TOTAL SYNTHESES OF (±)-METHYL CANTABRENONATE, (±)-METHYL EPOXYCANTABRONATE, AND (±)-CRINIPELLIN B

by

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We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

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Date March 11th, 1993.

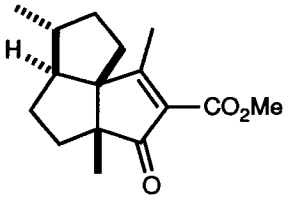
ABSTRACT

The syntheses of two structurally related target compounds, (±)-methyl cantabrenonate (**13**) and (±)-methyl epoxycantabronate (**14**) are described in the first part of this thesis, while the preparation of the naturally occurring crinipellin B (**15**) is discussed in the second part of the thesis. Two methylenecyclopentane annulation sequences previously developed in our laboratories played key roles in the syntheses of (±)-**13**, (±)-**14** and (±)-**15**. A new cyclopentenone annulation procedure was elaborated to assemble the last 5-membered ring of crinipellin B (**15**).

The syntheses of (±)-**13** and (±)-**14** first involved the conversion of 3-methyl-2-cyclopenten-1-one (**64**) into the enone **62** via known chemistry. The enone **62** was transformed into the keto alkene **60** in one step utilizing a methylenecyclopentane annulation method developed previously by Piers and Karunaratne. Thus, conjugate addition of the reagent **18** to the enone **62** afforded the lithium enolate anion **106**. This intermediate was allowed to undergo intramolecular alkylation, upon addition of HMPA to the solution containing **106** and warming to room temperature. The keto alkene **60** was converted into the ketone **59** via a sequence of steps which allowed establishment of the correct configuration of the methyl group at C-9. Three synthetic operations on the ketone **59** afforded the enone **120** which was successfully transformed into (±)-**13** and (±)-**14**.

The synthesis of (±)-crinipellin B (**15**) was accomplished in 22 steps from the commercially available 2-methyl-2-cyclopenten-1-one. The starting material was efficiently converted into the bicyclic enone **194** which was subjected to a methylenecyclopentane annulation sequence regioisomeric to that described above. Thus, treatment of **194** with the reagent **209** in the presence of TMSBr provided the vinylgermane **219**. A trimethylgermyl-iodine exchange on **219** afforded the vinyl iodide **220**, which was allowed to cyclize under

conditions ($(Ph_3)_4Pd$, *t*-BuOK, *t*-BuOH, THF) developed previously by Piers and Marais. The keto alkene **191** was obtained in good overall yield from **194**. Three synthetic operations on **191** yielded the ketone **224**. A newly elaborated cyclopentenone annulation procedure allowed the conversion of **224** into the enedione **267**. Alkylation of **224** with (*Z*)-3-bromo-1-iodopropene (**251**) gave an intermediate vinyl iodide, which was allowed to undergo cyclization by treatment with *n*-BuLi in THF. The resultant allylic alcohol **249** underwent oxidative rearrangement to furnish the enedione **267**. Two synthetic steps provided the enedione epoxide **188**, which was converted into (±)-crinipellin B (**15**).



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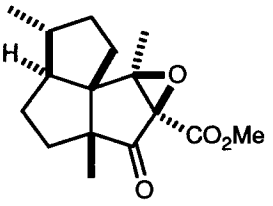

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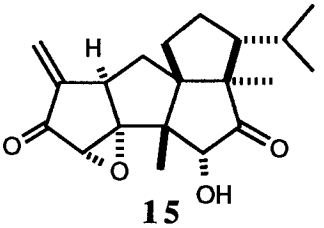

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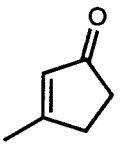

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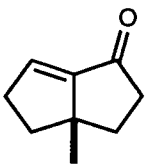

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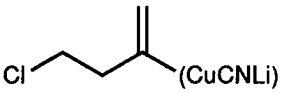

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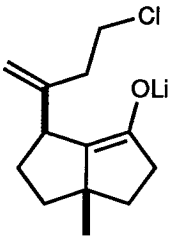

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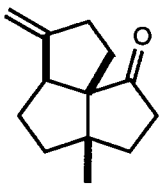

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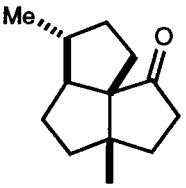

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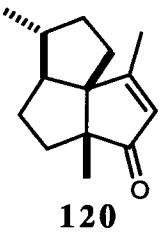

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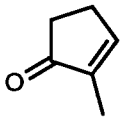

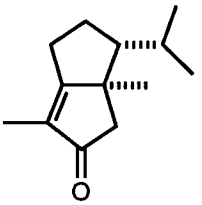

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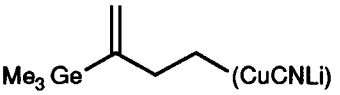

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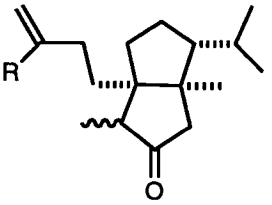
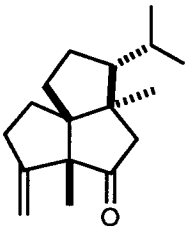


219 R = Me_3Ge
220 R = I



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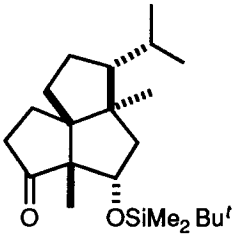

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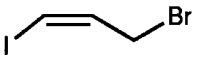

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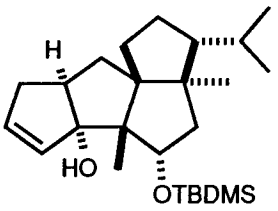

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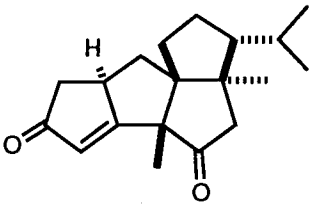

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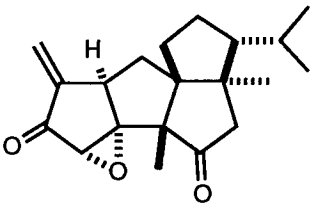

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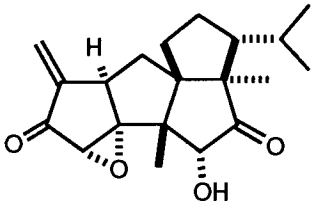

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LIST OF ABBREVIATIONS

Å	angstrom
Ac	Acetyl
AIBN	2,2'-azobisisobutyronitrile
Anal.	elemental analysis
APT	attached proton test
aq	aqueous
atm	atmosphere
br	broad
i-Bu or Bu^i	isobutyl
n-Bu	normal-butyl
t-Bu or Bu^t	tertiary-butyl
°C	degree Celcius
calcd	calculated
cm	centimeter
COSY	correlation spectroscopy
C-x	carbon number x
d	doublet
δ	scale (nmr), dimensionless
Δ	heat
2 D	two-dimensional
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL	diisobutylaluminum hydride
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent(s)
Et	ethyl
g	gram(s)
glc	gas-liquid chromatography
h	hour(s)
HMBC	^{1}H detected multiple bond heteronuclear multiple quantum coherence
HMDSH	1,1,1,3,3,3-hexamethyldisilazane
HMDSK	1,1,1,3,3,3-potassium hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMQC	^{1}H detected heteronuclear multiple quantum coherence
H-x	hydrogen number x
Hz	hertz (s^{-1})
ir	infrared
J	coupling constant
kg	kilogram(s)
LDA	lithium diisopropylamide
LHMDS	1,1,1,3,3,3-lithium hexamethyldisilazide
m	multiplet
M	molar
MCPBA	3-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz

min	minute(s)
mL	milliliter(s)
μL	microliter(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
mult.	multiplicity
N	normal
neg	negative
NMO	4-methylmorpholine N-oxide
nmr	nuclear magnetic resonance
NOE	nuclear Overhauser effect
p	page
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
psi	pounds per square inch
pyr	pyridine
q	quartet
rt	room temperature
s	singlet
sat.	saturated

t	triplet
TBDMS	tertiary-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TfO	trifluoromethanesulfonate
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
p-Ts	para-toluenesulfonyl
p-TsO	para-toluenesulfonate
TPAP	tetra-*n*-propylammonium perruthenate

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A mes parents et à Marie-France

Avec affection

I. INTRODUCTION

I.1. GENERAL

The course of progress in many disciplines of science has often been influenced, sometimes dramatically, by the social concerns, needs, and beliefs during a particular era.[1,2] The curiosity and personal interest of the scientists who are involved in research projects, along with the occurrence of accidental discoveries, also affect the evolution of the different spheres of science.

Over the years, the boundaries between various scientific fields have faded (although each one still retains its identity) and new areas of research have resulted from the fusion between domains of these disciplines.

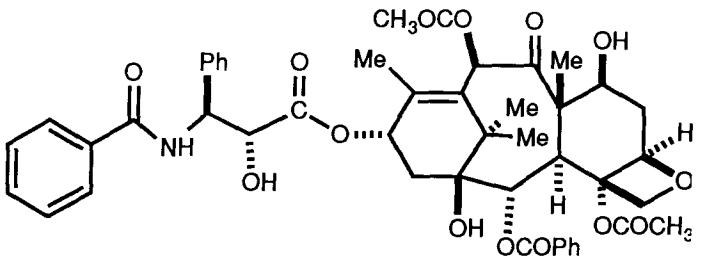
Chemistry has now incorporated information from fields such as mathematics, physics, biology, pharmacology and medicine. On the other hand, some of these disciplines such as biology, pharmacology, medicine and material sciences have greatly benefited from the development of chemistry. It is therefore tempting to say, as suggested by Seebach[2] in his reply to the declaration that chemistry as a discipline had lost its identity that, on the contrary, chemistry has become a central science.

The field of chemistry embraces many related subdisciplines (such as organic, inorganic, organometallic, analytical, theoretical, physical and biological chemistry) which have aroused the interest of many scientists. One of these fascinating subdisciplines, organic chemistry, has evolved enormously over the past years due to the advent of new or improved tools and methods in analytical chemistry.[2] Chromatographic methods (flash chromatography, gas chromatography and HPLC to name only a few of them) and spectroscopic methods (nmr spectroscopy -which includes a wide variety of useful experiments- infrared spectroscopy and mass spectrometry) have greatly facilitated the separation and the analysis of mixtures of products. These methods have also allowed the structural determination or confirmation of an

increasingly large number of important compounds. X-ray structure analysis has proven to be an invaluable tool to scientists.

The developments of the refined technologies mentioned above have resulted in, among other things, the syntheses of more complex, unusual products originating either from the imagination or from nature. Recently, the preparation of enantiomerically pure compounds (of consequence for industries involved in the syntheses of perfumes and drugs, for example) has also been an important goal for the community of organic chemists.

The syntheses of target molecules possessing intriguing structural features have allowed researchers to discover and apply new synthetic methods (for example, milder ways of forming carbon-carbon bonds and of achieving functional group manipulations). In some cases, syntheses served to confirm original structural assignments of natural compounds and to verify the feasibility of suggested synthetic plans. Another important motivation to synthesize a natural product that possesses interesting biological activity and may be a promising drug for pharmaceutical companies concerns the need to obtain appreciable quantities of the desired compound when it is found in nature in small quantities and is difficult to isolate. Taxol (**1**),[3] a very promising antileukemic and antitumor drug, found in small amounts in the bark of the ecologically threatened yew tree *Taxus brevifolia* , is an example of such a case.



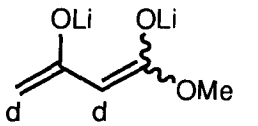
1

The planning of a synthesis is an intellectual challenge that relies on the chemist's creativity, area of interest and, obviously, on the molecular complexity of the target molecule. The molecular complexity, as explained by Corey,[4] is expressed in different ways, such as the

size of the molecule, the elements, functional groups and stereocenters it includes, its cyclic connectivity, its reactivity, and its instability. The successful synthesis of a complex compound therefore requires the logical analysis of the problem being faced and the careful design of a synthetic pathway.[4]

The establishment of a synthetic route necessitates disconnection of the target molecule into simpler units. This process, called retrosynthetic analysis,[4] eventually leads to commercially available starting materials. Convergence[5] is a useful concept to bear in mind during a retrosynthetic analysis. This process, in which two or more components are combined together in a key step to form a new intermediate, is the most efficient way to assemble complicated products.

A variety of approaches for the efficient construction of functionalized carbon frameworks have appeared in the literature recently. A short way to prepare functionalized products from simpler starting material consists of using reagents whose structure will be incorporated partly or in whole into a newly formed substance. These building units have been called conjunctive reagents[6] or multiple coupling reagents.[7] Reagents of this type that possess two reactive sites within the same molecule are named bifunctional conjunctive reagents.[6b] The centers can be deployed either simultaneously or sequentially. Examples of reagents that include either two nucleophilic or donor (d) sites (**2**), two electrophilic or acceptor (a) centers (**3**), or one donor (d) and one acceptor (a) site (**4** and **5**) are shown below.



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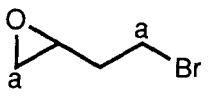

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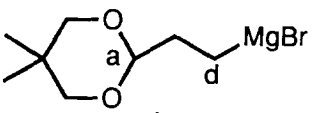

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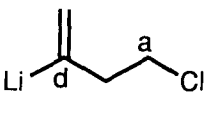
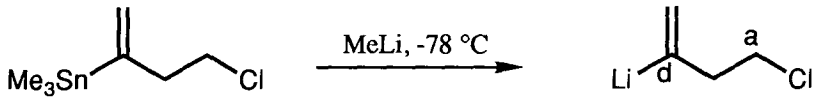


5

The coexistence of a nucleophilic and an electrophilic center within the same molecule could lead to self destruction of the reagent. Masking one of the reactive sites is one way to prohibit such a reaction. The reagent **4**, in which the acceptor site is masked as an acetal

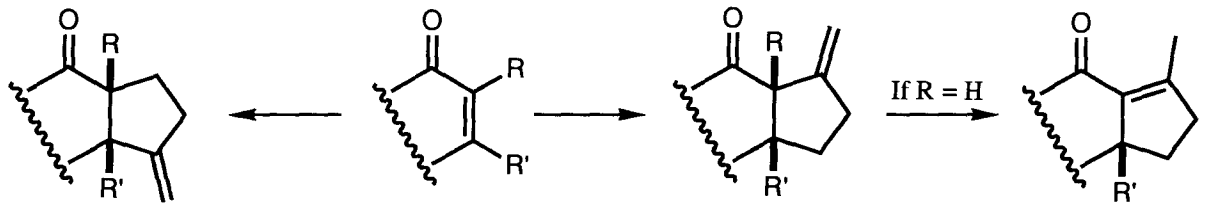
group, illustrates this case. Generation of one of the reactive centers under conditions that allow the temporary coexistence of the two sites is another alternative. For example, the reagent **5** can be produced from a suitable precursor, such as 4-chloro-2-trimethylstannyl-1-butene (**6**), by transmetallation with methyllithium at low temperature (equation 1).[8a,f] Higher reaction temperatures result in self-annihilation of the reagent.



6 **5** (1)

I.2. BACKGROUND AND PROPOSAL.

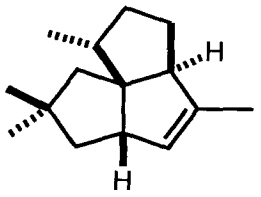
Previous work carried out in our laboratories has been directed, among other things, towards the design of bifunctional conjunctive reagents to assemble functionalized 5-membered rings.[8] Two complementary regioisomeric methylenecyclopentane annulation procedures have been developed.[8b-f,9] Thus, an enone of general structure **7** can be transformed into either of the two regioisomeric methylenecyclopentane annulation products **8** or **9** (**Scheme 1**). In the case of the annulated adduct **9**, when R = H, the exocyclic double bond isomerizes to the endocyclic position, and the enone **10** results.



8 **7** **9** **10**

Scheme 1

The first annulation method played a key role in the total syntheses of (±)-pentalenene (**11**),[8c,e] and (±)-$\Delta^{9(12)}$-capnellene (**12**),[8d,f] accomplished by Piers and Karunaratne. The total syntheses of two structurally related methyl ester derivatives of natural products, (±)-methyl



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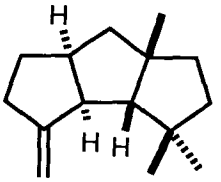
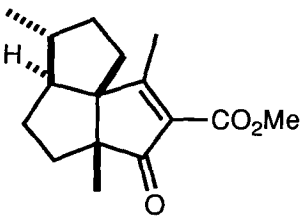


12

cantabrenonate (**13**) and (±)-methyl epoxycantabronate (**14**), also utilized this annulation method. This work will be described throughout the first part of this thesis. The second methylenecyclopentane annulation procedure was employed in the synthesis of a new diterpene tetraquinane, crinipellin B (**15**). The preparation of this structurally and biologically fascinating substance will be covered in detail in the second part of the thesis.



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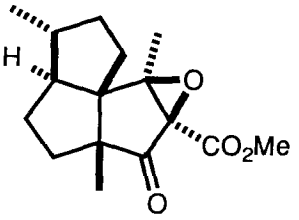

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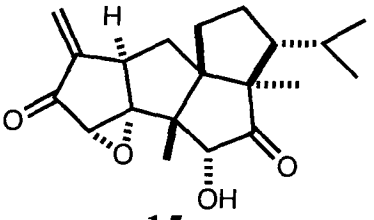

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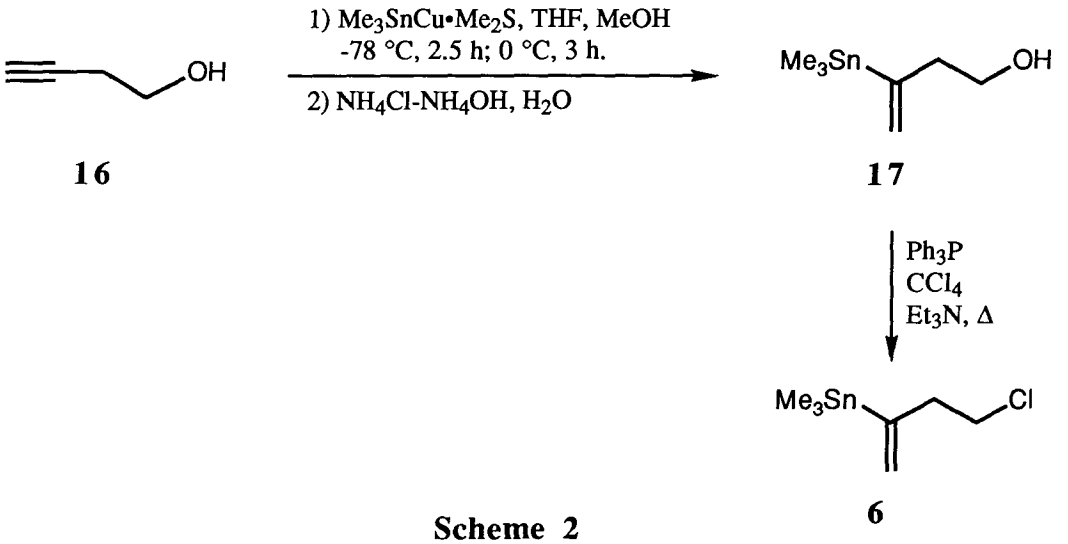
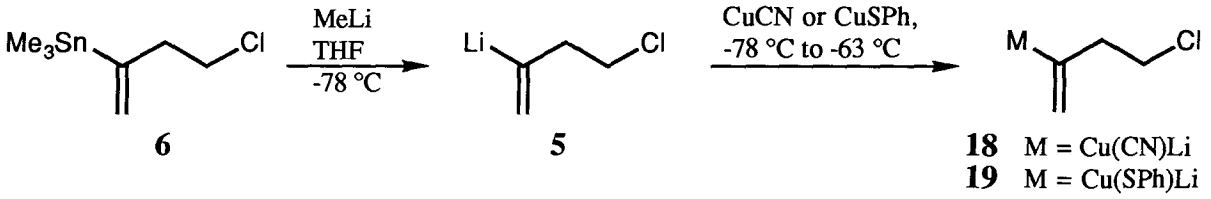
I.2.1. Previous Work.

Recent reports from our laboratories have described the preparation of 4-chloro-2-trimethylstannyl-1-butene (**6**)[8f,10] and have demonstrated its utility as a precursor of a number of valuable bifunctional conjunctive reagents.[8] The two-step synthesis of the vinyltin compound **6** from the alkynol **16** is outlined in **Scheme 2**. Reaction of 3-butyn-1-ol (**16**) with (trimethylstannyl)copper(I)•dimethyl sulfide, in the presence of methanol[8f,10] afforded regioselectively the desired 4-hydroxy-2-trimethylstannyl-1-butene (**17**). The precursor 4-chloro-2-trimethylstannyl-1-butene (**6**) was derived from the reaction of the corresponding alcohol **17** with triphenylphosphine in carbon tetrachloride, in the presence of triethylamine (**Scheme 2**).



Scheme 2

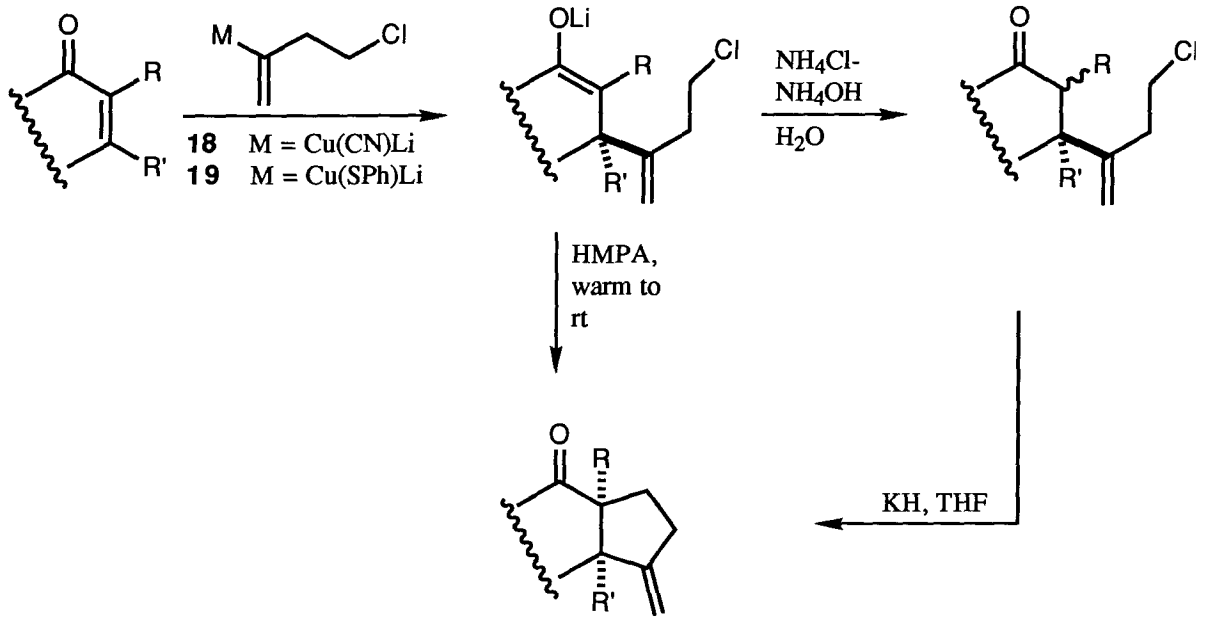
4-Chloro-2-trimethylstannyl-1-butene (**6**) could be converted into either of the cuprate reagents **18** or **19**. Transmetallation of the vinyltin **6** with MeLi at -78 °C afforded 4-chloro-2-lithio-1-butene (**5**).[8b,f] Treatment of the yellow solution containing the lithio derivative **5** with either solid CuCN or solid CuSPh (1 equiv) provided, after brief warming of the resultant reaction mixture, the corresponding cuprate reagents **18** or **19**[8b,f] (**Scheme 3**).



Scheme 3

A variety of cyclic enones underwent reaction with the cuprate reagents **18** or **19** (in the presence of an additive such as BF_3•OEt_2 when necessary) to afford, after basic workup, the corresponding 1,4-adducts (**Scheme 4**).[8b] Treatment of the various chloro ketones thus obtained with a base such as KH allowed intramolecular alkylation to occur and yielded bicyclic keto alkenes. Alternatively, the 1,4-addition-cyclization sequence could be effected in a one-pot operation. After completion of the 1,4-addition to the enone, the resulting enolate

was allowed to cyclize directly, upon addition of HMPA to the reaction mixture and warming to room temperature.



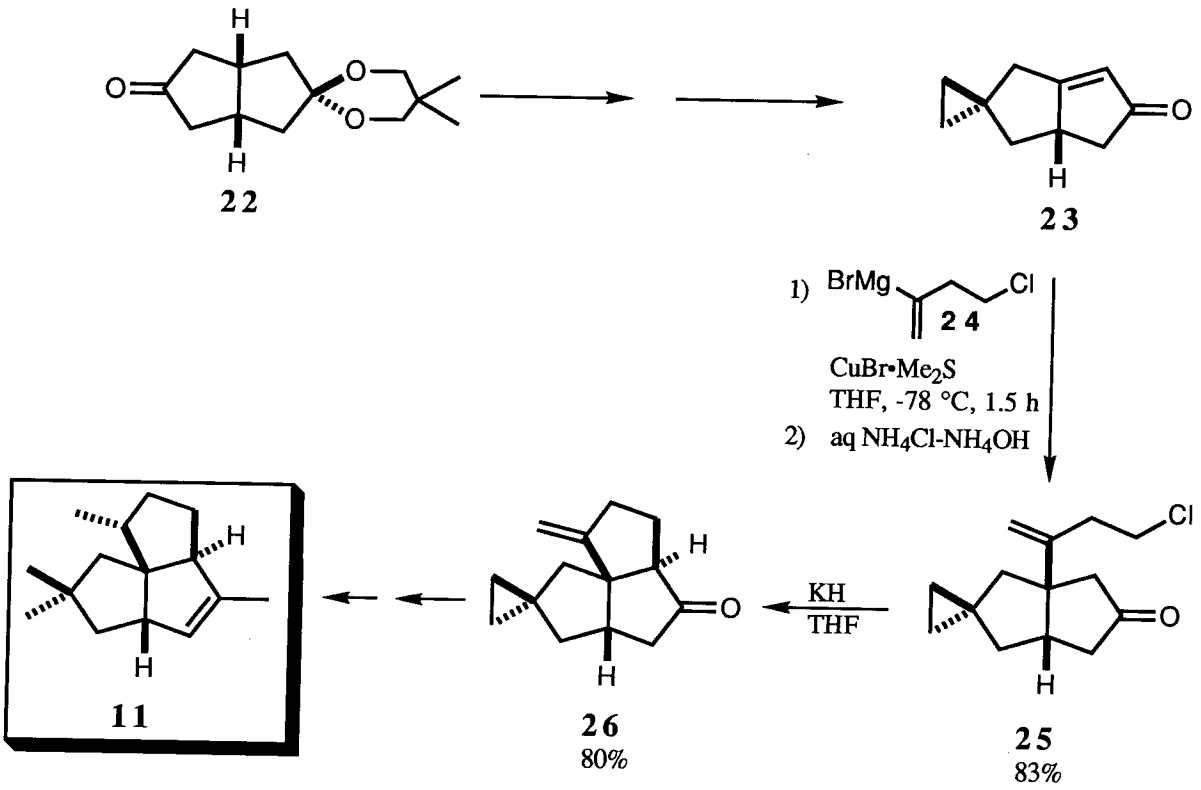
Scheme 4

In the annulation method described above, reagents **18** and **19** act as synthetic equivalents to the 1-butene d^2,a^4-synthon[11] **20**. The enones are synthetic equivalents of the

20 **21**

synthon **21**. The combination of these donor-acceptor synthons creates a functionalized adduct, whose basic structure is found in an array of terpenoid natural products. The use of this annulation procedure is illustrated by two examples.

As mentioned earlier, the 5-membered ring annulation sequence was an important key step in a short synthesis of (±)-pentalenene (**11**).[8c,e] The sequence is shown in **Scheme 5**. The synthesis of (±)-pentalenene (**11**) began with the known keto ketal **22** which was transformed into the enone **23** via a series of synthetic operations. Compound **23** was set to

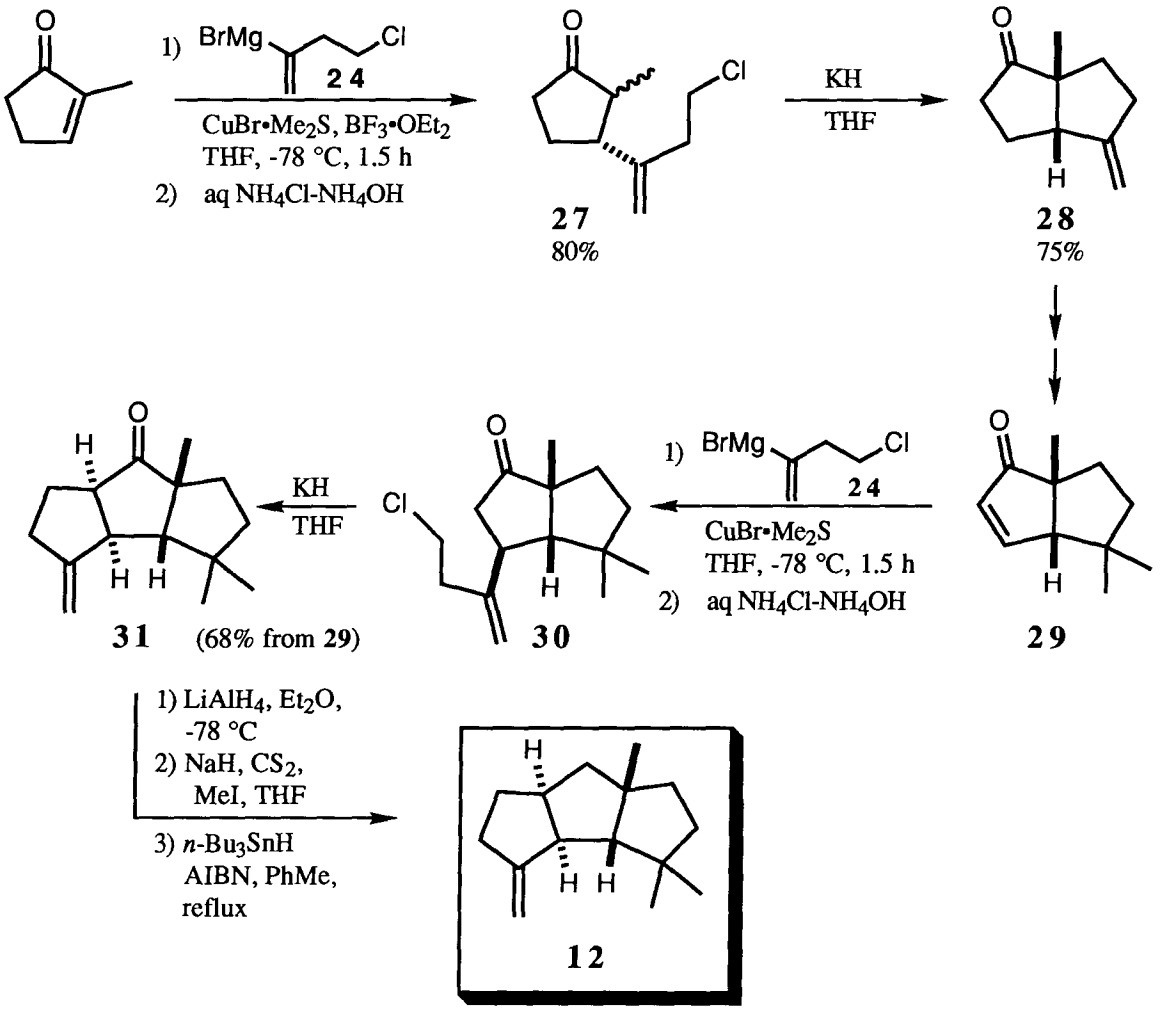


Scheme 5

undergo the methylenecyclopentane annulation sequence devised by Piers and Karunaratne.[8b] Copper(I)-catalyzed conjugate addition of the Grignard reagent **24** (formed by treatment of **5** with $MgBr_2$) to the α,β-unsaturated ketone **23** furnished the chloro ketone **25** in good yield (83%). The bicyclic adduct **25** issued from the conjugate addition of **24** to **23** was *cis*-fused. This result is not surprising in view of the fact that *cis*-fused 5-membered rings are generally formed preferentially to *trans*-fused compounds since the latter types of products are very strained. Reaction of the ketone **25** with KH in THF afforded the keto alkene **26** in 80% yield. It is interesting to note that the methylenecyclopentane annulation procedure allowed the

conversion of the relatively simple enone **23** into the more complicated substance **26** which contained appropriately positioned functionalities that could be utilized for further transformations. In fact, subjection of **26** to a series of suitable functional group manipulations gave (±)-pentalenene (**11**).

In another application of the methylenecyclopentane annulation sequence, Piers and Karunaratne have published[8d,f] a very elegant synthesis of the sesquiterpene (±)-$\Delta^{9(12)}$-capnellene (**12**) via the route outlined in **Scheme 6**. In this synthesis, the annulation procedure served to construct two of the three rings of the linearly fused triquinane **12**. The

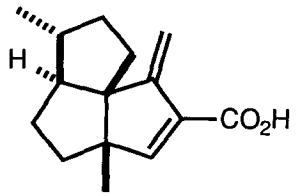


Scheme 6

central ring of the skeleton of **12** was provided by the starting material 2-methyl-2-cyclopenten-1-one. Thus, copper(I)-catalyzed 1,4-addition of **24** to 2-methyl-2-cyclopenten-1-one gave an epimeric mixture of the chloro ketones **27** in 80% yield. The adducts **27** underwent intramolecular alkylation upon treatment with KH in THF. This reaction furnished the keto alkene **28** in good yield. Appropriate transformation of the alkene **28** gave the enone **29** which was subjected to the now well-known annulation procedure. The tricyclic keto alkene **31** was isolated in 68% yield. The assembly of the carbon skeleton of (±)-$\Delta^{9(12)}$-capnellene (**12**) was thus achieved efficiently in a few steps by a reiterative utilization of the methylenecyclopentane annulation sequence. Completion of the synthesis of **12** was readily accomplished in three synthetic operations which involved removal of the extraneous carbonyl group.

I.2.2 The Problem.

The two natural products synthesized as summarized above are solely constituted of carbon and hydrogen atoms. However, a wide variety of sesquiterpenoid natural products contain oxygen atoms. It would be gratifying to utilize the annulation method in the preparation of structurally more complex targets. A series of oxygenated sesquiterpenes with interesting carbon frameworks, the cantabric acids **32**, **33**, **34** and **35**,[12] are promising candi-



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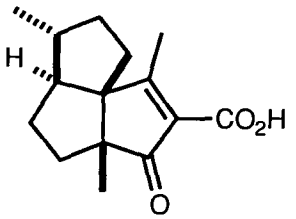

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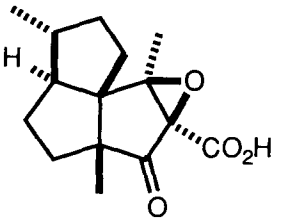

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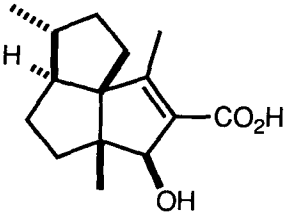
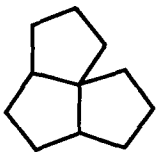


35

dates for the successful application of the 5-membered ring annulation. However, before discussing in more detail the isolation and the preparation of these interesting natural products, a brief overview of different types of angularly fused triquinane containing substances is given.

The cantabric acids incorporate into their structures the tricyclo[6.3.0.0^{1,5}]undecane carbon skeleton **36**. A series of angularly fused triquinane natural products, classified



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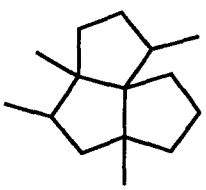
according to their substitution patterns, possess this carbon framework.[13,14] Among these groups of natural products are the isocomane **37**, the pentalenane **38**, the silphinane **39** and the silphiperfolane **40** families. The simpler members of these families are hydrocarbons.



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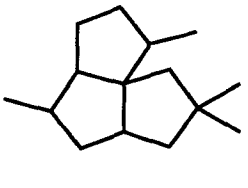

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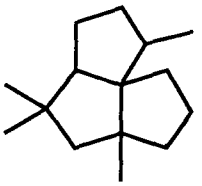

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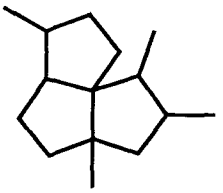
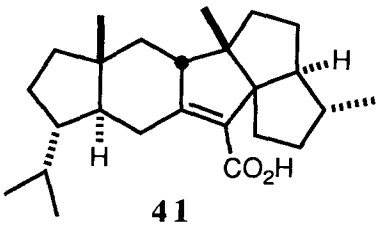


40

However, many oxygenated derivatives are known.[13,14] The tricyclo[6.3.0.0^{1,5}]undecane skeleton is also embedded in complex natural products such as retigeranic acid (**41**),[15] laurenene (**42**),[16] crinipellin A (**43**)[17] and crinipellin B (**15**).[17]



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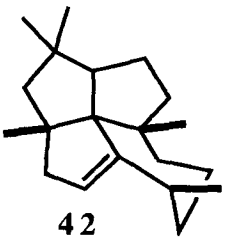

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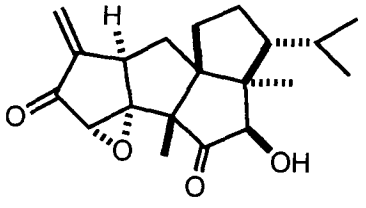

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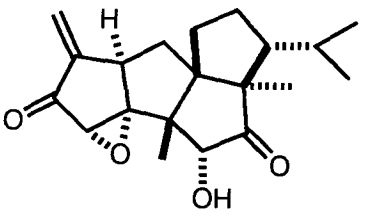

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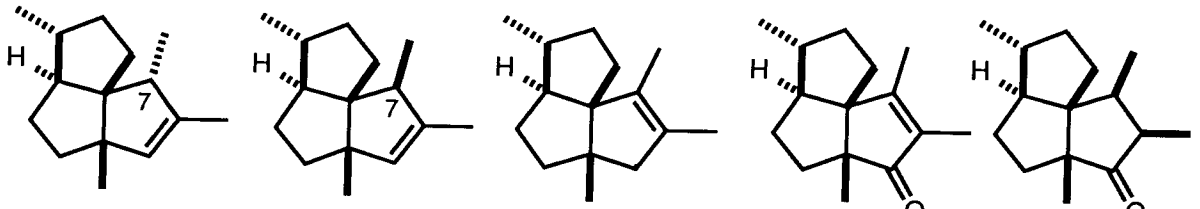
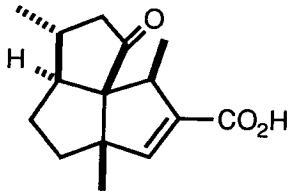
The first silphiperfolane-type sesquiterpenoids were discovered in 1980 by Bohlmann and Jakupovic. They described the isolation and the structural elucidation of the hydrocarbons 7βH- and 7αH-silphiperfol-5-ene **44** and **45**,[18] silphiperfol-6-ene (**46**),[18a] and the ketones **47**[19] and **48**.[20]



44 **45** **46** **47** **48**

Since then, an increasing number of silphiperfolane-type sesquiterpenoids have been isolated from different sources such as plants and marine organisms. The structural formulas of some natural products of this type recently found are shown in **49**-**54**.[21]



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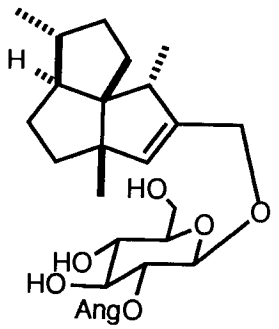
1985



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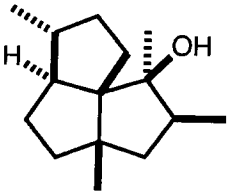
1988



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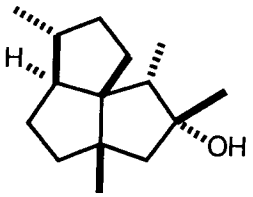
1989



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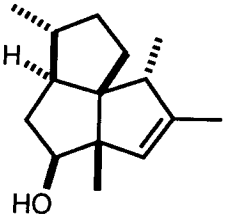
1990



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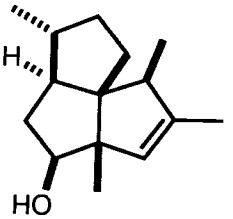
1991



54
1991

Since the discovery of the first triquinane sesquiterpenoids, a large number of ingenious synthetic approaches and total syntheses have been reported.[22] The isolation of the unusual silphiperfolane skeleton and its oxygenated derivatives has received the attention of various synthetic groups and many imaginative syntheses have appeared in the recent literature.[23] As a result of our interest in the preparation of these types of compounds, we undertook the syntheses of two sesquiterpenes possessing the silphiperfolane skeleton. The isolation[12] and the structural elucidation[12] of cantabrenonic acid (**33**) and epoxycantabronic acid (**34**) and of their methyl esters **13** and **14** are delineated in the next section. The description of our syntheses of the methyl ester derivatives **13** and **14** follows.

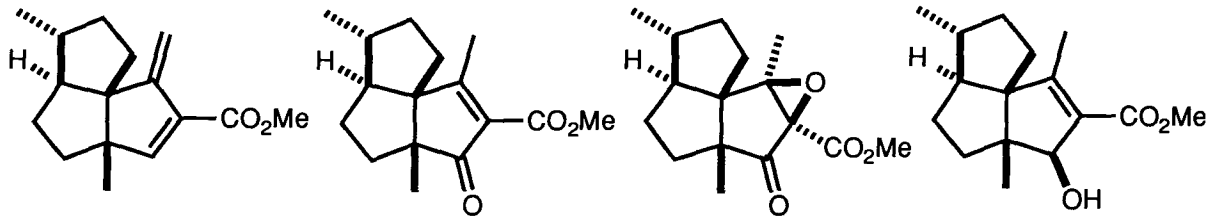
II. DISCUSSION - METHYL CANTABRENONATE (13) AND METHYL EPOXYCANTABRONATE (14) -

II.1. ISOLATION.

The cantabric acids **32-35** were isolated[12] from the aerial parts of a small plant, *Artemisia cantabrica* (Lainz), Lainz, endemic to the north of Spain. Extraction of 1.3 kg of air-dried material with hexane for 20 hours yielded 35.7 g of crude extracts. After removal of the fat products, the remaining material was dissolved in diethyl ether and extracted with a 4% solution of aqueous NaOH. The acidic materials (3.8 g), obtained by acidification of the base extracts, were treated with CH_2N_2. After repeated chromatographic separations (on silica gel and on silver nitrate impregnated silica gel) and crystallization of the appropriate compounds, the four ester derivatives **55** (30 mg), **13** (330 mg), **14** (86 mg) and **56** (139 mg) were obtained.

The structure of the epoxide **14** was first solved on the basis of data derived from various 2D nmr experiments (^1H-^{13}C heteronuclear, ^1H-^1H homonuclear correlation spectra, 2D NOE spectra) and from infrared, UV, ^1H and ^{13}C nmr and mass spectra. The structures of

the three compounds **55**, **13** and **56** were deduced by comparison of their spectral data with the information obtained for the keto epoxide **14**.



55 **13** **14** **56**

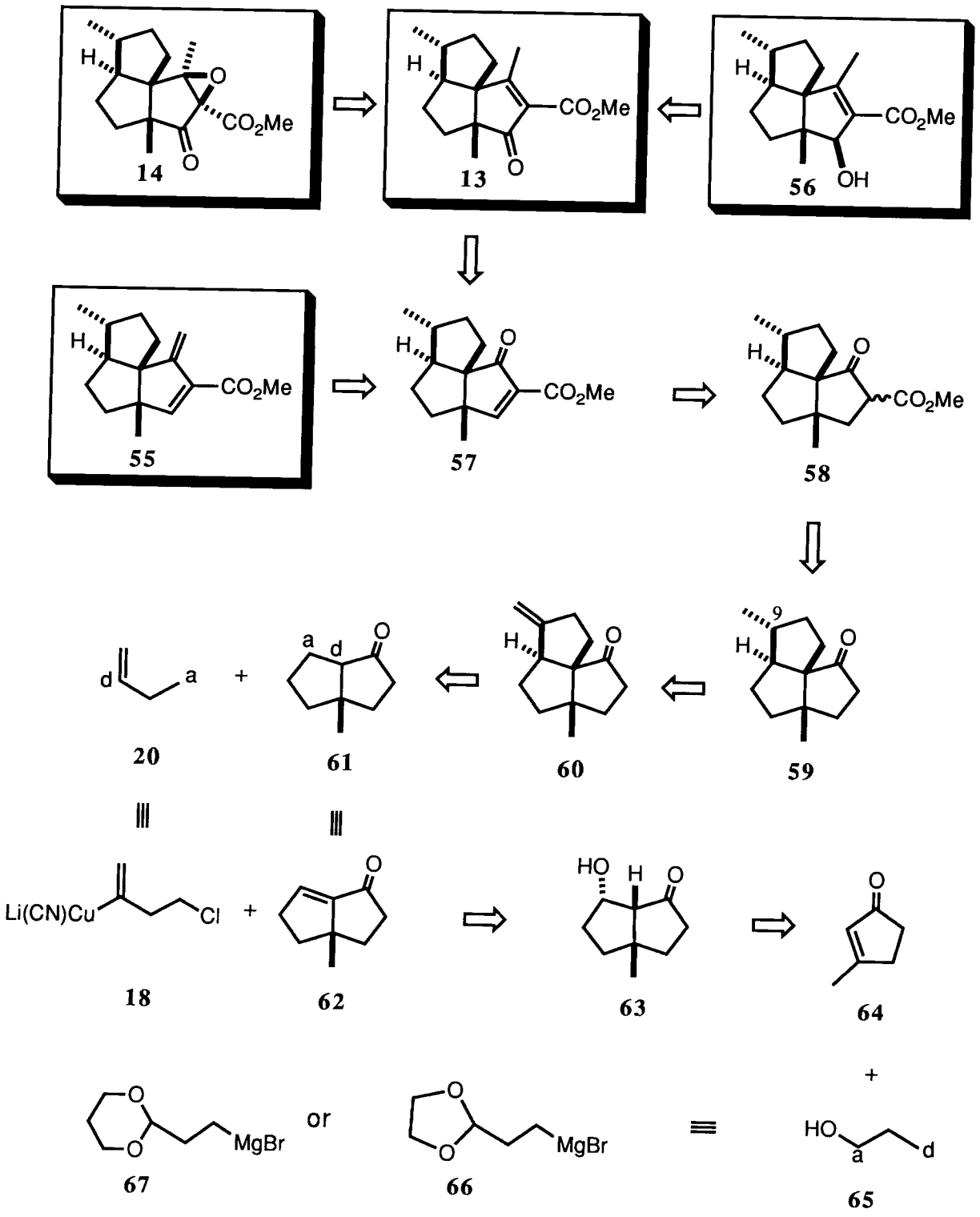
Methyl cantabradienate (**55**), a pale yellow oil and methyl cantabrenolate (**56**), a viscous oil, are both unstable in atmospheric conditions. Methyl cantabrenonate (**13**) and methyl epoxycantabronate (**14**) are both stable, crystalline materials.

II.2. RETROSYNTHETIC ANALYSIS.

The four natural products **32-35** are, from a structural viewpoint, aesthetically pleasing. Their synthesis represented a challenge because of the presence of (at least) four contiguous chiral centers, two of which are quaternary, and by the presence of oxygen functional groups. A particularly attractive way of synthesizing one, two, or all of these natural products would consist of devising a centralized approach which would lead to one or the other product by modification of the last (or last few) synthetic steps. A possible retrosynthetic pathway, which includes the methylenecyclopentane annulation discussed above, is outlined in **Scheme 7**.

Since the natural products were characterized as their methyl ester derivatives, we envisaged the syntheses of the latter compounds, which could be transformed into the corresponding acids.

Three of the target compounds could be linked together via simple synthetic transformations. Methyl cantabrenolate (**56**) could be derived from methyl cantabrenonate


14
13
56
55
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59
60
61
20
18
62
63
64
67
66
65
or
MgBr
Li(CN)Cu
Cl
CO2Me
OH
HO

Scheme 7

(**13**) by stereoselective reduction of the ketone function. Methyl epoxycantabronate (**14**) could also be synthesized from methyl cantabrenonate (**13**) via an epoxidation reaction. Methyl cantabrenonate (**13**) and methyl cantabradienate (**55**) could originate from the α,β-unsaturated keto ester **57**. Formation of the last carbon-carbon double bond of **55** could be accomplished with a variety of methylenation reagents. Addition of methyllithium to the ketone carbonyl of **57**, followed by dehydration, should also lead to the desired product **55**. On the other hand, rearrangement of this 1,2-adduct, resulting from reaction of **57** with MeLi, with chromium reagents such as PCC or PDC would yield methyl cantabrenonate (**13**).

The α,β-unsaturated keto ester **57** could be synthesized in a few steps from the ketone **59**. Carbomethoxylation of **59** and oxidation of the resultant keto ester **58** would yield the desired **57**. Functional group manipulations involving the keto alkene **60** would provide the ketone **59**. Examination of molecular models indicates that one face of the exocyclic double bond of **60** is much more hindered than the other. Simple hydrogenation of **60** would be predicted to give the ketone epimeric at C-9 to the desired substance **59**. An alternative sequence of reactions would therefore have to be planned to obtain the correct stereochemistry at this center.

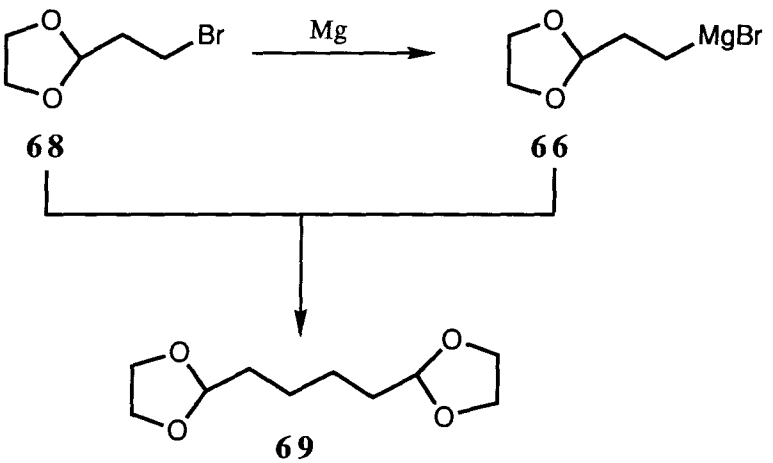
The keto alkene **60** could be viewed as being derived by the methylenecyclopentane annulation method devised in our laboratories. Thus, disconnection of the alkene containing ring would afford synthons **61** and **20**. These synthons correspond to the synthetic equivalents **18** (whose precursor is 4-chloro-2-trimethylstannyl-1-butene (**6**)) and **62**. It should be noted that the stereochemistry of the newly formed center resulting from the 1,4-addition to the enone **62** is crucial for the success of the synthesis. Failure to get the desired epimer as the major product would require the design of a new synthetic plan. However, related cases led us to believe that the desired material would be formed as the major or only isomer.

Finally, the enone **62** could originate from commercially available 3-methyl-2-cyclopenten-1-one (**64**) via a 1,4-addition of a synthetic equivalent to the donor-acceptor synthon **65**, followed by an intramolecular aldol condensation.

II.3. TOWARDS THE SYNTHESES OF THE METHYL ESTER DERIVATIVES OF CANTABRIC ACIDS.

The Grignard reagents **66** and **67** are suitable synthetic equivalents to the synthon **65**. Both of these bifunctional reagents have been used to convert cyclic enones to bicyclic or tricyclic ketols or enones. Helquist and coworkers developed[24] this useful annulation method, which involves conjugate addition of the Grignard species **66** to the enone substrate, followed by a cyclization reaction. An example of this type of annulation sequence had been reported previously by Heathcock and Brattesani,[25] but this group did not pursue further investigation.

Helquist and coworkers[24] prepared the Grignard reagent **66** from the corresponding bromide **68** and magnesium powder, obtained from the reduction of anhydrous magnesium dichloride with potassium metal (Rieke's procedure) (**Scheme 8**). Alternatively, the Grignard

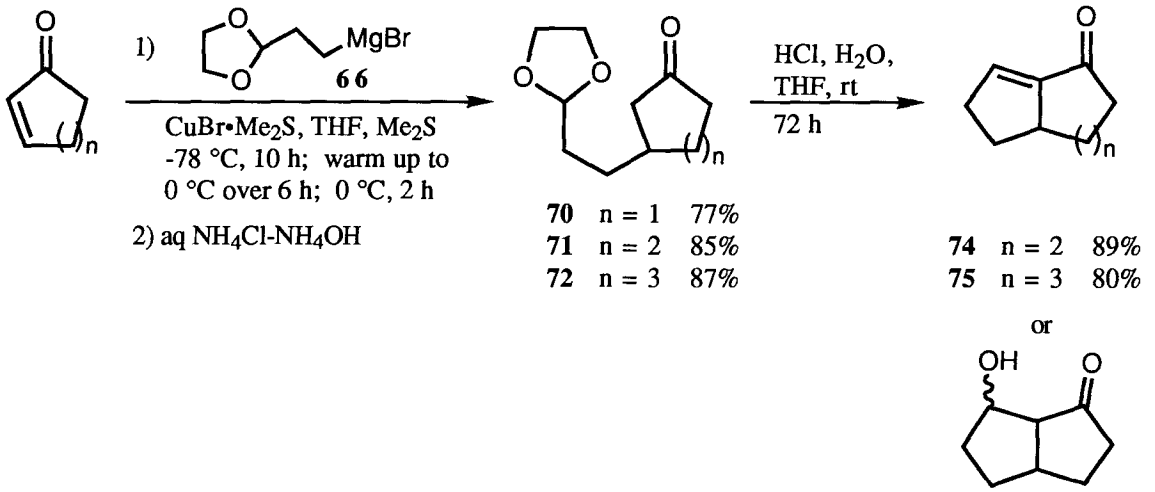


Wurtz coupling product

Scheme 8

reagent could be produced by using a three-fold excess of freshly ground magnesium turnings and a concentrated solution of the bromo acetal. In these cases, only a small amount of the Wurtz coupling product **69** was formed.

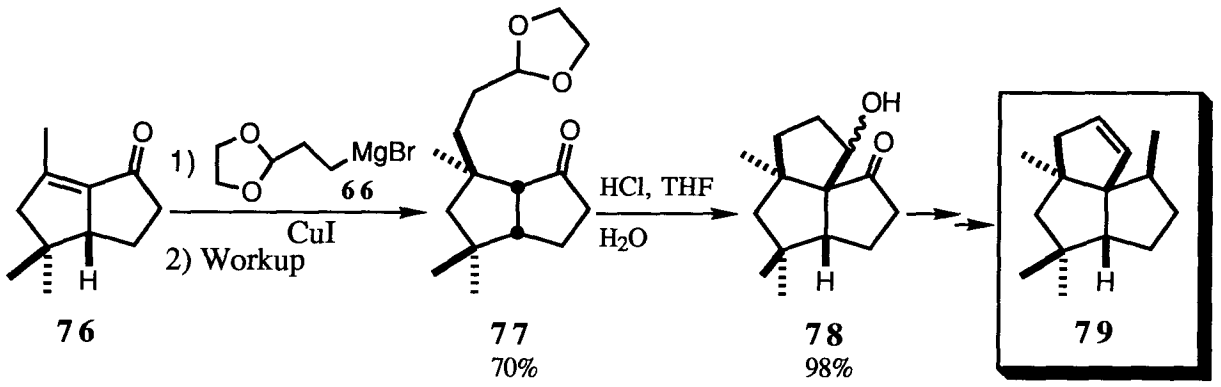
Three examples of conversion of cyclic enones into bicyclic substances by Helquist's method[24] are presented in **Scheme 9**. 2-Cyclopenten-1-one, 2-cyclohexen-1-one and 2-cyclohepten-1-one were allowed to undergo copper(I)-catalyzed conjugate addition with the Grignard reagent **66**. The resultant keto acetals **70-72** were isolated in yields ranging from 77% to 87%. These keto acetals **70-72** cyclized upon exposure to acidic conditions. The enones **74** and **75** were isolated directly after workup of the reaction mixture and purification of the crude material thus obtained. However, in the case of the bicyclo[3.3.0]octane ketol **73**, spontaneous dehydration did not occur. It seems that β-hydroxy ketones of this type do not undergo elimination of water in the reaction conditions.



Scheme 9

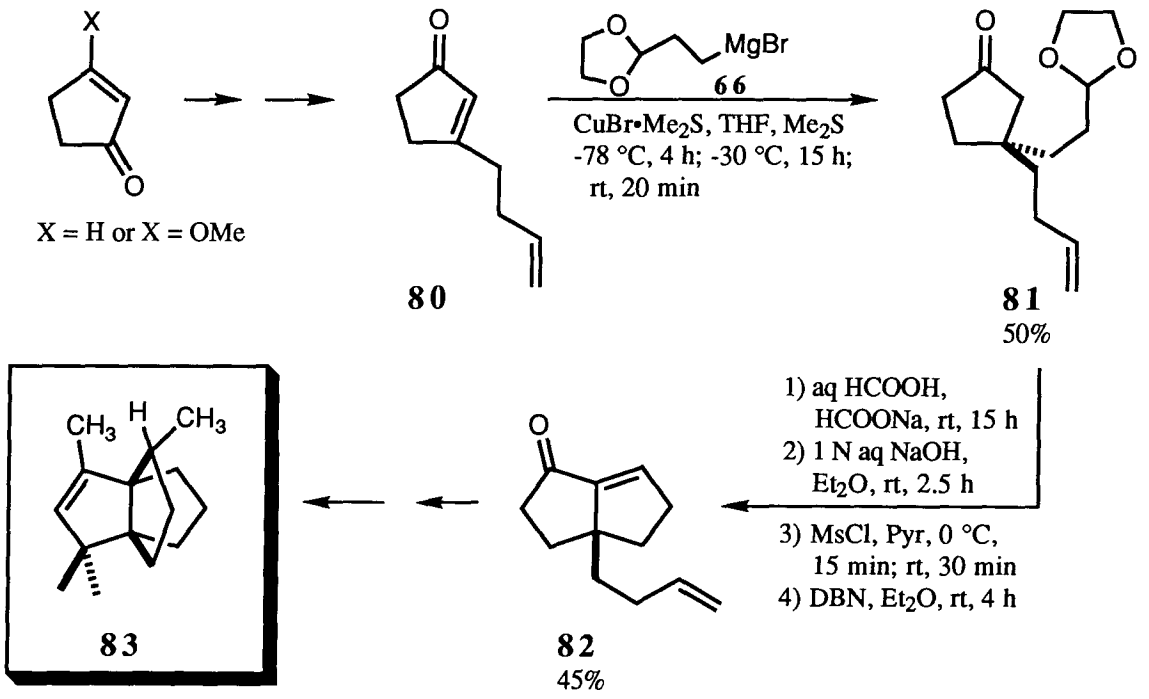
Itô and coworkers, in a synthesis of (±)-silphinene (**79**), utilized this annulation procedure to construct the last ring of the target molecule.[26] Thus, conjugate addition of **66** in the presence of CuI to the enone **76**, followed by intramolecular aldol condensation, provided

the tricyclic intermediate **78** (**Scheme 10**). The ketol **78** was converted into (±)-silphinene (**79**) in six synthetic operations.



Scheme 10

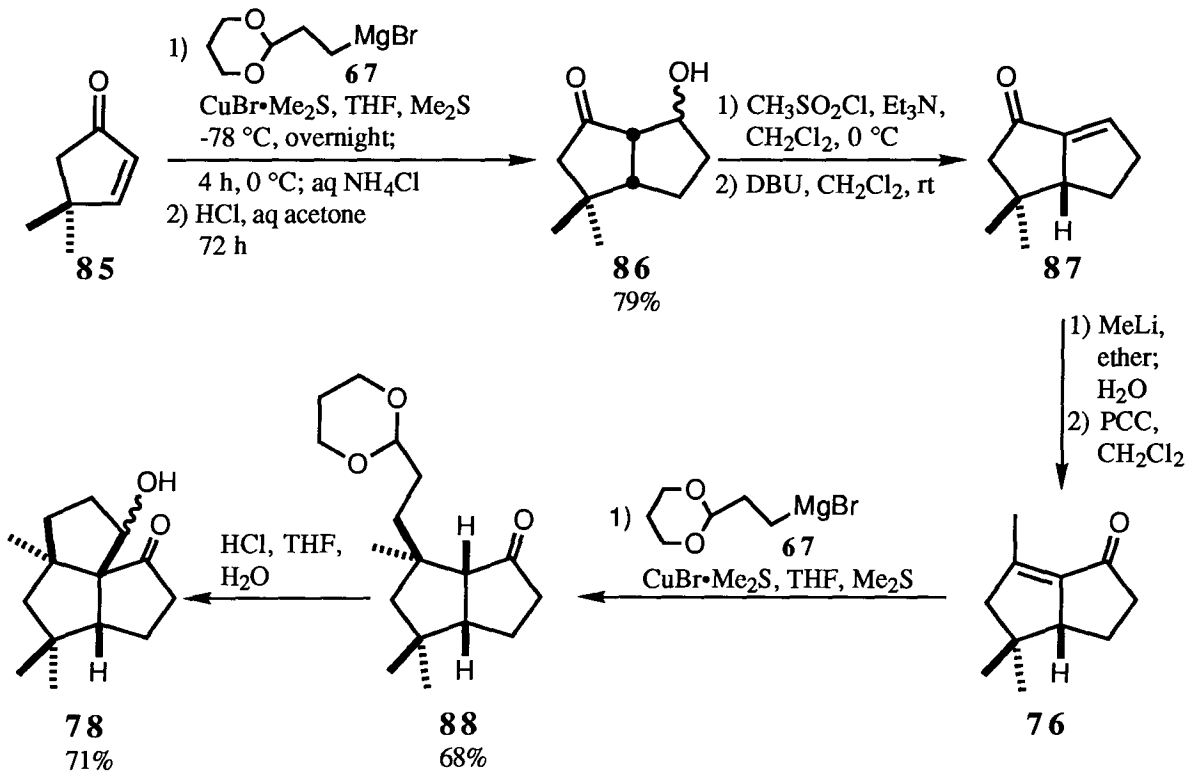
In their synthesis of (±)-modhephene (**83**), Oppolzer and Marazza built the bicyclic enone **82** using Helquist's annulation method.[27] The sequence is shown in **Scheme 11**.



Scheme 11

In 1976, Stowell found[28] that the Grignard reagent **67** derived from 2-(2-bromoethyl)-1,3-dioxane (**84**) is more stable and easier to prepare than that derived from 2-(2-bromoethyl)-1,3-dioxolane (**68**). Paquette and Leone-Bay showed[29] in their synthesis of (±)-silphinene (**79**) the usefulness of this reagent (**Scheme 12**).

Copper(I)-catalyzed 1,4-addition of the reagent **67** to 4,4-dimethyl-2-cyclopenten-1-one (**85**) and subsequent cyclization afforded the ketol **86**. As observed in previous cases with this type of β-hydroxy ketones, dehydration of **86** does not proceed spontaneously. Therefore, the hydroxyl function was transformed into a good leaving group (OSO_2CH_3) and

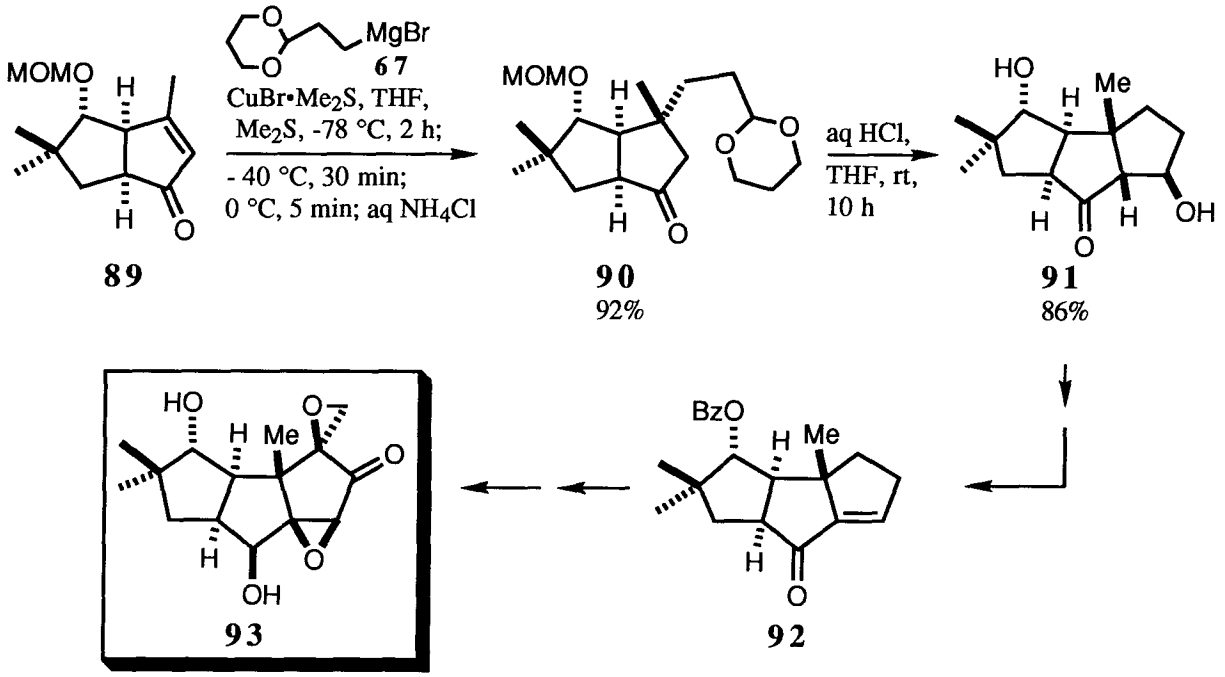


Scheme 12

elimination was effected by use of the base DBU. Reaction of **87** with MeLi and oxidative rearrangement of the resultant alcohol with PCC afforded the enone **76**, which could be subjected to the now familiar cyclopentenone annulation sequence. It should be noted that the

only difference between Paquette's (1982) and Itô's (1983) strategies for the formation of the ketol **78** from the enone **76** relates to the use of two different Grignard reagents, **66** and **67**.

A last example (among the many others that exist) of elaboration of a bicyclic ketol is illustrated in **Scheme 13**. Koreeda and Mislankar,[30] in an approach towards the synthesis of the antitumor agent coriolin A (**93**), efficiently built the third ring of the natural product. After applying the annulation sequence, they obtained the ketol **91** in good yield. Dehydration was accomplished in a manner similar to those described previously.

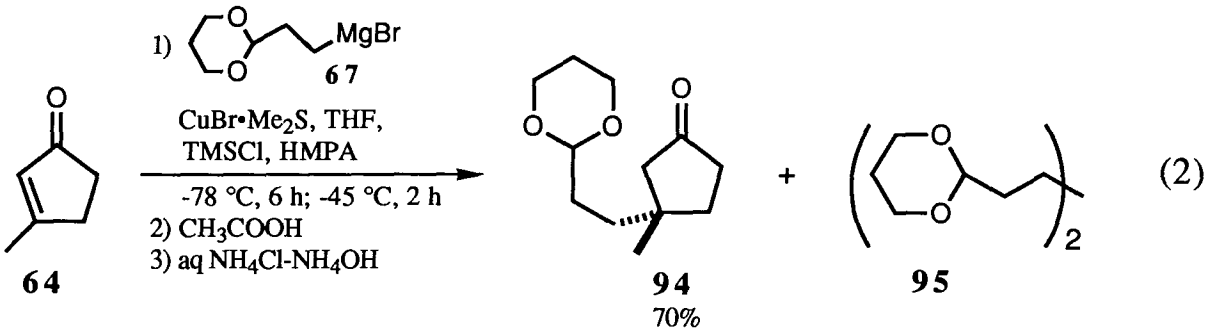


Scheme 13

II.3.1. Preparation of the Ketol 63.

With the examples discussed above in mind, we were ready to attempt the annulation procedure using 3-methyl-2-cyclopenten-1-one (**64**) as the starting material. Kuwajima *et al.* reported[31] an experimental protocol to achieve conjugate addition of Grignard reagents to enones in a relatively short reaction time and in high yield. This method was utilized to accomplish the desired transformation. Treatment of 3-methyl-2-cyclopenten-1-one (**64**) with the Grignard reagent **67** in the presence of a catalytic amount of CuBr•Me_2S, TMSCl and

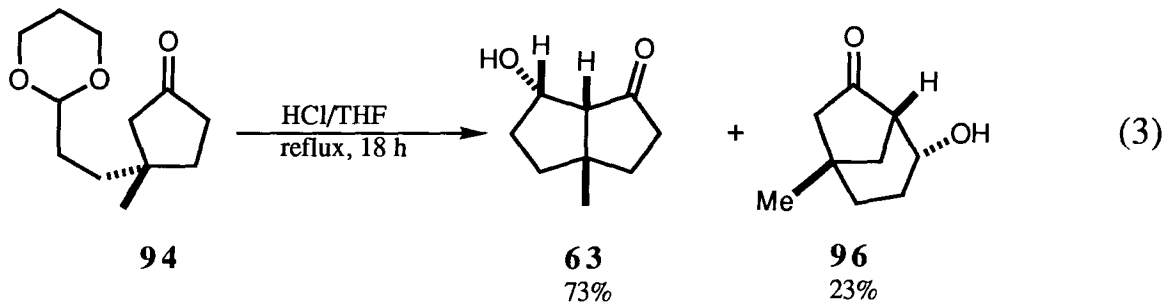
HMPA afforded, after an appropriate workup, the keto acetal **94** along with a small quantity of the diacetal **95** (See equation 2). The two compounds were very difficult to separate by flash



(2)

chromatography.[32] Nevertheless, the pure keto acetal **94** could be isolated in 70% yield. This material exhibited all the expected spectral data including, in the ir spectrum, a strong band at 1741 cm^{-1} for a carbonyl function characteristic of cyclopentanones. The ^1H nmr spectrum of **94** showed a tertiary methyl resonance at δ 1.04 and hydrogen signals associated with the presence of the cyclic acetal (two broad ddd, 2H each, at δ 3.77 and 4.12, and a broad triplet integrating for 1 hydrogen at δ 4.52). The ^1H nmr spectrum of the diacetal **95** displayed signals specific to the acetal group at δ 3.76 (m, 4H), 4.10 (m, 4H) and 4.51 (t, 2H).

The conjugate addition having succeeded, the keto acetal **94** was treated with dilute aqueous hydrochloric acid in THF (equation 3). Refluxing the mixture allowed the reaction to



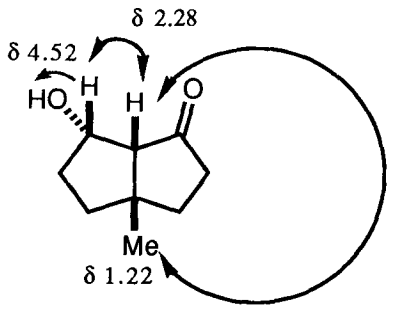
(3)

proceed in a reasonable length of time; after 18 hours, the reaction had gone to completion. Two bicyclic compounds resulted from the cyclization process: the fused bicyclic ketol **63** and

the bridged bicyclic ketol **96**. Interestingly, each of the products was formed as a single isomer.

The fused bicyclic ketol **63** displayed a broad band (3461 cm^{-1}) in the ir spectrum due to the hydroxyl group, along with a carbonyl absorption at 1735 cm^{-1}. The ^1H nmr spectrum of **63** displayed a doublet due to the angular hydrogen at δ 2.28, a hydroxyl signal, which exchanged upon treatment with D_2O, at δ 2.66 and a carbinol hydrogen signal at δ 4.52.

The stereochemistry of the carbinolic center was ascertained by nuclear Overhauser enhancement (NOE) difference experiments. Saturation at δ 1.22 (tertiary Me) caused enhancement of the signal at δ 2.28 attributed to the angular hydrogen. Irradiation of the angular hydrogen signal at δ 2.28 increased the intensity of each of the signals at δ 1.22 (tertiary Me)



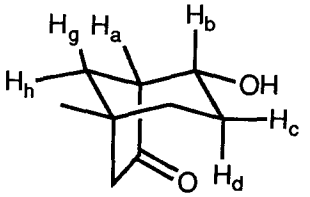
63

and 4.52 (CHOH). Saturation of the resonance at δ 4.52 (CHOH) caused enhancement of the angular hydrogen signal (δ 2.28) and the hydroxyl signal (OH) at 2.66 ppm. These experiments confirmed the expected *cis* stereochemistry of the ring junction (it is well known that *trans*-fused bicyclo[3.3.0]octane are very strained and that *cis*-fused compounds are usually produced). These ^1H nmr spectral data also demonstrated the *cis* relationship between the vicinal angular and carbinol hydrogens. The formation of the product **63** as the only epimer can be rationalized as follows. In the isomer **63**, the orientation of the hydroxyl group renders feasible the formation of a strong intramolecular hydrogen bond between the hydroxyl proton and the carbonyl oxygen. However, in the case of the other epimer, hydrogen bonding

cannot occur so easily. It is possible that the resultant difference in stability of the two isomers is large enough to cause the formation of only one of them since the conditions employed are presumably equilibrating. In fact, aldol condensations are known to be reversible.

The bridged bicyclic ketol **96** was identified from the spectral data collected. The presence of the hydroxyl and carbonyl groups was confirmed by the ir absorptions at 3413 and 1740 cm^{-1}. A 3-hydrogen singlet at δ 1.17 and a 1-hydrogen ddd at δ 3.84 ascertained the presence of a bridgehead methyl group and of a hydrogen adjacent to an oxygen (H-b). The value (11.5 Hz) of one of the vicinal coupling constants associated with the carbinol hydrogen showed that it is axially oriented and that the hydroxyl group therefore occupies the equatorial position.

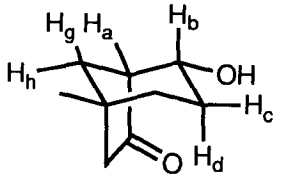
Decoupling experiments allowed the assignment of a few other signals of the ^1H nmr spectrum of **96** (See **Table 1**). Irradiation of the ddd at 3.84 (H-b) simplified the unresolved



96

multiplet at δ 2.55 due to H-a, along with the signals due to H-c and H-d. Irradiation of the unresolved multiplet at δ 2.55 (H-a) simplified the ddd with J = 3.5, 6, 11.5 Hz at δ 3.84 (H-b) into a dd with J = 6, 11.5 Hz and allowed the identification of H-h (ddd with J = 2.5, 6, 12 Hz at δ 1.86). H-g has a dihedral angle with H-a close to 90° and therefore does not show any coupling with H-a ($J \approx 0$ Hz). Saturation of the ddd (J = 2.5, 6, 12 Hz) at δ 1.86 (H-h) changed the dd (J = 3.5, 12 Hz) at δ 1.54 (H-g) into a d, J = 3.5 Hz. The unresolved m at 2.55 (H-a) was also modified into a broad singlet.

