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UNIVERSITY OF ALBERTA

A NEW POLYENE CYCLIZATION PROCESS
AND
ITS SYNTHETIC APPLICATIONS

by

DAQING SUN 

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

FALL, 1998

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FACULTY OF GRADUATE STUDIES AND RESEARCH

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Abstract

The first chapter of this thesis describes a new polyene cyclization process promoted by the cross conjugated α-carbomethoxy enone system. Several enone esters (**10**, **29**, **33**, **37**, **41**, **46** and **57**) have been successfully prepared and their cyclization examined. The results illustrate that the cross conjugated β-keto ester system could serve as a highly effective promoter for cationic cyclization, which occurred readily with high regio- and stereoselectivity and also with an unusual termination process involving halogen atom incorporation when a metal halide was used as the reagent. In essence, this cyclization process allows for expeditious construction of a variety of polycyclic ring systems, such as decalin (e.g., compounds **11**, **18** and **25**), hydrindane (**47** and **48**) and hydroazulene (**58**), with concomitant incorporation of a number of diverse functionalities. This newly developed polyene cyclization is expected to have broad utility in the synthesis of polycyclic natural and unnatural compounds.

The second chapter presents the successful application of the polyene cyclization to facilitate the first total synthesis, in racemic form, of dehydrochamaecynenol **93**, an acetylenic sesquiterpene isolated from the essential oil of the Benihi tree (*Chamaecyparis formosensis* Matsum., Cupressaceae), and a new synthesis, also in racemic form, of occidentalol **61**, a sesquiterpene constituent of the wood of Eastern white cedar (*Thuja occidentalis L.*). Enone ester **10** was readily prepared in four steps from 3-ethoxy-6-methyl-2-cyclohexenone. Treatment of **10** with zinc iodide resulted in its cyclization to give iodide **18**. This compound served as a common intermediate leading to both of the aforementioned natural products. Compound

18 was elaborated to give (±)-dehydrochamaecynenol *via* three major operations. These include conversion of the β-keto ester into an allylic alcohol (**18**→**96**), oxidation of the iodo group to the corresponding ketone (**97**→**98**), and installation of the acetylene unit *via* aldehyde **101** using an array of rather standard reactions. For the synthesis of (±)-occidentalol, aldehyde **101** was first subjected to epimerization. Two major operations were carried out from aldehyde **102** thus obtained to complete the synthesis: transformation of the aldehyde group to an isopropyl alcohol unit (**102**→**111**) and deoxygenation of the hydroxy group (**111**→**61**) .

A formal total synthesis of the naturally occurring (-)-dehydrochamaecynenol **93** is described in the last chapter. Making use of the Meyers' general approach to optically active 4,4-disubstituted cyclohexenones, (+)-enone **16** was prepared from the commercially available lactam **112**. Carbomethoxylation and oxidation of (+)-**16** gave (+)-enone ester **10**. This compound was transformed, *via* the newly developed polyene cyclization process, to (-)-iodide **18**, the racemic modification of which had served as an advanced intermediate in the total synthesis of (±)-dehydrochamaecynenol **93** carried out in our laboratory.

Dedicated to my family

Acknowledgements

I would like to express my most profound gratitude to my research director, Professor H.J. Liu, for his support, wisdom, and encouragement throughout this Ph.D. program. His interest and invaluable assistance in the preparation of this thesis are also greatly appreciated.

I would also like to thank all the members of our research group with whom I've had a chance to work. They have provided a very sociable and enjoyable working environment.

Thanks are extended to the excellent technical staff of the chemistry department. This work would not have been accomplished without their help: Dr. A.M. Hogg, L. Harrower, D. Morgan, J. Olekszyk, and A. Jordan in the Mass Spectrometry Laboratory, R. Swindlehurst, D. Formanski, and J. Hoyle in the Spectral Services Laboratory, D. Mahlow and A. Dunn in the Microanalytical Laboratory, Dr. T.T. Nakashima, T. Brisbane, G. Bigam, L. Kong, and G. Aarts in the NMR Spectroscopy Laboratory, Dr. R. Mcdonald in the X-ray laboratory as well as all the personnel in the Electronic, Glass Blowing and Machine Shops. I would also like to thank the University of Alberta for financial support.

Finally, I would like to give my special thanks to my wife, Weihong Chen, for her understanding and unconditional support during my whole Ph.D program.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ac	Acetyl
a	anti-phase
APT	Attached Proton Test
Bn	Benzyl
br	broad
Bu	butyl
calcd.	calculated
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminum hydride
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
eq.	equivalent
Et	ethyl
FTIR	Fourier Transform Infrared Spectroscopy
h	hour
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
J	coupling constant
IR	Infrared Spectroscopy
LDA	Lithium Diisopropylamide
m	multiplet
M	Molar

M^+	Molecular ion
Me	Methyl
MHz	Megahertz
min	minute
mmol	millimole
mol	mole
mp	melting point
Ms	Mesyl
m/z	mass to charge ratio
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
p	para
p	phase
PP	Pyrophosphate
p-TsOH	*p*-Toluenesulfonic Acid
Ph	Phenyl
py	pyridine
q	quartet
R	generalized alkyl group or substituent
r.t.	room temperature
s	singlet
SET	Single Electron Transfer
t	tertiary
t	triplet
tlc	thin-layer chromatography
TBAF	Tetrabutylammonium Fluoride

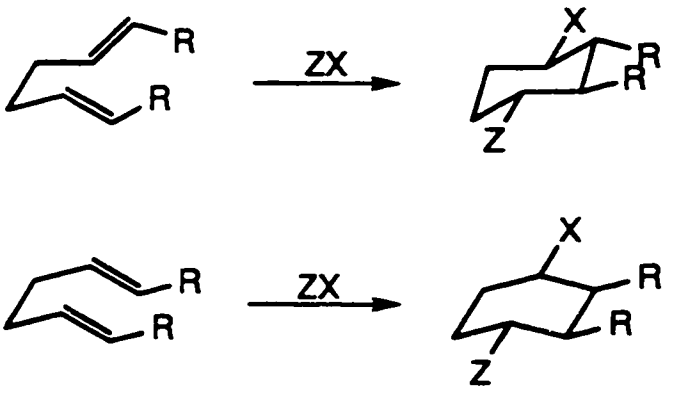
TBDMS	*t*-Butyldimethylsilyl
THF	Tetrahydrofuran

Chapter One

Polyene cyclization promoted by the cross conjugated α-carbomethoxy enone system

Introduction

Polyene cyclization, also known as cationic cyclization, is a powerful synthetic tool for the preparation of alicyclic compounds. Its attractiveness lies in the potential control of stereochemistry and the readiness with which highly substituted carbon-carbon bonds may be formed. The synthetic application of this method has been the subject of several reviews.[1-4] The development of the method of polyene cyclization is derived from the classical structure investigations on terpenes, together with speculation on their biosynthesis and stereochemistry. In 1955, Stork and Eschenmoser pointed out that polyene cyclization with a 1,5-diene occurred in a defined conformation (chair or boat) by antiperiplanar addition to the double bonds (Scheme 1).[5,6]

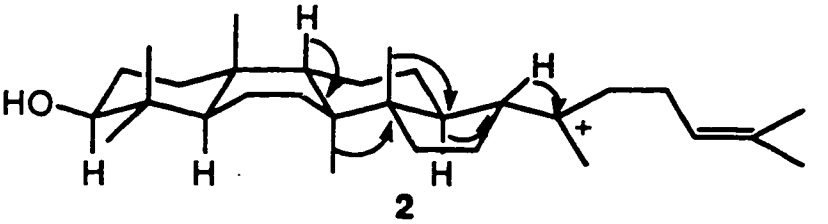


Scheme 1

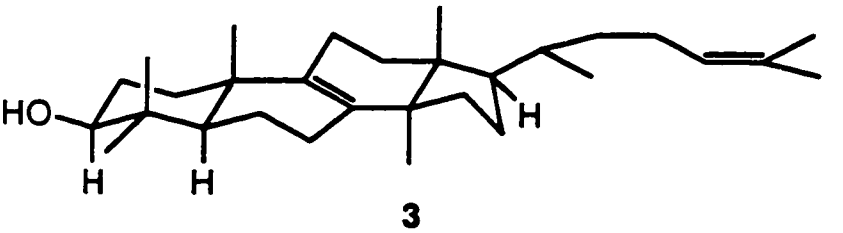
Their hypothesis allows the prediction of the relative stereochemistry of the cyclization products and establishes a synthetic strategy, although the hypothesis is not universally applicable. The general concept of stereoelectronic control of polyene cyclization also stimulated these studies on rationalization of the course of many biological cyclizations. Nevertheless, enzymes are required to promote occasionally observed anti-Markovnikov

regio-orientation, and also to induce preference for boat-like transition states.[3] One of the most familiar processes of this type is the tetracyclization of squalene oxide **1** towards the steroid skeleton. The polycyclic structures formed from squalene can be rationalized in terms of the way in which squalene may be folded on the enzyme surface. Scheme 2 shows the conversion of **1** into lanosterol **3** as an example. Thus, protonation of the epoxy moiety in **1** generates the cationic center at C-2, which attacks by the 6,7-olefinic bond generating a cationic center at C-6. Subsequent cyclization involving C-6, C-10 and C-14 yields the *trans, trans, trans*-fused ring system found in the cationic species **2**, which is considered a hypothetical intermediate for lanosterol **3**.[7]

1
chair-boat-chair-boat conformation



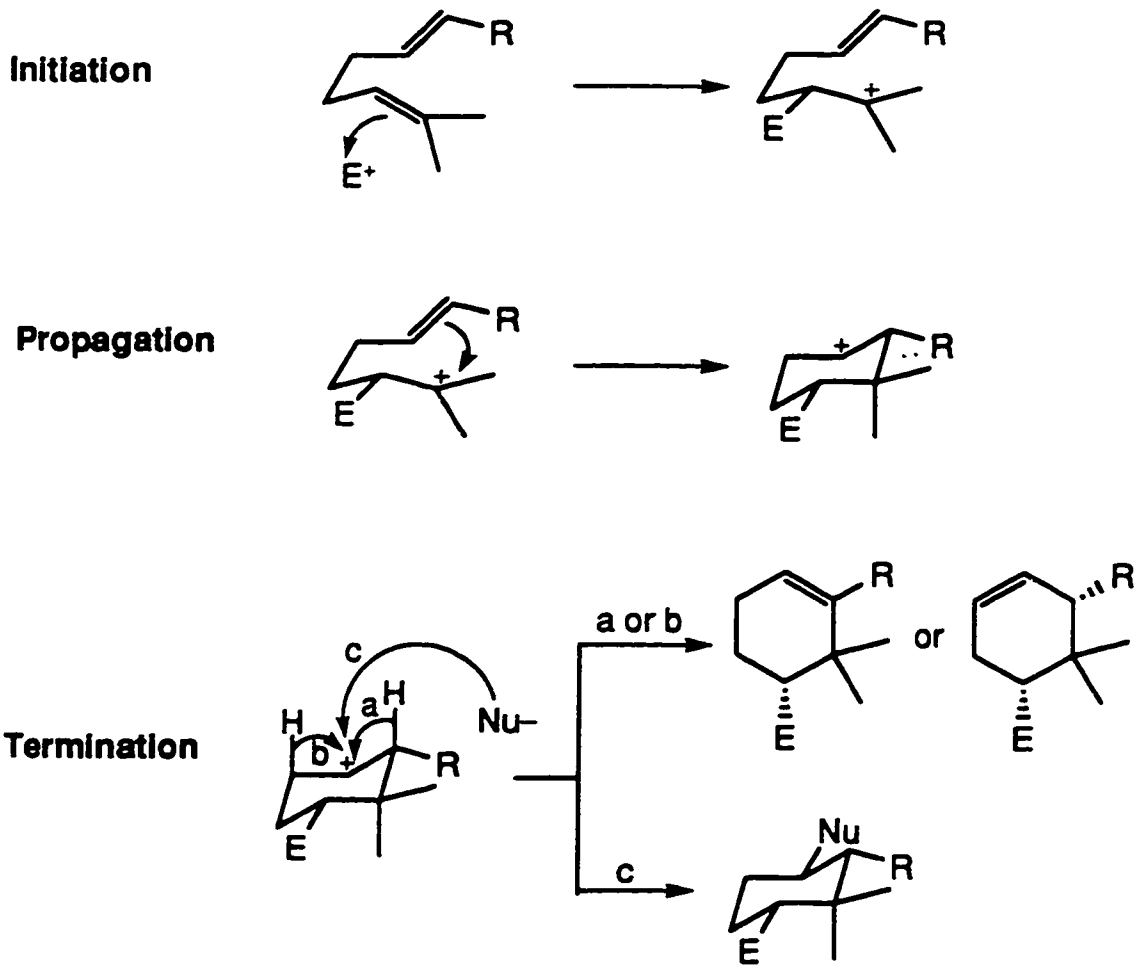
2



3

Scheme 2

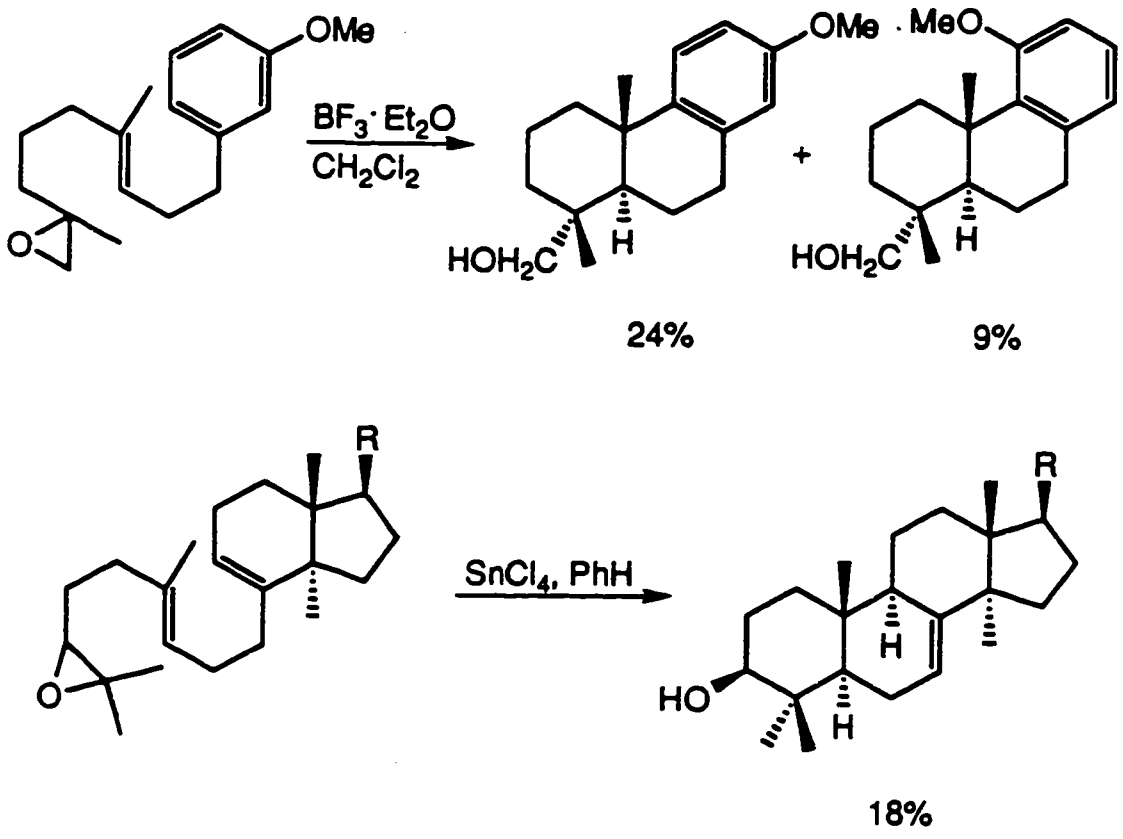
In general, the success of the polyene cyclization process depends on the method of initiation, the nucleophilicity of the participating double bond(s), and the process of termination.[2] Although its mechanism is not well established, a simplified representation involving carbocations is depicted in Scheme 3 with a simple 1,5-diene as an example. However, this does not exclude concerted and partly concerted mechanisms.



Scheme 3

Initiation of Cyclization

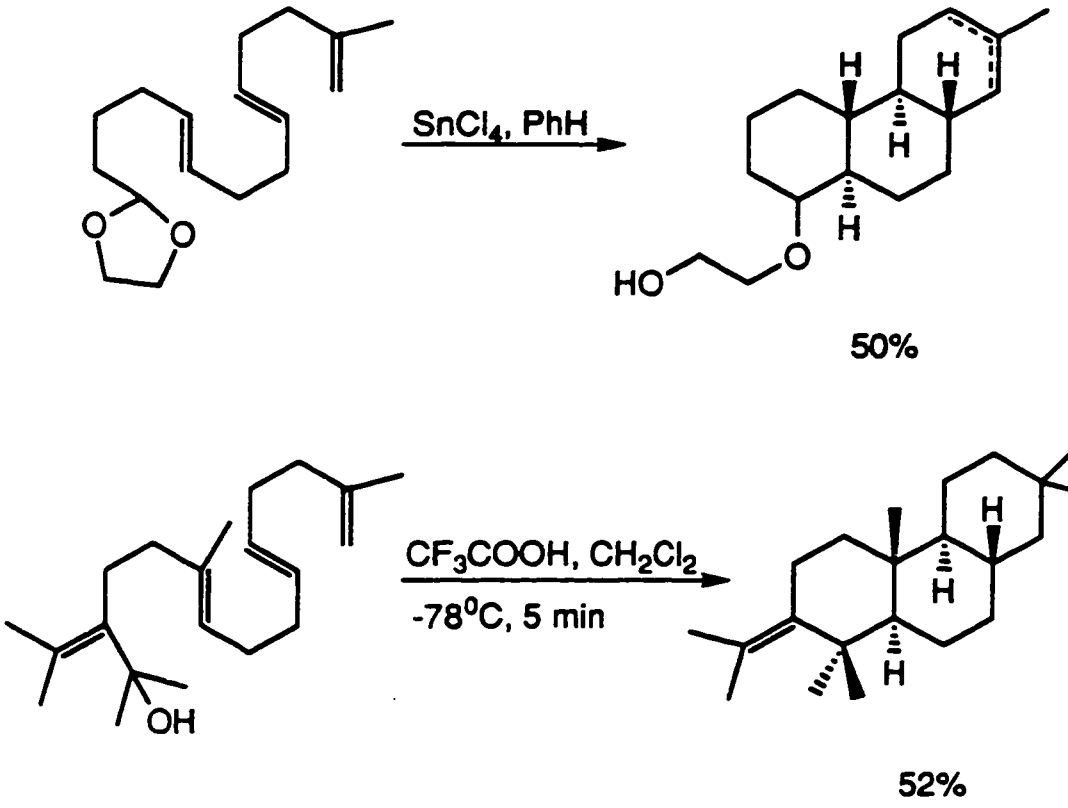
In general, the cyclization can be initiated by formation of a cation either by electrophilic addition to a double bond or by ionization, usually from an sp^3-hybridized carbon. Brønsted and Lewis acids have been the most frequently used electrophiles. Protonation of the terminal olefinic bond was used in early attempts to initiate polyene cyclization. Unfortunately, these reactions resulted in complex mixtures of partially cyclized products.[6,8,9] The difficulties encountered were attributed to the lack of regioselectivity in the protonation process as well as the occurrence of competing reactions, such as addition and isomerization, due to the strong conditions generally applied. Therefore, the use of an appropriately positioned functional group as an initiator is a common practice.

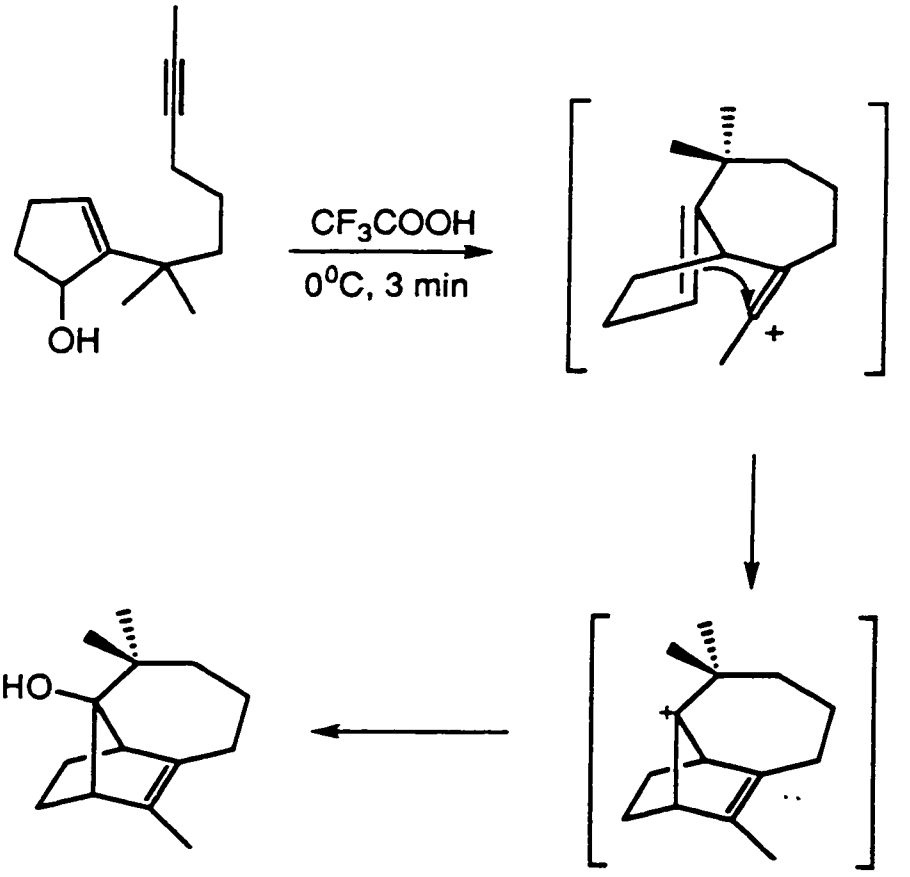


Scheme 4

Protonation of an epoxy functionality was applied to initiate the cyclization in a biomimetic fashion similar to the one shown in Scheme 2 for biological processes. The initiation method has been studied by van Tamelen[10,11] and Goldsmith.[12] The results have given valuable insights into the biosynthesis of terpenes. However, from the preparative point of view, it is only useful for monocyclizations, while bi- and tri-cyclizations occur only in poor yields. Two examples[12,13] are illustrated in Scheme 4.

Initiation by the use of substrates with acetal and allylic alcohol functionalities was first introduced by Johnson[3,14] and accounts for many synthetic applications. Selected examples[3] are illustrated in Scheme 5.



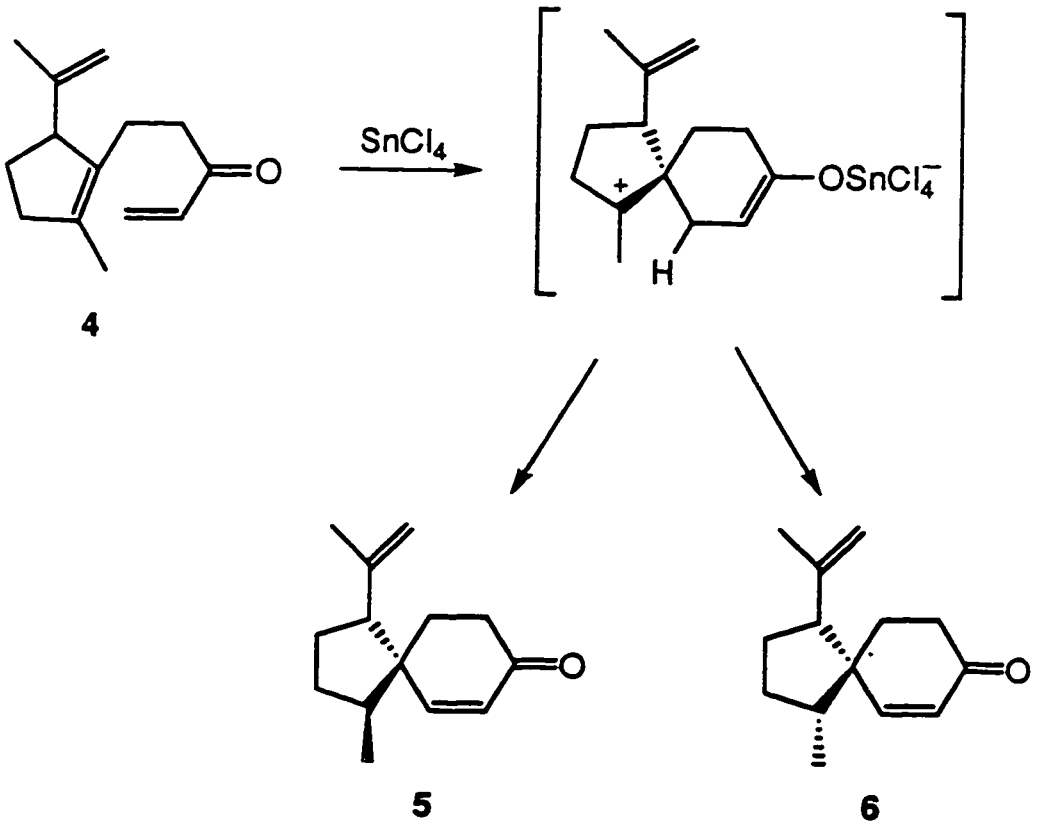


Scheme 5

The use of α,β-unsaturated carbonyl systems as initiators for cationic cyclization has been studied and some synthetic applications have been reported.[15-21] Naegeli[21] reported the intramolecular cyclization of enones by forming an enone·($SnCl_4$) complex as initiator. When enone **4** was treated with stannic chloride at room temperature, two isomeric conjugated spiroketones **5** and **6** were formed in a combined yield of 59% (Scheme 6).

