STUDIES TOWARD A TOTAL SYNTHESIS OF (±)-SUBERGORGIC ACID

by

VELJKO DRAGOJLOVIC

B. Sc., University of Belgrade, 1986

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

DEPARTMENT OF CHEMISTRY

We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

October 1993

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

(Signature) _____

Department of CHEMISTRY

The University of British Columbia
Vancouver, Canada

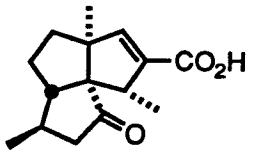
Date 19. OCTOBER 1993

ABSTRACT

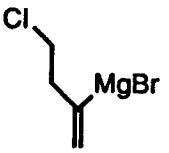
This thesis describes synthetic studies directed towards the total synthesis of (±)-subergorgic acid (**8**) and the development of methodology for the conversion of cyclopentanones into cyclopentenones.

In the synthetic studies directed towards the total synthesis of (±)-subergorgic acid (**8**), the known keto ketal **101** was converted into the enone **100**. Copper(I)-catalyzed conjugate addition of the Grignard reagent **91** to the enone **100**, followed by intramolecular alkylation of the intermediate enolate anion, provided the triquinane **99**. Sequential deoxygenation of the keto function in **99** and oxidative cleavage of the double bond provided the ketone **103**. The ketone **103** was converted into dienedione **98** *via* a four step sequence, involving Saegusa oxidation to give **156**, deketalization of the ketal function and benzeneseleninic acid anhydride (BSA) mediated dehydrogenation of the intermediate **157**. The dienedione **98** was alkylated to provide **107**.

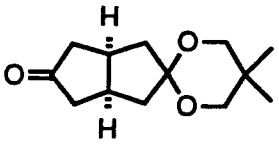
Conversion of the enone **157** into the dienedione **98** required the development of new methodology for the conversion of cyclopentanones into the corresponding cyclopentenones. Reactions of di- and triqiunanes such as **133** and **157** with BSA provided the corresponding enones **250** and **98**, respectively.



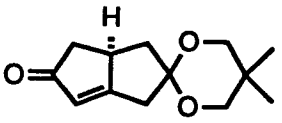
8



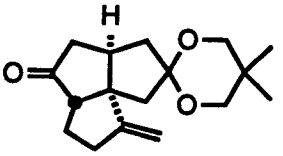
91



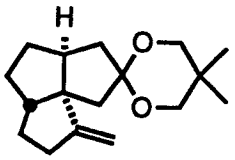
101



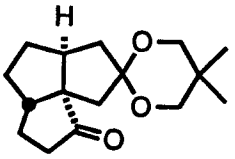
100



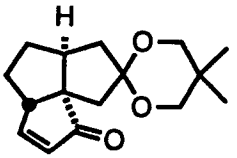
99



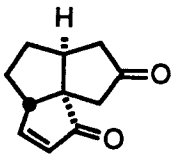
102



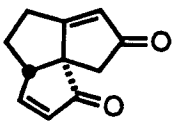
103



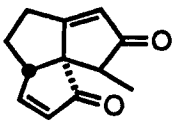
156



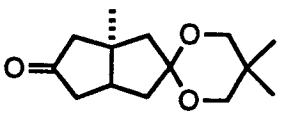
157



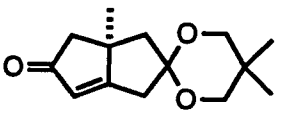
98



107



133



250

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ac	-	acetyl
AIBN	-	2,2'-azo*bis*(isobutyronitrile)
Anal.	-	elemental analysis
APT	-	attached proton test
aq.	-	aqueous
Bn	-	benzyl
b.p.	-	boiling point
br	-	broad
BSA	-	benzeneseleninic acid anhydride
BTA	-	benzenetelurinic acid anhydride
Bu	-	butyl
n-Bu	-	*normal*-butyl
t-Bu or Bu^t	-	*tertiary*-butyl
Bz	-	benzoyl
calcd.	-	calculated
cat.	-	catalytic
cm	-	centimeter
COSY	-	correlation spectroscopy
m-CPBA	-	3-chloroperoxybenzoic acid
CSA	-	10-camphorsulfonic acid
Δ	-	heat
d	-	doublet
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	-	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	diisobutylaluminum hydride
DIPHOS	-	1,2-*bis*(diphenylphosphino)ethane
DMAP	-	4-(*N,N*-dimethylamino)pyridine
DMF	-	*N,N*-dimethylformamide
DMPU	-	*N,N'*-dimethylpropyleneurea
DMSO	-	dimethyl sulfoxide
equiv.	-	equivalent(s)
Et	-	ethyl
g	-	gram(s)

GLC	-	gas-liquid chromatography
HMPA	-	hexamethylphosphoramide
hr	-	hour(s)
HRMS	-	high resolution mass spectroscopy
Hz	-	hertz
IR	-	infrared
LDA	-	lithium diisopropylamide
LRMS	-	low resolution mass spectroscopy
L-Selectride	-	lithium tri-*sec*-butylborohydride
M	-	molar
m	-	multiplet
m	-	meta
Me	-	methyl
mg	-	milligram(s)
MHz	-	megahertz
min	-	minute(s)
mL	-	milliliter(s)
μL	-	microliter(s)
mmol	-	millimole(s)
mol	-	mole(s)
m.p.	-	melting point
Ms	-	methanesulfonyl
mult.	-	multiplicity
N	-	normal
NMR	-	nuclear magnetic resonance
nOe	-	nuclear Overhauser enhancement
p	-	page
p	-	para
PCC	-	pyridinium chlorochromate
PDC	-	pyridinium dichromate
Ph	-	phenyl
pp	-	pages
ppm	-	parts per million
PPTS	-	pyridinium *p*-toluenesulfonate
PROPHOS	-	1,3-*bis*(diphenylphosphino)propane
Py	-	pyridine

q	-	quartet
r t	-	room temperature
s	-	singlet
t	-	triplet
t	-	tertiary
TBDMS	-	*tertiary*-butyldimethylsilyl
T f	-	trifluoromethanesulfonyl
Tf_2NPh	-	*N*-phenyltrifluoromethanesulfonimide
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TMEDA	-	*N,N,N',N'*-tetramethylethylenediamine
TMS	-	tetramethylsilane
TMS-	-	trimethylsilyl
p-Ts	-	*para*-toluenesulfonyl
p-TSA	-	*para*-toluenesulfonic acid
-ve	-	negative

ACKNOWLEDGMENTS

I would like to thank my research supervisor, Professor Ed Piers, for his guidance and patience throughout the course of this studies. His advice on writing this thesis is greatly appreciated.

In addition, thanks are extended to the past and present members of the group for the intellectual and social interactions over the years. My thanks and best wishes to Dr. Livain Breau for many discussions, helpful suggestions and criticisms, and the care taken in proofreading this thesis. I would like to thank Professor Thomas Money and Mr. and Mrs. Keith Ellis for their contribution in proofreading this thesis. Special thanks are also due to Dr. Betty-Anne Story, Mrs. Chantal Soucy-Breau, Dr. Miguel Romero (1. ...d5), Mr. Anthony Dotse and Mr. Timothy Wong.

Financial assistance from the University of British Columbia in the form of a University Graduate Fellowship is also acknowledged.

"Never late were favors divine"

N. Machiavelli, *Letter to Vettori (1513).*

1 Introduction

1.1 General

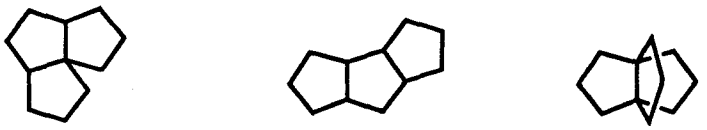
The rapid growth of organic chemistry over the past several decades has led to the development of a broad repertoire of synthetic tools. New methodologies, based on organoelement compounds, such as organoboron, organosilicon, organosulfur, and organophosphorus substances have contributed to a fundamental change in the understanding of synthetic organic chemistry. New concepts such as "umpolung"[1] and retrosynthetic analysis[2a,b] have emerged from research on the reactivity and properties of these reagents. In search for more efficient reagents, a number of research groups have now focused on the application of biochemical (enzymes, catalytic antibodies) and organometallic reagents. The latter field of research is particularly promising because it offers many advantages over the known methods with regard to selectivity, efficiency, cost and broad range of applicability.[3] Over the past decade alone, new developments in related fields, as well as development of adequate experimental techniques necessary to handle organometallic compounds, have made possible the introduction of hundreds of new reagents.

Until recently, the efforts of synthetic organic chemists were dedicated to target structures such as naturally occurring or theoretically interesting molecules. Due to the advances made concomitantly in medicinal and organometallic chemistry, and in part due to the way that funding is allocated to chemists, much of today's synthetic efforts have been shifted from interesting target structures

to the synthesis of biologically active molecules.[3,4] Following the trend of modern research, this thesis is largely concerned with the exploratory use of a bifunctional reagent toward the synthesis of the naturally occurring triquinane subergorgic acid.[5]

1.2 Silphiperfolane Sesquiterpenoids

Among synthetic organic chemists, triquinane molecules have been particularly popular targets.[6] The triquinanes are molecules which have three connected five membered rings. Depending on the arrangement by which the rings are interconnected they are divided into angular triquinanes **1**, linear triquinanes **2**, and propellanes **3** (**Chart 1**).



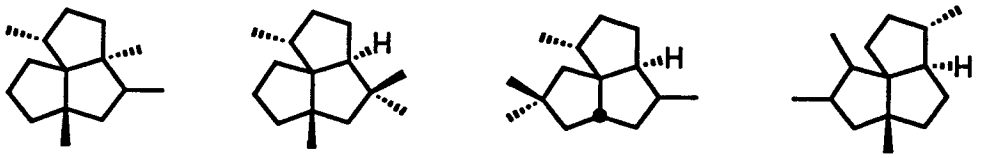
1 **2** **3**

Chart 1

The angular sesquiterpene triquinanes are subdivided into the following groups (represented as their parent hydrocarbons): isocomane (**4**), silphilinane (**5**), pentalenane (**6**), and silphiperfolane (**7**) (**Chart 2**).

The chemistry of triquinane natural products has been an area of extensive synthetic studies since the mid-1970s. This interest is in part due to their biological properties. For instance, some of them are pharmacologically active,[7] some are fragrant compounds.[8] It has been

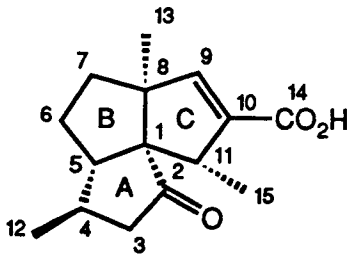
shown that subergorgic acid (**8**) exhibits cardiotoxic activity,[5] anticholinesterase activity,[9a] and activity against "Soman" toxicity in mice.[9b]



4 **5** **6** **7**

Chart 2

In recent years, a considerable effort has been directed towards synthesis of compounds with fused five-membered rings and the triquinanes provide convenient targets for the development and testing of new methodologies. It is a continuing effort of many research groups to find a general and versatile cyclopentane annulation method, such as the Diels-Alder reaction for the assembly of six-membered rings.[10]



8

1.3 Previous Synthetic Approaches

1.3.1 The Synthetic Problem

Several synthetic approaches to subergorgic acid (**8**) have appeared in the literature since 1988.

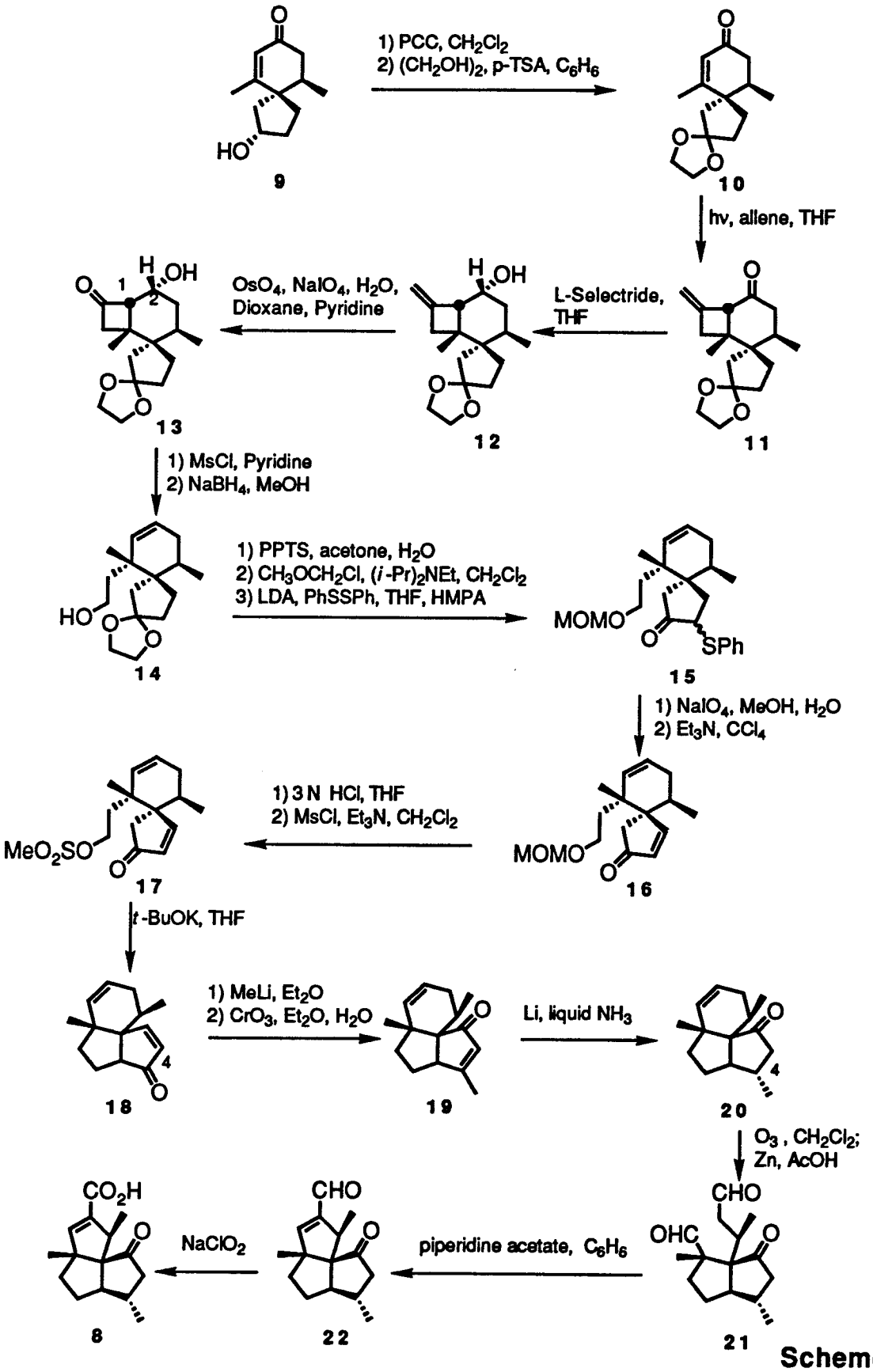
The principal difficulty encountered in the synthesis of subergorgic acid is related to the unusual functionality present in the molecule as compared with the other silphiperfolanes. Subergorgic acid has a keto function at position C-2, a feature that is unknown in other silphiperfolane molecules. Also, the configurational orientation of the C-15 methyl group is noteworthy.

1.3.2 A Total Synthesis of (±)-Subergorgic Acid (**8**) by C. Iwata and coworkers

The first total synthesis of (±)-subergorgic acid was reported in 1988 by C. Iwata and coworkers (**Scheme 1**).[11]

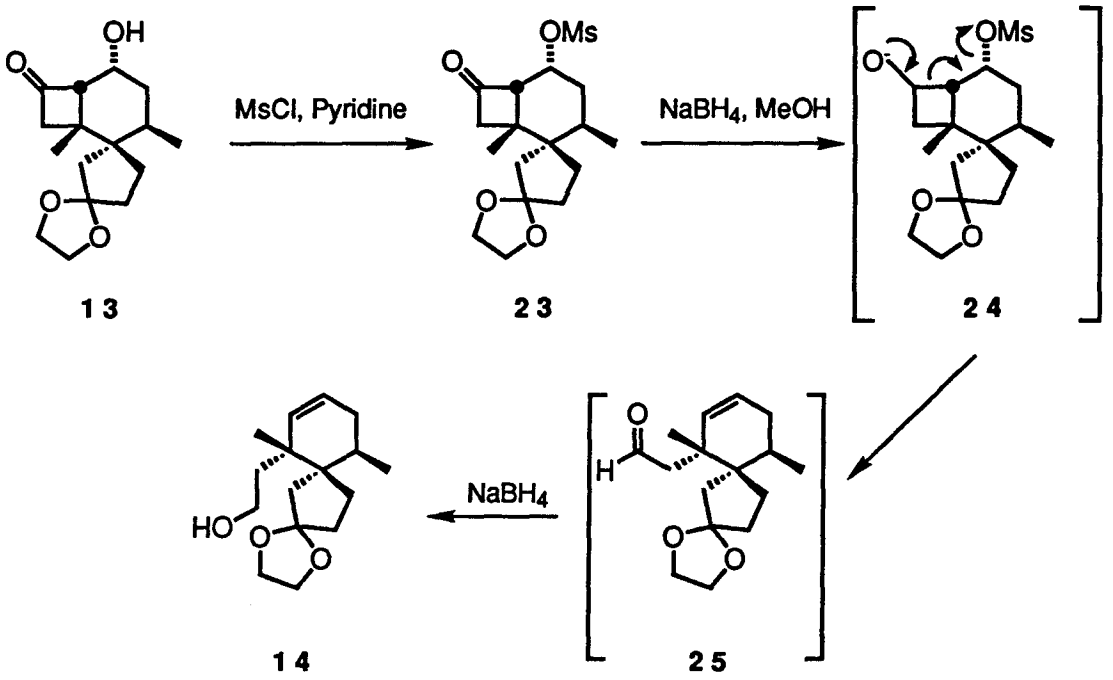
In their approach, the spiro enone **9** was utilized as the starting material. The compound **9** had been previously prepared by Iwata's group and had been used in the synthesis of several other natural products.[12] Oxidation, and selective protection of the newly formed keto group with ethylene glycol, gave the ketal enone **10**. The photochemical addition of allene to **10** afforded **11**.

L-Selectride (Aldrich) reduction of **11** provided the axial alcohol **12**. Oxidative cleavage of the double bond with a catalytic amount of osmium tetraoxide in presence of sodium periodate as cooxidant


1) PCC, CH_2Cl_2
2) $(CH_2OH)_2$, p-TSA, C_6H_6
hv, allene, THF
L-Selectride, THF
OsO_4, $NaIO_4$, H_2O, Dioxane, Pyridine
1) MsCl, Pyridine
2) $NaBH_4$, MeOH
1) PPTS, acetone, H_2O
2) CH_3OCH_2Cl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2
3) LDA, PhSSPh, THF, HMPA
1) $NaIO_4$, MeOH, H_2O
2) Et_3N, CCl_4
1) 3 N HCl, THF
2) MsCl, Et_3N, CH_2Cl_2
t-BuOK, THF
1) MeLi, Et_2O
2) CrO_3, Et_2O, H_2O
Li, liquid NH_3
O_3, CH_2Cl_2; Zn, AcOH
piperidine acetate, C_6H_6
$NaClO_2$
9
10
11
12
13
14
15
16
17
18
19
20
21
22
8

Scheme 1.

provided the hydroxy ketone **13**. Treatment of **13** with methanesulfonyl chloride in pyridine followed by sodium borohydride gave compound **14**. The transformation proceeds *via* a reduction of ketone **23**, a 1,4-elimination-fragmentation, and reduction of the *in situ* generated aldehyde **25** (**Scheme 2**).

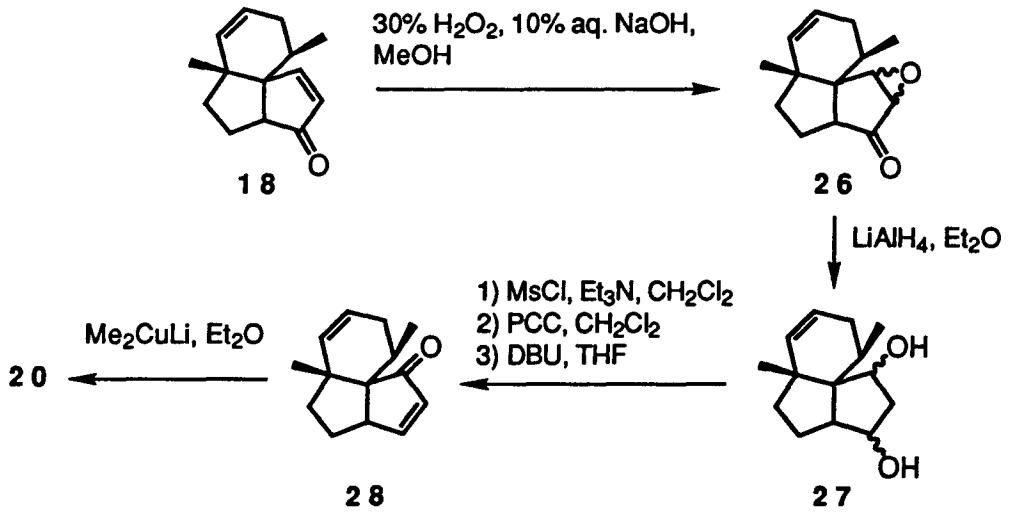


Scheme 2

With compound **14** in hand, it was necessary to conduct extensive functional group interconversions in order to prepare an intermediate suitable for cyclization to the tricyclic molecule **18**. The ketal function in **14** was removed by transketalization with PPTS in acetone and the hydroxy group was protected by treatment with chloromethyl methyl ether in the presence of *N,N*-diisopropylethylamine. Deprotonation of the resultant ketone with LDA removed the less sterically hindered proton to provide the kinetic enolate, which upon

addition of diphenyldisulphide afforded the α-phenylthio ketone **15**. Oxidation of **15** with sodium periodate gave the corresponding sulfoxide. The elimination of phenylsulphinic acid with triethylamine in carbon tetrachloride gave the enone **16**. The alcohol function of compound **16** was deprotected with 3 N hydrochloric acid in THF and subsequently treated with methanesulfonyl chloride and triethylamine in dichloromethane to afford **17**. The tricyclic product **18** was obtained from the treatment of compound **17** with potassium *t*-butoxide in THF.

In order to introduce a methyl group at C-4 (corresponding to the subergorgic acid numbering system), the compound **18** was treated with methyllithium to provide the tertiary alcohol, which upon chromium trioxide oxidation yielded the transposed enone **19**. Reduction of **19** with lithium in ammonia gave the ketone **20** and its C-4 epimer in a ratio of 6:1.



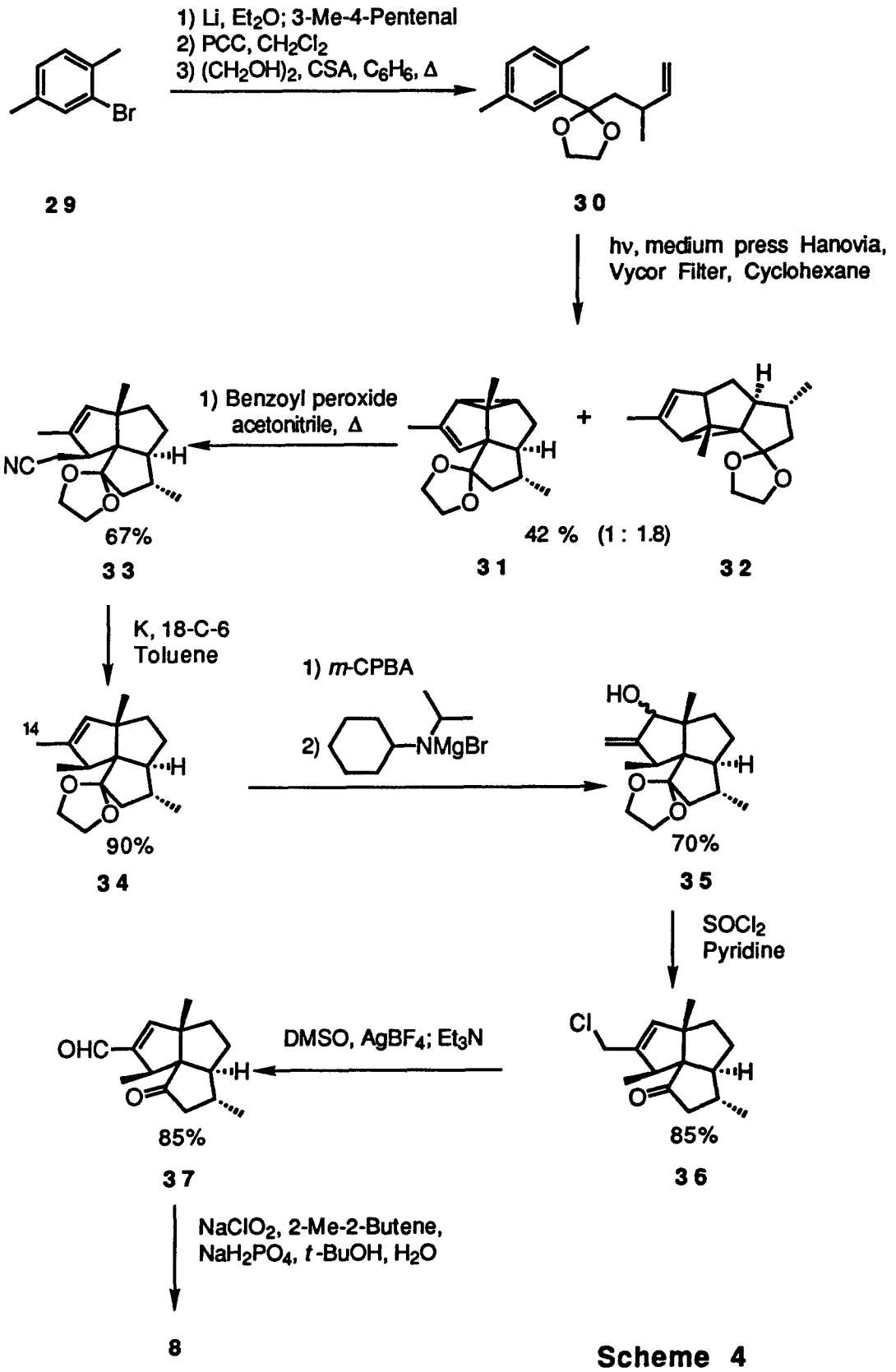
Scheme 3

Alternatively, it is possible to prepare **20** in a more stereoselective manner *via* a lengthier route (**Scheme 3**). The enone **18** was epoxidized with alkaline hydrogen peroxide to give **26** as an isomeric mixture. Upon lithium aluminum hydride reduction, the compound **27** was obtained as a mixture of diastereoisomers. The siteselective mesylation of the less sterically hindered C-4 hydroxy function of **27**, followed by a PCC oxidation of the C-2 hydroxy group gave the corresponding β-mesyloxyketone, which upon addition of DBU induced elimination to gave the enone **28**. Stereoselective addition of lithium dimethylcuprate to the enone **28** afforded the intermediate **20** and its C-4 isomer in a ratio of 20:1.

Preparation of dialdehyde **21** was accomplished by ozonolysis of the keto alkene **20** (**Scheme 1**). Treatment of dialdehyde **20** with piperidine acetate in benzene gave the triquinane aldehyde **22**. The IR and partial ^{1}H NMR spectral data of **22** were reported as having been recorded in chloroform and deuterochloroform, respectively. Both spectra were actually recorded in carbon tetrachloride.[13] Oxidation of aldehyde **22** with sodium chlorite provided (±)-subergorgic acid (**8**).

1.3.3 A Total Synthesis of (±)-Subergorgic Acid (8) by P. Wender and M. deLong

In 1990 a considerably shorter synthesis of (±)-subergorgic acid was published by P. Wender and M. deLong (**Scheme 4**).[14] Although assembly of the triquinane skeleton was very expeditious, the sequence proceeded in a low overall yield.


1) Li, Et2O; 3-Me-4-Pentenal
2) PCC, CH2Cl2
3) (CH2OH)2, CSA, C6H6, Δ
Br
29
30
hv, medium press Hanovia,
Vycor Filter, Cyclohexane
1) Benzoyl peroxide
acetonitrile, Δ
NC
H
+
67%
42 % (1 : 1.8)
33
31
32
K, 18-C-6
Toluene
1) m-CPBA
2) NMgBr
14
HO
90%
70%
34
35
SOCl2
Pyridine
DMSO, AgBF4; Et3N
OHC
Cl
O
85%
85%
37
36
NaClO2, 2-Me-2-Butene,
NaH2PO4, t-BuOH, H2O
8

Scheme 4

Their approach was based on the arene-alkene photocycloaddition strategy previously applied in the synthesis of several polycyclic sesquiterpenes.[15] The benzylic ketal **30** necessary for the cycloaddition step was prepared from the bromoxylene **29** and 3-methyl-4-pentenal.

Photolysis of the benzylic ketal **30** provided two products **31** and **32** in a 1:1.8 ratio and in 42% overall yield, the desired adduct being the minor product **31**. According to the authors, the relatively low yield of the reaction may be due in part to the introduction of three contiguous quaternary centers. The preference for the formation of **32** over **31** was claimed to be due to the greater strain in **31** arising from an increased steric interaction between the angular quaternary methyl substituent and the ketal function relative to that in **32**.

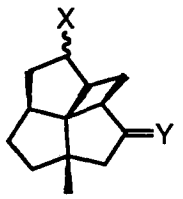
Free radical addition of the C-centered radical prepared from acetonitrile to the vinylcyclopropane **31** gave the nitrile **33**, which upon treatment with potassium metal afforded the decyanated product **34**. The preparation of the angular triquinane **34** completed the assembly of the carbon skeleton of subergorgic acid.

Attempts to functionalize the allylic C-14 position in **34** with selenium dioxide, *N*-bromosuccinimide, and palladium acetate were unsuccessful, and a lengthier sequence had to be developed. The alkene **34** was epoxidized, and subsequently rearranged upon treatment with bromomagnesium *N*-cyclohexyl-*N*-isopropylamide to give the allylic alcohol **35**. As expected, the transformation of alcohol **35** to the chloride **36** was accompanied by an allylic rearrangement and by hydrolysis of the ketal function. A formal synthesis of subergorgic acid was completed by oxidation of the chloride **36** to the aldehyde **37**.

Surprisingly, the data obtained from the ^1H NMR and IR spectra and the melting point of the aldehyde **37** were different from those previously reported.[13] Nonetheless, oxidation of the aldehyde **37** gave (±)-subergorgic acid, spectroscopically identical with the natural product.

1.3.4 Synthetic Studies Towards the Synthesis of (±)-Subergorgic Acid (**8**) by M. Crimmins and coworkers

A recent synthetic study towards the preparation of subergorgic acid was published by M. Crimmins.[16] The approach by Crimmins' group is based on a free-radical reduction-fragmentation reaction of a [4.5.5.5] fenestrane, of general structure **38**.

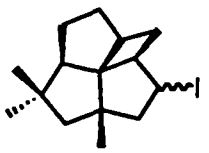


X= OC(S)SMe, OC(S)OPh

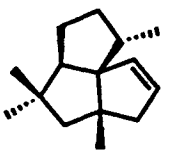
Y= O, 

38

A strategy for the preparation of such fenestranes, involving an intramolecular photocycloaddition, was developed earlier.[17]



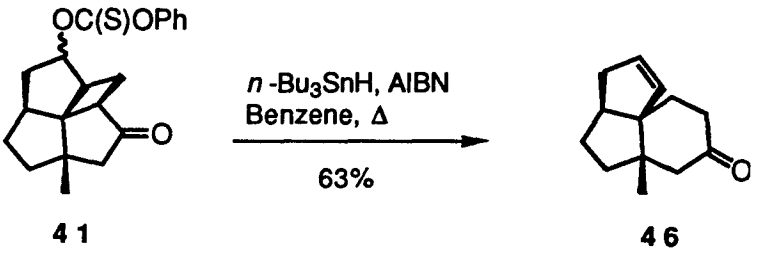
n-Bu_3SnH (1.0 eq.)
Benzene, 80 °C



39 **40**

Scheme 5

Crimmins' approach had already been successfully applied to the total synthesis of (±)-silphinene (**40**) (**Scheme 5**).[18] However, when the radical precursor **41** was subjected to the same reaction conditions the expected triquinane product was not isolated. Instead, the ring expanded product **46** was obtained (**Scheme 6**).

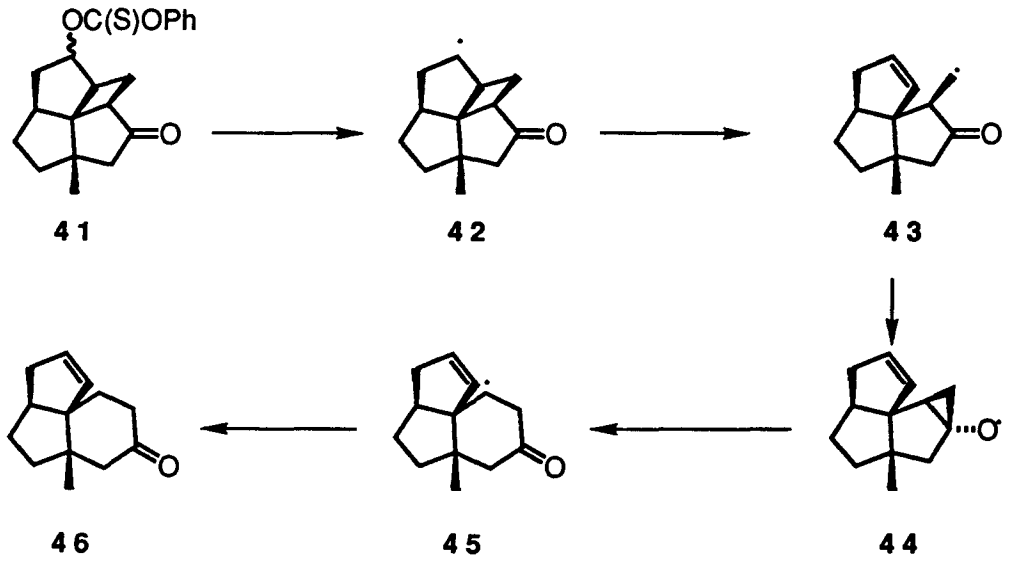


41 **46**

Scheme 6

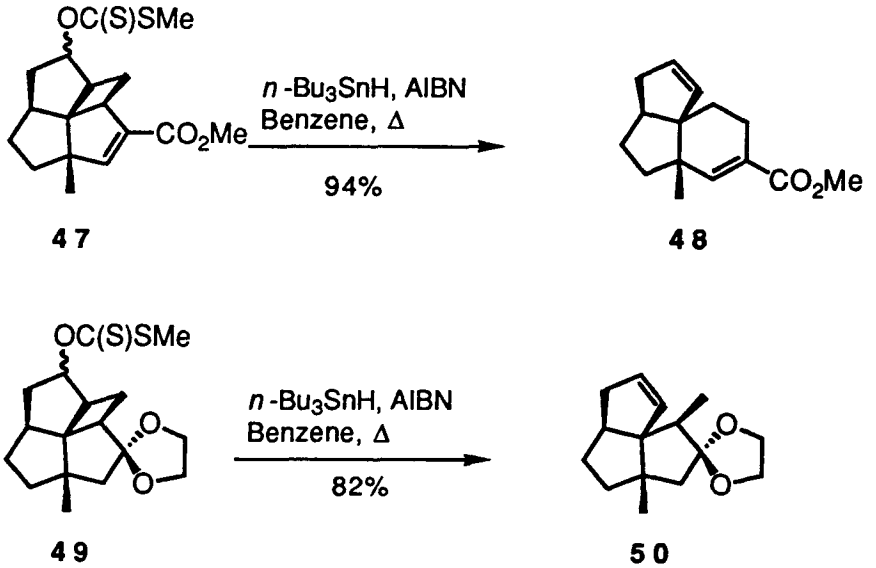
The proposed mechanism for the formation of **46** is shown in **Scheme 7**. Reaction of **41** with the tributyltin radical generates the cyclobutylcarbinyl radical **42**, which fragments to produce a primary radical **43**. This latter species then undergoes cyclization to produce the cyclopropyl alkoxy radical **44**. The radical species **44** rearranges to the more stable secondary radical **45**, which is in turn reduced with tributyltin hydride to provide the ring expanded product **46**.

In accordance with the proposed mechanism the methyl xanthate **47** provided the cyclohexene **48**. In contrast, the ketal **49** lacking a π-bond adjacent to the intermediate primary radical, undergoes a simple fragmentation to produce the triquinane **50** (**Scheme 8**), which may be a suitable precursor for the synthesis of (±)-subergorgic acid (**8**).



Scheme 7

Although **46** was not the desired intermediate, it is similar in structure to the alkene **18,** which was converted to subergorgic acid by Iwata and coworkers. Furthermore, use of an appropriate free radical precursor should provide **18**, thus accomplishing a formal synthesis of subergorgic acid.



Scheme 8

1.3.5 Enantioselective Total Synthesis of (-)-Subergorgic Acid (**8**) by L. Paquette and coworkers

The first enantioselective total synthesis of (-)-subergorgic acid (**8**) has been accomplished by Paquette and coworkers (**Scheme 9**).[19]

Their approach employed the readily accessible 2-methyl-1,3-cyclopentanedione (**51**) as the starting material. Alkylation of **51** with 3-bromo-2-methylpropene gave the dione **52**. This compound was stereoselectively reduced with sodium borohydride in methanol, and the corresponding racemic alcohol was converted to the chloroacetate. Enzymatic hydrolysis with Lipase P-30 of the racemic chloroacetate provided the ketol **54** in 50% yield and 100% enantiomeric purity, and the keto ester **53** in 45% yield (100% enantiomeric purity).

The desired enantiomer **53**, was converted into the enone **55** *via* a four-step sequence of reactions and in 52% overall yield.

Copper(I)-catalyzed conjugate addition of the Grignard reagent to **55** in the presence of TMSCl and DMAP gave the trimethylsilyl enol ether **56**. Treatment of **56** with titanium tetrachloride in dichloromethane provided the cyclized products **57** as a mixture of diastereomers in 63% overall yield.

The mixture of diastereomers was irradiated in presence of phenyliodonium diacetate and iodine in benzene to provide the keto ketal **58** in 75% yield. The keto function in **58** was reduced to provide the alkane **59** by means of a three-step procedure and in 43% overall yield.

The ketal **59** was hydrolyzed, and the ketone **60** was converted to the corresponding enol triflate by treatment with potassium

bis(trimethylsilyl)amide and *N*-phenyltriflimide in the presence of TMEDA in THF. The enol triflate was reduced to the corresponding alkene in a palladium-catalyzed reaction involving formic acid and tri-*n*-butylamine. The alkene thus obtained was deprotected upon exposure to hydrofluoric acid to provide the alcohol **61**.

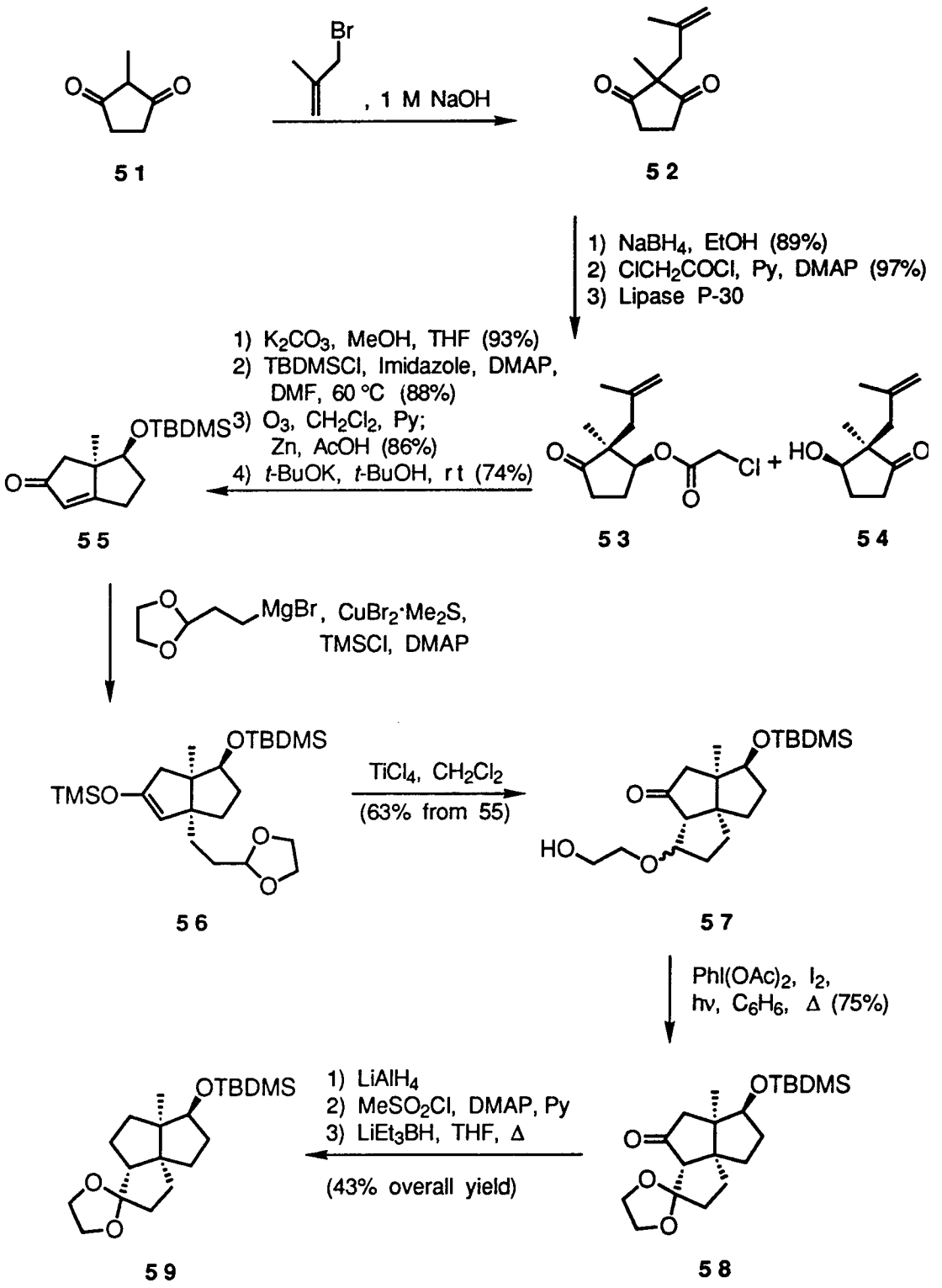
Steric hindrance present in **61** resulted in some difficulties during the oxidation step. Several reagents (Swern's, Jones', PCC on Celite or molecular sieves) failed to provide satisfactory results. However, the alcohol function was oxidized to the corresponding ketone in excellent yield (90%) using PCC on alumina. The α-methoxycarbonyl group in compound **62** was introduced according to Mander's procedure.[20]

Conversion of a ketone function in **62**, into the corresponding enone moiety was found to be difficult. Indeed, oxidation of **62** with DDQ in refluxing benzene produced **63** in very low yield. Oxidation of compound **62** under milder conditions, DDQ in the presence of silica gel in benzene at room temperature, gave the enone **63** in 67% yield.

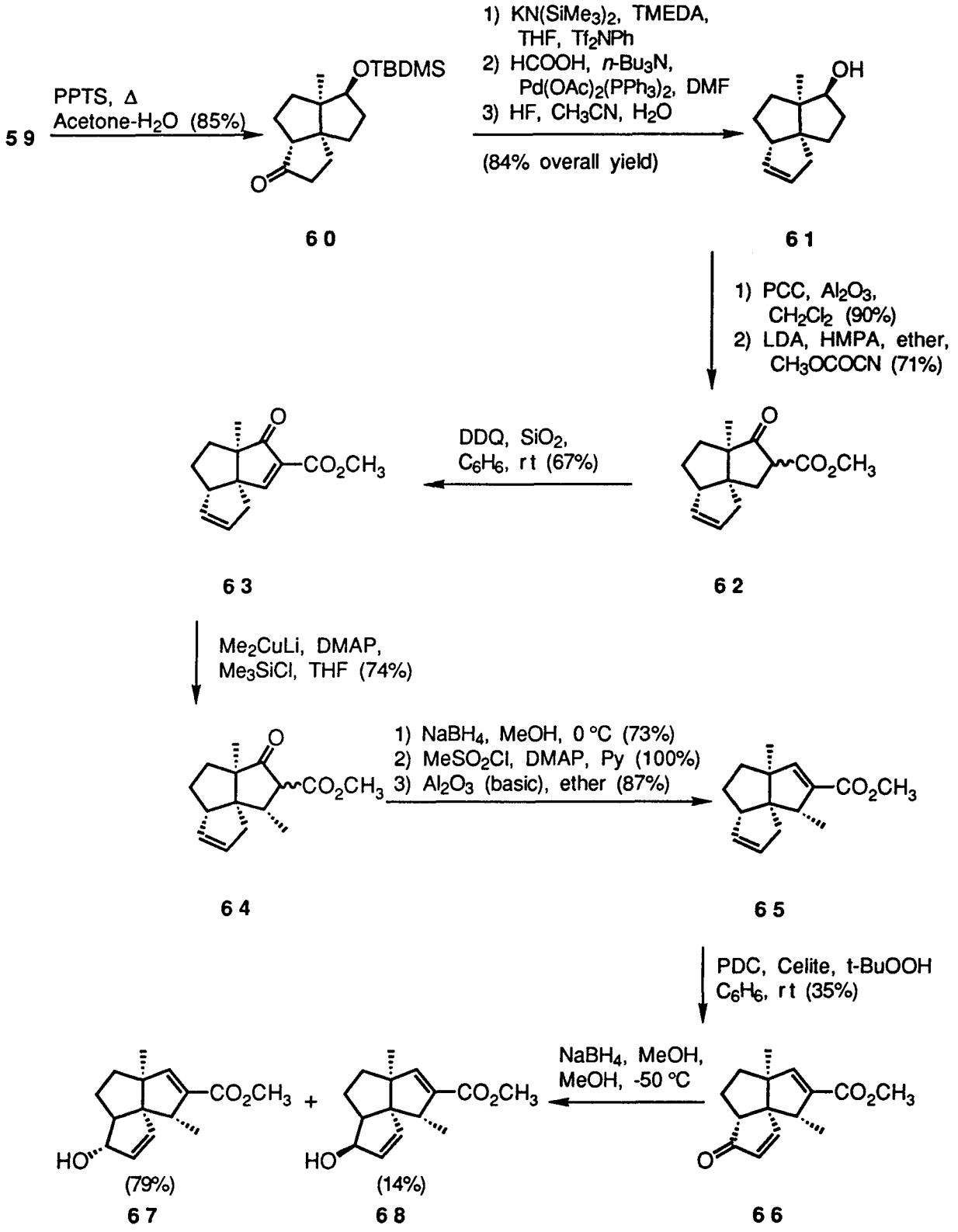
Stereoselective conjugate addition of lithium dimethylcuprate to **63** in the presence of DMAP and TMSCl in THF provided **64** as a single isomer.

