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(DICHLOROCERIO)ACETONITRILE IN ORGANIC SYNTHESIS AND SYNTHETIC STUDIES ON FORSKOLIN, PHYLLANTHOCIN AND AN UNNATURAL ANTIFEEDANT

by

NAIM H. AL-SAID

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

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Dedicated to my family

Abstract

Chapter one of this thesis describes the formation and synthetic application of the cerium(III) derivative of acetonitrile. This reagent was found to add effectively to saturated ketones including the sterically hindered ones and to undergo exclusive 1,2-addition with conjugated enones to give β-hydroxynitriles in excellent yields. The potential use of the cerium(III) reagents derived from propionitrile and isobutyronitrile were also examined. These reagents were found to be considerably less reactive.

In the second chapter of this thesis, the results obtained from the synthetic studies on forskolin (**1**) are described. The adduct **48** was formed from the Diels-Alder reaction of dienone ester **46** and diene **47**. Hydrosilylation of adduct **48** followed by hydrolysis and reduction gave diol **65**. The reduction of the hydroxy methylene to an angular methyl in this diol was studied through two approaches. In the first approach, the diol was transformed into benzyl ether **70** in four steps: cyclization induced by *N*-bromosuccinimide, dehydrobromination, xanthate formation and tri-*n*-butyltin hydride reduction. In the second approach, diol **65** was transformed into tricyclic system **85** *via* zinc dust reduction of a methanesulfonate derivative. Also described in this chapter, are studies carried out on adduct **96**. Adduct **96** was

successfully converted into acetal **106** through reduction of the enone system to a saturated ketone followed by acetal formation.

In chapter three, an efficient approach to *cis*-epoxy diacetate **5**, a synthetic antifeedant, is described. The use of chloro compound **14** and acetate **15** was assessed, and both furnished the enol ether **18**. Methoxy derivative **16** was successfully elaborated to alcohol **25** in four steps: simultaneous reduction of the ketone and ester using lithium aluminum hydride, catalytic hydrogenation, acetylation and ether cleavage with *B*-Br-9-BBN. Alcohol **25** was also prepared from adduct **28** *via* an alternative route. Finally, the alcohol **25** was subjected to a reaction sequence involving selenide formation, oxidative elimination and treatment with MCPBA, producing *cis*-epoxy diacetate **5**.

Chapter four describes the synthetic studies on phyllanthocin (**2**) which were carried out as far as butyrolactone **109**. Photocycloaddition of ester enone **104** with 1,1-dimethoxyethene followed by hydrolysis of the acetal moiety gave diketone **105**. The four-member ring was expanded through selective Baeyer-Villiger oxidation using MCPBA to afford keto lactone **107**. The ketone carbonyl was reduced to a methylene unit *via* thioacetal formation and Ra-Ni desulfurization to form butyrolactone**109**.

Acknowledgments

Foremost, I would like to express my most profound gratitude to Professor H. J. Liu for his invaluable guidance and willing support throughout this work. His enthusiasm, patience and wisdom all helped to pave the way. His personal involvement and assistance in the preparation of this thesis are also greatly appreciated.

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Finally, my special thanks are also extended to my wife, Lamya, for her unconditional support during my Ph. D program.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

a	antiphase
Ac	acetyl
APT	attached proton test
AIBN	azobisisobutyronitrile
Bn	benzyl
br	broad
B-Br-9-BBN	*B*-bromo-9-borabicyclo[3.3.1]nonane
cims	chemical ionization mass spectrum
NBS	*N*-bromosuccinimide
MCPBA	*m*-chloroperbenzoic acid
d	doublet
DBU	1,5-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent

Eq.	equation
gem	geminal
h	hour
HMPA	hexamethylphosphoramide
hrms	high resolution mass spectrum
ir	infrared
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
mp	melting point
min	minutes
Ms	methanesulfonyl
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
p	phase
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PDCP	phenyl dichlorophosphate

Ph	phenyl
PSP	*N*-(phenylseleno)phthalmide
p.s.i.	pound per square inch
pyr	pyridine
q	quartet
Ra-Ni	Raney nickel
r.t	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	tetramethylsilane
TPP	tetraphenylporphine

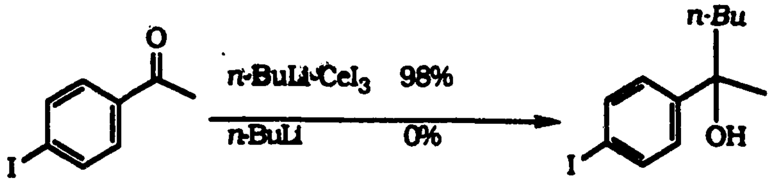
CHAPTER 1

(DICHLOROCERIO)ACETONITRILE IN ORGANIC SYNTHESIS

Introduction

The nucleophilic addition of organometallic reagents to ketones is one of the most versatile reactions in synthetic organic chemistry.[1] However, the desired addition product cannot always be obtained in satisfactory yield as a result of side reactions such as enolization, conjugate addition, condensation and reduction. From a synthetic viewpoint, it is always desirable to improve the yield of the addition product and to eliminate any secondary products resulting from side reactions.

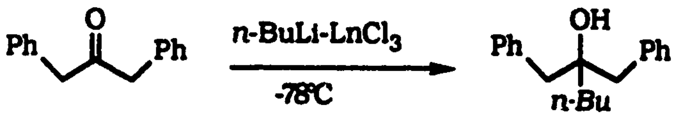
In 1982, Imamoto *et al.*[2] reported for the first time the preparation of tertiary alcohols from ketones by using organocerium(III) reagents ($RCeX_2$). The reagents were generated *via* transmetallation of organolithium reagents with cerium(III) iodide in tetrahydrofuran at -65°C. Nucleophilic addition of these reagents to ketones proceeded readily giving the corresponding tertiary alcohols in excellent yields. The most interesting example was the addition of *n*-butylcerium(III) iodide to *p*-iodoacetophenone, from which a near-quantitative yield of alcohol **1** was isolated (Eq. 1). This result is in sharp contrast to that employing *n*-butyllithium, from which neither the desired product was isolated nor the starting material was recovered, probably due to the metal-halogen exchange.



(1)

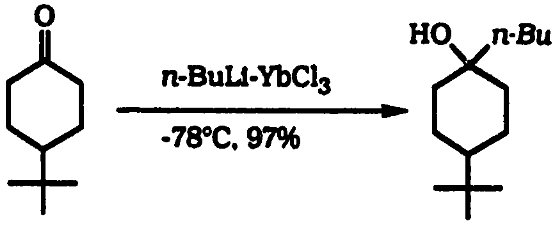
1

After this interesting observation, Imamoto *et al.*[3] examined the use of commercially available lanthanide chlorides ($CeCl_3 \cdot 7H_2O$, $LaCl_3 \cdot 7H_2O$, $NdCl_3 \cdot 6H_2O$, $PrCl_3 \cdot 7H_2O$, $SmCl_3 \cdot 6H_2O$ and $YbCl_3 \cdot 6H_2O$). The salts were dried and then treated with *n*-butyllithium in tetrahydrofuran at -78°C. Reaction of the resulting organometallic complex with ketones (Eq. 2 and 3) provided excellent yields of the addition products. These results



(2)

(Ln = Ce, 96%; La, 96%; Nd, 98%; Pr, 85%; Sm, 60%)



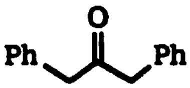
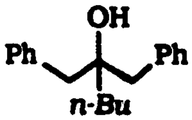
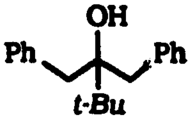
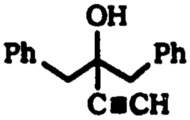
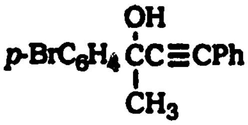
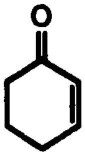
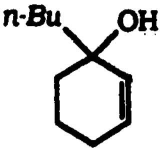
(3)

indicate that lanthanides (Ce, La, Nd, Pr, Sm and Yb) are suitable for transmetallation and the organometallic compounds thus produced can undergo efficient nucleophilic addition with ketones. Among the lanthanides examined, cerium(III) chloride is regarded to be the best for the reaction because it is available at a moderate price and is easily dried.

The organocerium(III) chloride reagents were conveniently generated by transmetallation of the corresponding lithium reagents with cerium(III) chloride in tetrahydrofuran at -78°C (Eq. 4). The organocerium(III) reagents showed high propensity towards ketones, probably due to a more effective coordination with the carbonyl group than that of lithium or magnesium. They were found to react cleanly with a variety of ketones giving the expected alcohols (Table 1-I). The salient feature is the high yields of the addition products of these reagents to easily enolizable ketones, such as 1,3-diphenyl-2-propanone (Table 1-I, Entries 1, 3 and 5). Under similar reaction conditions, the use of the corresponding Grignard or lithium reagents gave the products in low yields as a result of proton exchange, due to the strong basicity of these reagents (Table 1-I, Entries 2, 4 and 6).[4] Furthermore, contrary to the *tert*-butyl Grignard reagent which acts as a reducing agent rather than a nucleophile, the *tert*-butylcerium reagent provided a satisfactory yield of the addition product with 1,3-diphenyl-2-propanone (Table 1-I, Entries 3 and 4).[4]

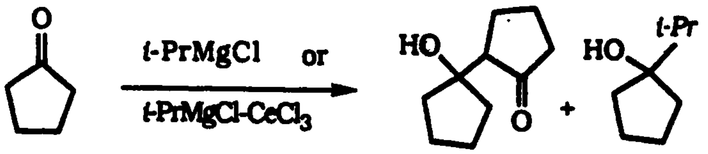
$$\mathrm{RLi} \xrightarrow[-78^{\circ}\mathrm{C}]{\mathrm{CeCl_3,\ THF}} \mathrm{RCeCl_2} + \mathrm{LiCl} \qquad (4)$$

Table 1-I. Comparison of the Reactivity of Organocerium, Grignard and Lithium Reagents.

Entry	Ketone	Reagent	Product	Yield (%)
1		n-BuCeCl$_2$		96
2	"	n-BuMgBr	"	10
3	"	t-BuCeCl$_2$		65
4	"	t-BuMgBr	"	0
5	"	HC≡CCeCl$_2$		95
6	"	HC≡CLi	"	60
7	p-BrC$_6$H$_4$COCH$_3$	PhC≡CCeCl$_2$	 $p\text{-BrC}_6\text{H}_4\overset{\text{OH}}{\underset{\text{CH}_3}{\text{C}}}\text{C}\equiv\text{CPh}$	95
8	"	PhC≡CLi	"	0
9		n-BuCeCl$_2$		98
10	"	n-BuMgBr	"	48

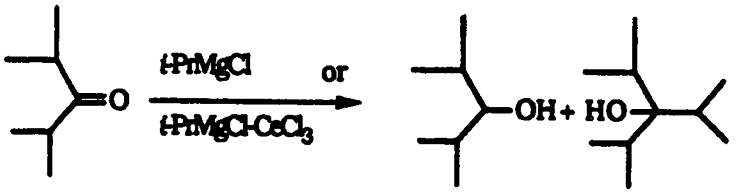
As a consequence of the above results, Imamoto *et al.*[5] extended their investigation to the addition of organocerium reagents to conjugated enones. Cerium reagents were found to have higher reactivity and better selectivity for 1,2-addition than the corresponding magnesium or lithium reagents. *n*-Butylcerium(III) chloride for example, reacted cleanly with 2-cyclohexenone, providing the allylic alcohol in excellent yield, while *n*-butylmagnesium bromide produced 1,2- and 1,4-addition products in 48% and 21% yield, respectively (Table 1-I, Entries 9 and 10).

Imamoto and coworkers[5,6] also studied the use of Grignard reagents in combination with cerium(III) chloride ($RMgX-CeCl_3$). The reagents were easily prepared by addition of a Grignard reagent to cerium(III) chloride in tetrahydrofuran at 0°C. It was noted that the cerium(III) chloride promoted Grignard addition to ketones could be performed at 0°C instead of -78°C required for organolithium derived cerium reagents. Easily enolizable ketones were subjected to nucleophilic addition using $RMgX-CeCl_3$ with remarkable suppression of enolate formation. For example, the reaction of *i*-PrMgCl with cyclopentanone provided an 88% yield of aldol condensation product **2** along with a 3% yield of addition product **3**. In sharp contrast, in the presence of cerium(III) chloride the reaction provided the addition product **3** in 80% yield (Eq. 5). Moreover, the reduction of carbonyl compounds with Grignard reagents having a β-hydrogen is also suppressed in the presence of cerium(III) chloride. An example is the reaction of 2,4-dimethyl-3-pentanone with *i*-PrMgCl. In the absence of $CeCl_3$, the reduction product **4** was produced in 58% yield. On the other hand, a 52% yield of the addition product **5** was isolated when the Grignard reagent was coupled with $CeCl_3$ (Eq. 6). These promising results prompted Imamoto *et al.*[6] to study the reaction of conjugated enones with the



(5)

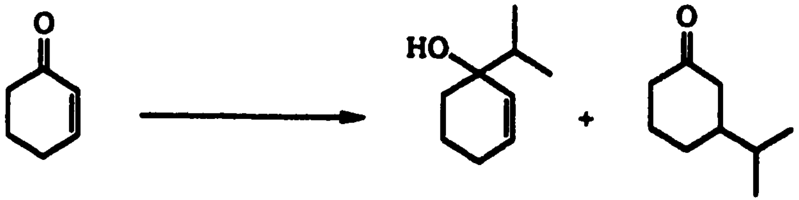
2 **3**



(6)

4 **5**

$RMgX$-$CeCl_3$ system. In the presence of $CeCl_3$ most of the reactions were found to give 1,2-addition adducts in considerably higher yields than those obtained using RMgX alone. An example is given in (Eq. 7).

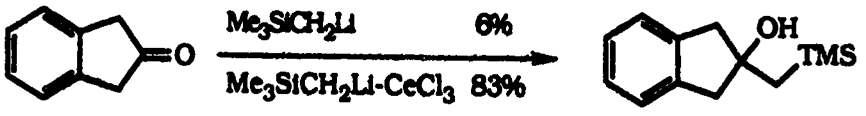


(7)

i-PrMgCl	12%	53%
i-PrMgCl-$CeCl_3$	91%	5%

In summary, organocerium reagents undergo efficient nucleophilic addition with saturated and α,β-unsaturated ketones, including those highly susceptible to enolization or conjugate addition. It can be concluded that organocerium reagents are less basic than the lithium or Grignard counterparts. Organocerium reagents show high selectivity for 1,2-addition towards conjugated enones and a pronounced affinity towards the carbonylic double bond, ascribed mainly to the strong affinity of trivalent cerium towards the oxygen atom. These characteristics, combined with the fact that cerium(III) chloride is commercially available and easily dried, promise broad synthetic utility of organocerium reagent methodology.

During the last several years cerium mediated reagents have been extensively applied to the preparation of a great number of key intermediates in organic synthesis. Johnson *et al.*[7] made use of an organocerium reagent to circumvent the high basicity and lack of chemoselectivity of the conventional Peterson's methylenation reagent Me_3SiCH_2Li.[8] As an example, the reaction of 2-indanone with Me_3SiCH_2Li-$CeCl_3$ resulted in an excellent yield of the desired 2-hydroxy silane **6** (Eq. 8).

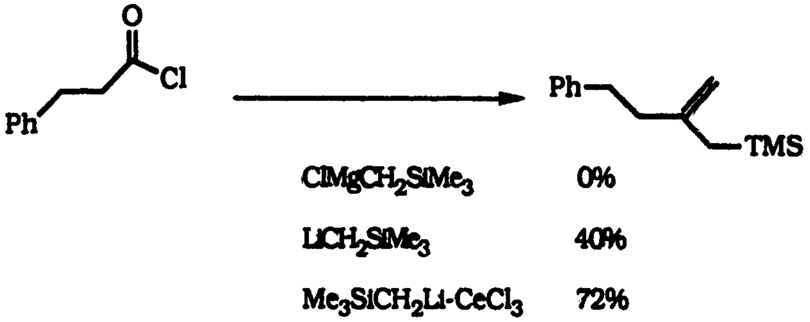


(8)

6

Allylsilanes were prepared in good yields based on the addition of organocerium reagents to carboxylic acid derivatives

(Eq. 9 and 10).[9-12] The use of organolithium or Grignard reagents with acid chlorides is known to afford only low yields of allylsilanes. The use of cerous chloride altered the chemoselectivity of the reaction of Grignard reagents with some acetal esters. For example, the reaction of Me_3SiCH_2MgCl with the ester shown in Eq. 10 gave a mixture of products in which the only new carbon-carbon bond formed was in ester **7**, resulting from an elimination-addition-elimination reaction sequence. In contrast, upon addition of cerium(II) chloride, the allylsilane **8** was obtained in 37% yield.[12]



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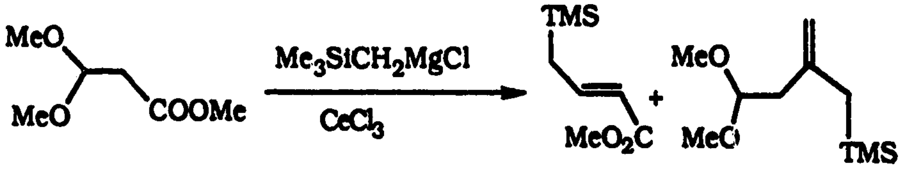
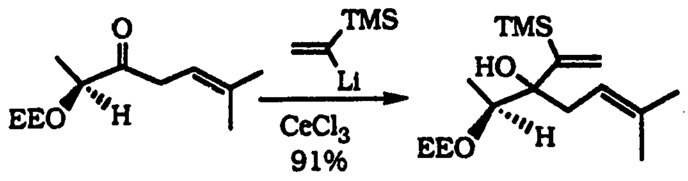


(10)

7 **8**

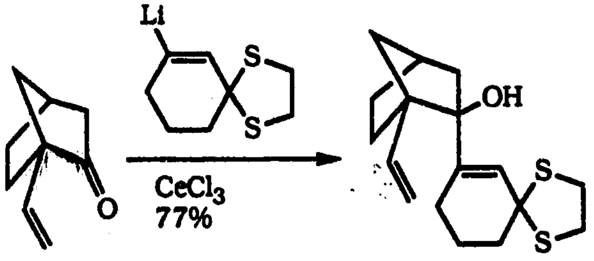
Tsuchihashi *et al.*[13] accomplished a highly enantio- and diastereocontrolled synthesis of chiral pheromone eldanolide. As a key operation, the vinyl silane moiety was introduced by the use of an organocerium reagent to afford the addition product **9** in 91% yield (Eq. 11). The same transformation using the corresponding lithium or Grignard reagent was unsatisfactory (<40% yield) due to the high enolizability of the ketone.



9

(11)

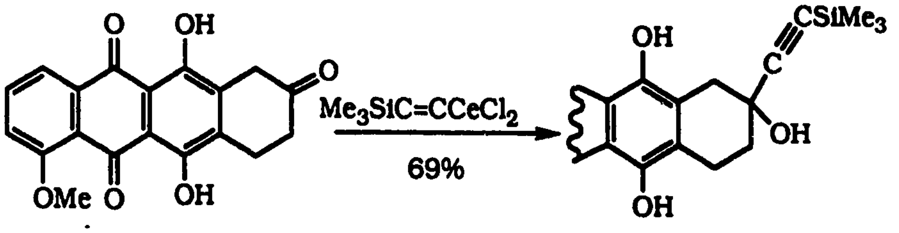
The use of the anionic oxy-cope rearrangement for asymmetric induction has been extensively investigated by Paquette *et al.*[14-18] The required intermediates were readily formed by nucleophilic addition of alkenylcerium reagents to β,γ-unsaturated ketones (Eq. 12). The use of the corresponding organolithium or magnesium reagents was shown to give the addition products in low yields.



(12)

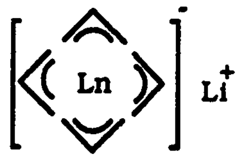
Terashima,[19] Tamura[20-24] and White[25] used an ethynylcerium reagent in the synthesis of several key intermediates of natural products. They found that the 2-trimethylsilylethynylcerium(III) reagent reacts efficiently with highly enolizable ketones to give the addition products.

Tamura *et al.*[21] used an alkynylcerium reagent in the synthesis of various antitumor agents such as the daunomycin derivative shown in Eq. 13.



(13)

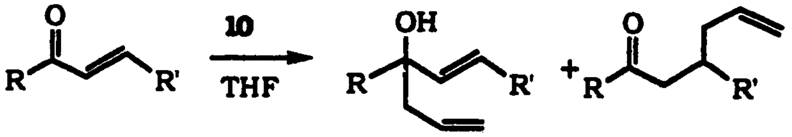
Fukuzawa *et al.*[26] were interested in the easily prepared π-allyl-lanthanoid ate complexes **10** and explored their use as allyl transfer agents. The ate complexes were prepared by treatment of tetra-allyltin with anhydrous lanthanide trichloride at room temperature (Eq. 14). Addition of α,β-unsaturated carbonyl compounds to the ate complex (Eq. 15) resulted in a high degree of 1,2-regioselectivity to furnish 3-hydroxy-1,5-dienes in good yields (Table 1-II). Treatment of chalcone (Eq. 15, R = R' = Ph) with allyllithium gave a mixture of 1,2- and 1,4-adducts in a ratio of 40 : 60, showing an almost complete lack of selectivity. However, the ate complex **10** showed a dramatic improvement in regioselectivity. The 1,2-regioselectivity of allylation is rationalized by the strong oxophilicity and hardness of the metal species.[27]



Ln = Ce, Nd, Sm, Gd, or Dy.

10

$$(CH_2{=}CH\text{-}CH_2)_4Sn + 4\,n\text{-}BuLi \xrightarrow[\text{THF, r. t.}]{LnCl_3} \mathbf{10} + n\text{-}Bu_4Sn + 3\,LiCl_3 \qquad (14)$$



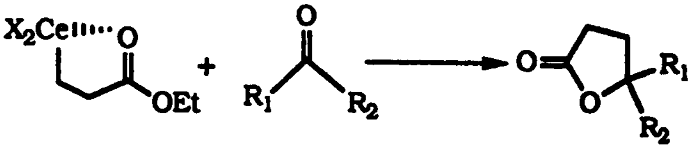
(15)

Table 1-II. Comparison of the Reactivities of Allyllithium and Allylcerium(III) Ate Complex **10** Towards Conjugated Enones.

Entry	Enone	Metal	Yield	Isomer ratio (1,2 : 1,4)
1	2-Cyclohexenone	Li	64	84 : 16
2	2-Cyclohexenone	Ce	96	99 : 1
3	Chalcone	Li	99	40 : 60
4	Chalcone	Ce	90	75 : 25

Fukuzawa *et al.*[28] also reported that the reaction of ethyl 3-haloesters with cerium metal in tetrahydrofuran proceeded smoothly in the presence of a trace of iodine to give cerium ester homoenolates **11**. Treatment of cerium ester homoenolate (**11**) with various ketones at room temperature afforded γ-lactones **12**

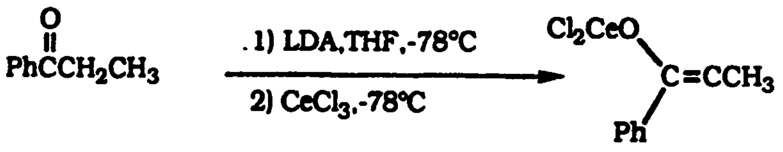
(Eq. 16) in good yields (40-70%). On the other hand, the use of magnesium metal failed to give any γ-lactones even after heating.



(16)

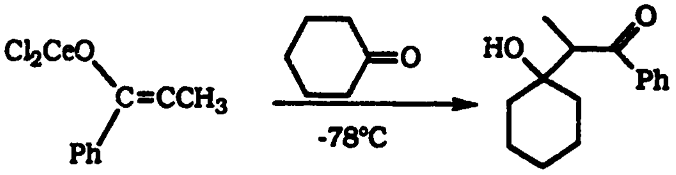
11 **12**

The pronounced nucleophilicity of organocerium reagents prompted Imamoto *et al.*[29] to study the cerium mediated aldol reaction. Cerium enolates such as **13** were generated by transmetallation of the corresponding lithium enolates with cerium(III) chloride in tetrahydrofuran at -78°C (Eq. 17). The generated cerium enolates were then allowed to react with ketones at the same temperature (Eq. 18). Generally higher yields, than those obtained using lithium enolates, of the desired aldol products such as **14** were achieved by the use of cerium enolates. The new process, in which the cerium(III) ion likely played a more effective role than the lithium ion in the chelating process with the intermediate leading to the aldol adduct, supressed retro-aldol and/or proton exchange. However, similar stereoselectivity was observed for both reagents. The stereochemical outcome can be rationalized by assuming that the transmetallation of lithium enolates with cerium(III) chloride occurred without change in the geometry of the enolates.



(17)

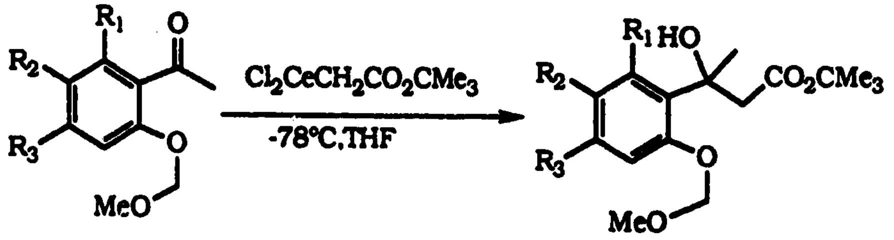
13



(18)

14

Cerium ester enolate $Cl_2CeCH_2COOCMe_3$ was reported for the first time by Nagasawa *et al.*[30] This reagent, which was generated by transmetallation of $LiCH_2COOCMe_3$ with $CeCl_3$, was found to react efficiently with acetophenone derivatives to furnish β-hydroxy esters **15** in excellent yields (Eq. 19). No side reactions, such as dimerization or self-condensation, were detected. In comparison, the use of the lithium enolate of *tert*-butyl acetate or the Reformatsky type reactions under a wide variety of conditions afforded only recovered starting materials.

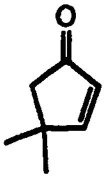
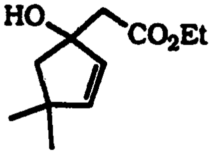
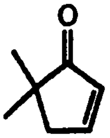
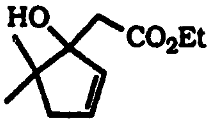
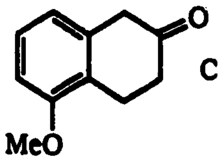
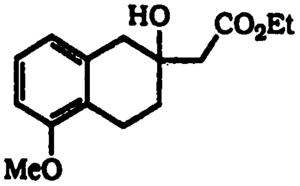
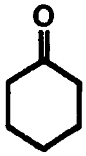
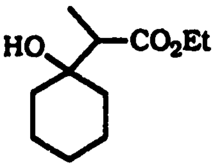
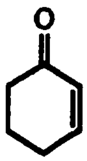
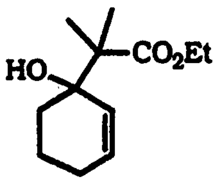


(19)

15

The addition of cerium ethyl ester enolates to different ketones was studied in detail in our laboratory.[31] Some of the results of this study are compiled in Table 1-III. It was found that unsubstituted (Entries 1 and 2), mono (Entry 4) and disubstituted (Entry 5) cerium(III) ester enolates were all excellent nucleophiles which added to carbonyl compounds efficiently to furnish β-hydroxy esters. They exhibited complete 1,2-regioselectivity. Sterically hindered ketones (Entry 2) and highly enolizable ketones (Entry 3) also gave excellent yields of the addition

Table 1-III. Addition of Cerium(III) Ester Enolates to Ketones.

Entry	Ketone	Enolate	Product	Yield (%)
1		$Cl_2CeCH_2CO_2Et$ $LiCH_2CO_2Et$		100 50
2		$Cl_2CeCH_2CO_2Et$ $LiCH_2CO_2Et$		97 60
3		$Cl_2CeCH_2CO_2Et$		92
4		$Cl_2CeCH(CH_3)CO_2Et$		94
5		$Cl_2CeC(CH_3)_2CO_2Et$		92

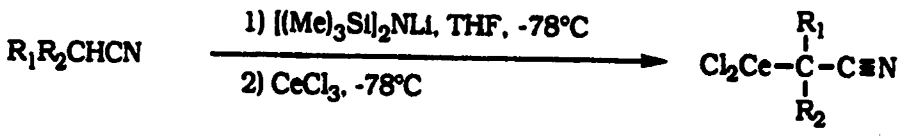
products. More importantly, this newly developed class of reagents gave better yields of β-hydroxy esters than the corresponding lithium reagents.

These interesting results prompted us to investigate the cerium mediated addition of the acetonitrile carbanion to ketones. The first part of this thesis describes the first example of such an addition process.

Results and Discussion

The addition of nitrile stabilized carbanions to the carbonyl moiety plays an important role in carbon-carbon bond formation.[32] However, this addition is often complicated by enolization, reversibility and conjugate addition. The regioselectivity of the addition to conjugated enones varies as a function of substrate, nitrile, reaction temperature and solvent. The results of our investigation will be presented in this section.

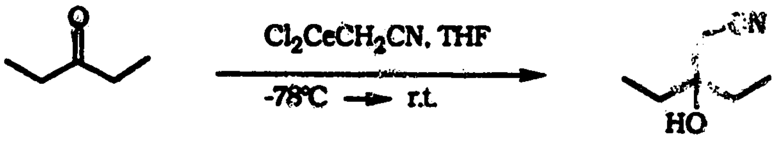
(Dichlorocerio)acetonitrile (**16**), (dichlorocerio)propionitrile (**17**) and (dichlorocerio)isobutyronitrile (**18**) were generated by transmetallation of the corresponding lithium salts with cerium(III) chloride in tetrahydrofuran at -78°C according to Eq. 20. Exploratory studies on the addition of cerium acetonitrile anion **16** to a ketone were carried out using diethyl ketone. In the reaction of cerium reagent **16** with diethyl ketone (1 equiv.) the formation of the addition product **19** was not detected at -78°C (Eq. 21). However, the product **19** was slowly formed when



$$R_1R_2CHCN \xrightarrow[\text{2) CeCl}_3\text{, -78°C}]{\text{1) [(Me)}_3\text{Si]}_2\text{NLi, THF, -78°C}} Cl_2Ce-\overset{R_1}{\underset{R_2}{C}}-C\equiv N \qquad (20)$$

$R_1, R_2 = H$	**16**
$R_1 = CH_3, R_2 = H$	**17**
$R1 = R_2 = CH_3$	**18**

the reaction temperature was raised to about -30°C. After one hour at room temperature, a 40% yield of the desired



(21)

19

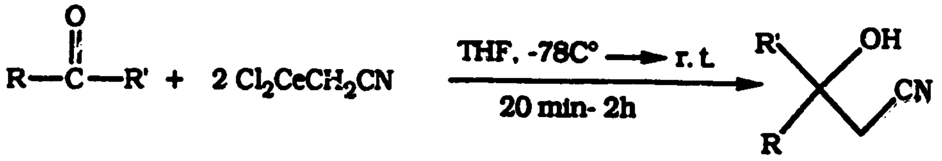
addition product **19** was isolated. Extended reaction time at room temperature did not improve the yield of the addition product. However, by using two equivalents of the cerium reagent, a quantitative yield of **19** was effected. The infrared (ir) spectrum of the β-hydroxynitrile **19** displayed a hydroxy absorption at 3474 cm^{-1} and a nitrile absorption at 2250 cm^{-1}. Its high resolution mass spectrum (hrms) showed no molecular ion but a peak at m/z 109.0891, corresponding to the loss of water was observed. The molecular formula of compound **19** was confirmed by elemental analysis and by chemical ionization mass spectrum (cims). Using ammonia as the reagent gas, a $[M+NH_4]^+$ peak was observed at m/z 145, consistent with the formula $C_7H_{13}NO$. The ^1H nmr spectrum of compound **19** displayed a singlet at δ 2.50, due to the methylene protons next to the cyano group.

To study the general scope and limitation of the addition reaction, several structurally diverse ketones were subjected to treatment with the cerium salt **16** under similar conditions (2 equiv. of Cl_2CeCH_2CN, -78°C to r.t.). The results are summarized in Table 1-IV. Without exception, the addition products were isolated in excellent yields. The addition of (dichlorocerio)acetonitrile **16** to acetophenone resulted in the formation of β-hydroxynitrile **20** in 82% yield (Entry 2). The structure of this compound was confirmed by its spectroscopic data. Its ir spectrum showed hydroxy and nitrile absorption bands at 3450 and 2256 cm^{-1}, respectively. The hrms exhibited the molecular ion at m/z 161.0843, consistent with the molecular formula $C_{10}H_{11}NO$. The ^{1}H nmr spectrum displayed the protons next to the nitrile as a singlet at δ 2.75.

It has been established by Trost *et al.*[33] that the addition of lithioacetonitrile to both cyclohexanones and cyclohexenones is highly axial-selective. To study the stereoselectivity of the newly developed cerium acetonitrile reagent, 4-*tert*-butylcyclohexanone was treated with **16** (Entry 5). The addition product was isolated in 96% yield as a mixture of two diastereomers **23** and **24** in a ratio of 2.2:1 as determined by high resolution ^{1}H nmr and ^{13}C nmr spectra.

Trost *et al.* studied the addition of lithioacetonitrile to 4-*tert*-butylcyclohexanone and observed the formation of **23** and **24** in a 5:1 ratio. The ir spectrum of the product mixture formed from the cerium acetonitrile addition displayed hydroxy and nitrile absorption bands at 3252 and 2240 cm^{-1}, respectively. The hrms showed the molecular ion at m/z 195.1622, corresponding to the required formula $C_{12}H_{21}NO$. Elemental analysis further

Table 1-IV. Addition of (Dichlorocerio)acetonitrile (16) to Saturated Ketones.



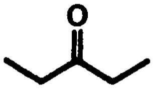
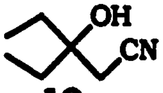
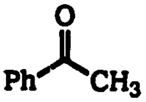
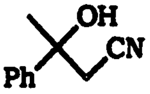
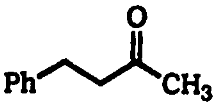
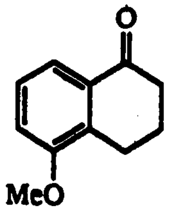
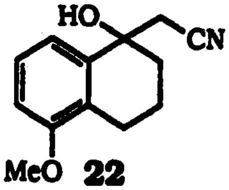
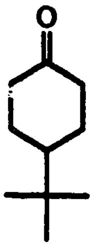
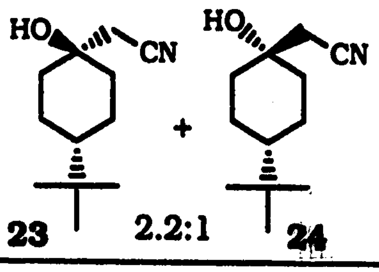
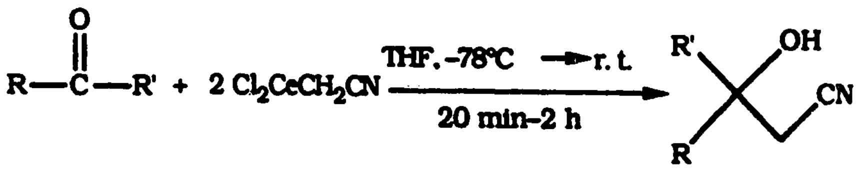
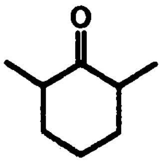
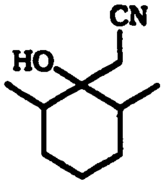
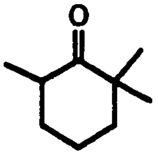
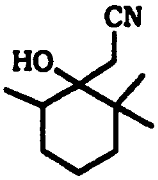
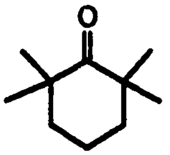
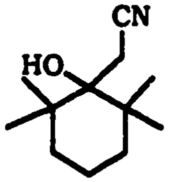
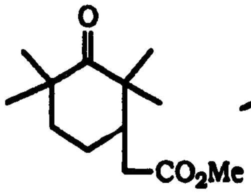
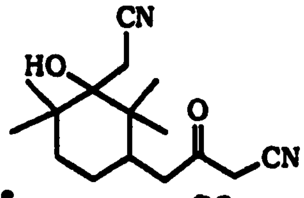
Entry	Ketone	Product	Yield (%)
1		 **19**	100
2		 **20**	82
3		 **21**	82
4		 **22**	88
5		 **23** 2.2:1 **24**	96

Table 1-IV (con'd). Addition of (Dichlorocerio)acetonitrile (**16**) to Saturated Ketones.



Entry	Ketone	Product	Yield (%)
6		 **25**	96
7		 **26**	88
8		 **27**	70
9		 **28**	55

confirmed this molecular formula. The ^{1}H nmr spectrum of the mixture displayed the methylene protons next to the nitrile at δ 2.62 for the major isomer and δ 2.55 for the minor isomer. The stereochemistry of the isomers was deduced from the ^{13}C nmr spectrum of the mixture which showed two sets of signals. The methylene carbon bearing the cyano group chain appeared at δ 27.21 and δ 32.94 for the major and the minor isomer, respectively. In addition, the carbinol carbon appeared at δ 70.79 for the major isomer and δ 69.40 for the minor isomer. The axial methylene of the acetonitrile side chain is known to appear at higher field than the equatorial isomer due to the steric compression.[33,34]

The effective steric bulk of the reagent may account for the difference in selectivity observed for the cerium and lithium reagents. Theoretical studies suggest that the lithium salt of acetonitrile prefers to place the metal ion close to the nitrogen atom in a partially bridged bent ketenimine structure, which minimizes the effective steric bulk of the nucleophile.[35,36] The more covalent metal appears to increase covalency with carbon. The resulting increase in steric demand of the nucleophile enhances the nonbonding interaction and makes the axial attack less favorable. The aggregation of the reagent may also have considerable effect.[33]

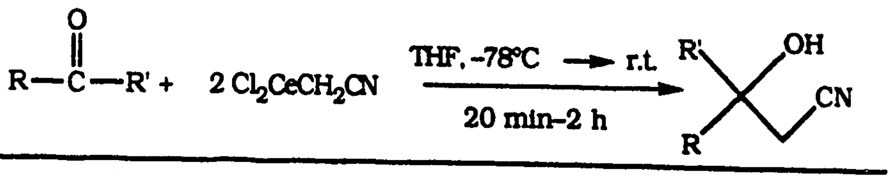
The carbonyl in 2,6-dimethylcyclohexanone (Table 1-IV, Entry 6) is sterically hindered by the adjacent methyl groups, hampering the addition of the nucleophile to the carbonyl. The addition of cerium reagent **16** to a mixture of *cis*- and *trans*-2,6-dimethylcyclohexanone however, occurred easily to give β-hydroxynitrile **25** in 96% yield as an inseparable mixture consisting at least two diastereomers in a ratio of *ca.* 5:2, as determined by ^{1}H nmr spectroscopy. The mixture showed a hydroxy absorption band at 3511 cm^{-1} and a nitrile band at 2252 cm^{-1} in the ir spectrum. Its hrms showed the molecular ion at m/z 167.1309, consistent with the molecular formula $C_{10}H_{17}NO$. The ^{1}H nmr spectrum displayed two singlets at δ 2.64 and δ 2.48, the former due to the methylene next to the cyano group of the major isomer and the latter due to those of the minor isomer.

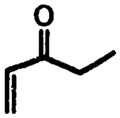
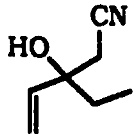
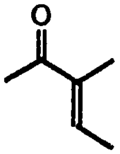
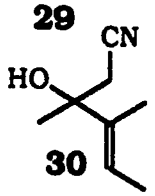
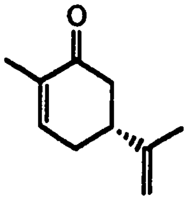
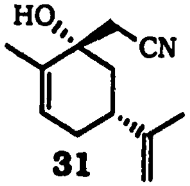
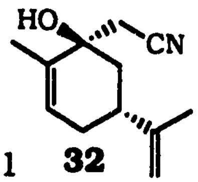
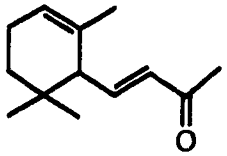
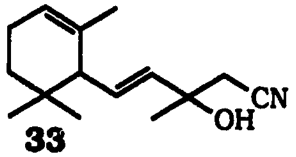
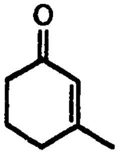
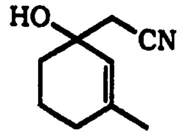
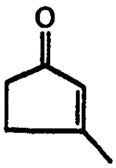
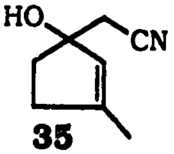
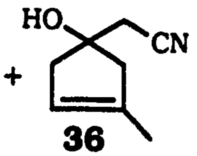
These promising results led us to undertake an investigation on highly hindered ketones. The carbonyl groups in 2,2,6-trimethylcyclohexanone (Entry 7) and 2,2,6,6-tetramethylcyclohexanone (entry 8) are highly congested due to the presence of several neighboring methyl groups. The addition of (dichlorocerio)acetonitrile, nevertheless, proceeded smoothly to afford the corresponding alcohols in good yields. The reaction of 2,2,6-trimethylcyclohexanone with the cerium reagent gave an 88% yield of the addition product **26** as a mixture of two inseparable diastereomers in a 4:1 ratio as determined by ^{1}H nmr analysis. This result was far superior to that obtained using lithioacetonitrile which furnished only a 36% yield of the same mixture. The presence of four α-methyl groups in 2,2,6,6-tetramethylcyclohexanone did not inhibit the addition of the cerium reagent. The reaction gave a 70% yield of the desired addition product **27**. The ir spectrum of **27** showed a hydroxy absorption at 3484 cm^{-1}. Its hrms showed the molecular ion at m/z 195.1621 consistent with the molecular formula of $C_{12}H_{21}NO$.

The reaction of 3-(carbomethoxymethyl)-2,2,6,6-tetramethylcyclohexanone (Entry 9) was also studied. Interestingly, treatment of this keto ester with (dichlorocerio)acetonitrile (**16**) gave compound **28** in 55% yield. This compound, which was obviously formed *via* the addition of the reagent to both the ketone and the ester carbonyl, showed a hydroxy absorption peak at 3530 cm^{-1}, a carbonyl at 1729 cm^{-1} and a cyano absorption at peak at 2245 cm^{-1}. Its cims showed a $[M+NH_4]^+$ peak at m/z 294 consistent with the molecular formula $C_{16}H_{24}N_2O_2$. The ^1H nmr and ^{13}C nmr spectra provided conclusive evidence for the formation of **28**. The ^1H nmr spectrum displayed two AB systems centered at δ 3.51 and δ 2.74, each integrating to two protons. The former was readily assigned to the hydrogens flanked by the carbonyl group and the cyano group and the latter to the protons of the acetonitrile moiety. In the ^{13}C nmr spectrum, a carbonyl carbon was observed at δ 197.54 along with two cyano carbons at δ 118.91 and 113.92.

Having successfully studied the reactivity of (dichlorocerio)acetonitrile (**16**) towards saturated ketones, we then set out to investigate its regioselectivity towards conjugated enones. The results obtained for several selected compounds are summarized in Table 1-V. In all cases, the addition reaction was found to proceed readily and with complete 1,2-regioselectivity.

Table 1-V. Addition of (Dichlorocerio)acetonitrile (**16**) to Conjugated Enones.



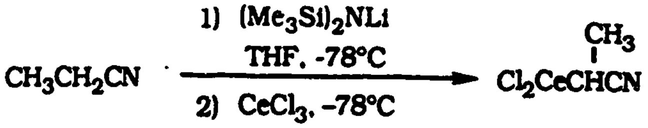
Entry	Enone	Product	Yield (%)
1		 **29**	82
2		 **30**	98
3		 **31** +  **32** 5:1	100
4		 **33**	76
5		 **34**	93
6		 **35** +  **36**	95

The addition of (dichlorocerio)acetonitrile (**16**) to ethyl vinyl ketone furnished the expected product **29** in 82% yield (Table 1-V, Entry 1). The ir spectrum of this compound displayed a hydroxy absorption band at 3457 cm^{-1} and a nitrile absorption at 2250 cm^{-1}. The hrms showed the molecular ion at m/z 125.0839, in agreement with the expected molecular formula $C_7H_{11}NO$. When the same ketone was treated with lithioacetonitrile in tetrahydrofuran at -78°C, only a 53% yield of the same addition product was isolated.

The addition of the cerium acetonitrile reagent **16** to (*R*)-carvone (Table 1-V, Entry 3) proceeded with good axial selectivity to give a quantitative yield of the addition products **31** and **32** in a 5:1 ratio. The ir spectrum of the product mixture confirmed the presence of a hydroxy group with an absorption at 3458 cm^{-1}. The hrms of this mixture provided the molecular ion at m/z 191.1318, corresponding to the formula $C_{12}H_{17}NO$. The ^{1}H nmr spectrum displayed two signals in the vinylic region at δ 5.72 and δ 5.60, integrating to a ratio of 1:5. The ^{13}C nmr displayed two carbinol carbons, the carbon bearing the equatorial hydroxy group at δ 71.91 (major) and the carbon with the axial hydroxy group at δ 71.15 (minor). The preference for axial attack of the cerium nitrile reagent **16** is lower than that of corresponding lithium reagent which was shown to proceed with complete axial selectivity.[33] This also may be due to the increased metal covalency to the carbon.[33-35]

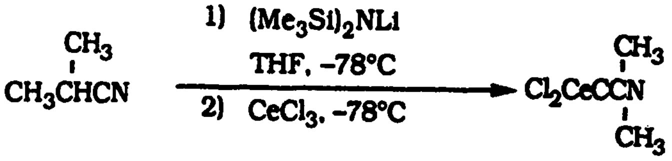
The addition of cerium acetonitrile anion to several other enones (Table 1-V, Entries 2, 4 and 5) were also found to occur readily to give the expected products in high yield. As the only exception, the addition of this reagent to 3-methyl-2-cyclopenten-1-one furnished an inseparable mixture of two isomers **35** and **36**. The ir spectrum of this mixture displayed a hydroxy absorption peak at 3440 cm^{-1}. Its hrms displayed the molecular ion at m/z 137.0843, corresponding to molecular formula $C_8H_{11}NO$. The ^1H nmr showed two vinylic signals at δ 5.95 and δ 5.41 integrating to a ratio of 1:2. The unexpected formation of the major isomer **36** was apparently the result of the isomerization of the double bond. The cause of this isomerization however, remains to be determined.

The results presented above expand the synthetic utility of the rapid growing methodology involving cerium(III) chloride. The high efficiency observed for the addition of cerium reagent **16** to ketones in terms of yield and regioselectivity as well as the substantial difference in the reactivity between the lithium[32,37] and cerium salts derived from acetonitrile led us to undertake a further investigation of the addition of mono- and di-substituted cerium acetonitriles **17** and **18**. These two reagents were prepared by transmetallation of the corresponding organolithium reagents (Eq. 22 and 23).



$$\mathrm{CH_3CH_2CN} \xrightarrow[\text{2) CeCl}_3\text{, -78°C}]{\text{1) (Me}_3\text{Si)}_2\text{NLi}\;\text{THF, -78°C}} \mathrm{Cl_2Ce\overset{\overset{\displaystyle CH_3}{|}}{C}HCN} \qquad (22)$$

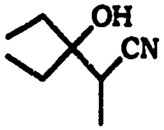
17



$$\mathrm{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCN} \xrightarrow[\text{2) CeCl}_3\text{, -78°C}]{\text{1) (Me}_3\text{Si)}_2\text{NLi}\;\text{THF, -78°C}} \mathrm{Cl_2Ce\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CN} \qquad (23)$$

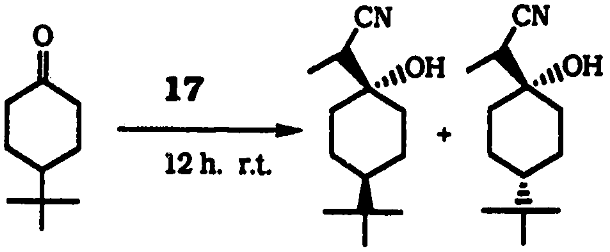
18

After one hour at room temperature, the addition of the mono-substituted cerium reagent **17** to diethyl ketone furnished the expected product **37** in 42% yield. It was possible to increase the yield of the addition product to 63% by performing the reaction at room temperature for 12 h. The ir spectrum of adduct **37** displayed hydroxy and nitrile absorptions at 3483 and 2240 cm^{-1}, respectively. The cims of this compound displayed a $[M+NH_4]^+$ peak at m/z 159, consistent with the molecular formula $C_8H_{15}NO$. The ^{1}H nmr spectrum displayed a quartet at δ 2.86 due to the proton adjacent to the nitrile.



37

To study the effect of the methyl substituent on the axial selectivity of the cerium nitrile reagent, the reaction of 4-*tert*-butylcyclohexanone and the cerium reagent **17** was carried out (Eq. 24). The addition products **38** and **39** were isolated in 63% yield in a 1.1:1 ratio. The use of lithiopropionitrile was reported by Trost *et al.* to give **38** and **39** in a 1.3:1 ratio.[37] The ir spectrum of the product mixture from the addition of cerium reagent **17** displayed a hydroxy absorption at 3440 cm^{-1} and nitrile absorption at 2242 cm^{-1}. Its hrms confirmed the exact mass of the product as indicated by the molecular ion at m/z 209.1782, consistent with the molecular formula $C_{13}H_{23}NO$. The ^{1}H nmr spectrum showed that the proton adjacent to the nitrile group in the major isomer resonated at δ 3.00 whereas the corresponding proton of the minor isomer appeared at δ 2.60. The ^{13}C nmr spectrum displayed two sets of signals with the methine carbon bearing the cyano group at δ 38.90 (a) for the minor isomer and at δ 31.07 (a) for the major. By selective off-resonance experiments, the major signal at δ 31.07 (a) was unequivocally confirmed to correspond to the carbon bearing the proton at δ 3.00. On the basis of this observation it was concluded that the addition of the propionitrile anion to the cyclohexanone was predominantly axial and the major isomer was identified as compound **38**. By recrystallization, a pure sample of the major isomer was obtained. This substance displayed a signal for the hydrogen neighboring the nitrile group at δ 3.00.



(24)

38 **39**

Attempts to add the disubstituted cerium acetonitrile reagent **18** to diethyl ketone were unsuccessful. In each case the starting material was recovered when the reaction was carried out at room temperature. In refluxing tetrahydrofuran, the reagent was found to undergo extensive decomposition. These results are in contrast to the corresponding lithium reagent from which the addition product was formed in good yield.[38]

In conclusion, we have developed an efficient procedure for the synthesis of β-hydroxynitriles making use of (dichloro-cerio)acetonitrile (**16**) as a reagent. This new procedure proved to be especially useful for nucleophilic addition involving sterically hindered ketones. Another salient feature is the high regioselectivity with conjugated enones. In each case examined, only the 1,2-addition product was formed.

Experimental

General.

Melting points (mp) were determined on a Köfler hot stage apparatus and are uncorrected.

Infrared (ir) spectra were recorded using Nicolet 7199 FTIR and Nicolet MX-1 FTIR spectrophotometers.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on Bruker WH-200 (200 MHz), Bruker AM-300 (300 MHz) and Bruker AM-400 (400 MHz) spectrometers. Tetramethyisilane (TMS) was used as an internal reference. The spectral data are reported in delta (δ) units relative to the TMS reference line. Multiplicities (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constants (reported to within ±0.5 Hz), number of protons and the assigned proton(s) are given in parentheses. Nuclear Overhauser enhancement (nOe) experiments were obtained after computer subtraction of the uncoupled spectrum from the irradiated spectrum. Positive enhancements were defined as signals possessing an antiphase with respect to the irradiated signal. Immediately before the experiment each sample was deoxygenated by passing helium gas through the solution for 5-10 min.

Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were taken using a Bruker AM-300 (75.5 MHz) spectrometer and signals are reported in delta (δ) units relative to TMS reference line using the solvent peaks ($CDCl_3$) as internal standard. Carbon-13 multiplicities were derived from off-resonance or Attached Proton Test (APT).[39] Methyl, methine and aldehydic carbonyls groups are shown as signals possessing antiphase (a) with respect to the $CDCl_3$ signal, whereas methylene and quaternary carbon atoms and carbonyl groups (acid, ester and ketone) appear in phase (p) with it.

High resolution mass spectra (hrms) were obtained using a Kratos AEI MS-50 mass spectrometer and are reported as m/z. Chemical ionization mass spectra (cims) were obtained using a Kratos AEI MS-12 instrument, with ammonia as the reagent gas.

Elemental analyses were determined by using a Perkin Elmer 240-B elemental analyzer for C, H and N detection.

