STUDIES IN DI- AND SESTERTERPENOID SYNTHESIS

by

MIGUEL ANGEL ROMERO MARTINEZ DEL SOBRAL

B.Sc., National University of México, 1984
M.Sc., National University of México, 1986

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Department of CHEMISTRY

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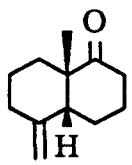
ABSTRACT

Stereoselective 9-step conversions of the ketone **17** into the tricyclic ketone **31** via two similar synthetic pathways are described. The highly stereoselective steps involved in the preparation of **31** were: a) the Lewis acid-catalyzed reaction of the silyl enol ethers **50** and **60** with the ethylene ketal of 3-buten-2-one to produce the diketones **37** and **39**, respectively, b) the hydrogenation of the enone **32** to give the ketone **56**, and c) the Birch reduction of the enone **61** to give **31**. Compound **31** contains the correct relative configuration at each of the corresponding chiral centers present in the target molecule **16** and, therefore, appears to be an ideal intermediate for a projected total synthesis of (±)-**16** (initially believed to be the sesterterpenoid suvanine).

A 15-step total synthesis of the antimicrobial diterpene (±)-8-isocyano-10(14)-amphlilectadiene (**23**) from the intermediate **24** is described. The key steps in the synthesis of (±)-**23** involved the stereoselective Birch reduction of **24**, the epimerization of the aldehyde **91** to the corresponding α-formyl isomer, and the degradation of the carboxylic acid function of **95** to an isonitrile group.

The last part of the synthetic work described in this thesis resulted in a 15-step conversion of the ketone **17** into the tricyclic ketone **164**. Of particular note in this sequence of reactions are: a) the palladium(0)-catalyzed coupling reaction of the enol triflate **143** with lithium cyanide to produce the nitrile **144**, b) the stereoselective alkylation of **144** to give compound **148**, and c) the stereoselective Birch reduction of the enone **163** to produce **164**. The methodology employed in the construction of the tricyclic intermediate **164** contributes to the development of a general route towards the synthesis of the spongiane diterpenes **18-22**.



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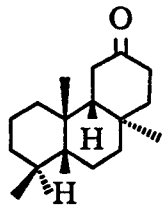

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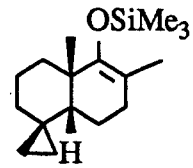

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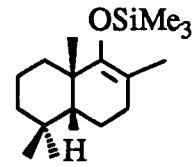

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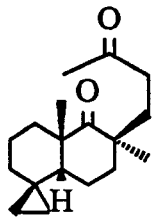

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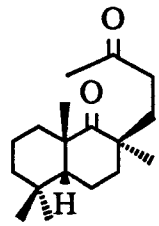

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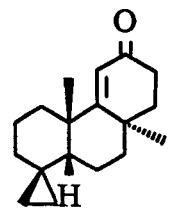

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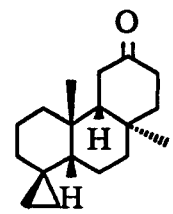

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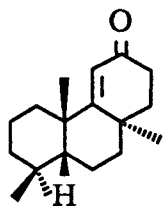

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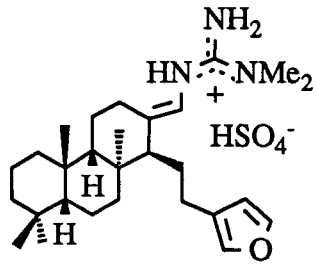

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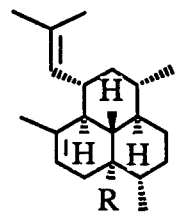
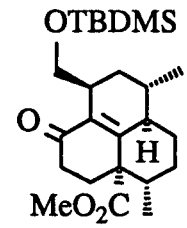


23 R= NC
95 R= CO_2H



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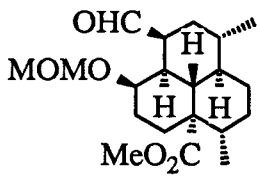

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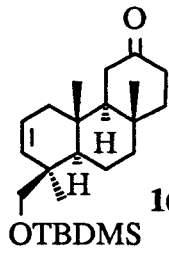

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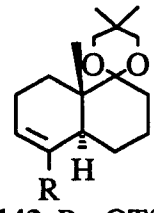
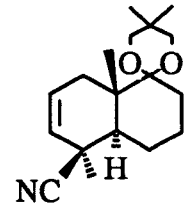


143 R= OTf
144 R= CN



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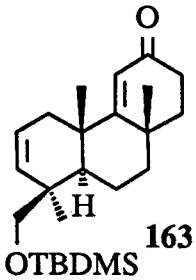

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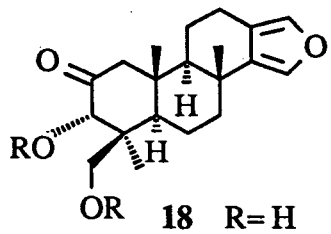
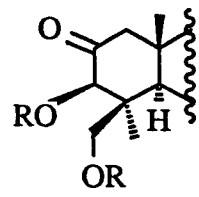
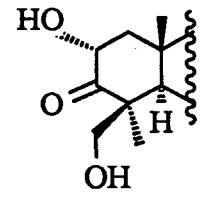


18 R= H
19 R= Ac



20 R= H
21 R= Ac



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Ac	-	acetyl
aq	-	aqueous
Bn	-	benzyl
br	-	broad
Bu	-	butyl
cat	-	catalytic
COSY	-	correlated spectroscopy
m-CPBA	-	meta-chloroperoxybenzoic acid
Δ	-	heat
d	-	doublet
DIBAL	-	diisobutylaluminum hydride
DMAP	-	4-N,N-dimethylaminopyridine
DME	-	1,2-dimethoxyethane
DMF	-	N,N-dimethylformamide
DMSO	-	dimethylsulfoxide
DPPA	-	diphenylphosphoryl azide
equiv	-	equivalent(s)
Et	-	ethyl
g	-	gram(s)
gem	-	geminal
glc	-	gas-liquid chromatography
h	-	hour(s)
HMPA	-	hexamethylphosphoramide

Hz	-	hertz
ir	-	infrared
K	-	ketal function
LDA	-	lithium diisopropylamide
m	-	multiplet
M	-	molar
Me	-	methyl
mg	-	milligram(s)
MHz	-	megahertz
min	-	minute(s)
mmol	-	millimole(s)
mp	-	melting point
mol	-	mole(s)
MOM	-	methoxymethyl
Ms	-	methanesulfonyl
nmr	-	nuclear magnetic resonance
nOe	-	nuclear Overhauser enhancement
PCC	-	pyridinium chlorochromate
Ph	-	phenyl
Pr	-	propyl
Pyr	-	pyridine
q	-	quartet
rt	-	room temperature
s	-	singlet
sec	-	secondary
t	-	triplet

tert	-	tertiary
TBDMS	-	tert-butyldimethylsilyl
TfO	-	trifluoromethanesulfonate
Tf_2NPh	-	N-phenyltrifuoromethanesulfonimide
THF	-	tetrahydrofuran
tlc	-	thin layer chromatography
TMS	-	trimethylsilyl
p-TsO	-	para-toluenesulfonate
Ts	-	para-toluenefulfonyl
v	-	volume
w	-	weight
$w_{1/2}$	-	peak width at half height
⇅	-	reflux

ACKNOWLEDGEMENTS

I am deeply grateful to my research supervisor, Professor Edward Piers, for his guidance and patience, as well as for the outstanding example I believe he sets as an educator and as a scientist. It has indeed been a privilege and a pleasure to work with him as a member of his research group.

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INTRODUCTION

I. General

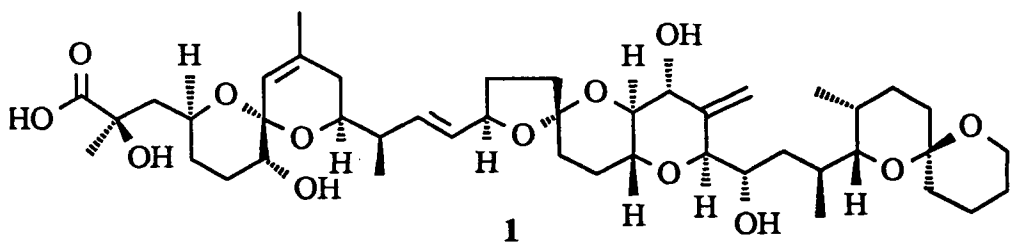
Marine organisms are the source of a large number of diverse organic compounds. During the last decade scientists have become increasingly aware of the importance of marine natural products. This awareness has given rise to multidisciplinary efforts to discover and study marine natural products with interesting structural and biological properties. Microorganisms, algae, fish, sponges, molluscs, and coelenterates are some examples of marine organisms that have been studied as sources of natural products.[1]

Marine natural products are of importance to humankind because they play a significant role in maintaining an equilibrium in marine ecosystems and they often exhibit interesting pharmacological properties. For this reason, chemical ecology and pharmacological studies using marine natural products have been increasing rapidly in nature and extent.[1] However, many aspects of these natural compounds, such as their biological function and potential applications, are yet to be discovered.

From a synthetic organic chemist's point of view, the unusual, synthetically challenging, and aesthetically pleasing structures that natural products of marine origin exhibit, offer an incentive to attempt their synthesis. More importantly, perhaps, the syntheses of natural products often allow the confirmation of original structural assignments, prove the efficiency of new synthetic methods, or test the viability of a

synthetic plan. Furthermore, the synthesis of natural products provides an opportunity to discover reactions which can be relevant to chemical theory or useful in the development of new synthetic methods. Unfortunately, the amount of material isolated from natural sources is sometimes limited and, thus, amounts sufficient for extensive biological tests are not available. Chemical synthesis has the potential to provide the necessary amounts of the natural products, or their analogues, for this purpose.

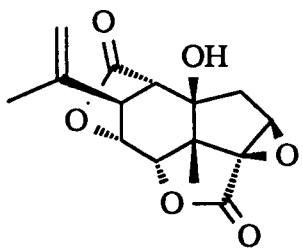
Some of the most interesting marine natural products that have been isolated so far are produced by sponges. It is believed that some of these substances act as chemical defence agents against predators, thus facilitating the survival of these fragile and physically unprotected organisms.[1c] Among the many types of organic substances that have been isolated from sponges are alkaloids, acetylenic compounds, fatty acids, halogenated compounds, macrolides, polyethers, and terpenoids. In the brief discussion given below, the structural diversity of some natural products isolated from sponges will be illustrated. At least one synthesis has been reported for each of the examples mentioned.



1

(+)-Okadaic acid (**1**), one of the most complex polyether metabolites isolated from marine sources is the causative toxin of diarrhetic shellfish poisoning in Europe.[2]

Compound **1** was isolated from the sponge *Halichondria okadai* and from the dinoflagellate *Procentrum lima*. However, the latter is believed to be the progenitor of okadaic acid.[3] A total synthesis of this structurally interesting compound by Isobe and coworkers has been reported in a series of papers.[4a-e] Picrotoxinin (**2**), a known toxin isolated from terrestrial organisms, was isolated from the sponge *Spirastrella inconstans*.[5] Corey and Pearce[6a] and Niwa et al.[6b] have synthesized this compound. The antimicrobial sesterterpenoid palauolide (**3**), which inhibits the growth of *Bacillus subtilis* and *Staphylococcus aureus*, has been isolated from at least three different species of sponges collected from Palau, Western Caroline Islands.[7] Piers and Wai[8] carried out a synthesis of (±)-**3** via a 17-step sequence of reactions, starting from 3,6-dimethyl-2-cyclohexen-1-one. Two syntheses of (+)-euryfuran (**4**),[9] a compound isolated from the sponges *Euryspongia*[10] and *Dysidea herbacea*,[11] led to the assignment of its absolute configuration.



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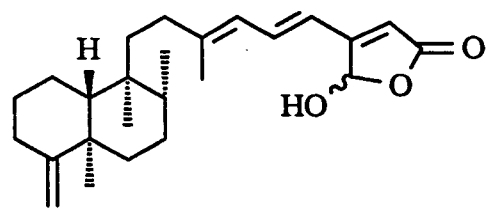

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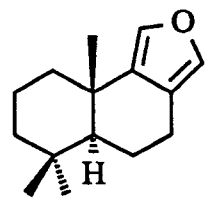
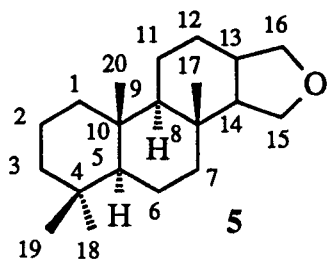


4

Isoagatholactone (**6**) and compounds **7-10**, which are metabolites of *Spongia officinalis*,[12] all bear the 'spongian' carbon skeleton **5**. Compounds **6**[13a-c] and **8-10**[13d,14] were synthesized by three research groups.



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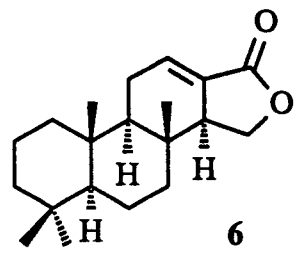

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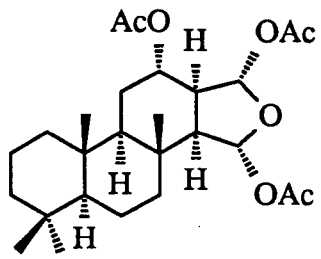

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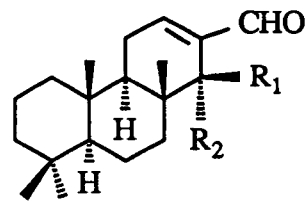
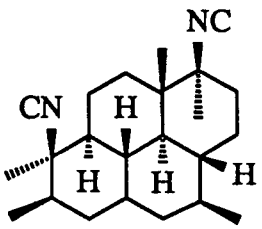
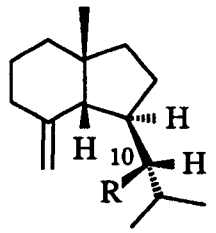


8 R_1=CHO, R_2=H
9 R_1=H, R_2=CHO
10 R_1=CH_2OAc, R_2=H

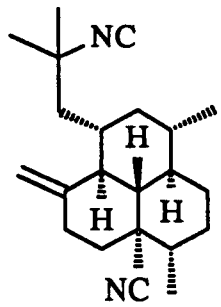
The largest group of naturally occurring isocyanides are produced by marine organisms. More than twenty such derivatives are currently known.[15] The isocyanides are often found as members of triads with the corresponding isothiocyanates and formamides.

The structurally unusual compounds (+)-axamide-1 (**11**), (+)-axisonitrile-1 (**12**), and (+)-axisothiocyanate-1 (**13**) were isolated from the sponge *Axinella cannabina*.[16] A total synthesis of (±)-**11**, (±)-**12** and their corresponding C_{10} epimers was carried out by Piers et al.[17] (+)-7,20-Diisocyanoadociane (**14**) was isolated from a sponge of the species *Amphimedon*[18] and was synthesized by Corey and Magriotis,[19] thus allowing the assignment of its absolute configuration. (-)-8,15-Diisocyano-11(20)-amphilectene (**15**)





11 R=NH-CHO
12 R=NC
13 R=NCS

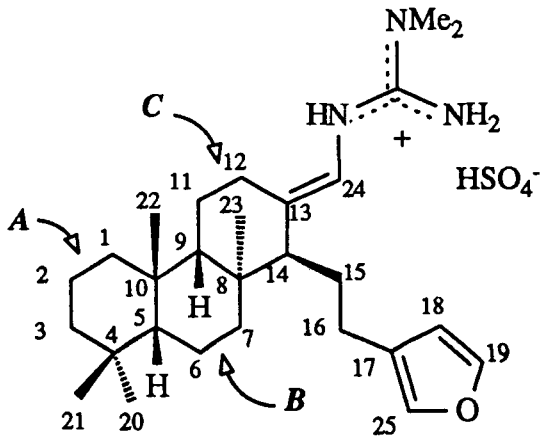


14 **15**

is a structurally related diisocyano derivative isolated from the sponge *Hymeniacidon amphilecta*.[20] A 20-step stereocontrolled synthesis of (±)-**15** was recently completed by Piers and Llinas-Brunet.[21]

II. Objectives

IIa. Synthesis of suvanine



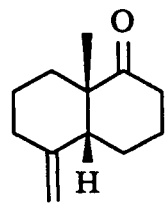
16

Suvanine is a tricyclic sesterterpenoid isolated from sponges collected at Suva Harbor, Fiji Island, and Palau. Although it was initially thought that the sponges from which suvanine was isolated belonged to the genus *Ircinia*,[22a] a reexamination indicated that they belong to the genus *Coscinoderma*.[22b] Primarily on the basis of an analysis of the spectral data, suvanine was initially assigned the structure **16**.[22a]

Suvanine is toxic to goldfish at 10 μg/mL,[22a] for this reason, it has been suggested that this substance plays a chemical defensive role for the sponges from which it is isolated.

The initially proposed structure of suvanine (**16**) is particularly interesting because it contains an uncommon arrangement of functional groups (a guanidinium bisulfate and a furan ring), and because it presents novel and synthetically challenging stereochemical features (a cis-syn-trans fused *ABC* ring system, five contiguous chiral centers, and an axially oriented side chain bound to C_{14}).

The structurally and pharmacologically interesting features of suvanine made it an attractive and challenging target for synthesis. This motivated us to attempt a stereocontrolled total synthesis of (±)-**16**. The cis *AB* ring junction of **16** was a structural characteristic that suggested the use of compound **17** as a starting material.

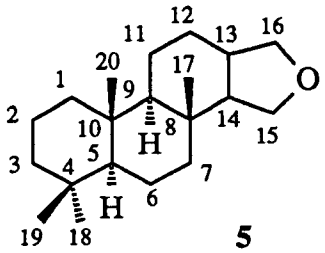


17

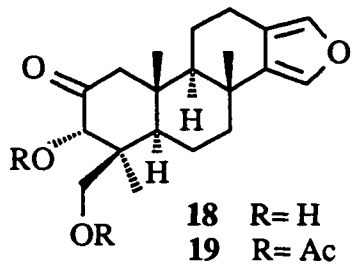
The ketone **17**, a useful and versatile synthetic intermediate, had been prepared previously in our laboratory via an efficient annulation reaction sequence.[23]

IIb. Synthesis of spongiadiols

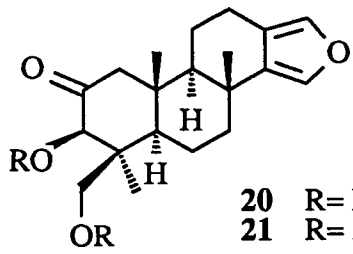
Many diterpenes with the 'spongian' carbon skeleton **5** have been isolated from various sponges and nudibranchs. Spongiadiol (**18**), spongiadiol diacetate (**19**), epispongiadiol (**20**), epispongiadiol diacetate (**21**) and isospongiadiol (**22**) are furanoditerpenoids in which carbon atoms 2, 3 and 19 are oxygenated. This oxygenation pattern is different from that of the majority of the other members of the spongian family of diterpenoids.[24]



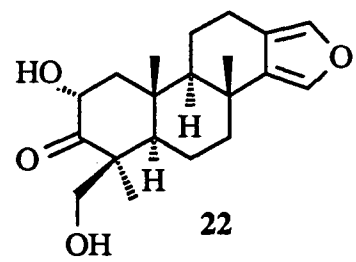
5



18 R= H
19 R= Ac



20 R= H
21 R= Ac

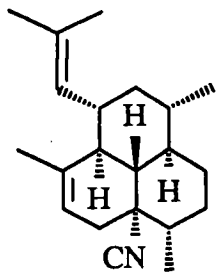


22

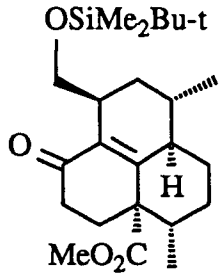
The diterpenoids **18-22**[25a-d] are produced by sponges of the genus *Spongia* which have been collected from places like Chub Cay, Bahamas[25d] and the Great Barrier Reef, Australia.[25a] The spongiadiols exhibit antiviral and cytotoxic properties.[25c,d] For example, an extract from a Caribbean sponge, *Spongia* sp., containing compounds **18, 20** and **22**, exhibited activity against *Herpes simplex* virus, type 1 (HSV-1), and P388 murine leukemia cells.[25d]

The pharmacological properties of the spongiadiols, as well as their structurally interesting functional group distribution, led us to attempt the development of a general synthetic approach to (some of) these substances. In this work, as in the case of the planned synthesis of (±)-**16**, we envisaged that the ketone **17** would be a suitable starting material.

IIc. Synthesis of (±)-8-isocyano-10,14-amphilectadiene



23



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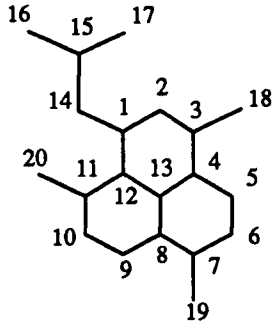


25

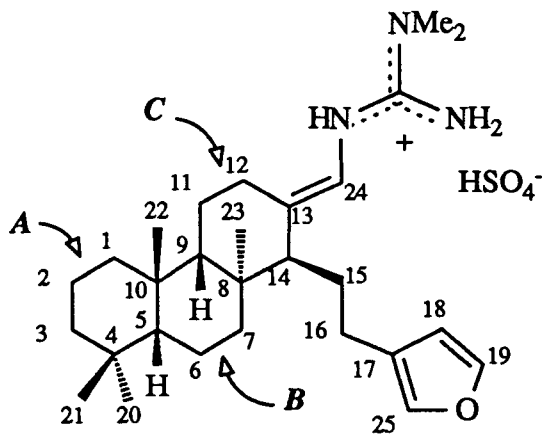
The diterpene 8-isocyano-10,14-amphilectadiene (**23**), a compound that inhibits the growth of the microorganisms *Staphylococcus aureus* and *Bacillus subtilis*, was isolated from the Palauan sponge *Halichondria* sp.[26] The isonitrile **23** contains the same 'amphilectane' carbon skeleton **25** as 8,15-diisocyano-11(20)-amphilectene (**15**), a natural product referred to previously (see p.5). The fact that **23** exhibits a synthetically challenging structure (it presents an array of seven contiguous chiral centers), and is also an antimicrobial substance, made it a tempting objective for a total synthesis. Since a total synthesis of (±)-**15** had been completed in our laboratory,[21] it was envisaged that (±)-**23** could be synthesized from the enone **24**, a precursor used in the synthesis of the diisocyanide (±)-**15**.

Thus, the objectives of the work described in this thesis were as follows: 1) to develop a general approach to the synthesis of the series of 'spongian' diterpenes (±)-**18**-**22**; 2) to synthesize the diterpene isonitrile (±)-**23**; and 3) to synthesize the sesterterpene (±)-**16**. It should be noted at the outset, however, that the last objective was not achieved. While we were at an advanced stage of our synthesis of (±)-**16**, a publication appeared[22b] which showed that the initial structural assignment for suvanine was incorrect. Further details will be given in the forthcoming discussion.

DISCUSSION

III. Regarding an approach to the total synthesis of "(±)-suvanine" (16)

IIIa. Isolation and structural elucidation of suvanine

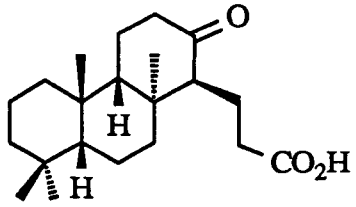


16

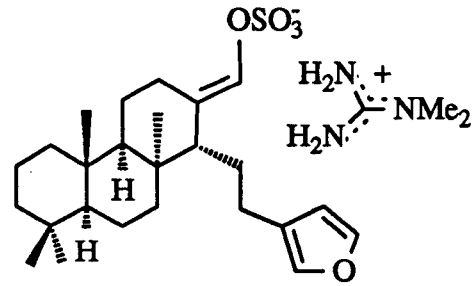
In 1983, Crews and coworkers[22a] isolated a new sesterterpene from the dichloromethane extract of a previously undescribed sponge collected in Suva Harbor, Fiji Island. At that time the sponge was believed to belong to the genus *Ircinia*, but later it was shown to belong to the genus *Coscinoderma*.[22b] This new compound, named

suvanine, is thought to be a defensive substance for the sponge, as suggested by its toxicity to goldfish (10 μg/mL). The amorphous solid (mp 218°C) isolated from the sponge extract exhibited $[\alpha]_D$ +9.5° and ir (KBr) 3400, 3240, 1640 cm^{-1}. The presence of a guanidine group was suggested by the following data: uv λ_{max} 210 nm (ϵ 10 500, 0.01 N NaOH in absolute EtOH) and 200 nm (ϵ 13 000 in MeOH) (the uv λ_{max} of guanidine hydrochloride is 212 nm (ϵ 790, aqueous EtOH), the ϵ increases to >10 000 when the guanidine group is conjugated to a C=O or C=C).[22a] Elemental analysis established the formula $C_{28}H_{45}N_3O{\cdot}H_2SO_4$ for suvanine. The authors were not able to corroborate this formula by mass spectrometry since the highest m/z cluster appeared at 371 and 370 (by chemical ionization field desorption mass spectrometry). The high resolution mass spectrum exhibited peaks at 371.2920 and 370.2843, corresponding to formulae of $C_{25}H_{39}O_2$ (calcd. 371.2952) and $C_{25}H_{38}O_2$ (calcd. 370.2873). The authors explained the conflicting mass spectral evidence by stating that "A possible rationalization could be OH^- displacement of the guanidinium ion subunit under thermal or electron impact conditions."[22a] The ^{13}C nmr spectral evidence showed that only one oxygen (furan ring) could be located (δ 142.9 d, 138.8 d, 124.9 s and 111.0 d). Surprisingly, the remaining nmr spectral evidence (^1H nmr, ^{13}C nmr, and ^1H homonuclear correlation spectroscopy (COSY) nmr spectrum) for suvanine seemed to be in accord with the structure **16**, which was initially assigned to the natural product. The nmr data (^1H nmr, ^1H nOe difference spectra, and a ^1H-^{13}C heteronuclear COSY nmr spectrum) for the ozonolysis degradation product of suvanine also seemed to be consistent with its proposed structure **26**.

In 1988, Crews and coworkers[22b] reported that **27** is the correct structure of suvanine. The authors realized that the previously reported structure (**16**) was incorrect when the pyridinium salt of suvanine was fortuitously isolated after treating suvanine with acetic anhydride in pyridine. This experiment, according to the authors, indicated

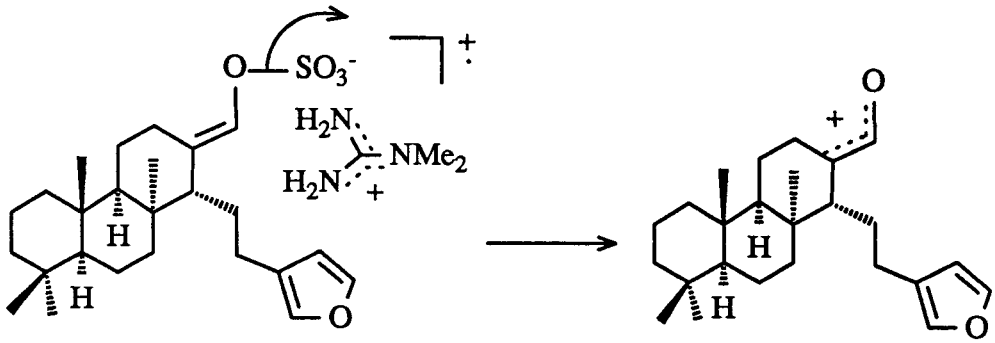


26



27

that "...suvanine might be a dimethyl guanidinium salt of an enol sulfate rather than the sulfate salt of a dimethyl guanidinium enamine."[22b] It also became evident that the structure **16** was incorrect when additional ^{1}H-^{13}C COSY nmr data were interpreted. The apparently contradictory mass spectral results published in the earlier paper[22a] were

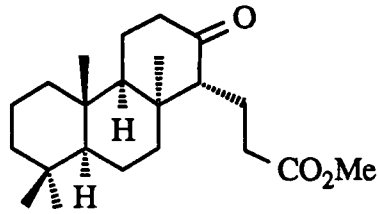


27a **27b** m/z 370

Scheme 1

now explained by ascribing the m/z 370 fragment **27b** to a fragmentation of **27a** in which cleavage of an O-S bond takes place (Scheme 1). A reinterpretation of the nmr spectral data published initially, plus additional two-dimensional nmr data (^{1}H-^{13}C COSY nmr spectrum), indicated that suvanine possesses an *AB* trans, *BC* cis ring stereochemistry. The stereochemical assignments were confirmed by an X-ray analysis

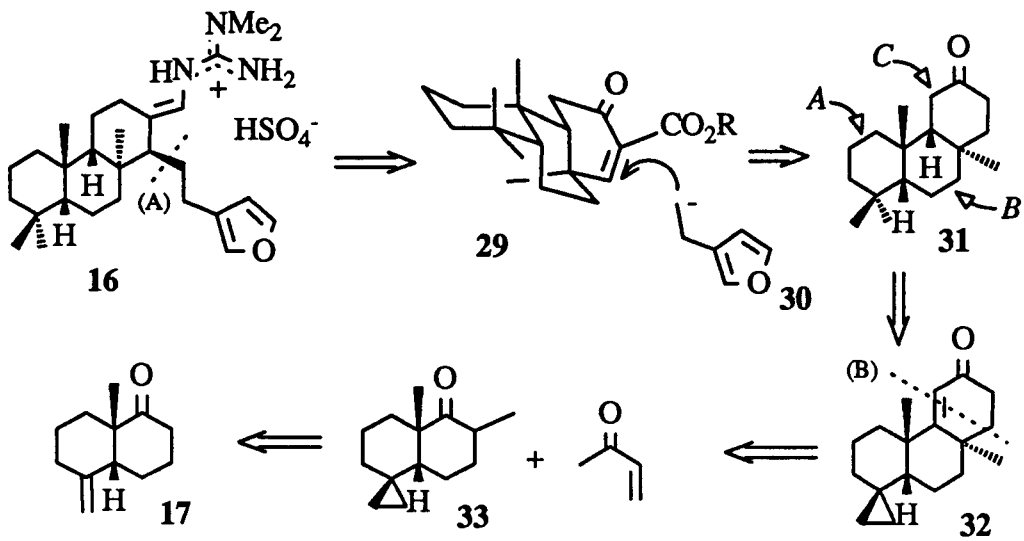
of a degradation product derived from ozonolysis of (±)-suvanine, followed by lithium aluminum hydride reduction of the resultant keto ester **28**. It is interesting to note that the ozonolysis product which was used to prepare the X-ray sample was the keto ester **28**, a compound that was not mentioned in the initial publication.[22a]



28

When the work described in this thesis was initiated, the correct structure of suvanine (**27**) had not yet been published and, therefore, we began with an attempt to synthesize (±)-**16**. However, when the correct structure of suvanine (**27**) was reported,[22b] we decided to conclude this phase of our work. This decision was taken because the proposed synthetic plan for (±)-**16** was not applicable to the synthesis of (±)-**27**. Furthermore, the structural characteristics of **27** are not as novel as those of compound **16**, since many natural products exist which have an *AB* trans ring junction and a related carbon skeleton.[27a-c] Consequently, it was decided not to pursue the synthesis of (±)-**27**. This section of the thesis will describe the work done on the synthesis of (±)-**16** to the stage reached when the correct structure of suvanine (**27**) was published.

IIIb. Retrosynthetic analysis

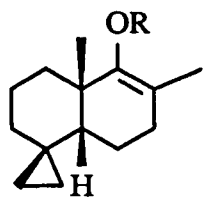


Scheme 2

A crucial problem that must be addressed in any plan to synthesize (±)-**16** is the stereoselective introduction of the correct relative configuration at each of the five contiguous chiral centers. Our retrosynthetic analysis (Scheme 2) was based on the proposal that compound **16** could be prepared from the keto ester **29**, a compound that would be generated by the disconnection (A) of the target molecule, along with the appropriate functional group interconversions. Examination of molecular models suggested that a suitable nucleophile (synthetically equivalent to the synthon[28a] **30**) would add to the β carbon of the enone function in **29** from the (sterically less hindered) β (top) face of the molecule. It was envisaged that compound **29** could readily be synthesized from the ketone **31**. Compound **31** could, in turn, be prepared from the enone **32** via a sequence of reactions involving dissolving metal reduction of its enone function and hydrogenolysis of the cyclopropane ring. It was expected[29a,f] that the

dissolving metal reduction step would lead to the more stable system in which rings *B* and *C* are trans-fused. Structure **32** suggested the use of a Robinson annulation transform[28b] (disconnection (B)), which would lead to the ketone **33**. Finally, it seemed likely that **33** could be prepared by cyclopropanation and alkylation of the ketone **17**, the starting material for the synthesis.

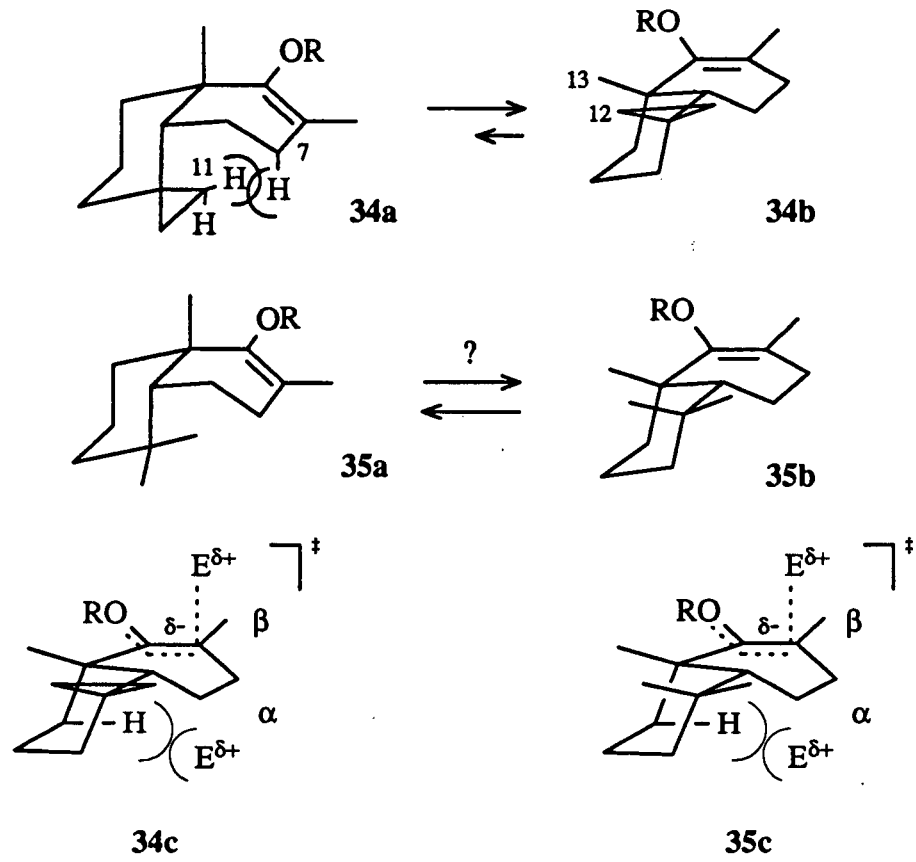
It was expected that the key synthetic reaction (i.e., the alkylation of the enolate anion prepared from **33**) in the sequence **33** → **32** would occur in a stereoselective manner. In relation to this point, it has been suggested that stereoelectronic control is not as important as steric hindrance (when the latter is present) in determining the direction of attack of electrophiles on ketone enolate anions.[29b] It is also believed that the transition state geometries (six membered rings) in enolate alkylations are reactant-like, thus resembling more closely the geometry of the planar enolate anion.[29e] Thus, a molecular model of the more stable conformer of the enolate (R= counterion) or enol (R= H) **34** shows quite clearly that attack of electrophiles should occur preferentially



34

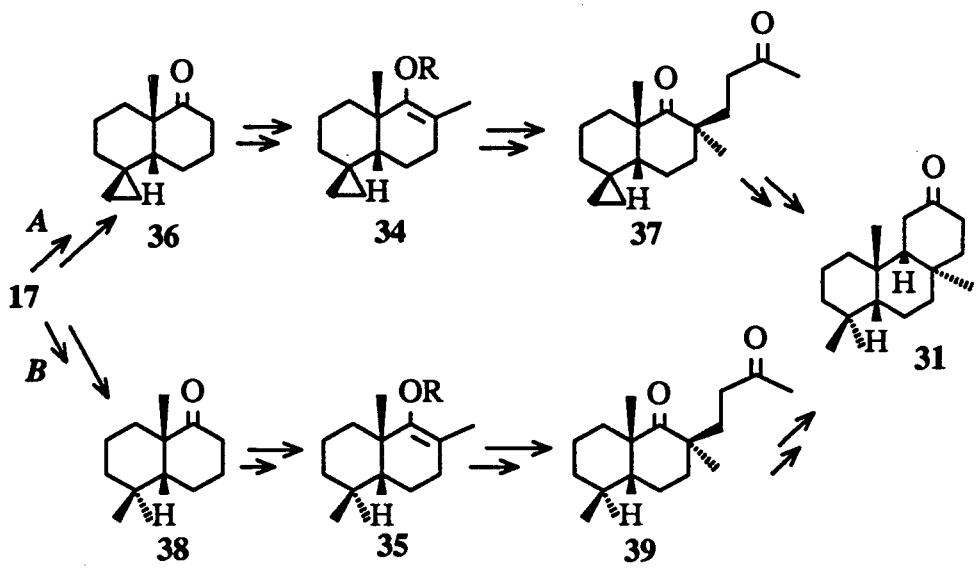
from the (sterically less hindered) β (convex) face via the conformer **34b** (Scheme 3). On the other hand, conformer **34a** (which seems to be less stable than **34b** due to a severe steric interaction between a C-11 methylene hydrogen and the C-7 pseudoaxial hydrogen) would present steric hindrance to incoming electrophiles from both the α and the β face of the enol(ate). Thus, it was predicted that reaction of **34** with electrophiles should occur via a transition state that might be represented by **34c** (Scheme 3).

Examination of molecular models seems to indicate that the effect of the



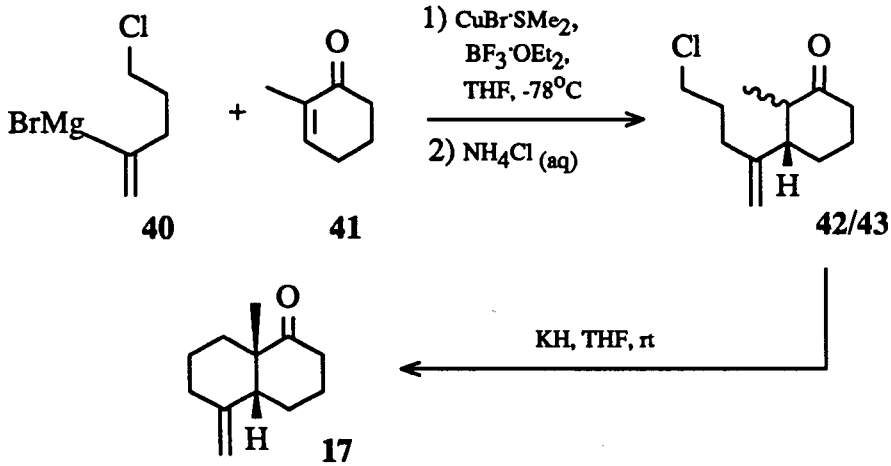
Scheme 3

cyclopropane ring on the relative stabilities of the two chair-like conformers **34a** and **34b** would be different from that of the corresponding gem-dimethyl moiety in conformers **35a** and **35b** (Scheme 3). The position of the equilibrium **35a**⇌**35b** was not easy to predict. However, in this case it also seemed likely that the transition state geometry for the alkylation would be analogous to **34c** (i.e., **35c**), since both faces of the enolate double bond in **35a** are sterically hindered. To what degree these conformational effects would affect the stereoselectivities of the reactions to be used in constructing ring *C* was not easy to predict. Thus, an investigation of this point was pursued to determine the comparative efficiencies of the two alternative synthetic routes ***A*** and ***B*** shown in Scheme 4.



Scheme 4

IIIc. Methylenecyclohexane annulation leading to **17**

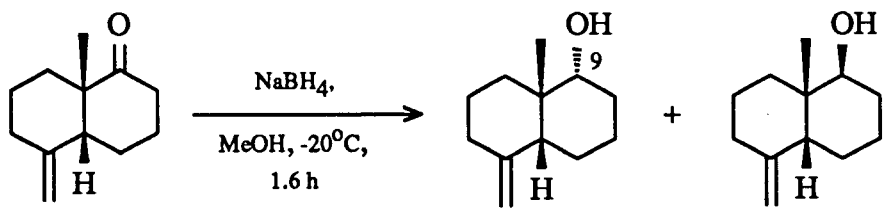


Scheme 5

In 1984, a new methylenecyclohexane annulation sequence based on the concept of "bifunctional conjunctive reagents"[30] was developed in our laboratory. This sequence proved to be useful, for example, in the preparation of the bicyclic ketone **17**[23] (Scheme 5), which contains adequate functional and stereochemical features that would enable its eventual transformation to (±)-**16**, the initially proposed structure for suvanine.

The Grignard reagent **40** is a bifunctional reagent prepared by transmetallation[23] of 5-chloro-2-(trimethylstannyl)-1-pentene[31] with methyllithium in THF at -78°C, followed by addition of anhydrous magnesium bromide-etherate.[32] The reagent **40** underwent conjugate addition to the enone **41**[33] under the conditions shown in Scheme 5, to provide **42/43**, a mixture of epimers. Cyclization of the mixture (crude or purified) by treatment with potassium hydride in THF provided exclusively the desired cis-fused annulated product **17**, in yields ranging from 78 to 90 %.

IIId. Synthesis of the ketone **36**. Preparation of the alcohols **44-47**.



17 **44** 9:1 **45**

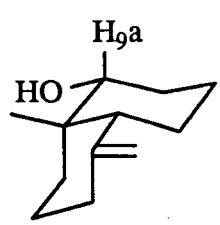
98%

(1)

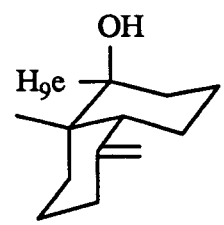
Sodium borohydride reduction of the ketone **17** (methanol, -20°C, 1.6 h) afforded a 9:1 (glc analysis) mixture of the epimeric alcohols **44** and **45**, in 98 % yield (equation 1). A pure sample of each of the isomeric alcohols **44**and **45** was obtained by column

chromatography of the mixture on silica gel. The ir spectrum of **44** (the major isomer) exhibited absorptions at 3385, 3067, 1646 and 1082 cm^{-1} indicating the presence of an alcohol function and an exocyclic methylene group. The ^1H nmr spectrum of **44** exhibited multiplets at δ 4.69-4.66 and 4.66-4.63 due to the olefinic protons and a doublet of doublets at δ 3.32 (J= 13,5 Hz) due to the (axial) proton on C-9 (suvanine numbering system). The relative stereochemistry of **44** was determined by correlation (ir, EIMS, and ^1H nmr spectrum) with a sample obtained by hydrolysis of its corresponding MOM-ether derivative. The relative stereochemistry and conformation of this derivative was determined by F. Fleming[34] in our laboratories.

The alcohol **45** exhibited ir absorptions at 3389, 3067, 1646 and 1050 cm^{-1}, confirming the presence of hydroxyl and exocyclic methylene functions. The ^1H nmr spectrum of **45** showed two singlets at δ 4.68 and 4.66 due to the olefinic protons and a broad singlet at δ 3.50 ($w_{1/2}$=12 Hz, this signal changed to $w_{1/2}$=10 Hz upon addition of D_2O) due to the (equatorial[35]) proton on C-9. These data indicate that **44** and **45** exist primarily in the conformations **44a** and **45a**, respectively.



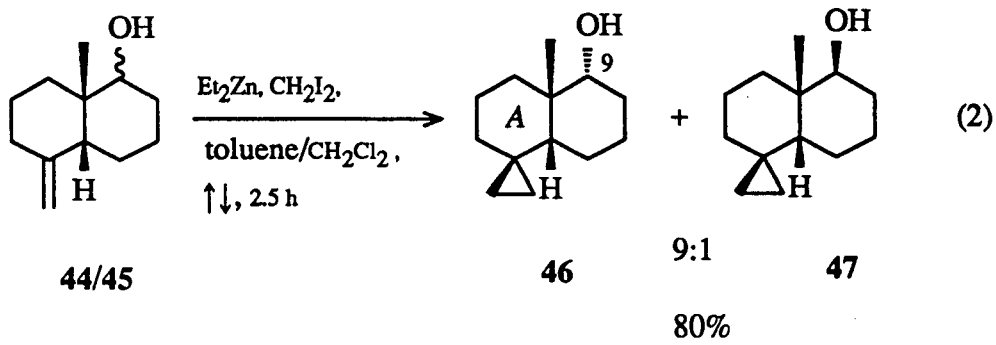
44a



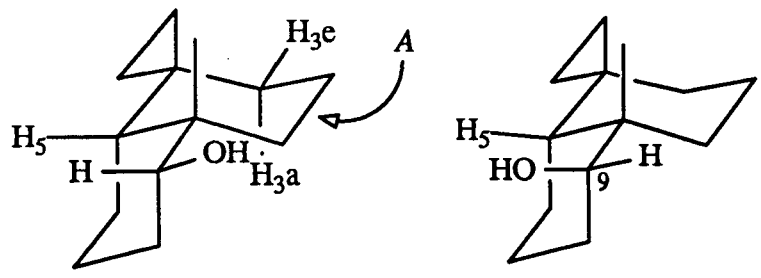
45a

The mixture of alcohols **44** and **45** was subjected to a cyclopropanation reaction using diethylzinc/methylene iodide[36a-d] (equation 2). The reagent used is a convenient alternative to the widely used Simmons-Smith reagent (zinc-copper couple/methylene iodide).[36e] Thus, reaction of the mixture of alcohols **44/45** with the Et_2Zn/CH_2I_2 reagent

in a refluxing 5:1 mixture of toluene and methylene chloride gave a chromatographically separable 9:1 mixture of the epimeric alcohols **46** and **47**, respectively. The ir spectrum



of **46** exhibited absorptions at 3382 and 1050 cm^{-1} due to the alcohol function. The ^1H nmr spectrum of **46** showed a multiplet at δ 3.27, which, upon addition of D_2O, was transformed to a doublet of doublets (J= 11,5 Hz). This signal was assigned to the (axial) proton on C-9. The signals due to H_3e and H_5 (see the conformational formula **46a**) appeared at δ 0.57 (dm, J=12Hz) and 0.47-0.32 (m), respectively. The assignment of these resonances to H_5 and H_3e was suggested by their 'abnormal' chemical shifts. The high field chemical shifts exhibited by these protons and by the corresponding protons in most of the cyclopropanated derivatives described in this thesis, suggest that they are being diamagnetically shifted due to the shielding effect of the adjacent cyclopropane ring.[37a,b] In this particular case, for example, ring *A* in compound **46** has a



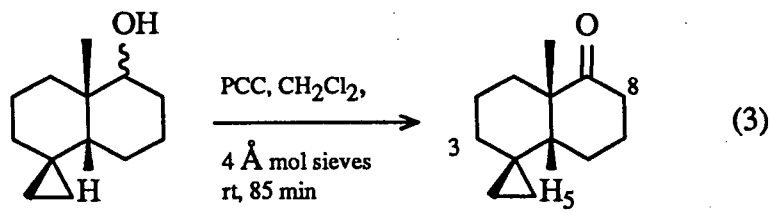
46a **47a**

conformation (**46a**) such that the two equatorial hydrogen atoms H_3e and H_5 fall within the shielding zone of the cyclopropyl ring. The particular assignment of the signals for H_3e and H_5 in compound **46** was confirmed by the following ^1H nmr decoupling experiments: irradiation of the broad dd at δ 1.90 (J=12,12 Hz) due to H_3a caused the collapse of the signal at 0.57 (dm, J=12Hz) (due to H_3e) to a broad singlet; irradiation of the signal at δ 0.57 caused the collapse of the signal at 1.90 due to H_3a to a broad doublet (J=12 Hz) and simplified (a w-coupling[38] was lost) the multiplet at 0.47-0.32 due to H_5.

The ^1H nmr spectrum of **47** exhibited a broad singlet at δ 3.35 ($w_{1/2}$=8 Hz, sharpened upon addition of D_2O) due to the (equatorial) C-9 proton. Since **47** was epimeric with **46** (at C-9) the conformation of **47** was thus established as **47a**.

When the cyclopropanation reaction was attempted on the ketone **17**, the results were not satisfactory. Side products were formed and a considerable amount of starting material was recovered even when an excess of reagents was employed. However, when the reaction was carried out on the mixture of alcohols **44** and **45**, the process was clean and efficient. The fact that a carbonyl group can interfere with the success of the modified Simmons-Smith cyclopropanation has precedent.[39]

Oxidation of the 9:1 mixture of alcohols **46** and **47** with pyridinium chlorochromate (PCC)[40] in dichloromethane (equation 3) gave, in high yield, the ketone **36** as a colorless oil. Compound **36** exhibited, in its ir spectrum, a strong absorption at 1703 cm^{-1} due to the carbonyl stretching vibration. The ^1H nmr spectrum of **36**



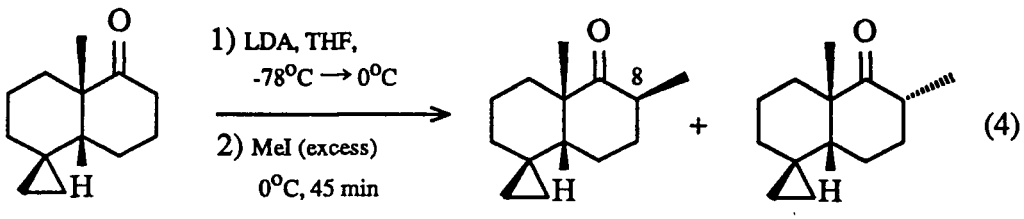
(3)

91%

46/47 **36**

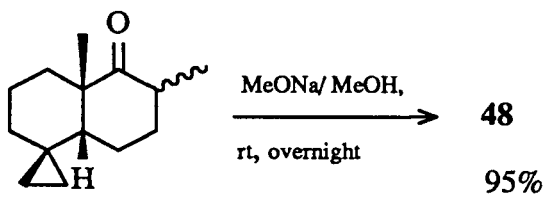
displayed a ddd (J=13,13,6 Hz) at δ 2.58 due to the axial proton at C-8, a dd (J=13,4 Hz) at δ 0.77 due to H_5 and a broad doublet at δ 0.65 (J=13 Hz) due to H_3e.

IIIe. Alkylation of the ketone **36**. Preparation of the ketones **48** and **49**.



36 **48** ~1.3:1 **49**

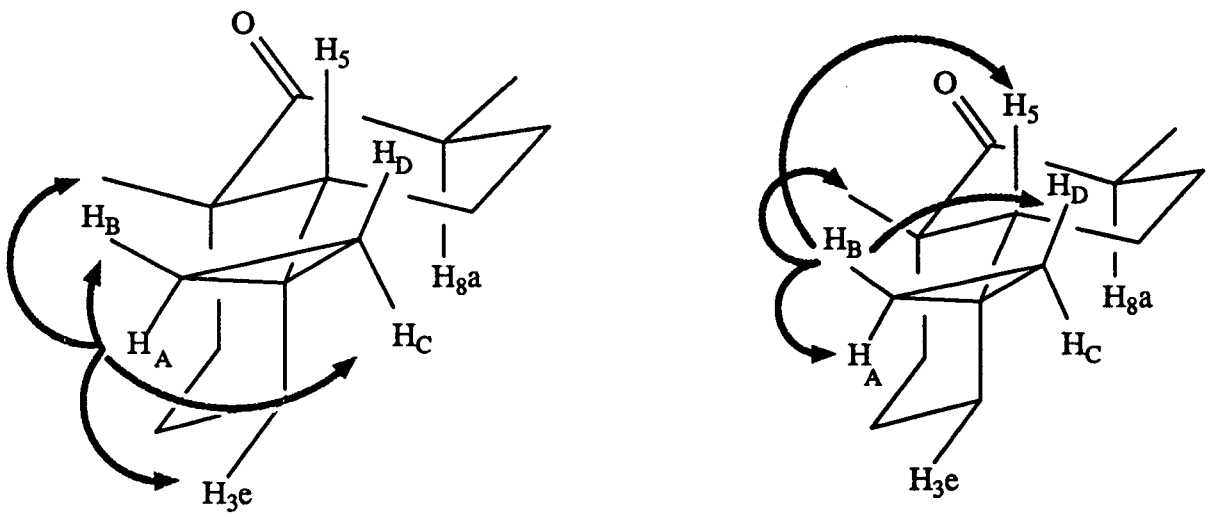
95%



95%

48/49

Monoalkylation of the ketone **36** by deprotonation with lithium diisopropylamide (LDA) and addition of methyl iodide gave a mixture of the ketones **48** and **49** in high yield (equation 4). A small amount of this mixture of ketones was epimerized with sodium methoxide in methanol, cleanly affording the ketone **48** (equation 5). The ^1H nmr spectrum of **48** exhibited a signal at δ 2.68 (ddq, J=13,6,6 Hz) due to the axial proton on C-8 (H_8a) (see the conformational formula **48a**). The angular and the secondary methyl protons appeared at δ 1.29 and δ 1.00 as a singlet and a doublet (J=6 Hz), respectively. The signals due to H_5 (dd, J=13,4 Hz) and H_3e (br d, J=13.5 Hz) appeared at δ 0.75 and 0.66, respectively, suggesting the conformation shown in **48a**. In



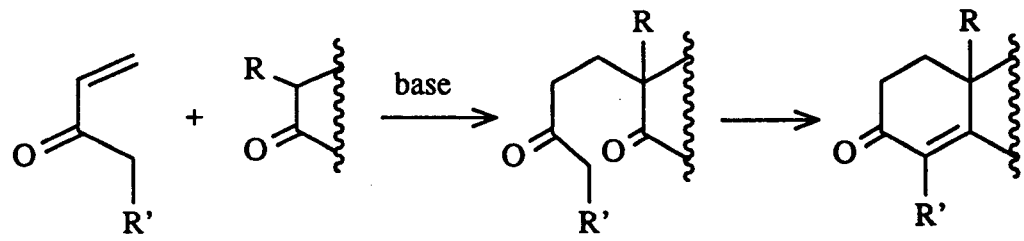
48a

order to confirm the proposals regarding the preferred conformation and relative configuration of **48a**, the following series of nOe difference experiments were done: irradiation of the signal at δ 0.47-0.41 (H_A) caused enhancement of the signals at 1.29 (s, angular methyl protons), 0.66 (br d, J=13.5 Hz, H_3e), 0.40-0.32 (m, H_B) and 0.21-0.08 (m, H_C); irradiation of the multiplet at δ 0.40-0.32 (H_B) caused enhancement of the signals at 1.29 (s, angular methyl protons), 0.75 (dd, H_5), 0.47-0.41 (m, H_A) and δ 0.14-0.08 (m, H_D). The results of these experiments are summarized by the arrows on the formula **48a**.