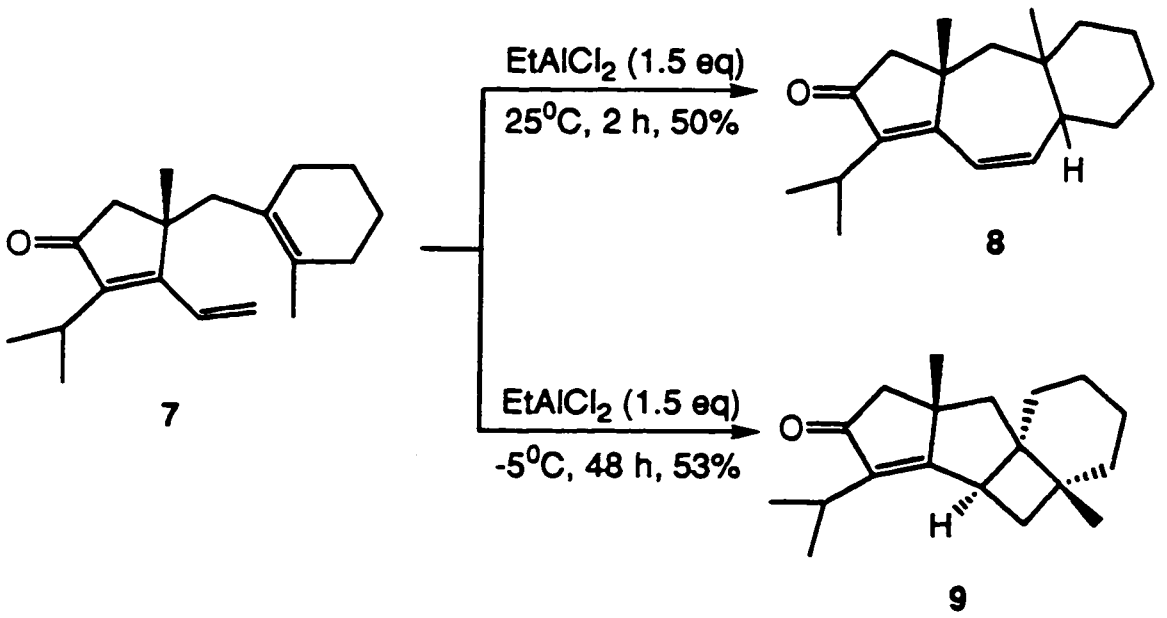
Majetich[15] carried out the polyene cyclization of the conjugated dienones using Lewis acid catalysis. In this process, treatment of **7** with excess ethylaluminum dichloride at low temperature gave tetracyclic enone **9** in 53% yield, while

reaction at room temperature led to a comparable yield of tricyclic dienone **8** (Scheme 7).



4 **5** **6**

Scheme 6



7 **8** **9**

Scheme 7

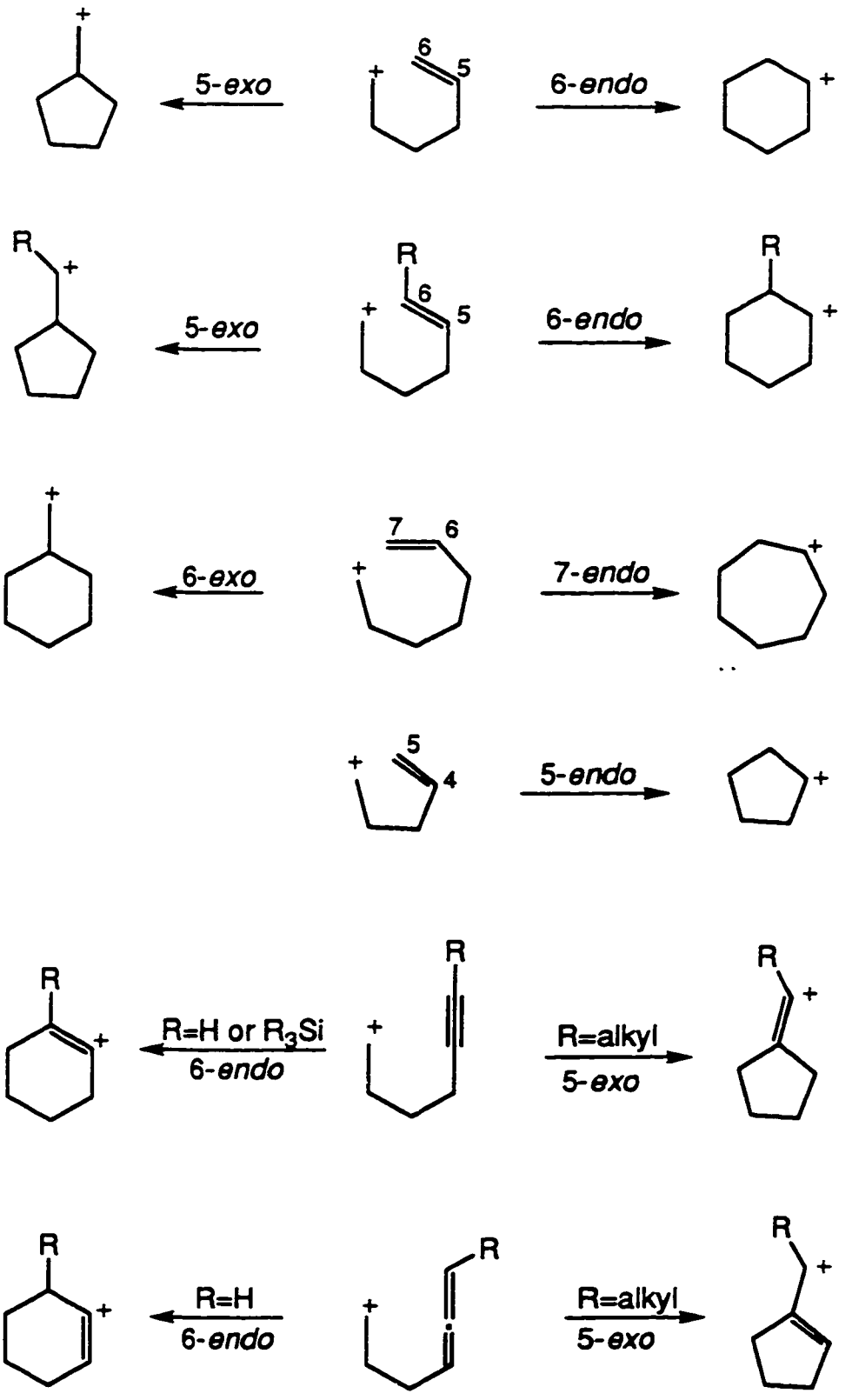
Propagation of Cyclization

After generation of the cationic center, the specific course of the cyclization depends on the initiator (functionality generating the carbocation) and the nucleophilicity of the double bond involved. However, some generalizations about the cyclization product have been established and are summarized in Scheme 8.

Where a double bond is 5,6 to the initiating center and electronically unbiased or substituted at C-5, then 6-*endo* cyclization is almost invariably favored over the 5-*exo* mode. When there is additional substitution at C-6 polarizing the double bond, then the 5-*exo* cyclization is preferred. In this case, the products of cyclization can be complicated by the cyclopentylmethyl cation undergoing rearrangement following the cyclization.

A double bond 6,7 to the initiating center leads to 6-*exo* cyclization, unless this contravenes the Markovnikov rule, in which case 7-*endo* cyclization takes place. With 4,5 double bonds, the 5-*endo* cyclization is seldom observed in accord with the Baldwin rules.

The participation of allenyl and alkynyl moieties usually results in the formation of the ring. Alkynyl groups at carbons 5 and 6 relative to the cationic center cyclize in a 6-*endo* manner when the terminal group is hydrogen or silyl. However, dialkylalkynes have kinetic preference for 5-*exo* cyclization. In certain cases, the 5-*exo* cations can rearrange to the thermodynamically more stable 6-*endo* ions.

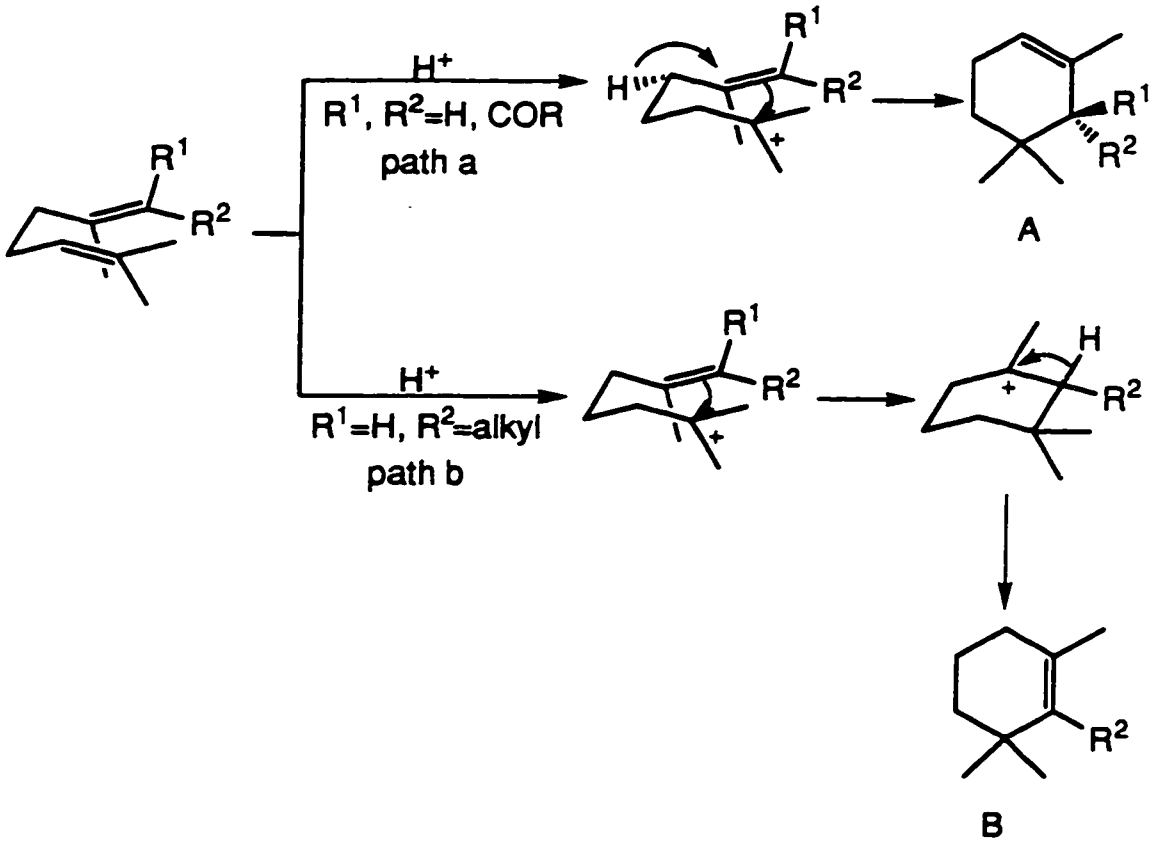

5-exo
6-endo
5-exo
6-endo
6-exo
7-endo
5-endo
R=H or R3Si
6-endo
R=alkyl
5-exo
R=H
6-endo
R=alkyl
5-exo

Scheme 8

Similar behavior is observed for 6,7-alkynes. The terminal alkynes give 7-membered rings, while dialkylakynes undergo 6-*exo* cyclization to cyclohexanes. An allenyl group 4,5,6 relative to the initiating center with at least one terminal alkyl group induces 5-membered ring formation, whereas with a CH_2 terminus both 5- and 6-membered rings have been observed.

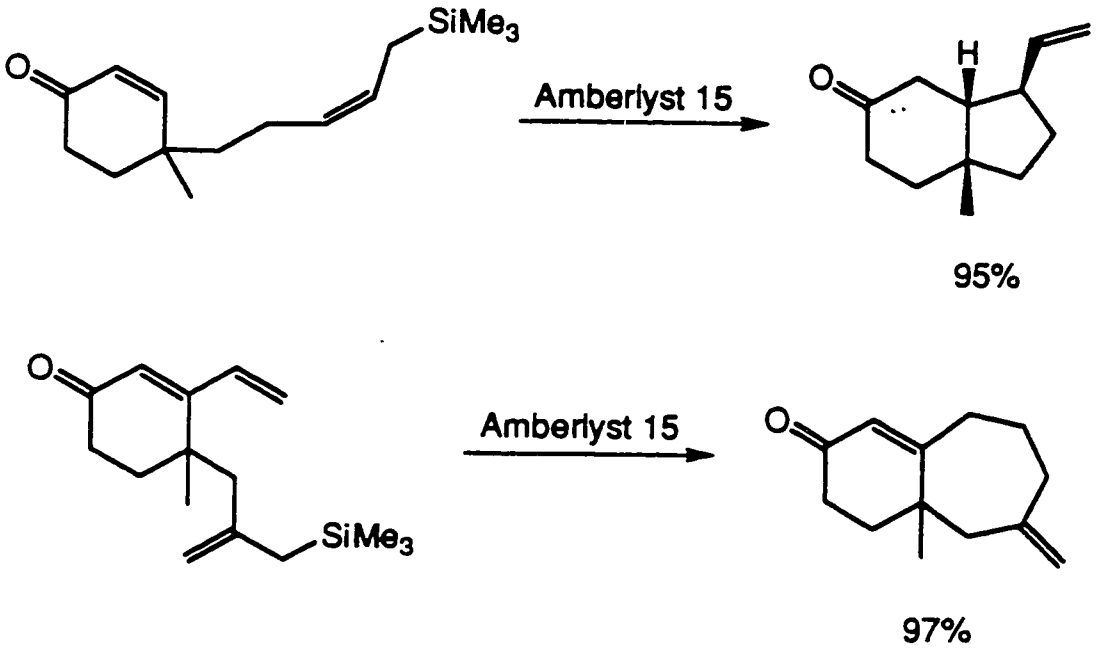
When substituents are bonded to sp^3-hybridized carbons between the reacting double bonds for the 6-membered ring formation, the model with the substituent adopting an equatorial disposition in the chair-like transition state has strong predictive value.

Termination of Cyclization



Scheme 9

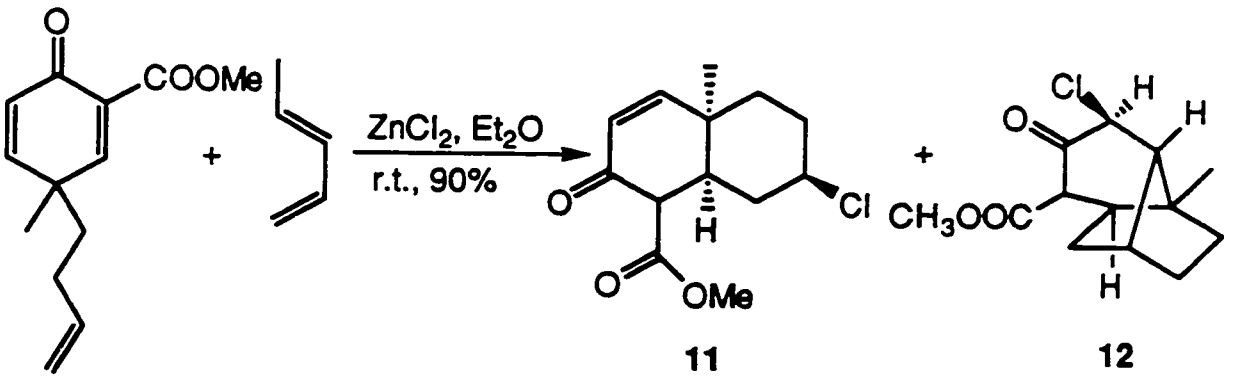
A synthetically useful cationic cyclization must be terminated by one mechanism giving a single product. Termination can be achieved by elimination and/or attack by an internal or external nucleophile as shown in Scheme 3. Proton elimination can be regioselective or random. Extensive studies by Schinz[22-24] and Semenovskii[25] on the cyclization of geraniol and its derivatives suggested that when nucleophilicity of the double bond is low, a concerted cyclization-elimination (path a, Scheme 9), is favored over the two-step process, since only isomer A was obtained when an electron withdrawing group is conjugated to the second double bond. Otherwise, the formation of the cyclized carbocation leads to the most stable alkene B (path b).



Scheme 10

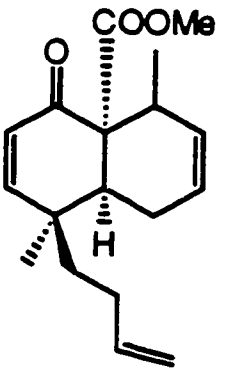
Proton elimination is the most common termination mode for tertiary cations and also for secondary cations when the cyclizing reagent is a Lewis acid. With Brϕnsted acids, nuclephilic attack is often observed and is usually stereoselective. The lack of predictability when alkenes terminate cyclization

has led to the development of terminators whereby the products can be more precisely anticipated.[2] Schinzer[26] introduced the silyl group as a terminator for the polyene cyclization of enones in the presence of a catalyst. Using this process, enones were cyclized to the corresponding bicyclic compounds in good yields (Scheme 10).



10 **11** **12**

Scheme 11



13

During the course of our synthetic studies on *cis*-clerodanes, enone ester **10** was subjected to Diels-Alder reaction under Lewis acid catalysis. Interestingly, treatment of **10** and *trans*-piperylene in the presence of zinc chloride gave rise to cyclic compounds **11** and **12** (Scheme 11), instead of the expected Diels-

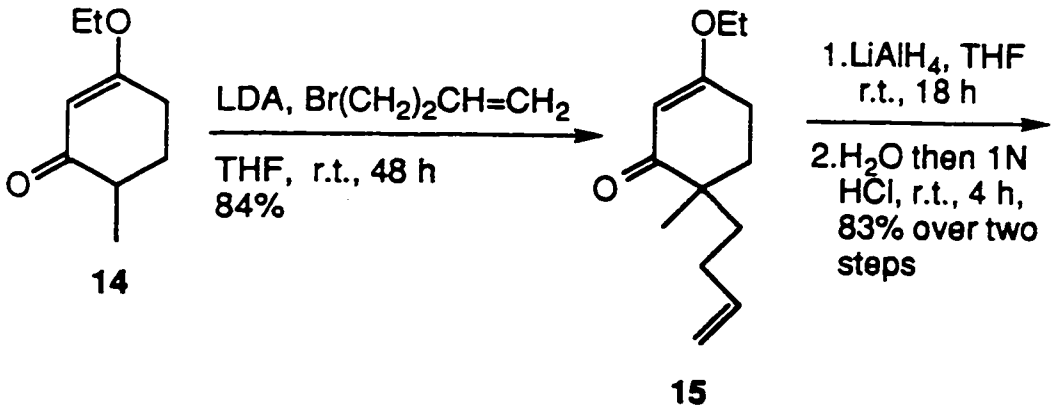
Alder adduct **13**. These observed products were apparently formed *via* intramolecular cyclization promoted by the cross conjugated enone ester system. As a result of this serendipitous discovery, we have carried out an extensive study on the polyene cyclization promoted by the cross conjugated α-carbomethoxy enone system. The results will be discussed in the following section.

Results and discussion

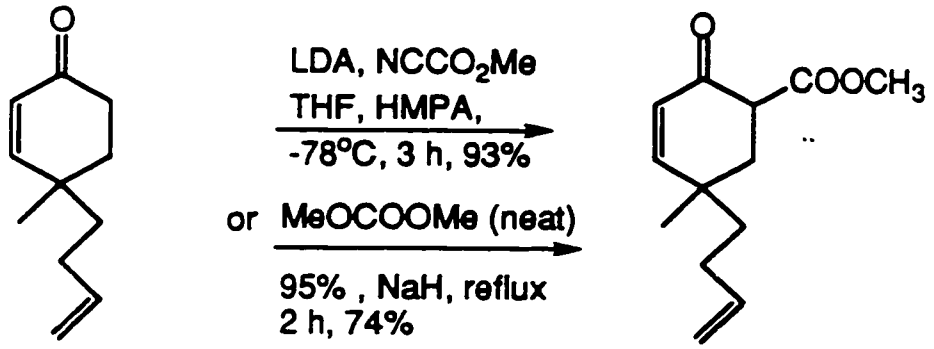
The study on polyene cyclization promoted by the cross conjugated α-carbalkoxy enone system began with enone ester **10**. This compound was readily prepared from 3-ethoxy-6-methyl-2-cyclohexenone (**14**)[27] *via* a sequence involving four synthetic operations as shown in Scheme 12.

Stork-Danheiser alkylation of enone **14** with lithium diisopropylamide (LDA) and 4-bromo-1-butene followed by flash chromatography gave compound **15** in 84% yield. This compound was reduced with lithium aluminum hydride, followed by hydrolysis with dilute hydrochloric acid to give cyclohexenone **16** in 83% yield over two steps. The structure of **16** was assigned by spectroscopic methods. The ir spectrum showed a carbonyl absorption at 1684 cm^{-1}, indicating the presence of an enone. In the ^1H nmr spectrum, two doublets at δ 6.70 and 5.90 with the same coupling constant (J=10 Hz) were attributed to the two vinylic protons of the enone moiety. Three additional vinylic protons appeared at δ 5.80 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.04 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.96 (dddd J=10, 1.5, 1.5, 1.5 Hz). The methyl group appeared at δ 1.15 as a sharp singlet. The high resolution mass spectrum showed a molecular ion peak at m/z 164.1199, corresponding to the molecular formula $C_{11}H_{16}O$. The elemental analysis was also in agreement with the molecular composition. The carbomethoxy group was introduced by treating **16** with sodium hydride and dimethyl carbonate to give keto ester **17** in 74% yield as a mixture of three isomers (two epimers and an enol tautomer) in a ratio of 1:1:3 as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{13}H_{18}O_3$ by elemental analysis and by its high resolution mass spectrum

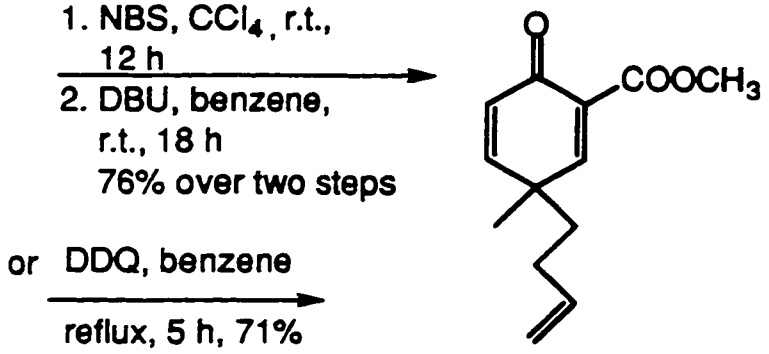
displaying a molecular ion peak at m/z 222.1256. Keto ester **17** could also be prepared in 93% yield using LDA and methyl cyanoformate.[28]



14 **15**



16 **17**



10

Scheme 12

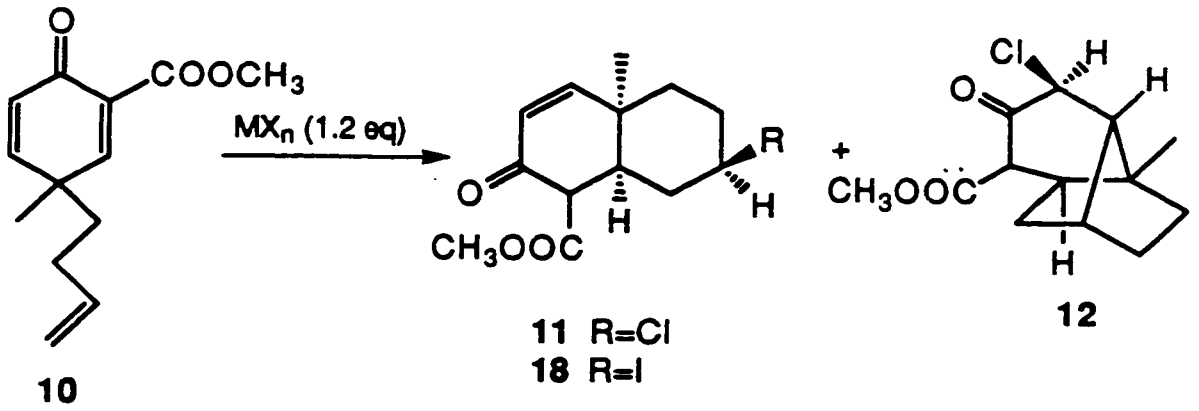
Oxidation of **17** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[29-30] in refluxing benzene gave the required enone ester **10** (71% yield). The ir spectrum showed two carbonyl absorptions at 1742 and 1665 cm^{-1}, indicating the presence of an ester and an enone, which were corroborated by the signals in the ^1H nmr spectrum at δ 7.50 (d, J=3 Hz, H_3), 6.75 (dd, J=10, 3 Hz, H_5), 6.32 (d, J=10 Hz, H_6) and 3.87 (s, 3H, OCH_3). Three additional vinylic protons appeared at δ 5.70 (dddd, J=17, 10, 6.5, 6.5 Hz), 4.97 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.95 (dddd J=10, 1.5, 1.5, 1.5 Hz), and an additional methyl singlet was observed at δ 1.31. The high resolution mass spectrum displayed a molecular ion peak at m/z 220.1098. This along with the elemental analysis confirmed the required molecular formula $C_{13}H_{16}O_3$. Compound **10** could also be prepared in 76% yield using a bromination-dehydrobromination process by sequential treatment with *N*-bromosuccinimide (NBS) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

With enone ester **10** in hand, we were able to study its cyclization using various Lewis acids and temperatures. The particular Lewis acids (zinc chloride, stannic chloride, aluminum chloride and zinc iodide) were chosen because they had been noted previously as appropriate catalysts for the related polyene cyclizations. The results are summarized in Table 1.