All isolated products were found to be at least 95% pure, as determined by tlc and nmr.

Materials

The carbonyl compounds employed in this study were commercially available except 2,2,6,6-tetramethylcyclohexanone and 3-(carbomethoxymethyl)-2,2,6,6-tetramethylcyclohexanone. The former was prepared from 2,6-dimethylcyclohexanone using the conventional method (NaH, THF, MeI), and the latter was prepared following a reported procedure.[40]

Reactions requiring anhydrous conditions were performed in flame-dried glassware, assembled and allowed to cool while being purged with an inert gas. Reactions were carried out under argon or nitrogen gas and monitored by thin-layer chromatography using Merck aluminum-backed plates precoated with silica gel 60 GF_{254}. Ultraviolet active materials were detected by visualization of the chromatogram under UV light (254 or 350 nm). The visualization of the chromatogram was completed by dipping in an ethanol solution of vanillin (1%, w/v) and sulfuric acid (2%, w/v) followed by heating using a heat gun. Alternatively an aqueous solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%, w/v) in sulfuric acid (3%, w/v) was used as dipping solution, followed by hot plate charring.

Products were purified either by bulb-to-bulb distillation using a Kugelrohr apparatus or by flash chromatography[41] using silica gel of 230-400 mesh. Solvents were dried and distilled prior to use as follows: tetrahydrofuran (THF), dimethoxyethane (DME) and diethyl ether from a blue-purple solution of sodium benzophenone ketyl under an argon atmosphere; acetonitrile, benzene, pyridine and dichloromethane from calcium hydride; acetone from potassium carbonate; liquid ammonia from sodium metal.

Anhydrous cerium(III) chloride.

Cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) was finely ground in a mortar and transferred to a round bottomed flask. The flask was heated gradually to about 120°C under reduced pressure (*ca.* 2 torr) in a Kugelrohr distillation apparatus for 4 h. The dried cerium chloride was cooled to room temperature and used directly or stored in an oven at about 90°C.

Generation of (dichlorocerio)acetonitrile Cl_2CeCH_2CN (16).

n-Butyllithium (1 mmol) in hexane was added dropwise to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 1 mmol) in tetrahydrofuran (20 mL) under an argon atmosphere at -78°C followed by a solution of acetonitrile (1 mmol) in tetrahydrofuran (5 mL). After the reaction mixture was stirred at -78°C for 10 min, anhydrous cerium(III) chloride (1 mmol) was added with vigorous stirring for 20 min to give **16**.

Generation of (dichlorocerio)propionitrile $Cl_2CeCH(CH_3)CN$ (17).

The above procedure described for the preparation of **16** was followed using propionitrile in place of acetonitrile.

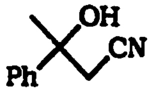
Generation of (dichlorocerio)isopropionitrile $Cl_2CeC(CH_3)_2CN$ (18).

The above procedure described for the preparation of **16** was followed using isopropionitrile in place of acetonitrile.

3-ethyl-3-Hydroxypentanenitrile (19).

A solution of diethyl ketone (0.3 g, 3.5 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (7 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 20 min. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was subjected to flash chromatography on silica gel (25% ethyl acetate in hexane) to give **19** (0.45 g, 100%). Further purification was carried out by bulb-to-bulb distillation (50°C, 0.5 torr): ir ($CHCl_3$ cast) 3474 (OH) and 2250 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 2.50 (s, 2H, $-CH_2CN$), 1.65 (qd, $J = 8$, $J' = 2$ Hz, 4H, $-CH_2CH_3$) and 0.94 (t, $J = 8$ Hz, 6H, $-CH_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 117.74 (p), 73.23 (p), 30.97 (p), 2 x 28.18 (p) and 2 x 7.62 (a); hrms m/z 109.0891 (M^+-H_2O, calcd. for $C_7H_{11}N$: 109.0891); cims $[M+NH_4]^+$ 145. Anal. Calcd. for $C_7H_{13}NO$: C 66.11, H 10.30, N 11.01; found: C 66.35, H 10.24, N 10.80.

3-Hydroxy-3-phenylbutanenitrile (20).

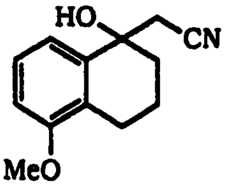


A solution of acetophenone (0.42 g, 3.5 mmol) in tetrahydrofuran (5 mL) was added to cerium reagent **16** at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 30 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to afford **20** (0.463 g, 82%): ir ($CHCl_3$ cast) 3450 (OH) and 2256 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 2.75 (s, 2H, -$C\mathbf{H}_2CN$) and 1.69 (s, 3H, -$C\mathbf{H}_3$); hrms M^+ 161.0843 (calcd. for $C_{10}H_{11}NO$: 161.0841). Anal. Calcd. for $C_{10}H_{11}NO$: C 74.51, H 6.88, N 8.69; found: C 74.56, H 6.96, N 8.75.

3-Hydroxy-3-methyl-5-phenylpentanenitrile (21)

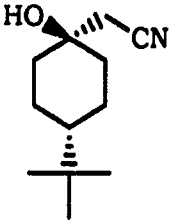
A solution of benzylacetone (0.44 mL, 3 mmol) in tetrahydrofuran (5 mL) was added to cerium reagent **16** (6 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 20 min. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to furnish **21** (0.57 g, 100%): ir ($CHCl_3$ cast) 3467 (OH) and 2253 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 7.25 (m, 5H, aromatic **H**), 2.70 (dd, J = 10 , J' = 7 Hz, 2H, PhC**H**$_2$-), 2.54 (d, J = 17 Hz, 1H, -C**H**HCN), 2.50 (d, J = 17 Hz, 1H, -CH**H**CN), 1.90 (ddd, J = J' = 7, J'' = 3 Hz, -C**H**$_2$-) and 1.40 (s, 3H,-C**H**$_3$); hrms M^+ 189.1166 (calcd. for $C_{12}H_{15}NO$: 189.1154).

1-(Cyanomethyl)-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronapthalene (22).

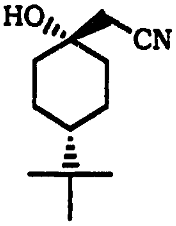


A solution of 5-methoxy-1-tetralone (0.44 g, 2.5 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (5 mmol) at -78°C, then the solution was warmed to room temperature. After 1 h the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (35% ethyl acetate in hexane) afforded **22** (0.48 g, 88%): ir ($CHCl_3$ cast) 3463 (OH) and 2260 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 7.28-7.16 (m, 2H, aromatic **H**), 6.78 (dd, *J* = 8, *J'* = 1 Hz, 1H, aromatic **H**), 3.82 (s, 3H, -OC**H**$_3$), 2.90 (d, *J* = 17 Hz, 1H, -C**H**HCN), 2.78 (d, *J* = 17 Hz, 1H, -CH**H**CN), 2.68 (t, *J* = 6 Hz, 2H, ArC**H**$_2$-) and 2.60-1.70 (m, 4H, -C**H**$_2$C**H**$_2$-); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 156.93 (p), 140.17 (p), 127.14 (a), 125.88 (p), 117.29 (p), 117.39 (a), 109.28 (a), 70.64 (p), 55.45 (a), 36.36 (p), 31.67 (p), 22.95 (p), and 19.19 (p); hrms M^+ 217.1105 (calcd. for $C_{13}H_{15}NO_2$: 217.1103). Anal. Calcd. for $C_{13}H_{15}NO_2$: C 71.87, H 6.96, N 6.45; found: C 71.79, H 7.08, N 6.37.

trans-1-(Cyanomethyl)-4-tert-butylcyclohexanol (23) and cis-1-(Cyanomethyl)-4-tert-butylcyclohexanol (24).



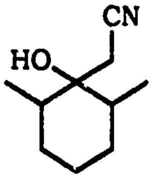
23



24

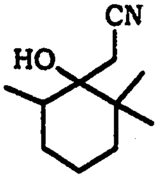
A solution of 4-*tert*-butylcyclohexanone (0.69 g, 4.5 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (9 mmol) at -78°C, and then the reaction mixture was warmed to room temperature. Stirring was continued for 90 min. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to afford **23** and **24** (2.2:1, 0.84 g, 96%) as a mixture: ir ($CHCl_3$ cast) 3252 (OH) and 2240 cm^{-1} (CN); ^{1}H nmr (300 MHz, $CDCl_3$) δ 2.62, 2.55 (2.2:1, each s, 2H total, -$C\mathbf{H}_2CN$), 0.92-0.9 (m, 8H, -$C\mathbf{H}_2$-) and 0.88 (s, 9H, -$C(C\mathbf{H}_3)_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 117.77 (p), 117.63 (p), 70.79 (p), 69.40 (p), 47.26 (a), 47.17 (a), 38.19 (p), 36.96 (p), 32.94 (p), 32.32 (p), 32.16 (p), 27.49 (a), 27.21 (p), 24.42 (p) and 22.13 (p); hrms M^+ 195.1622 (calcd. for $C_{12}H_{21}NO$: 195.1623). Anal. Calcd. for $C_{12}H_{21}NO$: C 73.80, H 10.84, N 7.17; found: C 73.84, H 10.78, N 7.21.

1-(Cyanomethyl)-2,6-dimethylcyclohexanol (25).



A solution of 2,6-dimethylcyclohexanone (0.377 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (9 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 1 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in hexane) to give the addition product **25** (0.484 g, 96%) as a mixture consisting of at least two diastereomers in *ca.* 5:2 ratio: ir ($CHCl_3$ cast) 3511 (OH) and 2252 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 2.64 (s, 2H, -CH_2CN) and 0.97 (d, $J = 7$ Hz, 6H, -CH_3) for the major, 2.48 (s, 2H, -CH_2CN.) and 1.07 (d, $J = 6.5$ Hz, 6H, -CH_3) for the minor; hrms M^+ 167.1309 (calcd. for $C_{10}H_{17}NO$: 167.1309). Anal. Calcd. for $C_{10}H_{17}NO$: C 71.81, H 10.25, N 8.37; found: C 71.86, H 9.95, N 8.14.

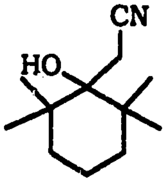
1-(Cyanomethyl)-2,2,6-trimethylcyclohexanol (26).



A solution of 2,2,6-trimethylcyclohexanone (0.42 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (6 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 1 h. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography. Elution using 15% ethyl acetate in hexane gave the addition product **26** (0.48 g, 88%) as a mixture of two diastereomers in a 1:4 ratio: ir ($CHCl_3$ cast) 3483 (OH) and

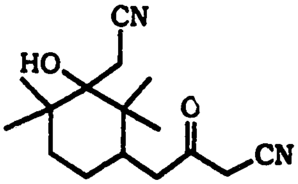
2250 cm^{-1} (CN); ^{1}H nmr (300 MHz, CDCl$_3$) δ 2.62 (d, *J* = 17 Hz, 1H, -CHHCN), 2.59 (d, *J* = 17 Hz, 1H, -CHHCN), 2.10 and 2.00 (1:4, each m, 1H total, -CH-) and 1.21-1.00 (m, 9H, 3 x CH$_3$); hrms M$^+$ 181.1469 (calcd. for $C_{11}H_{19}NO$: 181.1467).

1-(Cyanomethyl)-2,2,6,6-tetramethylcyclohexanol (27).



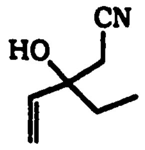
A solution of 2,2,6,6-tetramethylcyclohexanone (0.31 g, 2 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (8 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 1 h. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexane) to give the addition product **27** (0.274 g, 70%): ir (CHCl$_3$ cast) 3484 (OH) and 2256 cm^{-1} (CN); ^{1}H nmr (300 MHz, CDCl$_3$) δ 2.21 (s, 2H, -CH$_2$CN), 1.80-1.30 (m, 6H, -CH$_2$-), 1.10 and 1.08 (s each, 6H each, 4 x CH$_3$); hrms M$^+$ 195.1621 (calcd. for $C_{12}H_{21}NO$: 195.1623).

1-(Cyanomethyl)-3-(cyano-2-oxopropyl)-2,2,6,6-tetramethylcyclohexanol (28).



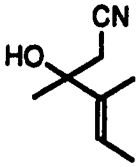
A solution of 3-(carbomethoxymethyl)-2,2,6,6-tetramethylcyclohexanone (0.32 g, 1.4 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (2.8 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 1 h. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (25% ethyl acetate in hexane) gave the addition product **28** (0.171 g, 55%): ir ($CHCl_3$ cast) 3550 (OH), 2245 (CN) and 1729 cm^{-1} (C=O); ^1H nmr (300 MHz, $CDCl_3$) δ 3.54, (d, J = 19 Hz, 1H, -COC**H**HCN), 3.48 (d, J = 19 Hz, 1H, -COCH**H**CN), 2.76 (d, J = 17 Hz, 1H, -C**H**HCN), 2.72 (d, J = 17 Hz, 1H, -CH**H**CN), 1.12, 1.10, 1.05, and 0.80 (each s, 3H each, 4 x C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 197.54 (p), 118.91 (p), 113.92 (p), 77.68 (p), 44.22 (p), 42.62 (p), 39.37 (p), 37.51 (a), 35.97 (p), 32.46 (p), 28.01 (a), 24.71 (a), 24.71 (p), 24.44 (a), 21.78 (p) and 19.97 (a); cims $[M+NH_4]^+$ 294.

3-Ethyl-3-hydroxy-4-pentenenitrile (29)



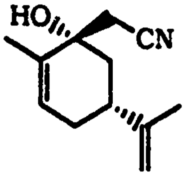
A solution of ethyl vinyl ketone (0.252 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (6 mmol) at -78°C. The reaction mixture was warmed to room temperature. After 10 min the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and then extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to give **29** (0.31 g, 82%): ir ($CHCl_3$ cast) 3457 (OH) and 2250 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 5.82 (dd, J = 17 Hz, J' = 10 Hz, 1H, =C**H**-), 5.35 (dd, J = 17 Hz, J' = 1 Hz, 1H, =CH**H**), 5.25 (dd, J = 10 Hz, J' = 1 Hz, 1H, =C**H**H), 2.55 (s, 2H, -C**H**$_2$CN), 1.65 (m, 2H, -C**H**$_2$-) and 0.88 (t, J = 7 Hz, 3H, -C**H**$_3$); hrms M$^+$ 125.0839 (calcd. for $C_5H_{11}NO$: 125.0841).

(*E*)-3-Hydroxy-3,4-dimethyl-4-hexenenitrile (30).



A solution of (*E*)-3-methyl-3-pentene-2-one (0.294 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (6 mmol) at -78°C. The reaction mixture was warmed to room temperature. After 2 h the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and then extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel (20% ethyl acetate in hexane) gave **30** (0.409 g, 98%): ir ($CHCl_3$ cast) 3458 (OH) and 2245 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 5.50 (m, 1H, =C**H**CH_3), 2.65 (s, 1H, -C**H**$_2$CN), 1.68 (m, 3H, vinylic -C**H**$_3$), 1.64 (dd, *J* = 7, *J'* = 1 Hz, 3H, vinylic -C**H**$_3$) and 1.46 (s, 3H, -C**H**$_3$); hrms M^+ 139.0997 (calcd. for $C_8H_{13}NO$: 139.0997). Anal. Calcd. for $C_8H_{13}NO$: C 69.03, H 9.41, N 10.06; found: C 69.32, H 9.16, N 10.09.

(1S, 5R)-1-(Cyanomethyl)-2-methyl-5-(isopropenyl)-2-cyclohexen-1-ol (31) and (1R, 5R)-1-(Cyanomethyl)-2-methyl-5-(isopropenyl)-2- cyclohexen-1-ol (32).



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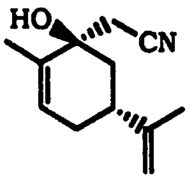

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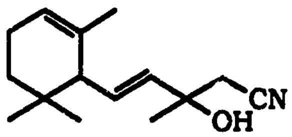
A solution of (*R*)-carvone (0.457 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** at -78°C. Then the reaction mixture was warmed to room temperature. Stirring was continued for 30 min. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and was extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to give the addition products **31** and **32** as a mixture of diastereomers (5:1, 0.602 g, 100%): ir ($CHCl_3$ cast) 3458 (OH) and 2240 cm^{-1} (CN): ^1H nmr (300 MHz, $CDCl_3$) δ 5.60 (br s, 1H, =C**H**-), 4.78 (d, J = 2 Hz, 2H, =C**H**$_2$), 2.80 (d, J = 17 Hz, 1H, -C**H**HCN) and 2.60 (d, J = 17 Hz, 1H, -CH**H**CN) for the major and 5.72 (br s, 1H, =C**H**), 2.75 (d, J = 17 Hz, -C**H**HCN) and 2.65 (d, J = 17 Hz, 1H, -CH**H**CN) for the minor; ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 147.70 (p), 134.96 (p), 126.10 (a), 117.31 (p), 109.91 (p), 71.91 (p), 41.15 (p), 39.12 (p), 30.73 (p), 28.42 (p), 20.75 (a) and 16.58 (a) for the major isomer and δ 147.88 (p), 133.10 (p), 128.75 (a), 117.31 (p), 109.71 (p), 71.915 (p), 41.28 (p), 36.88 (p), 30.96 (p), 29.33 (p), 20.75 (a) and 17.22 (a) for the minor isomer; hrms M^+ 191.13[illegible] (calcd. for $C_{12}H_{17}NO$: 191.1310). Anal. Calcd. for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32; found: C 75.04, H 8.87, N 6.99.

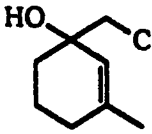
(*E*)-3-Hydroxy-3-methyl-5-(2,6,6-trimethyl-2-cyclohexenyl)-4-pentenenitrile (33).



A solution of α-ionone (0.58 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (6 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 2 h, then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to furnish **33** (0.53 g, 76%): ir ($CHCl_3$ cast) 3454 (OH) and 2255 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 5.58 (m, 2H, C**H**=C**H**-), 5.42 (s, 1H, =C**H**-), 2.58 (s, -C**H**$_2$CN), 1.58 (br s, 3H, allylic C**H**$_3$), 1.44, 0.90

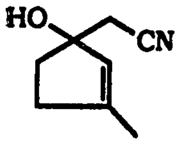
and 0.84 (each s, 3H each, 3 x CH_3): hrms M^+ 233.1781 (calcd for $C_{15}H_{23}NO$: 233.1780).

1-(Cyanomethyl)-3-methyl-2-cyclohexen-1-ol (34).



A solution of 3-methyl-2-cyclohexen-1-one (0.33 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (6 mmol) at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 3 h, then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography on silica gel (25% ethyl acetate in hexane) gave the addition product **34** (0.42 g, 93%): ir ($CHCl_3$ cast) 3414 (OH) and 2250 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 5.45 (s, 1H, =C**H**-), 2.57 (d, J = 17 Hz, 1H, -CH**H**CN), 2.53 (d, J = 17 Hz, -C**H**HCN) and 1.72 (br s, 3H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 140.95 (p), 123.87 (a), 117.47 (p), 68.37 (p), 35.08 (p), 31.49 (p), 29.78 (p), 23.46 (a) and 18.92 (p); hrms m/z 133.0889 (M^+-H_2O, calcd. for $C_9H_{11}N$: 133.0889).

1-(Cyanomethyl)-3-methyl-2-cyclopenten-1-ol (35) and 1-(Cyanomethyl)-3-methyl-3-cyclopenten-1-ol (36).



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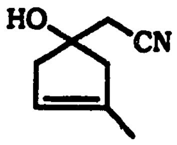

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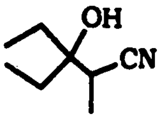
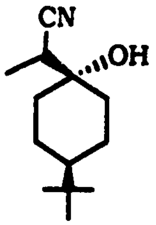
A solution of 3-methyl-2-cyclopentenone (0.288 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **16** (6 mmol) at -78°C. The reaction mixture was warmed to room temperature and stirred further for 30 min. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography on silica gel (30% ether in hexane) gave the addition products **35** and **36** (1:2, 0.39 g, 95%) as an inseparable mixture: ir ($CHCl_3$ cast) 3440 (OH) and 2251 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 5.41 (m, 1H, =C**H**-), 2.66 (d, J = 17 Hz, 1H, -CH**H**CN), 2.62 (d, J = 17 Hz, 1H, -CH**H**CN), 1.79 (br d, 3H, vinylic $C\mathbf{H}_3$) for the major, and δ 5.95 (m, 1H, =C**H**-), 2.84 (s, 2H, $-C\mathbf{H}_2CN$) for the minor; hrms M^+ 137.0843 (calcd. for $C_8H_{11}NO$: 137.0841).

3-Ethyl-3-hydroxy-2-methylpentanenitrile (37).



A solution of diethyl ketone (0.26 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **17** (6 mmol) at -78°C, and then the reaction mixture was warmed to room temperature. After stirring for 12 h the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to give the addition product **37** (0.28 g , 63%): ir ($CHCl_3$ cast) 3483 (OH) and 2240 cm^{-1} (CN); ^1H nmr (300 MHz, $CDCl_3$) δ 2.86 (q, J = 7 Hz, 1H, -C**H**CN), 1.64 (m, 4H , -C**H**$_2$-) and 1.26 (d, J = 7 Hz, 3H, -C**H**$_3$); cims $[M+NH_4]^+$ 159.

***trans*-1-(1-Cyanoethyl-4-*tert*-butylcyclohexanol (38) and *cis*-1-(1-Cyanoethyl-4-*tert*-butylcyclohexanol (39).**



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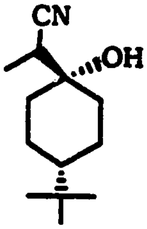

39

A solution of 4-*tert*-butylcyclohexanone (0.462 g, 3 mmol) in tetrahydrofuran (5 mL) was added to the cerium reagent **17** at -78°C, and the reaction mixture was warmed to room temperature. Stirring was continued for 12 h after which the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to give a mixture of two diastereomers **38** and **39** (0.40 g, 63%) in a ratio of 1.1:1: ir ($CHCl_3$ cast) 3440 (OH) and 2242 cm^{-1} (CN); ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.00, 2.60 (1.1:1, each q, $J = 7$ Hz each, 1H total, -C**H**CN), 1.35 (d, 3H, $J = 7$ Hz, -CHC**H**$_3$) and 0.85 (s, 9H, -C(C**H**$_3$)$_3$. Recrystallization from hexane gave a single isomer: mp 123-124°C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.00 (q, $J = 7$ Hz, 1H, -C**H**CN), 0.85 (s, 9H, -C(C**H**$_3$)$_3$; ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 121.52 (p), 71.71 (p), 47.10 (a), 38.90 (p), 34 (p), 32.24 (p), 31.07 (a), 27.55 (a), 24.08 (p), 23.76 (p) and

11.56 (a); hrms M^+ 209.1782 (calcd. for $C_{13}H_{23}NO$: 209.1780). Anal. Calcd. for $C_{13}H_{23}NO$: C 74.59, H 11.07, N 6.69; found: C 74.65, H 10.85, N 7.02.

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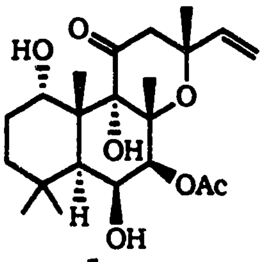
CHAPTER 2

SYNTHETIC STUDIES ON FORSKOLIN

Introduction

Forskolin (**1**), a highly oxygenated labdane diterpene, is the major constituent of the methanol extract of the roots of the Indian herb *Coleus forskohlii*, isolated for the first time by Bhat *et al.*[1] in 1977. With forskolin, several forskolin related diterpenoids **2**-**5** were isolated. The structures of these secondary metabolites were elucidated by a combination of extensive spectroscopic studies and chemical reactions (acetylation and basic hydrolysis). These studies, combined with biogenetic considerations, led Bhat and coworkers to propose the gross structure **1** for the major component (0.1% of the dry weight) forskolin, formula **2** for 1,9-dideoxyforskolin, formula **3** for 7-deacetylforskolin, formula **4** for 1,9-dideoxy-7-deacetylforskolin and formula **5** for 6-acetyl-7-deacetylforskolin. The structure of forskolin (**1**)



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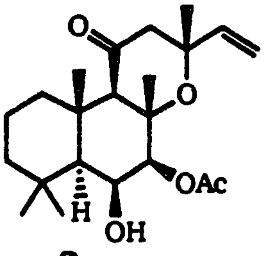

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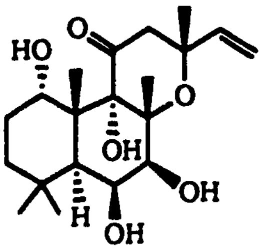

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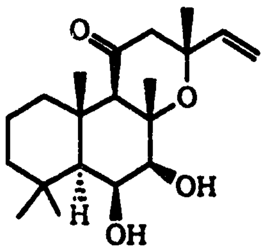

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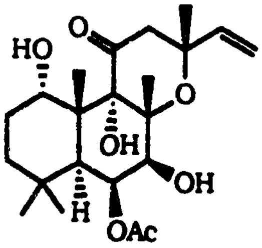
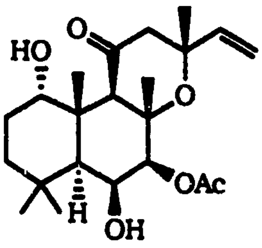


5

was unequivocally confirmed by a single crystal X-ray analysis on its 1-benzyl-7-deacetyl-7-bromoisobutyryl derivative.

Several years later Bhat *et al.*[2] reported the isolation of 9-deoxyforskolin (**6**) from the same herb. This compound differs from forskolin only in lacking the α-hydroxyl at C-9. More recently Kandelwal *et al.*[3] reported the isolation and characterization of yet another secondary metabolite from the roots of the same plant. The only difference observed in the ^{1}H nmr spectra of the newly separated compound and forskolin was the absence of the resonance at δ 4.45 for the 1α-CHOH which led to the assignment of this new forskolin derivative as 1-deoxyforskolin (**7**). The structure of **7** was confirmed by its synthesis from 1,9-dideoxy forskolin (**2**). 7,9-Dideoxyforskolin (**8**) was also isolated from the same herb.[4]



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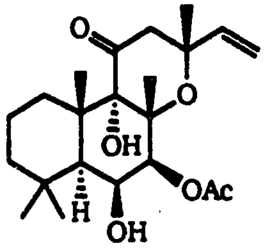
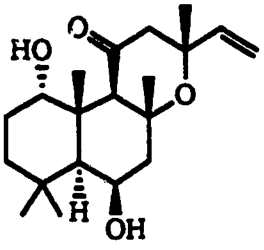


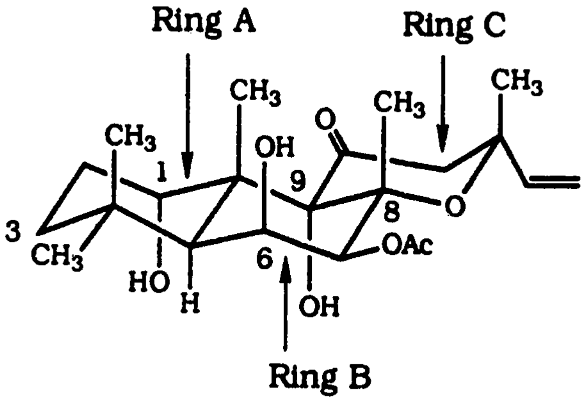
7



8

As far as the physiological activity is concerned, the extracts of the roots from *C. forskohlii* have been used locally as a traditional medicine for centuries.[5] The physiological properties were traced to forskolin (**1**). Pharmacologically, forskolin is characterized by its potent positive inotropic activity and blood pressure lowering properties in normotensive and hypotensive laboratory animals,[2] as well as its platelet aggregation inhibitory activity and reduction of intraocular pressure in man.[6] This broad range of physiological activity has been attributed to the direct stimulation of the catalytic unit of the adenylate cyclase system.[7,8] Clinical studies on forskolin show promising results in the treatment of diseases such as glaucoma, asthma and congestive cardiovascular disorders.[9,10] The poor solubility of forskolin in physiologically acceptable media is a limiting factor in biological studies. Therefore, water soluble derivatives of forskolin have been synthesized and have been shown to possess some or all of the properties of the parent compound.[10]

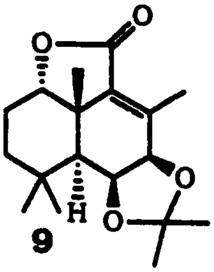
Forskolin is one of the most oxygenated secondary metabolites yet isolated. In addition, its decalin based molecular framework accommodates eight asymmetric centers, seven of them being contiguous and six of them being centered in ring B. Examination of the molecular model of forskolin reveals that the



1

hydroxy groups at C1, C6 and C9 are axially oriented whereas the only acylated hydroxy group at C7 is equatorially oriented, indicating that selective acylation of the C7 hydroxy group is very likely based on the steric hindrance of the other axially oriented hydroxy groups. The β-alkoxy ketone in ring C makes it reasonable to assume that this type of array might be easily constructed *via* 1,4-addition of alkoxide or hydroxide to an acetylenic ketone. This molecular architecture, together with its fascinating pharmacological properties makes forskolin a synthetically challenging target molecule. Indeed, these properties have attracted the attention of synthetic chemists worldwide. A number of studies of the chemistry of forskolin have been reported, including an acid-catalyzed rearrangement of the ether ring,[11] various selective reactions of the hydroxy groups,[12,13] the preparation of 12-halo derivatives,[14] studies on the formation of the ether ring,[15] oxidation/reduction[16] and hydroxylation of 9-deoxyforskolin to forskolin.[17]

Recently, there has been a flurry of synthetic activity directed towards the synthesis of the forskolin skeleton.[18-34] To date there have been three approaches culminating in the total synthesis of forskolin.[35-38] Surprisingly, all of these approaches were based on intramolecular cycloaddition and all proceeded through the intermediacy of lactone **9** first synthesized by Ziegler *et al.*[39]

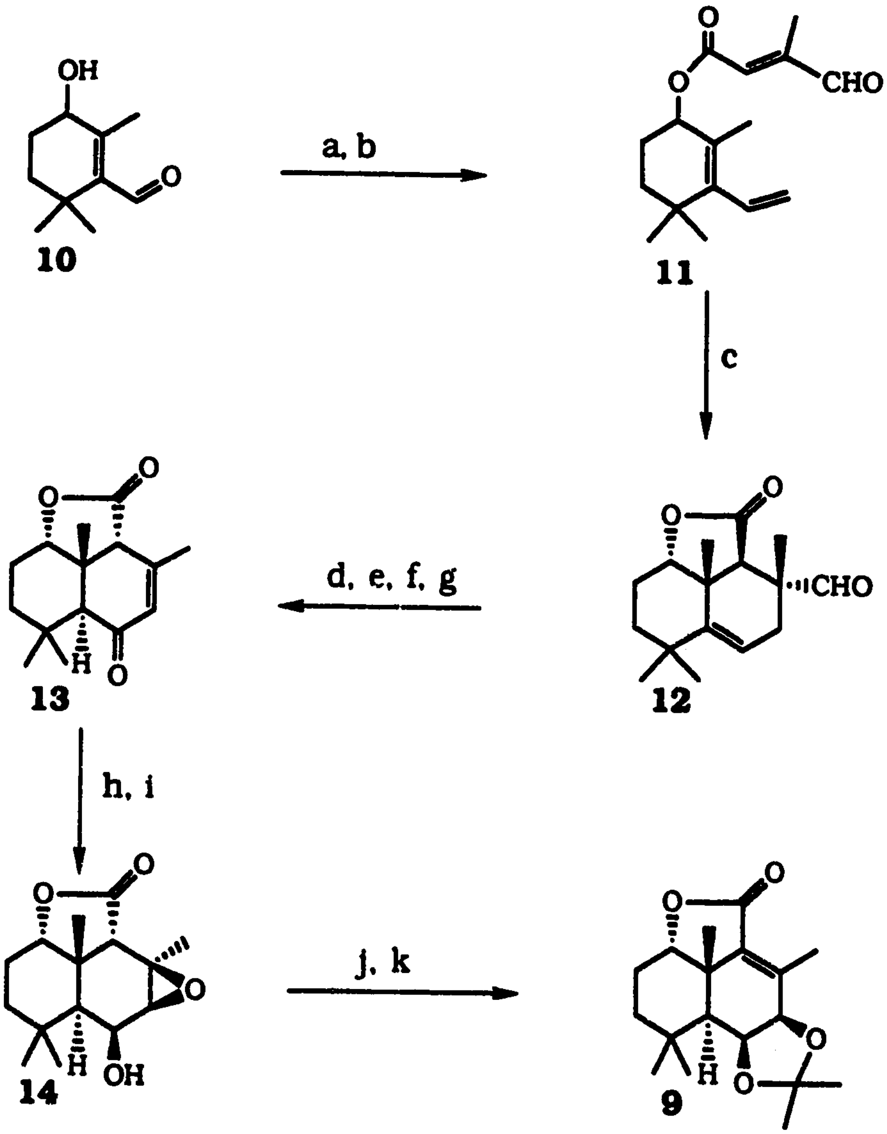


9

The first total synthesis of forskolin was achieved by the group of Ziegler in 1987. Their approach to this challenging molecule is based on a stereospecific intramolecular Diels-Alder reaction to assemble the AB-ring system.[39] The ester **11**, possessing all the carbons required for rings A and B, was derived from aldehyde **10**. Methylenation of this aldehyde followed by esterification with (*E*)-3-methyl-2-oxo-2-butenoic acid provided ester **11**. The aldehyde group was incorporated into the dienophile of ester **11**, first to direct the endo-transition state and then to establish the appropriate oxidation level of ring B. Thermolysis of this ester in a sealed tube resulted in the formation of Diels-Alder adduct **12**. Adduct **12** was subsequently converted into the key intermediate, lactone **9**, by two series of functional group manipulations (Scheme 2-1).[39] In the first series, the olefin and the aldehyde group in **12** were elaborated to the enone system in ketone **13**. The conversion of this ketone to lactone **9** was achieved by a second series of chemical transformations including reduction, directed epoxidation, base treatment and protection of the resulting diol as an acetonide.

Ziegler *et al.*[40] successfully converted the racemic lactone **9** into dihydropyranone **20**, the enantiomerically pure form of which

Scheme 2-I



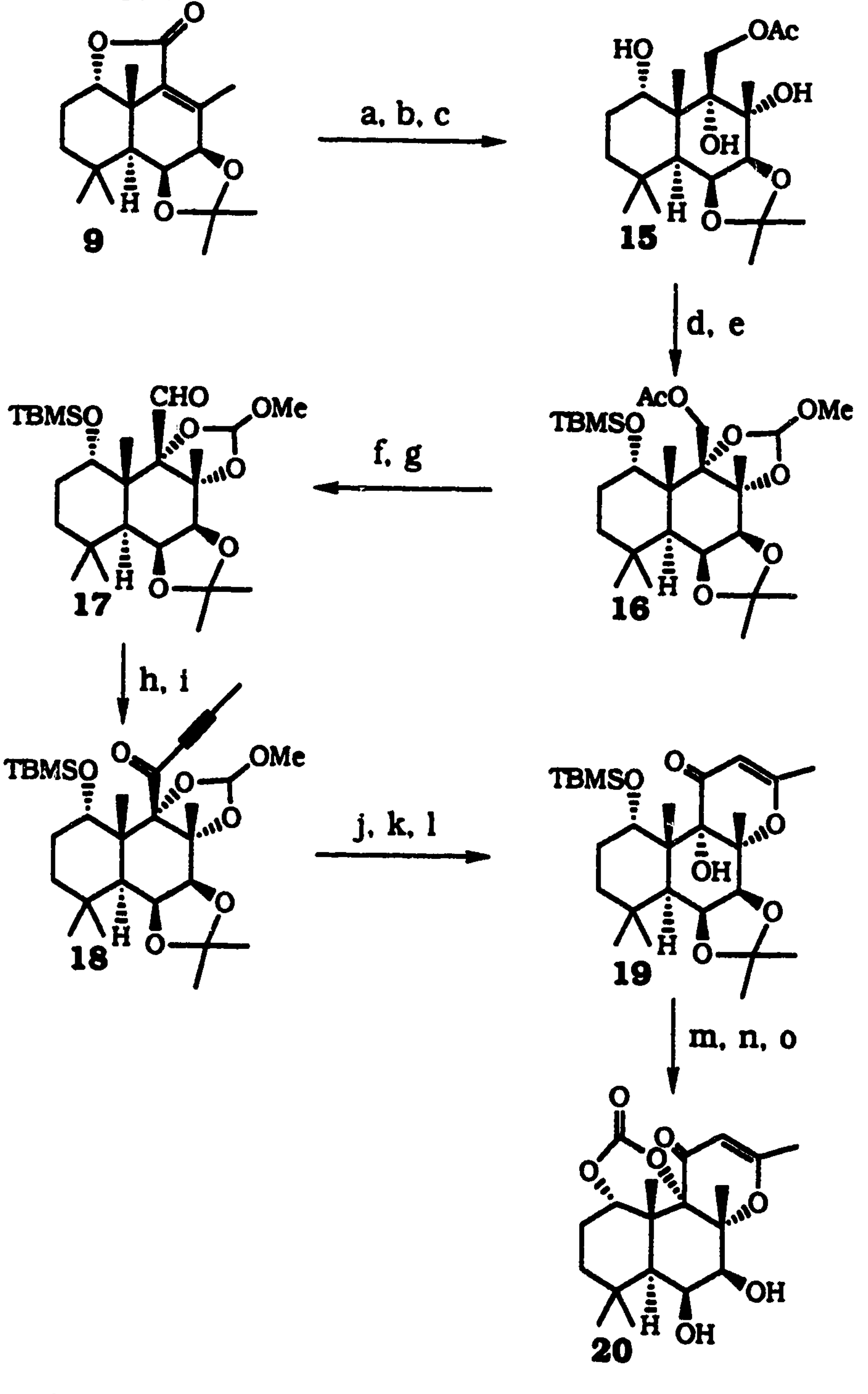
a) $Ph_3P=CH_2$, THF; b) (*E*)-3-methyl-4-oxo-2-butenoic acid, DCC, DMAP; c) PhH, 120°C; d) BH_3, THF; e) Jones reagent; f) CH_3OK, CH_3OH; g) $Pb(AcO)_4$, Pyr; h) $LiBH_4$, Li_2CO_3, EtOH; i) $VO(acac)_2$, *t*-BuOOH, CH_2CH_2; j) LDA, THF; k) 2,2-dimethoxypropane, *p*-TsOH.

was obtained by degradation of natural forskolin.[41] They elaborated ring C by a 1,4-addition of methoxide anion to acetylenic ketone **18**, prepared from **9** *via* intermediates **15-17**, followed by acid catalyzed cyclization to provide dihydropyranone **19**. Final linkage with the degradation product was achieved through a series of functional group manipulations as illustrated in Scheme 2-II.

The degradation product **20** failed to react with $(CH_2{=}CH)_2Cu(CN)Li_2$, so a photochemical route was developed to reconvert this compound to forskolin. Irradiation of **20** in the presence of allene provided a single photoadduct **21**. Following the protection of the vicinal diol in **21** as its cyclic carbonate, the exo double bond was subjected to ozonolysis to give a mixture of diketone **22** and benzyl ester **23**. Cleavege of the major product, diketone **22**, produced benzyl ester **23**. The cleavage reaction established the regiochemistry of the photoaddition product, but the issue of stereochemistry was confirmed only after transformation of the cleavge product **23** into forskolin as shown in Scheme 2-III.[35]

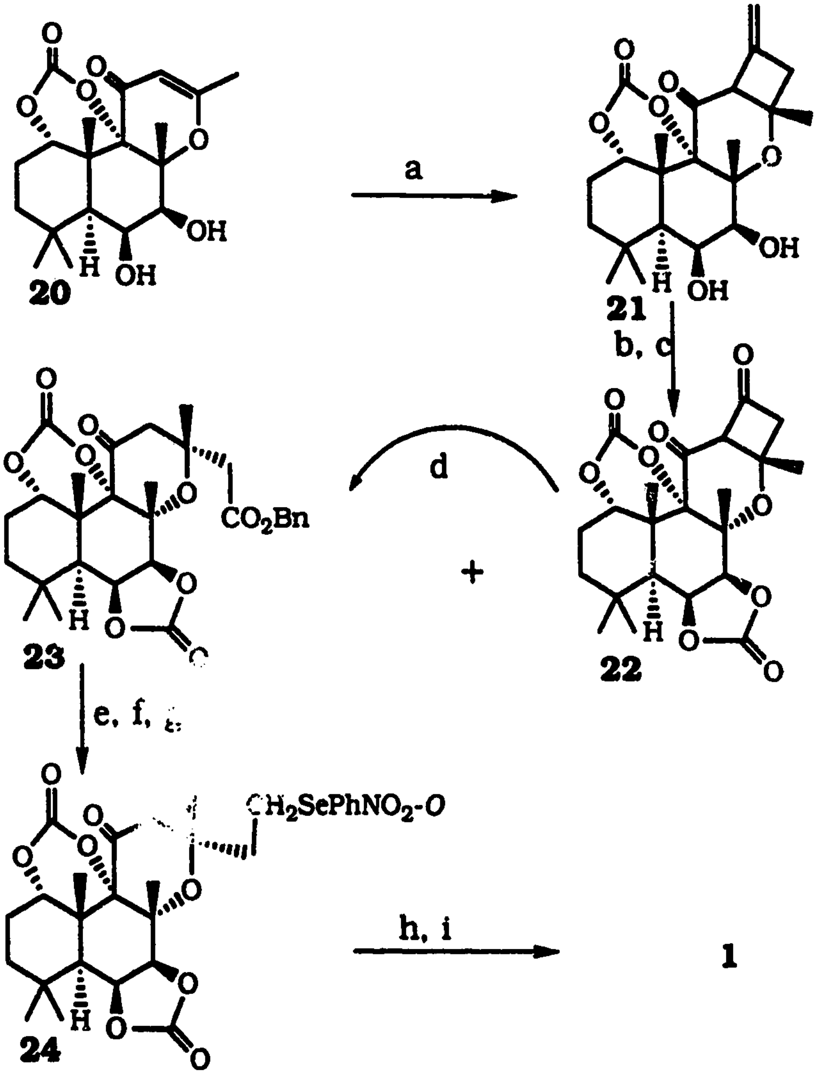
One year later Zeigler and coworkers were able to achieve the addition of vinyl anion to the α-face of their intermediate **19** using $(CH_2{=}CH)_2Cu(CN)Li_2$ in the presence of BF_3-etherate. By doing so they finished the first total synthesis of the target molecule as shown Scheme 2-IV.[42]

Scheme 2- II



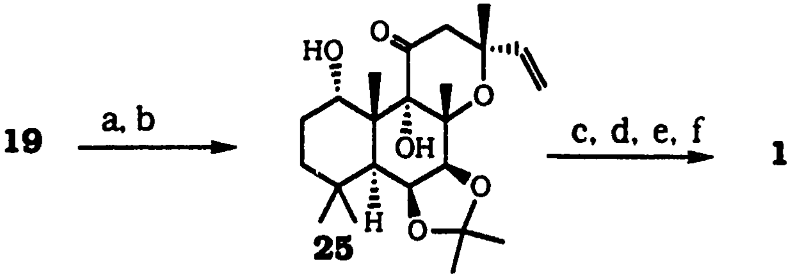
a) $LiAlH_4$, Et_2O; b) *N*-acetylimidazole, DBU, PhH; c) OsO_4,Pyr; d) TBMSOTf, 2,6-lutidine, CH_2Cl_2; e) neat $CH(OMe)_3$, *p*-TsOH; f) KOH, MeOH, THF; g) CrO_3·2Pyr, CH_2Cl_2; h) 1-lithiopropyne, THF; i) CrO_3·2Pyr, CH_2Cl_2; j) 3N HCl, THF (1:25), then MeOH-NH_3; k) KOH, MeOH; l) *p*-TsOH, PhH; m) $(n\text{-Bu})_4NF$, THF; n) $COCl_2$, Pyr, CH_2Cl_2; o) 3N HCl, THF (1:5).

Scheme 2-III



a) allene, $h\nu$; b) $COCl_2$, CH_2Cl_2, DMAP; c) O_3, CH_2Cl_2, BnOH, DMSO; d) Pyr, DMAP, BnOH; e) $H_2/Pd(C)$; f) BH_3, THF; g) *o*-NO_2-PhSeCN, (*n*-Bu)$_3$P, then 30% H_2O_2, THF; h) NaOH, MeOH; i) Ac_2O, Pyr, 0°C.

Scheme 2-IV

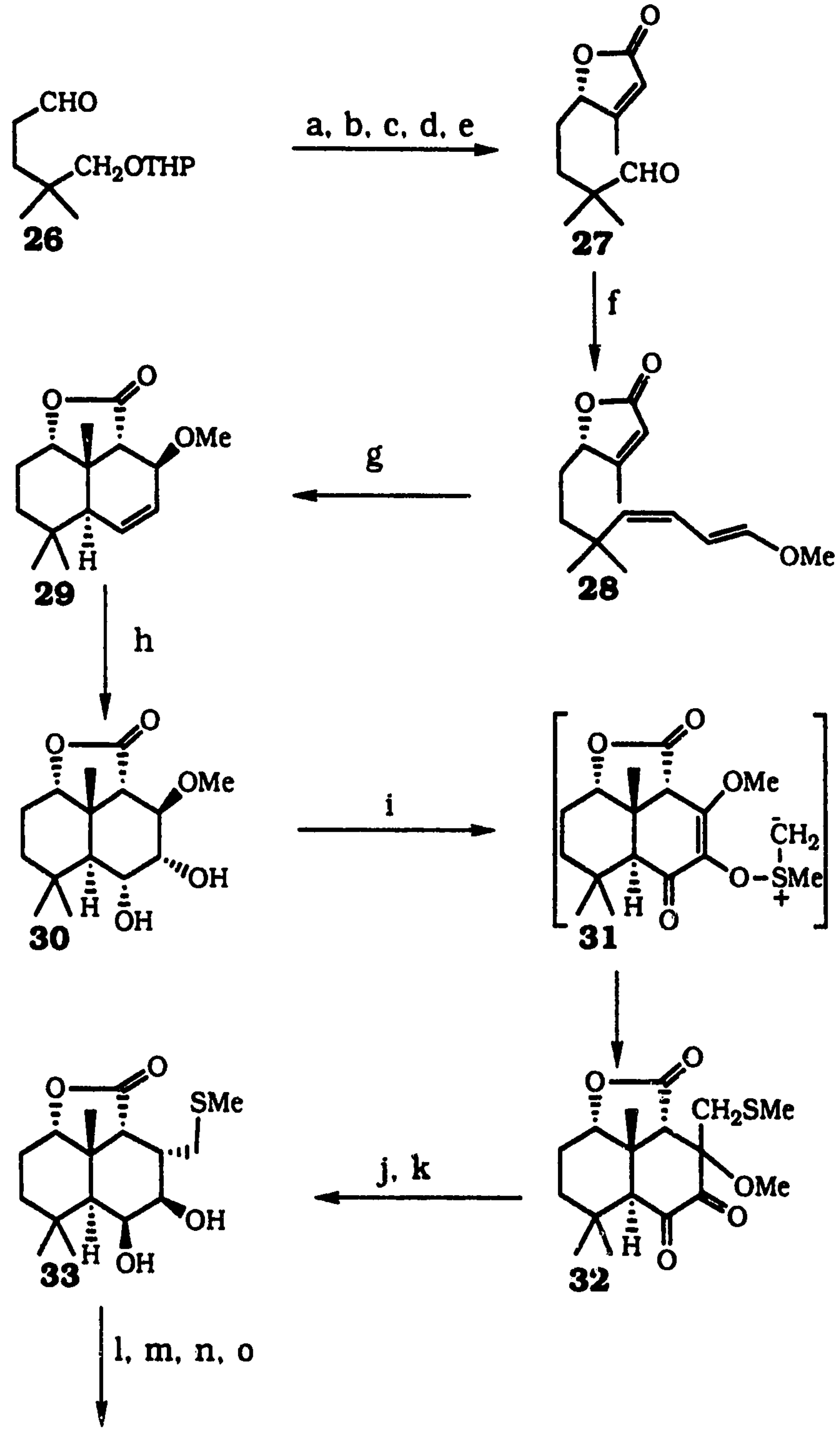


25

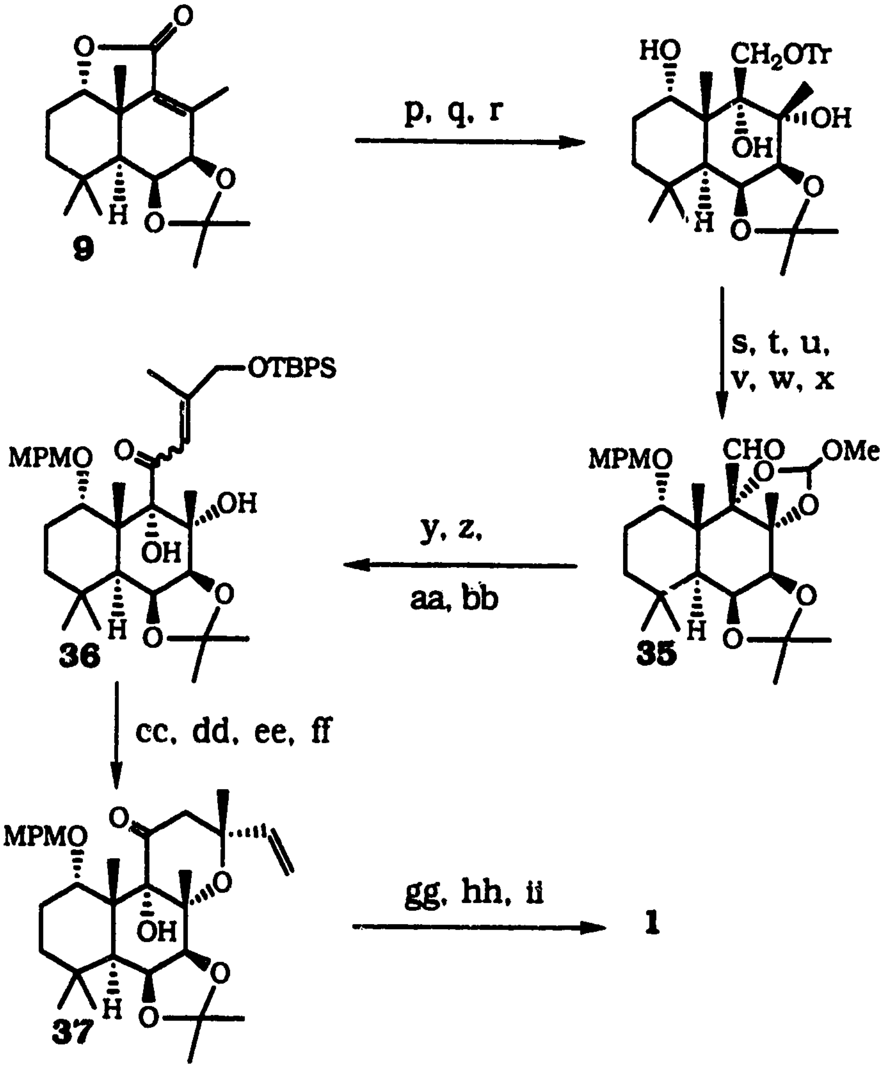
a) $(CH_2=CH)_2Cu(CN)Li_2$, $BF_3.Et_2O$; b) $(n\text{-}Bu)_4NF$, THF; c) $COCl_2$, Pyr, CH_2Cl_2; d) 3N HCl, dioxane; e) 2N NaOH, MeOH; f) Ac_2O, Pyr, 0°C.

