom: GORKA ETXEBARRIA JARDI
Data: 01/04/09 11:22:25 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
O
OBn
O
O
3k
8
7
6
5
4
3
2
1
ppm
4.54
2.00
2.03
3.52
2.00
8.33
2.08

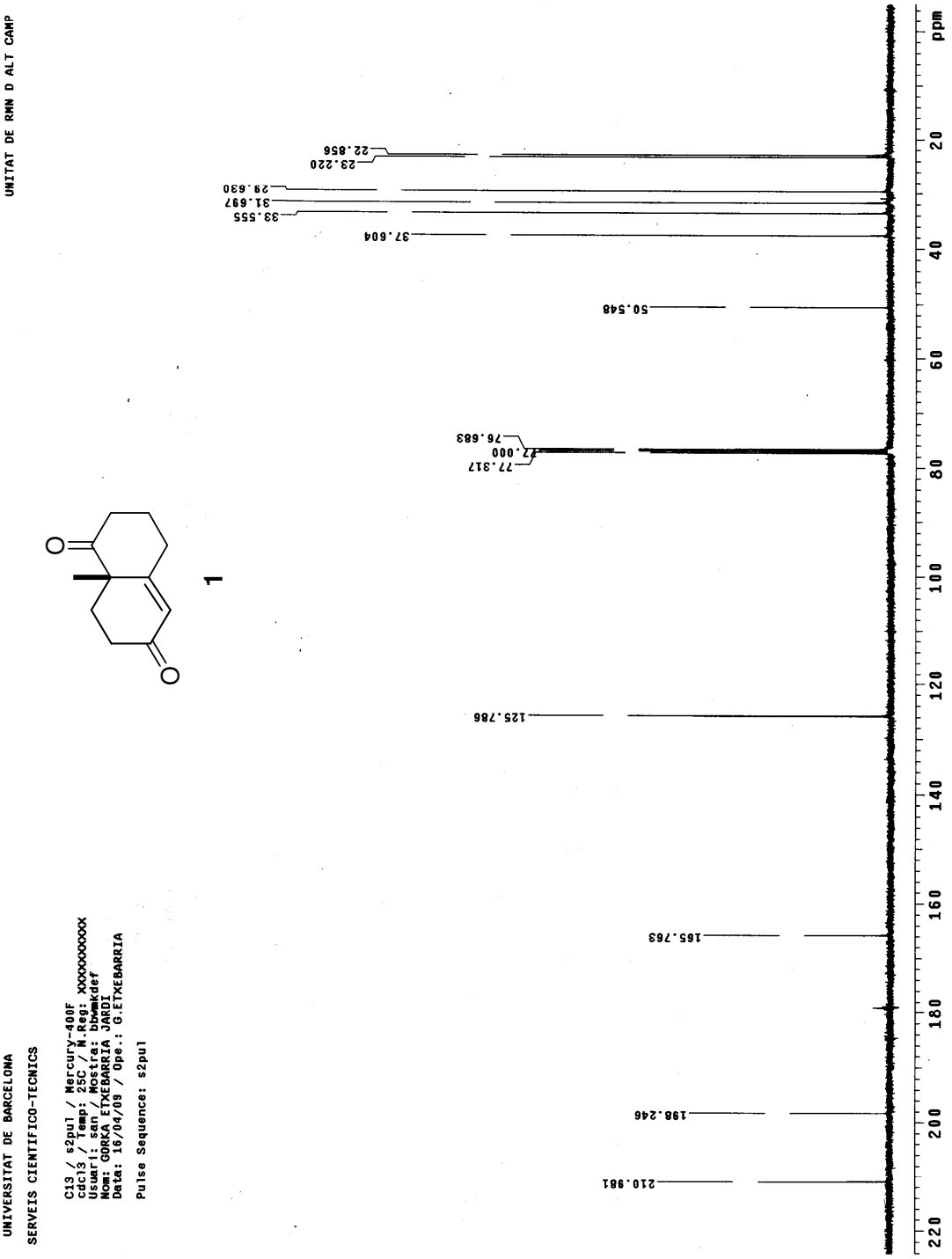

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
Equip: Mercury-400F
C13 / Solvent: cdcl3 / Temp: 25 C
N.Reg: T5002002200915206
Usuari: san / Mostra: bb830col
Nom: GORKA ETXEBARRIA JARDI
Data: 01/04/09 11:21:35 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
OBn
3k
O
O
O
O
209.889
207.621
138.304
128.326
127.588
127.536
77.317
77.000
76.683
72.688
69.731
67.734
67.726
38.424
32.146
29.866
27.470
24.846
17.112
ppm

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bbwmkdef
Nom: GORKA ETXEBARRIA JARDI
Data: 16/04/09 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul



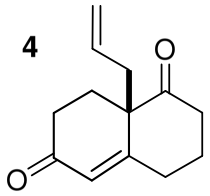
1

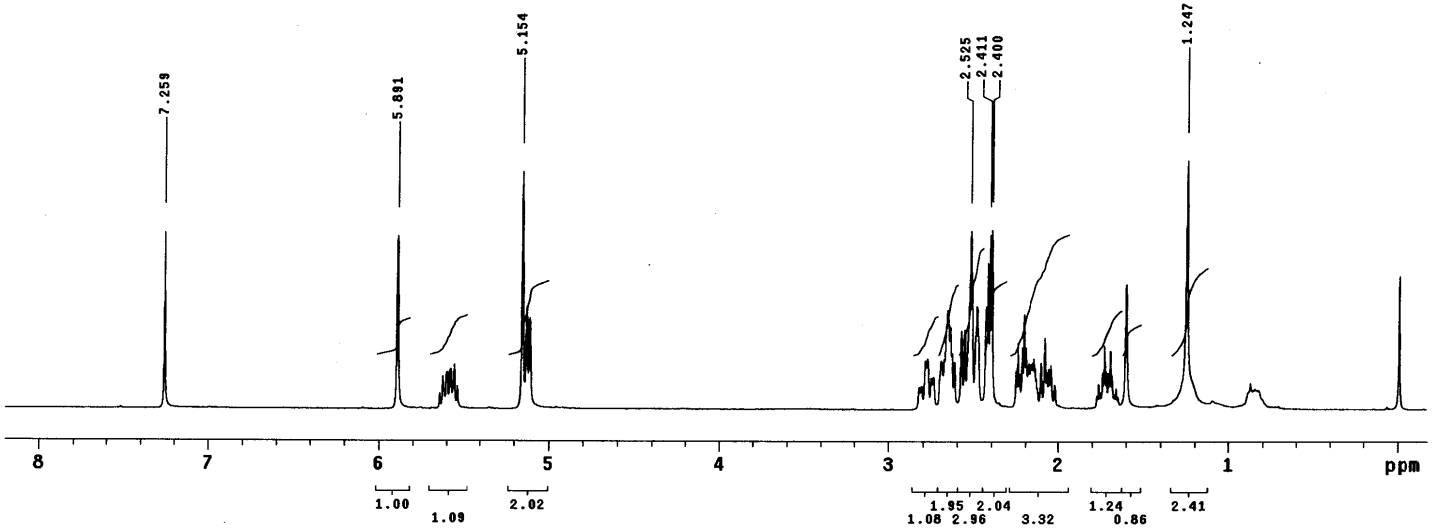

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: bbmmkdef
Nom: GORKA ETXEBARRIA JARDI
Data: 16/04/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
O
O
1
210.981
198.246
165.763
125.786
77.317
77.000
76.683
50.548
37.604
33.555
31.697
29.630
23.220
22.856
ppm

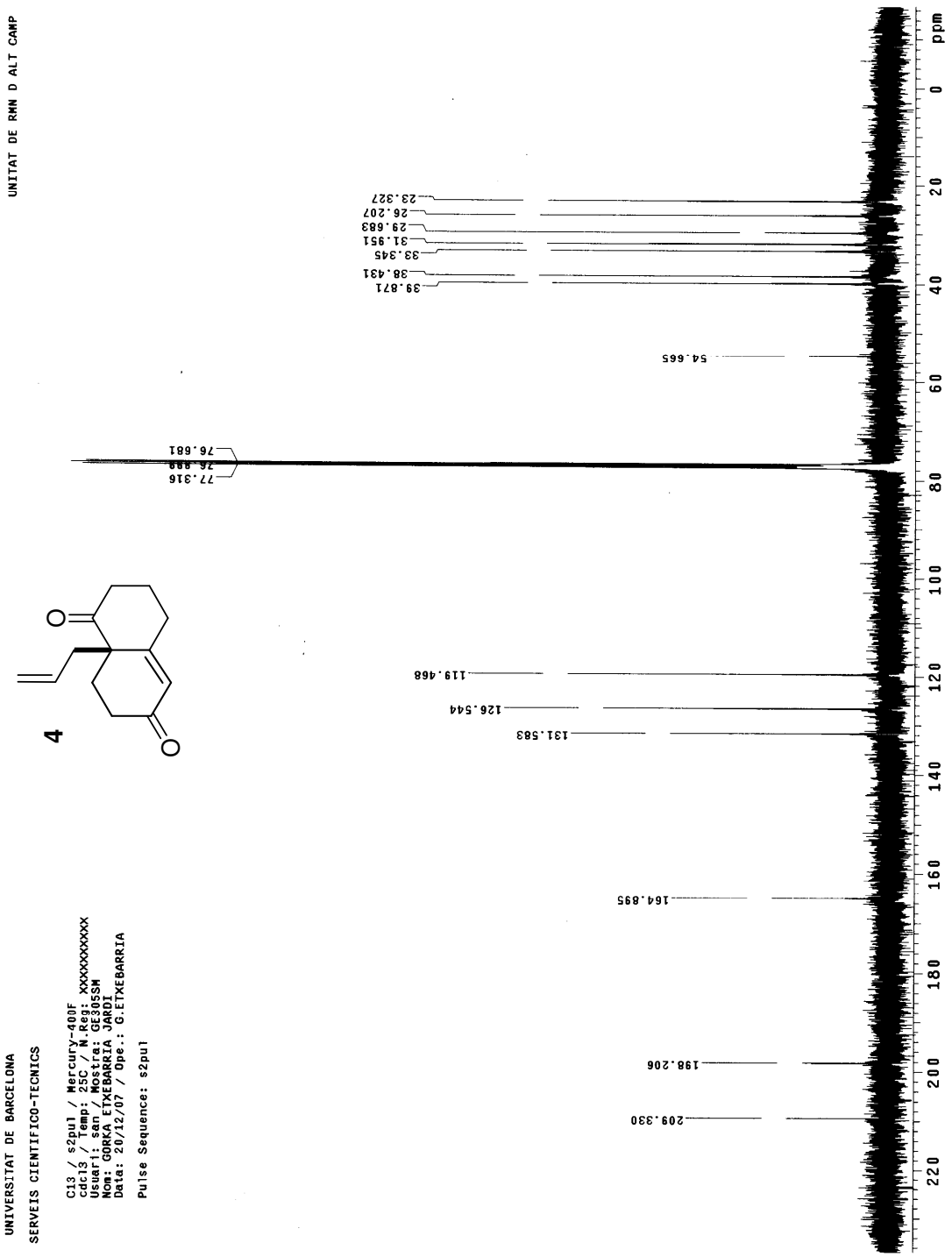
SERVEIS CIENTIFICO-TECNICS

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: GE305SM_RERUN
Nom: GORKA ETXEBARRIA JARDI
Data: 21/12/07 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul






UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: GE305SM
Nom: GORKA ETXEBARRIA JARDI
Data: 20/12/07 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
4
209.330
198.206
164.895
131.583
126.544
119.468
77.316
76.888
76.681
54.665
39.871
38.431
33.945
31.951
29.683
26.207
23.327
ppm

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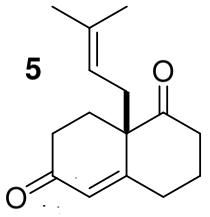
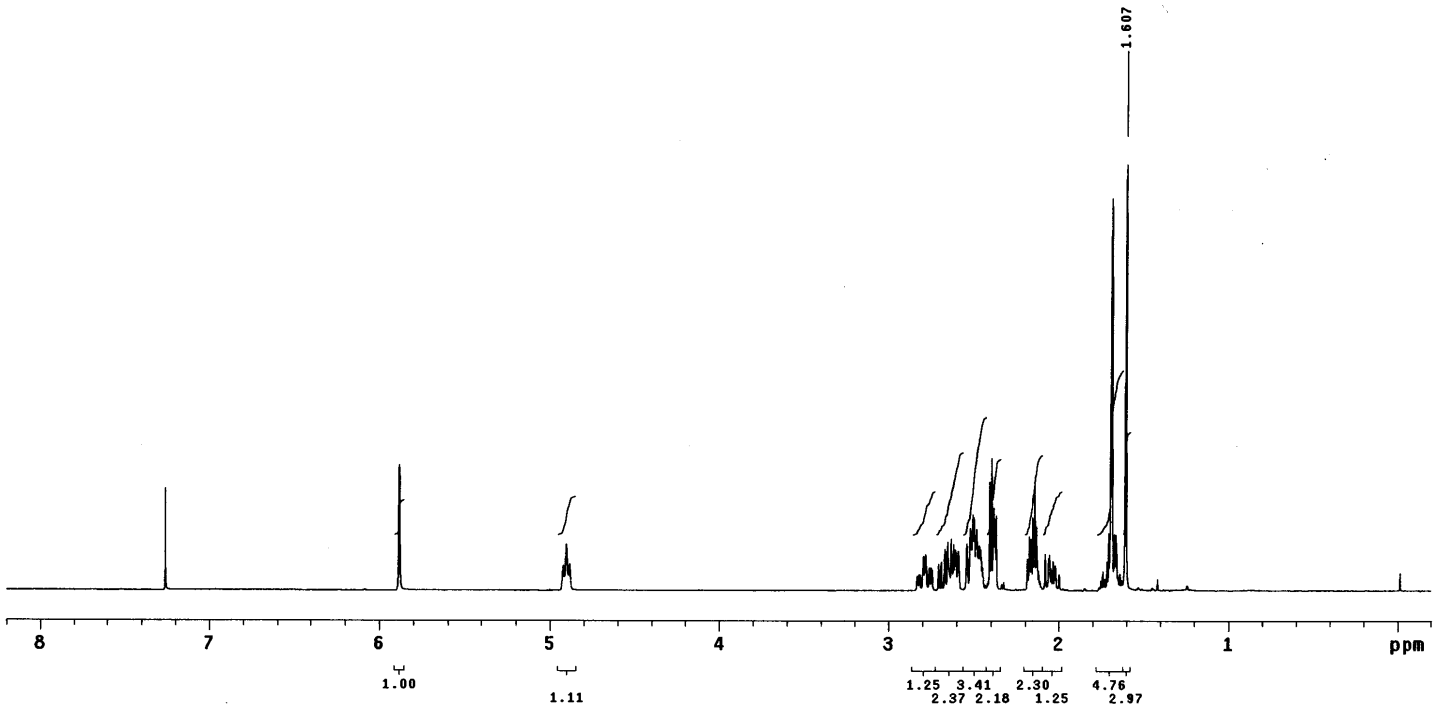
SERVEIS CIENTIFICO-TECNICS

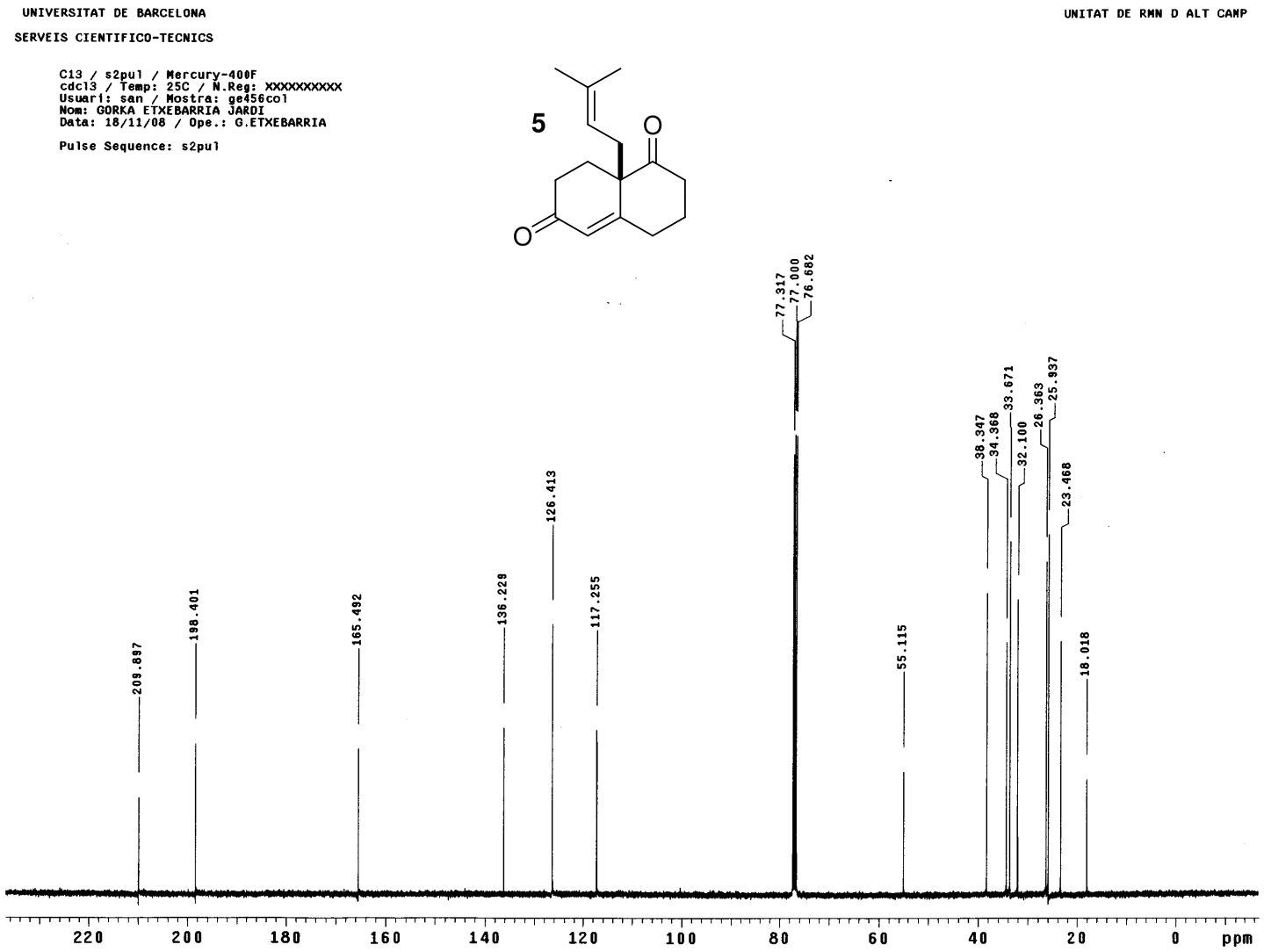
UNITAT DE RMN D ALT CAMP

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge456col
Nom: GORKA ETXEBARRIA JARDI
Data: 18/11/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul






UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ge456col
Nom: GORKA ETXEBARRIA JARDI
Data: 18/11/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
5
O
O
77.317
77.000
76.682
209.897
198.401
165.492
136.228
126.413
117.255
55.115
38.347
34.368
33.671
32.100
26.363
25.937
23.468
18.018
220
200
180
160
140
120
100
80
60
40
20
0
ppm

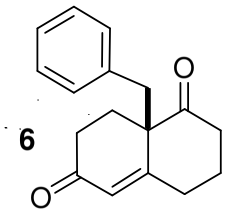
UNIVERSITAT DE BARCELONA

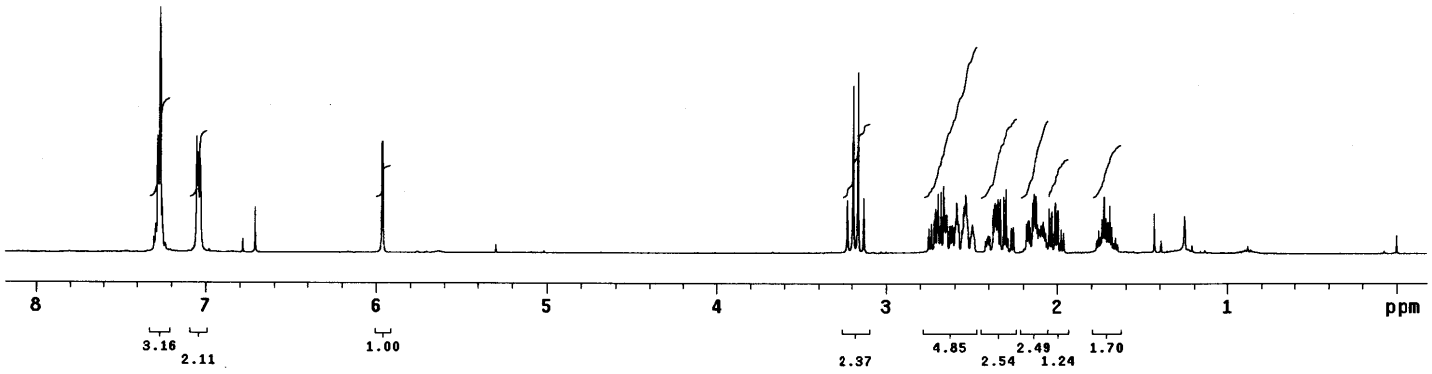
SERVEIS CIENTIFICO-TECNICS

UNITAT DE RMN D ALT CAMP

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb773col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/10/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul





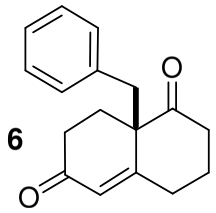
UNIVERSITAT DE BARCELONA

SERVEIS CIENTIFICO-TECNICS

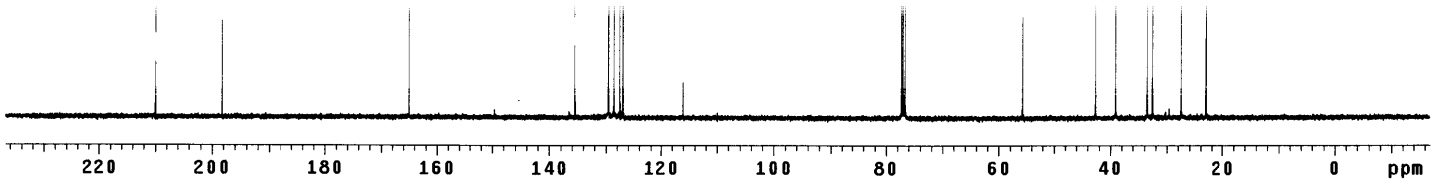
UNITAT DE RMN D ALT CAMP

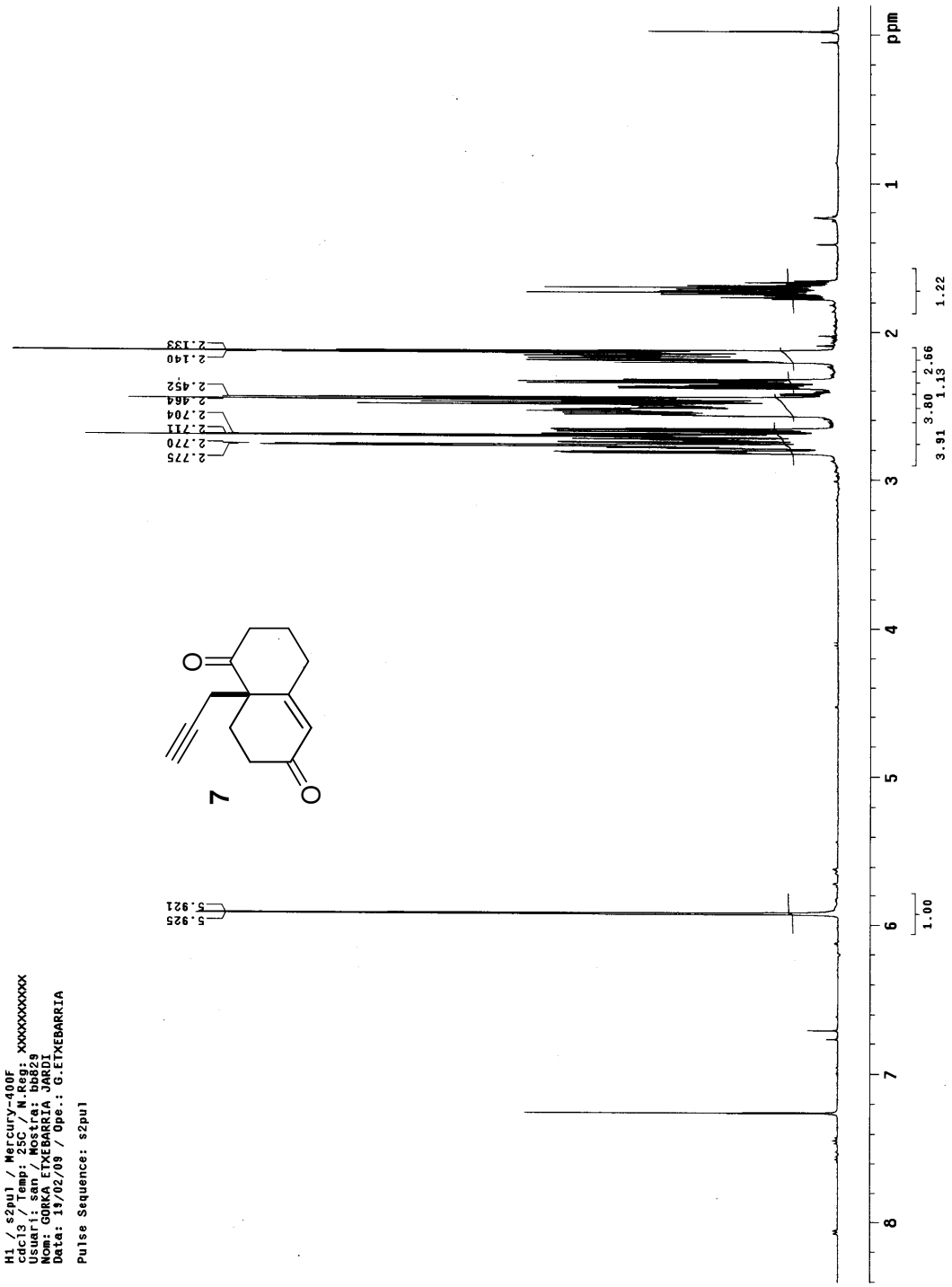
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb773col
Nom: GORKA ETXEBARRIA JARDI
Data: 16/10/08 / Ope.: G.ETXEBARRIA

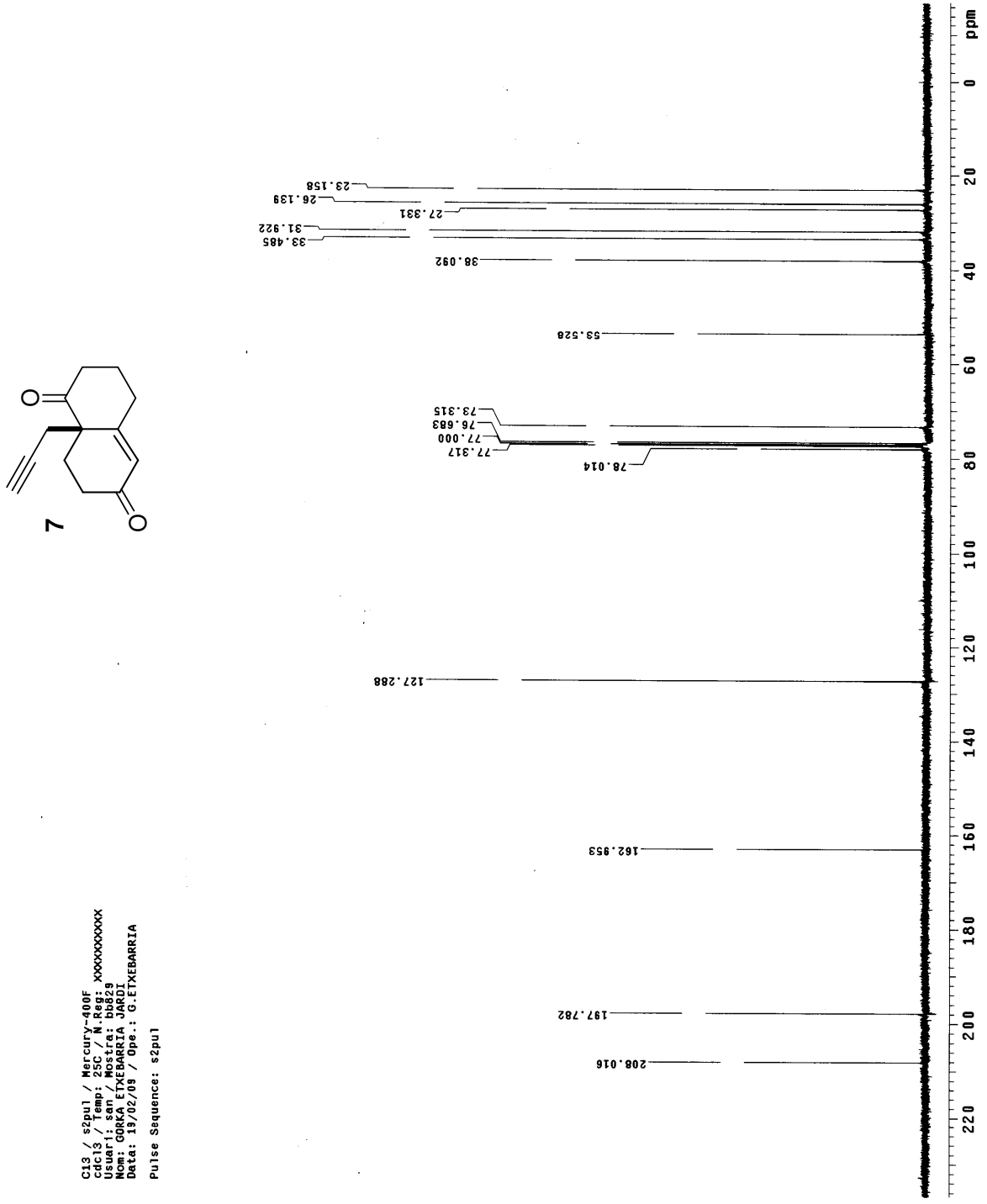
Pulse Sequence: s2pul

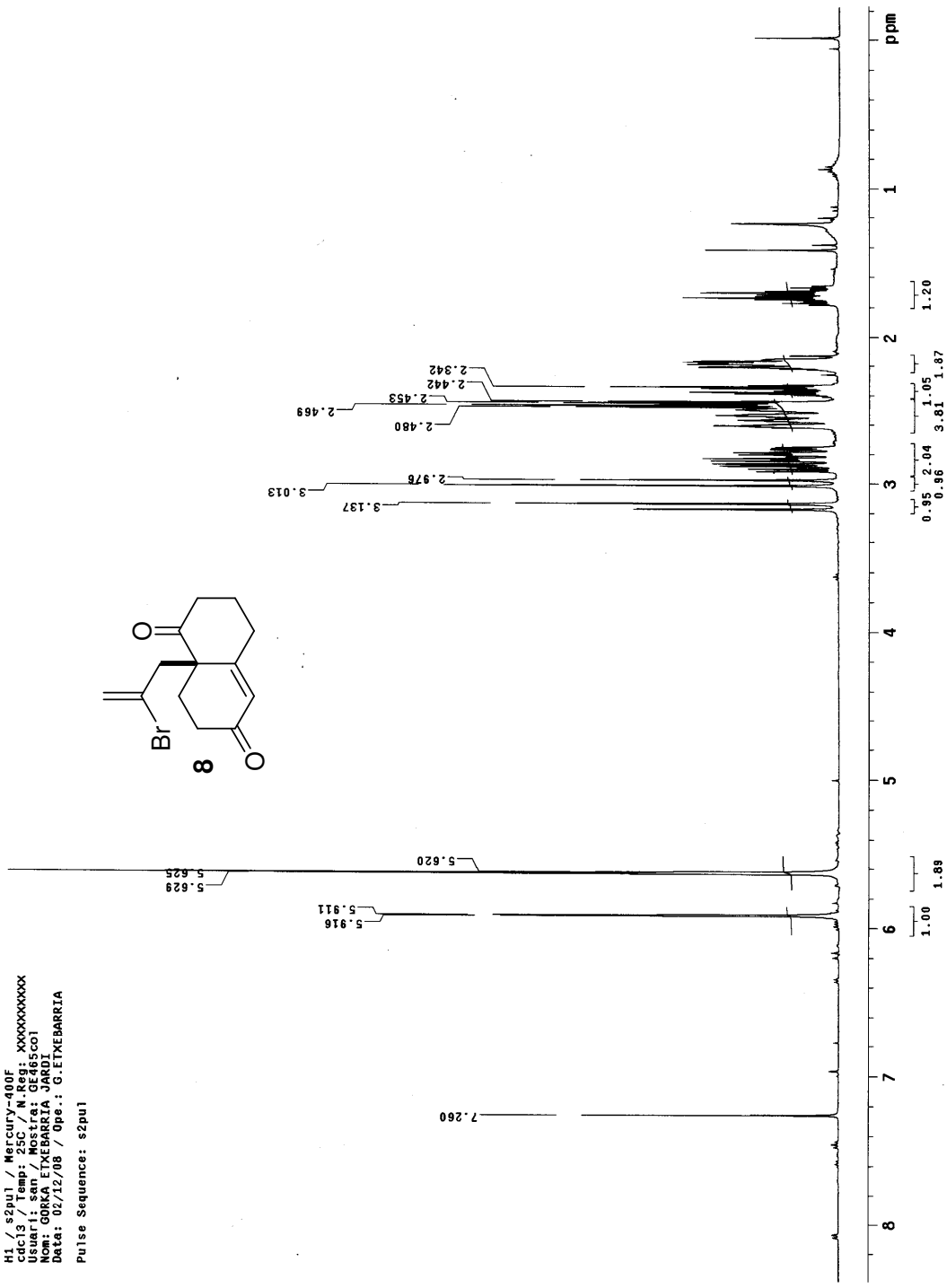


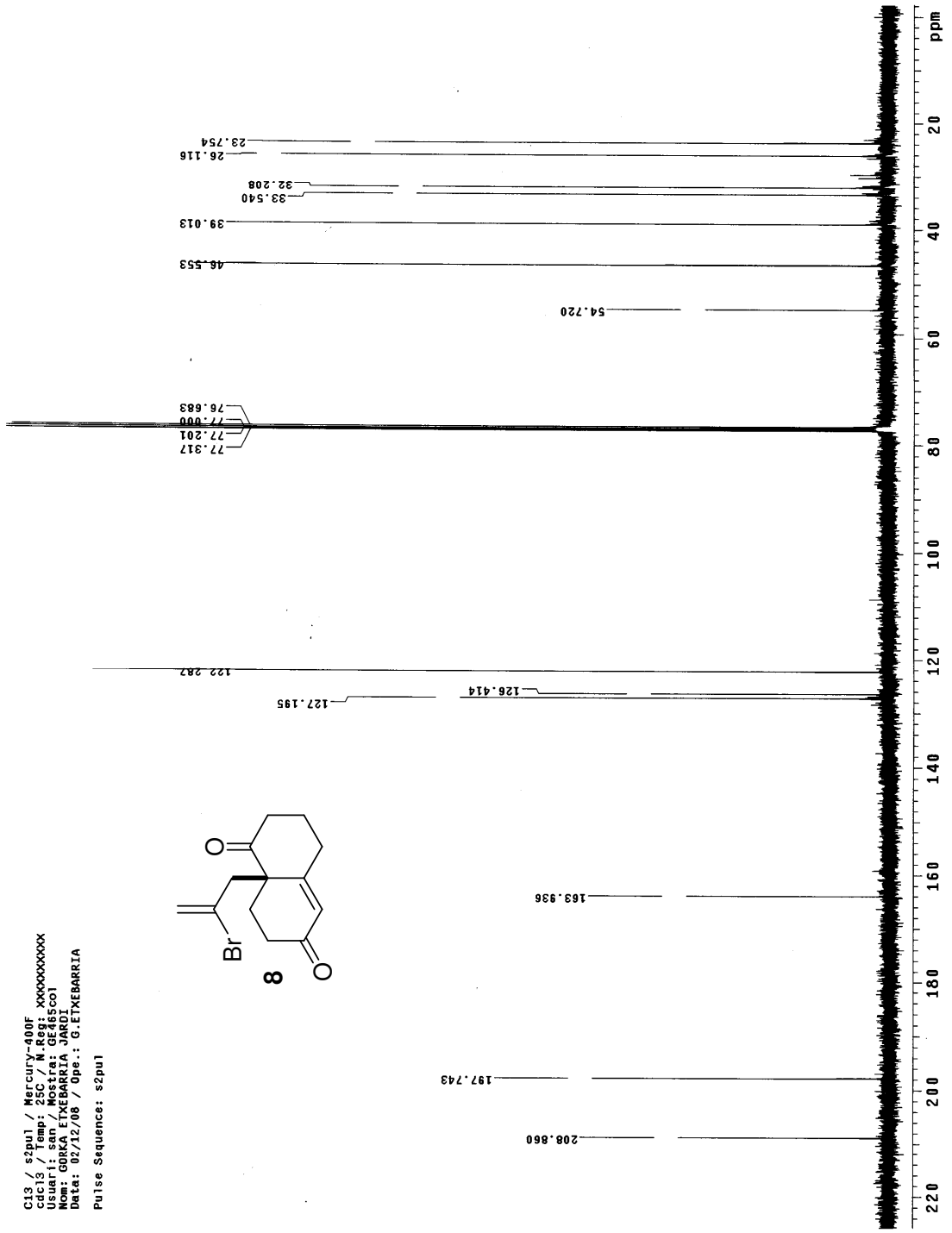
6




H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: bb829
Nom: GORKA ETXEBARRIA JARDI
Data: 19/02/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
5.925
5.921
2.775
2.770
2.711
2.704
2.464
2.452
2.140
2.133
7
ppm
1.00
3.91
3.80
1.13
2.66
1.22


