TOTAL SYNTHESIS OF (+)-8-ISOCYANO-10-CYCLOAMPHILECTENE

by

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We accept this thesis as conforming

to the required standard.

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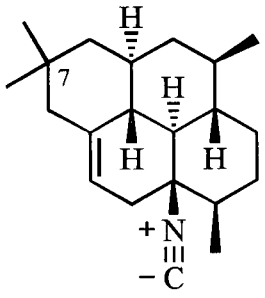
Abstract

A 36-step synthesis of the tetracyclic diterpene (+)-8-isocyano-10-cycloamphilectene (**11**) from (*R*)-pulegone (**40**) is described. An efficient four-step process gave **38** from **40** with complete regioselectivity in the introduction of the carbon-carbon double bond. Methoxycarbonylation and reduction were followed by stereocontrolled alkylation and produced **16**. Treatment of the enol trifluoromethanesulfonate derived from **16** under conditions ($Pd(PPh_3)_4$, LiCl, THF, reflux) appropriate for an intramolecular Stille-type coupling gave the bicyclic compound **18**. A highly face- and regioselective Diels—Alder cycloaddition process gave the tricyclic compound **54**. The bromine atom in **54** was reductively removed in a samarium(II) induced protiodebromination process, and three further synthetic steps gave compound **21**. At this point, the configurations at four of the seven stereocentres had been set and attention was turned towards the introduction of the fourth required carbocyclic ring. Allylic oxidation, reduction of the carbon-carbon double bond by catalytic hydrogenation and a two-step methoxycarbonylation process gave the intermediate **65** which was transformed into **32** by an efficient five-step synthetic sequence in which the introduction of C-7 of the cycloamphilectane skeleton was an important step. An aldol condensation reaction followed by a chemoselective reduction gave compound **30** which was subjected to an alkylation, epimerization, alkylation sequence wherein the *gem*-dimethyl function was installed yielding the ketone **81**. At this point, the complete carbon skeleton with the correct configuration at each stereogenic centre for the natural product was in hand. Deoxygenation and degradation of the ester function to an isocyanide group completed the synthesis of **11**.



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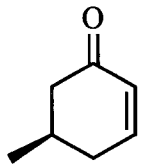

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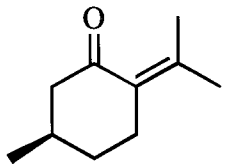

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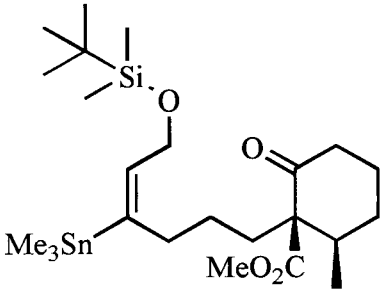

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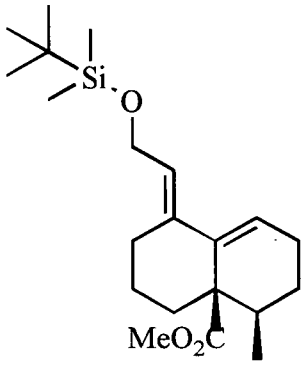

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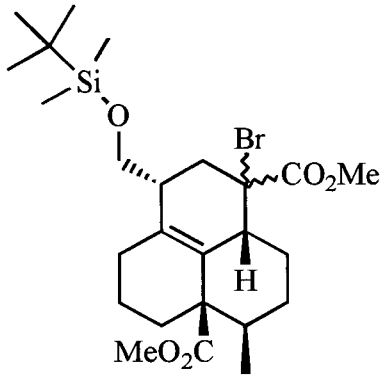

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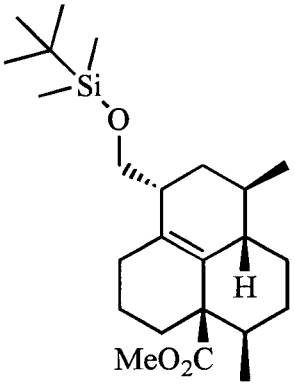

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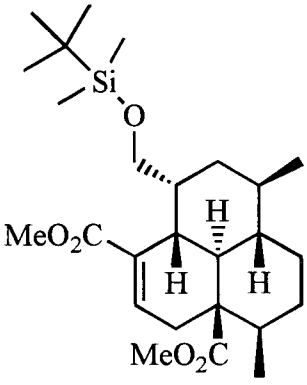

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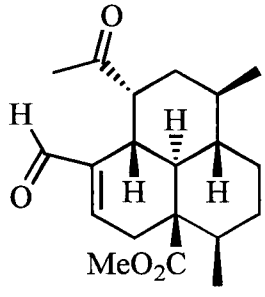

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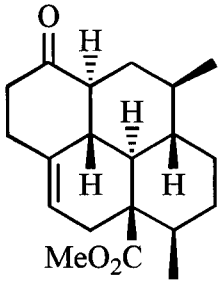

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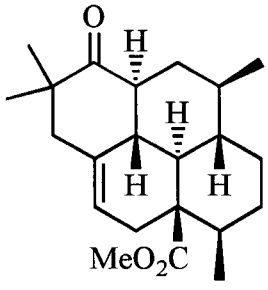

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List of Abbreviations and Acronyms

Ac	acetyl (CH_3CO-)
AIBN	2,2'-azobisisobutyronitrile
Anal.	elemental analysis
aq	aqueous
bp	boiling point
br	broad
Bu	butyl (C_4H_9-)
c	concentration in g per 100 mL
cat.	catalytic
C-x	carbon number x
calcd	calculated
m-CPBA	*m*-chloroperoxybenzoic acid
δ	chemical shift
d	doublet
DCI	desorption chemical ionization
DIBAL-H	diisobutylaluminum hydride
DMAP	*N,N*-dimethylamino-pyridine
DMP	3,5-dimethylpyrazole
DMSO	dimethylsulfoxide
equiv	equivalent(s)
et al.	(Latin) And others.
eV	electron volt
EI	electron ionization
Et	ethyl (C_2H_5-)
ga	gauge
glc	gas—liquid chromatography
h	hour(s)
H-x	hydrogen on carbon number x
HMPA	hexamethylphosphor - amide
hplc	high performance liquid chromatography
hrms	high resolution mass spectrum
in situ.	(Latin) In its original position.
L-Selectride®	lithium triethylborohydride
lrms	low resolution mass spectrum
LDA	lithium diisopropylamide

m	multiplet
m	meta
Me	methyl (CH_3-)
min	minute(s)
MOM	methoxymethyl (CH_3OCH_2-)
mp	melting point
n	normal (as an alkane)
NMO	*N*-methylmorpholine *N*-oxide
[O]	oxidation
p	pseudo
PCC	pyridinium chloro-chromate
Ph	phenyl (C_6H_5-)
ppm	part per million
Pr	propyl (C_3H_7-)
psi	pounds per square inch
q	quartet
rt	ambient temperature
s	singlet
sec	secondary (as an alkane)
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tert	tertiary (as an alkane)
Tf	trifluoromethanesulfonyl (CF_3SO_2-)
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	tetramethylsilane
TPAP	tetra-*n*-propylammonium perruthenate
Ts	tosyl (*p*-$CH_3C_4H_4SO_2$-)
uv	ultraviolet
xs.	excess

Acknowledgements

I would like to take this opportunity to express my gratitude to my professor Dr. Edward Piers. I have admired his dedication to science, his ongoing commitment to his students' success and his willingness to share his wisdom; I consider myself fortunate to have worked under his direction.

The generous gift of an authentic sample of the naturally occurring (-)-8-isocyano-10-cycloamphilectene ((-)-**11**) and accompanying spectra from Professor T. Higa of the Department of Marine Sciences, University of the Ryukyus, Nishihara, Okinawa, Japan is gratefully acknowledged.

The equipment used to develop the hydrogenation chemistry employed in the stereoselective reduction of the α,β-unsaturated ketone **22** was lent by Dr. Brian Cliff of the UBC Chemistry department. We greatly appreciate the loan of this equipment.

I am personally indebted to the members of the Piers research group with whom I have had the pleasure of working. Their friendship, thoughtful discussions and kind advice have enriched my time at UBC, and were instrumental in the successful conclusion of my research.

Finally, financial support in the form of Research and Teaching Assistantships from the University of British Columbia is gratefully acknowledged.

Introduction

General Introduction

The synthesis of organic molecules of all levels of complexity involves the conversion of available substances of known structure, through a sequence of particular, controlled chemical reactions, into other substances bearing a desired molecular structure. Through the process of rational synthetic design, organic chemists can create molecules designed to test structural theory or a theoretical hypothesis, or to be tested for medicinal value or for commercial use.

The tools of the synthetic organic chemist are the chemical transformations that are at one's disposal. Broadly speaking, these chemical transformations can be classified as either those in which a new carbon-carbon bond is formed or those in which functional groups are changed or interconverted. Over the years, a vast array of chemical reactions have been developed to carry out these transformations in the laboratory. These reactions vary in nature from those involving simple organic reactants to more complicated clusters of ligands around transition metals. Some reactions may be carried out under standard conditions whereas others require conditions that rigorously exclude atmospheric oxygen, moisture or both.

It has long been the practice of synthetic organic chemists to use the tools of organic chemistry to attempt the synthesis of natural products. The synthesis of substances occurring in nature provides a measure of the conditions and powers of science. The synthesis of a natural product has traditionally served as an independent proof of its proposed structure. Now, synthesis often serves as an artificial source of the material if the isolation of the material from the natural source is not viable. Furthermore, it is through synthetic chemistry that analogues of natural products can be prepared. It is through studies of these compounds that the key

structural features responsible for the biological reactivity of natural products, such as analgesics and insect antifeedants, can and have been elucidated. Finally, natural product synthesis provides the student of organic chemistry with a wide range of experience in the laboratory with various chemical reaction conditions as well as practical techniques, and as such, it serves as excellent training.

Synthetic organic chemistry also plays a key role in the development of medicinal substances such as anticancer and antibiotic and antiviral antiinfective agents. It is often stated by organic chemists that synthetic organic chemistry drives the pharmaceutical industry. Indeed a primary source of employment for chemists trained in the field of organic synthesis is with the major drug houses. These companies often have extensive and well funded research programs that have led to many interesting and useful discoveries. But to what extent does synthetic organic chemistry actually play a role in the design and development of medicinal substances? A recent article published in the Journal of Natural Products[1] serves to illustrate this role very well. In their article, the authors conducted a survey of anticancer and antiinfective agents approved for use by either the United States Food and Drug Administration or comparable agencies in other countries during the period of 1983 to 1994. Their data[2] shows that nearly 90% of the substances considered could be traced in origin or in their development to synthetic organic chemistry. More specifically, the authors found that new approved drugs, for the period of 1983 to 1994, that are classified as analgesics, antidepressants, antihistamines, antihypertensives, anxiolytics, cardiotonics, hypnotic drugs and antifungal agents were all exclusively synthetic in origin. In addition, over two thirds of the new antiinflammatory substances were synthetic in origin.

Compounds in the pre-New Drug Application phase up to the end of 1995 were also included in the survey. For these substances, the author's survey[2] shows that more than half could be traced in origin or in their development to synthetic organic chemistry.

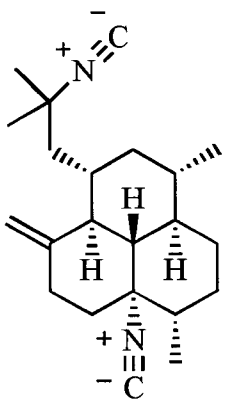
For the period of 1959 to 1973, an article[3] published in the American Journal of Pharmacology reveals, in a survey similar to that in the Journal of Natural Products article, that approximately 60% of all substances prescribed by physicians in the United States were of synthetic origin.

So it can be seen that synthetic organic chemistry does indeed play a leadership role in the development of medicinal substances. Although natural products chemists, molecular biologists and pharmacologists also play a key role in the discovery of chemotherapeutics, such as analgesics, antiallergics, antiinflamatories, antivirals, immunosuppressants, anesthetics and coronary drugs to name only a few, it is synthetic organic chemists that see the majority of these medicinal agents through their various levels of development and finally to public availability.

Synthetic organic chemistry also has had dramatic effects on other industrial areas. Developments in the fields of insect antifeedants and selective pesticides have made agricultural operations more efficient and environmentally friendly. Advances in polymer chemistry have resulted from improvements in monomer synthesis and reaction catalysis. Thermoplastic and thermosetting polymers have resulted from research in organic chemistry. These polymers have afforded substances with such varied uses as synthetic fibers, films, pipes coatings, molded articles and so forth.

Background

Previous work in our laboratories has been directed towards, among other things, the total synthesis of racemic modifications of the amphilectane diterpenoids 8,15-diisocyano-11(20)-amphilectane (**1**),[4] whose levorotatory antipode has been isolated from the marine sponge *Hymemiacidon amphilecta*,[5] and 8-isocyano-10,14-amphilectadiene (**2**),[6] whose levorotatory antipode has been isolated from the Palauan sponge *Halichondria* sp.[7] These compounds share the amphilectane carbon skeleton **3** and contain the somewhat uncommon isocyanide moiety.



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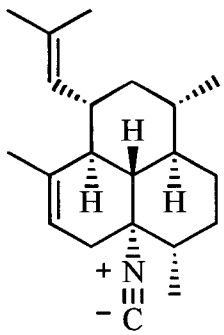

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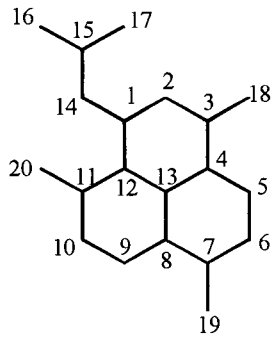
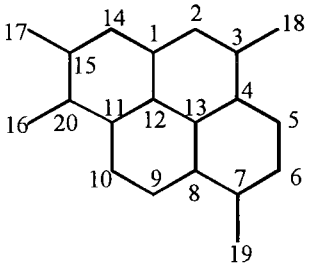


3

The largest group of naturally occurring isocyanides discovered so far has come from marine organisms. These compounds often display marked cytotoxic activity.[5,8] More than 40 naturally occurring isocyanides have been reported[9] to date. The isocyanides are often found with the corresponding isothiocyanate, formamide and amine derivatives.[8,10]

A diterpene isocyanide from the structurally similar adocaine family, which share the carbon skeleton **4**, (+)-7,20-diisocyanoadociane (**5**) was isolated from a sponge of the genus

Amphimedon,[11] and has been synthesized by Corey and Magriotis,[12] thus allowing assignment of its absolute configuration.



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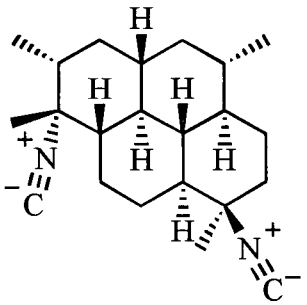

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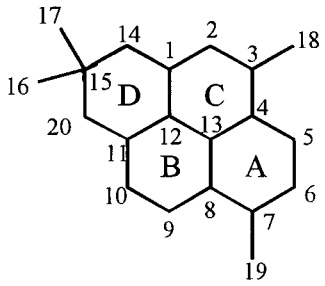

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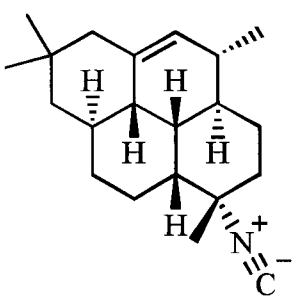
A group of diterpene isocyanides and formamides, bearing the carbon skeleton **6**, have been isolated from a marine sponge *Adocia* sp.,[5] from a Palauan sponge of the genus *Halichondra*[7] and from the dorsal mantle of nudibranchs that feed upon Halichondrid sponges.[7,13] These compounds have been named the cycloamphilectanes and include such compounds as 7-isocyano-1-cycloamphilectene (**7**), 7-isocyano-11-cycloamphilectene (**8**), 8-isocyano-1(12)-cycloamphilectene (**9**), 8-formamido-1(12)-cycloamphilectene (**10**) and 8-isocyano-10-cyclo-amphilectene (**11**). Mixtures containing the compounds **9**, **10** and **11** displayed marked *in vitro* antimicrobial activity, particularly against gram positive bacteria,[5] but showed no *in vivo* activity



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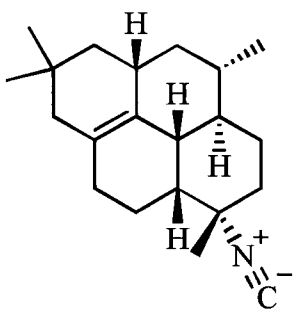

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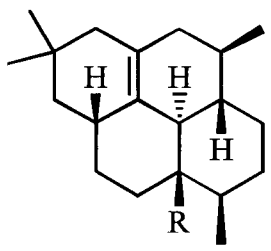
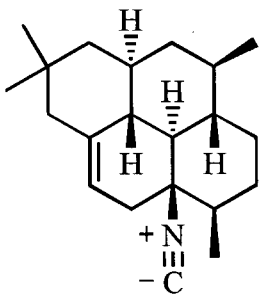


9 R= —N≡C

10 R= —NHCHO



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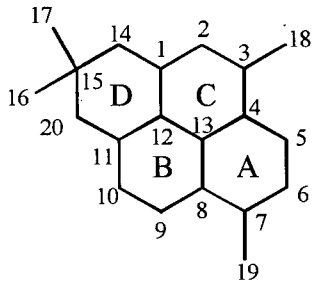


6

other than marked toxicity.[5] Bergquist has proposed[14] that the presence of isocyanides, as well as the corresponding isothiocyanate, formamide and amine derivatives, in marine organisms may confer an advantage by helping to preserve the specificity of association of the sponge and its preferred microfloral symbionts.

8-Isocyano-10-cycloamphilectene (**11**) can be seen as a regular diterpene arising from a formal cyclization of an isoprene derived 20 carbon precursor as shown in Figure 1.[15] The isoprene subunits are indicated by the heavy bonds. Their connectivity is shown as normal bonds and the theoretical cyclizations are shown with broken-line bonds. At least three different foldings of the C_{20} precursor can lead to the required skeleton.

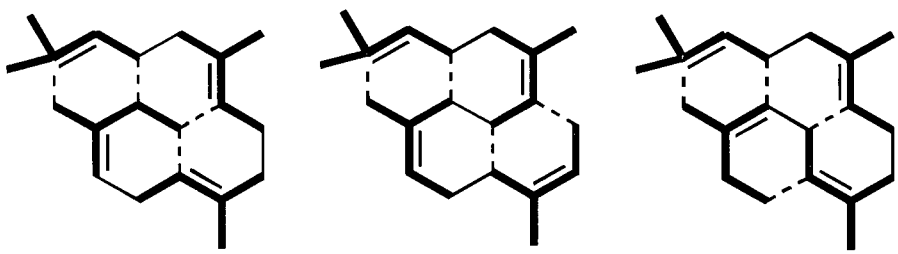


Figure 1: Possible Arrangements of Isoprene Units Leading to the Cycloamphilectane Carbon Skeleton

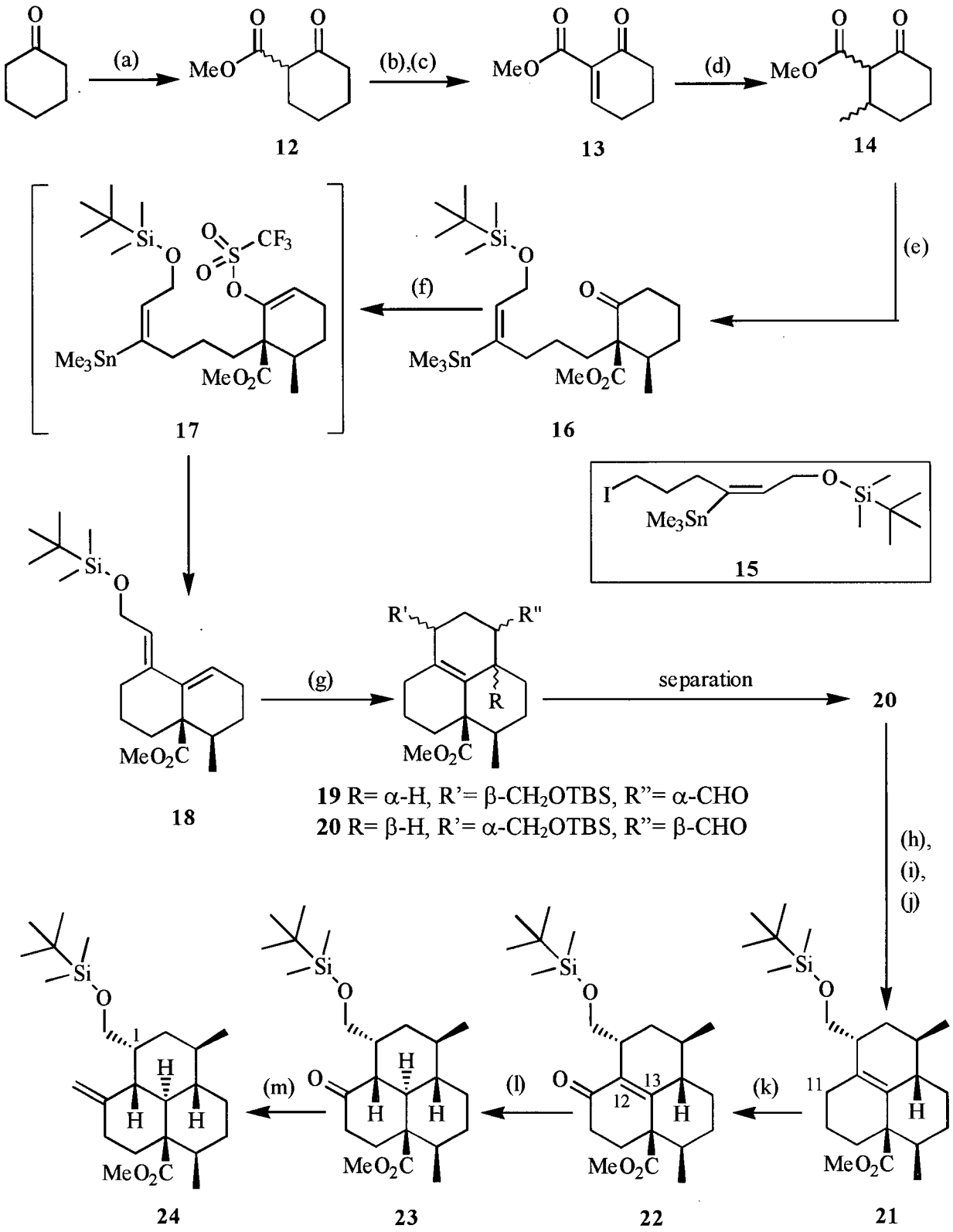
Although the syntheses of (±)-**1** and (±)-**2** have been delineated elsewhere,[4,6] a brief summary of the synthetic route to (±)-**1** will be presented at this point, as a portion of the

synthesis of (+)-**11** was based thereupon. (±)-**1** was synthesized from cyclohexanone in 24 steps (see Scheme 1).

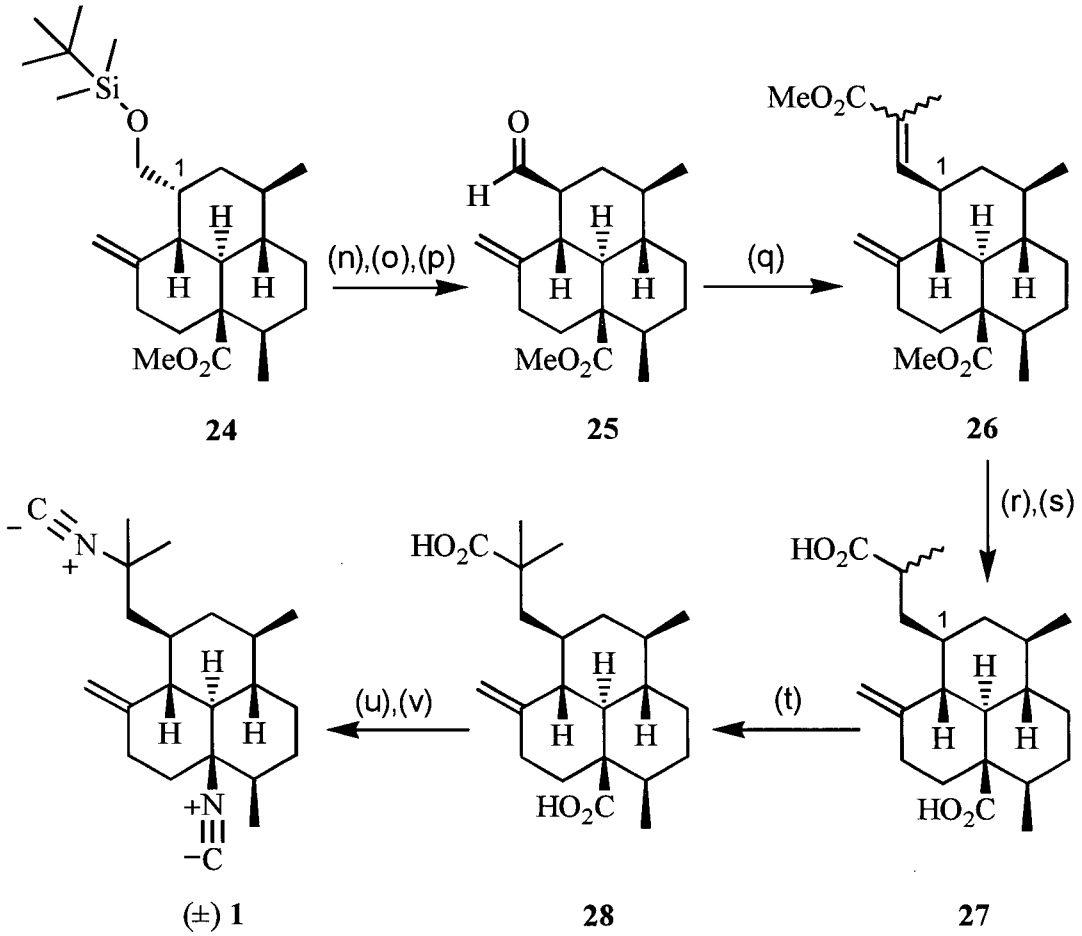
Cyclohexanone was transformed into the β-keto ester **14** by a four step process. Methoxycarbonylation of cyclohexanone by the method[16] of Ruest *et al.* gave the β-keto ester **12**. Benzeneselenation, followed by oxidation—elimination of the selenide gave 2-(methoxycarbonyl)-2-cyclohexenone (**13**). 2-(Methoxycarbonyl)-3-methylcyclohexanone (**14**) was prepared by reaction of the β-keto ester (**13**) with either lithium methyl(phenylthio)cuprate[17] or more recently[4] with lithium methyl(cyano)cuprate.[18]

The β-keto ester **14** was transformed into the diene **18** by an efficient two step process. Alkylation of the potassium enolate anion of the β-keto ester **14** in refluxing toluene with the iodide **15** proceeded regio- and stereoselectively and the ketone **16** was isolated in 70% yield. The conversion of the ketone **16** into the diene **18** was accomplished by conversion of the ketone **16** into the corresponding enol trifluoromethanesulfonate **17**, followed by a palladium(0)-catalyzed intramolecular coupling process.[19] These latter two stages were carried out in a one-pot process and proceeded in 86% overall yield.

Diels—Alder reaction of the diene **18** with acrolein proceeded regioselectively but, unfortunately, gave all four of the possible diastereomeric adducts. Equilibration of this mixture, with sodium methoxide—methanol, followed by chromatographic separation gave two isomeric aldehydes, **19** (minor) and **20** (major). The ratio of the two substances was approximately 3:7, respectively. The synthesis was continued with the major component, aldehyde **20**, whereas the minor product, aldehyde **19** was not synthetically useful. Conversion of the formyl function in aldehyde **20** to a methyl group was accomplished efficiently by known methods, giving the ester **21** in 79% overall yield.



Scheme 1: (continued next page)



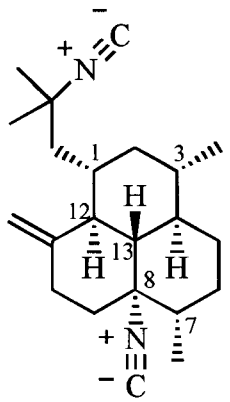
Scheme 1: Synthesis of (±) **1** Reagents (a) NaH, cat. KH, dimethylcarbonate, THF; (b) KH, THF; PhSeBr; (c) *m*-CPBA, THF; (d) MeCu(CN)Li, THF; (e) KH, toluene; **15** (f) LDA, THF; $PhNTf_2$; $Pd(PPh_3)_4$; (g) acrolein, benzene; NaOMe, MeOH; (h) DIBAL-H, THF; (I) TsCl, DMAP, CH_2Cl_2; (j) Super-Hydride®, THF; (k) CrO_3—3,5-dimethylpyrazole, CH_2Cl_2; (l) Na, *tert*-BuOH, NH_3; (m) Zn, CH_2Br_2, $TiCl_4$, CH_2Cl_2; (n) *n*-Bu_4NF, THF; (o) $(COCl)_2$, Me_2SO, CH_2Cl_2; Et_3N; (p) NaOMe, MeOH; (q) $[(MeO)_2$-$POC(Me)CO_2Me]K$, 18-Crown-6, THF; separation; (r) PhSeNa, THF, HMPA; (s) Li, NH_3; (t) xs. LDA, THF; xs. MeI; (u) diphenylphosphoryl azide, toluene; Me_3Si-$(CH_2)_2OH$, Et_3N; *n*-Bu_4NF, THF; acetic formic anhydride, Et_2O; (v) PPh_3, CCl_4, Et_3N.

Treatment of the ester **21** with chromium trioxide—3,5-dimethylpyrazole complex in methylene chloride served to introduce an oxygen function at C-11 (amphilectane numbering) and the α,β-unsaturated ketone **22** was isolated in 77% yield. Stereoselective reduction of the C-12 to C-13 carbon-carbon double bond was accomplished by alkali metal—ammonia reduction. The best and most consistent results were obtained with the use of an excess of sodium metal as the reductant. Thus, treatment of the α,β-unsaturated ketone **22** with 15 equiv of sodium and 2 equiv of *tert*-butyl alcohol in ammonia—diethyl ether gave the ketone **23** with the correct stereochemistry at C-12 and C-13, (amphilectane numbering).

Treatment of the ketone **23** with the reagent[20] derived from zinc dust, CH_2Br_2 and $TiCl_4$ provided the required alkene **24**. The correct stereochemistry was established at C-1 (amphilectane numbering) by a deprotection, oxidation, epimerization sequence and gave the aldehyde **25**. Subjection of the aldehyde **25** to a Wittig-Horner reaction with the potassium salt of trimethyl 2-phosphonopropionate gave a mixture of the geometrically isomeric α,β-unsaturated esters **26**, which were separated by column chromatography on silica gel.

Treatment of the (*E*)-isomer of the α,β-unsaturated esters **26** with the highly nucleophilic reagent sodium benzeneselenide in THF—hexamethylphosphoramide degraded both ester functions to their corresponding carboxylic acids and the carbon-carbon double bond on the C-1 (amphilectane numbering) side chain was then reduced utilizing a dissolving metal reduction. In a subsequent step, alkylation of the trianion derived from reaction of the dicarboxylic acid with an excess of LDA with methyl iodide gave the dicarboxylic acid **28**, thus introducing the final required carbon atom for the amphilectane carbon skeleton.

To complete the total synthesis, the acid functions of **28** were converted into isocyanide groups. This transformation was accomplished by an efficient three stage process that had been developed for this purpose in our laboratories. The details of this process will be discussed later.



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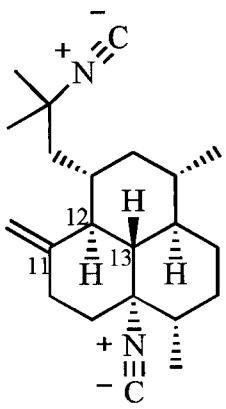
Thus, the synthetic efforts described above resulted in the first total synthesis of (±)-8,15-diisocyano-10(20)-amphilectene (**1**). The key features of the described total synthesis were the reactions which formed the second and third rings, namely an intramolecular Stille type coupling and a Diels—Alder reaction, respectively. The configurations at C-1 and C-3 (amphilectane numbering) were established under thermodynamic control whereas those of C-4, C-7, C-8, C-12 and C-13 were established under conditions of kinetic control.

Objective and Goals

The overall objective of the work described in this thesis was to complete a total synthesis of 8-isocyano-10-cycloamphilectene (**11**). The facts that the diterpene isocyanide **11** possesses a synthetically challenging structure (a tetracyclic compound with an array of seven contiguous stereogenic centres), and that it is an antimicrobial compound made it a tempting target for total



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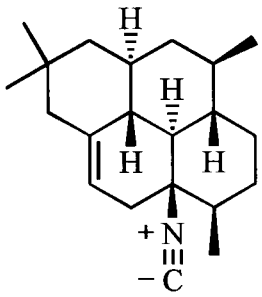

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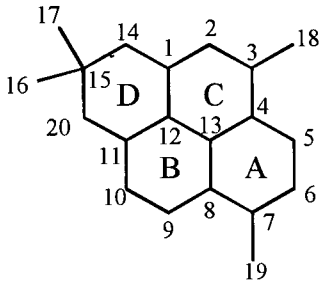

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synthesis. In the course of the planning of the synthetic route, a number of additional sub-goals became apparent.

In their communication[5] disclosing the structure of (-)-8-isocyano-10-cycloamphilectene (**11**), the authors were able to determine the relative stereochemistry of **11**, from X-ray diffraction data, but were unable to provide the absolute configuration of the molecule. Thus, it was decided to use a synthetic sequence that would determine the absolute configuration of (-)-8-isocyano-10-cycloamphilectene (**11**). To achieve this goal, the synthetic plan was to synthesize a single enantiomer of the diterpene isocyanide **11** and to compare the optical rotations of the synthetic and natural materials. For this plan to be successful, the absolute configuration of the intermediate at the point where the enantiomeric excess would be introduced into the synthesis would have to be known unambiguously.

Upon examination of the previous syntheses, especially that of (±)-8,15-diisocyano-10(20)-amphilectene (**1**), with an eye towards the planned total synthesis, two further goals were apparent. Firstly, it was hoped that the synthetic route could be made more efficient at the stage where the third carbocyclic ring, (ring C), of the skeleton was formed. In the previous syntheses, the Diels—Alder chemistry employed for this purpose gave facial selectivity that were at best 7:3

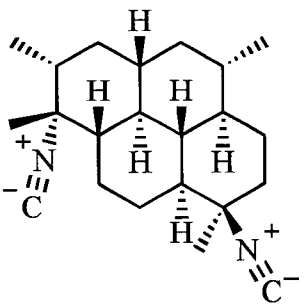
in favour of the required isomer. Thus, a second goal for this synthesis was to modify this chemistry to improve the facial selectivity of this reaction.

Secondly, in the stages where the allylic oxidation served to functionalize C-11 (amphilectane numbering) and subsequently where an alkali metal—ammonia reduction served to saturate the C-12 to C-13 carbon-carbon double bond and set the stereochemistry at these centres, it was not unusual, especially when working on larger or preparative scales, for each reaction to proceed in only about 60% yield. This gave an overall yield for this two step process in the range of 30 to 35%. In the planned synthesis, this transformation would occur at a point where a considerable amount of chemistry remained to be done. Clearly, the loss of a large amount of material, as much as 70%, at this point would be both inconvenient and discouraging. Thus, a third goal for this synthesis was to attempt to find a more efficient method of effecting the overall transformation from the alkene **21** to the ketone **23**.

Finally, in the data reported[5] for the natural product, the absorption for the isocyanide function in the ir spectrum, 2245 cm^{-1}, seems anomalous. The accepted range for this absorption is 2100 to 2180 cm^{-1}.[21] A fourth and final (minor) goal for this synthesis was to attempt to confirm the reported value and thus determine whether this compound displays abnormal behaviour, or if the reported value was in error.

Discussion

Isolation and Characterization of (-)-8-Isocyano-10-cycloamphilectene (11)



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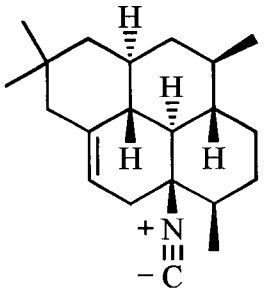

11

In 1980 Kaslauskas and coworkers, at the Roche Research Institute of Marine Pharmacology, reported the isolation of 6 new tri- and tetracyclic diterpene isocyanides from a marine sponge of the genus *Adocia*.[5] The mother liquors from the direct crystallization of diisocyanoadocaine (**5**), representing about 1% of the dry weight of the sponge, contained a highly complex mixture of mono- and diisocyanides. The mono- and diisocyanides were separated by silica gel column chromatography. The monoisocyanides were then purified by exhaustive hplc on a Magnum® 9 silica gel column using methylene chloride and then 4:1 hexane—diisopropyl ether as the eluents. The diisocyanides were purified using the same column and 3:2 hexane—diisopropyl ether as the eluting solvent. Although most of the compounds were not obtained in sufficient quantity to allow chemical correlation spectroscopy, some of the compounds were highly crystalline.

The diterpene (-)-8-isocyano-10-cycloamphilectene (**11**) possessed spectral data[5] requiring 7 degrees of unsaturation, suggesting a tetracyclic carbon skeleton, a single isocyanide group, and a single trisubstituted carbon-carbon double bond. These features were confirmed by single crystal X-ray analysis, which also gave the relative stereochemistry at the seven

stereogenic centres. The colourless solid has a melting point of 88 - 89 °C, an optical rotation of -21.7° (c = 2, chloroform), a peak at m/z = 297 amu (5% relative intensity) in the mass spectrum and an absorption at 2245 cm^{-1} in the ir spectrum. The ^{1}H nmr spectrum displayed a broad singlet at δ = 5.20 ppm while the ^{13}C nmr spectrum showed signals at δ = 154.4, 137.5, 115.2, 62.8, 49.0, 47.6, 46.2, 44.0, 43.1, 42.7, 40.6, 38.0, 37.7, 37.2,† 32.2, 31.6, 29.8, 29.5, 25.1, 19.5 and 15.2 ppm.

Retrosynthetic Analysis

The strategy for the construction of 8-isocyano-10-cycloamphilectene (**11**) was based upon the recognition that the diene **18**, previously prepared in our laboratories,[22] would serve as a suitable intermediate. A possible retrosynthetic pathway, leading to this proposed starting material, the diene **18**, is outlined in Scheme 2.

Since it has been demonstrated by Piers *et al.*[4,6] that a methoxycarbonyl group at C-8 (cycloamphilectane numbering), in systems similar to **11**, can be efficiently converted into the isocyanide function required for the natural product, it seemed highly probable that 8-isocyano-10-cycloamphilectene (**11**) would be available from the ester **29**.

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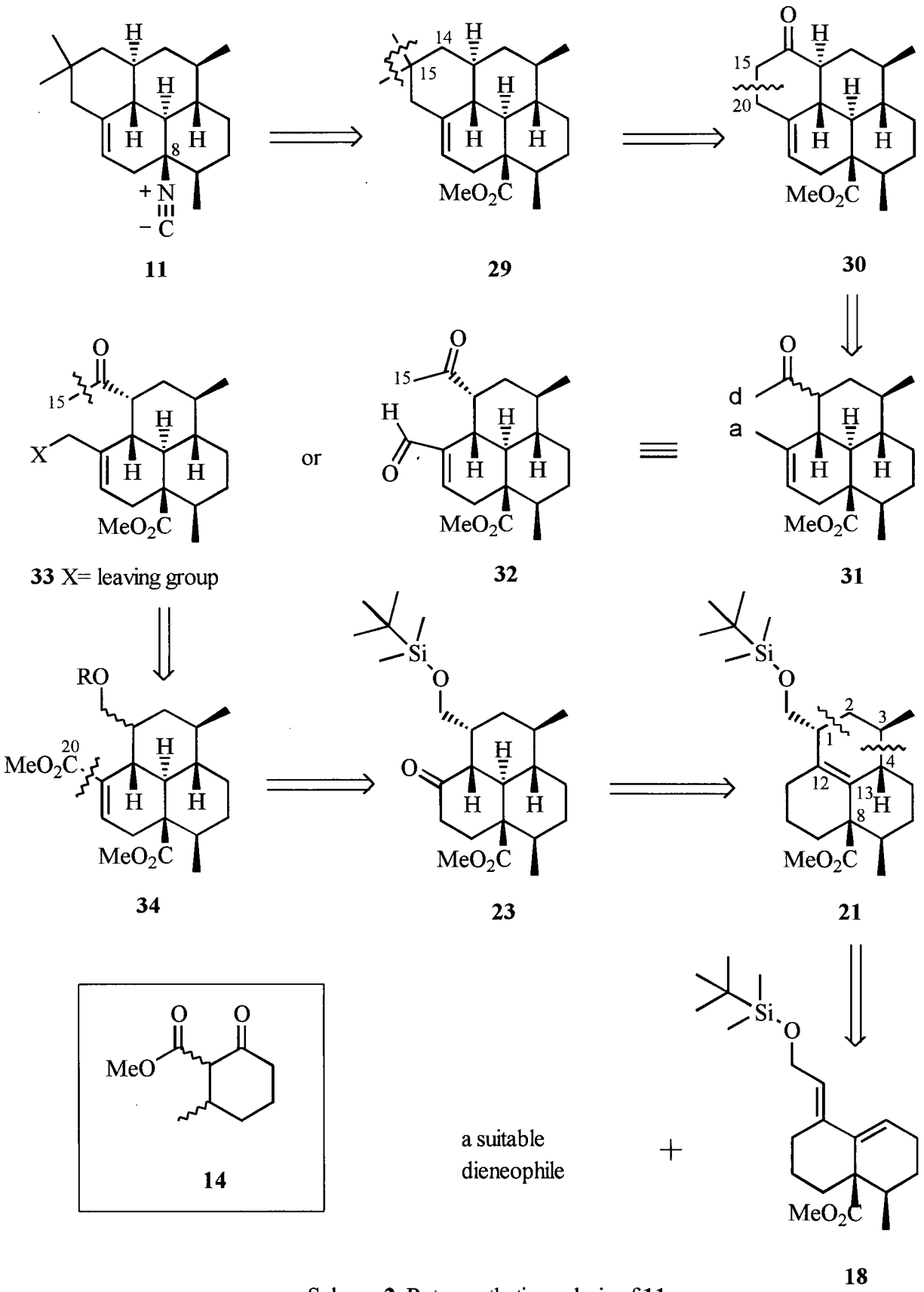
† This signal was not mentioned in the data reported[5] by Kazlauskas *et al.* but was present in the ^{13}C nmr spectrum of an authentic sample of (-)-8-isocyano-10-cycloamphilectene. The spectrum and the sample were provided to us by Prof. T. Higa of the Department of Marine Sciences, University of the Ryukyus, Nishihara, Okinawa, Japan.



Scheme **2**: Retrosynthetic analysis of **11**

Disconnection of the methyl groups at C-15 and introduction of an oxygen function at C-14 would give an intermediate such as the ketone **30**. Synthetically, introduction of the methyl groups was expected to be accomplished by an alkylation, epimerization, alkylation sequence. The C-14 carbonyl oxygen would then be removed by a suitable reduction protocol.

Theoretical disconnection of the bond between C-15 and C-20 (cycloamphilectane numbering) of the ketone **30** would lead to a tricyclic synthon such as **31**, of which compounds such as the keto aldehyde **32** or the ketone **33** would be the synthetic equivalents. The ring closure could be accomplished by an intramolecular alkylation or aldol condensation process. Either of the compounds **32** or **33** should be readily available from the diester **34** by an appropriate sequence of reactions of which the introduction of the C-15 carbon atom would be the key step. The diester **34** could, in turn, be made from the ketone **23** in a few synthetic steps in which the addition of the C-20 carbon atom would be an important step.

It has already been shown[4,6] that the ketone **23** can be prepared from the alkene **21** in two synthetic steps. Allylic oxidation followed by stereoselective reduction of the C-12 to C-13 (amphilectane numbering) carbon-carbon double bond has been employed to achieve this transformation. As alluded to in the introduction section, the efficiency of this two-step transformation was inconsistent, due to the capricious nature of the individual steps. Therefore, at this stage of the present work a more efficient overall conversion of the ester **21** to the ketone **23** would be sought.

Disconnection of the bonds between C-1 and C-2 (amphilectane numbering) and between C-3 and C-4 would lead to the diene **18** and some suitable 3 carbon moiety. It was expected from previous work[4] done in the racemic series, that a Diels—Alder cycloaddition reaction would proceed to give the desired regiochemical outcome, but that the facial selectivity of the

process would be less than desired. It was hoped that the C-8 ester function could be used to provide a steric driving force and that a suitable dienophile could be found to give a high proportion of products resulting from the required facial selectivity. As stated above, the diene **18** had previously been prepared in our laboratories, in racemic form, from 2-(methoxycarbonyl)-3-methylcyclohexanone (**14**).

Introduction of Enantiomeric Excess

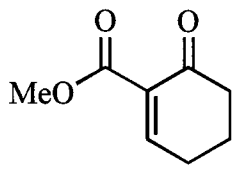
There are two methods available to the organic chemist for the introduction of an enantiomeric excess into a synthetic organic molecule. One method is to use, as the initial starting material or as a substrate at some suitable step, a chiral building block that is either enriched in, or exclusively, a single enantiomer. These building blocks typically are compounds derived from natural sources and include simple terpenoids, amino acids and carbohydrates.

The other method is to carry out an enantioselective chemical reaction, one in which the reagent or substrate itself is chiral, by virtue, for example, of it possessing a chiral auxiliary. Both of these methods were considered for the total synthesis of 8-isocyano-10-cycloamphilectene (**11**).

A third method that one could use to secure a single enantiomer of a natural product is to prepare the racemic modification of the natural material and then carry out a resolution as the final step. Although this method is not technically a chiral method of synthesis, it does offer the advantage of producing, for comparative study, both enantiomers of the natural product. It should be noted, however, that the resolution of a racemate still requires either introduction of a chiral auxiliary, yielding diastereomers that can (hopefully) be separated by conventional

chromatography, or by direct chromatographic separation of the enantiomers, utilizing a chiral stationary or mobile phase. Furthermore, because one does not know if a resolution will be successful until it is attempted, there is much more uncertainty involved in attempting to obtain an enantiomerically pure synthetic material in this manner.

The first option that was considered for the synthesis of enantiomerically pure 8-isocyano-10-cycloamphilectene (**11**) was to carry out early in the synthetic sequence an enantioselective chemical reaction. A convenient point at which to carry out such a reaction would be the conjugate addition of the methyl group to the unsaturated keto ester **13**. This was considered a favourable point for two reasons. Firstly, the unsaturated keto ester **13** is achiral. Thus the facial selectivity of the conjugate addition process would be the only factor that would need to be considered. Secondly, and as importantly, the unsaturated keto ester **13** could be readily made in large quantities by known methods.[4]



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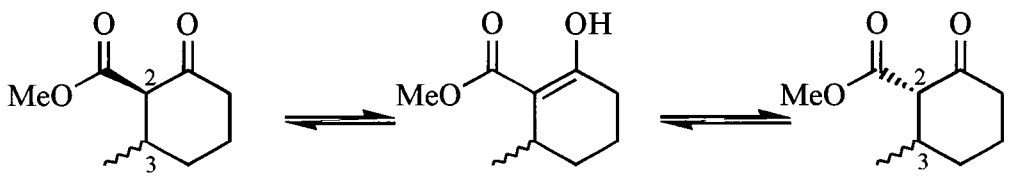
Conjugate addition to the unsaturated keto ester **13** would in fact introduce two stereogenic centres into the product, the β-keto ester **14**, and it would thus seem that diastereo-selectivity would be important. However, it is known that both epimeric forms of the β-keto ester function of compounds such as the β-keto ester **14** are readily available to the molecule (see Figure 2). These epimeric forms inter-convert through its tautomeric form, the enol **36**, and this

enol form is readily accessible to the molecule. Therefore, the stereochemistry of the molecule at C-2 cannot be defined, as the two epimers at that centre are in equilibrium, and the absolute configuration of the β-keto ester **14** is simply a function of the stereochemistry at C-3.

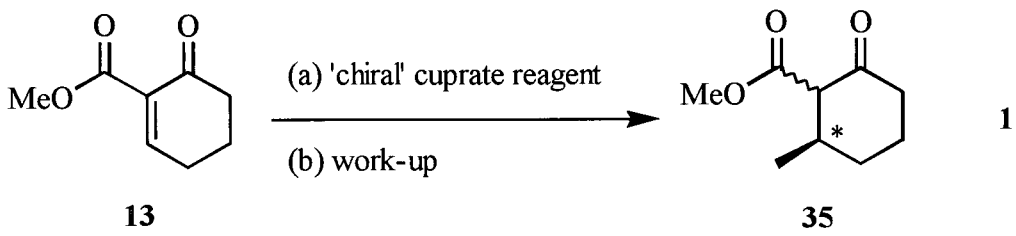
Furthermore, the configuration of the carbon atom bearing the methoxycarbonyl moiety would be set by an alkylation process as the next synthetic step and the stereochemical outcome of this process was well known to be dictated by the orientation of the methyl group at the adjacent carbon atom, C-3. Thus it was obvious that the only stereogenic centre that needed to be considered in the production of a single enantiomer of the β-keto ester **14**, and in the planned synthesis of 8-isocyano-10-cycloamphilectene (**11**), was that bearing the methyl group, C-3.



14 **36** **14**

Figure 2: Equilibration of the Epimers of a β-Keto Ester Through Its Enol Form

In the racemic syntheses of 8,15-diisocyano-10(20)-amphilectene (**1**)[4] and of 8-isocyano-10(14)-amphilectadiene (**2**),[6] the methyl group at C-3 of the β-keto ester **14** was introduced by conjugate addition, using an organocuprate reagent, of a methyl group to the unsaturated keto ester **13**. It was clear that if the introduction of this methyl group, to give the β-keto ester **14**, could be controlled in an enantioselective sense, then the desired enantiomeric excess for the synthesis could be introduced in this way (see Equation 1). The necessary transformation could be carried out by treatment of the β-keto ester **13** with an appropriate chiral cuprate reagent to produce a single, desired isomer such as the β-keto ester **35**.



13 35 1

Conjugate addition of organometallic reagents such as organocuprates and Grignard reagents to α,β-unsaturated carbonyl compounds is an important and well known method of assembling organic molecules. In these reactions, the organic portion of the organometallic reagent adds to the β-carbon atom of the α,β-unsaturated aldehyde, ester or ketone, giving first a resonance stabilized α-carbanion and then, after protonation or some other form of quenching, the β-substituted product (see Figure 3). This methodology has also been applied to other systems yielding resonance stabilized α-carbanions upon conjugate addition, such as 1-nitro- or 1-sulfinylalkenes. The primary advantage of these reactions is that they allow the direct introduction of non-stabilized organic moieties into an organic structure with high chemo- and regioselectivity, starting from substrates which are generally readily available.