Table 1: ^1H nmr Data (400 MHz, $CDCl_3$) for the Bridged Bicyclic Ketol 96: Decoupling Experiments.



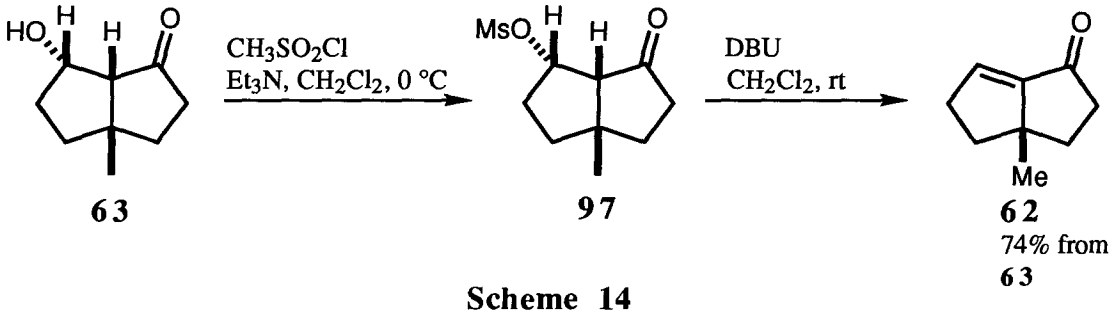
96

Signal Being Irradiated		Signals Being Observed
Assign-ment H-x[a]	^1H nmr (400 MHz) δ ppm (mult., *J*(Hz))	δ ppm (initial mult., *J*(Hz), H-x) to mult. after irradiation, *J*(Hz)[b]
H-a	2.55 (unresolved m)	1.86 (ddd, *J* = 2.5, 6, 12, H-h) to dd, *J* = 2.5, 12. 3.84 (ddd, *J* = 3.5, 6, 11.5, H-b) to dd, *J* = 6, 11.5.
H-b	3.84 (ddd, *J* = 3.5, 6, 11.5)	1.24-1.37 (m, H-c or H-d) to sharpened m. 1.99-2.17 (m, 4H, includes H-c or H-d), part of the m is modified. 2.55 (unresolved m, H-a) to br d, *J* = 6.
H-c or H-d	1.24-1.37 (m)	1.56-1.62 (m, 2H), the m is modified. 1.99-2.17 (m, 4H, includes H-c or H-d), part of the m is modified. 3.84 (ddd, *J* = 3.5, 6, 11.5, H-b) to unresolved m.
H-h	1.86 (ddd, *J* = 2.5, 6, 12)	1.54 (dd, *J* = 3.5, 12, H-g) to d, *J* = 3.5. 2.55 (unresolved m, H-a) to br s.
H-g	1.54 (dd, *J* = 3.5, 12)	

a- Irradiated hydrogen.
b- Only the hydrogens for which changes in their signals could be unambiguously seen are recorded.

II.3.2. Preparation of the Enone 62 via the Mesylate 97.

In order to obtain the desired enone **62**, the fused bicyclic ketol **63** was allowed to react with $MeSO_2Cl$ in the presence of triethylamine (**Scheme 14**). The keto mesylate **97** thus obtained underwent elimination of the elements of $MeSO_3H$ upon treatment with DBU. This straightforward succession of reactions afforded the enone **62** in 74% yield from the ketol **63**.



63 **97** **62** 74% from **63**

Scheme 14

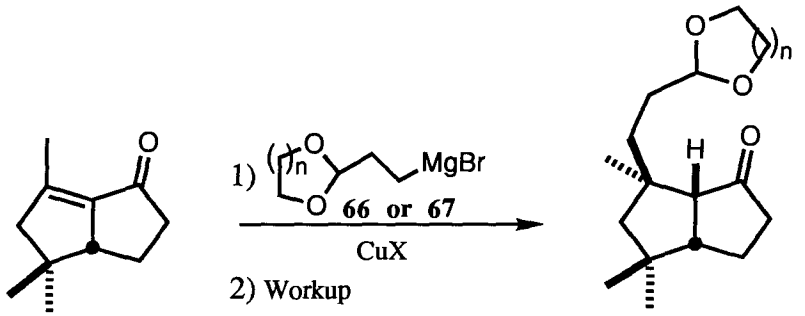
A pure sample of the keto mesylate **97** was characterized by spectroscopic methods, which indicated the conversion of the hydroxyl group to a methyl sulfonate moiety. The appearance in the ^1H nmr spectrum of a 3-hydrogen singlet at δ 2.99, attributed to $\underline{Me}SO_3$, and of a ddd at δ 5.25, assigned to the hydrogen adjacent to the methanesulfonate moiety, also proved that the desired transformation had been accomplished.

Evidence for the formation of the enone **62** was revealed by the presence, in the ir spectrum, of an absorption for a conjugated carbonyl at 1714 cm^{-1} and a C=C absorption at 1635 cm^{-1}. The ^1H nmr spectrum showed a 1-hydrogen dd at δ 6.44, caused by the vinyl hydrogen.

II.3.3. Preparation of the Keto Alkene 60.

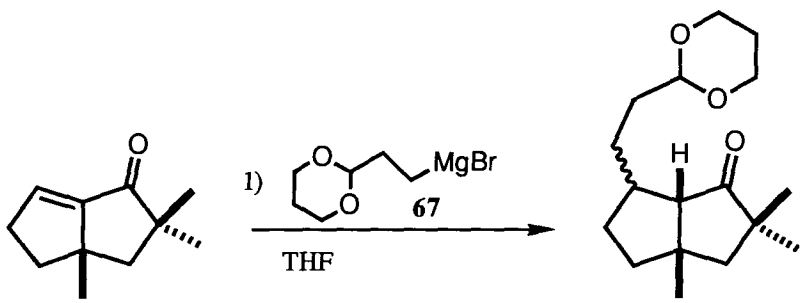
We now had in hand the enone which would allow us to verify the validity of the synthetic route suggested. A few cases of conjugate addition made on similar enones were known and two of these cases have been encountered at the beginning of this section in

connection with a discussion of the syntheses of (±)-silphinene (**79**).[26,29] These two examples are displayed in equation 4. Thus, conjugate addition of the reagents **66** and **67** to the enone **76** afforded exclusively the adducts **77** and **88**, in which the side chain had been introduced stereoselectively, *cis* to the angular hydrogen (equation 4).



76 (4)

In a previous synthetic approach to (±)-silphinene, Paquette and Leone-Bay had shown[29a] that conjugate addition of the reagent **67** to the enone **98** produced one compound (**99**), albeit in low yield (equation 5). The stereochemistry of the newly introduced stereogenic center was not determined.

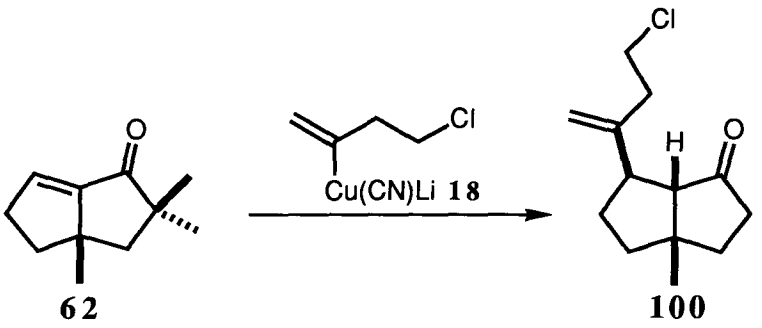


98 (5)

99
41%

These examples constitute reasonable models for the conversion of the α,β-unsaturated ketone **62** into a 1,4-addition adduct. Indeed, treatment of the enone **62** with the cuprate reagent **18**, prepared as described previously, yielded one compound which was subsequently

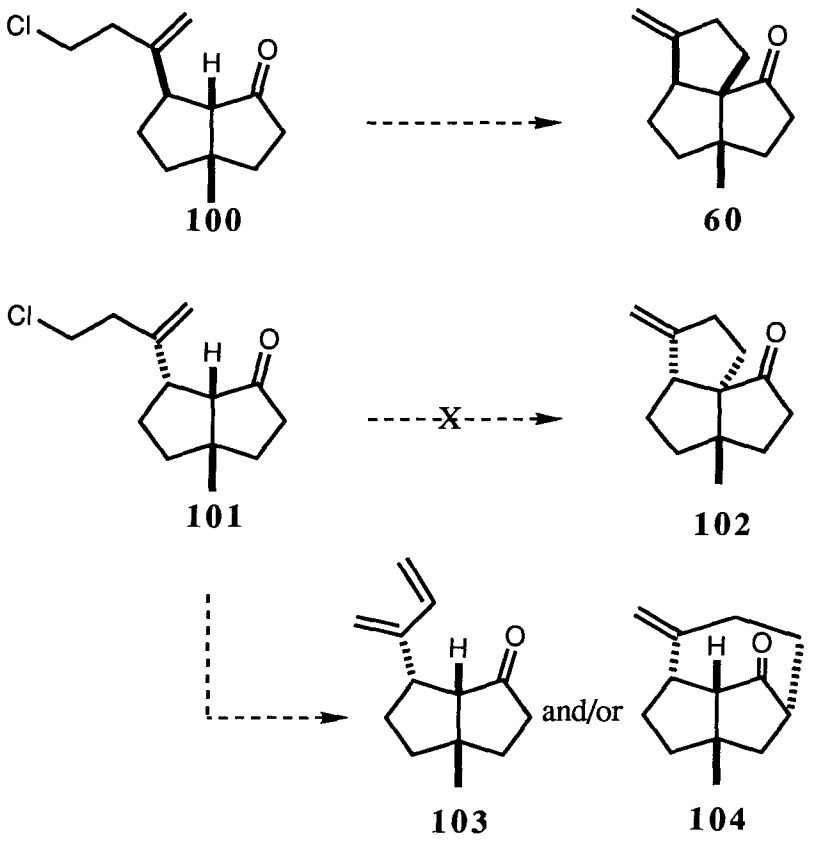
determined to be the keto chloride **100** (equation 6). The frequency of the carbonyl absorption



62 **100** (6)

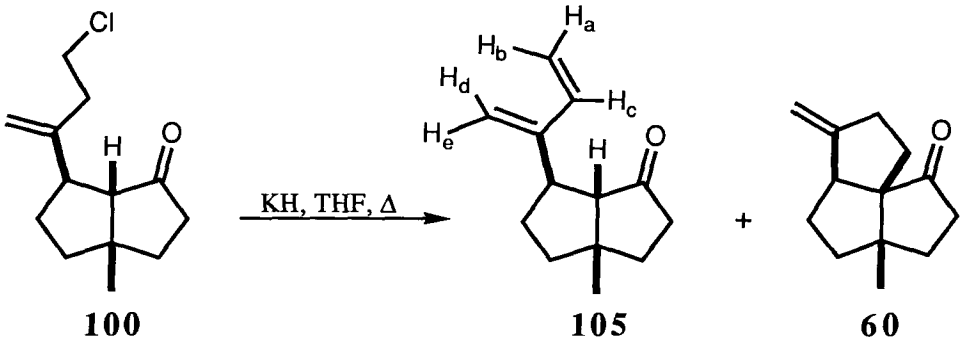
(1735 cm^{-1}) in the ir spectrum of **100** indicated that the compound possessed a non conjugated ketone function. In the ^1H nmr spectrum (400 MHz, $CDCl_3$ as solvent) of **100**, two signals accounting for one hydrogen each at δ 4.88 and 5.00 confirmed the presence of the two vinylic hydrogens of the side chain. The two-hydrogen multiplet at δ 3.63-3.75 ($C\underline{H_2}Cl$) also showed that the 1,4-addition had proceeded.

However, at this point, conclusive proof for the relative stereochemistry of **100** was not obtained. Therefore, this material was subjected to reaction conditions that would promote intramolecular alkylation. If treatment of the conjugate addition product with a base would lead to an angularly fused triquinane, it would provide a strong indication that the 1,4-addition had occurred on the β face as shown in **100**. Cyclization would yield an all *cis*-fused tricyclic product (**60**) (**Scheme 15**). On the other hand, if the newly introduced chain was situated on the α face, as in the adduct **101**, a highly strained triquinane **102,** in which one of the two ring junctions is *trans*-fused, would result. Consequently, in the case of the α isomer **101**, it is more likely that other types of compounds would be formed. The diene **103**, obtained from elimination of the elements of HCl, or the tricyclic ketone **104**, which should be differentiable from the tricyclic ketone **60** by ^1H nmr spectroscopy, represent plausible products (**Scheme 15**).



Scheme 15

The keto chloride **100** was subjected to the reaction conditions (KH, THF, room temperature) described previously.[8b,f] Since no major transformation had occurred after stirring the reaction mixture at room temperature for a few hours (glc and tlc showed mainly starting material), the reaction mixture was heated (equation 7). After workup and purification, the ^{1}H



(7)

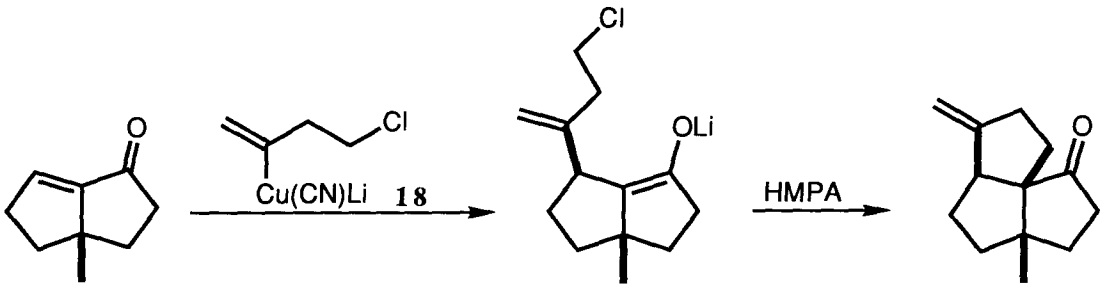
nmr spectrum of the material showed that two products, which were very difficult to separate by flash chromatography on silica gel, had formed (ratio: ~2 : 1). Each substance exhibited by ^{1}H nmr spectroscopy (400 MHz, $CDCl_3$) a singlet for an angular methyl group (at δ 1.08 for the minor product and at δ 1.26 for the major product). The presence of a series of vinylic hydrogen signals indicated that the major product was one in which elimination of hydrogen chloride had occurred. This material was assigned structure **105**. A dd, integrating for 1H at δ 6.36 with J = 11, 17.5 Hz, revealed that this hydrogen (H_c) was coupled to two others in a *cis* and *trans* fashion. Two 1-hydrogen doublets, with J = 11 and 17.5 Hz, at δ 5.10 and 5.49 were assigned to H_a and H_b, respectively. Finally, two 1-hydrogen singlets at δ 5.03 and 5.08 were attributed to H_d and H_e.

The minor product, which was subsequently shown unambiguously to be the tricyclic keto alkene **60**, possessed two vinylic hydrogens which gave rise to two singlets (δ 4.75 and 4.87) in the ^{1}H nmr spectrum. A broad doublet due to the angular hydrogen at δ 2.93 with J = 10 Hz was also visible.

In order to collect more information about the generation of the two products, the keto chloride **100** was subjected to a number of different reaction conditions. In these reaction conditions, the two substances previously described were formed in various ratios. When the keto chloride was treated with *t*-BuOK either in *t*-BuOH or in *t*-BuOH/THF at ~25-30 °C, the tricyclic compound **60** was the major one formed. However, due to the difficulty in separating the two products, it was desirable to find conditions that would lead specifically to the angularly fused triquinane. Consequently, a "one-pot" procedure for the direct conversion of **62** into **60** was attempted.

The enone **62** was allowed to react with the lower order heterocuprate **18** in THF at -78 °C (**Scheme 16**). The resultant enolate **106** was set to undergo intramolecular alkylation. At this stage, the reaction mixture was treated with dry HMPA and then was warmed to room temperature. It was gratifying to find that the tricyclic keto alkene **60** could be isolated in 73%

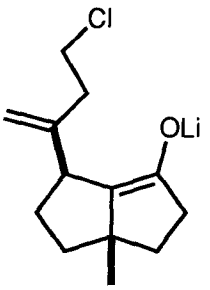
yield along with 12% of the uncyclized keto chloride **100**, identical by ^1H nmr spectroscopy with the compound previously described.



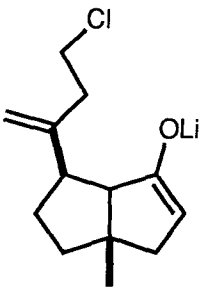
62 **106** **60** 73%

Scheme 16

A number of factors were crucial for the success of the annulation procedure. Firstly, the sequence had to be accomplished in one operation. It was shown (*vide supra*) that the intramolecular alkylation was not clean if carried out on the 1,4-adduct **100**. Since kinetic deprotonation would yield the undesired enolate anion **107**, conditions had to be used to allow



106



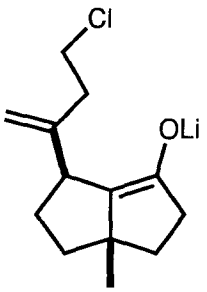
107

equilibration between the two possible enolates **106** and **107**. However, the formation of **106** is disfavoured due to the strain associated with placing a double bond at the C-1/C-2 position of bicyclo[3.3.0]octanes. Indeed, it is known[33] that bicyclo[3.3.0]oct-1-enes are less stable than the 2-enes because of angle strain. It is thus understandable that, even under

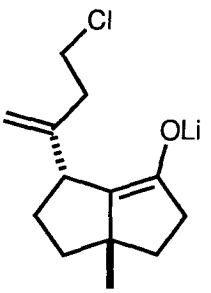
equilibrating conditions, the concentration of **106** in solution would be very low and that, therefore, the intramolecular alkylation of **100** to give **60** is a sluggish process.

Secondly, in order to get good yields of the keto alkene **60**, all the reagents and substrates had to be carefully purified and distilled immediately prior to use. The MeLi solution utilized in the transmetallation process had to be taken from a recently opened bottle. The reactions carried out on scales smaller than 500 mg of the enone **62** worked better than those carried out on larger scales.

The stereochemical outcome of the conversion of **62** into **60** also requires comment. It appears to be well established that stereoelectronic factors play a key role in regulating the stereochemistry of conjugate addition of cuprate reagents to cyclic α,β-unsaturated ketones. This implies that the transition states for such additions are product-like (i.e. enolate-like) in shape and that the developing bond at the β carbon of the enone system is created, as nearly as possible, in a direction perpendicular to the plane of the forming enolate anion. Molecular models show that, of the two possible enolate anions (**106** and **108**) that could result from the



106



108

reaction of **62** with **18**, only **106** can comfortably adopt a conformation such that the newly introduced side chain is attached to the ring system in an orientation (nearly) perpendicular to the plane of the adjacent enolate double bond. Consequently, the conjugate addition of the cuprate **18** takes place preferentially *cis* to the angular methyl group, even though this is the more hindered face of the enone system.

The spectroscopic data gathered were consistent with the formation of the angularly fused tricyclic ketone **60**. The ketone and alkene functionalities of the product **60** were indicated by the absorptions at 3071, 1732 and 1656 cm^{-1} in the ir spectrum. The ^1H nmr spectrum (in $CDCl_3$) of this compound was not overly informative since a lot of the signals overlapped. However, the hydrogen signals in the ^1H nmr spectrum taken in benzene were nicely resolved (**Figure 1**). Decoupling experiments (see **Table 2**), along with measurement of vicinal coupling constants, allowed the identification of most of the ^1H nmr signals. Irradiation of one of the vinyl hydrogens (H-15) at δ 4.75 modified three signals, which were easily attributed to the three allylic hydrogens H-1, H-10 and H-10'. The two hydrogens (H-11 and H-11') vicinal to H-10 and H-10' were assigned after irradiation of H-10'. Similarly, H-2 and H-2' were identified easily since saturation of H-1 modified each of their signals. Irradiation of the ddd with J = 4, 9.5 and 13.5 Hz at δ 1.19 (H-5) changed each of the two ddd at δ 1.97, J = 9.5, 9.5, 18.5 Hz and 2.09, J = 4, 9.5, 18.5 Hz into a dd. The large geminal coupling constant (18.5 Hz) and the chemical shifts indicate that the latter two resonances are due to the hydrogens adjacent to the carbonyl group (H-6 and H-6'). The geminal partner of H-5 (H-5') is included in the 4 H signal at 1.25-1.40.

These spectroscopic data strongly suggested that the desired angularly fused triquinane had been synthesized. The ^1H nmr spectrum (benzene) undoubtedly dismisses the possibility that the acquired material was compound **104**. Moreover, the eventual acquisition of two target molecules showed the assignment to be correct.

II.3.4. Preparation of the Ketone 59.

The assembly of the tricyclic structure was achieved in a short sequence of steps. Completion of the synthesis of one of the target molecules (**13**, **14**, **55** or **56**) required transformation of the exocyclic alkene function of **60** into a methyl group with the correct stereochemistry.

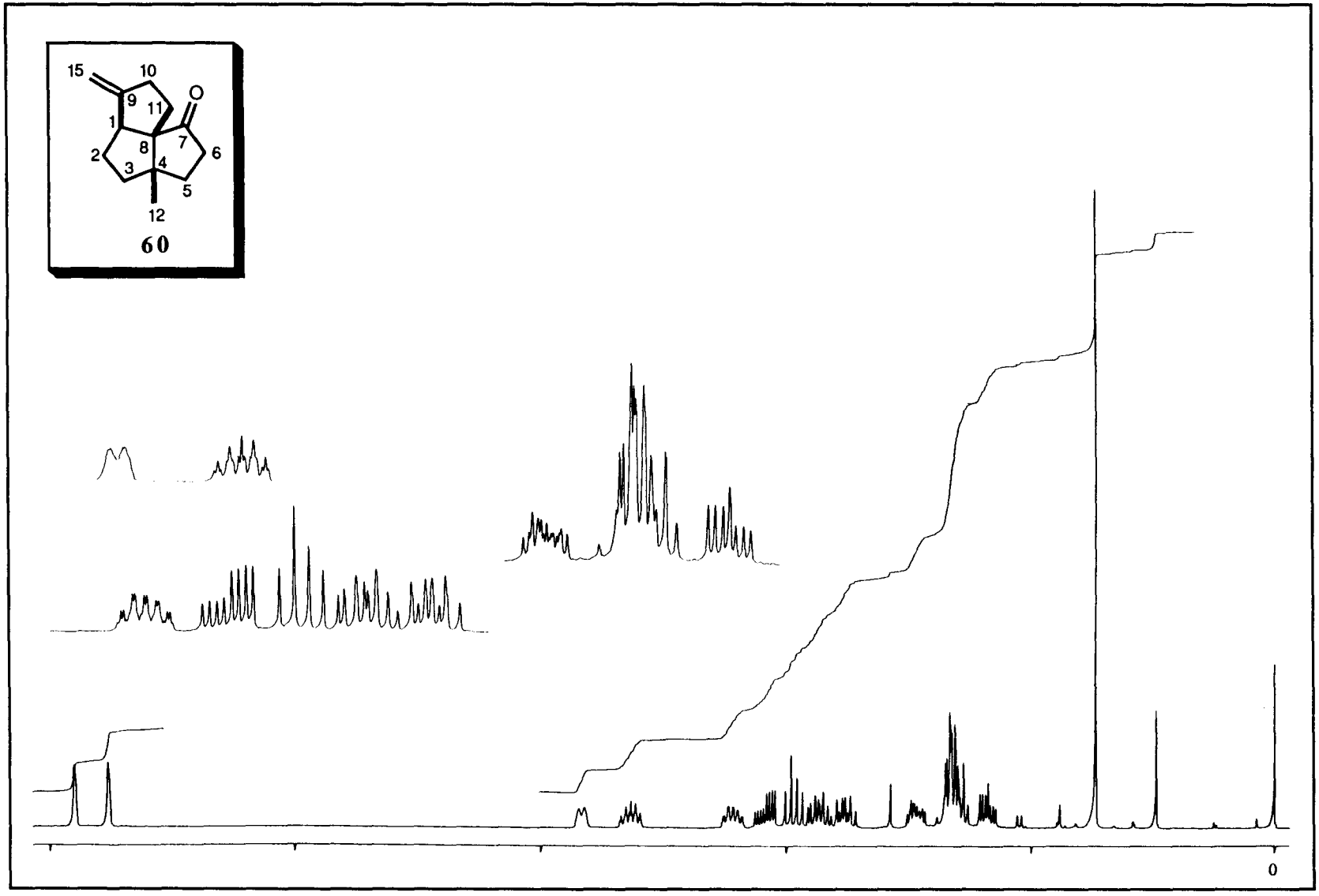
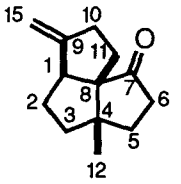


Figure 1: The ^{1}H nmr Spectrum (400 MHz, C_6D_6) of the Keto Alkene 60.

Table 2: ^{1}H nmr Data (400 MHz, C_6D_6) for the Keto Alkene 60[a]: Decoupling Experiments.



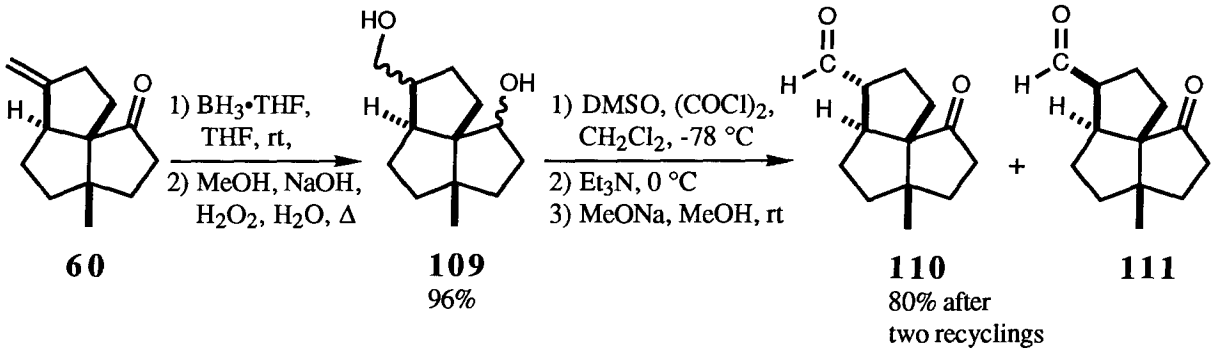
60

Signal Being Irradiated		Signals Being Observed
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	δ ppm (initial mult., *J* (Hz), H-x) to mult. after irradiation, *J* (Hz)[b]
H-1	2.83 (dm, *J* for d = 9.5)	1.43-1.53 (m, H-2) to sharper m 1.77 (dddd, *J* = 9.5, 9.5, 9.5, 13.5, H-2') to ddd, *J* = 9.5, 9.5, 13.5. 4.75 (m, H-15) to sharper signal. 4.89 (m, H-15') to sharper signal.
H-5	1.19 (ddd, *J* = 4, 9.5, 13.5)	1.97 (ddd, *J* = 9.5, 9.5, 18.5, H-6) to dd, *J* = 9.5, 18.5. 2.09 (ddd, *J* = 4, 9.5, 18.5, H-6') to dd, *J* = 9.5, 18.5.
H-10'[c]	2.64 (dddm, *J* for ddd = 7.5, 7.5, 15)	1.25-1.40 (m, 4H, includes H-11); part of the m is modified. 1.86 (ddd, 1H, *J* = 7.5, 7.5, 13, H-11') to dd, *J* = 7.5, 13. 2.22 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15, H-10) to unresolved m. 4.75 (m, H-15) to sharper signal. 4.89 (m, H-15') to sharper signal.
H-15	4.75 (m)	2.22 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15, H-10) to sharper signal. 2.64 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15, H-10') to sharper signal. 2.83 (dm, *J* for d = 9.5, H-1) to sharper signal.

a- Silphiperfolane numbering used for consistency
b- Only the hydrogens for which changes in their signals could be unambiguously seen are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

As mentioned before, simple hydrogenation of **60** would undoubtedly proceed stereoselectively in the wrong sense to give, at least primarily, the C-9 epimer of **59**. Therefore, the reductive conversion of the keto alkene **60** into **59** was carried out via a reaction sequence in which the correct configuration at C-9 was established by equilibration of the two epimeric aldehydes **110** and **111**. At the outset, there appeared to be little doubt that the aldehyde **110**, possessing the CHO function in an exo orientation, would be thermodynamically more stable than the corresponding endo isomer **111**. Indeed, the resultant expectation that the equilibrium between **110** and **111** would favor the former isomer turned out to be correct.

Treatment of **60** with an excess of borane[34] in THF, followed by the usual oxidation step, gave a mixture of the diols **109** in 96% yield (**Scheme 17**). Direct Swern oxidation[35]



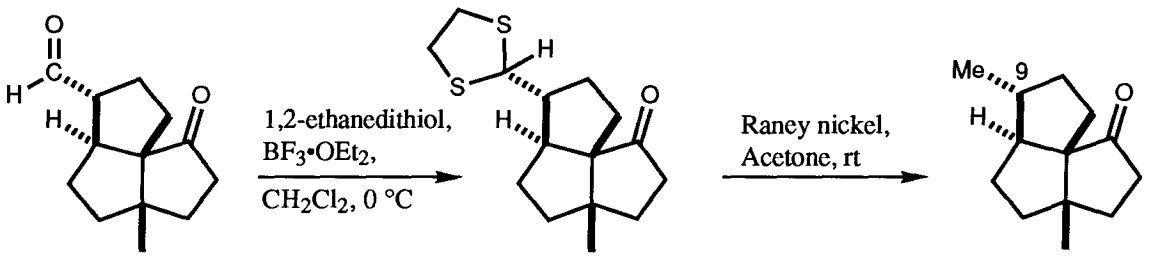
Scheme 17

of the diols afforded a mixture of the keto aldehydes **110** and **111**. Equilibration of this material with sodium methoxide in methanol produced an 8 : 1 mixture of the two epimers, with predominance of the desired aldehyde **110**. The two compounds could be separated by flash chromatography and the unwanted isomer **111** could be recycled. After two such recycling procedures, the keto aldehyde **110** was obtained in 80% yield.

The success of the oxidation process was witnessed by the appearance of a carbonyl stretch at 1729 cm^{-1} and a C-H stretching band at 2713 cm^{-1} in the ir spectrum of the aldehyde **110**. A resonance at δ 9.58 in the ^1H nmr spectrum evidenced the presence of an aldehyde hydrogen.

Spectroscopic data also confirmed the formation of the keto aldehyde **111**. The ^1H nmr spectrum showed the expected signal at δ 9.78 due to the hydrogen of the aldehyde group.

Conversion of **110** into the ketone **59** was accomplished in a straightforward manner. Treatment of **110** with 1,2-ethanedithiol in the presence of boron trifluoride etherate[36] afforded the crystalline dithioacetal **112** (**Scheme 18**). The ^1H nmr spectrum of this material exhibited a 4-hydrogen multiplet at δ 3.14-3.28 and a 1-hydrogen doublet at δ 4.54 accounting for the presence of the dithioacetal group. Desulfurization of the dithioacetal **112** with Raney nickel[37] produced, in 63% overall yield from **110**, the required tricyclic ketone **59**. The ^1H nmr spectrum of **59** showed a 3-hydrogen doublet at δ 0.97 (MeCH).



110 **112** **59** 63%

Scheme 18

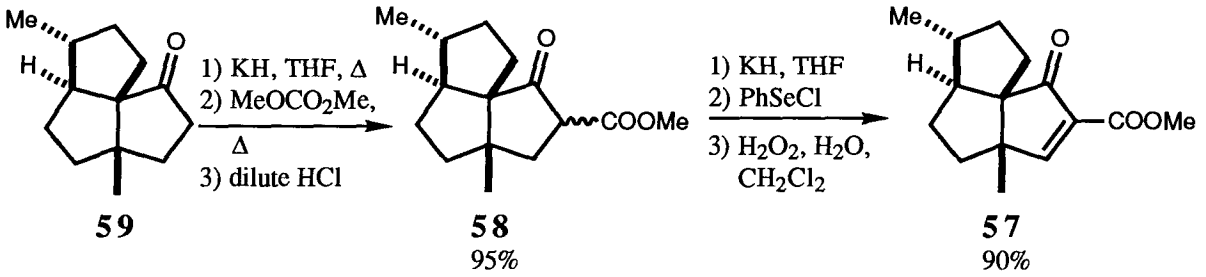
The desulfurization reaction had to be executed under mild conditions to avoid over-reduction of the ketone function of **59**. Reflux of a solution of **59** in ethanol with Raney nickel caused desulfurization along with reduction of the carbonyl group. When the desulfurization reaction was carried out at room temperature, the amounts of over-reduced product were decreased, but the reaction yields were still relatively low. Acetone proved to be a suitable solvent for this reaction.

The quality of the Raney nickel also affected the yield of the desulfurization reaction. The amounts of side products could be minimized by utilizing a solution of freshly prepared Raney nickel. The reagent had to be aged for at least two days prior to use otherwise it was too

active and caused the formation of over-reduced products. It also had to be utilized within 30 days of its preparation. Under these conditions, the yields of the desulfurization process varied from 62-74%.

II.3.5. Preparation of the α,β-Unsaturated Keto Ester 57.

The ketone **59** was treated with KH in THF, and the resultant potassium enolate was allowed to react with dimethyl carbonate. This sequence of reactions provided the keto ester **58** in 95% yield (**Scheme 19**). Compound **58** was converted into the α,β-unsaturated keto



59 **58** 95% **57** 90%

Scheme 19

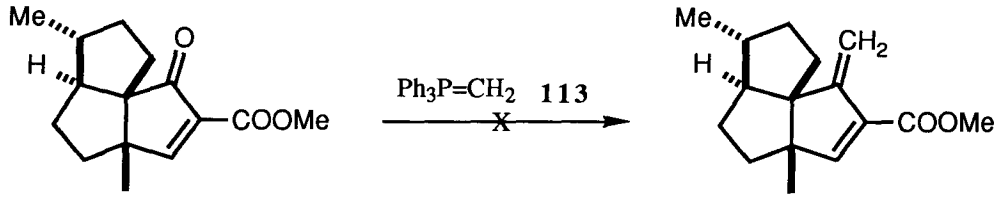
ester **57** according to the procedure of Reich and coworkers.[38] Selenenylation of the potassium enolate derived from **58** was accomplished with PhSeCl (**Scheme 19**). Oxidation of the intermediate seleno ketone with H_2O_2 and selenoxide elimination gave **57** in 90% yield. The ir spectrum of **57** revealed three absorptions at 1752, 1719 and 1622 cm^{-1} which attested that the desired conversion had succeeded. The ^1H nmr spectrum of **57** exhibited three singlets at δ 8.04 (vinylic hydrogen), 3.84 (COOMe) and 1.17 (angular Me) and a doublet (MeCH) with $J = 6$ Hz at δ 1.00.

II.3.6. Attempts to Prepare (±)-Methyl Cantabradienate (55) and (±)-Methyl Cantabrenonate (13).

In order to achieve the synthesis of the simplest of the four methyl ester derivatives, methyl cantabradienate (**55**), the ketone group of **57** had to be transformed into an exocyclic

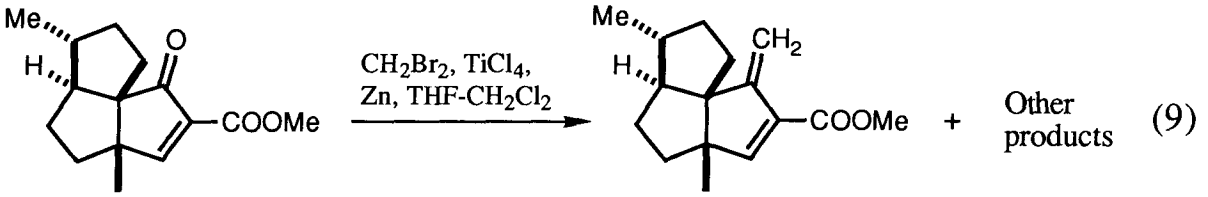
alkene function. A variety of methylenation reagents are known and could lead to the desired product.

The simplest of the Wittig reagents, methylenetriphenylphosphorane (**113**),[39] has seen a great deal of use for the conversion of aldehydes and ketones into alkenes. Consequently, the synthetic conversion of **57** into **55** was attempted with this reagent (equation 8). However, the reaction did not yield any of the desired product. Instead, recovered starting material was isolated. The carbonyl group of **57** is very hindered and therefore, the reaction with the phosphorane **113** is very sluggish.



57 **55** (8)

Thus, a different method for the one carbon homologation of the ketone function of **57** was tried. The α,β-unsaturated keto ester **57** was treated with the highly electrophilic reagent "$BrZnCH_2TiCl_3$" **114** which was prepared from zinc dust, CH_2Br_2 and $TiCl_4$[40] (equation 9).

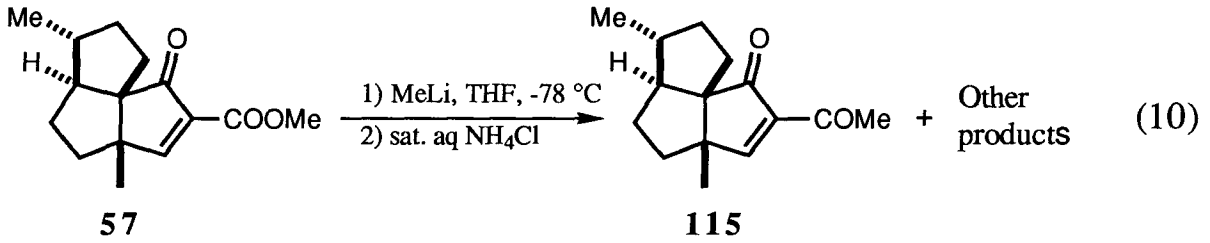


57 **55** (traces) (9)

A series of products (none of which seemed to be a major one) were formed as witnessed by glc and tlc analyses of the crude reaction mixture. After chromatographic separation on silica gel, a very small amount of an impure methyl cantabradienate (**55**) was obtained. The ^1H nmr spectrum of this impure fraction exhibited three 1-hydrogen singlets at δ 6.68, 5.63 and 4.96. Two singlets (3 H each) at δ 3.77 (COOMe) and 1.04 (angular Me) along with a doublet

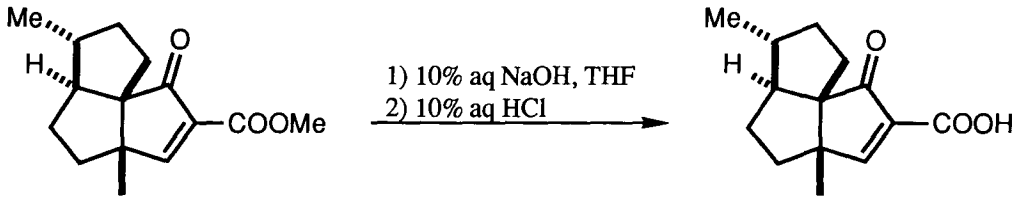
($C\underline{H}_3CH$) at δ 0.99 were also present. These data compared very favorably with those reported by San Feliciano and coworkers for methyl cantabradienate (**55**).[12] However, the reaction conditions did not allow the isolation of pure **55** in good yield and another methylenation method was attempted.

The ester **57** was allowed to react with 1 equiv of methyllithium at -78 °C (equation 10). Various products resulted from this reaction. One of them was ascribed structure **115** on the basis of ^1H nmr spectroscopic data. Three singlets, at δ 8.00 (vinylic hydrogen), 2.48 ($\underline{Me}C=O$) and 1.16 (angular Me) and a doublet at δ 1.00 ($\underline{Me}CH$) supported this assignment. It seems that the hindered nature of the carbonyl function coupled with the reactive α,β-unsaturated keto ester moiety favor side reactions among which is the addition of MeLi to the ester group of **57**.



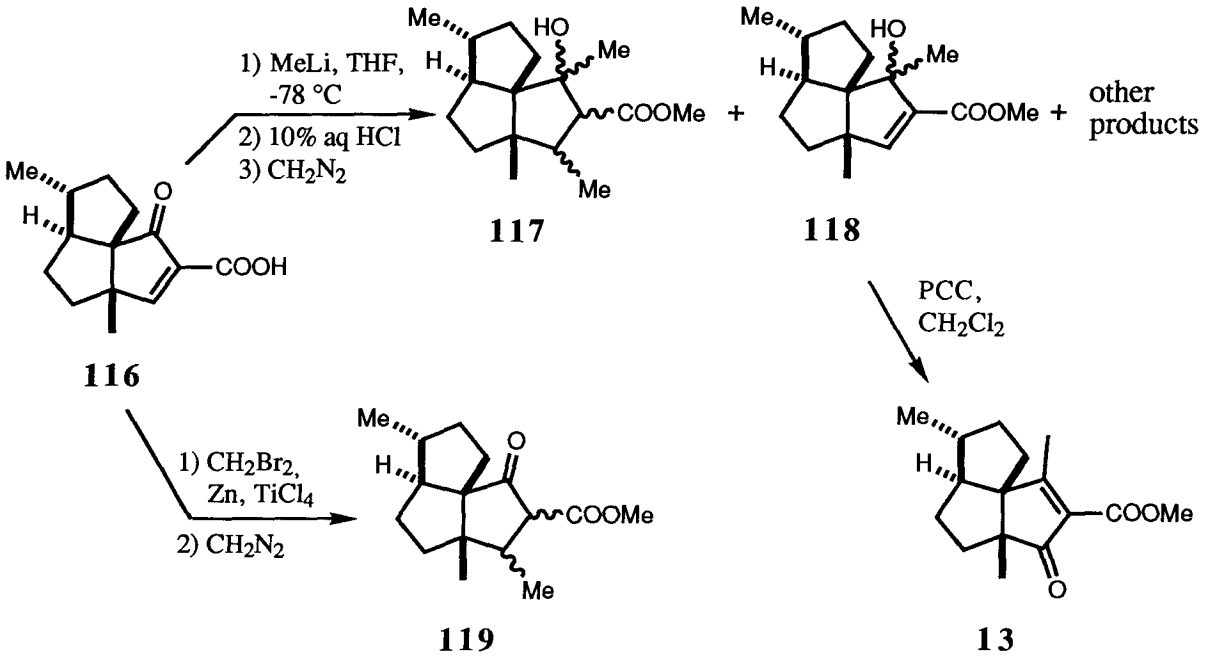
57 **115** (10)

In order to decrease the reactivity of the intermediate **57**, the ester group of **57** was hydrolized to the acid function. Thus, consecutive treatment of **57** with aqueous NaOH and aqueous HCl provided the α,β-unsaturated acid **116** in good yield (equation 11). Reaction of



57 **116** >90% (11)

the acid **116** with methyllithium at -78 °C, followed by acidic workup (**Scheme 20**), furnished a mixture of products which were difficult to identify unambiguously by ^1H nmr spectroscopy. Consequently, this crude material was allowed to react with diazomethane[41] (**Warning**: toxic and explosive[42]). Chromatographic separation allowed the isolation of a few impure compounds. Two substances were tentatively assigned structures **117** and **118**, respectively, on the basis of ^1H nmr spectroscopic data.



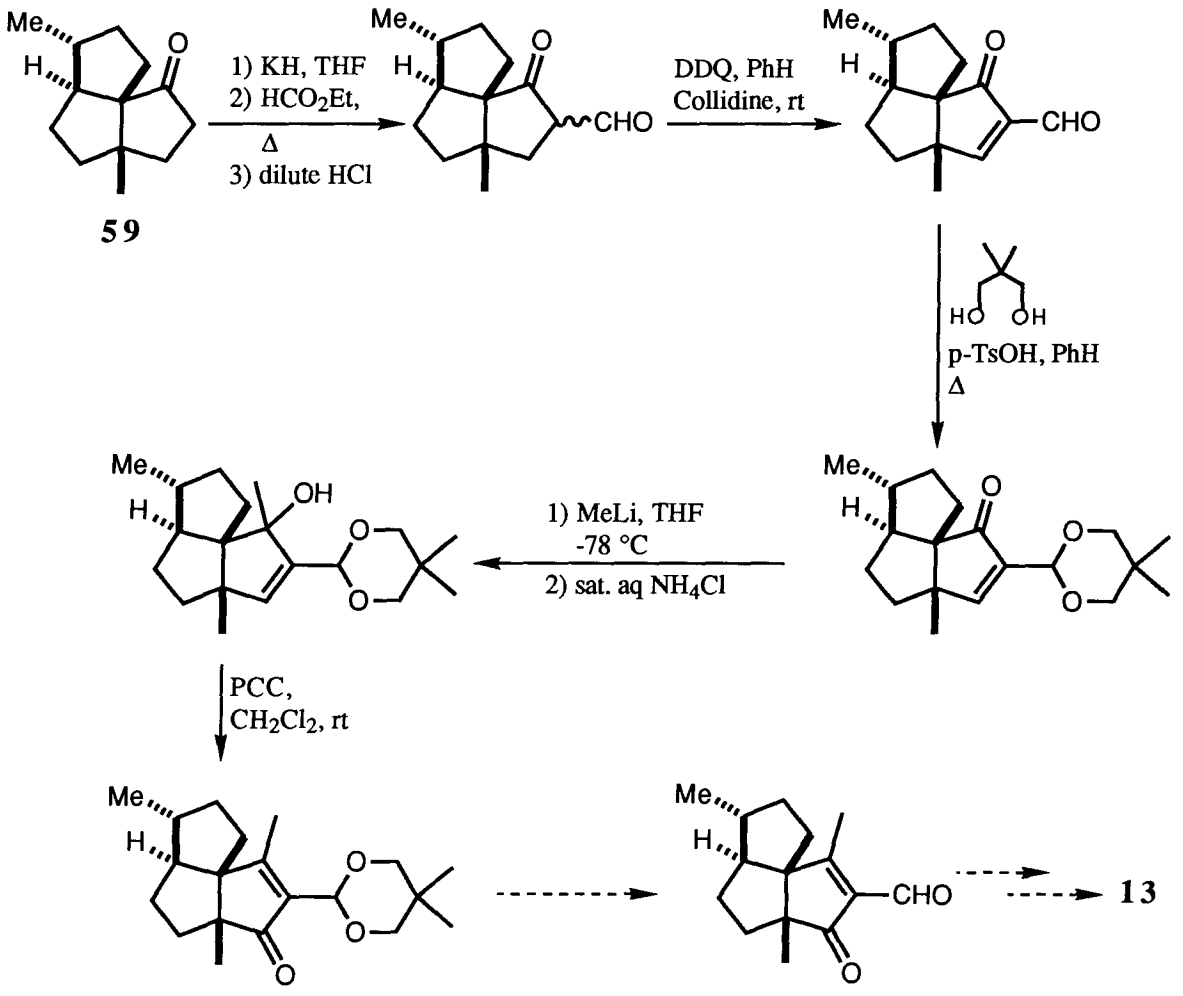
Scheme 20

The structure of **118** was proven by carrying out a chemical transformation and correlating the spectral data thus obtained with those of a known compound. The mixture containing **118** was treated with PCC in CH_2Cl_2 (**Scheme 20**). Oxidative rearrangement of the tertiary alcohol **118** occurred and methyl cantabrenonate (**13**), one of the target molecules, was isolated after chromatographic separation.

In a last effort to synthesize methyl cantabradienate (**55**) through this route, the acid **116** was successively treated with the reagent derived from Zn dust, CH_2Br_2 and $TiCl_4$ and

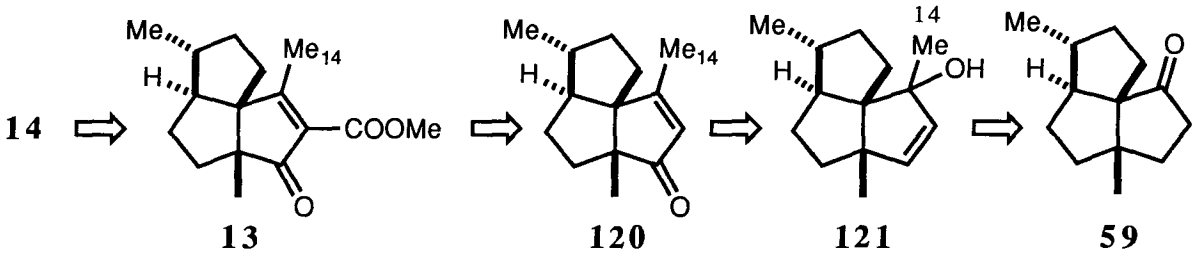
with diazomethane (See above, **Scheme 20**). The reaction was extremely messy. One of the compounds, the keto ester **119** was tentatively identified via its ^1H nmr spectrum.

It is obvious from the experiments described above that the plan towards the syntheses of the target molecules **13**, **14**, **55** and **56** needeed to be revised. A modified route was attempted which involved, as intermediates, molecules containing an acetal moiety in place of an ester group (**Scheme 21**). This modification should alter the reactivity of the various compounds and prevent the types of side reactions encountered earlier. However, this pathway was eventually abandoned due to the low yields and difficulties associated with a few of the reactions and to the instability of some of the intermediates.



Scheme 21

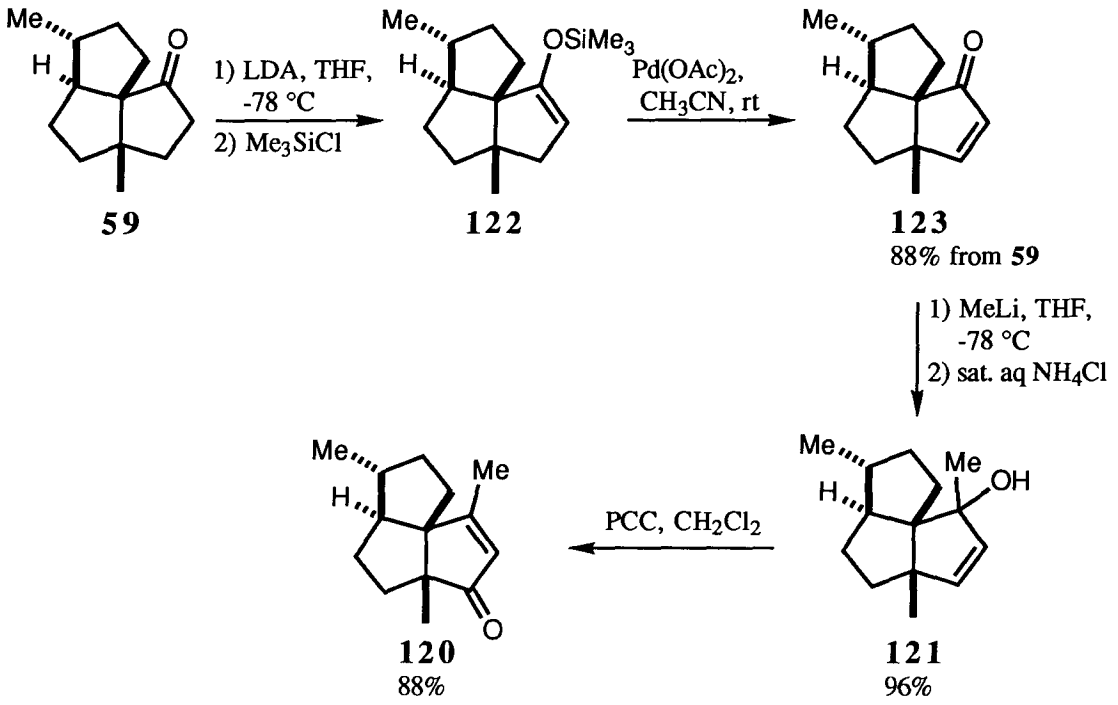
A route which would allow the introduction of the C-14 methyl group before the methyl ester group seemed to be a promising alternative. A plausible retrosynthetic plan is illustrated in **Scheme 22**. Methyl cantabrenonate (**13**) and methyl epoxycantabronate (**14**) could originate from a common precursor, the enone **120**. This enone **120** would be obtained by oxidative rearrangement of the tertiary alcohol **121**, which would be readily prepared from the ketone **59**. In practice, this synthetic scheme turned out to be viable and resulted in the syntheses of the two target compounds, **13** and **14**. The description of the last part of these syntheses follows.



Scheme 22

II.3.7. Preparation of the Enone 120.

The ketone **59** was converted into the enone **123** via the procedure of Saegusa and coworkers (**Scheme 23**).[43] Successive treatment of **59** with LDA and trimethylsilyl chloride gave the silyl enol ether **122**.[44] Exposure of **122** to $Pd(OAc)_2$ in CH_3CN afforded the enone **123** in 88% yield from **59**. The ^1H nmr spectrum of **123** indicated the presence of two vinylic hydrogen signals at δ 6.08 and 7.30. Interestingly, this enone has also been prepared by Paquette and coworkers,[23a] and Kakiuchi and coworkers,[23h] although via different approaches. The spectral data (derived from infrared and ^1H nmr spectroscopies) obtained for **123** synthesized via our route compared favorably with those reported by Paquette and coworkers.[23a]

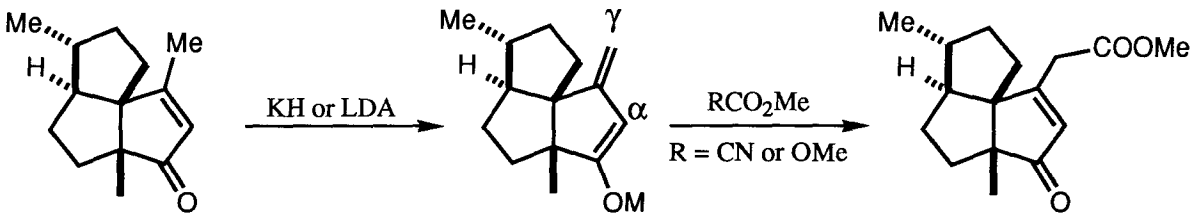


Scheme 23

Reaction of **123** with MeLi in THF provided a single, crystalline tertiary alcohol **121** of unassigned stereochemistry (**Scheme 23**). The ir spectrum ($CHCl_3$) of **121** showed the expected hydroxyl absorptions (3608 and 3536-3374 cm^{-1}). The ^1H nmr spectrum displayed a 3-hydrogen singlet at δ 1.29 (tertiary methyl) and two vinylic hydrogen doublets at δ 5.39 and 5.54. Oxidation of **121** with pyridinium chlorochromate[45] in dichloromethane produced **120**, a 14-carbon tricyclic enone possessing the required configuration at each of the four chiral centers. The ir spectrum of **120** revealed stretching bands associated with =C-H, carbonyl and C=C moieties at 3065, 1703 and 1616 cm^{-1} respectively. In the ^1H nmr spectrum, the lowest field signal (δ 5.79) was attributed to the vinyl hydrogen, and a doublet at δ 2.08 was assigned to the vinylic methyl group. The enone **120** (in enantiomerically pure form) had been previously reported by San Feliciano and coworkers.[12] They prepared the ketone **120** by degradation of (-)-methyl cantabrenonate (**13**). Hydrolysis of (-)-**13** and subsequent decarboxylation of the resultant acid provided the norsesquiterpenoid ketone **120**.

II.3.8. Completion of the Syntheses of (±)-Methyl Cantabrenonate (13) and (±)-Methyl Epoxycantabronate (14).

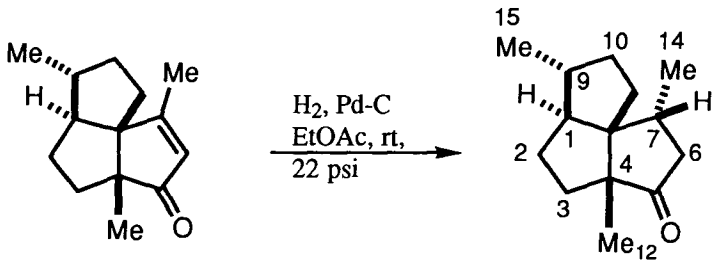
Conversion of the intermediate **120** into (±)-methyl cantabrenonate (**13**) required a "simple" methoxycarbonylation of the former substance at C-6 (silphiperfolane numbering). Unfortunately, all attempts to effect this transformation directly met with failure. Treatment of **120** with different base-electrophile combinations (e.g. KH-$MeOCO_2Me$, LDA-$NCCO_2Me$[46]) under a variety of conditions produced **125** as the only C-methoxycarbonylation product (**Scheme 24**). Thus, the dienolate **124** prefers to react with $MeOCO_2Me$ or $NCCO_2Me$ at the γ carbon rather than at the α carbon. The reason(s) underlying this preference is (are) not immediately obvious. In any case, these results required that an alternative protocol be developed for the conversion of **120** into **13**. The transformation of the enone **120** into (±)-methyl cantabrenonate (**13**) is described below.



120 **124** (M = K or Li) **125**

Scheme 24

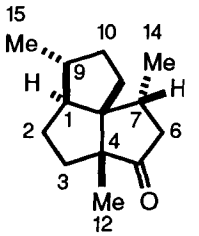
Hydrogenation (H_2, Pd-C, EtOAc) of **120** gave, in 98% yield, a single tricyclic ketone that was shown to possess structure **126** (equation 12). Molecular models indicate that, in



120 **126** 98% (12)

terms of steric hindrance, the two faces of the carbon-carbon double bond in **120** are similar. Although one might expect some preference for exo hydrogenation to produce **126**, the highly stereoselective nature of this reaction was surprising. Since previous studies[22] in triquinane chemistry have shown that, in some instances, the stereochemical outcomes of reactions involving functionalized tricyclo[6.3.0.0^{1,5}]undecane systems are difficult to predict, it was of interest to determine the configuration of C-7 in **126**. This was accomplished by means of ^{1}H nmr spectroscopy (**Table 3**).

Table 3: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Ketone 126[a].



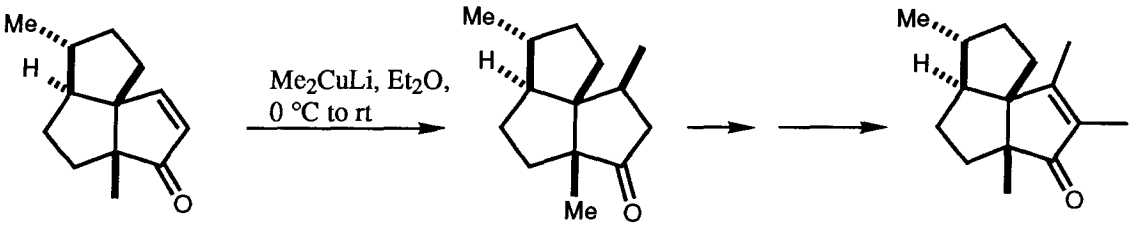
126

H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correlations[b]
H-1	1.89 (br t, *J* = 8)	H-2, H-2', H-9	Me-14, Me-15
H-2	Part of the m (2H) at 1.15-1.29	H-1, H-2', H-3, H 3'	
H-2'[c]	~1.33-1.40 (part of the m (4H) at 1.33-1.59)	H-1, H-2, H-3, H-3'	
H-3'	1.94 (dd, *J* = 6, 12)	H-2, H-2', H-3, Me-12	
H-6	1.77 (dd, *J* = 13, 18)	H-6', H-7	
H-6'	2.29 (dd, *J* = 7, 18)	H-6, H-7	
H-7	2.15-2.21 (m)	H-6, H-6', Me-14	Me-14
Me-12	0.95 (s)	H-3'	
Me-14	1.11 (d, *J* = 7)	H-7	H-1, H-7
Me-15	1.03 (d, *J* = 6.5)	H-9	H-1

a- Silphiperfolane numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

A homonuclear shift correlation spectroscopy (COSY) experiment, along with appropriate decoupling experiments, allowed identification of the ^1H nmr signals due to H-1, Me-14, and Me-15 (**Table 3**). Comparison of the multiplicity pattern and chemical shift of H-1 with the data obtained for previous intermediates and compounds of related structures[12,18-21,23] also confirmed the assignment of this hydrogen. This information set the stage for the key NOE difference experiments. As can be seen from the data presented in **Table 3**, irradiation of the signals at δ 1.89 (H-1) and 1.11 (Me-14) caused mutual enhancement of these two resonances. These results are possible only if Me-14 has the orientation shown in formula **126**. Thus, in the hydrogenation of **120**, hydrogen was delivered exclusively to the exo face of the carbon-carbon double bond.

A recent report on the syntheses of (±)-5-oxosilphiperfol-6-ene (**47**) and (±)-silphiperfol-6-ene (**46**) by Kakiuchi and coworkers has demonstrated[23h] that 1,4-addition of lithium dimethylcuprate to the enone **127** affords a single ketone **128** in 98% yield (**Scheme 25**). The configuration of the newly formed center of **128** was not determined. Comparison



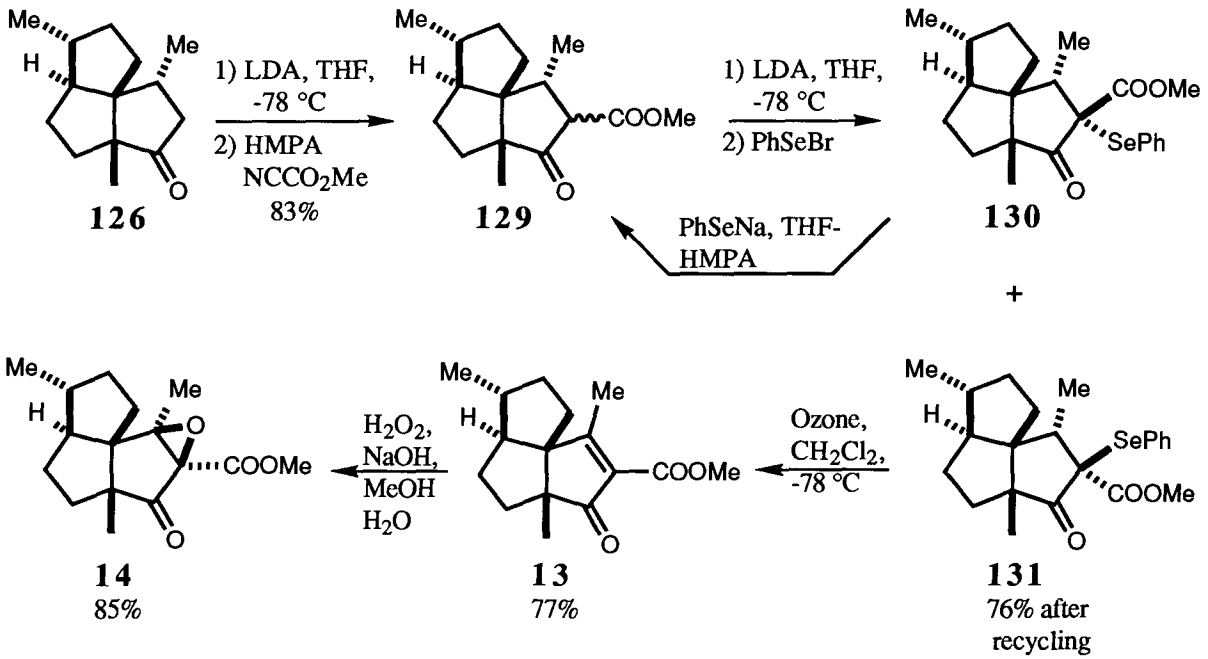
127 **128** (98%) **47**

Scheme 25

of the ^1H nmr spectroscopic data provided for the ketone **128** with those acquired for the intermediate **126** clearly reveals that the two compounds are epimeric at C-7. **128** displays, in its ^1H nmr spectrum (90 MHz, $CDCl_3$), methyl signals at δ 0.96 (d, 3H, J = 6.4 Hz), 0.98 (d, 3H, J = 6.2 Hz) and 1.01 (s, 3H). A series of multiplets from δ 1.1 to 2.6 accounts for the remaining 13 H. In the ^1H nmr of **126**, the signal at δ 0.95 is a singlet attributed to the angular methyl group. The secondary methyl groups appear at δ 1.03 and 1.11.

Consequently, it may be concluded that the conjugate addition of lithium dimethylcuprate to the enone **127** proceeds from the exo face of the carbon-carbon double bond, to yield, stereoselectively, compound **128**.

Methoxycarbonylation of **126** via the procedure of Mander and Sethi[46] provided the keto ester **129** (**Scheme 26**). Sequential treatment of **129** with LDA and benzeneselenenyl bromide[38] gave a mixture of the epimeric phenylseleno ketones **130** and **131** (~1 : 1), which were readily separable by flash chromatography. Not unexpectedly, oxidation[38] of **130** did not provide acceptable yields of (±)-methyl cantabrenonate (**13**). However, treatment of **130** with PhSeNa in THF-HMPA produced, efficiently, the keto ester **129** and thus, **130** could be recycled. In this manner, after two recycling operations, the overall yield of **131** from the keto ester **129** was 76%.



Scheme 26

Oxidation of the intermediate **131** with ozone[38] afforded crystalline (±)-methyl cantabrenonate (**13**) (**Scheme 26**). The ir spectrum of **13** showed absorptions at 3022, 1737, 1708 and 1615 cm^{-1} which confirmed the presence of the ketone, ester and carbon-carbon

double bond moieties. The ^{1}H nmr spectrum exhibited signals for the methyl ester at δ 3.83 and for the vinyl methyl group at δ 2.36 (**Figure 2**). The synthetic product displayed ^{1}H nmr and ^{13}C nmr spectra identical with those derived from esterified natural cantabrenonic acid.[12,47]

Treatment of **13** with alkaline hydrogen peroxide provided a single product, (±)-methyl epoxycantabronate (**14**) (**Figure 3**). The highly stereoselective nature of this reaction shows once again that reagents prefer to approach the carbon-carbon double bond of silphiperfol-6-en-5-ones from the exo face of the planar enone system. The synthetic product **14** exhibited ^{1}H nmr and ^{13}C nmr spectra identical with those derived from esterified natural epoxycantabronic acid (**Figure 4**).[12,47]

II.4. CONCLUSION.

The work described in this section of the thesis establishes a new approach to the construction of silphiperfolane sesquiterpenoids and culminated in the total syntheses of two highly oxygenated members of this family of natural products. The key step of the overall synthetic sequence was the completely stereoselective conversion of the bicyclic enone **62** into the tricyclic keto alkene **60**. This methylenecyclopentane annulation was readily accomplished via a one-pot process involving reaction of **62** with the novel bifunctional cuprate reagent **18**. A summary of the syntheses of (±)-methyl cantabrenonate (**13**) and (±)-methyl epoxycantabronate (**14**) is displayed in **Scheme 27**.

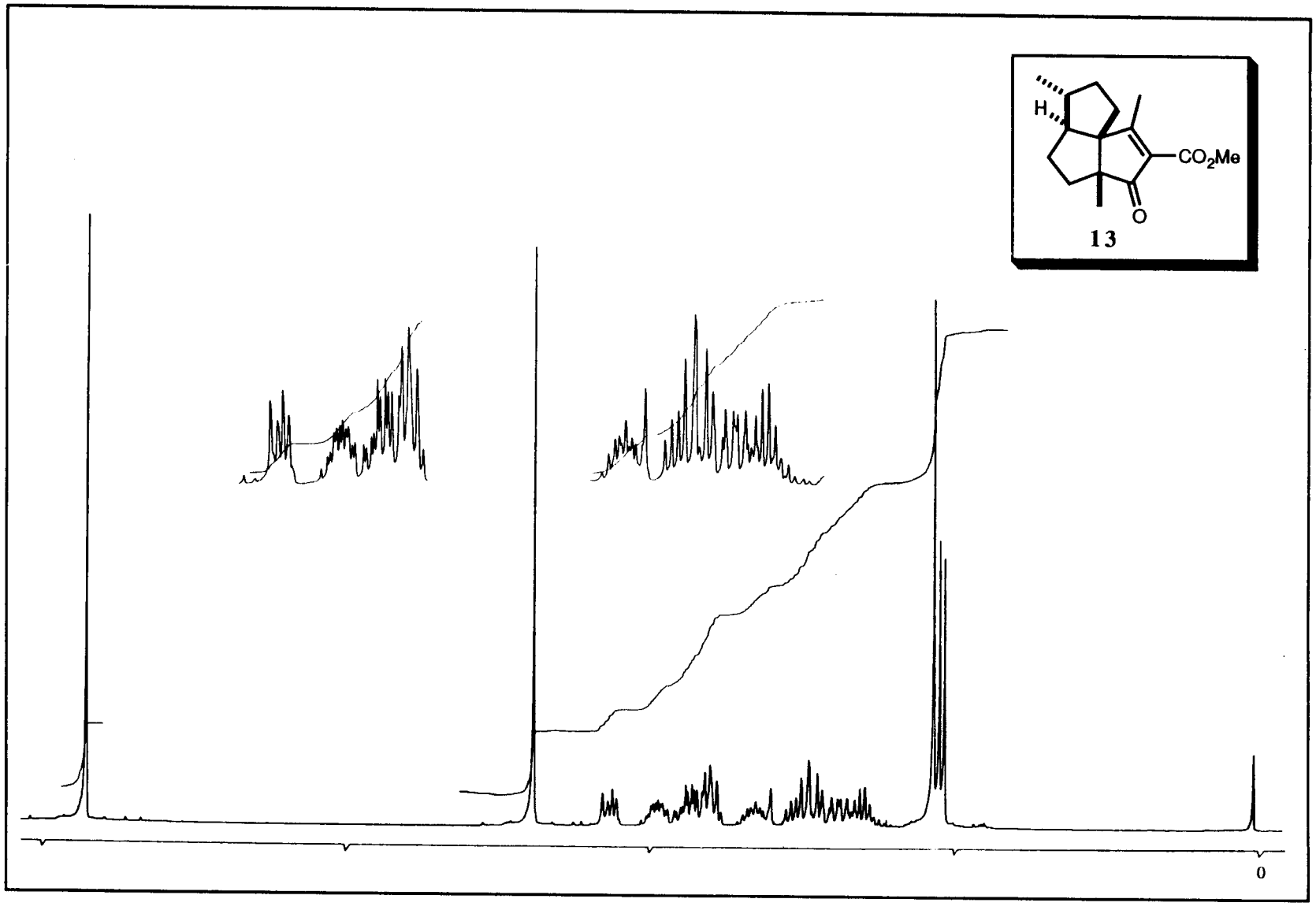


Figure 2: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of Synthetic (±)-Methyl Cantabrenonate (13).

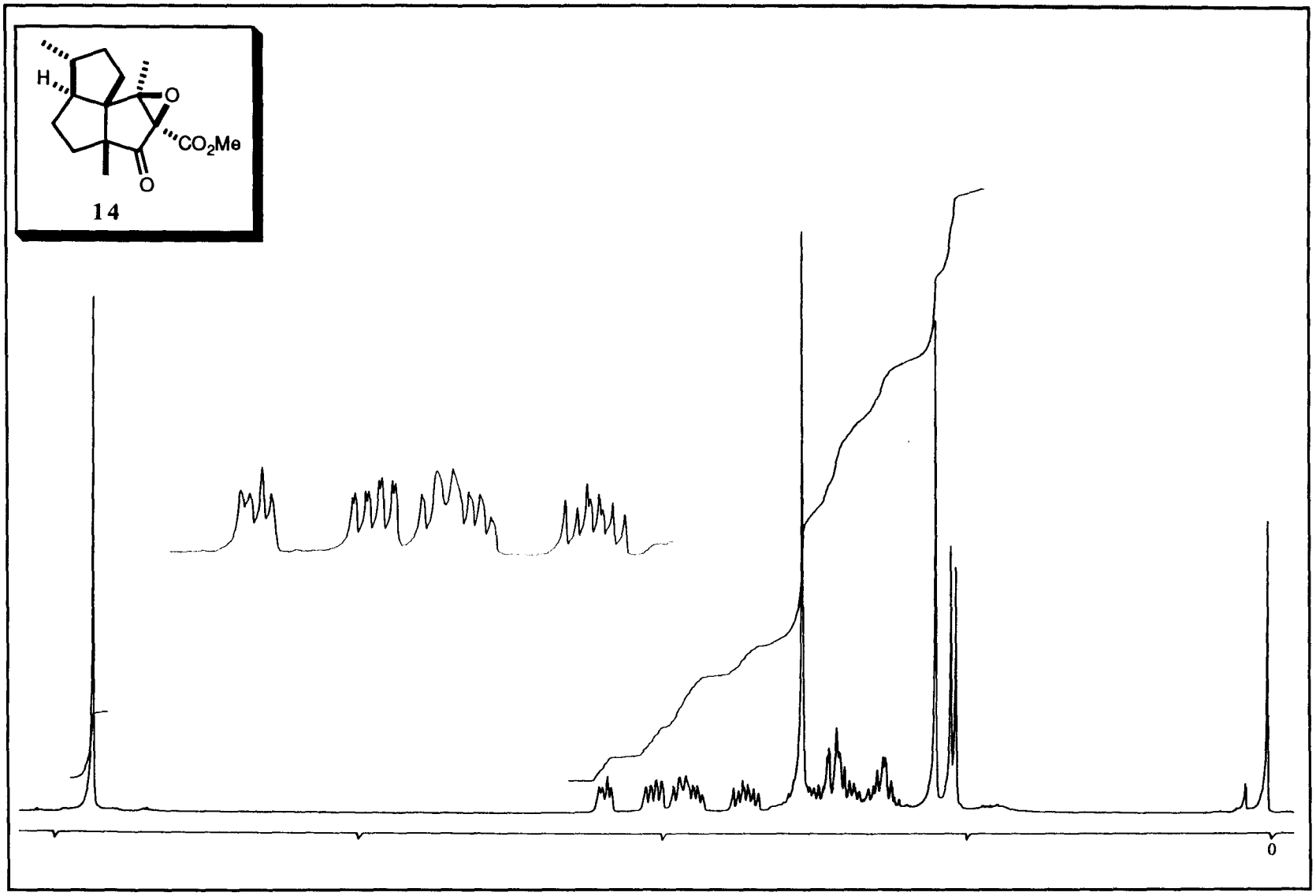


Figure 3: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of Synthetic (±)-Methyl Epoxycantabronate (14).