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: bb829
Nom: GORKA ETXEBARRIA JARDI
Data: 19/02/09 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
208.016
197.782
162.953
127.288
78.014
77.317
77.000
76.683
73.315
55.528
38.092
33.485
31.922
27.381
26.139
23.158
ppm
0
20
40
60
80
100
120
140
160
180
200
220
O
O
7


H1 /s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari:san / Mostra: GE465col
Nom: GORKA ETXEBARRIA JARDI
Data: 02/12/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
8
Br
O
O
7.260
5.829
5.825
5.620
5.916
5.911
3.137
3.013
2.976
2.480
2.469
2.453
2.442
2.342
ppm
1
2
3
4
5
6
7
8
1.00
1.89
0.95
2.04
0.96
1.05
3.81
1.87
1.20


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: GE465co1
Nom: GORKA ETXEBARRIA JARDI
Data: 02/12/08 / Ope.: G.ETXEBARRIA
Pulse Sequence: s2pul
208.860
197.743
163.936
127.195
126.414
122.282
77.317
77.201
77.000
76.683
54.720
46.553
39.013
33.540
32.208
26.116
23.754
O
Br
O
8
ppm
220
200
180
160
140
120
100
80
60
40
20

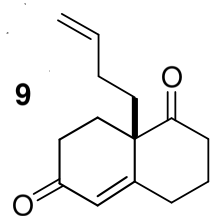
UNIVERSITAT DE BARCELONA

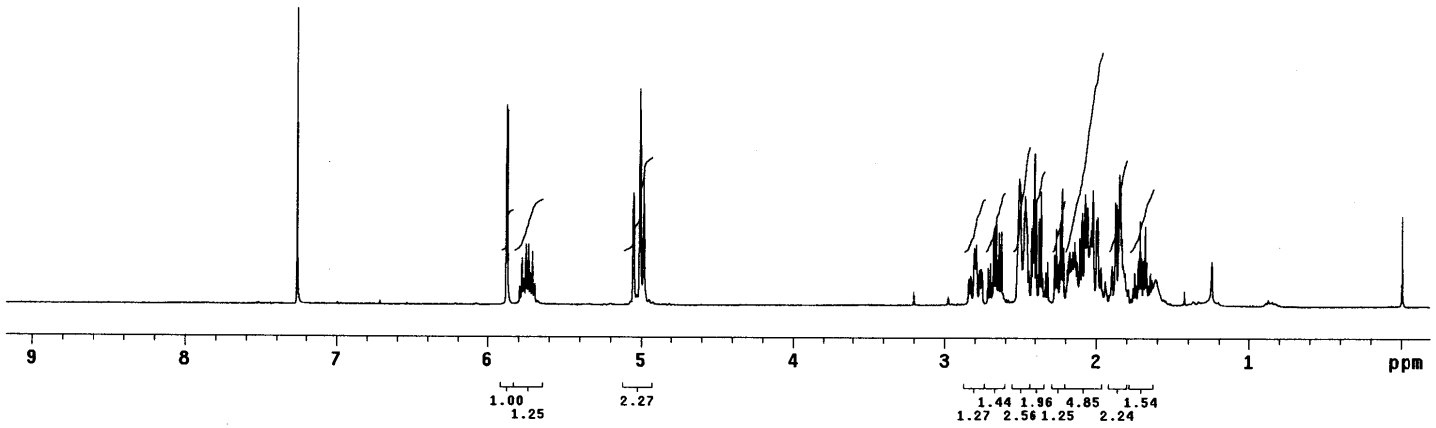
SERVEIS CIENTIFICO-TECNICS

UNITAT DE RMN D ALT CAMP

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: GE_A1a06
Nom: GORKA ETXEBARRIA JARDI
Data: 31/10/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul





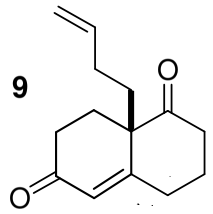
UNIVERSITAT DE BARCELONA

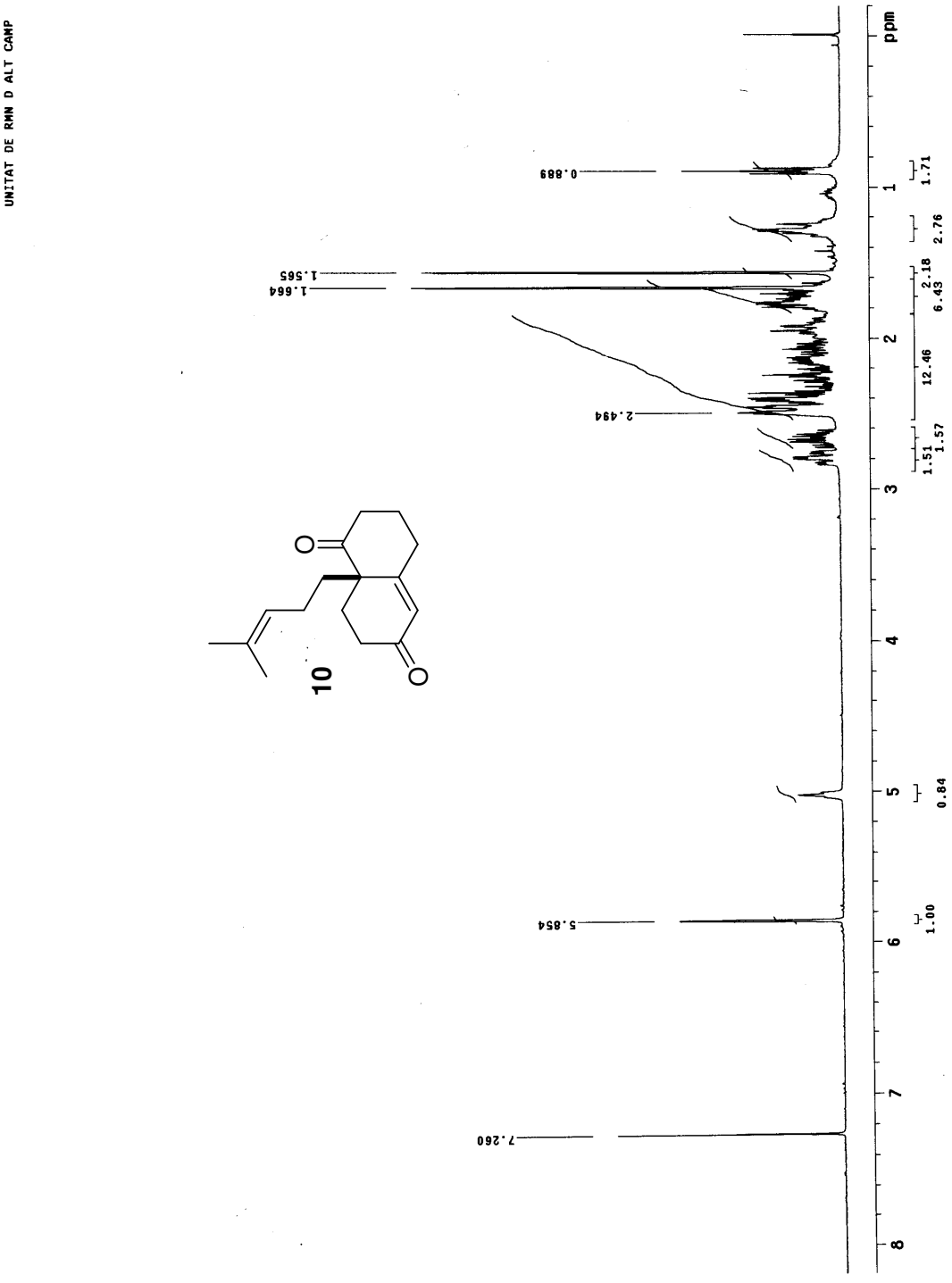
SERVEIS CIENTIFICO-TECNICS

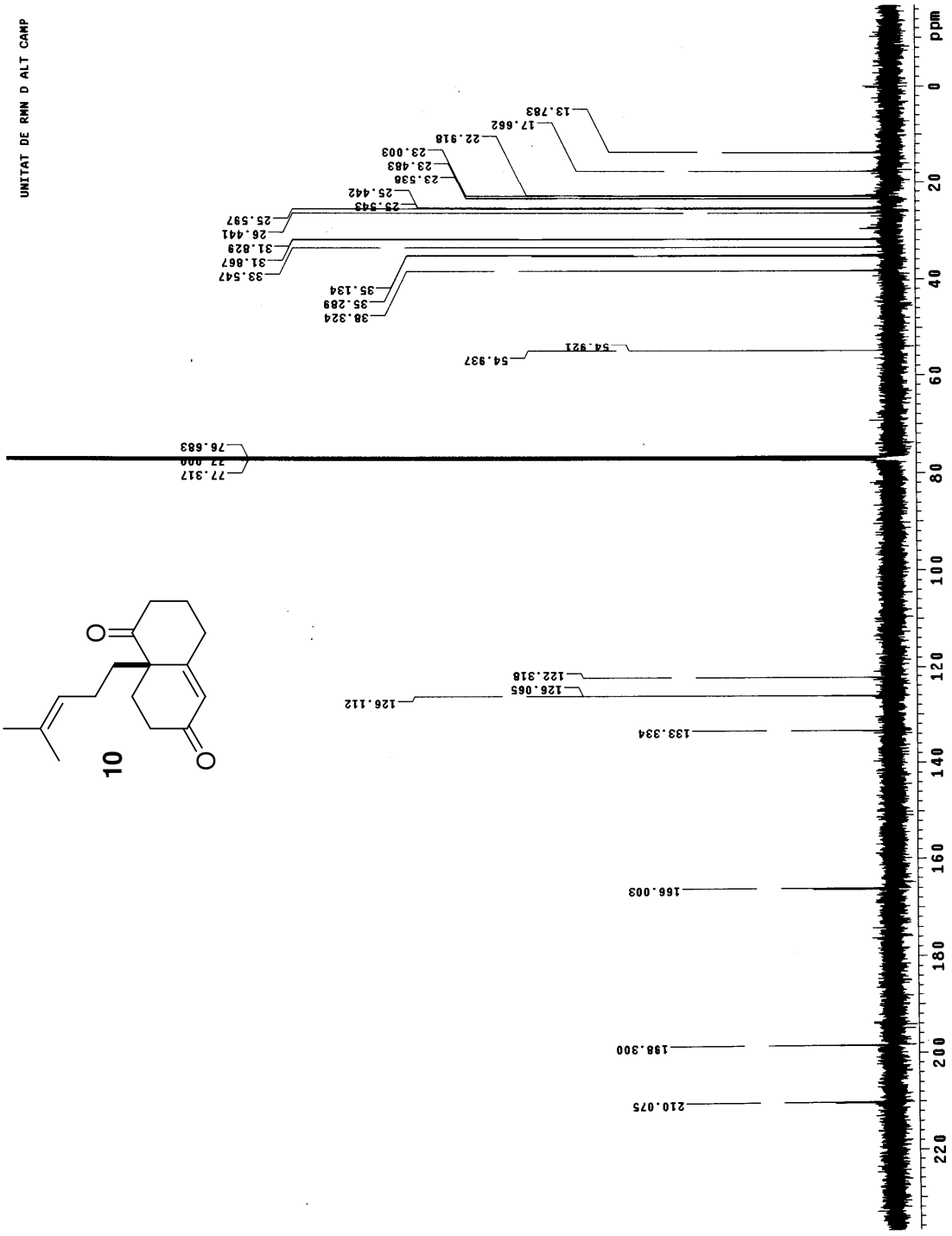
UNITAT DE RMN D ALT CAMP

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: GE_A1a06
Nom: GORKA ETXEBARRIA JARDI
Data: 31/10/08 / Ope.: G.ETXEBARRIA

Pulse Sequence: s2pul




UNITAT DE RMN D ALT CAMP
0.889
1.565
1.664
2.494
5.854
7.260
ppm
1
2
3
4
5
6
7
8
1.71
2.76
2.18
6.43
12.46
1.51
1.57
0.84
1.00
O
O
10


UNITAT DE RMN D ALT CAMP
ppm
0
20
40
60
80
100
120
140
160
180
200
220
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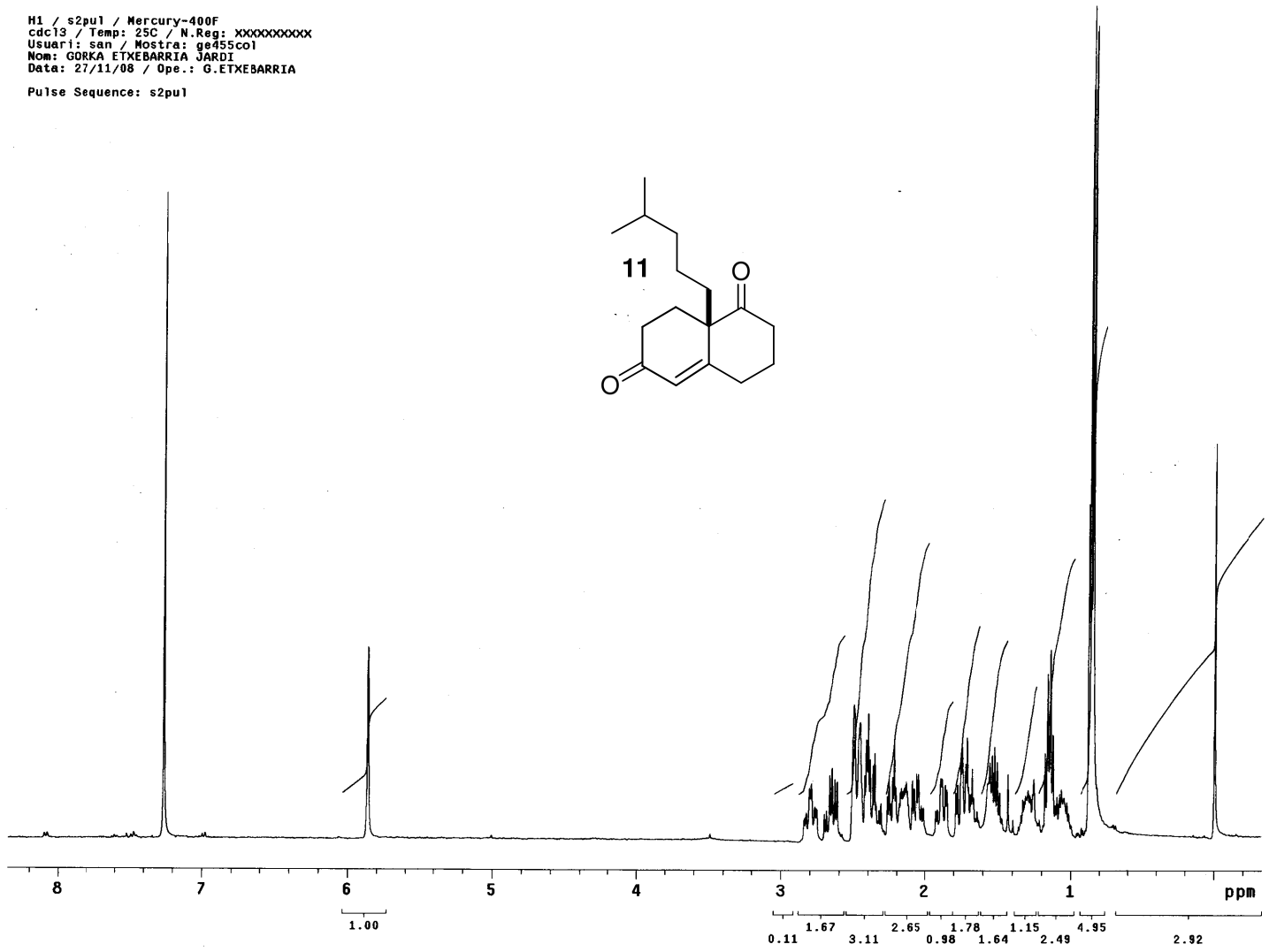
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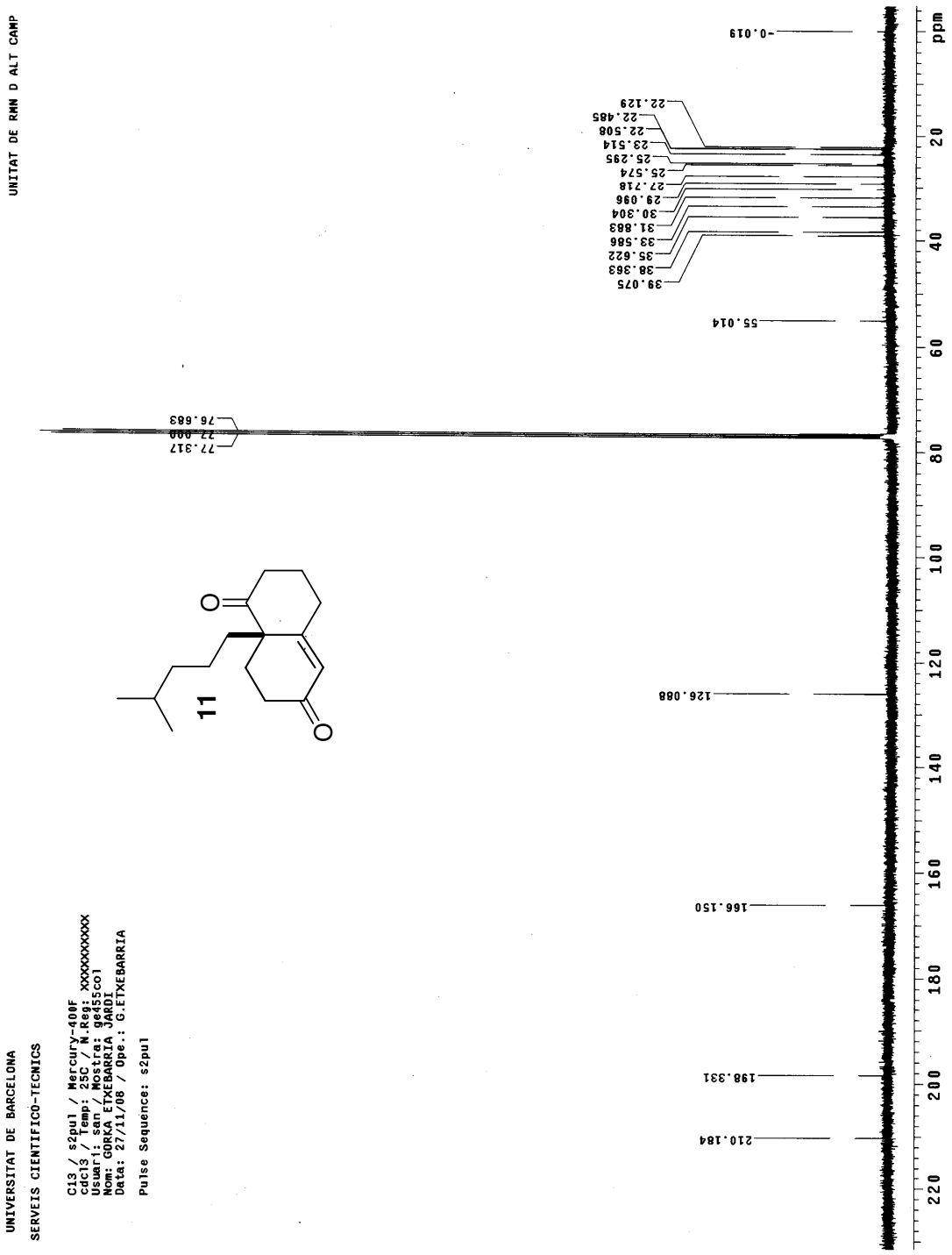
UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
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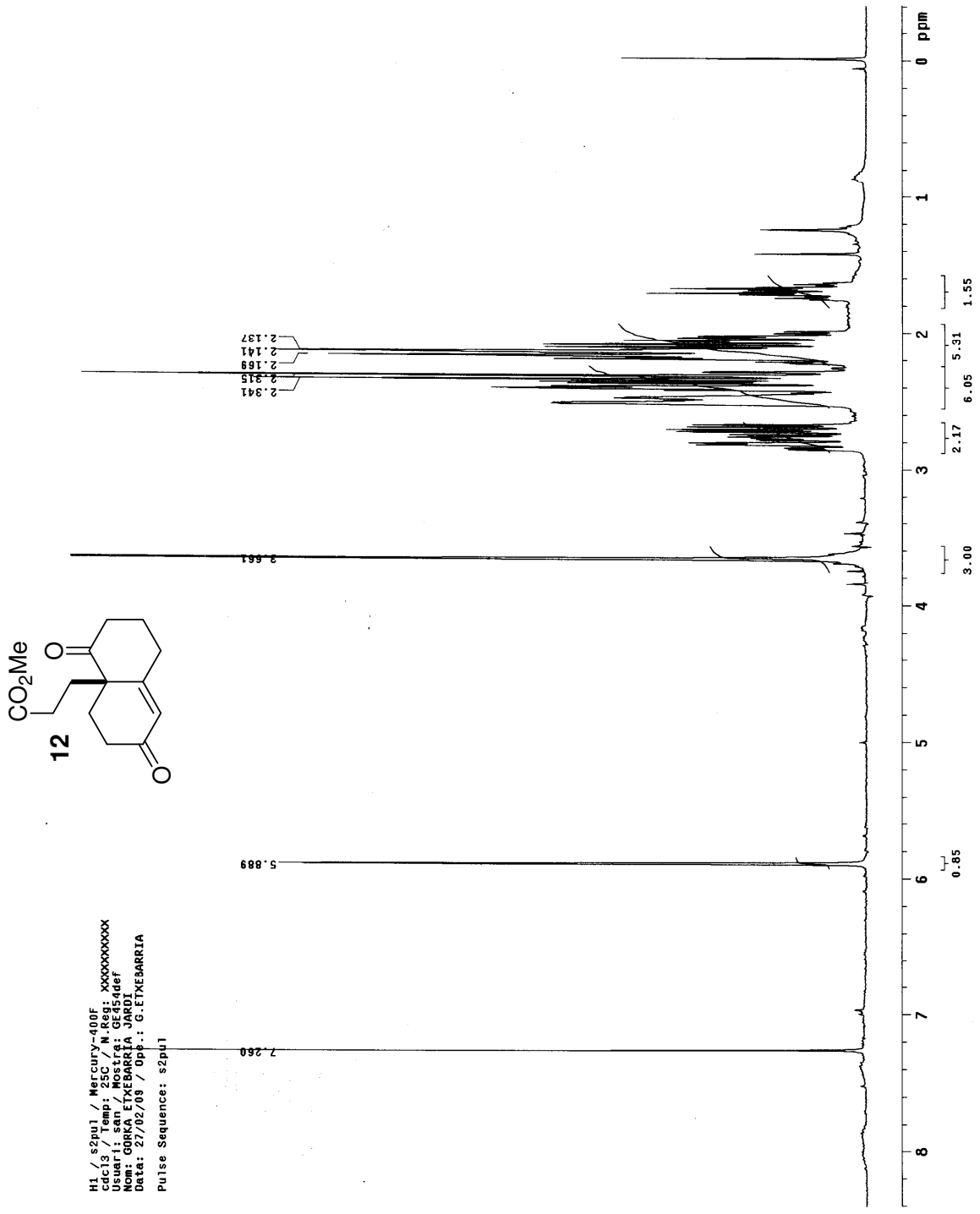
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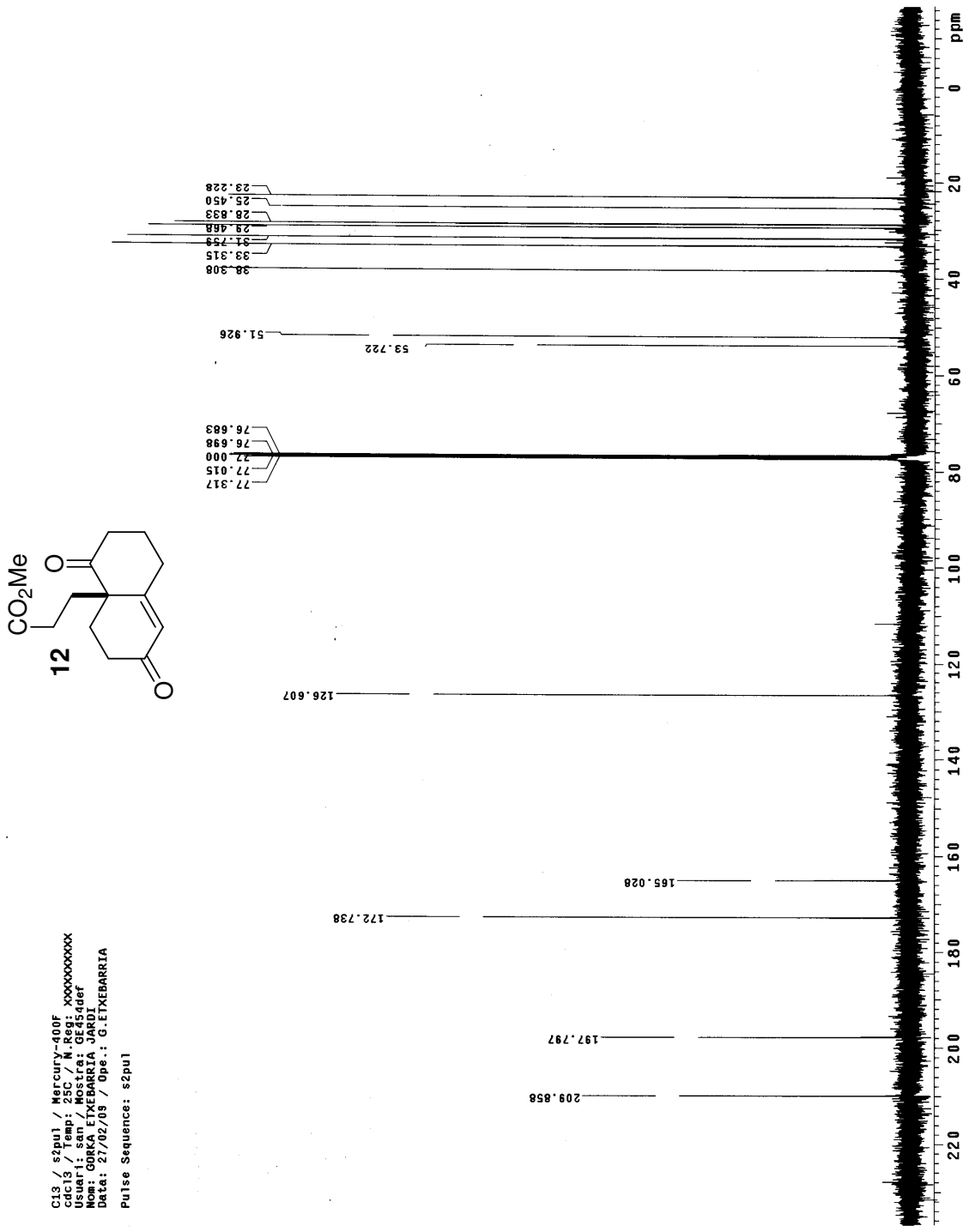
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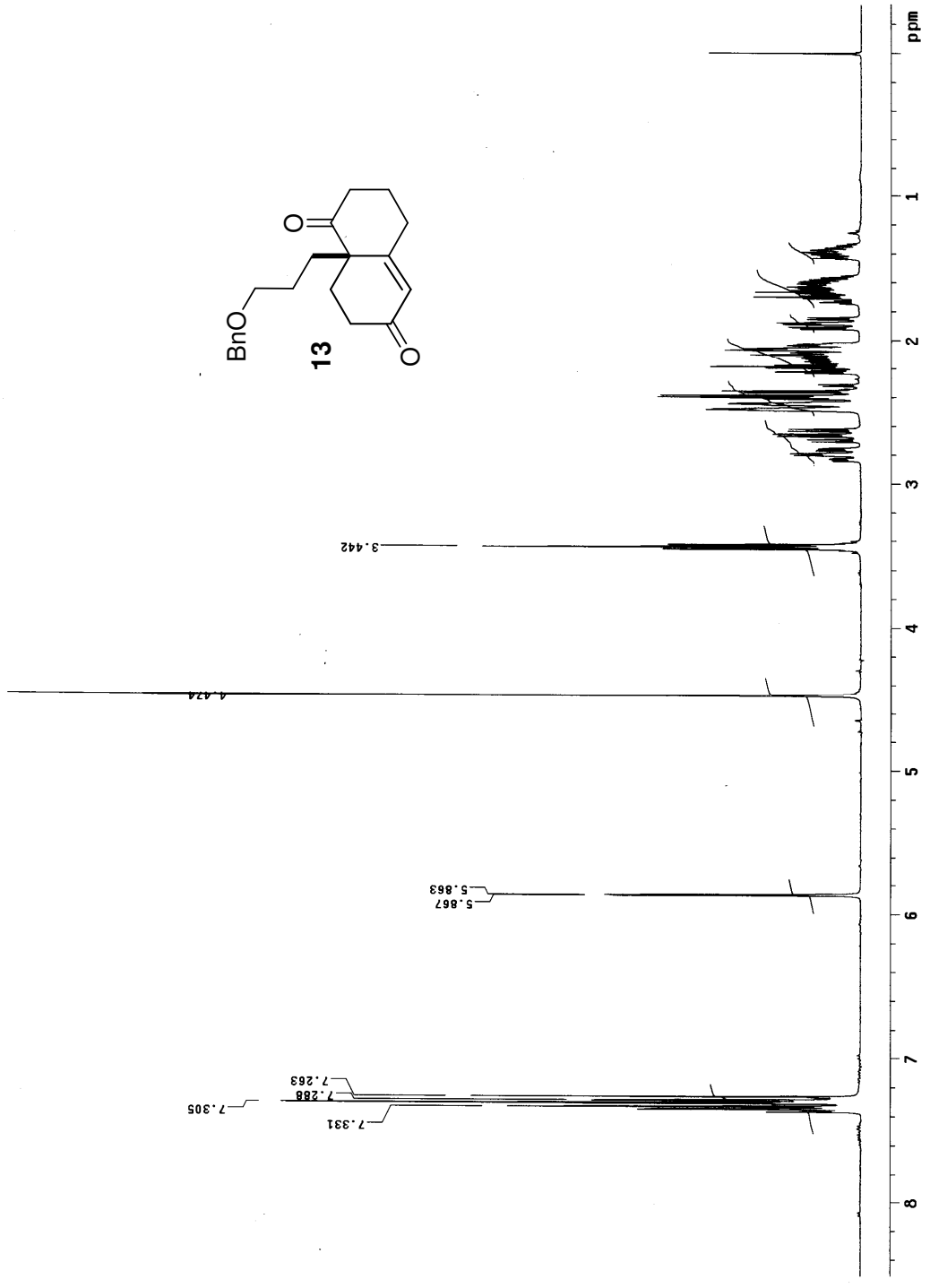
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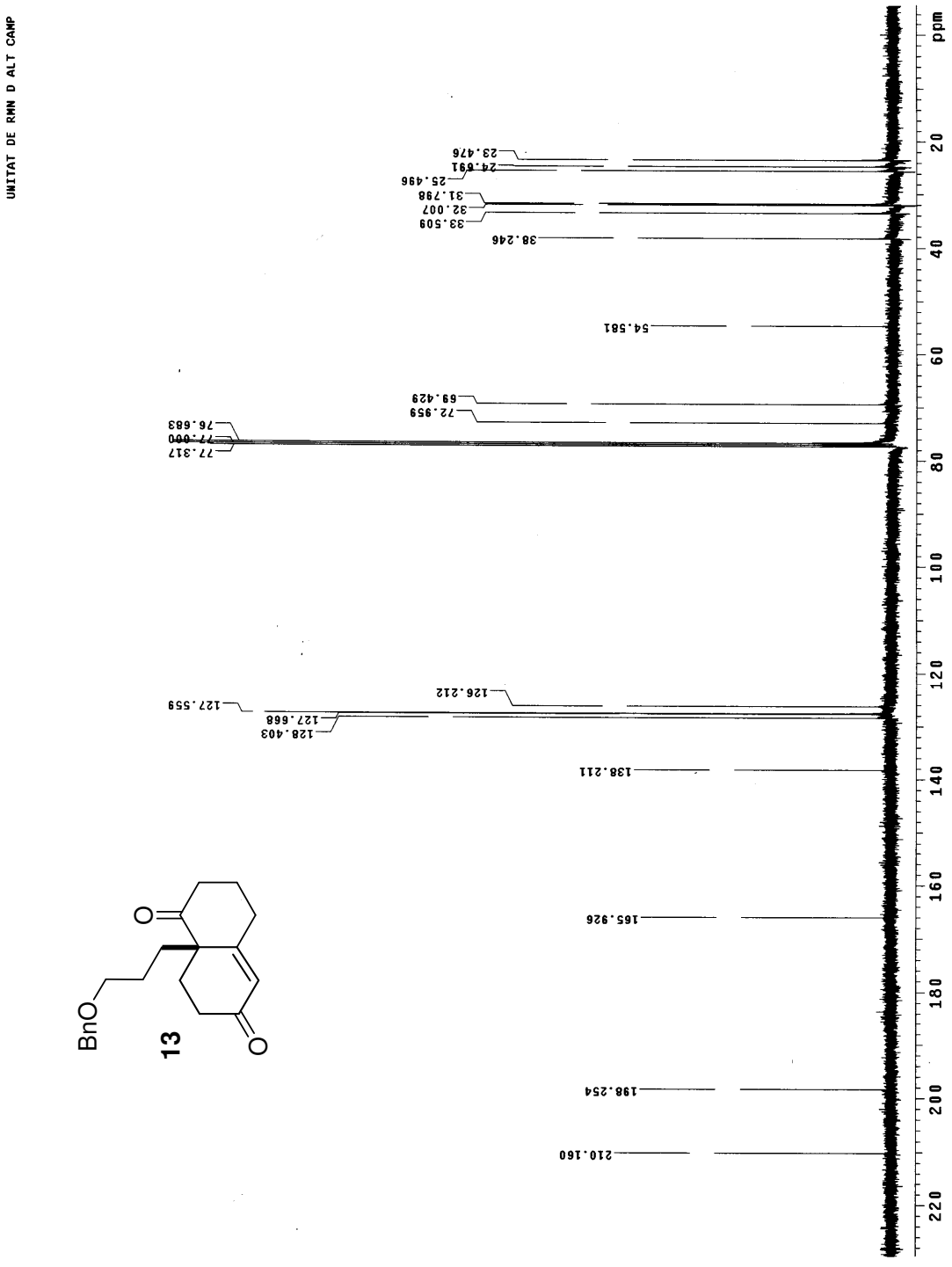
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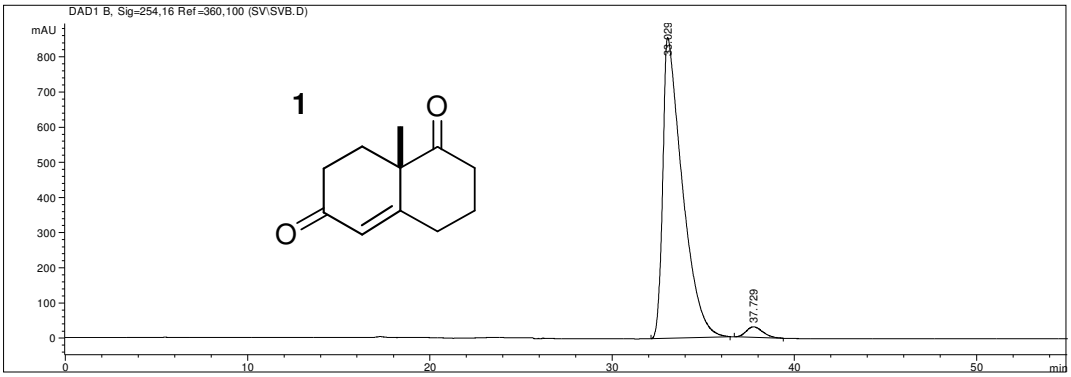
B (Chiralcel OD-H, 96:4 hex:i-PrOH, 0.6 ml/min, λ= 254 nm)