The β-keto ester function of **64** was converted to an α,β-unsaturated ester moiety (see **65**) *via* a procedure previously used by Crimmins in the synthesis of pentalenic and deoxypentalenic acids.[21]

In order to set the functionality for the introduction of the C-4 methyl group by conjugate addition, an allylic oxidation of **65** was required. However, presumably due to steric hindrance, the use of the usual reagents to affect such a transformation failed to produce the desired compound **71**, and instead caused decomposition of the

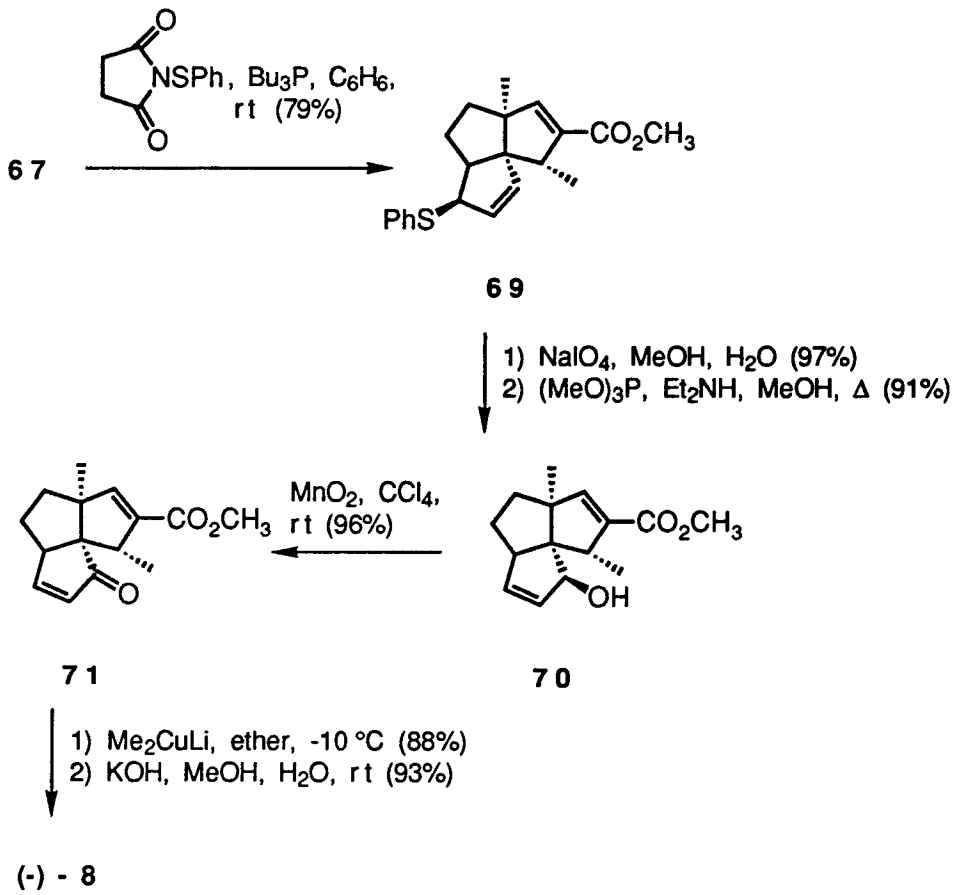

Br
, 1 M NaOH
51
52
1) NaBH4, EtOH (89%)
2) ClCH2COCl, Py, DMAP (97%)
3) Lipase P-30
1) K2CO3, MeOH, THF (93%)
2) TBDMSCl, Imidazole, DMAP, DMF, 60 °C (88%)
3) O3, CH2Cl2, Py; Zn, AcOH (86%)
4) t-BuOK, t-BuOH, rt (74%)
OTBDMS
Cl
HO
53
54
55
MgBr, CuBr2·Me2S, TMSCl, DMAP
TMSO
TiCl4, CH2Cl2
(63% from 55)
56
57
PhI(OAc)2, I2, hν, C6H6, Δ (75%)
1) LiAlH4
2) MeSO2Cl, DMAP, Py
3) LiEt3BH, THF, Δ
(43% overall yield)
58
59

Scheme 9



59 60 61 63 62 64 65 66 67 68

Scheme 9 cont.



Scheme 9 end

substrate. Alternatively, oxidation of **65** with PDC in the presence of Celite and *t*-butylhydroperoxide produced **66** in satisfactory yield (35%, 69% based on recovered **65**).

The enone **66** was transposed into the enone **71** *via* a lengthy procedure, involving five steps and in 53% overall yield.

Chemoselective conjugate addition of lithium dimethylcuprate to the enone **71** produced (-)-methylsubergorgate as a single isomer, which upon hydrolysis afforded the (-)-subergorgic acid (**8**).

The sequence **66**→**71** illustrates the difficulties encountered in the introduction of C-2 keto group. The sequence **18**→**28** (**Scheme 3**, page 7) applied by the Iwata's group also involved five steps and

proceeded in 47% yield. The more conventional sequence **18**→**20** (**Scheme 1**, page 5) introduced the desired keto function and the C-4 methyl group in three steps (73% yield), but with a modest stereoselectivity. Wender's group prepared the precursor **30** which already contained the C-4 methyl substituent and the required C-2 carbonyl function (protected as a ketal moiety) (**Scheme 4**, page 9), and thus avoided later problems connected with functionalization of the A-ring (structure **8**, page 3). However, due to steric congestion caused by the generation of three contiguous quaternary centers during the cycloaddition, as well as sensitivity of the ketal function to the reaction conditions, the desired product **31**, was obtained in only 15% yield. Crimmins' group did not report any attempt to introduce the C-2 keto function.

1.4 Retrosynthetic Analysis

Introduced and developed by Corey,[2] the retrosynthetic, or antithetic, analysis is a logical method for theoretically disconnecting the target molecule into smaller fragments. Starting with the target molecule, bonds between carbon atoms are theoretically disconnected, in a process reverse of a synthetic reaction. Simpler fragments, thus obtained had been called synthons. Recently, the term synthon has been applied and misused to denote any intermediate, including the actual reagent (synthetic equivalent of a synthon). To alleviate the problem, Corey has introduced a more descriptive term retron instead of synthon.[2b]

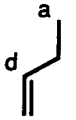
The process of disconnecting the target molecule into smaller fragments is repeated until simple commercially or otherwise available precursors are obtained. Steps reverse of synthetic reactions are called transforms.

In the course of an actual synthesis, a function obtained is often in the wrong oxidation state, possesses the wrong polarity or is otherwise unsuitable for the next transformation. It is then necessary to conduct functional group interchange (FGI), and introduce appropriate functionality for the next conversion.

1.5 Previous Work

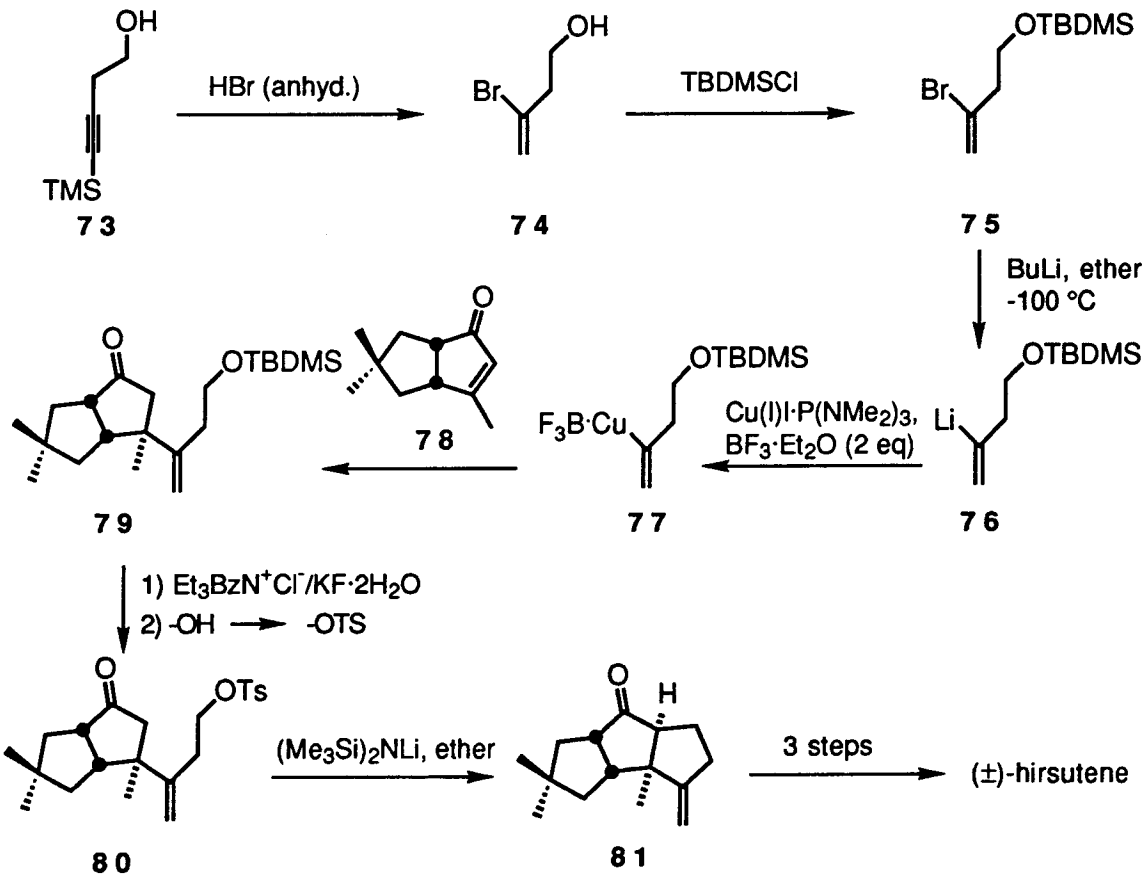
An access to several triquinane natural products has been achieved by means of bifunctional conjunctive reagents. According to Trost,[22] "The term conjunctive reagent is introduced to focus on those reagents which are simple building blocks that are incorporated in whole or in part into a more complex system and to differentiate them from reagents that operate on but are not normally incorporated into a substrate." Therefore, a bifunctional conjunctive reagent is a reagent with two reactive sites that is incorporated into a substrate molecule with the exception of heteroatoms.

Among the numerous bifunctional reagents developed as a result of extensive research by a number of groups, the following are chosen for the purpose of illustration.



72

The reagent **77**, a synthetic equivalent of the synthon **72**, was developed by Magnus' group[23] and was applied in the total synthesis of (±)-hirustene (**Scheme 10**). The starting material, 4-(trimethylsilyl)-3-butyn-1-ol (**73**), can be easily prepared from 3-butyn-1-ol, according to procedure of Boeckman.[24] Reaction of **73** with anhydrous hydrogen bromide provided the vinyl bromide **74**. The alcohol function of **74** was protected as the *t*-butyldimethylsilyl ether **75** and halogen metal exchange with *t*-butyllithium gave the vinyllithium **76**. The intermediate **76** was treated with copper(I) iodide-hexamethylphosphorous triamide complex to give the vinylcopper reagent **77**.

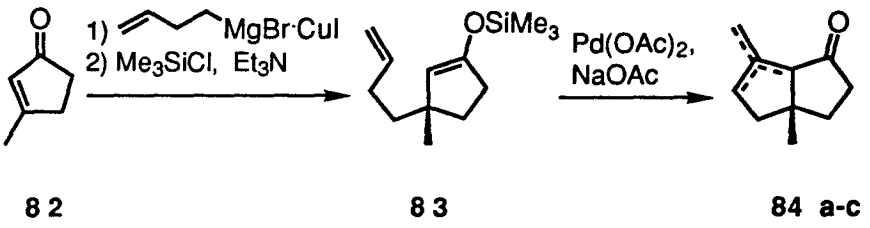


73 **74** **75** **76** **77** **78** **79** **80** **81**

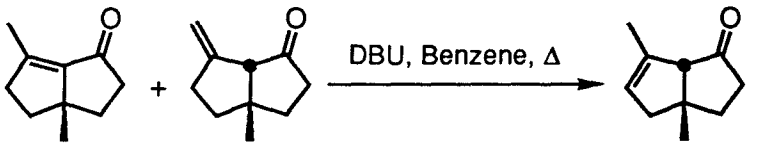
Scheme 10

The 1,4-addition of the vinylcopper reagent to the enone **78** provided the ketone **79**. The latter substance was converted to the tosylate **80**. The cyclized product **81** was obtained from treatment of compound **80** with lithium *bis*(trimethylsilyl)amide.

The work carried out by Ikegami (**Scheme 11**)[25] and Pattenden (**Scheme 12**)[26] illustrates the increasing role of bifunctional reagents.



82 **83** **84 a-c**

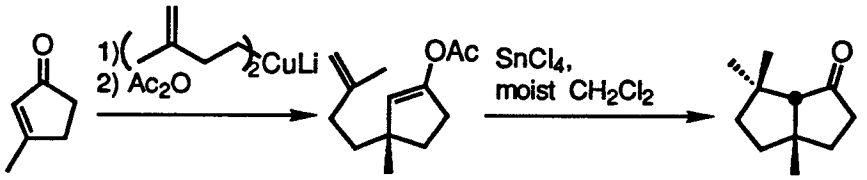


84 a **84 b** **84 c**

Scheme 11

Ikegami's group used copper (I) catalyzed addition of 3-butenylmagnesium bromide to 3-methyl-2-cyclopenten-1-one (**82**), followed by trapping of the intermediate enolate with trimethylsilyl chloride to provide the trimethylsilyl enol ether **83**. Palladium acetate induced cyclization of **83** provided three diquinane isomers **84a-c**. Interestingly, the major isomer was the diquinane **84c** with an endocyclic bond in the β,γ-position with respect to the carbonyl group. Furthermore, DBU-catalyzed isomerization in refluxing benzene converted the mixture of products to the compound **84c**.

The Pattenden approach utilized 1,4-addition of lithium *bis*(3-methyl-3-butenyl)cuprate to 3-methyl-2-cyclopenten-1-one, followed by trapping of the resulting intermediate enolate with acetic anhydride. Cyclization of **85** was accomplished by treatment with tin tetrachloride in moist dichloromethane to provide the compound **86** (**Scheme 12**).

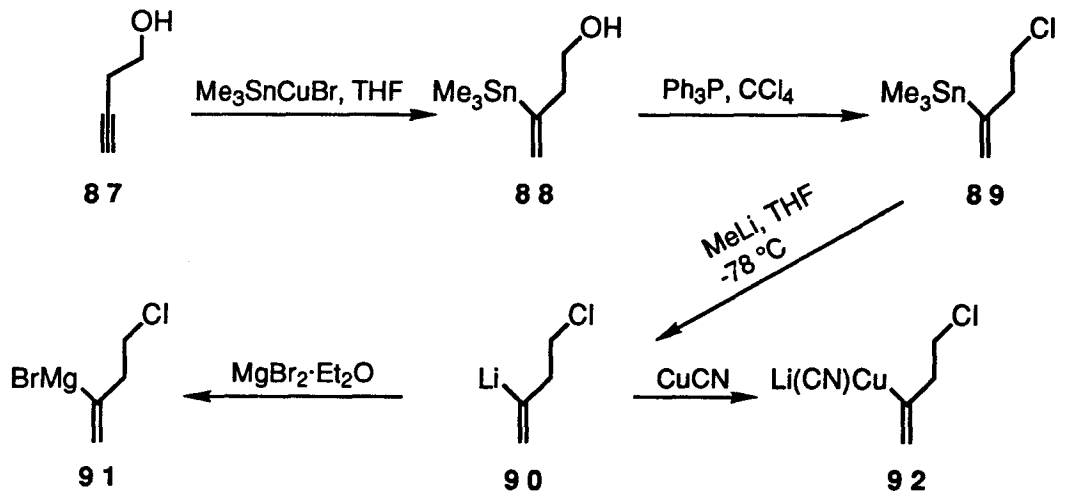


82 **85** **86**

Scheme 12

The bifunctional reagents **91** and **92**, which have been developed in our laboratory, correspond to the 1-butene d^2,a^4-synthon **72** and, in each case, include both a nucleophilic and an electrophilic center within the same molecule. The required precursor to the bifunctional reagents was prepared using organotin methodology.[27] Reaction of 3-butyn-1-ol (**87**) with (trimethylstannyl)copper(I)-dimethylsulphide complex provided 3-trimethylstannyl-3-buten-1-ol (**88**). Alcohol **88** was subsequently converted to the corresponding chloro derivative **89**, by treatment with triphenylphosphine in carbon tetrachloride (**Scheme 13**). Transmetalation of **89** with methyllithium in THF at -78 °C provided the vinyllithium **90**, and addition of magnesium bromide-etherate complex converts the vinyllithium intermediate to the vinylmagnesium bromide reagent **91**. In the presence of a catalytic amount of copper bromide-dimethyl sulfide complex the reagent **91**

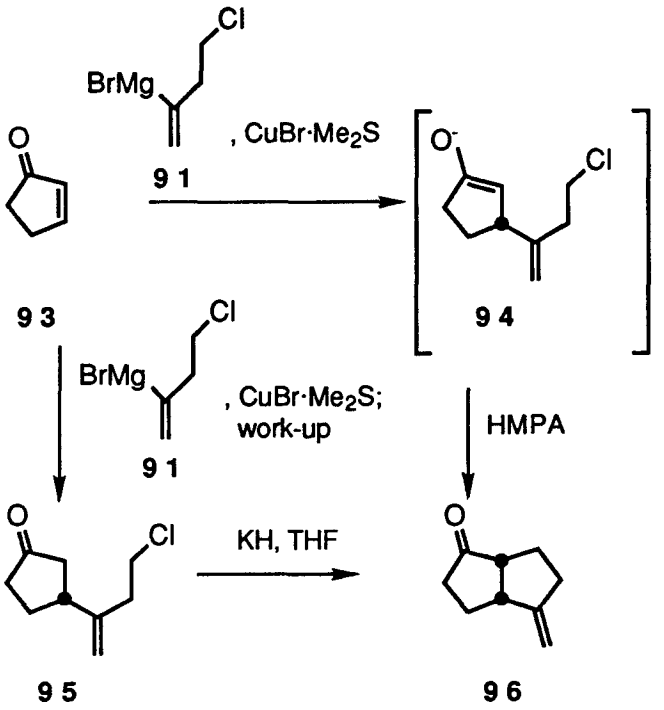
undergoes 1,4-conjugate addition to enones. Alternatively, the addition of copper cyanide to the vinyllithium **90** provides the organocuprate reagent **92**. The organocuprate reagent thus formed *in situ* is a synthetic equivalent of the bifunctional synthon **72**. While there is a similarity between the reagent **77** (**Scheme 10**, page 21), and the reagents **91** and **92** used in our work, the former reagent is less efficient. After the first step (i.e. 1,4-addition), the protected acceptor site in **77** must undergo two additional transformations before annulation can be completed.



Scheme 13

The reagent **91** undergoes efficient Cu(I)-catalyzed 1,4-addition to enones such as **93** to provide enolate anions such as **94** (**Scheme 14**).[28] The latter species can be cyclized by adding a suitable additive (HMPA is the most commonly used). Alternatively, the enolate **94** can be protonated to give the chloro ketone **95**. The compound **95** was cyclized upon treatment with potassium hydride in THF. Using either

protocol, the cyclized product **96** is formed cleanly and in a good overall yield. The naturally occurring triquinanes (±)-$\Delta^{9(12)}$capnellene[28], (±)-pentalenene[29], (±)-methyl cantabrenonate[30] and (±)-methyl epoxycantabronate[30] have already been successfully prepared via routes in which the described annulation sequence played a key role.



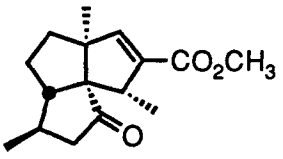
Scheme 14

1.6 Research Objectives

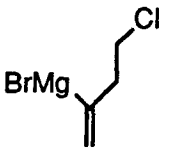
As mentioned earlier, subergorgic acid (**8**) is a structurally unique silphiperfolene sesquiterpenoid, in that it is the only one having a keto function at C-2. Successful total synthesis have confirmed the previously assigned structure.[5,11] Nonetheless, a shorter total

synthesis, which would produce subergorgic acid in a good yield, remains a challenge.

In a retrosynthetic sense, access to the triquinane skeleton of subergorgic acid may be possible based on the described methylenecyclopentane annulation sequence. Furthermore, the desired keto function at C-2 can be obtained by the oxidation of the methylene group derived from the bifunctional reagent **91**. Thus, it was decided to attempt the synthesis of (±)-subergorgic acid (**8**) *via* a synthetic route which involves the annulation sequence as its key transformation.



8



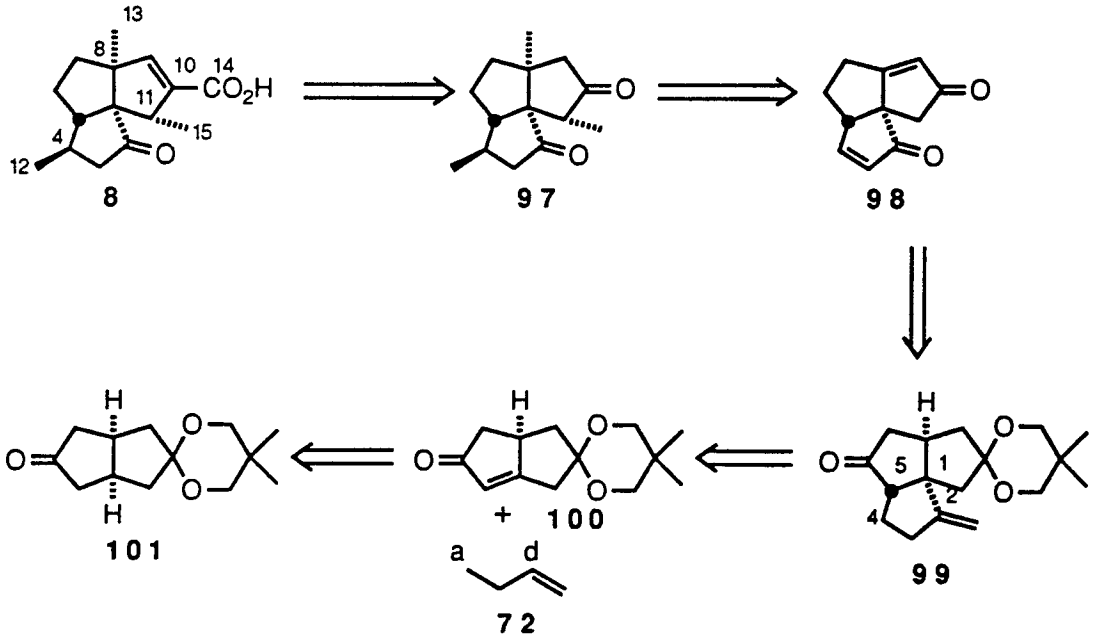
91

2 DISCUSSION

2.1 Retrosynthetic Analysis of (±)-Subergorgic Acid (8)

The retrosynthetic analysis of (±)-subergorgic acid (**8**), as depicted in **Scheme 15**, was based on the methylenecyclopentane annulation methodology, which would allow the assembly of an angular triquinane skeleton. Once the skeleton had been assembled, the functionalities and substituents were to be introduced.

Thus, disconnection of the carbon-carbon bond between C-10 and C-14 in (±)-subergorgic acid (**8**) would lead to the diketone **97**. Disconnections of the carbon-carbon bonds between C-4 and C-12, between C-8 and C-13, and between C-11 and C-15 would produce the dienedione **98**, which should be accessible from the tricyclic keto ketal **99** *via* functional group interconversions (FGI's).



Scheme 15

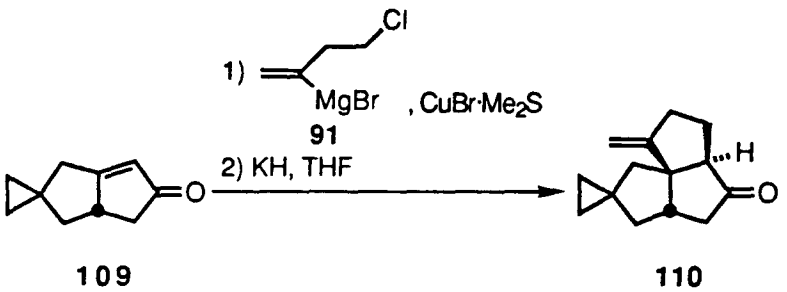
Disconnections between C-1 and C-2 and between C-4 and C-5 in the key intermediate, tricyclic keto ketal **99**, leads to the bifunctional synthon **72** and the enone ketal **100**. A synthetic equivalent of the bifunctional synthon **72** is the Grignard reagent **91** (**Scheme 13**, p 24), and the enone ketal **100** should be accessible from the known keto ketal **101**.

2.2 The Synthetic Plan

In accordance with the retrosynthetic analysis described above, the following synthetic plan was devised (**Scheme 16**).

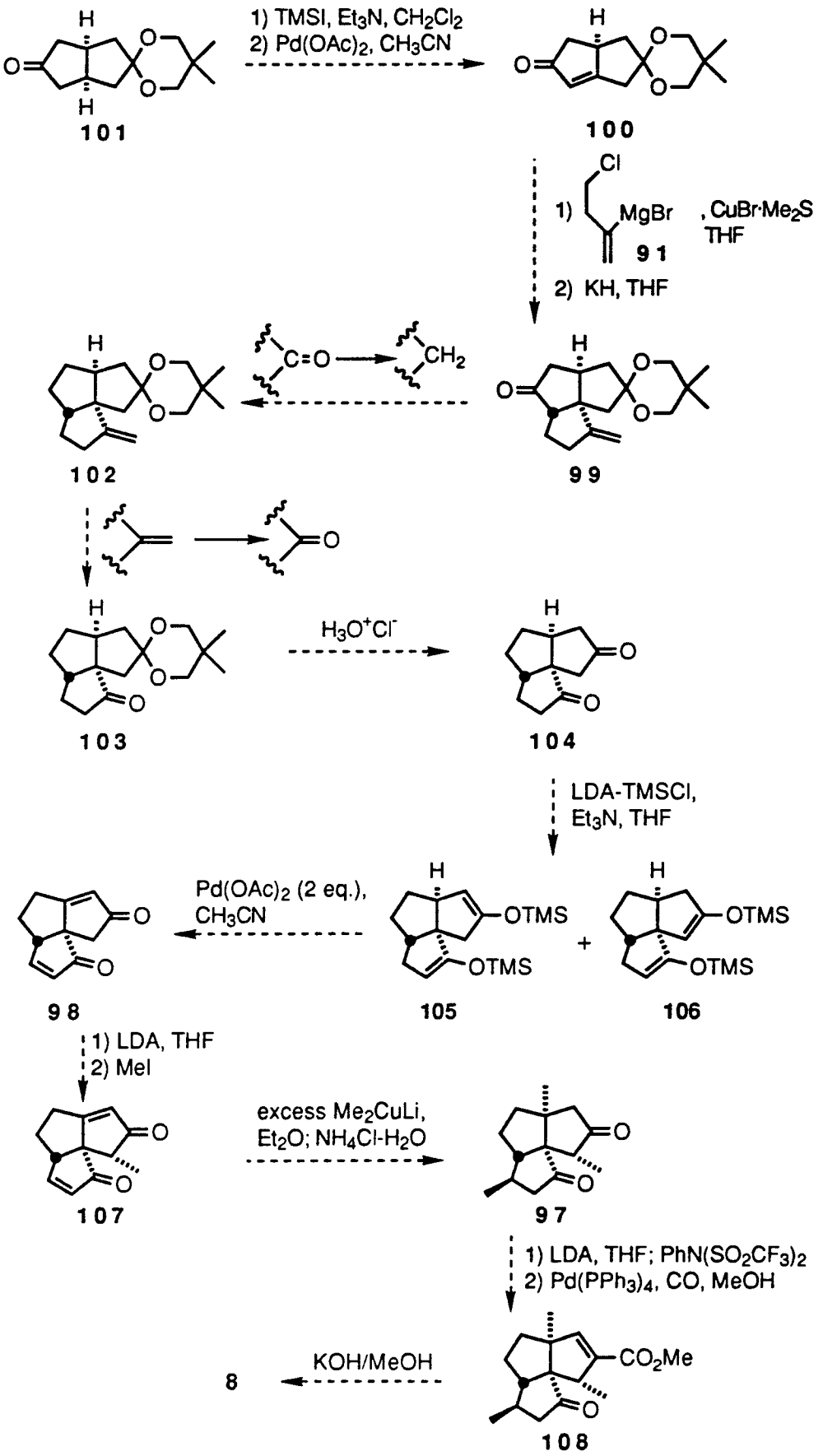
The readily available keto ketal **101** was chosen as starting material. Saegusa oxidation[31] of **101** *via* the corresponding enol silyl ether, was expected to provide the enone ketal **100**.

It was anticipated that the copper(I)-catalyzed reaction of the reagent **91** with the enone ketal **100**, followed by intramolecular alkylation of the intermediate chloro ketone, would provide the tricyclic keto ketal **99**. The methylenecyclopentane annulation sequence on the structurally similar enone **109** had been successfully accomplished in our laboratory (**Scheme 17**).[29]



109 **110**

Scheme 17


1) TMSI, Et3N, CH2Cl2
2) Pd(OAc)2, CH3CN
101
100
1) MgBr 91, CuBr·Me2S, THF
2) KH, THF
C=O
CH2
102
99
H3O+Cl-
103
104
LDA-TMSCl, Et3N, THF
Pd(OAc)2 (2 eq.), CH3CN
OTMS
OTMS
OTMS
OTMS
98
105
106
1) LDA, THF
2) MeI
excess Me2CuLi, Et2O; NH4Cl-H2O
107
97
1) LDA, THF; PhN(SO2CF3)2
2) Pd(PPh3)4, CO, MeOH
CO2Me
KOH/MeOH
8
108

Scheme 16

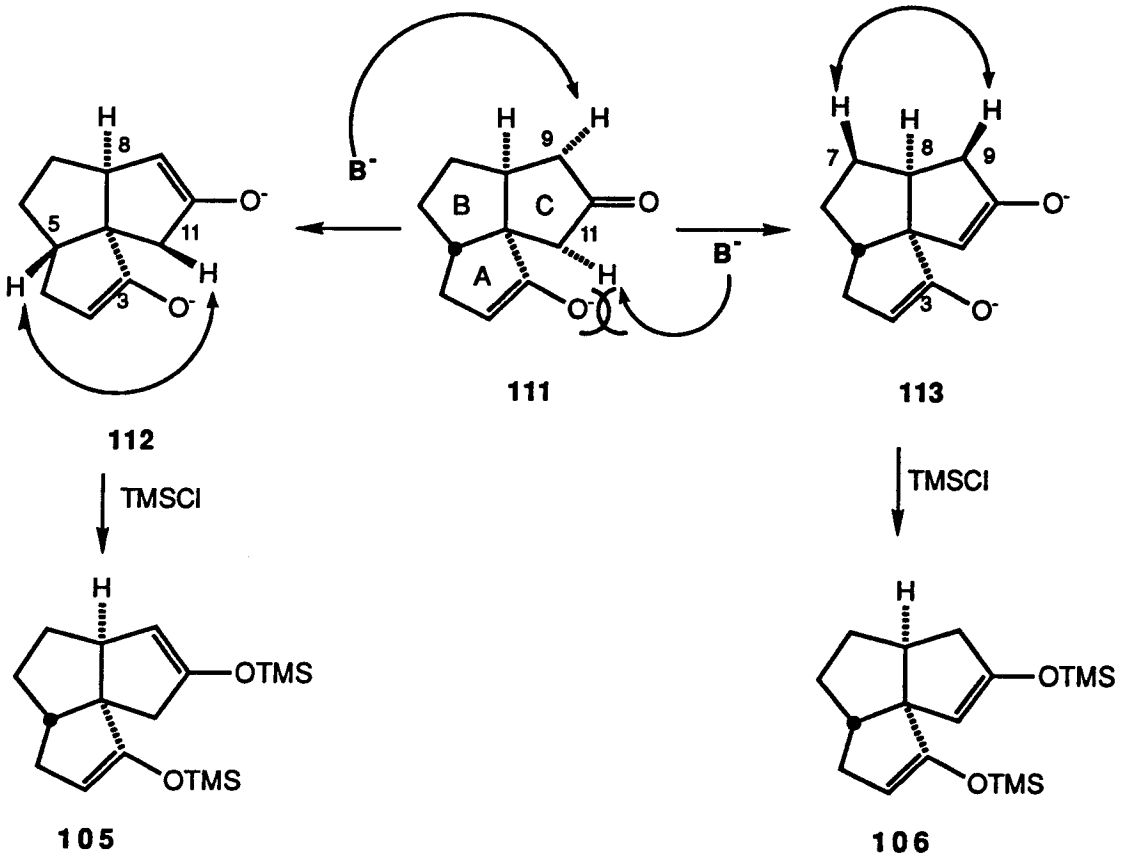
Deoxygenation of the C-6 keto function in the keto ketal **99** would produce the tricyclic ketal alkene **102**. Barton's deoxygenation procedure, involving a xanthate as an intermediate, is a method of choice to accomplish such a transformation.[32]

Oxidative cleavage of the double bond in **102** would give the keto ketal **103**, thus solving the problem of the introduction of the C-2 carbonyl group (pp 18-19). Reagents commonly used for such a transformation in polyquinane chemistry are ozone,[33] osmium tetroxide-sodium periodate[34] and ruthenium tetroxide-sodium periodate.[35]

Acid-mediated deprotection of the keto ketal **103** would give the tricyclic diketone **104**.

Treatment of **104** with LDA followed by TMSCl could produce two possible regioisomeric *bis*enol silyl ethers **105** and **106**. It was envisioned that the double Saegusa oxidation[31] of *bis*enol silyl ether **105** would yield the dienedione **98.** Based on an inspection of molecular models, it was concluded that the formation of the desired **105** would be favoured in a kinetically controlled reaction (**Scheme 18**). The presence of the A-ring enolate moiety, in the intermediate **111**, should prevent formation of the undesired enolate **113**, due to steric hindrance and electrostatic interaction with an approaching base. Trapping of the "kinetic" enolate **112** with TMSCl would provide the *bis*enol silyl ether **105**. Alternatively, one could use thermodynamically controlled reaction conditions to favour the formation of the *bis*enol silyl ether **105**. Once formed the enolate **112** should be more stable than **113** (**Scheme 18**), primarily due to an interaction between the β-hydrogen at C-7 and β-hydrogen at C-9 in

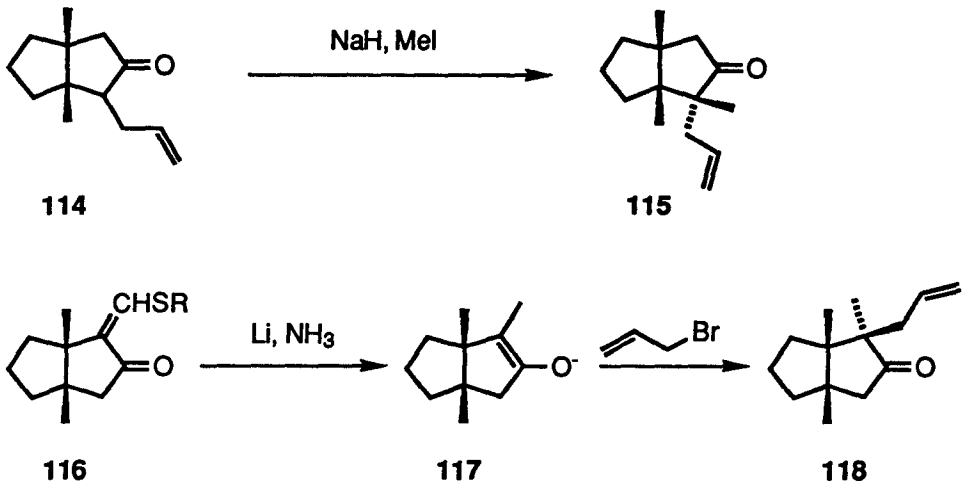
113. The corresponding interaction in the enolate **112**, i.e. between the hydrogen at C-5 and the β-hydrogen at C-11, is less severe. Furthermore, the distance between the angular proton at C-8 and the enolate oxygen at C-3 is shorter in **113** as compared to **112**. Thus, the dienolate **112** was expected to be both kinetically and thermodynamically favoured.



Scheme 18

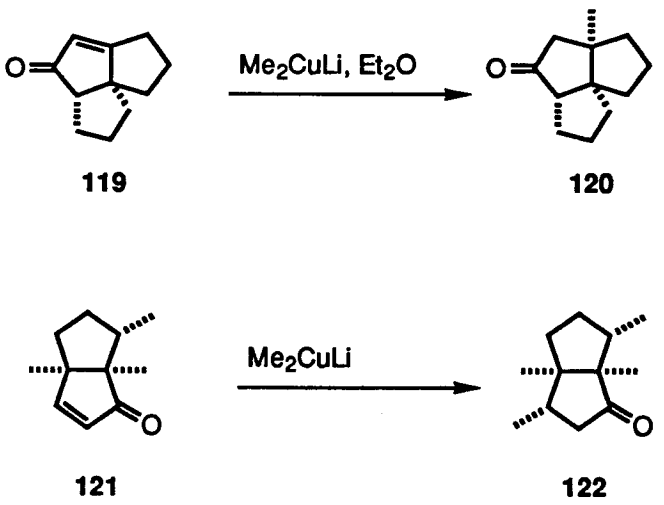
Removal of the most acidic C-11 proton in dienedione **98**, in a kinetically controlled reaction, followed by treatment with iodomethane should provide the compound **107**. The relative configuration of the newly introduced C-11 methyl group is expected to be as drawn. A literature survey did not provide any examples of

alkylation on a substrate similar to the dienedione **98**. Alkylations of the saturated diquinanes[36,37] have shown that the approach of an alkylating agent from the less hindered convex α-face should be preferred, even in the presence of a methyl substituent at the neighboring angular position (**Scheme 19**).



Scheme 19

The double addition of lithium dimethylcuprate to the dienedione **107** should provide the diketone **97**. The addition of both methyl groups in **97** should proceed to give the desired relative stereochemistry as shown in **Scheme 16**. Literature precedents indicate that lithium dimethylcuprate addition provides *cis*-fused diquinanes,[38] and an addition to A-ring of enone **107** would take place from the less hindered convex face (**Scheme 20**, see also **Scheme 3**, p 7).[39]



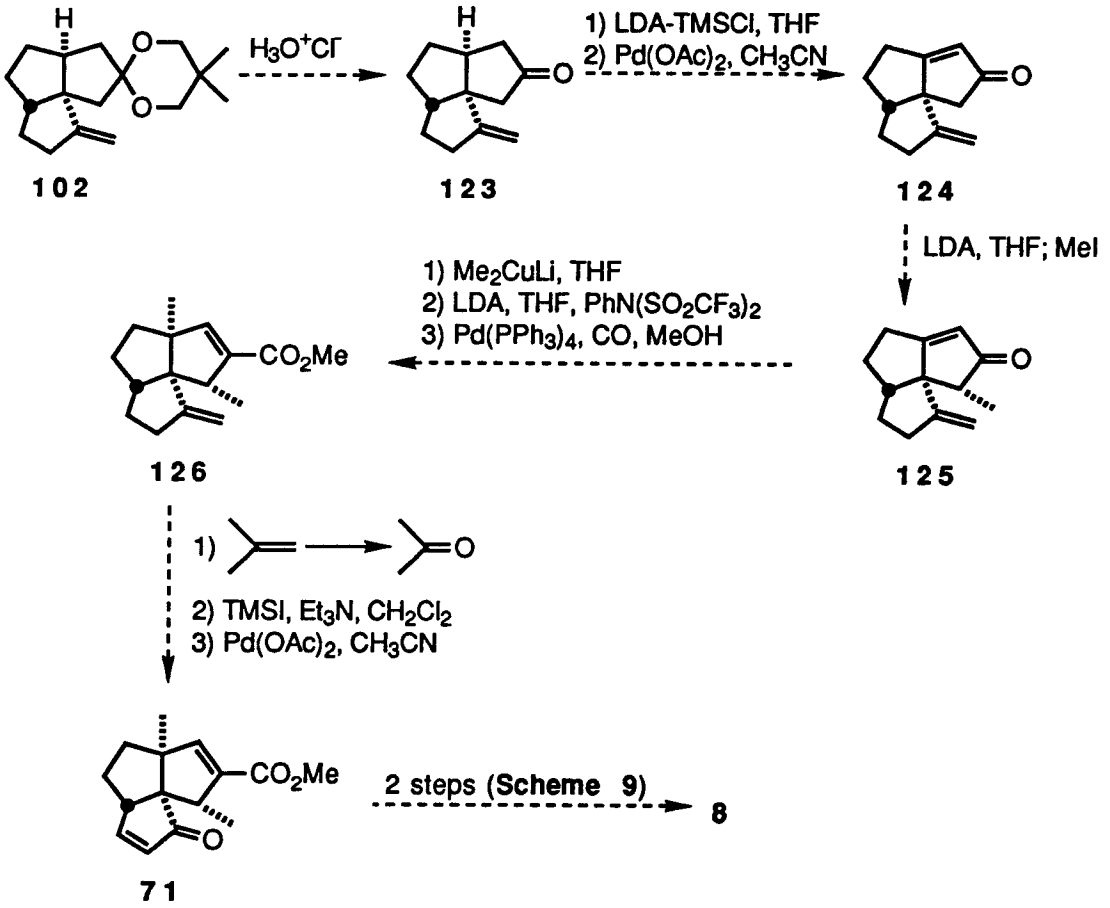
Scheme 20

Kinetically controlled reaction of the diketone **97** with 2.2 equiv. of a base should provide the corresponding *bis*enolate. The site selective transformation of the sterically less hindered C-10 enolate function of the *bis*enolate into a vinyl triflate moiety, followed by a palladium-catalyzed methoxycarbonylation,[40] would produce methyl subergorgate **108**. Hydrolysis of methyl subergorgate (**108**) upon base treatment would give the target subergorgic acid (**8**).

Some difficulties were anticipated in the execution of the plan outlined above. Specifically, it was felt that the double Saegusa transformation, i.e. from **104** → **98**, as well as the double lithium dimethylcuprate addition, i.e. from **107** → **97** (**Scheme 16**), could be problematic. Therefore, an alternative route was devised.

The following synthetic sequence was developed so that, should it be necessary, these transformations could be conducted sequentially (**Scheme 21**). The plan was modified so that after the preparation of the keto alkene **123** from the ketal alkene **102**, the difference in chemical reactivity between the keto and the alkene functions could be

exploited. Saegusa conversion of the keto alkene **123** would produce the keto diene **124**. Generation of the "kinetic" enolate from **124** and subsequent alkylation with methyl iodide would give **125**. Lithium dimethylcuprate addition followed by the previously described McMurry procedure,[40] would be expected to provide the compound **126**. Chemoselective cleavage of the exocyclic double bond, followed by a Saegusa transformation, should provide the intermediate **71**, which was recently converted to subergorgic acid by the Paquette's group.[19]

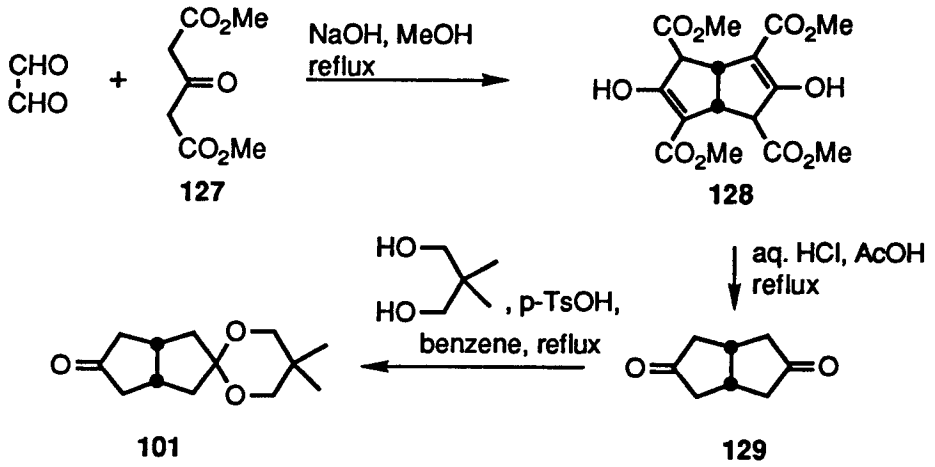


Scheme 21

2.3 Studies Toward a Total Synthesis of (±)-Subergorgic Acid

2.3.1 Preparation of the Starting Materials **89** and **101**

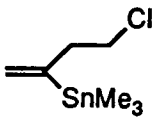
The diketone **129** was prepared from dimethyl 1,3-acetonedicarboxylate (**127**) and glyoxal according to the Weiss and Cook's procedure.[41] The substrate **129** was converted into the keto ketal **101**, using a procedure developed previously in our laboratory (**Scheme 22**).[42]



127 **128** **101** **129**

Scheme 22

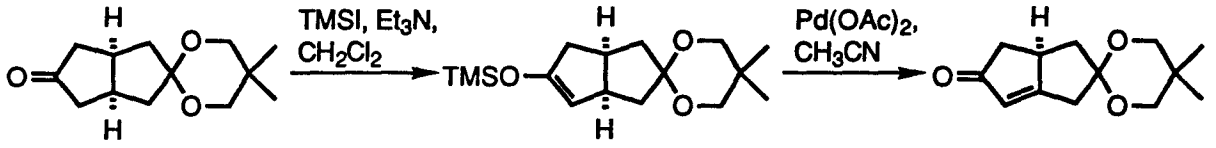
4-Chloro-2-trimethylstannyl-1-butene (**89**) was synthesized following a well established method from our laboratory (**Scheme 13**, page 23).[27]



89

2.3.2 Preparation of the Enone Ketal **100**

The known keto ketal **101** was converted into the enol silyl ether **130**, by treatment with trimethylsilyl iodide and triethylamine in dichloromethane.[43] The compound **130** was oxidized with palladium acetate in acetonitrile[31] to give the enone ketal **100** in 72% overall yield (**Scheme 23**).