Another total synthesis of forskolin was reported by Ikegami[36] and coworkers in 1988. Like Zeigler, Ikegimi also utilized an intramolecular Diels-Alder reaction. However unlike Zeigler who used a cyclic starting material with the required hydroxy group at C1 to serve as ring A and diene, Ikegima , in his approach to the AB ring system, selected a properly functionalized acyclic starting material to serve as ring A and dienophile. The Zeigler intermediate **9** was also envisaged by the Ikegami group as a key intermediate as illustrated in Scheme 2-V. Aldehyde **26** was converted to the Diels-Alder precursor **28** by a series of chemical reactions including lactone formation. Thermolysis of this compound in the presence of thiophenol gave lactone **29**. The missing methyl group at C8 was introduced by Moffatt oxidation of **30** which was accompanied by a [2,3]-sigmatropic rearrangement of the sulfur ylid **31** to give **32**. Reductive removal of the methoxy group by sodium telluride followed by borane reduction secured the required

Scheme 2-V


CHO
CH₂OTHP
26
a, b, c, d, e
O
O
CHO
27
f
O
O
OMe
28
g
O
O
OMe
H
29
h
O
O
OMe
OH
H
OH
30
i
O
O
OMe
CH₂
O-SMe
+
H
O
31
O
O
CH₂SMe
OMe
O
H
O
32
j, k
O
O
SMe
OH
H
OH
33
l, m, n, o

Scheme 2-V (cont'd)

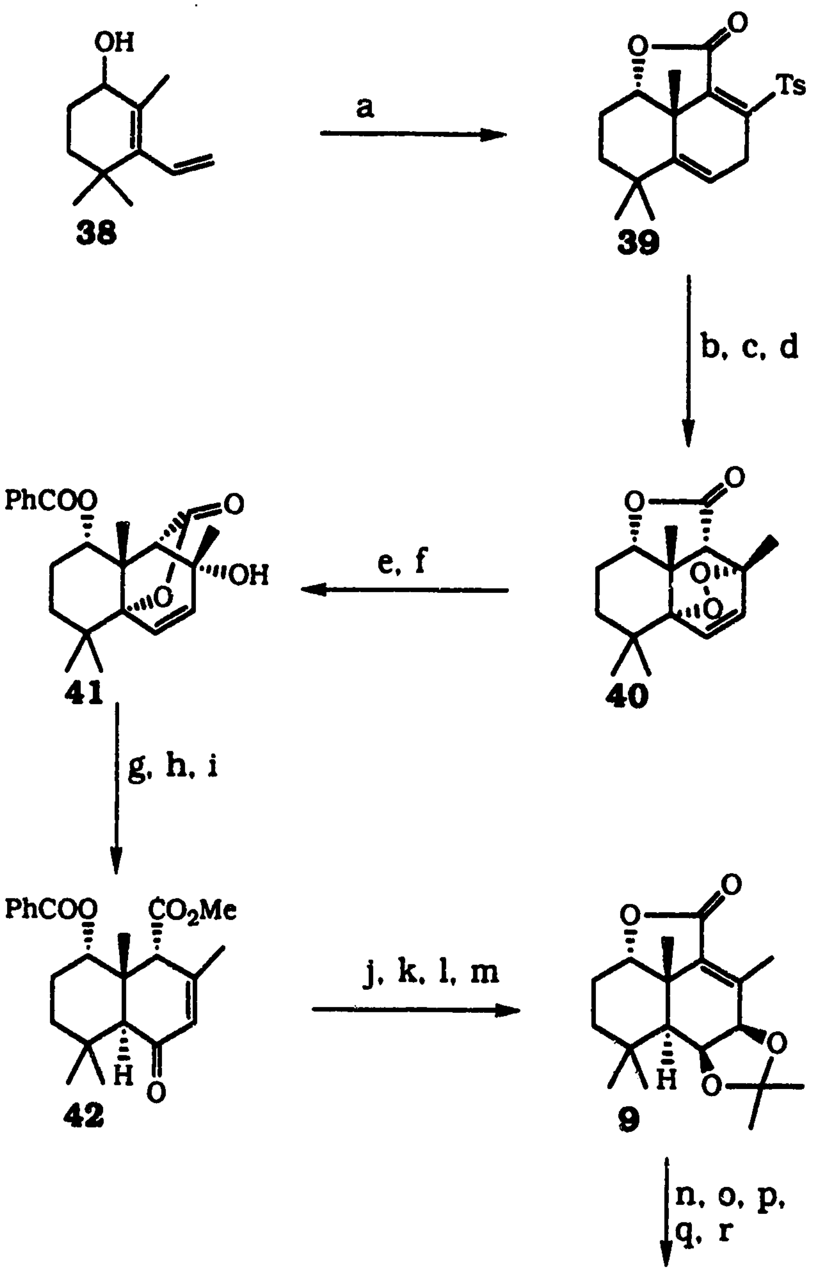


a) $LiC\equiv CCO_2Me$, THF, -78°C; b) dihydropyran, *p*-TsOH, CH_2Cl_2; c) $LiMe_2Cu$, THF, -70°C; d) *p*-TsOH, MeOH; e) PCC, CH_2Cl_2; f) $MeOCH{=}CHCH_2P^+Ph_3Br$, *n*-BuLi, -78°C, THF; g) PhSH, $PhCH_3$, sealed tube, 220°C; h) OsO_4, Me_3N-O, Pyr, *t*-BuOH-H_2O, reflux; i) SO_3·Pyr, Et_3N, DMSO; j) NaTeH, EtOH; k) *t*-$BuNH_2$-BH_3, MeOH; l) $Me_2C(OMe)_2$, *p*-TsOH, PhH; m) MCPBA, CH_2Cl_2; n) $CaCO_3$, $PhCH_3$, reflux; o) LiOMe, THF; p) $LiAlH_4$, Et_2O; q) TrCl, DMAP, 1,2-dichloroethane; r) OsO_4, Pyr, then H_2S, $CHCl_3$-dioxane; s) NaH, *p*-$MeOC_6H_4CH_2Cl$, HMPA, THF; t) *p*-TsOH, $CHCl_3$-MeOH; u) Ac_2O, Pyr; v) $HC(OMe)_3$, *p*-TsOH; w) $LiAlH_4$, Et_2O; x) SO_3·Pyr, DMSO; y) $LiC\equiv CCH_2OTBPS$, -78°C,THF; z) MnO_2, PhH; aa) $LiMe_2Cu$, Et_2O, -78°C; bb) 3N HCl-THF, then KOH-MeOH-THF; cc) PhSeCl, CH_2Cl_2, then Ra-Ni (W-2), EtOH; dd) $(n\text{-}Bu)_4NF$,THF; ee) *o*-$O_2NC_6H_4SeCN$, $(n\text{-}Bu)_3P$, THF; ff) 30% H_2O_2, CH_2Cl_2; gg) DDQ, CH_2Cl_2-H_2O, then K_2CO_3, MeOH; hh) 10% aq. $HClO_4$-THF; ii) Ac_2O, Pyr, 0°C.

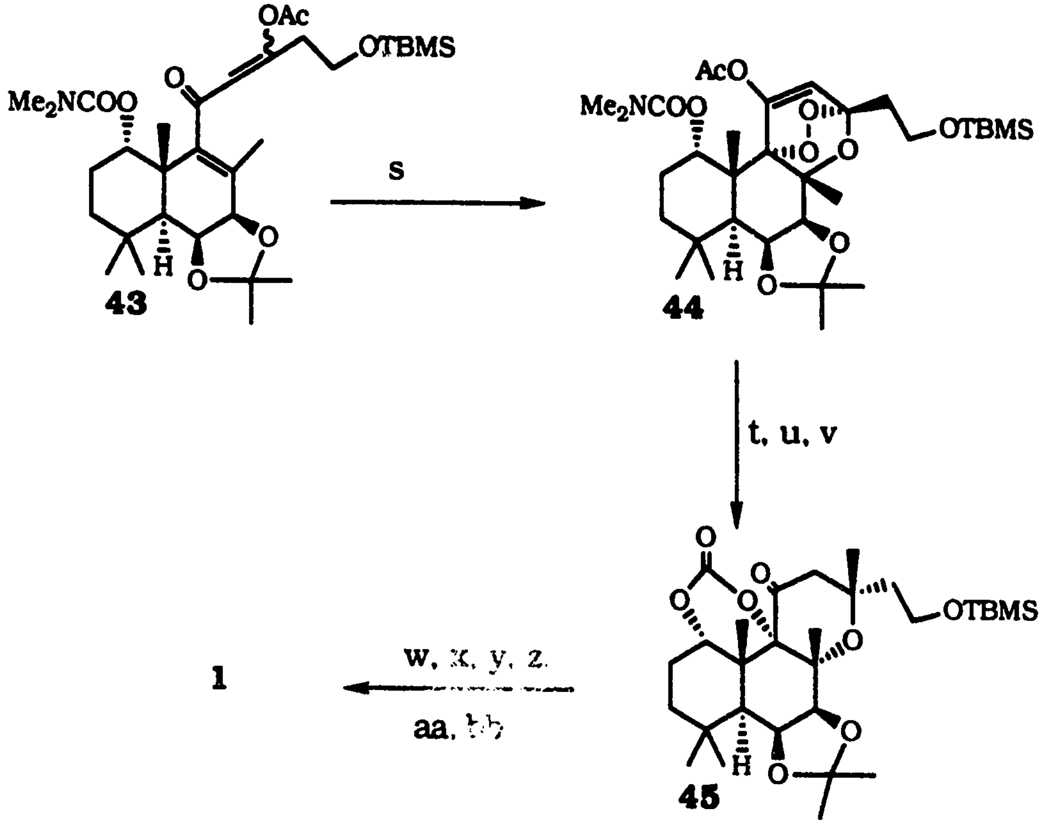
β-configuration of the hydroxy groups at C6 and C7. The reduction product **33** was elaborated to Ziegler intermediate **9** in four steps. Intermediate **9** was then transformed to forskolin by a sequence similar to that used by Ziegler including the crucial ring C formation.

The third total synthesis was published by Corey and his collaborators.[37,38] In their approach to forskolin, Corey and coworkers also constructed the AB ring system utilizing an intramolecular Diels-Alder reaction strategy. The same starting material as that used by Zeigler *et al.* was applied to serve as the diene portion and ring A. However, they used a different dienophile moiety. Mixing alcohol **38** and *p*-toluenesulfonylacetylenic acid afforded adduct **39** as the product of sequential esterification and Diels-Alder reaction. The missing methyl group at C8 was introduced by 1,4-addition to the α,β-unsaturated lactone moiety. Subsequent double bond isomerization and photoperoxidation of the conjugated diene gave endoperoxide **40** which was then converted to the Ziegler intermediate as outlined in Scheme 2-VI. Irradiation of **43**, derived from **9**, in the presence of methylene blue in chloroform solution saturated with oxygen, resulted in photocyclization to a pyrane and subsequent [4+2] addition of singlet oxygen to form the endoperoxide **44**. This key step to form ring C of forskolin was completely stereoselective. Enol acetate cleavage, β-elimination and

Scheme 2-VI


OH
38
a
O
O
Ts
39
b, c, d
O
O
O
O
40
e, f
PhCOO
O
OH
O
41
g, h, i
PhCOO
CO2Me
H
O
42
j, k, l, m
O
O
H
O
O
9
n, o, p,
q, r

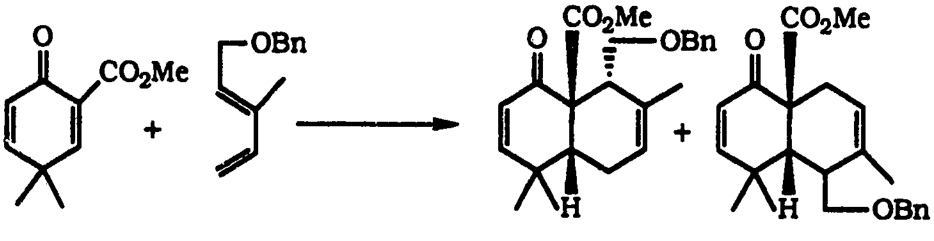
Scheme 2-VI (cont'd)



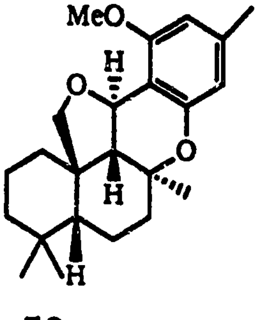
a) TsC≡CCOOH, $CHCl_3$; b) Me_2CuLi, $BF_3 \cdot Et_2O$; c) DBN; d) O_2, *hν*, $CHCl_3$, methylene blue; e) Al/Hg, THF, H_2O; f) $(PhCO)_2O$, DMAP, $ClCH_2CH_2Cl$; g) PCC, CH_2Cl_2; h) Al/Hg, THF, H_2O; i) CH_2N_2, Et_2O; j) DIBALH, $PhCH_3$; k) $Mo(CO)_6$, *t*-BuOOH; l) KOH, MeOH; m) 2,2-dimethoxypropane, *p*-TsOH; n) LiC≡CCH_2OTBMS, THF; o) Me_2NCOCl, silver triflate, CH_2Cl_2; p) K_2CO_3, THF, ethylene glycol, then 2N oxalic acid; p) TBMSCl, imidazole, DMF; r) thallous oxide, then AcOCl; s) O_2, *hν*, methylene blue, $CHCl_3$; t) NaOEt, $(n\text{-}Bu)_3P$, EtOH; u) Ac_2O, 100°C; v) $MeCuPBu_3$, $BF_3 \cdot Et_2O$; w) 2% HF, CH_3CN-H_2O; x) *o*-$O_2NPhSeCN$, $(n\text{-}Bu)_3P$; y) H_2O_2, THF; z) AcOH, H_2O; aa) LiOH, THF; bb) Ac_2O, Pyr, 0°C.

reduction of the hydroperoxide thus formed, were achieved in a single step using sodium ethoxide with tributylphosphine. This was followed by an array of rather standard transformations to complete the synthesis. Corey and coworkers also reported an enantioselective synthesis of the starting material **38**, which was converted to tryclic lactone **39**.[38]

In the last two decades, the Lewis acid catalyzed intermolecular Diels-Alder reaction of dienone ester **46** has been investigated extensively in our laboratory. This compound was shown to be an excellent dienophile. Its reaction with a variety of dienes occurred readily with a high degree of regio- and stereoselectivity to give 4,4-dimethyl-1-decalone directly.[43] With diene **47**, for example, it afforded the predominant adduct **48** along with a small amount of **49**. Adduct **48** was successfully elaborated to isosiccanin methyl ether **50**.[44]



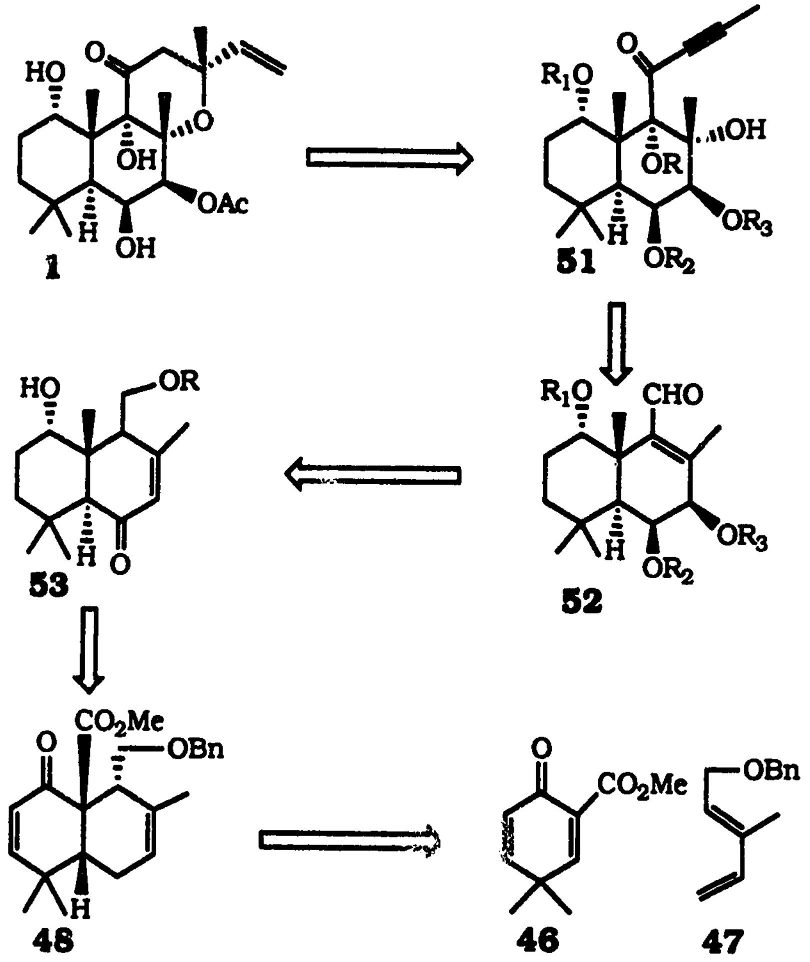
46 **47** **48** **49**



50

The Diels-Alder reaction of **46** and **47** could also serve as a key step in the synthesis of forskolin (**1**). In our approach towards the synthesis of this challenging molecule, bicyclic system **51** was visualized, as illustrated in the retrosynthetic analysis in Scheme 2-VII, as a later stage intermediate. This intermediate could, in principle, be derived from adduct **48** *via* the following three major synthetic operations; (1) reduction of the enone system to an alcohol, (2) conversion of the ester to a methyl (**48**→**53**), and (3) adjustment of the oxidation level of the existing functionalities (**53**→**52**) and the eventual incorporation of a propynyl group (**52**→**51**). Details of the effort made towards the synthesis of a precursor of the type of **51** are outlined in the second chapter of this thesis.

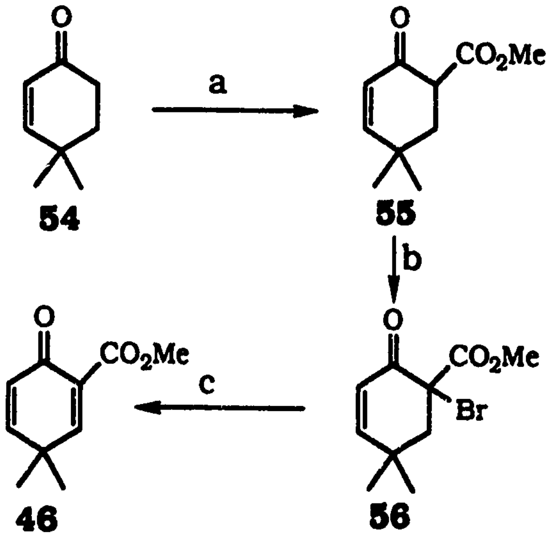
Scheme 2-VII


HO
OH
OAc
OH
H
1
R$_1$O
OH
OR
OR$_3$
OR$_2$
H
51
R$_1$O
CHO
OR$_3$
OR$_2$
H
52
HO
OR
H
O
53
CO$_2$Me
OBn
H
48
O
CO$_2$Me
46
OBn
47

Results and Discussion

The known dienophile, dienone ester **46**, is readily available in three steps. Carbomethoxylation of 4,4-dimethyl-2-cyclohexen-1-one (**54**)[45] with dimethyl carbonate and sodium hydride afforded keto ester **55**. The first sample of the dienone ester **46** was prepared from the keto ester **55** by direct oxidation using selenium oxide.[46] However, the purification after large scale reactions presented a serious problem resulting in low yield of the desired product. Therefore, an improved procedure applied recently in our group was followed.[47] This two-step transformation was achieved by treatment of the keto ester **55** with *N*-bromosuccinimide to give bromide **56** followed by dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene to give the dienone ester **46**.

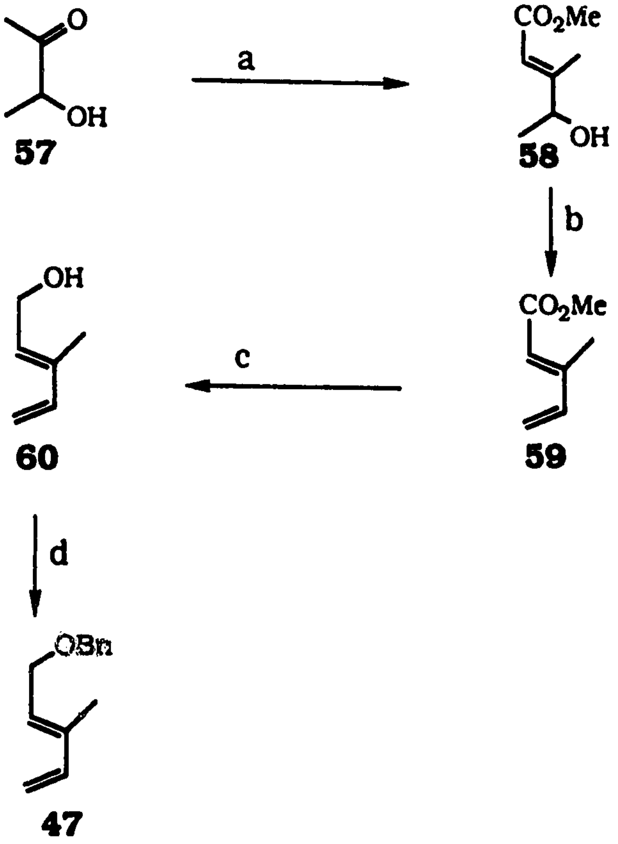
Scheme 2-VIII



a) $(MeO)_2CO$, NaH, DME; b) NBS, CCl_4; c) DBU, PhH.

Benzyl ether **47** was used as the counterpart for the initial Diels-Alder reaction. The benzyl group was selected in light of its stability under acidic and basic conditions and its ease of removal under specific conditions such as hydrogenolysis. Previously in this group, a mixture of *cis* and *trans* diene **47** was prepared and used for the Diels-Alder addition. Only the *trans* isomer was shown to participate in the Diels-Alder reaction leaving the *cis* isomer intact. For the present studies, a different method for the synthesis of the pure *trans* diene was investigated. Alcohol **58** was envisioned as a valuable intermediate. It was readily prepared *via* a Witting reaction of (carbomethoxymethylene)triphenylphosphorane and 3-hydroxy-2-butanone (**57**)[48] as shown in Scheme 2-IX. Dehydration of alcohol **58** over anhydrous copper sulfate[49] furnished ester **59** in 50% yield. The ir spectrum of this ester showed the carbonyl absorption band at 1722 cm^{-1}. Its high resolution mass spectrum (hrms) displayed a molecular ion at m/z 126.0678, suggesting the molecular formula $C_7H_{10}O_2$. The ^1H nmr spectrum of **59** displayed a doublet of doublets of doublets centered at δ 6.42, readily attributed to H_4. A strong singlet due to the methoxy was observed at δ 3.75. The ester group was reduced with lithium aluminium hydride to give alcohol **60**. The ir spectrum of the reduction product confirmed the absence of the ester carbonyl group and displayed a hydroxy absorption band at 3330 cm^{-1}. The hrms showed a molecular ion at m/z 98.0730, corresponding to the molecular formula $C_6H_{10}O$. The ^1H nmr spectrum showed the methylene protons next to the hydroxy group at δ 4.28 and the methyl group at δ 1.78.

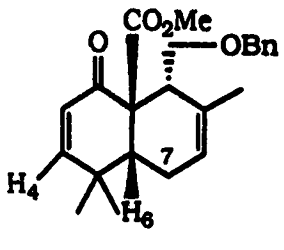
Scheme 2-IX



a) $(Ph)_3PCHCO_2Me$, PhH, 93%; b) $CuSO_4$, 50%; c) $LiAlH_4$, Et_2O, 79%; d) NaH, BnBr, THF, 60%.

Finally, benzylation of alcohol **60** with sodium hydride and benzyl bromide in tetrahydrofuran afforded the desired diene **47**. This diene did not display the molecular ion in the hrms. Instead, an $[M+H]^+$ peak at 189.1279 was observed. Its ^1H nmr did confirm the presence of five aromatic protons at δ 7.35, two allylic methylene protons at δ 4.15 and a vinylic methyl at δ 1.75.

Previously the Diels-Alder addition of benzyl ether **47** to the dienone ester **46** was carried out under ferric chloride catalysis at low temperature (-20°C) over a long reaction period to give the adduct **48** and the undesired regioisomer **49** in 84% and 8% yield, respectively (based on 64% consumption of the dienophile). When zinc chloride was used as a Lewis acid catalyst a 74% yield of the desired compound **48** was obtained as the only adduct after 36 h at 25°C. Thus, zinc chloride proved to be a better catalysis than ferric chloride. The adduct **48** displayed two strong carbonyl bands in its ir spectrum one at 1726 cm^{-1} for the ester and the other at 1689 cm^{-1} for the enone. Its hrms showed the molecular ion at m/z 368.1978, in agreement with the molecular formula $C_{23}H_{28}O_4$, which was further confirmed by elemental analysis. The structure of the addition product was confirmed by ^1H nmr spectroscopic analysis which indicated the presence of five aromatic protons and three vinylic protons. The β-proton (H_4) of the enone system resonated at δ 6.26 as a doublet of doublets due to the the long range coupling with H_6 which



48

appeared at δ 2.56 (ddd). This type of four-bond coupling is typical for those protons oriented in a 'W' fashion to each other[50] as shown in Figure 2-I. This coupling was confirmed by decoupling experiments. Irradiation of the signal at δ 6.26 caused the collapse of the signal at δ 2.56 to a doublet of doublets. Furthermore, when the signal at δ 2.56 was irradiated, it caused the collapse not only of the signal at δ 6.26 to a doublet, but also of the signals at δ 2.21 and 1.90, corresponding to the methylene proton attached to C7. The two doublets of doublets at δ 4.08 and 3.52 were assigned to the methylene protons next to the benzyloxy group. Three singlets at δ 1.84, 1.15 and 1.10 indicated the presence of the three methyl groups.

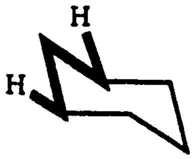
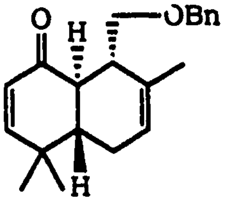


Figure 2-I. Long range 'W' coupling in cyclohexane ring.

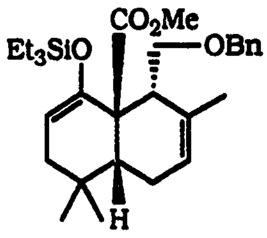
After the preparation of **48**, our synthetic plan called for conversion of the carbomethoxy functionality to a methyl group. This could, in principle, be accomplished either by a decarbomethoxylation-alkylation sequence or reduction to an alcohol followed by deoxygenation. The decarboxylation approach was investigated first. Thus, the adduct **48** was subjected to decarbomethoxylation in the presence of sodium hydroxide. This reaction furnished enone **61**. Its ir spectrum showed an enone carbonyl absorption band at 1671 cm^{-1}. Its hrms exhibited the molecular ion at m/z 310.1938, in accordance with the molecular formula $C_{21}H_{26}O_2$. The ^1H nmr spectrum displayed a doublet at δ 6.56 representing the β–proton of the enone system, as well as two doublets of doublets at δ 3.78 and 3.65 for the methylene protons adjacent to the benzyloxy group. The *trans*-stereochemistry at the ring junction was tentatively assigned based on the thermodynamic conditions applied.



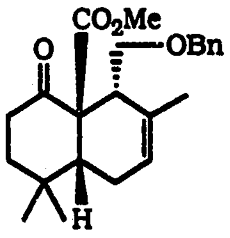
61

Having the enone **61** in hand, the subsequent step required was the methylation of the ketone. Treatment of **61** with methyl iodide in tetrahydrofuran at room temperature or at 64°C using either sodium hydride or potassium hydride as a base resulted invariably in the recovery of the starting material. When xylene was used as a solvent, the starting material also remained unchanged. When the stronger base lithium diisopropylamide (LDA) was used, partial isomerization of the starting material to the *cis* isomer was observed without apparent formation of the desired product.

The reduction-deoxygenation route was then examined. Among the known methods, selective catalytic hydrogenation[51,52] was unlikely to succeed because of the presence of the isolated double bond in ring B. A Birch type[53] reduction was inappropriate since it could also effect the removal of the benzyl protecting group. However, hydrosilylation appeared to be a suitable solution. The reaction can be carried out using tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst) and triethylsilane.[54] Accordingly, the enone system was transformed into saturated ketone by 1,4-addition of triethylsilane to give the silyl enol ether **62**. The crude product, without purification, was immediately treated with tetra-*n*-butylammonium fluoride to give the saturated ketone **63**. Its ir spectrum showed two carbonyl absorption bands at 1733 and 1716 cm^{-1} for the ester and ketone, respectively. A molecular ion at m/z 370.2147 in the hrms confirmed the molecular formula $C_{23}H_{30}O_4$. The assigned structure was further verified by ^1H nmr spectroscopy. It showed five aromatic protons at δ 7.23 and one vinylic proton at δ 5.30. Two singlets at δ 3.60 and 1.82 were observed and readily attributed to the methoxy and the vinylic methyl, respectively.

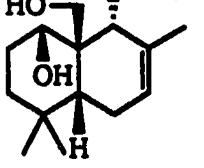


62

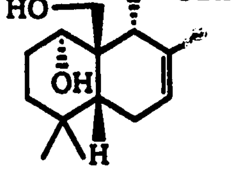


63

Ketone **63** was subjected to reduction with an excess of diisobutylaluminium hydride in ether. After work up, two compounds were isolated. The less polar compound, obtained in 14% yield, was identified as diol **64**. This product showed the hydroxy absorption band at 3425 cm^{-1} in the ir spectrum. Its hrms displayed the molecular ion at m/z 344.2397, in agreement with the required formula $C_{22}H_{32}O_3$. The ^{1}H nmr spectrum displayed the vinylic proton at δ 5.60 and the benzylic protons at δ 4.62 and 4.42. The major product **65**, isolated in 72% yield, also showed a hydroxy absorption (3400 cm^{-1}) in its ir spectrum. Its hrms showed the molecular ion at m/z 344.2364, corresponding to the molecular formula $C_{22}H_{32}O_3$. The ^{1}H nmr spectrum displayed the vinylic proton at δ 5.44 and the benzylic protons as an AB system centered at 4.58. Two doublets of doublets at δ 4.10 and 3.78 were attributed to the methylene protons next to the benzyloxy group. The stereochemistry of the secondary hydroxy group in the reduction products **64** and **65** was assigned tentatively based on the assumption that the hydride ion was delivered preferentially from the sterically less hindered face. This assignment was confirmed later by the chemical transformation of **65** to the bromide **69**. When lithium aluminium hydride was used as a reducing agent, epimer **65** was produced exclusively, in 86% yield, from saturated ketone **63**.



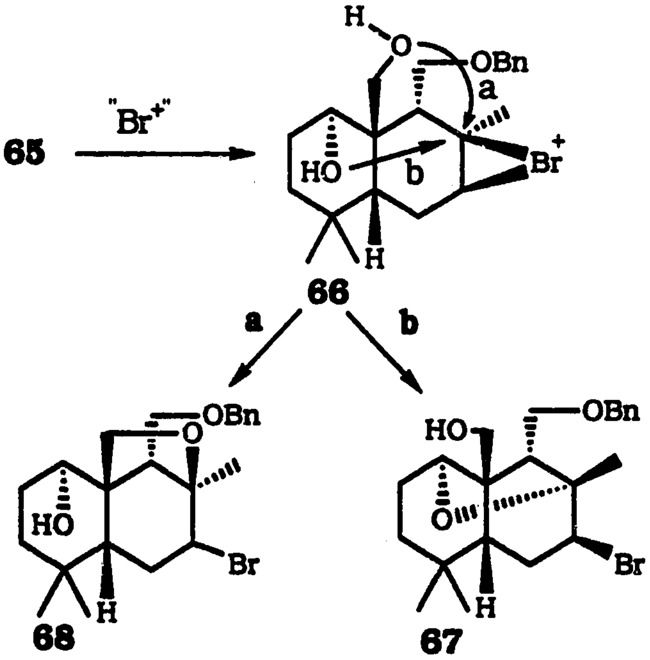
64



65

To deoxygenate the primary alcohol selectively, its differentiation from the secondary one was required. Conceptually, this could be achieved by an intramolecular cyclization induced by a bromine cation. As illustrated in Scheme 2-X, the addition of a bromine cation is expected to occur from the sterically less hindered side. Subsequent attack on the incipient "exo" bromonium ion **66** by the secondary hydroxyl *via* path **b** (path **a** leading to **68** involving the primary hydroxyl is sterically unfavorable) should give rise the desired ether **67**. This

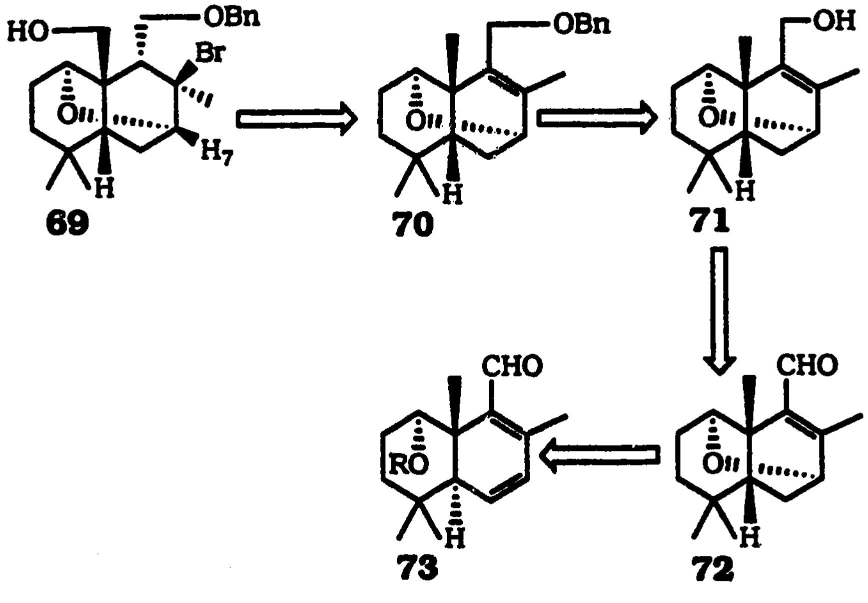
Scheme 2-X



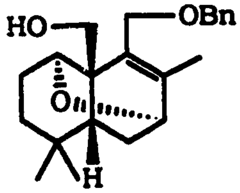
projected process not only allows easy differentiation of the two hydroxy groups, but also provides a convenient means for the eventual incorporation of the hydroxy groups required for the ring B of the target molecule.

The attempted brominaton of diol **65** with *N*-bromosuccinimide (NBS) alone was not satisfactory. A complex mixture was formed. On the other hand, treatment of diol **65** with two equivalents of sodium hydride and two equivalent of NBS afforded a single product in 81% yield. Based on the spectroscopic data, this product was assigned to the structure **69**. It showed a hydroxy absorption band at 3451 cm^{-1} in the ir spectrum. The hrms was very informative as to which hydroxyl had participated in the cyclization process. It did not show the molecular ion. However, peaks at m/z 393.1246 and 391.1264 due to the of loss of formaldehyde unit were observed. The loss of fomaldehyde is possible only if the primary hydroxy group is present. Further evidence for the proposed structure was obtained from the ^{1}H nmr spectrum. It displayed three methyl singlets at δ 1.46, 1.08 and 1.02 and a doublet of doublets at δ 3.22 (1H). Upon addition of D_2O, the latter signal disappeared along with the collapse of a doublet of doublets at δ 3.55 to a doublet. This observation suggested the presence of a hydroxymethylene unit. The regiochemistry of the cyclic ether was tentatively assigned based on decoupling experiments and the observed chemical shift of H_7. Irradiation of the signal at δ 4.18 (dd, H_7), caused the collapse of the two signals at δ 2.55 (dd, H_{6ax}) and 2.05 (ddd, H_{6eq}) to a doublet and a doublet of doublets, respectively. The stereochemistry of the center bearing the bromine atom could not be unambiguously determined and its assignment was made based on mechanistic considerations. Although the anticipated product **67** was not formed, the isolation of compound **69** in high yield was equally encouraging. Its transformation to the potentially useful advanced intermediate **73** could conceivably be carried out *via* compounds **70-72** as outlined in Scheme2-XI.

Scheme 2-XI

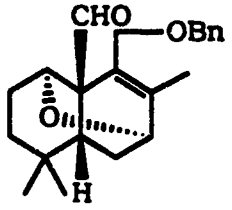


Bromide **69** was converted to the corresponding unsaturated alcohol **74** in 78% yield by dehydrobromination using pyridine as a base. The ir spectrum of the unsaturated alcohol exhibited the hydroxy absorption band at 3440 cm^{-1}. Its hrms supported the molecular formula of $C_{22}H_{30}O_3$ by displaying the molecular ion at m/z 342.2196. The ^{1}H nmr did not show any signals corresponding to vinylic protons, indicating the presence of a tetrasubstituted double bond. The benzylic protons resonated at δ 4.56 (d) and 4.52 (d). The methyl singlet at δ 1.46 in the ^{1}H nmr spectrum of the starting material was replaced by a vinylic methyl singlet at δ 1.86. As required by the formation of **74**, the structural assignment of its precursor **69** was confirmed.



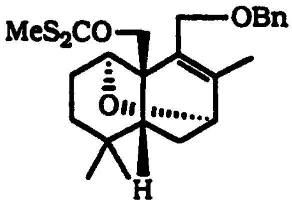
74

The successful dehydrobromination set the stage for deoxygenation. Two methods were attempted. It is well known that a thioacetal can be reduced to the corresponding hydrocarbon with Raney-nickel.[55] Thus, the unsaturated alcohol **74** was subjected to oxidation with pyridinium dichromate[56] to give aldehyde **75** in a quantitative yield. The carbonyl absorption band was observed at 1712 cm^{-1} in the ir spectrum. Its hrms showed the molecular ion at m/z 340.2030, corresponding to the molecular formula $C_{22}H_{28}O_3$. The singlet at δ 10.10 in ^{1}H nmr spectrum was readily assigned to the aldehydic proton. The methylene protons next to the benzyloxy group were observed at δ 4.15 and 3.85. The attempted thioacetal formation from aldehyde **75** with 1,2-ethanedithiol in dichloromethane in the presence of boron trifluoride etherate resulted, unfortunately, in a complex mixture of products.

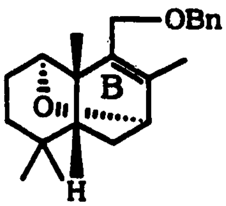


75

A second procedure for the required deoxygenation was then explored. Barton[57] has demonstrated that, upon treatment with tri-*n*-butyltin hydride, S-alkyl xanthates undergo smooth reductive cleavage of the alkyl oxygen bond. Thus, **74** was converted to xanthate **76** by sequential treatment with *n*-butyllithium, carbon disulfide and methyl iodide. The structure of this xanthate was discerned from its spectral data. Its ir spectrum displayed a strong band at 1220 cm^{-1} due to the carbon sulfur double bond. In agreement with the assigned structure, the hrms showed the molecular ion at m/z 432.1805, due to the formula $C_{24}H_{32}O_3S_2$. Its ^1H nmr spectrum exhibited a broad resonance at δ 5.24 and a doublet at δ 4.93 (J = 12 Hz) for the methylene protons next to the xanthate. This assignment was confirmed by decoupling experiments. Irradiation of the broad signal at δ 5.24 caused the collapse of the doublet at δ 4.93 to a singlet. The aromatic protons appeared as a multiplet centered at δ 7.35. Heating xanthate **76** with tri-*n*-butyltin hydride and a catalytic amount of azobisisobutyronitrile (AIBN) in xylene yielded benzyl ether **70** in 88% yield. The hrms displayed the molecular ion at m/z 326.2242 verifying the molecular formula $C_{22}H_{30}O_2$. Its ^1H nmr spectrum exhibited the aromatic protons at δ 7.34 and the benzylic protons at δ 4.47 as a singlet. Four other singlets (1.88, 1.46, 1.18 and 0.95) were assigned for the methyl groups.



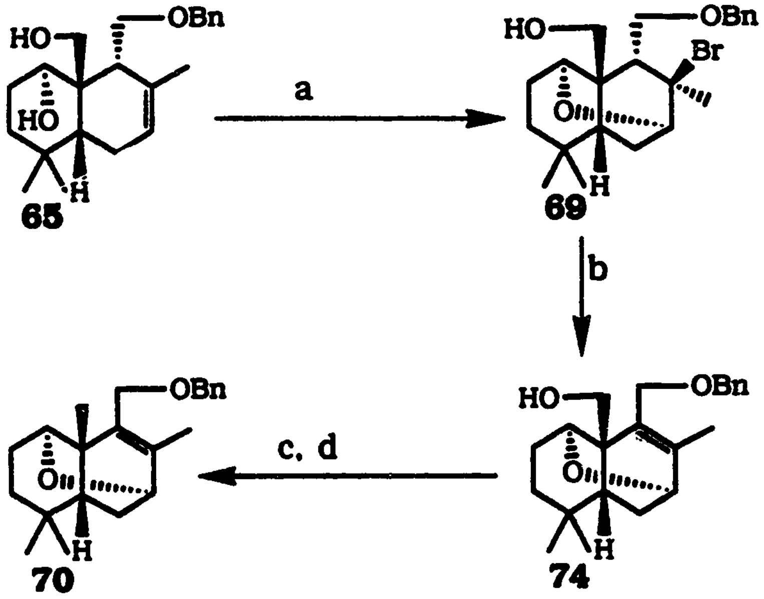
76



70

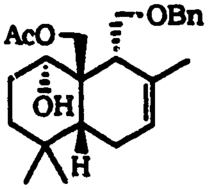
In order to modify ring B, the benzyl group needs to be removed. Catalytic hydrogenolysis of **70** was attempted using Pd-C in ethyl acetate-hexane, hexane or ethanol. No reaction was observed even after an extended period of time. However, when a few drops of 5% HCl were added to the reaction mixture, a complex mixture was formed. Similar results were obtained using ethyl acetate-hexane as solvent. Another commonly used method for debenzylation is the dissolving metal reduction.[58] Treatment of benzyl ether **70** with lithium metal in liquid ammonia at -78°C, followed by gradual warming of the solution to room temperature, resulted in complete decomposition of the starting material. The tlc of the reaction mixture indicated the presence of more than seven products. When ammonia was replaced by ethylamine[59] the reduction was shown to be equally ineffective. Several other methods (TMS-NaI,[60-62] AcCl-NaI,[63] BF_3-EtSH[64,65]) for cleavage of the ether linkage were also examined. Unfortunately, none of these methods prove to be effective. In all cases, extensive decomposition of the starting material was observed. As a result of these discouraging findings, the approach summarized in Scheme 2-XII was abandoned and a new route was investigated.

Scheme 2-XII



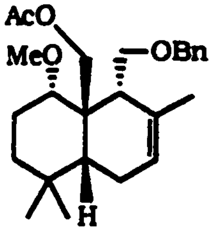
a) 2 eq. NaH, NBS, Et_2O, 81%; b) Pyr, 78%; c) n-BuLi, THF, then CS_2, MeI, 100%; d) $(n\text{-Bu})_3SnH$, AIBN, xylene, 88%.

Starting from diol **65**, the new plan was to protect the secondary alcohol with a protecting group, such as methyl ether, that could survive hydrogenolysis and/or dissolving metal reduction conditions. Towards this goal, the primary hydroxy group was protected [illegible] an acetate, since it could easily be removed later under mild basic conditions. The acetylation was achieved using acetic anhydride in pyridine in the presence of a catalytic amount of 4-dimethylaminopyridne (DMAP) to give acetate **77** in quantitative yield. The ir spectrum of this acetate displayed the hydroxy absorption at 3520 cm^{-1} and the ester carbonyl band at 1740 cm^{-1}. The molecular ion was observed at m/z 386.2452 in its hrms, in accord with the molecular formula $C_{24}H_{34}O_4$. Its ^{1}H nmr exhibited the aromatic protons at δ 7.35 and the vinylic proton at δ 5.52. The methylene protons next to acetate were observed at δ 4.15 (d) and 3.88 (d).

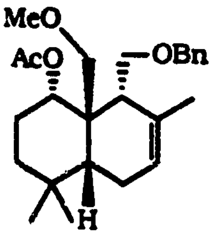


77

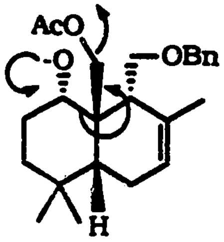
The attempted methylation of **77** with methyl iodide using potassium hydride or sodium hydride as a base was not satisfactory. Under a variety of conditions, the reaction consistently gave four products. After careful chromatography, two major compounds were obtained as an inseparable mixture. The ^{1}H nmr spectrum of this mixture exhibited two methoxy and two acetate groups. It is believed that the starting material underwent partial acyl migration prior to methylation. Based on this assumption, compounds **78** and **79** were proposed as the major components of this mixture. The remaining two minor compounds, which could have arisen from the fragmentation of alkoxide **80**, were not identified.



78

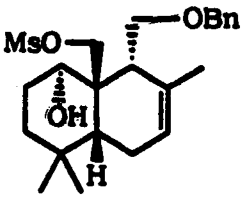


79



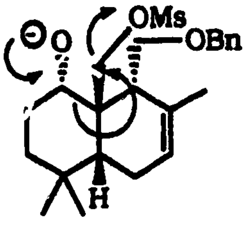
80

It is well documented that sulfonates can be reduced to the corresponding hydrocarbons with triethylborohydride[66-69] or with zinc dust and sodium iodide in a polar solvent.[70] Thus, the selective mesylation of the primary hydroxy group present in diol **65** was attempted. Treatment of diol **65** with one equivalent of methanesulfonyl chloride and pyridine in dichloromethane[71] gave the desired mesylate **81**. This compound displayed the hydroxy absorption band at 3420 cm^{-1} in its ir spectrum. The molecular ion was observed at m/z 422.2150 in its hrms, in accord with the molecular formula $C_{23}H_{34}O_5S$. The structural assignment was further substantiated by its ^{1}H nmr spectrum which exhibited a broad singlet at δ 5.50 for the vinylic proton, two doublets (*J* = 10 Hz each) at δ 4.29 and 3.93 for the methylene protons next to the mesylate group, and an intense singlet at δ 3.00 for the methyl group of the mesylate.



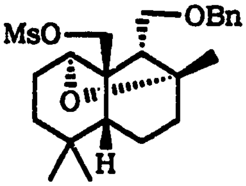
81

The reductive cleavage of the methanesulfonyloxy group was attempted using lithium triethylborohydride in tetrahydrofuran. A very polar compound was formed. By direct comparison, this compound was identified as diol **65**. The regeneration of diol **65** resulted apparently from the cleavage of the oxygen-sulfur bond instead of the desired oxygen-carbon bond, a fragmentation problem encountered with hindered mesylates.[72] The reduction of **81** with sodium iodide and zinc dust was examined. Unfortunately it resulted in extensive decomposition of the starting material. To avoid this problem, methylation of the hydroxy group of **81** was attempted with sodium hydride or potassium hydride and methyl iodide, however, without any success. This reaction provided a complex mixture of products as indicated by tlc analysis. This result was not completely surprising. Mesylate **81**, like acetate **77**, could undergo fragmentation induced by alkoxide formation as illustrated in



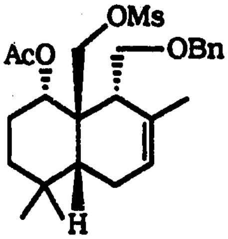
82

formula **82**. To avoid alkoxide formation, the method reported by Howells[73] involving methyl trifluoromethanesulfonate in pyridine was attempted. When this method was applied to **81**, the spectroscopic data of the product revealed that cyclic ether **83** had been formed rather than the desired product. The formation of the cyclic ether resulted from protonation of the double bond followed by intramolecular nucleophilic attack at the carbocation thus generated. The ir spectrum of the cyclic ether **83** displayed two absorption bands for the mesylate at 1356 and 1176 cm^{-1}. Its hrms showed the molecular ion at m/z 422.2128, equivalent to the molecular formula $C_{23}H_{34}O_5S$. Its ^1H nmr displayed the benzylic protons as a singlet at δ 4.50 . The two doublets at δ 4.42 and 4.25 were attributed to the methylene protons adjacent to the mesylate. Four methyl resonances were observed at δ 2.77, 1.30, 1.10 and 1.00.



83

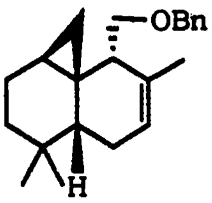
Another protecting group, that might survive under the conditions required for the reduction of the mesylate with zinc dust, is an ester. Thus mesylate **81** was converted to acetate **84**



84

using acetic anhydride and DMAP in pyridine This acetate displayed the carbonyl absorption at 1737 cm^{-1} in the ir spectrum. Its hrms failed to show the molecular ion, but a peak at m/z 356.1600, corresponding to the loss of a unit of benzyl alcohol was observed. The ^{1}H nmr spectrum confirmed the structure of the acetylation product **84**. It displayed a resonance at δ 5.40 for the vinylic proton and a doublet of doublets at δ 4.96 for the methine proton next to the acetate. Furthermore, it displayed five methyl groups at δ 2.97, 2.00, 1.75, 0.99 and 0.78.

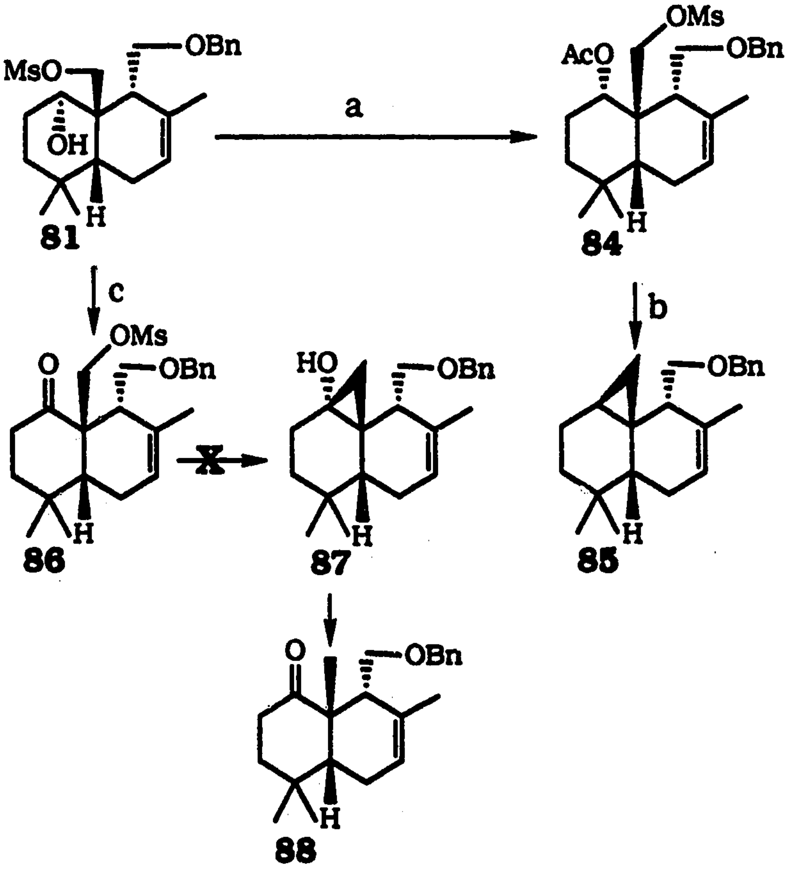
Treatment of acetate **84** with sodium iodide and zinc dust furnished a single product. Unfortunately, this product was readily identified as the undesired product **85** based on the spectroscopic data. In the ir spectrum, the product did not display a carbonyl or hydroxy absorption. The chemical formula of $C_{22}H_{30}O$ was confirmed by the molecular ion in the hrms at m/z 310.2297. The ^{1}H nmr spectrum provided conclusive evidence for the proposed structure. It showed two abnormally high-field doublets of doublets at δ 0.43 and 0.07 due to the cyclopropane protons. Three methyl singlets were observed at δ 1.85, 0.80 and 0.78 and the vinylic proton resonated at δ 5.40.



85

The above result obtained previously and summarized in Scheme 2-XIII, led us to investigate yet another approach to tackle this synthetic problem. This new approach involved the preparation of ketone **86**. This ketone could give rise to cyclopropanol **87** upon treatment with zinc dust and lithium iodide. Ring opening of the cyclopropanol under suitable conditions is expected to give the desired compound **88**. Thus, **81** was subjected to oxidation using pyridinium dichromate in dichloromethane.[56] This reaction provided the expected ketone

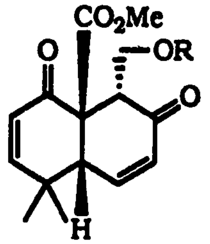
Scheme 2-XIII



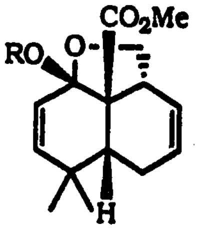
a) Ac_2O, Pyr, DMAP, 100%; b) Zn, NaI, DMF, 66%; c) PDC, CH_2Cl_2, 88%.

86. A carbonyl absorption band was observed at 1700 cm^{-1} in the ir spectrum. The molecular ion was not observed in the hrms. However, a peak at m/z 312.1395 due to the loss of the benzyl alcohol unit was displayed. In the ^{1}H nmr spectrum, five aromatic protons centered at δ 7.34 and two benzylic protons were observed at δ 4.41. Treatment of ketone **86** with zinc dust and sodium iodide led to complete decomposition of the starting material without the formation of the desired cyclopropanol **87**.

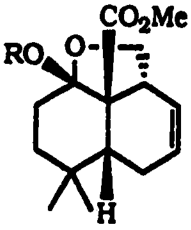
As a consequence of the above negative findings, a substantial modification of the synthetic scheme was deemed necessary. It was decided to replace the diene **47** used in the initial Diels-Alder reaction with 2,4-pentadien-1-ol. The adduct expected from its addition to dienophile **46** could, in principle, be converted to dienone ester **89** to facilitate the isomerization of the *cis* decalin system to the required *trans* in early stages of the synthesis. Alternatively, it could be transformed into acetal **90** or **91** to facilitate the differentiation of the existing functionalities.



