THE UNIVERSITY OF CALGARY

SYNTHETIC APPROACHES TO THELEPOGINE AND HADINECINE

by

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Abstract

This dissertation describes two studies of the enantioselective syntheses of pyrrolizidine alkaloids.

In the first part an enantioselective synthesis of (R)-3,4,8,8a-tetrahydro-8a-(2-allyl)-1,6-(2H,7H)-naphthalenedione and (R)-3,4,8,8a-tetrahydro-8a-allyl-5-methyl-1,6-(2H,7H)-naphthalenedione was developed via Robinson annulation of 2-allylcyclohexane-1,3-dione with ethyl and and methyl vinyl ketone respectively, using L-proline and L-phenylalanine for the chiral induction. Degradation of the angular allyl groups furnished (S)-3,4,8,8a-tetrahydro-8a-(((2-methoxy-ethoxy)-methoxy)methyl)-1,6-(2H, 7H)-naphthalenedione-1-ethylene acetal and (S)- 3,4, 8,8a-tetrahydro- 8a- ((methoxymethoxy)methyl) -5- methyl-1,6-(2H,7H) -naphthalenedione-1-ethylene acetal in 25% and 11% overall yield, and an enantiomeric excess of >99% and 75% respectively.

(R)-3,4,8,8a-Tetrahydro-8a-(2-allyl)-1,6-(2H,7H)-naphthalenedione was then used in an approach to thelepogine. Thus, 1,4-methylation of (R)-3,4,8,8a-tetrahydro-8a-(2-allyl)-1,6-(2H,7H)-naphthalenedione and subsequent olefination of C-5, furnished (4aS,8aR)-3,4,4a,7,8,8a-octahydro-8a-allyl-4a-methyl-5-methylene-1,6-(2H,5H)-naphthalenedione in 80% overall yield, which was further elaborated to (1R,4aR,5S,8aR)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahydro- 8a -allyl -1-((methoxymethyl)oxy) -4a- methyl -6- methylene -5- (3' (2'- N- benzyloxycarbonyl-amino)propanoic acid)naphthalene methyl ester.

Two short enantioselective syntheses of hadinecine, an unusual 1-hydroxypyrrolizidine alkaloid are described in part two. These syntheses confirmed the structure for hadinecine originally assigned on the basis of spectrometric evidence and constituted the first enantioselective syntheses of a 1-hydroxypyrrolizidine alkaloid.

Acknowledgements

I wish to express my sincerest gratitude to my supervisor, Dr. M. H. Benn for his guidance and encouragement during my project.

I am also indebted to Dr. E. A. Dixon and T. S. Sorensen for their guidance during Dr. Benn's leaves, and Dr. Yamdagni, Dr. Q. Wu and Ms. D. Fox for their technical assistance.

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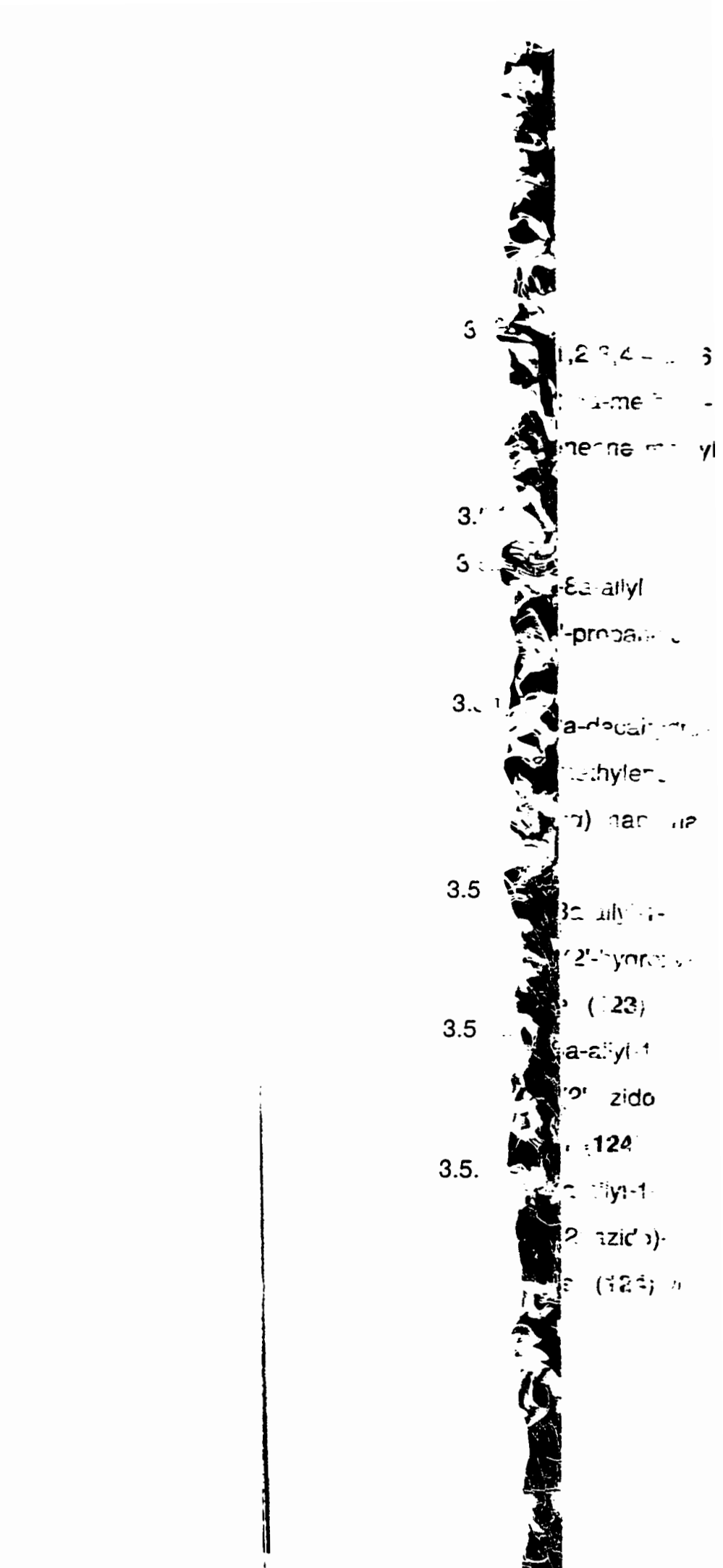

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List of Schemes (continued)

List of Abbreviations

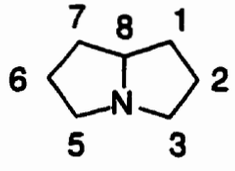
Å	angstrom
Ac	acetyl
Anal.	elemental analysis
Ar	aryl
bp	boiling point
br	broad
Bu	butyl
^{o}C	degrees Celsius
calcd	calculated
Cbz	Carbobenzyloxy (benzyloxycarbonyl)
cm^{-1}	reciprocal centimetres-wavenumbers
^{13}C-NMR	carbon-13 nuclear magnetic resonance
COSY	correlation spectroscopy
d	doublet
DIBAL	Diisobutylaluminium hydride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DMAP	4-Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
dt	doublet of triplets
E	electrophile
ee	Enantiomeric excess

eq	equivalent
Et	ethyl
g	grams
h	hours
H^+	acid
HETCOR	heteronuclear correlation spectroscopy
HMPA	Hexamethylphosphoramide
^{1}H-NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectrum
(+)-MTPA-Cl	(R)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride
Hz	Hertz
IBX	o-Iodoxybenzoic acid
IR	infrared
i	iso
J	coupling constant
k	kilo
LDA	lithium diisopropylamide
lit.	literature
M	molar
m	multiplet
M^+	molecular ion
m/z	mass to charge ratio
Me	methyl
MCPBA	m-chloroperoxybenzoic acid
mg	milligrams
MHz	megahertz
min	minutes

ml	millilitres
mmol	millimoles
mol	moles
mp	melting point
MS	mass spectrometry
NOE	nuclear Overhauser effect
ox.	oxidation
p.	page
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million
Pr	propyl
R	generalized alkyl group or substituent
R.T.	room temperature
s	singlet
t	triplet
t-	tertiary
TBDMS	t-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Tr	trityl
Ts	p-toluenesulfonyl
UV	ultraviolet spectrum

1. Introduction

The pyrrolizidine alkaloids (PAs) comprise a large set of natural products characterised by the presence of a heterocyclic system based on 1-azabicyclo-[3,3,0]octane **1**. PAs have attracted considerable attention because of associated



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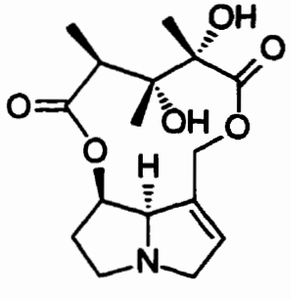
biological properties, in particular the health-hazards which they pose for humans and domestic stock when ingested, and their role as mediaters in insect-plant relationships. Comprehensive recent reviews of their occurrence and biological properties have been published, and the reader is referred to those publications for further aspects on these topics.[1]

The vast majority of known PAs are esters of hydroxylated derivatives of **1**, whereby the nitrogenous alcohol parts are known as necines, and the esterifying acids are called the necic acid component. Some typical pyrrolizidine alkaloids are moncrotaline **2**, retrorsine **3**, rosmarinine **4**, echinatine **5**, supinidine **6** and crotanecine **7**.



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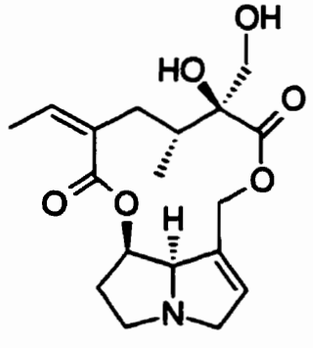

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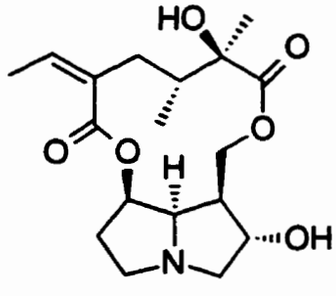

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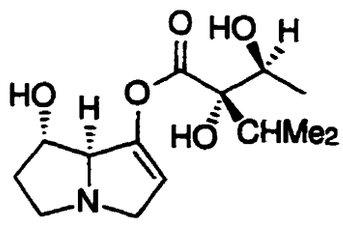

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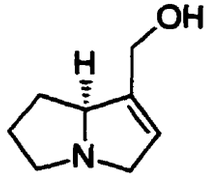

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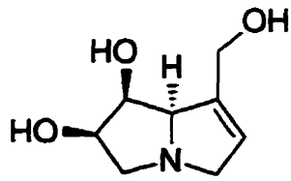

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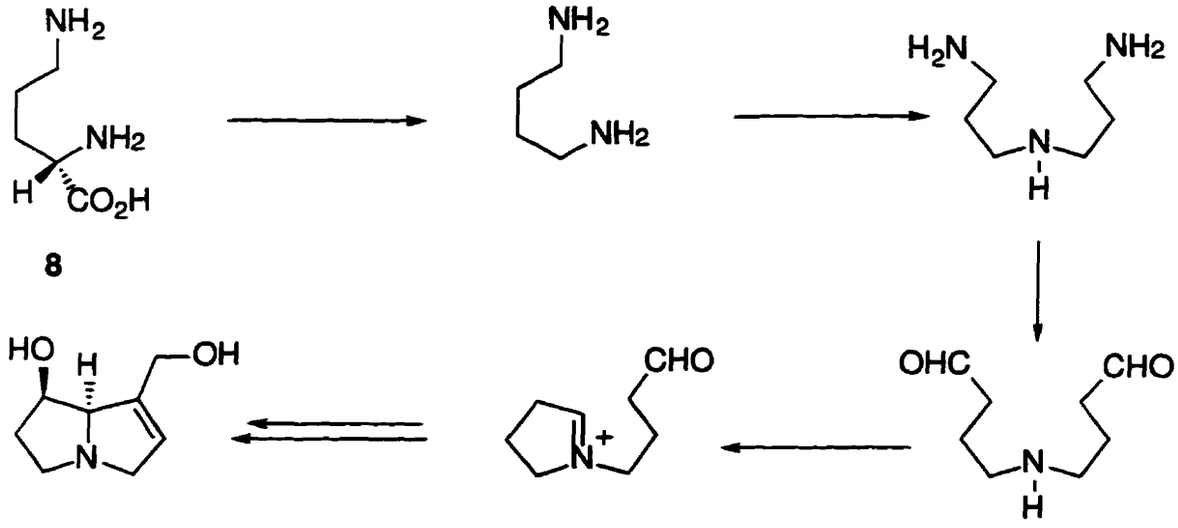
From a biosynthetic point of view, the necine unit of these PAs are now known to be derived from L-ornithine **8** as depicted below.[1c] Much less common



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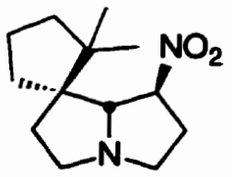
are PAs which are not necine derivatives, but instead contain the heterocyclic ring in a skeleton which appears to be partly or entirely derived from some source other than ornithine. Examples are nitropolyzonamine **9**,[2] loline **10**[3] and thelepogine **11**.[4]



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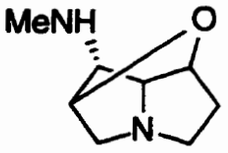

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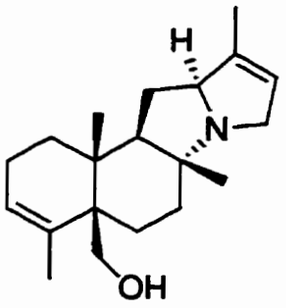
The work presented in the following chapters, describes two studies: (1) An approach to the total synthesis of thelepogine **11**; and (2) the synthesis of hadinecine **12**, a typical PA unit.



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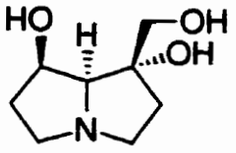

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1.2. References

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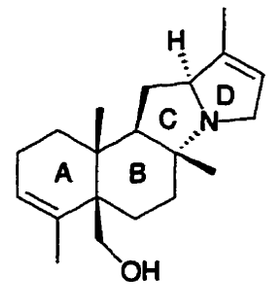
2. Part 1: Towards the Synthesis of Thelepogine

2.1. History of Thelepogine

Thelepogine **11** was isolated from the Australian grass *Thelepogon elegans* Roth (ex. Roemer & Schult) in minute amounts by W. D. Crow in 1960.[1] Its structure and absolute configuration were established by x-ray diffraction of the N-methyl derivative of thelepogine. Thelepogine is a very unusual pyrrolizidine alkaloid (PA). Although it contains the characteristic pyrrolizidine bicyclic structure (ring C and D in **11**), it is the only alkaloid of this family which contains a *cis*-decalin moiety (ring A and B in **11**). The biosynthetic construction of pyrrolizidines



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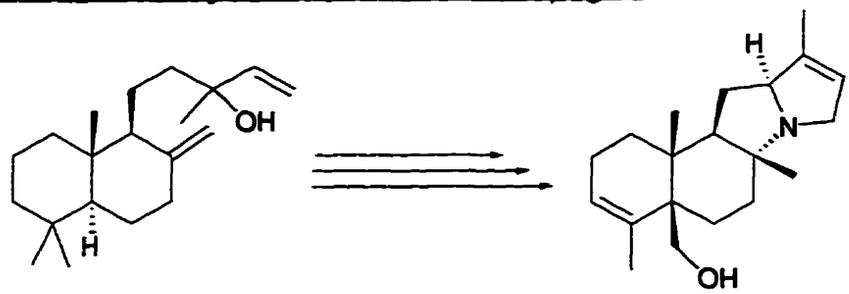
from ornithine has been well established for the more common necine-derived alkaloids (see page 2).[2a] However, the biosynthesis of thelepogine is not known, although a speculative route has been suggested by J. Fridrichsons *et al.*.[1b] In this, they pointed at the similarity of thelepogine and labdadien (mannoöl) derivatives, and they suggest that the carbon skeleton of thelepogine may be derived via 8(17),14-labdadien-13-ol **13**.

Scheme 1: Possible Biosynthetic Route to Thelepogine

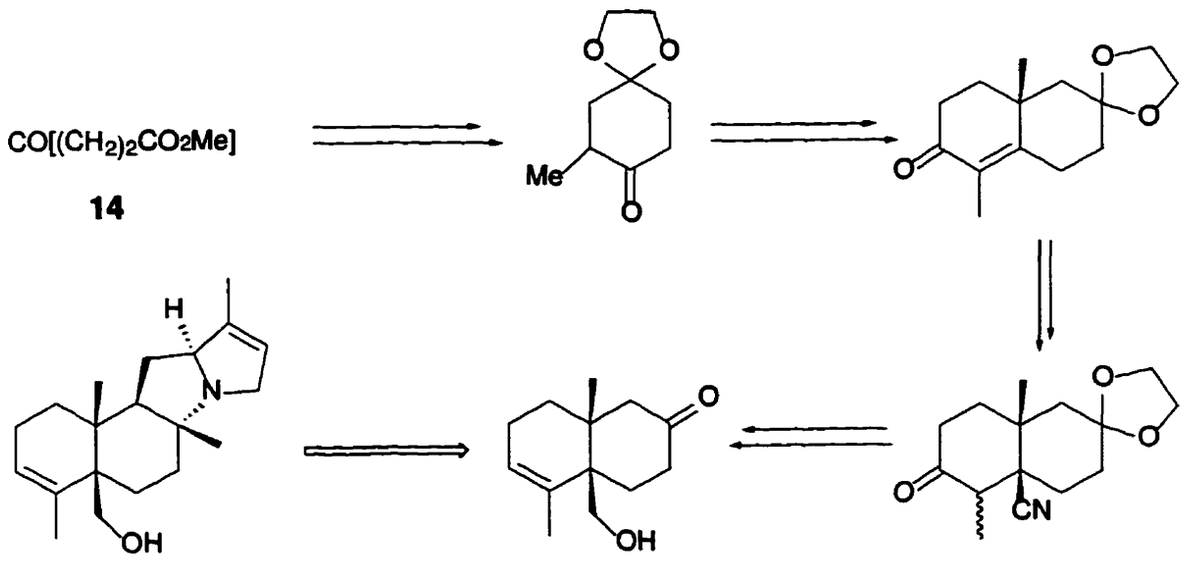


13 **11**

PAs have been intensively investigated in pharmacological, metabolic as well as in toxicological studies.[2] Thelepogine is one of the few pyrrolizidine alkaloids, which has been virtually neglected,[3] due to the small amount available from this plant, as well as the lack of a synthetic route for its production. For these reasons, we decided to explore synthetic routes towards this pyrrolizidine alkaloid.

Up to now, only one synthetic approach towards thelepogine appears to have been reported. In 1975, Kelly *et al.*[4] anounced their objective of making

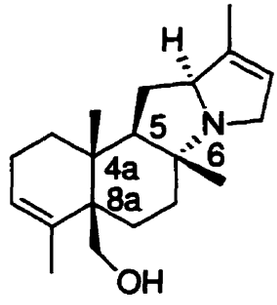
Scheme 2: Kelly *et al.*'s Approach to Thelepogine



thelepogine, and synthesized the racemic intermediate **15** in a lengthy 12 step synthesis starting from dimethyl ketopimelate **14**. No further paper has been published, and we assume that Kelly *et al.* might have run into problems in building on the pyrrolizidine system, and abandoned the project.

2.2. Retrosynthetic Analysis of Thelepogine

From a synthetic point of view, the array of tertiary and quaternary carbons along the C-8a, C-4a, C-5 to C-6 loop, and their *syn*-relationship is striking and was considered to be the main challenge in synthesizing thelepogine. Thus, we



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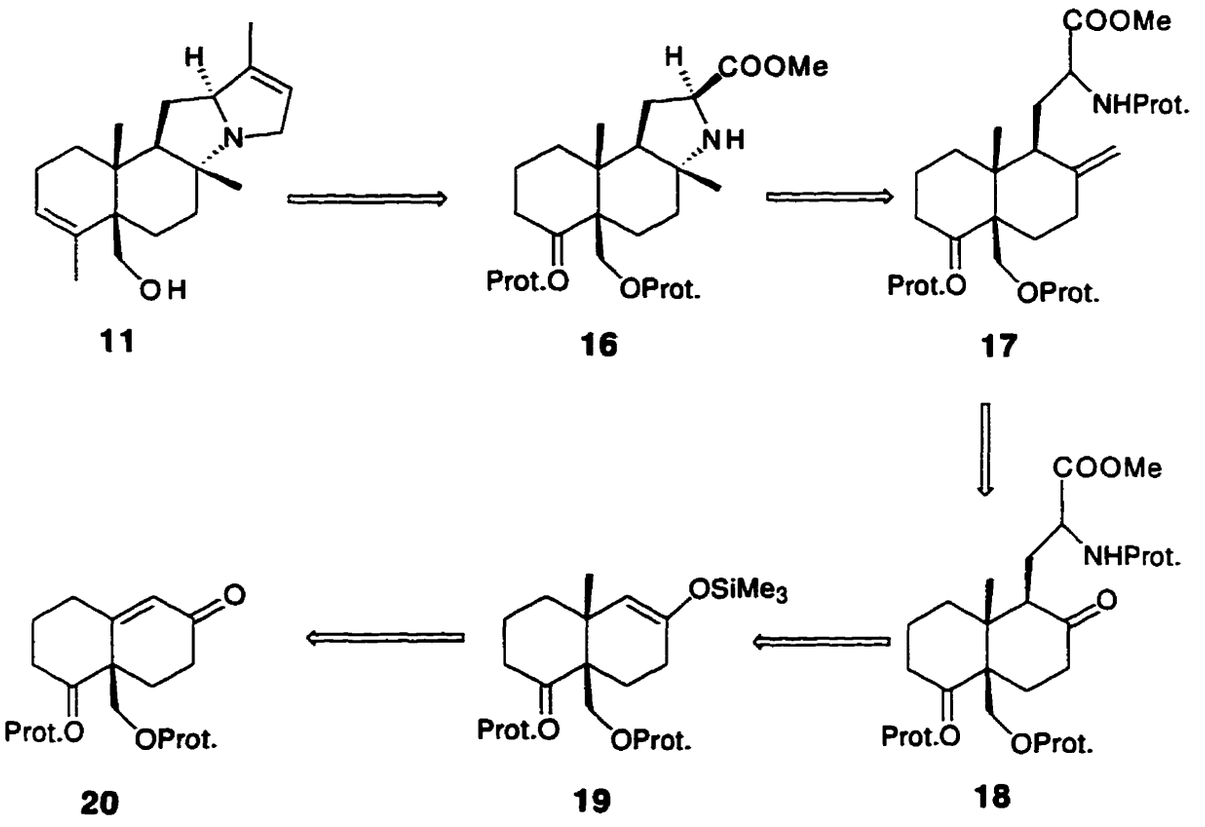
decided to disconnect thelepogine in such a way that most of the C-8a to C-6 backbone was installed at an early stage of the synthesis. For this reason, we disconnected thelepogine as schown in scheme 3, which led us to a 3-stage assembly of this alkaloid: (1) formation of the A/B-system **20**; (2) addition of ring-C to provide tricyclic intermediate **16**; and (3) the final construction of ring-D, together with the functional group manipulation required to give **11**.

Stage 1 consisted of finding an efficient synthesis for an angular hydroxymethyl analogue of the Wieland-Miescher ketone **20**, which will be discussed in chapter **2.3**. For stage 2, we envisioned that **19** could be prepared

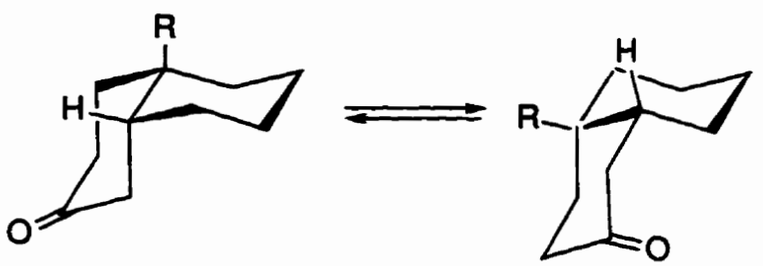
Scheme 3: Retrosynthetic Analysis of Thelepogine



from **20** via an organocopper-induced *syn* -1,4-methylation[5] with the subsequent trapping of the intermediate enolate as the silyl enol ether **19**. Michael addition of **19** to 2-acetamidoacrylate and olefination of C-6 should furnish **17**. Thermodynamically controlled amidomercuration[6] of **17**, induced by mercury(II) trifluoroacetate, followed by $NaBH_4$ reduction should then afford the desired tricyclic intermediate **16**, in which we expected the ester functionality to prefer the β-orientation as shown.

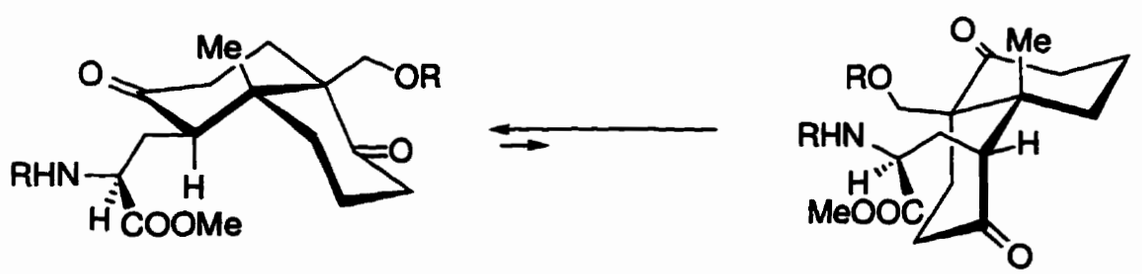
cis-Decalins are known to have two interconverting chair-chair conformations; a steroidal conformation and a non steroidal conformation (see scheme 4).[7] This property can be elegantly used for the stereochemical requirements for the synthesis of thelepogine. The addition of 2-acetamido-acrylate to **19** can give two stereoisomers at C-5, **18** and **21**, and four possible

Scheme 4: Low Energy Conformations of *cis*-Decalins



steroidal conformation non steroidal conformation

Scheme 5: Low Energy Conformations of (**18**) and (**21**)

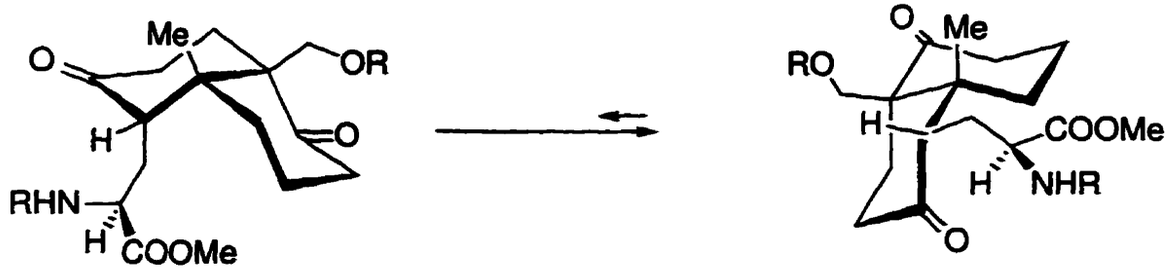


Δ Hf: -226.19 kcal/mol

18a

Δ Hf: -224.62 kcal/mol

18b



Δ Hf: -222.95 kcal/mol

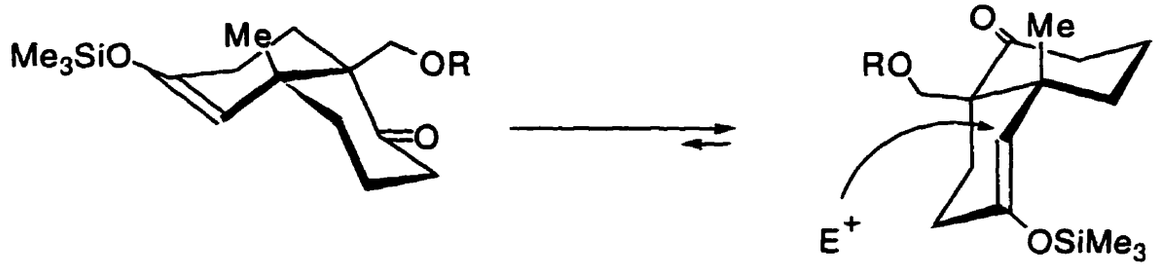
21a

Δ Hf: -228.16 kcal/mol

21b

chair-chair conformations respectively. Semiempirical calculations[#] revealed that the undesired **21** is the most stable product in the non steroidal conformation **21b** by 1.97kcal/mol, and equilibration of **18** has to be prevented. The non steroidal conformation of the silyl enol ether **19b** is 2.02kcal/mol more

Scheme 6: Low Energy Conformations of (19)



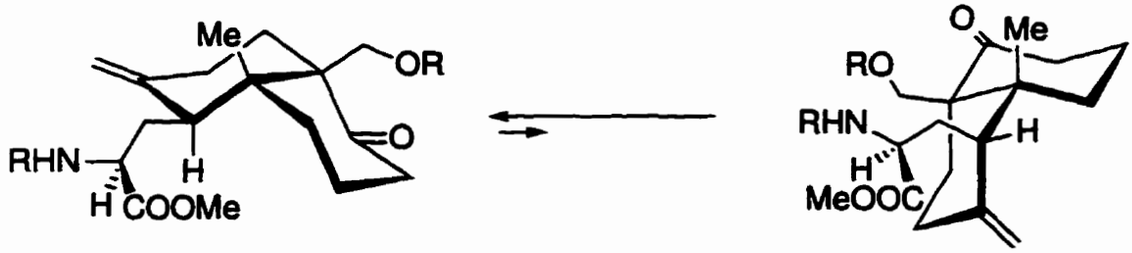
19a

19b

stable than the steroidal conformation of **19a**. In the preferred conformation **19b**, the α-face is effectively blocked by ring B, and an axial attack of an electrophile should occur from the β-face preferentially, furnishing **18** under kinetically controlled reaction conditions, which then might be converted to the exo-methylene derivative **17**.

[#] For simplicity, semiempirical calculations were conducted with OMe as -OR and NH_2 as NHR.

Scheme 7: Low Energy Conformations of (17)



Δ Hf: -176.44 kcal/mol

17a

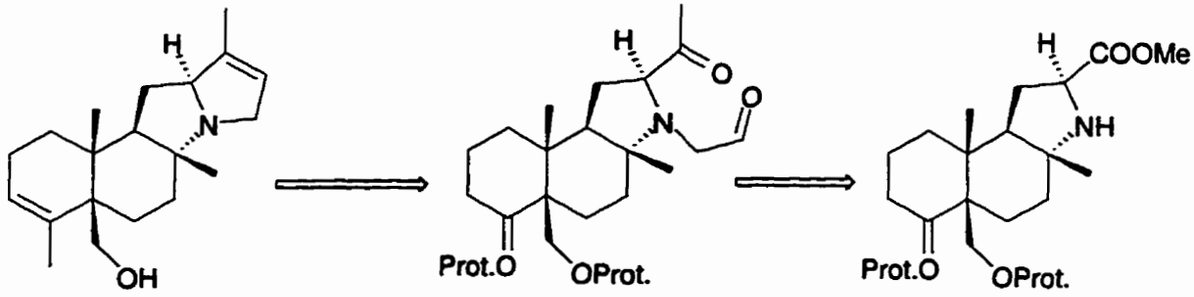
Δ Hf: -171.15 kcal/mol

17b

On the other hand, the mercury induced ring closure requires **17** to be in the steroidal conformation **17a.** In fact, the amino acid side chain at C-5 should effectively lock **17** in the required conformation **17a** as determined by semi-empirical calculations (see scheme 7).

In stage 3, we envisioned the attachment of ring-D by means of an intramolecular McMurry coupling of intermediate **22**. Functional group manipulation at C-1 and deprotection of the angular hydroxymethyl group would complete the synthesis of thelepogine.

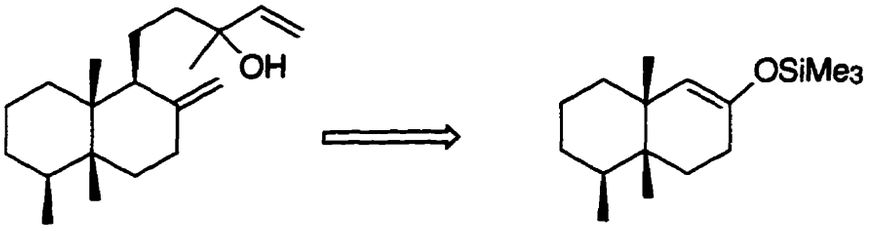
Scheme 8: Retrosynthetic Analysis of Stage 3



11 **22** **16**

It should be noted that our approach to thelepogine in which the introduction of the nitrogen and construction of the heterocyclic system occur after making the A/B *cis*-decalin unit is utilitarian, i.e. intermediates such as **17**, **19** and **20**, or the methodology worked out for their preparation, could be used for the synthesis of other natural products. This is a matter to which we will return, but can be illustrated here with nakamurol A **23**,[8] a terpenoid which has been recently isolated from the marine sponge *Agelas nakamurai* Hoshino and is currently being tested for pharmalogical properties.

Scheme 9: Retrosynthetic Analysis of Nakamurol A (**23**)



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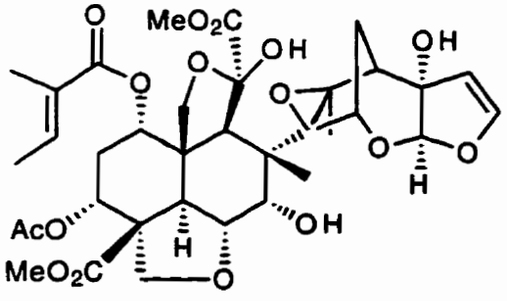
2.3. Step 1: Synthesis of Angular Hydroxymethyl Protected Wieland-Miescher Ketone Derivatives

2.3.1. Introduction

Numerous terpenoidal natural products have been described, in which a decalin ring system carries an oxygenated angular methyl group, and several of them exhibit remarkable biological activities eg. the insect antifeedants azadirachtin **24**[9] and clerodin **25**,[10] perrottetianal A **26**,[11] the farnesyl-transferase inhibitors andrastine A **27a** and B **27b**,[12] pisiferic acid **28**,[13] and the anti-HIV agent tripterifordin **29**.[14]



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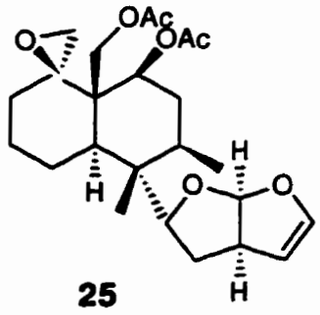

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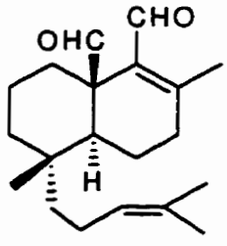

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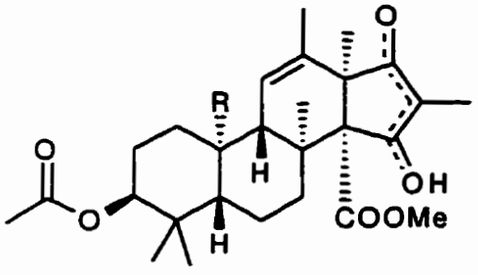
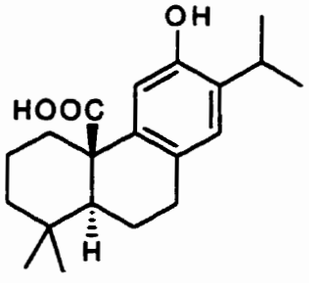


27a: R=CHO, **27b**: R=CH_2OH



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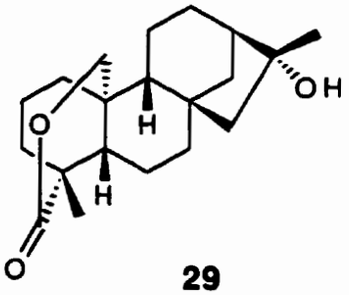
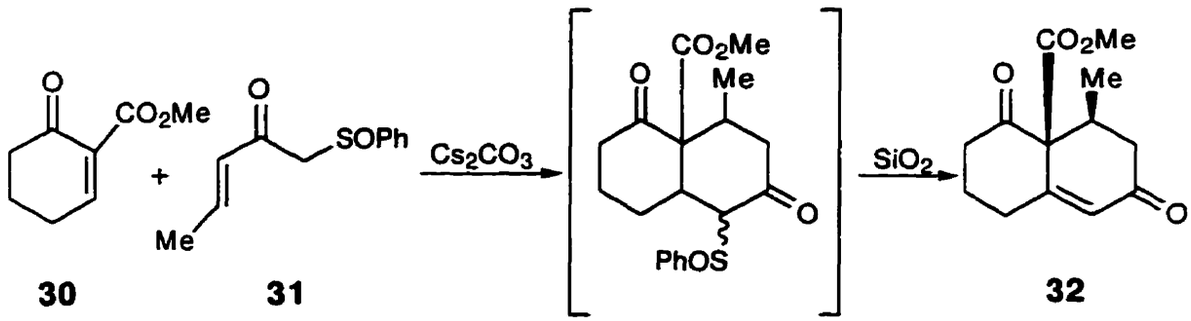


29

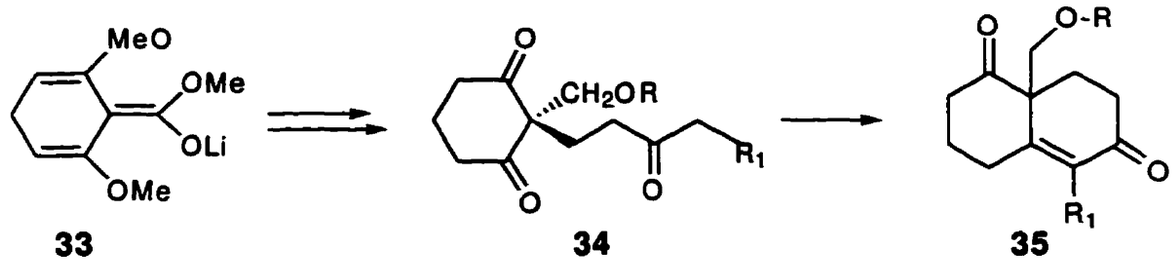
As a consequence, considerable effort has been spent to synthesize such natural products, or simple angular functionalized methyl decalin analogs of them.[15]

For this purpose, Wieland-Miescher ketone derivatives bearing an angular hydroxymethyl group (or a masked hydroxyl group) are particularly valuable intermediates, which may offer a facile entry into numerous angular functionalised terpenoids. With this in mind, Deslongchamps *et al.*[16] synthesized racemic **32** via cyclisation of 2-carbomethoxy-2-cyclohexenone **30** with 1-phenylsulfinyl-3-penten-2-one **31** in good yield (70%).



30 **31** **32**

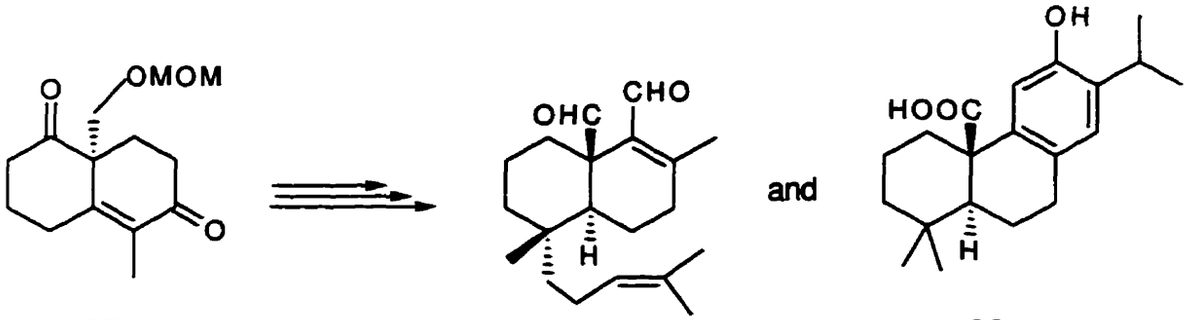
In an another approach, Uda *et al.*[17] and Mander *et al.*[18] independently synthesized **35b**, **35c** and **35a** respectively, via alkylation of a dihydrodimethoxybenzene derivative **33** followed by a Robinson annulation. Mander *et al.* chose the MOM protecting group for the hydroxymethyl chain in **34a** and **34c**. Unfortunately, the Robinson annulation proved to be very problematic, and



33 **34** **35**

a: R=MOM, R_1=H; **b:** R=MEM, R_1=H; **c:** R=MOM, R_1=Me

only piperidinium benzoate as a catalyst induced the ring closure in **34a**, albeit in moderate yield (43%). In the case of **34c**, all attempts by Mander *et al.* to cyclise it to **35c** failed. Uda *et al.* used the MEM protecting group for the hydroxymethyl chain, and L-proline induced ring closure of **34b** yielded **35b** (57%, ee=75%). They were successful with intermediate **34c** as well, and L-phenylalanine induced ring closure gave **35c** (88%, ee=85%), which was further used for the total synthesis of (+)-perrottetianal A **26**, (+)-pisiferic acid **28** and its derivatives.

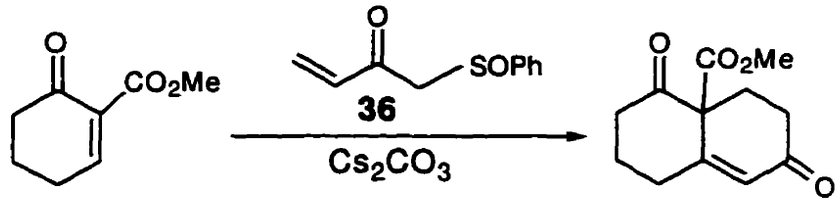


35c **26** **28**

Although, these two angular hydroxymethyl protected Wieland-Miescher derivatives **35a** and **35b**, prepared by Uda *et al.*,[17] and Mander *et al.*,[18] were suitable for our purposes, the difficulties in the final Robinson annulation and the potential use of such intermediates encouraged us to investigate alternative strategies for their preparation.

