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TOTAL SYNTHESIS OF *cis*-CLERODANE DITERPENOIDS: (±)-6β-ACETOXY-2-OXOKOLAVENOOL AND (±)-2-OXO-5α,8α-13,14,15,16-TETRANORCLEROD-3-EN-12-OIC ACID

by

KAK-SHAN SHIA 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Spring, 1996

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UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **TOTAL SYNTHESIS OF *cis*-CLERODANE DITERPENOIDS: (±)-6β-ACETOXY-2-OXOKOLAVENOOL AND (±)-2-OXO-5α,8α-13,14,15,16-TETRANORCLEROD-3-EN-12-OIC ACID** submitted by **KAK-SHAN SHIA** in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY.**

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Date: Dec. 15, 1995

Dedicated to my family

Abstract

A general synthetic approach to diterpenoids of the *cis*-clerodane family has been developed, culminating in the first total synthesis, in racemic form, of (±)-6β-acetoxy-2-oxokolavenool (**85**) and (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**86**). The key operation involved is the face-selective Diels-Alder reaction of dienone ester **90** and *trans*-piperylene, giving rise to adduct **87** containing the decalin nucleus and correct stereogenic centers common to many *cis*-clerodane diterpenoids.

Dienophile **90** was readily prepared from 3-ethoxy-6-methyl-2-cyclohexenone (**93**) according to the synthetic sequence outlined in Scheme 13. Alkylation of **93** with methyl bromoacetate followed by reduction with lithium aluminum hydride gave diol **95** which was subjected to selective benzylation and acid-catalyzed hydrolysis to give enone **96**. This compound was subjected to carbomethoxylation using methyl cyanoformate to give enone ester **97**. A double bond was then introduced via a phenylselenenylation-oxidative elimination process to afford dienone ester **90**.

The Diels-Alder adduct **87**, produced from **90** and *trans*-piperylene under zinc chloride catalysis (Scheme 15), served as a common intermediate for the synthesis of **85** and **86**. Conjugate addition of lithium dimethylcuprate to **87** followed by lithium aluminum hydride reduction using the ensuing enolate furnished hydroxy ketone **100**.

The hydroxy group of this compound was subsequently removed by a three-step operation: conversion of **100** to the corresponding mesylate, Zn-NaI reduction of the mesylate, and ring opening of the resulting cyclopropanol **102**. The transformation of ketone **104** thus obtained to the natural acid **86** was carried out via the synthetic sequence outlined in Scheme 16. Wolff-Kishner reduction of **104** gave an inseparable mixture of olefins **115** and **116** (3:1), which was subjected to photooxygenation in the presence of acetic anhydride, pyridine and 4-dimethylaminopyridine using 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine as a photosensitizer to give enone **117**. Debenzylation of **117** with ferric chloride followed by Jones oxidation led to the completion of the total synthesis of (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**86**).

For the synthesis of (±)-**85** (Scheme 19), ketone **104** was reduced with lithium aluminum hydride. Reductive debenzylation of the resulting alcohol **119** gave rise to diol **128**, the primary alcohol of which was selectively oxidized with $(Ph_3P)_3RuCl_2$ to the aldehyde level. Wittig reaction of aldehyde **129** thus formed with (α-methoxyethylidene)triphenylphosphorane followed by acid hydrolysis gave ketone **131**. Photooxygenation of this ketone under conditions similar to those used for the preparation of **117** resulted in enone acetate **132**. Finally, addition of vinylmagnesium bromide gave (±)-6β-acetoxy-2-oxokolavenool (**85**).

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I would like to express my sincerest gratitude to Professor H. J. Liu for his ever willing support, guidance, and assistance throughout this work. His encouragement, patience and wisdom made all these years a lot more enjoyable. His interest and invaluable assistance in the preparation of this thesis are also greatly appreciated.

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I wish to thank Professor J. M. Stryker for invaluable discussions and insights, Mr. T. W. Ly and Dr. A. Morales for typing and proofreading parts of the thesis.

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LIST OF ABBREVIATIONS

Ac	acetyl
APT	Attached Proton Test
Ar	Aryl
Bn	benzyl
br	broad
Bu	butyl
cims	chemical ionization mass spectrum
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
eq	equivalent(s)
Et	ethyl
h	hour
HMPA	hexamethylphosphoramide
hrms	high resolution mass spectrum
i	iso
ir	infrared
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
min	minutes
m.p.	melting point

Ms	methanesulfonyl
nmr	nuclear magnetic resonance
NOE	Nuclear Overhauser Enhancement
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
Pyr.	pyridine
q	quartet
r. t.	room temperature
t	tert
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl

TOTAL SYNTHESIS OF *cis*-CLERODANE DITERPENOIDS: (±)-6β–ACETOXY-2-OXOKOLAVENOOL AND (±)-2-OXO-5α,8α-13,14,15,16-TETRANORCLEROD-3-EN-12-OIC ACID

Introduction

During the last thirty years, over eight hundred diterpenoids and nor-diterpenoids with the clerodane carbon skeleton (Figure 1) have been isolated.[1]

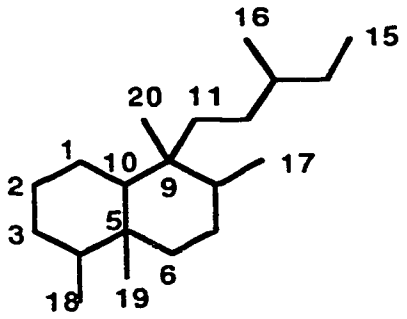
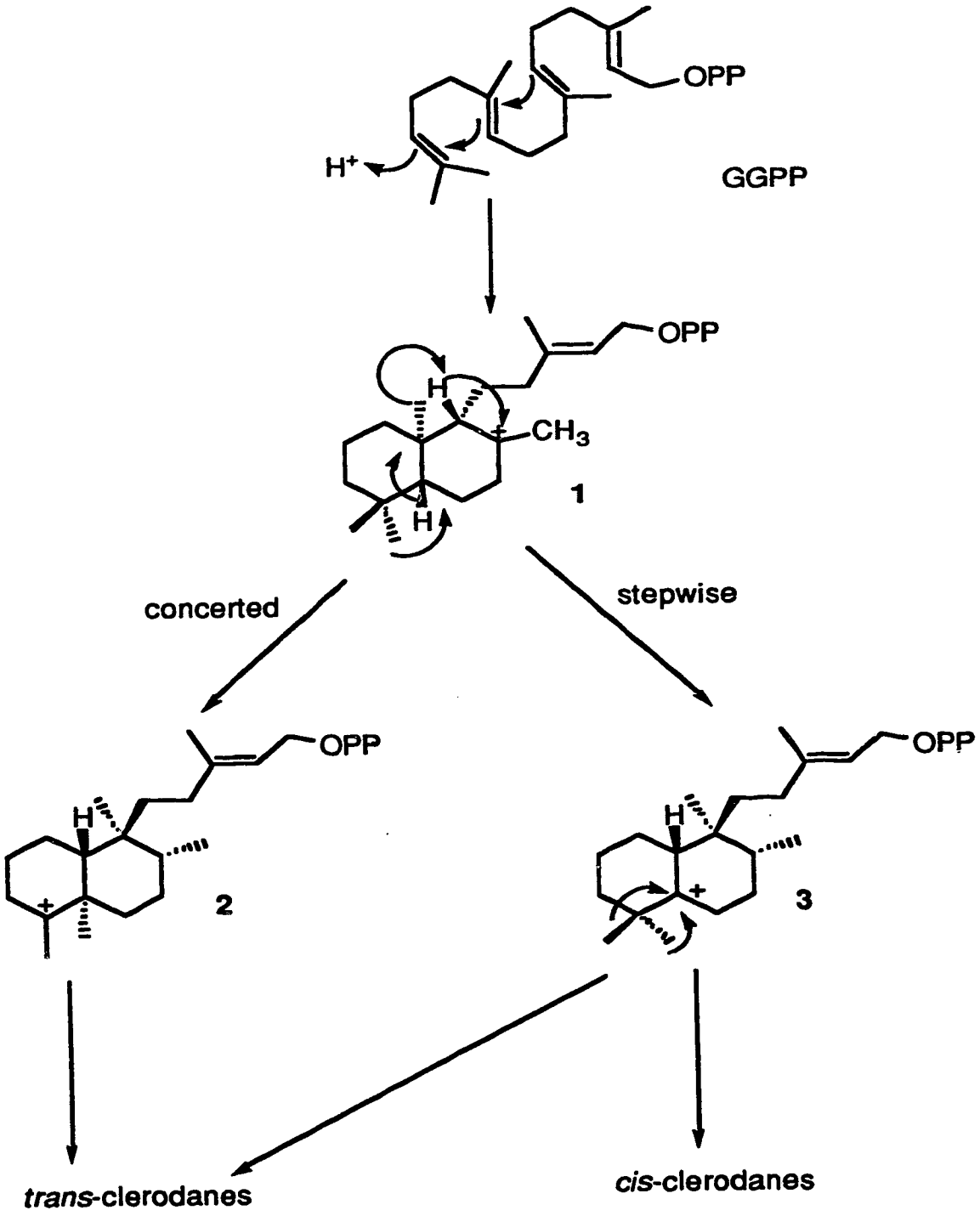


Figure 1 clerodane

A further division of the clerodanes leads to the *cis* and *trans* series of compounds, depending on the stereochemistry of the decalin ring junction. From a biosynthetic point of view, the clerodanes appear to be related to the labdanes via a series of methyl and hydride shifts. The labdane skeleton (**1**) is itself derived from geranyl geranyl pyrophosphate (GGPP) as shown in Scheme 1.[2] Although this represents a simplification of the overall biogenetic route, it involves many parallel pathways to yield a multitude of clerodane natural products.

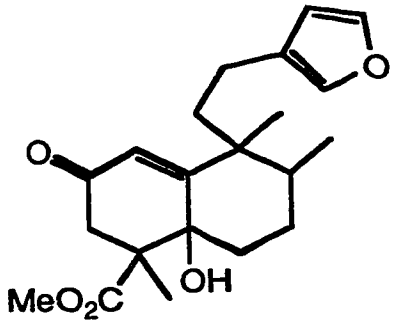
The *trans* clerodanes may arise via a concerted migration process to intermediate **2**, while the *cis* clerodanes require a stepwise mechanistic pathway with a "pause" at intermediate **3**. This can then

lead to either *cis* or *trans* compounds, depending on which of the C4



Scheme 1

methyl groups is going to migrate. This proposed biosynthetic pathway is supported, inter alia, by the isolation of the partially rearranged labdane compounds chettaphanin (**4**)[3] and salmantic acid (**5**).[4]



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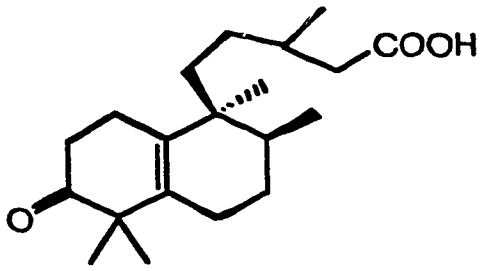


5

Due to our synthetic interest in the naturally occurring *cis*-clerodane diterpenoids, an emphasis on various features of this series of compounds is further discussed. *cis*-Clerodanes are a novel class of diterpenes which have been found in nature in rapidly increasing numbers.[5,6] According to the absolute stereochemistry of the A-B ring junction, *cis*-clerodanes can be classified into two subgroups, namely, *cis*-normal-clerodane (5α, 10α-*cis*-clerodane) and *cis*-ent-clerodane (5β, 10β-*cis*-clerodane) as illustrated in Figures 2 and 3, respectively. Although the stereochemistries at C5, C9 and C10 are opposite to each other, these two subgroups are diastereomeric rather than enantiomeric because both usually have a α-methyl group at the C8 position. In order to clarify these terminologies, a more detailed outline of the proposed biosynthetic route for *cis*-normal and *cis*-ent clerodanes is depicted in Scheme 2. Starting from geranyl geranyl pyrophosphate (GGPP), enzyme catalyzed cyclization generates

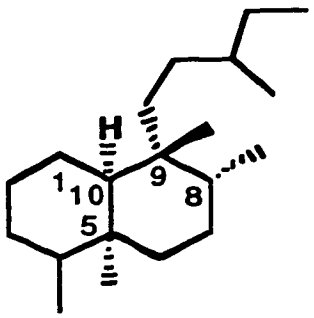


Figure 2 *cis*-normal-clerodane

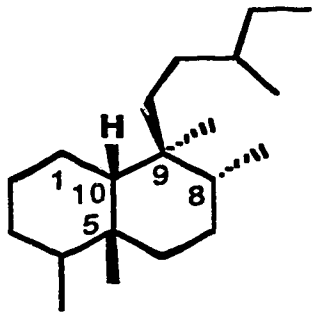
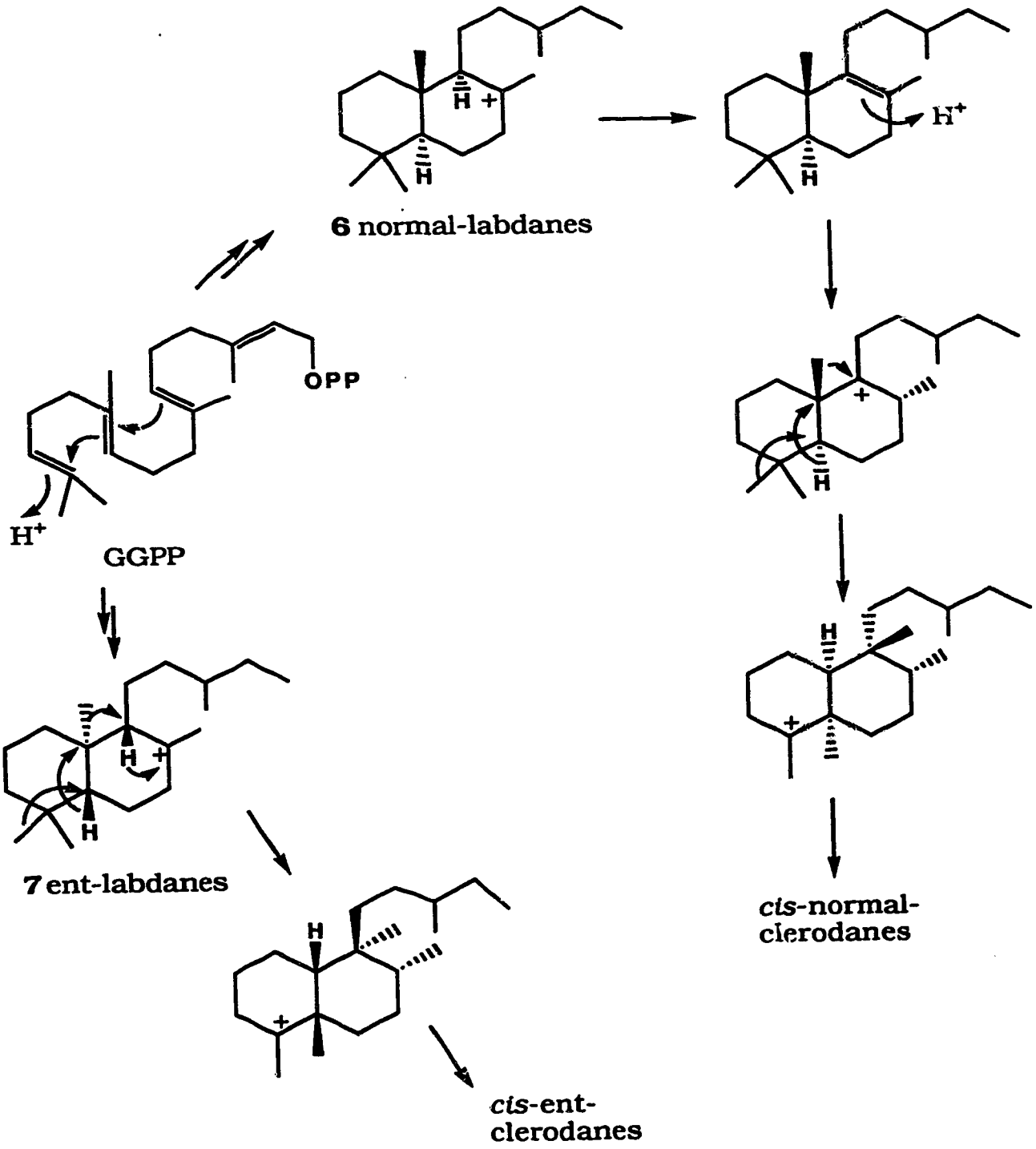


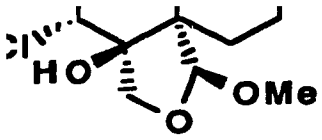
Figure 3 *cis*-ent-clerodane

normal-labdane and ent-labdane skeletons **6** and **7**, respectively. Subsequent rearrangement of **6** and **7** results in the formation of *cis*-normal- and *cis*-ent-clerodane, respectively.

The structure of the first *cis*-clerodane diterpenoid isolated from the compositae, gutrierolide (**8**),[7] was determined by X-ray analysis as a C5α, C10α-*cis*-clerodane. Perhaps triggered by this finding and the growing number of such *cis*-clerodanes reported from other plant families, the absolute stereochemistries of a pair of solidago clerodanes, solidagoic acid A (**9**) and solidagoic acid B (**10**),[8] and a series of structurally closely related natural clerodanes[9] were studied exhaustively. These compounds were assigned as 5α,10α-*cis*-ring junctions indicating a normal-labdane origin. Initially, an attempt was made to correlate acid **9** with (-)-hardwickiic acid (**11**), a *trans*-clerodane with established stereochemistry. Comparison of **12** (derived from acid **9** according to Scheme 3) with **13** (derived from **11**) revealed significant differences in the ^{1}H nmr chemical shifts proving the nonequivalence of the two parent structures. Attempts were then made to correlate **9** with plathyterpenone (**14**),[10] a


6 normal-labdanes
OPP
H+
GGPP
7 ent-labdanes
cis-normal-clerodanes
cis-ent-clerodanes

Scheme 2



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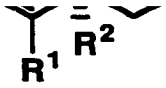
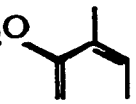
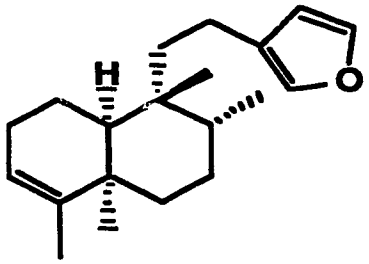


9 R^1=Me, R^2=CO_2H

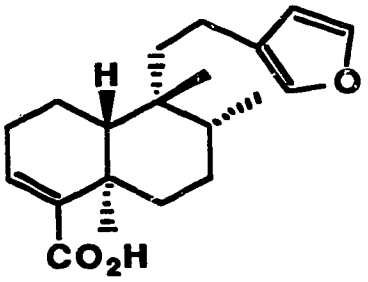
10 R^1=CH_2O  , R^2=CO_2H

9 → 1. CH_2N_2, ether; 2. $LiAlH_4$, THF; 3. CrO_3, pyr.; 4. ethylene glycol, $NH_2NH_2 \cdot H_2O$, KOH



12

Scheme 3



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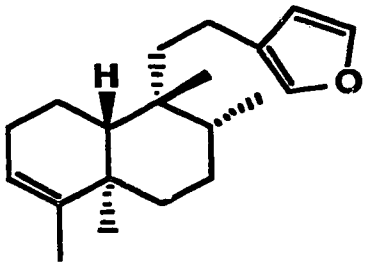
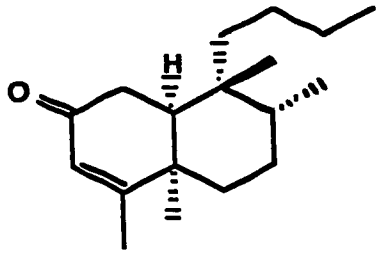


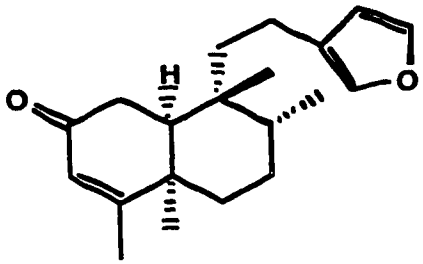
13

lerodane whose stereochemistry and constitution have been ously defined. Oxidation of **12** with Sarratt reagent slowly uced the enone **15**. Comparison of the circular dichroism (CD) ts obtained for **14** and **15** suggested a *cis*-A-B ring fusion for **15**

identical to that of **14**. Therefore, **9** and **10** were assigned to have a 5α,10α-*cis*-ring junction indicating a normal labdane origin.



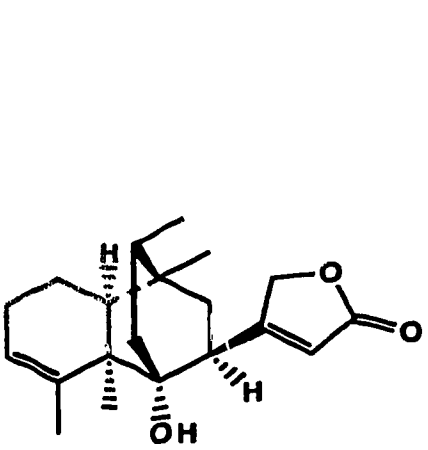
14
Negative Cotton Effect (α -33)



15
Negative Cotton Effect (α -46)

Prompted by the identification of tricyclosolidagolactone (**16**), a *cis*-normal-clerodane from *S. altissima*, Niwa and Yamamura reinvestigated the bitter principal of *S. altissima*.[11] They proposed that the biogenesis of **16** involved a precursor that was constitutionally identical to the first proposed structure for solidagolactone V (**17**) but belonging to the *cis*-clerodane class. The reinvestigation consequently revised the structures of solidagolactones II-VIII (Figure 4) and the corresponding elongatolides (proposed by McCrindle and Okazaki as *trans*-ent-clerodanes)[12,13] to *cis*-normal-clerodanes.[14] The absolute stereochemistry of the solidagolactone series was confirmed by X-ray analysis of the C_6 bromobenzoate derivative of desacylsolidagolactone VIII (**18**).[15] This confirmation also brought about these piscicidal compounds as the first examples for 5α,10α-*cis*-clerodane diterpenes with absolute configurations unambiguously assigned.

A group of *cis*-ent-clerodanes **19-24**[15] were isolated from *S. arguta*. The absolute stereochemistry of these compounds was corroborated by



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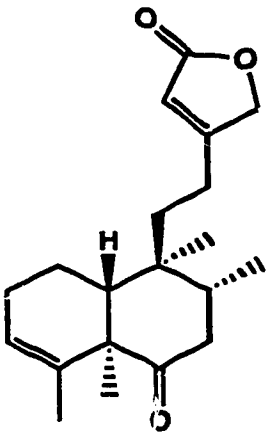

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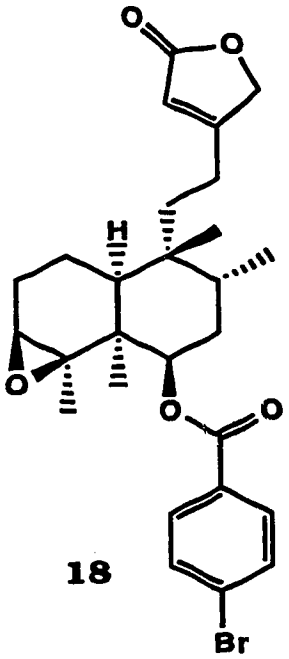

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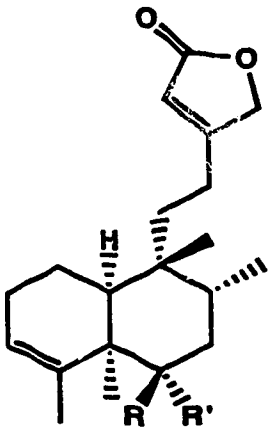
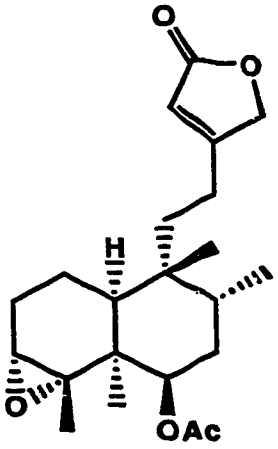
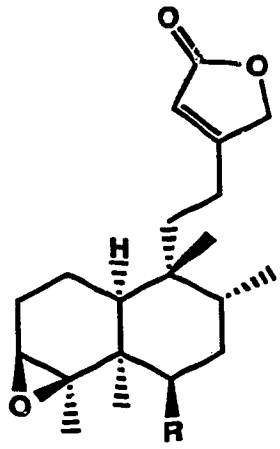


II R = OAng, R' = H
III R = OTig, R' = H
IV R = OH, R' = H
V R, R' = O



VI



VII R = OAng
VIII R = OTig

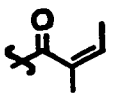
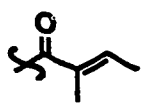
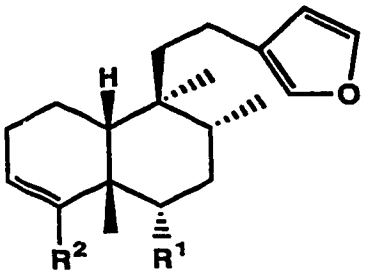
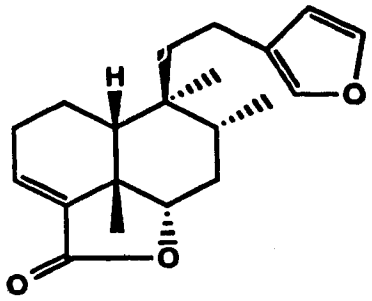
Ang =  , Tig = 

Figure 4. solidagolactones



19 R^1 =H, R^2 = Me
20 R^1 = H, R^2 = CH_2OH
21 R^1 = H, R^2 = CH_2OAc
22 R^1 = OH, R^2 = CH_2OH
23 R^1 = OH, R^2 = CH_2OAc



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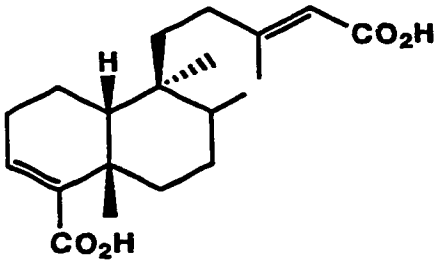

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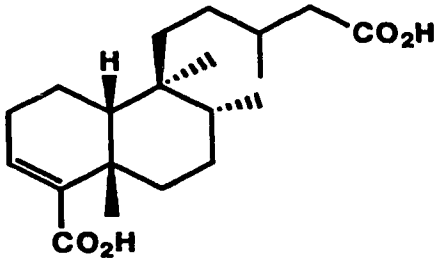

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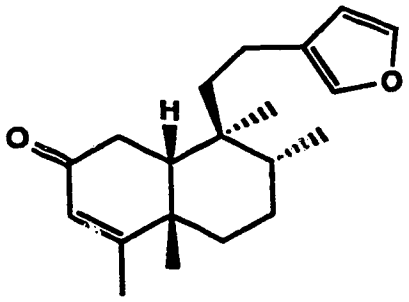
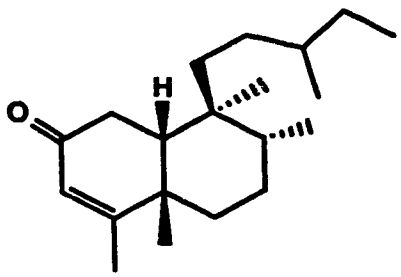


27
Positive Cotton Effect (α +65)



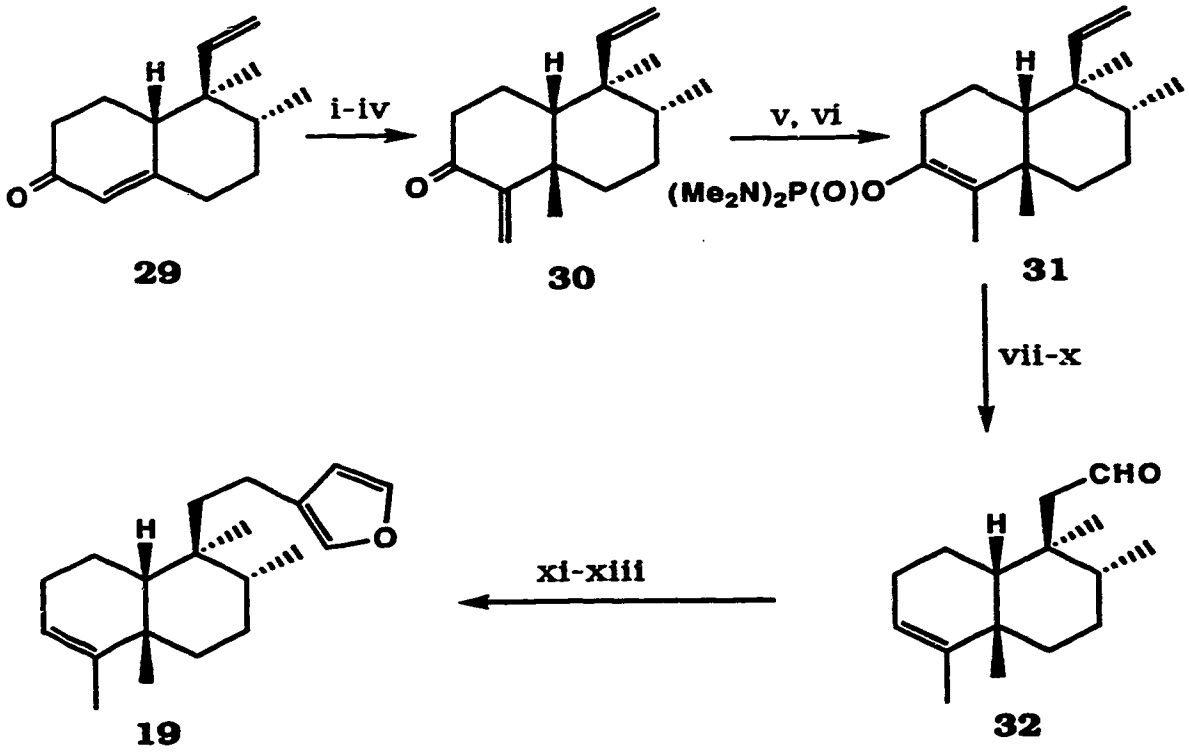
28
Positive Cotton Effect (α +64)

X-ray analysis and chemical interconversions.[16,17] First, a nonheavy atom X-ray analysis of **24** established the relative stereochemistry. Then lactone **24** was transformed chemically into the co-occurring compounds **22** and **23**. Finally a study of the optical data for compound **19** confirmed the absolute configuration of these compounds and other compounds with similar structures such as haplopappic acid (**25**),[18] cistodioic acid (**26**) and related compounds. It was observed that the CD data for haplopappic acid, a clerodane from *S. arguta* , and the cistodioic acid related series of compounds had a common pattern which is opposite to the CD pattern detected for solidagoic acids **A** and **B**. For example, the two enones **27** and **28**, derived respectively from compound **19** and cistodioic acid (**26**), have positive cotton effects for the n-π^* transtion of nearly equal amplitude (α +65 for **27** and α +64 for **28**). On the other hand, plathyterpenone **14** and enone **15** derived from solidagoic acid **A** each has a negative and weaker cotton effect (α -46 and α -33). It is noteworthy that enone **15** has been isolated recently from *vellozia bicolor* L. B. Smith and characterized as a natural product.[19]

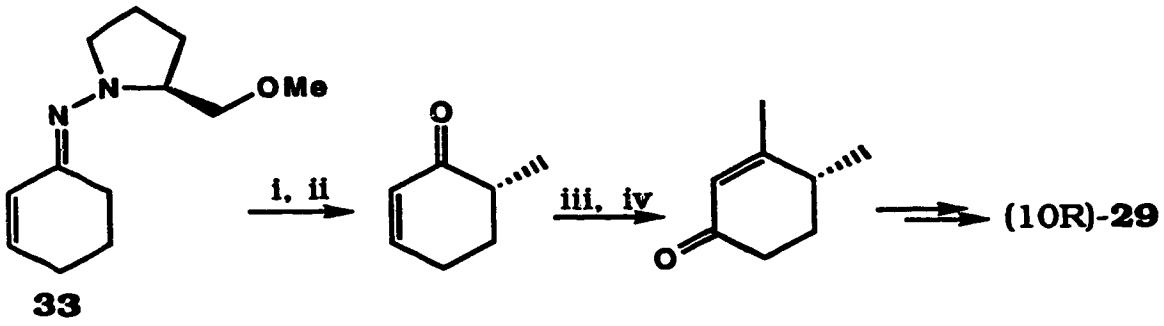
To date, more than four hundred diterpenoids of the *cis*-clerodane family have been isolated from various natural sources. Their interesting biological activities and the challenging chemical structures have prompted three total syntheses and two formal total syntheses by a Japanese research group and one asymmetric total synthesis by Piers' group.

In 1983, Tokoroyama and coworkers[20] reported the first total synthesis of a naturally occurring *cis*-clerodane, 15,16-epoxy-*cis*-cleroda-3,13(16),14-triene (**19**). The key intermediate in the synthesis was the octanone derivative **29** which was readily prepared from 3,4-dimethyl-2-cyclohexenone in 60% overall yield. The introduction of the C_5 angular methyl group was accomplished by 1,4-addition of lithium dimethylcuprate. Trapping of the ensuing enolate with formaldehyde was followed by the conversion of the resulting alcohol to a mesylate. Subsequent elimination of the mesylate using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave enone **30** which was subjected to 1,4-reduction with L-selectride. Treatment of the resulting enolate with N,N,N',N'-tetramethyldiaminophosphorochloridate afforded intermediate **31**. Selective hydroboration-oxidation of the vinyl group followed by reductive removal of the phosphorodiamidate moiety and Swern oxidation gave aldehyde **32**. Addition of 3-furyllithium to the aldehyde followed by acetylation and reductive cleavage of the resulting acetate unit using lithium in liquid ammonia led to the formation of the natural compound **19** in racemic form in an overall yield of 3% from **29** (Scheme 4).

In 1987, Tokoroyama and co-workers[21] reported the preparation of the octalone intermediate **29** in optically active form. The key step was the modified Ender's asymmetric alkylation, in which the methylation of cyclohexenone (S)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP)-hydrazone **33** with methyl *p*-toluenesulphonate



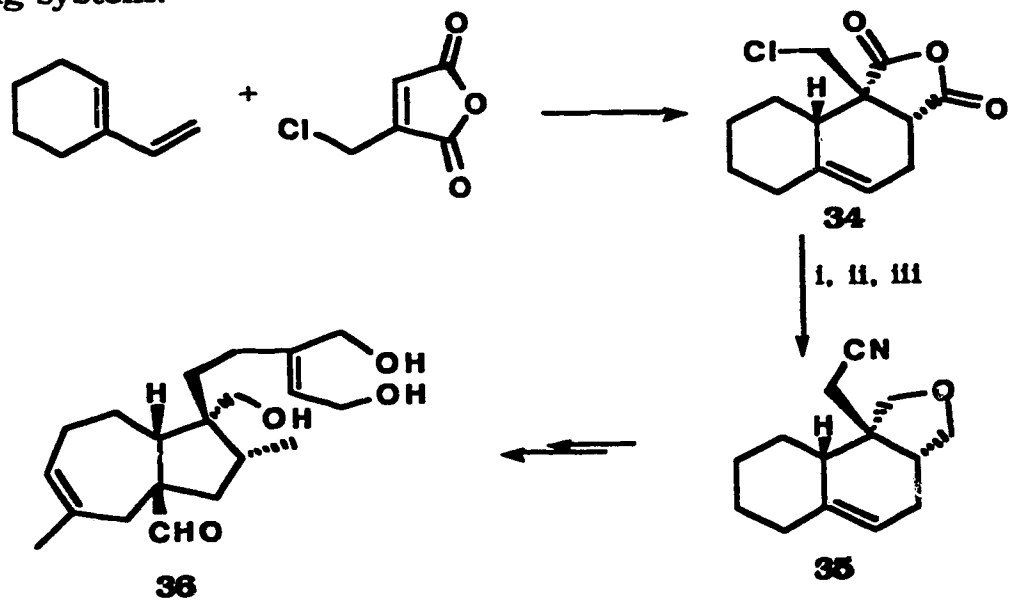
Scheme 4. Reagents. i, Me_2CuLi; ii, HCHO; iii, $MeSO_2Cl$, Et_3N; iv, DBU; v, LiB(CHMeEt)$_3$H; vi, $(Me_2N)_2POCl$, Et_3N; vii, B_2H_6; viii, H_2O_2, NaOH; ix, Li, $EtNH_2$, *t*-BuOH; x, Me_2SO, $(COCl)_2$, then Et_3N; xi, 3-furyllithium; xii, Ac_2O, pyridine; xiii, Li, liq. NH_3.



Scheme 5. Reagents. i, *i*-Pr_2Li, THF, then *p*-TsOMe; ii, MeI, then 2 M HCl, pentane; iii, MeLi, ether; iv, PCC, CH_2Cl_2.

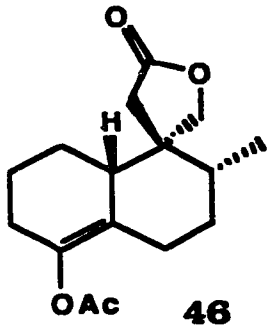
gave 6-methyl-2-cyclohexenone in excellent optical purity (Scheme 5). Subsequent addition of methyllithium to the ketone carbonyl followed by oxidation with pyridinium chlorochromate (PCC) furnished (4R)-3,4-dimethyl-2-cyclohexenone, which was then converted into the (10R)-octalone intermediate **29**. Thus, a formal asymmetric synthesis of compound **19** was achieved.