IIIf. Preparation of the silyl enol ether **50**. Synthesis of the diketone **37**.

Having prepared the ketones **48** and **49**, some modifications of the Robinson annulation reaction[41a,b] were tried for the next stage of the synthesis. The Robinson annulation reaction is a useful procedure for the addition of a six-membered ring to a

ketone that has an enolizable hydrogen. The overall process may be illustrated in general terms by the conversion of **51** into **54** (equation 6). Thus, a substrate ketone **52**



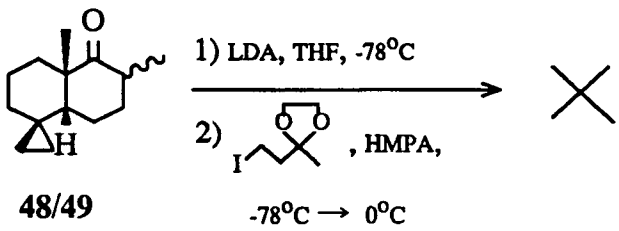
(6)

51 **52** **53** **54**

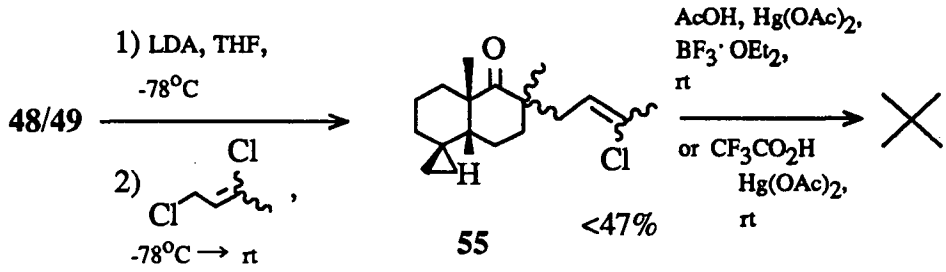
R,R'= H, alkyl

is treated with an enone **51** in the presence of a base. The resultant Michael addition product, the 1,5-diketone **53**, undergoes an intramolecular aldol condensation and subsequent dehydration to give the product **54**. However, due to side reactions such as polymerization, the use of an enone **51** as the Michael acceptor in the reaction with a specific enolate anion under aprotic conditions is not always successful. Therefore, it is often necessary to use modified reagents and/or a different type of reaction (e.g., an alkylation reaction or a Lewis-acid catalyzed reaction).

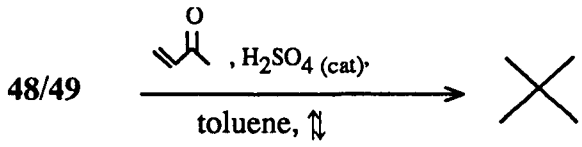
In order to carry out the desired annulation reaction on the mixture of ketones **48/49**, some of the procedures found in the literature were tried (equations 7 to 10). In attempts to alkylate the lithium enolate prepared from the mixture of ketones **48/49** with the ethylene ketal of 4-iodo-2-butanone[42] (in the presence of HMPA), only unidentified products and recovered starting material were obtained (equation 7). When the alkylating agent used was 1,3-dichloro-2-butene (mixture of isomers, the 'Wichterle reagent'),[41a,b,d] a low yield of the (inseparable and slightly impure) mixture of the α-(3-chloro-2-butenyl) ketones **55** was obtained (equation 8). The conditions required to hydrolyze this mixture of vinylic chlorides to the corresponding methyl ketones are quite harsh,[41d] and resulted in extensive decomposition of the substrate. An acid-catalyzed



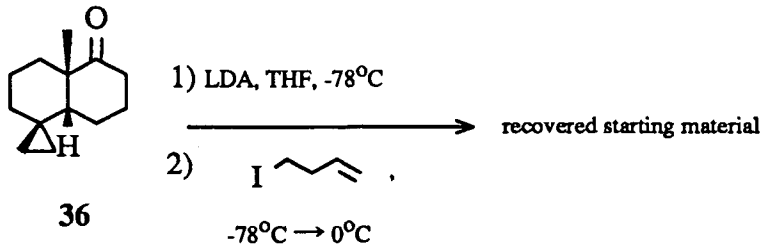
(7)



(8)



(9)

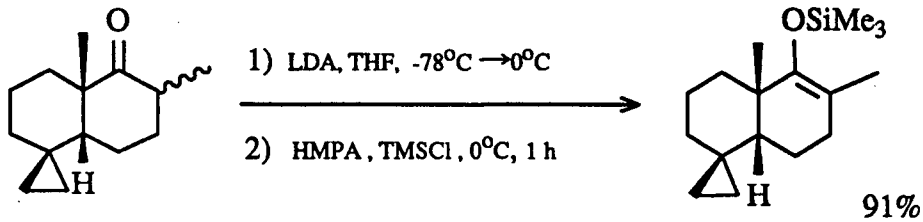


(10)

Robinson annulation[43] was also attempted (equation 9). However, this procedure led to the formation of intractable material. In a related approach to the construction of ring *C*, an attempt to alkylate the lithium enolate of the ketone **36** with 4-iodo-1-butene was made, but also proved to be unsuccessful (equation 10).

In 1985, Huffman et al.[41f] published an efficient variation of the Robinson annulation which, in the initial step, consisted of the Lewis acid catalyzed reaction of silyl enol ethers with vinyl ketones or the ethylene ketal of 3-buten-2-one (a

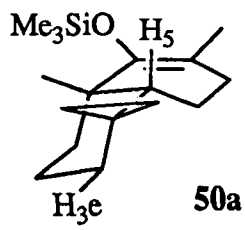
Mukaiyama-type reaction). The reactions are carried out at low temperatures (-80°C to -100°C) in dichloromethane and the Lewis acids used are $TiCl_4$ or mixtures of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$. These reactions usually afford mixtures of the 1,5-diketone and the corresponding monoketal. Treatment of the crude reaction mixture with aqueous acid gives the diketone.



(11)

48/49 **50**

In order to use this Lewis acid catalyzed method, the TMS enol ether **50** was prepared using a modification of a known literature procedure.[44] Thus, HMPA and TMS-Cl were added to a cold (0°C) THF solution of the lithium enolate prepared from the mixture of the ketones **48** and **49**. After workup and column chromatography of the crude product, high yields of the TMS enol ether **50** were consistently obtained (equation 11). Conducting this reaction in the absence of HMPA, or employing other procedures described in the literature,[45] gave lower yields of the desired product. The ir spectrum of **50** exhibited absorptions at 1673 and 840 cm^{-1} due to the double bond and the trimethylsilyl group, respectively. The ^1H nmr spectrum of **50** showed singlets at δ 1.54

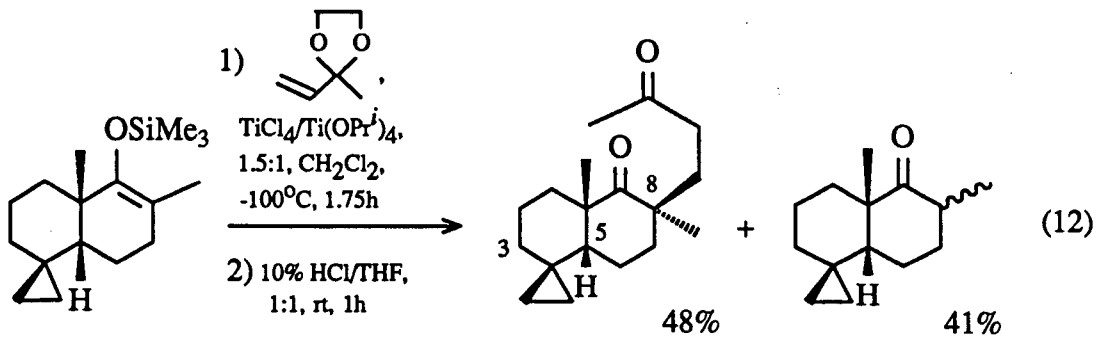


50a

and 0.20, indicating the presence of the vinylic methyl group and the trimethylsilyl group, respectively. A two-proton multiplet at δ 0.62-0.50 was assigned to the equatorial

proton at C-3 (H_3e) and the proton on C-5 (H_5). Thus, the ^1H nmr data suggests that the TMS enol ether **50** exists primarily in the conformation shown in **50a**.

The silyl enol ether **50** and the ethylene ketal of 3-buten-2-one (prepared from 3-buten-2-one according to the procedure published by Hahn)[46] were added to a cold (-100°C) mixture of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ in dichloromethane. The mixture was stirred at -100°C for 1.75 h. Subsequent treatment of the crude product mixture with a 1:1

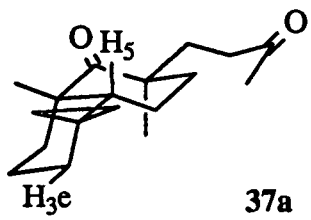


50 **37** **48/49** (12)

solution of 10% aqueous hydrochloric acid and THF, followed by chromatography of the material thus obtained, afforded the 1,5-diketone **37** in moderate yield (48%). Additionally, a 12.5:1 (glc analysis) mixture of the ketones **48** and **49** was obtained in 41% yield (equation 12). Analysis of the desired product **37** by glc, indicated the presence of ~3% of another compound, likely the C-8 epimer of **37**. Since it was feasible to recycle the mixture of ketones **48/49**, and since the reaction had proceeded with high stereoselectivity, we considered this procedure to be satisfactory for our synthetic work.

The relative configuration at C-8 of **37** was not known at this stage of our work. However, ^1H nmr spectroscopy experiments involving a subsequent synthetic intermediate derived from **37** (see Part IIIg of this Discussion Section) showed conclusively that this substance possessed the indicated stereochemistry. The ir spectrum of compound **37** exhibited absorptions at 1716 and 1689 cm^{-1} due to the two

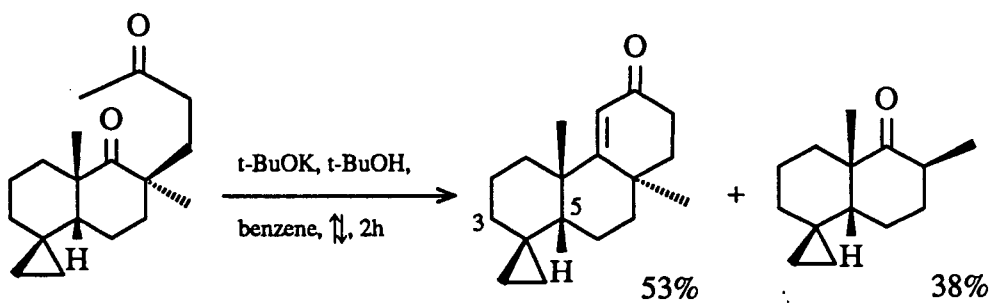
carbonyl groups. The ^{1}H nmr spectrum of **37** exhibited a three-proton singlet at δ 2.12 due to the methyl ketone moiety, and two broad doublets at 0.75 (J=12 Hz) and 0.64



37a

(J=14 Hz) which could be assigned to the equatorial proton on C-3 and the proton on C-5 (or vice versa). The presence of the latter two signals indicated that compound **37** exists primarily in the conformation **37a**.

IIIg. Preparation of the enone **32**. Synthesis of the ketone **56** and determination of its relative configuration.



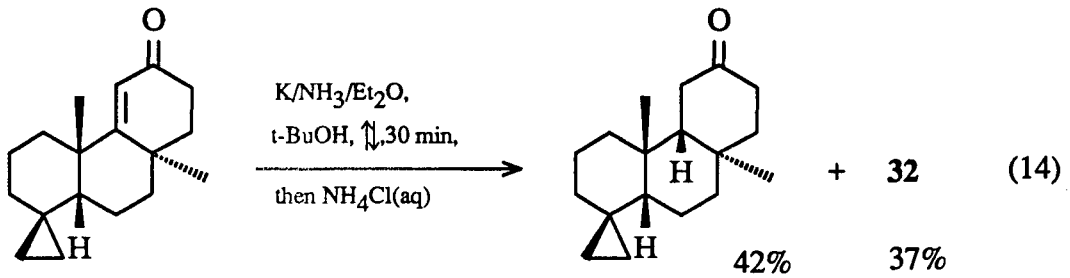
(13)

37 **32** **48**

Treatment of the diketone **37** with potassium tert-butoxide/tert-butyl alcohol in refluxing benzene gave, after workup and column chromatography of the crude product, the (uv active) enone **32** in 53% yield (equation 13). The ketone **48**, obtained as a side product (38% yield) in this reaction, was formed via a retro-Michael process. The ir spectrum of **32** showed absorptions at 1667 and 1592 cm^{-1} due to the enone carbonyl

group and the conjugated carbon-carbon double bond, respectively. The ^1H nmr spectrum of **32** exhibited a singlet at δ 6.02, due to the vinyl proton. The broad doublet at δ 0.64 (J=14 Hz) and the doublet of doublets at δ 0.59 (J=13,3.5 Hz) were assigned to the equatorial proton at C-3 and the proton at C-5, respectively.

The enone **32** was subjected to a dissolving metal reduction[29c,f] using potassium in ammonia/diethyl ether in the presence of tert-butyl alcohol. After workup and column

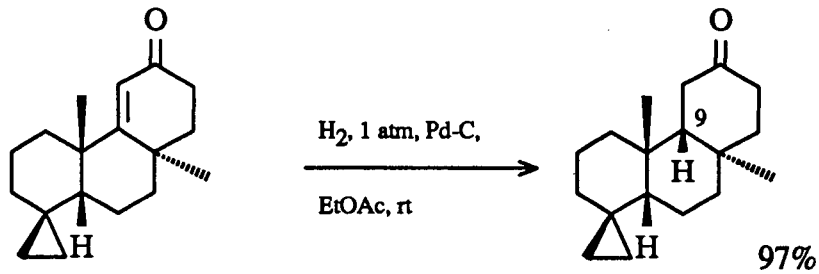


32 **56**

chromatography of the crude product mixture, the ketone **56** was obtained in 42% yield, together with a fair amount (37%) of the starting material **32** (equation 14).

It has been well established[29f] that the alkali metal-ammonia reduction of substances possessing the bicyclo[4.4.0]oct-1-en-3-one moiety usually produces the corresponding trans-fused bicyclo[4.4.0]octan-3-ones. Thus, although the reason(s) underlying the stereoselective nature of this process has been the subject of a number of discussions in the literature,[29f-h] the stereochemistry of the reduction product **56** (equation 14) could be assigned as shown with a good degree of confidence.

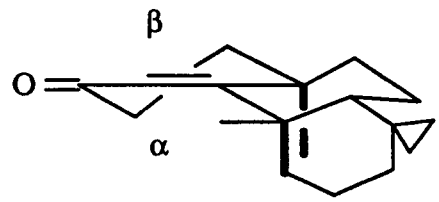
The catalytic hydrogenation of **32** (palladium-on-charcoal)[29d] gave the ketone **56** in high yield (equation 15). It is known that heterogeneous catalytic hydrogenations of enones such as **32** proceed via the cis addition of hydrogen to the (sterically) less hindered side of the double bond.[29d] Examination of a molecular model of **32** shows that in conformer **32a** the α (bottom) face of the enone moiety is hindered by the pseudo axial



(15)

32 **56**

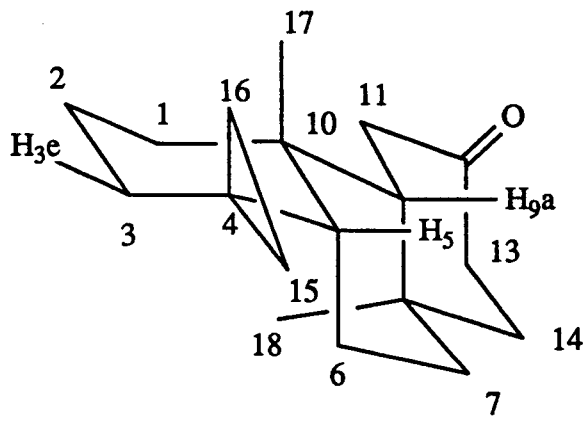
methyl and methylene groups (heavy bonds in formula **32a**). Therefore, it seemed highly likely that the reaction would take place from the sterically more open, β (top) face of the molecule to produce **56**.



32a

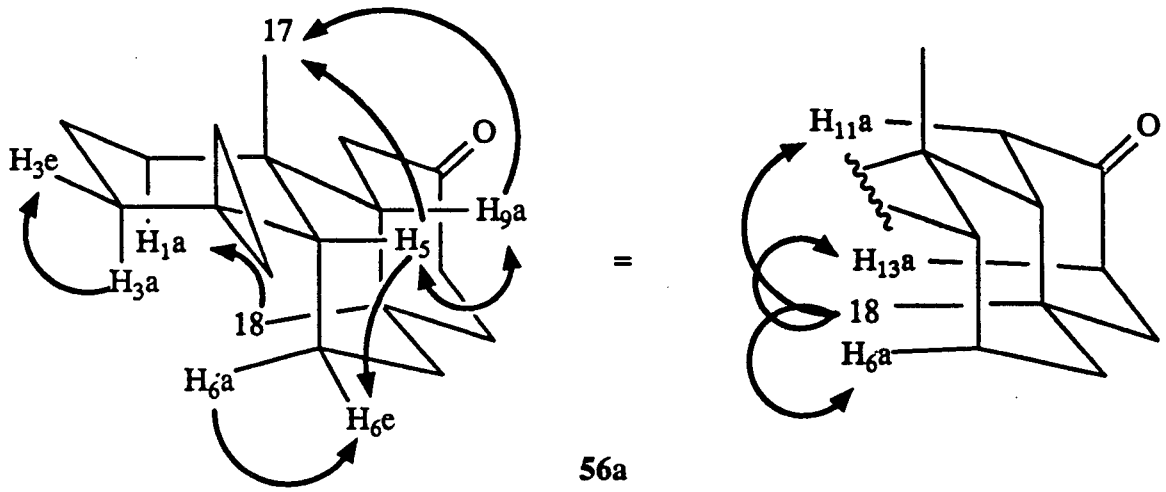
The ir spectrum of **56** showed an absorption at 1713 cm^{-1} due to the carbonyl group. The ^1H nmr spectrum of **56** (Figure 1, p.32) exhibited signals for the four protons alpha to the ketone function at δ 2.45 (ddd, J=14,14,7 Hz), 2.42 (ddd, J=14,3,3 Hz), 2.29 (m), and 2.29 (dd, J=14,14 Hz) ($H_{13}a$, $H_{11}e$, $H_{13}e$, and $H_{11}a$, respectively; see formula **56a**). A doublet of doublets at δ 1.28 (J=14,3 Hz) was ascribed to H_9a. A broad doublet (J=13 Hz) at δ 0.60 and a doublet of doublets (J=14,4 Hz) at 0.33 were assigned to the equatorial hydrogen atom on C-3 (H_3e) and the hydrogen atom on C-5, respectively.

The relative stereochemistry and the conformation of **56** were determined by ^1H nmr homonuclear spin decoupling and ^1H-^1H nOe difference experiments. Thus, in decoupling experiments, irradiation of the overlapping signals at δ 2.45 ($H_{13}a$) and 2.42



56a

($H_{11}e$) simplified the multiplet at 1.70-1.40 ($H_{14}e$) and caused the collapse of the signals at 1.39 ($H_{14}a$) to a broad doublet (J=14 Hz) and 1.28 (H_9a) to a doublet (J=14 Hz); irradiation of the overlapping signals at δ 2.29 ($H_{13}e$, $H_{11}a$) simplified the multiplet at 1.70-1.40 ($H_{14}e$) and caused the collapse of the signals at 1.39 ($H_{14}a$) to a dd (J=14,14 Hz) and 1.28 (H_9a) to a doublet (J=3 Hz); irradiation of the signal at δ 1.28 (H_9a) caused the collapse of the signals at 2.42 ($H_{11}e$) to a dd (J=14,3 Hz) and 2.29 ($H_{11}a$) to a doublet (J=14 Hz). In nOe difference experiments, irradiation of the overlapping signals at δ 1.89 (H_6a) and 1.84 (H_3a) caused enhancement of the signals at 1.47 (dq, J=14,4 Hz, H_6e) and 0.60 (br d, J=13 Hz, H_3e); irradiation of the signal at δ 1.28 (H_9a) caused enhancement of the signals at 1.09 (s, C_{17} methyl protons) and 0.33 (dd, J=14,4 Hz, H_5); irradiation of the signal at δ 1.20 (C_{18} methyl protons) caused enhancement of the signals at 2.45 (ddd, J=14,14,7 Hz, $H_{13}a$), 2.29 (dd, J=14,14 Hz, $H_{11}a$), 1.84 (ddd, 14,14,5 Hz, H_6a) and 1.62 (ddd, J=14,14,5 Hz, H_1a); irradiation of the signal at δ 0.33 (H_5) caused enhancement of the signals at 1.47 (dq, J=14,4 Hz, H_6e), 1.28 (dd, J=14,3 Hz, H_9a) and 1.09 (C_{17} methyl protons). The results of these nOe experiments are represented by the arrows in the conformational formulas shown below.



56a

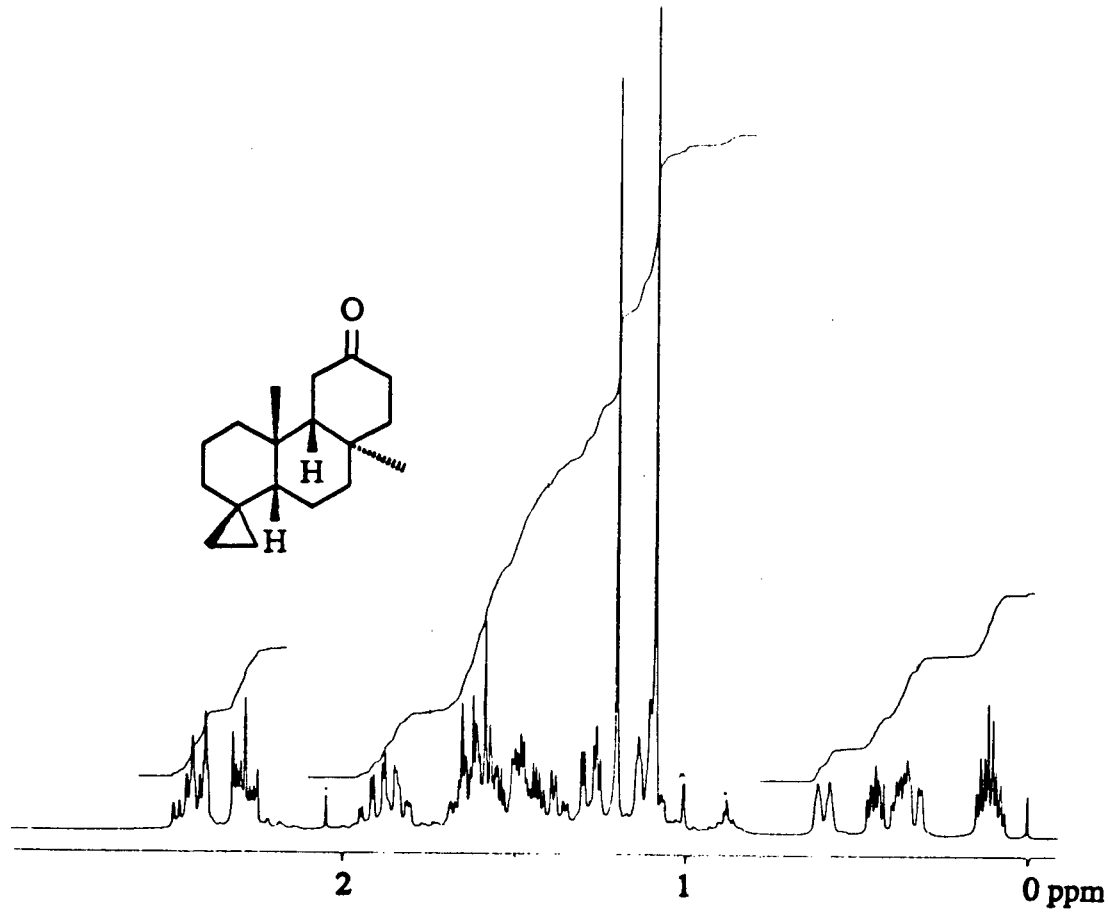


Figure 1. The ^1H nmr spectrum ($CDCl_3$, 400 MHz) of compound **56**.

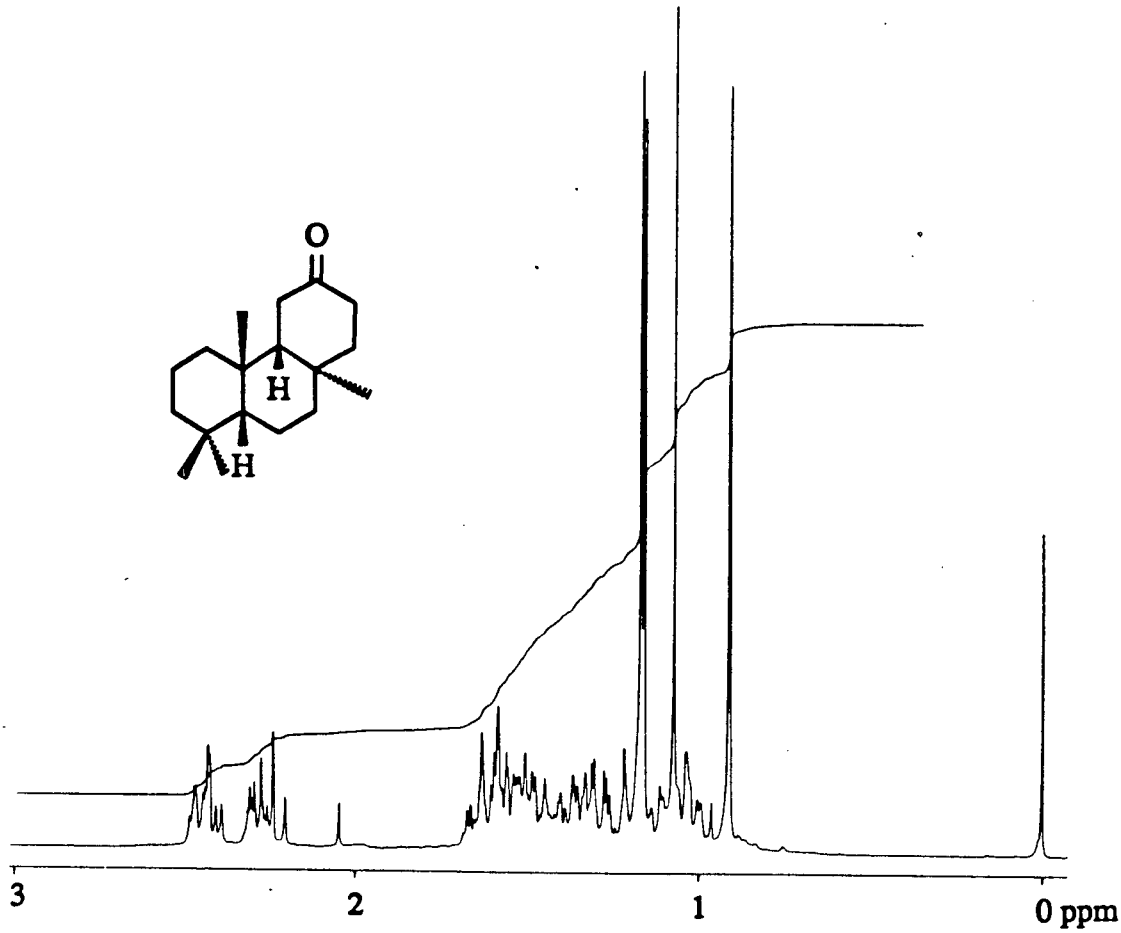
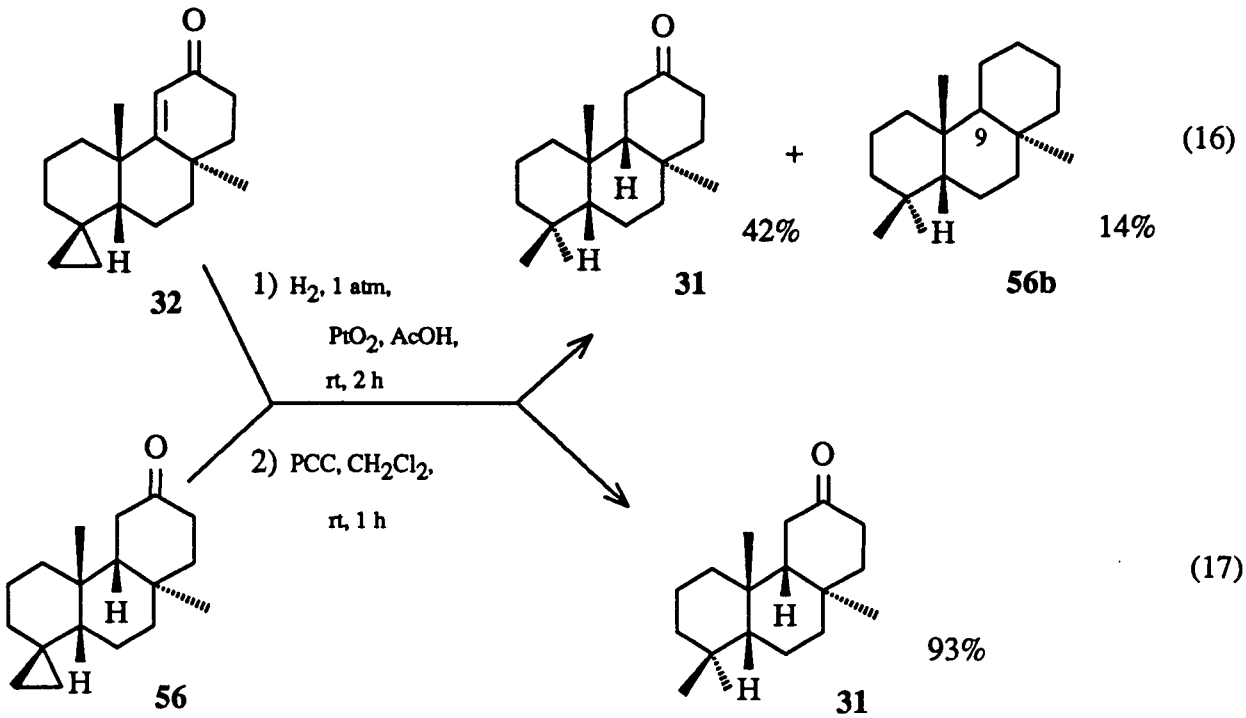


Figure 2. The ^1H nmr spectrum ($CDCl_3$, 400 MHz) of compound **31**.

IIIh. Preparation of the ketone **31**.

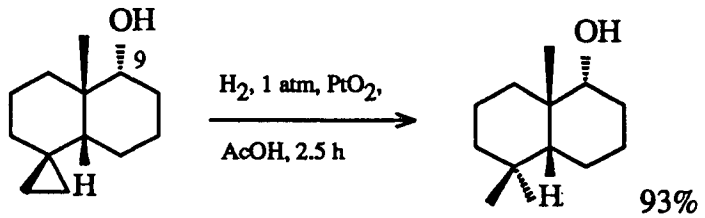
Hydrogenation-hydrogenolysis (Adams' catalyst/glacial acetic acid)[47] of the enone **32**, followed by oxidation (PCC/dichloromethane) of the resultant product mixture, gave a 42% yield of the ketone **31**. Some of the tricyclic hydrocarbon **56b** (its configuration at C-9 was not determined) was also produced (equation 16). Better results were obtained when the ketone **56** was subjected to the same sequence of reactions (hydrogenolysis and oxidation, equation 17). In this case, the ketone **31** was obtained as the only product in 93% yield. Compound **31** exhibited an ir absorption at



1713 cm^{-1} due to the carbonyl group. The ^1H nmr spectrum of **31** (Figure 2, p.33) displayed four (three-proton) singlets at δ 1.17, 1.16, 1.08, and 0.92 due to the presence of four methyl groups. On the other hand, the ^1H nmr spectrum of compound **56b** exhibited four (three-proton) singlets at δ 1.17, 1.08, 0.97, and 0.88.

The synthetic work described above resulted in the 9-step stereoselective conversion of the ketone **17** into the tricyclic ketone **31** in 14% overall yield. Of particular note in this sequence were: (a) the highly stereoselective Mukaiyama-type reaction of the silyl enol ether **50** with the ethylene ketal of 3-buten-2-one to produce **37** (equation 12) and (b) the highly stereoselective hydrogenation of the enone **32** to give the ketone **56** (equation 15).

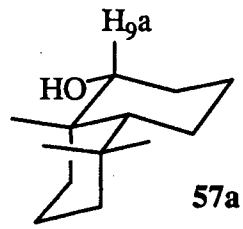
IIIi. Synthesis of the ketone **31** via the "gem-dimethyl route." Preparation of the ketone **38**.



(18)

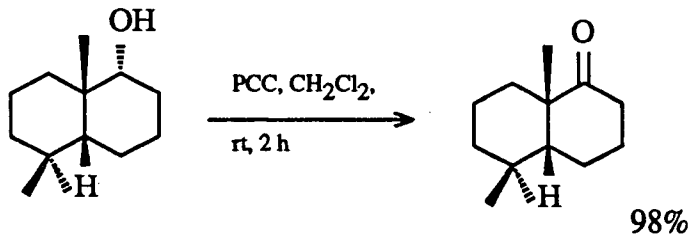
46 **57**

Hydrogenolysis of **46** (Adams' catalyst/glacial acetic acid)[47] afforded the alcohol **57** in excellent yield (equation 18). The ir spectrum of this compound exhibited absorptions at 3281 and 1042 cm^{-1} due to the C-OH function and a doublet at 1386 and 1365 cm^{-1} due to the gem-dimethyl moiety. The ^1H nmr spectrum of **57** exhibited a doublet of doublets at δ 3.23 (J=13,4 Hz) due to the (axial) proton on C-9. The methyl



57a

groups in compound **57** gave rise to three-proton singlets at δ 1.25, 1.15, and 0.86. Based on the coupling constants associated with the C-9 proton, it was possible to infer that **57** exists primarily in the conformation represented by **57a**.



(19)

57 **38**

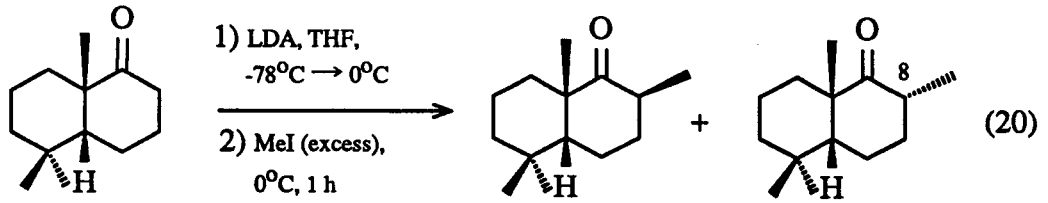
The alcohol **57** was oxidized with PCC in dry dichloromethane[40] to give the ketone **38** in high yield (equation 19). The ir spectrum of this material showed an

absorption at 1703 cm^{-1} due to the carbonyl group. The ^1H nmr spectrum of **38** exhibited three singlets at δ 1.26, 0.97, and 0.85 due to the methyl groups. A comparison of this data with the reported[48] chemical shifts for the angular methyl groups in cis-1-decalones (δ 1.20-1.05) tentatively suggested the assignment of the signal at δ 1.26 to the angular methyl group on **38**.

IIIj. Alkylation of the ketone **38**. Preparation of the ketones **58** and **59**.

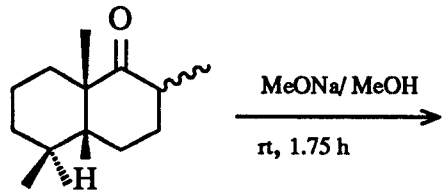
Monoalkylation of the ketone **38** by deprotonation with lithium diisopropylamide (LDA) and addition of methyl iodide gave a 4.2:1 (glc) mixture of the ketones **58** and **59**, respectively, in 81% yield (equation 20). The ^1H nmr spectrum of this mixture indicated that the ratio of the two products was ~5:1. Equilibration of a sample of this mixture of ketones with sodium methoxide in methanol afforded the two substances, **58** and **59**, in ratio of 1:6.2 (glc), respectively (equation 21). Column chromatography of this mixture gave a fraction which contained the ketone **59** exclusively, thus allowing its characterization. The ir spectrum of **59** showed an absorption at 1703 cm^{-1} due to the carbonyl group. The ^1H nmr spectrum of **59** exhibited a signal at δ 2.87 (ddq, J=14,7,7 Hz) due to the (axial) proton on C-8. A doublet at δ 0.99 (J=7 Hz) was assigned to the secondary methyl group.

In order to determine the configuration and the conformation of **59** a series of decoupling experiments was carried out, with the following results. Irradiation of the signal at δ 2.87 (ddq, J=14,7,7 Hz, H_8a) caused the collapse of the signals at 2.04 (br ddd, J=14,7,6 Hz, H_7e) to a broad dd (J=14,6 Hz), 1.73 (dddd, J=14,14,14,6 Hz, H_7a) to a ddd (J=14,14,6 Hz) and 0.99 (d, J=7 Hz, secondary methyl protons) to a singlet;



38 **58** 4.2:1 (glc) **59**
81%

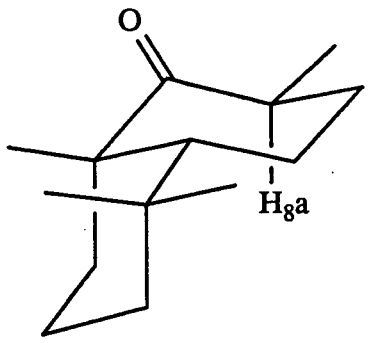
(20)



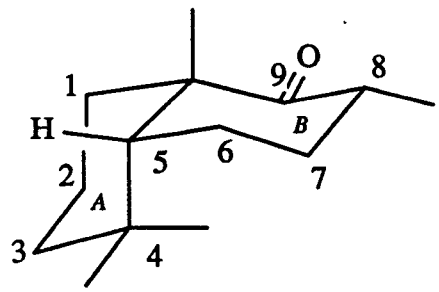
58/59 1:6.2 (glc) (21)

58/59 4.2:1 (glc)

irradiation of the signal at δ 2.04 (br ddd, J=14,7,6 Hz, H_7e) caused the collapse of the signals at 2.87 (ddq, J=14,7,7 Hz, H_8a) to a dq (J=14,7 Hz) and 1.73 (dddd, J=14,14,14,6 Hz, H_7a) to a ddd (J=14,14,6 Hz), simplified the multiplet at 2.26-2.13 (H_6a) and sharpened the broad doublet (J=6 Hz) at 1.64 (H_5); irradiation of the signal at δ 1.73 (dddd, J=14,14,14,6 Hz, H_7a) caused the collapse of the signals at 2.87 (ddq, J=14,7,7 Hz, H_8a) to a dq (J=7,7 Hz), 2.04 (br ddd, J=14,7,6, H_7e) to an unresolved multiplet, and



58a



59a

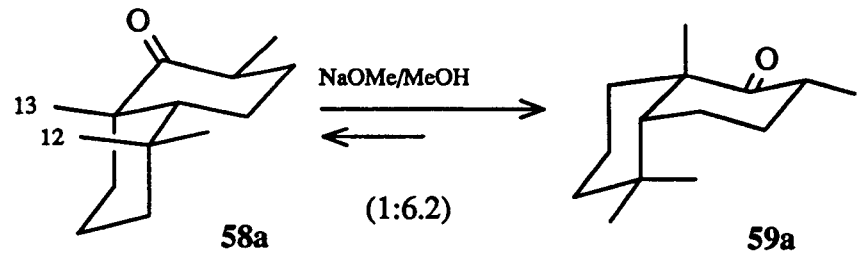
1.86 (br dd, J=14,6 Hz, H_6e) to a broad doublet (J=14 Hz), and simplified the multiplet at 2.26-2.13 (H_6a); irradiation of the signal at δ 1.86 (br dd, J=14,6 Hz, H_6e) simplified the

signals at 2.26-2.13 (m, H_6a) and 1.73 (dddd, J=14,14,14,6 Hz, H_7a) and caused the collapse of the signal at 2.04 (br ddd, J=14,7,6 Hz,H_7e) to a dd (J=14,7 Hz); irradiation of the multiplet at δ 2.26-2.13 (H_6a) simplified the signals at 1.86 (H_6e), 1.73 (H_7a) and 2.04 (H_7e), and caused the collapse of the broad doublet at 1.64 (J=6 Hz, H_5) to a broad singlet. These results clearly indicated that H_5 (located via the sequence of irradiations mentioned above) has an equatorial orientation with respect to ring *B*. This orientation was suggested by the w-coupling between H_5 and H_7e and also by the magnitude (6 Hz) of the coupling between H_5 and H_6a. Furthermore, the absence of coupling of H_5 to H_6e suggested that the dihedral angle between the C-H_5 and C-H_6e bonds was close to 90°. Thus, the preferred conformation of **59** can be represented as **59a**.

From the ^1H nmr spectrum of the 4.2:1 (glc) mixture of ketones **58** and **59**, it was possible to observe the presence of a signal for the major compound (**58**) at δ 2.59 (ddq, J=14,7,7 Hz) due to the axial proton on C-8 (H_8a). Since **58** was epimeric at C-8 with compound **59**, it was inferred that the more stable conformation of **58** is **58a**.

Examination of molecular models and a qualitative conformational analysis of **58a** and **59a** does not lead to a definitive statement as to why, upon equilibration (MeONa/MeOH), **59a** predominates over **58a** (see equation 22). Thus, the conformational analysis of **58a** reveals the following 1,3-steric interactions: one CH_3-CH_3 diaxial, three CH_3-H syn-axial, and three CH_2-H syn-axial. The corresponding analysis for **59a** shows one CH_3-CH_2 diaxial, four CH_3-H syn-axial, and one CH_3-Csp^2 diaxial interaction.

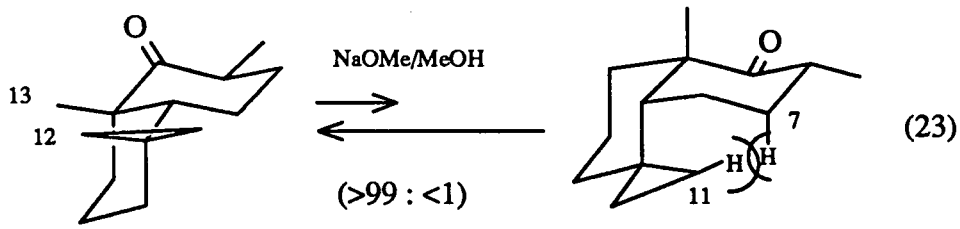
It is interesting to compare the results derived from the equilibration of **58** and **59** with those obtained from treatment of mixtures of **48** and **49** with NaOMe in MeOH. As shown above, **59** (see conformer **59a**) is more stable than **58** (see conformer **58a**). In contrast, equilibration of **48** and **49** leads to the exclusive formation of the epimer **48**. The latter observation can be rationalized as follows. A careful examination of



58a **59a** (22)

1,3-diaxial interaction	CH_3-CH_3	CH_3-CH_2
1,3-syn-axial interaction	3xCH_3-H 3xCH_2-H	4xCH_3-H
1,3-sp^2-axial interaction	———	CH_3-Csp^2

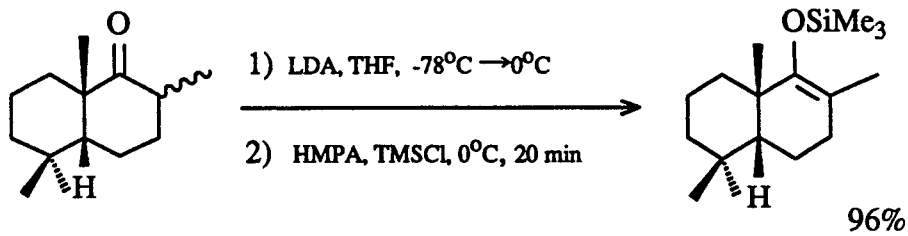
molecular models of conformers **48a** and **49a** reveals the presence of a severe steric interaction between a C-11 methylene hydrogen and a C-7 (axial) hydrogen in conformer **49a**. On the other hand, the C-12/C-13 1,3-diaxial interaction in conformer **48a**



48a **49a** (23)

(CH_2-CH_3, see equation 23) appears to be noticeably less severe than the corresponding interaction in conformer **58a** (CH_3-CH_3, see equation 22). It appears that the contribution of these two effects shifts the position of the equilibrium (23) far to the left.

IIIk. Preparation of the silyl enol ether **60**. Preparation of the diketone **39.**

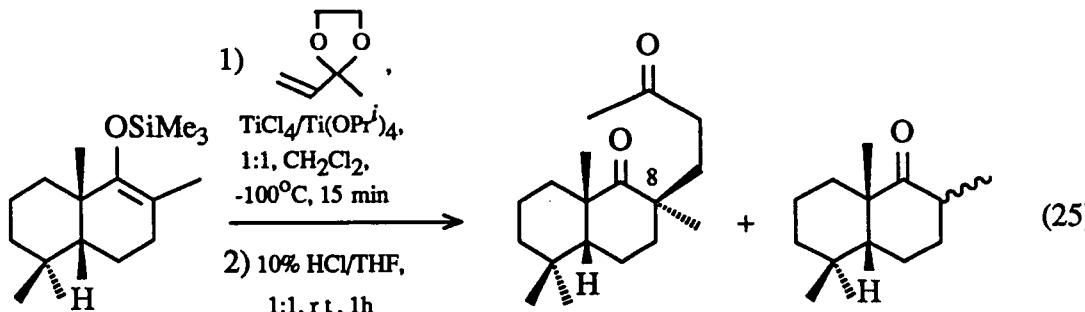


96%

(24)

58/59 **60**

HMPA and chlorotrimethylsilane were added successively to a cold (0°C) THF solution of the lithium enolate prepared from the mixture (4.2:1, glc) of the ketones **58/59**. The silyl enol ether **60** was thus produced in 96% yield (equation 24). The ir spectrum of compound **60** exhibited absorptions at 1680 and 843 cm^{-1} due to the C-C double bond and the trimethylsilyl group, respectively. The ^1H nmr spectrum of **60** showed singlets at δ 1.50 and 0.20, indicating the presence of the vinylic methyl group and the trimethylsilyl group, respectively.



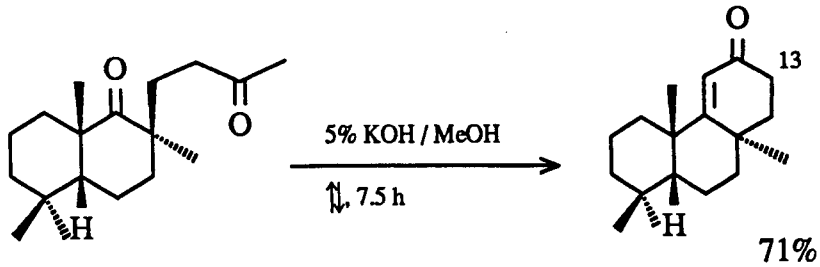
45% 24%

(25)

60 **39** **58/59**

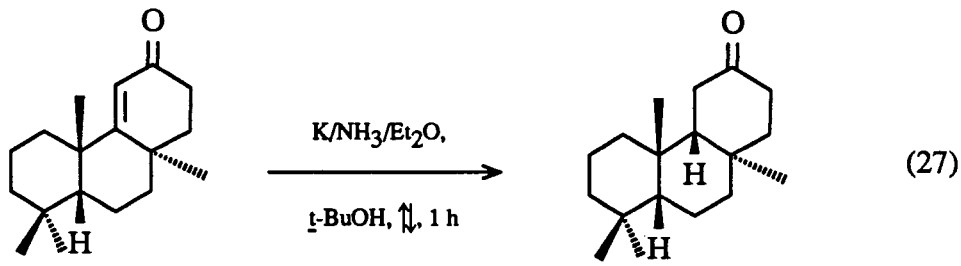
The silyl enol ether **60** and the ethylene ketal of 3-buten-2-one[46] were added to a cold (-100°) mixture of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ in dichloromethane and the mixture was stirred at -100°C for 15 min. Subsequent treatment of the crude product mixture with a 1:1 solution of 10% aqueous hydrochloric acid and THF, followed by column chromatography of the resultant material, afforded the 1,5-diketone **39** in 45% yield and a ~1:7 mixture of the ketones **58** and **59** in 24% yield (equation 25). In this case, the desired product **39** was completely homogeneous by glc analysis. The diketone **39** exhibited ir absorptions at 1718 and 1688 cm^{-1} due to the presence of the two carbonyl groups. The ^1H nmr spectrum of **39** exhibited one proton signals at δ 2.40 (ddd, J=18,10,6 Hz) and 2.22 (ddd, J=18,9,7 Hz) due to the two diastereotopic protons adjacent to the side-chain carbonyl function. A singlet at δ 2.13 could readily be assigned to the methyl group bonded to the carbonyl group. At this stage of the synthesis, the relative configuration of **39** at C-8 was not known. Elucidation of this point had to wait until the conversion of **39** into the previously prepared tricyclic ketone **31** (vide infra) had been completed.

IIII. Preparation of the enone **61.** Synthesis of the ketone **31** and determination of its relative configuration.



39 **61** (26)

The diketone **39** underwent internal aldol condensation-dehydration in the presence of a 5% solution of potassium hydroxide in methanol (reflux, 7.5 h). After workup and column chromatography of the crude product, the (uv active) enone **61** was obtained in 71% yield (equation 26). Under these conditions, no retro-Michael products were obtained (compare with equation 13). The ir spectrum of **61** showed absorptions due to the α,β-unsaturated carbonyl group and the enone C-C double bond at 1666 and 1587 cm^{-1}, respectively. The ^1H nmr spectrum of **61** exhibited a singlet at δ 6.08 due to the vinylic proton and two signals at 2.59 (ddd, J=18,15,6 Hz) and 2.37 (ddd, J=18,6,2 Hz) due to the axial and equatorial protons on C-13, respectively.



(27)

61 **31** 62%

The enone **61** was subjected to a dissolving metal reduction using potassium in ammonia/diethyl ether in the presence of tert-butyl alcohol.[29c,f] The reaction mixture was refluxed for 1 h. After workup and column chromatography of the product mixture, the ketone **31** was obtained in 62% yield, together with a fair amount (34%) of the recovered starting material **61** (equation 27). The ketone **31**, obtained in this way, was physically and spectroscopically indistinguishable from the same compound obtained, as described previously, from **32** and **56** (see equations 16 and 17). Thus, the relative configurations of the diketone **39** and the enone **61** were unambiguously established.

IIIm. Conclusions

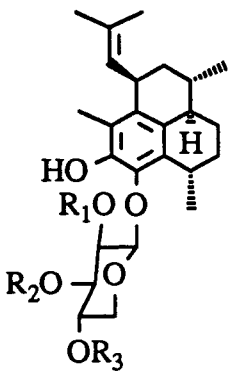
The synthetic work described in Sections IIId-IIIh (pp.18-34) resulted in a stereoselective 9-step conversion of the ketone **17** into the tricyclic ketone **31** (14% overall yield), while that discussed in Sections IIIi-IIIl (pp.35-42) performed the same overall conversion **17**→**31** (also in 9 steps) in ~10% yield. Thus, there was no significant difference in the overall efficiency of the synthetic pathways ***A*** and ***B*** (see Scheme 4, p.17) leading to **31**.