2.3.2. Attempted Synthesis of Angular Hydroxymethyl Protected Wieland-Miescher Ketone Derivatives by Deslongchamps' route

Deslongchamps *et al.*'s approach appealed to us since the required precursor, 1-phenylsulfoxyl-3-buten-2-one **36**, is a known compound and despite its tendency to polymerize, it has been successfully used for 1,4-addition reactions, e.g. condensation with 2-methyl-1,3-cyclopentanedione.[19] Further, in case of a successful construction of **37**, an enantioselective approach could be tested by using a chiral auxiliary on the ester functionality of 2-carbomethoxy-2-cyclohexen-1-one **30** and (or) by using chiral 1-phenylsulfinyl-3-buten-2-one **36**.



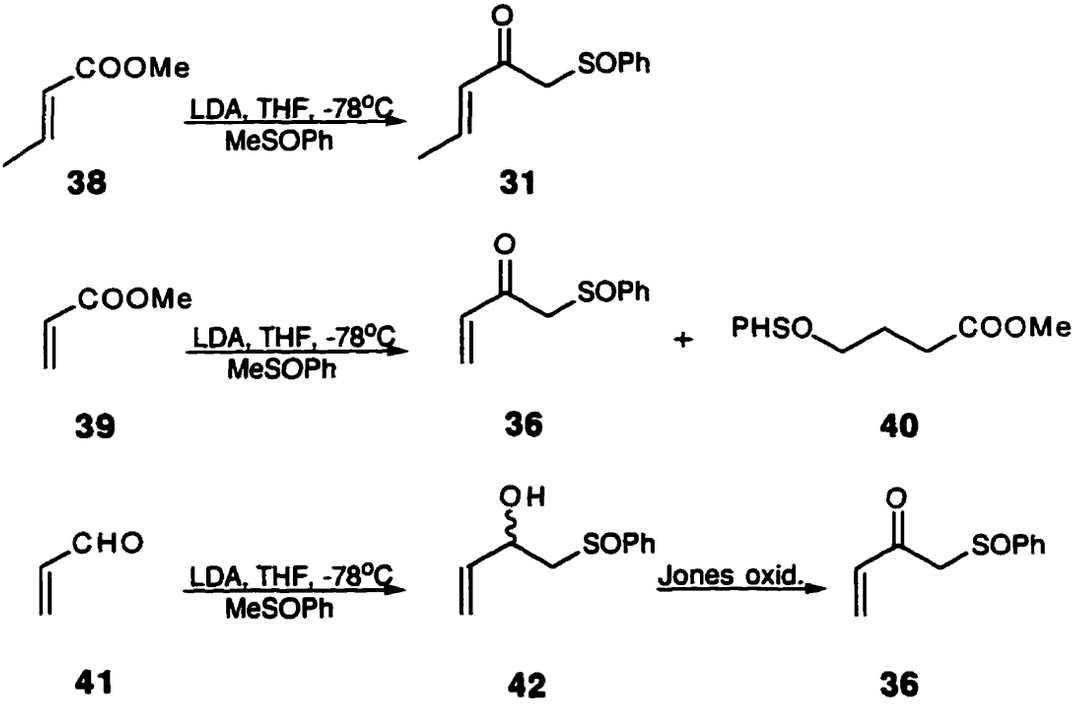
30 **37**

Unfortunately, the literature procedure for the synthesis of 1-phenylsulfinyl-3-buten-2-one[19] is tedious, and the required starting material, 2, 3, 4-trichloro-1-butene, is no longer commercially available, or readily prepared. So we decided to try a different approach.

Deslongchamps synthesized 1-phenylsulfinyl-3-penten-2-one **31** by a 1,2-addition of methyl phenyl sulfoxide to methyl crotonate **38**.[16] This very direct route was very appealing to us, since chiral methyl phenyl sulfoxides have been shown to be a very useful auxiliary in the synthesis of optically active compounds,[20] and they are commercially available, or can be made according to an Organic Synthesis procedure.[21] Thus, methyl phenyl sulfoxide is an ideal

starting material for an enantioselective synthesis of **36**. In testing the feasability of synthesizing **36** according to this approach, we first used racemic methyl phenyl sulfoxide.

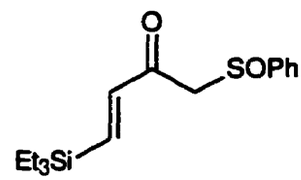
Unfortunately, a direct synthesis of **36** via 1,2-addition of methyl phenyl sulfoxide to methyl acrylate **39** gave an inseparable mixture of **36** and the 1,4-addition product **40** in a ratio of about 1:1 according to ^{1}H-NMR. We therefore decided to use a two-step approach, starting from acrolein. The 1,2-addition of methyl phenyl sulfoxide to acrolein **41** yielded smoothly **42** as a diastereomeric mixture. Oxidation of **42** with Jones' reagent then gave **36** in an overall yield of 52%.



The known 2-carbomethoxy-2-cyclohexen-1-one **30** was made from cyclohexanone via carbomethoxylation and selenoxide β-elimination according to a literature procedure,[22] with slight modification.

With both of our precursors in hand, we tried the cyclisation reaction according to Deslongchamps' procedure (Cs_2CO_3 (0.5 eq.), CH_2Cl_2, rt). However, the Nazarov reagent **36**, rapidly polymerized when Cs_2CO_3 was added to a solution of **30** in CH_2Cl_2. Changing the reaction conditions, or the base did not improve the situation. The lability of **36** was also clearly seen when it was stored at -20°C, where it polymerized within 2 days. Thus, the vinylic system in **36** seems to be too unstable, compared to the crotyl group in **31**, for a successful cyclisation.

In order to increase the stability of the vinylic system in **36** towards polymerisation, we decided to introduce an easily removable functionality at the 4-position of **36**. We thought, that a triethylsilyl or trimethylsilyl protecting group would be ideal candidates, as they should increase the stability of **36**, while the silyl protecting group could subsequently be cleaved during an acidic work up. Thus, we decided to synthesize **43** and **44**.



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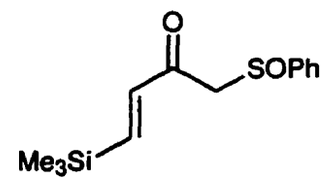
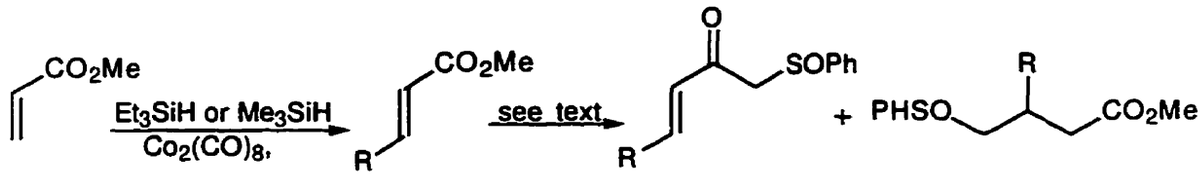


44

Methyl acrylate **39** was reacted with triethylsilane in presence of a catalytic amount of $Co_2(CO)_8$ according to a general literature procedure,[23] yielding **45** in 81%. Deprotonation of methyl phenyl sulfoxide with LDA, and addition of **45** gave the 1,2-addition product **43** in quantitative yield. Similarly, **44** was synthesized from methyl acrylate **39**. However in this case, the 1,2-addition reaction of methyl phenyl sulfoxide to **46**, gave only ca. 11% of the 1,2-addition

product **44**, as well as ca. 20% of the 1,4-addition product **47**, and a complex mixture, in which the 1,4-addition product of diisopropyl amine to **46** appeared to be the main component according to ^{1}H-NMR. Changing the base from diisopropyl amine to hexamethyldisilazane improved the yield greatly, and the 1,2-addition product **44** was isolated in 60% yield, together with 12% of the 1,4-addition product **47**.

However, and most disappointingly, when **43** and **44** were reacted with 2-carbomethoxy-2-cyclohexen-1-one **30** and Cs_2CO_3 (0.5 eq.) in CH_2Cl_2, they

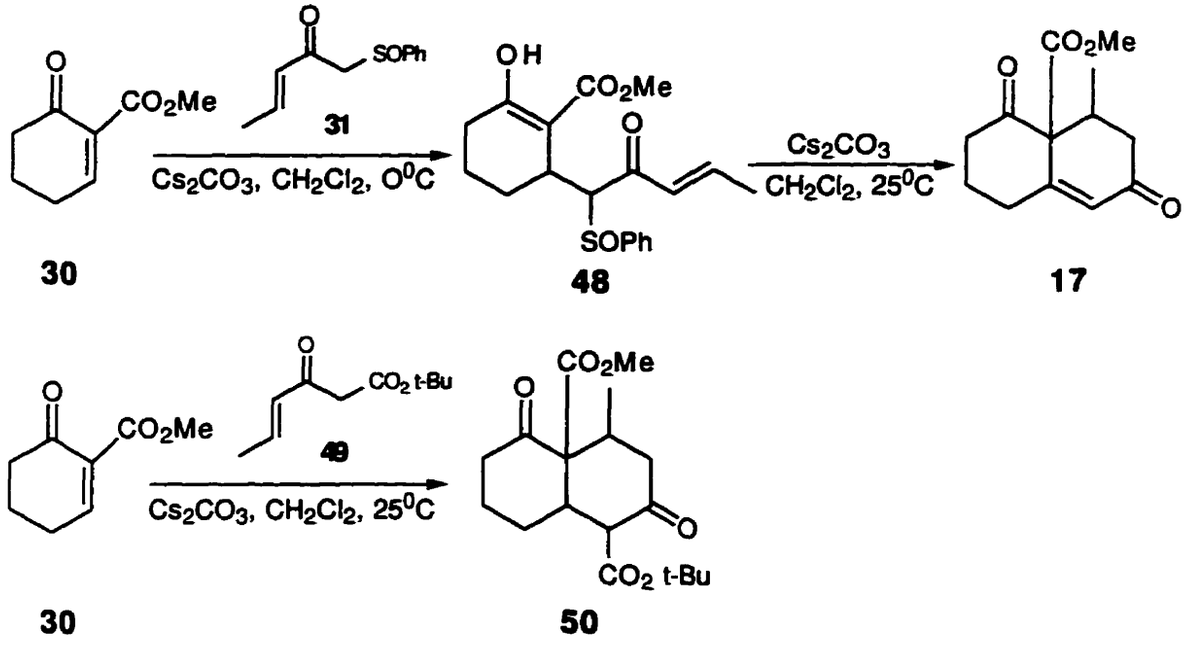


39 **45/46** **43/44** **47**

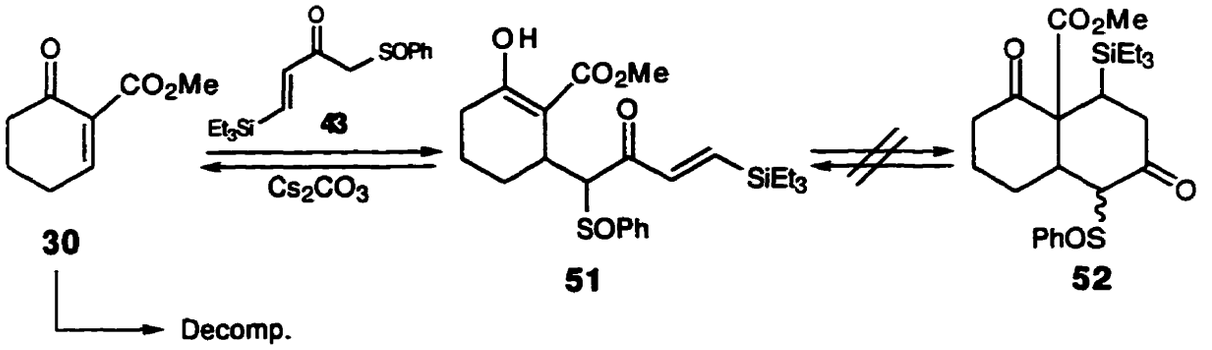
43, **45** : R= $SiEt_3$
44, **46** and **47** : R= $SiMe_3$

were recovered in near quantitative yields, together with a complex mixture from decomposed **30**.

Mechanistically, the cycloaddition reaction can occur by means of a double Michael addition reaction or via a Diels-Alder mechanism. Deslongchamps *et al.*[16] noted, that in the case of the analogous Nazarov reagent **31**, the mechanism is most likely a double Michael addition reaction, as they were able to isolate the intermediate **48** after the first Michael addition reaction of **30** with **31**. However, when the cycloaddition reaction was conducted with **49**, the Diels-Alder mechanism was said to be favoured.



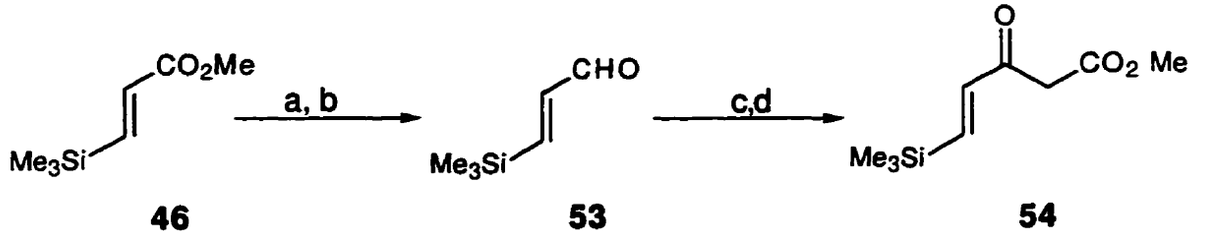
Somewhat surprised by our results, and to evaluate the reason for the failed cycloaddition in our system, we undertook a ^{1}H-NMR study of the reaction of **30** with **43** (3eq.) and Cs_2CO_3 (0.5 eq.) in $CDCl_3$. It was observed, that **30** slowly reacted with **43** and after 5h, no starting material was present as indicated by the disappearance of the diastereotopic methylene protons in **43**, instead several doublets were seen between 5.6-5.9ppm. When the reaction was continued over one day, those doublets slowly disappeared, and the starting material **43** was seen again as well as decomposition products from **30**. This result indicated that the first Michael addition does occur, yielding intermediate **51**, but the latter does not undergo the second Michael addition. Instead, **30** slowly decomposes, and the reversibility of the Michael addition drives the reaction to the left. The Michael addition mechanism for Nazarov analog sulfoxides, as noted by Deslongchamps *et al.*, seemed to be valid for our system too, and we thought that a change to a Diels-Alder mechanism, by using an ester analog instead of the sulfoxides **43** and **44**, might succeed. In order to test this



hypothesis, we synthesized compound **54** as follows.

The ester **46** was reduced with DIBAL-H, and the alcohol product was oxidized with Collins' reagent, yielding **53** in an overall yield of 48%. A 1,2-addition of methyl acetate in THF at -78°C, and subsequent oxidation then gave **54** in 71% yield.

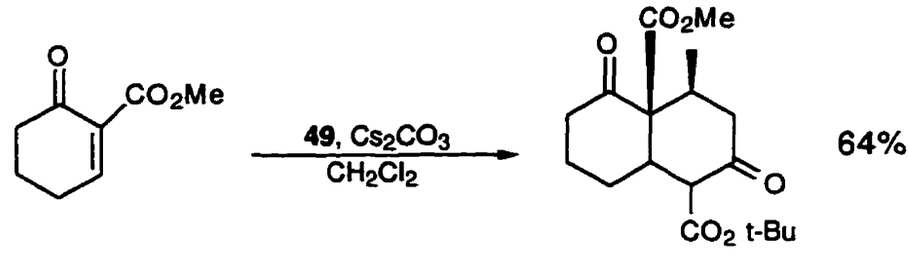
However, when the cyclisation reaction was tried on **30** with Cs_2CO_3 in several solvent systems (CH_2Cl_2, DMF, acetonitrile), we only recovered **54** as well as a complex mixture of decomposed **30**. The reason for the failure of the



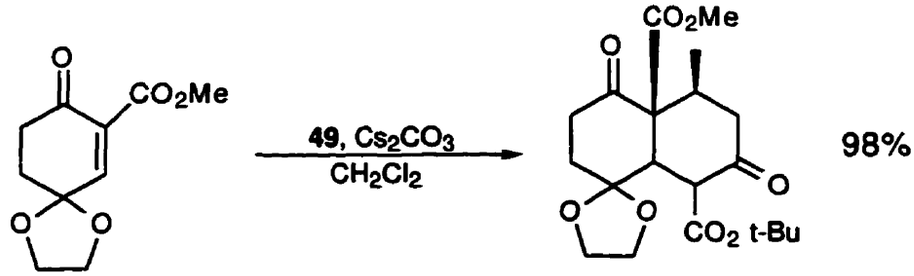
Reaction conditions: a) DIBAL-H (2.2eq.), CH_2Cl_2, -78°C; b) Collins' reagent (10eq.), CH_2Cl_2, 0°C; c) Methyl acetate (1.3eq.), HMDS (1.3eq.), Bu-Li (1.3eq.), THF, -78°C; d) Jones' reagent (1.3eq.), acetone, 0°C.

cycloaddition reaction is not obvious. Steric hindrance of the trimethyl silyl group might be a factor and the reaction might need somewhat elevated conditions. However, the lability of **30** prevents the use of higher temperature or longer reaction time.

Although **30** has been used successfully by several research groups, the lability of **30** is known. Liu *et al.*[24] noted that **30** is a rather unstable compound which enolizes and deteriorates readily. In our hands, this was also clearly seen when **30** was stirred alone in CH_2Cl_2 with Cs_2CO_3 (0.5eq.) at room temperature, whereby **30** decomposed within 2h. The stability of **30** can be dramatically improved according to Liu *et al.* by using γ-carbon geminally substituted derivatives, whereby the facile enolization of this centre is blocked. This was also noted by Deslongchamps *et al.*,[16] who interpreted the marked improvement of the yield of **56** with **49** (compared to **30**) as the result of the increased stability of



30 **56**

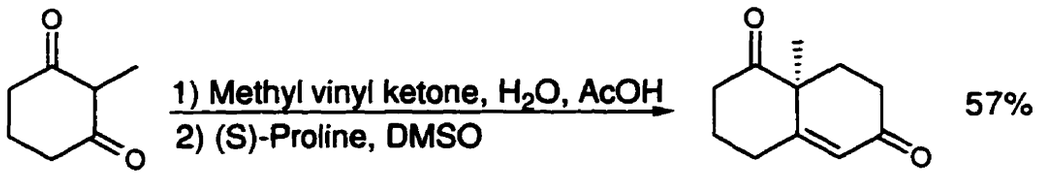


55 **57**

55. Although a reasonable second generation approach for our needs would be to block the γ-carbon (e.g. using a γ-dithiolane analog of **55** and desulfurize at a later stage), which should increase the stability of the dienophile and therefore allow us to run the reaction at elevated temperature, but we did not explore this route, as we had found an alternative approach, which was successful, and convenient.

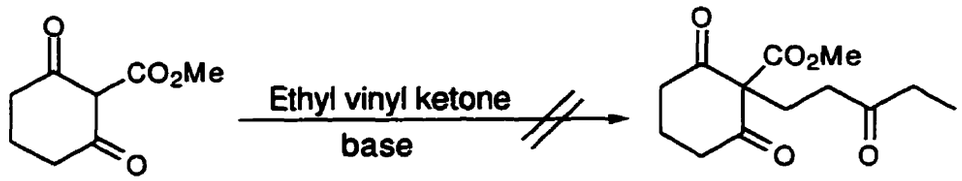
2.3.3. Synthesis of Angular Hydroxymethyl Wieland-Miescher Ketones via Degradation of an Angular Allyl Moiety

The Wieland-Miescher ketone **59** is a well known compound, and high enantioselectivity has been reported in its preparation by the Robinson annulation of 2-methyl-1,3-cyclohexandione **58** with methyl vinyl ketone using (S)-proline as catalyst.[25]



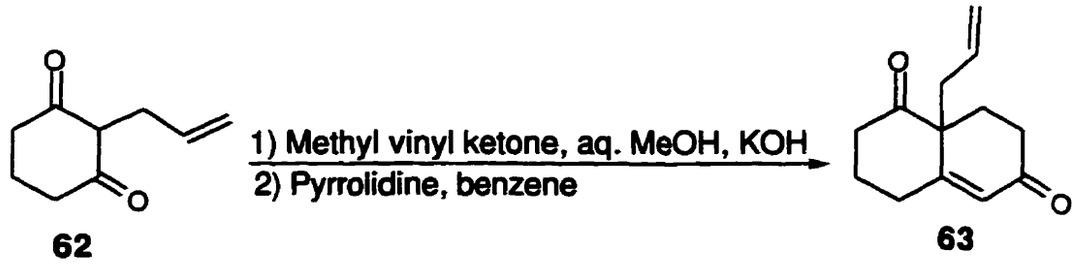
58 **59**

In order to construct angular methyl functionalised Wieland-Miescher ketones, it is tempting to use an alkoxycarbonyl cyclohexandione derivative (cf. **60**) for the Robinson annulation. Mander *et al.* tried this very direct route, but failed to obtain intermediate **61** under various conditions.[18] However, 2-



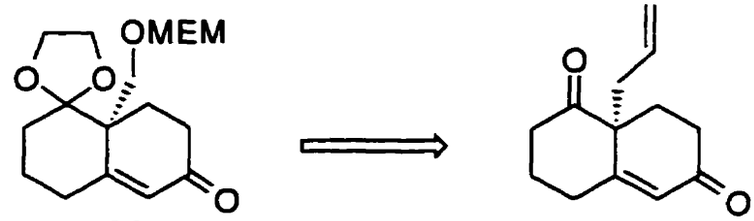
60 **61**

allylcyclohexa-1,3-dione **62** is known to react smoothly with methyl vinyl ketone, yielding the racemic Wieland-Miescher analog with an angular allyl moiety **63** after pyrrolidine induced Robinson annulation.[26] We decided to try to prepare **63** enantioselectively by means of an asymmetric Robinson annulation. Degradation



62 **63**

of the allyl moiety in **63** to a hydroxymethyl group, and protection of the hydroxy- and ketone group should then yield our target molecule **64**.

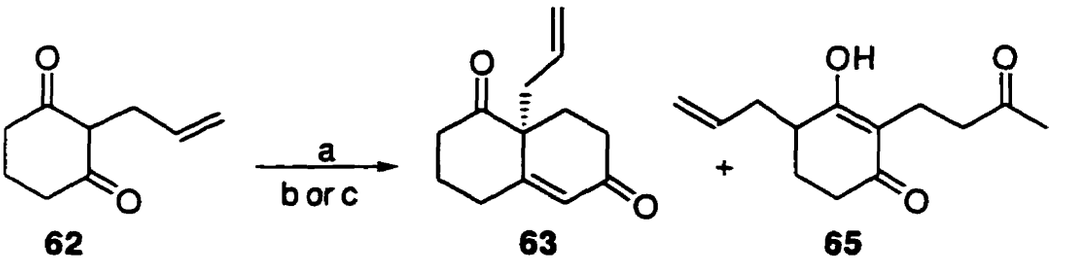


64 **63**

2.3.3.1. Synthesis of (S)-3,4,8,8a-Tetrahydro-8a-(((2-methoxy-ethoxy)methoxy)methyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (64).[27]

We started our approach from the readily available 2-allylcyclohexane-1,3-dione **62**, which was synthesized from 1,3-cyclohexanedione according to a literature procedure.[28] Initial attempts to reproduce the synthesis of racemic **63**, via the intermediate Michael addition product and subsequent Robinson annulation with pyrrolidine as base,[26b] yielded a two component mixture, which was separated by column chromatography to give 4-allyl-2-(3-oxobutyl)-1,3-cyclo-hexanedione **65** (52%), as well as the desired racemic **63** (18%). Further investigations revealed that the undesired byproduct **65** was mainly produced after the first Michael addition when all 2-allyl-1,3-cyclohexanedione had been

consumed. In the cited paper[26b] only a rather vague description of the amount of NaOH is given (one pellet of NaOH), which was approximated to be roughly 0.05 equivalents. We found that when the amount of NaOH was decreased to 0.02 equivalents, and the reaction was quenched as soon as no starting material could be detected by GC, a near quantitative yield of the intermediate Michael product was obtained. After pyrrolidine-induced Robinson annulation this gave **63** in 70% overall yield, together with minor amounts of **65** (10%).



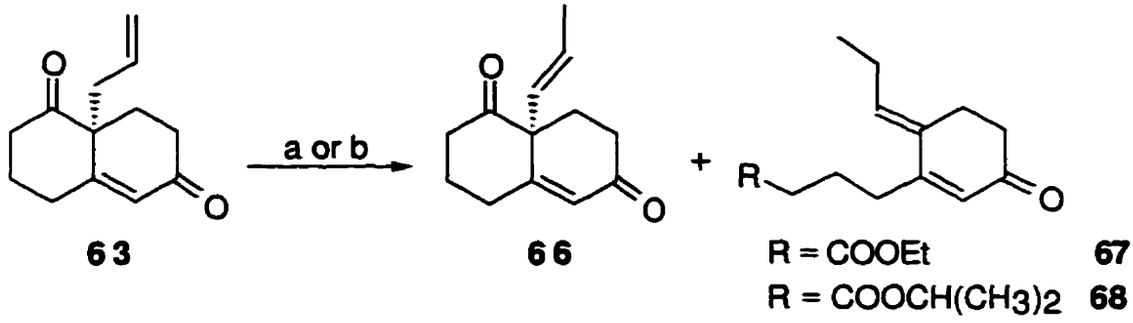
62 **63** **65**

Reaction conditions: a) Methyl vinyl ketone, 80% aq. MeOH, NaOH (cat.), reflux; b) L-Proline, DMSO, rt; c) Pyrrolidine, benzene, reflux.

For the asymmetric synthesis of **63**, we treated the crude intermediate Michael adduct directly with L-proline in DMSO at room temperature, obtaining **63** as a yellow oil (ee=80%),# which was homogeneous by ^{1}H and ^{13}C-NMR. When it was stored at 0^{o} for several days, only a fraction of the oil crystallized, and this turned out to be the pure racemic form of **63**. By diluting the scalemic mixture with hexanes/EtOH 3:1 and crystallizing out the racemic form of **63**, a convenient method was found to obtain nearly enantiomerically pure **63** (ee>99%).#

The enantiomeric excess of **63** was determined by means of a 1:1 molar mixture of the chiral shift reagent europium tris(d,d-dicampholylmethanate) and **63** in $CDCl_3$, which induced a $\Delta\delta_H$ of 0.15ppm for the H-5's of the two antipodes.

Compound **63** was then treated with $RhCl_3$ in ethanol giving **66** and **67** as a 1:1 mixture. Surprisingly, in other solvent systems (benzene, butyl ether and isopropanol), we did not detect any product after several hours at reflux. The catalytic effect of an acid in rearrangements with $RhCl_3$ is known[29] and indeed adding conc. HCl as a cocatalyst to a solution of **63** in isopropanol gave **66** in 70% yield as well as 5% of **68** .



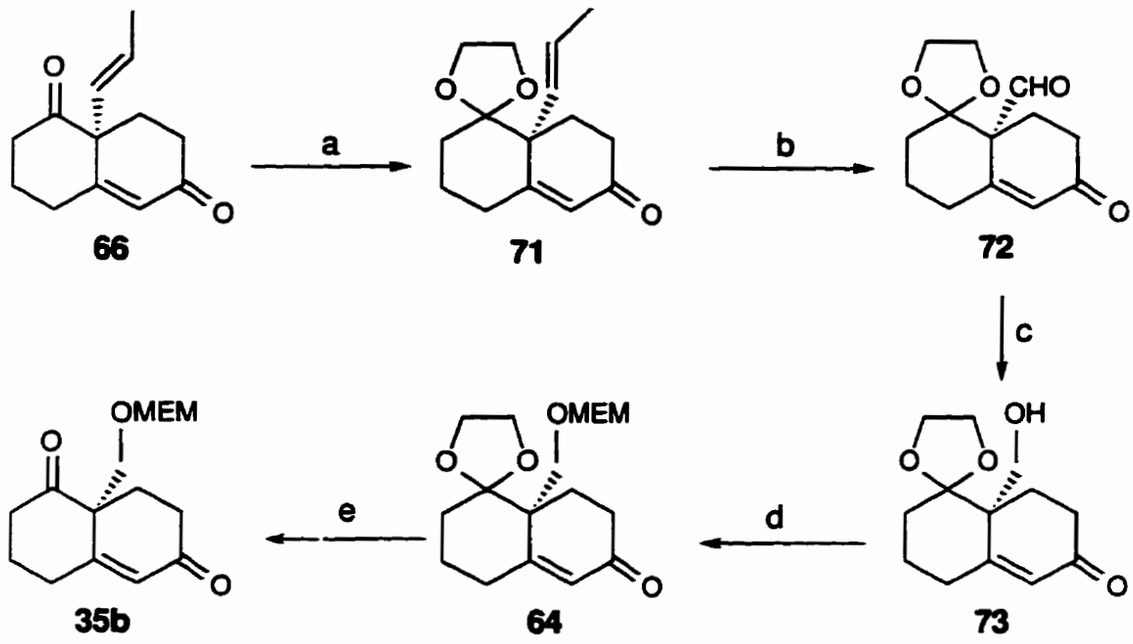
63 **66**

R = COOEt **67**

R = $COOCH(CH_3)_2$ **68**

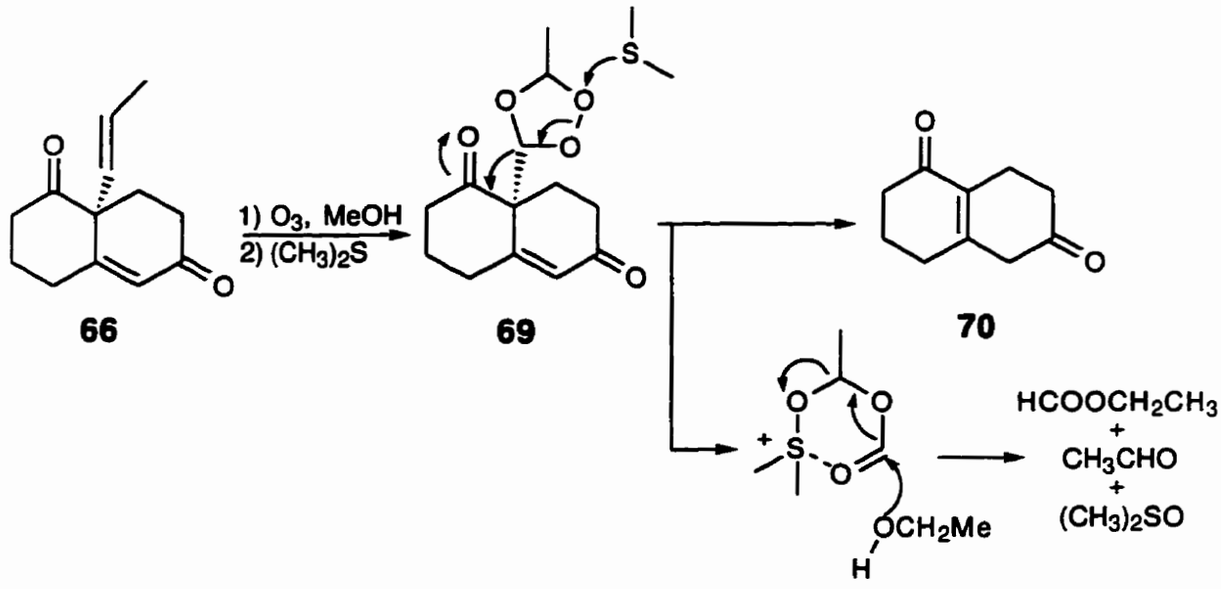
Reaction conditions: a) $RhCl_3$, EtOH, reflux; b) $RhCl_3$, 2-propanol, conc. HCl, reflux.

Compound **66** was then subjected to ozonolysis in ethanol at -78°C. But to our surprise, after work up we isolated only the known product **70**.[30] We suspected that the strong electron withdrawing environment next to the quaternary center affected the mechanism of the methyl sulfide induced reduction of the possible intermediate ozonide **69** (see scheme 10, p. 27), and that masking the ketone should change the outcome. Indeed, after protection of the ketone in **66** as a dioxolane **71** and ozonolysis, the aldehyde **72** was obtained quantitatively. Chemoselective reduction of **72** with $NaBH_4$[31] and protection of the hydroxy group in **73**, yielded the target molecule **64**. The absolute configuration of **64** was established by converting **64** into the known[17] compound **35b** by hydrolysis of the dioxolane with camphorsulfonic acid in acetone, yielding **35b** with the absolute stereochemistry as depicted.



Reaction conditions: a) 2-Ethyl-2-methyl-1,3-dioxolane, TsOH, ethylene glycol, rt; b) O_3, EtOH, -78°C, Me_2S; c) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), -78°C; d) MEMCl, diisopropylethylamine, CH_2Cl_2, reflux; e) Camphorsulfonic acid, acetone, reflux.

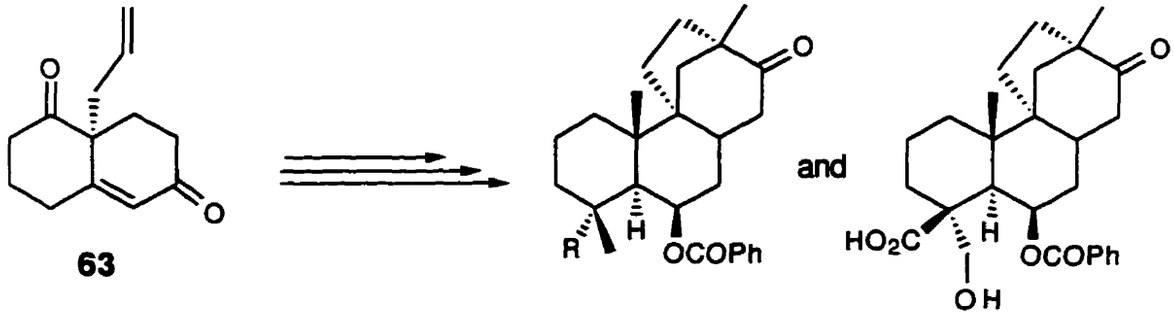
Scheme 10: A Suggested Mechanism for the Reduction of Ozonide (**69**)



Thus, we had developed a convenient synthetic route for an enantiomerically pure angular allyl Wieland-Miescher ketone in 53% yield, and an angular hydroxymethyl Wieland-Miescher ketone derivative in 7 steps and in an overall yield of 25% from 2-allylcyclohexane-1,3-dione **62**.

During the preparation of a manuscript, describing our work on the enantioselective synthesis of angular hydroxymethyl Wieland-Miescher ketones,[27] Ziegler *et al.*[32a] published a paper in which they used the racemic angular allyl Wieland-Miescher ketone **63** for the total synthesis of (±)-scopadulciol **75**, (±)-scopadulcic acid A **76** and B **74**. The latter proved to be a powerful *in vitro* inhibitor of H^+, K^+-ATPase,[32b] an anitiviral agent against Herpes simplex virus type 1 (HSV-1),[32c] and it also displays antitumor activity in human cells.[32d]

Scheme 11: Ziegler *et al.*'s Route to (±)-Scopadulciol (**75**), (±)-Scopadulcic acid A (**76**) and B (**74**).



74: R=CO_2H
75: R=CH_2CO_2H

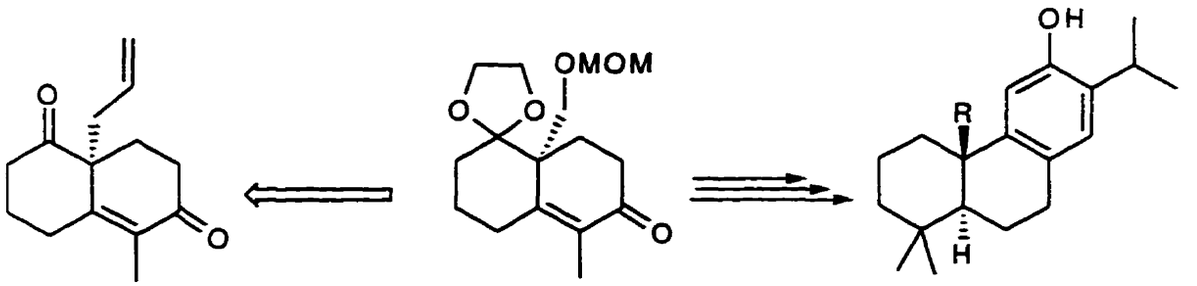
76

Ziegler *et al.* reported in the same paper preliminary studies on the asymmetric synthesis of **63** (ee=76%), using similar reaction conditions to ours (asymmetric Robinson annulation with L-proline as the base). The absolute configuration of their product **63**, was deduced from CD spectra, and is in agreement with the result obtained by us.

2.3.3.2 Synthesis of 3,4,8,8a-Tetrahydro-8a-allyl-1-((methoxy-methyl)oxy)-1,6-(2H,7H)-naphthalenedione (35c)

Encouraged by the successful degradation of the angular allyl Wieland-Miescher ketone **63**, we thought we might be able to apply the same methodology to the synthesis of **35c**, an intermediate, which has been used for the total synthesis of (+)-perrottetianal A **26**, (+)-pisiferol **79** and (+)-pisiferic acid **28** by Uda *et al.*.[11,15f] The (+)-pisiferic derivatives are particularly worthwhile target molecules, since they show a very broad range of biological activities (e.g.

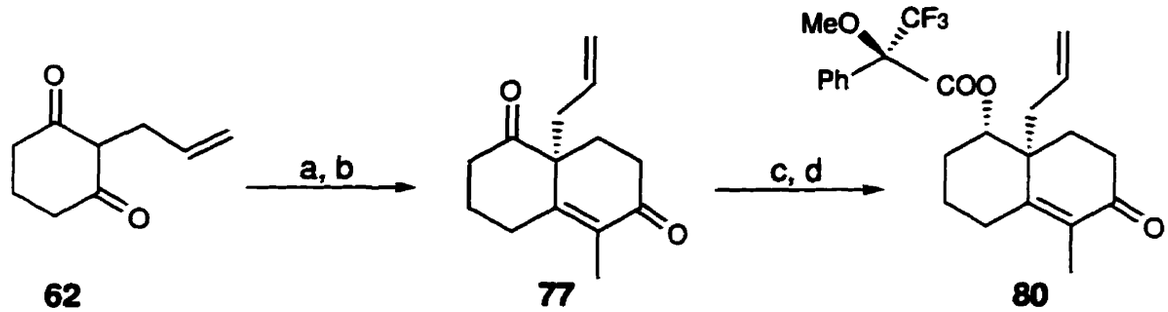
Scheme 12: Uda *et al.*'s Synthesis of (+)-Pisiferol (**79**) and (+)-Pisiferic acid (**28**)



77 **78** **79**:R=CH_2OH **28**:R=COOH

antifungal and antibiotic activities), and much research has been conducted towards the synthesis of these molecules.[33] The initial Michael adduct was obtained quantitatively from 2-allylcyclohexane-1,3-dione[28b] **62** and ethyl vinyl ketone, and was then subjected to a variety of Robinson annulation conditions. L-Phenylalanine in acetonitrile proved to be the best of these, and yielded **77** in 74% (see table 1). In order to determine the enantiomeric purity of **77**, we reduced the ketone chemoselectively with $NaBH_4$ in MeOH at -78°C. The crude alcohol was then esterified with the Mosher acid chloride[34], yielding the Mosher

ester **80** in 96% overall yield. ^{1}H-NMR and ^{19}F-NMR gave an enantiomeric excess of 75% for the chiral Mosher ester **80**. Unfortunately, the achiral as well as the chiral angular allyl Wieland-Miescher ketone **77** were oils, and a further

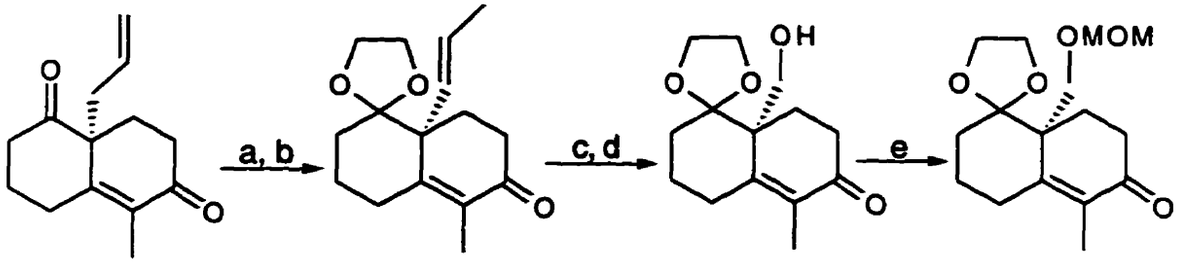


Reaction conditions: a) Ethyl vinyl ketone, 80% aq. MeOH, NaOH (cat.), reflux; b) L-Phenylalanine (1eq.), $HClO_4$ 70% (0.5eq.) acetonitrile, reflux, 24h.; c) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), -78°C; d) (R)-MTPA-Cl, DMAP, pyridine, 4d.

enantiomeric enrichment via crystallisation, analogous to that performed on **63** was not possible. With the scalemic angular allyl Wieland-Miescher ketone **77** in hand, we synthesized **81** by the protocol developed for **71**, which yielded **81** in excellent yield (86% from **77**). However, selective ozonolysis of the ethylidene group in **81** proved to be difficult, and a complex mixture was obtained in low yield, when the ozonolysis was conducted until no starting material was seen by TLC. Adding pyridine, performing the ozonolysis at lower temperature (-110°C), or using another solvent (CH_2Cl_2) for the ozonolysis did not improve the selectivity. However, careful ozonolysis of **81** at -78°C in EtOH, until ca.50% of the starting material had been consumed, as judged by TLC, and immediate reduction of the mixture with $NaBH_4$, yielded **82**, albeit in low yield (21%), as well as 25% of the starting material **81**. Protection of the angular hydroxymethyl group in **82** as the MOM-ether gave **78**, with an optical rotation of $[\alpha]^{25}_{D}$ +110° (c0.2, $CHCl_3$), [lit.[17] +127°] and an absolute configuration as depicted.