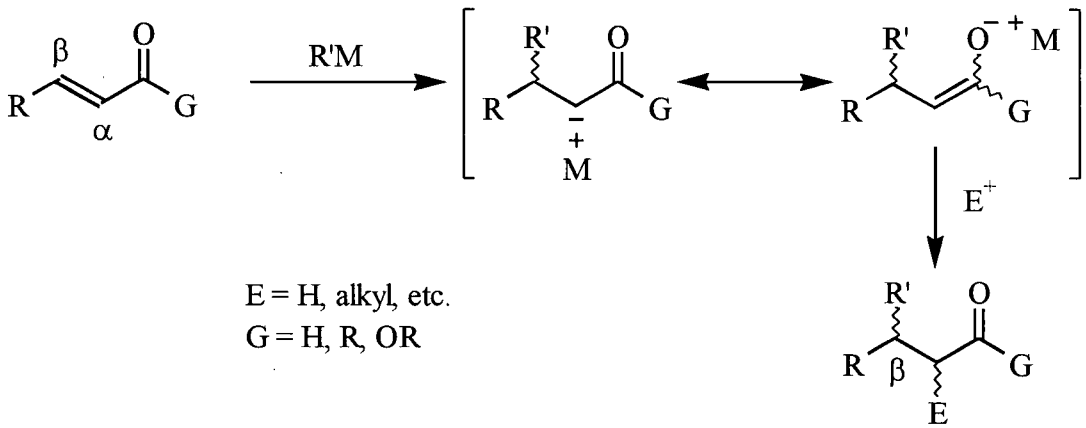


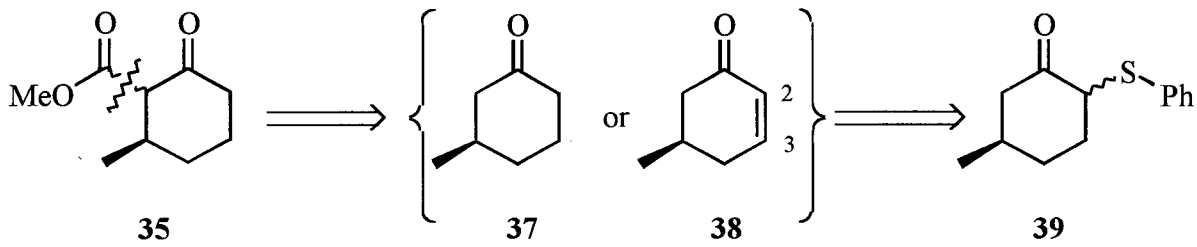
Figure 3: Conjugate Addition to α,β-Unsaturated Carbonyl Compounds

Enantioselective conjugate addition can be achieved either by reacting an achiral reagent with a chiral substrate or by reacting a chiral reagent with a prochiral substrate. For the present requirements, it was clear that the latter alternative would have to be employed. Thus, a method was sought in which a prochiral substrate, the β-keto ester **13**, would be treated with a chiral reagent which would induce the enantioselective conjugate addition of a methyl group onto the substrate.

This subject has been thoroughly reviewed[23] by Rossiter and Swingle. Although much has been established on the utility of such chiral cuprate reagents, the reported enantio-selectivities were typically poor. Furthermore, the chemical yields of the reported reactions were highly variable. Consequently it was decided to attempt to introduce the required chirality through a method in which the starting material for the synthesis was drawn from the pool of chiral substrates.

A retrosynthetic analysis of the keto ester **35** (see Scheme 3) suggested that this compound could be prepared by *C*-methoxycarbonylation of the enolate anion derived from 3-methylcyclohexanone (**37**). The enantiomer of the ketone **37** with the *R*-configuration at C-3 is commercially available as a single stereoisomer and it seemed at first glance that this compound would serve as a good starting point for our synthesis. It was recognized, however, that it might be difficult to chemoselectively methoxycarbonylate the ketone **37** as there is little chemical difference between the protons on either side of the carbonyl group in terms of their accessibility to a base. Indeed, initial attempts at the selective deprotonation of **37**, using LDA as the base under various conditions and monitoring of the generated enolate anion by its reaction with triisopropylsilyl chloride, gave essentially a 1:1 mixture of silyl enol ethers. Producing a mixture

of methoxycarbonylated products was undesirable as the chromatographic separation of β-keto esters is hampered by their tendency to 'streak' rather than to run as discrete bands on silica gel.



35 **37** **38** **39**

Scheme 3: Retrosynthetic analysis of **35**

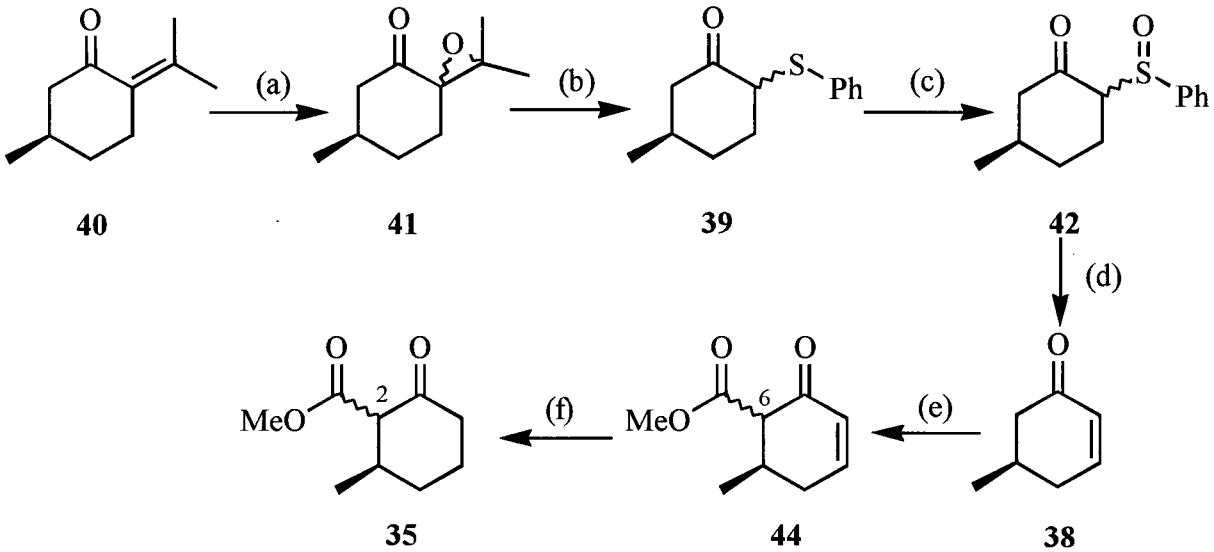
The same retrosynthetic disconnection could also lead to 5-methyl-2-cyclohexenone (**38**). It was expected that the deprotonation of this compound could be kinetically controlled and that methoxycarbonylation of the appropriate enolate anion, followed by hydrogenation of the C-2 to C-3 carbon-carbon double bond, would give the desired β-keto ester **35**. Furthermore, it had been shown previously, by work[24] done in our research laboratories as well as work[25] found in the chemical literature, that the α,β-unsaturated ketone **38** was readily accessible in an enantiomerically pure form from pulegone (**40**), a commercially available monoterpene isolated from oils derived from plants of the *Labiatae* family. Thus, work was started upon the synthesis of a single enantiomer of the required β-keto ester **35** from pulegone.

Preparation of the β-Keto Ester 35

The first key intermediate required for synthesis of 8-isocyano-10-cycloamphilectene (**11**) was the β-keto ester **35**. The β-keto ester **35** was prepared according to the synthetic sequence outlined in Scheme 4. A solution of (1*R*)-(+)-pulegone (**40**) in methanol was treated with 30%

aqueous hydrogen peroxide in 25% aqueous potassium hydroxide solution by a modification of the method[25a] of Katsuhara to provide a mixture of the *cis*- and *trans*-pulegone epoxides (**41**). It was found that proper temperature control was essential for the success of the reaction. The oxidation reaction is quite exothermic and, in order to avoid the formation of by-products, the addition of the base solution to the reaction mixture was carried out dropwise such that the temperature of the reaction mixture did not rise above 10 °C. Work-up of the reaction mixture gave the desired product in nearly quantitative yield as a mixture of diastereomers. The ir spectrum of the product mixture showed a strong absorption at 1740 cm^{-1} consistent with the carbon-oxygen stretching of a ketone carbonyl function and absorptions at 1260 and 919 cm^{-1} for the epoxide function, indicating the successful formation of the product, the epoxides **41**.

The sulfides **39** were prepared from the mixture of the epoxides by a modification of the

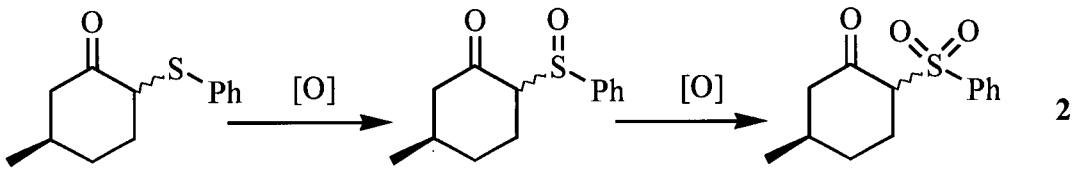


Scheme 4: Synthesis of **35** Reagents (a) H_2O_2, NaOH, MeOH, water; (b) PhSNa, THF; (c) CH_3CO_3H, CH_2Cl_2; (d) $CaCO_3$; (e) LDA – HMPA, THF; MeO_2CCN, THF; (f) H_2, Pd/C, Et_2O.

method[25b] of Avery *et al.* Thus, thiophenoxide opening of the epoxides **41** with concomitant retro-aldol expulsion of acetone gave the regioisomerically pure sulfides **39** in nearly quantitative yield as a mixture of diastereomers, which could be carried on to the next step directly. In their work,[25b] Avery *et al.* used an excess of sodium thiophenoxide to open the epoxide moiety; however, in our studies it was found that if very pure reagents were employed, the reaction could be accomplished with equimolar quantities of the reactants. This change produced a much cleaner reaction and allowed the reaction to be carried out at a concentration much higher than that previously reported.[25b] The mixture of products **39** showed, in the ir spectrum, an absorption at 3059 cm^{-1} for the aromatic carbon-hydrogen stretch, a strong absorption at 1713 cm^{-1} for the carbonyl function and an absorption at 692 cm^{-1} for the carbon-sulfur linkage.

It is well known[26] that sulfides can be oxidized to sulfoxides by many different oxidizing agents. Further oxidation of the sulfoxide, to yield the sulfone, is normally a slower process and is competitive only when fairly strong oxidants are employed (see Equation 2). Early attempts to oxidize the sulfides **39** by the method[27] of Oppolzer and Petrizilka gave varying results. Commercial *m*-chloroperoxybenzoic acid (*m*-CPBA) is sold as a mixture of *m*-CPBA and *m*-chlorobenzoic acid, with the peracid making up between 57 and 86% by weight. The reagent also tends to be quite wet and methylene chloride solutions of the reagent often freeze at the temperatures required for the selective oxidation reaction. As a result of these two factors it was difficult to consistently obtain the desired amount of oxidant for the reaction and, as *m*-CPBA is a strong enough oxidant to efficiently carry out the oxidation of the sulfoxide to the sulfone, the over-oxidized by-product, sulfone **43**, often contaminated the product mixture. Although the sulfone contaminant could be removed from the desired sulfoxide by column chromatography on

silica gel, this process was inconvenient, especially on larger scales, and an alternative oxidation method was sought.



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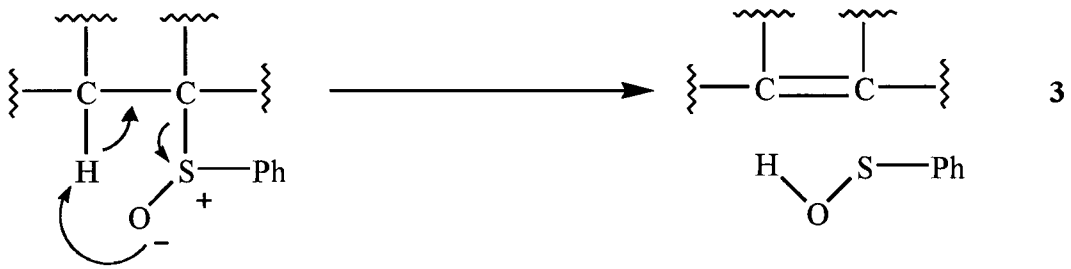
39 **42** **43**

Avery *et al.* have reported[25b] the synthetic utility of the magnesium salt of mono-peroxyphthalic acid hexahydrate[28] to carry out this oxidation. This reagent is provided in known concentration but is not especially soluble in the water—ethanol mixtures required for the oxidation reaction. Thus, on larger scale quantities, the volume of the reaction mixture made its handling somewhat difficult. Furthermore, upon completion of the extractive work-up, large amounts of drying agent were required to dry the ether—ethanol solution and the mixture was often difficult to filter. So, although the over-oxidation problem had been addressed by the use of this method, it was still hoped that an operationally more convenient method might be found to carry out the desired oxidation.

When the oxidation of the sulfide **39** was attempted with peracetic acid, the desired sulfoxide **42** was isolated in essentially quantitative yield. The oxidant is commercially available as a 32% solution by weight in aqueous acetic acid and typically contains about 6% hydrogen peroxide. The presence of the hydrogen peroxide contaminant, however, did not seem to interfere with the desired reaction as none of the over-oxidized product sulfone **43** was detected. Thus one equivalent of peracetic acid was added to a well stirred methylene chloride solution of the sulfide **39** that had been cooled to 0 °C. The reaction was very rapid as demonstrated by tlc

analysis of aliquots from the reaction mixture. Saturated aqueous sodium thiosulfate solution was then added to reduce excess oxidant (mostly hydrogen peroxide). To facilitate the work-up of the reaction mixture, the two phase system was poured into about two volumes of diethyl ether. Acetic acid was removed from the organic phase as its sodium salt by washing the organic phase with saturated aqueous sodium bicarbonate. Removal of the solvent from the dried organic phase gave the sulfoxide **42** as a yellow oil which solidified upon standing. This material showed, in the ir spectrum, a strong absorption at 1046 cm^{-1} for the sulfoxide function as well as absorptions at 3051 and 1704 cm^{-1} for the aromatic C-H and carbonyl stretches, respectively. The solidified material was sufficiently pure to be carried directly on to the next step.

It is well known[29] that sulfoxides bearing a β-hydrogen undergo elimination upon pyrolysis in the presence of a base and this method has been used for the conversion of many ketone, aldehydes and esters into their α,β-unsaturated derivatives.[29] A temperature of about 80 °C is required to effect the elimination reaction. The elimination is a *syn* process, proceeding through a pseudo 5-membered ring internal elimination mechanism, analogous to that of the Cope reaction (see Equation 3).



3

Previously in our laboratories, the conversion of the sulfoxide **42** into (5*R*)-5-methyl-2-cyclohexenone (**38**) had been accomplished by heating a mixture of the sulfoxide **42**, calcium carbonate and carbon tetrachloride to its boiling point. Filtration of the reaction mixture

followed by careful removal of the carbon tetrachloride by distillation gave the product, the α,β-unsaturated ketone **38**. Carbon tetrachloride is a poisonous substance,[30] a carcinogen[30] and has recently been listed under the Canadian Chlorofluorocarbon Control Act as an ozone depleting substance.[31] Thus it was considered appropriate to seek an alternative preparation of the α,β-unsaturated ketone **38**.

The first concerns in finding an alternative solvent for the elimination reaction were 1) the solubility of the sulfoxide **42** in the solvent, as it was believed that the reaction would be faster in the solution state, and, 2) the boiling point of the solvent. Because it was known that the pyrolysis reaction required a temperature of about 80 °C to proceed, solvents with boiling points of greater than that temperature were initially considered. The first solvent tried was butanone, which has a boiling point of 80 °C. The sulfoxide **42** was found to be very soluble in butanone, thus a mixture of the sulfoxide **42**, calcium carbonate and butanone were heated to the boiling point and stirred under reflux. Glc analysis of the liquid phase showed, after as little as 15 min, the presence of the desired product. After 16 h of heating, the mixture was cooled to rt and isolation of the product as described for the carbon tetrachloride procedure was attempted. Unfortunately, although there is a large difference in the boiling points of the α,β-unsaturated ketone **38** and butanone (approximately 120 °C), it proved impossible to separate these materials completely by fractional distillation, presumably due to the formation of an azeotrope. As the next step of the sequence called for a reaction of the ketone function of the α,β-unsaturated ketone **38**, the presence of butanone in the product mixture would clearly interfere if not removed. Thus, although butanone seemed initially promising as an environmentally innocuous alternative to carbon tetrachloride, for the present purpose it did not prove to be appropriate.

It was noted that the sulfoxide **42** was also soluble in some of the low molecular mass hydroxylic solvents. Although the boiling points of ethanol, 78 °C, and propanol, 97 °C, would likely have been suitable for the facilitation of the pyrolysis reaction, it was feared that the separation of these solvents from the product would prove problematic. Because the presence of an alcohol would be detrimental to the course of the next reaction in the sequence and it seemed likely that it would be difficult to obtain the desired α,β-unsaturated ketone **38** in a pure form, the elimination reaction was not attempted in these solvents.

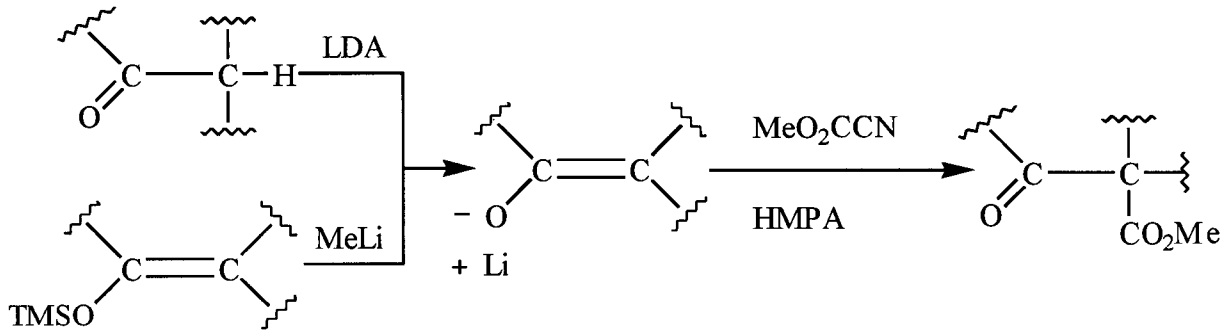
The sulfoxide **42** is very soluble in methylene chloride. The boiling point of this solvent (40 °C), is however insufficient to facilitate the elimination reaction. An attempt was made to carry out the desired elimination reaction in a sealed tube, thus allowing the contents to be heated above the boiling point of the solvent. For this reaction, a soluble base that could not react with a proton source to form a gas was thought to be more appropriate than calcium carbonate, and imidazole was chosen as a suitable candidate. Equimolar amounts of the sulfoxide **42** and imidazole were dissolved in methylene chloride and placed in a sealed tube. The tube was heated to 90 °C and this temperature was maintained for a period of 8 h. The tube was cooled to rt and opened. A two phase system had formed, the upper phase being a clear, yellow liquid and the lower being a more viscous, dark yellow oil. The top layer was carefully removed by pipette and the methylene chloride was evaporated under a stream of argon. The residue, upon distillation, provided the desired α,β-unsaturated ketone **38** in 90% yield. Although this method proved an excellent one for the production of the α,β-unsaturated ketone **38** on a relatively small scale, the requirement for specialized equipment, to safely handle the pressures developed by the reaction on preparative scales, precluded its use as a method for the large scale production of the α,β-unsaturated ketone **38**.

Running the elimination reaction in solvents less volatile than the α,β-unsaturated ketone **38** was also considered as an alternative. It was hoped that the product of the elimination reaction could then be distilled directly from the reaction mixture. Tri(ethylene glycol), bp 285 °C, was first considered as reaction medium for this purpose. Although the sulfoxide **42** is not especially soluble in tri(ethylene glycol), it was hoped that the reaction could be carried out at a temperature above the melting point of the sulfoxide **42**. Thus a mixture of the sulfoxide **42**, calcium carbonate and tri(ethylene glycol) was heated to 120 °C. The reaction's progress was monitored in the following manner. A sample of the liquid phase was removed and partitioned between water and diethyl ether and then glc analysis was carried out on the diethyl ether phase. The presence of the desired product was noted after 1 h and the reaction mixture was heated for 8 h. Unfortunately, attempts to distill the product from the reaction mixture gave only low yields of the desired α,β-unsaturated ketone **38**. Furthermore, this material was invariably contaminated with tri(ethylene glycol). This is not surprising as the difference in the boiling points of the α,β-unsaturated ketone **38** and tri(ethylene glycol) is only about 80 °C. Attempts at running the reaction for longer periods of time did not significantly affect the yield of the product. As it was unlikely that subsequent work on this reaction could provide an efficient process for the production of the α,β-unsaturated ketone **38**, this method for its preparation was not investigated further.

A logical extension of the above attempt was to carry out the elimination reaction in the absence of a solvent, and this method in the end proved to be the best choice for running the elimination reaction without using carbon tetrachloride. Thus, 1 equiv of the sulfoxide **42** and 2 equiv of dry calcium carbonate were ground together in a mortar, to ensure that they were thoroughly mixed, and the mixture was transferred to a round-bottomed flask. The flask was

fitted with a vacuum trap and the apparatus was placed under reduced pressure (about 0.3 Torr). The flask containing the sulfoxide-base mixture was heated (90 °C) to facilitate the elimination reaction while the vacuum trap was cooled (-78 C) to trap the product. The reaction was allowed to proceed for 3 hours after which time the apparatus was brought to atmospheric pressure and then allowed to come to rt. Although the base was dried prior to use, the condensate was often found to be wet. The condensate was dissolved in pentane and the solution was dried over magnesium sulfate. The pentane was then removed by distillation and the residue was distilled to give an excellent yield (91%) of the desired α,β-unsaturated ketone **38**. Gratifyingly, this material proved to be identical with that previously produced in our laboratory by the method using carbon tetrachloride as the solvent.

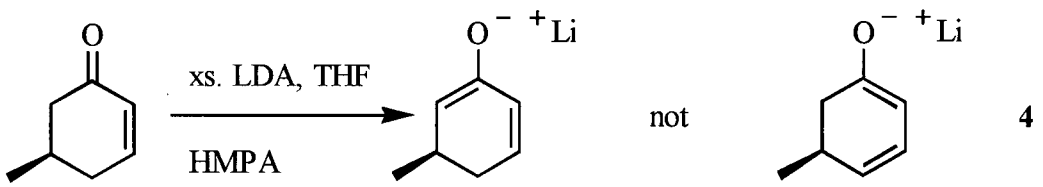
With the α,β-unsaturated ketone **38** in hand, attention was turned towards the synthesis of the required β-keto ester **44**. It was expected that the excellent methodology for the regioselective synthesis of these systems by reaction of the lithium enolate anions of ketones with methyl cyanoformate, as developed[32] by Mander and Sethi, would serve to accomplish this transformation (see Scheme 5). Methyl cyanoformate (Mander's reagent) reacts smoothly with lithium enolate anions of ketones, prepared directly or through the corresponding trimethylsilyl enol ether, in the presence of hexamethylphosphoramide to provide, after appropriate work-up, the desired β-keto esters. Whereas the reaction of lithium enolate anions with alkyl halo-formates or with *O*-alkoxycarbonyl carbonates also serves to accomplish the described transformation, the product is invariably a mixture of *O*- and *C*-alkoxycarbonylated products[33] with the exact product composition being dependent upon such factors as the reaction temperature, stoichiometry, solvent, the counter-ion to the enolate anion, the leaving group in the reagent and steric congestion in the substrate.[32] Mander's reagent, on the other hand, reacts with



Scheme 5: Methoxycarbonylation with Mander's reagent

lithium enolate anions of ketones exclusively on the carbon of the enolate anion; none of the enol carbonate that would result from the reaction occurring at the oxygen of the enolate anion is observed.

The α,β-unsaturated ketone **38** was chosen as the substrate for this reaction because the required lithium enolate **45**, as opposed to lithium enolate **46**, was readily available by reaction of the α,β-unsaturated ketone **38** with LDA under conditions of kinetic control (see equation 4). As LDA can add in a conjugate fashion to α,β-unsaturated ketones, the base actually employed was a complex of LDA and hexamethylphosphoramide. This complex, when used as a base, is more basic and less nucleophilic than is LDA alone.[34] Because hexamethylphosphoramide was introduced at the enolate anion formation stage, none was added prior to the introduction of the Mander's reagent, as would be typical for Mander and Sethi's protocol. This modification to the procedure did not seem to affect the course of the reaction.



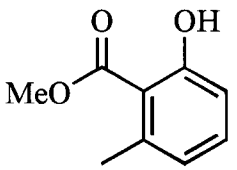
38 **45** **46** **4**

Thus, addition of a solution of Mander's reagent in THF to a solution of the lithium enolate anion **45**, prepared by reaction of the α,β-unsaturated ketone **38** and LDA—hexamethylphosphoramide complex in THF solution at -48 °C, gave, after work-up and purification of the crude product by column chromatography on silica gel, the β-keto ester **44** in 78% yield. The product exists as a mixture of epimers at C-6. This material showed, in the ir spectrum, strong absorptions at 1742 and 1678 cm^{-1} and weaker absorptions at 1650 and 1622 cm^{-1}, for the β-keto ester functions of the two epimers of the product. In the ^1H nmr spectrum, two singlets were observed at δ 3.67 and 3.74 ppm representing the protons from the methoxy groups of the minor and major epimers, respectively. Comparison of the integrals for these resonances showed that the epimers of the product existed in the ratio of about 5:1.

All that now remained to complete the synthesis of the β-keto ester **35** was the hydrogenation of the carbon-carbon double bond in the β-keto ester **44**. Hydrogenation over a platinum metal catalyst was expected to be the most effective method for this transformation. Of the metals considered as catalysts, including platinum, palladium, rhodium and ruthenium, palladium seemed to be the candidate most likely to give a high yield of the desired product. Platinum black, prepared from Adam's catalyst *in situ*, was thought to be too reactive a catalyst, as it is known to hydrogenate the carbon-oxygen double bonds of ketones under relatively mild conditions,[35] while supported platinum catalysts tend to be as reactive or more reactive than is platinum black.[36] Rhodium catalysts are most often used for hydrogenation of aromatic and heteroaromatic systems at relatively low temperatures and pressures.[37] Furthermore, rhodium catalysts are more readily poisoned than are palladium catalysts.[38] Finally, ruthenium catalysts were also thought to be too reactive for the desired transformation. Ruthenium catalysts, similar to platinum catalysts, are known to hydrogenate aliphatic ketones under relatively mild

conditions.[37,38] Palladium on charcoal was selected to effect the desired reduction as this catalyst is known to be the best catalyst for the reduction of olefins and acetylenes.[39] Disubstituted carbon-carbon double bonds, in most cases, are hydrogenated at rt and just above atmospheric pressure. Furthermore, palladium on charcoal seems to be the most effective of the platinum metal catalysts for the reduction of olefins conjugated to carbonyl groups, especially ketones.[40]

Thus, the β-keto ester **44** was hydrogenated under hydrogen at atmospheric pressure and at 0 °C, using 5 mol % of 10% palladium on charcoal. The reaction was run using diethyl ether as the solvent and was complete within 30 min. For this reaction, it was essential that the catalyst be saturated with hydrogen thoroughly prior to the introduction of the substrate. Failure to do so resulted in the production of significant amounts of a fairly polar compound that displayed, in the ^{1}H nmr spectrum, three one-proton signals in the aromatic region of the spectrum. This material was assumed to be the phenol **47**, the product of dehydrogenation of the enol form of the β-keto ester **44**.



47

Filtration of the reaction mixture through a short pad of Celite® to remove the catalyst, followed by removal of the solvent from the filtrate and distillation of the residue gave the desired β-keto ester **35** in nearly quantitative yield. This material existed as a mixture of epimers at the C-2 position. β-Keto ester **35** displayed, in the ir spectrum, four strong absorptions at 1748, 1714, 1651 and 1615 cm^{-1}, representing the β-keto ester functions of the two epimers of

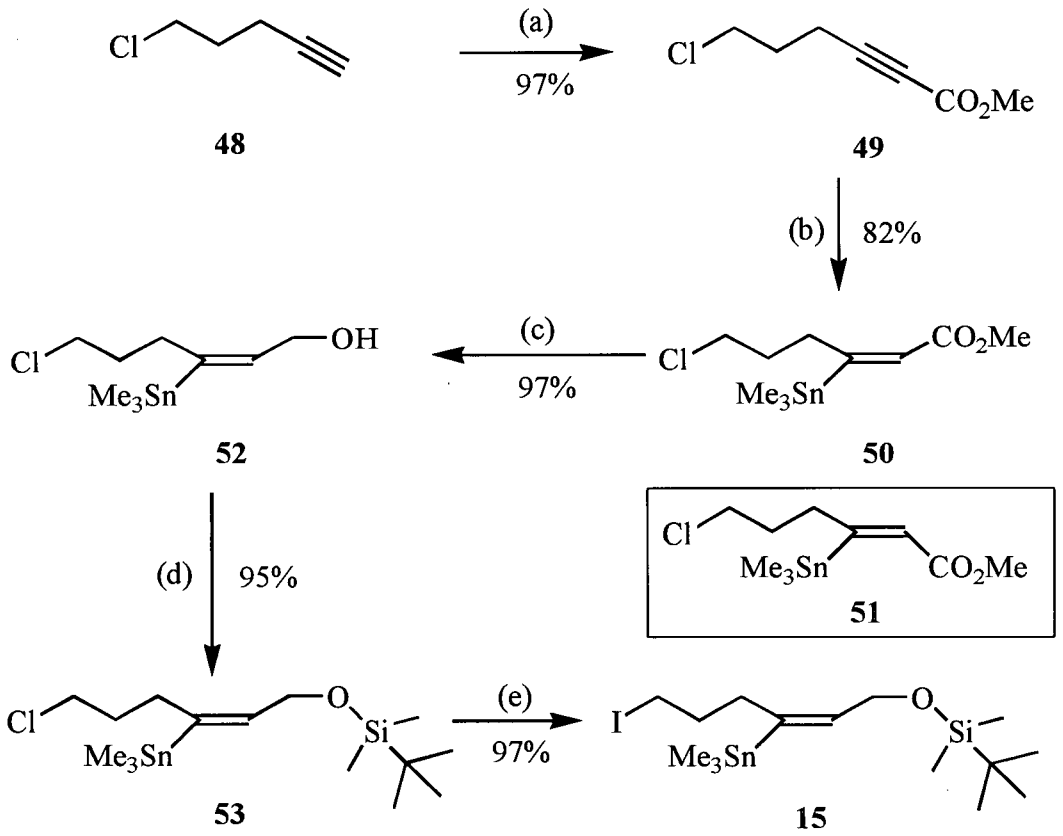
the product. The ^{1}H nmr spectrum of this material showed no resonances in the olefinic region of the spectrum, indicating that the carbon-carbon double bond reduction had gone to completion. Furthermore, resonances were observed at δ 3.71 and 3.75 ppm for the protons of the methoxy groups of the minor and major epimers, respectively. Integration of these resonances showed the epimers to exist, in chloroform solution, in the ratio of about 9:1. Some nmr samples, especially those that had been left standing at rt for extended periods of time, showed a resonance at approximately δ 12 ppm, presumably for the hydroxylic proton of the enol form of the β-keto ester function. A signal at m/z = 170 amu was observed in the mass spectrum, confirming the molecular mass of the product.

Thus, the β-keto ester **35** was prepared from the naturally occurring (*R*)-pulegone (**40**) by a 6 step series of reactions that proceeded in 65% overall yield.

Preparation of the Iodide 15

The next step in the synthesis called for the alkylation of some suitable enolate anion derivative of the β-keto ester **35** with (*E*)-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-iodo-3-(trimethylstannyl)-2-hexene (**15**). The iodide **15** had been previously prepared in our laboratory[41] and, for the present study, the iodide **15** was prepared by a modification of this method (see Scheme 6).

Methyl 6-chloro-2-hexynoate (**49**) was prepared by a modification of the method[41a] of Piers *et al.* In this modified procedure, the base employed was *tert*-butyllithium instead of methyllithium. *tert*-Butyllithium takes on a deep yellow colour in THF solution. The advantage of this procedural change was that this property could be used to indicate when exactly one equiv



Scheme 6: Synthesis of **15** Reagents (a) *tert*-BuLi, THF; MeO_2CCl; (b) Me_3SnCu-(CN)Li, MeOH, THF; (c) DIBAL-H, Et_2O; (d) TBSCl, imidazole, CH_2Cl_2; (e) NaI, acetone.

of the base had been added to the reaction mixture. Thus, *tert*-butyllithium solution was added slowly to a solution of 5-chloro-1-pentyne (**48**) in THF at -78 °C until a very pale yellow colour persisted for a period of 1 min after the addition of the base was terminated. Upon completion of the reaction and subsequent work-up, a cleaner crude product was generated than was the case when methyllithium was employed as the base. In fact, tlc and glc analyses showed that the only detectable organic component in the crude product was the desired alkynic ester **49**, and the column chromatography step, which was required in the previous method,[41a] could be eliminated. Distillation of the crude product gave the alkynic ester **49** in nearly quantitative yield. This

compared to a yield of 81% from the previous method. The distillate produced ir and ^{1}H nmr spectra which were identical with those previously reported[41a] for the alkynic ester **49**.

Methyl (*E*)-6-chloro-3-(trimethylstannyl)-2-hexenoate (**50**) was prepared from the alkynic ester **49** by the method of Piers *et al.*[41a] Thus, reaction of the alkynic ester **49** with lithium (trimethylstannyl)(cyano)cuprate in the presence of methanol provided, stereoselectively, the required α,β-unsaturated ester **50**. After chromatographic separation and distillation of the resulting crude material, the α,β-unsaturated ester **50** was isolated in 82% yield. Also isolated was the isomeric methyl (*Z*)-6-chloro-3-(trimethylstannyl)-2-hexenoate (**51**) in 8% yield. Both of these materials showed ^{1}H nmr spectra identical with those previously reported[41a] for these compounds.

(*E*)-6-Chloro-3-(trimethylstannyl)-2-hexen-1-ol (**52**) was prepared from the α,β-unsaturated ester **50** by the method[41c] of Piers and Friesen. Thus, DIBAL-H reduction of the α,β-unsaturated ester **50**, followed by appropriate work-up gave the alcohol **52** in nearly quantitative yield. The alcohol **52** displayed ir and ^{1}H nmr spectra identical with those previously reported for this compound.[41c]

(*E*)-6-Chloro-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-(trimethylstannyl)-2-hexene (**53**) was prepared from the alcohol **52** by a modification of a standard technique. In this modification, methylene chloride was used to replace the standard *N,N*-dimethylformamide as reaction solvent. The result of this modification was to eliminate the usual aqueous work-up required to remove the *N,N*-dimethylformamide. Under the present modification, all that was required was simple filtration of the reaction mixture through a short pad of silica gel, to remove the imidazole—HCl salt by-product of the reaction. Removal of the solvent gave the product, which was sufficiently pure to be carried on to the next step without further purification. Thus,

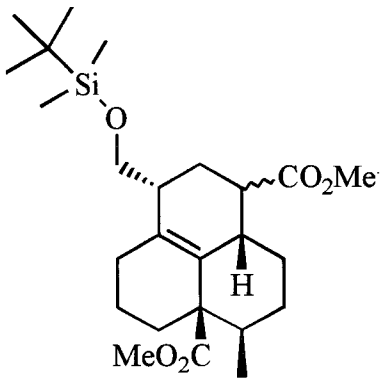
reaction of the alcohol **52** with slight excesses of imidazole and *tert*-butyldimethylsilyl chloride in methylene chloride gave, after appropriate work-up, the desired chloride **53** in nearly quantitative yield. This material produced ir and ^{1}H nmr spectra identical with those reported[41c] previously for this compound.

(*E*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-iodo-3-(trimethylstannyl)-2-hexene (**15**) was prepared from the chloride **53** by a standard halide exchange reaction. Thus, treatment of the chloride **53** with an excess of sodium iodide in acetone gave, after appropriate work-up of the reaction mixture and distillation of the crude product, the desired iodide **15** in nearly quantitative yield. The distillate produced ir and ^{1}H nmr spectra identical with those reported[41c] previously for this compound.

Thus the required alkylating agent, iodide **15**, was prepared from 5-chloro-1-pentyne (**48**), in 71% overall yield, by an efficient 5 stage process.

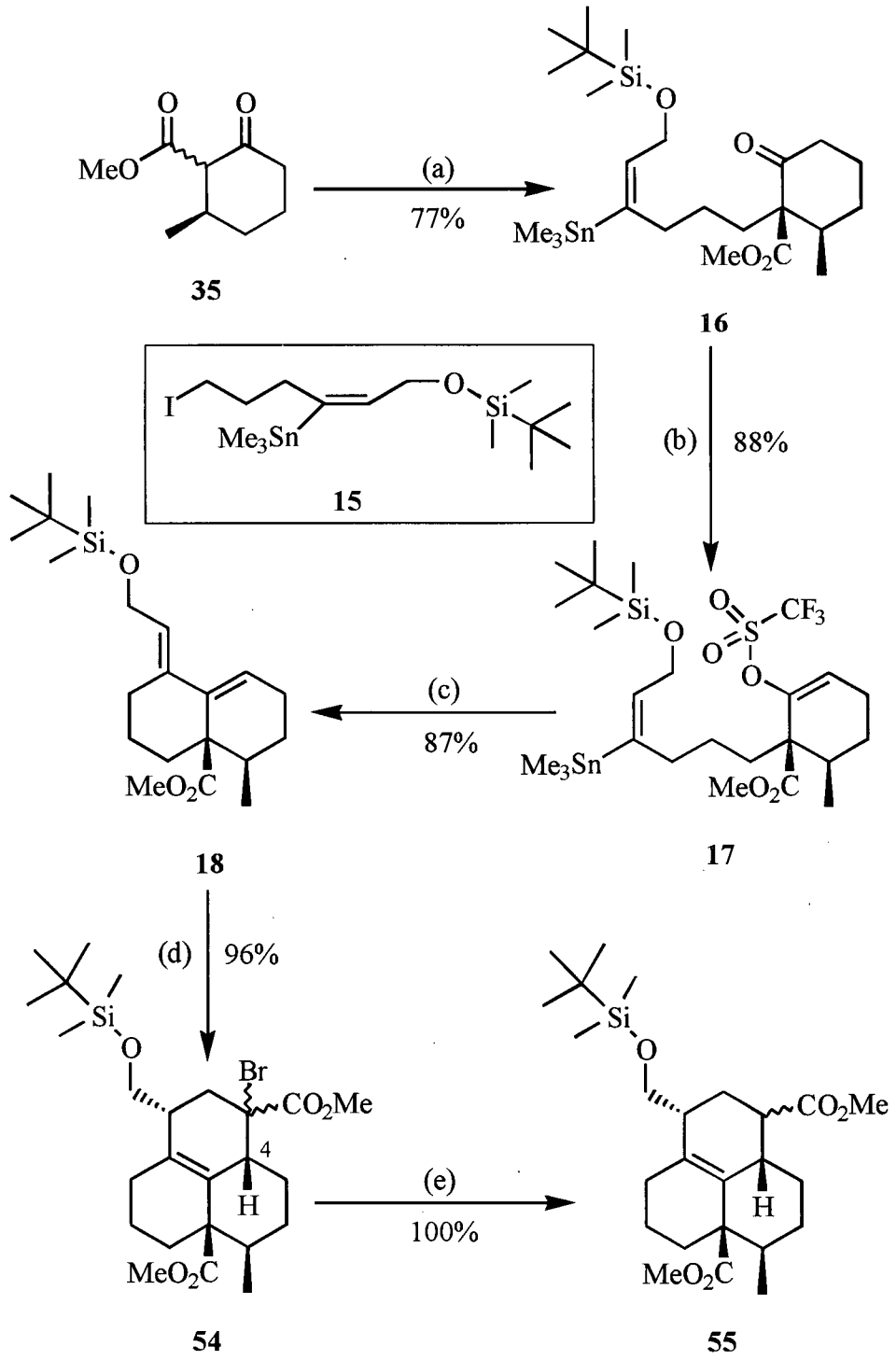
Preparation of the Tricyclic Diester 55

The next key intermediate required for the synthesis of 8-isocyano-10-cycloamphilectene (**11**), according to the retrosynthetic plan, was the tricyclic diester **55**. This compound was prepared according to the route summarized in Scheme 7. The first step was the alkylation of an appropriate derivative of the β-keto ester **35** with iodide **15** to produce methyl (2*R*,3*R*)-2-[(*E*)-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-(trimethylstannyl)-4-hexenyl]-3-methylcyclohexanone-2-carboxylate (**16**). β-Keto esters are known to be especially difficult to alkylate due to the stability of the enolate anions derived from them. Lithium and sodium enolates of β-keto



55

esters often exhibit very little reactivity with normal electrophiles, such as alkyl halides. Potassium enolates tend to be more reactive towards alkylations; however, the product is often a mixture of reaction of the electrophile at the carbon and the ketonic oxygen of the enolate anion. The product of *O*-alkylation is of course an enol ether and as such is sensitive to acid hydrolysis; the β-keto ester portion of the starting material can be thus regenerated and recovered to be used again. Therefore, if the alkylating agent is readily available and the compound is not sensitive to the conditions required for the acid hydrolysis, the competition between *C*- and *O*-alkylation does not present a serious problem for the synthetic plan. However, in the present example, the planned reaction failed to meet both of the above mentioned criteria. The alkylating agent, iodide **15**, whereas it could be prepared readily in quantity, was the product of a five-step process and thus represented a fair investment of time and resources. Furthermore, the alkylation product, ketone **16**, contains an alkenylstannane function, a group that is well known to be quite sensitive to acid hydrolysis. The conditions that would be required to hydrolyze the enol ether product of *O*-alkylation would almost certainly result in protiodestannylation of the product.



Scheme 7: Synthesis of **55** reagents (a) KH, toluene; **15**; (b) LDA, THF; $PhNTf_2$, THF; (c) $Pd(PPh_3)_4$, LiCl, THF; (d) methyl 2-bromoacrylate, benzene; (e) SmI_2, MeOH, THF.

Additives may be employed to increase the reactivity of these enolate anions, such as hexamethylphosphoramide or a crown ether such as 18-crown-6 or 15-crown-5. These additives make the enolate anions more reactive by selectively complexing with the cation, providing a more exposed, and thus more reactive, anion. Unfortunately, these additives also tend to make the enolate anion harder, increasing the likelihood of reaction on the oxygen atom of the enolate anion.[42] Thus, whereas additives often increase the overall yield of alkylated product, a concomitant increase in the proportion of *O*-alkylated product may result.

The alkylation of the β-keto ester **35** with the iodide **15** had been attempted under a variety of conditions.[4] Lithium enolates were found to be unreactive even under forcing conditions. The use of sodium hydride as the base and THF or 1,2-dimethoxyethane as solvent gave good conversions of the starting material (as high as 75%), but the reaction times tended to be very long, running to several days at reflux on occasion. The product mixture, upon analysis, was found to contain about 20% of the unwanted *O*-alkylated material. The use of potassium hydride as the base and the same solvents as above gave about the same yield of alkylated products by a considerably faster reaction, being complete in 36 to 48 h. Perhaps not surprisingly, however, the product mixture was found to contain about 25% of the *O*-alkylated material. The use of potassium hydride as base in THF solvent in the presence of 2 equiv of 18-crown-6 gave complete conversion within 24 h, but in this case, the *O*-alkylated material was the major isolated product.

Eventually it was found that the use of an aromatic hydrocarbon solvent promoted the *C*-alkylation process.[4] The use of potassium hydride as base and benzene as solvent at reflux gave an extremely sluggish reaction but when toluene was substituted for benzene, the reaction

was found to be complete within 4 days. The product mixture was found to contain less than 10% of the *O*-alkylated product and the isolated yield of the ketone **16** was 66%.

For the present work, an experiment was attempted in which *o*-xylene was substituted for the toluene solvent. It was hoped that reaction at the higher temperature (xylene has a boiling point of 140 °C whereas that of toluene is 110 °C), would accelerate the reaction while maintaining the low proportion of *O*-alkylation that had been observed in other hydrocarbon solvents. From the previous work, an inverse correlation between the isolated yield of the product and the duration of the reaction was noted. It seems likely that some decomposition of the product was occurring over time in the reaction mixture, thus it was hoped that a shorter reaction time would give a better isolated yield of the desired ketone **16**. This optimism was, of course, balanced against the realization that the planned higher reaction temperature could itself lead to decomposition of the product.

In the event, the use of potassium hydride as the base and *o*-xylene as the solvent gave complete reaction within 16 h. The amount of *O*-alkylated material was comparable to that formed when toluene was employed as the solvent. The required ketone **16** was isolated, after appropriate work-up and distillation of the crude product, in 77% yield, representing a modest increase over that observed with the previous conditions. The distillate displayed ir, ^{1}H nmr and mass spectral data identical with those previously observed[4] for the racemic modification of this compound. In addition, a hexane solution of **16** displayed an $[\alpha]_D$ of -126°.

Thus, it would seem that the hypothesis that some decomposition of the product with time under the conditions of the reaction was probably correct. Furthermore it would seem that if this decomposition was occurring, it must be due to the continued exposure to the base and

that any thermal effect must be of lesser importance as in these experiments the factor varied had been the reaction temperature.

The stereochemical outcome of this alkylation reaction, as depicted in **16**, was known from precedent[4] and can be explained in the following manner. The two lowest energy conformations of the potassium enolate anion derived from the β-keto ester **35** are depicted in Figure 4 as structures **35a** and **35b**. These conformations are in equilibrium under the conditions of the alkylation reaction.

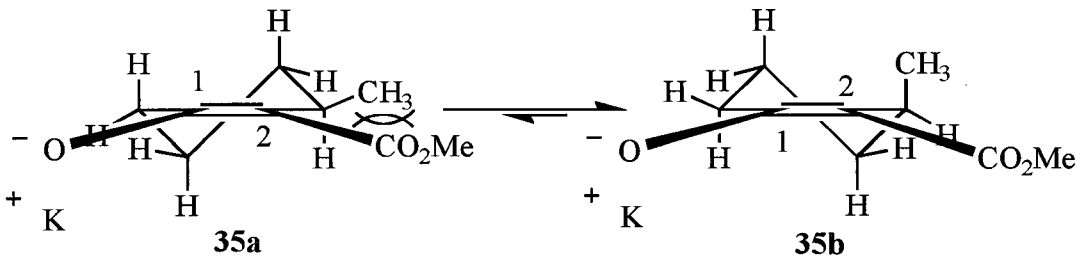


Figure 4: The Equilibrium Between the 2 Lowest Energy Conformations of the Potassium Enolate Anion of the β-Keto Ester **35**

The conformer **35a** suffers from a severe steric interaction between the methoxycarbonyl group on C-2 and the secondary methyl group. As a result of this allylic strain, the equilibrium shown favours conformer **35b**, despite the axial orientation of the methyl group in this conformation. The presence of this axial methyl group effectively blocks access to the enolate anion from the top face, (as shown in Figure 4), and the approach of the electrophile, iodide **15**, occurs from the bottom face. On the basis of this simple steric argument, the expected stereochemical outcome of the alkylation reaction would be that shown in **16**, that is with the alkyl chain on C-2 *trans* to the C-3 methyl group.

Considering the effect of stereoelectronic control, on the other hand, one would also predict the alkylation of the enolate anion **35b** from the bottom face (as shown in Figure 4), if the reaction has a late or product-like transition state.[43] Approach of the iodide **15** from the bottom face leads to a product in a chair conformation through a chair-like transition state whereas approach from the top face leads to a product in a twist boat conformation through a boat-like transition state. The chair-like transition state is lower in energy than is the boat-like transition state and thus, would be the favoured reaction pathway. Based upon this stereoelectronic argument and the above steric argument, the configuration of the product **16** was assigned with confidence.

The next step in the synthesis called for the formation of the enol trifluoromethanesulfonate of the ketone **16**, methyl (3*R*,4*R*)-3-[(*E*)-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-(trimethylstannyl)-4-hexenyl)-4-methyl-2-[(trifluoromethanesulfonyl)oxy]cyclohexene-3-carboxylate (**17**). This procedure was carried out using conditions[44] developed by McMurry and Scott. The reagent employed was *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$), a commercially available trifluoromethanesulfonating agent. It is often contaminated with a small amount of unknown material. The presence of this contaminant does not seem to affect the course of the reaction and excellent conversions of a ketone into the corresponding enol trifluoromethanesulfonate are possible by simply utilizing a slight excess of the reagent. For the present reaction, however, a problem arose in that the trifluoromethanesulfonating agent and the enol trifluoromethanesulfonate **17** proved to be almost inseparable by column chromatography, and separation of the excess reagent from the product, especially on large scales, was inconvenient.

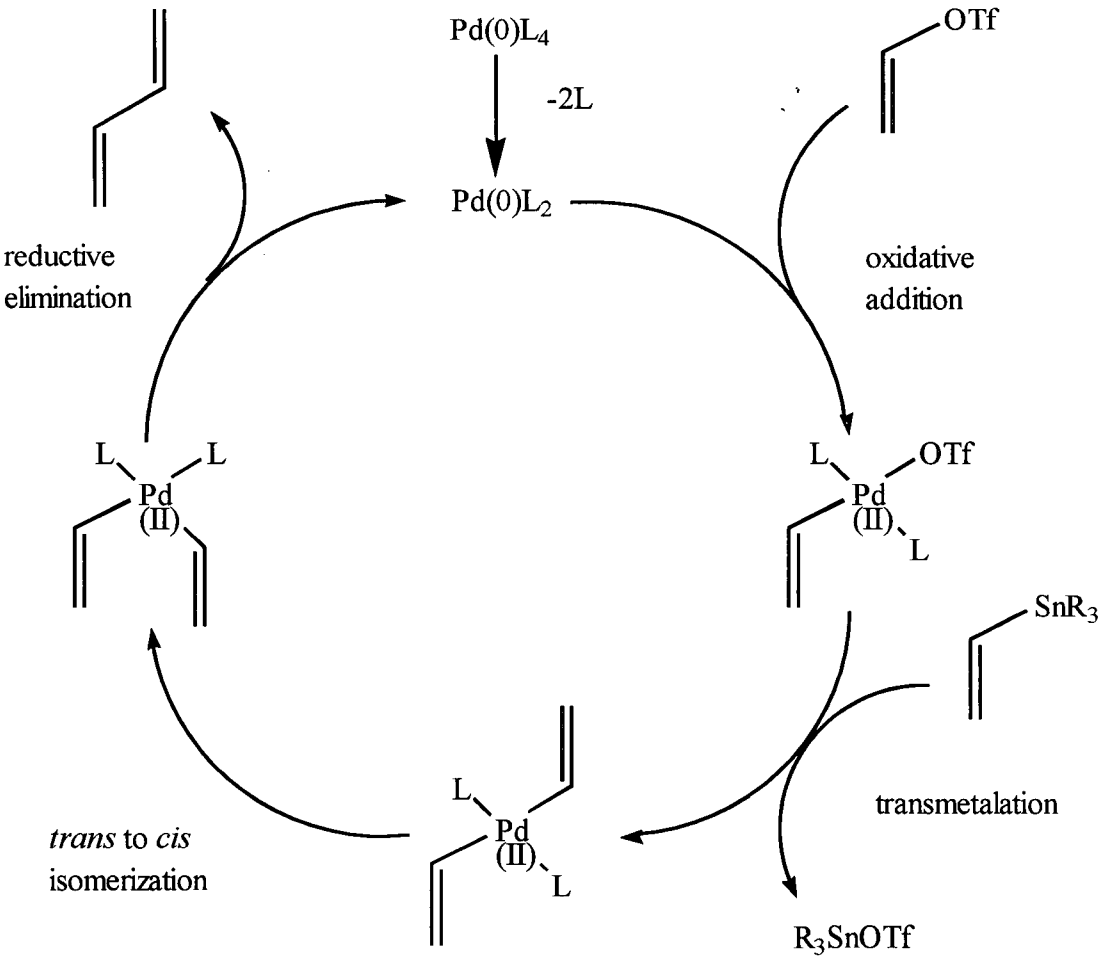
Fortunately, the contaminant in the *N*-phenyltrifluoromethanesulfonimide was readily detectable, either by the observance of any pale gray or yellow colour in the reagent or, even

better, by the detection of any amine odour in the reagent. In such cases, the reagent could be readily purified before use by column chromatography on silica gel. The purified reagent, when stored in the dark in tightly stoppered vials, seemed to be stable indefinitely. When the purified reagent was used in the reaction, it was found that equimolar quantities of the ketone **16** and the reagent could be employed and only a slight excess of the base was required.