89



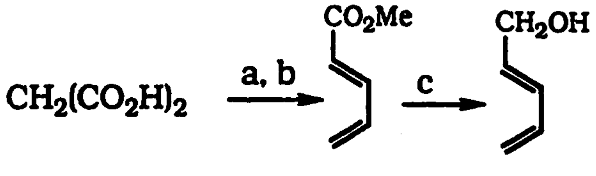
90



91

The required diene was readily prepared according to Scheme 2-XIV. Condensation of malonic acid **(92)** and acrolein **(93)**[74] gave 2,4-pentadienoic acid, which, without purification, was converted to its methyl ester **94**. The ester was then reduced to the corresponding alcohol **95** using lithium aluminium hydride.

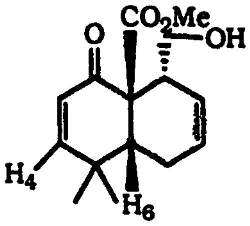
Scheme 2-XIV



92 **94** **95**

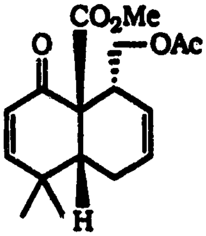
a) $CH_2{=}CHCHO$ (**93**), Pyr; b) MeOH, H_2SO_4(cat), 36%; c) $LiAlH_4$, Et_2O, 75%.

The Diels-Alder reaction between alcohol **95** and dienone ester **46** provided adduct **96** in excellent yield (95%). Adduct **96** displayed the hydroxy absorption band at 3400 cm^{-1}, the ester carbonyl at 1724 cm^{-1} and the enone carbonyl at 1678 cm^{-1}. Although the molecular ion was not observed in the hrms, a fragment at m/z 234.1252 for the formula $C_{14}H_{18}O_3$ resulting from the loss of formaldehyde was displayed. Its molecular formula was substantiated by cims which exhibited a peak at m/z 265 for $[M+H]^+$. The ^1H nmr spectrum showed a doublet of doublets at δ 6.38 and a doublet at δ 5.96 for the respective β– and α-protons of the enone system. The β-proton H_4 appeared as a doublet of doublets due to its long range coupling with H_6. This was confirmed by a decoupling experiment. Irradiation of the signal at δ 6.38 caused the collapse of the signal corresponding to H_6 at 2.64 (ddd) to a doublet of doublets. The other two vinylic protons appeared at δ 5.78 and 5.60. The resonances representing the *gem*-dimethyl were observed at δ 1.17 and 1.14 as singlets. The ^{13}C nmr spectrum displayed two carbonyl signals at δ 197.36 (p) and 174.37 (p), corresponding to the ketone and the ester, respectively.



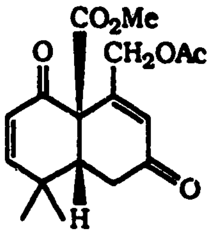
96

A simple procedure for the conversion of olefins to enones was developed by the group of Mehelich.[75] It involved photooxygenation of olefins in dichloromethane in the presence of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) as photosensitizer, acetic anhydride and a base. When this procedure was applied to adduct **96** only the acetylation product **97** was isolated. This adduct displayed two carbonyl absorptions at 1736 and 1668 cm^{-1}, for the esters and the enone, respectively. Its hrms did not show the molecular ion. However, a peak at



97

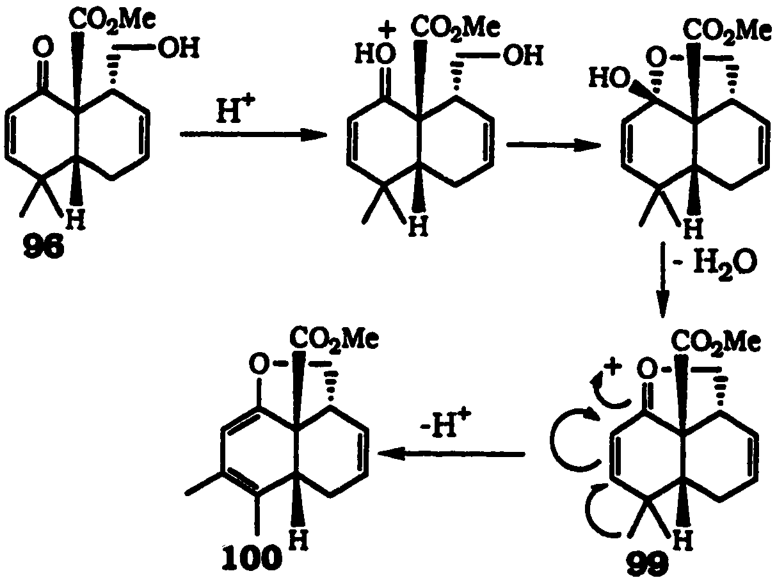
m/z 246.1252 for the fragment M^+-AcOH and the elemental analysis supported the molecular formula $C_{17}H_{22}O_5$. Its ^1H nmr displayed the β-proton of the enone system at δ 6.30 as a doublet of doublets and the α-proton at δ 5.90 as a doublet. Two strong singlets due to the methoxyl and the acetate were observed at δ 3.75 and 2.05, respectively. The ^{13}C nmr spectrum exhibited seventeen signals in accordance with the structure of the product. The isolation of compound **97** was apparently the result of its low reactivity towards photooxygenation, probably due to the presence of the electron-withdrawing acetyl group. When the photooxygenation of **96** was carried out in carbon tetrachloride in the presence of TPP only, the starting material was consumed fairly rapidly (24 h). Addition of acetic anhydride and pyridine to the reaction mixture resulted in the generation of an enone system. To our disappointment however, the product was identified as the regioisomer **98** of the desired compound **89** based on the following spectral data. It showed absorptions at 1739 cm^{-1} for the esters and 1675 cm^{-1} for the enone carbonyl in the ir spectrum. Its hrms displayed the molecular ion at m/z 320.1263 in accordance with the formula $C_{17}H_{20}O_6$. The ^1H nmr spectrum exhibited three vinylic proton resonances at δ 6.70 (d, $J = 10$ Hz), 6.25 (t, $J = J' = 2$ Hz) and 6.05 (d, $J = 10$ Hz). The methylene protons next to the acetate appeared as a doublet ($J = 2$ Hz) at δ 4.73.



98

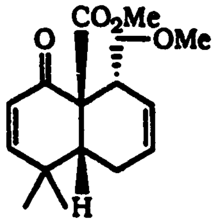
The conversion of alcohol **96** to acetal **90** (R = CH_3) was then explored. Treatment of **96** with methanol in refluxing benzene in the presence of *p*-toluenesulfonic acid afforded a single product. This product showed, as expected, only one carbonyl absorption in its spectrum at 1731 cm^{-1}. The ^1H and ^{13}C nmr spectra, however, indicated that it was enol ether **100** instead the desired acetal **90**. The ^1H nmr spectrum showed a methoxy group at δ 3.70 and three vinylic protons at δ 5.95 (dddd), 5.58 (m) and 5.10 (s). The methylene protons next to the ethereal oxygen appeared at δ 4.45 (dd) and 4.02 (dd). Furthermore, two signals typical for vinylic methyl groups were observed at δ 1.75 and 1.65. The ^{13}C nmr spectrum displayed a carbonyl signal at δ 174.93 (p) for the ester and two signals at δ 155.94 (p) and 96.41 (a) due to the enol ether. The resonances at δ 129.14 (a) and 125.27 (a) for the disubstituted olefin and at δ 127.87 (p) and 123.88 (p) for the tetrasubstituted olefin also in support of the structure **100**. The assignment was further confirmed by the hrms which showed the molecular ion at m/z 246.1256. It is believed that the product was formed through the intermediacy of **99** as illustrated in Scheme 2-XV. When the above reaction was carried out in the absence of methanol, the same enol ether was obtained.

Scheme 2-XV



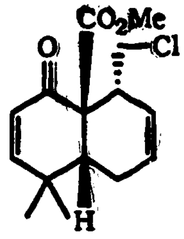
As an alternative method for the acetal formation, alcohol **96** was heated in methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid. A single product was isolated in 85% yield. The spectroscopic data unequivocally confirmed the formation of ether **101**. The ir spectrum showed carbonyl absorption bands at 1728 and 1684 cm^{-1} for the ester and enone, respectively. The required molecular formula $C_{16}H_{22}O_4$ was confirmed by elemental analysis and by hrms which displayed the molecular ion at m/z 278.1515. In the ^{1}H nmr spectrum, four vinylic protons were observed at δ 6.28, 5.88, 5.68 and 5.55. The methylene protons adjacent to the methoxyl appeared at δ 3.86 and 3.55. Two methoxy groups were observed at δ 3.71 and 3.31. The ^{13}C nmr spectrum was also in agreement with structure **101**.

It displayed two carbonyl signals at δ 195.97 (p) and 174.49 (p). The formation of the undesired ether **101** could be rationalized by involving the intermediacy of **99**. Nucleophilic attack at its oxonium ion-activated methylene carbon by methanol would give the ether **101**.



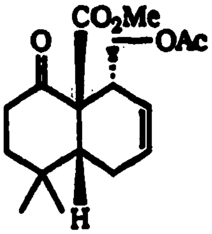
101

Another procedure for the ketal formation, reported by Chan and coworkers, was also explored.[76] This method involved the use of trimethylsilyl chloride and methanol. When the experiment was performed with alcohol **96**, the chloro compound **102** was obtained. In the ir spectrum, two carbonyl absorption bands at 1728 and 1686 cm^{-1} were observed in accord with the proposed structure for the product **102**. The hrms displayed a pair of molecular ions at m/z 284.1014 and 282.0993 for the required chemical formula $C_{15}H_{19}O_3Cl$, which was further confirmed by elemental analysis. In further agreement with the assigned structure, the ^{1}H nmr showed one methoxy group at δ 3.76. The methylene protons adjacent to the chloride appeared at δ 4.20 and 3.50. The formation of chloride **102** was most likely induced by the hydrogen chloride generated *in situ* from trimethylsilyl chloride and methanol. In support of this rationale was the observation that treatment of **96** with hydrogen chloride acid in tetrahydrofuran gave the same product **102**.



102

With the unexpected formation of **98**, **101** and **102**, the inability of **96** to undergo ketal formation was realized. It was thought that the carbon-carbon double bond of the enone system might have contributed to these discouraging results. Hence, the selective reduction of the enone double bond was attempted with triethylsilane in the presence of Wilkinson's catalyst. Unfortunately, the reaction gave no less than six products after the crude reaction mixture was treated with tetra-*n*-butylammonium fluoride. In an attempt to improve the reduction, the hydroxy group in **96** was protected with an acetyl group. Acetylation of **96** provided **97** in quantitative yield. Hydrosilylation of **97** proceeded smoothly to give the desired ketone **103** in excellent yield. The ir spectrum of

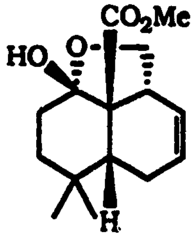


103

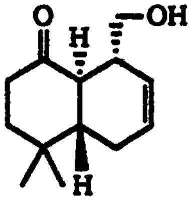
ketone **103** showed three carbonyl absorptions at 1739, 1725 and 1709 cm^{-1}. The molecular ion was observed in the hrms at m/z 308.1623, confirming the formula $C_{17}H_{24}O_5$. Its ^1H nmr spectrum exhibited two vinylic protons at δ 5.78, the methylene protons next to the acetate at δ 4.40 and 4.17 and the methoxy protons at δ 3.75.

Ketone **103** subsequently was treated with methanolic potassium carbonate for the removal of its acetyl group. Two products were formed. Based on the spectroscopic data, the less polar compound (11%) was assigned to structure **104**. It showed the hydroxy absorption at 3508 cm^{-1} and the ester carbonyl stretch at 1704 cm^{-1} in the ir spectrum. The molecular ion was not observed in the hrms, but a peak at m/z 248.1413 due to loss of water was displayed. The required chemical formula $C_{15}H_{22}O_4$ was confirmed by elemental analysis. In the ^1H nmr spectrum, a multiplet centered at δ 6.10 for the vinylic protons as well as two doublets of doublets for the methylene protons next to the ethereal oxygen at δ 4.39 and 3.40 were observed. A strong singlet at δ 3.70 due to the methoxy protons was also present. Furthermore, the ^{13}C nmr spectrum confirmed the presence of the ester carbonyl and the hemiketal carbon, displaying resonances at δ 180.18 (p) and 104.64 (p). The major product obtained in 70% yield was characterized as the undesired keto alcohol **105**. This compound showed, in the ir spectrum, the hydroxy and the carbonyl absorption bands at 3448 and

1712 cm^{-1}, respectively. The molecular ion was observed in the hrms at m/z 208.1461, corresponding to the formula $C_{13}H_{20}O_2$. Its ^1H nmr spectrum displayed two vinylic protons centered at δ 5.70 and the methylene protons next to the hydroxyl at δ 3.58. Two methyl singlets at δ 1.22 and 1.15 were also displayed. The formation of the major product **105** *via* a decarbomethoxylation process was rather surprising. Obviously, this side reaction must be suppressed in order to effectively transform acetate **103** into hemiketal **104**. The development of an improved procedure turned out to be unnecessary, as it was recognized shortly thereafter that the desired compound **104** could be produced directly from alcohol **96** by sodium borohydride reduction in methanol. To our delight, 1,4-addition occurred instead of the intended 1,2-addition. This was followed by hemiketal formation to give **104** in a modest yield (46%).

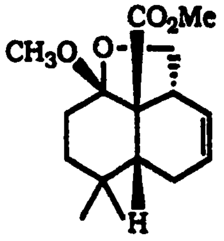


104

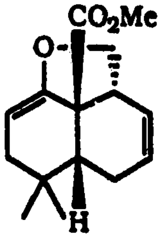


105

Having compound **104** in hand, the acetal formation was attempted using *p*-toluenesulfonic acid in benzene and methanol at 40°C. After work-up, two products were isolated. Based on the spectroscopic data the major product (51%) was identified as the desired acetal **106**. The ester carbonyl absorption was observed at 1738 cm^{-1} in the ir spectrum. Its hrms did not display the molecular ion, but a peak at m/z 248.1410, due to loss of methanol, was observed. In the ^1H nmr spectrum the two methoxy groups appeared at δ 3.68 and 3.22. In addition, two vinylic protons were observed at 5.95. The minor product (35%) was assigned to the structure **107**. This enol ether showed the ester carbonyl absorption band at 1725 cm^{-1} in the ir spectrum. The molecular ion was observed in the hrms at m/z 250.1569, in agreement with the chemical formula $C_{15}H_{22}O_3$. The ^1H nmr spectrum displayed three vinylic protons at δ 5.80, 5.50 and 4.88. The methoxy protons appeared at δ 3.75. The ^{13}C nmr spectrum, lent further support to the assigned structure, displaying two signals at δ 151.78 (p) and 94.31 (a) for the vinyl ether moiety.



106



107

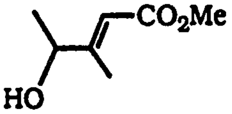
In order to complete the synthesis of the AB ring system of forskolin, the ester group in the key intermediate **106** needed to be reduced to a methyl group. This was expected to be achieved first by converting the ester group in ketal **106** into an alcohol and subsequent deoxygenation of the resulting alcohol. Work towards the fulfilment of this goal will be carried out in our laboratories in the near future.

Experimental

General Procedures and Materials

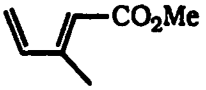
Refer to Chapter 1, Experimental Section for a detailed description of the general procedures and materials.

Methyl (*E*)-4-hydroxy-3-methyl-2-pentenoate (58).



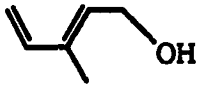
A vigorously stirred solution of (carbomethoxymethylene)-triphenylphosphorane (116.90 g, 0.35 mol) and 3-hydroxy-2-butanone **57** (26.4 g, 0.30 mol) in benzene (700 mL) was refluxed for 48 h. After concentration, the reaction product was subjected to bulb-to-bulb disillation (70°C, 3 torr) to give alcohol **58** (40.2 g, 93%): ir ($CHCl_3$ cast) 3450 (OH), 1719 (C=O, ester) and 1655 cm^{-1} (C=C); ^1H nmr (300 MHz, $CDCl_3$) δ 5.98 (m, 1H, -C**H**=), 4.27 (q, J = 6 Hz, 1H, -C**H**OH), 3.71 (s, 3H, -OC**H**$_3$), 2.12 (d, 3H, J = 1.5 Hz, =CC**H**$_3$) and 1.32 (d, J = 6 Hz, 3H, -C**H**$_3$); hrms M$^+$ 144.0787 (calcd. for $C_7H_{12}O_3$: 144.0786).

Methyl (*E*)-3-methyl-2,4-pentadienoate (59).



A vigorously stirred suspension of alcohol **58** (5.76 g, 40 mmol) and anhydrous copper(II) sulfate (6.38 g, 40 mmol) in a round bottom flask connected to a distillation apparatus and a vacuum line (25 torr), was immersed into a preheated (130°C) oil bath. The distillate was dried over anhydrous magnesium sulfate, filtered and distilled under reduced pressure (25°C, 6 torr) to give diene **59** (2.54 g, 50%): ir ($CHCl_3$ cast) 1722 (C=O, ester) and 1640 cm^{-1} (C=C); ^1H nmr (300 MHz, $CDCl_3$) δ 6.42 (ddd, $J = 17$, $J' = 10.5$, $J'' = 1$ Hz, 1H, =C**H**-), 5.80 (bs, 1H, =C**H**CO_2Me), 5.64 (d, $J = 17$ Hz, 1H, =C**H**H), 5.40 (d, $J = 10.5$, 1H, =CH**H**), 3.75 (s, 3H, OCH_3) and 2.28 (s, 3H, -CH_3); hrms M^+ 126.0678 (calcd. for $C_7H_{10}O_2$: 126.0681).

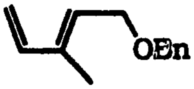
(*E*)-3-Methyl-2,4-pentadien-1-ol (60).



A solution of diene **59** (1.26 g, 10 mmol) in ether (10 mL) was added dropwise to a suspension of lithium aluminium hydride (370 mg, 10 mmol) in ether (10 mL) at 0°C. After stirring at 0°C for 2 h, the reaction mixture was poured into an ice-cold 10%

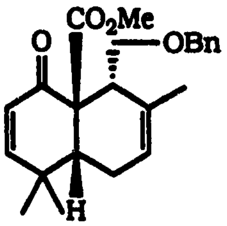
aqueous solution of H_2SO_4 (2 mL). The organic layer was separated and the aqueous layer extracted with ether (2 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel (35% ethyl acetate in hexane) furnished alcohol **60** (0.78 g, 79%): ir ($CHCl_3$ cast) 3330 (OH) and 1609 cm^{-1} (C=C); ^1H nmr (300 MHz, $CDCl_3$) δ 6.38 (dd, J = 18, J' = 11 Hz, 1H, =C**H**-), 5.65 (t, J =7 Hz, 1H, =C**H**CH_2OH), 5.22 (d, J = 18 Hz, 1H, =C**H**H), 5.06 (d, J = 11 Hz, 1H, =CH**H**), 4.28 (d, J = 7 Hz, 2H, -C**H**$_2$OH) and 1.78 (s, 3H, -C**H**$_3$); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) 140.74 (a), 136.16 (p), 130.56 (a), 113.00 (p), 59.21 (p) and 11.81 (a); hrms M^+ 98.0730 (calcd. for $C_6H_{10}O$: 98.0732).

(*E*)-5-Benzyloxy-3-methyl-1,3-pentadiene (47).



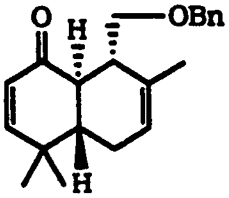
A solution of alcohol **60** (1.90 g, 19.4 mmol) in tetrahydrofuran (50 mL) was added dropwise to a suspension of sodium hydride (80% in oil, 0.69 g, 23 mmol) in tetrahydrofuran (10 mL) at 0°C. Benzyl bromide (3.97 g, 19.4 mmol) was added to this solution and the resulting mixture was stirred at room temperature for 24 h. The solution was cooled to 0°C and the excess sodium hydride was destroyed with water (10 mL). The organic layer was separated and the aqueous layer extracted with ether (2 x 50 mL). The combined organic solutions were dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the concentrate by flash chromatography on silica gel (5% ethyl acetate in hexane) gave diene **47** (2.2 g, 60%): ir ($CHCl_3$ cast) 1640 (C=C), 1600 (C=C) and 1101 cm^{-1} (C-O-C); ^1H nmr (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 6.40 (dd, $J = 17$, $J' = 11$ Hz, 1H, =C**H**-), 5.67 (m, 1H, =C**H**CH_2OBn), 5.18 (dd, $J = 17$, $J' = 1$ Hz, 1H, =C**H**H), 5.03 (dd, $J = 11$, $J' = 1$ Hz, 1H, =CH**H**), 4.52 (s, 2H, -OC**H**$_2$Ph), 4.15 (d, $J = 7$ Hz, 2H, -C**H**$_2$OBn) and 1.75 (br s, 3H, -C**H**$_3$); hrms m/z 189.1279 (M^++H, calcd. for $C_{13}H_{17}O$: 189.1279).

(1R*, 6R*, 10R*)-10-Benzyloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (48).



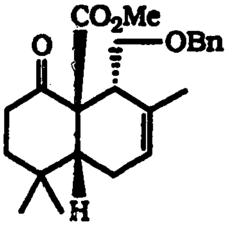
A solution of enone ester **46** (10.35 g, 55 mmol), diene **47** (11.22 g, 60 mmol) and zinc chloride (7.5 g, 55 mmol) in dichloromethane (200 mL) was stirred vigorously at room temperature for 36 h. The solution was washed with water. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (5% ethyl acetate in hexane) to give adduct **48** (15.0 g, 74%): mp 80-81°C (hexane); ir ($CHCl_3$ cast) 1726 (C=O, ester) and 1689 cm^{-1} (C=O, enone); ^1H nmr (400 MHz, $CDCl_3$) δ 7.23 (m, 5H, aromatic **H**), 6.26 (dd, J = 11, J' = 2 Hz, 1H, -C**H**=CHCO), 5.88 (d, J = 11 Hz, 1H, =C**H**CO-), 5.22 (br s, 1H, -C**H**=CCH$_3$), 4.48 (d, J = 12 Hz, 1H, -OC**H**HPh), 4.42 (d, J = 12 Hz, 1H, -OCH**H**Ph), 4.08 (dd, J = 10, J' = 7 Hz, -C**H**HOBn), 3.54 (s, 3H, -OC**H**$_3$), 3.52 (dd, J = 10, J' = 3 Hz, -CH**H**OBn), 2.56 (ddd, J = 11, J' = 7, J'' = 2 Hz, **H**$_6$), 2.21 (m, 1H, -**H**HC$_7$-), 1.90 (m, 1H, -H**H**C$_7$-), 1.84 (br s, 3H, =CC**H**$_3$), 1.15 and 1.10 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 196.25 (p), 174.61 (p), 152.78 (a), 138.43 (p), 132.95 (p), 128.17 (a), 127.71 (a), 127.59, (a) 127.34 (a), 126.72 (a), 119.65 (a), 72.49 (p), 70.29 (p), 60.12 (p), 52.02 (a), 46.70 (a), 46.64 (a), 37.61 (p), 27.83 (a), 27.68 (a), 27.19 (p) and 20.83 (a); hrms M^+ 368.1978 (calcd. for $C_{23}H_{28}O_4$: 368.1988). Anal. Calcd. for $C_{23}H_{28}O_4$: C 74.97, H 7.66; found: C 74.65, H 7.79.

(1R*, 6S*, 10S*)-10-Benzyloxymethyl-5,5,9-trimethylbicyclo[4.4.0]-deca-3,8-dien-2-one (61).



Adduct **48** (1.0 g, 2.72 mmol) and sodium hydroxide (1.0 g, 25 mmol) were dissolved in 2-propanol (50 mL) and heated to reflux for 6 h. After cooling to room temperature, the mixture was diluted with water (100 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography on silica gel (10% ethyl acetate in hexane) afforded enone **61** (0.80 g, 95%): ir ($CHCl_3$ cast)1671 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 7.30 (m, 5H, aromatic **H**), 6.56 (d, J = 10 Hz, 1H, -C**H**=CHCO), 5.82 (d, J = 10 Hz, 1H, =C**H**CO-), 5.62 (br s, 1H, -C**H**=CCH$_3$), 4.52 (d, J = 12 Hz, 1H, -OC**H**HPh), 4.48 (d, J = 12 Hz, 1H, -OCH**H**Ph), 3.78 (dd, J = 10, J' = 2.5 Hz, 1H, -C**H**HOBn), 3.65 (dd, J = 10, J' = 3 Hz, 1H, -CH**H**OBn), 1.60 (br s, 3H, =CC**H**$_3$), 1.13 and 1.05 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 310.1938 (calcd. for $C_{21}H_{26}O_2$: 310.1933).

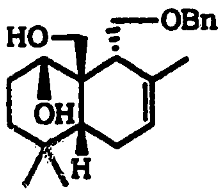
(1R*, 6R*, 10R*)-10-Benzyloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-one (63).



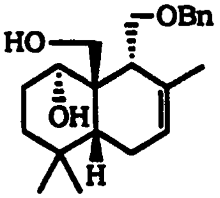
Adduct **46** (5 g, 13.6 mmol), triethylsilane (5.82 g, 50 mmol) and tris-(triphenylphosphine)rhodium(I) chloride (0.10 g, 0.11 mmol) were suspended in benzene (50 mL). The resulting mixture was stirred at 50°C for 12 h. Then additional triethylsilane (5.82, 50 mmol) was added and the resulting mixture was stirred at 50°C for 24 h. The solvent was evaporated and the residue was diluted with hexane (50 mL). The mixture was filtered through a short layer of silica gel. The filtrate was concentrated and the residue redissolved in tetrahydrofuran (50 mL). To this solution, a 1M solution of tetra-*n*-butylammonium fluoride (48 mL, 48 mmol) in tetrahydrofuran was added dropwise. The reaction mixture was stirred for 4 h at room temperature and then concentrated. Flash chromatography on silica gel (5% ethyl acetate in hexane) gave ketone **63** (4.60 g, 91%): ir ($CHCl_3$ cast) 1733 (C=O, ester) and 1716 cm^{-1} (C=O); ^1H nmr (200 MHz, $CDCl_3$) δ 7.23 (m, 5H, aromatic **H**), 5.30 (br s, 1H, -C**H**=CCH_3), 4.43 (d, *J* = 12 Hz, 1H, -OC**H**HPh), 4.37 (d, *J* = 12 Hz, 1H, -OCH**H**Ph), 4.02 (dd, *J* = 11, *J′* = 7 Hz, 1H,

-C**H**HOBn), 3.60 (s, 3H, $-OCH_3$), 3.44 (dd, $J = 11$, $J' = 3$ Hz, 1H, -CH**H**OBn), 1.82 (br s, 3H, $=CCH_3$), 1.15 and 0.91 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 370.2147 (calcd. for $C_{23}H_{30}O_4$: 370.2143).

(1S*, 2R*, 6R*, 10R*)-10-Benzyloxymethyl-1-hydroxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (64) and (1S*, 2S*, 6R*, 10R*)-10-Benzyloxymethyl-1-hydroxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (65).



64



65

A. Using diisobutylaluminium hydride.

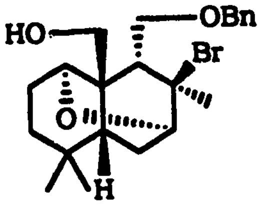
A solution of diisobutylaluminium hydride (1.06 g, 6 mmol) in ether (10 mL) was added slowly to ketone **63** (370 mg, 1 mmol) dissolved in ether (20 mL) at 0°C. After stirring at room temperature for 12 h, the reaction mixture was cooled to 0°C and ice-cold water was added until the excess diisobutylaluminium hydride was destroyed. The resulting mixture was extracted with ether, then the ether solution was washed with aqueous 5% HCl and brine solution, dried over anhydrous magnesium sulfate.

filtered and concentrated. Flash chromatography (20% ethyl acetate in hexane) of the residue on silica gel gave diol **64** (48.9 mg, 14%): ir ($CHCl_3$ cast) 3425 cm^{-1} (OH); ^{1}H nmr (200 MHz, $CDCl_3$) δ 7.32 (m, 5H, aromatic **H**), 5.64 (br d, J = 6 Hz, 1H, -C**H**=), 4.62 (d, J = 12 Hz, 1H, -OC**H**HPh), 4.42 (d, J = 12 Hz, 1H, -OCH**H**Ph), 3.82 (d, J = 10 Hz, 1H, -C**H**HOH), 3.72 (d, J = 10 Hz, 1H, -CH**H**OH), 3.32 (dd, J = 10, J' = 3 Hz, 1H, -CH**H**OBn), 3.17 (t, J = 10 Hz, -C**H**HOBn), 1.8 (br s, 3H, =CC**H**$_3$), 0.84 and 0.76 (each s, 3H each *gem*-dimethyl); hrms M$^+$ 344.2352 (calcd. for $C_{22}H_{32}O_3$: 344.2351). Further elution gave diol **65** (250 mg, 72%): ir ($CHCl_3$ cast) 3400 cm^{-1} (OH); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.32 (m, 5H, aromatic **H**), 5.44 (br s, 1H, -C**H**=), 4.59 (d, J = 12 Hz, 1H, -OC**H**HPh), 4.57 (d, J = 12 Hz, 1H, -OCH**H**Ph), 4.10 (t, J =J' = 10 Hz, 1H, -C**H**HOBn), 3.78 (dd, J = 1, J' = 3 Hz, 1H, -CH**H**OBn), 3.68 (d, J = 11 Hz, 1H, -CH**H**OH), 3.58 (m, 1H, -C**H**OH), 3.32 (d, J = 10 Hz, 1H, -C**H**HOH), 1.74 (br s, 3H, =CC**H**$_3$), 0.94 and 0.78 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 344.2364 (calcd. for $C_{22}H_{32}O_3$: 344.2351).

B. Using lithium aluminium hydride.

Ketone **63** (1 g, 2.70 mmol) was dissolved in ether (20 mL) and added dropwise to a suspension of lithium aluminium hydride (0.11 g, 3 mmol) in ether at 0°C. The reaction mixture was stirred at room temperature for 12 h. It was then cooled to 0°C and a 10% aqueous solution of H_2SO_4 (5 mL) was added. The organic layer was washed with brine solution, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography on silica gel (25% ethyl acetate in hexane) furnished diol **65** (0.80 g, 86%), which was shown to be identical in all respects to that obtained previously.

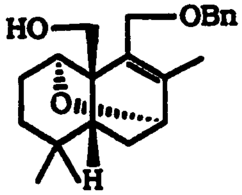
(1S*, 5R*, 7R*, 9R*, 8S*, 10S*)-9-Benzyloxymethyl-8-bromo-10-hydroxymethyl-4,4,8-trimethyl-11-oxatricyclo[5,3,1,$0^{5,10}$]-undecane (69).



A solution of diol **65** (160 mg, 0.465 mmol) in ether (5 mL) was added to a suspension of sodium hydride (80% in oil, 279 mg 0.92 mmol) in ether (5 mL) at 0°C. After warming to room temperature, a solution of *N*-bromosuccinimide (178 mg, 1 mmol) in ether (5 mL) was added and the mixture stirred for 24 h. The ether solution was washed with brine solution, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the concentrate by flash chromatography on silica gel (15% ethyl acetate in hexane) gave bromide **69** (160 mg, 81%): ir ($CHCl_3$ cast) 3451 cm^{-1} (OH); ^1H nmr (300 MHz, $CDCl_3$)

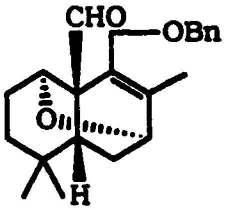
δ 7.38 (m, 5H, aromatic **H**), 4.62 (d, *J* = 11 Hz, 1H, -OC**H**HPh), 4.53 (d, *J* = 11 Hz, 1H, -OCH**H**Ph), 4.18 (dd, *J* = 11, *J'* = 7 Hz, 1H, -C_7**H**O-), 3.80-3.55 (m, 5H, -C**H**$_2$OH, -C**H**$_2$OBn, and -C_1**H**O-), 2.68 (dd, *J* = 9.5, *J'* = 3.5 Hz, **H**$_9$), 2.55 (dd, *J* = 15, *J'* = 7 Hz, **H**$_{6ax}$), 2.20 (d, *J* = 10 Hz, **H**$_5$), 2.05 (ddd, *J* = 15, *J'* = 10, *J''* = 7 Hz, **H**$_{6eq}$), 1.42 (br s, 3H, =CC**H**$_3$), 1.08 and 1.02 (each s, 3H each, *gem*-dimethyl); hrms m/z 393.1246 and 391.1264 (M^+-CH_2O, calcd. for $C_{21}H_{28}O_2Br$: 393.1252 and 391.1273).

(1S*, 5R*, 7R*, 10S*)-9-Benzyloxymethyl-10-hydroxymethyl-4,4,8-trimethyl-11-oxatricyclo[5,3,1,$0^{5,10}$]undec-8-ene (74).



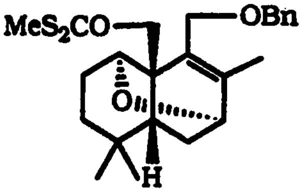
A solution of bromide **69** (1.00 g, 2.55 mmol) in pyridine (20 mL) was refluxed for 12 h. After cooling to 0°C, the mixture was poured into aqueous 5% H_2SO_4 (50 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (20% ethyl acetate in hexane) of the residue on silica gel gave unsaturated alcohol **74** (680 mg, 78%): ir ($CHCl_3$ cast) 3440 cm^{-1} (OH); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 4.56 (d, *J* = 11.5 Hz, 1H, -OC**H**HPh), 4.52 (d, *J* = 11.5 Hz, 1H, -OCH**H**Ph), 4.36 (dd, J = 8.5, J' = 5.5 Hz, 1H, -C**H**O-), 4.33 (d, J = 12 Hz, 1H, -C**H**HOH), 4.28 (d, J = 12 Hz, 1H, -CH**H**OH), 4.40 (m, 3H, -C**H**$_2$OBn and -C**H**O-), 1.86 (s, 3H, =CC**H**$_3$), 1.26 and 0.98 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 342.2196 (calcd. for $C_{22}H_{30}O_3$: 342.2195).

(1S*, 5R*, 7R*, 10S*)-9-Benzyloxymethyl-10-formyl-4,4,8-trimethyl-11-oxatricyclo[5,3,1,0^{5,10}]undec-8-ene (75).



Pyridinium dichromate (300 mg, 0.80 mmol) was added to a solution of **74** (60 mg, 0.175 mmol) in dichloromethane (10 mL). After stirring at room temperature for 12 h, the solvent was removed under reduced pressure and the residue redissolved in hexane and filtered through a short layer of silica gel. The filtrate was concentrated to give aldehyde **75** (59.5 mg, 100%): ir (CHCl$_3$ cast) 1712 cm^{-1} (C=O, aldehyde); ^{1}H nmr (300 MHz, CDCl$_3$) δ 10.1 (s, 1H, -C**H**O), 7.36 (m, 5H, aromatic **H**), 4.45 (d, J = 12 Hz, 1H, -OC**H**HPh), 4.39 (d, J = 12 Hz, 1H, -OCH**H**Ph), 4.15 (d, J = 11.5 Hz, 1H, -C**H**HOBn), 4.11 (dd, J = 3.5, J' = 1 Hz, 1H, -C**H**O-), 3.85 (d, J = 11.5 Hz, 1H, -CH**H**OBn), 3.82 (br d, J = 2 Hz, 1H, -C**H**O-), 1.86 (s, 3H, =CC**H**$_3$), 0.96 and 0.92 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 340.2030 (calcd. for $C_{22}H_{28}O_3$: 340.2038).

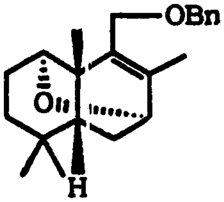
(1S*, 5R*, 7R*, 10S*)-9-Benzyloxymethyl-10-methylmercapto-thiocarbonyloxymethyl-4,4,8-trimethyl-11-oxatricyclo-[5,3,1,$0^{5,10}$]undec-8-ene (76).



n-Butyllithium (1.64 mmol) was added to a solution of alcohol **74** (560 mg, 1.64 mmol) in tetrahydrofuran (10 mL) at -78°C. The reaction mixture was warmed to -30°C and then carbon disulfide (126 mg, 1.66 mmol) was added with vigorous stirring. The resulting mixture was warmed to room temperature and then methyl iodide (284 mg, 2 mmol) was added. After 12 h, the reaction mixture was diluted with methanol (1 mL) and then the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (10% ethyl acetate in hexane) afforded xanthate **76** (705 mg, 100%): ir (CHCl$_3$ cast) 1220 cm^{-1} (C=S); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.35 (m, 5H, aromatic **H**), 5.24 (br s, 1H, -C**H**HOCS-), 4.93 (d, *J* = 12 Hz, 1H, -CH**H**OCS), 4.42 (d, *J* = 11 Hz, 1H, -OCH**H**Ph), 4.40 (d, *J* = 11 Hz, 1H, -OC**H**HPh), 4.15-4.00 (m, 3H, -C**H**$_2$OBn and

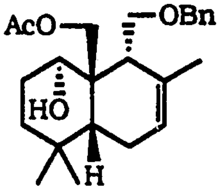
-C**H**O-), 2.55 (s, 3H, -SC**H**$_3$), 1.88 (s, 3H, =CC**H**$_3$), 1.09 and 0.98 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 432.1805 (calcd. for $C_{24}H_{32}O_3S_2$: 432.1792).

(1S*, 5R*, 7R*, 10S*)-9-Benzyloxymethyl-4,4,8,10-tetramethyl-11-oxatricyclo[5,3,1,0^{5,10}]undec-8-ene (70).



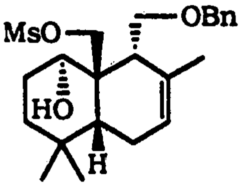
Xanthate **76** (600 mg, 1.39 mmol), tri-*n*-butyltin hydride (814 mg, 2.80 mmol) and azobisisobutyronitrile (AIBN, 20 mg, 0.122 mmol) were dissolved in xylene (20 mL). The solution was degassed by bubbling argon through it for 10 min and then refluxed for 1 h. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (5% ethyl acetate in hexane) to give benzyl ether **70** (400 mg, 88%); ir ($CHCl_3$ cast) 1058 cm^{-1}(C-O); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, aromatic **H**), 4.47 (s, 2H, -OC**H**$_2$Ph), 4.12 (s, 2H, -C**H**$_2$OBn), 4.03 (dd, *J* = 4, *J'* = 1 Hz, 1H, -C**H**O-), 3.26 (dd, *J* = *J'* = 1.5 Hz, 1H, -C**H**O-), 1.88, 1.46, 1.18 and 0.95 (each s, 3H each, 4 x -C**H**$_3$); hrms M$^+$ 326.2242 (calcd. for $C_{22}H_{30}O_2$: 326.2246).

(1S*, 2S*, 6R*, 10R*)-1-Acetoxymethyl-10-benzyloxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (77).



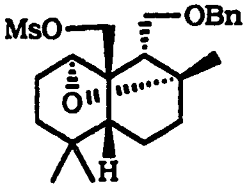
Acetic anhydride (0.041 mL, 0.43 mmol) was added to a solution of diol **65** (130 mg, 0.38 mmol) in pyridine (10 mL) containing a catalytic amount of 4-dimethylaminopyridne (DMAP, 10 mg). The reaction mixture was stirred at room temperature for 48 h and then it was diluted with ether (100 mL) and washed with 5% aqueous HCl (10 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (20% ethyl acetate in hexane) of the residue on silica gel gave acetate **77** (132 mg, 100%); ir ($CHCl_3$ cast) 3520 (OH), 1740 cm^{-1} (C=O, ester): ^1H nmr (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 5.52 (br s, 1H, -C**H**=), 4.55 (d, *J* = 11 Hz, 1H, -OC**H**HPh), 4.53 (d, *J* = 11 Hz, 1H, -OCH**H**Ph), 4.15 (d, *J* = 10 Hz, 1H, -CH**H**OAc), 3.91 (dd, *J* = 11, *J'* = 5 Hz, 1H, -C**H**HOBn), 3.88 (d, *J* = 10 Hz, 1H, -CH**H**OAc), 3.72 (dd, *J* = 11, *J'* = 1 Hz, 1H, -C**H**HOBn), 3.55 (m, 1H, -C**H**OH), 2.05 (s, 3H, C**H**$_3$COO$_2$-), 1.70 (br s, 3H, =CC**H**$_3$), 1.02 and 0.88 (each s, 3H each, *gem*-dimethyl); hrms M^+ 386.2452 (calcd. for $C_{24}H_{34}O_4$: 386.2456). Anal. Calcd. for $C_{24}H_{34}O_4$: C 74.58, H 8.87; found: C 74.77, H 9.10.

(1S*, 2S*, 6R*, 10R*)-10-Benzyloxymethyl-1-methanesulfonyloxymethyl-5,5,9- trimethylbicyclo[4.4.0]dec-8-en-2-ol (81).



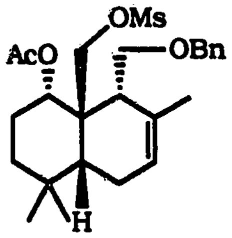
Methanesulfonyl chloride (300 mg, 2.63 mmol) was added to a solution of diol **65** (806 mg, 2.34 mmol) in dichloromethane (50 mL) containing pyridine (1 mL). The resulting mixture was stirred at room temperature. After 15 h, the mixture was diluted with dichloromethane (20 mL) and 2% aqueous HCl (10 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (70% ether in hexane) of the residue on silica gel gave mesylate **81** (870 mg, 88%): ir ($CHCl_3$ cast) 3420 (OH), 1600 and 1580 (C=C), 1355 and 1175 cm^{-1} ($-OSO_2-$); ^1H nmr (400 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 5.50 (br s, 1H, -C**H**=), 4.58 (d, *J* = 11 Hz, 1H, -OC**H**HPh), 4.52 (d, *J* = 11 Hz, 1H, -OCH**H**Ph), 4.29 (d, *J* = 10 Hz, 1H, -CH**H**OMs), 4.08 (dd, *J* = 10.5, *J'* = 8 Hz, 1H, -CH**H**OBn), 3.93 (d, *J* = 10 Hz, 1H, -C**H**HOMs), 3.72 (dd, *J* = 10 .5, *J'* = 2 Hz, 1H, -CH**H**OBn), 3.55 (m, 1H, -C**H**OH), 3.00 (s, 3H, $-OSO_2CH_3$), 1.70 (br s, 3H, $=CCH_3$), 1.00 and 0.82 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 136.44, 129.46, 128.67, 128.32, 128.28, 125.00, 73.52, 72.81, 70.86, 68.43, 45.08, 43.75, 38.93, 36.90, 33.37, 32.92, 28.07, 26.04, 24.51 and 22.75; hrms M$^+$ 422.2150 (calcd. for $C_{23}H_{34}O_5S$: 422.2173). Anal. Calcd. for $C_{23}H_{34}O_5S$: C 65.37, H 8.11, S 7.58; found: C 65.34, H 8.18, S 7.51.

(1S*, 5R*, 8R*, 9R*, 10S*)-9-Benzyloxymethyl-10-methanesulfonyloxymethyl-4,4,8-trimethyl-11-oxatricyclo[6.2.1.0^{5,10}]-undecane (83).



Mesylate **81** (80 mg, 0.19 mmol), pyridine (2 mL) and methyl trifluoromethanesulfonate (156 mg, 0.95 mmol) were dissolved in dichloromethane (5 mL). The resulting mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and washed with 2% aqueous HCl. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (70% dichloromethane in hexane) of the residue on silica gel gave the cyclic ether **83** (60 mg, 75%): ir ($CHCl_3$ cast) 1356 and 1176 cm^{-1} ($-OSO_2-$); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 4.50 (s, 2H,-OC**H**$_2$Ph), 4.42 (d, *J* = 10 Hz, 1H, -CH**H**OMs), 4.25 (d, *J* = 10 Hz, 1H, -C**H**HOMs), 3.86 (br s, 1H, -C**H**O-), 3.65 (d, *J* = 5 Hz, 2H, -C**H**$_2$OBn), 2.77 (s, 3H, -OSO$_2$C**H**$_3$), 2.35 (t, *J* = *J'* = 5 Hz, **H**$_9$), 1.30 (s, 3H, -OCC**H**$_3$), 1.10 and 1.00 (each s, 3H each, *gem*-dimethyl); hrms M^+ 422.2128 (calcd. for $C_{23}H_{34}O_5S$: 422.2132).

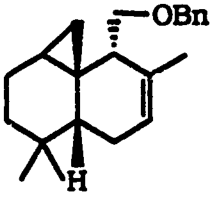
(1S*, 2S*, 6R*, 10R*)-2-Acetoxy-10-benzyloxymethyl-1-methanesulfonyloxymethyl-5,5,9- trimethylbicyclo[4.4.0]dec-8-ene (84).



DMAP (20 mg, 0.16 mmol) and acetic anhydride (0.50 mL, 5.3 mmol) were added to a stirred solution of mesylate **81** (211 mg, 0.50 mmol) in pyridine (5 mL) at 0°C. Then the resulting mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was poured into 2% aqueous HCl (20 mL) and extracted with dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (20% ethyl acetate in hexane) of the residue on silica gel gave acetate **84** (231 mg, 100%): ir ($CHCl_3$ cast) 1737 (C=O, ester), 1357 and 1176 cm^{-1} ($-OSO_2-$); ^1H nmr (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 5.40 (br s, 1H, -C**H**=), 4.94 (dd, J = 10, J' = 6 Hz, 1H, -C**H**OAc), 4.51 (d, J = 12 Hz, 1H, -OCH**H**Ph), 4.48 (d, J = 12 Hz, 1H, -OC**H**HPh), 4.17 (dd, J = 9, J' = 3 Hz, 1H, -C**H**HOBn), 4.00 (d, J = 9 Hz, 1H, -C**H**HOMs), 3.97 (d, J = 9 Hz, 1H, -CH**H**OMs), 3.56

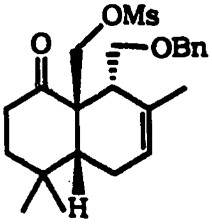
(dd, $J = 9$, $J' = 6$ Hz, 1H, -CH**H**OBn), 2.97 (s, 3H, -OSO$_2$C**H**$_3$), 2.00 (s, 3H, -C**H**$_3$CO$_2$-), 1.75 (br s, 3H, =CC**H**$_3$), 0.99 and 0.78 (each s, 3H each, *gem*-dimethyl); hrms m/z 356.1671 (M$^+$-C$_6$H$_5$CH$_2$OH, calcd. for C$_{18}$H$_{28}$O$_5$S: 356.1657).

(1S*, 2R*, 6R*, 10R*)-2-Benzyloxymethyl-3,7,7-trimethyltricyclo[8,1,0,0^{1,6}]undec-5-ene (85).



Acetate **84** (180 mg, 0.39 mmol), zinc dust (300 mg, 4.5 mmol), sodium iodide (600 mg, 4mmol) and hexamethylphosphoramide (2 mL) were suspended in dimethylformamide (5 mL). The resulting mixture was immersed into a preheated (140°C) oil bath and heated for 6 h. Upon cooling to room temperature, it was poured into water and extracted with ether. The organic layer was washed with 2% aqueous HCl, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the concentrate by flash chromatography on silica gel (15% ethyl acetate in hexane) gave compound **85** (80 mg, 66%): ir (CHCl$_3$ cast) 1099 cm^{-1} (C-O-C); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.33 (m, 5H, aromatic **H**), 5.40 (br d, $J = 8$ Hz, 1H, -C**H**=), 4.45 (s, 2H, -C**H**$_2$Ph), 3.50 (m 2H, -C**H**$_2$OBn), 1.85 (br s, 3H, =CC**H**$_3$), 0.80 and 0.78 (each s, 3H each, *gem*-dimethyl), 0.43 (dd, *J* = 9.8, *J'* = 4 Hz, 1H, cyclopropane-**H**), 0.07 (dd, *J* = 6, *J'* = 4 Hz, 1H, cyclopropane **H**); hrms M$^+$ 310.2297 (calcd. for $C_{22}H_{30}O$: 310.2297).

(1S*, 2S*, 6R*, 10R*)-10-Benzyloxymethyl-1-methanesulfonyloxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-one (86).



Pyridinium dichromate (PDC, 577 mg, 1.53 mmol) was added to a solution of **81** (108 mg, 0.256 mmol) in dichloromethane (70 mL). The resulting mixture was stirred at room temperature for 15 h. The reaction mixture was filtered through a thin layer of silica gel. The filtrate was concentrated to give ketone **86** (95 mg, 88%): ir (CHCl$_3$ cast) 1700 (C=O), 1370 and 1180 cm^{-1} (-OSO$_2$-); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.34 (m, 5H, aromatic **H**), 4.41 (s, 2H, -OC**H**$_2$Ph), 4.22 (d, *J* = 9 Hz, 1H, -CH**H**OMs), 4.01 (d, *J* = 9 Hz, 1H, -C**H**HOMs), 3.45 (dd, *J* = 10, *J'* = 7 Hz, 1H, -CH**H**OBn), 3.27 (dd, *J* = 10, *J'* = 7 Hz, 1H, -C**H**HOBn), 2.90 (s, 3H, -SO$_2$C**H**$_3$), 1.78 (s, 3H, =CC**H**$_3$), 1.00 and 0.92 (each s, 3H each, *gem*-dimethyl); hrms m/z 312.1395 (M$^+$-$C_6H_5CH_2OH$, calcd. for $C_{16}H_{24}O_4S$: 312.1395).

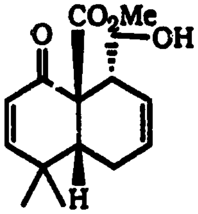
Methyl (*E*)-2,4-pentadienoate (94).

Acrolein (60 g, 1.07 mmol) was added gradually to a vigorously stirred solution of malonic acid (90 g, 0.87 mmol) in pyridine (300 mL) at 0°C. After the addition was completed (3 h), the reaction mixture was heated at 35°C with stirring for 6 h. After cooling to room temperature and dilution with ether (300 mL), the resulting solution was washed with ice-cold aqueous 10% hydrochloric acid. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was dissolved in methanol (200 mL) containing a few drops of sulfuric acid. The resulting mixture was refluxed for 2 h, poured into ice-water (100 mL) and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled at room temperature under reduced pressure (6 torr) to give methyl ester **94** (35 g, 36%): ir ($CHCl_3$) 1724 (C=O, ester), 1640 and 1600 cm^{-1} (C=C); ^1H nmr (300 MHz, $CDCl_3$) δ 7.28 (dd, J = 15.5, J' = 11 Hz, 1H, -C**H**=$CHCO_2$-), 6.45 (ddd, J = 17, J' = J'' = 11 Hz, 1H, CH_2=C**H**-), 5.92 (d, J = 15.5, -C**H**CO_2-), 5.61 (d, J = 17 Hz, 1H, **H**HC=), 5.5 (d, J = 11 Hz, 1H, H**H**C=) and 3.70 (s, 3H, -OC**H**$_3$); hrms M^+ 112.0527 (calcd. for $C_6H_8O_2$: 112.0524).

(*E*)-2,4-pentadien-1-ol (95).

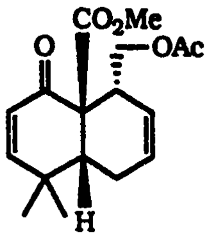
A solution of **94** (23 g, 0.21 mol) in ether (100 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (8 g, 0.22 mol) in ether (170 mL) at -25°C. After the addition was completed, the reaction mixture was stirred at 0°C for 2 h and then poured slowly into aqueous 10% NaOH. The aqueous layer was separated and extracted with ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled (35°C, 3 torr) to give diene **95** (13 g, 75%): ir 3320 cm^{-1} (OH); ^1H nmr (300 MHz, $CDCl_3$) δ 6.38-6.28 (m, 1H, =C**H**-**H**C=), 5.84 (dt, *J* = 15, *J'* = 6 Hz, 1H, =C**H**CH_2OH), 5.23 (dd, *J* = 16, *J'* = 2 Hz, 1H, **H**HC=), 5.10 (dd, *J* = 10, *J'* = 3 Hz, H**H**C=) and 4.16 (d, *J* = 6 Hz, 2H, -C**H**$_2$OH); hrms M^+ 84.0579 (calcd. for C_5H_8O: 84.0575).

(1R*, 6R*, 10R*)-1-Carbomethoxy-10-hydroxymethyl-5,5-dimethylbicyclo[4.4.0]dec-3,8-dien-2-one (96).