Table 1: Robinson Annulation of (**62**)

Reagents/Conditions	**77** (%)	$[\alpha]^{25}_D$	ee
L-Proline (1eq.), DMSO, 60°C, 2d.	20	-	N/A
L-Proline (1eq.), acetonitrile, reflux, 2d	31	-	N/A
D-Valine (1eq.), acetonitrile, reflux, 36h	49	-62.4°	53%
L-Phenylalanine (1eq.), $HClO_4$ 70% (0.5eq.) acetonitrile, reflux, 24h.	74	+89.0°	75%



77 **81** **82** **78**

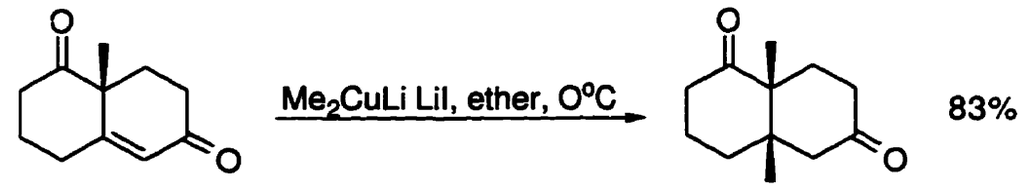
Reaction conditions: a) $RhCl_3$, 2-propanol, conc. HCl, reflux; b) 2-Ethyl-2-methyl-1,3-dioxolane, TsOH, ethylene glycol, rt; c) O_3, EtOH, -78°C; d) $NaBH_4$, MeOH/CH_2Cl_2 (1:1), -78°C; e) MOMCl, diisopropylethylamine, CH_2Cl_2, reflux;

Although Uda *et al.*'s intermediate **78** for the synthesis of (+)-perrottetianal A **26**, (+)-pisiferol **79** and (+)-pisiferic acid **28** was obtained through this route, the overall yield was only 11%, as compared to 36% in Uda *et al.*'s[17] synthesis, and we decided not to pursue our route any further.

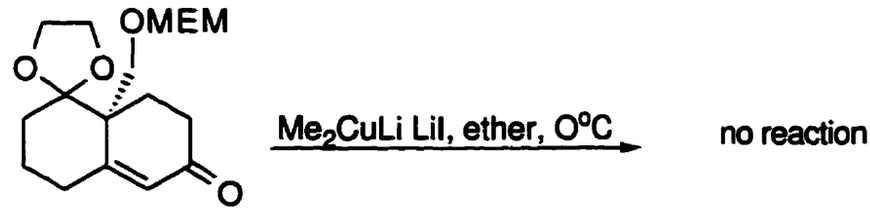
2.4. Stage 2: Synthesis of the A,B,C System of Thelepogine

2.4.1. Conjugated Addition of Lithium Dimethylcuprate to Angular Wieland-Miescher Ketones.

After we developed a synthesis of intermediate **64**, the plan was to introduce the C-4a methyl group by a conjugate addition of lithium dimethylcuprate, followed by *in situ* trapping of the enolate with trimethylsilyl chloride. However, when we tried the conjugate addition of lithium dimethylcuprate to **64**, analogous to the standard method which works nicely on the simple Wieland-Miescher ketone **59**,[35] we recovered the starting material **64** quantitatively. Even when we used rate accelerating additives such as TMSCl,[36] we only isolated the starting material. We suspected that one reason might be the



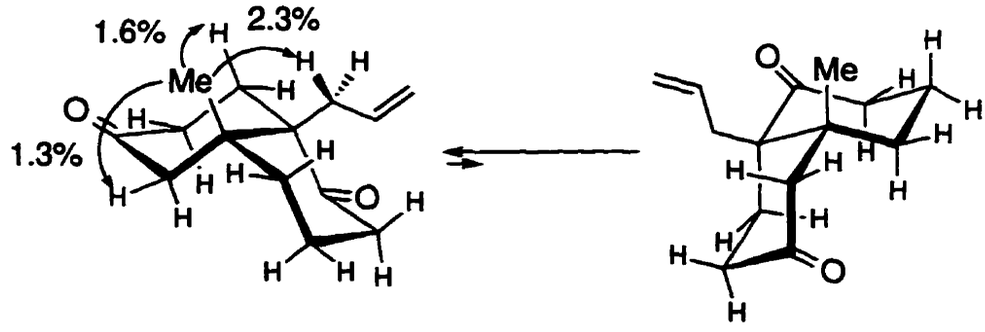
59 **83**



64

highly oxygenated environment[#] of **64**, and we decided to try the conjugate addition reaction of lithium dimethylcuprate on the angular allyl Wieland-Miescher ketone **63**. Lithium dimethylcuprate in ether (entry 1, table 2) and with TMSCl as an additive (entry 2, table 2), and lithium dimethylcuprate in THF (entry 3, table 2) did not react, and only the starting material **63** was isolated. But using lithium dimethylcuprate and TMSCl in THF at -78°C (entry 4, table 2) gave the angular allyl *cis*-decalin **87**, as well as the 1,2-addition product **88** in a ratio of 1:1 after an acidic (10% aqueous HCl) work up. The relative stereochemistry of **87** was assigned by NOE experiments, which confirmed the *cis* configuration of the C(4a) methyl relative to the C(8a) allyl group (scheme 13). As discussed on page 8, *cis*-decalins can exist in two low energy conformations. ^{1}H-NMR and ^{13}C-NMR of **87** revealed one major conformer at room temperature, which was assigned by NOE

Scheme 13: Low Energy Conformations of (87)

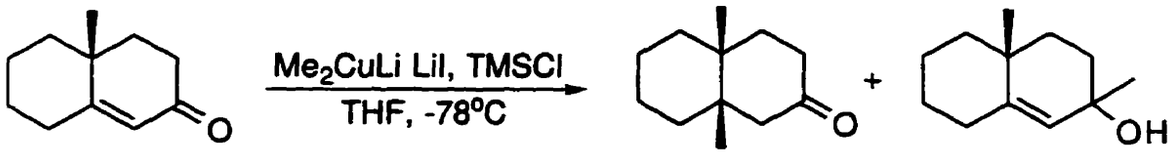


87a **87b**

[#] The inertness of the Gilman reagent towards C-1 protected dioxolane Wieland-Miescher ketones has also been observed by Smith *et al.*. Thus, 3,4,8,8a-tetrahydro-8a-methyl-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal does not react with the Gilman reagent (personal communication of R. A. Smith to MHB).

experiments to conformation **87a**. Semiempirical calculations on both conformers supported this, as conformation **87a** is 0.629kcal/mol more stable than conformation **87b**.

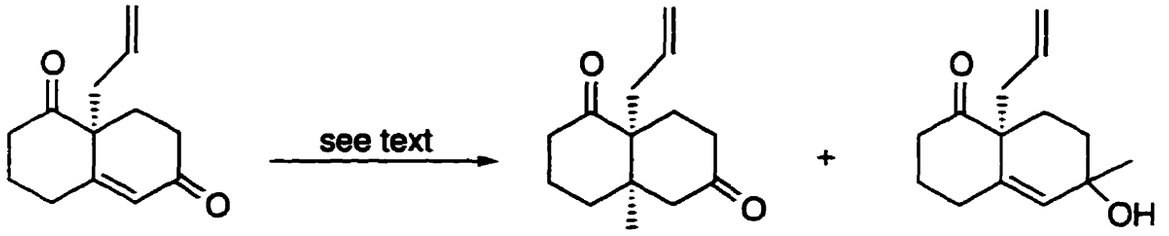
In order to improve the yield of **87**, we decided to try other organocuprates. Lithium dimethylcuprate in THF at -78°C with $BF_3{\cdot}Et_2O$ as an additive, gave the 1,2-addition product **88** as the sole product (entry 5, table 2). Higher order cuprates such as ($Li_2Me_2Cu(CN)$, $Li_2Me_2Cu(CN)$/TMSCl, $Li_2Me_2Cu(CN)$/ $BF_3{\cdot}Et_2O$) failed to react with **63** (entries 5-9, table 2). Dimethylzinc[37] and a methyltitanium ate-reagent,[38] which have been used for 1,4-addition to highly sterically demanding enones also failed to react with **63** (entries 10-11, table 2). However, **63** reacted smoothly with lithium dimethylcuprate/TMSCl in ether (0°C) when HMPA (3eq.) was added, yielding **87**, as well as the 1,2-addition product **88**, in a ratio of 3:1 (entry 12, table 2). The competitive formation of 1,2-addition products during Gilman addition reaction on sterically demanding systems is a recognised problem, e.g. Corey *et al.*[39] and Smith *et al.*[40] obtained a mixture of **85** and **86** in a ratio of ca. 2:1 on reacting **84** with lithium dimethylcuprate



84 **85** **86**

and TMSCl in THF.[41] Smith *et al.*[40] undertook an extensive study on the Gilman addition reaction on **84** and subsequent trapping of the enolate with TMSCl. When the reaction of **84** was conducted at -60°C, they were able to monitor the progress of the reaction over several hours and observed, that the 1,2-addition

Table 2: 1,4 Versus 1,2-Methylation of (**63**)

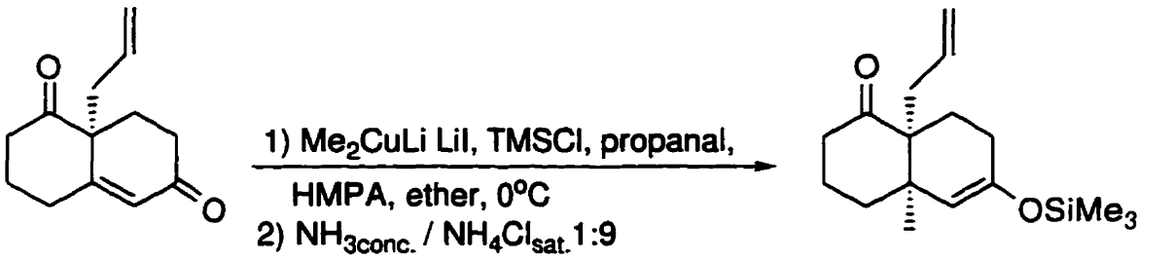


63 **87** **88**

Entry	Reagent, conditions	**63** (%)	**87**(%)	**88**(%)
1	CuI (3eq.), MeLi (6eq.), ether, 0°C,3h	100	-	-
2	CuI (3eq.), MeLi (6eq.), ether, TMSCl (6eq.), 0°C	100	-	-
3	CuI, 2MeLi, THF, -78°C --> 0°C	100	-	-
4	CuI (3eq.), MeLi (6eq.), TMSCl (6eq.), THF, -78°C	-	44	54
5	CuI (3eq.), MeLi (6eq.), BF_3·EtO_2 (6eq.), THF, -78°C, 4h	-	-	100
6	CuCN (3eq.), MeLi (6eq.), ether, -78°C --> 0°C	100	-	-
7	CuCN (3eq.), MeLi (6eq.), THF, -78°C --> 0°C	100	-	-
8	CuCN (3eq.), MeLi (6eq.),Me_3SiCl (6eq.), THF, -78°C ->0°C	100	-	-
9	CuCN (3eq.), MeLi (6eq.), BF_3·EtO_2 (2eq.), ether, -78°C ->20°C	100	-	-
10	$(Me)_2Zn$, $Ni(acac)_2$, ether, 0°C -> rt.	100	-	-
11	$MeTi(O^iPr)_4MgCl$, $Ni(acac)_2$, THF, -30°C -> rt.	100	-	-
12	CuI (3eq.), MeLi(6eq.),TMSCl (6eq.),HMPA (3eq.), ether, 0°C	-	75	25
12	CuI (3eq.), MeLi (6eq.), TMSCl (6eq.), HMPA (3eq.) propionaldehyde (1.5eq.), ether, 0°C	-	98	2

product **86** is formed rapidly at the beginning of the reaction (ca.20% of **86** after 30min. next to ca. 30% of **85**) and remained constant as the 1,4-addition continues. In light of this result, it seemed possible that there might be a species, which is highly reactive towards 1,2-addition and we thought that prior addition of an aldehyde might intercept this species. Indeed addition of 1.5 equivalents of propanal prior to the addition of **63** dramatically increased the yield of the 1,4-addition product **87** to 96% and only minute amounts (ca. 2%) of the 1,2-addition product **88** were detected in the crude product by ^{1}H-NMR (entry 12, table 2).

In order to obtain the silyl enol ether **89**, we changed the work up procedure from an aqueous 10% HCl to a slightly basic ($NH_{3conc.}/NH_4Cl_{conc.}$ 1:9, pH 8.0) work up, which gave the silyl enol ether **89** in 95% yield on a 50mg scale.



63 **89**

To test the possibility of using a somewhat more advanced precursor for the Gilman addition reaction, we tried the same procedure on **64**, **66**, **71** and **94**. Of these, **66** reacted smoothly and gave **90** in 90% yield, as well as 5% of the 1,2-addition product **96** (entry 1, table 3). Unfortunately, the intermediate TMS enol ether was somewhat unstable and hydrolyzed easily on attempted purification by column chromatography (silica gel and aluminum oxide were tried). In order to increase the stability of the enol ether, we tried the reaction with TBDMSCl instead of TMSCl. However, the yield dropped to 48% of **91** (entry 2, table 3). Under those conditions, **71** and **64** did not react, and only the starting

Table 3: 1,4-Addition of Wieland-Miescher Ketone Derivatives

R_1, R_2: O, R_3: -CH=CHCH$_3$:	**66**	**90**
R_1, R_2: O, R_3: -CH=CHCH$_3$:	**66**	**91**
R_1, R_2: -O(CH$_2$)$_2$O-, R_3: -CH=CHCH$_3$:	**71**	**92**
R_1, R_2: -O(CH$_2$)$_2$O-, R_3: -CH$_2$OMEM:	**64**	**93**
R_1: -OMOM, R_2: H, R_3: -CH$_2$CH=CH$_3$:	**94**	**95**

Entry	Starting material	Reagents	STM (%)	1,4-Addition product (%)*	1,2-Addition product (%)*
1	**66**	a, d	-	90 (**90**)	5** (**96**)
2	**66**	b, d	-	48 (**91**)***	-
3	**71**	a, c	99	-	-
4	**64**	a, c	98	-	-
5	**94**	a,c	-	26 (**95**)	51**(**97**)

Reagents, conditions: a) CuI (3eq.), MeLi (6eq.), TMSCl (3eq.), propanal (1.5eq.), HMPA (3eq.), ether, 0°C; b) CuI (3eq.), MeLi (6eq.), TBDMSCl (3eq.), propanal (1.5eq.), HMPA (3eq.), ether, 0°C-->rt.; c) 10% aqueous HCl; d) NH_3 conc./NH_4Cl conc. 1:9.

* No. of product in brackets

** **96** and **97** were isolated as the dehydrated Δ4a, 6 diene

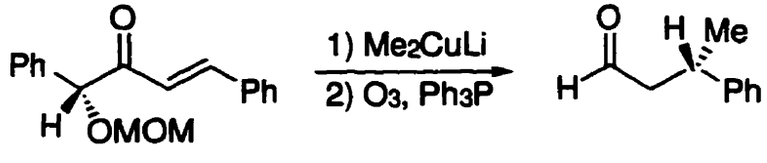
*** Isolated as the TBDMS enol ether **91**

materials were isolated (entries 3-4, table 3). With **94**, which was made by selective $NaBH_4$ reduction of C-1 ketone and protection of the alcohol as the MOM ether, a mixture of **95** and the 1,2-addition product **97** in a ratio of 26:51 was obtained (entry 5, table 3).

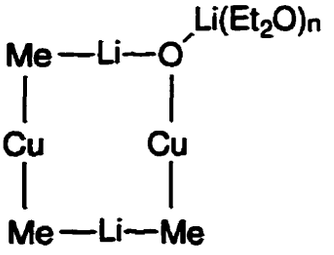
2.4.2. What is the Effect of Adding Propanal to the Gilman Reagent?

During the initial optimization of the 1,4-addition reaction on **63** on a 50mg scale, the best results were obtained when propanal, **63**, TMSCl and HMPA were added sequentially to a Gilman solution in ether. This gave the 1,4-addition product **87** reproducibly in >90% yield. When we scaled the reaction up to 200mg, in 1 out of 2 runs we obtained a greasy and sticky MeCu precipitate after adding HMPA, and after work up a mixture of the 1,4-addition product **87** and the 1,2-addition product **88** in a ratio of *ca.* 3:2. However, the reaction again proceeded cleanly when instead of adding **63** and TMSCl sequentially, a premixed solution of **63** and TMSCl was added to the Gilman reagent, or a mixture of propanal and the Gilman reagent. In both cases, we obtained a very fine yellow precipitate of MeCu.

Corey *et al.*[42] observed a similar phenomena during the 1,4-methylation of **98**. They noted, that the addition of 0.33 equivalents of water to the Gilman



98 **99**



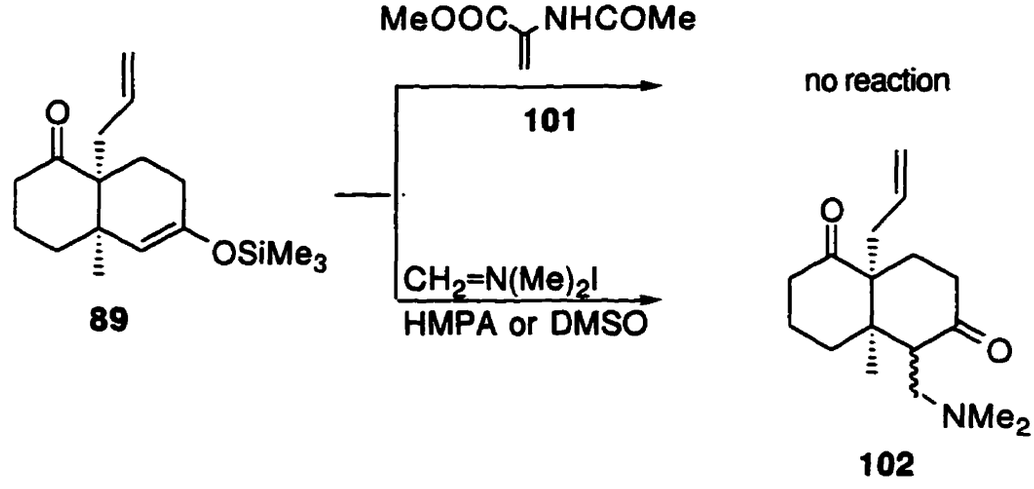
100

reagent gave a very fine precipitate of polymeric MeCu. Adding **98** to this mixture, markedly improved the yield of **99**. They suggest that adding water modifies the Gilman reagent and methyloxidocopperlithium **100** might be the active reagent. Our observations suggest, that the initial formation of a suitable fine crystalline precipitate of MeCu is the important factor in suppressing the 1,2-addition reaction. Thus, adding propanal to the Gilman reagent yields a very fine yellow crystalline precipitate of MeCu, which gave reproducible yields of > 90%. On the other hand, without this modification, the precipitate is a greasy mixture and the yield of **87** dropped markedly.

2.4.3. Trapping of Silyl Enol Ether (89)

Our failure to achieve a conjugate 1,4-methylation of the angular hydroxymethyl Wieland-Miescher derivative **64**, changed our synthetic approach towards thelepogine, in that we decided to use **89** and degrade the allyl group at a later stage.

Although C-5 of **89** is sterically demanding, it was tempting to try a direct approach, and install the side chain by means of a Mukaiyama-Michael reaction with 2-acetamidoacrylate **101**. Not surprisingly, the reaction failed under several reaction conditions and catalysts ($TiCl_4$, $TiCl_4/Ti(O^iPr)_4$, $SnCl_4$, $TrClO_4$, $LiClO_4$ in ether) and only the starting material was isolated. Therefore, we decided to use a more reactive electrophile, and introduce an exo-methylene group at C-5, which has the advantage of constructing an enone system, which is less sterically demanding, and more exposed to a further elaboration. After initial attempts to couple **89** with iodomethyl phenyl sulphide failed,[43] we decided to try the highly reactive Eschenmoser salt, which has been used to trap sterically demanding silyl enol ethers under very mild conditions (CH_2Cl_2 at -78°C to room temperature).[44] When we used CH_2Cl_2 and DME as the solvent, no reaction was observed, and



only the starting material was isolated. However, **89** reacted smoothly at room temperature, when HMPA or DMSO were used as a solvent, yielding **102** in 80%. **102** was then methylated in quantitative yield and the trimethylamino product was subjected to DBU-induced Hofmann elimination in acetone. To our surprise, we isolated the aldol condensation product **104**, besides the enone **103** in a 1:1 ratio (entry 1, table 4). In order to improve the yield of **103**, we tried THF as a solvent (entry 2, table 4) and a SiO_2 induced elimination (entry 3, table 4), which gave **103** and **104** in a ratio of 1:3 and 4:1 respectively. Although the SiO_2-induced Hofmann elimination gave a reasonable yield of 57% of **103**, the separation of **103** from the side product **104** proved to be difficult by column chromatography on a 50mg scale. An alternative method for the traditional Hofmann elimination is the oxidation of tertiary amines and subsequent Cope elimination at elevated temperature of the N-oxide.[45] Thus, when **102** was oxidized with MCPBA in CH_2Cl_2 at 0^oC to room temperature, we were pleasantly surprised to isolate the exo-methylene product **103** directly in quantitative yield (entry 4, table 4).

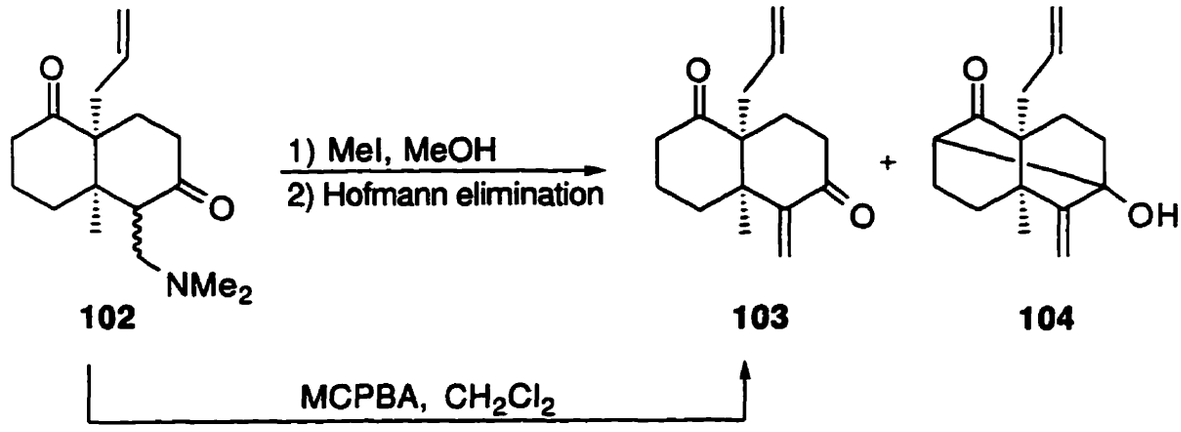
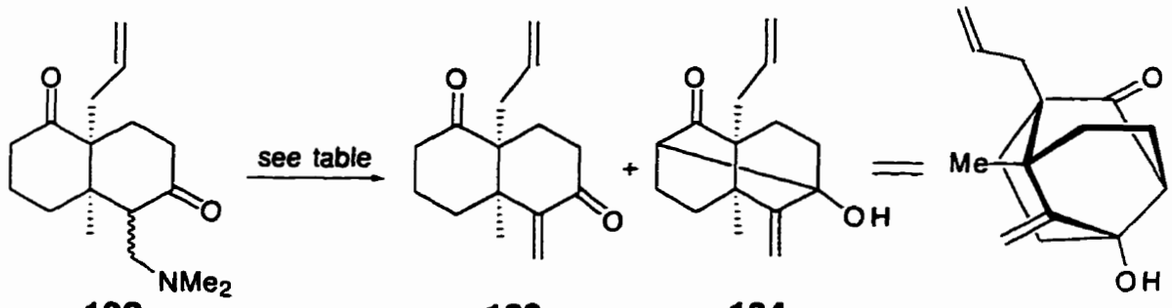


Table 4: Elimination Reaction of (**102**)

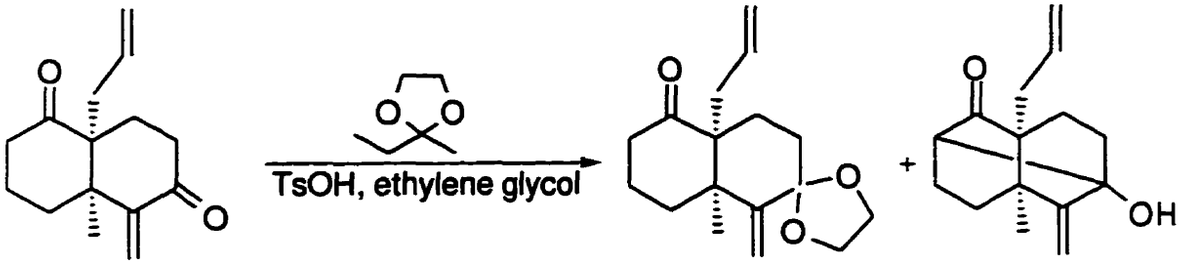


102 **103** **104**

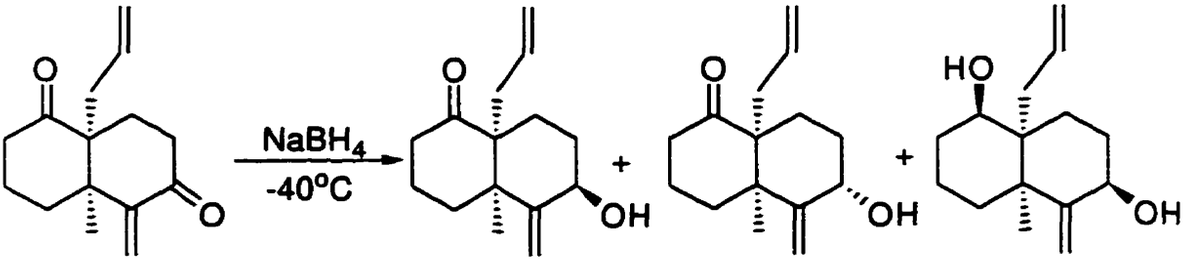
Entry	Reagents/Conditions	**103 : 104**	crude yield (%)
1	1) MeI (10eq.), MeOH; 2) DBU (3eq.), acetone, rt overnight	1:1	95
2	1) MeI (10eq.), MeOH; 2) DBU (3eq.), THF, rt overnight	1:3	85
3	1) MeI (10eq.), MeOH; 2) SiO_2 (10w. eq.), toluene, reflux, 1.5h	4:1	100
4	MCPBA 80% (1.2eq.), CH_2Cl_2, $0^o \rightarrow$rt., 20min.	100:0	100

2.4.4. Selective Protection of Ketone C-1 of (**103**)

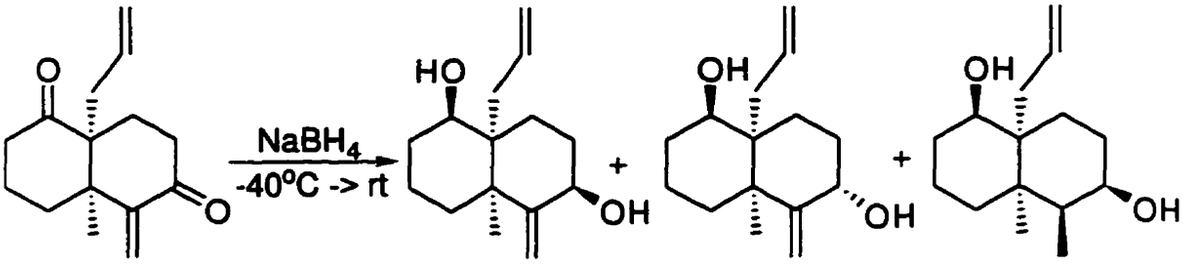
At this stage, we were faced with the problem of protecting the C-1 ketone in the presence of the enone system. Attempted protection of the C-1 ketone as a dioxolane, gave instead the C-6 protected product **105** (44%), besides the aldol condensation product **104** (30%); while selective reduction with $NaBH_4$ at -40°C gave the allylic alcohols **106** (57%) and **107** (18%), besides the diol **108** (7%).



103 **105** **104**

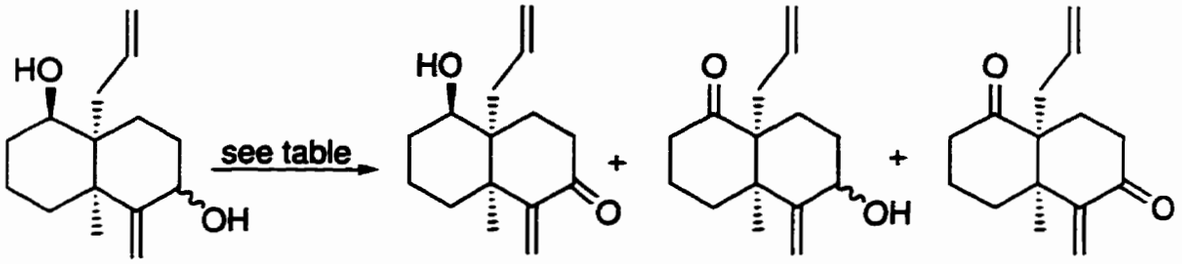


103 **106** **107** **108**



103 **108** **109** **110**

Table 5: Selective Oxidation of Alcohol C-1 in (**108/109**)

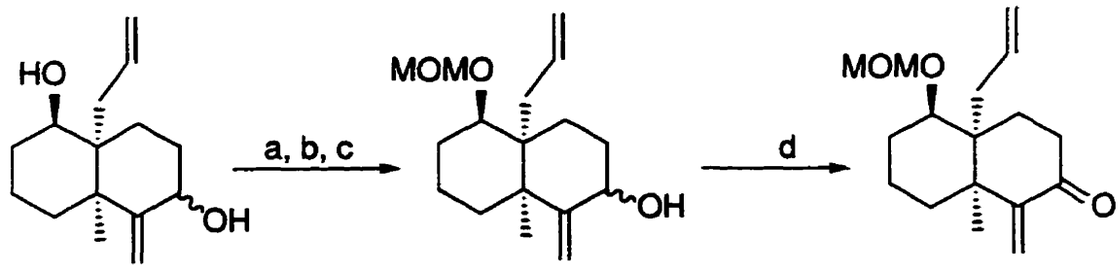


108/109 **111** **106/107** **103**

Reagents/Conditions	**111** (%)	STM (%)	**103** (%)	**106/107** (%)
MnO_2 [46](10eq.), CH_2Cl_2, rt., 4d.	ca. 5	95	-	-
Ag_2CO_3 on Celite[47] (5eq.), benzene, rf, 8h	ca. 2	98	-	-
DMAP·$HCrO_3Cl$[48] (4eq.), CH_2Cl_2, rt, 8h	15	20	60	5
DMSO (1.2eq.), $(COCl)_2$, Et_3N, CH_2Cl_2, -70°C (10min.), -20°C (15min.)	25	20	25	15
IBX, (1,2eq.), DMSO, rt., 4h	10	-	90	-
IBX, (1,2eq.), DMSO/THF 1:1, 0°C, 4.5h	41#	-	13#	-
IBX, (1,2eq.), DMSO/CH_2Cl_2 1:1, -20°C, 5h	-	100	-	-
Dess-Martin reagent, (1,2eq.), CH_2Cl_2, 0°C, 15min.	4	-	96	-
Dess-Martin reagent, (1,2eq.), CH_2Cl_2, -20°C, 2h.	36	8	46	10
Dess-Martin reagent, (1,2eq.), CH_2Cl_2, -40°C, 6h.	-	100	-	-

Isolated yield

We therefore decided to reduce both ketone functions in **103** and then oxidize the allylic alcohol selectively. A $NaBH_4$ reduction of **103** yielded a diastereomeric mixture of **108** and **109** in a ratio of 73:27 in 94% yield besides 4% of **110**. Although several reagents are known to oxidize allylic alcohols selectively, those reagents we tried (table 5) were not very selective and yielded **111**, a diastereomeric mixture of the allylic alcohol **106/107**, as well as the diketone **103**. The best reagent turned out to be IBX (2-iodoxybenzoic acid), which yielded **111**, **106/107** and the diketone **103** in a ratio of 75:2:23 according to ^{1}H-NMR of the crude reaction mixture. Unfortunately, **111** turned out to be unstable on silica gel so we focused on the selective protection of alcohol C-1. Preliminary investigations showed that the allylic alcohol in **108/109** can be selectively protected as a TMS-ether at -40°C. Thus, a one pot sequence of silylating **108/109** with TMSCl, protecting the C-1 alcohol as a MOM-ether and subsequent cleavage of the TMS-ether during an acidic work up was developed, which gave **112/113** in 59% yield. The diastereomeric mixture **112/113** was then oxidized with IBX in DMSO, yielding **114** in quantitative yield.

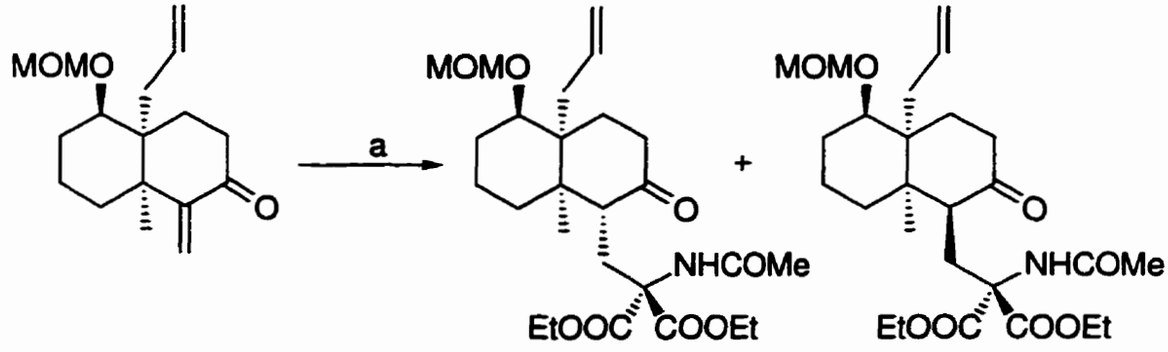


108/109 **112/113** **114**

Reagents, conditions: a) TMSCl, diisopropylethylamine, CH_2Cl_2, -40°C -> 0°C; b) MOMCl, diisopropylethylamine, CH_2Cl_2, 0°C -> reflux; c) 10% aqueous HCl; d) IBX, DMSO, rt.

2.4.5. Elaboration of C-5 of (**114**)

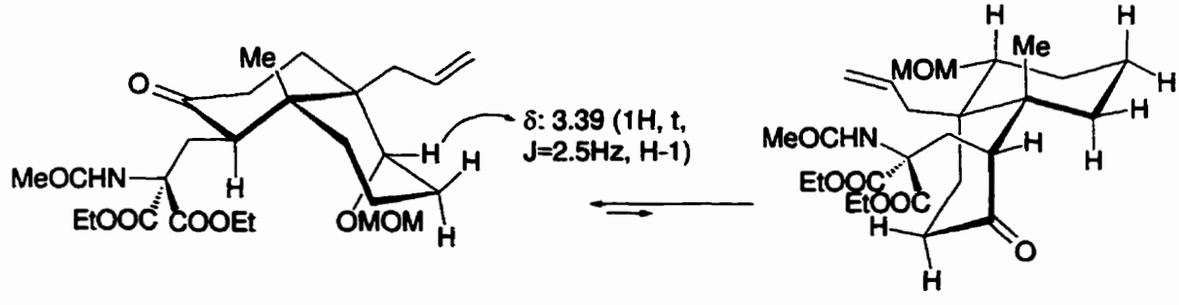
With intermediate **114** in hand, we turned our attention towards the Michael addition. To our delight, **114** reacted smoothly with diethyl acetamidomalonate yielding **115** in 47% yield, besides 31% of the C-5 stereoisomer **116**. Conformational analysis of the two stereoisomers predicted



114 **115** **116**

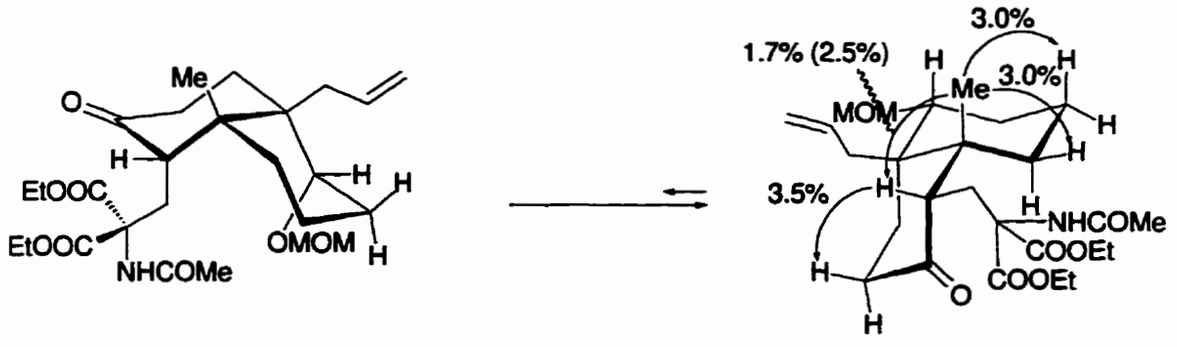
Reagents, conditions: a) EtONa, diethyl acetamidomalonate, EtOH, 0°C-->15°C.