Compound **31** contains, with the correct relative configurations, four of the five contiguous chiral centers present in the target molecule **16**.

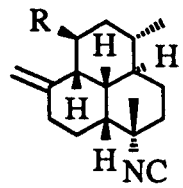
With respect to sequence ***B***, the stereoselective Mukaiyama reaction leading to **39** (equation 25, p.40) and the highly stereoselective Birch reduction of the enone **61** (equation 27, p.42) are especially noteworthy. Interestingly, the stereochemical outcome of the Mukaiyama reaction was very similar to that of the corresponding reaction (equation 12, p.27) in sequence ***A***. In a different context, it should be mentioned that the reaction conditions that led to the efficient production of the enone **61** (equation 26, p.41) were to have been tried for the conversion of **37** into the enone **32** (see equation 13, p.28). Also, the hydrogenation conditions (as applied to the enone **32**; see equation 15, p.30) were to have been tested on the enone **61**. However, at this stage of the syntheic work the correct structure of suvanine (**27**) was reported.[22b] Consequently, for the reasons explained earlier (see section IIIa), we concluded this part of our work.

IV. Total synthesis of (±)-8-isocyano-10,14-amphilectadiene (23)

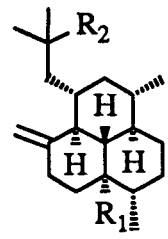
IVa. Compounds structurally related to the parent hydrocarbon amphilectane **25**



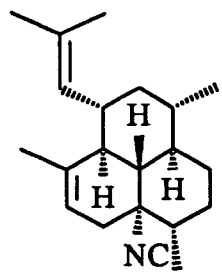
62 R_1=R_2=R_3= H
63 R_1= Ac, R_2=R_3= H
64 R_2= Ac, R_1=R_3= H
65 R_3= Ac, R_1=R_2= H



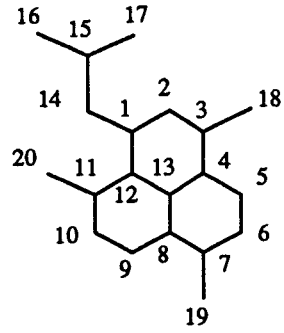
66 R= $CH{=}CMe_2$
67 R= $CH_2C(Me){=}CH_2$
68 R= $CH_2C(\text{-}NC)Me_2$



69 R_1= NC, R_2= NHCHO
15 R_1=R_2= NC



23

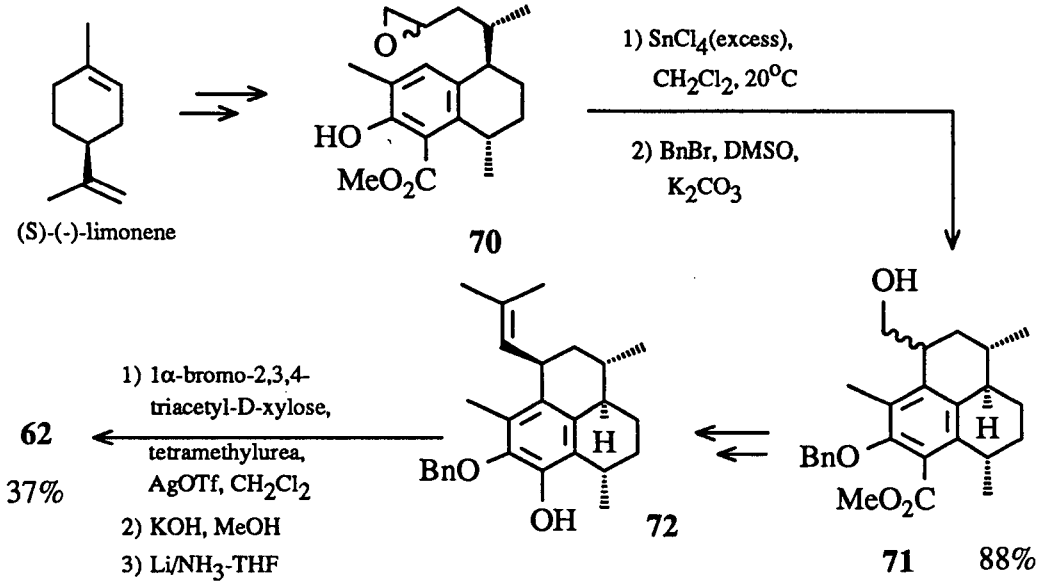


25

The compounds **15** (see p.5), **62-69**, and the isonitrile 8-isocyano-10,14-amphilectadiene (**23**) which was the objective of our synthetic effort, are diterpenoids isolated from marine sources that bear the amphilectane carbon skeleton of the parent hydrocarbon **25**. Thus, it is pertinent to discuss briefly some aspects of the work related

to the isolation and structural elucidation of compounds **15** and **62-69**, as well as to the total synthesis of **62** (vide infra).

The pseudopterosins A-D[49] (**62-65**) have been isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae* and show antiinflammatory and analgesic activities. The structure of pseudopterosin C (**64**) was determined by X-ray crystallography. The identification of the pentose portion of **64** as 3-O-acetyl-β-xylopyranose allowed the assignment of its absolute configuration. On the other hand, the structures of pseudopterosins A, B, and D (**62**, **63**, and **65**) were established on the basis of spectral analyses.[49]



Scheme 6

A total synthesis of (-)-pseudopterosin A (**62**) has been carried out by Broka et al.[50] (see Scheme 6). Thus, a 19-step sequence starting from (*S*)-(-)-limonene led to the epoxide **70**. Subjection of **70** to an intramolecular Friedel-Crafts alkylation, followed by benzylation of the phenolic hydroxyl group, gave **71**, which possesses the tricyclic part of the basic amphilectane skeleton. The alcohol **71** was transformed (in 8 steps) to the

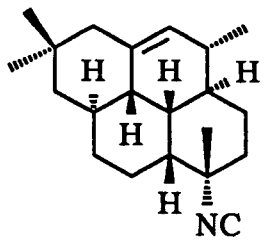
intermediate **72**. Finally, glycosidation of **72** was followed by deacetylation and cleavage of the benzyl unit with lithium in ammonia to give the desired natural product **62**.

The isonitriles **66-68** were isolated from an *Adocia* sp. sponge by Kazlauskas et al.[51] The structure of **66** was determined by X-ray diffraction analysis, whereas the structures of **67** and **68** were proposed on the basis of a comparison of their spectra with those of compound **66**.

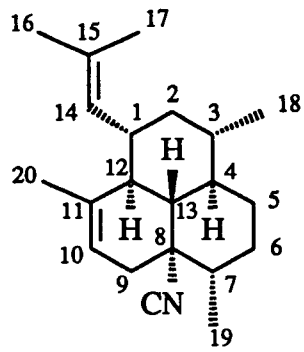
The diterpenoid isonitriles **69** and **15** were isolated from the Caribbean sponge *Hymeniacidon amphilecta* by Faulkner and coworkers.[20] A single crystal X-ray diffraction analysis allowed the structural determination of the diisocyanide **15**, a compound which exhibited antibiotic activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Candida albicans*. A total synthesis of (±)-**15** has been completed by Piers and Llinas-Brunet.[21] The synthesis of compound **24** (see pp.8,9), a key intermediate in their synthesis of (±)-**15**, is discussed in section IVd of this thesis since it is directly related to our total synthesis of (±)-**23**.

IVb. Isolation and structural elucidation of 8-isocyano-10,14-amphilectadiene (**23**)

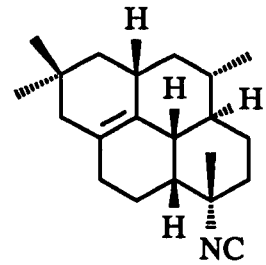
In 1987, Faulkner and coworkers[26] reported the isolation of three new diterpene isonitriles from the hexane extract of the Palauan sponge *Halichondria* sp., namely, 7-isocyano-1-cycloamphilectene (**73**), 7-isocyano-11-cycloamphilectene (**74**), and (-)-8-isocyano-10,14-amphilectadiene (**23**). Compound **23** bears the parent "amphilectane" skeleton **25**, was the minor constituent of the hexane extract (0.066% of dry weight) of the sponge, and decomposed slowly on storage at -20°C. Compound **23** also exhibited antimicrobial activity by inhibiting *Staphilococcus aureus* and *Bacillus*



73



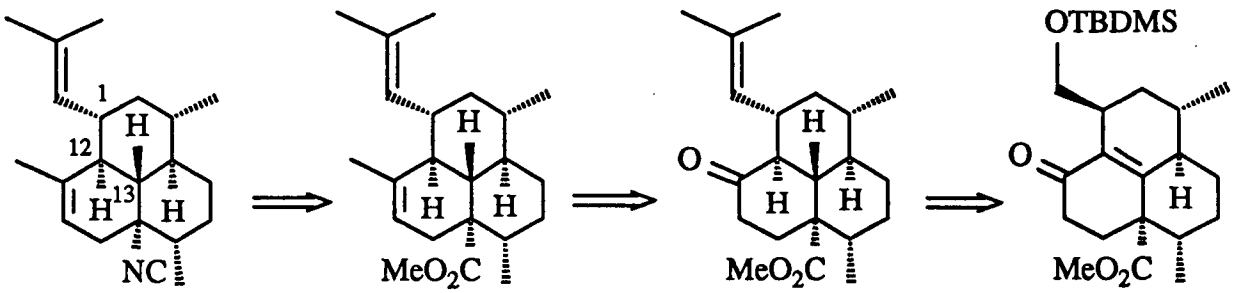
23



74

subtilis at 5 μg/disk in the standard disk assay.[26] The structures of **73** and **74** were determined by Faulkner and coworkers[26] using a combination of spectral and X-ray analyses, whereas that of **23** was determined primarily on the basis of spectral data. Compound **23** (isolated as an oil) exhibited $[\alpha]_D$ -79.8° (c=2.0, $CHCl_3$) and an ir ($CHCl_3$) absorption at 2130 cm^{-1}. The ^1H nmr spectrum of **23** exhibited signals at δ 1.66 (d, 3H, J=1 Hz), 1.57 (d, 3H, J=1 Hz), and 5.15 (br d, 1H, J=7 Hz) due to the isobutenyl group. The signal at δ 5.15 was coupled to a signal at δ 2.24 (m, 1H, J=12,12,7,4 Hz), which was assigned to the axial proton on C-1. The two doublets at δ 0.88 (d, 3H, J=3.6 Hz) and 1.02 (d, 3H, J=6 Hz) were assigned to the secondary methyl groups. The ^{13}C nmr spectrum of **23** showed signals at δ 154.5 (br s) and 63.3 (br s), due to the tertiary isonitrile function and signals at δ 137.6 (s), 133.4 (d), 126.6 (s), and 118.8 (d) due to two carbon-carbon double bonds. Furthermore, ^1H COSY and decoupling experiments allowed the establishment of the relative stereochemistry at C-1, C-12, and C-13. On the other hand, since the (C-3)-(C-8) stereochemistry is identical in all other amphilectenes, Faulkner and coworkers[26] assigned the relative stereochemistry of **23** as 1*S**,3*S**,4*R**,7*S**,8*R**,12*S**,13*S**.

IVc. Retrosynthetic analysis

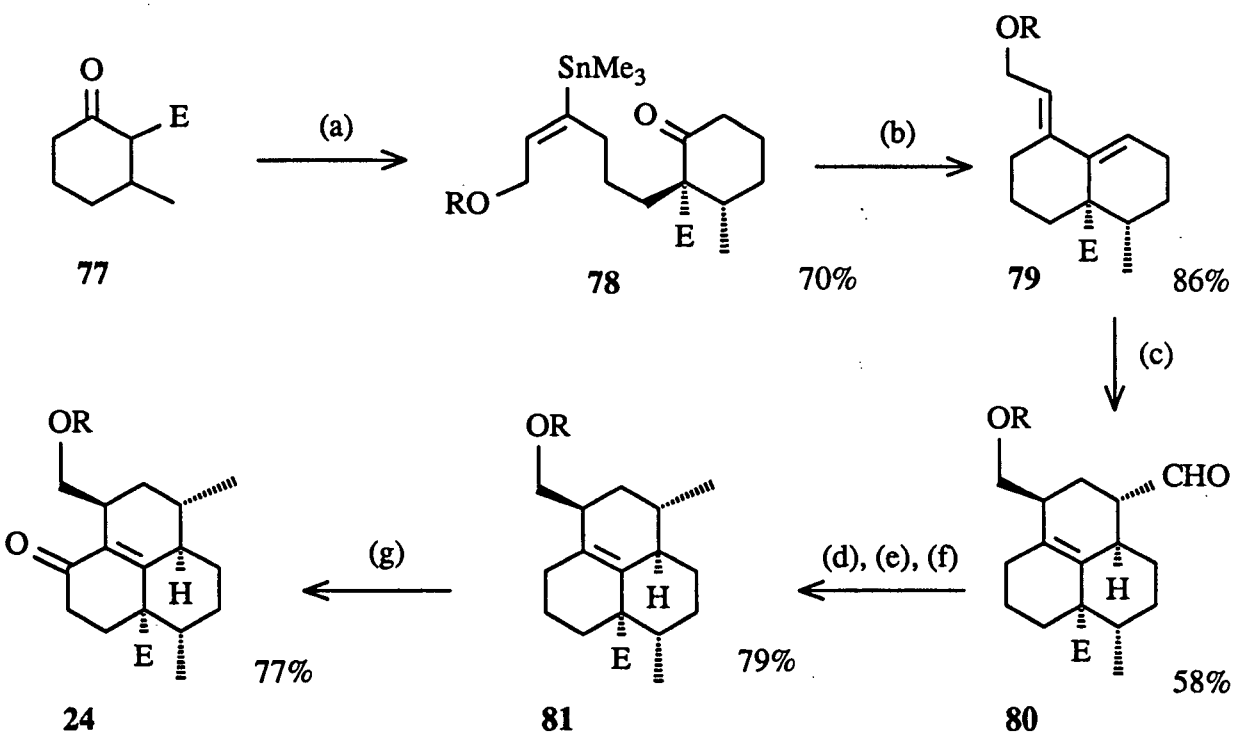


23 **75** **76** **24**

The strategy for the construction of 8-isocyano-10,14-amphilectadiene (**23**) was based on the recognition that the keto ester **24** (previously prepared in our laboratories)[21] would serve as a suitable starting material. Thus, a comparison of structures **23** and **24** shows that it was necessary to degrade the ester function of **24** to an isonitrile and to elaborate the protected alcohol moiety into an isobutenyl group. In addition, the correct relative stereochemistry for three contiguous chiral centers (at C-1, C-12 and C-13) had to be established. The transformation of the ester function to an isonitrile was left for the last steps of the synthesis, since it is known that **23** decomposes slowly at -20°C[26] and that the isonitrile function could give rise to side-reactions during certain synthetic manipulations.[52] Furthermore, it was envisaged that the ester diene **75** could readily be synthesized from the ketone **76** using, for example, the Pd(0)-catalyzed coupling of a regioselectively generated enol triflate with tetramethyltin.[53a-c] Finally, it seemed likely that **76** could be prepared by transforming the siloxymethyl fragment in **24** to an axially oriented formyl group. Epimerization of the latter compound to give the (presumably more stable) aldehyde with an equatorially oriented formyl group would then be followed by its eventual transformation into the required isobutenyl moiety via Wittig-type methodology.

IVd. Preparation of the keto ester **24**

The keto ester **24** (Scheme 7) was prepared according to the sequence developed in our laboratories by Piers and Llinas-Brunet[21] en route to their synthesis of the diterpenoid (±)-8,15-diisocyano-11(20)-amphilectene (**15**). Thus, stereoselective alkylation[54] of the potassium enolate of 2-(methoxycarbonyl)-3-methylcyclohexanone (**77**) with (*E*)-1-(*tert*-butyldimethylsiloxy)-6-iodo-3-(trimethylstannyl)-2-hexene[55] gave the keto ester **78.** An efficient 'one pot' sequence (formation of the enol triflate of **78**,[56c] followed by an intramolecular Pd(0)-catalyzed coupling reaction[55,57]) afforded the diene **79** with complete retention of the exocyclic double bond stereochemistry.



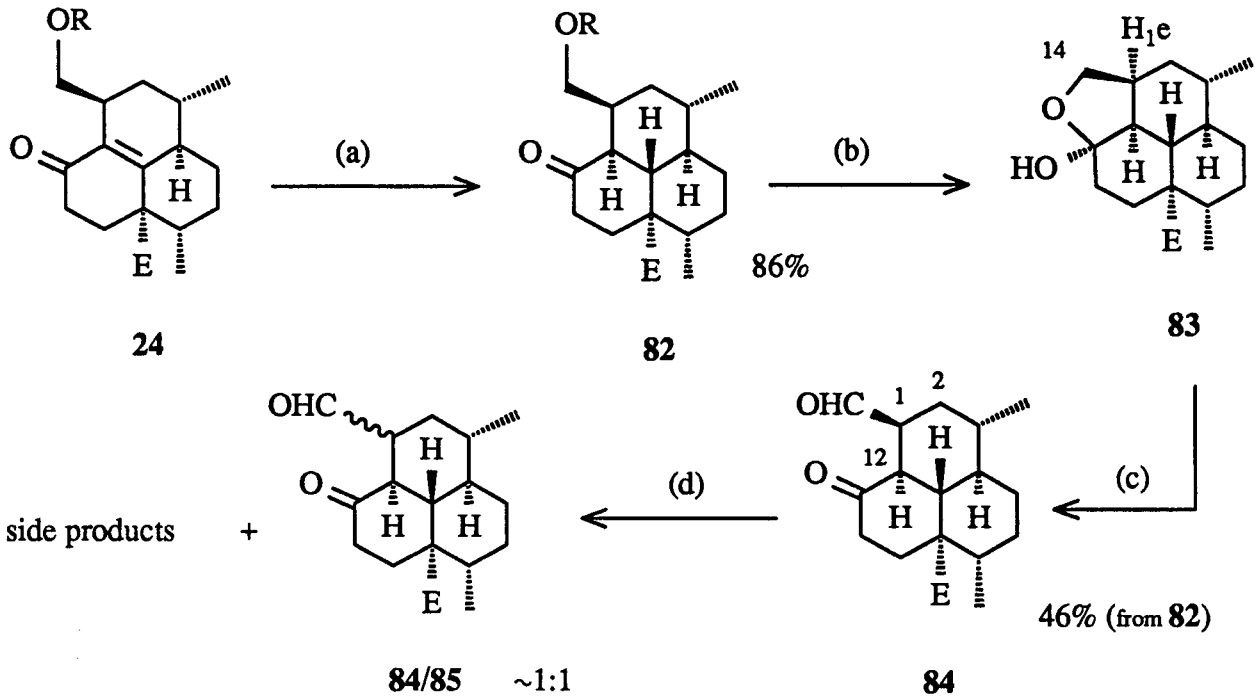
Scheme 7. Reagents and conditions: R=Si(*t*-Bu)Me_2, E=CO_2Me; (a) KH, PhMe; (*E*)-1-(tert-butyldimethoxysiloxy)-6-iodo-3-(trimethylstannyl)-2-hexene, ⇅, 48 h;

(b) LiN(*i*-Pr_2), THF, -48°C, 1 h; PhN(SO_2CF_3)$_2$, rt, 30 min; (Ph_3P)$_4$Pd (0.07 equiv), ⇅, overnight; (c) propenal, PhH, ⇅, 20h; NaOMe, MeOH; (d) $NaBH_4$, MeOH; (e) *p*-$MeC_6H_4SO_2Cl$, pyridine, *p*-(N,N-dimethylamino)pyridine, CH_2Cl_2; (f) $LiEt_3BH$, THF, rt, 3 h; NaOH, H_2O_2, THF; (g) CrO_3-3,5-dimethylpyrazole, CH_2Cl_2, 0°C, 1.5 h.

A regioselective Diels-Alder reaction of **79** with propenal gave a mixture of four of the eight possible stereoisomers. Upon subjecting the crude mixture to epimerization with sodium methoxide in methanol (affording two isomeric aldehydes), followed by column chromatography, the desired isomer (**80**) was isolated in 58% yield. The structure of **80** was assigned on the basis of previous work on the Diels-Alder reactions of dienes structurally similar to **79**.[55] The transformation of **80** into **81** was effected via sodium borohydride reduction, *p*-toluenesulfonation of the resulting primary alcohol, and reductive displacement of the *p*-toluenesulfonate with lithium triethylborohydride.[58] Finally, **24** was prepared via the allylic oxidation of **81** with CrO_3-3,5-dimethylpyrazole.[59]

IVe. Initial attempt to synthesize the keto ester **76**

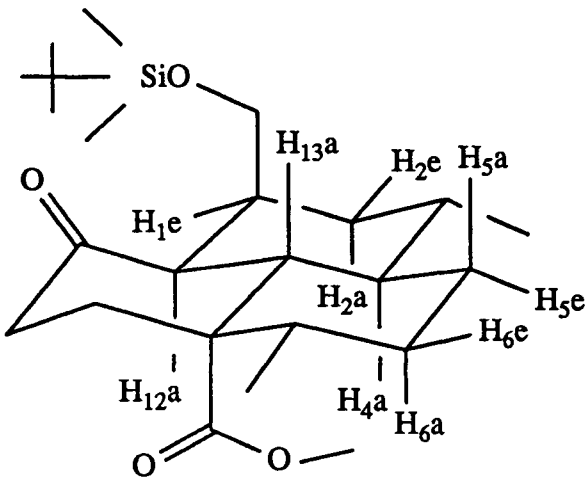
Following our retrosynthetic analysis (section IVc of this Discussion), the ketone **82** was prepared by a dissolving metal reduction of **24** with sodium in ammonia in the presence of tert-butyl alcohol[29c,f] (Scheme 8). Workup and column chromatography of the product thus obtained gave the keto ester **82**[60] in 86% yield.



Scheme 8. Reagents and conditions: R= Si(*t*-Bu)Me_2, E= CO_2Me; (a) Na, *t*-BuOH, NH_3, ⇅, 40 min; (b) *n*-Bu_4NF, THF, rt, 2.5 h; (c) PCC, NaOAc, CH_2Cl_2, 45 min; (d) NaOMe, MeOH, rt, overnight.

The ir spectrum of **82** showed strong absorptions at 1724 and 1707 cm^{-1} due to the ester and ketone carbonyl groups, respectively. The ^1H nmr of **82** (see formula **82a**) exhibited a one-proton multiplet at δ 2.53 due to H_1e, a dd (J=13,4 Hz) at 2.32 due to $H_{12}a$, a dddd (J=13,3,3,3 Hz) at 2.08 due to H_5e, a ddd (J=13.5,3,3 Hz) at 1.88 due to H_2e, a one-proton dddd (J=11,11,11,3 Hz) at 1.74 due to H_4a, a dd (J=13,11 Hz) at 1.56 due to $H_{13}a$, a three-proton multiplet at 1.47-1.32 due to H_6a, H_6e, and H_5a, and a ddd (J=13.5,13.5,3.5 Hz) at 1.12 due to H_2a.

In ^1H nmr homonuclear decoupling experiments (see formula **82a**), irradiation of the signal at δ 1.12 (H_2a) simplified the multiplet at 2.53 (H_1e) and caused the collapse of the signal at 1.88 (H_2e) to a broad singlet; irradiation of the signal at δ 1.88



82a

(H_2e) simplified the multiplet at 2.53 (H_1e) and transformed the signal at 1.12 (H_2a) into a doublet of doublets, (J=13.5,3.5 Hz); irradiation of the signal at δ 2.08 (H_5e) simplified the multiplet at 1.47-1.32 (H_6a, H_6e, H_5a) and caused the collapse of the signal at 1.74 (H_4a) to a ddd (J=11,11,11 Hz); irradiation of the signal at δ 2.32 ($H_{12}a$) simplified the multiplet at 2.53 (H_1e) and caused the collapse of the signal at 1.56 ($H_{13}a$) to a doublet (J =11 Hz).

Based on the arguments given in sections IIIb and IIIg of this Discussion, it was expected that the alkali metal-ammonia reduction of **24** would give the product in which the six-membered rings are trans-fused. The ^1H nmr spectral data discussed above strongly supported this assumption. Thus, the J values (13,11 Hz) associated with the coupling between $H_{13}a$ and $H_{12}a$ and between $H_{13}a$ and H_4a, respectively, indicates that $H_{13}a$ is trans and diaxial to both $H_{12}a$ and H_4a. Furthermore, the value of J_{H1-H12} (4 Hz) is consistent with an equatorial (H_1e)-axial ($H_{12}a$) relationship. Thus, the stereochemistry of the reduction product **82** can be assigned with confidence.

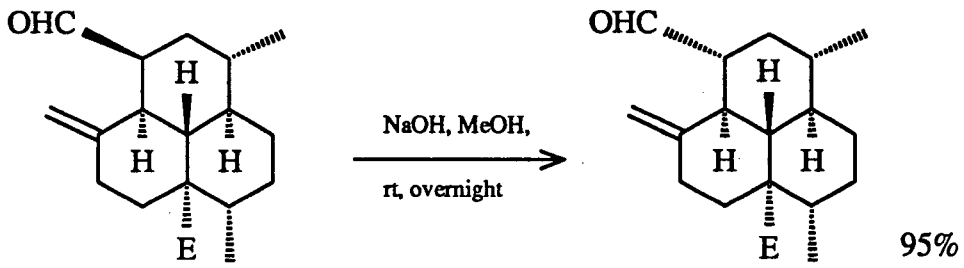
In the next step, treatment of **82** with a solution of tetra-*n*-butylammonium

fluoride in THF gave the unstable hemiketal **83** as a colorless oil. The ir spectrum of **83** (crude product) exhibited absorptions at 3402 due to the O-H function and 1723 cm^{-1} due to the methyl ester function. The ^1H nmr spectrum of **83** (crude product) exhibited two (one-proton) multiplets at δ 4.00 (dd, J=8,8 Hz) and δ 3.77 (dd, J=10,8 Hz) due to the C-14 methylene protons and a complex multiplet at δ 3.05-2.94 probably due to H_1e.

Oxidation of the crude compound **83** (PCC, NaOAc, CH_2Cl_2, rt), followed by workup and chromatography of the material thus obtained, gave the keto aldehyde **84** in 46% yield (from **82**). The ir spectrum of this compound exhibited an absorption at 1723 cm^{-1} due to the carbonyl groups. The ^1H nmr spectrum of **84** exhibited a broad singlet at δ 9.61 due to the formyl group proton, a multiplet at δ 3.38-3.32 due to H_1e, a doublet of doublets at δ 2.40 (J=12,4 Hz) (partially overlapped by a multiplet at δ 2.47-2.35) due to $H_{12}a$, and a ddd at δ 2.10 (J=14,3,3 Hz) due to H_2e. In decoupling experiments, irradiation of the multiplet at δ 3.38-3.32 (H_1e) sharpened the singlet at δ 9.61 (formyl group proton), and caused the collapse of the signals at δ 2.40 ($H_{12}a$) to a doublet (J=12 Hz) and δ 2.10 (H_2e) to a dd (J=14,3 Hz). Also, a dd (J=14,14 Hz) at δ 1.40 (due to H_2a) then stood out from the complex signals in the region δ 1.60-1.24.

With the hope of obtaining the keto aldehyde **85**, possesing the equatorially oriented CHO group, the aldehyde **84** was subjected to epimerization with sodium methoxide in methanol (room temperature, overnight). However, after chromatography of the crude product on silica gel, a mixture (~1:1 by ^1H nmr analysis) of the epimeric aldehydes **84** and **85** was obtained in low yield along with a considerable amount of unidentified side-products. The ^1H nmr spectrum of the crude mixture obtained after workup clearly exhibited a doublet at δ 9.74 (J=2 Hz) and a broad singlet at 9.61 due to the formyl protons of **85** and **84**, respectively. Also, three-proton singlets at δ 3.78 and 3.72 were observed and assigned to the methyl ester protons of **85** and **84**, respectively.

Treatment of the aldehyde **86**, an intermediate in the Piers-Llinas-Brunet synthesis of the diterpenoid **15**,[21] with sodium methoxide-methanol under conditions very similar to those described above, produced the C-1 epimer **87** in excellent yield (equation **28**). This result suggests that the impediment for the complete epimerization



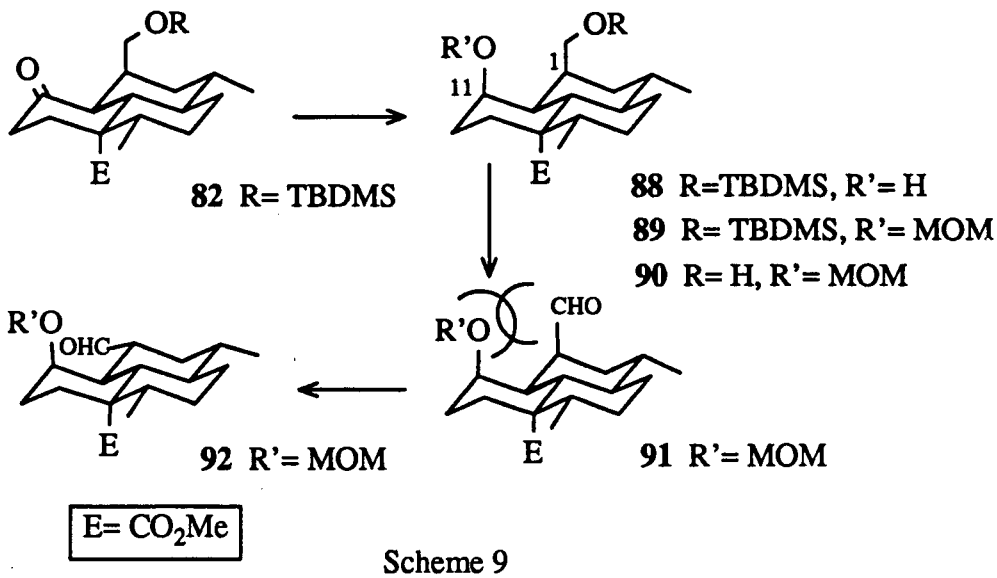
(28)

86 **87**

of **84** is not steric in nature. Perhaps an unfavorable dipole-dipole repulsion between the equatorial CHO group and the C-11 carbonyl group in **85** destabilizes this epimer. In any case, due to the unsatisfactory result of this experiment, a different approach (described in the next section) for the preparation of **76** from the intermediate **24** was undertaken.

IVf. Synthesis of the keto ester **76**. Alternative synthetic plan

In light of the failure to epimerize efficiently the aldehyde **84**, an alternative approach to the preparation of a compound with the desired configuration at C-1, was undertaken. Thus, it seemed likely that the presence of an axial substituent on C-11 would cause a 1,3-diaxial interaction with the axial formyl group on C-1, leading the latter to adopt the preferred equatorial orientation under epimerization conditions



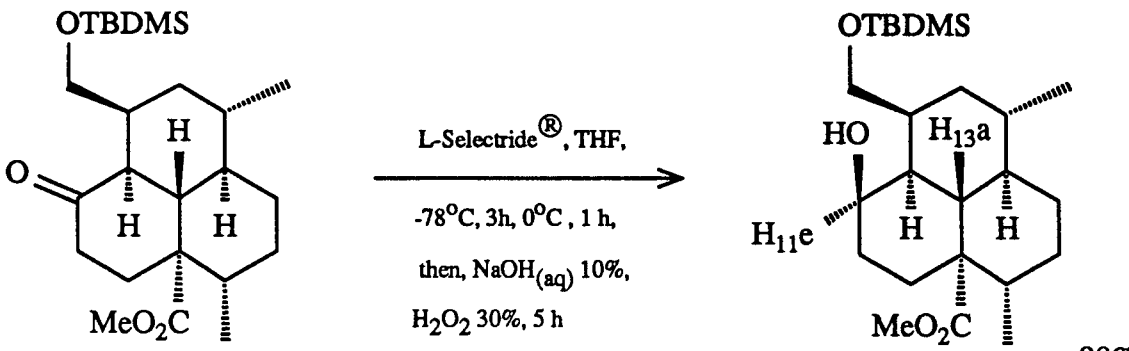
Scheme 9

(Scheme 9). Our plan consisted of performing a stereoselective reduction of **82**, followed by conversion of the resultant alcohol **88** into the methoxymethyl (MOM) ether **89**. A chemoselective cleavage of the silyl ether function in **89** and subsequent oxidation of the resultant primary alcohol **90** would give the aldehyde **91**. Finally, **91** would (presumably) be easily epimerized to the aldehyde **92** under basic conditions, thus establishing the correct stereochemistry at C-1 (Scheme 9).

IVg. Preparation of the compounds **88** and **89**

It is well known[61a-d] that the reduction of cyclohexanones with sterically demanding hydride reducing agents normally produces a predominance of the corresponding axial alcohol. In this regard, the tri-*sec*-butylborohydrides[61d] are especially effective and, therefore, were considered as the reagents of choice for the stereoselective reduction of the keto ester **82**.

Reduction of the keto ester **82** with lithium tri-*sec*-butylborohydride ("L-Selectride®")[61d] in THF at -78°C afforded, after workup and chromatography, the alcohol **88** in 98% yield (equation 29). The ^{1}H nmr spectrum of **88** exhibited a triplet

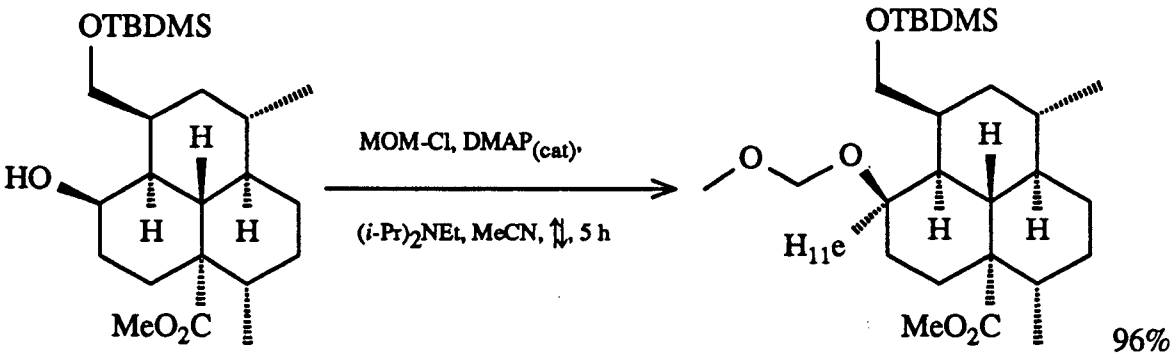


(29)

82 **88**

(J=2.5 Hz, D_2O exchanged) at δ 5.26 due to the alcohol function, a broad singlet ($w_{1/2}$=7.5 Hz) at 3.91 due to the equatorial proton $H_{11}e$, and a dd (J=11.5,11.5 Hz) at 1.66 due to $H_{13}a$. Therefore, as indicated by the $w_{1/2}$ value of 7.5 Hz for $H_{11}e$,[35] the reduction had taken place with the desired stereoselectivity, giving the axially oriented OH function in compound **88**.

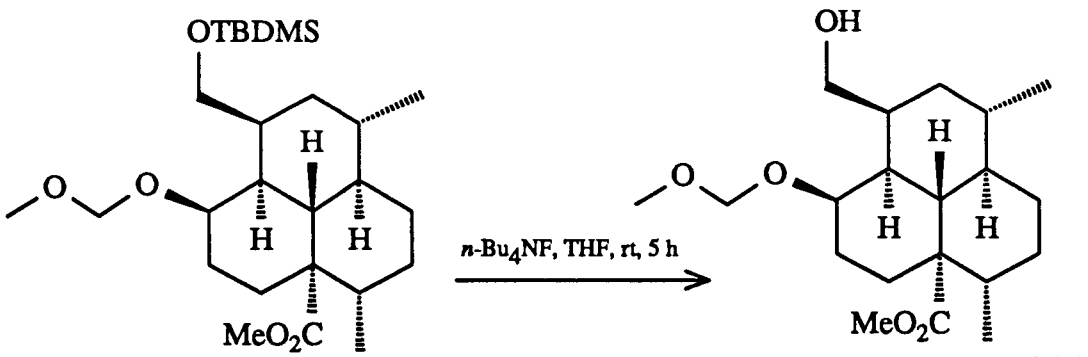
When the alcohol **88** was treated with chloromethyl methyl ether in the presence of N,N-diisopropylethylamine and a catalytic amount of DMAP,[62] the ester acetal **89** was obtained in 96% yield after workup and column chromatography (equation 30). The ^{1}H nmr spectrum of **89** exhibited singlets at δ 4.65 (2H) and 3.39 (3H), respectively, due to the five protons associated with the methoxymethyl group. Singlets at δ 3.72 (1H, $w_{1/2}$=7.5 Hz), 3.66 (3H), 0.90 (9H), 0.03 (3H), and 0.02 (3H) were assigned to $H_{11}e$, the carbomethoxy protons, and the tert-butyldimethylsilyl protons, respectively.



(30)

88 **89**

IVh. Preparation of the compounds **90, 91** and **92**

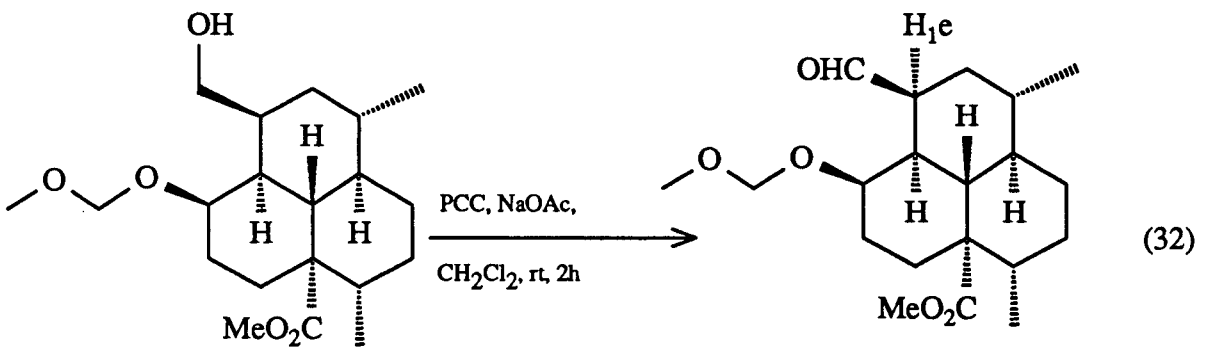


(31)

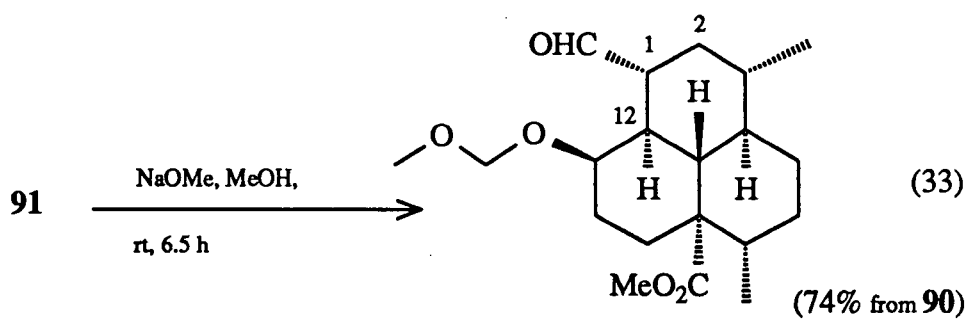
89 **90**

Cleavage of the tert-butyldimethylsilyl ether function in **89** was carried out by employing the conditions reported by Corey and Venkateswarlu[63], namely, with

tetra-*n*-butylammonium fluoride in THF at room temperature. After workup and column chromatography of the crude product on silica gel, the alcohol **90** was obtained in 96% yield (equation 31). The ir spectrum of **90** exhibited absorptions at 3417 and 1723 cm^{-1} due to the hydroxyl and methyl ester functions, respectively. The ^1H nmr spectrum of **90** showed a multiplet at δ 4.73-4.67 due to the CH_3O-$C\underline{H}_2$-O- protons. The one-proton multiplets at δ 3.86 (transformed to a dd, J=12,6 Hz when D_2O was added) and 3.59 (ddd, J=12,7,4 Hz; transformed to a dd, J=12,4 Hz when D_2O was added) were assigned to the diastereotopic $C\underline{H}_2OH$ protons. Moreover, the triplet (J=7 Hz) at δ 3.20 disappeared when D_2O was added and was thus assigned to the hydroxyl proton.



90 **91** (32)



91 (33)

(74% from **90**)

92

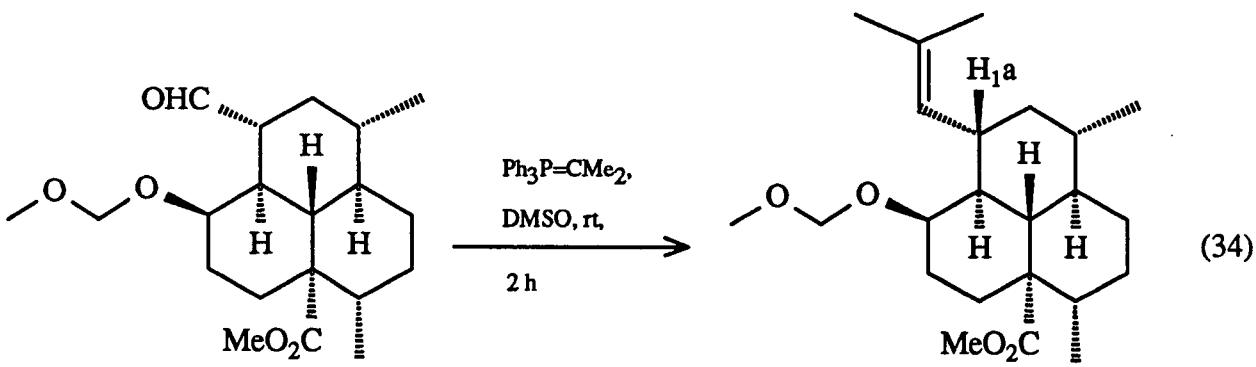
The alcohol **90** was oxidized with PCC in the presence of sodium acetate to give the crude aldehyde **91** (equation 32). The ^1H nmr spectrum of the crude product **91** exhibited a doublet at δ 10.00 (J=6 Hz) due to the formyl group proton and a one-proton multiplet at 2.39-2.32 due to H_1e. In a ^1H nmr decoupling experiment, irradiation of the

doublet at δ 10.00 simplified the signal at 2.39-2.32 to a multiplet with $w_{1/2}$=8 Hz. This experiment thus indicated that the H_1e proton is equatorial.[35]

The crude aldehyde (**91**) was subjected to epimerization with sodium methoxide in methanol at room temperature. Glc analysis of the reaction mixture showed that no starting material remained after 6.5 h. After workup and chromatography of the crude product, the aldehyde **92** was isolated in 74% yield (from **90**, see equations 32 and 33). The ir spectrum of **92** showed an absorption at 1724 cm^{-1} due to the aldehyde and ester functions. The ^1H nmr spectrum of **92** exhibited a doublet (J=3.5 Hz) at δ 9.58 due to the formyl group proton, a dddd (J=12,11.5,3.5,3.5 Hz) at 2.67 due to H_1a, and a dd (J=10,3.5 Hz) at 1.73 due to H_2e (this proton is not coupled to H_3a). In a decoupling experiment, irradiation of the signal at δ 9.58 transformed the multiplet at 2.67 (H_1a) into a ddd (J=12,11.5,3.5 Hz). The two large coupling constants associated with the signal due to H_1a indicated that this proton is axially oriented and that, therefore, the CHO function had the desired equatorial orientation. In a second decoupling experiment, irradiation of the signal at δ 2.67 (H_1a) caused, inter alia, collapse of the doublet at 9.58 (CHO) to a singlet and the dd at 1.73 (H_2e) to a doublet (J=10 Hz). The ^1H nmr data summarized above showed clearly that the desired epimerization reaction (at C-1) had taken place.

IVi. Preparation of the compounds **76** and **93**

Wittig olefination of the aldehyde **92** using conditions similar to those reported by Christenson and Willis[64] (isopropylidenetriphenylphosphorane in DMSO) gave, after workup and chromatography of the crude product on silica gel, the ester alkene **93** in fair



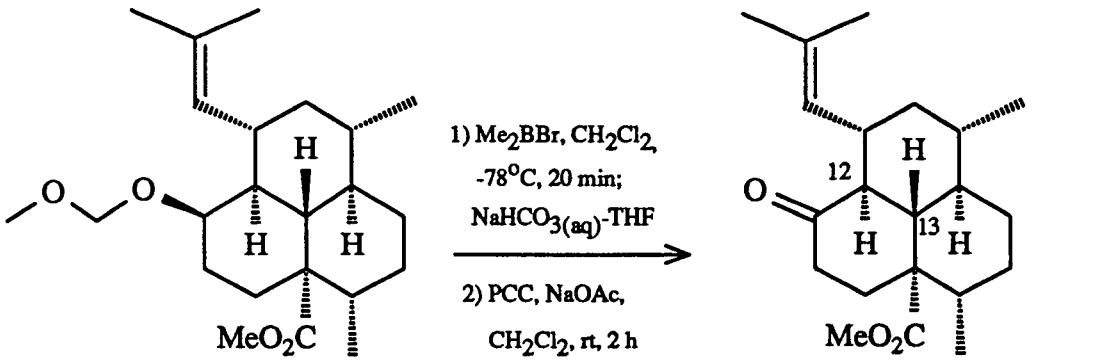
(34)

92 **93** ~(67-93%)

to good yields (equation 34). In spite of the inconsistent yields and the occasional presence of inseparable impurities in the product, the reaction conditions used were far superior when compared to other alternatives that were also tested.[65a,b] The ^{1}H nmr spectrum of **93** exhibited a broad doublet (J=10 Hz) at δ 4.89 due to the olefinic proton, a multiplet at 2.45-2.23 due to H_1a, and two (three-proton) doublets (J=1 Hz) at 1.66 and 1.59 due to the vinyl methyl groups. In a decoupling experiment, irradiation of the doublet at δ 4.89 (vinyl proton) simplified the multiplet at 2.45-2.23 (H_1a) and caused the collapse of the doublets at 1.66 and 1.59 (vinyl methyl groups) to the corresponding singlets.

The cleavage of MOM ethers usually requires strongly acidic conditions (for example HCl/MeOH,[66a] PhSH/BF_3.OEt_2[66b]) which may restrict their utilization in organic synthesis. However, Y. Guindon et al.[66c] have found that MOM, MEM ((2-methoxyethoxy)methyl), and MTM ((methylthio)methyl) ethers can be cleaved at -78°C by Me_2BBr (under milder conditions) to give, after aqueous workup, the parent alcohols in excellent yield.

Cleavage of the MOM-ether function in **93** with dimethylboron bromide in dichloromethane at low temperature (-78°C)[66c] was followed by immediate oxidation



(35)

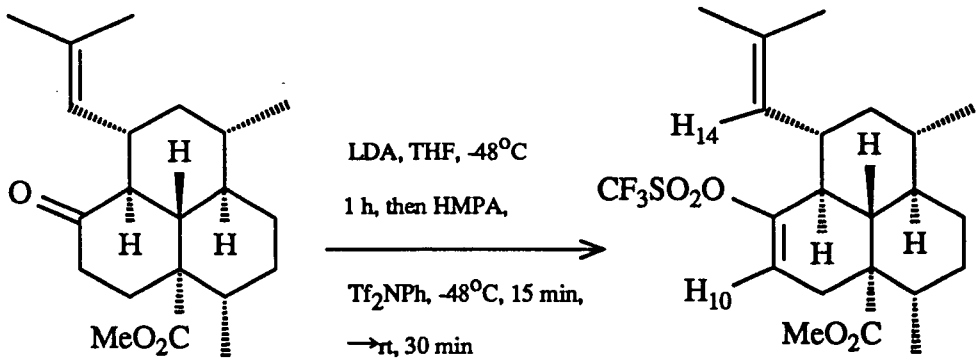
85%

93 **76**

(PCC-sodium acetate) of the resultant (unstable) crude alcohol (equation 35). Column chromatography of the crude product on silica gel and recrystallization (pentane-Et_2O) of the solid thus obtained afforded the keto ester **76** in good yield (85% from **93**). However, significant amounts of unidentified side products were produced if the acetal cleavage reaction was allowed to proceed for more than 20 min. The ir spectrum of the keto ester **76** showed two strong absorptions at 1724 and 1717 cm^{-1} due to the ester and ketone carbonyl groups, respectively. The ^1H nmr spectrum of **76** exhibited a doublet of multiplets (J=9 Hz) at δ 4.67 due to the vinylic proton, a one-proton dd (J=11.5,10 Hz) at 2.27 due to $H_{12}a$, two (three-proton) doublets at 1.73 (J=1.5 Hz) and 1.62 (J=1 Hz) due to the vinyl methyl groups, and a one-proton dd at 1.17 (J=12.5,11.5 Hz) due to $H_{13}a$.

IVj. Preparation of the compounds **75** and **94**

Two methods[56a,b] for the preparation of enol trifluoromethanesulfonates (enol triflates) were known before their synthesis via the trapping of regioselectively generated enolate anions with N-phenyltrifluoromethanesulfonimide (Tf_2NPh) was devised by



(36)

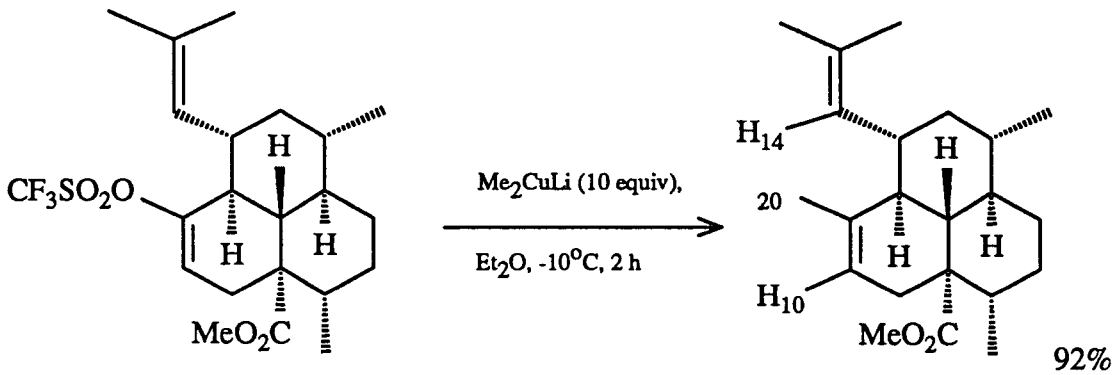
76 **94** (67%, based on recovered starting material)

McMurry.[56c] The most common was the reaction of trifluoromethanesulfonic anhydride (triflic anhydride) with ketones in the presence of a mild nonnucleophilic base.[56a] This method normally leads to the production of the thermodynamically more stable product (that with the more substituted double bond). The second method consisted of trapping enolate anions with triflic anhydride.[56b] However, the more reactive enolates (for example, those produced from monoketones) have the tendency to undergo C-sulfonation[56d] under these conditions. However, with McMurry's N-phenyltriflimide reagent it is possible to trap a variety of enolates generated in a number of ways to provide (in a more versatile way) the corresponding enol triflates.

Using a modification of the procedure published by McMurry,[56c] the keto ester **76** was deprotonated with LDA in THF and the solution of the resultant enolate anion was treated sequentially with HMPA and Tf_2NPh. After workup and column chromatography of the crude product on silica gel, the enol triflate **94** was obtained in 52% yield (67% based on recovered starting material, see equation 36). The ir spectrum of **94** showed strong absorptions at 1728 and 1207 cm^{-1} due to the ester and sulfonate

(symmetric stretching vibration of SO_2) groups, respectively. The ^1H nmr spectrum of **94** exhibited broad doublets at δ 5.73 (J=7 Hz) and 5.04 (J=8 Hz) due to H_{10} and H_{14}, respectively.

With the enol triflate **94** in hand, we proceeded to carry out a coupling reaction with lithium dimethylcuprate[67] (Gilman's cuprate) under the conditions reported by Ireland et al.[68] Thus, treatment of compound **94** with a freshly prepared solution of lithium dimethylcuprate in dry ether at -10°C, followed by workup and chromatography (silica gel) of the material thus obtained, provided the ester diene **75** in 92% yield (equation 37). The ^1H nmr spectrum of **75** exhibited a one-proton multiplet at δ



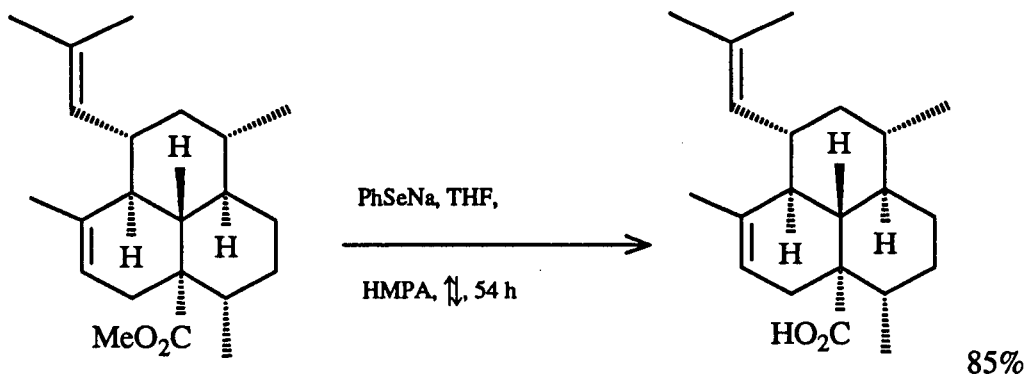
(37)

94 **75**

5.39-5.34 due to H_{10}, a one-proton doublet of multiplets (J=9 Hz) at 5.09 due to H_{14}, and three (three-proton) doublets at 1.63, 1.56, and 1.60 (all with J=1 Hz) due to the vinylic methyl groups. Thus, it was clear that the desired coupling process had taken place.