A solution of enone ester **46** (0.9 g, 5 mmol), diene **95** (0.59 g, 7 mmol) and zinc chloride (0.68 g, 5 mmol) in dichloromethane (60 mL) was stirred at room temperature for 12 h. The solution was washed with water and the organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (30% ethyl acetate in hexane) to give adduct **96** (1.26 g, 95%): ir 3400 (OH), 1724 (C=O, ester) and 1678 (C=O, enone), 1620 cm^{-1} (C=C); ^{1}H nmr (300 MHz, CDCl$_3$) δ 6.38 (dd, J = 10, J' = 2 Hz, 1H, -C**H**=CHCO-), 5.96 (d, J = 10 Hz, 1H, =C**H**CO-), 5.78 (dddd, J = 10, J' = J'' = J''' = 2 Hz, 1H, -C**H**=), 5.60 (m, 1H, =C**H**-), 4.08 (br s, 1H, -C**H**HOH), 3.75 (br s, 1H,-CH**H**OH), 3.72 (s, 3H, -OC**H**$_3$), 2.88 (br s, 1H, $\mathbf{H}_{10}$), 2.64 (ddd, J = 11, J' = 6, J'' = 2 Hz, 1H, $\mathbf{H}_6$), 2.25 (m, 1H, $\mathbf{H}_7$), 2.00 (m, 1H, $\mathbf{H}_7$), 1.17 and 1.14 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, CDCl$_3$) δ 197.36 (p), 174.37 (p), 154.21 (a), 126.59 (a), 125.53 (a), 124.77 (a), 62.02 (p), 60.66 (p), 52.40 (a), 47.76 (a), 46.33 (a), 38.04 (p), 27.76 (a), 27.60 (a) and 27.52 (p); hrms m/z 234.1252 (M$^+$-CH$_2$O, calcd. for C$_{14}$H$_{18}$O$_3$: 234.1256); cims (M+H)$^+$ 265.

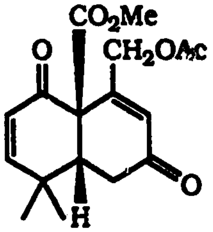
(1R*, 6R*, 10R*)-10-Acetoxymethyl-1-carbomethoxy-5,5,-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (97).



A solution of alcohol **96** (264 mg, 1 mmol) in dichloromethane (20 mL) containing pyridine (0.5 mL) and acetic anhydride (0.19 mL, 2 mmol) was stirred at room temperature for 12 h. The resulting solution was washed three times with ice-cold 10% aqueous HCl. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in hexane) to afford acetate **97** (305 mg, 100%): ir ($CHCl_3$ cast) 1736 (C=O, esters) and 1680 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 6.30 (dd, J = 10.5, J' = 2 Hz, 1H, -C**H**=CHCO), 5.90 (d, J = 10.5 Hz, 1H, =C**H**CO-), 5.70-5.57 (m, 2H, -C**H**=C**H**-), 4.53 (dd, J = 11, J' = 9 Hz, 1H, -C**H**HOAc), 4.30 (dd, J = 11, J' = 4.5 Hz, 1H, -CH**H**OAc), 3.75 (s, 3H, -OC**H**$_3$), 2.50 (s, 3H, C**H**$_3$CO$_2$-), 1.16 and 1.12 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 195.48 (p), 174.19 (p), 170.71 (p), 152.89 (a), 126.68 (a) 125.78 (a), 124.78 (a), 65.51 (p), 59.62 (p), 52.52 (a), 47.00 (a), 43.57 (a), 37.95 (p), 28.02 (a), 27.92 (a), 27.43 (p) and 21.05 (a); hrms m/z 246.1252

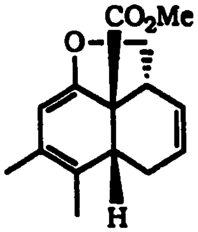
(M$^+$-AcOH, calcd. for $C_{15}H_{18}O_3$: 246.1255). Anal. Calcd. for $C_{17}H_{22}O_5$: C 66.65, H 7.24; found: C 66.78, H 7.24.

(1R*, 6R*)-10-Acetoxymethyl-1-carbomethoxy-5,5-dimethylbicyclo[4.4.0]deca-3,9-diene-2,8-dione (98).



A solution of adduct **96** (92 mg, 0.35 mmol) and TPP (10 mg) in carbon tetrachloride (200 mL) was placed in a photooxygenation apparatus and irradiated with two 200W tungsten lamps for 24 h, while a gentle stream of oxygen was bubbled through the reaction mixture. Acetic anhydride (0.076 mL, 0.7 mmol), pyridine (0.056 mL, 0.7 mmol) and DMAP (5 mg) were then added. After 3 h, the solution was concentrated and the residue redissolved in ether (50 mL). The ether solution was washed with 5% aqueous HCl (10 mL) and 5% aqueous Na_2CO_3 (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (40% ethyl acetate in hexane) to give dienone **99** (58 mg, 43%): ir ($CHCl_3$ cast) 1739 (C=O, esters) and 1675 cm^{-1} (C=O, enones); ^{1}H nmr (300 MHz, $CDCl_3$) δ 6.70 (d, J = 10 Hz, 1H, -C**H**=CHCO), 6.25 (t, $J = J' = 2$ Hz, 1H, -C=C**H**CO), 6.05 (d, $J = 10$, 1H, -CH=C**H**CO), 4.73 (d, $J = 2$ Hz, 2H, -C**H**$_2$OAc), 3.82 (s, 3H, -OC**H**$_3$), 2.11 (s, 3H, C**H**$_3$CO$_2$), 1.22 and 1.08 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 320.1263 (calcd. for $C_{17}H_{20}O_6$: 320.1259).

(5R*, 9R*, 12R*)-12-Carbomethoxy-3,4-dimethyl-11-oxatricyclo[7.2.1.0^{5,12}]dodeca-1, 3, 7-triene (100).



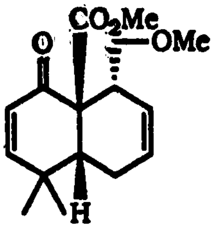
A. With methanol.

Adduct **96** (30 mg, 0.12 mmol), *p*-TsOH (5 mg) and methanol (0.01 mL, 0.24 mmol) were dissolved in benzene (30 mL). The mixture was refluxed with azeotropic removal of water for 3 h and concentrated. Purification of the concentrate by flash chromatography on silica gel (15% ethyl acetate in hexane) furnished enol ether **100** (20 mg, 68%): ir (CHCl$_3$ cast) and 1731 cm^{-1} (C=O, ester); ^{1}H nmr (300 MHz, CDCl$_3$) δ 5.95 (dddd, $J = 10$, $J' = 6$, $J'' = J''' = 2$ Hz, 1H, -C**H**=CH-), 5.58 (m, 1H, -CH=C**H**-), 5.10 (s, 1H, -CH=CO-), 4.45 (dd, $J = 8$, $J' = 6$ Hz, 1H, -C**H**HO-), 4.02 (dd, $J = 8$, $J' = 1$ Hz, 1H, -CH**H**O-), 3.70 (s, 3H, -OC**H**$_3$), 2.91 (br s, 1H, **H**$_9$) 2.65 (dd, $J = 11$, $J' = 6$ Hz, 1H, **H**$_5$), 2.20 (m, 1H, **H**$_6$), 1.75 and 1.65 (each s, 3H each, vinylic C**H**$_3$); ^{13}C nmr (CDCl$_3$) δ 174.93 (p), 155.94 (p) 129.14 (a), 125.27 (a), 124.87 (p), 123.88 (p), 96.41 (a), 75.97 (p), 53.73 (p), 52.50 (a), 41.74 (a), 38.84 (a), 24.56 (p), 17.71 (a) and 17.58 (a); hrms M$^+$ 246.1256 (calcd. for $C_{15}H_{18}O_3$: 246.1255).

B. Without methanol

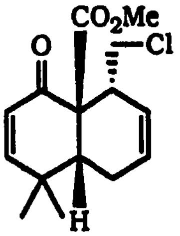
Adduct **96** (53 mg, 0.2 mmol) and *p*-TsOH (10 mg) were dissolved benzene (20 mL). The mixture was refluxed with azeotropic removal of water for 3 h and concentrated. The concentrate was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to furnish triene**100** (40 mg, 82%).

(1R*, 6R*, 10R*)-1-Carbomethoxy-10-methoxymethyl-5,5-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (101).



A solution of **96** (150 mg, 0.57 mmol) and *p*-TsOH (20 mg) in methanol (10 mL) was refluxed for 48 h. After concentration, the residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) giving ether **101** (135 mg, 85%): ir 1728 (C=O, ester) and 1684 cm^{-1} (C=O, enone); ^{1}H nmr 300 MHz, CDCl$_3$) δ 6.28 (dd, J = 10, J' = 2 Hz, 1H, -C**H**=CHCO-), 5.88 (d, J = 10 Hz, -CH=C**H**CO-), 5.68 (m, 1H, -C**H**=CH-), 5.55 (m, 1H, -CH=C**H**-), 3.86 (dd, J = 10, J' = 9 Hz, 1H, -C**H**HOCH$_3$), 3.71 (s, 3H, -COOC**H**$_3$), 3.55 (dd, J = 10, J' = 5 Hz, 1H, -CH**H**OCH$_3$), 3.31 (s, 3H, -OC**H**$_3$), 1.18 and 1.13 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, CDCl$_3$) δ 195.97 (p), 174.49 (p), 152.66 (a), 126.79 (a), 126.61 (a), 124.03 (a), 73.89 (p), 58.63 (a), 58.43 (p), 52.23 (a), 47.14 (a), 44.17 (a), 37.90 (p), 2 x 27.69 (a) and 27.56 (p); hrms M$^+$ 278.1515 (calcd. for $C_{16}H_{22}O_4$: 278.1518). Anal. Calcd. for $C_{16}H_{22}O_4$: C 69.03, H 7.97; found: C 68.98, H 8.04.

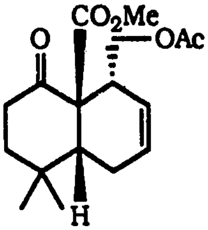
(1R*, 6R*, 10R*)-1-Carbomethoxy-10-chloromethyl-5,5-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (102).



Trimethylsilyl chloride (0.045 mL, 0.36 mmol) and methanol (0.03 mL) were added to a solution of **96** (45 mg, 0.18 mmol) in dichloromethane (10 mL) at room temperature. After 30 min the solution was concentrated and the residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) giving chloride **102** (48 mg, 94%): mp 76-77°C (hexane); ir 1728 (C=O, ester) and 1686 cm^{-1} (C=O, enone), 1620 cm^{-1} (C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 11, *J'* = 3 Hz, 1H, -C**H**=CHCO-), 5.90 (d, *J* = 11 Hz, -CH=C**H**CO-), 5.87 (ddd, *J* = 10, *J'* = 4, *J''* = 2 Hz, 1H, -CH=C**H**-), 5.63 (m, 1H, -C**H**=CH-), 4.20 (t, *J* = 11, *J'* = 11 Hz, 1H, -C**H**HCl), 3.76 (s, 3H, -COOC**H**$_3$), 3.50 (dd, *J* = 11, *J'* = 3 Hz, 1H, -CH**H**Cl), 1.16 and 1.13 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 195.41 (p), 174.13 (p), 153.16 (a), 126.65 (a), 125.41 (a), 125.91 (a), 60.20(p), 52.64 (a), 47.40 (a), 47.29 (a), 46.05 (p), 38.08 (p), 27.91 (a), 27.84 (a) and 27.65 (p); hrms M^+ 284.1014 and 282.1022 (calcd. for $C_{15}H_{19}O_3Cl$: 284.1014 and 282.1022). Anal. Calcd. for $C_{15}H_{19}O_3Cl$: C 63.72, H 6.77, Cl 12.54; found: C 63.78, H 6.68, Cl 12.60.

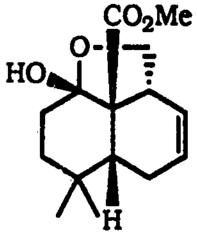
In another experiment, adduct **96** (250 mg, 0.95 mmol) was dissolved in tetrahydrofuran (50 mL) saturated with HCl gas at 0°C. The mixture was stirred at 25°C for 2 days. Removal of the solvent followed by crystallization from hexane gave chloride **102** (258 mg, 95%).

(1R*, 6R*, 10R*)-10-Acetoxymethyl-1-carbomethoxy-5,5,-dimethylbicyclo[4.4.0]dec-8-en-2-one (103).



Acetate **97** (520 mg, 1.7 mmol), triethylsilane (5.82 g, 10 mmol) and tris-(triphenylphosphine)rhodium(I) chloride (0.12 g, 0.13 mmol) were dissolved in benzene (20 mL). The solution was heated at 50°C for 36 h. The solvent was evaporated and the residue was diluted with tetrahydrofuran (30 mL). To the resulting solution, a solution of tetra-*n*-butylammonium fluoride (0.89 g, 3.4 mmol) in tetrahydrofuran was added dropwise. The reaction mixture was stirred for 12 h at room temperature and then concentrated. The concentrate was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to give ketone **103** (475 mg, 90%): ir ($CHCl_3$ cast) 1739, 1725 (C=O, ester) and 1709 cm^{-1} (C=O); ^1H nmr (300 MHz, $CDCl_3$) δ 5.78 (s, 2H, -C**H**=C**H**-), 4.40 (dd, J = 11.5, J' = 6 Hz, 1H, -C**H**HOAc), 4.17 (dd, J = 11.5, J' = 4 Hz, 1H, -CH**H**OAc), 3.75 (s, 3H, -OC**H**$_3$), 2.02 (s, 3H, C**H**$_3$CO$_2$-), 1.15 and 1.12 (each s, 3H each, *gem*-dimethyl); hrms M^+ 308.1623 (calcd. for $C_{17}H_{24}O_5$: 308.1623).

(1S*, 5R*, 9R*, 12R*)-12-Carbomethoxy-1-hydroxy-4,4,-dimethyl-11-oxatricyclo[7.2.1.$0^{5,12}$]dodec-7-ene (104) and (1R*, 6R*, 10R*)-10-Hydroxymethyl-5,5-dimethylbicyclo[4.4.0]dec-8-en-2-one (105).



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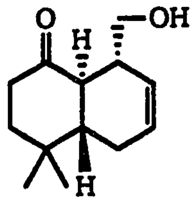


105

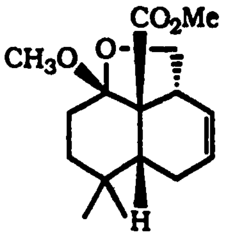
Ketone **103** (250 mg, 0.812 mmol) and potassium carbonate (0.50 g, 5 mmol) were dissolved in methanol (30 mL). The mixture was stirred at room temperature for 4 days and then diluted with water. The aqueous solution was extracted with dichloromethane. The extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the concentrate by flash chromatography on silica gel (20% ethyl acetate in hexane) furnished hemiacetal **104** (18.5 mg, 11%): ir ($CHCl_3$ cast) 3508 (OH) and 1704 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 6.02-6.20 (m, 2H, -C**H**=C**H**-), 4.39 (dd, $J = 9.5$, $J' = 7.5$ Hz, 1H, -C**H**HO-), 3.70 (s, 3H, -OC**H**$_3$), 3.40 (dd, $J = 7.5$, $J' = 5$ Hz, 1H, -CH**H**O-) and 0.9 (s, 6H, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 180.18 (p), 132.16 (a), 130.05 (a), 104.64 (p), 75.26 (p), 57.44 (p), 52.53 (a), 48.83 (a), 43.48 (a), 33.33 (p), 31.32 (p), 31.20 (p), 30.62 (a), 27.58 (a) and 25.47 (p); hrms m/z 248.1413 (M^+-H_2O, calcd. for $C_{15}H_{20}O_3$: 248.1412).

Anal. Calcd. for $C_{15}H_{22}O_4$: C 67.65, H 8.33, found: C 67.85, H 8.12. Further elution gave alcohol **105** (150 mg, 70%): ir ($CHCl_3$ cast) 3448 (OH) and 1712 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 5.80-5.62 (m, 2H, -**CH**=**CH**-), 3.58 (d, J = 4.5 Hz, 2H, -**CH**$_2$OH), 1.22 and 1.15 (each s, 3H each, *gem*-dimethyl); hrms M^+ 208.1461 (calcd. for $C_{13}H_{20}O_2$: 208.1463).

Hemiacetal 104 from alcohol 96

Sodium borohydride (200 mg, 5.4 mmol) was added in portions to alcohol **96** (152 mg, 0.58 mmol) in ethanol (10 mL) and the resulting solution stirred at room temperature for 12 h. The solution was diluted with water and extracted with dichloromethane. The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the concentrate by flash chromatography on silica gel (20% ethyl acetate in hexane) furnished hemiacetal **104** (67 mg, 46%).

(1S*, 5R*, 9R*, 12R*)-12-Carbomethoxy-1-methoxy-4,4,-dimethyl-11-oxatricyclo[7.2.1.0^{5,12}]dodec-7-ene (106) and (5R*, 9R*, 12R*)-12-Carbomethoxy-4,4,-dimethyl-11-oxatricyclo-[7.2.1.0^{5,12}]dodeca-1,7-diene (107)



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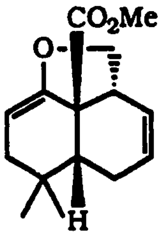

107

Hemiacetal **104** (55 mg, 0.21 mmol), methanol (1 mL) and *p*-TsOH (5 mg) were dissolved in benzene. The resulting mixture was heated at 40°C for 2 h. After concentration, the residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to furnish acetal **106** (30 mg, 51%): ir ($CHCl_3$ cast) 1738 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 5.95 (m, 2H, -C**H**=C**H**-), 4.08 (dd, J = 10, J' = 7 Hz, 1H, -C**H**HO-), 3.68 (s, 3H, -COOC**H**$_3$), 3.45 (dd, J = 7, J' = 6 Hz, 1H, -CH**H**O-), 3.22 (s, 3H, -OC**H**$_3$), 1.08 and 0.9 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, $CDCl_3$) δ 175.17 (p), 129.34 (a) 128.98 (a), 108.17 (p), 72.77 (p), 59.14 (p), 51.95 (a), 47.70 (a), 46.15 (a), 41.44 (a), 32.86 (p), 31.02 (a), 30.42 (a), 24.93 (p) and 24.24 (p); hrms m/z 248.1410 (M^+-MeOH, calcd. for $C_{15}H_{20}O_3$: 248.1412); Further elution gave enol ether **107** (18 mg, 35% yield); ir 1725 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 5.80 (m, 1H, -C**H**=CH-), 5.50 (m, 1H, -CH=C**H**-), 4.88 (t, J = J' = 4 Hz, 1H,

-C**H**=CO-), 4.24 (dd, J = 9, J' = 6 Hz, 1H, -OC**H**H-), 3.84 (dd, J = 9, J' = 2 Hz, 1H, -OCH**H**-), 3.75 (s, 3H,-OC**H**$_3$), 0.98 and 0.96 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr APT (75.5 MHz, CDCl$_3$) δ 176.61 (p), 151.78 (p), 127.40 (a), 124.36 (a), 94.31 (a), 72.60 (p), 52.41 (a), 52.14 (p), 44.15 (a), 39.87 (a), 35.03 (p), 33.27 (p), 28.83 (a), 28.77 (a) and 23.77 (p); hrms M$^+$ 250.1569 (calcd. for $C_{15}H_{22}O_3$: 250.1569).

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CHAPTER 3

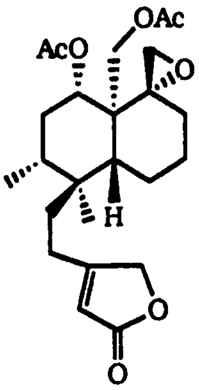
TOTAL SYNTHESIS OF AN UNNATURAL ANTIFEEDANT

Introduction

Pests and diseases reduce the yield and impair the quality of crops produced worldwide. Despite the high expenditure on insecticides, a good portion of the crops planted continue to be lost to feeding insects and other pests. Insecticides and fungicides currently in use rely upon the use of broad spectrum chemicals. These often kill other insects, including the pest's natural enemies. As insects develop resistance to such toxic chemicals, larger amounts of pesticides are required, resulting in a negative impact on the fragile ecosystem and pollution of the environment. The failure of insecticides and fungicides to protect crops efficiently from pests and diseases because they have developed a resistance to these chemical is becoming more frequent. Thus alternative methods of pest control are being sought.[1]

Plants have highly intricate chemical defence systems. These chemicals are known as repellents, attractants, insect growth regulators and antifeedants. Among these potential crop protecting agents, insect antifeedants have attracted research interest due to their effect on a wide range of major crop pests. The current use of insect antifeedants is limited because commercially developed insect antifeedants must meet increasingly stricter requirements including high activity at low concentration, not yielding toxic metabolites, selective toxicity

towards the target species and easy application.[2] Most natural insect antifeedants, e. g. ajugarin I (**1**),[3,4] jodrellin B (**2**)[5] and the most potent known antifeedant azadirachtin (**3**),[6-8] are highly complex polyoxygenated molecules,[9] which are not readily prepared. Their isolation from natural resources is also limited as a result of their low abundance and the high cost of separation procedures.[2]



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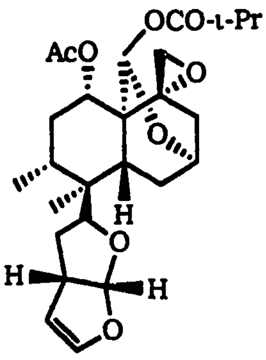

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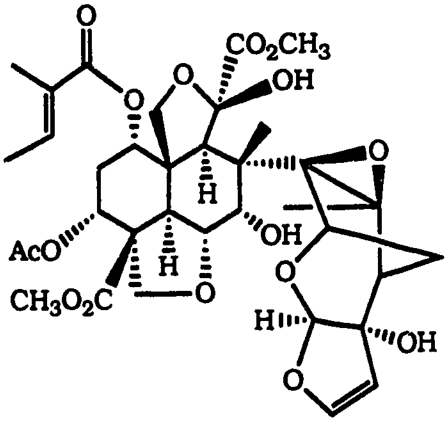
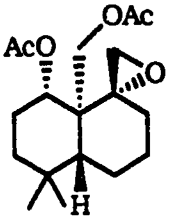


3

The complexity of the structure of known antifeedants, combined with the fact that more effective crop protection agents are required, have made the synthesis of any of these compounds a major objective. A more practical approach is to synthesize less complex analogs of these compounds. Although there has been little study of the structure-activity relationship with respect to antifeedant activity,[10-13] nevertheless some progress has been made. This progress has resulted in the development of structurally less complex antifeedant compounds, which partially retain the structure of their naturally occurring counterparts.

Among these products are *trans*- and *cis*-epoxy diacetates, **4**[12,14] and **5**.[15] Despite being structurally quite different from the natural product, ajugarin I, they still retain the epoxy and the diacetate units, and show good antifeedant activity towards *Locusta migratoria*. When the *cis*-epoxy diacetate **5** was tested against *Locusta migratoria* at 1000 ppm, a 72% inhibition of feeding was observed. Even the very simple model compound **6**, was found to be active against Egyptian cotton leaf worm and almost as potent as the natural product, azadirachtin (**3**).[16]



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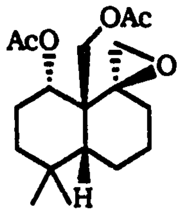

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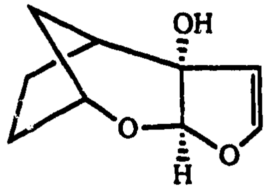
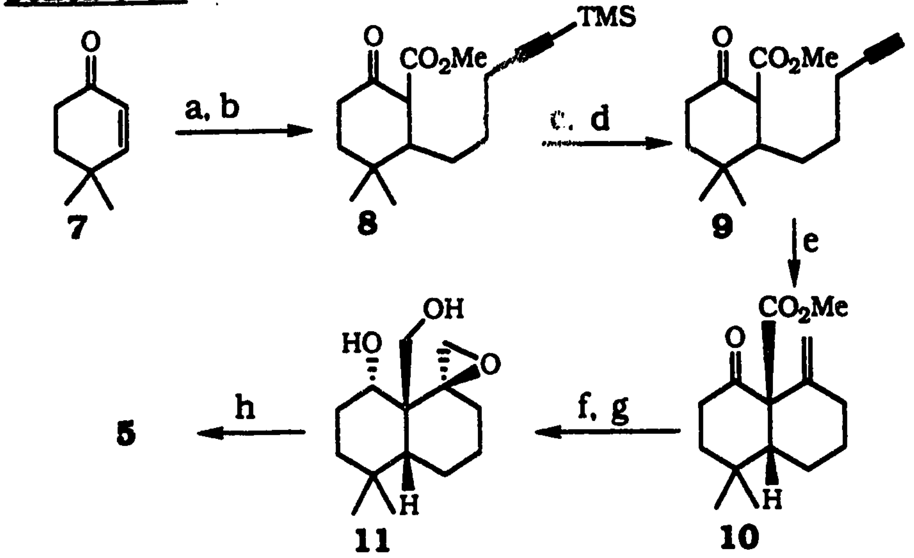


6

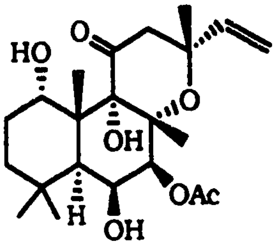
The only synthetic route to the *cis*-epoxy diacetate **5** has been published by Ley *et al.* [15] and is shown in Scheme 3-I. Copper catalyzed conjugate addition of the Grignard reagent to enone **7** and subsequent trapping of the resultant enolate with methyl chloroformate afforded adduct **8**. Cyclization of the modified adduct **9** under Lewis acid catalysis gave *cis*-decalin **10**. Reduction of **10** followed by epoxidation and acetylation furnished the desired *cis*-epoxy diacetate **5**.

Scheme 3-I



a) $Me_3SiC{\equiv}C(CH_2)_2CH_2MgI$-CuI; b) MeOCOCl; c) $AgNO_3$; d) KCN; e) ZnI_2, heat, toluene; f) $LiAlH_4$, ether; g) $VO(acac)_2$, *t*-BuOOH, PhH; h) Ac_2O, Pyr, DMAP.

In our synthetic studies towards forskolin (**12**), the adduct **13** (Chapter 2, compound **96**) was synthesized in a completely regioselective manner and in high yield based on a Diels-Alder strategy. Other derivatives **14**, **15**, **16** (Chapter 2, compounds **102**, **97** and **101**, respectively) of this adduct were also prepared. The transformation of these compounds to the *cis*-epoxy diacetate **5** was explored and the results are presented in this chapter.



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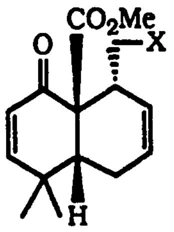
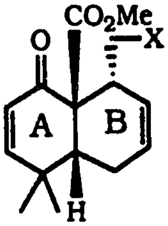


13 X = OH **14** X = Cl

15 X = OAc **16** X = OMe

Results and Disscusion

Our approach for addressing the *cis*-decalin system with proper functional groups has relied on one notion: that the requisite decalin system, possessing *cis* ring fusion stereochemistry and appropriate oxidation level at key centers, could be achieved in a single concerted step by means of a Diels-Alder reaction. In connection with the synthetic studies on forskolin, we have already prepared several compounds **13-16**, which could, in principal, be used for the synthesis of the *cis*-epoxy diacetate **5**.

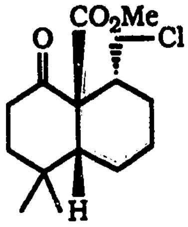


13 X = OH **14** X = Cl

15 X = OAc **16** X = OMe

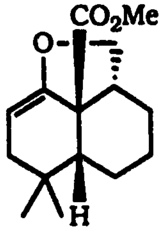
Conversion of any of these compounds to the target molecule requires two major operations: the reduction of the existing carbon-carbon double bonds and carbonyls and the introduction of an *exo* double bond to the B-ring. The former operation could, in principle, be carried out in two steps. First, simultaneous reduction of both double bonds using hydrogenation, and second, stepwise or simultaneous reduction of the ketone and ester to the alcohol level. The latter operation could be achieved by elimination of an appropriate leaving group. In accordance with this general strategy, the chloro derivative **14** was considered to be the best candidate, since chlorides are generally stable towards many reducing agents and the chloride ion is also a reasonable leaving group.

Hydrogenation of the chloro derivative **14** using Pd-C as a catalyst resulted in formation of two products. The less polar product obtained in 70% yield was identified as the desired compound **17**. Its ir spectrum exhibited the ester and enone carbonyl absorption bands at 1741 and 1721 cm^{-1}, respectively. The hrms confirmed the molecular formula $C_{15}H_{23}O_3Cl$ by displaying a pair of peaks at m/z 288.1311 and 286.1333, typical for the chlorine isotopes. The ^{1}H nmr spectrum displayed two doublets of doublets at δ 3.90 and 3.36, due to the methylene protons adjacent to the chlorine atom. The singlet at δ 3.78 was assigned to the carbomethoxy group.



17

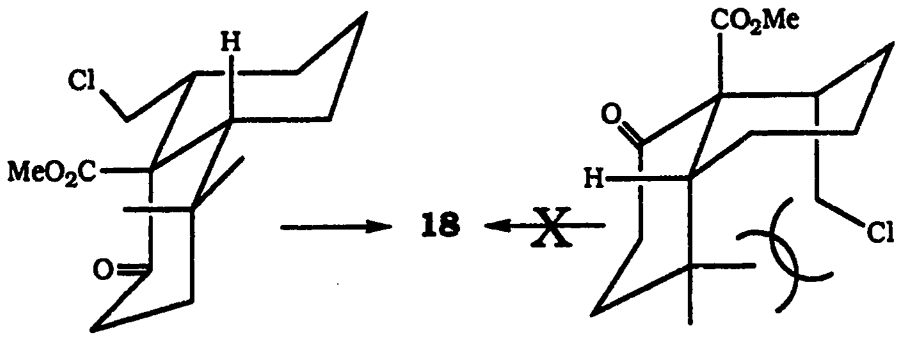
Based on the following spectroscopic data, structure **18** was assigned to the minor product. The ir spectrum showed only one carbonyl absorption band at 1729 cm^{-1}. Its hrms indicated the absence of chlorine, displaying a molecular ion at m/z 250.1569, corresponding to the formula $C_{15}H_{22}O_3$. The ^1H nmr spectrum showed one vinylic proton as a doublet of doublets ($J = J' = 4$ Hz) at δ 4.88. A methyl singlet at δ 3.72 was observed for the methyl ester. The ^{13}C nmr spectrum was in agreement with the proposed structure. It displayed signals at δ 176.61 (p) for the ester carbonyl, δ 150.87 (p) for the α-carbon of the enol ether and δ 94.81 (a) for the β-carbon of the enol ether.



18

Although the formation of enol ether **18** was not promising for the desired reactivity of chloride **17** , its dehydrochlorination for the incorporation of an *exo*-double bond was, nevertheless, attempted. Among the several methods available for dehydrochlorination, the use of the bicyclic amidine 1,8-diazabicycl-[5.4.0]-undec-7-ene (DBU)[17] was tested first. Treatment of **17** with DBU furnished a single product. This product was identified as the enol ether **18**. The same product was also isolated when potassium *tert*-butoxide was used as a base.

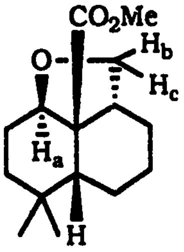
It is well known that the *cis*-decalin system can adopt two-chair conformations. These two possible conformations for the chloro compound **17** are illustrated in Figure 3-I and labelled as **17A** and **17B**. Conformer **17A** is thermodynamically more favored than conformer **17B**, since the chloromethyl group at C10 is axially oriented in conformer **17B**, while in **17A** this large group is equatorial. Inspection of Dreiding models of these conformations reveals that the more stable conformer **17A** can cyclize to form enol ether **18**.



17A **17B**

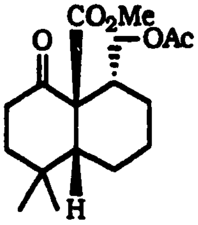
Figure 3-I. Possible Conformations of Compound **17**

Since dehydrochlorination of **17** proved to be troublesome and as both the ketone and the ester in this intermediate must eventually be reduced to the alcohol level and then acetylated, we turned our attention to the selective reduction of the ketone in order to avoid the cyclic enol ether formation. The reduction was first attempted with sodium borohydride[18] in ethanol at room temperature. The starting material was recovered unchanged. When the reaction was subsequently performed in refluxing tetrahydrofuran, a single product was formed. Unfortunately, this compound was shown by the following spectral data to be the cyclic ether **19**. In the ir spectrum neither hydroxy nor ketone absorption were present. The hrms indicated the absence of the chlorine atom. The ^1H nmr spectrum displayed three resonances, each as a doublet of doublets, at δ 3.97 (12, 4 Hz), 3.93 (9, 6 Hz) and 3.58 (9, 2 Hz), attributable to the three protons adjacent to the ether linkage, H_a, H_b and H_c, respectively. A sharp methyl singlet at δ 3.70 indicated that the ester group had survived the reduction. This was further confirmed by the ^{13}C nmr spectrum which exhibited the ester carbonyl at δ 176.33 (p). The same product was obtained using lithium borohydride.[19,20] Attempts were also made to reduce the ketone and the ester simultaneously using lithium aluminium hydride or diisobutylaluminium hydride. In each case, a complex mixture was obtained.



19

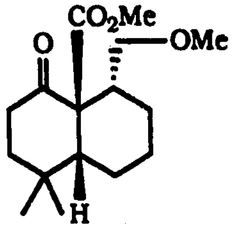
Since experiments with the chloro compound **17** met with little success, we turned out attention to the acetate derivative **15** as potential synthetic intermediate. In principle, an ester in which the alkoxy group has a β-hydrogen could be pyrolysed to give the corresponding olefin and acid.[21] Prior to pyrolysis the unsaturated carbon-carbon bonds in acetate **15** should be reduced. Thus, acetate **15** was hydrogenated over Pd-C to furnish the saturated ketone **20**. The ir spectrum of this product displayed two carbonyl absorptions at 1741 and 1720 cm^{-1}, for the esters and ketone respectively. Its hrms showed the molecular ion at m/z 310.1777, corresponding to the formula $C_{17}H_{26}O_5$. The ^{1}H nmr spectrum displayed the methylene protons next to the acetate at δ 4.28 and 4.11, each as a doublet of doublets. In addition, it showed four singlets at δ 3.78, 2.00, 1.14 and 0.98, each integrated for three protons, corresponding to the four methyl groups.



20

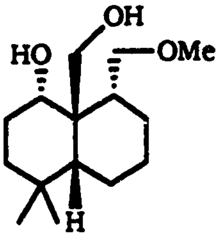
The saturated ketone **20**, was then subjected to pyrolysis at 300°C. Unfortunately the reaction gave again the enol ether **18** without formation of the desired olefin.

On the basis of the above results, it was concluded that a leaving group attached to the B-ring was incompatible with the presence of ketone or hydroxy group in A-ring. Consequently, subsequent studies were carried out using compound **16** possessing a stable methoxy group. Hydrogenation of **16** proceeded readily to furnish the saturated ketone **21**. The ir spectrum of this product displayed two carbonyl absorption bands at 1734 and 1721 cm^{-1}. Its hrms showed the molecular ion at m/z 282.1826, corresponding to the formula $C_{16}H_{26}O_4$. The ^{1}H nmr spectrum displayed the methoxy singlets at δ 3.73 and δ 3.33. It also showed a pair of doublets of doublets at δ 3.59 and 3.35 for the methylene proton next to the methoxy group.



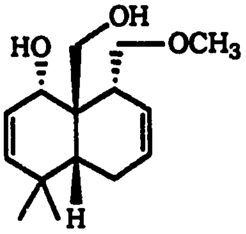
21

In order to install the acetate units present in the target molecule, both the ketone and the ester were required to be first reduced then acetylated. Simultaneous reduction of these functionalities was achieved with excess lithium aluminium hydride to afford saturated diol **22** in 37% yield. A broad hydroxy absorption band at 3425 cm^{-1} was observed in its ir spectrum. The hrms of **22** displayed a fragment at m/z 238.1932, corresponding to a molecular formula of $C_{15}H_{26}O_2$, resulting from the elimination of one molecule of water. A singlet at δ 3.35 in the ^{1}H nmr spectrum corresponded to the methoxy group. The stereochemistry of the secondary hydroxyl was tentatively assigned to be *trans* to the angular hydroxymethylene based on the expected addition of hydride ion from the convex side of the molecule.



22

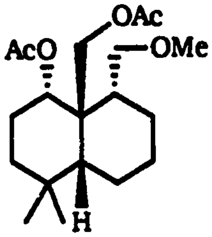
To improve the yield of diol **22** obtained from **16**, the reductions were carried out in reverse order. Eth[illegible] **16** was first subjected to treatment with lithium aluminium hydride. Unsaturated diol **23** was obtained in 68 % yield. The ir spectrum of this compound showed a hydroxy absorption peak at 3308 cm^{-1}. Its hrms displayed the expected molecular ion at m/z 252.1719 for the formula $C_{15}H_{24}O_3$. This molecular formula was confirmed by elemental analysis. The ^{1}H nmr spectrum exhibited a broad singlet, integrated for one proton, at δ 4.28, for the methine proton adjacent to the hydroxy group. Two doublets (*J* = 10 Hz each) at δ 3.79 and 3.47 were assigned to the protons adjacent to the primary hydroxy group.



23

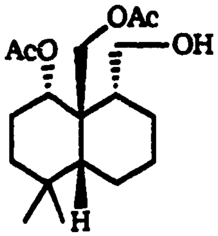
Compound **23** was subsequently subjected to hydrogenation over Adams catalyst. To our delight, the product obtained in excellent yield was identified as the saturated diol **22**.

Continuing with the synthesis, the saturated diol **21** was acetylated using excess acetic anhydride and a catalytic amount of 4-dimethylaminopyridine(DMAP)[22] in pyridine to furnish the desired diacetate **24**. This product was readily identified by its ir spectrum which showed an intense ester carbonyl absorption at 1733 cm^{-1}. Its hrms failed to give the molecular ion peak, but showed a fragment at m/z 280.2036, due to the loss of an acetic acid unit. The elemental analysis corroborated the required molecular formula $C_{19}H_{32}O_5$. The ^1H nmr spectrum displayed the acetoxymethyl protons as an AB quartet at δ 4.11 and 4.09 (*J* = 11 Hz each) and the methine proton adjacent to the acetate unit at δ 4.66 as a doublet of doublets with two small coupling constants of 2 Hz each. This coupling pattern was indicative of an equatorial orientation for the proton, in support of the assigned stereochemistry.



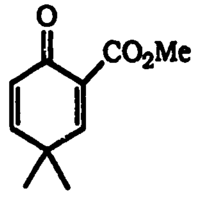
24

The transformation of the diacetate **24** to the target compound **5** required the conversion of its methoxymethyl group to a methylene unit for the eventual introduction of an epoxide. Towards this end, the diacetate **24** was subjected to deprotection. Several methods[23] were explored for the cleavage of the methyl ether. When the diacetate **24** was treated with trimethylsilyl chloride-sodium iodide[24] or with boron tribromide[25], a complex mixture was formed. However, when it was treated with *B*-bromo-9-borabicyclo[3.3.1]nonane[26] (*B*-Br-9-BBN) at room temperature, the reaction proceeded cleanly to give a single product, which was shown by the spectroscopic data to be the desired alcohol **25**. The ir spectrum exhibited a hydroxy absorption at 3450 cm^{-1} and an ester carbonyl band at 1738 cm^{-1}. Its hrms failed to show the molecular ion but registered a fragment at m/z 206.1678, corresponding to the loss of two units of acetic acid. The elemental analysis corroborated the molecular formula $C_{18}H_{30}O_5$. The ^{1}H nmr spectrum showed the absence of the methoxy group. It exhibited a broad singlet at δ 4.72 for the methine proton next to the acetate. Two methyl singlets at δ 2.12 and 2.08 were observed for the acetates.

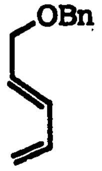


25

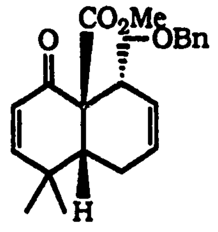
Although the conversion of the adduct **16** to alcohol **25** went well, we felt that the protection of the hydroxy group in adduct **12** as a benzyl ether would be beneficial, since the hydrogenation of the double bonds and hydrogenolysis of the benzyl group could, in principle, be achieved in a single reaction using palladium as a catalyst. Consequently, 2,4-pentadienol was converted to its benzyl ether derivative **26** using benzyl bromide and sodium hydride. Diels-Alder reaction between enone ester **27** and diene **26** in the presence of zinc chloride in dichloromethane afforded the expected adduct **28**. The ir spectrum of this adduct showed an ester carbonyl absorption at 1726 cm^{-1} and an enone absorption at 1688 cm^{-1}. Its hrms displayed the molecular ion at m/z 354.1842, corresponding to the molecular formula $C_{22}H_{26}O_4$. The ^{1}H nmr spectrum displayed a doublet of doublets (J = 10, J' = 2.5 Hz) at δ 6.26 and a doublet (J = 10 Hz) at δ 5.88 due to the β-proton and α-proton of the enone system, respectively. The benzylic protons were observed at δ 4.48 as a singlet, while the methylene protons next to the benzyloxy group appeared as a pair of doublets of doublets at δ 3.95 (10, 8.5 Hz) and 3.66 (10, 5 Hz).



27



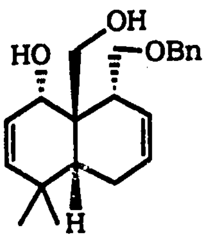
26



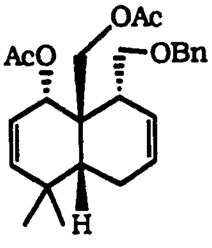
28

Reduction of **28** with lithium aluminium hydride furnished alcohol **29**. The hydroxy absorptions were observed as a broad band at 3390 cm^{-1} in the ir spectrum. Although the hrms of **28** did not show the molecular ion peak, the cims displayed the [M+H]$^+$ peak at 329, corresponding to the molecular formula

$C_{21}H_{28}O_3$. The ^1H nmr spectrum showed a total of four vinylic protons. The two doublets at δ 4.50 and 4.40 were assigned to the the benzylic protons. It also displayed the *gem*-dimethyl at δ 1.00 and 0.88.



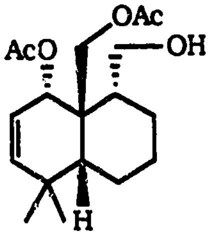
29



30

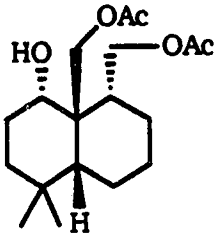
Acetylation of **28** was carried out in tetrahydrofuran using excess acetic anhydride, DMPA and pyridine in tetrahydrofuran to afford diacetate **30** in quantitative yield. The ir spectrum confirmed the absence of the hydroxy group and the presence of acetates with a strong absorption band at 1734 cm^{-1}. The hrms showed the molecular ion at m/z 412.2255, in agreement with the molecular formula $C_{25}H_{32}O_5$. In the ^1H nmr spectrum, the benzylic protons resonated at δ 4.48 as a singlet and the methylene protons adjacent to the acetate appeared at δ 3.96 also as a singlet. Four methyl singlets were observed at δ 2.05, 1.98, 1.03 and 0.96.

With the diacetate **30** in hand, we proceeded to explore the simultaneous reduction of the two double bonds and the hydrogenolysis of the benzyl group. Thus, diacetate **30** was hydrogenated for three hours using Pd-C as a catalyst. The tlc analysis of the reaction mixture indicated the formation of a single compound and complete consumption of the starting material. The product, isolated in quantitative yield, was assigned, based on its spectroscopic data, to structure **31**. Unfortunately the double bond in the A-ring had survived the hydrogenation apparantly due to the steric hindrance. The ir spectrum of **31** displayed a hydroxy absorption at 3400 cm^{-1}. It also showed an ester carbonyl band at 1740 cm^{-1}. The elemental analysis and hrms correlated well with the molecular formula $C_{18}H_{28}O_5$ required for the assigned structure. The ^{1}H nmr spectrum displayed one vinylic proton at δ 5.67 as a doublet of doublets and the other at δ 5.53 as a doublet. The allylic proton was observed as a doublet at δ 4.85. The two doublets at δ 4.30 and 3.85 were assigned to the methylene protons adjacent to the acetate. Four methyl groups were observed at δ 2.15, 2.05, 1.08 and 1.02. Attempts to induce complete reduction by extending the reaction time or increasing the hydrogen pressure met with little success. Invariably, alcohol **31** was formed as the exclusive product. When Adams catalyst was used, a complex mixture was produced.



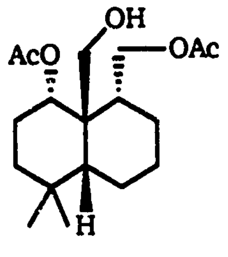
31

Alcohol **31** was subjected to further hydrogenation using Adams catalyst. After an extended reaction time (48 h), two products were formed. These compounds were separated by flash chromatography. The less polar compound, obtained in 12% yield, was characterized as alcohol **32**. The hydroxy and the ester carbonyl absorption bands were observed in the ir spectrum at 3520 and 1740 cm^{-1}, respectively. The hrms failed to show the molecular ion peak, but registered a peak at m/z 266.1879, due to the loss of an acetic acid unit from the molecular formula $C_{16}H_{26}O_3$. The ^{1}H nmr spectrum displayed a pair of doublets of doublets at δ 4.37 (J = 11, J' = 4 Hz) and 4.24 (J = 11, J' = 7 Hz) for the methylene protons of the acetoxymethyl group attached to C10. The methylene protons of the acetoxymethyl group were observed as an AB quartet at δ 4.12 and 4.03 (J = 12 Hz). The methine proton next to the hydroxy group was displayed as a broad singlet at δ 3.68. The major compound exhibited, in the ir spectrum, a hydroxyl and an ester carbonyl at 3500 and 1736 cm^{-1}, respectively. Its hrms showed a fragment at m/z 206.1668, corresponding to the formula $C_{14}H_{22}O$ resulting from the elimination of two units of acetic acid. In the ^{1}H nmr spectrum, the down field broad singlet at δ 4.68 indicated that the acetate unit in A-ring was intact. Two doublets of doublets at

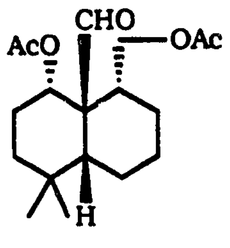


32

δ 4.52 and 3.65 were assigned to the methylene protons next to the acetate. Based on these spectroscopic data the major product was assigned to structure **33**. Chemical evidence for the assignments to **32** and **33** were obtained from the oxidation of **33**. When the diacetate **33** was subjected to oxidation using pyridinium chlorochromate (PCC)[27] the product obtained was characterized as the aldehyde **34**. Its ir spectrum showed two carbonyl absorption bands at 1733 and 1713 cm^{-1}, due to the acetates and the aldehyde, respectively. The hrms of this aldehyde did not register the molecular ion peak, but showed a peak at m/z 176.1564, due to the formula $C_{13}H_{20}$ $(M^+-2\,x\,AcOH-CH_2O)$. The aldehydic proton was observed, in the ^1H nmr spectrum, at δ 9.30 as a singlet. The signal due to the methine proton next to the acetate appeared at δ 5.40. Two doublets of doublets were observed at δ 3.92 and 3.78 due to the methylene protons next to the acetate.



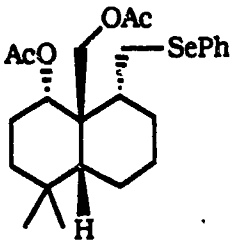
33



34

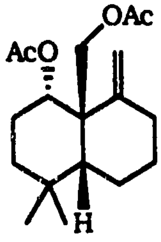
When the hydrogenation of alcohol **31** with Adams catalyst was monitored by tlc, it was observed that the formation of the products **32** and **33** was very slow. This could be because the reduction was faster than the acyl migration. Based on this argument, the reaction was repeated under the same conditions but it was terminated after 2 h. In spite of the fact that the tlc failed to show any change, the residue obtained after filtration and concentration was characterized as the desired product **25**. Its spectroscopic data were in good agreement with those obtained previously.

The final stage of the projected synthesis called for the conversion of the primary hydroxy group in **25** to an exocyclic double bond. The best known method for dehydration of primary alcohols, involves the conversion of the hydroxy group into a phenylselenide followed by oxidative-elimination. Using *N*-(phenylseleno)phthalimide (PSP) combined with tri-*n*-butylphosphine,[28] alcohol **25** was converted efficiently to phenylselenide **35**. This compound exhibited an ester carbonyl absorption at 1737 cm^{-1} in its ir spectrum. The cims showed the $[M+NH_4]^+$ peak at m/z 484, corresponding to the molecular formula $C_{24}H_{34}O_4Se$. This formula was further confirmed by elemental analysis. The ^1H nmr spectrum displayed the methine proton adjacent to the acetate group at δ 4.83 as a doublet of doublets and the methylene protons next to the other acetate unit at δ 4.05 and 3.81, each as a doublet.



35

Oxidative-elimination of phenylselenide **35** was accomplished using *m*-chloroperbenzoic acid in dichloromethane followed by refluxing in carbon tetrachloride to furnish the desired diacetate **36**. The ir spectrum of this compound showed the ester carbonyl absorption band at 1741 cm^{-1}. Its hrms exhibited a peak at m/z 248.1773, corresponding to the elimination of a molecule of acetic acid. The molecular composition of **36** was confirmed by its cims which showed the $[M+NH_4]^+$ peak at 326. In the ^{1}H nmr spectrum the vinylic protons were displayed as two doublets of doublets ($J = J' =$ 1.5 Hz) at δ 5.32 and 5.06. The methine proton adjacent to the acetate appeared at δ 4.94, while the methylene protons next to the other acetate were observed at δ 4.38 and 4.02.