Retention time (min)	Area	Area %
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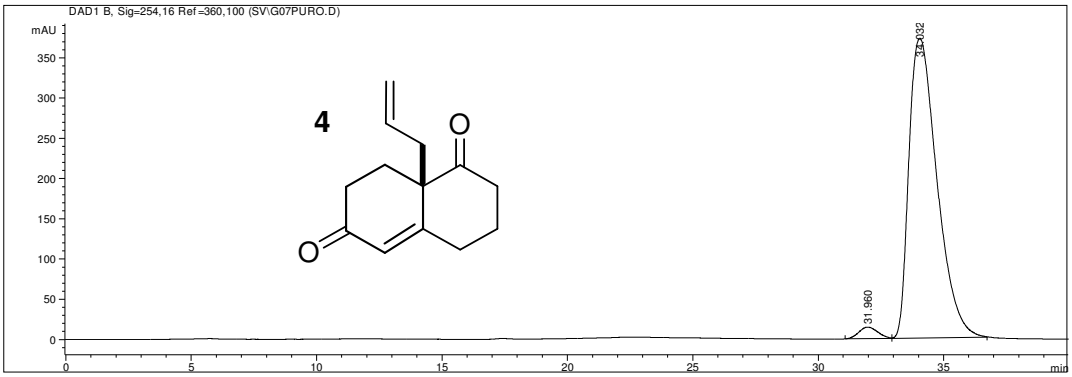
ee (%) = 94		

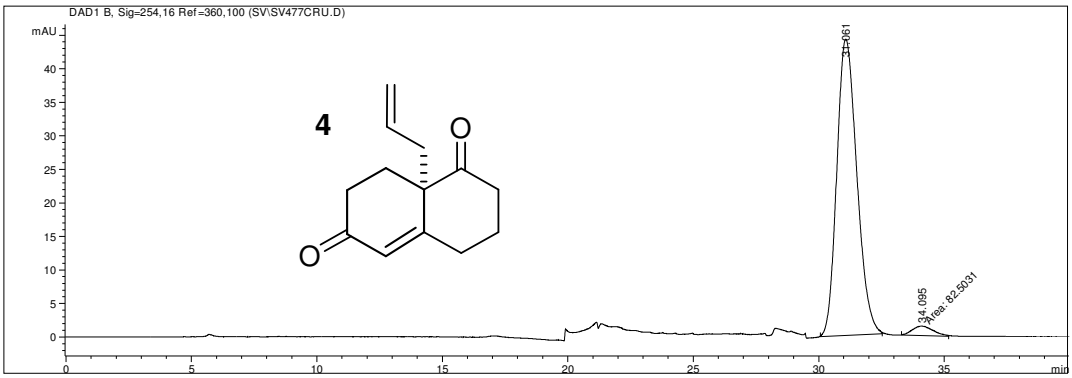
G07 PURO

Ee = 96 %



SV477 (ENANTIOMERO)

Ee = 96 %



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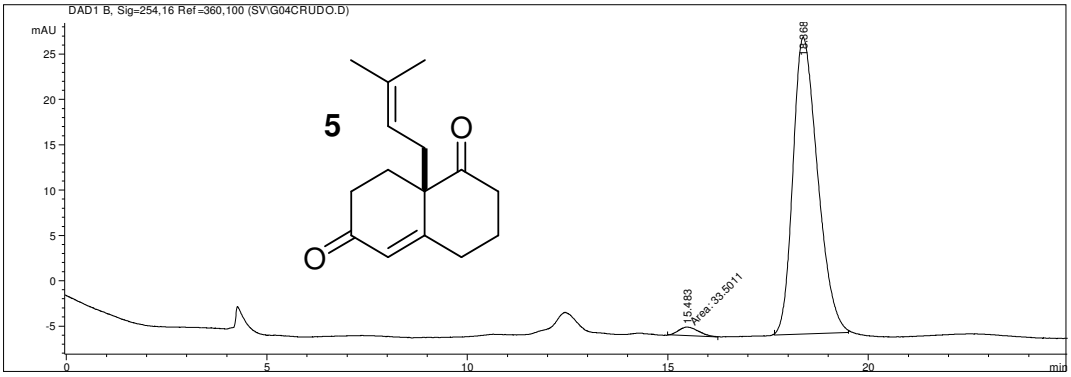

G05 crudo
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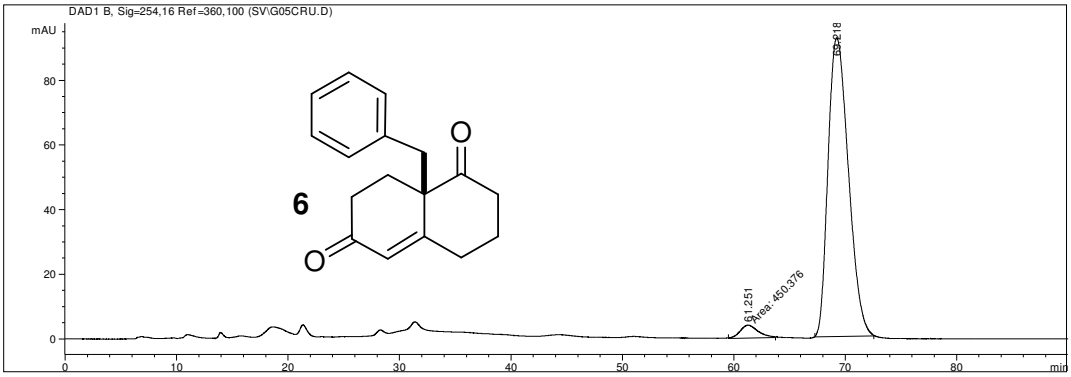

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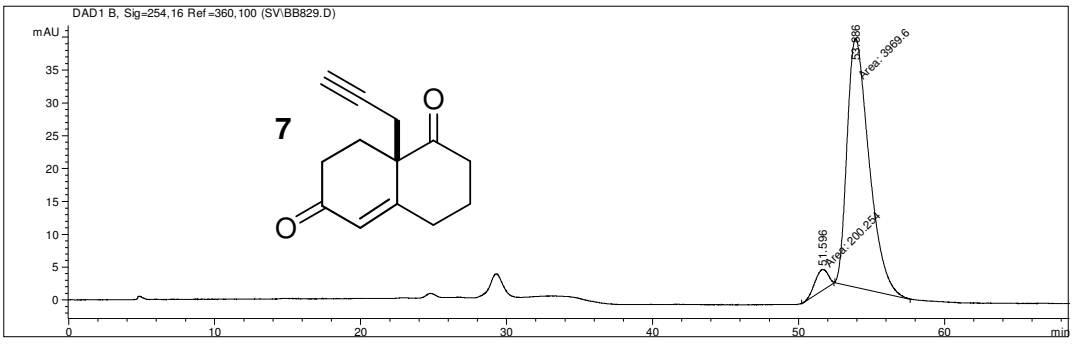
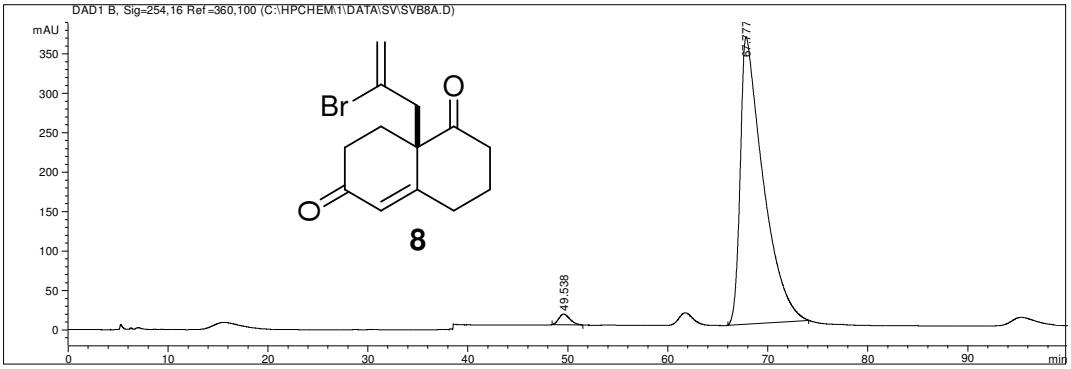


Retention time (min)	Area	Area %
51.596	200.2	4.80
53.886	3969.6	95.20
ee (%) = 90		

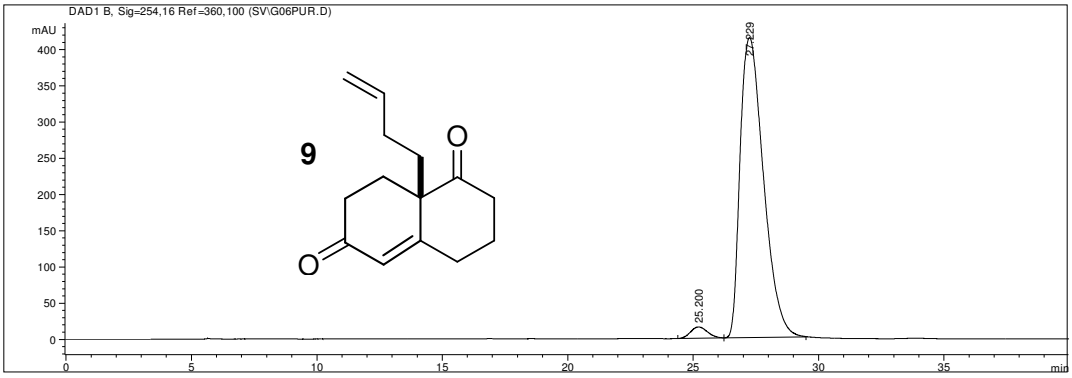
B8 (Chiralcel OD-H, 96:4 hex:i-PrOH, 0.6 ml/min, λ= 254 nm)



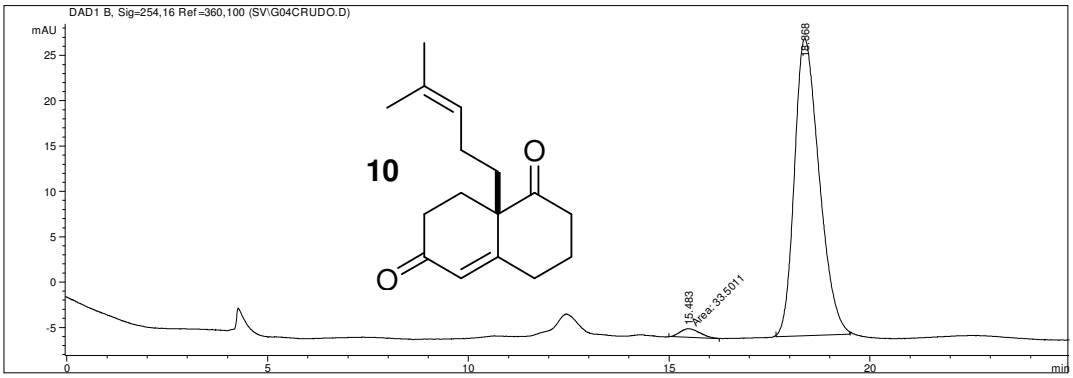
ee = 96 %

G06

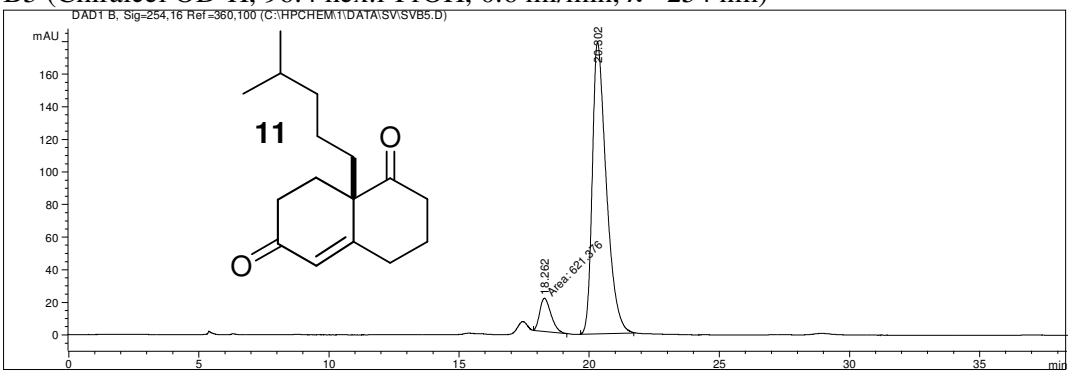
ee = 96 %



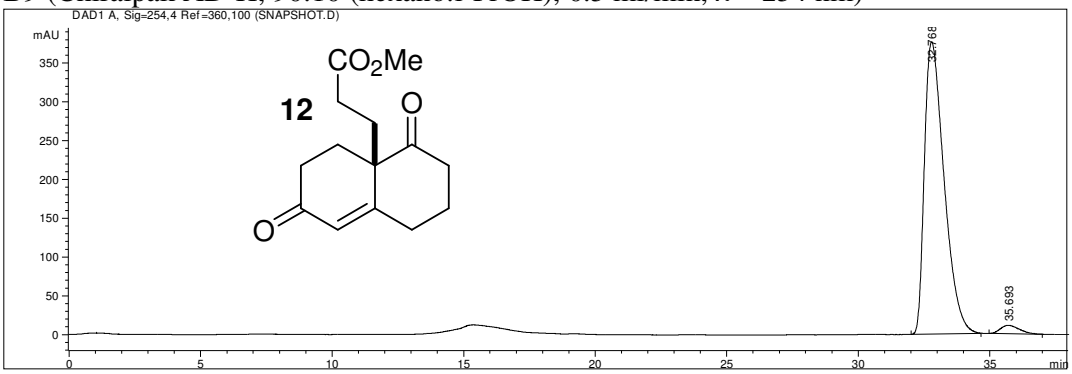
ee = 96 %



B5 (Chiralcel OD-H, 96:4 hex:i-PrOH, 0.6 ml/min, λ= 254 nm)

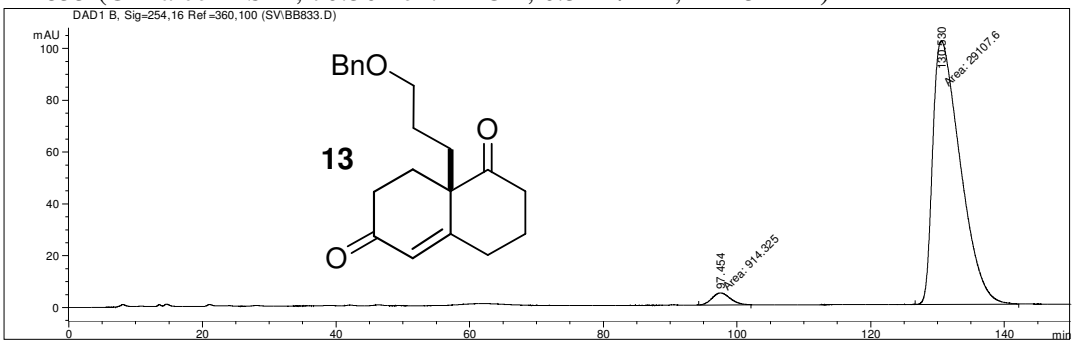


B9 (Chiralpak AD-H, 90:10 (hexano:i-PrOH), 0.5 ml/min, λ = 254 nm)



Ret. Time	Area %
32.768	97.2999
35.693	2.7001

BB833 (Chiralcel AS-H, 70:30 hex:i-PrOH, 0.5 ml/min, λ= 254 nm)



Retention time (min)	Area	Area %
97.454	914.3	3.05
130.530	29107.6	96.95
ee (%) = 94		

Communication

Total Synthesis of (−)-Anominine

Ben Bradshaw*, Gorka Etxebarria-Jardí and Josep Bonjoch*

Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain

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DOI: 10.1021/ja101994q

Publication Date (Web): April 12, 2010

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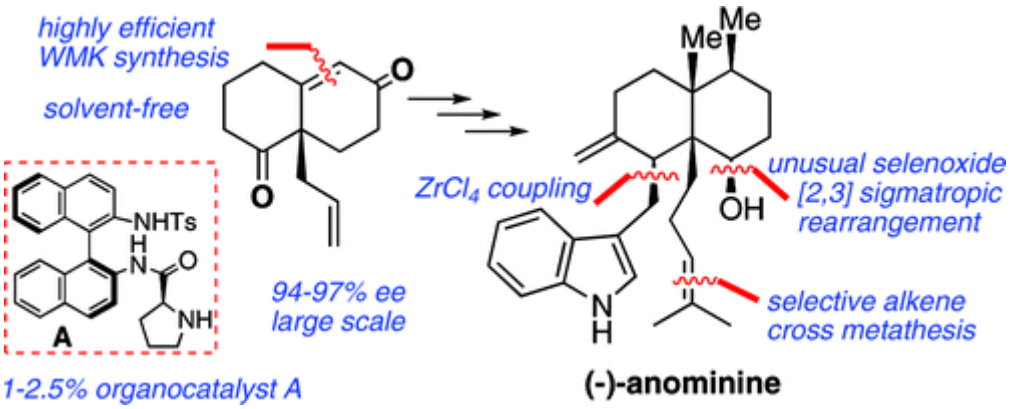
Abstract



The first total synthesis of anominine has been achieved, and the absolute configuration of the product has been determined. The key features include the development of a new, highly efficient organocatalyzed method for the asymmetric synthesis of Wieland−Miescher ketone building blocks, an unusual selenoxide [2,3]-sigmatropic rearrangement, and a $ZrCl_4$-catalyzed indole coupling as well as several chemoselective transformations controlled by the structurally congested nature of the bicyclic core.

J|A|C|S COMMUNICATIONS

Published on Web 04/12/2010

Total Synthesis of (−)-Anominine

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Many fungi produce specially adapted morphological structures called sclerotia that are critical to the long-term survival and propagation of the species. A systematic study of the sclerotia of *Aspergillus* spp. by Gloer's group several years ago led to the isolation of many unique, biologically active secondary metabolites.[1] Among these, our interests have focused on diterpenoids with novel ring structures characterized by two quaternary carbons at the decalin ring junction[2] and up to six contiguous stereocenters all arranged in a cis configuration (Figure 1). To date, none of these highly congested and structurally challenging diterpenoids have been synthesized,[3] nor have their absolute configurations been established.

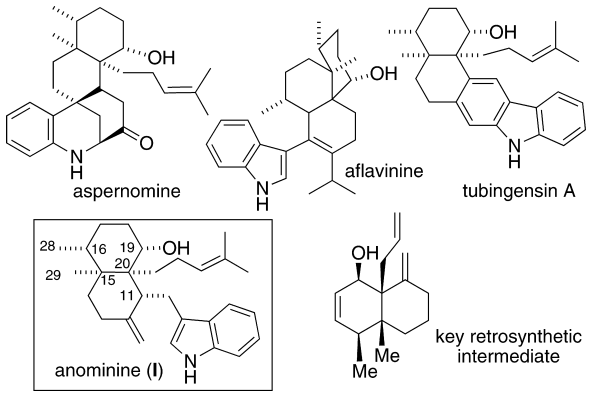
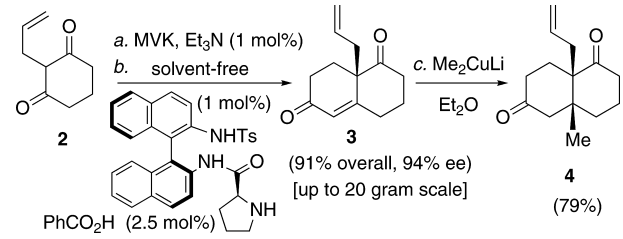


Figure 1. Representative diterpenoids with a common structural motif.

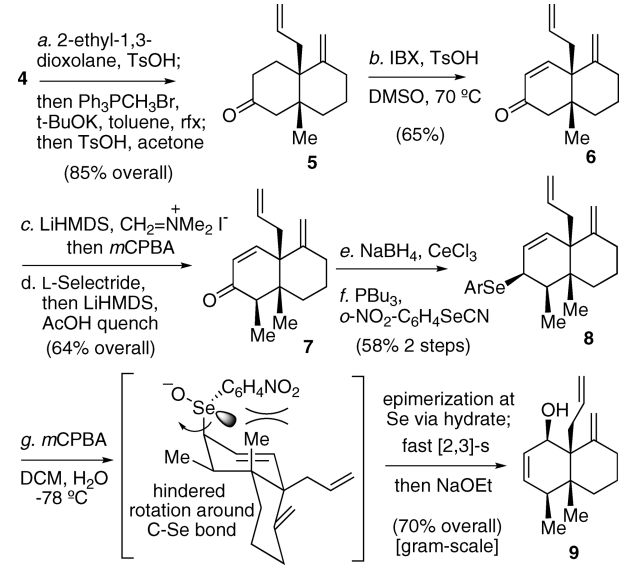
Focusing our attention on the synthesis of anominine (**1**),[4] most likely the parent structure from which the other metabolites are biogenetically derived,[5] we envisaged a retrosynthetic intermediate (depicted in Figure 1) embodying the four contiguous stereocenters of the terpene core and various double bonds that could be used as flexible handles to introduce further structural complexity. The final successful route to anominine began with the generation of the two quaternary stereogenic centers, the one at C20 being set up first by an asymmetric Robinson annulation of dione **2** (Scheme 1). A longstanding and unresolved problem in organic synthesis is the efficient preparation of Wieland−Miescher ketone-type compounds in high enantioselectivity, thus avoiding multiple purifications and recrystallizations. In an attempt to address this issue, we carried out an extensive survey of reaction conditions and organocatalysts. Starting from **2**, we found that **3** could be prepared in highly enantioenriched form (97% ee) using 2.5% *N*-Ts-(S_a)-binam-L-Pro as the catalyst under solvent-free conditions. Furthermore, we found that this method was general and could be applied to a wide range of substrates.[6] In the most optimized version, in which the catalyst loading was reduced to just 1%,[7] large quantities of the enantioenriched building block **3** (96% yield, 94% ee) could be secured. The high purity of **3** meant that it could be used without purification in the subsequent conjugated addition reaction to give **4** and set up the second quaternary center.

Scheme 1. Organocatalyzed Asymmetric Synthesis of **3**



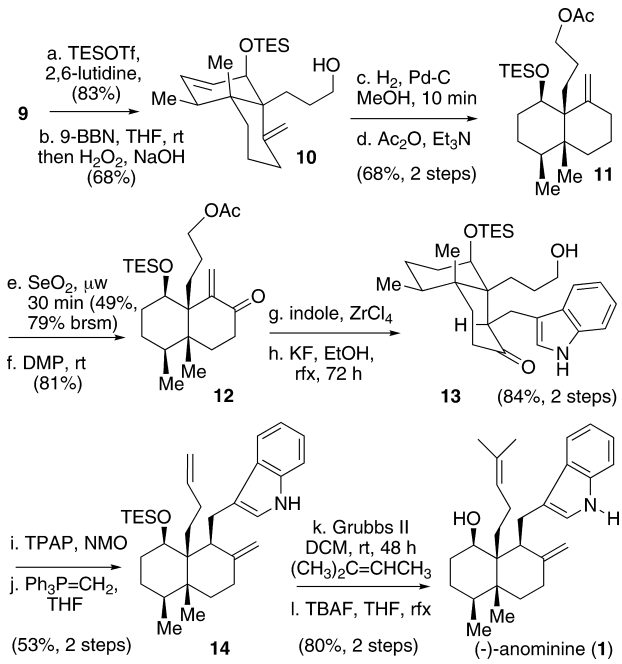
A second relay procedure introduced the double bond at C11 by chemoselective protection of the less hindered carbonyl group of **4** followed by a Wittig methylenation and acid quench of the initially formed acetal (Scheme 2). Oxidation of ketone **5** with IBX in the presence of TsOH[8] formed the endocyclic enone **6**, which not only ensured the regioselectivity for the next alkylation step but also provided the necessary functionality for the rearrangement required to install the oxygen atom at C19. With the contiguous quaternary carbons in place, we then found that many attempted transformations failed, particularly when the reactive site was adjacent to one of the quaternary centers. For example, alkylation to introduce the C28 methyl with LiHMDS/MeI/HMPA was precluded by the predominance of O-alkylation, and plans to move the oxygen from C17 to C19 by a Wharton transposition were also thwarted by the unreactive nature of the internal double bond toward epoxidation. However, reaction of the lithium enolate of **6** with Eschenmoser's salt followed by *m*-CPBA oxidation of the resulting

Scheme 2. Synthesis of Key Intermediate **9**



10.1021/ja101994q

Scheme 3. Completion of the Synthesis of (−)-Anominine



β-aminoketone led to the exocyclic enone, which after chemoselective reduction and equilibration yielded stereochemically pure **7**. Diastereoselective reduction of ketone **7** under low-temperature Luche conditions afforded the required alcohol, which under Grieco conditions gave the allylic selenide **8** set up to undergo a sigmatropic rearrangement. Once again, the *cis*-decalin quaternary centers had a great effect on the outcome of the reaction by not allowing the **8** → **9** rearrangement when the initial oxidation was carried out under dry conditions. In sharp contrast, the rearrangement in a wet medium proved to be very effective, giving a stable selenenate that was readily converted to the key intermediate **9**. Presumably, the (*S*)-selenoxide depicted in Scheme 2 cannot adopt the required conformation for the rearrangement process because of steric hindrance around the C17−Se bond, which is due to the bulkiness of the *o*-nitrophenyl group and the methyl group at C15. However, water-induced epimerization at the Se stereogenic center[9] led to the (*R*)-selenoxide, which could evolve to **9** through the [2,3]-sigmatropic rearrangement.

After causing so many setbacks, the steric hindrance of the molecule now worked to our advantage, as we could chemoselectively transform the triene **9** (Scheme 3). Thus, after its protection as a TES ether, selective hydroboration at the allyl side chain to give alcohol **10** and a selective hydrogenation at the internal double bond followed by acetylation gave **11**. Allylic oxidation followed by Dess−Martin oxidation afforded the exocyclic enone **12**. Although efficient conditions (bismuth triflate, CH_3CN) were developed for the coupling of the indole using model systems,[10] attempts to apply them to the sterically demanding enone **12** were unsuccessful.[11] After a systematic screen of Lewis acid catalysts, only zirconium tetrachloride[12] was able to smoothly generate the coupled product, which after treatment with KF in refluxing EtOH provided the all-cis diastereomer in which the acetate was simultaneously cleaved to give **13** in 84% overall yield. Oxidation with Ley's perruthenate followed by Wittig bishomologation of the keto aldehyde gave **14**. Selective olefin cross-metathesis[13] upon the methylene in the side chain and cleavage of the TES group delivered **1**, which showed NMR spectroscopic data identical to those reported for the natural product. The data obtained for **1**, $[\alpha]_D = -21.0$ (*c* 0.3, MeOH), resulted in the assignment of **1** as *ent*-anominine and the absolute configuration depicted in Figure 1 for the natural (+)-anominine (**I**) {lit[4] $[\alpha]_D$ +23.6 (*c* 0.85, MeOH)}.

In summary, the first synthesis of anominine has been achieved. Keys to its success were the use of several chemoselective transformations controlled by the structurally congested nature of the bicyclic core and the development of a new, highly efficient method for the synthesis of Wieland−Miescher ketone compounds that should find wide application in natural product synthesis. This synthesis opens the way to access other related natural products from *Aspergillus* spp. via biomimetic processes, and work in this direction is now in progress.

Acknowledgment. This work was funded by the MICINN of Spain-FEDER through Project CTQ-2007-61338/BQU.

Supporting Information Available: Full experimental details and NMR spectral reproductions for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) Gloer, J. B. *Acc. Chem. Res.* **1995**, *28*, 343–350.
(2) The structural motif of *cis*-4a,8a-dialkyldecalin is also found in the rare thelepogane terpenoids. See: Díaz, S.; Cuesta, J.; González, A.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 7400–7406.
(3) For a conceptually elegant but ultimately unsuccessful approach to aflavinine, see: Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.; Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474–2484.
(4) Gloer, J. B.; Rinderknecht, B. L.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 2530–2532. Diterpenoid **I** was named nominine when it was isolated, but in 1982 the same name had been given to a hetisine-type aconite alkaloid. After consultation with Prof. Gloer (University of Iowa), it was decided to change the name of the indole diterpenoid **I** to anominine. .
(5) (a) Liu, Y.; McWhorter, W. W., Jr.; Hadden, C. E. *Org. Lett.* **2003**, *5*, 333–335. (b) Ho, G. A.; Nouri, D. H.; Tantillo, D. J. *Tetrahedron Lett.* **2009**, *50*, 1578–1581. (c) Marcos, I. S.; Moro, R. F.; Costales, I.; Escola, M. A.; Basabe, P.; Díez, D.; Urones, J. G. *Tetrahedron* **2009**, *65*, 10235–10242.
(6) For methodological studies in this field, see: Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C. *Adv. Synth. Catal.* **2009**, *351*, 2482–2490.
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(8) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.
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Total Synthesis of (–)-Anominine
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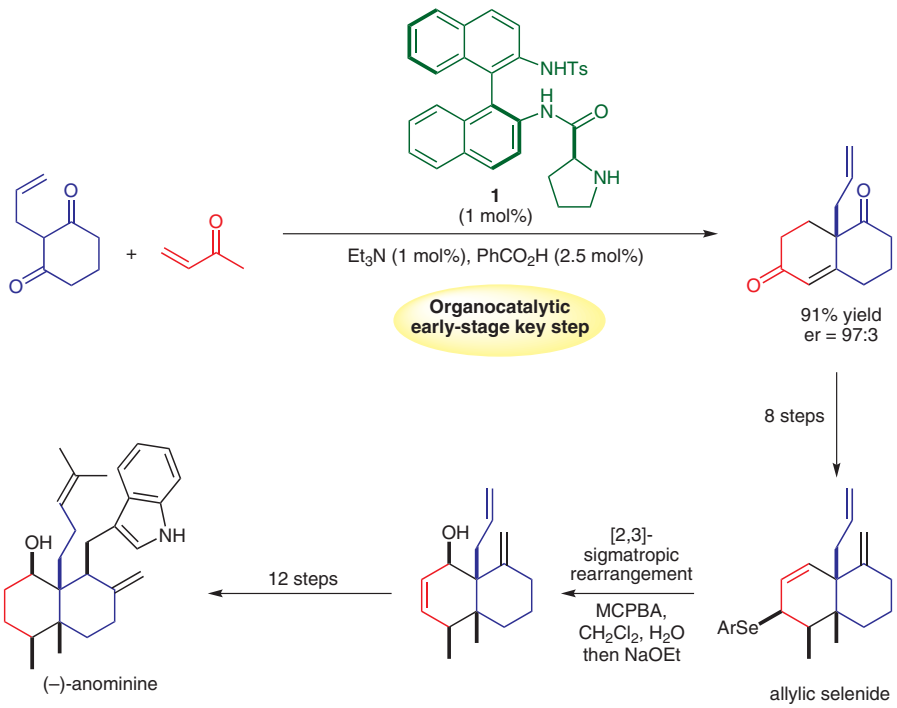
Total Synthesis of (–)-Anominine with an Organocatalytic Key Step



Significance: A concise 22-step total synthetic approach to (–)-anominine is reported. The first step of the synthesis is an organocatalytic Robinson annulation of a 1,3-diketone with methylvinyl ketone using prolinamide **1** as catalyst. The catalyst loading is remarkably low; only 1 mol% is necessary to furnish the first key intermediate in high yield with excellent enantioselectivity. After setting the first stereocenter, further transformations, among them a remarkable [2,3]-sigmatropic rearrangement of an allylic selenide, exploit the structurally congested nature of this bicyclic core for diastereoselectivity.

Comment: Synthetic approaches towards the diterpenoid metabolites of sclerotias from *Aspergillus* had been an unsolved synthetic challenge so far (e.g., S. Danishefsky et al. *J. Am. Chem. Soc.* **1985**, *107*, 2474). The reported sequence towards anominine is an elegant solution to this problem since only one transformation involves a chiral catalyst. This highly selective operation sets the stage for the development of the residual four stereocenters. The utilization of an organocatalytic reaction as the key step further underscores the great potential of organocatalysis in total synthesis.

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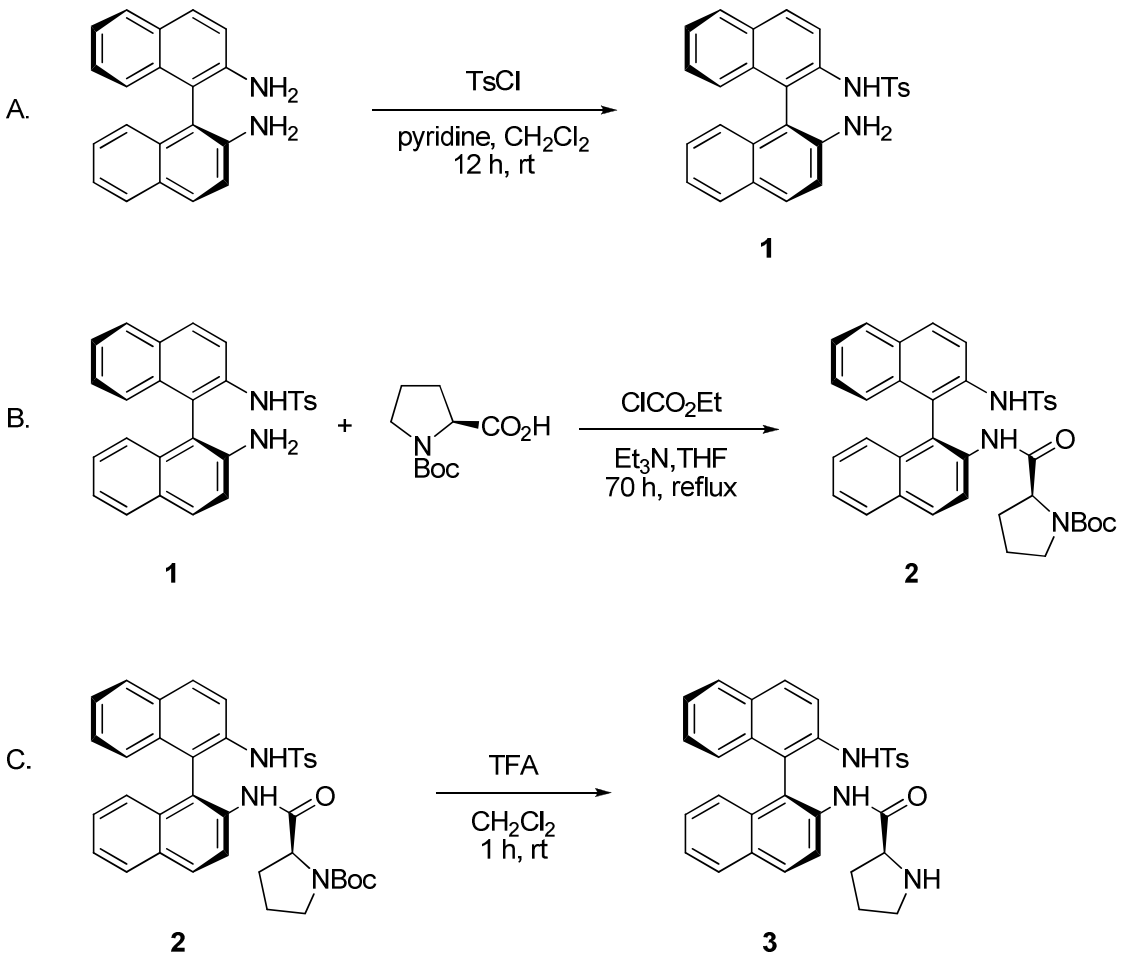
Category
Organo- and Biocatalysis

Key words
Robinson annulation
Wieland–Miescher ketones
diterpenoids
prolinamides

(*S*$_a$,*S*)-*N*-[2-(4-METHYLPHENYLSULFONAMIDO)-1,1´-BINAPHTHYL-2´-YL]-(*S*)-PYRROLIDINE-2-CARBOXAMIDE: AN ORGANOCATALYST FOR THE DIRECT ALDOL REACTION



Submited by Santiago F. Viózquez,[1] Gabriela Guillena,[1] Carmen Nájera,[1]Ben Bradshaw,[2] Gorka Etxebarria-Jardi,[2] and Josep Bonjoch[2]

1. Procedure

A. *(S$_a$)-N-[2´-Amino-(1,1´-binaphthalene)-2-yl]-4-methylbenzenesulfonamide*. A single-necked, 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum fitted with an argon inlet needle is charged with (*S$_a$*)-(−)-1,1'-Binaphthyl-2,2'-diamine ((*S$_a$*)-Binam, 3.03 g, 10.7 mmol, 1 eq) (Note 1) and flushed with argon. Anhydrous dichloromethane (DCM, 128 mL, 12 mL/mmol substrate) (Note 2) and dry pyridine (10.3 mL, 127.9 mmol, 12 eq) (Note 3) are added

by syringe. *p*-Toluenesulfonyl chloride (TsCl, 2.03 g, 10.7 mmol, 1 eq) (Note 4) is added in one portion by temporarily removing the septum and the brown solution is stirred overnight at room temperature (12 h) (Note 5). The reaction is quenched with 40 mL of water and the organic solvent is removed under reduced pressure (30 ºC, 30 mmHg). The mixture is transferred to 500 mL separatory funnel and extracted with 200 mL of ethyl acetate (EtOAc). The organic layer is washed with 2 M hydrochloric acid (5 × 30 mL) (Note 6), dried over magnesium sulfate and concentrated by rotary evaporation (40 ºC, 30 mmHg) to give 4.66-4.82 g (Note 7) of **1** as a pink foam which was used directly in the next step without further purification (Note 7).