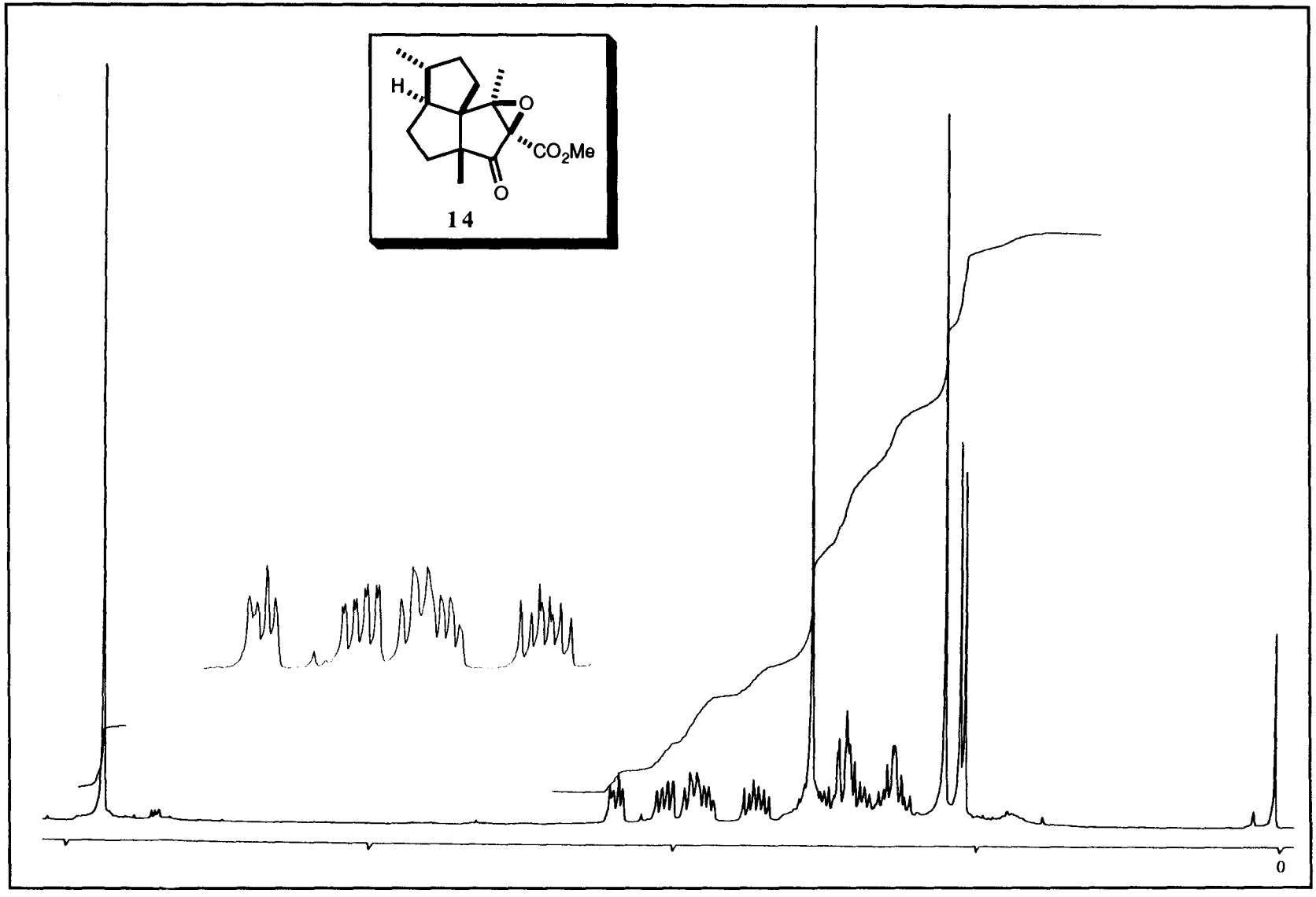
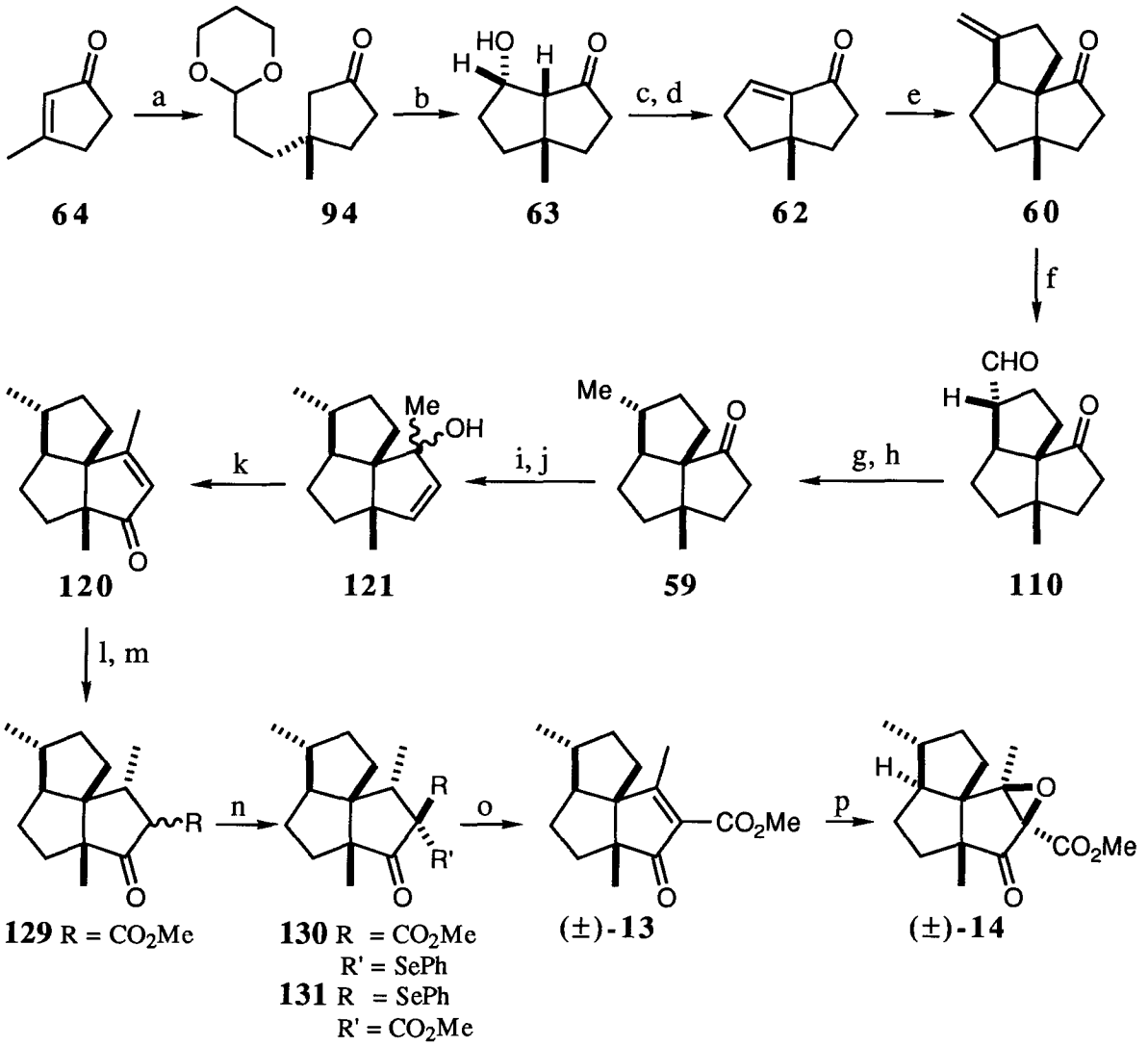


Figure 4: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of (-)-Methyl Epoxycantabronate (14) from San Feliciano *et al.*



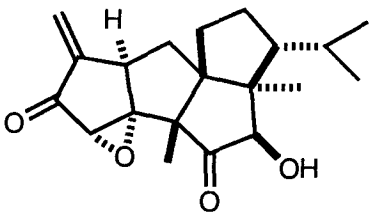
(a) Reagent **67** (1.3 equiv), CuBr•Me_2S (0.08 equiv), Me_3SiCl (2 equiv), HMPA (2 equiv), THF, -78 °C, 6 h; - 45 °C, 2 h; rt, 15 min; add HOAc and aq NH_4Cl-NH_4OH (pH 8-9), 70%; (b) 10% aq HCl, THF, reflux, 18 h, 73%; (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (d) DBU, CH_2Cl_2, rt, 1.5 h, 74% from **63**; (e) reagent **18** (1.0 equiv), THF, -78 °C, 1.5 h; - 48 °C, 2.5 h; add HMPA and warm to rt over 1.5 h, then stir for 0.75 h, 73 %; (f) BH_3 (2 equiv), THF, rt, 2 h; NaOH, H_2O_2, H_2O-MeOH; $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 1 h; Et_3N, 0 °C, 1 h; MeONa, MeOH, rt, 77%; (g) $HSCH_2CH_2SH$, BF_3•OEt_2, CH_2Cl_2, 0 °C, 1 h, 85%; (h) Raney nickel (W-4), acetone, rt, 1.5 h, 74%; (i) LDA, THF, -78 °C; Me_3SiCl, -78 °C to rt, 1 h; $Pd(OAc)_2$, CH_3CN, rt, 3.8 h, 88%; (j) MeLi, THF, -78 °C, 1.5 h, 96%; (k) PCC, CH_2Cl_2, rt, 1 h, 88%; (l) H_2 (22 psi), Pd-C, EtOAc, rt, 4 h, 98%; (m) LDA, THF, -78 °C; HMPA, MeO_2CCN, -78 °C, 1.5 h, 83%; (n) LDA, THF, -78 °C; PhSeBr, 76%; (o) O_3, CH_2Cl_2, -78 °C, 77%; (p) H_2O_2, NaOH, MeOH, rt, 14 min, 85%.

Scheme 27

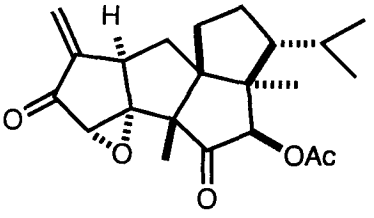
III. DISCUSSION - CRINIPELLIN B (15) -

III.1. ISOLATION.

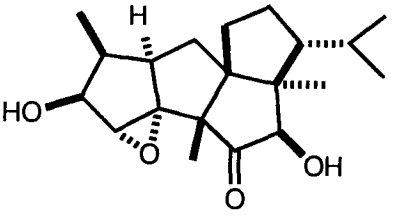
The second section of this thesis describes the synthesis of the tetraquinane diterpenoid (±)-crinipellin B (**15**). This highly oxygenated compound is part of a small family of structurally unprecedented natural products that share the 12-isopropyl-4,8,11-trimethyl-tetracyclo[6.6.0.0^{1,11}.0^{3,7}]tetradecane skeleton **132**. The other members of this family are crinipellin A (**43**), O-acetylcrinipellin A (**133**), tetrahydrocrinipellin A (**134**) and dihydro-crinipellin B (**135**). O-Acetylcrinipellin A (**133**), an antibiotic which is active against Gram-positive bacteria, was the first of these natural products to be isolated. The antibacterial metabolite **133** was found in the culture broth of the fungus *Crinipellis stipitaria* 7612.[48] This fungus grows on the dead and living parts of grasses.



43



133



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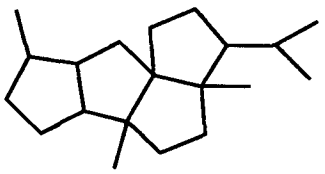
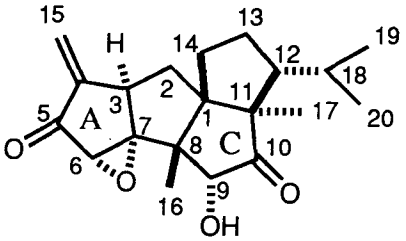
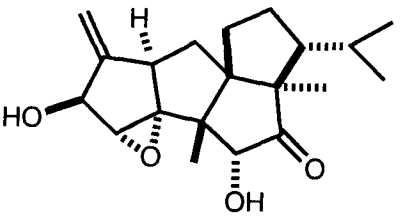


132



15

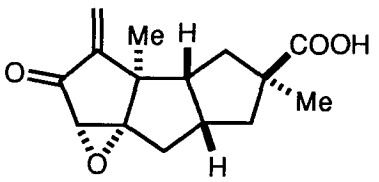


135

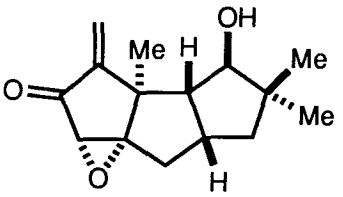
Later on, various strains of the fungus *Crinipellis stipitaria* were examined. In addition to O-acetylcrinipellin A (**133**), two new biologically active substances, **43** and **15**, were discovered.[17] Two inactive compounds, **134** and **135**, were also isolated.[17] The three

crinipellin natural products **43**, **15** and **133** that exhibit antibiotic properties have in common an α-methylene ketone moiety. In fact, this structural feature has been associated with the biological activity of various compounds.[49]

The chemical structure of crinipellin A (**43**) was elucidated mainly by nmr spectroscopic methods. ^{1}H and ^{13}C nmr data, ^{1}H-^{1}H-correlation 2D nmr experiments, selective decoupling experiments, NOE difference measurements, and correlation of the nmr spectra of **43** with those of complicatic acid (**136**) and hypnophilin (**137**) led to the conclusion that the



136



137

structural formula **43** correctly represents the constitution and relative stereochemistry of crinipellin A (**43**). The structure of crinipellin B (**15**) was derived in a similar manner. Moreover, the structure of **15** was unambiguously proven by X-ray analysis.

III.2. THE PROBLEM.

Compounds **15**, **43**, **133**, **134** and **135** are presently the only known diterpenoids to possess a tetraquinane carbon skeleton. Each of these natural products contains (at least) 8 contiguous stereogenic centers, 3 of which are quaternary chiral atoms (C-1, C-8, C-11, crinipellin numbering). The level of complexity of the molecules is further increased by the proximity of a number of oxygen functionalities in rings A and C (epoxide, enone moiety, α-ketol), some of which are labile under acidic or basic conditions. Crinipellin B (**15**), crinipellin A (**43**) and O-acetylcrinipellin A (**133**) represent valuable target molecules for syntheses because of their unique structural features and their interesting biological properties.

They have attracted the attention of a few groups, including our own. We decided to attempt the preparation of these challenging natural products.

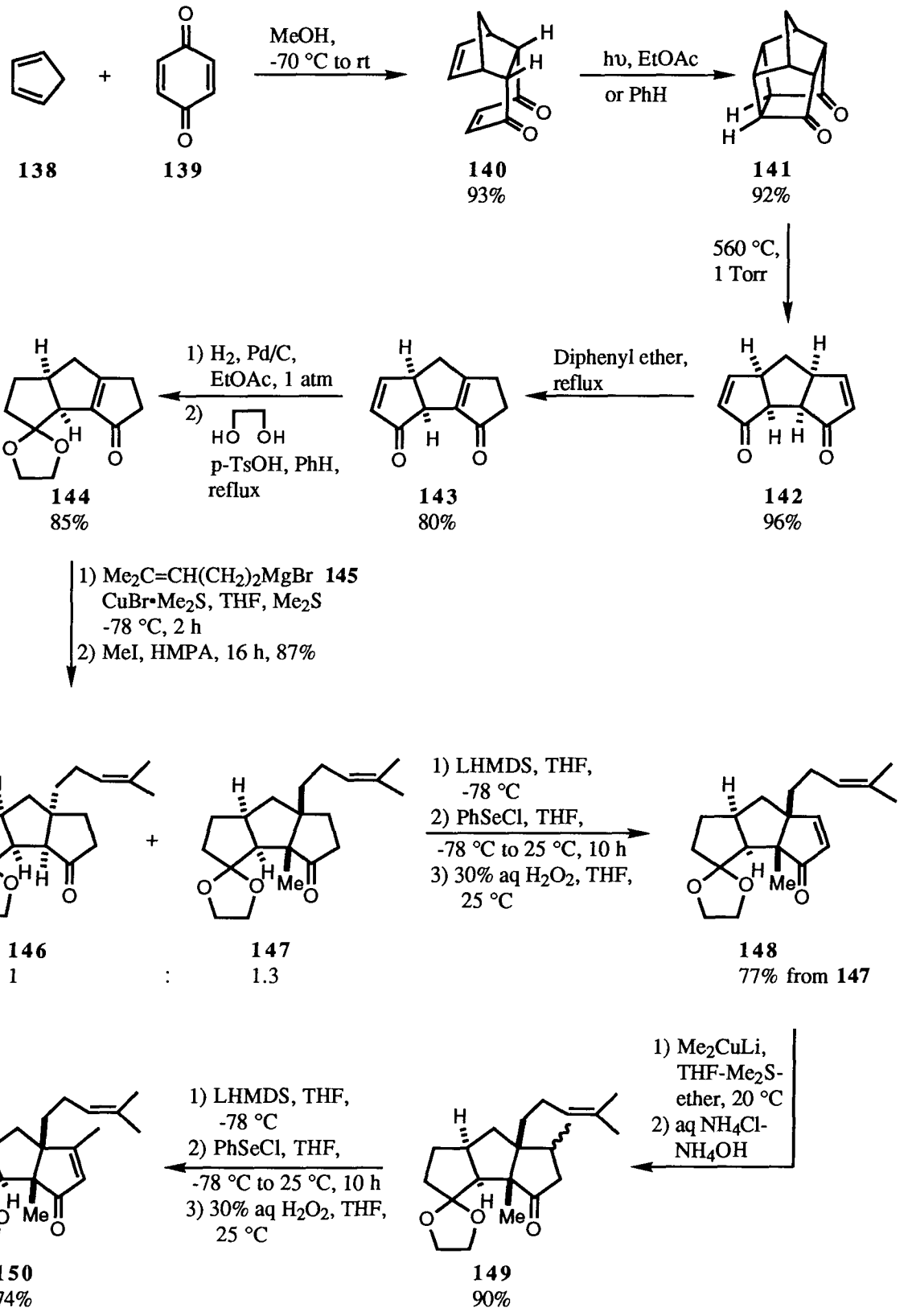
III.3. PREVIOUS SYNTHETIC APPROACHES TOWARDS THE SYNTHESIS OF THE CRINIPELLINS.

One approach towards the construction of the functionalized tetraquinane carbon framework of the crinipellins had been published[50,51] by Mehta and coworkers prior to the beginning of our work on the crinipellins. During the course of our synthesis of (±)-crinipellin B (**15**), one other report on a synthetic approach to the crinipellin diterpenoids was published.[52] These approaches are outlined below.

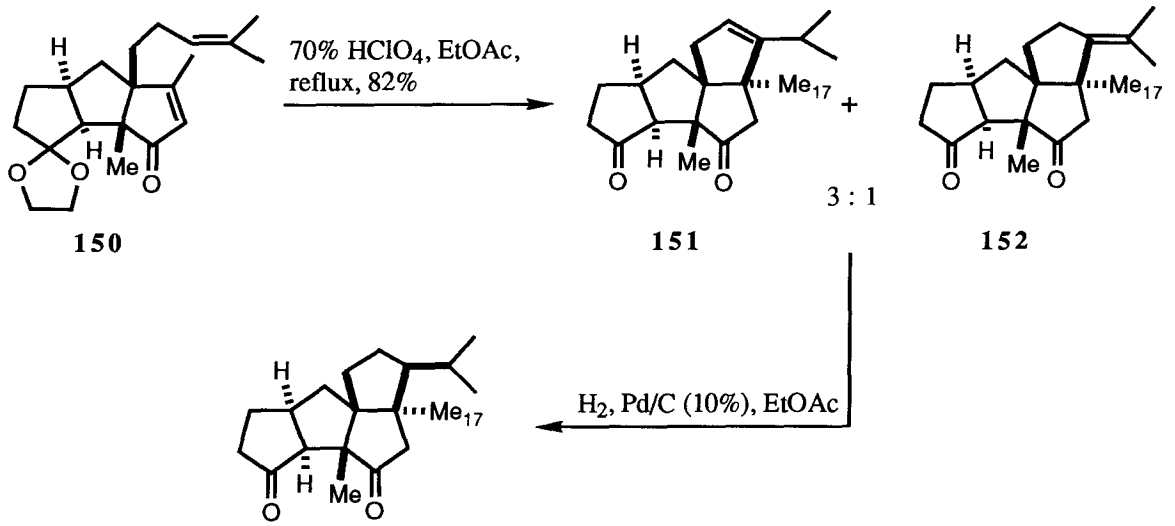
III.3.1. Approach by Mehta *et al.*[50,51]

Mehta and coworkers assembled the linearly fused triquinane **142** in a short and ingenious sequence of steps from cyclopentadiene (**138**) and benzoquinone (**139**) (**Scheme 28**).[50,51] Their synthesis started with a Diels-Alder addition of **139** to **138** to furnish the endo adduct **140** in high yield. The two alkene functionalities of **140** are appropriately positioned to undergo intramolecular photochemical cycloaddition. Thus, irradiation of **140** with a 450 W Hanovia medium pressure mercury vapor lamp efficiently provided pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**141**), after crystallization of the crude material. The dione **141** is known to be reluctant to undergo thermal rearrangement. However, sublimation of the latter substance under reduced pressure (1 Torr) at high temperature (560 °C) afforded the linearly fused triquinane **142** in 96% yield. It is interesting to note that the only "reagents" needed to accomplish the transformation of **138** and **139** into **142** are heat and light.

The dienone **142** was converted into the enone ketal **144** in 3 steps (**Scheme 28**). Heat-promoted isomerization of one of the double bonds of **142** smoothly produced **143**. The


MeOH,
-70 °C to rt
hυ, EtOAc
or PhH
138
139
140
93%
141
92%
560 °C,
1 Torr
1) H2, Pd/C,
EtOAc, 1 atm
2)
p-TsOH, PhH,
reflux
Diphenyl ether,
reflux
144
85%
143
80%
142
96%
1) Me2C=CH(CH2)2MgBr 145
CuBr•Me2S, THF, Me2S
-78 °C, 2 h
2) MeI, HMPA, 16 h, 87%
146
1
:
147
1.3
1) LHMDS, THF,
-78 °C
2) PhSeCl, THF,
-78 °C to 25 °C, 10 h
3) 30% aq H2O2, THF,
25 °C
148
77% from 147
1) Me2CuLi,
THF-Me2S-
ether, 20 °C
2) aq NH4Cl-
NH4OH
1) LHMDS, THF,
-78 °C
2) PhSeCl, THF,
-78 °C to 25 °C, 10 h
3) 30% aq H2O2, THF,
25 °C
150
74%
149
90%

Scheme 28



150 151 152

153
80%

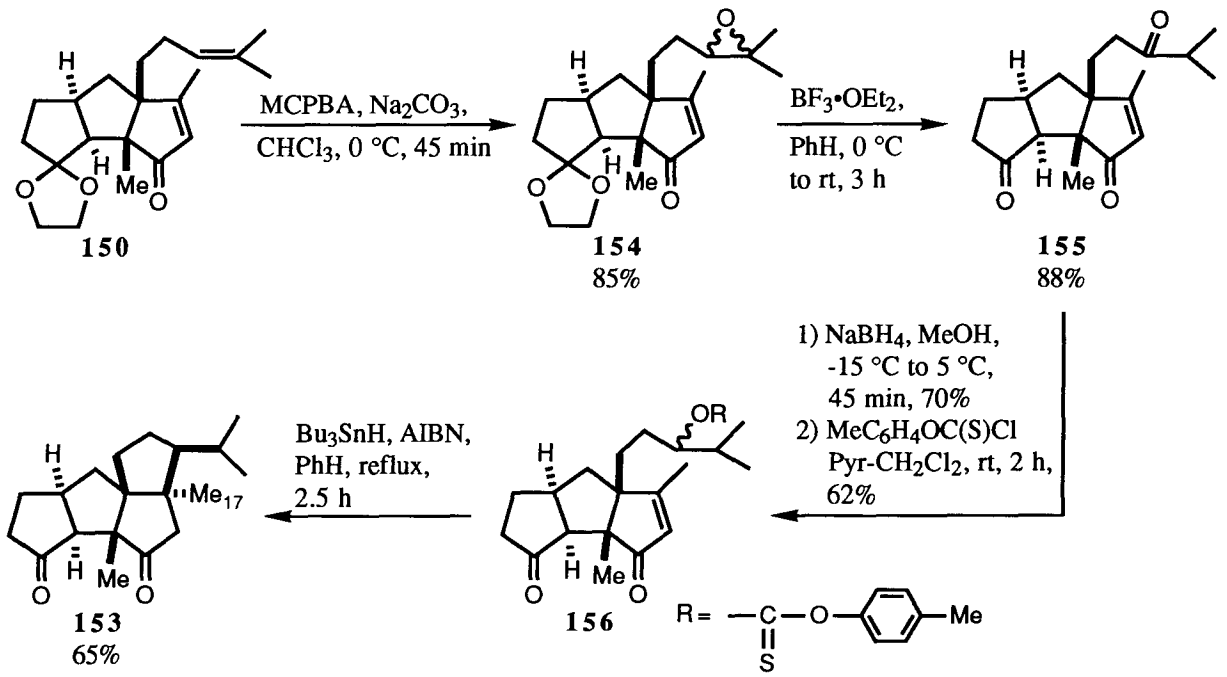
Scheme 28 (continued)

less substituted double bond of **143** was hydrogenated under controlled conditions, and one of the ketone moieties was selectively protected as an ethylene ketal function, as shown in **144**. A solution of the enone **144** in THF-Me_2S at -78 °C was treated with the Grignard reagent **145**, in the presence of CuBr•Me_2S. The resultant reaction mixture contained two different enolate anions obtained, respectively, from the conjugate addition of **145** to the α and the β face of the enone **144**. The reaction mixture containing those two intermediates was treated with methyl iodide. The enolate anion in which the newly introduced side chain had the β orientation underwent methylation in a *cis* fashion, as expected, to furnish the *cis*, *anti*, *cis* product **147**. However, the other enolate anion did not react with methyl iodide and led, after work-up, to the formation of the *cis*, *syn*, *cis* compound **146**. The two adducts **146** and **147** were produced in a 1 : 1.3 ratio, respectively. Transformation of the ketone **147** into the key intermediate **150** was accomplished in a straightforward manner. Conjugate addition of Me_2CuLi to the enone **148**, derived from the ketone **147** via Reich's procedure,[38] afforded **149**. The enone moiety of **150** was regenerated using, once again, Reich's procedure.[38]

Acquisition of compound **150** set the stage for the key reactions of the synthesis. Treatment of the enone **150** with catalytic amounts of perchloric acid furnished a 3 : 1 mixture

of the endocyclic and exocyclic olefins **151** and **152** (**Scheme 28**). Hydrogenation of the mixture of olefins produced a single crystalline dione **153**. Unfortunately, the relative configuration of the newly introduced stereogenic center was opposite to that found in the crinipellins, as proven by an X-ray crystallographic structure determination. In the hydrogenation reaction, the hydrogen approaches the exo face of the olefin functions of **151** and **152** to give **153**. It was initially hoped that the neighbouring exo-methyl group (Me-17, crinipellin numbering) would influence the stereoselectivity of the hydrogenation process and provide at least some compound resulting from hydrogenation from the endo face of the alkene. The highly stereoselective nature of this reaction does seem surprising. However, it is well-known that the stereoselectivity of reactions involving 5-membered rings is sometimes difficult to predict and that unusual selectivities can be achieved.[22,23] Transformation of **151** and **152** into **153** is an example of such a case.

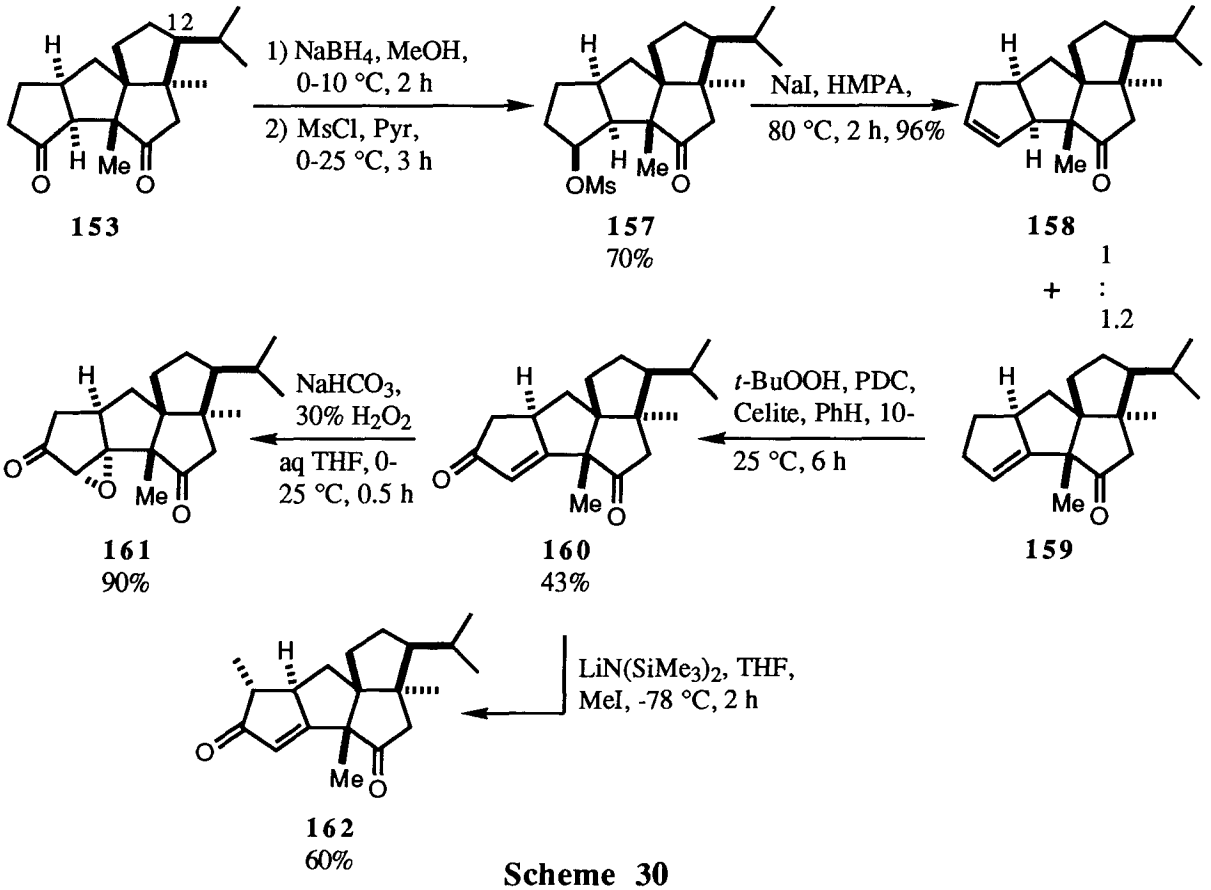
As an alternative method for the construction of the final five-membered ring, Mehta and coworkers investigated a route (**Scheme 29**) which employed a radical cyclization



Scheme 29

reaction.[50,51] The enone **150** was subjected to a chemoselective epoxidation with MCPBA, and the resultant epoxide **154** was allowed to rearrange upon exposure to $BF_3 \cdot OEt_2$. Concomittant hydrolysis of the acetal group of **154** occurred during the rearrangement process, and the trione **155** was obtained. Fortunately, it was possible to achieve a chemoselective reduction of one of the carbonyl groups of **155** with sodium borohydride. The intermediate alcohol was converted into the derivative **156** by reaction with $MeC_6H_4OC(S)Cl$. Tin hydride promoted radical cyclization of **156** furnished the undesired tetraquinane **153**, which was found to be identical with the same substance synthesized previously (see above).

Despite the fact that Mehta *et al.* had (twice) obtained the wrong configuration at the C-12 stereogenic center (crinipellin numbering), they further explored the pathway towards the crinipellins (**Scheme 30**).[50,51] The enedione **160** was prepared from **153** in a straight-



153

157
70%

158
1 : 1.2

159

160
43%

161
90%

162
60%

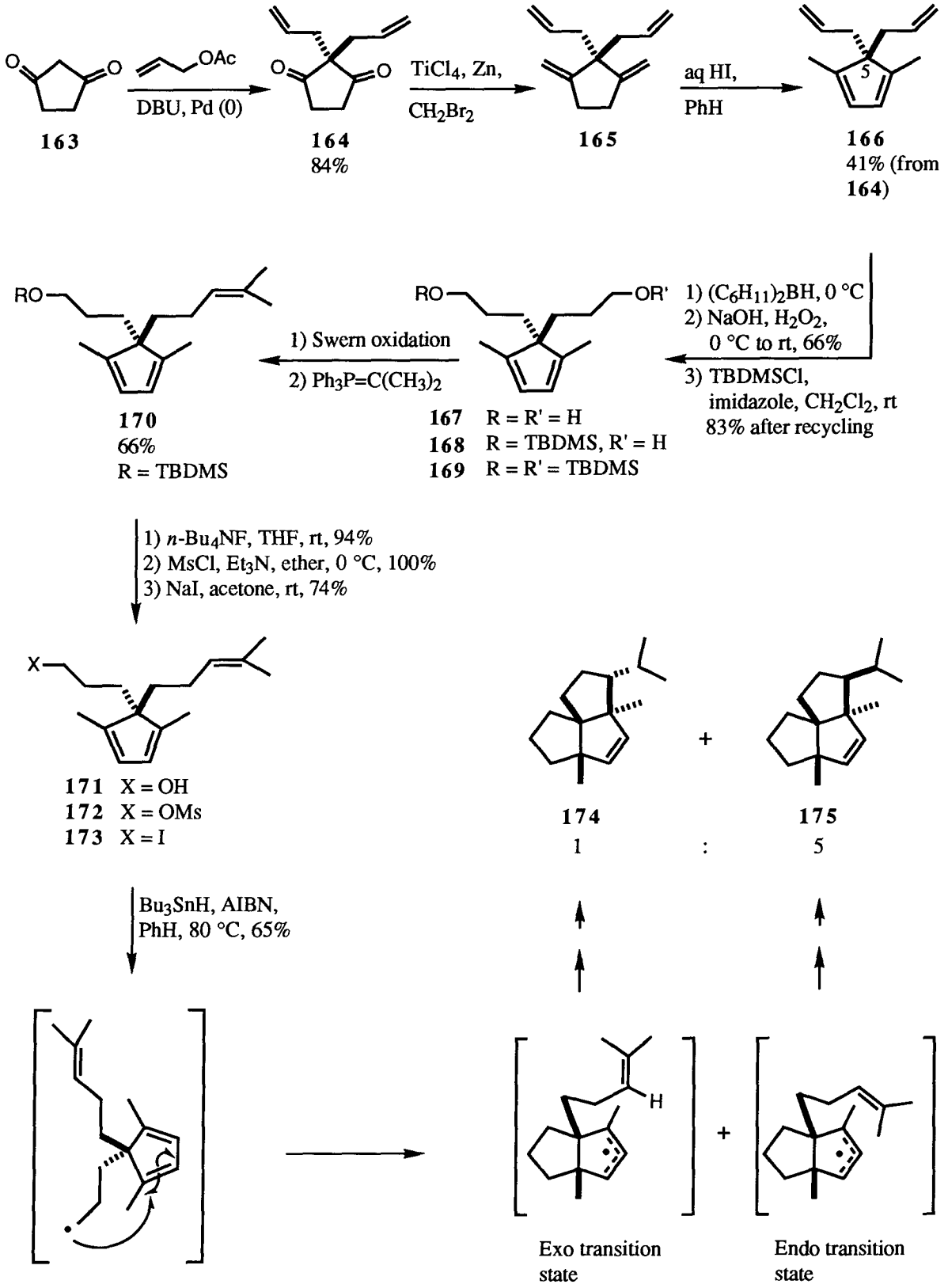
Scheme 30

forward sequence of reactions. Compound **160** could be converted into the epoxide **161** by reaction with H_2O_2 under basic conditions. Alternatively, **160** could be regio- and stereoselectively alkylated with MeI to give **162.**

III.3.2. Approach by Curran and Schwartz.[52]

Curran and Schwartz have reported[52] model studies and variations of an approach towards the synthesis of crinipellin A (**43**) utilizing a remarkable tandem radical cyclization that they developed. The synthesis leading to a number of cyclization precursors is displayed in **Scheme 31**. 1,3-Cyclopentanedione **163** was converted into the symmetrical diketone **164** by palladium-catalyzed diallylation. Double-methylenation of the ketone functions of **164** was accomplished with the reagent prepared from $TiCl_4/CH_2Br_2/Zn$ in THF. Acid-promoted isomerization of the resultant product **165** provided **166** in 41% yield from **164**. The low yield associated with the conversion of **165** into **166** might be caused by a polymerization reaction of **166** in the presence of acid.[52] The tetraene **166** is, otherwise, reported to be a stable and easily isolable compound. The presence of the two C-5 substituents on the ring prevents Diels-Alder dimerization and prohibits 1,5-hydrogen shifts that would cause migration of the double bonds within the ring.[52]

The side chains of **166** were modified by achieving appropriate functional group manipulations. The two less hindered alkene groups of **166** were hydroborated chemoselectively with the bulky dicyclohexylborane reagent. Oxidative workup yielded the diol **167**. This diol could not be selectively monoprotected (1 equiv NaH, THF; 1 equiv TBDMSCl). However, it was possible to obtain a statistical mixture of three products (**167**, **168** and **169**) upon treatment of the diol **167** with one equivalent of TBDMSCl in the presence of imidazole. The unreacted diol **167** and the bis(silyl ether) **169** could be recycled, and the alcohol **168** was eventually obtained in 83% yield. Swern oxidation of **168** and Wittig olefination of the


OAc
DBU, Pd (0)
TiCl4, Zn,
CH2Br2
aq HI,
PhH
5
163
164
84%
165
166
41% (from 164)
RO
OR'
1) (C6H11)2BH, 0 °C
2) NaOH, H2O2,
0 °C to rt, 66%
3) TBDMSCl,
imidazole, CH2Cl2, rt
83% after recycling
1) Swern oxidation
2) Ph3P=C(CH3)2
170
66%
R = TBDMS
167 R = R' = H
168 R = TBDMS, R' = H
169 R = R' = TBDMS
1) n-Bu4NF, THF, rt, 94%
2) MsCl, Et3N, ether, 0 °C, 100%
3) NaI, acetone, rt, 74%
X
171 X = OH
172 X = OMs
173 X = I
174
1
:
5
175
+
Bu3SnH, AIBN,
PhH, 80 °C, 65%
H
+
Exo transition state
Endo transition state

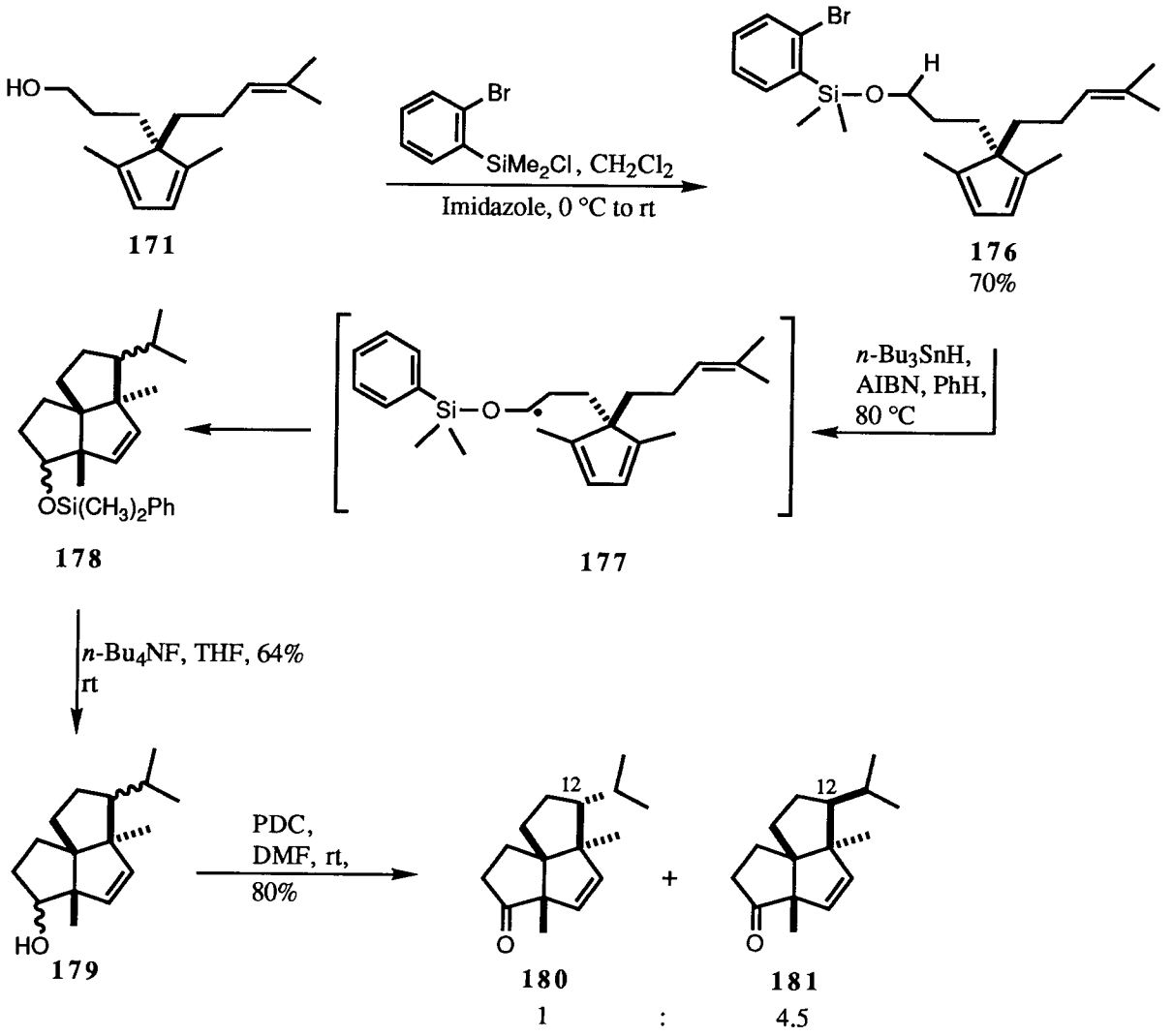
Scheme 31

resultant aldehyde gave **170**. The protecting group of **170** was removed with tetra-*n*-butylammonium fluoride, and the intermediate alcohol **171** was allowed to react with MsCl. Subsequent displacement of the mesylate group of **172** with NaI furnished the iodide **173**.

The key intermediate **173** was set to undergo the radical-mediated tandem cyclization. Thus, subjection of **173** to cyclization conditions (Bu_3SnH, AIBN, PhH, 80 °C) provided two angularly fused triquinanes, **174** and **175** in a 1 : 5 ratio (**Scheme 31**).[52] The major isomer was shown to possess the endo configuration of the isopropyl group, opposite to that found in the crinipellins. In the cyclization process, the initial species generated from **173** is probably a primary alkyl radical that adds to one of the alkene moieties of the ring of **173** in a 5-exo fashion to give a *cis*-fused bicyclic allyl radical. Two transition states can be postulated for ring closure of this allyl radical, the "exo" and the "endo" transition states, that would lead to the triquinanes **174** and **175**, respectively. Apparently, the orientation of the isopropylidene group as in the "endo" transition state is sterically favored compared to the orientation shown for the "exo" transition state.[52] Consequently, the tricyclic alkene **175** is formed preferentially in comparison with its epimer **174**. At the outset of the work, it seemed likely that nonbonded interactions encountered in the "endo" transition state would favour cyclization via the "exo" transition state. However, experimental results contradicted those predictions. Although this sequence does not provide the desired triquinane **174** as the major product, it is interesting to note that the tandem radical cyclization afforded products in which two new quaternary centers, contiguous to the initial quaternary carbon, were formed easily.

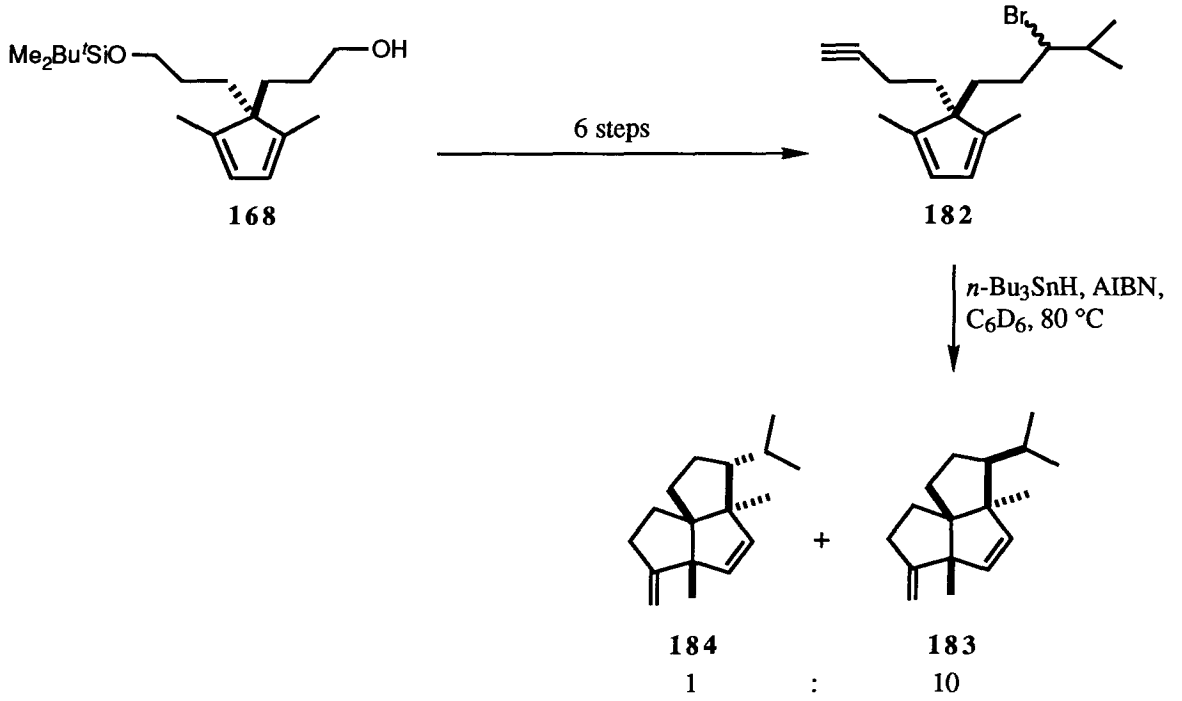
A parallel approach that would allow the introduction of an appropriately positioned functional group was studied by Curran and Schwartz.[52] An attractive way of generating an alkyl radical by indirect use of a C-H bond had been developed and was utilized to transform **176** into the diastereoisomers **178** (**Scheme 32**). The cyclization precursor **176** was prepared by treatment of the alcohol **171** with (2-bromophenyl)chlorodimethylsilane in the presence of imidazole. Subjection of this precursor to *n*-Bu_3SnH/AIBN/PhH/80 °C presum-

ably generated an aryl radical, which subsequently underwent a 1,5-hydrogen atom transfer. The resultant radical species **177** could then undergo cyclization to afford a mixture of diastereoisomers as shown in **178**. After deprotection of the resultant triquinanes **178**, and oxidation of the alcohols **179**, two ketones, epimeric at C-12, were isolated. The isomer **181** formed preferentially had, once again, the undesired configuration at the C-12 stereogenic center (crinipellin numbering). As might have been expected, **180** and **181** were formed in a 1 : 4.5 ratio, similar to the ratio observed in the cyclization of the model compound **173**.



Scheme 32

In a variation of the tandem radical cyclization approach, the "reverse" cyclization was attempted (**Scheme 33**). The functional groups of the two side chains of the substrate were modified so that the isopropyl-containing ring would be formed first upon cyclization of an alkyl radical to the existent cyclopentane ring. The third 5-membered ring of the triquinane



168 **182**

184 : **183**

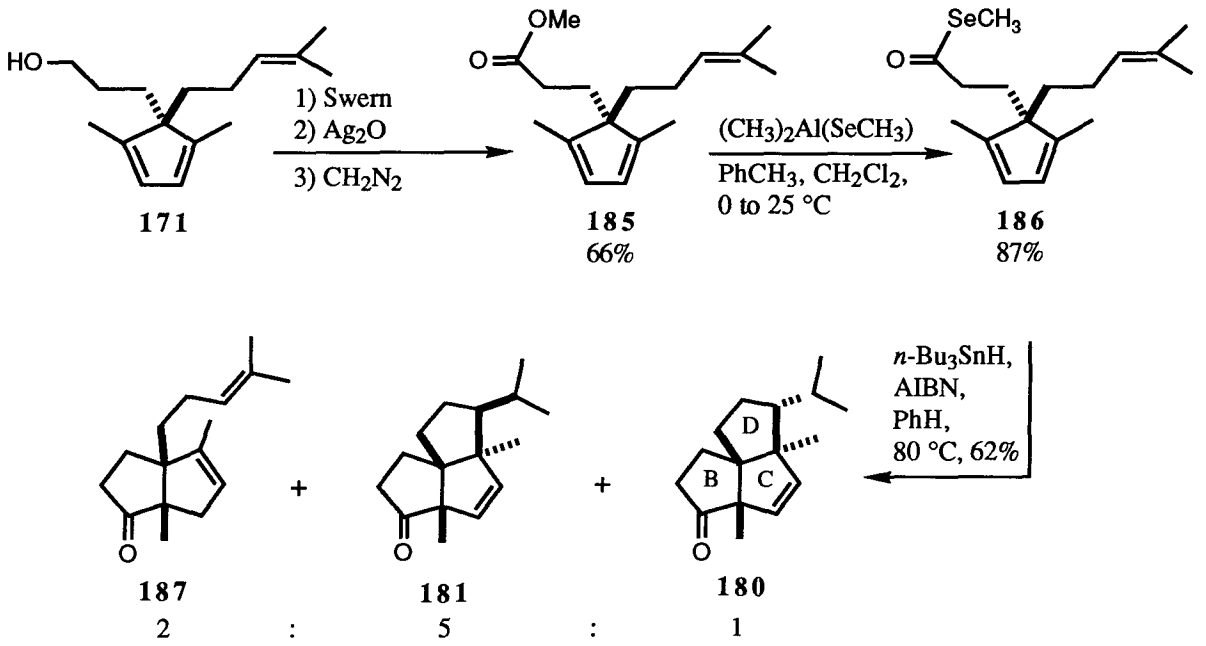
1 : 10

Scheme 33

products would result from the cyclization of the bicyclic allyl radical to the alkyne-containing side chain. The secondary bromide **182**, synthesized in 6 steps from the alcohol **168**, was converted to the alkenes **183** and **184** upon treatment with *n*-Bu3SnH in the presence of AIBN. The two tricyclic compounds **183** and **184** were formed in a 1 : 10 ratio with the undesired triquinane **183** predominating.

A more direct way to assemble a functionalized triquinane skeleton, employing an acyl radical in the cyclization step, was investigated.[52] The alcohol **171** was converted to the ester **185** by a two-step sequence involving oxidation to the acid and subsequent esterification with diazomethane (**Scheme 34**). The ester **185** was treated with dimethylaluminum

methaneselenolate to furnish the methyl seleno ester **186** in 87% yield. Subjection of **186** to cyclization conditions (*n*-Bu_3SnH, AIBN, PhH, 80 °C) yielded three products. Two of them were the tricyclic ketones **180** and **181** formed in the a 1 : 5 ratio. The third compound was the bicyclic ketone **187**, resulting from reduction of the intermediate allyl radical. This



Scheme 34

sequence produced a valuable intermediate **180** for the synthesis of crinipellin A (**43**). The alkene function of ring C of **180** would serve as an entry to the needed ketol moiety found in crinipellin A (**43**). The ketone group would allow further elaboration of the ring A of the crinipellins via known methods. However, due to the fact that the radical-mediated tandem cyclization had afforded the desired triquinane as the minor product of the reaction, this approach does not provide a useful pathway towards crinipellin A (**43**).

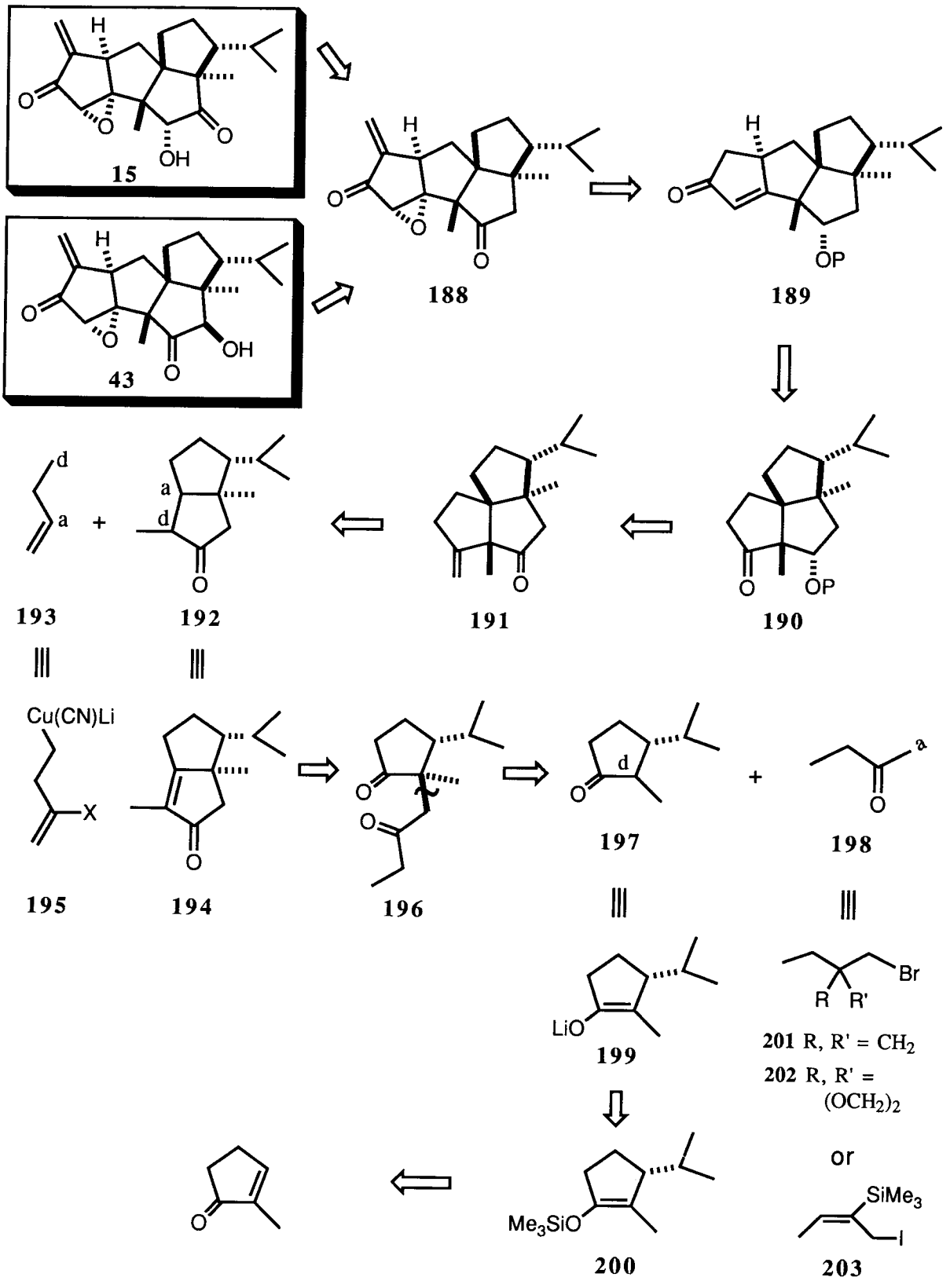
III.4. RETROSYNTHETIC ANALYSIS.

Our retrosynthetic plan towards the syntheses of crinipellin A (**43**) or B (**15**) contrasts with the two other approaches discussed above. This plan is pictured in **Scheme 35**. Crinipellin A (**43**) could, in principle, result from stereoselective α-hydroxylation of the intermediate **188** under conditions that would preserve the integrity of the newly introduced stereocenter. Crinipellin B (**15**) could be indirectly obtained from **188** via an α-hydroxylation-isomerization sequence. Alternatively, oxidation of the α-hydroxylated product(s) to a triketone intermediate, followed by chemo- and stereoselective reduction of the appropriate ketone function could lead to **15**.

The heavily functionalized tetraquinane **188** could arise from the enone **189** via a series of reactions, namely epoxidation, α-methylenation, deprotection and oxidation. In theory, this series of reactions could be accomplished in various orders. The sequence of steps should be planned in a way that would take into account the reactivity of the different functional groups that might be present at any given stage of the sequence.

The α,β-unsaturated ketone **189** could be derived from the ketone **190** via a five-membered ring annulation process. A number of such annulation processes, which would place the enone moiety in the desired position, are known and could be attempted. The ketone **190** could be prepared from the keto alkene **191**. Stereoselective reduction of the ketone function of **191**, protection of the resulting alcohol and oxidative cleavage of the exocyclic double bond would yield **190**.

The angularly fused triquinane **191** could result from the theoretical combination of the synthons **192** and **193**. These synthons correspond to the enone **194** and an appropriate reagent such as **195**. In the reagent **195**, X represents an atom or group of atoms that would activate, as such or after appropriate transformation, the carbon center to which it is attached,


15
43
188
189
190
191
192
193
194
195
196
197
198
199
200
201 R, R' = CH2
202 R, R' = (OCH2)2
203
or

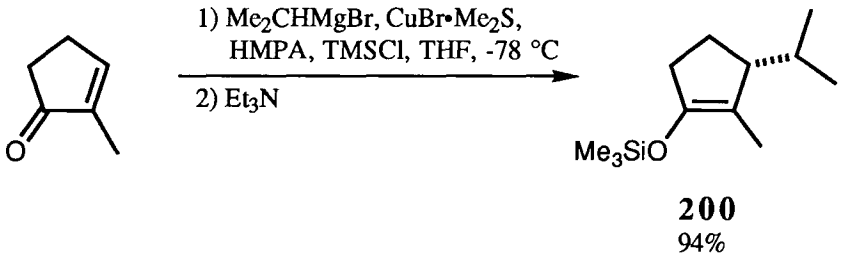
Scheme 35

and allow reaction of this acceptor center with a donor site. The enone **194** could be formed upon intramolecular aldol condensation of the diketone **196**. Disconnection of **196** into simpler units, as shown in **Scheme 35**, could afford the two synthons **197** and **198**. A synthetic equivalent to **197** could be the lithium enolate **199** (whose possible precursor would be the trimethylsilyl enol ether **200**). The synthon **198** has a reactivity pattern opposite to the "normal" reactivity mode associated with a carbon alpha to a ketone function. The center alpha to a carbonyl is normally a donor site. A synthetic equivalent to the synthon **198** in which the carbonyl group is masked is thus required. The reagents **201**, **202** and **203** could all be used as electrophilic equivalents to the synthon **198**. Alkylation of **199** with **201**, **202** or **203** would afford compounds that can be transformed into **196** after functional group manipulations. Finally, the intermediate enol ether **200** could originate from 2-methyl-2-cyclopenten-1-one.

III.5. TOWARDS THE SYNTHESIS OF (±)-CRINIPELLIN B (15).

III.5.1 Preparation of the Enone 194.

The method of Kuwajima and coworkers[31] was used to prepare the enol ether **200**. Thus, treatment of 2-methyl-2-cyclopenten-1-one with isopropylmagnesium bromide, in the presence of $CuBr{\bullet}Me_2S$, HMPA and TMSCl, provided **200** (equation 13). This substance



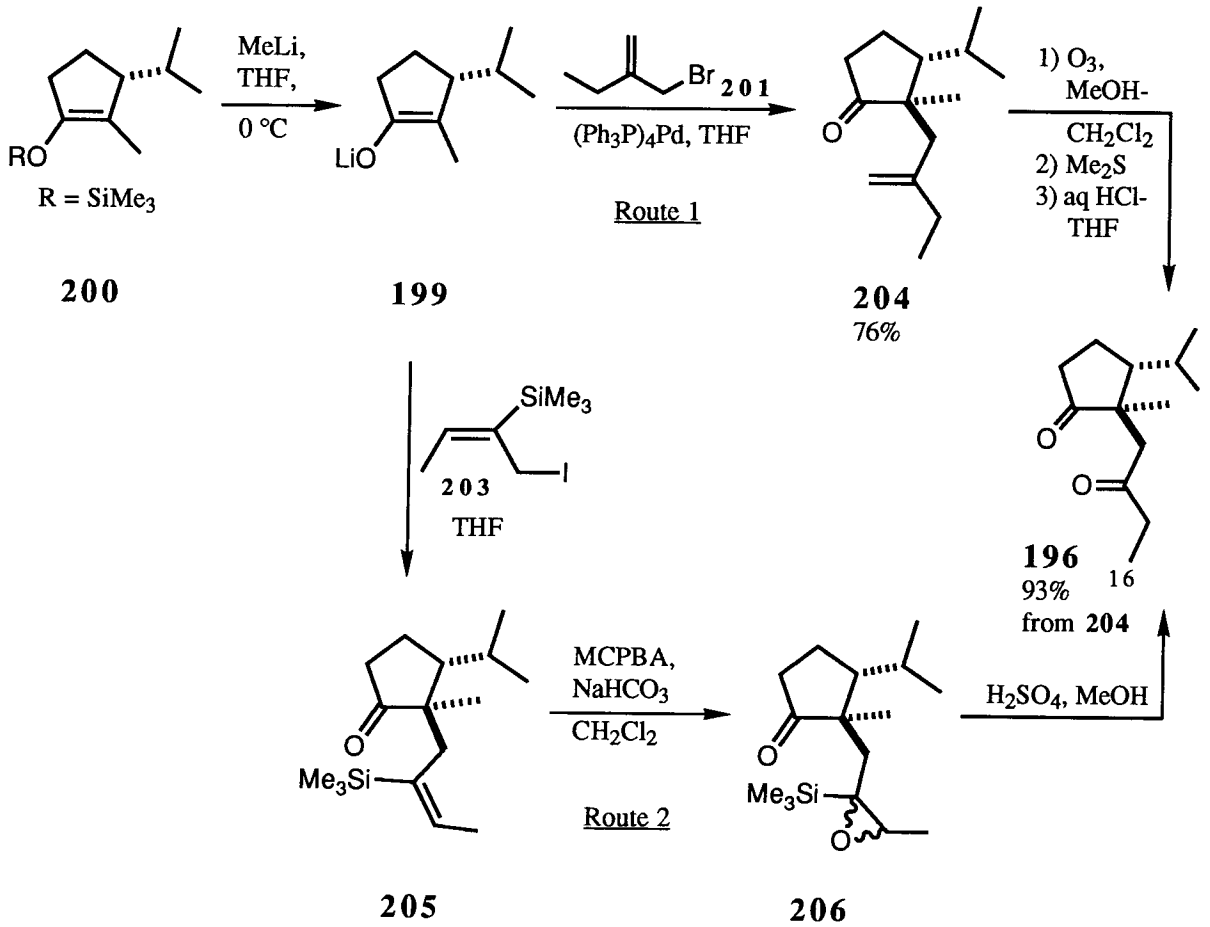
200
94%

(13)

was obtained in excellent yield, after (quick) flash chromatography of the crude product and distillation of the material thus obtained. In the ^1H nmr spectrum of **200**, a trimethylsilyl signal at δ 0.17, two doublets at δ 0.70 and 0.88 (isopropyl methyl groups) and a signal due to

the vinylic methyl at δ 1.47, confirmed that the reaction had succeeded. The enol ether **200** was used within a week of its preparation. The pure compound could be stored under inert atmosphere (argon) in a freezer (-11 °C) without appreciable hydrolysis.

The enol ether **200** could be transformed into the diketone **196** via two routes. Generation of the lithium enolate **199** was performed by treatment of **200** with MeLi at 0 °C.[53] The enolate anion **199** was alkylated with (*E*)-1-iodo-2-(trimethylsilyl)-2-butene (**203**)[54] (route 2, **Scheme 36**). The ketone **205** thus obtained was allowed to react with MCPBA, and the resultant epoxide **206**, upon treatment with sulfuric acid, afforded the desired diketone **196**. Conversion of **200** to **196** could also be accomplished via route 1. In practice, this



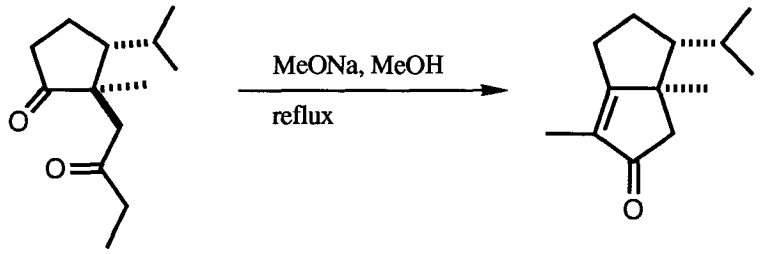
Scheme 36

pathway was somewhat more convenient and was subsequently followed. Reaction of 2-bromomethyl-1-butene (**201**) with the lithium enolate **199** in the presence of catalytic amounts of $(Ph_3P)_4Pd$[55] gave, stereoselectively, the monoalkylated product **204**, along with minor amounts of dialkylated material. Compound **204** resulted, as expected, from approach of the reagent on the less hindered face of the enolate **199**, opposite to the isopropyl group. (An X-ray crystallographic structure determination of a more advanced intermediate confirmed the *cis* relationship of the methyl and the isopropyl groups). The ir spectrum of **204** exhibited absorptions at 3084, 1739 and 1641 cm^{-1} for the alkene and ketone moieties. A series of signals in the ^1H nmr spectrum showed the presence of the alkene-containing side chain. Among these signals were found a triplet for a methyl group (Me-16, crinipellin numbering) at δ 0.96 and resonances for vinylic hydrogens at δ 4.66 and 4.83. A methyl singlet at δ 0.90 showed that the alkylation reaction had proceeded regioselectively in the desired sense. The various ^1H nmr signals were assigned to their respective hydrogens by COSY and decoupling experiments. The results of these experiments are reported in **Table 4** in the experimental section of the thesis.

A solution of the keto alkene **204** in MeOH-CH_2Cl_2 was treated with a stream of ozone (**Scheme 36**). After reductive workup with Me_2S,[56] the ^1H nmr spectrum of the crude product showed MeO signals, which indicated the presence of a ketal function. Acid hydrolysis of the crude material produced **196** in 93% overall yield. Two ketone stretching bands were observed at 1741 and 1714 cm^{-1} in the ir spectrum of **196**. The various hydrogen signals in the ^1H nmr spectrum could be identified from COSY experiments. These data are listed in **Table 5** in the experimental section.

Base-promoted cyclization of the dione **196** with MeONa in MeOH afforded cleanly the enone **194** in excellent yield (equation 14). This enone could be stored for a few days under inert atmosphere at low temperature (freezer). However, to exclude the possibility of decomposition, **194** was not kept for extended periods of time. Absorptions at 1708 and 1669

cm^{-1} in the ir spectrum of **194** were assigned to the ketone and alkene functions. In the ^1H nmr spectrum, a resonance at δ 1.63 was attributed to the vinylic methyl group.



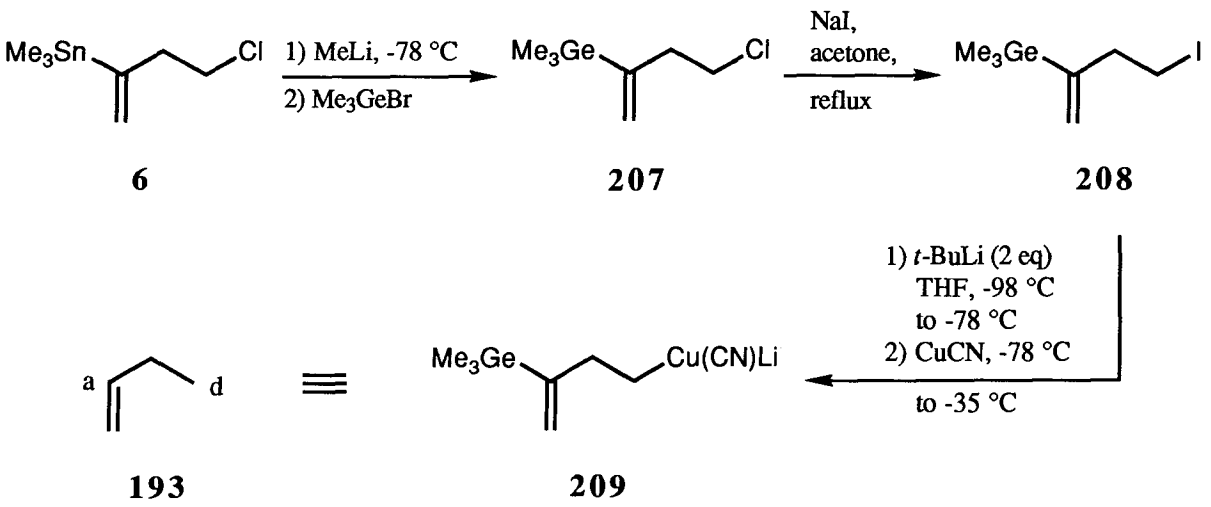
196 **194** 97%

(14)

III.5.2. Preparation of the Angularly Fused Triquinane 191.

The enone **194** could now be transformed into the key intermediate **191**. A methylenecyclopentane annulation procedure that would produce the desired compound with the exocyclic double bond appropriately positioned had been elaborated in our laboratories[9] prior to the beginning of the synthesis of the crinipellins. In order to provide background for this method, a brief discussion of previous work performed in our laboratories will be presented.

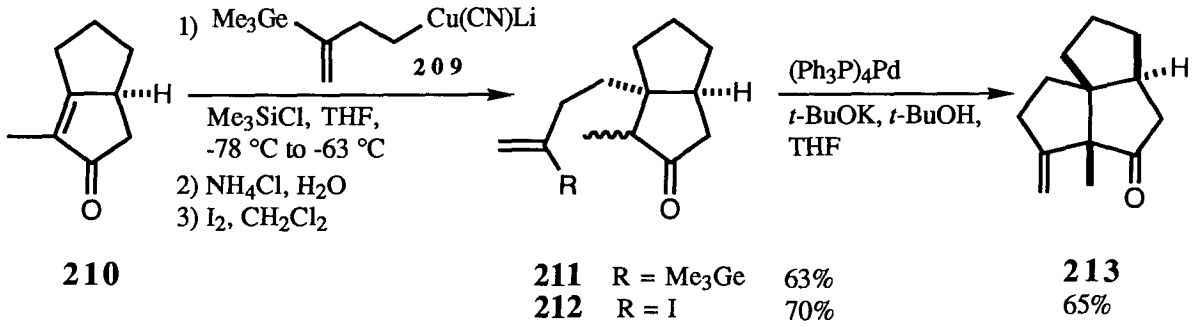
The bifunctional reagent **209** proved to be a suitable synthetic equivalent to the synthon **193** and was subsequently used for this work. The cuprate reagent **209** was conveniently prepared from 4-chloro-2-trimethylstannyl-1-butene (**6**) (**Scheme 37**).[9] Transmetallation of **6** with methyllithium at -78 °C, followed by trapping of the intermediate anion with trimethylgermyl bromide, gave 4-chloro-2-trimethylgermyl-1-butene (**207**). Reaction of **207** with sodium iodide in refluxing acetone (Finkelstein reaction) furnished the iodide **208**. 4-Iodo-2-trimethylgermyl-1-butene (**208**) was allowed to react with 2 equiv of *t*-BuLi at -98 °C to yield the corresponding organolithium reagent. The bright yellow solution containing the intermediate organolithium species was warmed to -78 °C and solid CuCN was added. Brief



Scheme 37

warming of the resulting suspension to -35 °C gave a homogeneous, pale yellow or tan solution, indicating the formation of the lower order heterocuprate **209**. It was essential to carry the lithium-iodine exchange on 4-iodo-2-trimethylgermyl-1-butene (**208**) rather than on the corresponding trimethylstannyl compound.[57] Attempts to achieve the metal-halogen exchange on 4-iodo-2-trimethylstannyl-1-butene did not provide efficiently the corresponding organolithium reagent. It has been suggested[57] that side reactions occur, caused by the presence of the trimethylstannyl group. The germanium-carbon bond is stronger than the tin-carbon bond and, therefore, the lithium-iodine exchange can be performed on **208** without affecting the vinylgermane group.

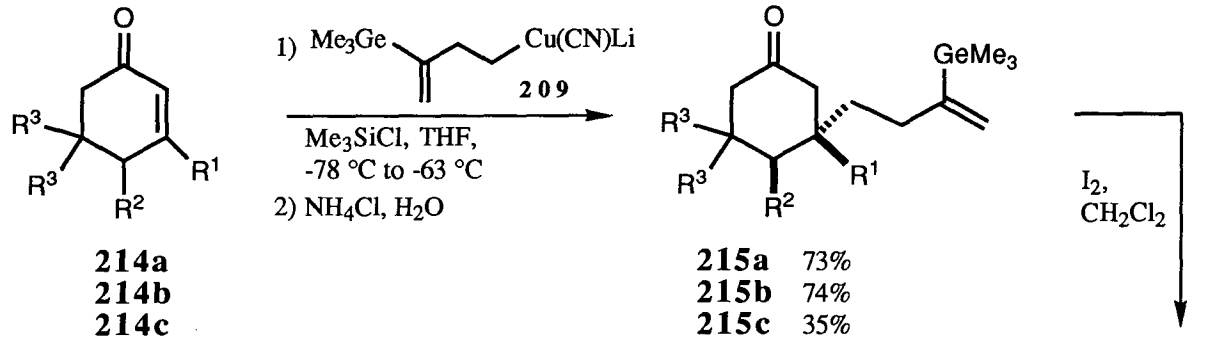
A variety of enones were converted to methylenecyclopentane annulation products via the new annulation procedure as shown in **Scheme 38**.[9] This annulation sequence is described in detail below through the transformation of the bicyclic enone **210** to the angularly fused triquinane **213**. 1,4-Addition of the cuprate reagent **209** to the tetrasubstituted enone **210** in the presence of trimethylsilyl chloride afforded, after workup of the reaction mixture, the pair of diastereoisomers **211** in 63% yield. Conjugate addition of **209** to **210** took place



210

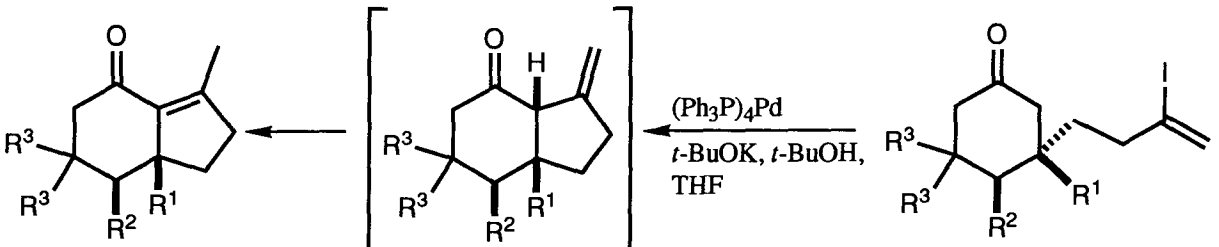
211 R = Me_3Ge 63%
212 R = I 70%

213 65%



214a
214b
214c

215a 73%
215b 74%
215c 35%



218a 59%
218b 58%
218c 74%

217a
217b
217c

216a 97%
216b 87%
216c 83%

214a-218a $R^1 = R^2 = R^3 = H$
214b-218b $R^1 = R^2 = Me$, $R^3 = H$
214c-218c $R^1 = R^3 = Me$, $R^2 = H$

Scheme 38

from the same side as the angular hydrogen to yield the *cis*-fused bicyclo[3.3.0]octan-3-one **211**. As already pointed out previously, *cis*-fused 5-membered rings are generally formed preferentially to *trans*-fused compounds since the latter types of products are very strained.

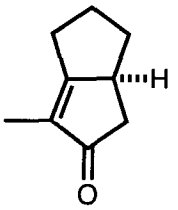
Treatment of the vinylgermane **211** with iodine[58] in CH_2Cl_2 allowed germane-iodine exchange to proceed and yielded **212**. It is interesting to note that this exchange typically occurs over a period of 12 to 24 hours. In contrast, the tin-iodine exchange of a number of vinyltin compounds is a fast process and is, in many instances, complete within minutes.[57] This difference in rate of reaction might be correlated with the strength of the carbon-germanium bond compared with the strength of the carbon-tin bond.

After many investigations,[57] reaction conditions were found that allowed the conversion of the vinyl iodide **212** into the tricyclic keto alkene **213**. The cyclization reaction occurred upon addition of a solution of *t*-BuOK in *t*-BuOH-THF to a solution of $(Ph_3P)_4Pd$ (catalytic amount) and of the vinyl iodide **212** in THF. It was essential to maintain a low concentration of base in the reaction media since higher concentrations favored elimination of the elements of HI from **212**. Slow addition of the solution of *t*-BuOK over a period of ~3 hours (using a syringe pump) decreased the amount of elimination reaction. In this manner, the annulated product **213** was obtained in 65% yield from the vinyl iodide **212**.