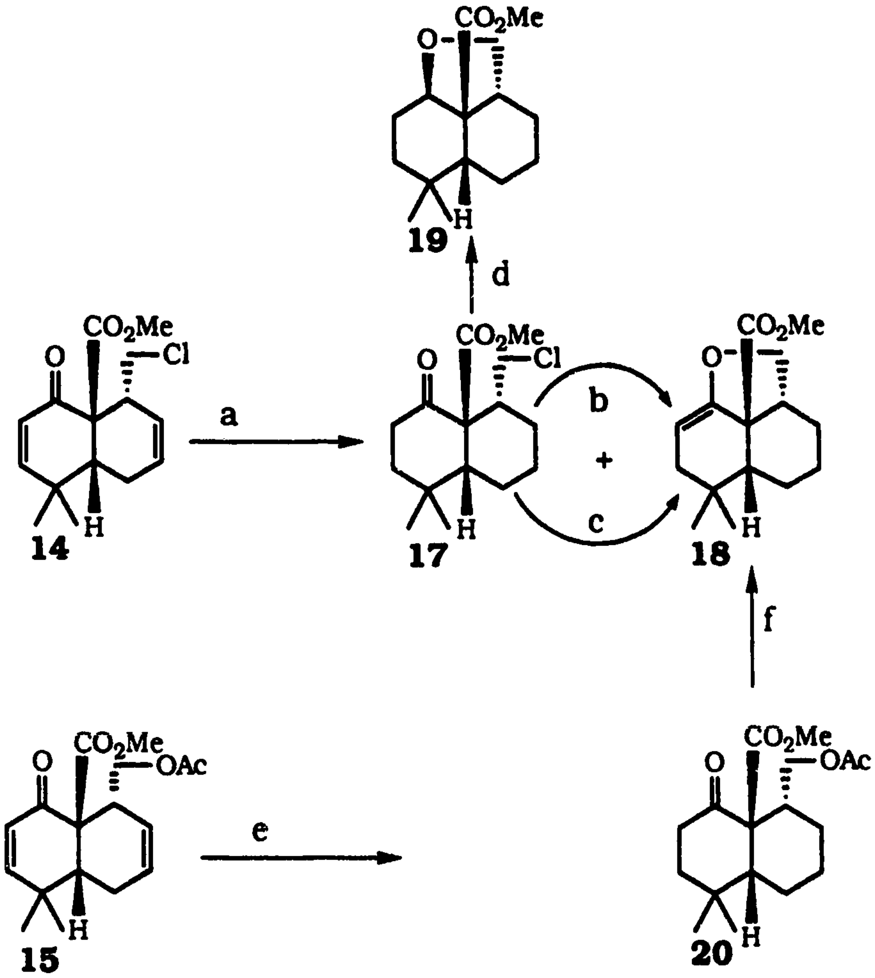


36

Finally, epoxidation of **36** using *m*-chloroperbenzoic acid furnished the target molecule **5**. Its ir spectrum showed an absorption at 1740 cm^{-1} for the acetates. The cims displayed a $[M+NH4]^+$ peak at 342, corresponding to the formula $C_{18}H_{28}O_4$, which was further confirmed by elemental analysis. The ^{1}H nmr spectrum showed a doublet of doublets at δ 4.88 for the methine proton next to the acetate. The methylene protons of the angular acetoxymethyl group appeared at δ 4.29 and 4.03 as a pair of doublets. Its ^{13}C nmr spectrum exhibited a total of eighteen signals consistent with the structure. These spectroscopic data were in excellent agreement with those reported.[15]

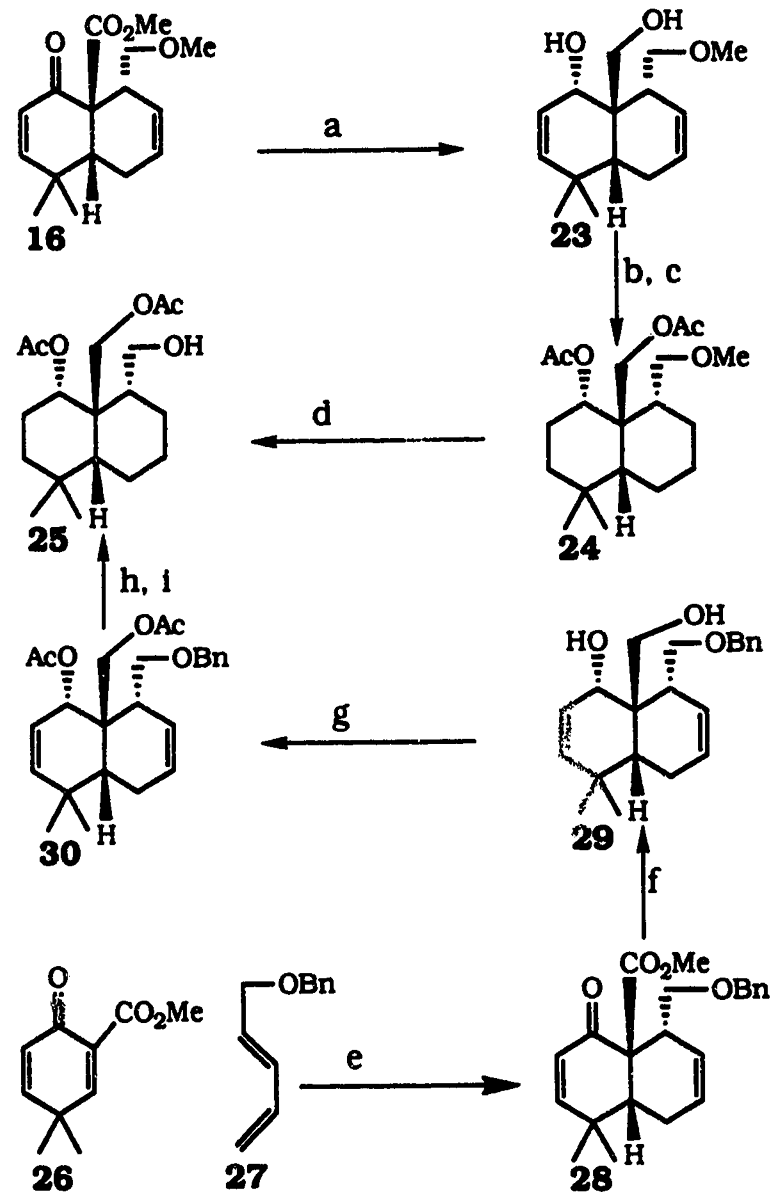
In summary, although the chloro compound **17** and the saturated ketone **20** failed to fulfill our expectations, an interesting intermediate **18** was prepared from these compounds as shown in Scheme 3-II. An efficient (more than 45% overall yield) route to alcohol **25** was achieved *via* ethers **16** or **28**, as illustrated in Scheme 3-III. Intermediate **25** was transformed efficiently to the target *cis*-epoxy diacetate **5** in 69% yield over five steps according to Scheme 3-IV.

Scheme 3-II



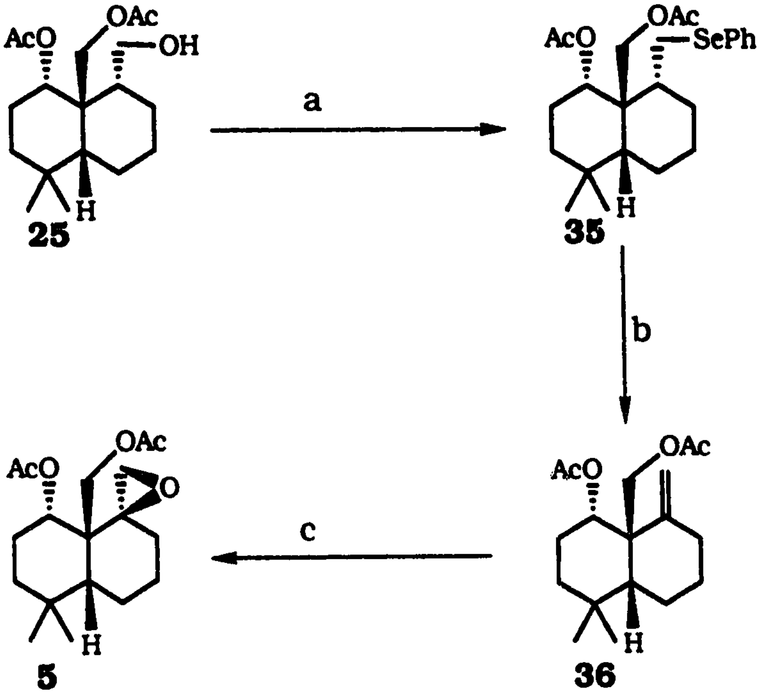
a) H_2/Pd-C, EtOAc-hexane, 82%; b) DBU, PhH, 100%; c) *t*-BuOK, *t*-BuOH, 57%; d) $NaBH_4$, THF, 56%; or $LiBH_4$, *i*-PrOH, 75%; e) H_2/Pd-C, 96%, EtOAc-hexane, ; f) 300°C, 25%.

Scheme 3-III



a) $LiAlH_4$, Et_2O, 68%; b) H_2/Pt, EtOAc, hexane, 97%; c) Ac_2O, Py, DMAP, 82%; d) *B*-Br-9-BBN, CH_2Cl_2, 85%; e) $ZnCl_2$, CH_2Cl_2, 71%; f) $LiAlH_4$, Et_2O, 65%; g) Ac_2O, Py, DMAP, 100%; h) H_2/Pd-C, EtOAc, hexane, 100%; i) H_2/Pt, EtOAc, hexane, 97%.

Scheme 3-IV



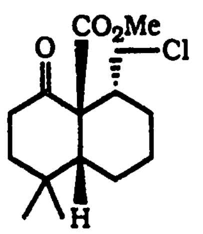
a) PSP, (n-Bu)$_3$P, THF, 94%; b) i. MCPBA, CH$_2$Cl$_2$; ii. CCl$_4$, Et$_2$NH, ↑↓, 88%; c) MCPBA, CH$_2$Cl$_2$, 85%.

Experimental

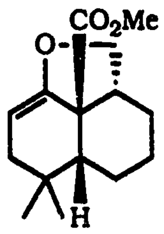
General Procedures and Materials.

Refer to Chapter 1, Experimental Section for a detailed description of general procedures and materials data.

(1R*, 6R*, 10R*)-1-Carbomethoxy-10-chloromethyl-5,5-dimethylbicyclo[4.4.0]decan-2-one (17) and (5R*, 9R*, 12R*)-12-Carbomethoxy-4,4,-dimethyl-11-oxatricyclo[7.2.1.$0^{5,12}$]dodec-1-ene (18)



17



18

A mixture of chloro derivative **14** (200 mg, 0.71 mmol) and Pd-C (10 mg) in ethyl acetate and hexane (1:1, 200 mL) was hydrogenated (40 p.s.i. of hydrogen) for 2 h. The catalyst was removed by filtration through celite and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to give chloro compound **17** (143 mg, 70%): ir ($CHCl_3$ cast) 1741 (C=O, ester) and 1721 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.90 (dd, $J = 11$, $J' = 9$ Hz, 1H, -C**H**HCl), 3.78 (s, 3H, -OC**H**$_3$), 3.36 (dd,

$J = 11$, $J' = 2.5$ Hz, 1H, -CH**H**Cl), 1.13 and 0.98 (s each, 3H each, *gem*-dimethyl); hrms M$^+$ 288.1311 and 286.1333 (calcd. for $C_{15}H_{23}O_3Cl$: 288.1306 and 286.1335). Further elution gave enol ether **18** (23 mg, 13%): mp 68-69°C (hexane); ir ($CHCl_3$ cast) 1729 cm^{-1} (C=O, ester); ^{1}H nmr (300 MHz, $CDCl_3$) δ 4.88 (t, $J = 4$ Hz, 1H, -C**H**=CO-), 4.05 (dd, $J = 8.5$, $J' = 4.5$ Hz, 1H, -C**H**HO-), 3.72 (s, 3H,-OC**H**$_3$), 3.71 (d, $J = 8.5$ Hz, 1H, -CH**H**O-), 0.95 and 0.92 (s each, 3H each, *gem*-dimethyl); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 176.61 (p), 150.87 (p), 94.81 (a), 72.61 (p), 53.35 (p), 52.27 (a), 44.41 (a), 44.19 (a), 34.90 (p), 32.93 (p), 26.74 (a), 28.12 (a), 28.04 (p), 24.30(p) and 23.23 (p); hrms M$^+$ 250.1569 (calcd. for $C_{15}H_{22}O_3$: 250.1569).

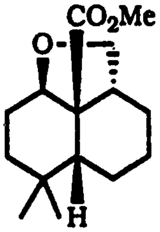
Enol ether 18 from chloro compound 17 using DBU.

A solution of **17** (200 mg, 0.7 mmol) and DBU (250 mg, 1.6 mmol) in dry benzene (50 mL) was stirred at room temperature for 72 h. The resulting reaction mixture was washed with aqueous 10% HCl (3 x 50 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent left enol ether **18** (177 mg, 100%).

Enol ether 18 from chloro compound 17 using *tert*-BuOK.

A solution of **17** (30 mg, 0.105 mmol) and potassium *tert*-butoxide (117 mg, 1.05 mmol) in *tert*-butyl alcohol (20 mL) was refluxed for 20 h. The resulting reaction mixture was concentrated. The residue was purified by flash chromatography on silica gel (15% AcOEt in hexane) to give enol ether **18** (15 mg, 57%).

(1R*, 5R*, 9R*, 12R*)-12-Carbomethoxy-4,4,-dimethyl-11-oxatricyclo[7.2.1.0^{5,12}]dodecane (19).



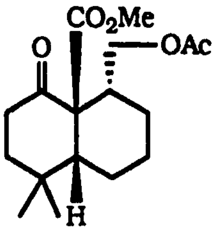
Using sodium borohydride

A mixture of chloro compound **17** (300 mg, 1.05 mmol) and sodium borohydride (397 mg, 10.5 mmol) in tetrahydrofuran (100 mL) was refluxed for 24 h. After the resulting solution was cooled to room temperature it was diluted with a 5% aqueous solution of NaOH (30 mL) and extracted with dichloromethane (2 x 150 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (30% ethyl acetate in hexane) to give cyclic ether **19** (150 mg, 56%): ir ($CHCl_3$ cast) 1735 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 3.97 (dd, $J = 12$, $J' = 4$ Hz, 1H, -C**H**O-), 3.93 (dd, $J = 9$, $J' = 6$ Hz, 1H, -C**H**HO-), 3.69 (s, 3H, -OC**H**$_3$), 3.58 (dd, $J = 9$, $J' = 2$ Hz, 1H, -CH**H**O-), 0.90 and 0.87 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 176.33 (p), 76.32 (a), 72.06 (p), 52.62 (p), 51.25 (a), 45.98 (a), 43.00 (a), 35.11 (p), 34.46 (p), 29.22 (a), 28.43 (p), 28.37 (a), 24.25 (p), 23.65 (p) and 22.78 (p); hrms M^+ 252.1716 (calcd. for $C_{15}H_{24}O_3$: 252.1726).

Ether 19 from chloro compound 17 using lithium borohydride

Freshly prepared $LiBH_4$ (91 mg, 4.2 mmol) was added to a solution of **17** (120 mg, 0.42 mmol) in isopropyl alcohol (10 mL). The resulting solution was refluxed for 2 h, diluted with a 5% aqueous solution of NaOH (30 mL) and extracted with dichloromethane (3 x 15 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (30% ethyl acetate in hexane) to give ether **19** (80 mg, 75%).

(1R*, 6R*, 10R*)-10-Acetoxymethyl-1-carbomethoxy-5,5-dimethylbicyclo[4.4.0]decan-2-one (20).

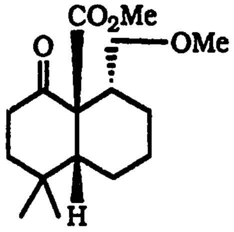


A mixture of acetate **15** (100 mg, 0.318 mmol) and Pd-C (20 mg) in ethyl acetate and hexane (1:1, 50 mL) was hydrogenated (50 p.s.i. of hydrogen) for 48 h. The catalyst was removed by filtration through celite and the filtrate was concentrated to afford saturated ketone **20** (95 mg, 96%): ir ($CHCl_3$ cast) 1741 (C=O, ester) and 1720 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 4.28 (dd, J = 11.5, J' = 7.5 Hz, 1H, -C**H**HOAc), 4.11 (dd, J = 11.5, J' = 3 Hz, 1H, -C**H**HOAc), 3.78 (s, 3H, -OC**H**$_3$), 2.00 (s, 3H, C**H**$_3$COO-), 1.14 and 0.98 (each s, 3H each, *gem*-dimethyl); hrms M^+ 310.1777 (calcd. for $C_{17}H_{26}O_5$: 310.1780).

Enol ether 18 from ketone 20.

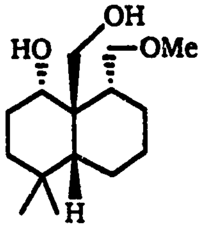
Saturated ketone **20** (98 mg, 0.32 mole) was placed in a reaction vessel equipped with a cold condenser. It was immersed into a preheated (300°C) sand bath for 10 min. After cooling to room temperature, the reaction mixture and the condensate on the cold condenser were taken into dichloromethane and then concentrated. The residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexane) to give the enol ether **18** (20 mg, 25%).

(1R*, 6R*, 10R*)-1-Carbomethoxy-10-methoxymethyl-5,5-dimethylbicyclo[4.4.0]decan-2-one (21).



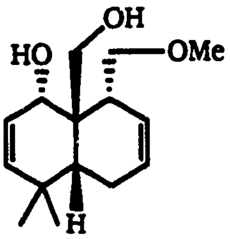
A mixture of methoxy derivative **16** (210 mg, 0.755 mmol) and Adams catalyst (15 mg) in ethyl acetate and hexane (1:1, 50 mL) was hydrogenated (50 p.s.i. of hydrogen) for 5 h. The catalyst was removed by filtration through celite and the solution was concentrated to afford saturated ketone **21** (198 mg, 93%): ir ($CHCl_3$ cast) 1734 (C=O, ester) and 1721 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.73 (s, 3H, -COOC**H**$_3$), 3.59 (dd, J = 10, J' = 6.5 Hz, -C**H**HOCH$_3$), 3.33 (dd, J = 10, J' = 4 Hz, -CH**H**OCH$_3$), 3.33 (s, 3H, -OC**H**$_3$), 1.15 and 0.98 (each s, 3H each, *gem*-dimethyl); hrms M^+ 282.1826 (calcd. for $C_{16}H_{26}O_4$: 282.1831).

(1R*, 2R*, 6S*, 10S*)-1-Hydroxymethyl-10-methoxymethyl-5,5-dimethylbicyclo[4.4.0]decan-2-ol (22).



Lithium aluminium hydride (100 mg , 2.7 mmol) was added to a solution of saturated ketone **21** (102 mg, 0.36 mmol) in ether (50 mL) at 0°C. The reaction mixture was stirred at room temperature for 24 h. It was then cooled to 0°C and a 10% aqueous solution of H_2SO_4 (5 mL) was added. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography on silica gel (30% ethyl acetate in hexane) of the residue furnished saturated diol **22** (35 mg, 37%) as a white solid: mp 91-92°C (hexane); ir ($CHCl_3$ cast) 3425 cm^{-1} (OH); ^1H nmr (300 MHz, $CDCl_3$) δ 3.83-3.50 (m, 5H), 3.45 (dd, J = 11.5, J' = 5 Hz, 1H, -C**H**HOCH_3), 3.35 (s, 3H, -OC**H**$_3$), 1.10 and 0.96 (each s, 3H each, *gem*-dimethyl); hrms m/z 238.1928 (M^+-H_2O, calcd. for $C_{15}H_{26}O_2$: 238.1932); cims $[M+H]^+$ 257. Anal. Calcd. for $C_{15}H_{28}O_3$: C 70.26, H 11.01; found: C 70.59, H 10.86.

(1S*, 2S*, 6R*, 10R*)-1-Hydroxymethyl-10-methoxymethyl-5,5-dimethylbicyclo[4.4.0]deca-3,8-dien-2-ol (23).

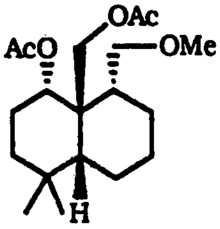


Lithium aluminium hydride (200 mg , 5.4 mmol) was added to a solution of ether **16** (200 mg, 0.72 mmol) in ether (50 mL) at 0°C. The reaction mixture was stirred at room temperature for 24 h. It was then cooled to 0°C and a 10% aqueous solution of H_2SO_4 (5 mL) was added. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. Chromatography on silica gel (30% ethyl acetate in hexane) of the residue furnished diol **23** (120 mg, 68%) as a white solid: mp 120-121°C (hexane and ethyl acetate); ir ($CHCl_3$ cast) 3308 cm^{-1} (OH); ^1H nmr (300 MHz, $CDCl_3$) δ 5.71 (m, 1H, -C**H**=CH-), 5.60 (dd, *J* = 10.5, *J'* = 2 Hz, 1H, -C**H**=CHCHOH), 5.50 (m, 1H, -CH=C**H**-), 5.36 (dd, *J* = 10.5, *J'* = 3 Hz, 1H, =C**H**CHOH), 4.28 (br s, 1H, -C**H**OH), 3.95 (dd, *J* = *J'* = 9.5 Hz, -C**H**HOCH$_3$), 3.79 (d, *J* = 10 Hz, 1H, -CH**H**OH), 3.47 (d, *J* = 10 Hz, 1H, -C**H**HOH), 3.30 (dd, *J* = 9.5, *J'* = 2, 1H, -CH**H**OCH$_3$), 3.28 (s, 3H, -OC**H**$_3$), 1.02 and 0.88 (each s, 3H each, *gem*-dimethyl); hrms M^+ 252.1719 (calcd. for $C_{15}H_{24}O_3$: 252.1725). Anal. Calcd. for $C_{15}H_{24}O_3$: C 71.39, H 9.59; found: C 71.37, H 9.61.

Saturated diol 22 from unsaturated diol 23.

A mixture of unsaturated diol **23** (200 mg, 0.79 mmol) and Adams catalyst (50 mg) in ethyl acetate and hexane (1:1, 100 mL) was hydrogenated (50 p.s.i. of hydrogen) for 24 h. The catalyst was removed by filtration through celite and the filtrate was concentrated to give saturated diol **22** (200 mg, 97%).

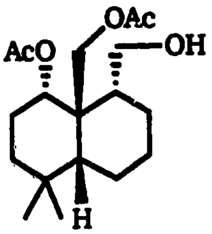
(1S*, 2S*, 6R*, 10R*)-2-Acetoxy-1-acetoxymethyl-10-methoxymethyl-5,5-dimethylbicyclo[4.4.0]decane (24).



A solution of saturated diol **22** (2.58 g, 10.02 mmol) in pyridine (50 mL) containing DMAP (30 mg) and acetic anhydride (3.82 mL, 40.08 mmol) was stirred in the dark at room temperature for 24 h. The resulting solution was poured into dichloromethane (200 mL) and washed three times with ice-cold 10% aqueous HCl (150 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in hexane) to afford diacetate **24** (2.80 g, 82%): mp 54-55°C (ethyl acetate); ir ($CHCl_3$ cast) 1733 cm^{-1} (C=O, esters);

^{1}H nmr (300 MHz, CDCl$_3$) δ 4.66 (t, $J = J' = 2$ Hz, 1H, -C**H**OAc), 4.11 (d, $J = 10$ Hz, 1H, -C**H**HOAc), 4.09 (d, $J = 10$ Hz, 1H, -CH**H**OAc), 3.42 (dd, $J = 10$, $J' = 4$ Hz, 1H, -CH**H**OCH$_3$), 3.20 (s, 3H, -OC**H**$_3$), 3.05 (dd, $J = 10$, $J' = 7$ Hz, 1H, -CH**H**OCH$_3$), 2.05 (s, 3H, C**H**$_3$CO$_2$-), 2.02 (s, 3H, C**H**$_3$CO$_2$-), 1.00 and 0.90 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 170.75 (p), 169.62 (p), 74.10 (p), 72.59 (a), 66.53 (p), 58.77 (a), 43.51 (a), 42.02 (p), 41.74 (a), 33.35 (p), 33.09 (a), 30.14 (a), 29.47 (p), 28.28 (p), 26.22 (p), 25.72 (p), 24.41 (p), 21.75 (a) and 20.93 (a); hrms m/z 280.2036 (M$^+$-AcOH, calcd. for $C_{17}H_{28}O_3$: 280.2038). Anal. Calcd. for $C_{19}H_{32}O_5$: C 67.03, H 9.47; found: C 67.28, H 9.48.

(1S*, 2S*, 6R*, 10R*)-2-Acetoxy-1-acetoxymethyl-10-hydroxymethyl-5,5-dimethylbicyclo[4.4.0]decane (25).

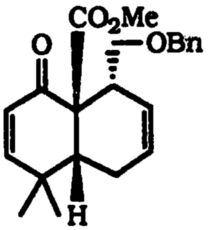


A solution of diacetate **24** (1.62 g, 5 mmol) and *B*-Br-9-BBN (1 M, 5 mL, 5 mmol) in dichloromethane (50 mL) was stirred at room temperature for 24 h. The resulting mixture was washed with a 2% aqueous solution of NaOH (10 mL) and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated.. The residue was purified through a short column of silica gel to give alcohol **25** (1.38 g, 85%): mp 117-118°C (hexane); ir ($CHCl_3$ cast) 3450 (OH) and 1738 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 4.72 (br s, 1H, -C**H**OAc), 4.28 (d, *J* = 12 Hz, 1H, -C**H**HOAc), 4.10 (d, *J* = 12 Hz, 1H, -CH**H**OAc), 3.85 (dd, *J* = 11 Hz, *J'* = 3.5 Hz, 1H, -C**H**HOH), 3.32 (dd, *J* = 11, *J'* = 7 Hz, 1H, -CH**H**OH), 2.12 (s, 3H, C**H**$_3$CO$_2$-), 2.08 (s, 3H, C**H**$_3$CO$_2$-), 1.08 and 0.95 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 170.90 (p), 169.65 (p), 72.46 (a), 66.24 (p), 63.29 (p), 43.92 (a), 43.36 (a), 41.96 (p), 33.20 (p), 32.88 (a), 30.06 (a), 29.37 (p), 27.58 (p), 26.08 (p), 25.46 (p), 24.26 (p), 21.59 (a) and 20.82 (a); hrms m/z 206.1678 (M^+-2 x AcOH, calcd. for $C_{14}H_{22}O_1$: 206.1671). Anal. Calcd. for $C_{18}H_{30}O_5$: C 66.23, H 9.26; found: C 66.61, H 8.94.

5-Benzyloxy-1,3-pentadiene (26).

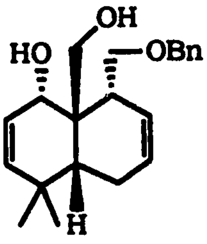
To a suspension of NaH (80% in oil, 3.6 g, 0.12 mmol) in tetrahydrofuran (50 mL) at 0°C was added dropwise a solution of 2,4-pentadien-1-ol (8.2 g, 0.1 mol) in tetrahydrofuran (50 mL) followed by benzyl bromide (17.1 g, 0.1 mol) in tetrahydrofuran (50 mL). The reaction mixture was stirred at room temperature for 24 h and then cooled to 0°C. The excess of NaH was destroyed with water (20 mL) and the mixture was extracted with dichloromethane (4 x 50 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated to leave diene **26** (10.79 g, 62%): ir ($CHCl_3$ cast) 1960 (C=C), 1099 cm^{-1} (C-O-C); ^1H nmr (300 MHz, $CDCl_3$) δ 7.30 (m, 5H, aromatic **H**), 6.40-6.20 (m, 2H, =C**H**-C**H**=), 5.80 (m, 1H, =C**H**CH_2OBn), 5.22 (dd, *J* = 16, *J'* = 2 Hz, 1H, **H**HC=), 4.50 (s, 2H, -OC**H**$_2$Ph), 4.50 (d, *J* = 6 Hz, 2H, -C**H**$_2$O-).

(1R*, 6R*, 10R*)-10-Benzyloxymethyl-1-carbomethoxy-5,5-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (28).



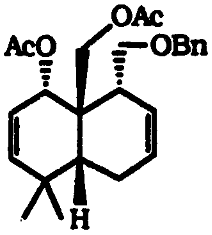
A solution of enone ester **27** (1.8 g, 1 mmol), diene **26** (1.74 g, 1 mmol) and zinc chloride (1.36 g, 1 mmol) in dichloromethane (100 mL) was stirred vigorously at room temperature for 2 days. At the end of this time the solution was washed with water. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to give adduct **28** (2.51 g, 71%): ir ($CHCl_3$ cast) 1726 (C=O, ester) and 1688 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, CDCl$_3$) δ 7.22-7.36 (m, 5H, aromatic **H**), 6.26 (dd, *J* = 10, *J*′ = 2.5 Hz, 1H, -C**H**=CHCO), 5.88 (d, *J* = 10 Hz, 1H, =C**H**CO-), 5.72 (ddd, *J* = 10, *J*′ = 5, *J*″ = 2 Hz, 1H, -C**H**=CH-), 5.55 (m, 1H, -CH=C**H**-), 4.48 (s, 2H, -OC**H**$_2$Ph), 3.95 (dd, *J* = 10, *J*′ = 8.5 Hz, 1H, -C**H**HOBn), 3.66 (dd, *J* = 10, *J*′ = 5 Hz, -CH**H**OBn), 3.55 (s, 3H, -OC**H**$_3$), 1.15 and 1.10 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 196.01 (p), 174.47 (p), 152.63 (a), 138.53 (p), 128.26 (a), 127.76 (a), 127.45 (a), 126.82, (a) 126.75 (a), 124.02 (a), 72.84 (p), 71.51 (p), 58.49 (p), 52.17 (a), 47.22 (a), 44.29 (a), 37.29 (p), 27.91 (a) and 27.60 (p); hrms M$^+$ 354.1842 (calcd. for $C_{22}H_{26}O_4$: 354.1831).

(1S*, 2S*, 6R*, 10R*)-10-Benzyloxymethyl-1-hydroxymethyl-5,5-dimethylbicyclo[4.4.0]deca-3,8-dien-2-ol (29).



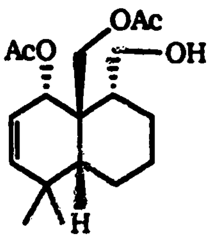
Lithium aluminium hydride (0.42 g, 11.35 mmol) was added to a solution of adduct **28** (2.00 g, 5.65 mmol) in ether (50 mL) at 0°C. The reaction mixture was warmed to room temperature. After 24 h, it was cooled to 0°C and a 10 % aqueous solution of H_2SO_4 (10 mL) was added. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (30 % ethyl acetate in hexane) to give alcohol **29** (1.2 g, 65%) as a white solid: mp 90-91°C (ethyl acetate and hexane); ir (CHCl$_3$ cast) 3390 cm^{-1} (OH); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.35 (m, 5H, aromatic **H**), 5.78-5.28 (m, 4H, vinylic **H**), 4.50 (d, J = 11 Hz, 1H, -OC**H**HPh), 4.40 (d, J = 11 Hz, 1H, -OCH**H**Ph), 4.08 (d, J = 10 Hz, 1H, -C**H**HOH), 3.78 (dd, J = J' = 9 Hz, 1H, -CH**H**OBn), 3.47 (d, J = 10 Hz, 1H, -CH**H**OH), 3.42 (dd, J = 9, J' = 2 Hz, -C**H**HOBn), 1.00 and 0.88 (each s, 3H each, *gem*-dimethyl); cims [M+H]$^+$ 329 (calcd. for $C_{21}H_{29}O_3$: 329). Anal. Calcd. for $C_{21}H_{28}O_3$: C 76.79, H 8.59; found: C 77.03, H 8.29.

(1S*, 2S*, 6R*, 10R*)-2-Acetoxy-1-acetoxymethyl-10-benzyloxymethyl-5,5-dimethylbicyclo[4.4.0]deca-3,8-diene (30).



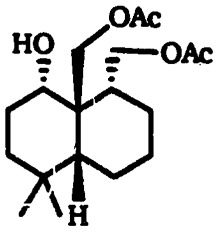
A tetrahydrofuran (50 mL) solution of alcohol **29** (1.0 g, 3.05 mmol), pyridine (5 mL), DMAP (30 mg) and acetic anhydride (2 mL, 21 mmol) was stirred in the dark at room temperature for 24 h. The resulting solution was poured into cooled 10% aqueous HCl (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated to leave a colorless syrup of diacetate **30** (1.26 g, 100%): ir (CHCl$_3$ cast) 1734 cm^{-1} (C=O, esters); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.34 (m, 5H, aromatic **H**), 5.90 (m, 1H, -C**H**=CH-), 5.72 (m, 1H, -CH=C**H**-), 5.43-5.50 (m, 3H, vinylic and -C**H**OAc), 4.48 (s, 2H, -OC**H**$_2$Ph), 3.96 (s, 2H, -C**H**$_2$OAc), 3.69 (dd, *J* = 9, *J'* = 4 Hz, 1H, -C**H**HOBn), 3.45 (dd, *J* = 11, *J'* = 9 Hz, 1H, -CH**H**OBn), 2.05 (s, 3H, C**H**$_3$CO$_2$-), 1.98 (s, 3H, C**H**$_3$CO$_2$-), 1.03 and 0.96 (each s, 3H each, *gem*-dimethyl); hrms M$^+$ 412.2255 (calcd. for C$_{25}$H$_{32}$O$_5$: 412.2249).

(1S*, 2S*, 6R*, 10R*)-2-Acetoxy-1-acetoxymethyl-10-hydroxymethyl-5,5-dimethylbicyclo[4.4.0]dec-3-ene (31).



A mixture of diacetate **30** (120 mg, 0.29 mmol) and 10 % Pd-C (30 mg) in ethyl acetate and hexane (1:1, 50 mL) was hydrogenated (50 p.s.i. of hydrogen) for 3 h. The catalyst was removed by filtration through celite and the filtrate was concentrated to afford alcohol **31** (94 mg, 100%): ir (CHCl$_3$ cast) 3400 (OH) and 1740 cm^{-1} (C=O, ester); ^{1}H nmr (300 MHz, CDCl$_3$) δ 5.67 (dd, *J* = 10, *J'* = 5 Hz, 1H, -CH=C**H**CHOAc), 5.53 (d, *J* = 10 Hz, 1H, -C**H**=CHCHOAc), 4.85 (d, *J* = 5 Hz, 1H, -C**H**OAc), 4.30 (d, *J* = 12 Hz, 1H, -C**H**HOAc), 3.87 (dd, *J* = 11, *J'* = 3.5 Hz, 1H, -CH**H**OH), 3.85 (d, *J* = 12 Hz, 1H, -CH**H**OAc), 3.38 (dd, *J* = 11, *J'* = 7 Hz, 1H, -C**H**HOH), 2.15 (s, 3H, CH_3CO_2-), 2.05 (s, 3H, CH_3CO_2-), 1.08 and 1.02 (each s, 3H each, *gem*-dimethyl); hrms m/z 264.1723 (M^+-AcOH, calcd. for $C_{16}H_{24}O_3$: 264.1725). Anal. Calcd. for $C_{18}H_{28}O_5$: C 66.64, H 8.70; found: C 66.83, H 8.73.

(1S*, 2S*, 6R*, 10R*)-1,10-Bis(acetoxymethyl)-2-hydroxy-5,5-dimethylbicyclo[4.4.0]decane (32) and (1S*, 2S*, 6R*, 10R*)-2-Acetoxy-10-acetoxymethyl-1-hydroxymethyl-5,5-dimethylbicyclo[4.4.0]decane (33).



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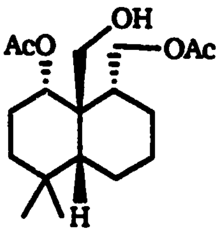
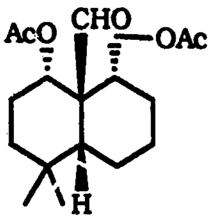


33

A mixture of alcohol **31** (150 mg, 0.465 mmol) and Adams catalyst (30 mg) in ethyl acetate and hexane (1:1, 100 mL) was hydrogenated (50 p.s.i. of hydrogen) for 48 h. The catalyst was removed by filtration through celite and the filtrate was concentrated. Flash chromatography on silica gel afforded alcohol **32** (20 mg, 12%): ir ($CHCl_3$ cast) 3520 (OH) and 1740 cm^{-1} (C=O, esters); ^{1}H nmr (300 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 11, *J'* = 4 Hz, 1H, -C**H**HOAc), 4.24 (dd, *J* = 10 *J'* = 7 Hz, 1H, -CH**H**OAc), 4.12 (d,

J = 12 Hz, 1H, -CHHOAc), 4.03 (d, J = 12 Hz, 1H, -CHHOAc), 3.68 (br s, 1H, -CHOH), 2.10 (s, 3H, CH_3CO_2-), 2.05 (s, 3H, CH_3CO_2-), 1.04 and 0.95 (each s, 3H each, *gem*-dimethyl); hrms m/z 266.11879 (M$^+$-AcOH, calcd. for $C_{16}H_{26}O_3$: 266.1882). Further elution gave alcohol **33** (80 mg, 53%): ir ($CHCl_3$ cast) 3500 (OH) and 1736 cm^{-1} (C=O, esters); ^{1}H nmr (300 MHz, $CDCl_3$) δ 4.68 (br s, 1H, -CHOAc), 4.52 (dd, J = 11, J' = 3 Hz, 1H, -CHHOAc), 3.76 (d, J = 12 Hz, 1H, -CHHOH), 3.70 (d, J = 12 Hz, 1H, -CHHOH), 3.65 (dd, J = 11, J' = 8 Hz, 1H, -CHHOAc), 2.10 (s, 3H, CH_3CO_2-), 2.04 (s, 3H, CH_3CO_2-), 1.19 and 0.98 (each s, 3H each, *gem*-dimethyl); hrms m/z 206.1668 (M$^+$-2 x AcOH, calcd. for $C_{14}H_{22}O$: 206.1670).

(1S*, 2S*, 6R*, 10R*)-2-Acetoxy-10-acetoxymethyl-1-formyl-5,5-dimethylbicyclo[4.4.0]decane (34).



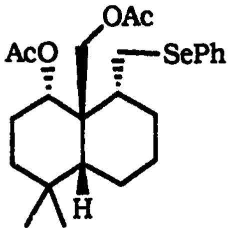
A solution of alcohol **33** (20 mg, 0.06 mmol) and PCC (100 mg, 0.46 mmol) in dichloromethane (20 mL) was stirred at room temperature. After 24 h, the reaction mixture was filtered through a short column of silica gel to give, after concentration, aldehyde **34** (15 mg, 77%): ir ($CHCl_3$ cast) 1733 (C=O, esters) and 1713 cm^{-1} (C=O, aldehyde); ^{1}H nmr (300 MHz, $CDCl_3$) δ 9.30

(s, 1H, -CHO), 5.40 (br s, 1H, -CHOAc), 3.92 (dd, $J = 12$, $J' = 5$ Hz, -CH**H**OAc), 3.78 (dd, $J = 12$, $J' = 7$ Hz, -CH**H**OAc), 2.12 (s, 3H, CH_3CO_2-), 2.00 (s, 3H, CH_3CO_2-), 0.98 and 0.82 (each s, 3H each, *gem*-dimethyl); hrms m/z 176.1564 (M^+-AcOH-CH_2O, calcd. for $C_{13}H_{20}$: 176.1565); cims $[M+H]^+$ 325.

Saturated alcohol 25 from unsaturated alcohol 31.

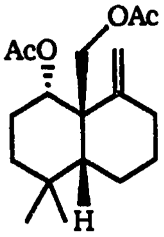
A mixture of alcohol **31** (0.5 g, 1.55 mmol) and platinum oxide (50 mg) in ethyl acetate and hexane (1:1, 100 ml) was hydrogenated (50 p.s.i. of hydrogen) for 2 h. The catalyst was removed by filtration through celite and the filtrate was concentrated to afford alcohol **25** (492 mg, 97%) as a white solid.

(1S*, 2S*, 6R*, 10R*)-2-Acetoxy-1-acetoxymethyl-5,5-dimethyl-10-phenylselenomethylbicyclo[4.4.0]decane (35).



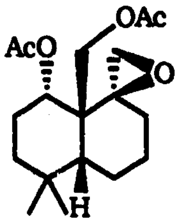
Alcohol **25** (326 mg, 1 mmol), tri-*n*-butylphosphine (0.51 g, 2 mmol) and *N*-(phenylseleno)phthalimide (0.61 g, 2 mmol) were dissolved in degassed tetrahydrofuran (50 mL). After stirring at room temperature for 1.5 h, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to give selenide **35** (450 mg, 94%): ir ($CHCl_3$ cast) 1737 cm^{-1} (C=O, esters); ^1H nmr (300 MHz, $CDCl_3$) δ 7.45 (m, 2H, aromatic **H**), 7.21 (m, 3H, aromatic **H**), 4.83 (dd, $J = J' =$ 2 Hz, 1H, -C**H**OAc), 4.05 (d, J = 12 Hz, 1H, -C**H**HOAc), 3.81 (d, J = 12 Hz, 1H, -CH**H**OAc), 3.26 (dd, J = 12, J' = 1.5 Hz, 1H, -C**H**HSePh), 2.33 (t, J = 12 Hz, 1H, -CH**H**SePh), 0.99 and 0.93 (each s, 3H each, *gem*-dimethyl); cims M^+ 466 (calcd. for $C_{24}H_{34}O_4Se$: 466). Anal. Calcd. for $C_{24}H_{34}O_4Se$: C 61.93, H 7.36; found: C 61.86, H 7.35.

(1S*, 2S*, 6R*)-2-Acetoxy-1-acetoxymethyl-5,5-dimethyl-10-methylenebicyclo[4.4.0]decane (36).



To a solution of selenide **35** (300 mg, 0.65 mmol) in dichloromethane (20 mL) at 0°C was added MCPBA (264 mg, 1.3 mmol). After 2 h at room temperature, the solution was washed with a saturated aqueous solution of Na_2CO_3. The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated and the residue was dissolved in carbon tetrachloride (20 mL) containing a few drops of diethylamine. The resulting mixture was refluxed for 30 min and concentrated. The residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexane) to afford diacetate **36** (178 mg, 88%): ir ($CHCl_3$ cast) 1741 (C=O, esters), 1630 cm^{-1} (C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.32 (dd, $J = J' = 1.5$ Hz, 1H, =C**H**H), 5.06 (dd, $J = J' = 1.5$ Hz, 1H, =CH**H**), 4.95 (dd, $J = 12$, $J' = 4$ Hz, 1H, -C**H**OAc), 4.38 (d, $J = 11$ Hz, 1H, -C**H**HOAc), 4.02 (d, $J = 11$ Hz, 1H, -CH**H**OAc), 2.05 (s, 3H, C**H**$_3$COO-), 2.03 (s, 3H, C**H**$_3$COO-), 1.08 and 0.97 (each s, 3H each, *gem*-dimethyl); hrms m/z 248.1773 (M$^+$-AcOH, calcd. for $C_{16}H_{24}O_2$: 248.1776); cims [M+NH$_4$]$^+$ 326.

(1S*, 2S*, 6R*, 10S*)-2-Acetoxy-1-acetoxymethyl-5,5-dimethylbicyclo[4.4.0]decane-10-spiro-2'-oxirane (5).



A solution of diacetate **36** (200 mg, 0.65 mmol) and MCPBA (160 mg, 0.8 mmol) in dichloromethane (20 mL) was stirred at room temperature. After 8 h, the resulting solution was washed with saturated aqueous Na_2CO_3. The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated and the residue purified by flash chromatography on silica gel (15% ethyl acetate in hexane) to afford cis-epoxy diacetate **5** (180 mg, 85%) as a white solid mp 65-66°C (petroleum ether): ir ($CHCl_3$ cast) 1740 cm^{-1} (C=O, esters); ^{1}H nmr (300 MHz, $CDCl_3$) δ 4.88 (dd, J = 8.5, J' = 4.5 Hz, 1H, -CHOAc), 4.29 (d, J = 12 Hz, 1H, -CHHOAc), 4.03 (d, J = 12 Hz, 1H, -CHHOAc), 3.19 (d, J = 4.5 Hz , 1H, -CHHO-), 2.51 (d, J = 4.5 Hz, 1H, -CHHO-), 2.09 (s, 3H, CH_3COO-), 2.05 (s, 3H, CH_3COO-), 1.09 and 1.04 (each s, 3H each, *gem*-dimethyl); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 170.67 (p), 170.11 (p), 72.66 (a), 62.74 (p), 58.49 (p), 52.73 (p), 43.69 (a), 43.62 (p), 37.10 (p), 33.74 (p), 33.59 (p), 31.48 (a), 28.48 (a), 25.09 (p), 22.61 (p), 21.79 (p), 21.30 (a) and 20.95 (a); hrms 264.1729 (M$^+$-AcOH, calcd. for $C_{16}H_{24}O_3$: 264.1726); cims [M+NH4]$^+$ 342. Anal. Calcd. for $C_{18}H_{28}O_5$: C 66.63, H 8.70; found: C 66.85, H 8.72.

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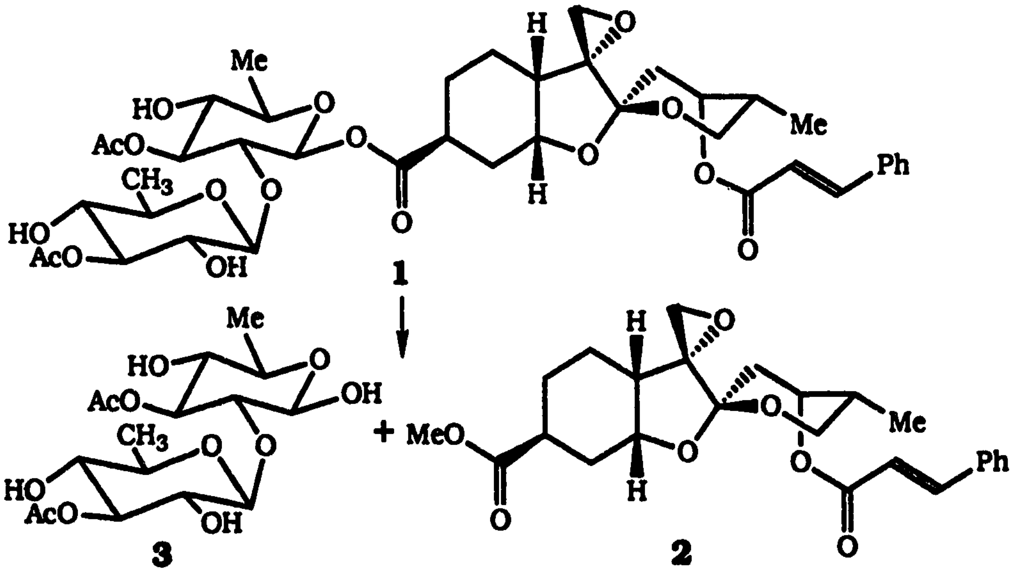
CHAPTER 4

SYNTHETIC STUDIES ON PHYLLANTHOCIN

Introduction

The *Phyllanthus* genus (Euphorbiaceae) is very common in tropical areas in Central America. Several plants from this group have a history of human medicinal usage, including the primitive medical treatment of cancer.[1] In the course of their search for tumor inhibitor agents of plant origin, Kupchan and colleagues found that the ethanol extract of the root of *Phyllanthus acuminatus* Vahl showed significant activity against P388 lymphocytic leukemia in mice. These interesting pharmacological properties were traced to a novel sesquiterpene bisabolane glycoside, (+)-phyllanthoside (**1**). Selective methanolysis of phyllanthoside (**1**) yielded the corresponding aglycone methyl ester (+)-phyllanthocin (**2**) and the disaccharide moiety, phyllanthose (**3**) as shown in Scheme 4-I.[2]

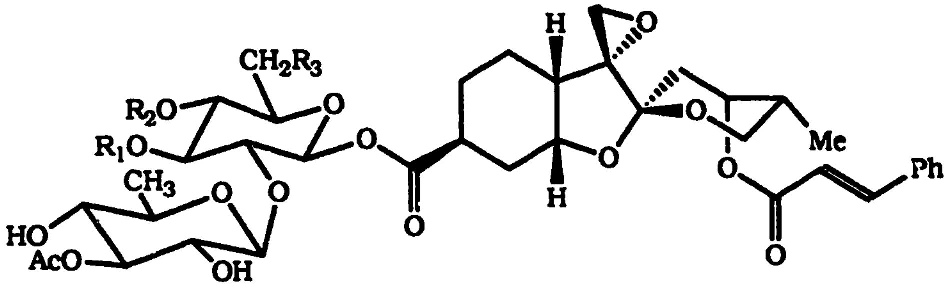
Scheme 4-I



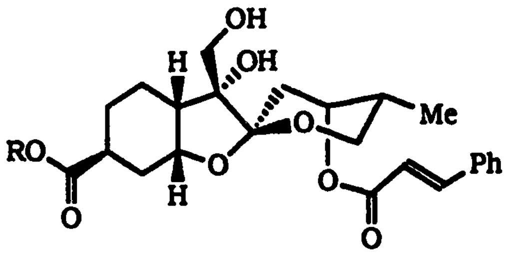
Although the structure of the aglycone moiety phyllanthocin (**2**) was secured *via* single X-ray analysis,[2] the exact structure of the sugar moiety, phyllanthose (**3**), and the absolute configuration of phyllanthoside and phyllanthocin remained unknown until 1982, when Collum reported the first total synthesis of phyllanthocin.[3] The exact structure of phyllanthose was achieved based on detailed interpretation of its spectroscopic data and X-ray crystallographic studies.[4,5] In subsequent explorations Pettit and coworkers reported the isolation and characterization of a group of antineoplastic glycosides, closely related in structure to phyllanthoside (**1**), namely, phyllanthostatin 1(**4**),[6] phyllanthostatin 2 (**5**)[1] and phyllanthostatin 3 (**6**).[1] Phyllanthoside and phyllanthostatins 1 and 2 were all found to possess the same aglycone moiety, differing only in the position of the acetate unit in the disaccharide portion of the molecule. On the other hand, phyllanthostatin 3 possesses a different aglycone unit, with a disaccharide unit identical to that found in phyllanthoside. Methanolysis of phyllanthostatin 3 yielded phyllanthocindiol (**7**). The structures are shown in Scheme 4-II.

Medicinal interest in these glycosides stems principally from the discovery that phyllanthoside (**1**) and phyllanthostatin 1 (**4**) are potent inhibitors of several NCI (National Cancer Institute) tumor cell lines, including human breast cancer. The biological

Scheme 4-II



	R1	R2	R3
phyllanthoside (1)	Ac	H	H
phyllanthostatin 1 (4)	H	Ac	H
phyllanthostatin 2 (5)	Ac	H	OH

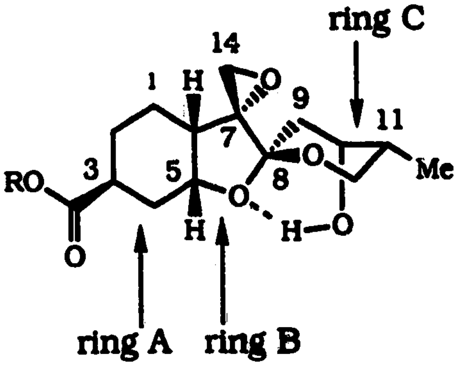


phyllantostatin 3 (6) R as in phyllanthoside

phyllanthocindiol (7) R = CH_3

activity, in combination with their challenging structure, makes these glycosides attractive synthetic molecules. Although the aglycone moiety, phyllanthocin (**2**), retains none of the biological activity of phyllanthoside, it has attracted considerable synthetic effort inspired by the spiroketal architecture.

Upon inspection of the phyllanthocin skeleton one can easily visualize several structural features. Seven asymmetric centers are distributed about the tetracyclic skeleton. All the carbon atoms of the tetrahydrofuran ring (ring B) are stereogenic centers. Ring B has two spiro fusions (spiroepoxide and spiroacetal). The epoxide moiety has an *endo* oriented oxygen relative to the *cis* fused bicyclic subunit, indicating that a standard C7 olefin epoxidation strategy might not be successful, but that epoxidation *via* methylene transfer to the less hindered *exo* face of a C7 carbonyl would be more attractive. The C8 spiroacetal has the thermodynamically more stable configuration, with stabilization by anomeric effect and the equatorially oriented methyl group at C11. This arrangement places the two methylene



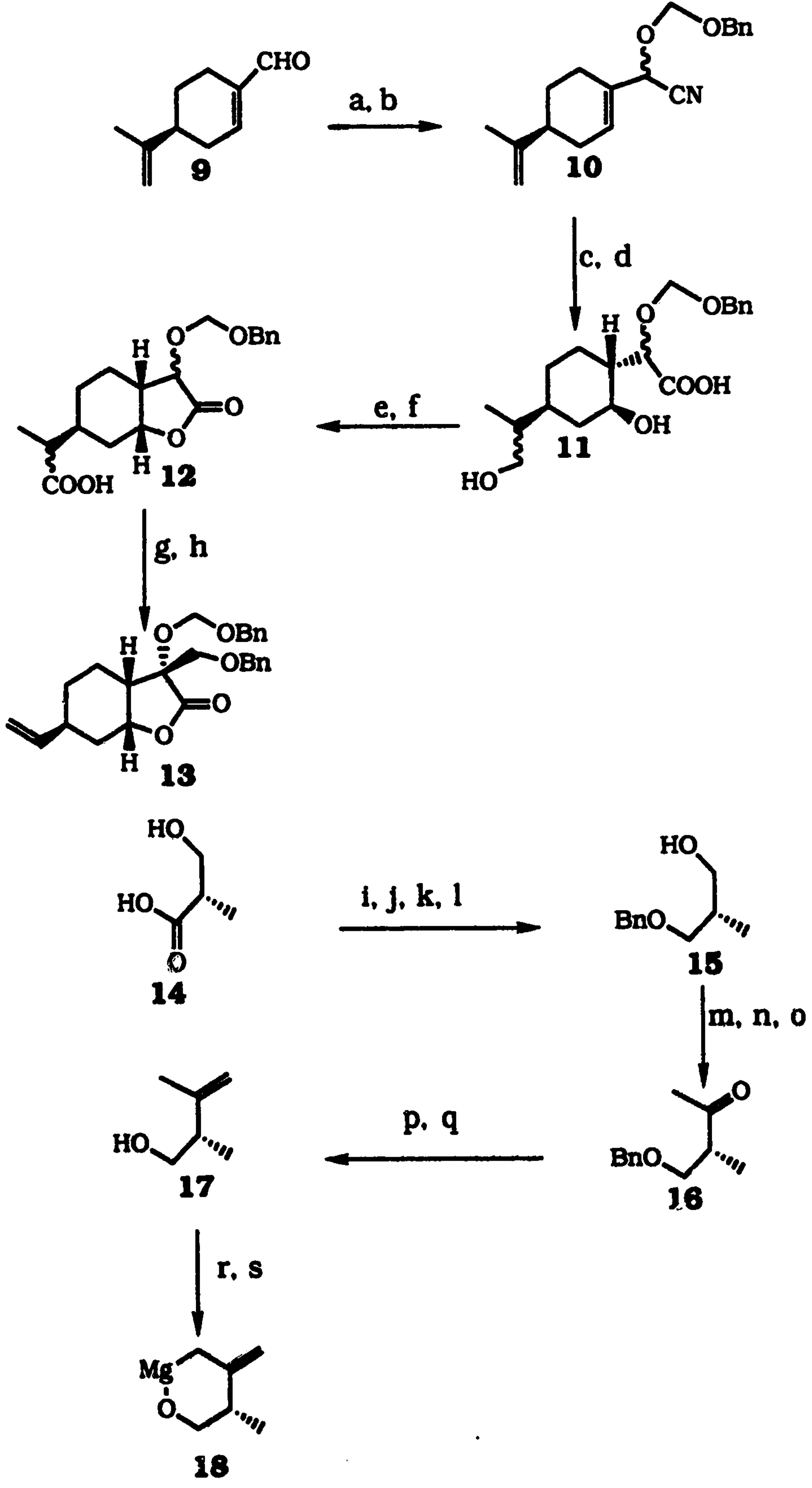
8

groups (C9 and C14) attached to ring B (tetrahydrofuran ring) *trans* to each other. It seems reasonable to assume that the spiroketal formation in this series arose from a biosynthetic precursor prior to cinnamoylation, with preference for this configuration resulting from the favorable intramolecular hydrogen bonding indicated in formula **8**.