Scheme 14: Conformation of (**115**)



steroidal conformation nonsteroidal conformation

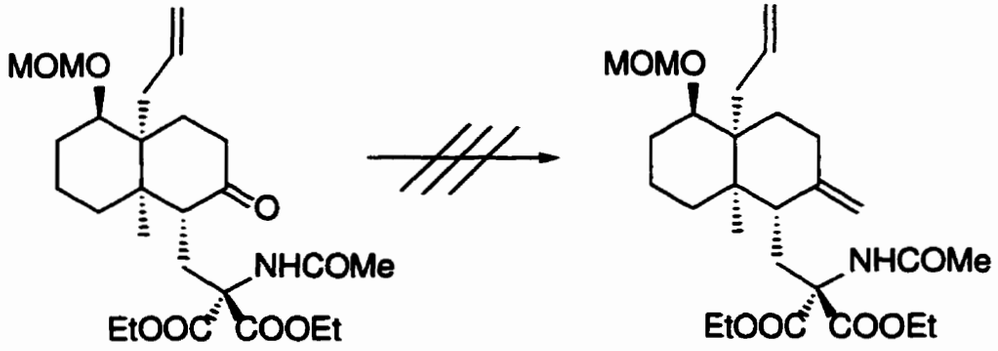
Scheme 15: Conformation of (**116**)



steroidal conformation

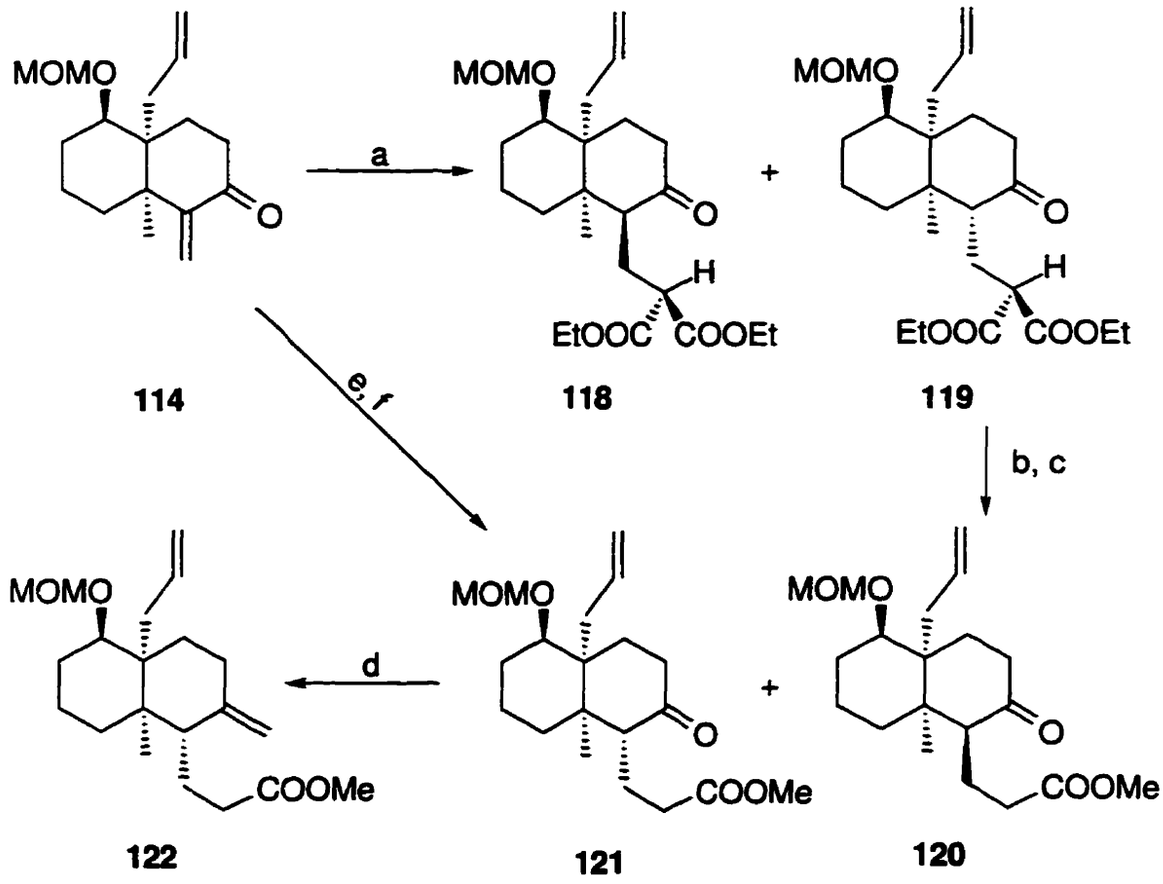
nonsteroidal conformation

115 to be locked in the steroidal conformation and **116** in the nonsteroidal conformation . Consequently, H-1 of **115** is in an equatorial position and H-1 of **116** in an axial position. Thus, the two stereoisomers can be easily distinguished by comparison of the H-1 coupling constants. In practice, H-1 of **115** had 2J's of 2.5Hz (at 3.39ppm) but H-1 of **116** was severely overlapped by the two diastereotopic ethyl ester groups at 4.25-4.09ppm and the coupling constants could not be obtained. An NOE experiment however, confirmed the structure of **116**. Compound **115** was then subject to several olefination protocols. Wittig,[49] Lombardo[50] and the Peterson reagents[51] did not furnish **117**, and only the



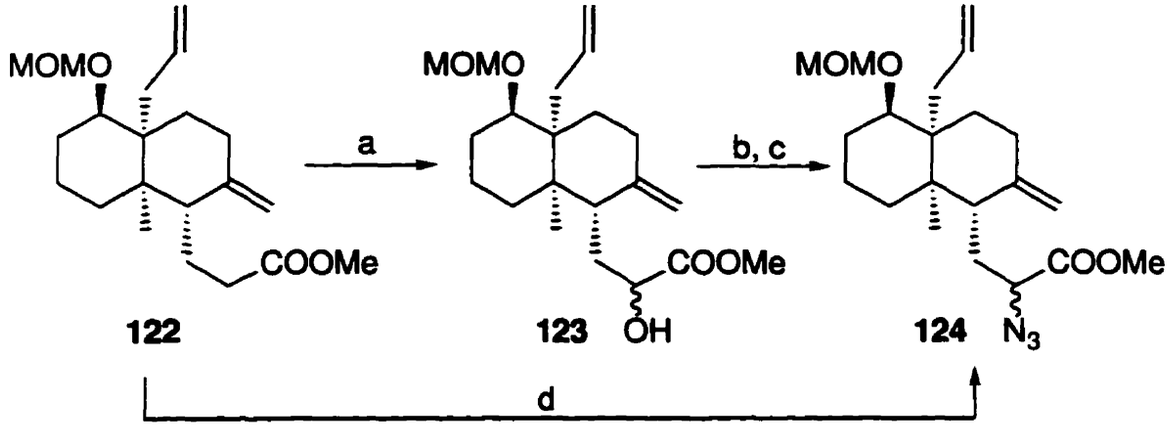
115 **117**

starting material **115** was isolated. There are some literature precedents[52] that olefination reactions proceed sluggish or not at all with bulky α-alkylated ketones and we strongly suspected that the acetamidomalonate side chain in **115** might be the reason for the failed olefination reactions. Therefore, we decided to synthesize the less bulky ester derivative **121**, in order to test this hypothesis. Intermediate **114** was reacted with dimethylmalonate in MeOH, yielding **119** (73%) and the C-5 epimer **118** (13%). **119** was selectively saponified with KOH



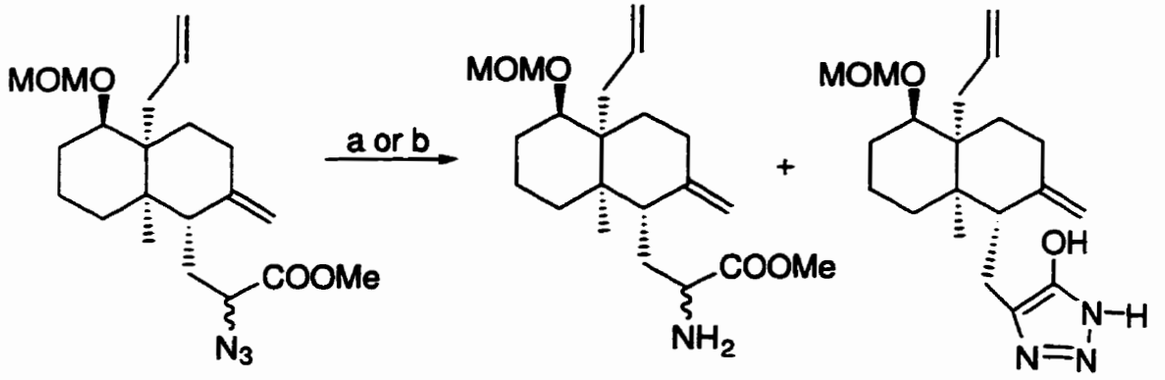
Reagents, conditions: a) MeONa, dimethyl malonate, MeOH, 0°C-->15°C; b) NaOH, MeOH 80%; c) p-xylene, reflux, d) Lombardo reagent, CH_2Cl_2, room temperature; e) MeONa, methyl phenylsulfonylacetate, MeOH, 15°C; f) 5% Sodium amalgam, Na_2HPO_4, MeOH.

in aqueous 80% MeOH in quantitative yield, and the carboxylic acid obtained was then decarboxylated in refluxing p-xylene to furnish **121** (30%) and the C-5 epimer **120** (21%). To our delight, **121** reacted smoothly with the Lombardo reagent, giving **122** in 98% yield. However, despite much effort to optimize the decarboxylation, the overall reaction was low yielding and isomerisation of C-5 was a serious problem. We circumvented this problem by using methyl phenysulfonylacetate instead of dimethyl malonate for the Michael addition on **114**. The crude diastereomeric addition product was directly desulfurized with 5% sodium amalgam in MeOH,[53] giving **121** in an excellent 87% overall yield as well as 5% of the epimer **120.** Compound **122** was then hydroxylated with 2-benzenesulfonyl-3-phenyloxaziridine[54] yielding a diastereomeric mixture of **123a** and **123b** in a ratio of 1:1 in 70% yield. Although the diastereomeric mixture could be readily separated by column chromatography, we used the mixture directly for further elaboration. Thus **123** was converted to the triflate, which was immediately reacted with NaN_3 furnishing **124** as a diastereomeric mixture in

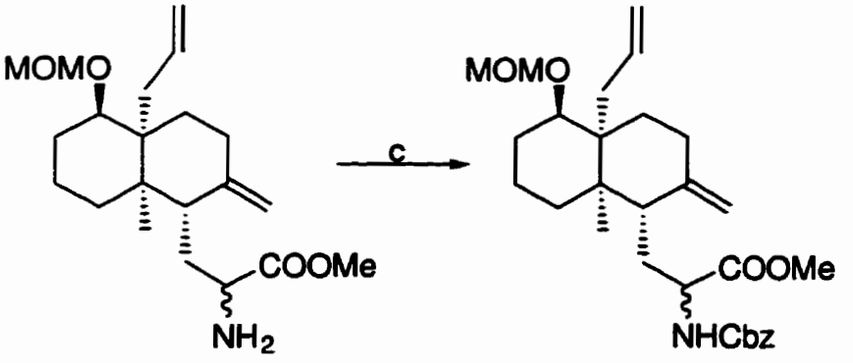


Reagents, conditions: a) LHMDS, 2-benzenesulfonyl-3-phenyloxaziridine, THF -78°C; b) TFAA, 2,6-lutidine, CH_2Cl_2, -78°C; c) NaN_3, dibenzo-18-crown-6, CH_3CN, rt. d) LHMDS, 2,4,6-triisopropylbenzenesulfonyl azide, THF, -78°C.

44% overall yield besides 21% of the starting material **123**. In order to shorten the overall sequence from **122** to **124**, we tried a direct azidation of **122** with 2,4,6-triisopropylbenzenesulfonyl azide. Although the azide **123** was isolated in 75% yield, the purity of this material was only ca. 70%[#] after chromatographic



124 **125** **126**



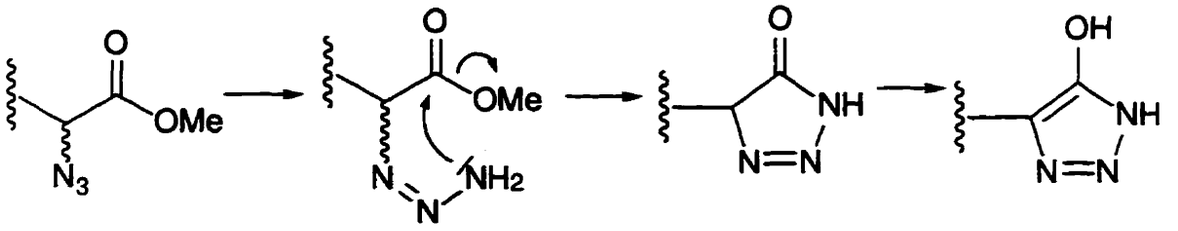
125 **127**

Reagents, conditions: a) H_2, Lindlar catalyst, MeOH, rt.; b) Triphenylphosphine, H_2O, THF, rt.; c) Cbz-Cl, pyridine, CH_2Cl_2, rt.

[#] The reaction of 2,4,6-triisopropylbenzenesulfonyl azide with enolates can yield azides as well as diazo compounds depending on the methods used for the cleavage of the intermediate triazene (R-NH-N=N-SO_2Ph).[55]

purification according to ^{1}H and ^{13}C-NMR analysis, so we decided to use the somewhat more elaborate first route for further experiments. With **124** in hand, we needed a mild method to reduce the azide **124** without reducing the double bonds. Literature precedence suggested the use of H_2 in presence of Lindlar's catalyst.[56] However, to our surprise we isolated the triazole **126** as the main product in 69% yield, besides the readily separable amines **125** (22%).

Scheme 16: Mechanism for the Reduction of (124) to Triazine (126)



124 **128** **126**

Mechanistically, the catalytic hydrogenation of azides is not well understood, but triazenes $RN{=}NNH_2$ have been suggested as intermediates.[57] Thus, we think that the azide **124** is partly reduced to **128**, and an intramolecular S_N2 attack of the triazene successfully competes with the further reduction of **128** to yield the amine **125**. Nevertheless, reducing the azide **124** with triphenylphosphine/H_2O gave the amines **125a/125b** cleanly, which were separately protected as the Cbz carbamates **127a** and **127b**.

With **127a** and **127b** in hand, we tried the Hg(II) trifluoroacetate induced ring-closure. Unfortunately, preliminary results indicated that a competing reaction between the MOM protected C-1 carbinol and the angular allyl moiety was massively predominant. Thus, **127a** and **127b** reacted immediately, when

each was exposed to 2 equivalents of Hg(II) trifluoroacetate in nitromethane. ^{1}H-NMR of the crude products showed a complex mixture in which the signals for the MOM methoxy group and the protons of the allylic moiety were missing , but more discouraging, the exomethylene protons could be clearly seen.

Thus, in a second generation approach, this side reaction would have to be suppressed by either degrading the angular allylic moiety, or changing the C-1 protecting group, prior to attempting the amino-mercuration cyclisation reaction. Unfortunately, financial reasons, and time did not allow us to pursue this alternative, and the project was discontinued at this point.

2.5. Conclusion

Although we were unable to achieve our objective of a total synthesis of thelepogine, the first stage of our approach furnished some useful intermediates of wider use in natural product synthesis.

Thus, racemic 3,4,8,8a-tetrahydro-8a-(2-allyl)-1,6-(2H,7H)-naphthalenedione **63** has been used in the total synthesis of the biologically active scrophulariaceae-terpenes.[32] Our enantioselective synthesis of (R)-3,4,8,8a-tetrahydro-8a-(2-allyl)-1,6-(2H,7H)-naphthalenedione constitutes the formal synthesis of these terpenes, and will allow the synthesis of optically active scrophulariaceae-terpenes for further biological evaluations.

Similarly, our new route to (S)-3,4,8,8a-tetrahydro-8a-(((2-methoxyethoxy)-methoxy)methyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal **78** and (S)-3,4,8,8a-tetrahydro-8a-((methoxymethoxy)methyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal **35c** allows easy access to angular hydroxymethyl Wieland-Miescher ketones, and constitutes a formal synthesis of (+)-perrottetianal A **26** and (+)-pisiferic acid **28**.[11,15f]

Also, the methodology which we developed to build sterically congested *cis*-decalin systems should be applicable to the synthesis of 8(17),14-labdadiene-derived natural products, such as nakamurol A **23**.[8]

3. Experimental Part

3.1 General

General reaction conditions

Reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried with standard drying agents[58] and distilled before use.

Melting point

Melting points (mp.) were determined on a Leitz microscope hot-stage melting point apparatus, and are uncorrected.

Infrared Spectra (IR)

Infrared spectra were recorded on a Mattson Instrument 4030 Galaxy FT-IR spectrometer, as KBr-discs or solutions as specified, and characteristic absorptions are reported.

Proton Nuclear Magnetic Resonance Spectra (^{1}H-NMR)

^{1}H-NMR spectra were obtained on a Bruker AM-400 NMR spectrometer at 400MHz or a Bruker ACE-200 spectrometer at 200MHz. Chloroform (7.27ppm) was used as an internal standard for spectra recorded in deuterochloroform

($CDCl_3$), and water (4.80ppm) for spectra recorded in deuterium oxide (D_2O). COSY and HCS spectra were used to assign the different hydrogen atoms, whose chemical shifts (δ) are reported in parts per milion (ppm). Muliplicities are indicated by s = singlet, d = doublet, t = triplet, q = quartet, p= pentet and m = multiplet. Spin-spin coupling constants (J) are given in Hz.

Carbon Nuclear Magnetic Resonance Spectra (^{13}C-NMR)

^{13}C-NMR spectra were obtained on a Bruker AM-400 NMR spectrometer at 100 MHz or a Bruker ACE-200 spectrometer at 50MHz. Chloroform (77.00ppm) was used as an internal standard for spectra recorded in deuterochloroform ($CDCl_3$), and pyridine (135.91ppm) for spectra recorded in deuterium oxide (D_2O). Broad-band, DEPT and HCS spectra were used to assign the different carbon atoms, whose chemical shifts (δ) are reported in parts per million (ppm), with the multiplicity in parentheses.

Fluorine Nuclear Magnetic Resonance Spectra (^{19}F-NMR)

^{19}F-NMR spectra were obtained on a Bruker AM-400 NMR spectrometer using $CDCl_3$ as solvent, and external trifluoroacetic acid (TFA) as standard.
Chemical shifts (δ) are reported in parts per milion (ppm).

Optical Rotation

Optical rotations were recorded on a Rudolph AutoPol III polarimeter at the sodium D-line (589.5cm) using a 10cm light path. The solvents, concentrations and temperatures were as specified.

Gas-Liquid Chromatography (GC)

Gas chromatography (GC) was performed on a Shimadzu gas chomatograph GC 9A equipped with a flame ionization detector and a Megabore DB1 (15 m) column. The temperature program was 150°C for 5min., 10°C increase per min., 200°C for 20 min.

Thin Layer Chromatography (TLC)

Samples were spotted on Merck TLC aluminium sheets precoated with silica gel 60 F_{254} (layer thickness 0.2mm) and after elution with a suitable solvent system, developed in a iodine chamber, or with one of the following spray reagents:

- A 5% ammonium molybdate solution containing 12% w/v sulfuric acid followed by heating (ca. 120°C) for 5min. Dark blue spots were observed on a white background.
- A 2% Vanillin solution in ethanol containing 2% w/v sulfuric acid followed by heating (ca. 120°C) for 5min. Dark yellow to black spots were observed on a slightly yellow background.

Flash Chromatography

Flash chromatographic purification of reaction mixtures were performed on silica gel 60 (230-400 mesh) for small scale reactions (ca. 100mg) and on silica gel 60 (70-230 mesh) for scales above 100mg. The solvent systems used are indicated in brackets.

3.2 Synthesis of Angular Hydroxymethyl Wieland-Miescher Ketone Derivatives by Deslongchamps' route

3.2.1. Synthesis of 1-Phenylsulfinyl-3-buten-2-one (36)

3.2.1.1. 2-Hydroxy-1-Phenylsulfinyl-3-butene (42)

To a solution of diisopropylamine (722mg, 8.21mmol) in THF (5ml) was added a 1.86M BuLi solution in hexanes (2.21ml, 8.21mmol) at -78°C. After stirring the solution for 5 min. at -78°C, a solution of methyl phenyl sulfoxide (1.0g, 7.13mmol) in THF (2ml) was added and the solution was stirred for 15 min. at -78°C. Then, acrolein (440mg, 7.85mmol) was added and stirring continued for 30 min. at -78°C. The yellow solution was poured into ice/NH_4Cl (sat.) and extracted with $CHCl_3$ (3x15ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with ethyl acetate/hexane 3:1) yielding **42** as a yellow diastereomeric mixture in a ratio of 3:1 (940mg, 67%) which partly crystallized after 1 day in the refrigerator.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.64-7.48 (5H, m, Ph-H), 5.97-5.77 (1H, m, H-3), 5.45-5.15 (2H, m, H-4), 4.86-4.66 (1H, m, H-2), 3.91 (0.4H, s, OH), 3.79 (0.6H, s, OH), 3.10-2.72 (4H, m, H-1).

3.2.1.2. 1-Phenylsulfinyl-3-buten-2-one (**36**)

To a solution of **42** (200mg, 1.02mmol) in acetone (7ml) was added Jones' reagent[46] (0.55ml, 1.32mmol) at O°C and the viscous mixture was stirrred for 30 min. at O°C. The mixture was poured into ice/water and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with 10% aqueous $NaHCO_3$ (1x5ml), brine (3x5ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding **36** as a yellow oil (154mg, 78%).
^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.66-7.50 (5H, m, Ph-H), 6.44-5.93 (3H, ABC system, H-3, H-4), 4.13 (1H, d, J=13.6Hz, H-1), 3.95 (1H, d, J=13.6Hz, H'-1).
The ^{1}H-NMR was identical to that reported.[19] **36** was a very unstable compound which decomposed within 1 week when stored at -20°C, as well as during an attempt to collect a ^{13}C-NMR spectrum at room temperature.

3.2.2. Synthesis of 1-Phenylsulfinyl-4-(triethylsilyl)-3-buten-2-one (**43**)

3.2.2.1. Methyl (E)-3-(triethylsilyl) propenoate (**45**)

To a solution of methyl acrylate (4.3g, 50mmol) and $Co_2(CO)_8$ (137mg, 0.4mmol) in benzene (10ml) was added triethylsilane (1.17g, 10mmol) at 0°C and the black solution was stirred at room temperature for 3h. The solution was poured into ice/water and the water layer was extracted with $CHCl_3$ (3x15ml). The combined organic extracts were washed with brine (1x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by kugelrohr

distillation (90 - 120°C/20 Torr) yielding **45** as a clear oil (1.6g, 81%).
^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.28 (1H, d, J=19.0Hz, H-3), 6.26 (1H, d, J=19.0Hz, H-2), 3.80 (3H, s, OMe), 0.95 (9H, t, J=7.6Hz, $\underline{CH_3}CH_2Si$-), 0.64 (6H, q, J=7.6Hz, $CH_3\underline{CH_2}Si$-); ^{13}C-NMR ($CDCl_3$, 200 MHz): δ 166.2 (s, CO), 147.1 (d, C-3), 134.7 (d, C-2), 51.6 (q, OMe), 7.2 (t, $CH_3\underline{CH_2}Si$-), 3.0 (q, $\underline{CH_3}CH_2Si$-); MS *m/z* : 171 (M^+- Et, 88), 143 (100), 115 (27), 89 (13).

3.2.2.2. 1-Phenylsulfinyl-4-(triethylsilyl)-3-buten-2-one (**43**)

To a solution of diisopropylamine (0.44g, 4.2mmol) in THF (10ml) was added a 1.86M BuLi solution in hexanes (2.31ml, 4.3mmol) at -78°C. After stirring the solution for 5 min. at -78°C, a solution of methyl phenyl sulfoxide (294mg, 2.1mmol) in THF (2ml) was added and the mixture was stirred for 30 min. at -78°C. Then, **45** (400mg, 2.0mmol) was added and stirring continued for 20 min. at -78°C, after which the solution was poured into ice/NH_4Cl (sat.) and extracted with ether (3x20ml). The combined organic extracts were washed with brine (2x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with chloroform) yielding **43** as a yellow oil (650mg, 100%).
^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.62-7.45 (5H, m, Ph-H), 7.04 (1H, d, J=18.8Hz, H-4), 6.37 (1H, d, J=18.8Hz, H-3), 4.21 (1H, d, J=14.1Hz, H-1), 3.97 (1H, d, J=14.1Hz, H'-1), 0.95 (9H, t, J=7.7Hz, $\underline{CH_3}CH_2Si$-), 0.62 (6H, t, J=7.7Hz, $CH_3\underline{CH_2}Si$-);^{13}C-NMR ($CDCl_3$, 200 MHz): δ 198.4 (s, CO), 149.0 (d, C-4), 142.7 (d, C-3), 131.5 (d, Ph), 129.3 (d, Ph), 124.2 (d, Ph), 65.8 (t, C-1), 7.1 (t, $CH_3\underline{CH_2}Si$-), 2.8 (q, $\underline{CH_3}CH_2Si$-); MS *m/z* : 291 (M^+- Et, 16), 263 (41), 185 (34), 127 (100).

3.2.3. Synthesis of 1-Phenylsulfinyl-4-(trimethylsilyl)-3-buten-2-one (**44**)

3.2.3.1. Methyl (E)-3-(trimethylsilyl)propenoate (**46**)

Through a solution of methyl acrylate (4.3g, 50mmol) and $Co_2(CO)_8$ (137mg, 0.4mmol) in benzene (10ml) was bubbled trimethylsilane at 0°C, which was generated in a second flask by slowly adding trimethylsilylchloride (1.1g, 10mmol) to a suspension of $LiAlH_4$ (0.38g, 10mmol) in butyl ether (3ml) at ca.10°C.# After the trimethyl silylchloride was added, a slow stream of N_2 was bubbled through the apparatus and the trimethylsilane generating flask was warmed to room temperature. The dark benzene solution was stirred for 1h at 0°C and for additional 2h at room temperature, then the solution was poured into ice/water and the water layer was extracted with $CHCl_3$ (3x15ml). The combined organic extracts were washed with brine (1x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by kugelrohr distillation (90 - 100° C/20 Torr) yielding **46** as a clear oil (1.0g, 63%). The ^{1}H-NMR of **46** was identical to that reported in the literature.[23]

Any traces of acid were trapped by passing the trimethylsilane stream through a glass tube filled with ca. 10g. of soda lime.

3.2.3.2. 1-Phenylsulfinyl-4-(trimethylsilyl)-3-buten-2-one (**44**)

To a solution of hexamethyldisilazane (214mg, 1.33mmol) in THF (3ml) was added 2.15M BuLi solution in hexanes (0.648ml, 1.35mmol) at 0°C. The solution was stirred for 15 min. at 0°C and then methyl phenyl sulfoxide (93mg, 0.66mmol) dissolved in THF (1ml) was added at -78°C. After the solution was slowly warmed from -78°C to 0°C in 90 min., **46** (100mg, 0.63mmol) dissolved in THF (1ml) was added at -78°C and stirred for 15 min. at -78°C. The solution was poured into ice/NH_4Cl (sat.) and extracted with ether (3x15ml). The combined organic extracts were washed with brine (2x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with ethyl acetate/hexane 1:1) yielding **44** as a slightly yellow oil (101mg, 60%) besides the 1,4-addittion product **47** (23mg, 12%).

44: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.66-7.50 (5H, m, Ph-H), 7.03 (1H, d, J=19.2Hz, H-4), 6.40 (1H, d, J=19.2Hz, H-3), 4.18 (1H, d, J=13.6Hz, H-1), 3.96 (1H, d, J=13.6Hz, H'-1), 0.11 (9H, s, Me_3Si-); ^{13}C-NMR ($CDCl_3$, 400 MHz): δ 190.6 (s, CO), 151.5 (d, C-4), 143.2 (s, Ph), 141.4 (d, C-3), 131.6 (d, Ph), 129.3 (d, Ph), 124.2 (d, Ph), 65.7 (t, C-1), -2.0 (q, Me_3Si-).

47: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.73-7.51 (5H, m, Ph-H), 3.72 (3H, s, OMe), 2.98 (1H, dd, J=13.2Hz, 10.8Hz, H-4), 2.83 (1H, dd, J=13.2Hz, 3.2Hz, H'-4), 2.56 (1H, dd, J=16.2Hz, 7.4Hz, H-2), 2.50 (1H, dd, J=16.2Hz, 5.7Hz, H'-2), 1.43 (1H, dddd, J=10.8Hz, 3.2Hz, 7.4Hz, 5.7Hz, H-3), -0.06 (9H, s, Me_3Si-); ^{13}C-NMR ($CDCl_3$, 400 MHz): δ 173.7 (s, CO), 144.3 (s, Ph), 131.3 (d, Ph), 129.2 (d, Ph), 124.6 (d, Ph), 60.5 (t, C-4), 51.9 (q, OMe), 34.4 (t, C-2), 18.5 (d, C-3), -3.3 (q, Me_3Si-); MS *m/z* : 283 (M^+- Me, 1), 267 (M^+- OMe,1), 198 (43), 105 (83), 73 (100).

3.2.4. Synthesis of Methyl-5-(trimethylsilyl)-3-oxo-4-pentenoate (54)

3.2.4.1. (E)-3-(Trimethylsilyl)-2-propenol

To a solution of **46** (700mg, 4.42mmol) in CH_2Cl_2 (15ml) was added 1.5M DIBAL-H solution in toluene (6.5ml, 9.73mmol) at -78°C and the mixture was then stirred for 20 min. at -78°C. The solution was poured into ice/10% aqueous HCl and the mixture was stirred for 1h at 0°C. After the two phase mixture was separated, the water layer was extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (1x5ml), dried with $MgSO_4$ and carefully evaporated under reduced pressure. The residue was purified by kugelrohr distillation (60 - 80°C/20 Torr) yielding the title compound as a clear oil which contained *ca.* 10% toluene as judged by ^{1}H-NMR (448mg, 70% (based on a purity of 90%)).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.20 (1H, dt, J=18.8Hz, 4.4Hz, H-2), 5.93 (1H, dd, J=18.8Hz, 1.7Hz, H-3), 4.19 (2H, dd, J=4.4Hz, 1.7Hz, H-1), 1.48 (1H, b, OH), 0.09 (9H, s, Me_3Si-); ^{13}C-NMR ($CDCl_3$, 400 MHz): δ 144.8 (d, C-2), 129.6 (d, C-3), 65.6 (t, C-1), -1.4 (q, Me_3Si-); GC/MS *m/z*: 115 (M^+- Me, 63), 75 (100), 61 (48).

3.2.4.2. (E)-3-(Trimethylsilyl)-2-propenal (53)

To a solution of Collins' reagent[46] (5.4g, 20.7mmol) in CH_2Cl_2 (25ml) was added (E)-3-(trimethylsilyl)-2-propenol (300mg, 2.07mmol (based on a purity of 90%)) dissolved in CH_2Cl_2 (4ml) at 0°C. The mixture was stirred for 15 min. at 0°C, and

then poured into ice/water. After the two phase mixture was separated, the water layer was extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with 10% aqueous HCl (1x10ml), brine (1x10ml), 10% aqueous $NaHCO_3$ (1x10ml), brine (1x10ml) and dried with $MgSO_4$. After careful evaporation of the organic solution under reduced pressure, the residue was purified by kugelrohr distillation (50-70°C/100 Torr) yielding **53** as a clear oil which contained *ca.* 10% toluene as judged by ^{1}H-NMR (150mg, 68% (based on a purity of 90%)).
53: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 9.53 (1H, d, J=7.6Hz, H-1), 7.20 (1H, d, J=18.7Hz, H-3), 6.52 (1H, dd, J=18.7Hz, 7.6Hz, H-2), 0.19 (9H, s, Me_3Si-); ^{13}C-NMR ($CDCl_3$, 200 MHz): δ 194.6 (s, C-1), 158.5 (d, C-3), 144.2 (d, C-2), -2.0 (q, Me_3Si-); GC/MS *m/z* : 113 (M^+- Me, 100), 83 (28), 73 (31), 59 (47).

3.2.4.3. Methyl 5-(trimethylsilyl)-3-hydroxy-4-pentenoate

To a solution of hexamethyldisilazane (142mg, 0.88mmol) in THF (4ml) was added a 2.15M BuLi solution in hexanes (0.408ml, 0.88mmol) at 0°C. The solution was stirred for 30 min. at room temperature and then methyl acetate (65mg, 0.88mmol) was added at -78°C. After the solution was stirred for 45 min. at -78°C, **53** (96mg, 0.68mmol, (based on a purity of 90%)) dissolved in THF (1ml) was added and stirred for 15 min. at -78°C. The solution was poured into ice/NH_4Cl (sat.) and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by kugelrohr distillation (70 - 90°C/0.025 Torr) yielding the title compound as a clear oil (99mg, 87%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.06 (1H, dd, J=18.7, 4.5Hz, H-4), 5.95 (1H, dd, J=18.7, 1.0Hz, H-5), 4.54-4.52 (1H, m, H-3), 3.72 (3H, s, OMe), 2.88-2.86 (1H, br.,

-OH), 2.63-2.48 (2H, m, H-2, H'-2), 0.08 (9H, s, Me_3Si-); ^{13}C-NMR ($CDCl_3$, 400 MHz): δ 172.7 (s, C-1), 145.8 (d, C-5), 130.5 (d, C-4), 70.3 (d, C-3), 51.8 (q, -OMe), 40.9 (t, C-2), -1.4 (q, Me_3Si-); GC/MS *m/z* : 187 (M^+- Me, 26), 113 (61), 89 (83), 75 (100).

3.2.4.4. Methyl 5-(trimethylsilyl)-3-oxo-4-pentenoate (**54**)

To a solution of methyl 5-(trimethylsilyl)-3-hydroxy-4-pentenoate (84mg, 0.405mmol) in acetone (3ml) was added Jones' reagent[46] (0.202ml, 0.527mmol) at 0°C and the mixture was stirred for 20 min. The mixture was poured into ice/water and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with 10% aqueous $NaHCO_3$ (1x5ml), brine (3x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by kugelrohr distillation (70 - 90°C/0.025 Torr) yielding **54** as a clear oil (67mg, 81%) which existed in $CDCl_3$ as a keto-enol tautomeric mixture in a ratio of 27:73. **54**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.75 (1H, d, J=1.4Hz, OH-enol), 7.12 (1H, d, J=19.2Hz, H-5 ketone), 6.93 (1H, d, J=18.7Hz, H-5 enol), 6.52 (1H, d J=19.2Hz, H-4 ketone), 6.23 (1H, dd, J=18.7Hz, 1.4Hz, H-4 enol), 5.10 (1H, s, H-2 enol), 3.78 (3H, s, OMe enol), 3.75 (3H, s, OMe ketone), 3.66 (2H, s, H-2 ketone), 0.17 (9H, s, Me_3Si- ketone), 0.14 (9H, s, Me_3Si- enol); ^{13}C-NMR ($CDCl_3$, 400 MHz): δ 192.1 (s, C-3 ketone), 173.3 (s, C-1 ketone), 168.5 (s, C-1 enol), 149.8 (d, C-5 ketone), 141.2 (d, C-4 ketone), 140.6 (d, C-5 enol), 137.1 (d, C-4 enol), 91.3 (d, C-2 enol), 52.4 (q, OMe ketone), 51.3 (q, OMe enol), 45.8 (t, C-2 ketone), -1.7 (q, Me_3Si-enol), -1.8 (q, Me_3Si- ketone); MS *m/z* : 200 (M^+, 38), 185 (M^+-Me, 70), 143 (67), 127, (84), 45 (100).

3.2.5. Synthesis of 2-Carbomethoxycyclohex-2-en-1-one (30)

3.2.5.1. 2-Carbomethoxycyclohexanone

This compound was made from cyclohexanone (3.9g, 39.7mmol) according to a literature procedure[59] yielding the title compound as a clear oil (5.44g, 87%, [lit.[59] 93%]) which had the same spectroscopic properties as those reported[59].

3.2.5.2. 2-Carbomethoxycyclohex-2-en-1-one (30)

To a solution of phenylselenenyl chloride (515mg, 2.69mmol) in CH_2Cl_2 (40ml) was added pyridine (223mg, 2.82mmol) at 0°C. After 15min. a solution of 2-carbomethoxycyclohexanone (400mg, 2.56mmol) in CH_2Cl_2 (6ml) was added and the mixture was stirred for 20min. at 0°C. The solution was then poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (1x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was dried at 0.025Torr for 5h,# yielding the

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Liotta *et al.*[22] did not isolate the intemediate selenium compound, but instead carried out the oxidation *in situ*. However, we noticed traces of starting material (ca. 3-5%) after the oxidation (according to ^{1}H-NMR), even when the amount of phenylselenenyl chloride/pyridine was increased to 1.5eq. Therefore we isolated the intermediate selenium compound and removed any residual starting material by drying the crude product under high-vacuum.

crude intermediate 2-carbomethoxy-2-(phenylselenenyl)cyclohex-2-en-1-one as a yellow oil. This was dissolved in CH_2Cl_2 (20ml), cooled to 0°C and 30% aqueous H_2O_2 (0.3ml, 2.64mmol) was added. The mixture was stirred for 30 min, with an additional amount of 30% aqueous H_2O_2 (0.3ml, 2.64mmol) added after 10 min. and after 20 min. The reaction was quenched by adding water (10ml) and after separation of the two phase mixture, the organic phase was washed with 10% aqueous $NaHCO_3$ (1x5ml) and brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure yielding **30** as a yellow oil (355mg, 90%), which had the same spectroscopic properties as reported.[22]

3.3. Synthesis of (S)-3,4,8,8a-Tetrahydro-8a-(((2-methoxyethoxy)-methoxy) methyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (64).

3.3.1. 2-Allyl-1,3-cyclohexanedione (62)

This compound was made according to a literature procedure[28b] with a slight modification of the work up procedure.

To a mixture of 1,3-cyclohexanedione (11g, 98.1mmol) and Cu (300mg, 4.7mmol) in 10% aqueous KOH (33ml, 98.1mmol) was slowly added allyl bromide (14.3g, 117.7mmol) at room temperature and the mixture was stirred for 3h at room temperature. The mixture was basified by adding 10% aqueous NaOH at 0°C and filtered through Celite 545. The filtrate was washed with $CHCl_3$ (2x20ml) and acidified with $HCl_{conc.}$ at 0°C. The suspension was extracted with $CHCl_3$ (3x40ml), washed with brine (1x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The crystals obtained were recrystallized with benzene (40ml), yielding **62** as colourless crystals (9.0g, 60%, [lit.[28b] 79%]). Mp.123-124°C, [lit.[28b] mp.123-124°C]; The spectroscopic properties of this compound were identical to those reported.[28b]

3.3.2. (R)-3,4,8,8a-Tetrahydro-8a-(2-allyl)-1,6-(2H,7H)-naphthalenedione (63)

Method A: Synthesis of Racemic (63) according to Reusch *et al.*

Racemic **63** was synthesized according to a published procedure[26b] from **62** (500mg, 3.28mmol), yielding a crude two component mixture, which was separated by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1), yielding 4-(2-allyl)-2-(3-oxobutyl)-1,3-cyclohexanedione **65** as brown crystals (379mg, 52%). besides the desired product **63** as colourless crystals (121mg, 18%, [lit.[26b] 52%]).

63: mp. 59-61°C, [lit.[26b] mp. 61.5-62.5°C]; ^{1}H-NMR#(400 MHz, $CDCl_3$): δ 5.86 (1H, s, H-5), 5.61 - 5.50 (1H, m, $-CH_2-\underline{CH}=CH_2$), 5.12 - 5.08 (2H, m, $-CH_2-CH=\underline{CH_2}$), 2.77 - 2.05 (11H, m), 1.70 - 1.66 (1H, m, H'-3); ^{13}C- NMR (400 MHz, $CDCl_3$: DEPT): δ 209.0 (s, C-1), 197.9 (s, C-6), 164.6 (s, C-4a), 131.3 (d, $-CH_2-\underline{CH}=CH_2$), 126.2 (d, C-5), 119.1 (t, $-CH_2-CH=\underline{CH_2}$), 54.4 (s, C-8a), 39.5 (t, C-4), 38.1 (t, C-9), 33.1 (t, C-7), 31.6 (t, C-2), 25.9 (t, C-8), 23.0 (t, C-3); Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.35; H, 7.67; IR (5% in CCl_4, cm^{-1}): 1680, 1713.

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^{1}H-NMR (100 MHz, $CDCl_3$) according to Reusch *et. al.*:[26b] δ 5.8 (m, 1H), 5.2 (m, 3H), 2.0-2.9 (m, 12H). Those data are somewhat erroneous in that H'-3 at 1.70-1.66 ppm was not reported and instead was assumed to be underneath the unresolved multiplets between 2.0-2.9 ppm. However, COSY and HSC spectra clearly revealed that a multiplet at 1.70-1.66 ppm has to be assigned to H'-3.

65: mp. 81-82°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.83-5.72 (1H, m, CH_2=C<u>H</u>-CH_2-), 5.07-5.02 (2H, m, <u>CH_2</u>=CH-CH_2-), 2.65-2.57 (3H, m, CH_2=CH-<u>CH_2</u>-, -<u>CH_2</u>CH_2COCH_3), 2.42-2.34 (4H, m, H-6, -CH_2<u>CH_2</u>$COCH_3$), 2.31-2.23 (1H, m, H-4), 2.14-2.08 (1H, m, CH_2=CH-<u>CH_2</u>-), 2.13-1.99 (1H, m, H'-5), 1.96 (3H, s, -CH_2CH_2CO<u>CH_3</u>), 1.70-1.60 (1H, m, H-5); ^{13}C- NMR (400 MHz, $CDCl_3$: DEPT): δ 199.8 (s, -CH_2CH_2<u>C</u>OCH_3), 178.8 (s, C-3), 155.9 (s, C-1), 136.4 (d, CH_2=C<u>H</u>-CH_2-), 133.2 (s, C-2), 116.6 (t, <u>CH_2</u>=CH-CH_2-), 45.4 (d, C-5), 34.1 (t, CH_2=CH-<u>CH_2</u>-), 33.1 (t, C-6 or -CH_2<u>CH_2</u>$COCH_3$), 31.9 (t, C-6 or -CH_2<u>CH_2</u>$COCH_3$), 26.7 (t, C-5), 21.1 (t, -<u>CH_2</u>CH_2COCH_3), 21.1 (q, -CH_2CH_2CO<u>CH_3</u>); MS *m/z* : 222 (M^+, 44), 204 (35), 176 (33), 163 (45), 154 (57), 55 (100).

<u>Method B: Improved Synthesis of Racemic (**63**)</u>

A solution of 2-allylcyclohexane-1,3-dione **62** (1.0g, 6.57mmol), 10% aqueous KOH (0.074 ml, 0.13 mmol) and methyl vinyl ketone (0.69g, 9.9mmol) in 80% aqueous MeOH (40ml) was refluxed for 75min. The solution was poured into ice/water, acidified with 10% aqueous HCl and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The crude intermediate Michael adduct was dissolved in benzene (15ml), and pyrrolidine (0.1ml, 1.35mmol) was added. The solution was refluxed through a Dean-Stark trap until water ceased to be formed (ca. 30min.). The solution was poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1), yielding **63** (0.93g, 70%) and **65** (0.22g, 15%) as white crystals. The

spectroscopic properties of **63** and **65** were the same as those reported in the previous experiment.

Enantioselective Synthesis of (**63**) with L-Proline

The crude Michael adduct was synthesised from 2-allylcyclohexa-1,3-dione **62** (10g, 65.7 mmol) according to our procedure for racemic **63**.

The residual oil obtained was dissolved in DMSO (130ml) and L-proline (7.56g, 65.7 mmol) was added. The mixture was stirred overnight at room temperature. The dark mixture was poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x75ml). The combined organic extracts were washed with brine (2x10ml), dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1) and kugelrohr distillation (90-120°C/0.025 Torr) yielding **63** as a yellow oil (8.8g, 66%, ee = 80%).#

The scalemic mixture was dissolved in hexane/MeOH 3:1 (30ml) and stored at 0°C overnight. The crystals which separated were removed by filtration, yielding racemic **63** (860mg, 6.4%)# as white crystals. The supernatant was evaporated under reduced pressure and the residue kugelrohr-distilled (90-120°C/0.025 Torr) yielding enantiomerically pure **63** as a yellow oil (7.1g, 53%).#

The enantiomeric excess of **63** was determined by means of a 1:1 molar mixture of the chiral shift reagent europium tris(d,d-dicampholylmethanate) and **63** in $CDCl_3$, which induced a $\Delta\delta$ of 0.15ppm to the H-5's of the two antipodes in the ^{1}H-NMR.

63: $[\alpha]^{25}_D$ + 90° (c1.1, $CHCl_3$); The spectroscopic properties of this compound were identical to those of racemic **63**.

3.3.3. (R)-3,4,8,8a-Tetrahydro-8a-(1-propenyl)-1,6-(2H,7H)-naphthalenedione (66)

In Ethanol as Solvent with Catalytic Amounts of $RhCl_3 \cdot 3\ H_2O$

A mixture of **63** (300mg, 1.47mmol), $RhCl_3 \cdot 3\ H_2O$ (39mg, 0.147mmol) in EtOH (20ml) was refluxed for 9h. Evaporation under reduced pressure of the red solution, followed by column chromatography of the oily residue on silica gel (elution with hexane/ethyl acetate 2:1) gave recovered starting material **63** (90mg, 30%), **66** (99mg, 33%) and **67** (110mg,30%) as slightly yellow oils.

66: $[\alpha]^{25}_D$ -55.1° (c1.1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.95 (1H, s, H-5), 5.54 (1H, dq, J = 15.6, 6.5 Hz, -CH=CHCH$_3$), 5.23 (1H, dq, J = 15.6, 1.2 Hz, -CH=CHCH$_3$), 2.69 - 2.02 (9H, m), 1.69 (3H, dd, J = 6.5, 1.2 Hz, -CH=CHCH$_3$), 1.68-1.55 (1H, m, H'-3); ^{13}C- NMR (400 MHz, $CDCl_3$: DEPT): δ 208.5 (s, C-1), 198.6 (s, C-6), 163.1 (s, C-4a), 130.0 (d), 129.1 (d), 127.6 (d), 57.8 (s, C-8a), 38.6 (t, C-4), 33.3 (t, C-7), 32.3 (t, C-2), 29.5 (t, C-8), 22.6 (t, C-3), 17.9 (q, -CH=CHCH$_3$); MS *m/z* : 204 (M^+, 41), 176 (15), 147 (15), 119 (81), 106 (95), 91 (100); HRMS *m/z* (M^+) calc. 204. 1150, obsd. 204. 1157; IR (5% in CCl_4, cm^{-1}): 1679, 1717.