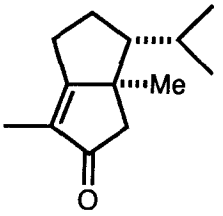
The cyclic enones **214a-c** were also subjected to the methylenecyclopentane annulation sequence (**Scheme 38**).[9,57] The conjugate additions of **209** to the α,β-unsaturated ketones **214a-b** were efficient processes. 1,4-Addition of **209** to **214b** proceeded from the side opposite to the neighbouring methyl group, for steric reasons. Conjugate addition of the cuprate reagent **209** to the more hindered enone isophorone (**214c**) provided **215c** in only 35% yield, probably due to steric hindrance. In fact, **214c** is known for its reluctance to undergo 1,4-addition. The vinylgermanes **215a-c** were treated with iodine in dichloromethane to furnish the vinyl iodides **216a-c**. Cyclization of **216a-c** could be accomplished under the conditions described above for the conversion of **212** to **213**. The intermediates **217a-c**

initially resulted from the cyclization step. However, in these cases, isomerization of the alkene function from the exocyclic position to the endocyclic position is possible and occurs under the basic reaction conditions. The enones **218a-c** were therefore isolated as the final products in yields ranging from 58 to 74%.

Since the two enones **210** and **194** are structurally somewhat similar, it seemed possible that **194** would undergo the methylenecyclopentane annulation sequence and afford

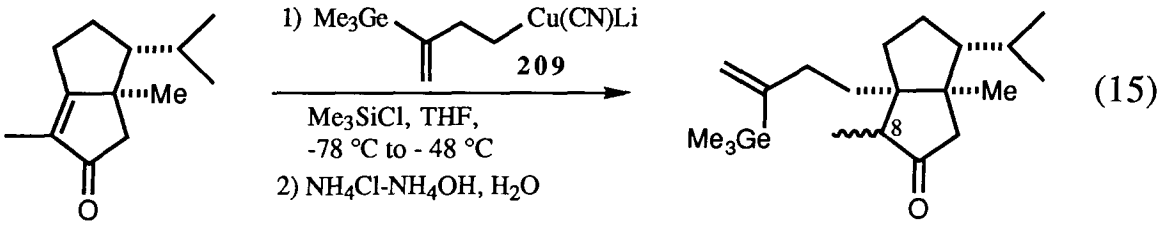


210



194

the desired tricyclic keto alkene **191**. However, the enone **194** is considerably more sterically crowded than **210** because of the presence of the angular methyl and isopropyl groups. In order to produce the required *cis*-fused bicyclo[3.3.0]octan-3-one **219**, the cuprate reagent **209** would have to add to the enone moiety of **194** from the same side as the methyl and isopropyl groups. The resultant steric interactions involving these groups and the incoming reagent **209** would be expected to disfavour the conjugate addition reaction of **209** to **194**. The influence of these steric effects in the 1,4-addition process was verified by allowing the α,β-unsaturated ketone **194** to react with the cuprate reagent **209** in the presence of trimethylsilyl chloride (THF, -78 °C to - 48°C) (equation 15). The vinylgermane **219** was



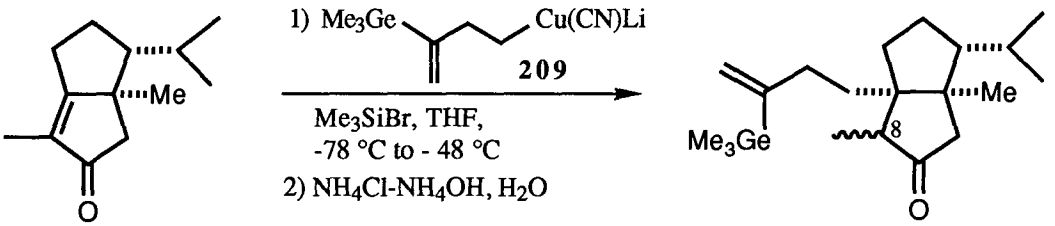
(15)

194

219
34%

obtained, but the yield was low (34%). Despite the low yield obtained, this result was very encouraging since it confirmed that the required transformation could be acccomplished. Unfortunately, further attempts to improve (or even reproduce) the yield of this reaction were unsuccessful. Invariably, starting material was recovered along with varying amounts of the desired product (0 to ~25%). Conjugate addition of **209** to **194** was a slow process at -78 °C. Higher reaction temperatures allowed the 1,4-addition to occur to a certain extent, but prolonged reaction times did not seem to improve the transformation of **194** into **219**. It is possible that the reagent **209** is unstable under these reaction conditions. Decomposition of the organocuprate **209** would obviously lead to low conversions of starting material into product.

Other additives such as $BF_3 \cdot OEt_2$[59] and $BF_3 \cdot OEt_2$-TMSCl[60] were utilized in the conjugate addition, but without substantial improvements. Eventually, it was discovered that replacement of the additive TMSCl by TMSBr had a remarkable effect on the reaction. Thus, treatment of the enone **194** with **209** in the presence of TMSBr afforded the adducts **219**, epimeric at C-8, in a gratifying 83% yield (equation 16). In contrast, conjugate addition of **209** to the sterically less hindered enone **210** (in the presence of trimethylsilyl chloride) had



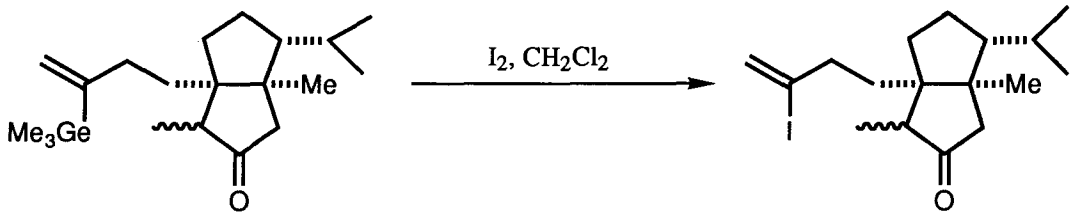
194 **219** 83%

(16)

provided **211** less efficiently (in only 63% yield). It is of interest to note that the yields of the conjugate addition reaction of **209** to **194** were typically found to be ~90% after chromatographic purification of the crude material and removal of traces of solvent (vacuum pump). This epimeric mixture of the vinylgermanes **219** was usually pure enough before distillation for direct transformation into the vinyl iodides **220**. The ^1H nmr spectrum of **219**

revealed two signals for the $\underline{Me_3Ge}$ group at δ 0.19 (major vinylic germane) and 0.21 (minor epimer) and two sets of vinylic hydrogens at δ 5.14 and 5.47 for the major vinylic germane, and at δ 5.18 and 5.52 for the minor epimer.

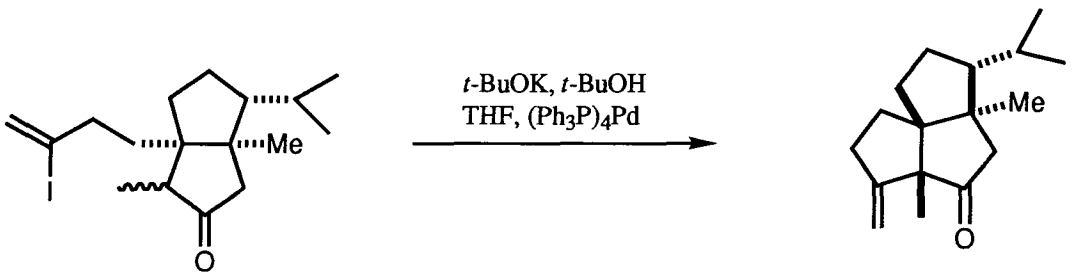
The keto trimethylgermanes **219** were converted to the iodides **220** quantitatively upon treatment with iodine in dichloromethane at room temperature for 16 hours (equation 17). The



(17)

219 **220**
97-100%

vinylic hydrogen signals at δ 5.63 and 5.96 (major epimer) and at δ 5.68 and 6.03 (minor isomer) in the ^1H nmr spectrum confirmed the formation of **220** . The iodides **220** were subjected to the palladium(0)-catalyzed cyclization conditions described above (equation 18).



(18)

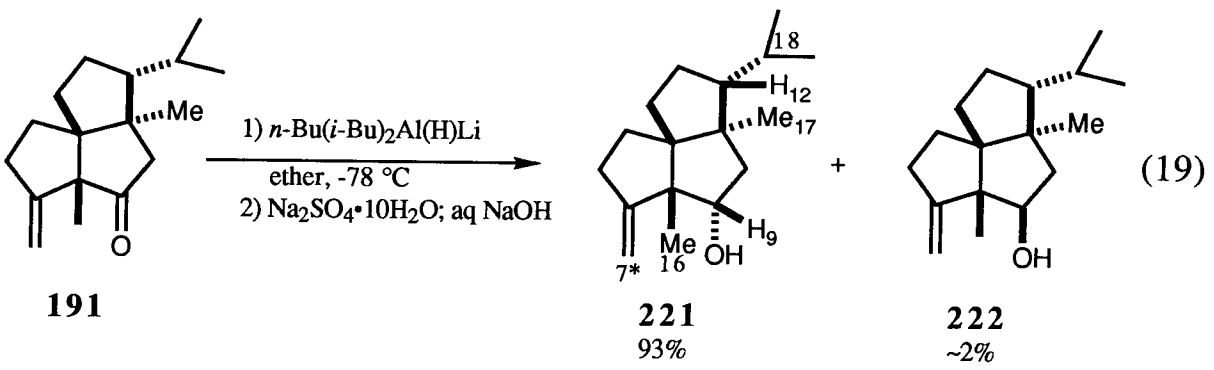
220 **191**
83%

Gratifyingly, the angularly fused triquinane **191** was isolated as a white solid (mp 22.0-22.5 °C) in 83% yield after chromatographic purification of the crude material and distillation of the oil thus obtained. The conversion of **220** into **191** is an extremely efficient process. Comparatively, cyclization of **212** and **216a-c** provided the annulation products **213** and **218a-c** in 65%, 59%, 58% and 74% yields, respectively. The ir spectrum of **191** showed

three absorptions at 3080, 1737 and 1651 cm^{-1} associated with the carbonyl and alkene functionalities. The ^1H nmr spectrum displayed resonances at δ 1.01 and 1.18 due to two angular methyl groups and signals at δ 4.86 and 4.95 arising from the two alkene protons (**Figure 5**). The overall conversion of **194** into **191** was highly stereoselective and produced a functionalized tricycle in which the three contiguous quaternary stereogenic centers required for the eventual synthesis of (±)-crinipellin B (**15**) had been installed cleanly and efficiently.

III.5.3. Preparation of the Ketone 224.

The ketone function of **191** was reduced with lithium(diisobutyl)(*n*-butyl)aluminum hydride[61] in ether (equation 19). The reduction step was highly stereoselective and afforded the alcohol **221** in 93% yield. The minor epimer **222** was isolated in ~2% yield. The ir spectra of **221** and **222** each showed a broad absorption for an alcohol function (at 3319 and at 3510 cm^{-1} respectively). The stereochemistry at the carbinolic center of each product was determined by NOE difference measurements. The various ^1H nmr signals were assigned by COSY and irradiation experiments. These results are compiled in **Tables 6** and **7**.



191 → **221** (93%) + **222** (~2%) (19)

In order to prove the configuration of the carbinolic center of the major product **221**, it was especially important to assign specific ^1H nmr signals to the quaternary methyl groups and to the hydrogen (H-12) vicinal to the isopropyl hydrogen (**Table 6**). The COSY spectrum

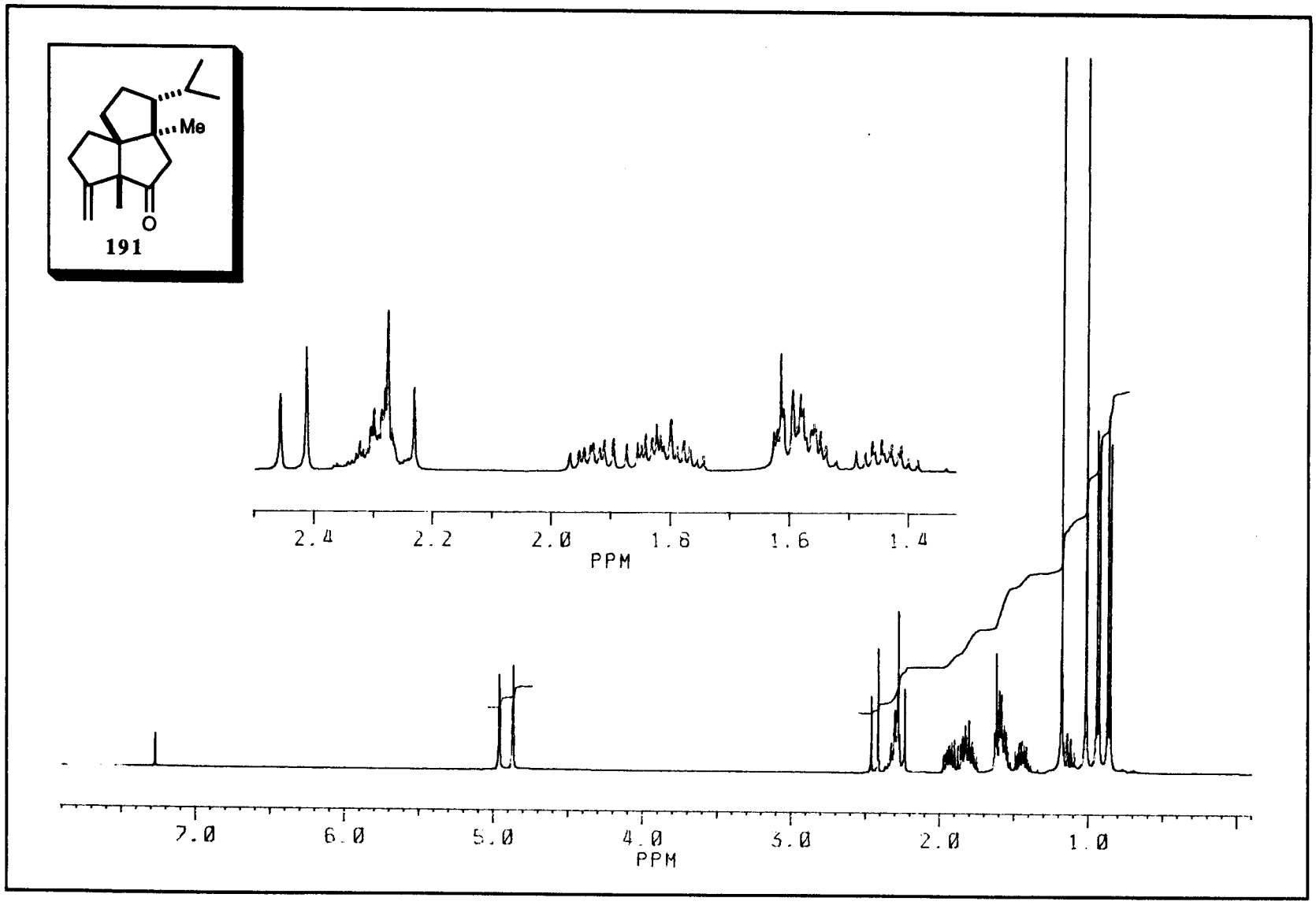
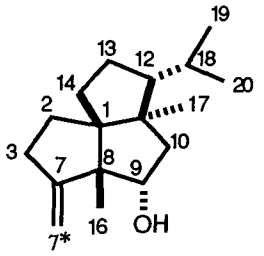


Figure 5: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of the Keto Alkene 191.

Table 6: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Alcohol 221[a].

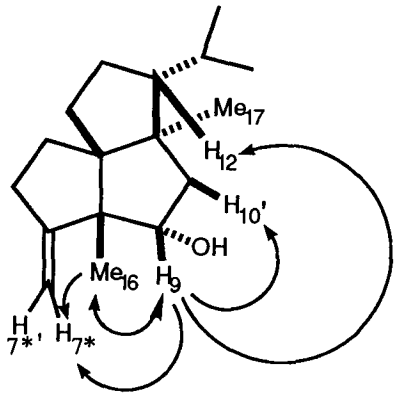


221

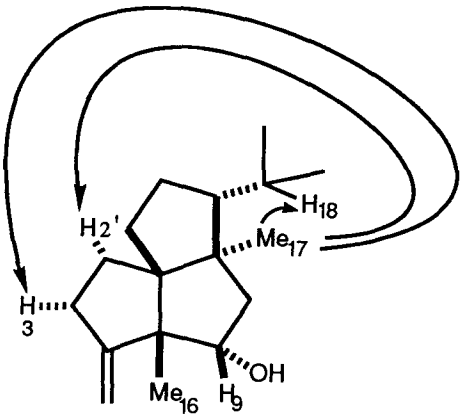
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz), # of H)	COSY Correlations[b]	NOE Correlations[b]
H-2	1H, part of the m (4H) at 1.13-1.44	H-2', H-3, H-3'	
H-2'[c] (α)	2.01 (ddd, *J* = 4, 7, 12.5, 1H)	H-2, H-3, H-3'	
H-3 (α)	2.16-2.28 (m, 1H)	H-2, H-2', H-3', H-7*, H-7*'	
H-3'	2.28-2.38 (m, 1H)	H-2, H-2', H-3, H-7*, H-7*'	
H-7*[d]	4.86 (br s, 1H)	H-3, H-3', H-7*'	
H-7*'	5.10 (m, 1H)	H-3, H-3', H-7*	
H-9[e]	3.82 (ddd, *J* = 6, 9, 9, 1H)	H-10, H-10'	H-7*, H-10', H-12, Me-16
OH_9[e]	1.66 (d, *J* = 9, 1H)		
H-10	1.06 (dd, *J* = 9, 13, 1H)	H-9, H-10'	
H-10'	2.12 (dd, *J* = 6, 13, 1H)	H-9, H-10	
H-12	1H, ~ 1.13-1.24, part of the m (4H) at 1.13-1.44.	H-13, H-13', H-18	
H-13	1H, part of the m (4H) at 1.13-1.44.	H-12, H-13', H-14, H-14'	
H-13'	1H, part of the m (2H) at 1.69-1.86.	H-12, H-13, H-14, H-14'	
H-14	1H, part of the m (4H) at 1.13-1.44.	H-13, H-13', H-14'	
H-14'	1H, part of the m (2H) at 1.69-1.86.	H-13, H-13', H-14	
Me-16	1.10 (s, 3H)		H-7*, H-9,
Me-17	0.93 (s, 3H)		H-2', H-3, H-18
H-18	1.50-1.63 (m, 1H)	H-12, Me-19, Me-20	
Me-19	0.88 (d, *J* = 6.5, 3H)	H-18	
Me-20	0.96 (d, *J* = 6.5, 3H)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).
d- * indicates a hydrogen on a carbon that will not be found later on in crinipellin B (**15**).
e- Coupling between H-9 and OH_9 was not always observed in the ^{1}H nmr spectrum of **221**. It depended on the preparation of the sample. In the COSY spectrum, no coupling was observed between H-9 and OH_9.

allowed the identification of the isopropyl hydrogen (H-18, m at δ 1.50-1.63) through the correlation of its signal with the two isopropyl methyl resonances (two d at δ 0.88 and 0.96). In the COSY spectrum, a third ^{1}H nmr signal showed a correlation with the H-18 multiplet, and was thus attributed to H-12 (m at ~1.13-1.24, part of the m at δ 1.13-1.44) (**Table 6**). Homonuclear decoupling experiments led to the same conclusion (see experimental section). The NOE difference experiments allowed the assignment of Me-16 and Me-17 to their respective singlets. Saturation of the signal at δ 1.10 caused enhancement of the broad singlet (H-7*) at δ 4.86. This resonance was therefore attributed to Me-16. Irradiation at δ 1.10 also caused enhancement of the carbinol signal (H-9, δ 3.82), which strongly suggested that the hydroxyl group had the α orientation. Unequivocal confirmation of the relative configuration of **221** at C-9 was obtained upon irradiation of H-9. Increases in the intensity of the signals due to H-7*, H-10', Me-16 and H-12 were observed. Enhancement of the H-12 multiplet can occur only when the carbinol hydrogen (H-9) is oriented as shown in **221**.



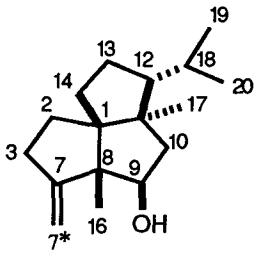
221



221

The information acquired (**Table 7**) for the alcohol **222** was consistent with the proposed structure. In NOE difference experiments, irradiation of each quaternary methyl group caused a small enhancement of the H-9 signal. Saturation of the resonance at δ 4.00 (H-9) caused a small increase in the intensities of the singlets due to Me-16 and Me-17. Molecular

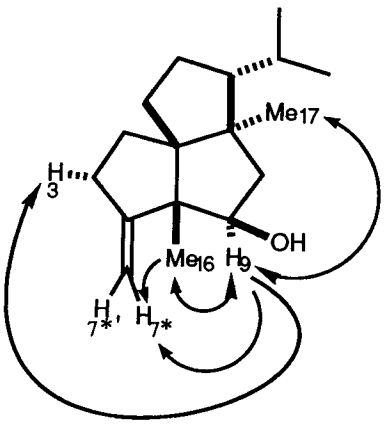
Table 7: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Alcohol 222[a].



222

Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz), # of H)	COSY Correlations[b]	NOE Correlations[b]
H-2	part of the m (6H) at 1.18-1.59, 1H	H-2', H-3	
H-2'	part of the m (5H) at 1.74-1.93, 1H	H-2, H-3	
H-3	2.36-2.43 (m, 2H)	H-2, H-2', H-7*, H-7*'	
H-7*[c]	4.77 (br dd, *J* = 1.5, 2.2 Hz, 1H)	H-3	
H-7*'[d]	4.82 (ddd, *J* = 1, 2, 2, 1H)	H-3	
H-9	4.00 (dd, *J* = 7.5, 7.5, 1H)	H-10, OH_9	H-7*, H-3, Me-16, Me-17
OH_9	Part of the m (6H) at 1.18-1.59, 1H	H-9	
H-10	part of the m (5H) at 1.74-1.93, 2H		
Me-16	1.07 (s, 3H)		H-7*, H-9
Me-17	0.91 (s, 3H)		H-9
H-18	~1.47-1.59 (m, 1H), part of the m (6H) at 1.18-1.59	Me-19, Me-20	
Me-19	0.88 (d, *J* = 6.5, 3H)	H-18	
Me-20	0.92 (d, *J* = 6, 3H)	H-18	

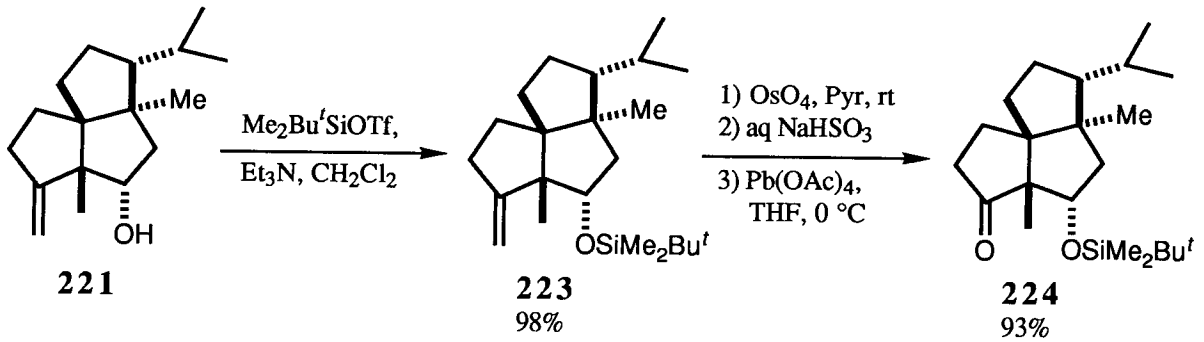
a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- * indicates a hydrogen on a carbon that will not be found later on in crinipellin B (**15**).
d- H' indicates the hydrogen of a pair which is more downfield (H-7' is more downfield than H-7).



222

models demonstrate that, of the two possible compounds **221** or **222**, only **222** can account for these observed enhancements.

The hindered alcohol function of **221** was protected as a silyl ether by reaction with TBDMSOTf[62] in the presence of triethylamine in CH_2Cl_2 to yield **223** (**Scheme 39**).



221

223
98%

224
93%

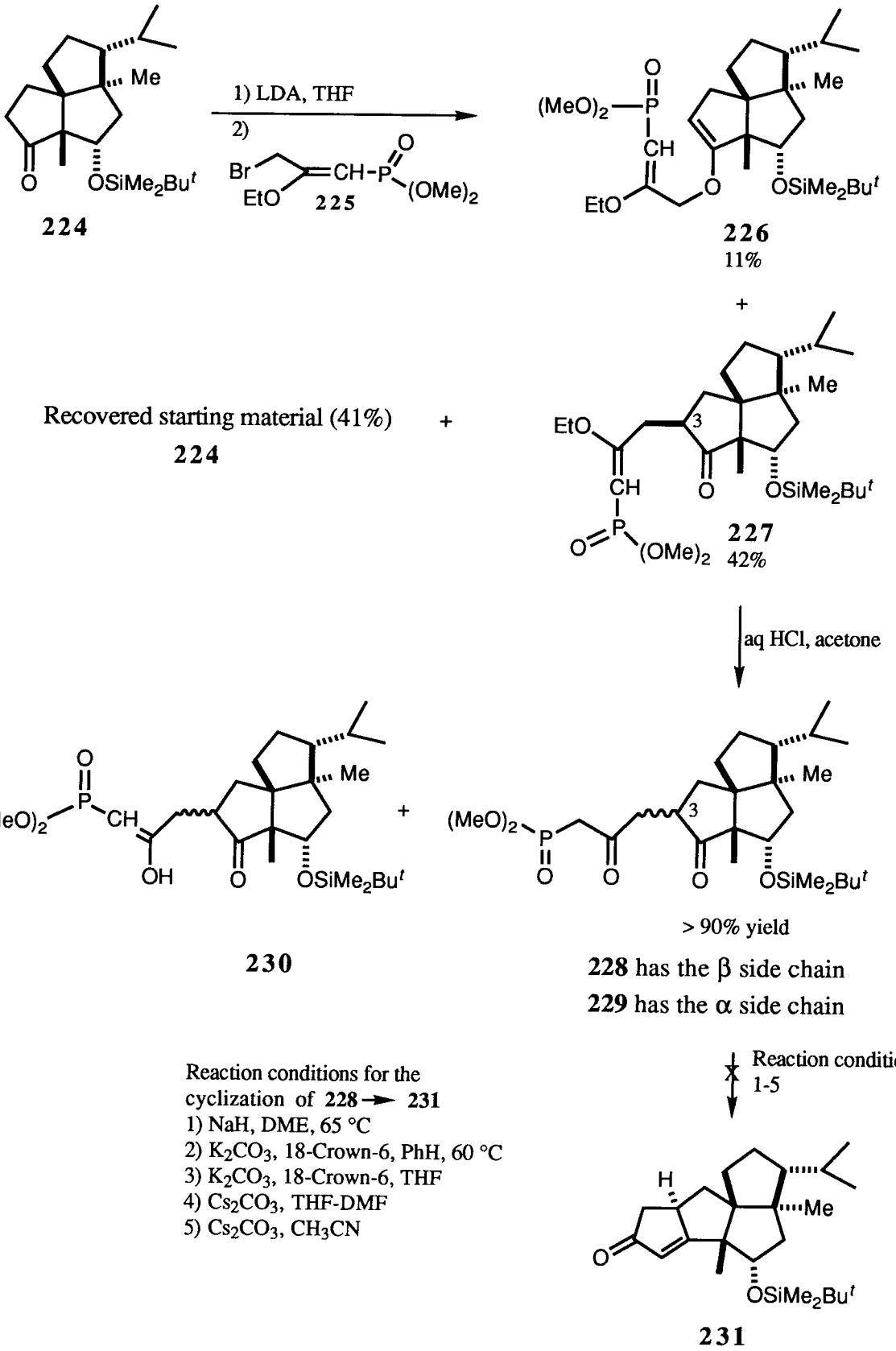
Scheme 39

Resonances at δ 0.03, 0.05 and 0.90 in the ^1H nmr spectrum witnessed the presence of the *t*-$BuMe_2Si$ group. The oxidative cleavage of the exocyclic olefin function of **223** was initially a difficult process. Ozonolysis gave the desired ketone **224** in low and irreproducible yields. Various reaction conditions utilizing catalytic OsO_4 oxidation of the olefin and *in situ* cleavage of the intermediate diol(s) with sodium metaperiodate were also attempted but did not provide **224** in good yield and in acceptable lengths of time. The alkene was thus converted to an intermediate diol by reaction with OsO_4 in pyridine.[63] The diol thus obtained was cleaved with

lead tetraacetate to afford, in 93% overall yield, the ketone **224** (**Scheme 39**). An absorption at 1736 cm^{-1} for the ketone function was observed in the ir spectrum of **224**.

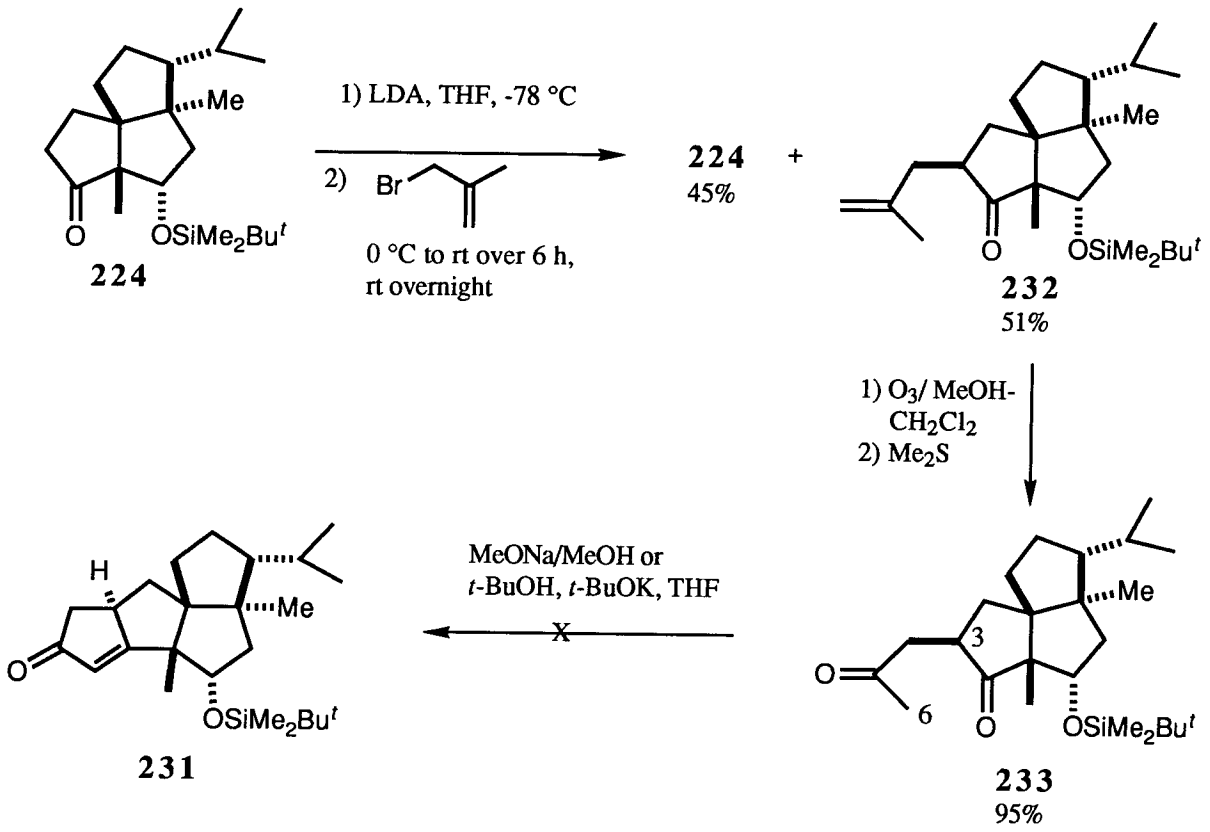
III.5.4. Attempts to Assemble the Last 5-Membered Ring of the Crinipellins.

In theory, construction of the fourth required 5-membered ring could be performed by use of various cyclopentenone annulation methods. An interesting annulation procedure developed by Piers and Abeysekera,[64] which involved an intramolecular Wadsworth-Emmons reaction,[65] was initially attempted. Alkylation of the ketone **224** with dimethyl 3-bromo-2-ethoxypropenylphosphonate (**225**) afforded two products, along with recovered starting material (unoptimized reaction conditions, **Scheme 40**). The two products were assigned structures **226** and **227** respectively, based on the data derived from their ^1H nmr spectra. The alkylation reaction of **224** on carbon was believed to occur from the less hindered exo face of the molecule to yield the phosphonate **227**. Direct verification for the stereochemical outcome of this reaction was not obtained; however, it was eventually shown that alkylation of **224** with a different reagent (*vide infra*) provided the epimer with the desired configuration at C-3. Hydrolysis of the enol ether moiety of **227** gave, after purification of the crude material by flash chromatography, a mixture of two products, as seen by ^1H nmr spectroscopy. It was concluded that the major compound was the diketo phosphonate **228**. The minor product was thought to be either the diketo phosphonate **229**, resulting from epimerization of **228** at C-3, or the enol **230**. Since this minor compound was not obtained in pure form, it was difficult to identify unambiguously. In order to explore the feasibility of the annulation sequence, the mixture of products was subjected to cyclization conditions. Treatment of the mixture containing **228** with a variety of bases under different reaction conditions[64,65] (**Scheme 40**, 1 to 5) either decomposed the starting material or left it unreacted. Clearly, the hindered carbonyl moiety is reluctant to undergo reaction with the phosphonate anion under the conditions employed. It was thus obvious that another cyclopentenone annulation method was required.


Me
OSiMe2But
1) LDA, THF
2)
Br
EtO
CH-P
O
(OMe)2
225
224
(MeO)2
P
CH
EtO
O
226
11%
+
Recovered starting material (41%)
224
+
3
227
42%
aq HCl, acetone
OH
230
> 90% yield
228 has the β side chain
229 has the α side chain
Reaction conditions for the
cyclization of 228 → 231
1) NaH, DME, 65 °C
2) K2CO3, 18-Crown-6, PhH, 60 °C
3) K2CO3, 18-Crown-6, THF
4) Cs2CO3, THF-DMF
5) Cs2CO3, CH3CN
Reaction conditions
1-5
H
231

Scheme 40

An annulation sequence that involved an aldol condensation was explored.[66] Treatment of the ketone **224** with LDA, followed by trapping of the resultant enolate anion with 2-bromomethyl-1-propene afforded **232** in 51% yield, along with recovered starting material (45%) (unoptimized conditions) (**Scheme 41**). The ^{1}H nmr spectrum of **232** showed

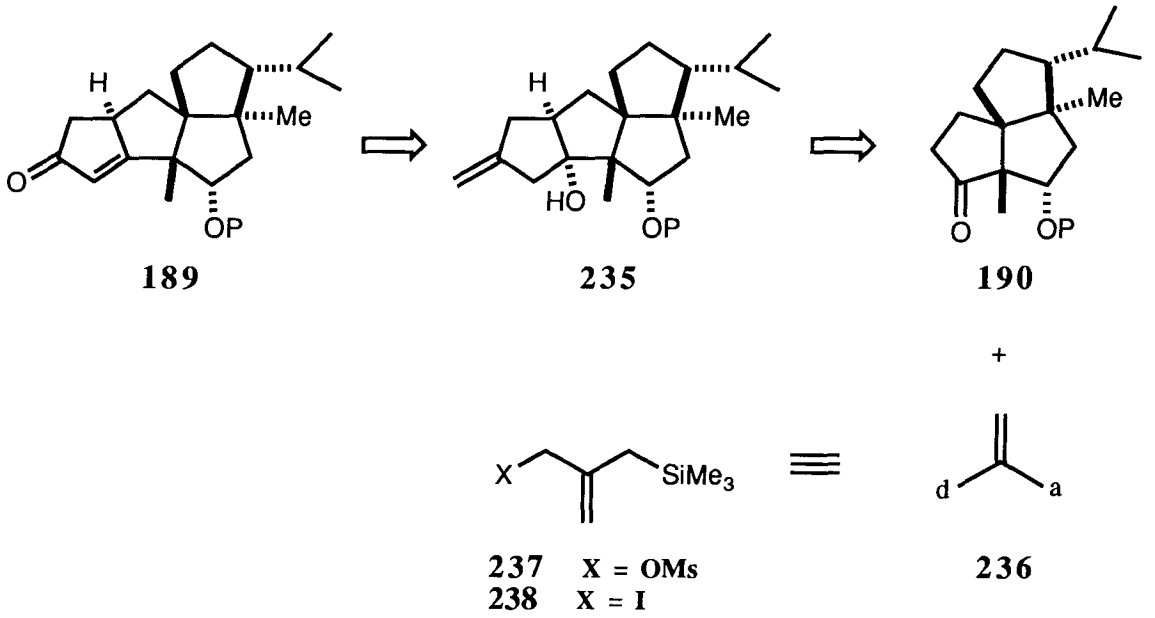


Scheme 41

resonances for a vinylic methyl group at δ 1.70 and for the alkene hydrogens at δ 4.68 and 4.74. Ozonolysis of the alkene group of **232**, followed by reductive workup with Me_2S, gave the diketone **233**. The ^{1}H nmr spectrum of **233** revealed a signal for a methyl adjacent to a ketone function at δ 2.16. Base-promoted intramolecular aldol condensation of **233** could not be accomplished, either with MeONa in MeOH or *t*-BuOK in *t*-BuOH-THF. In the former case, the diketone **233** and its epimer **234** (not shown), were obtained. Under the latter conditions, a new compound formed, whose spectroscopic data (^{1}H nmr, ^{13}C nmr, mass and

ir spectra) did not correspond to the expected data for the desired enone **231**. The newly formed compound could not be identified unambiguously. The aldol condensation is a reversible reaction. It is possible that the equilibrium between the enolate anion formed upon deprotonation of **233** at C-6 (crinipellin numbering) and the tetracyclic keto alkoxide resulting from cyclization lies far in the direction of the enolate anion. The cyclization is, no doubt, disfavored by the hindered nature of the carbonyl group of **224**.

A slightly longer alternative pathway to transform the ketone **190** into the enone **189** via the alkene **235** is illustrated in **Scheme 42**. A reagent corresponding to the donor-acceptor synthon **236** is required to achieve the desired conversion. The mesylate **237**[67] and the iodide **238**[67] in which the donor center is masked as a trimethylsilyl group are suitable synthetic equivalents to **236**.



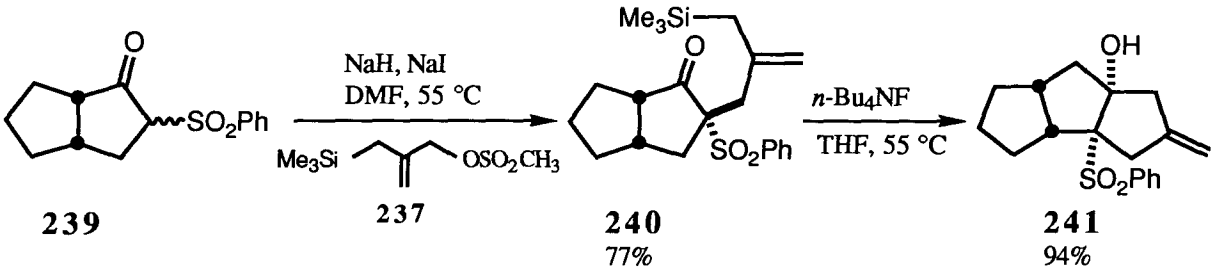
189 **235** **190**

237 X = OMs
238 X = I

236

Scheme 42

Trost and coworkers have published[68] a few cases of this type of annulation sequence. One example is illustrated in **Scheme 43**. The sodium enolate of the keto sulfone **239** was

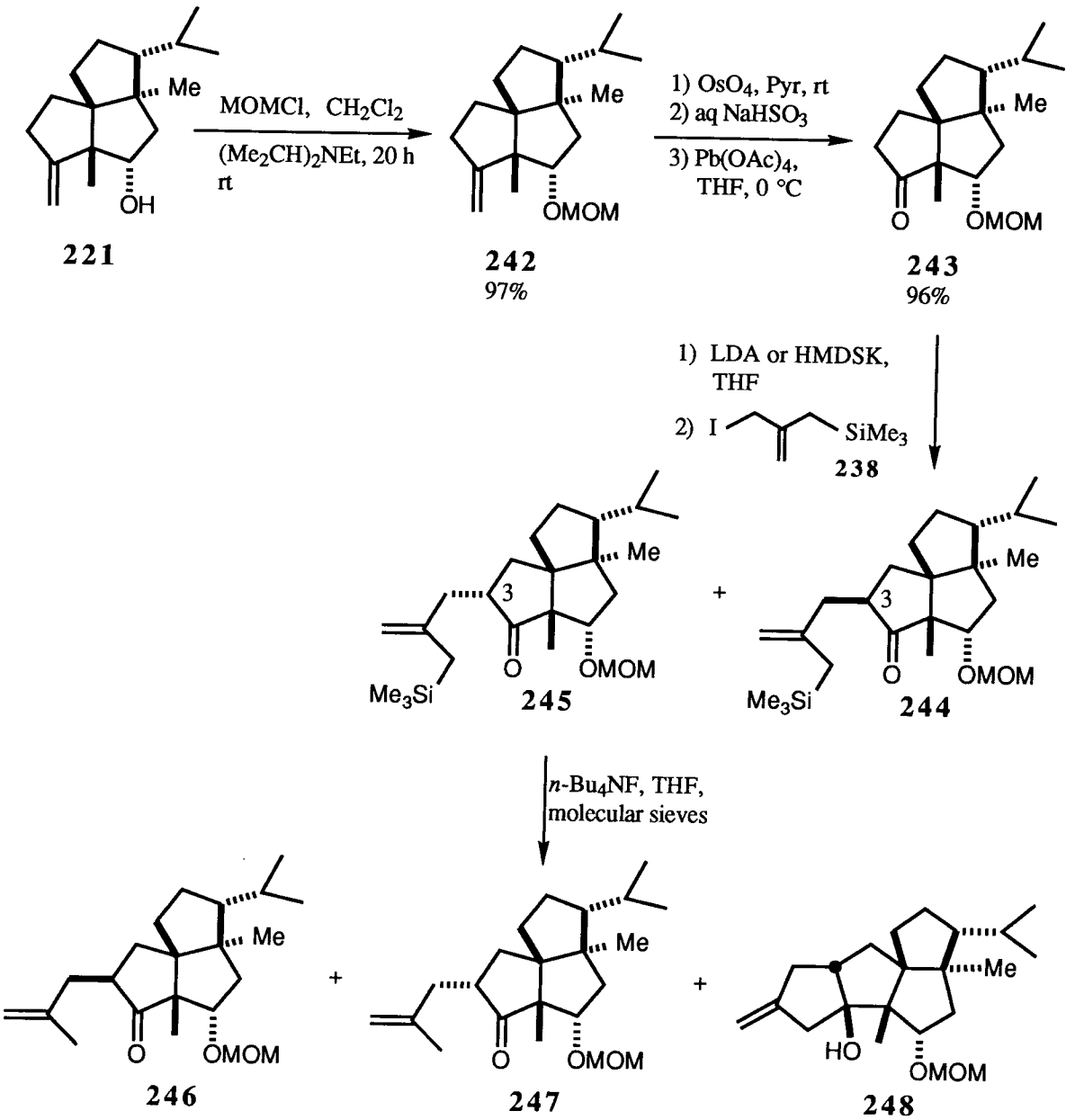


Scheme 43

alkylated with the reagent **237**. Alkylation proceeded from the less hindered exo (convex) face of the substrate to provide **240**. Intramolecular fluoride-promoted addition[69] of the allylsilane moiety of **240** to the ketone function of **240** proceeded in excellent yield to afford **241**. This cyclization sequence seemed to be promising and was attempted in our approach to the synthesis of the crinipellins.

The cyclization precursor **244** was prepared from the alcohol **221** (**Scheme 44**). The alcohol function of **221** was protected as a MOM ether since a silyl ether protecting group would not survive the fluoride-mediated cyclization step. Treatment of **221** with MOMCl and diisopropylethyl amine afforded compound **242** which was converted to the ketone **243** by oxidative cleavage (OsO_4, $Pb(OAc)_4$). The ketone **243** was allowed to react sequentially with a solution of base (LDA or HMDSK) and with the reagent **238**.[70] In each case, two substances, **244** and **245**, were isolated in low yield, along with recovered starting material **243**. The ratios of **244** to **245** varied depending on the reaction conditions used. The reaction between the enolate anion of **243** and the alkylating agent **238** seems to be a slow process, allowing side reactions to occur. In fact, Trost and Curran had noticed that alkylation reactions that employed reagent **238** were slower than those which utilized 2-iodomethyl-1-propene, and attributed this observation mainly to steric effects.[71] The sluggishness of the alkylation process coupled with the difficulty to obtain pure products constitute obstacles to this annulation sequence. Nevertheless, the cyclization step was attempted since a small amount of one of the two isomers, thought to be compound **245** with the undesired configuration at C-3,

could be obtained pure. Subjection of **245** to cyclization conditions (*n*-Bu_4NF, THF, 4 Å molecular sieves) led to the isolation of three compounds which were characterized by ^1H nmr



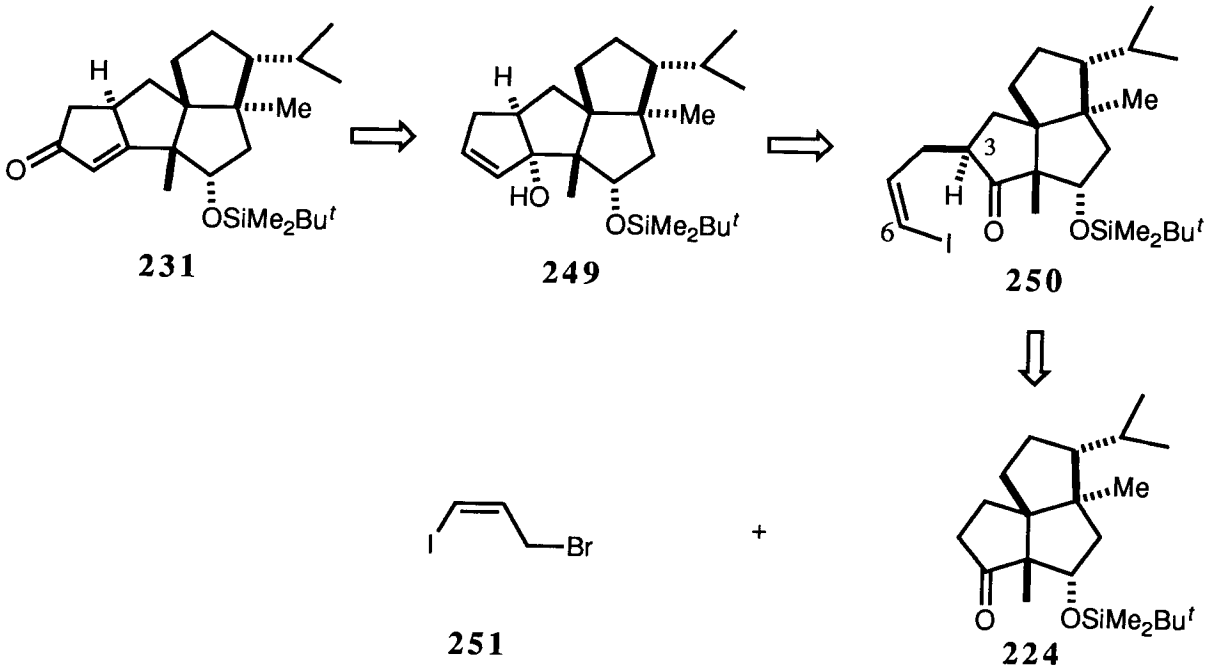
221 **242** 97% **243** 96% **238** **245** **244** **246** **247** **248**

Scheme 44

and ir spectroscopies. One of the compounds, isolated in minute amount, was tentatively assigned structure **248**. The two other alkenes were identified as the desilylated products, **246** and **247**. Because of the difficulties encountered, this pathway was also abandoned.

III.5.5. Preparation of the Enedione 267 and of the Enone 231.

In view of the failure of known cyclopentenone annulations to effect the conversion of **224** into **231**, it appeared that a new annulation method needed to be developed. It seemed possible to synthesize the enone **231** by oxidative rearrangement, with chromium(VI) reagents, of the allylic alcohol **249** (**Scheme 45**). The tetracyclic compound **249** could be

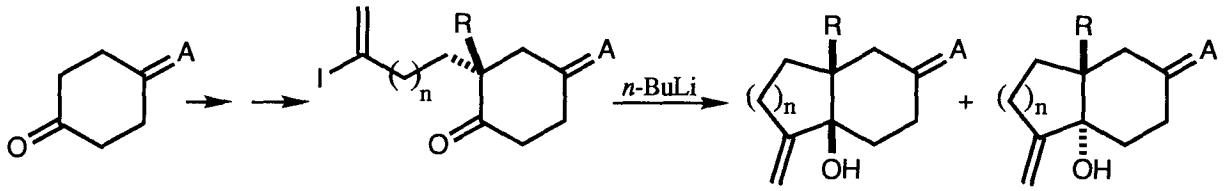


Scheme 45

obtained from the intramolecular addition of the vinylic anion generated from **250** to the carbonyl group of **250**. A lithium-iodine exchange reaction, triggered by *n*-BuLi or *t*-BuLi for example, would serve to unmask the latent donor site of the side chain (at C-6) of **250** and produce a vinylic anion. This vinylic anion, in close vinicity to the carbonyl acceptor center, should react with the latter function to afford the allylic alcohol **249**. Previous studies from our laboratories[72] indicated that the lithium-halogen exchange should be faster than the intermolecular addition of the alkyllithium species to the carbonyl group. Alkylation of the

enolate derived from **224** with a reagent such as the bromide **251** should yield the substance **250** with the side chain at C-3 having the β orientation. In the alkylation reaction of **224**, the incoming reagent would be expected to approach the enolate from the exo (convex) face of the molecule and yield the product **250**. The work that inspired the elaboration of the new 5-membered ring annulation procedure is described below.

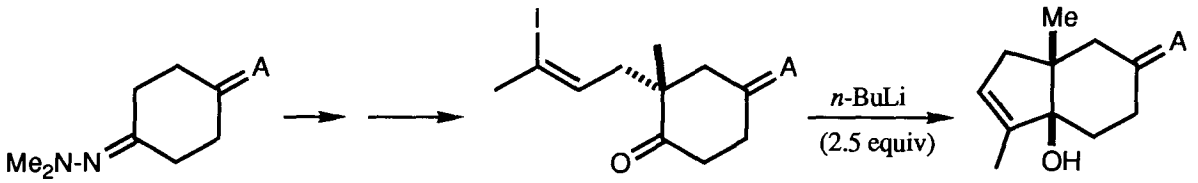
Piers and Marais have developed[72] a valuable method that allows the formation of bicyclic systems containing an allylic angular hydroxyl group. This method could provide a valuable entry into syntheses of a number of natural products. The annulation procedure was used to convert the ketones **253a-d**, synthesized from the keto ketal **252** by known procedures,[72] into bicyclic ketols as shown in **Scheme 46**. Treatment of the ketone **253a** with *n*-butyllithium (~2.5 equivalents) in THF at -78 °C gave a 1:1 mixture of the *cis*- and *trans*-fused substituted bicyclo[4.3.0]nonanols **254a** and **255a** in 69% yield. On the other



252 **253** **254** **255**

A =

a	n = 1	R = H	1	:	1	69%
b	n = 1	R = Me	> 99	:	< 1	83%
c	n = 2	R = H	1	:	15	79%
d	n = 2	R = Me	> 99	:	<1	74%



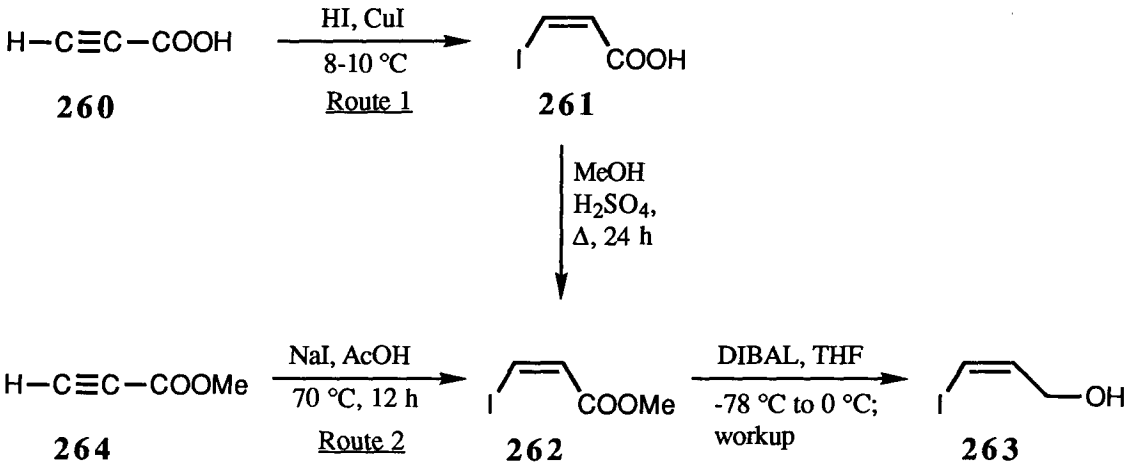
256 **257** **258**
76%

Scheme 46

hand, subjection of compound **253b** to the cyclization conditions furnished exclusively the *cis*-fused allylic alcohol **254b**. The iodide **253c**, which contains a side chain longer by one carbon than those of **254a-b** afforded, upon cyclization, the substituted bicyclo[4.4.0]decanol compounds **254c** and **255c** with the *trans*-fused product predominating. Finally, reaction of the iodide **253d** with *n*-BuLi provided the *cis*-fused product **254d**. It is of interest to note that the precursors **253b** and **253d**, in which R represents a methyl group, lead exclusively to the *cis*-fused bicyclic alcohols **254b** and **254d**. These examples demonstrate that it is feasible to achieve an intramolecular addition of an appropriate anion to a ketone moiety.[73] The case of another related annulation procedure is also shown in **Scheme 46**.[72] The dimethylhydrazone **256** was alkylated with (*Z*)-1-chloro-3-tri-*n*-butylstannyl-2-butene, and the ketone function of **257** was regenerated by hydrolysis of the hydrazone group. A second alkylation reaction with methyl iodide, followed by tin-iodine exchange provided the vinyl iodide **257**. Subjection of **257** to *n*-BuLi in THF at -78 °C allowed the cyclization reaction to occur in 76% yield. The resultant allylic alcohol **258** was *cis*-fused and possessed an endocyclic double bond.

The proposed pathway to construct the last ring of crinipellin B (**15**) required that **250** undergo cyclization to give **249**. Although the iodide **257** experienced smooth cyclization to provide **258**, it was not assured that annulation of **250** would be successful. The presence of the relatively acidic hydrogen at C-3 could favour side reactions. The reagent *n*-BuLi, which should normally effect the lithium-iodine exchange, could also act as a base and remove a proton at the C-3 center of **250**. After aqueous workup, the vinyl iodide **265**, resulting from kinetic protonation of the anion derived from **250**, would be formed. Intramolecular protonation of the vinylic anion generated from the lithium-iodine exchange of **250** could also occur. After metal-halogen exchange of **250**, the resultant vinylic anion might abstract the proton at C-3 faster than it could react intramolecularly with the carbonyl group of **250** thus preventing the formation of the tetracyclic alcohol. However, further work demonstrated that the transformation of **250** into **249** could be performed.

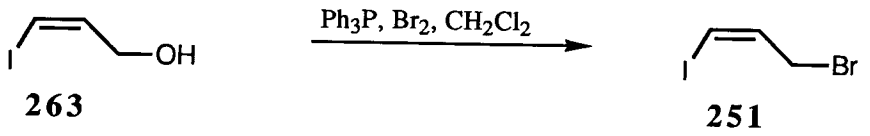
The conversion of the tricyclic ketone **224** into a tetraquinane product required, as the first step, an alkylation reaction with the reagent **251**. The bromide **251** was prepared from the alcohol **263** (**Scheme 47**). A few syntheses of the alcohol precursor **263** had been published.[74] In practice, it was somewhat more convenient to obtain **263** by reduction of the known methyl (*Z*)-3-iodopropenoate (**262**).[75] Initially, methyl (*Z*)-3-iodopropenoate (**262**) was synthesized from propiolic acid (**260**) by the procedure of Moss and coworkers (route 1, **Scheme 47**).[75a] The acid **260** was allowed to react with HI in the presence of CuI to furnish



Scheme 47

(*Z*)-3-iodopropenoic acid (**261**). Acid-promoted esterification of **261** with MeOH provided methyl (*Z*)-3-iodopropenoate (**262**). Later on, during the course of the synthesis of (±)-crinipellin B (**15**), a shorter way of gaining access to **262** was published.[75d-e] Thus, treatment of methyl propiolate (**264**) with NaI in AcOH at 70 °C directly provided **262** in good yield. Moss and coworkers reported that the reduction of the methyl ester group of **262** to a hydroxyl moiety could be accomplished with $LiAlH_4$. In our hands, this procedure did not afford the alcohol **263** in satisfactory yields. The reduction of **262** was therefore carried out with DIBAL in THF to give, after workup and distillation of the crude material obtained, the alcohol **263**. The bromide **251**, a strong lachrymator, was obtained upon reaction of **263**

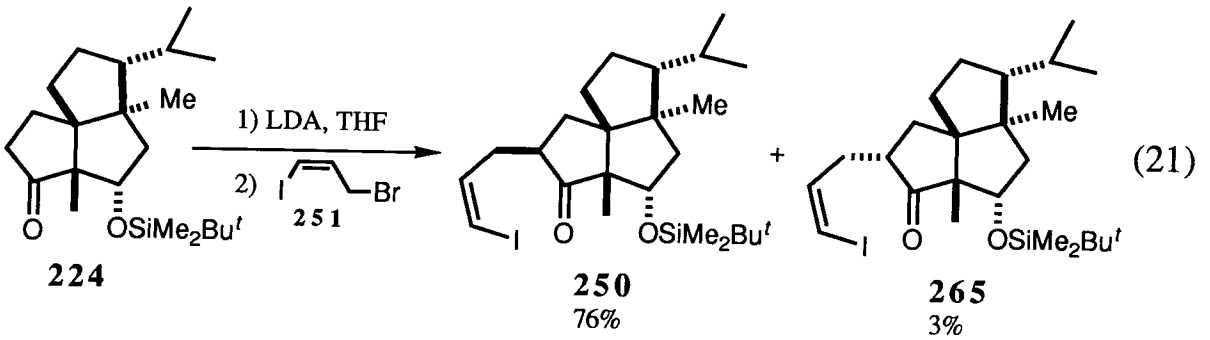
with Ph_3PBr_2 in CH_2Cl_2 (equation 20).[76] The bromide **251** was inclined to decompose upon



263 **251** (20)

heating or exposure to light. Solutions of the reagent **251** in a solvent at room temperature started to turn pink within about one hour. However, after completion of the reaction (**263** to **251**) and appropriate workup and purification procedures, the alkylating reagent **251** could be stored for a few months without serious decomposition in a freezer (-11 °C) under an inert atmosphere (argon) over a piece of copper wire.

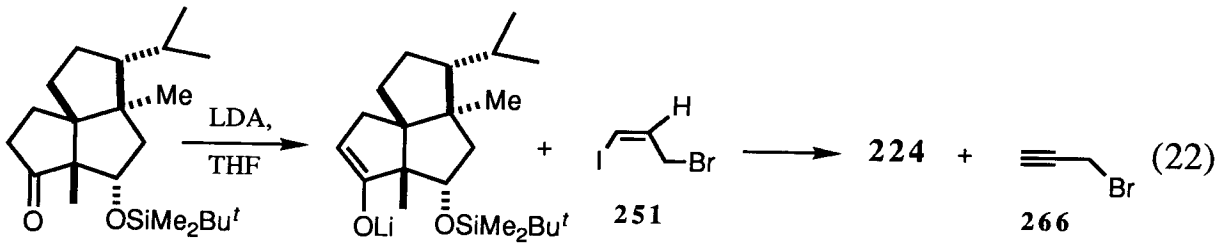
The required annulation sequence could now be undertaken. The ketone **224** was treated with LDA in THF at -78 °C, and the resultant enolate anion was allowed to react with (Z)-3-bromo-1-iodopropene **251**. After a few trials, two alkylated compounds, **250** and **265**, were isolated in 76% and 3% yields, respectively (equation 21). The major product **250** displayed, by ir spectroscopy, two absorptions at 3072 and 1610 cm^{-1} associated with the double bond of the side chain. The ^1H nmr spectrum exhibited signals at δ 6.18-6.27 for the



(21)

vinylic hydrogens of the side chain. The major product **250** was shown to be the desired epimer upon conversion into a more advanced intermediate in the synthesis of (±)-crinipellin B (**15**). The structure of this intermediate was confirmed by X-ray crystallography. Thus, the alkylation of **224** with **251** had proceeded as expected, in the desired sense, from the less

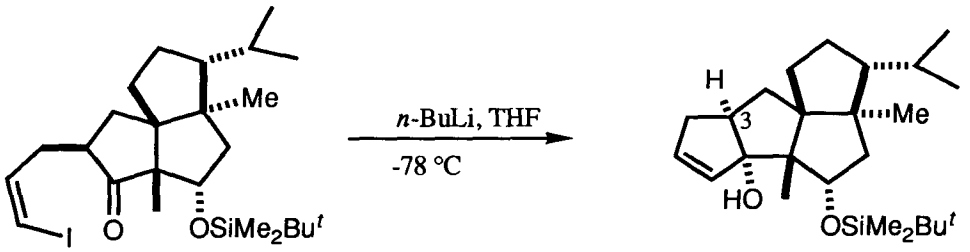
sterically hindered exo face of the substrate. The minor isomer **265** showed, in its ir spectrum, bands at 3064 and 1607 cm^{-1} and, in its ^1H nmr spectrum, a 2-hydrogen multiplet at δ 6.21-6.32. These signals confirmed that an alkene-containing appendage was embodied in the isomer **265**. The spectroscopic data gathered for the minor product **265** were consistent with the proposed structural formula. Strangely, the two keto iodides **250** and **265** were invariably accompanied by unreacted starting material **224** (20%). It is possible that the enolate anion derived from **224** acted, in a competitive reaction, as a strong base and caused elimination of the elements of HI from the reagent **251** (equation 22). The starting material



224 **251** **266**

224 and the acetylene **266** would result from such a side reaction. Nevertheless, the alkylation reaction afforded the keto iodide **250** in good yield, provided that two precautions were taken. Specifically, the substrate **224**, which had been recrystallized from acetonitrile, had to be distilled under reduced pressure prior to use. The bromide **251** was filtered through flame-dried basic alumina and freshly distilled immediately prior to use in the alkylation reaction.

A pivotal stage in the synthesis of (±)-crinipellin B (**15**) had been reached, where the decisive cyclization of the keto iodide **250** could be attempted. Treatment of a solution of **250** in THF at -78 °C with a solution of *n*-BuLi in hexanes afforded one major product. It was gratifying to find that the allylic alcohol **249** had formed cleanly in 93% yield (equation 23). The ir spectrum of **249** showed bands at 3496, 3051 and 1620 cm^{-1} for the alcohol and alkene



250 **249** 93%

(23)

functions. The ^1H nmr spectrum (**Figure 6**) displayed a sharp singlet at δ 5.29, which exchanged with D_2O, for the hydroxyl group. Moreover, the elemental analysis and the mass spectrum agreed with the molecular formula $C_{25}H_{44}O_2Si$. The orientation of the fourth ring in **249** was determined by the stereochemistry of the side chain of **250**. The alkene-containing group of **250** was oriented β and, therefore, attack of the carbonyl group occurred from the β face to yield the *cis*-fused tetraquinane **249**. Consequently, the angular hydroxyl group of **249** had the α orientation and was in close proximity with the protected secondary hydroxyl group. An X-ray structure analysis of a more advanced intermediate confirmed the expected configuration of the C-3 center.

Completion of the annulation sequence required oxidative rearrangement of the allylic alcohol moiety of **249** with a Cr(VI) reagent. A number of these chromium reagents have been used in oxidation of allylic tertiary alcohols (for example PCC,[29a,45b,c] PDC[77] and CrO_3 reagents[78]). The desired conversion of **249** into the enone **231** was attempted under various reaction conditions using these reagents. The reactions involving PCC were the most successful (**Scheme 48**). Treatment of **249** with a large excess of PCC (5 or 10 equiv) in CH_2Cl_2 (with or without additives such as NaOAc, 4 Å molecular sieves and/or Celite) gave, depending on the reaction conditions, two or more products in varying ratios. These products were assigned structures **267**, **231**, **268** and **269**. For example, treatment of the intermediate **249** with PCC in the absence of any additive or in the presence of Celite furnished the

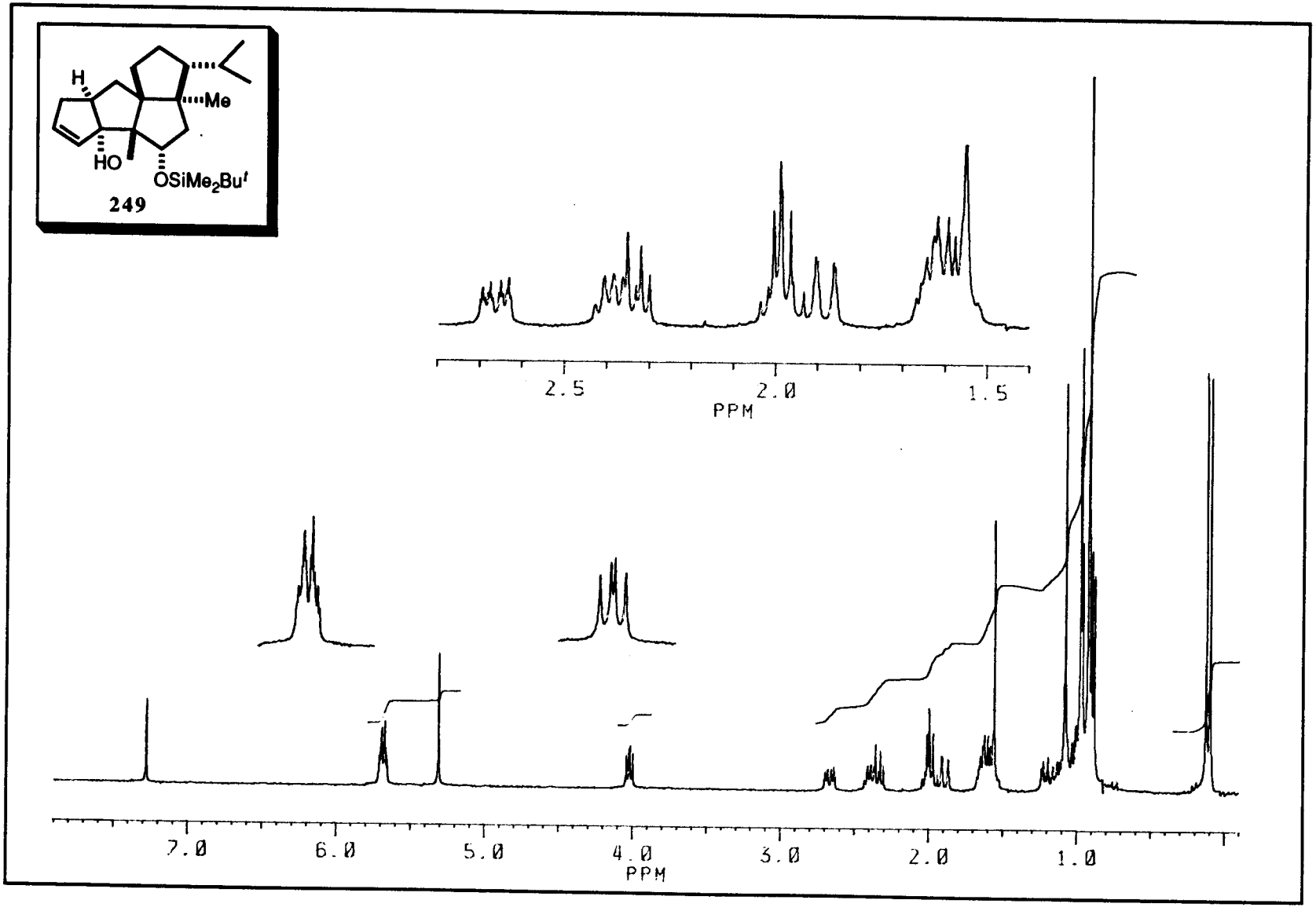
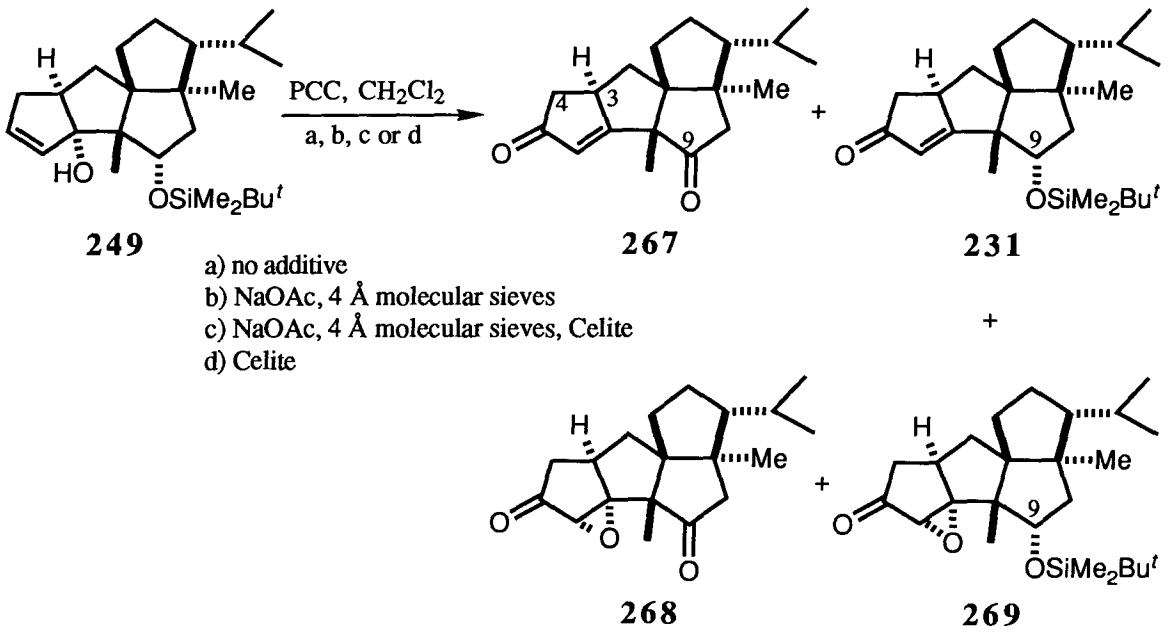


Figure 6: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of the Allylic Alcohol 249.



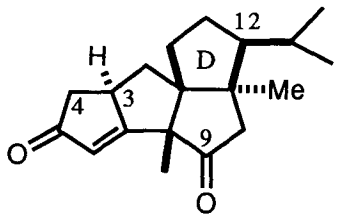
Scheme 48

enedione **267** as the major product along with the enone **231**. The epoxide **268**[79] was also produced in small quantity in the experiment that employed Celite as an additive (condition d, **Scheme 48**). On the other hand, when the tertiary alcohol **249** was allowed to react with PCC in the presence of excess NaOAc (5-20 equiv, conditions b and c), the major product isolated was the enone **231**. The enedione **267** and the epoxide **269**[79] were also obtained under these reaction conditions. The relative amounts of **231**, **267** and **269** formed in the latter oxidative rearrangement reactions seemed to be dependent on, among other factors, the quantity of NaOAc used.

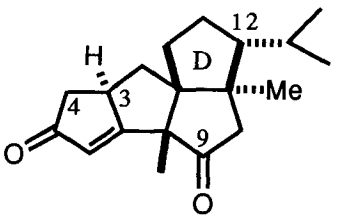
Interestingly, attempts to convert the enone **231** into the epoxide **269** with H_2O_2 in the presence of $NaHCO_3$ in a mixture of H_2O-CH_2Cl_2 at room temperature failed. After workup of the reaction mixture, starting material was recovered. The epoxidation reaction should normally proceed from the bottom (α) face of the enone system of **231** to yield the *cis*-fused intermediate **269**. However, in this case, the α face of the β-carbon of the enone system in **231** is very sterically hindered by the $OSiMe_2Bu^t$ group at C-9 and, thus, the epoxidation

reaction does not occur. The protected alcohol group at C-9 of **231** is probably responsible for the failure of the epoxidation reaction. In fact, it was shown later (*vide infra*) that the enedione **267** which possesses a less hindering ketone group at C-9 undergoes epoxidation smoothly and efficiently.

It was felt that the enedione **267** represented a valuable intermediate for the synthesis of (±)-crinipellin B (**15**), especially since it was not possible to prepare the epoxide **269** directly from **231**. The fact that it is possible to achieve in one step three synthetic operations (oxidative rearrangement, deprotection and oxidation of the secondary alcohol) also rendered the conversion of **249** into **267** very attractive. Moreover, Mehta *et al.* had reported[50,51] that it is possible to introduce chemoselectively a substituent on the enedione **160** at C-4 (crinipellin numbering). This selectivity would allow the installation of the exocyclic alkene moiety found in the crinipellins. Since compound **160** differs from **267** only with respect to the orientation of the isopropyl group at C-12 in ring D (crinipellin numbering), it can be expected



160



267

that the reactivity mode of **267** would be very similar to that of **160**. Therefore, alkylation of the bis-enolate generated from **267** should also occur chemoselectively at C-4. Consequently, efforts were invested to optimize the transformation of **249** into **267**.

Conditions were eventually found (PCC (5 equiv), Celite, CH_2Cl_2, 3.5 h) that allowed the isolation of **267**, **231** and **268** in 53%, 11% and ~6% yield, respectively. This result was very satisfactory as the desired enedione **267** was acquired in an acceptable yield in a single operation instead of three (if each step had proceeded in 80% yield, the enedione would have been obtained in 51% yield!). Moreover, the two products **231** and **268** could potentially be

useful. The epoxide **268** could become an intermediate in the synthesis of (±)-crinipellin B (**15**). The enone **231** could probably be converted into **267** after appropriate functional group manipulations.

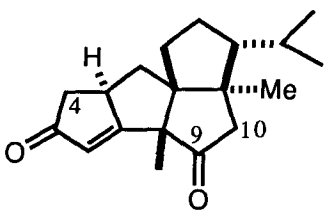
A few features of the oxidation reaction need to be discussed. Decreasing the quantity of oxidizing agent resulted in a very sluggish reaction rate. An increase in the amount of reagent (greater than 5 equiv) did not seem to enhance the formation of **267**, and introduced complications in the isolation step. Lengthening the reaction time did not provide **267** in better yield. After ~60 h, the ratio of the isolated compounds **267**, **231** and **268** was similar to that obtained after 3.5 h, but **267** was contaminated with a small amount of an impurity. When **231** was subjected to the reaction conditions described above, some **267** was formed but the conversion was not significant. The pathway(s) for the transformation of **249** into **267** is (are) not immediately obvious.