Thus, sequential treatment of the ketone **16** with LDA and purified *N*-phenyltrifluoromethanesulfonimide in THF gave, after appropriate work-up, the enol trifluoromethanesulfonate **17** in 88% yield. This material displayed, in the ir spectrum, an absorption at 1216 cm^{-1} characteristic of the sulfonate function. The ^{1}H nmr spectrum exhibited a multiplet around δ 6 ppm that integrated to 1 proton for the newly formed olefinic proton. In the ^{13}C nmr spectrum, 4 resonances were observed for the olefinic carbons, at δ 120, 140, 144 and 148 ppm, and a quartet was observed at δ 118 ppm for the carbon of the trifluoromethyl group. The molecular ion was not observed in the mass spectrum; however, peaks for the molecular weight minus a methyl group and the molecular weight plus an ammonium cation were observed by desorption chemical ionization. Elemental analysis for carbon, hydrogen and sulfur gave results within acceptable limits. Finally, a hexane solution produced of **17** an $[\alpha]_D$ of -150°.

The next step of the synthesis called for an intramolecular Stille type coupling reaction in which a carbon-carbon single bond is formed between the olefinic carbons of the compound **17** bearing the trifluoromethanesulfonate and trimethylstannyl functions, yielding the diene **18**. The methodology for this ring forming reaction has been extensively investigated in our laboratory[41b,41c,45] and by others[46] in recent years. The overall pathway for this process is thought to be as shown in Scheme 8.

The starting point for the catalytic cycle is believed to be the dissociation of two of the triphenylphosphine ligands from the tetrakis(triphenylphosphine)palladium(0) to give the co-ordinatively unsaturated active catalyst, bis(triphenylphosphine)palladium(0). This catalyst then



Scheme 8: Reaction Pathway for the Palladium Catalyzed Coupling Reaction

oxidatively inserts into the carbon-oxygen bond of the enol trifluoromethanesulfonate moiety. The next step is a transmetalation reaction at the olefinic carbon bearing the trimethylstannyl function. This forms a '*trans*' bis(vinyl) palladium(II) species and gives the by-product of the reaction, trimethylstannyl trifluoromethanesulfonate. After a rearrangement of the ligands on the palladium dication, the coupled reaction product, diene **18**, is formed by a reductive elimination process, which concomitantly regenerates the active catalyst.

A high quality catalyst is essential for coupling reactions of this type, and since tetrakis(triphenylphosphine)palladium(0) is quite sensitive to oxidation, the catalyst required for this synthesis was prepared from palladium(II) chloride. A high yield of the catalyst tetrakis(triphenylphosphine)palladium(0) was obtained in one step from palladium(II) chloride following the procedure[47] of Coulson *et al.*

Treatment of a THF solution of the enol trifluoromethanesulfonate **17** with 10 mol percent of tetrakis(triphenylphosphine)palladium(0) at reflux under an atmosphere of argon provided, after appropriate work-up, chromatographic purification and distillation of the crude product, the diene **18** in 87% yield. The distillate produced ir, ^{1}H nmr, ^{13}C nmr and mass spectral data identical with those from the previously produced[4] racemic modification of this compound. In addition, a hexane solution of **18** showed an $[\alpha]_D$ of +236°. The 400 MHz ^{1}H nmr spectrum of the diene **18** is included in the Appendix as Figure 8.

The formation of the third ring of the required tetracyclic skeleton was to be achieved through a Diels—Alder reaction of the diene **18**. In previous work in our laboratories, the necessary cycloaddition reaction had been carried out using either methyl acrylate[48] or acrolein.[4] Both dienophiles gave high yields of Diels—Alder adducts; however, the reaction utilizing acrolein as the dienophile proceeded much more rapidly than that with methyl acrylate.

Unfortunately, neither reaction proceeded with a high degree of facial selectivity, although both proceeded with complete regioselectivity.

The best results were achieved by treating the diene with an excess of acrolein in refluxing benzene. In this case, all four of the possible (regioselective) Diels—Alder adducts were formed. The desired face from which the dienophile was to approach was that opposite the angular methoxycarbonyl group. It was hoped that the presence of this angular group would effectively block the approach of the dienophile from what is shown as the top face (see Figure 5). Indeed, if the reaction were to occur through the *endo* transition state, examination of molecular models suggests that approach of the dienophile from this face would be hindered by the angular methoxycarbonyl group. In fact, a 7:3 mixture, in terms of facial selectivity, was

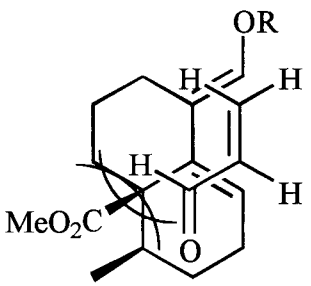


Figure 5: *Endo* Approach of the Dienophile from the Face Bearing the Angular Ester

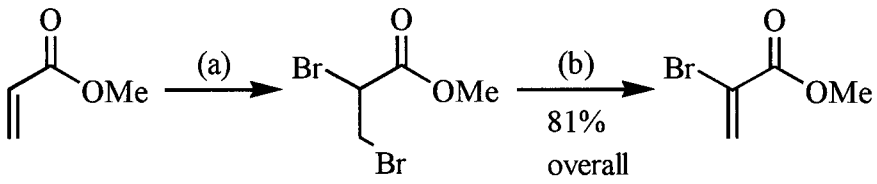
observed in favour of the dienophile approaching from the side opposite the angular methoxycarbonyl group. Of the minor component of this mixture, 93% was found to be to product of Diels—Alder reaction through an *exo* transition state whereas only 7% was that from an *endo* transition state.[4]

Because the stereochemistry at C-4 (cycloamphilectane numbering) was set during the course of this reaction, and the synthetic plan did not allow for an opportunity to correct for the

introduction of the wrong stereochemistry at this centre, a 7:3 mixture of products due to the partial lack of facial selectivity of the Diels—Alder reaction meant that fully 30% of the material had to be discarded at this point in the synthesis. Examination of the results of the experiment described above did however suggest a remedy for this situation. The results suggested that the angular methoxycarbonyl group was capable of acting as a blocking group. Of the product mixture, only about 2% (7% of 30%) arose from the top face *endo* transition state. Thus, when the dienophile approached such that the aldehyde was oriented towards the angular ester, a steric repulsion was encountered and the cyclization reaction was unlikely to proceed. When the dienophile approached from the top face in a manner leading towards an *exo* transition state, the group that was oriented towards the angular ester was a proton. This interaction must lead to considerably less steric repulsion as this arrangement led to reaction 14 times more often than did the opposite arrangement. It was proposed that if the proton were to be replaced with a group large enough to produce a considerable steric repulsion with the angular ester, then the Diels—Alder reaction through the top face would be effectively eliminated.

Introducing a bromine atom on the α-carbon of the dienophile seemed to be an ideal choice. A bromine atom is much larger than a hydrogen atom[49] and was expected to provide the required steric demand on the approach of the dienophile. Furthermore, the product of the Diels—Alder reaction would then be an α-bromo carbonyl compound and many methods of effecting the reduction of an α-bromo carbonyl compound to the parent carbonyl compound are known.

The best choice for the dienophile proved to be methyl 2-bromoacrylate. This compound was readily synthesized from methyl acrylate, which is commercially available and inexpensive.



Scheme 9: Synthesis of Methyl 2-Bromoacrylate
Reagents (a) Br_2, $CHCl_3$; (b) Et_3N, Et_2O, pentane.

Also, as will be discussed later, the Diels—Alder adduct **54**, an α-bromo ester was conveniently reduced to the parent ester in a straightforward manner.

The preparation of methyl 2-bromoacrylate was modeled upon a literature procedure[50] for the preparation of 2-bromoacrolein (see Scheme 9). Methyl 2-bromoacrylate was prepared from methyl acrylate by an efficient, two step addition—elimination process. Thus, treatment of methyl acrylate with 1 equiv of bromine in chloroform solution provided methyl 2,3-dibromo-acrylate which was immediately dehydrobrominated by treatment with 1 equiv of triethylamine in 1:1 ether—pentane. Filtration of the reaction mixture to remove the triethylamine hydrobromide salt, followed by removal of the solvent from the filtrate and distillation of the derived residue gave the desired methyl 2-bromoacrylate in good yield. A deuteriochloroform solution of this material showed, in the ^1H nmr spectrum, a three proton singlet at δ 3.8 ppm and 2 one proton doublets at δ 6.2 and 6.9 ppm. This material was found to be prone to polymerization as a neat liquid, even at low temperatures; however, it could be stored for extended periods of time at -35 °C as a solution in dry benzene.

Treatment of the diene **18** with an excess of methyl 2-bromoacrylate in refluxing benzene, gave, after removal of the solvent and purification of the derived residue by column chromatography on silica gel, a nearly quantitative yield of the Diels—Alder adducts. This

material displayed, in the ir spectrum, strong absorptions at 1740 and 1732 cm^{-1} for the 2 ester functions. Examination of the ^1H nmr spectrum of the product showed it to be a mixture of a major and a minor isomer. Comparison of the integrals for the broad doublets at δ 2.81 and 2.86 ppm, arising from the minor and major isomers, respectively, showed the isomers to be in the ratio of about 4:1.

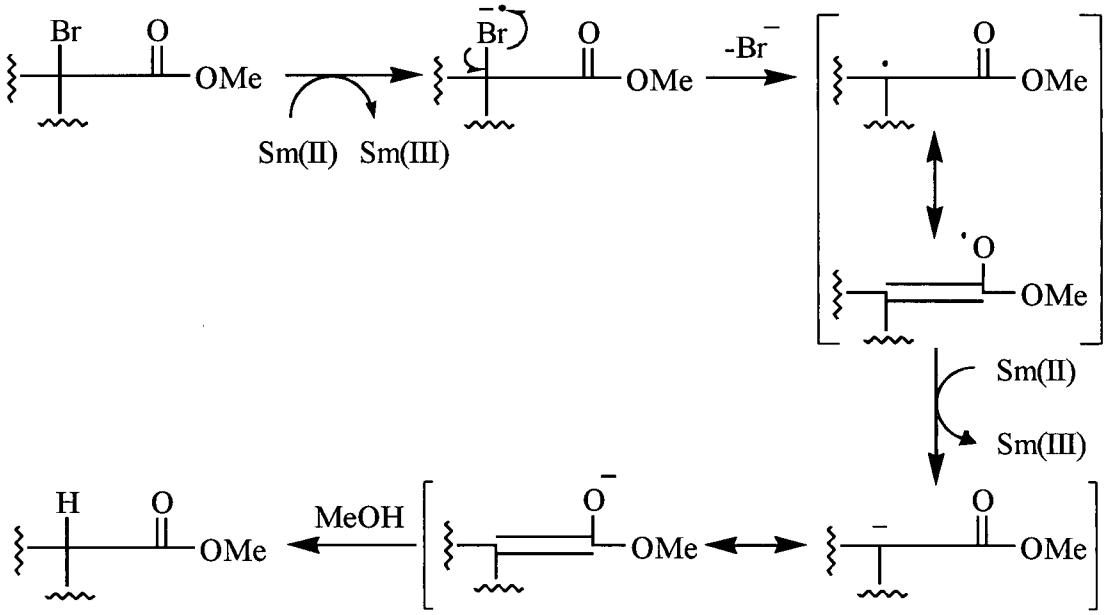
It was satisfying to note that, using the distinctive pairs of singlets arising from the methoxy protons of each isomer as a diagnostic tool, the product mixture comprised only 2 isomers, suggesting that the introduction of the bromine atom into the dienophile had had the desired effect of controlling the facial selectivity of the reaction. Because the synthetic plan required this synthesis and that of 8,15-diisocyano-11(20)-amphilectene[4] to converge in a few synthetic steps, further proof of the structure of the Diels—Alder adducts was not sought at this point.

The next step in the synthetic plan called for the reduction of the carbon-bromine bond of the diesters **54**. The methodology chosen to carry out this transformation was that introduced by Girard *et al.*[51] and developed by others.[52] A wide range of α-heterosubstituted ketones and esters have been reduced under extremely mild conditions by the action of samarium diiodide, providing the unsubstituted carbonyl compound in good to excellent yields.[53]

The samarium diiodide reagent required for this step was prepared from samarium metal and methylene iodide following a slight modification of the procedure of Molander and Hahn.[54] For the success of this preparation, both high quality samarium metal and oxygen free, dry THF are required and conditions had to be maintained such that atmospheric oxygen was rigorously excluded. Thus, addition of 1 equiv of methylene iodide to a stirred suspension of -40 mesh samarium metal in an appropriate amount of THF produced, after 16 h of stirring, a deep blue

solution of samarium diiodide. The concentration of the derived reagent was taken to be that of the limit of solubility of samarium diiodide in THF, about 0.1 M.[55] A method[55] to determine the actual concentration of a THF solution of samarium diiodide has been disclosed by Wipf and Venkatraman.

Since esters do not undergo reduction with samarium diiodide,[51] the mechanism of the reduction of α-halo esters is presumably direct reduction of the halide (see Scheme 10).[52]



Scheme 10: Mechanism of the Samarium(II) Reduction of an α-Halo Ester

Samarium(II) acts as a one electron reducing agent and gives samarium(III) as a stable by-product. The first equiv of the samarium diiodide donates an electron to the halide atom, producing a radical anion. Homolytic cleavage of the halogen carbon bond splits off a bromide anion and leaves a resonance stabilized radical. The second equiv of the samarium diiodide donates an electron to the radical, giving an enolate anion, which is then protonated by the methanol co-solvent, providing the reduced product.

Addition of a solution of the diesters **54** in 3:1 THF—methanol to 2 equiv of a THF—samarium diiodide solution at -78 °C gave, after appropriate work-up and purification by column chromatography, a residue that provided, upon distillation, the diesters **55** in nearly quantitative yield. The distillate displayed, in the ir spectrum, a strong absorption at 1735 cm^{-1} for the carbonyl functions. Apparently the absorptions for the 2 different esters overlap. The molecular ion was observed in the mass spectrum, at m/z = 450 amu, and high resolution measurement of this mass confirmed the expected molecular formula. Elemental analysis for carbon and hydrogen produced results within accepted limits. Thus it was clear that the desired reduction had taken place.

Examination of the ^1H nmr spectrum produced from the distillate showed that the product was a mixture of two compounds, presumably epimers at C-3 (amphilectane numbering). By comparison of the integrals of pairs of signals that could be assigned to the same function in the two epimers with confidence, such as the doublets at δ = 1.0 and 1.1 ppm, corresponding to the secondary methyl group at C-7, the ratio of the epimers was found to be 1:1. This result was not surprising. Examination of molecular models of the enolate anion intermediate in the reduction pathway (see Figure 6) demonstrated that the two faces of the enolate anion were equally accessible to a proton source. Thus, this protonation was not expected to occur stereo-selectively.

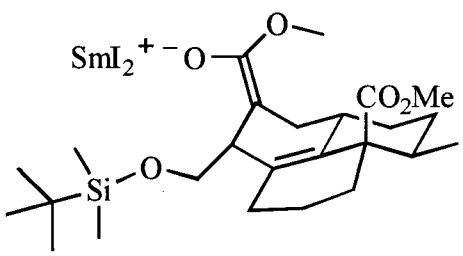
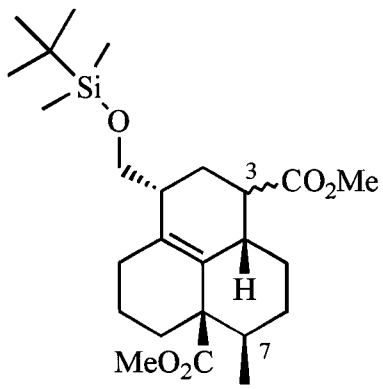


Figure 6: Conformational Diagram of the Enolate Anion Intermediate Hydrogen atoms have been omitted.



55

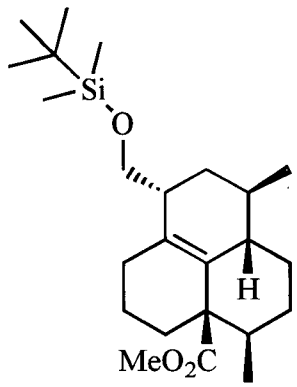
Examination of molecular models of the two epimers of the product did suggest, however, that the epimer with the methoxycarbonyl group in the β orientation would be the thermodynamically more stable epimer. In this system, the β orientation at C-3 (amphilectane numbering) puts the methoxycarbonyl group in a pseudo-equatorial position. The epimeric position has the methoxycarbonyl in a pseudo axial position, where it experiences an eclipsing steric interaction with the silyloxymethyl group at C-1, which also occupies a pseudo axial position. Thus, epimerization of the product of the reduction reaction, the diesters **55**, should yield material that is enriched in the C-3β epimer. It is this epimer which was required for the continuation of the synthesis.

Attempts to epimerize the product mixture under normal conditions for epimerization of aldehydes and ketones, sodium methoxide in methanol at reflux, however, did not lead to any substantial enrichment of either epimer, as judged by ^{1}H nmr and glc analyses. Apparently, the relatively low acidity of the proton α to the secondary methoxycarbonyl group makes the deprotonation of the ester unfavourable and the epimerization reaction is exceedingly slow.

Attempts to epimerize the product mixture under more forcing conditions, potassium *tert*-butoxide in *tert*-butanol - THF mixtures, led to some enrichment of one epimer, as judged by ^{1}H nmr analysis. Unfortunately, after a short period of time, the product mixture began to become contaminated with additional compounds. Judging from the appearance of new singlets in the ^{1}H nmr spectrum at around δ 1.1 ppm, these new compounds were probably *tert*-butyl esters of the diesters **55**, presumably arising from transesterification. As a result of the problems associated with epimerization of **55**, this approach to enrich the composition of the desired isomer was abandoned.

Thus, the tricyclic diesters **55** were synthesized from the β-keto ester **35** by a 5 step sequence that proceeded in 57% overall yield.

Preparation of the Ester 21



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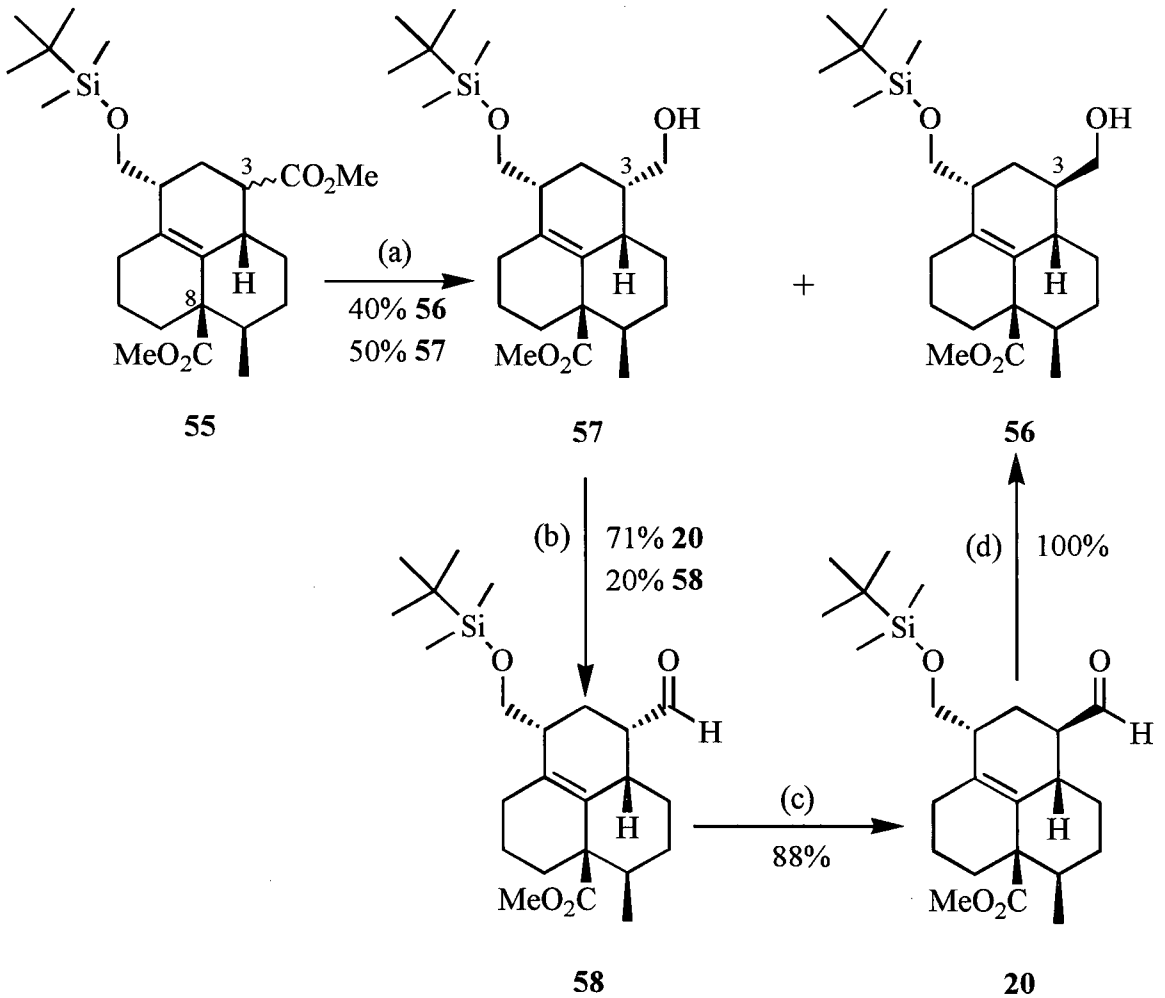
Although the diesters **55** formed a mixture that was inseparable by column chromatography on silica gel, it was known from the previous synthetic work that the corresponding epimers with an aldehyde moiety at C-3 (amphilectane numbering), aldehydes **20** and **58**, instead of the secondary methoxycarbonyl group, were easily separated by this technique. Thus, the synthetic plan was modified in the following way. The diesters **55** would be reduced to the alcohols **56** and **57**. The hindered nature of the angular ester function at C-8 was expected to make a chemoselective reduction of the C-3 methoxycarbonyl group straightforward. If the alcohols **56** and **57** proved to be separable, then the alcohol **56**, bearing the required C-3β hydroxymethyl group, a known compound[4] and thus readily identified by comparison of ^{1}H nmr data, would be set aside. The epimeric alcohol **57** would be converted to the required alcohol **56** by an oxidation, epimerization and reduction sequence as outlined in Scheme **11**. If the alcohols

56 and **57** did not prove to be separable, the mixture would be oxidized to the separable aldehydes **20** and **58**. The C-3β epimer would be reduced to the required alcohol **56** while the C-3α epimer would be subjected to an epimerization - reduction sequence to maximize the yield of the required stereoisomer.



Scheme 11: Synthesis of **56** Reagents (a) DIBAL-H, Et_2O; work-up; (b) oxalyl chloride, DMSO, CH_2Cl_2; Et_3N; (c) NaOMe, MeOH; DIBAL-H, Et_2O; work-up.

The diesters **55** were reduced to a mixture of the alcohols **56** and **57** by standard methodology. Thus reduction of the esters with DIBAL-H led to a 90% yield of the two

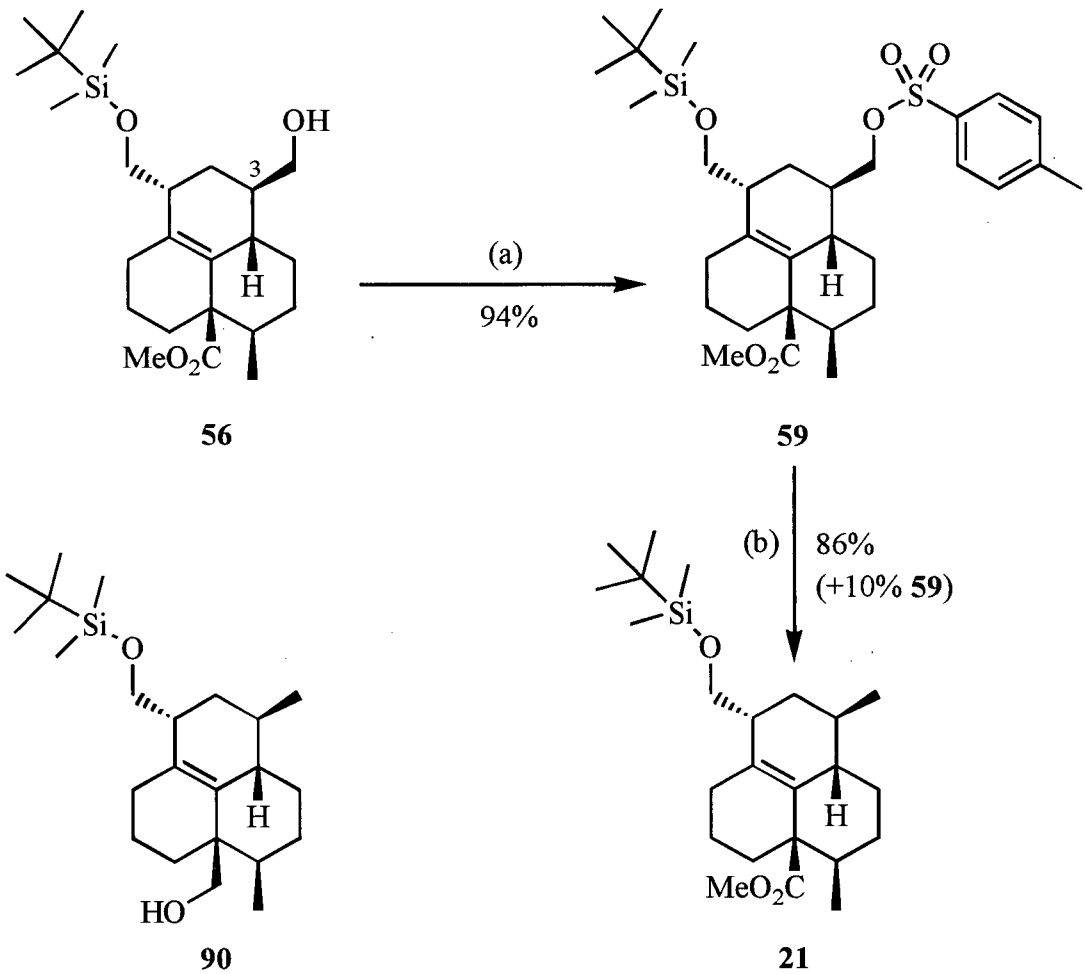
epimeric alcohols. These alcohols proved to be readily separable by column chromatography on silica gel. The less polar isomer proved to be, upon comparison of ^{1}H nmr data, the C-3β epimer, alcohol **56**, which was isolated in 50% yield. This material produced ir, ^{1}H nmr, ^{13}C nmr and mass spectra which proved to be identical with those previously reported[4] for the racemic modification of this compound. In addition, a hexane solution of **56** displayed an $[\alpha]_D$ of -88°. The more polar isomer, alcohol **57** was isolated in 40% yield. This material displayed, in the ir spectrum, absorptions at 3410 and 1729 cm^{-1} for the OH and carbonyl stretches, respectively, confirming that the reaction had succeeded. Elemental analysis for carbon and hydrogen gave results within accepted limits. A hexane solution of **57** displayed an $[\alpha]_D$ of -87°.

Following the above described plan, alcohol **57** was subjected to the following oxidation, epimerization, reduction sequence to convert it into the alcohol **56**. The most consistent results for the oxidation step of this sequence were obtained using the Swern method.[56] Appropriate work-up and purification of the crude product by column chromatography on silica gel gave the aldehyde **20** in 71% yield and the aldehyde **58** in 20% yield. Although the starting material for this oxidation reaction was a single isomer, the product was invariably the above described mixture of aldehydes. Apparently, the aldehyde **58**, assumed to be the first formed product of the reaction, epimerizes during the final stage of the Swern protocol, where an excess of triethylamine is employed.

The aldehyde **58** was taken up in dry methanol and, at 0 °C, a small amount of sodium hydride was added. The solution of the aldehyde and sodium methoxide thus obtained was allowed to warm to rt. When the epimerization was judged to be complete, typically overnight, the sodium methoxide was quenched with aqueous citric acid solution. Appropriate work-up and purification of the crude product by column chromatography on silica gel gave the aldehyde **20** in

88% yield and the aldehyde **58** in 8% yield. These materials, as well as the above isolated aldehyde **20** produced ^{1}H nmr spectra identical with those reported[4] for the racemic materials.

The alcohol **56** was derived from the aldehyde **20** by a standard reduction protocol. Thus, reaction of the aldehyde **20** with 1 equiv of DIBAL-H produced, after appropriate work-up, the desired alcohol **56** in nearly quantitative yield. This material produced ir, ^{1}H nmr and mass spectra identical with those from the above described alcohol **56**, produced directly from the reduction of the diesters **55**.



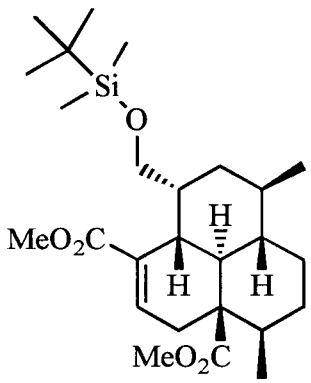
Scheme 12: Synthesis of **21** Reagents (a) TsCl, DMAP, CH_2Cl_2; (b) Super-Hydride®, THF.

With the alcohol **56** in hand, the stage was set for the reduction of the C-3 (amphilectane numbering) hydroxymethyl group to a methyl group, (see Scheme 12). This transformation was accomplished efficiently by known methods. Thus, treatment of the alcohol **56** with *p*-toluenesulfonyl chloride in methylene chloride containing 4-(*N*,*N*-dimethylamino)pyridine provided the *p*-toluenesulfonate **59** in 94% yield, after appropriate work-up and purification by column chromatography on silica gel. This material, in the ir spectrum, displayed a strong absorption at 1178 cm^{-1} for the sulfonate function. The ^1H nmr spectrum showed a 3 proton singlet at $\delta = 2.46$ ppm and 2 two proton doublets at $\delta = 7.36$ and 7.80 ppm. These data support the introduction of the *p*-toluenesulfonate moiety into the molecule. Desorption chemical ionization mass spectrometry produced masses corresponding to the molecular ion plus a proton and the molecular ion plus an ammonium cation, and a high resolution measurement of the former mass confirmed the molecular formula of the product. A hexane solution of the *p*-toluenesulfonate **59** produced an $[\alpha]_D$ of -63°.

Reaction of the *p*-toluenesulfonate **59** with excess Super-Hydride® in THF[57] afforded the tricyclic ester **21** in 95% yield, based on recovered *p*-toluenesulfonate **59** (10%). This material produced ir, ^1H nmr, ^{13}C nmr and mass spectra identical with those previously reported[4] for the racemic material. In addition, a hexane solution of the distilled product produced an $[\alpha]_D$ of -74°.

Thus the desired ester **21** was prepared from the diesters **55** by a three step process that proceeded in 70% overall yield. The yield of the diesters **55** was optimized through the use of an epimerization sequence which converted the alcohol **57** into the alcohol **56**.

Preparation of the α,β-Unsaturated Ester 65



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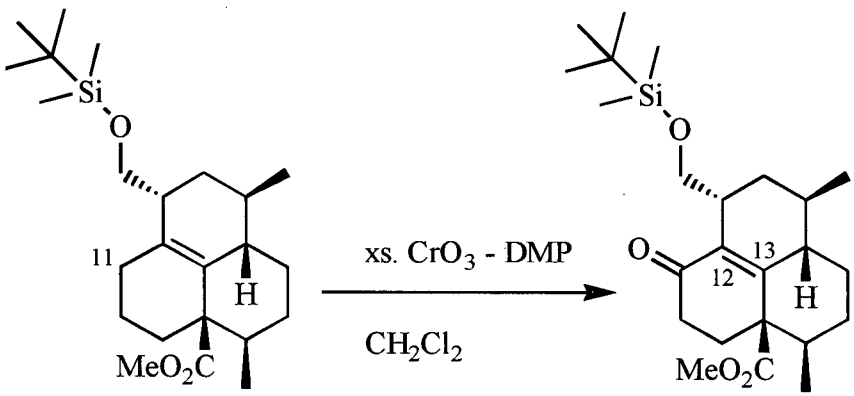
At this stage of the synthesis, a carbonyl function had to be introduced at C-11 (amphilectane numbering) of the intermediate tricyclic ester **21**. A carbonyl function at C-11 was envisioned to serve as the necessary 'handle' for the construction of the fourth ring required for the completion of the cycloamphilectane skeleton. An allylic oxidation was chosen to functionalize C-11. This transformation had, in the previous work,[4] been accomplished by the action of chromium trioxide—dimethylpyrazole complex. The use of this oxidant system was reported[58] by Corey and Fleet in 1973 for oxidation of many primary and secondary alcohols. In 1978, it was discovered,[59] by Salmond *et al.*, that this methodology could be applied to the oxidation of allylic methylene groups (see Equation 5).



5

21 **22**

As stated in the introduction section, the yield of this reaction was highly variable, especially on larger scales. The reaction itself seemed to proceed smoothly; analysis of the reaction mixture by tlc showed the tricyclic ester **21** was converted to a single, more polar component. The success of the reaction seemed to be linked to the dryness to the diethyl ether required for the work-up. The procedure called for the reaction mixture, at the completion of the oxidation, to be poured into dry diethyl ether to precipitate the reagent complex. The mixture of product and reagent, which is used in vast excess to achieve a reasonable reaction rate, was separated by column chromatography of this slurry on Florisil®. The column was eluted with dry diethyl ether and the product was isolated from the appropriate fractions of the eluate. The use of diethyl ether dried by distillation from sodium metal, as described in the general experimental section, produced the best results. However, this was only convenient for reactions on fairly small scales. For example, on a 200 mg scale, much less than 1 mmol, about 0.5 L of diethyl ether was required for the dilution of the reaction mixture and to run the column. The use of diethyl ether that was less dry seemed to promote degradation of the product, presumably by further oxidation by the chromium reagent. Crude products isolated from reactions where non-dried diethyl ether was employed were strongly coloured and had a burnt odour. These reactions invariably suffered from low yields.

Although it would have been advantageous to find an alternative method of carrying out this allylic oxidation, no suitable procedure was identified. The best results, considering a balance between the efficiency of the transformation on small scales and the logistical considerations of the reaction on a preparative scale, were obtained when the reaction was carried out on a scale of about 600 mg or 1.5 mmol of **21**. Thus, treatment of the tricyclic ester

21 with chromium trioxide—3,5-dimethylpyrazole complex[59] in methylene chloride solution afforded, after work-up and distillation of the crude product, the desired α,β-unsaturated ketone **22** in 73% yield. This material produced ir, ^{1}H nmr, ^{13}C nmr and mass spectra identical with those from the previously reported[4] racemic material. In addition, a hexane solution of distilled **22** produced an $[\alpha]_D$ of -43°.

As no method was found to improve the above-described allylic oxidation, which was seen as a limitation in the previous synthetic work,[4] attention was focused on the next stage of the synthesis. The synthetic plan now called for the reduction of the C-12 to C-13 carbon-carbon double bond (amphilectane numbering). This reduction had to occur stereoselectively at C-13 to provide the correct configuration at this centre. As the carbonyl function at C-11 could be used to correct the configuration at C-12, and the required configuration was the thermodynamically more stable one (assuming the required orientation of the C-H bond at C-13), the stereochemical outcome of the reduction reaction at this centre was of less concern.

In the previous synthesis,[4] the conversion of the α,β-unsaturated ketone **22** into the ketone **23** was accomplished by a dissolving metal reduction using sodium in liquid ammonia - diethyl ether solution in the presence of *tert*-butyl alcohol.[60] On small scales, up to about 20 mg, the product was obtained in good yield. On preparative scales, however, the reaction gave inconsistent results and often gave significant amounts of by-products. In some cases, the by-products made up the major portion of the product mixture and, in all cases, represented an irretrievable loss of material.[4] The capricious nature of this reaction was discouraging and an alternative method of achieving this transformation was sought.

Examination of molecular models of the α,β-unsaturated ketone **22** suggested that the side opposite to the angular methoxycarbonyl group at C-8 (amphilectane numbering) is more

open in terms of approach of a reagent to the C-12 to C-13 carbon-carbon double bond, (see Figure 7). Approach from the top face of the molecule is hindered by the methoxycarbonyl function whereas approach from the bottom face is hindered by the pseudoaxial *tert*-butyldimethylsilyloxymethyl group at C-1. Both of these groups are attached to carbons allylic to the double bond. However, the geometry of the ring system forces the *tert*-butyl-dimethylsilyloxymethyl group to be splayed out somewhat from what is a normal axial position. The methoxycarbonyl group at C-8, on the other hand, is rigidly held in an orientation almost perpendicular to the double bond. Thus, the bottom face of the molecule seems to be more

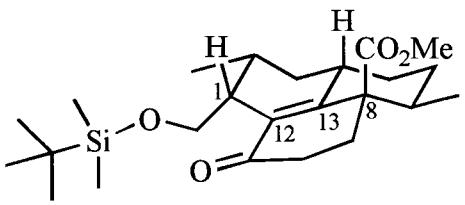
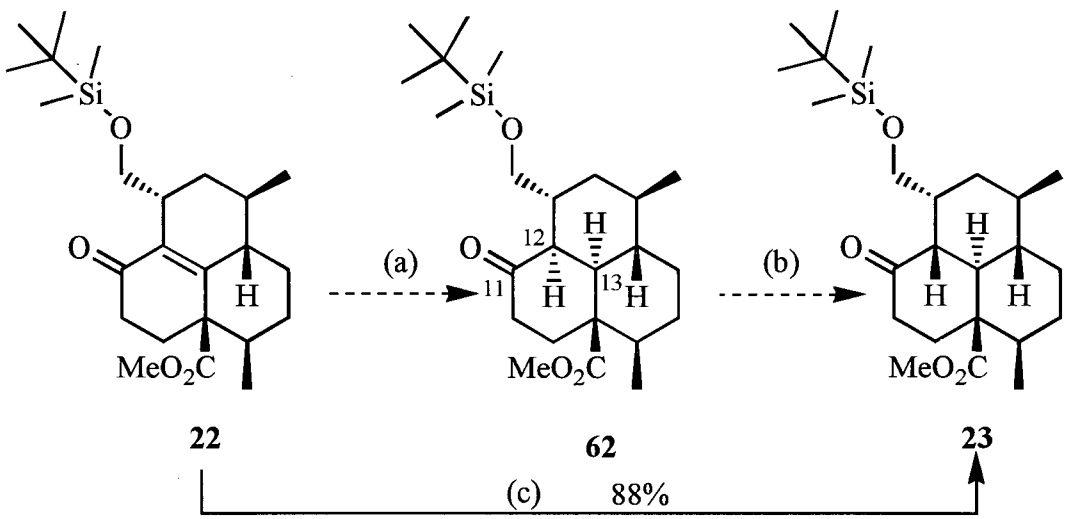


Figure 7: Conformational Diagram of **22**
Some hydrogen atoms have been omitted.



Scheme 13: Synthesis of **23** Reagents (a) hydrogenation; (b) epimerization; (c) H_2, 10% Pd/C. 0.3 M methanolic KOH, 45 psi.

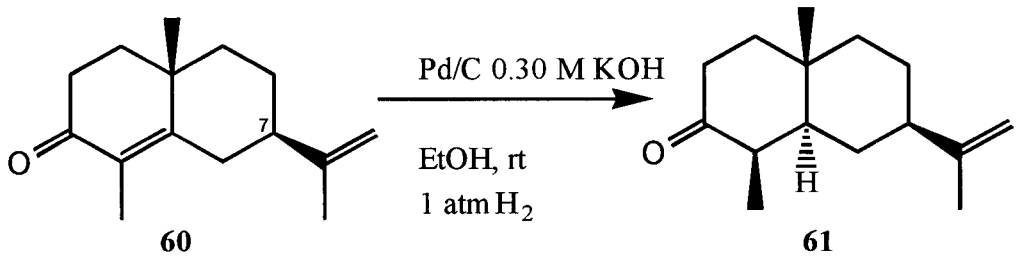
open than is the top. It was decided to attempt a direct hydrogenation of the α,β-unsaturated ketone **22**, and hoped that the angular ester at C-8 could be relied upon, as it was in the Diels—Alder step, to provide the necessary steric influence and set the correct configuration at C-13, (see Scheme 13).

Hydrogenation is well known to give the product of *syn* addition of the elements of hydrogen to an unsaturated system. Thus, if the hoped for steric control would be exerted and the required configuration were to be established at C-13 (amphilectane numbering), then the "wrong" configuration would be produced at C-12. However, the stereochemical outcome at C-12 was not an immediate concern because, as explained above, the carbonyl function at C-11 could be used to correct the configuration at this centre.

Of more immediate concern was whether or not any reaction in the planned transformation would take place. Whereas mono- and disubstituted double bonds tend to add hydrogen, under conditions of catalytic hydrogenation, readily, at rt and just over 1 atm of hydrogen, trisubstituted carbon-carbon double bonds often require pressures of 100 atm or more and tetrasubstituted double bonds often require elevated temperatures and pressures, on the order of 275 °C and 100 atm.[61] Double bonds common to two rings, as is the case in the desired reaction, are the most difficult to hydrogenate and often prove to be inert to catalytic hydrogenation.[61]

Preliminary attempts to achieve this transformation with heterogeneous catalysts, palladium and platinum black, palladium on carbon and activated charcoal, and the homogenous Crabtree[62] and Wilkinson[63] catalysts, were not successful. In fact, no reaction was observed at all and the α,β-unsaturated ketone **22** was recovered in nearly quantitative yield after each attempt.

It is known that the acidity or basicity of the reaction medium can have a profound effect on the efficiency or rate of hydrogenation reactions.[35] The effect of the pH of the reaction medium is not predictable, however. In some cases addition of a base will give an increase in the rate of hydrogenation whereas in others a sharp decrease is observed. During the course of a literature search, a particularly encouraging example[64] was noted (see Equation 6).



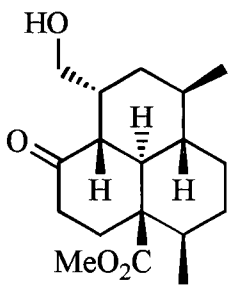
60 **61** **6**

In this example, the conjugated carbon-carbon double bond of *epi* cyperone (**60**) was chemoselectively hydrogenated in preference to the C-7 vinyl group when the reaction was run in a moderately basic medium. In this case, the addition of the base gave a rate enhancement for the hydrogenation of the enone function sufficient to allow isolation of the ketone **61** without any reduction of the more sterically accessible vinyl group. The example does not exactly model the planned transformation in that the double bond that was hydrogenated in **60** was not common to two rings. However, the double bond was tetrasubstituted and the rate enhancement was quite remarkable. These observations made a trial reaction seem worthy of investigation.

An attempt to carry out the hydrogenation of the α,β-unsaturated ketone **22** under the conditions[64] of Howe and McQuillan, 5 mol % of 10% palladium on charcoal, rt, 0.3 M sodium hydroxide in methanol, 1 atm H_2, did not lead to any hydrogenated product. This result was not too discouraging as the enone system in the α,β-unsaturated ketone **22** is more sterically hindered than that in *epi* cyperone. When the reaction was repeated at 45 psi, the

α,β-unsaturated ketone **22** was consumed after about 8 days. The reaction was monitored periodically by tlc analysis and 2 products, one of polarity similar to that of α,β-unsaturated ketone **22** and the other of much higher polarity, were observed. The spot for the more polar product seemed to increase in intensity with time. When the spot corresponding to the α,β-unsaturated ketone **22** had disappeared completely, the reaction was stopped. The catalyst was removed by filtration and water was added to the filtrate. The filtrate was neutralized by addition of 1 M aqueous citric acid, and after an aqueous work-up and separation of the product mixture by column chromatography on silica gel, the two products were isolated.

One product was of polarity similar to that of the α,β-unsaturated ketone **22** and made up about 70% of the weight of the product mixture. Comparison of a ^{1}H nmr spectrum produced from this material with that of the known racemic ketone **23** showed that these materials were spectroscopically identical. Apparently, the hydrogenation reaction had been successful and, under the basic conditions of the reaction, the first formed product, presumably ketone **62**, had epimerized to the thermodynamically more stable ketone **23**.



63

The second product, the more polar material, made up about 30% of the weight of the product mixture and was not especially stable in its pure state. In the ir spectrum, a strong absorption was observed at 3400 cm^{-1}, indicating that the material was an alcohol. It seemed

likely that the material was alcohol **63**. This assumption was confirmed in that reaction of the more polar component with *tert*-butyldimethylsilyl chloride and imidazole in methylene chloride produced the ketone **23**. Clearly, the *tert*-butyldimethylsilyl protecting group is not completely stable to the conditions of the hydrogenation reaction.

Although it was reasonably straightforward to reprotect any material that had been deprotected during the course of the reaction, it was desirable to find conditions such that a reprotection step would not be necessary. Furthermore, the total amount of material isolated, the desired product plus the 'reprotected' product, did not account for all of the expected material. It was clear from the data accumulated during the course of the reaction that the alcohol **63** was forming more slowly than was the ketone **23**. It was hoped that the overall rate of the reaction could be increased such that the reduction reaction would be complete before the de-silylation reaction had proceeded to a significant extent.

The first factor to be varied was the amount of the catalyst employed. After some experimentation, it was found that if between 20 and 25 mol % of the catalyst was employed, the reaction was complete after 48 h and no material corresponding to the alcohol **63** was detected. Thus, reaction of the α,β-unsaturated ketone **22** with hydrogen at 45 psi with 25 mol % of 10% palladium on charcoal in 0.3 M methanolic potassium hydroxide led to the ketone **23** in 88% yield. This reaction could readily be performed on a multi-gram scale.

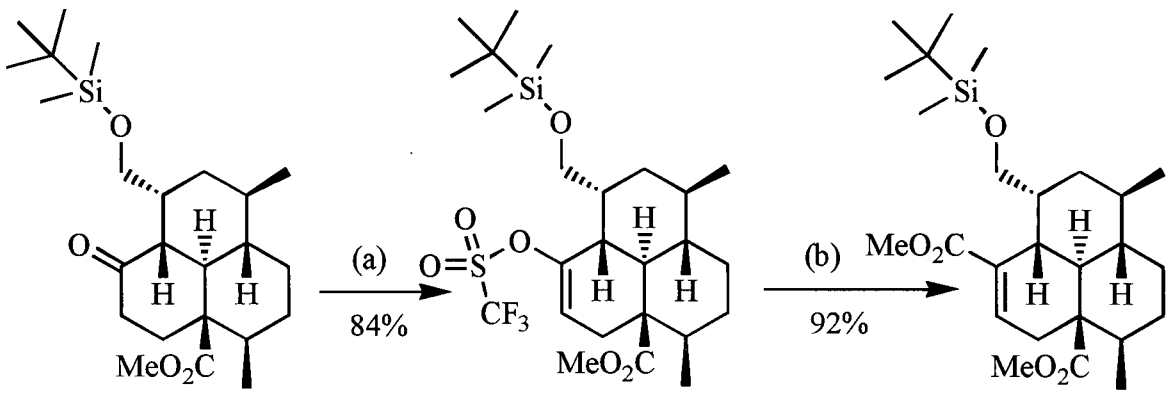
The work-up of the hydrogenation reaction deserves comment. On larger scales, the amount of methanol present during the aqueous work-up tended to carry over a fair amount of water into the organic phase. The high water content made the organic phase difficult to dry and the dried solutions were often difficult to filter. It was desirable to remove the methanol by evaporation prior to the aqueous work-up and after the mixture had been filtered; however, it

was feared that concentrating the mixture in the presence of the potassium hydroxide would lead to decomposition of the product. The methanol could be evaporated after the potassium hydroxide was neutralized, but this was not seen as a significant improvement.

In the end, ethyl acetate was added to the filtered reaction mixture and the mixture was stirred for 1 h. The potassium hydroxide saponified the ethyl acetate, giving ethanol and relatively harmless potassium acetate. The solvent was then evaporated and the residue, which was taken up in diethyl ether, washed once with saturated aqueous sodium chloride and dried, gave the product in a straightforward manner.

The recrystallized product produced ir, ^{1}H nmr, ^{13}C nmr and mass spectra identical with those previously reported[4] for the racemic ketone **23**. In addition, a hexane solution of the product **23** produced an $[\alpha]_D$ of -36°. The 400 MHz ^{1}H nmr spectrum of the ketone **23** is included in the Appendix as Figure 9.

With the ketone **23** in hand, attention was turned to the completion of the synthesis of the diester **65**. This material was prepared in two steps from the ketone **23** (see Scheme 14). The first step in this sequence called for the preparation of the enol trifluoromethanesulfonate **64**.