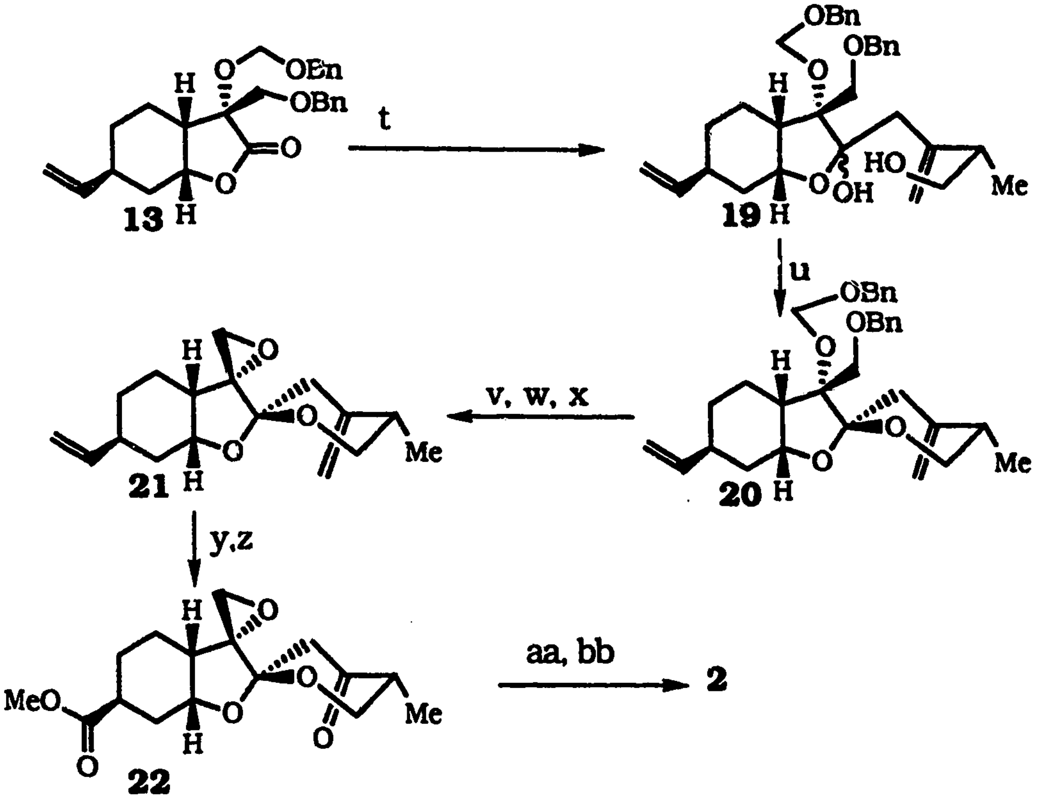
To date, six different total synthesis of phyllanthocin (**2**),[3,7-11], one of (+)-phyllanthoside (**1**)[12], (+)-phyllanthostatin 1 (**4**)[13], (+) phyllanthostatin 2 (**5**)[13] and (+)-phyllanthostatin 3 (**6**)[13] and two of (+)-phyllanthocindiol (**7**)[14,15] have been reported. These approaches proceeded through different strategies, however they shared the basic dissection of the molecule into three rings.

Collum[3] reported the first total synthesis of (+)-phyllanthocin (**2**). The details of his work are illustrated in Scheme 4-III. Starting from the optically active and commercially available (S)-(-)-perilla aldehyde (**9**), the AB bicyclic butyrolactone system was built. The isopropenyl group directed the required configuration in ring A at early stages and later it was degraded to provide the ester group at C3. Initial conversion of the aldehyde group into cyanohydrin provided the missing carbon for the AB bicyclic system to form the butyrolactone moiety and kept the proper oxidation level at C7 to form the epoxide at later stages. On the basis of Brown's stereoselective oxidative hydroboration of limonene, protected perilla aldehyde **10** was elaborated to diol **11**.

Scheme 4-III


CHO
9
a, b
OBn
O
CN
10
c, d
H
O
OBn
COOH
OH
HO
11
e, f
H
O
OBn
O
O
COOH
H
12
g, h
O
OBn
H
OBn
O
O
H
13
HO
HO
O
14
i, j, k, l
HO
BnO
15
m, n, o
O
BnO
16
p, q
HO
17
r, s
Mg
O
18

Scheme 4-III (con'd)

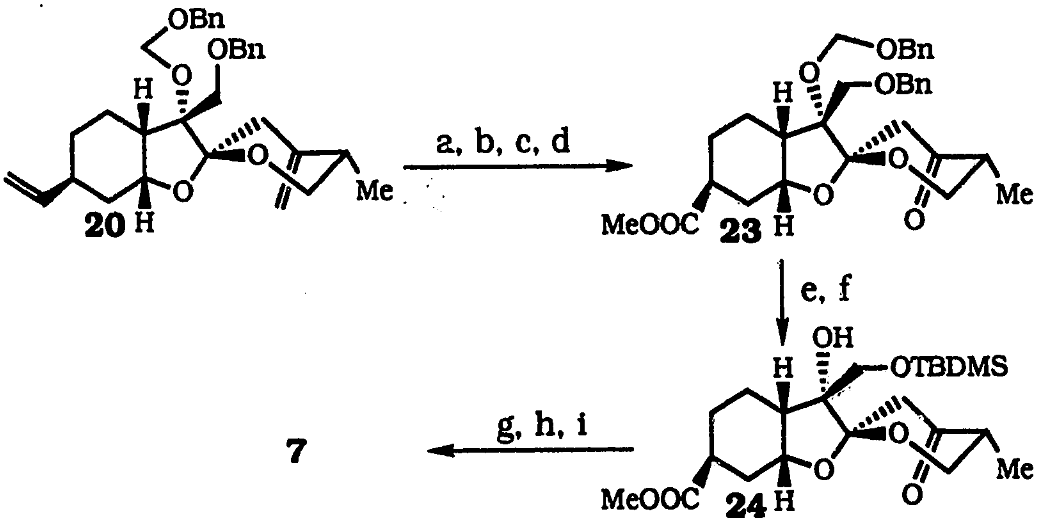


a) KCN, AcOH, Et_2O; b) $BnOCH_2Cl$, Pyr, 60°C; c) Thexylborane, then H_2O_2, AcONa, -40°C; d) KOH, EtOH, 100°C; e) $EtO_2CN{=}NCO_2Et$, PPh_3, THF, -20°C; f) CrO_3-H_2SO_4, acetone; g) $Pb(OAc)_4$, $Cu(OAc)_2$, PhH, Pyr, 80°C; h) LDA, THF, HMPA, $BnOCH_2Cl$; i) DHP, CH_2Cl_2, *p*-TsOH, 0°C; j) $LiAlH_4$, THF, 0°C; k) KH, THF, BnBr; l) *p*-TsOH, EtOH, reflux; m) CrO_3-H_2SO_4, acetone; n) $(COCl)_2$, PhH, 50°C; o) $(Me)_2CuLi$, THF, -78°C; p) Ph_3PCH_2, THF, 0°C; q) Li, NH_3, -78°C; r) *t*-BuOK, *n*-BuLi, hexane; s) $MgBr_2$, THF; t) **18**, Et_2O, 60°C; u) $ZnCl_2$, CH_2Cl_2, -20°C; v) Li, NH_3; w) MsCl, TEA; x) DBU, PhH; y) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, H_2O, CH_3CN, CCl_4; z) CH_2N_2; aa) K-Selectride, THF, 0°C; bb) *trans*-PhCH=CHCOCl, CH_2Cl_2, Pyr, DMAP.

The stereochemistry of the secondary alcohol center was corrected by phosphonium salt induced lactonization which proceeded with complete inversion of that center. The extra carbon suitably fuctionalized to form the spiroepoxide by S_N2 reaction was introduced from the *exo* face of the lactone to give butyrolactone **13**. The key intermediate **18** having all the carbons necessary for ring C was coupled to the lactone moiety to give **19**. Subsequent treatment with Lewis acid to effect the spiroketal formation provided the correct configuration at C8 in tricyclic **20**. After epoxide formation, the epoxide **21** was transformed to phyllanthocin by a series of chemical reactions including oxidative cleavage, reduction and finally cinnamoylation.

Collum[14] also reported the first total synthesis of (+)-phyllanthocindiol (**7**) following a similar reaction sequence, as illustrated in Scheme 4-IV. This synthesis established the relative and absolute configuration of the aglycone unit of this series of natural products.

Scheme 4-IV

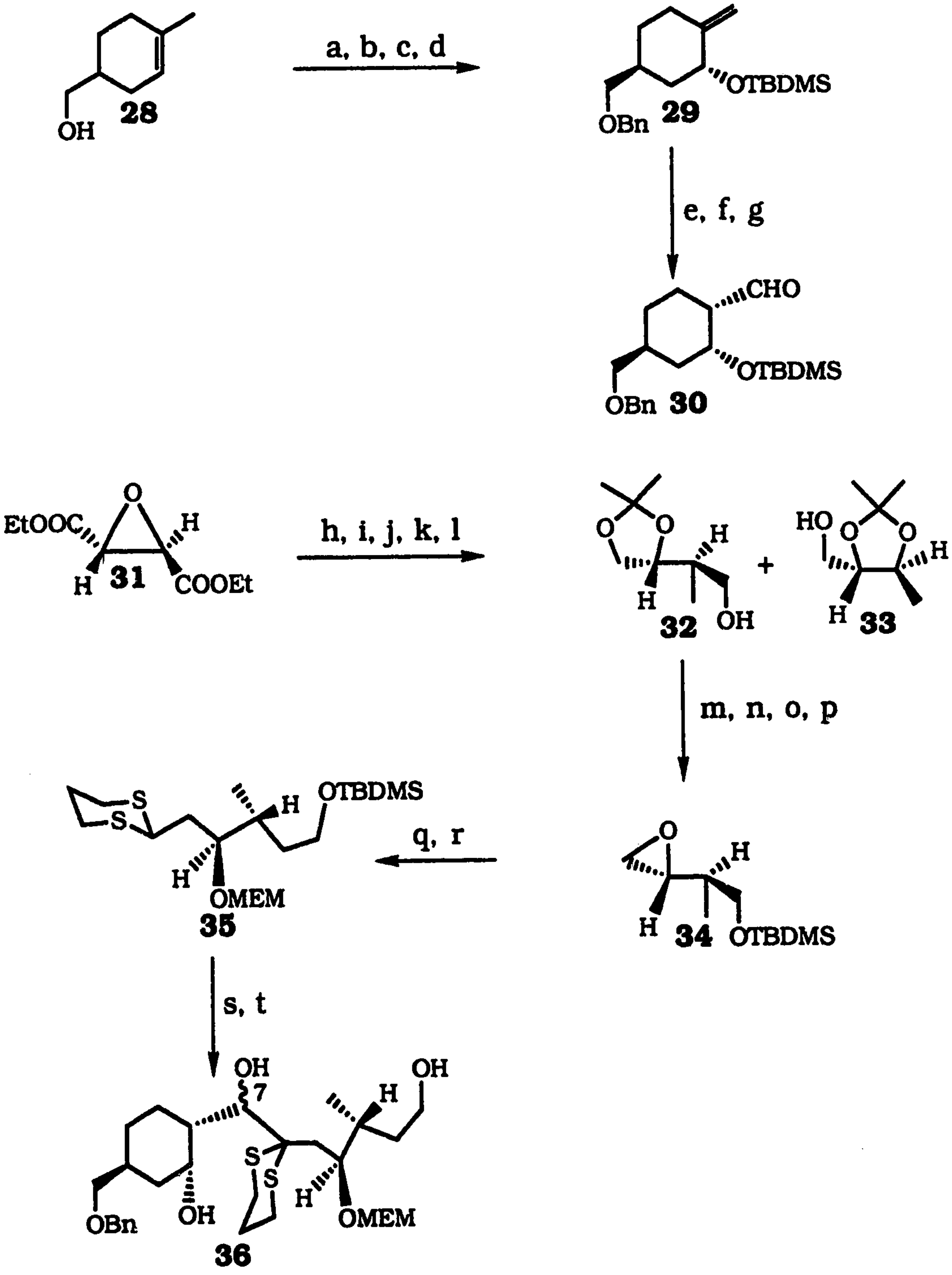


a) O_3, CH_2Cl_2, -78°C; b) Me_2S; c) CrO_3-H_2SO_4, acetone, -10°C; d) CH_2N_2, Et_2O, 0°C; e) Pd/C, H_2; f) TBDMS-Cl; f) K-Selectride, THF, 0°C, or $NaBH_4$; h) *trans*-PhCH=CHCOCl, CH_2Cl_2, DMAP; i) $(n\text{-Bu})_4NF$, THF.

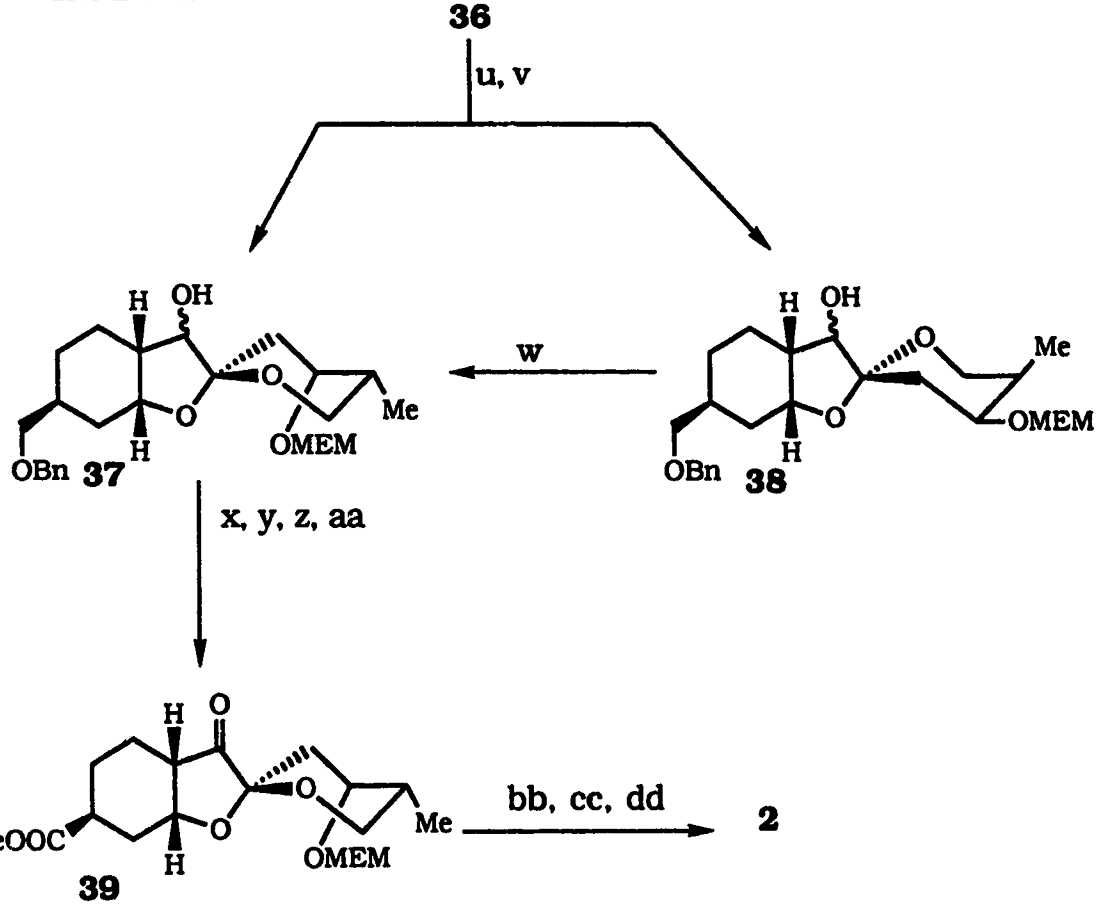
Another total synthesis of (+)-phyllanthocin (**2**) was achieved by Williams and Sit[7] *via* a highly convergent route, shown in Scheme 4-V. Their approach utilized carboxaldehyde **30** as ring A and dithiane **35** to serve as a carbanion and a latent carbonyl equivalent. Starting from natural tartaric acid, the optically active dithiane component contained all but one of the required carbon centers for rings B and C along with properly protected hydroxy groups. Coupling of the anion generated from dithiane **35** with carboxaldehyde **30** afforded adduct **36** as a diastereomeric mixture due to the alcohol center C7. The diastereomeric mixture at this center was of no consequence since this center was oxidized to the corresponding carbonyl at a later stage. After the hydroxy groups were made available for spiroketalization, hydrolysis of the dithiane moiety followed by treatment with protic acid resulted in a mixture of natural and unnatural configurations at C8. However, the unnatural isomer was converted to the desired one using Lewis acid. The spiroepoxide moiety was constructed *via* addition of methyleneoxysulfurane with selective attack from the less hindered carbonyl center in **39**. Finally routine cinnamoylation finished the synthesis of the target molecule.

A third total synthesis of (+)-phyllanthocin, outlined in Scheme 4-VI, was published by Burke and coworkers in 1985.[8,16,17] Unlike the previous two synthesis, in which the starting material possessed a six-membered ring to act as ring A,

Scheme 4-V

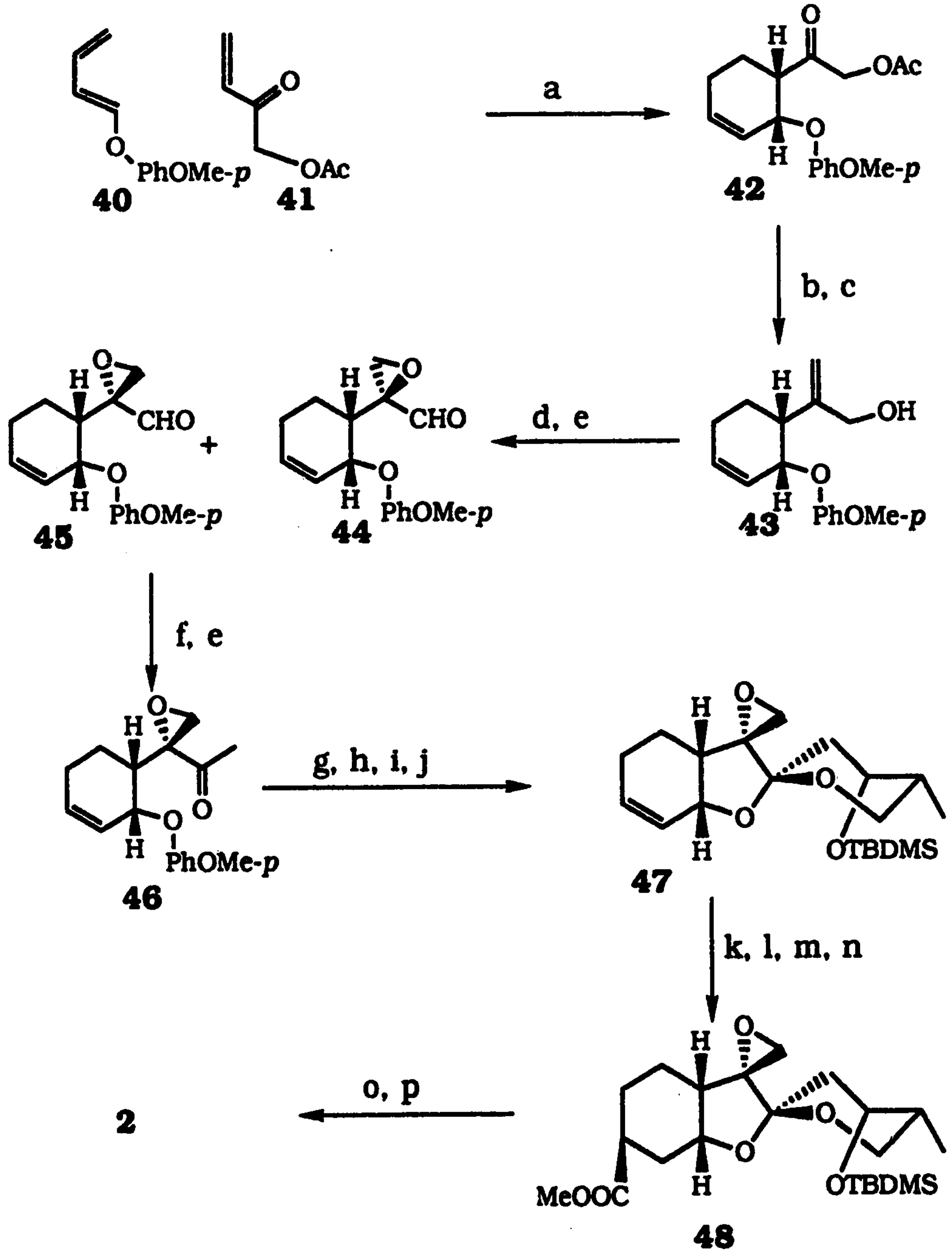

OH
28
a, b, c, d
OTBDMS
OBn
29
e, f, g
CHO
OTBDMS
OBn
30
EtOOC
O
H
H
31
COOEt
h, i, j, k, l
O
O
H
H
32
OH
+
HO
O
O
H
H
33
m, n, o, p
O
H
H
34
OTBDMS
q, r
S
S
H
OTBDMS
H
OMEM
35
s, t
OH
7
OH
H
S
S
H
OMEM
OBn
OH
36

Scheme 4-V (con'd)



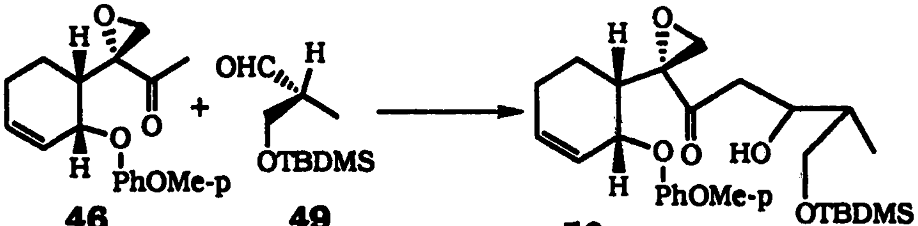
a) BnBr, NaH, THF; b) MCPBA, CH_2Cl_2; c) Lithio-2,6-dimethylpiperidine, ether, 50°C, Carius tube; d) TBDMS-Cl, DMF, DMAP; e) B_2H_6, THF, then H_2O_2; f) resolution with (-)-camphanic acid, then KOH, MeOH; g) PCC, CH_2Cl_2; h) $LiMe_2Cu$, Et_2O, -78°C; i) DHP, Et_2O, *p*-TsOH; j) $LiAlH_4$, Et_2O; k) *p*-TsOH, MeOH; l) Acetone, *p*-TsOH; m) TBDPS-Cl, DMAP, CH_2Cl_2; n) Ethanedithiol, $CHCl_3$, *p*-TsOH; o) TsCl, TEA, CH_2Cl_2; p) NaH, THF; q) 2-Lithio-1,3-dithiane, THF, -25°C; r) MEM-Cl, DMAP; s) *t*-BuLi, THF, HMPA, -78°C, then **30**; t) $(n\text{-}Bu)_4NF$, THF; u) $HgCl_2$,HgO, aq. CH_3CN; v) TFA, CH_2Cl_2; w) $Mg(O_2CCF_3)_2$, THF; x) H_2CrO_4, aq. acetone; y) H_2, Pd/C, MeOH; z) $CrO_3 \cdot H_2SO_4$; aa) CH_2N_2; bb) $ZnBr_2$, CH_2Cl_2; cc) Methyleneoxysulfurane, DMSO, THF; dd) *trans*-PhCH=CHCOCl, CH_2Cl_2, DMAP.

Scheme 4-VI



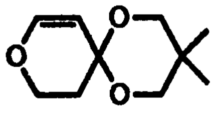
a) PhH, 75°C; b) Ph_3PCH_2, -100°C; c) K_2CO_3, MeOH; d) *t*-BuOOH, (+)-diethyl tartarate, $Ti(O\text{-}t\text{-}Bu)_4$, CH_2Cl_2, -23°C; e) Me_2SO, $(COCl)_2$, TEA, CH_2Cl_2, -60°C; f) MeLi, THF, -78°C; g) LDA, THF, then **49**; h) DDQ, CH_2Cl_2, H_2O; i) aq. HF, CH_3CN; j) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; k) 8 mol % $[(COD)RhOAc]_2$, PhH, CO, H_2, 76°C; l) NaOMe, MeOH; m) H_2CrO_4, aq. acetone; n) CH_2N_2, Et_2O; o) aq. HF, CH_3CN; p) *trans*-PhCH=CHCOCl, DMAP, CH_2Cl_2.

Burke built a functionalized cyclohexene **42** *via* a Diels-Alder reaction. This intermediate contains all the carbon centers for the AB ring system except the ester group at C3. However, the double bond was sufficient to introduce the ester group at a later stage. The adduct **42** was converted to the optically active epoxyketone **46** in four steps, including Sharpless asymmetric epoxidation which provided the optically active intermediate and the epoxide subunit. Cross aldol coupling of the enolate of the epoxyketone **46** with optically active aldehyde **49** yielded the aldol adduct **50** (Eq. 1). The establishment of the C8 spiroketal moiety was initiated after oxidative cleavage of the protected allylic alcohol and hydrolysis of the silyl protecting group using aqueous hydrofluoric acid. Catalytic hydroformylation of **47** represented a complicated problem in terms of the regioselectivity and stereochemistry of the products.

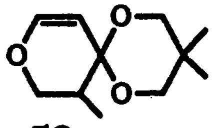


46 + **49** → **50** (1)

Smith and coworkers devoted an extensive effort towards the total synthesis of this family of natural products. Their work, summarized in Scheme 4-VII for phyllanthocin, resulted in the total synthesis of (+)-phyllanthocin **2**,[9,15] (+)-phyllanthostatin 1,[13] 2[13,18] and 3[13] (**4**, **5** and **6**) (+)-phyllanthocindiol (**7**)[15] and (+)-phyllanthocide (**1**).[12,19] Consequently, Smith and coworkers were the first to synthesize the five natural products. Smith's approach to phyllanthocin was somewhat similar to that reported by Williams. Both employed a fuctionalized cyclohexane-carboxaldehyde which served as ring A and an electrophile in the key step involving the bond formation between C7 and C8. However, Williams utilized a 1,3-dithiane derivative as the nucleophile to serve as ring C in later stages, whereas Smith derived the nucleophile from dihydropyrane **58**. Smith prepared the optically active aldehyde **53** from acyclic aldehyde **51** *via* a stereoselective intramolecular Prins reaction followed by ozonolysis. Spiroacetalization was carried out with camphorsulfonic acid. Chemoselective spiroepoxidation was achieved with dimethylsulfoxonium methylide. The introduction of the missing methyl group at C11 was somewhat troublesome under standard kinetic conditions. However, this problem was solved by employing silyl enol ether chemistry. The synthesis was completed by a series of chemical transformations including the C3 methoxycarbonyl formation, reduction of the C10 carbonyl and cinnamoylation. Recently, Smith and coworkers improved their approach by using a nucleophile **59** with the methyl group already at the appropriate center.

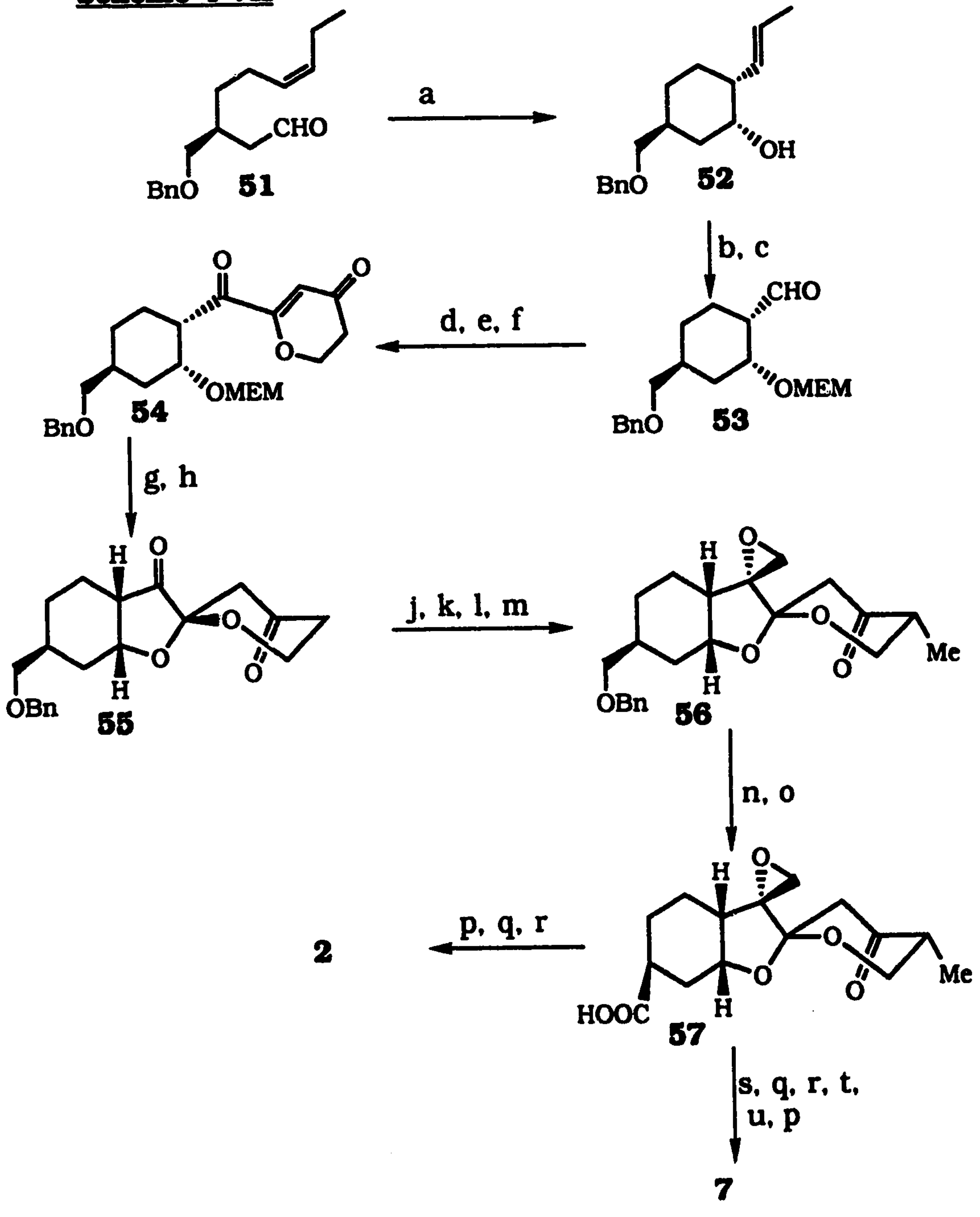


58



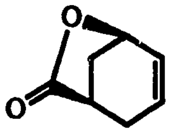
59

Scheme 4-VII

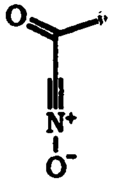


a) Me_2AlCl, CH_2Cl_2; b) MEMCl; c) O_3, -78°C, then Ph_3P; d) Lithium salt of **58**, THF, HMPA; e) H_3O^+; f) Swern oxidation, CH_2Cl_2; g) $ZnBr_2$; h) CSA, PhH; i) sodium dimethoxysulfonium methylide, DMSO, THF; j) LDA; k) TMSCl; l) n-Bu(Me)$_3$NF, -78°C, then MeI; m) DBU, THF; n) H_2, Pd/C, MeOH; o) RuO_4-$NaIO_4$, CH_3CN, CCl_4, H_2O; p) CH_2N_2; q) $NaBH_4$; r) *trans*-PhCH=CHCOCl, DMAP, Pyr; s) TMS-Cl, THF; t) *N*-methylpyrrolidine, 130°C; u) (n-Bu)$_4$NF.

Another synthesis of (+)-phyllanthocin (**2**), outlined in Scheme 4-VIII, was reported by Martin and collaborators.[10] Martin utilized an isoxazoline ring as a β-hydroxy ketone equivalent in a highly convergent synthesis. Three subunits **60**, **61** and **62**, were condensed together to provide the target molecule. The enantiomerically pure lactone **60** was derived from an asymmetric Diels-Alder reaction. The crucial [3+2] cycloaddition between **60** and **61** provided the desired addition product in modest yield. The lactone moiety in the starting material fulfilled its role as a control element, and was subsequently modified in a straightforward manner including methanolysis and deoxygenation to give **64**. The coupling process between the two subunits **64** and **62** required a chelation controlled aldol reaction that provided a mixture of *anti* and *syn* adducts. The conversion of the undesired *syn* isomer to the required *anti* isomer was achieved successfuly utilizing inversion tactics in three steps. The latent β-hydroxy ketone array required for spiroketalization resulted from liberation of the isoxazoline moiety using Raney nickel. Treatment of the reduction product



60



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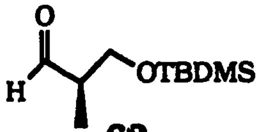
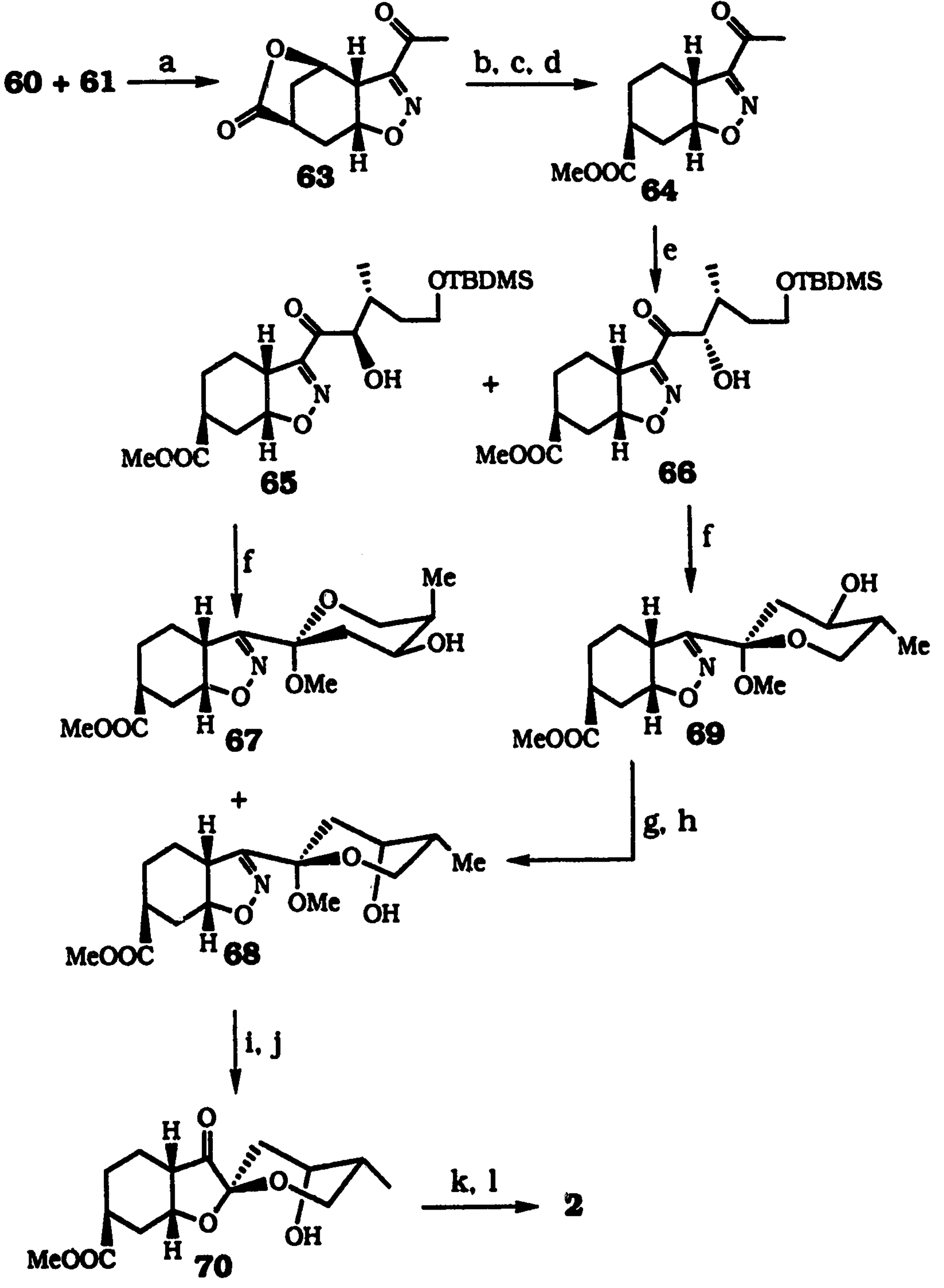


62

Scheme 4-VIII

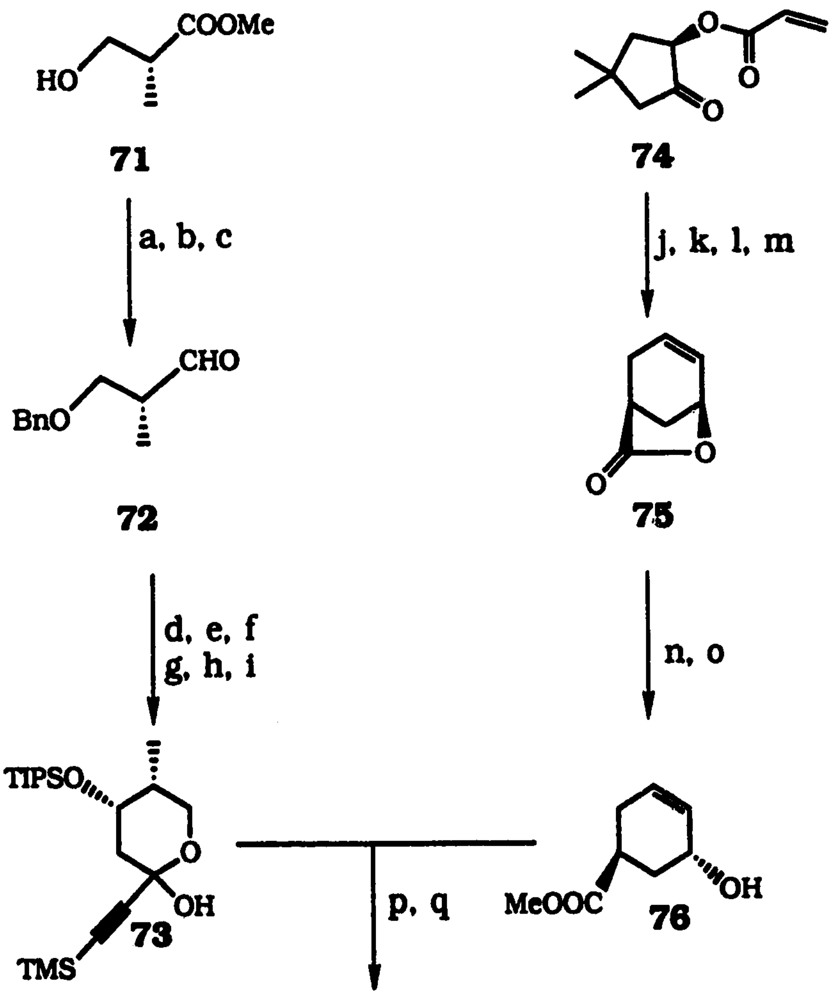


a) $PhCH_3$, reflux; b) K_2CO_3, MeOH; c) PhOSCCl, DMAP, CH_2CH_2; d) $(n\text{-}Bu)_3SnH$, cat. AIBN, PhH, reflux; e) LDA, THF, -78°C, then **62**; f) aq. HF, MeOH; g) Py-SO_3, DMSO, TEA; h) L-Selectride, THF, -78°C; i) H_2, W-2 Raney-Nickel, $B(OH)_3$, MeOH; j) CF_3SO_3H, CH_2Cl_2; k) $Me_2SO{=}CH_2$, THF, 0°C; l) *trans*-PhCH=CHCOCl, DMAP, CH_2Cl_2.

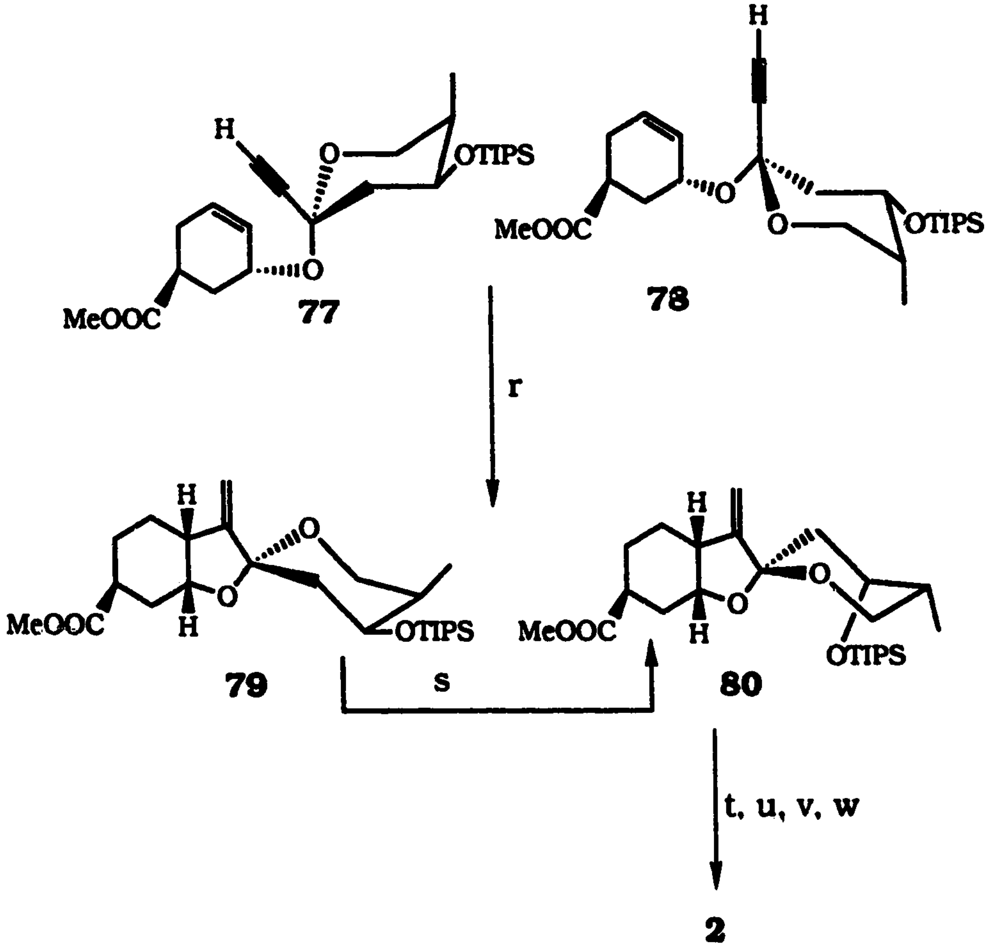
with trifluoromethanesulfonic acid effected the spiroketalization process. The synthesis of phyllanthocin was completed according to the protocol previously reported by Williams.

The most recent synthesis of phyllanthocin, summarized in Scheme 4-IX, was reported by Trost and coworkers.[11,20] Trost dismantled the target molecule into two halves, **73** and **76**. Like Martin, Trost obtained the optically active hydroxy ester **76**

Scheme 4-IX



Scheme 4-IX (con'd)

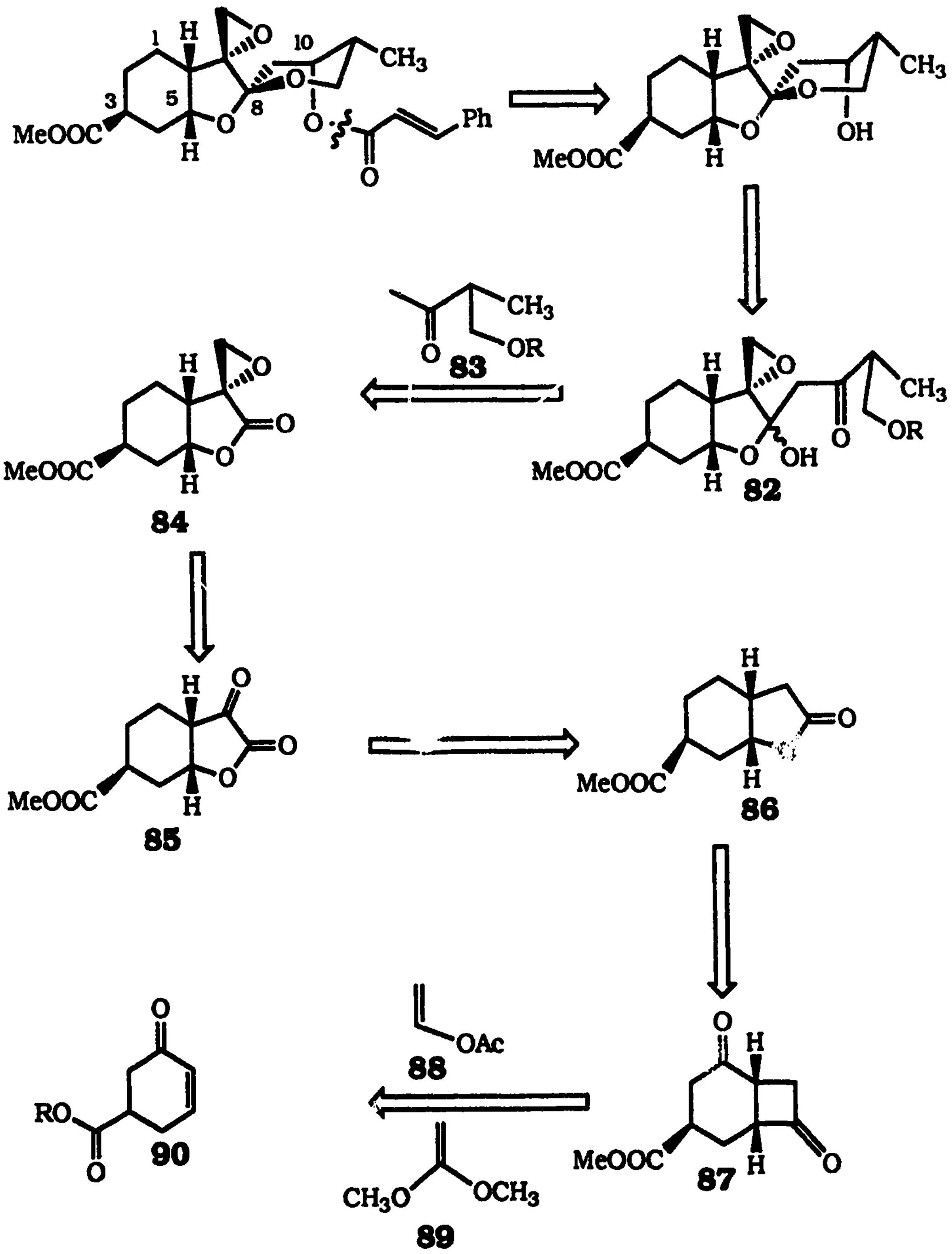


a) $PhCH_2OC(=NH)CCl_3$, CF_3SO_3H, CH_2Cl_2; b) $LiAlH_4$, THF, -30°C; c) $(COCl)_2$, DMSO, TEA, -60°C; d) $CH_2=CHCH_2TMS$, $SnCl_4$, CH_2Cl_2, -78°C; e) TIPS-OSO_2CF_3, 2,6-lutidine, CH_2Cl_2; f) $NaIO_4$, $KMnO_4$, *t*-BuOH; g) H_2, Pd/C; h) pyridinium *p*-toluenesulfonate, PhH; i) $Me_3SiC{\equiv}CLi$, THF, -78°C; j) 1,3-butadiene, $TiCl_4$, CH_2Cl_2, Et_2O; k) LiOH, THF-H_2O; l) KI, I_2, $NaHCO_3$, H_2O; m) DBU, PhH; n) Na_2CO_3, MeOH; o) dppe, DEAD, HCO_2H, TEA, THF; p) K10 montmorillonite clay; q) MeOH, K_2CO_3, r) polymethylsilanol, $[(dba)_3Pd_2CHCl_3]$, AcOH; s) $Mg(CF_3COO)_2$, CF_3COOH, CH_2Cl_2; t) HF, CH_3CN; u) O_3, CH_3OH, -78°C; v) methylsulfonium methylide; w) *trans*-PhCH=CHCOCl, DMAP, CH_2Cl_2.

via an asymmetric Diels-Alder reaction. The lactol half **73** was derived from commercially available methyl isobutyrate **71** in either enantiomeric form. After glycosidic coupling between **73** and **76** using montmorillonite clay, the products **77** and **78** were subjected to reductive cyclization to form ring B. Following the literature sequence of epoxidation and cinnamoylation the synthesis of phyllanthocin was completed.

Our approach to building the bicyclic AB ring system of the phyllanthocin skeleton differs from those reported previously. Scheme 4-X illustrates our retrosynthetic analysis. We envisioned that the construction of the tricyclic system could be achieved by aldol coupling between epoxybutyrolactone **84** and the carbanion derived from ketone **83**. In this case the protected β-hydroxy group would be part of the spiroacetal moiety. Epoxybutyrolactone **84** would be derived from ketone **85** and sulfonium ylid in order to obtain the correct stereochemistry at C7 by addition from the sterically less hindered β-face of the ketone group. Ketone **85** could be generated from butyrolactone **86** by oxidation. Butyrolactone **86**, in turn, could be synthesized by selective oxidation of diketone **87**. We envisioned the preparation of this key intermediate *via* [2+2] photocycloaddition of vinyl acetate (**88**) or 1,1-dimethoxyethene (**89**) to enone **90**,[21] which already possessed the required ester group. The details of this work, which resulted in the synthesis of the benzyl derivative of the advanced intermediate **86**, are described in this chapter.

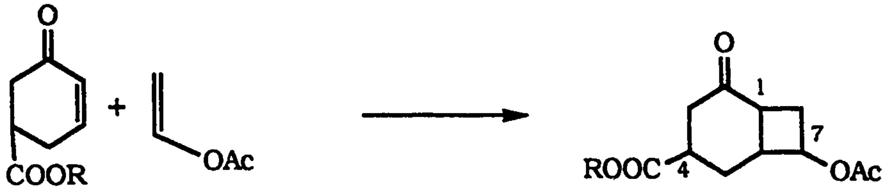
Scheme 4-X


1
3
5
8
10
H
O
CH3
MeOOC
Ph
OH
OR
83
82
84
85
86
87
88
OAc
89
CH3O
OCH3
90
RO

Results and Discussion

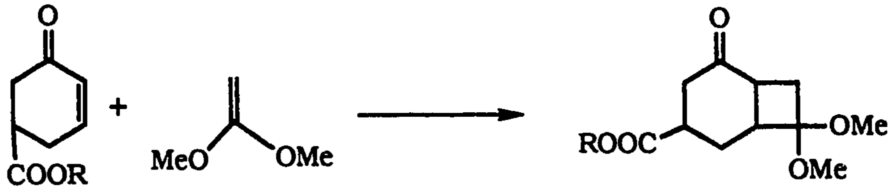
From the retrosynthetic perspective, the projected intermediate **86** is presumably available after functional group manipulation of the initially generated [2+2] photoadducts **91** and/or **92**. These adducts could be constructed by photocycloaddition of enone **90** with vinyl acetate (**88**, Eq. 2) or 1,1-dimethoxyethene (**89**, Eq. 3). Their cyclobutanone derivative, in turn, could be converted to a butyrolactone ring system after Baeyer-Villiger oxidation..

The selection of enone **90** as the precursor for ring A of phyllanthocin stemmed from the following considerations. First, ring B could be fused to the enone system *via* a [2+2]-photocycloaddition reaction. Second, the ester (or equivalent) group required for the target molecule is present. Third, this functionality hopefully would induce a desired influence on the relative stereocontrol during the photochemical reaction. Vinyl acetate and 1,1-dimethoxyethene were chosen as the counterpart in the respective [2+2] photocycloaddition reaction because they are known to add preferentially in a head-tail fashion to enones. Thus, with enone **90** they should provide adducts with an oxygenated carbon at the C7 center. Of the two olefins, the use of 1,1-dimethoxyethene was preferred, since its photoadduct **92** could be more easily converted to butyrolactone **86**. Nevertheless vinyl acetate was explored first due to its availability.