IVk. Preparation of the carboxylic acid **95**

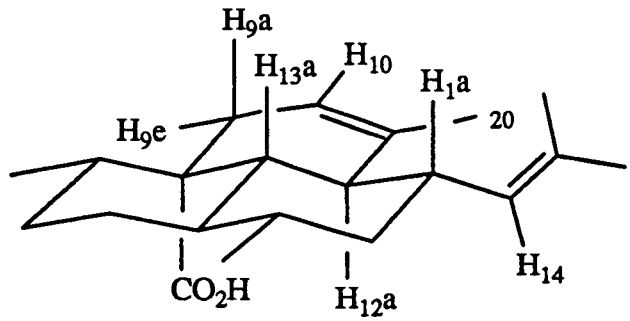
It was anticipated that the ester **75** would be relatively unreactive under normal saponification conditions due to steric hindrance towards acyl oxygen cleavage. Therefore, the benzeneselenide induced S_N2 cleavage reaction[69] was chosen in order to transform **75** into the desired carboxylic acid **95.** This was considered as an optimum



(38)

75 **95**

alternative since in sterically hindered methyl esters the methyl carbon is less hindered than the carbonyl carbon. In the event, conversion of the ester diene **75** into the acid **95** was efficiently carried out by refluxing a solution of **75** and the highly nucleophilic sodium benzeneselenide in THF-HMPA[69] for 54 h (equation 38). After workup, column chromatography and recrystallization (pentane-Et_2O) of the product, the carboxylic acid **95** was obtained in 85% yield. The ir spectrum of this material exhibited a broad absorption at 3280-2380 and a strong absorption at 1687 cm^{-1}, both due to the carboxyl function. The ^1H nmr spectrum of **95** exhibited the following characteristic signals: a multiplet at δ 5.45-5.36 due to H_{10}, a doublet of multiplets (J=9 Hz) at 5.10 due to H_{14}, a



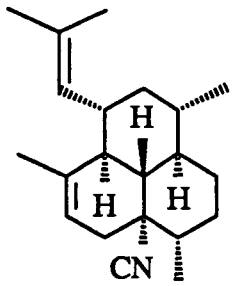
95a

doublet of doublets (J=17,6 Hz) at 2.80 due to H_9e, a multiplet at 2.21-2.10 due to H_1a, a broad doublet (J=17 Hz) at 1.71 due to H_9a, and two (three-proton) doublets (J=1 Hz each) at 1.64 and 1.56 due to the isobutenyl methyl groups. In ^1H nmr homonuclear decoupling experiments, irradiation of the signal at δ 5.45-5.36 (H_{10}) caused the collapse of the signal at 2.80 (H_9e) to a doublet (J=17 Hz) and sharpened the doublet at 1.71 (H_9a); irradiation of the signal at δ 5.10 (H_{14}) caused the collapse of the signal at 2.21-2.10 (H_1a) to a ddd (J=10.5,10.5,4 Hz) and changed the doublets at 1.64 and 1.56 (J=1 Hz each, isobutenyl methyl groups) to singlets.

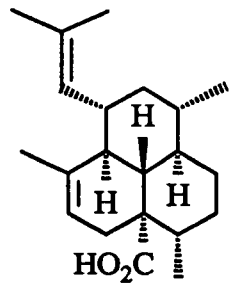
IVl. Model studies for the degradation of the carboxyl group of **95** to the isonitrile function of **23**. Preparation of the compounds **96, 99, 104,** and **105**

A model study was undertaken to optimize the conditions for the efficient conversion of the carboxylic acid **95** to the target compound **23**. The carboxylic acid **96** was chosen as a suitable model since its structure resembled that of the "lower part" of structure **95** and furthermore its precursor (compound **97**)[70a] was readily available.

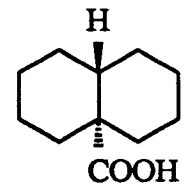
Previous work done in our laboratories[70b] using the model compound **98** for the



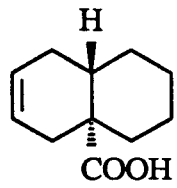
23



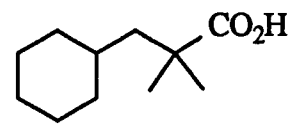
95



96



97

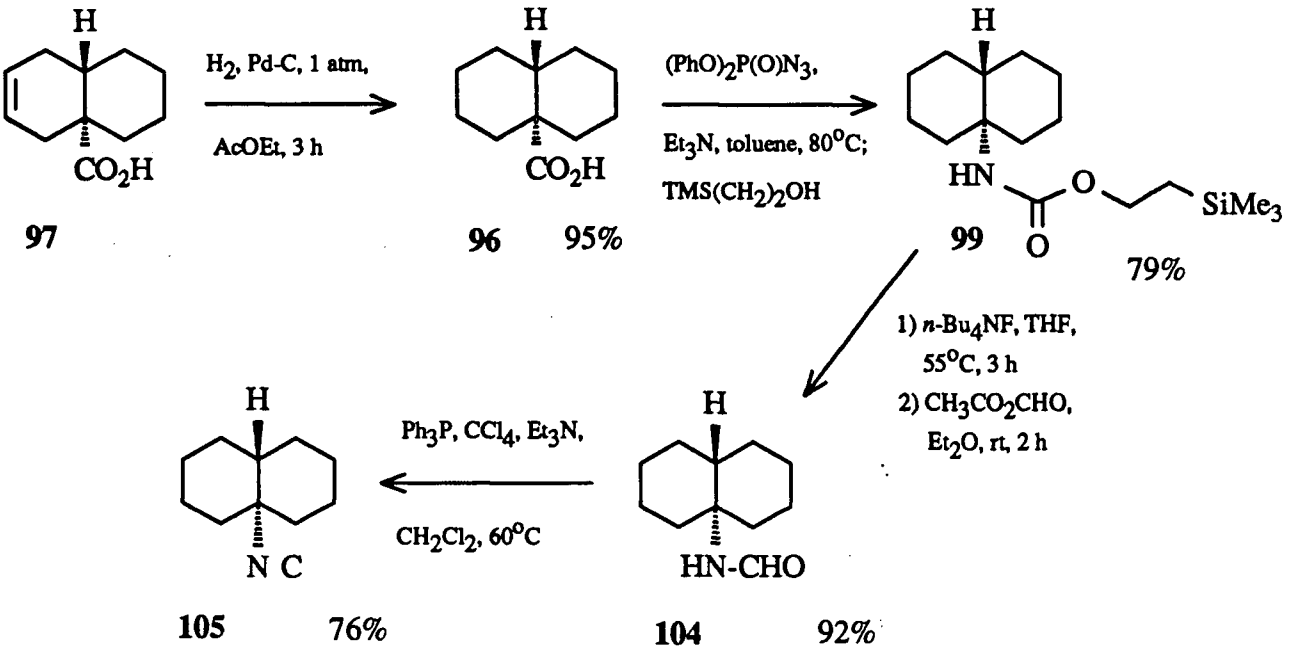


98

preparation of its corresponding isonitrile showed that the sequence of transformations: acid (**98**) → acid chloride → acyl azide → isocyanate, was not efficient. Therefore, an alternative route (as set out below) was implemented for the model compound **96**.

Catalytic hydrogenation[29d] of **97** (Pd-C, 10% Pd content) in ethyl acetate afforded the carboxylic acid **96** in 95% yield, after workup and recrystallization (petroleum ether-Et_2O) of the crude product (Scheme 10). The ir spectrum of **96** showed absorptions at 3400-2400, 1695 and 936 cm^{-1} due to the carboxyl function.

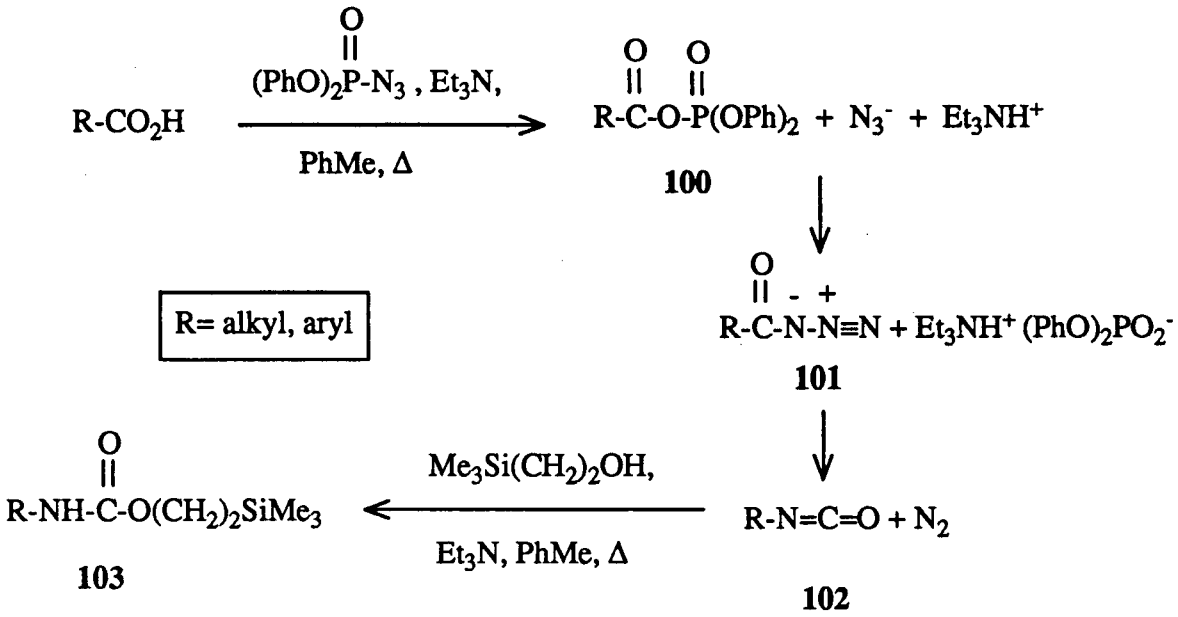
Treatment of **96** with diphenylphosphorazidate (DPPA) and triethylamine in toluene at 80°C for 2 h (formation of the isocyanate)[71] was followed by the addition of 2-(trimethylsilyl)ethanol.[72] After 1.5 h (80°C), additional amounts of 2-(trimethylsilyl)ethanol and triethylamine were added and the mixture was stirred at 80°C for 36 h. Workup and column chromatography of the crude product afforded the carbamate **99** in 79% yield (Scheme 10). The ir spectrum of **99** exhibited absorptions at 3456 due to the N-H stretching vibration, 1729 due to the carbonyl group ("amide I



Scheme 10

band"), and at 1504 cm^{-1} due to the N-H bending vibration ("amide II band"). The ^1H nmr spectrum of **99** displayed a broad singlet at δ 4.37 due to the carbamate (N-H) proton, a triplet (J=8 Hz) at 4.12 due to protons on the methylene group adjacent to the carbamate function (-$C\underline{H}_2$-O_2C-NH-), and a singlet at 0.04 due to the trimethylsilyl group.

The conversion of the acid **96** into the carbamate **99** described above involves a reaction protocol that is simpler and less laborious than the classical procedure. Presumably the first intermediate formed in the reaction is the mixed anhydride **100**, followed by the formation of the carboxylic acid azide **101**[71] (as illustrated in Scheme 11). Under the reaction conditions **101** undergoes a Curtius rearrangement to form the isocyanate **102**, which is finally allowed to react with 2-trimethylsilylethanol[72] to form the carbamate **103**.

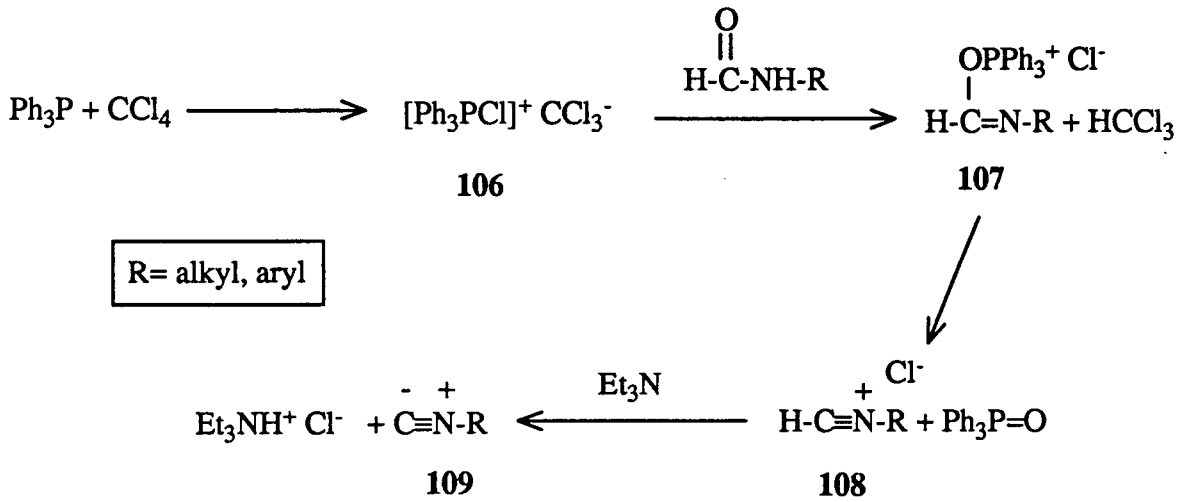


Scheme 11

The carbamate **99** (Scheme 10) was cleaved with tetra-*n*-butylammonium fluoride in warm THF.[72] The resultant amine (crude product) was treated immediately with acetic formic anhydride[73] in diethyl ether. After workup and recrystallization (petroleum ether-Et_2O) of the crude product, the formamide **104** was obtained in 92% yield. The ir spectrum of **104** showed absorptions at 3304 due to the N-H stretching vibration, 3060 due to the first overtone of the N-H in plane bending vibration (at 1529 cm^{-1}), and 1662 cm^{-1} due to the carbonyl stretching vibration. The ^1H nmr spectrum of **104** suggested the presence of a mixture (~1:1) of cisoid and transoid rotamers. The one-proton doublets at δ 8.21 (J=1.5 Hz) and 8.16 (J=13 Hz) were readily assigned to the formyl group proton of the cisoid and transoid rotamers, respectively.

Treatment of the formamide **104** with triphenylphosphine, triethylamine and carbon tetrachloride in dichloromethane[74] for 2 h at 60°C was followed by addition of an extra amount of carbon tetrachloride. The reaction mixture was stirred at 60°C for a

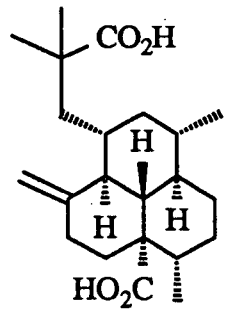
further 2 h. After workup, column chromatography on silica gel of the crude product, and recrystallization (pentane-Et_2O) of the solid thus obtained, the isonitrile **105** was obtained in 76% yeld (Scheme 10). The ir spectrum of **105** displayed an absorption at 2119 cm^{-1} due to the isonitrile function (in comparison, aliphatic nitriles absorb in the region 2260-2240 cm^{-1}). The ^1H nmr of **105** exhibited eight- and nine-proton multiplets at δ 1.90-1.59 and 1.52-1.10, respectively.



Scheme 12

The dehydration reaction involved in the conversion of the formamide **104** into the isonitrile **105** is believed to be a stepwise process, illustrated generally in Scheme 12.[74] Thus, the salt **106** formed initially from Ph_3P and CCl_4, reacts with the formamide (general formula R-NHCHO) to give the intermediate **107** and $CHCl_3$. Elimination of the elements of triphenylphosphine oxide from **107** followed by triethylamine-promoted removal of HCl from the resultant intermediate **108**, would give the isonitrile **109**. Deuterium labelling experiments showed that the proton on the chloroform that is produced comes exclusively from the N-H moiety.[74]

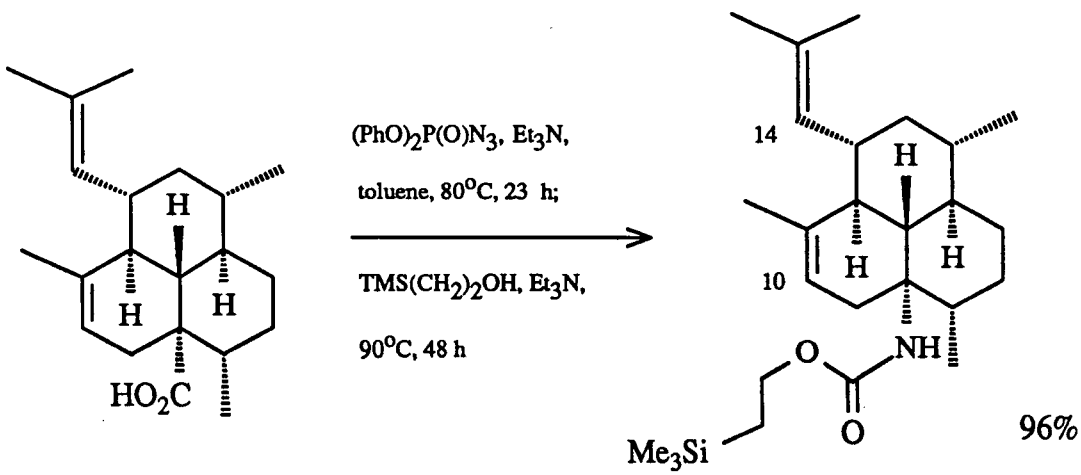
Noteworthily, in the work described above (Scheme 10), the carboxylic acid **96** was transformed into the isonitrile **105** using a five-step sequence of reactions with an overall yield of 52%. This model study served as an informative prelude to the



110

subsequent successful conversions of the dicarboxylic acid **110** and the monocarboxylic acid **95** into the amphilectane diterpenoids **15**[21] (see p.5) and **23** (vide infra), respectively.

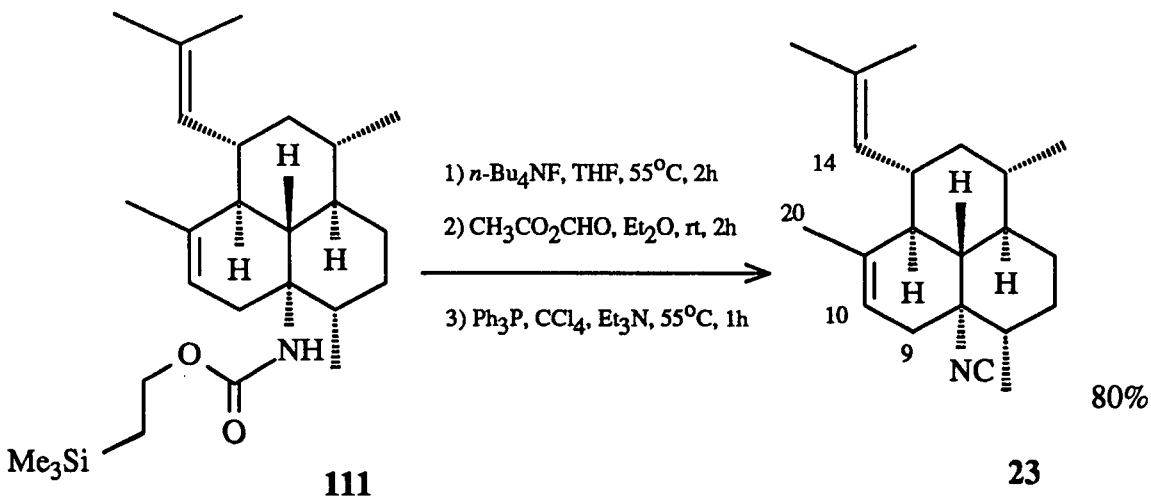
IVm. Synthesis of (±)-8-isocyano-10,14-amphilectadiene (23). Preparation of the carbamate **111**



(39)

95 **111**

Having completed successfully the model study for the degradation of a tertiary carboxyl function to the corresponding isonitrile group, we proceeded to attempt the corresponding sequence of reactions on the carboxylic acid **95**. Towards this end, a stirred solution of the acid **95** in dry toluene was treated sequentially with triethylamine and diphenylphosphorazidate.[71] The resulting solution was stirred at 80°C for 23 h and then 2-(trimethylsilyl)ethanol[72] and triethylamine were added. After the mixture had been stirred at 90°C for 24 h, additional amounts of 2-(trimethylsilyl)ethanol and triethylamine were added and the solution was stirred for a further 24 h at 90°C. Workup and column chromatography (silica gel) of the crude product thus obtained afforded the carbamate **111** in 96% yield (equation 39). The ir spectrum of **111** exhibited absorptions at 3446, 1736, and 1508 cm^{-1} due to the carbamate function. The ^1H nmr spectrum of **111** displayed a broad doublet (J=5 Hz) at δ 5.34 due to H_{10}, a dm (J=9 Hz) at 5.11 due to H_{14}, a broad singlet at 4.27 due to the N-H proton, a two-proton multiplet at 4.13-4.02 due to the -CH_2-O(CO)- protons, and a nine-proton singlet at 0.03 due to the trimethylsilyl protons.



(40)

The next step in the sequence involved treatment of **111** with tetra-*n*-butylammonium fluoride in warm THF[72] for 2 h. Workup was followed by

treatment of the crude oil thus obtained with a solution of acetic formic anhydride in dry ether.[73] The reaction mixture was stirred at room temperature for 2 h. After workup, the crude oil was dissolved in dry dichloromethane. Triphenylphosphine, carbon tetrachloride, and triethylamine[74] were added to the solution and the mixture was stirred at 55°C for 1 h (see equation 40). Workup and column chromatography of the mixture on silica gel afforded the isonitrile (±)-**23** in 80% yield (from the carbamate **111**) as a white solid, mp 79-81°C (recrystallization from pentane-Et_2O). The ir spectrum of synthetic (±)-8-isocyano-10,14-amphilectadiene ((±)-**23**) exhibited an absorption at 2126 cm^{-1} due to the isonitrile function. The ^1H nmr (400 MHz) spectrum of (±)-**23** exhibited a multiplet ($w_{1/2}$=11 Hz) at δ 5.26 due to H_{10}, a doublet of multiplets (J=9 Hz) at 5.15 due to H_{14}, a broad dd at 2.45 (J=17,4.5 Hz) due to H_9e, and a three-proton doublet at 1.69 (J=1 Hz) due to the C_{20} methyl protons. The isobutenyl group gave rise to a pair of three-proton doublets at δ 1.66 (J=1 Hz) and 1.57 (J=1 Hz). The remaining methyl group signals appeared as doublets at δ 1.02 (J=6.5 Hz) and 0.88 (J=6 Hz).

The spectral data derived from our synthetic (±)-**23** was in accord with the data reported by Faulkner and coworkers[26] (^1H, ^{13}C nmr, and high resolution EIMS) for natural (-)-8-isocyano-10,14-amphilectadiene (**23**). For comparison purposes the ^1H and ^{13}C nmr spectral data reported for the natural material and those derived from our synthetic material are compiled in Tables 1 and 2, respectively. Furthermore, a direct comparison of the ^1H nmr (300 MHz) spectrum of natural (-)-**23**[75] and the ^1H nmr (400 MHz) spectrum of synthetic (±)-**23** was possible (see Figures 3 and 4).

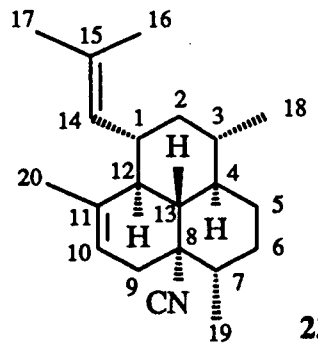
Table 1: ^{1}H nmr spectral data for natural (-)-8-isocyano-10,14-amphilectadiene ((-)-**23**) and synthetic (±)-8-isocyano-10,14-amphilectadiene ((±)-**23**)

Reported data:

^{1}H nmr ($CDCl_3$, 360 MHz) δ 5.26 (m, 1H, $w_{1/2}$=11 Hz, $\underline{H}_{10}$), 5.15 (br d, 1H, J=9 Hz, $\underline{H}_{14}$), 2.45 (br dd, 1H, J=17,4.4 Hz, $\underline{H}_9$), 2.24 (m, 1H, J=12,12,7,4 Hz, $\underline{H}_1$a), 2.04 (m, 1H, $\underline{H}_{12}$a), 2.0 (m, 2H), 1.69 (d, 3H, J=0.9 Hz, C_{20} methyl protons), 1.66 (d, 3H, J=1.0 Hz), 1.57 (d, 3H, J=1.1 Hz), 1.02 (d, 3H, J=6 Hz), 0.88 (d, 3H, J=6.3 Hz).

Our data:

^{1}H nmr ($CDCl_3$, 400 MHz) δ 5.26 (m, 1H, $w_{1/2}$=11 Hz, $\underline{H}_{10}$), 5.15 (dm, 1H, J=9 Hz, $\underline{H}_{14}$), 2.45 (br dd, 1H, J=17, 4.5 Hz, $\underline{H}_9$e), 2.31-2.19 (m, 1H, $\underline{H}_1$a), 2.12-1.92 (m, 3H), 1.69 (d, 3H, J=1 Hz, C_{20} methyl protons), 1.66 (d, 3H, J=1 Hz, isopropylidene methyl protons), 1.57 (d, 3H, J=1 Hz, isopropylidene methyl protons), 1.02 (d, 3H, J=6.5 Hz, methyl protons), 0.88 (d, 3H, J=6 Hz, methyl protons).



23

Table 2: ^{13}C nmr spectral data for natural (-)-8-isocyano-10,14-amphilectadiene ((-)-**23**) and synthetic (±)-8-isocyano-10,14-amphilectadiene ((±)-**23**)

==========

Reported data:

^{13}C nmr ($CDCl_3$, 50.3 MHz) δ 15.4 (q), 17.6 (q), 19.6 (q), 25.1 (q), 25.7 (q), 29.2 (t), 29.8 (t), 37.2 (d), 37.9 (t), 40.6 (d), 41.4 (d), 42.1 (d), 43.5 (t), 44.8 (d), 49.6 (d), 63.3 (br s), 118.8 (d), 126.6 (s), 133.4 (d), 137.6 (s), 154.5 (br s).

Our data:

^{13}C nmr (75.3 MHz, $CDCl_3$, proton decoupled) δ 15.4, 17.5, 19.5, 25.1, 25.7, 29.1, 28.8, 37.2, 37.9, 40.6, 41.4, 42.1, 43.5, 44.8, 49.5, 63.2 (t, $J_{C-^{14}N}$=4.5 Hz), 118.8, 126.7, 133.4, 137.6, 154.4 (t, $J_{C-^{14}N}$=4.5 Hz).

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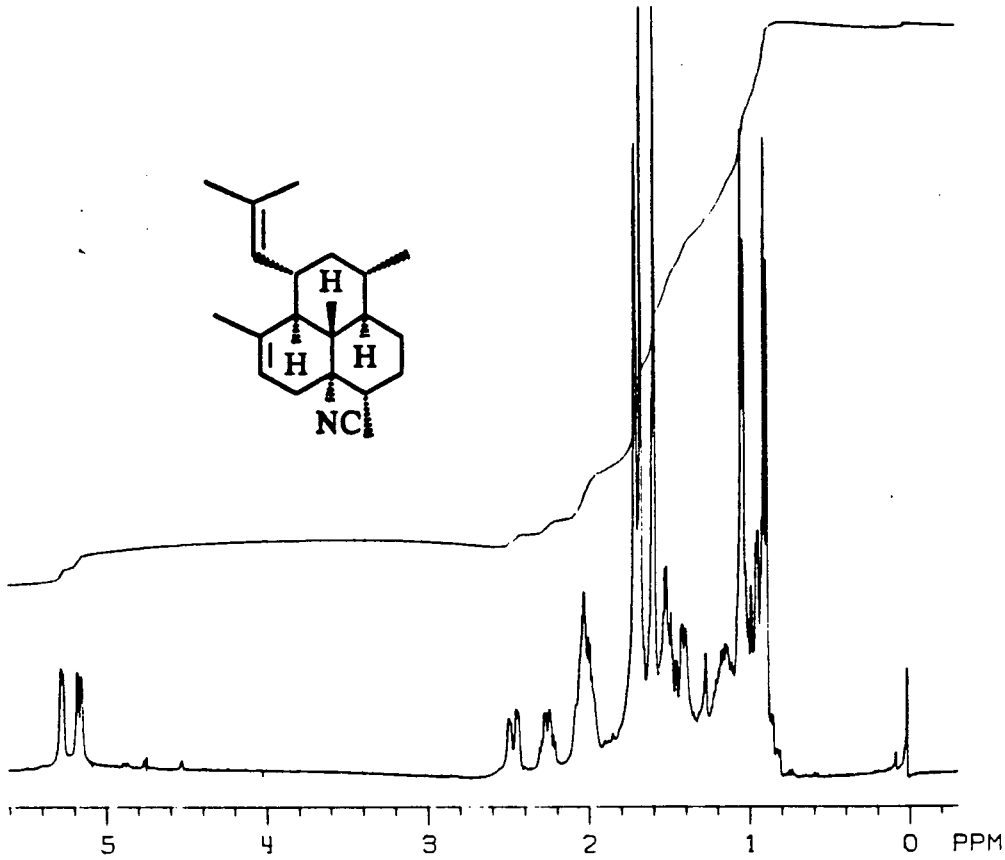


Figure 3: The ^1H nmr ($CDCl_3$, 300 MHz) spectrum of natural 8-isocyano-10,14-amphilectadiene

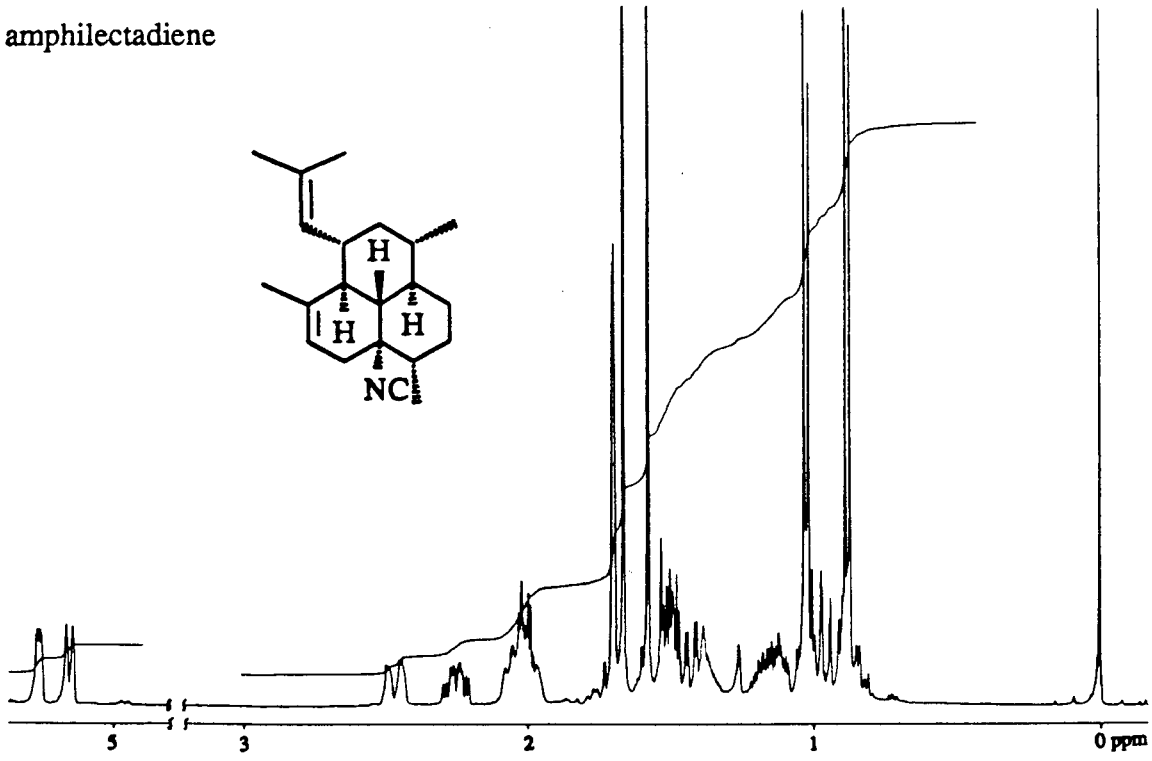
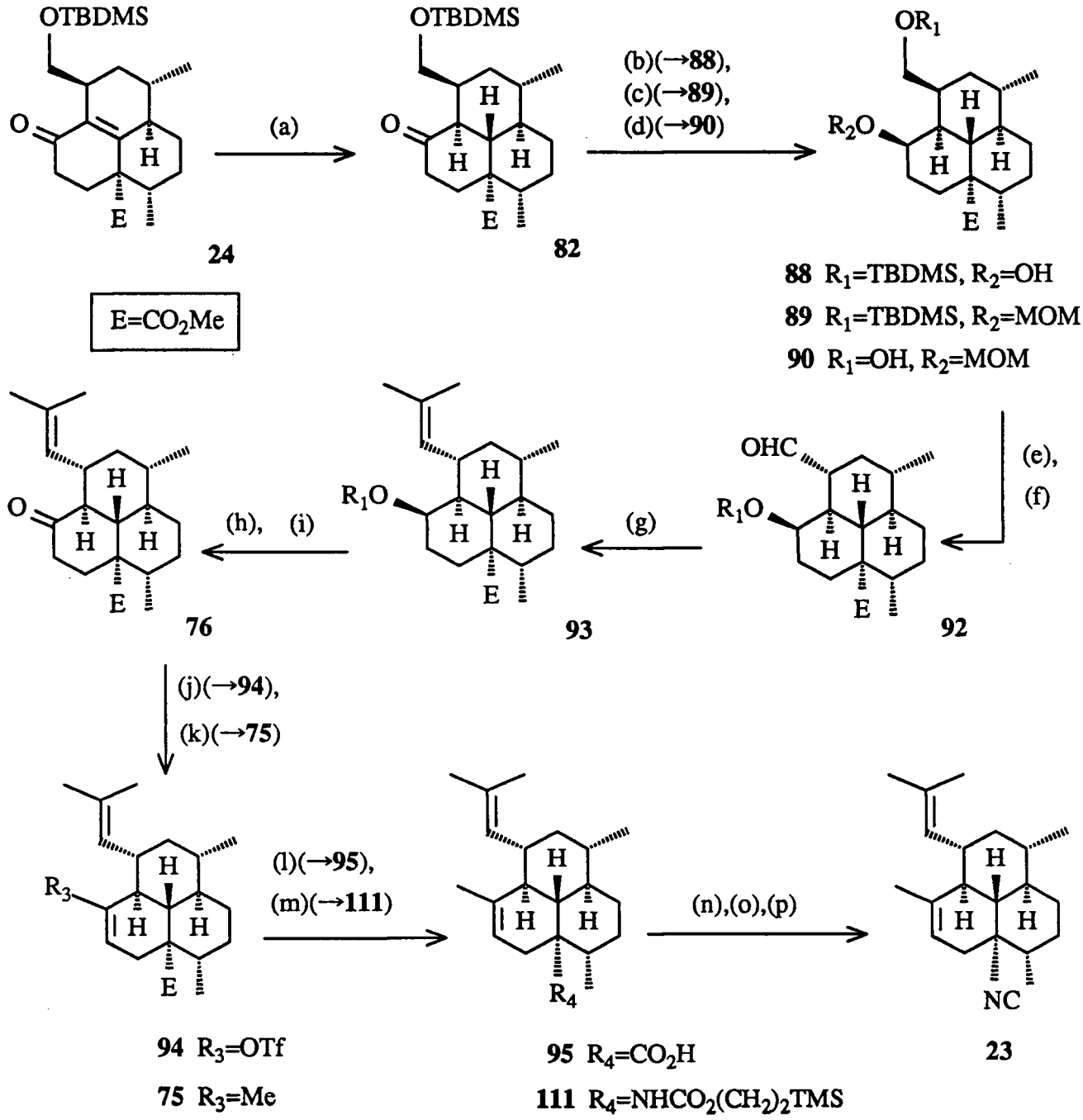


Figure 4: The ^1H nmr ($CDCl_3$, 400 MHz) spectrum of synthetic (±)-8-isocyano-10,14-amphilectadiene



Scheme 13

Reagents and conditions: (a) Na, NH_3, *t*-BuOH, ⇅, 40 min; isoprene, $NH_4Cl_{(aq)}$,(83%);

(b) L-Selectride®, THF, -78°C, 3h; 0°C, 1h; $NaOH_{(aq)}$10%, $H_2O_{2(aq)}$30%, 5h, (98%);

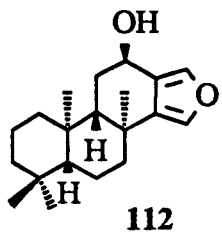
(c) MOM-Cl, DMAP, (i-Pr)$_2$NEt, MeCN, ⇅, 5h, (96%); (d) n-Bu$_4$NF, THF, rt, 5h, (96%); (e) PCC, NaOAc, CH_2Cl_2, rt, 2h; (f) NaOMe, MeOH, rt, 6.5h (74% from **30**); (g) $Ph_3P{=}CMe_2$, DMSO, rt, 2h, ~(67-93%); (h) Me_2BBr, CH_2Cl_2, -78°C, 20 min; $NaHCO_{3(aq)}$-THF; (i) PCC, NaOAc, CH_2Cl_2, rt, 2h, (85% from **33**); (j) LDA, THF, -48°C, 1h; HMPA, Tf_2NPh, -48°C, 15 min; rt, 30 min, (67%); (k) Me_2CuLi(10 equiv), Et_2O, -10°C, 2h, (92%); (l) PhSeNa, THF, HMPA, ⇅, 54h, (85%); (m) $(PhO)_2P(O)N_3$, Et_3N, toluene, 80°C, 23h; TMS$(CH_2)_2$OH, Et_3N, 90°C, 48h, (96%); (n) n-Bu$_4$NF, THF, 55°C, 2h; (o) CH_3CO_2CHO, Et_2O, rt, 2h; (p) Ph_3P, CCl_4, Et_3N, CH_2Cl_2, 55°C, 1h (80% from **37**).

IVn. Conclusion

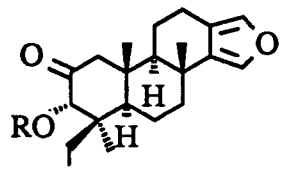
The work summarized in sections IVf-IVm constitutes the successful (15 step) total synthesis of (±)-8-isocyano-10,14-amphilectadiene ((±)-**23**) from the intermediate **24** in ~18% overall yield (Scheme 13). To our knowledge, this is the first total synthesis of this biologically and structurally interesting natural product.

V. Development of a general synthetic approach to the spongiadiols, a group of natural products belonging to the "spongian" family of diterpenoids.

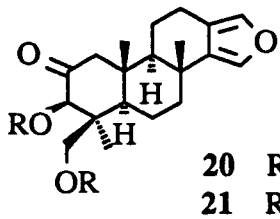
Va. Previous syntheses of furanoditerpenoids possessing the "spongian" carbon skeleton



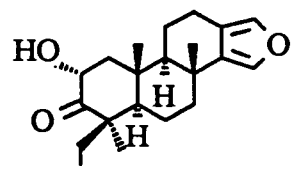
112



18 R= H
19 R= Ac

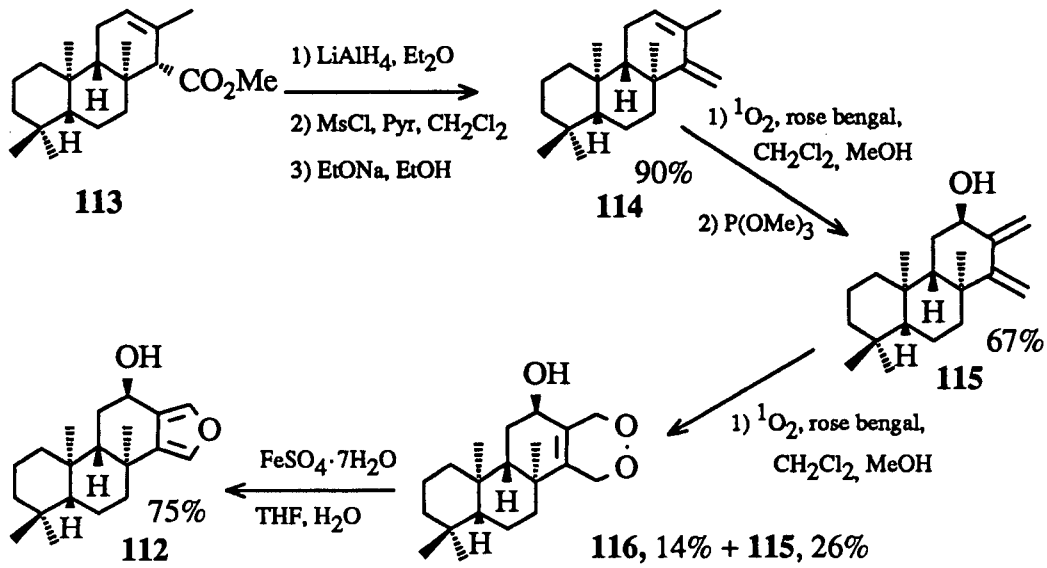


20 R= H
21 R= Ac



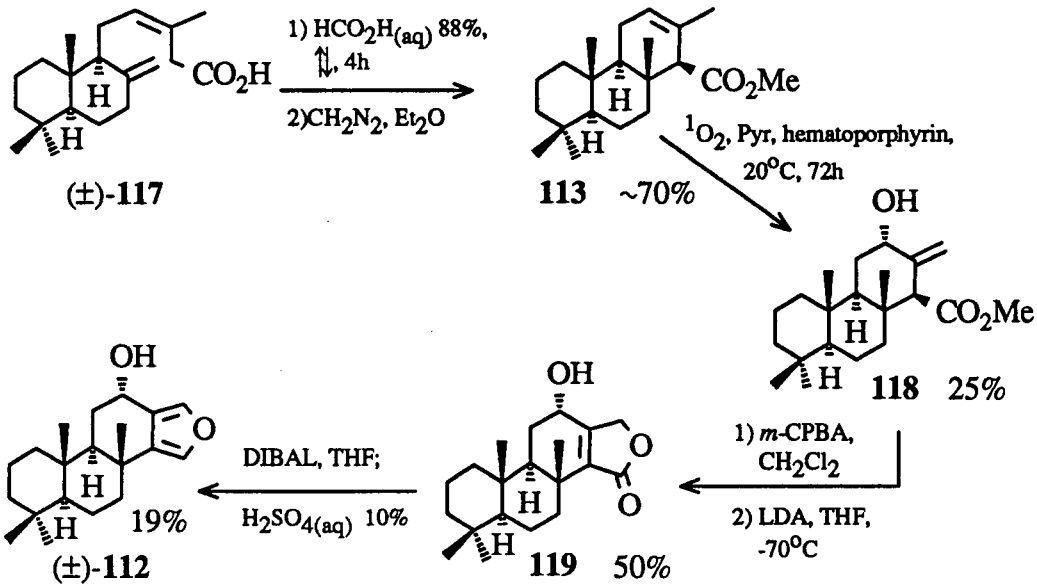
22

In 1981 E.A. Ruveda and coworkers[13b] synthesized *ent*-12α-hydroxyspongia-13(16),14-diene (**112**), an intermediate which bears the basic carbon skeleton of spongiadiol (**18**) and the related furanoid diterpenes **19-22** (see p.7). The authors prepared compound **112** using the readily available methyl isocopalate (**113**)[76] as starting material (Scheme 14). Thus, the diene **114**, obtained by conversion of the methoxycarbonyl moiety in **113** into an exocyclic double bond, was subjected to photooxygenation[77] to yield the diene **115**. Diels-Alder addition of singlet oxygen to compound **115** gave the cyclic peroxide **116** in low yield. Treatment of **116** with ferrous sulfate in aqueous tetrahydrofuran gave the target compound **112** in 75% yield (see Scheme 14).



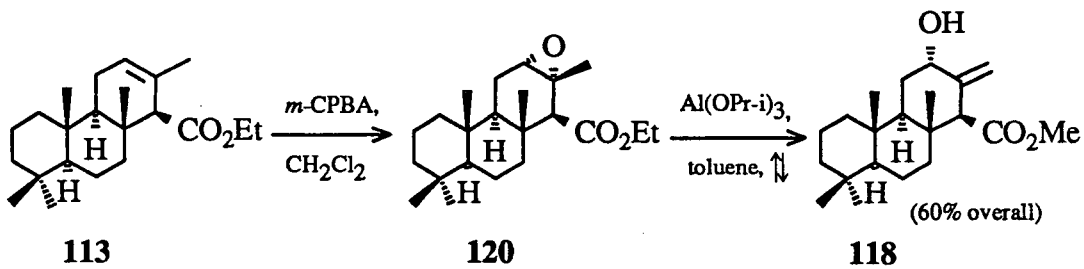
Scheme 14

In a related approach to the synthesis of (±)-12α-hydroxyspongia-13(16),14-diene ((±)-**112**), Nakano and Hernandez[13c] used (±)-labda-8(20),13-dien-15-oic acid (**117**) as a starting material (Scheme 15). Thus, cyclization of **117** was followed by methylation of the carboxyl group to give (±)-**113**. Photooxygenation of (±)-**113** gave a low yield of the allylic alcohol **118** together with other side products. Subsequent epoxidation of **118** and treatment of the resulting product with lithium diisopropylamide led to the butenolide **119**. Subsequent reduction of **119** with DIBAL gave the furanoditerpenoid (±)-**112** in 19% yield along with some starting material (**119**). Since it is relevant for the construction of ring *D* of the spongiadiols, it should be pointed out that Minato and Nagasaki[78] have obtained higher yields for the DIBAL reduction-dehydration of 3,4-disubstituted and 3-substituted butenolides to the corresponding furans.



Scheme 15

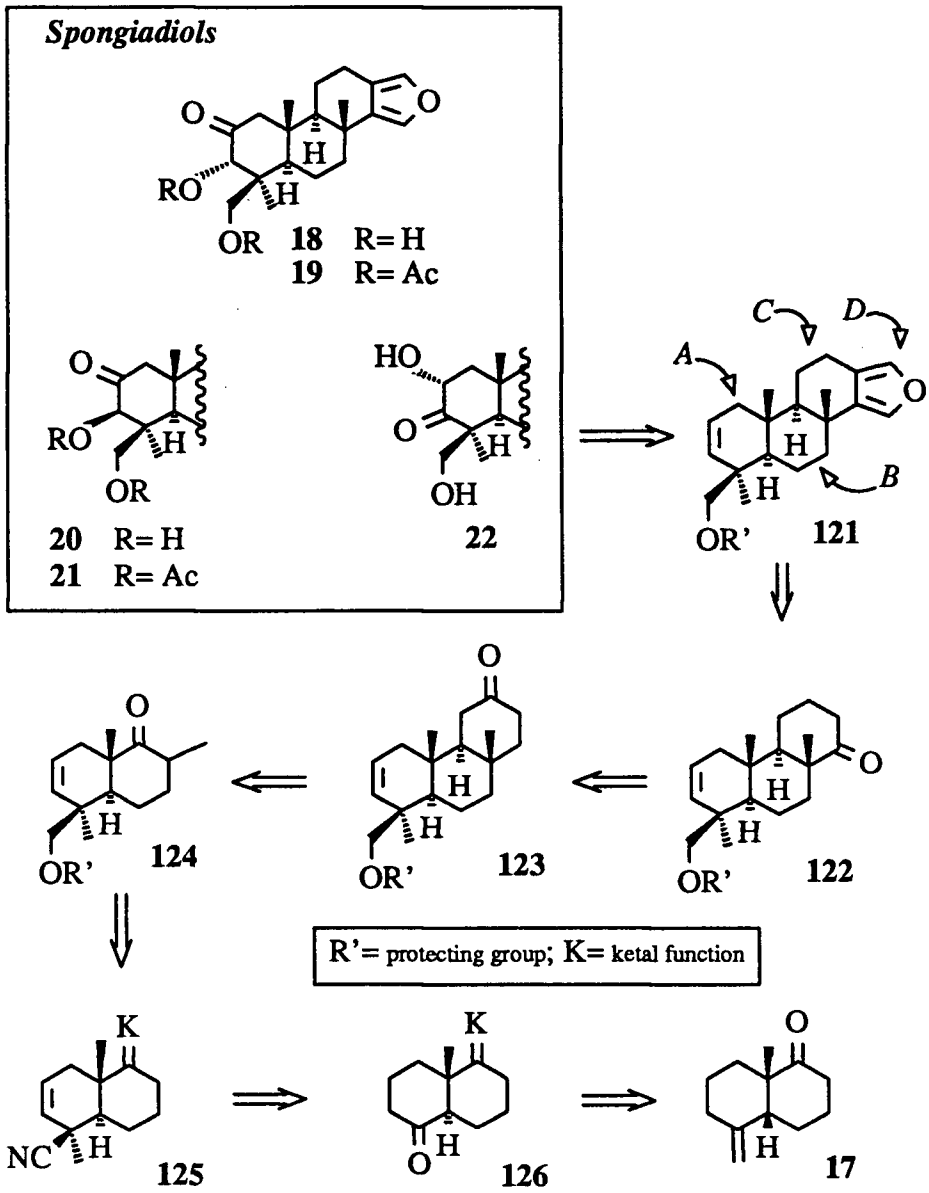
In relation to the transformation of **113** into **118** (see Scheme 15), it should be mentioned that E.A. Ruveda and coworkers[13d] have also synthesized compound **118** from **113** in 60% overall yield using a different approach (see Scheme 16).



Scheme 16

Vb. Retrosynthetic analysis

Our retrosynthetic analysis (Scheme 17) was based on the proposal that the spongiadiols **18-22** could be prepared from the common intermediate **121** via suitable

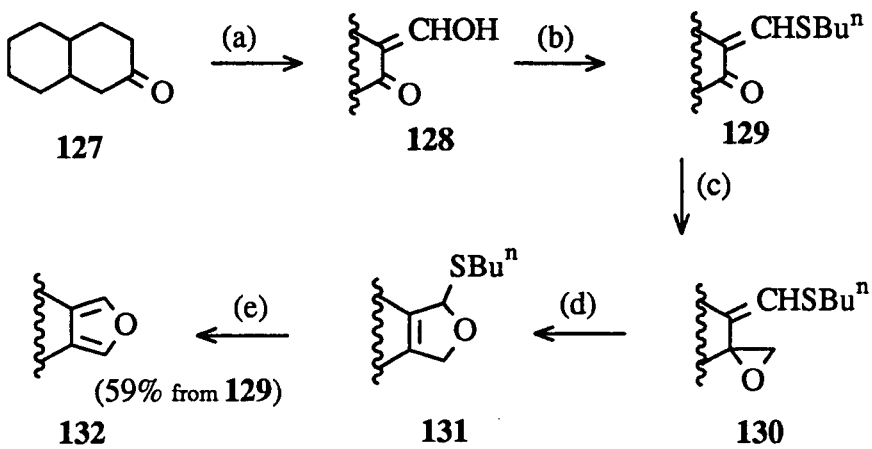


Scheme 17

functionalization of the double bond in ring *A*. It was envisaged that the furan ring in compound **121** could be introduced by appropriate use of the ketone function in **122**. A number of methods (apart from the ones mentioned in section Va of this thesis) have been reported[79] for the construction of 3,4-fused furans from ketones. Of particular interest is the method published by Price and Schore[80a] (see example in Scheme 18). This sequence has been used successfully in a natural product synthesis,[80b] and seems to

be one of the best methods available (in terms of the number of steps and yield) for the preparation of 2,3-fused furans from six-membered cyclic ketones .

In the next retrosynthetic step (Scheme 17), a 1,3-carbonyl transposition[81] of the ketone **122** would lead to the intermediate **123**. The ketone **123** could in turn be prepared from the bicyclic ketone **124** via a stereoselective Robinson annulation-Birch reduction sequence. With respect to the Michael addition step in the Robinson annulation, it seemed reasonable to predict that attack of electrophiles would occur from the sterically less hindered α face of the enol or enolate anion of **124**.