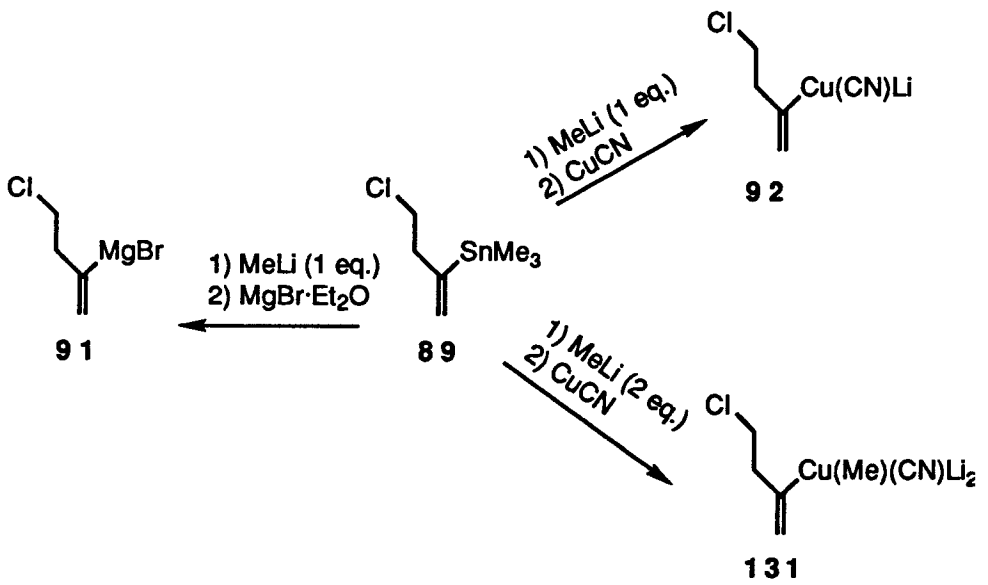
101 **130** **100**

Scheme 23

2.3.3 Preparation of the Tricyclic Ketone **99**

With the enone **100** in hand we were prepared to undertake one of the key transformations of the sequence, namely the assembly of the triquinane skeleton.

In order to optimize the efficiency of methylenecyclopentane annulation sequence, the Grignard reagent **91**, as well as the lower (**92**) and the higher (**131**) order cuprate reagents were prepared from 4-chloro-2-trimethylstannyl-1-butene (**89**) *via* 2-lithio-4-chloro-1-butene (**90**). 2-Lithio-4-chloro-1-butene (**90**) was generated by the transmetallation of 4-chloro-2-trimethylstannyl-1-butene (**89**) with methyllithium (**Scheme 24**).

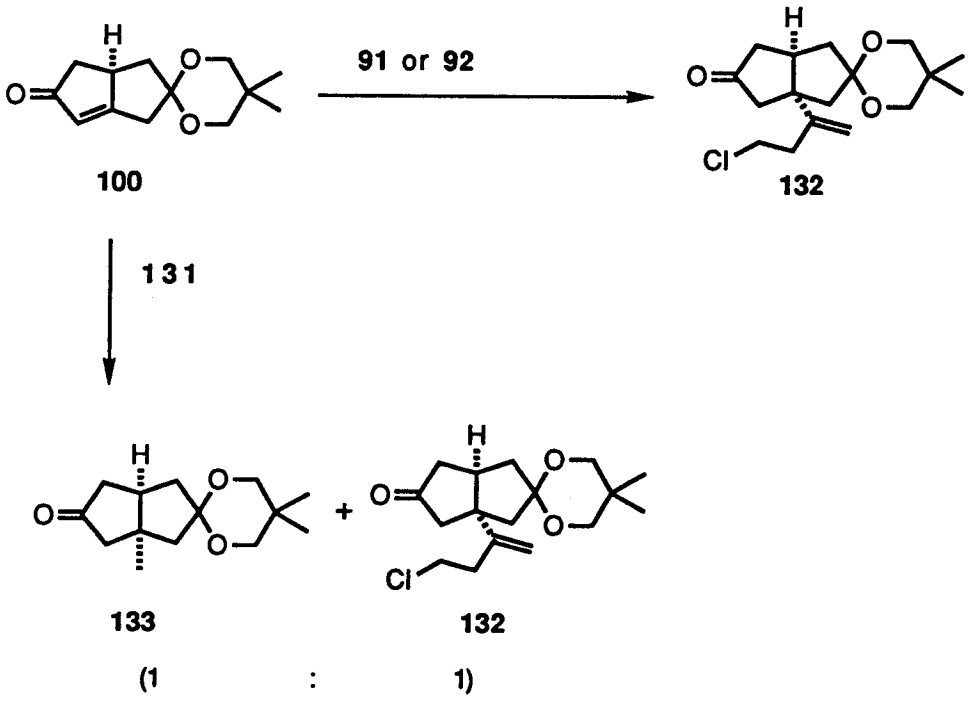


Scheme 24

Usually, one equivalent of methyllithium is added to a solution of the vinylstannane reagent to provide the corresponding vinyllithium reagent. If two equivalents of methyllithium are used, an equimolar solution of the vinyllithium and methyllithium is obtained. Addition of copper(I) cyanide to this solution generates a higher order cuprate reagent. Such reagents readily undergo 1,4-conjugate addition reactions, generally transferring a specific group selectively. "Dummy" ligands such as the cyano and alkyne groups are not transferred.[44] The methyl group in higher order cuprates is considered to be a "dummy" ligand as often vinyl or other alkyl groups are transferred preferentially. Thus, we expected reagent **131** to transfer the vinyl group selectively. To our surprise, the methyl group transferred with equal ease to the enone **100**, producing a 1:1 mixture of the chloro ketone **132** and the 1-methyl ketone **133** (**Scheme 25**). A literature search has revealed that although in most cases a vinyl group is transferred preferentially, in a few examples competitive transfer of

the methyl group was observed.[45] The reason for such an anomalous behavior is not known. Attempts to suppress the side reaction using different reaction conditions failed. Therefore, the use of the higher order cuprate reagent **131** was abandoned.

We next tried using the lower order cuprate reagent **92.** This reagent underwent efficient 1,4-addition to the ketal enone **100**, providing chloro ketone **132** in good yield. However, reproducibility of the reaction was poor as several trials led to the recovery of large quantities of the starting ketal enone **100**. This leads one to speculate that the stability of the vinylcuprate reagent **92** may be questionable.



Scheme 25

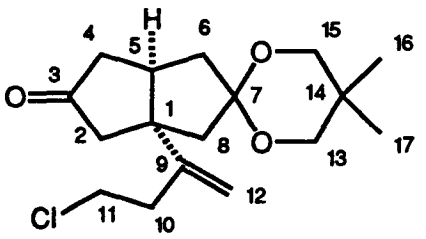
It was decided to investigate a copper(I)-catalyzed 1,4-addition of the Grignard reagent **91** to the enone **100**. Thus, treatment of the vinyllithium **90** with magnesium bromide-etherate complex, provided

the corresponding Grignard reagent **91**. The Grignard reagent was subsequently employed in the copper bromide-dimethyl sulfide catalyzed 1,4-addition to the ketal enone **100**, consistently providing the chloro ketone **132** in good yield (77%).

Incidentally, when reagents **91** or **92** were employed, a small amount of the 1-methyl keto ketal **133** was isolated, indicating that a small amount of methyllithium was present in the reaction mixture. Therefore, transmetallation of 4-chloro-2-trimethylstannyl-1-butene (**89**) with methyllithium does not proceed to completion and instead an equilibrium must have been established (**Scheme 26**). Studies by Roberge have confirmed the existence of such equilibria.[46]

Scheme 26

The IR spectrum of the chloro ketone **132** indicated the presence of a five-membered cyclic ketone (1742 cm^{-1}), a double bond (1638 cm^{-1}), and a C-O bond (1116 cm^{-1}). The ^1H NMR spectrum of **132** was assigned with the aid of homonuclear correlation (COSY) experiments (**Table 1**). The singlets at 0.96 and 0.97 indicate the presence of gem-dimethyl moiety. Signals at 3.45 and 3.48 are due to the ketal methylene protons, and a triplet at 3.67 is assigned to the protons of the chloro methylene moiety. The olefinic protons exhibit signals at 4.91 and 5.01.



132

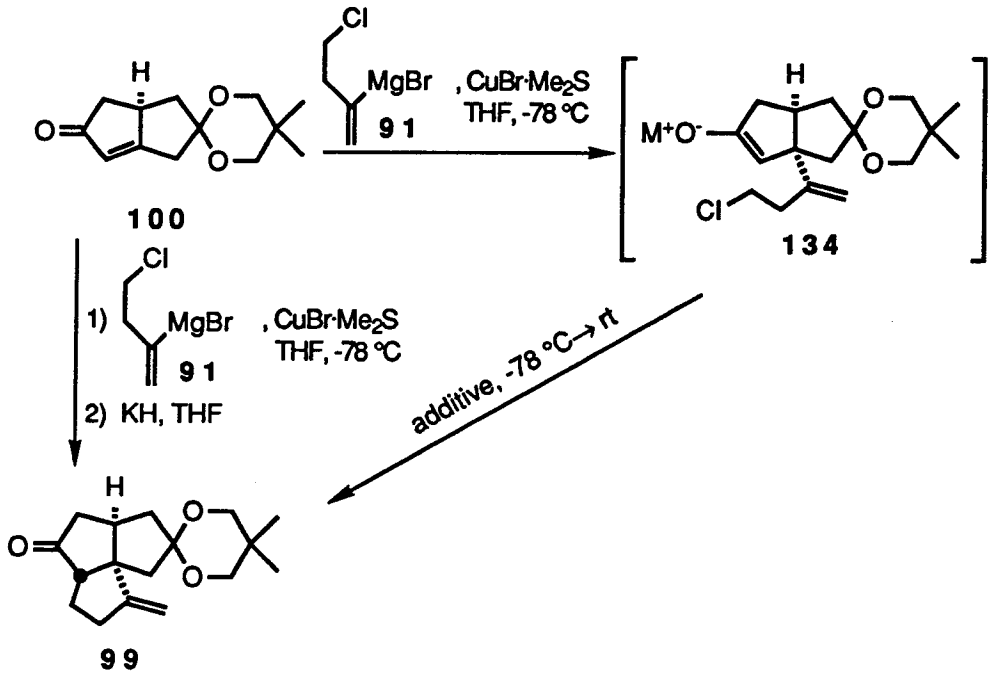
Table 1. ^{1}H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the chloroketone **132**.

H-x (assignment)	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY Correlations[a]
H-4α or β	2.43	H-5
H-5	2.89	H-4α or β, H-6α and β
H-6β	2.36	H-5, H-6α
H-6α	1.87	H-5, H-6β
ketal CH_2's	3.45 & 3.48	H-16 & H-17
H-16 & H-17	0.96 & 0.97	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

After preparation of the chloro ketone **132** was made efficient, our attention turned to the one-pot conversion of **100** to **99**. It is known that the enolates obtained after conjugate addition can be trapped with electrophiles, and that such reactions are aided by complexing agents.[47] Thus, after **134** was formed *in situ* (**Scheme 27**), subsequent addition of a complexing agent provided tricyclic keto ketal **99**. The role of an additive is to complex with the metal ion in the intermediate enolate **134** and thus promote intramolecular alkylation of the carbanion. The ratio of cyclized product **99** to the uncyclized product **132** depended on whether or not an additive was employed prior to warming up of the

reaction mixture. Results are summarized in the **Table 2**. The best results were obtained when 2 equivalents of either HMPA or DMPU were used as an additive. Due to the high toxicity of HMPA, DMPU was chosen as the additive in subsequent reactions. Under these conditions, the isolated yield of the cyclized product **99** was 81% and was accompanied by 4% of the uncyclized chloro ketone **132**, which could be efficiently cyclized upon treatment with potassium hydride in THF.



Scheme 27

Alternatively, the chloro ketone **132** could be isolated in 77% yield, and then cyclized in 94% yield upon treatment with potassium hydride.

Table 2. Methylenecyclopentane annulation of the enone ketal **100**

Entry	Additive	**99/132**[a]	yield of **99**(%)
(1)	(none)	50/50	74[b]
(2)	TMEDA (4 eq.)	90/10	75
(3)	HMPA (2 eq.)	95/5	80
(4)	DMPU (2 eq.)	95/5	81

a) GLC ratio; b) Isolated yield of **99** after treatment of a mixture with KH/THF.

The IR spectrum of the ketone **99** indicated the presence of a five-membered cyclic ketone (1741 cm^{-1}), a double bond (1651 cm^{-1}) and a C-O single bond (1119 cm^{-1}). The ^1H NMR spectrum (400 MHz, $CDCl_3$) (**Figure 1**) of the ketone **99** is consistent with the proposed structure. The signals were assigned with the aid of homonuclear correlation (COSY, 400 MHz $CDCl_3$) experiments (**Table 3**), as well as decoupling experiments (400 MHz) (**Table 4**). The doublets at 2.19 and 2.32 are due to two isolated protons at the C-11. The olefinic protons at C-12 exhibit resonances at 4.97 and 5.02, while the angular protons at C-8 and C-5 exhibit signals at 2.57 and 2.61, respectively. The ketal group remained intact as evidenced by the presence of singlets at 0.90 and 0.92 which are due to the protons at the two geminal methyl groups C-16 and C-17. They exhibit long range coupling with the signals at 3.40 and 3.47, due to the four ketal methylene protons at C-12 and C-14.

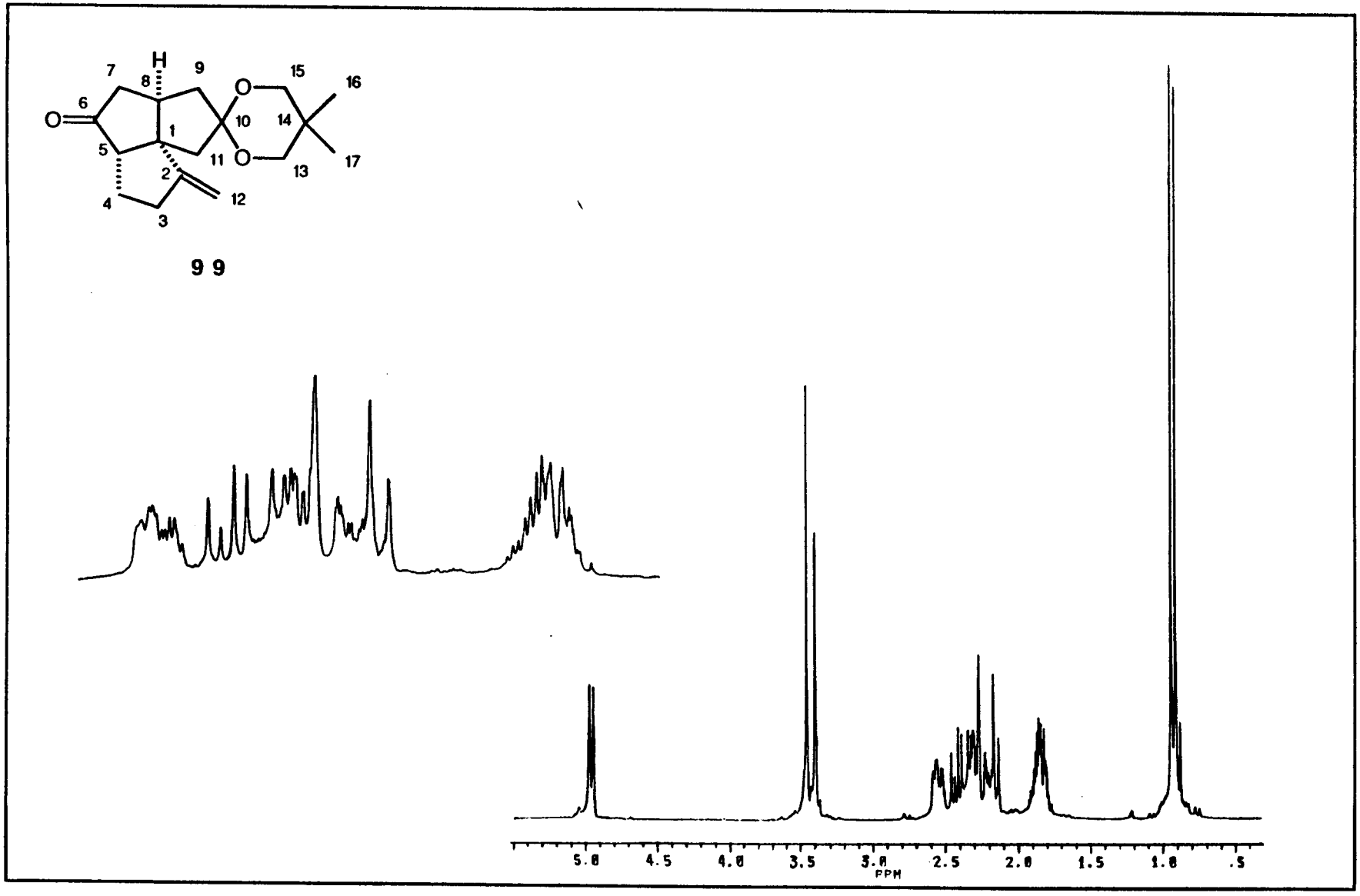


Figure 1. The ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of the keto alkene **99**.

Table 3. ^{1}H NMR (400 MHz, $CDCl_3$) and COSY (400 MHz, $CDCl_3$) data for the keto alkene **99**.

H-x (assignment)	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY correlations
H-4α & β H-9α or β	1.80-1.96	H-5, H-8
H-5 and H-8	2.57 & 2.61	H-4α & β, H-7α & β, H-9α & β
H-7α or β	2.47	H-7β or α, H-8
ketal CH_2's	3.42, 3.46 & 3.50	H-16 & H-17
H-16 & H-17	0.90 & 0.93	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

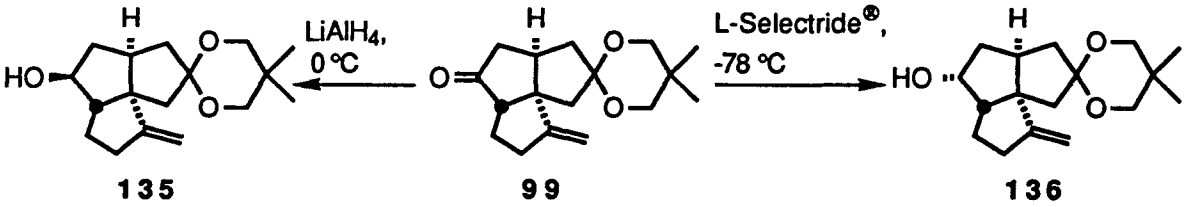
Table 4. ^{1}H NMR (400 MHz, $CDCl_3$) and decoupling experiments (400 MHz, $CDCl_3$) data for the keto alkene **99**.

irradiated signals		observed signals	
assignment H-x	^{1}H NMR (400 MHz, $CDCl_3$)	δ ppm (mult. *J*, H-x)	mult. after irradiation
H-4α and β (H-9 also irradiated)	1.80-1.96	2.18-2.42 (m, 4H, H-3α and β, H-7, H-9) 2.57 (m, H-8) 2.61 (m, H-5)	sharpened m dd (*J*=9.0, 3.0) s
H-11α or β	2.19	2.32 (m, H-11β or α)	s
H-5 & H-8	2.57 and 2.61	1.80-1.96 (m, 3H, H-4α & β,H-9α or β) 2.18-2.42 (m, 4H, H-3α and β, H-7, H-9)	sharpened m sharpened m
H-12	4.98 and 5.01	2.18-2.42 (m, 4H, H-3α and β, H-7, H-9)	sharpened m

2.3.4. Preparation of the Alcohols **135** and **136**

Extensive use has been made of the Barton-McCombie deoxygenation for the removal of secondary hydroxyl groups in polyquinanes.[23,29,48] The alcohols are easily converted in a good yield to the corresponding xanthates. In order to deoxygenate the tricyclic keto ketal **99**, *via* the Barton-McCombie procedure,[32] the corresponding alcohols **135** or **136** are required as precursors. Ketone **99** was reduced by sodium borohydride to provide a mixture of the epimeric alcohols **135** and **136**. These were converted to the corresponding methyl xanthates for our initial trials (*vide infra*).

Later in our work, in order to improve the yield of the deoxygenation sequence, the corresponding phenyl thionocarbonates were investigated instead of the xanthates **137** and **138**. Results from earlier work in our laboratory indicated that the stereochemistry of alcohols may have an effect on the yield and ease of preparation of phenyl thionocarbonate derivatives, and subsequently on the yield of deoxygenated product.[49]



135 **99** **136**

Scheme 28

Several reducing agents were investigated in order to obtain, in a pure form, each of the stereoisomeric alcohols **135** and **136**. Results of the reductions are summarized in the **Table 5**. The best results

were obtained when lithium aluminum hydride and L-Selectride (Aldrich) were used as reducing agents (**Scheme 28**). Isolated yields of the isomeric alcohols **135** and **136** were 97% and 92%, respectively.

Table 5. Reduction of the tricyclic ketone **99**

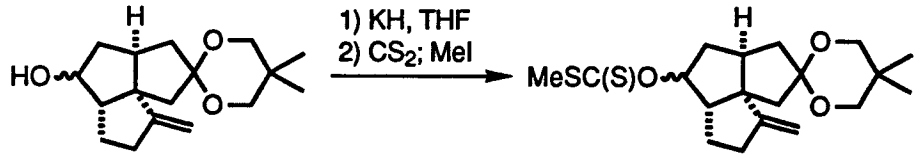
Entry	Reducing Agent	**135/136**[a]	Yield (%)
(1)	$LiAlH_4$	>98/<2	97[c]
(2)	$NaBH_4$	75/25	97[b]
(3)	DIBAL-H	20/80	96[b]
(4)	L-Selectride	4/96	92[c]

a) ^1H NMR ratio; b) Isolated yield of the mixture of epimeric alcohols; c) Isolated yield of the major epimer.

2.3.5 Preparation of the Methyl Xanthates **137** and **138**

The Barton-McCombie procedure required the conversion of alcohols **135** and **136** to their corresponding methyl xanthates **137** and **138**.

An isomeric mixture of alcohols **135** and **136** (3:1 ratio), was deprotonated with potassium hydride in THF. Treatment of the corresponding mixture of potassium alkoxides with carbon disulfide followed by methyl iodide, gave (78%) a mixture of the methyl xanthates **137** and **138**, in a ratio of approximately 3:1 (as determined from the ^1H NMR spectrum of the isolated product) (**Scheme 29**).

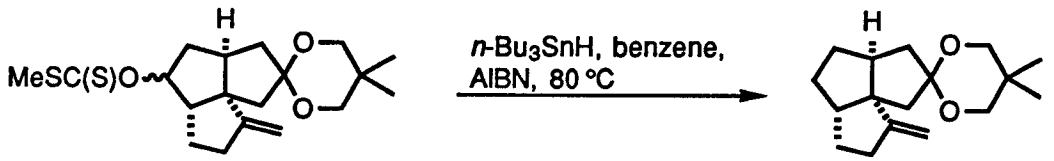


135/136 **137/138**

Scheme 29

2.3.6 Reduction of the Methyl Xanthates **137** and **138**

The mixture of methyl xanthates **137** and **138** was reduced with tributyltin hydride in refluxing benzene in the presence of a catalytic amount of AIBN as a radical initiator (**Scheme 30**). The deoxygenated product **102** was obtained in 50% yield.

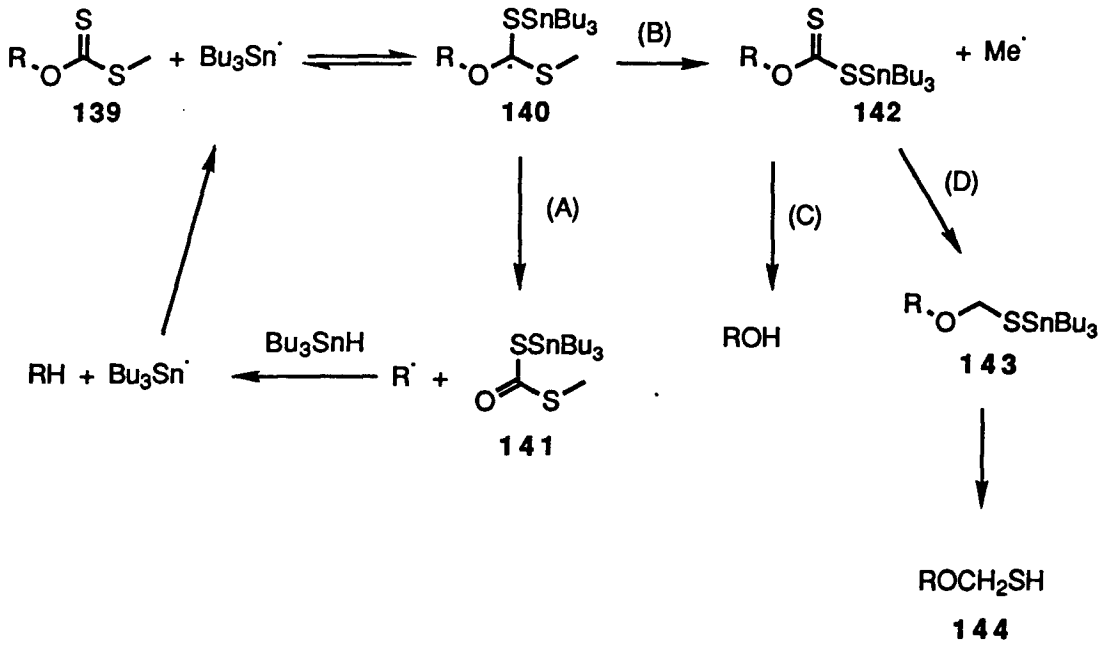


137/138 **102**

Scheme 30

The reason for the relatively low yield is probably due to the competing reactions in which the intermediate **140** can be involved (**Scheme 31**). Extensive studies on Barton-McCombie deoxygenation have established a radical chain mechanism.[50] Addition of a tributyltin radical to the thiocarbonyl bond provides the adduct radical **140** which can then undergo β-fragmentation *via* pathway A to generate an alkyl radical and the compound **141**. The alkyl radical then abstracts a hydrogen atom from tributyltin hydride propagating the free radical chain reaction. Alternatively, the intermediate **140** can undergo β-fragmentation of

the methyl-sulfur bond (pathway B) to provide a methyl radical and compound **142**. In this case the methyl radical abstracts a hydrogen from tributyltin hydride to propagate the chain reaction. Compound **142** hydrolyzes during work up to provide the starting alcohol (pathway C). Alternatively, it may undergo further reduction (pathway D) to provide the hemithioacetal **144**. The existence of pathway D has not been confirmed by mechanistic studies, and an alternative suggestion is that the compound **144** may arise from the participation of an alternative pathway in the reduction of the xanthate **139**.

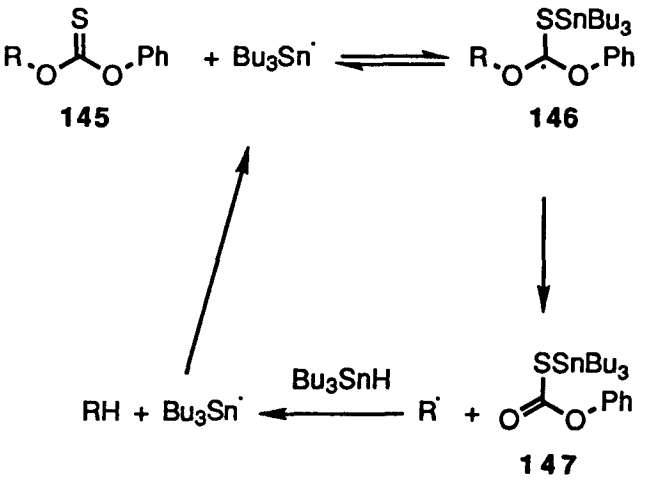


Scheme 31

From a synthetic point of view, the low yield obtained in the deoxygenation of xanthates **137** and **138** was not satisfactory. In order to improve yield of Barton-McCombie deoxygenation procedure, Robins and coworkers investigated the use of a number of thionocarbonate derivatives of the corresponding alcohols.[51] The

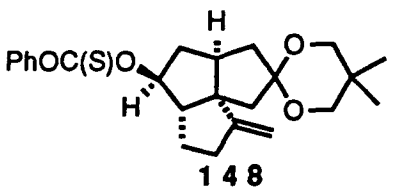
phenyl thionocarbonates have shown to be suitable intermediates for this transformation.

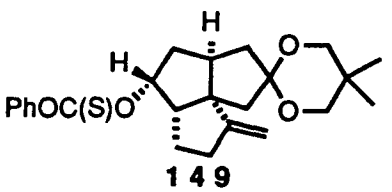
It is claimed that the main advantage in using phenyl thionocarbonates instead of methyl xantates in a such deoxygenation processes is that the former substrates limit side reactions (**Scheme 32**). Phenyl thionocarbonates have an unreactive phenyloxy function instead of the thiomethyl group. Thus, the pathway B (**Scheme 31**) does not participate in evolution of the intermediate **146**. The only pathway available is the β-fragmentation between the alkyl group and one of the oxygen atoms. The bond between the phenyl group and the other oxygen is stronger and thus does not fragment under the reaction conditions.



Scheme 32

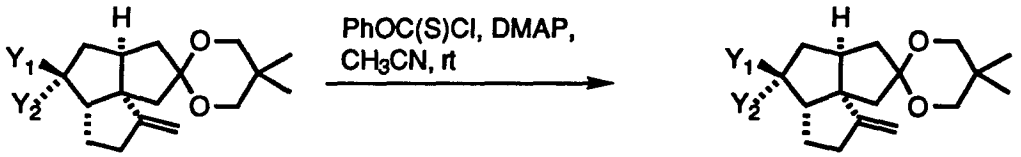
Therefore, it was decided to investigate deoxygenation of the corresponding phenyl thionocarbonates **148** and **149**.





2.3.7 Preparation of the Phenyl Thionocarbonates **148** and **149**

The phenyl thionocarbonates **148** and **149** were prepared in 76% and 71% yield, respectively, from the reaction between the corresponding alcohols **135** and **136** and phenyl chlorothionoformate, in the presence of DMAP (**Scheme 33**).[51]



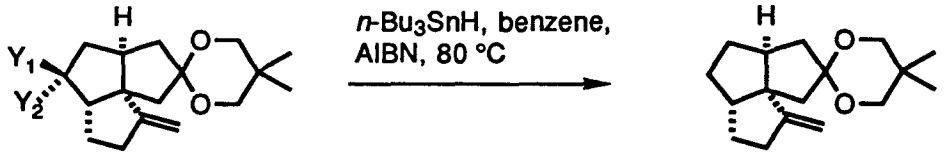
135: Y_1= -OH; Y_2= -H
136: Y_1= -H; Y_2= -OH

148: Y_1= -OC(S)OPh; Y_2=-H (71%)
149: Y_1= -H; Y_2= -OC(S)OPh (76%)

Scheme 33

2.3.8 Reduction of the Phenyl Thionocarbonates **148** and **149**

Following the deoxygenation procedure developed by Robins et al.,[51] the phenyl thionocarbonates **148** and **149** were reduced in refluxing benzene with tributyltin hydride and a small amount of AIBN, as a radical initiator (**Scheme 34**). The yield of the alkene ketal **102** thus obtained was 87% from **148** (83% from **149**), and, thus, the overall yield for the three step deoxygenation procedure *via* the phenyl thionocarbonate **148** was 60% (58% *via* **149**). This is a significant improvement over the deoxygenation procedure utilizing the methyl xanthates, which provided the tricyclic ketal **102** in only 37% overall yield.



148: Y_1= -OC(S)OPh; Y_2=-H
149: Y_1= -H; Y_2= -OC(S)OPh

102 (87%)
(83%)

Scheme 34

2.3.9 Stereochemistry of the Alcohols **135** and **136**, and the Phenyl Thionocarbonates **148** and **149**

Both of the epimeric alcohols **135** and **136** underwent phenyl thionocarbonate formation, and subsequent deoxygenation with equal ease. Nonetheless, the relative stereochemistry of each epimer was of interest and ^{1}H NMR studies were carried out to determine the configuration at the hydroxy bearing center in each of these substances.

The tentative assignment of the signals in the proton NMR spectra were confirmed with the aid of homonuclear correlation (COSY) experiments (**Table 6**).

The nOe difference spectra of the alcohol **135** were obtained to determine the relative stereochemistry of protons at C-5, C-6 and C-8. The absence of nOe enhancement between the H-5 and H-6 suggests that these protons are in a *trans* relationship (**Figure 2**). Furthermore, irradiation of the signal due to H-6 led to enhancement of the signals assigned to H-4α, H-7α and H-8 protons. The reciprocal enhancement between H-4α and H-6 indicate that the stereochemistry of H-6 proton is α.

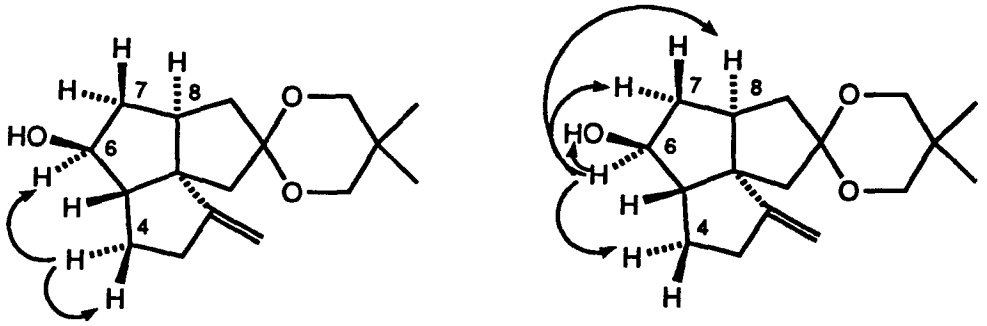


Figure 2. nOe experiments on the alcohol **135**

Table 6. ^{1}H NMR (400 MHz, $CDCl_3$), COSY (200 MHz, $CDCl_3$) and nOe (400 MHz, $CDCl_3$) data for the alcohol **135**.

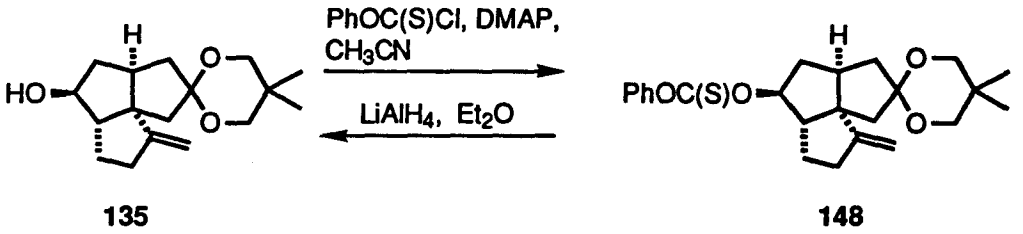
Assignment H-x	^{1}H NMR (400MHz, $CDCl_3$) δ	COSY correlations[a]	nOe correlations
H-4β	1.85	H-4α, H-5	
H-4α	1.37	H-4β, H-5	1.85 (H-4β) 3.84 (H-6)
H-5	2.20	H-4α & β, H-6	
H-6	3.84	-OH, H-5, H-7α & β	1.37 (H-4α) 2.14 (H-7α or β) 2.30 (H-8) 3.06 (-OH)
-OH	3.06	H-6	3.84 (H-6)
H-7α or β	1.67	H-6, H-7α or β	2.14 (H-7α or β) 3.84 (H-6)
H-7α or β	2.14	H-6, H-7α or β	
H-11α or β	2.06	H-11β or α	2.45 (H-11)
H-11β or α	2.45	H-11α or β	2.06 (H-11)
H-13 & H-15	3.44 & 3.51	H-16 & H-17	
H-16 & H-17	0.91 & 0.99	H-13 & H-15	

a) Only those COSY correlations that could be unambigously assigned are recorded

Unfortunately, it was not possible to selectively conduct nOe experiments on the alcohol **136** as the signals of interest (signals due

to protons at C-4, C-5, C-7 and C-8) in the proton NMR spectrum were overlapping. Although results of nOe experiments on the alcohol **135** indicated that the stereochemistry of the hydroxyl group is β, further studies on the corresponding phenyl thionocarbonates were carried out. The proton NMR spectra of the corresponding phenyl thionocarbonates gave better signal dispersion and thus were more suitable for this study.

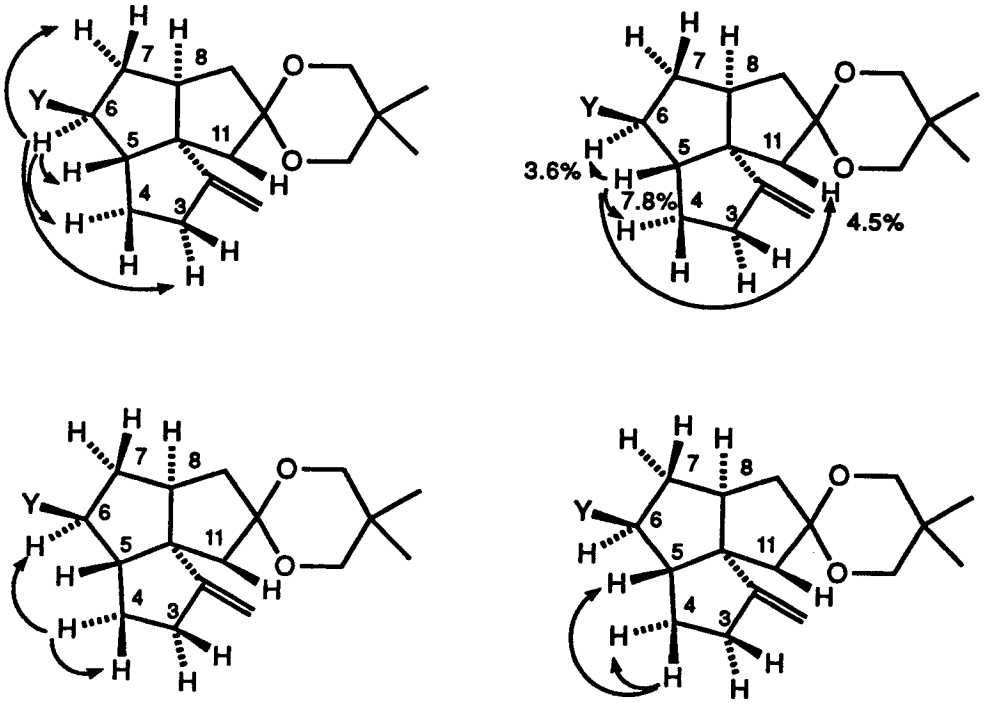
To verify that the preparation of the phenyl thionocarbonate derivative occurs with the retention of stereochemistry, a lithium aluminum hydride reduction of **148** was carried out. The alcohol thus obtained displayed spectral data which were identical with those of the starting alcohol **135** (**Scheme 35**).



135 **148**

Scheme 35

The results of nOe difference experiments on the phenyl thionocarbonate **148** are summarized in the **Figure 3** and **Table 7**. Irradiation of the signal due to H-6 caused enhancement of the signals assigned to H-3α, H-4α, H-5 and H-7α. Irradiation of the signals due to H-4α and H-5 caused enhancement of the signal due to H-6. The reciprocal enhancement between H-6 and H-4α indicates that the stereochemistry of C-6 proton is α.



Y=-OC(S)OPh

Figure 3. nOe experiments on the phenyl thionocarbonate **148**

The nOe enhancement between H-5 and H-6 protons is probably due to a conformation of the triquinane skeleton of **148** in which the H-5 and H-6 protons are relatively close to one another. However, the magnitude of the nOe (3.6%) at proton H-6 when proton H-5 was irradiated is much smaller compared with the corresponding enhancement in compound **149** (11.2%).

Table 7. ^1H NMR (400 MHz, $CDCl_3$), COSY (200 MHz, $CDCl_3$) data and nOe experiments (400 MHz, $CDCl_3$) for the phenyl thionocarbonate **148**.

Assignment H-x	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]	nOe correlations
H-4α	1.60	H-4β, H-5	1.87 (H-4β) 5.32 (H-6)
H-4β	1.87	H-4α, H-5	1.60 (H-4α) 2.69 (H-5)
H-5	2.69	H-4α & β, H-6	1.87 (H-4β) 2.20 (H-11β) 5.32 (H-6)
H-6	5.32	H-5, H-7α and β	1.60 (H-4α) 2.32-2.50 (H-3α & H-7α) 2.69 (H-5)
H-7β	1.93	H-6, H-7α	
ketal CH_2's	3.49	H-16 & H-17	
H-16 & H-17	0.93 & 1.02	ketal CH_2's	

a) Only those COSY correlations that could be unambigously assigned are recorded

The nOe difference experiments on the phenyl thionocarbonate **149** (**Figure 4** and **Table 8**) have shown that irradiation of the signal due to the H-6 proton caused enhancement of the H-5, H-7β and H-9β proton resonances. The irradiations of H-5 and H-9β protons caused nOe enhancement of the H-6 proton. Thus we concluded that the stereochemistry of the latter proton is β.

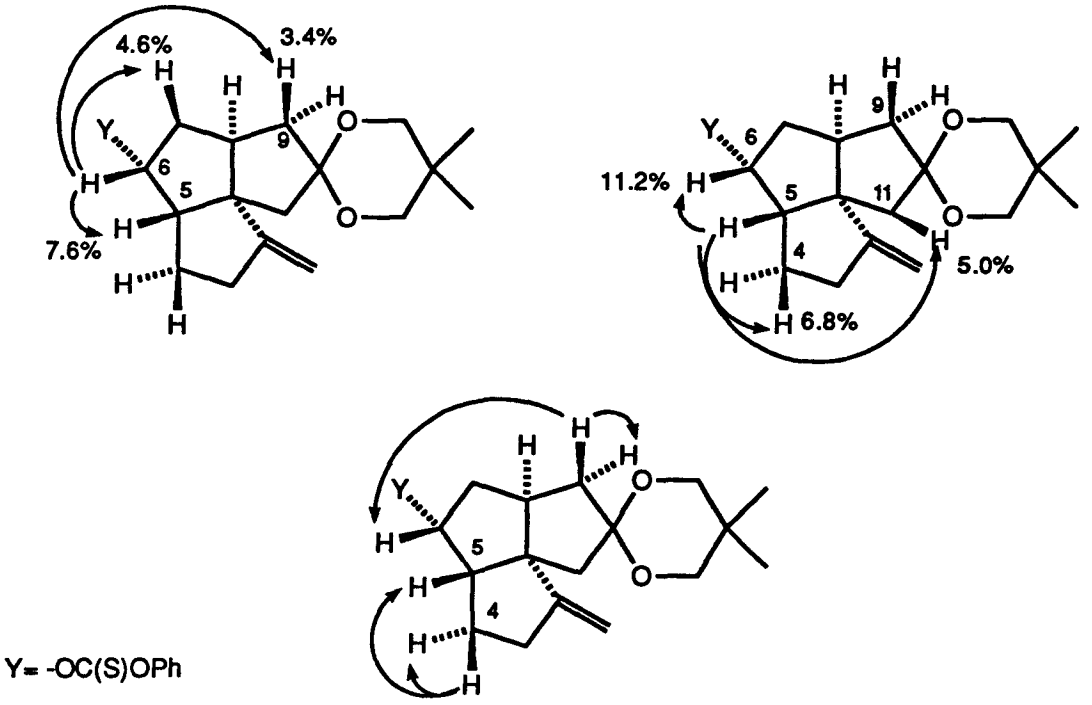


Figure 4. nOe experiments on the phenyl thionocarbonate **149**

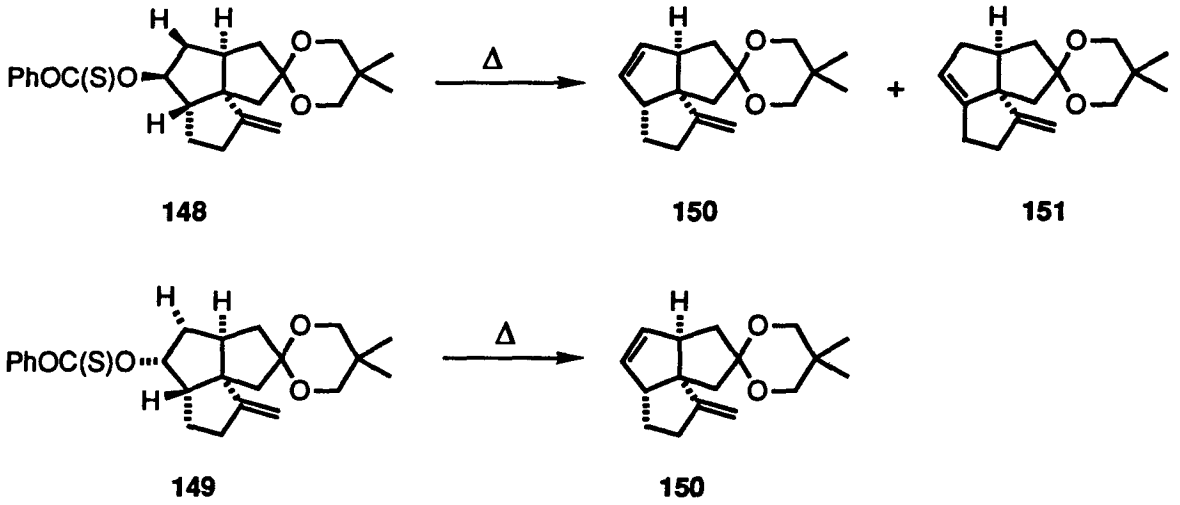
Additional support for the assigned stereochemistry of the phenyl thionocarbonates was obtained from GLC analysis. Retention times for the phenyl thionocarbonates **148** and **149** were close to that of the deoxygenated product **102**. Thus, it was concluded that under the conditions of GLC analysis the phenyl thionocarbonates **148** and **149** underwent elimination to provide the corresponding alkenes **150** and **151** (**Scheme 36**). Phenyl thionocarbonates undergo pyrolytic elimination in a mechanism which involves a six-membered transition state (Ei mechanism).[52] Such eliminations are *syn* and, therefore, the position of the double bond will be determined by the available *cis* β-hydrogens. The compound **148** has two β-hydrogens *cis* to the phenyl thionocarbonate moiety and is expected to provide two alkenes **150** and **151**. On the other hand, phenyl thionocarbonate **149** has only one β-hydrogen *cis* to the phenyl thionocarbonate moiety and is expected to

provide only the alkene **150**. As expected, GLC analysis of the phenyl thionocarbonate **148** exhibited two peaks with very similar retention times corresponding to the two isomeric alkenes **150** and **151**, while GLC analysis of phenyl thionocarbonate **149** exhibited a single peak due to the alkene **150** that can be produced by elimination.