The most recent synthesis of *cis* compound **19** was also accomplished by Tokoroyama and co-workers[22] by utilizing a completely different approach. The synthesis began with the Diels-Alder reaction of 1-vinylcyclohexene with (chloromethyl)maleic anhydride.[23] The adduct **34** was then converted to compound **35** which was previously used as an intermediate in the synthesis of portual (**36**)[24] (Scheme 6), a diterpene with the *cis*-clerodane substitution pattern and a rearranged A-B ring system.



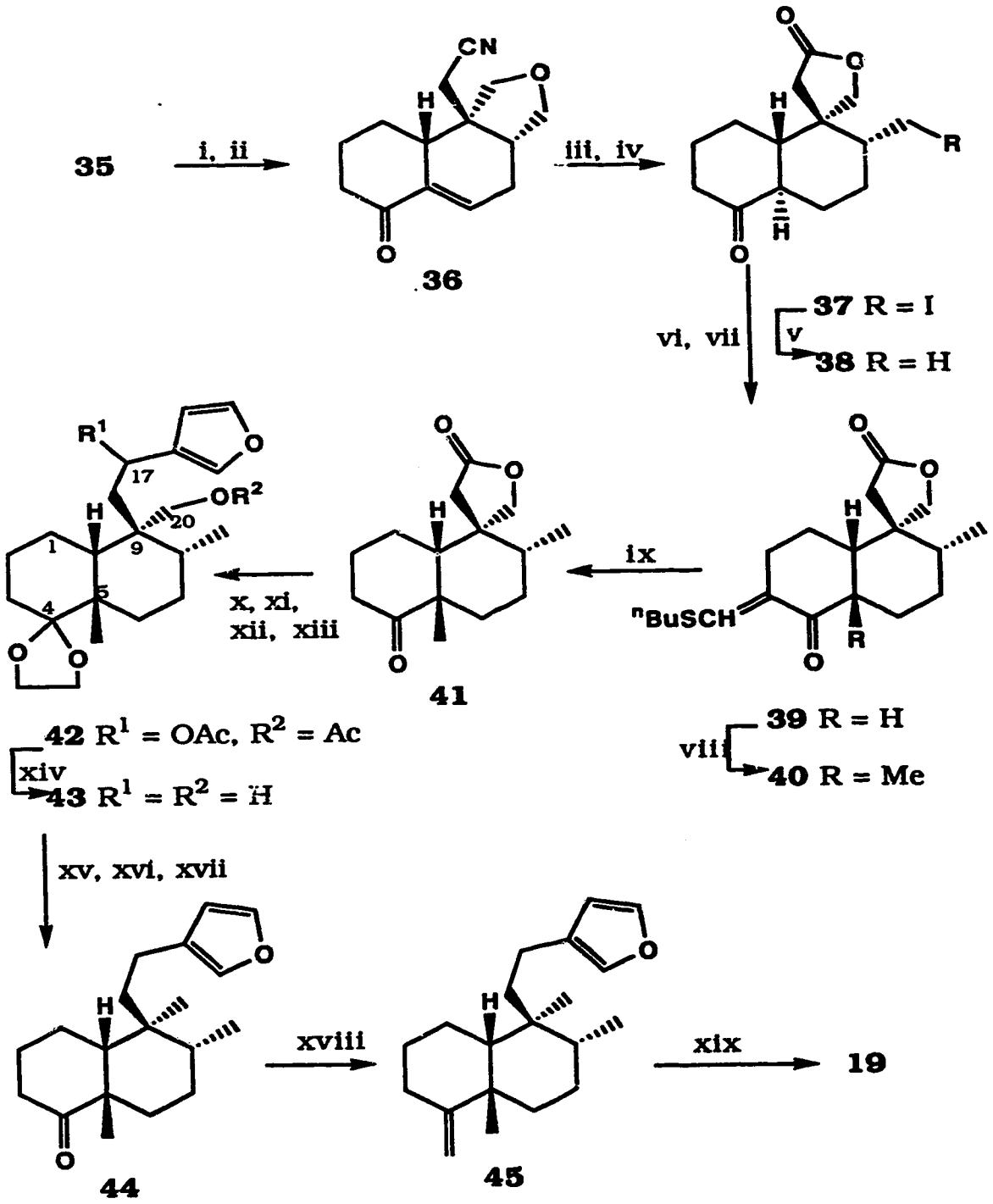
Scheme 6. Reagents. i, $LiAlH_4$; ii, TsCl, pyridine; iii, NaCN, NaI.

Starting from **35**, key synthetic operations towards **19** consisted of: (1) the introduction of the *cis* angular methyl group at C_5, (2) the construction of the side chain by appendage of a 3-furyl ring and deoxygenation at C_{17} and C_{20}, and (3) the elaboration of the vinyl methyl group in ring A from the C_4 carbonyl group (Scheme 7). Initial attempts to introduce the angular methyl group by carbene addition to the enol acetate **46** derived from compound **38** were unsuccessful. The problem was eventually solved by alkylating **39** using Ireland's procedure with methyl iodide and a large excess of potassium *t*-amyloxide (25-30 equivalents), furnishing the methylated compound **40** in 74% yield. The last phase of the synthesis was the introduction of a vinyl methyl group in ring A from compound **44**. Difficulties were encountered in methylation with various organometallic reagents. The problem was eventually overcome by using Nozaki's reagent to afford compound **45**, which was isomerized to the natural product **19** by Brown's procedure.

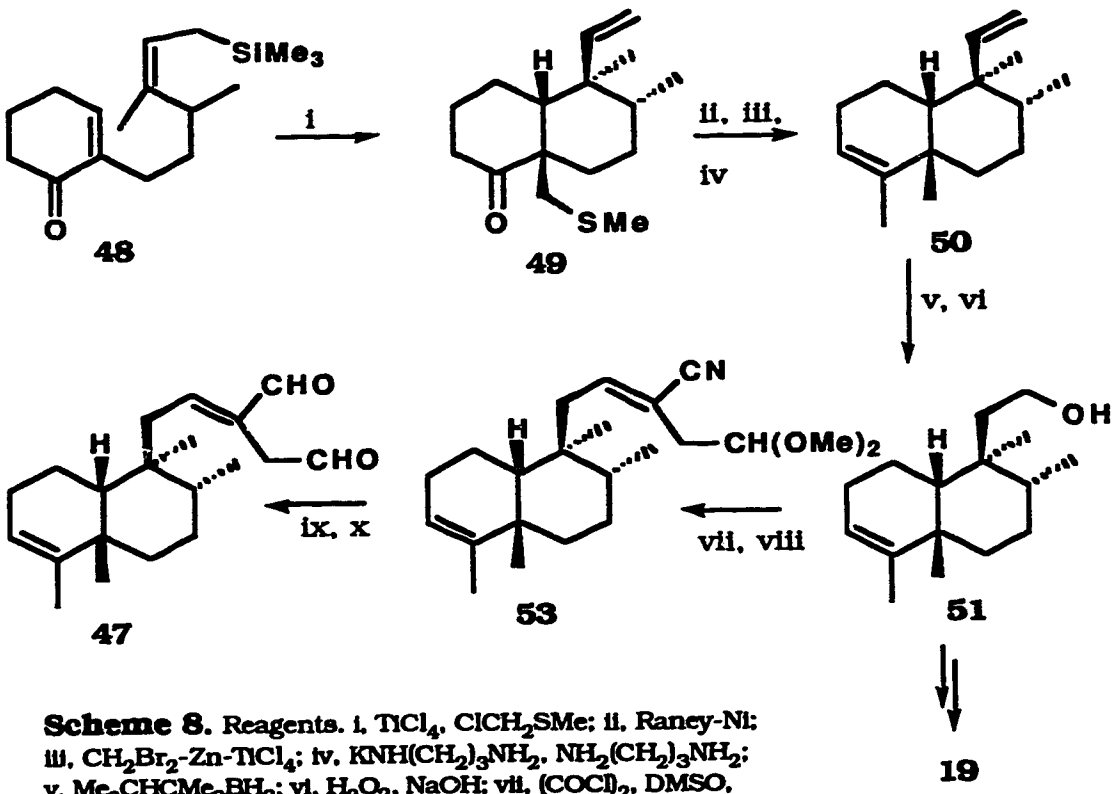


46

The total synthesis of another *cis*-clerodane, linaridial (**47**), was reported by the same research group in 1987.[25] The key operation of the synthesis differed from the other examples in that the *cis*-clerodane skeleton was constructed by means of a stereocontrolled



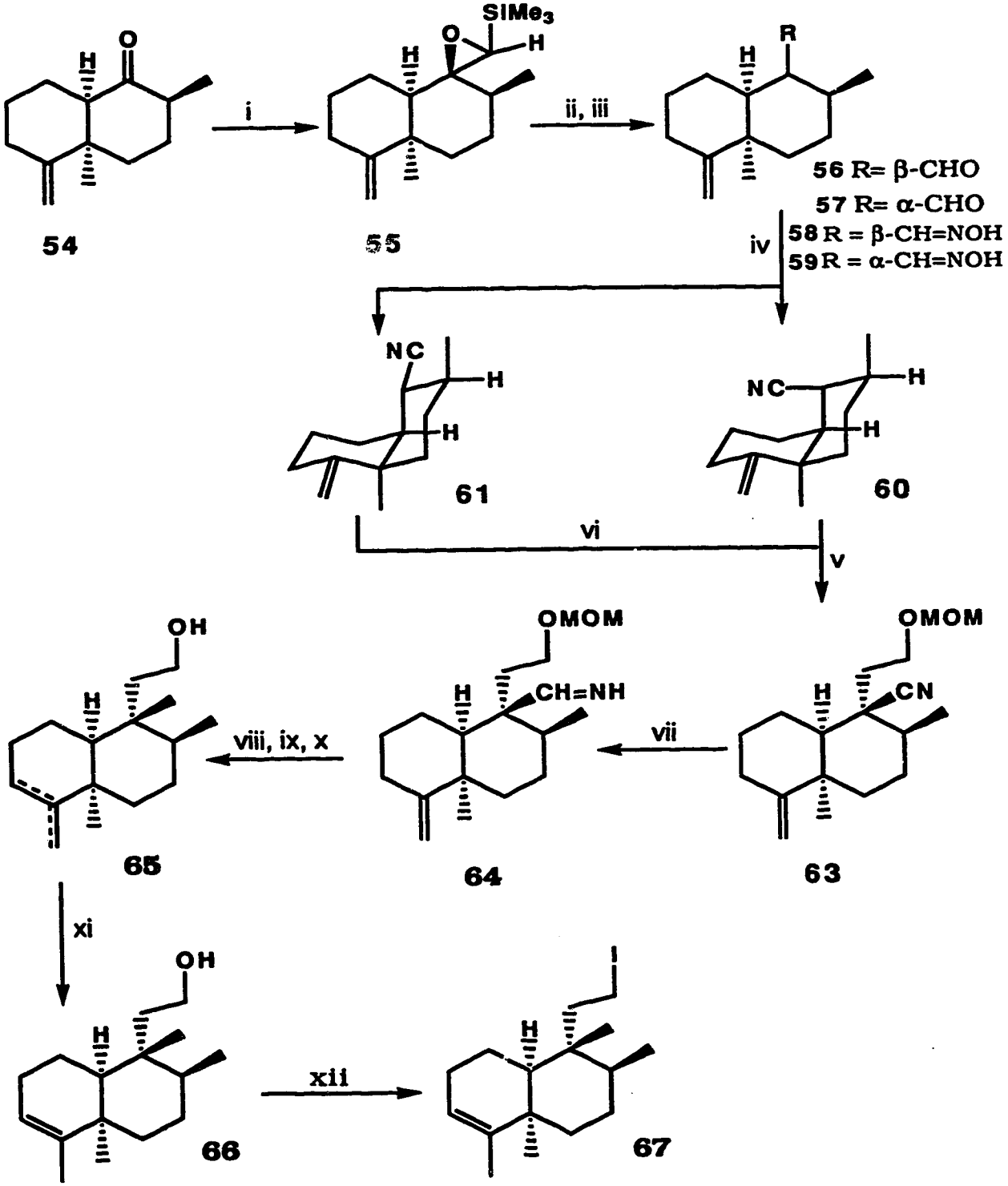
Scheme 7. Reagents. i, SeO_2; ii, MnO_2; iii, H_2, Pd-C; iv, 57% HI-H_2O, P, AcOH; v, Zn, AcOH; vi, HCO_2Et, NaH; vii, *n*-BuSH, *p*-TsOH; viii, MeI, *t*-$C_5H_{11}OK$; ix, H_2O, KOH, $HOCH_2CH_2OH$; x, $HOCH_2CH_2OH$, *p*-TsOH; xi, 3-furyllithium; xii, $NaAl(OCH_2CH_2OMe)_2H_2$; xiii, Ac_2O, pyridine; xiv, Li, liq. NH_3; xv, CrO_3•2pyridine; xvi, NH_2NH_2•H_2O, KOH, $HOCH_2CH_2OH$; xvii, 1 M HCl; xviii, Zn-CH_2Br_2-$TiCl_4$; xix, $KNH(CH_2)_3NH_2$.



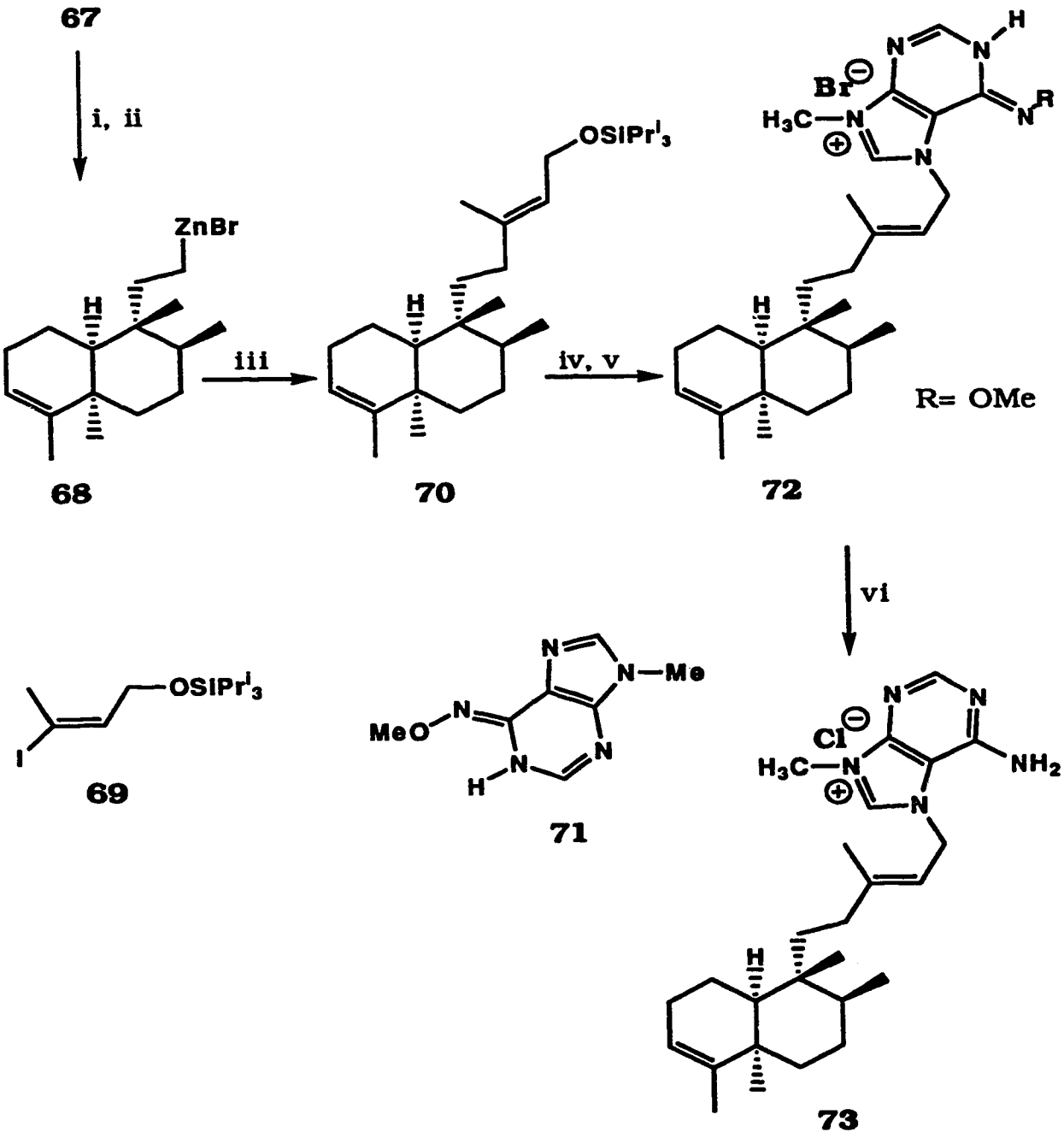
Scheme 8. Reagents. i, $TiCl_4$, $ClCH_2SMe$; ii, Raney-Ni; iii, CH_2Br_2-Zn-$TiCl_4$; iv, $KNH(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$; v, $Me_2CHCMe_2BH_2$; vi, H_2O_2, NaOH; vii, $(COCl)_2$, DMSO, then Et_3N; viii, $(EtO)_2POCH(CN)CH_2CH(OMe)_2$ (**52**), NaH; ix, DIBAL, Et_2AlCl; x, 1 M HCl.

cyclization of diene **48** under $TiCl_4$ catalysis followed by trapping of the metal enolate with a reactive electrophile, chloromethyl methyl sulfide, to give compound **49**. After reduction of the sulfide by Raney-Ni, the C4 vinylic methyl was introduced in a similar fashion as in the previously discussed synthesis, yielding compound **50**. Selective hydroboration of **50** afforded intermediate **51** which was used in the formal synthesis of natural product **19**. Starting from **51**, Swern oxidation followed by Horner-Smith condensation of the resulting aldehyde with **52** gave compound **53**. Subsequent reduction of the cyano group and hydrolysis of the acetal moiety afforded linaridial **47** (Scheme 8).

Most recently, the total synthesis of (-)-agelasine A (**73**),[26] a *cis*-normal-clerodane, was achieved by Piers and coworkers. In the synthesis, intermediate **54**, prepared from (3R)-3-methyl cyclohexanone in nine steps, was converted to compound **55** using the reagent $[Me_3Si(Cl)CH]Li$ to avoid epimerization of one or both of the stereogenic centers adjacent to the carbonyl group. Sequential treatment of **55** with boron trifluoride etherate and hydrochloric acid provided aldehydes **56** and **57**. Conversion of this mixture into the corresponding oximes followed by dehydration gave the epimeric nitriles **60** and **61**, respectively. Alkylation of each of the nitriles with iodoethyl methoxymethyl ether (**62**) gave cyano ether **63**. Transformation of the nitrile functionality into a methyl group was carried out by reduction with diisobutylaluminium hydride (DIBAL) to imine **64** followed by a modified Wolff-Kishner reduction, resulting in the formation of a 2:1 mixture of the exocyclic and endocyclic olefins **65**. Subsequent hydrolysis and isomerization of the double bond provided the olefinic alcohol **66** in high yield. Alcohol **66** was converted to the corresponding iodide **67**, which was subjected to lithium-iodine exchange and $ZnBr_2$ treatment to form the organozinc reagent **68**. Cross coupling of **68** with the vinyl iodide **69** afforded compound **70**. Upon treatment with triphenylphosphine dibromide, **70** was transformed directly into the corresponding allylic bromide which was treated immediately with an adenine derivative **71** to give intermediate **72**. Eventually, the total synthesis was accomplished by reductive removal of the methoxy group followed by ion exchange with aqueous NaCl to afford the natural product **73**. (Schemes 9 and 10).



Scheme 9. reagents. i, $[Me_3Si(Cl)CH]Li$, TMEDA, THF; ii, $BF_3{\cdot}Et_2O$, CH_2Cl_2; MeOH, HCl; iii, DMF, pyridine, $H_2NOH{\cdot}HCl$; iv, $SOCl_2$, DMAP, CH_2Cl_2; v, LDA, THF, HMPA, $ICH_2CH_2OCH_2OMe$ (**62**); vi, KDA, THF, **62**; vii, DIBAL, DME viii, H_2NNH_2 (excess), DEG,140°C; ix, KOH, DEG,220-230°C; x, PPTS, Me_3COH; xi, *p*-TsOH, $CHCl_3$; xii, Ph_3P, I_2, CH_2Cl_2, imidazole.

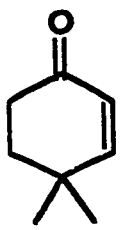


Scheme 10. reagents. i, *t*-BuLi, Et_2O; ii, $ZnBr_2$, THF-Et_2O; iii, $Pd_2(dba)_3$, Ph_3As, THF-Et_2O. **69**; iv, Ph_3PBr_2, CH_2Cl_2; v, Bu_4NI, DMA, **71**; vi, Zn, MeOH, H_2O; NaCl, H_2O.

Although more than eight hundred clerodane diterpenoids have been isolated and identified, less than thirty total syntheses were reported. Among them, only four were ascribed to the *cis*-clerodanes as described above. The limited success in approaches to the *cis*-series of compounds is probably due to relatively few methods available for the construction of the *cis*-decalin nucleus as compared with those available for the *trans*-decalin system.

In recent years, an extensive study of the Diels-Alder chemistry of 4,4-dimethyl-2-cyclohexenones **74-78** and several closely related cross-conjugated cyclic unsaturated carbonyl compounds **79-82** has been carried out in our laboratories.[27-33] On the basis of these studies, a general synthetic scheme (Scheme 11) which would facilitate the rapid assembly of a variety of *cis*-clerodane diterpenes, especially the highly oxygenated ones, via a general intermediate **84** has been conceived.

The relative stereochemistry of the three contiguous chiral centers C_5, C_9 and C_{10} (clerodane numbering) of **84** is expected to be arranged in the same manner as those of the natural *cis*-clerodanes via this Diels-Alder approach based on the steric consideration. It is highly conceivable that, if R^2 is bulkier than R^1, the addition of the diene to dienophile **83** would occur preferentially from the sterically less hindered R^1 face. This approach[34] has now been experimentally realized, culminating in the first total synthesis of 6β-acetoxy-2-oxokolavenool (**85**)[35] and 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**86**)[19] in racemic form.



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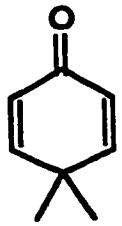

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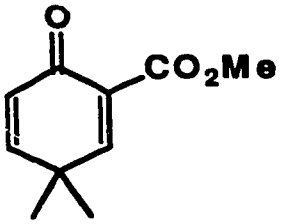

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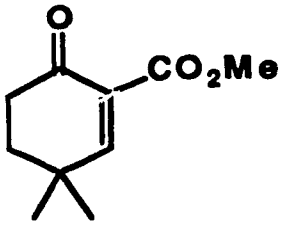

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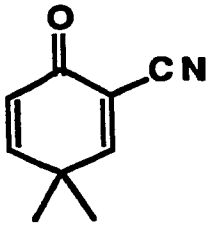

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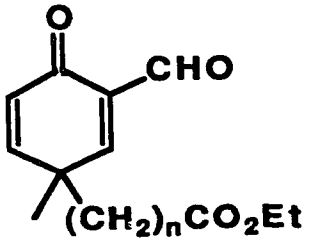
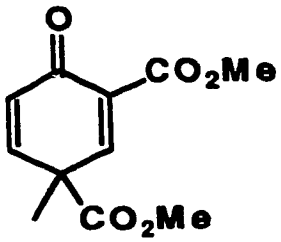


79 n=0
80 n=1
81 n=2



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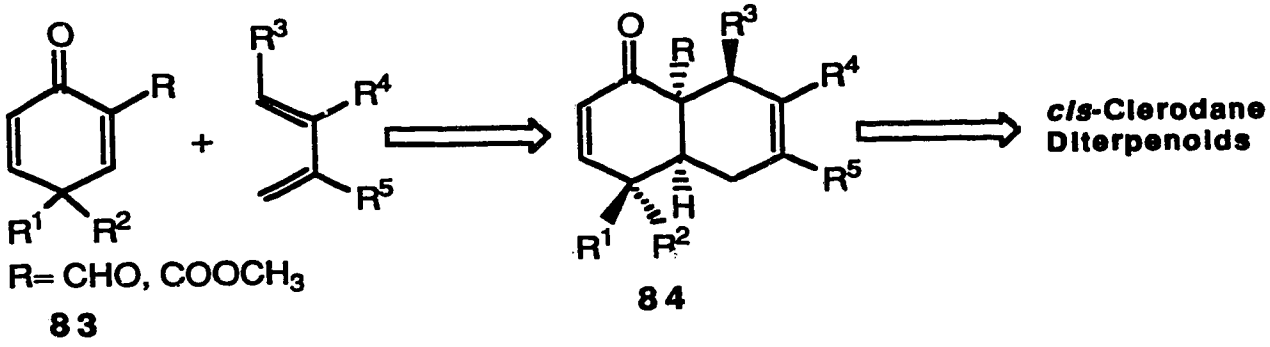


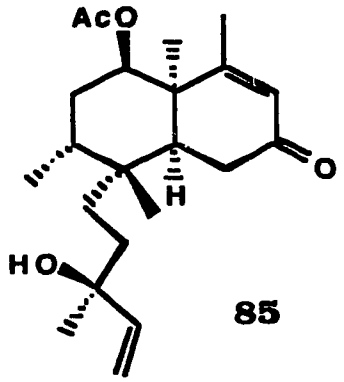
R= CHO, $COOCH_3$

83

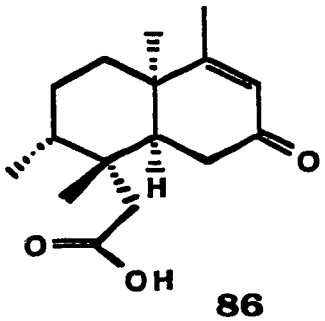
84

Scheme 11

6β-Acetoxy-2-oxokolavenool (**85**) was isolated by Bohlmann and Zdero from the aerial parts of three Mexican *Stevia* species, and its structure was deduced using spectroscopic methods (ir, mass, ^{1}H and ^{13}C nmr).



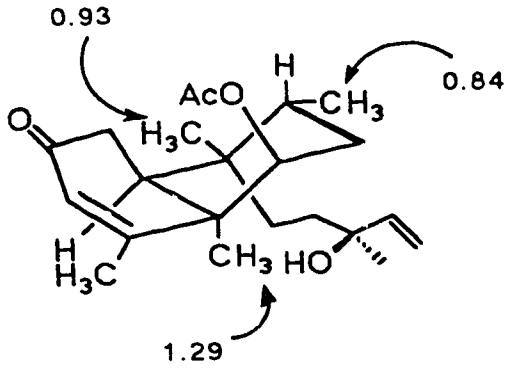
85



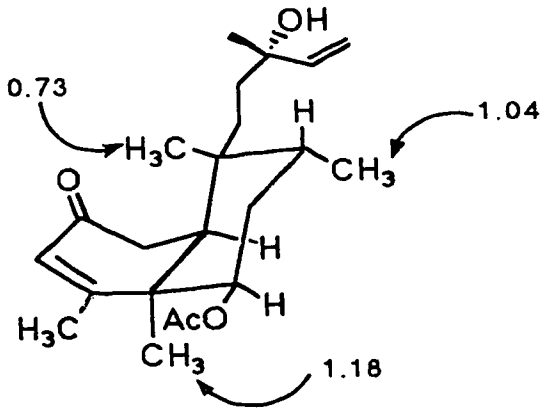
86

It is worth noting an unusual feature in the ^1H nmr spectrum ($CDCl_3$) of this compound. According to Bohlmann, its ^1H nmr spectrum measured at room temperature was very difficult to interpret because the C8 methyl doublet and the C9 methyl singlet overlapped as a broad, dwarf singlet at δ 0.93 ppm. When the temperature was lowered to -50^{0}C, however, two distinct sets of signals were observed, two doublets for the C8 methyl at δ 0.84 and 1.04 and two singlets for the C9 methyl at δ 0.93 and 0.73. On the basis of these ^1H nmr data, Bohlmann proposed that there are two major conformational isomers of this compound (Figure 5). It was assumed that a fast equilibrium exists between these two conformers at room temperature, resulting in the above unusual characteristics in the ^1H nmr spectrum.

2-Oxo-5α,8α–13,14,15,16–tetranorclerod-3-en-12-oic acid (**86**) was isolated from the ethyl acetate extracts of the roots, stem and leaf sheaths of *vellozia bicolor* L. B. Smith by Garcez *et al.* in 1994. The structure was deduced based on spectroscopic methods (ir, mass, ^1H and ^{13}C nmr).



Conformation I (C_6 β-acetate: axial)



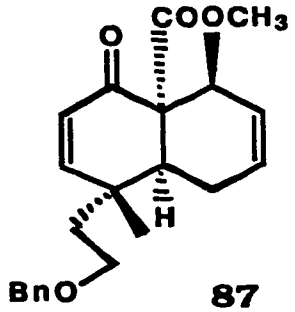
Conformation II (C_6 β-acetate: equatorial)

Figure 5. Methyl ^{1}H-nmr chemical shifts (δ, $CDCl_3$) for the two conformations of **85**

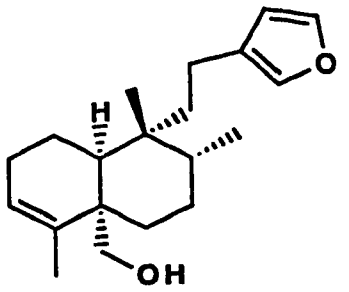
There have been no reports on the biological activities of the two *cis*-clerodanes **85** and **86**, but the clerodanes (both *cis*- and *trans*-clerodanes) in general are best known for their insect antifeedant properties and related insecticidal properties.[36,37] For instance, solidago clerodanes are usually described as the bitter principal of the root tissue and act as a natural antifeedant. Solidagolactones have also been shown to possess potent piscicidal activities against killifish.[38] From an agricultural point of view, clerodanes are potential pesticides with high efficacy and low toxicity. There have been considerable

current interests in searching for natural pesticides like clerodanes and their analogues.[39]

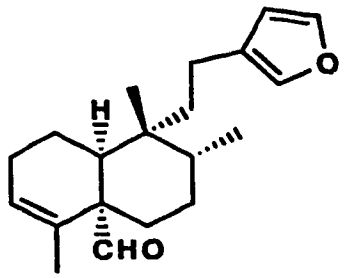
In the following section, the synthetic work leading to (±)-6β-acetoxy-2-oxokolavenool (**85**) and (±)-2-oxo-5α,8α-13,14,15,16-tetranor-clerod-3-en-12-oic acid (**86**) via an intermolecular Diels-Alder approach with adduct **87** as a common key intermediate is described. It is highly conceivable that this approach can also be applied to the synthesis of many other *cis*-clerodane diterpenoids, including solidagolactones and those listed in Figure 6.



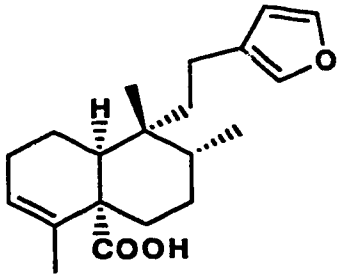
87



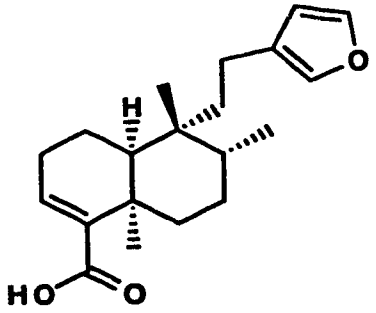
solidago alcohol



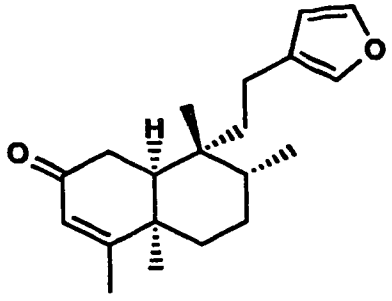
solidago aldehyde



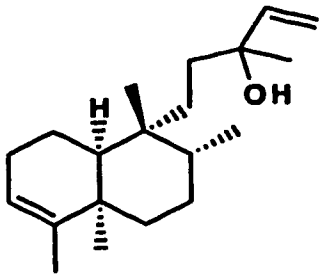
solidagoic acid A



tinotufolin B



15,16-epoxy-2-oxo-5α,8α-cleroda-3,13(16),14-triene

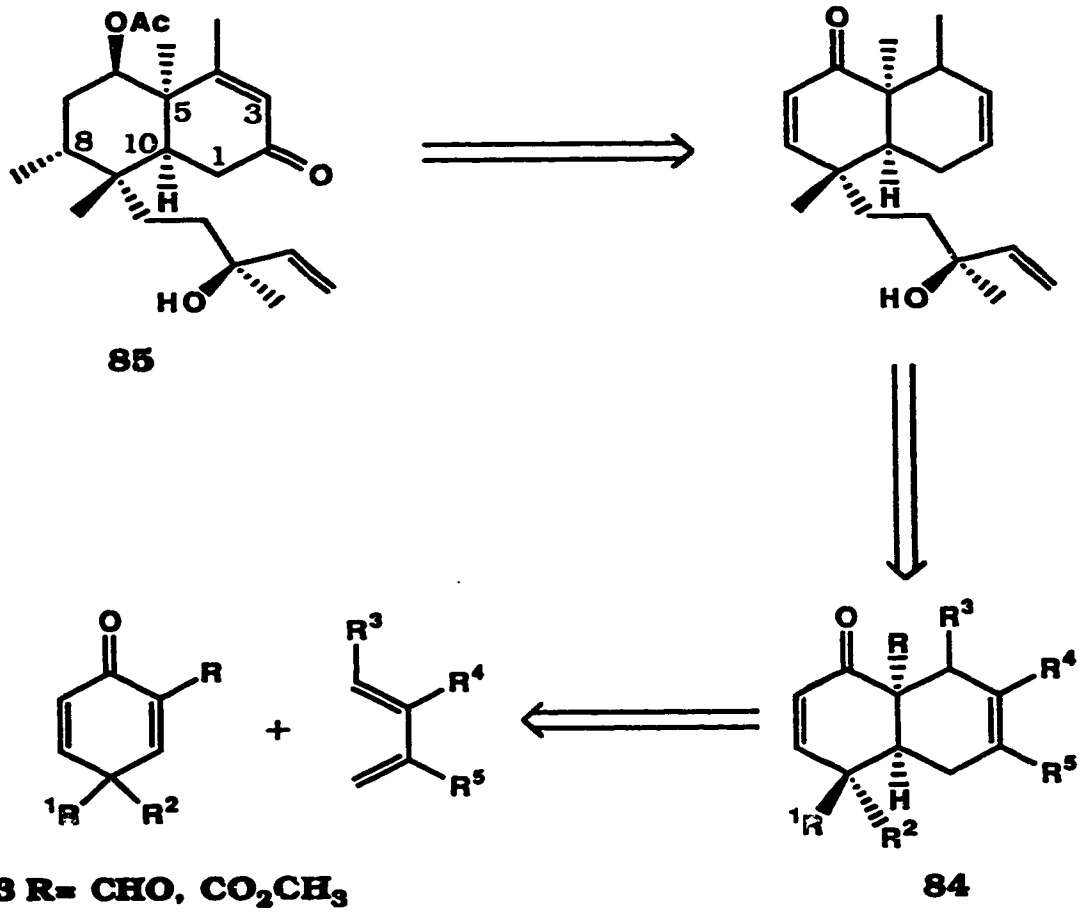


plathyterpol

Figure 6 *cis*-clerodane diterpenoids

Results and Discussion

As outlined in the retrosynthetic analysis in Scheme 12 , our approach to the *cis*-clerodane system differs from others primarily in the construction of the *cis*-decalin system. Since almost all of the natural *cis*-clerodanes have three contiguous chiral centers (C_5, C_9, and C_{10}) arranged in a special manner as shown in 6β-acetoxy-2-oxokolavenool (**85**), the facial selectivity of the cycloaddition (**83**→**84**) is crucial to



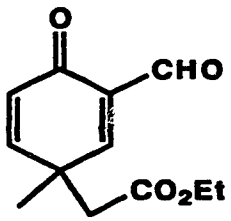
85

83 R= CHO, CO_2CH_3

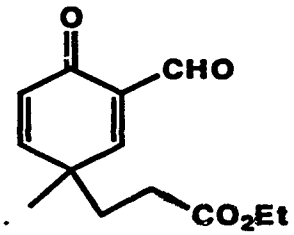
84

Scheme 12

the success of this Diels-Alder approach. As a result, we have carried out an extensive study on the facial selective Diels-Alder reactions of several dienophiles such as compounds **88**, **89**, and **90** with a general structure **83** (Scheme 12). In principle, compounds **91**[33] and **92**[33] obtained as the major products from the reactions of **88** and **89** with *trans*-piperylene are excellent candidates for the construction of *cis*-clerodane diterpenoids. In practice, however, these Diels-Alder adducts are unstable and difficult to isolate in pure form. Therefore, a more practical dienophile **90** was adopted. This compound was readily prepared from 3-ethoxy-6-methyl-2-cyclohexenone (**93**) according to the synthetic sequence shown in Scheme 13.