67: ^{1}H-NMR (400 MHz, $CDCl_3$, (Wieland-Miescher ketone numbering)): δ 5.97 (1H, t, J=7.3Hz, C=CHCH$_2$CH$_3$), 5.81 (1H, d, J=3.9Hz, H-5), 4.11 (q, J=7.1Hz, -COOCH$_2$CH$_3$), 2.65 (2H, t, J=7.5Hz, H-8), 2.44-2.19 (8H, m), 1.89-1.79 (2H, m,

H-3), 1.24 (3H, t, J=7.1Hz, -COOCH$_2$CH$_3$), 1.05 (3H, t, J=7.5Hz, C=CHCH$_2$CH$_3$); ^{13}C- NMR (400 MHz, CDCl$_3$: DEPT): δ 199.6 (s, C-6), 173.0 (s, -COOCH$_2$CH$_3$), 158.7 (s, C-4a), 134.5 (d, -C=CHCH$_2$CH$_3$), 132.1 (s, C-8a), 125.4 (d, C-5), 60.3 (t, -COOCH$_2$CH$_3$), 37.1 (t), 33.6 (d), 32.4 (t), 25.0 (t), 23.9 (t), 21.8 (t), 14.2 (q), 13.8 (q); MS *m/z* : 250 (M^+,100), 221 (15), 205 (23), 163 (81), 91(95).

In Isopropyl Alcohol, HCl and Catalytic Amounts of RhCl$_3$·3 H$_2$O

To a solution of **63** (4.0g, 19.6mmol) in isopropyl alcohol (140ml) was added RhCl$_3$·3 H$_2$O (258mg, 0.98mmol) and 8 drops of HCl$_{conc.}$ from a Pasteur pipet. After refluxing the mixture for one hour the same amount of RhCl$_3$·3 H$_2$O and HCl$_{conc.}$ as above were added and the mixture was refluxed for another hour. Evaporation of the red solution under reduced pressure gave a red oil which was diluted with diethyl ether (200ml). The red suspension was stirred for 30min. at room temperature and then filtered, yielding RhCl$_3$·hydrate (250mg) as red crystals. The supernatant was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1) which gave **66** (2.9 g) along with **68** as a slightly yellow oil, (201mg, 3.9%). The main fraction was further purified by kugelrohr distillation (100-140°C/0.025Torr) yielding **66** as slightly yellow oils (2.8g, 70%).

The spectroscopic properties of **66** were the same as those obtained in the previous experiment.

68: ^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.99 (1H, t, J = 7.3 Hz, -C=CHCH$_2$CH$_3$), 5.82 (1H, s, H-5), 5.00 (1H, hpt. J = 6.3 Hz, (CH$_3$)$_2$CHOOC-), 2.67 (2H, t, J = 7.1 Hz, H-8), 2.43-2.30 (8H, m), 1.85 (2H, m, H-3), 1.22 (6H, d, J = 6.3 Hz, (CH$_3$)$_2$CHOOC-), 1.06 (3H, t, J = 7.6 Hz, -C=CHCH$_2$CH$_3$); ^{13}C- NMR (400 MHz, CDCl$_3$: DEPT): δ

199.6 (s, C-6), 172.5 (s, $(CH_3)_2CHO\underline{OC}$-), 158.8 (s, C-4a), 134.5 (d, -C=$\underline{CH}CH_2CH_3$), 132.1 (s, C-8a), 125.4 (d, C-5), 67.7 (d, $(CH_3)_2\underline{CH}OOC$-), 37.1 (t), 34.1 (t), 32.5 (t), 25.1 (t), 24.0 (t), 21.8 (t), 21.8 (q, $(\underline{CH_3})_2CHOOC$-), 13.8 (q, -C=$CHCH_2\underline{CH_3}$); MS *m/z* : 264 ($M^+$,82), 222 (75), 163 (100), 91 (80); HRMS *m/z* (M^+) calc. 264.1725, obsd. 264. 1711; IR (5% in CCl_4, cm^{-1}): 1674, 1730.

3.3.4. Ozonolysis of (66), Attempted Synthesis of (S)-3,4,8,8a-Tetrahydro-8a-(formyl)-1,6-(2H,7H)-naphthalenedione

A solution of **66** (100mg, 0.49mmol) in ethanol (15ml) was ozonised for 1h at -78°C until no starting material was detected by TLC. The solution was degassed by passing a stream of N_2 through the solution for 10 min and then excess methyl sulfide (1ml) was added at -78°C. The solution was stirred for 4h as the acetone/CO_2 bath was allowed to warm to room temperature, then poured into ice/water and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 1:2) yielding the known compound[30] **70** as yellow, somewhat oily crystals (70mg, 85%).

70: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.0 (1H, s, H-5), 2.70-2.66 (2H, m), 2.46-2.42 (4H, m), 2.32-2.29 (2H, m), 2.05-1.99 (2H, m, H-3); ^{13}C- NMR (400 MHz, $CDCl_3$): δ 208.0 (s, C-6), 197.3 (s, C-1), 152.9 (s, C-4a), 132.3 (s, C-8a), 44.8 (t), 38.1 (t), 37.5 (t), 30.5 (t), 22.3 (t), 21.6 (t); MS *m/z* : 164 (M^+,97), 136 (52), 108 (75), 79 (100).

The ^{1}H-NMR was in agreement with that reported.[30]

3.3.5. (R)-3,4,8,8a-Tetrahydro-8a-(1-propenyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**71**)

A mixture of **66** (2.75 g, 13.5mmol), 2-ethyl-2-methyl-1,3-dioxolane (10.1ml, 80.8 mmol), ethylene glycol (0.15 ml, 2.7mmol) and p-toluenesulfonic acid monohydrate (0.192g, 1mmol) was stirred at room temperature for 24h. The solution was poured into ice/water, basified with 10% aqueous NH_3 and extracted with $CHCl_3$ (5x50ml). The combined organic extracts were washed with brine (2x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1) yielding **71** as a yellow oil (2.50 g, 75%).

71: $[\alpha]^{25}_D$ + 132° (c1.1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.98 (1H, d, J=2.1Hz, H-5), 5.61 (1H, dq, J=15.9, 1.6Hz, -CH=CHCH$_3$), 5.32 (1H, dq, J=6.4, 15.9Hz, -CH=CHCH$_3$), 4.00 - 3.95 (4H, m, -OCH$_2$CH$_2$O-), 2.40-2.22 (4H, m), 1.73 (3H, dd, J=6.4, 1.6Hz, -CH=CHCH$_3$), 1.79 - 1.65 (6H, m); ^{13}C- NMR (400 MHz, $CDCl_3$: DEPT): δ 199.6 (s, C-6), 164.5 (s, C-4a), 130.2 (d), 128.2 (d), 127.9 (d), 111.7 (s, C-1), 65.3 (t, -OCH$_2$CH$_2$O-), 64.9 (t,-OCH$_2$CH$_2$O-), 52.9 (s, C-8a), 33.1 (t), 31.9 (t), 31.4 (t), 25.5 (t), 21.8 (t), 18.1 (q, -CH=CHCH$_3$); MS *m/z* : 248 (M^+,21), 119 (11), 105 (18), 99 (100), 91 (31), 55 (90); HRMS *m/z* (M^+) calc. 248.1412, obs. 248.1399; IR (5% in CCl_4, cm^{-1}): 1678.

3.3.6. (S)-3,4,8,8a-Tetrahydro-8a-(formyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**72**)

A solution of **71** (1.7g, 6.9 mmol) in ethanol (200 ml) was ozonised for 2.5h at -78°C until no starting material was detected by TLC. The solution was degassed by passing a stream of N_2 through the solution for 10min and then excess methyl sulfide (10ml) was added at -78°C. The solution was stirred for 4h while being allowed to warm to room temperature. After removal of the solvent under reduced pressure, **72** was obtained as white crystals (1.62g, 100%).

72: mp. 121 - 122°C; $[\alpha]^{25}_D$ +203° (c1.1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.76 (1H, s, -CHO), 6.01 (1H, d, J=0.7 Hz, C-5), 4.10 - 3.98 (4H, m, -O$\underline{CH_2CH_2}$O-), 2.41-1.50 (10H, m); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 200.5 (s, -CHO), 197.7 (s, C-6), 159.4 (s, C-4a), 128.5 (d, C-5), 109.6 (s, C-1), 65.5 (t, -OCH$_2\underline{CH_2}$O-), 65.0 (t, -O$\underline{CH_2}$CH$_2$O-), 61.9 (s, C-8a), 33.8 (t), 33.3 (t), 32.7 (t), 21.6 (t), 21.3 (t); MS *m/z* : 236 (M^+,22), 207 (12), 148 (12), 99 (100); Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.11; H, 6.89; IR (KBr, cm^{-1}): 1655, 1711.

3.3.7. (S)-3,4,8,8a-Tetrahydro-8a-(hydroxymethyl)-1,6-(2H,7H)-naphthalene-dione-1-ethylene acetal (**73**)

To a solution of **72** (1.25g, 5.3mmol) in CH_2Cl_2/MeOH 1:1 (30ml) was added $NaBH_4$ (1.0g, 26.45mmol) at -78°C. The suspension was stirred for 45 min. and then quenched with acetone (5ml) and stirred for 30min.. The suspension was poured into ice/water, basified with 10% aqueous NaOH and extracted with $CHCl_3$ (3x30ml). The combined organic extracts were washed with brine

(2x10ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding **73** as white crystals (1.21g , 96%).

73: mp. 105 - 108°C; $[\alpha]^{25}_D$ +117° (c1.1, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.88 (1H,s, H-5), 4.13 (1H, d, J=11.9Hz, -$\underline{CH_2}$OH), 4.04 - 3.93 (4H, m, -O$\underline{CH_2CH_2}$O-), 3.67 (1H, dd, J=10.2Hz, 11.9Hz, -$\underline{CH_2}$OH), 3.09 (1H, d, J=10.2Hz, -$CH_2\underline{OH}$), 2.49-1.62 (10H, m); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 198.9 (s, C-6), 163.5 (s, C-4a), 127.3 (d, C-5), 112.9 (s, C-1), 65.4 (t, -O$\underline{CH_2}CH_2$O-), 64.6 (t, -O$CH_2\underline{CH_2}$O-), 64.5 (t, -$\underline{CH_2}$OH), 49.6 (s, C-8a), 33.8 (t), 32.2 (t), 30.7 (t), 21.7 (t), 21.5 (t); MS *m/z* : 238 (M^+,8), 208 (32), 164 (45), 99 (100); Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.62. Found: C, 65.24; H, 7.67; IR (KBr, cm^{-1}): 1653.

3.3.8. (S)-3,4,8,8a-Tetrahydro-8a-(((2-methoxyethoxy)methoxy)methyl)-1,6-(2H, 7H)-naphthalenedione-1-ethylene acetal (**64**)

To a solution of **73** (200 mg, 0.84 mmol) and N, N-diisopropylethylamine (0.716 g, 5.5mmol) in CH_2Cl_2 (10ml) was added 2-methoxyethoxymethyl chloride (0.627g, 5.1mmol) at 0°C. The solution was stirred at 0°C for 10 min. and then slowly warmed and refluxed for 3h. The mixture was poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 1:1), yielding **64** as a clear oil (240 mg, 88 %).

64: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.93 (1H, s, H-5), 4.65 (1H, d, J=6.8Hz, -O$\underline{CH_2}OCH_2CH_2OCH_3$), 4.63 (1H,d, J=6.8Hz, -O$\underline{CH_2}$O $CH_2CH_2OCH_3$), 4.02 (1H, d, J=9.6Hz, -CH_2O-), 3.96-3.91 (4H, m, -O$\underline{CH_2CH_2}$O-), 3.74 (1H, d, J=9.6Hz,

-CH_2O-), 3.62-3.49 (4H, m, -$OCH_2O\underline{CH_2CH_2}OCH_3$), 3.35 (3H, s, -$OCH_2O$-$CH_2CH_2O\underline{CH_3}$), 2.61-2.24 (5H, m), 1.94-1.67 (5H, m); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 199.9 (s, C-6), 163.4 (s, C-4a), 127.6 (d, C-5), 111.8 (s, C-1), 95.6 (t, -$O\underline{CH_2}OCH_2CH_2OCH_3$), 72.2 (t, -$OCH_2O\underline{CH_2CH_2}OCH_3$), 71.6 (t, -$OCH_2O$-$\underline{CH_2CH_2}OCH_3$), 67.0 (t, -$CH_2O$-), 65.3 (t, -$O\underline{CH_2}CH_2O$-), 64.7 (t, -$OCH_2\underline{CH_2}O$-), 58.9 (q, -$OCH_2OCH_2CH_2O\underline{CH_3}$), 49.2 (s, C-8a), 34.9 (t), 32.1 (t), 30.9 (t), 24.8 (t), 22.2 (t); MS *m/z* : 326 (M^+, 12), 251 (15), 221 (45), 99 (100); HRMS *m/z* (M^+) calc. 326.1729, obs. 326.1707; IR (5% in CCl_4, cm^{-1}): 1674.

3.3.9. (S)-3,4,8,8a-Tetrahydro-8a-(((2-methoxyethoxy)methoxy)methyl)-1,6-(2H, 7H)-naphthalenedione (**35b**)

A mixture of **64** (35mg, 0.11mmol) and (±)-camphorsulfonic acid (30mg, 0.13mmol) in acetone (4ml) was refluxed for 15h. The solution was poured into 10% aqueous Na_2CO_3/ice and extracted with $CHCl_3$ (3x2ml). The combined organic extracts were washed with brine (2x2ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 1:2), yielding the known compound **35b** as a clear oil (24mg, 80%).

35b: $[\alpha]^{25}_D$ + 102.8° (c0.14, $CHCl_3$), [lit.[17] $[\alpha]_D$ +76.6° (c0.14, $CHCl_3$) for an ee of 75%, which gives a calculated value of $[\alpha]_D$ +102° for enaniomerically pure **35b**].

35b had spectroscopic properties identical with those published.[17]

3.4. Synthesis of (S)-3,4,8,8a-Tetrahydro-8a-((methoxymethoxy) methyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (35c).

3.4.1. (R)-3,4,8,8a-Tetrahydro-8a-allyl-5-methyl-1,6-(2H,7H)-naphthalenedione (77)

A solution of 2-allylcyclohexane-1,3-dione **62** (3.0g, 19.7mmol), 10% aqueous KOH (0.11ml, 0.39mmol) and ethyl vinyl ketone (2.49g, 29.6mmol) in 80% aqueous MeOH (120ml) was refluxed for 3h. The solution was poured into ice/water, acidified with 10% aqueous HCl and extracted with $CHCl_3$ (3x30ml). The combined organic extracts were washed with brine (2x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residual oil was dissolved in acetonitrile (100ml) and L-phenylalanine (3.25g, 19.7mmol) and 70% aqueous $HClO_4$ (0.862ml, 9.86mmol) were added. The mixture was refluxed for 24h, then poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x50ml). The combined organic extracts were washed with brine (2x20ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was kugelrohr-distilled (120-140°C/0.025 Torr) yielding **77** as a yellow oil (3.27g, 76%).

77: $[\alpha]^{25}_D$ + 89° (c1.0, $CHCl_3$) ^{1}H-NMR (200MHz, $CDCl_3$): δ 5.63-5.43 (1H, m, -CH_2<u>CH</u>=CH_2), 5.12-5.03 (2H, m, -CH_2CH=<u>CH_2</u>), 2.95-1.91 (11H, m), 1.78 (3H, d, J=1.3Hz, Me), 1.79-1.61 (1H, m, H-3'); ^{13}C-NMR (200MHz, $CDCl_3$: DEPT): δ 209.9 (s, C-1), 197.3 (s, C-6), 157.2 (s, C-4a), 131.8 (d, -CH_2<u>CH</u>=CH_2), 131.2 (s, C-5), 118.7 (t, -CH_2CH=<u>CH_2</u>), 54.5 (s, C-8a), 40.0 (t), 37.7 (t), 32.8 (t), 27.1 (t), 25.7 (t), 21.9 (t), 11.2 (q); MS *m/z* : 218 (M^+, 67), 177 (100), 149 (89), 91 (42); HRMS *m/z* (M^+) calc. 218.1309, obs. 218.1301; IR (5% in CCl_4, cm^{-1}): 1673, 1717.

3.4.2. Determination of the Enantiomerical Excess of (77)

The Mosher esters were made from chiral as well as from racemic **77**. The yields obtained from the achiral starting material are indicated in brackets.

3.4.2.1. (1S, 8aR)-1,2,3,4,8,8a-Hexahydro-8a-allyl-1-hydroxy-5-methyl-6-(7H)-naphthalenone

To a solution of **77** (50mg, 0.23mmol) in CH_2Cl_2/MeOH 1:1 (2ml) was added $NaBH_4$ (43mg, 1.15mmol) at -78°C. The suspension was stirred for 90min. and then quenched with acetone (0.5ml) and stirred for 30min. The suspension was poured into ice/water, basified with 10% aqueous NaOH and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x3ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding the title compound as a clear oil (51mg , 100%, [51mg, 100%]).

^{1}H-NMR (200MHz, $CDCl_3$): δ 5.81-5.71 (1H, m, -CH_2<u>CH</u>=CH_2), 5.13-5.01 (2H, m, -CH_2CH=<u>CH_2</u>), 3.58 (1H, d, J=11.2Hz, H-1), 2.66-1.70 (11H, m), 1.77 (3H, d, J=0.9Hz, Me), 1.34-1.29 (1H, m, H-3); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 199.1 (s, C-6), 159.2 (s, C-4a), 134.9 (d, -CH_2<u>CH</u>=CH_2), 131.2 (s, C-5), 117.6 (t, -CH_2CH=<u>CH_2</u>), 77.2 (d, C-1), 45.3 (s, C-8a), 36.3 (t), 33.6 (t), 29.9 (t), 29.5 (t), 27.3 (t), 23.6 (t), 11.2 (q, Me); MS *m/z* : 220 (M^+, 45), 202 (20), 179 (93), 161 (100), 149 (59), 91 (41); HRMS *m/z* (M^+) calc. 220.1463, obs. 220.1466; IR (5% in CCl_4, cm^{-1}): 1667.

3.4.2.2. Mosher ester of (77)

A mixture of (+)-MTPA-Cl[#] (30mg, 0.12mmol), DMAP (14.5mg, 0.12mmol), the alcohol of the previous experiment (13.1mg, 0.06mmol), pyridine (0.4ml) and CH_2Cl_2 (0.4ml) was kept in a sealed flask for 4 days. The mixture was poured into ice/10% aqueous HCl and extracted with $CHCl_3$ (3x2ml). The combined organic extracts were washed with brine (2x1ml), Na_2CO_3 sat. (1x1ml), again with brine (2x1ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding the Mosher ester **80** (25mg, 96%, [24mg, 92%]) as a clear oil.

Mosher ester **80**: ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.56-7.40 (5H, m, Ph), 5.64-5.51 (1H, m, -CH_2<u>CH</u>=CH_2), 5.05-4.96 (3H, m, C-1, -CH_2CH=<u>CH_2</u>), 3.58 (3H, d, J=1.2Hz, OMe), 2.71-1.44 (12H, m), 1.81 (3H, s, Me); ^{19}F-NMR (300MHz, $CDCl_3$): δ 5.03 (s, CF_3).

Mosher ester **80** from racemic **77**: The ^{1}H-NMR was similar to that of the chiral Mosher ester **80**. However, the diastereomeric -OMe groups were clearly resolved (δ: 3.58 (d, J=1.2Hz), 3.51 (d, J=1.1Hz). ^{19}F-NMR (300MHz, $CDCl_3$): δ 5.14 (s, CF_3), 5.03 (s, CF_3).

According to ^{1}H-NMR and ^{19}F-NMR, the enantiomeric excess of the chiral Mosher ester **80** was 75%.

[#] (+)-MTPA-Cl was made from (+)-MTPA (60mg, 0.26mmol) as described by Mosher *et al.* .[60]

3.4.3. (R)-3,4,8,8a-Tetrahydro-8a-(1-propenyl)-5-methyl-1,6-(2H,7H)-naphthalenedione

This compound was made from **77** (1.0g, 4.48mmol) by a procedure analogous to that for **66**.

The crude product was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 3:1), yielding the title compound as a yellow oil (950mg, 95%).

$[\alpha]^{25}_{D}$ -84° (c0.14, $CHCl_3$), ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.47 (1H, dq, J=19.3, 6.4Hz, -CH=CHCH$_3$), 5.30 (1H, dq, J=19.3,1.5Hz, -CH=CHCH$_3$), 2.79-1.65 (10H, m), 1.84 (3H, d, J=0.4Hz, Me), 1.72 (3H, dd, J=6.4, 1.5Hz, -CH=CHCH$_3$); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 209.7 (s, C-1), 198.1 (s, C-6), 155.2 (s, C-4a), 133.1 (s, C-5), 129.9 (d), 129.8 (d), 57.8 (s, C-8a), 38.3 (t), 33.1 (t), 29.6 (t), 28.4 (t), 20.3 (t), 18.0 (q, -CH=CHCH$_3$), 11.2 (q, Me); MS *m/z* : 218 (M^+, 100), 175 (36), 162 (85), 133 (78), 105 (56); HRMS *m/z* (M^+) calc. 218.1307, obs. 218.1314; IR (5% in CCl_4, cm^{-1}): 1671, 1716.

3.4.4. (R)-3,4,8,8a-Tetrahydro-5-methyl-8a-(1-propenyl)-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**81**)

This compound was made from (R)-3,4,8,8a-tetrahydro-8a-(1-propenyl)-5-methyl-1,6-(2H,7H)-naphthalenedione (834mg, 3.82mmol) by the procedure given for **71**. The crude product was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 4:1), yielding **81** as a yellow oil (860mg, 91%).

81: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.58 (1H, d, J=15.9Hz, -CH=CHCH$_3$), 5.21 (1H, dq, J=15.9, 6.4Hz, -CH=CHCH$_3$), 4.01-3.93 (4H, m, -OCH$_2$CH$_2$O-), 2.65-1.63

(10H, m), 1.82 (3H, d, J=1.4Hz, Me), 1.71 (3H, d, J=6.4Hz, -CH=CHCH$_3$); ^{13}C-NMR (400MHz, CDCl$_3$: DEPT): δ 199.0 (s, C-6), 157, 1 (s, C-4a), 132.9 (d), 131.0 (d), 65.2 (t, -OCH$_2$CH$_2$O-), 64.8 (t, -CCH$_2$CH$_2$O-), 52.8 (s, C-8a), 32.9 (t), 31.0 (t), 26.8 (t), 24.9 (t), 21.4 (t), 18.1 (q, -CH=CHCH$_3$), 11.2 (q, Me); MS *m/z* : 262 (M^+, 47), 218 (10), 162 (10), 99 (100), 91 (45); HRMS *m/z* (M^+) calc. 262.1558, obs. 262.1570.

3.4.5. (S)-3,4,8,8a-Tetrahydro-8a-(formyl)-5-methyl-1,6-(2H,7H)-naphthalene-dione-1-ethylene acetal

A solution of **81** (200mg, 0.76mmol) in ethanol (30ml) was ozonised for 1h at -78°C until the ratio between starting material and product was ca. 1:1 according to TLC. The solution was degassed by passing a stream of N_2 through the solution for 10min and then excess methyl sulfide (3ml) was added at -78°C. The solution was stirred for 4h while it was warmed to room temperature.

After removal of the solvent under reduced pressure, a mixture of the title compound (^{1}H-NMR (400 MHz, CDCl$_3$): δ 9.78 (1H, s, -CHO)) and starting material was obtained in a ratio of ca. 1:1. The mixture (120mg) was used directly for the next step.

3.4.6. (S)-3,4,8,8a-Tetrahydro-8a-(hydroxymethyl)-5-methyl-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**82**)

The crude product-mixture from the ozonolysis (120mg, *ca.* 0.24mmol) was dissolved in CH_2Cl_2/MeOH 1:1 (4ml), cooled to -78°C, and $NaBH_4$ (45mg, 1.2mmol) was added. The suspension was stirred for 45 min. at -78°C, quenched with acetone (1ml) and stirred for an additional 30min. The suspension was poured into ice/water, basified with 10% aqueous NaOH and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x4ml), dried with $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 3:1), yielding **82** as a clear oil (41mg, 21% over two steps), besides starting material **73** (51mg, 25% over two steps).

82: ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 198.3 (s, C-6), 156.1 (s, C-4a), 132.2 (s, C-5), 113.2 (s, C-1), 65.4 (t), 64.9 (t), 64.4 (t), 49.7 (s, C-8a), 33.5 (t), 30.2 (t), 27.2 (t), 21.4 (t), 21.1 (t), 11.5 (q, Me); MS *m/z* : 252 (M^+, 34), 222 (4), 178 (20), 99 (100), 55 (69); HRMS *m/z* (M^+) calc. 252.1362, obs. 252.1376;

The ^{1}H-NMR and IR were identical to those reported.[17]

3.4.7. (S)-3,4,8,8a-Tetrahydro-8a-((methoxymethoxy)methyl)-5-methyl-1,6-(2H,7H)-naphthalenedione-1-ethylene acetal (**78**).

To a solution of **82** (41mg, 0.16mmol) and N, N-diisopropylethylamine (139mg, 1.1mmol) in CH_2Cl_2 (3ml) was added chloromethyl methyl ether (78mg, 0.97mmol) at 0°C. The solution was stirred at 0°C for 30min. and then slowly warmed and refluxed for 4h. The mixture was poured into ice/10% aqueous HCl

and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x4ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 1:1), yielding **78** (39mg, 82%) as a clear oil which crystallized after 2 days.

78: mp. 84-87°C; [lit.[17] 109.5-111°C]; $[\alpha]^{25}_D$ +110° (c0.2, $CHCl_3$), [lit.[17] +127°]; ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 199.4 (s, C-6), 155.8 (s, C-4a), 132.2 (s, C-5), 112.4 (s, C-1), 96.6 (t, $-CH_2O-\underline{CH_2}OMe$), 72.4 (t, $-\underline{CH_2}O-CH_2OMe$), 65.4 (t, $-O\underline{CH_2}CH_2O-$), 64.6 (t, $-OCH_2\underline{CH_2}O-$), 55.4 (q, $-CH_2O-CH_2O\underline{Me}$), 49.5 (s, C-8a), 34.7 (t), 30.6 (t), 27.0 (t), 24.3 (t), 21.9 (t), 11.6 (q, -Me); MS *m/z* : 296 (M^+, 8), 222 (7), 99 (100), 45 (90); HRMS *m/z* (M^+) calc. 296.1610, obs. 296.1624.

The ^{1}H-NMR and IR were identical to those reported.[17]

3.5. Stage 2: Synthesis of the A, B, C System of Thelepogine

3.5.1.. 1,4-Methylation of Wieland-Miescher Ketone Derivatives

3.5.1.1. (4aR,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-4a-methyl-1,6-(2H,5H)-naphthalenedione (87)

In THF with $LiCuMe_2$/TMSCl

To a suspension of CuI (140mg, 0.73mmol) in THF (4ml) was slowly added a 1.51M MeLi solution in diethyl ether (0.97ml, 1.46mmol) at 0°C. The clear solution was stirred for 5min. at 0°C,# then cooled to -78°C, and a solution of **63** (50mg, 0.24mmol) and TMSCl (160mg, 1.47mmol) dissolved in THF (1ml) was added. The mixture was stirred for 1h at -78°C. The mixture was poured into 10% aqueous HCl/ice, and stirred for 20min. The solution was extracted with $CHCl_3$ (3x10ml), and the combined organic extracts were washed with brine (1x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue obtained was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 6:1), yielding **87** as white crystals (24mg, 44%), as well as **88** as a faintly yellow oil (29mg, 54%).

Me_2CuLi was tested for any excess MeLi by means of the Gilman test.[61]

87: mp: 85-87°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.60-5.51 (1H, m, -CH_2<u>CH</u>=CH_2), 5.13-5.02 (2H, m, -CH_2CH=<u>CH_2</u>), 2.78 (1H, dd, J=14.0, 7.2Hz, -<u>CH_2</u>CH=CH_2), 2.65-2.34 (3H, m), 2.45 (1H, d, J=13.5Hz, H-5ax.), 2.26-2.04 (1H, m, H-8eq.), 2.13-2.04 (1H, m, -<u>CH_2</u>CH=CH_2), 2.01-1.85 (4H, m), 1.87 (1H, dd, J=13.5, 2.4Hz, H-5eq.), 1.53-1.46 (1H, m, H-8ax.), 1.39-1.32 (1H, m, H-4eq.), 1.01 (3H, d, J=1.2Hz, Me), ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 213.1 (s), 211.5 (s), 132.3 (d, -CH_2<u>CH</u>=CH_2), 118.6 (t, -CH_2CH=<u>CH_2</u>), 55.0 (s, C-8a), 50.4 (t, C-5), 45.4 (s, C-4a), 39.1 (t), 38.3 (t), 38.2 (t), 34.1 (t, C-4), 28.3 (t, C-8), 23.0 (q, C-4a-<u>Me</u>), 21.8 (t, C-3); MS *m/z* : 220 (M^+, 100%), 179 (12), 151 (30), 137 (35), 95 (41), 55 (67).

88: ^{1}H-NMR (200MHz, $CDCl_3$): δ 5.65-4.95 (1H, m, -CH_2<u>CH</u>=CH_2), 5.49 (1H, s, H-5), 5.13-5.01 (2H, m, -CH_2CH=<u>CH_2</u>), 2.70-1.48 (13H, m), 1.22 (3H, s, Me); ^{13}C-NMR (200MHz, $CDCl_3$: DEPT): δ 211.4 (s, C-1), 140.8 (s, C-4a), 132.4 (d), 131.7 (d), 118.5 (t, -CH_2CH=<u>CH_2</u>), 68.5 (s, C-6), 54.6 (s, C-8a), 40.7 (t), 38.5 (t), 34.3 (t), 30.8 (t), 28.8 (q, Me), 25.7 (t), 24.3 (t); MS *m/z* : 202 (M^+ -H_2O, 11), 161 (23), 105 (29), 75 (100).

<u>In THF with $LiCuMe_2/BF_3$</u>

To a suspension of CuI (140mg, 0.73mmol) in THF (4ml) was slowly added a 1.51M MeLi solution in diethyl ether (0.97ml, 1.46mmol) at 0°C. The clear solution was stirred for 5min. at 0°C, then cooled to -78°C, and BF_3·Et_2O (208mg, 1.47mmol) was slowly added. The solution was stirred for 5min. at -78°C, and then **63** (50mg, 0.24mmol) dissolved in THF (1ml) was added, and the mixture was stirred for 2h at -78°C. The mixture was poured into ice/buffered

aqueous NH_4Cl (pH 8.0) and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x4ml), dried with $MgSO_4$ and evaporated under reduced pressure yielding **88** as a pale yellow oil (49mg, 91%), which had the same spectroscopic properties as those obtained in the previous experiment.

With HMPA as Cosolvent and in the Presence of Propanal

To a suspension of CuI (560mg, 2.94mmol) in diethyl ether (16ml) was slowly added a 1.39M MeLi solution in diethyl ether (4.23ml, 5.87mmol) at 0°C. The clear solution was stirred for 5min. at 0°C and then propanal (85mg, 1.47mmol) was added. After stirring the mixture for 2min., a solution of **63** (200mg, 0.98mmol) and TMSCl (320mg, 2.94mmol) dissolved in diethyl ether (2ml) was added, followed by HMPA (526mg, 2.94mmol). The yellow supension was stirred for 10min. at 0°C, and then poured into 10% aqueous HCl/ice, stirred for 20min. and extracted with $CHCl_3$ (3x20ml). The combined organic extracts were washed with brine (1x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue obtained was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 6:1), yielding **87** (259mg, 91%) as a yellow oil and **88** (8mg, 4%).

Compounds **87** and **88** had the same spectroscopic properties as those obtained previously.

3.5.1.2. TMS-enol ether of (4aR,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-4a-methyl-1,6-(2H,5H)-naphthalenedione (**87**)

To a suspension of CuI (2.80g, 14.7mmol) in diethyl ether (60ml) was slowly added a 1.39M MeLi solution in diethyl ether (21.15ml, 29.4mmol) at 0°C. The clear solution was stirred for 5min. at 0°C and propanal (426mg, 7.34mmol) dissolved in diethyl ether (4ml) was added slowly, within 5min. To the yellow mixture was quickly added a solution of **63** (1.0g, 4.90mmol) and TMSCl (1.60g, 14.7mmol) in diethyl ether (4ml) and a solution of HMPA (2.63g, 14.7mmol) in diethyl ether (4ml). The yellow suspension was stirred for 15min. at 0°C, and then poured into ice/buffered aqueous NH_4Cl (pH 8.0) and extracted with $CHCl_3$ (3x100ml). The combined organic extracts were washed with brine (1x50ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue obtained was quickly purified by column chromatography on silica gel at 0°C (elution with hexane/ethyl acetate 15:1), yielding **89** as a yellow oil (1.36g, 95%). **89** was very unstable and hydrolyzed rapidly even when stored at -40°C. Hence, it was used immediately for the next step.

89: ^{1}H-NMR (200MHz, $CDCl_3$): δ 5.63-5.45 (1H, m, $-CH_2\underline{CH}=CH_2$), 5.09-4.98 (2H, m, $-CH_2CH=\underline{CH_2}$), 4.98 (1H, s, H-5), 2.61-1.36 (12H, m), 1.04 (3H, s, Me), 0.15 (9H, s, $-OSi\underline{Me_3}$).

3.5.1.3. (4aR,8aR)-3,4,4a,7,8,8a-Octahydro-8a-(1-propenyl)-4a-methyl-1,6-(2H,5H)-naphthalenedione (**90**)

Compound **66** (50mg, 0.24mmol) was methylated as described for **63**. Although the silyl enol ether of **90** was positively identified in the crude product (^{1}H-NMR (200MHz, $CDCl_3$): δ 4.50 (1H, s, H-5), 1.01 (3H, s, Me), 0.14 (9H, s, $-SiMe_3$)), several attempts to purify it by column chomatography (silica gel, aluminium oxide) failed. Instead, the hydrolyzed products **90** (42mg, 90%) and **96** (2mg, 5%) were isolated as yellow oils.

90: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.81 (1H, dd, J=15.7, 1.6Hz, -CH=CH-CH_3), 5.41 (1H, dq, J=15.7, 6.5Hz, -CH=CH-CH_3), 2.67 (1H, ddd, J=14.6, 13.5, 7.7Hz, H-2ax.), 2.60-2.53 (1H, m, H-7ax.), 2.49-2.43 (1H, m, H-8eq.), 2.42 (1H, d, J=13.5, H-5ax.), 2.29-2.23 (1H, m, J=14.6Hz, H-2eq.), 2.23-2.16 (1H, m, H-7eq.), 2.06 (1H, dt, J=13.6, 4.8Hz, H-4ax.), 1.93-1.79 (2H, m, H-3), 1.80 (1H, dd, J=13.5, 2.4Hz, H-5eq.), 1.71-1.63 (1H, m, H-8ax.), 1.67 (3H, dd, J=6.5, 1.6Hz, -CH=CH-CH_3), 1.29-1.24 (1H, m, H-4eq.), 0.94 (3H, d, J=0.8Hz, Me), ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 211.5 (s), 211.2 (s), 130.9 (d, -CH=CH-CH_3), 128.6 (d, -CH=CH-CH_3), 57.0 (s, C-8a), 49.7 (t, C-5), 44.9 (s, C-4a), 38.6 (t, C-7), 37.5 (t, C-2), 34.2 (t, C-4), 28.8 (t, C-8), 23.0 (q, Me), 21.5 (t, C-3), 18.6 (q, -CH=CH-CH_3); MS *m/z* : 220 (M^+, 96), 177 (45), 123 (79), 107 (80), 93 (84), 41 (100).

96: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.81 (1H, s, H-5), 5.64 (1H, t, J=4.2Hz, H-7), 5.53-4.93 (1H, m, -CH=CH-CH_3), 5.20 (1H, dd, 15.4,1.7Hz, -CH=CH-CH_3), 2.82-1.50 (8H, m), 1.69 (3H, s, Me), 1.63 (3H, J=6.3, 1.7Hz, -CH=CH-CH_3); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 212.2 (s, C-1), 137.2 (s), 136.2 (s), 130.9 (d), 128.4 (d), 122.9 (d), 121.4 (d), 52.9 (s, C-8a), 35.0 (t), 28.8 (t), 27.3 (t),24.6 (t), 23.3 (q), 17.8 (q); MS *m/z* : 202 (M^+, 35), 160 (40), 145 (71), 131 (39), 41 (100).

3.5.1.4. TBDMS-enol ether of (4aR,8aR)-3,4,4a,7,8,8a-Octahydro-8a-(1-propenyl)-4a-methyl-1,6-(2H,5H)-naphthalenedione (**91**)

To a suspension of CuI (280mg, 1.46mmol) in diethyl ether (8ml) was slowly added a 1.51M MeLi solution in diethyl ether (1.94ml, 2.92mmol) at 0°C. The clear solution was stirred for 5min. at 0°C and then propanal (85.2mg, 1.46mmol) was added. After stirring the mixture for 2min., **66** (100mg, 0.48mmol) dissolved in diethyl ether (1ml) was added, followed by HMPA (264mg, 1.46mmol) . The yellow supension was stirred for 15min. at 0°C, and then triethylamine (437mg, 4.32mmol), TBDMSCl (664mg, 4.32mmol) and HMPA (264mg, 1.46mmol) were added. The yellow suspension was warmed to room temperature and stirred for 30min. The mixture was poured into ice/buffered aqueous NH_4Cl (pH 8.0) and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (2x8ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue obtained was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 8:1), yielding **91** (78mg, 48%) as yellow crystals.

91: mp. 45-47°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.72 (1H, dd, J=15.6, 1.5Hz, -CH=CH-CH_3), 5.43 (1H, dq, J=6.4, 15.6Hz, -CH=CH-CH_3), 4.53 (1H, s, H-5), 2.48-1.60 (9H, m), 1.68 (3H, dd, J=6.4, 1.5Hz, -CH=CH-CH_3), 1.43-1.36 (1H, m, H-4eq.), 1.02 (3H, s, Me), 0.90 (9H, s, -Si-C(Me)$_3$), 0.09 (3H, s, Me), 0.08 (3H, s, Me); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 211.0 (s, C-1), 151.4 (s, C-6), 131.1 (d, -CH=CH-CH_3), 127.2 (d, -CH=CH-CH_3), 113.8 (d, C-5), 56.0 (s, C-8a), 40.9 (s, C-4a), 38.9 (t), 35.6 (t), 27.2 (t), 26.6 (t), 25.7 (q, Me), 25.6 (q, SiC(Me)$_3$), 24.9 (t), 22.5 (t), 18.6 (q, -CH=CH-CH_3), 17.9 (s, SiC(Me)$_3$), -4.3 (q, Me), -4.5 (q, Me); MS *m/z* : 334 (M^+, 11), 319 (25), 277 (28), 150 (15), 73 (100).

3.5.1.5. (1S,8aR)-1,2,3,4,8,8a-Hexahydro-8a-allyl-1-hydroxy-6-(7H)-naphthaleneone#

To a suspension of $NaBH_4$ (278mg, 7.34mmol) in CH_2Cl_2 (10ml) was added MeOH (10ml) at room temperature. The suspension was stirred for 1min. at room temperature and immediately cooled to -78°C. To the clear solution was added a solution of **63** (300mg, 1.47mmol) in MeOH/CH_2Cl_2 1:1 (2ml), and after stirring for 1.5h at -78°C, the mixture was poured into ice/water, basified with 10% aqueous NaOH and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding the title compound as a clear oil (303mg, 100%), which had the same spectroscopic properties as reported.[32]

3.5.1.6. (1S,8aR)-1,2,3,4,8,8a-Hexahydro-8a-allyl-1-((methoxymethyl)-oxy)-6-(7H)-naphthaleneone (**94**)

To a solution of the alcohol described above (167mg, 0.81mmol) and $^iPr_2NEt$ (366mg, 2.83mmol) in CH_2Cl_2 (8ml) was added chloromethyl methyl ether (196mg, 2.43mmol) at 0°C. The solution was slowly heated and refluxed for 3.5h. The solution was poured into 5% aqueous $NaHCO_3$/ice and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x3ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 3:1) yielding **94** as a clear oil (143mg, 71%), which which had the same spectroscopic properties as reported.[32]

For clarity, the numbering is retained as in previous names.

3.5.1.7. (1S,4aR,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxymethyl)-oxy)-4a-methyl-6-(7H)-naphthaleneone (**95**)

To a suspension of CuI (114mg, 0.60mmol) in diethyl ether (8ml) was slowly added a 1.39M MeLi solution in diethyl ether (0.86ml, 1.2mmol) at 0°C. The clear solution was stirred for 5min. at 0°C and then propanal (17.4mg, 0.30mmol) was added. After stirring the mixture for 2min., **94** (50mg, 0.2mmol) dissolved in diethyl ether (1ml), TMSCl (65mg, 0.60mmol) was added followed by HMPA (107mg, 0.60mmol). The yellow supension was stirred for 20min. at 0°C, and then poured into 10% aqueous HCl/ice, stirred for 30min. and extracted with ethyl acetate (3x10ml). The combined organic extracts were washed with water (1x5ml), brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue obtained was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 6:1), yielding **95** (13mg, 26%) and **97** (25mg, 51%) as clear oils.

97: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.10-6.01 (1H, m, -CH_2C<u>H</u>=CH_2), 5.74 (1H, s, H-5), 5.28 (1H, t, J=3.3Hz, H-7), 5.01-4.88 (2H, m, -CH_2CH=C<u>H</u>$_2$), 4.75 (1H, d, J=6.9Hz, -O<u>C</u>H$_2$OMe), 4.62 (1H, d, J=6.9Hz, -O<u>C</u>H$_2$OMe), 3.46 (1H, t, J=7.6Hz, H-1), 3.40 (3H, s, -OCH$_2$O<u>Me</u>), 2.42-1.88 (9H, m), 1.73 (3H, s, Me), 1.35-1.22 (1H, m); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 138.7 (s), 138.1 (d, -CH_2-<u>C</u>H=CH_2), 134.3 (s), 123.8 (d), 121.1 (d), 114.7 (t, -CH_2CH=C<u>H</u>$_2$), 95.8 (t, -O<u>C</u>H$_2$OMe), 83.5 (d, C-1), 55.4 (q, -OCH$_2$O<u>Me</u>), 39.7 (s, C-8a), 37.1 (t), 31.6 (t), 27.4 (t), 24.7 (t), 24.0 (t), 23.4 (q, C(6)-<u>Me</u>); MS *m/z* : 248 (M^+, 11), 203 (42), 145 (98), 91 (61), 45 (100).