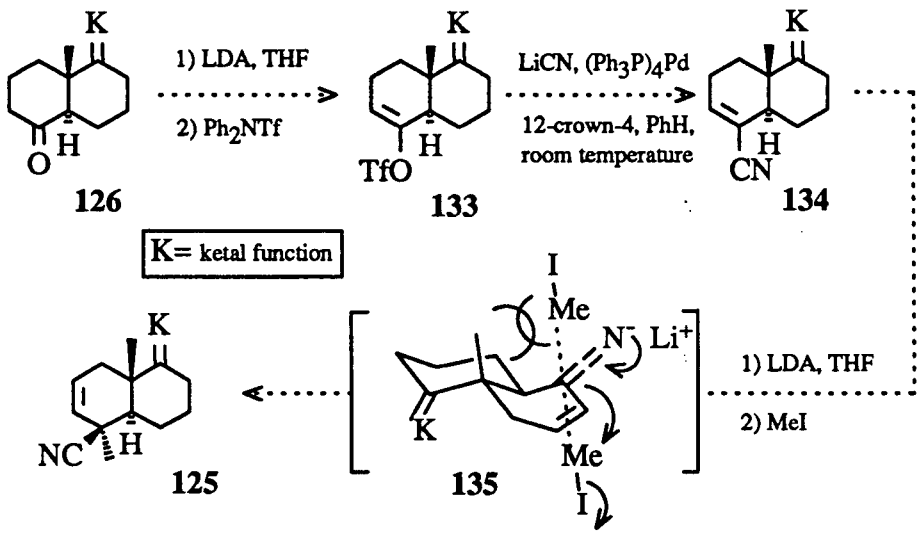


Scheme 18. Reagents and conditions: (a) NaOMe, EtOCHO, THF; (b) *n*-C_4H_9SH, *p*-TsOH, C_6H_6, ⇅; (c) CH_2=SMe_2, DME; (d) 24h, room temperature; (e) $HgSO_4$, Et_2O.

Following the intramolecular aldol condensation-dehydration of the Michael adduct obtained from **124**, a dissolving metal reduction would afford the more stable *B-C* trans-fused ring system **123** (see sections IIIb and IIIg of this Discussion). It was envisaged that compound **124** (Scheme 17) could be prepared from the ketal nitrile **125**. This could be achieved, in principle, by a diisobutylaluminum hydride (DIBAL) reduction of **125**, a sodium borohydride reduction of the resulting aldehyde, and then a

deprotection-protection sequence to give **124**.

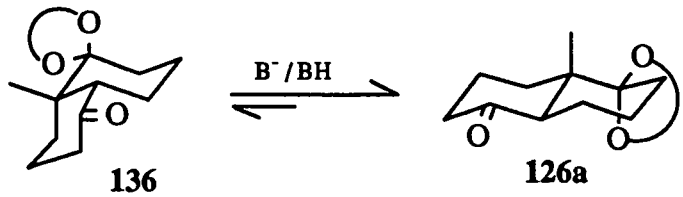
It was expected that the ketone **126** could be readily transformed into the nitrile **125** via methodology recently developed in our laboratories. This transformation would involve the palladium (0)-catalyzed coupling of the enol triflate **133** (prepared from **126**) with lithium cyanide[82] to give the α,β-unsaturated nitrile **134** (see Scheme 19). The next step would consist of the site-selective methylation of the conjugated enolate of **134**, namely **135**, to give the nitrile **125**. It was expected that this alkylation would proceed via the stereoselective attack of the electrophile from the sterically less hindered α face of the conjugated anion **135** (Scheme 19). Attack of the incoming electrophile from the β face of the enolate would be hindered by the angular methyl group as shown in formula **135**.



Scheme 19

Finally, the trans-fused keto ketal **126** was to be prepared from the readily available cis-fused ketone **17**[23] (see section IIIc of this thesis) via a sequence of reactions which would involve conversion of the carbonyl group into a ketal function, oxidative cleavage of the exocyclic double bond, and base-catalyzed epimerization of the ketone **136** thus obtained. It was expected, on the basis of a qualitative conformational analysis

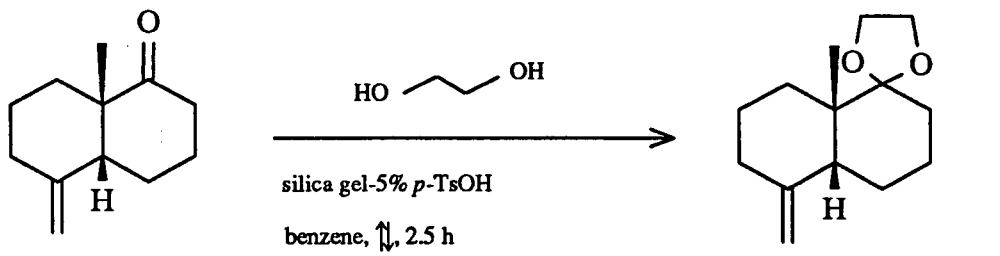
and an examination of molecular models, that the equilibrium in this base-catalyzed epimerization (see equation 41) would lie in favor of the trans-fused keto ketal **126** (represented by formula **126a**).



136 **126a** (41)

1,3-syn-axial interaction	1 × CH_3-H 2 × O-H 3 × CH_2-H	3 × CH_3-H 3 × O-H
1,3-CH_3-C_{sp^2}-syn-axial interaction	1 × CH_3-C_{sp^2}	1 × CH_3-C_{sp^2}
gauche interaction	2 × CH_3-O 1 × CH_2-O	1 × CH_3-O 1 × CH_2-O

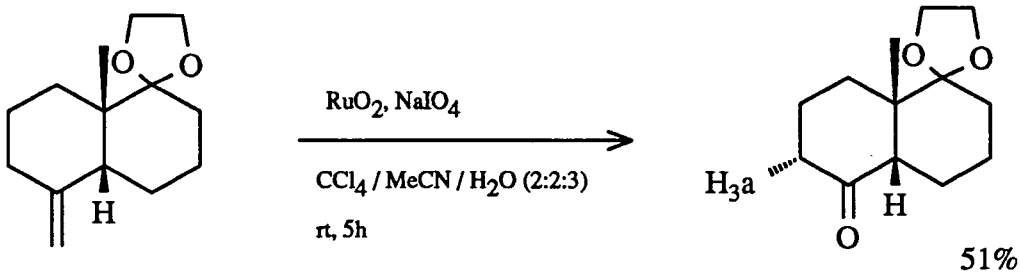
Vc. Initial attempt to establish a synthetic sequence. Preparation of the ketals **137-139**



17 **137** 84% (42)

In order to gain access to the ketal alkene **137**, a stirred mixture of the ketone **17**,[23] ethylene glycol, a small amount of silica gel containing 5% *p*-toluenesulfonic acid (*p*-TsOH),[83] and benzene was refluxed under a Dean-Stark water trap for 2.5 h. Workup

and column chromatography of the material thus obtained afforded the ketal alkene **137** in 84% yield (equation 42). The ir spectrum of **137** did not exhibit a carbonyl stretching absorption; however, it did show absorptions at 3067 and 1650 cm^{-1} due to the exocyclic double bond. The ^1H nmr spectrum of compound **137** displayed a two-proton multiplet at δ 4.66-4.60 due to the exocyclic methylene protons, a four-proton multiplet at 4.03-3.87 due to the ketal protons, and a singlet at 0.88 due to the angular methyl group protons.

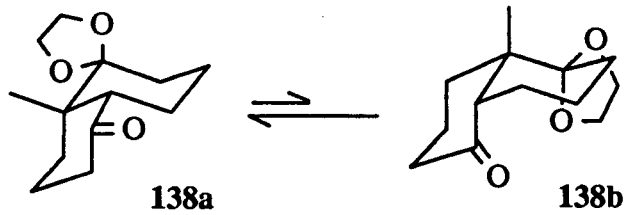


(43)

51%

137 **138**

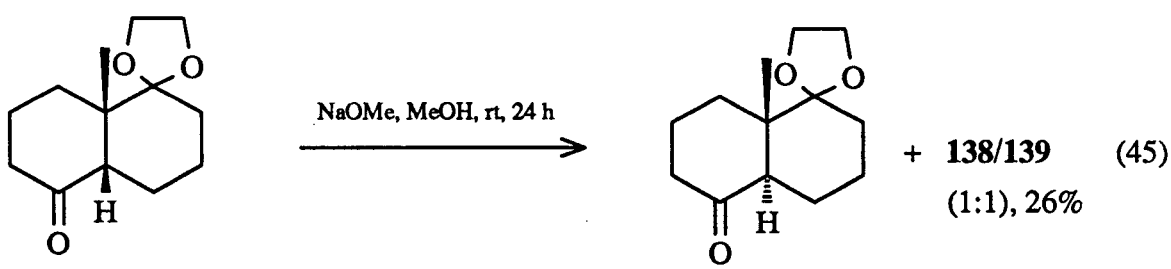
Following the method described by Sharpless and coworkers[84], the ketal alkene **137** was subjected to an oxidative cleavage of the exocyclic double bond using RuO_2 (7 mol %)-$NaIO_4$ in a mixed solvent system containing carbon tetrachloride, acetonitrile, and water. After the mixture had been stirred vigorously at room temperature for 2h, glc analysis of the organic phase showed a substantial amount of remaining starting material. Therefore, additional amounts of the solvent mixture and ruthenium (IV) oxide were added and vigorous stirring was continued for 3 h. Column chromatography (silica gel) of the material obtained after workup, afforded the keto ketal **138** in 51% yield (equation 43). The ir spectrum of **138** showed an absorption at 1712 cm^{-1} due to the newly formed carbonyl group. The ^1H nmr spectrum of this compound exhibited a four-proton multiplet at δ 4.02-3.87 due to the ketal protons and a ddd at 2.49 (J=13,12,7 Hz), most likely due to H_3a. The available spectral data did not allow an unambiguous assignment



138a **138b** (44)

for the conformation of **138**, however, it seemed reasonable to assume (on the basis of a qualitative conformational analysis) that the preferred conformation for **138** would be represented by formula **138a** (see equation 44).

In order to prepare the desired trans-fused bicyclic ketone **139**, the keto ketal **138** was subjected to epimerization with sodium methoxide in methanol at room temperature for 24 h. After workup, gas-liquid chromatographic analysis of the crude mixture showed the presence of the starting material (**138**) and the desired product (**139**) in a ratio of ~1:4.8, respectively. This mixture of ketones proved to be difficult to separate by column chromatography; however, it was possible to isolate **139** in pure form in 66% yield after chromatography and recrystallization (pentane-Et_2O) of the material thus obtained. The remaining material (26%) consisted of a 1:1 mixture of **138** and **139** (equation 45).



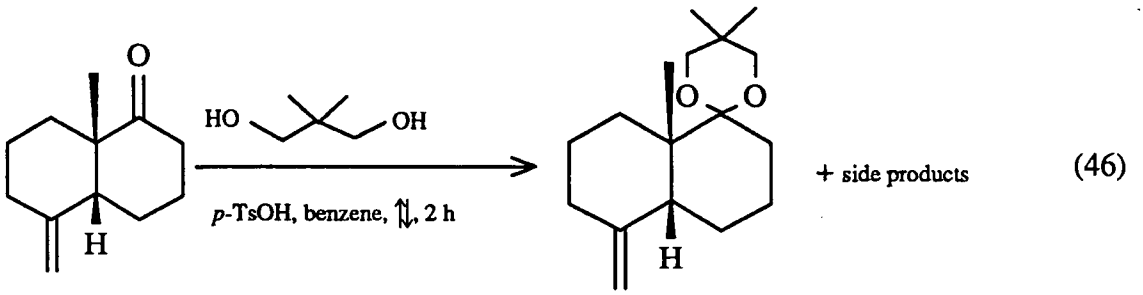
(45)

138 **139** 66%

The difficulties encountered with the purification of **139** and the low product yield obtained in the oxidative cleavage of the exocyclic olefin in **137** led us to try a

different approach. Thus, it was hoped that the use of the 2,2-dimethyl-1,3-propanediol ketal of **17**, and related intermediates, would allow their facile purification since it has been our observation that such ketals are often easily crystallized. Furthermore, we expected to have better yields in the transformation of the exocyclic double bond to the corresponding ketone function by means of an ozonolysis reaction.[85] The results of these modifications are described in the following Section.

Vd. Preparation of the ketals **140-142**

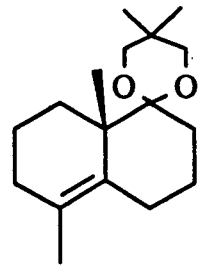


(46)

17 **140** 68%

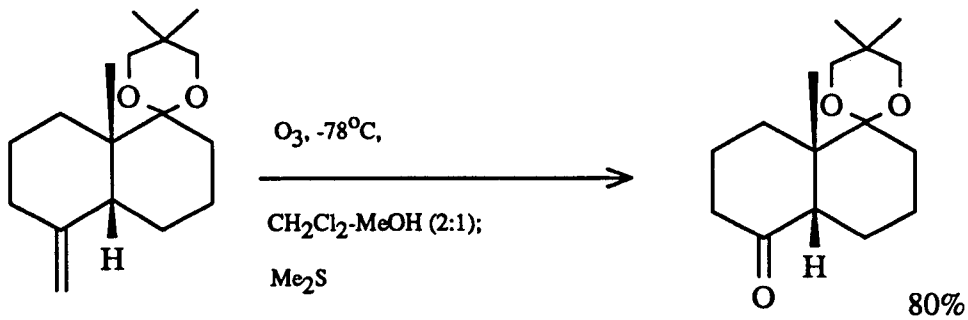
In order to protect the ketone function of compound **17**, a solution of **17**, 2,2-dimethyl-1,3-propanediol, and *p*-TsOH in dry benzene was refluxed for 2 h under a Dean-Stark water trap. Workup, column chromatography of the crude product on silica gel, and recrystallization (pentane) of the material thus obtained afforded the ketal alkene **140** in 68% yield (equation 46). The ir spectrum of **140** exhibited absorptions at 1650 and 1106 cm^{-1} due to the exocyclic double bond and the ketal function, respectively. The ^1H nmr spectrum of **140** showed a two-proton multiplet at δ 4.69-4.59 due to the exocyclic methylene protons. The methylene protons of the ketal function gave rise to two (one-proton) doublets (J=12 Hz) at δ 3.70 and 3.64 and two (one-proton) doublet of doublets (J=12,3 Hz) at 3.32 and 3.27. The expected singlets for the protons due to the three methyl groups appeared at δ 1.19, 1.08, and 0.71.

Apart from the major product **140**, an inseparable mixture (4.6:1, glc analysis) of two other products was also isolated after column chromatography. On the basis of



140a

spectral data, it was concluded that the major component of the mixture was the ketal alkene **140a**. The structure of the minor compound is still unknown to us. The ir spectrum of the mixture did not exhibit absorptions due to the C-H stretching vibration for the exocyclic methylene group. However, the presence of the ketal function was indicated by a strong absorption at 1109 cm^{-1}. The ^1H nmr spectrum of the mixture showed signals due to the ketal methylene protons at δ 3.72 (d, J=11 Hz), 3.57 (d, J=11 Hz), 3.36 (dd, J=11,3 Hz), and 3.29 (dd, J=11,3 Hz) and a broad singlet due to the vinyl methyl group at δ 1.62. No signals at lower field than δ 3.72 were observed and it was therefore clear that the compounds did not possess olefinic protons.

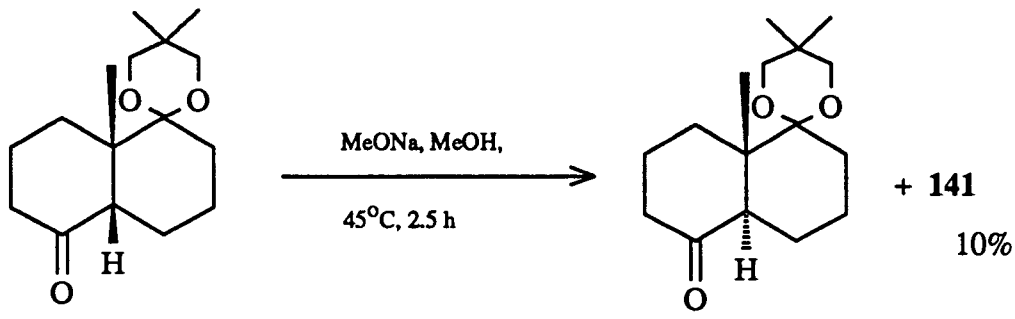


(47)

140 **141**

With the ketal alkene **140** in hand we proceeded to carry out the oxidative cleavage of the exocyclic double bond. Thus, ozonolysis[85] of **140**

(dichloromethane-methanol solution, -78°C), followed by reduction of the intermediate with dimethyl sulfide (equation 47), gave, after workup, column chromatography of the crude product, and recrystallization (pentane-Et_2O), the keto ketal **141** in 80% yield. The ir spectrum of this product exhibited a carbonyl stretching absorption band at 1710 cm^{-1}. The ^1H nmr spectrum of **141** showed a two-proton broad doublet (J=11 Hz) at δ 3.64 and a two-proton multiplet at 3.35-3.24 due to the ketal methylene protons. The three singlets at δ 1.16, 1.11, and 0.90 were assigned to the methyl group protons.



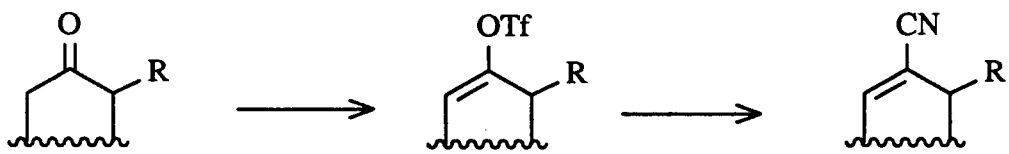
(48)

141 **142** 89%

The keto ketal **141** was subjected to epimerization by treatment with sodium methoxide in methanol at 45°C for 2.5 h. Workup and column chromatography of the material thus obtained afforded the keto ketal **142** in 89% yield. Some starting material (10%) was also recovered (see equation 48). It should be noted that the mixture of ketones **142** and **141** was easy to separate by column chromatography, as opposed to the case of the mixture of ketones **138** and **139** referred to (Section Vc of this Discussion). Furthermore, the ratio of trans- to cis-fused product was improved from ~4.8:1 (for the keto ketals **139** and **138**) to ~9:1 (for the keto ketals **142** and **141**). The ir spectrum of compound **142** showed an absorption due to the carbonyl group at 1713 cm^{-1}. The ^1H nmr of this material exhibited three (three-proton) singlets at δ 1.20, 0.85, and 0.73 due to the tertiary methyl groups.

Ve. Preparation of the enol triflate **143** and its Pd(0)-catalyzed coupling with lithium cyanide. Preparation of the α,β-unsaturated nitrile **144**

In 1989, Piers and Fleming[82] reported a novel reaction in which enol trifluoromethanesulphonates (enol triflates) underwent efficient coupling with lithium cyanide in the presence of catalytic amounts of 12-crown-4 and tetrakis(triphenylphosphine)palladium(0). This reaction, which is analogous to the nickel(0)- or palladium(0)-catalyzed coupling reactions of alkenyl halides with potassium cyanide,[86a-c] allows the site-selective conversion of unsymmetrically substituted ketones into α,β-unsaturated nitriles (scheme 20). This coupling process has



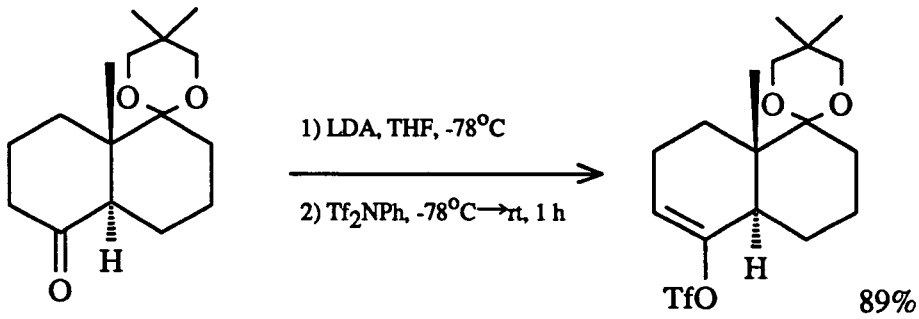
145 **146** **147**

Scheme 20

been used successfully in the total synthesis of the trans-clerodane diterpenoid (±)-stephalic acid.[87]

The method mentioned above seemed to be perfectly suited for the eventual construction of the hydroxymethyl moiety attached to ring *A* of the spongiadiols (see the retrosynthetic analysis in section Vb of this Discussion). Thus, selective deprotonation of the keto ketal **142** with LDA at -78°C and reaction of the resultant enolate anion with N-phenyltrifluoromethanesulfonimide (Tf_2NPh)[56c] gave, after workup and column chromatography, the enol triflate **143** in 89% yield (equation 49). This material, even

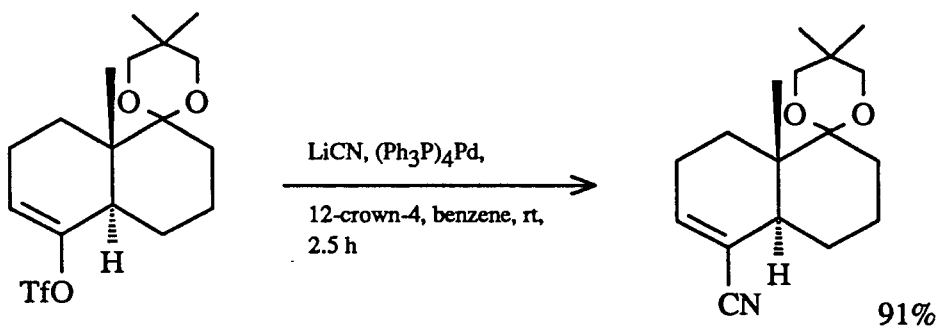
after recrystallization from pentane-Et_2O, was occasionally contaminated with traces of Tf_2NPh. However, this impurity did not affect the outcome of the subsequent coupling



(49)

142 **143**

reactions. The ir spectrum of compound **143** showed an absorption band at 1211 cm^{-1} due to the sulfonate function (symmetric stretching vibration of the SO_2 group). The ^1H nmr spectrum of this material exhibited a one-proton multiplet at δ 5.68-5.62 due to the vinyl proton and three singlets at 1.14, 0.93, and 0.71 due to the methyl group protons.



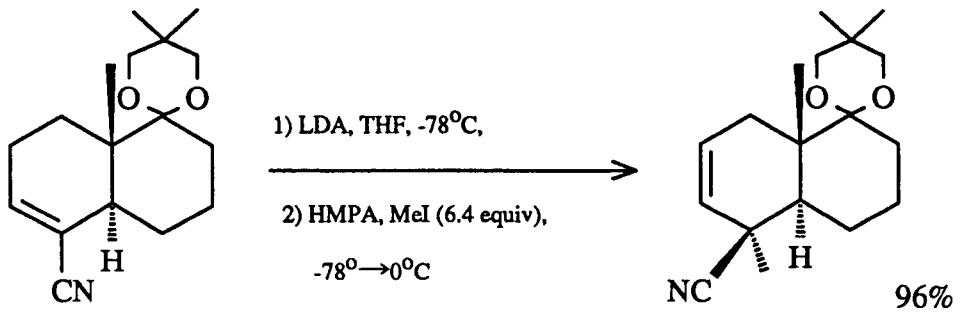
(50)

143 **144**

Clean and efficient conversion of **143** into the α,β-unsaturated nitrile **144** was accomplished by treating the enol triflate **143** with LiCN, $(Ph_3P)_4Pd$, and 12-crown-4 in benzene at room temperature (equation 50). Column chromatography and recrystallization (pentane-Et_2O) of the crude reaction product afforded the

α,β-unsaturated nitrile **144** in 91% yield. The ir spectrum of the nitrile **144** showed an absorption at 2209 cm^{-1} due to the nitrile function. The ^1H nmr spectrum of **144** displayed a one-proton multiplet at δ 6.60-6.53 due to the vinyl proton, and exhibited the usual signals due to the ketal function and the three tertiary methyl groups.

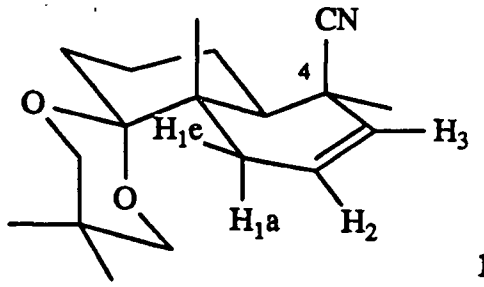
Vf. Preparation of the nitrile **148**



(51)

144 **148**

The next step in the sequence was the stereoselective deconjugative alkylation of the α,β-unsaturated nitrile **144**. Towards this end, deprotonation (LDA, THF, -78°C) of **144** was followed by addition of dry HMPA and an excess of methyl iodide (equation 51). Workup and column chromatography on silica gel of the product thus obtained, afforded exclusively the β,γ-unsaturated nitrile **148** as a white crystalline solid (recrystallized from hexane-Et_2O) in 96% yield. The ir spectrum of the nitrile **148** displayed an absorption at 2229 cm^{-1} due to the nitrile function. The ^1H nmr spectrum of **148** (Figure 5) showed two (one-proton) multiplets at δ 5.92-5.85 and 5.49-5.42 due to the vinylic protons H_2 and H_3, respectively, a broad doublet (J=18 Hz) at 2.73 due to H_1a, and a doublet of doublets (J=18,6 Hz) at 2.00 due to H_1e. In ^1H nmr decoupling experiments, irradiation of the signal at δ 5.49-5.42 (H_3) simplified the multiplet at



148a

5.92-5.85 (H_2) and sharpened the doublet at 2.73 (H_1a); irradiation of the signal at δ 5.92-5.85 (H_2) simplified the multiplet at 5.49-5.42 (H_3) and caused the collapse of the doublet of doublets at 2.00 (H_1e) to a doublet (J=18 Hz) (see formula **148a**). The stereochemical outcome of this highly stereoselective reaction was not rigorously established. However, based on the argument given in the retrosynthetic analysis discussion (section Vb and Scheme 19), we were confident that the relative configuration of the newly formed center (C-4) was as shown in formula **148a**.

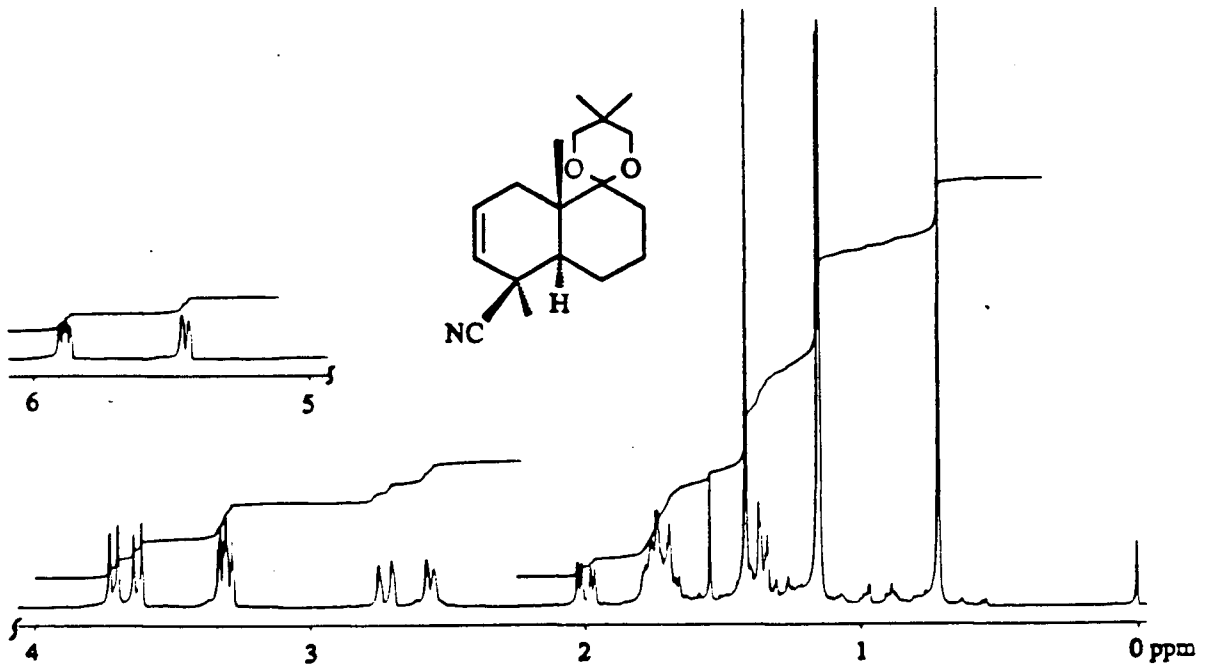
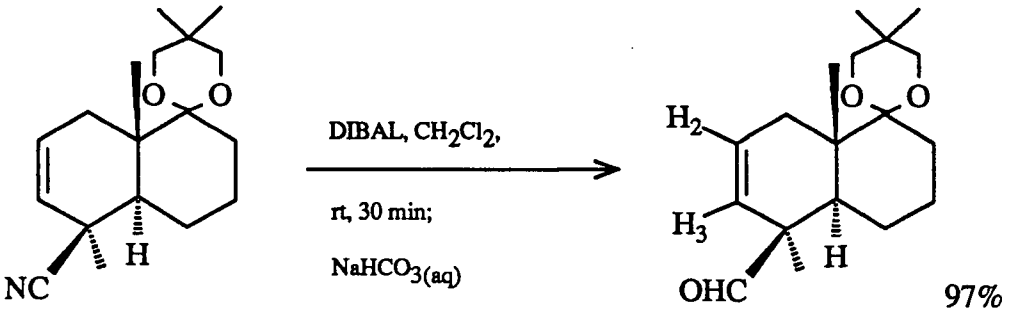


Figure 5. The ^1H nmr spectrum ($CDCl_3$, 400 MHz) of compound **148**.

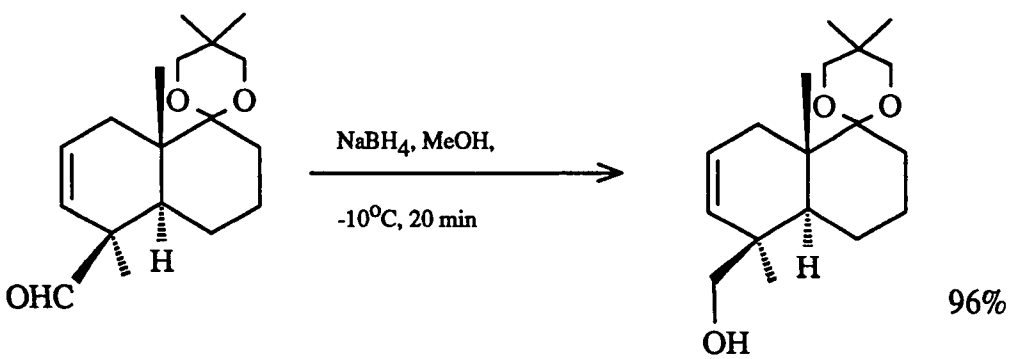
Vg. Reduction of the nitrile **148**. Preparation of compounds **149** and **150**



(52)

148 **149**

Reduction of the nitrile **148** was efficiently accomplished using diisobutylaluminum hydride (DIBAL)[88] (equation 52). Column chromatography on silica gel of the material obtained after workup gave the aldehyde **149** in 97% yield. The ir spectrum of this material showed a strong absorption at 1718 cm^{-1} due to the aldehyde carbonyl group. The ^1H nmr spectrum of **149** exhibited a one-proton singlet at δ 9.76 due to the formyl proton, a one-proton multiplet at 5.34 due to H_3, and a doublet of doublets (J=10,2 Hz) at 5.34 due to H_2.

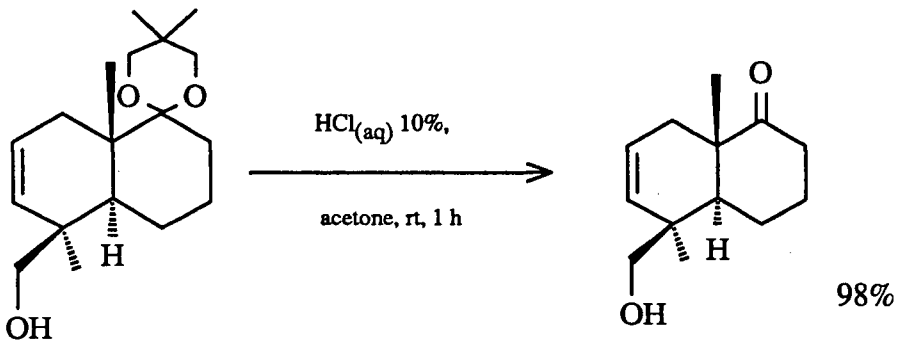


(53)

149 **150**

Reduction of the aldehyde **149** with sodium borohydride in dry methanol at -10°C proceeded cleanly (equation 53). Workup and solvent removal (vacuum pump) from the material thus obtained gave the alcohol **150** in 96% yield as a colorless oil that was homogeneous by tlc and glc analyses. The ir spectrum of this material showed an absorption at 3350 cm^{-1} due to the OH function. The ^1H nmr spectrum of **150** confirmed the presence of the hydroxymethyl moiety by exhibiting two (one-proton) doublets (J=11 Hz) at δ 3.62 and 3.49, and a broad singlet (D_2O exchanged) at 1.54.

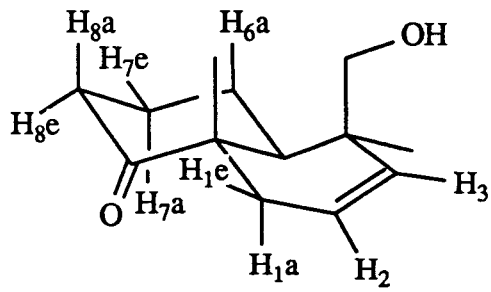
Vh. Preparation of the keto alcohol **151** and the ketone **152**



150 **151** 98% (54)

To a stirred solution of the alcohol **150** in acetone was added hydrochloric acid (10% aqueous solution). The reaction mixture was stirred at room temperature for 1 h. Workup and column chromatography on silica gel of the material thus obtained, afforded the keto alcohol **151** in 98% yield (equation 54). The ir spectrum of **151** exhibited an O-H stretching absorption at 3453 cm^{-1} and a carbonyl absorption at 1704 cm^{-1}. In the ^1H nmr spectrum of **151**, the vinyl protons appeared at δ 5.74 and 5.54 (ddd, H_2, J=10,6,2 Hz and dd, H_3, J=10,3 Hz, respectively). Other resonances exhibited were: two

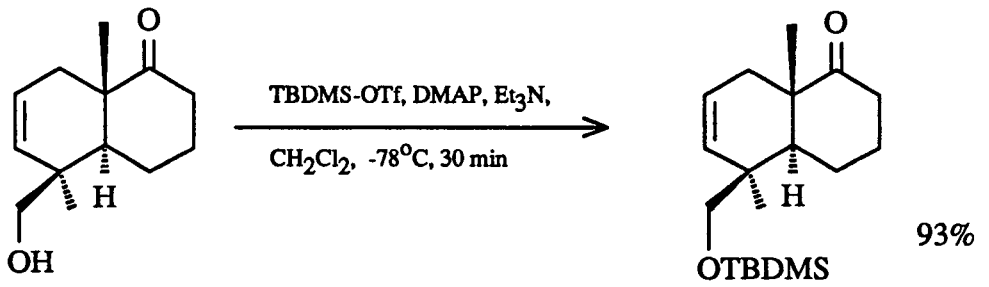
(one-proton) doublet of doublets (J=11,6 Hz each) at δ 3.74 and 3.70 due to the methylene protons of the hydroxymethyl moiety (each of these signals collapsed to a doublet (J=11 Hz) when D_2O was added), a ddd (J=14,14,7 Hz) at 2.60 due to H_8a (see formula **151a**), a broad doublet (J=18 Hz) at 2.38 due to H_1a, a dddd (J=14,2,2,2 Hz) at 2.29 due to H_8e, a one-proton multiplet at 2.18-2.08 due to H_7e, a doublet of doublets at 1.99 (J=18,6 Hz) due to H_1e, a one proton dddd (J=12,12,12,4 Hz) at 1.74 due to H_6a, and a one-proton multiplet at 1.63-1.47 due to H_7a. In ^1H nmr proton decoupling



151a

experiments, irradiation of the signal at δ 5.74 (H_2) simplified the signal at 5.54 (H_3) to a doublet (J=3 Hz), the broad doublet at 2.38 (H_1a) was sharpened and the dd at 1.99 (H_1e) collapsed to a doublet (J=18 Hz); irradiation of the signal at δ 2.60 (H_8a) simplified the signals at 2.29 (H_8e, to an unresolved multiplet), 2.18-2.08 (H_7e) and 1.63-1.47 (H_7a); irradiation of the signal at δ 2.18-2.08 (H_7e) simplified the signals at 2.60 (H_8a), 2.29 (H_8e, collapsed to a doublet of multiplets, J=14 Hz), 1.74 (H_6a, collapsed to a ddd, J=12,12,12 Hz), and 1.63-1.47 (H_7a).

Conversion of the keto alcohol **151** into its tert-butyldimethylsilyl (TBDMS) ether was accomplished using a slight modification of a literature procedure[89] (equation 55). Thus, to a cold (-78°C) solution of **151**, 4-N,N-dimethylaminopyridine (DMAP), and triethylamine in dry dichloromethane was added tert-butyldimethylsilyl-trifluoromethanesulfonate (TBDMS-OTf). The mixture was stirred at -78°C for 30 min.

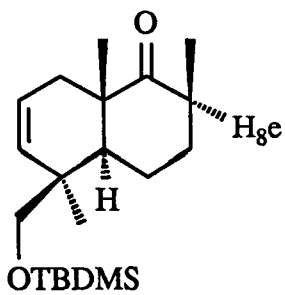


(55)

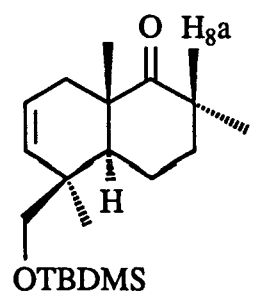
151 **152**

Workup and column chromatography (silica gel) of the mixture thus obtained afforded the ketone **152** in 93% yield. When the reaction was carried out with TBDMS-Cl instead of TBDMS-OTf (under conditions identical with those described above) or with TBDMS-Cl and imidazole in DMF,[63] the yields of **152** were lower. The ir spectrum of the ketone **152** exhibited a strong absorption at 1710 cm^{-1} due to the carbonyl function. The ^1H nmr spectrum of **152** displayed two one-proton doublets (J=10 Hz each) at δ 3.60 and 3.56 due to the methylene protons in the $-CH_2-O$(TBDMS) moiety. The nine-proton singlet at δ 0.91 and the three-proton singlets at 0.04 and 0.03 were assigned to the tert-butyldimethylsilyl group protons.

Vi. Preparation of the ketones **153** and **154**

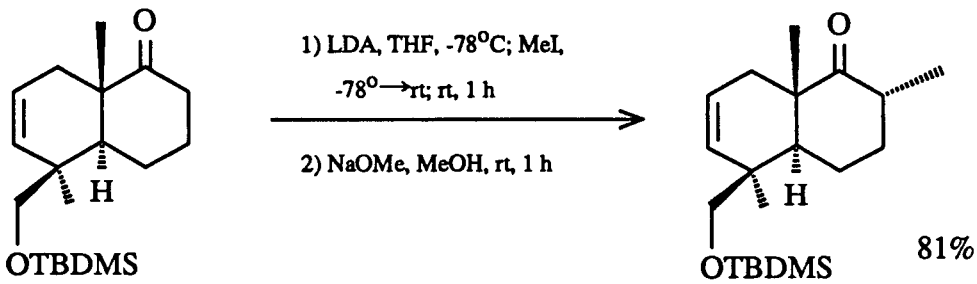


153



154

Monoalkylation of the ketone **152** proceeded cleanly. Thus, deprotonation (LDA, THF) of **152** and methylation (methyl iodide) of the resultant enolate anion gave two products. After workup and column chromatography on silica gel, two fractions were obtained. The first fraction consisted of a mixture of the epimers **153** and **154** in 57% yield. The second fraction contained exclusively the ketone **153** in 39% yield. The mixture of epimers obtained from the first fraction was subjected to epimerization (sodium methoxide in methanol). After workup and column chromatography on silica gel, the ketone **154** was obtained as the only product in 88% yield. The ^{1}H nmr spectrum of compound **153** exhibited a one-proton doublet of quartets (J=8,8 Hz) at δ 2.64 due to the equatorial proton H_8e and a doublet (J=8 Hz) at 1.13 due to the secondary methyl group protons. On the other hand, the ^{1}H nmr spectrum of **154** displayed a one-proton ddq (J=12,6,6 Hz) at δ 2.68 due to the axial proton H_8a and a doublet (J=6 Hz) at 1.00 due to the secondary methyl group protons.



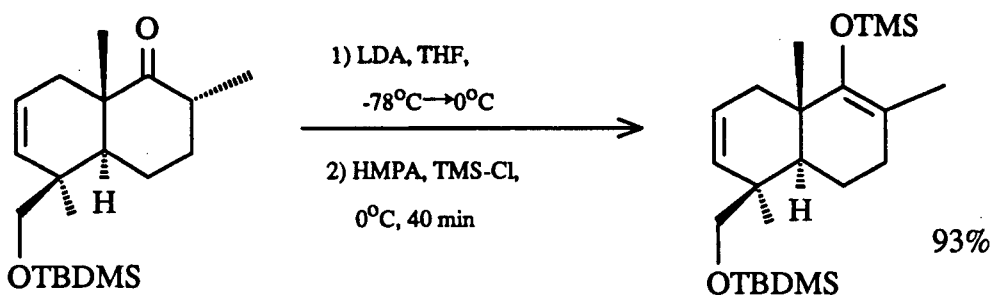
(56)

152 **154**

Certainly, it would have been possible to carry out the next transformation (vide infra) using a mixture of the ketones **153** and **154**. However, it was desired to confirm the reproducibility of the alkylation reaction on a larger scale, as well as to have increased amounts of pure **154**. Furthermore, it was found that it was easier to separate traces of dialkylated product and/or starting material from **154**, obtained after epimerization, than from the mixture of **153** and **154** obtained after the alkylation of **152**.

Thus, the alkylation-epimerization steps were carried out sequentially, using conditions very similar to those outlined above. In this way, **154** was produced from **152** in 81% overall yield (equation 56).

Vj. Preparation of compounds **155**, **156**, and **157**

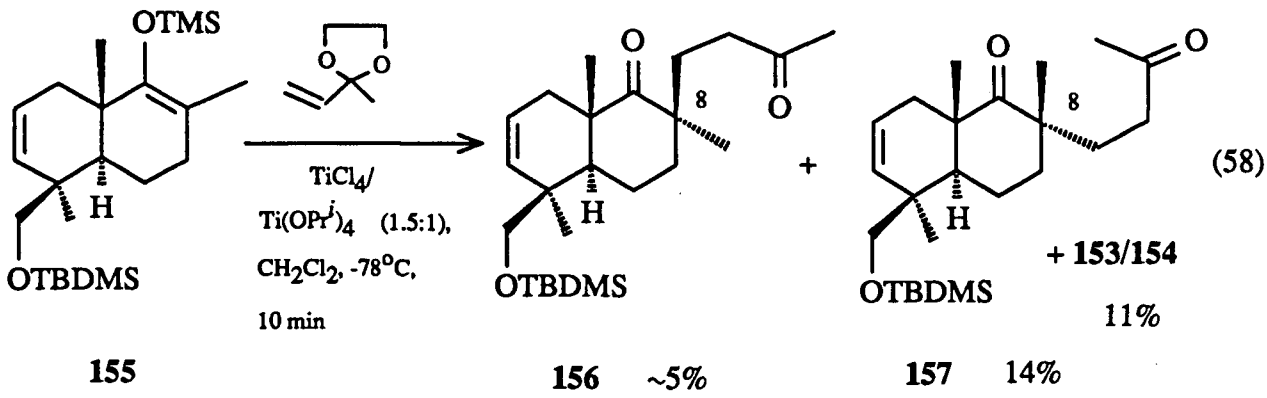


(57)

154 **155**

The synthesis of the diketone **157** involved the Lewis acid-promoted Michael-type addition of the enol silyl ether **155** onto the ethylene ketal of 3-buten-2-one. Therefore, the trimethylsilyl enol ether **155** was first prepared using a modification of a known literature procedure.[44] Thus, to a cold (0°C) solution of the lithium enolate of **154** in dry THF were added HMPA and TMS-Cl and the reaction mixture was stirred at 0°C for 40 min. Following workup, column chromatography on silica gel of the crude product afforded the silyl enol ether **155** in 93% yield (equation 57). The ir spectrum of **155** exhibited characteristic absorptions at 1676 and 842 cm^{-1} due to the enol ether double bond and the trimethylsilyl group, respectively. The ^1H nmr spectrum of **155** showed a three-proton singlet at δ 1.54 due to the vinylic methyl group and two (nine-proton) singlets at 0.91 and 0.22 due to the tert-butyl and trimethylsilyl group protons, respectively.

The Michael-type addition step of the six-membered ring annulation sequence was carried out by adding the ethylene ketal of 3-buten-2-one (prepared from



155 156 ~5% 157 14% (58)

3-buten-2-one according to the procedure published by Hahn)[46] to a cold (-78°C) mixture of $TiCl_4$ and $Ti(OPr^i)_4$ in dry dichloromethane. After the mixture had been stirred at -78°C for 5 min, a solution of the trimethylsilyl enol ether **155** in dry dichloromethane was added and the reaction mixture was stirred for a further 10 min period. After workup, thin layer chromatographic analysis of the crude product mixture showed the presence of four compounds and a considerable amount of intractable "baseline" material. Column chromatography of this mixture afforded the desired diketone **157** in 14% yield, the epimeric (and somewhat impure, 90% by glc analysis) diketone **156** in ~5% yield, and the ketones **153** and **154** in 6 and 5% yield, respectively (equation 58).

When a Michael addition was attempted under conditions very similar to those described above, except for the use of TBDMS-OTf as Lewis acid, a large number of (polar) unidentified compounds were produced. Another attempt to prepare the Michael adduct **157** by slowly adding 3-buten-2-one to a cold (-10°C) ethereal solution of the mixture **153/154** in the presence of a catalytic amount of sodium ethoxide[90] also failed. In this case, only the ketone **154** was recovered.

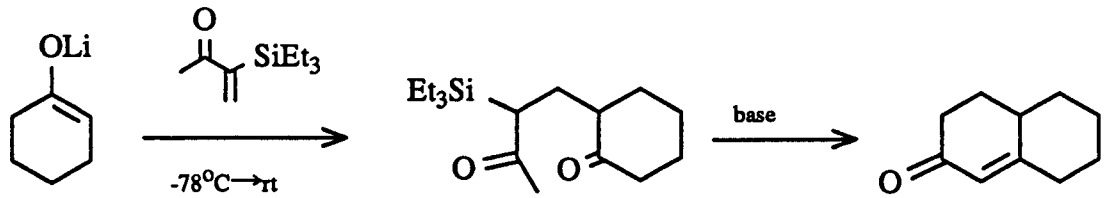
The ir spectrum of **157** exhibited two strong absorptions at 1718 and 1695 cm^{-1} due to the two carbonyl functions. The ^1H nmr spectrum of **157** exhibited a three-proton singlet at δ 2.16 due to the methyl ketone moiety. The three (nine-, three-, and

three-proton) singlets which appeared at δ 0.91, 0.04, and 0.03, respectively, were assigned to the tert-butyldimethylsilyl protecting group. The remaining methyl group signals appeared as three-proton singlets at δ 1.19, 1.18, and 1.08.

The ir spectrum of the (somewhat impure) diketone **156** exhibited two strong absorptions at 1719 and 1694 cm^{-1} due to the two carbonyl groups. The ^1H nmr of this material displayed a singlet at δ 2.14 due to the methyl ketone moiety. Three singlets appeared at δ 0.91, 0.04, and 0.03 and were assigned to the tert-butylsilyl protecting group. The remaining methyl group signals appeared as singlets at δ 1.13, 1.07, and 0.99.

Examination of molecular models indicates that electrophilic attack on the enol ether **155** would occur preferentially from the α (less hindered) side of the molecule. However, the relative configurations at C-8 of compounds **156** and **157** were not known with certainty at this stage of our work. Later, ^1H nmr spectroscopy experiments involving a synthetic intermediate derived from **157** (see Part Vm of this Discussion Section) showed conclusively that the diketone **157** possessed the indicated stereochemistry. Nevertheless, at this point, it was decided that any further attempts to produce **157** in a more efficient way would be carried out after the relative stereochemisty of this product had been confirmed. Thus, the next two synthetic steps were carried out with the available material (vide infra).

In spite of having obtained a low yield of **157**, the stereochemical outcome of the reaction suggested that other approaches to its construction could be promising. An example of such approach would be the reaction of the lithium enolate of **154** (represented by formula **154a** in Scheme 22) with the Michael acceptor 3-triethylsilyl-3-buten-2-one under aprotic conditions. The previous success of this reaction is illustrated by the preparation of the bicyclo[4.4.0]oct-1-en-3-one **160** from the lithium enolate **158** (see Scheme 21).[91] Another possibility would be the reaction of the

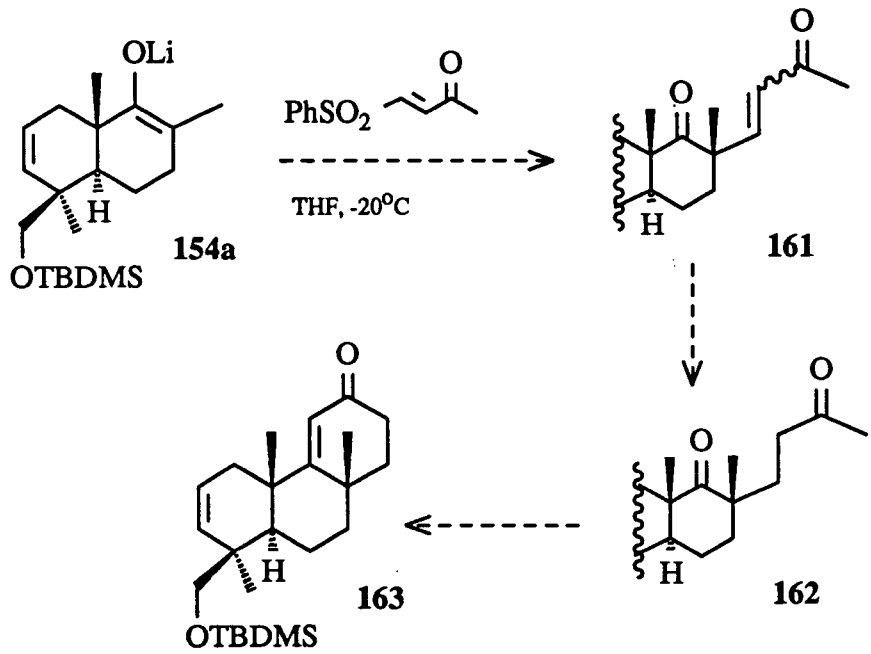


158 **159** **160**

80% overall

Scheme 21

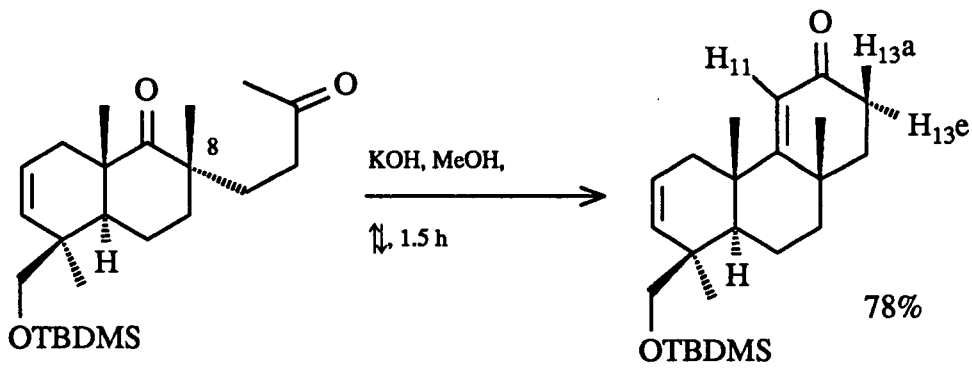
lithium enolate **154a** with (E)-4-(phenylsulphonyl)-3-buten-2-one[41i] to produce the enone **161** (Scheme 22). Chemoselective reduction of the conjugated carbon-carbon



Scheme 22

double bond in adduct **161** to give **162**, followed by an aldol condensation-dehydration sequence of reactions would produce the desired enone **163**.

Vk. Preparation of compound **163**



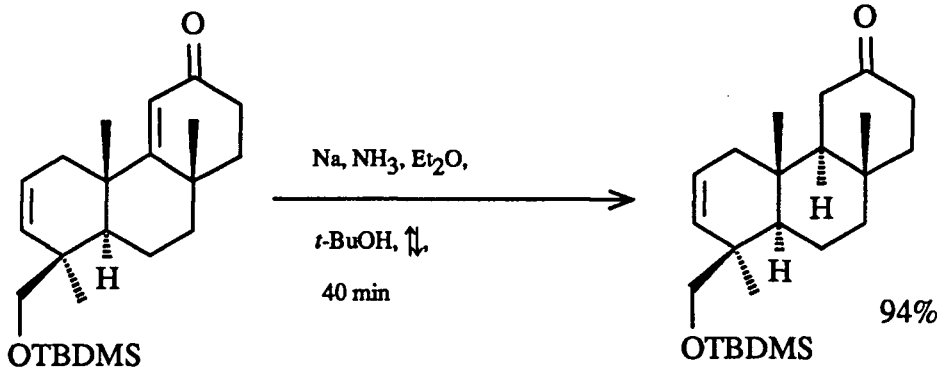
(59)

157 **163**

Treatment of the diketone **157** with a 5% solution of potassium hydroxide in refluxing methanol gave, after workup and column chromatography of the crude product, the enone **163** in 78% yield (equation 59). The ir spectrum of the enone **163** exhibited absorptions at 1671 and 1617 cm^{-1} due to the enone function. The ^1H nmr spectrum of **163** displayed a broad singlet at δ 5.85 due to the vinyl proton H_{11}. A ddd (J=18,15,5 Hz) at δ 2.58 and a broad doublet (J=18 Hz) at 2.38 could be assigned to $H_{13}a$ and $H_{13}e$, respectively.