88



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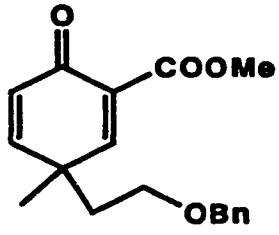
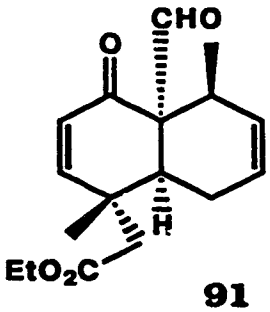


90



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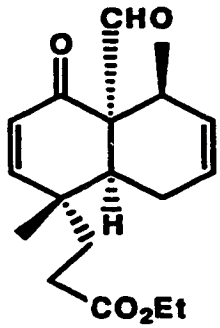
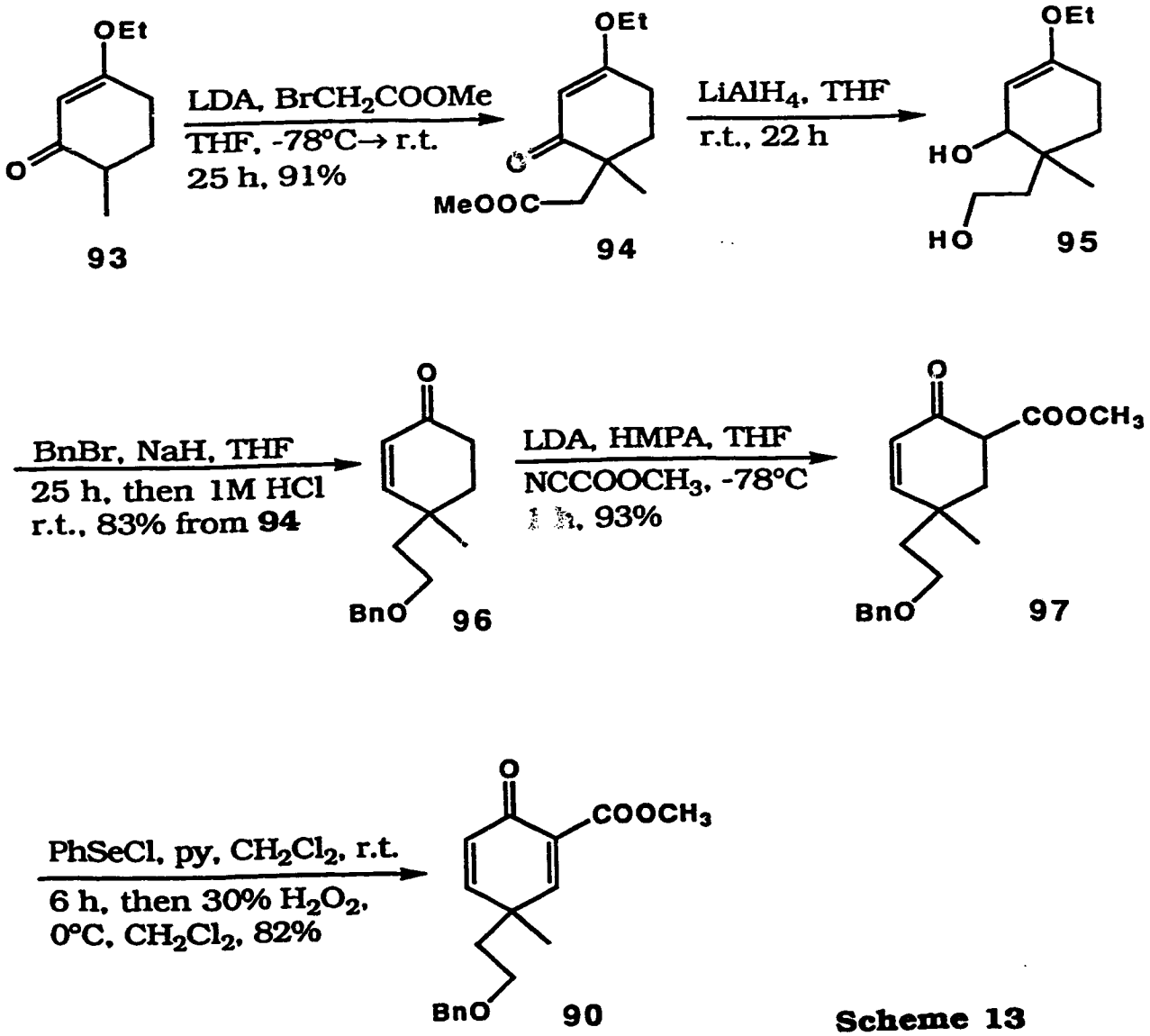


92

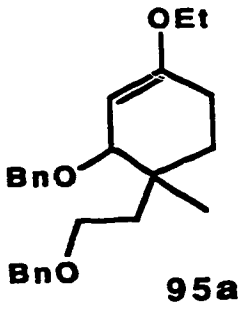
Stork-Danheiser alkylation[40] of **93** with methyl bromoacetate followed by bulb-to-bulb distillation gave enone ester **94** in 91% yield.



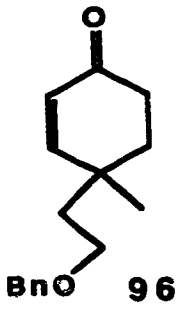
Scheme 13

This compound was reduced with lithium aluminum hydride[41] to give a diastereomeric mixture of two unstable diols **95** in nearly equal amounts. Without further purification, the mixture of diols **95** was

immediately subjected to selective benzylation with a slight excess of sodium hydride and benzyl bromide. This was followed by treatment of the crude product with dilute hydrochloric acid to give cyclohexenone **96** in 83% yield over three steps. Later on, it was found that, even benzylation occurred at both hydroxyls when excess benzyl bromide was applied, the bis-benzylated product **95a** could also be converted into **96** easily under the same hydrolysis conditions. The ir spectrum of compound **96** showed a carbonyl absorption at 1680 cm^{-1}, indicating the presence of an α,β-unsaturated ketone. In the



95a



96

^1H nmr spectrum, signals at δ 7.30 (m, 5H) and 4.49 (s, 2H) were attributed to the benzyl group. Two doublets at δ 6.65 (J=10 Hz) and 5.57 (J=10 Hz) corresponded to the β and α protons of the conjugated enone moiety. The methyl group appeared at δ 1.30 as a sharp singlet. The high resolution mass spectrum showed a molecular ion peak at m/z 244.1459 corresponding to the molecular formula $C_{16}H_{20}O_2$. The elemental analysis was also in agreement with the molecular composition.

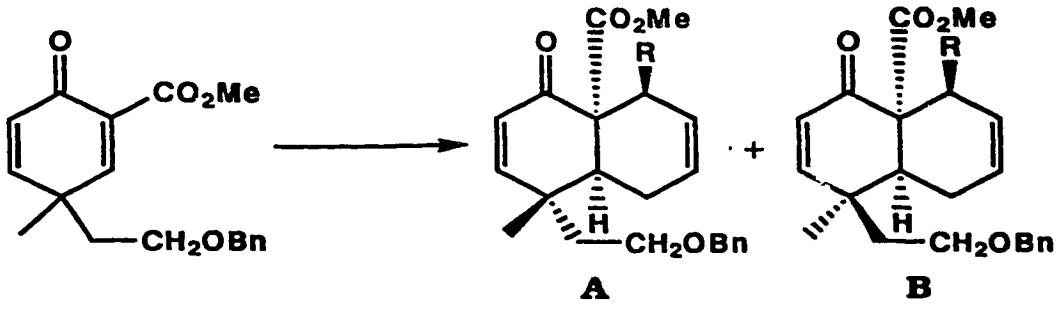
Enone **96** was subjected to carbomethoxylation using lithium diisopropylamide (LDA) and methyl cyanoformate[42] to give keto ester

97 as a mixture of three isomers (a pair of epimers and an enol ester) in a ratio of 2:1.4:1 as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{18}H_{22}O_4$ by the elemental analysis and the high resolution mass spectrum displaying a molecular ion peak at m/z 302.1515. Keto ester **97** could also be prepared using sodium hydride and dimethyl carbonate albeit in lower yield (54%).

Keto ester **97** was treated with phenylselenenyl chloride in the presence of pyridine.[43] Oxidative elimination of the resulting selenide with hydrogen peroxide gave the required dienone ester **90** in 82% yield. In the ir spectrum of **90**, the appearance of carbonyl absorptions at 1741 and 1664 cm^{-1} revealed the presence of an enone and an ester system, which were corroborated by the signals of the ^1H nmr spectrum at δ 7.59 (d, J=3 Hz, 1H) for the C_3 proton, δ 6.78 (dd, J=10, 3 Hz, 1H) and 6.29 (d, J=10 Hz, 1H) for the vinylic protons of the enone moiety, and δ 3.80 for the methoxy group of the ester. The methyl singlet appeared at δ 1.32. The high resolution mass spectrum displayed a molecular ion peak at m/z 300.1352. This along with the elemental analysis confirmed the desired formula $C_{18}H_{20}O_4$.

With this dienophile in hand, the facial selective Diels-Alder cycloadditons with 1,3-butadiene and *trans*-piperylene were investigated under a variety of conditions. The results are summarized in Table 1. In all cases examined with *trans*-piperylene, two adducts **87** and **98** were formed in a ratio of 3.5:1 to 5:1 depending mainly upon the temperature at which the reaction was carried out. It was

Table 1. Diels-Alder reactions of dienophile **90**



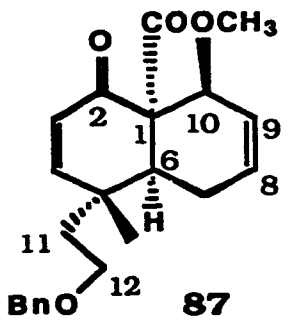
entry	diene	catalyst (eq)	solvent	temp (°C)	time (h)	product (A:B)	yield (%)[a]
1	R = Me	$ZnCl_2$ (3)	ether	24	17	3.5:1	95
2	R = Me	$ZnCl_2$ (3)	ether	0	24	4:1	95
3	R = Me	$ZnCl_2$ (3)	CH_2Cl_2	0	24	4:1	95
4	R = Me	ZnCl2 (3)	CH_2Cl_2	-20	36	5:1	95
5	R = Me	$FeCl_3$ (2)	CH_2Cl_2	-78~24	1	4:1	85
6	R = Me	$FeCl_3$ (2)	CH_2Cl_2	-55	21	5:1	95
7	R = H	$ZnCl_2$ (3)	CH_2Cl_2	24	13	3:1	31[b]

[a] The yields are for isolated products based on the amount of the starting material applied.

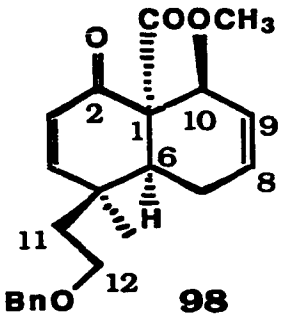
[b] The starting material was recovered in 65%.

observed that neither the solvent nor the catalyst used had a large influence on the distribution of products. The ratio of the products was generally improved by lowering the temperature. However, the

improvement was fairly small. The yields for these reactions were all excellent except when ferric chloride was used as a catalyst at room temperature in which case some decomposition occurred. The decomposition could be ascribed to the cleavage of the benzyl group of the dienophile or adducts, leading eventually to some side reactions such as cyclization involving the deprotected alcohol and the enone moiety.



87



98

The Diels-Alder adducts **87** and **98** were readily separated by flash chromatography. For the less polar major isomer **87**, the ir spectrum showed carbonyl absorptions at 1725 (C=O, ester) and 1690 cm^{-1} (C=O, enone). In the ^1H nmr spectrum (Table 2), the splitting pattern (ddd, J=10, 7, 2 Hz) of the C_6 proton at δ 2.75 clearly demonstrated that this isomer was an *ortho* adduct. The benzyl moiety was retained as indicated by a multiplet at δ 7.32 (5H) and two doublets at δ 4.52 (J=13 Hz) and 4.48 (J=13 Hz). Signals at δ 6.29 (dd, J=10, 2 Hz) and 5.91 (d, J=10 Hz) were attributed to the vinylic protons of the enone system. Two more vinylic protons were observed at δ 5.58 (ddd, J=10, 4, 2 Hz) and 5.50 (ddd, J=10, 7, 3 Hz) for the isolated double bond. A methoxy group appeared at δ 3.68. Other

methyl signals appeared at δ 1.22 (d, J=7 Hz) and 1.10 (s). In the ^{13}C APT nmr spectrum, a total of 20 signals were observed. Two carbonyl signals appeared at δ 196.33 and 174.54. Seven signals appeared in the region between δ 152.22 and 123.36. From the unusually high intensity of the signal at δ 127.57, it can be concluded that overlaps occurred for the benzene ring carbons. The high resolution mass spectrum showed a molecular ion peak at m/z 368.1980 corresponding to the required molecular formula $C_{23}H_{28}O_4$, which was also supported by the elemental analysis. For the more polar minor compound **98**, the ir spectrum showed carbonyl absorptions at 1726 (C=O, ester) and 1689 cm^{-1} (C=O, enone). In the ^1H nmr spectrum (Table 2), the doublet of doublets of doublets (J=10, 7, 2 Hz) observed for the C_6 proton at δ 2.68 suggested that this isomer was also an *ortho* adduct. The benzyl group appeared at δ 7.31 (m, 5H) and 4.50 (s, 2H). Signals at δ 6.29 (dd, J=10, 2 Hz) and 5.85 (d, J= 10 Hz) were attributed to the vinylic protons of the enone system. The other two vinylic protons resonated at δ 5.56 (ddd, J= 10, 4, 2 Hz) and 5.47 (ddd, J=10, 7, 3 Hz). The sharp singlet at δ 3.71 was ascribed to the methoxy group of the ester functionality. Two other methyl groups were observed at δ 1.26 (d, J= 7 Hz) and 1.15 (s). In the ^{13}C APT nmr spectrum, a total of 21 signals were observed. Among them, two carbonyl carbons appeared at δ 196.23 and 174.65; eight signals appeared between δ 152.03 and 123.37. The high resolutoin mass spectrum showed a molecular ion peak at m/z 368.1984 corresponding to the formula $C_{23}H_{28}O_4$, which was supported by elemental analysis.

Table 2. ^1H nmr data for adducts **87** and **98**

87			**98**	
δ (in ppm)	multiplicity (J in Hz)	proton	δ (in ppm)	multiplicity (J in Hz)
5.92	d (10)	H_3	5.85	d (10)
6.29	dd (10, 2)	H_4	6.29	dd (10, 2)
2.75	ddd (10, 7, 2)	H_6	2.68	ddd (10, 7, 2)
2.19	dm (18)	$H_{7\alpha}$	2.30	dddd (19, 7, 4, 3)
1.95	dm (18)	$H_{7\beta}$	2.02	dm (19)
5.50	ddd (10, 7, 3)	H_8	5.47	ddd (10, 7, 3)
5.57	ddd (10, 4, 2)	H_9	5.56	ddd (10, 4, 2)
2.83	m	H_{10}	2.75	m
1.78	dd (14, 7)	H_{11a}	1.93	ddd (14, 8, 6)
1.72	dd (14, 7)	H_{11b}	1.64	ddd (14, 8, 6)
3.58-3.66	m (2H)	H_{12}	3.54-3.66	m (2H)
3.69	s	OMe	3.71	s
1.10	s	C_5 Me	1.15	s
1.22	d (7)	C_{10} Me	1.26	d (7)

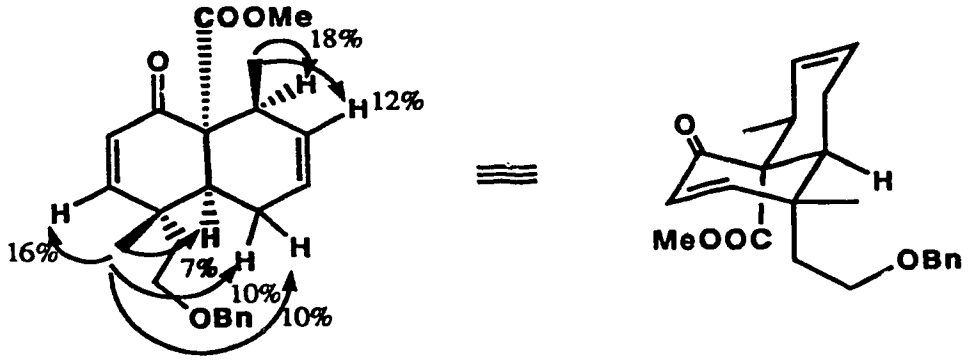


Figure 7 NOE experiment of compound **87**

To determine the stereochemistries of adducts **87** and **98**, extensive NOE experiments were carried out for both compounds. For the major compound **87**, irradiation of the C_5 methyl at δ 1.10 resulted in enhancements for H_4 (15.5%), H_6 (6.9%), $H_{7\alpha}$ (10.2%) and $H_{7\beta}$ (10.2%) (Figure 7). Irradiation of the C_{10} methyl resulted in 17.7% enhancement for H_{10} and 11.8% for H_9. Therefore, structure **87** was assigned to the major compound. As for the minor compound, irradiation of the C_5 methyl at δ 1.15 resulted in enhancements for the methoxy methyl (2.8%), the C_4 vinylic proton (8.4%), and the C_6 proton (10%) (Figure 8). No enhancements were observed for $H_{7\alpha}$ and $H_{7\beta}$. Irradiation of the C_{10} methyl group resulted in a 27.3% enhancement for H_{10} and a 14.1% enhancement for H_9. Structure **98** was therefore assigned to the minor product. At that time, the relative stereochemistry at the C_{10} position of **87** and **98** could not be confirmed based on the NOE experiments. The configuration of this center in each case was tentatively assigned based on the previously

observed preferential *endo*-to-ketone addition of *trans*-piperylene to several dienophiles resembling compound **90**. The structural assignments were substantiated by spectroscopic analyses of several more advanced intermediates including an X-ray analysis on compound **103** (vide infra).

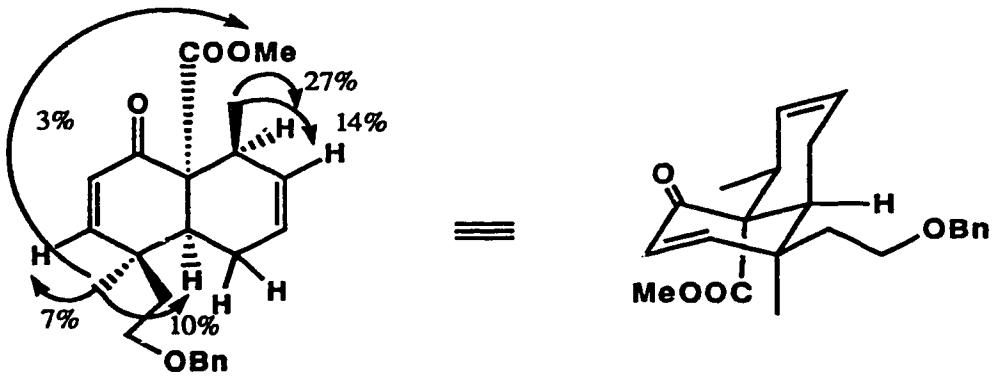
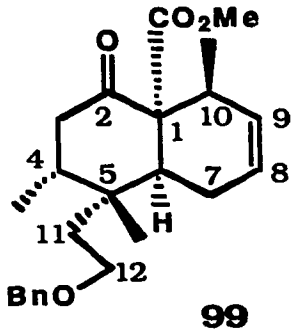


Figure 8 NOE experiment of compound **98**

Adduct **87** was used to carry on the synthesis of *cis*-clerodanes, since it possesses the required stereochemical arrangements. Those *cis*-clerodanes such as solidagolactones II-VIII, solidagoic acid A, and 6β-acetoxy-2-oxokilavenooi (**85**) as illustrated in Figures 4 and 6, were selected as our primary target molecules, with the latter compound **85** as the immediate synthetic target.

The next phases of the synthesis involve: (1) introduction of a methyl group to C_4; (2) conversion of the angular ester group into a methyl group; (3) isomerization of the C_8-C_9 double bond to the C_9-C_{10} position along with oxygenation at the C_8 position; (4) modification of the side chain. The C_4 methyl was introduced simply by a 1,4-

addition process in which compound **87** was treated with 3 equivalents of lithium dimethylcuprate in ether at 0°C for 1 h, resulting in a quantitative yield of the 1,4-addition product **99**. The ir spectrum of **99** showed an intense carbonyl absorption at 1718 cm^{-1}.



99

In the high resolution mass spectrum, the molecular ion peak appeared at m/z 384.2037, corresponding to the formula $C_{24}H_{32}O_4$. In the ^1H nmr spectrum (Table 3), signals corresponding to the vinylic protons of the enone moiety present in the starting material disappeared. A sharp singlet at δ 3.72 was attributed to the methoxy group. Three characteristic methyl groups resonated at δ 1.12 (d, J=7 Hz), 0.95 (s), and 0.89 (d, J=6.5 Hz). In the ^{13}C APT nmr spectrum, two carbonyl carbons were observed at δ 206.00 (ketone) and 174.83 (ester). Six signals for the olefinic and aromatic carbons were observed at δ 138.54, 130.28, 128.41, 127.73, 127.60, and 123.01. An NOE experiment was also carried out for **99** . Irradiation of the signal at δ 2.52 (H_{10}) resulted in a 5.6% enhancement for the C_6 proton, an 11.5% enhancement for the C_9 proton and a 4.3% enhancement for the C_{10} methyl (Figure 9). These results were in agreement with the assigned stereochemistry of C_{10}.

Table 3. ^1H nmr data for compound **99.**

Proton	δ (in ppm)	multiplicity (J in Hz)
$H_{3\alpha}$	2.14	m
$H_{3\beta}$	2.83	m
H_4	2.15	m
H_6	2.77	dd (10, 7)
$H_{7\alpha}$	2.13	m
$H_{7\beta}$	1.96	dddd (19, 10, 4, 2)
H_8	5.50	ddd (10, 6, 3)
H_9	5.57	ddd (10, 3, 2)
H_{10}	2.52	m
H_{11}	1.64-1.81 (2 H)	m
H_{12a}	3.73	m
H_{12b}	3.57	ddd (10, 9, 9)
OMe	3.72	s
$C_{10}Me$	1.12	d (7)
C_5Me	0.95	s
C_4Me	0.89	d (6.5)

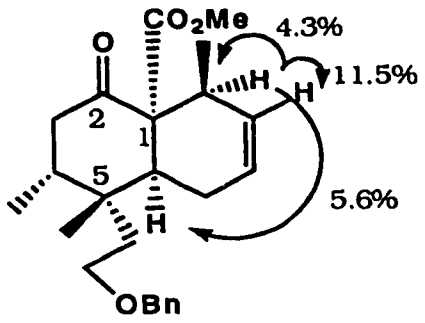
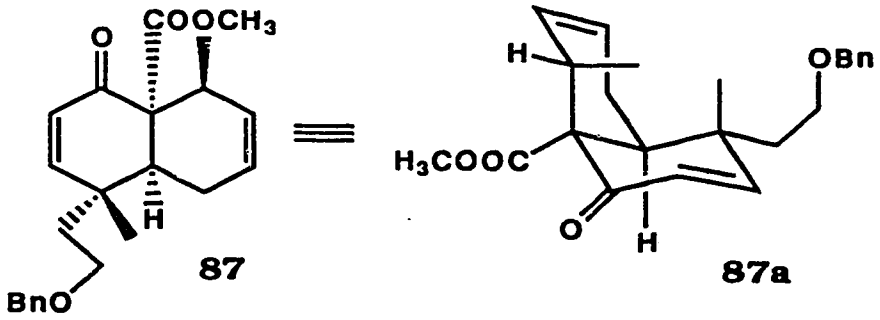


Figure 9 NOE experiment of compound **99**

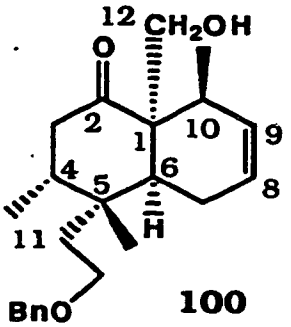
The stereochemistry of C4 could not be determined at this stage. It was later deduced by the X-ray analyses carried out on the advanced intermediates **103** and **122**. The complete stereoseletivity observed for the 1,4-addition reaction leading to keto ester **99** could well be the result of axial addition of lithium dimethylcuprate to confomer **87a** of the staring enone **87**.



The next phase of synthesis was to transform the carbomethoxyl group into the angular methyl. Standard operation involves its reduction to the aldehyde or alcohol level followed by deoxygenation. In the present case, this commonly used procedure presents a practical problem as a selective reduction of an ester group in the presence of a

more reactive ketone carbonyl is required. This problem was solved experimentally in the following manner.

Enone **87** was subjected to 1,4-addition with lithium dimethylcuprate under the conditions described previously. When the reaction was complete, an excess (3-5 eq.) of lithium aluminium hydride was added at -10°C. The resulting mixture was allowed to warm up to 0°C and kept at this temperature for 1 h. In this way the ensuing enolate from the 1,4-addition reaction served as an effective protection for the ketone carbonyl and the desired selective reduction of the ester group was easily implemented. Keto alcohol **100** thus obtained showed the absorption bands at 3448 and 1692 cm^{-1} in its ir spectrum indicating the formation of the hydroxyl group and the retention of ketone functionality. In the ^1H nmr spectrum (Table 4), two vinylic protons



100

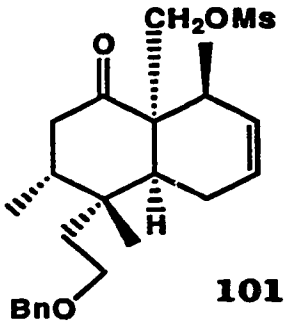
appeared at δ 5.85 and 5.75. Two signals at δ 3.58 (d, J=11 Hz) and δ 3.45 (d, J=11 Hz) were assigned to the methylene protons adjacent to the hydroxy group. A triplet at δ 3.55 (t, J=7 Hz) was attributed to the protons attached to the bnezyloxy-bearing carbon. Three methyl groups appeared at δ 1.10 (d, J=7 Hz), 0.97 (s) and 0.89 (d, J=6 Hz).

Table 4. ^{1}H nmr data for compound **100**

proton	δ (in ppm)	multiplicity (J in Hz)
$H_{3\alpha}$	2.35	dd (10.5, 10.5)
$H_{3\beta}$	2.14	m
H_4	2.14	m
H_6	2.00	t (7.3)
H_{7a}	2.07	m
H_{7b}	2.14	m
H_8	5.85	dt (10, 4.5)
H_9	5.75	dd (10, 5)
H_{10}	2.50	m
H_{11}	1.60	m (2H)
H_{12a}	3.57	d (11)
H_{12b}	3.45	d (11)

In the ^{13}C APT nmr spectrum, a total of 21 signals were observed. A carbonyl carbon appeared at δ 219.94. Six olefinic and aromatic carbon signals were present at δ 138.30, 132.20, 128.21, 127.65 and 126.60. Although the high resolution mass spectrum did not show the molecular ion peak, the chemical ionization mass spectrum displayed two peaks at m/z 374 and 357 corresponding to $[M+NH_4]^+$ and $[M+H]^+$, respectively. The elemental analysis also lent support to the desired molecular formula $C_{23}H_{32}O_3$.

In further studies, the hydroxyl group of keto alcohol **100** was removed via the corresponding mesylate prepared in quantitative yield using methanesulfonyl chloride and triethylamine. The ^1H nmr spectrum of keto mesylate **101** displayed two vinylic protons at δ 5.91 and 5.67 as multiplets. Two doublets for the methylene protons α to

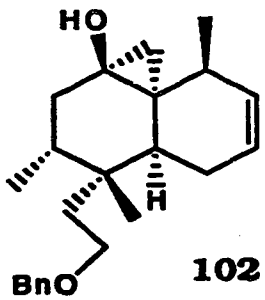


101

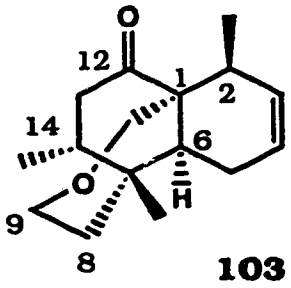
the mesylate functionality appeared at δ 4.51 and 4.04. The characteristic methyl signal of the mesylate group was shown at δ 2.96 as a sharp singlet. In the ir spectrum, a carbonyl absorption at 1701 cm^{-1} and two bands due to S=O at 1357 and 1176 cm^{-1} were observed. The high resolution mass spectrum gave a molecular ion

peak at m/z 434.2127, corresponding to the desired molecular formula $C_{24}H_{34}O_5S$. In its ^{13}C APT nmr spectrum, a total of 22 signals were observed. The resonance at δ 213.39 confirmed the presence of a ketone carbonyl carbon. Two olefinic and the phenyl carbons were displayed at δ 138.45, 130.93, 128.43, 127.80, 127.61, and 127.40.

Reduction of mesylate **101** with sodium iodide and zinc dust in *N,N*-dimethylformamide (DMF)[44] at 130°C gave rise to a 55% yield of cyclopropanol **102** and a 30% yield of tricyclic ketone **103**. In the IR spectrum of **102**, a broad and strong hydroxyl absorption appeared at 3436 cm^{-1} at the expense of the carbonyl absorption at around 1700 cm^{-1} previously observed for the starting compound **101**. In the ^1H nmr spectrum, a pair of doublets at δ 0.58 and 0.52 were assigned to the methylene protons of the cyclopropane ring. The benzyl group was retained as indicated by the signals at δ 7.32 (m, 5H) and 4.50 (s, 2H). Two vinylic protons appeared at δ 6.22 and 5.96 as multiplets. Methyl groups were observed at δ 1.08 (s), 1.06 (d, J=7 Hz), and 0.83 (d, J=7 Hz). The high resolution mass spectrum showed a molecular ion peak at m/z 340.2393, consistent with the molecular formula $C_{23}H_{32}O_2$.



102



103

In order to improve the yield of cyclopropanol **102**, a potentially useful intermediate for the next transformation, we have repeated the NaI/Zn reduction process more than twelve times by using different solvents, such as DMF, hexamethylphosphoramide (HMPA), 1,2-dimethoxyethane (DME), etc., and varying the reaction temperatures from 80 to 145°C. Experimental results showed that the conditions described earlier were the best. It should also be pointed out that the moist DMF containing *ca.* 0.15% of water gave the highest yield.

Ketone **103** was produced as a crystalline compound with a mp of 74.5-76.0°C after three recrystallizations from ethyl acetate/*n*-hexane. The ir spectrum of this tricyclic ketone showed a strong absorption at 1704 cm^{-1} for the ketone carbonyl. In the ^1H nmr spectrum, two vinylic protons were observed at δ 5.53 as a multiplet and the characteristic signals for the benzyl group were absent. Two neopentyl protons adjacent to the ether oxygen appeared at δ 4.21 and 3.61, each as a doublet. The other two protons adjacent to the ether oxygen atom were displayed at δ 4.00 as a multiplet. A molecular ion peak at m/z 248.1788 in the high resolution mass spectrum was in agreement with the molecular formula $C_{16}H_{24}O_2$.

Ketone **103** was subjected to X-ray crystallographic analysis. The crystal structure shown in Figure 10 made unambiguous the assignment of the configurations of the five contiguous stereogenic centers along C_1, C_4, C_5, C_6, and C_{10} present in **103** and its precursors.

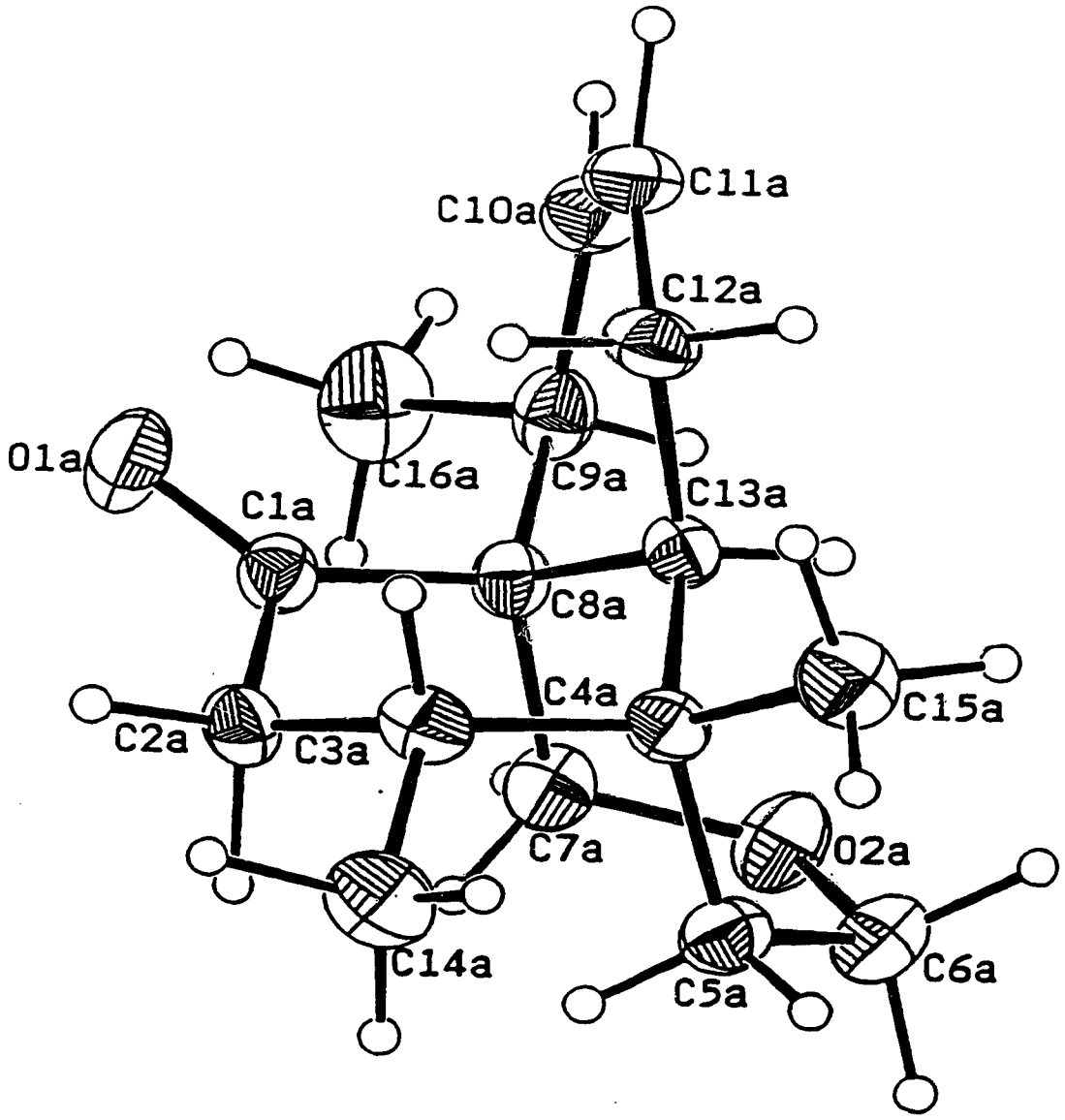
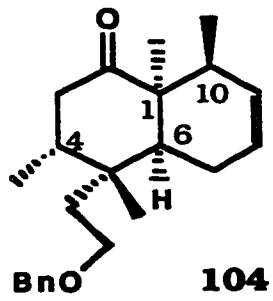


Figure 10. X-ray structure of compound **103**

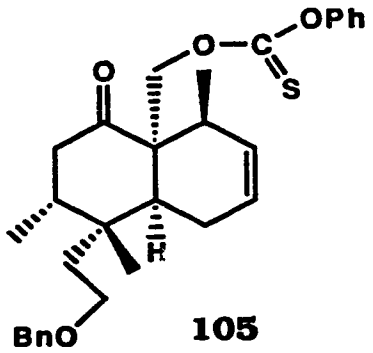
Upon exposure to a trace amount of *p*-toluenesulfonic acid in methylene chloride at room temperature, the cyclopropane ring of compound **102** underwent rapid cleavage to give the desired ketone **104** in quantitative yield. The ring opening could also be effected by treatment of cyclopropanol **102** with aqueous hydroxide in HMPA at 140°C, resulting in a 90% yield of the desired product. The ir spectrum of compound **104** showed a strong absorption at 1695 cm^{-1},



104

indicating the formation of the ketone functionality, which was also supported by the resonance at δ 217.10 in the ^{13}C APT nmr. In its high resolution mass spectrum, the molecular ion peak was shown at m/z 340.2390 in accordance with the formula $C_{23}H_{32}O_2$. In the ^{1}H nmr spectrum, the high field resonances of the cyclopropyl protons previously observed at δ 0.58 and 0.52 disappeared. Instead, a sharp singlet emerged at δ 1.27, attributable to the formation of the angular methyl group. Three other methyl groups were found at δ 1.00 (d, J=7 Hz), 0.98 (s) and 0.91 (d, J=6.5 Hz). Two vinylic protons were displayed at δ 5.85 and 5.74 as multiplets. The benzyl group was retained as indicated by the signals at δ 7.31 (m, 5H), and 4.50 (s, 2H).