95: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.02-5.89 (1H, br. m, -CH_2C<u>H</u>=CH_2), 5.13-4.98 (2H, br. m, -CH_2CH=C<u>H</u>$_2$), 4.74 (1H, d, J=6.9Hz, -O<u>C</u>H$_2$OMe), 4.58 (1H, d, J=6.9Hz, -O<u>C</u>H$_2$OMe), 3.69 (1H, br. s, H-1), 3.40 (3H, s, -OCH$_2$O<u>Me</u>), 2.90-1.1

(14H, br. m), 1.09 (3H, br.s, Me); ^{13}C-NMR (400MHz, $CDCl_3$): δ 212.0 (C-6), 135.6 (br, -CH_2-$\underline{C}H$=CH_2), 117.0 (br, -CH_2-CH=$\underline{C}H_2$), 96.0 (br., -O$\underline{C}H_2$OMe), 55.8 (-OCH$_2$O$\underline{Me}$), 51.5 (br., C-5), 37.1, 35.2, 33.8 (br.) 28.4, 25.6 (br.), 24.3 (br.), 18.1 (br.); ^{1}H-NMR (400MHz, DMSO-d_6, 373K): δ 6.02-5.91 (1H, m, -CH_2C$\underline{H}$=CH_2), 5.13-5.01 (2H, m, -CH_2CH=C$\underline{H}_2$), 4.68 (1H, d, J=6.5Hz, -O$\underline{C}H_2$OMe), 5.59 (1H, d, J=6.5Hz, -O$\underline{C}H_2$OMe), 3.78 (1H, t, J=3.6Hz, H-1), 3.32 (3H, s, -OCH$_2$O$\underline{Me}$), 2.70 (1H, dd, J=14.2, 6.0Hz, -$\underline{C}H_2$CH=CH_2), 2.38-1.25 (13H, m), 1.02 (3H,.s, Me); ^{13}C-NMR (400MHz, DMSO-d_6, DEPT, 373K): δ 209.5 (s, C-6), 135.6 (d, -$CH_2$$\underline{C}H$=$CH_2$), 115.8 (t, -$CH_2$CH=$\underline{C}H_2$), 95.5 (t, -O$\underline{C}H_2$OMe), 76.4 (d, C-1), 54.6 (q, -OCH$_2$O$\underline{Me}$), 51.0 (t, C-5), 36.1 (t), 34.3 (t), 32.7 (t), 27.4 (t), 25.1 (t), 23.5 (q, -Me), 17.6 (t); MS *m/z* : 266 (M^+, 8), 248 (4), 234 (8), 221 (31), 195 (32), 163 (40), 79 (58), 45 (100).

3.5.2. Synthesis of (4aS,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-4a-methyl-5-methylene-1,6-(2H,5H)-naphthalenedione (**103**)

3.5.2.1. (4aR,5S,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-5-(N,N-dimethylamino-methyl)-4a-methyl-1,6-(2H,5H)-naphthalenedione (**102**)

To a solution of **89** (1.36g, 4.65mmol) in HMPA or DMSO (30ml) was added Eschenmoser's salt (1.28g, 6.98mmol). The yellow solution was stirred overnight at room temperature, then poured into ice/5% aqueous Na_2CO_3 and extracted with ethyl acetate (3x50ml). The combined organic extracts were washed with water (2x20ml), brine (1x20ml), dried with $MgSO_4$ and evaporated under reduced

pressure. The residue was purified by column chromatography on silica gel (elution with MeOH), yielding **102** (1.03g, 80%) as white crystals.

102: mp. (racemic mixture) 99-101°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.54-5.43 (1H, m, -CH_2C<u>H</u>=CH_2), 5.09-5.04 (2H, m, -CH_2CH=C<u>H</u>$_2$), 2.92 (1H, dd, J=12.6, 8.6Hz, C(5)H-C<u>H</u>$_2$NMe_2), 2.76-2.43 (5H, m), 2.45 (1H, d, J=8.6Hz, ,H-5), 2.30-2.22 (1H, m), 2.16 (6H, s, -N<u>Me</u>$_2$), 2.13-1.9 (5H, m), 1.77-1.73 (1H, m, H-4eq.), 1.42 (1H, ddd, J=13.2, 5.1Hz, H-8ax.), 0.79 (3H, s, Me); ^{13}C-NMR (400MHz, $CDCl_3$: DEPT): δ 212.7 (s), 211.7 (s), 132.0 (d, -CH_2-<u>C</u>H=CH_2), 118.7 (t, -CH_2-CH=<u>C</u>H$_2$), 56.7 (s, C-8a), 52.7 (t, C(5)H-<u>C</u>H$_2$-NMe_2), 52.4 (d, C-5), 49.2 (s, C-4a), 46.1 (q, N<u>Me</u>$_2$), 39.6 (t, -<u>C</u>H$_2$-CH=CH_2), 39.5 (t, C-7), 38.4 (t, C-2), 30.4 (t, C-4), 29.2 (t, C-8), 21.1 (t, C-3), 18.3 (q, Me); MS *m/z* : 277 (M^+, 25), 262 (11), 236 (23), 165 (26), 58 (100).

<u>3.5.2.2. (4aR,5S,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-5-(N,N,N-trimethylamino-methyl)-4a-methyl-1,6-(2H,5H)-naphthalenedione</u>

To a solution of **102** (548mg, 1.98mmol) in MeOH (12ml) was added iodomethane (2.80g, 19.8mmol). The solution was stirred overnight at room temperature, then evaporated under reduced pressure, yielding the title compound (828mg, 100%) as beige crystals.

Mp. (racemic mixture) 241-243°C; ^{1}H-NMR (200MHz, D_2O): δ 5.66-5.45 (1H, m, -CH_2C<u>H</u>=CH_2), 5.22-5.07 (2H, m, -CH_2CH=C<u>H</u>$_2$), 4.16 (1H, dd, J=13.7, 8.4Hz, C(5)H-C<u>H</u>$_2$NMe_3), 3.34 (1H, d, J=13.7Hz, C(5)H-C<u>H</u>$_2$NMe_3), 3.08 (9H, s, -N<u>Me</u>$_3$), 2.92-1.60 (13H, m), 0.84 (3H, s, Me); ^{13}C-NMR (200MHz, D_2O): δ 219.2 (s), 215.1 (s), 133.7 (d, -CH_2-<u>C</u>H=CH_2), 120.9 (t, -CH_2-CH=<u>C</u>H$_2$), 62.3 (t, C(5)H-

$\underline{CH_2}$-NMe_3), 58.8 (s, C-8a), 55.6 (q, $N\underline{Me_3}$), 53.6 (s, C-4a), 50.2 (d, C-5), 41.2 (t), 40.4 (t), 40.0 (t), 31.0 (t), 30.5 (t), 22.5 (t, C-3), 19.3 (q, Me).

3.5.2.3. (4aS,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-4a-methyl-5-methylene-1,6-(2H,5H)-naphthalenedione (**103**) via Hofmann Elimination

With DBU as Base in Acetone

A mixture of the ammonium salt described above (60mg, 0.143mmol) and DBU (87mg, 0.572mmol) in acetone (3ml) was stirred overnight at room temperature, then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (1x3ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with toluene/ethyl acetate 4:1), yielding **103** (12mg, 36%) and **104** (13mg, 39%) as clear oils.

103: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.92 (1H, s, C(5)=C$\underline{H_2}$), 5.84-5.72 (1H, m, -$CH_2C\underline{H}$=CH_2), 5.25 (1H, s, C(5)=C$\underline{H_2}$), 5.12-5.03 (2H, m, -CH_2CH=C$\underline{H_2}$), 2.81 (1H, dd, J=14.0, 5.2Hz, -C$\underline{H_2}CH$=CH_2), 2.65-1.61 (11H, m), 1.13 (3H, s, Me); ^{13}C-NMR (400MHz, $CDCl_3$,DEPT): δ 213.1 (s, C-1), 202.1 (s, C-6), 151.9 (s, C-5), 134.1 (d, -CH_2-$\underline{C}H$=CH_2), 119.6 (t), 117.9 (t), 54.4 (s, C-8a), 48.3 (s, C-4a), 37.5 (t), 36.2 (t), 35.9 (t), 33.8 (t), 25.6 (t), 22.5 (q, Me), 22.1 (t); MS *m/z* : 232 (M^+, 100), 217 (25), 204 (11), 199 (19), 189 (22), 91 (89).

104: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.01-5.92 (1H, m, -$CH_2C\underline{H}$=CH_2), 5.23 (1H, s, C(5)=C$\underline{H_2}$), 5.03 (1H, s, C(5)=C$\underline{H_2}$), 5.10-5.01 (2H, m, -CH_2CH=C$\underline{H_2}$), 2.38-2.25

(3H, m, H-2 and -C<u>H</u>$_2$CH=CH$_2$), 2.01 (1H, s, OH), 1.85-1.52 (6H, m, H-3, H-7, H-4ax., H-8eq.), 1.32-1.18 (2H, m, H-8ax., H-4eq.), 1.15 (3H, s, Me); ^{1}H-NMR (400MHz, C_6D_6): δ 6.17-6.03 (1H, m, -CH$_2$C<u>H</u>=CH$_2$), 5.18 (1H, s, C(5)=C<u>H</u>$_2$), 5.08-5.93 (2H, m, -CH$_2$CH=C<u>H</u>$_2$), 4.81 (1H, s, C(5)=C<u>H</u>$_2$), 2.33-2.21 (3H, m, H-2 and -C<u>H</u>$_2$CH=CH$_2$), 1.62-0.85 (9H, m), 0.86 (3H, s, Me); ^{13}C-NMR (400MHz, $CDCl_3$,DEPT): δ 218.3 (s), 159.3 (s, C-5), 135.4 (d, -CH$_2$-<u>C</u>H=CH$_2$), 117.3 (t, -CH$_2$-CH=<u>C</u>H$_2$), 102.5 (t, C(5)=<u>C</u>H$_2$), 76.7 (s, C-6), 57.8 (d, C-2), 55.7 (s, C-8a), 47.4 (s, C-4a), 35.1 (t, C-7), 33.7 (t,-<u>C</u>H$_2$-CH=CH$_2$), 33.3 (t, C-4), 27.5 (t, C-8), 23.3 (t, C-3), 16.6 (q, Me); ^{13}C-NMR (400MHz, C_6D_6): δ 216.2 (s), 159.5 (s, C-5), 136.2 (d, -CH$_2$-<u>C</u>H=CH$_2$), 117.1 (t, -CH$_2$-CH=<u>C</u>H$_2$), 102.3 (t, C(5)=<u>C</u>H$_2$), 76.5 (s, C-6), 58.2 (d, C-2), 55.6 (s, C-8a), 47.2 (s, C-4a), 35.6 (t, C-7), 34.1 (t,-<u>C</u>H$_2$-CH=CH$_2$), 33.6 (t, C-4), 27.6 (t, C-8), 23.4 (t, C-3), 16.6 (q, Me); MS *m/z* : 232 (M^+, 22), 217 (21), 204 (19), 189 (44), 124 (100).

<u>With DBU as Base in THF</u>

A mixture of the ammonium salt described above (30mg, 0.072mmol) and DBU (43.5mg, 0.286mmol) in THF (3ml) was stirred overnight at room temperature. Since no reaction was observed by TLC, the mixture was refluxed for 7h, then poured into 10% aqueous HCl/ice and extracted with ethyl acetate (3x5ml). The combined organic extracts were washed with brine (1x3ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding a mixture of **103** and **104** in a ratio of 24:76 (12mg, 85%) according to ^{1}H-NMR.

With SiO_2 in Toluene

A mixture of the ammonium salt described above (200mg, 0.477mmol) and silica gel (2.0g) in toluene (30ml) was refluxed for 90min. The mixture was filtered and the silica gel washed with ethyl acetate (10ml). The combined filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with toluene/ethyl acetate 4:1), yielding **103** (64mg, 57%) as white crystals and **104** (14mg, 13%) as a clear oil
Compound **103** and **104** had the same spectroscopic properties as those previously prepared.

3.5.2.4. (4aS,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-4a-methyl-5-methylene-1,6-(2H,5H)-naphthalenedione (**103**) via Cope Elimination

To a solution of **102** (1.02g, 3.68mmol) in CH_2Cl_2 (30ml) was added in one portion MCPBA 80% (952mg, 4.41mmol) at 0°C. The clear solution was stirred for 20min. at room temperature, then poured into 5% aqueous Na_2CO_3/ice and extracted with $CHCl_3$ (3x40ml). The combined organic extracts were washed with water (1x20ml) and brine (1x20ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding **103** (854mg, 100%) as white crystals, which had the same spectroscopic properties as those of the previous preparations.

3.5.3. Selective Protection of C-1 in (4aS,8aR)-3,4,4a,7,8,8a-Octahydro-8a-allyl-4a-methyl-5-methylene-1,6-(2H,5H)-naphthalenedione (**103**)

3.5.3.1. Attempted Protection of the Carbonyl C-1 in (**103**) as a Dioxolane

A solution of **103** (176mg, 0.758mmol), 2-ethyl-2-methyl-1,3-dioxolane (529mg, 4.55 mmol), ethylene glycol (9.4mg, 0.152mmol) and p-toluenesulfonic acid monohydrate (10.7mg, 0.057mmol) in benzene (1ml) was stirred at room temperature for 2.5h. The solution was poured into 5% aqueous $NaHCO_3$/ice and extracted with $CHCl_3$ (3x4ml). The combined organic extracts were washed with brine (1x3ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 4:1) yielding **105** as a clear oil (92mg, 44%), the Aldol condensation product **104** (53mg, 30%) and starting material **103** (34mg, 20%). **104** had the same spectroscopic properties as those of the previous preparations.

105: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.81-5.69 (1H, m, -CH_2C<u>H</u>=CH_2), 5.38 (1H, d, J=0.6Hz, C(5)=C<u>H</u>$_2$), 5.01 (1H, d, J=0.6Hz, C(5)=C<u>H</u>$_2$), 5.03-4.95 (2H, m, -CH_2CH=C<u>H</u>$_2$), 3.97-3.88 (4H, m, -O<u>C</u>H_2<u>C</u>H_2O-), 2.89-2.75 (1H, m, H'-8), 2.65-2.53 (2H, m, H'-2, H'-7), 2.41-2.32 (1H, m, H'-4), 2.30-2.19 (1H, m, H-2), 1.98-1.75 (5H, m, H-3, H-7, -<u>C</u>H_2-CH=CH_2), 1.59-1.50 (1H, m, H-4), 1.39-1.30 (1H, m, H-8), 1.05 (3H, s, Me); ^{13}C-NMR (400MHz, $CDCl_3$,DEPT): δ 214.1 (s, C-1), 149.4 (s, C-5), 135.2 (d, -CH_2<u>C</u>H=CH_2), 116.8 (t, -CH_2CH=<u>C</u>H_2), 111.3 (t, C(5)=<u>C</u>H_2), 107.9 (s, C-6), 64.4 and 63.8 (t, -O<u>C</u>H_2<u>C</u>H_2O-), 55.4 (s, C-8a), 48.0 (s, C-4a), 38.0 (t, C-2), 35.2 (t, C-7), 33.4 (t, C-8), 32.0 (t, -<u>C</u>H_2CH=CH_2), 25.4 (t, C-4), 22.7 (t, C-3), 22.5 (q, Me); MS *m/z* : 276 (M^+, 6), 235 (43), 105 (24), 99 (88), 41 (100).

3.5.3.2. Attempted Selective Reduction of C-1in (**103**)

To a suspension of $NaBH_4$ (155mg, 4.09mmol) in CH_2Cl_2 (3ml) was added MeOH (3ml) at room temperature. The mixture was stirred at room temperature for 1min. and the solution obtained was cooled to -40°C. A solution of **103** (95mg, 0.409mmol) in MeOH/CH_2Cl_2 1:1 (1ml) was added to the clear solution and stirred for 1h at -40°C. The solution was poured into ice/water, basified with 10% aqueous NaOH and extracted with $CHCl_3$ (3x4ml). The combined organic extracts were washed with brine (2x3ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with toluene/ ethyl acetate 3:1) yielding **106** as white crystals (54mg, 51%), **108** as white crystals (6mg, 7%) and **107** as a semicrystalline oil (17mg, 18%).

106: mp. 116-120°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.84-5.73 (1H, m, -CH_2<u>CH</u>=CH_2), 5.26 (1H, d, J=1.4Hz, C(5)=<u>CH_2</u>), 5.03-4.95 (3H, m, C(5)=<u>CH_2</u> and -CH_2CH=<u>CH_2</u>), 4.59 (1H, dd, J=5.3, 11.2Hz, H-6), 2.75-2.42 (3H, m), 2.29-2.20 (2H, m), 1.99-1.80 (5H, m), 1.68-1.28 (3H, m), 1.05 (3H, s, Me); ^{13}C-NMR (200MHz, $CDCl_3$,DEPT): δ 214.9 (s, C-1), 154.0 (s, C-5), 135.8 (d, -CH_2<u>CH</u>=CH_2), 116.6 (t, -CH_2CH=<u>CH_2</u>), 106.7 (t, C(5)=<u>CH_2</u>), 69.1 (d, C-6), 55.6 (s, C-8a), 48.0 (s, C-4a), 37.5 (t), 34.0 (t), 33.8 (t), 31.4 (t), 26.3 (t), 22.7 (t), 21.0 (q, Me); MS *m/z* : 234 (M^+, 4), 216 (6), 175 (13), 105 (88), 41 (100).

108: mp. 104-106°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.85-5.70 (1H, br. s,, -CH_2<u>CH</u>=CH_2), 5.18 (1H, s, C(5)=<u>CH_2</u>), 5.15-5.02 (2H, m, -CH_2CH=<u>CH_2</u>), 4.94 (1H, s, C(5)=<u>CH_2</u>), 4.40 (1H, br. s, H-6), 3.61 (1H, s, H-1), 2.52-1.05 (12H, m), 1.36 (3H, br. s, Me); ^{13}C-NMR (400MHz, $CDCl_3$,DEPT): δ 157.3 (br. s, C-5), 134.7 (br. d, -CH_2<u>CH</u>=CH_2), 117.3 (t, -CH_2CH=<u>CH_2</u>), 105.3 (br. t, C(5)=<u>CH_2</u>), 71.5 (d,

C-1 or C-6), 69.0 (br. d, C-1 or C-6), 55.7 (s, C-8a), 43.4 (br. s, C-4a), 35.5 (br. t), 32.3 (br. t), 32.0 (br. t), 29.1 (br. t), 26.5 (br. t), 20.9 (br. q, Me), 17.2 (br. t); ^{1}H-NMR (400MHz, DMSO-d_6, 373K): δ 5.88-5.73 (1H, m, -CH_2<u>CH</u>=CH_2), 5.19 (1H, d, J=1.6Hz, C(5)=<u>CH_2</u>), 5.05-4.96 (2H, m, -CH_2CH=<u>CH_2</u>), 4.81 (1H, d, J=1.6Hz, C(5)=<u>CH_2</u>), 4.23 (1H, dd, J=11.1, 5.3Hz, H-6), 4.10-3.89 (1H, br. s, -OH), 3.46 (1H, t, J=2.9Hz, H-1), 2.58 (1H, dd, J=13.7, 6.0Hz, -<u>CH_2</u>CH=CH_2), 2.09-2.00 (1H, m), 1.91-1.18 (11H, m), 1.31 (3H, s, Me), 1.05-0.98 (1H, m); ^{13}C-NMR (400MHz, DMSO-d_6, 373K): δ 157.5 (C-5), 135.3 (-CH_2<u>CH</u>=CH_2), 115.5 (-CH_2CH=<u>CH_2</u>), 104.9 (C(5)=<u>CH_2</u>), 69.1 (C-6 or C-1), 67.2 (C-6 or C-1), 42.6 (C-8a), 42.2 (C-4a), 34.8, 31.8, 31.2, 28.5, 25.6, 20.8 (Me), 16.7 (t); MS *m/z* : 236 (M^+, 2), 218 (8), 195 (14), 177 (45), 159 (77), 41 (100).

107: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.08-5.95 (1H, m, -CH_2<u>CH</u>=CH_2), 5.09-4.95 (2H, m, -CH_2CH=<u>CH_2</u>), 4.92 (1H, s, C(5)=<u>CH_2</u>), 4.76 (1H, s, C(5)=<u>CH_2</u>), 4.17 (1H, dd, J=3.4, 2.1Hz, H-6), 2.50-1.23 (12H, m), 1.13 (3H, s, Me); ^{13}C-NMR (400MHz, $CDCl_3$,DEPT): δ 156.4 (s, C-5), 136.7 (d, -CH_2<u>CH</u>=CH_2), 116.1 (t, -CH_2CH=<u>CH_2</u>), 105.9 (t, C(5)=<u>CH_2</u>), 73.4 (d, C-6), 56.4 (s, C-8a), 47.0 (s, C-4a), 43.0 (t), 35.9 (t), 34.9 (t), 27.3 (t), 23.8 (t), 19.6 (q, Me); MS *m/z* : 234 (M^+, 7), 216 (5), 193 (20), 175 (36), 147 (55), 105 (72), 41 (100).

3.5.4. Selective Oxidation of (1R,4aS,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-4a-methyl-5-methylene-1,6-naphthalenediol (**108/109**)

3.5.4.1. (1R,4aS,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-4a-methyl-5-methylene-1,6-naphthalenediol (**108/109**)

To a suspension of $NaBH_4$ (163mg, 4.30mmol) in CH_2Cl_2 (3ml) was added MeOH (3ml) at room temperature. The mixture was stirred at room temperature for 1min. and the solution obtained was cooled to -40°C. A solution of **103** (100mg, 0.43mmol) in MeOH/CH_2Cl_2 1:1 (1ml) was added to the clear solution and stirred for 30min. at -40°C and 6h at 0°C. Then $NaBH_4$ (82mg, 2.15mmol) was added, and the suspension was stirred overnight in a thawing ice bath. The mixture was poured into ice/water, basified with 10% aqueous NaOH and extracted with $CHCl_3$ (3x4ml). The combined organic extracts were washed with brine (2x3ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with toluene/ ethyl acetate 3:1) yielding **108** (53mg, 52%) and **109** as white crystals (14mg, 14%), next to **110** as a semi-crystaline oil (4mg, 4%).

Compound **108** had the same spectroscopic properties as those of the previous preparations.

109: mp. 112-115°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.2-6.05 (1H, br. s, -CH_2<u>CH</u>=CH_2), 5.26 (1H, s, C(5)=<u>CH_2</u>), 5.18-5.01 (2H, m, -CH_2CH=<u>CH_2</u>), 4.90 (1H, s, C(5)=<u>CH_2</u>), 4.31 (1H, br. s, H-6), 3.78 (1H, br. s, H-1), 2.71-2.09 (1H, br m), 2.30-1.40 (12H, m), 1.06 (3H, br. s, Me); ^{13}C-NMR (400MHz, $CDCl_3$,DEPT): δ 154.8 (br. s, C-5), 137.6 (br. d, -CH_2<u>CH</u>=CH_2), 116.9 (t, -CH_2CH=<u>CH_2</u>), 105.1 (br.

t, C(5)=$\underline{CH_2}$), 71.1 (br. d, C-1 or C-6), 69.8 (br. d, C-1 or C-6), 56.3 (br. s, C-8a), 45.2 (br. s, C-4a), 36.6 (br. t), 31.9 (br. t), 31.0 (br. t), 26.8 (br. t), 25.9 (br. t), 20.5 (br. q, Me); ^{1}H-NMR (400MHz, DMSO-d_6, 373K): δ 6.09-5.98 (1H, m, -$CH_2\underline{CH}$=CH_2), 5.20 (1H, d, J=1.8Hz, C(5)=$\underline{CH_2}$), 4.98-4.90 (2H, m, -CH_2CH=$\underline{CH_2}$), 4.88 (1H, d, J=1.8Hz, C(5)=$\underline{CH_2}$), 4.12 (1H, dd, J=10.4, 5.4Hz, H-6), 3.65 (1H, t, J=6.4Hz, H-1), 2.05 (1H, dd, J=14.3, 8.2Hz, -$\underline{CH_2}$CH=CH_2), 1.95-1.87 (2H, m), 1.74-1.35 (9H, m), 1.06 (3H, d, -Me); ^{13}C-NMR (400MHz, DMSO-d_6, 373K): δ 155.6 (C-5), 137.5 (-$CH_2\underline{CH}$=CH_2), 114.3 (-CH_2CH=$\underline{CH_2}$), 104.9 (C(5)=$\underline{CH_2}$), 68.3 (C-6 or C-1), 67.9 (C-6 or C-1), 43.8 (C-8a), 43.5 (C-4a), 34.1, 32.2, 29.9, 29.6, 25.6 (-Me), 24.3, 19.0; MS *m/z* : 236 (M^+, 9), 218 (28), 203 (37), 177 (95), 159 (85), 41 (100).

110: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.93-5.84 (1H, m, -$CH_2\underline{CH}$=CH_2), 5.19-5.09 (2H, m, -CH_2CH=$\underline{CH_2}$), 3.81 (1H, dd, J=5.7, 2.8Hz, H-6), 3.59 (1H, t, J=2.7Hz, H-1), 2.59-2.53 (1H, m, -$\underline{CH_2}$CH=CH_2), 2.32-2.26 (1H, m, -$\underline{CH_2}$CH=CH_2), 2.00-1.14 (11H, m), 1.15 (3H, m, -Me), 0.98 (3H, d, J=7.2Hz, C(5)H-$\underline{Me}$); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 135.5 (d, -$CH_2\underline{CH}$=CH_2), 117.2 (t, -CH_2CH=$\underline{CH_2}$), 73.2 (d, C-6 or C-1), 72.0 (d, C-6 or C-1), 42.7 (s, C-8a), 41.4 (d, C-5), 38.5 (s, C-4a), 31.3 (t), 30.6 (t), 29.4 (t), 28.9 (t), 22.5 (t), 22.4 (q), 16.7 (t), 11.4 (t); MS *m/z* : 238 (M^+, 4), 220 (15), 197 (17), 179 (100), 95 (44), 41 (53).

3.5.4.2. Selective Oxidation of (**108**/**109**) with o-Iodoxybenzoic Acid (IBX)

Synthesis of o-Iodoxybenzoic Acid (IBX)

IBX was made according to a literature procedure[62] from o-iodobenzoic acid on a 10g. scale. The literature procedure was somewhat modified by stirring the thick suspension by means of a mechanical stirrer and by washing the crystals with acetone and diethyl ether instead of ethanol, as suggested by Frigerio *et al.*,[63] yielding IBX in 75-85% yield, which had the same spectroscopic properties as reported.[63]

Selective Oxidation of (**108**/**109**) with IBX

A suspension of IBX (174mg, 0.621mmol) in DMSO (1.9ml) was stirred at room temperature until a clear solution was obtained (*ca.*15min.). To the solution was added THF (1.9ml). The clear solution was cooled to 0°C, and a solution of (**108**/**109**) (122mg, 0.516mmol) in THF (0.2ml) was added. The solution was stirred for 4.5h at 0°C until no starting material was detected, according to TLC (elution with hexanes/acetone 3:1), then poured into 5% aqueous Na_2CO_3/ice and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with water (1x3ml) and brine (1x3ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with toluene/ ethyl acetate 2:1) yielding **111** (50mg, 41%) as a clear oil and **103** (16mg, 13%) as white crystals.

111: ^{1}H-NMR (200MHz, $CDCl_3$): δ 6.2-5.91 (1H, br. m, -CH_2C<u>H</u>=CH_2), 5.92 (1H, s, C(5)=C<u>H</u>$_2$),.5.35-5.03 (2H, m, -CH_2CH=C<u>H</u>$_2$), 5.11 (1H, s, C(5)=C<u>H</u>$_2$), 3.79 (1H, br. s, H-1), 2.90-1.30 (13H, br. m), 1.22 (3H, br. s, Me); ^{13}C-NMR (200MHz, $CDCl_3$): δ 203.0 (s, C-6), 153.7 (br. s, C-5), 135.7 (br. d, -CH_2-C<u>H</u>=CH_2), 119.4 (t), 117.6 (t), 71.2 (d, C-1), 35.6 (t), 34.8 (br. t), 34.6 (br. t), 30.0 (t), 25.2 (t), 24.3 (br. q, Me), 18.2 (br. t); ^{1}H-NMR (400MHz, DMSO-d_6, 373K): δ 6.05-5.93 (1H, m, -CH_2C<u>H</u>=CH_2), 5.74 (1H, d, J=1.4Hz, C(5)=C<u>H</u>$_2$), 5.21 (1H, d, J=1.4Hz, C(5)=C<u>H</u>$_2$), 5.10-4.97 (2H, m, -CH_2CH=C<u>H</u>$_2$), 4.25 (1H, d, J=4.2Hz, -OH), 3.62 (1H. ddd, J=7.0, 4.2, 3.5, H-1), 2.79 (1H, dd, J=14.2, 6.2Hz, -C<u>H</u>$_2$CH=CH_2), 2.41-2.36 (2H, m), 2.12-2.02 (2H, m), 1.73-1.41 (7H, m), 1.21 (3H, s, -Me); ^{13}C-NMR (400MHz, DMSO-d_6, 373K, DEPT): δ 200.9 (s, C-6), 154.2 (s, C-5), 135.9 (d, -CH_2C<u>H</u>=CH_2), 117.7 (t, -CH_2CH=C<u>H</u>$_2$ or C(5)=C<u>H</u>$_2$), 115.6 (t, -CH_2CH=C<u>H</u>$_2$ or C(5)=C<u>H</u>$_2$), 68.6 (d, C-1), 44.1 (s, C-8a), 41.7 (s, C-4a), 34.7 (t), 33.9 (t), 33.2 (t), 28.8 (t), 24.3 (t), 23.3 (q, -Me), 17.9 (t); MS *m/z* : 234 (M^+, 10), 216 (12), 193 (61), 175 (72), 105 (68), 91 (100).

Compound **103** had the same spectroscopic properties as those of the previous preparations.

3.5.4.3. Selective Oxidation of (**108/109**) with the Dess-Martin Reagent

Synthesis of the Dess-Martin Oxidant

The Dess-Martin oxidant was made according to a literature procedure[64] from IBX on a 1g. scale. The literature procedure was somewhat modified by draining the solvent off by syringe instead of filtering the crystals under N_2, because of the small scale of the reaction, yielding the Dess-Martin oxidant in 70-75% yield, which had the same spectroscopic properties as reported.[64]

Selective Oxidation of (**108/109**) with the Dess-Martin Reagent

To a solution of the Dess-Martin oxidant (35mg, 0.081mmol) in CH_2Cl_2 (2ml) was added a solution of **108/109** (16mg, 0.068mmol) in CH_2Cl_2 (0.5ml) at -20°C. The solution was stirred for 2h at -20°C, then poured into 10% aqueous $Na_2S_2O_3$/ice and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with 5% aqueous $NaHCO_3$ (2x2ml) and brine (1x2ml), dried with $MgSO_4$ and evaporated under reduced pressure yielding a crude mixture (19mg), consisting of **111** (36%), **108/109** (8%) **103** (46%) and **106/107** (10%) according to ^{1}H-NMR.

3.5.5. Indirect Selective Protection of (**108/109**)

To a solution of **108/109** (371mg, 1.57mmol) in CH_2Cl_2 (9ml) was added N,N-diisopropylethylamine (244mg, 1.88mmol) and TMSCl (179mg, 1.65mmol) at -40°C. The clear solution was stirred at -40°C for 20min. and at 0°C for 10min.. Then N,N-diisopropylethylamine (671mg, 5.18mmol) and chloromethyl methyl ether (379mg, 4.71mmol) was added at 0°C and the yellow solution was slowly warmed and refluxed for 3h. The solution was poured into 10% aqueous HCl/ice, diethyl ether (30ml) was added and the mixture was stirred at room temperature for 75min. The mixture was extracted with $CHCl_3$ (3x30ml). The combined organic extracts were washed with brine (1x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with toluene/ ethyl acetate 5:1) yielding **112** (195mg, 44%).and **113** (65mg, 15%) as clear oils.

112: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.84-5.68 (1H, br. m, -CH_2<u>CH</u>=CH_2), 5.21 (1H, s, C(5)=<u>CH_2</u>), 5.09-4.95 (3H, m, C(5)=<u>CH_2</u> and -CH_2CH=<u>CH_2</u>), 4.70 (1H, d, J=6.8Hz, -O<u>CH_2</u>OMe), 4.57 (1H, d, J=6.8Hz, -O<u>CH_2</u>OMe), 4.42 (1H, br. m, H-6), 3.40-3.39 (1H, m, H-1), 3.38 (3H, s, -OCH_2O<u>Me</u>), 2.69-2.61 (1H, m, -<u>CH_2</u>$CH=CH_2$), 2.10-1.05 (11H, m), 1.33 (3H, s, -Me); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 157.4 (s, C-5), 134.6 (d, -CH_2-<u>CH</u>=CH_2), 116.9 (t, -CH_2-CH=<u>CH_2</u>), 105.4 (t, C(5)=<u>CH_2</u>), 96.8 (t, -O<u>CH_2</u>OMe), 79.2 (d, C-1), 69.1 (d, C-6), 55.8 (q, -OCH_2O<u>Me</u>), 43.6 (s, C-8a), 43.4 (s, C-4a), 35.6 (t), 32.4 (t, -<u>CH_2</u>$CH=CH_2$), 32.0 (t), 26.9 (t), 25.6 (t), 20.7 (q, -Me), 16.0 (t); ^{1}H-NMR (400MHz, $CDCl_3$, 330K): δ 5.83-5.71 (1H, m, -CH_2<u>CH</u>=CH_2), 5.22 (1H, s, C(5)=<u>CH_2</u>), 5.05-4.98 (3H, m, C(5)=<u>CH_2</u> and -CH_2CH=<u>CH_2</u>), 4.70 (1H, d, J=6.6Hz, -O<u>CH_2</u>OMe), 4.57 (1H, d, J=6.6Hz, -O<u>CH_2</u>OMe), 4.41 (1H, dd, J=10.4, 4.9Hz, H-6), 3.44 (1H, br. s, H-1), 3.39 (3H, s, -OCH_2O<u>Me</u>), 2.65 (1H, dd, J=14.2,

5.8Hz, -$\underline{CH_2}CH=CH_2$), 2.10-1.05 (11H, m), 1.34 (3H, s, -Me); MS *m/z* : 280 (M^+, 1), 262 (1), 235 (4), 220 (4), 218 (16), 177 (35), 159 (68), 91 (55), 45 (100).

113: ^{1}H-NMR (200MHz, $CDCl_3$): δ 6.11-5.75 (1H, br. m, -$CH_2\underline{CH}=CH_2$), 5.32-4.81 (4H, br. m, C(5)=$\underline{CH_2}$ and -$CH_2CH=\underline{CH_2}$), 4.68 (1H, br. s, -O$\underline{CH_2}$OMe), 4.53 (1H, br. s, -O$\underline{CH_2}$OMe), 4.31 (1H, br. s, H-6), 3.72-3.60 (1H, br. m, H-1), 3.34 (3H, s, -$OCH_2O\underline{Me}$), 2.65-2.51 (1H, br. m, -$\underline{CH_2}CH=CH_2$), 2.21-1.50 (11H, br. m), 1.09 (3H, br. s, -Me); ^{13}C-NMR (200MHz, $CDCl_3$): δ 155.1 (br., C-5), 137.8 (br., -CH_2-$\underline{CH}=CH_2$), 115.1 (br., -CH_2-$CH=\underline{CH_2}$), 104.9 (br., C(5)=$\underline{CH_2}$), 95.3 (br., -O$\underline{CH_2}$OMe), 76.3 (br., C-1), 69.8 (br., C-6), 55.9 (-$OCH_2O\underline{Me}$), 45.5 (br.), 44.0 (br.), 36.3 (br.), 32.0 (br.), 30.9 (br.), 27.4 (br.), 27.2 (br.), 22.9 (br., -Me), 25.5 (br.), 20.2 (br.); ^{1}H-NMR (400MHz, DMSO-d_6, 373K): δ 6.03-5.92 (1H, m, -$CH_2\underline{CH}=CH_2$), 5.22 (1H, d, J=1.8Hz, C(5)=$\underline{CH_2}$), 4.99-4.89 (2H, m, -$CH_2CH=\underline{CH_2}$), 4.80 (1H, d, J=1.8Hz, C(5)=$\underline{CH_2}$), 4.60 (1H, d, J=6.6Hz, -O$\underline{CH_2}$OMe), 4.48 (1H, d, J=6.6Hz, -O$\underline{CH_2}$OMe), 4.14 (1H, dd, J=9.8, 5.6Hz, H-6), 3.59 (1H, dd, J=9.7, 4.0Hz, H-1), 2.53 (1H, dd, J=14.4, 6.6Hz, -$\underline{CH_2}CH=CH_2$), 1.99-1.40 (11H, m), 1.07 (3H, s, -Me); ^{13}C-NMR (400MHz, DMSO-d_6, DEPT, 373K): δ 155.2 (s, C-5), 136.8 (d, -CH_2-$\underline{CH}=CH_2$), 114.4 (t, -CH_2-$CH=\underline{CH_2}$), 105.6 (t, C(5)=$\underline{CH_2}$), 94.8 (t, -O$\underline{CH_2}$OMe), 76.0 (d, C-1), 68.2 (d, C-6), 54.4 (q, -$OCH_2O\underline{Me}$), 43.5 (s, C-8a), 41.5 (s, C-4a), 34.7 (t), 32.0 (t), 29.8 (t), 25.9 (t), 25.4 (q, -Me), 24.5 (t), 18.9 (t); MS *m/z* : 280 (M^+, 1), 262 (7), 218 (24), 159 (51), 105 (44), 91 (42), 45 (100).

3.5.6. (1R,4aS,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxymethyl)-oxy)-4a-methyl-5-methylene-6-(5H)-naphthaleneone (114)

To a solution of **112/113** (150mg, 0.54mmol) in DMSO (5ml) was slowly added a solution of IBX (195mg, 0.70mmol) in DMSO (1ml) at room temperature. The clear solution was stirred for 90min. at room temperature, then poured into 5% aqueous Na_2CO_3/ice and extracted with ethyl acetate (3x10ml). The combined organic extracts were washed with water (2x5ml) and brine (1x5ml), dried with $MgSO_4$ and evaporated under reduced pressure yielding **114** (147mg, 99%) as a clear semicrystalline oil.#

114: ^{1}H-NMR (200MHz, $CDCl_3$): δ 6.05-5.80 (1H, br. m, -CH_2<u>CH</u>=CH_2), 5.80 (1H, s, C(5)=<u>CH_2</u>), 5.19 (1H, s, C(5)=<u>CH_2</u>), 5.18-5.02 (2H, m, -CH_2CH=<u>CH_2</u>), 4.68 (1H, d, J=7.0Hz, -O<u>CH_2</u>OMe), 4.53 (1H, d, J=7.0Hz, -O<u>CH_2</u>OMe), 3.57 (1H, br. s, H-1), 3.34 (3H, s, -OCH_2O<u>Me</u>), 2.85-1.3 (12H, br. m), 1.24 (3H, br. s, -Me); ^{13}C-NMR (200MHz, $CDCl_3$): δ 203.1 (C-6), 154.7 (C-5), 135.0 (-CH_2-<u>CH</u>=CH_2), 119.0 (-CH_2CH=<u>CH_2</u> or C(5)=<u>CH_2</u>), 116.8 (-CH_2CH=<u>CH_2</u> or C(5)=<u>CH_2</u>), 96.0 (-O<u>CH_2</u>OMe), 77.8 (C-1), 55.7 (-OCH_2O<u>Me</u>), 44.7 (C-8a), 42.4 (C-4a), 35.6, 33.8

The crude product **114** was sufficiently pure according to ^{1}H-NMR and ^{13}C-NMR, when ethyl acetate was used as an extraction solvent. When $CHCl_3$ was used as an extraction solvent in a preliminary experiment, the product was contaminated with ca. 5-10% DMSO. On purifying the crude product by column chromatography on silica gel, only ca. 50% of **114** was isolated, presumably due to decomposition. The lability of **114** was also observed when it was stored at -20°C over more than 2 days, after which about 10% had decomposed, according to ^{1}H-NMR.

(br.), 25.6, 24.4 (t), 22.4 (-Me), 18.2; ^{1}H-NMR (400MHz, DMSO-d_6, 373K): δ 6.05-5.91 (1H, m, -CH_2CH=CH_2), 5.75 (1H, s, C(5)=CH_2), 5.25 (1H, s, C(5)=CH_2), 5.13-5.03 (2H, m, -CH_2CH=CH_2), 4.67 (1H, d, J=6.6Hz, -OCH_2OMe), 4.57 (1H, d, J=6.6Hz, -OCH_2OMe), 3.54 (1H, dd, J=6.8, 3.7Hz, H-1), 3.31 (3H, s, -OCH_2OMe), 2.71 (1H, dd, J=14.4, 6.1Hz, -CH_2CH=CH_2), 2.41-1.30 (11H, m), 1.22 (3H, s, -Me); ^{13}C-NMR (400MHz, DMSO-d_6, DEPT, 373K): δ 200.6 (s, C-6), 154.7 (s, C-5), 135.0 (d, -CH_2-CH=CH_2), 118.0 (t, -CH_2CH=CH_2 or C(5)=CH_2), 115.9 (t, -CH_2CH=CH_2 or C(5)=CH_2), 95.3 (t, -OCH_2OMe), 76.9 (d, C-1), 54.7 (q, -OCH_2OMe), 44.3 (s, C-8a), 41.8 (s, C-4a), 34.5 (t), 33.8 (t), 33.5 (t), 24.9 (t), 24.4 (t), 22.6 (q, -Me), 17.7 (t); MS *m/z* : 278 (M^+, 10), 263 (6), 246 (15), 237 (16), 233 (28), 205 965), 175 (44), 91 (61), 45 (100).