23 **64** **65**

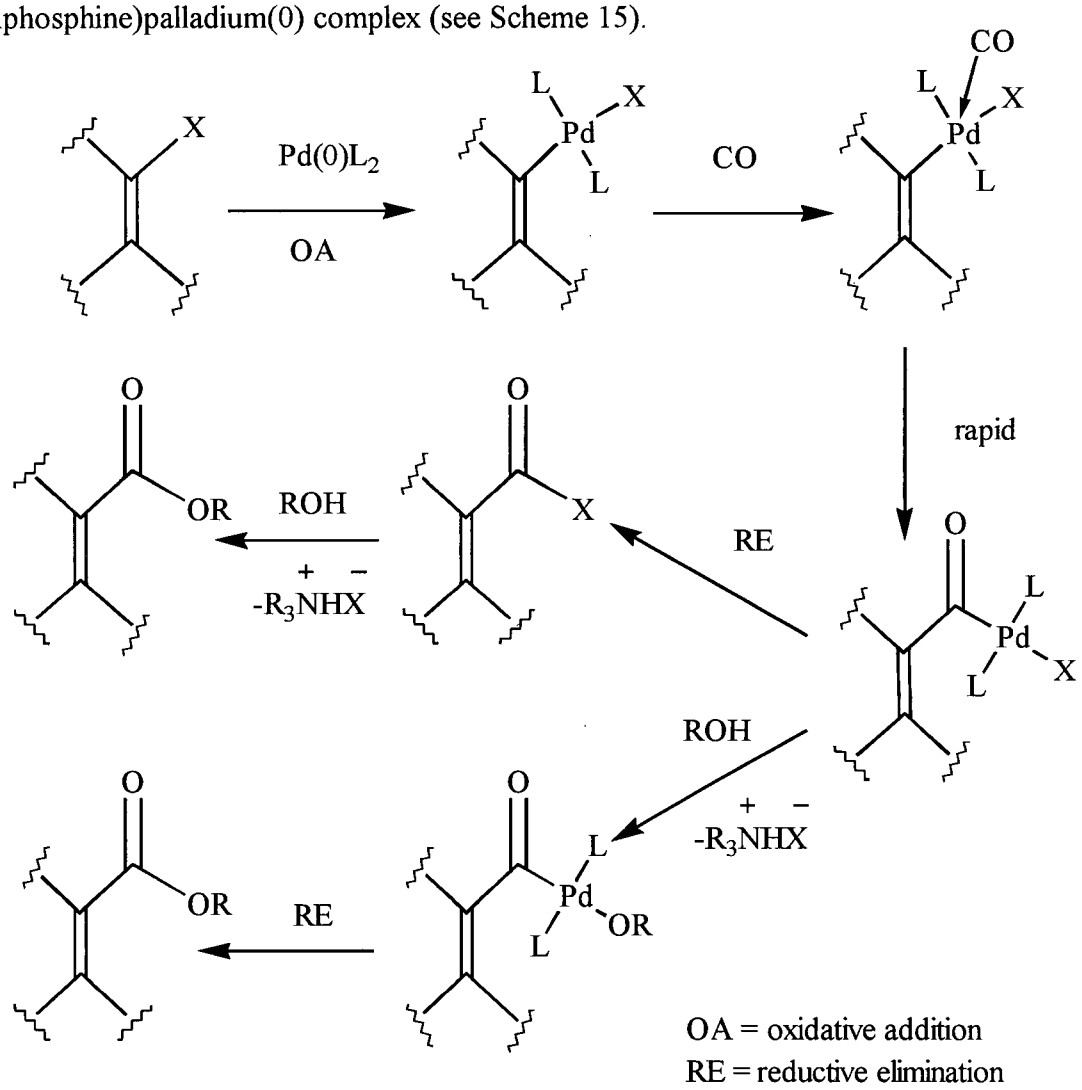
Scheme 14: Synthesis of **65** Reagents (a) LDA, THF; $PhNTf_2$, THF; (b) CO, LiCl, Et_3N, $Pd(PPh_3)_4$, MeOH.

The enol trifluoromethanesulfonate **64** was prepared from the ketone **23** by the method[20] of McMurry and Scott, in a manner similar to that used for the preparation of the enol trifluoromethanesulfonate **17**. In this case, the temperature of the reaction mixture had to be raised to between -30 and -20 °C in order to attempt to drive the formation of the enolate anion towards completion, and 1.35 equiv of LDA was employed. Even so, there was always unreacted starting material in the product mixture. The use of larger excesses of the base led to extensive decomposition of the starting material. Although this result was dissatisfying, the described conditions led to an excellent mass balance for the reaction and, thus, very little material was lost at this step as a result of the incomplete formation of the enolate anion.

In the event, the ketone **23** was deprotonated by LDA in THF solution and reaction of the enolate anion with *N*-phenyltrifluoromethanesulfonimide led to, after appropriate work-up and purification by column chromatography on silica gel, the enol trifluoromethanesulfonate **64** in 84% yield. Removal of the solvent from those fractions of the eluate from the column that contained the unreacted starting material produced 13% of the ketone **23**. The enol trifluoromethanesulfonate **64** displayed, in the ir spectrum, a strong absorption at 1211 cm^{-1} for the sulfonate function. The ^1H nmr spectrum showed a new 1 proton doublet at δ = 5.8 ppm. These data showed that the desired reaction had taken place. In the mass spectrum, a mass of m/z = 554 amu was detected for the molecular ion and a high resolution measurement of this mass confirmed the expected molecular formula. In addition, a hexane solution of the product **64** produced an $[\alpha]_D$ of -39°. The 400 MHz ^1H nmr spectrum of the enol trifluoromethanesulfonate **64** is included in the Appendix as Figure 10.

The enol trifluoromethanesulfonate **64** was converted into the diester **65** by a palladium catalyzed methoxycarbonylation reaction. This reaction was modeled upon chemistry[65] described

by Schoenberg *et al.* in which the alkoxycarbonylation reaction is carried out with aryl, benzyl and vinylic halides. These halides react with carbon monoxide and an alcohol at or below 100 °C in the presence of a *tert*-amine and a catalytic amount of a tris- or tetrakis-(triphenylphosphine)palladium(0) complex (see Scheme 15).



Scheme 15: Palladium(0) Catalyzed Methoxycarbonylation Pathway

As was the case in the palladium(0)-catalyzed Stille-type coupling, which was described for the preparation of the diene **18**, the first step in this alkoxycarbonylation process is an oxidative addition of the carbon-halide bond. The carbon monoxide then coordinates to the

palladium centre, and rapidly inserts into the carbon-palladium single bond. At this point, two pathways are possible, both leading to the same product. The palladium atom may reductively eliminate, leaving an acyl halide. This acyl halide would rapidly react with the alcohol, usually used as the solvent, to give the product and a *tert*-amine—HX salt. Alternatively, a solvent molecule may displace the halide bound to the palladium atom, splitting off HX as the *tert*-amine—HX salt. Reductive elimination at this point gives the product.

Because palladium(0), derived from tetrakis(triphenylphosphine)palladium(0), is known to oxidatively add the carbon-oxygen bond of an enol trifluoromethanesulfonate, the analogous reaction with an enol trifluoromethanesulfonyl ether, such as the trifluoromethanesulfonate **64**, should be straightforward. As is common practice with intermolecular Stille type couplings involving enol trifluoromethanesulfonyl ethers, lithium chloride was added to the reaction mixture. This soluble source of chloride ion aids the reaction by displacing the trifluoromethanesulfonate on the palladium atom after the initial oxidative addition. The complex with the trifluoromethanesulfonate tends to decompose to insoluble material, removing the palladium from the catalytic cycle as well as destroying the substrate. The complex with the chloride ligand is more stable under the reaction conditions and gives a more efficient reaction.

Thus, reaction of the enol trifluoromethanesulfonate **64** with carbon monoxide at 1 atm in methanol solvent in the presence of triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) at 70 °C gave, after appropriate work-up, purification by column chromatography on silica gel and distillation of the oil obtained, the diester **65** in 92% yield. In the ir spectrum, this material displayed a strong absorption at 1723 cm^{-1} for the (coincident) carbonyl stretches. The ^1H nmr spectrum showed 2 three proton singlets at $\delta = 3.6$ and 3.7 ppm for the 2 methoxy groups and a 1 proton resonance at $\delta = 6.8$ ppm for the olefinic proton of the

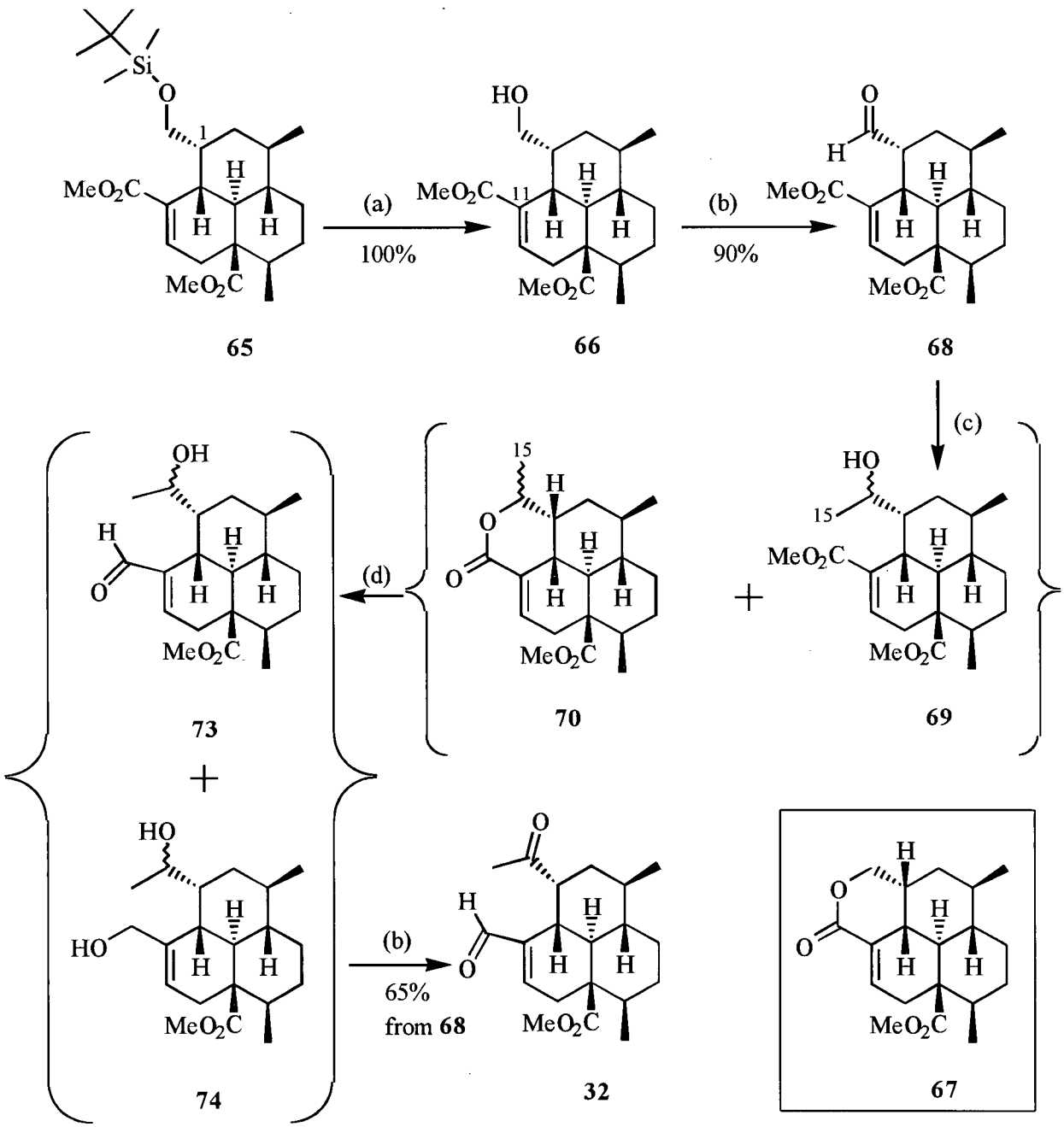
α,β-unsaturated ester. These data support the conclusion that the desired reaction had taken place. In the mass spectrum, a mass of m/z = 464 amu was observed for the molecular ion and a high resolution measurement of this mass confirmed the molecular formula. Elemental analysis of the distilled product for carbon and hydrogen gave results within accepted limits. In addition, a hexane solution of the product **65** produced an $[\alpha]_D$ of -90°.

Thus, the diester **65** was prepared, based upon recovered starting material in the formation of the enol trifluoromethanesulfonate step, in 57% overall yield in four steps from the ester **21**. The second step of the conversion of the ester **21** into the ketone **23** was carried out by catalytic hydrogenation, replacing the previous dissolving metal reduction method that had been problematic. The third goal for the synthetic work, therefore, had been at least partially realized, (see page 13).

Preparation of the Keto Aldehyde 32

At this stage, the synthetic plan called for the conversion of the diester **65** into a substrate that would be suitable to undergo reaction to form the fourth ring required for the synthesis of the cycloamphilectane carbon skeleton. It was envisaged that this ring would be constructed through an intramolecular aldol condensation reaction. In order to carry out this transformation, the keto aldehyde **32** was required. The keto aldehyde **32** was prepared from the diester **65** in 5 synthetic steps (see Scheme 16).

The first step of this process required the removal of the *tert*-butyldimethylsilyl protecting



Scheme 16: Synthesis of **32** Reagents (a) $Pd(OAc)_2$, water, acetone; (b) cat. TPAP, NMO, 4 Å mol. sieves, CH_2Cl_2; (c) MeMgBr, Et_2O; (d) xs. DIBAL-H, Et_2O; work-up.

group from the C-1 (amphilectane numbering) *tert*-butyldimethylsilyloxymethyl group. Attempts to remove the protecting group using fluoride ion, derived form tetra-*n*-butylammonium fluoride, in wet THF solvent did not lead to any of the expected alcohol **66**. The only organic product isolated from this reaction displayed, in the ^{1}H nmr spectrum, the typical hallmarks of the expected carbon skeleton, the 2 three-proton doublets for the secondary methyl groups and the olefinic proton for the α,β-unsaturated ester, but only one signal that could be attributed to methoxy protons. In the ir spectrum, the product did not show the expected absorption around 3400 cm^{-1} for the hydroxyl group. Thus, it is likely that the product of this reaction was the lactone **67**. Apparently, under the conditions of the reaction, the *tert*-butyldimethylsilyl group was cleaved and the intermediate alkoxide anion (or the alcohol **66**, formed by protonation of the intermediate alkoxide anion by the solvent) reacts further in a lactonization process with the methoxycarbonyl group at C-11 to give the lactone **67** and an equiv of methanol. Even though the product of the lactonization gives a 6 membered ring, this lactonization process was expected to be slow under neutral conditions. However, the conditions described above are fairly basic and the fluoride ion from the reagent, which was used in slight excess, was undoubtedly catalyzing the lactonization reaction. Clearly, an alternative method to accomplish the deprotection reaction was required.

Attempts to remove the protecting group under acidic conditions, 1 M hydrochloric acid in aqueous THF at rt, did lead to some of the desired product, the alcohol **66**, but this process was fairly slow and the product mixture was invariably contaminated with the above described lactone **67**. Evidently, the acidic conditions of this process were also catalyzing the lactonization reaction. Because the lactone **67** represented a significant portion of the reaction mixture and a

loss of the material that was not easily recovered, this method of carrying out the desired deprotection reaction was also abandoned.

Recent work[66] by Wilson *et al.* has led to the development of a method for the cleavage of *tert*-butyldimethylsilyl protecting groups to form alcohols under nearly neutral conditions. This interesting process involves using a palladium(II) complex in wet acetone as solvent and proton source. The optimal conditions were found to be 5 mol % of the catalyst and 5 equiv of water at rt with the apparatus protected from light and under these conditions, several primary and secondary alcohols were prepared from their silyl protected derivatives. These results were encouraging and when the described conditions were applied to the present reaction, the desired alcohol **66** was obtained in excellent yield without contamination by the lactone **67**.

Thus, a solution of the diester **65** in acetone was treated with water and 6 mol % of chlorobis(acetonitrile)palladium(II) in the dark for a period of 18 h. Appropriate work-up followed by purification of the crude product by column chromatography on silica gel, gave the required alcohol **66** in nearly quantitative yield. In the ir spectrum, the product displayed an absorption at 3422 cm^{-1} for the primary alcohol OH stretch. The ^1H nmr spectrum displayed three-proton singlets at δ = 3.6 and 3.7 ppm for the 2 methoxy groups. As this material was prone to lactonization upon standing, further characterization was not carried out.

The next step in the synthetic plan called for the oxidation of the primary alcohol **66** to give the aldehyde **68**. The oxidation conditions had to be carefully chosen so that the lactonization of the starting material, known from the above work to be a relatively facile process, would be avoided. Oxidation using the previously described Swern conditions was not attempted as the reagent is known to be fairly acidic and it was feared that the acidity of the reagent would tend to catalyze the undesired lactonization process.

The oxidation method that was used was that employing tetra-*n*-propylammonium perruthenate, a mild and convenient oxidant for alcohols developed[67] by Griffith and Ley. Tetra-*n*-propylammonium perruthenate is a commercially available, air-stable and non-volatile substance which readily converts primary alcohols to aldehydes and secondary alcohols to ketones without competing carbon-carbon double bond cleavage for unsaturated or allylic systems.[67] In the presence of *N*-methylmorpholine *N*-oxide, the reagent can be used catalytically.[67]

In the event, treatment of the alcohol **66** with 7 mol % of tetra-*n*-propylammonium perruthenate in methylene chloride in the presence of *N*-methylmorpholine *N*-oxide and 4 Å molecular sieves gave, after appropriate work-up, the required aldehyde **68** in 90% yield. This material displayed in the ir spectrum an absorption at 2722 cm^{-1} for the aldehydic C-H stretch. In the ^1H nmr spectrum, this material displayed a 1 proton singlet at $\delta = 9.6$ ppm for the aldehyde proton. These data indicated the desired transformation had taken place. Since this material quickly began to yellow upon standing, it was used in the next reaction without delay and, thus, it was not further characterized.

At this point in the synthesis, the introduction of the C-15 carbon atom (amphilectane numbering) into the carbon skeleton was undertaken. This carbon was to be added by reaction of the aldehyde with an appropriate nucleophilic organometallic reagent such as a methyllithium or a methyl Grignard reagent, to provide, after appropriate work-up, the alcohols **69**. The primary factor that had to be considered in the planning of this transformation was the selectivity of the addition. The chosen reagent had to be chemoselective for addition to the aldehyde function over either 1,2- or 1,4-addition to the α,β-unsaturated ester function. The carbon atom of an aldehyde carbonyl is more electrophilic than that of an ester and much more electrophilic

than that of an α,β-unsaturated ester. Thus, chemoselectivity in this reaction was not expected to be problematic. The nucleophile chosen was methylmagnesium bromide. This reagent is a good nucleophile and is less reactive than methyllithium, thus, the addition reaction was expected to be controllable in a chemoselective sense.

The best conditions found for this reaction were as follows. A solution of the aldehyde **68** in diethyl ether was treated with 3 equiv of methylmagnesium bromide solution at -78 °C for a period of 30 min. Quenching of the reaction mixture at -78 °C, followed by appropriate work-up and removal of the solvent gave a colourless oil. Analysis of this oil by tlc showed it to be a mixture of two major and two minor components. The major components were both more polar than the minor components. All four were uv active.

Although initially disconcerting, the presence of four products in the reaction mixture was not entirely unexpected. The nucleophilic addition of the Grignard reagent to the carbon atom of the aldehyde carbonyl was not expected to proceed with any great degree of face selectivity. Examination of molecular models did not suggest that the aldehyde **68** would adopt any particular conformation that would lead to the reagent being added selectively to one face of the aldehyde versus the other. Thus, the initial reaction was expected to lead to 2 epimeric alkoxide anions that, upon protonation, would give two epimeric alcohols, **69**.

It was known from the work done on the de-silylation reaction, (diester **65** → alcohol **66**) that the alcohol **66** tended to lactonize readily. Intramolecular cyclization of the 2 epimeric alkoxide anions described above, in a manner like that observed with the alcohol **66**, would lead to 2 epimeric lactones, **70**. Therefore, the presence of 4 components in the product mixture isolated from this reaction could easily be rationalized. The major two products, the more polar two components observed by tlc analysis, were taken to be the alcohols **69**, whereas the two

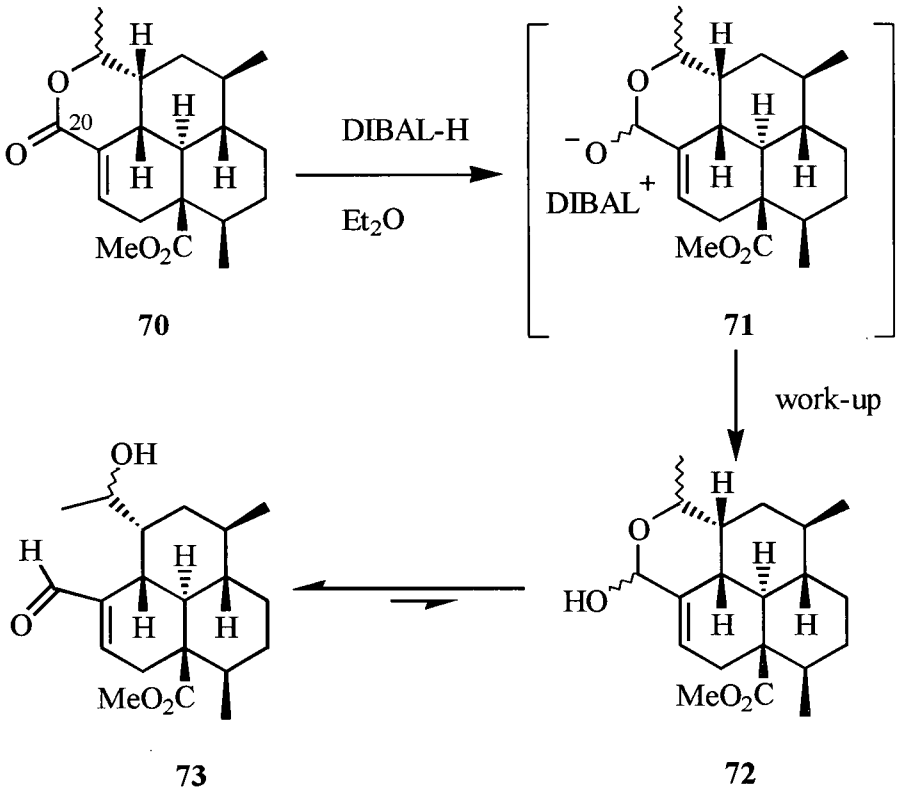
minor products were taken to be the lactones **70**. Both of these materials contain α,β-unsaturated ester-type functions, and thus, both sets of compounds would be expected to be uv active. No further spectroscopic evidence in support of the products' identities was gathered.

The presence of 4 components in the product mixture from the Grignard addition was of little synthetic consequence as the next step in the sequence called for reduction of the above product mixture to provide the diols **74**. It was believed that reduction of either the alcohols **69** or the lactones **70** would lead to the diols **74** and it was hoped that the predicted product mixture could be characterized at this point.

The product mixture derived from the above reaction was dissolved in diethyl ether and treated with an excess of DIBAL-H. Work-up of the reaction mixture, under appropriate conditions, led to a semi-solid foam as the crude product. Analysis of this product by tlc, quite surprisingly, showed it to be a mixture of four components, similar to the product mixture isolated from the Grignard reaction. As was the case for the Grignard product mixture, the product mixture of this reduction reaction consisted of two more polar compounds and two less polar compounds. The more polar compounds appeared to be the major components while the less polar compounds were the minor components. The minor components were uv active, whereas the major components were not.

These observations led to the conclusion that the product was a mixture of the expected diols **74** and the aldehydes **73**. A rationalization of this conclusion is as follows. Reaction of the alcohols **69** with 3 equiv of DIBAL-H, the first to deprotonate the alcohol and the second and third to reduce the ester moiety at C-11 (amphilectane numbering) would lead to, after work-up, the diols **74**. Because the alcohols **69** were epimeric at C-14, the product of this reaction, the diols **74**, would also be epimeric. Furthermore, as the alcohols **69** were the major components of

the Grignard product mixture, it is reasonable that their reduction products would constitute the



70 **71** **73** **72**

Scheme 17: Formation of **73** from **70**

major portion of the reduction product mixture. The diols **74** would not be expected to be uv active at 254 nm.

Whereas it was expected that the lactones **70** would react with 2 equiv of DIBAL-H to provide the diols **74**, the formation of the aldehydes **73** is readily explained (see Scheme 17). Delivery of a hydride ion to C-20 (amphilectane numbering) would lead to the aluminum alk-oxide salt **71**. Apparently, this salt was stable under the reaction conditions. Upon work-up, the salt was hydrolyzed to give the lactols **72**. The lactols **72** were of course in equilibrium with the open hydroxy aldehyde form, the aldehydes **73**, and the equilibrium apparently favours the latter

form. That the equilibrium favours the open form is clear in that the α,β-unsaturated aldehyde function present in this form would explain the observed uv activity. As above, two epimeric aldehydes were formed from the lactones **70**.

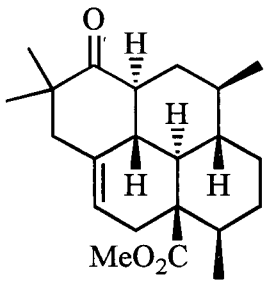
The complexity of the above product mixture was disappointing, but again was of little synthetic consequence. The next step of the synthetic plan called for an oxidation reaction that would provide a single compound from the four components of the product mixture, if the above conclusions had been drawn correctly. Thus, no attempt was made to further purify or characterize this mixture and it was taken directly on to the next step.

The product mixture from the reduction reaction was oxidized using the previously described method[67] of Griffith and Ley. Thus, the product mixture was treated with a catalytic amount of tetra-*n*-propylammonium perruthenate in methylene chloride in the presence of *N*-methylmorpholine *N*-oxide and 4 Å molecular sieves. Gratifyingly, analysis of the reaction mixture showed that it contained a single major component that was less polar than any of the four starting materials. After appropriate work-up and purification by column chromatography on silica gel, the product was obtained as a clear, colourless oil. The keto aldehyde **32** was isolated in 65% yield. This yield is for the 3 steps from the aldehyde **68**. Given the complexity of the intermediate reaction mixtures and the lack of full purification at each intermediate step, this efficiency was highly satisfying. The product **32** displayed, in the ir spectrum, an absorption at 2715 cm^{-1}, for the aldehydic C-H stretch and strong absorptions at 1723 and 1683 cm^{-1}, for the carbonyl stretches of the ketone and ester (coincident, 1723) and aldehyde (1683). The ^1H nmr spectrum showed a one-proton singlet at δ = 9.3 ppm for the proton of the aldehyde and a 3-proton singlet at δ = 2.0 ppm, within the δ = 1.96 to 2.10 ppm multiplet, for the protons of the methyl ketone. In the mass spectrum, a mass of m/z = 332 amu was observed for the molecular

ion and a high resolution measurement confirmed the expected molecular formula. A chloroform solution of the product **32** gave an $[\alpha]_D$ of -44°.

Thus, the keto aldehyde **32** was prepared from the diester **65** in 5 synthetic steps. The overall yield of this process was 59%. The 400 MHz ^{1}H nmr spectrum of the keto aldehyde **32** is included in the Appendix as Figure 11.

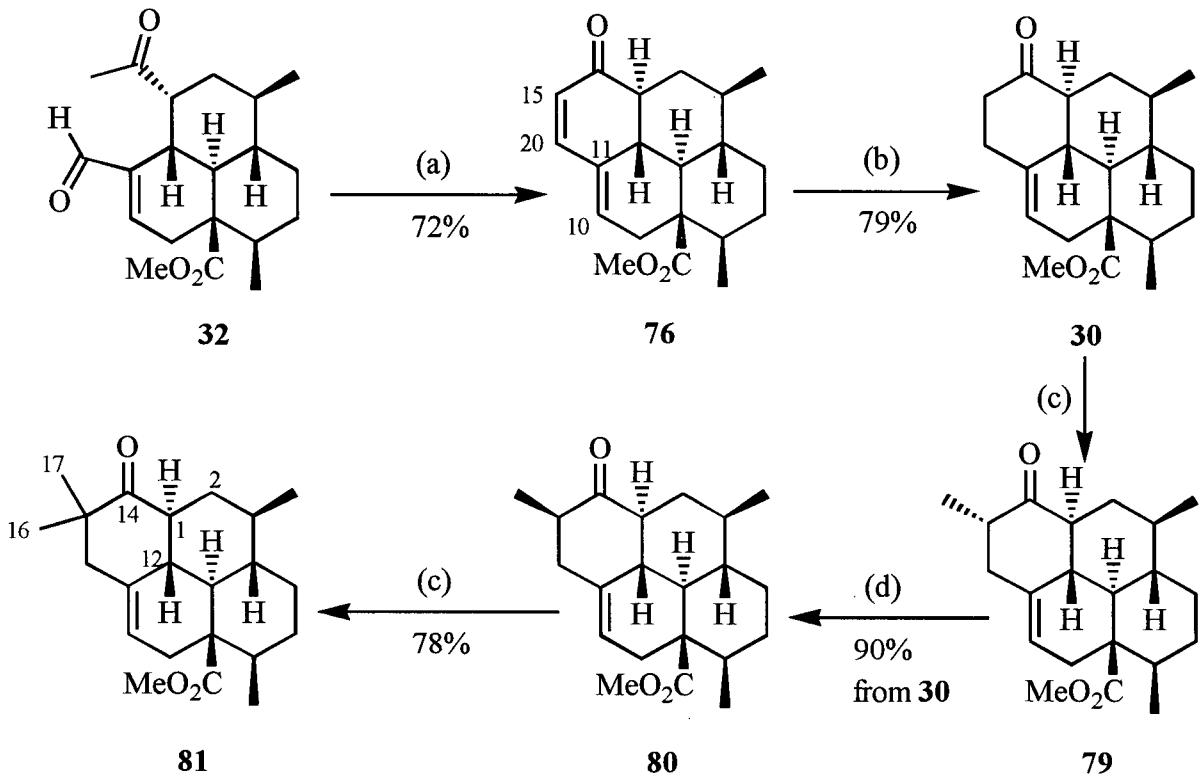
Preparation of the Ketone 81



81

With the keto aldehyde **32** in hand, the closure of the fourth ring and the introduction of the last 2 required carbon atoms for the synthesis of the cycloamphilectane carbon skeleton could finally be addressed. The synthetic plan called for the ring closure to proceed by an intra-molecular aldol condensation. After a selective reduction of the C-15 to C-20 carbon-carbon double bond of **76** (cycloamphilectane numbering), the C-16 and C-17 carbons would be installed into **30** by an alkylation, epimerization, alkylation reaction protocol (**30→79→80→81**, see Scheme 18).

After some experimentation, the best conditions for the ring closure reaction were found to be as follows. The aldol condensation was carried out under conditions of basic catalysis in



Scheme 18: Synthesis of **81** Reagents (a) 2.5 M methanolic KOH, MeOH, 4 Å mol. sieves; (b) $(PPh_3)_3RhCl$, Et_3SiH; 6 M HCl, THF; cat. TPAP, NMO, 4 Å mol. sieves, CH_2Cl_2; (c) LDA, THF; HMPA; MeI; (d) NaOMe, MeOH.

methanol as solvent in the presence of dry 4 Å molecular sieves to absorb the liberated water. The most consistent results, in terms of efficiency of the process, were obtained when the aldol was allowed to form for extended periods of time at rt followed by a brief period of heating to drive the dehydration reaction to completion. When the heating period was omitted, the reaction invariably produced mixtures of the desired product and unreacted starting material, despite tlc analysis of the reaction mixture suggesting the reaction had gone to completion. Presumably, the dehydration reaction was driven to completion when the sample of the reaction mixture was applied to the tlc plate by the silica gel, which is itself a good desiccant.

Thus, a suspension of the keto aldehyde **32** and crushed 4 Å molecular sieves was made basic by the addition of a few drops of 2.5 M methanolic potassium hydroxide and stirred at rt for 18 h before being warmed to 50 °C and stirred at that temperature for 2 h. Appropriate work-up, purification by column chromatography on silica gel and recrystallization of the derived crude product, gave the dienone **76** in 72% yield. This material displayed, in the ir spectrum, strong absorptions at 1711 and 1676 cm^{-1}, for the carbonyl stretches for the ester and ketone functions, respectively, and a strong absorption at 1638 cm^{-1}, for the carbon-carbon double bonds. The ^1H nmr spectrum showed 3 one-proton resonances at δ = 5.9, 6.1 and 6.9 ppm for the 3 olefinic protons. In the mass spectrum, a mass at m/z = 314 amu was observed for the molecular ion and a high resolution measurement of this mass confirmed the expected molecular formula. Elemental analysis for carbon and hydrogen gave results within accepted limits. A chloroform solution of the recrystallized product produced an $[\alpha]_D$ of -215°. The 400 MHz ^1H nmr spectrum of the dienone **76** is included in the Appendix as Figure 12.

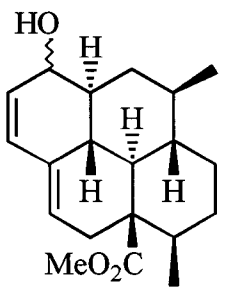
At this point, the synthetic plan called for a chemoselective reduction of the C-15 to C-20 (cycloamphilectane numbering) carbon-carbon double bond. It was imagined that this transformation would be difficult to achieve. The cycloamphilectane skeleton required that the C-10 to C-11 double bond be left untouched. Previously in this work, a catalytic hydrogenation process was used to effect the reduction of an α,β double bond of an α,β-unsaturated ketone. A search of the chemical literature revealed that it is known that catalytic hydrogenation can be used to effect the reduction of the γ,δ double bond of an α,β-γ,δ-dienone.[68] This, of course is the exact opposite of the required result. The α,β-unsaturation, however, was a disubstituted double bond at the edge of the molecule, whereas the γ,δ-unsaturation is trisubstituted and more internal. The α,β-unsaturation was, therefore, more accessible to the surface of a heterogenous catalyst

and it was possible that the rate of its hydrogenation might have been significantly higher than that of the γ,δ-unsaturation.

Thus, a small amount of the dienone **76** was treated with palladium on charcoal under an atmosphere of hydrogen in methanol for 10 min. Filtration, followed by removal of the solvent led to a virtually quantitative mass recovery of material that did not show any signals whatsoever in the olefinic region of its ^{1}H nmr spectrum. Clearly, another method of effecting this transformation was required.

Fortunato and Ganem have reported[69] an interesting method for the conversion of α,β-unsaturated ketones and esters into synthetically useful enolate anions. β-Unsubstituted cyclic α,β-unsaturated ketones, especially those in 6 membered rings, upon treatment with lithium or potassium tri-*sec*-butylborohydride, were shown to undergo selective 1,4-reduction to ketone enolate anions which could then be reacted with various electrophiles. Acyclic α,β-unsaturated ketones, on the other hand, displayed mainly 1,2-reduction products. The report of these results was quite encouraging.

Unfortunately, treatment of the dienone **76** under the conditions[69] described by the authors led only to the isolation of the alcohol **77**. Presumably, the presence of the γ,δ-unsaturation in some way makes the dienone less prone to 1,4-reduction and the reagent delivers the hydride in a 1,2-fashion.



77

Other reagents or methods attempted for the selective reduction included diimide, generated from potassium azodicarboxylate,[70] palladium catalyzed conjugate reduction with tri-*n*-butyltin hydride[71] and a copper(I) bromide—lithium trimethoxyaluminum hydride complex.[72] In each case, the reaction returned only starting material.

After much experimentation, the method that was chosen to effect the selective reduction of the dienone **76** involved rhodium catalyzed hydrosilation by the method[73] of Ojima *et al.* The authors found that, in the presence of Wilkinson's catalyst,[63] α,β-unsaturated ketones react with triethylsilane to provide the corresponding enol silyl ethers in good to excellent yields; only conjugated double bonds are affected. Saturated ketones react to give alkyl silyl ethers. This reaction was reported[73] to work best when run without a solvent.

Thus, the dienone **76** was suspended in triethylsilane and the suspension was heated to 60 °C. At this temperature, the starting material dissolved and a pale yellow solution was obtained. The catalyst was added as a solution in methylene chloride and the methylene chloride added was immediately driven off by evaporation under a stream of dry argon. The reaction was allowed to proceed for 30 min after which time the mixture was cooled to rt. Work-up of the reaction mixture gave an oil which, by tlc analysis, was a mixture of compounds of similar polarity to the starting material and compounds much less polar than the starting material.

The above crude product, assumed to be a mixture of silyl enol ethers and their corresponding hydrolysis products, was taken up in THF and treated with aqueous hydrochloric acid to hydrolyze any silyl ethers that were present. Analysis of this mixture, again by tlc, showed it to consist of compounds of polarity similar to that of the starting material and of compounds of polarity greater than that of the starting material. This material was taken to be a

mixture of the desired product and products of the hydrosilation of the dienone carbonyl. Appropriate work-up of the hydrolysis reaction mixture gave an oily solid.

This solid was immediately treated under the above described[67] tetra-*n*-propylammonium perruthenate oxidation conditions. Gratifyingly, analysis of this reaction mixture, by tlc, showed it to consist of a single component in addition to the starting material, dienone **76**. The rf of the new material was similar to that of the starting material. Work-up of this reaction, followed by purification of the crude product by column chromatography on silica gel and recrystallization of the resulting solid, gave the ketone **30** in 79% yield from the dienone **76**. Also isolated was 11% of the starting material, dienone **76**.

The ketone **30** displayed, in the ir spectrum, a strong absorption at 1712 cm^{-1}, for the (coincident) carbonyl stretches. The ^1H nmr spectrum showed a single resonance in the olefinic region, a doublet of doublets at δ = 5.6 ppm. A mass of m/z = 316 amu was observed in the mass spectrum, for the molecular ion, and a high resolution measurement of this mass confirmed the expected molecular formula. A chloroform solution of the recrystallized product produced an $[\alpha]_D$ of -37°.

The *gem*-dimethyl function, representing the last two carbon atoms missing from the cycloamphilectene skeleton, was introduced by standard alkylation chemistry. Thus, treatment of the ketone **30** with 2 equiv of LDA in THF at -78 °C followed by addition of hexamethylphosphoramide and methyl iodide, gave, after appropriate work-up and separation by column chromatography on silica gel, two products in a ratio of about 5:2. Both products showed, in the ^1H nmr spectrum, a new 3 proton doublet for the introduced secondary methyl group. The major component showed the new resonance at δ = 1.09 ppm while the minor component showed the new resonance at δ = 0.99 ppm.

Treatment of the major component under epimerizing conditions (sodium methoxide, methanol, rt) cleanly converted it into the minor component. Thus, the major component from the alkylation reaction was the ketone **79** while the minor component was the thermodynamically more stable ketone **80**. After appropriate work-up, the material isolated from the epimerization reaction was combined with the minor component isolated from the alkylation reaction. Recrystallization gave the ketone **80** in 90% yield from the ketone **30**. This material displayed, in the ir spectrum, a strong absorption at 1713 cm^{-1}, for the (coincident) carbonyl stretches. The ^1H nmr spectrum displayed three 3-proton doublets at δ = 0.86, 0.97 and 0.99 ppm for the three secondary methyl groups and a 1 proton resonance at δ = 5.6 ppm for the olefinic proton. A mass of m/z = 330 amu was observed in the mass spectrum for the molecular ion and a high resolution measurement of this mass confirmed the expected molecular formula for the ketone **80**. An elemental analysis for carbon and hydrogen produced results within accepted limits. A chloroform solution of the recrystallized material produced an $[\alpha]_D$ of -28°.

Treatment of the ketone **80** with 3 equiv of LDA in THF at -48 °C followed by addition of hexamethylphosphoramide and methyl iodide gave, after appropriate work-up and purification by column chromatography on silica gel, the ketone **81** as a colourless oil in 78% yield. This material displayed, in the ir spectrum, strong absorptions at 1720 and 1705 cm^{-1}, for the carbonyl stretches. In the ^1H nmr spectrum, two 3-proton singlets were observed at δ = 1.0 and 1.1 ppm for the *gem*-dimethyl function. A mass of m/z = 344 amu was observed in the mass spectrum for the molecular ion and a high resolution measurement of this mass confirmed the expected molecular formula. A chloroform solution of the product gave an $[\alpha]_D$ of +5°.

At this point, it was possible to assign the stereochemistry at C-1 (cycloamphilectane numbering). With the introduction of the second methyl group of the *gem*-dimethyl function, the

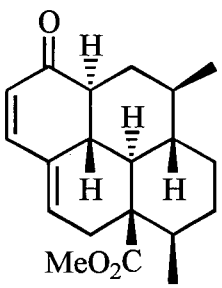
^{1}H nmr spectrum of the ketone **81** was simplified considerably, compared to those of the ketones **30**, **79** or **80**, in that only a single proton remained α to the C-14 carbonyl group. A sample of the ketone **81** was dissolved in methyl alcohol-*d* and the solution was treated with a small amount of sodium hydride. The resulting very pale yellow solution was heated to reflux and maintained at this temperature for 16 h. A ^{1}H nmr spectrum of the worked-up and purified product lacked the ddd at δ = 2.3 ppm that was previously present in the spectrum of the ketone **81**. Thus the signal at δ = 2.3 ppm could be assigned to H-1 with confidence. Inspection of the coupling constants for this signal, J = 12, 12 and 3 Hz, suggested that the orientation of this proton had to be α. In this orientation, two large coupling constants, to H-2β and H-12, and one smaller coupling constant, to H-2α, would be expected. In the β-orientation, 3 smaller and approximately equal coupling constants would be expected. Clearly, the configuration at C-1 was that with the proton in the α-orientation. This is the required configuration for the carbon skeleton of 8-isocyano-10-cycloamphilectene (**11**).

With the peak pattern for H-1 established, it was possible to look back at the ^{1}H nmr spectra of the ketones **30**, **79** and **80** to attempt to establish the C-1 stereochemistry in these compounds. In the ^{1}H nmr spectrum of the C-15β methyl compound, ketone **80**, a ddm was observed at δ = 2.1 ppm, within the δ = 1.93 to 2.15 ppm multiplet, that showed the same coupling constants for the large couplings, J = 12 Hz, as that observed for H-1 in the ketone **81**. In the ^{1}H nmr spectrum of the C-15α methyl compound, ketone **79**, a ddd was observed at δ = 2.2 ppm, within the δ = 2.12 to 2.26 ppm multiplet, that also showed the same coupling constants as did H-1 from the ketone **81**. Similarly for the ketone **30**, a ddd was observed at δ = 2.1 ppm with coupling constants J = 12, 12 and 3 Hz, again the same as those for the ketone **81**.

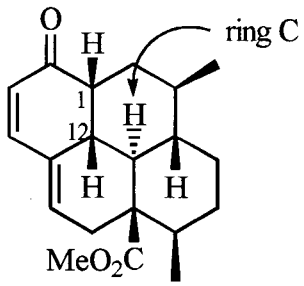
These data suggest that the configuration at C-1 for each of these compounds was that with H-1 in the α-orientation. These observations were the basis for the assignment of the configuration at C-1 in the ketones **30**, **79** and **80**.

Upon examination of molecular models of the dienone **76**, it seemed that the epimer with H-1 in the α-orientation would show a pattern of coupling constants similar to that observed for the α,β-saturated compounds. Upon similar examination of the other C-1 epimer, it was not clear what conformation the molecule would adopt. In any case, upon examination of the ^{1}H nmr spectrum of the dienone **76** it was not possible to assign the C-1 proton with any degree of certainty.

Comparison of the two molecular models of the C-1 epimers of the dienone (**76** and **78**) did suggest, however, that the C-1α epimer (**76**) had a lower energy ground state than did the C-1β epimer (**78**). The C-1β epimer suffers from a severe eclipsing interaction along the C-1 to C-12 carbon-carbon single bond as well as a 'flagpole' type interaction across the (boat-like) C-ring. The C-1α epimer, on the other hand, lacks these steric interactions. Thus, on the basis of these arguments, and the fact that the ring closure reaction was run under conditions that could equilibrate the two epimers, the configuration at C-1 for the product of this reaction was assigned as α.



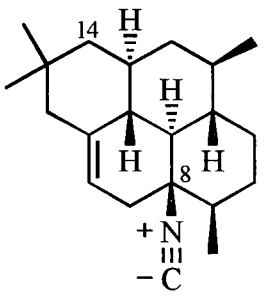
76



78

Thus the ketone **81** was prepared from the keto aldehyde **32** in 5 synthetic steps in 44% overall yield, based on recovered starting material for the selective reduction step. At this point, the carbon skeleton with the correct configuration for the target molecule at each stereogenic centre, was complete.

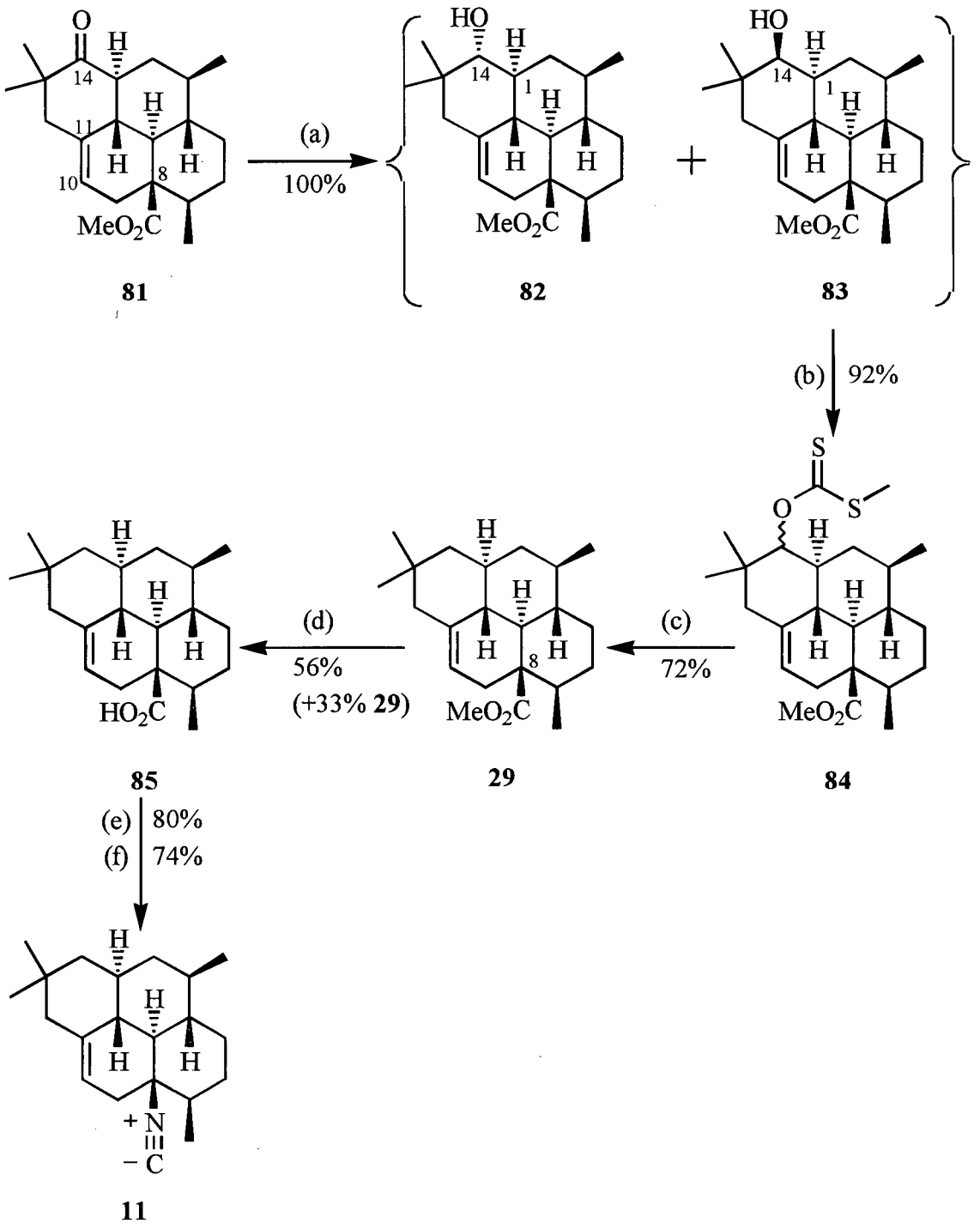
Preparation of (+)-8-Isocyano-10-cycloamphilectene (11)



11

With the required carbon skeleton constructed, all that remained for the total synthesis of the diterpene isocyanide **11** was the reduction of the C-14 (cycloamphilectane numbering) ketone function to a methylene group and the conversion of the methyl ester moiety attached to C-8 into an isocyanide group (see Scheme 19). As the C-14 ketone is fairly hindered, flanked on one side by a *gem*-dimethyl group and on the other by a tertiary carbon, the method of effecting its reduction had to be one that was not sensitive to steric crowding. The procedure chosen for this reduction involved, as the key step, the excellent deoxygenation methodology[74] developed by Barton and McCombie.

Numerous methods have been developed for the deoxygenation of alcohols. For primary alcohols, reduction of a suitable derivative of the alcohol is common. The Super-Hydride®



Scheme 19: Completion of the Total Synthesis of **11** Reagents (a) $NaBH_4$, MeOH; (b) LDA, THF; HMPA; CS_2; MeI; (c) *n*-Bu_3SnH, cat. AIBN, toluene; (d) PhSeNa, HMPA, THF; (e) $(PhO)_2PON_3$, Et_3N, toluene; 2-trimethylsilylethanol, Et_3N; (f) *n*-Bu_4NF, THF; work-up; acetic formic anhydride, Et_2O; work-up; PPh_3, CCl_4, Et_3N, CH_2Cl_2.

reduction of the *p*-toluenesulfonate **59** to the ester **21** was an example of this methodology. Many primary alcohols have also been converted to their corresponding halides. The alkane is then available by hydrogenolysis of the halide. This method can be extended to secondary alcohols where S_N2 processes take place readily. Tertiary alcohols can usually be dehydrated readily and the hydrocarbon is then accessible through hydrogenation of the olefin.

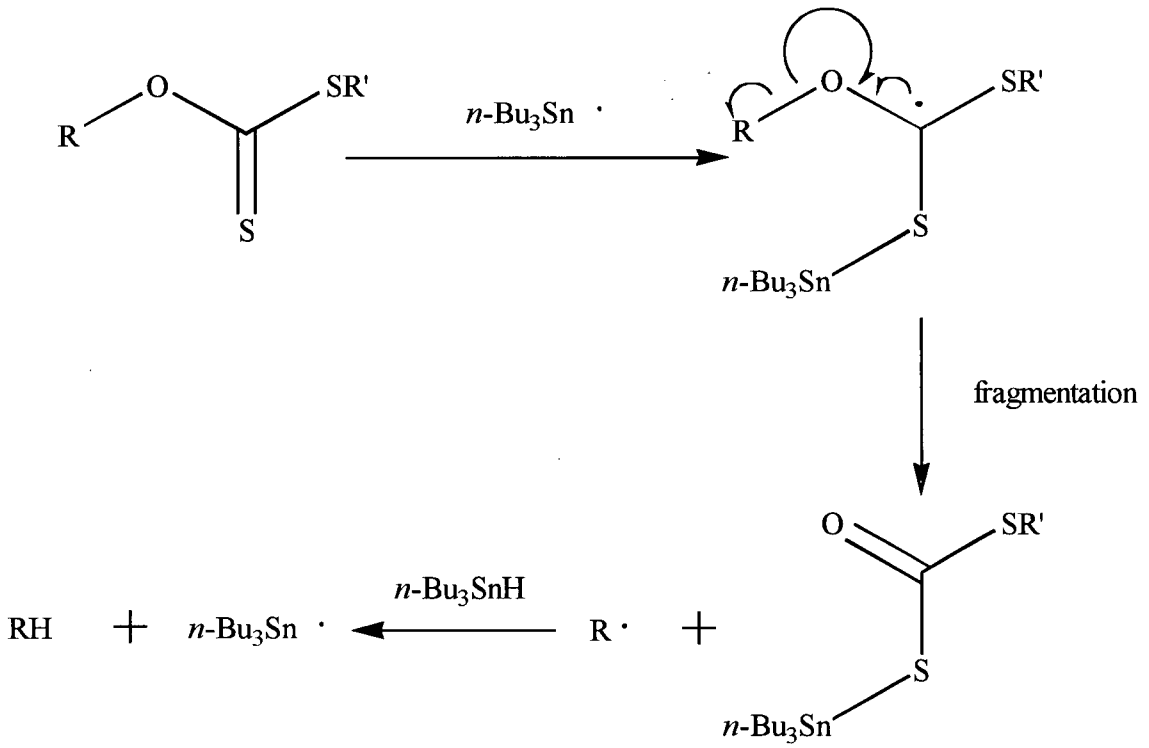
These processes, except of course for the hydrogenation processes, are ionic in principle. They have limitations and disadvantages as soon as complex, polyfunctional compounds, where competing processes may detract from the yield of the desired reduction reaction, are used as substrates. Furthermore, when secondary or tertiary alcohols are used as the substrate, the reduction reaction tends to be more difficult. The main reason for this is that, in cases of high steric demand, nucleophilic substitution reactions take place in low yields if at all. Also, rearrangements and eliminations are common side reactions when carbocations appear as intermediates.