When enone ester **10** was treated with anhydrous zinc chloride at room temperature in diethyl ether, compounds **11** and **12** were formed in 90% yield in 2.6:1 ratio. When zinc chloride was replaced by aluminum chloride, a remarkable enhancement of the reaction rate as well as selectivity was observed. The reaction occurred almost instantaneously even at -78°C and bicyclic compound **11** was produced exclusively in 75% yield. The use of zinc

iodide as a reagent led to the formation of iodide **18** as the sole product in 85% yield. On the other hand, when stannic chloride was used as a reagent and dichloromethane as a solvent, a rapid cyclization took place giving tricyclic compound **12**, instead of bicyclic compound **11**, as the predominant product. Two other Lewis acids, ethylaluminum chloride and titanium tetrachloride, were also examined. These reagents were found to be also effective, but the product selectivity in favor of the bicyclic compound was inferior to that using aluminum chloride.

Table 1. Polyene cyclization of compound **10** using various Lewis acids



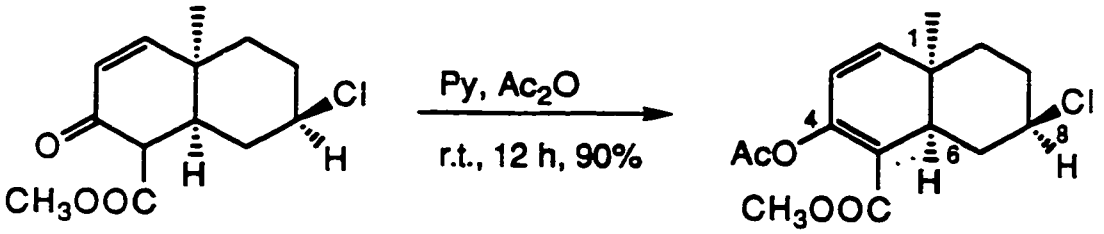
10

11 R=Cl
18 R=I

12

Lewis acid	solvent	temp (°C)	time	yield (%)	ratio (**11**:**12**)
$ZnCl_2$	Et_2O	25	3 h	90	2.6 : 1
$AlCl_3$	Et_2O	-78	15 min	75	1 : 0
$EtAlCl_2$	CH_2Cl_2	-78	1 h	78	2.1 : 1
$TiCl_4$	CH_2Cl_2	-78	2 min	86	3 : 1
$SnCl_4$	CH_2Cl_2	-78	5 min	92	1 : 2.5
ZnI_2	Et_2O	25	3 days	85	**18** only

Compound **11** showed a molecular ion peak at m/z 256.0868 in its high resolution mass spectrum, which was consistent with the molecular formula $C_{13}H_{17}ClO_3$. Compound **11** was obtained as an inseparable mixture of isomers due to the presence of the highly enolizable and epimerizable β-keto ester moiety. The regiochemistry and stereochemistry of this compound was assigned as follows. Treatment of compound **11** with acetic anhydride in pyridine gave rise to the corresponding enol acetate **19** (Scheme 13) whose structure was confirmed by spectroscopic methods, especially nmr spectroscopy with the assistance of NOE experiments.



11 **19**

Scheme 13

The ir spectrum of acetate **19** displayed two carbonyl absorptions at 1766 and 1711 cm^{-1}. The high resolution mass spectrum showed a molecular ion peak at m/z 298.0982, corresponding to the required molecular formula $C_{15}H_{19}ClO_4$, which was also supported by elemental analysis. In the ^1H nmr spectrum, the splitting pattern (ddd, J=12.5, 4.5, 2 Hz) observed for the C_6 proton at δ 2.62 suggested that this compound was *cis*-fused. The additional coupling (2 Hz) was due to the long range *w*-coupling with H_2 at δ 5.97 (dd, J=10, 2 Hz). This type of coupling is possible only for the *cis* system. In the ^{13}C APT nmr spectrum, a total of 15 signals was obtained. Two carbonyl signals appeared at δ 168.5 and 165.4. There were four signals between δ 151.6 and 116.2, indicating the presence of two carbon-carbon double bonds. The

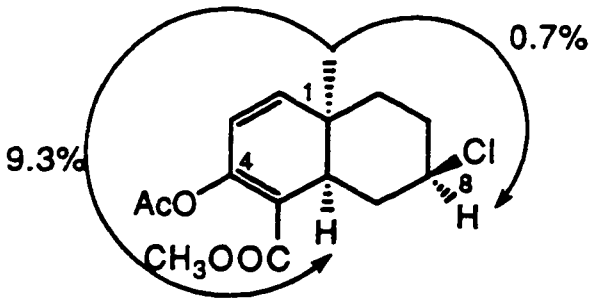
regiochemistry of compound **19** was confirmed by ^1H nmr decoupling experiments. The complete ^1H nmr data of compound **19** are shown in Table 2.

Table 2. ^1H nmr data of compound **19**

Proton	δ (in ppm)	Multiplicity (J in Hz)
H_2	5.97	dd (10, 2)
H_3	5.70	d (10)
OMe	3.80	s
H_8	3.70	m
H_6	2.62	ddd (12.5, 4.5, 2)
H_{7e}	2.22	dddd (13, 4, 4, 2)
MeC=O	2.17	s
H_{9e}	2.05	dddd (14, 3, 3, 1.5)
H_{10e}	1.72	ddd (14, 3, 3)
H_{7a}, H_{9a}	1.50-1.65	m
H_{10a}	1.35	ddd (14, 14, 3)
C_1 Me	1.04	s

The *cis* ring junction of compound **19** was further confirmed by NOE experiments which also provided useful information for assigning the

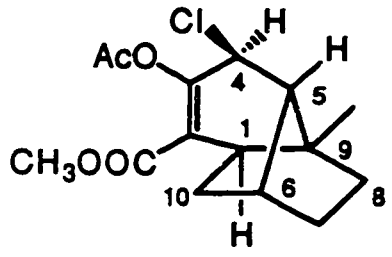
stereochemistry of C_8. As shown in Figure 1, irradiation of the C_1 methyl at δ 1.04 resulted in enhancements of H_6 (9.3%) and H_8 (0.7%). Based on the above spectral data, structures **11** and **19** could be assigned to the bicyclic compound and the corresponding enol acetate, respectively.



19

Figure 1. NOE data of compound **19**

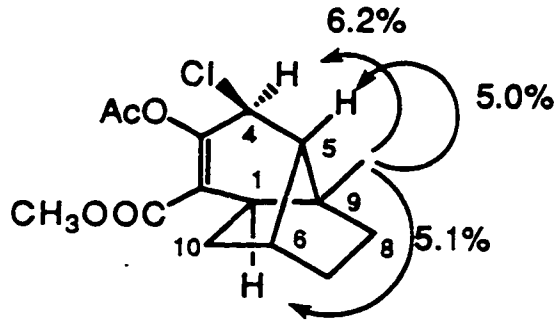
Similar acetylation of tricyclic compound **12** afforded enol acetate **20**. Its structure was also verified spectroscopically. The high resolution mass spectrum showed a molecular ion peak at m/z 298.0963, corresponding to the molecular formula $C_{15}H_{19}ClO_4$, which was supported by elemental analysis. The ir spectrum displayed two carbonyl absorptions at 1765 and 1719 cm^{-1}. The ^{13}C APT nmr spectrum displayed only one set of signals, including two carbonyl signals at δ 168.6 and 164.8 as well as two olefin signals at δ 149.6 and 130.7. The complete assignment of the ^1H nmr spectrum (Table 3) was assisted by extensive ^1H nmr decoupling experiments.



20

Table 3. ^1H nmr data of compound **20**

Proton	δ (in ppm)	Multiplicity (J in Hz)
H_4	4.90	d (7)
OMe	3.75	s
H_6	2.65	m
H_1	2.55	dd (7, 2)
MeC=O	2.20	s
H_5	2.08	dd (7, 1)
H_7, H_8, H_{10} (two each)	1.20-1.90	m
C_9 Me	1.15	s



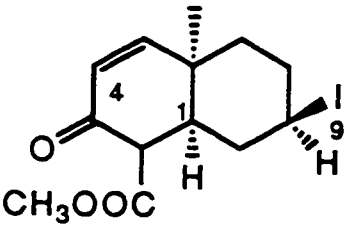
20

Figure 2. NOE data of compound **20**

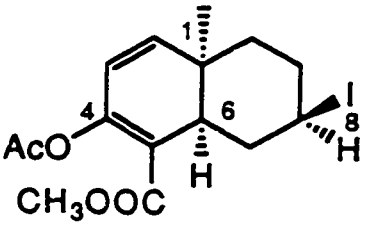
The stereochemistry of enol acetate **20** was also assigned on the basis of NOE experiments (Figure 2). Irradiation of the C_9 methyl at δ 1.15 resulted in

enhancements of H_5 (5.0%), H_4 (6.2%) and H_1 (5.1%). Thus, the tricyclic compound and its acetate were assigned to structures **12** and **20**, respectively.

The iodo compound was assigned to structure **18** based on structure **21** of its acetate, which was established by spectroscopic methods.



18



21

In the ir spectrum of acetate **21**, two carbonyl absorptions were observed at 1765 and 1709 cm^{-1}. The ^1H nmr spectrum assignments are summarized in Table 4. In the ^{13}C APT nmr spectrum, a total of 15 signals were observed. The carbonyl carbons appeared at δ 168.5 and 165.4. The appearance of four signals at δ 151.5, 145.2, 123.9 and 116.2 indicated the presence of two carbon-carbon double bonds. The high resolution mass spectrum displayed a molecular ion peak at m/z 390.0389, which corresponded to the formula $C_{15}H_{19}IO_4$.

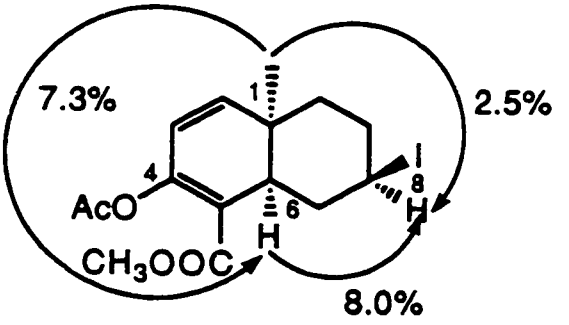


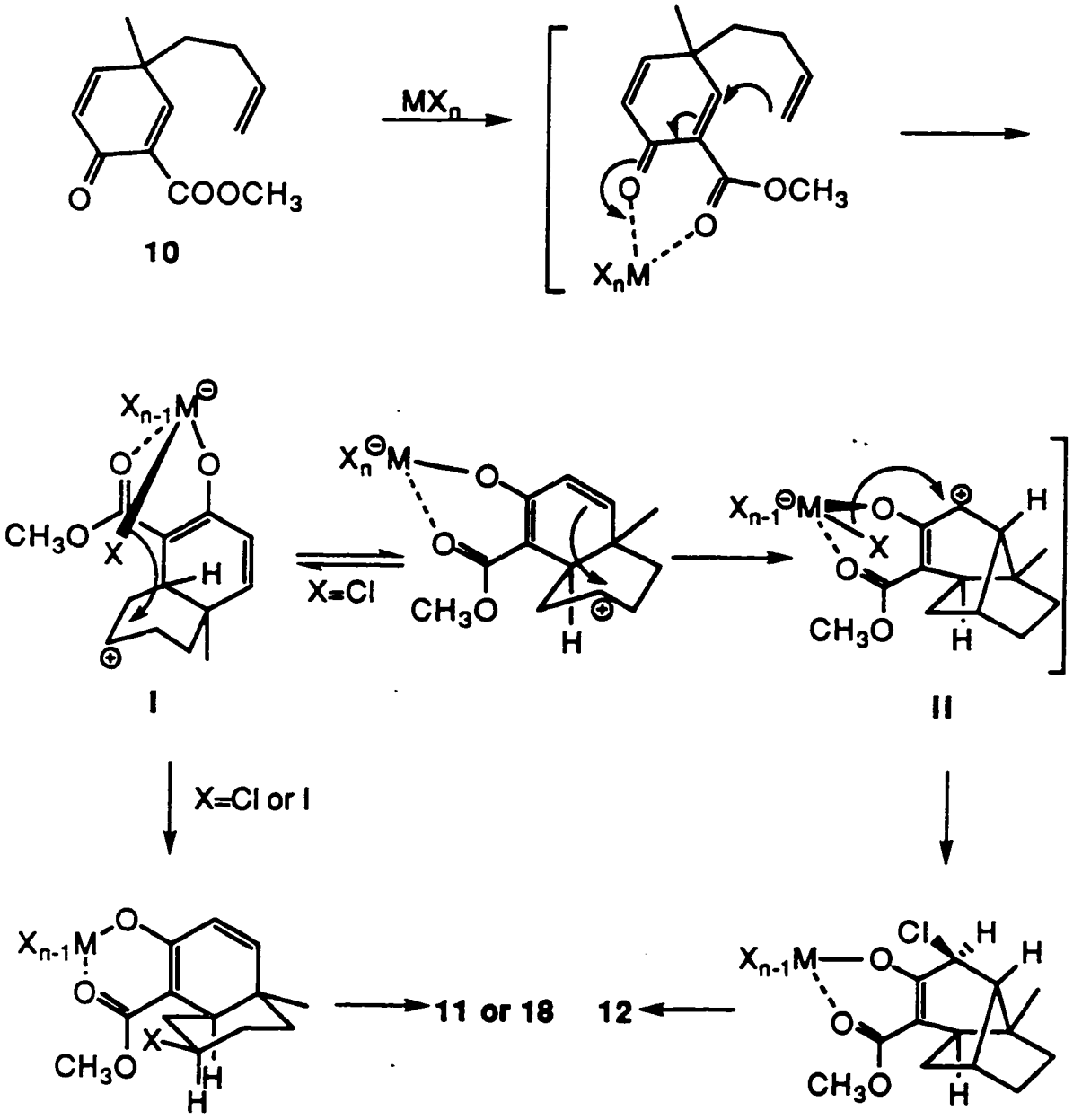
Figure 3. NOE data of compound **21**

The all-*cis* relationship of H_6, H_8 and the angular methyl group was deduced by NOE experiments. As shown in Figure 3, irradiation of the C_1 methyl at δ 0.95 resulted in enhancements of H_6 (7.3%) and H_8 (2.5%), whereas irradiation of H_6 led to a 8.0% enhancement of H_8.

Table 4. ^1H nmr data of compound **21**

Proton	δ (ppm)	Multiplet (J in Hz)
H_2	6.00	dd (9.5, 1.5)
H_3	5.80	d (9.5)
H_8	4.00	dddd (12, 12, 4, 4)
OMe	3.75	s
H_6	2.60	ddd (12, 4, 1.5)
H_{7e}	2.50	m
H_{9e}	2.36	m
MeC=O	2.20	s
H_{7a}, H_{10e}	1.82-2.10	m
H_{9a}	1.58	m
H_{10a}	1.43	m
C_1 Me	0.95	s

In addition to its high efficiency, the regio- and stereoselectivity observed for the above cyclization process as well as the unusual mode of termination *via* halide formation are of considerable interest. A mechanistic rationale is depicted in Scheme 14.



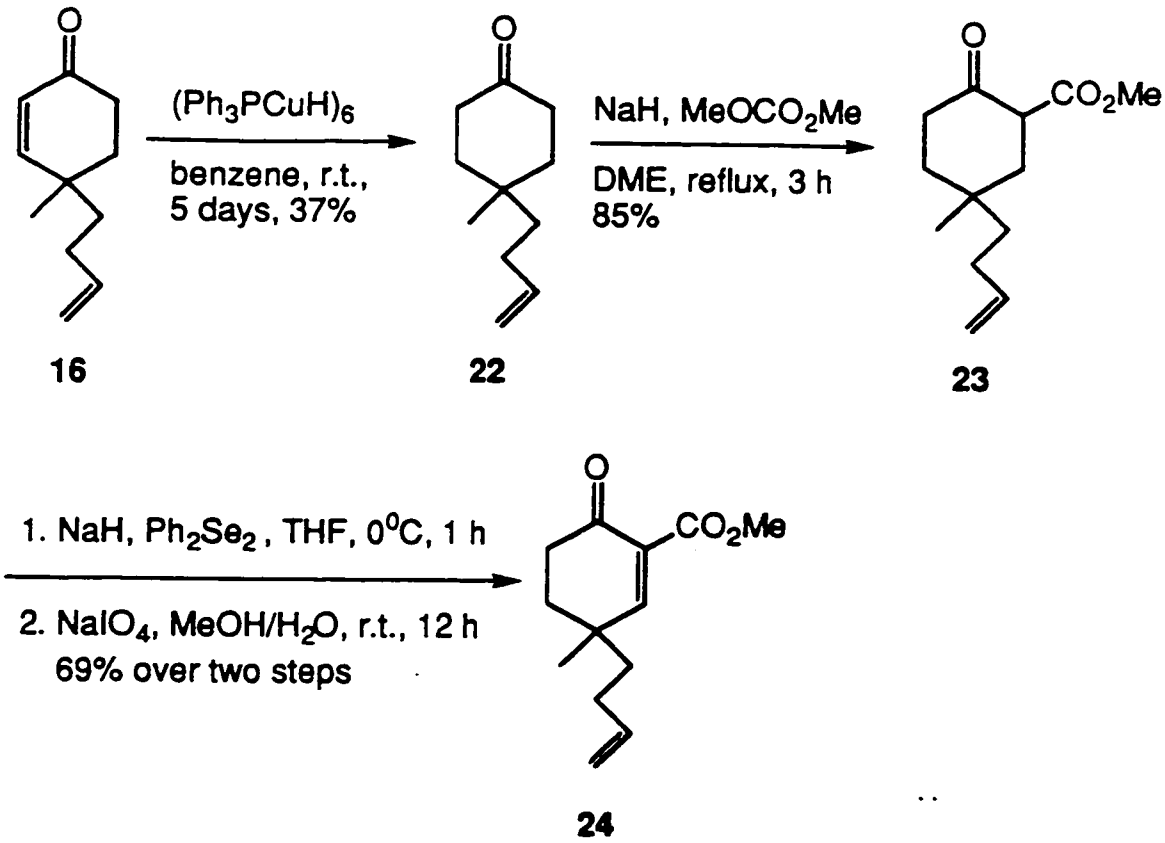
Scheme 14

It is conceivable that halide formation with the specific stereochemistry in all cases **11**, **12** and **18** is a result of intramolecular transfer of the halide ion from the metal to the incipient carbocation **I** or **II**. It is also noteworthy that the formation of tricyclic compound **12** requires the participation of the β-carbon of the conjugated enone system. This is rather unusual, but could be explained by invoking the intermediacy of the allyl carbocation **II**. The ratio between the bicyclic and tricyclic compounds produced depends on the Lewis acid used. It is probable that, when zinc iodide or aluminum chloride is used as a reagent, the intermediate **I** rapidly delivers a halide to the carbon cation in an intramolecular fashion. Thus, the bicyclic compound is produced as the sole product. On the other hand, when stannic chloride is used, the corresponding intermediate delivers the chloride somewhat less effectively, allowing participation of the β-carbon of the conjugated enone system leading eventually to the preferential formation of the tricyclic compound.

At this point, we became interested in evaluating the potential influence of the additional carbon-carbon double bond present in enone ester **10** on the observed facile cyclization. Towards this end, enone ester **24** was prepared and its cyclization investigated.

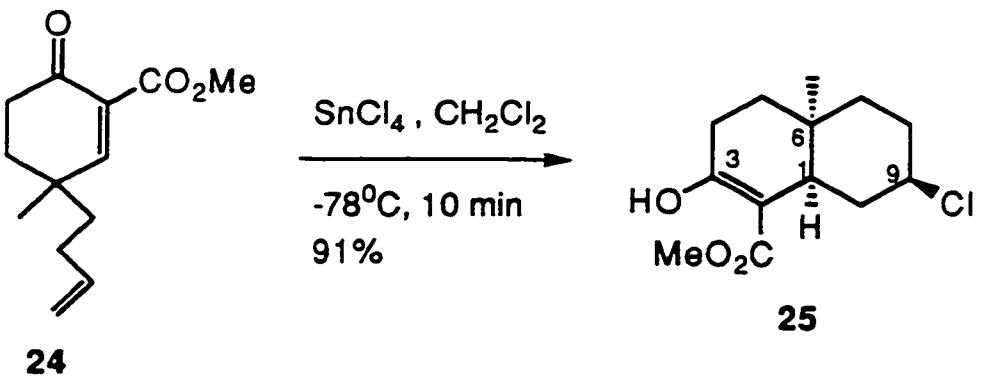
The preparation of enone ester **24** started with reduction of the conjugated carbon-carbon double bond of enone **16** (Scheme 15). The most popular method, catalytic hydrogenation, was not suitable, as the isolated carbon-carbon double bond would be reduced indiscriminately. Hydrosilylation using Wilkinson's catalyst and dissolving metal reduction were then considered to selectively reduce the conjugated double bond. Unfortunately, complicated results were observed in both cases. We then turned to a useful reducing

agent, the hexamer of (triphenylphosphine)copper hydride $(Ph_3PCuH)_6$.[33] It was reported that the reagent was effective and selective in reducing the carbon-carbon double bonds of conjugated ketones, aldehydes, esters, nitriles, and sulfones in the presence of isolated olefins, carbonyls, halogens and typical oxygenated functionalities. When enone **16** was treated with 0.5 equivalent of $(Ph_3PCuH)_6$ at room temperature for 5 days, a 37% yield of ketone **22** was obtained along with the recovered starting material. The structure of ketone was readily assigned to be **22** by the normal spectroscopy. In the ir spectrum, the carbonyl absorption appeared at 1716 cm^{-1}. In the ^1H nmr spectrum, three vinylic protons appeared at δ 5.83 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.30 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.95 (dddd J=10, 1.5, 1.5, 1.5 Hz). A methyl singlet was found at δ 1.08. The ^{13}C APT nmr spectrum displayed a carbonyl carbon at δ 212.5 and two vinylic carbons at δ 139.1 and 114.4 indicating the presence of a carbon-carbon double bond. The high resolution mass spectrum showed a molecular ion peak at m/z 166.1358 corresponding to the formula $C_{11}H_{18}O$. Carbomethoxylation of **22** with dimethyl carbonate and sodium hydride afforded keto ester **23** in 85% yield as a mixture of keto and enol forms in a ratio of 1:2 as indicated by its ^1H nmr spectrum. Its molecular formula was confirmed as $C_{13}H_{20}O_3$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 224.1409. Phenylselenenylation using diphenyl diselenide and sodium hydride, followed by oxidative elimination with sodium periodate furnished enone ester **24** in 69% yield. The ir spectrum of this compound displayed carbonyl absorptions at 1745 cm^{-1} for the ester and 1686 cm^{-1} for the ketone. In the ^1H nmr spectrum, a sharp singlet at δ 7.40 was observed for H_3. Three additional vinylic protons appeared at δ 5.80 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.05 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.99 (dddd J=10, 1.5, 1.5, 1.5 Hz).



Scheme 15

With keto ester **24** in hand, we were able to examine its cyclization. When compound **24** was treated with stannic chloride in methylene chloride at -78°C for 10 min, it cyclized readily to give compound **25** in a 91% yield (Scheme 16). The ir spectrum showed absorptions at 3600 (OH, enol), 1652 (C=O, enol ester) and 1614 cm^{-1} (C=C, enol). The ^1H nmr spectrum indicated that this compound existed exclusively in the enol form. The enol proton appeared at δ 12.3 as a singlet. A multiplet at δ 3.80 was attributed to the proton attached to the carbon with a chlorine. The methoxy and methyl singlets appeared at δ 3.75 and 0.90, respectively. The ^{13}C APT nmr spectrum displayed a carbonyl carbons at δ 172.8 and two vinylic carbons at δ 172.0 and 100.6. Its molecular formula $C_{13}H_{19}ClO_3$ was in agreement with the molecular ion peak observed at m/z 258.1020 in the high resolution mass spectrum.



24 **25**

Scheme 16

For comparison, enones **16** and **17** were also subjected to similar treatment with stannic chloride. No reaction was observed for the former compound even after 24 h at room temperature. In the latter case, the starting material was intact at low temperature. At room temperature, a complex mixture was formed upon complete consumption of the starting material, which took about 2 h.

From the above findings, it could be concluded that the cross conjugated β-keto ester system can serve as an excellent promoter for cationic cyclization. The cyclization is highly efficient in terms of the yield of product and the high degree of regio- and stereochemical control.