Vl. Preparation of the ketone **164**

The next step in the synthetic sequence required the stereoselective generation of the *B/C* trans-fused ring junction to produce the ketone **164**. The enone **163** was subjected to a dissolving metal reduction using sodium in ammonia-diethyl ether in the presence of tert-butyl alcohol (equation 60). The reaction mixture was refluxed for 40 min. After workup and column chromatography of the product mixture, the ketone **164** was obtained in 94% yield. The relative stereochemistry of this product was established



(60)

163 **164**

on the basis of ^{1}H nmr experiments (vide infra). The ir spectrum of compound **164** showed a strong absorption at 1711 cm^{-1} due to the carbonyl group. The ^{1}H nmr spectrum of **164** (Figure 6) exhibited a dd (J=11,2 Hz) at δ 5.60 and a ddd (J=11,6,2 Hz) at 5.49 due to the vinyl protons H_3 and H_2, respectively (see formula **164a**). Two (one-proton) doublets (J=10 Hz each) appeared at δ 3.60 and 3.49 and were assigned to the methylene protons of the -CH_2-OTBDMS moiety. A ddd (J=16,16,6 Hz) at δ 2.46 was ascribed to H_{13}a and the three-proton multiplet at 2.34-2.25 was assigned to protons H_{11}a, H_{11}e, and H_{13}e. A one-proton broad doublet (J=18 Hz) at δ 1.27 was assigned to H_5. The one-proton doublet of doublets (J=18,6 Hz) at δ 1.90 was assigned to the pseudo-equatorial proton H_1e. From the four-proton multiplet at δ 1.66-1.38, three protons were assigned to H_1a, H_{14}a, and H_{14}e. The three-proton singlets at δ 1.14, 1.05, and 0.89 were assigned to the C-17, C-18, and C_{20} methyl group protons, respectively. The nine-proton singlet at δ 0.90 and the three-proton singlets at 0.03 and 0.02 were due to the tert-butyldimethylsilyl group.

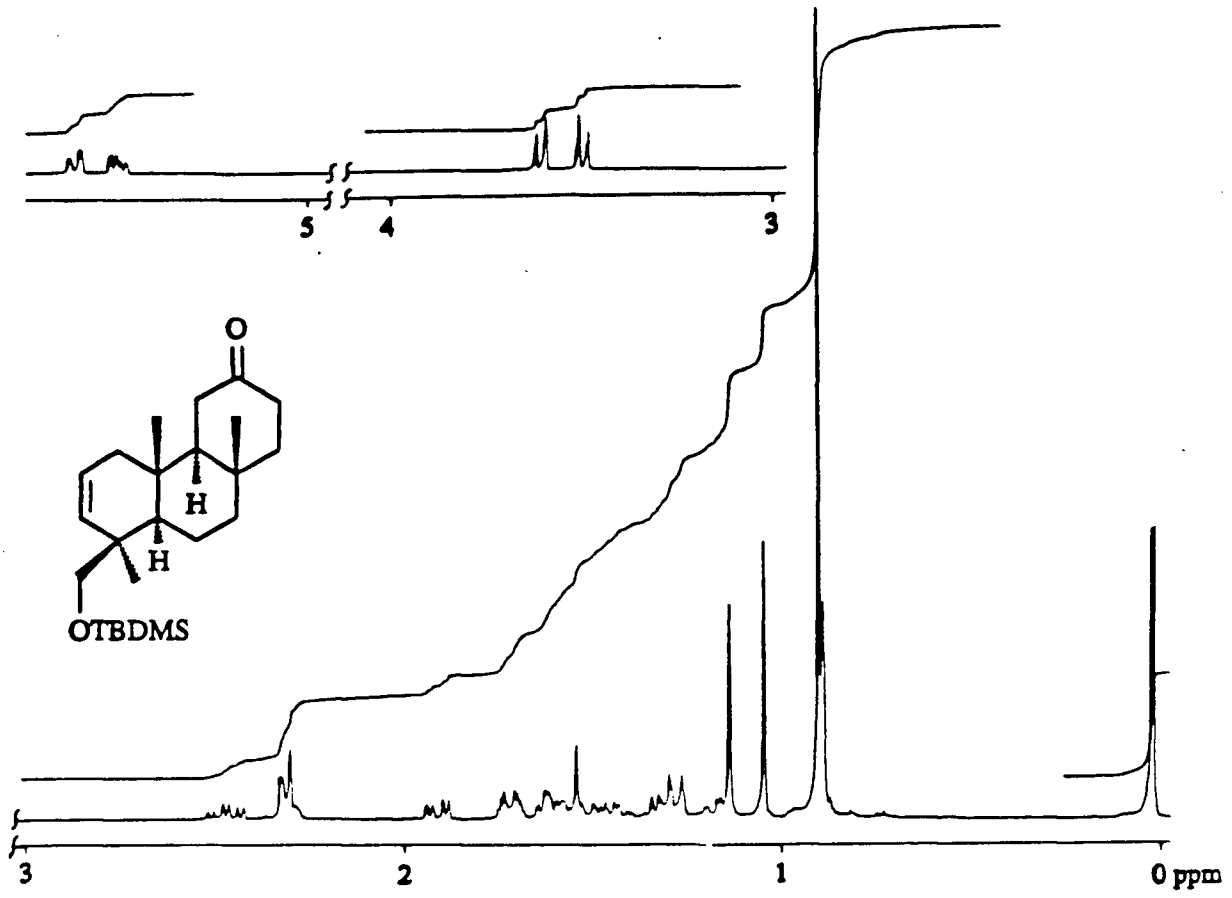
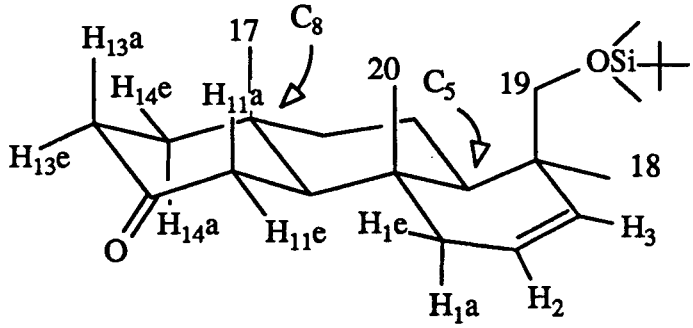


Figure 6. The ^1H nmr spectrum ($CDCl_3$, 400 MHz) of compound **164**.

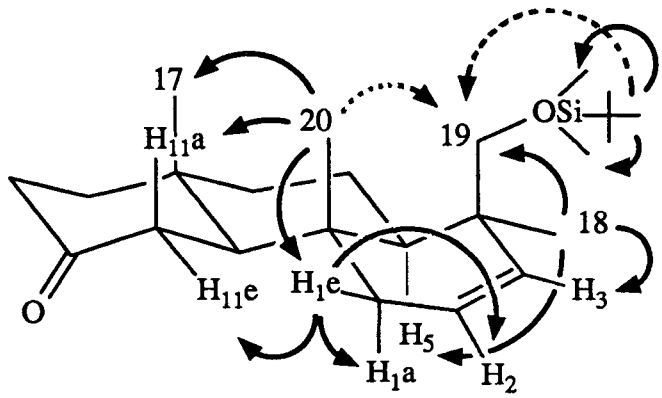
In ^1H nmr decoupling experiments (see formula **164a**), irradiation of the signal at δ 1.90 (H_1e) simplified the signals at 5.49 (H_2) and the four-proton multiplet at 1.66-1.38 (due to the decoupling of H_1a); irradiation of the signal at δ 2.46 ($H_{13}a$) simplified the three-proton multiplet at 2.34-2.25 (due to the decoupling of $H_{13}e$) and the four-proton multiplet at 1.66-1.38 (due to the decoupling of $H_{14}e$ and $H_{14}a$).

The following nOe difference experiments corroborated the proposed structure for **164**. Thus, irradiation of the signal at δ 1.90 (H_1e) caused enhancement of the signals



164a

at 5.49 (ddd, J=11,6,2 Hz, H_2), 2.34-2.25 (multiplet, $H_{11}e$) and 1.60 (broad doublet, J=18 Hz, H_1a); irradiation at δ 0.89 (C_{20} methyl protons, tert-butyl protons) caused



164b

enhancement of the signals at 3.60 (doublet, J=10 Hz, C_{19} methylene proton), 2.34-2.25 (multiplet, $H_{11}a$), 1.90 (dd, J=18,6 Hz, H_1e) and the singlets at 1.14 (C_{17} methyl protons), 0.03 and 0.02 (both signals due to protons on the methyl groups bonded to Si); irradiation of the signal at δ 1.05 (C_{18} methyl protons) caused enhancement of the signals at 1.27 (dd, J=13,3 Hz, H_5; in this case the signal does not appear as a broad doublet but as a sharp dd), 3.49 (doublet, J=10 Hz, C_{19} methylene proton) and 5.60 (dd, J=11,2 Hz, H_3). These nOe experiments are summarized by the arrows shown in the conformational formula **164b** (vide supra).

The spectral data discussed above confirmed the expected stereochemical outcome for the Birch reduction of the enone **163** (see Section IIIg of this Discussion). That is, the *B* and *C* rings of **164** are indeed, as expected, trans-fused. This stereochemistry was indicated by the nuclear Overhauser enhancement of the signals due to $H_{11}a$ and $H_{11}e$ upon irradiation of the signals due to C-20 and H_1e, respectively. From an examination of molecular models it appears that these enhancements would be very unlikely in the case of the corresponding *B/C* cis-fused ring system. On the other hand, the (expected) relative configuration at C-8 was confirmed by the nuclear Overhauser enhancement of the C-17 methyl group signal upon irradiation of the C-20 methyl group signal. Finally, the relative stereochemistry at C-4 was established on the basis of the nuclear Overhauser enhancement of the signal due to H_5 upon irradiation of the signal due to the C-18 methyl group. It should be noted that the relative stereochemistry at C-4 cannot be established on the basis of the enhancement of the C-19 methylene proton signal upon the simultaneous irradiation of the signals due to the C-20 methyl group (δ 0.89) and the *t*-butyl group (δ 0.90) (see arrows with a broken line in formula **164b**).

Vm. Conclusion

The synthetic work described above resulted in a fifteen-step conversion of the ketone **17** into the tricyclic ketone **164** in 3 % overall yield. The palladium(0)-catalyzed coupling reaction to produce the nitrile **144** (equation 50, p.91), the stereoselective alkylation to produce compound **148** (equation 51, p.92), and the stereoselective reduction of the enone **163** (equation 60, p.104) were key steps in our sequence. On the other hand, the synthesis of the Michael adduct **157** from the silyl enol ether **155**

(equation 58, p.100) leaves much to be desired. A much needed improvement in the yield of this step would substantially increase the efficiency of our synthetic route. To this end some suggestions have been made in section Vj of this Discussion. However, due to time constraints, none of these were attempted. Another point worth considering in future work is the potential utility of an intermediate such as **150** (see p.94) as a suitable model for the functionalization of ring *A*.

In conclusion, the methodology employed in the construction of the tricyclic intermediate **164** allowed for the stereoselective construction, with the correct relative configuration, of five of the six chiral centers present in the spongiadiols. Therefore, this appears to be a viable general route towards the total synthesis of the spongiadiol family of diterpenoids.

EXPERIMENTAL

VI. General

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker model WH 400 spectrometer using deuteriochloroform as the solvent and tetramethylsilane (TMS) as an internal standard. In some cases in which trialkylsilyl groups were present, the resonance positions were determined relative to the chloroform signal (δ 7.25).[92] Signal positions are given in parts per million (δ) from TMS. The multiplicity, number of protons, coupling constants, and assignments (where possible) are indicated in parentheses. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; $w_{1/2}$, peak width at half height. In cases where a proton is coupled with the same coupling constant to two, three, four or five protons which are chemically and magnetically non-equivalent the designations 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.[93] 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 using deuteriochloroform as the solvent and TMS as the internal standard. Signal positions are given in parts per million (δ) from TMS.

Infrared (ir) spectra were obtained on liquid films or using KBr pellets, employing a Perkin-Elmer model 1710 FT spectrophotometer. Low resolution mass

spectra (low res. ms) were recorded on a AEIMS9/DS55SM (1964, In-House 1980) or on a Kratos MS50/DS55SM (1974) spectrometer. High resolution mass spectra (used whenever Exact Mass is quoted) were recorded on a Kratos/AE1 MS 50 or MS 902 spectrometer. All compounds which were characterized by high resolution mass measurements were homogeneous by glc and tlc analyses.

Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

Gas-liquid chromatography (glc) was performed on either a Hewlett-Packard model 5880 or model 5890 capillary gas chromatograph, both using a flame ionization detector and a 25 m x 0.21 mm fused silica column coated with cross-linked SE-54.

Thin layer chromatography (tlc) was performed on commercially available aluminum backed silica gel plates (E. Merck, type 5554). Visualization was accomplished with iodine vapor, ultraviolet light or a 5 % solution of ammonium molybdate in 10 % aqueous sulfuric acid (w/v). Column chromatography (flash type[94]) was done on 230-400 mesh silica gel (E. Merck, silica gel 60).

Melting points (uncorrected) were measured on a Fischer-Johns melting point apparatus. Distillation temperatures (uncorrected) are indicated as air-bath temperatures of Kugelrohr (bulb-to-bulb) distillations.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon, with dry solvents and in oven or flame-dried glassware.

Concentration 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 the use of the following baths: acetone/ice (-10°C), aqueous calcium chloride/CO_2 (-20 to -40°C),[95] acetone/CO_2 (-78°C), liquid nitrogen/dry methanol (-100°C).

All temperatures are recorded in degrees Celsius (°C).

VII. Solvents and reagents

Petroleum ether refers to a hydrocarbon mixture with b.p. 30-60°C. Ether refers to diethyl ether. Tetrahydrofuran, ether, and benzene were distilled from sodium benzophenone ketyl. Dichloromethane and carbon tetrachloride were distilled from phosphorus pentoxide. Iodomethane was passed through a short column (Pasteur pipette) of basic alumina (activity I) before use. Diisopropylamine, triethylamine, hexamethylphosphoramide, dimethyl sulfoxide, and acetonitrile were distilled from calcium hydride and stored over activated 4Å molecular sieves.

Ethanol and methanol were distilled from magnesium. tert-Butyl alcohol was distilled and dried over activated powdered 3Å molecular sieves. Dimethylformamide was dried over activated 4Å molecular sieves and distilled before use.

Trimethylsilyl chloride was dried by refluxing over calcium hydride and was distilled before use.

Solutions of methyllithium in ether (low halide content) and methyllithium-lithium bromide complex in ether, were obtained from Aldrich Chemical Co., Inc. and were standardized using the procedure of Kofron and Baclawski.[96]

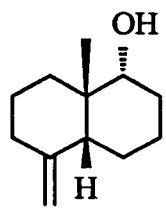
Lithium diisopropylamide (LDA) was prepared by the addition of a solution of methyllithium-lithium bromide complex (1.0 equiv.) in ether to a solution of diisopropylamine (1.05 equiv.) in anhydrous tetrahydrofuran at -78°C. The resulting colorless or slightly yellow solution was stirred at 0°C for 10 min before being used.

Diphenyl phosphorazidate was prepared as described by Yamada and coworkers.[71] Formic acetic anhydride was prepared as described by Huffman.[73] Copper(I) bromide-dimethyl sulfide complex was prepared by the method described by Wuts.[97]

Triphenylphosphine was purified by recrystallization from methanol-ethyl acetate.

All other reagents were commercially available and were utilized without further purification.

Preparation of the alcohols **44** and **45**



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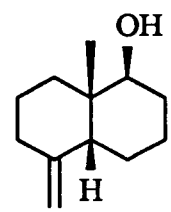


45

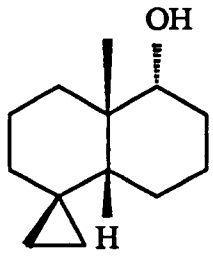
To a cold (-20°C), stirred solution-suspension of sodium borohydride (0.420 g, 11.100 mmol) in dry methanol (27 mL) was added a solution of the ketone **17**[23] (1.750 g, 9.830 mmol) in dry methanol (10 mL). The reaction mixture was stirred at -20°C for 100 min. A saturated aqueous solution of ammonium chloride (10 mL) was added slowly and the mixture was allowed to warm to room temperature. The methanol was removed under reduced pressure and brine (20 mL) was added to the residue. The mixture was extracted with dichloromethane (3x50 mL). The combined extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (130 g, 9:1 petroleum ether-ethyl acetate). Distillation (air-bath temperature 70-75°C/0.4 Torr) of the oil thus obtained provided 1.750 g (98 %) of the alcohols **44/45** (9:1 mixture of epimers by glc analysis).

When the same experiment was carried out on a different scale it was possible to isolate a pure sample of each of the isomeric alcohols **44** and **45**. Compound **44** exhibited on ir (film): 3385, 3067, 1646, 1082 cm^{-1}; ^1H nmr (400 MHz) δ 4.69-4.66 (m, 1H, vinyl proton), 4.66-4.63 (m, 1H, vinyl proton), 3.32 (dd, 1H, J=13,5 Hz, CH-OH), 2.22 (td, 1H, J=13,5 Hz), 2.10 (dd, 1H, J=13,5 Hz), 1.87 (dd, 1H, J=13,4 Hz), 1.83-1.22 (m, 11H, simplified upon addition of D_2O), 1.04 (s, 3H, methyl protons). Exact Mass. calcd. for $C_{12}H_{20}O$: 180.1514; found: 180.1512.

The minor isomer **45** exhibited on ir (film): 3389, 3067, 1646, 1050 cm^{-1}; ^1H nmr (400 MHz) δ 4.68 (s, 1H, vinyl proton), 4.66 (s, 1H, vinyl proton), 3.50 (br s, 1H, CH-OH), 2.31-2.16 (m, 2H), 2.07 (dt, 1H, J=13,5 Hz), , 1.92-1.34 (m, 10H), 0.99 (s, 3H, methyl protons), 1.05-0.95 (m, 1H). Exact Mass. calcd. for $C_{12}H_{20}O$: 180.1514; found: 180.1507.

Preparation of the alcohols **46** and **47**

The mixture of alcohols **44/45** was dissolved in dry dichloromethane (5 mL) and dry air was slowly passed through the stirred solution at room temperature. Diiodomethane (3 mL, 37.200 mmol) was added and then a 1.6 M solution of diethylzinc in toluene (24 mL, 38.400 mmol) was added over a period of 15 min. **(Explosion Hazard: The air current should never be introduced after the reagents have been mixed together under an inert atmosphere).** The resulting solution was refluxed for 2.5 h under an atmosphere of dry air. The mixture was allowed to cool to room temperature and 10 % hydrochloric acid (20 mL) was added. The phases were separated and the aqueous layer was extracted with Et_2O (2x50 mL). The combined extract was



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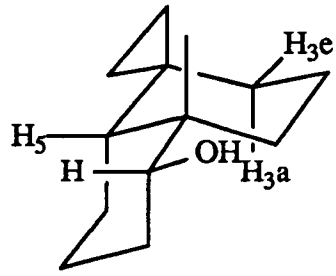
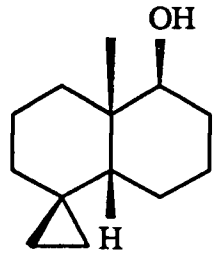


46a



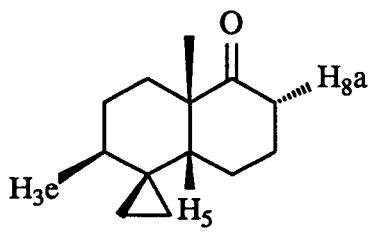
47

washed with a saturated aqueous solution of ammonium chloride (1x10 mL) and brine (2x10 mL) and then was dried (K_2CO_3) and concentrated. Column chromatography of the residual material on silica gel (120 g, 9:1 petroleum ether-ethyl acetate) and distillation (air-bath temperature 79-84°C/0.8 Torr) of each of the products thus obtained afforded 1.350 g (72 % from the alcohols **44/45**) of the alcohol **46** and 0.150 g (8 % from the alcohols **44/45**) of the alcohol **47**. The alcohol **46** exhibited ir (film): 3382, 3065, 1050 cm^{-1}; ^1H nmr (400 MHz) δ 3.27 (m, 1H, C<u>H</u>-OH, D_2O addition transforms the signal to a dd, <u>J</u>=11,5 Hz), 1.90 (br dd, 1H, <u>J</u>=12,12 Hz, <u>H</u>$_3$a), 1.80-1.13 (m, 11H), 1.30 (s, 1H, -O<u>H</u>, D_2O exchanged), 1.24 (s, 3H, methyl protons), 0.57 (dm, 1H, <u>J</u>=12 Hz, <u>H</u>$_3$e), 0.47-0.32 (m, 3H, two cyclopropyl protons, <u>H</u>$_5$), 0.11-0.00 (m, 2H, cyclopropyl protons). In decoupling experiments, irradiation of the signal at δ 1.90 (H_3a) caused the collapse of the signal at δ 0.57 (H_3e) to a broad singlet; irradiation of the signal at δ 0.57 (H_3e) caused the collapse of the signal at 1.90 (H_3a) to a broad doublet (<u>J</u>=12 Hz) and simplified the multiplet at δ 0.47-0.32 (H_5). <u>Exact Mass</u> calcd. for $C_{13}H_{22}O$: 194.1671;

found: 194.1671.

The alcohol **47** showed ir (film): 3434, 3067, 1067 cm^{-1}; ^1H nmr (400 MHz) δ 3.35 (br s, 1H, $w_{1/2}$=8 Hz, sharpened upon addition of D_2O), 1.98-1.40 (m, 11H), 1.43 (br s, 1H, -OH, D_2O exchanged), 1.18 (s, 3H, methyl protons), 0.72 (dd, 1H, J=13,5 Hz), 0.56 (dm, 1H, J=13 Hz), 0.42-0.30 (m, 2H, cyclopropyl protons), 0.12-0.04 (m, 2H, cyclopropyl protons). Exact Mass calcd. for $C_{13}H_{22}O$: 194.1671; found: 194.1664.

Preparation of the ketone **36**

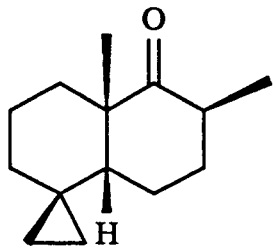


36

To a stirred slurry (room temperature) of pyridinium chlorochromate (3.000 g, 13.917 mmol) and 4 Å molecular sieves (0.900 g) in dry dichloromethane (38 mL) was added a solution of a 9:1 mixture of the epimeric alcohols **46** and **47** (1.500 g, 7.730 mmol) in dry dichloromethane (8 mL). The reaction mixture was stirred at room temperature for 85 min. Diethyl ether (30 mL) was added and the mixture was filtered through a column of Florisil (30 g, elution with Et_2O). Concentration of the eluate and distillation (air-bath temperature 65-70°C/0.8 Torr) of the remaining oil gave 1.350 g (91 %) of the tricyclic ketone **36** which exhibited ir (film): 3068, 1703, 1374 cm^{-1}; ^1H nmr (400 MHz) δ 2.58 (ddd, 1H, J=13,13,6 Hz, H_8a), 2.25 (dm, 1H, J=13 Hz), 2.14-1.95 (m, 3H), 1.90 (ddd, 1H, J=11,11,5 Hz), 1.78-1.42 (m, 4H), 1.29 (s, 3H, methyl protons), 1.23 (br d, 1H, J=13 Hz), 0.77 (dd, 1H, J=13,4 Hz, H_5?), 0.65 (br d, 1H, J=13 Hz, H_3e?),

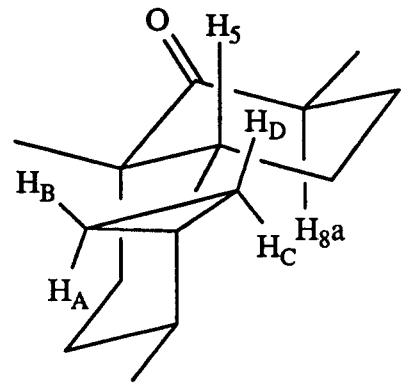
0.49-0.32 (m, 2H, cyclopropyl protons), 0.25-0.08 (m, 2H, cyclopropyl protons). Exact Mass calcd. for $C_{13}H_{20}O$: 192.1515; found:192.1513.

Preparation of the ketones **48** and **49**

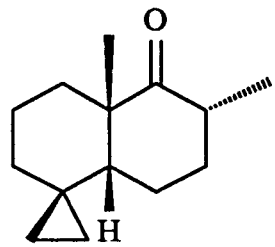


48

=



48a



49

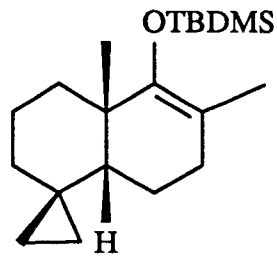
To a cold (-78°C), stirred solution of LDA (1.660 mmol) in dry THF (7.4 mL) was added a solution of the ketone **36** (0.290 g, 1.510 mmol) in dry THF (1.5 mL, washing with 1.5 mL of THF). The solution was stirred at -78°C for 15 min and at 0°C for 20 min. Methyl iodide (1 mL, 16.060 mmol) was added rapidly and the reaction mixture was stirred at 0°C for 45 min. Water (5 mL), a 5 % aqueous solution of sodium thiosulfate (5 mL) and Et_2O (5 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (3x20 mL). The combined extract was washed with brine (2x10 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil that was shown (glc) to consist of two products in a ratio of 1.3:1 .

Subjection of this mixture to column chromatography on silica gel (30 g, 98:2 petroleum ether-ethyl acetate), followed by distillation (air-bath temperature 70-75°C/1 Torr) of the oil thus obtained, furnished 0.297 g (95 %) of a mixture of ketones **48** and **49** as a colorless oil, which exhibited ir (film): 3068, 1703, 1374 cm^{-1}; ^1H nmr (400 MHz) (selected signals) δ 2.68, 2.63-2.52 (ddq, m, 1H total, ratio of signals ~1.3:1, J=13,6,6 Hz), 1.29, 1.22 (s, s, 3H total, ratio of signals ~1.3:1), 1.03, 1.00 (d, d, 3H total, ratio of signals ~1:1.3, J=6 Hz in each case), 0.66, 0.60 (br d, br d, 1H total, ratio of signals ~1.3:1, J=13.5 Hz in each case), 0.48-0.33 (m, 2H, cyclopropyl protons), 0.23-0.08 (m, 2H, cyclopropyl protons). Exact Mass calcd. for $C_{14}H_{22}O$: 206.1671; found 206.1678.

A solution of the epimeric mixture of ketones **48** and **49** (0.020 g, 0.097 mmol) in a 0.4 M solution of sodium methoxide in methanol (1 mL) was stirred overnight at room temperature. The solvent was removed under reduced pressure and a saturated aqueous solution of ammonium chloride (1 mL) and Et_2O (1 mL) were added. The layers were separated and the aqueous phase was extracted with Et_2O (2x2 mL). The combined extract was washed with brine (1x2 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil that was shown (glc) to consist nearly exclusively of the ketone **48**. Column chromatography (silica gel, 2 g, 98:2 petroleum ether-ethyl acetate) of the oil thus obtained afforded 0.019 g (95 %) of the ketone **48** after removal of traces of solvent (vacuum pump). This compound exhibited ir (film): 3068, 1703, 1375 cm^{-1}; ^1H nmr (400 MHz) δ 2.68 (ddq, 1H, J=13,6,6 Hz, H_8a), 2.15 (dddd, 1H, J=13,13,13,3.5 Hz), 2.08-1.98 (m, 2H), 1.93 (ddd, 1H, J=13,13,4.5 Hz), 1.77-1.54 (m, 3H), 1.35-1.15 (m, 2H), 1.29 (s, 3H, angular methyl protons), 1.00 (d, 3H, J=6 Hz, secondary methyl protons), 0.75 (dd, 1H, J=13,4 Hz, H_5), 0.66 (br d, 1H, J=13.5 Hz, H_3e), 0.47-0.41 (m, 1H, H_A), 0.40-0.32 (m, 1H, H_B), 0.21-0.08 (m, 2H, H_C, H_D). In a decoupling experiment, irradiation of the signal at δ 1.00 (secondary methyl protons) caused the collapse of the signal at δ 2.68 (H_8a) to a dd (J=13,6 Hz). In nOe difference

experiments, irradiation of the signal at δ 0.47-0.41 (H_A) caused enhancement of the signals at δ 1.29 (s, angular methyl protons), δ 0.66 (br d, J=13.5 Hz, H_3e), δ 0.40-0.32 (m, H_B) and δ 0.21-0.08 (m, H_C); irradiation of the multiplet at δ 0.40-0.32 (H_B) caused enhancement of the signals at δ 1.29 (s, angular methyl protons), δ 0.75 (dd, H_5), δ 0.47-0.41 (m, H_A) and δ 0.14-0.08 (m, H_D). Exact Mass calcd. for $C_{14}H_{22}O$: 206.1671; found 206.1678.

Preparation of the silyl enol ether **50**

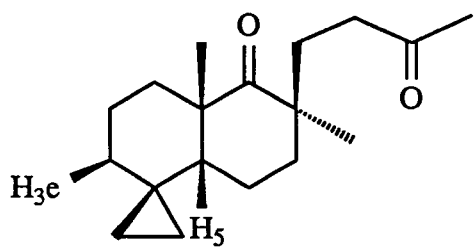


50

To a cold (-78°C), stirred solution of LDA (5.335 mmol) in dry THF (36 mL) was added a solution of a ~1.3:1 mixture of the ketones **48** and **49** (1.000 g, 4.850 mmol) in 5 mL of dry THF and the solution was stirred for 20 min. The solution was warmed to 0°C and stirred for 20 min. Hexamethylphosphoramide (0.86 mL, 4.850 mmol) and chlorotrimethylsilane (0.10 mL, 5.820 mmol) were added successively. After the reaction mixture had been stirred at 0°C for 1 h, 1,1,1,3,3,3-hexamethyldisilazane (0.5 mL) was added and the solvent was removed under reduced pressure. Pentane (50 mL) was added to the residue and after the mixture had been stirred for a few seconds, the solution was decanted. To the residue was added saturated aqueous sodium bicarbonate (20 mL) and the mixture was extracted with pentane (2x20 mL). The combined extract

was mixed with the previously decanted solution, the solution was washed with brine (3x40 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (silica gel, 130 g, 95:5 pentane-triethylamine). Removal of the volatile material (vacuum pump) from the appropriate fractions gave 1.282 g (91 %) of the silyl enol ether **50** as a colorless oil that exhibited ir (film): 3067, 1673, 1189, 840 cm^{-1}; ^1H nmr (400 MHz) δ 2.15-1.70 (m, 4H), 1.65-1.40 (m, 5H), 1.54 (s, 3H, vinyl methyl protons), 1.19 (s, 3H, methyl protons), 0.62-0.50 (m, 2H), 0.45-0.30 (m, 2H, cyclopropyl protons), 0.20 (s, 9H, $-Si(C\underline{H}_3)_3$), 0.16-0.04 (m, 2H, cyclopropyl protons). Exact Mass calcd. for $C_{17}H_{30}O_2Si$: 278.2065; found: 278.2067.

Preparation of the diketone **37**

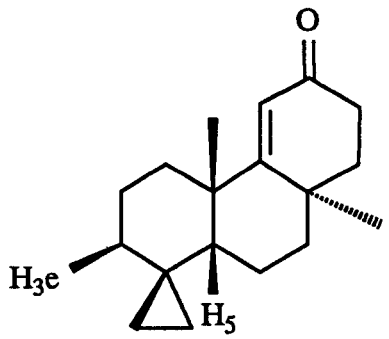


37

To a cold (-78°C), stirred solution of freshly distilled $TiCl_4$ (0.05 mL, 0.397 mmol) in dry dichloromethane (0.4 mL) was added freshly distilled $Ti(OPr\text{-}i)_4$ (0.075 mL, 0.270 mmol). The mixture was stirred at -78°C for 5 min and then was cooled to -100°C. A solution of the ethylene ketal of 3-buten-2-one[46] (0.10 mL, 1.100 mmol) and the silyl enol ether **50** (0.095 g, 0.342 mmol) in dry dichloromethane (1.5 mL) was added. The mixture was stirred at -100°C for 1.75 h. After the reaction mixture had

been treated with water (2 mL), dichloromethane was added (2 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with dichloromethane (2x10 mL). The combined extract was washed with brine (2x4 mL) and the solvent was removed under reduced pressure. The residual material thus obtained was dissolved in 8 mL of a 1:1 solution of THF and 10 % hydrochloric acid and the mixture was stirred at room temperature for 1 h. A saturated aqueous solution of sodium bicarbonate was added slowly until the solution reached pH 7. The mixture was extracted with Et_2O (3x25 mL). The combined extract was washed with brine (1x20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude oil thus obtained was purified by column chromatography (silica gel, 10 g, 95:5 petroleum ether-ethyl acetate). Collection of the appropriate fractions and removal of traces of solvent (vacuum pump) from one of the oils thus obtained gave 0.028 g (41 %) of a 12.5:1 mixture (glc analysis) of the ketones **48** and **49**. Distillation (air- bath temperature 120-130°C/0.4 Torr) of an oil obtained from other fractions gave the diketone **37** (0.045 g, 48 %) as a colorless oil. Glc analysis of this material showed that it was contaminated with ~3 % of another compound, likely the C_8-epimer of **37**. This material exhibited ir (film): 3066, 1716, 1689, 1371 cm^{-1}; ^1H nmr (400 MHz) δ 2.40-2.20 (m, 2H), 2.20-2.00 (m, 1H), 2.12 (s, 3H, -(CO)-C$\underline{H}_3$), 1.99-1.83 (m, 2H), 1.82-1.40 (m, 5H), 1.34 (br d, 1H, $\underline{J}$=12 Hz), 1.30-1.15 (m, 1H), 1.27 (s, 3H, methyl protons), 1.19 (s, 3H, methyl protons), 0.75 (br d, 1H, $\underline{J}$=12 Hz, $\underline{H}_5$?), 0.64 (br d, 1H, $\underline{J}$=14Hz, $\underline{H}_3$e?), 0.47-0.33 (m, 2H, cyclopropyl protons), 0.27-0.10 (m, 2H, cyclopropyl protons). Exact Mass calcd. for $C_{18}H_{28}O_2$: 276.2090; found: 276.2090.

Preparation of the enone 32

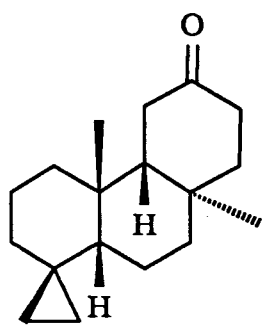


32

To a solution of the diketone **37** (0.600 g, 2.174 mmol) in 70 mL of dry benzene were added potassium tert-butoxide (0.150 g, 1.300 mmol) and tert-butyl alcohol (1 mL, 10.70 mmol). The reaction mixture was refluxed under a Dean-Stark water trap for 2 h. The solution was allowed to cool to room temperature and a saturated aqueous solution of ammonium chloride (25 mL) was added. The layers were separated and the aqueous phase was extracted with a 1:1 solution of petroleum ether-ethyl acetate (2x30 mL). The combined extract was washed with brine (1x20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography (silica gel, 50 g, 95:5 petroleum ether-ethyl acetate). Solvent removal (water aspirator, then vacuum pump) from the appropriate fractions gave 0.170 g (38 %) of the ketone **48**. Removal of the solvent from the fractions containing the major product, followed by distillation (air-bath temperature 124-129°C/0.5 Torr), gave 0.305 g (53 %) of the enone **32** as a colorless oil. This material exhibited ir (film): 3062, 1667, 1592, 1374 cm^{-1}; ^1H nmr (400 MHz) δ 6.02 (s, 1H, vinyl proton), 2.59 (ddd, 1H, J=18,14,5 Hz), 2.37 (ddd, 1H, J=18,5,2), 2.08 (dddd, 1H, J=13,13,13,3 Hz), 2.01-1.79 (m, 3H), 1.76-1.38 (m, 5H), 1.38 (br s, 6H, methyl

protons), 1.31 (ddd, 1H, J=13,13,3.5 Hz), 1.12 (br d, 1H, J=14 Hz), 0.64 (br d, 1H, J=14 Hz, H_3e), 0.59 (dd, 1H, J=13,3.5 Hz, H_5), 0.55-0.47 (m, 1H, cyclopropyl proton), 0.45-0.36 (m, 1H, cyclopropyl proton), 0.25-0.10 (m, 2H, cyclopropyl protons). Exact Mass calcd. for $C_{18}H_{26}O$: 258.1983; found: 258.1989.

Preparation of the ketone **56**



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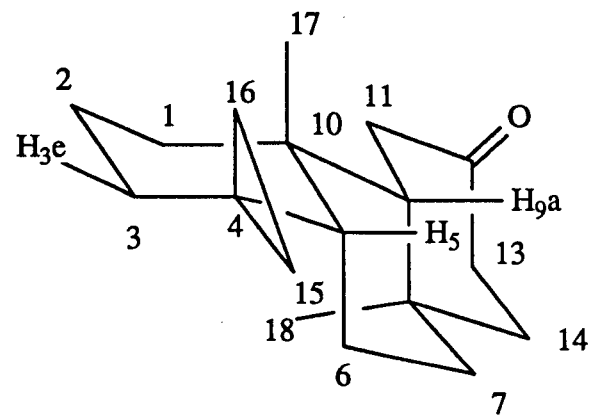


56 **56a**

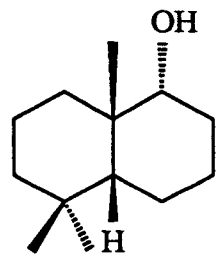
Procedure a. To a cold (-78°C), stirred solution of potassium (0.035 g, 0.895 mmol) in ammonia (5 mL, freshly distilled from sodium) was added a solution of the enone **32** (0.019 g, 0.074 mmol) and tert-butyl alcohol (6μL, 0.059 mmol) in dry Et_2O (0.5 mL). The reaction mixture was refluxed for 30 min. A saturated aqueous solution of ammonium chloride (1 mL) was added and the ammonia was removed using a warm water bath (~45°C). Diethyl ether (5 mL) and water (3 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with Et_2O (2x10 mL). The combined extract was dried ($MgSO_4$) and concentrated. The crude product thus obtained was purified by column chromatography on silica gel (0.85 g, Pasteur pipette, 95:5 petroleum ether-ethyl acetate). Removal of traces of solvent from each of the oils

thus obtained gave 0.007 g (37 %) of the enone **32** as an oil and 0.008 g (42 %) of the desired ketone **56** as a white crystalline solid, mp 99-100°C (recrystallization from pentane).

Procedure b. To a solution (room temperature) of the enone **32** (0.185 g, 0.717 mmol) in ethyl acetate (10 mL) was added palladium on activated carbon (0.018 g, 10 % palladium content). The mixture was stirred under hydrogen gas (1 atm) for 7 h. The mixture was filtered through a plug of Florisil (2 g, elution with ethyl acetate) and the solvent was removed under reduced pressure. After removal of traces of solvent (vacuum pump) from the resulting oil and recrystallization from pentane, 0.180 (97 %) of the ketone **56** was obtained as a white crystalline solid, mp 99-100°C. This material exhibited ir (KBr): 3065, 1713, 1386 cm^{-1}; ^1H nmr (400 MHz) δ 2.45 (ddd, 1H, J=14,14,7 Hz, $H_{13}a$), 2.42 (ddd, 1H, J=14,3,3 Hz, $H_{11}e$), 2.29 (dd, 1H, J=14,14 Hz, $H_{11}a$), 2.29 (m, 1H, $H_{13}e$), 1.89 (dddd, 1H, J=14,14,14, 3.5 Hz, H_6a), 1.84 (ddd, 1H, J=13,13,3 Hz, H_3a), 1.70-1.40 (m, 6H), 1.39 (ddd, 1H, J=14,14,5 Hz, $H_{14}a$), 1.28 (dd, 1H, J=14,3 Hz, H_9a), 1.20 (s, 3H, C_{18} methyl protons), 1.12 (br d, 1H, J=14 Hz, H_1e?), 1.09 (s, 3H, C_{17} methyl protons), 0.60 (br d, 1H, J=13 Hz, H_3e), 0.48-0.41 (m, 1H, cyclopropyl proton), 0.41-0.33 (m, 1H, cyclopropyl proton), 0.33 (dd, 1H, J=14,4 Hz, H_5), 0.16-0.06 (m, 2H, cyclopropyl protons). In decoupling experiments, irradiation of the overlapping signals at δ 2.45 ($H_{13}a$) and 2.42 ($H_{11}e$) simplified the multiplet at δ 1.70-1.40 ($H_{14}e$) and caused the collapse of the signals at δ 1.39 ($H_{14}a$) to a broad doublet (J=14 Hz) and δ 1.28 (H_9a) to a doublet (J=14 Hz); irradiation of the overlapping signals at δ 2.29 ($H_{13}e$, $H_{11}a$) simplified the multiplet at δ 1.70-1.40 ($H_{14}e$) and caused the collapse of the signals at δ 1.39 ($H_{14}a$) to a dd (J=14,14 Hz) and δ 1.28 (H_9a) to a doublet (J=3 Hz); irradiation of the signal at δ 1.28 (H_9a) caused the collapse of the signals at δ 2.42 ($H_{11}e$) to a dd (J=14,3 Hz) and δ 2.29 ($H_{11}a$) to a doublet (J=14 Hz). In nOe difference experiments, irradiation of the overlapping signals at δ 1.89 (H_6a) and δ

1.84 (H_3a) caused enhancement of the signals at δ 1.47 (dq, J=14,4 Hz, H_6e) and δ 0.60 (br d, J=13 Hz, H_3e); irradiation of the signal at δ 1.28 (H_9a) caused enhancement of the signals at δ 1.09 (s, C_{17} methyl protons) and δ 0.33 (dd, J=14,4 Hz, H_5); irradiation of the signal at δ 1.20 (C_{18} methyl protons) caused enchancement of the signals at δ 2.45 (ddd, J=14,14,7 Hz, $H_{13}a$), δ 2.29 (dd, J=14,14 Hz, $H_{11}a$), δ 1.84 (ddd, 14,14,5 Hz, H_6a) and δ 1.62 (ddd, J=14,14,5 Hz, H_1a?); irradiation of the signal at δ 0.33 (H_5) caused enhancement of the signals at δ 1.47 (dq, J=14,4 Hz, H_6e), δ 1.28 (dd, J=14,3 Hz, H_9a) and δ 1.09 (C_{17} methyl protons). Exact Mass calcd. for $C_{18}H_{28}O$: 260.2140; found: 260.2138.

Preparation of the alcohol **57**

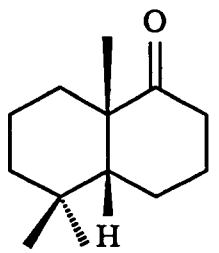


57

To a stirred solution (room temperature) of the alcohol **46** (0.317 g, 1.634 mmol) in glacial acetic acid (5 mL) was added platinum(IV) oxide (0.037 g, 0.163 mmol). The mixture was stirred under hydrogen gas (1 atm) for 2.5 h. The mixture was filtered through a plug of Florisil (6 g, elution with ethyl acetate) and the eluate was neutralized by adding slowly a saturated aqueous solution of sodium bicarbonate (~10 mL) and enough solid potassium carbonate to bring the aqueous phase to pH 7. The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 mL). The combined extract was washed with brine (1x10 mL) and dried ($MgSO_4$). The solvent

was removed under reduced pressure, affording 0.297 g (93 %) of the alcohol **57** as a white solid exhibiting mp 91-93°C (recrystallization from pentane); ir (KBr): 3281, 1386, 1365, 1042 cm^{-1}; ^1H nmr (400 MHz) δ 3.23 (dd, 1H, J=13,4 Hz, CH-OH), 1.77-1.35 (m, 8H), 1.34-1.13 (m, 2H), 1.25 (s, 3H, methyl protons), 1.15 (s, 3H, methyl protons), 1.04 (br dd, 1H, J=12,5 Hz), 0.86 (s, 3H, methyl protons). Exact Mass calcd. for $C_{13}H_{24}O$: 196.1827; found: 196.1827.

Preparation of the ketone **38**

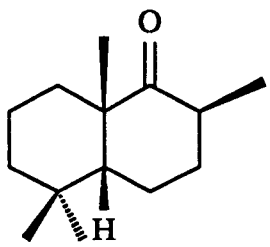


38

To a stirred slurry (room temperature) of pyridinium chlorochromate (0.400 g, 1.836 mmol) in dry dichloromethane (10 mL) was added a solution of the alcohol **57** (0.200 g, 1.020 mmol) in dry dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 2 h. Diethyl ether (5 mL) was added and the resultant suspension was filtered through a column of Florisil (8 g, elution with Et_2O). Removal of the solvent from the eluate, followed by distillation (air-bath temperature 70-75°C/1 Torr) of the residual oil, gave 0.195 g (98 %) of the ketone **38** as a colorless oil that exhibited ir (film): 1703, 1387, 1366 cm^{-1}; ^1H nmr (400 MHz) δ 2.70-2.56 (m, 1H), 2.35-2.20 (m, 2H), 2.19-2.00 (m, 2H), 2.00-1.80 (m, 2H), 1.65-1.45 (m, 2H), 1.44-1.25 (m, 3H), 1.26 (s, 3H, methyl protons), 1.18 (ddd, 1H, J=12,3 Hz), 0.97 (s, 3H, methyl

protons), 0.87 (ddd, 1H, J=13,13,5 Hz), 0.85 (s, 3H, methyl protons). Exact Mass calcd. for $C_{13}H_{22}O$: 194.1670; found: 194.1664.

Preparation of the ketones **58** and **59**



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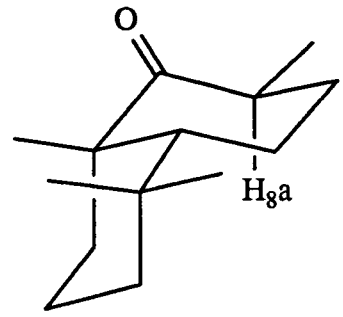
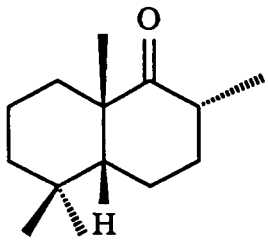


58 **58a**



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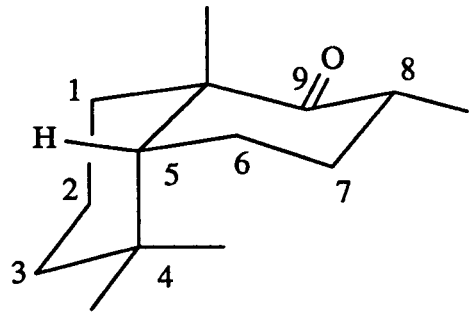


59 **59a**

To a cold (-78°C), stirred solution of LDA (2.268 mmol) in dry THF (15 mL) was added a solution of the ketone **38** (0.400 g, 2.062 mmol) in dry THF (1 mL, washing with 1 mL of THF). The solution was stirred at -78°C for 20 min and at 0°C for 20 min. Methyl iodide (2 mL, 32.120 mmol) was added rapidly and the reaction mixture was stirred at room temperature for 1 h. Water (10 mL), a 5 % aqueous solution of sodium

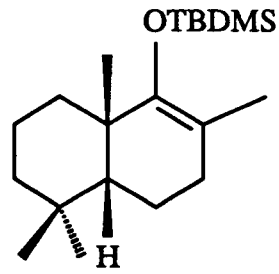
thiosulfate (8 mL) and Et_2O (10 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (3x40 mL). The combined extract was washed with brine (2x30 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil that was shown (glc) to consist of two products in a ratio of 4.2:1. Subjection of this mixture to column chromatography on silica gel (40 g, 98:2 petroleum ether-ethyl acetate), followed by distillation (air-bath temperature 70-75°C/1 Torr) of the oil thus obtained, furnished 0.346 g (81 %) of a mixture of ketones **58** (major compound) and **59** as a colorless oil exhibiting ir (film): 1702, 1390, 1377 cm^{-1}; ^1H nmr (400 MHz) δ 2.87, 2.59 (ddq, ddq, 1H total, ratio of signals ~1:5, J=14,7,7 Hz in each case, H_8a), 1.29, 1.28 (s, s, 3H total, ratio of signals ~5:1, met hyl protons),0 1.08, 0.95, 0.87, 0.78 (s, s, s, s, 6H total, ratio of signals ~5:1:5:1, methyl protons); 1.03, 0.99 (d, d, 3H total, ratio of signals ~5:1, J=7 Hz in each case, C_{23} methyl protons). Exact Mass calcd. for $C_{14}H_{24}O$: 208.1827; found: 208.1819.

A solution of the epimeric mixture of ketones **58** and **59** (0.005 g, 0.024 mmol) in a 0.2 M solution of sodium methoxide in methanol (1 mL) was stirred for 1.75 h at room temperature. The solvent was removed under reduced pressure. Dichloromethane (1 mL), water (1 mL) and a saturated aqueous solution of ammonium chloride (1 mL) were added and the layers were separated. The aqueous phase was extracted with dichloromethane (2x3 mL). The combined extract was washed with brine (1x3 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil which was shown to consist (glc) of the ketones **59** and **58** in a ratio of 6.2:1. Column chromatography (silica gel, 0.85 g, Pasteur pipette, 98:2 petroleum ether-ethyl acetate) of the oil thus obtained enabled the collection of a fraction which contained the ketone **59** exclusively (glc analysis). Solvent removal from this fraction and distillation of the oil thus obtained (air-bath temperature 70-75°C/1 Torr) afforded a sample (homogeneous by tlc and glc analyses) of the ketone **59** which exhibited ir (film): 1703, 1378, 1366 cm^{-1};

^{1}H nmr (400 MHz) δ 2.87 (ddq, 1H, J=14,7,7 Hz, H_8a), 2.29 (br d, 1H, J=13 Hz), 2.26-2.13 (m, 1H, H_6a), 2.04 (br ddd, 1H, J=14,7,6, H_7e), 1.86 (br dd, 1H, J=14,6 Hz, H_6e), 1.73 (dddd, 1H, J=14,14,14,6 Hz, H_7a),1.64 (br d, 1H, J=6 Hz, H_5), 1.59 (dddt, 1H, J=13,13,13,6 Hz, H_{3a}), 1.36 (dddt, 1H, J=13,4,4,4 Hz, H_3e), 1.33-1.25 (m, 1H), 1.28 (s, 3H, methyl protons), 1.16 (ddd, 1H, J=13,13,4 Hz), 0.99 (d, 3H, J=7 Hz, secondary methyl protons), 0.95 (s, 3H, methyl protons), 0.85 (ddd, 1H, J=13,13,4 Hz), 0.78 (s, 3H, methyl protons). In decoupling experiments, irradiation of the signal at δ 2.87 (H_8a) caused the collapse of the signals at δ 2.04 (H_7e) to a broad dd (J=14,6 Hz), δ 1.73 (H_7a) to a ddd (J=14,14,6 Hz) and δ 0.99 (secondary methyl protons) to a singlet; irradiation of the signal at δ 2.04 (H_7e) caused the collapse of the signals at δ 2.87 (H_8a) to a dq (J=14,7 Hz) and δ 1.73 (H_7a) to a ddd (J=14,14,6 Hz), simplified the multiplet at δ 2.26-2.13 (H_6a) and sharpened the broad doublet at δ 1.64 (H_5); irradiation of the signal at δ 1.73 (H_7a) caused the collapse of the signals at δ 2.87 (H_8a) to a dq (J=7,7 Hz), δ 2.04 (H_7e) to an unresolved multiplet and δ 1.86 (H_6e) to a broad doublet (J=14 Hz), and simplified the multiplet at δ 2.26-2.13 (H_6a); irradiation of the signal at δ 1.86 (H_6e) simplified the signals at δ 2.26-2.13 (H_6a) and δ 1.73 (H_7a) and caused the collapse of the signal at δ 2.04 (H_7e) to a dd (J=14,7 Hz); irradiation of the multiplet at δ 2.26-2.13 (H_6a) simplified the signals at δ 1.86 (H_6e), δ 1.73 (H_7a) and δ 2.04 (H_7e), and caused the collapse of the broad doublet at δ 1.64 (H_5) to a broad singlet. Exact Mass calcd. for $C_{14}H_{24}O$: 208.1827; found: 208.1819.