Since the reductive removal of mesylate with zinc metal and sodium iodide led to the formation of the unexpected cyclopropanol **102** as well as a considerable amount of the tricyclic ketone **103**, several other approaches were explored in attempts to produce the desired ketone **104** more effectively. In one approach, keto alcohol **100** was converted to the corresponding thiocarbonate **105** in 72% yield by treatment with phenyl chlorothionoformate and pyridine in dichloromethane at room temperature. The ir spectrum of **105**



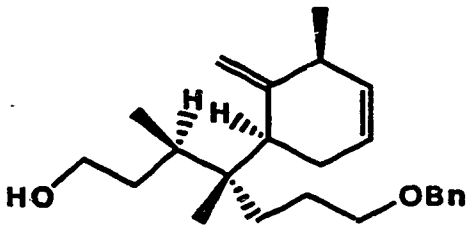
105

displayed a ketone carbonyl band at 1703 cm^{-1} and thionocarbonyl absorptions at 1290 and 1200 cm^{-1}. Its ^1H nmr exhibited signals at δ 7.30 and 7.00 for a total of ten aromatic protons. The methylene protons next to the phenyl thionocarbonate unit were observed at δ 4.67 (d, J=10.5 Hz) and 4.41 (d, J=10.5 Hz). The two benzylic protons were displayed at δ 4.43 as an intense singlet. Three methyl groups were shown at δ 1.00 (d, J=7 Hz), 0.98 (s), and 0.86 (d, J=7 Hz). Although the high resolution mass spectrum failed to register the molecular ion peak, the chemical ionization mass spectrum displayed

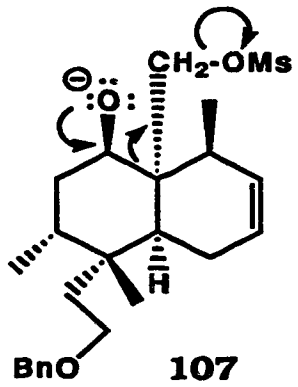
two peaks at 494 and 477, corresponding to $[M+NH_4]^+$ and $[M+H]^+$, respectively.

Subsequent reduction of compound **105** with tri-*n*-butyltin hydride in toluene at 80°C in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) gave, unfortunately, a complex mixture of products. As a result, this approach was abandoned and another route was then examined.

It was reported that hindered sulfonates could be reduced to the corresponding hydrocarbons with triethylborohydride (Super hydride).[45-48] When mesylate **101** was subjected to reduction using excess lithium triethylborohydride in tetrahydrofuran, a polar compound **106** was formed. This result was not totally surprising, since mesylate **101** could undergo Grob fragmentation induced by alkoxide formation as illustrated in formula **107**. The resulting



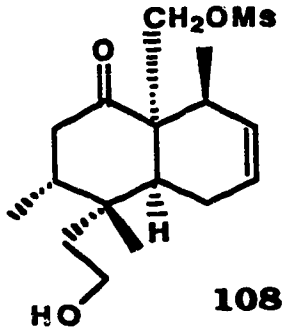
106



107

aldehyde could then undergo reduction to give alcohol **106**. Its ir spectrum showed a broad hydroxyl absorption at 3342 cm^{-1}. The ^1H nmr spectrum displayed two new vinylic protons at δ 4.97 (s) and 4.89 (s) in addition to the existing olefinic protons at δ 5.63 (m) and 5.41 (m). The benzyl group remained intact as shown by the aromatic and benzylic signals at δ 7.31 (m) and 4.48 (s). The high resolution mass spectrum failed to show the molecular ion, but a peak at m/z 274.1934, corresponding to the loss of a piperylene unit, was observed. In chemical ionization mass spectrum, two peaks appearing at m/z 343 and 360 were in accordance with $[M+H]^+$ and $[M+NH_4]^+$ units.

An attempt was also made to modify mesylate **101** before reduction. Upon treatment of mesylate **101** with ferric chloride[49] in dichloromethane at room temperature, the benzyl group was removed cleanly in forty minutes to provide the corresponding alcohol **108** in 77% yield. Its ir spectrum showed a strong carbonyl absorption at



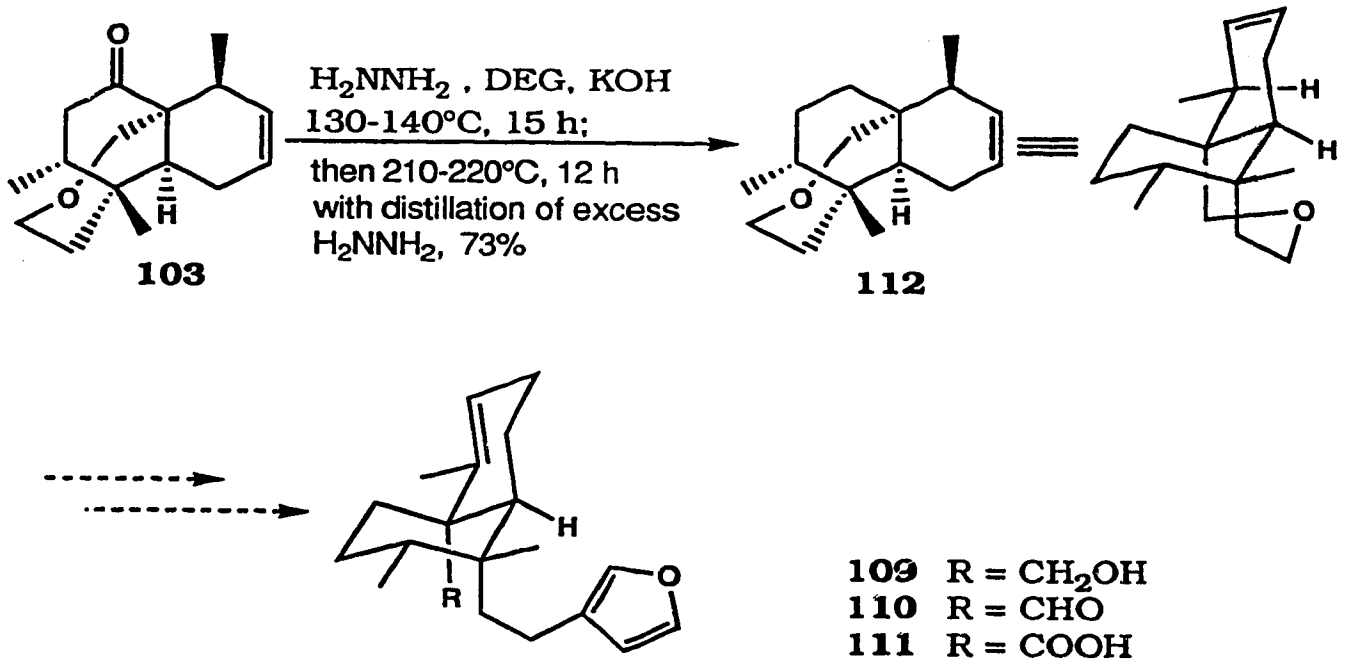
108

1701 cm^{-1} and a broad hydroxyl band at 3443 cm^{-1}. The absence of the benzyl unit in the ^1H nmr spectrum indicated that debenzylation had taken place. The methylene protons adjacent to the hydroxyl were shown at δ 3.79 and 3.59, each as a multiplet. The survival of the mesylate moiety was verified by its intense methyl singlet at δ 3.06 (s). No molecular ion peak was detected in the high resolution mass spectrum, but fragments were observed at m/z 326.1562 and 278.1777, corresponding to the loss of a H_2O and a CH_3SO_3H unit, respectively.

Alcohol **108** was subjected to reduction with zinc metal and sodium iodide under conditions described previously. Not unexpectedly, the reaction gave rise to the undesired cyclic ether **103** exclusively in 94% yield. This result indicated clearly an appropriate protection of the alcohol is necessary prior to the reduction step. This is under current investigation.

Although cyclic ether **103** was not useful for our immediate synthetic purpose, it is a rather interesting compound from a different prospect. The cyclic ether ring can be considered as an excellent protecting group for the angular hydroxymethyl group. It can also be regarded as a latent hydroxymethyl at C_1 and a haloethyl unit at C_5 upon cleavage with a number of halogen containing reagents, such as boron tribromide and trimethylsilyl iodide. As such, this compound **103** can serve as a highly useful synthetic intermediate for a large number of natural products of the *cis*-clerodane family possessing an oxygenated angular methyl group, such as solidago alcohol (**109**), solidago

aldehyde (**110**), and solidagoic acid A (**111**). To prepare these compounds from **103** (Scheme 14), the reduction of its ketone carbonyl to the hydrocarbon level is required. This transformation has been carried out using a Wolff-Kishner reduction process. Compound

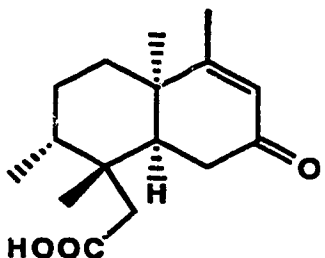


Scheme 14

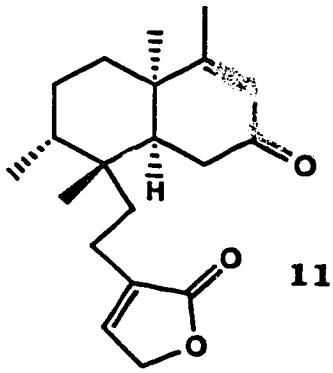
103 was treated with an excess of anhydrous hydrazine and potassium hydroxide in diethylene glycol at 130-140°C to form the corresponding hydrazone.[50] The reaction mixture was then heated at 220°C for 12 h with removal of water and excess hydrazine. The desired product **112** was obtained in 73% yield. Its ir spectrum showed the complete absence of carbonyl absorption. In the ^1H nmr spectrum, two vinylic protons were displayed at δ 5.60 (m) and 5.34 (m), similar to those present in the ^1H nmr spectrum of the starting

compound, suggesting that no migration of the double bond occurred during the reduction. A total of sixteen peaks were found in the ^{13}C APT nmr spectrum with olefinic carbons at δ 131.31 and 124.12 . The high resolution mass spectrum exhibited a molecular ion peak at m/z 234.1986, corresponding to the desired formula $C_{16}H_{26}O$. This approach to the naturally occurring compounds **109-111** is being continued in our laboratory.

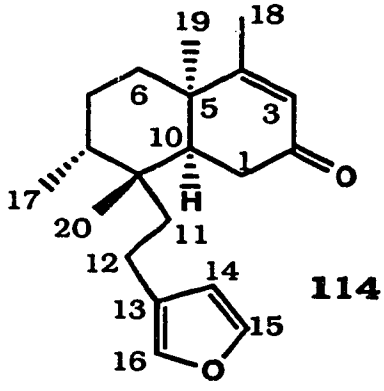
While improvements on the formation of ketone **104** were examined, the synthetic project was advanced using this compound prepared in five steps from dienone ester **90** (Scheme 15). In principle, ketone **104** can serve as a key intermediate for two groups of *cis*-clerodane diterpenes, one with an oxygen atom at C_6 (clerodane numbering), e.g. 6β-acetoxy-2-oxokolavenool (**85**), and the other without an oxygen atom at C_6 such as 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**86**) and its congeners **113** and **114**.[19] The total synthesis of compounds **85** and **86** have been accomplished in racemic form as follows.



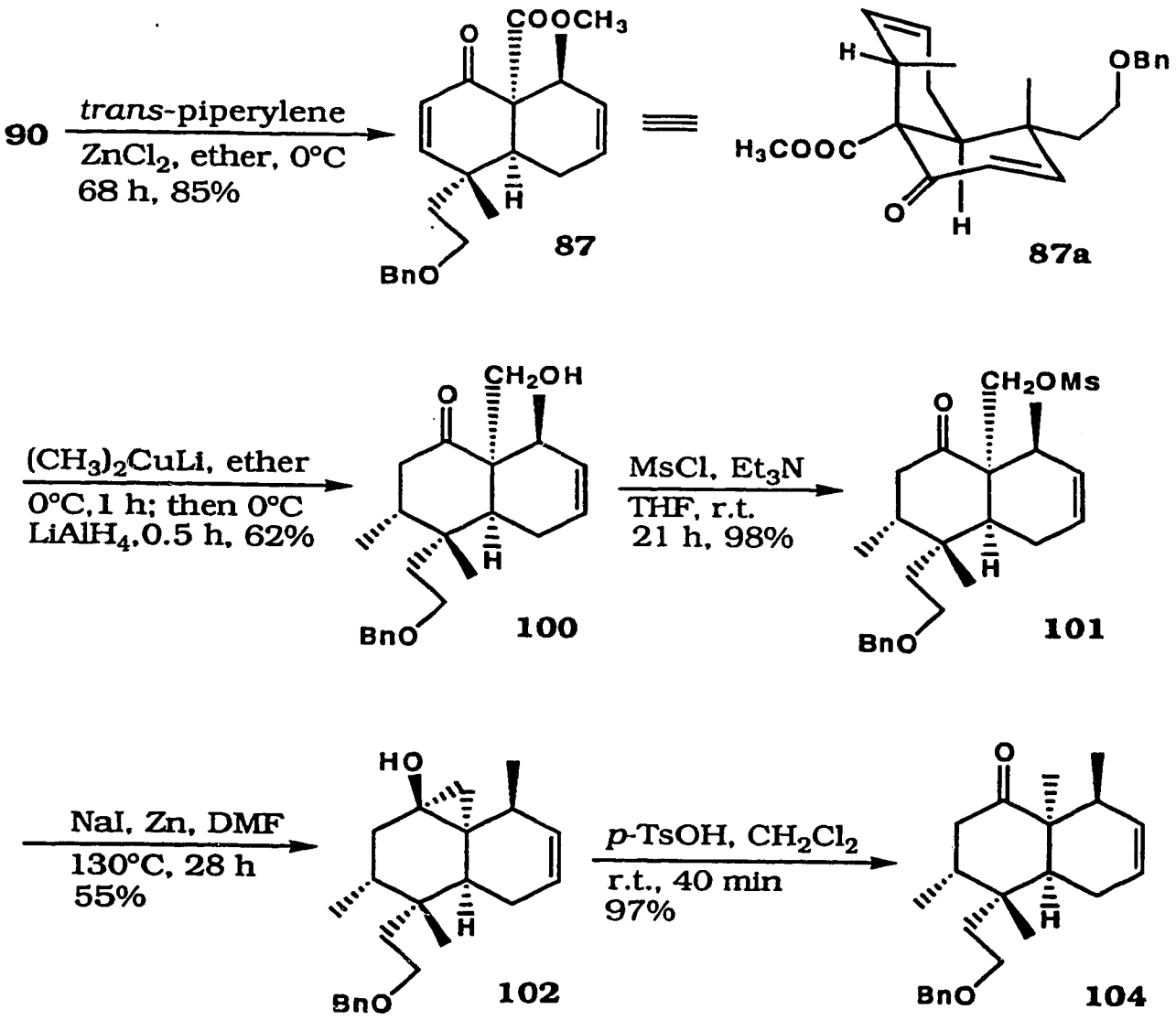
86



113



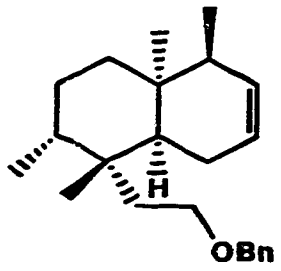
114



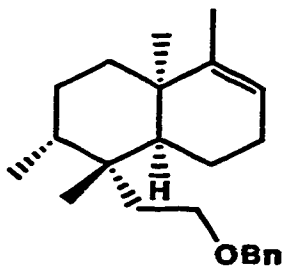
Scheme 15

Subjection of intermediate **104** to Woff-Kishner reduction under the same conditions effecting the transformation of **103** to **112** afforded a 3:1 mixture of two isomeric olefins **115** and **116** in 60% yield. The

ratio of these isomers were determined by ^1H nmr analysis based on the integrals of the vinylic protons at δ 5.57 (m) and δ 5.29 (m) for **115** and δ 5.32 (br m) for **116**. The benzyl group was intact as



115

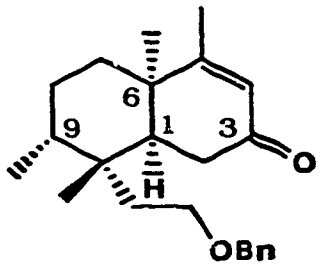


116

indicated by the aromatic protons at δ 7.32 and benzylic methylene protons at δ 4.55. The absence of the ketone carbonyl was clearly indicated by the ir spectrum. The high resolution mass spectrum did not show the molecular ion peak. A fragment due to the loss of a *trans*-piperylene unit was however present at 258.1983, corresponding to the formula $C_{18}H_{26}O$.

Subsequent photooxygenation[51] (tungsten lamps) of this mixture with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine in carbon tetrachloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine gave a 56% yield of enone **117** along with an unidentified product. Compound **117** displayed a strong ir absorption at 1662 cm^{-1} for an enone carbonyl. In its ^1H nmr spectrum, the resonance at δ 5.87 (br s) was assigned to the enone proton. The enone methyl group was observed at δ 1.95 (d, J=1.5 Hz) as a doublet

and the remaining three methyls were present at δ 1.25 (s), 0.97 (d, J=7 Hz) and 0.85 (s). The high resolution mass spectrum showed a



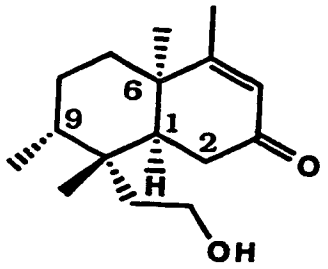
117

molecular ion peak at m/z 340.2400 in agreement with the desired molecular formula $C_{23}H_{32}O_2$.

The regiochemistry observed for the photooxygenation reaction was somewhat unusual. Instead of forming an enone system with a less substituted double bond following the "normal" regiochemical course of photooxygenation reaction,[51] the double bond moved towards the carbon center possessing a greater number of substituents. The unusual regiochemistry in the present case was nevertheless quite expectable based on the model studies on several structurally closely related compounds in this series. The results of these model studies will be discussed later.

Having compound **117** in hand, subsequent deprotection of **117** was carried out by treatment with ferric chloride (3 eq) in dichloromethane at room temperature. The desired compound **118** was obtained in 82% yield. The absence of signals due to the benzyl

group in the ^1H nmr spectrum revealed that debenzylation had occurred. The broad singlet at δ 5.89 (1H) and the doublet at δ1.96 (3H, J=1.5 Hz) were attributed to the enone proton and the vinylic methyl, respectively. Methylene protons α to the ketone showed resonances at δ 2.75 (1H, dd, J=18, 6 Hz) and δ 2.59 (1H, dd, J=18, 3Hz). Other methyl groups were observed at δ 1.27 (s), 1.11 (d, J=7 Hz), and 0.89 (s). Its high resolution mass spectrum displayed a molecular ion at m/z 250.1931, consistent with the expected molecular formula $C_{16}H_{26}O_2$. In the ir spectrum, two absorption bands at 3439 cm^{-1} and 1659 cm^{-1} were due to the hydroxy group and the enone carbonyl, respectively.



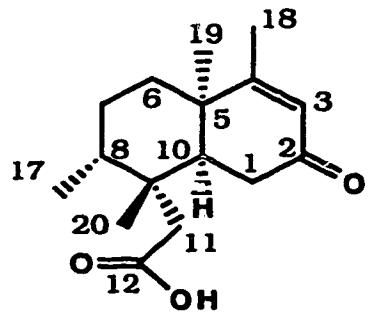
118

The final step of the synthesis of **86** from **118** requires the oxidation of its terminal hydroxy group to a carboxylic acid. This transformation was fulfilled by Jones oxidation. Treatment of **118** with Jones reagent in acetone at room temperature gave rise to the desired target compound **86** in 63% yield. The reaction occurred rapidly and green precipitates were observed during the oxidation process. In the ir spectrum, the broad band at 3300-2450 cm^{-1} along with a strong absorption at 1725 cm^{-1} indicated the presence of a carboxylic

functionality. The retention of an enone system was verified by a carbonyl absorption at 1628 cm^{-1}. The ^1H nmr spectrum also confirmed that oxidation had taken place. This was demonstrated by the resonances at δ 2.56 (1 H, d, J=15 Hz) and δ 2.21 (1 H, d, J=15 Hz) (recorded in chloroform-d using a 300 MHz instrument) due to the methylene protons α to the carboxylic group. The enone proton was found at δ 5.90 as a broad singlet. Its high resolution mass spectrum showed a molecular ion peak at m/z 264.1721, consistent with the molecular formula $C_{16}H_{24}O_3$. Fragments at m/z 249.1488 and 204.1509, due to the loss of a methyl and an acetic acid unit respectively, were also observed. The identity of the synthetic **86** and the natural material was established by a comparison of their ^1H nmr spectral data[19] shown in Table 5, collected, in each case, in chloroform-d solution containing a small amount of pyridine-d_5. Thus, the total synthesis of (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**86**) has been accomplished from ketone **104** in four steps as outlined in Scheme 16.

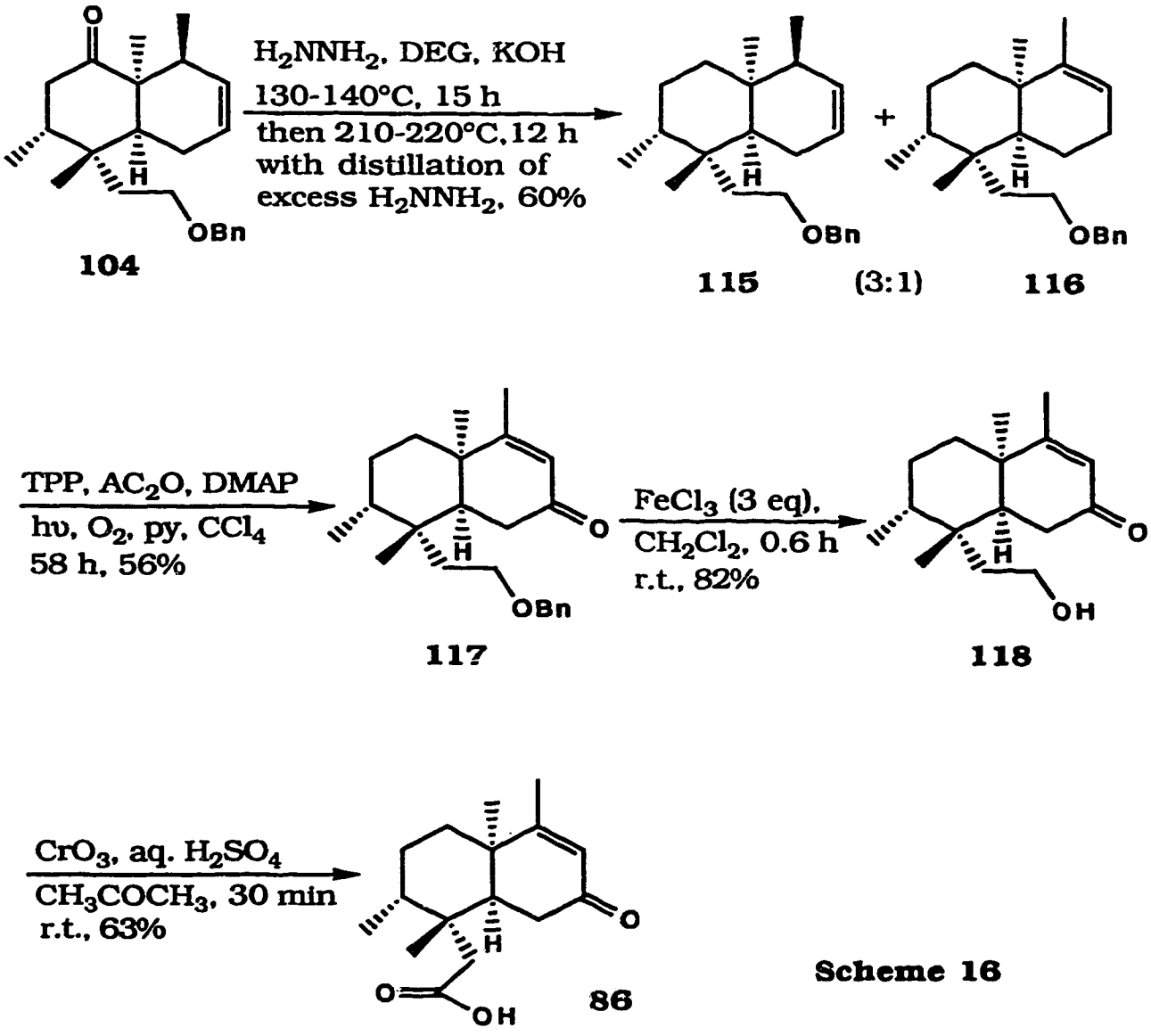
Towards the synthesis of 6β-acetoxy-2-oxokolavenool (**85**) which contains an oxygen functionality at C_6 (clerodane numbering), ketone **104** was subjected to reduction using lithium aluminium hydride in tetrahydrofuran at 0°C. Alcohol **119** was obtained in virtually quantitative yield as a single stereoisomer. The stereochemistry of newly generated chiral center could be tentatively assigned as shown, assuming that the hydride ion was delivered from sterically less hindered convex face of the starting compound **104**. This assignment was substantiated by the ^1H nmr spectrum which showed a broad

Table 5. ^{1}H nmr data of synthetic **86** and 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid



Natural (100 MHz, $CDCl_3$-C_5D_5N)		Synthetic (200 MHz, $CDCl_3$-C_5D_5N)		
δ (ppm)	(multiplicity; J in Hz)	proton	δ (ppm)	(multiplicity; J in Hz)
2.52	(dd; 18, 3)	H_{1a}	2.54	(dd; 18, 2.5)
2.82	(dd; 18, 6)	H_{1b}	2.79	(dd; 18, 6.5)
5.90	(br s)	H_3	5.90	(br s)
		H_{10}	2.13	(dd; 6.5, 2.5)
2.61	(d; 15)	H_{11a}	2.59	(d; 15)
2.22	(d; 15)	H_{11b}	2.24	(d; 15)
1.11	(d; 8)	H_{17}	1.09	(d; 7.5)
1.97	(br s)	H_{18}	1.97	(d; 1)
1.28	(s)	H_{19}	1.29	(s)
1.15	(s)	H_{20}	1.13	(s)
7.70	(br s)	$COO^{\ominus}\ C_5D_5NH^{\oplus}$ [a]	3.06	(br s)

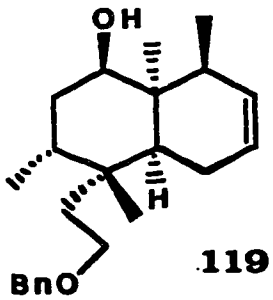
[a] This acidic proton is solvent and concentration dependent.



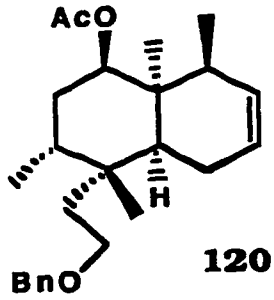
Scheme 16

singlet at δ 3.71 for the methine proton adjacent to the hydroxyl group. The half width of this singlet was found to be 7 Hz, suggesting

an equatorial orientation of the proton. In agreement with the structural assignment, the ^{1}H nmr spectrum also displayed the benzyl group with a multiplet at δ 7.33 and a pair of doublets (J=12 Hz each) at δ 4.55 and 4.49. Vinylic protons appeared at δ 5.79 (m) and 5.56 (ddd, J=10.5, 2 Hz). The ir spectrum showed a broad hydroxyl absorption at 3487 cm^{-1}. No ketone carbonyl absorption was detected. The ^{13}C APT nmr spectrum also revealed the disappearance of the ketone functionality and showed a total of 21 signals with chemical shifts lower than 140 ppm. Although the molecular ion peak was not found in the high resolution mass spectrum, a fragment at m/z 274.1927 due to the loss of a *trans*-piperylene unit (C_5H_8) was observed.



119



120

To verify the structure of **119**, it was subjected to acetylation using acetic anhydride in pyridine in the presence of a small amount of 4-dimethylaminopyridine. Interestingly, the reaction proceeded very slowly. Even at refluxing temperature, only 10% conversion was observed over a long period of 26 h. This result indicated that the hydroxy group was highly hindered as one would expect from the depicted stereochemistry. The ir spectrum of compound **120** showed a strong absorption at 1733 cm^{-1} indicating the presence of an ester

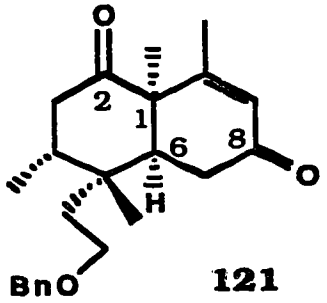
group. In the ^1H nmr spectrum, the acetate moiety was observed at δ 1.94 as an intense singlet. The adjacent proton appeared at δ 4.72 as a broad singlet. The half width of this singlet was found again to be 7 Hz, in agreement with a pseudo-axial orientation of the acetate unit.

At this stage, a series of experiments were carried out in order to determine suitable conditions for the migration of the carbon-carbon double bond with regiochemical control. Migration of the double bond present in alcohol **119** to the Δ^9 position is crucial to the successful synthesis of the target molecule **85**. Similar migration of the double bond in a suitable intermediate is also required for the synthesis of the natural acid **86** (*vide supra*). On the other hand migration of the double bond to the C_7 position may provide useful intermediates for the construction of a number of other diterpenoids of the *cis*-clerodane family (*vide infra*).

One good method for the migration of the carbon-carbon double bond with concomitant incorporation of an allylic oxygen functionality, which is highly desirable for our synthetic purpose, is the photooxygenation process. Ketone **104** and alcohol **119** which are potential synthetic intermediates towards **85**, were selected for the model studies.

A solution of **104**, acetic anhydride, pyridine, tetraphenylporphine and 4-dimethylaminopyridine in carbon tetrachloride was bubbled with a gentle stream of oxygen and irradiated with two 200W tungsten lamps for 56 h. After flash chromatography and recrystallization from ethyl

acetate/n-hexane, enedione **121** was obtained in 90% yield. Compound **121** appeared as colorless crystals and displayed a mp of 102-103 °C. The ir spectrum of this compound showed absorptions at 1711 cm^{-1} for the ketone carbonyl group and 1667 cm^{-1} for the enone carbonyl. In the ^{1}H nmr spectrum the resonances at δ 5.96 (q,



121

J=1.5 Hz) and δ 1.74 (d, J=1.5 Hz) were assigned to the enone proton and the vinylic methyl, respectively. The presence of an enone was also comfirmed by the ^{13}C APT nmr spectrum which displayed signals at δ 197.47 (enone carbonyl) and 160.86 (β-carbon of the enone). The high resolution mass spectrum showed a molecular ion peak at m/z 354.2205, corresponding to the expected molecular formula $C_{23}H_{30}O_3$, which was also supported by the elemental analysis data.

Recrystallization of this compound from ethyl acetate/*n*-hexane produced colorless needle shaped crystals which were suitable for X-ray diffraction analysis. The crystal structure shown in Figure 11 clearly demonstrated that the enone system of **121** was arranged in such a way with the double bond at the Δ^9 position.

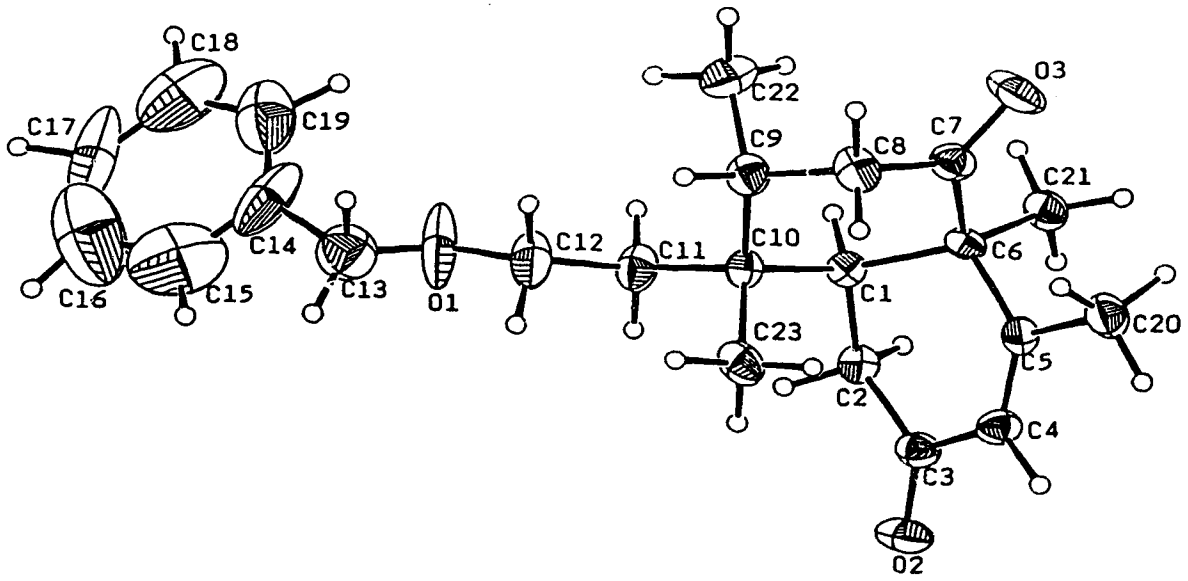
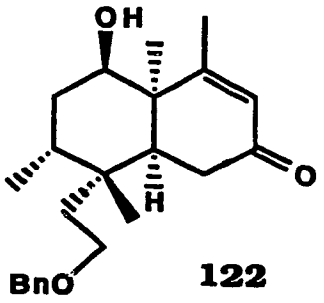
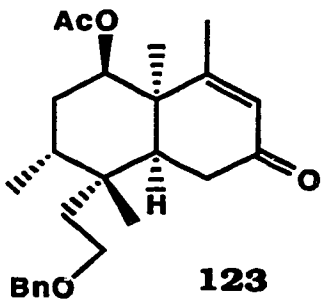


Figure 11. The three dimensional X-ray crystallographical structure of compound **121**

Similarly, when compound **119** was subjected to photooxygenation under the conditions described above for 23 h, enone alcohol **122** and enone acetate **123** were obtained in 60% and 15% yield, respectively. Compound **122** was completely converted to **123** by treatment with pyridine and acetic anhydride in dichloromethane at room temperature within 20 min. This result obviously revealed that the hydroxy group of **122** is much less hindered than that of the starting compound **119** in which the double bond is at Δ^8 position. For compound **122**, the ir spectrum showed absorption at 3448 cm^{-1} for the hydroxyl and 1653 cm^{-1} for the enone carbonyl. In the ^1H nmr spectrum, the enone proton resonated at δ 6.01 as a broad singlet. The methine proton next to the hydroxy group was observed at δ 3.84



122



123

as a broad singlet with a half width of 8 Hz, indicating its equatorial orientation. Although the high resolution mass spectrum did not display the molecular ion peak, a fragment at m/z 338.2247 due to the loss of a H_2O molecule was present. As for compound **123**, its ir spectrum showed two strong carbonyl absorptions at 1736 cm^{-1} (C=O, ester) and 1667 cm^{-1} (C=O, enone). The high resolution mass spectrum displayed the molecular ion peak at m/z 398.2465, supporting the correct molecular formula $C_{25}H_{34}O_4$. The presence

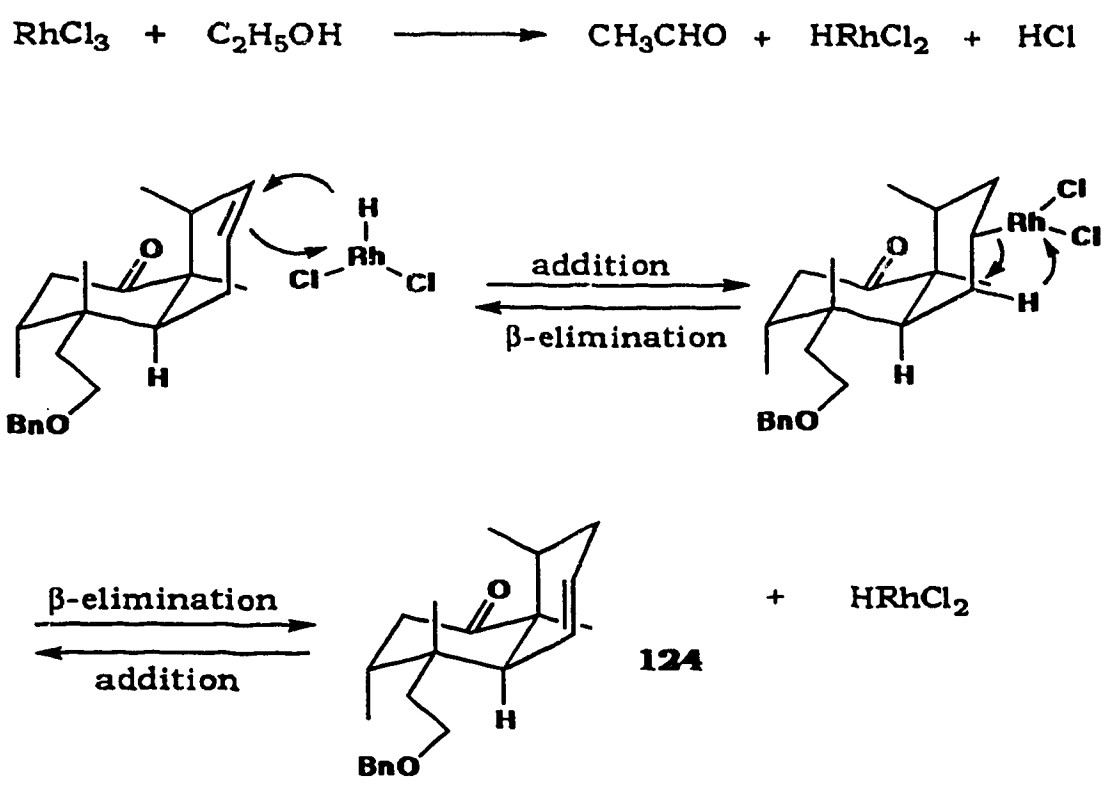
of the enone system was further confirmed by the singlets at δ 5.93 for the enone proton and δ 1.91 for the vinylic methyl group in the ^1H nmr spectrum. The proton adjacent to the acetate functionality was observed at δ 5.06 as a doublet of doublets (J=4.5, 2 Hz) and the rather small coupling constants again suggested the equatorial orientation of the proton. Remarkably, the above photooxygenation reactions are very sensitive to "solvent effect". When dichloromethane, also a common solvent for photooxygenation reaction, instead of carbon tetrochloride was applied, no reaction was observed even after an extended period of reaction time. The reason for this effect remains unclear, but the longer lifetime of singlet oxygen in carbon tetrachloride seems to be an important factor.