3.5.7. (1R,4aR,5R,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-5-((methyl)diethylacetamidomalonate))-6-(5H)-naphthaleneone (**115**)

To a solution of diethyl acetamidomalonate (406mg, 1.87mmol) in EtOH (7ml) was added a EtONa solution (0.86mmol, 19.7mg Na in 0.7ml EtOH) at 0°C. After the solution was stirred for 10min. at 0°C, a solution of **114** (217mg, 0.78mmol) in benzene (2ml) was added, and the solution was stirred for 20min. at 15°C. The mixture was poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (1x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with toluene/ ethyl acetate 2:1) yielding **115** as a semicrystalline oil (180mg, 47%), as well as a mixture of diethyl acetamidomalonate and **116**, which was further purified by column

chromatography on silica gel (elution with acetone/hexane 1:3) yielding **116** as a semicrystalline oil (119mg, 31%).

115: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.67 (1H, s, NH), 5.94-5.83 (1H, m, $-CH_2\underline{CH}=CH_2$), 5.20-5.11 (2H, m, $-CH_2CH=\underline{CH_2}$), 4.66 (1H, d, J=6.9Hz, $-O\underline{CH_2}OMe$), 4.54 (1H, d, J=6.9Hz, $-O\underline{CH_2}OMe$), 4.23-4.11 (4H, m, 2x $-COO\underline{CH_2}CH_3$), 3.39 (1H, t, J=2.5Hz, H-1), 3.36 (3H, s, $-OCH_2O\underline{Me}$), 2.91 (1H, dd, J=13.8, 5.1Hz, $-\underline{CH_2}CH=CH_2$), 2.64-2.59 (2H, m, C(5)H-$\underline{CH_2}$- and H-5), 2.46-2.32 (3H, m, $-\underline{CH_2}CH=CH_2$, C(5)H-$\underline{CH_2}$- and H-7), 2.06 (1H, ddd, J=12.8, 3.6 and 2.9Hz, H-7eq.), 1.97 (3H, s, COMe), 1.96-1.85 (1H, m, H-8ax.), 1.77-1.73 (1H, m, H-2), 1.63-1.48 (3H, m, H-8, H-3 and H-2), 1.40-1.31 (1H, m, H-3), 1.26 (3H, t, J=7.2Hz, $-COOCH_2\underline{CH_3}$), 1.22 (3H, t, J=7.1Hz, $-COOCH_2\underline{CH_3}$), 1.21-1.11 (2H, m, H-4), 1.19 (3H, s, -Me); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 211.4 (s, C-6), 169.2 (s), 168.8 (s), 167.9 (s), 134.4 (d, $-CH_2-\underline{CH}=CH_2$), 117.8 (t, $-CH_2CH=\underline{CH_2}$), 96.6 (t, $-O\underline{CH_2}OMe$), 79.0 (d, C-1), 65.4 (s, C(5)$CH_2-\underline{C}$-$(COOEt)_2NHCOMe$), 62.7 (t, $-COO\underline{CH_2}CH_3$), 62.0 (t, $-COO\underline{CH_2}CH_3$), 55.9 (q, $-OCH_2O\underline{Me}$), 51.9 (d, C-5), 45.8 (s, C-8a), 43.3 (s, C-4a), 37.4 (t, C-7), 32.3 (t, $-\underline{CH_2}CH=CH_2$), 30.1 (t, C-8), 29.8 (t, C-4), 25.8 (t, C-2), 25.1 (t, C(5)H-$\underline{CH_2}$-), 22.8 (q, $-CO\underline{Me}$), 20.5 (q, -Me), 16.5 (t, C-3), 13.9 (t, $-COOCH_2\underline{CH_3}$), 13.7 (t, $-COOCH_2\underline{CH_3}$); MS *m/z* : 495 (M^+, 8), 450 (10), 390 (15), 217 (79), 171 (51), 45 (100).

116: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.68 (1H, s, NH), 5.94-5.88 (1H, m, $-CH_2\underline{CH}=CH_2$), 4.94-4.87 (2H, m, $-CH_2CH=\underline{CH_2}$), 4.78 (1H, d, J=7.1Hz, $-O\underline{CH_2}OMe$), 4.58 (1H, d, J=7.1Hz, $-O\underline{CH_2}OMe$), 4.25-4.09 (5H, m, 2x $-COO\underline{CH_2}CH_3$ and H-1), 3.36 (3H, s, $-OCH_2O\underline{Me}$), 2.85 (1H, br. d, J=9.6Hz, H-5), 2.65 (1H, dd, J=9.6, 14.5Hz, C(5)H-$\underline{CH_2}$-), 2.59-2.50 (2H, m, $-\underline{CH_2}CH=CH_2$ and H-7), 2.38 (1H, d, J=14.5Hz, C(5)H-$\underline{CH_2}$-), 2.22-2.12 (3H, m, $-\underline{CH_2}CH=CH_2$, H-7 and H-4ax.), 1.98 (3H, s, COMe), 1.97-1.91 (1H, m, H-2), 1.66-1.54 (3H, m, H-2, H-3 and H-4eq.), 1.51-1.38 (3H, m, H-3 and H-8), 1.27 (3H, t, J=7.2Hz,-

$COOCH_2\underline{CH_3}$), 1.21 (3H, t, J=7.2Hz, $-COOCH_2\underline{CH_3}$), 0.72 (3H, s, -Me); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 212.2 (s, C-6), 169.2 (s), 169.1 (s), 167.9 (s), 137.3 (d, $-CH_2-\underline{CH}=CH_2$), 115.7 (t, $-CH_2CH=\underline{CH_2}$), 94.9 (t, $-O\underline{CH_2}OMe$), 75.1 (d, C-1), 65.4 (s, $C(5)CH_2-\underline{C}-(COOEt)_2NHCOMe$), 62.8 (t, $-COO\underline{CH_2}CH_3$), 62.0 (t, $-COO\underline{CH_2}CH_3$), 55.6 (q, $-OCH_2O\underline{Me}$), 49.3 (s, C-8a), 47.2 (d, C-5), 44.0 (s, C-4a), 37.8 (t, C-7 or $-\underline{CH_2}CH=CH_2$), 35.8 (t, C-7 or $-\underline{CH_2}CH=CH_2$), 30.8 (t, C-8), 29.1 (t, C-4), 27.0 (t, C(5)H-$\underline{CH_2}$-), 26.4 (t, C-2), 23.0 (q, -CO$\underline{Me}$), 19.6 (t, C-3), 19.1 (q, -Me), 13.8 (t, $-COOCH_2\underline{CH_3}$), 13.7 (t, $-COOCH_2\underline{CH_3}$); MS *m/z* : 495 (M^+, 15), 450 (18), 390 (24), 360 (25), 217 (86), 171 (54), 45 (100).

3.5.8. Synthesis of (1R,4aR,5R,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxy-methyl)oxy)-4a-methyl-5-(3'-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**121**) via Decarboxylation of (**119**)

3.5.8.1. (1R,4aR,5R,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxy-methyl)oxy)-4a-methyl-5-(methyl(dimethylmalonate))-6-(5H)-naphthaleneone (**119**)

To a solution of dimethylmalonate (429mg, 3.25mmol) in MeOH (20ml) was added a MeONa solution (2.38mmol, 55mg Na in 3ml MeOH) at 0°C. After the solution was stirred for 10min. at 0°C, a solution of **114** (603mg, 2.17mmol) in benzene (4ml) was added, and the solution was stirred for 30min. at 15°C, then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with brine (1x10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column

chromatography on silica gel (elution with toluene/ ethyl acetate 6:1) yielding **119** (649mg, 73%) and **118** (116mg, 13%) as clear oils.

119: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.90-5.79 (1H, m, -CH_2<u>CH</u>=CH_2), 5.13-5.05 (2H, m, -CH_2CH=<u>CH_2</u>), 4.63 (1H, d, J=7.0Hz, -O<u>CH_2</u>OMe), 4.50 (1H, d, J=7.0Hz, -O<u>CH_2</u>OMe), 3.65 (6H, s, 2xCOOMe), 3.33 (1H, t, J=2.5Hz, H-1), 3.31 (3H, s, -OCH_2O<u>Me</u>), 3.32-3.28 (1H, m, H-5), 2.85 (1H, dd, J=13.8, 4.9Hz, -<u>CH_2</u>$CH=CH_2$), 2.49 (1H, d, J=10.6Hz, -<u>CH</u>$(COOMe)_2$), 2.42-2.31 (2H, m, -<u>CH_2</u>$CH=CH_2$, H-7), 2.18-2.05 (2H, m, H-7, C(5)H-<u>CH_2</u>-), 1.88 (1H, dt, J=14.1, 4.2Hz, H-8ax.), 1.82-1.70 (2H, m, H-2, C(5)H-<u>CH_2</u>-), 1.68-1.45 (3H, m, H-2, H-3, H-8eq.), 1.40-1.31 (1H, m, H-3), 1.24 (3H, s, -Me), 1.29-1.10 (2H, m, H-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 211.2 (s, C-6), 169.8 (s, <u>CO</u>OMe), 169.7 (s, <u>CO</u>OMe), 134.2 (d, -CH_2-<u>CH</u>=CH_2), 117.7 (t, -CH_2CH=<u>CH_2</u>), 96.5 (t, -O<u>CH_2</u>OMe), 78.9 (d, C-1), 55.7 (q, -OCH_2O<u>Me</u>), 54.0 (d, -<u>CH</u>$(COOMe)_2$), 52.3 (q, -COO<u>Me</u>), 52.1 (q, -COO<u>Me</u>), 50.3 (d, C-5), 45.2 (s, C-8a), 42.9 (s, C-4a), 37.5 (t, C-7), 32.1 (t, -<u>CH_2</u>$CH=CH_2$), 30.0 (t, C-8), 29.5 (t, C-4), 24.9 (t, C-2), 21.9 (t, C(5)H-<u>CH_2</u>-), 20.7 (q, -Me), 16.5 (t, C-3); MS *m/z* : 410 (M^+, 5), 379 (9), 347 (20), 205 (29), 45 (100).

118: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.02-5.91 (1H, m, -CH_2<u>CH</u>=CH_2), 4.93-4.91 (2H, m, -CH_2CH=<u>CH_2</u>), 4.78 (1H, d, J=7.0Hz, -O<u>CH_2</u>OMe), 4.58 (1H, d, J=7.0Hz, -O<u>CH_2</u>OMe), 4.25 (1H, dd, J=10.5, 4.2Hz, H-1), 3.73 (3H, s, -COO<u>Me</u>), 3.72 (3H, s, -COO<u>Me</u>), 3.44 (1H, dd, J=10.9, 3.6Hz, -<u>CH</u>$(COOMe)_2$), 3.37 (3H, s, -OCH_2O<u>Me</u>), 2.85 (1H, d, J=10.7Hz, H-5), 2.63-2.53 (2H, m, , C-7, -<u>CH_2</u>$CH=CH_2$), 2.28-2.15 (4H, H-7, H-4, -<u>CH_2</u>$CH=CH_2$, C(5)H-<u>CH_2</u>-), 2.05-1.96 (1H, m, H-2), 1.82 (1H, m, C(5)H-<u>CH_2</u>-), 1.72-1.45 (6H, m, H-2, H-3, H-4, H-8), 0.77 (3H, s, -Me); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 212.4 (s, C-6), 170.1 (s, <u>CO</u>OMe), 169.9 (s, <u>CO</u>OMe), 137.4 (d, -CH_2-<u>CH</u>=CH_2), 115.8 (t, -CH_2CH=<u>CH_2</u>), 95.1 (t, -O<u>CH_2</u>OMe), 74.9 (d, C-1), 55.7 (q, -OCH_2O<u>Me</u>), 52.6 (q, -COO<u>Me</u>), 52.5 (q, -COO<u>Me</u>), 50.0 (d, -<u>CH</u>$(COOMe)_2$), 49.3 (d, C-5), 48.8 (s, C-8a), 43.8 (s, C-4a),

38.0 (t, C-7), 35.8 (t, -$\underline{CH_2}CH=CH_2$), 30.9 (t, C-8), 29.0 (t, C-4), 26.6 (t, C-2), 22.8 (t, C(5)H-$\underline{CH_2}$-), 19.4 (t, C-3), 18.7 (q, -Me); MS *m/z* : 410 (M^+, 5), 379 (9), 347 (20), 205 (29), 45 (100).

3.5.8.2. (1R,4aR,5R,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxy-methyl)oxy)-4a-methyl-5-(methyl(monomethylmalonate))-6-(5H)-naphthaleneone

To a mixture of **119** (196mg, 0.48mmol) in 80% aqueous MeOH (6ml) was added a solution of KOH (134mg, 2.39mmol) in 80% aqueous MeOH (1ml) and the yellow solution was stirred for 45min. at room temperature, then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x5ml), dried with $MgSO_4$ and evaporated under reduced pressure yielding the title compound (186mg, 98%) as a yellow oil.

^{1}H-NMR (200MHz, $CDCl_3$): δ 9.5-8.6 (1H, br. s, -COOH), 6.03-5.81 (1H, m, -$CH_2\underline{CH}=CH_2$), 5.20-5.08 (2H, m, -$CH_2CH=\underline{CH_2}$), 4.69 (1H, d, J=6.9Hz, -O$\underline{CH_2}$OMe), 4.56 (1H, d, J=6.9Hz, -O$\underline{CH_2}$OMe), 3.72 (3H, s, COOMe), 3.41-3.36 (2H, m, H-1, H-5), 3.37 (3H, s, -$OCH_2O\underline{Me}$), 2.93-2.82 (1H, m, -$\underline{CH_2}CH=CH_2$), 2.69-1.20 (14H, m), 1.29 (3H, s, -Me); ^{13}C-NMR (200MHz, $CDCl_3$, DEPT): δ 212.0 (s, C-6), 173.5 (s, $\underline{CO}$OH),170.0 (s, $\underline{CO}$OMe), 134.3 (d, -CH_2-$\underline{CH}=CH_2$), 118.0 (t, -$CH_2CH=\underline{CH_2}$), 96.7 (t, -O$\underline{CH_2}$OMe), 79.1 (d, C-1), 55.9 (q, -$OCH_2O\underline{Me}$), 54.4 (d, -$\underline{CH}$COOMe), 52.5 (q, -COO$\underline{Me}$), 50.4 (d, C-5), 45.5 (s, C-8a), 43.2 (s, C-4a), 37.7 (t, C-7), 32.3 (t, -$\underline{CH_2}CH=CH_2$), 30.3 (t, C-8), 29.7 (t, C-4), 25.2 (t, C-2), 22.4 (t, C(5)H-$\underline{CH_2}$-), 21.0 (q, -Me), 16.7 (t, C-3); MS *m/z* : 396 (M^+, 1), 378 (2), 352 (4), 275 (46), 205 (48), 44 (100).

3.5.8.3. (1R,4aR,5R,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxy-methyl)oxy)-4a-methyl-5-(3'-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**121**)

A solution of the monomethyl malonate described above (578mg, 1.46mmol) in p-xylene (50ml) was refluxed for 4h. The solution was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (elution with toluene/ ethyl acetate 5:1) yielding **121** (154mg, 30%) as white crystals, as well as **120** (108mg, 21%) as a clear oil.

121: mp. 73-75°C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.92-5.84 (1H, m, -CH_2C<u>H</u>=CH_2), 5.18-5.09 (2H, m, -CH_2CH=C<u>H</u>$_2$), 4.68 (1H, d, J=6.8Hz, -O<u>C</u>H_2OMe), 4.55 (1H, d, J=6.8Hz, -O<u>C</u>H_2OMe), 3.62 (3H, s, COOMe), 3.41-3.34 (2H, m, H-1, H-5), 3.37 (3H, s, -OCH_2O<u>Me</u>), 2.94-2.89 (1H, m, -<u>C</u>H_2CH=CH_2), 2.60-1.15 (15H, m), 1.29 (3H, s, -Me); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 209.4 (s, C-6), 174.0 (s, <u>C</u>OOMe), 134.4 (d, -CH_2-<u>C</u>H=CH_2), 117.7 (t, -CH_2CH=<u>C</u>H$_2$), 96.6 (t, -O<u>C</u>H_2OMe), 79.1 (d, C-1), 56.3 (d, C-5), 55.8 (q, -OCH_2O<u>Me</u>), 51.3 (q, -COO<u>Me</u>), 45.4 (s, C-8a), 43.0 (s, C-4a), 37.9 (t, C-7), 33.3 (t, -<u>C</u>H_2COOMe), 32.2 (t, -<u>C</u>H_2CH=CH_2), 30.1 (t, C-8), 29.8 (t, C-4), 25.1 (t, C-2), 21.1 (q, -Me), 17.7 (t, C(5)H-<u>C</u>H_2-), 16.7 (t, C-3); MS *m/z* : 352 (M^+, 5), 321 (8), 275 (34), 217 (41), 45 (100).

120: ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.03-5.92 (1H, m, -CH_2<u>C</u>H=CH_2), 4.97-4.88 (2H, m, -CH_2CH=<u>C</u>H$_2$), 4.79 (1H, d, J=7.1Hz, -O<u>C</u>H_2OMe), 4.58 (1H, d, J=7.1Hz, -O<u>C</u>H_2OMe), 4.32 (1H, dd, J=10.4, 4.1Hz, H-1), 3.65 (3H, s, -COO<u>Me</u>), 3.38 (3H, s, -OCH_2O<u>Me</u>), 2.83 (1H, d, J=10.6Hz, H-5), 2.65-1.40 (16H, m), 0.76 (3H, s, -Me); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 212.8 (s, C-6), 174.2 (s, <u>C</u>OOMe), 137.5 (d, -CH_2-<u>C</u>H=CH_2), 115.7 (t, -CH_2CH=<u>C</u>H$_2$), 95.8 (t, -O<u>C</u>H_2OMe), 74.7 (d, C-1), 55.7 (q, -OCH_2O<u>Me</u>), 51.5 (q, -COO<u>Me</u>), 49.3 (d, C-5), 49.1 (s, C-8a), 43.7 (s, C-4a),

38.1 (t), 35.8 (t), 32.8 (t), 30.9 (t), 29.1 (t), 26.5 (t), 19.6 (t), 18.8 (q, -Me), 18.2 (t), 17.3 (t); MS *m/z* : 352 (M^+, 14), 320 (12), 275 (30), 235 (40), 45 (100).

3.5.9. Synthesis of (1R,4aR,5R,8aR)-1,2,3,4,4a,7,8,8a-Octahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-5-(3'-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**121**) via Methyl-phenylsulfonyl Acetate Addition

To a solution of methylphenylsulfonylacetate (1.62g, 5.03mmol) in MeOH (50ml) was added a MeONa solution (3.69mmol, 84.8mg Na in 4ml MeOH) at 0°C. After the solution was stirred for 10min. at 0°C, a solution of **114** (933mg, 3.35mmol) in benzene (5ml) was added. The solution was stirred for 75min. at 15°C, then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x15ml). The combined organic extracts were washed with brine (1x10ml), dried with $MgSO_4$ and evaporated under reduced pressure, yielding a mixture of diastereomers and excess methyl phenylsulfonylacetate. The crude mixture (2.6g) was dissolved in MeOH (50ml), Na_2HPO_4 (7.15g, 33.5mmol) and 5% sodium amalgam (23.2g, 33.5mmol Na) were added added at 0°C. The mixture was stirred at 0°C for 30min. and 1h at room temperature, then poured into 5% aqueous Na_2CO_3l/ice. After draining off the mercury, the mixture was extracted with $CHCl_3$ (3x15ml). The combined organic extracts were washed with water (1x30ml) and brine (1x30ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with toluene/ ethyl acetate 1:1) yielding **121** (1.03g, 87%) as white crystals and **120** (59mg, 5%).

120 and **121** had the same spectroscopic properties as those of the previous preparations.

3.5.10. Synthesis of (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**122**)

3.5.10.1. The Lombardo Reagent

The Lombardo reagent was made according to a modified literature procedure.[50] Instead of stirring the mixture at 0°C for 3 days, the Lombardo reagent was stored at 0°C in the refrigerator for 5 days. The activity of the Lombardo reagent was determined as follows: 1ml of the Lombardo reagent was added to a solution of cyclooctanone (100mg, 0.548mmol) in CH_2Cl_2 (2ml) at room temperature. The mixture was stirred for 15min. and an analytical sample of the reaction mixture was poured into 10% aqueous HCl/ice and extracted with ethyl acetate. The organic extract was then analysed by GC, giving an average activity for the Lombardo reagent of ca. 37.9mmol/100ml.

3.5.10.2. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**122**)

To a solution of **121** (500mg, 1.42mol) in CH_2Cl_2 (10ml) was slowly added the Lombardo reagent (6.5ml, 2.85mmol) at room temperature. The mixture was stirred for 10min. at room temperature, then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x10ml). The combined organic extracts were washed with water (1x10ml), brine (1x10ml), dried with $MgSO_4$ and evaporated under

reduced pressure, yielding **122** (487mg, 98%) as a yellow oil which had the same spectroscopic properties as the one previously isolated.

3.5.11. Synthesis of (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl -6- methylene-5- (3' (2'- N- benzyloxycarbonyl amino)propanoic acid)naphthalene methyl ester (**127**)

3.5.11.1. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'(2'-hydroxy)-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**123**)

To a solution of KHMDS[65] (365mg, 2.27mmol) in THF (9ml) was added a solution of **122** (265mg, 0.76mmol) in THF (3ml) at -78°C. The red solution was stirred at -78°C for 30min. and then a solution of 2-(phenylsulfonyl)-3-phenyloxaziridine[66] (593mg, 2.27mmol) in THF (3ml) was added. The mixture was stirred for 20min. at -78°C, then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x 30ml). The combined organic extracts were washed with water (1x 10ml), brine (1x 10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with CH_2Cl_2 to remove the excess 2-(phenylsulfonyl)-3-phenyloxaziridine, and then toluene/ ethyl acetate 8:1) yielding a diastereomeric mixture of **123** (194mg, 70%) as a clear oil.

An analytical sample of the epimeric mixture was carefully separated by column chromatography on silica gel (elution toluene/ ethyl acetate 8:1) yielding **123a** and **123b** as clear oils.

123a: R_f: 0.6 (toluene/ethyl acetate 3:1);^{1}H-NMR (400MHz, $CDCl_3$): δ 5.88-5.78 (1H, m, -CH_2<u>C</u>H=CH_2), 5.14-5.05 (2H, m, -CH_2CH=<u>CH_2</u>), 4.93 (1H, d, J=1.3Hz, C(6)=<u>CH_2</u>), 4.69 (1H, d, J=6.8Hz, -O<u>CH_2</u>OMe), 4.60 (1H, s, C(6)=C<u>H_2</u>), 4.57 (1H, d, J=6.8Hz, -O<u>CH_2</u>OMe), 4.22 (1H, dd, J=10.8, 1.9Hz, -<u>C</u>H(OH)COOMe), 3.80 (3H, s, -COOMe), 3.39 (3H, s, -OCH_2O<u>Me</u>), 3.33 (1H, t, J=2.8Hz, H-1), 2.77-2.73 (1H, m, -<u>CH_2</u>CH=CH_2), 2.60 (1H, d, J=11.4Hz, H-5), 2.50-2.44 (1H, m, -<u>CH_2</u>CH=CH_2), 2.26 (1H, m, H-7), 2.14-2.08 (1H, m, H'-7), 1.91 (1H, ddd, J=14.1, 11.4, 1.8Hz, -C(5)H-<u>CH_2</u>-), 1.78-1.71 (1H, m, H-2), 1.69-1.51 (5H, m, H'-2, H'-3, H'-4, H'-8, -C(5)H-<u>CH_2</u>-), 1.40-1.35 (2H, m, H-8, H-3), 1.22 (3H, s, -Me), 0.99-0.95 (1H, m, H-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 176.5 (s, -<u>C</u>OOMe), 148.0 (s, C-6), 135.1 (d, -CH_2-<u>C</u>H=CH_2), 117.1 (t, -CH_2CH=<u>CH_2</u>), 107.2 (t, C(6)=<u>CH_2</u>), 96.9 (t, -O<u>CH_2</u>OMe), 80.3 (d, C-1), 69.2 (d, -<u>C</u>H(OH)COOMe), 55.8 (q, -OCH_2O<u>Me</u>), 52.5 (q, -COO<u>Me</u>), 44.9 (d, C-5), 43.4 (s, C-8a), 41.0 (s, C-4a), 32.9 (t, C-7), 32.0 (t, -<u>CH_2</u>CH=CH_2), 30.6 (t, -C(5)H-<u>CH_2</u>-), 30.55 (t, C-8), 29.3 (t, C-4), 25.5 (t, C-2), 21.7 (q, -Me), 16.8 (t, C-3); MS *m/z* : 366 (M^+, 2), 335 (5), 293 (17), 263 (15), 45 (100).

123b: R_f: 0.5 (toluene/ethyl acetate 3:1); ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.89-5.78 (1H, m, -CH_2<u>C</u>H=CH_2), 5.14-5.07 (2H, m, -CH_2CH=<u>CH_2</u>), 4.92 (1H, d, J=1.0Hz, C(6)=<u>CH_2</u>), 4.69 (1H, d, J=6.8Hz, -O<u>CH_2</u>OMe), 4.68 (1H, s, C(6)=C<u>H_2</u>), 4.56 (1H, d, J=6.8Hz, -O<u>CH_2</u>OMe), 4.16 (1H, dd, J=12.8, 5.2Hz, -<u>C</u>H(OH)COOMe), 3.79 (3H, s, -COOMe), 3.38 (3H, s, -OCH_2O<u>Me</u>), 3.30 (1H, t, J=2.8Hz, H-1), 2.77-2.71 (1H, m, -<u>CH_2</u>CH=CH_2), 2.43 (1H, d, J=10.1Hz, H-5), 2.42-2.36 (1H, m, -<u>CH_2</u>CH=CH_2), 2.24-2.09 (2H, m, H-7), 1.87-1.81 (2H, m, -C(5)H-<u>CH_2</u>-), 1.76-1.71 (1H, m, H-2), 1.68-1.50 (4H, m, H'-2, H'-3, H'-4, H'-8), 1.43-1.32 (2H, m, H-8, H-3), 1.19 (3H, s, -Me), 1.02-0.98 (1H, m, H-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 175.9 (s, -<u>C</u>OOMe), 148.2 (s, C-6), 135.1 (d, -CH_2-<u>C</u>H=CH_2), 117.1 (t, -CH_2CH=<u>CH_2</u>), 107.1 (t, C(6)=<u>CH_2</u>), 96.9 (t, -O<u>CH_2</u>OMe), 80.3 (d, C-1), 70.5 (d,

-CH(OH)COOMe), 55.8 (q, -OCH_2OMe), 52.2 (q, -COOMe), 45.1 (d, C-5), 43.4 (s, C-8a), 41.1 (s, C-4a), 32.9 (t, C-7), 32.0 (t, -$CH_2CH=CH_2$), 30.4 (t, C-8), 30.1 (t, -C(5)H-CH_2-), 29.0 (t, C-4), 25.5 (t, C-2), 21.4 (q, -Me), 16.8 (t, C-3); MS *m/z* : 366 (M^+, 5), 334 (5), 263 (14), 45 (100).

3.5.11.2. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'(2'-azido)-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**124**)

To a solution of **123** (288mg, 0.79mmol) and 2,6-lutidine (236mg, 2.21mmol) in CH_2Cl_2 (8ml) was added triflic anhydride (554mg, 1.98mmol) at -78°C. The solution was stirred at -78°C for 30min., then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x 30ml). The combined organic extracts were washed with water (1x 10ml), brine (1x 10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in acetonitrile (8ml), NaN_3 (204mg, 3.16mmol) and dibenzo-18-crown-6 (28mg, 0.08mmol) were added and the mixture was stirred overnight at room temperature. The mixture was poured into H_2O/ice and extracted with $CHCl_3$ (3x 30ml). The combined organic extracts were washed with water (1x 10ml), brine (1x 10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexanes / ethyl acetate 6:1) yielding a diastereomeric mixture of **124** (136mg, 44%) as a clear oil, as well as starting material **123** (60mg, 21%).

124: ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.89-5.73 (2H, m, 2x-$CH_2CH=CH_2$), 5.14-5.05 (4H, m, 2x-$CH_2CH=CH_2$), 4.93 (1H, s, C(6)=CH_2), 4.92 (1H, s, C(6)=CH_2), 4.67 (1H, d, J=6.8Hz, -OCH_2OMe), 4.66 (1H, d, J=7.0Hz, -OCH_2OMe), 4.56-4.53

(4H, m, 2xC(6)=C<u>H2</u>, 2x-O<u>CH2</u>OMe), 3.89 (1H, dd, J=11.6, 2.1Hz, -<u>CH</u>N3COOMe), 3.82 (1H, dd, J=10.7, 3.5Hz, -<u>CH</u>N3COOMe), 3.79 (6H, s, 2x-COOMe), 3.37 (3H, s, -OCH2O<u>Me</u>), 3.36 (3H, s, -OCH2O<u>Me</u>), 3.31 (1H, s, H-1), 3.29 (1H, s, H-1), 2.80-2.69 (2H, m, 2x-<u>CH2</u>CH=CH2), 2.50-2.35 (26H, m), 1.24 (3H, s, -Me), 1.20 (3H, s, -Me), 1.05-0.95 (2H, m, 2xH-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 171.8 (s, -<u>CO</u>OMe), 171.0 (s, -<u>CO</u>OMe), 147.3 (s, 2xC-6), 134.9 (d, 2x-CH2-<u>CH</u>=CH2), 117.1 (t, 2x-CH2CH=<u>CH2</u>), 107.2 (t, C(6)=<u>CH2</u>), 106.9 (t, C(6)=<u>CH2</u>), 96.7 (t, 2x-O<u>CH2</u>OMe), 80.1 (d, 2xC-1), 61.1 (d, -<u>CH</u>N3COOMe), 60.8 (d, -<u>CH</u>N3COOMe), 55.7 (q, 2x-OCH2O<u>Me</u>), 52.4 (q, -COO<u>Me</u>), 52.3 (q, -COO<u>Me</u>),45.6 (d, 2xC-5), 43.3 (s, C-8a), 43.2 (s, C-8a), 41.2 (s, C-4a), 41.1 (s, C-4a), 32.8 (t, C-7), 32.7 (t, C-7), 32.0 (t, -<u>CH2</u>CH=CH2), 31.9 (t, -<u>CH2</u>CH=CH2), 30.4 (t, C-8), 30.3 (t, C-8), 29.0 (t, C-4), 28.9 (t, C-4), 27.0 (t, -C(5)H-<u>CH2</u>-), 26.9 (t, -C(5)H-<u>CH2</u>-), 25.4 (t, C-2), 25.3 (t, C-2), 21.4 (q, -Me), 21.3 (q, -Me),16.7 (t, C-3), 16.6 (t, C-3); MS *m/z* : 363 (M^+-N_2, 34), 348 (25), 305 (35), 304 (75), 302 (100), 45 (95); IR (5% in CCl_4, cm^{-1}): 2103, 1749.

<u>3.5.11.3. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'(2'-azido)-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**124**) via Direct Azidation of (**122**)</u>

To a solution of KHMDS[67] (441mg, 2.74mmol) in THF (12ml) was added a solution of **122** (320mg, 0.91mmol) in THF (2ml) at -78°C. The red solution was stirred at -78°C for 30min. and then a solution of 2,4,6-triisopropyl-benzenesulfonyl azide[68] (848mg, 2.74mmol) in THF (2ml) was added and stirred for 5min at -78°C. Acetic acid (329mg, 5.48mmol) was added at -78°C and the mixture was stirred for 1.5h at room temperature. The solution was poured into

10% aqueous HCl/ice and extracted with $CHCl_3$ (3x 30ml). The combined organic extracts were washed with water (1x 10ml), 10% aqueous Na_2CO_3 (1x 10ml), water (1x 10ml) and brine (1x 10ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexanes / ethyl acetate 10:1) yielding a impure diastereomeric mixture of **124** (260mg, ca. 59%) as a yellow oil. The main compound had the same spectroscopic properties as the one previously isolated. Nevertheless, some impurities were seen in the ^1H and ^{13}C NMR, and the isolated material was judged to be *ca.* 70% pure.

3.5.11.4. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'(2'-amino)-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**125**) via Hydrogenation of (**124**)

A solution of **124** (106mg, 0.27mmol) in EtOH (8ml) was stirred with Lindlar catalyst (20mg, 5% $Pd/CaCO_3$) under ca. 1.8atm of H_2 for 4h. The mixture was fitered through Celite 545 and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexanes / ethyl acetate 2:1 -> 1:2) yielding **126** (71mg, 69%), **125a** (11mg, 11%) and **125b** (11mg, 11%) as semicrystalline oils.

126: ^1H-NMR (400MHz, $CDCl_3$): δ 10.7-10.3 (1H, br. s, -C=C-OH), 5.89-5.77 (1H, m, $-CH_2CH=CH_2$), 5.13-5.04 (2H, m, $-CH_2CH=CH_2$), 4.83 (1H, s, C(6)=CH_2), 4.72 (1H, d, J=6.8Hz, $-OCH_2OMe$), 4.67 (1H, s, C(6)=CH_2), 4.59 (1H, d, J=6.8Hz, $-OCH_2OMe$), 3.41 (3H, s, $-OCH_2OMe$), 3.34 (1H, s, H-1), 2.85-2.72 (4H, m, $-CH_2CH=CH_2$, H-5, -C(5)H-CH_2-), 2.52-2.46 (1H, m, $-CH_2CH=CH_2$), 2.27-2.15 (1H, m, H'-7), 2.11-2.03 (1H, m, H-7), 1.82-1.59 (5H, m, H-2, H'-3, H'-4, H'-8),

1.49-1.38 (1H, m, H-8), 1.38 (3H, s, -Me), 1.18-1.11 (1H, m, H-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 156.4 (s, -C=C-OH), 147.8 (s, C-6), 135.1 (d, -CH_2-CH=CH_2), 117.2 (t, -CH_2CH=CH_2), 108.0 (t, C(6)=CH_2), 96.9 (t, -OCH_2OMe), 80.5 (d, C-1), 77.2 (s, -C=C-OH), 55.8 (q, -OCH_2OMe), 48.3 (d, C-5), 43.5 (s, C-8a), 41.2 (s, C-4a), 32.7 (t, C-7), 32.0 (t, -CH_2CH=CH_2), 30.4 (t, C-8), 28.9 (t, C-4), 25.5 (t, C-2), 21.9 (q, -Me), 18.7 (t, -C(5)H-CH_2-), 16.9 (t, C-3); MS *m/z* : 361 (M^+, 37), 333 (M^+-N_2, 64), 230 (64), 133 (79), 55 (100); HRMS *m/z* (M^+) calc. 361.2363, obs. 361.2365; IR (5% in CCl_4, cm^{-1}): 3199, 3109, 2988.

125a: R_f: 0.4 (hexane/ethyl acetate 1:2); ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.88-5.78 (1H, m, -CH_2CH=CH_2), 5.12-5.06 (2H, m, -CH_2CH=CH_2), 4.92 (1H, s, C(6)=CH_2), 4.69 (1H, d, J=6.9Hz, -OCH_2OMe), 4.62 (1H, s, C(6)=CH_2), 4.57 (1H, d, J=6.9Hz, -OCH_2OMe), 3.74 (3H, s, -COOMe), 3.47 (1H, d, J=8.5Hz, -CHNH_2COOMe), 3.39 (3H, s, -OCH_2OMe), 3.30 (1H, s, H-1), 2.76-2.71 (1H, m, -CH_2CH=CH_2), 2.38-2.32 (1H, m, -CH_2CH=CH_2), 2.26 (1H, d, J=10.5Hz, H-5), 2.22-2.08 (2H, m, H-7), 1.88-1.45 (7H, m, -C(5)H-CH_2-, H-2, H-3, H-4, H-8), 1.39-1.28 (2H, m, H-3', H-8'), 1.19 (3H, s, -Me), 1.03-.99 (1H, m, H-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 176.8 (s, -COOMe), 148.2 (s, C-6), 135.2 (d, -CH_2-CH=CH_2), 117.1 (t, -CH_2CH=CH_2), 106.9 (t, C(6)=CH_2), 96.9 (t, -OCH_2OMe), 80.3 (d, C-1), 55.8 (q, -OCH_2OMe), 54.1 (d, -CHNH_2COOMe),51.7 (q, -COOMe), 46.1 (d, C-5), 43.4 (s, C-8a), 41.1 (s, C-4a), 32.9 (t, C-7), 32.0 (t, -CH_2CH=CH_2), 30.7 (t, -C(5)H-CH_2-), 30.4 (t, C-8), 28.9 (t, C-4), 25.5 (t, C-2), 21.4 (q, -Me), 16.8 (t, C-3); MS *m/z* : 365 (M^+, 1), 350 (14), 306 (58), 88 (71), 45 (100).

125b: R_f: 0.2 (hexane/ethyl acetate 1:2); ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.89-5.78 (1H, m, -CH_2CH=CH_2), 5.14-5.04 (2H, m, -CH_2CH=CH_2), 4.92 (1H, s, C(6)=CH_2), 4.69 (1H, d, J=6.9Hz, -OCH_2OMe), 4.66 (1H, s, C(6)=CH_2), 4.57 (1H, d, J=6.9Hz, -OCH_2OMe), 3.73 (3H, s, -COOMe), 3.45 (1H, br. s, -CHNH_2COOMe), 3.39 (3H, s, -OCH_2OMe), 3.37 (1H, t, J=2.4Hz, H-1), 2.77-2.73 (1H, m,

-$\underline{CH_2}CH=CH_2$), 2.58 (1H, d, J=10.9Hz, H-5), 2.49-2.44 (1H, m, -$\underline{CH_2}CH=CH_2$), 2.25-2.15 (1H, m, H-7), 2.13-2.07 (1H, m, H-7'), 1.94-1.85 (1H, m, -C(5)H-$\underline{CH_2}$-), 1.78-1.71 (1H, m, H-2), 1.68-1.53 (5H, m, H'-2, H'-3, H'-4, H'-8, -C(5)H-$\underline{CH_2}$-), 1.41-1.32 (2H, m, H-8, H-3), 1.22 (3H, s, -Me), 1.00-0.97 (1H, m, H-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 177.8 (s, -$\underline{CO}$OMe), 148.0 (s, C-6), 135.2 (d, -CH_2-$\underline{CH}$=CH_2), 117.0 (t, -$CH_2CH=\underline{CH_2}$), 107.3 (t, C(6)=$\underline{CH_2}$), 96.9 (t, -O$\underline{CH_2}$OMe), 80.4 (d, C-1), 55.8 (q, -$OCH_2O\underline{Me}$), 55.9 (d, -$\underline{CH}NH_2COOMe$),52.0 (q, -COO$\underline{Me}$), 45.4 (d, C-5), 43.4 (s, C-8a), 41.0 (s, C-4a), 33.0 (t, C-7), 32.1 (t, -$\underline{CH_2}CH=CH_2$), 30.6 (t, C-8), 30.4 (t, -C(5)H-$\underline{CH_2}$-), 29.3 (t, C-4), 25.5 (t, C-2), 21.7 (q, -Me), 16.8 (t, C-3); MS *m/z* : 365 (M^+, 3), 350 (36), 306 (68), 88 (85), 45 (100).

3.5.11.5. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'(2'-amino)-propanoic acid)-6-(5H)-naphthaleneone methyl ester (**125**) via Triphenylphosphine Reduction of (**124**)

A solution of **124** (100mg, 0.26mmol), triphenylphosphine (71mg, 0.27mmol) in 80% aqueous THF (2ml) was stirred overnight. The solution was evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$, dried with $MgSO_4$, and again evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexanes / ethyl acetate 1:1 -> 1:2) yielding **125a** (38mg, 30%) and **125b** (39mg, 31%) as clear oils, which had the same spectroscopic properties as those of the previous preparations.

3.5.11.6. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'(2'-N-benzyloxycarbonylamino)-propanoic acid)naphthalene methyl ester (**127a**)

To a solution of **125a** (37mg, 0.11mmol) in CH_2Cl_2 (2ml) was added pyridine (15.5mg, 0.196mmol) and benzyl chloroformate (27.9mg, 0.163mmol). The mixture was stirred for 1h at room temperature, then poured into 10% aqueous HCl/ice and extracted with $CHCl_3$ (3x 5ml). The combined organic extracts were washed with water (1x 2ml) and brine (1x 2ml), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with hexanes / ethyl acetate 5:2) yielding **127a** (47mg, 91%) as a yellow oil.

127a: R_f: 0.8 (hexane/ethyl acetate 1:2); ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.40-7.27 (5H, m, Ph-H), 5.87-5.78 (1H, m, -CH_2C<u>H</u>=CH_2), 5.17-5.07 (5H, m, -NHCbz, -CH_2CH=C<u>H</u>$_2$, -CH_2-), 4.96 (1H, s, C(6)=C<u>H</u>$_2$), 4.70 (1H, s, C(6)=C<u>H</u>$_2$), 4.68 (1H, d, J=6.7Hz, -OC<u>H</u>$_2$OMe), 4.56 (1H, d, J=6.7Hz, -OC<u>H</u>$_2$OMe), 4.42 (1H, t, J=9.4Hz, -C<u>H</u>NHCbz), 3.74 (3H, br. s, -COOMe), 3.38 (3H, s, -OCH$_2$O<u>Me</u>), 3.29 (1H, s, H-1), 2.71-2.66 (1H, m, -C<u>H</u>$_2$CH=CH$_2$), 2.35-2.29 (2H, m, H-5, -C<u>H</u>$_2$CH=CH$_2$), 2.24-2.10 (2H, m, H-7), 1.96 (1H, t, J=12.4Hz, -C(5)H-C<u>H</u>$_2$-), 1.74 (1H, d, J=12.9Hz, H-2), 1.65-1.51 (5H, m, H'-2, H'-3, H'-4, H'-8, -C(5)H-C<u>H</u>$_2$-), 1.37-1.34 (2H, m, H-8, H-3), 1.17 (3H, s, -Me), 0.96-0.93 (1H, m, H-4); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 173.8 (s, -C<u>O</u>OMe), 156.4 (s, -NHCO-), 147.4 (s, C-6), 136.3 (s, Ph), 134.9 (d, -CH_2-C<u>H</u>=CH_2), 128.5 (d, Ph), 128.1 (d, Ph), 127.9 (d, Ph), 117.2 (t, -CH_2CH=C<u>H</u>$_2$), 107.4 (t, C(6)=C<u>H</u>$_2$), 96.8 (t, -OC<u>H</u>$_2$OMe), 80.3 (d, C-1), 66.9 (t, -CH_2-), 55.7 (q, -OCH$_2$O<u>Me</u>), 52.9 (d, -C<u>H</u>NHCbz), 52.2 (q, -COO<u>Me</u>), 45.3 (d, C-5), 43.3 (s, C-8a), 40.9 (s, C-4a), 32.8 (t, C-7), 32.0 (t, -C<u>H</u>$_2$CH=CH$_2$), 30.3 (t, C-

8), 29.1 (t, C-4), 28.4 (t, -C(5)H-$\underline{CH_2}$-), 25.4 (t, C-2), 21.7 (q, -Me), 16.7 (t, C-3); MS *m/z* : 499 (M^+, 0.3), 484 (0.2), 440 (1.3), 318 (13), 107 (50), 45 (100).