Preparation of the silyl enol ether **60**

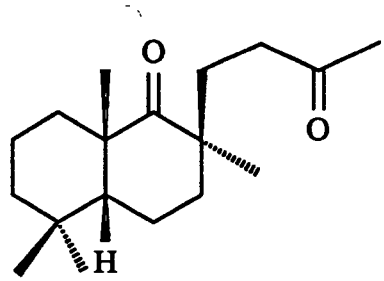
To a cold (-78°C), stirred solution of LDA (1.724 mmol) in dry THF (11.7 mL) was added a solution of the ketones **58** and **59** (0.326 g, 1.567 mmol, 4.2:1 mixture of



60

epimers) in 2 mL of dry THF and the solution was stirred for 30 min. The solution was warmed to 0°C and stirred for 15 min. Hexamethylphosphoramide (0.29 mL, 1.595 mmol) and freshly distilled chlorotrimethylsilane (0.23 mL, 1.812 mmol) were added successively. After the reaction mixture had been stirred at 0°C for 20 min, 1,1,1,3,3,3-hexamethyldisilazane (0.25 mL) was added and the solvent was removed under reduced pressure. Pentane (50 mL) was added to the residue and after the mixture had been stirred for a few seconds, the solution was decanted. To the residue was added saturated aqueous sodium bicarbonate (20 mL) and the mixture was extracted with pentane (2x20 mL). The combined extract was mixed with the previously decanted solution. The solution was washed with brine (3x10 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (silica gel, 25 g, 95:5 pentane-triethylamine). Removal of the volatile material (vacuum pump) from the appropriate fractions gave 0.420 g (96 %) of the silyl enol ether **60** as a colorless oil. This material exhibited ir (film): 1680, 1253, 1190, 843 cm^{-1}; ^1H nmr (400 MHz) δ 2.15-1.96 (m, 2H), 1.96-1.80 (m, 2H), 1.70-1.58 (m, 1H), 1.50 (s, 3H, vinyl methyl protons), 1.45-1.03 (m, 6H), 1.13 (s, 3H, methyl protons), 1.00 (s, 3H, methyl protons), 0.94 (s, 3H, methyl protons), 0.20 (s, 9H, -Si($C\underline{H}_3$)$_3$). Exact Mass calcd. for $C_{17}H_{32}OSi$: 280.2222; found: 280.2220.

Preparation of the diketone **39**

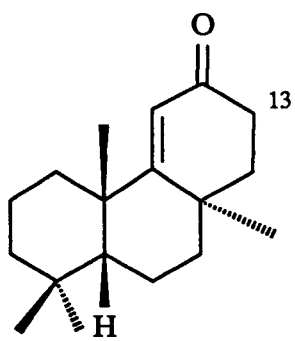


39

To a stirred solution (room temperature) of freshly distilled $TiCl_4$ (0.18 mL, 1.630 mmol) in dry dichloromethane (12 mL) was added freshly distilled $Ti(OPr\text{-}i)_4$ (0.49 mL, 1.630 mmol). The mixture was stirred at room temperature for 3 min and then was cooled to -100°C. A solution of the ethylene ketal of 3-buten-2-one[46] (0.44 mL, 4.840 mmol) and the silyl enol ether **60** (0.415 g, 1.482 mmol) in dry dichloromethane (3.3 mL) was added. The mixture was stirred at -100°C for 15 min. After the reaction mixture had been treated with water (20 mL), dichloromethane (10 mL) was added and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with dichloromethane (2x50 mL). The combined extract was washed with brine (1x20 mL) and the solvent was removed under reduced pressure. The residual material thus obtained was dissolved in 35 mL of a 1:1 solution of THF and 10 % hydrochloric acid and the mixture was stirred at room temperature for 1 h. A saturated aqueous solution of sodium bicarbonate was added slowly until the aqueous phase was neutral. The mixture was extracted with Et_2O (3x30 mL). The combined extract was washed with brine (1x20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude oil thus obtained was purified by column chromatography (silica gel, 30 g, 9:1 petroleum ether-ethyl acetate). Collection

of the appropriate fractions and removal of traces of solvent (vacuum pump) from the oil thus obtained gave 0.073 g (24 %) of a ~1:7 mixture of the ketones **58** and **59**. Distillation (air-bath temperature 120- 130°C/0.4 Torr) of an oil obtained from other fractions gave (0.186 g, 45 %) of the diketone **39** as a colorless oil. This material exhibited ir (film): 1718, 1688, 1367 cm^{-1}; ^1H nmr (400 MHz) δ 2.40 (ddd, 1H, J=18,10,6 Hz, -$C\underline{H}_2$-(CO)-), 2.22 (ddd, 1H, J=18,9,7 Hz, -$C\underline{H}_2$-(CO)-), 2.13 (s, 3H, -(CO)-$C\underline{H}_3$), 2.18-1.65 (m, 7H), 1.58-1.35 (m, 3H), 1.35-1.25 (m, 1H), 1.28 (s, 3H, methyl protons), 1.25-1.15 (m, 1H), 1.15-1.00 (m, 1H), 1.07 (s, 3H, methyl protons), 1.04 (s, 3H, methyl protons), 0.89 (s, 3H, methyl protons). Exact Mass calcd. for $C_{18}H_{30}O_2$: 278.2246; found: 278.2247.

Preparation of the enone **61**

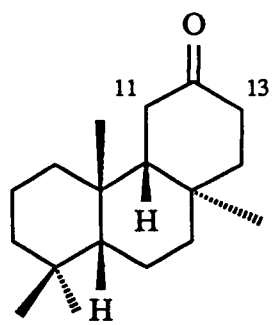


61

The diketone **39** (0.015 g, 0.054 mmol) was dissolved in 1 mL of a 5 % solution of potassium hydroxide in methanol and the reaction mixture was refluxed for 7.5 h. The solution was allowed to cool to room temperature and was neutralized with a 10 % solution of hydrochloric acid. The aqueous phase was extracted with Et_2O (3x5 mL).

The combined extract was washed with brine (1x5 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography (silica gel, 0.85 g, Pasteur pipette, 9:1 petroleum ether-ethyl acetate). Solvent removal under reduced pressure and distillation (air-bath temperature 120-125°C/0.1 Torr) of the oil thus obtained, afforded 0.01 g (71 %) of the enone **61** as a colorless oil, which exhibited ir (film): 3057, 1666, 1587, 1377 cm^{-1}; ^1H nmr (400 MHz) δ 6.08 (s, 1H, vinyl proton), 2.59 (ddd, 1H, J=18,15,6 Hz, H_{13}a), 2.37 (ddd, 1H, J=18,6,2 Hz, H_{13}e), 1.90-1.55 (m, 7H), 1.50-1.20 (m, 5H), 1.39 (s, 3H, methyl protons), 1.33 (s, 3H, methyl protons), 1.23 (s, 3H, methyl protons), 1.13 (br d, 1H, J=12 Hz), 0.97 (s, 3H, methyl protons). Exact Mass calcd. for $C_{18}H_{28}O$: 260.2140; found: 260.2139.

Preparation of the ketone **31**



31

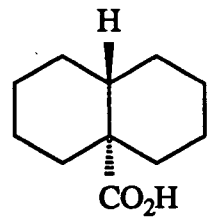
Procedure a. To a cold (-78°C), stirred solution of potassium (0.144 g, 3.690 mmol) in ammonia (8 mL, freshly distilled from sodium) was added a solution of the enone **61** (0.032 g, 0.123 mmol) and tert-butyl alcohol (23μL, 0.246 mmol) in dry Et_2O (0.5 mL). The reaction mixture was refluxed for 1 h. Isoprene was added until the blue

color of the solution disappeared. The ammonia was removed using a stream of argon. Diethyl ether (10 mL) and a saturated aqueous solution of ammonium chloride (5 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with Et_2O (3x10 mL). The combined extract was washed with brine (1x10 mL), dried ($MgSO_4$) and concentrated. The crude product thus obtained was purified by column chromatography on silica gel (3 g, 95:5 petroleum ether-ethyl acetate). Removal of traces of solvent (vacuum pump) from the materials thus obtained gave 0.011 g (34 %) of the enone **61** as an oil and 0.020 g (62 %) of the desired ketone **31** as a white crystalline solid, mp 80- 81°C (recrystallization from petroleum ether).

Procedure b. To a stirred solution (room temperature) of the ketone **56** (0.017 g, 0.065 mmol) in glacial acetic acid (2 mL) was added platinum (IV) oxide (0.002 g, 0.009 mmol). The mixture was stirred under hydrogen gas (1 atm) for 2 h. The mixture was filtered through a plug of Florisil (0.6 g, Pasteur pipette, elution with ethyl acetate) and the eluate was neutralized by adding slowly a saturated aqueous solution of sodium bicarbonate (~3 mL) and enough solid potassium carbonate to bring the aqueous phase to pH 7. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x5 mL). The combined extract was washed with brine (1x5 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual material was dissolved in dry dichloromethane (0.5 mL). The solution was added (room temperature) to a stirred slurry of pyridinium chlorochromate (0.028 g, 0.131 mmol) in dry dichloromethane (1.5 mL). The reaction mixture was stirred for 1 h. Diethyl ether (3 mL) was added and the mixture was filtered through a plug of Florisil (~0.6 g, elution with Et_2O). Removal of the solvent under reduced pressure and column chromatography of the residual oil thus obtained (silica gel, 0.85 g, Pasteur pipette, 95:5 petroleum ether-ethyl acetate), afforded 0.016 g (93 %) of the ketone **31** as a crystalline solid, mp 80-81°C (recrystallization from petroleum ether). This material (which was identical

with the main product obtained from procedure a) exhibited ir (KBr): 1713, 1389 cm^{-1}; ^1H nmr (400 MHz) δ 2.50-2.38 (m, 2H, $\underline{H}_{13}a$, $\underline{H}_{11}e$), 2.29 (dddd, 1H, J=15,5,2,2 Hz, $\underline{H}_{13}e$), 2.25 (dd, 1H, J=15,15 Hz, $\underline{H}_{11}a$), 1.70-0.98 (m, 14H), 1.17 (s, 3H, methyl protons), 1.16 (s, 3H, methyl protons), 1.08 (s, 3H, methyl protons), 0.92 (s, 3H, methyl protons). Exact Mass calcd. for $C_{18}H_{30}O$: 262.2297; found 262.2299.

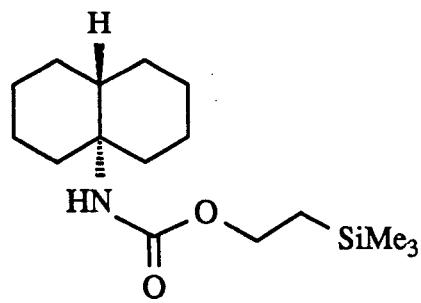
Preparation of the acid **96**



96

To a stirred solution of the acid **97**[70a] (0.125 g, 0.694 mmol) in ethyl acetate (3 mL) was added palladium on activated carbon (0.010 g, 10 % palladium content) at room temperature. The mixture was stirred under hydrogen gas (1 atm) for 3 h. The mixture was filtered through a plug of Florisil (2 g, elution with ethyl acetate) and the solvent was removed under reduced pressure from the filtrate. After removal of traces of solvent (vacuum pump), 0.120 g (95 %) of the saturated acid **96** was obtained as a white solid, mp 128-131°C (petroleum ether-ethyl acetate); ir (KBr): 3024, 1695, 936 cm^{-1}; ^1H nmr (400 MHz) δ 2.09 (br d, 2H, J=12 Hz), 1.93-1.68 (m, 4H), 1.67-1.54 (m, 2H), 1.45-1.10 (m, 9H). Exact Mass calcd. for $C_{11}H_{18}O_2$: 182.1307; found: 182.1306.

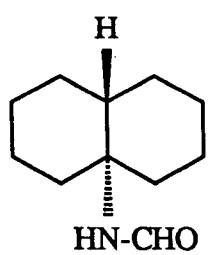
Preparation of the carbamate **99**



99

To a stirred (room temperature) solution of the acid **96** (0.078 g, 0.429 mmol) in toluene (0.3 mL) were added diphenylphosphorazidate[71] (120 μL, 0.600 mmol) and triethylamine (62 μL, 0.443 mmol). The solution was stirred at 80°C for 2 h and then 2-(trimethylsilyl)ethanol (0.30 mL, 2.10 mmol) was added. After the mixture had been stirred for 1.5 h, additional 2-(trimethylsilyl) ethanol (0.20 mL, 1.4 mmol) and triethylamine (62 μL, 0.443 mmol) were added. The reaction mixture was stirred at 80°C for 36 h. The solvent was removed under reduced pressure (water aspirator, then vacuum pump) and Et_2O (3 mL) was added to the residue. The resultant solution was filtered through a plug of silica gel (10 g, elution with Et_2O). The eluate was concentrated and the crude product was purified by column chromatography on silica gel (100 g, 98:2 petroleum ether-Et_2O). Traces of solvent were removed (vacuum pump) from the material thus obtained, affording 0.100 g (79 %) of the carbamate **99** as a colorless oil. This compound exhibited ir (film): 3456, 1729, 1504 cm^{-1}; ^1H nmr (400 MHz) δ 4.37 (br s, 1H, $w_{1/2}$=12 Hz, -NH-(CO)O-), 4.12 (t, 2H, J=8 Hz, -O-CH_2-CH_2-), 2.50 (br d, 2H, J=14 Hz), 1.70 (br d, 2H, J=14 Hz), 1.65-1.21 (m, 9H), 1.15 (ddd, 2H, J=12,12,3 Hz), 1.05-0.94 (m, 4H), 0.04 (s, 9H, methyl protons). Exact Mass calcd. for $C_{16}H_{31}NO_2Si$: 297.2124; found: 297.2122.

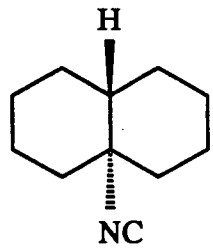
Preparation of the formamide **104**



104

To a stirred solution (room temperature) of the carbamate **99** (0.055 g, 0.185 mmol) in dry THF (1.7 mL) was added a 1 M solution of tetra-*n*-butylammonium fluoride in THF (0.70 mL, 0.70mmol). The solution was stirred at 55°C for 3 h. The solvent was removed under reduced pressure and petroleum ether (30 mL) and a 4:1 solution (30 mL) of saturated aqueous ammonium chloride and concentrated ammonium hydroxide were added to the residue. The phases were separated and the aqueous phase was extracted with petroleum ether (2x30 mL). The combined extract was washed successively with an aqueous solution of saturated ammonium chloride (1x30 mL) and brine (2x30 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (water aspirator, then vacuum pump). The crude oil thus obtained was dissolved in dry Et_2O (1.5 mL) and formic acetic anhydride[73] (0.2 mL, 0.19 mmol) was added. The solution was stirred at room temperature for 2 h. Water (2 mL) and Et_2O (5 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (2x3 mL) and the combined extract was washed with brine (1x5 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and recrystallization (petroleum ether-Et_2O) of the material thus obtained gave 0.031 g (92 % from the carbamate **99**) of the formamide **104** as a white solid, mp 140-143°C; ir (KBr): 3304, 3060, 1662, 1529 cm^{-1}; ^1H nmr (400 MHz) δ 8.21 (d, 0.5 H, J=1.5 Hz, -CHO), 8.16 (d, 0.5H, J=13 Hz, -CHO), 6.08 (br s, 0.5H, -NH-CHO), 5.01 (br s, 0.5H, -NH-CHO), 3.01 (br t, 1H, J=8 Hz), 2.65 (br d, 1H, J=14 HZ), 1.85 (br d, 1H, J=14 Hz), 1.81-1.65 (br t, 2H, J=14 Hz), 1.60-1.49 (m, 2H), 1.49-1.02 (m, 10H). Exact Mass calcd. for $C_{11}H_{19}NO$: 181.1467; found: 181.1472.

Preparation of the isonitrile **105**

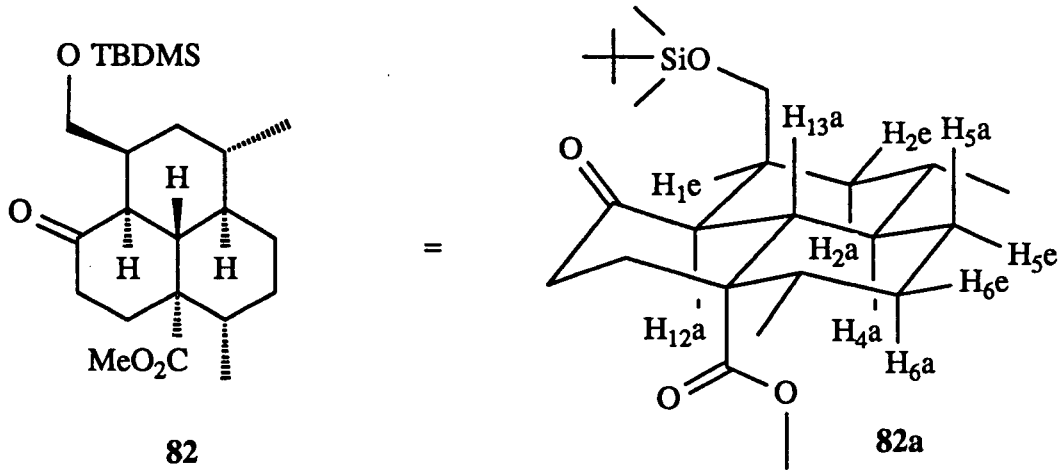


105

To a stirred solution (room temperature) of the formamide **104** (0.020 g, 0.110 mmol) in dry dichloromethane (0.5 mL) were added triphenylphosphine (0.040 g, 0.153 mmol), CCl_4 (12 μL, 0.113 mmol) and triethylamine (20 μL, 0.143 mmol). The reaction mixture was stirred at 60°C for 2 h . An additional amount of CCl_4 (12 μL) was added and stirring was continued for 2 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The solid residue thus obtained was washed several times with a 97:3 pentane-Et_2O solution. The combined washings were concentrated and the crude product was purified by column chromatography (silica gel, 10 g, 99:1 pentane-Et_2O). Recrystallization (pentane-Et_2O) of the material thus obtained afforded 0.0136 g (76 %) of the isonitrile **105** as a white solid, mp 33-35°C; ir (KBr): 2119, 1450 cm^{-1}; ^1H nmr (400 MHz) δ 1.90-1.59 (m, 8H), 1.52-1.10 (m, 9H). Exact Mass calcd. for $C_{11}H_{17}N$: 163.1361; found: 163.1356.

Preparation of the ketone **82**

A solution of the enone **24**[21] (0.0350 g, 0.083 mmol) and tert-butyl alcohol (17 μL, 0.180 mmol) in dry Et_2O (0.8 mL) was added via cannulation to a stirred solution of sodium (0.029 g, 1.261 mmol) in ammonia (3 mL, freshly distilled from sodium). The

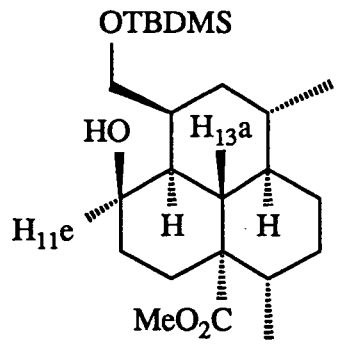


82 **82a**

reaction mixture was refluxed for 40 min. Isoprene was added dropwise until the blue color of the solution disappeared. A saturated solution of aqueous ammonium chloride (10 mL) and Et_2O (5 mL) were added successively. While the resultant mixture was stirred for 4 h, it was warmed occasionally with a water bath (~45°C) and Et_2O was added occasionally. The layers were separated and the aqueous phase was extracted with Et_2O (2x10 mL). The combined extract was dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica gel (20 g, 9:1 petroleum ether-Et_2O), affording 0.0300 g (86 %) of the ketone **82** as a white solid, mp 79-81°C (recrystallization from pentane); ir (film): 1724, 1707, 838, 776 cm^{-1}; ^1H nmr (400 MHz) δ 3.68 (s, 3H, -OC$\underline{H}_3$), 3.65 (dd, 1H, $\underline{J}$=10,5.5 Hz, -C$\underline{H}_2$-OSiMe$_2$Bu-$\underline{t}$), 3.60 (dd, 1H, $\underline{J}$=10,10 Hz, -C$\underline{H}_2$-OSiMe$_2$Bu-$\underline{t}$), 2.62 (ddd, 1H, $\underline{J}$ =13.5,8,3.5 Hz), 2.53 (m, 1H, $\underline{H}_1$e), 2.50-2.35 (m, 2H), 2.32 (dd, 1H, $\underline{J}$=13,4 Hz, $\underline{H}_{12}$a), 2.08 (dddd, 1H, $\underline{J}$ =13,3,3,3 Hz, $\underline{H}_5$e), 1.88 (ddd, 1H, $\underline{J}$=13.5,3,3 Hz, $\underline{H}_2$e), 1.74 (dddd, 1H, $\underline{J}$ =11,11,11,3 Hz, $\underline{H}_4$a), 1.56 (dd, 1H, $\underline{J}$=13,11 Hz, $\underline{H}_{13}$a), 1.52 (m, 1H), 1.47-1.32 (m, 3H, $\underline{H}_6$a, $\underline{H}_6$e, $\underline{H}_5$a), 1.28 (m, 1H), 1.12 (ddd, 1H, $\underline{J}$ =13.5,13.5, 3.5 Hz, $\underline{H}_2$a), 1.00-0.79 (m, 1H), 0.95 (d, 3H, $\underline{J}$=6 Hz, methyl protons), 0.90 (d, 3H, $\underline{J}$ =6 Hz, methyl protons), 0.89 (s, 9H, $\underline{t}$-butyl protons), 0.05 (s, 3H, methyl protons), 0.03 (s, 3H, methyl protons). In decoupling experiments,

irradiation of the signal at δ 1.12 (H_2a) simplified the multiplet at δ 2.53 (H_1e) and caused the collapse of the signal at δ 1.88 (H_2e) to a broad singlet; irradiation of the signal at δ 1.88 (H_2e) simplified the multiplet at δ 2.53 (H_1e) and caused the collapse of the signal at δ 1.12 (H_2a) to a d of d, (J=13.5,3.5 Hz); irradiation of the signal at δ 2.08 (H_5e) simplified the multiplet at δ 1.47-1.32 (H_6a, H_6e, H_5a) and caused the collapse of the signal at δ 1.74 (H_4a) to a ddd (J=11,11,11 Hz); irradiation of the signal at δ 2.32 (H_{12}a) simplified the multiplet at δ 2.53 (H_1e) and caused the collapse of the signal at δ 1.56 (H_{13}a) to a doublet (J =11 Hz). Exact Mass calcd. for $C_{23}H_{39}O_4Si$ (M^+-Me): 407.2618; found: 407.2610.

Preparation of the alcohol **88**

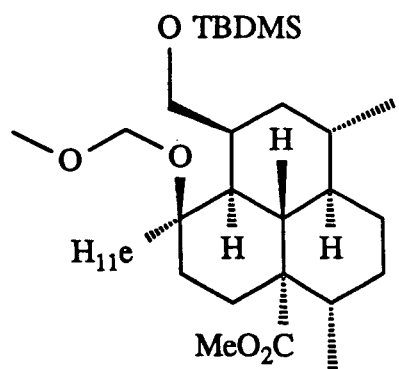


88

To a cold (-78°C), stirred solution of the ketone **82** (0.06 g, 0.142 mmol) in dry THF (3.30 mL) was added a 1.0 M solution of lithium tri-*sec*-butylborohydride in THF (0.20 mL, 0.200 mmol). The solution was stirred for 3 h at -78°C and for 1 h at 0°C. A 10 % aqueous solution of sodium hydroxide (0.5 mL) and a 30 % aqueous solution of hydrogen peroxide (0.33 mL) were added and the mixture was stirred at room

temperature for 5 h. Water (20 mL) and diethyl ether (20 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3x25 mL) and the combined extract was washed successively with a 5 % aqueous solution of sodium bisulfite (1x20 mL) and brine (2x20 mL). The extract was dried ($MgSO_4$) and concentrated. Column chromatography of the crude product on silica gel (10 g, 9:1 pentane-Et_2O) and removal of traces of solvent (vacuum pump) from the material thus obtained, afforded 0.059 g (98 %) of the alcohol **88** as a colorless oil. This product exhibited ir (film): 3453, 1724, 1256, 1170, 1072 cm^{-1}; ^1H nmr (400 MHz) δ 5.26 (t, 1H, J=2.5 Hz, -OH, D_2O exchanged), 4.10 (dd, 1H, J=9.5,11 Hz, -CH_2-OSiMe$_2$Bu-t), 3.91 (br s, 1H, $w_{1/2}$=7.5 Hz, $H_{11}e$, sharpened when D_2O is added), 3.66 (s, 3H, -(CO)OCH_3), 3.49 (br d, 1H, J=11 Hz, -CH_2-OSiMe$_2$Bu-t), 2.16 (ddd, 1H, J=13,3.5,3.5 Hz), 2.00-1.86 (m, 3H), 8.20 (m, 1H), 1.66 (dd, 1H, J=11.5,11.5 Hz, $H_{13}a$), 1.81-1.10 (m, 8H), 0.96 (d, 3H, J=7 Hz, methyl protons), 0.89 (s, 9H, t-butyl protons), 0.93-0.80 (m, 2H), 0.84 (unresolved d, 3H, methyl protons), 0.10 (s, 3H, methyl protons), 0.09 (s, 3H, methyl protons). Exact Mass calcd. for $C_{24}H_{42}O_3Si$ (M^+-H_2O): 406.2903; found: 406.2903.

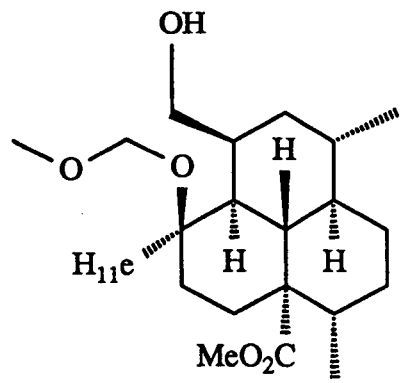
Preparation of the ester acetal **89**



89

To a stirred solution (room temperature) of the alcohol **88** (0.279 g, 0.596 mmol) in dry acetonitrile (7.1 mL) were added successively N,N-diisopropylethylamine (0.47 mL, 2.70 mmol), 4-N,N-dimethylaminopyridine (0.003 g, 0.025 mmol) and chloromethyl methyl ether (0.20 mL, 2.60 mmoL). The mixture was refluxed for 5 h and then was allowed to cool to room temperature. The solvent was removed under reduced pressure. Diethyl ether (40 mL) and a saturated aqueous solution of sodium bicarbonate (20 mL) were added to the crude product. The layers were separated and the aqueous phase was extracted with Et_2O (2x40 mL). The combined extract was washed with brine (2x40 mL) and dried ($MgSO_4$). Removal of the solvent and column chromatography of the crude oil thus obtained (silica gel, 45 g, 9:1 pentane-Et_2O) gave 0.295 g (96 %) of the ester acetal **89** as a colorless oil, after removal of traces of solvent (vacuum pump). This compound exhibited ir (film) 1724, 1082, 1045 cm^{-1}; ^1H nmr (400 MHz) δ 4.65 (s, 2H, -O-C$\underline{H}_2$-OMe), 3.87 (dd, 1H, J=10.5, 5.5 Hz, -C$\underline{H}_2$-OSiMe$_2$Bu-t), 3.72 (br s, 1H, $w_{1/2}$=7.5 Hz, $\underline{H}_{11}$e), 3.66 (s, 3H, -(CO)OC$\underline{H}_3$), 3.61 (dd, 1H, J=10.5,10.5 Hz, -C$\underline{H}_2$-OSiMe$_2$Bu-t), 3.39 (s, 3H, -O-CH$_2$-OC$\underline{H}_3$), 2.18 (m, 1H), 2.05-1.6 (m, 5H), 1.58-1.10 (m, 8H), 0.93 (d, 3H, J=6.5 Hz, methyl protons), 0.90 (s, 9H, t-butyl protons), 0.86 (d, 3H, J=6.5 Hz, methyl protons), 1.07-0.80 (m, 2H), 0.03 (s, 3H, methyl protons), 0.02 (s, 3H, methyl protons). Exact Mass calcd. for $C_{24}H_{43}O_4Si$ (M^+-C_2H_5O): 423.2931; found: 423.2932.

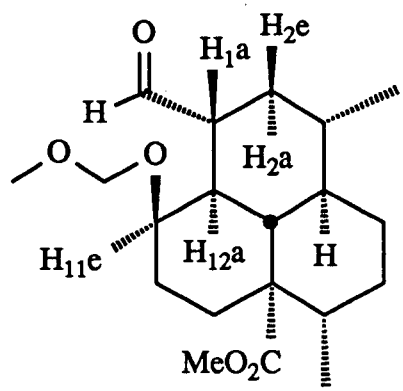
Preparation of the alcohol **90**



90

To the ester acetal **89** (0.085 g, 0.182 mmol) was added a 1 M solution of tetra-*n*-butylammonium fluoride in THF (2.44 mL, 2.44 mmol). The solution was stirred at room temperature for 5 h. A saturated aqueous solution of sodium bicarbonate (10 mL) was added and the resultant mixture was extracted with Et_2O (3x20 mL). The combined extract was washed with brine (2x20 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and column chromatography of the crude product (silica gel, 14 g, 7:3 Et_2O-petroleum ether) afforded, after removal of traces of solvent (vacuum pump) from the oil thus obtained, 0.062 g (96 %) of the alcohol **90** as a colorless oil. This compound exhibited ir (film): 3417, 1723, 1039 cm^{-1}; ^1H nmr (400 MHz) δ 4.73-4.67 (m, 2H, -O-C$\underline{H}_2$-OMe), 3.92-3.81 (m, 1H, -C$\underline{H}_2$-OH, transformed to a dd, J=12,6 Hz when D_2O was added), 3.88 (br s, 1H, $\underline{H}_{11}$e), 3.68 (, 3H, -(CO)OC$\underline{H}_3$), 3.59 (ddd, 1H, J=12,7,4 Hz, -C$\underline{H}_2$-OH, transformed to a dd, J =12,4 Hz when D_2O was added), 3.44 (s, 3H, -CH_2-OC$\underline{H}_3$), 3.20 (t, 1H, J=7 Hz, -O$\underline{H}$, D_2O exchanged), 2.24-2.15 (m, 1H), 2.09 (ddd, 1H, J=13,6,3 Hz), 2.04-1.94 (m, 2H), 1.92-1.71 (m, 2H), 1.71-1.15 (m, 9H), 0.95 (d, 3H, J=7 Hz, methyl protons), 1.01-0.82 (m, 1H), 0.85 (d, 3H, J=6 Hz, methyl protons). Exact Mass calcd. for $C_{20}H_{34}O_5$: 354.2406; found: 354.2408.

Preparation of the aldehyde **92**

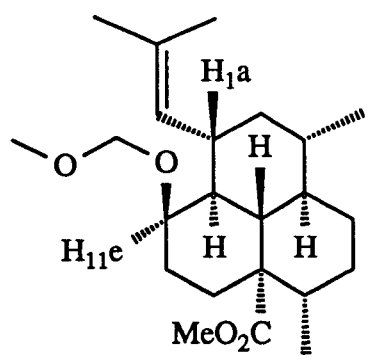


92

To a stirred slurry of pyridinium chlorochromate (0.280 g, 1.300 mmol) and sodium acetate (0.028 g, 0.619 mmol) in dry dichloromethane (9 mL) (room temperature) was added a solution of the alcohol **90** (0.218 g, 0.619 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred for 2 h at room temperature. Dry Et_2O (10 mL) was added and the mixture was filtered through a column of Florisil (20 g, elution with Et_2O). The solvent was removed from the eluate under reduced pressure and the crude product was dissolved in dry methanol (3.5 mL). A 0.20 M solution of sodium methoxide in methanol (0.3 mL) was added and the solution was stirred at room temperature for 6.5 h. The solvent was removed under reduced pressure and Et_2O (30 mL) and a saturated aqueous solution of ammonium chloride (10 mL) were added to the residue. The aqueous phase was extracted with Et_2O (2x30 mL) and the combined extract was washed with brine (1x30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography on silica gel (35 g, 7:3 petroleum ether-Et_2O). Collection of the appropriate fractions, concentration and removal of traces of solvent (vacuum pump)

afforded 0.161 g (74 %) of the aldehyde **92** as a colorless oil exhibiting ir (film): 2704, 1724, 1377, 1042 cm^{-1}; ^1H nmr (400 MHz) δ 9.58 (d, 1H, J=3.5 Hz, -CHO), 4.65 (d, 1H, J=7 Hz, -O-CH_2-OMe), 4.56 (d, 1H, J =7 Hz, -O-CH_2-OMe), 3.69 (br s, 4H, -(CO)OCH_3, $H_{11}e$), 3.37 (s, 3H, -CH_2-OCH_3), 2.67 (dddd, 1H, J=12, 11.5,3.5,3.5 Hz, H_1a), 2.28 (m, 1H), 2.10-1.85 (m, 3H), 1.73 (dd, 1H, J=10,3.5 Hz, H_2e), 1.60-1.02 (m, 9H), 0.94 (d, 3H, J=6 Hz, methyl protons), 0.91 (d, 3H, J=7 Hz, methyl protons), 1.00-0.81 (m, 1H). In decoupling experiments, irradiation of the signal at δ 9.58 (formyl group proton) caused the collapse of the dddd at δ 2.67 (H_1a) to a ddd (J=12,11.5,3.5 Hz); irradiation of the signal at δ 2.67 (H_1a) caused the collapse of the doublet at δ 9.58 (formyl group proton) to a singlet, simplified the multiplets at δ 2.10-1.85 ($H_{12}a$?) and δ 1.60-1.02 (H_2a ?), and changed the dd at δ 1.73 (H_2e) to a doublet (J=10 Hz). Exact Mass calcd. for $C_{19}H_{28}O_4$ (M^+-CH_4O): 320.1987; found: 320.1990.

Preparation of the ester alkene **93**



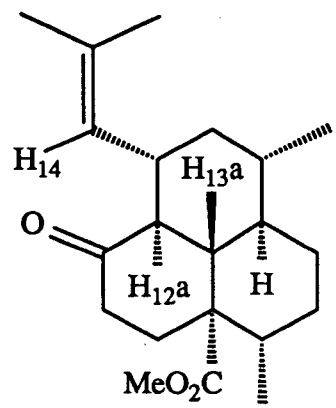
93

Sodium hydride (0.021 g, 80 % dispersion in oil, 0.700 mmol) was placed in a flame dried, three-necked flask equipped with a reflux condenser and was washed with

pentane (3x0.5 mL). The system was alternately evacuated (vacuum pump) and filled with argon (3 times). Freshly distilled dimethyl sulfoxide (7 mL) was introduced and the stirred mixture was heated at 70°C until evolution of hydrogen ceased. The transparent solution thus obtained was allowed to cool to room temperature. Isopropyltriphenylphosphonium bromide (0.278 g, 0.720 mmol, recrystallized from pentane- dichloromethane and dried overnight, (vacuum pump)) was added in small portions through the top of the condenser. A current of argon was introduced via a needle inserted through a septum on the flask while the phosphonium bromide was being added. The dark red solution obtained after the addition was stirred at room temperature for 15 min. A solution of the aldehyde **92** (0.062 g, 0.164 mmol) in dry dimethyl sulfoxide (2 mL) was added using a cannula. The reaction mixture was stirred for 2 h at room temperature. Water (40 mL) was added and the mixture was extracted with 1:1 pentane-Et_2O (2x40 mL). Solid NaCl was added to the aqueous phase which was then extracted with 1:1 pentane-Et_2O (1x40 mL) and pentane (1x40 mL). The combined extract was washed with water (5x20 mL) and brine (2x20 mL), was dried ($MgSO_4$) and then was concentrated. The crude product thus obtained was purified by column chromatography on silica gel (10 g, 92:8 petroleum ether-Et_2O). Collection of the appropriate fractions, concentration and removal of traces of solvent (vacuum pump) gave 0.062 g (~93 %, small amount of Et_2O present) of the ester alkene **93** as a colorless oil exhibiting ir (film): 1725, 1376, 1171, 1147, 1045 cm^{-1}; ^1H nmr (400 MHz) δ 4.89 (br d, 1H, J=10 Hz, vinyl proton), 4.63 (d, 1H, J=6 Hz, O-C$\underline{H}_2$-OMe), 4.53 (d, 1H, J=6 Hz, -O-C$\underline{H}_2$-OMe), 3.57 (s, 3H, -(CO)-OC$\underline{H}_3$), 3.65 (br s, 1H, $w_{1/2}$=8 Hz, $\underline{H}_{11}$e), 3.35 (s, 3H, -CH_2-OC$\underline{H}_3$), 2.45-2.33 (m, 1H, $\underline{H}_1$a), 2.32 -2.24 (m, 1H), 2.05-1.80 (m, 4H), 1.66 (d, 3H, J=1 Hz, isopropylidene methyl protons), 1.59 (d, 3H, J=1 Hz, isopropylidene methyl protons), 1.58-1.10 (m, 9H), 0.98-0.80 (m, 1H), 0.90 (d, 3H, J=7 Hz, methyl protons), 0.86 (d, 3H, J=7 Hz, methyl protons). In a decoupling experiment irradiation of the

doublet at δ 4.89 (vinyl proton) simplified the multiplet at δ 2.45-2.23 (H_1a) and caused the collapse of the doublets at δ 1.66 and δ 1.59 (isopropylidene methyl protons) to the corresponding singlets. Exact Mass calcd. for $C_{23}H_{38}O_4$: 378.2770; found: 378.2765.

Preparation of the keto ester **76**

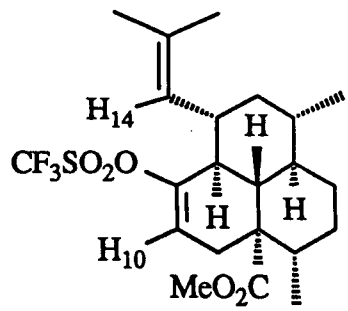


76

To a cold (-78°C), stirred solution of the ester alkene **93** (0.062 g, 0.164 mmol) in dry dichloromethane (1.5 mL) was added a 1.3 M solution of dimethylboron bromide (0.195 mmol) in dry dichloromethane (0.15 mL). After the solution had been stirred at -78°C for 20 min, THF (2.1 mL) and a saturated aqueous solution of sodium bicarbonate (1 mL) were added simultaneously. The mixture was warmed to room temperature. Brine (5 mL) and Et_2O (5 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (2x5 mL). The combined extract was washed with brine (1x5 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (water aspirator, then vacuum pump) and the crude product was dissolved in dry dichloromethane (1 mL). This solution was added using a cannula (washing with 0.5 mL of dry dichloromethane) to a stirred slurry of pyridinium chlorochromate (0.095 g, 0.440

mmol) and anhydrous sodium acetate (0.012 g, 0.146 mmol) in dry dichloromethane (2 mL). The mixture was stirred at room temperature for 2 h. Diethyl ether (3 mL) was added and the resultant suspension was filtered through a column of Florisil (10 g, elution with Et_2O). Removal of the solvent from the eluate gave a crude product that was purified by column chromatography (silica gel, 11 g, 9:1 pentane-Et_2O). Removal of traces of solvent (vacuum pump) from the material thus obtained afforded 0.046 g (85 %) of keto ester **76** as a white solid, mp 91-93°C (recrystallization from pentane-Et_2O); ir (KBr) 1724, 1717, 1375 cm^{-1}; ^1H nmr (400 MHz) δ 4.67 (dm, 1H, J=9 Hz, H_{14}), 3.77 (s, 3H, $-CO_2CH_3$), 2.82 (ddd, 1H, J=13.5,6,3 Hz), 2.65-2.54 (m, 1H), 2.48 (ddd, 1H, J =13.5,13.5,6 Hz), 2.33-2.23 (m, 1H), 2.27 (dd, 1H, J=11.5,10 Hz, $H_{12}a$), 1.06 (dq, 1H, J=13.5,3.5 Hz), 1.96 (m, 1H), 1.73 (d, 3H, J=1.5 Hz, isopropylidene methyl protons), 1.62 (d, 3H, J=1 Hz, isopropylidene methyl protons), 1.57-1.24 (m, 7H), 1.17 (dd, 1H, J=12.5,11.5 Hz, $H_{13}a$), 0.93 (d, 3H, J =7 Hz, methyl protons), 0.88 (d, 3H, J=6 Hz, methyl protons), 0.97-0.78 (m, 1H). Exact Mass calcd. for $C_{21}H_{32}O_3$: 332.2351; found: 332.2344.

Preparation of the enol triflate **94**

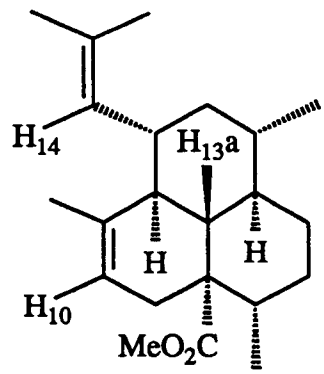


94

To a cold (-48°C), stirred solution of LDA (0.561 mmol) in dry THF (1.1 mL) was added a solution of the keto ester **76** (0.046 g, 0.139 mmol) in dry THF (0.5 mL, washing with 0.5 mL of dry THF). The solution was stirred for 1 h. A solution of hexamethylphosphoramide (25μL, 0.138 mmol) and N-phenyltrifluoromethanesulfonimide (0.150 g, 0.420 mmol) in dry THF (0.5 mL) was added. The reaction mixture was stirred for 15 min, was allowed to warm to room temperature, and then was stirred for an additional 30 min. The solution was poured into a vigorously stirred saturated aqueous solution of sodium bicarbonate (15 mL). The mixture was extracted with pentane (3x20 mL) and the combined extract was washed with brine (2x10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (8 g, pentane, then 97:3 pentane-Et_2O). After removal of traces of solvent from each fraction, 0.01 g of the starting material was recovered and 0.0335 g (67 %, based on recovered starting material) of the enol triflate **94** was obtained as a colorless oil. The enol triflate **94** exhibited ir (film): 1728, 1207 cm^{-1}; ^{1}H-nmr (400 MHz) δ 5.73 (br d, 1H, J=7 Hz, H_{10}), 5.04 (br d, 1H, J =8 Hz, H_{14}), 3.64 (s, 3H, -(CO)OCH_3), 3.03 (dd, 1H, J=18,7 Hz), 2.25-2.38 (m, 2H), 2.10 (m, 1H), 1.83 (m, 1H), 1.66 (d, 3H, J=1 Hz, isopropylidene methyl protons), 1.57 (d, 3H, J=1 Hz, isopropylidene methyl protons), 0.90 (d, 3H, J=7 Hz, methyl protons), 0.88 (d, 3H, J=6 Hz, methyl protons); Exact Mass calcd. for $C_{22}H_{31}F_3O_5S$: 464.1844; found: 464.1852.

Preparation of the ester diene **75**

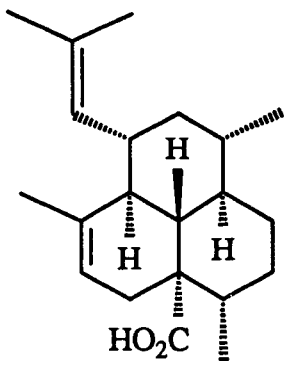
A solution of the enol triflate **94** (0.066 g, 0.142 mmol) in dry Et_2O (0.5 mL, washing with 0.5 mL of Et_2O) was added to a cold (-10°C) solution of Me_2CuLi[68] (1.422



75

mmol) in Et_2O (4 mL). The reaction mixture was stirred at -10°C for 2 h. A saturated aqueous solution of ammonium chloride-ammonium hydroxide (pH=8, 10 mL) was added and stirring was continued for 1 h. The mixture was extracted with Et_2O (3x20 mL). The combined extract was washed with brine (1x20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (11 g, 97:3 pentane-Et_2O). Removal of traces of solvent (vacuum pump) from the material thus obtained gave 0.043 g (92 %) of the ester diene **75** as a colorless oil, which exhibited ir (film): 1726, 1456, 1381 cm^{-1}; ^1H nmr (400 MHz) δ 5.39-5.34 (m, 1H, $\underline{H}_{10}$), 5.09 (dm, 1H, $\underline{J}$=9 Hz, $\underline{H}_{14}$), 3.62 (s, 3H, -(CO)OC$\underline{H}_3$), 2.83 (br dd, 1H, $\underline{J}$=17,6 Hz), 2.14 (ddd, 1H, $\underline{J}$=10.5,10,5 Hz), 2.04-0.95 (m, 1H), 1.84 (br dd, 1H, $\underline{J}$=10.5,10.5 Hz), 1.75-1.48 (m, 2H), 1.63 (d, 3H, $\underline{J}$=1 Hz, isopropylidene methyl protons), 1.60 (br d, 3H, $\underline{J}$=1 Hz, vinylic methyl protons), 1.56 (d, 3H, $\underline{J}$=1 Hz, isopropylidene methyl protons), 1.48-1.34 (m, 3H), 1.18 (dd, 1H, $\underline{J}$=10.5,10.5 Hz, $\underline{H}_{13}$a), 1.14-0.80 (m, 4H), 0.88 (d, 3H, $\underline{J}$=6 Hz, methyl protons), 0.84 (d, 3H, $\underline{J}$=6.5 Hz, methyl protons). Exact Mass calcd for $C_{22}H_{34}O_2$: 330.2559; found: 330.2561.

Preparation of the acid **95**



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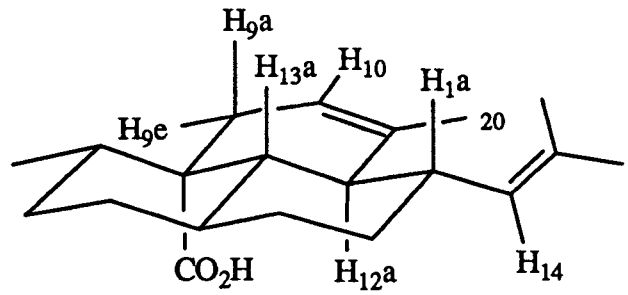
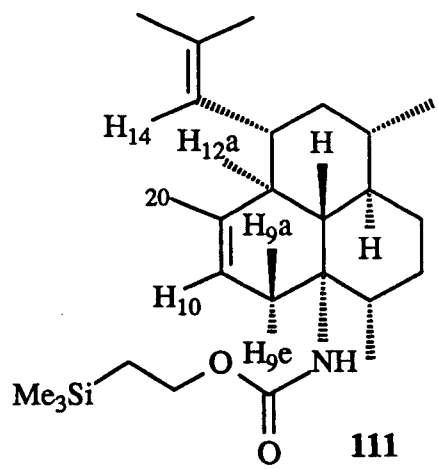


95 **95a**

An 80 % dispersion of sodium hydride (0.05 g, 1.67 mmol) in mineral oil was washed with dry THF (3x1 mL). To this material was added dry THF (2.5 mL). The stirred mixture was cooled to at 0°C, and then benzeneselenol (0.17 mL, 1.600 mmol) and hexamethylphosphoramide (0.565 mL, 3.250 mmol) were added. The resulting orange colored solution was transferred by cannulation to a flask equipped with a reflux condenser. To this solution (room temperature) was added a solution of the ester diene **75** (0.05 g, 0.150 mmol) in dry THF (2x0.5 mL). The mixture was refluxed for 54 h, cooled to room temperature, and the solvent was removed under reduced pressure. To the residual material thus obtained were added slowly water (2 mL) and a 10 % solution of hydrochloric acid (2 mL). The mixture was extracted with Et_2O (5x15 mL). The combined extract was washed with water (5x20 mL) and brine (5x20 mL). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, 8 g; 4:1, then 3:2 hexane-Et_2O). After removal of traces of solvent (vacuum pump) from the material thus obtained, 0.0405 g (85 %) of the acid **95** was obtained as a white solid, mp 174-176°C (recrystallization from pentane-Et_2O); ir (KBr): 3280-2380 (br), 1687, 1444, 1277 cm^{-1}; ^1H nmr (400 MHz) δ 5.45-5.36 (m, 1H,

$\underline{H}_{10}$), 5.10 (dm, 1H, $\underline{J}$=9 Hz, $\underline{H}_{14}$), 2.80 (dd, 1H, $\underline{J}$=17,6 Hz, $\underline{H}_9$e), 2.21-2.10 (m, 1H, $\underline{H}_1$a), 2.10-2.01 (m, 1H), 1.95 (br dd, 1H, $\underline{J}$=10.5,10.5 Hz, $\underline{H}_{12}$a), 1.71 (br d, 1h, $\underline{J}$=17 Hz, $\underline{H}_9$a), 1.64 (d, 3H, $\underline{J}$=1 Hz, isopropylidene methyl protons), 1.63 (d, 3H, $\underline{J}$=1 Hz, C_{20} methyl protons), 1.56 (d, 3H, $\underline{J}$=1 Hz, isopropylidene methyl protons), 1.21 (dd, 1H, $\underline{J}$=10.5, 10.5 Hz, $\underline{H}_{13}$a), 1.14-1.00 (m, 1H), 0.93 (d, 3H, $\underline{J}$=6.5 Hz, methyl protons), 0.87 (d, 3H, $\underline{J}$=6.5 Hz, methyl protons). In decoupling experiments, irradiation of the signal at δ 5.45-5.36 (H_{10}) caused the collapse of the signal at δ 2.80 (H_9e) to a doublet ($\underline{J}$=17 Hz) and sharpened the doublet at δ 1.71 (H_9a); irradiation of the signal at δ 5.10 (H_{14}) caused the collapse of the signal at δ 2.21-2.10 (H_1a) to a ddd ($\underline{J}$=10.5,10.5,4 Hz) and changed each of the doublets at δ 1.64 and 1.56 (isopropylidene methyl protons) to a singlet. Exact Mass calcd. for $C_{21}H_{32}O_2$: 316.2403; found: 316.2403.

Preparation of the carbamate **111**



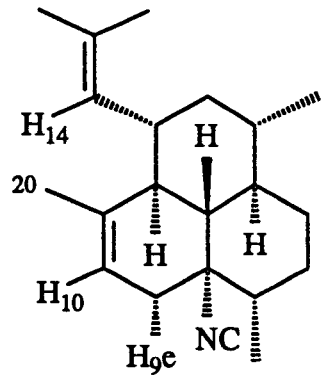
111

To a stirred solution (room temperature) of the acid **95** (0.019 g, 0.06 mmol) in dry toluene (0.3 mL) were added triethylamine (14 μL, 0.100 mmol) and diphenylphosphoryl azide (14 μL, 0.070 mmol). The solution was stirred at 80°C for 23

h and then 2-(trimethylsilyl)ethanol (0.100 mL, 0.700 mmol) and triethylamine (0.100 mL, 0.720 mmol) were added. After the mixture had been stirred at 90°C for 24 h, additional 2-(trimethylsilyl)ethanol (0.100 mL) and triethylamine (0.100 mL) were added. The reaction mixture was stirred at 90°C for 24 h. The solvent was removed under reduced pressure (water aspirator, then vacuum pump) and Et_2O (3 mL) was added to the residue. The resultant solution was filtered through a plug of silica gel (2 g, elution with Et_2O). The eluate was concentrated and the crude product was purified by column chromatography on silica gel (20 g, 95:5 pentane-Et_2O). After removal of traces of solvent (vacuum pump) from the oil thus obtained, 0.025 g (96 %) of the carbamate **111** was obtained as a colorless oil. This compound exhibited ir (film): 3446, 3035, 1736, 1508, 1250, 1224 cm^{-1}; ^1H nmr (400 MHz) δ 5.34 (br d, 1H, J=5 Hz, H_{10}), 5.11 (dm, 1H, J=9 Hz, H_{14}), 4.27 (br s, 1H, $w_{1/2}$=4 Hz, -(CO)-NH-), 4.13-4.02 (m, 2H, -(CO)O-CH_2-), 3.68 (br d, 1H, J=16 Hz, H_9e), 2.30-2.20 (m, 1H), 2.00 (dddd, 1H, J=13,4,4,4 Hz), 1.81 (br dd, 1H, J=10,10 Hz, H_{12}a), 1.73 (br d, 1H, J=16 Hz, H_9a), 1.68-1.64 (m, 6H, isopropylidene methyl protons, C_{20} methyl protons), 1.58 (d, 3H, J=1 Hz, isopropylidene methyl protons), 1.55-1.10 (m, 8H), 1.00-0.85 (m, 2H), 0.96 (d, 3H, J=7 Hz, methyl protons), 0.88 (d, 3H, J=7 Hz, methyl protons), 0.80-0.70 (m, 1H), 0.03 (s, 9H, methyl protons). Exact Mass calcd. for $C_{26}H_{45}NO_2Si$: 431.3219; found: 431.3228.