Table 8. ^{1}H NMR (400 MHz, $CDCl_3$), COSY (200 MHz, $CDCl_3$) and nOe (400 MHz, $CDCl_3$) data for the phenyl thionocarbonate **149**.

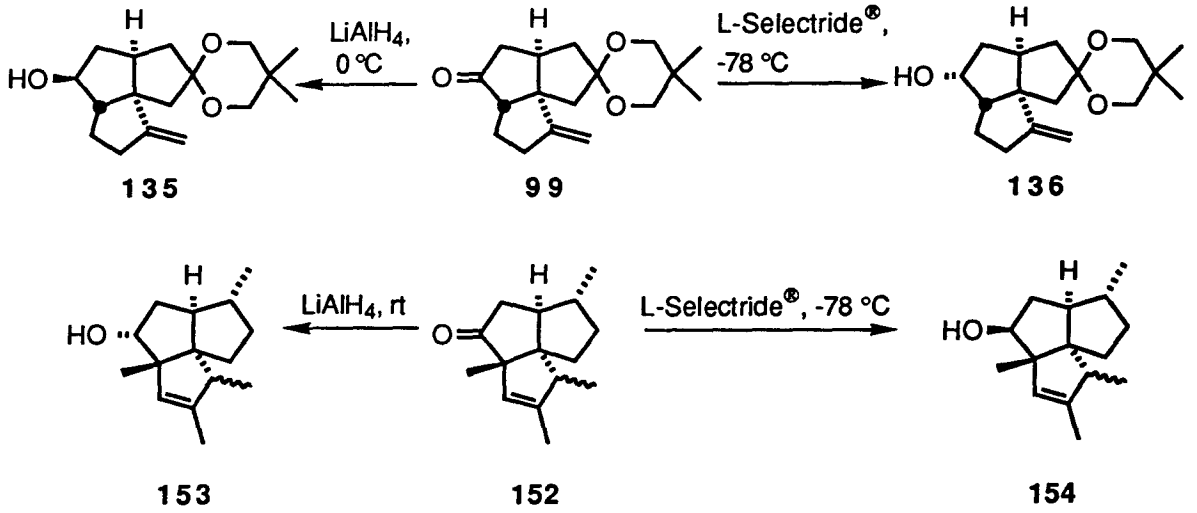
Assignment H-x	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]	nOe correlations
H-4β	1.71	H-5	1.61 (H-4α) 2.79 (H-5)
H-4α	1.61	H-5	
H-5	2.79	H-4α & β, H-6	1.71 (H-4β) 2.19 (H-11β) 5.81 (H-6)
H-6	5.81	H-5, H-7α & β	1.90 (H-9β) 2.07-2.15 (H-7α & β) 2.79 (H-5)
H-7α & β	2.07-2.15	H-6	
H-9β	1.90	H-9α	2.19 (H-9α) 5.81 (H-6)
H-9α	2.19	H-9β	
ketal CH_2's	3.46	H-16 & H-17	
H-16 & H-17	0.91 & 0.98	ketal CH_2's	

a) Only those COSY correlations that could be unambigously assigned are recorded



Scheme 36

It is interesting to note the complete reversal in stereochemistry resulting from the reduction of ketone **99** with L-Selectride and lithium aluminum hydride, as compared with that obtained by the reduction of ketone **152** mentioned previously (**Scheme 37**).[8] This can be attributed to the presence of an angular methyl group in the compound **152**, as opposed to a proton in ketone **99**. It has been proposed that the reduction of ketones with nonsterically demanding metal hydrides (such as lithium aluminum hydride) is controlled primarily by torsional strain in the transition state, while reduction with bulky reagents (such as L-Selectride) is controlled primarily by the degree of steric hindrance of the carbonyl group.[53]



135 **99** **136**

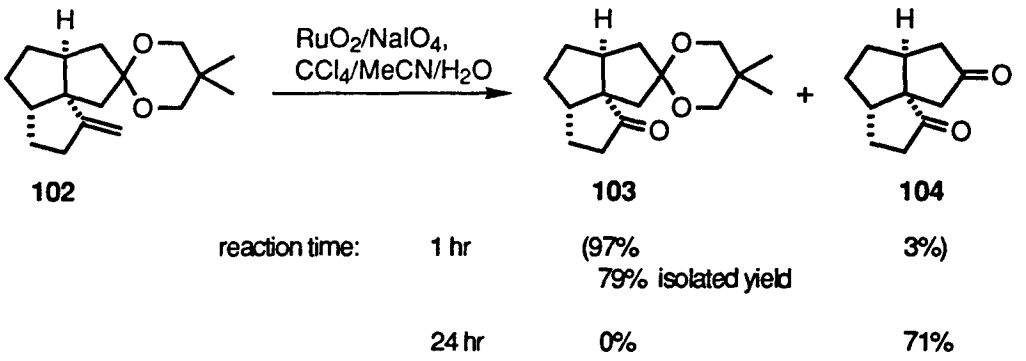
153 **152** **154**

Scheme 37

2.3.10 Preparation of the Tricyclic Keto Ketal **103**

The keto ketal **103** was synthesized by a ruthenium(VIII) catalyzed oxidation of the ketal alkene **102**. Ruthenium tetroxide was used instead of osmium tetroxide, the usual reagent used in such reaction, because ruthenium tetroxide is less expensive and less toxic. The reaction was carried out in a mixture of solvents (2:2:3 carbon tetrachloride/acetonitrile/water), according to Sharpless' procedure.[54]

As the newly formed keto ketal **103** has an acid sensitive ketal group, the reaction must be carefully monitored to prevent ketal hydrolysis. If the reaction is carried out at room temperature for 1 hr the keto ketal **103** is obtained in 79% yield, accompanied by 3% (as determined by GLC analysis of the crude product) of the diketone **104**. However, if the reaction time was extended to 24 hr, the only product was the diketone **104**, obtained in 71% yield (**Scheme 38**).

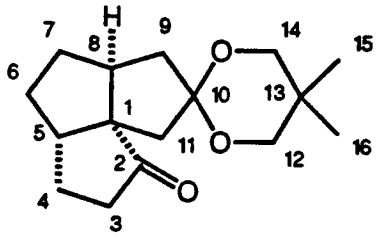


Scheme 38

It is possible to completely suppress hydrolysis of the ketal group by using a phosphate buffer (pH 7.2). However, the use of a buffered solution decreased the solubility of sodium periodate, thus a greater volume of water was necessary and the work-up was complicated by presence of a large amount of precipitated salts. For these reasons the procedure using a buffered system of solvents was abandoned.

The IR spectrum of the keto ketal **103** indicated presence of a five-membered cyclic ketone (1731 cm^{-1}) and a C-O single bond (1114 cm^{-1}). The HRMS of **103** gave an exact mass of 264.1728 mass units. The calculated exact mass for **103** is 264.1726. The ^1H NMR spectrum is consistent with the assigned structure and the resonances were assigned with the aid of homonuclear correlation (COSY, 400 MHz $CDCl_3$) experiments (**Table 9**).

The COSY spectrum of the keto ketal **103** is shown in **Figure 5**.



103

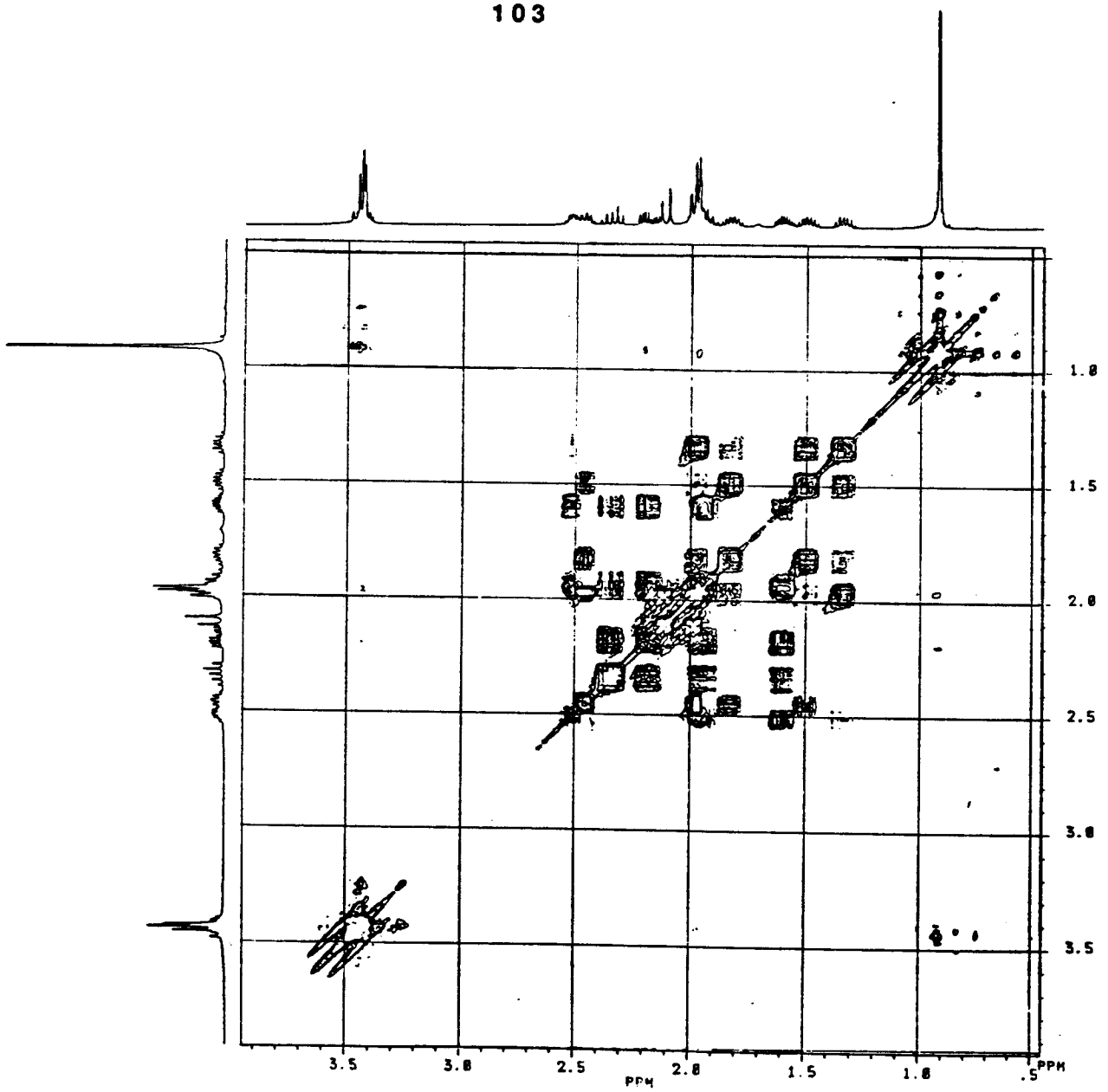


Figure 5. The COSY (400 MHz, $CDCl_3$) spectrum of the keto ketal **103**.

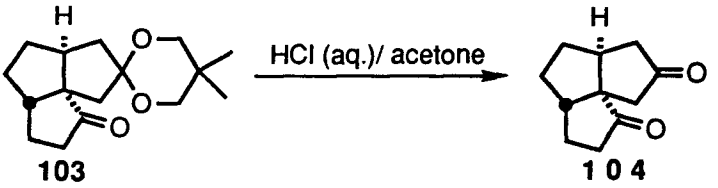
Table 9. ^{1}H NMR and COSY (400 MHz, $CDCl_3$) data for the keto ketal **103**.

H-x (assignment)	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-3α or β	2.23	H-3α or β, H-4α & β
H-3α or β	2.39	H-3α or β, H-4α & β
H-4α or β	1.64	H-3α & β, H-4α or β, H-5
H-5	2.55	H-4α and β, H-6α and β
H-7β	1.38	H-7α, H-9β
H-9β	1.54	H-7β, H-8, H-9α
H-8	2.50	H-7α, H-9α and β
H-9α	1.87	H-7α, H-8, H-9β
ketal CH_2's	3.48	H-15 & H-16
H-15 & H-16	0.92 & 0.93	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

2.3.11 Preparation of the Diketone **104**

The keto ketal **103** was deketalized by treatment with a 1:1 mixture of 5% hydrochloric acid and acetone to provide the diketone **104**, which was obtained in 93% yield (**Scheme 39**). The diketone **104** was subsequently used in studies directed towards preparation of the dienedione **98**. The diketone **104** exhibited expected spectral characteristics, including a high resolution mass spectrum, which gave an exact mass of 178.0994 mass units (calculated exact mass for **104** is 178.0994). Absence of the C-O bond absorption in the IR spectrum indicated that the ketal function had been removed.



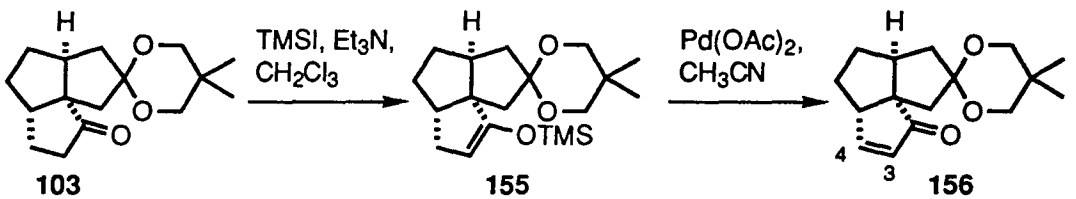
103 104

Scheme 39

It is interesting to note that compound **104** is relatively unstable, as compared with other compounds prepared during the execution of this synthetic sequence. Even when stored in a freezer (-4 °C) under an argon atmosphere, the diketone **104** quickly darkened, and turned black in a few days. Thus, the diketone **104** was used immediately after preparation or was freshly distilled before use.

2.3.12 Preparation of the Tricyclic Enone Ketal **156**

The tricyclic keto ketal **103** was converted to the enol silyl ether **155** using trimethylsilyl iodide and triethylamine in methylene chloride. Oxidation of the enol silyl ether **155** with palladium acetate in acetonitrile[31] gave the enone ketal **156** in 74% overall yield (**Scheme 40**). The IR spectrum of **156** exhibited absorptions at 1697 and 1584 cm^{-1} due to the enone moiety, and an absorption at 1122 cm^{-1} due to the C-O single bond. In the ^1H NMR spectrum of **156**, resonances at 6.14 (dd, 1H, *J*=5.5, 2.0 Hz) and 7.43 (dd, 1H, *J*=5.5, 2.5 Hz) are due to the enone protons H-3 and H-4, respectively.

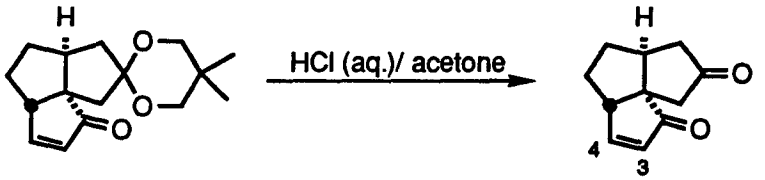


103 155 156

Scheme 40

2.3.13 Preparation of the Tricyclic Enedione **157**

Acid-mediated deketalization of the tricyclic enone ketal **156**, as described in section 2.3.11 (pp 62-63), provided the tricyclic enedione **157** in 93% yield. The IR spectrum of the enedione **157** indicated the presence of five-membered cyclic ketone (1739 cm^{-1}) and enone (1702, 1584 cm^{-1}). The ^1H NMR spectrum was assigned with the aid of homonuclear correlation (COSY, 200 MHz $CDCl_3$) experiments (**Table 10**). Enone protons H-3 and H-4 exhibited resonances at 6.24 (dd, 1H, *J*=5.7, 1.7 Hz) and 7.55 (dd, 1H, *J*=5.7, 2.6 Hz), respectively.



156 **157**

Scheme 41

Table 10. ^1H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the enedione **157**.

H-x (assignment)	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-3	6.24	H-4, H-5
H-4	7.55	H-3, H-5
H-5	3.19	H-3, H-4, H-6β
H-8, H-9α or β	2.70	H-7α & β, H-11α or β
H-11α or β	2.33	H-11α or β
H-11α or β	2.86	H-11α or β

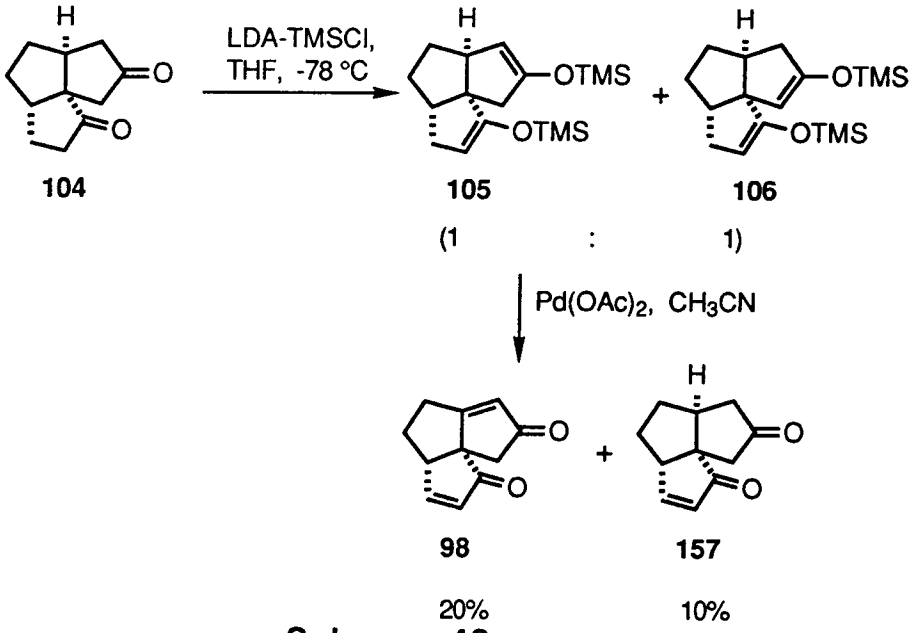
a) Only those COSY correlations that could be unambigously assigned are recorded

In contrast to the diketone **104**, the enedione **157** is quite stable and can be kept at room temperature for weeks without any observable deterioration.

2.3.14 Preparation of the Tricyclic Dienedione **98**

2.3.14.1 Saegusa Oxidation of the Enol Silyl Ethers **105** and **164**

The diketone **104** was converted to a mixture of the *bis*enol silyl ethers **105** and **106** upon treatment with LDA-TMSCl according to the procedure of Corey et al.[55] A GLC analysis of the crude product indicated that the two *bis*enol silyl ethers were formed in a ratio of about 1:1. Oxidation of this 1:1 mixture of **105** and **106** with palladium acetate gave the dienedione **98** and enedione **157** in 20% and 10% yield, respectively (**Scheme 42**).



104 **105** **106**

(1 : 1)

98 **157**

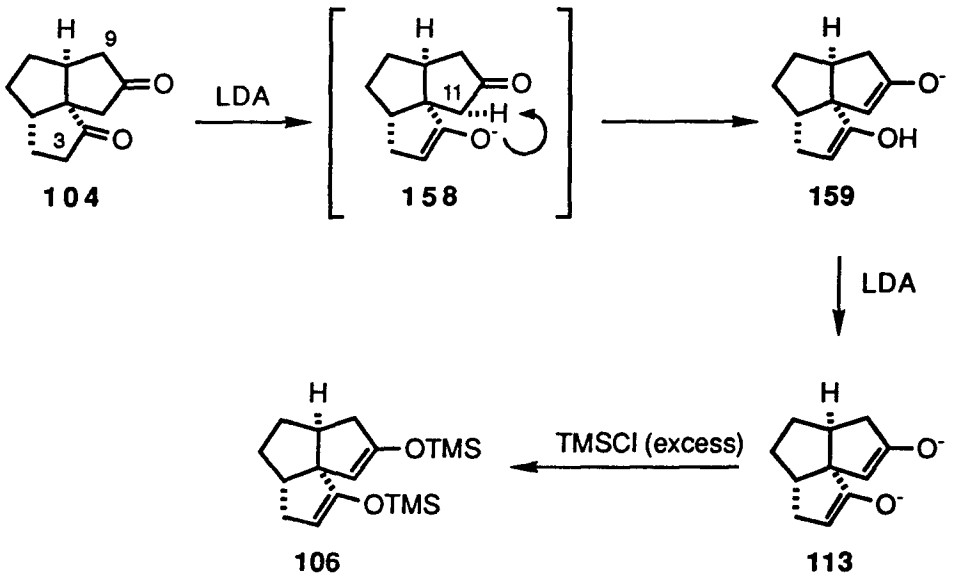
20% 10%

Scheme 42

Our first attempts to improve the conversion yield of **104** into **98** using this procedure were directed towards the regioselective formation of the *bis*enol silyl ether **105**. A variety of more hindered bases were used instead of LDA. These include both lithium and potassium *bis*(trimethylsilyl)amides, lithium tetramethylpiperidide and lithium *bis*(phenyldimethylsilyl)amide. The reactions were carried out in THF at -78 °C, in an attempt to prepare the kinetically favored *bis*enol silyl ether.

Alternatively, we attempted to prepare the *bis*enol silyl ether **105** under thermodynamic conditions, by treatment of the diketone **104** with TMSBr-Et_3N in DMF,[56] or TMSI-Et_3N in CH_2Cl_2.[43] The mixture of *bis*enol silyl ethers was unstable and did not provide a useful ^1H NMR spectrum (LRMS: 322, M^+; 307, $[M-15]^+$). In all cases, the results were similar in that the ratio of regioisomers **105** and **106** was close to 1:1, as determined by GLC analysis. The subsequent oxidation with palladium acetate produced consistently the dienedione **98** and the enedione **157** in ≈ 2:1 ratio and in a low yield.

Formation of a relatively large amount of the *bis*enol silyl ether **106** may be rationalized by proposing the following pathway, which may compete with the pathway described in **Scheme 18** (p 31). The base first abstracts the least hindered C-3 proton to give the lithium enolate **158** (**Scheme 43**). This enolate may then, in an intramolecular reaction, abstract the C-11 proton and thus produce the undesired enolate **159**. Deprotonation of **159** with a second equivalent of base, followed by treatment with trimethylsilyl chloride, would produce **106**.



104 158 159 106 113

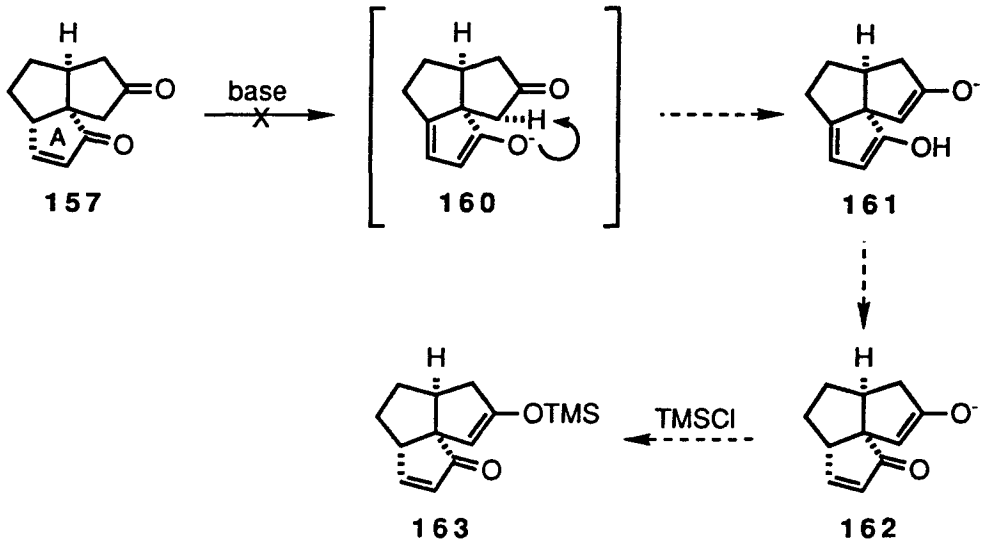
Scheme 43

If this rationale is correct then the use of a more hindered base is of no benefit as it would only increase the difference in reactivity between the C-9 and C-3 protons, and thus favor the pathway described in **Scheme 43**.

Therefore, it was decided to execute the oxidation steps sequentially. It was assumed that the A-ring enone functionality of enedione **157** would not react with a base, since the resulting enolate **160** would be very strained (**Scheme 44**).

The enedione **157** was treated with a variety of bases (LDA, lithium and potassium *bis*(trimethylsilyl)amides and lithium *bis*(phenyldimethylsilyl)amide) in THF at -78 °C. Unfortunately, GLC analysis of the crude mixture indicated that two products were formed in a 1:1 ratio. These products were concluded to be the two regioisomeric enol silyl ethers **163** and **164**. Subsequent oxidation of this mixture of enol silyl ethers **163** and **164** with palladium acetate

met with no more success than the previous attempts to oxidize *bis*enol silyl ethers **105** and **106**.



Scheme 44

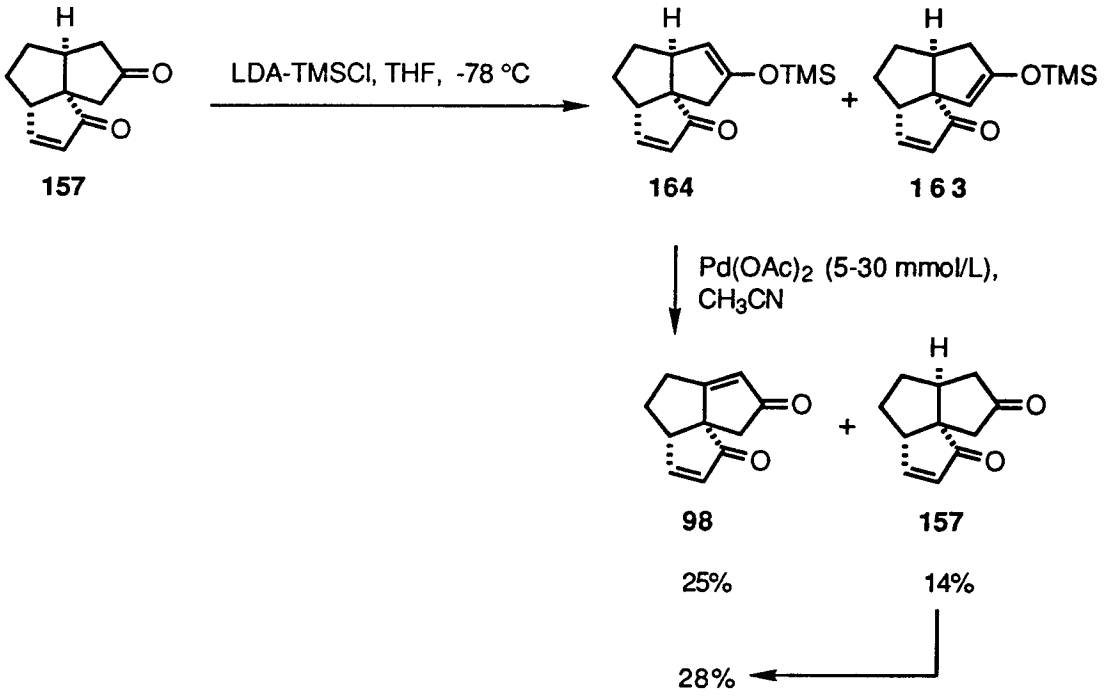
The material balances in the conversions of the diketone **104** or the enedione **157** to the dienedione **98** were very low. The low yield may in part be attributed to overoxidation of the products, to adsorption or occlusion of reaction products by the precipitated palladium, or possibly to the irreversible complexation of the products to palladium(0).

Assuming that the loss of material is due to the complexation of the product to the palladium(0), several modifications were attempted to minimize this interaction. Reactions were conducted under higher dilution (5-30 mmol/L of the substrate) than normal (250 mmol/L of the substrate). Under such conditions, it was necessary to extend the reaction time from 2 to 24 hr. Higher dilutions were considered impractical.

Various phosphine ligands, such as triphenylphosphine, DIPHOS, PROPHOS were added to the reaction mixture in hope that these ligands

would replace any dienedione **98** that may be complexed to palladium(0). Also, sonication of the precipitated palladium(0) obtained from the reaction mixture with various solvents was investigated.

Unfortunately, all of these attempts failed to significantly improve the yield of **98**. Oxidation of the enol silyl ether **164** (in a mixture with the enol silyl ether **163**) (**Scheme 45**) under higher dilution conditions provided only a moderate improvement and a 28% overall yield of the dienedione **98** was achieved after reoxidation of the recovered enedione **157**.

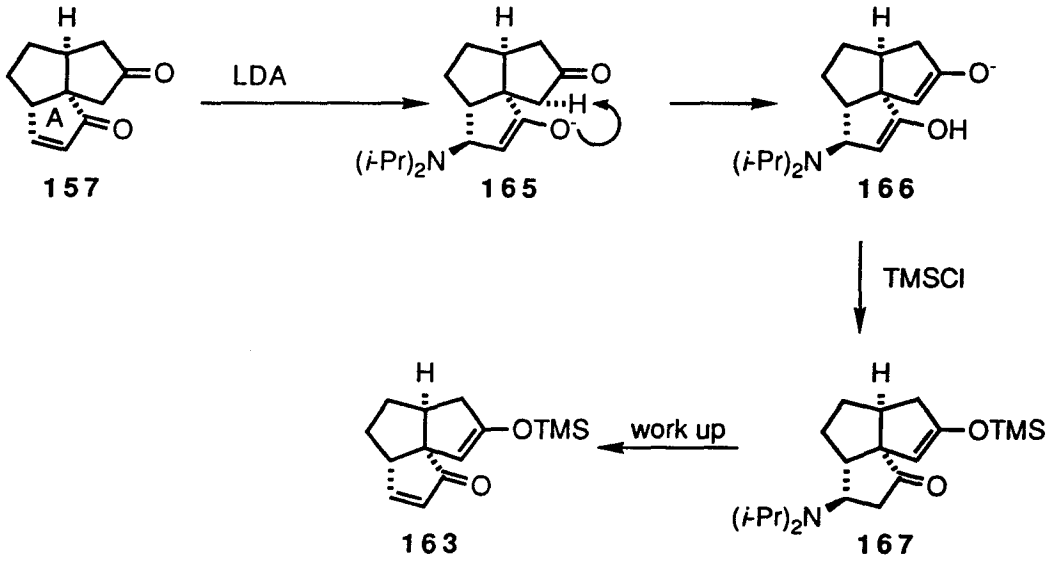


Scheme 45

2.3.14.2 Reexamination of the Saegusa Procedure

It was later found from a study on the alkylation of the dienedione **98** that the 1,4-addition of amide bases to the A-ring enone

functionality occurs with ease (Section 2.3.15, p 80). We speculated that the reason for the lack of selectivity in formation of the enol silyl ether **164** was that the intermediate enolate obtained after the addition, would abstract a C-11 proton yielding the undesired enol silyl ether **163** after the treatment with trimethylsilyl chloride (**Scheme 46**). The results from the alkylation of dienedione **98** indicated that it might be possible to prevent 1,4-addition of a base to the enone function of **157** by use of lithium tetramethylpiperidide under carefully controlled conditions.



157 **165** **166** **163** **167**

Scheme 46

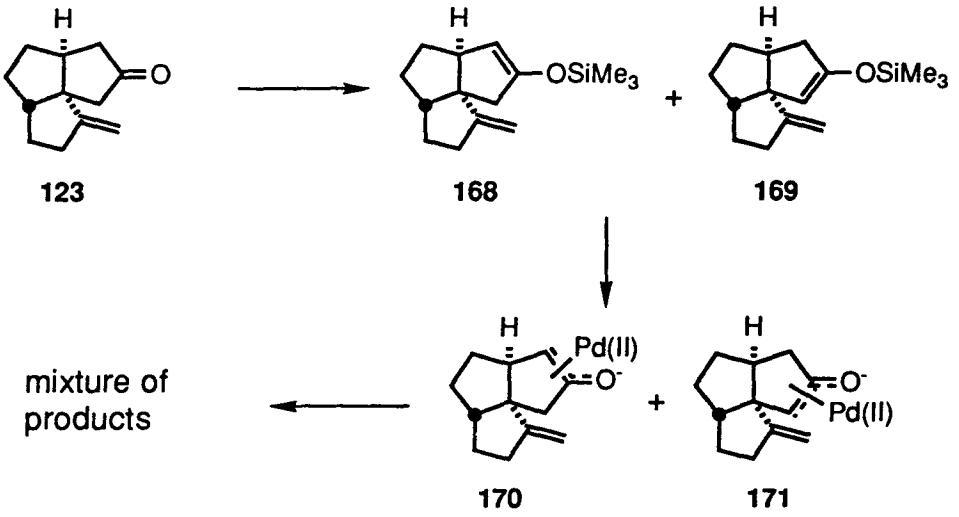
Thus, treatment of the enedione **157** with 1.1 equivalent of lithium tetramethylpiperidide at -78 °C, followed by an excess of trimethylsilyl chloride provided predominantly the enol silyl ether **164** (97% by GLC analysis of the crude product). Treatment of the enedione **157** with a larger excess of lithium tetramethylpiperidide significantly reduced selectivity of the formation of **164**. Subsequent

oxidation of **164** with palladium acetate, in DMF, provided the dienedione **98**. Application of this sequence successively on 5.6 and 8.2 mg of the enedione **157** gave the dienedione **98** in 42% and 46% yields respectively. Thus, one may assume that if the reactions were performed on a larger scale better yields would be obtained, and this may represent a more convenient procedure for preparation of large quantities of **98**.

Unfortunately, this development occurred toward the end of our research, after the study on the preparation of the dienedione **98** was concluded. For this reason, only limited quantities of the enedione **157** were available for reexamination of the Saegusa procedure. Therefore, this route was not fully evaluated.

2.3.14.3 Attempted Saegusa Oxidation of the Enol Silyl Ether **168**

As the yields of conversion of compounds **104** and **157** into the dienedione **98** were unsatisfactory, it was decided to attempt the introduction of the enone functionality earlier on in the synthesis, as shown in **Scheme 21** (p 34). To this end, the tricyclic ketal alkene **102** was deketalized and the resulting keto alkene **123** was converted to a mixture of the corresponding enol silyl ethers **168** and **169**. A GLC analysis of the crude product mixture indicated that the two enol silyl ethers were formed in a ratio of about 2:1. This mixture was treated with palladium acetate to provide a complex mixture of products (**Scheme 47**), none of which was the desired enone **124** (**Scheme 21**, p 34).

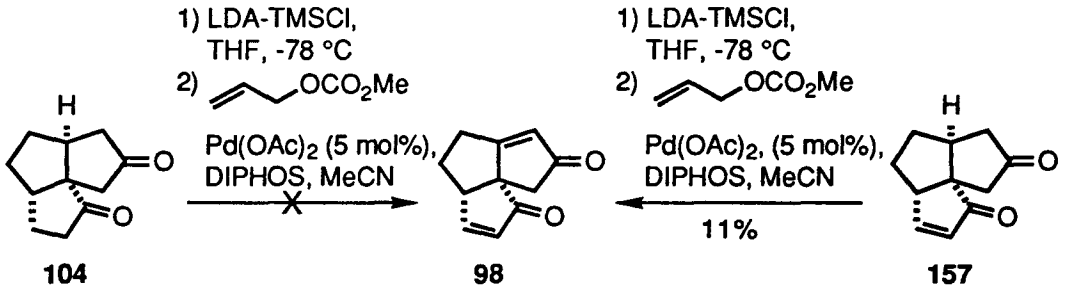


Scheme 47

2.3.14.4 Other Palladium Oxidations

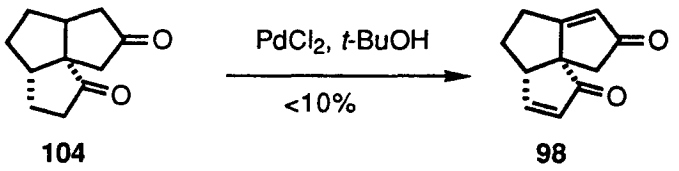
After our attempts to prepare **98** by means of the enol silyl ether/palladium acetate procedure proved unsatisfactory, other procedures involving palladium(II) salts were investigated.

The diketone **104** was converted to the corresponding *bis*enol silyl ethers, and subjected to the palladium(II)-catalyzed oxidation, according to the procedure of Tsuji.[57] A mixture of products was obtained, none of which was the desired dienedione **98** (**Scheme 48**). When the enedione **157** was used as the starting material the dienedione **98** was obtained in 11% yield, accompanied with a mixture of other products which were not identified.



Scheme 48

The diketone **104** was consumed within 2 hr when treated with palladium(II) chloride in hot *t*-butanol;[58] however, the dienedione **98** was produced in a very low yield (<10%) (**Scheme 49**).



Scheme 49

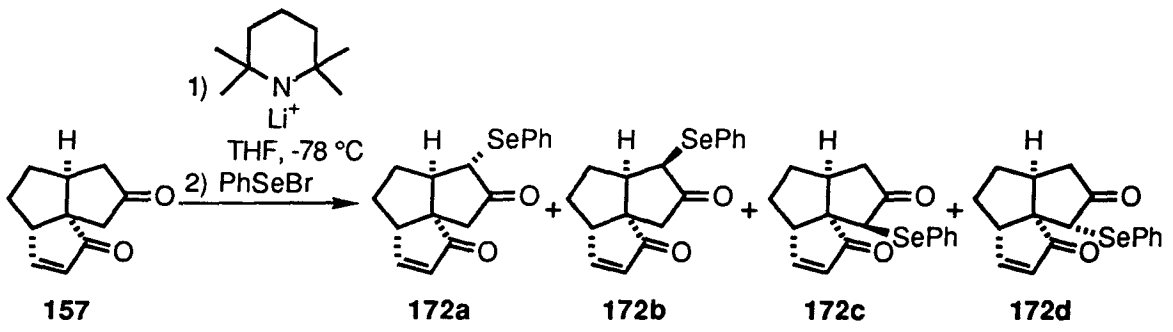
2.3.14.5 Oxidation-Elimination of the α-Phenylseleno Ketone **172a**

After the palladium based methods failed to achieve satisfactory conversion of the diketone **104** or the enedione **157** to the dienedione **98**, our attention turned to selenium-based reagents.

Conversion of the enedione **157** into the α-phenylseleno ketone **172a**, using an excess of lithium tetramethylpiperidide followed by phenylselenyl bromide,[59] was attempted (**Scheme 50**). A mixture of four products was obtained (as determined by a TLC analysis of the crude product mixture). The mixture may be composed of all the four possible isomers **172a-d**. This result was not completely surprising in view of the lack of selectivity observed in formation of the enol

silyl ethers **105** and **106** (p 65), as well as in the formation of **163** and **164** (when using an excess of lithium tetramethylpiperidide, p 70). Separation of this mixture by gravity column chromatography provided one pure compound tentatively assigned as **172a** (21%), and a mixture of the three remaining products. Assuming that these three products were all phenylseleno ketones, their combined yields would be 31%. This mixture was separated by a second gravity column chromatography to provide another pure compound and a mixture of the other two. It should be noted that the conclusion that all of the products are α-phenylselenyl ketones is only tentative, and no analytical studies were performed on any of the products. All three fractions were independently subjected to hydrogen peroxide oxidation-elimination sequence. The major product **172a** provided the dienedione **98**.

In conclusion, although there are problems in the selective preparation of the desired α-phenylseleno ketone **172a**, the subsequent phenylselenenic acid elimination is a feasible method for accomplishing the desired transformation.



Scheme 50

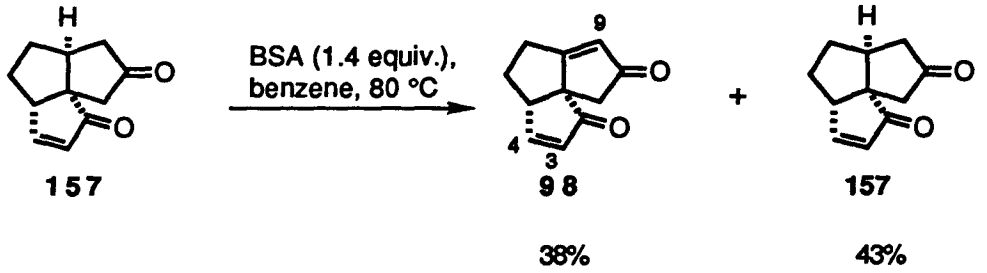
2.3.14.6 Oxidation of the Enone **157** with Benzeneseleninic Acid Anhydride

In the late-1970s and early-1980s, Barton's group reported, in a series of papers, the use of benzeneseleninic acid anhydride (BSA) to oxidize steroidal ketones to enones.[60-62] An interesting feature of this reaction is that the α-phenylselenoxy ketone is formed directly and, if appropriately positioned, undergoes *syn*-elimination immediately. Furthermore, the formation of the α-phenylselenoxy ketone is reversible. This allows for the equilibration of intermediates that cannot eliminate.

The drawback of this method is that benzeneseleninic anhydride and other selenium byproducts are powerful oxidants which may react further with the enone produced, thus diminishing the yield of the latter substance.

The enedione **157** was subjected to BSA oxidation under various reaction conditions. After extensive research, optimal conditions for conversion of the enedione **157** to the dienedione **98** were found. The reaction was allowed to proceed until consumption of approximately 50% of the starting enedione **157** (by GLC analysis of the reaction mixture) had been achieved (**Scheme 51**). Attempted separation, by drip column chromatography, of the mixture thus obtained resulted in a poor resolution due to tailing of dienedione **98** and a modified procedure had to be applied. Separation of the mixture was achieved by gravity column chromatography using TLC grade silica gel without binder.[63] Under these conditions, the dienedione **98** and the recovered enedione **157** were obtained in yields of 38% and 43%, respectively.

Recycling the enedione **157** twice provided the dienedione **98** in 59% overall yield.



Scheme 51

The IR spectrum of the dienedione **98** indicated the presence of two five-membered cyclic enones (1713, 1630, 1585 cm^{-1}). The ^1H NMR spectrum of **98** was assigned with the aid of homonuclear correlation (COSY) experiments (**Table 11**). The presence of signals due to olefinic protons (δ 6.02 (d, 1H, H-9, *J*=1.9 Hz), 6.32 (dd, 1H, H-3, *J*=5.6, 1.3 Hz) and 7.78 (dd, 1H, H-4, *J*=5.6, 3.0 Hz)) was consistent with the structural formula **98**.

The ^1H NMR (400 MHz, $CDCl_3$) spectrum of the dienedione **98** is shown in **Figure 6.**

Table 11. ^1H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the dienedione **98**.

H-x (assignment)	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-3	6.32	H-4
H-4	7.78	H-3
H-6α	2.27	H-7α
H-7α	2.59	H-6α
H-11α or β	2.39	H-11β or α
H-11β or α	2.63	H-11α or β

a) Only those COSY correlations that could be unambigously assigned are recorded

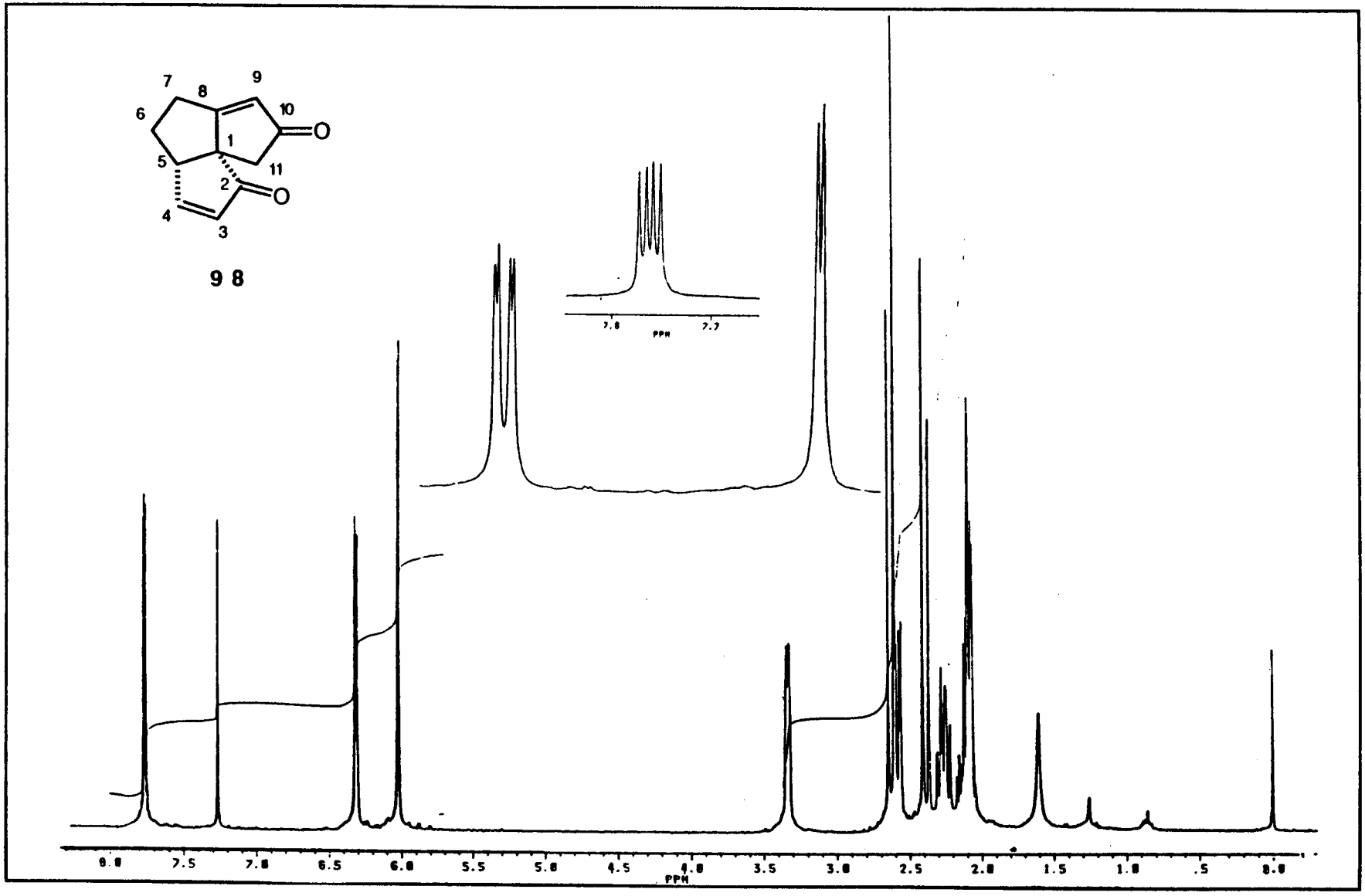
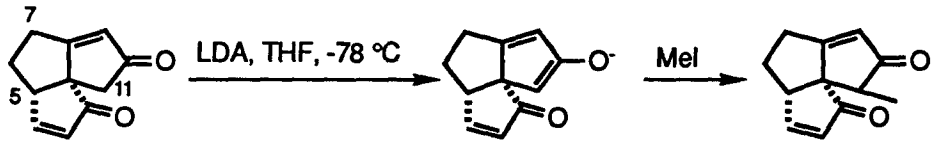


Figure 6. The ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of the dienedione **98**.