Thus, the above described reaction protocols tend to fail especially in cases where secondary alcohols are the required reduction substrates. Radical reactions offer themselves as alternatives to ionic reactions. Radicals are not solvated, to the extent that ions are, and as such are less susceptible to steric factors. Moreover, radical reactions take place under neutral conditions and so are ideally suited for application to sensitive, polyfunctional molecules. The method of Barton and McCombie describes deoxygenation reactions in which the carbon-oxygen bond is cleaved through a homolytic process, giving carbon based radicals that are subsequently quenched by a hydrogen atom donor.

When *O*-alkyl thiobenzoates and *O*-alkyl *S*-methyl dithiocarbonates derived from secondary alcohols were heated with tri-*n*-butylstannane, in a suitable solvent, the corresponding

alkanes were isolated in high yield.[74]

The mechanism for the reduction reaction is shown in Scheme 20.[74] Heating of tri-*n*-butylstannane provides a source of tri-*n*-butylstannyl radicals. The stannyl radical adds to the thiocarbonyl, forming a thermodynamically stable tin-sulfur single bond and a radical on the thiocarbonyl carbon. Fragmentation of this radical leads to the alkyl radical (R·) and the



Scheme 20: Mechanism of the Barton Deoxygenation of a Dithiocarbonate

tributylstannyl thiol acid ester. The major driving force for this reaction is obtained in going from thiocarbonyl to carbonyl.[74] Tri-*n*-butylstannane then donates a hydrogen atom to the alkyl radial in a chain propagating step, giving the reduced product and a tri-*n*-butylstannyl radical.

The Barton method has been applied to various *O*-alkyl thioesters, *O*-alkyl thioimidazolides and *O*-alkyl dithiocarbonates. Excellent results[75] have been obtained using the *O*-alkyl *S*-methyl dithiocarbonate derivative in toluene and 2,2'-azobisisobutyronitrile as a radical initiator.

To apply the Barton method to the present problem, the ketone function at C-14 (cycloamphilectane numbering) of the ketone **81** had to be reduced to an alcohol. This reduction was carried out by a standard technique. The ketone **81** was dissolved in dry methanol and reacted with sodium borohydride at rt. Appropriate work-up led to the isolation of a nearly quantitative yield of the alcohols **82** and **83**, epimers at C-14. In the ir spectrum, this mixture displayed an absorption at 3502 cm^{-1}, for the secondary alcohol OH stretch and a strong absorption at 1723 cm^{-1}, for the ester carbonyl stretch. A mass spectrum, taken on the mixture, showed a mass at m/z = 346 amu for the molecular ion and a high resolution measurement of this mass confirmed the expected molecular formula.

In the ^1H nmr spectrum of the mixture of **82** and **83**, two resonances were observed at δ = 3.1 and 3.2 ppm for the carbinol protons of the two epimers. The resonance at δ = 3.1 ppm was a doublet with a coupling constant of 11 Hz. That at δ = 3.2 ppm was a broad singlet. Integration of these signals showed the epimers to be present in a ratio of ~5:2, respectively. The signal at δ = 3.1 ppm could be assigned to the alcohol **82** with confidence; similarly, the signal at δ = 3.2 ppm was assigned to the alcohol **83**. Examination of molecular models shows that the alcohol **82**, with the hydroxyl group in the equatorial orientation, has the carbinol proton *anti* to the proton at C-1 (cycloamphilectane numbering). The alcohol **83**, with the hydroxyl in the axial orientation, has the carbon-hydrogen bond of the carbinol proton roughly perpendicular to that of the C-1 proton. Referring to the vicinal Karplus correlation,[76] one would expect the carbinol

proton of the alcohol **82** to show a large coupling while that of the alcohol **83** would show little or no coupling. The data from the ^{1}H nmr spectrum bears out these expectations. Thus the reduction reaction gave the alcohol **82** as the major product and the alcohol **83** as the minor product. The mixture was carried on to the next step.

After some experimentation, the best conditions found for the formation of the required *O*-alkyl *S*-methyl dithiocarbonates **84** were as follows. A solution of the alcohols **82** and **83** in THF was added to a solution of LDA in the same solvent and allowed to react at -48 °C. Addition of dry hexamethylphosphoramide, followed by dry carbon disulfide, gave, *in situ*, the *O*-alkyl dithiocarbonate anion which was treated with methyl iodide to provide the dithiocarbonates **84**. After appropriate work-up and purification by column chromatography on silica gel, the dithiocarbonates **84** were isolated as a yellow oil in 92% yield.

In the ir spectrum, the product mixture displayed strong absorptions at 1723 and 1196 cm^{-1}, for the carbonyl and thiocarbonyl stretches, respectively. The ^{1}H nmr spectrum showed a doublet at δ = 5.7 ppm (J = 13 Hz) and a broad singlet at δ = 5.8 ppm for the carbinol protons of the epimers of the product. Integration of these resonances showed them to be in the ratio of ~5:2, as was the ratio for the alcohols **82** and **83**. The dithiocarbonates **84** were carried on to the Barton deoxygenation protocol as a mixture.

The dithiocarbonates **84** were deoxygenated under the conditions[75] described by Tatsuta *et al.* Thus, slow addition of a solution of 2,2'-azobisisobutyronitrile in toluene to a hot solution of the dithiocarbonates **84** in toluene led to, after appropriate work-up and purification by column chromatography on silica gel, the deoxygenated ester **29** in good yield. In the ir spectrum, this material displayed a strong absorption at 1724 cm^{-1}, for the carbonyl stretch. A mass of 330 amu was observed in the mass spectrum for the molecular ion and a high resolution

measurement of this mass confirmed the expected molecular formula. A chloroform solution of the purified product produced an $[\alpha]_D$ of -53°.

The successful deoxygenation reaction, leading to the ester **29**, represented the completion of the carbon skeleton of the cycloamphilectanes, with the configuration correct at each stereogenic centre for the target natural product, 8-isocyano-10-cycloamphilectene (**11**). With the ester **29** in hand, the only chemistry remaining to complete the total synthesis of the diterpene isocyanide was the conversion of the methyl ester moiety attached to C-8 (cycloamphilectane numbering) into an isocyanide group.

The first step in this transformation called for the conversion of the C-8 ester moiety into the corresponding carboxylic acid. It was anticipated[4] that the ester **29** would be relatively unreactive under normal saponification conditions. The mechanism of saponification requires the addition of hydroxide ion to the carbonyl carbon and the resultant formation of a tetrahedral intermediate. There already exists a relatively high degree of steric hindrance around the C-8 (cycloamphilectane numbering) methoxycarbonyl group, and formation of a tetrahedral intermediate from the ester would result in severe steric interactions.

To alleviate this expected problem, the reagent chosen for the hydrolysis of the C-8 (cycloamphilectane numbering) ester was the highly nucleophilic phenyl selenide anion.[77] This reagent cleaves esters by S_N2 cleavage of the carbon-oxygen bond between the methyl group and the oxygen. During the course of the reaction, the carboxylate function remains trigonal. Since no new steric interactions are introduced, the reaction tends to proceed smoothly.

Phenyl selenide anion seemed to be an ideal reagent for the required reaction. Its high polarizability makes it a powerful nucleophile.[77] A powerful nucleophile is required to overcome the relatively poor leaving group tendencies of the carboxylate, which is displaced in the reaction.

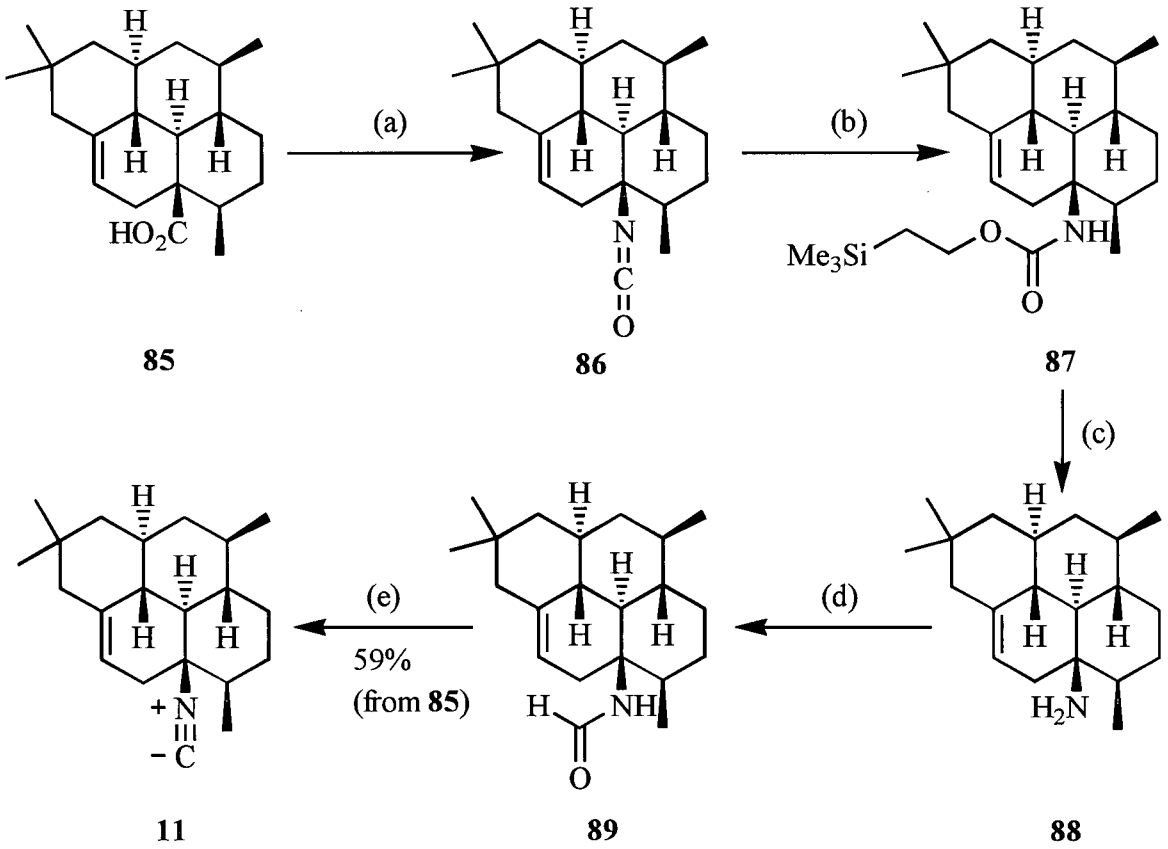
Sodium phenyl selenide is an extremely weak base and is relatively easy to generate, either by deprotonation of benzeneselenol with sodium hydride in a suitable solvent or by reduction of diphenyldiselenide with sodium metal. Sodium borohydride may also be employed as the reductant but, in this case a relatively unreactive phenyl selenide—borane complex is formed.[77]

In the event, conversion of the ester **29** into the carboxylic acid **85** was carried out by heating a solution of the ester **29** and sodium phenyl selenide in THF—hexamethylphosphoramide solution to reflux for 72 h. After appropriate work-up and purification of the crude product mixture by column chromatography on silica gel, the acid **85** was isolated in 56% yield. Also isolated was 33% of the unreacted ester **29**. In the ir spectrum, the product displayed absorptions at 3400-2450 and 1692 cm^{-1}, due to the carboxyl function. A chloroform solution of the product produced an $[\alpha]_D$ of -70°.

With the acid **85** in hand, the stage was set for the conversion of the acid to the required isocyanide function and the completion of the total synthesis of 8-isocyano-10-cycloamphilectene (**11**). Fortunately, methodology[4] appropriate for this transformation had been well worked out in our laboratories for the previous syntheses of the amphilectane diterpenoids. The individual stages of this efficient, two pot process are given in Scheme 21.

A solution of the acid **85** in dry toluene was treated sequentially with triethylamine and diphenylphosphoryl azide[78] and stirred at 85 °C for a period of 22 h. During this time aliquots of the reaction mixture were removed periodically and checked by ir analysis. The peaks due to the acid function, 3400-2450 and 1692 cm^{-1}, disappeared within 2 h and were replaced by a peak at 1766 cm^{-1}, presumably due to the acyl azide intermediate. After 22 h, the peak at 1766 cm^{-1} had itself disappeared and had been replaced by a peak at 2250 cm^{-1}, from the isocyanate **86**. 2-(Trimethylsilyl)ethanol and additional triethylamine were added and the temperature was raised

to 100 °C. After 20 h at this temperature, additional portions of these latter two reagents were added and the reaction was allowed to proceed for a further 24 h. Appropriate work-up, followed by purification of the crude product by column chromatography on silica gel, gave the

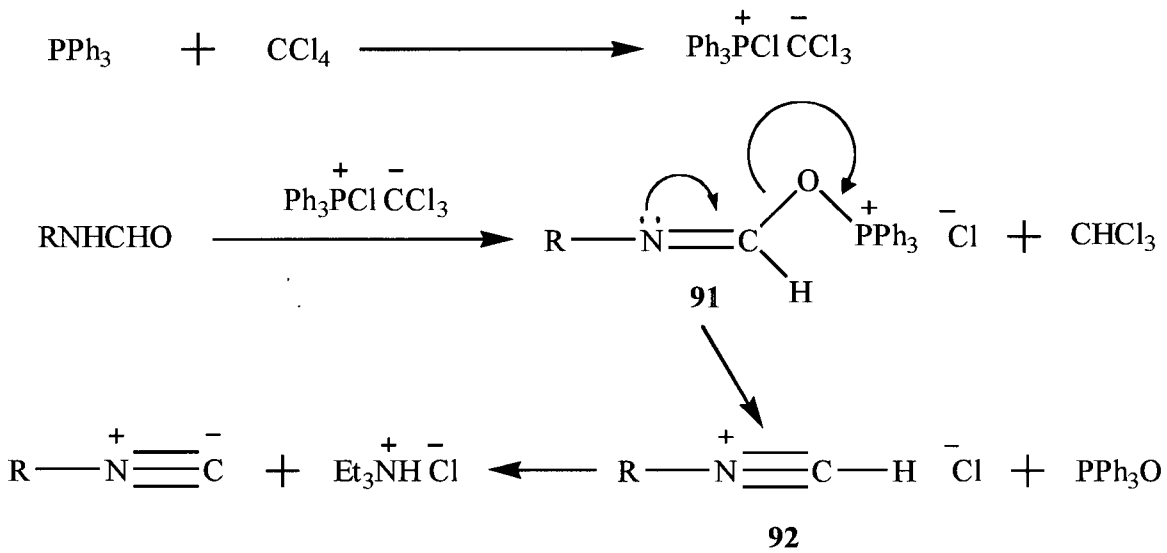


Scheme 21: Intermediates in the Conversion of **85** into **11** Reagents (a) $(PhO)_2PON_3$, Et_3N, toluene; (b) 2-trimethylsilylethanol, Et_3N; (c) TBAF, THF; work-up; (d) acetic formic anhydride, Et_2O; (e) PPh_3, CCl_4, Et_3N, CH_2Cl_2.

carbamate **87** in 80% yield. This material displayed, in the ir spectrum, absorptions at 3446, 1736 and 1508 cm^{-1}, for the carbamate function, and was taken directly onto the next step.

The next step in the sequence involved treatment of the carbamate **87** with tetra-*n*-butylammonium fluoride in THF. The product amine **88** was isolated after an aqueous work-up.

This material was treated immediately with acetic formic anhydride, which was prepared by the method[79] of Huffman. The crude formamide **89**, isolated after an aqueous work-up of the reaction mixture, was immediately treated with triphenylphosphine, carbon tetrachloride and triethylamine, to effect the dehydration—deprotonation reaction and generate the isocyanide function.



Scheme 22: Mechanism of the Stepwise Dehydration of a Formamide

The dehydration reaction is believed to proceed in a stepwise manner (see Scheme 22).[80] The triphenylphosphine and the carbon tetrachloride react to form a salt which reacts with the formamide to give the intermediate **91** and an equiv of chloroform. Elimination of an equiv of triphenylphosphine oxide gives the intermediate **92**. The isocyanide is formed by deprotonation of the intermediate **92** by triethylamine. Evidence for this mechanism exists in that deuterium labeling experiments have shown that the proton on the chloroform formed in the reaction comes exclusively from the N-H moiety.[80]

After appropriate work-up, followed by purification of the crude product by column

chromatography on silica gel and recrystallization of the solid thus obtained from methanol—water, 8-isocyano-10-cycloamphilectene (**11**) was obtained in 74% yield from the carbamate **87**. The spectral and physical data recorded for this material, along with the data reported for the natural material, are presented in Table I. The melting point of the recrystallized material was 87-89 °C. Satisfyingly, in the ir spectrum, the product displayed a strong absorption at 2133 cm^{-1}, for the isocyanide, indicating the success of the functional group transformation. The ^{1}H nmr spectrum showed only one resonance above δ = 2.5 ppm, a broad doublet at 5.22 that integrated for one proton. The ^{13}C nmr spectrum showed resonances for 21 carbons. In the mass spectrum, a mass of m/z = 297 amu was observed and a high resolution measurement of this mass confirmed the expected molecular formula. A chloroform solution of the recrystallized material produced an $[\alpha]_D$ of +23°. The 400 MHz ^{1}H nmr spectrum of (+)-8-isocyano-10-cyclo-amphilectene (**11**) is included in the Appendix as Figure 13.

The melting point, ^{1}H nmr and mass spectral data are in exact accord with those published[5] for the natural product. The ir and ^{13}C nmr data for the synthetic material do not fully agree with those published for the natural material. For comparative purposes, the ^{13}C nmr data for the natural[5] and synthetic 8-isocyano-10-cycloamphilectenes are collected in Table I. The absorption in the ir spectrum for the isocyanide function determined for the synthetic material is in the range one would expect for an isocyanide function.[21] That reported for the natural material does not fall within the expected range for an isocyanide. Clearly the reported value was in error. Curiously the value reported, 2245 cm^{-1}, does fall exactly within the range one would expect for a cyanide. As for the ^{13}C nmr data, Kaslauskas *et al.* reported[5] 20 resonances and the synthetic material displayed 21. It should be noted that the 20 resonances reported for the natural material are in exact accord with 20 of the signals found for the synthetic material and

that one would expect to observe 21 resonances if all of the carbons had significantly different chemical shifts. The extra resonance observed for the synthetic material was at $\delta = 37.2$ ppm. It seems likely that the extra resonance was omitted in the communication disclosing the natural material. The $[\alpha]_D$ values for the natural and synthetic material agreed in magnitude but differed in sign. Thus, it was clear that the enantiomer of the natural material had been synthesized. In other words, the structure that was depicted as the natural product, 8-isocyano-10-cycloamphilectene (**11**), is actually the other enantiomer of the natural material. An authentic sample[81] of (-)-8-isocyano-10-cycloamphilectene ((-)-**11**), displayed ^{1}H and ^{13}C nmr spectra in exact accord with the synthetic material.

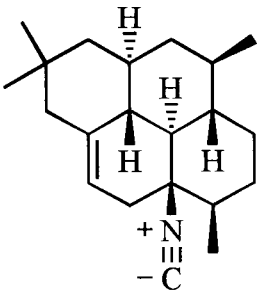
Thus, the dextrorotatory antipode of the natural material was prepared from the ketone **81** in 6 synthetic steps and 46% overall yield. The above described synthetic efforts culminated in the total synthesis of (+)-8-isocyano-10-cycloamphilectene (**11**) in 32 steps and 2% overall yield from the β-keto ester **35**. To our knowledge, this work represents the first total synthesis of a cycloamphilectane diterpenoid and, specifically, the first total synthesis of (+)-8-isocyano-10-cycloamphilectene (**11**).

Table I: Comparison of ^{13}C nmr Data for the Natural 8-Isocyano-10-cycloamphilectene ((-)-**11**) and the Synthetic 8-Isocyano-10-cycloamphilectene ((+)-**11**)

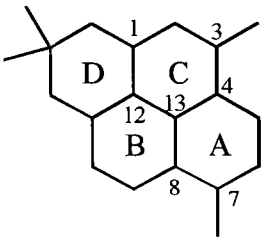
Resonance	Chemical Shift Observed[5] in (-)-**11** (ppm)	Chemical Shift Observed in (+)-**11** (ppm)
a	15.2	15.2
b	19.5	19.5
c	25.1	25.1
d	29.5	29.5
e	29.8	29.8
f	31.6	31.7
g	32.2	32.2
h	37.2‡	37.2
i	37.7	37.7
j	38.0	38.0
k	40.6	40.6
l	42.7	42.7
m	43.1	43.0
n	44.0	43.9
o	46.2	46.2
p	47.6	47.6
q	49.0	49.0
r	62.8	62.8
s	115.2	115.2
t	137.5	137.6
u	154.4	154.4

‡ This resonance, absent from the reported data,[5] was observed in the ^{13}C nmr spectrum of an authentic sample[81] of the natural product.

Conclusions



11



The work described in the discussion section of this thesis constitutes the successful total synthesis of (+)-8-isocyano-10-cycloamphilectene (**11**). This compound was synthesized in 32 steps from the β-keto ester **35** which in turn was synthesized in four steps from commercially available (5*R*)-(+)-pulegone (**40**). Overall, the 36 step linear sequence proceeded in approximately 2% yield.

The synthesis was convergent at two points, one involving the iodide **15**, prepared from commercially available 5-chloro-1-pentyne by a 5 stage process that proceeded in 71% overall yield and the other involving methyl 2-bromoacrylate, prepared from commercially available methyl acrylate by a one pot two-step process that proceeded in 81% yield. To our knowledge, this was the first total synthesis of this biologically active and structurally interesting natural product.

The key features of the described total synthesis were the reactions which formed the second, third and fourth rings, namely an intramolecular Stille-type coupling, a Diels – Alder reaction and an intramolecular aldol condensation reaction, respectively. The configurations at C-1, C-3 and C-12 (cycloamphilectane numbering) were established under thermodynamic

control whereas those of C-4, C-8 and C-13 were established under kinetic control. The configuration at C-7 was that from the commercially obtained starting material for the synthesis, (5*R*)-(+)-pulegone (**40**).

Because the optical rotation of the natural and synthetic materials agreed in magnitude but differed in sign, it was clear that the synthetic material was the other enantiomer of the natural product. Thus, the first goal of the synthesis (see page 12) to establish the absolute configuration of the natural product, was realized. The absolute configuration of the natural product is opposite to that depicted in structure **11**.

At the stage where the C-ring of the carbon skeleton was formed, the facial selectivity of the Diels - Alder process was improved over that employed in the amphilectane syntheses. The previous syntheses showed, at best, a 7:3 facial selectivity whereas the Diels - Alder process in the synthetic efforts described herein proceeded with complete facial selectivity. Thus, the second goal of the synthesis was also realized (see page 12).

The third goal of the synthesis (see page 13) to improve the efficiency of the somewhat problematic process wherein the ester **21** was converted into the ketone **23**, was only partly realized. Here, a more efficient and convenient process was found to carry out the reduction step of the sequence, but no alternative for the allylic oxidation step was found.

Finally, the reported value for the ir absorption of the isocyanide function of 8-isocyano-10-cycloamphilectene (**11**) would seem to be in error. The value determined for the synthetic material was in the expected range for this absorption, and the natural product does not display any abnormal behaviour. Thus the fourth and final goal of the synthesis was also realized (see page 13).

Experimental Section

General

Data Acquisition and Presentation

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures refer to air bath temperatures of Kugelrohr type distillations and are uncorrected. Boiling points refer to wet-bulb stillhead temperatures, measured with a thermometer, and are uncorrected. Pressures quoted (reduced pressures) refer to that of the manifold to which the apparatus was attached.

Infrared spectra were recorded either on thin films between sodium chloride plates (liquid samples) or on 1 to 2 weight percent potassium bromide pellets (solid samples) using a Perkin-Elmer model 1600 Fourier transform infrared spectrometer with internal calibration.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on Bruker model AC-200, WH-400 or AVA-500 spectrometers at 200.132 MHz, 400.100 MHz, or 500.130 MHz, respectively, using deuteriochloroform ($CDCl_3$) as the solvent unless otherwise noted. Signal positions (δ values) are given in ppm from TMS and were measured relative to that of chloroform (δ 7.26 ppm). Coupling constants (J values) are given in Hz. The multiplicity, integration, coupling constant(s) and assignment (when known) are given in parenthesis. Tin - hydrogen and tin - carbon coupling constants quoted are the average for those displayed by ^{117}Sn and ^{119}Sn.

Carbon nuclear magnetic resonance (^{13}C nmr) were recorded on Bruker model AC-200, Varian model XL-300, Bruker models AM-400 or AVA-500 spectrometers at 50.323 MHz, 75.4 MHz, 100.614 MHz or 125.757 MHz, respectively, using $CDCl_3$ as the solvent unless otherwise noted. Signal positions (δ values) are given in ppm from TMS and were measured relative to that of $CDCl_3$ (δ 77.0 ppm).

Low and high resolution electron impact (EI) mass spectra were recorded on Kratos MS50 or MS80 mass spectrometers at 70 eV. Low and high resolution desorption chemical ionization (DCI) mass spectra were recorded with a Delsi Nermag model R-10-10C mass spectrometer using either ammonia, isobutane or methane or mixtures of these materials as the ionizing gas. These analyses were performed by the UBC Mass Spectrometry Laboratory.

Elemental analyses were performed on a Carlo Erba model 1106 CHN elemental analyzer or on a Fisons EA model 1108 elemental analyzer or using standard micro-analytical techniques. These analyses were carried out by Mr. P. Borda of the UBC Microanalytical Laboratory.

Optical rotations of samples were measured with a Perkin-Elmer model MC-241 polarimeter at 589 nm (sodium 'D' line) and 436 nm.

High performance liquid chromatography was performed using a Waters 600E Multisolvent Delivery System connected in series to a Waters 486 Tunable Absorbance Detector and a Waters 410 Differential Refractometer. Preparative liquid chromatography was done on a Waters Prep 500 system using normal phase silica gel columns. Gas-liquid chromatographic analyses were performed on Hewlett-Packard models 5880A or 5890 capillary gas chromatographs employing commercial fused silica columns (20 m x 0.21 mm x 30 μm) coated with cross-linked 5% phenyl 95% methyl silicone. Thin layer chromatography was carried out on commercial aluminum backed silica gel 60 plates (E. Merck, type 5554, 0.2 mm on aluminum).

Visualization was accomplished by ultraviolet light (254 nm), commercial 20% w/v phosphomolybdic acid in ethanol, aqueous ceric ammonium molybdate, basic aqueous potassium permanganate and/or iodine. Liquid—solid chromatography (column chromatography) was performed with either 230-400 mesh silica gel (E. Merck, silica gel 60) using apparatus described[82a] by Still *et al.* and the method described by Williams *et al.*[82b] or type H 5 - 25 μm silica gel (Sigma, tlc grade silica) using the method described by Taber.[82c]

Compounds that were submitted for high resolution mass spectrometry and elemental analysis were typically homogenous by tlc analysis and/or greater than 95% pure by glc analysis. In a few cases, these analyses were carried out on mixtures that other analytical methods had shown to be epimeric in nature.

All reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame or oven dried, unless otherwise stated. Glass syringes, stainless steel needles and Teflon® cannulae were oven dried prior to use. Plastic syringes were flushed with dry argon.

Removal of solvent refers to concentration using a rotary evaporator at ~15 Torr, followed by evacuation under reduced pressure (rotary vacuum pump, ~0.05 Torr) if appropriate.

Cold temperatures were maintained by use of the following baths: 0 °C, ice—water; -10 °C, ice—acetone; -20 °C, -30 °C, -40 °C and -48 °C, Dry Ice®—aqueous calcium chloride (27, 35, 41 and 47 g of $CaCl_2$ per 100 ml of H_2O), respectively; -78 °C, Dry Ice®—acetone; -198 °C, liquid nitrogen.

Reference to a glove box and operations carried out in a glove box refer to a Vacuum Atmospheres Company Dri-Box. The glove box allows storage and manipulation of materials under an atmosphere of dry argon.

Solvents and Reagents

The argon gas used was commercial grade and was purchased from either Matheson Gas Products or Praxair Canada Incorporated. Dry argon refers to argon passed through concentrated sulfuric acid, potassium hydroxide pellets and Drierite® prior to use.

Solvents and reagents were purified and dried using accepted procedures. Petroleum ether refers to a hydrocarbon mixture with bp 35-60° C. Aqueous NH_4Cl—NH_4OH (pH 8) refers to saturated NH_4Cl (aq) adjusted to pH 8 (pH paper) by the addition of 30% NH_4OH (aq). Dry THF, ether or toluene refer to THF, ether or toluene heated to reflux over and distilled from sodium metal under an atmosphere of dry argon. Dry methylene chloride, benzene or methanol refer to methylene chloride, benzene or methanol heated to reflux over and distilled from calcium hydride under an atmosphere of dry argon.

Lithium diisopropylamide solution was prepared by dropwise addition of a solution of *tert*-butyllithium in pentane to a stirred solution of diisopropylamine (1.0 equiv) in dry THF at -78 °C until a pale yellow colour persisted for 1 minute. Addition of 0.1 equiv of additional diisopropylamine gave a colourless solution of the base, which was then ready for immediate use.

Methyl iodide was dried and purified by filtration through oven dried basic alumina followed by distillation from calcium hydride. Samarium metal (-40 mesh) was purchased from Cerac Specialty Inorganics and stored in a glove box. (*R*)-(+)-Pulegone was 'purem' grade

purchased from Fluka Chemie AG and was used as received. Super-Hydride® is lithium triethylborohydride solution in THF. Carbon monoxide was C. P. grade purchased from Matheson Gas Products.

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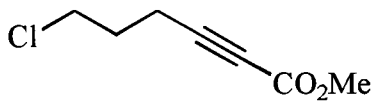
Procedures

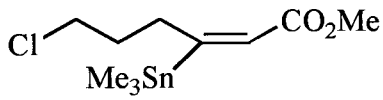
Preparation of Methyl 6-Chloro-2-hexynoate (**49**)[83]



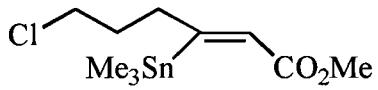
49

A solution of 5-chloro-1-pentyne (**48**) (24.38 g, 237.6 mmol) in dry THF (600 mL) was stirred magnetically and cooled to -78 °C. A solution of *tert*-butyllithium in pentane (188 mL, 1.26 M) was added by syringe. At the end of the addition, the solution took on a very pale yellow colour. The reaction mixture was stirred for an additional 5 min and then methyl chloroformate (22.0 mL, 285 mmol) was added by syringe. The yellow colour disappeared but returned a few minutes later. After the mixture had been stirred for 10 min, the cooling bath was removed and the mixture was allowed to warm to rt. The solvent was removed from the yellow reaction mixture. The residue was suspended in diethyl ether (300 mL) and then poured into saturated NH_4Cl (aq) (25 mL) and water (75 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with saturated NaCl (aq) (3 x 100 mL), dried over $MgSO_4$ and filtered. Removal of the solvent gave the crude product which was essentially homogenous by glc and tlc (developed with 10:1 petroleum ether - diethyl ether, visualized with the phosphomolybdic acid dip) analyses. Distillation of the crude product (bp 61-63 °C at 0.17 Torr) gave the alkynic ester **49** (37.19 g, 97%) as a clear, colourless oil. This material displayed ir and ^1H nmr spectra identical with those previously reported[41a] for this compound.

Preparation of Methyl (*E*)-6-Chloro-3-(trimethylstannyl)-2-hexenoate (**50**)



50

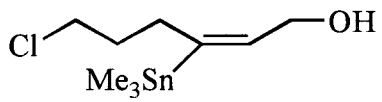


51

A solution of hexamethyldistannane (57.6 mL, 90.4 g, 276 mmol) in dry THF (1.10 L) was stirred magnetically and cooled to -78 °C. A solution of methyllithium in diethyl ether (181 mL, 1.4 M) was added by syringe and the resulting pale yellow, cloudy mixture was stirred for 25 min. Copper(I) cyanide (24.7 g, 276 mmol) was added in 1 portion. The resulting bright yellow mixture was warmed to -40 °C and stirred at that temperature for 30 min. The colour changed from yellow through orange to deep red during the stirring time. The solution was cooled to -78 °C and dry methanol (11.6 mL, 287 mmol) was added by syringe. A solution of the alkynic ester **49** (36.92 g, 229.9 mmol) in dry THF (100 mL) was added to the reaction flask by cannula. The resulting yellow solution was stirred for 4 h. The reaction vessel was opened to the atmosphere and aqueous NH_4Cl - NH_4OH (pH 8) (600 mL) was added. The cold bath was removed and the mixture was allowed to warm to rt and then vigorously stirred for 16 h. The phases were separated and the deep blue aqueous phase was extracted with diethyl ether (3 x 500 mL). The flocculent purple precipitate was kept with the organic phase. The combined organic phases were washed with saturated NaCl (aq) (3 x 500 mL), dried over $MgSO_4$ and filtered. Removal of the solvent gave the crude product (90 g) as a clear, yellow oil. Upon tlc analysis (developed with 19:1 petroleum ether - diethyl ether, visualized with the phosphomolybdic acid dip), this material proved to be a mixture of a major component and a slightly less polar minor component. Separation and purification was achieved by preparative

liquid chromatography (two 8 cm (width) by 32 cm (length) silica gel columns, 2% diethyl ether in petroleum ether, flow rate 200 mL/min, refractive index detection) on 8 to 10 mL portions of the crude product. Combination of appropriate fractions followed by removal of the solvent and distillation (bp 124-128 °C at 1.20 Torr) of the residue gave the α,β-unsaturated ester **50** (61.30 g, 82%) as a clear, colourless oil. Similar treatment (bp 120-124 °C at 1.20 Torr) gave the minor component, which proved to be methyl (*Z*)-6-chloro-3-(trimethylstannyl)-2-hexenoate (**51**), (7.81 g, 10%) also as a clear, colourless oil. These materials showed ^{1}H nmr spectra identical with those previously reported for these compounds.[41a]

Preparation of (*E*)-6-Chloro-3-(trimethylstannyl)-2-hexen-1-ol (**52**)

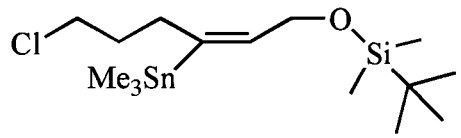


52

A solution of the α,β-unsaturated ester **50** (37.08 g, 114.0 mmol) in dry diethyl ether (700 mL) was stirred magnetically and cooled to -78 °C. A solution of DIBAL-H in hexanes (239 mL, 1.0 M) was added in 50 mL portions by syringe and the colourless solution was stirred for 1 h after which time tlc analysis (developed with 4:1 petroleum ether - diethyl ether; visualized with the phosphomolybdic acid dip) showed the reaction to be complete. The cold bath was removed and the solution was allowed to warm to rt. The reaction vessel was opened to the atmosphere and diethyl ether (500 mL) was added. Saturated NH_4Cl (aq) (20 mL) was added, cautiously at first, and the mixture was vigorously stirred for 4 h, after which time a thick,

white slurry had formed. Magnesium sulfate (2 g) and Celite® (5 g) were added and the mixture was stirred for an additional 10 min. A short column (5 cm high in a 10 cm (width) coarse sintered glass funnel) of 230-400 mesh silica gel was prepared and this was topped with a thin (1 cm) layer of Celite®. The reaction mixture was filtered through the column and the column was washed with diethyl ether (300 mL). Removal of the solvent from the combined filtrates, followed by treatment of the residue under reduced pressure (vacuum pump), gave the alcohol **52** (32.79 g, 97%) as a clear, very pale yellow oil. This material could be used without further purification. Ir and ^{1}H nmr spectra of this material were identical with those previously reported[84] for this compound.

Preparation of (*E*)-6-Chloro-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-(trimethylstannyl)-2-hexene (**53**)

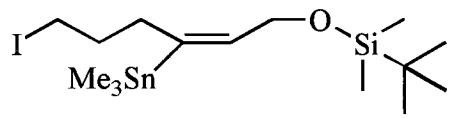


53

A solution of the alcohol **52** (19.36 g, 65.10 mmol) in dry methylene chloride (1 L) was stirred magnetically and cooled to -10 °C. Imidazole (5.76 g, 84.6 mmol) was added, followed by *tert*-butyldimethylsilyl chloride (10.8 g, 71.7 mmol). A white precipitate formed immediately. The mixture was stirred for 3 h, during which time the cold bath was allowed to melt and the mixture was allowed to warm to rt. The reaction vessel was opened to the atmosphere and petroleum ether (500 mL) was added. A short (5 cm high in a 10 cm (width) coarse sintered glass funnel) column of 230-400 mesh silica gel was prepared. The reaction mixture was filtered

through the column and the column was washed with petroleum ether (250 mL). Removal of the solvent from the filtrate gave the crude product (28 g) as a clear, colourless oil. Purification of this material was accomplished by preparative liquid chromatography (two 8 cm (width) by 32 cm (length) silica gel columns, 0.25% ethyl acetate in petroleum ether, flow rate 200 mL/min, refractive index detection) on 8 to 10 mL portions of the crude product. Removal of the solvent from the appropriate fractions, followed by treatment of the residue under reduced pressure (vacuum pump) gave the chloride **53** (25.40 g, 95%) as a clear, colourless oil. This material could be used without further purification. This material showed ir and ^{1}H nmr spectra identical with those previously reported[84] for this compound.

Preparation of (*E*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-iodo-3-(trimethylstannyl)-2-hexene (**15**)

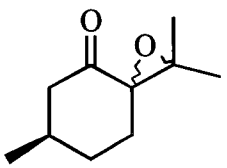


15

A solution of the chloride **53** (25.20 g, 61.21 mmol) and sodium iodide (46.0 g, 307 mmol) in acetone (300 mL) was stirred magnetically and heated to reflux for a period of 3 days. At this time, the mixture contained a white precipitate and glc analysis of the liquid phase showed that the starting material had been consumed. The mixture was cooled to rt and the solvent was removed. Water (200 mL) and diethyl ether (300 mL) were added to the residue. The mixture was shaken and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were dried over $MgSO_4$. The dried solution was filtered and the solvent was removed to isolate the crude product (32 g) as a clear,

very pale yellow oil. Distillation (180-190 °C at 0.12 Torr) gave the iodide **15** (29.87 g, 97%) as a clear, colourless oil. Ir and ^{1}H nmr spectra of this material were identical with those previously reported[84] for this compound.

Preparation of {(1*R*,4*R*)-4,8-Epoxy-3-oxo-*p*-menthane and (1*R*,4*S*)-4,8-Epoxy-3-oxo-*p*-menthane} (**41**)



41

A solution of (*R*)-(+)-pulegone (**40**) (47.13 g, 309.7 mmol) in methanol (250 mL) was stirred magnetically and cooled in an ice - water bath until its temperature had fallen below 4 °C. Aqueous hydrogen peroxide (30% by wt, 125 mL, 1.10 mol) was added and the temperature again was allowed to fall below 4 °C. A solution of potassium hydroxide (37.5 g, 0.67 mol) in water (125 mL) was prepared and cooled to rt. The potassium hydroxide solution was added, dropwise from an addition funnel over a period of about 1 h, to the pulegone solution, at a rate such that the temperature of the reaction mixture did not rise above 10 °C. The mixture was stirred for an additional 4.5 h, maintaining the temperature between 4 and 10 °C. At this time, glc analysis of the reaction mixture showed that the starting material had been consumed. The mixture was poured into saturated NaCl (aq) (500 mL) and this mixture was extracted with diethyl ether (3 x 500 mL). The combined organic phases were washed with saturated NaCl (aq) (2 x 200 mL) and dried over $MgSO_4$ for a period of 6 h. Removal of the solvent followed by

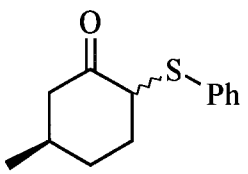
treatment of the residue under reduced pressure (vacuum pump) gave the epoxides **41** (50.01 g, 96%) as a clear, colourless oil. Analysis of the oil by glc showed it to be a mixture of the two expected diasteriomers in a ratio of ~65 : 35. This ratio is in agreement with that previously reported for this mixture.[85] This material, which could be used without further purification, displayed:

ir (film): 1740, 1260, 919 cm^{-1}.

^1H nmr (400 MHz): δ = {(1.04 (d, *J* = 7 Hz), 1.06 (d, *J* = 6 Hz)), 3 H, C-1 -CH_3}, {(1.18 (s), 1.19 (s)), 3 H, 3° -CH_3}, 1.40 (s, 3 H, 3° -CH_3), 1.70 - 2.05 (m, 4 H), {(2.12 - 2.22 (m), 2.57 (ddd, *J* = 13, 3, 3 Hz)), 1 H}, 2.38 (br s, 2 H).

Anal. calcd. for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.55, H 9.65.

Preparation of {(2*R*,5*R*)-5-Methyl-2-(phenylthio)cyclohexanone and (2*S*,5*R*)-5-Methyl-2-(phenylthio)cyclohexanone} (**39**)



39

Sodium hydride (7.49 g, 312 mmol) was placed in a dry 3 necked 2 L round-bottomed flask. The flask was equipped with a condenser and the ports were capped with rubber septa. Dry THF (900 mL) was added and the suspension was stirred magnetically at rt. The reaction vessel was equipped with a vent, by piercing the septum on the condenser with a 16 ga needle,

and benzenethiol (32.1 mL, 312 mmol) was added, slowly, by syringe. The resulting white suspension was stirred for 1 h and then a solution of the epoxide **41** (50.0 g, 297 mmol) in dry THF (100 mL) was added by cannula. The vent was removed. The mixture was heated to reflux for a period of 16 h after which time the yellow solution was cooled to rt and poured into water (500 mL). Diethyl ether (300 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 200 mL). The combined organic phases were dried over $MgSO_4$ and filtered. Removal of the solvent from the dried solution, followed by treatment of the residue under reduced pressure (vacuum pump), gave the sulfides **39** (65.1 g, 99%), as a mixture of a yellow oil and a white solid. The title compound exists as a mixture of epimers at C-2. Analysis of the mixture by glc showed the diastereomers to be in the ratio of ~65 : 35, consistent with that of the starting material, the epoxides **41**. This material, which was used without further purification, displayed:

^{1}H nmr (400 MHz): δ = 0.98 - 1.08 (m, 3 H), 1.33 - 1.47 (m, 1 H), 1.60 - 2.36 (m, 5 H), 2.62 - 2.82 (m, 1 H), 3.70 - 3.90 (m, 1 H), 7.18 - 7.53 (m, 5 H).

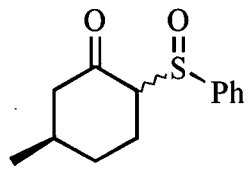
lrms (EI): m/z = 220 (23%, M^+).

A small amount of the mixture was washed with pentane to separate the liquid phase from the solid phase. Removal of the solvent from both fractions followed by treatment of the residual oil and solid (separately) under reduced pressure (vacuum pump) gave samples that displayed:

ir (film): 3059, 1713, 750, 692 cm^{-1}.

ir (KBr): 3068, 1704, 754, 692 cm^{-1}.

Preparation of {(2*R*,5*R*)-5-Methyl-2-(phenylsulfinyl)cyclohexanone and (2*S*,5*R*)-5-Methyl-2-(phenylsulfinyl)cyclohexanone} (**42**)

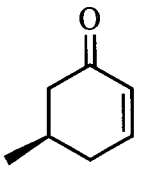


42

A solution of the sulfides **39** (65.33 g, 296.6 mmol) in methylene chloride (1 L) was stirred magnetically and cooled to 0 °C. Peracetic acid (32% by wt in dilute acetic acid, 70.5 mL, 297 mmol) was added dropwise over a period of 10 min from an addition funnel and the mixture was stirred for an additional 10 min. At this time, tlc analysis of the reaction mixture (developed with 4:1 petroleum ether - diethyl ether, visualized with the phosphomolybdic acid dip) showed the reaction to be complete. Saturated $Na_2S_2O_3$ (aq) (100 mL) was added and the 2 phase system was stirred vigorously for 5 min. The mixture was poured into diethyl ether (2.3 L) and the layers were separated. The organic phase was washed successively with water (500 mL), 1:1 saturated $NaHCO_3$ (aq) - water (3 x 350 mL) and finally with saturated NaCl (aq) (2 x 100 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The resulting viscous yellow oil was placed under reduced pressure (vacuum pump) to remove the last traces of solvent and, upon standing, it solidified to give a pale yellow mass. This material, the sulfoxides **42**, weighed 70.74 g (~100%), and was used without further purification. The title compound is a mixture of diastereomers both at C-2 and at the sulfoxide sulfur. This material displayed:

ir (KBr): 3051, 1704, 1046 cm^{-1}.

Preparation of (5*R*)-(-)-5-Methyl-2-cyclohexenone (**38**)



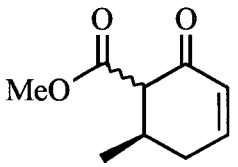
38

Dry calcium carbonate was prepared in the following manner. Calcium carbonate (~20 g) was placed in a beaker and heated in an oven at 140 °C for a period of 16 hr. The beaker was transferred to a vacuum desiccator containing a beaker of phosphorus pentoxide. The desiccator was placed under reduced pressure (vacuum pump) and maintained under static vacuum for a period of 16 h and then brought to atmospheric pressure with a supply of dry argon.

The sulfoxides **42** (11.74 g, 49.68 mmol) and dry calcium carbonate (9.95 g, 99.4 mmol) were mixed thoroughly and then placed in a 250 mL round-bottomed flask. The flask was fitted with a vacuum trap and the apparatus was evacuated to a pressure of 0.070 Torr. The vacuum trap flask was cooled to -78 °C and the reaction flask was heated in an oil bath to 90 °C. This temperature was maintained for 3 h. The oil and cooling baths were removed and the apparatus was brought to rt and atmospheric pressure. The crude product, 5.5 g of a clear, colourless oil was taken up in pentane (75 mL) and the solution was dried over $MgSO_4$. This material was filtered and the pentane was removed by distillation at atmospheric pressure though a Vigreux column. The residue was distilled (60 - 70 °C at 16 Torr) to provide the α,β-unsaturated ketone **38** (4.98 g, 91%) as a clear, colourless oil. This oil produced ir and ^1H nmr spectra identical with those previously reported[86] for this compound. In addition, this material displayed:

optical rotation: $[\alpha]_D^{26}$ -90° (c = 7.8, chloroform), $[\alpha]_{436}^{26}$ -219° (c = 7.8, chloroform); lit.[87]: $[\alpha]_D^{25}$ -90° (c = 2.6, chloroform).

Preparation of Methyl (5*R*)-5-Methyl-2-cyclohexenone-6-carboxylate (**44**)



44

A solution of LDA in dry THF (40 mL) was prepared at -78 °C in the usual way from dry diisopropylamine (4.07 mL, 29.1 mmol) and a solution of *tert*-butyllithium in pentane (16.5 mL, 1.76 M). Dry HMPA (4.74 mL, 27.3 mmol) was added rapidly, by syringe, and the resulting pale yellow solution was stirred for 15 min. A solution of the α,β-unsaturated ketone **38** (2.00 g, 18.2 mmol) in dry THF (10 mL) was added by cannula and the mixture was stirred for 90 min. A solution of methyl cyanoformate (2.16 mL, 27.2 mmol) in dry THF (10 mL) was added by cannula and the resulting yellow solution was stirred for 2 h. The reaction vessel was opened to the atmosphere. Diethyl ether (20 mL) and saturated NH_4Cl (aq) (20 mL) were added. The mixture was allowed to warm to rt with efficient stirring. The layers were separated. The aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed. The crude product, a yellow oil, was purified by column chromatography (180 g of 230-400 mesh silica gel, 7 cm (width) column, 5:4 petroleum ether - diethyl ether). The appropriate fractions were combined and concentrated to provide the β-keto ester **44** (2.38 g, 78%) as a clear, colourless oil which solidified upon

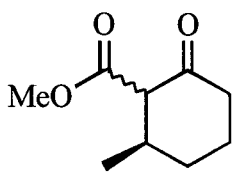
standing. The title compound exists as a mixture of epimers at the C-6 position. The ratio of the epimers varied from experiment to experiment. Upon prolonged standing, especially in solution, the enol form of the keto ester function, as well as the two C-6 epimers, could be observed in the ^{1}H nmr spectrum. The solid material from the above described experiment, which was used without further purification, displayed:

mp: 71-73 °C.

ir (KBr): 1742, 1678, 1650, 1622, 1589, 1438 cm^{-1}.

^{1}H nmr (400 MHz): δ = 1.05 (d, 2.5 H, J = 7 Hz, C-5 -CH_3: major isomer), 1.01 (d, 0.5 H, J = 7 Hz, C-5 -CH_3: minor isomer), 2.10 (ddddd, 1 H, J = 10, 10, 10, 3, 3 Hz, H-4β: both isomers), 2.40 -2.65 (m, 2 H, H-4α and H-5: both isomers), 3.10 (d, 0.82 H, J = 12 Hz, H-6: major isomer), 3.37 (d, 0.18 H, J = 3 Hz, H-6: minor isomer), 3.67 (s, 0.5 H, CH_3O-: minor isomer), 3.74 (s, 2.5 H, CH_3O-: major isomer), 6.04 (ddd, 1 H, J = 10, 3, 1 Hz, H-2: both isomers), 6.95 (ddd, 0.82 H, J = 10, 6, 3 Hz, H-3: major isomer), 7.02 (ddd, 0.18 H, J = 10, 6, 3 Hz, H-3: minor isomer).

Preparation of Methyl (3*R*)-3-Methylcyclohexanone-2-carboxylate (**35**)



35

Palladium on activated charcoal (10% by wt, 1.13 g, 1.06 mmol) was placed in a round-bottomed flask which was then thoroughly flushed with argon and capped with a rubber septum. Dry diethyl ether (90 mL) was added by syringe. Magnetic stirring was started and the suspension was cooled to -78 °C. The catalyst was presaturated by 3 cycles of evacuating the flask (water aspirator) and then refilling it with hydrogen. The reaction flask was warmed to 0 °C. A solution of the β-keto ester **44** (3.57 g, 21.3 mmol) in dry diethyl ether (10 mL) was added to the reaction flask by cannula. A positive pressure of hydrogen was maintained (balloon) and the mixture was stirred vigorously for 30 min. The septum was removed and the atmosphere of hydrogen was displaced with a stream of argon. Celite® (3 g) was added and the mixture was filtered through a short column (1.5 cm in a 150 mL medium sintered glass funnel) of Celite®. The solid was washed with diethyl ether (50 mL). Removal of the solvent from the combined filtrates, followed by distillation (60 - 80 °C, 0.30 Torr) of the residue, gave the β-keto ester **35** (3.68 g, 97%) as a clear, colourless oil which semi-solidified on standing to give a mixture of a clear, colourless oil and a colourless, crystalline solid. The ratio of the epimers varied over time and from experiment to experiment. The title compound exists as a mixture of epimers at the C-6 position. The liquid phase produced the following ir data:

ir (film): 1748, 1714, 1651, 1615, 1440, 1285, 1223 cm^{-1}.