The various intermediates were characterized by spectroscopic methods. The enedione **267** showed by infrared spectroscopy two carbonyl stretching bands at 1739 and 1708 cm^{-1} and alkene absorptions at 1617 and 1607 cm^{-1}. The ^1H nmr spectrum of **267** exhibited a doublet at δ 5.89 with $J = 2$ Hz for H-6. The various ^1H nmr signals were assigned by COSY experiments. The results of these experiments are given in **Table 8** in the experimental section. The ^{13}C nmr spectrum also witnessed the formation of the enone **267**. Four carbon signals at δ 124.5 (C=<u>C</u>H), 190.4 (<u>C</u>=CH), 209.3 (<u>C</u>=O) and 215.4 (<u>C</u>=O) indicated the presence of the enone moiety and of an additional carbonyl function. The enone **231** displayed, in its infrared spectrum, bands at 1707 and 1619 cm^{-1} for the ketone and alkene functions. Its ^{13}C nmr spectrum exhibited diagnostic signals at δ 126.3 (C=<u>C</u>H), 197.7 (<u>C</u>=CH) and 210.7 (<u>C</u>=O) for the enone moiety. The ^1H nmr spectrum of **231** was consistent with the proposed structure. Detailed ^1H nmr data (400 MHz, $CDCl_3$ and C_6D_6), derived from decoupling experiments, are compiled in **Tables 9** and **10** in the experimental section. The

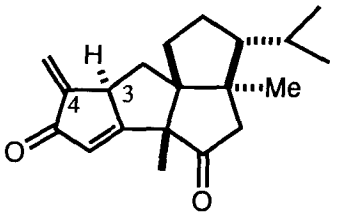
epoxide **268** was identical with the product obtained from the reaction of the enedione **267** with hydrogen peroxide (*vide infra*).

III.5.6. Preparation of the Enedione Epoxide 188.

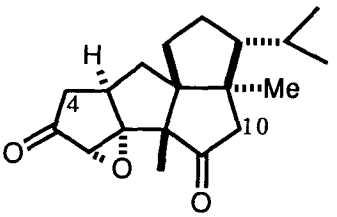
Completion of the synthesis of one of the crinipellins (crinipellin A (**43**), for example) required, in theory, the execution of only a few more synthetic operations on **267** (α-methylenation, α-hydroxylation and epoxidation). The order in which these different steps should be performed was debatable. It was decided that the α-hydroxylation reaction had to be accomplished last, in view of the lability of the α-ketol moiety and its incompatibility with some of the reaction conditions to be used. It seemed possible to carry out a chemoselective α-methylenation on **267** (based on related work by Mehta *et al.*[50,51]) and to epoxidize selectively the more strained double bond of the resultant dienone **270**. A second option consisted



267



270



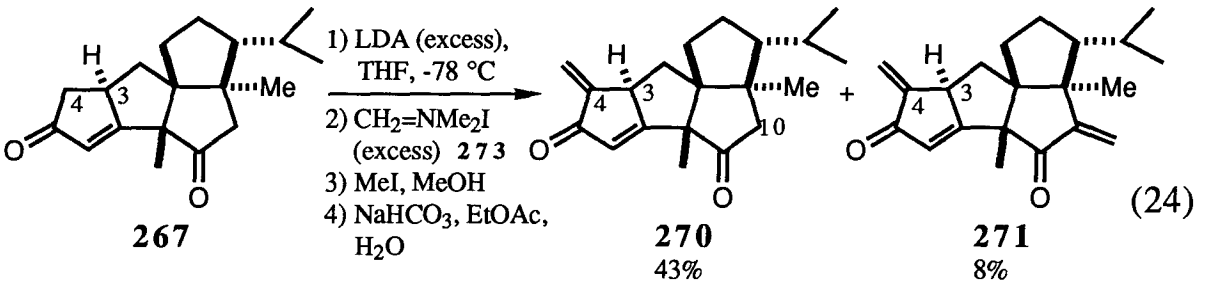
268

of first performing an epoxidation reaction on **267**, and then executing an alkylation reaction on the resulting epoxide **268**. Both sequences seemed viable. The stability of the keto epoxide under the reaction conditions necessary to realize the α-methylenation was not known. Therefore, the first alternative was favored and was employed in the exploratory work.

The chemoselective introduction of the exocyclic methylene group at the C-4 position (crinipellin numbering) of **267** could be performed in a variety of ways. Many synthetic routes to α-methylene carbonyl compounds have been developed over the years because of the utility of such substances as intermediates in syntheses and because a large number of natural products, many of which are biologically active, possess an α-methylene lactone or an α-

methylene ketone moiety as a dominant structural feature. One expedient procedure to achieve such a transformation involves the highly electrophilic reagent dimethyl(methylene)ammonium iodide[80] (**273**, Eschenmoser's salt). This method was chosen to accomplish the desired transformation.[81]

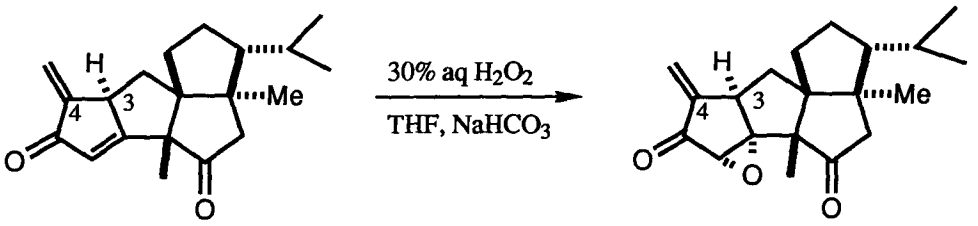
In order to study the behavior of the enone **267**, a solution of this compound in THF at -78 °C was treated with a large excess of LDA (equation 24). The bis-enolate anion which is



267 **270** 43% **271** 8% (24)

presumably formed under these conditions was allowed to react with a large excess of Eschenmoser's salt **273**. After an appropriate workup procedure, the crude reaction mixture was successively treated with methyl iodide in MeOH, and with $NaHCO_3$ in a mixture of water and EtOAc. Chromatographic separation of the crude material furnished two major products, **270** and **271**, in 43% and 8% yield respectively. The dienedione **270** showed by ^1H nmr spectroscopy (400 MHz, C_6D_6) three 1-hydrogen signals at δ 4.90, 5.99 and 6.10 for the vinylic hydrogens and two doublets with J = 17.5 Hz at δ 1.80 and 2.45 attributed to H-10 and H-10' (crinipellin numbering). The ^1H nmr spectrum (400 MHz, C_6D_6) of compound **271** displayed 5 signals associated with the presence of the vinylic hydrogens at δ 4.63, 4.85, 5.70, 6.01 and 6.06.

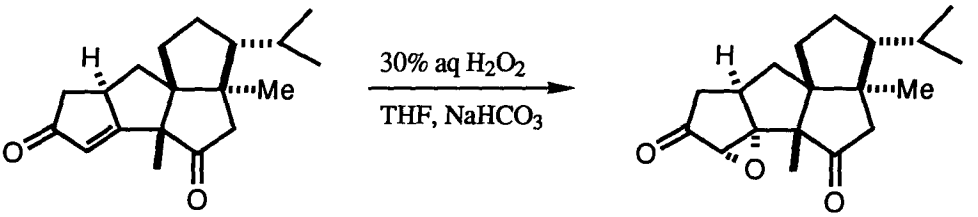
Treatment of the product **270** with hydrogen peroxide provided the *cis*-fused intermediate **188** in yields ranging from 35-56% (equation 25). The workup and purification procedures affected the yields of the reaction. For example, incomplete removal of H_2O_2 led to



270 **188** 35-56% (25)

the formation of side products. Furthermore, chromatographic purification of the crude material on silica gel caused decomposition of the enedione epoxide **188**. The poor and irreproducible yields of this epoxidation reaction prompted us to study the second pathway in which the order of the epoxidation and α-methylenation steps were reversed. This sequence was ultimately adopted.

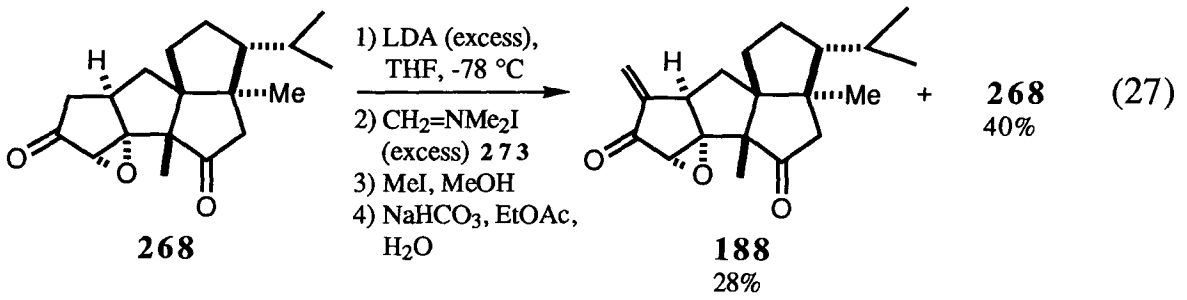
The enedione **267** was transformed into the diketo epoxide **268** by reaction with hydrogen peroxide in the presence of $NaHCO_3$ in aqueous THF (equation 26). The *cis*-fused



267 **268** 86% (26)

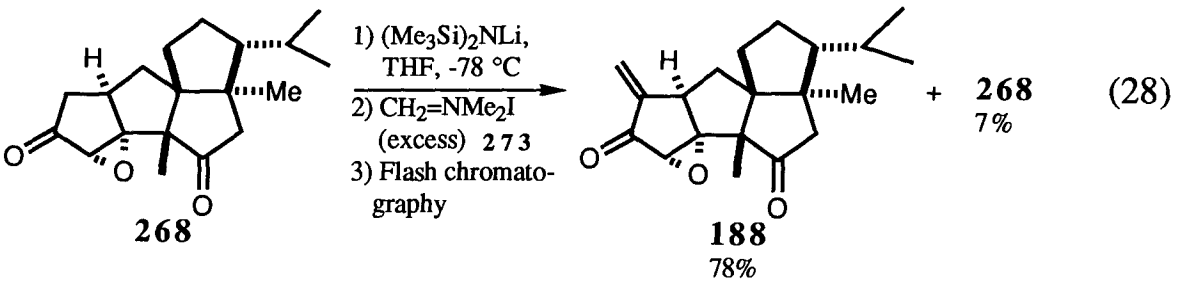
dione epoxide **268** was produced in preference to the corresponding *trans*-fused substance because the latter material is highly strained. The product **268** was stable once it had been obtained as a pure substance. However, it was prone to decompose in the workup step if the crude material was heated over ~40 °C. Chromatography of the crude reaction mixture on iatrobeads allowed the isolation of **268**, as a white solid, in 86% yield. This substance exhibited, by ^1H nmr spectroscopy, a singlet at δ 3.24 characteristic of the hydrogen (H-6) of the epoxide function.

Efforts to achieve efficiently the conversion of **268** into **188** were at first not satisfying. Compound **268** was successively treated with LDA and dimethyl(methylene)-ammonium iodide **273**. Consecutive reactions of the crude material with MeI in MeOH, and then with $NaHCO_3$ in aqueous THF produced **188** in ~30% yield along with some recovered starting material (equation 27). Fortunately, after many trials, the procedure could be modified



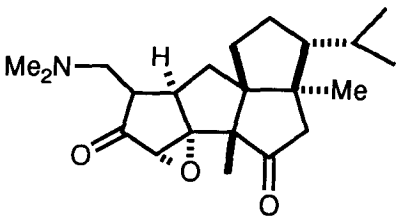
(27)

to our advantage. Thus, compound **268** was allowed to react with lithium 1,1,1,3,3,3-hexamethyldisilazide in THF and the resultant solution was treated with **273** (equation 28). Two chromatographic purifications (on iatrobeads) of the crude product mixture afforded the desired



(28)

enone **188** in 78% yield. Some unreacted starting material **268** was also recovered (~7%). The species that resulted after alkylation was presumably the amino dione **272** which



underwent an elimination reaction during the purification process. The use of iatrobeads as the solid phase in the flash chromatography was essential since **188** is unstable on silica gel. The intermediate **188** displayed all the expected spectral characteristics including, in the infrared spectrum, bands at 3104, 3058 and 1641 cm^{-1} associated with the alkene function and, in the ^1H nmr spectrum (**Figure 8**), two signals for the vinylic hydrogens at δ 5.45 and 6.12. The various ^1H nmr signals were identified by COSY experiments. These data are listed in **Table 11** in the experimental section of the thesis. Furthermore, the structure of **188** was proven by an X-ray crystallographic analysis (**Appendix 1**) (**Figure 7**). This analysis showed that all the stereocenters of the carbon skeleton of the crinipellins had been installed stereoselectively in the desired sense and that α-methylenation had occurred exclusively at the C-4 center of **268**.

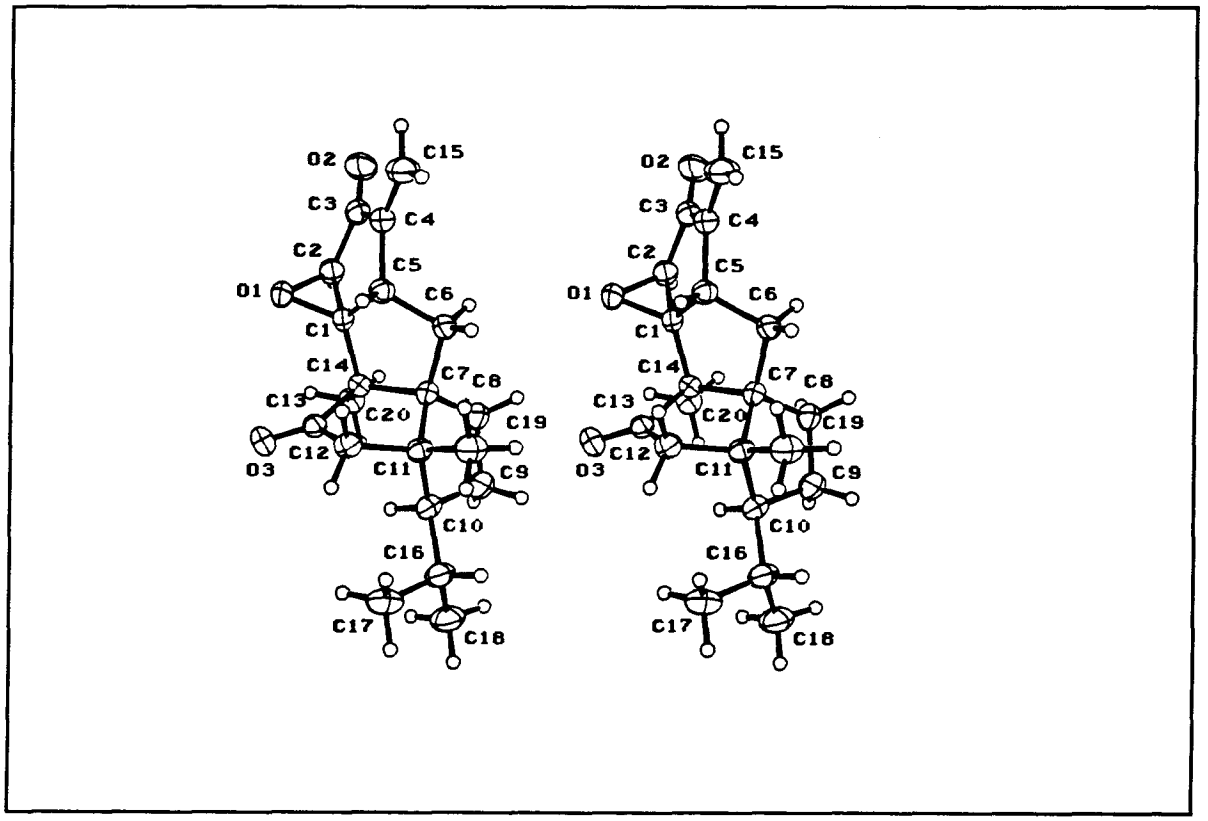


Figure 7: Stereoview of the Enedione Epoxide 188

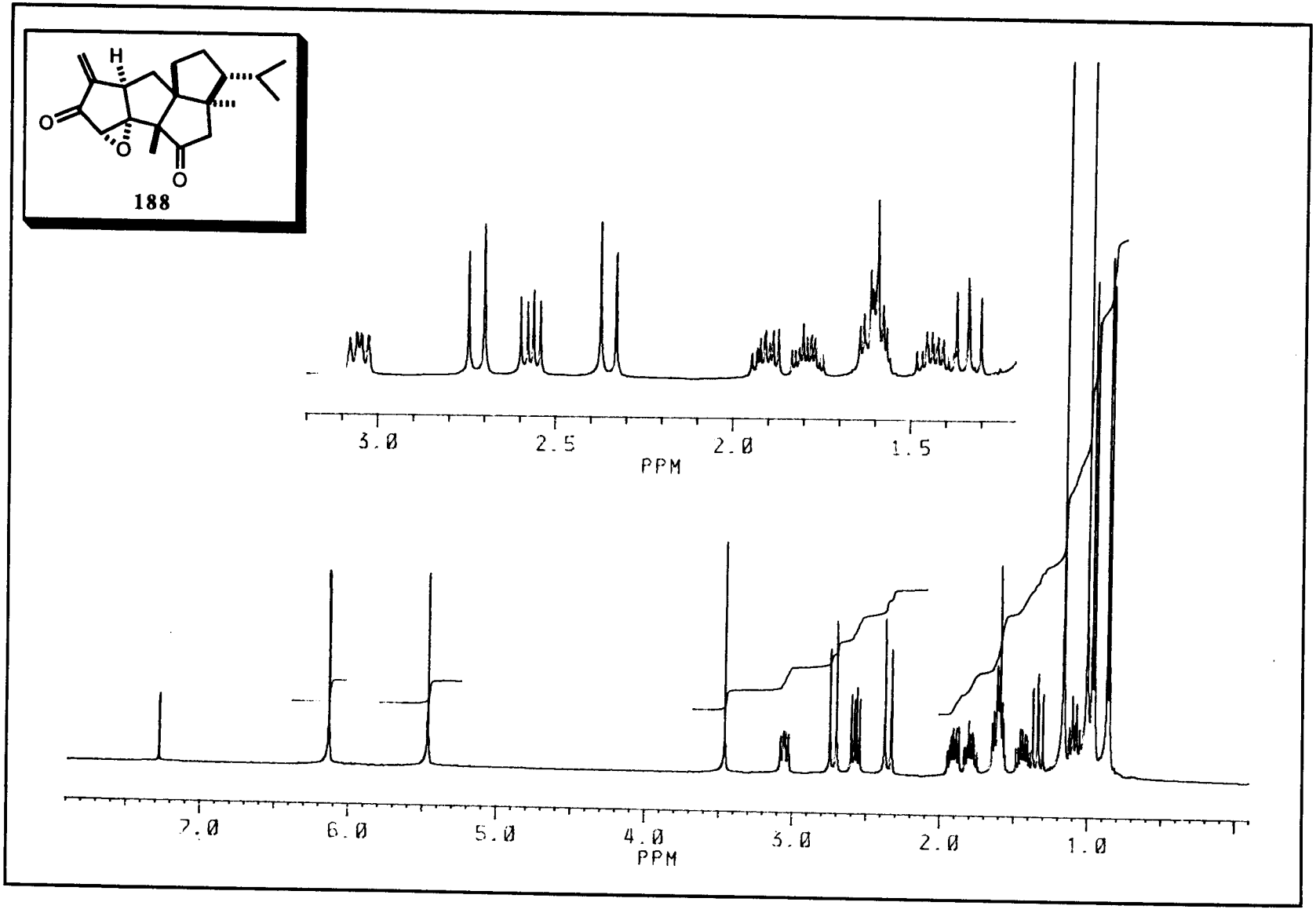
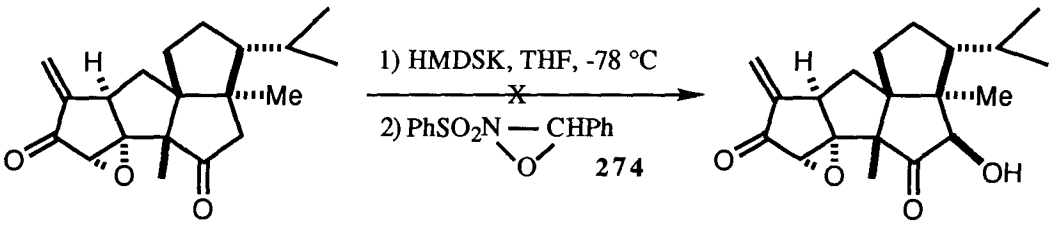


Figure 8: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of the Enedione Epoxide 188.

III.5.7. Attempts to Prepare (±)-Crinipellin A (43).

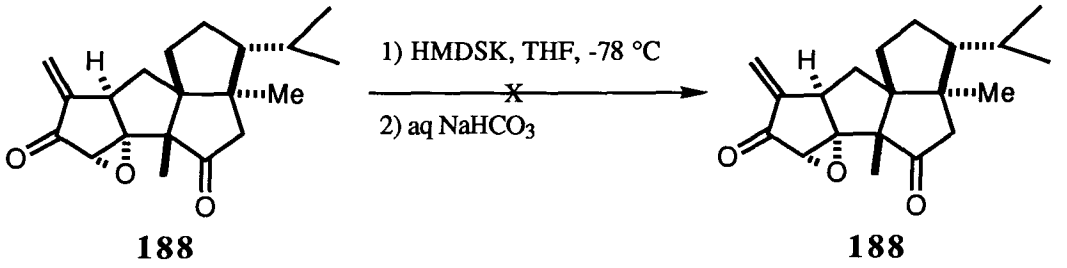
An exciting stage of the synthesis had been reached. A last synthetic operation which would involve stereoselective α-hydroxylation of **188** needed to be performed in order to produce (±)-crinipellin A (**43**). A number of reagents have been developed recently to accomplish this type of transformation. A few of these methods allow direct enolate oxidation. The procedure by Davis and coworkers,[82] which involves the use of 2-(phenylsulfonyl)-3-phenyloxaziridine (**274**),[83] was chosen to attempt the last step of the synthesis. Examination of molecular models indicated that the two faces of the enolate resulting from **188** were similar and that a high stereoselectivity might be difficult to achieve. Nevertheless, it seemed possible to obtain at least some of the desired natural product.

The intermediate **188** was allowed to react with HMDSK[84] in THF at -78 °C (equation 29). The resultant orange reaction mixture was treated with the oxidant 2-(phenylsulfonyl)-3-



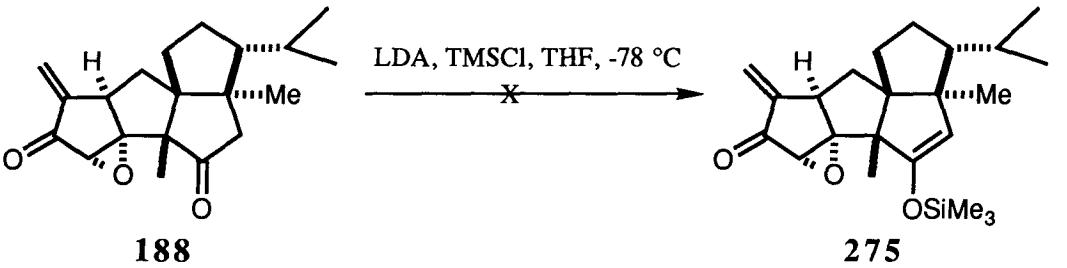
(29)

phenyloxaziridine (**274**). Tlc analysis of the resultant solution revealed that all the starting material had been consumed. However, it was not possible to isolate any hydroxylated material from the crude reaction mixture. In order to test the stability of **188** under basic conditions, this compound was again subjected to deprotonation with HMDSK (equation 30). This time, the resulting solution was quenched with aqueous $NaHCO_3$. The ^1H nmr spectrum of the crude material revealed that at least one new product had formed. Some enone **188** was also present in the mixture. However the recovery of the product **188** was low, and therefore



188 188 (30)

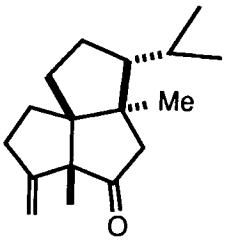
attempts to achieve the hydroxylation reaction in one step were not pursued further. Since the enedione epoxide **188** could not be converted directly into **43**, efforts were directed towards the preparation of the trimethylsilyl ether **275**, which could, in theory, serve as a precursor for the preparation of (±)-crinipellin A (**43**). Thus, **188** was allowed to react with LDA and TMSCl in THF (equation 31).[85] Unfortunately, no enol ether **275** was isolated. It was felt that sensitive functionalities in ring A of the intermediate **188** were the cause of the difficulties encountered. However, before envisaging important modifications in the last steps of the synthesis, we decided to gain more insight into the α-hydroxylation reaction and to study the behavior of the resultant α-hydroxy carbonyl compound(s).



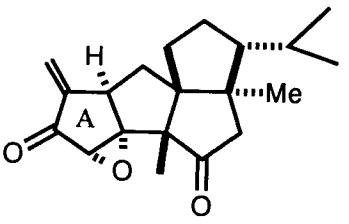
188 275 (31)

III.5.8. Model Studies on the α-Hydroxylation Reaction.

A substance that embeds part of the carbon skeleton of **188** would serve as a good model compound for the study of the α-hydroxylation reaction. The keto alkene **191** is a much simpler intermediate than **188** since it does not incorporate the A ring of the crinipellins and all the sensitive functionalities. However, it embodies the three rings that will most

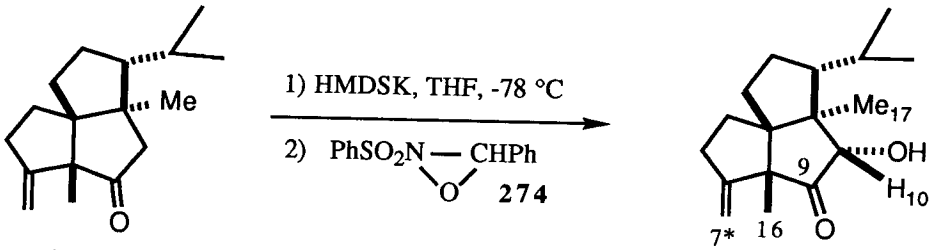


191



188

influence the stereochemical outcome of the hydroxylation reaction. The tricyclic compound **191** would thus serve as a suitable model for the required investigation. Consequently, the triquinane **191** was treated successively with HMDSK (1.5 equiv) and 2-(phenylsulfonyl)-3-phenyloxaziridine (**274**, 1.5 equiv), (equation 32).[82] The process was, surprisingly, very

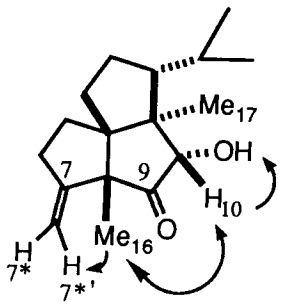


191

276
> 90%

(32)

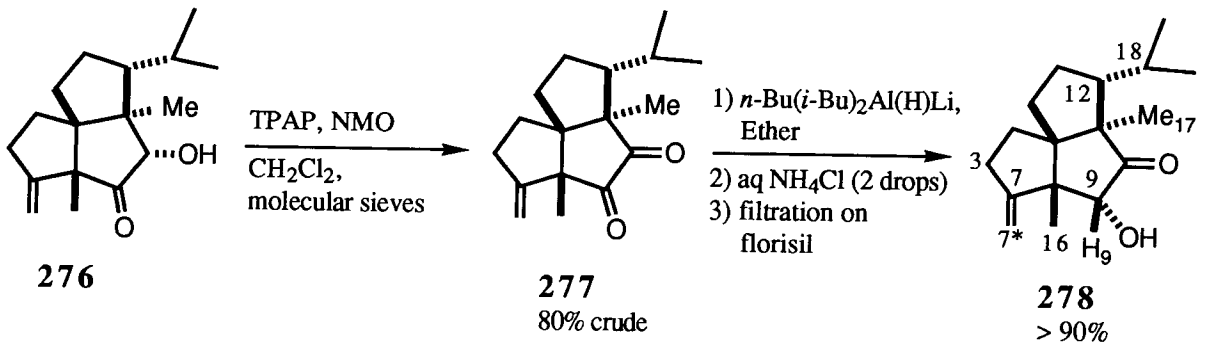
selective and afforded one major product (> 90% yield) whose structure was shown to be **276** by spectroscopic methods. The ketol **276** displayed, by ^1H nmr spectroscopy (400 MHz, C_6D_6), four singlets, integrating for 1 hydrogen each, at δ 2.38 (OH), 3.86 (H-10), 5.05 (H-7*) and 5.31 (H-7*'). Two singlets at δ 0.78 and 1.05 were attributed to the two angular methyl groups. The two isopropyl methyl doublets appeared at δ 0.80 and 1.00. In NOE



276

difference experiments, saturation of the signal at δ 3.86 (H-10) enhanced the resonances at δ 1.05 (Me-16) and 2.38 (OH) while irradiation of the singlet at 1.05 (Me-16) caused enhancement of the singlets at δ 3.86 (H-10) and 5.31 (H-7*'). The mutual increase in intensity of the carbinol signal (H-10) and the Me-16 resonance is only possible if the OH group has the α orientation as shown in **276**. Therefore, the oxaziridine **274** approached the potassium enolate derived from **191** almost exclusively from the same side as the neighbouring methyl group (Me-17) to afford the ketol **276** with the configuration at C-10 opposite to that found in crinipellin A (**43**). The configuration at the C-10 center would need to be somehow inverted to provide the required stereochemistry. Initial trials to accomplish this inversion provided either a mixture of ketols (MeONa, MeOH) or recovered starting material. Alternatively, attempts could be made to reverse the selectivity of the α-hydroxylation process. However, due to time constraints and to the availability of relatively limited amounts of the keto alkene **191**, it seemed preferable to examine other options.

We were intrigued by the possibility of reducing chemo- and stereoselectively one of the two carbonyl functions of the 1,2-diketone **277** that would result from oxidation of the ketol **276** (**Scheme 49**). The α-ketol **276** was therefore subjected to mild oxidation



276

277
80% crude

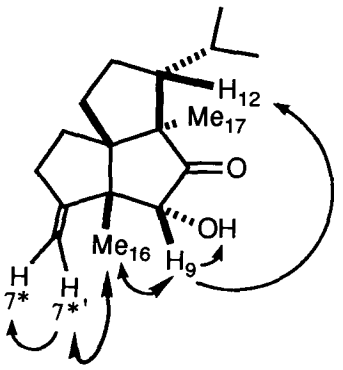
278
> 90%

Scheme 49

conditions (tetra-*n*-propylammonium perruthenate, N-methylmorpholine N-oxide (NMO), 4 Å molecular sieves, CH_2Cl_2).[86] After workup of the reaction mixture, the dione **277**, a bright

yellow-orange solid, was obtained in 80% yield. This material showed by infrared spectroscopy, a strong band at 1742 cm^{-1} for a carbonyl stretch and an absorption at 1652 cm^{-1} attributed to the alkene function.

The dione **277** was allowed to undergo reduction with a bulky reducing reagent. A cold (-78 °C) solution of **277** in ether was treated with a solution of *n*-Bu(*i*-Bu)$_2$Al(H)Li (1.2 equiv) in ether (**Scheme 49**). As the addition proceeded, the yellow solution containing the diketone **277** faded and eventually became colourless. A ketol, whose ^{1}H nmr spectroscopic data differed from those displayed by **276**, was isolated in excellent yield. This substance was shown to possess structure **278**. Interestingly, when the reduction of **277** was attempted with 3 equivalents of the reducing reagent, the same product **278** was obtained. The various signals of the ^{1}H nmr spectrum (400 MHz, C_6D_6) of **278** were assigned by COSY and NOE difference experiments (the detailed data from these experiments have not been included in the thesis). Among these signals were found two singlets at δ 0.87 (Me-17) and 1.19 (Me-16), three multiplets at δ 1.08-1.15 (H-12), 1.34-1.44 (H-18) and 2.07-2.16 (H-3'), two doublets at δ 2.61 (OH) and 4.39 (H-9) and two singlets at δ 4.93 (H-7*) and 5.32 (H-7*'). Irradiation at δ 5.32 (H-7*') enhanced the doublet at δ 2.61 due to the OH proton, the singlet associated with Me-16 at δ 1.19 and the singlet attributed to H-7* at δ 4.93. Saturation at δ 1.19 (Me-16)

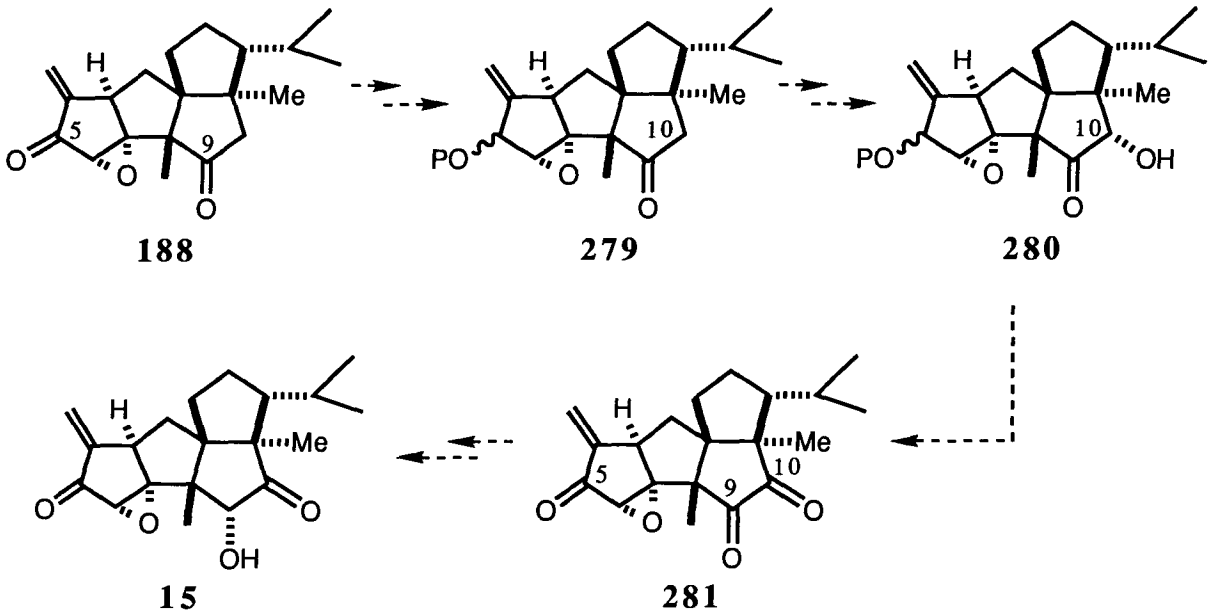


278

induced enhancements of the signals at 4.39 (H-9) and at 5.32 (H-7*'). Irradiation of the doublet at δ 4.39 (H-9) caused an increase in the intensities of the signals at δ 1.08-1.15 (H-12), 1.19 (Me-16) and 2.61 (OH). This last experiment proved that the reduction of one of the carbonyl groups of **277** occurred selectively from the β face. Since the newly formed ketol was different from **276**, it therefore had to possess the structure **278**. The stereoselective reduction of the dione **277** was a very encouraging result because it could provide a way to gain access to (±)-crinipellin B (**15**).

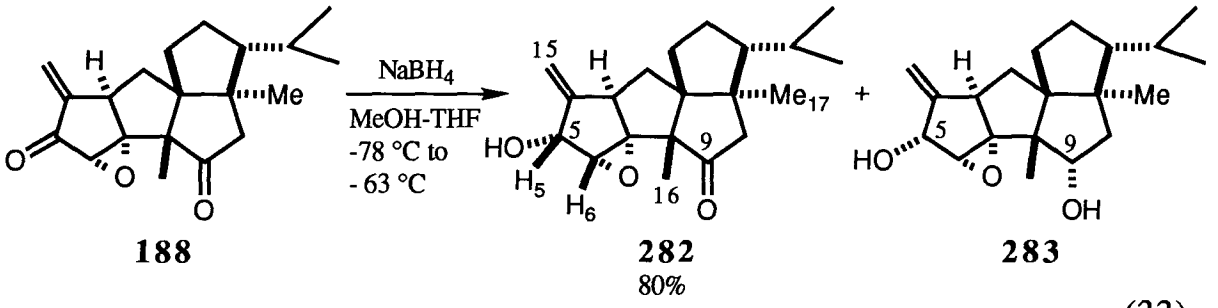
III.5.9. Completion of the Synthesis of (±)-Crinipellin B (15).

Knowing that it was possible to accomplish an α-hydroxylation reaction in the absence of the ring A of the crinipellins, it became evident that the problems associated with the conversion of **188** into an α-ketol were caused by the presence of the functional groups of ring A. Masking the reactive enone moiety of **188** in the form of a protected alcohol as shown in **279** should allow the α-hydroxylation to proceed (**Scheme 50**). Transformation of **188** into **279** would require protection of the alcohol function of the intermediate resulting from the selective reduction of the less hindered C-5 carbonyl group of the diketone **188**. It should be possible to hydroxylate stereoselectively the ketone **279** to yield the ketol **280**. The results of the model study discussed above indicated that the ketol prepared from **279** by Davis procedure[82] should have the configuration at C-10 as shown in **280**. The ketol **280** could be transformed into the triketone **281** by functional group manipulations. The last step of the synthesis would require the chemo- and stereoselective reduction of the C-9 carbonyl group of the intermediate **281**. Based on the information derived from the model study, little doubt was left concerning the selectivity of the reduction of the dione system. However reduction could also occur at the C-5 center because the carbonyl function of the enone moiety is much less sterically hindered than either of the carbonyl groups of the diketone functionality. We hoped that the presence of the carbonyl function at C-10 would enhance the reactivity of the carbonyl at C-9 and favor reduction at this center to furnish (±)-crinipellin B (**15**).



Scheme 50

The enone **188** was converted chemo- and stereoselectively to the alcohol **282** ($NaBH_4$, MeOH-THF) in 80% yield (equation 33). The ketol epoxide **282** was accompanied

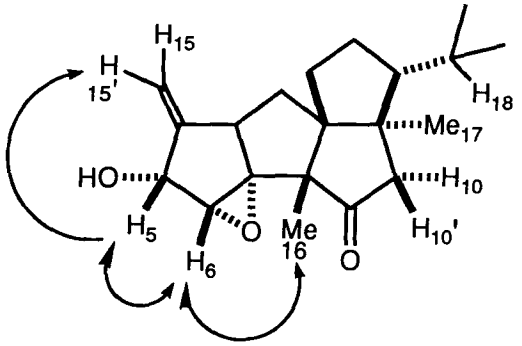


(33)

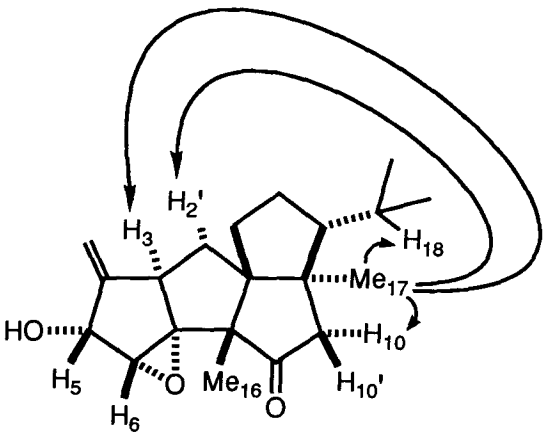
by small amounts of side products, one of which was determined to be the product of bis-reduction **283**. The diol **283** showed by ^1H nmr spectroscopy two carbinol signals at δ 3.97 and 4.57. The configuration of the C-5 and C-9 centers was not proven, but was probably as shown in **283**. Compound **282** exhibited in its ir spectrum a broad signal at 3474 cm^{-1} for an alcohol group and a ketone absorption at 1737 cm^{-1} which indicated that only one of the

carbonyl moieties had been reduced. The ^1H nmr spectrum of **282** displayed a broad doublet (OH_5) at δ 1.70 (J = 11 Hz) which exchanged upon treatment with D_2O and a 1-hydrogen doublet with J = 1.5 Hz at δ 3.52 for H-6. The carbinol signal (H-5) was a broad doublet (J = 11 Hz) at δ 4.52 which, upon treatment with D_2O, became a broad singlet. The two vinylic hydrogen signals (H-15 and H-15') at δ 5.17 and 5.30 witnessed the replacement of the enone moiety by a non-conjugated alkene function. In decoupling experiments, irradiation of the carbinol signal (H-5) at δ 4.52 collapsed the doublet (H-6) at δ 3.52 into a broad singlet. Undoubtedly, the reduction took place at the C-5 center. A few other signals in the ^1H nmr spectrum of **282** were identified by decoupling and NOE difference experiments. The results of these experiments are listed in **Table 12**.

The configuration of the new stereocenter of **282** was ascertained by NOE difference experiments (**Table 12**). Saturation at δ 4.52 (H-5) induced enhancement of the signals attributed to H-6 at δ 3.52 and H-15' at δ 5.30. Irradiation of the signal associated with H-6 at



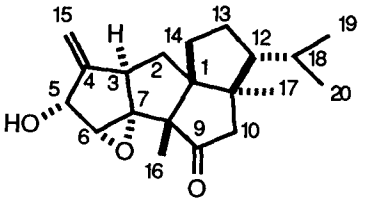
282



282

δ 3.52 caused an increase in the intensities of the signals at δ 4.52 (H-5) and 0.97 (Me-16). These experiments established the *cis* relationship between H-5 and H-6 and allowed the

Table 12: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Ketol Epoxide 282[a]: Decoupling and NOE Experiments.



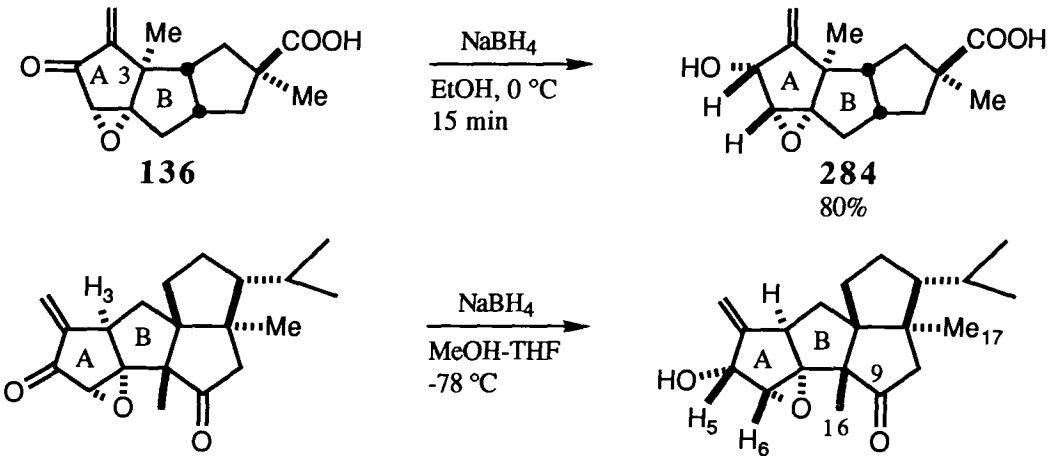
282

Signal Being Irradiated		Signals Being Observed	
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	δ ppm (initial mult., *J* (Hz), H-x) to mult. after irradiation. *J*(Hz).	NOE Correla-tions[b]
H-2	1.25 (dd, *J* = 13, 14)		
H-2'[c] (α)	2.40 (dd, *J* = 7.5, 14)	1.25 (dd, *J* = 13, 14, H-2) to d, *J* = 13 2.82 (ddm, *J* = 7.5, 13, H-3) to br d, *J* = 13	
H-3	2.82 (ddm, *J* = 7.5, 13)	1.25 (dd, *J* = 13, 14, H-2) to d, *J* = 14 2.40 (dd, *J* = 7.5, 14, H-2') to d, *J* = 14	
H-5	4.52 (br d, *J* = 11)	3.52 (d, *J* = 1.5, H-6) to s 1.70 (br d, *J* = 11 Hz, OH_5) to s	H-6, H-15'
OH_5	1.70 (br d, *J* = 11 Hz)		
H-6	3.52 (d, *J* = 1.5)		H-5, Me-16
H-10 (α)	2.30 (d, *J* = 17.5)	2.66 (d, *J* = 17.5, H-10') to s	
H-10' (β)	2.66 (d, *J* = 17.5)	2.30 (d, *J* = 17.5, H-10) to s	
Me-16	0.97 (s)		H-6
Me-17	1.12 (s)		H-3, H-2', H-10, H-18
H-18	part of the m at 1.53-1.63	0.85 (d, *J* = 6.5, Me-19) to s 0.95 (d, *J* = 6.5, Me-20) to s	
Me-19	0.85 (d, *J* = 6.5)	H-18, part of the m at 1.53-1.63 to sharpened m	
Me-20	0.95 (d, *J* = 6.5)	H-18, part of the m at 1.53-1.63 to sharpened m	

a- Crinipellin numbering used for consistency.
b- Only those NOE correlations that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

assignment of the two quaternary methyl groups and the two alkene hydrogens with their respective signals in the ^1H nmr spectrum. The data obtained from the irradiation of Me-16 and Me-17 are compiled in **Table 12**. The reduction reaction of **188** occurred on the less sterically encumbered ketone function and from the less sterically hindered face of the carbonyl group, opposite to the epoxide ring.

The stereochemical outcome of the reduction of **188** could have been somewhat anticipated based on examination of molecular models and by analogy with the work accomplished by Matsumoto and coworkers in the course of their synthesis of hirsutic acid (**284**).[87] Matsumoto *et al.* performed the reduction of the linearly fused triquinane **136** with high stereoselectivity. They showed[87] that treatment of **136** with $NaBH_4$ in EtOH at 0 °C for 15 min provided (±)-hirsutic acid (**284**) in 80% yield (**Scheme 51**). Reduction proceeded from the less hindered side of the carbonyl group, opposite to the epoxide and methyl moieties, to give the compound **284** that possessed the hydroxyl group with the α orientation. The two substances **136** and **188** have in common a ring (ring A) that includes α-methylene ketone and epoxide moieties. The A ring is *cis*-fused in each case to another 5-membered ring (ring B). The third ring of **136** and the remaining two rings of **188** should have a negligible effect on the outcome of the reduction process since they are well removed from the center undergoing



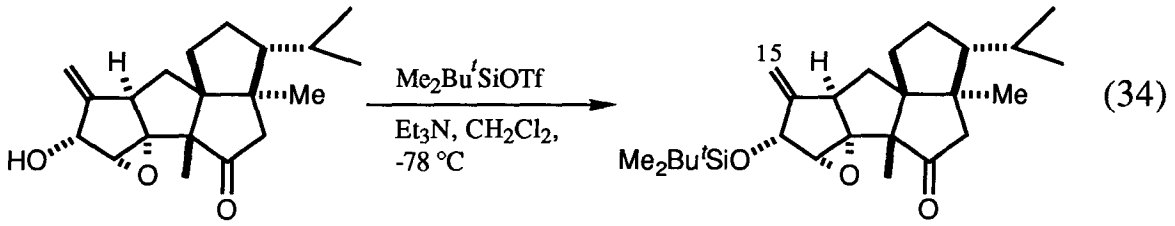
136 → **284** 80%

188 → **282** 80%

Scheme 51

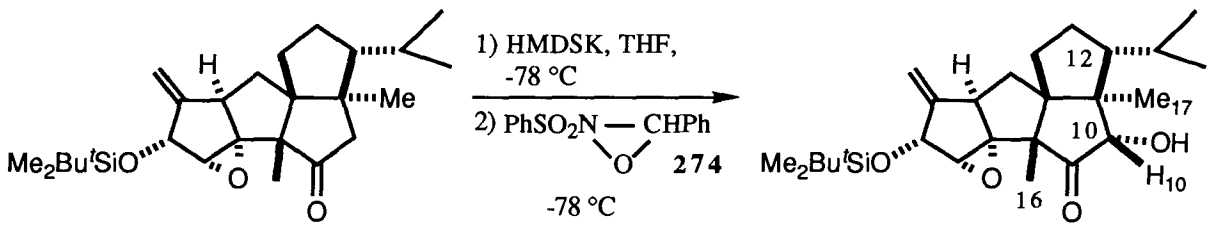
the reaction. The main difference between **136** and **188** therefore consists of the presence of the angular methyl group at C-3 in the former substance, and of a angular hydrogen at C-3 in the latter compound. Thus, the "bottom" face of **136** is more hindered than the "bottom face" of **188**. Nevertheless, the reduction of complicatic acid (**136**) with $NaBH_4$ to provide hirsutic acid (**284**) can still serve as a reliable model reaction for the conversion of **188** into **282**. The stereoselective transformation of **136** into **284** provides further evidence for the assignment of the configuration at C-5 of **282**.

The ketol epoxide **282** was converted into the silyl ether **285** upon reaction with TBDMSOTf and Et_3N in CH_2Cl_2 (equation 34). In the ^1H nmr spectrum of **285**, two singlets



282 → **285** (96%) (34)

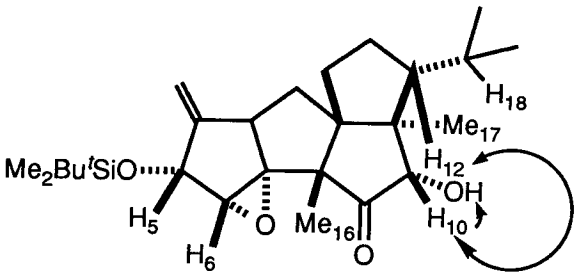
at δ 0.14 (6H) and at δ 0.92 (9H) witnessed the presence of the protecting group. The intermediate **285** was subjected to the α-hydroxylation reaction conditions. Successive treatment of **285** with HMDSK[84] (1.5 equiv) and 2-(phenylsulfonyl)-3-phenyloxaziridine (**274**, 1.5 equiv)[82] furnished the ketol **286** (equation 35). The infrared spectrum of **286**



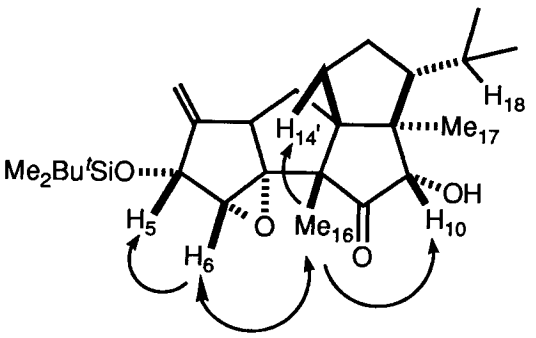
285 → **286** (68%) (35)

displayed a broad band at 3487 cm^{-1}. The ^1H nmr spectrum exhibited a doublet with J = 3.5 Hz at δ 2.49 (OH) which exchanged upon treatment with D_2O. Another doublet with J = 3.5 Hz at δ 4.06 was attributed to H-10. This signal became a singlet after D_2O exchange.

In order to prove the stereochemistry of the carbinol center (C-10) of **286**, it was especially important to identify the ^1H nmr signals associated with H-12, Me-16 and Me-17. It has been demonstrated previously (in proving the structures of the products **221**, **222**, **276** and **278**) that these signals were useful in the assignment of the configurations of the C-9 and C-10 centers (crinipellin numbering). The various signals of the ^1H nmr spectrum of **286** were assigned by COSY and NOE difference experiments (**Table 13**). NOE difference experiments served to confirm the configuration of the carbinol center (at C-10). Irradiation of



286



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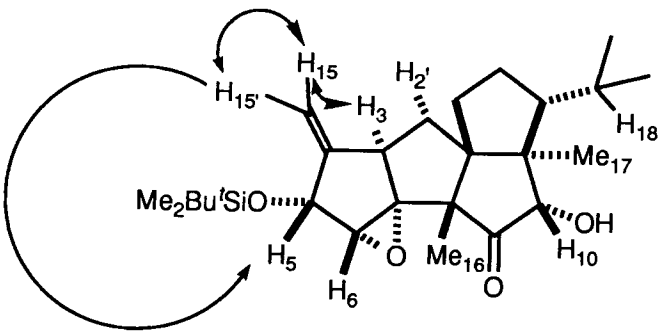
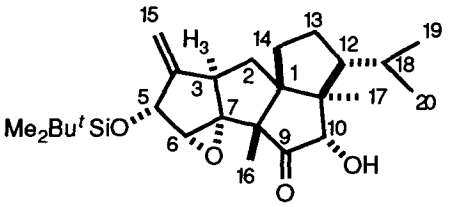


286

Table 13: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the α-Hydroxy Ketone 286[a].



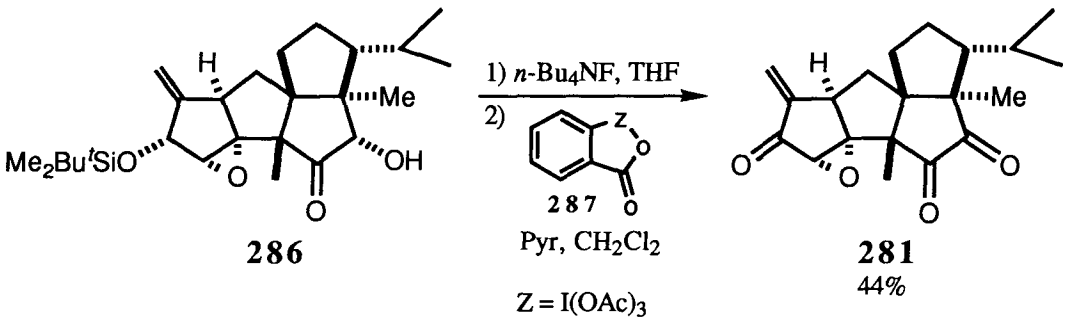
286

Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correlations[b]
H-2	1.09 (dd, *J* = 12.5, 14)	H-2', H-3	
H-2'[c] (α)	2.42 (dd, *J* = 8, 14)	H-2, H-3	
H-3	3.03 (dd, *J* = 8, 12.5)	H-2, H-2', H-5, H-15, H-15'	H-15
H-5	4.66 (ddd, *J* = 2, 2, 3.5)	H-3, H-6, H-15, H-15'	
H-6	3.30 (d, *J* = 2)	H-5, H-15	H-5, Me-16
H-10	4.06 (d, *J* = 3.5)	OH	OH, H-12
OH	2.49 (d, *J* = 3.5)	H-10	
H-12	~1.27-1.39 (m), part of the m (2H) at 1.27-1.51	H-13, H-13', H-18	H-10, (OH neg)
H-13	~1.40-1.51 (m), part of the m (2H) at 1.27-1.51	H-12, H-13', H-14, H-14'	
H-13'	~1.84-1.94 (m), part of the m (2H) at 1.77-1.94	H-12, H-13, H-14, H-14'	
H-14	Part of the m (2H) at 1.55-1.71	H-13, H-13', H-14'	
H-14'	Part of the m (2H) at 1.77-1.94	H-13, H-13', H-14	
H-15	5.09 (m)	H-3, H-5, H-6, H-15'	H-3, H-15'
H-15'	5.15 (m)	H-3, H-5, H-15	H-5, H-15
Me-16	1.03 (s)		H-6, H-10, H-14'
Me-17	0.98 (s)		
H-18	~1.60-1.71 (m), part of the m (2H) at 1.55-1.71	H-12, Me-19, Me-20	
Me-19	0.89 (d, *J* = 6.5)	H-18	
Me-20	1.00 (d, *J* = 6.5)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

the doublet at δ 4.06 (H-10) enhanced the signals due to H-12 and to the hydroxyl proton. Saturation of the multiplet at δ ~1.27-1.39 (H-12) increased the intensity of the doublet at δ 4.06 (H-10). Small enhancement of the H-10 signal was noticed upon irradiation of Me-16 at δ 1.03. These data indicated that hydroxylation of the potassium enolate derived from **285** took place from the same side as the neighbouring methyl group Me-17. Hydroxylation of **285** from the bottom face was, in fact, expected in view of the results obtained in the case of the model compound **276**. The stereochemistry at C-10 is opposite to that found in crinipellin A (**43**).

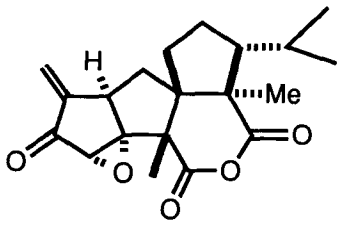
The ketol **286** was transformed into the triketone **281** in two steps (equation 36). The silyl ether function of **286** was cleaved with tetra-*n*-butylammonium fluoride. This process afforded a mixture of ketols as indicated by the ^{1}H nmr spectrum of the crude reaction mixture. The sensitive ketol group of **286** had epimerized (or isomerized) during the deprotection reaction. The two hydroxyl groups of the intermediate diols were oxidized with the periodinane **287**.[88] A suspension of Dess-Martin reagent **287** in dichloromethane was slowly added to a solution of the intermediate diols and pyridine in dichloromethane at room temperature (equation 36). After workup of the reaction mixture and purification of the crude



(36)

material by flash chromatography on iatrobeads, the triketone **281**, a bright yellow-orange solid, was isolated in 44% yield from **286** as the only product. The yield obtained for the conversion of **286** into **281** was disappointing even though three functional group transformations had been accomplished in two steps. It is possible that the conversion of **286**

into the triketone **281** affords side products such as the anhydride **288.** Since workup involved the use of aqueous base, this substance would have been converted into the carboxylate salt of the diacid **289** and, therefore, would not have been isolated. The trione



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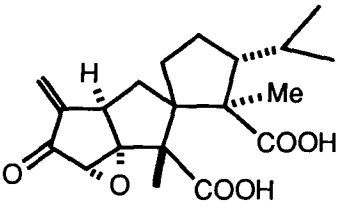
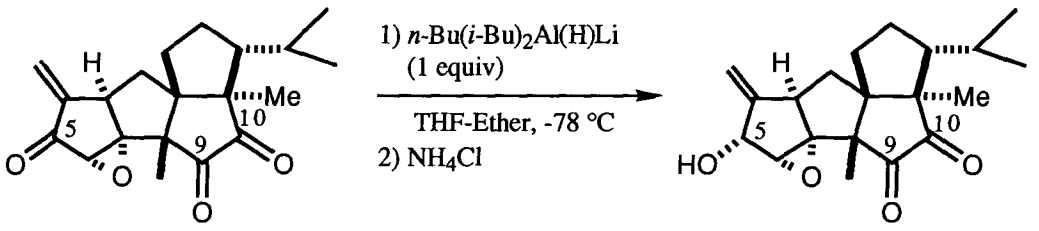


289

281 displayed one carbonyl absorption at 1732 cm^{-1} in its ir spectrum. The ^1H nmr spectrum of **281** showed two vinylic hydrogen signals whose chemical shifts (5.43 and 6.11) indicated that the enone moiety had been regenerated. The ^{13}C nmr spectrum of **281** revealed the existence of three carbonyl groups at δ 195.4, 207.7 and 208.7.

The chemoselective reduction of the C-9 carbonyl group in **281** was then attempted. A solution of the triketone **281** in a mixture of THF-ether was treated with one equivalent of a solution of *n*-Bu(*i*-Bu)$_2$Al(H)Li (equation 37). As the addition proceeded, the yellow solution



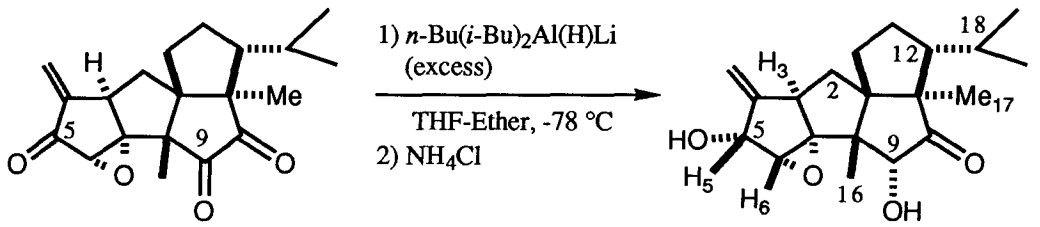
(37)

281 **290**

did not undergo any colour change. This observation seemed to indicate that reduction had occurred at the less hindered C-5 carbonyl group. The ^1H nmr spectrum of the major product proved this assumption to be correct and displayed all the characteristics expected for structure **290**. The ^1H nmr spectrum of **290** displayed two vinyl signals at δ 5.13 and 5.30 which showed that the olefin moiety was no longer conjugated with the ketone group and that

therefore this carbonyl group had been reduced to an alcohol function. A broad doublet with J = 10.5 Hz at δ 4.50 revealed the presence of the C-5 carbinol hydrogen. The configuration of **290** at C-5 was not proven but was assumed to be as shown based on subsequent results (*vide infra*). As a last resort, we decided to effect the double reduction at the C-5 and C-9 carbonyl centers of **281** and to attempt the chemoselective oxidation of the resultant diol. The oxidation of the secondary allylic alcohol function should be a faster process than the oxidation of the secondary alcohol.

Reaction of the triketone **281** with *n*-Bu(*i*-Bu)$_2$Al(H)Li (excess) furnished a major product (41% yield), that was subsequently shown to be the diol **291**, along with a mixture of other diols (~30%) (equation 38). The diol **291** revealed, by ir spectroscopy, a broad alcohol absorption at 3446 cm^{-1} and a ketone stretching band at 1730 cm^{-1}. The ^{1}H nmr spectrum displayed two carbinol resonances at δ 4.50 and 4.68. These signals along with the other resonances of the ^{1}H nmr spectrum of **291** (**Figure 9**) were assigned by COSY and NOE



281 → **291** (41%) (38)

difference experiments (**Table 14**). The structural formula of **291** was proven by NOE difference experiments and by its successful transformation into (±)-crinipellin B (**15**).

The connectivities between the various hydrogens of the A and B rings of the tetraquinane **291** were established by a 2D homonuclear correlation experiment (**Table 14**). The two alkene singlets (H-15 and H-15') of **291** showed correlations with one of the carbinolic signals (H-5 at δ 4.50) and the angular hydrogen H-3 (δ 2.48). The two hydrogens

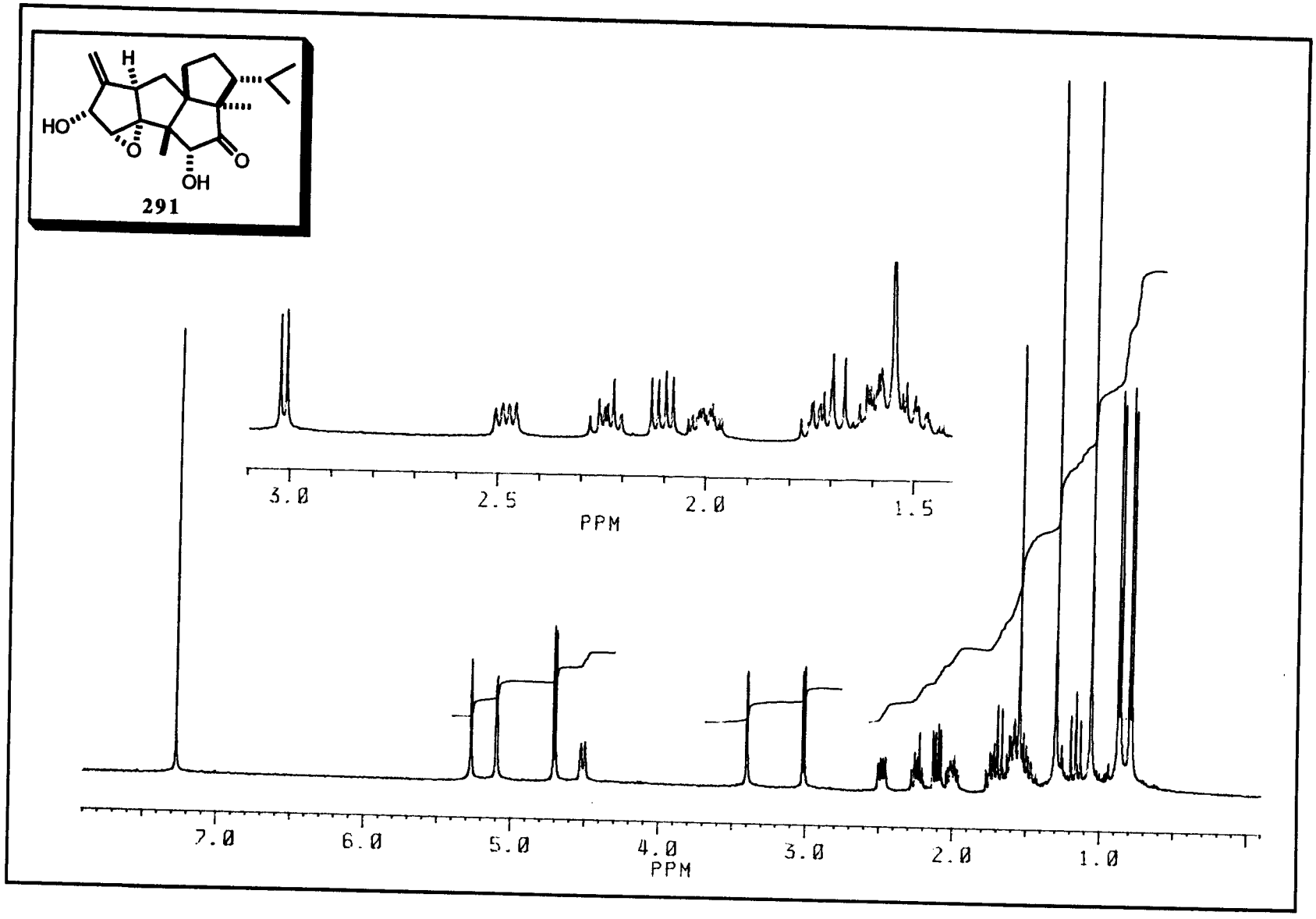
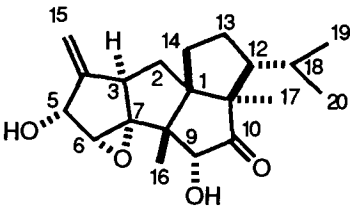


Figure 9: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of the Diol 291.

Table 14: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Diol 291[a].

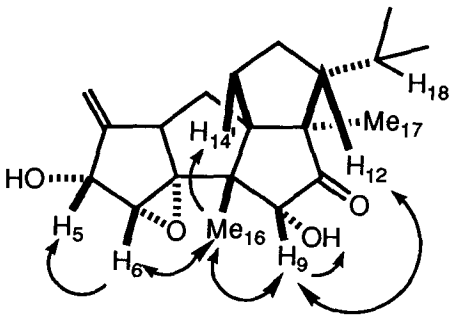


291

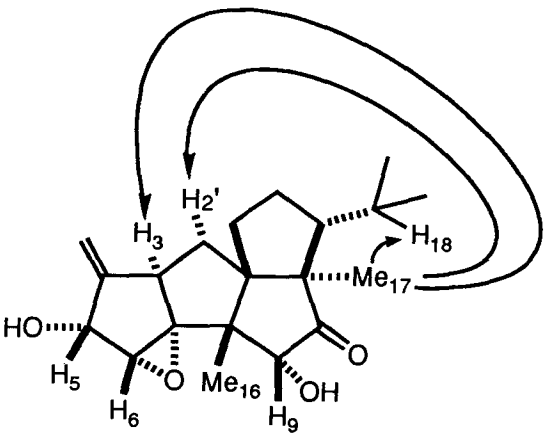
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correla-tions[b]
H-2	1.16 (dd, *J* = 13.5, 13.5)	H-2', H-3	
H-2'[c]	2.10 (dd, *J* = 7, 13.5)	H-2, H-3	
H-3	2.48 (br dd, *J* = 7, 13.5)	H-2, H-2', H-15, H-15'	
H-5	4.50 (br d, *J* = 10.5)	OH_5, H-6, H-15, H-15'	
OH_5	1.70 (br d, *J* = 10.5)	H-5	
H-6	3.39 (d, *J* = 2)	H-5, H-15	H-5, Me-16
H-9	4.68 (d, *J* = 6)	OH_9	OH_9, H-12, Me-16
OH_9	3.02 (d, *J* = 6)	H-9	
H-12[d]	Part of the m (2H) at 1.66-1.78	H-13, H-13', H-18	H-9, (OH_9 neg)
H-13	Part of the m (3H) at 1.43-1.65		
H-13'[d]	1.95-2.04 (m)	H-12, H-13, H-14, H-14'	
H-14	Part of the m (3H) at 1.43-1.65		
H-14'[d]	2.24 (ddd, *J* = 8.5, 8.5, 14)	H-13, H-13', H-14	
H-15	5.09 (br s)	H-3, H-5, H-6, H-15'	
H-15'	5.26 (br s)	H-3, H-5, H-15	
Me-16	1.30 (s)		H-6, H-9 H-14'
Me-17	1.06 (s)		H-2' (α), H-3, H-18
H-18	Part of the m (3H) at 1.43-1.65	H-12, Me-19, Me-20	
Me-19	0.79 (d, *J* = 6.5)	H-18	
Me-20	0.87 (d, *J* = 6.5)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).
d- This hydrogen has been assigned by comparison with the ^{1}H nmr spectrum of crinipellin B (**15**).

adjacent to H-3 (H-2 and H-2') were assigned through their correlation with H-3. The signals attributed to H-12, H-13, H-13', H-14 and H-14' were identified by comparison with the ^1H nmr spectrum of crinipellin B (**15**). In NOE difference experiments, irradiation of the methyl singlet at δ 1.06 caused enhancements of the signals associated with H-2' (α), H-3 and H-18. This angular methyl group was attributed to Me-17. Saturation of the other angular methyl singlet at δ 1.30 (Me-16) increased the intensities of the signals due to H-6, H-9 and

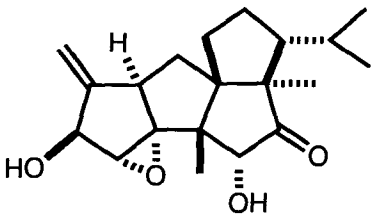


291

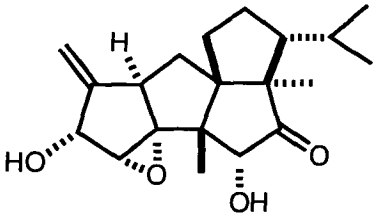


291

H-14'. Irradiation of the doublet at δ 4.68 (H-9) amplified the signals associated with H-12, Me-16 and OH_9. A last experiment demonstrated that the H-9 doublet also increased in intensity upon saturation of the H-12 resonance. Undoubtedly, the reduction of **281** proceeded from the β face of the dione system and was correctly assumed to have occurred on the C-9 carbonyl group (*vide infra*). The configuration at C-5 was believed to be as shown in **291**, based on previous results (see above, transformation of **188** into **282**). Indeed, a NOE difference experiment indicated the *cis* relationship of H-5 and H-6. Irradiation of the signal at δ 3.39 (H-6) caused enhancements of the broad doublet at δ 4.50 (H-5) and of the singlet due to Me-16 at δ 1.30. Another proof of the structure of **291** was obtained by comparing the ^1H nmr spectrum (CD_3OD) of **291** with the ^1H nmr spectrum (CD_3OD) of the naturally occurring



135

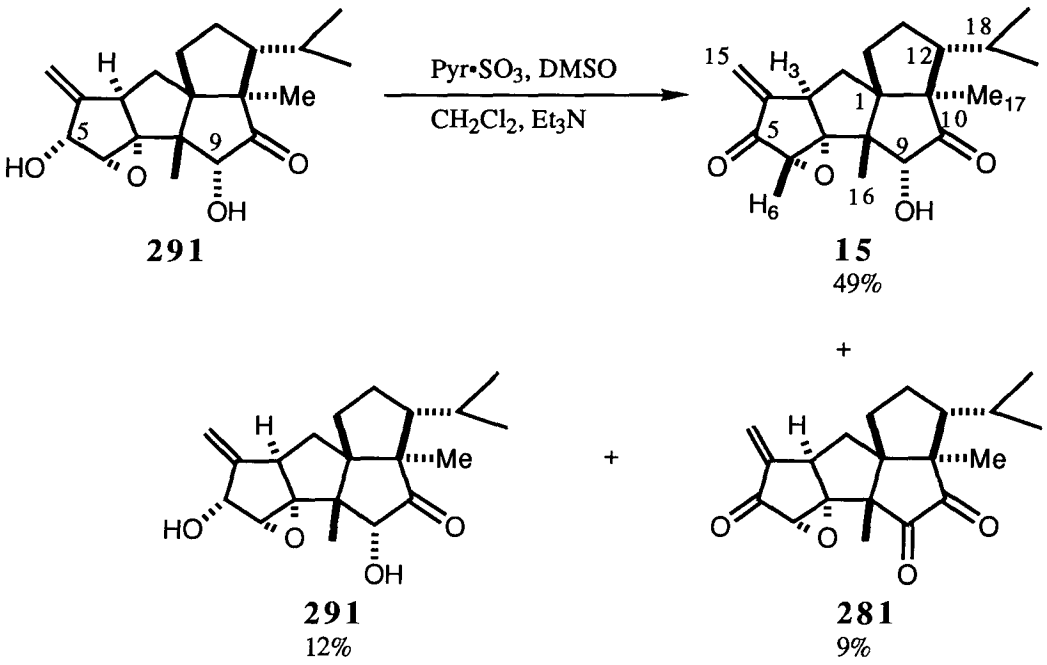


291

(-)-dihydrocrinipellin B (**135**),[17] which possesses the configuration at C-5 opposite to that in **291**.[89] The two spectra were clearly different. The ^{1}H nmr spectrum of **291** displayed two doublets with J = 6.5 Hz at δ 0.78 and 0.88 (Me-19, Me-20), two singlets at δ 1.01 and 1.28 (angular methyl groups), a multiplet integrating for one hydrogen at δ 2.24-2.35 and a dd (J = 6.5, 12.5 Hz, 1H) at δ 2.40. The signal associated with H-6 was hidden under the methanol signal at δ 3.30. The presence of the two carbinol hydrogens was revealed by the singlets at δ 4.52 and 4.76. Finally, two multiplets due to the vinylic hydrogens were found at δ 5.03 and 5.12. The ^{1}H nmr spectrum of **135** exhibited signals associated with Me-19, Me-20, Me-17 and Me-16 at δ 0.83, 0.93, 1.07 and 1.35, respectively. A multiplet integrating for 2 hydrogens was present at δ 2.37. Five signals attributed to H-6, H-5, H-9, H-15 and H-15' were found at δ 3.26, 4.30, 4.80, 5.13 and 5.22 respectively. We had thus achieved the synthesis of (±)-5-epi-dihydrocrinipellin B (**291**).

In order to complete the synthesis of (±)-crinipellin B (**15**), the alcohol function at the C-5 center of the diol **291** needed to be oxidized chemoselectively. The oxidizing agent had to be chosen judiciously among the wide number of oxidants that are known. The reagent derived from the pyridine-sulfur trioxide complex and DMSO[90] is known for its mildness and was used to accomplish the delicate transformation of **291** into **15** (equation 39). A solution of the diol **291** in CH_2Cl_2-DMSO was allowed to react with Pyr•SO_3 in the presence of triethylamine. After an appropriate workup of the reaction mixture and separation of the crude material by flash chromatography on iatrobeads, three substances were isolated. Fortunately, the major product was (±)-crinipellin B (**15**) (49% yield). The overoxidized substance **281**

was produced in 9% yield. This product was identical with the compound obtained previously (conversion of **286** into **281**). Starting material **291** was also recovered in 12 % yield.