3.5.11.7. (1R,4aR,5S,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-8a-allyl-1-((methoxymethyl)oxy)-4a-methyl-6-methylene-5-(3'(2'-N-benzyloxycarbonylamino)-propanoic acid)naphthalene methyl ester (**127b**)

125b (39mg, 0.115mmol) was protected as the Cbz amine **127b** analogous to the procedure for **127a**, yielding **127b** (49mg, 90%) as a clear oil.
127a: R_f: 0.5 (hexane/ethyl acetate 1:2); ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.39-7.29 (5H, m, Ph-H), 5.88-5.78 (1H, m, -$CH_2\underline{CH}$=CH_2), 5.37 (1H, d, J=7.6Hz, -NHCbz), 5.12-5.06 (4H, m, -CH_2CH=$\underline{CH_2}$, -CH_2-), 4.94 (1H, s, C(6)=$\underline{CH_2}$), 4.74 (1H, s, C(6)=$\underline{CH_2}$), 4.68 (1H, d, J=6.7Hz, -O$\underline{CH_2}$OMe), 4.56 (1H, d, J=6.7Hz, -O$\underline{CH_2}$OMe), 4.37 (1H, dd, J=14.1, 7.4Hz, -$\underline{CH}$NHCbz), 3.74 (3H, br. s, -COOMe), 3.38 (3H, s, -OCH$_2$O$\underline{Me}$), 3.29 (1H, s, H-1), 2.74-2.70 (1H, m, -$\underline{CH_2}$CH=CH_2), 2.36-2.31 (2H, m, H-5 and -$\underline{CH_2}$CH=CH_2), 2.21-2.08 (2H, m, H-7), 1.88-1.81(2H, m, -C(5)H-$\underline{CH_2}$-), 1.74 (1H, d, J=13.0Hz, H-2), 1.63-1.45 (5H, m, H-2', H-3, H-4, H-8), 1.39-1.31 (2H, m, H-3', H-8'), 1.16 (3H, s, -Me), 0.98-0.95 (1H, m, H-4'); ^{13}C-NMR (400MHz, $CDCl_3$, DEPT): δ 173.1 (s, -$\underline{CO}$OMe), 155.5 (s, -NHCO-), 147.7 (s, C-6), 136.2 (s, Ph), 135.0 (d, -CH_2-$\underline{CH}$=CH_2), 128.4 (d, Ph), 128.1 (d, Ph), 128.0 (d, Ph), 117.2 (t, -CH_2CH=$\underline{CH_2}$), 107.3 (t, C(6)=$\underline{CH_2}$), 96.8 (t, -O$\underline{CH_2}$OMe), 80.2 (d, C-1), 66.8 (t, -CH_2-), 55.8 (q, -OCH$_2$O$\underline{Me}$), 53.7 (d, -$\underline{CH}$NHCbz), 52.0 (q, -COO$\underline{Me}$), 45.3 (d, C-5), 43.3 (s, C-8a), 41.1 (s, C-4a), 32.8 (t, C-7), 32.0 (t, -$\underline{CH_2}$CH=CH_2), 30.3 (t, C-8), 28.9 (t, C-4), 28.1 (t, -C(5)H-$\underline{CH_2}$-), 25.4 (t, C-2), 21.3 (q, -Me), 16.7 (t, C-3); MS *m/z* : 499 (M^+, 0.7), 440 (1.4), 318 (32), 107 (82), 91 (100), 45 (90).

3.6 Molecular Modeling Experiments

Molecules of interest were modeled with Macromodel™ version 3.5a[69] and Spartan.[70] The procedure used to calculate the local and global minimum energy conformations is as follows. A structure with the correct stereochemistry was drawn in Macromodel™, and the local energy minimum conformation was calculated using the MM2 parameters. A Monte Carlo search was then conducted using the automatic set-up, the calculation of at least 1000 different conformations with an iteration of 1500. The conformations of interest were transferred to Spartan and the geometry's were optimized using the AM1 semiempirical calculation subroutine.

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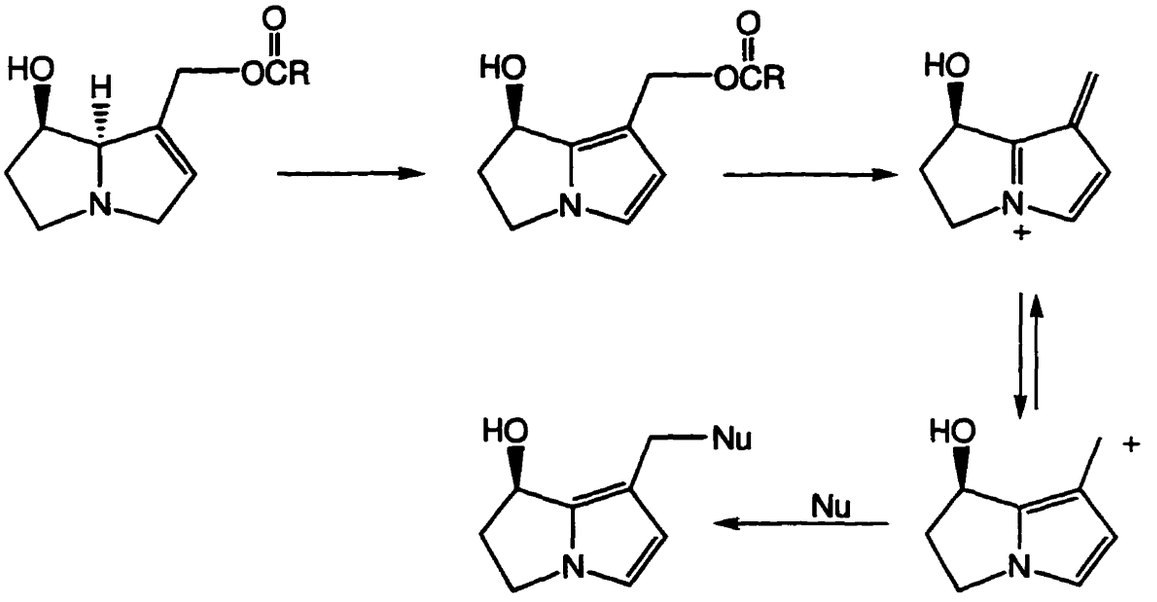
4. Part 2: Synthesis of Hadinecine

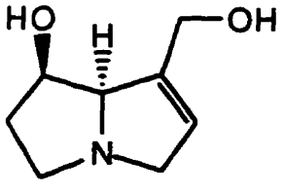
4.1. Introduction

The poisonous nature of *Senecio* and *Crotalaria* species to livestock has been known for centuries and has been documented as far back as 1787, when farmers in Great Britain suspected that Senecio *jacobaea L.* was harmful to their livestock.[1] Outbreaks of livestock diseases due to ingestion of *Senecio* or *Crotalaria* species were common all over the world during the turn of the century. Especially, during drought when food was in short supply. In most cases the livestock that ingested the infected pasture died within a few weeks of liver failure. Thus, the Pictou disease in Canada and the Winton disease in New Zealand, which killed thousands of animals, was caused by *Senecio* species, and the "Missouri River bottom disease" of horses, which raged through northwestern Nebraska in 1892 and killed more than 1800 animals, was believed to be caused by *Crotalaria* species.[1, 2] Even as recently as 1987, loss of livestock has been reported due to ingestion of these alkaloids.[3] Intoxication of humans can occur, especially when pyrrolizidine containing plants have grown among crops, and are milled along with the cereal. Thus, a severe outbreak of veno-occlusive disease of the liver occurred in Afghanistan in 1974, which affected 35,000 people.[4] In industrialized countries, it is less likely that pyrrolizidine contaminated cereal finds its way into the food chain. However, the recent trend in society towards "natural-nutrition and herbal-remedies", increases this health hazard tremendously.

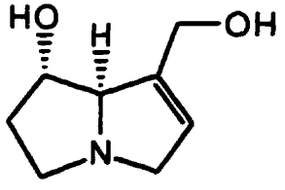
Scheme 1: Metabolism and Hepatotoxicity of PAs



Culvenor et al.[5] and Mattocks[6] were the first to suggest that the cytotoxic effects of PAs are associated with the reactivity of the allylic ester at C-1. Thus, PAs can act as highly reactive biological alkylating reagents. In order to form these toxic pyrrolic metabolites, it seems that the PAs must possess 1,2-unsaturation in the necine moiety, as well as being esterified at C-9. Some classic cytotoxic alkaloids are the allylic esters of the necines retronecine **1**, heliotridine **2** and supinidine **3**.



1



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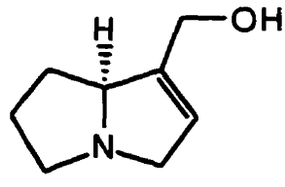
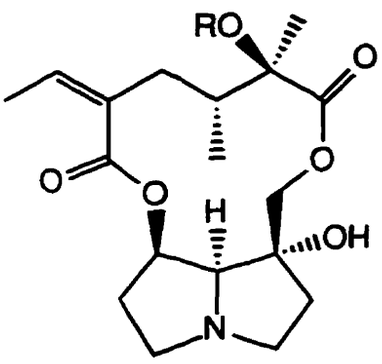
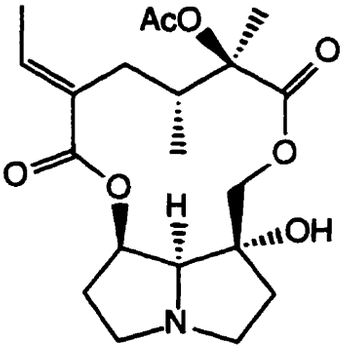


3

As a consequence of their biological activities, there has been continued interest in the PA content of *Senecio* species. Recently, during an investigation of the PAs of *Senecio hadiensis* Forsk., three new alkaloids (hadiensine **4**, 12-O-acetylhadiensine **5** and 12-O-acetylneohadiensine **6**) were isolated, and found to be derivatives of a previously unknown 1,7,9-pyrrolizidine triol named hadinecine **7**.[7] These were remarkable in as much that of the approximately 200 natural occurring pyrrolizidine alkaloids described to date, only four others are 1-hydroxylated, 7,9-di-O-angelyl-N-methyl-1-hydroxyplatynecinium chloride **8**,[8] curassanecine **9**,.[9] helibracteatine **10**[10] and helibracteatinine **11**.[10] Although



4: R=H
5: R=Ac



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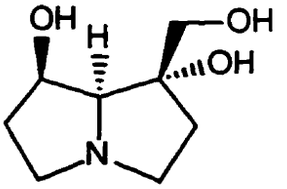
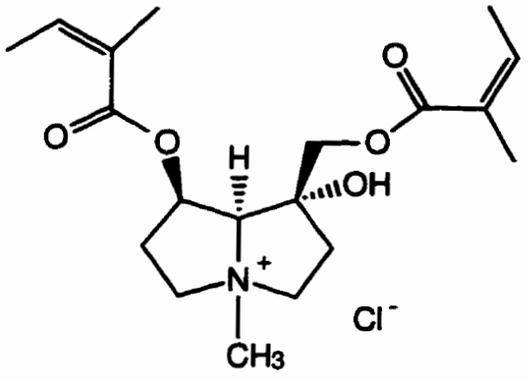


7

these alkaloids do not posses allylic esters at C-1, as the cytotoxic PAs described above, dehydration of the labile 1-hydroxy functionality would furnish the latter easily. Thus, these 1-hydroxy pyrrolizidines are potentially cytotoxic.

Our interest in synthesizing hadinecine stemmed from the fact that while the stereochemistry at C-7 and C-8 had been rigorously established by correlation of hadinecine with senecionine, that at C-1 rested on the observation that there was a down-field shift. of C-7 ^{1}H-NMR-signal by 0.25ppm on

acetylating of hadinecine at C-9. This was interpreted as revealing that H-7 and the acetate were *syn* to one other.[7] We proposed to check this by synthesizing **7**.



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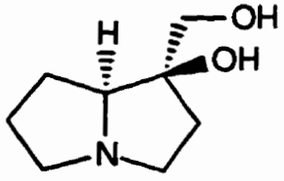

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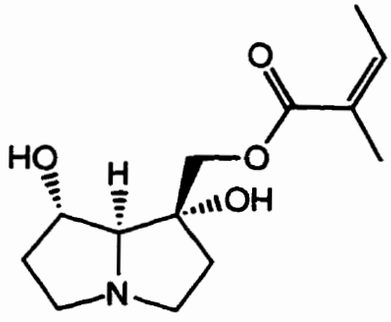

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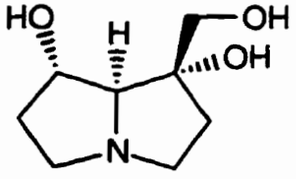
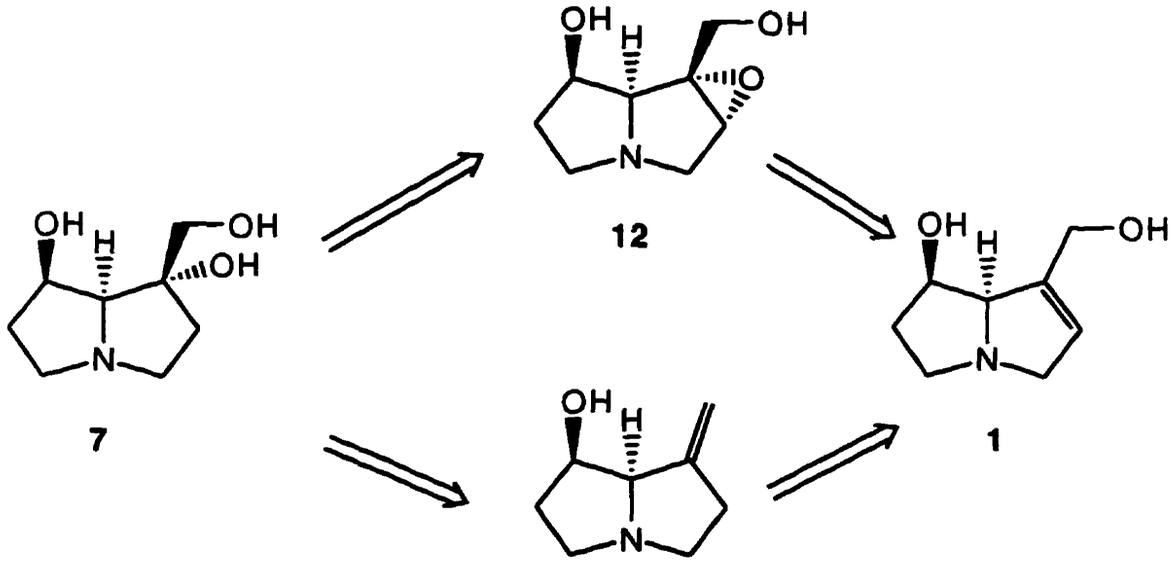


11

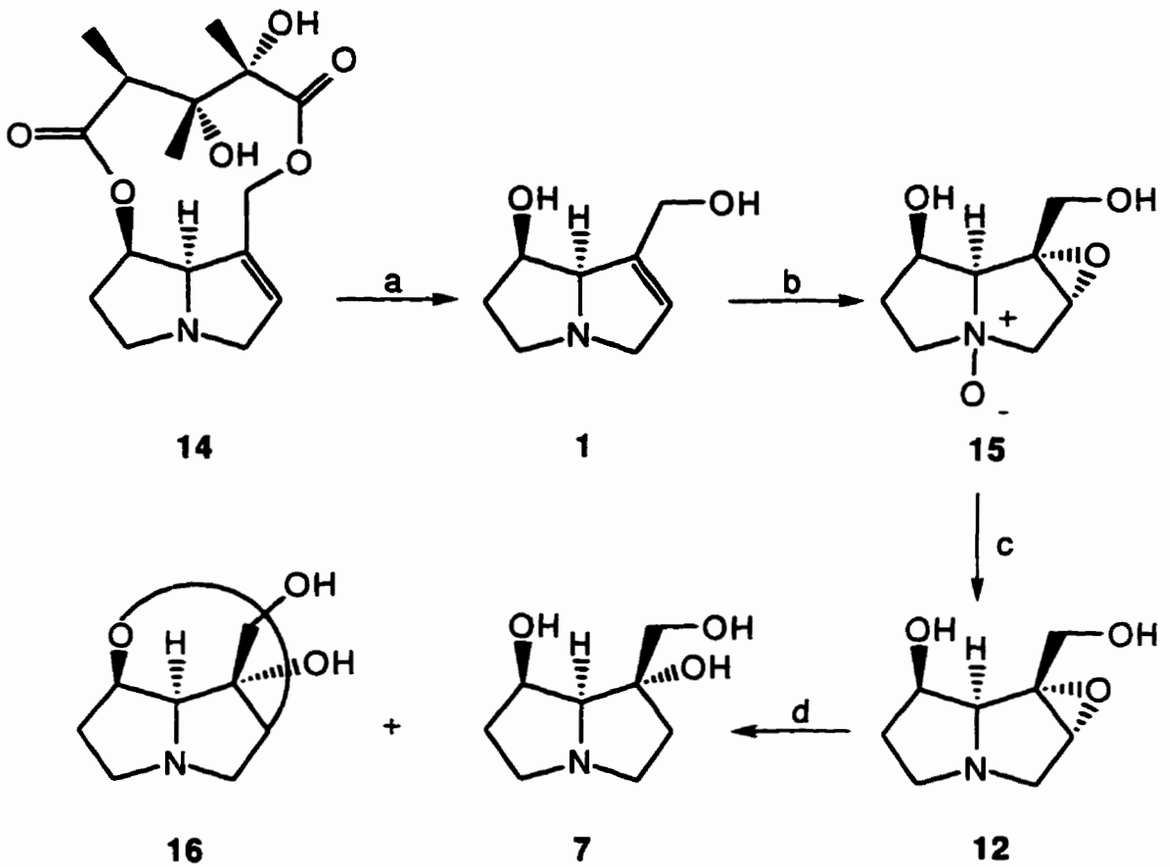
4.2. Synthesis of Hadinecine

Our retrosynthetic analysis of hadinecine suggested that it might be prepared from (+)-retronecine **1** by two routes (scheme 2), of which we decided to explore the first route via the known 1,2-α-epoxide **12**.[11]

Scheme 2: Retrosynthetic Analysis of Hadinecine



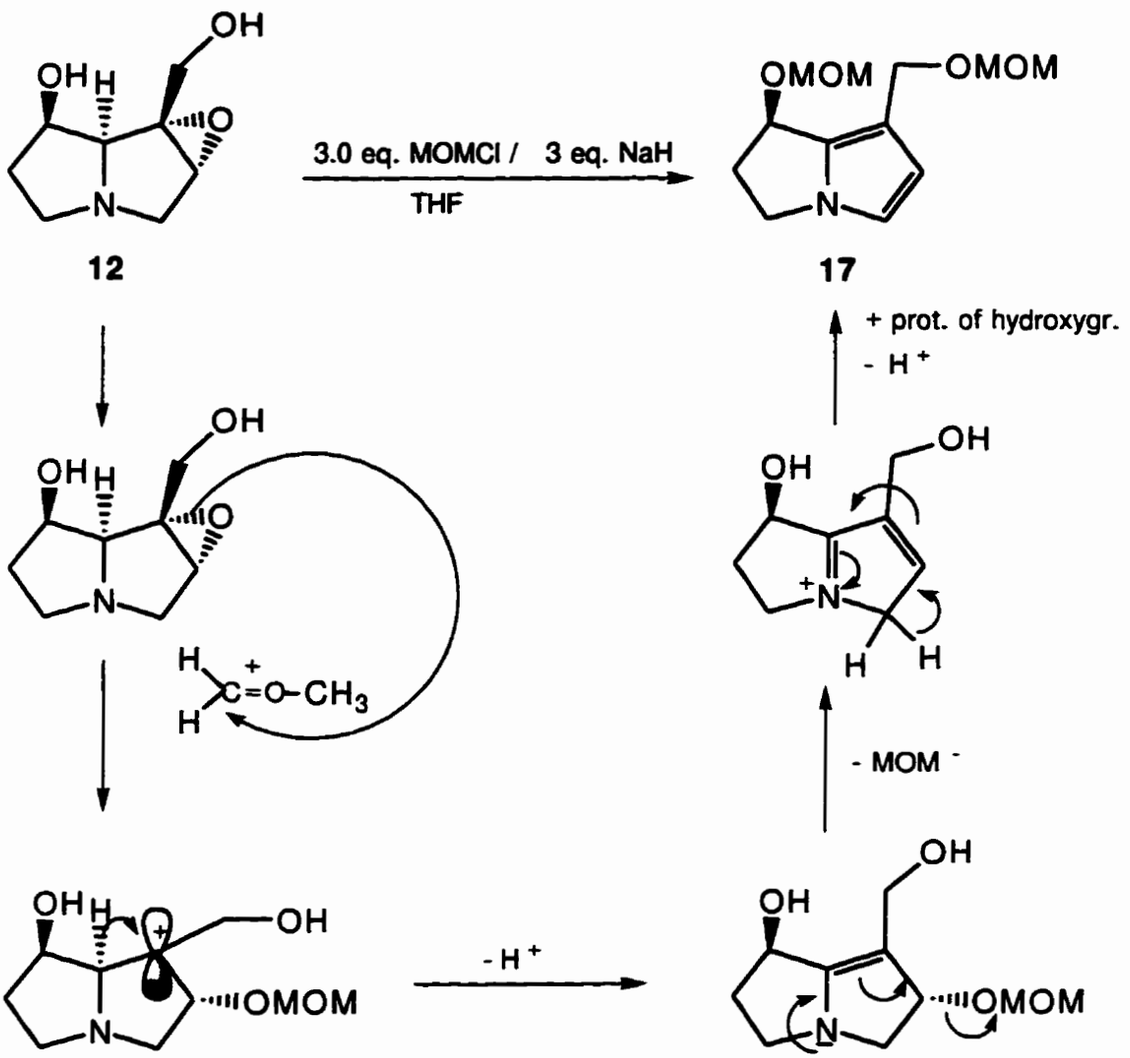
(+)-Retronecine **1** has been synthesized enantioselectively by a variety of methods[12] but we found it more convenient to obtain it by saponification of the commercially available crotaline **14** (Sigma Chemical Co.) with $Ba(OH)_2$ in H_2O, which furnished (+)-retronecine **1** in 94% yield. MCPBA epoxidation of **1** gave the N-oxide **15**, which was directly reduced with Zn/HOAc yielding **12** in 50% overall yield. Although catalytic hydrogenation of **12** yields rosmarinecine (2α,7β-



Reaction conditions: a) $Ba(OH)_2 \cdot 8H_2O$, water, rt.; b) MCPBA, CH_2Cl_2, reflux; c) Zn, AcOH; d) see text and table 1.

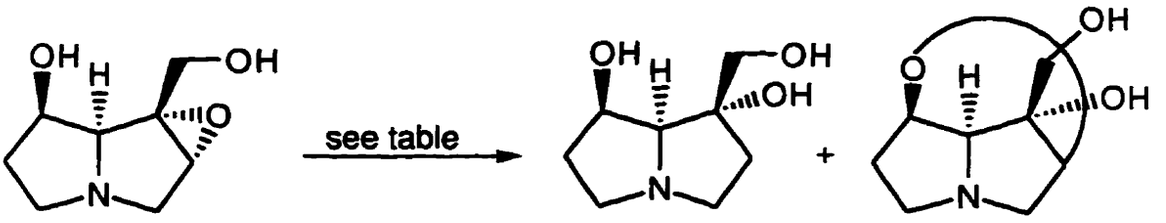
dihydroxy-1-hydroxymethyl-8α-pyrrolizidine) with no indication of formation of any **7**,[11] we reasoned that a S_N2 type hydride reduction of **12** might give **7**. To our surprise, reduction of **12** with Super-hydride® furnished the loline derivative **16** as the sole product. In order to prevent the intramolecular epoxy opening of **12** during the reduction, we decided to protect the hydroxy groups in **12**. Unfortunately, protection of **12** as the MOM ether failed due to the lability of the epoxide and the sterically hindered nature of the 7β-hydroxy group, and the 2,7-pyrrolizidine ether **17** was isolated in 85% yield. We then tried other reducing reagents for the reduction of **12**. However, of the various reducing reagents

Scheme 3: Possible Mechanism for the Epoxide Cleavage of (12)



which we tried, most yielded **16** as the major component (see table 1). DIBAL turned out to be the best and gave **7** in ca. 31% isolated yield, besides **16** (50%). Although, **7** was identical with the natural hadinecine according to ^{1}H-NMR and ^{13}C-NMR, residual aluminum components could be detected even after several chromatographic purifications. Therefore, we decided to try the alternative approach via the known 7β-hydroxy-8α-1-methylenepyrrolizidine **13**.[13]

Tabel 1: Reduction of 7β-Hydroxy-1-hydroxymethyl-1,2α-epoxy-8α-pyrrolizidine (**12**)

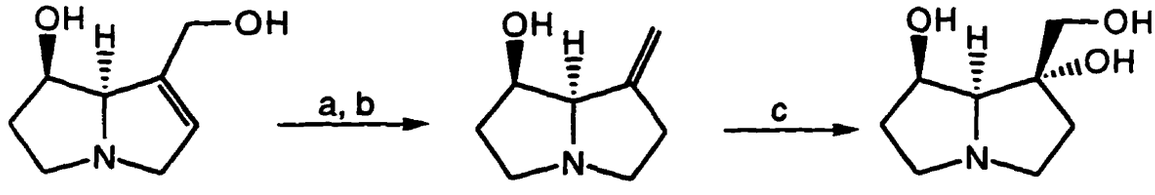


12 **7** **16**

Reagents/Conditions	**7** (%)	**16** (%)	Others (%)
Super-Hydride®, THF, -20°C -> rt.		75#	
$LiAlH_4$, THF, rt, 2days			STM
DIBAL-H, CH_2Cl_2, -40°C	30#	51#	
Red-Al, CH_2Cl_2, 0°C -> rt.	20	10	dec.
$NaBH_4$, EtOH, reflux	10	70	
H_2, Ra-Ni, EtOH			STM

Isolated yield

Following a literature procedure[13, 14] (+)- retronecine **1** was converted to **13**, which gave a mixture, consisting of 88% **13** and 12% 1-methyl-1,2-dehydro-pyrrolizidine in an overall yield of 72%. It was reasoned that *vicinal* dihydroxy-lation of **13** with OsO_4 should proceed from the α-face, *exo* to the folded bicyclo-system, to give hadinecine **7**. Indeed, treatment with OsO_4 (cat.), 4-methyl morpholine N-oxide in acetone / water (6:1) gave **7** in 56% yield, which was identical with the natural hadinecine.[7]



1 **13** **7**

Reaction conditions: a) $SOCl_2$; b) Zn, 1N H_2SO_4; c) OsO_4, NMO, acetone, water.

4.3 Conclusion

The syntheses of hadinecine confirmed the structure originally assigned on the basis of spectrometric evidence and constituted the first enantioselective syntheses of a 1-hydroxy pyrrolizidine alkaloid.

5. Experimental Part

5.1 General

For a general description of the reaction conditions, see chapter 3.1.

5.2. (+)-Retronecine (1)

A mixture of crotaline (Sigma Chem. Co., 800mg, 2.46mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (2.33g, 7.38mmol) and water (25ml) was stirred overnight. The suspension was filtered and the filtrate was saturated with CO_2. The suspension was filtered through Celite 545 and the filtrate was acidified with 10% aqueous H_2SO_4 at 0°C and again filtered through Celite 545. The clear solution was applied to a Dowex 1 ion-exchange resin (OH^--form) and eluted with water. The eluates were evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (20ml). Filtration through Celite 545 and evaporation of the solvent under reduced pressure, gave **1** (360mg, 94%) as white crystals.

1: mp.119-120°C, [lit.[15] mp.121°C]; $[\alpha]^{25}_D$ +52.4 (c0.825, EtOH), [lit.[15] $[\alpha]^{26}_D$ +50.20 (EtOH)]; The spectroscopic properties of this compound were identical to those reported.[15]

5.3. Epoxyisatinecine (7β-Hydroxy-1-hydroxymethyl-1,2α-epoxy-8α-pyrrolizidine -N-oxide, **15**)

To a solution of (+)-retronecine **1** (443mg, 2.85mmol) in CH_2Cl_2 (30ml) was added MCPBA 75% (2.63g, 11.42mmol) which was dried at room temperature under high vacuum for 6h prior to use. The mixture was refluxed overnight, and then extracted with water (2x20ml). The combined aqueous extracts were washed with CH_2Cl_2 (4x10ml) and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with $MeOH/CHCl_3/NH_3$ 5:4:1) yielding **15** (300mg, 56%) as slightly yellow crystals.
15: mp.105-110°C (decomp.); $[\alpha]^{25}_D$ -48.4 (c 1.0 (H_2O), [lit.[11] $[\alpha]^{21}_D$ -40.5 (c 1.2, H_2O]; ^{1}H-NMR (400 MHz, D_2O): δ 4.81 (1H, s, H-7α), 4.27 (1H, d, J=13.2 Hz, H-9), 4.19-4.03 (5H, m, H-5α, H-8α, H-2α, H-3), 3.89-3.83 (1H, m, H-5β), 3.84 (1H, d, J=13.2 Hz, H-9), 2.64-2.53 (1H, m, H-6α), 2.21-2.16 (1H, m, H-5β); ^{13}C-NMR (400 MHz, D_2O: DEPT): δ 89.8 (d, C-8), 74.5 (t, C-5), 74.2 (t, C-3), 70.8 (d, C-7), 66.5 (s, C-1), 60.8 (d, C-2), 59.3 (t, C-9), 34.7 (t, C-6); FABMS *m/z* : 188 (M^++1, 66), 172 (100), 155 (25), 119 (62).

5.4. Epoxyretronecine (7β-Hydroxy-1-hydroxymethyl-1,2α-epoxy-8α-pyrrolizidine, **12**)

A mixture of **15** (255mg, 1.36mmol), acetic acid (30ml) and Zn (5.1g, 78mmol) was stirred overnight at room temperature. The solution was then decanted from the residual Zn, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with $MeOH/CHCl_3/NH_3$

7:2:1). The crude product was dissolved in water (5ml) and applied to a Dowex 1 ion-exchange resin (OH^--form) and eluted with water. The eluates were evaporated under reduced pressure yielding **12** (206mg, 89%) as white crystals. **12**: mp.150-160°C (decomp.), [lit.[11] mp.172-173°C (decomp.)]; $[\alpha]^{25}_D$ -32.0 (c 0.5, H_2O, [lit.[11] $[\alpha]^{22}_D$ - 40.9 (c 0.95, H_2O]; ^{1}H-NMR (400 MHz, D_2O): δ 4.31 (1H, s, H-7α), 4.02 (1H, d, J=12.8Hz, H-9α), 3.78 (1H, s, H-8α), 3.74 (1H, d, J=12.8Hz, H-9β), 3.34-3.28 (2H, m, H-2α, H-3α), 3.06-3.02 (1H, m, H-5α), 2.67-2.60 (2H, m, H-5β, H-3β), 1.94-1.78 (2H, m, H-6); ^{13}C-NMR (200 MHz, D_2O: DEPT): δ 71.3 (d, C-7), 70.4 (d, C-2), 67.5 (s, C-1), 62.4 (d, C-8), 59.7 (t, C-9), 57.7 (d, C-3), 52.5 (t, C-5), 36.8 (t, C-6); MS *m/z* : 171 (M^+ 75), 154 (22), 127 (100), 109 (33), 96 (86), 55 (81).

5.5. Reductive Opening of Epoxyretronecine (12)

With Lithium Triethylborohydride (Super-hydride®)

A solution of **12** (8mg, 0.047mmol) in THF (1ml) was cooled to 0°C. A 1M solution of Super-hydride® in THF (0.234ml, 0.235mmol) was added and the mixture was stirred in a thawing ice bath overnight. To the clear solution was added water (1ml) and 5% aqueous HCl (1ml) at 0°C, and the mixture was stirred for 30 min. The solvent was evaporated under reduced pressure, and the residue was dissolved in water (1ml) and applied to a Dowex 1 ion-exchange resin (OH^--form) and eluted with water. The eluates were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (elution with

MeOH/$CHCl_3$/NH_3 7:2:1) yielding **16** (6mg, 75%) as a semicrystalline oil.

16: ^{1}H-NMR (D_2O, 400MHz): δ 5.05 (1H, dd, J=4.8Hz, 3.0Hz, H-7α), 4.15 (1H, dd, J=4.0Hz, 5.2Hz, H-2β), 3.92 (1H, d, J=3.0Hz, H-8α), 3.85 (1H, d, J=12.9Hz, H-9β), 3.76 (1H, d, J=12.9Hz, H-9α), 3.30 (1H, dd, J=12.4Hz, 5.2Hz, H-3β), 2.90 - 2.97 (3H, m, H-5α , H-5β, H-3α), 1.95 - 2.02 (1H, m, H-6β), 1.79 - 1.88 (1H, m, H-6α); ^{13}C-NMR (D_2O, 400MHz: DEPT): δ 94.8 (s, C-1), 84.6 (d, C-7), 77.3 (d, C-2),70.7 (d, C-8), 62.8 (t, C-3), 61.9 (t, C-9), 55.5 (t, C-5), 33.8 (t, C-6); MS *m/z* : 171 (M^+ 7), 154 (4), 128 (17), 82 (100), 68 (42), 55 (77).

With Diisobutylaluminium Hydride (DIBAL-H)

To a suspension of **12** (20mg, 0.12mmol) in CH_2Cl_2 (1ml) was added a 1.5M DIBAL-H solution in toluene (0.312ml, 0.48mmol) at -40^{o}C. The solution was stirred at -40^{o}C for 2h and then allowed to warm to room temperature overnight. To the solution was added water (1ml) at 0^{o}C and the suspension obtained was stirred for 30min., filtered through Celite 545 and the filtrates were evaporated. The crude product was purified by column chromatography on silica gel (elution with MeOH/$CHCl_3$/NH_3 5:4:1) yielding **16** (11mg, 51%) as a clear oil and **7** (6mg, 30%).

Compound **7** had the same spectroscopic properties as a sample of natural Hadinecine, while **16** had the same spectroscopic properties as those of the previous preparations.

5.6. Protection of the 7β-Hydroxy Group in Epoxyretronecine (12) as a MOM Ether

To a suspension of **12** (10mg, 0.058mmol) in THF (1ml) was added NaH 100% (4mg, 0.18mmol) and MOMCl (0.014ml, 0.18mmol) at -78°C. The suspension was stirred at -78°C for 1h and then slowly warmed to room temperature over 2h. The mixture was poured into ice/water and extracted with $CHCl_3$ (3x5ml). The combined organic extracts were washed with brine (2x5ml), dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with MeOH/$CHCl_3$/NH_3 7:2:1) yielding **17** (12mg, 85%) as a yellow oil.

17: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.63 (1H, d, J=2.6Hz, H-3), 6.26 (1H, d, J=2.6Hz, H-2), 5.13 (1H, q, J=6.1Hz, 1.5Hz, H-7α), 4.78 (1H, d, J=7.0Hz, $\underline{CH_2}OCH_3$), 4.70 (2H, s, $\underline{CH_2}OCH_3$), 4.62 (1H, d, J=7.0Hz, $\underline{CH_2}OCH_3$), 4.55 (1H, d, J=11.3Hz, H-9), 4.49 (1H, d, J=11.3Hz, H-9), 4.18-4.11 (1H, m, H-5β), 3.93-3.88 (1H, m, H-5α), 3.42 (3H, s, $CH_2O\underline{CH_3}$), 3.41 (3H, s, $CH_2O\underline{CH_3}$), 2.80-2.70 (1H, m, H-6β), 2.57-2.51 (1H, m, H-6β); ^{13}C-NMR ($CDCl_3$, 400 MHz: DEPT): δ 134.6 (s, C-8), 115.2 (d, C-3), 113.7 (s, C-1), 113.4 (d, C-2), 95.3 (t, $\underline{CH_2}OCH_3$), 94.6 (t, $\underline{CH_2}OCH_3$), 70.7 (d, C-7), 62.0 (t, C-9), 55.4 (q, $CH_2O\underline{CH_3}$), 55.1 (q, $CH_2O\underline{CH_3}$), 44.7 (t, C-5), 36.7 (t, C-6); MS *m/z* : 241 (M^+, 91), 211 (9), 179 (47), 150 (18), 117 (100), 84 (89).

5.7. 7β-Hydroxy-1-chloromethyl-1,2-dehydro-8α-pyrrolizidine Hydrochloride

This compound was prepared from (+)-retronecine (300mg, 1.93mmol) according to a literature procedure[14] yielding the title compound (250mg, 62%, [lit.[14] 50%]) as white crystals.

Mp.145-147°C, [lit.[14] mp.152-153°C], ^{1}H-NMR (D_2O, 200MHz): δ 5.79 (1H, s, H-2), 4.90 (1Hs, H-8α), 4.61-4.48 (2H, m, H-3α and H-7α), 4.24 (1H, d, J=15.9Hz, H-9'), 4.11 (1H, d, J=15.9Hz, H-9), 3.87-3.72 (2H, m, H-3β and H-5α), 3.25-3.10 (1H, m, H-5β), 2.15-2.03 (2H, m, H-6); ^{13}C-NMR (D_2O, 200 MHz: DEPT): δ 126.3 (d, C-2), 79.6 (d, C-8), 70.6 (d, C-7), 62.8 (t, C-9), 55.5 (t), 40.7 (t), 36.6 (t, C-6); MS *m/z* : 173 (M^+-HCl, 24), 138 (58), 129 (36), 94 (100), 80 (23).

5.8. 7β-Hydroxy-1-methylene-8α-pyrrolizidine (**13**)

This compound was prepared from the hydrochloride described above (240mg, 1.14mmol) according to a literature procedure[13] yielding a semicrystalline mixture of **13** and the 7β-hydroxy-1-methyl-1,2-dehydro-8α-pyrrolizidine isomer (115mg, 72%, [lit.[13] 94%]).

13: ^{1}H-NMR ($CDCl_3$, 200MHz): δ 5.28 (1H, d, J=2.0Hz, H-9'), 4.95 (1H, d, J=2.0Hz, H-9), 4.24 (1H, t, J=4.0Hz, H-7α), 4.01 (1H, s, H-8α), 3.29-3.11 (2H, m), 2.92-2.53 (4H, m), 2.15-1.89 (2H, m, H-6); ^{13}C-NMR ($CDCl_3$, 200 MHz: DEPT): δ 149.0 (s, C-1), 107.0 (t, C-9), 73.8 (d), 72.4 (d), 55.1 (t), 52.8 (t), 35.6 (t), 34.7 (t); GC/MS (method1): R_t: 6.2min. (88%), *m/z* : 139 (M^+, 32), 95 (100), 67 (42), R_t: 6.4min. (12%), *m/z* : 139 (M^+, 21), 95 (100), 80 (20), 53 (8).

The isomeric ratio was 88:12 (lit.[13] 4:1) as determined by GC/MS and ^{1}H-NMR integration of the *exo* -methylene protons of **13** (5.28ppm and 4.95ppm) and the endo methylene protons of the isomer (5.53ppm, t, J=1.8Hz).

5.9. Hadinecine (1α,7β-Dihydroxy-1-hydroxymethyl-8α-pyrrolizidine, **7**)

To a solution of **13** (90mg, 0.645mmol) in 80% aqueous acetone (20ml) was added NMO (152mg, 1.29mmol) and one crystal of OsO_4. The solution was stirred for 5h at room temperature and then evaporated under reduced pressure. The residue was immediately purified by column chromatography on silica gel (elution with MeOH/$CHCl_3$/NH_3 7:2:1) yielding **7** as a clear oil which crystallized after adding acetone (56mg, 57% based on a content of 88% of **13**).

7: mp.138-139°C, [lit.[7] 140-141°C]; ^{1}H-NMR (D_2O, 400 MHz): δ 4.15 (1H, d, J=3.2Hz, 4.9Hz, H-7α), 3.73 (1H, J=11.6Hz, H-9), 3.66 (1H, J=11.6Hz, H-9),3.13-3.01 (2H, m, H-3α, H-5α), 2.94 (1H, d, J=3.2Hz, H-8α), 2.65-2.56 (2H, m, H-3β, H-5β), 2.01-1.92 (1H, m, H-2α), 1.72-1.67 (2H, m, H-6), 1.49-44 (1H, m, H-2β); ^{13}C-NMR (D_2O, 400 MHz: DEPT): δ 85.0 (s, C-1), 80.6 (d, C-8), 72.2 (d, C-7), 66.4 (t, C-9), 54.9 (t, C-3), 54.2 (t, C-5), 36.8 (t, C-6), 35.9 (t,C-2).

The ^{1}H-NMR and ^{13}C-NMR spectra were superimposable upon that of an authentic sample of hadinecine. The IR and MS spectra were identical to those reported in the literature.[7]

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