The product mixture was well stirred to produce a suspension of the solid and liquid phases. A sample of the mixture displayed:

^{1}H nmr (400 MHz): δ = 1.03 (d, 2.7 H, J = 8 Hz, C-3 -CH_3: major isomer), 1.06 (d, 0.3 H, J = 8 Hz, C-3 -CH_3: minor isomer), 1.42 (ddd br d, 0.9 H, J = 12, 12, 12, 4 Hz, major isomer),

1.48 - 1.55 (m, 0.1 H, minor isomer), 1.73 (ddddd, 0.9 H, J = 13, 13, 13, 4, 4 Hz, major isomer), 1.85 - 1.97 (m, 1 H, both isomers), 2.00 - 2.17 (m, 1 H, both isomers), 2.22 - 2.38 (m, 2 H, H-3 and one undetermined proton: both isomers), 2.47 (d br dd, 0.9 H, J = 13, 4, 4 Hz, major isomer), 2.63 - 2.82 (m, 0.1 H, minor isomer), 3.05 (d, 0.9 H, J = 13 Hz, H-2: major isomer), 3.58 (d, 0.1 H, J = 3 Hz, H-2: minor isomer), 3.71 (s, 0.3 H, CH_3O-: minor isomer), 3.75 (s, 2.7 H, CH_3O-: major isomer).

lrms (EI): m/z = 170 (38%, M^+).

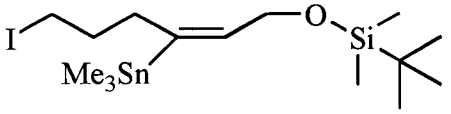
hrms (EI): calcd. for $C_9H_{14}O_3$: 170.0943; found: 170.0939.

A small sample of the solid was removed and washed with hexane (to remove the liquid phase) and placed under reduced pressure (vacuum pump). The ^1H nmr spectrum was run immediately after the sample was made up. The solid material displayed the following data:

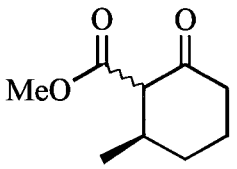
mp: 35 - 37 °C.

^1H nmr (400 MHz): δ: = 1.03 (d, 3 H, J = 8 Hz, $-CH_3$), 1.42 (ddd br d, 1 H, J = 12, 12, 12, 4 Hz), 1.73 (ddddd, 1 H, J = 13, 13, 13, 4, 4 Hz), 1.88 - 1.97 (m, 1 H), 2.00 - 2.09 (m (10 lines), 1 H), 2.22 - 2.34 (m, 2 H), 2.47 (d br dd, 1 H, J = 13, 4, 4 Hz), 3.05 (d, 1 H, J = 13 Hz, H-2 proton), 3.75 (s, 3 H, CH_3O-).

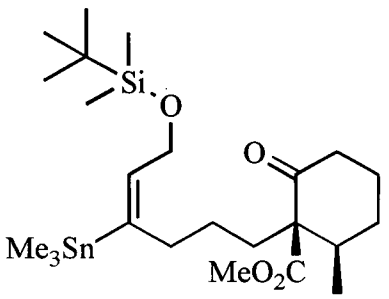
Preparation of Methyl (2*R*, 3*R*)-2-[(*E*)-6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-(trimethyl-stannyl)-4-hexenyl]-3-methylcyclohexanone-2-carboxylate (**16**)



15



35



16

A suspension of potassium hydride (0.32 g, 8.0 mmol) in dry *o*-xylene (20 mL) was stirred magnetically and cooled to 0 °C. A solution of the β-keto ester **35** (1.36 g, 8.00 mmol) in dry *o*-xylene (20 mL) was added to the reaction vessel by cannula. The mixture was stirred for 15 min to obtain a colourless solution. A solution of the iodide **15** (4.07 g, 8.00 mmol) in dry *o*-xylene (10 mL) was added to the reaction vessel by cannula. The solution was heated to reflux for a period of 16 h. During the first hour of the heating period the solution became cloudy, cleared and then again became cloudy. At the end of the heating period, the reaction mixture was composed of a white solid and a yellow solution. The mixture was cooled to rt and the solvent was removed under reduced pressure (vacuum pump). The residue was treated with saturated NH_4Cl (aq) (20 mL), water (20 mL) and diethyl ether (50 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed. The crude product, 4.45 g of a clear yellow oil, was purified by column chromatography (230 g of 230-400 mesh silica gel, 5.5 cm (width) column, 12:1 petroleum ether - diethyl ether). Combination

of the appropriate fractions and removal of the solvent, followed by distillation (160-180 °C at 0.10 Torr) of the residue gave the ketone **16** (3.37 g, 77%) as a clear, very pale yellow oil. This material displayed ir, ^{1}H nmr, low and high resolution (DCI) mass spectra identical with those previously reported[4a] for this compound. In addition, this material displayed:

^{13}C nmr (100 MHz): δ = -9.3 ($^1J_{Sn-C}$ = 340 Hz), -5.0 (2 carbons), 16.8, 18.4, 24.8, 25.4 ($^4J_{Sn-C}$ = 15 Hz), 26.1 (3 carbons), 30.2, 31.6, 33.9 ($^3J_{Sn-C}$ = 45 Hz), 39.3, 40.2, 51.6, 60.1 ($^2J_{Sn-C}$ = 71 Hz), 64.3, 140.5 ($^1J_{Sn-C}$ = 36 Hz), 145.0, 171.8, 207.6.

optical rotation: $[\alpha]_D^{25}$ -126° (c = 1.9, chloroform).

Also isolated during the column chromatography procedure, from the earlier fractions of eluate, was 0.65 g (16%) of the iodide **15**. None of the β-keto ester **35** was recovered.

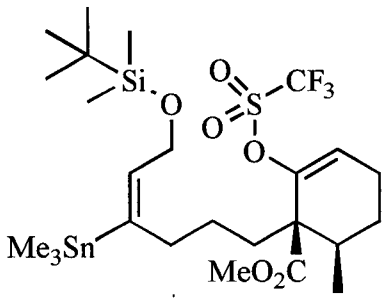
Purification of Commercial *N*-Phenyltrifluoromethanesulfonimide

A column was prepared employing 120 g of 230-400 mesh silica gel as the stationary phase and 10:1 petroleum ether - diethyl ether as the mobile phase. Commercial *N*-phenyl-trifluoromethanesulfonimide (5.0 g) was dissolved in the minimum amount of methylene chloride and this solution was loaded onto the top of the column. The column was eluted, with the above mentioned solvent mixture, and fractions were collected. Those fractions in which a colourless compound was observed to be crystallizing were pooled. Removal of the solvent, followed by

brief treatment under reduced pressure (vacuum pump), gave the title compound (4.8 g, 96% recovery) as a colourless, crystalline solid.

mp: 101 - 103 °C; lit.[88] mp: 101 - 103 °C.

Preparation of Methyl (3*R*, 4*R*)-3-[(*E*)-6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-(trimethylstannyl)-4-hexenyl]-4-methyl-2-[(trifluoromethanesulfonyl)oxy]cyclohexene-3-carboxylate (**17**)



17

A solution of LDA in dry THF (30 mL) was prepared in the usual way at -78 °C from dry diisopropylamine (0.410 mL, 2.93 mmol) and a solution of *tert*-butyllithium (1.72 mL, 1.7 M) in pentane. A solution of the ketone **16** (1.52 g, 2.79 mmol) in dry THF (20 mL) was added to the base solution by cannula. The very pale yellow solution was stirred for a period of 2 h. *N*-Phenyltrifluoromethanesulfonimide (1.00 g, 2.79 mmol) was added and the solution was stirred for 15 min. The mixture was warmed to 0 °C and stirred at this temperature for 15 min. The reaction vessel was opened to the atmosphere and ether (10 mL) was added. The solvent was removed and the crude product, 3.02 g of a clear, yellow oil, was purified by column chromatography (125 g of 230-400 mesh silica gel, 4 cm (width) column, 12:1 petroleum ether -

diethyl ether). Combination of the appropriate fractions, followed by removal of the solvent and treatment of the residue under reduced pressure (vacuum pump) gave the enol trifluoromethanesulfonate **17** (1.67 g, 88%) as a clear, colourless oil. This material displayed:

ir (film): 1740, 1417, 1216 cm^{-1}.

^1H nmr (400 MHz): δ = 0.08 (s, 6 H, -$(CH_3)_2$Si-), 0.12 (s, 9 H, $^2J_{Sn-H}$ = 54 Hz, $(CH_3)_3$Sn-), 0.90 (s, 9 H, $(CH_3)_3$CSi-), 0.93 (d, 3 H, J = 8 Hz, C-5 -CH_3), 1.18-1.30 (m, 2 H), 1.53 - 1.60 (m, 1 H), 1.69 -1.97 (m, 4 H), 2.12 -2.33 (m, 4 H), 3.71 (s, 3 H, CH_3O-), {(4.26 (dd, 1 H, J = 13, 6 Hz), 4.30 (dd, 1 H, J = 13, 6 Hz)), C-12 protons}, 5.68 (dd, 1 H, J = 6, 6 Hz, $^3J_{Sn-H}$ = 78 Hz, H-11), 5.98 - 6.02 (m, 1 H, H-1).

^{13}C nmr (75 MHz): δ = -9.9 ($^1J_{Sn-C}$ = 329 Hz), -5.5 (2 carbons), 16.3, 18.0, 23.1, 24.3, 25.6 (3 carbons), 25.8, 30.6, 33.1 ($^3J_{Sn-C}$ = 42 Hz), 34.8, 51.5, 54.3, 59.5 ($^2J_{Sn-C}$ = 70 Hz), 118.0 (q, $^1J_{F-C}$ = 313 Hz), 120.4, 140.4 ($^1J_{Sn-C}$ = 29 Hz), 144.0, 148.0, 171.0.

lrms (EI): m/z = 663 (56%, M^+-Me).

lrms (DCI): m/z = 663 (58%, M^+-Me), 694 (13%, $(M+NH_4)^+$).

Anal. calcd. for $C_{25}H_{45}F_3O_6SSiSn$: C 44.32, H 6.70, S 4.73; found: C 44.44, H 6.81, S 4.86.

optical rotation: $[\alpha]_D^{25}$ -150° (c = 2.7, chloroform).

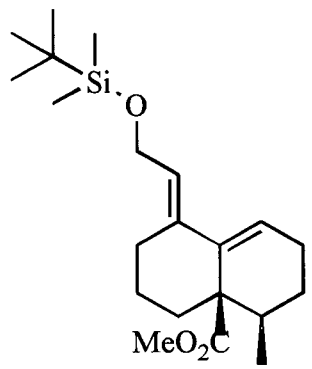
Preparation of Tetrakis(triphenylphosphine)palladium(0)[47]

For this reaction, all solvents were deoxygenated by sparging with helium gas at a rate of 100 mL per min for a period of 2 h.

An oven dried, 1 L round-bottomed flask equipped with 2 female and 1 male B 24 ground glass joints was brought into a glove box and charged with palladium(II) chloride (10.0 g, 56.4 mmol), triphenylphosphine (74.0 g, 282 mmol) and a magnetic stirrer bar. The 2 female joints were capped with rubber septa and the male joint with a 25 mL round-bottomed flask. The apparatus was removed from the glove box and connected to an argon line by a needle tipped Tygon® hose. Dimethyl sulfoxide (700 mL) was added by cannula. The suspension was stirred magnetically and placed in an oil bath. The oil bath was heated gradually to 140 °C and the mixture was stirred at this temperature for 30 min. A burgundy solution was produced. The oil bath was removed and stirring was restored as quickly as was possible. A vent was installed by piercing one of the septa with a 16 ga needle, and hydrazine hydrate (11.0 mL, 226 mmol) was added by syringe. The solution darkened in colour to a redder burgundy upon addition of the reducing agent. The mixture was stirred until the product began to crystallize. The unstirred reaction mixture was allowed to cool to rt. The 25 mL round-bottomed flask was replaced with a filtering funnel comprised of a 1 L flask fused to a coarse sintered glass funnel. The contents of the reaction flask were tipped into the filter and the solvent was allowed to run through the sinter under a positive pressure of argon. The filtrand, a yellow, crystalline solid, was washed with absolute ethanol (3 x 50 mL) followed by dry diethyl ether (4 x 50 mL) and then dried overnight in the filtering funnel under a positive pressure of argon. The filtering funnel was brought back into the glove box and the product, 63.2 g (97%) of yellow crystals was placed in foil wrapped vials for storage. The title compound could be kept in the glove box for periods of between 3 and 6 months, depending on the frequency of use, without significant loss of catalytic activity. For longer term storage, the vials were stored in a glove box freezer (-35 °C). The freshly prepared complex displayed:

Anal. calcd. for $C_{72}H_{60}P_4Pd$: C 74.84, H 5.23; found: C 74.82, H 5.36; lit.[47]: C 75.3, H 5.36.

Preparation of the Methyl (4aα,5α)-(+)-1,2,3,4,4a,5,6,7-Octahydro-1-[(*E*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethylidene]-5-methyl-4a-naphthalenecarboxylate (**18**)



18

A mixture of the enol trifluoromethanesulfonate **17** (2.70 g, 3.99 mmol), tetrakis-(triphenylphosphine)palladium(0) (0.230 g, 0.199 mmol) and dry THF (40 mL) was stirred magnetically and heated to reflux for a period of 24 h. The resulting black solution was cooled to rt and additional catalyst (0.200 g, 0.173 mmol) was added. The mixture was heated to reflux and heating was continued for an additional 24 h. The reaction mixture was cooled and most of the solvent was removed by rotary evaporation. The resulting black oil was prepurified by filtration through a short column (25 g in a 150 mL medium sintered glass funnel) of 230-400 mesh silica gel. The silica gel was washed with 1:1 petroleum ether - diethyl ether (220 mL) and the solvent was removed from the combined filtrates to isolate the crude product (1.45 g) as a clear, yellow oil. Purification by column chromatography (27 g of tlc grade silica gel, 3.5 cm (width) column, 9:1 petroleum ether - diethyl ether) provided, after removal of the solvent from

the appropriate fractions, 1.35 g of a clear, very pale yellow oil. This material was further purified by distillation (125-130 °C at 0.015 Torr) to finally yield the diene **18** (1.27 g, 87%) as a clear, colourless oil. This material displayed:

ir (film): 1728, 1432 cm^{-1}.

^1H nmr (400 MHz): δ = 0.05 (s, 6 H, $-(CH_3)_2Si-$), 0.75 - 0.92 (a singlet (at 0.89 for the $(CH_3)_3Si-$) overlapped with a doublet (for the C-5 2° $-CH_3$),12 H), 1.14 (ddd, 1 H, *J* = 13, 13, 4 Hz), 1.42 - 1.63 (m, 4 H), 1.70 - 1.83 (m, 2 H), 2.12 - 2.17 (m, 2 H), 2.51 (br d, 1 H, *J* = 15 Hz), 2.64 (br d, 1 H, *J* = 14 Hz), 3.62 (s, 3 H), {(4.15 (ddd, 1 H, *J* = 13, 6, 2 Hz), 4.22 (ddd, 1 H, *J* = 13, 6, 2 Hz)), C-2'protons}, 5.43 (ddd, 1 H, *J* = 6, 6, 2 Hz, H-1'), 5.75 (dd, 1 H, *J* = 4, 4 Hz, H-8).

^{13}C nmr (50 MHz): δ = -5.04, -4.96, 17.2, 18.2, 23.4, 25.5, 25.9 (3 carbons), 26.8, 28.6, 35.4, 39.4, 51.3, 52.6, 59.9, 124.1, 124.6, 140.7, 141.0, 173.6.

lrms (EI): m/z = 364 (8%, M^+).

hrms (EI): calcd. for $C_{21}H_{36}O_3Si$: 364.2434; found: 364.2426.

Anal. calcd. for $C_{21}H_{36}O_3Si$: C 69.18, H 9.95; found: C 69.35, H 10.00.

optical rotation: $[\alpha]_D^{23}$ +236 (c=5.0, hexane); $[\alpha]_{436}^{23}$ +547 (c=5.0, hexane).

Preparation of Methyl 2-Bromoacrylate[50]

A 250 mL round-bottomed flask equipped with a condenser was charged with a solution of methyl acrylate (18.7 mL, 208 mmol) in chloroform (82.5 mL) and the solution was stirred

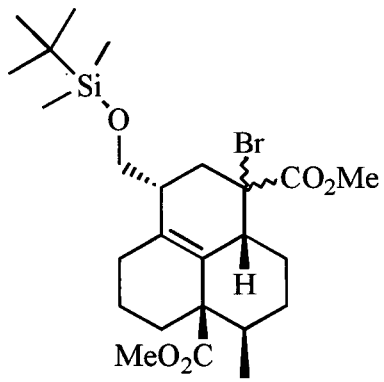
magnetically at rt. Bromine (10.7 mL, 207 mmol) was added, dropwise by syringe, and the resulting deep red solution was stirred for 3 h. The solvent was removed by rotary evaporation and the crude dibromide, a clear, yellow-orange oil, was transferred with diethyl ether (125 mL) to a 500 mL round-bottomed flask. Pentane (125 mL) was added and the solution was stirred at rt. Dry triethylamine (29.0 mL, 208 mmol) was added by syringe. The colour was destroyed immediately and the solution rapidly became turbid. After 10 min, the reaction mixture was a thick, white suspension. The mixture was stirred for 16 h and then suction filtered through a medium sintered glass filter funnel. The white solid was washed with pentane (100 mL) and the solvent was removed from the combined filtrates by rotary evaporation. For this operation, the bath in which the evaporating flask was immersed was filled with water at 15 °C. The residue was distilled (bp 69-71 °C at 48 Torr, lit.[50] 65 °C at 50 Torr) to provide 27.56 g (81%) of the title compound as a clear, colourless oil. This material displayed:

^{1}H nmr (400 MHz): δ = 3.80 (s, 3 H), 6.23 (d, 1 H, J = 2 Hz), 6.90 (d, 1 H, J = 2 Hz).

This material was diluted with dry benzene to provide a stock solution of methyl 2-bromoacrylate (0.50 g per mL of solution) and the solution was stored sealed under an atmosphere of argon at -35 °C. The solution showed no loss of activity (as a dienophile) after a period of 18 months although it had, after this time, taken on a pale yellow colour.

Preparation of {Dimethyl (1α,3β,6aα,7α,9aα)-2,3,4,5,6,6a,7,8,9,9a-Decahydro-1-bromo-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-7-methyl-1,6a[1*H*]-phenalenedicarboxylate and

Dimethyl (1β,3β,6aα,7α,9aα)-2,3,4,5,6,6a,7,8,9,9a-Decahydro-1-bromo-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-7-methyl-1,6a[1*H*]-phenalenedicarboxylate} (**54**)



54

A solution of the diene **18** (0.841 g, 2.31 mmol) and methyl 2-bromoacrylate (1.52 mL of 0.50 g/mL in benzene, 4.61 mmol) in dry benzene (25 mL) was stirred magnetically and was heated to reflux for a period of 44 h. The solvent was removed and the crude product, 1.74 g of a clear, yellow oil and a pasty white solid, was purified by column chromatography (130 g of 230-400 mesh silica gel, 4 cm (width) column,12:1 petroleum ether - diethyl ether). Removal of the solvent, followed by treatment of the residue under reduced pressure (vacuum pump), gave the epimeric product mixture **54** (1.17 g, 96%) as a clear, very pale yellow oil. Analysis of the ^{1}H nmr spectrum, by comparison of the integrals for the signals at δ = 0.85 (minor epimer) and 0.92 (major epimer), representing the tert-butyl protons from the 2 epimers, suggested the ratio of the products was about 4:1, but the identity of the major isomer was unknown. A sample of the product mixture displayed:

ir (film): 1740, 1732, 1447 cm^{-1}.

^{1}H nmr (400 MHz): δ = 0.03 - 0.10 (m, 6 H, -$(CH_3)_2$Si-), {(0.85 (s) and 0.92 (s)), 9 H, $(CH_3)_3$CSi-}, 1.10 (d, 3 H, J = 8 Hz, C-7 -CH_3), 1.15 - 1.29 (m, 2 H), 1.31 - 1.47 (m, 2 H), 1.55 - 2.10 (m, 5 H), 2.13 - 2.55 (m, 4 H), 2.81 (br d, 1 H, J = 13 Hz), 2.86 (br d, 1 H, J = 13 Hz), 3.50 - 3.89 (m, 8 H, contains singlets at 3.66, 3.69, 3.73 and 3.89 for the CH_3O- functions).

lrms (DCI): m/z = 530, 532 (55%, M^+).

Anal. calcd. for $C_{25}H_{41}O_5BrSi$: C 56.70, H 7.80; found: C 56.34, H 7.83.

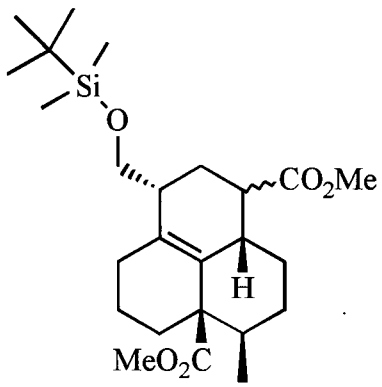
Preparation of Samarium Diiodide[54]

A 0.10 M solution of the title compound in oxygen free, dry THF was prepared in the following manner.

An oven dried B 19, B 24 two-necked 300 mL round-bottomed flask and solvent transfer bridge were brought into a glove box. The flask was charged with -40 mesh samarium metal powder (4.51 g, 30.0 mmol) and a magnetic stirrer bar. The B 19 joint was fitted with a rubber septum capped, vacuum stopcock equipped, straight inlet adapter and the solvent transfer bridge was fitted to the B 24 joint. The free end of the solvent transfer bridge was capped with a 25 mL round-bottomed flask. All of the ground glass joints were greased with Apiezon® type N vacuum grease and the apparatus was removed from the glove box. The solvent transfer bridge was connected to a double manifold argon - vacuum line and a positive pressure of argon was applied. The cap on the solvent transfer bridge was removed quickly and was replaced with a glass solvent bomb. The apparatus was evacuated and, under static vacuum, oxygen free, dry

THF (270 mL) was transferred from the bomb to the flask containing the samarium. To facilitate the transfer, the flask containing the samarium was cooled to -198 °C and the solvent bomb was stirred and heated to 30 °C. When the transfer was complete, the cooling bath was removed. The apparatus was opened to the argon side of the line and was allowed to warm to rt. The solvent transfer bridge was removed quickly and was replaced with a stopper. The mixture was stirred magnetically and methylene iodide (2.21 mL, 27.5 mmol) was added by Gastight® syringe through the inlet adapter. The reaction flask was wrapped in foil and the mixture was stirred for a period of 16 h. The resulting deep blue solution was ready for immediate use and could be stored indefinitely at rt in the dark.

Preparation of {Dimethyl (1α,3α,3aβ,6β,6aβ)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-6-methyl-3,6a[1*H*]-phenalenedicarboxylate and Dimethyl (1α,3β,3aβ,6β,6aβ)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl]-6-methyl-3,6a[1*H*]-phenalenedicarboxylate} (**55**)



55

A solution of samarium diiodide in oxygen free, dry THF (73 mL, 0.10 M) was transferred to a dry, thoroughly argon flushed, round-bottomed flask by Gastight® syringe, stirred magnetically and cooled to -78 °C. A solution of the diesters **54** (1.83 g, 3.45 mmol) in 3:1 dry THF - dry methanol (20 mL) was added, dropwise by cannula, to the samarium diiodide solution. At the end of the addition, the reaction mixture was pale green. The reaction mixture was stirred for a period of 5 minutes and the reaction flask was then opened to the atmosphere. A gentle stream of compressed air was blown into the flask until the reaction mixture was yellow in colour and the cooling bath was then removed. The reaction mixture was poured into saturated K_2CO_3 (aq) (20 mL) and shaken with diethyl ether (20 mL). The layers were separated. The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were dried over $MgSO_4$ and filtered. Removal of the solvent from the filtrate provided the crude product, 1.73 g of a clear, amber oil, which was purified by column chromatography (50 g of tlc grade silica gel, 4 cm (width) column, 4:1 petroleum ether - diethyl ether). The product epimers were isolated together. Combination of the appropriate fractions, followed by removal of the solvent and distillation (210 - 220 °C at 0.094 Torr) of the residue gave the diesters **55** (1.55 g, 100%) as a clear, very viscous, very pale yellow oil. Analysis of the ^{1}H nmr spectra derived from this material, by comparison of the integrals for the CH_3O- functions from the 2 epimers of the product, suggested the ratio of the products was about 1:1. The mixture **55** displayed:

ir (film): 1735, 1447, 1434 cm^{-1}.

^{1}H nmr (400 MHz): δ = {(0.044 (s), 0.045 (s), 0.060 (s)),6 H, -$(CH_3)_2$Si-}, {(0.86 (s), 0.90 (s)), 9 H, $(CH_3)_3$CSi-}, {(1.00 (d, J = 8 Hz), 1.10 (d, J = 8 Hz)), 3 H, C-6 -CH_3}, 1.16 - 1.27

(m, 1 H), 1.28 - 1.40 (m, 2 H), 1.44 - 1.52 (m, 1 H), 1.56 - 1.78 (m, 4 H), 1.80 - 2.06 (m, 3 H), 2.13 - 2.28 (m, 2 H), {(2.35 - 2.43 (m, 7 lines), 2.47 (br d, J = 13 Hz)), 1 H}, {(2.53 - 2.60 (m), 2.70 (ddd, J = 14, 2, 2 Hz)), 1 H}, 2.78 - 2.88 (m, 1 H), 3.47 (dd, 1 H, J = 11, 9 Hz, one of H-1'), 3.63 - 3.71 (m, contains singlets at 3.666, 3.673 (two overlapping), and 3.68 for the CH_3O- functions, and the other of H-1', 7 H).

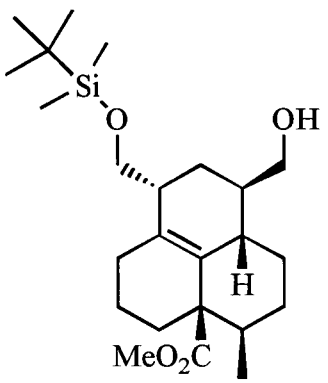
^{1}H nmr (C_6D_6, 400 MHz): δ = {(0.050 (s), 0.090 (s), 0.10 (s)), 6 H, -$(CH_3)_2$Si-}, {(0.96 (s), 0.99 (s)), 9 H, $(CH_3)_3$CSi-}, {(1.07 (d, J = 8 Hz), 1.21 (d, J = 8 Hz)), 3 H, C-6 -CH_3}, 1.11 - 1.17 (m, 1 H), 1.25 - 1.63 (m, 4 H), 1.65 - 2.12 (m, 7 H), 2.17 (br s, 1 H), {(2.27 (ddd, J = 14, 2, 2 Hz), 2.32 (br d, J = 13 Hz)), 1 H}, {(2.57 (br d, J = 15 Hz), 2.61 - 2.69 (m, 7 lines)), 1 H}, {(2.80 - 2.88 (m, 5 lines), 3.00 (br d, J = 12 Hz)), 1 H}, {(3.29 (s), 3.33 (s), 3.36 (s), 3.40 (s)), 6 H, CH_3O- functions}, 3.48 - 3.70 (m, 2 H, C-1' protons).

lrms (EI): m/z = 450 (0.3%, M^+).

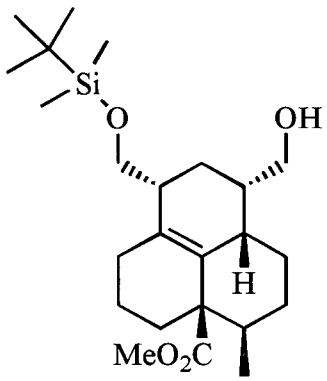
hrms (EI): calcd. for $C_{25}H_{42}O_5Si$: 450.2802; found: 450.2795.

Anal. calcd. for $C_{25}H_{42}O_5Si$: C 66.63, H 9.39; found: C 66.76, H 9.27.

Preparation of Methyl (1α,3β,3aβ,6β,6aβ)-(-)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-(hydroxymethyl)-6-methyl-6a[1*H*]-phenalenecarboxylate (**56**) and Methyl (1α,3α,3aβ,6β,6aβ)-(-)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]- 3-(hydroxymethyl)-6-methyl-6a[1*H*]-phenalenecarboxylate (**57**); Reduction of the Diesters **55**



56



57

A solution of the diesters **55** (2.82 g, 6.27 mmol) in dry diethyl ether (50 mL) was stirred magnetically and cooled to -78 °C. A solution of DIBAL-H in hexanes (13.2 mL, 1.0 M) was added in 3 portions at 1 min intervals by syringe and the colourless solution was stirred for 1 h. The cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred at this temperature for 20 min. Saturated NH_4Cl (aq) (0.5 mL) was added, dropwise at first, and, after the effervescence had subsided, diethyl ether (50 mL) was added. The two-phase system was stirred vigorously until a thick, white slurry had formed (about 20 min). Magnesium sulfate (1 g) and Celite® (2 g) were added to the slurry and the mixture was stirred for 2 h. A short column of Florisil® (3 cm high in a 150 mL medium sintered glass funnel) was prepared and the reaction mixture was filtered through the column. The solid material was washed with diethyl

ether (100 mL) and the solvent was removed from the combined filtrates. The crude product was separated and purified by column chromatography (50 g of tlc grade silica gel, 4 cm (width) column, 1:1 petroleum ether - diethyl ether). After combination of appropriate fractions, removal of the solvent and treatment of the residues under reduced pressure (vacuum pump), 2 compounds were isolated. The first component eluted was the 3β-CH_2OH compound, alcohol **56** (1.06 g, 40%) as a clear, colourless oil. The second component eluted was the 3α-CH_2OH compound, alcohol **57** (1.33 g, 50%) also as a clear, colourless oil.

The alcohol **56** displayed:

ir (film): 3494, 1723, 1463, 1084, 837 cm^{-1}.

^1H nmr (400 MHz): δ = 0.060 (s, 6 H, -$(CH_3)_2Si$-), 0.92 (s, 9 H, $(CH_3)_3CSi$-), 1.06 (d, 3 H, J = 9 Hz, C-6 CH_3-), 1.08 - 1.17 (m, 1 H), 1.27 (ddd, 1 H, J = 13, 13, 3 Hz), 1.36 - 1.68 (m, 8 H), 1.84 - 1.96 (m, 3 H), 2.10 - 2.23 (m, 3 H), 2.36 (br d, 1 H, J = 15 Hz), 3.46 - 3.60 (m, 7 lines, 2 H), 3.63 - 3.74 (m, 5 H, contains a singlet at 3.64 for the CH_3O- function).

^{13}C nmr (50 MHz): δ = -5.9, -5.2, 17.6, 18.1, 20.6, 26.2 (3 carbons), 31.0, 31.52, 31.54, 32.9, 34.5, 38.6, 42.1, 44.1, 45.2, 49.8, 53.1, 62.4, 65.2, 130.4, 135.8, 175.4.

lrms (DCI): m/z = 423 (100%, (M^+H), 440 (50%, $(M+NH_4^+)$).

hrms (DCI): calcd. for $C_{24}H_{43}O_4Si$: 423.2931; found: 423.2936.

Anal. calcd. for $C_{24}H_{42}O_4Si$ C 68.20, H 10.02; found: C 67.99, H 10.01.

optical rotation: $[\alpha]_D^{22}$ -88° (c=1.8, hexane); $[\alpha]_{436}^{22}$ -192° (c=1.8, hexane).

The alcohol **57** displayed:

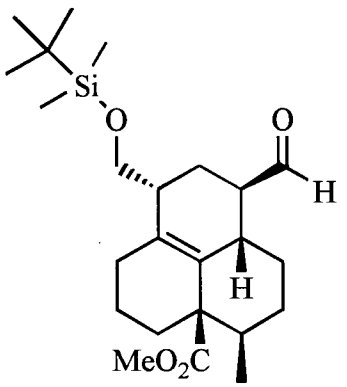
ir (film): 3417, 1723, 1450, 1039 cm^{-1}.

^1H nmr (400 MHz): δ = 0.040 (s, 6 H, -$(CH_3)_2$Si-), 0.90 (s, 9 H, $(CH_3)_3$CSi-), 1.10 (d, 3 H, J = 8 Hz, C-6 -CH_3), 1.16 - 1.40 (m, 6 H), 1.52 - 1.71 (m, 5 H), 1.80 - 2.10 (m, 3 H), 2.18 - 2.30 (m, 3 H), 3.54 (dd, 1 H, J = 12, 8 Hz), 3.60 - 3.72 (m, 6 H, contains a singlet at 3.65 for the CH_3O- function).

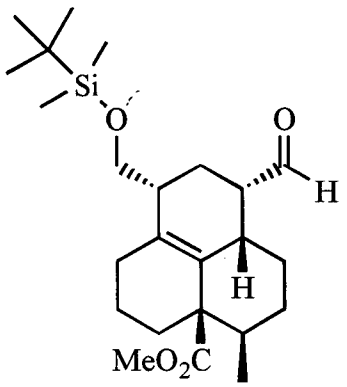
Anal. calcd. for $C_{24}H_{42}O_4Si$ C 68.20, H 10.02; found: C 68.37, H 10.03.

optical rotation: $[\alpha]_D^{29}$ -87° (c=6.4, hexane); $[\alpha]_{436}^{29}$ -192° (c=6.4, hexane).

Preparation of Methyl (1α,3β,3aβ,6β,6aβ)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-formyl-6-methyl-6a[1*H*]-phenalenecarboxylate (**20**) and Methyl (1α,3α,3aβ,6β,6aβ)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethyl-ethyl)dimethylsilyl]oxy]methyl]-3-formyl-6-methyl-6a[1*H*]-phenalenecarboxylate (**58**); Oxidation of the Alcohol **57**



20



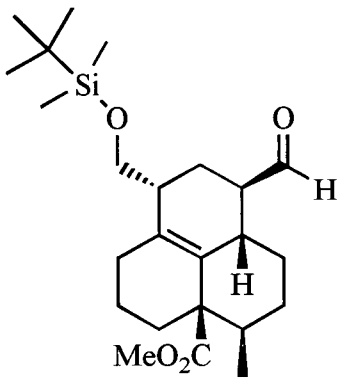
58

A solution of oxalyl chloride in methylene chloride (0.41 mL, 2.0 M) was diluted with dry methylene chloride (15 mL). The solution was stirred magnetically and cooled to -48 °C. Dry

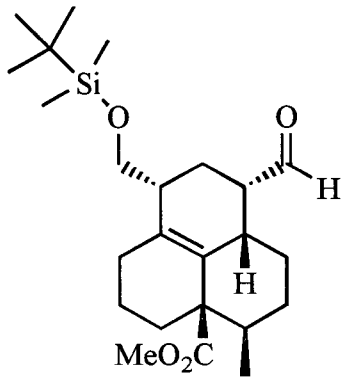
dimethyl sulfoxide (0.115 mL, 1.61 mmol) was added, dropwise, by syringe and, after the evolution of gas had ceased, the colourless solution was stirred for 2 min. A solution of the alcohol **57** (0.310 g, 0.734 mmol) in dry methylene chloride (5 mL) was added to the reaction flask by cannula. A white suspension was formed and the mixture was stirred for 15 min. Dry triethylamine (0.51 mL, 3.7 mmol) was added by syringe and the resulting colourless solution was stirred for 5 min. The cooling bath was removed and the reaction mixture was allowed to warm to rt. The contents of the reaction flask were added to water (5 mL), the mixture was shaken and the layers were separated. The aqueous phase was extracted with methylene chloride (3 x 5 mL) and the combined organic phases were washed with saturated NaCl (aq) (1 x 10 mL). The washed solution was dried over $MgSO_4$, filtered and the solvent was removed to give the crude product (0.34 g) as a clear, yellow oil. This oil was taken up in dry methanol (20 mL). The pale yellow solution was stirred magnetically and cooled to 0 °C. Sodium hydride (5 mg, 0.2 mmol) was added in 1 portion and the solution was stirred for 5 min. The cooling bath was removed. The reaction mixture was stirred at rt for a period of 16 h and then diluted with water (30 mL). The mixture was neutralized (pH paper) by dropwise addition of a 1.0 M citric acid (aq) solution and the methanol was removed by rotary evaporation. Diethyl ether (50 mL) was added to the residue, the mixture was shaken and the layers were separated. The organic phase was washed with saturated NaCl (aq) (3 x 10 mL), dried over $MgSO_4$, filtered and the solvent was removed. The crude product, 0.32 g of a clear, pale yellow oil, was separated and purified by column chromatography (27 g of tlc grade silica gel, 3½ cm (width) column, 6:1 petroleum ether - diethyl ether). Removal of the solvent from the appropriate fractions, followed by treatment of the residues under reduced pressure (vacuum pump), gave 0.218 g (71%) of the desired β-CHO product, aldehyde **20** and 0.061 g (20%) of the epimeric α-CHO product,

aldehyde **58**, both as clear, pale yellow oils. These compounds displayed ^{1}H nmr spectra identical with those of the racemic material[4a] and could be used without further purification.

Preparation of the Aldehydes **20** and **58**, Epimerization of the Aldehyde **58**



20



58

A solution of the aldehyde **58** (0.282 g, 0.671 mmol) in dry methanol (7 mL) was stirred magnetically and cooled to 0 °C. Sodium hydride (5 mg, 0.2 mmol) was added and the solution was stirred for 3 min. The cooling bath was removed and the solution was stirred at rt for a period of 16 h. The reaction mixture was poured into saturated NaCl (aq) (10 mL) and saturated NH_4Cl (aq) (5 mL) was added. This mixture was extracted with ethyl acetate (5 x 25 mL) and the solvent was removed from the extract. The residue was taken up in diethyl ether (90 mL) and this mixture was washed with saturated NaCl (aq) (1 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed to provide 0.29 g of a clear, pale yellow oil. This material was separated and purified by column chromatography (27 g of tlc grade silica gel, 3½ cm (width) column, 6:1 petroleum ether - diethyl ether). Removal of the solvent from the appropriate fractions, followed by treatment of the residues under reduced pressure (vacuum

pump), gave 0.248 g (88%) of the desired β-CHO product, aldehyde **20** and 0.023 g (8%) of recovered starting material, aldehyde **58**. Aldehyde **20**, which was used without further purification, displayed:

ir (film): 2858, 1724, 838, 776 cm^{-1}.

^1H nmr (400 MHz): δ = 0.060 (s, 6 H, -$(CH_3)_2$Si-), 0.90 (s, 9 H, $(CH_3)_3$CSi-), 1.02 (d, 3 H, *J* = 7 Hz, C-6 -CH_3), 1.05 - 1.16 (m, 1 H), 1.18 - 1.28 (m, 1 H), 1.34 - 1.42 (m, 1 H), 1.45 - 1.70 (m, 5 H), 1.80 - 1.90 (m, 2 H), 1.98 (ddd, 1 H, *J* = 13, 4, 4 Hz), 2.10 - 2.31 (m, 3 H), 2.46 (br d, 1 H, *J* = 13 Hz), 2.83 (br s, 1 H), 3.50 (dd, 1 H, *J* = 10, 8 Hz, one of H-1'), 3.67 (s, 3 H, CH_3O-), 3.68 (dd, 1 H, *J* = 10, 4 Hz, the other of H-1'), 9.62 (d, 1 H, *J* = 3 Hz, CHO-).

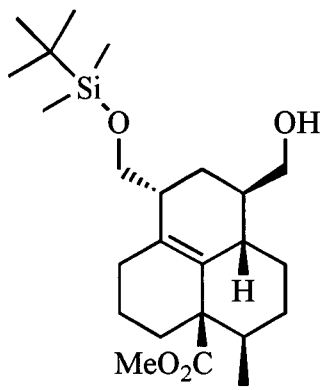
^{13}C nmr (50 MHz): δ = -5.4 (2 carbons), 18.1, 18.5, 20.7, 25.8 (3 carbons), 31.0, 31.4, 31.5, 31.7, 34.3, 35.1, 41.5, 42.3, 42.5, 51.0, 52.1, 64.7, 129.5, 134.0, 175.6, 199.2.

lrms (EI): m/z = 420 (12%, M^+).

hrms (EI): calcd. for $C_{24}H_{40}O_4Si$: 420.2695; found: 420.2693.

Anal. calcd. for $C_{24}H_{40}O_4Si$: C 68.53, H 9.58; found: C 68.78, H 9.59.

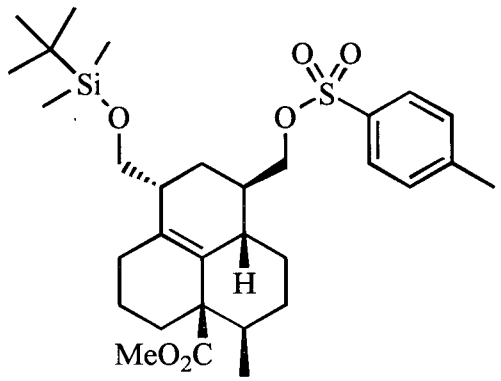
Preparation of the Alcohol **56**; Reduction of the Aldehyde **20**



56

A solution of the aldehyde **20** (0.889 g, 2.11 mmol) in dry diethyl ether (20 mL) was stirred magnetically and cooled to -78 °C. A solution of DIBAL-H in hexanes (2.50 mL, 1.0 M) was added by syringe and the colourless solution was stirred for a period of 30 min. The cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred at this temperature for 20 min. Saturated NH_4Cl (aq) (0.2 mL) was added, and, after the effervescence had subsided, diethyl ether (20 mL) was added. The 2 phase system was stirred vigorously until a thick, white slurry had formed (about 20 min). Magnesium sulfate (0.5 g) and Celite® (1 g) were added to the slurry and the mixture was stirred for 2 h. A column of 22 g of 230-400 mesh silica gel supported in a 4 cm (width) column topped by a 1 cm thick layer of Florisil® was prepared and the reaction mixture was filtered though the column. The column was washed with diethyl ether (200 mL) and the solvent was removed from the combined filtrates. The residual oil was treated under reduced pressure (vacuum pump) to provide the title compound (0.901 g, ~100%) as a clear, very pale yellow oil. This material produced ir, ^1H nmr and mass spectra identical with that of the above described alcohol **56**, prepared by reduction of the diesters **55** and was used without further purification.

Preparation of Methyl (1α,3β,3aβ,6β,6aβ)-(-)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-6-methyl-3-[[[(*p*-methylphenyl)sulfonyl]oxy]methyl]-6a[1*H*]-phenalenecarboxylate (**59**)



59

A solution of the alcohol **56** (0.890 g, 2.11 mmol) in dry methylene chloride (18 mL) was stirred magnetically at rt. 4-(*N*,*N*-Dimethylamino)pyridine (0.310 g, 2.53 mmol) was added in 1 portion followed by *p*-toluenesulfonyl chloride (0.443 g, 2.32 mmol), also in 1 portion. The reaction mixture was stirred for a period of 16 h and then poured into saturated $NaHCO_3$ (aq) (20 mL) and diethyl ether (50 mL). The mixture was shaken and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ (aq) (1 x 20 mL) and saturated NaCl (aq) (1 x 20 mL) before being dried over $MgSO_4$. The dried solution was filtered and the solvent was removed. The crude product, 1.29 g of a clear, pale yellow oil, was purified by column chromatography (50 g of tlc grade silica gel, 4 cm (width) column, 4:1 petroleum ether - diethyl ether). Removal of the solvent from the appropriate fractions, followed by treatment of the residue under reduced pressure (vacuum pump), gave the *p*-toluenesulfonate **59** (1.15 g, 94%) as a clear, very pale yellow oil. This material displayed:

ir (film): 1723, 1178, 837, 776 cm^{-1}.

^1H nmr (400 MHz): δ = -0.040 (s, 6 H, $-(CH_3)_2Si-$), 0.86 (s, 9 H, $(CH_3)_3CSi-$), 1.02 (d, 3 H, *J* = 7 Hz, 2° $-CH_3$), 1.22 (ddd, 1 H, *J* = 13, 13, 4 Hz), 1.29 - 1.40 (m, 2 H), 1.41 - 1.57 (m, 2 H), 1.59 - 1.68 (br s, 1 H), 1.70 - 1.78 (m, 2 H), 1.78 - 1.89 (m, 3 H), 2.00 - 2.17 (m, 4 H), 2.36 (br d, 1 H, *J* = 13 Hz), 2.46 (s, 3 H, $Ar-CH_3$), 3.43 (dd, 1 H, *J* = 10, 8 Hz, one of H-1' or H-1"), 3.59 (dd, 1 H, *J* = 10, 4 Hz, one of H-1' or H-1"), 3.64 (s, 3 H, CH_3O-), 3.91 (dd, 1 H, *J* = 10, 8 Hz, the other of H-1' or H-1"), 4.05 (dd, 1 H, *J* = 10, 4 Hz, the other of H-1' or H-1"), 7.36 (d, 2 H, *J* = 8 Hz, Ar-H), 7.80 (d, 2 H, *J* = 8 Hz, Ar-H).

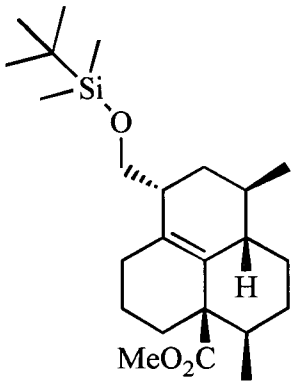
^{13}C nmr (50 MHz): δ = -5.5 (2 carbons), 17.0, 18.2, 19.5, 21.6, 25.3, 25.8 (3 carbons), 30.4, 31.3, 33.4, 34.5, 36.66, 36.73, 41.9, 44.0, 51.1, 51.5, 64.3, 73.2, 127.9 (2 carbons), 129.7 (2 carbons), 130.9, 132.9, 133.2, 144.5, 175.1.

lrms (DCI): m/z = 577 (11%, $(M+1)^+$), 594 (100%, $(M+NH_4^+)$).

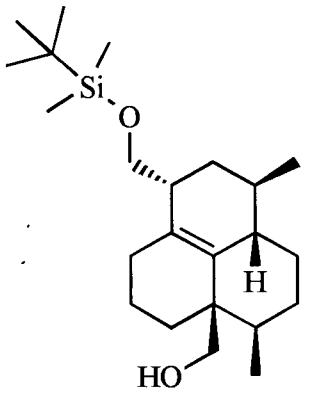
hrms (DCI): calcd. for $C_{31}H_{49}O_6SiS$ ($(M+1)^+$): 577.3019; found: 577.3028.

optical rotation: $[\alpha]_D^{22}$ -63° (c=1.8, hexane); $[\alpha]_{436}^{22}$ -137° (c=1.8, hexane).

Preparation of Methyl (1α,3β,3aβ,6β,6aβ)-(-)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dimethyl-6a[1*H*]-phenalenecarboxylate (**21**)



21



90

A solution of the *p*-toluenesulfonate **59** (3.50 g, 6.07 mmol) in dry THF (30 mL) was stirred magnetically at rt. A solution of Super-Hydride® in THF (12 mL, 1.0 M) was added by syringe and the solution was stirred for a period of 24 h. Water was cautiously added (until the effervescence had ceased) and then 30% aqueous H_2O_2 (1.5 mL) and 15% aqueous NaOH (1.5 mL) were added. The mixture was stirred for 40 min and then the contents of the reaction flask were poured into water (120 mL) and pentane (50 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with pentane (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed. The crude product, 2.87 g of a clear, pale yellow oil, was separated and purified by column chromatography (100 g of tlc grade silica gel, 5.5 cm (width) column, 12:1 petroleum ether - diethyl ether until the product had eluted then 4:1 petroleum ether - diethyl ether to elute the unreacted starting material). Removal of the solvent from the fractions containing the least polar compound, followed by distillation of the residue (145-150 °C at 0.040 Torr) gave the ester **21**

(2.12 g, 86%) as a clear, colourless oil. Removal of the solvent from the fractions containing the unreacted starting material, followed by treatment of the residue under reduced pressure (vacuum pump), gave 0.366 g (10%) of the *p*-toluenesulfonate **59**. Also isolated, from the fractions of polarity between that of the product and the starting material, was 0.0402 g (2%) of a clear, colourless oil, presumed to be the alcohol **90**.

The ester **21** displayed:

ir (film): 1725, 1462 cm^{-1}.

^1H nmr (400 MHz): δ = 0.060 (s, 6 H, -$(CH_3)_2$Si-), 0.90 (s, 9 H, $(CH_3)_3$CSi-), 0.96 (d, 3 H, J = 6 Hz, 2° -CH_3), 1.02 (d, 3 H, J = 6 Hz, 2° -CH_3), 1.20 - 1.31 (m, 2 H), 1.32 - 1.68 (m, 7 H), 1.76 (ddd, 1 H, J = 13, 4, 4 Hz), 1.87 (br d, 1 H, J = 16 Hz), 1.93 - 2.06 (m, 2 H), 2.10 (br s, 1 H), 2.14 - 2.26 (m, 1 H), 2.41 (br d, 1 H, J = 13 Hz), 3.45 (dd, 1 H, J = 10, 9 Hz, one of H-1'), 3.65 (s, 3 H, CH_3O-), 3.67 (dd, 1 H, J = 10; 5 Hz, the other of H-1').

^{13}C nmr (100 MHz): δ = -5.39, -5.36, 17.2, 18.3, 19.7, 20.6, 26.0 (3 carbons), 31.1, 31.36, 31.42, 31.5, 33.3, 34.5, 43.0, 43.78, 43.84, 50.8, 51.4, 64.9, 130.8, 134.0, 175.3.

lrms (EI): m/z = 406 (7.2%, M^+).

hrms (EI): calcd. for $C_{24}H_{42}O_3Si$: 406.2903; found: 406.2907.

Anal. calcd. for $C_{24}H_{42}O_3Si$: C 70.88, H 10.41; found: C 71.11, H 10.59.

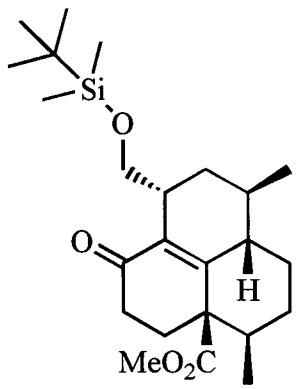
optical rotation: $[\alpha]_D^{25}$ -73.8° (c=4.0, hexane); $[\alpha]_{436}^{25}$ -158° (c=4.0, hexane).

The alcohol **90** displayed:

ir (film): 3335, 1467, 1040 cm^{-1}.