2.3.15 Alkylation of the Dienedione **98**

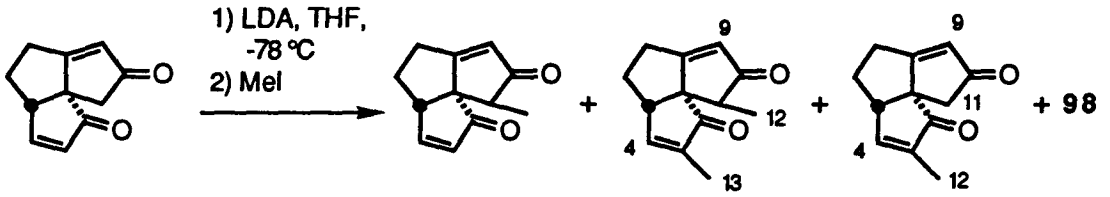
In order to prepare the 11-methyl dienedione **107**, the dienedione **98** was subjected to alkylation under kinetically controlled conditions. Treatment of **98** with LDA was expected to provide the "kinetic" enolate **173** (**Scheme 52**) by removal of the kinetically most acidic proton at C-11 (subergorgic acid numbering). Treatment of the enolate **173** with iodomethane was expected to provide the alkylated product **107**.



98 **173** **107**

Scheme 52

Alkylation of the dienedione **98** with LDA-MeI was very capricious. Mixtures of mono- and dialkylated products, some recovered dienedione **98**, as well as other unidentified products, which proved to be very difficult to separate from the 11-methyl dienedione **107**, were observed in the crude product mixtures (**Scheme 53**).

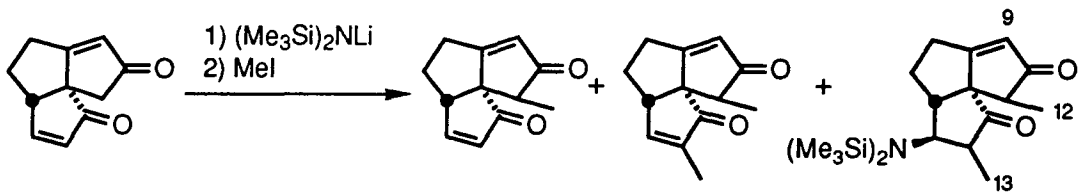


98 **107** **174** **175**

Scheme 53

The isolated byproducts **174** and **175** were identified on the basis of their ^1H NMR spectra ($CDCl_3$, 200 MHz). The 3,11-dimethyl dienedione **174** exhibited resonances due to Me-12 (δ 1.08, d, 3H), Me-13 (δ 1.81, s, 3H), H-5 (δ 3.28, br d, 1H), H-9 (δ 5.94, d, 1H) and H-4 (δ 7.33, d, 1H). The 3-methyl dienedione **175** exhibited resonances due to Me-12 (δ 1.82, s, 3H), H-11α or β (δ 2.36, d, 1H), H-11α or β (δ 2.61, d, 1H), H-5 (δ 3.18, m, 1H), H-9 (δ 6.00, d, 1H) and H-4 (δ 7.35, d, 1H).

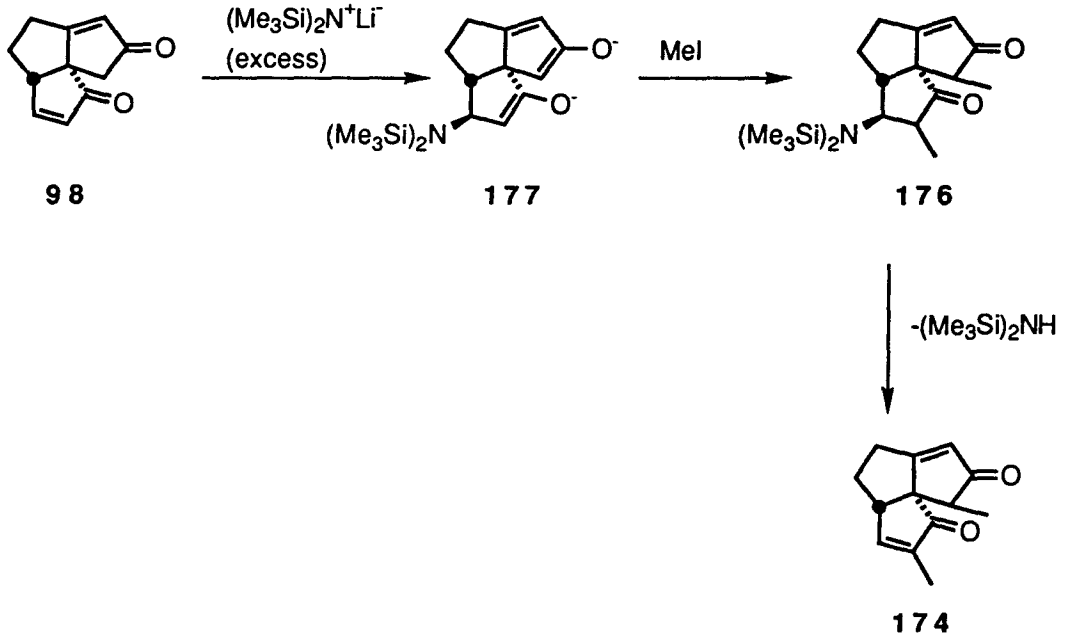
It was difficult to rationalize the significant amount of dialkylated product **174** obtained. In an attempt to improve selectivity of the alkylation a more bulky base, lithium *bis*(trimethylsilyl)amide, was employed. The mixture of products thus obtained was separated by radial chromatography and the components were characterized. A new product was isolated along with the desired 11-methyl dienedione **107**, and the 3,11-dimethyl dienedione **174**. This new product was identified as the 4-*bis*(trimethylsilyl)amino-3,11-dimethyl dienedione **176** (**Scheme 54**). The ^1H NMR spectrum ($CDCl_3$, 200 MHz) of compound **176** exhibited a signal at δ 0.25 (d, 18 H) due to the protons in trimethylsilyl groups. The resonances due to two methyl groups were overlapping at δ 1.05 (m, 6H, Me-12 and Me-13), and the olefinic proton exhibited a resonance at δ 5.98 (d, 1H, H-9).



98 **107** **174** **176**

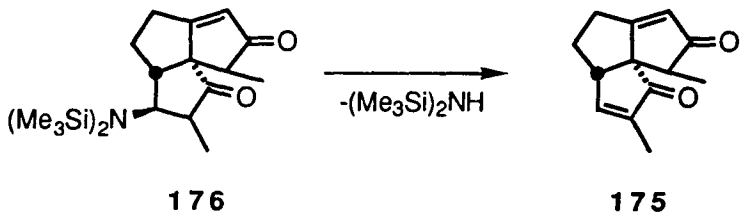
Scheme 54

The products **174** and **176** are a result of 1,4-addition of the base to the A-ring enone of **98** (**Scheme 55**), followed by subsequent trapping of the intermediate enolate **177** with iodomethane. This was an unexpected outcome, as lithium bases do not usually add in a 1,4-fashion to enones in THF at -78 °C.[64a]



Scheme 55

Compound **176** was moderately stable with a half life of approximately 24 hr in deuteriochloroform solution at room temperature. This material eliminated hexamethyldisilazane (**Scheme 56**) to provide the 3,11-dimethyl dienedione **174**.



Scheme 56

Lithium tetramethylpiperidide was used next as a non-nucleophilic base.[64b] The 11-methyl dienedione **107** was obtained in acceptable yield (53%) when 1.1 equivalent of base was used. Surprisingly, when larger excesses of base was employed, significant amounts of dialkylated product **174** was obtained. With these results in hand we reexamined the formation of enol silyl ethers from the enedione **157** (section 2.3.14.2, pp 69-71), and the subsequent palladium acetate oxidation.

The initial stereochemical assignment on the 11-methyl dienedione **107** was based upon the previously described prediction regarding the stereocontrol in the alkylation of the enolate anion **173** (pp 31-32). NOe difference experiments were performed in order to determine the configuration of the methyl group (**Figure 7**). The signals in the ^1H NMR spectrum were assigned with the aid of homonuclear correlation (COSY) (**Table 12**) and homonuclear decoupling experiments (**Table 13**). The presence of signals due to the C-11 methyl group (δ 1.10, d, 3H, *J*=8.0 Hz), and the C-11 proton (δ 2.60, q, 1 H, *J*=8.0 Hz, overlaps with H-6α (δ 2.60, dd, 1H, *J*=13.0, 6.5 Hz)), as well as the olefinic protons (δ 5.96 (d, 1H, H-9, *J*=2.0 Hz), 6.27 (dd, 1H, H-3, *J*=5.8, 1.5 Hz) and 7.74 (dd, 1H, H-4, *J*=5.8, 3.0 Hz)) are consistent with the assigned structure.

As there is an overlap between the signals due to H-6 and H-11 protons, a titration of the $CDCl_3$ solution of **107** with C_6D_6 was performed, in order to obtain a spectrum with signal dispersion suitable for nOe difference experiments.

Irradiation of the signal due to Me-12 caused enhancement of the signals due to H-11 (3.6%) and H-5 (2.4%). Irradiation of the signal due to H-11 provided some surprising results. Saturation of H-11 caused

negative enhancement of the H-4 and H-5 signals and, as expected, the reciprocal enhancement of the signal due to Me-12 was observed. The detection of a negative nOe could be characteristic of nuclei having a roughly linear arrangement.[65] Irradiation of the resonance due to the H-5 proton caused enhancement of the signal due to Me-12, and no enhancement of the signal due to H-11. An absence of nOe enhancement at H-11 when H-5 was irradiated, may be due to the cancellation between the direct positive and indirect (through Me-12) negative nOe. The results of nOe experiments indicate that the protons H-5, H-11 and Me-12, as well as H-4, H-11 and Me-12 exhibit "three spin effects".[65b] Therefore, nOe between those nuclei depends not only on the distance between the protons, but also on their geometry, and additional experiments are needed to determine their relative stereochemistry. Thus, it was not possible to unequivocally prove that this substance had the relative stereochemistry as depicted in **107** (**Scheme 16**, p 29).

Molecule **107** has three sp^2 carbons in each of the A and C rings. This flattens the molecule and changes the orientation of the protons of interest and the distances between them, as compared to a saturated triquinane ring system. Thus, usual nOe experiments which were successfully applied in determination of the stereochemistry of C-11 methyl group in other silphiperfolanes,[19,66,82b] did not provide a conclusive result in this case.

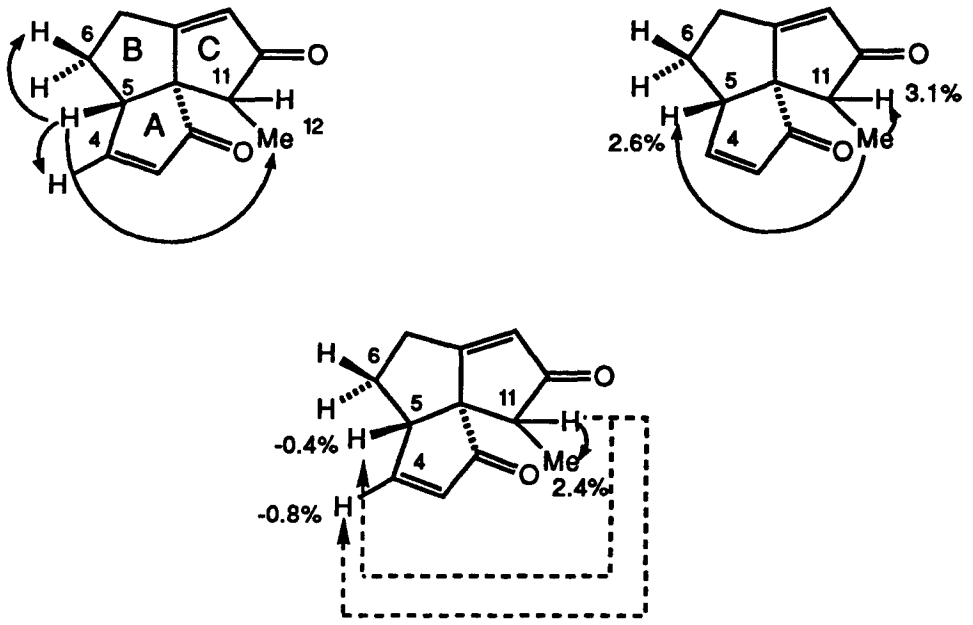


Figure 7. nOe experiments on the 11-Methyl Dienedione **107**

Table 12. ^{1}H NMR, COSY(200 MHz, $CDCl_3$) and nOe (400 MHz, $CDCl_3$-C_6D_6 (7:3)) data for the 11-methyl dienedione **107**

H-x (assign.)	^{1}H NMR (200 MHz, $CDCl_3$)	COSY correlation[a]	^{1}H NMR (400 MHz, $CDCl_3$-C_6D_6(7:3))	nOe correlations
H-3	6.27	H-4	-	-
H-4	7.74	H-3	-	-
H-5	-	-	3.05	0.94 (H-12) 1.62 (H-6β) 7.30 (H-4)
H-11	2.60	H-12	2.53	0.94 (H-12) 3.05 (-ve, H-5) 7.30 (-ve, H-4)
H-12	1.10	H-11	0.94	2.53 (H-11) 3.05 (H-5)

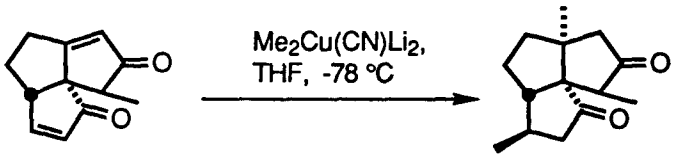
a) Only those COSY correlations that could be unambigously assigned are recorded

Table 13. Decoupling experiments (400 MHz, C_6D_6 and $CDCl_3$) data for the 11-methyl dienedione **107**.

irradiated signals		observed signals	
assignment H-x	^{1}H NMR (400 MHz, C_6D_6)	δ ppm (mult., *J* , H-x)	mult. after irradiation
H-5	2.45	1.05 (m, H-6α or β) 1.10 (m, H-6α or β) 5.75 (dd, (*J*=5.8, 1.5, H-3) 6.60 (dd, (*J*=5.8, 3.0 H-4)	sharpened m sharpened m d (*J*=5.8) d (*J*=5.8)
H-11	2.60	0.75 (q, H-12)	s
assignment H-x	H NMR(400 MHz, $CDCl_3$)	δ ppm (mult., *J* , H-x)	mult. after irradiation
H-4	7.74	3.42 (ddd, *J*=9.5, 3.0, 1.5, H-5) 6.27 (dd, *J*=5.8, 1.5, H-3)	br d d (*J*=1.5)
H-5	3.42	1.97 (ddd, *J*=13.0, 9.5, 6.5, H-6β) 6.27 (dd, *J*=5.8, 1.5, H-3) 7.74 (dd, *J*=5.8, 3.0, H-4)	dd (*J*=13.0, 6.5)) d (*J*=5.8) d (*J*=5.8)
H-6β	1.97	2.09 (m, H-7β) 2.27 (m, H-7α) 2.60 (m, H-6α) 3.42 (ddd, *J*=9.5, 3.0, 1.5, H-5)	sharpened m sharpened m sharpened m br d
H-9	5.96	2.27 (m, H-7α)	sharpened m
H-12	1.10	2.60 (q, *J*=8.0, H-11)	s

2.3.16 Lithium Dimethylcuprate Addition to 11-Methyl Dienedione **107**

The 11-methyl dienedione **107** was treated with an excess of dilithium dimethylcyanocuprate reagent in THF at -78 °C (**Scheme 57**).



107 **97**

Scheme 57

The major isolated product provided satisfactory IR (2928, 1708 cm^{-1}) and LRMS (220, M^+; 219, $[M-H]^+$; 205, $[M-Me]^+$; 191, $[M-CHO]^+$; 177, $[M-MeCO]^+$). Unfortunately, we were unable to obtain a sufficiently pure sample for proton NMR analysis. Thus, although it appears that the desired diketone **97** had been prepared, it was not possible to satisfactorily characterize the isolated compound. The reactions were carried out on a very small scale (less than 5 mg) and this may be the reason why a sufficient amount of pure product was not obtained.

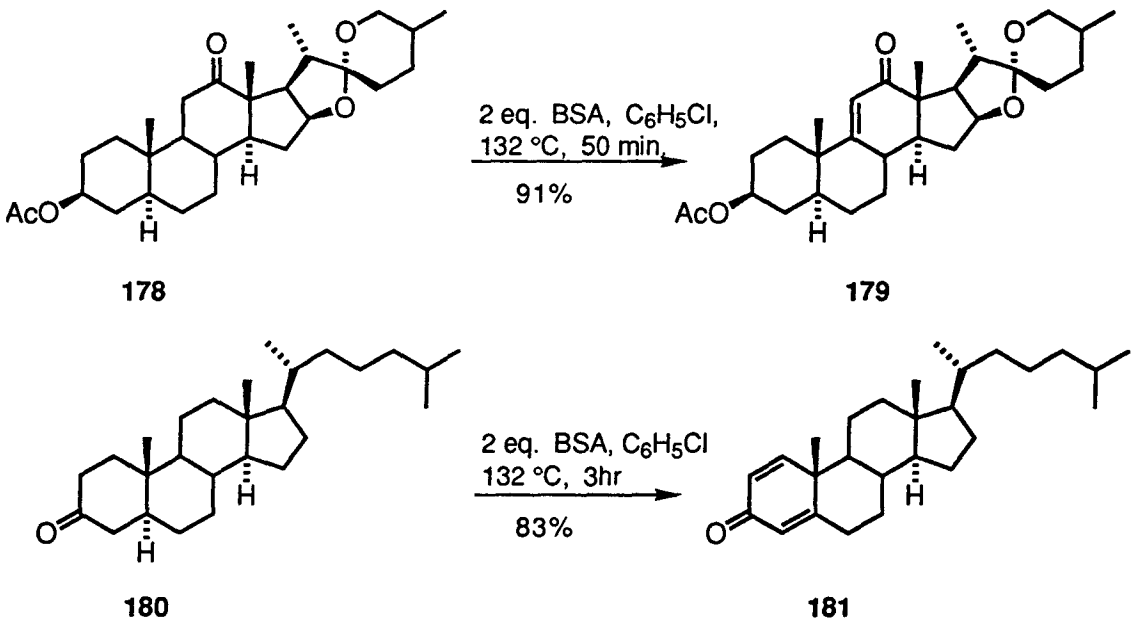
Since the product of this transformation was obtained in a small quantity and was impure, the following transformations could not be carried out. Therefore, we decided to conclude our research.

2.4 Preparation of Enones from Ketones: BSA Method

2.4.1 Introduction

In the course of this work, it became necessary to find a suitable procedure for the preparation of cyclopentenones from cyclopentanones. This led us to study the elimination of benzeneselenenic acid from α-phenylselenoxy ketones.

Barton's group dehydrogenated a number of steroidal and triterpenoid ketones using benzeneseleninic anhydride (BSA) in chlorobenzene at 95-132 °C (**Scheme 58**).[60,61]



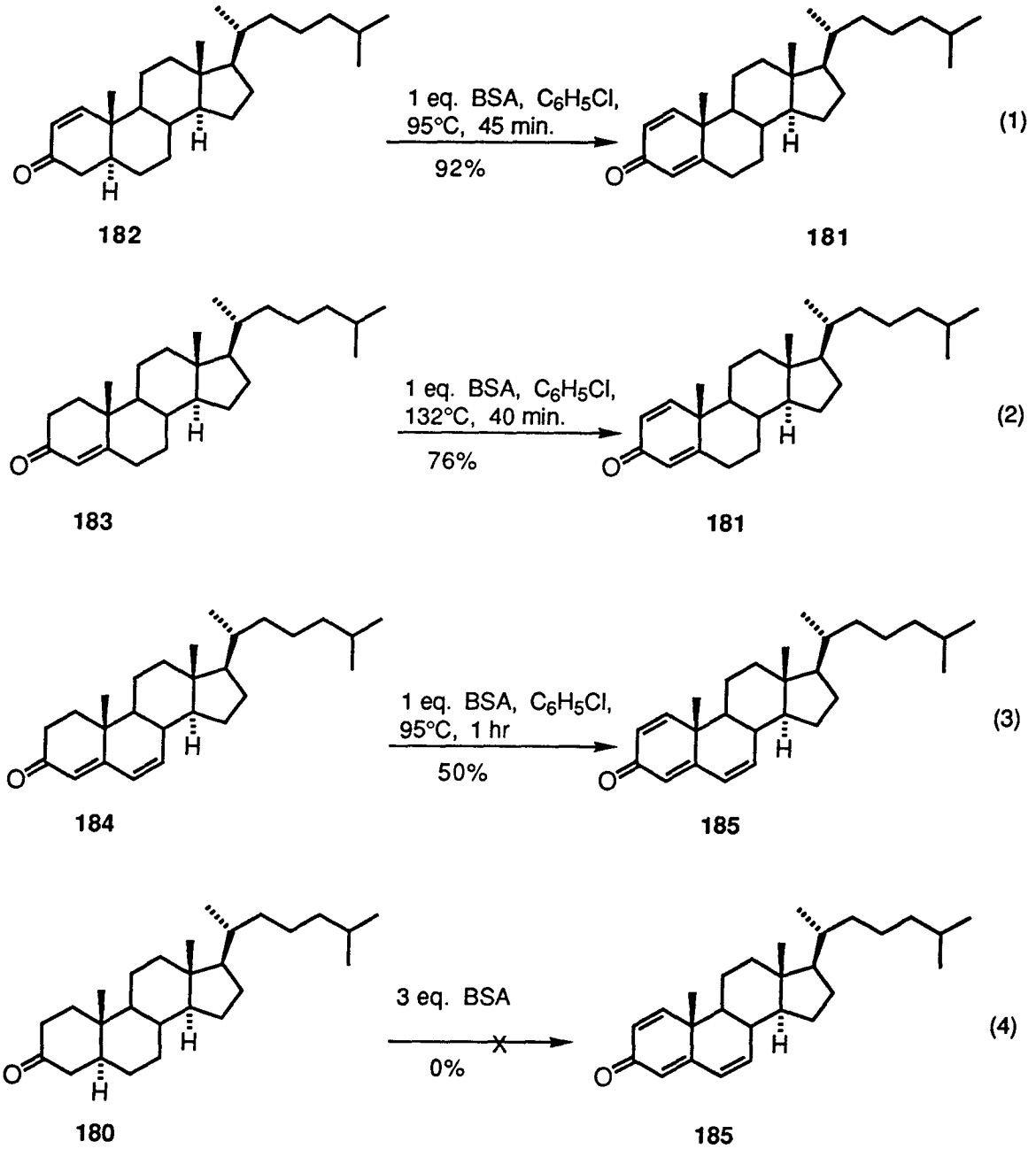
178 **179**

180 **181**

Scheme 58

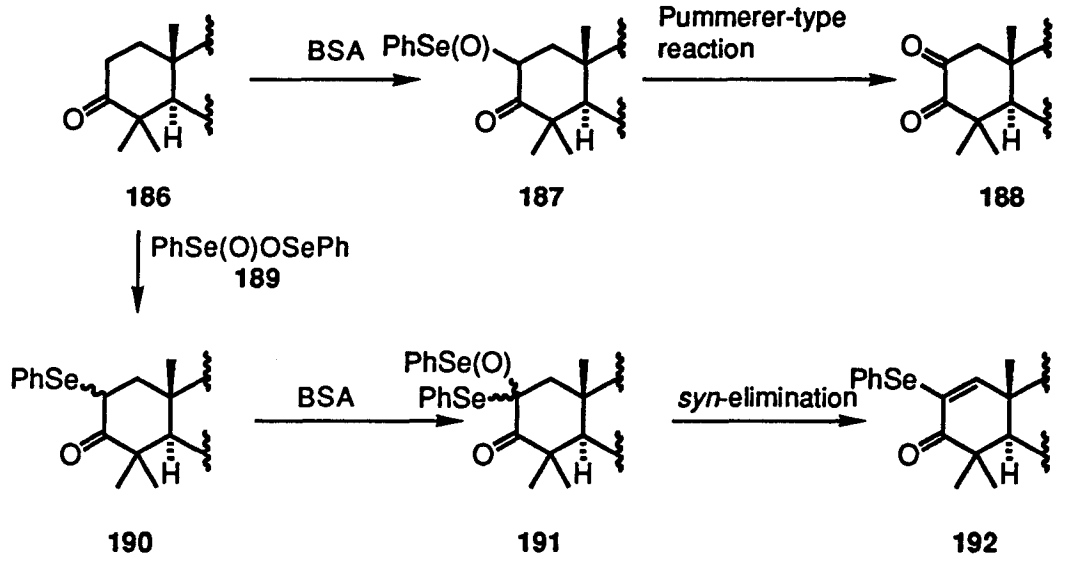
It should be noted that all the oxidations were performed on cyclohexanones. While in most cases yields were acceptable, the reaction was limited to the ketones with no acidic protons at one of the

α positions. In the cases of ketones with acidic protons at both α positions, 1,4-dien-3-ones were obtained (**Schemes 58** and **59**). Also, if there are protons at the γ position, the dehydrogenation could be carried further. In some cases such a transformation is not of preparative value (**Scheme 59**, entry 4).[60b]



Scheme 59

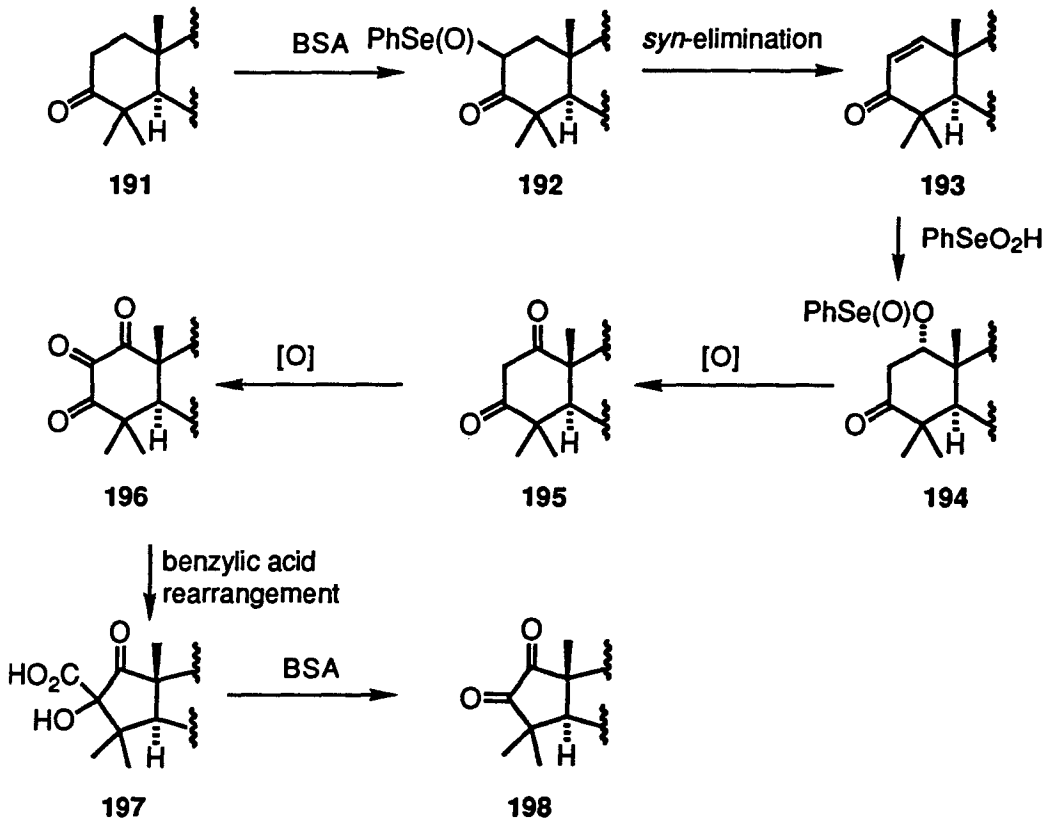
Due to the high reactivity of the reagent, as well as the vigorous reaction conditions employed (95-132 °C), the starting ketone often underwent side reactions (**Scheme 60**). An intermediate phenylselenoxy ketone can undergo Pummerer-type rearrangement to provide an α-diketone. Reaction of a ketone with BSA gives phenylselenoxy ketone and benzeneseleninic acid. Fragmentation of phenylselenoxy ketone provides an enone and benzeneselenenic acid. Condensation of benzeneseleninic with benzeneselenenic acid provides **189**. The latter compound could react with the starting ketone to give undesired products such as **192**.



Scheme 60

In some cases A-nor steroidal ketones were also observed. It has been suggested that these ketones were formed *via* a sequence of reactions involving nucleophilic addition to enone formed *in situ*, Pummerer rearrangement and benzylic acid rearrangement. This rationale is shown in **Scheme 61**.[60b]

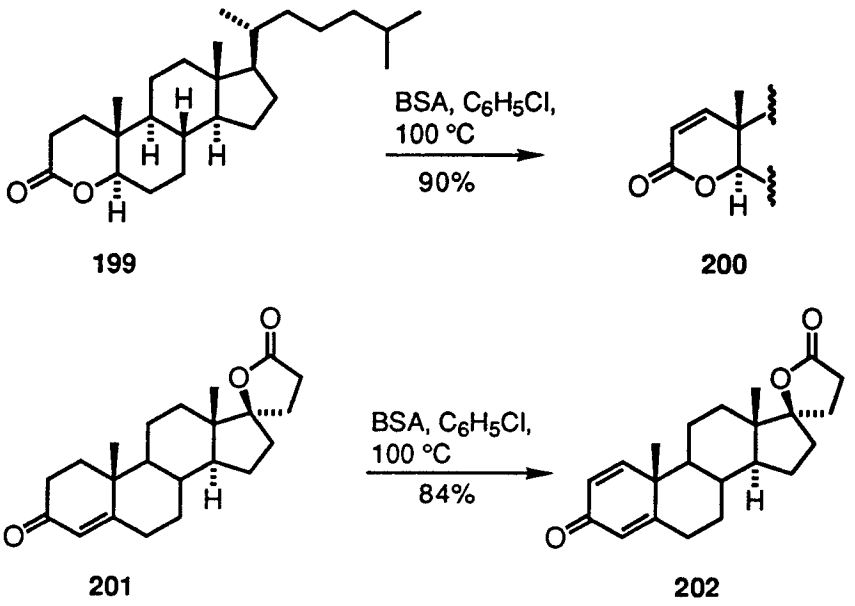
It is known that BSA has a lower reactivity toward olefins, compared to selenium dioxide. In a few reported examples, the allylic oxidation of olefins with BSA proceeded in a low yield after long reaction times (24 hr or longer).[61,62] It has been proposed that the lower "enephilicity" of BSA as compared to selenium dioxide is the reason for the higher chemoselectivity of the BSA reagent.[61] Thus, the presence of olefinic functional groups should not significantly affect the yields of enone formation.



Scheme 61

Oxidation of lactones with BSA has also been reported.[67] For example, the steroidal δ-lactone **199** was successfully dehydrogenated to the α,β-unsaturated lactone **200**. As expected, the lactone functions

are less reactive than the keto groups and the γ-lactone moiety of the compound **201** failed to react under the conditions employed (**Scheme 62**).

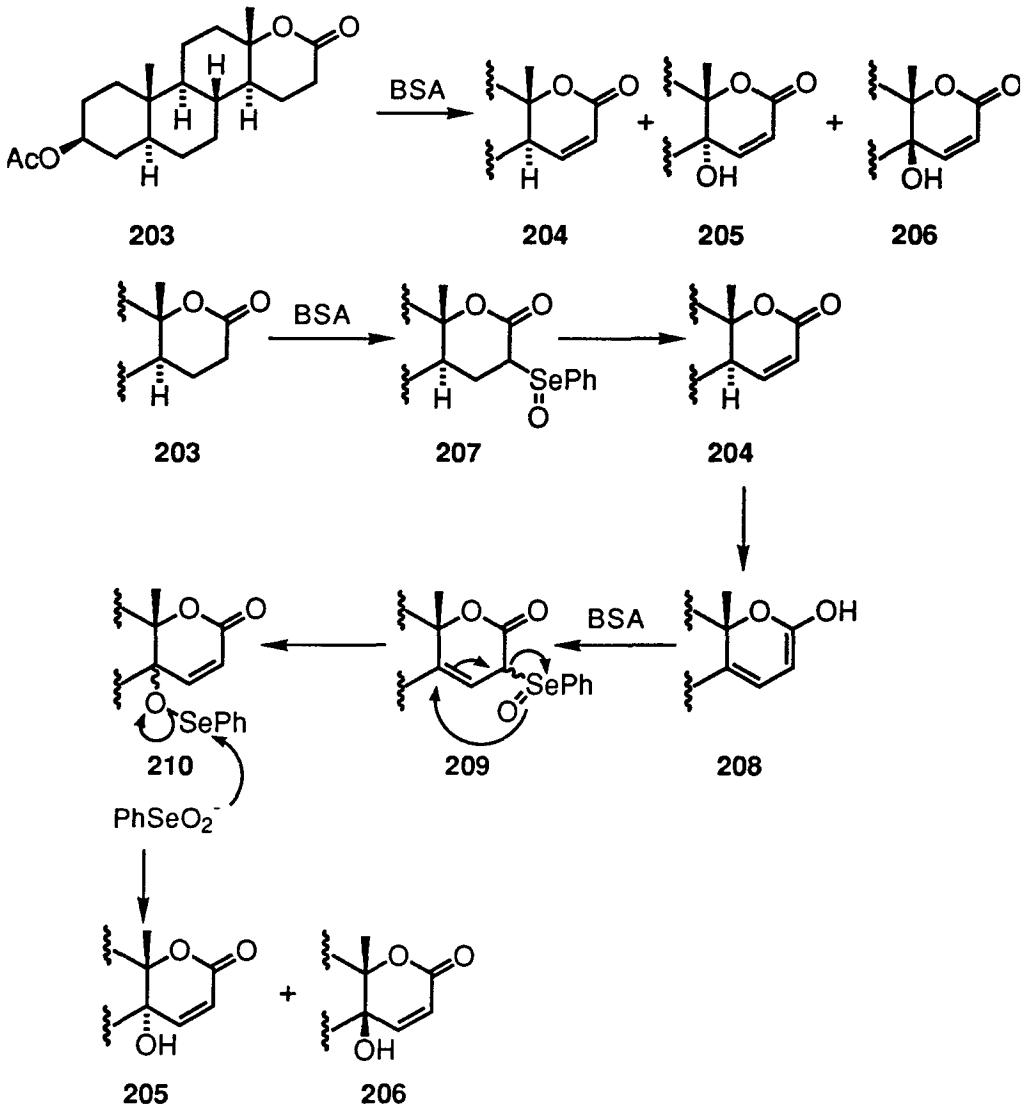


199 200

201 202

Scheme 62

In another example, the lactone **203** with a proton in the γ position underwent further allylic oxidation, and as a result the desired **204** and two epimeric alcohols **205** and **206** were obtained (**Scheme 63**). The proposed rationale for their formation is shown below.[67]



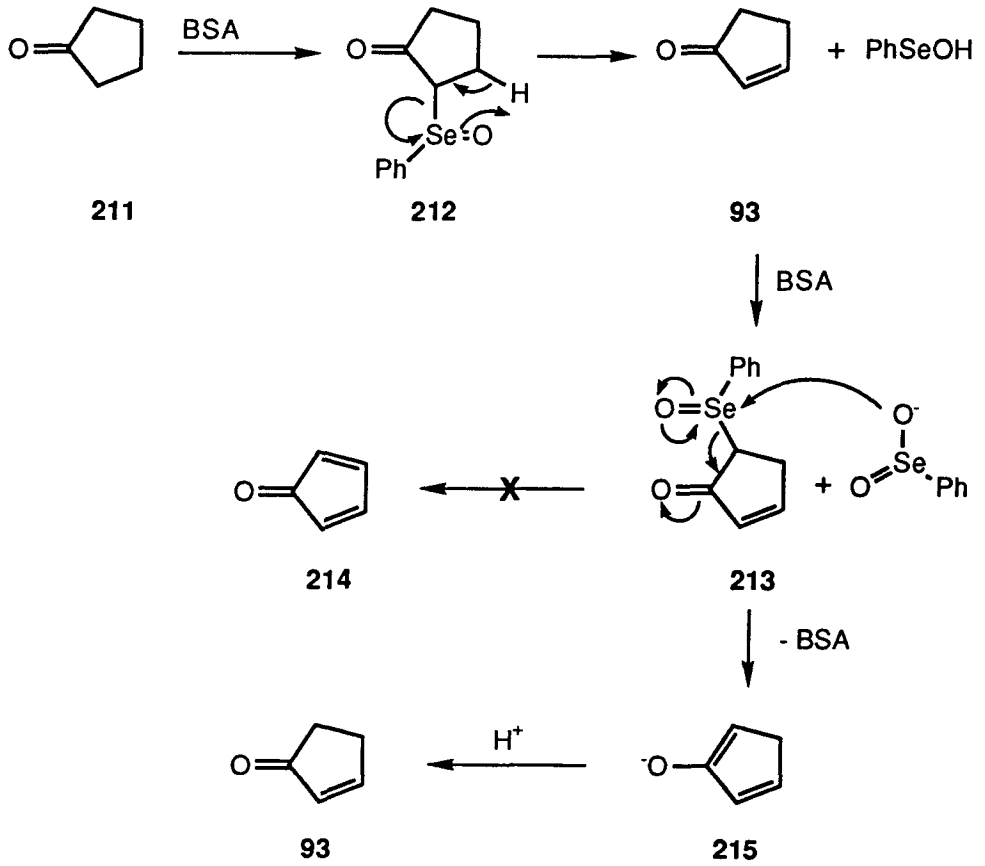
Scheme 63

2.4.2 Oxidation of Cyclopentanones

From the initial research described in section 2.3.14.6 (pp 74-75), it would seem that the phenylselenenic acid elimination is a feasible method for the preparation of dienedione **98**, provided that the α-phenylselenoxy ketone is easily available. The process involving BSA is particularly attractive since the elimination of benzeneselenenic acid

proceeds with equilibration of the intermediates that cannot eliminate. It has been shown from the research on cyclohexanones that dehydrogenation occurs, for as long as there are acidic hydrogen atoms (α, α', or γ) available to react with BSA, to produce dienones and trienones (**Schemes 58** and **59**). The enones thus formed often undergo further side reactions (**Scheme 61**).

Since the work of this thesis is restricted to cyclopentanones it is anticipated that difficulties associated with further dehydrogenation will not occur. The first elimination of benzeneselenenic acid would yield a cyclopentenone (**Scheme 64**), and the subsequent elimination of benzeneselenenic acid would lead to an antiaromatic cyclopentadieneone, which would be strongly disfavored.



Scheme 64

For that reason any formed α'-selenoxy enone would react with nucleophiles present (most likely benzeneseleninic acid) to regenerate the enone **93**.

Barton has shown that the five membered rings are much less reactive towards BSA than the six membered ring analogs.[67,68] The reason for a lower reactivity may be the smaller amount of enol tautomer present. For that reason there was some concern as to weather it would be possible to conduct the reaction under conditions that would be vigorous enough to affect the desired transformation without significant side reactions.

Surprisingly, the first experiments on the keto ketal **101** revealed that Barton's conditions (BSA in refluxing chlorobenzene) were too vigorous and that the reaction could proceed with a reasonable rate at much lower temperatures. The results of several reactions carried out under various conditions are listed in **Table 14**.

101 **100**

Table 14. BSA oxidation of the keto ketal **101**.

Entry	equiv. of BSA	solvent	temperature (°C)	reaction time (hr)	yield of **100** (%)
(1)	1.1	C_6H_5Cl	135	1.5	49(18)[a]
(2)	2.0	C_6H_5Cl	135	4.0	20
(3)	2.0	C_6H_6	80	2.0	55(15)
(4)	2.0	$CHCl_3$	60	3.5	49(24)[b]
(5)	2.0	CH_2Cl_2	40	4.5	44(22)[b]
(6)	1.5	CH_2Cl_2	17	72.0	15

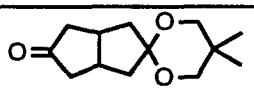
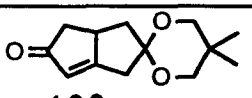
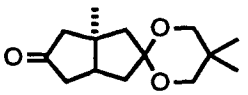
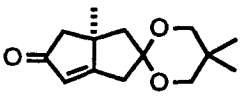
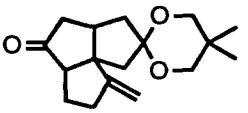
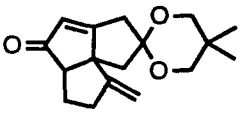
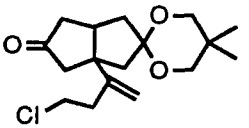
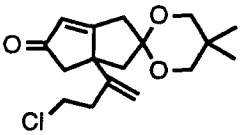
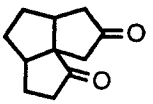
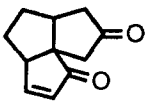
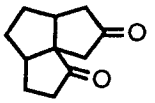
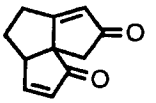
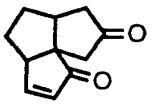
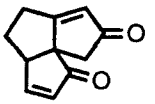
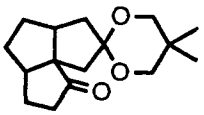
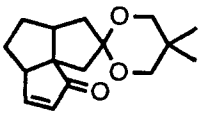
a) yield of the recovered keto ketal **101** is given in brackets; b) two additional unidentified products were obtained.

Optimum conditions for this oxidation reaction are shown in entry 3. The reactions in entries 4 and 5 provided similar mass balance. However two byproducts, which had to be separated from the enone, were obtained. The reaction described in entry 1 also deserves consideration, but was complicated by removal of high boiling chlorobenzene (b.p. 135 °C). Thus, the best yield of the enone **100** was obtained when 2.0 equivalents of BSA in benzene at 80 °C were used. The results of the oxidations of other cyclopentanones, conducted under similar reaction conditions, are listed in the **Table 15**.

This transformation is an example of what Turner called a "point reaction".[69] It provided an acceptable yield only within a relatively narrow range of conditions, and an excess of reagent or extended reaction times significantly lowered the yield. For that reason, the given conditions may not be optimal for other substrates, and more research could improve the yield of individual reactions. It is possible that the reaction conditions for the oxidation of substrates **99** and **132** (**Table 15**, entries 3 and 4 could be found. Indeed, the optimal procedure for the oxidation of enedione **157** is different (pp 74-75), and when using the procedure described in entry 3 (**Table 14**), the dienedione **98** was obtained in only 32% yield (**Table 15**, entry 7).

In the course of this work, several polyquinane ketones were oxidized using Saegusa's procedure.[31] The results are listed in **Table 15**. A comparison between the results obtained by the BSA oxidation and those obtained by Saegusa's method shows that the latter generally provides a higher yield (entries 1,3,8). However, in several specific examples the BSA method was superior (entries 2,5). Therefore it

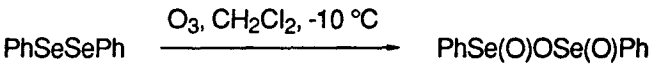
Table 15. Preparation of Enones from Ketones.

entry	substrate	BSA (equiv.)	product	solvent t (°C)	yield (%) (a)	(b)
(1)	 **101**	2.0	 **100**	C_6H_6 80 °C	55(15)[c]	72
(2)	 **133**	2.0	 **250**	C_6H_6 80 °C	51(35)[c]	42(9)[c]
(3)	 **99**	2.0	 **252**	C_6H_6 80 °C	0[d]	73
(4)	 **132**	2.0	 **254**	C_6H_6 80 °C	0[d]	-
(5)	 **104**	2.0	 **157**	$CHCl_3$ 60 °C	40	10[e]
(6)	 **104**	4.0	 **98**	$CHCl_3$ 60 °C	17	20[e]
(7)	 **157**	6.0	 **98**	C_6H_6 80 °C	32	42
(8)	 **103**	2.0	 **156**	C_6H_6 80 °C	62	74

a) BSA method; b) Saegusa's method; c) yield of recovered starting ketone is given in brackets; d) a mixture of unidentified products was obtained; e) A single conversion of **104** provided **98** and **157** in yields of 20% and 10%, respectively.