B. *(S_a,S)-tert-Butyl 2-[(2′-(4-methylphenylsulfonamido)-(1,1′-binaphthalene)-2-yl)-carbamoyl]-pyrrolidine-1-carboxylate*. A 250-mL, oven-dried, one-necked, round-bottomed flask fitted with a Teflon-coated magnetic stirring bar is charged with (*S*)-*N*-(*tert*-butoxycarbonyl)proline (Boc-L-Pro, 2.52 g, 11.7 mmol, 1.1 eq) (Note 9). The flask with a rubber septum fitted with an argon inlet needle is flushed with argon and anhydrous THF (100 mL, 10 mL/mmol substrate) (Note 10) and dry triethylamine (1.63 mL, 11.7 mmol, 1.1 eq) (Note 11) are added via syringe. The mixture is cooled to 0 ºC with an ice-water bath and ethyl chloroformate (0.9 mL, 11.7 mmol, 1.1 eq) (Note 12) is added dropwise via syringe whereupon a fine white precipitate is formed. The suspension is stirred 30 min at 0 ºC and then a solution of **1** (4.66 g, 10.6 mmol, 1 eq) in anhydrous THF (20 mL) (Note 10) is added dropwise at 0 ºC using a syringe. After the addition, a Dimroth condenser fitted with a rubber septum and argon inlet needle is connected to the flask and the mixture is refluxed under an argon atmosphere for 70 h before cooling to room temperature (Note 13). The suspension is filtered through a fluted filter paper and the residue is washed with EtOAc (2 × 50 mL) and the combined filtrates are concentrated by rotary evaporation (40 ºC, 40 mmHg) to give 7.1-7.5 g of **2** as a pink foam which is used directly in the next step.

C. *(S_a,S)-N-[2-(4-Methylphenylsulfonamido)-1,1′-binaphthyl-2′-yl]-pyrrolidine-2-carboxamide.* A 250-mL, one-necked, round-bottomed flask fitted with a Teflon-coated magnetic stirring bar is charged with **2** (7.1 g, 10.6 mmol, 1 eq) and technical grade DCM (80 mL, 8 mL/mmol substrate). Trifluoroacetic acid (TFA, 16 mL, 212 mmol, 20 eq) (Note 14) is added dropwise via syringe and the mixture is stirred at room temperature for 1 h. The reaction is quenched by addition of 2 M sodium

hydroxide (~60 mL) until pH ~ 8 (Note 8) and the organic layer is separated. The aqueous layer is extracted with DCM (3 × 50 mL) and the combined organic extracts are dried over magnesium sulfate, filtered and concentrated by rotary evaporation (40 ºC, 40 mmHg) until ~100 mL of DCM remained. Silica gel (30 g) (Note 15) is added to this solution and the mixture is evaporated until silica dryness which is then placed on the top of a wet-packed silica gel column (diameter: 7 cm , height: 7 cm, pre-treated with hexanes/EtOAc, 3:1). The column is eluted with hexane/EtOAc, 3:1 (600 mL) and 150 mL fractions were collected. The solvent was changed to hexane/EtOAc, 1:1 (1.5 L). then hexane/EtOAc, 1:3 (900 mL) then EtOAc (900 mL). The desired product is obtained in fractions 13-30, (R_f = 0.5, EtOAc; visualized by UV and $KMnO_4$ stain) which are concentrated by rotary evaporation (40 °C, 40 mmHg) to give 3.93-4.06 g as an off-white solid.

This material is dissolved in the minimum amount of dichloromethane (3-5 mL) and then hexane (~15 mL) is added until precipitation of the product. The white solid formed is filtered through a sintered-glass funnel (Note 16), rinsed with cold hexane (2 x 20 mL) and dried under vacuum for 6 h to give 3.6-3.9 g (63-68% over 3 steps) of **3** as a white powder (Note 17).

2. Notes

1. (S_a)-Binam was purchased from Aldrich Chemical Company and used as received.
2. Dichloromethane anhydrous (SureSeal tap/molecular sieves) was purchased from Fluka and used as received.
3. Pyridine was purchased from Aldrich Chemical Company and dried with 4Å molecular sieves.
4. TsCl was purchased from Aldrich Chemical Company and used as received.
5. The reaction is monitored by thin layer chromatography on silica gel (Merck silica gel 60 F_{254}) with 50% ethyl acetate in hexanes as the eluent and visualization with UV. The diamine starting material has R_f = 0.4 (UV active) and the tosyl product has R_f = 0.5 (UV active).

6. The combined acidic washings are neutralised until pH ~ 7 (Note 8) and extracted with DCM (3 × 30 mL) to recover the unreacted (S_a)-Binam. The combined organic layers are washed with brine, dried over magnesium sulfate and concentrated by rotary evaporation (40 ºC, 40 mmHg) to give 0.37-0.55 g (12-18%) of (S_a)-Binam along with traces of product.

7. The 4.66-4.82 g of material contained 15% of the ditosylated byproduct , as evidenced by the integration of the ^{1}H-NMR methyl groups of the mono- and ditosylated species. An amount of 10-15 % of ditosylated byproduct is always isolated along with the desired monotosylated product under these reaction conditions. This undesired byproduct is unseparable by usual column chromatography and is carried on until the end of the sequence. Compound **1** has been isolated,[3] but its purification was unnecessary for this procedure.

8. pH paper was used for monitorization.

9. *N*-(*tert*-Butoxycarbonyl)-L-proline was purchased from Aldrich Chemical Company and used as received.

10. Scharlau Chemie S.A. reagent grade tetrahydrofuran was purified by passage through activated alumina.

11. Triethylamine was purchased from Aldrich Chemical Company, kept under sodium cubes and used without further purification.

12. Ethyl chloroformate was purchased from Aldrich Chemical Company and used as received.

13. The reaction is monitored by thin layer chromatography on silica gel (Merck silica gel 60 F_{254}) with 3 elutions of 25% ethyl acetate in hexanes and visualization with UV. The amine starting material has R_f = 0.6 (UV active) and the Boc-proline product has R_f = 0.3 (UV active).

14. Trifluoroacetic acid was purchased from Aldrich Chemical Company and used as received.

15. The silica gel used was Kielsel 60, E.Merck, 0.040-0.063 mm (250-400 mesh). Both ethyl acetate and hexanes are analytical grade solvents purchased from Merck & Co., Inc.

16. Number 5 pore size filter was used.

17. The physical properties of compound **3** are as follows: R_f 0.5 (EtOAc); $[\alpha]_D^{20}$ -205 (*c* 1.04, $CHCl_3$); mp 200-202 ºC; IR (film) cm^{-1}: 663, 748, 814, 976, 1092,

1166, 1429, 1468, 1501, 1687, 2876, 3053, 3193, 3333; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.61-0.70 (m, 1H), 1.14-1.26 (m, 2H), 1.58-1.62 (m, 1H), 1.74-1.77 (m, 1H), 2.17-2.25 (m, 1H), 2.35 (s, 3H), 3.30 (dd, *J* = 3.9, 9.4 Hz, 1H), 6. 33 (brs, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.00-7.09 (m, 4H), 7.25-7.35 (m, 4H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.96 (d, *J* = 9.1, 1H), 8.09 (d, *J* = 9.1, 1H), 8.72 (d, *J* = 9.1, 1H), 9.22 (brs, 1H); ^{13}C RMN (75 MHz, $CDCl_3$) δ: 21.5, 25.1, 30.5, 46.0, 60.4, 116.8, 119.1, 119.3, 120.5, 124.0, 125.0, 125.1, 125.5, 127.3, 127.5, 128.1, 128.5, 129.4, 130.0, 130.4, 130.6, 130.1, 132.0, 132.4, 133.6, 135.6. 136.4, 143.8, 173.3; HRMS (EI) *m/z* calc. for $C_{32}H_{29}N_3O_3S$ [M^+]: 535.1930, found: 535.1927; The enantiomeric excess of the product is determined by HPLC analysis at 254 nm [Chiralpak AD-H, 80:20 hexanes: *i*-PrOH, 1mL/min: t_r = 105.4 min].

Safety and Waste Disposal Information

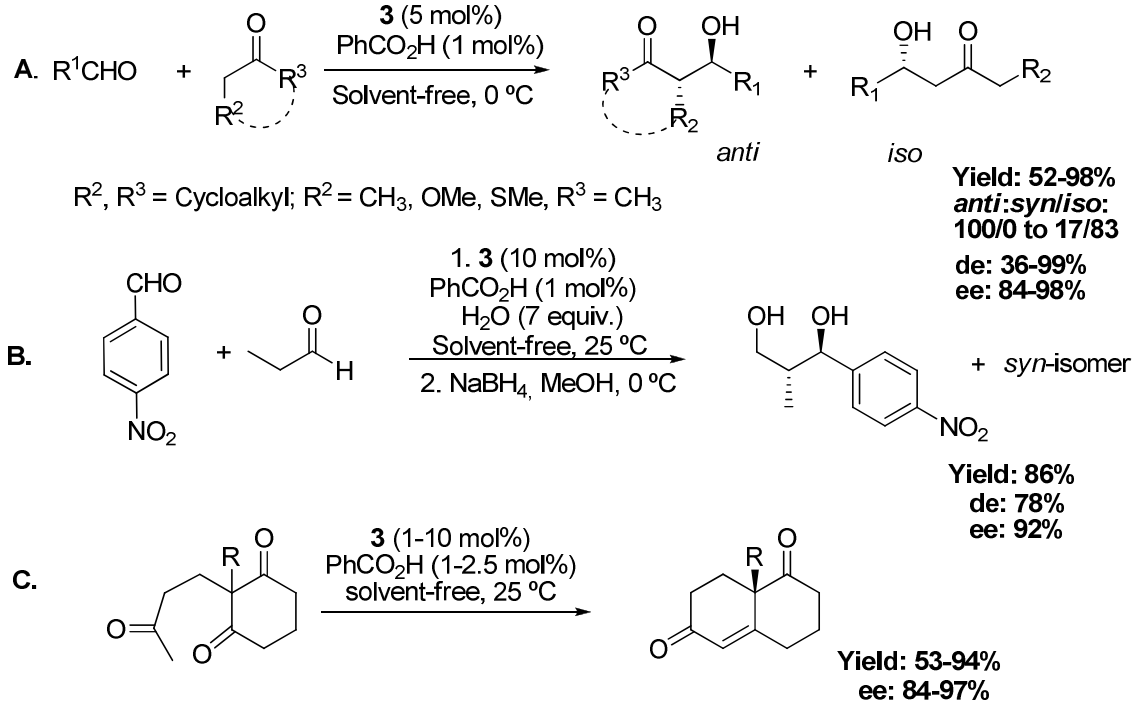
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The first generation of BINAM-prolinamides was introduced by several groups in 2006 to use in direct asymmetric aldol reactions[4-6] or other enantioselective processes.[7] (S_a,*S*)-*N*-(2-(4-Methylphenylsulfonamido)-1,1´-binaphthyl-2´-yl)-pyrrolidine-2-carboxamide (**3**) is a novel BINAM-prolinamide-type organocatalyst[4] that was developed by Nájera´s group[8] and others[6d] almost simultaneously. This (*S*a)-binam-L-prolinamide sulfonamide derivative **3**[8] was designed by replacing one proline residue in the first generation catalyst[6] with an acidic sulfonamide group that could activate the carbonyl group of the aceptor through hydrogen-bonding.[9] The efficiency of this catalyst when used with a small amount of benzoic acid as an additive has been proven in several aldol reaction processes, including the intermolecular aldol reaction between

aldehydes and ketones (A, Scheme 1), the cross-aldol reaction between aldehydes (B, Scheme 1), and the intramolecular aldol reaction for the synthesis of the Wieland Miescher ketone (WMK) and related analogues (C, Scheme 1).

Scheme 1. Aldol processes catalyzed by *N*-tosyl-(S_a)-binam-L-prolinamide **3**



For all the processses, solvent-free reaction conditions could be applied using low catalyst loadings, obtaining the corresponding aldol products with good yields and diastereo- and enantioselectivities comparable to those achieved with other structurally similar catalysts[10] under different reaction conditions. For instance, the large-scale synthesis of the Wieland-Miescher ketone[11] requires only 1 mol% of catalyst **3** (see accompanying article).[12]

The preparation of catalyst **3** described here is a variant of those which already exist,[8,9] and offers the following advantages:

1) Minimal purification steps: only the final product needs to be purified by chromatography.
2) The amide bond formation is efficiently accomplished using ethyl chloroformate, which avoids the use of $SOCl_2$ to form the acid chloride or the need for expensive coupling agents that, moreover, are difficult to remove at the end of the reaction.

This preparation can be also applied to obtain the enantiomer of the desired product, (R_a,*R*)-*N*-(2-(4-methylphenylsulfonamido)-1,1′-binaphthyl-2′-yl)-pyrrolidine-2-carboxamide.[13]

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12. Bradshaw, B.; Etxeberría-Jardí, G.; Bonjoch, J.; Viózquez, S. F., Guillena, G.; Nájera, C.; *Org. Synth.* **2010**, submitted

13. (R_a,*R*)-*N*-(2-(4-methylphenylsulfonamido)-1,1´-binaphthyl-2´-yl)-pyrrolidine-2-carboxamide has the same physical properties as the (S_a,*S*)-enantiomer aside from the optical rotation, which is almost equal but opposite: $[\alpha]_D^{20}$ 199 (*c* 1.1, $CHCl_3$); The enantiomeric composition was checked by the use of HPLC analysis at 254 nm [Chiralpak AD-H, 80:20 hexanes: *i*-PrOH, 1mL/min: t_r = 51.05 min].

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); Registry Number

(S_a)-(-)-1,1´-Binaphthyl-2,2´-diamine: (S_a)-(-)-1,1´-Bi(2-naphthylamine); (18531-95-8)

p-Toluenesulfonyl chloride: Tosyl chloride; (98-58-9)

Pyridine; (110-86-1)

N-(*tert*-Butoxycarbonyl)-L-proline; (15761-39-4)

Ethyl chloroformate: Carbonochloridic acid, ethyl ester; (541-41-3)

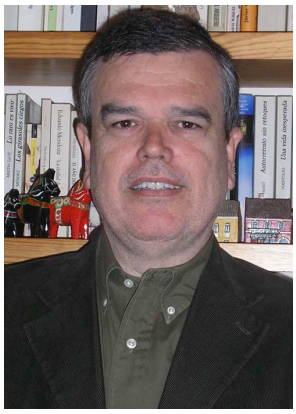
Triethylamine; (121-44-8)

Trifluoroacetic acid; (76-05-1)

Carmen Nájera obtained her B.Sc.(1973) from University of Saragossa and her PhD (1979) at the University of Oviedo under the supervision of J. Barluenga and M. Yus. She performed her postdoctoral work at the ETH (Zurich) with D. Seebach, at the Dyson Perrins Laboratory (Oxford) with J. E. Baldwin, at Harvard University with E. J. Corey, and at Uppsala University with J.-E. Bäckvall. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. Her scientific contributions are focused on synthetic organic chemistry such as sulfone chemistry, new peptide coupling reagents, oxime-derived palladacycles, asymmetric metal catalysis and organocatalysis.

Gabriela Guillena received her BSc degree (1993) from University of Alicante. After spending one year as postgraduate student in the group of D. Seebach at the ETH (Zurich), she returned to University of Alicante and received her MSc (1995) and PhD (2000) degrees under the supervision of C. Nájera. After two years as a posdoctoral fellow at research group of G. van Koten (University of Utrecht, Netherlands), she returned to The University of Alicante where she became Assistant Professor in 2003 and Associate Professor in 2008. Her current research interests are focused on new organic methodologies and asymmetric organocatalysis.

Santiago Viózquez was born in Alicante (Spain) in 1981. He received his B.S. degree in chemistry at the Universidad de Alicante in 2006. He is now pursuing his Ph.D. at the Universidad de Alicante under the supervision of G. Guillena and C. Nájera. His research concerns asymmetric organocatalysis with prolinamides derivatives.

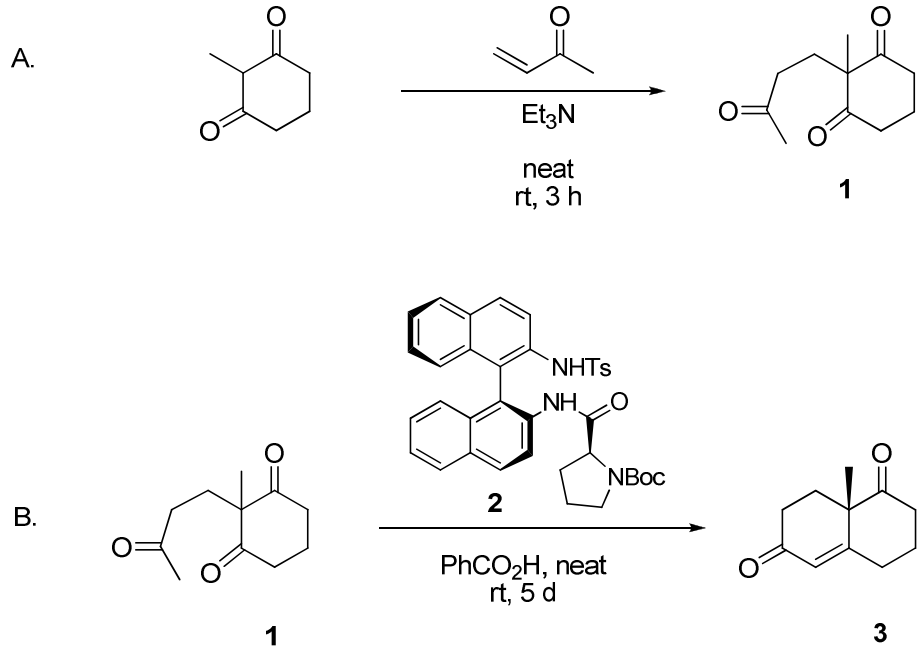


Josep Bonjoch was born in Barcelona (Catalonia, Spain) in 1952. He received his Ph.D. degree (1979) under the supervision of Prof. Joan Bosch at the University of Barcelona, Faculty of Chemistry. He then moved to the Faculty of Pharmacy at the same University, where he was promoted to Associate Professor (1984) and subsequently became Full Professor of Organic Chemistry in 1992. His main research involves the synthesis of complex nitrogen containing natural products, as a motive for developing new synthetic methodology.

Ben Bradshaw was born in 1974 in Southport, England. He studied Chemistry at the University of Manchester, where he obtained his PhD in 2001 under the supervision of Professor John Joule. After postdoctoral work with Professor Jim Thomas on the total synthesis of the Bryostatins he joined the group of Professor Josep Bonjoch at the University of Barcelona. In 2008 he was promoted to the position of assistant professor where his research interests include the application of organocatalysis to the total synthesis of complex natural products.

Gorka Etxebarria-Jardí was born in 1981 in Barcelona, Catalonia. He obtained his BSc in Chemistry (2004) and MSc in synthesis of antiretroviral nucleoside drugs (2005) from the University of Barcelona. In 2006, he joined the research group of Prof. Josep and is currently completing his Ph.D in asymmetric catalysis and natural product synthesis.

SYNTHESIS OF (*S*)-8a-METHYL-3,4,8,8a-TETRAHYDRO-1,6-(2*H*,7*H*)-NAPHTHALENEDIONE VIA *N*-TOSYL-(S_a)-BINAM-L-PROLINAMIDE ORGANOCATALYSIS



Submitted by Ben Bradshaw,[1] Gorka Etxebarria-Jardí,[1] Josep Bonjoch,[1] Santiago F. Viózquez,[2] Gabriela Guillena[2] and Carmen Nájera[2]

1. Procedure

A. A standard glass vial with stopper (Note 1) fitted with a Teflon-coated magnetic stirring bar is charged with 2-methyl-1,3-cyclohexanedione (10.0 g, 79.3 mmol, 1 eq) (Note 2), triethylamine (112 μL, 0.80 mmol, 0.01 eq) (Note 3) and methyl vinyl ketone (MVK, 7.15 mL, 87.2 mmol, 1.1 eq) (Note 4) and the heterogeneous mixture was stirred vigorously. The initial thick suspension slowly becomes more fluid as the solid dissolves to give a brown oil which is stirred at room temperature for 4 h (Note 5). This oil was transferred to a 500 mL flask using dichloromethane and concentrated by rotary evaporation (25 °C, 40 mmHg). A Teflon-coated magnetic stirring bar, 250 mL of diethyl ether, 0.5 g of decolorising charcoal are added and the flask fitted with a condenser and heated to reflux for 15 min. After cooling to room temperature the mixture is suction filtered through a sintered glass funnel (7 cm diameter, porosity 4) packed with silica (30 g, 2 cm depth) (Note 6) directly into a 1 L round bottomed flask. The funnel is washed with diethyl ether (3 × 50 mL), the filtrate

is partially concentrated by rotary evaporation (25 °C, 40 mmHg) and transferred to a 100 mL flask concentrated by rotary evaporation (25 °C, 40 mmHg) and then kept under high vacuum to a constant weight to give 14.54–14.64 g (93–94%) of the triketone **1** as a clear slightly yellow oil.

B. A standard glass vial with stopper (Note 1) fitted with a Teflon-coated magnetic stirring bar is charged with **1** (14.42 g, mmol, 1 eq) (Note 7), catalyst **2** (394 mg, mmol, 0.735 mmol, 0.01 eq) (Note 8) and benzoic acid (225 mg, 1.84 mmol, 0.025 eq) (Note 9). The mixture is stirred at room temperature for 5 d (Note 10). The reaction mixture is dissolved in diethyl ether (250 mL) and is transferred to a 500 mL separatory funnel. The mixture is washed with saturated aqueous sodium hydrogen carbonate (2 x 10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ (20 g) and filtered into a 500 mL round-bottomed flask. Decolorising charcoal (0.5 g) is added and the flask is fitted with a condenser and refluxed for 15 min. The mixture was cooled to room temperature, diluted with 250 mL of hexane and filtered with suction through a sintered glass funnel (7 cm diameter, porosity 4) packed with silica (30 g, 2 cm depth) (Note 11) directly into a 2 L round-bottomed flask. The funnel is washed with 1:1 diethyl ether/hexane mixture (10 x 100 mL) (Note 13). The filtrate is partially concentrated by rotary evaporation (25 °C, 40 mmHg), transferred to a 100 mL flask, concentrated by rotary evaporation (25 °C, 40 mmHg) kept under high vacuum (25 °C, 10 mmHg) and dried to a constant weight to afford 12.1–12.3 g (93–94% yield) of **3** as a slightly colored oil which crystallised on standing, ee = 92% (Note 14). To the crystals is added 25 mL of a 1:1 mixture of diethyl ether-hexane, the mixture was gently slurried and the supernatant removed by pipette. The final traces of solvent were removed by rotary evaporation (25 °C, 40 mmHg) to give 11.61–11.67 g, (89 %) of **3** as a brown crystalline solid, ee = 94% (Note 14).

2. Notes

1. To obtain good mixing the reaction should be performed in a standard glass vial (10 cm height, 3 cm wide).

2. 2-Methyl-1,3-cyclohexanedione was purchased from Aldrich Chemical Company or Alfa Aesar Chemical Company. All lots were found to contain impurities which had a detrimental effect on the reaction. It was therefore important to recrystallize

the dione twice as following: To the dione in a round-bottomed flask was added water (25 mL/g) and the mixture heated to reflux. Absolute ethanol was then added slowly to the mixture until all the solid had dissolved (approximately ~6.5 to 7 mL/g). The mixture was then allowed to cool to room temperature. The crystals were collected by filtration and washed with cold water (~0.4 mL/g). After the second recrystallisation the collected crystals were dried to constant weight in a dessicator and then subsequently stored at 0°C.

3. Triethylamine was purchased from Fluka Chemical Company and used without further purification.

4. Methyl vinyl ketone was purchased from Aldrich Chemical Company and used without further purification.

5. It may be necessary from time to time to tip the vial slightly to ensure any solid material adhering to the side of the vial comes into contact with the reaction mixture.

6. The silica gel was packed with diethyl ether according to the following method: The silica gel was first slurried with 200 mL of diethyl ether and then poured into the sintered glass funnel which was connected to the vacuum using a T-piece adaptor. A light vacuum was applied just until the diethyl ether was absorbed and the silica remained wet and compacted.

7. The product **1** was transferred from the 100 mL round-bottomed flask to the reaction vial via pipette. The material was not transferred using solvent followed by evaporation since it was difficult to remove all traces of solvent from the sample in the reaction vial.

8. Catalyst **2** was prepared according to the method described in the accompanying procedure.

9. Benzoic acid was purchased from Aldrich Chemical Company.

10. The initial orange solution darkens to black as the reaction progresses. Water generated condenses on the cylinder walls during the course of the reaction becoming very pronounced on days 4 to 5. The reaction progress was monitored by taking an aliquot of the reaction mixture and analysing by NMR.

11. The silica gel was packed with a 1:1 mixture of diethyl ether–hexane according to the method outlined in Note 6

12. The filtrate can be collected in smaller flasks and each fraction checked by NMR. The initial fractions deliver a white product whilst later washes the product is slightly coloured. However all fractions were found to be identical by NMR.

13. After the indicated washes are completed further washes can be applied and collected in seperate flasks to check that no material remains on the silica pad and to avoid the possible washing through of impurities and contamination of the main batch of product. The purity of individual fractions was evaluated by NMR.

14. The enantiomeric composition was checked by the use of HPLC analysis at 254 nm [Chiralcel OD-H, 96:4 hex:i-PrOH, 0.8 ml/min: major isomer t_r = 23.90 min; minor isomer: t_r = 26.79 min].The samples were obtained by dissolving all of the product in diethyl ether, taking an aliquot for analysis and then allowing the solvent to evaporate since the bulk crystallized product may not completely homogeneous. The supernatant was found to have an ee of 74–82%

Safety and Waste Disposal information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The Wieland-Miescher ketone (**3**)[3] is a useful synthetic building block for which a classical asymmetric procedure using (*S*)-proline was published forty years ago.[4] Although this method can be applied on a large scale in the laboratory, it has certain drawbacks, partly due to the enantiomeric excess (ee) of the product (only 70%). To obtain an enantiomerically pure sample from this material, a fractional crystallization procedure[5] allows the contaminating undesired enantiomer to be removed by the preferential crystallization of its racemic form, involving the loss of an equal amount of the desired enantiomer. Moreover, the success of the fractional crystallization has been found to depend strongly upon the ee and chemical purity of the partially enantiomerically enriched form of **3**. Thus, although the development of the currently used procedure has enabled a wide application of the enantiopure Wieland-Miescher ketone in natural product synthesis,[6,7] it requires considerable investment of time,

material, experience to achieve satisfactory results and generates considerable waste.

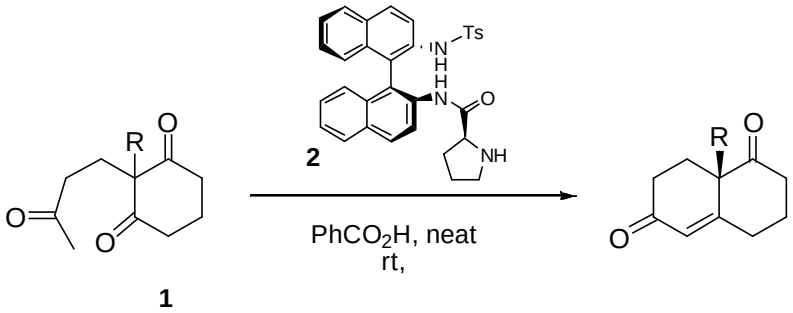
The advent of a plethora of new organocatalysts for aldol reactions has allowed Wieland-Miescher ketone (**3**) samples with high enantiomeric excess to be prepared without crystallization steps (86-92% ee),[8] but always operating on a very small scale (0.3-1.0 mmol of triketone (**2**) as starting material) due to the use of catalysts that are difficult to prepare catalysts (from 7 up to 15 steps) and high catalyst loadings (5 to 30 mol%).

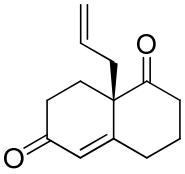
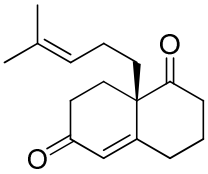
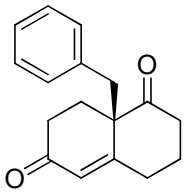
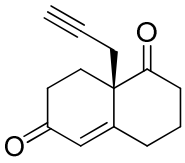
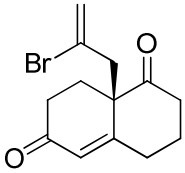
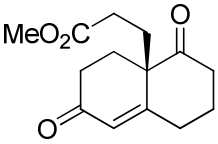
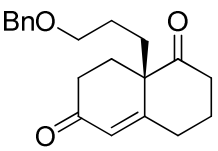
Using the method detailed here and the accompanying procedure for the organocatalyst **2**,[9] 12 g of the Wieland-Miescher ketone (94% ee) can be obtained in 88% overall yield from 2-methylcyclohexane-1,3-dione. This streamlined procedure[10, 11] has significant practical implications from the synthetic point of view since the sequence is performed with high atom efficiency, low catalyst loading (1%), negligible waste formation, and in both steps a short reaction workup and product purification, which enables a large-scale preparation of this bicyclic enedione.

This new methodology for constructing the Wieland-Miescher ketone has a broad application in the synthesis of analogs in which the methyl group is replaced by various other alkyl groups that are not easily obtained using proline as the organocatalyst. Under similar conditions,[10] several triketones undergo cyclization to afford Wieland-Miescher ketone analogs in high yield as shown in Table 1. Among these, a noteworthy compound for terpene synthesis is the allyl derivative,[12] which is prepared in 93% yield and 97% ee .

Furthermore with both enantiomers of the catalyst readily available the respective WMK enantiomers can be easily accessed.

Table 1. Synthesis of a variety of Weiland Meischer Ketone analogs using *N*-Tosyl-(S_a)-binam-L-prolinamide as catalyst.



entry	*catalyst 2 (x mol%)*	*benzoic acid (x mol%)*	*time (d)*	*Product*	*yield (%)*	*ee (%)*
1a	2.5	1	5		93	97
1b	1	2.5	6		96	94
2	5	1	10		59	96
3	5	1	10		70	94
4	5	1	4		78	90
5	10	1	4		70	96
6	10	1	8		71	95
7	5	1	4		78	94

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3. (a) Wieland, O.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215-2228. (b) Ramachandran, S.; Newman, M. S. *Org. Synth.* **1961**, *41*, 38-41.

4. (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed*. **1971**, *10*, 496-497
(b) Hajos, Z. G.; Parrish, D. R. *United States Patent* US 3975442, **1971**.

5. (a) Gutzwiller, J.; Bushshacher, P.; Fürst, A. *Synthesis* **1977**, 167-168. (b) Buchschacher, P.; Fürst, A. *Org. Synth.* **1985**, *63*, 37-43. (c) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53-56.

6. For Total Syntheses using the WMK up until 2007, see: Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry.* 2007, 18, 2249-2293 (references 242-256).

7. For recent applications see: (a) Smith III, A. B.; Kürti. L.; Davulcu, A. H.; Cho, Y. S. *Org. Process. Res. Dev.* **2007**, *11*, 19-24. (b) Hanessian, S.; Boyer, N.; Reddy, G. J.; Deschênes-Simard, B. *Org. Lett*. **2009**, *11*, 4640-4643. (c) Waalboer, D. C. J.; vanKalkeren, H. A.; Schaapman, M. C.; vanDelft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem*. **2009**, *74*, 8878-8881. (d) Ma, K.; Zhang, C.; Liu, M.; Chu, Y.; Zhou, L.; Hu, C.; Ye, D. *Tetrahedron Lett*. **2010**, *51*, 1870-1872. (e) Carneiro, V. M. T.; Ferraz, H. M. C.; Vieira, T. O.; Ishikawa, E. E.; Silva, L. F. Jr. *J. Org. Chem*. **2010**, *75*, 2877-2882 (f) Churruca, F.; Fousteris, M.; Ishikawa, Y.; Rekowski, M. W.; Hounsou, C.; Surrey, T.; Giannis, A. *Org. Lett*. **2010**, *12*, 2096-2099.

8. (a) Davies, S. G.; Russell, A. J.; Sheppard, R. L.; Smith, A. D.; Thompson, J. E. *Org. Biomol. Chem.* **2007**, 3190-3200. (b) Kanger, T.; Kriis K.; Laars, M.; Kailas, T.; Müürisepp, A.M.; Pehk, T.; Lopp. M. *J. Org. Chem.* **2007**, *72*, 5168-5173. (c) D'Elia, V.; Zwicknagl, H.; Reiser, O. *J. Org. Chem.* **2008**, *73*, 3262-3265. (d) Almasi, D.; Alonso, D. A.; Nájera, C. *Adv. Synth. Catal*. **2008**, *350*, 2467-2472. (e) Guillena, G.; Nájera, C.; Viózquez, S. F. *Synlett* **2008**, 3031-3035. (f). Zhang, X.-M.; Wang. M.; Tu, Y.Q.; Fan, C. A.; Jiang Y. J.; Zhang, S.Y.; Zhang, F. M. *Synlett* **2008**, 2831-2835.

9. Guillena, G.; Nájera, C.; Viózquez, S. F Bradshaw, B.; Etxeberría-Jardí, G.; Bonjoch, J. *Org. Synth. Catal.* **2011**, *88*, 0000-0000; (see preceeding paper).

10. For the initial procedure see: Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J.; Guillena, G.; Nájera, C.; Viózquez, S. F. *Adv. Synth. Catal*. **2009**, *351*, 2482-2490.

11. The originally published method required the use of 2% of organocatalyst and 0.5% of benzoic acid and provided the product in 94% yield and 94% ee. Both steps (alkylation and cyclisation) required flash column chromatography and therefore limited the scale and throughput of the reaction. The modified version has a slightly lower yield (89%) but uses less catalyst (1%) and eliminates the need for column chromatography.

12. (a) Nicolaou, K.C.; Roecker, A. J.; Monenschein, H.; Guntupalli, P.; Fullman, M. *Angew. Chem. Int. Ed*. **2003**, *42*, 3637-3642. (b) Bradshaw, B.; Etxeberría-Jardí, G.; Bonjoch, J. *J .Am. Chem. Soc.* **2010**, *132,* 5966–5967.

Appendix

Chemical Abstracts Nomenclature; (Registry Number)

(substance nomenclature, CAS number)

(S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphtalenedione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (8aS)- ; (33878-99-8)

2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione: 1,3-Cyclohexanedione, 2-methyl-2-(3-oxobutyl)- ; (85073-65-4)

2-Methyl-1,3-cyclohexanedione: 1,3-Cyclohexanedione, 2-methyl-; (1193-55-1)

N-Tosyl-(S_a)-binam-L-prolinamide: 2-Pyrrolidinecarboxamide, N-[(1S)-2'-[[(4-methylphenyl)sulfonyl]amino][1,1'-binaphthalen]-2-yl]-, (2S)-; (933782-38-8)

Methyl vinyl ketone: 3-Buten-2-one; (78-94-4)

(*R*)-8a-Allyl-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-(2-propen-1-yl)-, (8aR)- **;** (175774-65-9)

(*R*)-8a-(3-Methylbut-2-enyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-(3-methyl-2-buten-1-yl)-, (8aR)-; (1210056-49-7)

(*R*)-8a-Benzyl-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-(phenylmethyl)-, (8aR)-; (945423-29-0)

(*R*)-8a-(Prop-2-ynyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione; (1210056-50-0) no name

(*R*)-8a-(2-Bromo-2-propenyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione: 1,6(2H,7H)-Naphthalenedione, 8a-(2-bromo-2-propen-1-yl)-3,4,8,8a-tetrahydro-, (8aR); (1108206-43-4)

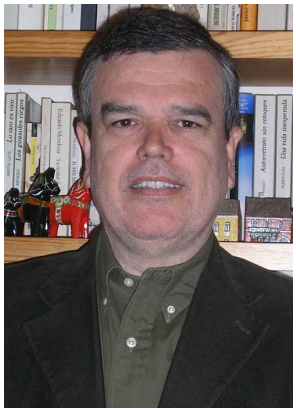
(*S*)-8a-(But-3-enyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione; (1210056-51-1) no name

(*S*)-8a-(4-Methylpent-3-enyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione; (1210056-52-2) no name

(*S*)-8a-(3-Methylpentyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione; (1210056-53-3) no name

(*R*)-8a-[(3-Methoxycarbonyl)ethyl]-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione; 4a(2H)-Naphthalenepropanoic acid, 1,3,4,5,6,7-hexahydro-4,7-dioxo-, methyl ester, (4aR)-: (1108206-39-8)

(*S*)-8a-[(3-Benzyloxy]propyl)-3,4,8,8a-tetrahydronaphtalene-1,6(2*H*,7*H*)-dione; (1210056-54-4) no name



Josep Bonjoch was born in Barcelona (Catalonia, Spain) in 1952. He received his Ph.D. degree (1979) under the supervision of Prof. Joan Bosch at the University of Barcelona, Faculty of Chemistry. He then moved to the Faculty of Pharmacy at the same University, where he was promoted to Associate Professor (1984) and subsequently became Full Professor of Organic Chemistry in 1992. His main research involves the synthesis of complex nitrogen containing natural products, as a motive for developing new synthetic methodology.