^{1}H nmr (400 MHz): δ = 0.050 (s, 6 H, -$(CH_3)_2$Si-), 0.83 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.90 (s, 9 H, $(CH_3)_3$CSi-), 0.97 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 1.00 - 1.08 (m, 1 H), 1.12 (ddd, 1 H, *J* = 13, 13, 4 Hz), 1.26 (s, 1 H), 1.35 - 1.59 (m, 7 H), 1.69 - 1.77 (m, 1 H), 1.82 (ddd, 1 H, *J* = 13, 3, 3 Hz), 1.86 - 1.98 (m, 2 H), 2.04 (br d, 1 H, *J* = 14 Hz), 2.10 - 2.20 (m, 2 H), 3.33 (br d, 1 H, *J* = 10 Hz), 3.47 (dd, 1 H, *J* = 10, 10 Hz), 3.68 (dd, 1 H, *J* = 11, 4 Hz), 3.84 (d, 1 H, *J* = 11 Hz).

Preparation of Methyl (1α,3β,3aβ,6β,6aβ)-(-)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dimethyl-9-oxo-6a[1*H*]-phenalenecarboxylate (**22**)



22

A magnetically stirred suspension of chromium trioxide (3.92 g, 39.2 mmol) in dry methylene chloride (100 mL) was cooled to -20 °C. 3,5-Dimethylpyrazole (3.77 g, 39.2 mmol) was added in 1 portion and the mixture was stirred for a period of 20 min. A deep red solution was produced. A solution of the ester **21** (0.637 g, 1.57 mmol) in dry methylene chloride (15 mL) was added to the chromium reagent by cannula. The solution was warmed to 0 °C, stirred at this temperature for a period of 2 h and then poured into diethyl ether (200 mL). A

column of Florisil® (9 cm high supported in an 8 cm (width) column) was prepared and the reaction mixture was filtered through the column. The column was washed with diethyl ether (600 mL) and the solvent was removed from the combined eluents. The crude product, 0.55 g of a brown, oily solid, was purified immediately by column chromatography (26 g of tlc grade silica gel, 3½ cm (width) column, 4:1 petroleum ether - diethyl ether). Removal of the solvent from the appropriate fractions followed by distillation (155-160 °C at 0.037 Torr) of the residue gave the α,β-unsaturated ketone **22** (0.480 g, 73%) as a clear, colourless oil which solidified on standing to provide a colourless, crystalline solid. This material displayed:

mp: 54 - 56 °C.

ir (KBr): 1726, 1674, 1462 cm^{-1}.

^1H nmr (400 MHz): δ = 0.026 (s, 3 H, one of $-(CH_3)_2Si-$), 0.053 (s, 3 H, the other of $-(CH_3)_2Si-$), 0.89 (s, 9 H, $(CH_3)_3CSi-$), 1.02 (d, 3 H, *J* = 6 Hz, 2° $-CH_3$), 1.03 (d, 3 H; *J* = 6 Hz, 2° $-CH_3$), 1.07 (ddd, 1 H, *J* = 12, 12, 5 Hz), 1.14 (ddd, 1 H, *J* = 13, 13, 5 Hz), 1.50 - 1.62 (m, 4 H), 1.66 (ddd, 1 H, *J* = 14, 14, 8 Hz), 1.95 (ddd, 1 H, *J* = 12, 2, 1 Hz), 2.16 - 2.30 (m, 2 H), 2.36 - 2.57 (m, 2 H), 2.67 (ddd, 1 H, *J* = 13, 2, 1 Hz), 2.97 (br dd, 1 H, *J* = 5, 3 Hz), 3.31 (dd, 1 H, *J* = 9, 9 Hz), 3.60 (dd, 1 H, *J* = 9, 4 Hz), 3.69 (s, 3 H, CH_3O-).

^{13}C nmr (50 MHz): δ = -5.4, -5.2, 17.1, 18.3, 20.7, 26.0 (3 carbons), 30.2, 30.5, 31.0, 31.2, 31.9, 34.8 (2 carbons), 43.4, 44.8, 51.7, 51.8, 64.8, 133.6, 158.9, 172.1, 197.9.

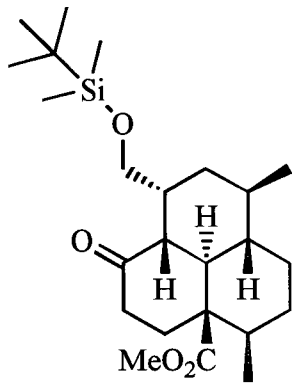
lrms (EI): m/z = 420 (0.63%, M^+).

hrms (EI): calcd. for $C_{24}H_{40}O_4Si$: 420.2696; found: 420.2693.

Anal. calcd. for $C_{24}H_{40}O_4Si$: C 68.52, H 9.59; found: C 68.31, H 9.67.

optical rotation: $[\alpha]_D^{21}$ -43° (c = 1.0, hexane); $[\alpha]_{436}^{21}$ -55° (c = 1.0, hexane).

Preparation of Methyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-(-)-Perhydro-1-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl]-3,6-dimethyl-9-oxo-6a[1*H*]-phenalenecarboxylate (**23**)



23

A suspension of 10% palladium on activated charcoal (0.490 g, 0.461 mmol) in methanolic potassium hydroxide (11 mL, 0.30 M) in a PYREX® reaction bomb was stirred magnetically on a Humboldt Vortex Hydrogenator and evacuated to water aspirator pressure (~25 Torr). The reaction bomb was compressed with hydrogen gas to a pressure of 45 psi and stirred for a period of 15 min. The stirrer was stopped and the pressure was released. The α,β-unsaturated ketone **22** (0.775 g, 1.84 mmol) was added in 1 portion, the stirrer was restarted and the bomb was repressurized with hydrogen as above. The mixture was stirred for a period of 48 h. The pressure was released and the catalyst was removed by filtration through a short column of Celite® (2 cm high supported in a 2 cm (width) column). The column was washed with methanol (15 mL). Ethyl acetate (20 mL) was added to the combined filtrates and the mixture was stirred for 1 h. The solvent was removed. The residue was taken up in diethyl ether (100 mL) and washed with saturated NaCl (aq) (1 x 20 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The residue, a clear, colourless oil which

solidified to a colourless, oily solid was recrystallized from pentane to provide the ketone **23** (0.684 g, 88%) as a colourless, crystalline solid. This material displayed:

mp: 79 - 81 °C.

ir (KBr): 1723, 1464 cm^{-1}.

^1H nmr (400 MHz): δ = 0.00 (s, 3 H, -$(CH_3)_2$Si-), 0.020 (s, 3 H, -$(CH_3)_2$Si-), 0.84 - 0.92 (m (overlapping d (2° -CH_3) and s ($(CH_3)_3$CSi-), 12 H), 0.95 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 1.12 (ddd, 1 H, *J* = 13, 13, 5 Hz), 1.22 - 1.59 (m, 7 H), 1.75 (dddd, 1 H, *J* = 11, 11, 11, 4 Hz), 1.87 (ddd, 1 H, *J* = 13, 3, 3 Hz), 2.07 (br dd, 1 H, *J* = 13, 3 Hz), 2.31 (dd, 1 H, *J* = 13, 4 Hz), 2.34 - 2.48 (m, 2 H), 2.49 - 2.56 (m, 1 H), 2.61 (ddd, 1 H, *J* = 13, 7, 3 Hz), 3.56 - 3.67 (m, (7 lines), 2 H), 3.67 (s, 3 H, CH_3O-).

^{13}C nmr (50 MHz): δ = -5.53, -5.45, 17.0, 18.2, 19.8, 25.9 (3 carbons), 30.6, 30.8, 32.3, 32.7, 36.1, 36.5, 37.8, 42.2, 42.9, 47.3, 50.5, 50.9, 51.2, 61.6, 173.6, 211.1.

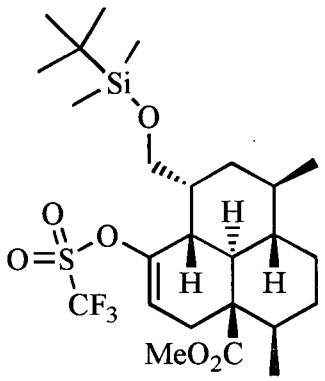
lrms (DCI): m/z = 422 (15%, M^+).

hrms (DCI): calcd. for $C_{24}H_{42}O_4Si$: 422.2853; found: 422.2845.

Anal. calcd. for $C_{24}H_{42}O_4Si$: C 68.20, H 10.02; found C 68.17, H 10.13.

optical rotation: $[\alpha]_D^{25}$ -36° (c = 2.4, hexane); $[\alpha]_{436}^{25}$ -48° (c = 2.4, hexane).

Preparation of Methyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-(-)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dimethyl-9-[[(trifluoromethyl)sulfonyl]oxy]-6a[1*H*]-phenalenecarboxylate (**64**)



64

A solution of LDA in dry THF (10 mL) was prepared at -78 °C in the usual way using dry diisopropylamine (0.134 mL, 0.958 mmol) and a solution of *tert*-butyllithium (0.614 mL, 1.56 M) in pentane. A solution of the ketone **23** (0.300 g, 0.711 mmol) in dry THF (3 mL) was added to the reaction flask by cannula. The pale yellow solution was stirred for 5 min and then warmed to -30 °C and stirred for a period of 3 h maintaining the temperature between -30 °C and -20 °C. A solution of *N*-phenyltrifluoromethanesulfonimide (0.279 g, 0.781 mmol) in dry THF (2 mL) was added to the reaction flask by cannula. The mixture was stirred for 10 min and then allowed to warm to rt. The pale yellow solution was diluted with diethyl ether (10 mL) and the solvent was removed. The crude product, 0.70 g of a clear, yellow oil, was purified by column chromatography (40 g of tlc grade silica gel, 4 cm (width) column, methylene chloride to elute the product and then 9:1 petroleum ether - diethyl ether to elute the unreacted starting material). Removal of the solvent from the appropriate fractions, followed by treatment of the residues

under reduced pressure (vacuum pump), gave the enol trifluoromethanesulfonate **64** (0.331 g, 84%) and recovered ketone **23** (0.039 g, 13%), both as clear, colourless oils. The title compound displayed:

ir (film): 1726, 1444, 1420, 1211 cm^{-1}.

^1H nmr (400 MHz): δ = 0.030 (s, 6 H, -$(CH_3)_2$Si-), 0.34 - 0.96 (contains 2 d (from the 2° -CH_3) overlapping with each other and 1 s (from the $(CH_3)_3$CSi-), 15 H), 1.19 (ddd, 1 H, J = 13, 13, 5 Hz), 1.23 - 1.51 (m, 6 H), 1.70 (dddd, 1 H, J = 13, 13, 13, 3 Hz), 1.79 (dd, 1 H, J = 18, 3 Hz), 1.94 (br d, 1 H, J = 14 Hz), 2.07 (br dd, 1 H, J = 13, 2 Hz), 2.21 (br s, 1 H), 2.55 - 2.63 (m, 1 H), 3.01 (dd, 1 H, J = 18, 8 Hz), 3.53 - 3.69 (m, 5 H, contains a singlet at 3.65 for the CH_3O- function), 5.77 (d, 1 H, J = 8 Hz).

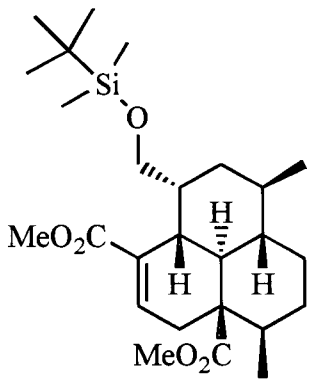
^{13}C nmr (50 MHz): δ = -5.6, -5.5, 16.9, 18.1, 19.5, 25.8 (3 carbons), 29.9, 30.2, 33.2, 34.2, 35.4, 36.5, 40.9, 42.3, 42.4, 46.3, 49.8, 51.1, 61.3, 118.5 (q, $^1J_{F\text{-}C}$ = 320 Hz), 118.6, 149.7, 172.9.

lrms (EI): m/z = 554 (3%, M^+).

hrms (EI): calcd. for $C_{25}H_{41}O_6F_3SSi$: 554.2346; found: 554.2360.

optical rotation: $[\alpha]_D^{25}$ -39° (c=11, hexane); $[\alpha]_{436}^{25}$ -68° (c=11, hexane).

Preparation of Dimethyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-(-)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dimethyl-6a,9[1*H*]-phenalenedicarboxylate (**65**)



65

A dry 50 mL B14 3-necked round-bottomed flask was brought into a glove box and charged with dry lithium chloride (0.049 g, 1.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.067 g, 0.058 mmol) and a magnetic stirrer bar. The middle joint was fitted with a rubber septum capped condenser. One outer joint was fitted with a Teflon® stopcock equipped inlet adapter and the other outer joint was fitted with a rubber septum. The stopcock was closed and the apparatus removed from the glove box. The inlet adapter was connected to a low pressure supply of carbon monoxide and the septum on the condenser was pierced with a 16 ga needle connected to a Tygon® hose connected to an oil bubbler. Dry methanol (15 mL) was added by syringe to the reaction flask and the mixture was stirred magnetically. The stopcock was opened and the apparatus was purged with a gentle flow of carbon monoxide for a period of 30 min. Dry triethylamine (0.161 mL, 1.16 mmol) was added by syringe, followed by a solution of the enol trifluoromethanesulfonate **64** (0.320 g, 0.578 mmol) in dry methanol (5 mL), by cannula.

The yellow suspension was heated to 70 °C and stirred at this temperature for a period of 3 h. The mixture was cooled to rt, opened to the atmosphere and filtered through a short column of Celite® (1 cm high supported in a 2 cm (width) column). The column was washed with methanol (10 mL) and the solvent was removed from the combined filtrates. The residue was taken up in diethyl ether (50 mL) and shaken with saturated NaCl (aq) (10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed. The crude product, 0.35 g of a clear, yellow oil, was purified by column chromatography (10 g of 230-400 mesh silica gel, 2 cm (width) column, 9:1 methylene chloride - diethyl ether). Removal of the solvent from the appropriate fractions, followed by distillation (160-165 °C at 0.050 Torr) of the residue, gave the α,β-unsaturated ester **65** (0.247 g, 92%) as a clear, colourless oil. This material displayed:

ir (film): 1723, 1254 cm^{-1}.

^1H nmr (400 MHz): δ = -0.020 (s, 6 H, $-(CH_3)_2Si-$), 0.82 - 0.87 (contains a singlet at 0.85 (for the $(CH_3)_3CSi-$ protons) overlapping with a doublet (for a 2° $-CH_3$), 12 H), 0.88 (d, 3 H, *J* = 6 Hz, 2° $-CH_3$), 1.18 - 1.50 (m, 7 H), 1.64 (dddd, 1 H, *J* = 10, 10, 10, 4 Hz), 1.75 (ddd, 1 H, *J* = 18, 4, 2 Hz), 1.85 (dd, 1 H, *J* = 10, 2 Hz), 2.06 (dd, 1 H, *J* = 13, 4 Hz), 2.44 - 2.52 (m, 1 H), 2.59 (br d, 1 H, *J* = 11 Hz), 3.02 (dd, 1 H, *J* = 18, 6 Hz), 3.43 (dd, 1 H, *J* = 10, 5 Hz), 3.53 (dd, 1 H, *J* = 10, 9 Hz), 3.62 (s, 3 H, CH_3O-), 3.68 (s, 3 H, CH_3O-), 6.77 (ddd, 1 H, *J* = 7, 2, 2 Hz, H-8).

^{13}C nmr (50 MHz): δ = -5.5 (2 carbons), 16.2, 17.0, 19.7, 25.9 (3 carbons), 30.0, 30.4, 33.5, 36.1, 36.2, 37.7, 39.8, 41.2, 42.5, 45.4, 49.7, 51.0, 51.2, 62.0, 133.3, 137.5, 167.6, 173.6.

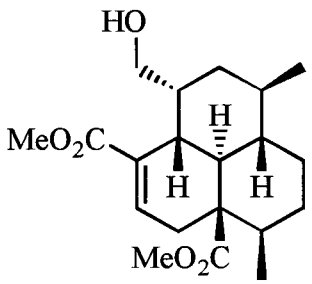
lrms (EI): m/z = 464 (13%, M^+).

hrms (EI): calcd. for $C_{26}H_{44}O_5Si$: 464.2959; found 464.2933.

Anal. calcd. for $C_{26}H_{44}O_5Si$: C 67.20, H 9.54; found C 67.19, H 9.45.

optical rotation: $[\alpha]_D^{25}$ -90° (c = 9.2, hexane); $[\alpha]_{436}^{25}$ -185° (c = 9.2, hexane).

Preparation of Dimethyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-(hydroxymethyl)-3,6-dimethyl-6a,9[1*H*]-phenalenedicarboxylate (**66**)



66

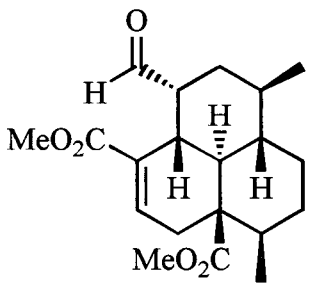
A solution of the α,β-unsaturated ester **65** (0.0314 g, 0.0676 mmol) in acetone (2 mL) was stirred magnetically at rt and the reaction flask was wrapped in foil. A single drop of water was added by Pasteur pipette followed by bis(acetonitrile)dichloropalladium(II) (1.0 mg, 0.0039 mmol). The red solution was stirred for a period of 18 h at the end of which time the reaction mixture was a yellow solution with a small amount of black precipitate. Most of the solvent was removed by rotary evaporation. For this operation, the evaporating flask was not immersed in a warm water bath, but rather periodically warmed in a cool water bath as frost began to accumulate on the evaporating flask. The crude product, a clear, brown oil, was purified immediately by column chromatography (2 g of tlc grade silica gel, 1½ cm (width) column, 1:2 petroleum ether - diethyl ether). The product-containing fractions were pooled and their solvent was removed as described above. The product, the alcohol **66**, 0.0242 g (~100%) was isolated

as a clear, colourless oil. This material, which was carried on to the next step without delay, displayed:

ir (film): 3422, 1721, 1436, 1253 cm^{-1}.

^1H nmr (400 MHz): δ = 0.85 (d, 3 H, J = 6 Hz, 2° $-CH_3$), 0.92 (d, 3 H, J = 6 Hz, 2° $-CH_3$), 1.12 - 1.23 (m, 1 H), 1.25 - 1.52 (m, 7 H), 1.66 (dddd, 1 H, J = 12, 12, 12, 4 Hz), 1.73 - 1.83 (m, 2 H), 2.06 (dd, 1 H, J = 18, 3 Hz), 2.53 - 2.67 (m, 2 H), 3.04 (dd, 1 H, J = 18, 8 Hz), 3.52 - 3.59 (m, 2 H), 3.62 (s, 3 H, CH_3O-), 3.70 (s, 3 H, CH_3O-), 6.82 (br d, 1 H, J = 7 Hz, H-8).

Preparation of Dimethyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-formyl-3,6-dimethyl-6a,9[1*H*]-phenalenedicarboxylate (**68**)



68

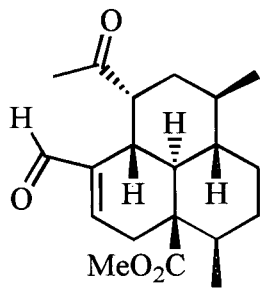
To the alcohol **66** (0.233 g, 0.666 mmol) in a 25 mL round-bottomed flask was added *N*-methylmorpholine *N*-oxide (0.160 g, 1.35 mmol) and dry powdered 4 Å molecular sieves (0.50 g). The flask was purged with argon and fitted with a rubber septum. Dry methylene chloride (10 mL) was added by syringe and the mixture was stirred magnetically. The suspension

was cooled to 0 °C and tetra-*n*-propylammonium perruthenate (0.016 g, 0.046 mmol) was added in 1 portion. The reaction mixture was warmed to 8 °C, stirred at this temperature for a period of 1 h and then filtered through a short column (5 g supported in a 2 cm (width) column) of tlc grade silica gel. The column was washed with methylene chloride and fractions were collected. Those fractions containing the major component (tlc developed with 2:1 petroleum ether - diethyl ether, visualized with uv light and the $KMnO_4$ dip, (rf: ~0.7)) were pooled. Removal of the solvent, followed by treatment of the residue under reduced pressure (vacuum pump), gave the aldehyde **68** (0.209 g, 90%) as a clear, colourless oil. This material, which was used without further purification, displayed:

ir (film): 2722, 1723, 1436, 1254 cm^{-1}.

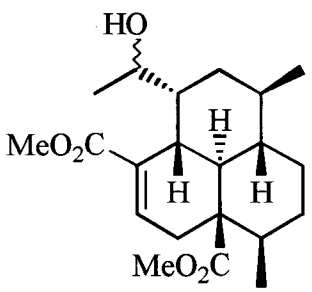
^1H nmr (400 MHz): δ = 0.85 (d, 3 H, J = 6 Hz, 2° -CH_3), 0.92 (d, 3 H, J = 6 Hz, 2° -CH_3), 1.03 - 1.17 (m, 1 H), 1.23 - 1.50 (m, 6 H), 1.69 (dddd, 1 H, J = 12, 12, 12, 4 Hz), 1.84 (br d, 1 H, J = 20 Hz), 2.02 (br dd, 1 H, J = 17, 3 Hz), 2.12 (ddd, 1 H, J = 17, 2, 2 Hz), 2.69 (br d, 1 H, J = 13 Hz), 3.09 (dd, 1 H, J = 20, 7 Hz), 3.31 - 3.37 (m, 1 H), 3.61 (s, 3 H, CH_3O-), 3.70 (s, 3 H, CH_3O-), 7.00 (ddd, 1 H, J = 7, 2, 2 Hz, H-8), 9.62 (s, 1 H, -CHO).

Preparation of Methyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-(-)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-acetyl-9-formyl-3,6-dimethyl-6a[1*H*]-phenalenecarboxylate (**32**)

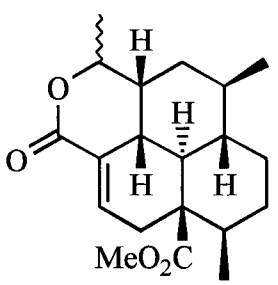


32

Step 1: Preparation of {Dimethyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-[(1'*R*)-1'-hydroxyethyl]-3,6-dimethyl-6a,9[1*H*]-phenalenedicarboxylate and Dimethyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-[(1'*S*)-1'-hydroxyethyl]-3,6-dimethyl-6a,9[1*H*]-phenalenedicarboxylate} (**69**) and {Methyl [(5*R*)-5-Methylpentanolido]-[4,3,2-c,d]-(1α,3α,3aα,6aα,7α,9aα,9bβ)-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1,7-dimethyl-6a[1*H*]-phenalenecarboxylate and Methyl [(5*S*)-5-Methyl-pentanolido]-[4,3,2-c,d]-(1α,3α,3aα,6aα,7α,9aα,9bβ)-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1,7-dimethyl-6a[1*H*]-phenalenecarboxylate} (**70**)



69

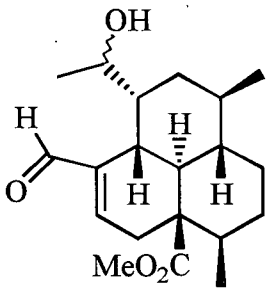


70

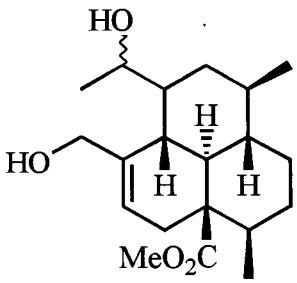
A solution of the aldehyde **68** (0.209 g, 0.601 mmol) in dry diethyl ether (10 mL) was stirred magnetically and cooled to -78 °C. A solution of methylmagnesium bromide (0.60 mL, 3.0 M) in diethyl ether was added by syringe and the solution was stirred for a period of 30 min. The cooling bath was removed and the reaction vessel was opened to the atmosphere. Saturated NH_4Cl (aq) (0.5 mL) was added, dropwise by pipette, and the mixture was allowed to warm to rt with efficient stirring. At rt, the mixture was comprised of a clear, colourless liquid and a white, pasty solid. The contents of the flask were triturated and small portions of $MgSO_4$ were added until a readily filterable mixture was obtained. Filtration followed by removal of the solvent from the filtrate gave the crude product, 0.219 g of a clear, colourless oil. For this operation, the evaporating flask was not immersed in a warm water bath, but rather periodically warmed in a cool water bath as frost began to accumulate in the evaporating flask. Analysis of this material by tlc (developed with 1:1 petroleum ether - diethyl ether, visualized with uv light and the $KMnO_4$ dip) showed it to be a mixture of 4 major components. The 2 major components of lower polarity, (rf: ~0.25 and ~0.22), were assigned to the lactones **70** while those of higher polarity, (rf: ~0.11 and ~0.08), were assigned to the alcohols **69**. This material was carried on to the next step without delay.

Step 2: Preparation of {Methyl (3aα,4α,6aα,7α,9β,9aα,9bβ)-3a,4,5,6,6a,7,8,9,9a,9b-Decahydro-1-formyl-9-[(1'*R*)-1'-hydroxyethyl]-4,7-dimethyl-3a[3*H*]-phenalenecarboxylate and Methyl (3aα,4α,6aα,7α,9β,9aα,9bβ)-3a,4,5,6,6a,7,8,9,9a,9b-Decahydro-1-formyl-9-[(1'*S*)-1'-hydroxyethyl]-4,7-dimethyl-3a[3*H*]-phenalenecarboxylate} (**73**) and {Methyl (1α,3β,3aβ,6β,6aβ,9aβ,9bα)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-[(1'*R*)-1'-hydroxyethyl]-9-(hydroxymethyl)-3,6-dimethyl-6a[1*H*]-phenalenecarboxylate and Methyl

(1α,3β,3aβ,6β,6aβ,9aβ,9bα)-2,3,3a,4,5,6,6a,7,9a,9b-Decahydro-1-[(1'*R*)-1'-hydroxyethyl]-9-(hydroxymethyl)-3,6-dimethyl-6a[1*H*]-phenalenecarboxylate} (**74**)



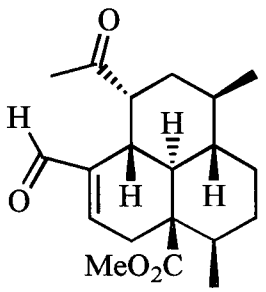
73



74

A solution of the above crude product (0.219 g) in dry diethyl ether (10 mL) was stirred magnetically and cooled to -78 °C. A solution of DIBAL-H (2.0 mL, 1.0 M) in hexanes was added by syringe and the solution was stirred for a period of 5 h. The cooling bath was removed, the reaction vessel was opened to the atmosphere and saturated NH_4Cl (aq) (6 drops) was added by pipette. Diethyl ether (10 mL) was added and the mixture was stirred vigorously for 3 h. Magnesium sulfate (0.5 g) and Celite® (1 g) were added, the mixture was stirred for 20 min and then was filtered through a pad of Celite® (1 cm high supported in a 2 cm (width) column). The solid was washed with diethyl ether (10 mL) and ethyl acetate (5 mL). The solvent was removed from the combined filtrates to isolate the crude product (0.181 g) as a clear, very pale yellow oil which formed a semi-solid foam under reduced pressure (vacuum pump). Analysis of this material by tlc (developed with 1:2 petroleum ether - diethyl ether, visualized with uv light and the $KMnO_4$ dip) showed it to be a mixture of 4 major components. The 2 major components of higher polarity, (rf: ~0.10 and ~0.18), were assigned to the diols **74** while those of lower polarity, (uv active spots of rf: ~0.25 and ~0.32), were assigned to the aldehydes **73**. The mixture was used without further purification.

Step 3: Preparation of the Keto Aldehyde **32**



32

To the above crude product (0.181 g) was added dry powdered 4 Å molecular sieves (0.25 g) and *N*-methylmorpholine *N*-oxide (0.35 g, 3.0 mmol). The flask was purged with argon and capped with a rubber septum. Dry methylene chloride (5 mL) was added by syringe. The suspension was stirred magnetically and cooled to 0 °C. Tetra-*n*-propylammonium perruthenate (0.042 g, 0.12 mmol) was added and the cooling bath was removed. The reaction mixture was warmed to 8 °C and stirred at this temperature for 2 h. A column was constructed employing 230-400 mesh silica gel (10 g) supported in a 3 cm (width) column and 9:1 methylene chloride - diethyl ether as the mobile phase. The reaction mixture was loaded onto the column and the column was run. Fractions were collected and those containing the product (rf: ~0.65, tlc developed with 1:2 petroleum ether - diethyl ether, visualized with uv light and the $KMnO_4$ dip) were combined. Removal of the solvent gave the keto aldehyde **32** (0.132 g, 65%, overall from **68**) as a clear, colourless oil. This material displayed:

ir (film): 2715, 1723, 1683, 1190 cm^{-1}.

^1H nmr (400 MHz): δ = 0.86 (d, 3 H, J = 6 Hz, 2° -CH_3), 0.90 (d, 3 H, J = 6 Hz, 2° -CH_3), 0.96 - 1.06 (m, 1 H), 1.45 - 1.66 (m, 6 H), 1.96 - 2.06 (m, 6 H, contains a singlet at 2.03 for the -$COCH_3$ function), 2.10 (ddd, 1 H, J = 19, 4, 2 Hz), 2.34 (br d, 1 H, J = 11 Hz), 3.21

(ddd, 1 H, J = 19, 6, 1 Hz), 3.58 (s, 3 H, CH_3O-), 3.96 (m, 1 H), 6.81 (ddd, 1 H, J = 6, 2, 2 Hz, H-8), 9.28 (s, 1 H, -CHO).

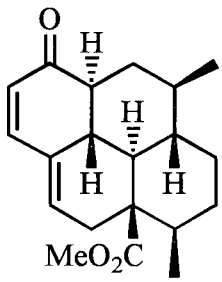
^{13}C nmr (50 MHz): δ = 16.9, 19.4, 29.1, 29.8, 30.0, 34.6, 36.6, 37.2, 37.9, 41.2, 42.4, 44.6, 47.8, 50.0, 51.0, 142.0, 152.7, 173.7, 194.7, 211.4.

lrms (EI): 332 (11%, M^+).

hrms (EI): calcd. for $C_{20}H_{28}O_4$: 332.1988; found: 332.1987.

optical rotation: $[\alpha]_D^{25}$ -44° (c = 1.4, chloroform); $[\alpha]_{436}^{25}$ -75° (c = 1.4, chloroform).

Preparation of Methyl (1α,3aα,4α,5aβ,10aα,10bβ,10cα)-(-)-1,2,3,3a,4,5,5a,6,10,10a,10b,10c-Dodecahydro-1,4-dimethyl-6-oxo-10a-pyrenecarboxylate (**76**)



76

A solution of the keto aldehyde **32** (0.220 g, 0.663 mmol) in dry methanol (12 mL) was stirred magnetically at rt. Powdered dry 4 Å molecular sieves (0.5 g) were added followed by 5 drops of 2.5 M methanolic sodium hydroxide by Pasteur pipette. The suspension was stirred at rt for a period of 18 h and then warmed to 50 °C and stirred at this temperature for 2 h. The cooled mixture was filtered through a short column (1 cm high supported in a 2 cm (width) column) of Celite®. The solid was washed with methanol (15 mL) and the solvent was removed from the combined filtrates. The residue was taken up in diethyl ether (40 mL) and the solution

was washed with portions (5 mL) of water until the last washing was neutral (pH paper). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The residue was purified by column chromatography (20 g of 230-400 mesh silica gel, 3 cm (width) column, 19:1 methylene chloride - diethyl ether). Removal of the solvent from the appropriate fractions gave pale yellow residue which was recrystallized from hexane to provide the dienone **76** (0.151 g, 72%) as a colourless, crystalline solid. This material displayed:

mp: 172 - 174 °C.

ir (KBr): 1711, 1676, 1638, 1457, 1436 1241, 1199, 810, 780 cm^{-1}.

^1H nmr (400 MHz): δ = 0.86 (d, 3 H, J = 6 Hz, 2° -CH_3), 0.92 (ddd, 1 H, J = 12, 12, 6 Hz), 1.00 (d, 3 H, J = 4 Hz, 2° -CH_3), 1.03 - 1.14 (m, 2 H), 1.31 (dd, 1 H, J = 11, 11 Hz), 1.40 - 1.70 (m, 4 H), 1.90 (br d, 1 H, J = 21 Hz), 2.04 - 2.21 (m, 4 H), 3.18 (dd, 1 H, J = 21, 6 Hz), 3.63 (s, 3 H, CH_3O-), 5.85 (d, 1 H, J = 10 Hz, H-7), 6.08 (br d, 1 H, J = 6 Hz, H-9), 6.93 (d, 1 H, J = 10 Hz, H-8).

^{13}C nmr (100 MHz): δ = 16.9, 19.5, 30.0, 30.3, 33.9, 37.1, 37.6, 40.6, 41.3, 41.7, 49.1, 49.6, 50.2, 51.2, 125.7, 132.6, 134.4, 146.0, 173.9, 200.6.

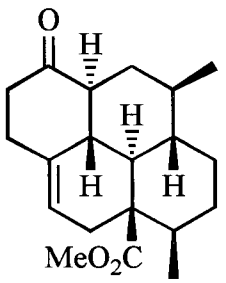
lrms (EI): m/z = 314 (13.5%, M^+).

hrms (EI): calcd for $C_{20}H_{26}O_3$: 314.1882; found: 314.1879.

Anal. calculated for $C_{20}H_{26}O_3$: C 76.40, H 8.33; found: C 76.10, H 8.30.

optical rotation: $[\alpha]_D^{25}$ -215° (c = 0.61, chloroform); $[\alpha]_{436}^{25}$ -311° (c = 0.61, chloroform).

Preparation of Methyl (1α,3aα,4α,5aα,10aα,10bβ,10cα)-(-)-1,2,3,3a,4,5,5a,6,7,8,10,10a,-10b,10c-Tetradecahydro-1,4-dimethyl-6-oxo-10a-pyrenecarboxylate (**30**)



30

Step 1: Preparation of the Intermediate **A**; Rhodium Catalyzed Reduction of the Dienone **76**

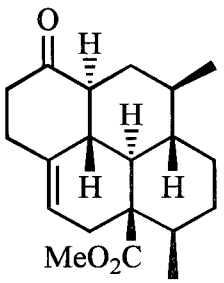
A 10 mL B 10 round-bottomed flask was charged with the dienone **76** (0.139 g, 0.438 mmol) and a magnetic stirrer bar. A rubber septum was fitted and the flask was thoroughly flushed with argon. Dry triethylsilane (1.5 mL) was added by syringe. Stirring was started and the suspension was heated to 60 °C. At this temperature, the starting material had dissolved to provide a pale yellow solution. The flask was vented by piercing the septum with an 18 ga needle. A solution of chlorotris(triphenylphosphine)rhodium(I) (0.042 g, 0.045 mmol) in dry methylene chloride (0.20 mL) was added to the reaction mixture by Gastight® syringe. The reaction mixture was stirred for 2 min (to allow the methylene chloride to be blown off) after which time the vent was removed. The mixture was stirred for a period of 1.5 h. The reaction mixture was cooled to 8 °C and then added to hexane (20 mL) by Pasteur pipette. The resulting suspension was allowed to stand for 15 min and then filtered through a fine sintered glass funnel. The solid was washed with hexane (2 x 5 mL) and the filtrates were combined. Removal of the solvent from the filtrates, followed by treatment of the residue under reduced pressure (vacuum

pump), gave the intermediate **A** (0.36 g) as a viscous, clear, yellow oil. This material was carried on to the next step immediately.

Step 2: Preparation of the Intermediate **B**; Hydrolysis of the Intermediate **A**

The above residue, intermediate **A**, was taken up in THF (25 mL) and the solution was stirred magnetically. Aqueous hydrochloric acid (0.3 mL, 6 M) was added by pipette and the yellow solution was stirred at rt for a period of 16 h. The mixture was then poured into diethyl ether (50 mL) and saturated NaCl (aq) (10 mL). The mixture was shaken and the layers were separated. The organic phase was washed successively with saturated $NaHCO_3$ (aq) (10 mL) and saturated NaCl (aq) (10 mL), dried over $MgSO_4$ and finally filtered. Removal of the solvent, followed by treatment of the residue under reduced pressure (vacuum pump), gave the intermediate **B** (0.32 g) as a yellow, oily solid. This material was carried on to the next step immediately.

Step 3: Preparation of the Ketone **30**; Oxidation of the Intermediate **B**



30

To the above residue, intermediate **B**, in a 25 mL B 14 round-bottomed flask was added powdered dry 4 Å molecular sieves (0.6 g), *N*-methylmorpholine-*N*-oxide (0.100 g) and a magnetic stirrer bar. A rubber septum was fitted and the flask was thoroughly flushed with dry argon. Dry methylene chloride (7 mL) was added and the suspension was stirred magnetically. Tetra-*n*-propylammonium perruthenate (0.015 g, 0.043 mmol) was added and the suspension was stirred for a period of 1 h. A column of 230 - 400 mesh silica gel (10 g supported in a 3 cm (width) column) was prepared and the reaction mixture was filtered through the column. The column was washed with methylene chloride and fractions were collected. Removal of the solvent from the appropriate fractions gave a pale yellow solid residue which was recrystallized once from 4:1 methanol - water to provide the ketone **30** (0.110 g, 79%, overall from **76**) as a colourless, crystalline solid. The column was further washed with 9:1 methylene chloride - diethyl ether and fractions containing the unconverted starting material were pooled. Removal of the solvent from these fractions, followed by treatment of the residue under reduced pressure (vacuum pump), provided the dienone **76** (0.015 g, 11%) as a pale yellow solid. The recrystallized ketone **30** displayed:

mp: 147 - 149 °C.

ir (KBr): 1712, 1458, 1439, 1203, 1147 cm^{-1}.

^1H nmr (400 MHz): δ = 0.86 (d, 3 H, *J* = 6 Hz, 2° $-CH_3$), 0.87 - 0.95 (m, 1 H), 0.97 (d, 3 H, *J* = 6 Hz, 2° $-CH_3$), 0.98 - 1.09 (m, 1 H), 1.12 - 1.70 (m, 6 H), 1.78 (br d, 1 H, *J* = 17 Hz), 1.89 (ddd, 1 H, *J* = 13, 3, 3 Hz), 1.96 - 2.06 (m, 2 H), 2.10 (ddd, 1 H, *J* = 12, 12, 3 Hz), 2.32 - 2.43 (m, 3 H), 2.47 - 2.56 (m, 1 H), 2.93 (dd, 1 H, *J* = 17, 6 Hz), 3.61 (s, 3 H, CH_3O-), 5.56 (dd, 1 H, *J* = 6, 2 Hz, H-9).

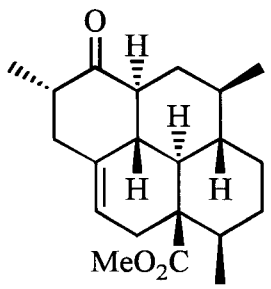
^{13}C nmr (50 MHz): δ = 17.0, 19.5, 30.2, 30.3, 33.7, 33.9, 36.2, 38.0, 41.0, 41.4, 41.7, 45.3, 49.8, 50.9, 51.8, 53.4, 121.0, 134.7, 174.2, 212.1.

lrms (EI): m/z = 316 (23%, M^+).

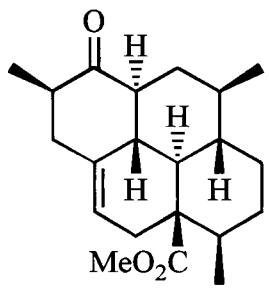
hrms (EI): calculated for $C_{20}H_{28}O_3$: 316.2039; found: 316.2033.

optical rotation: $[\alpha]_D^{24}$ -37° (c = 1.8, chloroform); $[\alpha]_{436}^{24}$ -48° (c = 1.8, chloroform).

Preparation of Methyl (1α,3aα,4α,5aβ,7β,10aα,10bβ,10cα)-1,2,3,3a,4,5,5a,6,7,8,10,10a,-10b,10c-Tetradecahydro-1,4,7-trimethyl-6-oxo-10a-pyrenecarboxylate (**79**) and Methyl (1α,3aα,4α,5aβ,7α,10aα,10bβ,10cα)-(-)-1,2,3,3a,4,5,5a,6,7,8,10,10a,10b,10c-Tetradecahydro-1,4,7-trimethyl-6-oxo-10a-pyrenecarboxylate (**80**); Alkylation of the Ketone **30**



79



80

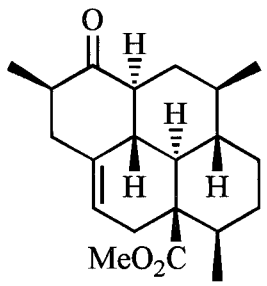
A solution of LDA in dry THF (2 mL) was prepared at -78 °C in the usual way from dry diisopropylamine (0.0190 mL, 0.137 mmol) and a solution of *tert*-butyllithium (0.0810 mL, 1.70 M) in pentane. A solution of the ketone **30** (0.0217 g, 0.0686 mmol) in dry THF (1 mL) was added to the LDA solution by cannula. The pale yellow solution was stirred for 2 h and then warmed to 0 °C. Dry hexamethylphosphoramide (0.0360 mL, 0.206 mmol) was added by syringe and the reaction mixture was recooled immediately to -78 °C and stirred at this temperature for 30 min. Methyl iodide (0.0210 mL, 0.343 mmol) was added by syringe and the solution was stirred for 30 min. The cooling bath was removed and the reaction mixture was allowed to warm to rt. The reaction mixture was stirred at this temperature for 20 min after which time it was poured into a mixture of diethyl ether (10 mL), saturated NaCl (aq) (3 mL) and water (3 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed. Analysis of this material by tlc (developed with 4:1 petroleum ether - diethyl ether, visualized with the ceric ammonium molybdate dip) showed the reaction had produced 2 products less polar than the starting material as well as a spot on the baseline. The crude product, 0.033 g of a clear, yellow film, was separated and purified by column chromatography (2 g of 230-400 mesh silica gel, 1.5 cm (width) column, 9:1 hexane - diethyl ether). Removal of the solvent from the fractions containing the less polar product gave a colourless solid (0.0060 g, 26%), which proved to be the C-7β ketone **80**. This material was not purified further at this point. Removal of the solvent from the fractions containing the more polar product, followed by treatment of the residue under reduced pressure (vacuum pump), gave a clear, colourless film (0.0147 g, 65%) which proved to be the C-7α ketone **79**. This

material was carried onto the next step without further purification. The material represented by the spot on the baseline was not isolated. The C-7α ketone **79** displayed:

ir (film): 1718, 1194, 1457, 1378, 1266, 737 cm^{-1}.

^1H nmr (400 MHz): δ = 0.85 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.87 - 0.95 (m, 1 H), 0.96 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 1.09 (d, 3 H, *J* = 7 Hz, 2° -CH_3), 1.16 - 1.27 (m, 2 H), 1.37 - 1.55 (m, 3 H), 1.56 - 1.70 (m, 2 H), 1.79 (br d, 1 H, *J* = 17 Hz), 1.93 (ddd, 1 H, *J* = 13, 3, 3 Hz), 1.96 - 2.10 (m, 2 H), 2.12 - 2.26 (m, 2 H), 2.47 - 2.57 (m, 2 H), 2.94 (dd, 1 H, *J* = 17, 6 Hz), 3.61 (s, 3 H, CH_3O-), 5.54 (br dd, 1 H, *J* = 6, 2 Hz, H-9).

Preparation of the C-7β Ketone **80**; Epimerization of the C-7α Ketone **79**



80

A solution of the C-7α ketone **79** (0.0147 g, 0.0445 mmol) in dry methanol (2 mL) was stirred magnetically and cooled to 0 °C. Sodium hydride (a spatula tip, about 0.5 mg) was added and the pale yellow solution was stirred for 10 min. The cooling bath was taken away and the mixture was stirred for a period of 16 h after which time the solvent was removed. The residue was taken up in diethyl ether (10 mL) and added to water (5 mL). A solution of citric acid (aq)

(2 drops, 1 M) was added by Pasteur pipette, the mixture was shaken and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed. The crude product, 0.018 g of a clear, yellow film, was purified by column chromatography (0.50 g of tlc grade silica gel, 8 mm (width) column, 4:1 hexane - diethyl ether). Removal of the solvent from the appropriate fractions gave the title compound (0.0145 g, 99%) as a colourless solid. This material was combined with the C-7β ketone isolated in the previous step and the lot was recrystallized once from 4:1 methanol - water to provide the C-7β ketone **80**. The product (0.0204 g, 90% from the ketone **30**) exists as a colourless, crystalline solid. This material displayed:

mp: 171 - 172 °C.

ir (KBr): 1713, 1457, 1376, 1195, 1175, 1147, 737 cm^{-1}.

^1H nmr (400 MHz): δ = 0.86 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.87 - 1.11 (m, 2 H), 0.97 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.99 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 1.21 (dd, 1 H, *J* = 13, 11 Hz), 1.24 (dd, 1 H, *J* = 11, 10 Hz), 1.35 - 1.52 (m, 3 H), 1.62 (ddd, 1 H, *J* = 11, 11, 4 Hz), 1.78 (dm, 1 H, *J* = 17 Hz), 1.85 (ddd, 1 H, *J* = 14, 3, 3 Hz), 1.93 - 2.15 (m, 4 H), 2.39 - 2.53 (m(9 lines)d, 1 H, *J* = 1 Hz), 2.54 (dd, 1 H, *J* = 14, 6 Hz), 2.92 (dddd, 1 H, *J* = 17, 6, 2, 2 Hz), 3.59 (s, 3 H, CH_3O-), 5.55 (ddd, 1 H, *J* = 6, 4, 2 Hz, H-9).

^{13}C nmr (100 MHz): δ = 14.3, 17.0, 19.5, 30.2, 30.4, 34.0, 36.2, 38.1, 41.4, 41.7, 43.4, 44.4, 46.3, 49.7, 50.9, 51.9, 53.6, 120.6, 135.0, 174.2, 213.1.

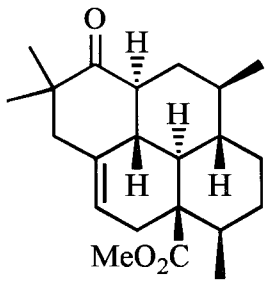
lrms (EI): m/z = 330 (1%, M^+).

hrms (EI): calculated for $C_{21}H_{30}O_3$: 330.2195; found 330.2188.

Anal. calculated for $C_{21}H_{30}O_3$: C 76.33, H 9.15; found C 76.15, H 9.07.

optical rotation: $[\alpha]_D^{25}$ -28° (c = 1.1, chloroform); $[\alpha]_{436}^{25}$ -30° (c = 1.1, chloroform).

Preparation of Methyl (1α,3aα,4α,5aβ,10aα,10bβ,10cα)-(+)-1,2,3,3a,4,5,5a,6,7,8,10,-10a,10b,10c-Tetradecahydro-1,4,7,7-tetramethyl-6-oxo-10a-pyrenecarboxylate (**81**)



81

A solution of LDA in dry THF (2 mL) was prepared at -78 °C in the usual way from dry diisopropylamine (0.0510 mL, 0.360 mmol) and a solution of *tert*-butyllithium (0.247 mL, 1.50 M) in pentane. A solution of the C-7β ketone **80** (0.0395 g, 0.120 mmol) in dry THF (2 mL) was added to the LDA solution by cannula. After it had been stirred for 10 min, the pale yellow solution was warmed to -48 °C and stirred at this temperature for a period of 2.5 h. Dry hexamethylphosphoramide (0.0840 mL, 0.480 mmol) was added by syringe and the pale yellow solution was stirred for 30 min. Methyl iodide (0.0370 mL, 0.600 mmol) was added by syringe, the mixture was stirred for 20 min and then the reaction mixture was warmed to 0 °C. Diethyl ether (2 mL) and water (1 mL) were added, the cooling bath was removed and the mixture was allowed to warm to rt. The contents of the reaction flask were poured into diethyl ether (10 mL) and water (5 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 5 mL) and the combined organic phases were washed successively with water (2 x 5 mL) and saturated NaCl (aq) (1 x 5 mL) before being dried over

$MgSO_4$. Filtration, followed by removal of the solvent, gave the crude product (0.045 g) as a clear, very pale yellow oil. Analysis of the oil by tlc (developed with 9:1 petroleum ether - diethyl ether, visualized with the ceric ammonium molybdate dip) showed that the reaction had produced 1 major and 1 minor component, both less polar than the starting material. The crude product was purified by column chromatography (0.80 g of tlc grade silica gel, 8 mm (width) column, 47:3 hexane - diethyl ether). Removal of the solvent from the fractions containing the major product, followed by treatment of the residue under reduced pressure (vacuum pump), gave the ketone **81** (0.0324 g, 78%) as a clear, colourless oil. This material displayed:

ir (film): 1720, 1705, 1457, 1441, 1384, 1192, 1144 cm^{-1}.

^1H nmr (400 MHz): δ = 0.86 (d, 3 H, J = 6 Hz, 2° $-CH_3$), 0.87 - 1.09 (m, 2 H), 0.97 (d, 3 H, J = 6 Hz, 2° $-CH_3$), 1.02 (s, 3 H, 3° $-CH_3$), 1.10 (s, 3 H, 3° $-CH_3$), 1.15 (dd, 1 H, J = 13, 2 Hz), 1.25 (dd, 1 H, J = 10, 10 Hz), 1.35 - 1.53 (m, 3 H), 1.61 (dddm, 1 H, J = 9, 9, 9 Hz), 1.82 (br d, 1 H, J = 17 Hz), 1.85 (ddd, 1 H, J = 13, 3, 3 Hz), 1.93 (br dd, 1 H, J = 11, 11 Hz), 2.06 (br dd, 1 H, J = 13, 4 Hz), 2.13 - 2.24 (m, 2 H), 2.31 (ddd, 1 H, J = 12, 12, 3 Hz), 2.92 (br dd, 1 H, J = 17, 6 Hz), 3.61 (s, 3 H, CH_3O-), 5.54 (br dd, 1 H, J = 6, 1 Hz, H-9).

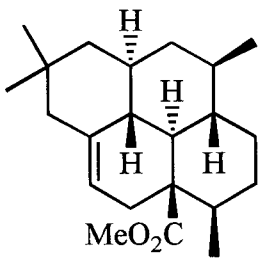
^{13}C nmr (100 MHz): δ = 17.0, 19.5, 24.5, 26.0, 30.2, 30.4, 34.4, 36.2, 38.3, 41.4, 41.7, 45.1, 46.2, 48.7, 49.2, 49.8, 50.9, 52.0, 121.9, 133.9, 174.2, 215.6.

lrms (EI): m/z = 344 (8.1%, M^+).

hrms (EI): calculated for $C_{22}H_{32}O_3$: 344.2351; found 344.2344.

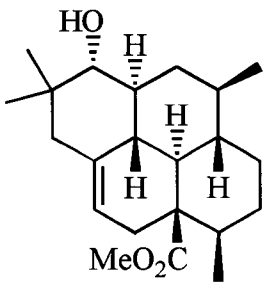
optical rotation: $[\alpha]_D^{25}$ +5° (c = 1.3, chloroform); $[\alpha]_{436}^{25}$ +47° (c = 1.3, chloroform).