Carbon-carbon double bond migration can also be effected directly by a number of reagents including Brønsted acids, iodine[52] and transition metal complexes[53-56] such as rhodium(III) trichloride. These reagents were explored using ketone **104** and keto alcohol **100** as model compounds.

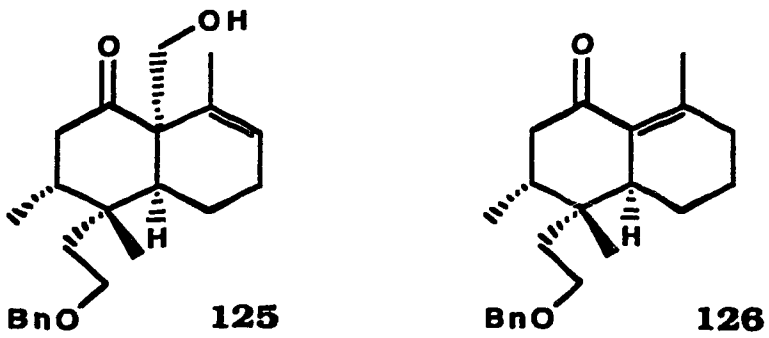
When compound **104** was treated with iodine in refluxing bezene, no reaction took place and the starting material was recovered intact. Identical result was obtained when ketone **104** was subjected to treatment with anhydrous *p*-toluenesulfonic acid in refluxing benzene or 1.2-dichloroethane over a long period of time. On the other hand, treatment of ketone **104** with rhodium(III) trichloride hydrate in refluxing ethanol for 8 h gave a single product in 92% yield. Interestingly, this product was characterized as Δ^7-olefin **124**,

showing two vinylic protons at δ 5.85 (m, 1 H) and 5.64 (dddd, J=11, 3, 1.5, 1.5 Hz, 1 H), instead of the expected Δ^9-isomer which is likely to be thermodynamically more stable. A rationale for this unexpected migratory aptitude is schematically depicted in Scheme 17. It is very likely that the migration of the double bond is controlled by the addition of the rhodium hydride species $HRhCl_2$ generated in *situ* to the sterically less hindered C8 carbon resulting in an equilibrium between the starting ketone **104** and the product **124**. It turns out that, between these two disubstituted olefins, isomer **124** is thermodynamically more stable.

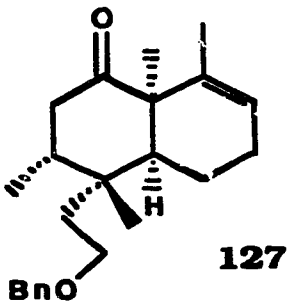
Interestingly enough, when ketone alcohol **100**, which contains an angular hydroxymethyl group instead of a methyl group as in ketone **104**, was treated with rhodium(III) trichloride (25 mole%) in rufluxing ethanol for 40 min, a 55% yield of the isomeric keto alcohol **125** was produced resulting from the migration of the double bond towards the more substituted carbon. A small amount (30%) of enone **126** was also isolated, apparently as a result of a concomitant retro-aldol reaction. Keto alcohol **125** was readily characterized by its ^1H nmr spectrum, in which the methyl doublet (δ 1.10, J=8 Hz) of the starting compound **100** was replaced by the vinylic methyl singlet at δ 1.55. As well, a single olefinic proton was observed at δ 5.45 as a multiplet in place of the signals at δ 5.75 and 5.85 for the vinylic protons of compound **100**. The interesting changeover of the migratory aptitude of the double bond could be rationalized by invoking the assistance, via complexion, of the hydroxyl group in the delivery of the rhodium hydride species to the C9 position.


RhCl3 + C2H5OH
CH3CHO + HRhCl2 + HCl
addition
β-elimination
β-elimination
addition
+ HRhCl2
124
BnO
H
Cl
Rh
O

Scheme 17


OH
O
H
BnO
125
126

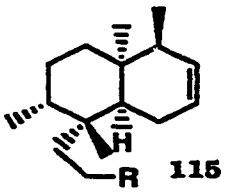
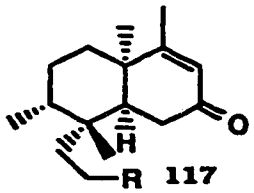
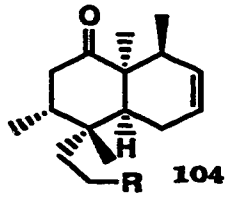
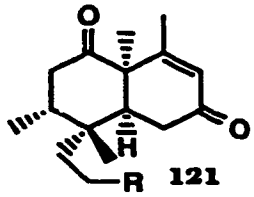
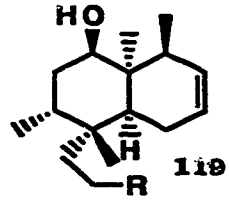
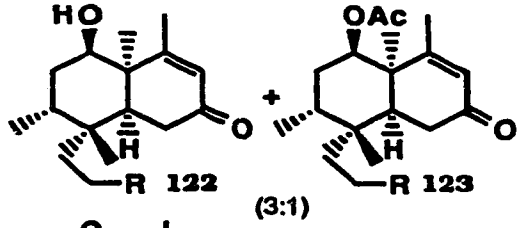
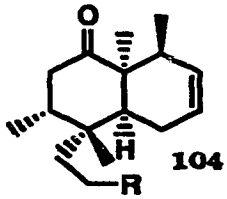
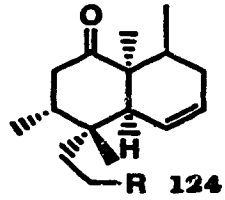
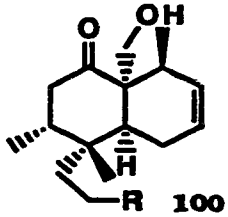
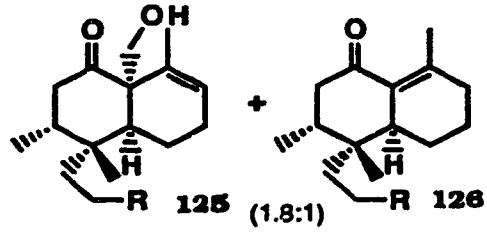
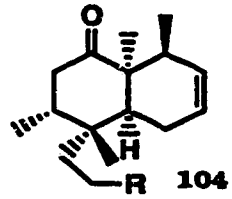
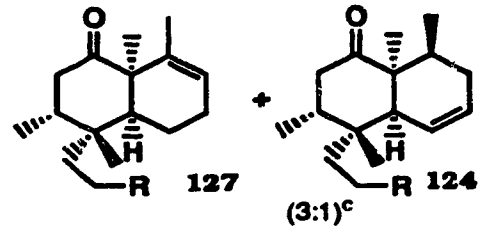
In another experiment, ketone **104** was treated with the acid exchange resin Amberlyst 15 in refluxing bezene . After 42 h, two isomeric compounds **127** and **124** were obtained in 81% yield in a ratio of 3:1 in favor of the former isomer. These isomers were found to be inseparable. The ^1H nmr spectrum showed two sets of signals. The minor signals were found to be identical with those of pure **124**. The major set contains a vinylic methyl signal at δ 1.52 (dd, J=3, 2 Hz) and a multiplet at δ 5.62 for a single vinylic proton, in agreement with structure **127**.



127

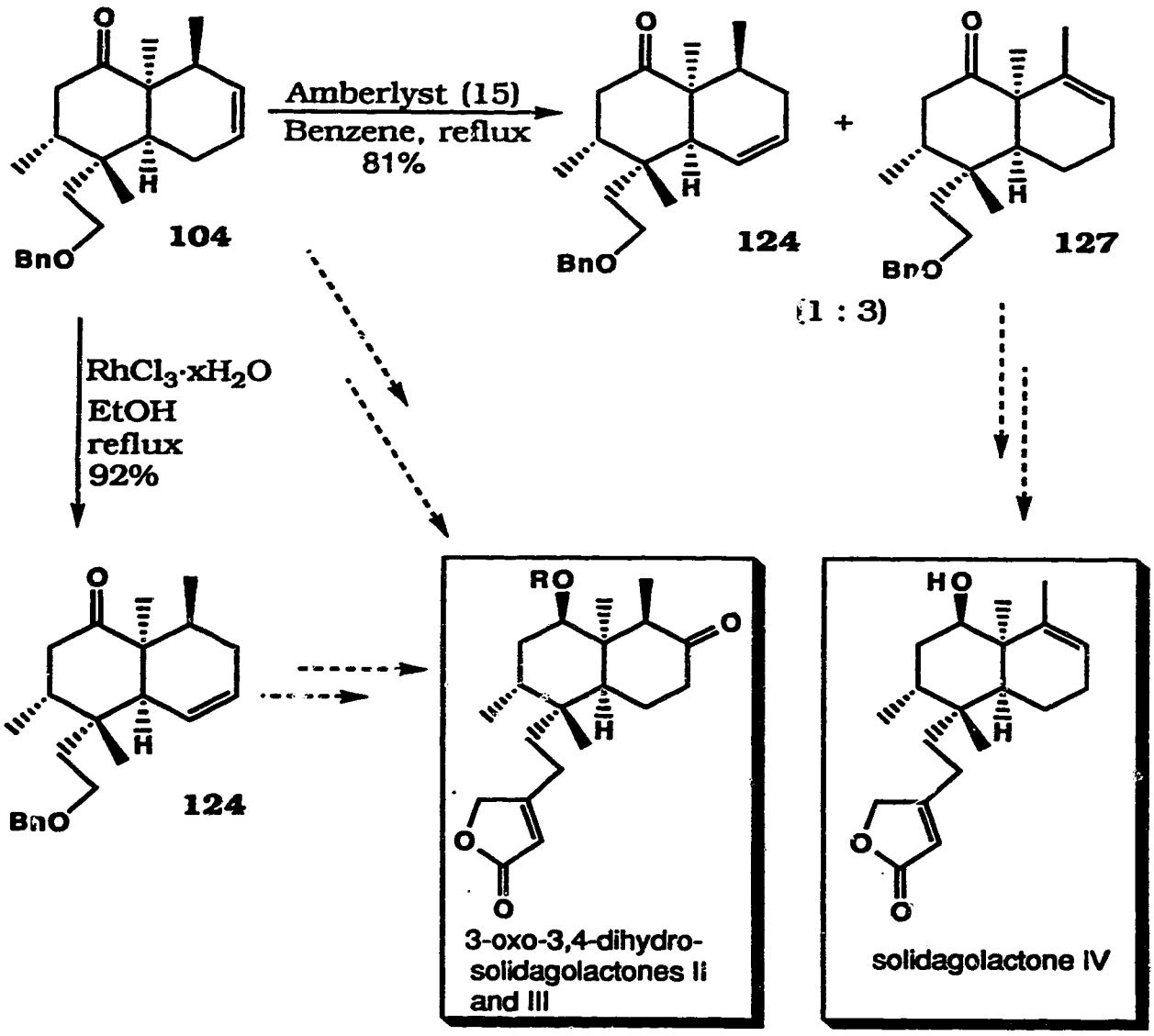
As shown in Table 6 which summarizes all the positive results obtained from the isomerization experiments, the double bond can be installed at various positions, virtually at will, under controlled conditions with several synthetic intermediates. This synthetic aspect is of considerable importance as it provides a higher degree of flexibility for the adaptation of the current synthetic approach to *cis*-clerodane diterpenoids. For instance, compounds **124** and **127** can, in principle, serve as advanced intermediates towards the synthesis of 3-oxo-3,4-dihydro-solidagolactones II, III and solidagolactone IV, respectively (Scheme 18).[57,58]

Table 6. The double-bond isomerization of several synthetic intermediates

compound[a]	condition	time (h)	yield (%)[b]	product (ratio)
 115	O_2, TPP, CCl_4 Ac_2O, DMAP, py, r.t., hυ	56	56	 117
 104	"	56	90	 121
 119	"	52	80	 122 + 123 (3:1)
 104	$RhCl_3 \cdot xH_2O$[d] EtOH, reflux	8	92	 124
 100	"	0.7	85	 125 + 126 (1.8:1)
 104	Amberlyst 15 PhH, reflux	42	81	 127 + 124 (3:1)[c]

[a] R = OBn. [b] The yields are isolated yields based on the starting material applied.

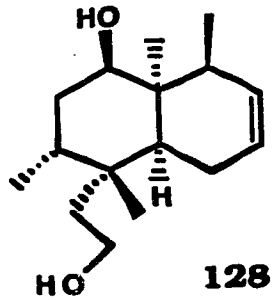
[c] The ratio was determined by ^1H nmr. [d] 25 mole %.


Amberlyst (15)
Benzene, reflux
81%
104
124
127
(1 : 3)
RhCl3·xH2O
EtOH
reflux
92%
124
3-oxo-3,4-dihydro-
solidagolactones II
and III
solidagolactone IV

Scheme 18

To complete the projected total synthesis of 6β-acetoxy-2-oxokolavenool (**85**) from alcohol **119**, two major operations are necessary: (1) modification of the C_5 side chain involving the incorporation of a 1-hydroxy-1-methyl-2-propenyl unit, and (2) to install an enone system using the existing double bond. Based on the previous experience, we were confident that the enone system could be introduced by a photooxygenation process. In order to minimize the functional groups in each synthetic stage, the former transformation was first explored.

Towards this end, alcohol **119** was subjected to debenzylation with lithium metal and ethylamine. The reduction was complete in 1 h, furnishing the corresponding diol **128** in 90% yield. In the ^1H nmr spectrum, the absence of any benzyl proton signals indicated that cleavage of the benzyl group had occurred cleanly. This was also



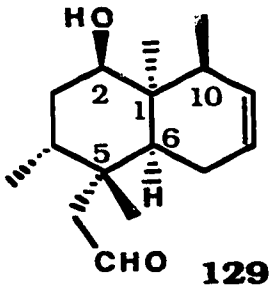
128

evident from the resonances at δ 3.87 (ddd, J=11, 11, 5.5 Hz) and 3.75 (ddd, J=11, 11, 5.5 Hz) due to the methylene protons next to the newly formed hydroxyl. Additional evidence was provided by the ir spectrum with a strong absorption band at 3387 cm^{-1} for hydroxyls.

The high resolution mass spectrum displayed a molecular ion peak at m/z 252.2089, in agreement with the expected molecular formula $C_{16}H_{28}O_2$.

The next crucial step according to the synthetic scheme was to oxidize the primary hydroxyl of diol **128** selectively to form an aldehyde.[59-63] Most of the commonly applied oxidizing agents oxidize the primary and secondary alcohols at comparable rates with preference for the secondary one. Several methods have been reported that permit the oxidation of secondary alcohols[64-66] in the presence of primary ones. There are only few efficient methods available for the preferential oxidation of primary alcohol over a secondary one. Among these, $RuCl_2(PPh_3)_3$-benzene system has been reported to be highly effective for the selective oxidation of primary hydroxyls. Thus, the use of this reagent was investigated.

Diol **128** was subjected to oxidation with dichlorotris-(triphenylphosphine)ruthenium (0.8 eq) in dry benzene at room temperature. The reaction was found to be very clean but quite slow. After 48 h, only 65% conversion took place. However, the desired hydroxy aldehyde **129** was produced virtually as the only product in 89% yield based on the consumed starting material. The reaction rate did not show any significant improvement over an extended period of reaction time (4 days) with additional $RuCl_2(PPh_3)_3$ (2 eq).



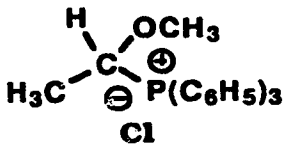
129

The ^{1}H nmr spectrum of compound **129** displayed an aldehydic proton at δ 9.98 as a doublet of doublets (dd, J=4, 1.5 Hz), indicating that the oxidation of the primary alcohol had taken place. That the secondary hydroxyl remained intact was suggested by the resonance at δ 3.75 (dd, J=4.5, 3Hz) for its neighboring proton. The ir spectrum showed two strong absorption bands at 3488 and 1717 cm^{-1}, characteristic of hydroxy group and aldehyde carbonyl. The presence of the aldehyde moiety was further verified by the absorption band at 2734 cm^{-1} in the ir spectrum and the signal at δ 204.52 in the ^{13}C APT nmr spectrum. The high resolution mass spectrum did not show the molecular ion peak, but two fragments due to the loss of H_2O and CH_3CHO molecules were present at m/z 232.1823 and 206.1673.

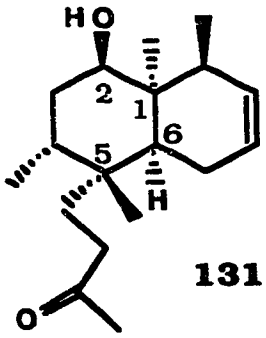
In order to confirm the structure of **129** unambigously, correlation with diol **128** was made by reduction of the aldehyde functionality with sodium borohydride in methanol. The product was identical with the starting compound **128** in all respects.

The introduction of the required "butenol" unit began with a Wittig reaction. α-Methoxyethyltriphenyl phosphonium chloride (**130**)[67] was deprotonated with *n*-butyllithium in THF at -78°C to form the

corresponding ylide, resulting in a blood-red solution. Upon treatment with this Wittig reagent at -40°C for 10 h, hydroxy aldehyde **129** was converted to an unstable enol ether which, without purification, was hydrolyzed in a mixture of aqueous 15% perchloric acid and distilled ether (1:1 ratio) at 0°C. After 1.5 h, the desired product **131** was formed in 66% yield. This compound showed absorption bands at 3572 cm^{-1} (OH) and 1714 cm^{-1} (C=O) in the infrared spectrum. In the high resolution mass spectrum, a molecular ion peak at m/z 278.2233 verified the molecular formula $C_{18}H_{30}O_2$. The structure was further substantiated by the ^1H nmr spectrum, which showed two multiplets at δ 5.80 and 5.56 for two vinylic protons, a singlet at δ 2.14 for the acetyl group, and four additional methyl groups at δ 1.13 (d, J=7.5 Hz), 1.06 (s), 0.92 (s) and 0.83 (d, J=7 Hz).



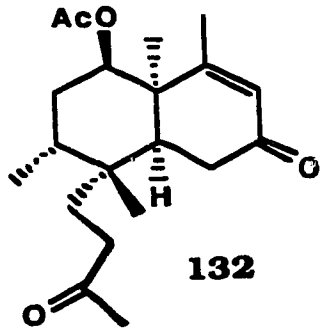
130



131

At this stage, the incorporation of the enone moiety present in the target molecule **85** was carried out via a photochemical process. Photooxygenation of **131** with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine in carbon tetrachloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine gave, as expected, the enone **132** in 61% yield. Compound **132** displayed three distinct carbonyl

bands at 1742, 1721 and 1671 cm^{-1}, corresponding to ester, ketone and enone, respectively. The high resolution mass spectrum showed a molecular ion peak at m/z 334.2134, consistent with the required molecular formula $C_{20}H_{30}O_4$, and a fragment at m/z 274.1925 due to the loss of a CH_3COOH molecule. In the ^1H nmr spectrum, the enone proton appeared at δ 5.95 as a broad singlet, whereas another broad singlet at δ 5.08 was due to the proton attached to the acetate-bearing



132

carbon. Three low-field methyl singlets were present at δ 2.19, 1.93 and 1.96. The former was due to the acetyl group and the latter were attributed to the vinylic methyl and the acetoxy group. Other characteristic signals included a singlet at 1.33 for the C_5 (clerodane numbering) methyl and a dwarf broad singlet at δ 0.96 responsible for both the C_8 and C_9 methyls .

The final step of the synthesis was to introduce a vinyl group to the saturated ketone carbonyl. Vinylmagnesium bromide was initially used to effect this transformation. It was envisioned that magnesium ion could coordinate with the two ketone carbonyl groups of compound **132** to facilitate the delivery of the vinyl group via path a (Figure 12) to

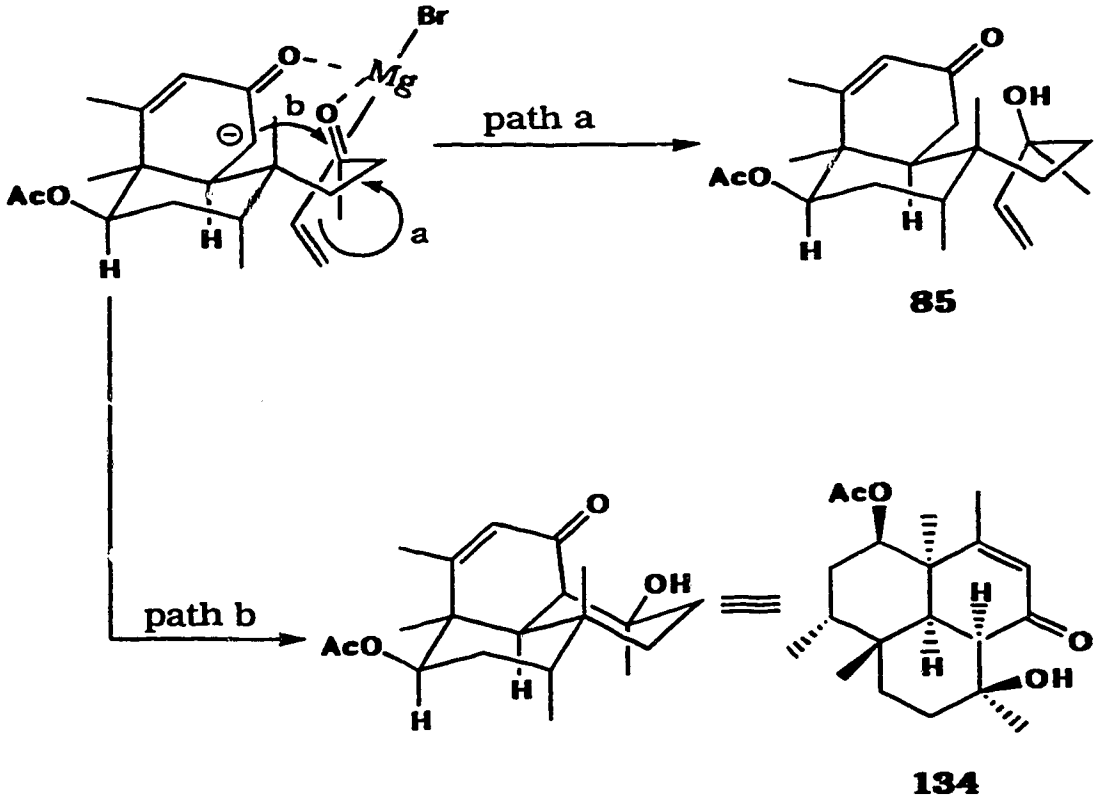
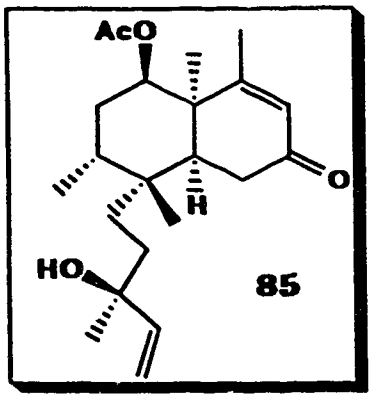
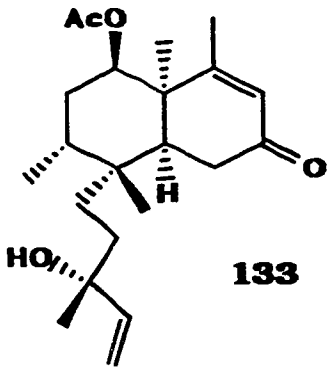


Figure 12 A proposed mechanistic pathway to **85** via 1,2-addition



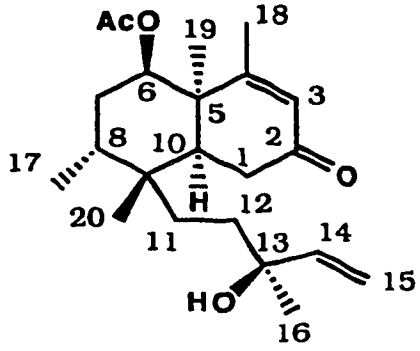


afford the desired compound **85**. Addition of vinylmagnesium bromide (2 eq) to compound **132** in THF was carried out at -20°C. After 30 min at -20°C and 3 h at 0°C and chromatographic purification, a mixture of two diastereomers **85** and **133** (1.5:1 by ^{1}H nmr analysis) was obtained in 40% yield along with a less polar product **134** (35% yield). Compounds **85** and **133** (1.5:1) appeared as a single spot on thin layer chromatography and could not be separated by flash chromatography. However, by a single preparative thin layer chromatography the ratio was enhanced from 1.5:1 to 4:1 in favor of the desired isomer **85**. Due to the limited quantity of the material, a further separation of these two epimers could not be carried out. The mixture of **85** and **133** showed a close resemblance to natural (+)-6β-acetoxy-2-oxokolavenool (**85**) in their ir and mass spectra (Table 7). In the ^{1}H nmr spectrum of the mixture, two sets of signals were observed. A comparison of the major set of signals of ^{1}H nmr spectrum of the 4:1 mixture of the synthetic **85** and its epimer **133** with that of natural (+)-6β-acetoxy-2-oxokolavenool (**85**) (Table 8) established the identity of the synthetic material and the natural product. The unexpected compound **134** was identified as an aldol product which was apparently produced via pathway b shown in Figure 12. This compound exhibited a molecular ion peak at m/z 334.2143, indicating a molecular formula of $C_{20}H_{30}O_4$. Its ir spectrum showed three distinct absorptions at 3423 (hydroxyl), 1737 (ester), and 1643 cm^{-1} (conjugated ketone). The presence of an enone and an acetate were also indicated by the broad doublet at δ 5.77 (J=1 Hz) and the sharp singlet at δ 2.12. The proton next to the acetate was displayed at δ 4.96 (dd, J= 13, 4 Hz) as a doublet of doublets with a large

Table 7. The ir and mass spectral data of natural (+)-6β-acetoxy-2-oxo-kolavenool (**85**) and the 4:1 mixture of synthetic **85** and its epimer **133**

	Natural **85**[35]	Synthetic **85/133** (4:1)
IR(CCl_4) cm^{-1}	3600 (OH)	3600 (OH)
	1745 (C=O, ester)	1741 (C=O, ester)
	1670 (C=CCO)	1670 (C=CCO)
	1245 (OAc)	1243 (OAc)
MS (m/z)	$C_{22}H_{34}O_4$ (Calcd. 362.2457)	$C_{22}H_{34}O_4$ (Calcd. 362.2457)
	362.246 (M^+)	362.2452 (M^+)
	344 (M- H_2O)	344.2352 ($C_{22}H_{32}O_3$)
	302 (M- HOAc)	302.2240 ($C_{20}H_{30}O_2$)
	284 (302- H_2O)	284.2134 ($C_{20}H_{28}O$)
	203 (284- C_4H_7O)	203.1434 ($C_{14}H_{19}O$)
	123 ($C_8H_{11}O$)	123.0807 ($C_8H_{11}O$)
	71 (C_4H_7O)	71.0497 (C_4H_7O)

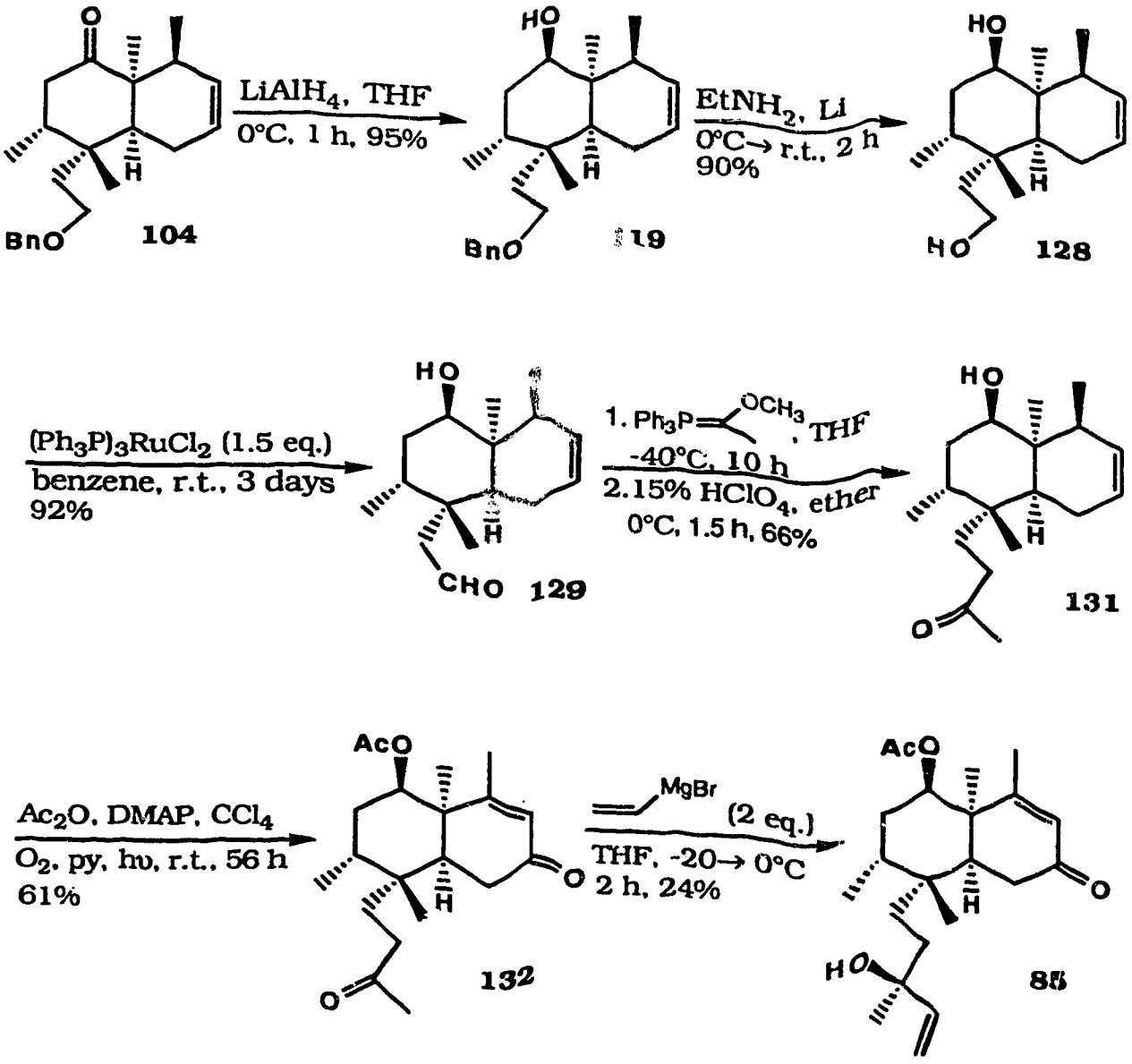
Table 8. ^{1}H nmr data of synthetic **85** and natural (+)-6β-acetoxy-2-oxokolavenool



Natural (400 MHz, $CDCl_3$)[35]			Synthetic (500 MHz, $CDCl_3$)	
δ (ppm)	(multiplicity; J in Hz)	proton	δ (ppm)	(multiplicity; J in Hz)
2.38	(m)	$H_1\alpha$	2.40	(m)
2.69	(dd; 17, 11)	$H_1\beta$	2.69	(dd; 17, 10.5)
5.93	(br s)	H_3	5.94	(br s)
5.05	(br s)	H_6	5.06	(br s)
5.86	(dd; 17.5, 11)	H_{14}	5.88	(dd; 17.5, 11)
5.20	(dd; 17.5, 1)	H_{15}t (*trans*)	5.21	(dd; 17.5, 1)
5.06	(dd; 11, 1)	H_{15}c (*cis*)	5.07	(dd; 11, 1)
1.28	(s)	H_{16}	1.29	(s)
0.93		H_{17}	0.95	(br s)
1.95		H_{18}	1.93	(br s)
1.32	(s)	H_{19}	1.32	(s)
0.93	(m)	H_{20}	0.95	(br s)
1.95	(m br)	OAc	1.95	(br s)

coupling constant of 13 Hz and a small one of 4 Hz, suggesting an axial orientation for this proton. A doublet of doublets attributed to the proton α to the ketone carbonyl resonated at δ 2.85 (J=4, 1 Hz). Its *cis* relationship with the center ring-junction proton was revealed by the small vicinal coupling constant of 4 Hz. The hydroxyl proton which appeared as a broad singlet at δ 6.29, was assigned based on a D_2O exchange experiment. In addition, the hydroxy group was assumed to possess β-orientation, a stereochemical requirement for effective hydrogen bonding with the ketone carbonyl suggested by the low absorption frequency of enone carbonyl (1643 cm^{-1}) in the ir spectrum and the downfield chemical shift of the hydroxyl proton (δ 6.29) in the ^1H nmr spectrum.

In conclusion, the total synthesis of (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**86**) and (±)-6β-acetoxy-2-oxokolavenool (**85**; 80% purity at present) has been accomplished in sixteen and seventeen steps, respectively, starting from 6-methyl-3-ethoxy-2-cyclohexen-1-one via synthetic sequences outlined in Schemes 13, 15, 16, and 19. More importantly, the synthetic approach demonstrated is highly flexible and promises general utility in the area of *cis*-clerodane diterpenoids which are large in number, challenging in structure, and potentially useful in biological activity.



Scheme 19

(±)-6β-acetoxy-2-oxokolavenool

Experimental

General

Melting points were recorded on a Kofler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department. Fourier transform infrared spectra were recorded on a Nicolet 7199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-80, Bruker WH-200, Bruker WH-300, Bruker WH-400 or Bruker AM-400 spectrometer using deuterochloroform ($CDCl_3$) as solvent unless otherwise stated. Tetramethylsilane (TMS) was used as an internal reference. Coupling constants are reported to ± 0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Varian UNITY-500 (125 MHz) spectrometer or a Bruker WH-300 (75 MHz) NMR spectrometer, and were obtained as solutions in deuterochloroform as the internal standard setting the central peak at 77.00 ppm. Carbon-13 multiplicities were derived from Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test).[68,69] Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuterochloroform signal, whereas methylene groups, quaternary carbons and carbonyl groups appear in phase (p) with it. Nuclear Overhauser Enhancement (NOE) experiments were

determined in the difference mode in which a control (undecoupled) spectrum was computer substracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements are deoxygenated with argon for 10 minutes prior to use. Two dimensional (2D) homonuclear correlation spectrum (COSY) was performed on the Varian UNITY-500 MHZ NMR machine using the standard proton parameters. High resolution electron impact mass spectra (hrms) were recorded using an A.E.I. model MS-50 mass spectrometer. Chemical ionization mass spectra (cims) were recorded on an A.E.I. MS-12 mass spectrometer, using ammonia as the reagent gas. Spectral data are reported as m/z values. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. X-ray analyses were performed by Professor Yu Wang and coworkers at National Taiwan University. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 20% ethyl acetate in petroleum ether means 20 parts of ethyl acetate by volume to 80 parts of petroleum ether by volume.

Materials

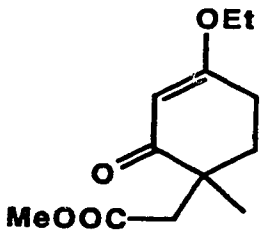
Unless otherwise stated, all materials used are commercially available. All compounds made are racemic. All reactions were carried out under a positive pressure of argon. Solvents were distilled under argon from appropriate drying agents before use. Tetrahydrofuran (THF), diethyl ether, toluene and 1,2-dimethoxyethane (DME) were freshly distilled from a blue or purple solution of sodium

benzophenone ketyl. Methanol was distilled from magnesium turnings. Acetone was predried with potassium carbonate, and then distilled from potassium permanganate. Alternatively, it was distilled from potassium permanganate, and then from potassium carbonate. Liquid ammonia was freshly distilled over sodium metal prior to use. Diisopropylamine was obtained by distillation from sodium hydroxide or potassium hydroxide. Pyridine, benzene, dichloromethane and triethylamine (TEA) were distilled from calcium hydride. Reactions requiring anhydrous conditions were performed using oven or flame-dried glassware, assembled and allowed to cool while being purged with argon. The term *in vacuo* refers to solvent removal using Buchi rotoevaporator under water aspirator pressure. Argon was passed through a column of 4 Å molecular sieves, with a self-indicating silica gel (coarse grained) as the indicator.