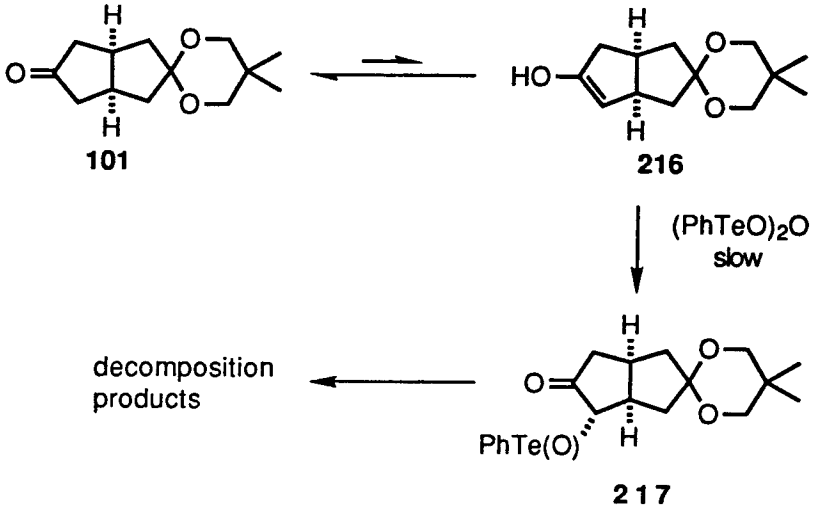
represents a complementary method to Saegusa's procedure when poor yields are obtained, or when Saegusa's method cannot be applied due to the presence of incompatible functional groups elsewhere in the molecule.

It should be noted that BSA was prepared by ozonization of diphenyldiselenide.[70] The commercially available BSA reagent[71] cannot be used in this reaction because it contains up to 30% benzeneseleninic acid.



Benzenetelurinic anhydride (BTA) was used as a substitute for BSA in an attempt to improve formation of the enone **100** from the ketone **101**.[72] However, instead of improving the yield of the desired enone, BTA failed to react with the keto ketal **101**, under the same reaction conditions (refluxing benzene, 80 °C). Under more vigorous reaction conditions (i.e. chlorobenzene, 135 °C), rapid reaction occurred, as indicated by the appearance of the deep red color of diphenyl diteluride. While the substrate **101** was consumed, no enone **100** could be observed. The GLC analysis of the reaction mixture indicated the presence of diphenylditeluride, the starting keto ketal **101**, and four additional products. After the work-up, 22% of the keto ketal **101** was recovered while byproducts were not isolated. It appears that the reaction between the benzeneteluric anhydride and the enol tautomer **216** to provide α-phenylteluroxy ketone is slower compared to the reaction using BSA, and it is possible that the starting material or the intermediate **217** underwent side reactions with benzeneteluric

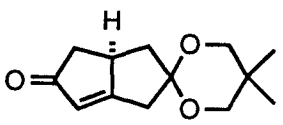
compounds (**Scheme 65**), similar to those described in **Schemes 60** and **61** (pp 86-87).



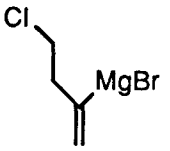
Scheme 65

3 Conclusion

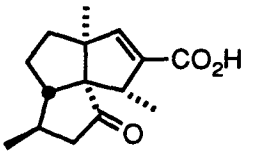
The work described herein represents a new approach to the construction of the silphiperfolane carbon skeleton. The methylenecyclopentane annulation was a key step in our sequence directed towards the total synthesis of (±)-subergorgic acid (**8**). This methylenecyclopentane annulation was readily accomplished *via* a one pot process involving a copper(I)-catalyzed reaction of the enone ketal **100** with the bifunctional reagent **91**.



100



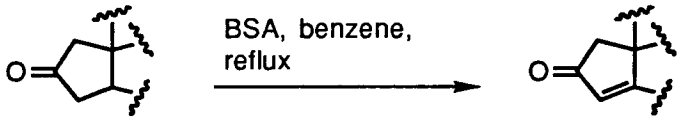
91



8

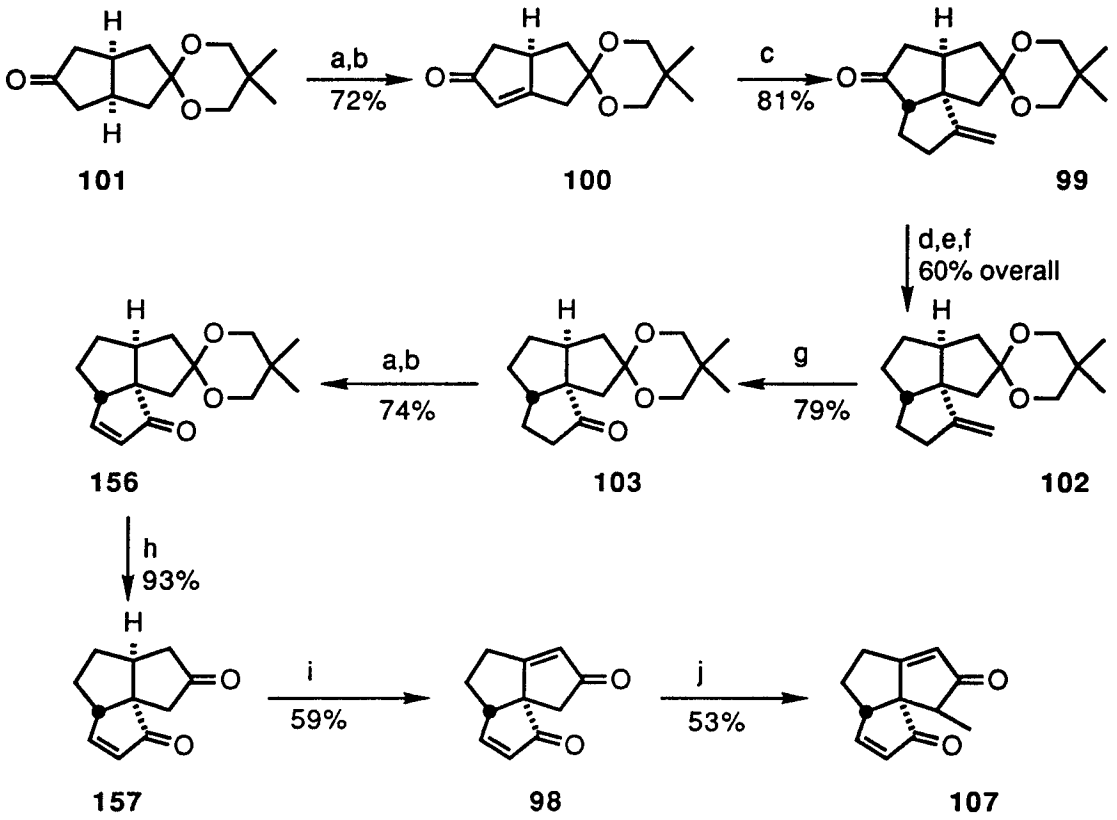
Oxidation of the alkene **102** provided efficiently the ketone **103** with the desired C-2 keto function. On the other hand, preparation and subsequent alkylation of the dienedione **98** provided **107** in less than satisfactory yields. An improvement in the yields of these two steps would substantially increase the overall efficiency of this route. To this end some improvements can be made in optimizing the modified Saegusa procedure described in section 2.3.14.2 (pp 69-71).

A brief study on the preparation of cyclopentenones disclosed that BSA can be used effectively for the synthetically useful conversion of cyclopentanones into cyclopentenones (**Scheme 66**). The procedure described herein has some advantages over those reported earlier in terms of reaction efficacy.



Scheme 66

The compound **107** was thus prepared in 12 steps and an overall yield of 6% from the known keto ketal **101** (**Scheme 67**).



a) TMSI, Et_3N, CH_2Cl_2, -78 °C; b) $Pd(OAc)_2$, MeCN, rt; c) **91**, CuBr·Me_2S, DMPU, THF, -78 °C; d) $LiAlH_4$, Et_2O, 0 °C; e) PhOC(S)Cl, DMAP, MeCN, rt; f) *n*-Bu_3SnH, AIBN, benzene, 80 °C; g) $RuO_2 \cdot xH_2O$, $NaIO_4 \cdot H_2O$, (2:2:3) CCl_4/MeCN/H_2O, rt; h) $H_3O^+Cl^-$/acetone, rt; i) BSA, benzene, 80°C; j) Li-tetramethylpiperidide, THF, -78 °C; followed by MeI.

Scheme 67

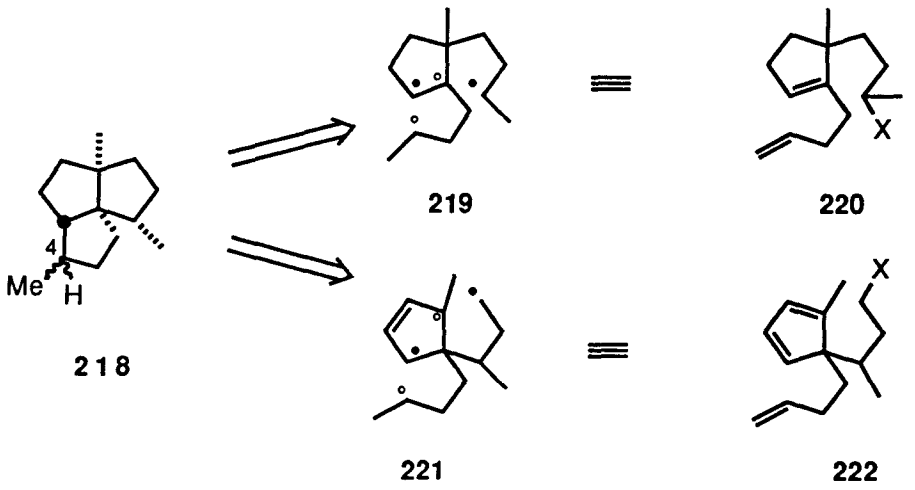
The employed methodology allowed for an efficient construction of the triquinane skeleton. Therefore this appears to be a viable general route towards the total synthesis of various molecules containing a triquinane skeleton. Future work involving a [2+2+1]-cyclization, as described in the Section 4 is also worth considering.

4 Design of an Alternative Sequence for the Synthesis of Subergorgic Acid

4.1 Recent Developments in Related Fields

An alternative and possibly enantioselective route for the preparation of subergorgic acid (**8**) can be based on recent developments in synthetic methodology and polyquinane chemistry.

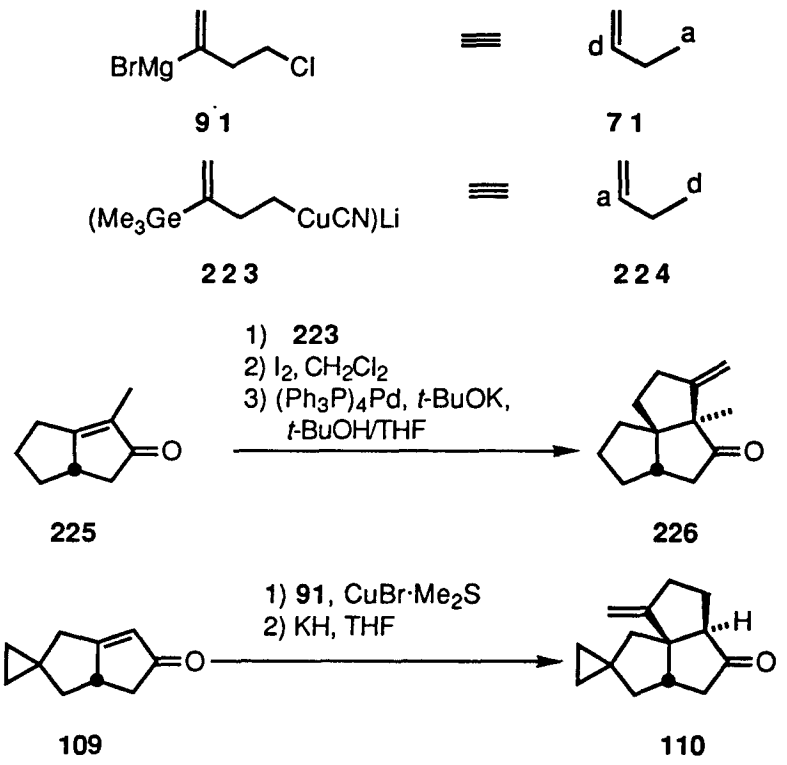
Developments in the field of free radical chemistry have found some application as a cyclopentane annulation method.[73] The work of Curran's group in the preparation of polyquinane molecules *via* a radical cyclization cascade is particularly noteworthy (**Scheme 68**).[74] In this case, the triquinane skeleton is assembled efficiently in one step and no protective groups are necessary. However, a serious drawback of this procedure is the lack of stereoselectivity at the C-4 center.[74b]



218 **219** **220** **221** **222**

Scheme 68

Recent work in our laboratory has produced the bifunctional reagent **223** which corresponds to an a^2,d^4-synthon **224** (**Scheme 69**). Addition of the reagent **223** to a cyclopentenone such as **225**, followed by cyclization provides a methylenecyclopentane moiety in which exocyclic methylene group is in different position,[75] as compared with the product of methylenecyclopentane annulation sequence using the bifunctional reagent **91**.[28,29]



91 ≡ **71**

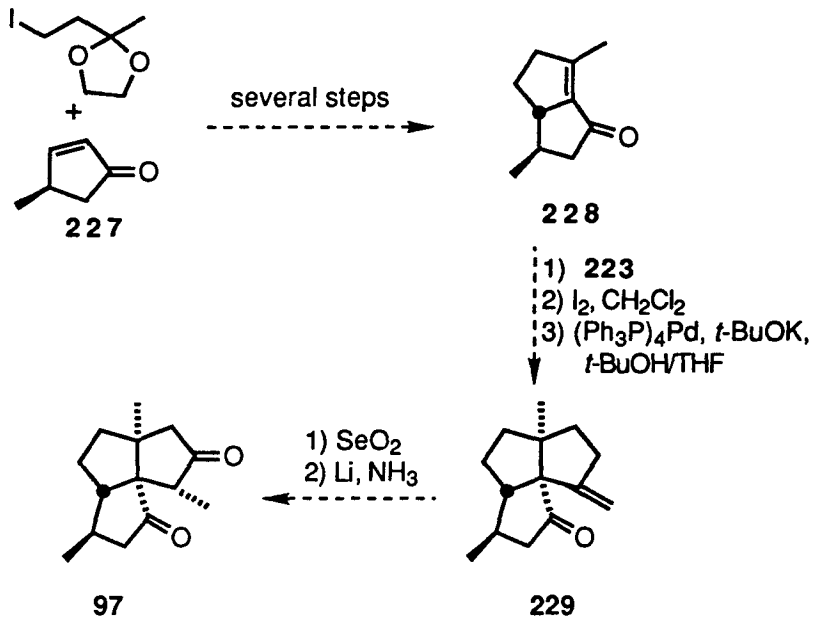
223 ≡ **224**

225 → **226**

109 → **110**

Scheme 69

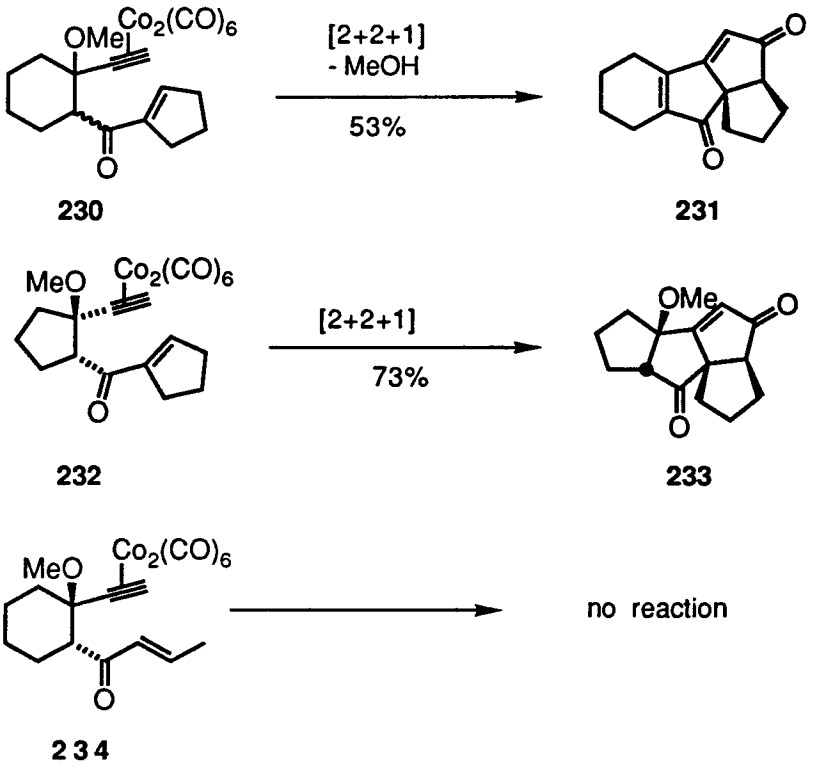
Assembly of the silphiperfolane skeleton may be more efficient with the reagent **223** than **91**, because all the carbon atoms from the substrate and the reagents would become part of the target molecule. A possible sequence for the synthesis of such a system is presented in the **Scheme 70**. The diketone **97** is an advanced intermediate in our original synthetic plan (**Scheme 16**, p 29).



Scheme 70

Finally, the recent disclosure of a Pauson-Khand reaction applied to an intramolecular [2+2+1] cyclization of alkynes, enones and carbon monoxide is of significance to the field of polyquinanes (**Scheme 71**).[76]

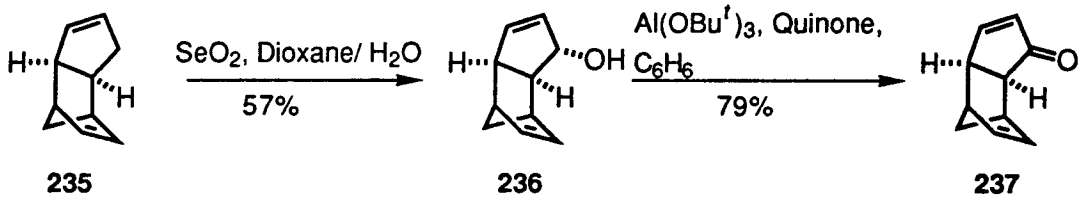
The methodologies presented above lead to a large number of alternative sequences for the synthesis of subergorgic acid. A sequence, considered to be most promising, is discussed in the following chapters.



Scheme 71

4.2 A Synthetic Plan Involving a [2+2+1] Cyclization

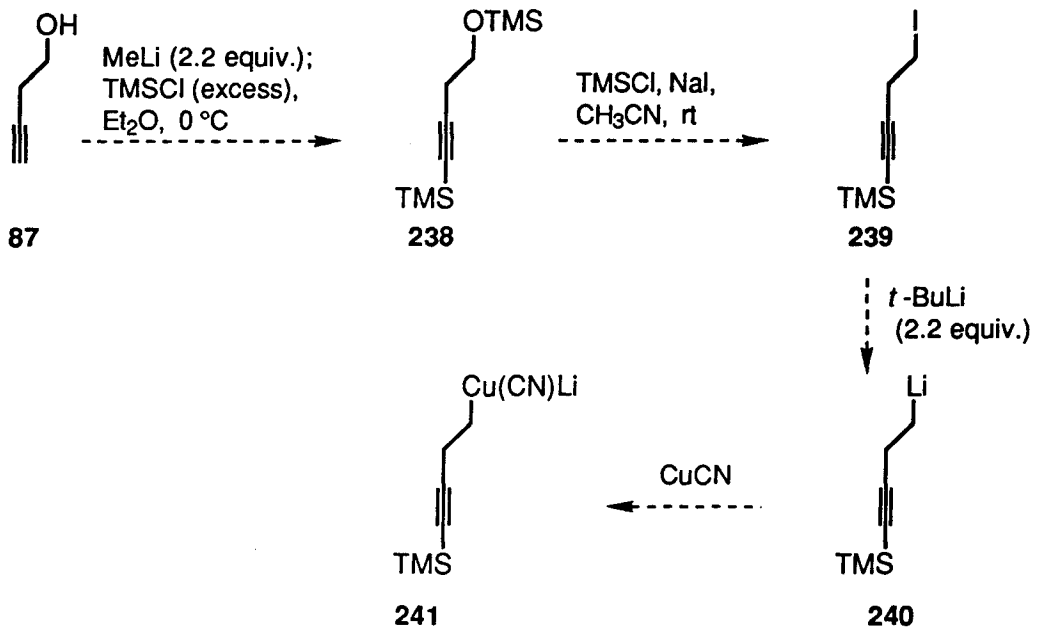
The readily available cyclopentadiene dimer **235** was chosen as a starting material. The dieneone **237** can be prepared in two steps, according to published procedures (**Scheme 72**).[77]



Scheme 72

The organocuprate reagent **241**, can be efficiently prepared from 3-butyn-1-ol (**87**) (**Scheme 73**). Reaction of **87** with 2.2 equiv. of

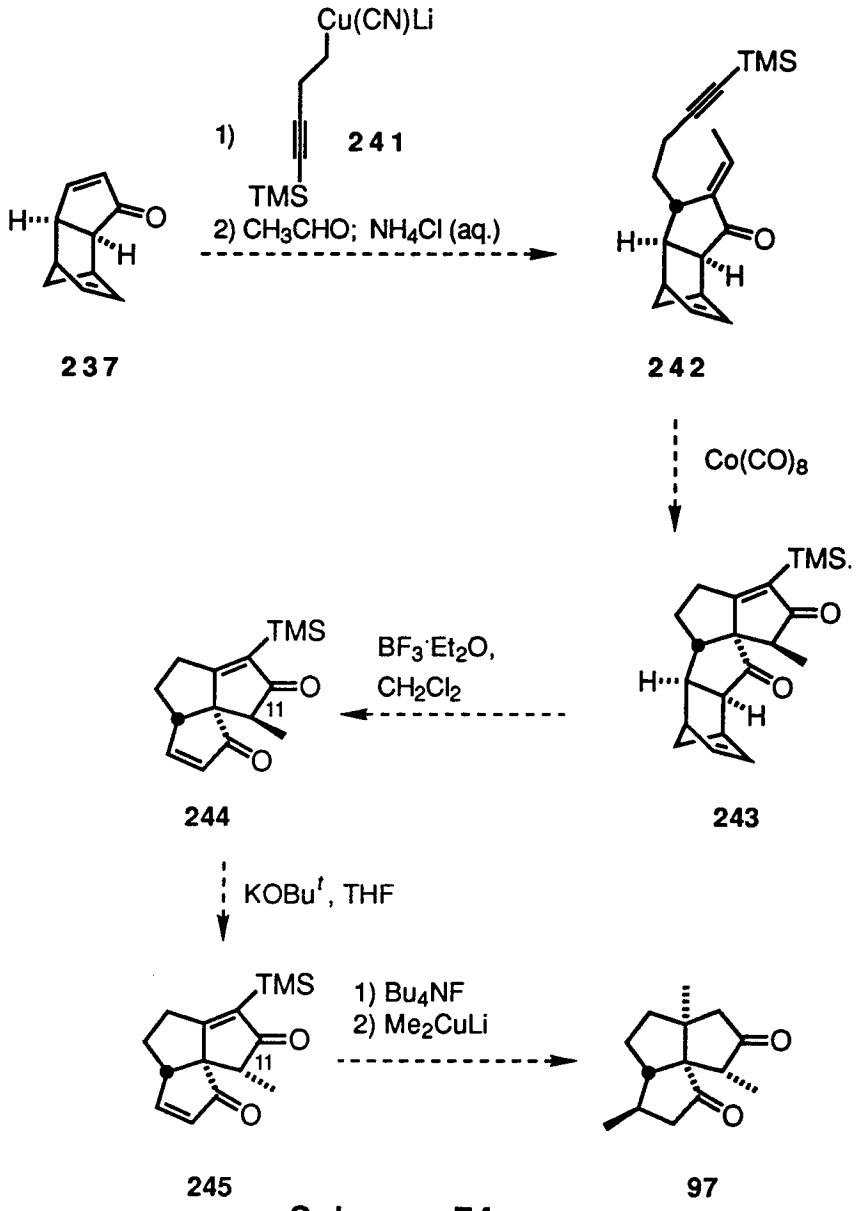
methyllithium followed by addition of an excess of trimethylsilyl chloride would produce **238**.[23] Conversion of trimethylsilyl ether to the corresponding iodide **239** can be accomplished according to a literature procedure.[78] Halogen metal exchange between the iodide **239** and 2.2 equiv. of *t*-butyllithium followed by addition of copper(I) cyanide would produce the organocuprate reagent **241**.[75]



Scheme 73

Addition of the organocuprate reagent **241** to the dieneone **237** (**Scheme 74**), followed by trapping of the resulting enolate with acetaldehyde would produce the corresponding alcohol. This intermediate alcohol is expected to undergo an elimination of water during the acidic work up to provide the enone **242**.[47] Alternatively, the intermediate keto alcohol can be isolated, the hydroxyl function transformed into a good leaving group (-OSO_2CH_3) and eliminated by treatment with DBU. According to literature precedents, the vinylic methyl group will be placed in a *trans* configuration relative to the

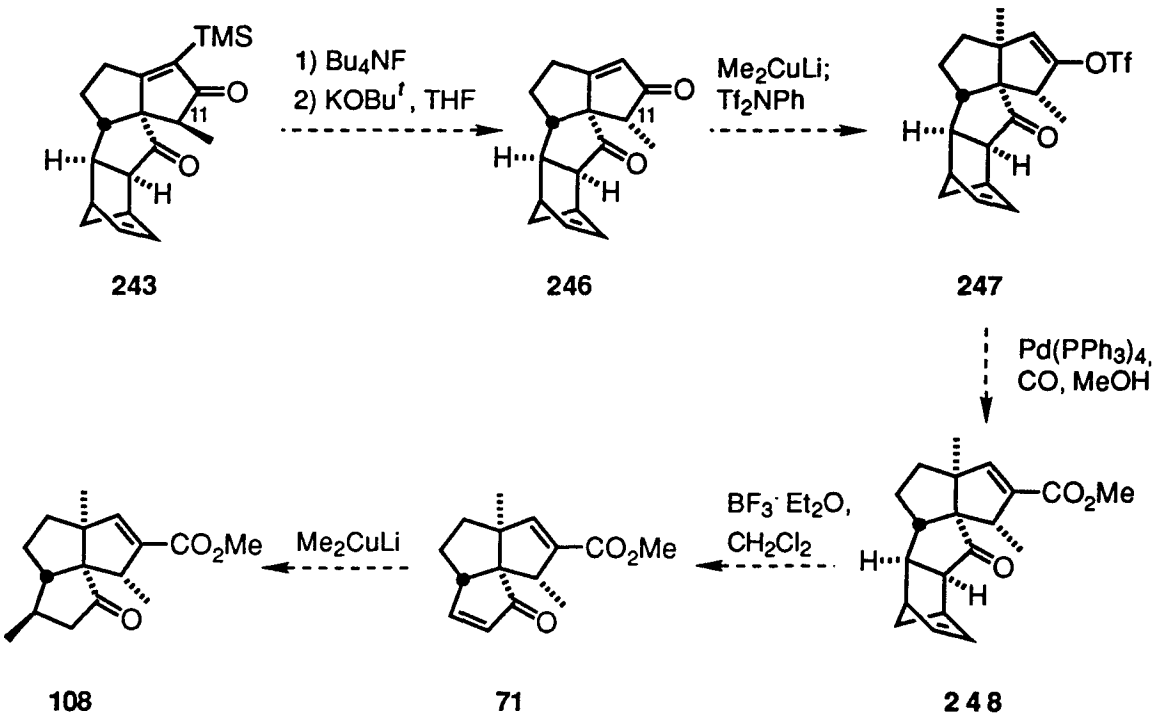
keto function.[79] This is not the desired orientation, since [2+2+1] addition proceeds with the retention of stereochemistry (i.e. *trans* substituents on the double bond will become *trans* substituents on the newly formed five-membered ring).[80c] The [2+2+1] cyclization of **242** using cobalt octacarbonyl as a promoter, is expected to produce the polyquinane **243**.[76,80c] In addition to cobalt octacarbonyl, several other metal complexes (e.g. Zr, Ti)[80] are known to mediate this cyclization. Their use could be investigated should the cyclization involving cobalt octacarbonyl provide an unsatisfactory yield of **243**. Alternatively, if the enone **242** fails to undergo an intramolecular Pauson-Khand reaction, the intermediate complex could be reduced to an allylic alcohol by treatment with $NaBH_4/CeCl_3$, and cyclized in a [2+2+1] reaction.[81] Upon completion of the [2+2+1] cyclization, the methyl group is expected to be in the β-position opposite to that in the naturally occurring subergorgic acid. Interestingly, several silphiperfolanes have a C-11 methyl group with β-stereochemistry.[82] Therefore, this sequence could be useful for an expedient synthesis of silphiperfolanes. The dienedione **244** can be prepared, in a retro Diels-Alder reaction, by treatment of the ketone **243** with boron trifluoride-etherate complex.[83] Base promoted equilibration of the C-11 methyl group in compound **244** (subergorgic acid numbering) would give **245**. Based on an inspection of molecular models, it was concluded that α-orientation of the C-11 methyl group (as in **245**) would be thermodynamically favored. Removal of the trimethylsilyl group, followed by the addition of lithium dimethylcuprate should yield **97**, a proposed intermediate in our original synthetic sequence (**Scheme 16**, p 29).



Scheme 74

Alternatively, the trimethylsilyl group in intermediate **243**, could be removed and the C-11 methyl group equilibrated under basic conditions to provide **246** (**Scheme 75**). The lithium dimethylcuprate addition followed by trapping of the intermediate enolate as vinyl triflate should provide **247**. The palladium catalyzed methoxycarbonylation of the vinyl triflate **247** would provide the ester

248. The retro Diels-Alder reaction, catalyzed by boron trifluoride-etherate complex, of the compound **248** would give the enone **71**. This enone was converted to subergorgic acid, *via* the ester **108**, by Paquette et al.[19]



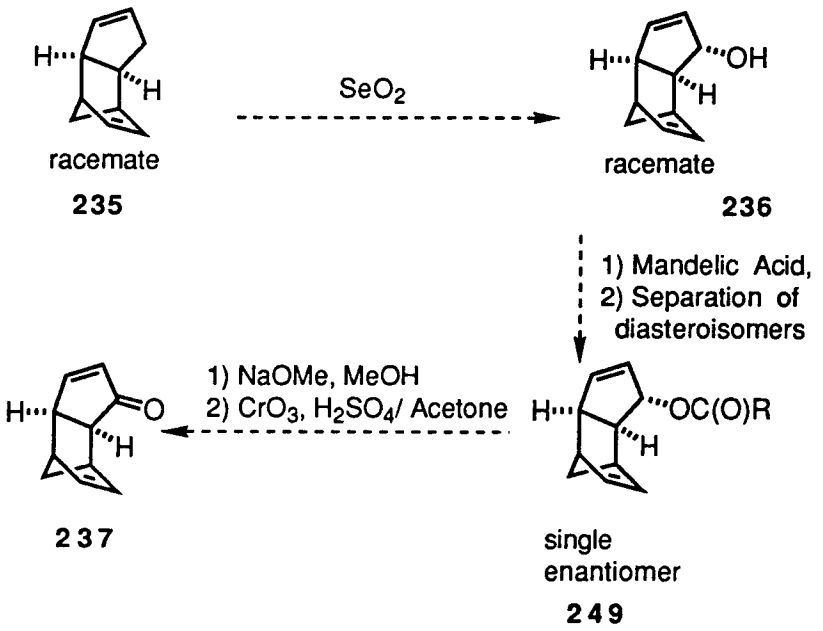
Scheme 75

4.3 A Synthetic Plan for an Enantioselective Synthesis of (-)-Subergorgic Acid

The synthetic sequence previously described in the section 4.2 which involves a [2+2+1] cycloaddition, could represent a convenient route for an asymmetric synthesis of (-)-subergorgic acid.

The synthetic sequence would begin with a resolution of the readily available cyclopentadienol **236** (**Scheme 76**). The racemic alcohol **236** could be converted to diastereomeric esters by

esterification with (+)-mandelic acid (or some other readily available chiral acid). Separation of these diastereomers by fractional crystallization or chromatography, followed by hydrolysis of the ester should provide the (+) and (-)-enantiomers of cyclopentadienol **236**. Jones' oxidation of a single enantiomer of alcohol **236** would provide the ketone **237** in its enantiomerically pure form. Upon completion of the synthetic sequence described in section 4.2 (**Schemes 74** and **75**), one enantiomer of dienone **237** would provide enantioselectively (-)-subergorgic acid. The enantiomer of dienone **237** would lead to the preparation of the unnatural (+)-subergorgic acid.



Scheme 76

5 Experimental

5.1 General

5.1.1 Data Acquisition and Presentation

Infrared (IR) spectra were recorded on liquid films (sodium chloride plates) or on potassium bromide discs, by means of a Perkin-Elmer model 1710 Fourier transform spectrophotometer (internal calibration).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on deuteriochloroform solutions (unless otherwise stated) using Varian model XL-300 or Bruker models AC-200 or WH-400 spectrometers. Signal positions are given in parts per million (δ) from tetramethylsilane (TMS) as the internal standard. Coupling constants (*J*-values) are reported in Hz and were measured on spectra judged to be first order. Data are reported in the format: chemical shift (δ) in ppm (multiplicity, number of protons, assignment (if possible), coupling constants). Assigned protons are reported in the form H-x, where x is the number of the hydrogen bearing carbon. The protons may lie either below the plane of the drawing (denoted by the letter α) or above it (β).

Carbon nuclear magnetic resonance (^{13}C NMR) spectra and the attached proton test (APT)[84] experiments were recorded on deuteriochloroform solutions at 75.3 MHz using the Varian spectrometer noted above, or the Bruker models AC-200 (50.5 MHz) or AMX-500 (125.8 MHz). Signal positions are given in parts per million

(δ) relative to deuteriochloroform (δ 77.0). Signals with negative intensities in the attached proton test (APT) experiments are indicated by (-ve) following the chemical shift.

Nuclear Overhauser enhancement (nOe)[85] difference experiments were recorded on a Bruker model WD-400 spectrometer.

^{1}H-^{1}H Homonuclear correlation (COSY)[86] experiments were recorded on Bruker models AC-200 or WD-400 spectrometers.

Low resolution and high resolution mass spectra were recorded with a Kratos/AEI MS 50 (70 eV) mass spectrometer. All compounds subjected to high resolution mass measurements were homogeneous by GLC and/or TLC analysis.

Microanalysis were performed on a Carlo Erba CHN elemental analyzer (Model 1106) in the microanalytical laboratory at the University of British Columbia.

Gas-liquid chromatography (GLC) analyses were performed on Hewlett-Packard models 5880 or 5890 capillary gas chromatographs, employing 25 m x 0.21 mm fused silica columns coated with cross-linked SE-54 and equipped with flame ionization detectors.

Thin layer chromatography (TLC) analyses were done on commercial aluminium-backed silica gel plates (E. Merck 5554). Visualization was accomplished with ultraviolet light, iodine vapor and/or heating the chromatogram under a hot air gun after immersion in 5% ammonium molybdate in 10% aqueous sulfuric acid. Conventional (drip) and flash column chromatography[90] were performed on 230-400 mesh silica gel (grade 60). In addition to column chromatography, separations were carried out on a centrifugally accelerated, radial, thin-layer

chromatograph (Chromatotron, Model 7924) using 1, 2 or 4 mm silica gel plates (grade 60, E. Merck 7749).

Concentration of the solvent under reduced pressure (water aspirator) refers to solvent removal on a Büchi rotary evaporator at 15 mm Hg.

Distillation temperatures (uncorrected) were recorded as air-bath temperatures required for short-path bulb-to-bulb (Kugelrohr) distillation. Melting points were measured on a Fisher-Johns apparatus and are uncorrected.

Temperatures of reaction mixtures refer to bath temperatures.

Cold bath temperatures were obtained by the following mixtures of solvents and coolants: 0 °C: ice/water; -10 °C: ice/acetone; -20 °C: 27g $CaCl_2$/100 mL H_2O/dry ice; -48 °C: 46g $CaCl_2$/100 mL H_2O/dry ice; -63 °C: chloroform/dry ice; -78 °C: acetone/dry ice.

All reactions were carried out under an atmosphere of dry argon using flame dried glassware unless stated otherwise.

5.1.2 Solvents and Reagents

Solvents and reagents were purified and dried using established procedures. THF and diethyl ether were distilled from sodium benzophenone ketyl. Carbon tetrachloride was distilled from P_2O_5. Acetonitrile, diisopropylamine, triethylamine, HMPA, DMPU, benzene, trimethylsilyl chloride, chloroform and dichloromethane were distilled from calcium hydride. Petroleum ether refers to a hydrocarbon fraction boiling between 30-60 °C.

Iodomethane was passed through a short column of flame dried basic alumina (activity I) before use.

Boron trifluoride-etherate was distilled under reduced pressure (55 °C/15 mmHg).

Solutions of methyllithium (LiBr complex) in diethyl ether, *n*-butyllithium in hexane and *t*-butyllithium in pentane were obtained from Aldrich Chemical Co. Inc. and were standardized using the method of Kofron and Baclawski.[87]

Magnesium bromide-etherate complex was prepared by the reaction of freshly distilled 1,2-dibromoethane with magnesium turnings (flame dried under argon atmosphere) in dry ether, with subsequent removal of ether under vacuum (0.1 mmHg) at room temperature.

Cuprous bromide-dimethyl sulfide complex was prepared by the method of Wuts.[88]

Benzeneseleninic acid anhydride was prepared by ozonization of diphenyl diselenide, and was recrystallized from benzene.[70]

Lithium diisopropylamide (LDA) and other lithium dialkylamides were prepared by the addition of a solution of methyllithium (1.0 equiv.) in diethyl ether to a solution of the appropriate amine (1.1 equiv.) in dry THF at -78 °C. The resulting solution was then stirred at 0 °C for 5 min before use.

Potassium hydride was obtained as 35% suspension in mineral oil from the Aldrich Chemical Company, inc. and was rinsed free of oil (with dry THF) and dried under stream of argon before use.

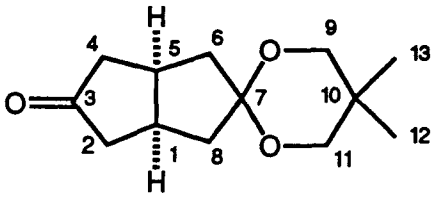
Aqueous NH_4Cl-NH_4OH (pH 8) was prepared by the addition of 50 mL of aqueous ammonium hydroxide (58%) to 1L of saturated aqueous ammonium chloride.

All other reagents were commercially available and were utilized without purification unless stated otherwise.

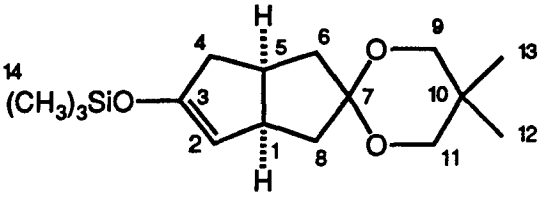
5.2 Experimental Procedures

5.2.1 Synthetic Studies Toward the Total Synthesis of (±)-Subergorgic Acid (8)

5.2.1.1 Preparation of the Enol Silyl Ether **130**



101



130

To a cold (-78 °C), stirred solution (argon atmosphere) of the keto ketal **101** (1.80 g, 8.0 mmol) in dry CH_2Cl_2 (100 mL), were added Et_3N (3.44 mL, 24 mmol) and Me_3SiI (2.35 mL, 16 mmol). After the mixture had been stirred at -78 °C for 30 min, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was allowed to warm to room temperature. The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the enol silyl ether **130** (2.19 g, 92%), as a colorless oil.

The product was used without further purification. The product was characterized with a sample obtained by distillation (120 °C/0.1 mm Hg).

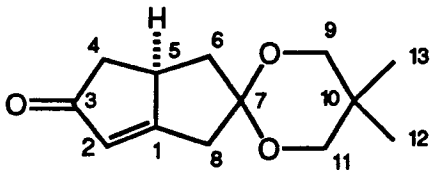
IR (neat): 2957, 1645, 1114 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.12 (s, 9H, Me_3Si-), 0.90 (s, 6H, Me-12 and Me-13), 1.49 (m, 2H), 1.94 (dd, 1H, *J*=4.2, 2.4 Hz), 2.18-2.32 (m, 2H), 2.36-2.62 (m, 2H), 3.03 (m, 1H, H-1), 3.38 (s, 2H, ketal CH_2), 3.42 (s, 2H, ketal CH_2), 4.55 (d, 1H, H-2, *J*=1.8 Hz).

Mass Spectrum, m/z (relative intensity): 296 (M^+, 37.8), 224 (6.3), 210 (24.6), 209 (73.7), 206 (59.0), 168 (28.7), 167 (100.0), 128 (87.0).

Exact Mass Calcd. for $C_{16}H_{28}O_3Si$: 296.1807, found: 296.1804.

5.2.1.2 Preparation of the Enone Ketal **100**



100

To a solution of $Pd(OAc)_2$ (1.59 g, 7.1 mmol) in 90 mL of dry acetonitrile at rt was added a solution of 2.09 g (7.1 mmol) of the crude enol silyl ether **130** in dry acetonitrile (10 mL). After the mixture had been stirred at rt for 2 hr, it was filtered through a short column of Florisil (2 cm x 5 cm). The column was washed with Et_2O and the combined filtrate was concentrated under reduced pressure. A GLC analysis of the residual oil showed that the enone **100** and ketone **101** were present in a ratio of 94:6. Flash chromatography (4 cm x 25 cm silica gel column, elution with 2:1 petroleum ether/EtOAc) of the residual material gave 1.29 g (72%) of enone **100** as a white solid. Recrystallization (hexane) provided long white needles that exhibited m.p. 84-86 °C.

IR (KBr): 2959, 1704, 1635, 1103 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.94, 1.01 (s, s, 3H each, Me-12 and Me-13), 1.40 (dd, 1H, H-6α or β, *J*=6.2, 6.2 Hz), 2.08 (dd, 1H, H-4α or β, *J*=9.0, 1.7 Hz), 2.60 (dd, 1H, H-4α or β, *J*=9.0, 3.0 Hz), 2.65 (dd, 1H, H-6α or β, *J*=6.2, 4.0 Hz), 2.87 (d, 1H, H-8α or β, *J*=9.0 Hz), 2.99 (d, 1H, H-8α or β, *J*=9.0 Hz), 3.12 (m, 1H, H-5), 3.47 (dd, 2H, ketal CH_2, *J*=5.0 Hz), 3.52 (dd, 2H, ketal CH_2, *J*=5.0 Hz), 5.89 (s, 1H, H-2).

Detailed ^1H NMR data, including those derived from COSY experiments, are given in **Table 16.**

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.36 (C-12), 22.40 (C-13), 30.08 (C-10), 38.15 (C-4), 42.05 (C-6 or C-8), 42.09 (C-6 or C-8), 43.42 (C-5), 71.65 (C-9), 72.55 (C-11), 109.01 (C-7), 125.76 (C-2), 185.62 (C-1), 209.66 (C-3).

Mass Spectrum, m/z (relative intensity): 222 (M^+, 100.0), 193 (5.2), 181 (6.4), 154 (21.7), 137 (30.8), 128 (28.8), 109 (71.7).

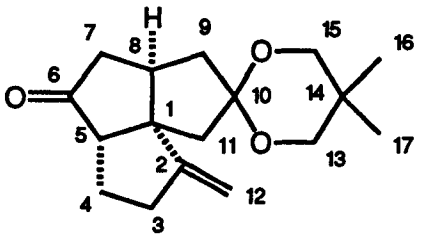
Exact Mass Calcd. for $C_{13}H_{18}O_3$: 222.1256, found: 222.1255.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16, found: C, 70.36; H, 8.30.

Table 16. ^1H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the enone **100.**

H-x (assignment)	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations
H-2	5.89	H-8α & β
H-4α or β	2.60	H-5, H-4α or β
H-4α or β	2.08	H-5, H-4α or β
H-5	3.12	H-4α & β, H-6α & β
H-6α or β	2.65	H-5, H-6α or β
H-6α or β	1.40	H-5, H-6α or β
H-8α & β	2.87 & 2.99	H-2
ketal CH_2's	3.47 & 3.52	H-12 & H-13
H-12 & H-13	0.94 & 1.01	ketal CH_2's

5.2.1.3 Preparation of the Tricyclic Ketone **99**



99

To a cold (-78 °C), stirred solution of the freshly distilled 4-chloro-2-trimethylstannyl-1-butene (**89**) (1.09 g, 4.28 mmol, 1.4 equiv.) in 100 mL of dry THF was added a solution of MeLi in Et_2O (2.85 mL, 1.5 M, 4.28 mmol, 1.4 equiv.). After the solution had been stirred at -78 °C for 15 min, solid $MgBr_2 \cdot Et_2O$ (1.10 g, 4.28 mmol, 1.4 equiv.) was added in one portion. After stirring at -78 °C had been continued for another 10 min period, solid $CuBr \cdot Me_2S$ (102 mg, 0.43 mmol, 0.14 equiv.) was added in one portion, followed by a solution of the enone **100** (678 mg, 3.05 mmol, 1.0 equiv.) in dry THF (5 mL). The mixture was stirred at -78 °C for 10 min and dry DMPU (0.74 ml, 6.1 mmol, 2.0 equiv.) was added. The solution was stirred for an additional 15 min at -78 °C and was allowed to warm up to rt. After stirring for 3 hr at rt, aqueous NH_4Cl-NH_4OH (pH 8) and Et_2O (50 mL) were added and the mixture was filtered through a short column of Florisil. The column was washed with Et_2O and the combined filtrate was concentrated under reduced pressure. Flash chromatography (2 cm x 15 cm silica gel column, elution with 3:1 petroleum ether/Et_2O) of the residual material, gave 683 mg (81%) of the tricyclic ketone **99** as a white solid. Recrystallization (methanol) provided a white cubic crystals that exhibited m.p. 59-61 °C.

IR (KBr): 2927, 1741, 1651, 1119 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.90, 0.93 (s, s, 3H each, Me-16 and Me-17), 1.80-1.96 (m, 3H, H-4α and β, H-9α or β), 2.19 (d, 1H, H-11 α or β, *J*=13.9 Hz), 2.32 (d, 1 H, H-11 α or β, *J*=13.9 Hz), 2.18-2.42 (m, 4H, H-3α and β, H-7α or β, H-9α or β), 2.47 (dd, 1H, H-7α or β, *J*=18.5, 9.0 Hz), 2.57 (m, 1H, H-8), 2.61 (m, 1H, H-5), 3.42 (d, 1H, ketal CH_2, *J*=11.2 Hz), 3.46 (d, 1H, ketal CH_2, *J*=11.2 Hz), 3.50 (s, 2H, ketal CH_2), 4.98 (t, 1H, H-12, *J*=1.8 Hz), 5.01 (t, 1H, H-12, *J*=1.8 Hz).