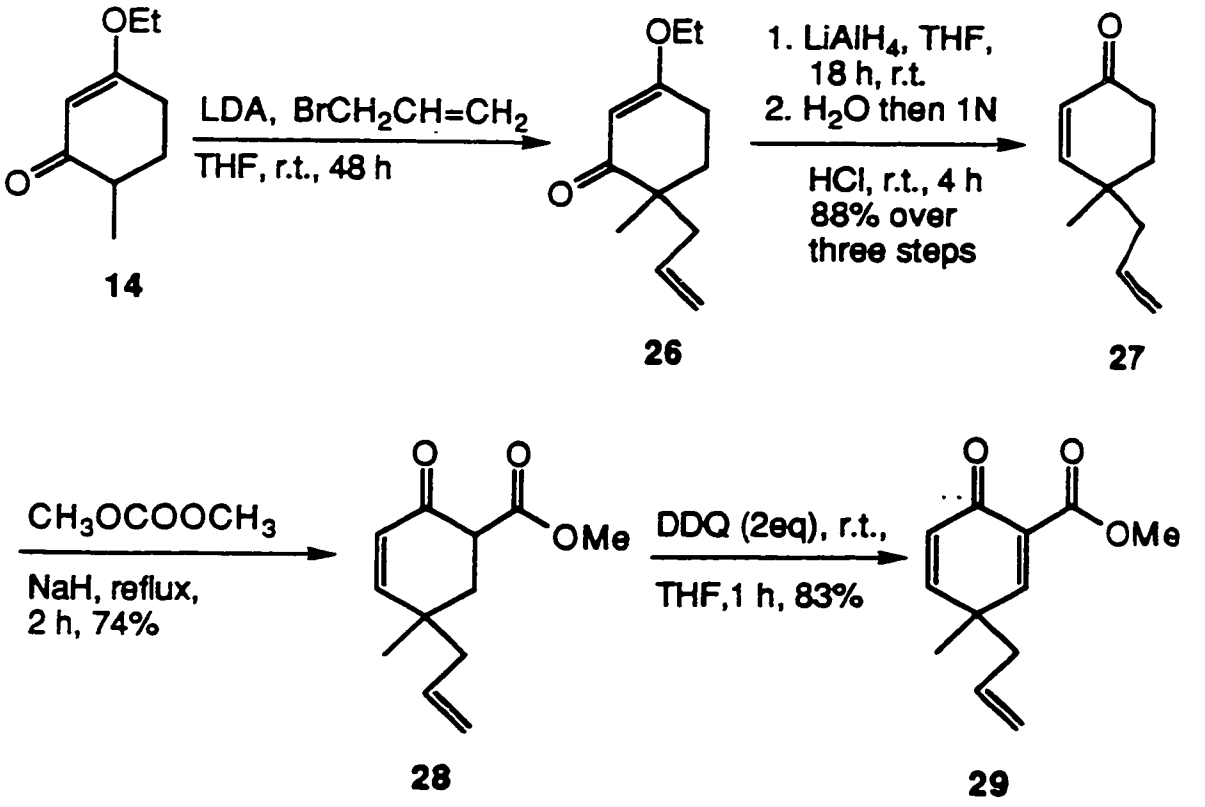
These encouraging results led us to examine the influence of the C_4 side chain on the cyclization. First, we decided to reduce the chain to a three-carbon unit. The required keto ester **29** was readily prepared from enone ester **14** according to Scheme 17.

Alkylation of **14** with LDA and allyl bromide afforded compound **26**. This compound was subjected to reduction with $LiAlH_4$, followed by acidic hydrolysis with 1 N HCl to afford enone **27** (88% yield from **14**), which displayed a

carbonyl absorption at 1681 cm^{-1} in its ir spectrum. In the ^1H nmr spectrum, the two vinylic protons of the enone moiety appeared at δ 6.65 and 5.87, each as a doublet with a coupling constant of 10 Hz. Three additional vinylic protons appeared at δ 5.77 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.08 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 5.04 (dddd J=10, 1.5, 1.5, 1.5 Hz). The high resolution mass spectrum displayed a molecular ion peak at m/z 150.1045 corresponding to the required formula $C_{10}H_{14}O$. Carbomethoxylation of **27** using dimethyl carbonate and sodium hydride afforded a 74% yield of keto ester **28** as a mixture three isomers in a ratio of 1:1:1 as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{12}H_{16}O_3$ by both the elemental analysis and the high resolution mass spectrum. The latter displayed a molecular ion peak at m/z 208.1095. Oxidation of **28** with DDQ in THF afforded enone ester **29** in 83% yield. The enone ester structure was assigned to be **29** by spectroscopic methods. In the ir spectrum, two carbonyl absorptions were observed at 1745 cm^{-1} (ester) and 1684 cm^{-1} (ketone). In the ^1H nmr spectrum, a doublet at δ 7.50 (J=3 Hz) was observed for H_3. Two vinylic protons of the enone system appeared at δ 6.76 (dd, J=10, 3 Hz) and 6.30 (d, J=10 Hz). Three additional vinylic protons appeared at δ 5.59 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.10 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 5.07 (dddd J=10, 1.5, 1.5, 1.5 Hz). The ^{13}C APT nmr spectrum displayed two carbonyl absorptions at δ 181.6 and 165.2, and six signals between δ 160.3 and 119.7 indicating the presence of three carbon-carbon double bonds. The high resolution mass spectrum showed a molecular ion peak at m/z 206.0943, corresponding to the required formula $C_{12}H_{14}O_3$.

With the desired enone ester **29** in hand, we then went on to examine its cyclization catalyzed by Lewis acid. Stannic chloride and zinc chloride were selected as reagents as it had been observed previously that these Lewis acids

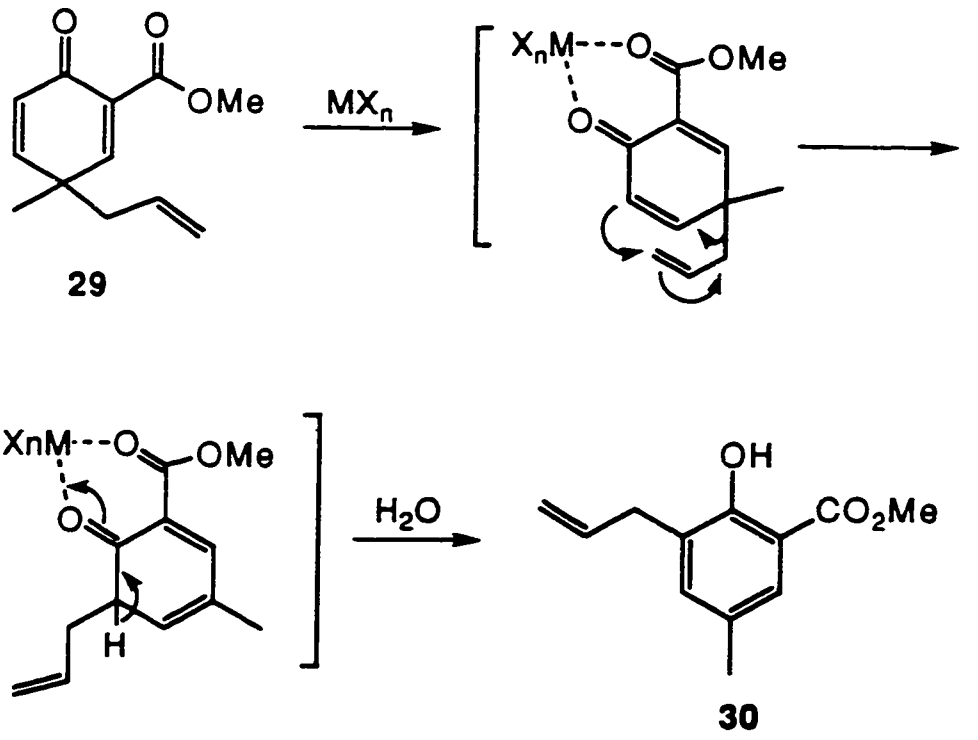
were suitable for the polyene cyclizations. Unfortunately, attempted cyclization of **29** using either of these Lewis acids resulted in the exclusive formation of the aromatization product **30**, presumably *via* a [3,3]-sigmatropic rearrangement as shown in Scheme 18. The results are outlined in Table 5.



Scheme 17

Table 5. Aromatization of compound **29** under Lewis acid catalysis

MX_n	solvent	temp (°C)	time	yield (%)
$ZnCl_2$	Et_2O	25	1 h	86
$SnCl_4$	CH_2Cl_2	-78	15 min	88

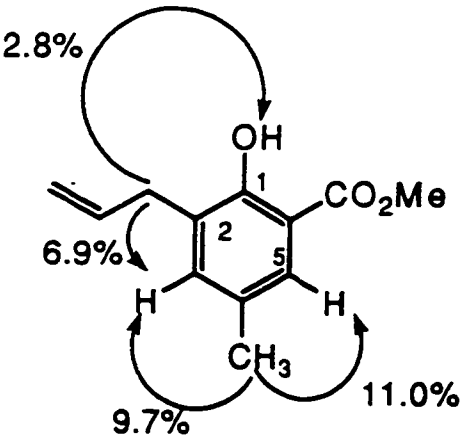


Scheme 18

The high resolution mass spectrum of compound **30** showed a molecular ion peak at m/z 206.0943 corresponding to the formula $C_{12}H_{14}O_3$. In the ir spectrum, the ester and phenol absorptions were observed at 1675 and 3171 cm^{-1}, respectively. The ^{13}C APT nmr spectrum displayed a carbonyl carbon at δ 171.0 and eight sp^2 carbons between δ 157.5 and 111.6 indicating the presence of a benzene ring and a carbon-carbon double bond. In the ^1H nmr spectrum, a sharp singlet at δ 10.8 was easily recognized for the phenolic proton. The two aromatic protons appeared at δ 7.55 (H_5) and 7.15 (H_3), each as a narrowly split doublet with a coupling constant of 1.5 Hz. From this coupling pattern, it is clear that the aromatic protons have a *meta* relationship.

The regiochemistry was further confirmed by NOE experiments. As shown in Figure 4, irradiation of the C_4 methyl at δ 2.30 resulted in enhancements of H_5

(11.0%) and H_3 (9.7%). Irradiation of the methylene group at δ 3.40 resulted in enhancements of the phenolic proton (2.8%) and H_3 (6.9%). Therefore, the aromatization product was assigned to structure **30**.



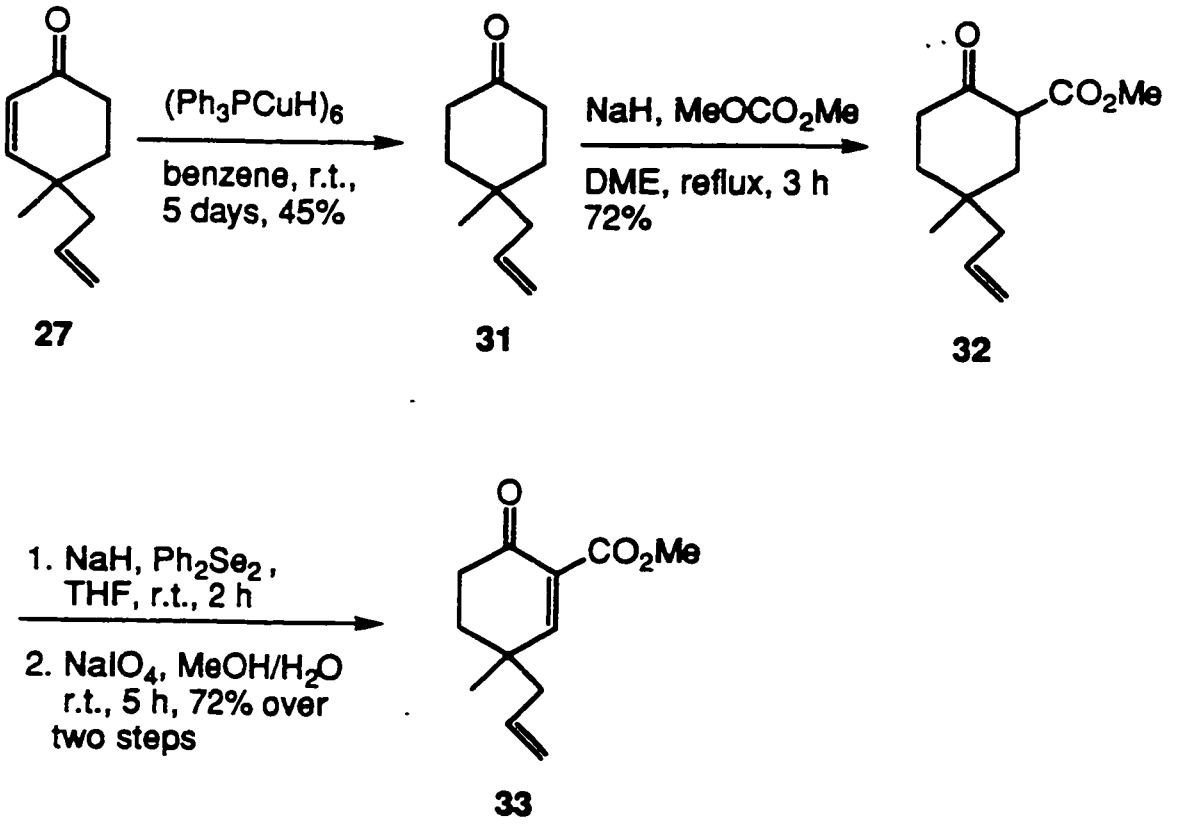
30

Figure 4. NOE data of compound **30**

The above results clearly indicated that the allyl migration-aromatization process occurred at a faster rate than the desired polyene cyclization. One possible solution to this problem would be to remove the carbon-carbon double bond required for the skeletal rearrangement.

Towards this end, enone **27** was subjected to reduction with the hexamer of (triphenylphosphine)copper hydride, $(Ph_3PCuH)_6$, to give ketone **31** in 45% yield (Scheme 19). The reaction was very slow and a substantial amount of the starting material was recovered after 5 days. Carbomethoxylation of **31** with dimethyl carbonate and sodium hydride afforded keto ester **32** in 72% yield as a mixture of keto and enol forms in a ratio of 1:9 as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{12}H_{18}O_3$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 210.1258. Phenylselenylation of **32** using diphenyl diselenide and sodium hydride,

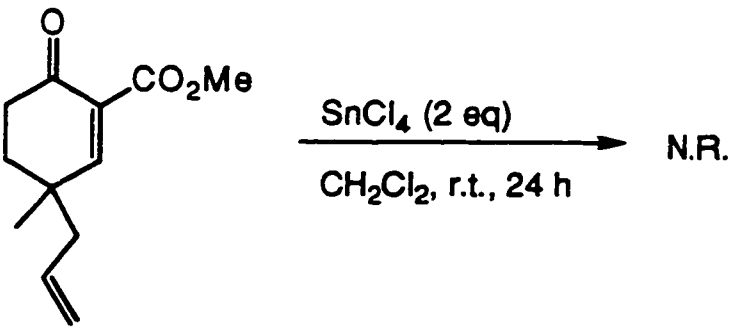
followed by oxidative elimination with sodium periodate gave enone ester **33** in 72% yield over two steps. The ir spectrum of this compound showed carbonyl absorptions at 1745 cm^{-1} for the ester and 1689 cm^{-1} for the ketone. In the ^1H nmr spectrum, a sharp singlet at δ 7.40 was observed for the C_3 proton. Three additional vinylic protons appeared at δ 5.78 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.19 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 5.15 (dddd J=10, 1.5, 1.5, 1.5 Hz). The methoxy and methyl singlets appeared at δ 3.80 and 1.22, respectively. The ^{13}C APT nmr spectrum displayed two carbonyl carbons at δ 194.4 and 165.2, and four signals between δ 163.4 and 119.5 due to the vinylic carbons. The high resolution mass spectrum showed a molecular ion peak at m/z 208.1111 corresponding to the required formula $C_{12}H_{16}O_3$.



27 **31** **32** **33**

Scheme 19

The cyclization of enone ester **33** was attempted using stannic chloride (Scheme 20). Unfortunately, no cyclization product was detected, and the starting material was recovered intact. Obviously, the allyl side chain was not long enough to facilitate the formation of a five-membered ring *via* the polyene cyclization process.



33

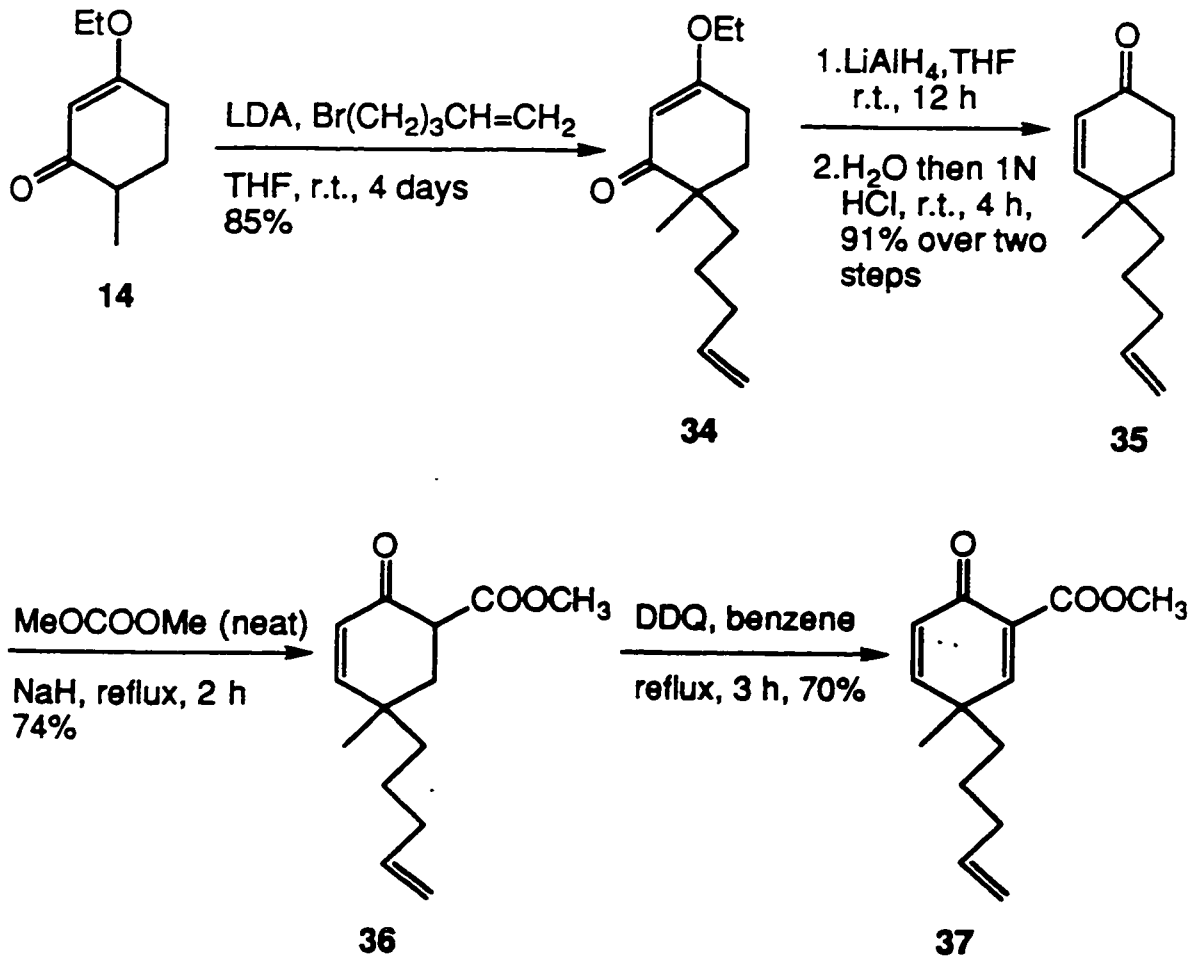
Scheme 20

At this point, we decided to extend the C_4 side chain to a five-carbon unit. The required enone ester **37** could be synthesized from enone **14** *via* a sequence similar to those used previously for the preparation of the analogous compounds (Scheme 21).

Alkylation of **14** with LDA and 5-bromo-1-pentene afforded an 85% yield of compound **34**, which displayed a carbonyl absorption at 1653 cm^{-1} in its ir spectrum. In the ^1H nmr spectrum, the vinylic proton of the enone system appeared at δ 5.25 as a sharp singlet. Three additional vinylic protons appeared at δ 5.78 (dddd, J=17, 10, 6.5, 6.5 Hz), 4.98 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.92 (dddd J=10, 1.5, 1.5, 1.5 Hz). The ethoxy group was inferred by the signals at δ 3.87 (q, J=7 Hz, 2H) and 1.35 (t, J=7 Hz, 3H). The ^{13}C APT nmr spectrum showed a carbonyl carbon at δ 204.1 and four vinylic carbons

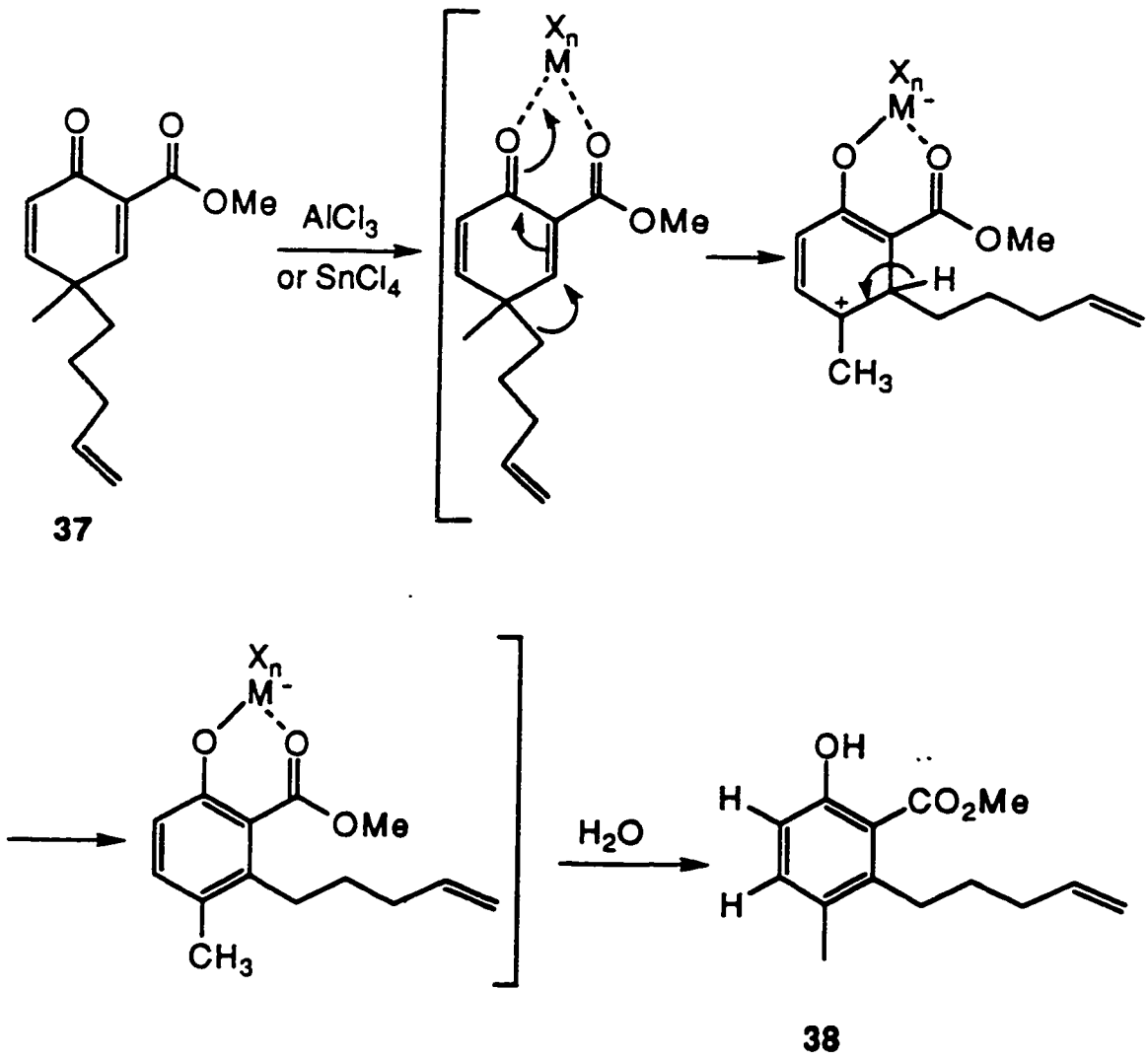
between δ 175.6 and 101.3. The high resolution mass spectrum displayed a molecular ion peak at m/z 222.1620 corresponding to the required formula $C_{14}H_{22}O_2$. Compound **34** was subjected to reduction with $LiAlH_4$, followed immediately by hydrolysis with 1 N HCl to give enone **35** in 91% yield over two steps. The ir spectrum of this compound showed a carbonyl absorption at 1682 cm^{-1}. In the ^1H nmr spectrum, two vinylic protons of the enone system appeared at δ 6.66 and 5.85. Three additional vinylic protons appeared at δ 5.77 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.00 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.93 (dddd J=10, 1.5, 1.5, 1.5 Hz). The ^{13}C APT nmr spectrum displayed the carbonyl carbon at δ 199.7 and four vinylic carbons between 159.3 and 114.4 indicating the presence of two carbon-carbon double bonds. In the high resolution mass spectrum, the molecular ion peak was shown at m/z 178.1356, in agreement with the required formula $C_{12}H_{18}O$. Carbomethoxylation of **35** using dimethyl carbonate and sodium hydride gave keto ester **36** (74% yield) as a mixture of keto and enol forms in a ratio of 1:1 as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{14}H_{20}O_3$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 236.1413. Oxidation of **36** with DDQ afforded, in 70% yield, the desired enone ester **37** which showed carbonyl absorptions at 1743 cm^1 for the ester and 1666 cm^{-1} for the ketone in its ir spectrum. In the ^1H nmr spectrum, a doublet at δ 7.47 (J=3 Hz) was observed for the C_3 proton. The vinylic protons of the enone system appeared at δ 6.72 (dd, J=10, 3 Hz) and 6.29 (d, J=10 Hz). Three additional vinylic protons appeared at δ 5.68 (dddd, J=17, 10, 6.5, 6.5 Hz), 4.97 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.93 (dddd J=10, 1.5, 1.5, 1.5 Hz). The ^{13}C APT nmr spectrum showed two carbonyl carbons at δ 181.6 and 165.1, and six vinylic carbons between δ 161.0 and 115.3. In the high resolution mass spectrum, the

molecular ion peak was found at m/z 234.1262, in agreement with the required formula $C_{14}H_{18}O_3$.



Scheme 21

With enone ester **37** in hand, we were able to examine its cyclization under Lewis acid catalysis. When enone ester **37** was treated with stannic chloride in ether at room temperature for 24 h, a 5% yield of the aromatization product **38** was formed along with the unreacted starting material. When stannic chloride was replaced with aluminum chloride and the reaction was carried out in ether at room temperature, the aromatization product **38** was formed in 75 % yield.