Flash chromatography developed by Still[70] was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for chromatography. Analytical thin layer chromatography (TLC) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a uv lamp (254 or 350 nm). For TLC, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, w/v) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate. Alternatively, an aqueous solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%,w/v) and sulfuric acid (3%, v/v) was used as the dipping

solution, followed by charring on a hot plate. 3-Ethoxy-6-methyl-2-cyclohexenone was prepared according to the procedure by Kende *et al.*[71]

6-(Carbomethoxymethyl)-3-ethoxy-6-methyl-2-cyclohexenone (94)

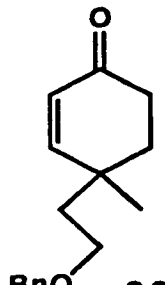


94

To a solution of diisopropylamine (8.3 mL, 59 mmol) in THF (7 mL) at 0°C under an argon atmosphere, was added *n*-BuLi (34 mL, 1.6 M in hexane) slowly. The mixture was stirred at 0°C for 15 min and then cooled down to -78°C. A solution of 3-ethoxy-6-methyl-2-cyclohexenone (7.65 g, 49 mmol) in THF (20 mL) was added dropwise over a period of 15 min. The resulting mixture was stirred at -78°C for 1 h, and methyl bromoacetate (9.6 mL, 98 mmol) was added in one portion. The mixture was allowed to warm up slowly to room temperature and stirred overnight. Saturated ammonium chloride was added and the mixture was extracted with ether (3 x 40 mL). The extracts were combined, washed with water, brine, and dried over magnesium sulfate. Filtration and concentration followed by bulb-to-bulb distillation at 128-130°C/0.7 torr gave rise to the pure alkylation

product **94** (10.2 g, 91% yield) as a light yellow oil: ir (CH_2Cl_2 cast) 1737 (C=O, ester) and 1654 cm^{-1} (C=O, enone); ^1H nmr (200 MHz) δ 5.29 (d, J = 1 Hz, 1 H, -C=C**H**-C=O), 3.91 (q, J = 7 Hz, 1 H, CH_3CHHO-), 3.90 (q, J = 7 Hz, 1 H, CH_3CHHO-), 3.62 (s, 3 H, -COOC**H**$_3$), 2.79 (d, J = 15.5 Hz, 1 H, -C**H**H$COOCH_3$), 2.35 (d, J = 15.5 Hz, 1 H, -CH**H**$COOCH_3$), 2.60-2.19 (m, 3 H), 1.81-1.67 (m, 1 H), 1.35 (t, J = 7 Hz, 3 H, C**H**$_3CH_2O$-), 1.16 (s, 3 H, -C**H**$_3$); ^{13}C nmr (APT) δ 200.18 (p), 174.54 (p), 171.64 (p), 101.31 (a), 63.87 (p), 50.84 (a), 42.33 (p), 41.76 (p), 31.56 (p), 26.08 (p), 22.33 (a) and 13.98 (a); hrms M^+ 226.1200 (calcd. for $C_{12}H_{18}O_4$: 226.1205). Anal. calcd. for $C_{12}H_{18}O_4$: C 63.70, H 8.02; found: C 63.70, H 8.39.

4-(2-Benzyloxyethyl)-4-methyl-2-cyclohexenone (96)

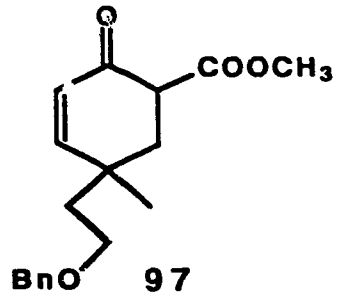


96

To a suspension of lithium aluminium hydride (0.81 g) in THF (20 mL) at 0°C under an argon atmosphere, was added dropwise the pure enone ester **94** (2.1 g) in THF (20 mL). The resulting suspension was stirred at 0°C for 1 h and then at room temperature for 21 h. To the mixture cooled to 0°C, were added alternatingly portions of water (0.12 mL) and 3 N NaOH (0.12 mL) over a period of 1 h. The resulting grey suspension was stirred for another hour and filtered. The residue

was washed thoroughly with ether. The filtrate was concentrated to give the crude product (1.9 g) which, without purification, was dissolved in THF (18 mL) and added to a suspension of sodium hydride (0.48 g, 11.4 mmol) in THF (20 mL) at 0°C under argon. The mixture was stirred at 0°C for 1 h, and then benzyl bromide (3.25 g, 19 mmol) was introduced. After stirring at room temperature for 25 h, the mixture was acidified (pH = 1-1.5) with 1 N HCl, and the resulting solution stirred for 2 h. After the hydrolysis was complete, the mixture was extracted with ether (3 x 30 mL). The extracts were combined and washed with saturated sodium bicarbonate, water and brine. After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product. Flash chromatography using ethyl acetate and hexane (20:80) gave compound **96** (1.88 g, 83% yield from **94**) as a light yellow oil. Alternatively, it could be distilled at 175°C/1 torr to give the pure product as a colorless oil: ir ($CHCl_3$ cast) 1680 (C=O, enone), 738 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.32 (m, 5 H, aromatic **H**), 6.75 (d, J = 10 Hz, 1 H, -C**H**=CH-C=O), 5.86 (d, J = 10 Hz, 1 H, -CH=C**H**-C=O), 4.49 (s, 2 H, -OC$\mathbf{H_2}$Ph), 3.51-3.64 (m, 2 H, -C$\mathbf{H_2}$OBn), 2.47 (m, 2 H), 2.02 (ddd, J = 15, 7, 7 Hz , 1 H, -C**H**HC=O), 1.73-1.90 (complex, 3 H), 1.18 (s, 3 H, -C$\mathbf{H_3}$); ^{13}C nmr (APT) δ 199.27 (p), 158.75 (a), 138.11 (p), 128.31 (a, 2 x aromatic **C**), 127.54 (a), 127.49 (a, 2 x aromatic **C**), 127.12 (a), 73.04 (p), 66.59 (p), 40.20 (p), 34.92 (p), 34.05 (p, 2 x -CH_2-) and 25.19 (a); hrms M^+ 244.1459 (calcd. for $C_{16}H_{20}O_2$: 244.1463). Anal. calcd. for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found C 78.93, H 8.52.

4-(2-Benzyloxyethyl)-6-carbomethoxy-4-methyl-2-cyclohexenone (97)



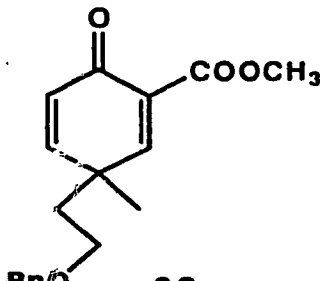
97

To a suspension of sodium hydride (4.21 g, 105 mmol) in THF (20 mL) under an argon atmosphere, was added dimethyl carbonate (17 mL, 180 mmol). The mixture was brought to boiling, and then a solution of enone **96** (11.3 g, 46 mmol) in THF (20 mL) was added dropwise over a period of 30 min. The resulting mixture was heated under reflux for 24 h and then cooled to 0°C. Ice-cold 1 N HCl (35 mL) was added cautiously to the mixture, and the resulting solution extracted with ether (3 x 50 mL). The extracts were combined and washed with water and brine. After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product. Flash chromatography using ethyl acetate and hexane (10:90) gave keto ester **97** (7.56 g, 54% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1744 (C=O, ester), 1681 (C=O, enone), 1626 and 1592 (C=C, enol ester), 738 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) three isomers in a ratio of 2:1.4:1; isomer 1: δ 7.32 (m, 5 H, aromatic **H**), 6.81 (dd, J = 10, 2 Hz, 1 H, -C**H**=CHCO), 5.90 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 4.48 (s, 2 H, -OC$\mathbf{H_2}$Ph), 3.78 (s, 3 H, -COOC$\mathbf{H_3}$),

3.50-3.65 (m, 2 H, -C**H**$_2$OBn), 1.64-2.50 (m), 1.21 (s, 3 H, -C**H**$_3$); isomer 2: δ 6.72 (dd, J = 10, 1.5 Hz, 1 H, -C**H**=CHCO), 5.92 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 4.49 (s, 2 H, -OC**H**$_2$Ph), 3.74 (s, 3 H, -COOC**H**$_3$), 1.18 (s, 3 H, -C**H**$_3$); isomer 3: δ 11.87 (s, 1 H, -C=C-O**H**), 6.11 (d, J = 10 Hz, 1 H, -C**H**=CHCO), 5.88 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 4.47 (s, 2 H, -OC**H**$_2$Ph), 3.73 (s, 3 H, -COOC**H**$_3$), 1.07 (s, 3 H, -C**H**$_3$); hrms M^+ 302.1515 (calcd. for $C_{18}H_{22}O_4$: 302.1518). Anal. calcd. for $C_{18}H_{22}O_4$: C 71.49, H 7.34; found C 71.41, H 7.39.

Alternatively, the above carbomethoxylation could be achieved by the following method in higher yield: *n*-Butyllithium (6.06 mL, 2.5M in hexane) was added to a stirred solution of anhydrous diisopropylamine (2.25 mL, 15.9 mmol) in THF (20 mL) at 0°C under an atmosphere of argon. After 30 min, the temperature was lowered to -78°C, a solution of enone **90** (1.85 g, 7.58 mmol) in THF (10 mL) added dropwise to the mixture over a period of 15 min, and stirring continued at 0°C for 1 h. The temperature was lowered again to -78°C, and then HMPA (1.45 mL, 8.34 mmol) was added, followed by the addition of methyl cyanoformate (0.91 mL, 11.4 mmol) in one portion. After stirring for 1 h at -78°C, the mixture was warmed up to room temperature and quenched with cold water (10 mL). The product was extracted into ether (3 x 20 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel (10% ethyl acetate in hexane) to afford compound **97** (2.1 g, 93% yield) as a yellowish oil.

4-(2-Benzyloxyethyl)-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (90)

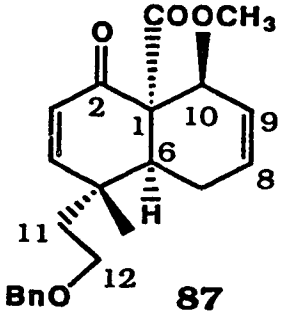


90

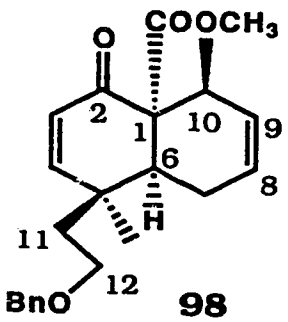
To a solution of phenylselenenyl chloride (1.10 g, 5.7 mmol) in dichloromethane (25 mL) at 0°C, was added pyridine (0.51 mL, 5.9 mmol) slowly. After 20 min, keto ester **97** (1.4 g, 4.6 mmol) in dichloromethane (10 mL) was added. The mixture was stirred at 0°C for 1 h and then at room temperature for 6 h. The organic layer was separated, washed with 10% HCl (2 x 10 mL) and cooled again to 0°C. A solution of 30% H_2O_2 (0.2 mL) was added. An additional 0.2 mL of 30% H_2O_2 was added after 5 min and again after 5 min until the white precipitate was formed. After an additional 20 min, H_2O (5 mL) was added. The organic layer was separated, and the aqueous solution extracted with dichloromethane (2 x 20 mL). The combined extracts were washed with water, saturated aqueous sodium bicarbonate, and brine. After being dried over $MgSO_4$, the solution was filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate and hexane (30:70) as the eluant to give dienone ester **90** (1.14 g, 82% yield) as a light yellow oil: ir (CH_2Cl_2 cast) 1741

(C=O, ester), 1664 (C=O, enone), 739 and 699 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.59 (d, J = 3 Hz, 1 H, -C**H**=C-$COOCH_3$), 7.21-7.36 (m, 5 H, aromatic **H**), 6.78 (dd, J = 10, 3 Hz, 1 H, -C**H**=CHC=O), 6.29 (d, J = 10 Hz, 1 H, -CH=C**H**C=O), 4.35 (s, 2 H, -OCH_2Ph), 3.80 (s, 3 H, -COOCH_3), 3.26-3.41 (m, 2 H, -CH_2OBn), 1.97-2.13 (m, 2 H, -CH_2CH_2OBn) and 1.32 (s, 3 H, -CH_3); ^{13}C nmr (APT) δ 181.59 (p), 165.03 (p), 160.88 (a), 153.52 (a), 137.77 (p), 130.53 (p), 129.19 (a), 128.34 (a, 2 x aromatic **C**), 127.62 (a, 2 x aromatic **C**), 73.15 (p), 66.66 (p), 52.18 (a), 41.05 (p), 40.54 (p), 25.98 (a); hrms M^+ 300.1353 (calcd. for $C_{18}H_{20}O_4$: 300.1361). Anal. calcd. for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.81, H 6.76.

(1R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (87) and (1R*, 5S*, 6S*, 10S*)-5-(2-benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo [4.4.0]deca-3,8-dien-2-one (98)



87



98

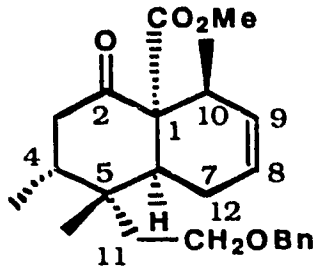
$ZnCl_2$ (1.0 g, 7.5 mmol) in a three-neck round bottom flask was fused under argon and then cooled to room temperature. Dry ether (25 mL) was added and the $ZnCl_2$ was crushed using a spatula to small pieces.

The mixture was stirred for 15 min until a fine suspension was formed. It was then cooled to 0°C and a solution of dienone ester **90** (0.75 g, 2.5 mmol) in ether (20 mL) was added dropwise. After the addition, the cloudy suspension turned clear presumably due to the complexation of the dienophile and $ZnCl_2$. *trans*-Piperylene (3.75 mL, 7.52 mmol) was added and the resulting mixture was stirred under argon at 0°C for 68 h. The solution was quenched by addition of water and made basic with saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ether (2 x 15 mL) and the combined extracts were washed with water, saturated sodium bicarbonate and brine. Drying ($MgSO_4$), filtration, concentration and flash chromatography using ethyl acetate and petroleum ether (5:95) gave adduct **87** (0.77 g, 84% yield) as a colorless oil: ir ($CHCl_3$ cast) 1725 (C=O, ester), 1690 (C=O, enone), 734 and 699 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.32 (m, 5 H, aromatic **H**), 6.29 (dd, J = 10, 2 Hz, 1 H, -C**H**=CHC=O), 5.92 (d, J = 10 Hz, 1 H, -CH=C**H**C=O), 5.57 (ddd, J = 10, 4, 2 Hz, 1 H, C-9 **H**), 5.50 (ddd, J = 10, 7, 3 Hz, 1 H, C-8 **H**), 4.52 (d, J = 14 Hz, 1 H, -OC**H**HPh), 4.48 (d, J = 14 Hz, 1 H, -OCH**H**Ph), 3.69 (s, 3 H, -COOC**H**$_3$), 3.58-3.66 (m, 2 H, -C**H**$_2$OBn), 2.83 (m, 1 H, C-10 **H**), 2.75 (ddd, J = 10, 7, 2 Hz, 1 H, C-6 **H**), 2.16 (dm, J = 18 Hz, 1 H, C-7 **H**$_\alpha$), 1.95 (dm, J = 18 Hz, 1 H, C-7 **H**$_\beta$), 1.78 (dd, J = 14, 7 Hz, 1 H, -C**H**HCH$_2$OBn), 1.72 (dd, J = 14, 7 Hz, 1 H, -CH**H**CH$_2$OBn), 1.22 (d, J = 7 Hz, 3 H, C-10 C**H**$_3$) and 1.10 (s, 3 H, C-5 C**H**$_3$); ^{13}C nmr (APT) δ 196.33 (p), 174.54 (p), 152.27 (a), 138.37 (p), 130.62 (a), 128.42 (a, 2 x aromatic **C**), 127.57 (a, 2 x aromatic **C**), 127.32 (a), 123.36 (a), 73.12 (p), 66.64 (p), 59.29 (p), 52.37 (a), 43.07 (a), 39.61 (p), 39.10 (p), 37.66 (a), 26.62 (p), 24.22

(a), and 16.87 (a); hrms M^+ 368.1980 (calcd. for $C_{23}H_{28}O_4$: 368.1987). Anal. calcd. for $C_{23}H_{28}O_4$: C 74.97, H 7.66; found: C 75.03, H 7.81.

Further elution gave adduct **98** (0.15 g, 16% yield) as a colorless oil: ir ($CHCl_3$ cast) 1726 (C=O, ester), 1689 (C=O, enone), 735 and 699 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.33 (m, 5 H, aromatic **H**), 6.29 (dd, J = 10, 2 Hz, 1 H, -C**H**=CHC=O), 5.85 (d, J = 10 Hz, 1 H, -CH=C**H**C=O), 5.56 (ddd, J = 10, 4, 2 Hz, 1 H, C-9 **H**), 5.47 (ddd, J = 10, 7, 3 Hz, 1 H, C-8 **H**), 4.51 (d, J = 14 Hz, 1 H, -OC**H**HPh), 4.49 (d, J = 14 Hz, 1 H, -OCH**H**Ph), 3.71 (s, 3 H, -COOC**H**$_3$), 3.54-3.66 (m, 2 H, -C**H**$_2$OBn), 2.75 (m, 1 H, C-10 **H**), 2.68 (ddd, J = 10, 7, 2 Hz, 1 H, C-6 **H**), 2.30 (dddd, J = 19, 7, 4, 3 Hz, 1 H, C-7 **H**$_\alpha$), 2.02 (dm, J = 19 Hz, 1 H, C-7 **H**$_\beta$), 1.93 (ddd, J = 14, 8, 6 Hz, 1 H, -C**H**HCH$_2$OBn), 1.64 (ddd, J = 14, 8, 6 Hz, 1 H, -CH**H**CH$_2$OBn), 1.26 (d, J = 7 Hz, 3 H, C-10 C**H**$_3$) and 1.15 (s, 3 H, C-5 C**H**$_3$); ^{13}C nmr (APT) δ 196.23 (p), 174.65 (p), 152.03 (a), 138.16 (p), 130.55 (a), 128.46 (a, 2 x aromatic **C**), 127.71 (a), 127.58 (a, 2 x aromatic **C**), 127.04 (a), 123.37 (a), 73.26 (p), 65.67 (p), 59.22 (p), 52.20 (a), 46.27 (a), 39.81 (p), 38.75 (a), 38.69 (p), 27.04 (p), 24.78 (a) and 16.69 (a); hrms M^+ 368.1984 (calcd. for $C_{23}H_{28}O_4$: 368.1987).

(1R*,4R*,5R*,6S*,10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (99)

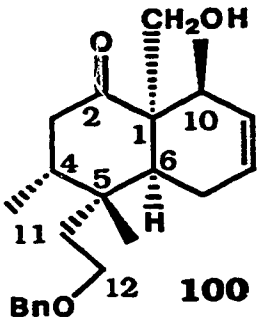


99

A mixture of CuI (179 mg, 0.94 mmol) and ether (10 mL) in a flame dried round bottom flask under argon was cooled to 0°C. Methyllithium (1.9 mL, 1.4 M in ether) was introduced dropwise (a yellow precipitate formed and then redissolved), and the mixture was stirred at 0°C for 1 h. Compound **87** (120 mg, 0.45 mmol) in ether (4 mL) was added slowly (a yellow precipitate formed), and the mixture was stirred for another hour. Saturated ammonium chloride was added, and the mixture was extracted with ether (3 x 15 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (10:90) gave compound **99** (117 mg, 94% yield) as a colorless oil: ir ($CHCl_3$ cast) 1718 (br, C=O, ester and ketone), 734 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.45 (m, 5 H, aromatic **H**), 5.57 (ddd, J = 10, 3, 2 Hz, 1 H, C-9 **H**), 5.50 (ddd, J = 10, 6, 3 Hz, 1 H, C-8 **H**), 4.56 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.49 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 3.73 (m, 1 H, -C**H**HOBn), 3.72 (s, 3 H, -COOC**H**$_3$), 3.57 (m, 1 H, -C**H**HOBn), 2.83 (m, 1 H, C-3 **H**), 2.77 (dd, J = 10, 7 Hz, 1 H, C-6 **H**), 2.52 (m, 1 H, C-10 **H**), 2.09-2.25 (m, 3 H), 1.95 (m, 1 H, C-7 **H**), 1.64-1.81 (m, 2 H, C-11

H_2), 1.12 (d, J = 7 Hz, 3 H, C-10 CH_3), 0.95 (s, 3 H, C-5 CH_3) and 0.89 (d, J = 6.5 Hz, 3 H, C-4 CH_3); ^{13}C nmr (APT) δ 206.00 (p), 174.83 (p), 138.54 (p), 130.28 (a), 128.41 (a, 2 x aromatic C), 127.73 (a, 2 x aromatic C), 127.60 (a), 123.01 (a), 73.39 (p), 67.15 (p), 62.49 (p), 52.42 (a), 46.40 (a), 46.32 (p), 40.25 (a), 38.89 (p), 38.44 (a), 32.11 (p), 24.86 (p), 24.27 (a) 16.29 (a) and 15.97 (a); hrms M^+ 384.2307 (calcd. for $C_{24}H_{32}O_4$: 384.2300).

(1S*,4R*,5R*,6S*,10S*)-5-(2-Benzyloxyethyl)-1-(1-hydroxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (100)

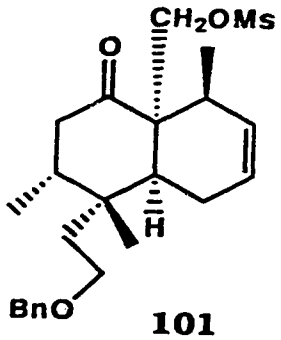


100

A suspension of CuI (1.4 g, 7.3 mmol) in ether (20 mL) in a flame dried round bottom flask was cooled to 0°C under argon. Methyllithium (10.5 mL, 1.4 M in ether) was added dropwise over a period of 5 min, and the resulting solution was stirred at 0°C for 1 h. Enone ester **87** (900 mg, 2.44 mmol) in ether (5 mL) was then introduced slowly over a period of 25 min. After the resulting yellow mixture was stirred for 1 h, lithium aluminium hydride (0.28 g, 7.3 mmol) was added. The reaction mixture turned into a dark suspension immediately after the addition of lithium aluminium

hydride. This dark suspension was stirred for 30 min. Saturated aqueous ammonium chloride (10 mL) was added carefully until gas evolution ceased followed by the addition of 3 N HCl (18 mL). The mixture was extracted with ether (4 x 20 mL). The combined extracts were washed with water (2 x 10 mL), saturated aqueous sodium bicarbonate and brine. Drying (magnesium sulfate), filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (20:80) gave alcohol **100** (501 mg, 61% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3448 (br, OH), 1692 (C=O, ketone), 736 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (500 MHz) δ 7.31 (m, 5 H, aromatic **H**), 5.85 (dt, J = 10, 4.5 Hz, 1 H, C-8 **H**), 5.75 (dd, J = 10, 5 Hz, 1 H, C-9 **H**), 4.49 (s, 2 H, -OC**H**$_2$Ph), 3.58 (d, J = 11 Hz, 1 H, -C**H**HOH), 3.55 (t, J = 7 Hz, 2 H, -C**H**$_2$OBn), 3.45 (d, J = 11 Hz, 1 H, -CH**H**OH), 3.26 (br s, 1 H, -O**H**), 2.50 (m, 1 H, C-10 **H**), 2.36 (dd, J = 10.5, 10.5 Hz, 1 H, C-3 **H**), 2.00-2.19 (complex, 5 H), 1.60 (m, 2 H), 1.10 (d, J = 7 Hz, 3 H, C-10 C**H**$_3$), 0.97 (s, 3 H, C-5 C**H**$_3$) and 0.89 (d, J = 6.5 Hz, 3 H, C-4 C**H**$_3$); ^{13}C nmr (APT) δ 219.94 (p), 138.30 (p), 132.36 (a), 132.20 (a), 128.21 (a, 2 x aromatic **C**), 127.65 (a, 2 x aromatic **C**), 126.60 (a), 73.25 (p), 69.36 (p), 67.01 (p), 55.24 (p), 45.95 (p), 41.63 (a), 37.32 (p), 35.07 (a), 34.84 (p), 33.03 (a), 22.67 (p), 22.53 (a), 17.31 (a) and 15.53 (a); cims $[M+NH_4]^+$ 374. Anal. calcd. for $C_{23}H_{32}O_3$: C 77.49, H 9.05; found: C 77.29, H 9.26.

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1-(1-mesyloxy methyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (101)

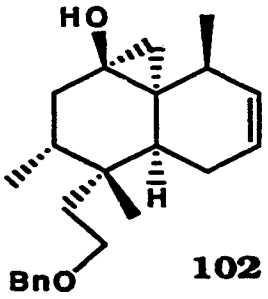


101

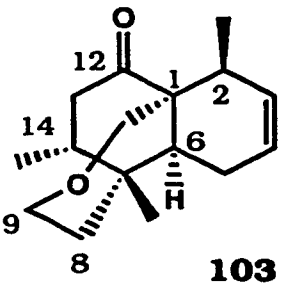
To a solution of alcohol **100** (110 mg, 0.31 mmol) and triethylamine (0.22 mL, 1.5 mmol) in THF (8 mL) at 0°C under an argon atmosphere, was added mesyl chloride (0.12 mL, 1.5 mmol) slowly. The reaction mixture was stirred at room temperature for 21 h, at which time 1 N HCl (3 mL) was added. The mixture was extracted with ether (3 x 15 mL), and the extracts were combined and washed with saturated aqueous sodium bicarbonate, water and brine. The solution was dried over magnesium sulfate, filtered and concentrated to afford the crude product which was purified by flash chromatography on silica gel. Elution with ethyl acetate and hexane (5:95) gave mesylate **101** (131 mg, 98% yield) as a colorless oil: ir (CH_2Cl_2 cast) 1701 (C=O, ketone), 1357 and 1176 (S=O), 737 and 699 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.35 (m, 5 H, aromatic **H**), 5.91 (m, 1 H, -C**H**=CH-), 5.67 (m, 1 H, -CH=C**H**-), 4.54 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.51 (d, J = 9.5 Hz, 1 H, -C**H**HOMs), 4.44 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 4.04 (d, J = 9.5 Hz, 1 H, -CH**H**OMs), 3.57 (m, 2 H, -C**H**$_2$OBn), 2.96 (s, 3 H, -OSO$_2$C**H**$_3$), 2.43 (dd, J = 7.5, 4.5 Hz, 1 H), 2.31 (dd, J = 16, 6 Hz, 1 H), 1.96-2.03 (complex, 5 H), 1.50-1.72 (complex, 2 H), 1.03 (d, J = 7 Hz, 3 H, C-10 C**H**$_3$), 1.00 (s, 3 H, C-5 C**H**$_3$) and 0.91 (d, J = 6.5 Hz, 3 H, C-4 C**H**$_3$);

^{13}C nmr (APT) δ 213.39 (p), 138.45 (p), 130.93 (a), 128.43 (a, 2 x aromatic **C**), 127.80 (a, 2 x aromatic **C**), 127.61 (a), 127.40 (a), 74.05 (p), 73.25 (p), 67.04 (p), 54.20 (p), 45.24, (p), 39.60 (a), 37.28 (p), 37.09 (a), 35.60 (a), 35.23 (p), 34.36 (a), 22.88 (p), 22.76 (a), 17.13 (a), 15.70 (a); hrms M^+ 434.2127 (calcd. for $C_{24}H_{34}O_5S$: 434.2127).

(1S*, 3S*, 5R*, 6R*, 7S*, 11S*)-6-(2-Benzyloxyethyl)-5,6,11-trimethyltricyclo[5.4.0.0^{1,3}]undec-9-en-3-ol (102) and (1S*, 2S*, 6S*, 7R*,14R*)-2,,7,14-trimethyl-10-oxatricyclo[5.4.3.0^{1,6}]tetradec-3-en-12-one (103)



102



103

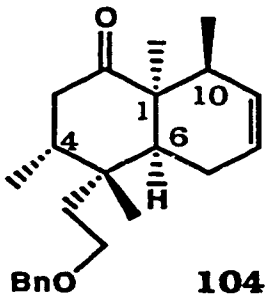
To a stirred solution of mesylate **101** (0.11 g, 0.25 mmol) in DMF (10 mL with 0.15% H_2O), were added sodium iodide (0.36 g, 2.5 mmol) and zinc powder (0.33 g, 5.0 mmol). The reaction mixture was immersed into a preheated oil bath at 130°C and maintained at that temperature for 28 h. The mixture was then filtered to remove excess sodium iodide and zinc powder. The filtrate was poured into water (6 mL) and extracted with 15% ethyl acetate in hexane (3 x 15 mL). The combined organic layers were then washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate

and hexane (6:94) to give tricyclic ketone **103** (19 mg, 30% yield) as a solid: mp 74.5-76.0°C (ethyl acetate - hexane); ir ($CHCl_3$ cast) 1704 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz) δ 5.53 (m, 2 H, -C**H**=C**H**-), 4.21 (d, *J* = 13.5 Hz, 1 H, -C**H**HO-), 4.00 (m, 2 H, -CH_2CH_2O-), 3.61 (d, *J* = 13.5 Hz, 1 H, -CH**H**O-), 2.63 (dd, *J* = 16.5, 8.5 Hz, 1 H, -C**H**HC=O), 2.10-2.36 (complex, 5 H), 1.92 (m, 1 H), 1.57 (dd, *J* = 5.5, 4.5 Hz, 1 H), 1.51 (dd, *J* = 5.5, 4.5 Hz, 1 H), 1.26 (d, *J* = 7.5 Hz, 3 H, C-2 C**H**$_3$), 1.05 (s, 3 H, C-7 C**H**$_3$), 0.98 (d, *J* = 6.5 Hz, 3 H, C-14 C**H**$_3$); ^{13}C nmr (APT) δ 211.87 (p), 131.85 (a), 123.00 (a), 69.54 (p), 65.68 (p), 58.11 (p), 49.81 (a), 46.78 (p), 38.79 (p), 38.75 (a), 36.59 (a), 35.52 (p), 27.23 (a), 25.22 (p), 16.72 (a), 15.92 (a); hrms M^+ 248.1788 (calcd. for $C_{16}H_{24}O_2$: 248.1778). Anal. calcd. for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found C 77.34, H 9.63. The X-ray structure analysis of this compound was carried out by Professor Yu Wang at National Taiwan University, and its crystal data are listed in appendix A.

Further elution gave compound **102** (47 mg, 55% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3436 (br, OH), 735 and 696 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.32 (m, 5 H, aromatic **H**), 6.22 (m, 1 H, -C**H**=CH-), 5.96 (m, 1 H, -CH=C**H**-), 4.50 (s, 2 H, -OC**H**$_2$Ph), 3.49 (t, *J* = 8 Hz, 2 H, -C**H**$_2$OBn), 1.92-2.23 (complex, 6 H), 1.56-1.72 (complex, 3 H), 1.46 (m, 1 H), 1.08 (s, 3 H, C-7 C**H**$_3$), 1.06 (d, *J* = 7 Hz, 3 H, C-2 C**H**$_3$), 0.83 (d, *J* = 7 Hz, 3 H, C-8 C**H**$_3$), 0.58 (dd, *J* = 5, 1.5 Hz, 1 H, cyclopropyl **H**), 0.52 (d, *J* = 5 Hz, 1 H, cyclopropyl **H**); hrms M^+ 340.2393 (calcd. for $C_{23}H_{32}O_2$: 340.2402). When alcohol **108** (22 mg, 0.06 mmol) was treated with sodium iodide (0.1 g, 0.6 mmol) and zinc dust (0.082 g, 1.2 mmol) in DMF (5 mL) at 126°C for

21 h, tricyclic ketone **103** (14.2 mg, 94% yield) was obtained after purification by chromatography.

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-one (104)

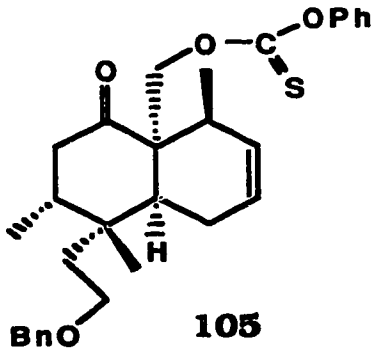


104

To a solution of compound **102** (60 mg, 0.18 mmol) in dichloromethane (5 mL) at room temperature, was added a crystal of *p*-toluenesulfonic acid. After stirring for 40 min, the reaction mixture was diluted with dichloromethane (6 mL) and then washed with saturated aqueous sodium bicarbonate, water, and brine. The organic solution was dried over $MgSO_4$, filtered and concentrated. Flash chromatography of the residue with 10% ethyl acetate in hexane gave **104** (58 mg, 97% yield) as a colorless oil: ir ($CHCl_3$ cast) 1695 (C=O, ketone), 735 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.31 (m, 5 H, aromatic **H**), 5.85 (m, 1 H, -C**H**=CH-), 5.72 (m, 1 H, -CH=C**H**-), 4.52 (d, *J* = 12 Hz, 1 H, -OC**H**HPh), 4.48 (d, *J* = 12 Hz, 1 H, -OCH**H**Ph), 3.57 (m, 2 H, -C**H**$_2$OBn), 2.23 (dd, *J* = 13, 9 Hz, 1 H, -C**H**HC=O), 2.21 (dd, *J* = 8, 4 Hz, 1 H), 2.04-2.18 (complex, 3 H), 1.96 (t, *J* = 7 Hz, 1 H), 1.58-1.71 (complex, 3 H), 1.27 (s, 3 H, C-1 C**H**$_3$), 1.00 (d, *J* = 7 Hz, 3 H, C-10 C**H**$_3$), 0.98 (s, 3 H, C-5 C**H**$_3$) and 0.91 (d,

J = 6.5 Hz, 3 H, C-4 CH_3); ^{13}C nmr (APT) δ 217.10 (p), 138.44 (p), 132.67 (a), 129.61 (a, 2 x aromatic C), 128.44 (a, 2 x aromatic C), 127.62 (a), 126.70 (a), 73.19 (p), 67.13 (p), 51.05 (p), 47.53 (a), 45.07 (p), 39.43 (a), 37.70 (p), 35.87 (a), 35.18 (p), 29.50 (a), 23.70 (p), 23.14 (a), 17.08 (a), 16.05 (a); hrms M^+ 340.2395 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

5-(2-Benzyloxyethyl)-1-(1-phenoxythiocarbonyloxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-ene (105)

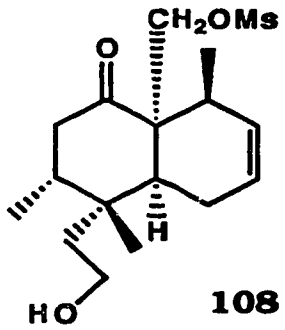


105

Keto alcohol **100** (0.12 g, 0.34 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0°C under an atmosphere of argon. 4-Dimethylaminopyridine (5 mg), pyridine (0.05 mL, 0.68 mmol) and phenyl chlorothionoformate (0.08 mL, 0.64 mmol) were introduced sequentially to the stirred solution. After stirring at room temperature for 20 h, the reaction mixture was poured into ice cold 1 M hydrochloric acid and extracted with ether (3 x 10 mL). The extracts were washed with ice-cold 1 M hydrochloric acid, water, dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash chromatography on silica gel eluting with 10% ethyl acetate in

hexane to give **105** (0.1 g, 70% yield) as a light yellow oil: ir (CH_2Cl_2 cast) 1703 (C=O, ketone), 1590 (C=C stretching, aromatic), 1290 and 1200 cm^{-1} (C=S); ^1H nmr (300 MHz) δ 7.16-7.39 (complex, 8 H, aromatic **H**), 7.00 (m, 2 H, aromatic **H**), 5.82 (m, 1 H, -C**H**=CH-), 5.61 (m, 1 H, -CH=C**H**-), 4.67 (d, *J* = 10.5 Hz, 1 H, -C**H**HOCSOPh), 4.43 (s, 2 H, -OC**H**$_2$Ph), 4.41 (d, *J* = 10.5 Hz, 1 H, -CH**H**OCSOPh), 3.53 (m, 2 H, -C**H**$_2$OBn), 2.34 (dd, *J* = 8, 3.5 Hz, 1 H), 2.24 (dd, *J* = 17, 6 Hz, 1 H, -C**H**HCO-), 1.93-2.19 (complex, 6 H), 1.61 (ddd, *J* = 8, 8, 2 Hz, 2 H), 1.00 (d, *J* = 7 Hz, 3 H, C-10 C**H**$_3$), 0.98 (s, 3 H, C-5 C**H**$_3$), 0.86 (d, *J* = 7 Hz, 3 H, C-4 C**H**$_3$); cims $[M+NH_4]^+$ 494.