Preparation of Methyl (1α,3aα,4α,5aβ,10aα,10bβ,10cα)-(-)-1,2,3,3a,4,5,5a,6,7,8,10,10a,-10b,10c-Tetradecahydro-1,4,7,7-tetramethyl-10a-pyrenecarboxylate (**29**)

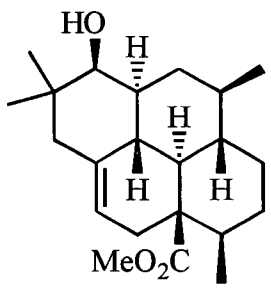


29

Step 1: Preparation of Methyl (1β,5aα,6α,8aα,9α,10aβ,10bα,10cβ)-1,2,3,5,5a,6,7,8,8a,9,-10,10a,10b,10c-Tetradecahydro-1-hydroxy-2,2,6,9-tetramethyl-5a-pyrenecarboxylate (**82**) and Methyl (1α,5aα,6α,8aα,9α,10aβ,10bα,10cβ)-1,2,3,5,5a,6,7,8,8a,9,10,10a,10b,10c-Tetradecahydro-1-hydroxy-2,2,6,9-tetramethyl-5a-pyrenecarboxylate (**83**)



82



83

A solution of the ketone **81** (0.0324 g, 0.0940 mmol) and 1-pentene (0.250 mL, 2.3 mmol) in dry methanol (3 mL) was stirred magnetically at rt. Sodium borohydride (7.0 mg, 0.19 mmol) was added and the solution was stirred for 45 min. Analysis of the reaction mixture by tlc (developed with 9:1 petroleum ether - diethyl ether, visualized with the ceric ammonium molybdate dip) showed that the starting material had been consumed. Solid ammonium chloride (10 mg) was added in several small portions and the mixture was stirred until the effervescence

had ceased. The solvent was removed. The residue was taken up in diethyl ether (10 mL) and water (2 mL) and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 2 mL) and the combined organic phases were washed with water (2 x 2 mL) before being dried over $MgSO_4$. Filtration, followed by removal of the solvent, gave the crude product (0.037 g) as a clear, colourless oil. Analysis of this oil by tlc (developed with 4:1 petroleum ether - diethyl ether, visualized with the ceric ammonium molybdate dip) showed it to contain 2 major components, both more polar than the starting material, along with a trace of material of similar rf to the starting material. This material was purified by column chromatography (0.25 g of tlc grade silica gel, 7.5 mm (width) column, 19:1 chloroform - diethyl ether). Fractions containing the 2 major components were pooled and produced, after removal of the solvent and treatment of the residue under reduced pressure (vacuum pump),a mixture of the title compounds (0.0327 g, ~100%) as a clear, colourless oil. This material could be used without further purification. Comparison of the integrals of the signal for the carbinol proton in the ^1H nmr spectrum (δ = 3.05 (for **82**) and 3.17 (for **83**)) gave the ratio of the products to be ~5:2 in favour of the alcohol **82**. The mixture displayed:

ir (film): 3502, 1723 (with a shoulder on the low frequency side), 1457, 1382, 1268, 1193, 758 cm^{-1}.

lrms (EI): m/z = 346 (21%, M^+).

hrms (EI): calculated for $C_{22}H_{34}O_3$: 346.2508; found: 346.2509.

A small amount of the mixture was separated under the chromatographic conditions listed above to provide samples of the 2 epimers of the title compound for ^1H nmr analysis.

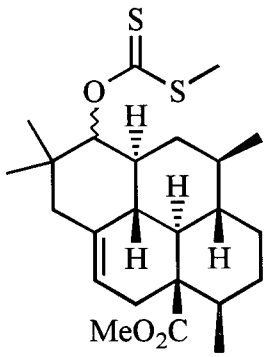
The alcohol **82** (the less polar epimer) displayed:

^{1}H nmr (400 MHz): δ = 0.77 (s, 3 H, 3° -CH_3), 0.82 - 1.80 (m, 12H), 0.86 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.97 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 1.00 (s, 3 H, 3° -CH_3), 1.87 (br s, 2 H), 2.03 (br d, 1 H, *J* = 12 Hz), 2.06 (ddd, 1 H, *J* = 12, 12, 3 Hz), 2.84 (dd, 1 H, *J* = 17, 6 Hz), 3.05 (d, 1 H, *J* = 11 Hz, H-1), 3.62 (s, 3 H, CH_3O-), 5.34 (br d, 1 H, *J* = 6 Hz, H-4).

The alcohol **83** (the more polar epimer) displayed:

^{1}H nmr (400 MHz): δ = 0.81 (s, 3 H, 3° -CH_3), 0.82 - 1.75 (m, 12 H), 0.85 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.97 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.99 (s, 3 H, 3° -CH_3), 1.80 - 1.90 (m, 1 H), 2.01 - 2.10 (m, 2 H), 2.22 (br d, 1 H, *J* = 15 Hz), 2.85 (dd, 1 H, *J* = 17, 6 Hz), 3.17 (br s, 1 H, H-1), 3.62 (s, 3 H, CH_3O-), 5.34 (dd, 1 H, *J* = 6, 2 Hz, H-4).

Step 2: Preparation of {Methyl (1α,3aα,4α,5aβ,6α,10aα,10bβ,10cα)-1,2,3,3a,4,5,5a,6,7,8,10,-10a,10b,10c-Tetradecahydro-1,4,7,7-tetramethyl-6-(*S*-methyl-*O*-dithiocarbonato)-10a-pyrenecarboxylate and Methyl (1α,3aα,4α,5aβ,6α,10aα,10bβ,10cα)-1,2,3,3a,4,5,5a,6,7,8,10,-10a,10b,10c-Tetradecahydro-1,4,7,7-tetramethyl-6-(*S*-methyl-*O*-dithiocarbonato)-10a-pyrenecarboxylate} (**84**)



84

A solution of LDA in dry THF (1 mL) was prepared at -78 °C in the usual way from dry diisopropylamine (0.0200 mL, 0.142 mmol) and a solution of *tert*-butyllithium (0.0850 mL, 1.70 M) in pentane. A solution of alcohols **82** and **83** (0.0246 g, 0.0710 mmol) in dry THF (1.5 mL) was added to the LDA solution by cannula. The pale yellow solution was warmed to -48 °C and stirred at this temperature for 30 min. Dry hexamethylphosphoramide (0.0370 mL, 0.213 mmol) was added, by syringe, followed by dry carbon disulfide (0.0210 mL, 0.355 mmol), by syringe. The mixture was stirred for 2 min and then the cooling bath was removed. The contents of the reaction flask were allowed to warm to rt. At rt, analysis of the reaction mixture by tlc (developed with 4:1 petroleum ether - diethyl ether, visualized with the ceric ammonium molybdate dip) showed that the starting materials had been consumed and replaced with baseline material. Methyl iodide (0.0220 mL, 0.355 mmol) was added by syringe and the reaction mixture was heated to reflux and stirred at this temperature for 20 min. To the cooled reaction mixture was added glacial acetic acid (5 drops), by Pasteur pipette, followed by diethyl ether (2 mL). The resulting yellow, cloudy mixture was poured into diethyl ether (10 mL) and water (5 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases were washed successively with water (1 x 5 mL) and saturated NaCl (aq) (1 x 5 mL) before being dried over $MgSO_4$. Filtration,

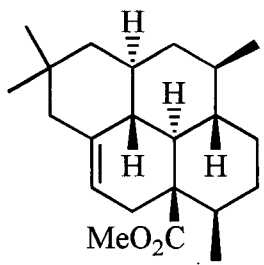
followed by removal of the solvent, gave the crude product (0.036 g) as a clear, yellow oil. Analysis of this oil by tlc (developed with 9:1 petroleum ether - diethyl ether, visualized by sight and then with the ceric ammonium molybdate dip) showed 2 major components had been produced. These spots were yellow and were less polar than the starting materials. Purification was accomplished by column chromatography (0.45 g of tlc grade silica gel, 8 mm (width) column, 15:1 hexane - diethyl ether). The fractions containing the product epimers were pooled. Removal of the solvent, followed by treatment of the residue under reduced pressure (vacuum pump), gave the dithiocarbonates **84** (0.0286 g, 92%) as a clear, yellow oil. This material, which was sufficiently pure to be carried on to the next step directly, displayed:

ir (film): 1723, 1457, 1225, 1203, 1196, 1052 cm^{-1}.

selected ^1H nmr (400 MHz): δ = 0.85 - 0.95 (5 lines, 12 H, methyl groups), {2.57 (s) and 2.59 (s), 3 H, S-CH_3 from the β- and α-epimers, respectively}, {3.63 (s) and 3.65 (s), 3 H, -OCH_3 from the α- and β-epimers, respectively}, 5.39 (br s, 1 H, H-9), {5.67 (d, J = 13 Hz) and 5.78 (br s), 1 H, H-6 from the α- and β-epimers, respectively}.

lrms (EI): m/z = 328 (33%, (M^+-HOC(S)SCH_3).

Step 3: Preparation of the Ester **29**



29

A solution of the dithiocarbonates **84** (0.0404 g, 0.0925 mmol) and tri-*n*-butylstannane (0.0500 mL, 0.185 mmol) in dry toluene (5 mL) was stirred magnetically and heated to reflux. A solution of 2,2'-azobisisobutyronitrile (0.100 mL, 0.033 M) in toluene was added to the yellow solution, dropwise by syringe, over a period of 1 min. The yellow colour had disappeared 1 min later, and after 4 min, a gray colour had started to develop. Heating was discontinued and the mixture was immediately cooled to ~8 °C. Analysis of the reaction mixture by tlc (developed with 9:1 petroleum ether - diethyl ether, visualized by sight and the ceric ammonium molybdate dip) showed that the starting materials (yellow) had been consumed and a single major component had formed. This material was less polar than the starting materials. The solvent was removed from the reaction mixture to isolate the crude product (0.089 g) as a dark oil. This material was purified by column chromatography (1 g of tlc grade silica gel, 8 mm (width) column, 49:1 hexane - diethyl ether). Removal of the solvent from the appropriate fractions gave the ester **29** (0.0312 g, ~100%) as a clear, colourless oil. This material was rigorously purified by hplc (100:1 hexane - diethyl ether, Econosil 5 μ silica gel, 4.6 by 250 mm column, 0.75 mL/min, uv detection at λ = 220 nm). The product was dissolved in hexane (~0.40 mL) and aliquots (0.025 mL, about 3 mg of compound) were injected for each run. The product proved to be a mixture of a major and a minor component. Removal of the solvent from the fractions containing the major component, followed by treatment of the residue under reduced pressure (vacuum pump), gave the ester **29** (0.0220 g, 72%) as a clear, colourless oil which slowly solidified on standing. Removal of the solvent from the fractions containing the minor component, followed by treatment of the residue under reduced pressure (vacuum pump), gave 0.0012 g (~4%) of a clear, colourless oil. The proton nmr spectrum of this material was similar

to that of the title compound except that it did not show a signal in the olefinic region. The ester **29** displayed:

mp: 80 - 81 °C.

ir (KBr): 1724, 1457, 1441, 1383, 1192, 1177 cm^{-1}.

^1H nmr (400 MHz): δ = 0.78 (s, 3 H, 3° $-CH_3$), 0.84 (d, 3 H, *J* = 6 Hz, 2° $-CH_3$), 0.85 - 0.88 (m, 1 H), 0.88 (s, 3 H, 3° $-CH_3$), 0.91 (d, 3 H, *J* = 6 Hz, 2° $-CH_3$), 0.93 (dd, 1 H, *J* = 12, 12 Hz), 1.04 - 1.10 (m, 2 H), 1.17 - 1.28 (m, 4 H), 1.34 - 1.46 (m, 3 H), 1.50 (ddd, 1 H, *J* = 13, 3, 3 Hz), 1.66 (ddd, 1 H, *J* = 11, 11, 4 Hz), 1.70 (dm, 1 H, *J* = 16 Hz), 1.77 (s, 2 H), 2.05 (d br ddd, 1 H, *J* = 12, 3, 3, 3 Hz), 2.82 (dd, 1 H, *J* = 16, 6 Hz), 3.61 (s, 3 H, CH_3O-), 5.29 (d br dd, 1 H, *J* = 6, 2, 2 Hz, H-9).

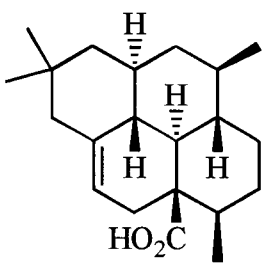
^{13}C nmr (100 MHz): δ = 17.1, 19.6, 25.2, 29.7, 30.67, 30.70, 31.7, 32.4, 36.1, 39.1, 41.5, 42.5, 43.2, 45.2, 46.4, 48.0, 49.9, 50.7, 50.8, 118.9, 137.7, 174.8.

lrms (EI): m/z = 330 (14%, M^+).

hrms (EI): calculated for $C_{22}H_{34}O_2$: 330.2559; found: 330.2551.

optical rotation: $[\alpha]_D^{25}$ -53° (c = 2.2, chloroform); $[\alpha]_{436}^{25}$ -112° (c = 2.2, chloroform).

Preparation of (3β,3aβ,8aα,10β,10aβ,10bα,10cβ)-(-)-1,2,3,3a,4,6,7,8,8a,9,10,10a,10b,10c-Tetradecahydro-3a-carboxy-3,7,7,10-tetramethylpyrene (**85**)



85

A suspension of sodium hydride (0.0160 g, 0.666 mmol) in dry THF (1 mL) was stirred magnetically at rt. Freshly distilled benzeneselenide (0.0710 mL, 0.666 mmol) was added, dropwise by syringe. A thick, white slurry was formed and was stirred for 5 min. Dry hexamethylphosphoramide (0.232 mL, 1.33 mmol) was added by syringe and the resulting orange solution was stirred for 1 h. A solution of the ester **29** (0.0220 g, 0.0666 mmol) in dry THF (1.5 mL) was added to the reaction flask by cannula. The solution was heated to reflux for a period of 72 h. The cooled mixture was poured into water (5 mL) and acidified (pH ~2, pH paper) by dropwise addition of 1.0 M HCl (aq). Diethyl ether (10 mL) was added, the mixture was shaken and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases were dried over $MgSO_4$. Filtration, followed by removal of the solvent, gave the crude product (0.15 g) as a yellow solid (mostly diphenyldiselenide). This material was separated by repeated column chromatography on 230-400 mesh silica gel, firstly with 9:1 petroleum ether - diethyl ether to separate the diphenyldiselenide and unreacted starting material from the product and then secondly with 8:1 petroleum ether - methylene chloride to separate the diphenyldiselenide from the unreacted starting material. Removal of the solvent from the fractions containing the product, followed by treatment of the residue under reduced pressure (vacuum pump), gave the carboxylic acid **85** (0.0119 g, 56%) as a colourless, crystalline solid. Removal of the solvent from the fractions containing the unreacted starting material gave 0.0073 g (33%) of the ester **29** as a clear, colourless oil which solidified upon standing. The title compound displayed:

mp: 179 - 181 °C.

ir (KBr): 3400 - 2450 (very br), 1692, 1457, 1384, 1364, 1272, 1220, 909, 735 cm^{-1}.

^{1}H nmr (400 MHz): δ = 0.80 (s, 3 H, 3° -CH_3), 0.83 - 0.91 (m, 1 H), 0.92 (s, 3 H, 3° -CH_3), 0.95 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 0.96 (d, 3 H, *J* = 6 Hz, 2° -CH_3), 1.00 (dd, 1 H, *J* = 13, 13 Hz), 1.07 - 1.17 (m, 2 H), 1.20 - 1.33 (m, 3 H), 1.40 - 1.57 (m, 5 H), 1.64 (dddd, 1 H, *J* = 13, 13, 13, 4 Hz), 1.77 (br d, 1 H, *J* = 17 Hz), 1.83 (br s, 2 H), 2.07 (dm, 1 H, *J* = 13 Hz), 2.81 (dd, 1 H, *J* = 17, 6 Hz), 5.33 (br d, 1 H, *J* = 6 Hz, H-5).

^{13}C nmr (100 MHz): δ = 17.0, 19.6, 25.2, 29.7, 30.2, 30.6, 31.9, 32.3, 36.2, 39.1, 41.3, 42.2, 43.1, 45.1, 46.4, 48.0, 49.5, 50.5, 118.8, 138.0, 178.6.

lrms (EI): m/z = 316 (4%, M^+).

hrms (EI): calculated for $C_{21}H_{32}O_2$: 316.2403; found: 316.2402.

optical rotation: $[\alpha]_D^{25}$ -70° (c = 1.2, chloroform); $[\alpha]_{436}^{25}$ -142° (c = 1.2, chloroform).

Preparation of Diphenylphosphoryl Azide[78]

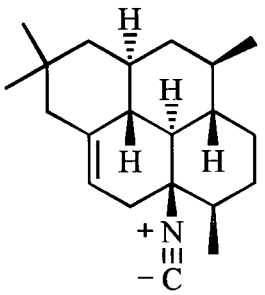
To a magnetically stirred suspension of sodium azide (0.627 g, 9.65 mmol) in dry acetone (10 mL) was added diphenyl chlorophosphate (2.00 mL, 9.65 mmol) by syringe. The white suspension was stirred for a period of 1 h. The reaction flask was fitted with a short path distillation apparatus and the solvent was distilled at atmospheric pressure. The receiver flask was replaced with a fresh flask and the apparatus was placed under reduced pressure (vacuum pump, ~0.1 Torr). The heating mantle was heated rapidly to 190 °C and then slowly to 225 °C. The product (1.95 g, 73%), which distilled when the heating mantle was between 215 and 225 °C, was obtained as an odourless, clear, colourless oil. This material showed, in the ir spectrum, a strong, sharp absorption at 2175 cm^{-1} (for the azide function).

Preparation of Acetic Formic Anhydride[79]

Sodium formate (20 g) was ground thoroughly with a mortar and pestle and then dried in an oven at 140 °C for a period of 18 h.

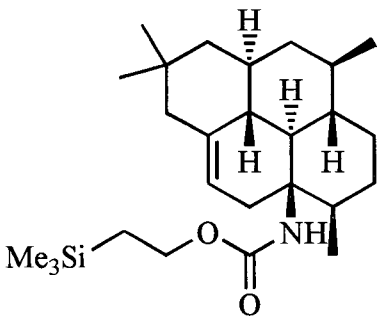
A dry, 3 necked, 100 mL, round-bottomed flask was charged with dry sodium formate (15.0 g, 0.221 mol), dry diethyl ether (12.5 mL) and a magnetic stirrer bar. The centre port was equipped with a septum capped, pressure equalizing dropping funnel charged with freshly distilled acetyl chloride (13.3 mL, 0.188 mol). One side port was equipped with a $CaCl_2$ drying tube topped condenser; the other with a thermometer. The contents of the flask were stirred and the acetyl chloride was added as rapidly as was possible, keeping the temperature of the reaction mixture in the range of 23 - 27 °C. After the addition was complete, the suspension was stirred for 5.5 h maintaining the temperature between 25 and 27 °C. The mixture was suction filtered and the solid was washed with diethyl ether (1 x 5 mL). The combined filtrates were transferred to a Vigreux column equipped distillation apparatus and most of the diethyl ether was distilled at atmospheric pressure. The flask containing the diethyl ether was replaced with a fresh flask and the cooled apparatus was placed under aspirator pressure. The residue was distilled. The product (10.3 g, 62%) was collected at 43 - 45 °C (41 Torr) and exists as a clear, colourless oil. This material was stored in a refrigerator in a polyethylene stoppered, round-bottomed flask and was used within 3 days of its preparation. The stopper was loosened daily to relieve any pressure that had built up.

Preparation of (3β,3aβ,8aβ,10β,10aβ,10bα,10cβ)-(+)-1,2,3,3a,4,6,7,8,8a,9,10,10a,10b,10c-Tetradecahydro-3a-isocyano-3,7,7,10-tetramethylpyrene (**11**) ((+)-8-isocyano-10-cycloamphilectene)



11

Step 1: Preparation of (1α,3aα,4α,5aβ,10aα,10bβ,10cα)-1,2,3,3a,4,5,5a,6,7,8,10,10a,10b,10c-Tetradecahydro-1,4,7,7-tetramethyl-10a-[*O*-[(2-trimethylsilyl)ethyl]-*N*-carbamato]pyrene (**87**)



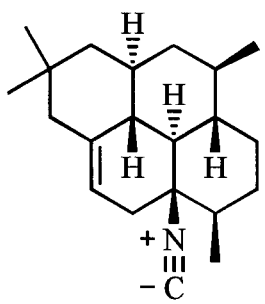
87

A solution of the carboxylic acid **85** (0.0110 g, 0.0348 mmol), dry triethylamine (0.010 mL, 0.070 mmol) and diphenylphosphoryl azide (0.011 mL, 0.052 mmol) in dry toluene (0.40 mL) was stirred magnetically and heated to 85 °C. After 2 h, analysis of the reaction mixture by ir spectroscopy showed that the absorptions due to the carboxylic acid function (3400 - 2450 and 1692 cm^{-1}) had disappeared and an absorption at 1766 cm^{-1} was now apparent. Heating was continued and the mixture was periodically checked by ir analysis. An absorption at 2250 cm^{-1} was observed to increase in intensity at the expense of the peak at 1766 cm^{-1}. After

22 h, the peak at 1766 cm^{-1} had completely disappeared. Dry triethylamine (0.10 mL, 0.70 mmol) and 2-(trimethylsilyl)ethanol (0.10 mL, 0.70 mmol) were added, both by syringe, and the colourless solution was heated to 100 °C. After 20 h at this temperature, additional 0.10 mL portions of dry triethylamine and 2-(trimethylsilyl)ethanol were added by syinge and heating was continued for an additional 24 h. At this time analysis by ir spectroscopy showed the absorption at 2250 cm^{-1} to have disappeared and a new absorption at 1736 cm^{-1} was now observed. The solvent and excess reagents were removed from the cooled reaction mixture and the residue was prepurified by filtration through 230-400 mesh silica gel (1.0 g, supported in a 7½ mm (width) column). The column was washed with diethyl ether (10 mL). Removal of the solvent from the filtrate gave 0.022 g of a clear, amber oil. This oil was purified by column chromatography (0.6 g of tlc grade silica gel, 8 mm (width) column, 9:1 hexane - diethyl ether). Removal of the solvent from the appropriate fractions, followed by treatment of the residue under reduced pressure (vacuum pump), gave the carbamate **87** (0.0120 g, 80%) as a clear, colourless oil. This material was used immediately in the next step. A sample displayed:

ir (film): 3446, 1736, 1508 cm^{-1}.

Step 2: Preparation of (+)-8-isocyano-10-cycloamphilectene (**11**)



11

To the carbamate **87** (0.0100 g, 0.0232 mmol) and a solution of tetra-*n*-butylammonium fluoride (0.20 mL, 1.0 M) in THF was added dry THF (0.50 mL). The pale yellow solution was stirred and heated to 60 °C for a period of 1.5 h, and then cooled to rt. The solvent and volatile materials were removed under reduced pressure. The residue was partitioned between hexane (15 mL) and 4:1 saturated NH_4Cl (aq) - 30% NH_3 (aq) (5 mL). The layers were separated. The aqueous phase was extracted with hexane (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed. The residue, a clear, colourless oil, was dissolved immediately in dry diethyl ether (0.50 mL) and the solution was stirred magnetically at rt. Acetic formic anhydride (0.040 mL, 0.23 mmol) was added by syringe, the solution was stirred for 2 h and then an additional portion of acetic formic anhydride (0.020 mL, 0.11 mmol) was added by syringe. The solution was stirred for a further h and then the solvent and excess reagent were removed under reduced pressure. The residue, a clear, pale yellow oil was partitioned between diethyl ether (5 mL) and water (3 mL). The layers were separated and the organic phase was washed with saturated NaCl (aq) (3 mL) before being dried over $MgSO_4$. Filtration, followed by removal of the solvent, gave a clear, pale yellow oil. To this residue was added immediately triphenylphosphine (0.015 g, 0.057 mmol). The mixture was dissolved in dry methylene chloride (0.50 mL) and stirred at rt. Dry triethylamine (0.020 mL, 0.14 mmol) and dry carbon tetrachloride (0.0060 mL, 0.062 mmol) were added, both by syringe. The solution was heated to reflux and maintained at this temperature for 2 h. The solvent was removed from the cooled reaction mixture and the resulting yellow residue was washed with 97:3 hexane - diethyl ether (10 mL) in several small portions. The solvent was removed from the washings to isolate the crude product (0.0096 g) as a pale yellow, oily solid. This residue was purified by column chromatography (0.3 g of tlc grade silica gel, 8 mm (width) column, the column was prepared

and loaded with hexane but eluted with 97 : 3 hexane - diethyl ether). Removal of the solvent from the appropriate fractions, followed by recrystallization of the resulting residue from 4:1 methanol - water, gave (+)-8-isocyano-10-cycloamphilectene (**11**) (0.0051 g, 74% from the carbamate **87**) as a colourless, crystalline solid. This material displayed:

mp: 87 - 89 °C; lit.[5] 88 - 89 °C (for (-)-8-isocyano-10-cycloamphilectene).

ir (KBr): 2912, 2864, 2133, 1454 cm^{-1}.

^1H nmr (400 MHz): δ = 0.81 (s, 3 H, 3° $-CH_3$), 0.86 - 0.97 (m, 2 H), 0.94 (d, 3 H, *J* = 7 Hz, 2° $-CH_3$), 0.95 (s, 3 H, 3° $-CH_3$), 1.03 (d, 3 H, *J* = 7 Hz, 2° $-CH_3$), 1.04 - 1.13 (m, 3 H), 1.19 - 1.29 (m, 1 H), 1.31 - 1.43 (m, 2 H), 1.46 (dddd, 1 H, *J* = 13, 13, 13, 4 Hz), 1.54 - 1.62 (m, 4 H), 1.89 (dd, 1 H, *J* = 14, 2 Hz), 1.95 (br d, 1 H, *J* = 15 Hz), 1.96 - 2.07 (m, 2 H), 2.45 (br dd, 1 H, *J* = 17, 5 Hz), 5.22 (br d, 1 H, *J* = 5 Hz, H-5).

^{13}C nmr (125 MHz): δ = 15.2, 19.5, 25.1, 29.5, 29.8, 31.7, 32.2, 37.2, 37.7, 38.0, 40.6, 42.7, 43.0, 43.9, 46.2, 47.6, 49.0, 62.8, 115.2, 137.6, 154.4.

lrms (EI): m/z = 297 (4.5%, M^+).

hrms (EI): calculated for $C_{21}H_{31}N$: 297.2456; found: 297.2453.

optical rotation: $[\alpha]_D^{24}$ +23° (c = 0.38, chloroform); $[\alpha]_{436}^{24}$ +42° (c = 0.38, chloroform); lit.[5] $[\alpha]_D^{20}$ -21.7° (c = 2, chloroform, for (-)-8-isocyano-10-cycloamphilectene).

The ^{1}H and ^{13}C nmr spectra as well as the low resolution mass spectral data for the (synthetic) (+)-8-isocyano-10-cycloamphilectene ((+)-**11**) were identical to those reported[5] for the (natural) (-)-8-isocyano-10-cycloamphilectene ((-) **11**).

References and Notes

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[2] The actual figures are as follows. For new approved drugs (1983 to 1994) a total of 520 substances were considered. The authors divided these into categories: substances of biologic derivation, unmodified natural products, compounds derived from a natural product, purely synthetic materials and finally synthetic materials that were modeled on a natural product as the parent compound. The latter three categories involve synthetic organic chemistry to varying degrees. Of the 520 substances, 462 (89%) fall into these three categories. For available anticancer drugs (through 1993) a total of 93 substances were considered under the above described system of categories. Of these 72 (77%) can be seen to be derived from synthetic organic chemistry. For pre-New Drug Approval substances (1989 to 1995) the authors considered 299 substances. Of these, 161 (54%) have their origin or can trace their development through synthetic organic chemistry.

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[81] We are indebted to Professor T. Higa of the Department of Marine Sciences, University of the Ryukyus, Okinawa, Japan for a sample of the natural occurring (-)-8-isocyano-10-cyclo-amphilectene ((-)-**11**) and accompanying ^{1}H and ^{13}C nmr spectra.

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Appendix

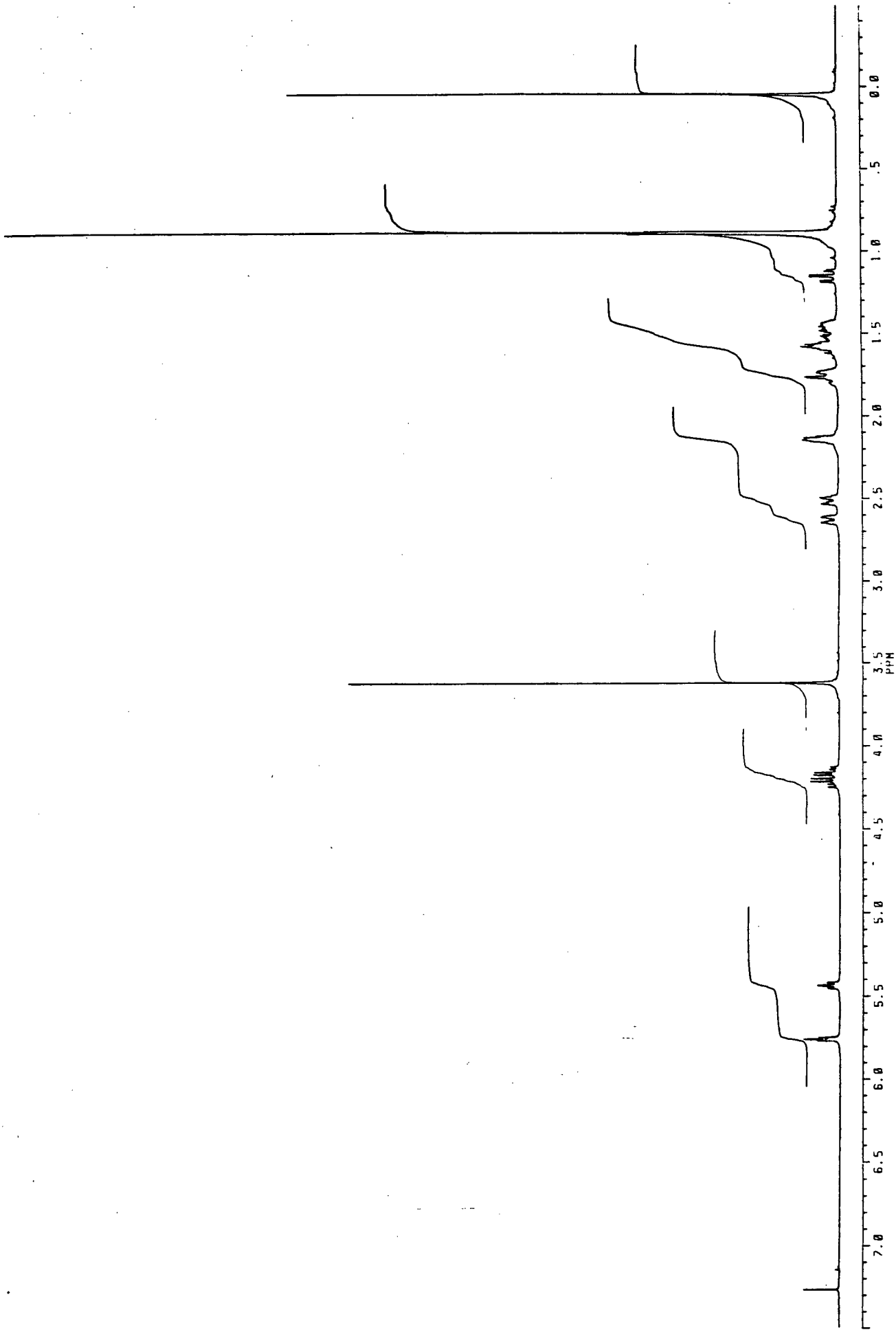

Figure 8. 400 MHz ^{1}H NMR spectrum of the diene 18 recorded in $CDCl_3$.

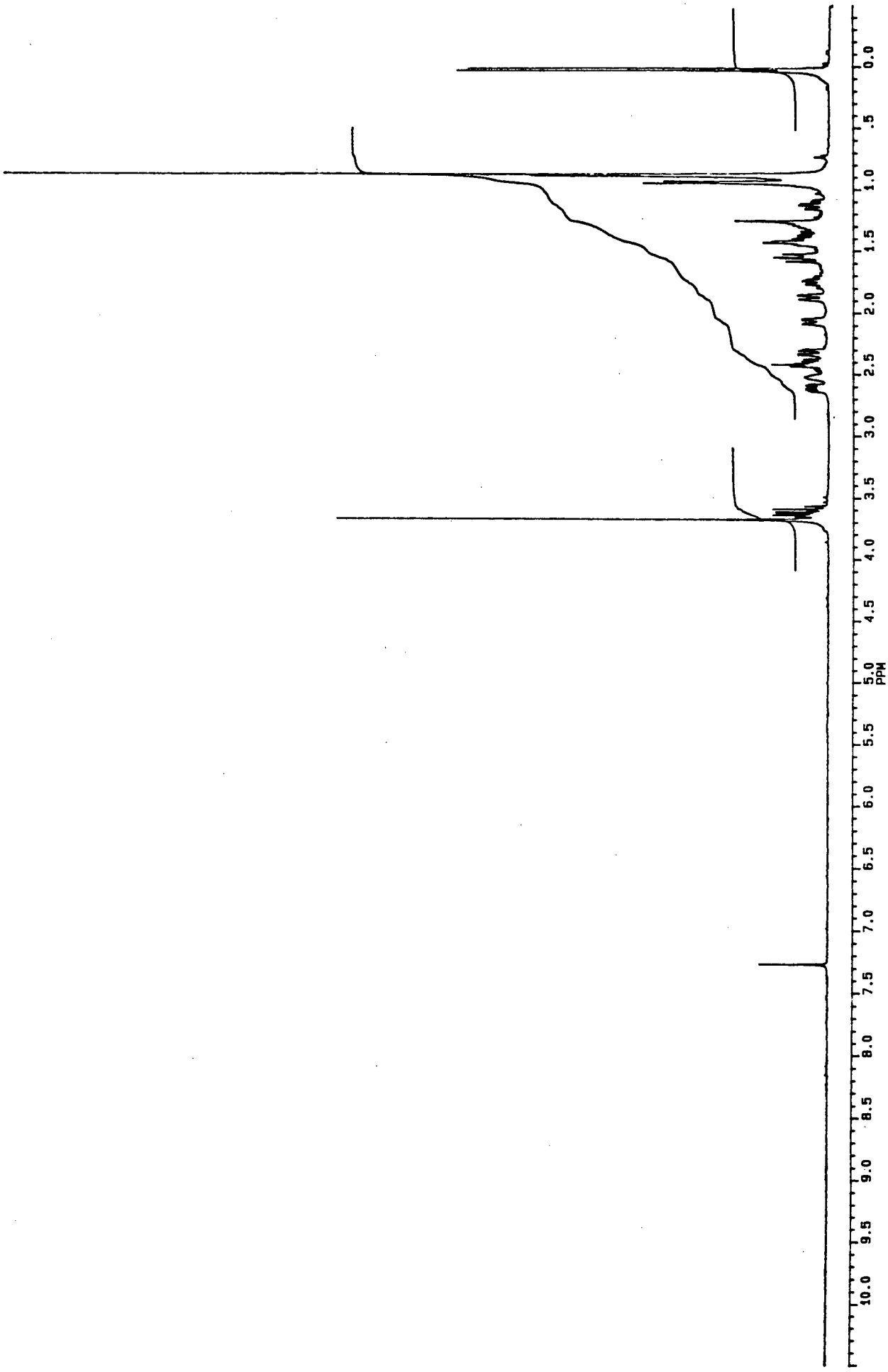

Figure 9. 400 MHz ^{1}H NMR spectrum of the ketone **23** recorded in $CDCl_3$.

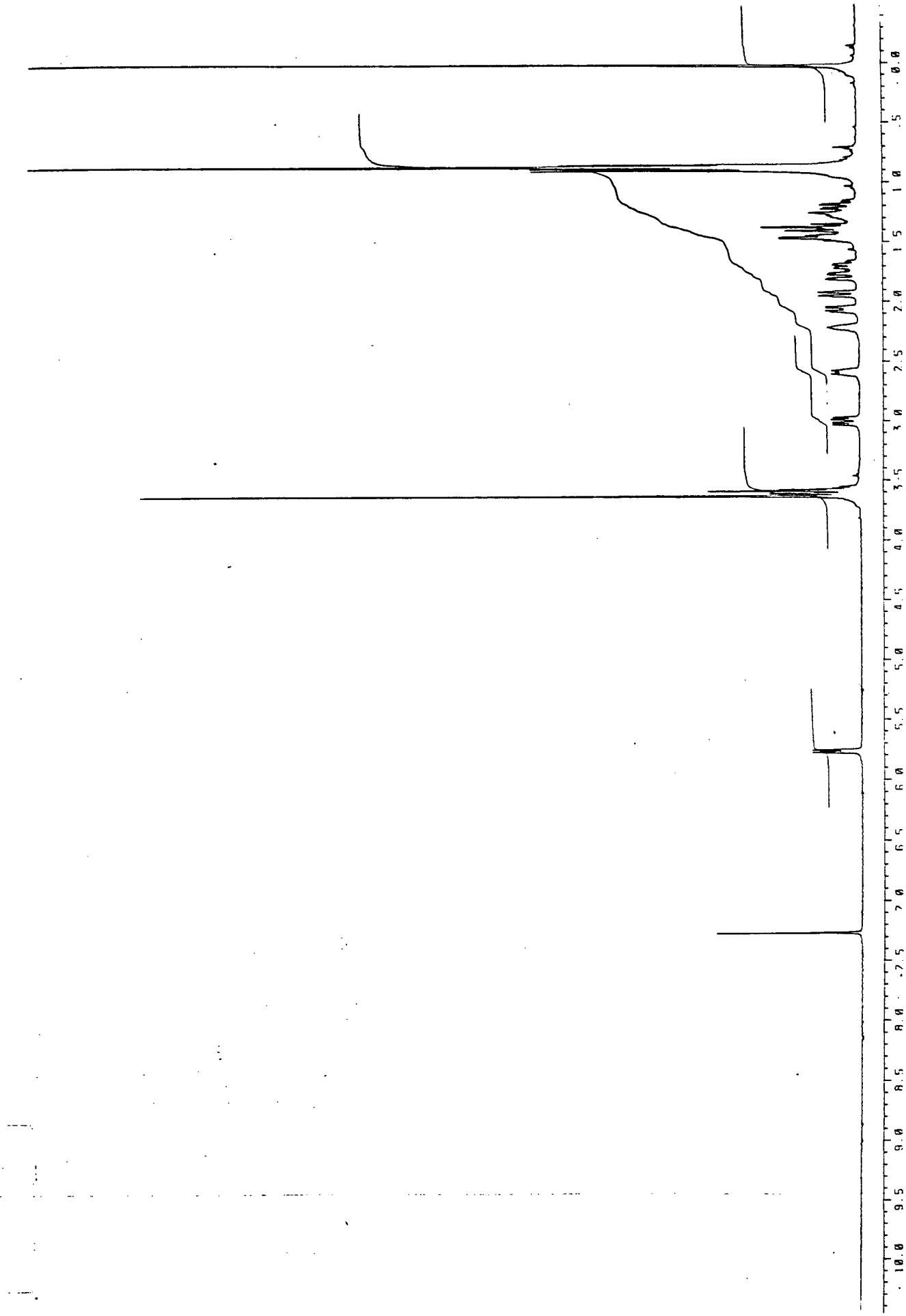

Figure 10. 400 MHz ^{1}H NMR spectrum of the enol trifluoromethanesulfonate **64** recorded in $CDCl_3$.

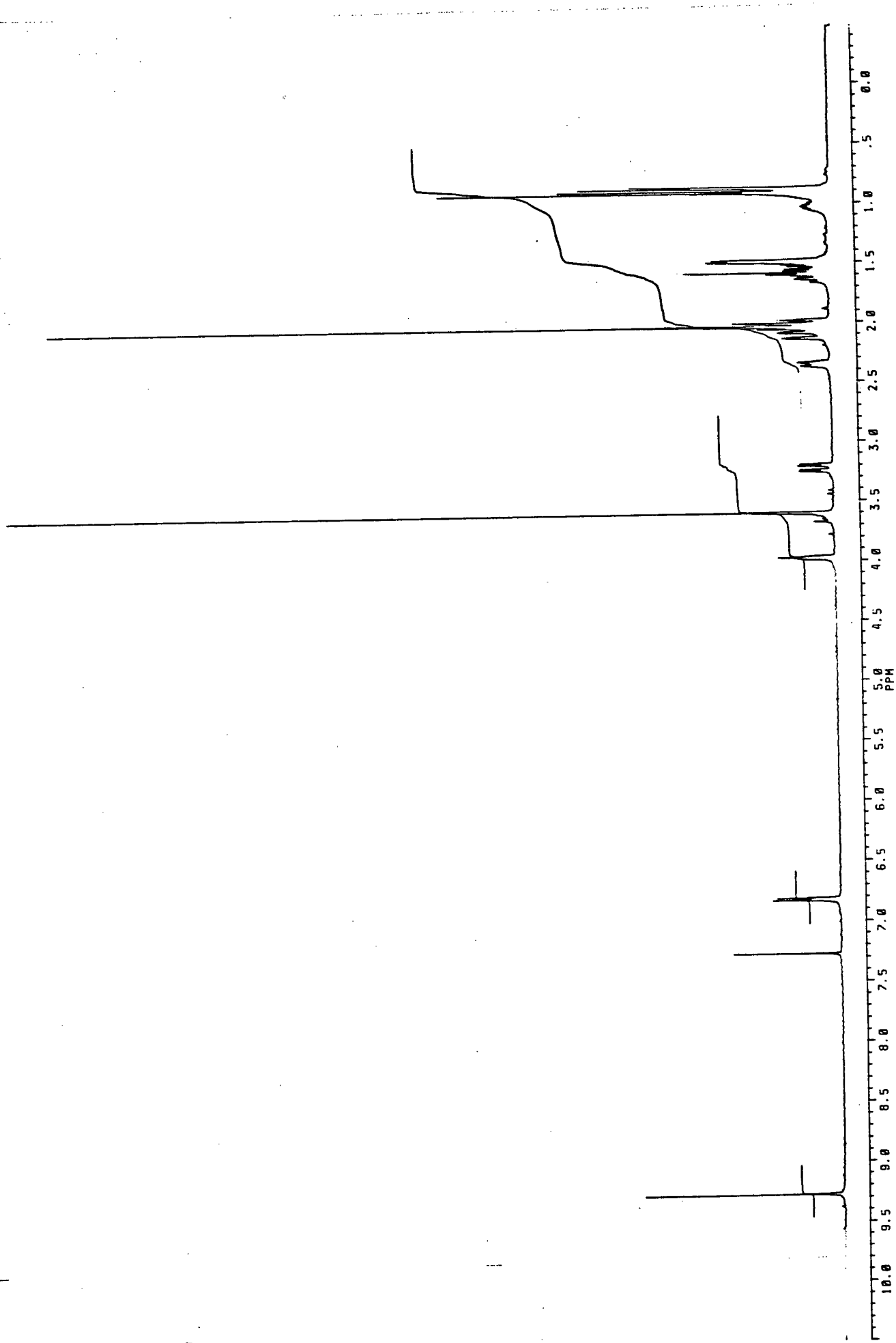

Figure 11. 400 MHz ^{1}H NMR spectrum of the keto aldehyde **32** recorded in $CDCl_3$.

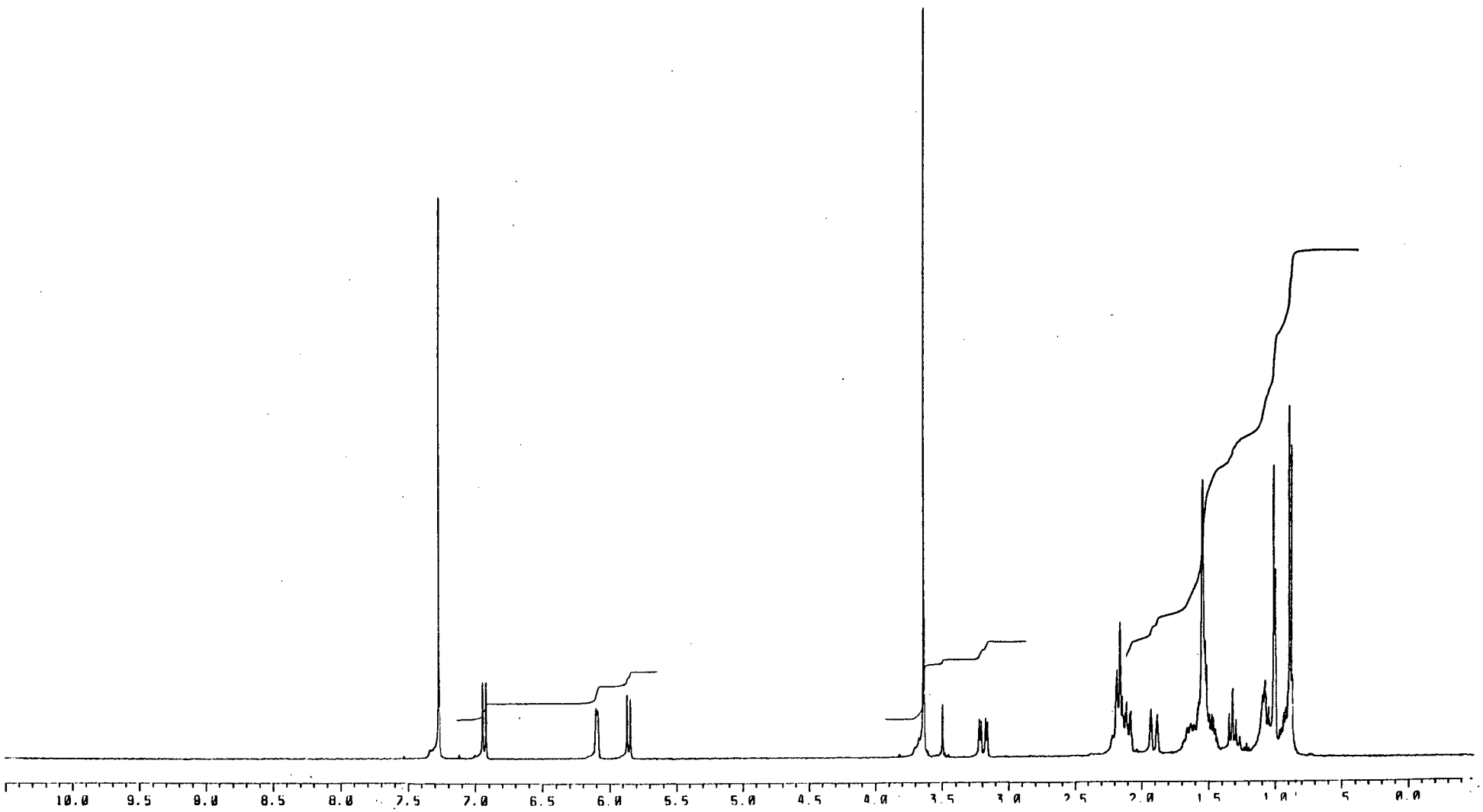

Figure 12. 400 MHz ^{1}H NMR spectrum of the dieneone **76** recorded in $CDCl_3$.

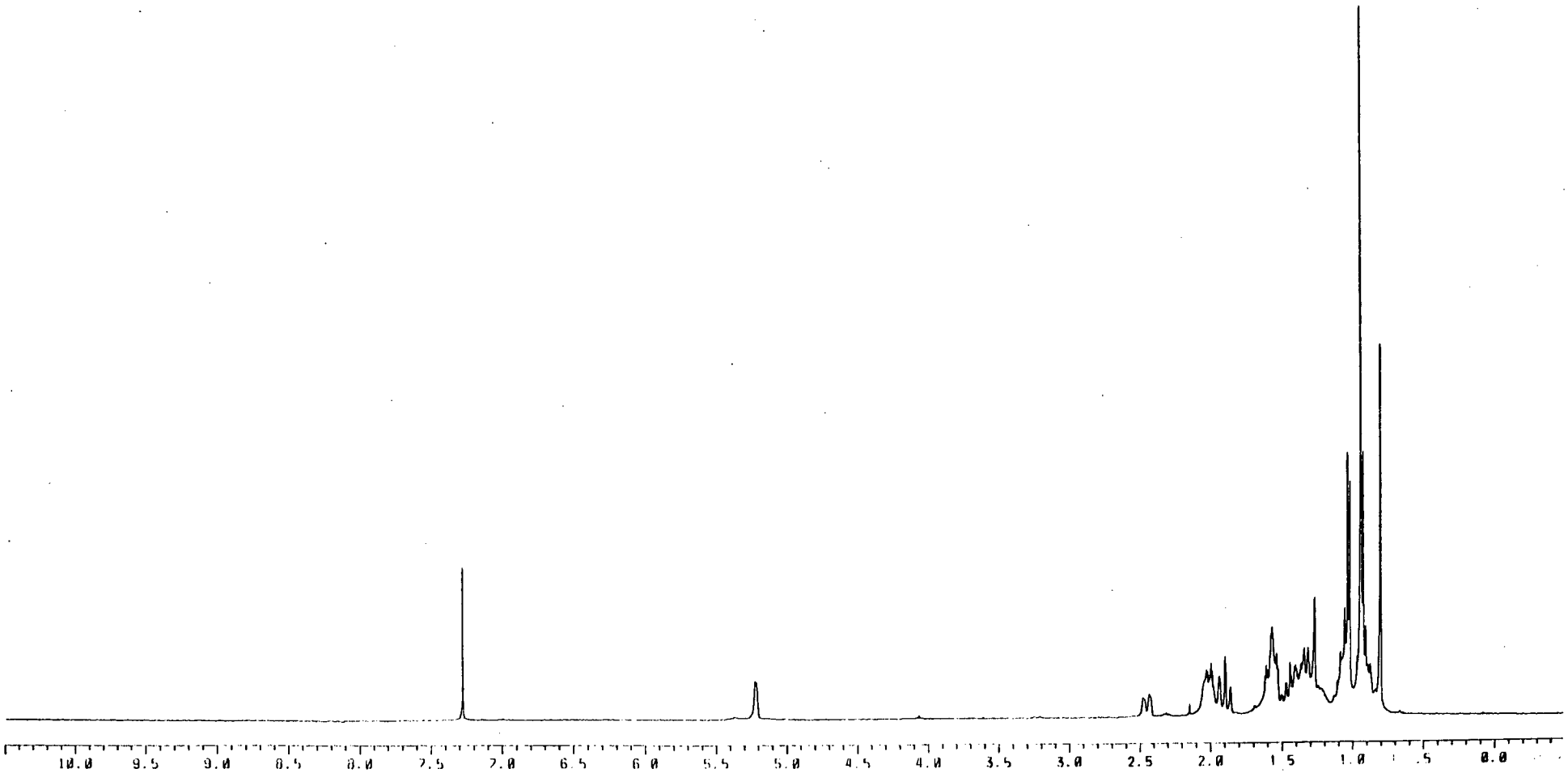

Figure 13. 400 MHz ^{1}H NMR spectrum of (+)-8-isocyano-10-cycloamphilectene (**11**) recorded in $CDCl_3$.