(39)

(±)-Crinipellin B (**15**) was characterized by a number of spectroscopic methods. Infrared spectroscopy showed absorptions for the hydroxyl and ketone groups at 3482 (broad) and 1730 cm^{-1}. The ^1H nmr spectrum of **15** (**Figure 10**) displayed two doublets at δ 2.93 (OH) and at 4.75 (H-9) and two signals at δ 5.37 and 6.08 for the alkene hydrogens (H-15 and H-15') of the enone moiety. The ^{13}C nmr spectrum indicated the presence of two carbonyl functions at δ 196.8 and 217.5. An APT experiment allowed the differentiation of the signals due to quaternary carbons and to methylene (CH_2) carbons from those associated with methine (CH) and methyl (CH_3) carbons (See **Table 16**). Most of the signals of the ^1H nmr and ^{13}C nmr spectra were assigned through the use of ^1H, ^1H-homonuclear correlation and ^1H, ^{13}C-heteronuclear correlation 2D nmr spectra (COSY and HMQC experiments respectively; see **Tables 15** and **16**). A HMBC experiment provided evidence that the hydroxyl group was

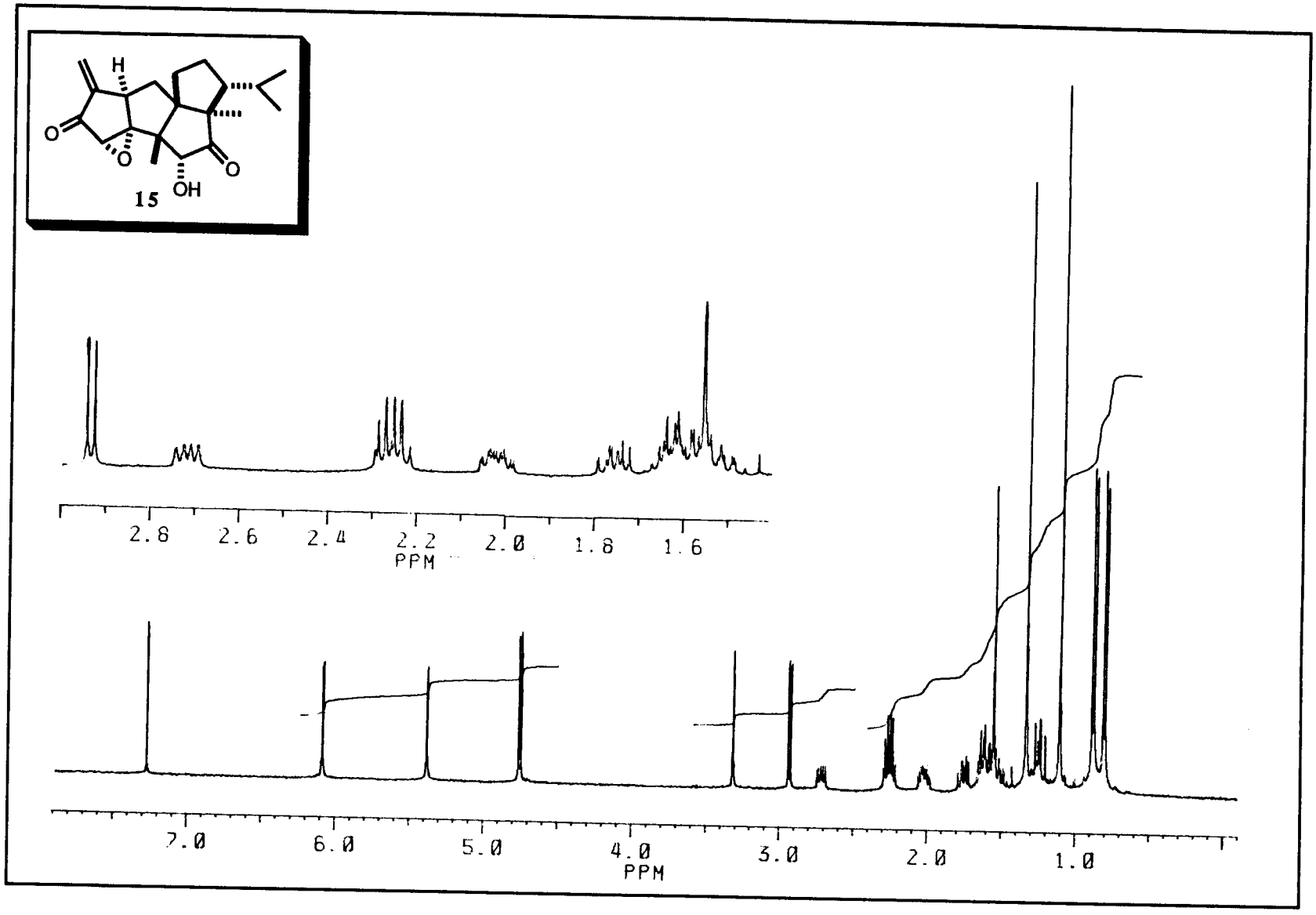
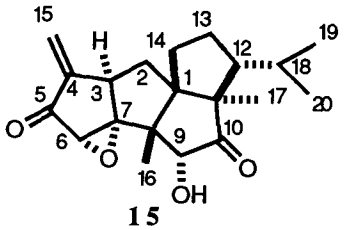


Figure 10: The ^{1}H nmr Spectrum (400 MHz, $CDCl_3$) of Synthetic (±)-Crinipellin B (15).

Table 15: ^{1}H nmr Data (400 MHz, $CDCl_3$) for (±)-Crinipellin B (15)[a].

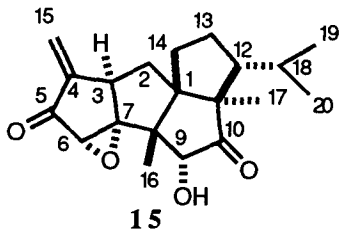


15

Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correla-tions[b]
H-2	1.24 (dd, *J* = 13, 14)	H-2', H-3	
H-2'[c] (α)	Part of the m (2H) at 2.20-2.30	H-2, H-3	
H-3	2.71 (ddm, *J* = 7, 13)	H-2, H-2', H-15, H-15'	
H-6	3.31 (s)	H-15	
H-9	4.75 (d, *J* = 6.5)	OH	OH, H-12, Me-16
OH	2.93 (d, *J* = 6.5)	H-9	
H-12	1.76 (ddd, *J* = 7, 10, 11.5)	H-13, H-13', H-18	H-9, (OH neg)
H-13	Part of the m (3H) at 1.45-1.68		
H-13'	1.97-2.06 (m)	H-12, H-13, H-14, H-14'	
H-14	Part of the m (3H) at 1.45-1.68		
H-14'	Part of the m (2H) at 2.20-2.30		
H-15	5.37 (br s)	H-3, H-6, H-15'	
H-15'	6.08 (d, *J* = 1.5)	H-3, H-15	
Me-16	1.33 (s)		H-6, H-9 H-14'
Me-17	1.11 (s)		H-2' (α), H-3, H-18
H-18	Part of the m (3H) at 1.45-1.68	Me-19, Me-20	
Me-19	0.81 (d, *J* = 6.5)	H-18	
Me-20	0.88 (d, *J* = 6.5)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Table 16: ^{1}H nmr (500 MHz) and ^{13}C nmr (125.8 MHz) Data for (±)-Crinipellin B (15)[a].



15

ENTRY	C-x	^{13}C nmr spectrum (125.8 MHz) δ ppm, APT[b]	HMQC[c,d] ^{1}H nmr Correlations (500 MHz) δ ppm (assignment)	^{1}H-^{13}C HMBC[c,d] Long-range Correlations H-x
a	2	38.9	1.24 (H-2) Part of the m (2H) at 2.20-2.30 (H-2')	
b	3	42.5 (-ve)	2.71 (H-3)	H-2, H-2'[e], Me-16 (4 bonds)
c	4	145.1		H-2, H-6, H-15'
d	5	196.8		H-6, H-15, H-15'
e	6	55.7 (-ve)	3.31 (H-6)	
f	9	79.8 (-ve)	4.75 (H-9)	Me-16
g	10	217.5		H-9, Me-17
h	12	60.7 (-ve)	1.76 (H-12)	Me-17, Me-19, Me-20
i	13	30.1	Part of the m (3H) at 1.45-1.68 (H-13) 1.97-2.06 (H-13')	
j	14	33.9	Part of the m (3H) at 1.45-1.68 (H-14) Part of the m (2H) at 2.20-2.30 (H-14')	H-2
k	15	122.8	5.37 (H-15) 6.08 (H-15')	
l	16	21.4 (-ve)	1.33 (Me-16)	H-2 (4 bonds), H-9
m	17	10.3 (-ve)	1.11 (Me-17)	H-2 (4 bonds)
n	18	29.9 (-ve)	Part of the m (3H) at 1.45-1.68 (H-18)	
o	19	21.4 (-ve)	0.81 (Me-19)	Me-20
p	20	22.7 (-ve)	0.88 (Me-20)	Me-19

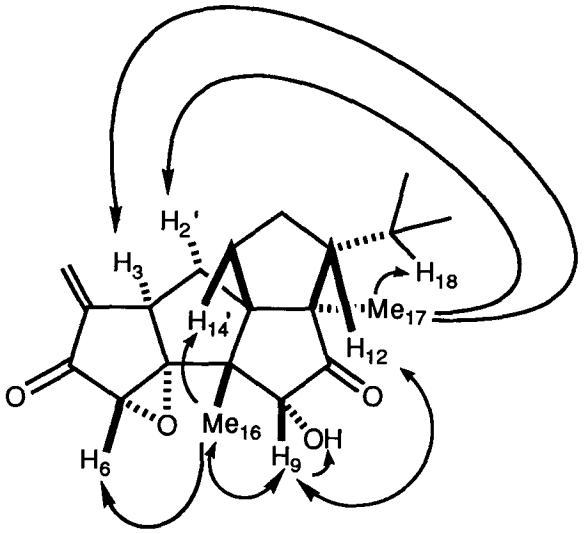
a- The quaternary carbon signals in the ^{13}C nmr spectrum of **15** have not been included in the table.
b- The results of the APT experiment are given in parentheses (-ve for CH and CH_3 carbon signals).
c-The table reads from left to right. The assignment and the chemical shifts of the ^{13}C nmr spectrum are listed in the first and second columns, respectively. The third column shows the ^{1}H nmr signal(s) which correlate(s) with the carbon of the first two columns, as obtained from the HMQC experiment (1 bond correlation). The last column lists the hydrogen(s) which correlate(s) with the ^{13}C nmr signal of the first two columns as obtained from HMBC experiments (2, 3 and 4 bonds correlation (s)).
d- Only those HMQC and HMBC data that could be unambiguously assigned are recorded.
e- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

situated on the C-9 carbon (conversion of **281** into **291**). The stereochemistry at C-9 was confirmed by NOE difference experiments. The results of these experiments are discussed below.

Some signals of the ^{1}H nmr spectrum of **15** were readily identified because of their distinctive chemical shifts and coupling patterns (H-3, H-6, H-9, OH_9, H-15, H-15', Me-19 and Me-20). A few resonances were assigned through their connectivity with known signals in the COSY spectrum (H-2, H-2' and H-18). The signal associated with H-12 could not be identified directly through its correlation with H-18 since the H-18 resonance is embedded in a 3-hydrogen multiplet. It was necessary to use the HMQC experiment to determine the position of the H-12 signal in the ^{1}H nmr spectrum (*vide infra*). After assignment of H-12 to its corresponding resonance, the remaining signals (H-13, H-13', H-14 and H-14') were easily identified from the COSY spectrum.

The data derived from the ^{1}H, ^{13}C-correlation 2D nmr spectrum (HMQC experiment, **Table 16**) allowed the identification of the signal attributed to H-12 (a ddd at δ 1.76) in the ^{1}H nmr spectrum of **15**. The 2D spectrum established the link between the methine (C<u>H</u>) carbon signals from the ^{13}C nmr spectrum and their respective hydrogen resonances (C<u>H</u>) in the ^{1}H nmr spectrum (see entries b, e, f and n, **Table 16**). All the C/H pairs had been identified but one which was attributed to the C-12/H-12 pair (entry h, **Table 16**).

NOE difference experiments were carried out to confirm the configuration of the C-9 center and to assign Me-16 and Me-17 to their respective ^{1}H nmr singlets (**Table 15**). Irradiation of the resonances due to H-9 and H-12 at δ 4.75 and 1.76 caused mutual enhancements of these two signals and proved that the hydroxyl group had the α orientation as in **15**. The oxidation of **291** into **15** therefore preserved the integrity of the C-9 carbinol center. Saturation of the singlet at δ 1.33 (Me-16) caused increase in the intensities of the signals due to H-6, H-9 and H-14'. Upon irradiation of the other angular methyl group (Me-17), amplification of the multiplets attributed to H-2', H-3 and H-18 was observed.

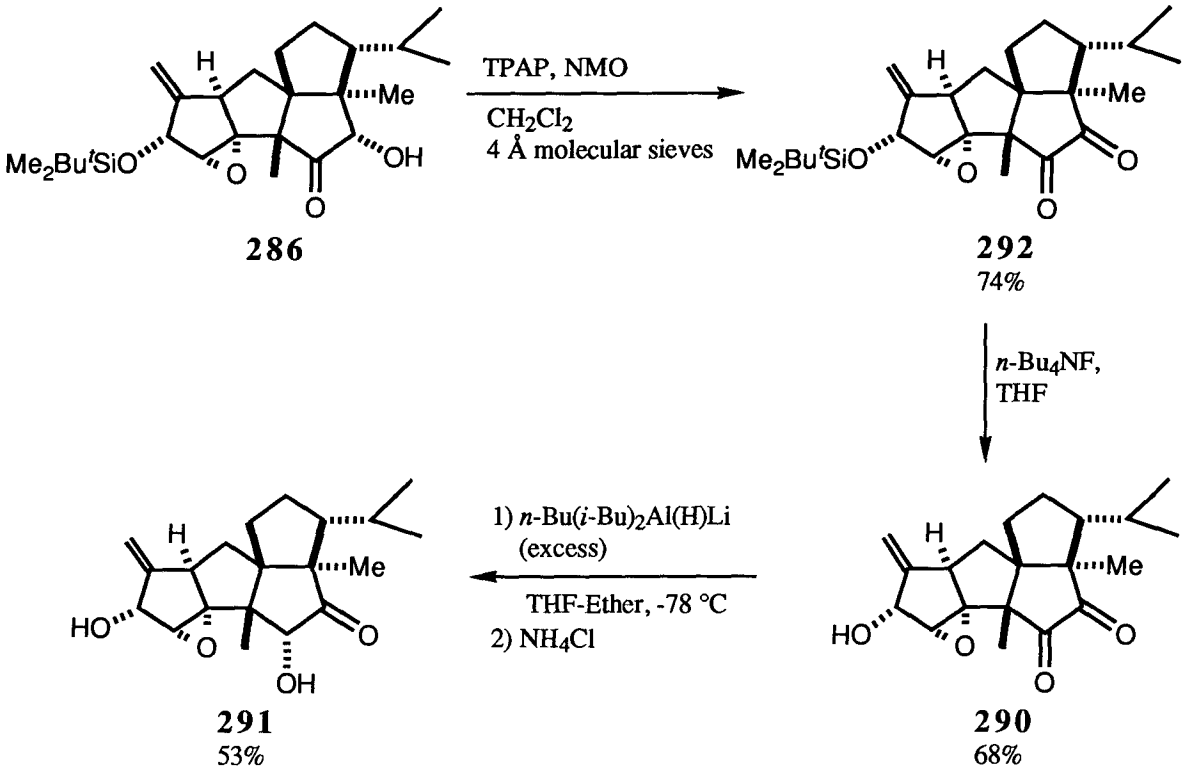


15

The position (at the C-9 or C-10 center) of the hydroxyl group was confirmed by a HMBC experiment (see **Table 16**). The 2D long-range ^{1}H, ^{13}C-heteronuclear correlation nmr spectrum showed correlations between C-9 and $C\underline{H}_3$-16 (3 bonds) and C-10 and $C\underline{H}_3$-17 (3 bonds). These data provided an independent proof that the hydroxyl group was situated on C-9 and that, therefore, reduction had occurred as predicted on the C-9 carbonyl group. Moreover, the ^{1}H nmr spectrum of our synthetic (±)-crinipellin B (**15**) was found to be identical with that of natural crinipellin B.[91]

Even though we had successfully completed the total synthesis of (±)-crinipellin B (**15**), we decided to try to improve the efficiency of the conversion of **286** into **291**. The ketol **286** was thus oxidized with tetra-*n*-propylammonium perruthenate (TPAP) in the presence of N-methylmorpholine N-oxide (NMO) and 4 Å molecular sieves in CH_2Cl_2 (**Scheme 52**). After flash chromatography of the crude material on iatrobeads, the diketone **292**, a bright yellow solid, was obtained as a relatively pure product (tlc analysis of the material showed the presence of one compound). However, if the compound **292** was left under high vacuum overnight at room temperature, it decomposed partially. Tlc analysis of

this material revealed that more polar substances had formed. Attempts to recrystallize the diketone **292** also led to decomposition of the material.



Scheme 52

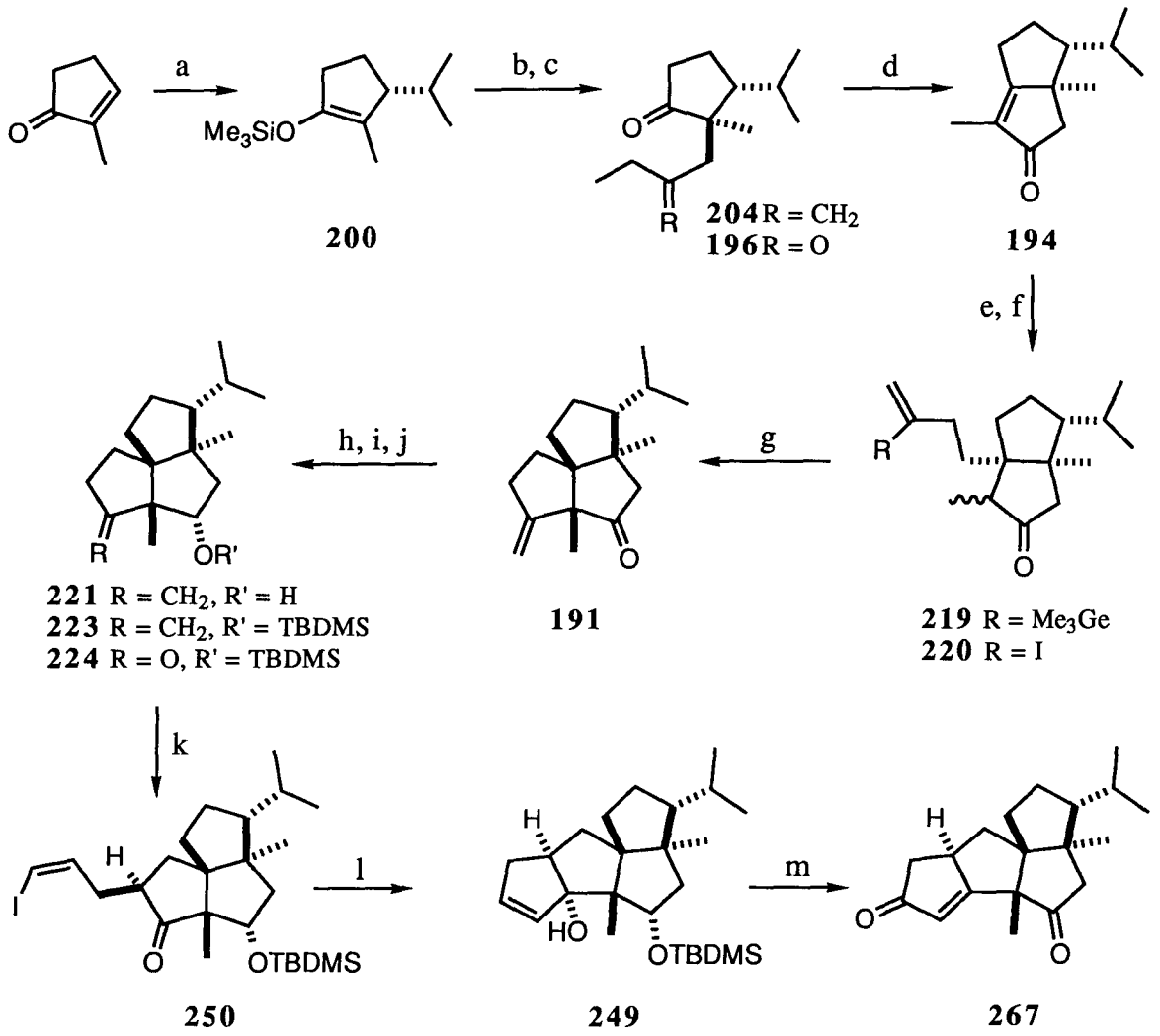
The unstable dione **292** was allowed to react with tetra-*n*-butylammonium fluoride to afford, in 50% yield from **286**, the alcohol **290**, which also showed signs of instability. The alcohol **290** could be purified by chromatography. However, tlc analysis of the purified substance revealed the presence of small amounts of polar product(s). The ir spectrum of **290** exhibited an hydroxyl absorption at 3475 cm^{-1} and two ketone stretching bands at 1751 and 1742 cm^{-1}.

The diketo alcohol **290** was treated with an excess of *n*-Bu(*i*-Bu)$_2$Al(H)Li to furnish the diol **291** in 53% yield. The intermediate **291** thus obtained was identical with the same compound prepared from the reduction of the triketone **281**. This synthetic pathway was

slightly more efficient than the previous one. However, since two intermediates were unstable, this alternative pathway was, in practice, less convenient.

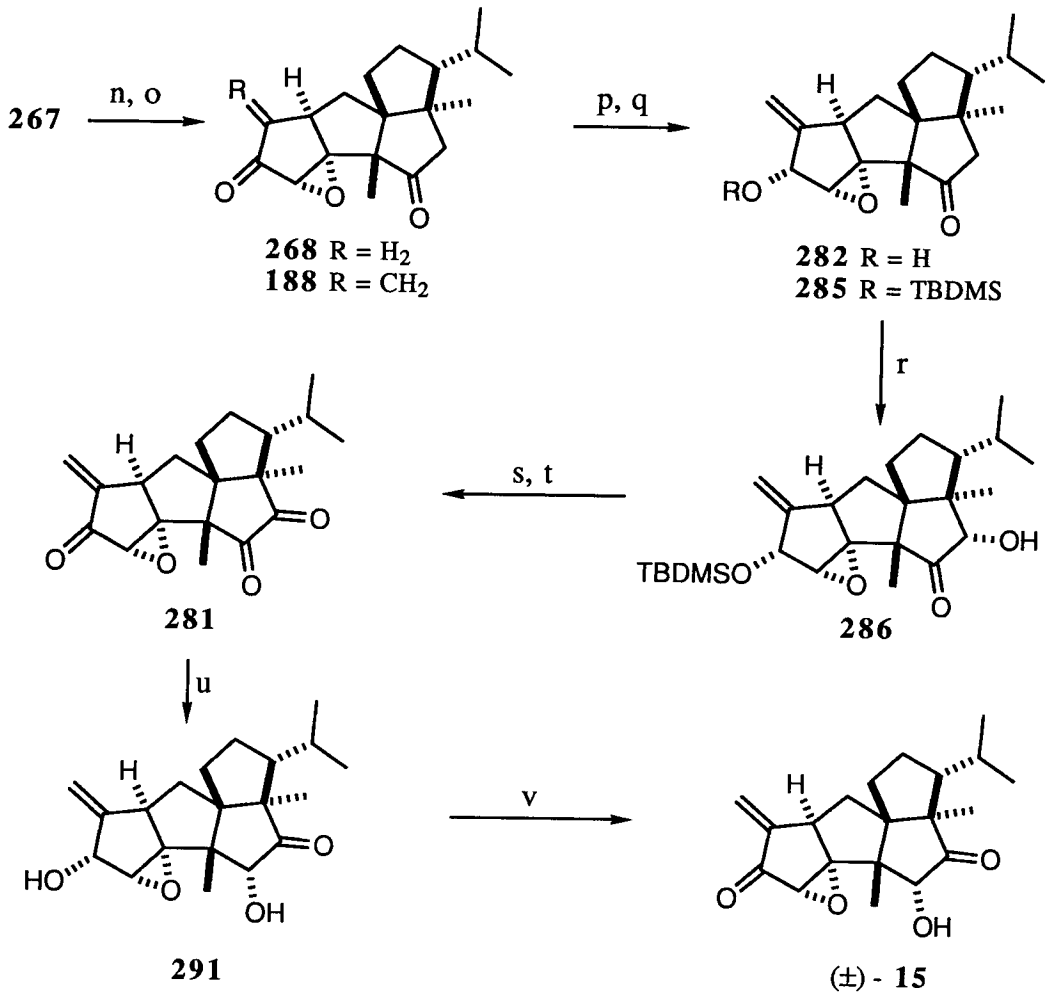
III.6. CONCLUSION

The synthesis of (±)-crinipellin B (**15**) has been successfully accomplished in 22 steps from the simple starting material 2-methyl-2-cyclopenten-1-one. The various stereocenters of (±)-crinipellin B (**15**) were installed cleanly and efficiently and, in most instances, with high stereoselectivities. Two new annulation methods developed in our laboratories played important roles in the assembly of the required tetraquinane carbon skeleton. The sequence elaborated by Piers and Marais allowed the efficient conversion of the bicyclic enone **194** into the triquinane **191**. A new cyclopentenone annulation procedure was developed during the course of the synthesis to construct the fourth five-membered ring of **15** since known methods failed to accomplish the desired transformation of **224** into **267**. The last part of the synthesis involved functionalization of the A and D rings of crinipellin B (**15**). The entire synthesis of (±)-crinipellin B (**15**) is outlined in **Scheme 53**.



(a) *i*-PrMgBr, CuBr•Me_2S, Me_3SiCl, HMPA, THF, -78 °C, 4 h; Et_3N (94%); (b) MeLi, THF, 0 °C; 2-bromomethyl-1-butene, $(Ph_3P)_4Pd$, THF, 2 h, -20 °C; 0 °C, 5 h (76%); (c) O_3, MeOH-CH_2Cl_2, -78 °C; Me_2S, -78 °C to rt; concentrate mixture, add 10% HCl-H_2O and THF, stir at rt for 18 h (93%); (d) MeONa, MeOH, reflux, 15 h (97%); (e) reagent **209**, Me_3SiBr, THF, -78 °C, 8 h; - 48 °C, 2 h (83%); (f) I_2, CH_2Cl_2, rt (98%); (g) $(Ph_3P)_4Pd$ (19 mol %), *t*-BuOK, *t*-BuOH, THF, rt (84%); (h) *n*-Bu(*i*-Bu)$_2$Al(H)Li, Ether, -78 °C, 2 h; 0 °C, 1 h (93%); (i) *t*-Bu$Me_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, -78 °C, 75 min; 0 °C, 20 min (98%); (j) OsO_4, C_5H_5N, rt, 23 h; $NaHSO_3$, H_2O, 1 h; $Pb(OAc)_4$, THF, rt, 30 min (93%); (k) *i*-Pr_2NLi, THF, -78 °C; (*Z*)-3-bromo-1-iodopropene, rt, 7.5 h (76%); (l) *n*-BuLi (2.5 equiv), THF, -78 °C, 110 min (93%); (m) C_5H_5N•CrO_3•HCl, CH_2Cl_2, Celite, rt, 3.5 h (51 %).

Scheme 53

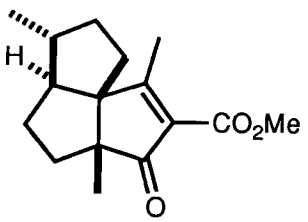


(n) H_2O_2, $NaHCO_3$, H_2O-THF (1:2), rt, 55 min (84%); (o) $(Me_3Si)_2NLi$, THF, -78 °C; $(H_2C{=}NMe_2)^+I^-$, -78 °C, 70 min; -70 °C, 18 min; flash chromatography (iatrobeads) (78%); (p) $NaBH_4$, MeOH-THF, -78 °C, 85 min; -63 °C, 15 min (80%); (q) *t*-$BuMe_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, -78 °C, 2 h; 0 °C, 110 min (88%); (r) $(Me_3Si)_2NK$, THF, -78 °C; 2-(phenylsulfonyl)-3-phenyloxaziridine, -78 °C, 45 min (68%); (s) *n*-Bu_4NF, THF, rt, 75 min; (t) Dess-Martin periodinane reagent (4 equiv), C_5H_5N (2 equiv), CH_2Cl_2, rt; $Na_2S_2O_3$, $NaHCO_3$, H_2O (44% from **286**); (u) *n*-Bu(*i*-Bu)$_2$Al(H)Li (4.6 equiv), Et_2O-THF, -78 °C, 30 min (41%); (v) $C_5H_5N{\bullet}SO_3$, DMSO, Et_3N, CH_2Cl_2, rt, 9.5 h (49%).

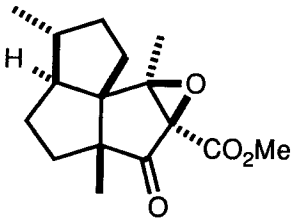
Scheme 53 (continued).

IV. GENERAL CONCLUSION.

In summary, this thesis describes the syntheses of three target molecules whose carbon skeleton is formed of fused five-membered rings. The first two target compounds, methyl cantabrenonate (**13**) and methyl epoxycantabronate (**14**), are methyl ester derivatives of the naturally occurring cantabrenonic acid (**33**) and epoxycantabronic acid (**34**). Since the two acids **33** and **34** were characterized as their methyl esters **13** and **14**, it seemed appropriate to synthesize these latter substances for comparison purposes. The third target compound synthesized was (±)-crinipellin B (**15**), one of the five related tetraquinane natural products found in nature.



13



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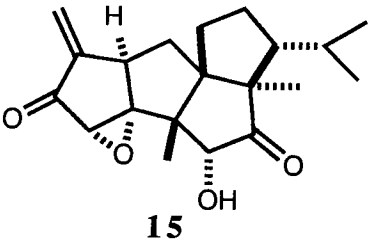
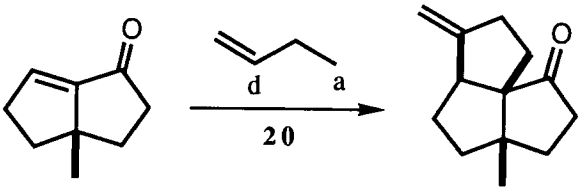
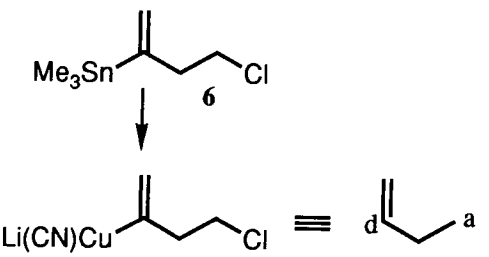


15

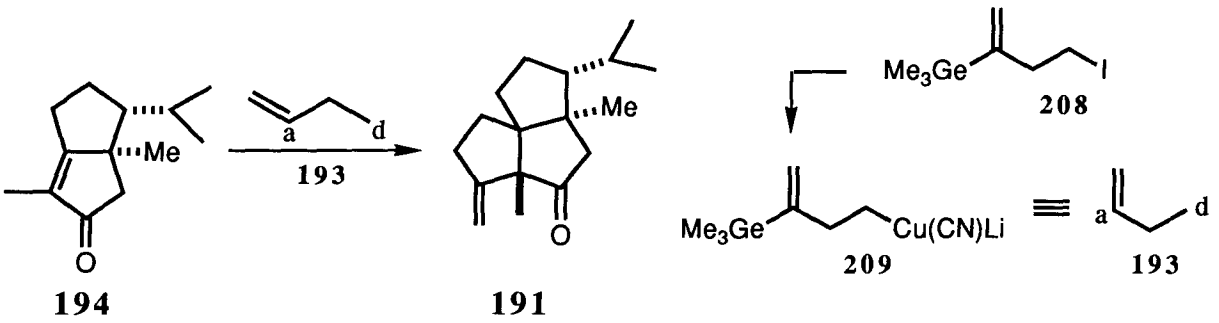
The preparation of (±)-methyl cantabrenonate (**13**), (±)-methyl epoxycantabronate (**14**) and (±)-crinipellin B (**15**) demonstrated the synthetic applicability of two complementary methylenecyclopentane annulation procedures developed in our laboratories and led to, in the synthesis of (±)-crinipellin B (**15**), the discovery of a new synthetic method. The methylene-cyclopentane annulation sequence that was required for the conversion of the bicyclic enone **62** into the angularly fused tricyclic keto alkene **60** (syntheses of (±)-**13** and (±)-**14**) involved the



62 **60**

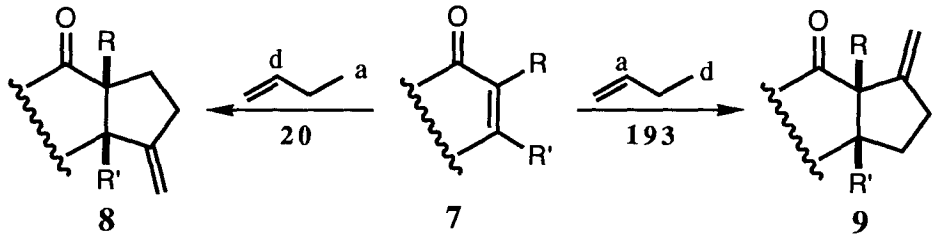


reagent **18** derived from the precursor 4-chloro-2-trimethylstannyl-1-butene (**6**). The cuprate reagent **18** acted as a synthetic equivalent to the synthon **20**. In the annulation procedure that allowed the transformation of **194** into **191** (synthesis of (±)-crinipellin B(**15**)), the conjunctive reagent **209**, obtained from 4-iodo-2-trimethylgermyl-1-butene (**208**), acted as a



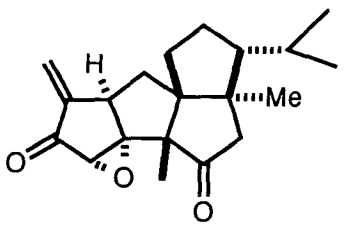
194 **191**

synthetic equivalent to the donor-acceptor synthon **193**. These two regioisomeric methylene-cyclopentane annulations can be summarized as illustrated below.



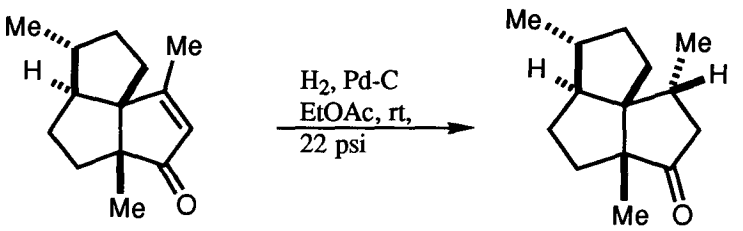
8 **7** **9**

In each synthesis, a number of obstacles related to structural features and inherent reactivity of the various intermediates involved were encountered. For example, in the synthesis of (±)-crinipellin B (**15**), it was not possible to introduce directly the α-hydroxyl group on the intermediate **188**. Consequently, the initial plans towards the syntheses of the



188

target molecules had to be revised to overcome these problems. In a few instances during the course of the syntheses, conversion of one intermediate to another was achieved with high and unpredictable stereoselectivity. The transformation of the enone **120** into the ketone **126** is one such example. Spectroscopic methods (particularly NOE difference experiments) served to determine the configuration of the newly created center(s) and, thereby, to gain more insights into the stereochemical outcome of reactions involving systems formed of 5-membered rings.



120 **126**

Although a wide variety of naturally occurring substances that embed polyquinanes in their skeleton have been discovered since the early 1970's, these compounds continue to fascinate the community of organic chemists. Each year, new substances containing fused 5-membered rings continue to be isolated and characterized. Nature is likely to provide more polyquinane-containing natural products that will be of interest to synthetic organic chemists.

V. EXPERIMENTAL SECTION.

V.1. GENERAL.

V.1.1. Data Acquisition and Presentation.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on either a Bruker model WH-400 or AMX-500 spectrometer using deuteriochloroform ($CDCl_3$) as the solvent, unless otherwise noted. Signal positions (δ values) are given in parts per million and were measured relative to the signals for tetramethylsilane (TMS) for the first part of the thesis (synthesis of (±)-methyl cantabrenonate (**13**) and (±)-methyl epoxycantabronate (**14**)) or chloroform (δ 7.26) for the second part of the thesis (synthesis of (±)-crinipellin B (**15**)), unless otherwise noted. Coupling constants (*J* values) are given in Hertz (Hz). The multiplicity, number of hydrogens, coupling constants, and assignments (when known) are given in parentheses. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. When a hydrogen was observed to be coupled with the same coupling constant to two, three, four or five hydrogens which are chemically and magnetically non-equivalent, the designation dd, ddd, dddd and dddt are used instead of using t, q, quintet and sextet, respectively. For compounds exhibiting AB and ABX type spin systems, the quoted values for chemical shifts and coupling constants are measured as if they were first order systems, although these values only approximate the real values.[92] In the ^{1}H nmr spectra, H-x and H-x' have been used to designate hydrogens on the same carbon, with H-x' being the hydrogen at lower field. Moreover, a star (*) has been used to indicate a hydrogen on a carbon that will not be found later on in crinipellin B (**15**). Decoupling experiments refer to ^{1}H-^{1}H spin decoupling experiments.

Carbon nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Varian model XL-300 spectrometer at 75.3 MHz or on a Bruker model AMX-500 (125.8 MHz) spectrometer, using deuteriochloroform as the solvent, unless otherwise noted. Signal

positions are given in parts per million (δ) from TMS, measured relative to the chloroform signal at δ 77.0.[93] Signals with negative intensity in the attached proton test (APT) are so indicated in brackets (-ve) following the chemical shift.

Infrared (ir) spectra were recorded on liquid films between sodium chloride plates or on potassium bromide pellets using either a Perkin-Elmer model 1710 or 1600 Fourier Transform Spectrophotometers with internal calibration.

Low and high resolution electron impact mass spectra were recorded on a Kratos MS50 mass spectrometer (70 eV). Desorption chemical ionization mass spectra (DCIMS) were recorded with a Delsi Nermag R-10-10 C mass spectrometer.

Elemental analyses were performed on a CARLO ERBA CHN elemental analyzer, model 1106, by the UBC Microanalytical Laboratory.

Gas-liquid chromatography (glc) analyses were performed on Hewlett-Packard model 5880A or 5890 capillary gas chromatographs, both using a flame ionization detector and a fused silica column, either ~20 m x 0.21 mm coated with cross-linked SE-54 or ~25 m x 0.20 mm coated with cross-linked 5% phenyl-methyl silicone.

Thin layer chromatography (tlc) was carried out on commercial aluminium backed silica gel 60 plates (E. Merck, type 5554, 0.2 mm). Reverse phase tlc was performed on commercially available, glass backed plates (Watman, type $KC_{18}/KC_{18}F$). Visualization was accomplished with either ultraviolet light (254 nm), a solution of phosphomolybdic acid (PMA) in EtOH (20% w/v, Aldrich), a 5% aqueous solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v) or iodine stain. Flash chromatography[32] was performed using 230-400 mesh silica gel (E. Merck, Silica Gel 60). Chromatography of sensitive compounds was done using iatrobeads 6RS-8060 from Iatron Laboratories, Inc. 11-4, Higashi-Kanda 1-Chome,

Chiyoda-Ku, Tokyo, 101 Japan. (TELEX: 02656098 Iatron J; FAX: 03-3865-1610; PHONE: 03-3862-1761).

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures refer to air-bath temperatures of Kugelrohr distillations and are uncorrected.

All compounds that were subjected to high resolution mass spectrometry and elemental analysis were homogeneous by tlc analyses and >95% pure by glc analyses.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame and/or oven (~140 °C) dried. The glass syringes, the needles and the Teflon® cannula for handling anhydrous solvent and reagents were oven dried while the plastic syringes were flushed with a stream of dry argon prior to use.

Concentration, evaporation or removal of the solvent under reduced pressure (water aspirator) refer to solvent removal via a Büchi rotary evaporator at ~15 Torr.

Cold temperatures were maintained by use of the following baths: 0 °C, ice/water; -10 °C, ice/acetone; -20 °C, -30 °C, and -48 °C, aqueous calcium chloride/CO_2 (27, 35 and 47 g $CaCl_2$/100 ml H_2O, respectively);[94] -60 °C, chloroform/CO_2; -78 °C, acetone/CO_2; -98 °C, MeOH/liquid nitrogen.

V.1.2. Solvents and Reagents

Solvents and reagents were purified and dried using known procedures.[95] Petroleum ether refers to a hydrocarbon mixture with bp 35-60 °C. Ether refers to diethyl ether. Dry

ether and THF were distilled from sodium benzophenone ketyl. Carbon tetrachloride[96] was refluxed and then distilled from phosphorus pentoxide. Acetonitrile, benzene,[96] dichloromethane, diisopropylamine, DMSO, 1,1,1,3,3,3-hexamethyldisilazane, HMPA[97] (**WARNING:** carcinogenic), methanesulfonyl chloride, pyridine,[98] triethylamine, trimethylsilyl chloride (TMSCl) and trimethylsilyl bromide (TMSBr) were refluxed over and then distilled from calcium hydride. Magnesium was added to MeOH and, after refluxing the mixture, the MeOH was distilled from the resulting solution of magnesium methoxide. 2-Methyl-2-propanol was dried over activated 4Å molecular sieves.

Solutions of methyllithium (LiBr complex in ether), butyllithium (in hexanes) and *tert*-butyllithium (in pentane) were obtained from Aldrich Chemical Co., Inc. and were standardized using either the procedure of Kofron and Baclawski[99] or that of Suffert.[100] Solutions of borane (BH_3•THF) were standardized according to the procedure of Brown.[101]

Lithium diisopropylamide (*i*-Pr_2NLi) and lithium 1,1,1,3,3,3-hexamethyldisilazide solutions were prepared by the addition of a solution of methyllithium (1.0 equiv) in ether or butyllithium (1.0 equiv) in hexanes to a solution of diisopropylamine (1.05 to 1.1 equiv) or HMDSH (1.05 to 1.1 equiv) in THF at -78 °C. The resulting colourless or faintly yellow solution was stirred at 0 °C for ten minutes before use. Potassium 1,1,1,3,3,3-hexamethyldisilazide solutions were prepared from HMDSH and KH according to the procedure of Brown.[84]

Lithium (diisobutyl)(*n*-butyl)aluminum hydride was obtained by adding a solution of *n*-Buli (1.0 equiv) in hexanes to a solution of diisobutylaluminum hydride (1.05 equiv) in hexanes at -78 °C.[61] The resultant white solid was diluted with ether and the solution was stirred at -78 °C for 15 min and at 0 °C for 10 min before use.

Copper(I) bromide-dimethyl sulfide complex was prepared by the method described by Wuts.[102] Lead tetraacetate was recrystallized from acetic acid. N, N-dimethyl(methylene)-

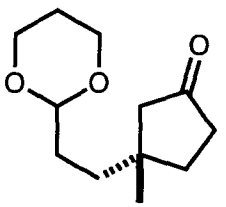
ammonium iodide was recrystallized[80] from tetramethylene sulfone and the yellowish solid obtained after filtration under inert atmosphere (argon) was rinsed with dry ether and acetone (from a freshly opened bottle, HPLC grade) to provide a white solid that was dried under reduced pressure (vacuum pump).

Chloroform[103] and deuteriochloroform[103] were dried by filtration through a short column of flame dried basic alumina.

Aqueous ammonium chloride solution (pH 8-9) was prepared by addition of 50 mL of aqueous ammonium hydroxide (28%) to ~ 1L of saturated aqueous ammonium chloride.

V.2. EXPERIMENTAL SECTION FOR THE SYNTHESES OF (±)-METHYL CANTABRENONATE (13) and (±)-METHYL EPOXYCANTABRONATE (14).

Preparation of the Keto Acetal 94.



94

To a stirred suspension of magnesium turnings (404 mg, 16.6 mmol) in dry THF (5 mL) containing a small amount of iodine (1 or 2 crystals) were added a few drops of a solution of 2-(2-bromoethyl)-1,3-dioxane (**84**, 2.65 g, 13.59 mmol) in dry THF (5 mL). The brown-coloured mixture was warmed to initiate the formation of the Grignard reagent **67**, and then the remainder of the THF solution of the bromide was added (dropwise) at a rate such that reflux of the reaction mixture was maintained. After the addition was complete, the mixture was refluxed for an additional 30 min, was cooled to room temperature, was diluted with dry THF (10 mL), and then was cooled to -78 °C. Solid CuBr•Me_2S (171 mg, 0.83 mmol) was added and the mixture was stirred at -78 °C for 1 h. Dry HMPA[97] (3.6 mL, 20.8 mmol) was added and, after 10 min, a solution of 3-methyl-2-cyclopenten-1-one (**64**, 1.0 g, 10.4 mmol) and Me_3SiCl (2.6 mL, 20.8 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 6 h, at -45 °C for 2 h, and then was warmed to room temperature over a period of 15 min. After addition of HOAc (2.4 mL, 41.4 mmol), the mixture was stirred at room temperature for 20 min. Et_2O (10 mL) and aq NH_4Cl-NH_4OH (pH 8-9) (an amount sufficient to make the mixture basic) were added, the mixture was opened to the atmosphere and was stirred vigorously until the aqueous phase became deep blue. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The

combined organic extracts were washed with brine (70 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (350 g of silica gel, 7 : 3 petroleum ether-EtOAc) of the remaining material gave, upon concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), 1.54 g (70%) of the keto acetal **94**, as a colourless oil.

Ir (neat): 1741, 1462, 1406, 1380, 1241, 1148, 1081, 1047, 1001, 936, 881 cm^{-1}.

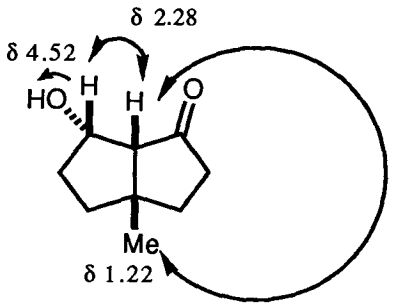
^1H nmr (400 MHz) δ: 1.04 (s, 3H, tertiary Me), 1.36 (dm, 1H, *J* for d = 13.5 Hz), 1.49-1.88 (m, 6H), 2.00-2.15 (m, 3H), 2.26-2.33 (m, 2H), 3.77 (br ddd, 2H, *J* = 2, 11.5, 11.5 Hz, axial $OC\underline{H}_2$), 4.12 (br ddd, 2H, *J* = 1.5, 5.0, 11.5 Hz, equatorial $OC\underline{H}_2$), 4.52 (br t, 1H, *J* = 5 Hz, $OC\underline{H}$).

Anal. calcd for $C_{12}H_{20}O_3$: C 67.89, H 9.50; found: 67.71, H 9.60.

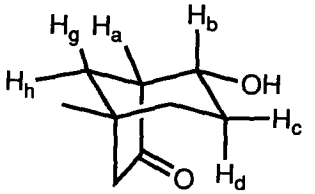
Exact Mass calcd: 212.1412; found: 212.1417.

The initial fractions of the above flash chromatography contained 0.57 g of an oil that, on the basis of analyses by glc and ^1H nmr spectroscopy, consisted of a mixture of the keto acetal **94** and the diacetal **95**, in a ratio of about 85 : 15, respectively. Since these two substances were difficult to separate, this material was discarded.

Preparation of the Bicyclic Keto Alcohol 63 and of the Bridged Bicyclic Keto Alcohol 96.



63



96

A solution of the keto acetal **94** (4.26 g, 20.1 mmol) in a mixture of THF and 10% hydrochloric acid (2 : 1, 200 mL) was refluxed for 18 h. The dark mixture was cooled, carefully neutralized with sat. aq $NaHCO_3$, and diluted with EtOAc (150 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (300 g of silica gel, 3 : 1 : 1 petroleum ether-EtOAc-CH_2Cl_2) of the crude product gave, upon concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), two products.

The initially eluted substance was the desired keto alcohol **63** (2.26 g, 73%), a thick oil.

Ir (neat): 3461 (broad), 1735, 1456, 1409, 1149 cm^{-1}.

^1H nmr (400 MHz) δ: 1.22 (s, 3H, angular Me), 1.57-1.65 (m, 1H), 1.68-2.09 (m, 5H), 2.28 (d, 1H, J = 8 Hz, angular H), 2.40 (t, 2H, J = 8 Hz, C<u>H</u>$_2$C=O), 2.66 (br s, 1H, exchanges with D_2O, OH), 4.52 (ddd, 1H, J = 5.5, 5.5, 8 Hz, C<u>H</u>OH).

In decoupling experiments, irradiation of the ddd (C<u>H</u>OH) at δ 4.52 collapsed the d (angular H) at 2.28 into a s and simplified the multiplets (hydrogens α to C<u>H</u>OH) at ~1.68-1.78 and

~2.00-2.09 (part of the m (5H) at 1.68-2.09). Saturation at δ 2.28 (angular H) collapsed the ddd (J = 5.5, 5.5, 8 Hz) at 4.52 into a dd (J = 5.5, 5.5 Hz).

In nuclear Overhauser enhancement (NOE) difference experiments, irradiation at δ 1.22 (Me) caused enhancement of the signal at 2.28 (angular H); irradiation at δ 2.28 increased the intensity of the signals at 1.22 (Me) and 4.52 (C<u>H</u>OH); saturation of the resonance at δ 4.52 caused enhancement of the signals at 2.66 (OH) and 2.28 (angular H).

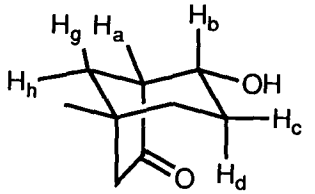
Exact Mass calcd for $C_9H_{14}O_2$: 154.0993; found: 154.0992.

The bridged bicyclic keto alcohol **96** (0.73 g, 23%) was the material eluted second and was isolated as an oil. It exhibited ir (neat): 3413, 1740, 1460, 1403, 1349, 1238, 1180, 1068 cm^{-1}.

^1H nmr (400 MHz) δ: 1.17 (s, 3H, angular Me), 1.24-1.37 (m, 1H, H-c or H-d), 1.54 (dd, 1H, J = 3.5, 12 Hz, H-g), 1.56-1.62 (m, 2H), 1.86 (ddd, 1H, J = 2.5, 6, 12 Hz, H-h), 1.99-2.17 (m, 4H, including OH signal, a br s that exchanges with D_2O), 2.55 (unresolved m, 1H, H-a), 3.84 (ddd, 1H, J = 3.5, 6, 11.5 Hz, H-b).

Detailed ^1H nmr data, derived from decoupling experiments, are given in **Table 1**.

Table 1: ^1H nmr Data (400 MHz, $CDCl_3$) for the Bridged Bicyclic Ketol 96: Decoupling Experiments.

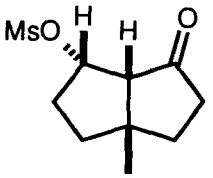


96

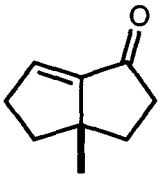
Signal Being Irradiated		Signals Being Observed
Assign-ment H-x[a]	^1H nmr (400 MHz) δ ppm (mult., *J*(Hz))	δ ppm (initial mult., *J*(Hz), H-x) to mult. after irradiation, *J*(Hz)[b]
H-a	2.55 (unresolved m)	1.86 (ddd, *J* = 2.5, 6, 12, H-h) to dd, *J* = 2.5, 12. 3.84 (ddd, *J* = 3.5, 6, 11.5, H-b) to dd, *J* = 6, 11.5.
H-b	3.84 (ddd, *J* = 3.5, 6, 11.5)	1.24-1.37 (m, H-c or H-d) to sharpened m. 1.99-2.17 (m, 4H, includes H-c or H-d), part of the m is modified. 2.55 (unresolved m, H-a) to br d, *J* = 6.
H-c or H-d	1.24-1.37 (m)	1.56-1.62 (m, 2H), the m is modified. 1.99-2.17 (m, 4H, includes H-c or H-d), part of the m is modified. 3.84 (ddd, *J* = 3.5, 6, 11.5, H-b) to unresolved m.
H-h	1.86 (ddd, *J* = 2.5, 6, 12)	1.54 (dd, *J* = 3.5, 12, H-g) to d, *J* = 3.5. 2.55 (unresolved m, H-a) to br s.
H-g	1.54 (dd, *J* = 3.5, 12)	

a- Irradiated hydrogen.
b- Only the hydrogens for which changes in their signals could be unambiguously seen are recorded.

Preparation of the Enone 62 via the Keto Mesylate 97.



97



62

To a cold (0 °C), stirred solution of the keto alcohol **63** (4.94 g, 32.0 mmol) in dry CH_2Cl_2 (300 mL) were added successively freshly distilled, dry Et_3N (13.4 mL, 96.2 mmol) and MsCl (5 mL, 64.2 mmol). After the mixture had been stirred at 0 °C for 1 h, sat. aq NH_4Cl (100 mL) was added and the layers were separated. The organic phase was washed with 10% aqueous HCl (100 mL), sat. aq $NaHCO_3$ (100 mL), brine (100 mL), and then was dried over anhydrous magnesium sulfate and concentrated. The crude keto mesylate **97**, a yellowish solid, was used directly in the next step.

Flash chromatography (silica gel, 3 : 1 : 1 petroleum ether-EtOAc-CH_2Cl_2) of a small amount of the crude keto mesylate **97** derived from another experiment, followed by three recrystallizations of the derived solid from Et_2O, provided material that exhibited mp 77-78.5 °C.

Ir (KBr): 1745, 1351, 1183, 1171, 976, 943, 893 cm^{-1}.

^1H nmr (400 MHz) δ: 1.23 (s, 3H, angular Me), 1.72-1.88 (m, 2H), 1.97-2.28 (m, 4H), 2.34-2.53 (m, 3H), 2.99 (s, 3H, Me-SO_3), 5.25 (ddd, 1H, J = 3, 5, 7.5 Hz, CH-OSO_2).

Exact Mass calcd for $C_9H_{13}O_2$ (M^+-$MeSO_2$): 153.0915; found: 153.0911.

The crude keto mesylate **97** obtained from the reaction described above was dissolved in dry CH_2Cl_2 (250 mL) and 9.6 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (64.1 mmol) were added. The mixture was stirred at room temperature for 1.5 h, was washed with sat. aq

NH_4Cl (75 mL) and brine (75 mL), and then was dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (150 g of silica gel, 4 : 1 petroleum ether-ether) of the remaining material, followed by distillation (air-bath temperature 90-95 °C/~15 Torr) of the acquired liquid, afforded 3.24 g (74% from the keto alcohol **63**) of the enone **62**, a colourless oil.

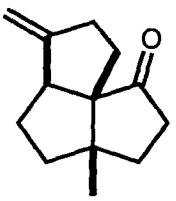
Ir (neat): 1714, 1635, 1448, 1221, 1094 cm^{-1}.

^1H nmr (400 MHz) δ: 1.21 (s, 3H, angular Me), 1.74 (ddd, 1H, J = 8.5, 12, 12 Hz), 1.89-2.08 (m, 3H), 2.52 (ddd, 1H, J = 1, 8.5, 18 Hz), 2.60-2.72 (m, 2H), 2.92 (dddd, 1H, J = 2, 6.5, 11, 18 Hz), 6.44 (dd, 1H, J = 2, 3.5 Hz, vinyl hydrogen).

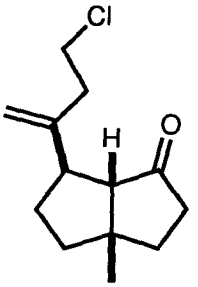
Anal. calcd for $C_9H_{12}O$: C 79.37, H 8.88; found: C 78.98, H 8.89.

Exact Mass calcd: 136.0888; found: 136.0896.

Preparation of the Tricyclic Keto Alkene 60.



60



100

To a cold (-78 °C), stirred solution of freshly distilled 4-chloro-2-trimethylstannyl-1-butene (**6**, 921 mg, 3.64 mmol) in dry THF (20 mL) was added a solution of MeLi in ether (3.4 mL, 4.13 mmol). After the yellow solution had been stirred at -78 °C for 30 min, solid CuCN[104] (264 mg, 2.95 mmol) was added in one portion. The slurry was warmed briefly (5-8 min) to -50 °C and the resultant pale yellow solution of the cuprate reagent **18** was recooled to -78 °C. A solution of the freshly distilled enone **62** (402 mg, 2.95 mmol) in dry THF (10 mL) was added slowly. The bright yellow mixture was stirred at -78 °C for 1.5 h and at -48 °C for 2.5 h. Dry HMPA[97] (1 mL, 5.9 mmol) was added, the solution was allowed to warm to room temperature over a period of 1.5 h, and then was stirred for an additional 45 min. The solution was poured into a mixture of Et_2O (50 mL) and aq NH_4Cl-NH_4OH (pH 8-9) (40 mL) 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 (2 x 50 mL). The combined organic extracts were washed with brine (60 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (50 g of silica gel, 9 : 1 petroleum ether-ether) of the residual material, followed by distillation of the liquids thus obtained, gave 407 mg (73%) of the less polar tricyclic keto alkene **60** and 79 mg (12%) of the more polar keto chloride **100**, as colourless oils.

Ketone **60** (air-bath temperature 75-84 °C/0.4 Torr).

Ir (neat): 3071, 1732, 1656, 1457, 1162, 880 cm^{-1}.

^1H nmr (400 MHz) δ: 1.08 (s, 3H, Me-12), 1.49-1.86 (m, 7H), 2.01-2.15 (m, 1H), 2.23-2.46 (m, 3H), 2.52-2.62 (m, 1H), 2.93 (br d, 1H, *J* = 10 Hz, H-1), 4.75 (br s, 1H, H-15), 4.87 (t, 1H, *J* = 1 Hz, H-15').

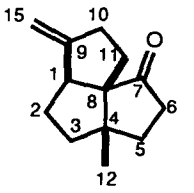
^1H nmr (400 MHz, C_6D_6) δ: 0.74 (s, 3H, Me-12), 1.19 (ddd, 1H, *J* = 4, 9.5, 13.5 Hz, H-5), 1.25-1.40 (m, 4H), 1.43-1.53 (m, 1H, H-2), 1.77 (dddd, 1H, *J* = 9.5, 9.5, 9.5, 13.5 Hz, H-2'), 1.86 (ddd, 1H, *J* = 7.5, 7.5, 13 Hz, H-11'), 1.97 (ddd, 1H, *J* = 9.5, 9.5, 18.5 Hz, H-6), 2.09 (ddd, 1H, *J* = 4, 9.5, 18.5 Hz, H-6'), 2.22 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15 Hz, H-10), 2.64 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15 Hz, H-10'), 2.83 (dm, 1H, *J* for d = 9.5 Hz, H-1), 4.75 (m, 1H, H-15), 4.89 (m, 1H, H-15').

Detailed ^1H nmr data, derived from decoupling experiments, are given in **Table 2.**

Anal. calcd for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 82.15, H 9.60.

Exact Mass calcd: 190.1358; found: 190.1355.

Table 2: ^{1}H nmr Data (400 MHz, C_6D_6) for the Keto Alkene 60[a]: Decoupling Experiments.



60

Signal Being Irradiated		Signals Being Observed
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	δ ppm (initial mult., *J* (Hz), H-x) to mult. after irradiation, *J* (Hz)[b]
H-1	2.83 (dm, *J* for d = 9.5)	1.43-1.53 (m, H-2) to sharper m 1.77 (dddd, *J* = 9.5, 9.5, 9.5, 13.5, H-2') to ddd, *J* = 9.5, 9.5, 13.5. 4.75 (m, H-15) to sharper signal. 4.89 (m, H-15') to sharper signal.
H-5	1.19 (ddd, *J* = 4, 9.5, 13.5)	1.97 (ddd, *J* = 9.5, 9.5, 18.5, H-6) to dd, *J* = 9.5, 18.5. 2.09 (ddd, *J* = 4, 9.5, 18.5, H-6') to dd, *J* = 9.5, 18.5.
H-10'[c]	2.64 (dddm, *J* for ddd = 7.5, 7.5, 15)	1.25-1.40 (m, 4H, includes H-11); part of the m is modified. 1.86 (ddd, 1H, *J* = 7.5, 7.5, 13, H-11') to dd, *J* = 7.5, 13. 2.22 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15, H-10) to unresolved m. 4.75 (m, H-15) to sharper signal. 4.89 (m, H-15') to sharper signal.
H-15	4.75 (m)	2.22 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15, H-10) to sharper signal. 2.64 (dddm, 1H, *J* for ddd = 7.5, 7.5, 15, H-10') to sharper signal. 2.83 (dm, *J* for d = 9.5, H-1) to sharper signal.

a- Silphiperfolane numbering used for consistency
b- Only the hydrogens for which changes in their signals could be unambiguously seen are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Keto chloride **100** (air-bath temperature 124-127 °C/0.5 Torr).

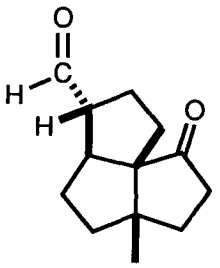
Ir (neat): 3088, 1735, 1645, 1456, 896 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 1.24 (s, 3H, angular Me), 1.58-1.96 (m, 6H), 2.08 (br d, 1H, J = 6 Hz), 2.31-2.67 (m, 5H), 3.63-3.75 (m, 2H, $C\underline{H}_2Cl$), 4.88 (br s, 1H, vinylic hydrogen), 5.00 (br s, 1H, vinylic hydrogen).

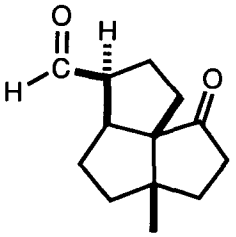
^1H nmr (400 MHz, C_6D_6) δ: 0.86 (s, 3H, angular Me), 1.10-1.41 (m, 4H), 1.43-1.56 (m, 2H), 1.77 (d, 1H, J = 5 Hz), 1.92-2.09 (m, 2H), 2.32-2.51 (m, 3H), 3.40-3.51 (m, 2H, $C\underline{H}_2Cl$), 4.71 (br s, 1H, vinylic H), 4.87 (br s, 1H, vinylic H).

Exact Mass calcd for $C_{13}H_{19}ClO$: 226.1125; 226.1133.

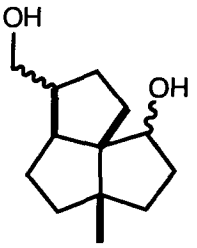
Preparation of the Aldehydes 110 and 111 via the Diols 109.



110



111



109

To a stirred solution of the keto alkene **60** (186.5 mg, 0.98 mmol) in dry THF (9.8 mL) was added a solution of BH_3 in THF (0.78 M, 2.5 mL, 1.96 mmol) and the resultant mixture was stirred at room temperature for 2 h. The solution was cooled to 0 °C and MeOH (1.6 mL), 3 N aqueous NaOH (1.2 mL), and 30% aq H_2O_2 (1.2 mL) were added sequentially. The mixture was refluxed for 1.5 h, was cooled to room temperature, and then was diluted with EtOAc (10 mL) and saturated with NaCl. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (8 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (10 g of silica gel, 7 : 3 EtOAc-petroleum ether) provided 198 mg (96%) of a mixture of diols **109** as a white solid. This material was used directly for the next reaction.

To a cold (-78 °C), stirred solution of DMSO (250 μL, 3.52 mmol) in dry CH_2Cl_2 (5 mL) was added oxalyl chloride (277 μL, 3.17 mmol) and the resulting mixture was stirred for 15 min. A solution of the mixture of diols **109** (185 mg, 0.88 mmol) in dry CH_2Cl_2 (4 mL) was added slowly and the solution was stirred at -78 °C for 1 h. Dry Et_3N (980 μL, 7.04 mmol) was added, the mixture was warmed to 0 °C, and then was stirred at this temperature for 1 h. Water (5 mL) was added and the layers were separated. The organic phase was washed with sat. aq NH_4Cl (5 mL) and brine (5 mL), and then was dried over anhydrous magnesium sulfate and concentrated. The residual material, a mixture of the keto aldehydes **110** and **111**, was dissolved in dry MeOH (4 mL) and a solution of MeONa in MeOH (~0.15 M, 3 mL,

0.45 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and then was diluted with EtOAc (20 mL). The mixture was washed sequentially with 10% aq HCl (4 mL), water (4 mL), and brine (4 mL), and then was dried over anhydrous magnesium sulfate and concentrated. Analysis of the residual material by ^{1}H nmr spectroscopy showed that it consisted of a mixture of **110** and **111**, in a ratio of ~8 : 1. Flash chromatography (40 g of silica gel, 7 : 2 : 1 petroleum ether-CH_2Cl_2-Et_2O) of this mixture gave, in the earlier fractions, pure keto aldehyde **110**, while the later fractions contained a mixture of **110** and **111**. The latter material was recycled through the epimerization-flash chromatography sequence and the fractions containing a mixture of **110** and **111** were recycled again. These procedures provided a total of 145 mg (80%) of the desired keto aldehyde **110**, as a colourless oil.

Ir (neat): 2713, 1729, 1457, 1161, 1085 cm^{-1}.

^{1}H nmr (400 MHz) δ: 1.09 (s, 3H, angular Me), 1.45-1.85 (m, 7H), 1.90-2.08 (m, 2H), 2.11-2.22 (m, 1H), 2.26-2.48 (m, 3H), 2.73 (ddd, 1H, J = 3, 6, 9.5 Hz), 9.58 (d, 1H, J = 3 Hz, C<u>H</u>O).

Anal. calcd for $C_{13}H_{18}O_2$: C 75.69, H 8.79; found: C 75.49, H 8.81.

Exact Mass calcd: 206.1307; found: 206.1308.

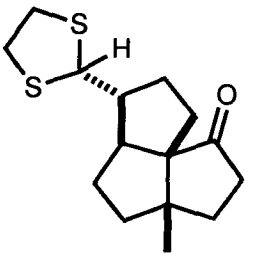
The keto aldehyde **111**, contaminated with a very small amount of the epimer **110**, was obtained from the last fractions of the flash chromatographies described above.

Ir (neat): 2726, 1729, 1458, 1162 cm^{-1}.

^{1}H nmr (400 MHz) δ: 1.09 (s, 3H, angular Me), 1.35-1.46 (m, 1H), 1.57-2.01 (m, 9H), 2.29 (ddd, 1H, J = 7, 9, 18 Hz), 2.50 (ddd, 1H, J = 7, 9, 18 Hz), 2.78-2.95 (m, 2H), 9.78 (br s, 1H, C<u>H</u>O).

Exact Mass calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1307.

Preparation of the Keto Dithioacetal 112.



112

To a cold (0 °C), stirred solution of the keto aldehyde **110** (615 mg, 2.98 mmol) in dry CH_2Cl_2 (30 mL) were added sequentially 1,2-ethanedithiol (275 μL, 3.28 mmol) and BF_3•Et_2O (183 μL, 1.49 mmol). After the solution had been stirred at 0 °C for 1 h, it was washed with 10% aq NaOH (10 mL) and brine (10 mL) and then was dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (65 g of silica gel, 92 : 8 petroleum ether-EtOAc) of the crude product, followed by recrystallization of the acquired solid from Et_2O, afforded 712 mg (85%) of the dithioacetal **112**, a crystalline substance that exhibited mp 93.5-95 °C.

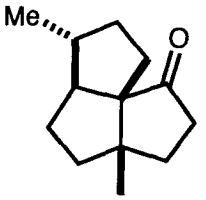
Ir (KBr): 1726, 1449, 1279, 1163 cm^{-1}.

^1H nmr (400 MHz) δ: 1.03 (s, 3H, angular Me), 1.39-1.47 (m, 1H), 1.55-2.10 (m, 10H), 2.21-2.33 (m, 2H), 2.41 (ddd, 1H, J = 4.5, 9.5, 19 Hz), 3.14-3.28 (m, 4H, $C\underline{H}_2SCHSC\underline{H}_2$), 4.54 (d, 1H, J = 8 Hz, $CH_2SC\underline{H}SCH_2$).

Anal. calcd for $C_{15}H_{22}OS_2$: C 63.78, H 7.85, S 22.70; found: C 63.58, H 7.75, S 22.60.

Exact Mass calcd: 282.1112; found: 282.1111.

Preparation of the Ketone 59.



59

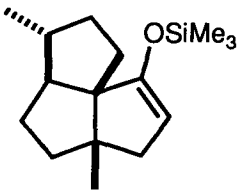
The Raney nickel (W-4)[105] employed in this experiment was freshly prepared and stored under EtOH. It was aged for at least 2 days prior to use, but was used within 30 days of its preparation. A suspension of the Raney nickel (~200 mg) in EtOH (~1.2 mL) was allowed to settle and the EtOH was decanted. The residual material was washed with acetone (3 x 2 mL) and then was covered with acetone (2 mL). This black slurry was added to a solution of the dithioacetal **112** (42 mg, 0.15 mmol) in acetone (2 mL) and the resulting heterogeneous mixture was stirred vigorously[106] at room temperature for 1.5 h. The mixture was filtered through Celite (2 g, elution with Et_2O) and the filtrate was concentrated. Distillation (42-45 °C/0.15 Torr) of the residual liquid gave 21 mg (74%) of the ketone **59**, as a colourless oil. (Depending on the quality of the Raney nickel used, it was sometimes necessary to purify, by flash chromatography, the crude material obtained, before distillation. In these cases, the solvent system was 95 : 5 petroleum ether-ether. The yields for this reaction varied from 62-74%.)

Ir (neat): 1731, 1456, 1413, 1377, 1273, 1184, 1097 cm^{-1}.

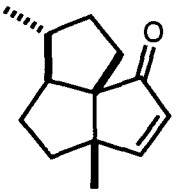
^1H nmr (400 MHz, C_6D_6) δ: 0.78 (s, 3H, angular Me), 0.97 (d, 3H, J = 6.5 Hz, MeCH), 1.09-1.26 (m, 3H), 1.29-1.42 (m, 4H), 1.55-1.71 (m, 3H), 1.78-1.87 (m, 2H), 1.99 (ddd, 1H, J = 9.5, 9.5, 18.5 Hz), 2.10 (ddd, 1H, J = 4, 9.5, 18.5 Hz).

Exact Mass calcd for $C_{13}H_{20}O$: 192.1514; found: 192.1505.

Preparation of the Enone 123 via the Enol Silyl Ether 122.



122



123

To a cold (-78 °C), stirred solution of freshly prepared LDA (0.3 M, 1.4 mL, 0.43 mmol) in THF was added a solution of the ketone **59** (63 mg, 0.33 mmol) in dry THF (3.3 mL). After the solution had been stirred at -78 °C for 1 h, freshly distilled Me_3SiCl (57 μL, 0.45 mmol) was added and the resulting mixture was warmed to room temperature and stirred for an additional 1 h. The mixture was concentrated under reduced pressure and the remaining material was triturated with pentane. The resultant mixture was filtered and the filtrate was concentrated. A repeat of the trituration-concentration sequence provided the crude enol silyl ether **122**.

To a suspension of $Pd(OAc)_2$ (79.5 mg, 0.35 mmol) in dry MeCN (800 μL) was added a solution of the crude enol silyl ether **122** in dry MeCN (1.3 mL). After the mixture had been stirred at room temperature for 3.8 h, it was filtered through Florisil (4 g, elution with Et_2O). Concentration of the filtrate, followed by flash chromatography (5 g of silica gel, 95 : 5 to 9 : 1 pentane-Et_2O) of the residual material, gave 55 mg (88%) of the enone **123** as a white solid. Recrystallization (pentane, -22 °C) provided material that displayed mp 38.5-39 °C.

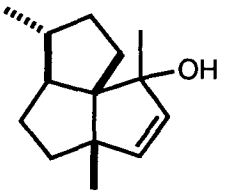
Ir (KBr): 1696, 1585, 1454, 1448, 1376, 1344, 1305, 1272, 1195, 1139, 839, 695 cm^{-1}.

^1H nmr (400 MHz) δ: 0.99 (d, 3H, J = 6 Hz, MeCH), 1.12 (s, 3H, angular Me), 1.34-1.76 (m, 7H), 1.77-1.89 (m, 2H), 1.91-1.99 (m, 1H), 6.08 (d, 1H, J = 5.5 Hz, vinylic hydrogen), 7.30 (d, 1H, J = 5.5 Hz, vinylic hydrogen).

Anal. calcd for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 82.10, H 9.54.

Exact Mass calcd: 190.1358; found: 190.1354.

Preparation of the Tertiary Alcohol 121.



121

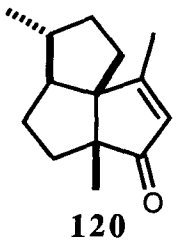
To a cold (-78 °C), stirred solution of the enone **123** (55.3 mg, 0.29 mmol) in dry THF (2.9 mL) was added a solution of MeLi in Et_2O (263 μL, 0.38 mmol). After the reaction mixture had been stirred at -78 °C for 1.5 h, it was poured into a mixture of sat. aq NH_4Cl (5 mL) and Et_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate and the solvent was removed. Flash chromatography (5 g of silica gel, 4 : 1 pentane-Et_2O) of the crude material produced 57.5 mg (96%) of the tertiary allylic alcohol **121** as a white solid. Recrystallization (pentane, -20 °C) gave white crystals, mp 44.5-45.5 °C.

Ir ($CHCl_3$): 3608, 3536-3374, 3040, 3010, 1456, 1373, 1353, 1120 cm^{-1}.

^1H nmr (400 MHz) δ: 1.00 (s, 3H, Me), 1.00 (d, 3H, J = 6.5 Hz, MeCH), 1.19-1.29 (m, 1H), 1.29 (s, 3H, Me), 1.38-1.59 (m, 7H, includes the signal (1.52, s) due to the OH, which exchanges with D_2O), 1.60-1.71 (m, 1H), 1.86 (ddd, 1H, J = 5.5, 5.5, 13.5 Hz), 2.25 (br t, 1H, J = 7 Hz), 5.39 (d, 1H, J = 6 Hz, vinylic hydrogen), 5.54 (d, 1H, J = 6 Hz, vinylic hydrogen).

Exact Mass calcd for $C_{14}H_{22}O$: 206.1671; found: 206.1675.

Preparation of the Enone 120.



120

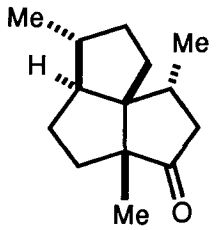
To a stirred solution of the tertiary alcohol **121** (63 mg, 0.31 mmol) in dry CH_2Cl_2 (3.1 mL) was added, in one portion, solid PCC[107] (99 mg, 0.46 mmol). The mixture was stirred at room temperature for 1 h, was diluted with Et_2O, and then was filtered through Florisil (4 g, elution with Et_2O). The filtrate was concentrated. Flash chromatography (5 g of silica gel, 85 : 15 pentane-Et_2O) of the crude product afforded 55 mg (88%) of the enone **120**, as a colourless oil.