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Hydroxyethyl)-1-(1-mesyloxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (108)

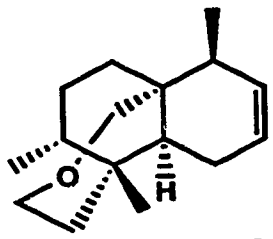


108

To a stirred solution of mesylate **101** (37 mg, 0.09 mmol) in dry dichloromethane (6 mL) under an atmosphere of argon, anhydrous $FeCl_3$ (52 mg, 0.31 mmol) was added in one portion and the reaction mixture was stirred at room temperature until its color changed to brown (*ca.* 50 min). Then, the reaction was quenched by addition of water (1 mL), and diluted with dichloromethane (5 mL). The aqueous

solution was separated and extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate and hexane (30:70) to give compound **108** (29 mg, 77% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3443 (OH, broad) and 1701 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz) δ 5.99 (m 1 H, -C**H**=CH-), 5.82 (m, 1 H, -CH=C**H**-), 4.59 (d, J = 9 Hz, 1 H, -C**H**HOMs), 3.92 (d, J = 9 Hz, 1 H, -CH**H**OMs), 3.79 (m, 1 H, -C**H**HOH), 3.59 (m, 1 H, -CH**H**OH), 3.06 (s, 3 H, $-OSO_2CH_3$), 2.37 (dd, J = 7, 7 Hz, 1 H), 2.10-2.19 (complex, 5 H), 2.01 (ddd, J = 13, 6.5, 6.5 Hz, 1 H), 1.67 (ddd, J = 13, 11, 6 Hz, 1 H), 1.63 (br s, 1 H, -O**H**), 1.25 (ddd, J = 13, 10, 4 Hz, 1 H), 1.02 (d, J = 7 Hz, 3 H, C-10 CH_3), 0.93 (s, 3 H, C-5 CH_3), 0.91 (d, J = 6.5 Hz, 3 H, C-4 CH_3); hrms $[M-H_2O]^+$ 326.1562 (calcd. for $C_{17}H_{26}SO_4$: 326.1552), $[M-CH_3SO_3H]^+$ 248.1777 (calcd. for $C_{16}H_{24}O_2$: 248.1776).

(1R*, 2S*, 6S*, 7R*, 14R*)-2,7,14-Trimethyl-10-oxatricyclo [5.4.3.0^{1,6}]tetradec-3-ene (112)

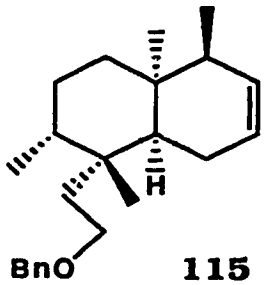


112

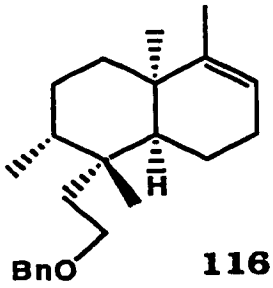
To a solution of ketone **103** (47 mg, 0.19 mmol) in diethylene glycol (10 mL) at room temperature, were added potassium hydroxide (60

mg, 1.14 mmol) and anhydrous hydrazine (0.21 mL, 7.6 mmol). The mixture was heated at 130-140°C for 12 h under argon. The temperature was then raised to 220°C to remove water and excess hydrazine using a Dean-Stark apparatus, and maintained at 210-220°C for a period of 10 h. The reaction mixture was then cooled, diluted with water (10 mL), acidified with aqueous NH_4Cl, and extracted with ethyl acetate (20 mL x 3). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give a yellow oil, which was chromatographed using 6% ethyl acetate in hexane as eluting solvent to afford **112** (32 mg, 73% yield) as a colourless oil: ir (CH_2Cl_2 cast) 3015 cm^{-1} (=CH); ^1H nmr (200 MHz) δ 5.60 (dm, J = 10 Hz, 1 H, -C**H**=CH-), 5.34 (ddd, J = 10, 4.5, 2 Hz, 1 H, -CH=C**H**-), 3.92 (m, 2 H, -CH_2CH_2O-), 3.88 (d, J = 13.5 Hz, 1 H, -C**H**HO-), 3.42 (d, J = 13.5 Hz, 1 H, -CH**H**O-), 2.00-2.32 (complex, 4 H), 1.79 (m, 2 H), 1.50 (m, 2 H), 1.05-1.33 (complex, 3 H), 0.97 (s, 3 H, C-7 CH_3), 0.85 (d, J = 7 Hz, 3 H, -CH_3), 0.84 (d, J = 7 Hz, 3 H, -CH_3); ^{13}C nmr (APT) δ 131.30 (a), 124.12 (a), 68.82 (p), 65.26 (p), 42.65 (a), 40.15 (p), 38.05 (p), 37.83 (a), 33.85 (a), 33.69 (p), 28.13 (p), 27.75 (a), 24.35 (p), 22.47 (p), 15.61 (a), 15.55 (a); hrms M^+ 234.1986 (calcd. for $C_{16}H_{26}O$: 234.1983).

(1S*, 2S*, 6R*, 7R*, 8R*)-7-(2-Benzyloxyethyl)-1,2,7,8-tetramethylbicyclo[4.4.0]dec-3-ene (115) and (1R*, 6S*, 7R*, 8R*)-7-(2-Benzyloxyethyl)-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene (116)



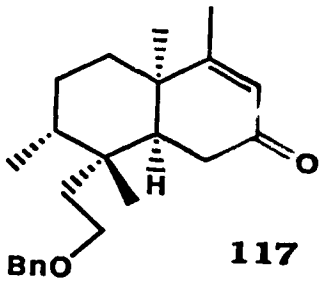
115



116

Using the same procedure mentioned above, compound **104** (28 mg, 0.08 mmol) was subjected to Wolff-Kishner reduction by treatment with potassium hydroxide (32 mg, 0.56 mmol) and anhydrous hydrazine (0.22 mL, 4.0 mmol) in 10 mL of diethylene glycol. After workup, the filtrate was concentrated and the resulting crude product was purified by flash chromatography with 5% ethyl acetate in hexane to furnish an inseparable 3:1 mixture of compounds **115** and **116** (16 mg, 60% yield) as a colorless oil: ir (CH_2Cl_2 cast) 736 and 697 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz): **115**: δ 5.57 (m, 1 H, -C**H**=CH-), 5.29 (m, 1 H, -CH=C**H**-), 4.57 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.50 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 3.54 (m, 2 H, -C**H**$_2$OBn), 1.14 (s, 3 H, -C**H**$_3$), 0.93 (s, 3 H, -C**H**$_3$), 0.87 (d, J = 7 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H, -C**H**$_3$); **116**: δ 5.32 (m, 1 H, -C=C**H**-), 4.52 (s, 2 H, -OC**H**$_2$Ph), 3.70 (m, 2 H, -C**H**$_2$OBn), 1.61 (s, 3 H, -CH=CC**H**$_3$), 1.17 (s, 3 H, -C**H**$_3$), 0.93 (d, J = 7 Hz, 3 H, -C**H**$_3$), 0.81 (s, 3 H, -C**H**$_3$); hrms $[M-C_5H_8]^+$ 258.1984 (calcd. for $C_{18}H_{26}O$: 258.1983); cims $[M+NH_4]^+$ 344.

(1S*, 6R*, 9R*, 10R*)-10-(2-Benzyloxyethyl)-5, 6, 9, 10-tetramethyl-bicyclo[4.4.0]dec-4-en-3-one (117)

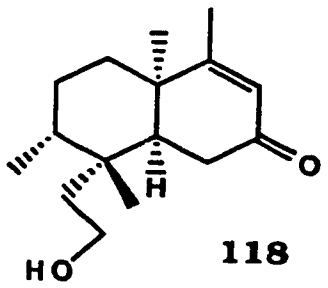


117

A solution of the 3:1 mixture of **115** and **116** (25 mg, 0.07 mmol), acetic anhydride (0.06 mL, 0.5 mmol), pyridine (0.05 mL, 0.5 mmol), a catalytic amount of 4-dimethylaminopyridine and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (2 mg) in dry carbon tetrachloride (40 mL) was saturated with oxygen for 20 min and then irradiated with two 200 W tungsten lamps for 56 h. During this period a gentle stream of oxygen was bubbled through the reaction mixture. After 56 h, irradiation was stopped and oxygen was bubbled through the solution for another 10 h. The reaction mixture was washed sequentially with saturated aqueous sodium bicarbonate (2 x 5 mL), 1 M hydrochloric acid (2 x 5 mL), saturated aqueous copper sulfate (1 x 5 mL), and saturated aqueous sodium chloride. After being dried over $MgSO_4$, the organic solution was filtered and concentrated. The resulting residue was subjected to flash chromatography using 5-15% ethyl acetate in hexane as the eluant to give **117** (15 mg, 56% yield) as a colorless oil as well as an unidentified UV active product (6.2 mg). For compound **117**: ir (CH_2Cl_2 cast) 1661 (C=O, enone), 736 and 697

cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.32 (m, 5 H, aromatic, **H**), 5.88 (br s, 1 H, -C=C**H**C=O), 4.48 (s, 2 H, -OC$\mathbf{H_2}$Ph), 3.50 (m, 2 H, -C$\mathbf{H_2}$OBn), 2.73 (dd, J = 18, 6 Hz, 1 H, -C**H**HC=O), 2.60 (dd, J = 18, 3 Hz, 1 H, -C**H**HC=O), 1.95 (d, J = 1.5 Hz, 3 H, C-5 C$\mathbf{H_3}$), 1.91 (dd, J = 6, 3 Hz, 1 H, C-1 **H**), 1.78-1.86 (complex, 2 H), 1.40-1.65 (complex, 5 H), 1.25 (s, 3 H, C-6 C$\mathbf{H_3}$), 0.97 (d, J = 7 Hz, 3 H, C-9 C$\mathbf{H_3}$), 0.86 (s, 3 H, C-10 C$\mathbf{H_3}$); hrms M^+ 340.2400 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

(1S*, 6R*, 9R*, 10R*)-10-(2-hydroxyethyl)-5,6,9,10-tetramethyl-bicyclo[4.4.0]dec-4-en-3-one (118)

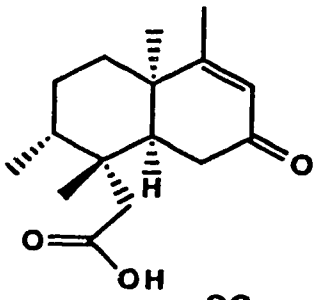


118

To a solution of compound **117** (4.0 mg, 0.012 mmol) in dry dichloromethane under an atmosphere of argon, was added anhydrous $FeCl_3$ (7 mg, 0.04 mmol) in one portion. After stirring for 50 min at room temperature, the reaction was quenched by addition of water (1 mL). The aqueous solution was separated and extracted with dichloromethane (2 x 6 mL). The combined organic layers was washed with brine, dried ($MgSO_4$), filtered and concentrated to give the crude product, which was purified by flash chromatography with

ethyl acetate and hexane (50:50) to afford **118** (2.4 mg, 82% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3439 (OH, broad) and 1651 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 5.89 (br s, 1 H, -C=C**H**C=O), 3.69 (t, *J* = 7.5 Hz, 2 H, -C**H**$_2$OH), 2.75 (dd, *J* = 18, 6 Hz, 1 H, -C**H**HC=O), 2.59 (dd, *J* = 18, 3 Hz, 1 H, -CH**H**C=O), 1.96 (br s, 3 H, C**H**$_3$CH=CHC=O), 1.92 (dd, *J* = 6, 3 Hz, 1 H, C-1 **H**), 1.79-1.88 (complex, 2 H), 1.40-1.68 (complex, 6 H), 1.27 (s, 3 H, C-6 C**H**$_3$), 1.11 (d, *J* = 7 Hz, 3 H, C-9 C**H**$_3$), 0.89 (s, 3 H, C-10 C**H**$_3$); hrms M^+ 250.1931 (calcd. for $C_{16}H_{26}O_2$: 250.1932), $[M-H_2O]^+$ 232.1825 (calcd. for $C_{16}H_{24}O$ 232.1827).

(±)-2-Oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (86)

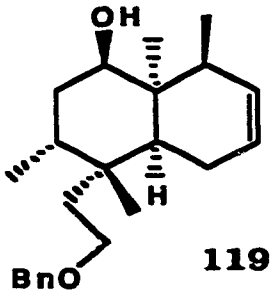


86

Enone **118** (1.5 mg, 0.006 mmol) was dissolved in acetone(4 mL, distilled over $KMnO_4$) and the solution was cooled to 10°C. Freshly prepared Jones reagent[72] (0.02 mL) was added dropwise, and the resulting solution stirred for 30 min at room temperature. Water was added to dissolve all green precipitates and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated

to give the crude product, which was subjected to flash chromatography using ethyl acetate and hexane (50:50) as the eluant to afford pure acid **86** (1.0 mg, 63% yield) as a white solid: ir (CH_2Cl_2 cast) 3300-2450 (OH, carboxylic acid), 1725 (C=O, carboxylic acid) and 1628 cm^{-1} (C=O, enone); ^1H nmr ($CDCl_3$, 300 MHz) δ 8.7 (br s, 1 H, -COO**H**), 5.90 (br s, 1 H,-C=C**H**C=O), 2.79 (dd, *J* = 18, 6.5 Hz, 1 H, -C**H**HC=O), 2.56 (d, *J* = 15 Hz, 1 H, -C**H**HCOOH), 2.48 (dd, *J* = 18, 2.5 Hz, 1 H, -CH**H**C=O), 2.21 (d, *J* = 15 Hz, 1 H, -CH**H**COOH), 2.07 (dd, *J* = 6.5, 2.5 Hz, 1 H, C-10 **H**), 2.00 (m, 1 H), 1.97 (d, *J* = 1 Hz, 3 H, C-4 C**H**$_3$), 1.85 (dm, *J* = 14 Hz, 1 H), 1.45-1.70 (m, 2 H), 1.30-1.36 (m, 1 H), 1.28 (s, 3 H, C-5 C**H**$_3$), 1.06 (s, 3 H, C-9 C**H**$_3$), 1.05 (d, *J* = 7.5 Hz, 3 H, C-8 C**H**$_3$); ^1H nmr ($CDCl_3$ -C_5D_5N , 200 MHz) δ 5.90 (br s, 1 H,-C=C**H**C=O), 3.06 (br s, 1 H, -$COO^-C_5D_5N^+$**H**), 2.79 (dd, *J* = 18, 6.5 Hz, 1 H, -C**H**HC=O), 2.59 (d, *J* = 15 Hz, 1 H, -C**H**HCOOH), 2.54 (dd, *J* = 18, 2.5 Hz, 1 H, -CH**H**C=O), 2.24 (d, *J* = 15 Hz, 1 H, -CH**H**COOH), 2.13 (dd, *J* = 6.5, 2.5 Hz, 1 H, C-10 **H**), 2.11 (m, 1 H), 1.97 (d, *J* = 1 Hz, 3 H, C-4 C**H**$_3$), 1.85 (dm, *J* = 14 Hz, 1 H), 1.50-1.75 (m, 3 H), 1.29 (s, 3 H, C-5 C**H**$_3$), 1.13 (s, 3 H, C-9 C**H**$_3$), 1.09 (d, *J* = 7.5 Hz, 3 H, C-8 C**H**$_3$); hrms M^+ 264.1721 (calcd. for $C_{16}H_{24}O_3$: 264.1725), $[M-CH_3]^+$ 249.1488 (calcd. for $C_{15}H_{21}O_3$: 249.1490), $[M-CH_3COOH]^+$ 204.1509 (calcd. for $C_{14}H_{20}O$: 204.1514).

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-ol (119)

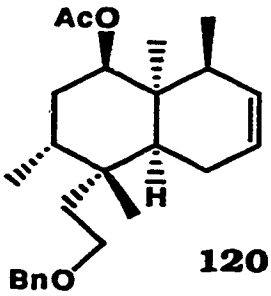


119

A suspension of lithium aluminumhydride (9.2 mg, 0.23 mmol) in THF (10 mL) was cooled to 0°C under an atmosphere of argon. A solution of compound **104** (40 mg, 0.12 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 1 h at 0°C. Water (3 mL) was added and the resulting mixture acidified with 1 M aqueous hydrochloric acid. The aqueous solution was extracted with ether (2 x 10 mL), and the combined organic layers was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the resulting residue with ethyl acetate and hexane (10:90) gave **119** (38 mg, 95% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3579 (OH, sharp) and 3487 (OH, broad), 735 and 697 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.33 (m, 5 H, aromatic **H**), 5.79 (dm, J = 10 Hz, 1 H, -C**H**=CH-), 5.56 (ddd, J = 10, 5, 2 Hz, 1 H, -CH=C**H**-), 4.55 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.49 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 3.71 (br s, 1 H, -C**H**OH), 3.67 (ddd, J = 11, 9, 5 Hz, 1 H, -C**H**HOBn), 3.56 (ddd, J = 11, 9, 5 Hz, 1 H, -CH**H**OBn), 2.30-2.50 (m, 2 H), 1.98-2.21 (complex, 4 H), 1.47-1.75 (complex, 4 H), 1.15 (d, J = 7.5 Hz, 3 H, C-10 C**H**$_3$), 1.12 (s, 3 H, C-1 C**H**$_3$), 1.03 (s, 3 H, C-5 C**H**$_3$), 0.87 (d, J = 7 Hz, 3 H, C-4 C**H**$_3$); ^{13}C nmr (APT) δ 138.62 (p), 132.31 (a), 128.67 (a), 128.42 (a, 2 x aromatic **C**), 127.65 (a, 2 x aromatic **C**), 127.59 (a), 73.28 (a), 73.18 (p), 67.71 (p), 41.86 (a), 40.67 (a), 39.64

(p), 38.71 (p), 35.76 (p), 35.26 (p), 30.52 (a), 28.42 (p), 27.52 (a), 26.37 (a), 15.56 (a), 15.09 (a); hrms $[M-C_5H_8]^+$ 274.1927 (calcd. for $C_{18}H_{26}O_2$ 274.1932); cims $[M+NH_4]^+$ 360.

(1S*, 2S*, 6S*, 7R*, 8R*, 10R*)-10-Acetoxy-7-(2-benzyloxyethyl)-1,2,7,8-tetramethylbicyclo[4.4.0]dec-3-ene (120)

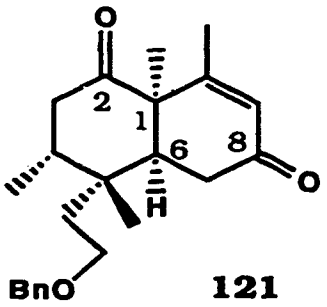


120

A solution of **119** (30 mg, 0.09 mmol), acetic anhydride (0.04 mL, 0.45 mmol) and a catalytic amount of 4-dimethylaminopyridine in pyridine (5 mL) was heated under reflux for 26 h. The reaction mixture was cooled to room temperature and diluted with 20 mL of ether. The solution was then sequentially washed with water, 1 M hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The ethereal solution was dried ($MgSO_4$), filtered and concentrated to give the light yellow oil, which was subjected to flash chromatography with 5% ethyl acetate in hexane to give acetate **120** (3.4 mg, 10% yield) as a colorless oil: ir (CH_2Cl_2 cast), 1733 (C=O, ester), 735 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.34 (m, 5 H aromatic **H**), 5.60 (m, 1 H, -C**H**=CH-), 5.33 (m, 1 H, -CH=C**H**-), 4.72 (br s, -C**H**OAc), 4.56 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.49 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 3.68 (ddd, J = 10.5, 9, 5 Hz, 1 H, -C**H**HOBn), 3.55

(ddd, J = 10.5, 9, 5 Hz, 1 H, -CHHOBn), 1.94 (s, 3 H, CH_3COO-), 1.86-2.35 (complex, 4 H), 1.49-1.79 (complex, 5 H), 1.16 (s, 3 H, C-1 CH_3), 1.02 (s, 3 H, C-7 CH_3), 0.89 (d, J = 7.5 Hz, 3 H, C-2 CH_3), 0.85 (d, J = 7 Hz, 3 H, C-8 CH_3); hrms $[M-AcOH]^+$ 324.2439 (calcd. for $C_{23}H_{32}O$ 324.2450); cims $[M+NH_4]^+$ 402.

(1R*, 4R*, 5R*, 6S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethyl bicyclo[4.4.0]dec-9-en-2,8-dione (121)

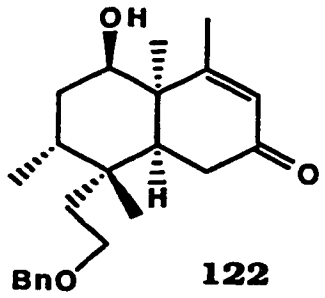


121

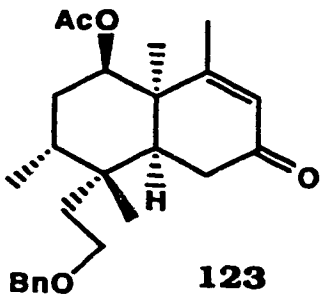
A gentle stream of oxygen was bubbled through a solution of ketone **104** (50 mg, 0.15 mmol), acetic anhydride (0.05 mL, 0.45 mmol), pyridine (0.04 mL, 0.45 mmol), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (5 mg) and 4-dimethylaminopyridine (3 mg) in carbon tetrachloride (40 mL) for 20 min. The bubbling was continued while the solution was irradiated with two 200 W tungsten light bulbs for 56 h. Bubbling was continued for another 12 h after stopping the irradiation. The solution was diluted with dichloromethane (20 mL) and then washed with saturated aqueous sodium bicarbonate (15 mL), aqueous 1 M HCl (15 mL) and saturated aqueous sodium chloride solution (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give the crude product, which was subjected to flash

chromatography (25% ethyl acetate in hexane) to afford enedione **121** (47 mg, 90% yield) as a solid: mp 102-103°C (ethyl acetate and hexane); ir (CH_2Cl_2 cast) 1711 (C=O, ketone), 1667 (C=O, enone), 739 and 699 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.30 (m, 5 H, aromatic **H**), 5.96 (q, J = 1.5 Hz, 1 H, -C=C**H**C=O), 4.48 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.44 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 3.49 (m, 2 H, -C**H**$_2$OBn), 2.64-2.72 (complex, 3 H), 2.23 (dd, J = 6, 3 Hz, 1 H), 2.16 (dd, J = 13.5, 4 Hz, 1 H), 2.03 (m, 1 H), 1.88 (ddd, J = 14, 7, 7 Hz, 1 H, -C**H**HCH$_2$OBn), 1.74 (d, J = 1.5 Hz, 3 H, C**H**$_3$-C=CHC=O), 1.52 (ddd, J = 14, 7, 7 Hz, 1 H, -CH**H**CH$_2$OBn), 1.37 (s, 3 H, C-1 C**H**$_3$), 1.10 (s, 3 H, C-5 C**H**$_3$), 0.86 (d, J = 7 Hz, 3 H, C-4 C**H**$_3$); ^{13}C nmr (APT) δ 211.54 (p), 197.47 (p), 160.86 (p), 138.47 (p), 128.48 (a, 2 x aromatic **C**), 127.68 (a), 127.55 (a, 2 x aromatic **C**), 73.20 (p), 65.87 (p), 53.31 (p), 49.51 (a), 44.64 (p), 39.42 (a), 38.84 (p), 37.85 (p), 35.20 (p), 23.28 (a), 22.36 (a), 20.83 (a), 15.29 (a); hrms M^+ 354.2205 (calcd. for $C_{23}H_{30}O_3$ 354.2195). Anal. calcd. for $C_{23}H_{30}O_3$: C 77.93, H 8.53; found C 77.71, H 8.50. An X-ray crystallographic analysis of this compound was performed by Professor Yu Wang at National Taiwan University, and its crystal data are listed in appendix B.

(1S*, 6R*, 7R*, 9R*, 10R*)-10-(2-Benzyloxyethyl)-7-hydroxy-5,6,9,10-tetramethylbicyclo[4.4.0]dec-4-en-3-one (122) and (1S*, 6R*, 7R*, 9R*, 10R*)-10-(2-Benzyloxyethyl)-7-acetoxy-5,6,9,10-tetramethylbicyclo[4.4.0]dec-4-en-3-one (123)



122

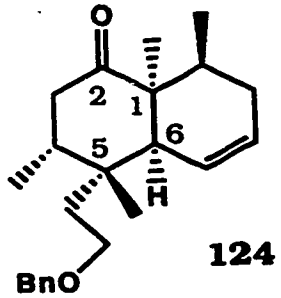


123

A mixture of the compound **119** (30 mg, 0.09 mmol), acetic anhydride (0.03 mL, 0.3 mmol), pyridine (0.02 mL, 0.27 mmol), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (5 mg) and 4-dimethylaminopyridine (3 mg) in carbon tetrachloride (40 mL) was irradiated with two 200 W tungsten lamps for 23 h. During this period a gentle stream of oxygen was bubbled through the solution. After reaction was complete, the mixture was sequentially washed with saturated aqueous sodium bicarbonate, 1 M aqueous solution of hydrochloric acid, saturated aqueous copper sulfate and saturated aqueous sodium chloride. Drying ($MgSO_4$), filtration and concentration gave the crude residue. Flash chromatography of the residue (20% ethyl acetate in hexane) gave the enone **123** (5 mg, 15% yield) as a light yellow oil: ir (CH_2Cl_2 cast) 1736 (C=O, ester), 1667 (C=O, enone), 738 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.35 (m, 5 H, aromatic **H**), 5.93 (br s, 1 H, -C=C**H**C=O), 5.06 (dd, J = 4.5, 2 Hz, 1 H, -C**H**OAc), 4.53 (d, J = 11.5 Hz, 1 H, -OC**H**HPh), 4.47 (d, J = 11.5 Hz, 1 H, -OCH**H**Ph), 3.55 (m, 2 H, -C**H**$_2$OBn), 2.68 (dd, J = 17.5, 13 Hz, 1 H, -C**H**$_\beta$HC=O), 2.39 (dm, J = 17.5 Hz, 1 H, -C**H**$_\alpha$HC=O), 2.00-2.17 (m, 2 H), 1.94 (br s, 3 H, C**H**$_3$COO-), 1.92 (br s, 3 H, C**H**$_3$C=CHC=O), 1.51-1.83 (complex, 4 H), 1.32 (s, 3 H, C-6 C**H**$_3$), 1.02 (br s, 3 H, C-10 C**H**$_3$), 0.93 (br d, J = 6 Hz, 3 H, C-9 C**H**$_3$); hrms M^+ 398.2465 (calcd.

for $C_{25}H_{34}O_4$: 398.2457); $[M+H]^+$ 399.2541 (calcd. for $C_{25}H_{35}O_4$ 399.2535). Further elution with 30% ethyl acetate in hexane afforded enone **122** (18 mg, 60% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3448 (OH, broad), 1653 (C=O, enone), 739 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.32 (m, 5 H, aromatic **H**), 6.01 (br s, 1 H, -C=C**H**C=O), 4.53 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.47 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 3.84 (br s, 1 H, -C**H**OH), 3.54 (m, 2 H, -C**H**$_2$OBn), 2.80 (dd, J = 17, 13 Hz, 1 H, -C**H**$_\beta$HC=O), 2.35 (dm, J = 17 Hz, 1 H, -C**H**$_\alpha$HC=O), 2.00-2.19 (complex, 2 H) ,1.97 (br s, 3 H, C**H**$_3$C=CHC=O), 1.77-1.96 (complex, 2 H), 1.45-1.71 (complex, 2 H), 1.28 (s, 3 H, C-5 C**H**$_3$), 1.00 (s, 3 H, C-10 C**H**$_3$), 0.92 (d, J = 7 Hz, 3 H,C-9 C**H**$_3$); hrms $[M+H]^+$ 357.2441 (calcd. for $C_{23}H_{33}O_3$: 357.2430), $[M-H_2O]^+$ 338.2247 (calcd. for $C_{23}H_{30}O_2$: 338.2245).

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1,4,5.10-tetramethylbicyclo[4.4.0]dec-7-en-2-one (124)

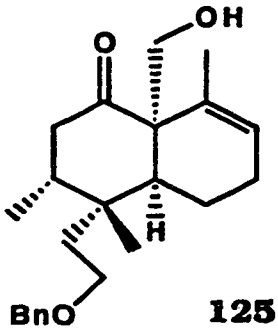


124

To a solution of ketone **104** (20 mg, 0.06 mmol) in ethanol (5 mL), was added rhodium chloride hydrate (10 mg, 0.04 mmol). The reaction mixture was then heated under reflux for 8 h. The resulting dark blue solution was poured into water (5 mL) and extracted with

ether (3 x 10 mL). The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was subjected to flash chromatography with 7% ethyl acetate in hexane to give isomer **124** (18 mg, 92% yield) as a colorless oil: ir ($CHCl_3$ cast) 1700 (C=O, ketone), 737 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.31 (m, 5 H, aromatic **H**), 5.85 (dm, *J* = 11 Hz, 1 H, -C**H**=CH-), 5.64 (dddd, *J* = 11, 3, 1.5, 1.5, Hz, 1 H, -CH=C**H**-), 4.53 (d, *J* = 11 Hz, 1 H, -OC**H**HPh), 4.49 (d, *J* = 11 Hz, 1 H, -OCH**H**Ph), 3.61 (m, 2 H, -C**H**$_2$OBn), 2.29 (dd, *J* = 3, 3 Hz, 1 H), 2.26 (dd, *J* = 7.5, 1.5 Hz, 1 H), 1.97-2.11 (m, 2 H), 1.82-1.96 (m, 2 H), 1.59-1.81 (complex, 3 H), 1.26 (s, 3 H, C-1 C**H**$_3$), 1.07 (s, 3 H, C-5 C**H**$_3$), 0.98 (d, *J* = 7 Hz, 3 H, C-10 C**H**$_3$), 0.89 (d, *J* = 7 Hz, 3 H, C-4 C**H**$_3$); hrms M^+ 340.2398 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

(1R*, 4R*, 5R*, 6S*)-5-(2-Benzyloxyethyl)-1-(1-hydroxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-9-en-2-one (125)

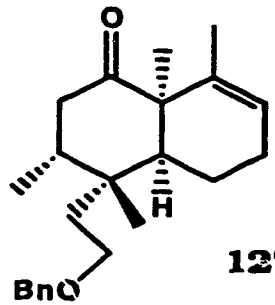


125

To a solution of compound **100** (21 mg, 0.06 mmol) in ethanol (7 mL), was added rhodium chloride hydrate (10 mg, 0.04 mmol). The reaction mixture was heated under reflux until its color turned deep

blue, and this usually took place within 30 min. Reflux was continued for another 20 min and then the reaction was quenched by addition of water followed by extraction with ether (2 x 10 mL), drying ($MgSO_4$), filtration and concentration. The crude product was purified by flash chromatography using ethyl acetate (5-10%) in hexane to afford compound **125** (9.8 mg, 50% yield) as a colorless oil: ir ($CHCl_3$ cast) 3533 (OH, broad), 1698, (C=O, ketone), 736 and 698 cm^{-1} (C-H bending, aromatic); ^1H nmr (300 MHz) δ 7.33 (m, 5 H, aromatic **H**), 5.74 (br s, 1 H, -C=C**H**-), 4.50 (s, 2 H, -OC**H**$_2$Ph), 4.07 (d, J = 12 Hz, 1 H, -C**H**HOH), 3.06 (m, 2 H, -C**H**$_2$OBn), 3.24 (d, J = 12 Hz, 1 H, -CH**H**OH), 2.61 (dd, J = 15, 5.5, Hz, 1 H, -C**H**HC=O), 2.43 (dd, J = 6, 2.5 Hz, 1 H, C-6 **H**), 1.95-2.25 (complex, 4 H), 1.59-1.97 (complex, 4 H), 1.55 (dd, J = 3, 2 Hz, 3 H, -C=CC**H**$_3$), 1.23 (s, 3 H, C-5 C**H**$_3$), 0.87 (d, J = 7 Hz, 3 H, C-4 C**H**$_3$); cims $[M+NH_4]^+$ 374, $[M+H]^+$ 357.

(1R*, 4R*, 5R*, 6S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethyl-bicyclo[4.4.0]dec-9-en-2-one (127)

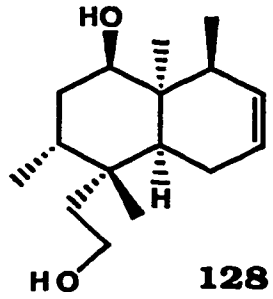


127

To a solution of **104** (12 mg, 0.035 mmol) in dry benzene (7 mL), was added a catalytic amount of Amberlyst 15 ion-exchange resin. The reaction mixture was heated under reflux for 48 h. The solution was

filtered and washed thoroughly with ethyl acetate. After being dried over $MgSO_4$, the solution was concentrated, and the residue was purified with flash chromatography with 5% ethyl acetate in hexane to give an inseparable 3:1 mixture of compounds **127** and **124** (9.5 mg, 80%) as a colorless oil: ^1H nmr (300 MHz): **127**: δ 5.62 (m, 1 H, -C=C**H**), 4.47 (s, 2 H, -OC**H**$_2$Ph), 3.51 (t, J = 7 Hz, 2 H, -C**H**$_2$OBn), 1.51 (dd, J = 4, 2 Hz, 3 H, -C=C-C**H**$_3$), 1.22 (s, 3 H, -C**H**$_3$), 1.16 (s, 3 H, -C**H**$_3$), 0.82 (d, J = 7 Hz, 3 H, C-4 C**H**$_3$).

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(2-Hydroxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-ol (128)

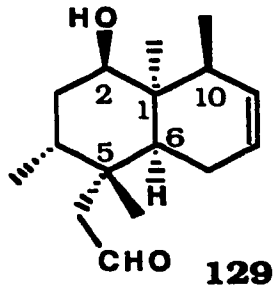


128

A reaction vessel equipped with a dry ice-acetone condenser was charged with 15 mL of anhydrous ethylamine and then immersed in an ice-water bath. Freshly cut, oil-free lithium (60 mg) was added to the amine and the mixture stirred under dry argon until the dark blue color appeared. A solution of compound **119** (40 mg, 0.12 mmol) in THF (2 mL) was added dropwise to the blue solution until the color was discharged. On reappearance of the blue color more of the reactant solution (compound **119** in THF) was added until the color was discharged again. This process was repeated until all of the

reactant solution was added. After the addition was complete, the reaction mixture was stirred until the blue color persisted. It was then allowed to warm up to room temperature and stirred for 2 h. The excess of lithium was destroyed by the addition of methanol with cooling (exothermic reaction). After all of the lithium had dissolved, the solvent was removed under reduced pressure and the residue was diluted with water, acidified with aqueous hydrochloric acid (1 M) and extracted with ether (3 x15 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography with 25% ethyl acetate in hexane to give product **128** (26 mg, 90% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3387 cm^{-1} (OH broad); ^1H nmr (300 MHz) δ 5.80 (dm, J = 10 Hz, 1 H, -C**H**=CH-), 5.75 (ddd, J = 10, 4, 2 Hz, 1 H, -CH=C**H**-), 3.87 (ddd, J = 11, 11, 5.5 Hz, 1 H, -C**H**HOH), 3.75 (ddd, J = 11, 11, 5.5 Hz, 1 H, -CH**H**OH), 3.74 (dd, J = 4.5, 3 Hz, 1 H, C-2 **H**), 2.38 (m, 1 H), 1.99-2.24 (complex, 4 H), 1.47-1.76 (complex, 6 H), 1.17 (s, 3 H, C-1 C**H**$_3$), 1.15 (d, J = 7.5 Hz, 3 H, C-10 C**H**$_3$), 1.02 (s, 3 H, C-5 C**H**$_3$), 0.87 (d, J = 7 Hz, 3 H, C-4 C**H**$_3$); ^{13}C nmr (APT) δ 132.32 (a), 128.68 (a), 73.27 (a), 60.15 (p), 41.99 (a), 40.69 (a), 39.70 (p), 39.21 (p), 38.85 (p), 35.24 (p), 30.47 (a), 28.43 (p), 27.59 (a), 26.42 (a), 15.58 (a), 15.11 (a); hrms M^+ 252.2089 (calcd. for $C_{16}H_{28}O_2$: 252.2089), $[M-H_2O]^+$ 234.1983 (calcd. for $C_{16}H_{26}O$: 234.1983).

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(1-Formylmethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-ol (129)



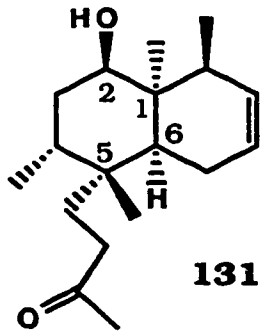
129

To a solution of **128** (70 mg, 0.28 mmol) in dry benzene (8 mL) under argon, was added $RuCl_2(PPh_3)_3$ (0.40 g, 0.42 mmol) in one portion. After being stirred for 3 days at room temperature, the solution turned black and precipitation occurred. The resulting mixture was diluted with ether and passed through a short silica gel column to remove black solids. Concentration gave the crude product, which was subjected to flash chromatography with ethyl acetate (5%) in hexane to furnish the aldehyde **129** (41 mg, 90% yield based on consumed starting material) as a colorless oil: ir (CH_2Cl_2 cast) 3572 (OH sharp), 3488 (OH broad), 2734 (C-H aldehyde) and 1717 cm^{-1} (C=O aldehyde); ^1H nmr (300 MHz) δ 9.98 (dd, *J* = 4, 1.5 Hz, 1 H, -C**H**=O), 5.81 (dm, *J* = 10 Hz, 1 H, -C**H**=CH-), 5.58 (ddd, *J* = 10, 4, 2, Hz, 1 H, -CH=C**H**-), 3.75 (dd, *J* = 4.5, 3 Hz, 1 H, -C**H**OH), 2.93 (ddd, *J* = 16.5, 4, 1.5 Hz, 1 H, -C**H**HCH=O), 2.31-2.51 (complex, 2 H, mixed with -O**H**), 2.29 (dd, *J* = 16.5, 1.5 Hz, 1 H, -CH**H**CH=O), 2.11-2.25 (complex, 3 H), 1.94 (ddd, *J* = 11, 6.5, 1 Hz, 1 H), 1.66 (ddd, *J* = 14, 2, 2 Hz, 1 H), 1.59 (dd, *J* = 6, 3 Hz, 1 H), 1.27 (d, *J* = 0.5 Hz, 3 H, C-1 C**H**$_3$), 1.16 (d, *J* = 7.5 Hz, 3 H, C-10 C**H**$_3$), 1.08 (s, 3 H, C-5 C**H**$_3$), 0.87 (d, *J* = 7 Hz, 3 H, C-4 C**H**$_3$); ^{13}C nmr (APT) δ 204.52 (a), 132.30 (a), 128.29 (a), 72.71 (a), 50.50 (p), 43.50 (a), 40.24 (a), 39.71 (p), 39.08 (p), 35.14 (p), 30.20 (a), 28.39 (p), 27.43 (a), 27.40 (a), 15.58 (a),

15.04 (a); hrms $[M-H_2O]^+$ 232.1823 (calcd. for $C_{16}H_{24}O$: 232.1827), $[M-CH_3CHO]^+$ 206.1673 (calcd. for $C_{14}H_{22}O$: 206.1670); cims $[M+NH_4]^+$ 268.2, $[M+H]^+$ 251.1.