90 **88** **91**

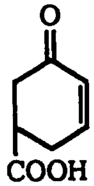
(2)



90 **89** **92**

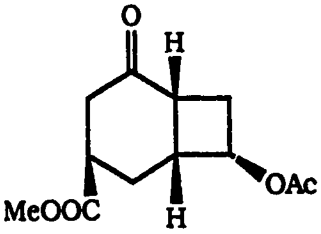
(3)

The preparation of **90** began with a Birch reduction of the commercially available *m*-anisic acid with sodium in liquid ammonia according to a documented procedure.[22] The product **93** displayed, in the ir spectrum, absorptions bands at 2900 and 1725 cm^{-1} for the acid and at 1678 cm^{-1} for the enone carbonyl. Its hrms showed the molecular ion at m/z 140.0474, in agreement with the molecular formula $C_7H_8O_3$. The ^1H nmr spectrum displayed a resonance at δ 7.00 assigned to the β-proton of the enone system. The α-proton of the enone system and the proton adjacent to the carboxy group were observed at δ 6.10 and 3.15, respectively.



93

Taking advantage of the known propensity of enones to participate efficiently in [2+2] photochemical cycloadditions,[23-25] a solution of enone acid **93** in benzene in the presence of excess vinyl acetate was irradiated for 8 h at 0°C. The crude adducts, without purification, were esterified with methyl iodide and potassium carbonate in acetone. This was followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene to give a mixture of four diastereomers. Treatment with DBU served two purposes. First, it effected complete epimerization of the *trans*-fused ring system to the more stable *cis*-fused one. Second, it eliminated those products which resulted from the head-to-head addition of vinyl acetate to the enone. The crude mixture was separated by flash chromatography into two parts. The less polar fraction consisted of a single isomer in 30% yield. The structure of this isomer was assigned to ketoester **94** based on the spectroscopic data obtained. In the ir



94

spectrum, it exhibited two carbonyl absorptions at 1730 cm^{-1} (esters) and 1710 cm^{-1} (ketone). The molecular ion was not observed in the hrms for this compound. However, a fragment at m/z 180.0784, due to the loss of acetic acid unit was observed.

The ^{1}H nmr spectrum of this compound displayed a distinctive resonance for each proton. By decoupling experiments, it was possible to achieve almost complete assignment of the spectrum. For example, irradiation of the signal at δ 2.95 (dddd) assigned for H_4, caused the partial collapse of the signals at δ 2.64 (ddd, $H_{3\alpha}$), δ 2.46 (dd, $H_{3\beta}$) and δ 1.85 (ddd, $H_{5\beta}$). The most noticeable feature of the ^{1}H nmr spectrum is the long range coupling (^{4}J) between protons. For the cyclohexane ring portion of the molecule, the signals at δ 2.64 ($H_{3\alpha}$) and 2.22 ($H_{5\alpha}$) exhibited a mutual coupling of 1.5 Hz. This type of coupling is typically observed for those protons diequatorially oriented in a "W" fashion.[26] In addition, long range four-bond couplings were observed between H_1 and H_7 (1.5 Hz) and between H_6 and $H_{8\alpha}$ (1Hz). The stereochemistry at C7 as well as the assignment of the methylene protons of the cyclobutane ring were difficult to determine from the coupling constants. The reported ranges of the vicinal coupling constants for J_{cis} and J_{trans} in cyclobutane often overlap (4.6-11.5 and 2-10.7 respectively).[27] Thus, the use of proton-proton coupling constants for the assignment of the relative stereochemistry of the protons in the cyclobutane ring is unreliable. However, a profound nuclear Overhauser effect (nOe)[28] would be expected to occur between *cis* protons. An nOe study on ketoester **94** provided evidence for the *exo* orientation of both the acetate group at C7 and the methyl ester at C4. It also provided conclusive support for the assignment of the ^{1}H nmr spectrum based on the decoupling experiments. Saturation of the signal at δ 4.75 (H_7) resulted in an enhancement of 18.5% for H_4 at δ 2.95 and 7.9% for $H_{8\alpha}$ at δ 2.60. Conversely, when the signal at δ 2.95 (H_4) was saturated, an enhancement of 17.7% was observed for H_7 at δ 4.75. These experiments indicated that the methine protons next to the esters were in close proximity and consequently established the *exo* orientation of both ester groups. Figure 4-I shows the results of the nOe experiments and Scheme 4-XI outlines diagrammatically the observed spin-spin couplings. The solid lines illustrate the three bond coupling (^3J) and the dashed lines indicate the four bond couplings (^4J). A summary of the ^1H nmr spectral data is compiled in Table 4-I.

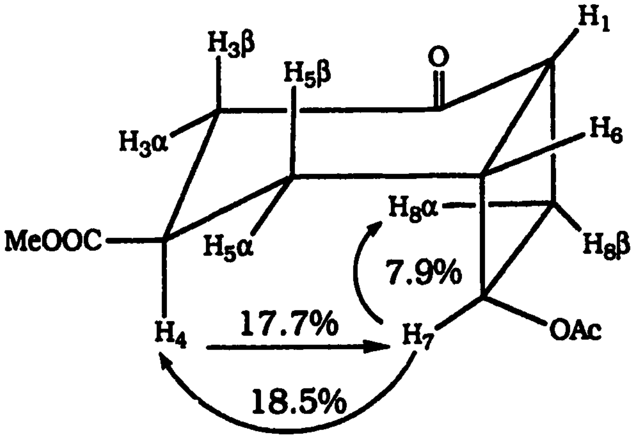
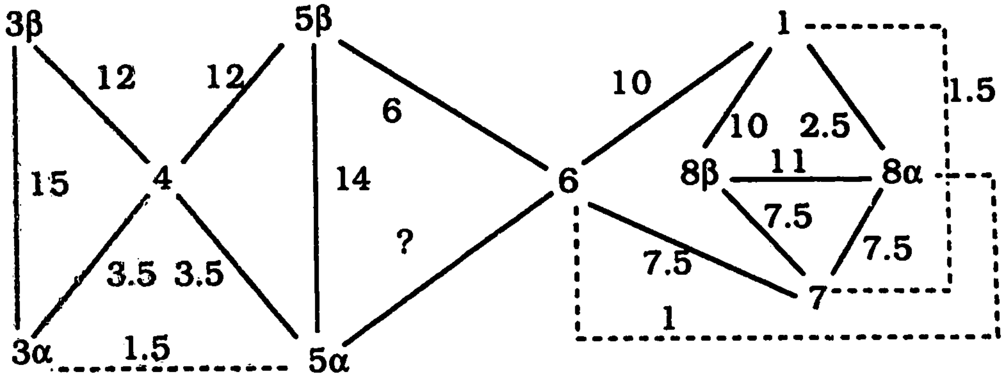


Figure 4-I. Structure of Compound **94** With nOe Results.

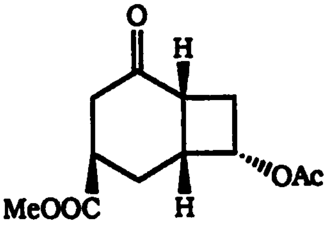


Scheme 4-XI. Spin-Spin Couplings Observed for Ketoester **94**

Table 4-I. 400 MHz ^1H nmr Data for Compound **94**.

Proton	Chemical Shift (δ)	Number of Hydrogen	Multiplicity (*J* in Hz)
H_7	4.75	1	dddd (1.5, 7.5, 7.5, 7.5)
H_6	3.07	1	m
H_4	2.95	1	dddd (3.5, 3.5, 12, 12)
H_1	2.77	1	dd (10)
$H_{3\alpha}$	2.64	1	ddd (1.5, 3.5, 15)
$H_{8\alpha}$	2.60	1	dddd (1, 2.5, 7.5, 11)
$H_{3\beta}$	2.46	1	dd (12, 15)
$H_{8\beta}$	2.22	1	ddd (7.5, 10, 11)
$H_{5\alpha}$	2.20	1	m
$H_{5\beta}$	1.85	1	ddd (6, 12, 14)

The more polar fraction consisted of three stereoisomers with a combined yield of 30%. The ir spectrum of this mixture displayed two carbonyl absorptions at 1735 cm^{-1} and 1707 cm^{-1}. The ^1H nmr spectrum exhibited only two multiplets centered at δ 5.05 and 4.65 for the methine protons next to acetates. Three methoxy singlets, however, were observed at δ 3.76-3.70 indicating the presence of the three diastereomers likely possessing structures **95**, **96** and **97**. Although diastereomer **95** was also suitable for the present work, no attempt was made to recover it. For the subsequent preliminary investigations, pure ketoester **94** was used.



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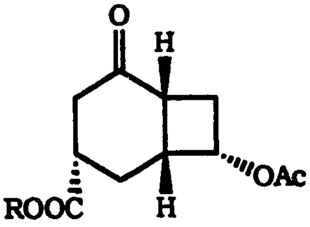

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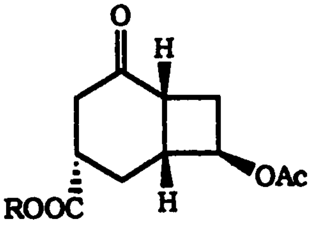
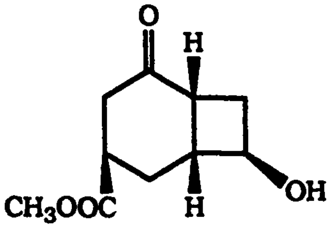


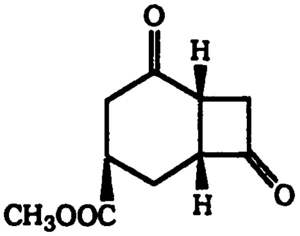
97

To introduce the C7 ketone carbonyl, ketoester **94** was treated with methanol in the presence of potassium carbonate at room temperature for 24 h. Alcohol **98** was produced in 67% yield. The ir spectrum of this compound showed absorptions at 3434 cm^{-1} for the hydroxy, 1734 cm^{-1} for the ester and 1708 cm^{-1} for the ketone. The cims using ammonia showed a $[M+NH_4]^+$ peak at m/z 216, consistent with formula $C_{10}H_{14}O_4$. The ^1H nmr spectrum displayed a multiplet at δ 3.95 for the methine proton adjacent to the hydroxy group and a strong singlet at δ 3.73 for the methoxy protons.



98

For the oxidation of the cyclobutanol moiety to cyclobutanone, initially we chose to employ activated dimethyl sulfoxide (DMSO)[29] as an oxidant. Thus, alcohol **98** was added to phenyl dichlorophosphate (PDCP) and DMSO in dichloromethane at -10°C. After 5 minutes, the reaction was allowed to warm to room temperature. The desired diketone **99** was produced but only in 18% yield. In another experiment, pyridinium dichlorochromate (PDC)[30] was used. In this case a complex mixture was formed with no detectable amount of the desired diketone. Diketone **99** displayed, in the ir spectrum, three



99

carbonyl absorptions at 1785 (cyclobutanone), 1725 (ester) and 1702 cm^{-1} (cyclohexanone). The hrms showed the molecular ion at m/z 196.0736, corresponding to the formula $C_{10}H_{12}O_4$. In

^1H nmr spectrum, the resonance of each proton was well defined. With the aid of decoupling experiments, it was possible to analyze the entire spectrum. The results are summarized in Figure 4-II, Table 4-II and Scheme 4-XII.

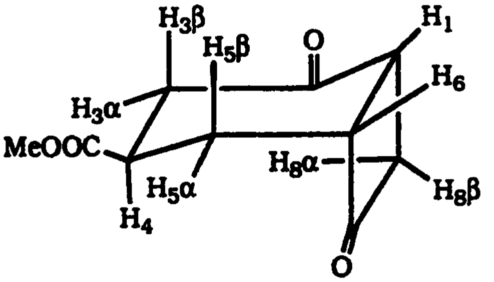
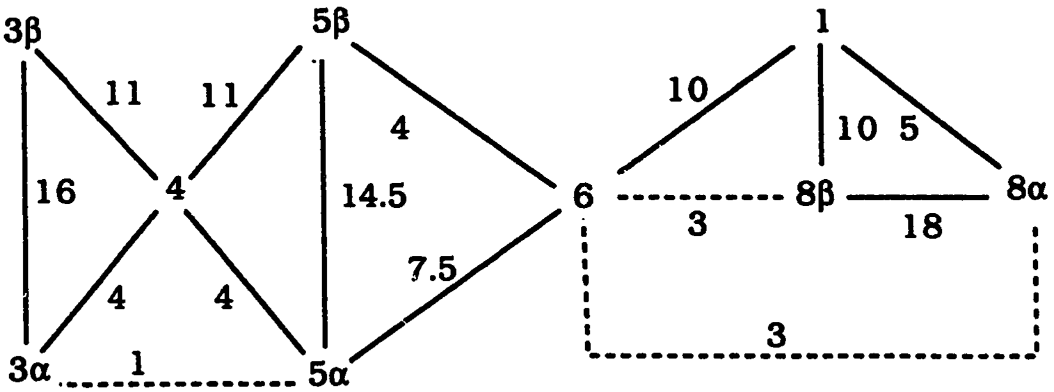


Figure 4-II. Structure of Diketone **99**

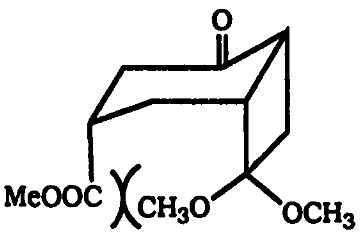
Table 4-II. 300 MHz ^1H nmr Data for Diketone **99**.

Proton	Chemical Shift (δ)	Number of Hydrogen	Multiplicity (*J* in Hz)
H_6	3.85	1	m
$H_{8\beta}$	3.54	1	ddd (3, 10, 18)
H_1	3.20	1	ddd (5, 10, 10))
$H_{8\alpha}$	3.10	1	ddd (3, 5, 18)
H_4	2.82	1	dddd (4, 4, 11,11)
$H_{3\alpha}$	2.75	1	ddd (1, 4, 16)
$H_{3\beta}$	2.56	1	dd (11, 16)
$H_{5\alpha}$	2.35	1	dddd (1, 4, 4, 14.5)
$H_{5\beta}$	1.93	1	ddd (7.5, 11, 14.5)



Scheme 4-XII. Spin-Spin Couplings Observed for Diketone **99**

Due to the low efficiency in oxidizing alcohol **98** to diketone **99**, an alternative route leading to the latter compound was sought. We decided to study the use of 1,1-dimethoxyethene in the initial photocycloaddition. The use of this olefin would lead to only two diastereomeric *cis*-fused photoadducts which could be easily converted to the corresponding cyclobutanones by hydrolysis. It might also enhance the desired diastereoselectivity of the photocycloaddition reaction. Of the two *cis*-photoadducts **100** and **101** produced with enone **102**, the latter adduct should experience less steric interaction and thus be produced preferentially.



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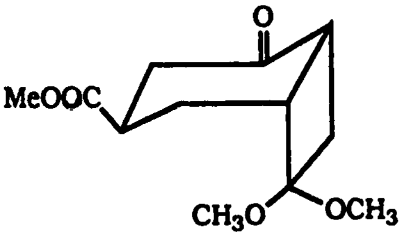
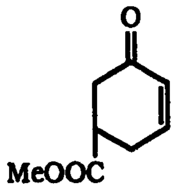


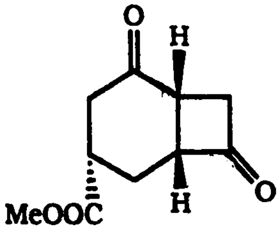
101

The carboxy group in enone **93** was protected prior to the photocycloaddition, because 1,1-dimethoxyethene is unstable in acidic media. We chose to protect the acid as its methyl ester. The esterification was effected smoothly using methyl iodide and potassium carbonate in acetone to give the required



102

enone ester **102**. The ir spectrum of this compound exhibited an ester band at 1734 cm^{-1} and an enone carbonyl absorption at 1682 cm^{-1}. Its hrms showed the molecular ion at m/z 154.0632 for the formula $C_8H_{10}O_3$. The ^{1}H nmr spectrum exhibited two vinylic protons at δ 6.98 and 6.50 and a strong singlet at δ 3.70 for the methoxy protons. Subsequently, a degassed benzene solution of the enone **102** and an excess of 1,1-dimethoxyethene was irradiated at 0°C for 12 h. The crude product without purification was immediately subjected to treatment with *p*-toluenesulfonic acid. After chromatographic separation, two compounds were obtained in pure form. The less polar compound isolated in 38% yield showed spectral data identical to those of diketone **99** obtained previously. The more polar isomer **103** was isolated in 30% yield. The ir spectrum of this compound displayed three carbonyl absorption at 1782 (cyclobutanone), 1725 (ester) and 1708 cm^{-1} (cyclohexanone). The molecular ion at m/z 196.0742, in the hrms, verified the molecular formula $C_{10}H_{12}O_4$. The ^1H nmr spectral data (Table 4-III) were also in full support of the structural assignment.

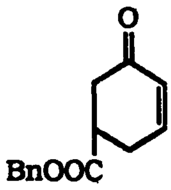


103

Table 4-III. 300 MHz ^1H nmr Data for Compound **103**.

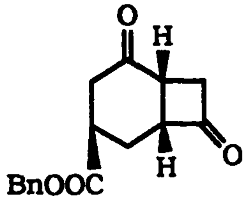
Proton	Chemical Shift (δ)	Number of Hydrogen	Multiplicity (*J* in Hz)
H_6	3.78	1	m
$H_{8\alpha}$	3.45	1	ddd (2.5, 11, 18)
$H_{8\beta}$	3.28	1	ddd (2.5, 5, 18)
H_1 and H_4	3.12	2	m
$H_{3\alpha}$	2.70	1	ddd (1, 5, 16.5)
$H_{3\beta}$	2.48	1	dd (5, 16.5)
$H_{5\alpha}$	2.31	1	dddd (1, 4, 4, 15)
$H_{5\beta}$	2.10	1	ddd (5.5, 8.5, 15)

The above results were encouraging. However, the low diastereoselectivity of the photochemical reaction left room for improvement. We felt that replacing the carbomethoxy group in the starting enone with a larger ester group would enhance the selectivity resulting in the preferential formation of the desired diastereomer . The carbobenzyloxy group was selected for this purpose. Esterification of the enone acid **103** with benzyl bromide and potassium carbonate in acetone provided enone ester **104**. Its ir spectrum displayed two carbonyl absorptions at 1737 cm^{-1} for the ester and 1678 cm^{-1} for the enone . The hrms showed the molecular ion at 230.0944, in agreement with the expected formula $C_{14}H_{14}O_3$. In the ^1H nmr spectrum, the aromatic protons appeared at δ 7.35 as a multiplet. Two vinylic protons were observed at δ 6.95 (ddd, $J = 10$, $J' = J'' = 4$ Hz) and 6.05 (ddd, $J = 10$, $J' = J'' = 2$ Hz) assigned for the β and α-proton of the enone system, respectively. The singlet at δ 5.15 was assigned for the benzylic protons.



104

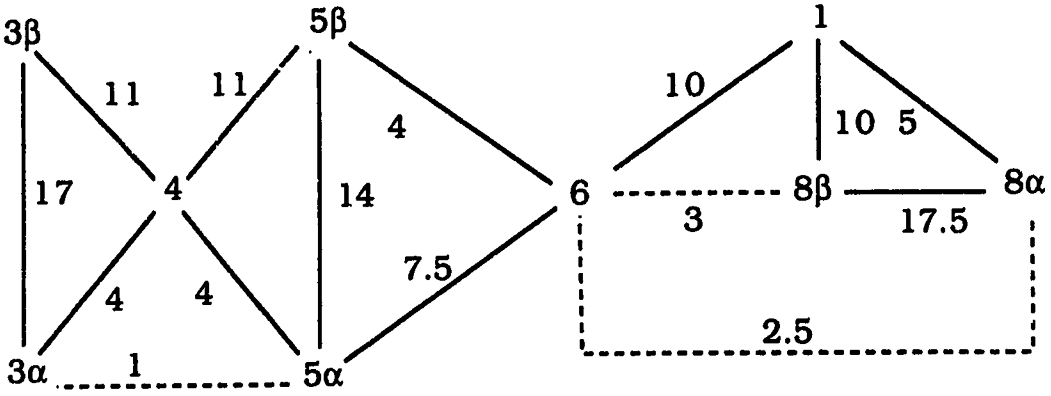
Enone ester **104** was irradiated at 0°C for 4 h in benzene in the presence of excess 1,1-dimethoxyethene. The crude product was subsequently treated with 15% aqueous hydrochloric acid in tetrahydrofuran for two days. After purification by flash chromatography, two products were isolated. The less polar compound **105**, obtained in 41% yield, showed in the ir spectrum, carbonyl absorptions at 1784 (cyclobutanone), 1731 (ester) and 1711 cm^{-1} (cyclohexanone). The hrms of this compound failed to show the molecular ion, however a peak at m/z 181.0500, due to the loss of benzyl group was observed. Comparing the ^1H nmr spectral data (Table 4-IV) and the coupling pattern (Scheme 4-XIII) of this compound with those of diketone **99**, led us to conclude that its stereochemistry was as depicted.



105

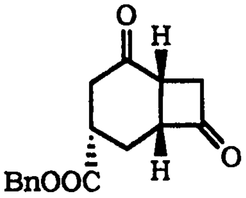
Table 4-IV. 300 MHz ^1H nmr Data for Compound **105**

Proton	Chemical Shift (δ)	Number of Hydrogen	Multiplicity (*J* in Hz)
H_6	3.80	1	m
$H_{8\beta}$	3.47	1	ddd (3, 10, 17.5)
H_1	3.15	1	ddd (5, 10, 10)
$H_{8\alpha}$	3.08	1	ddd (2.5, 5, 17.5)
H_4	2.85	1	dddd (4, 4, 11, 11)
$H_{3\alpha}$	2.74	1	ddd (1, 4, 17)
$H_{3\beta}$	2.56	1	dd (11, 17)
$H_{5\alpha}$	2.34	1	dddd (1, 4 , 4 ,14)
$H_{5\beta}$	1.93	1	ddd (7.5, 11, 14)



Scheme 4-XIII. Spin-Spin Couplings Observed for Compound **105**

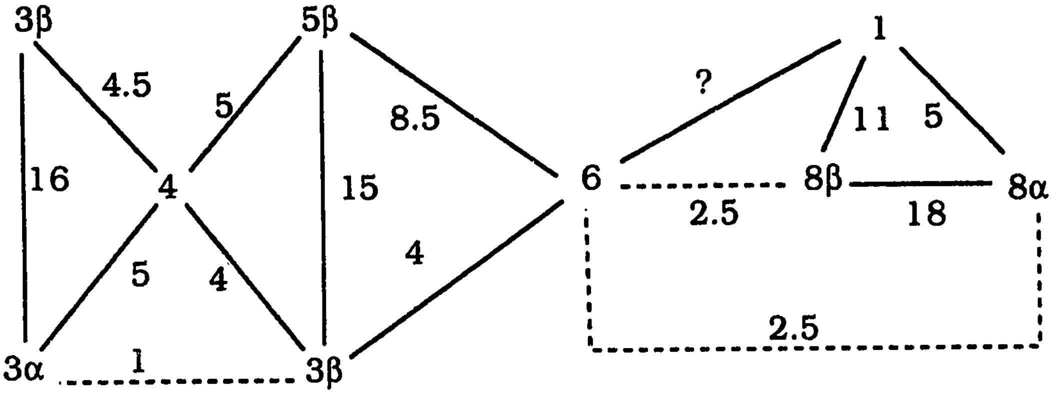
The more polar compound **106** was isolated in 30% yield. The ir spectrum of this isomer displayed carbonyl absorptions at 1783 (cyclobutanone) and 1725 cm^{-1} (ester and cyclohexanone). The molecular ion was not observed in the hrms for this compound, however a fragment was observed at m/z 181.0501, resulting from the loss of the benzyl group. From the ^{1}H nmr spectral data and the results of decoupling experiments, summarized in Table 4-V and Scheme 4-XIV, respectively, it was possible to establish the structure and the stereochemistry of this compound.



106

Table 4-V. 400 MHz ^{1}H nmr Data for Compound **106**.

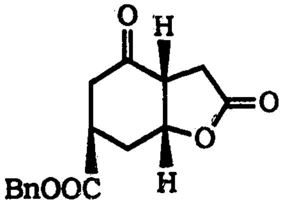
Proton	Chemical Shift (δ)	Number of Hydrogen	Multiplicity (*J* in Hz)
H_6	3.78	1	m
$H_{8\beta}$	3.42	1	ddd (2.5, 11, 18)
$H_{8\alpha}$	3.25	1	ddd (2.5, 5, 18)
H_1 and H_4	3.10	2	m
$H_{3\alpha}$	2.70	1	ddd (1, 5, 16)
$H_{3\beta}$	2.46	1	dd (4.5, 16)
$H_{5\alpha}$	2.32	1	dddd (1, 4, 4, 15)
$H_{5\beta}$	2.08	1	ddd (5, 8.5, 15)



Scheme 4-XIV. Spin-Spin Couplings Observed for Compond **106**.

Since the methyl ester enone **102** and the benzyl ester enone **104** gave almost the same distribution of diastereomers, we concluded that the alcohol part of the ester group in the starting enone played virtually no role in directing the photocycloaddition reaction.

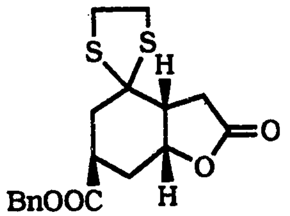
In continuation with our preliminary investigation on the synthesis of phyllanthocin (**2**), diketone **105** was subjected to Baeyer-Villiger oxidation[31,32] with *m*-chloroperbenzoic acid in dichloromethane in the presence of disodium phosphate as a buffer. The ir spectrum of the keto lactone **107** showed carbonyl absorptions at 1785 cm^{-1} for the γ-lactone and 1732 cm^{-1} for the ester and cyclohexanone. In the hrms, the molecular ion was observed at m/z 288.0997, confirming the molecular formula $C_{16}H_{16}O_4$. The ^1H nmr spectrum displayed the benzylic protons at δ 5.14 and the methine proton next to oxygen at δ 4.98.



107

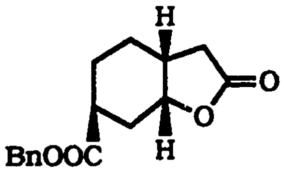
Following the generation of **107**, the next step required reduction of the ketone group to a methylene. Towards this end, we envisioned the use of Raney nickel (Ra-Ni)[33] reduction of a thioacetal. This method would avoid the application of strong acidic or basic conditions. Exposure of butyrolactone **107** to

1,2-ethanedithiol and boron trifluoride etherate furnished the desired thioacetal **108**, which showed, in the ir spectrum, a band at 1789 cm^{-1} for the butyrolactone and an absorption at 1730 cm^{-1} for the ester. The hrms exhibited the molecular ion at m/z 364.0806, in agreement with the molecular formula of $C_{18}H_{20}O_4S_2$. The ^{1}H nmr spectrum displayed the aromatic protons at δ 7.45 as a multiplet and the benzylic protons at δ 5.14 as a singlet. The methine proton next to the lactone oxygen was observed at δ 4.62.



108

Reduction of thioacetal **108** with Ra-Ni gave the expected butyrolactone **109** but in poor yield (18%). In the ir spectrum, it displayed two carbonyl absorptions at 1776 and 1730 cm^{-1} for the lactone and ester carbonyls, respectively. The molecular ion at m/z 274.1205 in the hrms was in agreement with the molecular formula $C_{16}H_{18}O_4$. The ^{1}H nmr spectrum displayed a singlet at δ 5.12 for the benzylic protons and a doublet of doublets at δ 4.16 for the methine proton next to the lactone oxygen. The low yield of this reaction could be attributed, in part, to the presence of the benzyl group which could undergo hydrogenolysis during the reduction process.



109

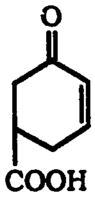
In order to increase the efficiency of removing the ketone carbonyl in **107**, other procedures, such as reduction to alcohol and then deoxygenation, have yet to be investigated. Alternatively, diketone **99**, in which the methyl ester should survive the Ra-Ni reduction conditions, could be used. Once the efficient preparation of **109** or its methyl ester analog is experimentally realized, the projected synthesis will proceed with installation of the C3 ketone carbonyl to give a compound of type **85** as planned.

Experimental

General Procedures and Materials

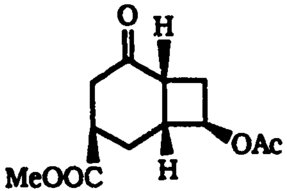
Refer to Chapter 1, Experimental Section for a detailed description of general procedures and materials data.

5-Oxo-3-cyclohexene-1-carboxylic acid (93).

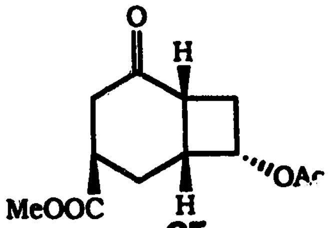


A solution of *m*-methoxybenzoic acid (30.0 g, 0.197 mol) in methanol (210 mL) was added slowly to freshly distilled liquid ammonia (400 mL) at -78°C. Sodium metal (18.0 g, 0.78 g-atom) was added in portions over 5 min, with rapid stirring using a mechanical stirrer. The solution was stirred further for 4 min, then ammonium chloride (90 g, 1.68 mol) was added with vigorous stirring. The mixture was allowed to warm to room temperature, allowing the ammonia to evaporate. The excess of methanol was removed by rotatory evaporator and the residue was dissolved in cold water. After the pH of the solution was adjusted to pH 1 using 1M aqueous hydrochloric acid, the solution was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The concentrate was dissolved in tetrahydrofuran (200 mL) and 1M aqueous hydrochloric acid (100 mL). The mixture was heated under reflux for 30 min and then concentrated. The residue was dissolved in dichloromethane. The organic phase was dried over magnesium sulfate, filtered and concentrated. Recrystallization of the residue from ether gave enone acid **93** (8.40 g, 30%): The concentrated mother liquor was subjected to flash chromatography (acetic acid and ethyl acetate in hexane, 1:40:59) to give another crop of **93** (9.10 g, 32%); mp 81-82°C (ether); ir ($CHCl_3$ cast) 2900 (br OH acid), 1725 (C=O, acid) and 1678 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 7.00 (ddd, $J = 10$, $J' = 4.5$, $J'' = 3.5$ Hz, 1H, -C**H**=CHCO), 6.10 (ddd, $J = 10$, $J' = J'' = 2$ Hz, 1H, -CH=C**H**CO), 3.15 (m, 1H, -C**H**COOH) and 2.70 (m, 4H); hrms 140.0474 (calcd. for $C_7H_8O_3$: 140.0473).

(1R*, 4R*, 6R*, 7R*)-7-Acetoxy-4-carbomethoxybicyclo[4.2.0]-octan-2-one (94) and a mixture of (1R*, 4R*, 6R*, 7S*)- (95), (1R*, 4S*, 6R*, 7S*)-(96) and (1R*, 4S*, 6R*, 7R*)-7-acetoxy-4-carbomethoxybicyclo[4.2.0]octan-2-one (97).



94



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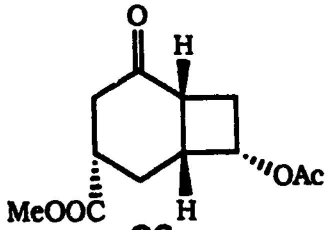
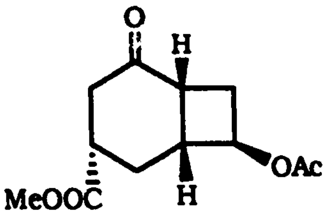


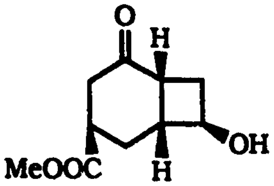
96



97

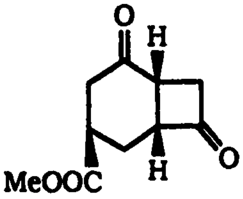
A degassed benzene (300 mL) solution of enone acid **93** (3.5 g, 25 mmol) and vinyl acetate (29 mL, 0.31 mol) were placed in a photochemical reaction vessel suspended in a Dewar flask filled with ice and water. The solution was irradiated using a 450-W Hanovia high pressure mercury lamp, through a Pyrex filter for 8 h. The solvent was removed *in vacuo*, and the residue was then dissolved in acetone (300 mL) . Potassium carbonate (17.27 g, 125 mmol) and methyl iodide (17.63 g, 125 mmol) were added and the resulting mixture was heated to reflux for 48 h. The solvent was removed *in vacuo*, and the residue was extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered and concentrated. The concentrate was dissolved in benzene (100 mL) containing DBU (9 mL, 60 mmol) and the reaction mixture was heated to reflux for 48 h. The reaction mixture was cooled to room temperature and washed with aqueous 5% hydrochloric acid (2 x 50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The concentrate was subjected to flash chromatography (30% ethyl acetate in hexane) to afford ketoester **94** (1.82 g, 30%): ir ($CHCl_3$ cast) 1730 (C=O, esters) and 1710 cm^{-1} (C=O, ketone); ^1H nmr (400 MHz, $CDCl_3$) δ 4.75 (dddd, $J = J' = J'' = 7.5$, $J''' = 1.5$ Hz, 1H, -C**H**OAc), 3.75 (s, 3H, -OC**H**$_3$), 3.07 (m, 1H, **H**$_6$), 2.95 (dddd, $J = J' = 12$, $J'' = J''' = 3.5$ Hz, 1H, **H**$_4$), 2.77(dd, $J = J' = 10$ Hz, **H**$_1$), 2.64 (ddd, $J = 15$, $J' = 3.5$, $J'' = 1.5$ Hz, 1H, **H**$_{3\alpha}$), 2.60 (dddd, $J = 11$, $J' = 7.5$, $J'' = 2.5$, $J''' = 1$ Hz, 1H, **H**$_{8\alpha}$), 2.45 (dd, $J = 15$, $J' = 12$ Hz, 1H, **H**$_{3\beta}$), 2.22 (ddd, $J = 11$, $J' = 10$, $J'' = 7.5$ Hz, 1H, **H**$_{8\beta}$), 2.20 (m, 1H, **H**$_{5\alpha}$), 2.04 (s, 3H, -OOCC**H**$_3$) and 1.85 (ddd, $J = 14$, $J' = 12$, $J'' = 6$ Hz, **H**$_{5\beta}$); hrms m/z 180.0784 (M^+-AcOH, calcd. for $C_{10}H_{12}O_3$: 180.0786). Continued elution afforded a mixture of three isomers **95**, **96** and **97** (1.85g, 31%): Only the following features in the spectra of the mixture are described; ir ($CHCl_3$ cast) 1735 (C=O, esters) and 1707 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 5.15, 4.65 (each m, -C**H**OAc) and 3.74, 3.72 and 3.70 (each s, -OC**H**$_3$).

(1R*, 4R*, 6R*, 7R*)-7-Hydroxy-4-carbomethoxybicyclo[4.2.0]-octan-2-one (98)



Keto ester **94** (100 mg, 0.42 mmol) and potassium carbonate (1 g, 7.3 mmol) were dissolved in methanol and stirred vigorously at room temperature for one day. The mixture was concentrated and the residue was extracted with dichloromethane (2 x 50 mL). The organic solution was concentrated to leave alcohol **98** (56 mg, 67%): ir ($CHCl_3$ cast) 3434 (OH), 1734 (C=O, ester) and 1708 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.95 (m, 1H, -CHOH), 3.73 (s, 3H, $-OCH_3$) and 2.88 (m, 3H); cims $[M+NH_4]^+$ 216.

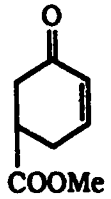
(1R*, 4R*, 6R*)-4-Carbomethoxybicyclo[4.2.0]octane-2,7-dione (99)



To a solution of dimethyl sulfoxide (DMSO) (0.4 mL, 5.65 mmol) in dichloromethane (15 mL) at -10°C, were added sequentially with stirring phenyl dichlorophosphate (PDCP)

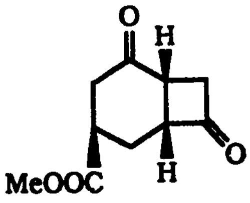
(0.5 mL, 3.4 mmol), triethylamine (0.8 mL, 5.65 mmol) and a solution of alcohol **98** (224 mg, 1.13 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at -10°C for 5 min, then allowed to warm up to room temperature. After 20 minutes, water (10 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography (15% ethyl acetate in hexane) to give **99** (40 mg, 18%): ir ($CHCl_3$ cast) 1785 (C=O, ketone), 1725 (C=O, ester) and 1702 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz, $CDCl_3$) δ 3.85 (m, 1H, $\mathbf{H}_6$), 3.72 (s, 3H, -OC$\mathbf{H}_3$), 3.54 (ddd, $J = 18$, $J' = 10$, $J'' = 3$ Hz, 1H,$\mathbf{H}_{8\beta}$), 3.20 (ddd, $J = J' = 10$, $J'' = 5$ Hz, 1H, $\mathbf{H}_1$), 3.10 (ddd, $J = 18$, $J' = 5$, $J'' = 3$ Hz, 1H, $\mathbf{H}_{8\alpha}$), 2.82 (dddd, $J = J' = 11$, $J'' = J''' = 4$ Hz, 1H, $\mathbf{H}_4$), 2.75 (ddd, $J = 16$, $J' = 4$, $J'' = 1$ Hz, 1H, $\mathbf{H}_{3\alpha}$), 2.56 (dd, $J = 16$, $J' = 11$ Hz,1H, $\mathbf{H}_{3\beta}$), 2.35 (dddd, $J = 14.5$, $J = J'' = 4$, $J''' = 1$Hz, 1H, $\mathbf{H}_{5\alpha}$) and 1.92 (ddd, $J = 14.5$, $J' = 11$, $J'' = 7.5$ Hz, 1H, $\mathbf{H}_{5\beta}$); ^{13}C nmr APT ($CDCl_3$,75.5 MHz) δ 208.73 (p), 206.99 (p), 173.34 (p), 58.61 (a), 52.29 (a), 51.05 (p), 41.90 (p), 38.33 (a), 34.83 (a) and 24.90 (p); hrms M^+ 196.0736 (calcd. for $C_{10}H_{12}O_4$: 196.0735). Anal. calcd. for $C_{10}H_{12}O_4$: C 61.22, H 6.16; found: C 61.04, H 6.24.

Methyl 5-oxo-3-cyclohexene-1-carboxylate (102).

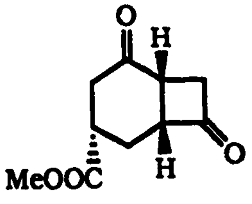


Potassium carbonate (4.15 g, 30 mmol) and methyl iodide (4.26 g, 30 mmol) were added to a solution of enone acid **93** (1.40 g, 10 mmol) in acetone (50 mL). The mixture was heated to reflux for 24 h. The solvent was removed by distillation and the residue was dissolved in dichloromethane and water. The organic solution was dried over magnesium sulfate, filtered and concentrated to furnish the enone ester **102** (1.30 g, 84%): ir ($CHCl_3$ cast) 1734 (C=O, ester) and 1682 cm^{-1} (C=O, enone); ^1H nmr (300 MHz, $CDCl_3$) δ 6.98 (ddd, J = 10.5, J' = 4.5, J'' = 3.5 Hz, 1H, -C**H**=CHCO), 6.50 (ddd, J = 10.5, J' = J'' = 2 Hz, 1H, -CH=C**H**CO), 3.70 (s, 3H, -OC**H**$_3$), 3.10 (m, 1H, -C**H**COOCH$_3$) and 2.65 (m, 4H); hrms M^+ 154.0632 (calcd. for $C_8H_{10}O_3$: 154.0629). Anal. calcd. for $C_8H_{10}O_3$: C 62.33, H 6.54; found: C 62.06, H 6.70.

(1R*, 4R*, 6R*)-4-Carbomethoxybicyclo[4.2.0]octane-2,7-dione (99) and (1R*, 4S*, 6R*)-4-Carbomethoxybicyclo[4.2.0]octane-2,7- dione (103).



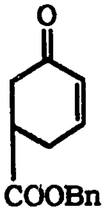
99



103

A degassed benzene (100 mL) solution of enone ester **102** (0.616 g, 4 mmol) and 1,1-dimethoxyethene (3.25 g, 40 mmol) were placed in a photochemical apparatus which was suspended in a Dewar flask filled with ice and water. The solution was irradiated using a 450-W Hanovia high pressure mercury lamp, through a Pyrex filter for 11 h. The solvent was removed in vacuo, and the residue was then dissolved in acetone (100 mL) containing *p*-TsOH (0.1 g). The resulting mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo*, and the concentrate was subjected to flash chromatography (30% ethyl acetate in hexane) to afford diketone **99** (300 mg, 38%): Continued elution afforded **103** (235 mg, 30%): ir ($CHCl_3$ cast) 1782 (C=O, ketone), 1725 (C=O, ester) and 1708 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.78 (m, 1H, $\mathbf{H}_6$), 3.65 (s, 3H, -OC$\mathbf{H}_3$), 3.45 (ddd, J = 18, J' = 11, J'' = 2.5 Hz, 1H, $\mathbf{H}_{8\alpha}$), 3.28 (ddd, J = 18, J' = 5, J'' = 2.5 Hz, 1H, $\mathbf{H}_{8\beta}$), 3.12 (m, 2H, $\mathbf{H}_1$ and $\mathbf{H}_4$), 2.70 (dd, J = 16.5, J' = 5, J'' = 1 Hz, 1H, $\mathbf{H}_{3\alpha}$), 2.48 (dd, *J* = 16.5, *J'* = 5 Hz, 1H, **H**$_{3\beta}$), 2.31 (dddd, *J* = 15, *J* = *J''* = 4, *J'''* = 1Hz, 1H, **H**$_{5\alpha}$) and 2.10 (ddd, *J* = 15, *J'* = 8.5, *J''* = 5.5 Hz, 1H, **H**$_{5\beta}$); ^{13}C nmr APT (CDCl$_3$,75.5 MHz) δ 208.59 (p), 207.88 (p), 174.62 (p), 57.76 (a), 52.27 (a), 51.27 (p), 41.74 (p), 39.89 (a), 34.35 (a) and 24.42 (p); hrms M$^+$ 196.0742 (calcd. for $C_{10}H_{12}O_4$: 196.0735). Anal. calcd. for $C_{10}H_{12}O_4$: C 61.22, H 6.16; found: C 60.67, H 6.23.

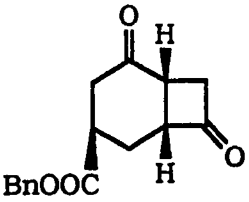
Benzyl 5-oxo-3-cyclohexene-1-carboxylate (104)

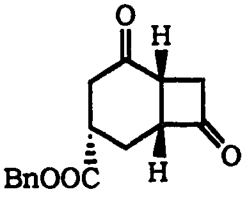


Potassium carbonate (4.15 g, 30 mmol) and benzyl bromide (1.71 g, 10 mmol) were added to a solution of enone acid **93** (1.40 g, 10 mmol) in acetone (20 mL). The mixture was heated to reflux for 6 h. The solvent was distilled and the residue was dissolved in dichloromethane and water. The organic solution was dried over magnesium sulfate, filtered and concentrated. Flash chromatography (15% ethyl acetate in hexane) of the residue furnished the enone ester **104** (2.18 g, 95%): ir (CHCl$_3$ cast) 1737 (C=O, ester) and 1678 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.35 (m, 5H, aromatic-**H**), 6.95 (ddd, *J* = 10, *J'* = *J''* = 4 Hz, 1H, -C**H**=CHCO), 6.05 (ddd, *J* = 10, *J'* = *J''* = 2 Hz, 1H, -CH=C**H**CO), 5.15 (s, 2H, -C**H**$_2$Ph) and 3.12 (m, 1H,

-CHCOOBn); ^{13}C nmr APT ($CDCl_3$,75.5 MHz) δ 196.42 (p), 172.38 (p), 147.52 (a), 135.34 (p), 129.49 (a), 128.85 (a), 128.31 (a), 128.15 (a), 127.89 (a), 127.77 (a), 66.40 (p), 39.48 (a), 39.31 (p) and 27.63 (p); hrms M$^+$ 230.0944 (calcd. for $C_{14}H_{14}O_3$: 230.0943).

(1R*, 4R*, 6R*)-4-Carbobenzyloxybicyclo[4.2.0]octane-2,7-dione (105) and (1R*, 4S*, 6R*)-4-Carbobenzyloxybicyclo[4.2.0]-octane-2,7-dione (106)

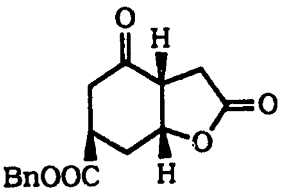

105


106

A degassed benzene (200 mL) solution of enone ester **104** (2.30 g, 10 mmol) and 1,1-dimethoxyethene (8.8 g, 100 mmol) was placed in a photochemical apparatus suspended in a Dewar flask filled with ice water. The solution was irradiated using a 450-W Hanovia high pressure mercury lamp, through a Pyrex filter for 4 h. The solvent was removed *in vacuo*, and the residue was then dissolved in acetone (50 mL) and 15% aqueous hydrochloric acid (20 mL). The resulting mixture was stirred at room temperature for two days. The solvent was removed *in vacuo*, and the concentrate was subjected to flash chromatography (30% ethyl acetate in hexane) to afford diketone **105** (1.08 g, 41%): ir ($CHCl_3$ cast) 1784 (C=O, ketone), 1731

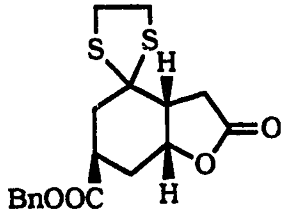
(C=O, ester) and 1711 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz, CDCl$_3$) δ 7.35 (m, 5H, aromatic-**H**), 5.15 (s, 2H, PhC**H**$_2$O-), 3.80 (m, 1H, $\mathbf{H}_6$), 3.47 (ddd, J = 17.5, J' = 10, J'' = 3 Hz, 1H, $\mathbf{H}_{8\beta}$), 3.15 (ddd, J = J' = 10, J'' = 5 Hz, 1H, $\mathbf{H}_1$), 3.08 (ddd, J = 17.5, J' = 5, J'' = 2.5 Hz, 1H, $\mathbf{H}_{8\alpha}$), 2.85 (dddd, J = J' = 11, J'' = J''' = 4 Hz, 1H, $\mathbf{H}_4$), 2.74 (ddd, J = 17, J' = 4, J'' = 1 Hz, 1H, $\mathbf{H}_{3\alpha}$), 2.56 (dd, J = 17, J' = 11 Hz, 1H, $\mathbf{H}_{3\beta}$), 2.34 (dddd, J = 14, J = J'' = 4, J''' = 1Hz, 1H, $\mathbf{H}_{5\alpha}$) and 1.93 (ddd, J = 14, J' = 11, J'' = 7.5 Hz, 1H, $\mathbf{H}_{5\beta}$); cims [M+NH$_4$]$^+$ 290. Continued elution afforded **106** (0.80 g, 29%): ir (CHCl$_3$ cast) 1783 (C=O, ketone), 1725 cm^{-1} (C=O, ester and ketone); ^{1}H nmr (400 MHz, CDCl$_3$) δ 3.78 (m, 1H, $\mathbf{H}_6$), 3.42 (ddd, J = 18, J' = 11, J'' = 2.5 Hz, 1H, $\mathbf{H}_{8\beta}$), 3.25 (ddd, J = 18, J' = 5, J'' = 2.5 Hz, 1H, $\mathbf{H}_{8\alpha}$), 3.10 (m, 2H, $\mathbf{H}_1$ and $\mathbf{H}_4$), 2.70 (dd, J = 16, J' = 5, J'' = 1 Hz, 1H, $\mathbf{H}_{3\alpha}$), 2.66 (dd, J = 16, J' = 4.5 Hz, 1H, $\mathbf{H}_{3\beta}$), 2.32 (dddd, J = 15, J = J'' = 4, J''' = 1Hz, 1H, $\mathbf{H}_{5\alpha}$) and 2.08 (ddd, J = 15, J' = 8.5, J'' = 5 Hz, 1H, $\mathbf{H}_{5\beta}$); hrms m/z 181.0501 (M$^+$-C$_7$H$_7$, calcd. for C$_9$H$_9$O$_4$: 181.0500); cims [M+NH$_4$]$^+$ 290.

(3aR*, 6R*, 7aR*)-6-Carbobenzyloxy-3,3a,5,6,7,7a-hexahydrobenzo[b]furan-2,4-dione (107).



To a solution of diketone **105** (340 mg, 1.30 mmol) in dichloromethane (20 mL) was added disodium hydrogen phosphate (0.95 g, 67 mmol) and MCPBA (85%, 272 mg, 1.34 mmol) at 0°C. The mixture was stirred at room temperature for 12 h. The mixture was washed with saturated aqueous sodium carbonate solution. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (30% ethyl acetate in hexane) to give the butyrolactone **107** (290 mg, 77%): ir ($CHCl_3$ cast) 1785 (C=O, butyrolactone), and 1732 cm^{-1} (C=O, ester and ketone); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.40 (m, 5H, aromatic **H**), 5.15 (s, 2H, -C**H**$_2$Ph), 4.98 (ddd, $J = J' = 6$, $J'' = 3.5$ Hz, 1H, -C**H**O-), 3.18 (dd, $J = 17$, $J' = 1.5$, 1H, -C**H**HCOO-), 2.78 (ddd, $J = 15$, $J' = 12$, $J'' = 2$ Hz, 1H, -CH**H**CHO-), 2.58 (dd, $J = 17$, $J' = 8$, 1H, -CH**H**COO-), and 2.18 (ddd, $J = 15$, $J' = 12$, $J'' = 3.5$ Hz, 1H, -C**H**HCHO-); hrms M^+ 288.0999 (calcd. for $C_{16}H_{16}O_4$: 288.0997).

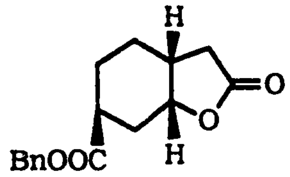
(3aR*, 6R*, 7aR*)-6-Carbobenzyloxy-4,4-ethylenedithio-3,3a,5,6,7,7a-hexahydrobenzo-[b]furan-2(3H)-one(108).



To a solution of butyrolactone **107** (640 mg, 2.30 mmol) in dichloromethane (30 mL) at 0°C, were added 1,2-ethanedithiol

(0.19 mL, 2.30 mmol) and boron trifluoride etherate (0.05 mL, 0.41 mmol). The mixture was stirred at room temperature for 24 h. The mixture was washed with cold aqueous 5% sodium hydroxide solution (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude product was subjected to flash chromatography (10% ethyl acetate in hexane) to give thioacetal **108** (290 mg, 69%): ir ($CHCl_3$ cast) 1789 (C=O, butyrolactone), and 1733 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 7.45 (m, 5H, aromatic **H**), 5.14 (s, 2H, -$C\mathbf{H}_2Ph$), 4.62 (m, 1H, -C**H**O-), 3.40-3.10 (m, 4H, -$SC\mathbf{H}_2C\mathbf{H}_2S$-); hrms M^+ 364.0806 (calcd. for $C_{18}H_{20}O_4S_2$: 364.0802).

(3aR*, 6R*, 7aR*)-6-Carbobenzyloxy-3a,5,6,7,7a-hexahydrobenzo-[b]furan-2(3H)-one (109).



A. Preparation of Raney Nickel (Ra-Ni, W-2)

Al-Ni alloy powder (9 g) was added in small portions to a stirred solution of sodium hydroxide (11.4 g, 285 mmol) in water (45 mL) at 0°C, ensuring that the temperature did not exceed 25°C. Once a slow evolution of hydrogen gas was observed, the suspension was allowed to warm up to room temperature, and then heated on a steam bath until the evolution of hydrogen gas had ceased. The suspension was then washed with water until the washing was neutral. The suspension was washed three times with isopropyl alcohol, and stored under isopropyl alcohol.

B. Reduction

Freshly prepared Ra-Ni (W-2, 6 mL) was added to a solution of thioacetal **108** (350 mg, 1.54 mmol) in benzene (30 mL). The mixture was stirred at room temperature for 18 h. The mixture was then filtered through a thin layer of silica gel and the residue washed with dichloromethane (200 mL). The combined filtrate was concentrated to leave butyrolactone **109** (80 mg, 19%): ir ($CHCl_3$ cast) 1776 (C=O, butyrolactone), and 1730 cm^{-1} (C=O, ester); ^1H nmr (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, aromatic **H**), 5.12 (s, 2H, -C**H**$_2$Ph), 4.61 (dd, $J = 6$, $J' = 4$ Hz, 1H, -C**H**O-), 2.68 (dd, $J = 17$, $J' = 7$ Hz, 1H, -C**H**HCOO-) and 2.22 (d, $J = 17$ Hz, -CH**H**COO-); hrms M^+ 274.1205 (calcd. for $C_{16}H_{18}O_4$: 274.1204).

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