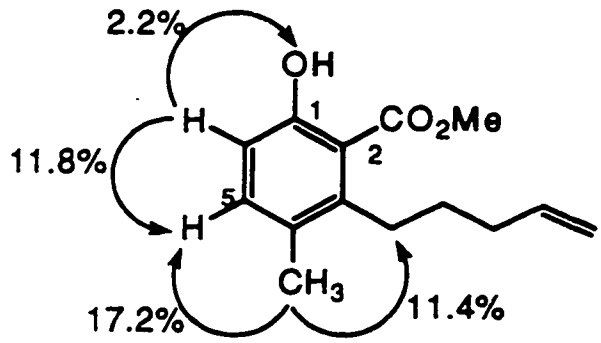


Scheme 22

The structure of the product was determined spectroscopically as follows. The high resolution mass spectrum showed a molecular ion peak at m/z 234.1254 corresponding to the formula $C_{14}H_{18}O_3$. In its ir spectrum, the carbonyl and hydroxyl absorptions were observed at 1732 and 3430 cm^{-1}, respectively. The ^{13}C APT nmr spectrum displayed a carbonyl carbon at δ 171.9 and eight sp^2 carbons between δ 160.1 and 113.0 indicating the presence of a benzene ring and a carbon-carbon double bond. In the ^1H nmr spectrum, a sharp singlet at δ

10.55 was easily recognized for the phenolic proton. Two doublets due to aromatic protons appeared at δ 7.20 (d, J=8 Hz) and 6.78 (d, J=8 Hz). From the coupling pattern, it is clear that these aromatic protons have an *ortho* relationship. The methoxy and methyl groups appeared at δ 3.98 and 2.28, respectively, each as a singlet.

The regiochemistry of the product was further confirmed by NOE experiments. As shown in Figure 5, irradiation of the C_4 methyl at δ 2.28 resulted in enhancements of H_5 (17.2%) and the methylene protons adjacent to the aromatic ring (11.4%). Irradiation of H_6 resulted in enhancements of the phenolic proton (2.2%) and H_5 (11.8%).



38

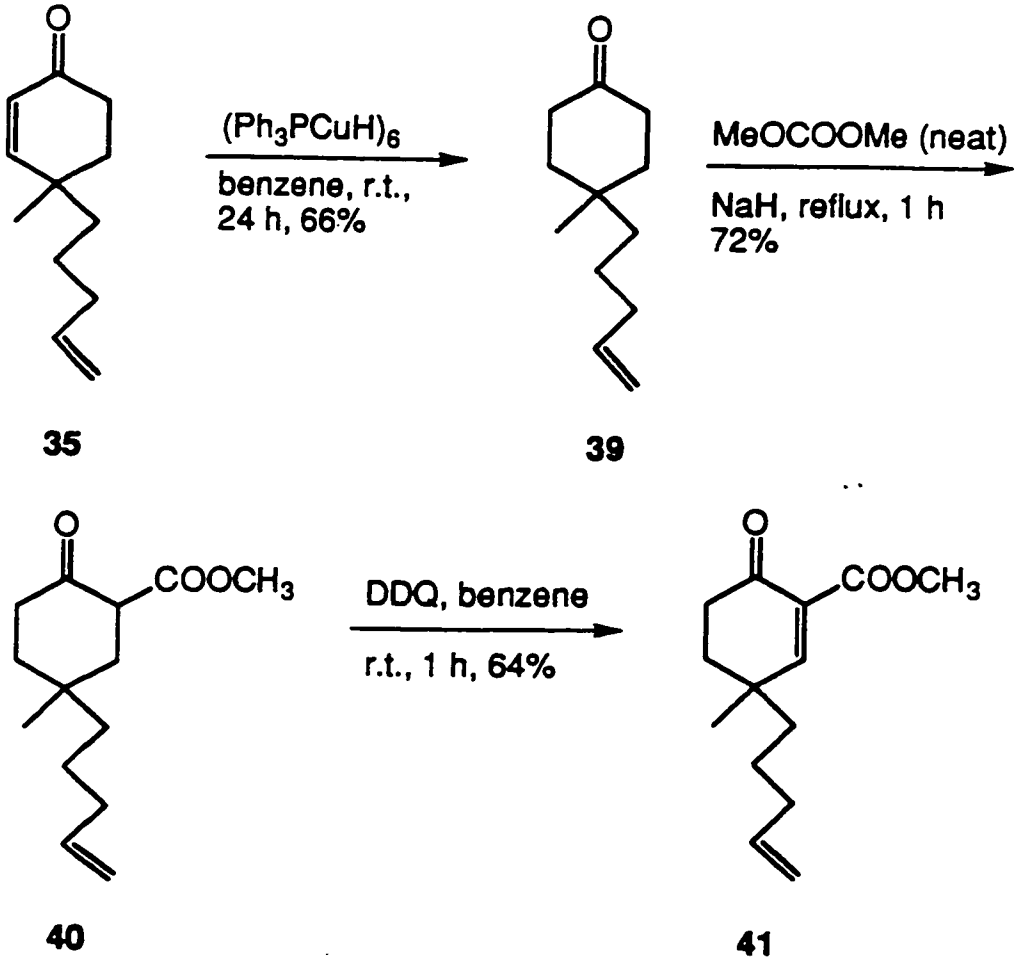
Figure 5. NOE data of compound **38**

The formation of phenol **38** could be rationalized by invoking a 1,2-alkyl shift followed by aromatization as shown in Scheme 22. More specifically, under Lewis acid catalysis, the pentenyl group migrates preferentially to the more electron deficient β-carbon of the enone system to form an allyl cation, which immediately undergoes aromatization to produce compound **38**. The preferential migration of the pentenyl group is in accord with the general

observation that the more substituted alkyl group migrates in preference to the less substituted alkyl group.[34-36]

To prevent the alkyl migration-aromatization process, a possible solution would be to remove the disubstituted carbon-carbon double bond. The preparation of the required enone ester **41** started with reduction of the conjugated carbon-carbon double bond of enone **35** (Scheme 23). When enone **35** was treated with $(Ph_3PCuH)_6$ at room temperature for 24 h, ketone **39** was obtained in 66% yield. The ir spectrum displayed a carbonyl absorption at 1716 cm^{-1}. In the ^1H nmr spectrum, three vinylic protons appeared at δ 5.81 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.02 (dddd, J=17, 1.5, 1.5, 1.5 Hz) and 4.96 (dddd, J=10, 1.5, 1.5, 1.5 Hz). A methyl singlet was found at δ 1.08. The ^{13}C APT nmr spectrum displayed a carbonyl carbon at δ 212.5 and two vinylic carbons at δ 139.1 and 114.4, indicating the presence of a carbon-carbon double bond. The high resolution mass spectrum showed a molecular ion peak at m/z 180.1513 corresponding to the formula $C_{12}H_{20}O$. Carbomethoxylation of **39** with dimethyl carbonate and sodium hydride afforded keto ester **40** in 72% yield as a mixture of keto and enol forms in a ratio of 1:1 as indicated by its ^1H nmr spectrum. Its molecular formula was confirmed as $C_{14}H_{22}O_3$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 238.1568. Oxidation of **40** with DDQ in benzene at room temperature for 1 h afforded, in 64% yield, the desired enone ester **41** which showed carbonyl absorptions at 1744 cm^{-1} for the ester and 1686 cm^{-1} for the ketone in its ir spectrum. In the ^1H nmr spectrum, a singlet at δ 7.38 was observed for the C_3 proton. Three additional vinylic protons appeared at δ 5.75 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.01 (dddd, J=17, 1.5, 1.5, 1.5 Hz) and 4.97 (dddd, J=10, 1.5, 1.5, 1.5 Hz). The methoxy and methyl groups were shown at δ 3.78 and 1.15, respectively, each as a singlet. The ^{13}C APT nmr

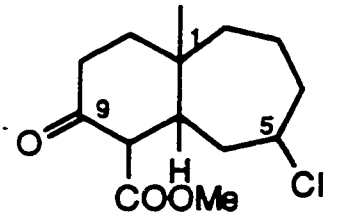
spectrum showed two carbonyl carbons at δ 194.5 and 165.3, and four vinylic carbons between δ 164.3 and 115.2. In the high resolution mass spectrum, the molecular ion peak was found at m/z 236.1413, in agreement with the required formula $C_{14}H_{20}O_3$.



Scheme 23

When compound **41** was treated with anhydrous zinc chloride in ether at room temperature overnight, no cyclization product was observed. However, when zinc chloride was replaced by aluminum chloride, the cyclization occurred quite rapidly at 0°C, and after 2 h, an inseparable mixture of chlorides **42**, which existed exclusively in the enol form in chloroform solution as indicated by the ^1H nmr spectrum, was formed in 50% yield, along with a small amount of

migration products. The ir spectrum (neat) of this mixture displayed absorptions at 3350, 1720, 1655 and 1615 cm^{-1} for a mixture of keto and enol forms, suggesting both tautomers were in existence in the neat form. The ^1H nmr spectrum showed two sets of signals corresponding to two chlorides in a ratio of 2:1. The C_5 proton of one isomer appeared at δ 5.65 as a multiplet, whereas the corresponding proton of the other isomer was observed at δ 4.05, also as a multiplet. The molecular formula was confirmed as $C_{14}H_{21}ClO_3$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 272.1176.

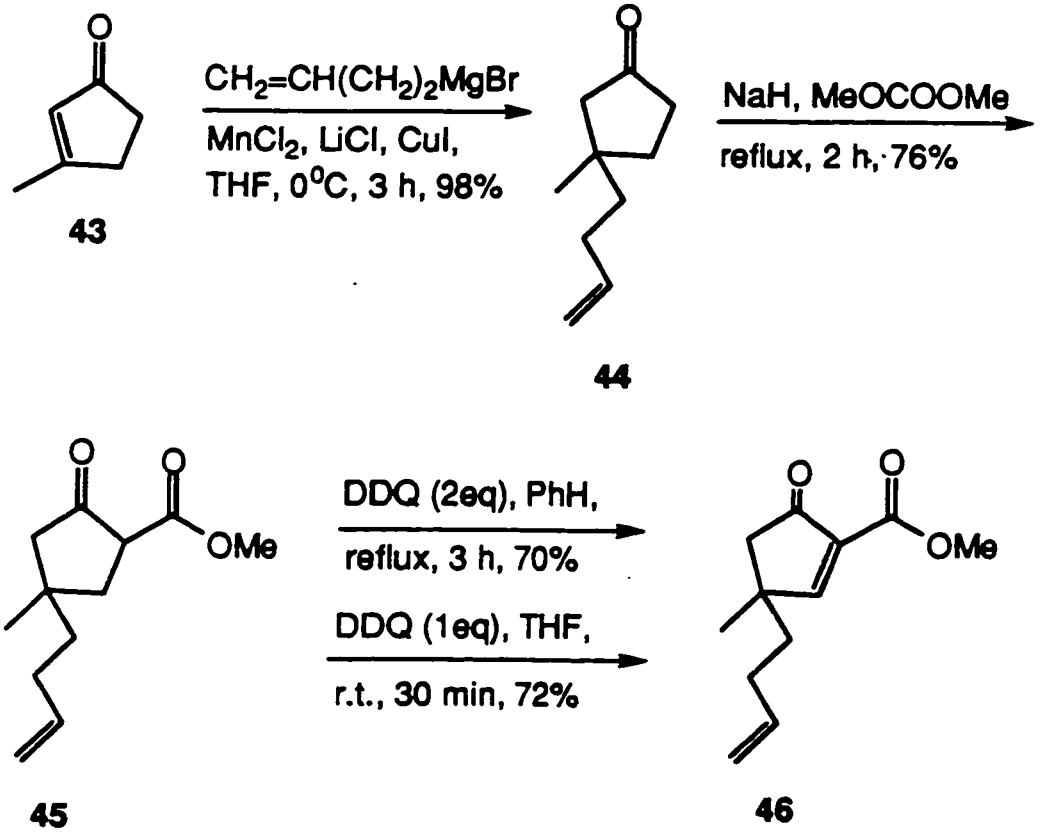


42

We have also successfully explored the use of the cross conjugated β-keto ester system to faciliate the formation of the highly functionalized hydrindane and hydroazulene ring systems *via* polyene cyclization. Dr. Roa, a former graduate student in our group developed a procedure for the preparation of keto ester **46** and carried out a primary study on its cyclization.[37] An improved synthesis of **46** (Scheme 24) and a thorough investigation of its cyclization have since been performed. The preparation started with the conjugate addition of a 3-butenyl unit to enone **43**. It was reported that the manganese and copper catalyzed conjugate addition of organomagnesium reagents can be successfully performed even with enones of low reactivity.[38] This method has been shown to be superior in terms of yield than other procedures involving various organocopper or cuprate reagents. When enone **43** was subjected to treatment with 3-butenylmagnesium bromide[39,40] at 0°C in THF in

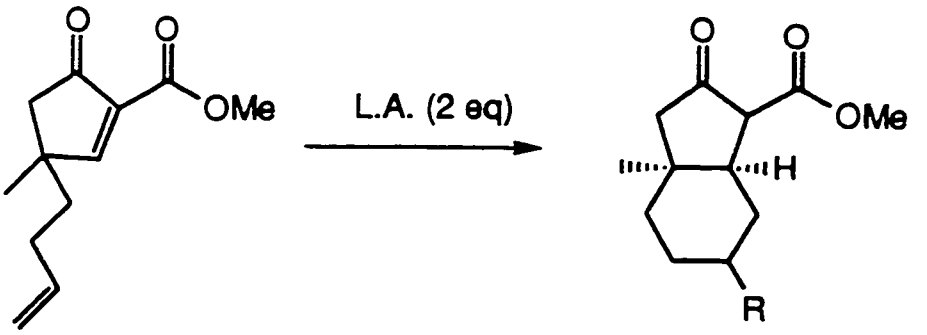
the presence of manganese chloride, cuprous chloride and lithium chloride, the 3,3-disubstituted cyclopentanone **44** was produced in virtually quantitative yield after 3 h. The ir spectrum of **44** displayed a carbonyl absorption at 1742 cm^{-1}. In the ^1H nmr spectrum, three vinylic protons appeared at δ 5.80 (dddd, J=17, 10, 6.5, 6.5 Hz), 5.01 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.93 (dddd J=10, 1.5, 1.5, 1.5 Hz). The ^{13}C APT nmr spectrum displayed a carbonyl carbon at δ 220.7 and two vinylic carbons at δ 138.7 and 114.5 indicating the presence of a carbon-carbon double bond. In the high resolution mass spectrum, the molecular ion peak was observed at m/z 152.1192, in agreement with the required formula $C_{10}H_{16}O$. Carbomethoxylation was carried out by the usual procedure. After compound **44** was treated with dimethyl carbonate and sodium hydride at reflux for 2 h, the corresponding keto ester **45** was isolated in 76% yield as a mixture of two diastereomers in a ratio of 1.5:1. Two carbonyl absorptions at 1756 and 1729 cm^{-1} were observed for the ketone and ester groups in the ir spectrum. In the ^1H nmr spectrum, the methoxy group was confirmed by the singlet displayed at δ 3.76. Two other singlets were found at δ 1.18 and 1.05 in a 1.5:1 ratio for a total of three protons. These signals could be attributed to the C_4 methyl groups of the two diastereomers. It is noteworthy that the degree of enolization of keto ester **45** was evidently very low, since the signal for H_2 observed at δ 3.36 as a multiplet had an integration for one proton. Also, the ^{13}C nmr spectrum showed two carbonyl carbons at δ 211.1 and 169.8. The high resolution mass spectrum displayed a molecular ion peak at m/z 210.1254, which corresponded to the formula $C_{12}H_{18}O_3$. Direct oxidation of **45** with 2 equivalents of DDQ in refluxing benzene for 3 h gave enone ester **46** in 70% yield. Interestingly, when THF was used as a solvent, a remarkable enhancement of the reaction rate was observed. The reaction occurred almost instantaneously even at room temperature and enone ester **46** was isolated in

72% yield after 30 min. The reasons could be that solubility of DDQ and enolization of compound **45** in THF are greater than these in benzene. The ir spectrum showed two carbonyl absorptions at 1753 and 1723 cm^{-1} for the ketone and the ester, respectively. Formation of the double bond was confirmed by the ^1H nmr spectrum, which displayed a singlet at δ 8.16 for the enone proton, and by the ^{13}C nmr signals at δ 179.4 and 134.6 due to the vinylic carbons of the enone moiety. The required formula $C_{12}H_{16}O_3$ was in agreement with the molecular ion peak observed at m/z 208.1098 in the high resolution mass spectrum.



Scheme 24

Table 6. Polyene cyclization of compound **46** using various Lewis acids



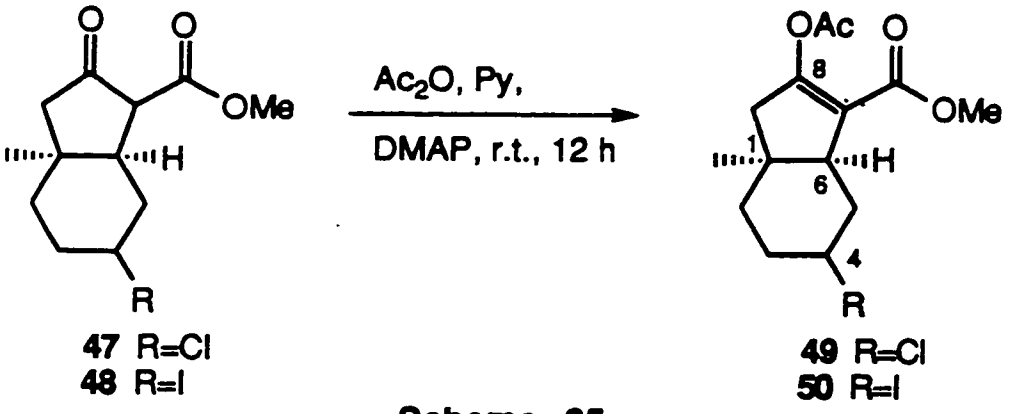
46

47 R=Cl
48 R=I

MX_n	R	solvent	temp. (°C)	time (h)	yield (%)
$ZnCl_2$	Cl	Et_2O	25	4	92
$AlCl_3$	Cl	Et_2O	-78	1	61
ZnI_2	I	Et_2O	25	12	71
$SnCl_4$	Cl	CH_2Cl_2	-78	1	58
AlI_3	I	Et_2O	-78	1	59

With keto ester **46** in hand, we proceeded to study its cyclization promoted by various Lewis acids. Zinc chloride, aluminum chloride, stannic chloride, zinc iodide and aluminum iodide were selected as reagents. When enone ester **46** was treated with anhydrous zinc chloride at room temperature in ether, the cyclization took place cleanly (Table 6). The ^1H nmr spectrum of the product **47** (92% total yield) showed the presence of four diastereomeric chlorides. In the ir spectrum, two carbonyl absorptions were observed at 1754 and 1727 cm^{-1} for the ketone and the ester, respectively. The formula $C_{12}H_{17}ClO_3$ was in agreement with the molecular ion peak found at m/z 244.0866 in its high

resolution mass spectrum. Using stannic chloride as a reagent, the cyclization occurred rapidly. It was found to be complete within 1 h even at -78°C. However, the yield of **47** (58%) was inferior. The use of zinc iodide as a reagent led to the formation of a mixture of diastereomeric iodides **48** in 71% yield. The ir spectrum of this mixture displayed two carbonyl absorptions at 1754 and 1727 cm^{-1} for the ketone and the ester, respectively. The formula $C_{12}H_{17}IO_3$ was in agreement with the molecular ion peak observed at m/z 336.0225 in the high resolution mass spectrum. Two other Lewis acids, aluminum chloride and aluminum iodide, were also examined in an attempt to improve diasteroselectivity of the cyclization. The results are shown in Table 6.



47 R=Cl
48 R=I

49 R=Cl
50 R=I

Scheme 25

The regiochemistry and stereochemistry of the cyclization products were determined as follows (Scheme 25). Treatment of **47** with acetic anhydride in pyridine gave rise to the corresponding enol acetate **49** whose structure was confirmed by spectroscopic methods, especially nmr spectroscopy with the assistance of NOE experiments. In the ir spectrum, two carbonyl absorptions were observed at 1771 cm^{-1} for the enol acetate and 1714 cm^{-1} for the ester. In the ^1H nmr spectrum, two signals were found at δ 3.83 and 4.60 in a ratio of 4.5:1 for a total of one proton. These signals could be attributed to H_4. In cyclohexanes, the equatorial proton attached to the carbon bearing a

heteroatom appears normally at a lower field in the ^1H nmr spectrum than the corresponding axial proton.[41] The C_4 proton of the major isomer appeared at δ 3.83 as a multiplet, whereas the corresponding proton of the minor isomer was observed at δ 4.60 also as a multiplet. For the major isomer, the ^{13}C APT nmr spectrum displayed two carbonyl carbons at δ 167.6 and 163.7 and two vinylic carbons at δ 159.2 and 122.3. The molecular formula was confirmed as $C_{14}H_{19}ClO_4$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 298.0982. The stereochemistry of the major isomer was confirmed by NOE experiments. As shown in Figure 6, irradiation of the C_1 methyl signal at δ 1.11 resulted in a 12.9% enhancement of the ring junction proton (H_6) at δ 2.53, whereas irradiation of H_4 at δ 3.76 resulted in a 4.0% enhancement of H_6.

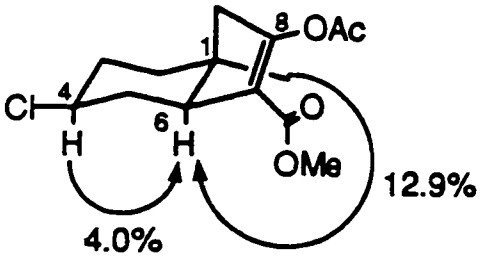


Figure 6. NOE data of the major isomer of compound **49**

Similarly, when compound **48** obtained from the zinc iodide promoted cyclization was subjected to acetylation under the conditions described above for 12 h, the corresponding enol acetate **50** was obtained as a mixture of two diastereomers in a ratio of 3.2 :1 in 71% yield. The ir spectrum showed two carbonyl absorptions at 1771 cm^{-1} for the enol acetate and 1714 cm^{-1} for the ester. In the ^1H nmr spectrum, the major isomer showed signals at δ 4.00 (dddd, J=12, 6.5, 3.5, 3.5 Hz) and 2.50 (ddd, J=10, 5, 1 Hz) for the C_4 and C_6 protons, respectively. The methoxy, acetoxy and methyl groups appeared at δ 3.70, 2.30 and 1.07, each as a singlet. The ^{13}C APT nmr spectrum displayed two carbonyl

carbons at δ 167.7 and 163.8, and two vinylic carbons at δ 159.6 and 120.1 for the major isomer. The molecular formula $C_{14}H_{19}IO_4$ was confirmed by the elemental analysis and the high resolution mass spectrum showing a molecular ion peak at m/z 378.0344. The stereochemistry of the major isomer was deduced from the NOE results compiled in Figure 7.

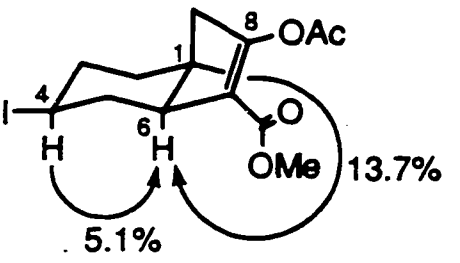
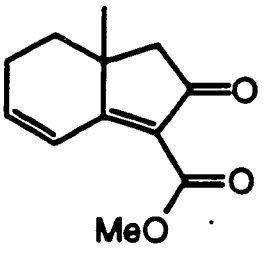
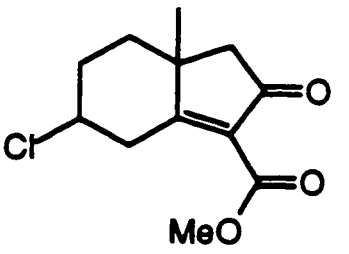


Figure 7. NOE data of the major isomer of compound **50**

Having successfully generated the highly functionalized bicyclo[4.3.0]nonane system from enone ester **46**, we became interested in the potential use of **47** in the synthesis of natural products, such as steroids. In order to set up B, C and D rings of the steroid skeleton *via* a Diels-Alder approach, the first step was to convert chlorides **47** to dienone **51**. This conversion was easily effected as follows. Oxidation of **47** with 1 equivalent of DDQ in THF at room temperature for 1 h gave dienone **51** (63% yield) along with a small amount of compound **52** (19% yield). Interestingly, when benzene was used as a solvent, 2 equivalents of DDQ were required. In this case, a 72% yield of compound **51** was isolated along with traces of compound **52** (5% yield).