Ben Bradshaw was born in 1974 in Southport, England. He studied Chemistry at the University of Manchester, where he obtained his PhD in 2001 under the supervision of Professor John Joule. After postdoctoral work with Professor Jim Thomas on the total synthesis of the Bryostatins he joined the group of Professor Josep Bonjoch at the University of Barcelona. In 2008 he was promoted to the position of assistant professor where his research interests include the application of organocatalysis to the total synthesis of complex natural products.

Gorka Etxebarria-Jardí was born in 1981 in Barcelona, Catalonia. He obtained his BSc in Chemistry (2004) and MSc in synthesis of antiretroviral nucleoside drugs (2005) from the University of Barcelona. In 2006, he joined the research group of Prof. Josep and is currently completing his Ph.D in asymmetric catalysis and natural product synthesis.

Carmen Nájera obtained her B.Sc.(1973) from University of Saragossa and her PhD (1979) at the University of Oviedo under the supervision of J. Barluenga and M. Yus. She performed her postdoctoral work at the ETH (Zurich) with D. Seebach, at the Dyson Perrins Laboratory (Oxford) with J. E. Baldwin, at Harvard University with E. J. Corey, and at Uppsala University with J.-E. Bäckvall. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. Her scientific contributions are focused on synthetic organic chemistry such as sulfone chemistry, new peptide coupling reagents, oxime-derived palladacycles, asymmetric metal catalysis and organocatalysis.

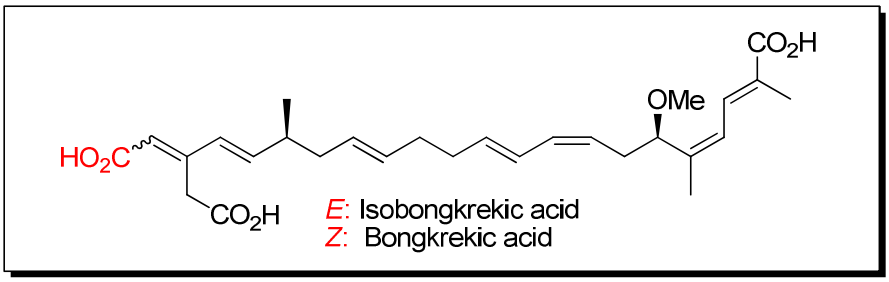
Gabriela Guillena received her BSc degree (1993) from University of Alicante. After spending one year as postgraduate student in the group of D. Seebach at the ETH (Zurich), she returned to University of Alicante and received her MSc (1995) and PhD (2000) degrees under the supervision of C. Nájera. After two years as a posdoctoral fellow at research group of G. van Koten (University of Utrecht, Netherlands), she returned to The University of Alicante where she became Assistant Professor in 2003 and Associate Professor in 2008. Her current research interests are focused on new organic methodologies and asymmetric organocatalysis.

Santiago Viózquez was born in Alicante (Spain) in 1981. He received his B.S. degree in chemistry at the Universidad de Alicante in 2006. He is now pursuing his Ph.D. at the Universidad de Alicante under the supervision of G. Guillena and C. Nájera. His research concerns asymmetric organocatalysis with prolinamides derivatives.

APPENDIX

Introduction

As a part of the PhD programme a research placement was done in Steven Ley's group in the University of Cambridge, United Kingdom. The project consisted in the enantioselective synthesis of iso- and bongkrekic acids (Scheme 1). Isobongkrekic acid (IBA, ***Z***) is a complex fatty triacid which was isolated from the fermentation of *Pseudomonas cocovenenans* in 1976.[1] Closely connected to its better known isomer bongkrekic acid (BA, ***E***),[2] they form a small family of toxic antibiotics with potent antiapoptotic activity. These compounds act as inhibitors of adenine nucleotide translocase, which mediates the ADP/ATP exchange in mitochondria.[3] As a consequence, these substances attracted the interest of many chemists, in particular, Corey and Tramontano devised a first very effective synthesis of BA in 1984,[4] while a second and longer total synthesis appeared two decades later.[5] However, the syntheses proved to be impractical due its linear and the large number of steps required, so as a consequence, a new highly efficient route was developed and is described here. During the course of this work, Shindo and Shishido published two greatly improved second generation syntheses.[6]



Scheme 1 Iso- and Bongkrekic Acids.

[1] (a) G. J. M. Lauquin, A-M. Duplaa, G. Klein, A. Rousseau, P. V. Vignais, *Biochemistry*, **1976**, *15*, 2323–2327. (b) S. Chatterjee, E. K. S. Vijayakumar, K. Roy, R. H. Rupp, B. N. Ganguli, *J. Org. Chem.,* **1988**, *53*, 4883–4886.

[2] For isolation, see: (a) A. G. van Veen, W. K. Mertens, *Rec. trav. Chim. Pays-Bas*, **1934**, *53*, 257–266. (b) For structure determination, see: J. de Bruin, D. J. Frost, D. H. Nugteren, A. Gaudemer, *Tetrahedron*, **1973**, *29*, 1541–1547.

[3] (a) P. J. F. Henderson, H. A. Lardy, *J. Biol. Chem.*, **1970**, *245*, 1319–1326. (b) M. Klingenberg, K. Grebe, H. W. Heldt, *Biochem. Biophys.Res. Commun.*, **1970**, *39*, 344–351. (c) M. Klingenberg, M. Appel, W. Babel, H. Aquila, *Eur. J. Biochem.*, **1983**, *131*, 647–654.

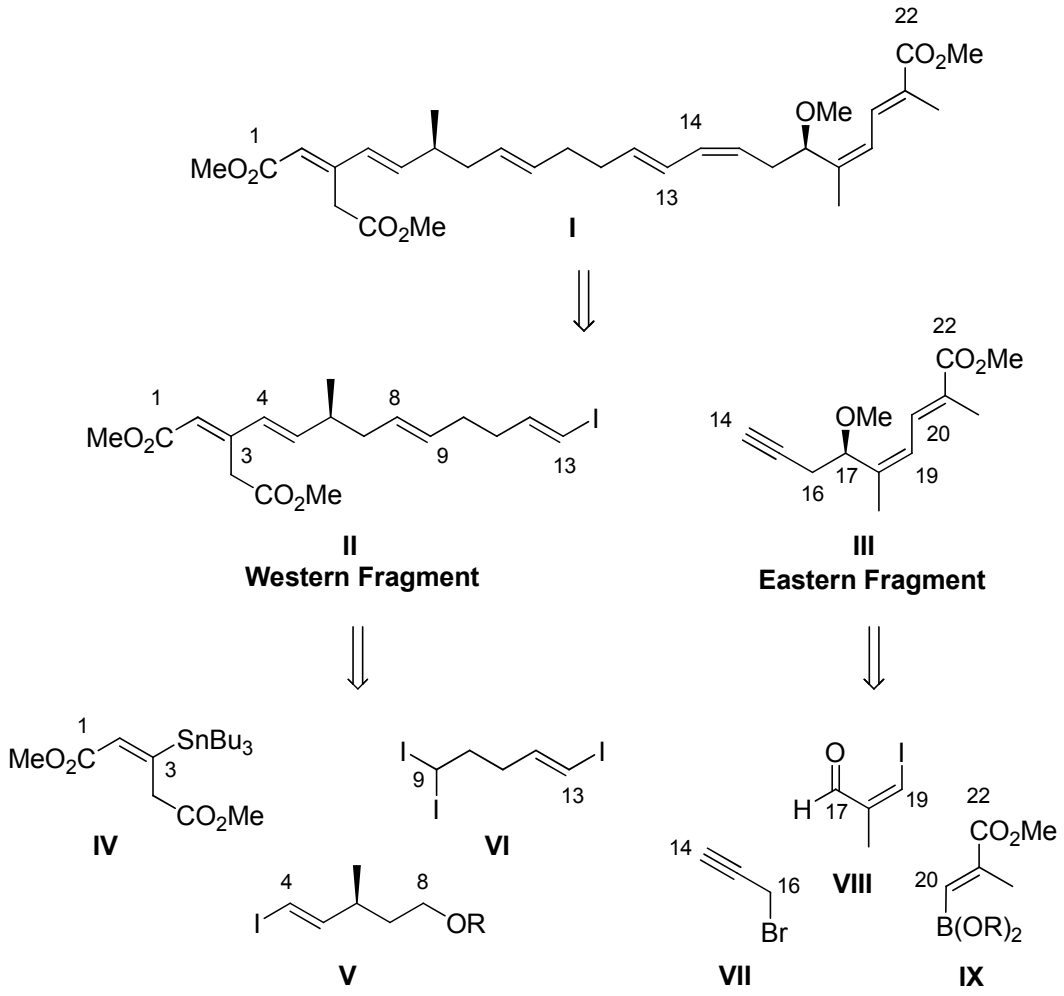
[4] E. J. Corey, A. Tramontano, *J. Am. Chem. Soc.*, **1984**, *106*, 462–463.

[5] M. Shindo, T. Sugioka, Y. Umaba, K. Shishido, *Tetrahedron Lett.*, **2004**, *45*, 8863–8866.

[6] (a) Y. Sato, Y. Aso, M. Shindo, *Tetrahedron Lett.*, **2009**, *50*, 4164–4166. (b) M. Kanematsu, M. Shindo, M. Yoshida, K. Shishido, Synthesis, **2009**, *17*, 2893–2904.

Retrosynthesis Analysis

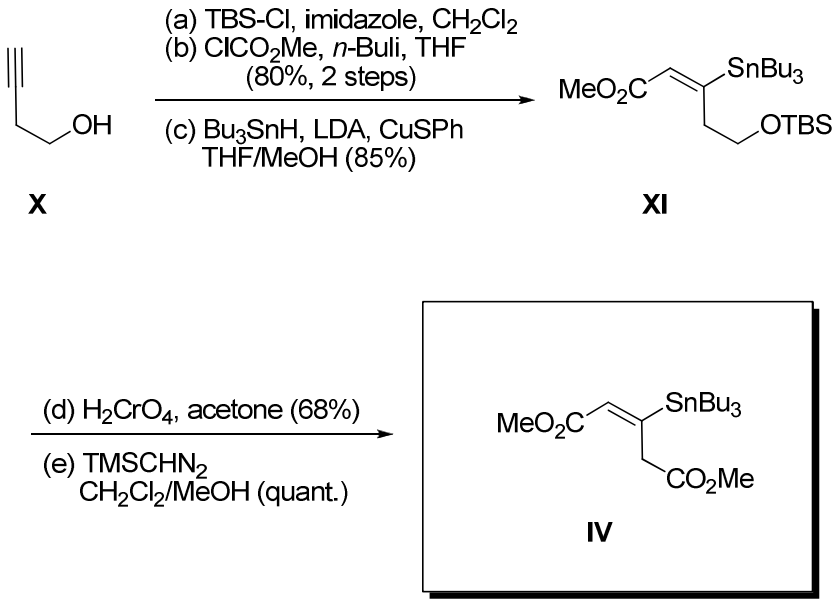
IBA has been primarily targeted as the centre of interest, since no synthesis has been reported, nor is any detailed biological evaluation currently available. Retrosynthetically, it was decided to focus on IBA trimethylester **I** as the main goal, which could be constructed via a Sonogashira coupling between the vinyl iodide **II** and the alkyne **III**. In order to provide access to the western fragment **II**, a sequence of coupling reactions between stannane **IV**, vinyl iodide **V** and novel triiodide **VI** was envisioned. Eastern fragment **III** was expected to arise via a Suzuki reaction between **VIII** and **IX** to form C19-C20 bond**,** and an asymmetric homopropargylation with bromide **VII** to generate C16-C17 bond.



Scheme 2 Retrosynthesis Analysis for Isobongkrekic Acid Trimethylester.

Synthesis of the Western Fragment

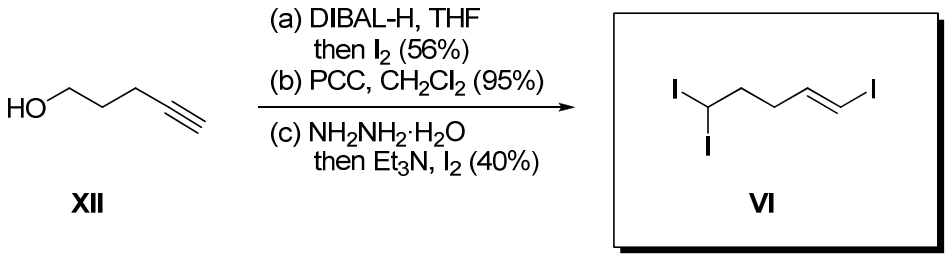
The preparation of stannane **IV** commenced from 3-butyn-1-ol **X** by a known sequence of silylation, homologation with methyl chloroformate, and a stereoselective Piers hydrostannylation reaction[7] to initially provide the stannane **XI** with yields similar to the literature process[8] (Scheme 3). Silyl ether **XI** was then treated with the Jones reagent to simultaneously deprotect and oxidise in situ the intermediate alcohol to the carboxylic acid. Stannane **IV** was finally obtained after a quantitative esterification using trimethylsilyldiazomethane. This approach proved to be reproducible and gave access to multigram quantities of the stannane **IV** ready for the Stille coupling.



Scheme 3 Synthesis of Stannane **IV**.

[7] E. Piers, H. E. Morton, *J. Org. Chem.*, **1980**, *45*, 4263–4264.
[8] (a) R. J. Maguire, S. P. Munt, E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2853–2863. (b) G. Chaume, C. Kuligowski, S. Bezzenine-Laffolée, L. Ricard, A. Pancrazi, J. Ardisson, *Synthesis*, **2004**, *18*, 3029–3036.

The next crucial component of the synthetic plan involved the preparation of the triiodide **VI**. This was designed as a new bidirectional coupling partner that effectively installs the unsymmetrical hexa-1,5-diene fragment (a common unit in a number of natural products)[9] by exploiting its orthogonal reactivity. Accordingly, pentynol **XII** was transformed in its corresponding *E*-vinyl iodide, following a known procedure[10] (Scheme 4). Subsequently, oxidation of the intermediate alcohol with pyridinium chlorochromate (PCC) gave optimal results. Formation of the *gem*-diiodide function was then achieved by employing a protocol developed by Sternhell and co-workers.[11] While this method is often low yielding, in this case we were pleased to obtain this new building block **VI** in an efficient and highly reproducible fashion.



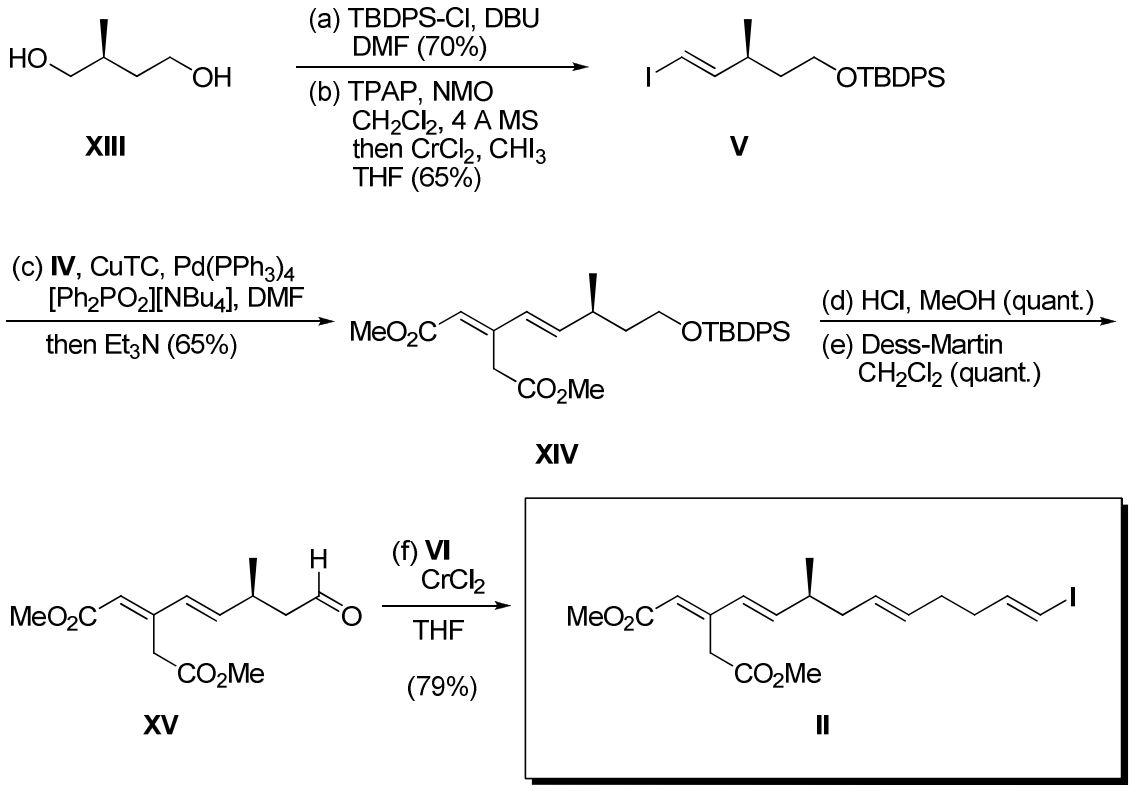
XII **VI**

Scheme 4 Synthesis of *gem*-Diiodide **VI**.

In order to synthesize the western fragment **II**, the commercially available, chiral diol **XIII** was monoprotected at the less hindered hydroxyl group at low temperature (Scheme 5). However, the oxidation of this product to the intermediate aldehyde was problematic owing to its instability. Nevertheless, inspired by the previous observations describing a sequential tetra-*n*-propylammonium perruthenate (TPAP) oxidation/Wittig reaction,[12] the one-pot TPAP oxidation immediately followed by a Takai reaction was investigated. This proceeded in a moderate 65% yield but was reproducible on multigram scale securing large quantities of **V**. Next, the crucial elaboration of the western diene

[9] For example, see the following: (a) Curacin family: W. H. Gerwick, P. J. Proteau, D. G. Nagle, E. Hamel, A. Blokhin, D. L. Slate, *J. Org. Chem.*, **1994**, *59*, 1243–1245. (b) Ajudazols family: R. Jansen, B. Kunze, H. Reichenbach, G. Höfle, *Eur. J. Org. Chem.*, **2002**, *91*, 7–921.
[10] H. J. Reich, E. K. Eisenhart, R. E. Olson, M. J. Kelly, *J. Am.Chem. Soc.*, **1986**, *108*, 7791–7800.
[11] A. Pross, S. Sternhell, *Aust. J. Chem.*, **1970**, *23*, 989–1003.
[12] R. N. MacCoss, E. P. Balskus, S. V. Ley, *Tetrahedron Lett.*, **2003**, *44*, 7779–7781.

geometry to distinguish IBA from BA was studied. The Stille-Migita coupling[13] was used for this process and involved modified conditions,[14] using a phosphonate salt as a tin scavenger and copper(I) thiophene-2-carboxylate (CuTC), as this proved to be the most efficient procedure (60% yield). The deprotection of diene **XIV** with HCl in methanol followed by a Dess-Martin oxidation led to aldehyde **XV**. Noteworthy in this reaction is that the absolute *S* configuration of the intermediate alcohol is not racemised (acidic conjugated γ-proton), and this observation was corroborated by the formation and analysis of the corresponding Mosher ester (er >95:5 in ^{1}H and ^{19}F NMR). Finally, aldehyde **XV** was subjected to a Takai olefination[15] using an excess of the triiodide **VI**. Pleasingly, vinyl iodide **II** was obtained stereoselectively as a single *E*-isomer in good yield (79%).



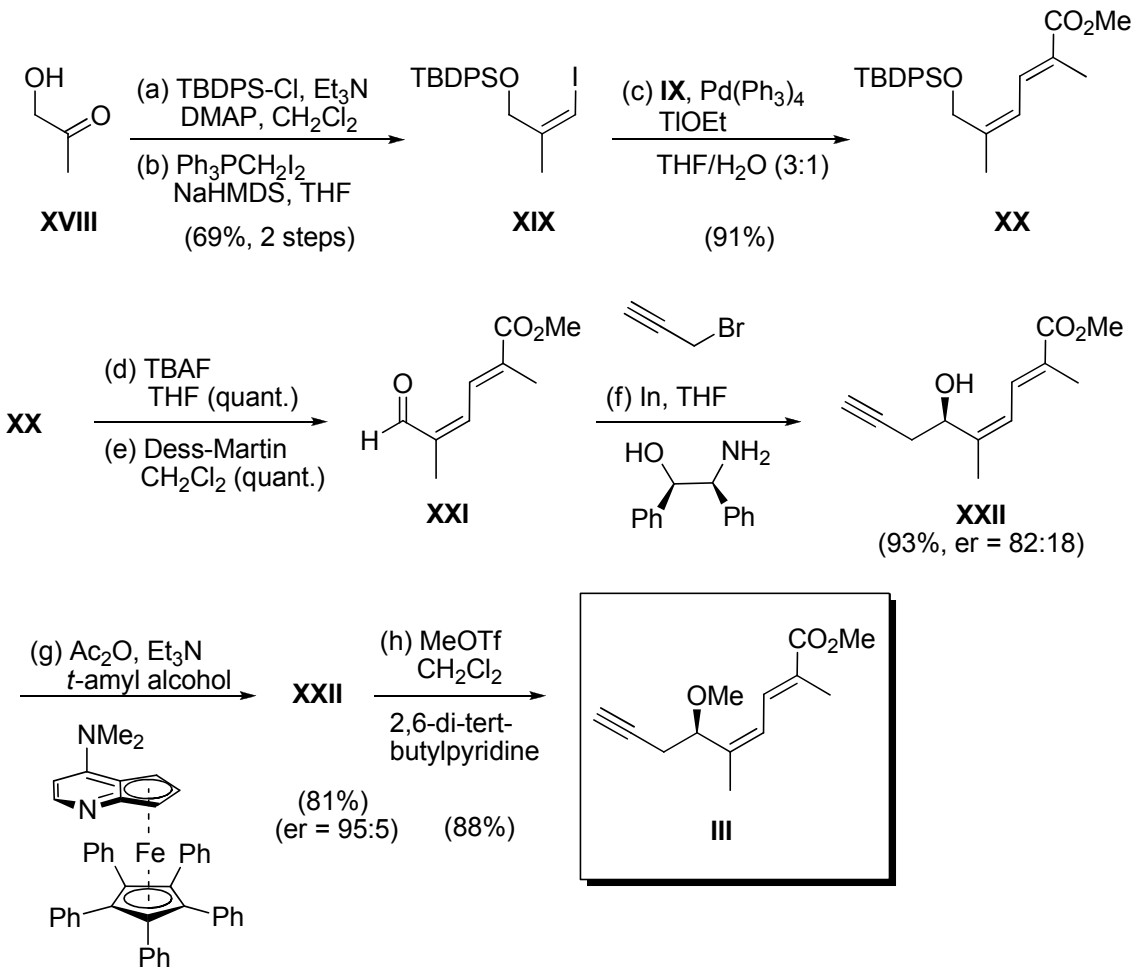
Scheme 5 Synthesis of Western Fragment **II**.

[13] (a) M. Kosugi, Y. Shimizu, T. Migita, *Chem. Lett.*, **1977**, 1423–1424. (b) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.*, **1979**, *101*, 4992–4998.
[14] A. Fürstner, J.-A. Funel, M. Tremblay, L. C. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, *Chem. Commun.*, **2008**, 2873–2875.
[15] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.*, **1986**, *108*, 7408–7410.

Synthesis of the Eastern Fragment

For fragment **IX**, its assembly arose from the initial formation of vinyl iodide **XVII** from diethyl 2-methylmalonate (**XVI**) by a known procedure involving a reaction with iodoform followed by decarboxylation/elimination.[16] Subsequently, vinyl iodide **XVII** was esterified under classical acidic conditions and then cross-coupled with the bis(pinacolato)diboron to give boronic ester **IX** in 84% yield (Scheme 6).[17] Access to multigram quantities of vinyl iodide **XIX** was achieved through a silylation of hydroxyacetone **XVIII** followed by a Wittig-Stork reaction.[18] With significant amounts of fragments **IX** and **XIX** in hand, different conditions for the key Suzuki-Miyaura coupling[19] could then be examined. As expected, the stereospecific formation of the *Z*,*E*-diene was complicated. Only when employing modified Kishi conditions[20] using thallium(I) ethoxide as a base, stereospecific coupling[21] was obtained in high yield (91%) on gram scale. Several alternative using less toxic bases were also investigated without success, accordingly with other syntheses observations.[22] In order to progress in the synthesis, diene **XX** was deprotected with TBAF and the resulting free-alcohol was oxidised to the aldehyde **XXI** using Dess-Martin periodinane. Expecting that the aldehyde would be prone to isomerisation, it was therefore used immediately in homopropargylation studies. The best conditions for this process turned out to be the use of indium as a metal source since this combines mildness and efficiency. When linked to its asymmetric version developed by Singaram,[23] excellent coupling was achieved giving homopropargylic alcohol **XXII** in good yield and acceptable enantiomeric ratio (er = 82:18).

[16] R. Baker, J. L. Castro, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 47–65.
[17] (a) T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508–7510. (b) B. Jin, Q. Liu, G. A. Sulikowski, *Tetrahedron*, **2005**, *61*, 401–408.
[18] G. Stork, K. Zhao, *Tetrahedron Lett.*, **1989**, *30*, 2173–2174.
[19] N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.*, **1985**, *107*, 972–980.
[20] (a) J. Uenishi, J.-M. Beau, R. W. Armstrong, Y. Kishi, *J. Am.Chem. Soc.*, **1987**, *109*, 4756–4758. (b) S. A. Frank, H. Chen, R. K. Kunz, M. J. Schnaderbeck, W. R. Roush, *Org. Lett.*, **2000**, *2*, 2691–2694.
[21] *Z,E*-Geommetry was confirmed by NOE studies.
[22] For example: (a) V. P. Ghidu, J. Wang, B. Wu, Q. Liu, A. Jacobs, L. J. Marnett, G. A. Sulikowski, *J. Org. Chem.*, **2008**, *73*, 4949–4955. (b) K. C. Nicolaou, A. L. Nold, R. R. Milburn, C. S. Schindler, K. P. Cole, J. Yamaguchi, *J. Am. Chem. Soc.*, **2007**, *129*, 1760–1768. (c) T. Shimizu, T. Satoh, K. Murakoshi, M. Sodeoka, *Org. Lett.*, **2005**, *7*, 5573–5576.
[23] L. C. Hirayama, K. K. Dunham, B. Singaram, *Tetrahedron Lett.*, **2006**, *47*, 5173–5176.



Scheme 6 Synthesis of Eastern Fragment.

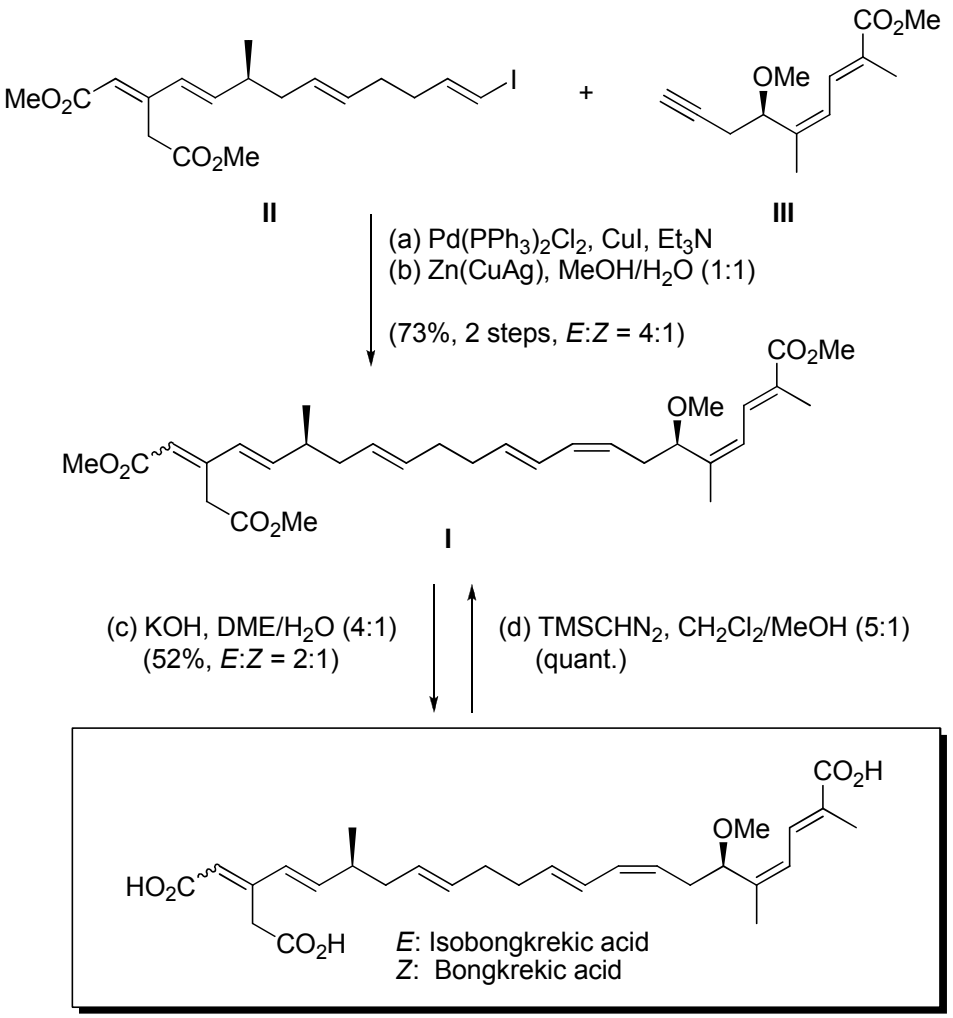
In order to enhance this ratio, enzymatic methods were considered, but all required a further deprotection step. A chemical process was preferred instead, with Fu's method being particularly attractive.[24] The commercial availability of the required iron DMAP catalyst meant that an enantiomeric ratio of 95:5 for the desired enantiomer could be rapidly attained in good yield.[25] This high enantioselectivity was sufficient to continue the synthesis. Finally, after several unsuccessful attempts, the hydroxyl group was methylated with methyl triflate and a hindered base[26] to give the desired eastern fragment **III**.

[24] S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun.*, **2000**, 1009–1010.
[25] The er was determined by ^{1}H and ^{19}F NMR of the corresponding Mosher ester.
[26] (a) J. Arnarp, L. Kenne, B. Lindberg, J. Lönngren, *Carbohydr. Res.*, **1975**, *44*, C5–C7. (b) Chen, S. H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834–5845.

Endgame

With the two hemispheres now available, their union via a Sonogashira coupling[27] was investigated and successfully achieved (Scheme 7). The use of triethylamine as solvent[28] achieved the optimal conversion with the minimum dimerization of **III** resulting from the Glaser coupling.[29] At this stage, a mixture of inseparable isomers and dimers was used directly in the following reduction reaction. Although chemoselective hydrogenation with Lindlar catalyst failed, this difficult regioselective *cis*-reduction of the conjugated alkyne could be achieved using a large excess of copper/silver activated zinc.[30] A separable 4:1 mixture of IBA (*E*) and BA (*Z*) trimethylesters was obtained in a satisfying yield of 73% over two steps. Believing that the final saponification may lead inexorably to further isomerization on the polyene, the two isomers at this stage were purified only for characterization and comparison with reported data. The mixture was then forwarded to the next step. Finally, the final and challenging tris-saponification process was attempted. After several unsuccessful attempts, it was found that by using a large excess of potassium hydroxide the two readily separable natural products IBA and BA (ratio 2:1) could be obtained. In order to prove that no racemisation occurred during this final step, IBA and BA were individually re-esterified to their corresponding trimethylesters and both afforded identical analytical data as the original substrates prior to their saponification.

[27] (a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.*, **1975**, *50*, 4467–4470. (b) H. A. Dieck, F. R. Heck, *J. Organomet. Chem.*, **1975**, *93*, 259–263.
[28] (a) J. A. Marshall, A. Piettre, M. A. Paige, F. Valeriote, *J. Org. Chem.* **2003**, *68*, 1771–1779. (b) D. Strand, T. Rein, *Org. Lett.*, **2005**, *7*, 199–202.
[29] C. Glaser, *Ber.*, **1869**, *2*, 422–424.
[30] (a) W. Bolland, N. Schroer, C. Sieler, M. Feigel, *Hel*V. *Chim. Acta*, **1987**, *70*, 1025–1040. (b) M. Avignon-Tropis, J. R. Pougny, *Tetrahedron*, **1989**, *30*, 4951–4952.



Scheme 7 Completion of the Synthesis.

In summary, the total synthesis of IBA and a new route to BA have been completed. The highly convergent route proved to be especially effective using only 13 steps as the longest linear path from commercially available material in a yield of 7.0% and 29 steps overall. This route therefore compares very favourable to all previous synthesis work in the area and also constitutes the shortest route so far to BA.[31] Highlights of this work include the formation of the three diene units by three different palladium cross couplings, the formation of the ether containing stereogenic center by an asymmetric homopropargylation followed by a chemical kinetic resolution, and finally, access to the new building blocks **IV**, **V**, **VI** and **IX**.

[31] Total synthesis in ref 6a: 19 steps as longest linear path from commercially available material and 41 steps overall. Total synthesis in ref 6b: 21 steps as longest linear path from commercially available material and 40 steps overall.

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Total Synthesis of the Anti-Apoptotic Agents Iso- and Bongkrekic Acids

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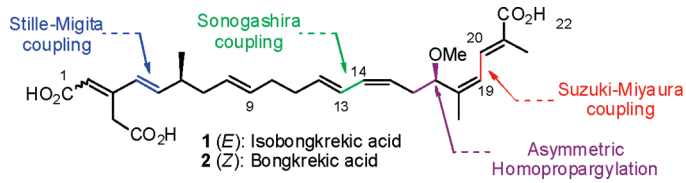
Received November 20, 2009

ABSTRACT



The first convergent total synthesis of isobongkrekic acid is reported involving three different stereospecific palladium cross-couplings for the formation of the diene units. Access to bongkrekic acid by this route is also demonstrated. These syntheses involve the formation of several potentially general building blocks.

Isobongkrekic acid (IBA, **1**) is a complex fatty triacid which was isolated from the fermentation of *Pseudomonas cocovenenants* in 1976.[1] Closely connected to its better known isomer bongkrekic acid (BA, **2**),[2] they form a small family of toxic antibiotics with potent antiapoptotic activity. These compounds act as inhibitors of adenine nucleotide translocase (ANT), which mediates the ADP/ATP exchange in mitochondria.[3] Mentioned in more than 700 publications, they are most commonly used to probe apoptosis mechanisms and to elucidate their link with mitochondrial function.[4] As a consequence, these substances attracted the interest of chemists. In particular, Corey and Tramontano devised a first very effective synthesis of BA in 1984,[5] while a second and longer total synthesis appeared some 20 years later.[6] Dissatisfied by this last approach, Shindo and Shishido continued to work in the area which culminated recently in two greatly improved second generation syntheses.[7] We too became interested in these molecules owing to the development of methods in our laboratory, which we deemed to be suitable to afford certain structural elements within these natural products.[8] In practice, however, while the methods proved to be unsatisfactory for either IBA and BA syntheses, a new highly efficient route has emerged leading to IBA (and BA), which we describe here. We have primarily targeted IBA as the center of our interest, since no synthesis has been reported, nor is any detailed biological evaluation currently available.

(1) (a) Lauquin, G. J. M.; Duplaa, A.-M.; Klein, G.; Rousseau, A.; Vignais, P. V. *Biochemistry* **1976**, *15*, 2323–2327. (b) Chatterjee, S.; Vijayakumar, E. K. S.; Roy, K.; Rupp, R. H.; Ganguli, B. N. *J. Org. Chem.* **1988**, *53*, 4883–4886.

(2) For isolation, see: (a) van Veen, A. G.; Mertens, W. K. *Rec. trav. Chim. Pays-Bas* **1934**, *53*, 257–266. (b) For structure determination, see: de Bruin, J.; Frost, D. J.; Nugteren, D. H.; Gaudemer, A. *Tetrahedron* **1973**, *29*, 1541–1547.