Further elution with 15% ethyl acetate in hexane gave starting material **128** (25 mg, 35%).

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(3-Oxobutyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-ol (131)

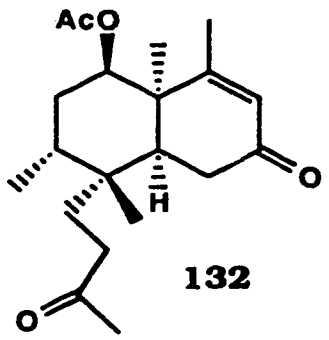


131

n-Butyllithium (0.32 mL, 1.6 M in hexanes, 0.5 mmol) was added to a solution of 1-methoxyethyltriphenylphosphonium chloride (0.19 g, 0.54 mmol) in THF (8 mL) at -42°C. After stirring at -40°C for 20 min (solution turned homogeneous with a blood-red color), a solution of aldehyde **129** (30 mg, 0.12 mmol) in THF (3 mL) was added slowly. The resulting mixture was stirred at -40°C for 10 h, and then water was added to quench the reaction. The aqueous solution was extracted with ether (3 x15 mL) and the combined organic extracts was dried ($MgSO_4$), filtered and concentrated. Without purification the crude Wittig product was dissolved in a solution of aqueous 20%

perchloric acid and distilled ether (1:1, 8 mL) and was then stirred at 0°C for 2 h. The reaction was quenched by addition of 0.5 N NaOH (2 mL) and diluted with ether (8 mL). The aqueous layer was extracted with ether (3 x 15 mL) and the combined extracts were washed with water, dried over $MgSO_4$, and concentrated. Flash chromatography (5-8% ethyl acetate in hexane) of the residue afforded ketone **131** (22 mg, 65% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3572 (OH) and 1714 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz) δ 5.80 (dm, J = 10.5 Hz, 1 H, -C**H**=CH-), 5.56 (ddd, J = 10.5, 5, 2 Hz, 1 H, -CH=C**H**-), 3.70 (br s, 1 H, -C**H**OH), 2.31-2.57 (complex, 3 H), 2.14 (s, 3 H, C**H**$_3$C=O), 1.95-2.24 (complex, 3 H), 1.62-1.77 (m, 2 H), 1.45-1.58 (m, 4 H), 1.13 (d, J = 7.5 Hz, 3 H, C-10 C**H**$_3$), 1.06 (s, 3 H, C-1 C**H**$_3$), 0.92 (s, 3 H, C-5 C**H**$_3$), 0.83 (d, J = 7 Hz, 3 H, C-4 C**H**$_3$); hrms M^+ 278.2235 (calcd. for $C_{18}H_{30}O_2$: 278.2245), $[M-H_2O]^+$ 260.2134 (calcd. for $C_{18}H_{28}O$: 260.2140).

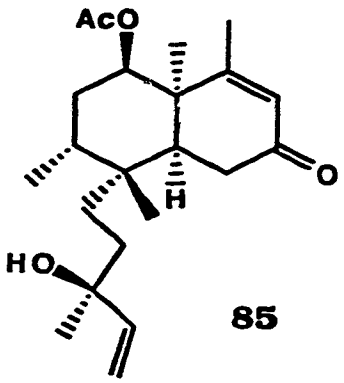
(1S*, 6R*, 7R*, 9R*, 10R*)-10-(3-Oxobutyl)-7-acetoxy-5,6,9,10-tetra methylbicyclo[4.4.0]dec-4-en-3-one (132)



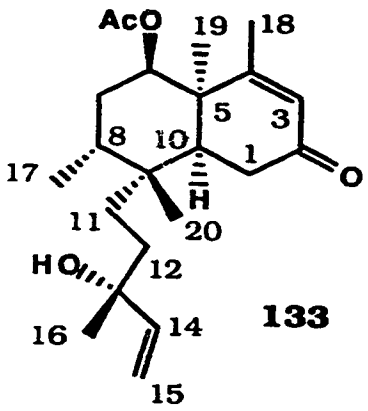
132

A solution of compound **131** (20 mg, 0.07 mmol), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (5 mg), acetic anhydride (0.07 mL, 0.35 mmol), pyridine (0.06 mL, 0.35 mmole), and 4-dimethylaminopyridine (3 mg) in carbon tetrachloride (40 mL) was placed in a photooxygenation apparatus and irradiated with two 200 W tungsten lamps for 56 h. During this period of time a gentle stream of oxygen was bubbled through the reaction mixture. After stopping the irradiation, bubbling was continued for another 18 h. The solution was then concentrated and the residue redissolved in ether (30 mL). The ethereal solution was washed with 1 M aqueous HCl (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel (35% ethyl acetate in hexane) to afford enone ester **132** (15 mg, 61% yield) as a colorless oil: ir (CCl_4 solution) 1742 (C=O, ester), 1721 (C=O, ketone) and 1671 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 5.95 (br s, 1 H, -C=C**H**C=O), 5.08 (br s, 1 H, -C**H**OAc), 2.72 (dd, J = 16.5, 12.5 Hz, 1 H, -C**H**$_\beta$HC=O), 2.42 (m, 3 H), 2.19 (s, 3 H, C**H**$_3$C=O, ketone), 1.85-2.07 (complex, 4 H), 1.96 (br s, 3 H, C**H**$_3$COO-), 1.93 (br s, 3 H, C**H**$_3$C=CHC=O), 1.51-1.70 (complex, 2 H), 1.33 (s, 3 H, C-6 C**H**$_3$), 0.96 (br s, 6 H, C-9 C**H**$_3$ and C-10 C**H**$_3$); hrms M^+ 334.2134 (calcd. for $C_{20}H_{30}O_4$: 334.2144), $[M-CH_3COOH]^+$ 274.1925 (calcd. for $C_{18}H_{26}O_2$: 274.1932).

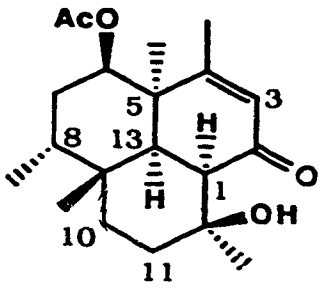
(±)-6β-Acetoxy-2-oxokolavenool (85), (±)-(5R, 6R, 8R, 9R, 10S, 13R)-13-Hydroxy-6-acetoxy-2-oxocleroda-3,14-diene (133) and (1R*, 5R*, 6R*, 8S*, 9R*, 12S*)-12-Hydroxy-6-acetoxy-4,5,8,9,12-pentamethyltricyclo[7.3.1.0^{5,13}]tridec-3-en-2-one (134)



85



133



134

To a solution of compound **132** (4.1 mg, 0.012 mmol) in THF (3 mL) at -20°C under an atmosphere of argon, was added vinylmagnesium bromide (24 μL, 1 M in THF, 0.024 mmol). The mixture was stirred at -20°C for 30 min and then at 0°C for an additional 1.5 h. Water (1 mL) and saturated aqueous NH_4Cl (1 mL) were added followed by extraction with ether (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was subjected to flash chromatography with 20% ethyl acetate in hexane to afford **134** (1.4 mg, 35% yield) as a white solid: ir (CH_2Cl_2 cast) 3423 (OH, broad), 1737 (C=O, ester) and 1643 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 6.29 (br s, 1 H, -O**H**), 5.77 (br d, J = 1 Hz, 1 H, -C=C**H**C=O), 4.96 (dd, J = 13, 4 Hz, 1 H, -C**H**OAc), 2.85 (dd, J = 4, 1 Hz, 1 H, -C**H**$_\alpha$C=O), 2.12 (s, 3 H, -OAc), 2.11 (d, J = 1.5 Hz, 3 H, C**H**$_3$C=CHC=O), 1.89-2.01 (complex, 3 H), 1.51-1.62 (complex, 5 H), 1.32 (s, 3 H, C-12 C**H**$_3$), 1.30 (s, 3 H, C-5 C**H**$_3$), 1.11 (d, J = 7 Hz, 3 H, C-8 C**H**$_3$), 0.97 (s, 3 H, C-9 C**H**$_3$); hrms M^+ 334.2143 (calcd. for $C_{20}H_{30}O_4$: 334.2144).

Further elution gave a 1.5:1 mixture of *cis*-clerodanes **85** and **133** (1.7 mg, 40% yield) as a colorless oil. The ratio was enhanced by a single preparative thin layer chromatography on silica gel, eluting with 15% ethyl acetate in hexane, from 1.5 : 1 to 4 : 1 (0.9 mg) with **85** as the major compound: ir (CCl_4 solution) 3600 (OH), 1741 (C=O, ester) and 1670 cm^{-1} (C=O, enone); hrms M^+ 362.2452 (calcd. for $C_{22}H_{34}O_4$: 362.2457); ^1H nmr (500 MHz): for isomer **85**: δ 5.94 (br s, 1 H, -C=C**H**C=O), 5.88 (dd, *J* = 17.5, 11 Hz, 1 H, C-14 **H**), 5.21 (dd, *J* = 17.5, 1 Hz, 1 H, C-15 $\mathbf{H}_t$), 5.07 (dd, *J* = 11, 1 Hz, 1 H, C-15 $\mathbf{H}_c$), 5.06 (br s, 3 H, -C**H**OAc), 2.69 (dd, *J* = 17, 10.5 Hz, 1 H, -C$\mathbf{H}_\beta$HC=O), 2.40 (m, 1 H, -C$\mathbf{H}_\alpha$HC=O), 1.95 (br s, 3 H, -OAc), 1.93 (br s, 3 H, C-4 C$\mathbf{H}_3$), 1.32 (s, 3 H, C-5 C$\mathbf{H}_3$), 1.29 (s, 3 H, C-13 C$\mathbf{H}_3$), 0.95 (br s, 6 H, C-8 C$\mathbf{H}_3$ and C-9 C$\mathbf{H}_3$); for isomer **133**: δ 5.95 (br s, 1 H, -C=C**H**C=O), 5.87 (dd, *J* = 17.5, 11 Hz, 1 H, C-14 **H**), 5.21 (dd, *J* = 17.5, 1 Hz, 1 H, C-15 $\mathbf{H}_t$), 5.08 (dd, *J* = 11, 1 Hz, 1 H, C-15 $\mathbf{H}_c$), 5.07 (br s, 3 H, -C**H**OAc), 2.71 (dd, *J* = 17, 10.5 Hz, 1 H, -C$\mathbf{H}_\beta$HC=O), 2.42 (m, 1 H, -C$\mathbf{H}_\alpha$HC=O), 1.95 (br s, 3 H, -OAc), 1.93 (br s, 3 H, C-4 C$\mathbf{H}_3$), 1.36 (s, 3 H, C-5 C$\mathbf{H}_3$), 1.29 (s, 3 H, C-13 C$\mathbf{H}_3$), 0.95 (br s, 6 H, C-8 C$\mathbf{H}_3$ and C-9 C$\mathbf{H}_3$).

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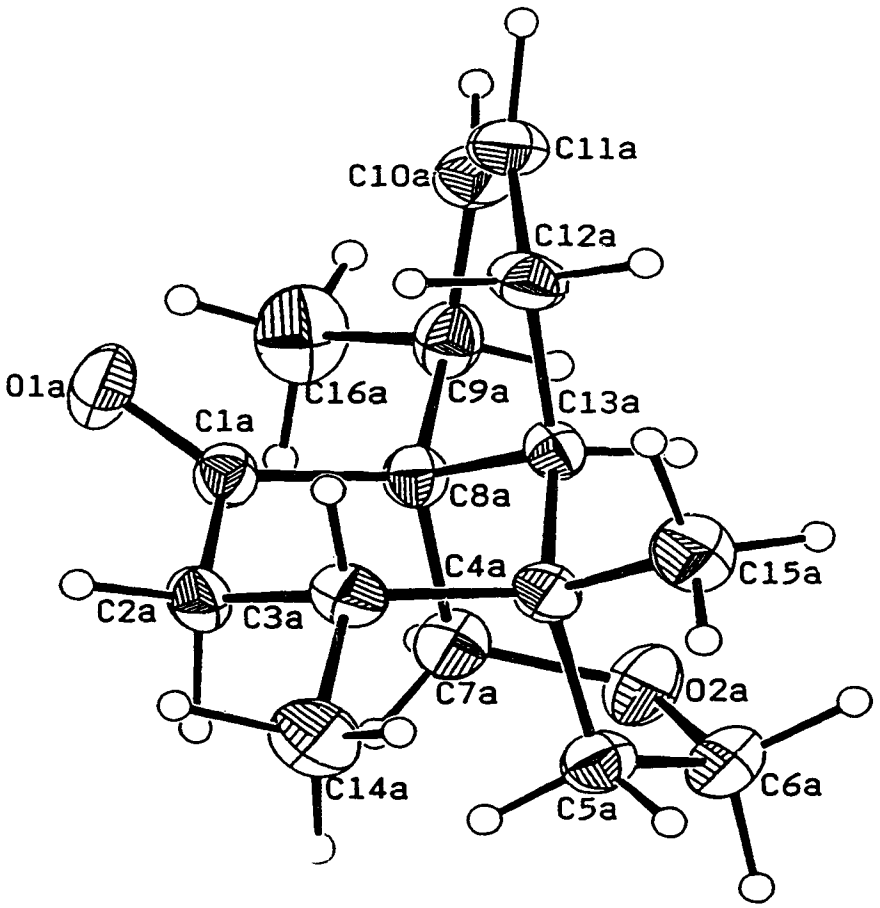
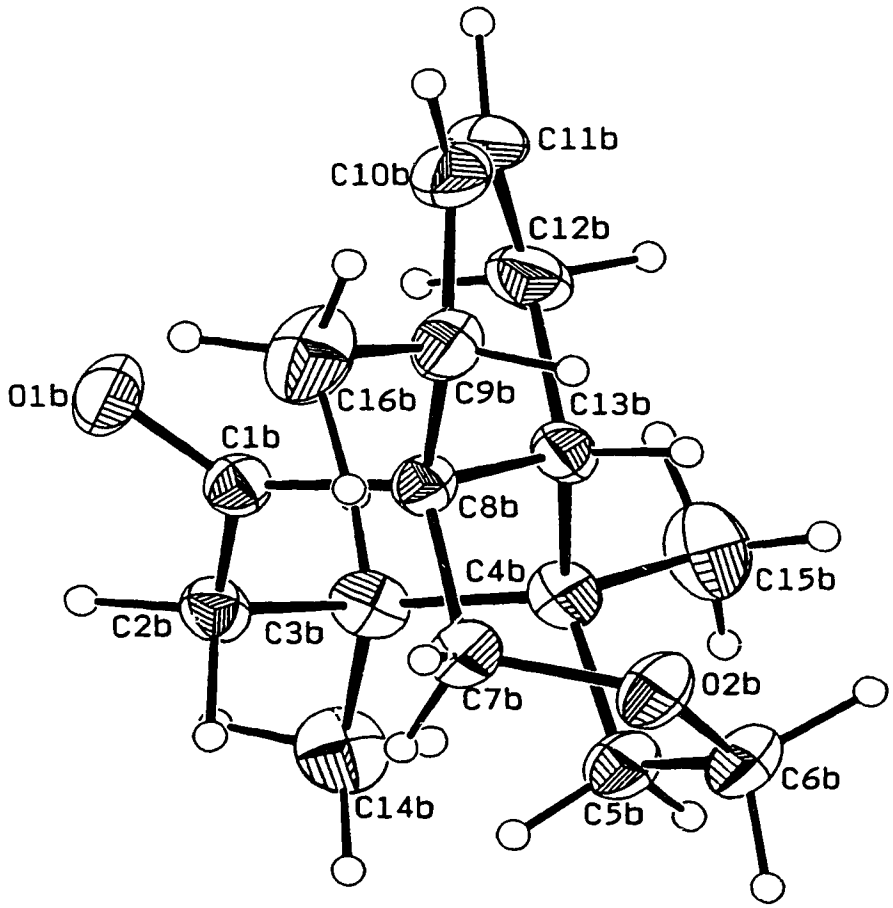
Appendix A

X-Ray Crystallographic Data for Compound 103

(the numbering in the Appendix is not the same as the normal numbering for the *cis*-clerodanes)




C11b
C10b
C12b
C16b
C9b
C13b
O1b
C1b
C8b
C4b
C15b
C2b
C3b
C7b
O2b
C6b
C14b
C5b

Experimental Details

Table. Crystal Data and Conditions for Crystallographic Data Collection and Structure Refinement

TITLE,	*** IC3739 ***
Formula ,	C16 H24 O2
FW ,	248.36
Diffractometer used,	Nonius
Space Group,	Monoclinic P 21/n
a(angstron),	13.310(4)
b(angstron),	12.1977(20)
c(angstron),	16.889(3)
beta(deg.),	95.88(3)
V(A**3),	2727.6(10)
Z ,	8
Dcalc(g.cm-3),	1.210
lambda(Angstron),	1.5418
F(000) ,	1091.
Unit cell detn: #;(2theta range),	25;(36.54 - 47.84 deg.)
Scan type,	theta/2theta
Scan width (deg),	2(0.80+0.14tan(theta))
Scan Speed (deg/min),	2.06-8.24
2 Theta(max),	140.0
h k l ranges ,	(-16; 16)(0; 14)(0; 20)
mu(cm-1),	7.431
Crystal size(mm),	0.50 X 0.50 X 0.60
Transmission,	0.910; 1.000
Temperature,	298.00
# of meas. reflns,	5134
# of obsed relfns (I > 2.0sig(I)),	4040
# of unique reflns,	5134
RF;RW ,	0.067;0.071
GoF,	4.30
Refinement program,	NRCVAX
# of atoms,	84
# of refined params,	518 (4040 out of 5134 reflns.)
Minimize function,	SUM(w|Fo-Fc|**2)
Unit weights were used	
g (2nd. ext. coeff.) x 10e4,	28.9(3)
(delta/sigma)max ,	0.0112
(D-map)max.min e/A**3 ,	-0.310; 0.270

NOTE :

RF = Sum(Fo-Fc)/Sum(Fo)

Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)]

GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]

3 standard reflns monitored every 3600 seconds, intensity variation < 2%

Bond Distance and Bond Angles

O1a-C1a	1.210(4)	O1b-C1b	1.211(4)
O2a-C6a	1.450(4)	O2b-C6b	1.450(4)
O2a-C7a	1.407(4)	O2b-C7b	1.404(4)
C1a-C2a	1.525(5)	C1b-C2b	1.525(5)
C1a-C8a	1.509(4)	C1b-C8b	1.509(4)
C2a-C3a	1.535(5)	C2b-C3b	1.538(5)
C2a-H2aa	1.13(3)	C2b-H2ba	1.11(3)
C2a-H2ab	1.00(3)	C2b-H2bb	1.05(3)
C3a-C4a	1.549(5)	C3b-C4b	1.551(5)
C3a-C14a	1.538(5)	C3b-C14b	1.537(5)
C3a-H3a	1.01(3)	C3b-H3b	1.03(3)
C4a-C5a	1.542(4)	C4b-C5b	1.551(5)
C4a-C13a	1.565(4)	C4b-C13b	1.560(5)
C4a-C15a	1.548(5)	C4b-C15b	1.542(5)
C5a-C6a	1.511(5)	C5b-C6b	1.513(5)
C5a-H5aa	0.96(3)	C5b-H5ba	0.90(4)
C5a-H5ab	0.94(4)	C5b-H5bb	0.98(3)
C6a-H6aa	1.08(3)	C6b-H6ba	1.08(4)
C6a-H6ab	1.05(3)	C6b-H6bb	1.07(3)
C7a-C8a	1.548(4)	C7b-C8b	1.543(4)
C7a-H7aa	0.94(4)	C7b-H7ba	0.99(3)
C7a-H7ab	1.00(3)	C7b-H7bb	0.94(3)
C8a-C9a	1.557(5)	C8b-C9b	1.555(4)
C8a-C13a	1.564(4)	C8b-C13b	1.555(4)
C9a-C10a	1.487(6)	C9b-C10b	1.476(6)
C9a-C16a	1.538(6)	C9b-C16b	1.543(6)
C9a-H9a	0.88(3)	C9b-H9b	1.00(3)
C10a-C11a	1.303(6)	C10b-C11b	1.300(7)
C10a-H10a	0.94(4)	C10b-H10b	0.94(5)
C11a-C12a	1.500(5)	C11b-C12b	1.504(6)
C11a-H11a	1.08(4)	C11b-H11b	1.00(4)
C12a-C13a	1.529(4)	C12b-C13b	1.543(5)
C12a-H12aa	1.06(4)	C12b-H12ba	1.01(3)
C12a-H12ab	0.99(3)	C12b-H12bb	1.01(4)
C13a-H13a	0.96(3)	C13b-H13b	0.95(3)
C14a-H14aa	1.17(4)	C14b-H14ba	1.10(4)
C14a-H14ab	0.99(4)	C14b-H14bb	0.88(4)
C14a-H14ac	0.87(4)	C14b-H14bc	1.07(4)
C15a-H15aa	0.99(3)	C15b-H15ba	0.94(3)
C15a-H15ab	0.92(4)	C15b-H15bb	1.14(5)
C15a-H15ac	1.10(4)	C15b-H15bc	0.93(5)
C16a-H16aa	0.97(5)	C16b-H16ba	0.96(4)
C16a-H16ab	1.13(6)	C16b-H16bb	1.25(7)
C16a-H16ac	0.94(4)	C16b-H16bc	0.90(6)

C6a-O2a-C7a	116.3(3)	C6b-O2b-C7b	116.64(25)
O1a-C1a-C2a	119.3(3)	O1b-C1b-C2b	119.4(3)
O1a-C1a-C8a	125.2(3)	O1b-C1b-C8b	125.0(3)
C2a-C1a-C8a	115.5(3)	C2b-C1b-C8b	115.6(3)
C1a-C2a-C3a	114.7(3)	C1b-C2b-C3b	114.8(3)
C1a-C2a-H2aa	108.8(16)	C1b-C2b-H2ba	108.4(16)
C1a-C2a-H2ab	111.1(17)	C1b-C2b-H2bb	110.9(17)
C3a-C2a-H2aa	107.9(16)	C3b-C2b-H2ba	108.3(16)
C3a-C2a-H2ab	109.4(17)	C3b-C2b-H2bb	113.0(17)
H2aa-C2a-H2ab	104.4(24)	H2ba-C2b-H2bb	100.2(24)

C2a-C3a-C4a	111.58(25)
C2a-C3a-C14a	109.1(3)
C2a-C3a-H3a	106.1(18)
C4a-C3a-C14a	114.6(3)
C4a-C3a-H3a	108.7(19)
C14a-C3a-H3a	106.3(18)
C3a-C4a-C5a	111.2(3)
C3a-C4a-C13a	108.75(25)
C3a-C4a-C15a	109.9(3)
C5a-C4a-C13a	111.72(25)
C5a-C4a-C15a	107.6(3)
C13a-C4a-C15a	107.6(3)
C4a-C5a-C6a	117.6(3)
C4a-C5a-H5aa	107.3(19)
C4a-C5a-H5ab	107.7(23)
C6a-C5a-H5aa	111.9(19)
C6a-C5a-H5ab	103.7(23)
H5aa-C5a-H5ab	108(3)
O2a-C6a-C5a	114.8(3)
O2a-C6a-H6aa	106.7(19)
O2a-C6a-H6ab	106.7(18)
C5a-C6a-H6aa	108.3(19)
C5a-C6a-H6ab	111.4(18)
H6aa-C6a-H6ab	108(3)
O2a-C7a-C8a	112.7(3)
O2a-C7a-H7aa	101.2(22)
O2a-C7a-H7ab	113.3(18)
C8a-C7a-H7aa	110.6(22)
C8a-C7a-H7ab	109.8(18)
H7aa-C7a-H7ab	108(3)
C1a-C8a-C7a	110.1(3)
C1a-C8a-C9a	115.0(3)
C1a-C8a-C13a	105.21(24)
C7a-C8a-C9a	106.9(3)
C7a-C8a-C13a	110.79(25)
C9a-C8a-C13a	108.8(3)
C8a-C9a-C10a	113.2(3)
C8a-C9a-C16a	115.0(3)
C8a-C9a-H9a	104.5(19)
C10a-C9a-C16a	110.8(3)
C10a-C9a-H9a	104.3(20)
C16a-C9a-H9a	108.3(19)
C9a-C10a-C11a	125.1(3)
C9a-C10a-H10a	119(3)
C11a-C10a-H10a	114(3)
C10a-C11a-C12a	122.3(3)
C10a-C11a-H11a	120.2(19)
C12a-C11a-H11a	117.5(19)
C11a-C12a-C13a	113.6(3)
C11a-C12a-H12aa	111.4(19)
C11a-C12a-H12ab	107.3(18)
C13a-C12a-H12aa	105.7(19)
C13a-C12a-H12ab	107.0(18)
H12aa-C12a-H12ab	111(3)
C4a-C13a-C8a	112.50(24)
C4a-C13a-C12a	112.58(25)
C4a-C13a-H13a	106.5(15)
C8a-C13a-C12a	110.5(3)
C8a-C13a-H13a	107.4(16)
C12a-C13a-H13a	106.9(15)

C2b-C3b-C4b	112.1(3)
C2b-C3b-C14b	108.2(3)
C2b-C3b-H3b	107.3(19)
C4b-C3b-C14b	115.0(3)
C4b-C3b-H3b	105.7(19)
C14b-C3b-H3b	108.1(19)
C3b-C4b-C5b	110.9(3)
C3b-C4b-C13b	108.9(3)
C3b-C4b-C15b	109.4(3)
C5b-C4b-C13b	111.8(3)
C5b-C4b-C15b	107.7(3)
C13b-C4b-C15b	108.1(3)
C4b-C5b-C6b	116.9(3)
C4b-C5b-H5ba	105.6(25)
C4b-C5b-H5bb	111.8(18)
C6b-C5b-H5ba	105(3)
C6b-C5b-H5bb	108.2(19)
H5ba-C5b-H5bb	108(3)
O2b-C6b-C5b	114.3(3)
O2b-C6b-H6ba	106.1(19)
O2b-C6b-H6bb	102.1(18)
C5b-C6b-H6ba	112.3(19)
C5b-C6b-H6bb	107.4(18)
H6ba-C6b-H6bb	114(3)
O2b-C7b-C8b	113.2(3)
O2b-C7b-H7ba	109.5(18)
O2b-C7b-H7bb	102.7(20)
C8b-C7b-H7ba	112.2(18)
C8b-C7b-H7bb	114.2(20)
H7ba-C7b-H7bb	104(3)
C1b-C8b-C7b	110.8(3)
C1b-C8b-C9b	113.9(3)
C1b-C8b-C13b	105.06(24)
C7b-C8b-C9b	107.5(3)
C7b-C8b-C13b	110.75(24)
C9b-C8b-C13b	108.8(3)
C8b-C9b-C10b	112.4(3)
C8b-C9b-C16b	114.7(3)
C8b-C9b-H9b	103.1(20)
C10b-C9b-C16b	112.1(3)
C10b-C9b-H9b	109.0(20)
C16b-C9b-H9b	104.8(20)
C9b-C10b-C11b	124.9(3)
C9b-C10b-H10b	116(3)
C11b-C10b-H10b	118(3)
C10b-C11b-C12b	122.9(3)
C10b-C11b-H11b	119.9(24)
C12b-C11b-H11b	117.0(24)
C11b-C12b-C13b	113.6(3)
C11b-C12b-H12ba	107.0(18)
C11b-C12b-H12bb	111.6(23)
C13b-C12b-H12ba	109.4(18)
C13b-C12b-H12bb	103.0(22)
H12ba-C12b-H12bb	112(3)
C4b-C13b-C8b	112.67(25)
C4b-C13b-C12b	112.2(3)
C4b-C13b-H13b	106.3(17)
C8b-C13b-C12b	110.2(3)
C8b-C13b-H13b	108.1(17)
C12b-C13b-H13b	107.1(17)

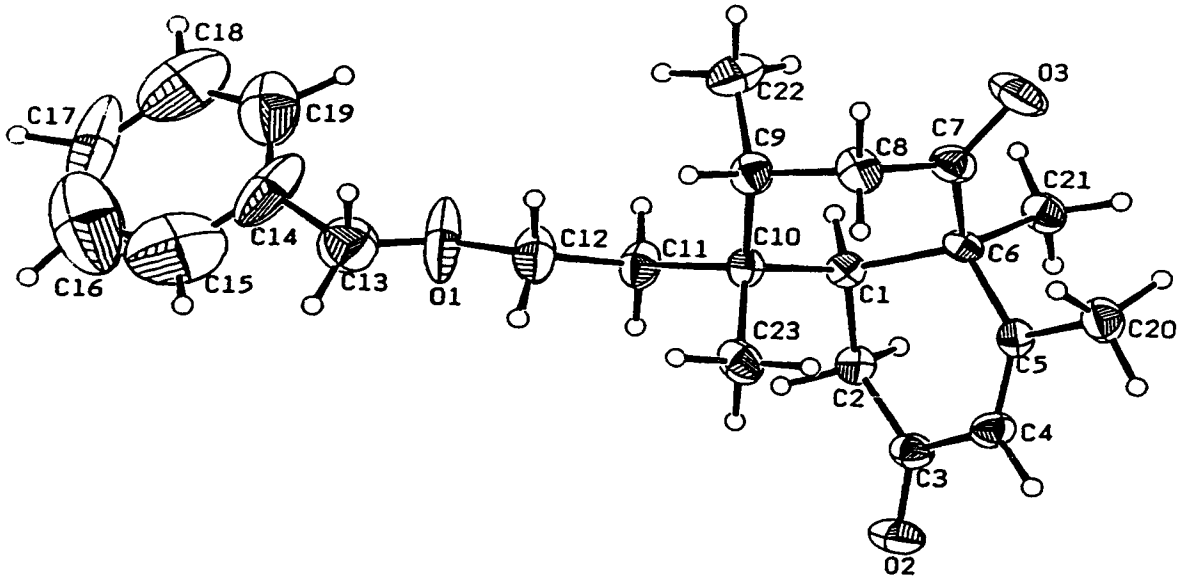
C3a-C14a-H14aa	104.9(20)
C3a-C14a-H14ab	112.9(22)
C3a-C14a-H14ac	108(3)
H14aa-C14a-H14ab	113(3)
H14aa-C14a-H14ac	105(3)
H14ab-C14a-H14ac	110(4)
C4a-C15a-H15aa	109.7(19)
C4a-C15a-H15ab	109.7(24)
C4a-C15a-H15ac	111.4(21)
H15aa-C15a-H15ab	106(3)
H15aa-C15a-H15ac	110(3)
H15ab-C15a-H15ac	108(3)
C9a-C16a-H16aa	112(3)
C9a-C16a-H16ab	113(3)
C9a-C16a-H16ac	102(3)
H16aa-C16a-H16ab	105(4)
H16aa-C16a-H16ac	108(4)
H16ab-C16a-H16ac	113(4)

C3b-C14b-H14ba	106.5(23)
C3b-C14b-H14bb	104(3)
C3b-C14b-H14bc	112.6(23)
H14ba-C14b-H14bb	105(3)
H14ba-C14b-H14bc	116(3)
H14bb-C14b-H14bc	110(3)
C4b-C15b-H15ba	109.2(21)
C4b-C15b-H15bb	111.5(24)
C4b-C15b-H15bc	106(3)
H15ba-C15b-H15bb	114(3)
H15ba-C15b-H15bc	102(4)
H15bb-C15b-H15bc	111(4)
C9b-C16b-H16ba	112.9(22)
C9b-C16b-H16bb	108(3)
C9b-C16b-H16bc	97(4)
H16ba-C16b-H16bb	117(4)
H16ba-C16b-H16bc	107(4)
H16bb-C16b-H16bc	110(5)

Appendix B

X-Ray Crystallographic Data for Compound 121

(the numbering in the Appendix is not the same as the normal numbering for the *cis*-clerodanes)



Experimental Details

Table. Crystal Data and Conditions for Crystallographic Data Collection and Structure Refinement

TITLE,	IC2855CU P B C A
Formula ,	C23 O3 H30
FW ,	354.48
Diffractometer used,	CAD4
Space Group,	Orthorhombic P bca
a(angstron),	11.0837(8)
b(angstron),	8.1077(7)
c(angstron),	44.428(4)
V(A**3),	3992.4(6)
Z ,	8
Dcalc(g.cm-3),	1.180
lambda(Angstron),	1.5418
F(000) ,	1536.
Unit cell detn: #;(2theta range),	25;(32.68 - 49.98 deg.)
Scan type,	theta/2theta
Scan width (deg),	2(0.80+0.14tan(theta))
Scan Speed (deg/min),	2.06-8.24
2 Theta(max),	120.0
h k l ranges ,	(0; 12)(0; 8)(0; 49)
mu(cm-1),	5.679
Crystal size(mm),	0.10 X 0.25 X 0.30
Transmission,	1.000; 1.000
Temperature,	298.00
# of meas. reflns,	2881
# of obsed relfns (I > 2.0sig(I)),	1557
# of unique reflns,	2864
RF;RW ,	0.068;0.067
GoF,	2.50
Refinement program,	NRCVAX
# of atoms,	59
# of refined params,	227 (1557 out of 2864 reflns.)
Minimize function,	SUM(w|Fo-Fc|**2)
Weights scheme,	(1/sigma(Fo))**2)
The weight modifier K in KFo**2 is,	0.000080
g (2nd. ext. coeff.) x 10**4,	0.33(3)
(delta/sigma)max ,	0.0877
(D -map)max,min e/A**3 ,	-0.300; 0.670

NOTE :
RF = Sum(Fo-Fc)/Sum(Fo)
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)]
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]

Filter factor = 12.46

Direct method : 304 E large, 100 E small, 6588 relationship

Bond Distances and Bond Angles

C1–C2	1.529(6)	C10–C11	1.547(7)
C1–C6	1.570(6)	C10–C23	1.545(7)
C1–C10	1.568(6)	C11–C12	1.516(7)
C2–C3	1.487(7)	C12–O1	1.449(7)
C3–C4	1.462(7)	O1–C13	1.231(11)
C3–O2	1.226(6)	O1–C13′	1.340(20)
C4–C5	1.329(7)	C13–C13′	1.052(23)
C5–C6	1.528(6)	C13–C14	1.627(13)
C5–C20	1.509(7)	C13′–C14	1.518(24)
C6–C7	1.520(6)	C14–C15	1.359(13)
C6–C21	1.537(6)	C14–C19	1.340(12)
C7–C8	1.491(7)	C15–C16	1.357(14)
C7–O3	1.217(6)	C16–C17	1.275(16)
C8–C9	1.521(7)	C17–C18	1.349(14)
C9–C10	1.543(7)	C18–C19	1.322(11)
C9–C22	1.535(7)		

C2–C1–C6	108.4(3)	C1–C10–C23	112.2(4)
C2–C1–C10	114.6(4)	C9–C10–C11	110.2(4)
C6–C1–C10	116.9(4)	C9–C10–C23	109.5(4)
C1–C2–C3	116.0(4)	C11–C10–C23	107.7(4)
C2–C3–C4	117.9(4)	C10–C11–C12	114.5(4)
C2–C3–O2	121.2(5)	C11–C12–O1	108.3(5)
C4–C3–O2	120.8(4)	C12–O1–C13	115.5(7)
C3–C4–C5	123.0(4)	C12–O1–C13′	117.4(10)
C4–C5–C6	121.3(4)	C13–O1–C13′	48.1(10)
C4–C5–C20	120.7(4)	O1–C13–C13′	71.4(13)
C6–C5–C20	117.7(4)	O1–C13–C14	104.6(8)
C1–C6–C5	112.2(3)	C13′–C13–C14	64.9(14)
C1–C6–C7	110.2(4)	O1–C13′–C13	60.5(12)
C1–C6–C21	109.9(4)	O1–C13′–C14	105.2(14)
C5–C6–C7	108.2(4)	C13–C13′–C14	76.2(15)
C5–C6–C21	107.0(3)	C13–C14–C13′	38.9(9)
C7–C6–C21	109.2(4)	C13–C14–C15	103.2(8)
C6–C7–C8	117.4(4)	C13–C14–C19	139.2(8)
C6–C7–O3	122.1(4)	C13′–C14–C15	138.7(10)
C8–C7–O3	120.5(4)	C13′–C14–C19	101.4(10)
C7–C8–C9	109.2(4)	C15–C14–C19	117.6(7)
C8–C9–C10	110.7(4)	C14–C15–C16	119.4(9)
C8–C9–C22	109.6(4)	C15–C16–C17	120.4(9)
C10–C9–C22	114.3(4)	C16–C17–C18	122.4(8)
C1–C10–C9	109.7(4)	C17–C18–C19	117.6(8)
C1–C10–C11	107.5(4)	C14–C19–C18	122.6(8)