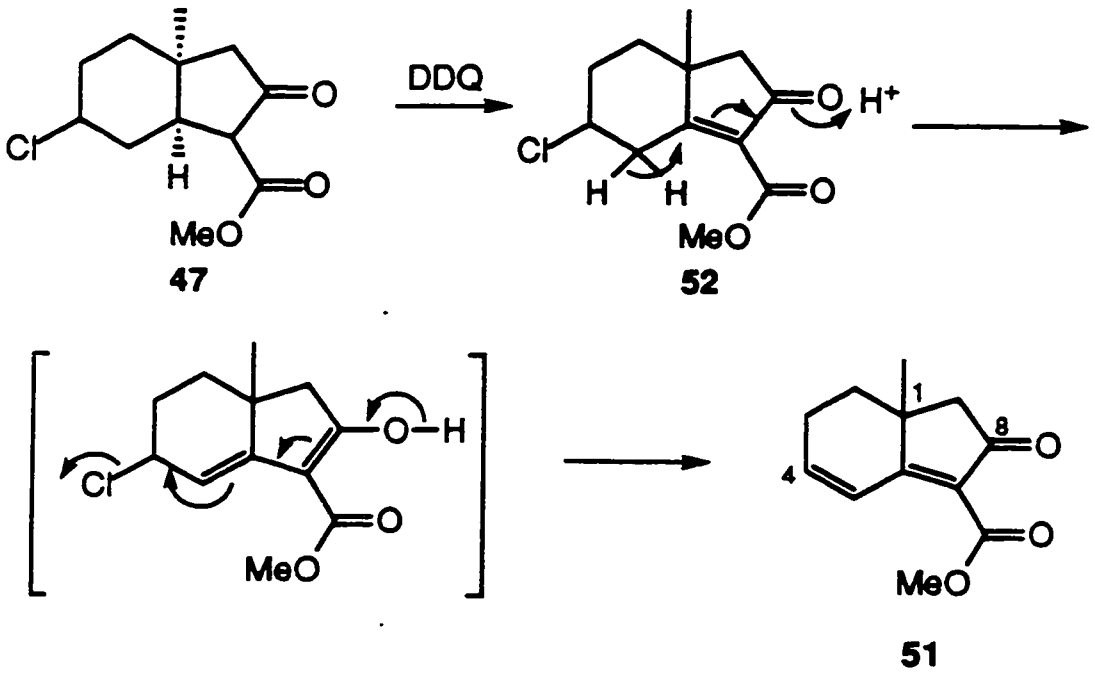


51



52

The major product **51** showed, in the ir spectrum, two carbonyl absorptions at 1740 and 1708 cm^{-1}. In the ^1H nmr spectrum, the signals at δ 7.21 (ddd, J=10, 2, 2 Hz) and 6.66 (ddd, J=10, 4, 4 Hz) were attributed to the vinylic protons. The ^{13}C APT nmr spectrum displayed two carbonyl carbons at δ 201.7 and 181.7, and four vinylic carbons between δ 163.6 and 122.9 indicating the presence of two carbon-carbon double bonds. The molecular formula was confirmed as $C_{12}H_{14}O_3$ by its high resolution mass spectrum displaying a molecular ion peak at m/z 206.0947. The high resolution mass spectrum of the minor product **52** displayed a molecular ion peak at m/z 242.0712 corresponding to the molecular formula $C_{12}H_{15}ClO_3$. The ir spectrum displayed two carbonyl absorptions at 1748 and 1721cm^{-1}. The ^1H nmr spectrum showed a signal at δ 3.70 as a multiplet due to the proton adjacent to the chlorine atom. Based on these spectral data, structures **51** and **52** were assigned to the major and minor products, respectively. A possible mechanism for the formation of the former compound is outlined in Scheme 26.



Scheme 26

Table 7. The Diels-Alder reaction of compound **51**

53 R=CH_3
54 R=H

MX_n	time (h)	diene[a]	yield (%)
$SnCl_4$	18	A	62
BF_3·OEt_2	24	A	59
$FeCl_3$	24	B	55
$SnCl_4$	72	B	58

[a] Diene A: 2,3-dimethylbutadiene; diene B: isoprene.

It was then possible to examine the Diels-Alder reactivity of compound **51**. 2,3-Dimethylbutadiene and isoprene were chosen as dienes. Stannic chloride, boron trifluoride and ferric chloride were selected as catalysts as it had been observed previously in our laboratories that these Lewis acids were highly suitable for related dienophiles. When dienone **51** was treated with 10 equivalents of 2,3-dimethylbutadiene in ether at room temperature for 18 h using stannic chloride as a catalyst, adduct **53** was formed as the only product in 62% yield based on the consumed starting material. A similar result was obtained using boron trifluoride etherate as a catalyst. When 2,3-dimethylbutadiene was replaced by isoprene, adduct **54** was isolated after 72

h under stannic chloride catalysis as the exclusive product in 58% yield based on the consumed starting material. With ferric chloride, the reaction was found to complete in 24 h at room temperature affording adduct **54** in 55% yield (Table 7).

Adduct **53** was obtained as white crystals, mp 110-112°C. The ir spectrum of this compound showed two carbonyl absorptions at 1734 and 1705 cm^{-1}. In the ^1H nmr spectrum, the signal at δ 3.07 (dd, J=5, 5 Hz) was assigned to the C_9 proton with the assistance of decoupling experiments. Interestingly, this proton was coupled to H_4 at δ 2.30 and H_{8a} at δ 2.30, but not to H_{8b} at δ 2.40 probably due to the *ca.* 90° dihedral angle of H_9, C_9, C_8 and H_{8b}. The methoxy and the angular methyl groups were observed at δ 3.73 and 1.35, respectively, each as a singlet. The vinylic methyl signals were found at δ 1.55 as a broad singlet. The ^{13}C APT nmr spectrum displayed two carbonyl carbons at δ 203.1 and 183.9, and four vinylic carbons between δ 165.6 and 122.8. The high resolution mass spectrum showed a molecular ion peak at m/z 288.1735, corresponding to the expected molecular formula $C_{18}H_{24}O_3$.

To assign the stereochemistry, NOE experiments were carried out. As shown in Figure 8, irradiation of the C_1 methyl group at δ 1.35 resulted in a 11.6% enhancement of H_9, whereas irradiation of H_9 resulted in a 12.1% enhancement of H_4.

The structure of adduct **53** was verified by its X-ray analysis. As clearly illustrated by the crystal structure shown in Figure 9, the C_1 methyl and the two ring junction protons (H_4 and H_9) are all *cis* to each other.

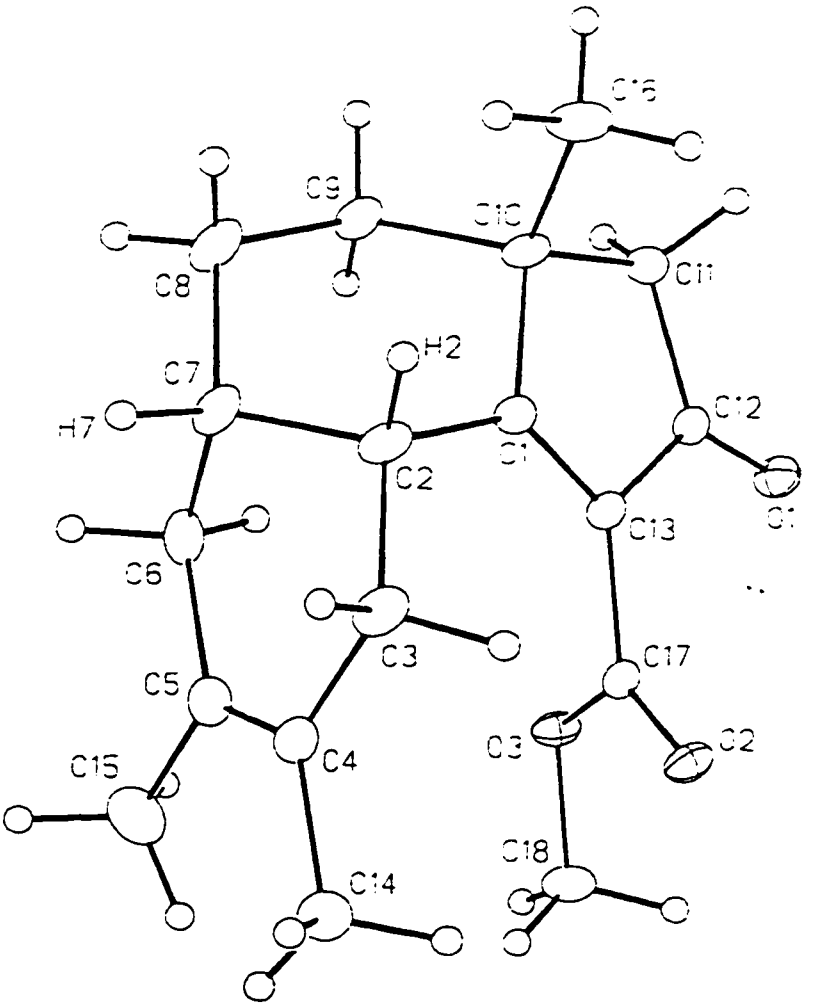
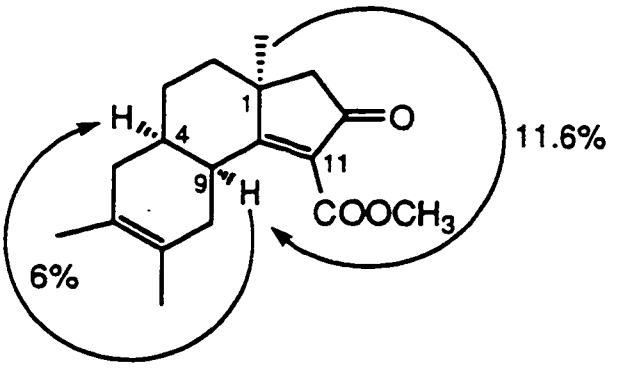
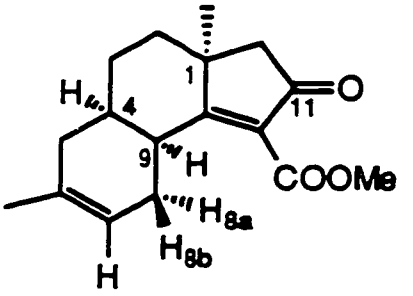


Figure 9. The three dimensional X-ray crystallographical structure of compound **53**



53

Figure 8. NOE data of compound **53**



54

Adduct **54** showed a molecular ion peak at m/z 274.1566 in the high resolution mass spectrum, in agreement with the required molecular formula $C_{17}H_{22}O_3$. Its ir and ^1H nmr spectra showed close resemblance to those of compound **53**. The ir spectrum displayed two carbonyl absorptions at 1734 and 1705 cm^{-1}. In the ^1H nmr spectrum, the ring junction proton H_9 appeared at δ 3.07 as a doublet of doublets (J=5, 5 Hz). The methoxy, vinylic and C_1 methyl groups appeared at δ 3.75, 1.58 and 1.35, respectively, each as a singlet. The signal at 2.58 with a large geminal coupling constant of 18 Hz and a small vicinal coupling constant of 5.5 Hz was attributed to H_{8a}. The ^1H nmr spectrum also showed a multiplet at δ 5.19 for the vinylic proton.

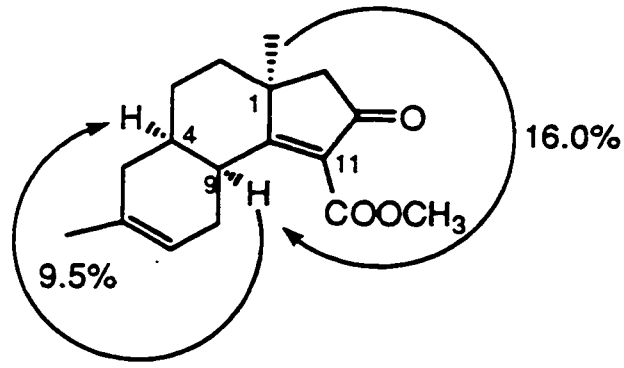


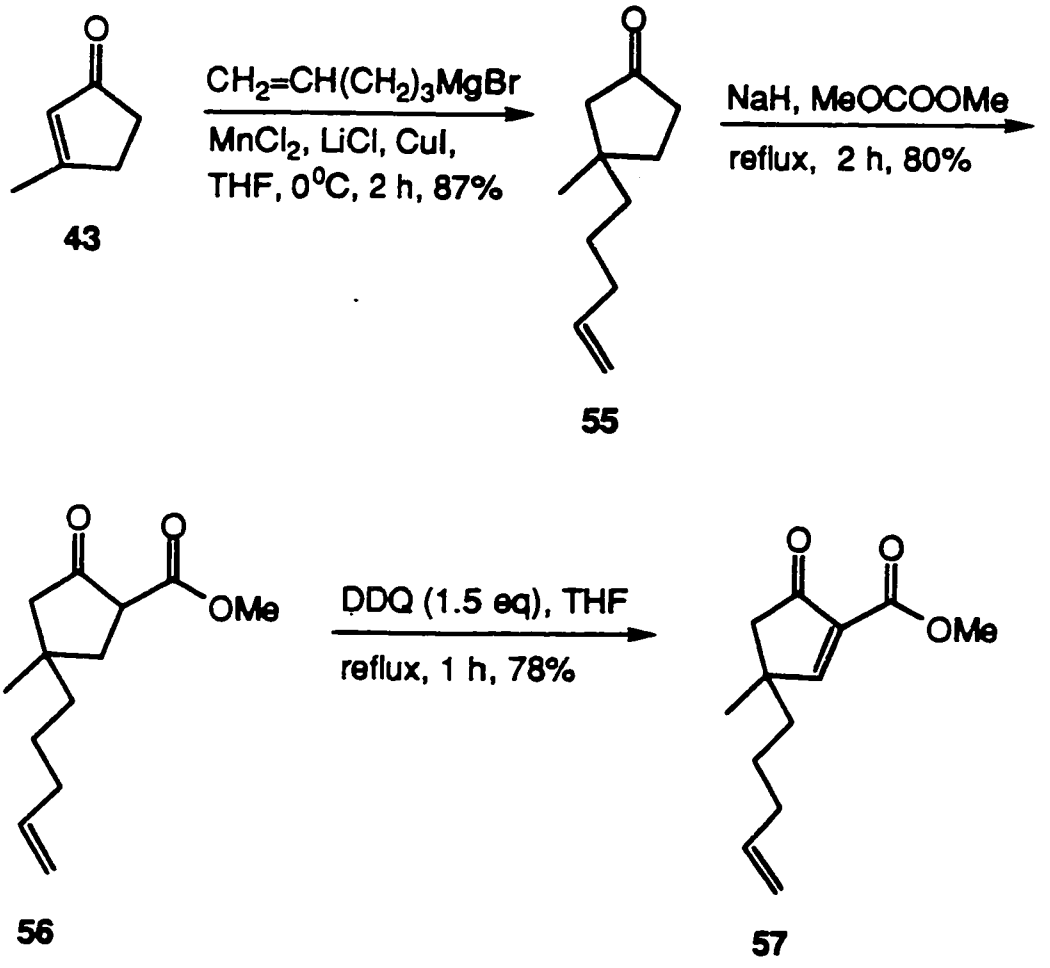
Figure 10. NOE data of compound **54**

The regiochemistry of adduct **54** was evident from the following ^1H decoupling experiment. Irradiation of the signal at δ 2.58 (H_{8b}) led to the simplification of the signal at δ 5.19 (H_7) from a doublet of doublets to a doublet. The all-*cis* relationship of H_4, H_9 and the angular methyl group was confirmed by NOE experiments (Figure 10). Irradiation of the C_1 methyl signal at δ 1.35 resulted in a 16.0% enhancement of H_9, whereas irradiation of H_9 resulted in a 9.5% enhancement of H_4.

From the above results obtained for the Diel-Alder additions, the following conclusions could be drawn. The remote carbon-carbon double bond of dienone ester **51** is more reactive towards dienes under Lewis acid catalysis. As such, dienone ester **51** and the related compounds may find use as synthetic intermediates to facilitate the construction of polycyclic natural products such as steroids *via* a Diels-Alder approach.

In continuation of our investigation on the polyene cyclization process, enone ester **57**, which could lead to the hydroazulene ring system, was prepared according to the synthetic sequence outlined in Scheme 27. When 3-methyl-2-cyclopentenone (**43**) was subjected to treatment with 4-pentenylmagnesium

bromide in the presence of maganese chloride, cuprous chloride and lithium chloride, cyclopentanone **55** was produced in 87% yield. The ir spectrum of this compound displayed a carbonyl absorption at 1731 cm^{-1}. The ^1H nmr spectrum showed three vinylic signals at δ 5.74 (dddd, J=17, 10, 6.5, 6.5 Hz), 4.95 (dddd, J=17, 1.5, 1.5, 1.5 Hz) and 4.90 (dddd, J=10, 1.5, 1.5, 1.5 Hz). The ^{13}C APT nmr spectrum displayed a carbonyl carbon at δ 219.5 and two vinylic carbons at δ 138.5 and 114.6 indicating the presence of a carbon-carbon double bond. The molecular formula was confirmed as $C_{11}H_{18}O$ by the elemental analysis and the high resolution mass spectrum displaying a molecular ion peak at m/z 166.1354.

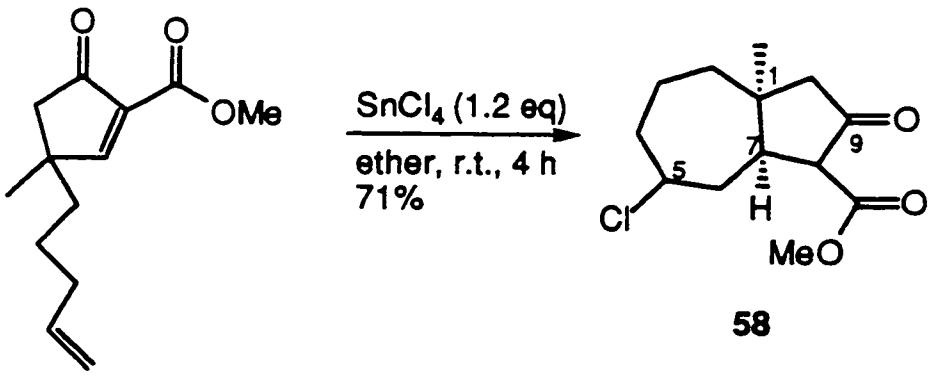


Scheme 27

Carbomethoxylation of **55** with dimethyl carbonate and sodium hydride gave keto ester **56** (80%) as a mixture of two epimeric keto forms and the corresponding enol in a ratio of 1.5:1 as indicated by the ^1H nmr spectrum. The high resolution mass spectrum displayed a molecular ion peak at m/z 224.1413, in agreement with the required molecular formula $C_{13}H_{20}O_3$. Direct oxidation of **56** with DDQ in THF at room temperature afforded the desired enone ester **57** in 78% yield. In the ir spectrum, two carbonyl absorptions were observed at 1754 and 1723 cm^{-1}. In the ^1H nmr spectrum, a sharp singlet at δ 8.12 was observed for the enone proton. Three additional vinylic protons appeared at δ 5.74 (dddd, J=17, 10, 6.5, 6.5 Hz), 4.95 (dddd J=17, 1.5, 1.5, 1.5 Hz) and 4.90 (dddd J=10, 1.5, 1.5, 1.5 Hz). The methoxy and methyl singlets were shown at δ 3.85 and 1.00, respectively.

With enone ester **57** in hand, we went on to examine its cyclization using Lewis acids. When compound **57** was treated with anhydrous zinc chloride in ether at room temperature overnight, no cyclization product was observed. However, when zinc chloride was replaced by stannic chloride, the cyclization occurred quite rapidly and, after 2 h at room temperature, an inseparable mixture of chlorides **58**, which existed exclusively in the enol form in chloroform solution as indicated by the ^1H nmr spectrum, was formed in 71% yield (Scheme 28). The ir spectrum (neat) of this mixture displayed absorptions at 3410, 1760, 1730, 1660 and 1620 cm^{-1} typical for a mixture of keto and enol forms, suggesting both tautomers were in existence in the neat form. The ^1H nmr spectrum showed two sets of signals corresponding to two chlorides in a ratio of 1:1. The C_5 proton of one isomer appeared at δ 4.45 as a multiplet, whereas the corresponding proton of the other isomer was observed at δ 3.85, also as a

multiplet. The molecular formula was confirmed as $C_{13}H_{19}ClO_3$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 258.1010.



57 58

Scheme 28

Evidence for the *cis* ring junction of the products was obtained by NOE experiments. As shown in Figure 11, irradiation of the C_1 methyl at δ 1.10 resulted in an enhancement of H_7 [9.25 (δ 3.00) and 8.4% (δ 2.36)] for both isomers. Therefore, structure **58** was assigned to the epimeric cyclization products.

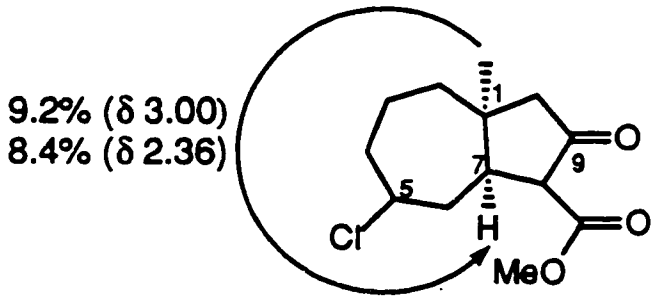
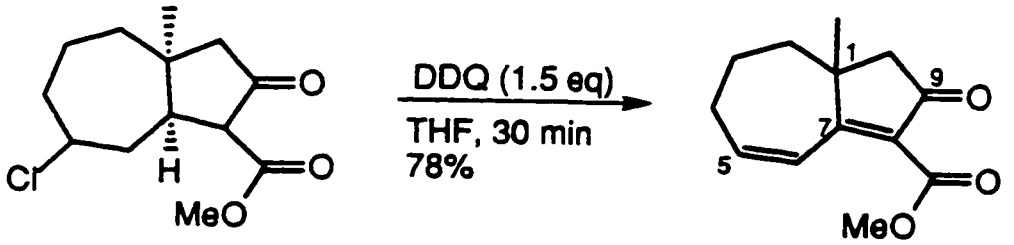


Figure 11. NOE data of chlorides **58**

The formation of the bicyclo[5.3.0]decane ring system was further confirmed by treatmwnt of **58** with DDQ in THF at room temperature to afford dienone ester **59** in 78% yield (Scheme 29). Its high resolution mass spectrum displayed a

molecular ion peak at m/z 220.1097, in agreement with the required formula $C_{13}H_{16}O_3$. The ir spectrum showed two carbonyl absorptions at 1742 cm^{-1} and 1712 cm^{-1}. Two vinylic protons appeared at δ 6.89 (ddd, J=12, 1, 1 Hz) and 6.32 (ddd, J=12, 6.5, 6.5 Hz). The methoxy and methyl groups were observed at δ 3.85 and 1.30, respectively, each as a singlet. The ^{13}C APT nmr spectrum confirmed the presence of two carbonyl signals at δ 208.0 and 185.1, and of two carbon-carbon double bonds with signals between δ 157.3 and 124.7.



58 **59**

Scheme 29

In conclusion, the results described above illustrated that the cross conjugated β-keto ester system could serve as a highly effective promoter for cationic cyclization, which occurred readily with regio- and stereoselectivity and also with an unusual termination process involving halogen atom incorporation when a metal halide was used as the reagent. In essence, this cyclization process allows for expeditious construction of a variety of polycyclic ring systems, such as decalin, hydrindane and hydroazulene, with a high level of functionalization. It is expected to have broad utility in the synthesis of polycyclic natural products. In the next two chapters, the successful application of this newly developed polyene cyclization process to facilitate the total synthesis of (±)-dehydrochamaeynenol and (±)-occidentalol is described.

Experimental

General

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

signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon for 10 min prior to use. High resolution electron impact mass spectra (hrms) were recorded using an A.E.I. model MS-50 mass spectrometer. Spectral data are reported as m/z values. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. X-ray analyses were performed by the structure determination laboratory of this dspartment. Concentrations of solvent systems used in column chromatography are given by volumes, e.g., ethyl acetate/hexane (20:80) means 20 parts of ethyl acetate by volume to 80 parts of hexane by volume.

Materials

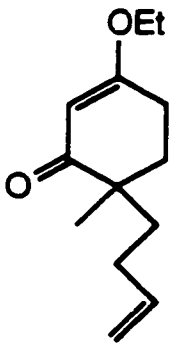
Unless otherwise stated, all materials used are commercially available. All compounds made are racemic. All reactions were carried out under a positive pressure of argon. Solvents were distilled under argon from appropriate drying agents before use. Tetrahydrofuran (THF), diethyl ether, toluene and 1,2-dimethoxyethane (DME) were freshly distilled from a blue or purple solution of sodium benzophenone ketyl. Diisopropylamine was obtained by distillation from sodium hydroxide or potassium hydroxide. Pyridine, benzene, dichloromethane and triethylamine (TEA) were distilled from calcium hydride. Reactions requiring anhydrous conditions were performed using oven or flame-dried glassware, assembled and allowed to cool while being purged with argon. Argon was passed through a column of 4 Å molecular sieves, with a self-indicating silica gel (coarse grained) as the indicator. Flash chromatography was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for

chromatography. Analytical thin layer chromatography (TLC) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a uv lamp (254 or 350 nm). For TLC, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, w/v) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate.

General Procedure for Alkylation Using LDA

To a solution of diisopropylamine (84.1 mmol, 1.3 eq.) in dry THF (60 mL) at 0°C under an argon atmosphere, was added *n*-BuLi (84.08 mmol, 1.3 eq.) slowly. The mixture was stirred at 0°C for 15 min and then cooled to -78°C. A solution of enone **14** (64.9 mmol, 1 eq.) in THF (20 mL) was added dropwise over a period of 15 min. The resulting mixture was stirred at -78°C for 1 h, and alkyl bromide (129.9 mmol, 2 eq.) was added in one portion. The mixture was allowed to warm slowly to room temperature and stirred overnight. Saturated ammonium chloride was added and the mixture was extracted with ether (3 x 50 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration followed by flash chromatography using ethyl acetate/hexane (5:95) as an eluent gave rise to the pure alkylation product.

6-(3-Butenyl)-3-ethoxy-6-methyl-2-cyclohexenone (15)



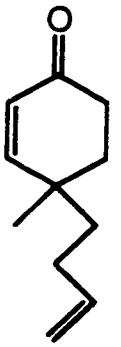
Alkylation of enone **14** (10 g, 64.9 mmol) with LDA (84.1 mmol) and 4-bromo-1-butene (13.5 mL, 134 mmol) at room temperature for 2 days gave compound **15** (8.9 g, 66%): ir (CH_2Cl_2 cast) 1650 (C=O, enone) cm^{-1}; ^1H nmr (200 MHz) δ 5.67 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.12 (s, 1H, C**H**=COEt), 4.87 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.79 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.78 (q, J=7 Hz, 2H, O**CH$_2$**), 1.25 (t, J=7 Hz, 3H, OCH_2**CH$_3$**), 2.35 (m, 2H), 1.70-2.20 (m, 3H), 1.35-1.70 (m, 3H), 1.00 (s, 3H, **CH$_3$**); ^{13}C nmr (75 MHz) δ 203.3 (p), 175.3 (p), 138.6 (a), 114.1 (p), 101.1 (a), 63.9 (p), 42.9 (p), 35.9 (p), 31.9 (p), 28.2 (p), 25.8 (p), 22.1 (a), 13.9 (a); hrms M^+ 208.1460 (calcd. for $C_{13}H_{20}O_2$: 208.1463). Anal. calcd. for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 75.10, H 9.79.