(3) (a) Henderson, P. J. F.; Lardy, H. A. *J. Biol. Chem.* **1970**, *245*, 1319–1326. (b) Klingenberg, M.; Grebe, K.; Heldt, H. W. *Biochem. Biophys. Res. Commun.* **1970**, *39*, 344–351. (c) Klingenberg, M.; Appel, M.; Babel, W.; Aquila, H. *Eur. J. Biochem.* **1983**, *131*, 647–654.

(4) For example, see: (a) Zamzami, N.; Susin, S. A.; Marchetti, P.; Hirsch, T.; Gomez-Monterrey, I.; Castedo, M.; Kroemer, G. *J. Exp. Med.* **1996**, *183*, 1533–1544. (b) de Graaf, A. O.; Meijerink, J. P. P.; van den Heuvel, L. P.; DeAbreu, R. A.; de Witte, T.; Jansen, J. H.; Smeitink, J. A. M. *Biochim. Biophys. Acta* **2002**, *1554*, 57–65. (c) Schubert, A.; Grimm, S. *Cancer Res.* **2004**, *64*, 85–93. (d) Liu, J.; St. Clair, D. K.; Gu, X.; Zhao, Y. *FEBS Lett.* **2008**, *582*, 1319–1324.

(5) Corey, E. J.; Tramontano, A. *J. Am. Chem. Soc.* **1984**, *106*, 462–463.

(6) Shindo, M.; Sugioka, T.; Umaba, Y.; Shishido, K. *Tetrahedron Lett.* **2004**, *45*, 8863–8866.

(7) (a) Sato, Y.; Aso, Y.; Shindo, M. *Tetrahedron Lett.* **2009**, *50*, 4164–4166. (b) Kanematsu, M.; Shindo, M.; Yoshida, M.; Shishido, K. *Synthesis* **2009**, *17*, 2893–2904.

(8) (a) Leyva, A.; Blum, F. E.; Hewitt, P. R.; Ley, S. V. *Tetrahedron* **2008**, *64*, 2348–2358. (b) Leyva, A.; Blum, F. E.; Ley, S. V. *Tetrahedron* **2008**, *64*, 4711–4717.

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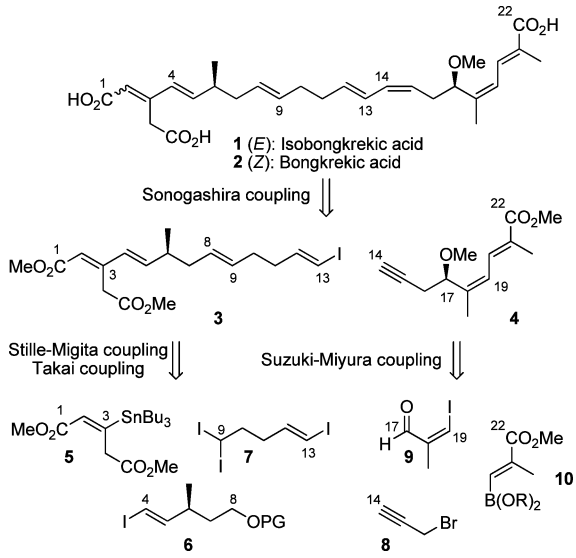
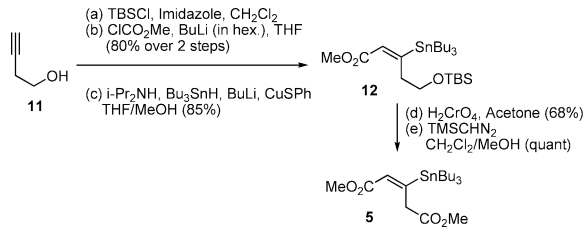
Retrosynthetically, we opted for the trimethylester of IBA ($IBAMe_3$) as our main target which could be constructed via a Sonogashira coupling between the vinyl iodide **3** and the alkyne **4**. In order to provide access to the vinyl iodide **3**, we envisioned the sequence of coupling reactions between stannane **5**, vinyl iodide **6**, and eventually novel triiodide **7**. Alkyne **4** was expected to arise via a Suzuki reaction and an asymmetric homopropargylation following anion generation from propargyl bromide **8** coupling with fragments **9** and **10** (Scheme 1).

Scheme 1. Retrosynthetic Analysis



The preparation of stannane **5** commenced from 3-butyn-1-ol (**11**) by a known sequence of silylation, homologation with methyl chloroformate, and a stereoselective Piers hydrostannylation reaction[9] to initially provide the stannane **12** with yields similar to the literature process (Scheme 2).[10]

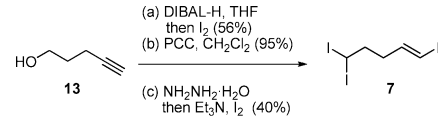
Scheme 2. Synthesis of Stannane **5**



Silyl ether **12** was then treated with the Jones reagent to simultaneously deprotect and oxidize in situ the intermediate alcohol to the carboxylic acid. Stannane **5** was finally obtained after a quantitative esterification using trimethylsilyldiazomethane. This approach proved to be reproducible and gave access to multigram quantities of the stannane **5** ready for the Stille coupling (Scheme 2).

The next crucial component of our synthesis plan involved the preparation of the triiodide **7**. This was designed as a new bidirectional coupling partner that effectively installs the unsymmetrical hexa-1,5-diene fragment (a common unit in a number of natural products)[11] by exploiting its orthogonal reactivity. Accordingly, pentynol (**13**) was transformed in its corresponding *E*-vinyl iodide, following a literature procedure (Scheme 3).[12] Subsequently, oxidation of the

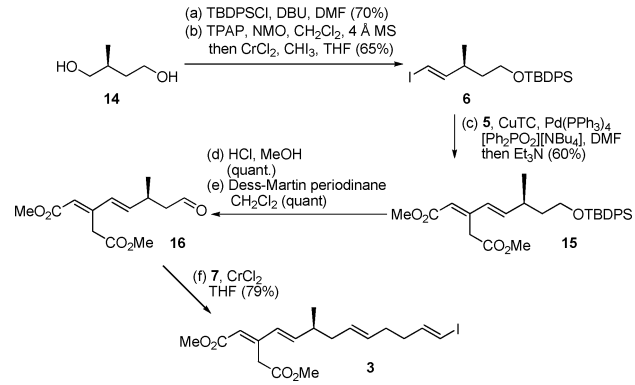
Scheme 3. Synthesis of *gem*-Diiodide **7**



intermediate alcohol with pyridinium chlorochromate gave optimal results. Formation of the *gem*-diiodide function was then achieved by employing a protocol developed by Sternhell et al.[13] While this method is often low yielding, in this case we were pleased to obtain this new building block **7** in an efficient and highly reproducible fashion.

In order to synthesize the homologated vinyl iodide **3**, the commercially available, chiral diol **14** was monoprotected at the less hindered hydroxyl group at low temperature (Scheme 4). However, the oxidation of this product to the

Scheme 4. Synthesis of Vinyl Iodide **3**



intermediate aldehyde was problematic owing to its instability. Nevertheless, inspired by our previous observations describing a sequential tetra-*n*-propylammonium perruthenate

(9) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263–4264.

(10) (a) Maguire, R. J.; Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853–2863. (b) Chaume, G.; Kuligowski, C.; Bezzenine-Laffolée, S.; Ricard, L.; Pancrazi, A.; Ardisson, J. *Synthesis* **2004**, *18*, 3029–3036.

(11) For example, see the following: (a) Curacin family: Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243–1245. (b) Ajudazols family: Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2002**, *91*, 7–921.

(12) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791–7800.

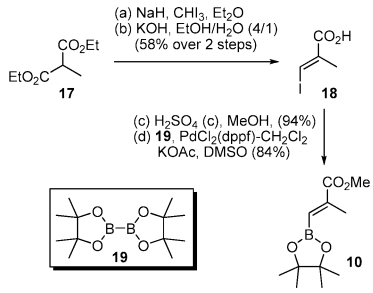
(13) Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989–1003.

(TPAP) oxidation/Wittig reaction,[14] we investigated use the TPAP oxidation immediately followed by a Takai reaction, in one-pot, to give vinyl iodide **6**. This proceeded in a moderate 65% yield but was reproducible on multigram scale.

Next, the crucial elaboration of the left-hand diene geometry to distinguish IBA from BA was studied. The Stille−Migita coupling[15] was used for this process and involved modified conditions[16] using a phosphonate salt as a tin scavenger as this proved to be the most efficient procedure (60% yield). The deprotection of diene **15** with HCl in methanol followed by a Dess−Martin oxidation led to aldehyde **16**. Noteworthy in this reaction is that the absolute *S* configuration of the intermediate alcohol is not racemized, and this observation was corroborated by the formation and analysis of the corresponding Mosher ester (er >95:5 in ^{1}H and ^{19}F NMR). Finally, aldehyde **16** was subjected to a Takai olefination[17] using an excess of the triiodide **7**. Pleasingly, vinyl iodide **3** was obtained stereoselectively as a single *E*-isomer in good yield (79%).

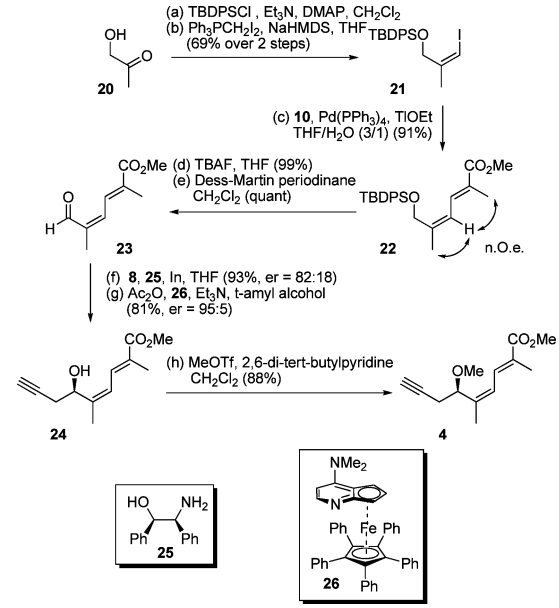
For fragment **10**, its assembly arose from the initial formation of vinyl iodide **18** from diethyl 2-methylmalonate (**17**) by a known procedure involving a reaction with iodoform followed by decarboxylation/elimination.[18] Subsequently, vinyl iodide **18** was esterified under acidic conditions and then cross-coupled with the bis(pinacolato)-diboron **19** to give boronic ester **10** in 84% yield (Scheme 5).[19]

Scheme 5. Synthesis of Boronic Ester **10**



Access to multigram quantities of vinyl iodide **21** was achieved through a silylation of hydroxyacetone **20** followed by a Wittig−Stork reaction (Scheme 6).[20] With significant amounts of fragments **21** and **10** in hand, different conditions for the key Suzuki−Miyaura coupling[21] could then be examined. As expected, the stereospecific formation of the *Z*,*E*-diene was complicated. Only when modified Kishi conditions,[22] using thallium ethoxide as a base, were employed did we obtain completely stereospecific coupling, confirmed by NOE studies, in high yield (91%) on gram scale. Several alternative less toxic bases were also investigated without success. These observations are in accord with other syntheses.[23]

Scheme 6. Synthesis of Alkyne **4**



In order to progress the synthesis, diene **22** was deprotected with TBAF and the resulting free-alcohol oxidized to the aldehyde **23** using Dess−Martin periodinane. We recognized that this aldehyde **23** would be prone to isomerization, and it was therefore used immediately in homopropargylation studies. The best conditions for this process turned out to be the use of indium as a metal source since this combines mildness and efficiency. When linked to its asymmetric version developed by Singaram,[24] excellent coupling was achieved giving homopropargylic alcohol **24** in good yield and acceptable enantiomeric ratio (er 82:18). In order to enhance this er, enzymatic methods were considered, but all required a further deprotection step. We therefore preferred a chemical process, with the method of Fu being particularly attractive.[25] The commercial availability of the required iron

(14) MacCoss, R. N.; Balskus, E. P.; Ley, S. V. *Tetrahedron Lett.* **2003**, *44*, 7779–7781.
(15) (a) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423–1424. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.
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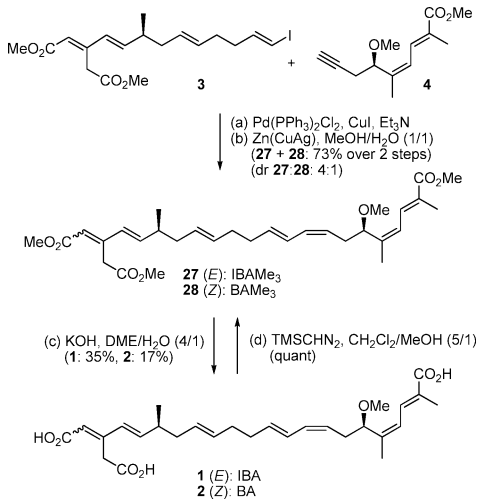
(18) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47–65.
(19) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510. (b) Jin, B.; Liu, Q.; Sulikowski, G. A. *Tetrahedron* **2005**, *61*, 401–408.
(20) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174.
(21) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980.
(22) (a) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758. (b) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691–2694.
(23) For example: (a) Ghidu, V. P.; Wang, J.; Wu, B.; Liu, Q.; Jacobs, A.; Marnett, L. J.; Sulikowski, G. A. *J. Org. Chem.* **2008**, *73*, 4949–4955. (b) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760–1768. (c) Shimizu, T.; Satoh, T.; Murakoshi, K.; Sodeoka, M. *Org. Lett.* **2005**, *7*, 5573–5576.
(24) Hirayama, L. C.; Dunham, K. K.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 5173–5176.

DMAP catalyst meant that we could rapidly attain an er of 95:5 for the desired enantiomer in a good yield.[26] This high enantioselectivity was sufficient to progress the synthesis. Finally, after several unsuccessful attempts, the hydroxyl group was methylated with methyl triflate and a hindered base to give the desired alkyne **4** (Scheme 6).[27]

With the two fragments **3** and **4** now available, their union via a Sonogashira coupling was investigated and successfully achieved (Scheme 7).[28] The use of triethylamine as solvent[29]

Scheme 7. Final Steps



realized the optimal conversion with the minimum dimerization of **4** resulting from the Glaser coupling.[30] At this stage, we advanced a mixture of inseparable isomers and dimers directly in the following reduction reaction. Although chemoselective hydrogenation with Lindlar catalyst failed, this regioselective *cis*-reduction of the alkyne, conjugated with an olefin, could be achieved using a large excess of copper/silver activated zinc.[31] A separable 4:1 mixture of $IBAMe_3$ (**27**) and $BAMe_3$ (**28**) was obtained in a satisfying yield of 73% over two steps. Believing that the final saponification may led inexorably to further isomerization on the polyene, the two isomers at this stage were purified only for characterization and comparison with reported data. The mixture was then forwarded to the next step. Finally, we dealt with the final and challenging tris-saponification process. After several unsuccessful attempts, we found that by using a large excess of potassium hydroxide we could obtain the two readily separable natural products IBA (**1**) and BA (**2**) (ratio 2:1). In order to prove that no racemisation occurred during this final step, IBA and BA were individually re-esterified to their corresponding $IBAMe_3$ and $BAMe_3$ and both afforded identical analytical data as the original substrates prior to their saponification.

In summary, the total synthesis of IBA and a new route to BA have been completed. The highly convergent route proved to be especially effective using only 13 steps as the longest linear path from commercially available material in a yield of 7.0% and 29 steps overall. This route therefore compares very favorably to all previous synthesis work in the area and also constitutes the shortest route so far to BA.[32] Highlights of this work include the formation of the three diene units by three different palladium cross couplings, the formation of the ether containing stereogenic center by an asymmetric homopropargylation followed by a chemical kinetic resolution, and finally access to the new building blocks **5**, **6**, and **10** and the new triiodide **7**.

Acknowledgment. We are grateful to EPSRC (to S.V.L., A.F., and A.L.), to le ministère français des affaires étrangères (to A.F.), and to el Ministerio de Ciencia e Innovacion de España (to G.E.-J.).

Supporting Information Available: Experimental data and characterization for all compounds provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902676T

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(28) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467–4470. (b) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259–263.

(29) (a) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771–1779. (b) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 199–202.

(30) Glaser, C. *Ber.* **1869**, *2*, 422–424.

(31) (a) Bolland, W.; Schroer, N.; Sieler, C.; Feigel, M. *Helv. Chim. Acta* **1987**, *70*, 1025–1040. (b) Avignon-Tropis, M.; Pougny, J. R. *Tetrahedron* **1989**, *30*, 4951–4952.

(32) Total synthesis in ref 7a: 19 steps as longest linear path from commercially available material and 41 steps overall. Total synthesis in ref 7b: 21 steps as longest linear path from commercially available material and 40 steps overall.

RESUM EN CATALÀ

Capítol 1. Introducció i Objectius

L'escleroci de fongs del gènere *Aspergillus* i *Claviceps* ha estat tradicionalment una font molt important en quant a aïllament i caracterització de nous compostos amb potencial farmacològic. La gran diversitat i ubiqüitat dels fongs fa que se n'obtinguin productes d'estructura i propietats biològiques molt diverses, un exemple dels quals es troba representat en la Figura 1.

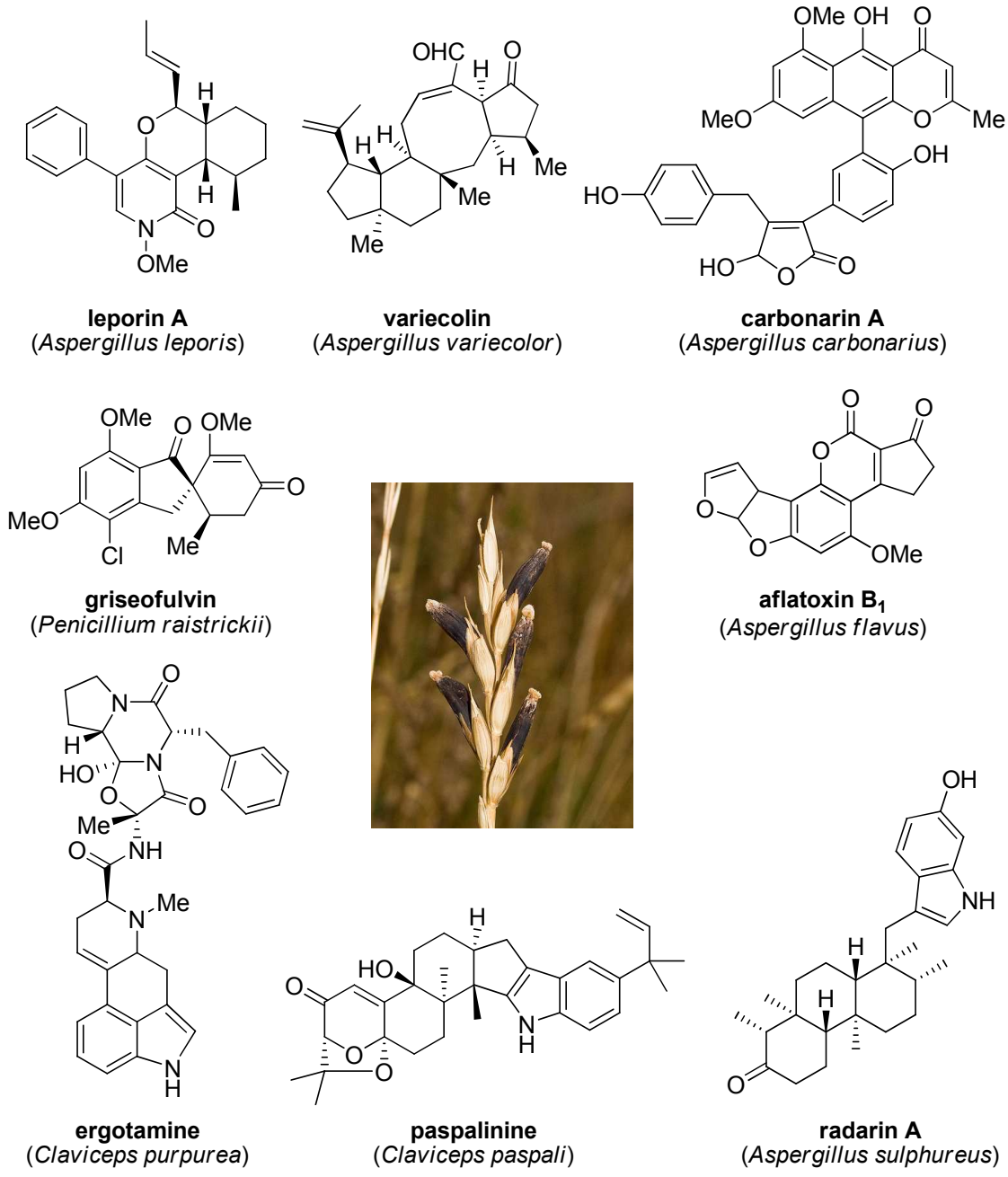


Figura 1. Productes naturals aïllats de fongs.

El grup del Prof. J. B. Gloer va fer un estudi profund de l'escleroci de fongs del gènere *Aspergillus* i hi trobà una família de nous compostos amb activitat insecticida que només diferien en el seu estat d'oxidació (Figura 2). Això els féu pensar que tots els compostos podien provenir del mateix precursor a través de la mateixa ruta biosintètica.

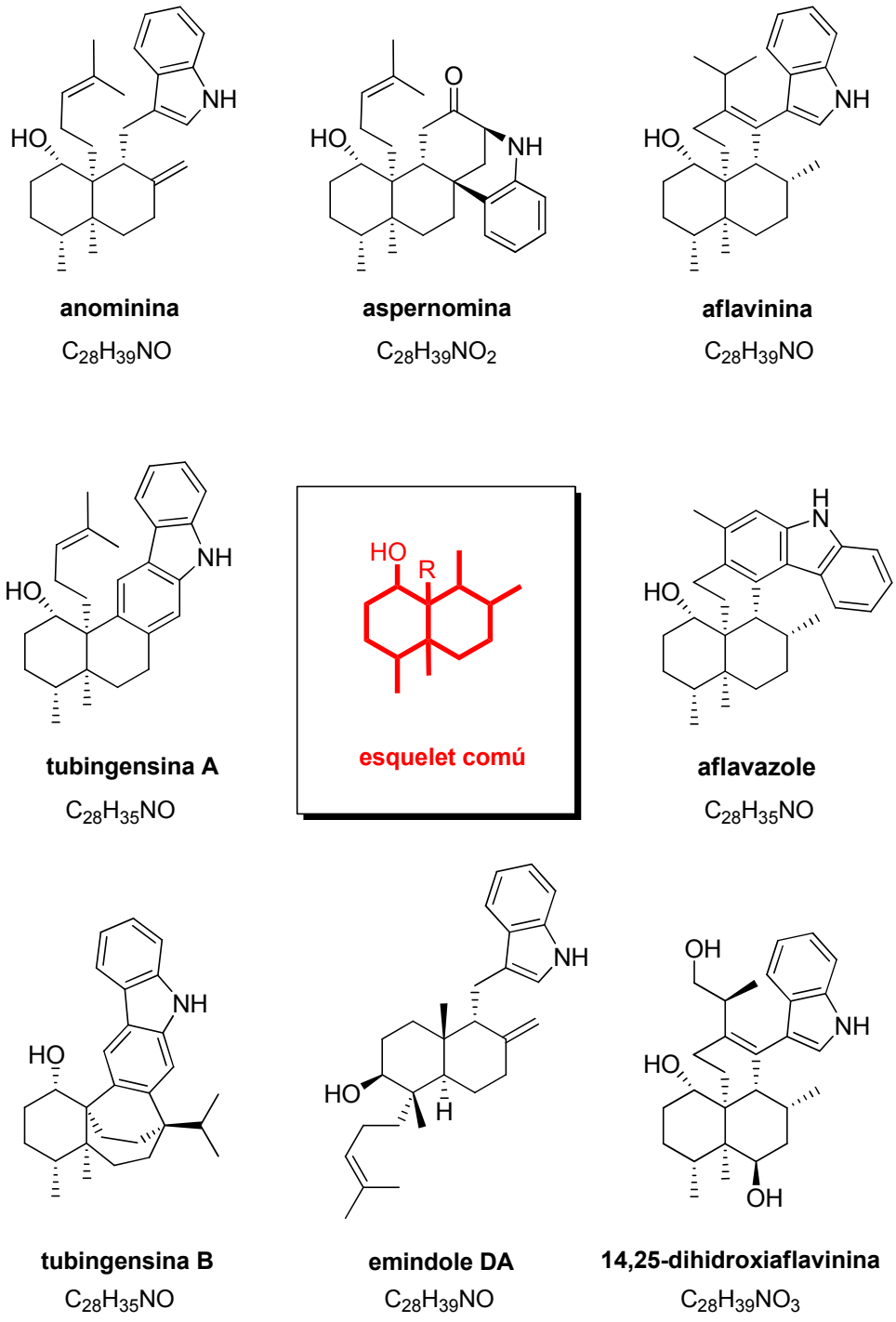
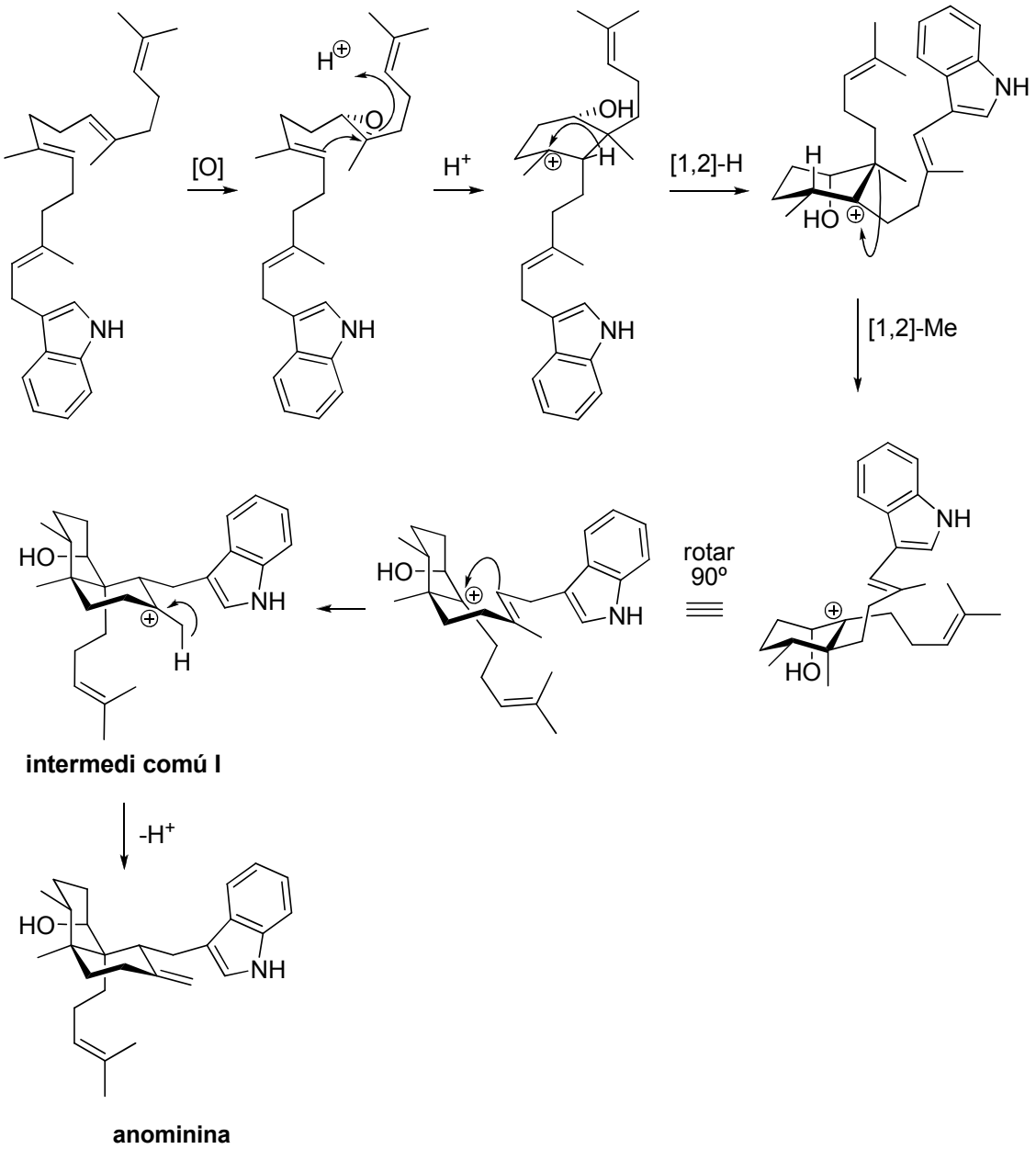


Figura 2. Exemple dels diterpenoids aïllats de fongs del gènere *Aspergillus.*

Biosíntesi

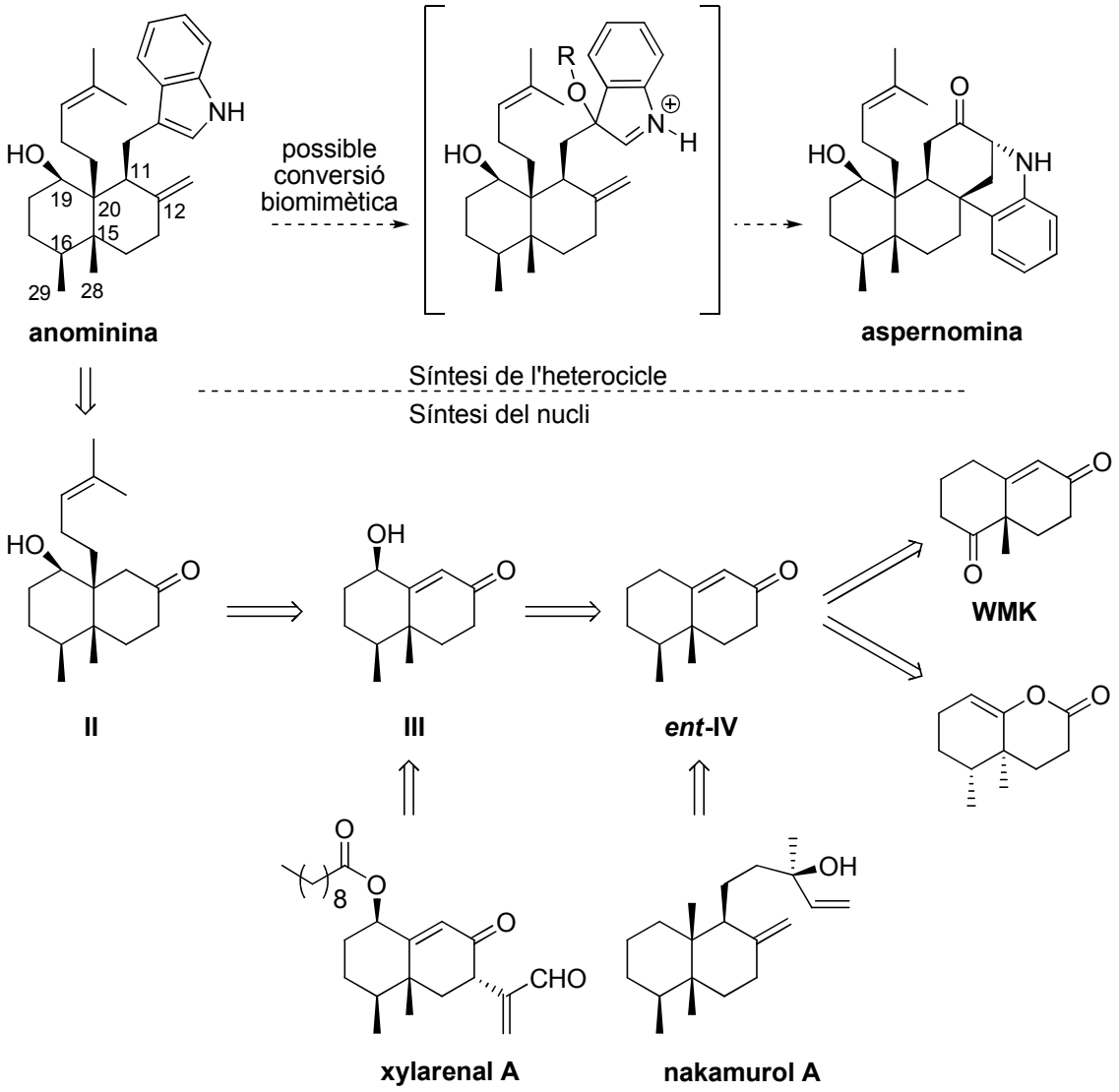
El compost que donaria lloc a tota la família de compostos és el geranilgeranil indole, que seria epoxidat per iniciar una seqüència de ciclacions i transposicions que portarien a l'anominina, i aquesta donaria lloc a tots els altres congèneres.



Esquema 1. Proposta de l'autor per a la ruta biosintètica que donaria lloc a l'anominina.

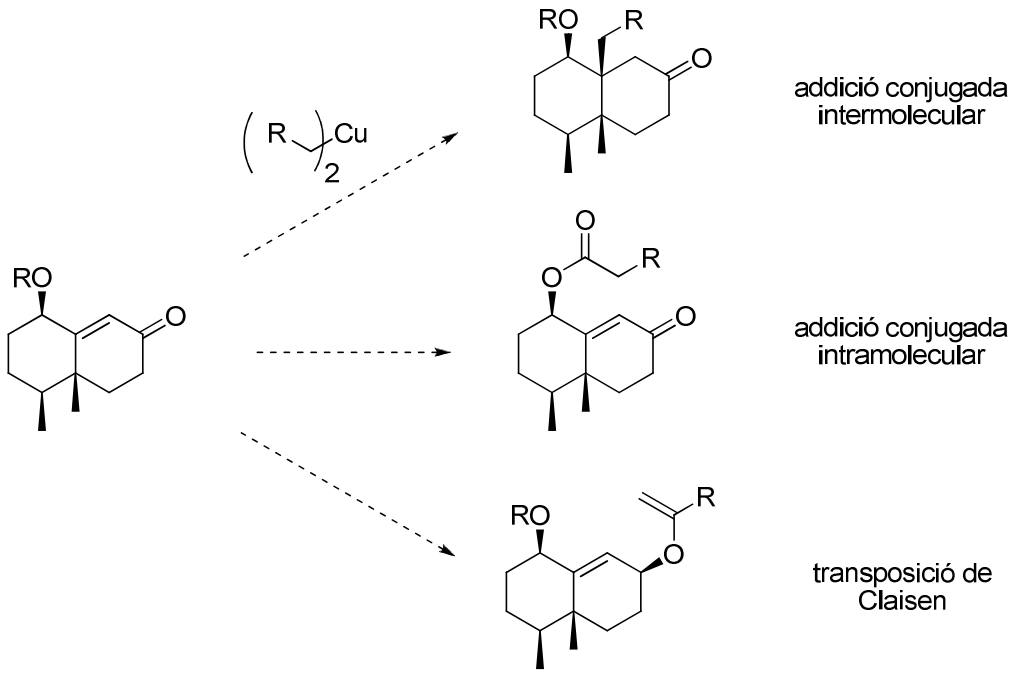
Síntesi de l'anominina. Estratègia inicial

Poc temps després de l'aïllament i elucidació estructural de l'anominina, el nostre grup d'investigació inicià un projecte de síntesi d'aquest producte natural. L'estratègia retrosintètica, representada en l'Esquema 2 , es dissenyà per tal de poder arribar al màxim nombre de productes naturals que fos possible. Així, els intermedis **III** i ***ent*-IV** també podien donar a lloc als productes d'origen marí xylarenal A i nakamurol A. D'aquesta manera, durant l'estudi sintètic envers l'anominina es prepararen i determinaren les estereoquímiques absolutes del xylarenal A i nakamurol A.



Esquema 2. Anàlisi retrosintètica inicial de l'anomininina i l'aspernomina.

Quan s'estudià la introducció de la cadena lateral per generar el carboni quaternari es plantejaren tres aproximacions: l'addició conjugada intermolecular d'un organometàl·lic; l'addició conjugada intramolecular mitjançant la funcionalització de l'alcohol al·lílic; i per transposició de Claisen d'un èter d'enol (Esquema 3). Malauradament, no es pogué introduir la cadena lateral que donaria lloc a l'anominina, tot i que sí que es prepararen els terpenoids xylarenal A i *ent*-nakamurol A. Per tant doncs, es desestimaren les tres aproximacions i s'abandonà aquesta estratègia retrosintètica.



Esquema 3. Aproximacions inicials per la introducció de la cadena lateral.

Objectius

-Desenvolupar una metodologia general que permeti la síntesi de 1,4a,5,8a-tetraalquildecahidronaftalens (*cis*-decalines polisubstituïdes) de forma enantiopura. Aplicació a la síntesi de diterpenoids d'origen marí aïllats de l'esponja *Agelas nakamurai*.

-Mitjançant l'experiència guanyada en la preparació de *cis*-decalines polisubstituïdes, afrontar la síntesi total del diterpenoid anominina.