Detailed ^1H NMR data, including those derived from COSY and decoupling experiments, are given in **Tables 3** and **4**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.39 (C-16, -ve), 22.43 (C-17, -ve), 27.59 (C-4), 30.03 (C-14), 33.74 (C-3), 42.06 (C-7), 44.25 (C-8, -ve), 45.02 (C-9 or C-11), 47.73 (C-9 or C-11), 58.80 (C-1), 60.21 (C-5, -ve), 71.55 (C-13), 72.41 (C-15), 105.37 (C-12), 108.76 (C-10), 159.79 (C-2), 221.90 (C-6).

Mass Spectrum, m/z (relative intensity): 276 (M^+, 12.3), 207 (37.5), 154 (8.6), 128 (100.0), 93 (27.1), 69 (64.0).

Exact Mass Calcd. for $C_{17}H_{24}O_3$: 276.1725, found: 276.1725.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75, found: C, 74.04; H, 8.69.

Table 3. ^{1}H NMR (400 MHz, $CDCl_3$) and COSY (400 MHz, $CDCl_3$) data for the Keto Alkene **99**.

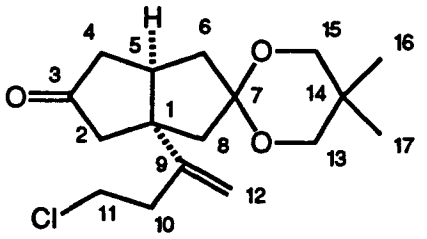
H-x (assignment)	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-4α & β H-9α or β	1.80-1.96	H-5, H-8
H-5 and H-8	2.57 & 2.61	H-4α & β, H-7α & β, H-9α & β
H-7α or β	2.47	H-7β or α, H-8
ketal CH_2's	3.42, 3.46 & 3.50	H-16 & H-17
H-16 & H-17	0.90 & 0.93	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

Table 4. ^{1}H NMR (400 MHz, $CDCl_3$) and decoupling experiments (400 MHz, $CDCl_3$) data for the Keto Alkene **99**.

irradiated signals		observed signals	
assignment H-x	^{1}H NMR (400 MHz, $CDCl_3$)	δ ppm (mult. *J*, H-x)	mult. after irradiation
H-4α and β (H-9 also irradiated)	1.80-1.96	2.18-2.42 (m, 4H, H-3α and β, H-7, H-9) 2.57 (m, H-8) 2.61 (m, H-5)	sharpened m dd (*J*=9.0, 3.0) s
H-11α or β	2.19	2.32 (m, H-11β or α)	s
H-5 & H-8	2.57 and 2.61	1.80-1.96 (m, 3H, H-4α & β,H-9α or β) 2.18-2.42 (m, 4H, H-3α and β, H-7, H-9)	sharpened m sharpened m
H-12	4.98 and 5.01	2.18-2.42 (m, 4H, H-3α and β, H-7, H-9)	sharpened m

5.2.1.4 Preparation of the Chloro Ketone **132**



132

To a cold (-78 °C), stirred solution of the freshly distilled 4-chloro-2-trimethylstannyl-1-butene (**89**) (101 mg, 0.42 mmol, 1.35 equiv.) in 20 mL of dry THF was added a solution of MeLi in Et_2O (0.33 mL, 1.5 M, 0.5 mmol, 1.6 equiv.). After the solution had been stirred at -78 °C for 15 min, solid $MgBr_2 \cdot Et_2O$ (129 mg, 0.5 mmol, 1.6 equiv.) was added in one portion. After stirring for another 10 min solid $CuBr \cdot Me_2S$ (23 mg, 0.09 mmol, 0.03 equiv.) was added in one portion, followed by a solution of the enone **100** (70 mg, 0.31 mmol, 1.0 equiv.) in dry THF (2 mL). The reaction mixture was stirred at -78 °C for another 30 min. Aqueous NH_4Cl-NH_4OH (pH 8) was added, followed by Et_2O and the resultant mixture was opened to the atmosphere and was stirred vigorously until the aqueous layer was blue. The phases were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (1 cm x 12 cm column, 2:1 petroleum ether/Et_2O) of the residual material, followed by distillation (120 °C/0.1 mmHg) of the liquid thus obtained, give 74.5 mg (77%) of the chloro ketone **135** as a colorless oil.

IR (neat): 2956, 1742, 1638, 1116 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96, 0.97 (s, s, 3H each, Me-16 and Me-17), 1.87 (dd, 1H, H-6α, *J*=14.5, 8.0 Hz), 2.22 (m, 3H, H-4α or β, H-8α & β), 2.36 (d, 1H, H-6β, *J*=14.5 Hz), 2.43 (m, 1H, H-4α or β), 2.54 (m, 4H, H-2α & β, H-10), 2.89 (ddd, 1H, H-5, *J*=16.0, 8.0, 2.5 Hz), 3.45 (s, 2H, ketal CH_2), 3.48 (s, 2H, ketal CH_2), 3.67 (t, 2H, H-11, *J*=8.0 Hz), 4.91 (s, 1H, H-12), 5.01 (s, 1H, H-12).

Detailed ^{1}H NMR data, including those derived from COSY experiments, are given in **Table 1**.

^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.37 (C-16 and C-17, -ve), 30.02 (C-14), 35.25, 40.72 (C-5, -ve), 41.53, 43.07, 43.49, 46.06, 49.50, 53.70 (C-1), 71.94 (C-13), 72.04 (C-15), 108.36 (C-7), 109.87 (C-12), 148.91 (C-9), 218.15 (C-3).

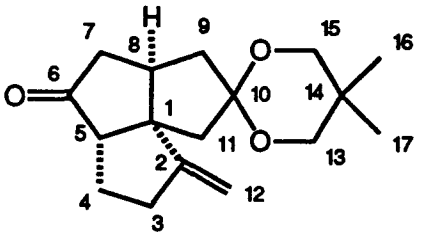
Mass Spectrum, m/z (relative intensity): 312 (M^+, 3.8), 277 (5.4), 243 (10.6), 155 (10.8), 129 (15.8), 128 (100.0), 69 (96.6).

Table 1. ^{1}H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the chloroketone **132**.

H-x (assignment)	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY Correlations[a]
H-4α or β	2.43	H-5
H-5	2.89	H-4α or β, H-6α and β
H-6β	2.36	H-5, H-6α
H-6α	1.87	H-5, H-6β
ketal CH_2's	3.45 & 3.48	H-16 & H-17
H-16 & H-17	0.96 & 0.97	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

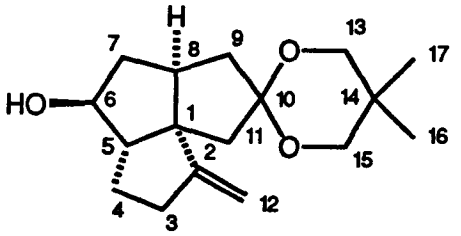
5.2.1.5 Preparation of Tricyclic Ketone **99** from Chloro Ketone **132**



99

To a stirred suspension of KH (13.2 mg, 0.33 mmol, 3 equiv.) in 2.5 mL of dry THF, was added a solution of the chloro ketone **132** (33 mg, 0.11 mmol, 1 equiv.) in dry THF. After the mixture had been stirred at rt for 3 hr, aqueous NH_4Cl was added, followed by Et_2O. The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual material thus obtained was distilled (120 °C/0.1 mm Hg) to give 27.4 mg (94%) of the ketone **99** as a colorless oil which solidified upon cooling to rt. The spectral properties observed for this material were identical with those described for the compound **99** obtained previously (pp 119-121).

5.2.1.6 Preparation of the Alcohol **135**



135

To a cold (0 °C), stirred suspension of $LiAlH_4$ (30 mg, 0.75 mmol, 1.5 equiv.) in 20 mL of dry THF was added a solution of the ketone **99** (158 mg, 0.57 mmol, 1 equiv.) in 2 mL of dry THF. After the mixture had been stirred at 0 °C for 30 min, solid $Na_2SO_4 \cdot 10H_2O$ was added in one portion. The slurry thus formed was filtered through a sintered glass funnel and the collected material was rinsed with Et_2O. The combined filtrates were dried ($MgSO_4$) and concentrated under reduced pressure to provide a crude product as a white solid. Recrystallization (pentane) provided 155 mg (97%) of the alcohol **135** as white cubic crystals that exhibited m.p. 80-81 °C.

IR (KBr): 3296, 2956, 1647, 1111 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.91, 0.99 (s, s, 3H each, Me-16 and Me-17), 1.37 (m, 1H, H-4α), 1.67 (dt, 1H, H-7α or β, *J*=13.3, 4.9 Hz), 1.85 (m, 1H, H-4β), 2.06 (d, 1H, H-11α or β, *J*=14 Hz), 2.14 (m, 1H, H-7α or β), 2.20 (m, 1H, H-5), 2.12-2.42 (m, 5H, H-3α and β, H-8, H-9α and β), 2.45 (d, 1H, H-11α or β, *J*=14 Hz), 3.06 (br, 1H, -OH, exchanges with D_2O), 3.44 (s, 2H, ketal CH_2), 3.51 (s, 2H, ketal CH_2), 3.84 (br, 1H, H-6), 4.84 (s, 1H, H-12), 4.86 (s, 1H, H-12).

Detailed ^1H NMR data, including those derived from COSY, nOe and decoupling experiments, are given in **Tables 6** and **17**.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.43 (C-16, -ve), 22.59 (C-17, -ve), 28.35 (C-4), 30.02 (C-14), 33.44 (C-7), 41.76 (C-9 or C-11), 41.96 (C-9 or C-11), 48.20 (C-3), 48.32 (C-8, -ve), 61.56 (C-1), 61.87 (C-5, -ve), 71.40 (C-13), 72.63 (C-15), 79.07 (C-6, -ve), 104.07 (C-10), 110.45 (C-12), 162.76 (C-2).

Mass Spectrum, m/z (relative intensity): 278 (M^+, 0.9), 260 (8.0), 240 (6.5), 207 (105), 128 (100.0).

Exact Mass Calcd. for $C_{17}H_{26}O_3$: 278.1882, found: 278.1884.

Table 6. ^1H NMR (400 MHz, $CDCl_3$), COSY (200 MHz, $CDCl_3$) and nOe (400 MHz, $CDCl_3$) data for the alcohol **135**.

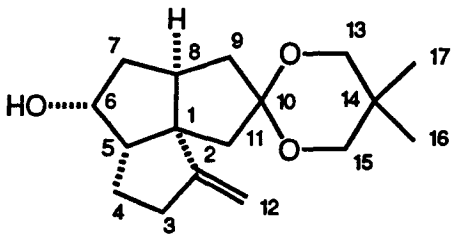
Assignment H-x	^1H NMR (400MHz, $CDCl_3$) δ	COSY correlations[a]	nOe correlations
H-4β	1.85	H-4α, H-5	
H-4α	1.37	H-4β, H-5	1.85 (H-4β) 3.84 (H-6)
H-5	2.20	H-4α & β, H-6	
H-6	3.84	-OH, H-5, H-7α & β	1.37 (H-4α) 2.14 (H-7α or β) 2.30 (H-8) 3.06 (-OH)
-OH	3.06	H-6	3.84 (H-6)
H-7α or β	1.67	H-6, H-7α or β	2.14 (H-7α or β) 3.84 (H-6)
H-7α or β	2.14	H-6, H-7α or β	
H-11α or β	2.06	H-11β or α	2.45 (H-11)
H-11β or α	2.45	H-11α or β	2.06 (H-11)
H-13 & H-15	3.44 & 3.51	H-16 & H-17	
H-16 & H-17	0.91 & 0.99	H-13 & H-15	

a) Only those COSY correlations that could be unambigously assigned are recorded

Table 17. Decoupling experiments (400 MHz, $CDCl_3$) data for the alcohol **135**

irradiated signals		observed signals	
assignment H-x	^{1}H NMR (400 MHz, $CDCl_3$)	δ ppm (mult., H-x)	mult. after irradiation
H-4α	1.37	1.85 (m, H-4β)	sharpened m
H-7α or β	1.67	2.14 (m, H-7α or β)	sharpened m
H-4β	1.85	1.37 (m, H-4α) 2.30 (m, H-3) 2.36 (m, H-3)	sharpened m sharpened m sharpened m
-OH	3.06	3.84 (m, H-6)	q (*J*=4.9 Hz)

5.2.1.7 Preparation of the Alcohol **136**



136

To a cold (-78 °C), stirred solution of L-Selectride (Aldrich) (400 μL of a 1.0 M solution in THF, 0.4 mmol, 2.0 equiv.) in 5 mL of dry THF was added a solution of the ketone **99** (55 mg, 0.20 mmol, 1 equiv.) in 2 mL of dry THF. After the solution had been stirred at -78 °C for 3 hr, a 5% solution of KOH in MeOH (30 μL) was added followed by 60 μL of H_2O_2 (30% wt. solution in water). The reaction mixture was filtered through a short column of Florisil, and eluted with Et_2O. The combined filtrates were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (1 cm x 6 cm silica gel column, eluting with 3:1

petroleum ether/ether) of the crude material produced 51 mg (92%) of the alcohol **136** as a white solid. Recrystallization (pentane) provided white needles that exhibited m.p. 80-82 °C.

IR (KBr): 3213, 2956, 1655, 1109 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.89, 0.98 (s, s, 3H each, Me-16 and Me-17), 1.33 (br s, 1H, -OH, exchanges with D_2O), 1.61 (m, 1H, H-4α or β), 1.68 (m, 1H, H-4α or β), 1.80 (m, 3H, H-7α and β, H-9α or β), 2.07 (d, 1H, H-11α or β, *J*=13.8 Hz), 2.17 (d, 1H, H-9α or β, *J*=12.1 Hz), 2.19 (d, 1H, H-11α or β, *J*=13.8 Hz), 2.33-2.47 (m, 4H, H-3α and β, H-5, H-8), 3.44 (dd, 4H, ketal CH_2's, *J*=11.5 Hz), 4.43 (q, 1H, H-6, *J*=6.6 Hz), 4.81 (s, 1H, H-12), 4.88 (s, 1H, H-12).

Detailed ^1H NMR data, including those derived from COSY experiments, are given in **Table 18**.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.45 (C-16, -ve), 22.63 (C-17, -ve), 23.83 (C-4), 29.95 (C-14), 35.06 (C-7), 40.11 (C-9 or C-11), 41.81 (C-9 or C-11), 46.73 (C-8, -ve), 48.13 (C-3), 57.46 (C-5, -ve), 60.67 (C-1), 72.05 (C-13 and C-15), 74.86 (C-6, -ve), 103.57 (C-12), 109.34 (C-10), 163.34 (C-2).

Mass Spectrum, m/z (relative intensity): 278 (M^+, 2.6), 260 (18.2), 240 (8.0), 207 (15.7), 128 (100.0).

Exact Mass Calcd. for $C_{17}H_{26}O_3$: 278.1882, found: 278.1883.

Table 18. ^{1}H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the alcohol **136**

Assignment H-x	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-4α or β	1.61	H-4α or β
H-4α or β	1.68	H-4α or β
H-6	4.43	H-7α & β
H-7α & β, H-9α or β	1.80	H-6, H-9α or β
H-9α or β	2.17	H-8, H-9β or α
H-11α or β	2.07	H-11β or α
H-11β or α	2.19	H-11α or β
ketal CH_2's	3.44	H-16 & H-17
H-16 & H-17	0.89 & 0.98	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

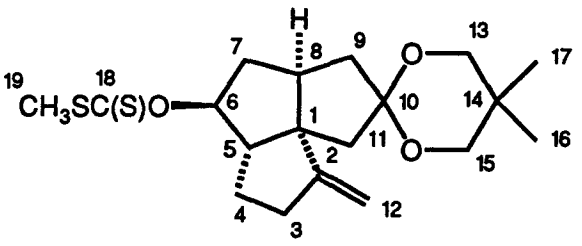
5.2.1.8 Sodium Borohydride Reduction of the Ketone **99**

To a cold (0 °C), stirred solution of the ketone **99** (352 mg, 1.28 mmol, 1.0 equiv.) in 1% KOH in MeOH (25 mL) was added solid $NaBH_4$ (75.2 mg, 1.9 mmol, 1.5 equiv.). After the reaction mixture had been stirred at 0 °C for 20 min, the MeOH was evaporated under reduced pressure and the residue partitioned between brine and Et_2O. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield 345.1 mg (97%) of alcohols **135** and **136**, as a 3:1 mixture of epimers.[89]

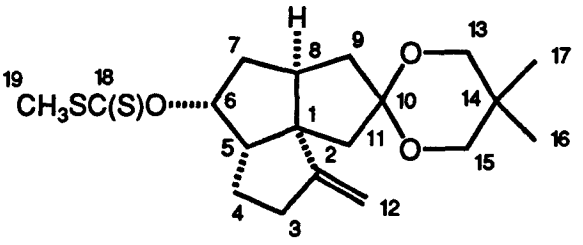
5.2.1.9 DIBAL-H Reduction of the Ketone **99**

To a cold (-78 °C), stirred solution of DIBAL-H (420 μL of 1.0 M solution in hexanes, 0.42 mmol, 2.0 equiv.) in 10 mL of dry THF was added a solution of the ketone **99** (58.6 mg, 0.21 mmol, 1 equiv.) in 2 mL of dry THF. After the solution had been stirred at -78 °C for 3 hr, a 5% solution of KOH in MeOH (30 μL) was added followed by 60 μL of H_2O_2 (30% wt. solution in water). The mixture was filtered through a short column of Florisil, and eluted with Et_2O. The combined filtrates were dried ($MgSO_4$) and concentrated under reduced pressure to provide 55.5 mg (95%) of alcohols **135** and **136**, as a 1:4 mixture of epimers.[89]

5.2.1.10 Preparation of the Methyl Xanthates **137** and **138**



137



138

To a cold (0 °C), stirred solution of the alcohols **135** and **136** (approx. 3:1 mixture of epimers) (217 mg, 0.78 mmol, 1.0 equiv.) in 10 mL of dry THF was added solid KH (56.2 mg, 2.34 mmol, 3.0 equiv.) in one portion. After the mixture had been stirred at rt for 2 hr, freshly distilled CS_2 (59 μL, 0.98 mmol, 1.25 equiv.) was added and the resulting mixture was stirred for an additional 1 hr. Freshly distilled

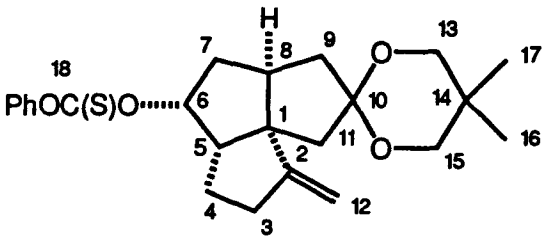
MeI (61 μL, 0.98, 1.25 equiv.) was added and the mixture was stirred for an 18 hr period. The reaction mixture was treated with 2 mL of water and 10 mL of Et_2O. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Drip column chromatography (2 cm x 15 cm silica gel column, 3:1 petroleum ether/Et_2O) of the crude product gave 223.8 mg (78%) of the xanthates **137** and **138** as a 3:1 mixture of epimers.[89]

IR (film): 2952, 1651, 1226 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ (signals due to the minor isomer are given in brackets): 0.91, 1.02 (0.92, 1.00) (s, s, 3H each, Me-16 and Me-17), 1.48 (1.60) (m, 1H), 1.90 (1.70) (m, 2H), 2.01-2.12 (m, 2H, both isomers), 2.12-2.50 (m, 7H, both isomers), 2.53 (2.51) (s, 3H, H-19), 2.67 (2.81) (m, 1H, H-6), 3.46-3.55 (m, 4H, ketal CH_2's, both isomers), 4.89 (s, 1H, H-12, both isomers), 4.99 (4.94) (s, 1H, H-12).

Mass Spectrum, m/z (relative intensity): 368 (M^+, 7.8), 261 (78.9), 175 (79.9), 149 (55.3), 128 (100.0), 91 (35.2).

5.2.1.11 Preparation of the Phenyl Thionocarbonate **149**



149

To a stirred solution of the alcohol **136** (45.3 mg, 0.16 mmol, 1.0 equiv.) in 8 mL of dry acetonitrile were added DMAP (80 mg, 0.65 mmol, 4.0 equiv.) and phenyl chlorothionocarbonate (33 μL, 0.24 mmol, 1.5 equiv.). After the reaction mixture had been stirred for 24 hr at rt, it was concentrated under reduced pressure The residue was partitioned between water (2 mL) and EtOAc (5 mL), and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic extracts were washed with 0.1 M HCl, followed by aqueous $NaHCO_3$ and brine. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Two sequential flash chromatographies (1 cm x 15 cm silica gel column, 3:1 hexanes/Et_2O; 1 cm x 12 cm silica gel column, 5:1 hexanes/Et_2O) of the residue thus obtained, provided 51 mg (76%) of the phenyl thionocarbonate **149** as a white solid that exhibited m.p. 89-91 °C (decomposes).

IR (KBr): 2955, 1775, 1737, 1650, 1594, 1491, 1112 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.91, 0.98 (s, s, 3H each, Me-16 and Me-17), 1.61 (m, 1H, H-4α), 1.71 (m, 1H, H-4β), 1.90 (dd, 1H, H-9β, *J*=13.4, 5.5 Hz), 2.07-2.15 (m, 2H, H-7α and β), 2.19 (m, 3H, H-9α, H-11α and β),

2.31-2.48 (m, 3H, H-3α and β, H-8), 2.79 (q, 1H, H-5, *J*=7.4 Hz), 3.46 (m, 4H, ketal CH_2's), 4.86 (s, 1H, H-12), 4.90 (s, 1H, H-12), 5.81 (q, 1H, H-6, *J*=7.4 Hz), 7.07 (m, 2H, Ph), 7.26 (m, 1H, Ph), 7.38 (m, 2H, Ph).

Detailed ^{1}H NMR data, including those derived from COSY, nOe and decoupling experiments, are given in **Tables 8** and **19**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.47 (C-16, -ve), 22.61 (C-17, -ve), 25.05, 30.03 (C-14), 34.81, 36.30, 41.44, 46.46 (C-5 or C-8, -ve), 48.45, 54.77 (C-5 or C-8, -ve), 60.76, 71.83 (C-13), 72.32 (C-15), 87.37 (C-6, -ve), 104.22, 109.03, 121.87, 121.91 (-ve), 126.40 (-ve), 129.44 (-ve), 153.31, 162.39, 194.64 (C-18).

Mass Spectrum, m/z (relative intensity): 260 (M-PhOC(S)OH, 13.0), 174 (13.3), 128 (79.5).

Exact Mass Calcd. for $C_{24}H_{30}SO_4$: 414.1865, found: 414.1860.

Table 19. Decoupling experiments (400 MHz, $CDCl_3$) data for the phenyl thionocarbonate **149**

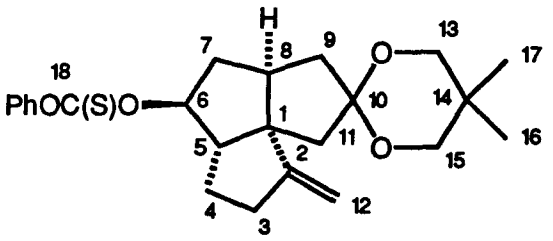
irradiated signals		observed signals	
assignment H-x	^{1}H NMR	^{1}H NMR (mult., *J*, H-x) δ	mult. after irradiation
H-5	2.79	1.61 (m, H-4α) 1.71 (m, H-4β) 5.81 (q, *J*= 7.4, H-6)	sharpened m sharpened m t (*J*=7.4)
H-6	5.81	2.79 (q, *J*= 7.4, H-5) 2.07-2.15 (m, H-7α & β)	t (*J*=7.4) sharpened m
H-8 (H-3α and β also irradiated)	2.31 -2.48	1.71 (m, H-4β) 1.90 (dd, *J*=13.4, 5.5, H-9β) 2.07-2.15 (m, H-7) 2.19 (m, H-9α)	sharpened m d (*J*=13.4) br d sharpened m
H-9β	1.90	2.19 (m, H-9α)	sharpened m
H-9α (H-11 also irradiated)	2.19	1.90 (dd, *J*=13.4, 5.5, H-9β) 2.31-2.48 (m, H-8)	s sharpened m

Table 8. ^1H NMR (400 MHz, $CDCl_3$), COSY (200 MHz, $CDCl_3$) and nOe (400 MHz, $CDCl_3$) data for the phenyl thionocarbonate **149**.

Assignment H-x	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]	nOe correlations
H-4β	1.71	H-5	1.61 (H-4α) 2.79 (H-5)
H-4α	1.61	H-5	
H-5	2.79	H-4α & β, H-6	1.71 (H-4β) 2.19 (H-11β) 5.81 (H-6)
H-6	5.81	H-5, H-7α & β	1.90 (H-9β) 2.07-2.15 (H-7α & β) 2.79 (H-5)
H-7α & β	2.07-2.15	H-6	
H-9β	1.90	H-9α	2.19 (H-9α) 5.81 (H-6)
H-9α	2.19	H-9β	
ketal CH_2's	3.46	H-16 & H-17	
H-16 & H-17	0.91 & 0.98	ketal CH_2's	

a) Only those COSY correlations that could be unambigously assigned are recorded

5.2.1.12 Preparation of the Phenyl Thionocarbonate **148**



148

Using the previously described procedure, the alcohol **135** (1.49 g, 5.36 mmol) was converted to the corresponding phenyl thionocarbonate **148** in 1.57 g (71%) isolated yield. The white solid thus obtained exhibited m.p. 83-86 °C (decomposes).

IR (KBr): 2953, 1784, 1652, 1592, 1491, 1123 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.93, 1.02 (s, s, 3H each, Me-16 and Me-17), 1.60 (m, 1H, H-4α), 1.87 (m, 1H, H-4β), 1.93 (m, 1H, H-7β), 2.07 (m, 1H, H-9α or β), 2.20 (m, 3H, H-11α and β, H-8), 2.32-2.50 (m, 4H, H-3α and β, H-7α, H-9α or β), 2.69 (m, 1H, H-5), 3.49 (m, 4H, ketal CH_2's), 4.91 (m, 1H, H-12), 4.98 (s, 1H, H-12), 5.32 (dd, 1H, H-6, *J*=11.3, 5.7 Hz), 7.10 (m, 2H, Ph), 7.28 (1H, Ph), 7.40 (m, 2H, Ph).

Detailed ^1H NMR data, including those derived from COSY and nOe experiments, are given in **Table 7**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.50 (C-16, -ve), 22.64 (C-17, -ve), 27.48, 30.06 (C-14), 33.24, 36.70, 41.06, 47.96 (C-3), 48.02 (C-8, -ve), 58.22 (C-5, -ve), 60.42 (C-1), 71.97 (C-13), 72.10 (C-15), 90.53 (C-6, -ve), 105.31 (C-12), 109.59 (C-10), 122.00 (Ph, -ve), 126.43 (Ph, -ve), 129.47 (Ph, -ve), 153.34 (Ph), 161.71 (C-2), 194.81 (C-18).

Mass Spectrum, m/z (relative intensity): 414 (M^+, 0.2); 260 (23.9); 175 (24.3); 141 (17.5); 128 (100.0).

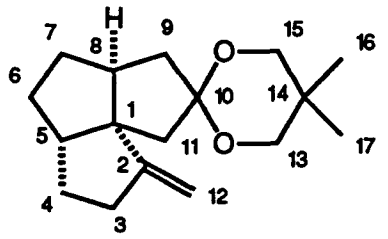
Exact Mass Calcd. for $C_{24}H_{30}SO_4$: 414.1864, found: 414.1864.

Table 7. ^1H NMR (400 MHz, $CDCl_3$), COSY (200 MHz, $CDCl_3$) data and nOe experiments (400 MHz, $CDCl_3$) for the phenyl thionocarbonate **148**.

Assignment H-x	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]	nOe correlations
H-4α	1.60	H-4β, H-5	1.87 (H-4β) 5.32 (H-6)
H-4β	1.87	H-4α, H-5	1.60 (H-4α) 2.69 (H-5)
H-5	2.69	H-4α & β, H-6	1.87 (H-4β) 2.20 (H-11β) 5.32 (H-6)
H-6	5.32	H-5, H-7α and β	1.60 (H-4α) 2.32-2.50 (H-3α & H-7α) 2.69 (H-5)
H-7β	1.93	H-6, H-7α	
ketal CH_2's	3.49	H-16 & H-17	
H-16 & H-17	0.93 & 1.02	ketal CH_2's	

a) Only those COSY correlations that could be unambigously assigned are recorded

5.2.1.13 Preparation of the Alkene **102** from the Xanthates **137/138**



102

To a stirred solution of the methyl xanthates **137** and **138** (3:1 ratio, 190 mg, 0.52 mmol, 1.0 equiv.) in 10 mL of dry benzene were added tributyltin hydride (210 μL, 0.78 mmol, 1.5 equiv.) and solid AIBN (10 mg, 0.06 mmol, 0.12 equiv.). After the reaction mixture had been heated to reflux for a 2 hr, the solution was concentrated under reduced pressure. Two consecutive flash chromatographies (2 cm x 15 cm silica gel column, eluting with 50 mL of petroleum ether followed by a 1 cm x 15 cm silica gel column eluting with 10:1 petroleum ether/Et_2O) of the residue thus obtained, produced a colorless oil. Distillation (80 °C/0.1 mmHg) of the crude product provided 67.8 mg (50%) of the ketal alkene **102** as a colorless oil.

IR (neat): 2954, 1728, 1650, 1123 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.91, 1.02 (s, s, 3H each, Me-16 and Me-17), 1.28 (m, 1H), 1.37 (m, 1H), 1.46 (m, 1H), 1.69-1.82 (m, 3H), 1.88 (m, 1H), 2.02 (d, 1H, H-11β, *J*=14.0 Hz), 2.16 (ddd, 1H, H-9α, *J*=13.5, 8.7, 1.8 Hz), 2.25 (d, 1H, H-11α, *J*=14.0, 1.8 Hz), 2.24-2.42 (m, 4H, H-3α and β, H-9β), 3.45 (s, 2H, ketal CH_2), 3.46 (d, 1H, ketal CH_2, *J*=11.0 Hz), 3.52 (d, 1H, ketal CH_2, *J*=11.0 Hz), 4.83 (br s, 1H, H-12), 4.91 (br s, 1H, H-12).

Detailed ^{1}H NMR data, including those derived from COSY and nOe experiments, are given in **Table 20**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.47 (C-16, -ve), 22.68 (C-17, -ve), 29.66, 30.02 (C-14), 30.92, 31.40, 34.35 (C-9 or C-11), 47.98 (C-3), 50.80 (C-8, -ve), 53.69 (C-5, -ve), 61.84 (C-1), 71.89 (C-13), 72.13 (C-15), 104.07 (C-12), 109.61 (C-10),163.42 (C-2).

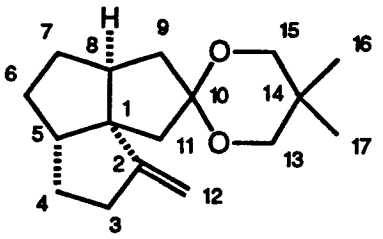
Mass Spectrum, m/z (relative intensity): 262 (M^+, 8.6), 167 (11.5, (128, 100.0), 119 (10.9).

Exact Mass Calcd. for $C_{17}H_{26}O_2$: 262.1932, found: 262.1930.

Table 20. Decoupling experiments (400 MHz, $CDCl_3$) on the ketal alkene **102**

irradiated signals		observed signals	
assignment H-x	^{1}H NMR (400 MHz, $CDCl_3$) δ	^{1}H NMR (mult., *J*, H-x)	mult. after irradiation
	1.88	1.37 (m) 1.46 (m) 1.69-1.82 (m, 3H)	sharpened m sharpened m sharpened m
H-11β	2.02 (d, *J*=14.0)	2.25 (dd, H-11α, *J*=14.0, 1.8)	d (*J*=1.8)
H-9α	2.16 (ddd, *J*=13.5, 8.7, 1.8)	1.69-1.82 (m, 3H) 2.24-2.42 (m, 4H) 2.25 (dd, H-11α, *J*=14.0, 1.8)	sharpened m sharpened m d(*J*=14.0)
H-11α	2.25 (d, *J*=14.0, 1.8)	2.02 (d, H-11β, *J*=14.0) 2.16 (ddd, H-9α, *J*=13.5, 8.7, 1.8)	s dd (*J*=13.5, 8.7)
H-12	4.91 (br s)	2.24-2.42	sharpened m

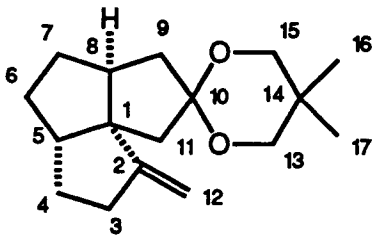
5.2.1.14 Preparation of the Alkene **102** from the Phenyl Thionocarbonate **148**



102

To a stirred solution of the phenyl thionocarbonate **148** (772 mg, 1.87 mmol, 1 equiv.) in dry benzene (50 mL) were added tributyltin hydride (1.0 mL, 3.73 mmol, 2 equiv.) and solid AIBN (15 mg, 0.1 mmol). After the reaction mixture had been heated to reflux for 2 hr, the solution was cooled to rt and concentrated under reduced pressure. Two consecutive column chromatographies (3 cm x 15 cm silica gel columns, eluting the first column with petroleum ether, and the second column with 5:1 petroleum ether/Et_2O) of the material thus obtained gave a colorless oil. The crude product thus obtained was distilled (80 °C/0.1 mm Hg) to provide 425 mg (87%) of the alkene **102**. The spectral properties observed for this material were identical with those described for the compound **102** obtained previously (pp 137-138).

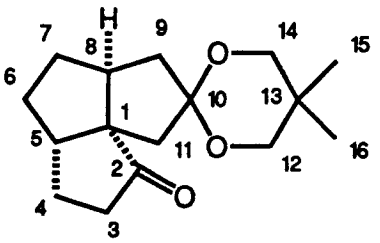
5.2.1.15 Preparation of the Alkene **102** from the Phenyl Thionocarbonate **149**



102

Using the previously described procedure, the phenyl thionocarbonate **149** (193.4 mg) was converted to the alkene **102** in 102.2 mg (83%) isolated yield. The spectral properties observed for this material were identical with those described for the compound **102** obtained previously (pp 137-138).

5.2.1.16 Preparation of the Keto Ketal **103**



103

To a stirred solution of the alkene **102** (101 mg, 0.39 mmol, 1 equiv.), in 6 mL of CCl_4, 6 mL of acetonitrile and 9 mL of water were added solid $NaIO_4 \cdot H_2O$ (329 mg, 1.54 mmol, 4 equiv.) and solid $RuO_2 \cdot xH_2O$ (5.5 mg, 0.04 mmol, 0.03 equiv.). After the reaction mixture had been

stirred at rt for 1 hr, the phases were separated and the aqueous layer was extracted with 2 mL CCl_4. Isopropanol (0.5 mL) was added to the combined organic extracts and stirring was continued at rt for another 1 hr period. The slurry was filtered through a column of Florisil (2 cm x 10 cm, eluting with Et_2O (50 mL)). The combined filtrates were concentrated under reduced pressure. Flash chromatography (1 cm x 12 cm silica gel column, 3:1 petroleum ether/Et_2O) and distillation (100 °C/0.1 mmHg) of the crude product produced 79 mg (79%) of the keto ketal **103** as a colorless oil.

IR (neat): 2952, 1732, 1114 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.92, 0.93 (s, s, 3H each, Me-15 and Me-16), 1.38 (m, 1H, H-7β), 1.54 (m, 1H, H-9β), 1.64 (m, 1H, H-4α or β), 1.87 (m, 1H, H-9α), 1.93-2.07 (m, 5H, H-11α or β, H-4α or β, H-6α and β, H-7α), 2.16 (m, 1H, H-11α or β), 2.23 (m, 1H, H-3α or β), 2.39 (m, 1H, H-3α or β), 2.50 (m, 1H, H-8), 2.55 (m, 1H, H-5), 3.48 (m, 4H, ketal CH_2's).

Detailed ^1H NMR data, including those derived from COSY experiments, are given in **Table 9**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.52 (C-15, -ve), 22.54 (C-16, -ve), 24.00, 29.94 (C-13), 32.48, 33.02, 36.58 (C-3), 39.95 (C-9 or C-11), 42.68 (C-9 or C-11), 47.68 (C-5 or C-8, -ve), 49.35 (C-5 or C-8, -ve), 64.74 (C-1), 71.45 (C-12), 72.67 (C-14), 109.84 (C-10), 224.47 (C-2).

Mass Spectrum, m/z (relative intensity): 264 (M^+, 4.3), 208 (21.6), 128 (100.0), 123 (24.2), 95 (13.5).

Exact Mass Calcd. for $C_{16}H_{24}O_3$: 264.1726, found: 264.1728.

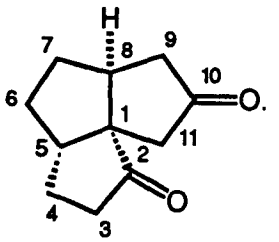
Anal. Calcd. for $C_{16}H_{24}O_3$: C 72.69%; H 9.15%, found: C 72.43%; H 9.04%.

Table 9. ^{1}H NMR and COSY (400 MHz, $CDCl_3$) data for the keto ketal **103**.

H-x (assignment)	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-3α or β	2.23	H-3α or β, H-4α & β
H-3α or β	2.39	H-3α or β, H-4α & β
H-4α or β	1.64	H-3α & β, H-4α or β, H-5
H-5	2.55	H-4α and β, H-6α and β
H-7β	1.38	H-7α, H-9β
H-9β	1.54	H-7β, H-8, H-9α
H-8	2.50	H-7α, H-9α and β
H-9α	1.87	H-7α, H-8, H-9β
ketal CH_2's	3.48	H-15 & H-16
H-15 & H-16	0.92 & 0.93	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

5.2.1.17 Preparation of Diketone **104**



104

A solution of the keto ketal **103** (46 mg, 0.17 mmol) in a mixture of acetone and 5% aqueous HCl (1:1, 10 mL) was stirred at rt for 20 min. Diethyl ether (5 mL) was added and the phases were separated. The aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organic extracts were washed with water, aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was concentrated under reduced pressure,

and the residual material distilled (90 °C/0.1 mmHg) give 28.9 mg (93%) of the diketone **104** as colorless oil.

IR (neat): 2955, 1741 cm^{-1}.

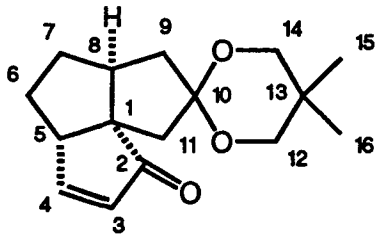
^1H NMR (400 MHz, $CDCl_3$) δ: 1.48 (dd, 1H, *J*=12.0, 6.0 Hz), 1.66 (m, 2H), 2.02-2.18 (m, 5H), 2.32 (ddd, 1H, *J*=18.5, 9.0, 6.0 Hz), 2.50 (ddd, 1H, *J*=16.5, 9.0, 0.5 Hz), 2.56 (m, 1H), 2.65 (dd, 1H, H-11α or β, *J*=18.5, 1.4 Hz), 2.68 (m, 1H), 2.72 (dd, 1H, H-11α or β, *J*=18.5, 1.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.21, 32.41, 33.40, 37.12 (C-3), 44.05 (C-9 or C-11), 45.77 (C-8, -ve), 46.26 (C-9 or C-11), 49.01 (C-5, -ve), 62.87 (C-1), 217.08 (C-10), 222.01 C-2).

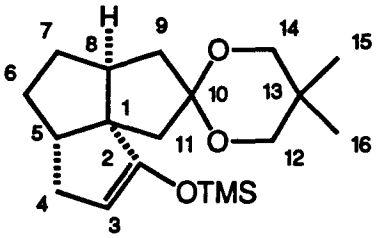
Mass Spectrum, m/z (relative intensity): 178 (M^+, 60.6), 150 (13.9), 136 (100.0), 123 (85.9).

Exact Mass Calcd. for $C_{11}H_{14}O_2$: 178.0994, found: 178.0994.

5.2.1.18 Preparation of the Enone Ketal **156** *via* the Enol Silyl Ether **155**



156



155

To a cold (-78 °C), stirred solution of the keto ketal **103** (360 mg, 1.36 mmol, 1.0 equiv.) in 100 mL of dry CH_2Cl_2 were added freshly distilled Et_3N (568 µL, 4.08 mmol, 3.0 equiv.) and Me_3SiI (387 µL, 2.7 mmol, 2.0 equiv.). After the mixture had been stirred at -78 °C for 2 hr, a saturated aqueous $NaHCO_3$ solution (20 mL) was added. The phases were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to gave the enol silyl ether **155**. IR (neat): 2953, 1645, 1113 cm^{-1}. This product was used without further purification.

To a stirred solution of $Pd(OAc)_2$ (305 mg, 1.36 mmol) in 100 mL of dry acetonitrile was added a solution of the crude enol silyl ether **155** in dry acetonitrile (5 mL). After the mixture had been stirred at rt for 2 hr, it was filtered through a short column of Florisil (1 cm x 5 cm, elution with Et_2O (50 mL)). Concentration of the filtrate under reduced pressure, followed by a flash chromatography (2 cm x 12 silica gel column, elution with 10:1 petroleum ether-EtOAc) of the residual

material, gave 264.2 mg (74%) of the enone ketal **156** as a white solid. Recrystalization (hexane) provided material that exhibited m.p. 87-88 °C.

IR (KBr): 2949, 1697, 1584, 1122 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.95, 1.01 (s, s, 3H each, H-15 and H-16), 1.52 (m, 3H), 1.79 (ddd, 1H, H-9α or β *J*=14.0, 7.0, 1.5 Hz), 2.11 (d, 1H, H-11α or β, *J*=14.0 Hz), 2.15 (m, 1H), 2.26 (ddd, 1H, H-9α or β, *J*=14.0, 10.0, 1.0 Hz), 2.43 (d, 1H, H-11α or β, *J*=14.0 Hz), 2.54 (m, 1H, H-8), 3.08 (br d, 1H, H-5, *J*=9.0 Hz), 3.50 (s, 2H, ketal CH_2), 3.47 (d, 1H, ketal CH_2, *J*=11.5 Hz), 3.56 (d, 1H, ketal CH_2, *J*=11.5 Hz), 6.14 (dd, 1H, H-3, *J*=5.5, 2.0 Hz), 7.43 (dd, 1H, H-4, *J*=5.5, 2.5 Hz).

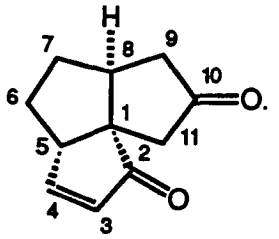
^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.42 (C-15, -ve), 22.56 (C-16, -ve), 27.05 (C-6 or C-7), 29.71 (C-6 or C-7), 30.00 (C-13), 40.94 (C-9 or C-11), 41.51 (C-9 or C-11), 46.35 (C-8, -ve), 55.26 (C-5, -ve), 63.29 (C-1), 71.97 (C-12), 72.38 (C-14), 109.27 (C-10), 133.17 (C-3, -ve), 166.39 (C-4, -ve), 212.83 (C-2).

Mass Spectrum, m/z (relative intensity): 262 (M^+, 81.6), 234 (16.6), 221 (11.7), 208 (11.9), 177 (27.1), 167 (59.1), 128 (100.0).

Exact Mass Calcd. for $C_{16}H_{22}O_3$: 262.1571, found: 262.1570.

Anal. Calcd. for $C_{16}H_{22}O_3$: C 73.25%; H 8.45%, found: C 73.06%; H 8.38%.

5.2.1.19 Preparation of the Enedione **157**



157

A solution of the enone ketal **156** (26.4 mg, 0.1 mmol) in a mixture of acetone and 5% aqueous HCl (1:1, 4 mL) was stirred at rt overnight. The reaction mixture was diluted with Et_2O (2 mL). The phases were separated and the aqueous layer extracted with Et_2O (3 x 3 mL). The combined extracts were washed with water, aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was concentrated under reduced pressure to gave 16.4 mg (93%) of the desired enedione **157** as a white solid. Recrystalization (hexane) provided white needles that exhibited m.p. 82-83 °C.

IR (KBr): 2929, 1739, 1702, 1584 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.70 (m, 3H, H-7α and β, H-6α), 2.05 (m, 2H, H-6β, H-9α or β), 2.33 (d, 1H, H-11α or β, *J*=18.7 Hz), 2.70 (m, 2H, H-8 and H-9α or β), 2.86 (d, 1H, H-11α or β, *J*=18.7, 1.1 Hz), 3.19 (br d, 1H, H-5, *J*=9.0 Hz), 6.24 (dd, 1H, H-3, *J*=5.7, 1.7 Hz), 7.55 (dd, 1H, H-4, *J*=5.7, 2.6 Hz).

Detailed ^1H NMR data, including those derived from COSY and nOe experiments, are given in **Table 10**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.04 (C-6 or C-7), 29.82 (C-6 or C-7), 42.70 (C-9), 44.11 (C-8, -ve), 46.39 (C-11), 54.47 (C-5, -ve), 61.57 (C-1), 133.28 (C-3, -ve), 166.06 (C-4, -ve), 212.00 (C-2), 217.50 (C-10).

Mass Spectrum, m/z (relative intensity): 176 (M^+, 81.6), 148 (23.0), 135 (77.2), 122 (30.4), 107 (65.1), 91 (100).

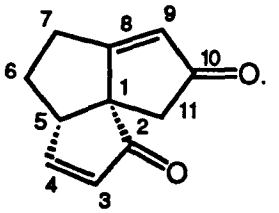
Exact Mass Calcd. for $C_{11}H_{12}O_2$: 176.0837, found: 176.0839.

Table 10. ^1H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the enedione **157**.