General Procedure for $LiAlH_4$ Reduction Followed by Acidic Hydrolysis

To a suspension of lithium aluminum hydride (74 mmol, 2.2 eq.) in THF (20 mL) at room temperature under an argon atmosphere, was added dropwise a solution of the alkylated enone (33.7 mmol, 1 eq.) in THF (10 mL). The resulting mixture was stirred at 0°C for 1 h and then at room temperature overnight. To this mixture, cooled to 0°C, was added water to destroy excess lithium aluminum hydride. The resulting mixture was stirred for another h and then acidified with 1 N HCl. The resulting solution was stirred for 4 h. After the hydrolysis was complete, the mixture was extracted with ether (3 x 50 mL). The extracts were combined and washed with saturated sodium bicarbonate (1 x 30 mL), water (1 x 50 mL) and brine (1 x 50 mL). After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude

product, which was subjected to flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give the enone.

4-(3-Butenyl)-4-methyl-2-cyclohexenone (16)



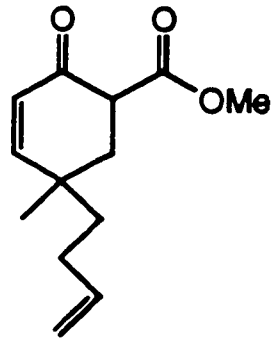
Compound **15** (7 g, 33.7 mmol) was subjected to reduction using $LiAlH_4$ (2.81 g, 74 mmol). This was followed by acidic hydrolysis to afford enone **16** (4.58 g, 92%): ir (CH_2Cl_2 cast) 1684 (C=O, enone) and 1646 (C=C) cm^{-1}; ^1H nmr (200 MHz) δ 6.70 (d, J = 10 Hz, 1H, C**H**=CHCO), 5.90 (d, J = 10 Hz, 1H, CH=C**H**CO), 5.80 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.04 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.96 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 2.45 (m, 2H), 2.15-1.87 (m, 3H), 1.87-1.70 (m, 1H), 1.60-1.48 (m, 2H), 1.15 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 197.2 (p), 157.1 (a), 138.7 (a), 127.8 (a), 114.6 (p), 40.2 (p), 35.2 (p), 34.3 (p), 33.5 (p), 28.7 (p), 24.6 (a); hrms M^+ 164.1199 (calcd. for $C_{11}H_{16}O$: 164.1201). Anal. calcd. for $C_{11}H_{16}O$: C 80.44, H 9.82; found: C 80.30, H 9.83.

General Procedure for Carbomethoxylation

To a stirred suspension of sodium hydride (4.6 mmol, 2.5 eq.) in dry dimethyl carbonate (7 mL) at room temperature under an argon atmosphere, was added

a solution of enone (1.8 mmol, 1 eq.) in dimethyl carbonate (3 mL). The reaction mixture was refluxed for several h and cooled to 0°C. A 1 N HCl solution (10 mL) was added cautiously to the mixture. The resulting aqueous solution was extracted with diethyl ether (3 x 50 mL), and the combined organic extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford the keto ester.

4-(3-Butenyl)-6-carbomethoxy-4-methyl-2-cyclohexenone (17)



Carbomethoxylation of **16** (300 mg, 1.8 mmol) with dimethyl carbonate (15 mL) for 2 h gave keto ester **17** (301 mg, 74%) as a yellowish oil: ir (CH_2Cl_2 cast) 3450 (OH, enol), 1747 (C=O, ester), 1694 (C=O, ketone), 1662 (C=O, enol ester) and 1626 (C=C, enol) cm^{-1}; ^1H nmr (200 MHz) a mixture of three isomers (two epimers and an enol) in a ratio of 1:1:3: δ 11.87 (s, 0.6H, OH), 6.70 (dd, J = 10, 1.5 Hz, 0.2H, CH=CHCO), 6.69 (dd, J = 10, 1.5 Hz, 0.2H, CH=CHCO), 6.05 (d, J = 10 Hz, 0.6H, CH=CHCO, enol form), 5.91 (d, J=10 Hz, 0.2H, CH=CHCO), 5.86 (d, J=10 Hz, 0.6H, CH=CHCO, enol form), 5.73 (d, J=10 Hz, 0.2H, CH=CHCO), 5.66-5.85 (m, 1H, $CH=CH_2$), 4.90-5.15 (m, 2H, $CH=CH_2$), 3.76, 3.75 (s, 3H, OCH_3), 3.65-3.45 (m, 0.4H, COCHCOOMe), 2.50-1.85 (m, 4H),

1.75-1.35 (m, 2H), 1.18, 1.15, 1.02 (s, 3H, CH_3); hrms M^+ 222.1256 (calcd. for $C_{13}H_{18}O_3$: 222.1256). Anal. calcd. for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found: C 70.20, H 8.25.

General Procedure for DDQ Oxidation

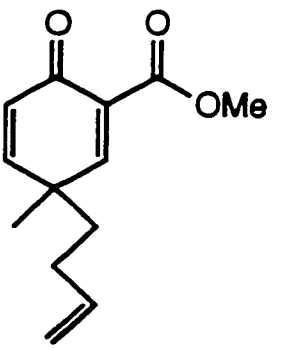
A. Using benzene as solvent

To a solution of keto ester (0.9 mmol, 1 eq.) in dry benzene (5 mL) at room temperature under an argon atmosphere, was added DDQ (1.8 mmol, 2 eq.). The mixture was stirred for 15 min, and then refluxed for 5 h. The reaction mixture was cooled and evaporated to dryness. The precipitate was removed by filtration after chloroform (15 mL) was added to the residue. The filtrate was concentrated, and the residue was subjected to flash chromatography using ethyl acetate/hexane (20:80) as an eluent to give the enone ester.

B. Using THF as solvent

To a solution of keto ester (0.9 mmol, 1 eq.) in THF (5 mL) at room temperature under an argon atmosphere, was added DDQ (0.9 mmol, 1 eq.). The mixture was stirred for 1 h and then evaporated to dryness. The precipitate was removed by filtration after chloroform (15 mL) was added to the residue. The filtrate was concentrated, and the residue was subjected to flash chromatography using ethyl acetate/hexane (20:80) as an eluent to give the enone ester.

4-(3-Butenyl)-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (10)



Compound **10** was prepared by DDQ oxidation using benzene as a solvent. Treatment of **17** (200 mg, 0.9 mmol) with DDQ (407 mg, 1.8 mmol) for 5 h afforded enone ester **10** (141 mg, 71%) as a yellow oil: ir (CH_2Cl_2) 1742 (C=O, ester), 1665 (C=O, ketone) and 1638 (C=C) cm^{-1}; ^1H nmr (200 MHz) δ 7.50 (d, J = 3 Hz, 1H, C**H**=CCOOMe), 6.75 (dd, J = 10, 3 Hz, 1H, C**H**=CHCO), 6.32 (d, J = 10 Hz, 1H, CH=C**H**CO), 5.70 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 4.97 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.95 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.87 (s, 3 H, O**CH**$_3$), 1.95-1.75 (m, 4H), 1.31 (s, 3H, **CH**$_3$); ^{13}C nmr (75 MHz) δ 181.6 (p), 165.2 (p), 160.6 (a), 153.6 (a), 137.2 (a), 131.8 (p), 129.7 (a), 115.5 (p), 52.4 (p), 42.1 (a), 39.7 (a), 29.3 (a), 25.7 (p); hrms M^+ 220.1098 (calcd. for $C_{13}H_{16}O_3$: 220.1099). Anal. calcd. $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.57, H 7.41.

General Procedure for Polyene Cyclization

A. Using $ZnCl_2$ as Reagent

Zinc chloride (0.57 mmol, 2.5 eq.) was flame-dried under an argon atmosphere for 5 min prior to the reaction. The reaction flask was cooled to 0°C and a solution of enone ester (0.23 mmol, 1 eq.) in dry diethyl ether (15 mL) was

added and the mixture was stirred under argon at room temperature. After several h, the starting material was completely consumed. Water was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The organic solutions were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (2:98) as an eluent to afford the cyclization product(s).

B. Using $SnCl_4$, $TiCl_4$ and Et_2AlCl as Reagents

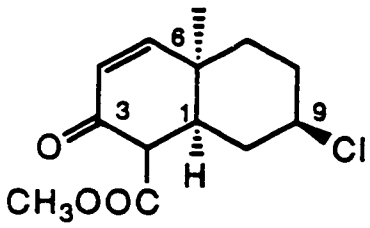
A solution of enone ester (0.23 mmol, 1 eq.) in dry dichloromethane (10 mL) was cooled to -78^{0}C under an argon atmosphere. Stannic chloride (0.34 mmol, 1.5 eq.) was added, and the mixture was stirred under the same conditions. After 45 min, the starting material was completely consumed. Water was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic solutions were washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give the cyclization product(s).

C. Using ZnI_2, $AlCl_3$ and AlI_3 as Reagents

To a stirred suspension of anhydrous zinc iodide (0.26 mmol, 1.2 eq.) in dry diethyl ether (10 mL) at room temperature under argon, was added a solution of enone ester (0.21 mmol, 1 eq.) in diethyl ether (5 mL). The reaction flask was protected from light. The reaction mixture was stirred for 3 days and then quenched with 1 N HCl solution. The aqueous solution was extracted with

diethyl ether (3 x 50 mL). The organic solution was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford the cyclization product(s).

(1S*, 6S*, 9R*)-2-Carbomethoxy-9-chloro-6-methylbicyclo[4.4.0]-dec-4-en-3-one (11) and (1S*, 4S*, 5S*, 9S*)-2-carbomethoxy-4-chloro-9-methyltricyclo[4.3.1.$0^{5,9}$]decan-3-one (12)



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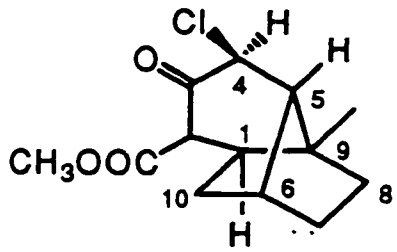
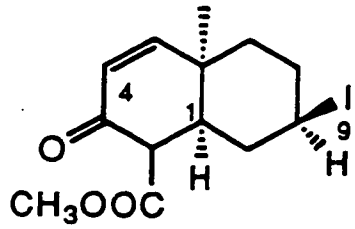


12

Enone ester **10** (500 mg, 2.3 mmol) was treated with zinc chloride (770 mg, 5.7 mmol) for 3 h, to give compounds **11** (376 mg, 65%) and **12** (144 mg, 25%). Compound **11**: ir (CH_2Cl_2 cast) 3180 (OH, enol), 1653 (C=O, enol ester) and 1626 (C=C, enol) cm^{-1}; ^1H nmr (300 MHz) a mixture of keto and enol forms in a ratio of 1:4: δ 11.85 (s, 0.8H, OH), 5.90-6.15 (m, 2H, CH=CH), 3.75, 3.70 (s, 3H, OCH_3), 3.60-3.80 (m, 1.2H, CHCl and COCHCOOMe), 2.40 (ddd, J=12, 4, 1.5 Hz, 1H, ring junction proton), 2.00-2.20 (m, 2H), 1.70 (m, 1H), 1.30-1.65 (m, 3H), 1.10, 0.90 (s, 3H, CH_3); hrms M^+ 256.0868, 258.0844 (calcd. for $C_{13}H_{17}ClO_3$: 256.0866, 258.0837). Compound **12**: ir (CH_2Cl_2 cast) 3210 (OH, enol), 1747 (C=O, ester), 1731 (C=O, ketone), 1657 (C=O, enol ester) and 1618 (C=C, enol) cm^{-1}; ^1H nmr (400 MHz) a mixture of keto and enol forms in a ratio of 1:1: δ 11.62 (s, 0.5H, OH), 4.80 (d, J=7.0 Hz, 1H, CHCl), 3.70-3.85 (m, 3.5H, OCH_3

and COCHCOOMe), 2.62 (m, 1H), 2.45 (m, 1H), 2.00-2.20 (m, 2H), 1.20-1.70 (m, 5H), 1.10, 1.05 (s, 3H, CH_3).

(1S*, 6S*, 9R*)-2-Carbomethoxy-9-iodo-6-methylbicyclo[4.4.0]dec-4-en-3-one (18)



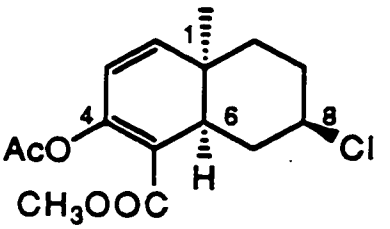
Enone ester **10** (460 mg, 2.1 mmol) was treated with zinc iodide (804 mg, 2.5 mmol) at room temperature for 3 days to give compound **18** (621 mg, 85%): ir (CH_2Cl_2 cast) 3200 (OH, enol), 1733 (C=O, ester), 1683 (C=O, ketone), 1652 (C=O, enol ester) and 1625 (C=C, enol) cm^{-1}; ^1H nmr (300 MHz) a mixture of three isomers in a ratio of 1:1:4.7: δ 11.85 (s, 0.7H, OH), 6.10-5.95 (m, 2H, CH=CH), 4.00 (dddd, J = 12, 12, 4, 4 Hz, 1H, CHI), 3.70-3.85 (m, 3.3H, OCH_3 and COCHCOOMe), 2.30-2.50 (m, 2H), 1.80-2.15 (m, 2H), 1.30-1.65 (m, 3H), 1.08, 1.02, 0.95 (s, 3H, CH_3); ^{13}C nmr (300 MHz) δ 172.4 (p), 165.0 (p), 147.9 (a), 123.2 (a), 97.9 (p), 51.6 (a), 42.0 (a), 41.9 (p), 40.7 (p), 37.7 (p), 36.2 (p), 26.7 (a), 25.9 (a); hrms M^+ 348.0222 (calcd. for $C_{13}H_{17}IO_3$: 348.0223).

General Procedure for Acetylation of β-Keto Ester

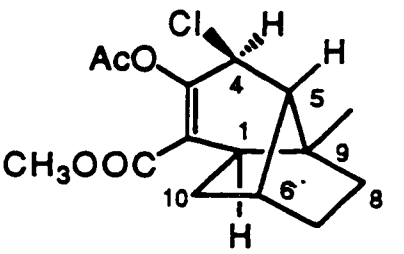
To a solution of keto ester (0.14 mmol) in pyridine (2 mL) at room temperature under an argon atmosphere, was added acetic anhydride (0.5 mL). The reaction mixture was stirred overnight, and pyridine was removed under

reduced pressure. Water was added and the resulting mixture was extracted with diethyl ether (3 x 50 mL). The ether extracts were washed with 1 N hydrochloric acid and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (5:95) as an eluent gave the enol acetate.

(1R*, 6R*, 8R*)-4-Acetoxy-5-carbomethoxy-8-chloro-1-methybicyclo [4.4.0]deca-2,4-diene (19) and (1R*, 4S*, 5S*, 9R*)-3-acetoxy-2-carbomethoxy-4-chloro-9-methyltricyclo[4.3.1.$0^{5,9}$]dec-2-ene (20)



19

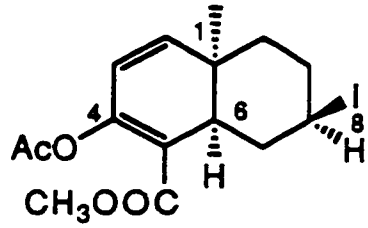


20

A 2.6:1 mixture of chlorides **11** and **12** (100 mg, 0.39 mmol) was treated with pyridine and acetic anhydride to give acetates **19** (76 mg, 65%) and **20** (29 mg, 25%). Compound **19**: ir (CH_2Cl_2 cast) 1766 (CH_3COO) and 1711 ($COOCH_3$) cm^{-1}; ^1H nmr (200 MHz) δ 5.97 (dd, J=10, 2.0 Hz, 1H, C**H**=CHCO), 5.70 (d, J=10 Hz, 1H, CH=C**H**CO), 3.80 (s, 3H, O**CH$_3$**), 3.67 (m, 1H, C**H**Cl), 2.62 (ddd, J=12.5, 4.5, 2 Hz, 1H, ring junction proton), 2.22 (dddd, J=13, 4, 4, 2 Hz, 1H, **H$_{7e}$**), 2.17 (s, 3H, C**H$_3$**CO), 2.05 (dddd, J=14, 3, 3, 1.5 Hz, 1H, **H$_{9e}$**), 1.72 (ddd, J=14, 3, 3 Hz, 1H, **H$_{10e}$**), 1.50-1.65 (m, 2H, **H$_{7a}$** and **H$_{9a}$**), 1.35 (ddd, J=14, 14, 3, 1H, **H$_{10a}$**), 1.04 (s, 3H, **CH$_3$**); ^{13}C nmr (300 MHz) δ 168.5 (p), 165.4 (p), 151.6 (p), 145.0 (a), 123.8 (a), 116.2 (p), 56.5 (a), 51.9 (a), 42.4 (a), 38.1 (p), 37.0 (p), 35.9 (p), 34.4 (p), 25.3 (a), 20.9 (a); hrms M^+ 298.0982,

300.0941 (calcd. for $C_{15}H_{19}ClO_4$: 298.0972, 300.0942). Anal. calcd. for $C_{15}H_{19}ClO_4$: C 60.30, H 6.41; found: C 60.24, H 6.46. Compound **20**: ir (CH_2Cl_2 cast) 1765 (CH_3COO) and 1719 ($COOCH_3$) cm^{-1}; ^1H nmr (300 MHz) δ 4.90 (d, J=7 Hz, 1H, **H_4**), 3.75 (s, 3H, OCH_3), 2.65 (m, 1H, **H_6**), 2.55 (dd, J=7.5, 2 Hz, 1H, **H_1**), 2.20 (s, 3H, CH_3CO), 2.08 (dd, J=7, 1 Hz, 1H, **H_5**), 1.20-1.90 (m, 6H), 1.15 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 168.6 (p), 164.8 (p), 149.6 (p), 130.7 (a), 60.1 (a), 55.9 (a), 52.1 (a), 50.7 (p), 43.7 (a), 41.3 (a), 40.6 (p), 35.9 (p), 31.1 (p), 20.8 (a), 16.7 (a); hrms M^+ 298.0963 (calcd. for $C_{15}H_{19}O_4Cl$: 298.0972).

(1R*, 6R*, 8R*)-4-Acetoxy-5-carbomethoxy-8-iodo-1-methylbicyclo-[4.4.0]deca-2,4-diene (21)



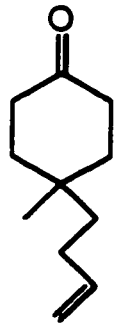
Acetylation of iodide **18** (100 mg, 0.29 mmol) with pyridine and acetic anhydride afforded acetate **21** (100 mg, 89%): ir (CH_2Cl_2 cast) 1765 (CH_3CO) and 1709 ($COOCH_3$) cm^{-1}; ^1H nmr (200 MHz) δ 6.00 (dd, J=9.5, 1.5 Hz, 1H, CH=CHCO), 5.80 (d, J=9.5 Hz, 1H, CH=CHCO), 4.00 (dddd, J=12, 12, 4, 4 Hz, 1H, CHI), 3.75 (s, 3H, OCH_3), 2.60 (ddd, J=12, 4, 1.5 Hz, 1H, ring junction proton), 2.50 (m, 1H, **H_{7e}**), 2.36 (m, 1H, **H_{9e}**), 2.20 (s, 3H, CH_3CO), 1.82-2.10 (m, 2H, **H_{7a} + H_{10e}**), 1.58 (m, 1H, **H_{9a}**), 1.43 (m, 1H, **H_{10a}**), 0.95 (s, 3H, CH_3); ^{13}C nmr (300 MHz) δ 168.5 (p), 165.4 (p), 151.6 (p), 145.0 (a), 123.8 (a), 116.2 (p), 56.5 (a), 51.9 (a), 42.4 (a), 38.1 (p), 37.0 (p), 35.9 (p), 34.4 (p), 25.3

(a), 20.9 (a); hrms M^+ 390.0325 (calcd. for $C_{15}H_{19}IO_4$: (390.0328). Anal. calcd. for $C_{15}H_{19}IO_4$: C 60.30, H 6.41; found: C 60.24, H 6.46.

General Procedure for Reduction with the Hexamer of (Triphenylphosphine)copper Hydride

A solution of enone (1.1 mmol, 1 eq.) in benzene (25 mL) was added to the hexamer of (triphenylphosphine)copper hydride (0.51 mmol, 0.5 eq.). The reaction mixture was stirred at room temperature under an argon atmosphere for several days, and then exposed to the atmosphere and stirred for 20 min. The mixture was filtered through a short column of silica gel, using ether/hexane (50:50) as an eluent. The filtrate was concentrated. The residue was subjected to flash chromatography with ethyl acetate/hexane (2:98) to afford the ketone.

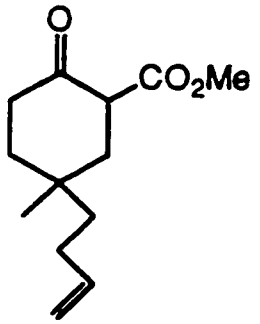
4-(3-Butenyl)-4-methylcyclohexanone (22)



Reduction of **16** (100 mg, 0.61 mmol) with the hexamer of (triphenylphosphine)copper hydride (600 mg, 0.31 mmol) in benzene at room temperature for 5 days gave ketone **22** (38 mg, 37%) along with the recovered starting material (45 mg): Ir (CH_2Cl_2 cast) 1716 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ 5.83 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.30 (dddd, J=17, 1.5, 1.5, 1.5

Hz, 1H, *trans* CH=C**H**H), 4.95 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 2.25-2.40 (m, 4H), 1.95-2.15 (m, 2H), 1.60-1.70 (m, 4H), 1.40-1.50 (m, 2H), 1.08 (s, 3H, C**H**$_3$); ^{13}C nmr (75 MHz) δ 212.5 (p), 139.1 (p), 114.4 (p), 39.8 (p), 37.6 (p, 2 x **C**), 37.3 (p, 2 x **C**), 32.3 (a), 28.3 (p), 23.9 (a); hrms M$^+$ 166.1358 (calcd. for $C_{11}H_{18}O$: 166.1358).

4-(3-Butenyl)-2-carbomethoxy-4-methylcyclohexanone (23)



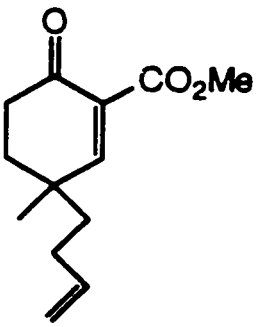
To a stirred suspension of sodium hydride (38 mg, 95%, 1.5 mmol) in DME (3 mL) at room temperature under an argon atmosphere, were added dimethyl carbonate (0.4 mL) and a solution of enone **22** (100 mg, 0.6 mmol) in DME (2 mL). The mixture was refluxed for 3 h and cooled to 0^{0}C. A 1 N HCl solution (10 mL) was added cautiously to the mixture. The resulting solution was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude product purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford keto ester **23** (115 mg, 85%) as a yellowish oil: ir (neat) 3200 (OH, enol), 1745 (C=O, ester) and 1718 (C=O, ketone), 1659 (C=O, enol ester), 1641 (C=C) and 1617 (C=C, enol) cm^{-1}; ^{1}H nmr (300 MHz) a mixture of keto and enol forms in a ratio of 1:2: δ 12.12 (s, 0.67 H, O**H**), 5.80 (m, 1H, C**H**=CH$_2$), 4.85-5.10 (m, 2H, CH=C**H**$_2$), 4.48-4.78 (m,

0.33 H, $COCHCOOCH_3$), 3.75, 3.74, 3.72 (s, 3H, OCH_3), 2.25 (m, 1H), 1.90-2.15 (m, 4H), 1.65 (m, 1H), 1.20-1.50 (m, 4H), 0.95, 0.93, 0.90 (s, 3H, CH_3); hrms M^+ 224.1409 (calcd. for $C_{13}H_{20}O_3$: 224.1413).

General Procedure for Phenylselenenylation and Oxidative Elimination

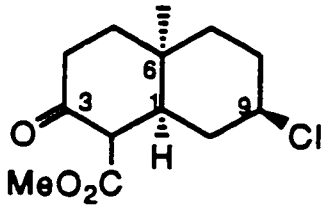
To a stirred solution of keto ester (0.38 mmol, 1 eq.) and sodium hydride (0.95 mmol, 2.5 eq.) in THF (10 mL) at 0^0C under an argon atmosphere, was added diphenyl diselenide (0.46 mmol, 1.2 eq.) in THF (5 mL). The mixture was stirred at 0^0C for 1 h and then 1 N HCl (5 mL) was added. The resulting mixture was extracted with ether (3 x 10 mL). The extracts were combined, washed with water and concentrated. The residue was dissolved in THF (3 mL), and a solution of $NaIO_4$ (1.14 mmol, 3 eq.) in MeOH-H_2O (7:3, 20 mL) was added dropwise at room temperature. The resulting mixture was stirred overnight. Water was added and the resulting aqueous solution extracted with diethyl ether (3 x 50 mL). The extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford the keto ester.