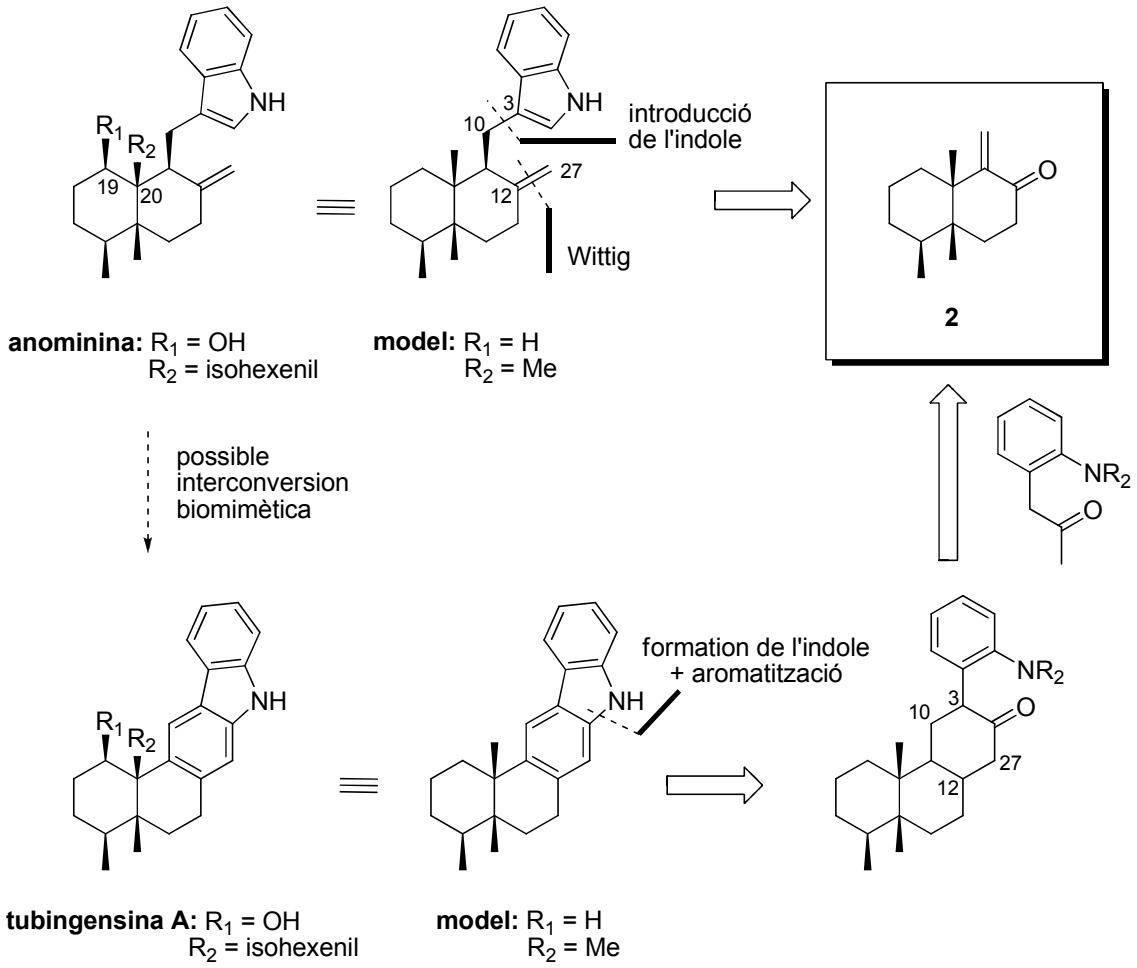
-Donat que el diterpenoid anominina sembla ser el precursor biogenètic de tota la família de compostos, intentar sintetitzar-los de forma biomimètica. En cas contrari, es prepararien intermedis sintètics que permetessin l'obtenció de tota la família per mètodes sintètics.

-Durant el transcurs de la tesi es varen ampliar els objectius ja que es necessitava una metodologia general que permetés preparar enantioselectivament derivats de la cetona de Wieland-Miescher, que serien usats com a precursors quirals per la síntesi del diterpenoid anominina.

Resultats

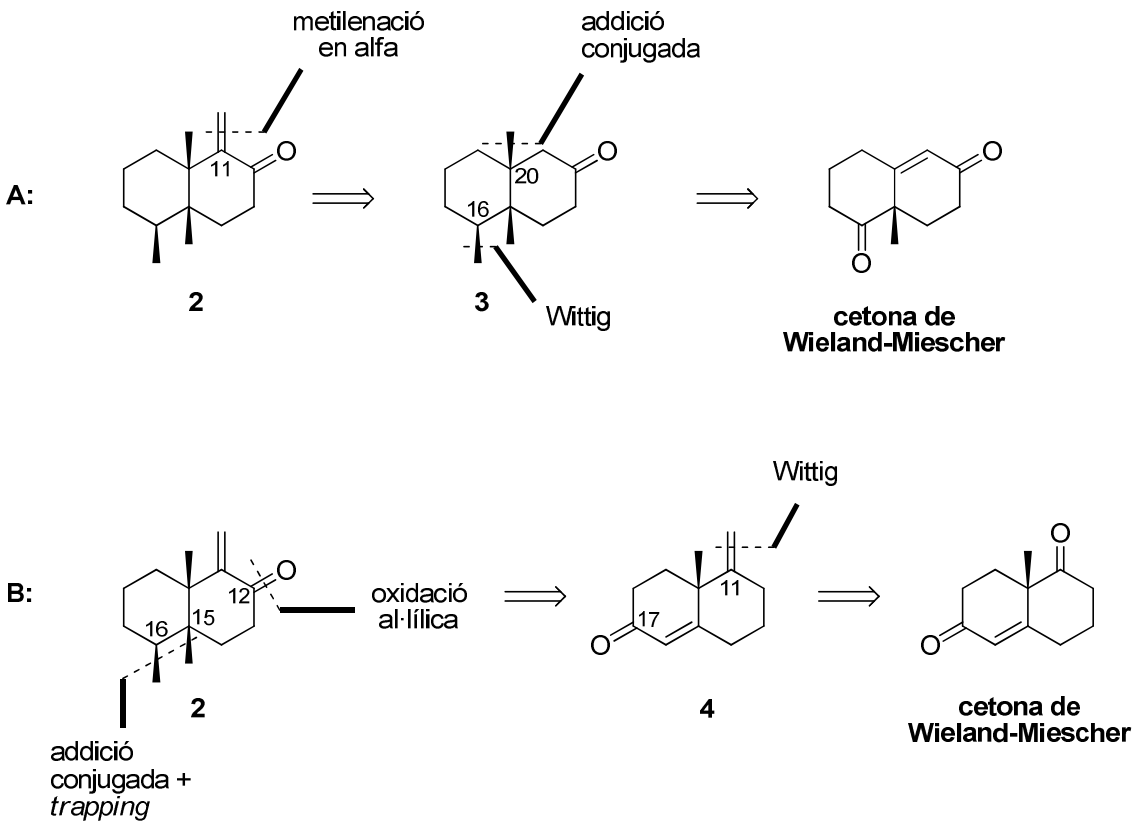
Capítol 2 . Estudis Model

Abans d'afrontar la síntesi del diterpenoid anominina es decidí fer un estudi model en que s'assajaria la introducció del fragment heterocíclic. El model escollit per l'estudi es troba representat en l'Esquema 4 i no comptava amb la funció oxigenada (R_1=H) i tenia un metil a C20 (R_2=Me). L'intermedi clau per a aquest estudi model era **2**, ja que permetia a la vegada, l'obtenció de l'estructura policíclica dels diterpenoids anominina i tubingensina A.



Esquema 4. Ruta sintètica per als estudis model.

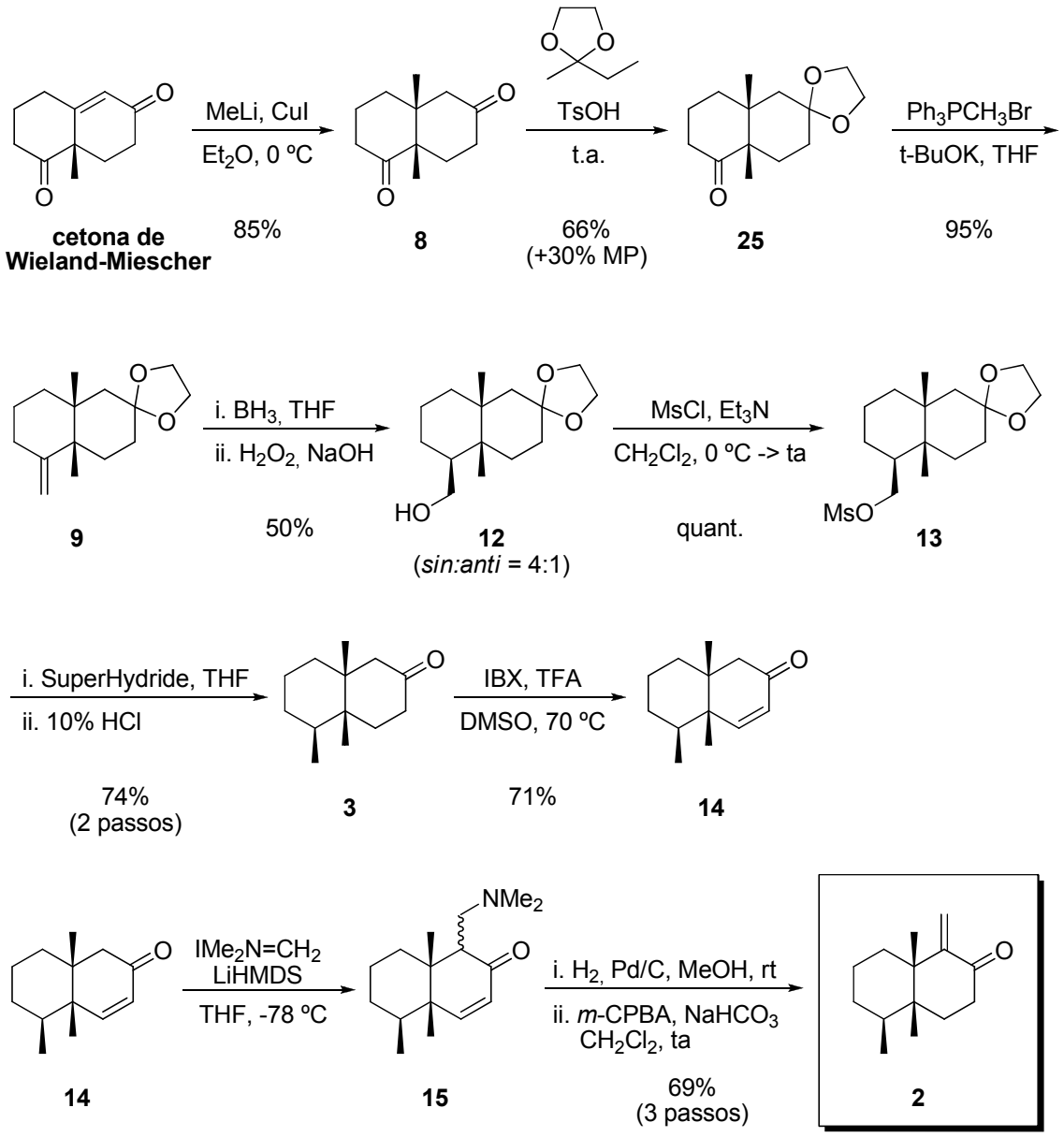
L'intermedi **2** al seu temps, pot provenir de la cetona de Wieland-Miescher en dues orientacions diferents (Esquema 5), i per tant, aquest estudi model va servir també per determinar quina seria l'orientació òptima de la cetona de Wieland-Miescher.



Esquema 5. Orientacions de la cetona de Wieland-Miescher que poden donar a lloc a **2**.

En l'orientació A els carbonils de la cetona de Wieland-Miescher corresponen a les posicions C12 i C16 (numeració biogenètica) de l'anominina. Així, s'introduí el metil angular mitjançant una reacció d'addició conjugada amb dimetilcuprat de liti (Esquema 6). Una seqüència de protecció quimioselectiva i reacció de Wittig proporcionà l'intermedi **9**. Aquest fou hidroborat en condicions oxidants per obtenir l'alcohol **12**, que posteriorment fou desfuncionalitzat mitjançant una seqüència de mesilació i desplaçament amb hidrur. Posteriorment,

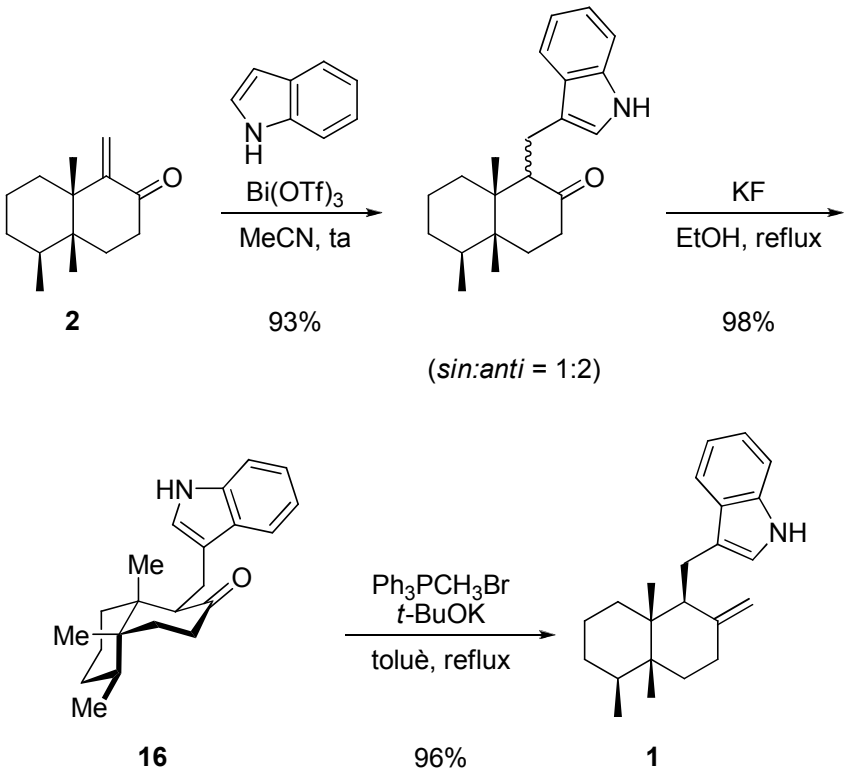
es desemmascarà el carbonil, es prepararà l'enona **14** per tal d'assegurar la regioquímica de l'alquilació d'Eschenmoser. Seguidament, s'hidrogenà per eliminar el doble enllaç endocíclic i finalment s'eliminà el grup dimetilamino per obtenir l'intermedi **2**.



Esquema 6. Obtenció de **2** mitjançant l'orientació A.

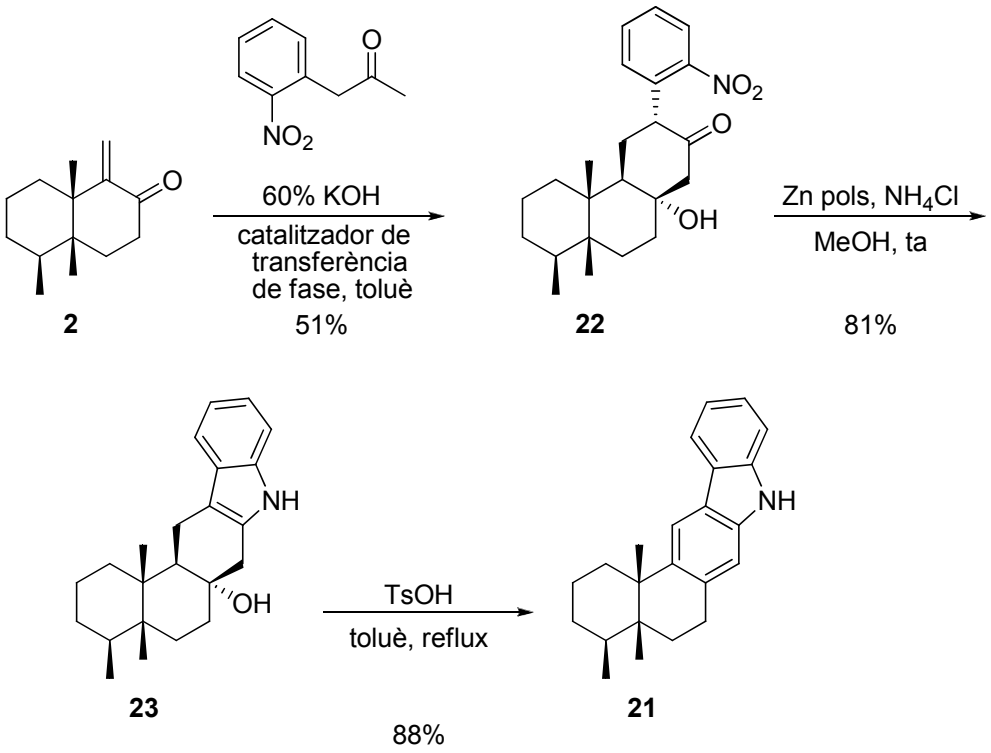
Síntesi de les estructures policícliques de l'anominina i la tubingensina A

Per completar la síntesi model de l'anominina només restava introduir el fragment heterocíclic. Això s'aconseguí mitjançant l'addició d'un l'àcid de Lewis com el triflat de bismut (III). La mescla diastereomèrica s'epimeritzà emprant una base suau com el fluorur potàssic. Finalment, s'introduí el metilè exocíclic i s'obtingué l'estructura policíclica de l'anominina.



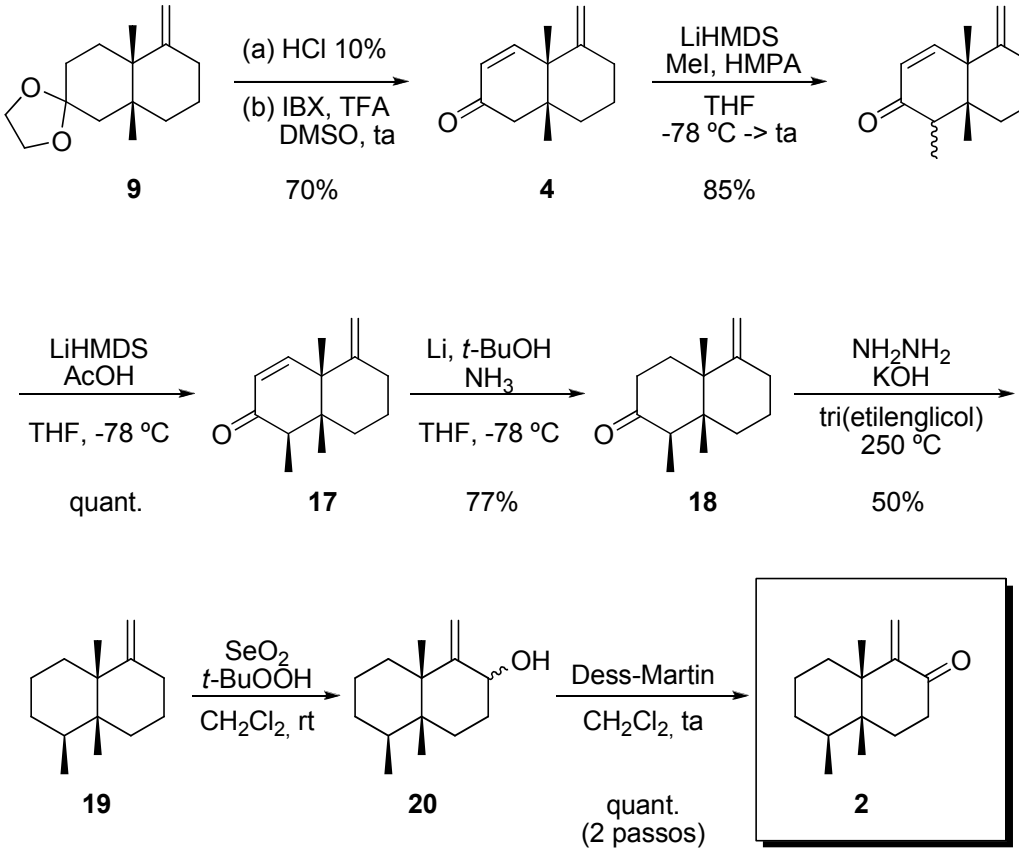
Esquema 7. Obtenció de l'estructura policíclica de l'anominina.

Per a la preparació de l'estructura policíclica de la tubingensina A es va partir del mateix intermedi **2**, i mitjançant una reacció aldòlica s'obtingué **22**. La reducció del grup nitro a amina generà *in situ* el derivat indòlic **23**, que posteriorment fou oxidat al carbazole **21** obtenint així l'estructura de tubingensina A.



Esquema 8. Obtenció de l'estructura policíclica de la tubingensina A.

Per comprovar quina orientació era més favorable es va partir del compost **9**, el qual fou desprotegit i oxidat per obtenir **4**. Per instal·lar el tercer metil de forma diastereoselectiva es va necessitar una etapa d'epimerització addicional ja que en l'alquilació s'obtenia una mescla de diastereòmers. Posteriorment, s'eliminà la funció enona mitjançant una reducció tipus Birch seguida d'una reducció de Wolff-Kishner. Finalment, una oxidació al·lílica catalitzada per diòxid seleni seguida per una oxidació amb el periodinà de Dess-Martin forní l'esmentat intermedi **2**.



Esquema 9. Obtenció de **2** mitjançant l'orientació B.

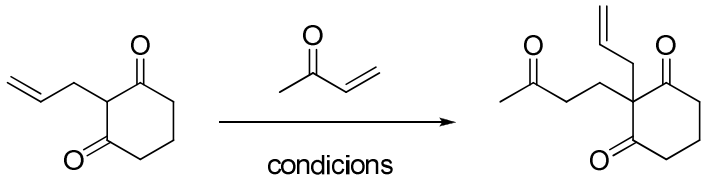
Capítol 3 . Síntesi Enantioselectiva de derivats de la cetona de Wieland-Miescher

El precursor per a la síntesi de l'anominina havia de ser un derivat de la cetona de Wieland-Miescher que tingués una funcionalització a la cadena lateral que en permetés la seva elaboració fins a la cadena complerta d'isohexenil. Per tant, es necessitava una metodologia que ens permetés la preparació enantioselectiva d'aquest tipus de compostos de manera fàcil i eficient. Donat que a la bibliografia no es trobaven mètodes descrits suficientment útils per a tal transformació, es decidí fer un estudi metodològic d'aquesta etapa.

Optimització de l'alquilació de la metil vinil cetona

Primerament, s'optimitzà la reacció d'alquilació de la metil vinil cetona (Taula 1), ja que serien necessàries grans quantitats del compost **35** i amb els mètodes descrits a la bibliografia no s'arribava a una conversió satisfactòria. La reacció en medi aquós donava rendiments notables, tant si era catalitzada per àcid o per base (Entrades 1 i 2). L'ús d'una base orgànica com el Triton B (hidròxid de benziltrimetilamoni) resultà en un rendiment baix (Entrada 3). En canvi, el rendiment fou del 92% quan s'emprà aigua amb una gota d'etanol, tot i que el temps de reacció fou massa llarg (Entrada 4). La reacció també funcionava sense solvent però amb rendiments baixos (Entrada 5). Quan s'emprà DMF com a solvent i amb la presència d'una quantitat catalítica de trietilamina el rendiment assolit fou del 87% (Entrada 6). Finalment, s'aconseguí augmentar el rendiment eliminant el solvent, reduint la quantitat de metil vinil cetona a 1.1 eq i utilitzant un 1 mol% de trietilamina com a base (Entrada 7). Cal dir que aquesta metodologia és molt útil i neta, ja que no utilitza solvents (la metil vinil cetona actua com a tal), només necessita tres hores de reacció per a obtenir un rendiment gairebé quantitatiu, i com a conseqüència de tot això, el cru de la reacció és molt net i la purificació és força senzilla.

Taula 1. Optimització de la reacció d'alquilació de la metil vinil cetona.



34 **35**

Entrada	Condicions	Rdt. (%)[a]
1	MVC[b] (2.5 eq), AcOH, H_2O, hidroquinona, 75 °C, 12 h	82
2	MVC[b] (1.5 eq), 10% KOH, 4:1 MeOH/H_2O, reflux, 75 min	82
3	MVC[b] (1.5 eq), triton B (0.1 eq), MeOH, 60 °C, 12 h	41
4	MVC[b] (2 eq), H_2O, gota d'EtOH, ta, 10 d	92
5	MVC[b] (2 eq), ta, 14 d	35
6	MVC[b] (3 eq), DMF, Et_3N (0.3 eq), 12 h	87
7	MVC[b] (1.1 eq), Et_3N (1 mol%), ta, 3 h	96

[a] Rendiment després de la purificació per cromatografia en columna.
[b] Metil vinil cetona.

El pas següent fou la tria del catalitzador que donés els rendiments químics i òptics més elevats. S'utilitzaren els catalitzadors representats en la Figura 3.

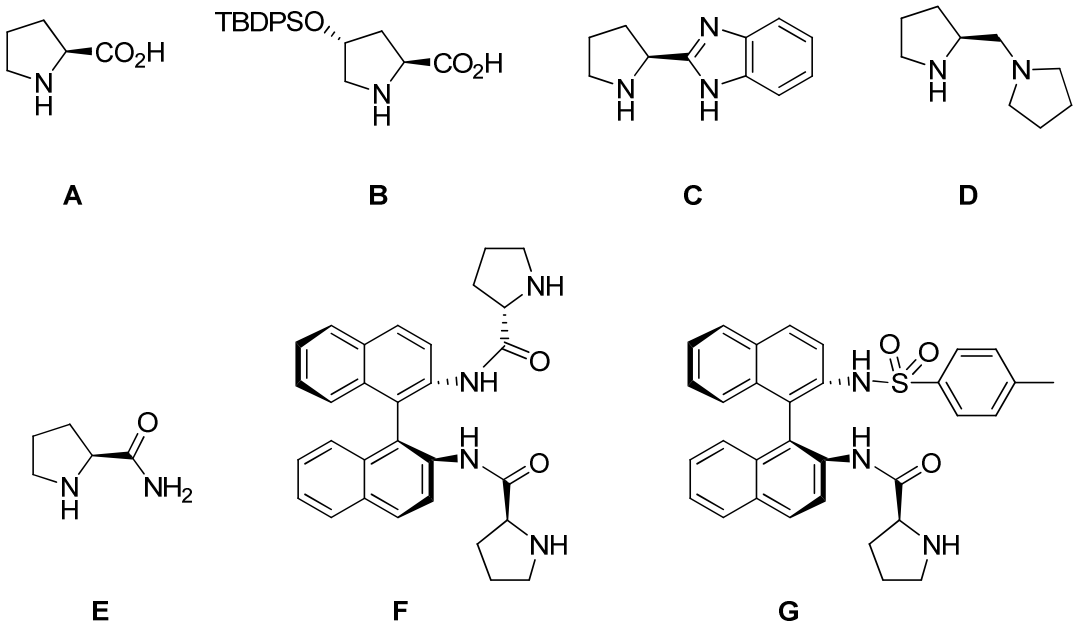
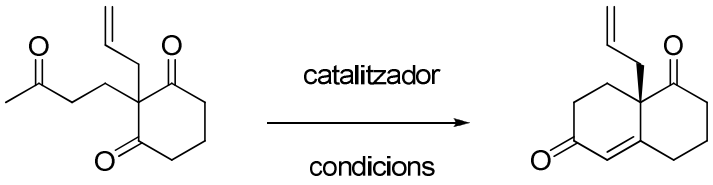


Figura 3. Catalitzadors emprats.

L'ús de L-prolina en DMSO en quantitats estequiomètriques proporcionava el producte **36** amb 72% i 84% ee (Entrada 1). Al disminuir la quantitat de prolina el rendiment augmentava en detriment de la puresa òptica (Entrades 2-4). L'ús de derivats de prolina com els catalitzadors B, C, D i F donà el producte amb rendiments elevats, tot i que amb baixa selectivitat (Entrades 5-7, 9). En canvi, l'ús de prolinamida proporcionà l'enona **36** amb un rendiment excel·lent i una enantioselectivitat notable (Entrada 8). El catalitzador G fou el que donà millors excessos enantiomèrics, tant ell com el seu enantiòmer (Entrades 10 i 11). L'ús de salmorra com a solvent no feu disminuir l'excés enantiomèric, però resultà en reaccions incomplertes (Entrada 12). Al disminuir la càrrega de catalitzador a 2.5 mol% s'aprecià un augment en l'enantioselectivitat sense detriment en el rendiment tot i que s'allargaren els temps de reacció (Entrada 13). Reduint encara més la quantitat de catalitzador no aportà cap millora en la selectivitat però resultà en reaccions extremadament lentes (Entrada 14). Al reduir el catalitzador fins a 1 mol% i al variar la quantitat d'àcid es va veure que es podien obtenir resultats semblants però amb menys càrrega de catalitzador (Entrades 15-17).

Taula 2. Reacció aldòlica intramolecular.

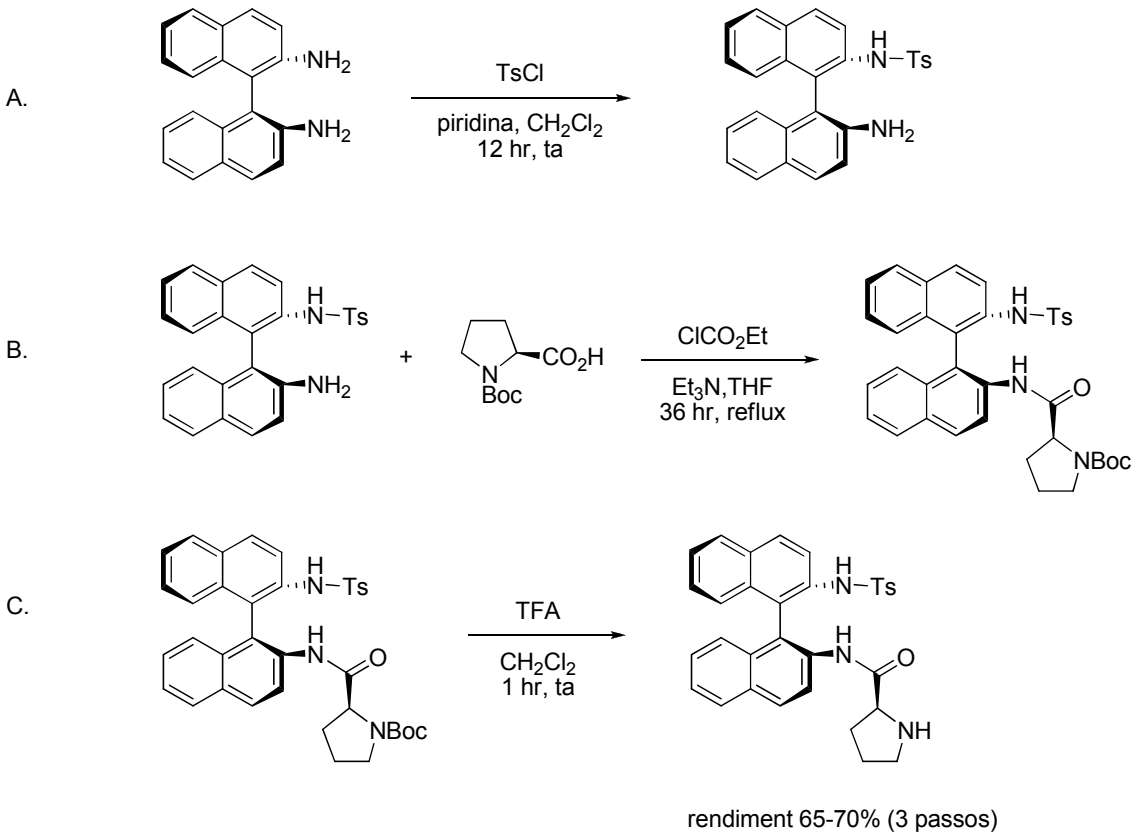


35 **36**

Entrada	Catalitzador (mol%)	Solvent	Temps	Rdt. (%)[a]	ee (%)[b]
1	**A** (100)	DMSO	24 h	72	84
2	**A** (50)	DMSO	24 h	76	64
3	**A** (25)	DMSO	48 h	80	74
4	**A** (5)	-	14 d	74	46
5	**B** (5)	salmorra	10 d	93	40
6	**C** (20)[c]	THF	24 h	90	34
7	**D** (5)[d]	-	24 h	93	8
8	**E** (5)[d]	-	24 h	96	82
9	**F** (5)[d]	-	24 h	87	32
10	**G** (5)[d]	-	24 h	93	94
11	***ent*-G** (5)[d]	-	24 h	93	94[e]
12	**G** (5)[d]	salmorra	36 h	76	94
13	**G** (2.5)[d,f]	-	5 d	93	97
14	**G** (1)[d]	-	20 d	86	96
15	**G** (1)[g]	-	1.5 d	94	88
16	**G** (1)[h]	-	3 d	92	92
17	**G** (1)[i]	-	6 d	93	94

[a] Rendiment després de la purificació per cromatografia en columna.
[b] Determinat per HPLC amb columna Chiralcel OD-H.
[c] Es va addicionar TFA (20 mol%).
[d] Es va addicionar àcid benzoic (1 mol%).
[e] Es va obtenir l'enantiòmer oposat.
[f] Reacció feta en escala de 3 g.
[g] Es va addicionar àcid benzoic (10 mol%).
[h] Es va addicionar àcid benzoic (5 mol%).
[i] Es va addicionar àcid benzoic (2.5 mol%).

La síntesi del catalitzador consta de 3 etapes amb un rendiment global del 65-70%. Parteix de *S*-Binam i s'hi introdueix un grup tosil. En la següent etapa, aquesta reacciona amb l'anhídrid mixt que es forma *in situ* entre la Boc-prolina i el cloroformiat d'etil. Finalment, s'elimina el grup Boc per tractament amb àcid trifluoroacètic.

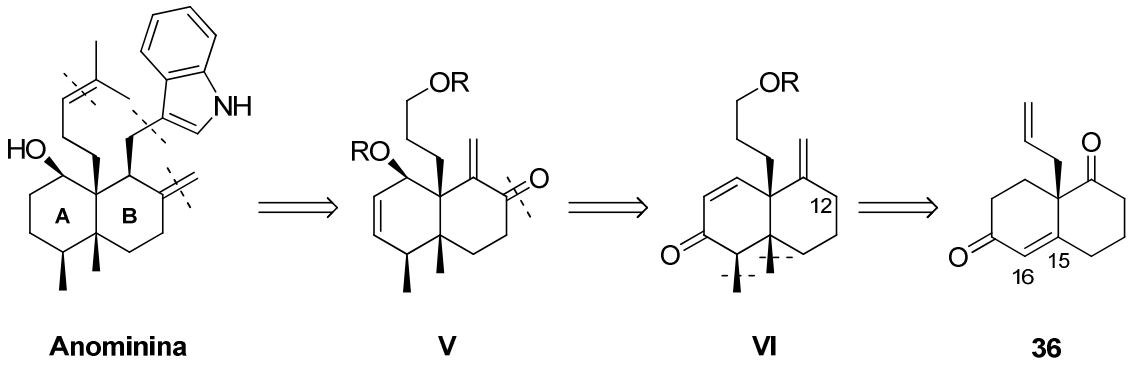


Esquema 10. Síntesi del catalitzador.

Capítol 4. Síntesi de la (–)-anominina

Un cop desenvolupada la metodologia que ens permetia preparar enantioselectivament derivats de cetona de Wieland-Miescher en grans quantitats i de forma senzilla, es decidí afrontar la síntesi total del diterpenoid anominina.

L'estratègia sintètica planifica introduir les insaturacions i l'indole en els últims trams de la síntesi. Per a poder introduir l'heterocicle per addició conjugada es necessita una enona exocíclica convenientment protegida tal com **V**. Aquesta pot provenir de **VI** via oxidació al·lílica per instal·lar l'enona i una transposició al·lílica per moure la funció de C17 a C19. Finalment **VI** provindria del derivat al·lílic de la cetona de Wieland-Miescher utilitzant la metodologia estudiada en el capítol 2, i aquesta provindria de la 1,3-ciclohexandiona mitjançant el protocol descrit al capítol 3. La tria de **36** és per dos motius. D'una banda aquest fou el que va donar millors rendiments i enantioselectivitats, i d'altra banda, la funció al·lílica ens permet elaborar la cadena complerta d'isohexenil.