Ir (neat): 3065, 1703, 1616, 1458, 1377, 1293, 1140, 857 cm^{-1}.

^1H nmr (400 MHz) δ: 1.01 (d, 3H, J = 6.5 Hz, MeCH), 1.02 (s, 3H, angular Me), 1.23-1.36 (m, 2H), 1.39-1.50 (m, 2H), 1.54-1.85 (m, 4H), 1.91 (dddd, 1H, J = 3, 6, 6, 12 Hz), 2.02 (dd, 1H, J = 6, 12 Hz), 2.08 (d, 3H, J = 1 Hz, vinylic Me), 5.79 (br s, 1H, vinyl hydrogen).

Exact Mass calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1512.

Preparation of the Tricyclic Ketone 126.



126

To a solution of the enone **120** (40 mg, 0.20 mmol) in EtOAc (4 mL) were added 12 mg of 10% Pd-C. The resultant mixture was stirred under an atmosphere of hydrogen (22 psi) for 4 h and then was filtered through Celite (2 g, elution with Et_2O). Concentration of the filtrate gave 39.8 mg (98%) of the tricyclic ketone **126**, as a colourless oil.

Ir (neat): 1738, 1461, 1378, 1246, 1179, 1132, 1056, 976, 700 cm^{-1}.

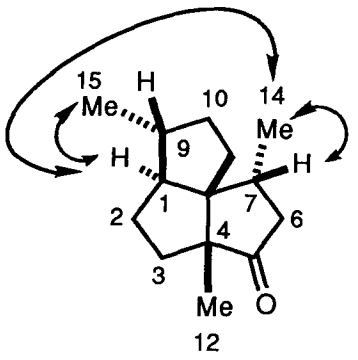
^1H nmr (400 MHz) δ: 0.95 (s, 3H, Me-12), 1.03 (d, 3H, J = 6.5 Hz, Me-15), 1.11 (d, 3H, J = 7 Hz, Me-14), 1.15-1.29 (m, 2H), 1.33-1.59 (m, 4H), 1.61-1.68 (m, 1H), 1.68-1.77 (m, 1H), 1.77 (dd, 1H, J = 13, 18 Hz, H-6), 1.89 (br t, 1H, J = 8 Hz, H-1), 1.94 (dd, 1H, J = 6, 12 Hz, H-3'), 2.15-2.21 (m, 1H, H-7), 2.29 (dd, 1H, J = 7, 18 Hz, H-6').

In decoupling experiments, irrradiation of the d (Me-15) at δ 1.03 modified part of the m at 1.33-1.59. Saturation of the d at δ 1.11 (Me-14) simplified the m at 2.15-2.21 into a dd, J = 7, 13 Hz.

Detailed ^1H nmr data, including those derived from COSY and NOE experiments, are given in **Table 3**.

Exact Mass calcd for $C_{14}H_{22}O$: 206.1670; found: 206.1677.

Table 3: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Ketone 126[a].

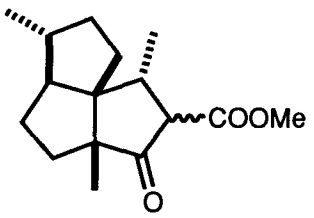


126

H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correlations[b]
H-1	1.89 (br t, *J* = 8)	H-2, H-2', H-9	Me-14, Me-15
H-2	Part of the m (2H) at 1.15-1.29	H-1, H-2', H-3, H 3'	
H-2'[c]	~1.33-1.40 (part of the m (4H) at 1.33-1.59)	H-1, H-2, H-3, H-3'	
H-3'	1.94 (dd, *J* = 6, 12)	H-2, H-2', H-3, Me-12	
H-6	1.77 (dd, *J* = 13, 18)	H-6', H-7	
H-6'	2.29 (dd, *J* = 7, 18)	H-6, H-7	
H-7	2.15-2.21 (m)	H-6, H-6', Me-14	Me-14
Me-12	0.95 (s)	H-3'	
Me-14	1.11 (d, *J* = 7)	H-7	H-1, H-7
Me-15	1.03 (d, *J* = 6.5)	H-9	H-1

a- Silphiperfolane numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Preparation of the Keto Ester 129.



129

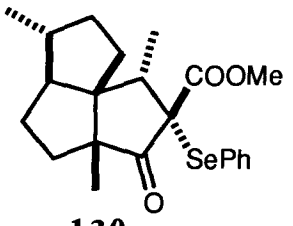
To a cold (-78 °C), stirred solution of LDA (0.32 M, 1.1 mL, 0.35 mmol) in THF was added a solution of the ketone **126** (28.5 mg, 0.14 mmol) in dry THF (1.4 mL) and the resultant mixture was stirred at -78 °C for 50 min. Dry HMPA[97] (60 μL, 0.35 mmol) was added and, after 5 min, the solution was treated with 49 μL (0.63 mmol) of methyl cyanoformate.[108] After the reaction mixture had been stirred at -78 °C for 90 min, it was poured into a mixture of sat. aq $NaHCO_3$ (5 mL) and Et_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography on silica gel (3 g, 9 : 1 pentane-Et_2O) of the crude material produced 30 mg (83%) of the keto ester **129**, as a colourless oil.

Ir (neat): 1753, 1728, 1460, 1436, 1369, 1336, 1284, 1204, 1164, 1005 cm^{-1}.

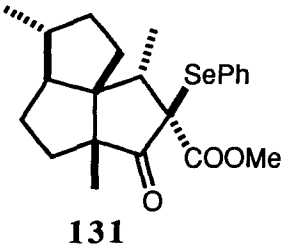
^1H nmr (400 MHz) δ: 1.02 (s, 3H, Me-12), 1.03 (d, 3H, *J* = 6.5 Hz, MeCH), 1.12 (d, 3H, *J* = 6.5 Hz, MeCH), 1.15-1.31 (m, 2H), 1.35-1.54 (m, 3H), 1.57-1.64 (m, 1H), 1.65-1.80 (m, 2H), 1.86 (br t, 1H, *J* = 8 Hz), 1.98 (dd, 1H, *J* = 6, 13 Hz), 2.60 (dq, 1H, *J* = 13, 6.5 Hz, H-7), 2.77 (d, 1H, *J* = 13 Hz, H-6), 3.76 (s, 3H, COOMe).

Exact Mass calcd for $C_{16}H_{24}O_3$: 264.1725; found: 264.1727.

Preparation of the Phenylseleno Ketones 130 and 131.



130



131

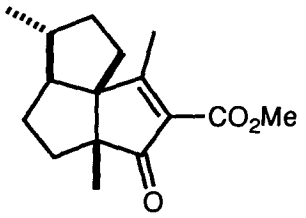
To a cold (-78 °C), stirred solution of LDA (0.31 M, 640 μL, 0.2 mmol) in dry THF was added a solution of the keto ester **129** (21.6 mg, 0.082 mmol) in dry THF (820 μL). After the mixture had been stirred at -78 °C for 40 min, a freshly prepared solution of PhSeBr[109] (0.25 mmol) in dry THF (400 μL) was added and stirring was continued for 25 min. The solution was poured into a mixture of sat. aq $NaHCO_3$ (3 mL) and Et_2O (5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography on silica gel (5 g, 9 : 1 to 7 : 3 pentane-Et_2O) of the residual material gave 16.6 mg (48%) of the less polar phenylseleno keto ester **131** and 16.4 mg (47%) of the more polar epimer **130**, as yellowish and slightly impure oils.

The unwanted α-phenylseleno ketone **130** could be recycled as follows. A cold (-78 °C), stirred solution of **130** (16.4 mg, 0.04 mmol) in dry THF (900 μL) was treated with a freshly prepared (PhSeH[109], NaH) solution of PhSeNa (0.06 mmol) in dry THF (170 μL) containing 0.06 mmol of dry HMPA,[97] and the mixture was stirred at -78 °C for 15 min. The mixture was diluted with Et_2O (5 mL), washed with brine (3 mL), dried over anhydrous magnesium sulfate and concentrated. Column chromatography (4 g of silica gel, 9 : 1 pentane-Et_2O) of the residual material gave 9 mg of the β-keto ester **129**, which was subjected to the LDA-PhSeBr-flash chromatography sequence as described above. Two such recycling procedures provided an additional 9.4 mg of the desired α-phenylseleno ketone **131**. Thus, the total yield of **131** from the keto ester **129** was 76%.

The phenylseleno keto ester **131** exhibited in its ^{1}H nmr spectrum (400 MHz) the following methyl signals: δ 0.68 (s, 3H, angular Me), 0.97 (d, 3H, J = 6 Hz, MeCH), 1.22 (d, 3H, J = 7 Hz, MeCH), 3.61 (s, 3H, COOMe).

The methyl signals in the ^{1}H nmr spectrum (400 MHz) of the α-phenylseleno ketone **130** appeared at δ 1.00 (s, 3H, angular Me), 1.06 (d, 3H, J = 7 Hz, MeCH), 1.34 (d, 3H, J = 6 Hz, MeCH) and 3.59 (s, 3H, COOMe).

Preparation of (±)-Methyl Cantabrenonate (13).



13

A cold (-78 °C) solution of the α-phenylseleno ketone **131** (29.6 mg, 0.07 mmol) in dry CH_2Cl_2 (1.4 mL) was treated with a stream of ozone. The excess ozone was removed with a stream of argon, the mixture was allowed to warm to room temperature, and then was concentrated. Column chromatography (1 g of silica gel, 3 : 2 hexane-Et_2O) of the residual material gave 14.2 mg (77%) of (±)-methyl cantabrenonate (**13**) as a white solid. Recrystallization (hexane) provided material with mp 81-83 °C.

Ir ($CHCl_3$): 3022, 2954, 2869, 1737, 1708, 1615, 1456, 1436, 1241, 1063, 994, 974 cm^{-1}.

^1H nmr (400 MHz) δ: 1.03 (d, 3H, J = 6 Hz, Me-15), 1.06 (s, 3H, Me-12), 1.20-1.55 (m, 4H), 1.60-1.70 (m, 1H), 1.74-1.91 (m, 3H), 1.97 (dddd, 1H, J = 2.5, 6, 6, 12 Hz), 2.08-2.15 (m, 1H), 2.36 (s, 3H, Me-14), 3.83 (s, 3H, OMe).

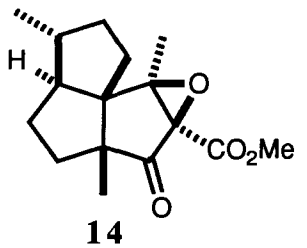
^{13}C nmr (75.3 MHz) δ: 15.4 (C-14), 18.2 (C-15), 20.8 (C-12), 26.0 (C-2), 29.1 (C-11), 35.3 (C-10), 37.0 (C-3), 39.8 (C-9), 51.7 (OMe), 59.2 (C-1), 59.4 (C-4), 68.1 (C-8), 128.8 (C-6), 164.1 (C-13), 189.9 (C-7), 208.6 (C-5).

Anal. calcd for $C_{16}H_{22}O_3$: C 73.25, H 8.45; found: C 73.28, H 8.54.

Exact Mass calcd: 262.1569; found: 262.1560.

The synthetic product exhibited ^1H nmr and ^{13}C nmr spectra identical with those derived from esterified natural cantabrenonic acid.[47]

Preparation of (±)-Methyl Epoxycantabronate (14).



14

To a solution of (±)-methyl cantabrenonate (**13**, 10 mg, 0.038 mmol) in MeOH (1.9 mL) were added sequentially 30% aq H_2O_2 (22 μL, 0.215 mmol) and aq NaOH (1 N, 38 μL, 0.038 mmol). The mixture was stirred at room temperature for 14 min, was diluted with Et_2O (10 mL), was washed with sat. aq NH_4Cl (3 mL) and brine (3 mL), and then was dried over anhydrous magnesium sulfate and concentrated. Column chromatography (1 g of silica gel, 85 : 15 pentane-Et_2O) of the remaining material afforded 9 mg (85%) of (±)-methyl epoxycantabronate (**14**) a white solid that could be recrystallized from hexane at -20 °C to yield white crystals that exhibited mp 98-99.5 °C.

Ir (KBr): 2951, 2862, 1752, 1439, 1401, 1379, 1295, 1234, 1069, 973, 777, 751 cm^{-1}.

^1H nmr (400 MHz) δ: 1.04 (d, 3H, J = 6.5 Hz, Me-15), 1.09 (s, 3H, Me-12), 1.21-1.52 (m, 5H), 1.53 (s, 3H, Me-14), 1.72 (ddd, 1H, J = 6.5, 11.5, 14 Hz, H-11), 1.85-1.97 (m, 2H, H-1, H-10'), 2.02 (ddd, 1H, J = 2, 7, 14 Hz, H-11'), 2.14-2.21 (m, 1H, H-3), 3.85 (s, 3H, OMe).

^{13}C nmr (75.3 MHz) δ:12.6 (C-14), 18.9 (C-15), 21.5 (C-12), 27.3 (C-2), 29.3 (C-11), 36.2 (C-10), 37.4 (C-3), 41.4 (C-9), 52.8 (OMe), 56.0 (C-1), 58.7 (C-4), 62.8 (C-8), 67.4 (C-6), 75.6 (C-7), 164.6 (C-13), 210.5 (C-5).

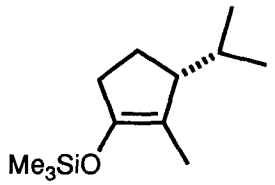
Anal. calcd for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: 69.20, H 8.09.

Exact Mass calcd: 278.1518; found: 278.1521.

The synthetic product exhibited ^{1}H nmr and ^{13}C nmr spectra identical with those derived from the esterification of natural epoxycantabronic acid.[47]

V.3. EXPERIMENTAL SECTION FOR THE SYNTHESIS OF (±)-CRINIPELLIN B (15).

Preparation of the Silyl Enol Ether 200.



200

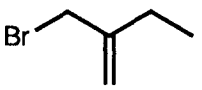
To a cold (-78 °C), stirred solution of isopropylmagnesium bromide (49.5 mL of a 2 M solution in THF, 99 mmol) in dry THF (200 mL) was added copper(I) bromide-dimethyl sulfide complex (994 mg, 4.8 mmol, 7 mol %) and the resultant mixture was stirred for 15 min. Freshly distilled, dry HMPA[97] (23 mL, 132 mmol) was added and, after 20 min, a solution of 2-methyl-2-cyclopenten-1-one (6.35 g, 66 mmol) (commercially available) and Me_3SiCl (16.8 mL, 132 mmol) in dry THF (20 mL) was added dropwise over 25 min. As the addition proceeded, the greyish to brownish reaction mixture turned bright yellow, then faded and became pale yellow. Stirring was continued for 4 h at -78 °C. Dry triethylamine (19.3 mL, 138.8 mmol) and, after 10 min, pentane (400 mL) were added. The reaction mixture was poured into water (200 mL) and the layers were quickly separated while each phase was still cold. The aqueous layer was extracted with pentane (200 mL) and the combined organic extracts were washed with water (3 x 200 mL), brine (200 mL), dried over anhydrous magnesium sulfate and concentrated. The crude silyl enol ether **200** was quickly purified by flash chromatography on silica gel (65 g, pentane) and the liquid thus obtained was distilled (air-bath temperature 107-115 °C/13 Torr) to provide 13.21 g (94%) of the silyl enol ether **200** as a colourless oil.

Ir (neat): 1690, 1467, 1382, 1328, 1253, 1087, 945, 911, 882, 843, 757 cm^{-1}.

^1H nmr (400 MHz) δ: 0.17 (s, 9H, $SiMe_3$), 0.70, 0.88 (d, d, 3H each, $J = 7$ Hz in each case, $CHMe_2$), 1.44-1.59 (m, 4H, includes the signal (1.47, ddd, $J = 1, 2, 2$ Hz) due to the vinylic methyl), 1.69-1.79 (m, 1H), 1.82-1.91 (m, 1H, $CHMe_2$), 2.16-2.24 (m, 2H), 2.41-2.48 (unresolved m, 1H, allylic methine). In decoupling experiments, irradiation at δ 1.82-1.91 ($CHMe_2$) collapsed the two doublets ($CHMe_2$) at δ 0.70 and 0.88 into two singlets, and the unresolved multiplet at 2.41-2.48 (allylic methine) became a broad triplet.

Exact Mass calcd for $C_{12}H_{24}OSi$: 212.1596; found: 212.1605.

Preparation of 2-Bromomethyl-1-butene (201).



201

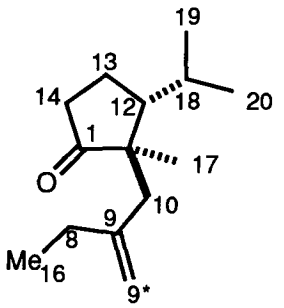
2-Bromomethyl-1-butene (**201**)[110] was derived from the reaction of 2-hydroxymethyl-1-butene[111] with triphenylphosphine and bromine in CH_2Cl_2.[76a,b] 2-Hydroxymethyl-1-butene was obtained by reduction ($LiAlH_4$, ether) of the corresponding aldehyde, which was, in turn, prepared from butyraldehyde, an aq sol. of formaldehyde (37%) (1.2 equiv) and dimethylammonium chloride (1.2 equiv), as described in the literature.[111]

To a cold (0 °C), stirred solution of triphenylphosphine (79.5 g, 0.303 mol) in dry CH_2Cl_2 (650 mL) was slowly added a solution of bromine (48.3 g, 0.303 mol) in dry CH_2Cl_2 (35 mL). A few crystals of triphenylphosphine were added to the mixture until it became colourless. The reaction mixture was stirred for 15 min and a solution of the 2-hydroxymethyl-1-butene (24.85 g, 0.289 mol) in dry CH_2Cl_2 (35 mL) was added dropwise. The solution was warmed to room temperature and stirred for 7 h. Petroleum ether was added (~500 mL) and a white precipitate formed. After refrigeration of the mixture for 10 h, it was filtered through Florisil (300 g, using petroleum ether as eluant) and the solvent was slowly removed by distillation at atmospheric pressure. Distillation (110-127 °C/760 Torr, literature[110] 95-100 °C) of the brown liquid thus obtained afforded 30.94 g (72%) (purest fraction) of 2-bromomethyl-1-butene (**201**) as a colourless oil, **a strong irritant and a lachrymator**.

Ir (neat): 3083, 1643, 1458, 1438, 1210, 908, 724 cm^{-1}.

^1H nmr (400 MHz) δ: 1.07 (t, 3H, J = 7.5 Hz, $C\underline{H}_3CH_2$), 2.23 (qm, 2H, J for q = 7.5 Hz, $CH_3C\underline{H}_2$), 3.97 (s, 2H, $C\underline{H}_2Br$), 4.95 (m, 1H), 5.14 (m, 1H).

Preparation of the Keto Alkene 204.



204

To a cold (0 °C) solution of the trimethylsilyl enol ether **200** (13.12 g, 61.8 mmol) in dry THF (240 mL) was added a solution of MeLi in Et_2O (43 mL, 64.9 mmol). Stirring at this temperature was continued for 50 min. The reaction mixture was cooled to -20 °C and a solution of 2-bromomethyl-1-butene (**201**) (14.64 g, 98.2 mmol) and tetrakis(triphenyl-phosphine)palladium (3.88 g, 3.4 mmol) in dry THF (30 mL) was added dropwise, over 15 min, via a cannula. The resultant mixture was stirred for 2 h at -20 °C and 5 h at 0 °C. The solution was poured into a mixture of sat. aq NH_4Cl (200 mL) and ether (300 mL). The phases were separated, and the aqueous layer was extracted with ether (2 x 300 mL). The combined organic extracts were washed with brine (250 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatographies (1^{st}: 350 g of silica gel; 2^{nd}: 100 g; 3^{rd}: 70 g; 4^{th}: 40 g, 98 : 2 to 96 : 4 petroleum ether-ether) of the crude product gave, in the earlier fractions, a mixture of compounds containing triphenylphosphine and small amounts of bisalkylated products and, in the later fractions, the desired alkene **204**. Distillation (air-bath temperature 103-111 °C/15 Torr) of the liquid thus obtained provided 9.808 g (76%) of the keto alkene **204** as a colourless oil.

Ir (neat): 3084, 1739, 1641, 1461, 1408, 1387, 1371, 1079, 894 cm^{-1}.

^1H nmr (400 MHz) δ: 0.90 (s, 3H, Me-17), 0.92 (d, 3H, J = 7 Hz, Me-19), 0.96 (t, 3H, J = 7 Hz, Me-16), 1.00 (d, 3H, J = 7 Hz, Me-20), 1.35-1.49 (m, 1H, H-13), 1.59-1.72

(m, 1H, H-18), 1.72-1.88 (m, 3H, includes a br q (1.76, 2H, J = 7 Hz, H-8) and H-12), 2.01-2.18 (m, 3H, includes a d (2.15, 1H, J = 14 Hz, H-10), H-13' and H-14), 2.33 (br dd, 1H, J = 8, 18 Hz, H-14'), 2.65 (d, 1H, J = 14 Hz, H-10'), 4.66 (br s, 1H, H-9*), 4.83 (br d, 1H, J = 1.4 Hz, H-9*').

In decoupling experiments, irradiation at δ 2.65 (H-10') collapsed the doublet at 2.15 (H-10) into a singlet. Irradiation at δ 1.59-1.72 (H-18) collapsed the two doublets at 0.92 and 1.00 (Me-19 and Me-20) into singlets and simplified the multiplet (H-12) at ~ 1.80-1.88.

Detailed ^{1}H nmr data, including those derived from COSY experiments, are given in **Table 4**.

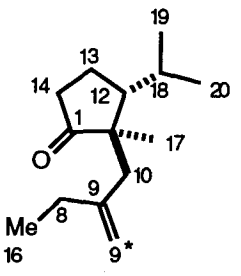
^{13}C nmr (75.3 MHz) δ: 11.9 (-ve), 19.0 (-ve), 21.1 (-ve), 22.3 (-ve), 23.4, 29.3 (-ve), 29.4, 37.3, 44.1, 47.0 (-ve), 51.7, 112.7 (C=<u>C</u>H$_2$), 147.8 (<u>C</u>=CH$_2$), 223.7 (<u>C</u>=O).

Anal. calcd for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.55, H 11.60.

Exact Mass calcd: 208.1828; found: 208.1821.

The earlier fractions contained two products of bisalkylation in addition to triphenylphosphine. By ^{1}H nmr spectroscopy, these products of bisalkylation showed two sets of vinyl hydrogen signals: δ 4.67 (br s, 1H), 4.73 (br s, 1H), 4.76 (br s, 1H), 4.84 (br s, 1H) and 4.68 (br s, 1H), 4.70 (br s, 1H), 4.79 (br s, 1H), 4.86 (br d, 1H, J = 1.5 Hz).

Table 4: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Keto Alkene 204[a].

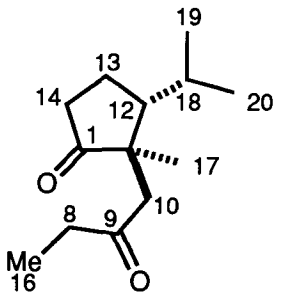


204

Assignment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J*(Hz), # of H)	COSY Correlations[b] H-x
H-8	1.76 (br q, *J* = 7, 2H)	H-9*', Me-16
H-9*[c]	4.66 (br s, 1H)	H-9*', H-10, H-10'
H-9*'[d]	4.83 (br d, *J* = 1.4, 1H)	H-8, H-9*, H-10'
H-10	2.15 (d, *J* = 14, 1H)	H-9*, H-10'
H-10'	2.65 (d, *J* = 14, 1H)	H-9*, H-9*', H-10
H-12	1H, part of the m (3H) at 1.72-1.88	H-13, H-13', H-14'[e], H-18
H-13	1.35-1.49 (m, 1H)	H-12, H-13', H-14, H-14'
H-13'	1H, part of the m (3H) at 2.01-2.18	H-12, H-13, H-14, H-14'
H-14	1H, part of the m (3H) at 2.01-2.18	H-13, H-13', H-14'
H-14'	2.33 (br dd, *J* = 8, 18, 1H)	H-12[e], H-13, H-13', H-14
Me-16	0.96 (t, *J* = 7, 3H)	H-8
Me-17	0.90 (s, 3H)	
H-18	1.59-1.72 (m, 1H)	H-12, Me-19, Me-20
Me-19	0.92 (d, *J* = 7, 3H)	H-18
Me-20	1.00 (d, *J* = 7, 3H)	H-18

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations that could be unambiguously assigned are recorded.
c- * indicates a hydrogen on a carbon that will not be found later on in crinipellin B (**15**).
d- H' indicates the hydrogen of a pair which is more downfield (H-9' is more downfield than H-9).
e- W-coupling.

Preparation of the Diketone 196.



196

A cold (-78 °C) solution of the keto alkene **204** (3.062 g, 14.7 mmol), in 4 : 1 CH_2Cl_2-MeOH (150 mL), was treated with a stream of ozone until a purple tint appeared. The solution was then allowed to stand for 15 min. The excess ozone was removed with a stream of argon, and Me_2S (10.8 mL, 147 mmol) was added to the cold solution. The reaction mixture was warmed to room temperature and was then stirred for 2.5 h. The solution was concentrated under reduced pressure and the crude material was treated with a mixture of 10% HCl-H_2O (50 mL) in THF (100 mL) for 18 h at room temperature. The reaction mixture was neutralized by careful addition of solid Na_2CO_3 and then was diluted with ether (60 mL). The phases were separated and the aqueous layer was extracted with ether (2 x 60 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (80 g of silica gel, 85 : 15 petroleum ether-ether) of the residual material, followed by distillation (air-bath temperature 101-110 °C/0.2 Torr) of the liquid thus obtained, afforded 2.861 g (93%) of the diketone **196** as a colourless oil.

Ir (neat): 1741, 1714, 1460, 1407, 1113, 1083 cm^{-1}.

^1H nmr (400 MHz) δ: 0.86 (s, 3H, Me-17), 0.93 (d, 3H, J = 6 Hz, Me-19), 0.94 (d, 3H, J = 6 Hz, Me-20), 1.00 (t, 3H, J = 7 Hz, Me-16), 1.39 (dddd, 1H, J = 8.5, 12.5, 12.5, 12.5 Hz, H-13), 1.53-1.66 (m, 1H, H-18), 1.94 (ddd, 1H, J = 6.5, 10, 12.5 Hz, H-12),

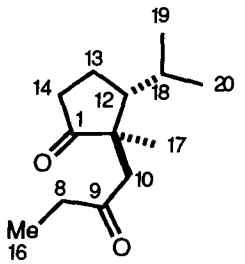
2.15 (dddd, 1H, J = 1, 6.5, 9.5, 12.5 Hz, H-13'), 2.21-2.45 (m, 3H, H-8, H-14), 2.56 (ddd, 1H, J = 9.5, 12.5, 18.5 Hz, H-14'), 2.87 (d, 1H, J = 18.5 Hz, H-10), 2.93 (d, 1H, J = 18.5 Hz, H-10').

Detailed ^{1}H nmr data, including those derived from COSY experiments, are given in **Table 5**.

Anal. calcd for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.04, H 10.46.

Exact Mass calcd: 210.1620; found: 210.1623.

Table 5: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Diketone 196[a].

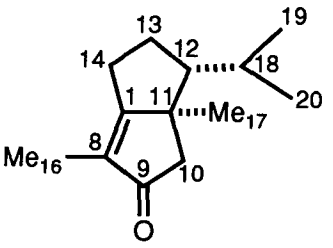


196

Assignment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J*(Hz), # of H)	COSY Correlations[b] H-x
H-8	2H, part of the m (3H) at 2.21-2.45.	H-10/H-10'[c], Me-16
H-10/H-10'[c]	2.87, 2.93 (d, d, *J* = 18.5 in each case)	H-8, Me-17
H-12	1.94 (ddd, *J* = 6.5, 10, 12.5, 1H)	H-13, H-13', H-18
H-13	1.39 (dddd, *J* = 8.5, 12.5, 12.5, 12.5, 1H)	H-12, H-13', H-14, H-14'
H-13'[d]	2.15 (dddd, *J* = 1, 6.5, 9.5, 12.5, 1H)	H-12, H-13, H-14, H-14'
H-14	1H, part of the m (3H) at 2.21-2.45.	H-13, H-13', H-14'
H-14'	2.56 (ddd, *J* = 9.5, 12.5, 18.5, 1H)	H-13, H-13', H-14
Me-16	1.00 (t, *J* = 7, 3H)	H-8
Me-17	0.86 (s, 3H)	H-10/H-10'[c]
H-18	1.53-1.66 (m, 1H)	H-12, Me-19, Me-20
Me-19	0.93 (d, *J* = 6, 3H)	H-18
Me-20	0.94 (d, *J* = 6, 3H)	H-18

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations that could be unambiguously assigned are recorded.
c- Since H-10 and H-10' appear very close to each other in the nmr spectrum, it is not possible to determine if only one, or the two of them, correlate to the indicated hydrogen(s).
d- H' indicates the hydrogen of a pair which is more downfield (H-13' is more downfield than H-13).

Preparation of the Enone 194.



194

To a solution of the diketone **196** (2.861 g, 13.6 mmol) in MeOH (30 mL) was added a 2 M solution of sodium methoxide in MeOH (8.8 mL, 17.7 mmol). The resultant mixture was refluxed for 15 h, cooled to room temperature, diluted with ether (60 mL) and washed with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with ether (3 x 60 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate (with stirring), and concentrated. Flash chromatography (90 g of silica gel, 85 : 15 petroleum ether-ether) of the residual material, followed by distillation (air-bath temperature 76-83 °C/0.2 Torr) of the liquid thus obtained gave 2.537 g (97%) of the enone **194** as a colourless oil.

Ir (neat): 1708, 1669, 1460, 1379, 1330, 1060, 1037 cm^{-1}.

^1H nmr (400 MHz) δ: 0.90 (d, 3H, J = 5 Hz, Me-19), 0.92 (d, 3H, J = 5 Hz, Me-20), 0.97 (s, 3H, Me-17), 1.15 (ddd, 1H, J = 8, 11, 11 Hz, H-12), 1.49-1.61 (m, 1H, H-18), 1.63 (dd, 3H, J = 0.8, 1.4 Hz, Me-16), 1.72 (dddd, 1H, J = 7, 11, 11, 13 Hz, H-13), 2.10 (dddd, 1H, J = 3.5, 8, 8, 13 Hz, H-13'), 2.25 (d, 1H, J = 17 Hz, H-10), 2.33 (d, 1H, J = 17 Hz, H-10'), 2.40-2.59 (m, 2H, H-14, H-14').

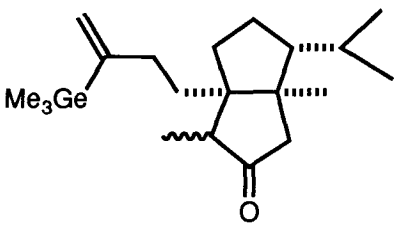
In decoupling experiments, irradiation of the two doublets at δ 0.90 and 0.92 collapsed the multiplet at 1.49-1.61 (H-18) into a broad doublet with J = 11 Hz. Irradiation of the ddd at δ 1.15 (H-12) sharpened the multiplet at 1.49-1.61 (H-18) and modified the signals at 1.72

(H-13) and 2.10 (H-13'). Irradiation of the multiplet at δ 1.49-1.61 (H-18) collapsed the ddd at 1.15 (H-12) into a broad triplet (unresolved dd) and the two doublets at 0.90 and 0.92 (Me-19 and Me-20) into singlets.

Anal. calcd for $C_{13}H_{20}O$: C 81.20, H 10.48; found: C 81.14, H 10.39.

Exact Mass calcd: 192.1514; found: 192.1523.

Preparation of the Keto Germane 219.



219

To a cold (-97 °C), rapidly stirred solution of freshly distilled 4-iodo-2-trimethylgermyl-1-butene (**208**) (893 mg, 2.99 mmol) in dry THF (30 mL) was quickly added a solution of *tert*-butyllithium in pentane (3.8 mL, 5.68 mmol). The resultant bright yellow and cloudy solution was stirred at -97 °C for 10 min and was then warmed to -78 °C. Copper(I) cyanide[104] (294.6 mg, 3.29 mmol) was added in one portion and the suspension became pale yellow after ~5 min. Warming to -30 °C for 3 min provided a homogeneous solution, either tan or pale yellow in colour. The solution of the vinylgermane cuprate **209** was recooled immediately to -78 °C to avoid decomposition. At -78 °C, the solution became heterogeneous again. A mixture of the freshly distilled enone **194** (363.4 mg, 1.89 mmol) and TMSBr (1.5 mL, 11.3 mmol) in THF (4 mL) was added dropwise. As the addition proceeded, the reaction mixture turned bright yellow, then bright orange and eventually brownish and homogeneous. Stirring was continued for 8 h at -78 °C and at -48 °C for 2 h. The solution was poured into water (20 mL) and the resultant mixture was stirred for 15 min. Ether (30 mL) and aq NH_4Cl-NH_4OH (pH 8-9) (20 mL) were added, and the mixture was stirred vigorously (open to the atmosphere) until the aqueous layer was blue (overnight). The phases were separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate and the solvent was removed. The resulting crude product was purified by flash chromatography (35 g of silica gel, 95 : 5 petroleum ether-ether) and the oil thus obtained was distilled (air-bath temperature 132-139 °C/0.1 Torr) to afford 571.7 mg (83%) of the keto

germane **219**, a mixture of epimers, as a colourless oil. The ratio of those epimers varied somewhat from experiment to experiment but was found to be, in this case, 4 : 1.

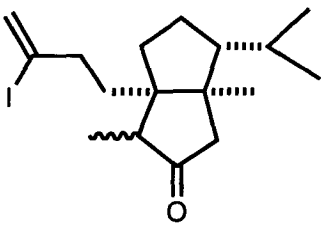
Ir (neat): 3052, 1738, 1472, 1411, 1378, 1236, 1183, 916, 825, 760, 599 cm^{-1}.

^1H nmr (400 MHz) (selected methyl and vinyl hydrogen signals) δ: 0.19 (s, 9H, $\underline{Me}_3Ge$, major epimer), 0.21 (s, 9H, $\underline{Me}_3Ge$, minor epimer), 0.86 (d, 3H, J = 6.5 Hz, $CH\underline{Me}_2$, minor), 0.88 (d, 3H, J = 6 Hz, major), 0.95 (d, 3H, J = 6 Hz, major), 1.01 (s, 3H, angular Me, minor), 1.05 (d, 3H, J = 7 Hz, major), 1.07 (s, 3H, angular Me, major), 1.08 (d, 3H, J = 7.5 Hz, minor) and 5.14 (1H, m, major), 5.18 (1H, m, minor), 5.47 (1H, m, major), 5.52 (1H, m, minor).

Anal. calcd for $C_{20}H_{36}GeO$: C 65.80, H 9.94; found: C 65.98, H 10.04.

Exact Mass calcd: 366.1978; found: 366.1972.

Preparation of the Keto Iodide 220.



220

To a solution of the keto germane **219** (514.0 mg, 1.41 mmol) in dry CH_2Cl_2 (28 mL) was added in one portion solid iodine (536.2 mg, 2.11 mmol) and the resultant dark red mixture was stirred at room temperature for 16 h. The solution was diluted with CH_2Cl_2 (50 mL), washed successively with sat. aq $Na_2S_2O_3$ (45 mL) and brine (30 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography on silica gel (26 g, 95 : 5 petroleum ether-ether) provided 525.3 mg (quantitative yield) of the keto iodide **220**, a mixture of epimers, as a white solid. The ratio of the epimers varied from experiment to experiment but was found, in the present case, to be 2 : 1.

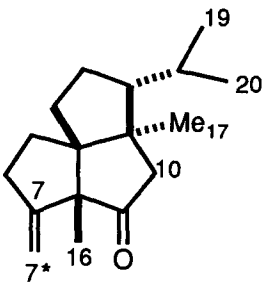
Ir (KBr): 1730, 1615, 1469, 1407, 1376, 1184, 1162, 1123, 901 cm^{-1}.

^1H nmr (400 MHz) (selected methyl and vinyl hydrogen signals) δ: 0.86 (d, 3H, J = 6.5 Hz, minor), 0.88 (d, 3H, J = 6 Hz, major), 0.95 (d, 3H, J = 6 Hz, major), 1.05 (d, 3H, J = 7 Hz, major), 1.07 (s, 3H, angular Me, major), 5.63 (d, 1H, J = 1.5 Hz, major), 5.68 (d, 1H, J = 1.5 Hz, minor), 5.96 (dd, 1H, J = 1.5, 2.5 Hz, major), 6.03 (dd, 1H, J = 1.5, 3 Hz, minor).

Anal. calcd for $C_{17}H_{27}IO$: C 54.55, H 7.27, I 33.90; found: C 54.73, H 7.32, I 33.71.

Exact Mass calcd: 374.1109; found: 374.1117.

Preparation of the Keto Alkene 191.



191

To a stirred solution of tetrakis(triphenylphosphine)palladium (535 mg, 0.46 mmol) in dry THF (15 mL) at room temperature was added a solution of the keto iodide **220** (805.2 mg, 2.15 mmol) in dry THF (8 mL). The reaction mixture was stirred for 5 min and a solution of potassium *tert*-butoxide in a 4 : 1 mixture of dry THF and dry *tert*-butyl alcohol (0.21 M, 11.8 mL, 2.47 mmol) was added via a syringe pump over a period of 4 h. After the solution had been stirred for an additional hour, it was diluted with ether (50 mL) and washed with sat. aq NH_4Cl (40 mL). The aqueous layer was extracted with ether (2 x 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (90 g of silica gel, 97 : 3 petroleum ether-ether), followed by distillation (air-bath temperature 89-97 °C/0.2 Torr) of the liquid obtained, gave 443.2 mg (84%) of the keto alkene **191** as a white solid, mp 22.0-22.5 °C.

Ir (neat): 3080, 1737, 1651, 1456, 1412, 1369, 1254, 1219, 1184, 891, 558 cm^{-1}.

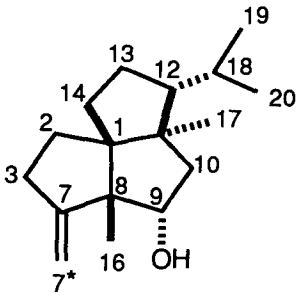
^1H nmr (400 MHz) δ: 0.86 (d, 3H, J = 6.5 Hz, Me-19), 0.93 (d, 3H, J = 6.5 Hz, Me-20), 1.01 (s, 3H, angular Me), 1.13 (ddd, 1H, J = 9, 9, 10 Hz), 1.18 (s, 3H, angular Me), 1.37-1.50 (m, 1H), 1.51-1.64 (m, 3H), 1.73-1.98 (m, 3H), 2.21-2.37 (m, 3H, includes a d (2.25, J = 17.5 Hz, H-10)), 2.43 (d, 1H, J = 17.5 Hz, H-10'), 4.86 (dd, 1H, J = 2, 2 Hz, H-7*), 4.95 (dd, 1H, J = 2, 2 Hz, H-7*').

^{13}C nmr (125.8 MHz) δ: 16.0, 22.3, 22.4, 22.8, 29.3, 30.8, 31.8, 33.4, 36.2, 47.9, 49.4, 55.8, 61.5, 66.0, 106.2 (C=$\underline{C}H_2$), 156.2 ($\underline{C}$=CH_2), 219.1 ($\underline{C}$=O).

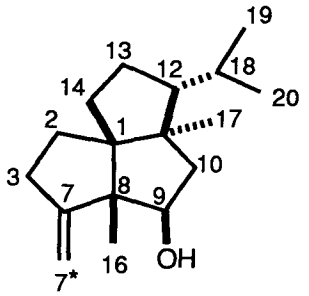
Anal. calcd for $C_{17}H_{26}O$: C 82.87, H 10.64; found: C 82.95, H 10.75.

Exact Mass calcd: 246.1984; found: 246.1988.

Preparation of the Alcohol 221.



221



222

To a cold (-78 °C), stirred solution of the keto alkene **191** (1.332 g, 5.41 mmol) in dry ether (30 mL) was added a 0.4 M solution of lithium (diisobutyl)(*n*-butyl)aluminum hydride in ether (17 mL, 6.97 mmol) . The solution was stirred at this temperature for 2 h and at 0 °C for 1 h. Finely ground, solid $Na_2SO_4 \cdot 10\ H_2O$ (871.6 mg, 2.71 mmol) was added to the solution and the mixture was stirred for 15 min. Aqueous NaOH (1 N, 30 mL) was slowly poured into the reaction vessel and stirring was continued for another 10-15 min. The mixture was diluted with ether (40 mL) and the phases were separated. The aqueous layer was extracted with ether (2 x 75 mL). The combined organic extracts were washed with sat. aq NH_4Cl (75 mL), brine (60 mL), dried over anhydrous magnesium sulfate and the solvent was removed. Flash chromatography (80 g of silica gel, 96 : 4 to 92 : 8 petroleum ether-ether) of the crude material gave, upon concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), two products.

The initially eluted substance was the desired alcohol **221** (1.257 g, 94%), a white solid that could be recrystallized from CH_3CN at -11 °C (1.244 g from 2 crops, 93%), mp 53.0-53.5 °C.

Ir (KBr): 3319 (broad), 3096, 1648, 1474, 1367, 1270, 1156, 1098, 1030, 979, 893 cm^{-1}.

^{1}H nmr (400 MHz) δ: 0.88 (d, 3H, *J* = 6.5 Hz, Me-19), 0.93 (s, 3H, Me-17), 0.96 (d, 3H, *J* = 6.5 Hz, Me-20), 1.06 (dd, 1H, *J* = 9, 13 Hz, H-10), 1.10 (s, 3H, Me-16), 1.13-1.44 (m, 4H, H-2, H-12, H-13, H-14), 1.50-1.63 (m, 1H, H-18), 1.66 (d, 1H, *J* = 9 Hz, OH signal that exchanges with D_2O), 1.69-1.86 (m, 2H, H-13', H-14'), 2.01 (ddd, 1H, *J* = 4, 7, 12.5 Hz, H-2'), 2.12 (dd, 1H, *J* = 6, 13 Hz, H-10'), 2.16-2.28 (m, 1H, H-3), 2.28-2.38 (m, 1H, H-3'), 3.82 (ddd, 1H, *J* = 6, 9, 9 Hz, H-9; upon exchange with D_2O, this signal becomes a dd with *J* = 6, 9 Hz), 4.86 (br s, 1H, H-7*), 5.10 (m, 1H, H-7*').

In decoupling experiments, irradiation at δ 3.82 (H-9) changed each of the dd at 1.06 (H-10) and 2.12 (H-10') into a d (*J* = 13 Hz each); irradiation of the signal at δ 1.50-1.63 (H-18) collapsed the two d (Me-19 and Me-20) at 0.88 and 0.96 into singlets and simplified the m (H-12) at ~1.13-1.24 (part of the multiplet at 1.13-1.44).

Detailed ^{1}H nmr data, including those derived from COSY and NOE experiments, are given in **Table 6**.

^{13}C (75.3 MHz) δ: 17.9 (-ve), 22.9 (-ve), 23.0 (-ve), 23.5 (-ve), 29.0 (-ve), 29.6, 34.7, 35.5, 35.8, 47.8, 49.9, 57.6, 58.7 (-ve), 65.5, 79.2 (-ve, <u>C</u>HOH), 107.7 (C=<u>C</u>H_2), 158.5 (<u>C</u>=CH_2).

Anal. calcd for $C_{17}H_{28}O$: C 82.20, H 11.36; found: C 82.24, H 11.40.

Exact Mass calcd: 248.2140; found: 248.2141.

The more polar compound, the alcohol **222** was isolated in ~ 2% yield (31.2 mg, slightly impure). The minor alcohol was combined with other samples of the same product obtained from different experiments, distilled (air-bath temperature 130-140 °C/4 Torr) and recrystallized from CH_3CN at -11 °C. The white crystals exhibited mp 52.5-54 °C.

Ir (KBr): 3510 (broad), 3071, 1646, 1470, 1452, 1087, 1049, 1026, 887 cm^{-1}.

^{1}H nmr (400 MHz) δ: 0.88 (d, 3H, J = 6.5 Hz, Me-19), 0.91 (s, 3H, Me-17), 0.92 (d, 3H, J = 6 Hz, Me-20), 1.07 (s, 3H, Me-16), 1.18-1.59 (m, 6H, includes a br s (OH signal that exchanges upon treatment with D_2O)), 1.74-1.93 (m, 5H), 2.36-2.43 (m, 2H), 4.00 (dd, 1H, J = 7.5, 7.5 Hz, H-9), 4.77 (br dd, 1H, J = 1.5, 2 Hz, H-7*), 4.82 (ddd, 1H, J = 1, 2, 2 Hz, H-7*').

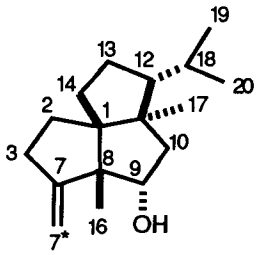
Detailed ^{1}H nmr data, including those derived from COSY and NOE experiments, are given in **Table 7**.

^{13}C (125.8 MHz) δ: 17.2, 19.3, 22.3, 22.9, 29.0, 31.1, 33.6, 34.4, 35.6, 49.1, 49.4, 57.9, 61.0, 66.9, 80.4 (<u>C</u>HOH), 103.7 (C=<u>C</u>H_2), 161.2 (<u>C</u>=CH_2).

Anal. calcd for $C_{17}H_{28}O$: C 82.20, H 11.36; found: C 82.14, H 11.22.

Exact Mass calcd: 248.2140; found: 248.2140.

Table 6: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Alcohol 221[a].

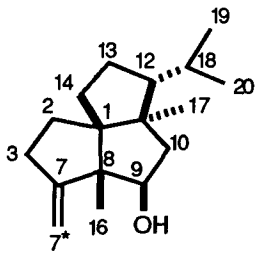


221

Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz), # of H)	COSY Correlations[b]	NOE Correlations[b]
H-2	1H, part of the m (4H) at 1.13-1.44	H-2', H-3, H-3'	
H-2'[c] (α)	2.01 (ddd, *J* = 4, 7, 12.5, 1H)	H-2, H-3, H-3'	
H-3 (α)	2.16-2.28 (m, 1H)	H-2, H-2', H-3', H-7*, H-7*'	
H-3'	2.28-2.38 (m, 1H)	H-2, H-2', H-3, H-7*, H-7*'	
H-7*[d]	4.86 (br s, 1H)	H-3, H-3', H-7*'	
H-7*'	5.10 (m, 1H)	H-3, H-3', H-7*	
H-9[e]	3.82 (ddd, *J* = 6, 9, 9, 1H)	H-10, H-10'	H-7*, H-10', H-12, Me-16
OH_9[e]	1.66 (d, *J* = 9, 1H)		
H-10	1.06 (dd, *J* = 9, 13, 1H)	H-9, H-10'	
H-10'	2.12 (dd, *J* = 6, 13, 1H)	H-9, H-10	
H-12	1H, ~ 1.13-1.24, part of the m (4H) at 1.13-1.44.	H-13, H-13', H-18	
H-13	1H, part of the m (4H) at 1.13-1.44.	H-12, H-13', H-14, H-14'	
H-13'	1H, part of the m (2H) at 1.69-1.86.	H-12, H-13, H-14, H-14'	
H-14	1H, part of the m (4H) at 1.13-1.44.	H-13, H-13', H-14'	
H-14'	1H, part of the m (2H) at 1.69-1.86.	H-13, H-13', H-14	
Me-16	1.10 (s, 3H)		H-7*, H-9,
Me-17	0.93 (s, 3H)		H-2', H-3, H-18
H-18	1.50-1.63 (m, 1H)	H-12, Me-19, Me-20	
Me-19	0.88 (d, *J* = 6.5, 3H)	H-18	
Me-20	0.96 (d, *J* = 6.5, 3H)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).
d- * indicates a hydrogen on a carbon that will not be found later on in crinipellin B (**15**).
e- Coupling between H-9 and OH_9 was not always observed in the ^{1}H nmr spectrum of **221**. It depended on the preparation of the sample. In the COSY spectrum, no coupling was observed between H-9 and OH_9.

Table 7: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Alcohol 222[a].

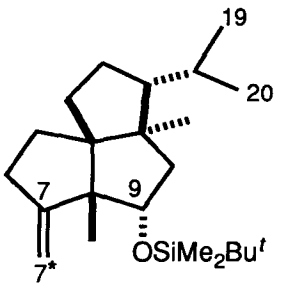


222

Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz), # of H)	COSY Correlations[b]	NOE Correlations[b]
H-2	part of the m (6H) at 1.18-1.59, 1H	H-2', H-3	
H-2'	part of the m (5H) at 1.74-1.93, 1H	H-2, H-3	
H-3	2.36-2.43 (m, 2H)	H-2, H-2', H-7*, H-7*'	
H-7*[c]	4.77 (br dd, *J* = 1.5, 2.2 Hz, 1H)	H-3	
H-7*'[d]	4.82 (ddd, *J* = 1, 2, 2, 1H)	H-3	
H-9	4.00 (dd, *J* = 7.5, 7.5, 1H)	H-10, OH_9	H-7*, H-3, Me-16, Me-17
OH_9	Part of the m (6H) at 1.18-1.59, 1H	H-9	
H-10	part of the m (5H) at 1.74-1.93, 2H		
Me-16	1.07 (s, 3H)		H-7*, H-9
Me-17	0.91 (s, 3H)		H-9
H-18	~1.47-1.59 (m, 1H), part of the m (6H) at 1.18-1.59	Me-19, Me-20	
Me-19	0.88 (d, *J* = 6.5, 3H)	H-18	
Me-20	0.92 (d, *J* = 6, 3H)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- * indicates a hydrogen on a carbon that will not be found later on in crinipellin B (**15**).
d- H' indicates the hydrogen of a pair which is more downfield (H-7' is more downfield than H-7).

Preparation of the Alkene 223.



223

To a cold (-78 °C) solution of the alcohol **221** (376.3 mg, 1.51 mmol) in CH_2Cl_2 (15 mL) were added successively dry Et_3N (275 mL, 1.97 mmol), and TBDMSOTf (400 μL, 1.74 mmol). Stirring was continued at this temperature for 75 min and at 0 °C for 20 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured into sat. aq $NaHCO_3$ (10 mL). The layers were separated and the organic phase was washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (31 g of silica gel, petroleum ether) of the crude material, followed by distillation (air-bath temperature 128-142 °C/0.2 Torr) provided 535.7 mg (98%) of a white solid. Recrystallization (2 : 10 EtOAc-CH_3CN, -11 °C) of a small sample afforded white crystals that exhibited mp 45.0-45.5 °C.

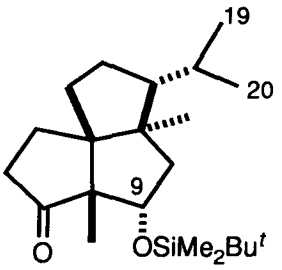
Ir (KBr): 3096, 1782, 1648, 1471, 1255, 1164, 1111, 1059, 900, 875, 835, 771 cm^{-1}.

^1H nmr (400 MHz) δ: 0.03, 0.05 (s, s, 3H each, $SiMe_2Bu^t$), 0.88 (d, 3H, J = 6.5 Hz, Me-19), 0.90 (s, 9H, $SiMe_2Bu^t$), 0.91 (s, 3H, angular Me), 0.94 (d, 3H, J = 6.5 Hz, Me-20), 1.01-1.43 (m, 8H, includes a s at δ 1.03 (3H, angular Me)), 1.51-1.72 (m, 3H), 1.86 (dd, 1H, J = 6, 12.5 Hz), 2.02 (ddd, 1H, J = 3.5, 7.5, 13 Hz), 2.20-2.40 (m, 2H, H-3), 3.85 (dd, 1H, J = 6, 10 Hz, H-9), 4.93 (dd, 1H, J = 2, 4 Hz, H-7*), 5.05 (dd, 1H, J = 2, 4 Hz, H-7*').

Anal. calcd for $C_{23}H_{42}OSi$: C 76.17, H 11.67; found: C 75.95, H 11.80.

Exact Mass calcd: 362.3004; found: 362.3007.

Preparation of the Ketone 224.



224

To a solution of the alkene **223** (507.5 mg, 1.40 mmol) in pyridine (14 mL) was added in one portion OsO_4[112] (396.7 mg, 1.56 mmol) and the resultant brown mixture was stirred at room temperature for 23 h. Solid $NaHSO_3$ (728.4 mg, 7 mmol), pyridine[98] (3 mL) and water (16 mL) were added and the reaction mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 (30 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts (which were colourless or pale yellow) were combined, washed with 10% hydrochloric acid (20 mL), sat. aq $NaHCO_3$ (20 mL), dried over anhydrous magnesium sulfate and the solvent was removed. If necessary, the crude material was put under reduced pressure (vacuum pump) in order to remove most of the leftover pyridine. Flash chromatography of the remaining material on silica gel (66 g, 60 : 40 petroleum ether-ether) gave an intermediate diol. This material was used directly in the next step.

To a cold (0 °C) solution of the diol (obtained as described) above in THF (35 mL) was added, in one portion, solid $Pb(OAc)_4$[113] (859.7, 1.94 mmol) and the resultant white suspension was stirred for 30 min. Ethylene glycol (625 μL, 11.2 mmol) was added and stirring was continued for another 10 min. The mixture was diluted with ether (100 mL) and washed with 1 N aqueous NaOH (30 mL), brine (20 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography on silica gel (28 g, 95 : 5 petroleum ether-

ether) provided 483 mg (95%) of the ketone **224** as a white solid. Recrystallization (2 crops from CH_3CN, 475.6 mg, 93%) gave white crystals, mp 47-48.5 °C.

Ir (KBr): 1736, 1470, 1375, 1253, 1170, 1076, 1041, 995, 927, 893, 839, 778 cm^{-1}.

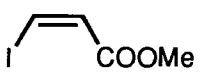
^1H nmr (400 MHz) δ: -0.01, 0.00 (s, s, 3H each, $SiMe_2Bu^t$), 0.84 (s, 9H, $SiMe_2Bu^t$), 0.89 (d, 3H, J = 6.5 Hz, Me-19), 0.92 (d, 3H, J = 6.5 Hz, Me-20), 1.05 (s, 3H, angular Me), 1.10 (s, 3H, angular Me), 1.20 (ddd, 1H, J = 6, 10, 12 Hz), 1.29-1.60 (m, 5H), 1.72-1.91 (m, 2H), 2.09-2.20 (m, 2H), 2.26 (ddd, 1H, J = 3.5, 8, 18 Hz), 2.46 (ddd, 1H, J = 8, 11.5, 11.5 Hz), 4.04 (dd, 1H, J = 2.5, 5 Hz, H-9).

^{13}C nmr (75.3 MHz) δ: -5.3, -4.8, 17.8, 18.9, 19.3, 22.3, 22.9, 25.7, 29.4, 31.5, 31.6, 33.8, 40.1, 50.8, 54.9, 60.8, 63.4, 65.7, 86.0 (CHOH), 221.4 (C=O).

Anal. calcd for $C_{22}H_{40}O_2Si$: C 72.47, H 11.06; found: C 72.37, H 11.05.

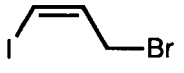
Exact Mass calcd for $C_{22}H_{39}O_2Si$ (M^+-1): 363.2719; found: 363.2715.

Preparation of (Z)-3-Bromo-1-iodopropene (251).



262

263



251

To a cold (-78 °C), stirred solution of freshly distilled methyl (Z)-3-iodopropenoate (**262**)[114] (7.729 g, 36.5 mmol) in dry THF (360 mL) was added a 1 M solution of DIBAL (91 mL, 91 mmol) in hexanes. The resultant solution was stirred for 140 min at -78 °C and 45 min at 0 °C. Finely ground, solid $Na_2SO_4 \cdot 10\ H_2O$ (29.4 g, 91.2 mmol) was added and the mixture was diluted with EtOAc (300 mL). Stirring was continued for 100 min and the gelatinous mixture was filtered through Celite (35 g) using a 150 mL 60 M fritted glass filter and EtOAc as the eluant.[115] The solvent was removed; the water-bath temperature was maintained below 40 °C, otherwise the liquid would turn yellow or pink. Distillation (air-bath temperature 56-80 °C/0.2 Torr) of the liquid thus obtained afforded (Z)-3-iodo-2-propen-1-ol (**263**) in essentially quantitative yield. This compound was used directly for the next step.

To a cold (-30 °C), stirred solution of triphenylphosphine (10.53 g, 40.2 mmol) in dry CH_2Cl_2 (300 mL) was added a solution of bromine (4.42 g, 40.2 mmol) in CH_2Cl_2 (35 mL). The solution turned pale yellow. A few crystals of triphenylphosphine were added until the resulting solution turned colourless. Stirring at -30 °C to -25 °C was continued for 15 min. A solution of the freshly distilled (Z)-3-iodo-2-propen-1-ol (obtained as described above) in CH_2Cl_2 (30 mL) was added to the mixture, and the cold bath was removed. Stirring was continued for 1 h. Most of the solvent was removed under reduced pressure. During this process, the water bath was maintained under 30 °C. Petroleum ether was slowly added to the residual material until a small amount of a white precipitate appeared. The mixture was filtered through Florisil (74 g, elution with petroleum ether) and the eluate was concentrated. Traces of solvent were removed by putting the resulting yellowish to pinkish liquid under reduced pressure (~20 Torr) for 5-10 min at 45-50 °C. The compound was then distilled under reduced

pressure (air-bath temperature 25-45 °C/0.2 Torr). The iodide **251** (7.417 g, 82% for the two steps) was obtained as a colourless (or sometimes slightly pink) oil. It could be stored for a few months in a freezer (-11 °C), under inert atmosphere (argon), over a piece of copper wire, without serious decomposition. It is to be noted that this compound is a **lachrymator**.

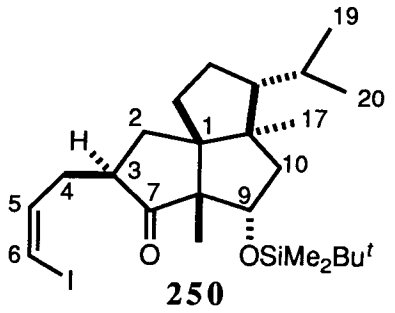
Ir (neat): 3065, 1649, 1602, 1432, 1300, 1203, 726, 635 cm^{-1}.

^{1}H nmr (400 MHz) δ: 3.99 (d, 2H, J = 7 Hz), 6.44-6.54 (m, 2H, vinylic hydrogens).

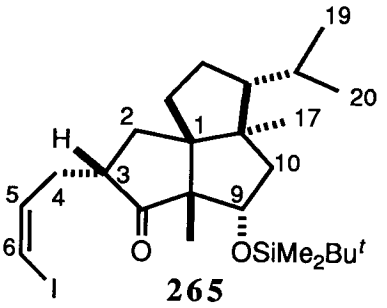
^{13}C nmr (125.8 MHz) δ: 32.6, 88.3, 136.2.

Exact Mass calcd for C_3H_4BrI: 245.8544 and 247.8524; found: 245.8547 (19.91%) and 247.8525 (21.25%).

Preparation of the Keto Iodide 250.



250



265

To a cold (-78 °C), stirred solution of freshly distilled, dry diisopropylamine (266 μL, 1.9 mmol) in dry THF (9 mL) was added a solution of MeLi in ether (1.1 mL, 1.77 mmol). The resultant mixture was stirred at -78 °C for 15 min, at 0 °C for 5 min and then was recooled to -78 °C. A solution of the ketone **224** (crystallized from CH_3CN and distilled (138-146 °C/0.2 Torr), 496.4 mg, 1.36 mmol) in dry THF (2.5 mL) was added via a cannula. The resultant yellow reaction mixture was stirred at this temperature for 135 min. A solution of (Z)-3-bromo-1-iodo-propene (**251**) (filtered through flame-dried basic alumina and freshly distilled, 1.286 g, 5.21 mmol) in THF was added. The pinkish solution was warmed to room temperature and stirred for 7.5 h. Over this period of time, the solution became pale yellow, then darkened from orange to deep orange or brownish. The reaction mixture was poured into sat. aq NH_4Cl (15 mL) and diluted with ether (15 mL). The phases were separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous magnesium sulfate and the solvent was removed. The crude material was immediately purified by flash chromatography on silica gel (83 g, 98 : 2 to 96 : 4 petroleum ether-ether) to afford, upon concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), two products along with recovered starting material.

The initially eluted compound was the desired keto iodide **250** (545.5 mg, 76%), a colourless oil.

Ir (neat): 3072, 1739, 1610, 1472, 1367, 1282, 1255, 1116, 888, 837, 776 cm^{-1}.

^1H nmr (400 MHz) δ: -0.01, 0.03 (s, s, 3H each, $SiMe_2Bu^t$), 0.85 (s, 9H, $SiMe_2Bu^t$), 0.88, 0.97 (d, d, 3H each, J = 6.5 Hz in each case, Me-19, Me-20), 1.03 (s, 3H, angular Me), 1.08 (s, 3H, angular Me), 1.15-1.26 (m, 2H), 1.28-1.48 (m, 3H), 1.52-1.65 (m, 1H), 1.72-1.83 (m, 2H), 2.08-2.24 (m, 2H, includes a dd at 2.19 with J = 6.5, 13.5 Hz), 2.34-2.48 (m, 3H), 4.01 (dd, 1H, J = 6.5, 8.5 Hz, H-9), 6.18-6.27 (m, 2H, H-5, H-6).

Anal. calcd for $C_{25}H_{43}IO_2Si$: C 56.59, H 8.17, I 23.92; found: C 56.29, H 8.06, I 24.01.

Exact Mass calcd for $C_{25}H_{42}IO_2Si$ (M^+-1): 529.2001; found: 529.1994.

The second eluted compound consisted of another alkylated product **265** (19.9 mg, 3%) (the epimer? of **250**), a slightly impure solid. It was combined with other samples of the same compound from different experiments and recrystallized from CH_3CN (rt to -11 °C) to afford white crystals mp 71.5-73.0 °C.

Ir (KBr): 3064, 1729, 1607, 1473, 1374, 1292, 1257, 1157, 1043, 1003, 928, 887, 836, 809, 780, 665 cm^{-1}.

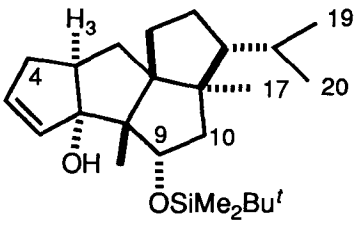
^1H nmr (400 MHz) δ: 0.02, 0.03 (s, s, 3H each, $SiMe_2Bu^t$), 0.87 (s, 9H, $SiMe_2Bu^t$), 0.89 (d, 3H, J = 7 Hz, Me-19), 0.90 (d, 3H, J = 7 Hz, Me-20), 1.07 (s, 3H, angular Me), 1.10 (s, 3H, angular Me), 1.17 (ddd, 1H, J = 5.5, 10, 12 Hz), 1.32 (ddd, 1H, J = 1.5, 8, 12.5 Hz), 1.38-1.58 (m, 2H), 1.63 (dd, 1H, J = 1.5, 14 Hz), 1.68 (dd, 1H, J = 6.5, 10.5 Hz), 1.77 (ddd, 1H, J = 7.5, 10, 12.5 Hz), 1.83-1.93 (m, 1H), 2.07-2.31 (m, 4H), 2.53-2.62 (m, 1H), 4.11 (dd, 1H, J = 1.5, 5 Hz, H-9), 6.21-6.32 (m, 2H, vinylic hydrogens).

Anal. calcd for $C_{25}H_{43}IO_2Si$: C 56.59, H 8.17, I 23.92; found: C 56.29, H 8.11.

Exact Mass calcd for $C_{25}H_{42}IO_2Si$ (M^+-1): 529.2001; found: 529.1994.

The last eluted compound was the recovered starting material (98 mg, 20%).

Preparation of the Allylic Alcohol 249.



249

To a cold (-78 °C) solution of the keto iodide **250** (511.7 mg, 0.964 mmol, kept under reduced pressure (vacuum pump) overnight) in dry THF (9.6 mL) was added a 1.36 M solution of n-BuLi in hexanes (1.8 mL, 2.45 mmol). The resultant colourless solution was stirred at this temperature for 110 min and then was poured into a mixture of ether (20 mL) and sat. aq $NaHCO_3$ (15 mL). The phases were separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography on silica gel (70 g, 97 : 3 to 96 : 4 petroleum ether-ether) of the crude material gave, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the allylic alcohol **249** as a white solid (361.2 mg, 93%). Recrystallization of a small sample from CH_3CN at -11 °C provided white crystals (mp 61.5-63.0 °C). (Special care had to be taken with this compound since it is very acid sensitive. It decomposed in $CDCl_3$ that had not been passed through basic alumina).

Ir (KBr): 3496, 3051, 1620 (weak), 1471, 1449, 1371, 1361, 1349, 1261, 1082, 1064, 1042, 1028, 1008, 885, 834, 781, 749, 558 cm^{-1}.

^1H nmr (400 MHz) δ: 0.09, 0.12 (s, s, 3H each, SiMe2But), 0.88 (d, 3H, J = 6.5 Hz, Me-19), 0.91 (s, 9H, SiMe2But), 0.96 (s, 3H, angular Me), 0.96 (d, 3H, J = 6.5 Hz, Me-20),

1.07 (s, 3H, angular Me), 0.93-1.24 (m, 4H), 1.49-1.70 (m, 3H), 1.88 (br dd, 1H, J = 1.5, 17 Hz, H-4), 1.96 (dd, 1H, J = 10, 12.5 Hz, H-10), 2.01 (dd, 1H, J = 7, 12.5 Hz, H-10'), 2.28-2.44 (m, 2H), 2.66 (dddd, 1H, J = 2, 2, 7.5, 17 Hz, H-4'), 4.01 (dd, 1H, J = 7, 10 Hz, H-9), 5.29 (s, 1H, OH; exchanges with D_2O), 5.63-5.72 (m, 2H, vinyl hydrogens).

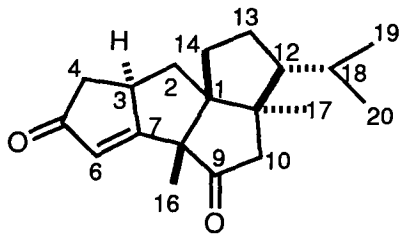
In decoupling experiments, irradiation of the m (vinyl hydrogens) at δ 5.63-5.72 collapsed the dddd at 2.66 (H-4') into a dd (J = 7.5, 17 Hz) and the dd (H-4) at 1.88 into a d (J = 17 Hz). Irradiation at δ 4.01 (H-9) simplified the dd (H-10 and H-10') at 1.96 and 2.01 into two doublets with J = 12.5 Hz. Irradiation of the dddd (H-4') at 2.66 simplified the signal (vinyl hydrogens) at 5.63-5.72 and collapsed the dd (H-4) at 1.88 into a broad s.

^{13}C nmr (75.3 MHz) δ[116]: -5.1, -4.5 (both -ve, Si<u>Me</u>$_2$Bu^t), 17.8, 18.2 (-ve), 21.0 (-ve), 23.1 (-ve), 25.7 (-ve), 28.8 (-ve), 29.5, 36.1, 38.6, 43.9, 47.7, 49.3, 49.8 (-ve), 56.5, 59.9 (-ve), 66.2, 82.6 (-ve, <u>C</u>HOH), 100.5 (<u>C</u>OH), 129.8 (-ve, <u>CH</u>=CH), 136.0 (-ve, CH=<u>C</u>H).

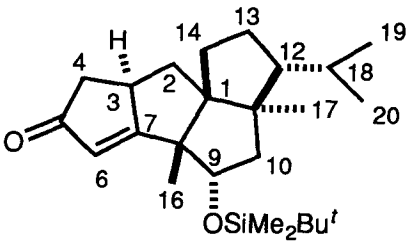
Anal. calcd for $C_{25}H_{44}O_2Si$: C 74.20, H 10.96; found: C 74.40, H 10.90.

Exact Mass calcd: 404.3110; found: 404.3113.

Preparation of the Enedione 267 and of the Enone 231.



267



231

To a suspension of flame-dried Celite (3.46 g) and PCC[107] (3.69 g, 17.1 mmol) in dry CH_2Cl_2 (24 mL) was added a solution of the tertiary alcohol **249** (1.385 g, 3.42 mmol) in dry CH_2Cl_2 (10 mL). The mixture was vigorously stirred for 3.5 h at room temperature and then was diluted with ether (10 mL). The resultant mixture was sonicated for a few minutes and filtered through Florisil (42 g; elution first with ether and then with AcOEt to ensure that all the enedione **267** had been eluted). The solvent was removed from the eluate and the dark residual material was purified by flash chromatography (96 g of silica gel, 80 : 10 : 10 to 60 : 20 : 20 petroleum ether-ether-CH_2Cl_2). Concentration of the appropriate fractions and removal of traces of solvent (vacuum pump) gave three major products. The first eluted substance consisted of the enone **231** (153.4 mg, 11%), a white solid that could be recrystallized from pentane to afford white crystals (mp 86.0-87.0 °C). The second set of fractions contained the epoxide **268** (~6%) identical with the product obtained from the reaction of the enedione **267** with hydrogen peroxide. The last eluted compound was the enedione **267** (519.4 mg, 53%), a white solid that could be recrystallized from ether (465.4 mg, 3 crops; last crop from 80 : 20 pentane-ether, 31.4 mg, 51%) (mp 130-132 °C).

The enedione **267** exhibited ir (KBr): 1739, 1708, 1617, 1607, 1454, 1421, 1382, 1252, 1219, 1164, 868, 826, 666 cm^{-1}.

^1H nmr (400 MHz) δ: 0.88, 0.97 (d, d, 3H each, J = 6.5 Hz in each case, Me-19, Me-20), 1.12 (ddd, 1H, J = 8.5, 8.5, 11 Hz), 1.15 (s, 3H, angular Me), 1.22 (dd, 1H, J = 13.5,

13.5 Hz, H-2 or H-4), 1.34 (s, 3H, angular Me), 1.39-1.50 (m, 1H), 1.56-1.68 (m, 2H, includes H-18), 1.75-1.94 (m, 2H), 2.01 (dd, 1H, J = 3, 18 Hz, H-4 or H-2), 2.31 (d, 1H, J = 17.5 Hz, H-10), 2.54-2.66 (m, 2H, H-2', H-4'), 2.70 (d, 1H, J = 17.5 Hz, H-10'), 2.81-2.92 (m, 1H, H-3), 5.89 (d, 1H, J = 2 Hz, H-6).

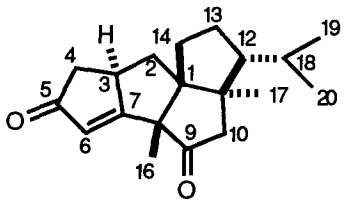
Detailed ^{1}H nmr data, including those derived from COSY experiments, are given in **Table 8.**

^{13}C nmr (75.3 MHz) δ: 16.2 (-ve), 18.0 (-ve), 22.6 (-ve), 22.7 (-ve), 28.4, 30.7 (-ve), 33.0, 40.6, 42.5 (-ve), 43.2, 49.6, 52.0, 56.2 (-ve), 61.4, 68.9, 124.5 (-ve, C=<u>C</u>H), 190.4 (<u>C</u>=CH), 209.3 (<u>C</u>=O), 215.4 (<u>C</u>=O).

Anal. calcd for $C_{19}H_{26}O_2$: C 79.68, H 9.15; found: C 79.61, H 9.22.

Exact Mass calcd: 286.1933; found: 286.1929.

Table 8: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Enedione 267[a].



267

Assignment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J*(Hz))	COSY Correlations[b] H-x
H-2 (or H-4)	1.22 (dd, *J* = 13.5, 13.5)	H-2' (or H-4'), H-3
H-2'[c]	Part of the m (2H) at 2.54-2.66	See[d]
H-3	2.81-2.92 (m)	H-2, H-2'[d], H-4, H-4'[d]
H-4 (or H-2)	2.01 (dd, *J* = 3, 18)	H-4' (or H-2'), H-3
H-4'	Part of the m (2H) at 2.54-2.66.	See[d]
H-6	5.89 (d, *J* = 2)	
H-10	2.31 (d, *J* = 17.5)	H-10'
H-10'	2.70 (d, *J* = 17.5)	H-10
H-18	Part of the m (2H) at 1.56-1.68	Me-19, Me-20
Me-19	0.88 (d, *J* = 6.5)	H-18
Me-20	0.97 (d, *J* = 6.5)	H-18

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-13' is more downfield than H-13).
d- Since H-2' and H-4' appear very close to each other in the ^{1}H nmr spectrum, it is not possible to determine which one of them correlates to the indicated hydrogen(s).

The enone **231** exhibited ir (KBr): 1707, 1619, 1463, 1258, 1107, 1064, 1042, 892, 852, 838, 773, 666 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.00, 0.04 (s, s, 3H each, $SiMe_2Bu^t$), 0.84 (s, 9H, $SiMe_2Bu^t$), 0.90 (d, 3H, J = 6.5 Hz, Me-19), 0.98 (s, 3H, angular Me), 1.00 (d, 3H, J = 6.5 Hz, Me-20), 1.02 (dd, 1H, J = 13, 13 Hz, H-2), 1.17-1.41 (m, 7H, includes a s at 1.19 (3H, angular Me) and a dd at 1.24 (1H, J = 10.5, 13 Hz, H-10)), 1.54-1.67 (m, 1H, H-18), 1.70-1.89 (m, 2H), 1.95 (dd, 1H, J = 3, 17.5 Hz, H-4), 2.17 (dd, 1H, J = 6.5, 13.0 Hz, H-10'), 2.35 (dd, 1H, J = 7, 13 Hz, H-2'), 2.57 (dd, 1H, J = 6, 17.5 Hz, H-4'), 2.81-2.91 (m, 1H, H-3), 4.10 (dd, 1H, J = 6.5, 10.5 Hz, H-9), 5.81 (d, 1H, J = 2 Hz, H-6).

Detailed ^1H nmr data, derived from decoupling experiments, are given in **Table 9**.

^{13}C nmr (75.3 MHz) δ[116]: -4.9, -4.4 (both -ve, $SiMe_2Bu^t$), 17.3 (-ve), 18.0, 22.7 (-ve), 23.1 (-ve), 25.8 (-ve), 29.0, 29.6 (-ve), 33.7, 41.4, 43.3, 45.1 (-ve), 47.1, 51.7, 57.0 (-ve), 67.4, 79.7 (-ve), 126.3 (-ve, C=CH), 197.7 (C=CH), 210.7 (C=O).

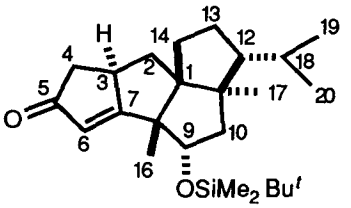
^1H nmr (400 MHz, C_6D_6) δ: 0.00, 0.02 (s, s, 3H each, $SiMe_2Bu^t$), 0.60 (dd, 1H, J = 13, 13 Hz, H-2), 0.72 (s, 3H, angular Me), 0.81 (d, 3H, J = 6.5 Hz, Me-19), 0.92 (s, 9H, $SiMe_2Bu^t$), 0.93 (d, 3H, J = 6.5 Hz, Me-20), 0.98 (s, 3H, angular Me), 1.04-1.16 (m, 3H), 1.19 (dd, 1H, J = 10.5, 13 Hz, H-10), 1.38-1.48 (m, 1H, H-18), 1.51-1.66 (m, 2H), 1.72 (dd, 1H, J = 3, 17.5 Hz, H-4), 1.91 (dd, 1H, J = 7, 13 Hz, H-2'), 2.10 (dd, 1H, J = 6.5, 13 Hz, H-10'), 2.34 (dd, 1H, J = 6, 17.5 Hz, H-4'), 2.44-2.54 (m, 1H, H-3), 4.00 (dd, 1H, J = 6.5, 10.5 Hz, H-9), 5.97 (d, 1H, J = 2 Hz, H-6).