Preparation of (±)-8-isocyano-10,14-amphilectadiene ((±)-23)

To a stirred solution (room temperature) of the carbamate **111** (0.020 g, 0.046 mmol) in dry THF (0.9 mL) was added a 1 M solution of tetra-n-butylammonium fluoride in THF (0.38 mL, 0.38 mmol). The solution was stirred at 55°C for 2 h. The

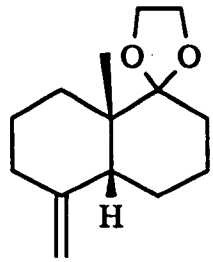


23

solvent was removed under reduced pressure and pentane (6 mL) and a 4:1 solution of saturated aqueous ammonium chloride and 30 % aqueous ammonium hydroxide (3.6 mL) were added to the residue. The phases were separated and the aqueous phase was extracted with pentane (2x6 mL). The combined extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure (water aspirator, then vacuum pump). The crude oil thus obtained was dissolved in Et_2O (0.9 mL) and formic acetic anhydride[73] (75 μL, 0.57 mmol) was added. The solution was stirred at room temperature for 2 h. Water (3 mL) and Et_2O (5 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (2x6 mL) and the combined extract was washed with brine (1x3 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (water aspirator, then vacuum pump). The crude oil thus obtained was dissolved (room temperature) in dry dichloromethane (0.4 mL) and triphenylphosphine (0.032 g, 0.122 mmol), CCl_4 (11 μL, 0.104 mmol) and triethylamine (43 μL, 0.308 mmol) were added. The mixture was stirred at 55°C for 1 h. The solvent was removed under reduced pressure and the residual material was washed several times with a 97:3 pentane-Et_2O solution. The combined washings were concentrated and the crude product was purified by column chromatography (silica gel, 5 g, initial elution with pentane, then the polarity

of the eluate was increased gradually to 97:3 pentane-Et_2O). Collection and concentration of the appropriate fractions gave 0.011 g (80 % from the carbamate **111**) of the isonitrile (±)-**23** as a white solid that exhibited mp 79-81°C (recrystallization from pentane-Et_2O). This compound exhibited ir (KBr): 2126, 1447, 1379 cm^{-1}; ^1H nmr (400 MHz) δ 5.26 (m, 1H, $w_{1/2}$=11 Hz, $\underline{H}_{10}$), 5.15 (dm, 1H, $\underline{J}$=9 Hz, $\underline{H}_{14}$), 2.45 (br dd, 1H, $\underline{J}$=17, 4.5 Hz, $\underline{H}_9$e), 2.31-2.19 (m, 1H), 2.12-1.92 (m, 3H), 1.69 (d, 3H, $\underline{J}$=1 Hz, C_{20} methyl protons), 1.66 (d, 3H, $\underline{J}$=1 Hz, isopropylidene methyl protons), 1.57 (d, 3H, $\underline{J}$=1 Hz, isopropylidene methyl protons), 1.02 (d, 3H, $\underline{J}$=6.5 Hz, methyl protons), 0.88 (d, 3H, $\underline{J}$=6 Hz, methyl protons). The ^1H nmr spectrum of this material was identical with that of natural 8-isocyano-10,14-amphilectadiene **23**[26]; ^{13}C nmr (75.3MHz, $CDCl_3$, proton decoupled) δ 15.4, 17.5, 19.5, 25.1, 25.7, 29.1, 28.8, 37.2, 37.9, 40.6, 41.4, 42.1, 43.5, 44.8, 49.5, 63.2 (t, $\underline{J}_{C-^{14}N}$=4.5 Hz), 118.8, 126.7, 133.4, 137.6, 154.4 (t, $\underline{J}_{C-^{14}N}$=4.5 Hz). These chemical shifts agree well with those published[26] for natural 8-isocyano-10,14-amphilectadiene. Exact Mass calcd. for $C_{21}H_{31}N$: 297.2457; found: 297.2461.

Preparation of the ketal alkene **137**

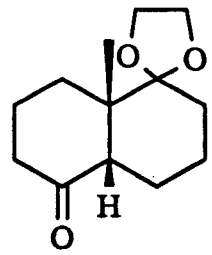


137

To a solution of the ketone **17**[23] (0.115 g, 0.646 mmol) in 2.6 mL of dry benzene was added 0.043 mL (0.775 mmol) of ethylene glycol, and 10 mg of silica gel containing 5% p-toluenesulfonic acid. The mixture was refluxed for 2.5 h under a Dean-Stark water trap. After the mixture had been cooled to room temperature, the solvent was removed under reduced pressure and the remaining crude material was subjected to column chromatography on silica gel (10 g, elution with 95:5 petroleum ether-Et_2O). Collection and concentration of the appropriate fractions, followed by removal of traces of solvent (vacuum pump) afforded 0.121 g (84%) of the ketal alkene **137** as a colorless oil which exhibited ir (film): 3067, 1650, 1092 cm^{-1}; ^1H nmr (400 MHz) δ 4.66-4.60 (m,2H,C=CH_2), 4.03-3.87 (m, 4H, ketal protons), 2.32-2.17 (m, 2H), 2.07 (dd, 1H, J=14,4 Hz), 1.90-1.47 (m, 6H), 1.43 (br d, 1H, J= 14 Hz), 1.38-1.17 (m, 3H), 0.88 (s, 3H, methyl protons). Exact Mass calcd. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1617.

Preparation of the keto ketal **138**

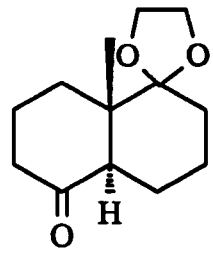
To a mixture of the ketal alkene **137** (0.074 g, 0.333 mmol), CCl_4 (2 mL), acetonitrile (2 mL), water (3 mL) and sodium periodate (0.300 g, 1.403 mmol) was added ruthenium (IV) oxide (0.003 g, 6.8 mol %). The mixture was stirred vigorously at



138

room temperature for 2 h. Gas-liquid chromatographic analysis of the organic phase at this stage showed that almost half of the starting material had not reacted. Therefore 1.5 mL of water, 1 mL of CCl_4, 1 mL of acetonitrile and 0.003 g of RuO_2 were added and vigorous stirring was continued for 3 h. Gas-liquid chromatographic analysis showed that no starting material was present in the reaction mixture. Dichloromethane (10 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3x10 mL) and the combined extract was dried ($MgSO_4$) and concentrated. The residue was diluted with 20 mL of Et_2O and the resultant mixture was filtered through a celite pad. Concentration of the filtrate gave a crude product which was purified by column chromatography on silica gel (10 g, 4:1 petroleum ether-Et_2O). Removal of traces of solvent (vacuum pump) from the oil thus obtained gave 0.038 g (51 %) of the ketone **138** as a colorless oil. This material was homogeneous by tlc and glc analyses and exhibited ir (film): 1712, 1089 cm^{-1}; ^1H nmr (400 MHz) δ 4.02-3.87 (m, 4H, ketal protons), 2.49 (ddd, 1H, J=13,12,7 Hz), 2.36 (dd, 1H, J=12,5 Hz), 2.25-2.19 (m, 1H), 2.11 (ddd, 1H, J=14,14,5 Hz), 2.04-1.94 (m, 1H), 1.92-1.69 (m, 4H), 1.67-1.50 (m, 4H), 0.95 (s, 3H, methyl protons). Exact Mass calcd. for $C_{14}H_{20}O_3$: 224.1412; found: 222.1414.

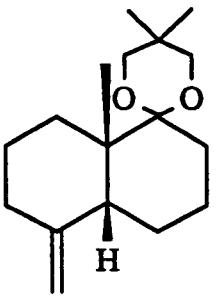
Preparation of the keto ketal **139**



139

The ketone **138** (0.038 g, 0.170 mmol) was dissolved in 1 mL of a 0.17 M solution of sodium methoxide in methanol. The solution was stirred at room temperature for 24 h. The solvent was removed under reduced pressure. Water (5 mL) and dichloromethane (5 mL) were added to the residue and the phases were separated. The aqueous phase was extracted with dichloromethane (3x5 mL) and the combined extract was dried ($MgSO_4$). Gas-liquid chromatographic analysis of this solution showed the presence of the starting material and the desired product **139** in a ratio of about 1:4.8, respectively. Removal of the solvent and subjection of the crude product to column chromatography (silica gel, 4g, 4:1 petroleum ether-Et_2O) gave 0.025 g (66%) of the pure keto ketal **139** after having removed traces of solvent (vacuum pump). This material exhibited mp 72-73°C (recrystallization from pentane-Et_2O). Combination of the remaining column fractions and the mother liquors from the recrystallization afforded 0.01 g of a 1:1 mixture of the product **139** and the starting material **138**. The keto ketal **139** showed ir (KBr): 1705, 1084 cm^{-1}; ^1H nmr (400 MHz) δ 4.06-3.90 (m, 4H, ketal protons), 2.64 (dd, 1H, J= 12,3 Hz), 2.34-2.25 (m, 2H), 2.05-1.92 (m, 2H), 1.90-1.76 (m, 1H), 1.74-1.50 (m, 5H), 1.49-1.39 (m, 2H), 0.92 (s, 3H, methyl protons). Exact Mass calcd. for $C_{14}H_{20}O_3$: 224.1413; found: 224.1417.

Preparation of the ketal alkene **140**

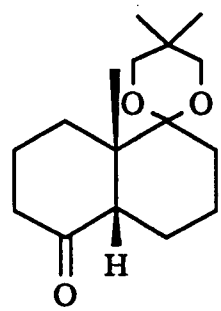


140

A stirred solution of the keto alkene **17**[23] (0.588 g, 3.303 mmol), 2,2-dimethyl-1,3-propanediol (0.515 g, 4.945 mmol) and p-toluenesulfonic acid (5 mg, 0.026 mmol) in 13.6 mL of dry benzene was refluxed for 2 h under a Dean-Stark water trap. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (60 g, 98:2 pentane-Et_2O). Collection and concentration of the appropriate fractions gave 0.596 g (68 %) of ketal alkene **140** as a white solid, which showed mp 76-77°C (recrystallization from pentane). This material exhibited ir (KBr): 3067, 1650, 1106 cm^{-1}; ^1H nmr (400 MHz) δ 4.69-4.59 (m, 2H, C=CH_2), 3.70 (d, 1H, J=12 Hz, ketal proton), 3.64 (d, 1H, J=12 Hz, ketal proton), 3.32 (dd, 1H, J=12,3 Hz, ketal proton), 3.27 (dd, 1H, J=12,3 Hz, ketal proton), 2.55 (br d, 1H, J=12 Hz), 2.30-2.18 (m, 2H), 2.05 (br dd, 1H, J=13,4 Hz), 1.87-1.69 (m, 2H), 1.68-1.49 (m, 3H), 1.48- 1.21 (m, 4H), 1.19 (s, 3H, methyl protons), 1.08 (s, 3H, methyl protons), 0.71 (s, 3H, methyl protons). Exact Mass calcd. for $C_{17}H_{28}O_2$: 264.2089; found: 264.2089. An inseparable mixture of two other products (0.216 g, 4.6:1 glc ratio) was also isolated as a colorless oil after removal of traces of solvent (vacuum pump). The major component was presumed to be the ketal alkene **140a** on the basis of the spectral

data obtained from this mixture: ir (film): 1472, 1394, 1109 cm^{-1}; ^1H nmr (400 MHz) δ 3.72 (d, J=11 Hz, ketal proton), 3.57 (d, J=11 Hz, ketal proton), 3.36 (dd, J=11, 3 Hz, ketal proton), 3.29 (dd, J=11,3 Hz, ketal proton), 2.60 (br d, J=14 Hz), 2.54 (br d, J=14 Hz), 1.82 (br d, J=17 Hz), 1.62 (br s, 3H, vinylic methyl protons), 1.44 (ddd, J=12,12,4 Hz), 1.18 (s, methyl protons), 1.13 (s, methyl protons), 0.70 (s, methyl protons).

Preparation of the keto ketal **141**

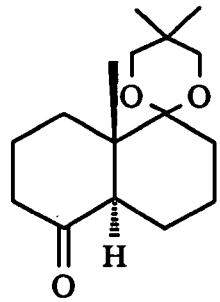


141

Ozone was bubbled into a cold (-78°C), stirred solution of the ketal alkene **140** (1.000 g, 3.788 mmol) in 150 mL of 2:1 dichloromethane-methanol until a pale blue tint appeared. The solution was purged with argon for 10 min while it was allowed to warm to room temperature. Dimethyl sulfide (3 mL) was added and the solution was stirred for 24 h at room temperature. Most of the solvent was evaporated in a stream of argon and the remainder was removed under reduced pressure. The residual material was taken up in 200 mL of Et_2O and the solution was washed successively with water (1x 50 mL) and brine (2x50 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Column chromatography of the crude product (silica gel, 70 g, 4:1 pentane-Et_2O) gave 0.804 g (80 %) of the keto ketal **141** as a white

crystalline solid that showed mp 104-105°C (recrystallization from pentane- Et_2O); ir (KBr): 1710, 1106 cm^{-1}; ^1H nmr (400 MHz) δ 3.64 (br d, 2H, J=11 Hz, ketal protons), 3.35-3.24 (m, 2H, ketal protons), 2.50-2.39 (m, 1H), 2.35 (dd, 1H, J=10,5 Hz), 2.23-2.12 (m, 3H), 2.12-2.01 (m, 1H), 1.92-1.69 (m, 3H), 1.68-1.35 (m, 4H), 1.16 (s, 3H, methyl protons), 1.11 (s, 3H, methyl protons), 0.90 (s, 3H, methyl protons). Anal. calcd. for $C_{16}H_{26}O_3$: C 72.14, H 9.84; found: C 72.44, H 9.91. Exact Mass calcd. 266.1885; found: 266.1886.

Preparation of the keto ketal **142**

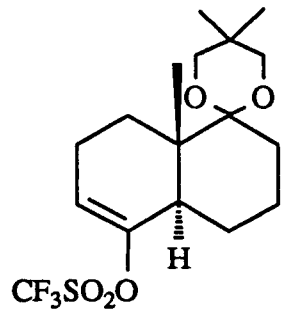


142

A solution of the keto ketal **141** (1.000 g, 3.759 mmol) in 25 mL of a 0.174 M solution of sodium methoxide in methanol was stirred at 45°C for 2.5 h. The solvent was removed under reduced pressure. Water (20 mL) and Et_2O (20 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (3x30 mL) and the combined extract was washed with brine (1x20 mL), dried ($MgSO_4$) and concentrated. Column chromatography of the residual material on silica gel (100 g, elution with 5:1 pentane- Et_2O), followed by removal of traces of solvent (vacuum pump) gave 0.100 g of recovered starting material **141** and 0.888 g (89 %) of the keto ketal **142** as a colorless oil

which showed ir (film): 1713, 1111 cm^{-1}; ^1H nmr (400 MHz) δ 3.70 (d, 1H, J=12 Hz, ketal proton), 3.66 (d, 1H, J=12 Hz, ketal proton), 3.37 (dd, 1H, J=12,3 Hz, ketal proton), 3.29 (dd, 1H, J=12,3 Hz, ketal proton), 2.70 (dd, 1H, J=13,3 Hz), 2.53 (br d, 1H, J=11 Hz), 2.34-2.24 (m, 3H), 2.06-1.95 (m, 1H), 1.91-1.74 (m, 2H), 1.66-1.50 (m, 2H), 1.50-1.17 (m, 3H), 1.20 (s, 3H, methyl protons), 0.85 (s, 3H, methyl protons), 0.73 (s, 3H, methyl protons). Exact Mass calcd. for $C_{16}H_{26}O_3$: 266.1885; found: 266.1886.

Preparation of the enol triflate **143**

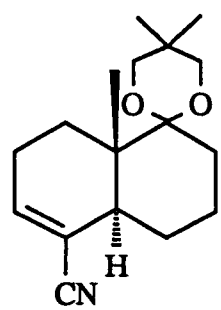


143

To a cold (-78°C) solution of lithium diisopropylamide (LDA) (3.672 mmol) in 10.1 mL of dry THF was added, via cannulation, a solution of the ketone **142** (0.888 g, 3.338 mmol) in 4 mL of dry THF. The solution was stirred for 30 min and then was warmed to 0°C for 5 min. After the reaction mixture had been recooled to -78°C, solid N-phenyltrifluoromethanesulfonimide (1.310g, 3.667 mmol) was added. The solution was allowed to warm to room temperature and was stirred for 1 h. The reaction mixture was filtered through a plug of silica gel (20 g, elution with Et_2O). Removal of the solvent from the filtrate gave a yellow oil. Upon careful purification of this material by column chromatography (silica gel, 80 g, 95:5,then 9:1 and finally 5:1 pentane-Et_2O),

1.184 g (89 %) of the enol triflate **143** was obtained as a white solid. This material, even after recrystallization from pentane-Et_2O, was contaminated with traces of N-phenyltrifluoromethanesulfonimide. However, this impurity did not affect the outcome of the next reaction. The (slightly impure) enol triflate **143** showed ir (KBr): 1417, 1211, 1113 cm^{-1}; ^1H nmr (400 MHz) δ 5.68-5.62 (m, 1H, vinyl proton), 3.69 (d, 1H, J=11 Hz, ketal proton), 3.63 (d, 1H, J=11 Hz, ketal proton), 3.37-3.26 (m, 2H, ketal protons), 2.92-2.83 (m, 1H), 2.58 (br d, 1H, J=12 Hz), 2.30-2.10 (m, 2H), 1.94-1.78 (m, 2H), 1.75 (br d, 1H, J=9 Hz), 1.72-1.65 m, 1H), 1.46-1.28 (m, 3H), 1.14 (s, 3H, methyl protons), 0.93 (s, 3H, methyl protons), 0.71 (s, 3H, methyl protons). Exact Mass calcd. for $C_{17}H_{25}F_3O_5S$: 398.1374; found: 398.1383.

Preparation of the nitrile **144**

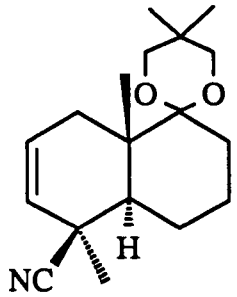


144

To a mixture of dry LiCN (0.106 g, 3.212 mmol) (previously dried under vacuum (pump) at 45°C for 2 h) , $(Ph_3P)_4Pd$ (0.176 g, 0.152 mmol) and 12-crown-4 (20 μL, 0.124 mmol) was added a solution of the enol triflate **143** (0.544 g, 1.367 mmol) in 8 mL of dry benzene and the resultant mixture was stirred at room temperature for 2.5 h. Water (4 mL) was added, the phases were separated and the aqueous layer was extracted with

Et_2O (3x50 mL). The combined extract was dried ($MgSO_4$) and the resulting solution was passed through a plug of Florisil (5 g, elution with Et_2O). Removal of the solvent under reduced pressure and chromatographic purification of the residual material (silica gel, 50 g, 9:1 pentane-Et_2O), afforded 0.344 g (91 %) of the nitrile **144** as a white crystalline solid. This material showed mp 123-124°C (recrystallization from pentane-Et_2O); ir (KBr): 3036, 2209, 1626, 1110, 1092 cm^{-1}; ^1H nmr (400 MHz) δ 6.60-6.53 (m, 1H, vinyl proton), 3.70 (d, 1H, J=11 Hz, ketal proton), 3.64 (d, 1H, J=11 Hz, ketal proton), 3.35-3.25 (m, 2H, ketal protons), 2.66-2.50 (m, 2H), 2.35-2.10 (m, 2H), 1.97-1.80 (m, 3H), 1.75-1.65 (m, 1H), 1.50-1.31 (m, 3H), 1.14 (s, 3H, methyl protons), 0.85 (s, 3H, methyl protons), 0.71 (s, 3H, methyl protons). Anal. calcd. for $C_{17}H_{25}O_2$: C 74.14, H 9.15, N 5.09; found: C 73.95, H 9.09 , N 5.10. Exact Mass calcd. 275.1885; found: 275.1891.

Preparation of the nitrile **148**



148

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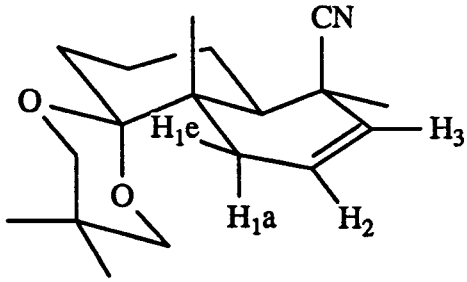


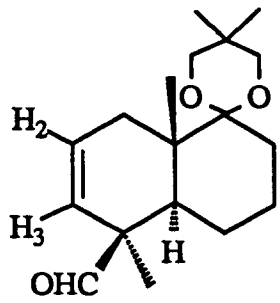
148a

To a solution of LDA (1.877 mmol) in 6.25 mL of dry THF at -78°C was added a solution of the nitrile **144** (0.344 g, 1.251 mmol) in 3 mL of dry THF. The reaction mixture was stirred for 15 min at -78°C and for 5 min at 0°C and then was recooled to

-78°C. Dry HMPA (0.22 mL, 1.27 mmol) and an excess of methyl iodide (0.5 mL, 8.0 mmol) were added successively and the reaction mixture was warmed to 0°C and stirred for 30 min. Aqueous sodium thiosulfate (5 % solution, 10 mL) and brine (15 mL) were added and the mixture was extracted with Et_2O (3x50 mL). The combined extract was washed with brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure, followed by column chromatography of the residual material (silica gel, 20 g, 5:1 hexane-Et_2O) gave 0.348 g (96 %) of the nitrile **148** as a white crystalline solid. This material showed mp 115-116°C (recrystallization from hexane-Et_2O); ir (KBr): 3027, 2229, 1113 cm^{-1}; ^1H nmr (400 MHz) δ 5.92-5.85 (m, 1H, $\underline{H}_2$), 5.49-5.42 (m, 1H, $\underline{H}_3$), 3.71 (d, 1H, J=12 Hz, ketal proton), 3.63 (d, 1H, J=12 Hz, ketal proton), 3.35-3.27 (m, 2H, ketal protons), 2.73 (br d, 1H, J=18 Hz, $\underline{H}_1$a), 2.60-2.53 (m, 1H), 2.00(dd, 1H, J=18,6 Hz, $\underline{H}_1$e), 1.82-1.64 (m, 5H), 1.42 (s, 3H, methyl protons), 1.45-1.30 (m, 1H), 1.15 (s, 3H, methyl protons), 1.14 (s, 3H, methyl protons), 0.71 (s, 3H, methyl protons). In decoupling experiments (see formula **148a**), irradiation of the signal at δ 5.49-5.42 (H_3) simplified the multiplet at 5.92-5.85 (H_2) and sharpened the doublet at 2.73 (H_1a); irradiation of the signal at δ 5.92-5.85 (H_2) simplified the multiplet at 5.49-5.42 (H_3) and caused the collapse of the doublet of doublets at 2.00 (H_1e) to a doublet (J=18 Hz). Anal. calcd. for $C_{18}H_{27}NO_2$: C 74.69, H 9.41, N 4.84; found: C 74.82, H 9.37, N 4.72. Exact Mass calcd. 289.2042; found: 289.2042.

Preparation of the aldehyde **149**

To a solution of the nitrile **148** (0.292 g, 1.010 mmol) in dry dichloromethane (13.4 mL) was added a hexane solution of diisobutylaluminum hydride (1.140 mmol). The solution was stirred at room temperature for 30 min. Water (20 drops) and saturated

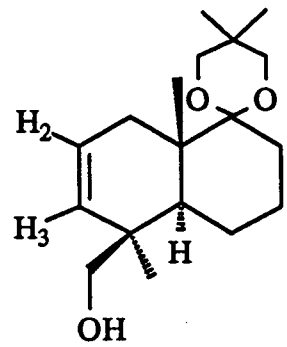


149

aqueous sodium bicarbonate (30 drops) were added and the mixture was stirred vigorously for 5 min. Diethyl ether (20 mL) was added and stirring was continued for 5 min. Enough $MgSO_4$ was then added to absorb the water. The mixture was filtered through a plug of Florisil (3 g, elution with Et_2O). Removal of the solvent from the eluate and column chromatography of the residue on silica gel (15 g, 17:3 hexane-Et_2O) gave 0.287 g (97 %) of the aldehyde **149** as a colorless oil after the last traces of solvent had been removed under reduced pressure (vacuum pump). This compound showed ir (film): 3015, 2718, 1718, 1113 cm^{-1}; ^1H nmr (400 MHz) δ 9.76 (s, 1H, -CHO), 5.99-5.91 (m, 1H, H_3), 5.34 (dd, 1H, J=10,2 Hz, H_2), 3.70 (d, 1H, J=11 Hz, ketal proton), 3.62 (d, 1H, J=11 Hz, ketal proton), 3.37-3.25 (m, 2H, ketal protons), 2.80 (br d, 1H, J=19 Hz), 2.55 (br d, 1H, J=12 Hz), 2.07-1.95 (m, 2H), 1.80- 1.71 (m, 1H), 1.68-1.60 (m, 1H), 1.45-1.10 (m, 3H), 1.17 (s, 3H, methyl protons), 1.13 (s, 3H, methyl protons), 1.01 (s, 3H, methyl protons), 0.71 (s, 3H, methyl protons). Exact Mass calcd. for $C_{18}H_{28}O_3$: 292.2038; found: 292.2032.

Preparation of the alcohol **150**

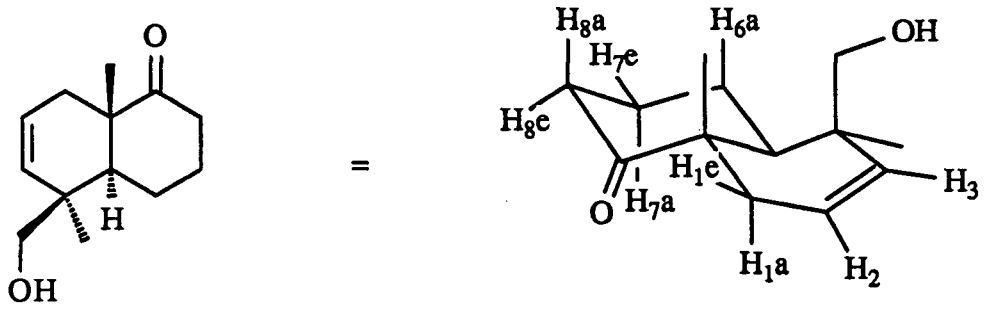
To a cold (-10°C), stirred solution of the aldehyde **149** (0.287 g, 0.983 mmol) in



150

9.8 mL of dry methanol was added sodium borohydride (0.019 g, 0.502 mmol) and the mixture was stirred at -10°C for 20 min. Water (1 mL) and a saturated aqueous solution of ammonium chloride (2 mL) were added and the reaction mixture was allowed to warm to room temperature. The methanol was removed under reduced pressure and brine (15 mL) was added to the residue. The mixture was extracted with dichloromethane (3x25 mL). The combined extract was washed with brine (1x25 mL) and dried ($MgSO_4$). Solvent removal under reduced pressure (water aspirator, then vacuum pump) gave 0.276 (96 %) of the alcohol **150** as colorless oil which was homogeneous by tlc and glc analyses. This material showed ir (film): 3350, 3012, 1112 cm^{-1}; ^1H nmr (400 MHz) δ 5.74 (ddd, 1H, J=10, 6, 3 Hz, H_2), 5.49 (dd, 1H, J=10,3 Hz, H_3), 3.70 (d, 1H, J=11 Hz, ketal proton), 3.67 (d, 1H, J=11 Hz, ketal proton), 3.62 (d, 1H, J=11 Hz, CH_2OH), 3.49 (d, 1H, J=11 Hz, CH_2OH), 3.33 (dd, 1H, J=11,4 Hz, ketal proton), 3.28 (dd, 1H, J=11,l4 Hz, ketal proton), 2.71 (br d, 1H, J=18 Hz), 2.56-2.48 (m, 1H), 1.97-1.86 (m, 2H), 1.70-1.53 (m, 2H), 1.54 (br s, 1H, D_2O exchanged, $-CH_2-OH$), 1.40-1.08 (m, 5H), 1.16 (s, 3H, methyl protons), 1.05 (s, 3H, methyl protons), 1.03 (s, 3H, methyl protons), 0.70 (s, 3H, methyl protons). Exact Mass calcd. for $C_{18}H_{30}O_3$: 294.2194; found: 294.2194.

Preparation of the keto alcohol **151**

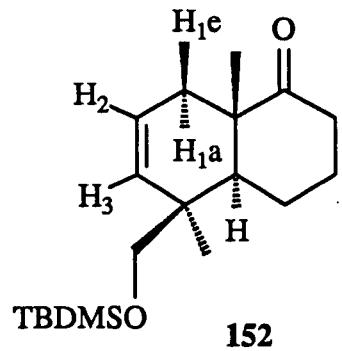


151 **151a**

To a stirred solution of the alcohol **150** (0.276 g, 0.939 mmol) in acetone (34 mL) was added a 10 % solution of aqueous hydrochloric acid (0.48 mL). The reaction mixture was stirred at room temperature for 1 h. A saturated aqueous solution of sodium bicarbonate (0.5 mL) was added and the acetone was removed under reduced pressure. The residual material was taken up in dichloromethane (80 mL) and brine was added. The phases were separated and the aqueous layer was extracted with dichlorometane (20 mL). The combined extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material obtained was purified by column chromatography on silica gel (20 g, 3:1 Et_2O- pentane). Distillation (air-bath temperature 160-170°C / 0.1 Torr) of the material thus obtained provided 0.192 g (98 %) of the keto alcohol **151** as a colorless oil, which exhibited ir (film): 3453, 3022, 1704 cm^{-1}; ^1H nmr (400 MHz) δ 5.74 (ddd, 1H, J=10,6,2 Hz, H_2), 5.54 (dd, 1H, J=10,3 Hz, H_3), 3.74 (dd, 1H, J=11,6 Hz, -CH_2-OH), 3.60 (dd, 1H, J=11,6 Hz, -CH_2-OH), 2.60 (ddd, 1H, J=14,14,7 Hz, H_8a), 2.38 (br d, 1H, J=18 Hz, H_1a), 2.29 (dddd, 1H, J=14,2,2,2 Hz, H_8e), 2.18-2.08 (m, 1H, H_7e), 1.99 (dd, 1H, J=18,6 Hz, H_1e), 1.91 (br d, 1H, J=13 Hz), 1.74 (dddd, 1H, J=12,12,12,4 Hz, H_6a), 1.66 (dd, 1H, J=13,3 Hz), 1.63-1.47 (m, 1H, H_7a), 1.31 (t, 1H, J=6 Hz,

CH_2-OH, D_2O exchanged, also the signals at δ 3.74 and 3.60 collapsed, each to a doublet of J=11 Hz), 1.20 (s, 3H, methyl protons), 1.09 (s, 3H, methyl protons). In decoupling experiments (see formula **151a**), irradiation of the signal at δ 5.74 (H_2) simplified the signal at 5.54 (H_3) to a doublet (J=3 Hz), the broad doublet at 2.38 (H_1a) is sharpened and the dd at 1.99 (H_1e) collapsed to a doublet (J=18 Hz); irradiation of the signal at δ 2.60 (H_8a) simplified the signals at 2.29 (H_8e), 2.18-2.08 (H_7e) and 1.63-1.47 (H_7a); irradiation of the signal at δ 2.18-2.08 (H_7e) simplified the signals at 2.60 (H_8a), 2.29 (H_8e), 1.74 (H_6a, collapsed to a ddd, J=12,12,12 Hz) and 1.63-1.47 (H_7a). Exact Mass calcd. for $C_{13}H_{20}O_2$: 208.1464; found: 208.1466.

Preparation of the ketone **152**

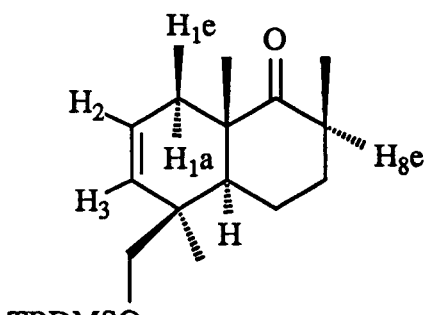


152

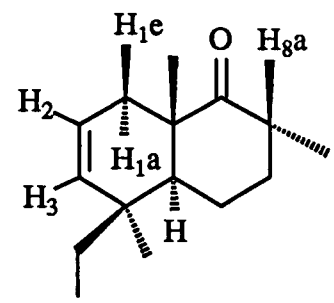
To a cold (-78°C) solution of the keto alcohol **151** (0.076 g, 0.365 mmol), 4-N,N-dimethylaminopyridine (0.0045 g, 0.037 mmol) and triethylamine (0.076 mL, 0.545 mmol) in dry dichloromethane (3.5 mL) was added tert-butyldimethylsilyl-trifluoromethanesulfonate (0.092 mL, 0.401 mmol). The solution was stirred for 30 min and then a saturated aqueous solution of sodium bicarbonate (5 mL) and Et_2O (10 mL) were added. The mixture was allowed to warm to room temperature and the phases were separated. The aqueous phase was extracted with Et_2O (2x20 mL). The combined

extract was washed with brine (1x20 mL) and dried ($MgSO_4$). Removal of the solvent, followed by column chromatography of the residue on silica gel (10 g, 95:5 pentane-Et_2O) and further removal of traces of solvent (vacuum pump) from the oils thus obtained gave 0.1095 g (93 %) of the ketone **152** as a colorless oil. Compound **152** exhibited ir (film): 3019, 1710, 1084, 852, 838 cm^{-1}; ^1H nmr (400 MHz) δ 5.63 (ddd, 1H, J=10,6,2 Hz, H_2), 5.52 (dd, 1H, J=10,3 Hz, H_3), 3.60 (d, 1H, J=10 Hz, -CH_2-$OSiMe_2Bu$-t), 3.56 (d, 1H, J=10 Hz, -CH_2-$OSiMe_2Bu$-t), 2.59 (ddd, 1H, J=14.14,7 Hz), 2.34 (br d, 1H, J=18 Hz, H_1a), 2.28 (dq, 1H, J=14,2 Hz), 2.15-2.06 (m, 1H), 1.96 (dd, 1H, J=18,6 Hz,H_1e), 1.91 (br d, 1H, J=14 Hz), 1.71 (dddd, 1H, J=13,13,13,4 Hz), 1.61 (dd, 1H, J=13,3 Hz), 1.58-1.43 (m, 1H), 1.18 (s, 3H, methyl protons), 1.04 (s, 3H, methyl protons), 0.91 (s, 9H, t-butyl protons), 0.04 (s, 3H, methyl protons), 0.03 (s, 3H, methyl protons). Exact Mass calcd. for $C_{15}H_{25}O_2Si$ (M^+-t-Bu): 265.1624; found: 265.1624; low resolution chemical ionization mass spectrum: M^+=322.

Preparation of the ketones **153** and **154**



153



154

To a cold (-78°C) stirred solution of LDA (0.046 mmol) in 0.23 mL of dry THF was added a solution of the ketone **152** (0.0135 g, 0.0415 mmol) in 0.25 mL of dry THF.

The solution was stirred at -78°C for 10 min and at 0°C for 10 min and then was recooled to -78°C. An excess of methyl iodide (~ 0.1 mL) was added and the reaction mixture was stirred at room temperature for 1 h. Water (1 mL), a 5% solution of aqueous sodium thiosulfate (1 mL) and ether (3 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (2x5 mL). The combined extract was washed with brine (1x3 mL) and dried ($MgSO_4$). Analysis of the solution by tlc showed the presence of two compounds. Solvent removal under reduced pressure and column chromatography of the residue on silica gel (Pasteur pipette, 0.86 g, 95:5 pentane-Et_2O) gave two fractions. The first fraction provided 8 mg (57 %) of a mixture of epimers **153** and **154** (tlc analysis). The second fraction consisted of 5.5 mg (39 %) of pure **153**. Traces of solvent were removed (vacuum pump) from both fractions. The 8 mg mixture of epimers was dissolved in 0.5 mL of a 0.174 M solution of freshly prepared sodium methoxide in methanol and the solution was stirred at room temperature for 1 h. A saturated aqueous solution of ammonium chloride (2 drops) was added and the methanol was removed under reduced pressure. Brine (3 mL) and Et_2O (5 mL) were added to the residue and the phases were separated. The aqueous phase was extracted twice with Et_2O (1x3 mL). The combined extract was dried ($MgSO_4$) and concentrated. The crude material thus obtained was purified as described above to afford 7 mg (88 %) of the pure epimer **154**.

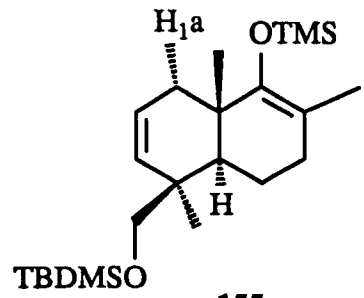
The alkylation-epimerization sequence was carried out using conditions very similar to those outlined above, but on a larger scale. Thus, the ketone **152** (0.258 g, 0.801 mmol) gave the ketone **154** (0.219 g, 0.651 mmol) in 81 % yield.

Compound **153** showed ir (film): 3023, 1708, 1083, 838 cm^{-1}; ^1H nmr (400 MHz) δ 5.64-5.53 (m, 2H, vinyl protons), 3.60 (d, 1H, J=10 Hz, -$C\underline{H}_2$-$OSiMe_2Bu$-t), 3.55 (d, 1H, J=10 Hz, -$C\underline{H}_2$-$OSiMe_2Bu$-t), 2.64 (dq, 1H, J=8,8 Hz, $\underline{H}_8$e), 2.13 (dd, 1H, J=18, 5 Hz, $\underline{H}_1$e), 2.05 (br d, 1H, J=18 Hz, $\underline{H}_1$a), 1.98-1.85 (m, 2H), 1.78-1.64 (m, 1H), 1.64-1.54

(m, 1H), 1.16 (s, 3H, methyl protons), 1.13 (d, 3H, J=8 Hz, methyl protons), 1.09 (s, 3H, methyl protons), 0.91 (s, 9H, t-butyl protons), 0.03 (s, 3H, methyl protons), 0.02 (s, 3H, methyl protons). Exact Mass calcd. for $C_{19}H_{33}O_2Si$ (M^+-Me): 321.2249; found: 321.2254; low resolution chemical ionization mass spectrum: M^+=336 .

Compound **154** showed ir (film): 3023, 1708, 1091, 838 cm^{-1}; ^1H nmr (400 MHz) δ 5.64 (ddd, 1H, J=10,7,2 Hz, H_2), 5.52 (dd, 1H, J=10,3 Hz, H_3), 3.61 (d, 1H, J=10 Hz, -CH_2-OSiMe$_2$Bu-t), 3.57 (d, 1H, J=10 Hz, -CH_2-OSiMe$_2$Bu-t), 2.68 (ddq, 1H, J=12,6,6 Hz, H_8a), 2.39 (br d, 1H, J=18 Hz, H_1a), 2.16-2.07 (m, 1H), 1.94-1.86 (m, 1H), 1.93 (dd, 1H, J=18,7 Hz, H_1e), 1.79 (dddd, 1H, J=13,13,13,4 Hz), 1.59 (dd, 1H, J=13,4 Hz), 1.30-1.15 (m, 1H), 1.17 (s, 3H, methyl protons), 1.03 (s, 3H, methyl protons), 1.00 (d, 3H, J=6 Hz, methyl protons), 0.91 (s, 9H, t-butyl protons), 0.04 (s, 3H, methyl protons), 0.03 (s, 3H, methyl protons). Exact Mass calcd. for $C_{19}H_{33}O_2Si$ (M^+-Me): 321.2249; found: 321.2257; low resolution chemical ionization mass spectrum: M^+=336.

Preparation of the silyl enol ether **155**



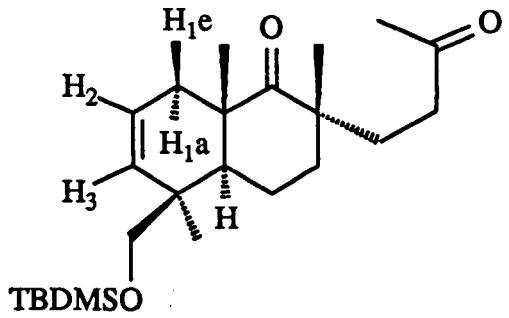
155

To a cold (-78°C) stirred solution of LDA (0.724 mmol) in 4.8 mL of dry THF was added a solution of the ketone **154** (0.219 g, 0.652 mmol) in 1.5 mL of dry THF and the solution was stirred for 30 min. The solution was warmed to 0°C and dry

hexamethylphosphoramide (0.127 mL, 0.724 mmol) and chlorotrimethylsilane (0.370 mL, 2.915 mmol) were added successively. After the reaction mixture had been stirred at 0°C for 40 min, 1,1,1,3,3,3-hexamethyldisilazane (0.8 mL) was added and the solvent was removed under reduced pressure. Pentane (50 mL) was added to the residue and after the mixture had been stirred for a few seconds, the solution was decanted. To the residue was added saturated aqueous sodium bicarbonate (10 mL) and the mixture was extracted with pentane (2x10 mL). The combined extract was mixed with the previously decanted solution, the solution was washed with brine (3x30 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (silica gel, 22 g, 93:5:2 pentane-Et_2O-triethylamine). Removal of the volatile material (vacuum pump) from the appropriate fractions gave 0.248 g (93 %) of the silyl enol ether **155**, a colorless oil that exhibited ir (film): 3024, 1676, 1091, 842 cm^{-1}; ^1H nmr (400 MHz) δ 5.64-5.57 (m, 2H, vinyl protons), 3.66 (d, 1H, J=10 Hz, -CH_2-$OSiMe_2Bu$-t), 3.48 (d, 1H, J=10 Hz,-CH_2-$OSiMe_2Bu$-t), 2.11-1.95 (m, 2H), 1.90 (d, 1H, J=18 Hz, H_1a), 1.80-1.72 (m, 1H), 1.59-1.52 (m, 1H), 1.54 (s, 3H, methyl protons), 1.42-1.15 (m, 2H), 1.05 (s, 3H, methyl protons), 1.03 (s, 3H, methyl protons), 0.91 (s, 9H, t-butyl protons), 0.22 (s, 9H, methyl protons), 0.03 (s, 6H, methyl protons). Exact Mass calcd. for $C_{23}H_{44}O_2Si_2$: 408.2880; found: 408.2877.

Preparation of the diketone **157**

To a cold (-78°C), stirred solution of freshly distilled $TiCl_4$ (0.02 mL, 0.162 mmol) in dry dichloromethane (0.86 mL) was added freshly distilled Ti(OPr-i)$_4$ (0.03 mL, 0.108 mmol). The mixture was stirred at -78°C for 5 min and then a solution of methyl vinyl ketone ethylene ketal (0.03 mL, 0.33 mmol) in dichloromethane (0.16 mL)



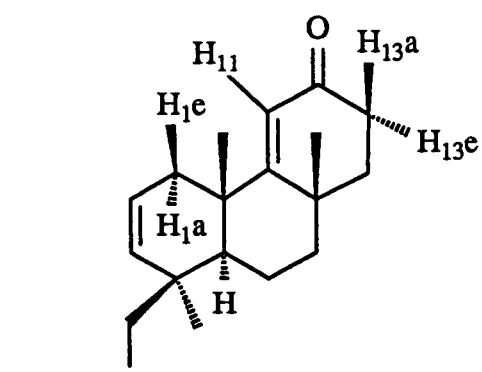
157

was added, and the mixture was stirred for 5 min. A solution of the trimethylsilyl enol ether **155** (0.044 g, 0.108 mmol) in dichloromethane (0.16 mL) was added, and the reaction mixture was stirred for 10 min. After the reaction mixture had been treated with 5% aqueous K_2CO_3 (0.5 mL), Et_2O (5 mL) was added and the mixture was allowed to warm to room temperature. Vigorous stirring was continued for 5 min and then $MgSO_4$ was added to eliminate the water. The slurry was filtered through a plug of Florisil (Pasteur pipette) and the collected material was rinsed several times with Et_2O. The solvent was removed from the filtrate under reduced pressure. Thin layer chromatographic analysis of the crude product showed the presence of four compounds and a considerable amount of "baseline" material. Column chromatography of this mixture (silica gel, 5g, 7:3 pentane-Et_2O) followed by removal of traces of solvent (vacuum pump) from each of the fractions gave 0.0025 g (6 %) of the ketone **153**, 0.0020 g (5 %) of the ketone **154**, 0.0020 g (~5 %) of the (somewhat impure) diketone **156**, and 0.0060 g (14 %) of the desired diketone **157**, all as colorless oils. The diketone **157** exhibited ir (film): 3022, 1718, 1695, 1086, 854, 838 cm^{-1}; ^1H nmr (400 MHz) δ 5.59 (ddd, 1H, J=10,6,2 Hz, H_2), 5.54 (dd, 1H, J=10,3 Hz, H_3), 3.61 (d, 1H, J=10 Hz, -CH_2-OSiMe$_2$Bu-t), 3.57 (d, 1H, J=10 Hz, -CH_2- OSiMe$_2$Bu-t), 2.46-2.29 (m, 2H), 2.22 (dd, 1H, J=18,6 Hz, H_1e), 2.16 (s, 3H, R-(CO)CH_3), 2.04 (br d, 1H, J=18 Hz, H_1a), 2.00-1.91 (m, 1H), 1.91-1.83 (m, 1H), 1.80 (dddd, 1H, J=14,14,14,4 Hz), 1.69 (ddd, 1H,

J=15,4,4 Hz), 1.64-1.48 (m, 2H), 1.25-1.13 (m, 1H), 1.19 (s, 3H, methyl protons), 1.18 (s, 3H, methyl protons), 1.08 (s, 3H, methyl protons), 0.91 (s, 9H, t-butyl protons), 0.04 (s, 3H, methyl protons), 0.03 (s, 3H, methyl protons). Exact Mass calcd. for $C_{20}H_{33}O_3Si$ (M^+-t-Bu): 349.2199; found: 349.2203; low resolution chemical ionization mass spectrum: M^+= 406.

The (somewhat impure, 90% glc) diketone **156** exhibited ir (film): 3018, 1719, 1694, 1087, 838 cm^{-1}; ^1H nmr (400 MHz) δ 5.68- 5.52 (m, 2H, H_2,H_3), 3.63 (d, 1H, J=10 Hz, -CH_2-$OSiMe_2Bu$-t), 3.54 (d, 1H, J=10 Hz, -CH_2-$OSiMe_2Bu$-t), 2.60-2.47 (m, 2H), 2.14 (s, 3H, -(CO)CH_3), 2.08 (br d, 1H, J=18 Hz), 1.13 (s, 3H, methyl protons), 1.07 (s, 3H, methyl protons), 0.99 (s, 3H, methyl protons), 0.91 (s, 9H, t-butyl protons), 0.04 (s, 3H, methyl protons), 0.03 (s, 3H, methyl protons). Exact Mass calcd. for $C_{24}H_{42}O_3Si$: 406.2903; found: 406.2900.

Preparation of the enone **163**

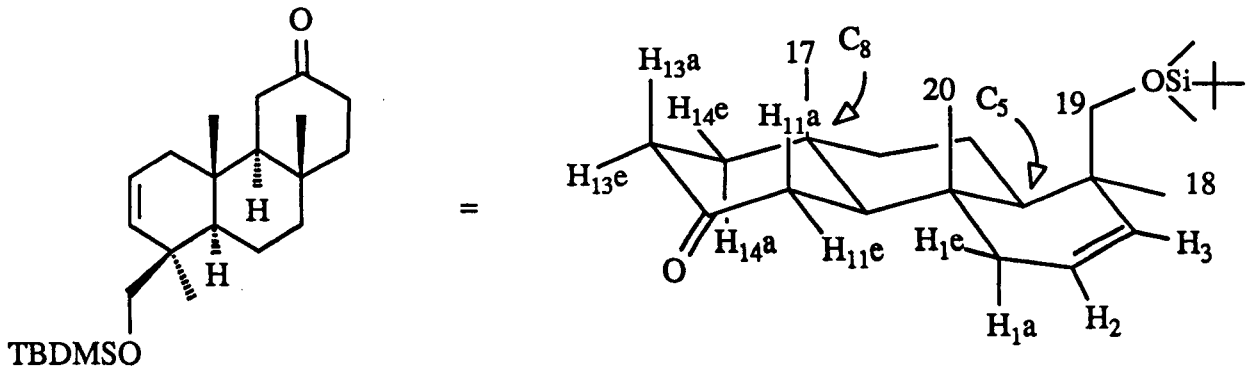


163

The diketone **157** (0.006 g, 0.015 mmol) was dissolved in 0.13 mL of a 5 % solution of potassium hydroxide in methanol and the solution was refluxed for 1.5 h.

Brine (2 mL) and a 10% solution of hydrochloric acid (3 drops) were added. The mixture was extracted with Et_2O (3x2 mL) and the combined extract was dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (Pasteur pipette, 0.86 g, 7:3 pentane-Et_2O). Concentration and removal of traces of solvent (vacuum pump) from the resultant oil gave 0.0045 g (78 %) of the enone **163** as a colorless oil exhibiting ir (film): 3028, 1671, 1617, 1078, 838 cm^{-1}; ^1H nmr (400 MHz) δ 5.85 (br s, 1H, $\underline{H}_{11}$), 5.65-5.65 (m, 2H, vinyl protons), 3.62 (d, 1H, J=10 Hz, -$C\underline{H}_2$-$OSiMe_2Bu$-t), 3.53 (d, 1H, J=10 Hz, -$C\underline{H}_2$-$OSiMe_2Bu$-t), 2.58 (ddd, 1H, J=18,15,5 Hz, $\underline{H}_{13}$a), 2.38 (br d, 1H, J=18 Hz, $\underline{H}_{13}$e), 2.21 (dd, 1H, J=18,5 Hz, $\underline{H}_1$e), 2.09 (br d, 1H, J=18 Hz, $\underline{H}_1$a), 1.88 (ddd, 1H, J=15,15,4 Hz), 1.82-1.62 (m, 5H), 1.49 (br d, 1H, J=13 Hz), 1.40-1.30 (m, 1H), 1.35 (s, 3H, methyl protons), 1.21 (s, 3H, methyl protons), 1.06 (s, 3H, methyl protons), 0.90 (s, 9H, t-butyl protons), 0.04 (s, 3H, methyl protons), 0.03 (s, 3H, methyl protons). Exact Mass calcd. for $C_{24}H_{40}O_2Si$: 388.2798; found: 388.2789.

Preparation of the ketone **164**



164 **164a**

To a cold (-78°C), stirred solution of sodium (0.004 g, 0.174 mmol) in ammonia (2 mL) (freshly distilled from sodium) was added a solution of enone **163** (0.004 g, 0.010 mmol) and tert-butyl alcohol (2 μL, 0.021 mmol) in Et_2O (0.1 mL). The solution was refluxed for 40 min and then was treated successively with isoprene, a saturated aqueous solution of ammonium chloride (2 mL), and Et_2O (2 mL). While the resulting mixture was stirred for 2 h, it was warmed occasionally with a water bath to eliminate the ammonia. Brine (2 mL) and Et_2O (2 mL) were added to the residual material and the phases were separated. The aqueous phase was extracted with Et_2O (2x3 mL). The combined extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Chromatography of the crude product thus obtained (silica gel, Pasteur pipette, 0.86 g, 7:3 pentane-Et_2O) gave 0.0038 g (94 %) of ketone **164** as a white crystalline solid, which exhibited mp 99-101°C (recrystallization from pentane-Et_2O). This compound exhibited ir (KBr):3069, 1711, 1472, 854, 836 cm^{-1}; ^1H nmr (400 MHz) δ 5.60 (dd, 1H, J=11,2 Hz, H_3), 5.49 (ddd, 1H, J=11,6,2 Hz, H_2), 3.60 (d, 1H, J=10 Hz, CH_2-$OSiMe_2Bu$-t), 3.49 (d, 1H, J=10 Hz, -CH_2-$OSiMe_2Bu$-t), 2.46 (ddd, 1H, J=16,16,6 Hz, $H_{13}a$), 2.34-2.25 (m, $H_{11}a$, $H_{11}e$, $H_{13}e$), 1.90 (dd, 1H, J=18,6 Hz, H_1e), 1.76-1.67 (m, 2H), 1.66-1.38 (m, 4H), 1.37-1.29 (m, 1H), 1.27 (br d, 1H, J=13 Hz, H_5), 1.18 (dd, 1H, J=13,4 Hz), 1.14 (s, 3H, C_{17} methyl protons), 1.05 (s, 3H, C_{18} methyl protons), 0.90 (s, 9H, t-butyl protons), 0.89 (s, 3H, C_{20} methyl protons), 0.03 (s, 3H, methyl protons), 0.02 (s, 3H, methyl protons). In decoupling experiments (see formula **164a**), irradiation of the signal at δ 1.90 (H_1e) simplified the signals at 5.49 (H_2) and at 1.66-1.38 (H_1a); irradiation of the signal at δ 2.46 ($H_{13}a$) simplified the signals at 2.34-2.25 ($H_{13}e$) and at 1.66- 1.38 ($H_{14}e$, $H_{14}a$). In nOe difference experiments, irradiation of the signal at δ 1.90 (H_1e) caused enhancement of the signals at 5.49 (ddd, J=16,6,2 Hz, H_2), 2.34-2.25 (multiplet, $H_{11}e$) and 1.60 (broad doublet, J=18 Hz, H_1a); irradiation at δ 0.89 (C_{20} methyl protons, tert-butyl protons) caused enhancement of the signals at 3.60 (doublet,

J=10 Hz, C_{19} methylene proton), 2.34-2.25 (multiplet, $H_{11}a$), 1.90 (dd, J=18,6 Hz, H_1e) and the singlets at 1.14 (C_{17} methyl protons), 0.03 and 0.02 (protons on the methyl groups bonded to Si); irradiation of the signal at δ 1.05 (C_{18} methyl protons) caused enhancement of the signals at 1.27 (dd, J=13,3 Hz, H_5), 3.49 (doublet, J=10 Hz, C_{19} methylene proton) and 5.60 (dd, J=11,2 Hz, H_3). Exact Mass calcd. for $C_{24}H_{42}O_2Si$: 390.2954; found: 390.2959.

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