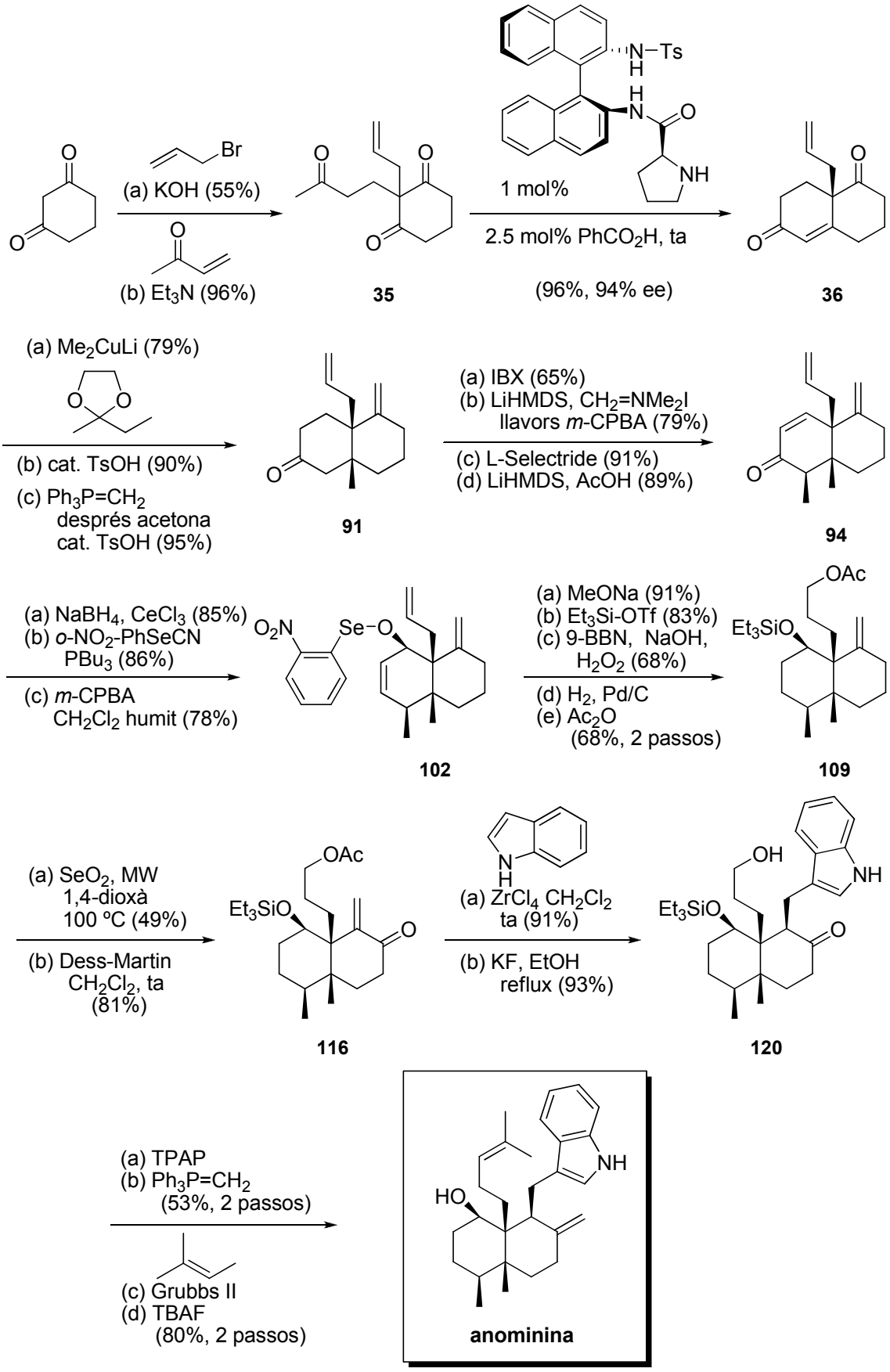


Esquema 11. Anàlisi retrosintètica de l'anominina.

La síntesi va partir de la 1,3-ciclohexandiona, en la qual s'introduïren els substituents al·lílic i 3-oxobutílic necessaris per a la preparació de **36** (segons la metodologia descrita en el capítol 3). L'addició de dimetilcuprat de liti va instal·lar el segon centre estereogènic. Una seqüència de protecció quimioselectiva, reacció de Wittig i desprotecció va donar el compost **91**, que va ser oxidat amb IBX per a dirigir exclusivament l'alquilació d'Eschenmoser al C16. La reducció de l'enona exocíclica resultant mitjançant L-Selectride [tris(*sec*-butil)borhidrur de liti] forní una mescla de diastereòmers, que fou epimeritzada per desprotonació i protonació en condicions cinètiques obtenint **94**. Aquest, fou reduït a l'alcohol sota condicions de Luche i convertit en èter de seleni mitjançant el protocol de Grieco. L'addició de *m*-CPBA resultà en la formació d'un selenòxid que, mitjançant una transposició [2,3]-sigmatròpica, va moure la funció oxigenada a C19.

A l'addicionar metòxid sòdic a **102** s'hidrolitzà l'enllaç Se-O, obtenint l'alcohol que seguidament fou protegit com a èter de silici. L'alquè exocíclic fou hidroborat mitjançant 9-BBN, mentre que l'endocíclic es va eliminar reductivament. Finalment, es protegí l'alcohol de la cadena lateral en forma d'acetat obtenint el compost **109**. Per instal·lar la funció enona desitjada, es procedí tal i com s'havia assajat anteriorment, és a dir, s'oxidà la posició al·lílica mitjançant diòxid de seleni i l'alcohol resultant va tornar ser oxidat mitjançant el periodinà de Dess-Martin obtenint **116**.

Per poder introduir el fragment indòlic es necessità fer assajos amb diferents àcids de Lewis, resultant el tetraclorur de zirconi el més favorable. La mescla de diastereòmers que s'obtingué fou epimeritzada sota condicions termodinàmiques mitjançant l'acció del fluorur potàssic fornint **120**. Sorprenentment, l'anterior epimerització també resultà en la desprotecció de l'alcohol de la cadena lateral. Aquest fou oxidat utilitzant el protocol de Ley i immediatament fou sotmès al reactiu de Wittig per obtenir la diolefina. Per completar la funcionalitació de la cadena lateral es procedí a fer una reacció de metàtesi creuada que va reaccionar quimioselectivament amb el doble enllaç menys impedit. Per últim, es va desprotegir l'alcohol mitjançant TBAF obtenint el diterpenoid anominina de forma enantiopura.



Esquema 12. Síntesi de l'anominina.

Capítol 6. Conclusions

-No es pot utilitzar el compost **III** com a precursor de la síntesi degut a la impossibilitat d'introduir la cadena lateral mitjançant cap de les metodologies emprades (addició conjugada, transposició de Claisen)

-L'orientació més favorable per a la síntesi del terpenoide anominina sembla ser l'orientació B, ja que l'intermedi **17** posseeix la funcionalització adequada per a poder transposar la funció oxigenada a la posició requerida. A més, aquesta orientació és més directa i més eficient en quant a rendiment.

-L'indole ha de ser introduït via addició conjugada, ja que no es pot fer per alquilació.

-L'ordre d'introducció d'estereocentres ha de ser el següent: primer s'ha d'introduir estereoselectivament la cadena lateral mitjançant una anel·lació de Robinson, i posteriorment s'ha d'introduir el segon centre quaternari mitjançant una reacció d'addició conjugada. Això és deu a la impossibilitat de fer-ho de forma inversa i a la necessitat d'introduir els centres quaternaris des del principi de la síntesi.

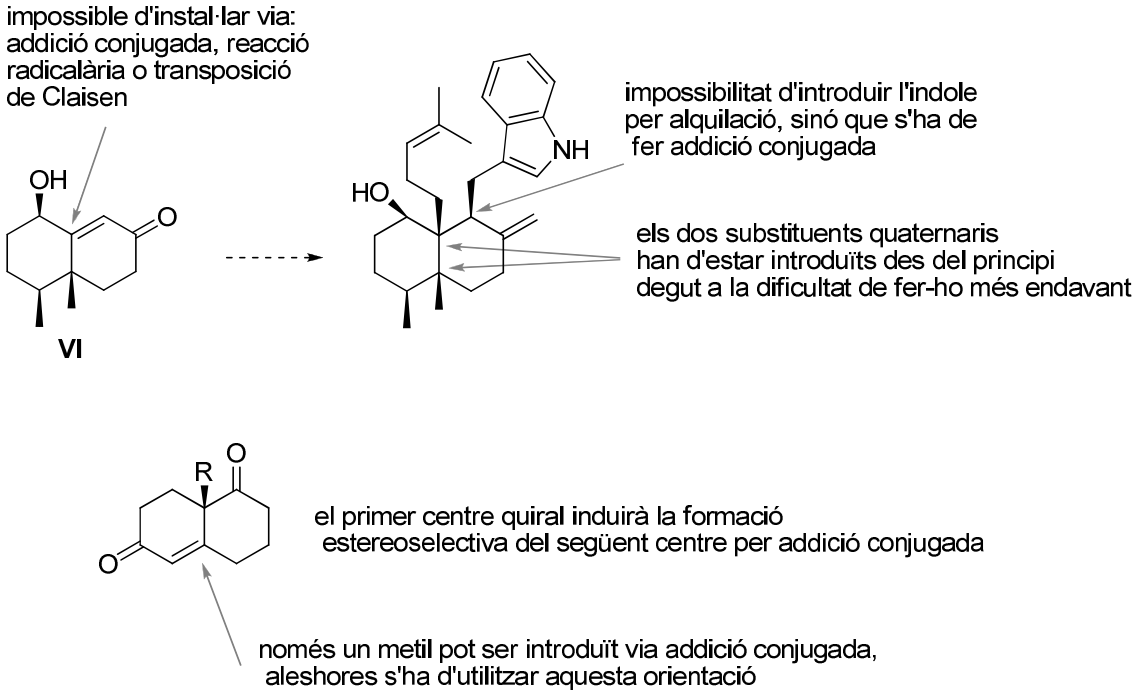
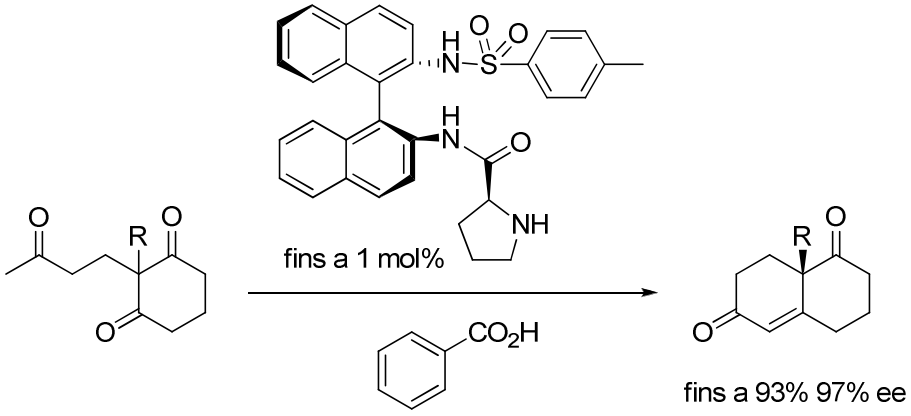


Figura 3. Conclusions.

-S'ha desenvolupat un procediment general, senzill i robust que permet la síntesi enantioselectiva de derivats de cetona de Wieland-Miescher. S'ha optimitzat l'etapa de l'addició de Michael (77-97%) així com també la reacció aldòlica intramolecular per diferents substrats de gran utilitat sintètica, superant els excessos enantiomèrics descrits anteriorment (84-97% ee).

-En general s'ha comprovat que a l'augmentar la llargada de cadena la velocitat de reacció disminueix, però a la vegada n'augmenta l'enantioselectivitat. D'altra banda, si s'augmenta la concentració d'àcid o de catalitzador, la velocitat de reacció augmenta en detriment de l'enantioselectivat.

-El procediment experimental és molt senzill, no utilitza solvents ni purificacions per cromatografia en columna, aconseguint així una metodologia sostenible i barata per a la síntesi de decalines polisubstituïdes que pot ser molt útil en la síntesi de productes naturals.



Esquema 13. Metodologia per a la preparació enantioselectiva de derivats de cetona de Wieland-Miescher.

-El diterpenoid anominina va ser preparat en 27 passos des de la 1,3-ciclohexandiona cosa que representa la primera síntesi total de l'esmentat producte natural. A més, se'n determinà l'estereoquímica absoluta per comparació de la rotació òptica amb la del producte natural.

-La metodologia desenvolupada és prou flexible per poder preparar altres diterpenoids de la família, ja que aquests comparteixen el nucli de decalina i només difereixen en l'estat d'oxidació.

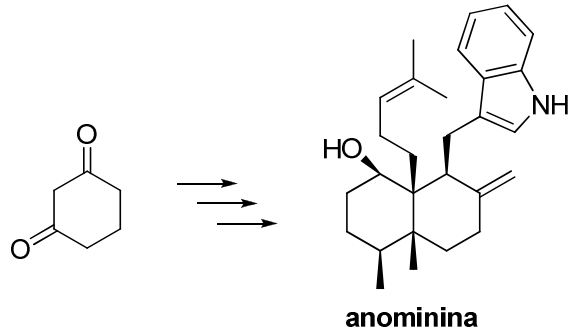


Figura 4. Síntesi de l'anominina a partir de la 1,3-ciclohexandiona.

Apèndix

Síntesi total dels àcids Iso- i Bongkrekic.

Com a part de la beca de doctorat, es va realitzar una estada al laboratori del professor Ley (Cambridge, Regne Unit). El projecte consistia en la síntesi d'aquests dos productes naturals d'origen bacterià.

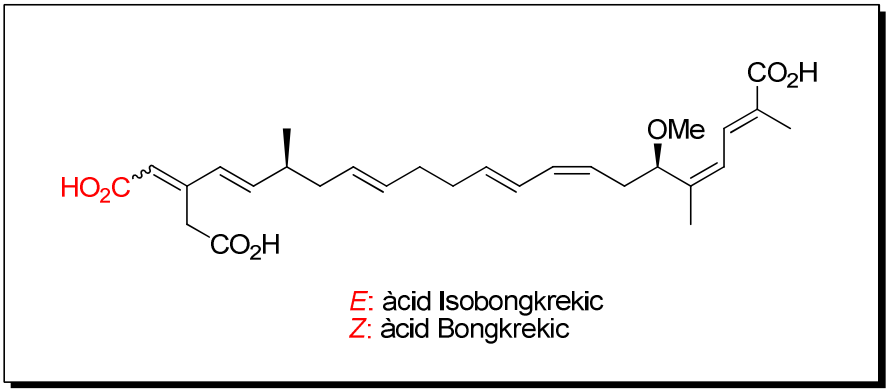
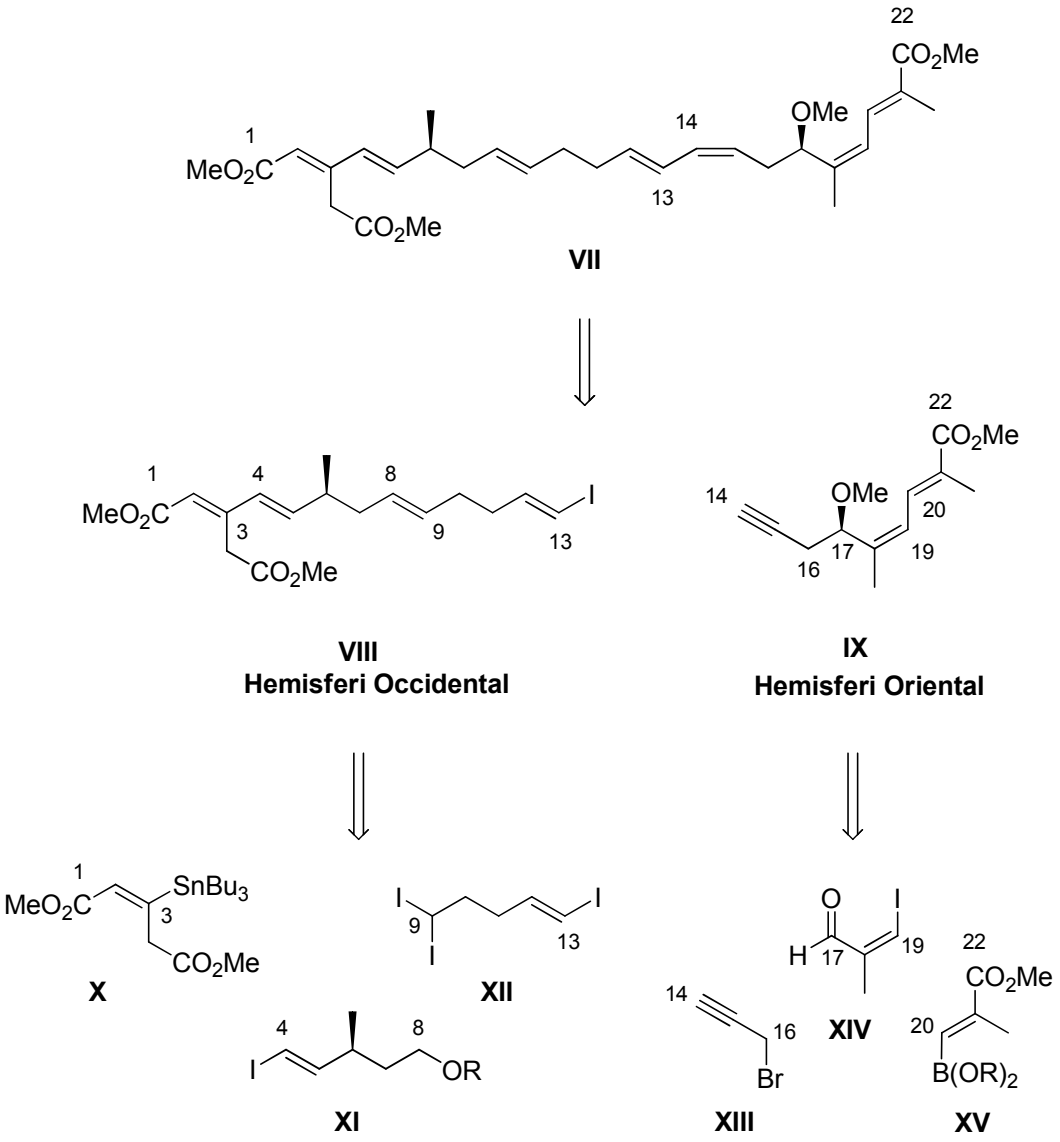


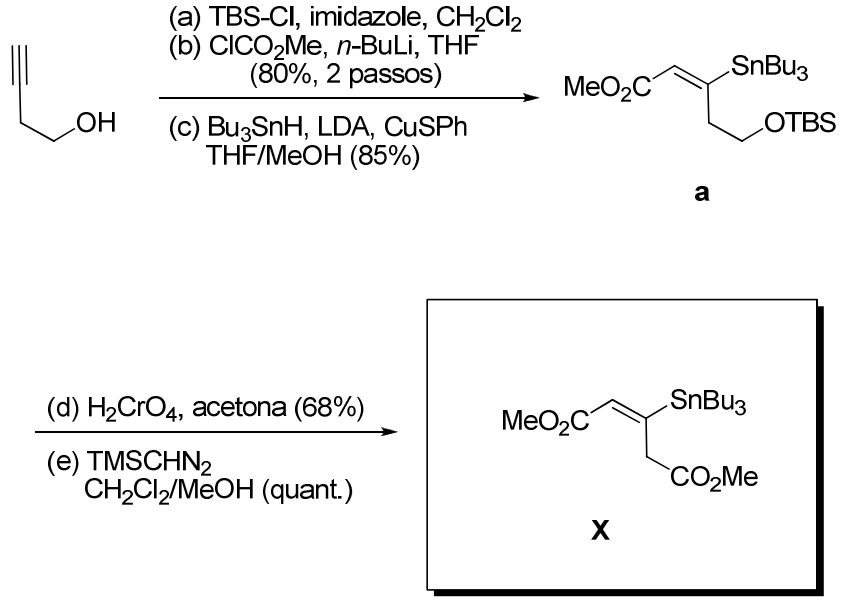
Figura 5. Àcids isobongkrekic i bongkrekic.

L'anàlisi retrosintètica adoptada consistia en la desconnexió de l'enllaç C13-C14 que revelava els fragments est i oest. L'hemisferi occidental a la vegada, es podia dividir en tres fragments que resulten de la desconnexió entre els enllaços C3-C4 i C8-C9. D'altra banda, l'hemisferi oriental es podia obtenir per unió dels fragments **XIII**, **XIV** i **XV**.



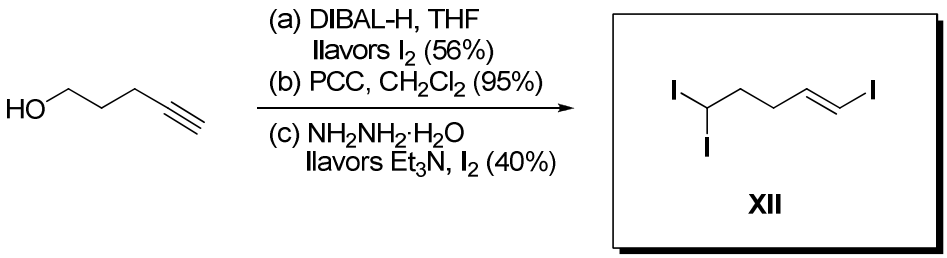
Esquema 14. Anàlisi retrosintètica de l'àcid isobongkrekic.

El fragment **X** es construí a partir de l'alcohol homopropargílic mitjançant una seqüència de reaccions coneguda. Així, la protecció de l'alcohol, homologació amb cloroformiat de metil i hidroestannilació de Piers generà **a**. Seguidament, es va emprar el reactiu de Jones que va desprotegir l'alcohol i el va oxidar fins a l'àcid carboxílic. Finalment, l'esterificació amb trimetilsilildiazometà forní l'estannà **X**.



Esquema 15. Preparació de l'estannà **X**.

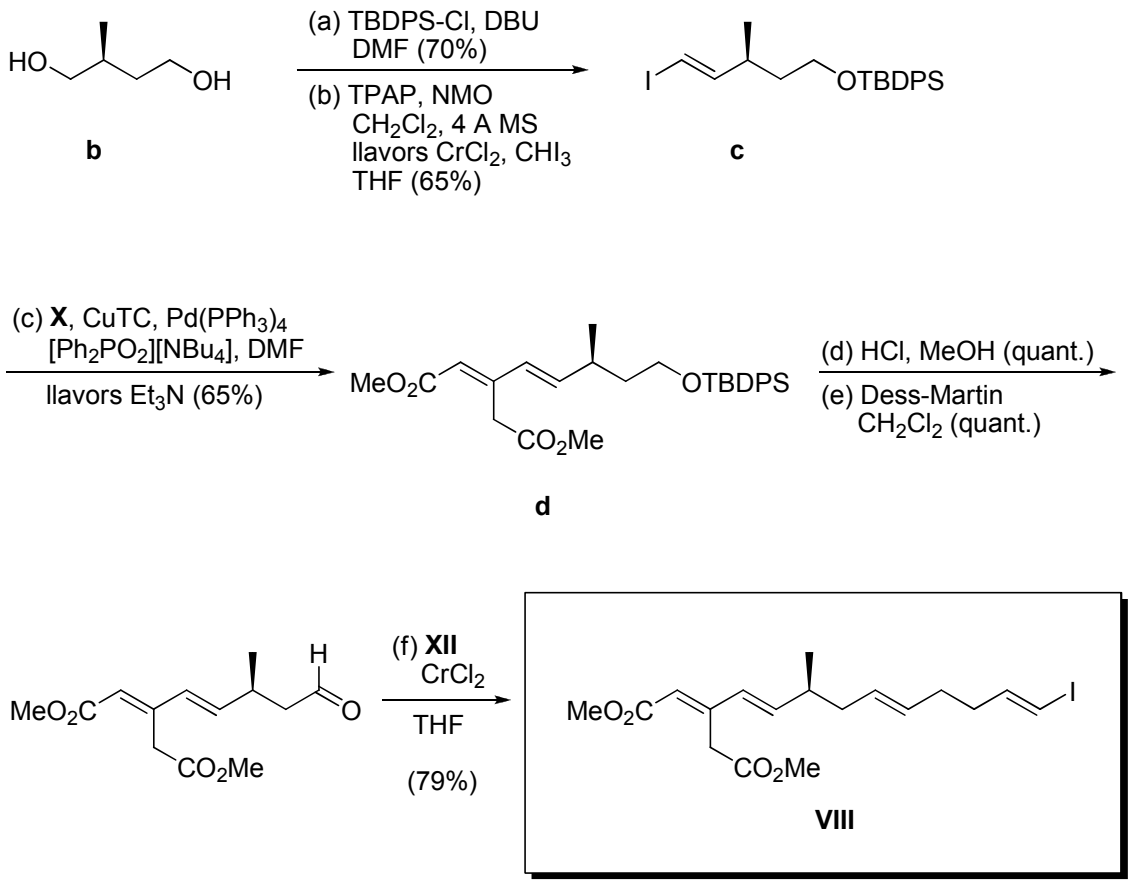
El triiodur **XII** es preparà a partir del pentinol que fou transformat en el corresponent iodur vinílic mitjançant la reducció amb hidrur de di(*iso*-butil)alumini i posterior reacció amb iode. Seguidament, l'aldehid obtingut per oxidació amb PCC es féu reaccionar amb hidrazina i iode, obtenint d'aquesta manera el *gem*-diiodur **XII**.



Esquema 16. Preparació del triodur **XII**.

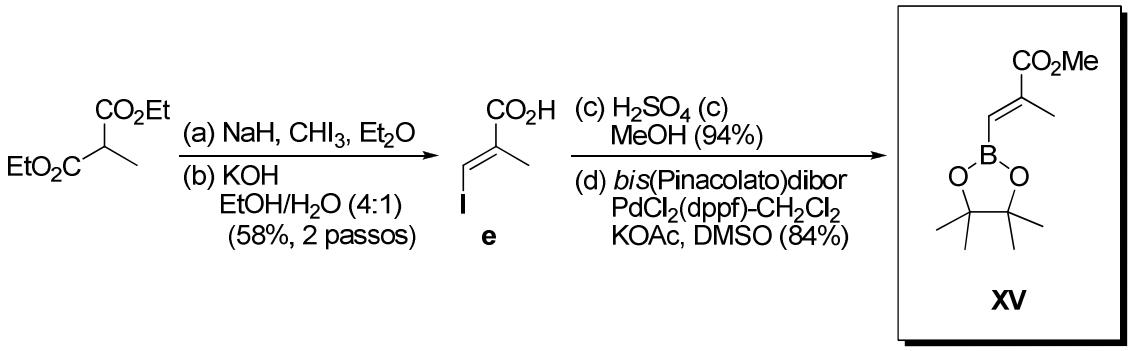
Per completar la preparació de l'hemisferi occidental es partí del diol comercial **b**, el qual va ser protegit selectivament a la posició menys impedida estèricament. Degut a l'inestabilitat de l'intermedi aldehid, s'hagué d'utilitzar un protocol de *one-pot* consistent en l'oxidació de Ley i posterior homologació emprant el protocol de Takai. Per acoblar els compostos **XI** amb **X** s'emprà una

modificació de la metodologia de Stille-Migita que generà **d**. El grup protector de silici fou eliminat per hidròlisi àcida i l'alcohol resultant fou oxidat amb el periodinà de Dess-Martin. Finalment, s'acoblà el triiodur **XII** mitjançant una olefinació de Takai per a obtenir l'hemisferi occidental **XIII**.



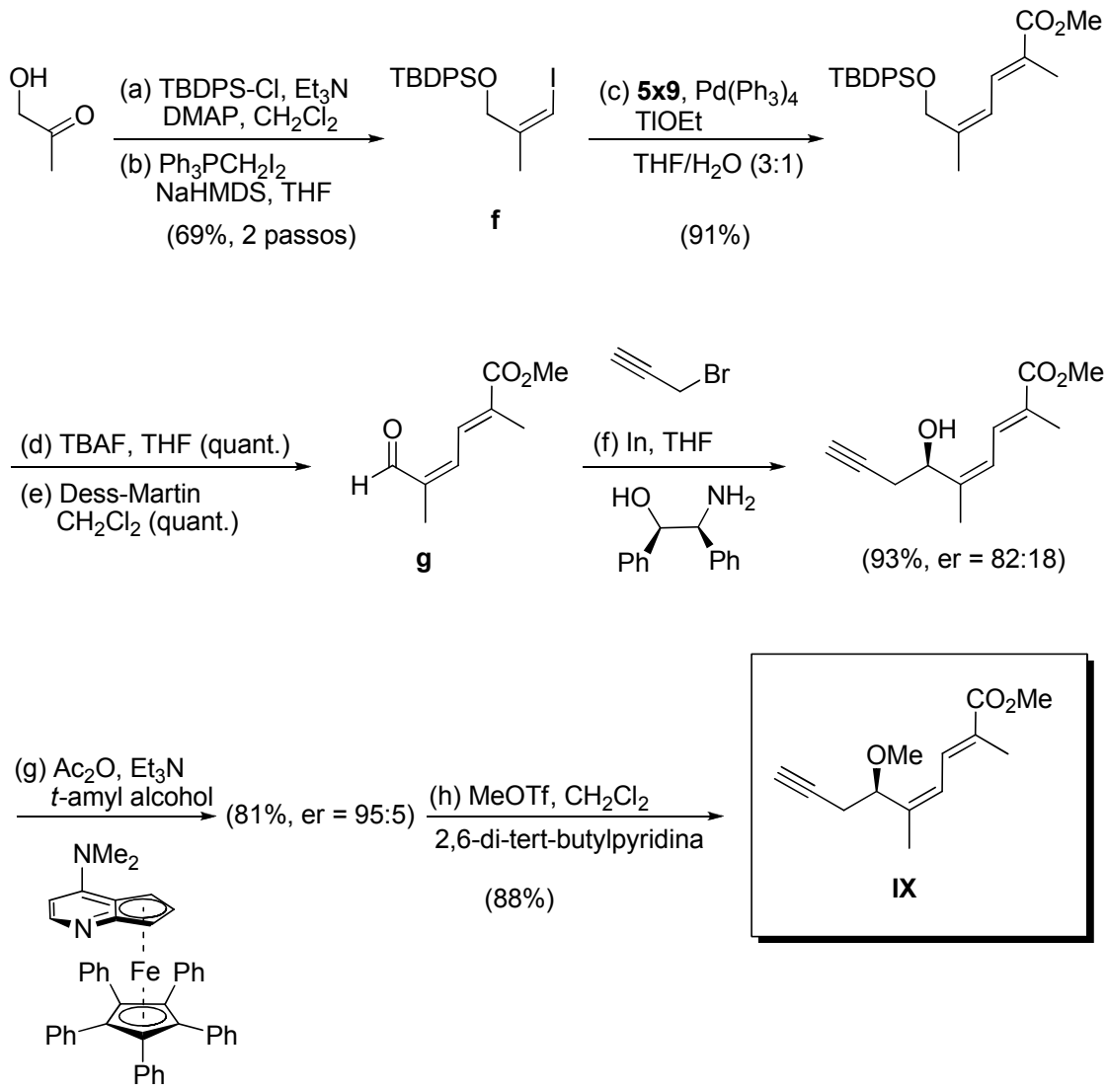
Esquema 17. Obtenció de l'hemisferi occidental **VIII**.

En quant a la síntesi del fragment **XV** es partí del metilmalonat de dietil, el qual fou alquilat amb iodoform i posteriorment es descarboxilà i s'eliminà obtenint **e**. L'esterificació en condicions àcides i la posterior introducció del boronat completà el fragment **XV**.



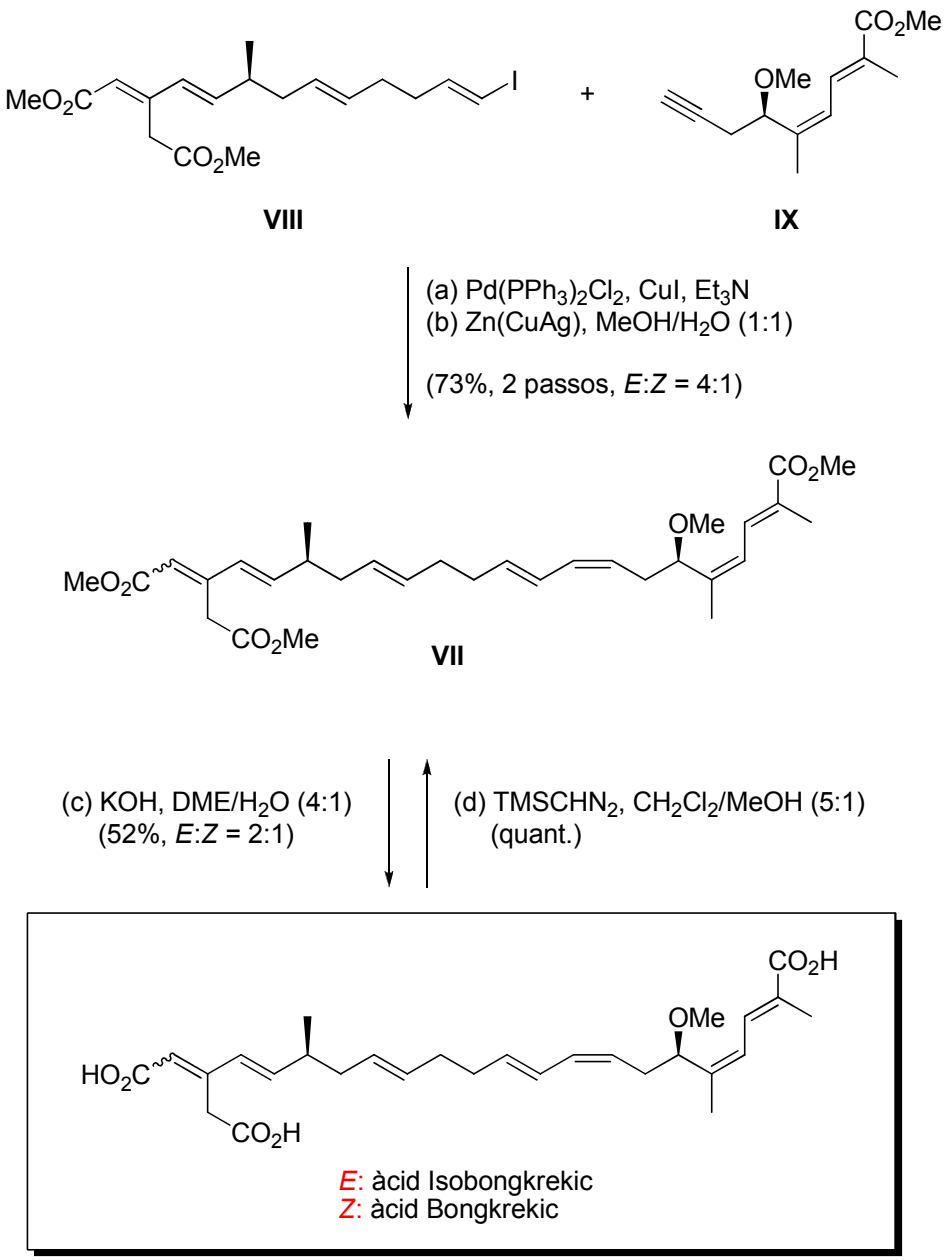
Esquema 18. Preparació del fragment **XV**.

La síntesi de l'hemisferi occidental continuà a partir de la hidroxiacetona, que fou protegida i seguidament es féu reaccionar emprant el protocol de Wittig-Stork per a obtenir **f**. Per a l'acoblament entre aquest fragment i **XV** es va examinar diferents condicions per a la reacció de Suzuki-Miyaura, sent la modificació de Kishi la que assegurà la completa selectivitat a favor del producte amb configuració *Z*. La desprotecció i oxidació de l'alcohol generà l'aldehid **g**, que fou immediatament emprat en la reacció d'homopropargilació asimètrica donant una mescla d'enantiòmers (er 82:18). Per separar l'enantiòmer desitjat s'emprà una resolució cinètica, la qual va acetilar selectivament el producte no desitjat. Després de separar els dos productes, **IX** fou metilat aconseguint així la síntesi de l'hemisferi oriental.



Esquema 19. Preparació del fragment **IX**.

Per unir els dos hemisferis s'utilitzà l'acoblament de Sonogashira, que malauradament, provocà una isomerització de l'enllaç C1-C2 donant una mescla d'isòmers *E*:*Z* en proporció 4:1. Per reduir el triple enllaç quimioselectivament s'assajà, sense èxit, la hidrogenació amb el catalitzador de Lindlar. Aquesta transformació s'aconseguí mitjançant zinc activat amb coure i plata obtenint una mescla separable dels èsters trimetílics de l'àcid isobongkrekic i bongkrekic. En aquest punt, els dos compostos foren caracteritzats i analitzats per comparació amb les dades dels respectius productes naturals. Finalment, la síntesi d'ambdós productes es realitzà mitjançant una saponificació amb hidròxid potàssic.



Esquema 20. Obtenció dels àcids isobongkrekic i bongkrekic.

Conclusions

-S'ha desenvolupat una metodologia general per a la síntesi d'àcids grassos poliinsaturats, obtenint el producte natural àcid isobongkrekic i el seu isòmer l'àcid bongkrekic.