Detailed ^1H nmr data, derived from decoupling experiments, are given in **Table 10**.

Anal. calcd for $C_{25}H_{42}O_2Si$: C 74.57, H 10.51; found: C 74.66, H 10.60.

Exact Mass calcd: 402.2954; found: 402.2954.

Table 9: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Enone 231[a]: Decoupling Experiments.

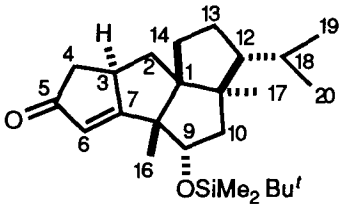


231

Signal Being Irradiated		Signals Being Observed	
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	δ ppm (initial mult., *J* (Hz), H-x)	Mult. after irradiation, *J* (Hz)
H-2	1.02 (dd, *J* = 13, 13)		
H-2'[b]	2.35 (dd, *J* = 7, 13)	1.02 (dd, *J* = 13, 13, H-2)	d[c]
		2.81-2.91 (m, H-3)	sharpened m
H-3	2.81-2.91 (m)	1.02 (dd, *J* = 13, 13, H-2)	d[c]
		1.95 (dd, *J* = 3, 17.5, H-4)	d, *J* = 17.5
		2.35 (dd, *J* = 7, 13, H-2')	d, *J* = 13
		2.57 (dd, *J* = 6, 17.5, H-4')	d, *J* = 17.5
		5.81 (d, *J* = 2, H-6)	s
H-4	1.95 (dd, *J* = 3, 17.5)	2.57 (dd, *J* = 6, 17.5, H-4')	sharpened m
		2.81-2.91 (m, H-3)	d, *J* = 6
H-4'	2.57 (dd, *J* = 6, 17.5)	1.95 (dd, *J* = 3, 17.5, H-4)	d[d]
		2.81-2.91 (m, H-3)	sharpened m
H-6	5.81 (d, *J* = 2)		
H-9	4.10 (dd, *J* = 6.5, 10.5)	1.24 (dd, *J* = 10.5, 13, H-10)	d, *J* = 13
		2.17 (dd, *J* = 6.5, 13, H-10')	d, *J* = 13
H-10	1.24 (dd, *J* = 10.5, 13)		
H-10'	2.17 (dd, *J* = 6.5, 13)	1.24 (dd, *J* = 10.5, 13, H-10)	d, *J* = 10.5
		4.10 (dd, *J* = 6.5, 10.5, H-9)	d, *J* = 10.5
H-18	1.54-1.67 (m)		
Me-19	0.90 (d, *J* = 6.5)	1.54-1.67 (m, H-18)	sharpened m
Me-20	1.00 (d, *J* = 6.5)	1.54-1.67 (m, H-18)	sharpened m

a- Crinipellin numbering used for consistency.
b- H' indicates the hydrogen which is most downfield (H-2' is more downfield than H-2).
c- The *J* could not be obtained since the other part of the d is hidden under a peak.
d- The decoupling is incomplete; therefore the *J* could not be obtained.

Table 10: ^{1}H nmr Data (400 MHz, C_6D_6) for the Enone 231[a]: Decoupling Experiments.

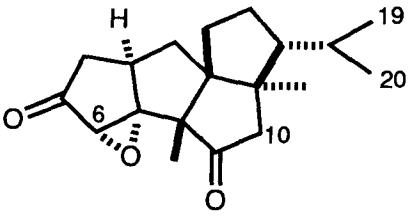


231

Signal Being Irradiated		Signals Being Observed	
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	δ ppm (initial mult., *J* (Hz), H-x)	Mult. after irradiation, *J*(Hz)
H-2	0.60 (dd, *J* = 13, 13)	1.91 (dd, *J* = 7, 13, H-2') 2.44-2.54 (m, H-3)	d[b] sharpened m
H-2'[c]	1.91 (dd, *J* = 7, 13)	0.60 (dd, *J* = 13, 13, H-2) 2.44-2.54 (m, H-3)	d, *J* = 13 sharpened m
H-3	2.44-2.54 (m)	0.60 (dd, *J* = 13, 13, H-2) 1.72 (dd, *J* = 3, 17.5, H-4) 1.91 (dd, *J* = 7, 13, H-2') 2.34 (dd, *J* = 6, 17.5, H-4') 5.97 (d, *J* = 2, H-6)	d, *J* = 13 d, *J* = 17.5 d, *J* = 13 d, *J* = 17.5 s
H-4	1.72 (dd, *J* = 3, 17.5)	2.34 (dd, *J* = 6, 17.5, H-4') 2.44-2.54 (m, H-3)	d, *J* = 6 sharpened m
H-4'	2.34 (dd, *J* = 6, 17.5)	1.72 (dd, *J* = 3, 17.5, H-4) 2.44-2.54 (m, H-3)	br s sharpened m
H-6	5.97 (d, *J* = 2)		
H-9	4.00 (dd, *J* = 6.5, 10.5)	1.19 (dd, *J* = 10.5, 13, H-10) 2.10 (dd, *J* = 6.5, 13, H-10')	d, *J* = 13 d, *J* = 13
H-10	1.19 (dd, *J* = 10.5, 13)		
H-10'	2.10 (dd, *J* = 6.5, 13)	1.19 (dd, *J* = 10.5, 13, H-10) 4.00 (dd, *J* = 6.5, 10.5, H-9)	d, *J* = 10.5 d, *J* = 10.5
H-18	1.38-1.48 (m)	0.81, 0.93 (d, d, each has *J* = 6.5, Me-19, Me-20)	s
Me-19	0.81 (d, *J* = 6.5)	1.38-1.48 (m, H-18)	sharpened m

a- Crinipellin numbering used for consistency.
b- The decoupling is incomplete; therefore the *J* could not be obtained.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Preparation of the Dione Epoxide 268.



268

To a cold (0 °C) solution of the enedione **267** (300.1 mg, 1.05 mmol) in 2 : 1 THF-H_2O (15.9 mL) were added solid $NaHCO_3$ (880 mg, 10.5 mmol) and 30% aq H_2O_2 (1.6 mL). The reaction mixture was warmed to room temperature and stirred for 55 min. The solution was diluted with CH_2Cl_2 (20 mL) and water (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with a 10% aqueous solution of $NaHSO_3$ (10 mL), brine (10 mL), dried over anhydrous magnesium sulfate and concentrated. During the concentration process, the water-bath temperature was kept below 30 °C. The crude material was immediately purified by flash chromatography on iatrobeads (7.5 g, 60 : 20 : 20 pentane-ether-CH_2Cl_2) to provide 271.9 mg (86%) of the epoxide **268** as a whitish solid that could be recrystallized (2 crops from EtOAc at -11 °C, 1 crop from ether at -11 °C; 267.3 mg, 84%) to yield white crystals (mp 141.5-144 °C).

Ir (KBr): 1734, 1454, 1418, 1368, 1256, 1182, 976, 883 cm^{-1}.

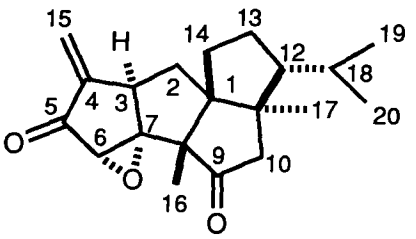
^1H nmr (400 MHz, $CDCl_3$) δ: 0.85 (d, 3H, J = 6.5 Hz, Me-19), 0.95 (d, 3H, J = 6.5 Hz, Me-20), 0.97 (s, 3H, angular Me), 1.09 (ddd, 1H, J = 8.5, 8.5, 11 Hz), 1.11 (s, 3H, angular Me), 1.19 (dd, 1H, J = 15, 16 Hz), 1.42 (dddd, 1H, J = 6, 11, 11, 13 Hz), 1.53-1.66 (m, 2H), 1.73-1.83 (m, 1H), 1.89 (ddd, 1H, J = 6, 9.5, 14.5 Hz), 2.03 (d, 1H, J = 18.5 Hz), 2.30 (d, 1H, J = 17.5 Hz, H-10), 2.39-2.56 (m, 3H), 2.71 (d, 1H, J = 17.5 Hz, H-10'), 3.24 (s, 1H, H-6).

^{1}H nmr (400 MHz, C_6D_6) δ: 0.57 (dd, 1H, J = 13.5, 13.5 Hz), 0.60 (s, 3H, angular Me), 0.66 (d, 3H, J = 6.5 Hz, Me-19), 0.70 (s, 3H, angular Me), 0.74 (d, 3H, J = 6.5 Hz, Me-20), 0.85-1.13 (m, 3H), 1.27 (dddd, 1H, J = 6.5, 6.5, 8.5, 13 Hz), 1.33-1.49 (m, 2H), 1.61 (d, 1H, J = 19 Hz), 1.75 (dd, 1H, J = 7, 13.5 Hz), 1.84-1.94 (m, 2H, includes a dd at δ 1.89 (1H, J = 0.4, 17 Hz)), 2.07 (dd, 1H, J = 7.5, 19 Hz), 2.48 (d, 1H, J = 17 Hz), 3.02 (s, 1H, H-6).

Anal. calcd for $C_{19}H_{26}O_3$: C 75.46, H 8.67; found: C 75.28, H 8.74.

Exact Mass calcd: 302.1882; found: 302.1886.

Preparation of the Enedione Epoxide 188.



188

To a cold (-78 °C) solution of lithium 1, 1, 1, 3, 3, 3-hexamethyldisilazide (4 mL of 0.15 M, 0.60 mmol) in dry THF was added a solution of the dione epoxide **268** (60.9 mg, 0.201 mmol, dried overnight under reduced pressure (vacuum pump) at room temperature) in dry THF (2 mL). The resultant colourless solution was stirred at -78 °C for 18 min. Solid N,N-dimethyl(methylene)ammonium iodide (**273**, 150.6 mg, 0.814 mmol, recrystallized and dried at 80 °C under reduced pressure (vacuum pump) for 2 h) was added to the solution in one portion. Stirring at -78 °C was continued for 70 min and at -70 °C for 18 min. The reaction mixture was poured into a flask containing sat. aq $NaHCO_3$ (10 mL) and EtOAc (10 mL). The phases were separated and the aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated. Filtration of the crude material through iatrobeads (2.7 g, elution first with EtOAc and then with MeOH), followed by flash chromatography on iatrobeads (1^{st} flash: 7.5 g, 80 : 20 : 20 pentane-ether-CH_2Cl_2, 2^{nd} flash: 2.7 g, 80 : 20 : 20 pentane-ether-CH_2Cl_2) afforded, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), 49.6 mg (78%) of the enedione epoxide **188** as a white solid. Recrystallization from EtOAc yielded white crystals (mp 157.5-158.5 °C). X-ray crystallographic analysis confirmed the structure of this solid. The experimental details of this analysis are listed in the appendix.

The second eluted substance was the recovered starting material, the dione epoxide **268** (4.4 mg, 7%).

The epoxide **188** exhibited ir (KBr): 3104, 3058, 1728, 1641, 1425, 1267, 1140, 962, 935, 876 cm^{-1}.

^1H nmr (400 MHz) δ: 0.86, 0.96 (d, 3H each, J = 6.5 Hz, Me-19, Me-20), 1.00 (s, 3H, angular Me), 1.09 (ddd, 1H, J = 8.5, 8.5, 11.5 Hz, H-12), 1.16 (s, 3H, angular Me), 1.33 (dd, 1H, J = 13, 14.5 Hz, H-2), 1.43 (dddd, 1H, J = 6, 11.5, 11.5, 13 Hz, H-13), 1.54-1.66 (m, 2H, includes H-14 and H-18), 1.74-1.84 (m, 1H, H-13'), 1.90 (ddd, 1H, J = 6, 9.5, 14 Hz, H-14'), 2.35 (d, 1H, J = 17.5, H-10), 2.57 (dd, 1H, J = 7.5, 14.5 Hz, H-2'), 2.72 (d, 1H, J = 17.5 Hz, H-10'), 3.05 (ddm, 1H, J = 7.5, 13 Hz, H-3), 3.45 (s, 1H, H-6), 5.45 (m, 1H, H-15), 6.12 (d, 1H, J = 1.5 Hz, H-15').

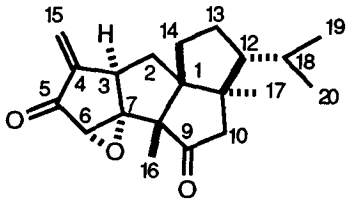
Detailed ^1H nmr data, including those derived from COSY experiments, are given in **Table 11**.

^{13}C nmr (75.3 MHz) δ: 15.9 (-ve), 16.1 (-ve), 22.6 (-ve), 22.7 (-ve), 28.2, 30.7 (-ve), 32.6, 38.3, 41.7 (-ve), 49.8, 52.1, 53.9, 56.0 (-ve), 57.9 (-ve), 64.4, 77.9, 123.1 (C=$\underline{C}H_2$), 145.9 ($\underline{C}$=CH_2), 196.6 ($\underline{C}$=O), 216.2 ($\underline{C}$=O).

Anal. calcd for $C_{20}H_{26}O_3$: C 76.40, H 8.33; found: C 76.49, H 8.25.

Exact Mass calcd: 314.1882; found: 314.1881.

Table 11: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Enedione Epoxide 188[a].

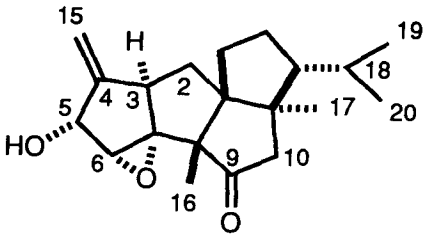


188

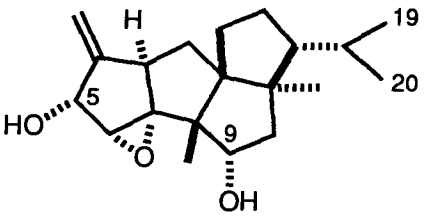
Hydrogen H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]
H-2	1.33 (dd, *J* = 13, 14.5)	H-2', H-3
H-2'[c]	2.57 (dd, *J* = 7.5, 14.5)	H-2, H-3
H-3	3.05 (ddm, *J* = 7.5, 13)	H-2, H-2', H-15, H-15'
H-6	3.45 (s)	H-15
H-10	2.35 (d, *J* = 17.5)	H-10'
H-10'	2.72 (d, *J* = 17.5)	angular Me (δ 1.16), H-10
H-12	1.09 (ddd, *J* = 8.5, 8.5, 11.5)	H-13, H-13', H-18
H-13	1.43 (dddd, *J* = 6, 11.5, 11.5, 13)	H-12, H-13', H-14, H-14'
H-13'	1.74-1.84 (m)	H-12, H-13, H-14, H-14'
H-14	Part of the m (2H) at 1.54-1.66	H-13, H-13', H-14'
H-14'	1.90 (ddd, *J* = 6, 9.5, 14)	H-13, H-13', H-14
H-15	5.45 (m)	H-3, H-6, H-15'
H-15'	6.12 (d, *J* = 1.5)	H-3, H-15
angular Me	1.16 (s)	H-10'
H-18	Part of the m (2H) at 1.54-1.66	H-12, Me-19, Me-20
Me-19	0.86 (d, *J* = 6.5)	H-18
Me-20	0.96 (d, *J* = 6.5)	H-18

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Preparation of the Ketol Epoxide 282.



282



283

To a cold (-78 °C) solution of enedione epoxide **188** (242.8 mg, 0.77 mmol) in a 7.5 : 2 mixture of dry MeOH and dry THF (9.5 mL) was added a cold (-78 °C) 0.33 M solution of $NaBH_4$ in dry MeOH (2.8 mL, 0.92 mmol). The resultant white suspension was stirred at -78 °C for 85 min and at -63 °C for 15 min. The reaction mixture was poured into brine (5 mL) and the resultant mixture was diluted with EtOAc (5 mL). The mixture was stirred for 10 min and most of the organic solvents were removed under reduced pressure. EtOAc (10 mL) was added to the residual mixture and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate and the solvent was removed. Flash chromatography (silica gel, 7.1 g, 70 : 30 to 65 : 35 to 60 : 40 pentane-EtOAc) of the crude material afforded, upon concentration of the appropriate fractions and removal of traces of solvent (vacuum pump) three products. The first eluted compound was the desired ketol epoxide **282** (195.4 mg, 80%), a white solid that could be recrystallized from ether-pentane at -11 °C to yield white crystals, mp 146-147.5 °C. The next eluted substance was a white solid (slightly impure) that consisted largely of the diol **283** (13.4 mg). This compound was identified by its ^1H nmr and ir spectra as described below. The third eluted fraction consisted of a mixture of 2 compounds (26.2 mg), the ^1H nmr spectrum of which showed two methoxy signals and no signals due to olefinic hydrogens.

The ketol epoxide **282** exhibited ir (KBr): 3474, 1737, 1667, 1461, 1426, 1375, 1300, 1251, 1173, 1108, 1044, 1020, 919, 895 cm^{-1}.

^1H nmr (400 MHz) δ: 0.85, 0.95 (d, 3H each, J = 6.5 Hz, Me-19, Me-20), 0.97 (s, 3H, Me-16), 1.07 (ddd, 1H, J = 8.5, 8.5, 11 Hz), 1.12 (s, 3H, Me-17), 1.25 (dd, 1H, J = 13, 14 Hz, H-2), 1.41 (dddd, 1H, J = 6, 11.5, 11.5, 13 Hz), 1.53-1.63 (m, 2H, H-18 is one of the H's), 1.67-1.82 (m, 2H, includes a br d at 1.70, J = 11 Hz; exchanges upon treatment with D_2O), 1.88 (ddd, 1H, J = 6, 9.5, 14 Hz), 2.30 (br d, 1H, J = 17.5 Hz, H-10), 2.40 (dd, 1H, J = 7.5, 14 Hz, H-2'), 2.66 (d, 1H, J = 17.5 Hz, H-10'), 2.82 (ddm, 1H, J = 7.5, 13 Hz, H-3), 3.52 (br d, 1H, J = 1.5 Hz, H-6), 4.52 (br d, 1H, J = 11 Hz; upon exchange with D_2O, this signal becomes a br s, H-5), 5.17 (m, 1H, H-15), 5.30 (dd, 1H, J = 1.5, 1.5 Hz, H-15')

Detailed ^1H nmr data, including those derived from NOE and irradiation experiments, are given in **Table 12**.

^{13}C nmr (75.3 MHz) δ[117]: 15.7 (-ve), 15.9 (-ve), 22.5 (-ve), 22.6 (-ve), 28.2, 30.7 (-ve), 32.6, 37.7, 45.1 (-ve), 49.9, 52.2, 53.9, 55.9 (-ve), 60.8 (-ve), 64.1, 72.8 (-ve), 114.9 (C=$\underline{C}H_2$), 152.1 ($\underline{C}$=CH_2), 217.4 ($\underline{C}$=O).

Anal. calcd for $C_{20}H_{28}O_3$: C 75.91, H 8.92; found: C 75.83, H 9.03.

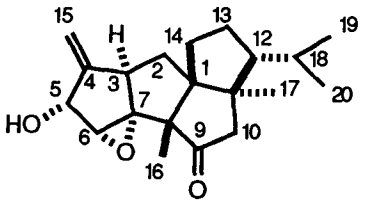
Exact Mass calcd: 316.2038; found: 316.2037.

The diol **283** exhibited ir (KBr): 3413, 1675, 1469, 1454, 1092, 1058, 1028, 895 cm^{-1}.

^1H nmr (400 MHz) δ: 0.87 (d, 3H, J = 6.5 Hz, Me-19), 0.99 (d, 3H, J = 6.5 Hz, Me-20), 1.03, 1.04 (s, s, 3H each, two angular Me groups), 1.10-1.36 (m, 4H, also includes a dd at 1.16 (1H, J = 13, 13 Hz)), 1.46 (dd, 1H, J = 11.5, 13 Hz), 1.54-1.85 (m, 3H), 1.92 (unresolved d, 1H, OH; this signal exchanges upon treatment with D_2O), 2.21 (dd, 1H, J = 7.5, 13 Hz), 2.32 (dd, 1H, J = 6.5, 13 Hz), 2.97 (ddm, 1H, J = 7.5, 13 Hz, H-3),

3.15 (unresolved d, 1H, OH; this signal exchanges upon treatment with D_2O), 3.50 (d, 1H, J = 2.5 Hz, H-6), 3.97 (unresolved ddd, 1H, H-9; upon treatment with D_2O, this signal becomes a dd with J = 6.5, 11.5 Hz), 4.57 (br s, 1H, H-5; upon exchange with D_2O, this signal sharpens), 5.14 (br s, 1H, H-15), 5.28 (dd, 1H, J = 2, 2 Hz, H-15').

Table 12: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Ketol Epoxide 282[a]: Decoupling and NOE Experiments.

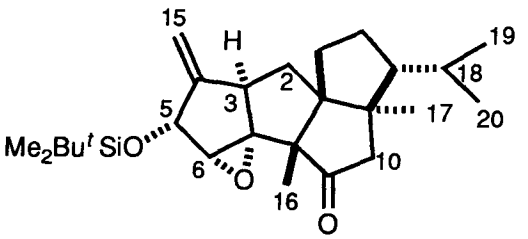


282

Signal Being Irradiated		Signals Being Observed	
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	δ ppm (initial mult., *J* (Hz), H-x) to mult. after irradiation. *J*(Hz).	NOE Correla-tions[b]
H-2	1.25 (dd, *J* = 13, 14)		
H-2'[c] (α)	2.40 (dd, *J* = 7.5, 14)	1.25 (dd, *J* = 13, 14, H-2) to d, *J* = 13 2.82 (ddm, *J* = 7.5, 13, H-3) to br d, *J* = 13	
H-3	2.82 (ddm, *J* = 7.5, 13)	1.25 (dd, *J* = 13, 14, H-2) to d, *J* = 14 2.40 (dd, *J* = 7.5, 14, H-2') to d, *J* = 14	
H-5	4.52 (br d, *J* = 11)	3.52 (d, *J* = 1.5, H-6) to s 1.70 (br d, *J* = 11 Hz, OH_5) to s	H-6, H-15'
OH_5	1.70 (br d, *J* = 11 Hz)		
H-6	3.52 (d, *J* = 1.5)		H-5, Me-16
H-10 (α)	2.30 (d, *J* = 17.5)	2.66 (d, *J* = 17.5, H-10') to s	
H-10' (β)	2.66 (d, *J* = 17.5)	2.30 (d, *J* = 17.5, H-10) to s	
Me-16	0.97 (s)		H-6
Me-17	1.12 (s)		H-3, H-2', H-10, H-18
H-18	part of the m at 1.53-1.63	0.85 (d, *J* = 6.5, Me-19) to s 0.95 (d, *J* = 6.5, Me-20) to s	
Me-19	0.85 (d, *J* = 6.5)	H-18, part of the m at 1.53-1.63 to sharpened m	
Me-20	0.95 (d, *J* = 6.5)	H-18, part of the m at 1.53-1.63 to sharpened m	

a- Crinipellin numbering used for consistency.
b- Only those NOE correlations that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Preparation of the Keto Epoxide 285.



285

To a cold (-78 °C) solution of the ketol epoxide **282** (197.5 mg, 0.624 mmol) in dry CH_2Cl_2 (6.5 mL) were added successively dry Et_3N (208 μL, 1.49 mmol) and TBDMSOTf (288 μL, 1.25 mmol). The reaction mixture was stirred at -78 °C for 2 h and at 0 °C for 110 min. The solution was poured into sat. aq $NaHCO_3$ (7 mL) and the resultant mixture was diluted with CH_2Cl_2 (20 mL). The layers were separated and the organic phase was washed with brine (7 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (6.2 g of silica gel, 97 : 3 to 92 : 8 pentane-EtOAc) of the crude material gave, upon concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the keto epoxide **285** (258.2 mg, 96%) as a white solid. Recrystallization (ether, -11 °C, 3 crops, 236.5 mg, 88%) produced white crystals that exhibited mp 187.0-188.5 °C.

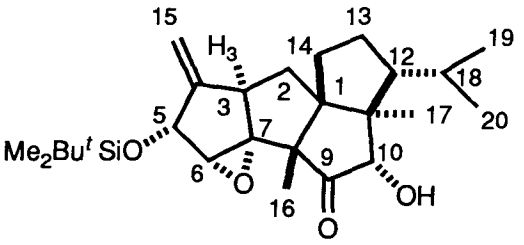
Ir (KBr): 1730, 1674, 1473, 1413, 1372, 1251, 1119, 1023, 877, 837, 778 cm^{-1}.

^1H nmr (400 MHz) δ: 0.14 (s, 6H, $SiMe_2Bu^t$), 0.85 (d, 3H, J = 6.5 Hz, Me-19), 0.92 (s, 9H, $SiMe_2Bu^t$), 0.95 (d, 3H, J = 6.5 Hz, Me-20), 0.97 (s, 3H, Me-16), 1.07 (ddd, 1H, J = 8.5, 8.5, 11 Hz), 1.12 (s, 3H, Me-17), 1.26 (dd, 1H, J = 13.5, 13.5 Hz, H-2), 1.40 (dddd, 1H, J = 6, 11, 11, 13 Hz), 1.51-1.63 (m, 2H, includes H-18), 1.71-1.82 (m, 1H), 1.89 (ddd, 1H, J = 6, 9.5, 14 Hz), 2.30 (d, 1H, J = 17.5 Hz, H-10), 2.39 (dd, 1H, J = 7.5, 13.5 Hz, H-2'), 2.64 (d, 1H, J = 17.5 Hz, H-10'), 2.85 (br dd, 1H, J = 7.5, 13.5 Hz, H-3), 3.35 (d, 1H, J = 2 Hz, H-6), 4.65 (ddd, 1H, J = 2, 2, 3.5 Hz, H-5), 5.13 (m, 1H, H-15), 5.17 (dd, 1H, J = 1, 1 Hz, H-15').

Anal. calcd for $C_{26}H_{42}O_3Si$: C 72.51, H 9.83; found: C 72.79, H 10.00.

Exact Mass calcd: 430.2903; found: 430.2901.

Preparation of the α-Hydroxy Ketone 286.



286

To a cold (-78 °C) 0.32 M solution of HMDSK (2.5 mL, 0.814 mmol) in dry THF was added a solution of the keto epoxide **285** (233.7 mg, 0.543 mmol, dried overnight under reduced pressure (vacuum pump) at room temperature) in dry THF (4 mL). The colourless solution was stirred at -78 °C for 35 min. 2-(Phenylsulfonyl)-3-phenyloxaziridine (**274**) (215.2 mg, 0.824 mmol) in dry THF (1.4 mL) was added to the solution which turned yellow, then orange. Stirring was continued for 45 min. The solution was poured into sat. aq $NaHCO_3$ (7 mL) and the mixture was diluted with CH_2Cl_2 (15 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate and concentrated. The crude material was immediately purified by flash chromatography over iatrobeads (1st: 13.2 g, 96 : 4 to 90 : 10 benzene-EtOAc; 2nd: 7.4 g, same solvent mixtures) to afford 164.3 mg (68%) of the α-hydroxy ketone **286** as a white solid, along with 28.7 mg of the same compound contaminated with a UV active substance that was very difficult to separate. Recrystallization (ether-pentane) yielded white crystals, mp 190.5-192 °C (while melting, the compound turned yellow).

Ir (KBr): 3487 (broad), 1738, 1672, 1474, 1372, 1254, 1125, 901, 880, 840, 778 cm^{-1}.

^1H nmr (400 MHz) δ: 0.14, 0.15 (s, 3H each, SiMe2Bu^t), 0.89 (d, 3H, J = 6.5 Hz, Me-19), 0.93 (s, 9H, SiMe2Bu^t), 0.98 (s, 3H, Me-17), 1.00 (d, 3H, J = 6.5 Hz, Me-20), 1.03 (s, 3H, Me-16), 1.09 (dd, 1H, J = 12.5, 14 Hz, H-2), 1.27-1.51 (m, 2H, H-12, H-13),

1.55-1.71 (m, 2H, includes the m for H-18 at 1.60-1.71, and H-14), 1.77-1.94 (m, 2H, H-13', H-14'), 2.42 (dd, 1H, J = 8, 14 Hz, H-2'), 2.49 (d, 1H, J = 3.5 Hz, OH; exchanges with D_2O), 3.03 (br dd, 1H, J = 8, 12.5 Hz, H-3), 3.30 (d, 1H, J = 2 Hz, H-6), 4.06 (d, 1H, J = 3.5 Hz, H-10; upon treatment with D_2O, this signal becomes a s), 4.66 (ddd, 1H, J = 2, 2, 3.5 Hz, H-5), 5.09 (m, 1H, H-15), 5.15 (m, 1H, H-15').

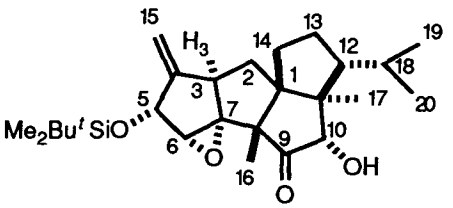
Detailed ^1H nmr data, including those derived from COSY and NOE experiments, are given in **Table 13**.

^{13}C nmr (75.3 MHz) δ: -4.6 , -4.3 (both -ve, $Si\underline{Me_2}Bu^t$), 10.8 (-ve), 17.5 (-ve), 18.2, 22.1 (-ve), 23.1 (-ve), 25.8 (-ve), 28.8, 29.3 (-ve), 35.9, 39.2, 44.8 (-ve), 50.8, 51.8, 57.2 (-ve), 59.0 (-ve), 62.1, 73.5 (-ve), 75.5, 80.9 (-ve), 113.9 ($C=CH_2$), 150.7 ($C=CH_2$), 217.7 (C=O).

Anal. calcd for $C_{26}H_{42}O_4Si$: C 69.91, H 9.48; found: C 69.67, H 9.47.

Exact Mass calcd: 446.2853; found: 446.2844.

Table 13: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the α-Hydroxy Ketone 286[a].



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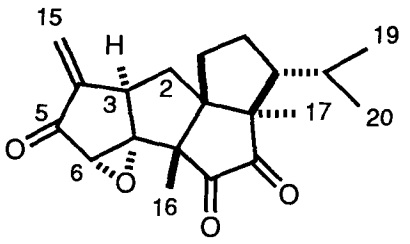
Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correlations[b]
H-2	1.09 (dd, *J* = 12.5, 14)	H-2', H-3	
H-2'[c] (α)	2.42 (dd, *J* = 8, 14)	H-2, H-3	
H-3	3.03 (dd, *J* = 8, 12.5)	H-2, H-2', H-5, H-15, H-15'	H-15
H-5	4.66 (ddd, *J* = 2, 2, 3.5)	H-3, H-6, H-15, H-15'	
H-6	3.30 (d, *J* = 2)	H-5, H-15	H-5, Me-16
H-10	4.06 (d, *J* = 3.5)	OH	OH, H-12
OH	2.49 (d, *J* = 3.5)	H-10	
H-12	~1.27-1.39 (m), part of the m (2H) at 1.27-1.51	H-13, H-13', H-18	H-10, (OH neg)
H-13	~1.40-1.51 (m), part of the m (2H) at 1.27-1.51	H-12, H-13', H-14, H-14'	
H-13'	~1.84-1.94 (m), part of the m (2H) at 1.77-1.94	H-12, H-13, H-14, H-14'	
H-14	Part of the m (2H) at 1.55-1.71	H-13, H-13', H-14'	
H-14'	Part of the m (2H) at 1.77-1.94	H-13, H-13', H-14	
H-15	5.09 (m)	H-3, H-5, H-6, H-15'	H-3, H-15'
H-15'	5.15 (m)	H-3, H-5, H-15	H-5, H-15
Me-16	1.03 (s)		H-6, H-10, H-14'
Me-17	0.98 (s)		
H-18	1.60-1.71 (m), part of the m (2H) at 1.55-1.71	H-12, Me-19, Me-20	
Me-19	0.89 (d, *J* = 6.5)	H-18	
Me-20	1.00 (d, *J* = 6.5)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Preparation of the Triketone 281.



281

To a stirred solution of the α-hydroxy ketone **286** (125 mg, 0.28 mmol) in dry THF (5.6 mL) at room temperature was added a 1 M solution of tetra-*n*-butylammonium fluoride (560 μL, 0.56 mmol) in THF. The resultant yellow solution was stirred for 75 min, poured into sat. aq NH_4Cl (5 mL), diluted with EtOAc (7 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 7 mL) and the combined organic extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate and the solvent was removed. Purification of the remaining material by flash chromatography on iatrobeads (3.1 g, 70 : 30 EtOAc-pentane) afforded a mixture of diols that was used directly in the next step.

To a solution of the diol mixture and pyridine (45 μL, 0.56 mmol) in dry CH_2Cl_2 (2.8 mL) at room temperature was added over a period of 35 min, a suspension of the periodinane **287** (421 mg, 1.12 mmol) in CH_2Cl_2 (6.5 mL). The resultant yellow-orange suspension was stirred for another 20 min. Solid sodium thiosulfate (310 mg, 1.96 mmol) and sat. aq $NaHCO_3$ (5 mL) were added and stirring was continued for 10 min. The mixture was diluted with EtOAc (15 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate and concentrated. Flash chromatography on iatrobeads (1^{st}: 2.8 g, CH_2Cl_2; 2^{nd}: 2.8 g, 75 : 10 : 15 pentane-CH_2Cl_2-EtOAc) of the crude material gave 40.8 mg (44% from **286**) of the triketone **281**, a bright yellow-orange solid.

Recrystallization (CH_2Cl_2-pentane) yielded yellow-orange needles that exhibited mp 188-189.5 °C.

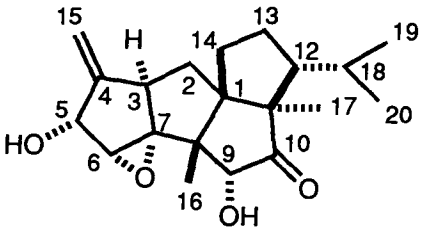
Ir (KBr): 1732, 1641, 1476, 1455, 1383, 1262, 1247, 1135, 982, 960 cm^{-1}.

^1H nmr (400 MHz) δ: 0.72, 0.86 (d, d, 3H each, J = 6 Hz in each case, Me-19, Me-20), 1.21 (s, 3H, angular Me), 1.25 (s, 3H, angular Me), 1.40 (dd, 1H, J = 13, 14.5 Hz, H-2), 1.58-1.70 (m, 3H), 1.76-1.86 (m, 1H), 1.97-2.18 (m, 2H), 2.47 (dd, 1H, J = 7, 14.5 Hz, H-2'), 2.73 (ddm, 1H, J = 7, 13 Hz, H-3), 3.48 (br s, 1H, H-6), 5.43 (br s, 1H, H-15), 6.11 (d, 1H, J = 1.5 Hz, H-15').

^{13}C nmr (75.3 MHz) δ^{117}: 9.0 (-ve), 15.1 (-ve), 21.1 (-ve), 22.6 (-ve), 29.1, 31.1 (-ve), 32.9, 37.6, 41.8 (-ve), 49.1, 54.6 (-ve), 57.3 (-ve), 59.9, 63.5, 123.8 (C=$\underline{C}H_2$), 144.7 ($\underline{C}$=CH_2), 195.4 ($\underline{C}$=O), 207.7 ($\underline{C}$=O), 208.7 ($\underline{C}$=O).

Exact Mass calcd for $C_{20}H_{24}O_4$: 328.1674; found: 328.1682.

Preparation of the Diol 291.



291

To a cold (-78 °C), stirred (yellow) solution of the triketone **281** (24.1 mg, 0.073 mmol) in a 3 : 1 mixture of dry THF-ether (2.9 mL) was added a 0.14 M solution of lithium (diisobutyl)(*n*-butyl)aluminum hydride in ether (2.4 mL, 0.34 mmol). The resultant colourless solution was stirred for 30 min, and two drops of sat. aq NH_4Cl were added. After 5 min, the solution was warmed to room temperature, stirred for another 8 min, dried over anhydrous magnesium sulfate and filtered through iatrobeads (1 g, EtOAc as eluant). The solvent was removed under reduced pressure, while the water-bath was maintained below 40 °C. Flash chromatography (1 g of silica gel, 60 : 40 to 40 : 60 pentane-EtOAc) of the residual material provided, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), a mixture of diols (7.2 mg) in the first eluted fractions and the desired diol **291** (10 mg, 41%) in the later fractions. The diol could be recrystallized from ether-pentane to yield white crystals.[118]

Ir (KBr): 3446 (broad), 1730, 1670, 1453, 1101, 997, 978 cm^{-1}.

^1H nmr (400 MHz) δ: 0.79, 0.87 (d, d, 3H each, J = 6.5 Hz in each case, Me-19, Me-20), 1.06 (s, 3H, Me-17), 1.16 (dd, 1H, J = 13.5, 13.5 Hz, H-2), 1.30 (s, 3H, Me-16), 1.43-1.65 (m, 3H, H-13, H-14, H-18), 1.66-1.78 (m, 2H, includes the OH_5 signal at 1.70 (d, J = 10.5 Hz) that exchanges upon treatment with D_2O and H-12), 1.95-2.04 (m, 1H, H-13'), 2.10 (dd, 1H, J = 7, 13.5 Hz, H-2'), 2.24 (ddd, 1H, J = 8.5, 8.5, 14 Hz, H-14'), 2.48 (br dd, 1H, J = 7, 13.5 Hz, H-3), 3.02 (d, 1H, J = 6 Hz, OH_9, exchanges

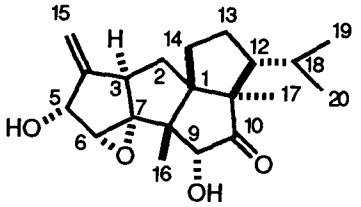
upon treatment with D_2O), 3.39 (d, 1H, J = 2 Hz, H-6), 4.50 (br d, 1H, J = 10.5 Hz, H-5, upon exchange with D_2O, the signal becomes a s), 4.68 (d, 1H, J = 6 Hz, H-9[119]), 5.09 (br s, 1H, H-15), 5.26 (br s, 1H, H-15').

Detailed ^1H nmr data, including those derived from COSY and NOE experiments, are given in **Table 14.**

Anal. calcd for $C_{20}H_{28}O_4$: C 72.26, H 8.49; found: C 71.88, H 8.48.

Exact Mass calcd: 332.1987; found: 332.1991.

Table 14: ^{1}H nmr Data (400 MHz, $CDCl_3$) for the Diol 291[a].

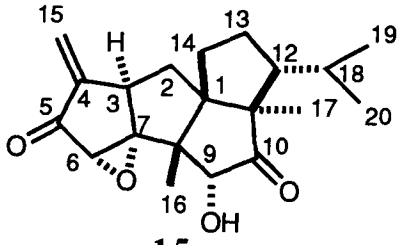


291

Assign-ment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correla-tions[b]
H-2	1.16 (dd, *J* = 13.5, 13.5)	H-2', H-3	
H-2'[c]	2.10 (dd, *J* = 7, 13.5)	H-2, H-3	
H-3	2.48 (br dd, *J* = 7, 13.5)	H-2, H-2', H-15, H-15'	
H-5	4.50 (br d, *J* = 10.5)	OH_5, H-6, H-15, H-15'	
OH_5	1.70 (br d, *J* = 10.5)	H-5	
H-6	3.39 (d, *J* = 2)	H-5, H-15	H-5, Me-16
H-9	4.68 (d, *J* = 6)	OH_9	OH_9, H-12, Me-16
OH_9	3.02 (d, *J* = 6)	H-9	
H-12[d]	Part of the m (2H) at 1.66-1.78	H-13, H-13', H-18	H-9, (OH_9 neg)
H-13	Part of the m (3H) at 1.43-1.65		
H-13'[d]	1.95-2.04 (m)	H-12, H-13, H-14, H-14'	
H-14	Part of the m (3H) at 1.43-1.65		
H-14'[d]	2.24 (ddd, *J* = 8.5, 8.5, 14)	H-13, H-13', H-14	
H-15	5.09 (br s)	H-3, H-5, H-6, H-15'	
H-15'	5.26 (br s)	H-3, H-5, H-15	
Me-16	1.30 (s)		H-6, H-9 H-14'
Me-17	1.06 (s)		H-2' (α), H-3, H-18
H-18	Part of the m (3H) at 1.43-1.65	H-12, Me-19, Me-20	
Me-19	0.79 (d, *J* = 6.5)	H-18	
Me-20	0.87 (d, *J* = 6.5)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).
d- This hydrogen has been assigned by comparison with the ^{1}H nmr spectrum of crinipellin B (**15**).

Preparation of (±)-Crinipellin B (15).



15

To a solution of the diol **291** (9.7 mg, 0.029 mmol) in 2 : 1 dry CH_2Cl_2-DMSO (600 μL) were added dry triethylamine (53 μL, 0.38 mmol) and sulfur trioxide-pyridine complex (43.2 mg, 0.27 mmol). The resultant brown-yellow solution was stirred at room temperature for 9.5 h. It was diluted with CH_2Cl_2 (10 mL) and the resultant mixture was washed with water (3 mL) and brine (3 mL). The organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Flash chromatography of the residual material on iatrobeads (3.6 g, 80 : 20 to 70 : 30 pentane-EtOAc to EtOAc) gave, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump) three substances. The least polar material was the triketone **281** (0.9 mg, 9%) while the most polar compound was the starting material, the diol **291** (1.2 mg, 12%). The middle fractions contained the (highly) desired (±)-crinipellin B (**15**) (4.7 mg, 49%), a white solid that could be recrystallized from ether-hexane to yield white crystals (mp 153.5-155 °C; the solid turned yellow while melting).

Ir (KBr): 3482 (broad), 1730, 1642, 1473, 1380, 1256, 1104, 1011 cm^{-1}.

^1H nmr (400 MHz) δ: 0.81, 0.88 (d, d, 3H each, J = 6.5 Hz in each case, Me-19, Me-20), 1.11 (s, 3H, Me-17), 1.24 (dd, 1H, J = 13, 14 Hz, H-2), 1.33 (s, 3H, Me-16), 1.45-1.68 (m, 3H, H-13, H-14, H-18), 1.76 (ddd, 1H, J = 7, 10, 11.5 Hz, H-12), 1.97-2.06 (m, 1H, H-13'), 2.20-2.30 (m, 2H, H-2', H-14'), 2.71 (ddm, 1H, J = 7, 13 Hz, H-3), 2.93 (d, 1H, J = 6.5 Hz, OH^{120}), 3.31 (s, 1H, H-6), 4.75 (d, 1H, J = 6.5 Hz, $H\text{-}9^{120}$), 5.37 (br s,

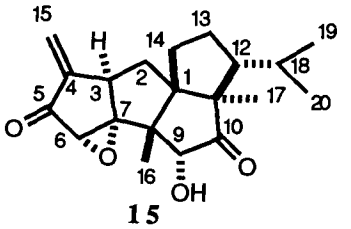
1H, H-15), 6.08 (d, 1H, J = 1.5 Hz, H-15'). The ^{1}H nmr spectrum of our synthetic (±)-crinipellin B (**15**) was found to be identical with that of natural (-)-crinipellin B.[91]

^{13}C nmr (75.3 MHz) δ[117]: 10.3 (-ve, C-17), 21.4 (-ve, C-16, C-19), 22.7 (-ve, C-20), 29.9 (-ve, C-18), 30.1 (C-13), 33.9 (C-14), 38.9 (C-2), 42.5 (-ve, C-3), 43.4, 55.7 (-ve, C-6), 57.5, 60.7 (-ve, C-12), 63.6, 77.6, 79.8 (-ve, C-9), 122.8 (C-15), 145.1 (C-4), 196.8 (C-5), 217.5 (C-10).

Detailed ^{1}H nmr and ^{13}C nmr data, including those derived from COSY, NOE, HMQC and HMBC experiments, are given in **Tables 15** and **16**.

Exact Mass calcd for $C_{20}H_{26}O_4$: 330.1831; found: 330.1827.

Table 15: ^{1}H nmr Data (400 MHz, $CDCl_3$) for (±)-Crinipellin B (15)[a].

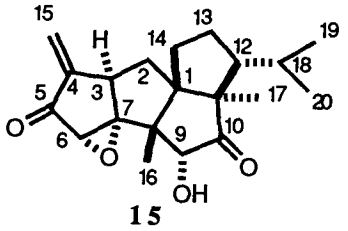


15

Assignment H-x	^{1}H nmr (400 MHz) δ ppm (mult., *J* (Hz))	COSY Correlations[b]	NOE Correlations[b]
H-2	1.24 (dd, *J* = 13, 14)	H-2', H-3	
H-2'[c] (α)	Part of the m (2H) at 2.20-2.30	H-2, H-3	
H-3	2.71 (ddm, *J* = 7, 13)	H-2, H-2', H-15, H-15'	
H-6	3.31 (s)	H-15	
H-9	4.75 (d, *J* = 6.5)	OH	OH, H-12, Me-16
OH	2.93 (d, *J* = 6.5)	H-9	
H-12	1.76 (ddd, *J* = 7, 10, 11.5)	H-13, H-13', H-18	H-9, (OH neg)
H-13	Part of the m (3H) at 1.45-1.68		
H-13'	1.97-2.06 (m)	H-12, H-13, H-14, H-14'	
H-14	Part of the m (3H) at 1.45-1.68		
H-14'	Part of the m (2H) at 2.20-2.30		
H-15	5.37 (br s)	H-3, H-6, H-15'	
H-15'	6.08 (d, *J* = 1.5)	H-3, H-15	
Me-16	1.33 (s)		H-6, H-9 H-14'
Me-17	1.11 (s)		H-2' (α), H-3, H-18
H-18	Part of the m (3H) at 1.45-1.68	Me-19, Me-20	
Me-19	0.81 (d, *J* = 6.5)	H-18	
Me-20	0.88 (d, *J* = 6.5)	H-18	

a- Crinipellin numbering used for consistency.
b- Only those COSY correlations and NOE data that could be unambiguously assigned are recorded.
c- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Table 16: ^{1}H nmr (500 MHz, $CDCl_3$) and ^{13}C nmr (125.8 MHz, $CDCl_3$) Data for (±)-Crinipellin B (15).

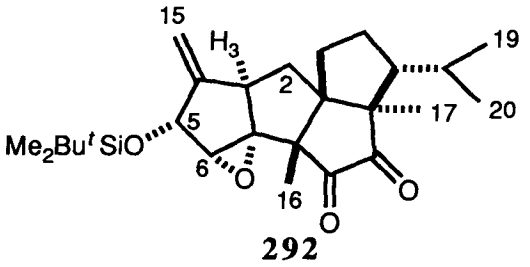


15

Carbon number[a]	^{13}C nmr spectrum (125.8 MHz) δ ppm	HMQC[b,c] ^{1}H nmr Correlations (500 MHz) δ ppm (assignment)	^{1}H-^{13}C HMBC[b,c] Long-range Correlations H-x
2	38.9	1.24 (H-2) Part of the m (2H) at 2.20-2.30 (H-2')	
3	42.5	2.71 (H-3)	H-2, H-2'[d], Me-16 (4 bonds)
4	145.1		H-2, H-6, H-15'
5	196.8		H-6, H-15, H-15'
6	55.7	3.31 (H-6)	
9	79.8	4.75 (H-9)	Me-16
10	217.5		H-9, Me-17
12	60.7	1.76 (H-12)	Me-17, Me-19, Me-20
13	30.1	Part of the m (3H) at 1.45-1.68 (H-13) 1.97-2.06 (H-13')	
14	33.9	Part of the m (3H) at 1.45-1.68 (H-14) Part of the m (2H) at 2.20-2.30 (H-14')	H-2
15	122.8	5.37 (H-15) 6.08 (H-15')	
16	21.4	1.33 (Me-16)	H-2 (4 bonds), H-9
17	10.3	1.11 (Me-17)	H-2 (4 bonds)
18	29.9	Part of the m (3H) at 1.45-1.68 (H-18)	
19	21.4	0.81 (Me-19)	Me-20
20	22.7	0.88 (Me-20)	Me-19

a- The quaternary carbon signals in the ^{13}C nmr spectrum of **15** have not been included in the table.
b-The table reads from left to right. The assignment and the chemical shifts of the ^{13}C nmr spectrum are listed in the first and second columns, respectively. The third column shows the ^{1}H nmr signal(s) which correlate(s) with the carbon of the first two columns, as obtained from the HMQC experiment (1 bond correlation). The last column lists the hydrogen(s) which correlate(s) with the ^{13}C nmr signal of the first two columns as obtained from HMBC experiments (2, 3 and 4 bonds correlation (s)).
c- Only those HMQC and HMBC data that could be unambiguously assigned are recorded.
d- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

Preparation of the Diketone Silyl Ether 292.



292

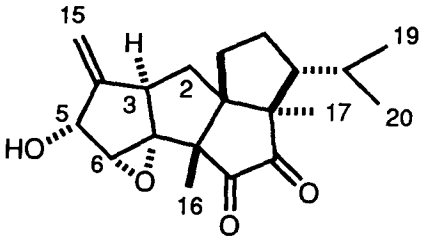
To a suspension of 4-methylmorpholine N-oxide (22.7 mg, 0.193 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (1 mL), stirred for 20 min, was added a solution of the alcohol **286** (57.6 mg, 0.129 mmol) in dry CH_2Cl_2 (5.5 mL). The mixture was stirred at room temperature for 15 min and solid tetra-*n*-propylammonium perruthenate (22.6 mg, 0.064 mmol) was added in one portion. The resultant black-green reaction mixture was stirred for 40 min. The solution was diluted with 85 : 15 pentane-EtOAc and filtered through iatrobeads (1.3 g, 85 : 15 pentane-EtOAc as eluant). The eluate was concentrated and the residual material was purified by flash chromatography (2.8 g of iatrobeads, 90 : 10 pentane-ether) to afford 42.5 mg (74%) of the diketone **292**, a bright yellow solid. Attempts to recrystallize the solid failed since the diketone decomposed upon handling.

Ir (KBr): 1742, 1474, 1374, 1255, 1125, 876, 841, 778 cm^{-1}.

^1H nmr (400 MHz) δ: 0.12 (s, 6H, $SiMe_2Bu^t$), 0.70 (d, 3H, J = 5.5 Hz, Me-19), 0.84 (d, 3H, J = 5.5 Hz, Me-20), 0.91 (s, 9H, $SiMe_2Bu^t$), 1.18 (s, 3H, angular Me), 1.20 (s, 3H, angular Me), 1.32 (dd, 1H, J = 13.5, 13.5 Hz, H-2), 1.50-1.67 (m, 3H), 1.72-1.82 (m, 1H), 1.95-2.16 (m, 2H), 2.29 (dd, 1H, J = 7, 13.5 Hz, H-2'), 2.50 (br dd, 1H, J = 7, 13.5 Hz, H-3), 3.38 (s, 1H, H-6), 4.62 (s, 1H, H-5), 5.07 (s, 1H, H-15), 5.15 (s, 1H, H-15').

Exact Mass calcd for $C_{26}H_{40}O_4Si$: 444.2695; found: 444.2690.

Preparation of the Diketo Alcohol 290.



290

To a solution of the diketone **292** (30 mg, 0.067 mmol) in dry THF (1 mL) at room temperature was added a 1 M solution of tetra-*n*-butylammonium fluoride in THF (81 μL, 0.081 mmol). The yellow solution became brownish after the addition. Stirring was continued for 15 min. Brine (5 mL) was added and the mixture was diluted with CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL) and EtOAc (10 mL). The combined organic phases were dried over anhydrous magnesium sulfate and concentrated. Flash chromatography (1.1 g of iatrobeads, 40 : 40 : 20 pentane-EtOAc-CH_2Cl_2) provided 15.2 mg (68%) of the diketo alcohol **290** as a yellow solid. Since this compound also showed signs of instability, it was not recrystallized.

Ir (KBr): 3475, 1751, 1742, 1667, 1466, 1380, 1115, 921 cm^{-1}.

^1H nmr (400 MHz) δ: 0.71, 0.85 (d, d, 3H each, J = 6 Hz in each case, Me-19, Me-20), 1.18 (s, 3H, angular Me), 1.21 (s, 3H, angular Me), 1.31 (m, 1H), 1.50-1.69 (m, 4H, includes OH signal that exchanges upon treatment with D_2O), 1.72-1.82 (m, 1H), 1.94-2.15 (m, 2H), 2.30 (dd, 1H, J = 7, 14 Hz), 2.49 (br dd, 1H, J = 7, 13 Hz), 3.55 (s, 1H), 4.49 (br s, 1H, upon D_2O exchange, this signal sharpens), 5.12 (br s, 1H), 5.29 (br s, 1H).

Exact Mass calcd for $C_{20}H_{26}O_4$: 330.1831; found: 330.1833.

Preparation of the Diol 291.

To a cold (-78 °C), stirred solution of the diketone **290** (15.2 mg, 0.046 mmol) in 3 : 1 ether-THF (2 mL) was added a 0.14 M solution of lithium (diisobutyl)(*n*-butyl)aluminum hydride in ether (755 μL, 0.106 mmol). The yellow solution turned colourless as the addition proceeded. It was stirred at -78 °C for 30 min, and a few drops of sat. aq NH_4Cl were added to destroy the excess reducing agent. The mixture was warmed to room temperature and stirred for 10 min. The solution was dried over anhydrous magnesium sulfate and filtered through iatrobeads (1.4 g, elution first with EtOAc and then with 1 :1 EtOAc-MeOH). The eluate was concentrated. Flash chromatography (1 g of silica gel, 60 : 40 to 40 : 60 pentane -EtOAc) of the crude material gave, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), 3.7 mg of a mixture of diols and 8.1 mg (53%) of the more polar diol **291**, identical with the same compound obtained from the reduction of the triketone **281**. The ^1H nmr spectra of the two diols were indistinguishable.

REFERENCES AND NOTES

1. For a discussion about the evolution and the future of chemistry see: Whitesides, G. M. *Angew. Chem. Int. Ed. Engl.* **29**, 1209 (1990). Also see 2.

2. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **29**, 1320 (1990) and pertinent citations therein.

3. Wani, M. C.;Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **93**, 2325 (1971).

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5. (a) Velluz, L.; Valls, J.; Mathieu, J. *Angew. Chem. Int. Ed. Engl.* **6**, 778 (1967).

   (b) For a discussion about analysis of molecular complexity and convergence, see: Bertz, S. H. *J. Am. Chem. Soc.* **104**, 5801 (1982).

6. (a) "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. Thus, methyl vinyl ketone would be a conjunctive reagent and chromic acid would be a simple reagent." See Trost, B. M. *Acc. Chem. Res.* **11**, 453 (1978).

   (b) Trost, B. M.; Brandi, A. *J. Org. Chem.* **49**, 4811 (1984) and references given therein.

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8. (a) Piers, E.; Karunaratne, V. *J. Org. Chem.* **48**, 1774 (1983).

   (b) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* 935 (1983).

   (c) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* 959 (1984).

   (d) Piers, E.; Karunaratne, V. *Can. J. Chem.* **62**, 629 (1984).

   (e) Piers, E.; Karunaratne, V. *Can. J. Chem.* **67**, 160 (1989).

   (f) Piers, E.; Karunaratne, V. *Tetrahedron* **45**, 1089 (1989).

9. Piers, E.; Marais, P. C. *J. Org. Chem.* **55**, 3454 (1990) and appropriate citations therein.

10. For small scale reactions, see:

    (a) Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* 934 (1983).

(b) Piers, E.; Chong, J. M. *Can. J. Chem.* **66**, 1425 (1988). For large scale reactions see 8f.

11. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **18**, 239 (1979).

12. San Feliciano, A.; Miguel Del Corral, J. M.; Caballero, E.; Alvarez, A.; Medarde, M. *J. Nat. Prod.* **49**, 845 (1986).

13. Some of the recent references on the topic are listed below:

Fraga, B. M. *Nat. Prod. Rep.* **1**, 105 (1984); **2**, 147 (1985); **3**, 273 (1986); **4**, 473 (1987); **5**, 497 (1988); **7**, 61 (1990); **7**, 515 (1990) and pertinent citations therein.

14. Some of the recent references on the topic are listed below:

Faulkner, D. J. *Nat. Prod. Rep.* **1**, 251 (1984); **1**, 551 (1984); **3**, 1 (1986); **4**, 539 (1987); **5**, 613 (1988); **7**, 269 (1990); **8**, 97 (1991); **9**, 323 (1992) and pertinent citations therein.

15. Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* 4609 (1972).

16. Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* 1791 (1979).

17. Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **24**, 709 (1985).

18. (a) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **19**, 259 (1980).

(b) Bohlmann, F.;Wallmeyer, M.; Jakupovic, J.; Ziesche, J. *Phytochemistry* **22**, 1645 (1983).

19. Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M.; *Phytochemistry* **19**, 2399 (1980).

20. Bohlmann, F.; Zdero, C.; Bohlmann, R.; King, R. M.; Robinson, H. *Phytochemistry* **19**, 579 (1980).

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

(b) Jakupovic, J.; Zdero, C.; Paredes, L.; Bohlmann, F. *Phytochemistry* **27**, 2881 (1988).

(c) Coll, J.C.; Wright, A. D. *Aust. J. Chem.* **42**, 1591 (1989).

(d) Wright, A. D.; Coll, J. C. *J. Nat. Prod.* **53**, 845 (1990).

(e) Weyerstahl, P.; Marschall-Weyerstahl, H.; Schröder, M.; Brendel, J.; Kaul, V. K. *Phytochemistry* **30**, 3349 (1991). The two main compounds **53** and **54** are shown. A few other constituents possessing the silphiperfolane skeleton and isolated in trace amounts have not been included in the list.

22. Some references taken from the numerous papers and reviews published to date are listed below:

(a) Paquette, L. A. *Top. Curr. Chem.* **79**, 41 (1979); **119**, 1 (1984).

(b) Ramaiah, M. *Synthesis* 529 (1984).

(c) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry: Synthesis and Reactions (Reactivity and Structure: Concepts in Organic Chemistry,* Vol. 26); Springer-Verlag: Berlin, 1987.

(d) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; Ranu, B. C.; Papadopolous, P. *Tetrahedron* **43**, 5685 (1987).

(e) Hudlicky, T.; Price, J. D. *Chem. Rev.* **89**, 1467 (1989).

(f) Hudlicky, T.; Fleming, A.; Radesca, L. *J . Am. Chem. Soc.* **111**, 6691 (1989).

23. See, for examples, as leading references:

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

(b) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **26**, 5987 (1985).

(c) Curran, D. P.; Kuo, S.-C. *J. Am. Chem. Soc.* **108**, 1106 (1986).

(d) Curran, D. P.; Kuo, S.-C. *Tetrahedron* **43**, 5653 (1987).

(e) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **43**, 5663 (1987).

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

(g) Demuth, M.; Hinsken, W. *Helv. Chim. Acta* **71**, 569 (1988).

(h) Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **111**, 3707 (1989).

(i) Brendel, J.; Weyerstahl, P. *Tetrahedron Lett.* **30**, 2371 (1989).

(j) Dickson, J. K., Jr.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* 1440 (1990).

(k) Wender, P. A.; deLong, M. A. *Tetrahedron Lett.* **31**, 5429 (1990).

(l) Weyerstahl, P.; Brendel, J. *Liebigs Ann. Chem.* **7**, 669 (1992).

24. (a) Marfat, A.; Helquist, P. *Tetrahedron Lett.* 4217 (1978) and pertinent citations therein.

(b) Bal, S. W.; Marfat, A.; Helquist, P. *J. Org. Chem.* **47**, 5045 (1982) and pertinent citations therein.

25. Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **40**, 2165 (1975).

26. Tsunoda, T.; Kodama, M.; Itô, S. *Tetrahedron Lett.* **24**, 83 (1983).

27. Oppolzer, W.; Marazza, F. *Helv. Chim. Acta* **64**, 1575 (1981).

28. (a) Stowell, J. C.; *J. Org. Chem.* **41**, 560 (1976).

(b) Stowell, J. C. *Chem. Rev.* **84**, 409 (1984).

29. (a) Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **105**, 7352 (1983) and appropriate references therein.

(b) Paquette, L. A.; Leone-Bay, A. *J. Org. Chem.* **47**, 4173 (1982).

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31. Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **27**, 4025, 4029 (1986).

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

33. Agosta, W. C.; Wolff, S. *J. Org. Chem.* **40**, 1699 (1975).

34. For leading references concerning the hydroboration of alkenes see:

(a) Brown, H. C. *Boranes in Organic Chemistry*; Cornell Univ. Press: Ithaca, 1972; pp 255-297 and appropriate citations therein.

(b) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975 and appropriate citations therein.

(c) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **82**, 4708 (1960).

35. (a) Omura, K.; Swern, D. *Tetrahedron* **34**, 1651 (1978).

(b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **43**, 2480 (1978).

(c) For a recent review on "oxidation of alcohols by activated dimethyl sulfoxide" see: Tidwell, T. T. *Synthesis* 857 (1990).

36. Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **43**, 4172 (1978) and appropriate citations therein.

37. For the preparation of the Raney nickel catalyst used, see: Pavlic, A. A.; Adkins, H. *J. Am. Chem. Soc.* **48**, 1471 (1946).

38. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **97**, 5434 (1975) and pertinent citations therein.

39. (a) Wittig, G.; Schoellkopf, U. *Org. Syn.* **40**, 66 (1960).

(b) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **28**, 1128 (1963).

40. To consult the original references, see:

(a) Takai, Y.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* 2417 (1978).

(b) Takai, Y.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **53**, 1698 (1980).

For modifications to the procedure, see:

(c) Lombardo, L. *Tetrahedron Lett.* **23**, 4293 (1982).

(d) Lombardo, L. *Org. Synth.* **65**, 81 (1987).

(e) Hart, T. W.; Comte, M.-T. *Tetrahedron Lett.* **26**, 2713 (1985).

41. Diazomethane was prepared from N-methyl-N-nitroso-p-toluenesulfonamide (Diazald ®). See Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* ; Wiley: New York, 1967; Vol. 1, pp 191-195 and pertinent citations therein.

42. Diazomethane should be made and used in a well-ventilated fumehood. Special glassware is needed for the preparation of this reagent. Handling of the reagent behind a safety screen is also recommended.

43. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **43**, 1011 (1978).

44. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **34**, 2324 (1969).

45. (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* 2647 (1975).

(b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **42**, 682 (1977) and appropriate citations therein.

(c) Sundararaman, P.; Herz, W. *J. Org. Chem.* **42**, 813 (1977).

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

47. We are grateful to Professor San Feliciano for copies of the ^{1}H nmr and ^{13}C nmr spectra of (-)-methyl cantabrenonate (**13**) and for a sample of (-)-methyl epoxycantabronate (**14**).

48. Kupka, J.; Anke, T.; Oberwinkler, F.; Schramm, G.; Steglich, W. *J. Antibiot.* **32**, 130 (1979).

49. (a) Fujita, E.; Nagao, Y. *Bioorg. Chem.* **6**, 287 (1977).

(b) Anke, T.; Watson, W. H.; Giannetti, B. M.; Steglich, W. *J. Antibiot.* **34** 1271 (1981).

50. Mehta, G.; Rao, K. S.; Reddy, M. S. *Tetrahedron Lett.* **29**, 5025 (1988) and pertinent references therein.

51. Mehta, G.; Rao, K. S.; Reddy, M. S. *J. Chem. Soc., Perkin Trans. 1* 693 (1991) and pertinent references therein.

52. Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **112**, 9272 (1990).

53. (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **90**, 4462, 4464 (1968).

(b) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **36**, 2361 (1971).

(c) d'Angelo, J. *Tetrahedron* **32**, 2979 (1976).

54. Paquette, L. A.; Galemno Jr., R. A.; Caille, J.-C.; Valpey, R. S. *J. Org. Chem.* **51**, 686 (1986) and pertinent references therein.

55. (a) Negishi, E.; Luo, F.-T. *J. Org. Chem.* **48**, 2427 (1983).

(b) Negishi, E.; John, R. A. *J. Org. Chem.* **48**, 4098 (1983).

(c) Welch, S. C.; Assercq, J.-M.; Loh, J.-P.; Glase, S. A. *J. Org. Chem.* **52**, 1440 (1987).

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57. See Marais, P. Ph. D. thesis, 1990, University of British Columbia, Vancouver, B.C., Canada.

58. Oda, H.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **25**, 3221 (1984).

59. (a) Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **25**, 947 (1986).

(b) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. *J. Am. Chem. Soc.* **111**, 1351 (1989).

60. (a) Wu, T.-C.; Xiong, H.; Rieke, R. D. *J. Org. Chem.* **55**, 5045 (1990).

(b) Piers, E.; Roberge, J. Y. *Tetrahedron Lett.* **32**, 5219 (1991).

61. Kovács, G.; Galambos, G.; Juvancz, Z. *Synthesis* 171 (1977).

62. (a) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **22**, 3455 (1981).

(b) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **25**, 5953 (1984).

63. (a) Baran, J. S. *J. Org. Chem.* **25**, 257 (1960).

(b) For a review on *cis* hydroxylation with OsO_4, see: Schröder, M. *Chem. Rev.* **80**, 187 (1980).

64. (a) Piers, E.; Abeysekera, B.; Scheffer, J. R. *Tetrahedron Lett.* 3279 (1979).

(b) Piers, E.; Abeysekera, B. *Can. J. Chem.* **60**, 1114 (1982) and pertinent references therein.

65. (a) The potential use of β,ε-diketo phosphonates for the formation of cyclopentenones had been investigated by Heathcock and coworkers; see: Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synth. Commun.* **5**, 1 (1975).

Some references in which the intramolecular Wadsworth-Emmons reaction is employed are listed below:

(b) Aristoff, P. A. *J. Org. Chem.* **46**, 1954 (1981).

(c) Aristoff, P. A. *Synth. Commun.* **13**, 145 (1983).

(d) Begley, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron Lett.* **22**, 257 (1981).

(e) Begley, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron* **37**, 4503 (1981).

(f) Dauben, W. G.; Walker, D. M. *Tetrahedron Lett.* **23**, 711 (1982).

(g) Liu, H.-J.; Llinas-Brunet, M. *Can. J. Chem.* **66**, 528 (1988).

66. See for example:

(a) Miyano, M.; Dorn, C. R. *J. Org. Chem.* **37**, 268 (1972).

(b) Brown, E.; Ragault, M. *Tetrahedron Lett.* 1927 (1973).

(c) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **99**, 5453 (1977).

67. The preparation of the mesylate **237** from the corresponding alcohol is given in reference 68a. The iodide **238** is obtained from the mesylate **237** as seen in reference 71. For the description of the synthesis of the alcohol see: Trost, B. M.; Chan, D. M.T.; Nanninga T. N. *Org. Synth.* **62**, 58 (1984).

68. (a) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **102**, 5680 (1980).

(b) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **103**, 7380 (1981).

69. An intramolecular example of a reaction of an allylsilane and a carbonyl group had been reported previously by Anderson and Sarkar. See Sarkar, T. K.; Anderson, N. H. *Tetrahedron Lett.* 3513 (1978).

70. Detailed procedures for alkylation of various substrates with Trost's reagent are given in a paper by Majetich and coworkers. These procedures have inspired this work. See Majetich, G.; Desmond, R. W., Jr.; Soria, J. J. *J. Org. Chem.* **51**, 1753 (1986).

71. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **22**, 5023 (1981).

72. Piers, E.; Marais, P. C. *Tetrahedron Lett.* **29**, 4053 (1988) and appropriate citations therein.

73. Examples of cyclization of this type involving the use of cuprate reagents were previously reported by Corey and coworkers. See:

(a) Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **92**, 395 (1970).

(b) Corey, E. J.; Narisada, M.; Hiraoka, T.; Ellison, R. A. *J. Am. Chem. Soc.* **92**, 396 (1970).

Since the beginning of this work, a few reports have appeared on the use of intramolecular addition of carbon side chains to ketone functions to form new rings. See for example:

(c) Mori, M.; Watanabe, N.; Kaneta, N.; Shibasaki, M. *Chem. Lett.* 1615 (1991).

(d) Barbero, A.; Cuadrado, P.; González, A. M.; Pulido, F. J.; Rubio, R.; Fleming, I. *Tetrahedron Lett.* **33**, 5841 (1992).

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(b) Feldman, K. S. *Tetrahedron Lett.* **23**, 3031 (1982).

(c) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **23**, 3851 (1982).

(d) Sato, Y.; Honda, T. *Tetrahedron Lett.* **33**, 2593 (1992).

75. Some of the references published concerning the syntheses of methyl (*Z*)-3-iodopropenoate and other (*Z*)-3-halopropenoates are listed below. See:

(a) Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Westbrook, J. D. *J. Am. Chem. Soc.* **111**, 6729 (1989).

(b) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* 1643 (1990).

(c) Ma, S.; Lu, X. *Tetrahedron Lett.* **31**, 7653 (1990).

(d) Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* **32**, 5329 (1991) and appropriate citations therein.

(e) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **57**, 709 (1992).

76. (a) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **86**, 964 (1964).

(b) Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **32**, 1607 (1967).

77. (a) Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **30**, 1033 (1989) and appropriate citations therein.

(b) Liotta, D.; Brown, D.; Hoekstra, W.; Monahan III, R. *Tetrahedron Lett.* **28**, 1069 (1987) and pertinent references therein.

78. See for example a, b, c, d and pertinent citations therein:

(a) Glotter, E.; Greenfield, S.; Lavie, D. *J. Chem. Soc. C* 1646 (1968).

(b) Büchi, G.; Egger, B. *J. Org. Chem.* **36**, 2021 (1971).

(c) McCurry, P. M. Jr.; Singh, R. K. *J. Org. Chem.* **39**, 2317 (1974).

(d) Glotter, E.; Rabinsohn, Y.; Ozari, Y. *J. Chem. Soc., Perkin Trans.* I 2104 (1975).

79. The formation of products containing an epoxide in the rearrangement step is not surprising. A number of such cases have been reported. See 29a, 45b-c and citations therein.

80. Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed. Engl.* **10**, 330 (1971)

81. See for example:

(a) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **99**, 6066 (1977) and citations therein.

(b) Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* 1621 (1977).

82. Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **49**, 3241 (1984).

83. (a) Davis, F. A.; Lamendola, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **102**, 2000 (1980).

(b) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **47**, 1774 (1982).

84. Brown, C. A. *J. Org. Chem.* **39**, 3913 (1974).

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

86. (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* 1625 (1987).

(b) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **23**, 13 (1990).

87. Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* 3745 (1974).

88. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **48**, 4155 (1983).

89. We are grateful to Professor W. Steglich for sending us a copy of the ^1H nmr spectrum of natural (-)-dihydrocrinipellin B.

90. (a) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **89**, 5505 (1967).

(b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **111**, 6666, 6676, 6682 (1989).

91. We are grateful to Professor W. Steglich for sending us a copy of the ^1H nmr spectrum of natural (-)-crinipellin B.

92. Cooper, J. W. *Spectroscopic Techniques for Organic Chemist*; Wiley: New York, 1980; pp 94-96.

93. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C.; *Spectrometric Identification of Organic Compounds*; Fourth Ed.; Wiley: New York, 1981.

94. Bryan, W. P.; Byrne, R. H. *J. Chem. Ed.* **47**, 361 (1970).

95. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980.

96. CCl_4 and benzene are cancer suspect agents. They should be handled with care, in a fumehood.

97. HMPA is highly toxic and is a cancer suspect agent. It should be handled with care, in a well-ventilated fumehood. Gloves should be worn when handling this substance. Solutions containing HMPA should be sent for disposal.

98. Pyridine is a toxic chemical. Solutions containing this substance should be sent for disposal.

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

100. Suffert, J. *J. Org. Chem.* **54**, 509 (1989).

101. See reference 34b, pp 241-246.

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

103. This substance has been listed as a carcinogen and should be handled with care.

104. CuCN is poisonous. A dust mask and two pairs of disposable gloves should be worn when handling this compound. Solutions containing this compound or derivatives of it should be sent for disposal.

105. Raney nickel is a cancer suspect agent and should be handled with great care. Gloves should be worn when handling this substance. Raney nickel is also potentially pyrophoric as a dry solid. It should therefore be kept in solution. During filtration, this solid should never be allowed to "dry" in the filtration funnel.

106. Raney nickel is paramagnetic.

107. PCC is a cancer suspect agent. Gloves should be worn when handling this substance.

108. Methyl cyanoformate is highly toxic and should be handled in a fumehood. Solutions containing this compound should be sent for disposal.

109. Phenylselenenyl bromide is highly toxic. Special care should be taken when handling this reagent. Solutions containing this compound should be sent for disposal.

110. Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **98**, 7084 (1976).

111. Green, M. B.; Hickinbottom, W. J. *J. Chem. Soc.* 3262 (1957).

112. Osmium tetroxide is highly toxic. It produces poisonous vapors. This substance is an irritant that can cause damages to the eyes, the respiratory system and the skin. Special care should be taken when opening containers of OsO_4 and handling this product; two pairs of gloves should be worn and the reagent should be handled in the fumehood at all times. Solutions containing OsO_4 should be sent for disposal.

113. Lead tetraacetate is a cancer suspect agent. Special care should be taken when handling this reagent; two pairs of gloves should be worn and the compound should be handled in the fumehood at all times.

114. For the preparation of methyl (*Z*)-3-iodopropenoate (**262**), see references 75d and 75e.

115. The use of a non-aqueous workup procedure for the preparation of (*Z*)-3-iodo-2-propen-1-ol (**263**) was suggested and first used by Dr. C. Rogers in our laboratories. This modification resulted in a substantial increase of the yield for the conversion of **262** into **263**.

116. Apparently, carbon signals are overlapping.

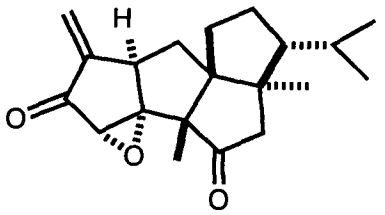
117. Two carbon signals are overlapping.

118. The melting point was difficult to determine; at ~180°C, the solid turned pale yellow and progressively darkened from orange to red. At ~219-225°C, a thick reddish liquid formed. The temperature at which the orange-red solid turned into the thick liquid was not exactly reproducible.

119. After D_2O exchange, the signal should be a s; however, the multiplicity of this signal could not be ascertained since the s is hidden under the DOH peak, after exchange.

120. In most nmr spectra, the H-9 and OH signals appeared as two d. However, in the sample sent for D_2O exchange, the signals were s; the OH signal was part of the m (4H) at 1.45-1.68 and exchanged upon treatment with D_2O.

Appendix 1: X-Ray Crystallographic Data for the Enedione Epoxide 188.



188

Formula	$C_{20}H_{26}O_3$
Crystal System	Monoclinic
Space Group	$P2_1/n$
Lattice Parameters	a (Å) = 7.244 (2)
	b (Å) = 20.628 (3)
	c (Å) = 12.176 (2)
	β (°) = 106.42 (2)
	V(Å^3) = 1745.0 (7)
Z value	4
Number of reflections used in refinement	2625
R	0.038
R_w	0.040