H-x (assignment)	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-3	6.24	H-4, H-5
H-4	7.55	H-3, H-5
H-5	3.19	H-3, H-4, H-6β
H-8, H-9α or β	2.70	H-7α & β, H-11α or β
H-11α or β	2.33	H-11α or β
H-11α or β	2.86	H-11α or β

a) Only those COSY correlations that could be unambigously assigned are recorded

5.2.1.20 Preparation of the Dienedione **98**



98

To a stirred solution of the enedione **157** (94.5 mg, 0.54 mmol, 1.0 equiv.) in dry benzene (20 mL) heated to reflux, was added solid benzeneseleninic anhydride (272 mg, 0.76 mmol, 1.4 equiv.) in small portions (every 5-7 min.) over a period of 3 hr and 15 min. After the reaction mixture had been stirred at 80 °C for a further 15 min, it was cooled and concentrated to a small volume under reduced pressure. Drip column chromatography (TLC grade silica gel without binder,[63] 10 g, (2.5 cm x 5 cm column), elution first with hexane until PhSeSePh was eluted, then with Et_2O until the enedione **157** was eluted, and finally with EtOAc to elute the dienedione **98**) of the residual material, gave 35.2 mg (38%) of the dienedione **98** as a white solid that exhibited m.p. 125-128 °C, and 40.5 mg (43%) of the recovered enedione **157** as a white solid.

The overall yield of the dienedione **98** was 54.8 mg (59%) after recycling twice the enedione **157**.

IR (KBr): 2926, 1713, 1630, 1585 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 2.10 (m, 2H, H-6β and H-7β), 2.27 (m, 1H, H-6α), 2.39 (d, 1H, H-11α or β, *J*=16.8 Hz), 2.59 (m, 1H, H-7α), 2.63 (d, 1H, H-11α or β, *J*=16.8 Hz), 3.33 (ddd, 1H, H-5, *J*=3.0, 1.3, 1.2 Hz),

6.02 (d, 1H, H-9, *J*=1.9 Hz), 6.32 (dd, 1H, H-3, *J*=5.6, 1.3 Hz), 7.78 (dd, 1H, H-4, *J*=5.6, 3.0 Hz).

Detailed ^{1}H NMR data, including those derived from COSY experiments, are given in **Table 11**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.77 (C-6 or C-7), 29.85 (C-6 or C-7), 46.36 (C-11), 48.34 (C-5, -ve), 67.42 (C-1), 125.65 (C-9, -ve), 132.80 (C-3, -ve), 166.45 (C-4, -ve), 182.81 (C-8), 207.65 (C-2 or C-10), 208.35 (C-2 or C-10).

Mass Spectrum, m/z (relative intensity): 174 (M^+, 91.7), 146 (59.0), 117 (100.0), 91 (74.9).

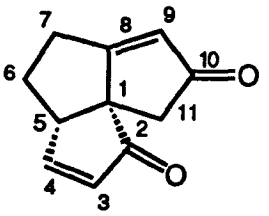
Exact Mass Calcd. for $C_{13}H_{18}O_3$: 174.0681, found: 174.0681.

Table 11. ^{1}H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the dienedione **98**.

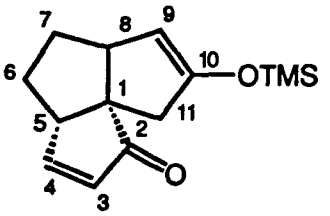
H-x (assignment)	^{1}H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-3	6.32	H-4
H-4	7.78	H-3
H-6α	2.27	H-7α
H-7α	2.59	H-6α
H-11α or β	2.39	H-11β or α
H-11β or α	2.63	H-11α or β

a) Only those COSY correlations that could be unambigously assigned are recorded

5.2.1.21 Preparation of Dienedione **98** *via* the Enol Silyl Ether **164**



98

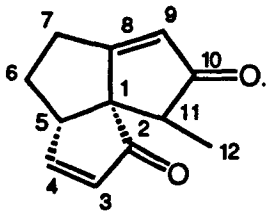


164

To cold (-78 °C) solution of lithium tetramethylpiperidide (0.033 mmol; 1.1 eq) in 2.5 mL THF was added the enedione **157** (5.6 mg, 0.03 mmol, 1 eq.), followed by Me_3SiCl (38 mL, 0.3 mmol, 10 eq.). After the mixture had been stirred at -78 °C for 10 min, the reaction was quenched by addition of Et_3N (0.5 mL), followed by a saturated aqueous $NaHCO_3$ solution (0.5 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2x1 mL). The organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. This material was used immediately in the following step.

To a solution of $Pd(OAc)_2$ (7.1 mg; 0.03 mmol) in 4 mL of dry DMF at rt was added a solution of the crude enol silyl ether **163** in dry DMF (1 mL). After the reaction mixture had been stirred at rt for 2 hr, it was filtered through a short column of Florisil (1 cm x 3 cm). The column was eluted with Et_2O (15 mL) and the combined filtrate was concentrated under reduced pressure. The resultant crude product was purified on silica gel (chromatotron, 1 mm plate, eluting with 90:10 CH_2Cl_2/Et_2O) to give 2.3 mg (42%) of diendione **98**. The spectral properties observed for this material were identical with those described for the compound **98** obtained previously (pp 148-149).

5.2.1.22 Preparation of the 11-Methyl Dienedione **107**



107

To a cold (-78 °C), stirred solution of lithium tetramethylpiperidide (0.046 mmol, 1.1 equiv.) in 3 mL of dry THF, was added a solution of the dienedione **98** (7.3 mg, 0.042 mmol, 1.0 equiv.) in 2 mL of dry THF. After the solution had been stirred at -78 °C for 10 min, freshly distilled iodomethane (103 μL, 2.1 mmol, 50 eq.) was added. The reaction mixture was stirred at -78 °C for an another 10 min period and 1 mL of aqueous $NaHCO_3$ and 1 mL Et_2O were added. The mixture was allowed to warm to rt, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 1 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residual material was dissolved in 0.5 mL of CH_2Cl_2 and purified on silica gel (chromatotron, 1 mm plate, eluting with 45:45:10 hexane/CH_2Cl_2/Et_2O) to give 4.2 mg (53%) of the 11-methyl dienedione **107** as a white solid that exhibited m.p. 134-135 °C.

IR (KBr): 2922, 1710, 1632, 1584 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.10 (d, 3H, H-12, *J*=8.0 Hz), 1.97 (ddd, 1H, H-6β, *J*=13.0, 9.5, 6.5 Hz), 2.09 (m, 1H, H-7β), 2.27 (m, 1H, H-7α, shows coupling with H-9 *J*=2.0 Hz), 2.60 (dd, 1H, H-6α, *J*=13.0, 6.5 Hz),

2.60 (q, 1H, H-11, *J*=8.0 Hz), 3.42 (ddd, 1H, H-5, *J*=9.5, 3.0, 1.5 Hz), 5.96 (d, 1H, H-9, *J*=2.0 Hz), 6.27 (dd, 1H, H-3, *J*=5.8, 1.5 Hz), 7.74 (dd, 1H, H-4, *J*=5.8, 3.0 Hz).

Detailed ^{1}H NMR data, including those derived from decoupling experiments, are given in **Table 13.**

^{1}H NMR (400 MHz, $CDCl_3$-benzene (7:3)) δ: 0.94 (d, 3H, H-12), 1.62 (m, 1H), 1.72 (dd, 1H), 1.98 (m, 1H), 2.26 (dd, 1H), 2.53 (q, 1H, H-11), 3.05 (br d, 1H, H-5), 5.84 (d, 1H, H-9), 6.05 (dd, 1H, H-3), 7.30 (dd, 1H, H-4).

Detailed ^{1}H NMR data, including those derived from COSY and nOe experiments, are given in **Table 12.**

^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.74 (C-12, -ve), 25.88 (C-6 or C-7), 30.11 (C-6 or C-7), 44.22 (C-5 or C-8, -ve), 50.46 (C-5 or C-8, -ve), 69.61 (C-1), 123.3 (C-9, -ve), 132.68 (C-3, -ve), 166.45 (C-4, -ve), 182.06 (C-8), 207.98 (C-2 or C-10), 212.63 (C-2 or C-10).

Mass Spectrum, m/z (relative intensity): 188 (M^+, 100); 173 (11.1); 160 (95.4); 145 (38.5).

Exact Mass Calcd. for $C_{12}H_{12}O_2$: 188.0838, found: 188.0841.

Table 12. ^{1}H NMR, COSY(200 MHz, $CDCl_3$) and nOe (400 MHz, $CDCl_3$-C_6D_6 (7:3)) data for the 11-methyl dienedione **107**

H-x (assign.)	^{1}H NMR (200 MHz, $CDCl_3$)	COSY correlation[a]	^{1}H NMR (400 MHz, $CDCl_3$-C_6D_6(7:3))	nOe correlations
H-3	6.27	H-4	-	-
H-4	7.74	H-3	-	-
H-5	-	-	3.05	0.94 (H-12) 1.62 (H-6β) 7.30 (H-4)
H-11	2.60	H-12	2.53	0.94 (H-12) 3.05 (-ve, H-5) 7.30 (-ve, H-4)
H-12	1.10	H-11	0.94	2.53 (H-11) 3.05 (H-5)

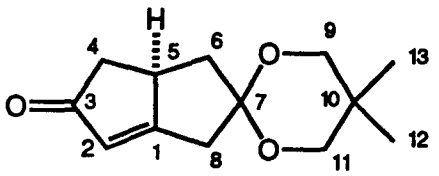
a) Only those COSY correlations that could be unambigously assigned are recorded

Table 13. Decoupling experiments (400 MHz, C_6D_6 and $CDCl_3$) data for the 11-methyl dienedione **107**.

irradiated signals		observed signals	
assignment H-x	^{1}H NMR (400 MHz, C_6D_6)	δ ppm (mult., *J* , H-x)	mult. after irradiation
H-5	2.45	1.05 (m, H-6α or β) 1.10 (m, H-6α or β) 5.75 (dd, (*J*=5.8, 1.5, H-3) 6.60 (dd, (*J*=5.8, 3.0 H-4)	sharpened m sharpened m d (*J*=5.8) d (*J*=5.8)
H-11	2.60	0.75 (q, H-12)	s
assignment H-x	H NMR(400 MHz, $CDCl_3$)	δ ppm (mult., *J* , H-x)	mult. after irradiation
H-4	7.74	3.42 (ddd, *J*=9.5, 3.0, 1.5, H-5) 6.27 (dd, *J*=5.8, 1.5, H-3)	br d d (*J*=1.5)
H-5	3.42	1.97 (ddd, *J*=13.0, 9.5, 6.5, H-6β) 6.27 (dd, *J*=5.8, 1.5, H-3) 7.74 (dd, *J*=5.8, 3.0, H-4)	dd (*J*=13.0, 6.5)) d (*J*=5.8) d (*J*=5.8)
H-6β	1.97	2.09 (m, H-7β) 2.27 (m, H-7α) 2.60 (m, H-6α) 3.42 (ddd, *J*=9.5, 3.0, 1.5, H-5)	sharpened m sharpened m sharpened m br d
H-9	5.96	2.27 (m, H-7α)	sharpened m
H-12	1.10	2.60 (q, *J*=8.0, H-11)	s

5.2.2 Preparation of Enones from Ketones: BSA Method

5.2.2.1 General Procedure: Oxidation of the Keto Ketal **101** to the Enone Ketal **100** (**Table 14**, entry 3)



100

To a heated (80 °C), stirred solution of the keto ketal **101** (27.9 mg, 0.125 mmol, 1 equiv.) in dry benzene (10 mL) was added solid BSA (90 mg, 0.25 mmol, 2 equiv.) in small portions. A few minutes after the first addition, the mixture become yellow due to the formation of PhSeSePh. The reaction was monitored by GLC and was complete upon addition of 2 equivalents of BSA. The reaction mixture was cooled, and concentrated under reduced pressure. The residual material was dissolved in 1 mL of CH_2Cl_2, and purified by a gravity column chromatography (1 cm x 12 cm silica gel column, 1:1 petroleum ether/Et_2O) to give 15.2 mg (55%) of the enone ketal **100** as a white solid, and 4.1 mg (15%) of the recovered ketone **101**. The spectral properties observed for this material were identical with those described for the compound **100** obtained previously (pp 117-118).

5.2.2.2 Oxidation of the Keto Ketal **101** to the Enone Ketal **100** (**Table 14**, entry 1)

To a heated (135 °C), stirred solution of the keto ketal **101** (33 mg, 0.15 mmol, 1 equiv.) in chlorobenzene (10 mL) was added solid BSA (55 mg, 0.16 mmol, 1.1 equiv.) in one portion. The mixture become yellow due to the formation of PhSeSePh. After the reaction mixture had been refluxed for 1.5 hr, it was cooled and concentrated under reduced pressure. The residual material was dissolved in 2 mL of CH_2Cl_2 and purified by a gravity column chromatography (1 cm x 12 cm silica gel column, 1:1 petroleum ether/Et_2O) to give 16 mg (49%) of the enone ketal **100** as a white solid, and 6 mg (18%) of the recovered ketone **101**. The spectral properties observed for this material were identical with those described for the compound **100** obtained previously (pp 117-118).

5.2.2.3 Oxidation of the Keto Ketal **101** to the Enone Ketal **100** (**Table 14**, entry 2)

To a heated (135 °C), stirred solution of the keto ketal **101** (22 mg, 0.1 mmol, 1 equiv.) in chlorobenzene (10 mL) was added solid BSA (72 mg, 0.2 mmol, 2 equiv.) in one portion. The mixture become yellow due to the formation of PhSeSePh. After the reaction mixture had been refluxed for 4 hr, it was cooled and concentrated under reduced pressure. The residual material was dissolved in 2 mL of CH_2Cl_2 and purified by a gravity column chromatography (1 cm x 12 cm silica gel

column, 1:1 petroleum ether/Et_2O) to give 4.5 mg (20%) of the enone ketal **100** as a white solid. The spectral properties observed for this material were identical with those described for the compound **100** obtained previously (pp 117-118).

5.2.2.4 Oxidation of the Keto Ketal **101** to the Enone Ketal **100** (**Table 14**, entry 4)

To a heated (60 °C), stirred solution of the keto ketal **101** (20.3 mg, 0.09 mmol, 1 equiv.) in chloroform (8 mL) was added in small portions BSA (66 mg, 0.18 mmol, 2 equiv.) over a period of 30 min. After the reaction mixture had been refluxed for another 3 hr, it was cooled and concentrated under reduced pressure. A GLC analysis of the mixture showed the presence of the enone ketal **100**, the keto ketal **101**, and two additional products. The residual material was dissolved in 2 mL of CH_2Cl_2 and purified by a gravity column chromatography (1 cm x 12 cm silica gel column, 1:1 petroleum ether/Et_2O) to give 9.9 mg (49%) of the enone ketal **100** as a white solid, and 4.9 mg (24%) of the recovered ketone **101**. The spectral properties observed for this material were identical with those described for the compound **100** obtained previously (pp 117-118).

5.2.2.5 Oxidation of the Keto Ketal **101** to the Enone Ketal **100** (**Table 14**, entry 5)

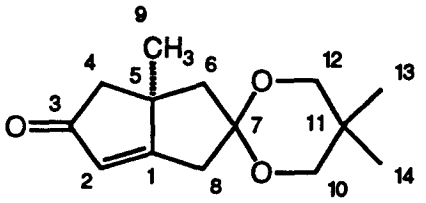
To a heated (40 °C), stirred solution of the keto ketal **101** (30 mg, 0.13 mmol, 1 equiv.) in dichloromethane (10 mL) was added solid BSA (49 mg, 0.14 mmol, 1.1 equiv.) in small portions over a period of 4.5 hr. The reaction mixture was cooled and concentrated under reduced pressure. A GLC analysis of the mixture showed the presence of the enone ketal **100**, the keto ketal **101**, and two additional products. The residual material was dissolved in 2 mL of CH_2Cl_2 and purified by a gravity column chromatography (1 cm x 12 cm silica gel column, 1:1 petroleum ether/Et_2O) to give 13 mg (44%) of the enone ketal **100** as a white solid, and 6.7 mg (22%) of the recovered ketone **101**. The spectral properties observed for this material were identical with those described for the compound **100** obtained previously (pp 117-118).

5.2.2.6 Oxidation of the Keto Ketal **101** to the Enone Ketal **100** (**Table 14**, entry 6)

To a stirred solution of the keto ketal **101** (21 mg, 0.09 mmol, 1 equiv.) in dichloromethane (8 mL) at rt was added solid BSA (51 mg, 0.14 mmol, 1.1 equiv.) in small portions over a period of 1.5 hr. After the reaction mixture had been stirred for 72 hr at 17 °C, it was concentrated under reduced pressure. The residual material was dissolved in 2 mL of CH_2Cl_2 and purified by a gravity column

chromatography (1 cm x 12 cm silica gel column, 1:1 petroleum ether/Et_2O) to give 3.2 mg (15%) of the enone ketal **100** as a white solid. The spectral properties observed for this material were identical with those described for the compound **100** obtained previously (pp 117-118).

5.2.2.7 Preparation of the 5-Methyl Enone **250**



250

To a heated stirred solution of the ketone **133** (18.9 mg, 0.08 mmol, 1.0 equiv.) in 3 mL of dry chloroform at reflux (60 °C) was added a solution of BSA 60.8 mg (0.17 mmol, 2.0 equiv.) in chloroform (15 ml) over the period of 30 min, using a syringe pump. Reflux (60 °C) was continued for another 3 hr period. The material obtained after evaporation of the reaction mixture was dissolved in 1 mL of CH_2Cl_2, and was purified by a gravity column chromatography (1 cm x 12 cm silica gel column, eluting with hexane, followed by 1:1 hexane/Et_2O) to gave 9.6 mg (51%) yield of the enone **250** as a white solid, accompanied with 6.7 mg (35%) of the starting keto ketal **133**.

IR (KBr): 2955, 1708, 1642, 1102 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.96, 1.03 (s, s, 3H each, Me-13 and Me-14), 1.29 (s, 3H, H-9), 1.78 (d, 1H, H-6α or β, J=13.3 Hz), 2.34 (d, 1H, H-

4α or β, *J*=18.7 Hz), 2.38 (d, 1H, H-4α or β, *J*=18.7 Hz), 2.45 (d, 1H, H-6α or β, *J*=13.3 Hz), 2.99 (dd, 1H, H-8α, *J*=17.2, 1.8 Hz), 3.08 (d, 1H, H-8β, *J*=17.2 Hz), 3.46 (d, 2H, ketal CH_2, *J*=7.4 Hz), 3.52 (d, 1H, ketal CH_2, *J*=11.4 Hz), 3.55 (d, 1H, ketal CH_2, *J*=11.4 Hz), 5.83 (d, 1H, H-2, *J*=1.8 Hz).

Detailed ^1H NMR data, including those derived from COSY experiments, are given in **Table 21**.

^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.32 (C-12 and C-13, -ve), 26.67 (C-9, -ve), 29.94 (C-11), 37.66 (C-4), 48.83 (C-5), 49.23 (C-8), 51.92 (C-6), 72.08 (C-10), 72.18 (C-12), 109.19 (C-7), 124.78 (C-2, -ve), 188.81 (C-1), 209.50 (C-3).

Mass Spectrum, m/z (relative intensity): 236 (M^+, 76.5); 221 (11.9); 151 (23.7); 79 (100).

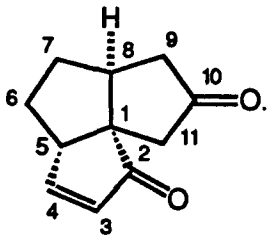
Exact Mass Calcd. for $C_{14}H_{20}O_3$: 236.1413, found: 236.1413.

Table 21. ^1H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the 5-methyl enone **250**.

H-x (assignment)	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-2	5.83	H-8α
H-6α or β	1.78	H-6β or α
H-6β or α	2.45	H-6α or β
H-8α	2.99	H-8β, H-2
H-8β	3.08	H-8α
ketal CH_2's	3.46, 3.52 & 3.55	H-13 & H-14
H-13 & H-14	0.96 and 1.03	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

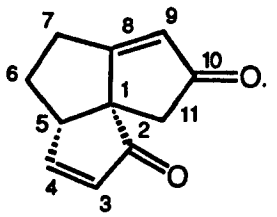
5.2.2.8 Preparation of the Enedione **157**



157

To a heated stirred solution of the diketone **104** (12 mg, 0.7 mmol, 1 equiv.) in 10 mL of dry $CHCl_3$ at reflux (60 °C) was added BSA (49 mg, 0.14 mmol, 2 equiv.) over the period of 30 min. The material obtained after concentration of the reaction mixture was dissolved in 1 mL of CH_2Cl_2, and purified by a gravity column chromatography (1 cm x 12 cm silica gel column, eluting with hexane, followed by 1:1 hexane/Et_2O) to give 4.7 mg (40%) of the enedione **157** as a white solid. The spectral properties observed for this material were identical with those described for the compound **157** obtained previously (pp 146-147).

5.2.2.9 Preparation of the Dienedione **98** from the Diketone **104**

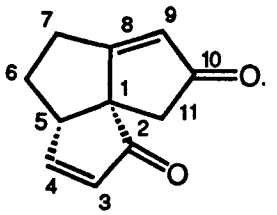


98

To a heated stirred solution of the diketone **104** (8.3 mg, 0.05 mmol, 1 equiv.) dissolved in 10 mL of dry $CHCl_3$ at reflux (60 °C), was

added BSA (78 mg, 0.2 mmol, 4 equiv.) over a 1 hr period. The material obtained after concentration of the reaction mixture was dissolved in 1 mL of CH_2Cl_2 and purified by a gravity column chromatography (1 cm x 15 cm silica gel column, eluting with 1:1 petroleum ether/Et_2O, followed by Et_2O, and finally with EtOAc) to give 1.4 mg (17%) of the dienedione **98** as a white solid. The spectral properties observed for this material were identical with those described for the compound **98** obtained previously (pp 148-149).

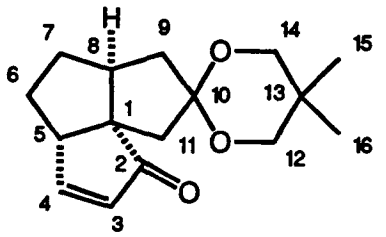
5.2.2.10 Preparation of the Dienedione **98** from the Enedione **157**



98

Using the general procedure 5.2.2.1, the enedione **157** (7.8 mg, 0.044 mmol, 1 equiv.) dissolved in 5 mL of dry benzene at reflux (80 °C), was treated with BSA (96 mg, 0.27 mmol, 6 equiv.) over a 3 hr period. The material obtained after concentration of the reaction mixture was dissolved in 1 mL of CH_2Cl_2, and purified by a gravity column chromatography (1 cm x 23 cm silica gel column, eluting with hexane, followed by 1:1 hexane/Et_2O, and finally with EtOAc) to give 2.5 mg (32%) of the dienedione **98** as a white solid. The spectral properties observed for this material were identical with those described for the compound **98** obtained previously (pp 148-149).

5.2.2.11 Preparation of the Enone Ketal **156**

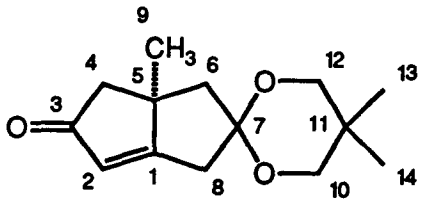


156

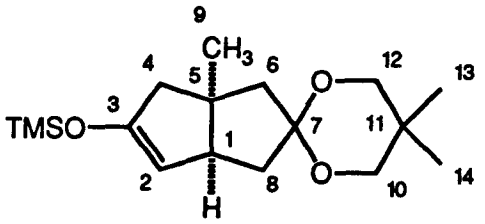
Using the general procedure 5.2.2.1, the keto ketal **103** (28 mg, 0.11 mmol, 1.0 equiv.) dissolved in 10 mL of dry benzene at reflux (80 °C), was treated with BSA (78 mg, 0.22 mmol, 2.0 equiv.). The material obtained after concentration of the reaction mixture was dissolved in 1 mL of CH_2Cl_2, and purified by a gravity column chromatography (2 cm x 5 cm TLC grade silica gel without binder,[63] eluting with hexanes until PhSeSePh was removed, then with 3:1 hexanes/Et_2O) to give 17.2 mg (62%) of the enone ketal **156** as a white solid. The spectral properties observed for this material were identical with those described for the compound **156** obtained previously (pp 144-145).

5.2.3 Preparation of Enones from Ketones: Saegusa Oxidation

5.2.3.1 Preparation of the Enone **250** *via* the Enol Silyl Ether **251**



250



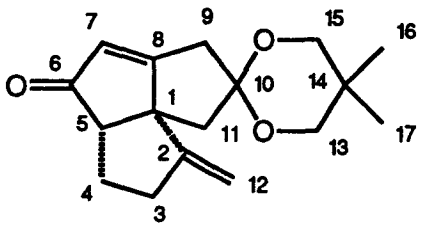
251

To a cold (-78 °C), stirred solution of LDA (0.14 mmol, 1.5 equiv.) in dry THF (4 mL) were added freshly distilled Me_3SiCl (120 μL, 0.9 mmol, 10 equiv.) and a solution of the keto ketal **133** (22 mg, 0.09 mmol, 1 equiv.) in dry THF (1 mL). After the mixture had been stirred at -78 °C for 5 min, freshly distilled Et_3N (1 mL) and saturated aqueous $NaHCO_3$ (1 mL) were added. The mixture was diluted with Et_2O (2 mL) and the phases were separated. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The enol silyl ether **251** (91% by GLC analysis of the crude product) thus obtained was distilled *in vacuo* (110 °C/0.1 mmHg).

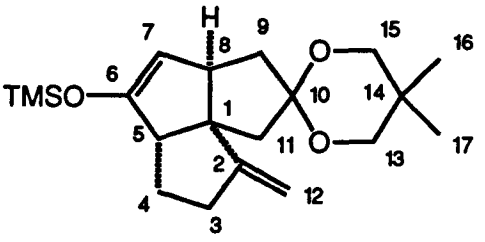
To a stirred solution of $Pd(OAc)_2$ (21 mg, 0.09 mmol) in 7 mL of dry acetonitrile was added a solution of the distilled enol silyl ether **251** in dry acetonitrile (1 mL). After the reaction mixture had been stirred for 5 hr and 30 min, the solution was filtered through a short column of Florisil (2 cm x 5 cm, eluting with 40 mL Et_2O). The combined filtrates were concentrated under reduced pressure. Flash chromatography (1 cm x 20 cm silica-gel column, 1:1 petroleum ether/Et_2O) of the residual

material, gave 9.2 mg (42%) of the enone **250** as a white solid and 2 mg (9%) of the recovered keto ketal **133**. The spectral properties observed for this material were identical with those described for the compound **250** obtained previously (pp 159-160).

5.2.3.2 Preparation of the Tricyclic Dieneone Ketal **252** *via* the Enol Silyl Ether **253**



252



253

To a cold (-78 °C), freshly prepared LDA solution (0.15 mmol, 1.5 equiv.) in dry THF (4 mL) were added freshly distilled Me_3SiCl (126 μL, 1.0 mmol, 10 equiv.) and a solution of the ketone **99** (28 mg, 1.0 mmol, 1 equiv.) in dry THF (1 mL). After the reaction mixture had been stirred at -78 °C for 5 min, freshly distilled Et_3N (1 mL) and saturated aqueous $NaHCO_3$ (1 mL) were added. The mixture was diluted with Et_2O (2 mL). The phases were separated, and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The enol silyl ether **253** thus obtained was distilled *in vacuo* (125 °C/0.1 mmHg). GLC analysis shows the presence of a single enol silyl ether (IR (neat): 2954, 1651, 1120 cm^{-1}). This material was used immediately in the following step.

To a stirred solution of $Pd(OAc)_2$ (23 mg, 1.0 mmol) in 9 mL of dry acetonitrile, was added a solution of the freshly distilled enol silyl ether **253** in dry actetonitrile (1 mL). After the reaction mixture had been stirred for 3 hr, the mixture was filtered through a short column of Florisil (2 cm x 5 cm eluting with 40 mL of Et_2O). Concentration of the filtrate, followed by flash chromatography (1 cm x 20 cm silica gel column, elution with 1:1 petroleum ether/Et_2O) of the residual material, gave 20.3 mg (73%) of the enone **252** as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ: 0.97, 1.01 (s, s, 3H each, Me-16 and Me-17), 1.73 (m, 1H, H-4β), 2.07 (m, 1H, H-4α), 2.19 (d, 1H, H-11α or β, J=14.5 Hz), 2.22 (m, 2H, H-3α and β), 2.61 (d, 1H, H-11α or β, J=14.5 Hz), 2.62 (br s, 1H, H-5), 2.94 (dd, 1H, H-9α, J=15.5, 2.0 Hz), 3.17 (d, 1H, H-9β, J=15.5 Hz), 3.49 (s, 2H, ketal CH_2), 3.53 (d, 1H, ketal CH_2, J=11.5 Hz), 3.58 (d, 1H, ketal CH_2, J=11.5 Hz), 5.00 (br s, 1H, H-12), 5.25 (br s, 1H, H-12), 5.91 (d, 1H, H-7, J=2.0 Hz).

Detailed ^1H NMR data, including those derived from COSY experiments, are given in **Table 22**.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.26 (C-16, -ve), 22.35 (C-17, -ve), 26.66, 29.97 (C-14), 32.63, 38.00, 47.73, 60.92 (C-5, -ve), 61.85 (C-1), 71.92 (C-13), 72.54 (C-15), 108.38 (C-12), 109.12 (C-10), 125.74 (C-7, -ve), 155.12 (C-2), 184.92 (C-8), 212.70 (C-6).

Mass Spectrum, m/z (relative intensity): 274 (M^+, 100); 246 (8.9); 189 (18.0); 186 (18.5); 159 (32.5); 146 (37.9); 128 (56.7); 117 (76.8).

Exact Mass Calcd. for $C_{17}H_{22}O_3$: 274.1569, found: 274.1569.

Table 22. ^1H NMR (400 MHz, $CDCl_3$) and COSY (200 MHz, $CDCl_3$) data for the dienone ketal **252.**

H-x (assignment)	^1H NMR (400 MHz, $CDCl_3$) δ	COSY correlations[a]
H-3α and β	2.22	H-4α and β, H-12
H-4β	1.73	H-3α and β, H-5
H-5	2.62	H-4β
H-7	5.91	H-9α
H-9α	2.94	H-9β, H-7
H-9β	3.17	H-9α
H-11α or β	2.19	H-11β or α
H-11β or α	2.61	H-11α or β
ketal CH_2's	3.49, 3.53 and 3.58	H-16 & H-17
H-16 & H-17	0.97 and 1.01	ketal CH_2's

a) Only those COSY correlations that could be unambigously assigned are recorded

6 References

1. a) G. Wittig, P. Davis, G. Koenig, *Chem. Ber.* ***84***, 627 (1951).
   b) D. Seebach, *Angew. Chem. Int. Ed. Engl.* ***18***, 239 (1979).

2. a) E.J. Corey, *Chem. Soc. Rev.* ***17,*** 111 (1988).
   b) E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*; Wiley: New York, 1989.

3. B. M. Trost, *Science* ***254,*** 1471 (1991).

4. D. Seebach, *Angew. Chem. Int. Ed. Engl.* ***29,*** 1320 (1990).

5. A. Groweiss, W. Fenical, H. Cun-heng, J. Clardy, W. Zhongde, Y. Zhongnian, L. Kanghou, *Tetrahedron Lett.* ***26***, 2379 (1985).

6. Reviews: a) L. A. Paquette, *Top. Curr. Chem.* ***79***, 41 (1979); ***119***, 1 (1984).
   b) L. A. Paquette, A. M. Doherty, *Reactivity and Structure Concepts in Organic Chemistry* ***26,*** 1 (1987).

7. S. Hartmann, J. Neeff, U. Heer, D. Mecke, *FEBS Lett.* ***93***, 339 (1978).

8. J. Brendel and P. Weyerstahl, *Tetrahedron Lett.* ***30***, 2371 (1989).

9. a) Bang-Hua Chen, Ke-Fang Jiao, Qing-E Ji and Hong-Qiang Song, *Journal of Molecular Structure (Teochem)* ***188***, 167 (1989);
   b) Xiefeng Tan, Hejue Ye, Lixian Zeng, Zhenguo Cui and Senyue He, *Zhongguo Haiyang Yaowu* ***9***, 11-12 (1990) (Ch); *Chemical Abstracts* ***115***: 35564g (1991).

10. Reviews: a) M. Ramaiah, *Synthesis*, 529 (1984).
    b) T. Hudlicky, J. D. Price, *Chem. Rev.* ***89***, 1467 (1989).
    c) A. K. Gupta, X. Fu, J. P. Snyder, J. M. Cook, *Tetrahedron* ***47***, 3665 (1991).

11. C. Iwata, Y. Takemoto, M. Doi, T. Imanishi, *J. Org. Chem.* ***53***, 1623 (1988).

12. a) C. Iwata, T. Fusaka, T. Fujiwara, K. Tomita, M. Yamada, *J. Chem. Soc. Chem Commun.*, 463 (1981).

b) C. Iwata, H. Kubota, M. Yamada, Y. Takemoto, S. Uchida, T. Tanaka, T. Imanishi, *Tetrahedron Lett.* ***25***, 3339 (1984).
c) C. Iwata, Y. Takemoto, H. Kubota, T. Kuroda, T. Imanishi, *Tetrahedron Lett.* ***26***, 3231 (1985).

13. Reference 14. note 7.

14. P. Wender, M. deLong, *Tetrahedron Lett.* ***31***, 5429 (1990).

15. P. Wender, S. Singh, *Tetrahedron Lett.* ***31***, 2517 (1990).

16. M. Crimmins, C. Dudek, A. W.-H. Cheung, *Tetrahedron Lett.* ***33***, 181 (1992).

17. M. Crimmins, S. Mascarella, L. Bredon, *Tetrahedron Lett.* ***26***, 997 (1985).

18. M. Crimmins, S. Mascarella, *Tetrahedron Lett.* ***28***, 5063 (1987).

19. L. A. Paquette, P. G. Meister, D. Friedrich, and D. R. Sauer, *J. Am. Chem. Soc.* ***115***, 49 (1993).

20. L. N. Mander and S. P. Sethi, *Tetrahedron Lett.* ***24***, 5425 (1983).

21. a) Crimmins, M.T., DeLoach, J.A., *J. Am. Chem. Soc.* ***108***, 800 (1986).
b) Crimmins, M.T., DeLoach, J.A., *J. Org. Chem.* ***49***, 2077 (1984).

22. B M. Trost, *Acc. Chem. Res.*, 453-461 (1978).

23. P. Magnus, D. Quagliato, *Organometallics* ***1***, 1243 (1982).

24. R. Boeckman, Jr., D. Blum, *J. Org. Chem.* ***39***, 3307 (1974).

25. M. Shibasaki, T. Mase, and S. Ikegami, *J. Am. Chem. Soc.* ***108***, 2090 (1986).

26. G. Pattenden, S. Teague, *Tetrahedron Lett.* ***23(51)***, 5471 (1982).

27. E. Piers and J. M.. Chong, *J. Chem. Soc. Chem. Commun.*, 934 (1983);
E. Piers and V. Karunaratne, *J. Org. Chem.* ***48***, 1774 (1983).

28. E. Piers and V. Karunaratne, *Tetrahedron* ***45***, 1089 (1989).

29 E. Piers and V. Karunaratne, *Can. J. Chem.* ***62***, 629 (1984).

30. E. Piers and J. Reanud, *Synthesis*, 74 (1992).

31. Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.* ***43***, 1011 (1978); Y. Ito, H. Aoyama, T. Hirao, A. Mochizuki, and T. Saegusa, *J. Am. Chem. Soc.* ***101***, 494 (1979).

32. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc. Perkin I*, 1574 (1975).

33. L. A. Paquette, R. A. Roberts, and G. J. Drtina, *J. Am. Chem. Soc.* ***106***, 6690 (1984).

34. S. H. Bertz, G. Lannoye, and J. M. Cook, *Tetrahedron Lett.* ***26***, 4695 (1985).

35. J. M. Dewanckele, F. Zutterman, and M. Vandewalle, *Tetrahedron* ***39***, 3235 (1983).

36. S. C. Welch, S. Chayabunjonglerd, and A. S. C. P. Rao, *J. Org. Chem.* ***45***, 4086 (1980).

37. S Nozoe, *Tetrahedron Lett.*, 195 (1976).

38. M. J. Knudsen and N. E. Shore, *J. Org. Chem.* ***49***, 5025 (1984).

39. J. Huguet, M. Karpf, and A. S. Dreiding, *Tetrahedron Lett.* ***24***, 4177 (1983).

40. a) J. E. McMurry and W. J. Scott, *Tetrahedron Lett.* ***24***, 979 (1983).
b) W. J. Scott and J. E. McMurry, *Acc. Chem. Res.* ***21***, 47 (1988).

41. a) G. Kubiak, J. M. Cook, U. Weiss, *J. Org. Chem.* ***49***, 561 (1984); S. H. Bertz, J. M. Cook, A. Gawish, and U. Weiss, *Org. Synth* ***64***, 27 (1985).
b) Review: A. K. Gupta, X. Fu, J. P. Snyder, and J. M. Cook, *Tetrahedron* ***47***, 3665 (1991).

42. E. Piers and N. Moss, *Tetrahedron Lett.* ***26***, 2735 (1985); N. Moss, Ph. D. Thesis, UBC, 1985. pp 240-242; B.-A. Story, Ph. D. Thesis, UBC, 1991. p 155.

43. R. D. Miller, D. R. McKaen, *Synthesis*, 730-732 (1979); V. Karunaratne, Ph. D. Thesis, UBC, 1985. pp 184-5.

44. B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, *Tetrahedron* ***40***, 5005 (1984).

45. B. H. Lipshutz, R. S. Wilhelm, *J. Am. Chem. Soc.* ***104***, 4696 (1982); B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, and D. Parker, *J. Org. Chem.* ***49***, 3928 (1984); J. A. Behling, K. A. Babiak, J. S. Ng, A. L. Campbell, R. Moretti, M. Koerner, and B. H. Lipshutz, *J. Am. Chem. Soc.* ***110***, 2641 (1988).

46. J. Roberge, Ph. D. Thesis, UBC, 1993. pp 27-36.

47. R. J. K. Taylor, *Synthesis*, 364 (1985).

48. a) L. Van Hijfte, R. D. Little, J. L. Petersen, and K. D. Moeller, *J. Org. Chem.* ***52***, 4647 (1987); K. Tatsuta, K. Akimoto, and M. Kinoshita, *J. Am. Chem. Soc.* ***101***, 6116 (1979); G. Mehta, A. N. Murthy, D. S. Reddy, and A. V. Reddy, *J. Am. Chem. Soc.* ***108***, 3443 (1986). b) T. Hudlicky, L. Radesca-Kwart, L.-G. Li, and T. Bryant, *Tetrahedron Lett.* ***29***, 3283 (1988).

49. B.-A. Story, Ph. D. Thesis, UBC, 1991. pp 87-92.

50. D. Crich and L. Quintero, *Chem. Rev.* ***89***, 1413 (1989).

51. M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.* ***103***, 932 (1981); M. J. Robins, J. S. Wilson, and F. Hansske, *J. Am. Chem. Soc.* ***105***, 4059 (1983).

52. J. March, *Advanced Organic Chemistry*; Wiley: New York, 1985. pp 896-900.

53. D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.* ***74***, 5828 (1952); M. Chérest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 2201 (1968); W.G. Dauben, G. J. Fonkin, and D. S. Noyce, *J. Am. Chem. Soc.* ***78***, 2579 (1956); W.G. Dauben, E. J. Blanz, J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.* ***78***, 3752 (1956); W. T. Wipke and P. Gund, *J. Am. Chem. Soc.* ***98***, 8107 (1976);

B. M. Trost and P. R. Seoane, *J. Am. Chem. Soc.* ***109***, 615 (1987);
Yun-Dong. Wu and K. N. Houk, *J. Am. Chem. Soc.* ***109***, 908 (1987);
Yun-Dong. Wu, K. N. Houk and B. M. Trost, *J. Am. Chem. Soc.* ***109***, 5560 (1987);
Yun-Dong. Wu and K. N. Houk, *Angew. Chem. Int. Ed. Engl.* ***31***, 1019 (1992).

54. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.* ***46***, 3936 (1981).

55. E. J. Corey and A. W. Gross, *Tetrahedron Lett.* ***25***, 495 (1984).

56. S. Ahmad, M. A. Khan, and J. Iqbal, *Synth. Commun.* ***18***, 1679 (1988).

57. J. Tsuji, I. Minami, and I. Shimizu, *Tetrahedron Lett.* ***24***, 5635 (1983);
I. Minami, K. Takahashi, I. Shimizu, and J. Tsuji, *Tetrahedron* ***42***, 2971 (1986).

58. E. Mincone, G. Ortaggi, and A. Sirna, *Synthesis*, 773 (1977).

59. D. L. J. Clive, *Tetrahedron* ***34***, 1049 (1978).

60. a) D. H. R. Barton, D. J. Lester, and S. V. Ley, *J. Chem. Soc. Chem Commun.*, 130 (1978).
b) D. H. R. Barton, D. J. Lester, and S. V. Ley, *J. Chem. Soc. Perkin Trans I*, 2209 (1980).
c) D. H. R. Barton, J. W. Morzycki, W. B. Motherwell, and S. V. Ley, *J. Chem. Soc. Chem Commun.*, 1044 (1981).

61. D. H. R. Barton and D. Crich, *Tetrahedron* ***41***, 4359 (1985).

62. T. Hori and K. B. Sharpless, *J. Org. Chem.* ***43***, 1689 (1978).

63. Sigma Chemical Co., **S-6628** Silica-Gel for Thin Layer Chromatography, Type H, Size 10-40 μ, binder: none.

64. a) R. A. Lee, C. McAndrews, K. M. Patel and W. Reusch, *Tetrahedron Lett.*, 965 (1973).
b) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.* ***95***, 582 (1973).

65. a) A. E. Derome, *Modern NMR Techcniques for Chemistry Research*; Pergamon: Oxford, 1987. pp 109-111.
b) J. K. M. Sanders and J. D. Mersh, *Prog. NMR Spec.* ***15***, 353 (1983).

66. F. Bohlmann and J. Jakupovic, *Phytochemistry* ***19***, 259 (1980) (the spectra have been errorneously reversed: P. Wender and S. K. Singh, *Tetrahedron Lett.* ***26***, 5987 (1985)).

67. D. H. R. Barton, R. A. H. F. Hui, S. V. Ley, and D. J. Williams, *J. Chem. Soc. Perkin Trans I*, 1919 (1982).

68. D. H. R. Barton, C. R. A. Godfrey, J. W. Morzycki, and W. B. Motherwell, *J. Chem. Soc. Perkin Trans I*, 1947 (1982).

69. S. Turner, *Design of Organic Syntheses*; Elsevier: Amsterdam, 1976; pp 21-22.

70. G. Ayrey, D. Barnard and D. T. Woodbridge, *J. Chem. Soc.*, 2089 (1962).

71. Aldrich Chemical Company, **21,301-2** Benzeneseleninic Anhydride, 70%. Contains ≤ 30% benzeneseleninic acid.

72. S. Uemura and S.-I. Fukuzawa, *J. Am. Chem. Soc.* ***105***, 2748 (1983); review: N. Petragnani and J. V. Comasseto, *Synthesis*, 793-817 and 898-919 (1991).

73. J. Mulzer, H.-J. Altenbach, M. Braun, K. Krohn, H.-U. Reissig, *Organic Synthesis Highlights*; VCH: New York, 1991. pp 126-130.

74. a) D. P. Curan, *Synlett*, 63 (1991).
b) D. P. Curan and S.-C. Kuo, *Tetrahedron* ***43***, 5653 (1987).

75. E. Piers and P. C. Marrais, *J. Org. Chem.* ***55***, 3454 (1990).

76. A. S. Gybin, W.A Smit, R. Caple, A. L. Veretenov, A. S. Shashkov, L. G. Vorontsova, M. G. Kurella, V. S. Chertkov, A. A. Carapetyan, A. Y. Kosnikov, M. S. Alexanyan, S. V. Lindeman, V. N. Panov, A. V. Maleev, Y. T. Struchkov and S. M. Sharpe, *J. Am. Chem. Soc.* ***114***, 5555 (1992).

77. M. Rosenblum, *J. Am. Chem. Soc.* ***79***, 3179 (1957).

78. T. Morita, S. Yoshida, Y. Okamoto, and H. Sakurai, *Synthesis*, 379 (1979).

79. M. Rowley and Y. Kishi, *Tetrahedron Lett.* ***29***, 4909 (1988); M. Rowley, M. Tsukamoto, and Y. Kishi, *J. Am. Chem. Soc.* ***111***, 2735 (1989).

80. a) E. Negishi, D. R. Swanson, F. E. Cederbaum, and T. Takahashi, *Tetrahedron Lett.* ***28***, 917 (1987).
b) T. V. Rajan Babu, W. A. Nugent, D. F. Taber, and P. J. Fagan, *J. Am. Chem. Soc.* ***110***, 7128 (1988).
c) review: N. E. Shore, *Chem. Rev.* ***88***, 1081 (1988).

81. W. A. Smit, A. S. Gybin, A. S. Shashkov, Y. T. Strychkov, L. G. Kyz'mina, G. S. Mikaelian, R. Caple, and E. D. Swanson, *Tetrahedron Lett.* ***27***, 1241 (1986).

82. a) P. Weyerstahl, H. Marschall-Weyerstahl, M. Schröder, J. Brendel, and V. K. Kaul, *Phytochemistry* ***30***, 3349 (1991).
b) J. Jakupovic, C. Zdero, L. Paredes, and F. Bohlmann, *Phytochemistry* ***27***, 2881 (1988).

83. A. P. Marchand and V. Vidyasagar, *J. Org. Chem.* ***53***, 4412 (1988).

84. S. L. Patt, J. N. Shoolery, *J. Magn. Res.* ***46***, 535 (1982).

85. Reference 65a. pp 97-127.

86. W. P. Aue, E. Barthold, R. R. Ernst, *J. Chem. Phys.* ***24***, 2229 (1975).

87. W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* ***41***, 1879 (1976).

88. P. G. M. Wuts, *Synth. Commun.* ***11***, 139 (1981).

89. As determined from analysis of ^{1}H NMR spectra.

90. W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* ***43***, 2923 (1978).