4-(3-Butenyl)-2-carbomethoxy-4-methyl-2-cyclohexenone (24)



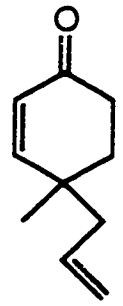
Phenylselenenylation of **23** (100 mg, 0.45 mmol) using diphenyl diselenide (167 mg, 0.54 mmol) and sodium hydride (29 mg, 1.1 mmol) followed by oxidative elimination with sodium periodate (286 mg, 1.3 mmol) gave enone ester **24** (69 mg, 69%) as a yellowish oil: ir (CH_2Cl_2 cast) 1745 (C=O, ester) and 1686 (C=O, ketone) cm^{-1}; ^1H nmr (400 MHz) δ 7.40 (s, 1H, C**H**=CCOOMe), 5.80 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.05 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.99 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.70 (s, 3H, O**CH$_3$**), 2.50-2.60 (m, 2H), 1.90-2.20 (m, 2H), 1.80 (m, 1H), 1.55-1.65 (m, 3H), 1.22 (s, 3H, C**H$_3$**).

(1S*, 6S*, 9R*)-2-Carbomethoxy-9-chloro-6-methylbicyclo[4.4.0]-decan-3-one (25)



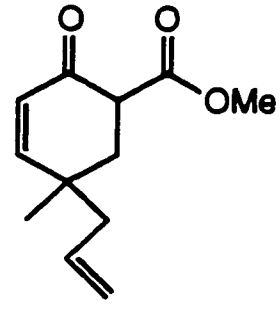
Using the general procedure for cyclization, a solution of enone ester **24** (50 mg, 0.23 mmol) in dichloromethylene (10 mL) was treated with stannic chloride (0.03 mL, 0.27 mmol) at -78°C for 10 min to give compound **25** (53 mg, 91%): ir (CH_2Cl_2 cast) 3600 (OH, enol), 1652 (C=O, enol ester) and 1614 (C=C, enol) cm^{-1}; ^1H nmr (300 MHz) δ 12.3 (s, 1H, O**H**), 3.80 (m, 1H, C**H**Cl), 3.75 (s, 3H, O**CH$_3$**), 2.50-2.60 (m, 3H), 1.90-2.20 (m, 2H), 1.65-1.85 (m, 2H), 1.35-1.65 (m, 3H), 1.05-1.35 (m, 1H), 0.90 (s, 3H, C**H$_3$**); ^{13}C nmr (75 MHz) δ 172.8 (p), 172.0 (p), 100.6 (p), 59.1 (a), 51.6 (a), 41.5 (p), 40.7 (a), 39.8 (p), 32.7 (p), 29.8 (p), 26.3 (p), 26.2 (a), 25.8 (p); hrms M^+ 258.1020, 260.0998 (calcd. for $C_{13}H_{19}ClO_3$: 258.1023, 260.0993).

4-Allyl-4-methyl-2-cyclohexenone (27)



Compound **27** was prepared from enone **14** using the general procedures for alkylation, $LiAlH_4$ reduction and acidic hydrolysis. Alkylation of **14** (4.5 g, 29.2 mmol) with LDA (32.0 mmol) and allyl bromide (4.89 g, 40.4 mmol) gave enone **26**, which was subjected to $LiAlH_4$ reduction and acidic hydrolysis to afford enone **27** (3.85 g, 88% overall): ir (CH_2Cl_2) 1681 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ 6.65 (d, J=10 Hz, 1H, C**H**=CHCO), 5.87 (d, J=10 Hz, 1H, C**H**=C**H**CO), 5.77 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.08 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 5.04 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 2.40-2.48 (m, 2H), 1.05-2.20 (m, 4H), 1.08 (s, 3H, CH_3); hrms M^+ 150.1045 (calcd. for $C_{10}H_{14}O$: 150.1045).

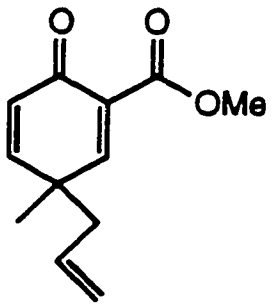
4-Allyl-6-carbomethoxy-4-methyl-2-cyclohexenone (28)



Using the general procedure, carbomethoxylation of **27** (300 mg, 2 mmol) with sodium hydride (126 mg, 95%, 5 mmol) and dimethyl carbonate (15 mL) for 2 h gave keto ester **28** (345 mg, 74%) as a yellow oil: ir (CH_2Cl_2 cast) 3320 (OH,

enol), 1745 (C=O, ester) and 1684 (C=O, ketone), 1640 (C=O, enol ester) and 1624 (C=C, enol) cm^{-1}; ^1H nmr (200 MHz) a mixture of three isomers in a ratio of 1:1:1: δ 11.90 (s, 0.33H, O**H**), 6.72 (dd, J = 10, 2 Hz, 0.33H, C**H**=CHCO), 6.68 (dd, J = 10, 2 Hz, 0.33H, C**H**=CHCO), 6.07 (dd, J = 10 Hz, 0.33H, C**H**=CHCO), 5.95 (dd, J = 10 Hz, 0.33H, CH=C**H**CO), 5.92 (dd, J = 10 Hz, 0.33H, CH=C**H**CO), 5.88 (dd, J = 10 Hz, 0.33H, CH=C**H**CO), 5.65-5.90 (m, 1H, C**H**=CH_2), 4.95-5.20 (m, 2H, CH=C$\mathbf{H_2}$), 3.79, 3.78 (s, 3H, OC$\mathbf{H_3}$), 3.55-3.70 (m, 0.67H, COC**H**COOMe), 1.85-2.60 (m, 4H), 1.20, 1.16, 1.03 (s, 3H, C$\mathbf{H_3}$); hrms M^+ 208.1095 (calcd. for $C_{12}H_{16}O_3$: 208.1100). Anal. calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 68.81, H 7.66.

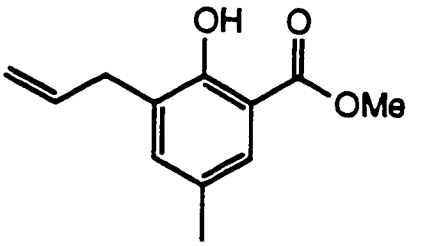
4-Allyl-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (29)



Compound **29** was prepared according to the general procedure for DDQ oxidation using THF as solvent. Oxidation of **28** (83 mg, 0.4 mmol) with DDQ (91 mg, 0.4 mmol) afforded enone ester **29** (68 mg, 83%): ir (CH_2Cl_2 cast) 1745 (C=O, ester) and 1684 (C=O, ketone) cm^{-1}; ^1H nmr (400 MHz) δ 7.50 (d, J=3 Hz, 1H, C**H**=CCOOCH_3), 6.76 (dd, J=10, 3 Hz, 1H, C**H**=CHCO), 6.30 (d, J=10 Hz, 1H, CH=C**H**CO), 5.59 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.10 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 5.07 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.85 (s, 3H, OC$\mathbf{H_3}$), 2.40 (d, J=7 Hz, 2H, C$\mathbf{H_2}$CH=CH_2), 1.45

(s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 181.6 (p), 165.2 (p), 160.3 (a), 153.3 (p), 131.7 (a), 131.5 (p), 129.4 (a), 119.7 (p), 60.4 (p), 52.4 (a), 44.5 (a), 24.8 (p); hrms M^+ 206.0943 (calcd. for $C_{12}H_{14}O_3$: 206.0937).

Methyl 3-Allyl-2-hydroxy-5-methylbenzoate (30)



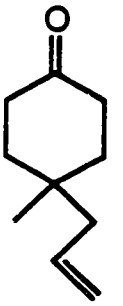
A. Using $ZnCl_2$ as Catalyst

A solution of enone **29** (62 mg, 0.3 mmol) was added to a mixture of anhydrous $ZnCl_2$ (80 mg, 0.59 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 h and water was added. The resulting mixture was extracted with ether (3 x 15 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (10:90) gave compound **30** (53 mg, 86%): ir (CH_2Cl_2) 3171 (OH) and 1675 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ 10.80 (s, 1H, **OH**), 7.55 (d, J=1.5 Hz, 1H, **H3**), 7.15 (d, J=1.5 Hz, 1H, **H5**), 6.02 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, **CH**=CH_2), 5.95 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=**CH**H), 5.08 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.95 (s, 3H, OCH_3), 3.40 (d, J=6.5, 2H, CH_2**CH**=CH_2), 2.30 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 171.0 (p), 157.5 (p), 136.9 (a), 136.4 (a), 128.3 (p), 127.8 (p), 127.7 (a), 115.8 (p), 111.6 (p), 52.2 (a), 33.7 (p), 20.5 (a); hrms M^+ 206.0943 (calcd. for $C_{12}H_{14}O_3$: 206.0941).

B. Using $SnCl_4$ as Catalyst

A solution of enone ester **29** (50 mg, 0.24 mmol) in dry dichlomethane (5 mL) was cooled to -78^{0}C under an argon atmosphere. Stannic chloride (0.03 ml, 0.27 mmol) was added, and the mixture was stirred under the same conditions. After 45 min, the starting material was completely consumed. Water was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic solutions were washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give compound **30** (54 mg, 88%).

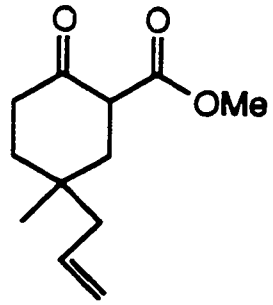
4-Allyl-4-methylcyclohexane (31)



Compound **31** was prepared according to the general procedure for reduction with $(Ph_3PCuH)_6$. Treatment of **27** (800 mg, 5.3 mmol) with the hexamer of (triphenylphosphine)copper hydride (2 g, 1 mmol) in benzene at room temperature for 5 days gave ketone **31** (365 mg, 45%) along with the recovered starting material (360 mg): Ir (CH_2Cl_2 cast) 1716 (C=O) cm^{-1}; ^{1}H nmr (300 MHz) δ 5.78 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.19 (dddd, J=17, 1.5, 1.5,

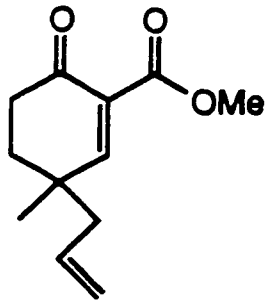
1.5 Hz, 1H, *trans* CH=CHH), 5.15 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CHH), 2.30-2.40 (m, 4H), 1.55-2.15 (m, 6H), 1.05 (s, 3H, CH_3); hrms M^+ 152.1196 (calcd. for $C_{10}H_{16}O$: 152.1201).

4-Allyl-2-carbomethoxy-4-methylcyclohexane (32)



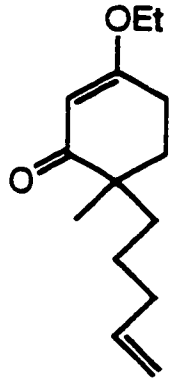
Compound **32** was prepared according to the general procedure for carbomethoxylation. Treatment of **31** (93 mg, 0.61 mmol) with sodium hydride (39 mg, 95%, 1.5 mmol) and dimethyl carbonate (4 mL) in refluxing DME (10 mL) for 3 h gave keto ester **32** (94 mg, 72%): ir (CH_2Cl_2 cast) 3200 (OH, enol), 1747 (C=O, ester), 1705 (C=O, ketone), 1658 (C=O, enol ester) and 1617 (C=C, enol) cm^{-1}; ^1H nmr (400 MHz) a mixture of keto and enol forms in a ratio of 1:9: δ 12.14 (s, 0.9H, OH), 5.75-5.85 (m, 1H, $CH=CH_2$), 4.95-5.10 (m, 2H, $CH=CH_2$), 3.75 (s, 3H, OCH_3), 3.60-3.85 (m, 0.1H, COCHCOOMe), 2.30 (m, 2H), 1.90-2.10 (m, 4H), 1.35-1.50 (m, 2H), 0.95 (s, 3H, CH_3); hrms M^+ 210.1258 (calcd. for $C_{12}H_{18}O_3$: 210.1256).

4-Allyl-2-carbomethoxy-4-methyl-2-cyclohexenone (33)



Compound **33** was prepared according to the general procedure for phenylselenenylation and oxidation. Phenylselenenylation of **32** (80 mg, 0.38 mmol) using diphenyl diselenide (142 mg, 0.46 mmol) and sodium hydride (24 mg, 95%, 0.95 mmol) followed by oxidative elimination with sodium periodate (244 mg, 1.14 mmol) gave enone ester **33** (57 mg, 72%): ir (CH_2Cl_2 cast) 1745 (C=O, ester) and 1689 (C=O, ketone) cm^{-1}; ^1H nmr (300 MHz) δ 7.40 (s, 1H, C**H**=CCOOMe), 5.78 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.19 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 5.15 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.80 (s, 3H, OCH_3), 2.55 (m, 2H), 2.35 (m, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 1.22 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 194.4 (p), 165.2 (p), 163.4 (a), 132.6 (a), 130.7 (p), 119.5 (p), 52.3 (a), 44.9 (p), 36.5 (p), 34.9 (p), 32.9 (p), 24.3 (a); hrms M^+ 208.1111 (calcd. for $C_{12}H_{16}O_3$: 208.1099).

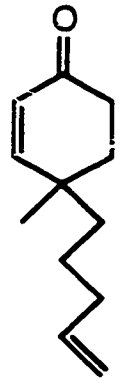
3-Ethoxy-6-methyl-6-(4-pentenyl)-2-cyclohexenone (34)



Using the general procedure, alkylation of enone **14** (1 g, 6.5 mmol) with LDA (7.2 mmol) and 5-bromo-1-pentene (3.44 g, 9.8 mmol) for 4 days gave compound **34** (7.4 g, 85%): ir (CH_2Cl_2 cast) 1653 (C=O, enone) cm^{-1}; ^1H nmr (300 MHz) δ 5.78 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.25 (s, 1H, C**H**=COEt), 4.98 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.92 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.87 (q, J=7 Hz, 2H, OCH_2), 2.39 (ddd,

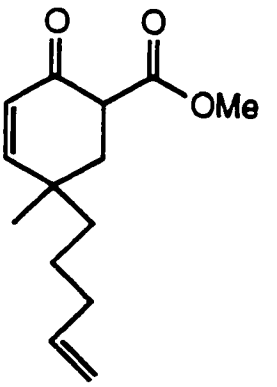
J=6, 2.5, 2.5 Hz, 2H), 2.20 (dd, J=13, 6.5 Hz, 2H), 1.89 (m, 1H), 1.71 (m, 1H), 1.35 (t, J=7 Hz, 3H, OCH_2CH_3), 1.30-1.60 (m, 4H), 1.08 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 204.1 (p), 175.6 (p), 138.7 (a), 114.5 (p), 101.3 (a), 64.1 (p), 43.2 (p), 36.4 (p), 34.3 (p), 32.1 (p), 26.0 (p), 23.4 (p), 22.3 (a), 14.2 (a); hrms M^+ 222.1620 (calcd. for $C_{14}H_{22}O_2$: 222.1616).

4-Methyl-4-(4-pentenyl)-2-cyclohexenone (35)



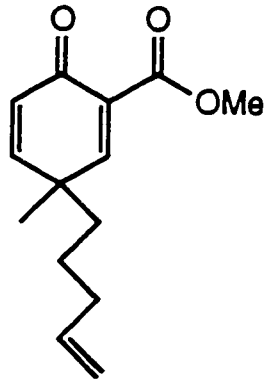
Compound **35** was prepared according to the general procedure for $LiAlH_4$ reduction followed by acidic hydrolysis. Compound **34** (0.7 g, 3.2 mmol) was subjected to reduction with $LiAlH_4$ (0.266 g, 6.9 mmol), followed by acidic hydrolysis to afford enone **35** (510 mg, 91%): ir (CH_2Cl_2 cast) 1682 (C=O, enone) cm^{-1}; ^1H nmr (300 MHz) δ 6.66 (d, J=10 Hz, 1H, CH=CHCO), 5.85 (d, J=10 Hz, 1H, CH=CHCO), 5.77 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, $CH=CH_2$), 5.00 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CHH), 4.93 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CHH), 2.45 (m, 1H), 1.90-2.10 (m, 3H), 1.75 (m, 1H), 1.20-1.60 (m, 5H), 1.15 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 199.7 (p), 159.3 (a), 138.3 (a), 127.4 (a), 114.4 (p), 40.4 (p), 35.8 (p), 34.2 (p), 34.1(p), 33.2 (p), 24.9 (a), 24.1 (p); hrms M^+ 178.1356 (calcd. for $C_{12}H_{18}O$: 178.1358).

6-Carbomethoxy-4-methyl-4-(4-pentenyl)-2-cyclohexenone (36)



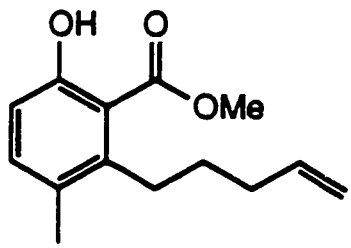
The general procedure for carbomethoxylation was used for the preparation of compound **36**. Treatment of **35** (356 mg, 2 mmol) with sodium hydride (125 mg, 95%, 5 mmol) and dimethyl carbonate (15 mL) for 2 h gave keto ester **36** (415 mg, 88%): ir (CH_2Cl_2 cast) 3370 (OH, enol), 1745 (C=O, ester) and 1682 (C=O, ketone), 1660 (C=O, enol ester), 1640 (C=C) and 1620 (C=C, enol) cm^{-1}; ^1H nmr (200 MHz) a mixture of three isomers in a ratio of 1:1:2: δ 11.88 (s, 0.5H, OH), 6.72 (dd, J = 10, 2 Hz, 0.25H, CH=CHCO), 6.67 (dd, J = 10, 2 Hz, 0.25H, CH=CHCO), 6.05 (dd, J = 10, 2 Hz, 0.5H, CH=CHCO), 5.92 (d, J=10 Hz, 0.25H, CH=CHCO), 5.87 (d, J=10 Hz, 0.5H, CH=CHCO), 5.76 (d, J=10 Hz, 0.25H, CH=CHCO), 5.68-5.88 (m, 1H, $CH=CH_2$), 4.91-5.09 (m, 2H, $CH=CH_2$), 3.79, 3.78 (s, 3H, OCH_3), 3.60 (dd, J=9, 5 Hz, 0.25H, COCHCOOMe), 3.53 (dd, J=8, 5 Hz, 0.25H, COCHCOOMe), 1.80-2.50 (m, 4H), 1.25-1.65 (m, 4H), 1.09, 1.15, 1.03 (s, 3H, CH_3); hrms M^+ 236.1413 (calcd. for $C_{14}H_{20}O_3$: 236.1413).

2-Carbomethoxy-4-methyl-4-(4-pentenyl)-2,5-cyclohexadienone (37)



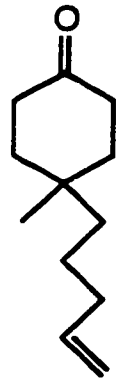
Compound **37** was prepared according to the general procedure for DDQ oxidation using benzene as solvent. Oxidation of **36** (250 mg, 1.1 mmol) with DDQ (481 mg, 2.4 mmol) for 3 h afforded enone ester **37** (174 mg, 70%): ir (CH_2Cl_2 cast) 1743 (C=O, ester) and 1666 (C=O, ketone) cm^{-1}; ^1H nmr (300 MHz) δ 7.47 (d, J=3 Hz, 1H, CH=$CCOOCH_3$), 6.72 (dd, J=10, 3 Hz, 1H, CH=CHCO), 6.29 (d, J=10 Hz, 1H, CH=CHCO), 5.68 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, CH=CH_2), 4.97 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CHH), 4.93 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CHH), 3.85 (s, 3H, OCH_3), 2.00 (m, 2H), 1.65 (m, 2H), 1.10-1.25 (m, 2H), 1.29 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 181.6 (p), 165.1 (p), 161.0 (a), 153.9 (a), 137.6 (a), 131.5 (p), 129.5 (a), 115.3 (p), 52.3 (a), 42.1 (p), 39.9 (p), 33.6 (p), 25.7 (a), 24.3 (a); hrms M^+ 234.1262 (calcd. for $C_{14}H_{18}O_3$: 234.1256).

Methyl 6-hydroxy-3-methyl-2-(4-pentenyl)benzoate (38)



A solution of enone **37** (70 mg, 0.3 mmol) was added to a mixture of $AlCl_3$ (48 mg, 0.36 mmol) in ether (15 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred for 12 h and water was added. The resulting mixture was extracted with ether (3 x 15 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (10:90) as an eluent gave compound **38** (50 mg, 72%): ir (CH_2Cl_2 cast) 3430 (OH) and 1732 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ 10.55 (s, 1H, O**H**), 7.20 (d, J=8 Hz, 1H, **H5**), 6.78 (d, J=8 Hz, 1H, **H6**), 5.85 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.06 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 5.03 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.98 (s, 3H, OCH_3), 2.85 (m, 2H), 2.28 (s, 3H, CH_3), 2.15 (m, 2H), 1.65 (m, 2H) ; ^{13}C nmr (75 MHz) δ 171.9 (p), 160.1 (p), 143.0 (p), 138.5 (a), 136.6 (a), 128.0 (p), 115.2 (a), 114.9 (p), 113.0 (p), 58.0 (a), 34.4 (p), 31.4 (p), 29.5 (p), 19.6 (a); hrms M^+ 234.1254 (calcd. for $C_{14}H_{18}O_3$: 234.1256).

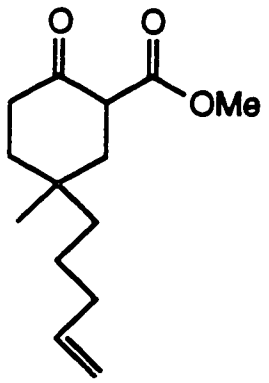
4-Methyl-4-(4-pentenyl)-cyclohexanone (39)



Reduction of **35** (200 mg, 1.1 mmol) with the hexamer of (triphenylphosphine)copper hydride (1 g, 0.5 mmol) in benzene at room temperature for 24 h gave ketone **39** (130 mg, 66%): ir (CH_2Cl_2 cast) 1716

(C=O) cm^{-1}; ^1H nmr (300 MHz) δ 5.81 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.02 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.96 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 2.25 (m, 3H), 2.00-2.15 (m, 2H), 1.60-1.75 (m, 4H), 1.30-1.50 (m, 5H), 1.08 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 212.5 (p), 139.1 (a), 114.4 (p), 39.8 (p), 37.6 (p, 2 x **C**), 37.3 (p, 2 x **C**), 34.5 (p), 32.3 (p), 24.0 (a), 23.2 (p); hrms M^+ 180.1513 (calcd. for $C_{12}H_{20}O$: 180.1513).

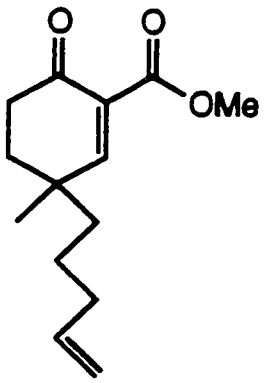
2-Carbomethoxy-4-methyl-4-(4-pentenyl)cyclohexanone (40)



To a stirred solution of sodium hydride (40 mg, 95%, 1.6 mmol) in DME (3 mL) at room temperature under an argon atmosphere, were added dimethyl carbonate (0.4 mL) and a solution of enone **39** (115 mg, 0.65 mmol) in DME (2 mL). The mixture was refluxed for 1 h and then cooled to 0°C. A 1 N HCl solution (10 mL) was added cautiously to the mixture. The resulting aqueous solution was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford keto ester **40** (107 mg, 72%) as a yellowish oil: ir (neat) 3460 (OH, enol), 1745 (C=O, ester), 1716 (C=O, ketone), 1659 (C=O, enol ester), 1640 (C=C) and 1620 (C=C, enol) cm^{-1} ; ^1H nmr (300 MHz) a mixture of keto and enol

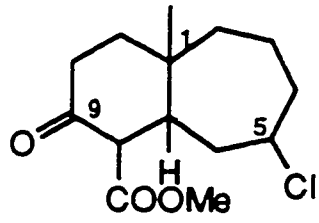
forms in a ratio of 1:1, δ 12.12 (s, 0.5H, OH), 5.70-5.90 (m, 1H, CH=CH_2), 4.95-5.10 (m, 2H, CH=CH_2), 3.75, 3.77, 3.78 (s, 3H, OCH_3), 3,60-3.80 (m, 0.5H, $COCHCOOCH_3$), 1.90-2.10 (m, 4H), 1.10-1.70 (m, 8H), 0.90, 0.91 (s, 3H, CH_3); hrms M^+ 238.1568 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

2-Carbomethoxy-4-methyl-4-(4-pentenyl)-2-cyclohexenone (41)



Compound **41** was prepared according to the general procedure for DDQ oxidation using benzene as solvent. Oxidation of **40** (100 mg, 0.42 mmol) with DDQ (191 mg, 0.84 mmol) for 1h afforded enone ester **41** (63 mg, 64%): ir (CH_2Cl_2 cast) 1744 (C=O, ester) and 1686 (C=O, ketone) cm^{-1}; ^1H nmr (300 MHz) δ 7.38 (s, 1H, CHCCOOMe), 5.75 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, CH=CH_2), 5.01 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CHH), 4.97 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CHH), 3.78 (s, 3H, OCH_3), 2.50 (m, 2H), 1.90-2.10 (m, 3H), 1.80 (m, 1H), 1.30-1.55 (m, 4H), 1.15 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 194.5 (p), 165.3 (p), 164.3 (a), 138.0 (a), 130.4 (p), 115.2 (p), 52.2 (a), 40.1 (p), 36.3 (p), 35.0 (p), 34.1 (p), 32.9 (p), 24.5 (a), 23.4 (p); hrms M^+ 236.1413 (calcd. for $C_{14}H_{20}O_3$: 236.1413).

8-Carbomethoxy-5-chloro-1-methylbicyclo[5.4.0]undecan-9-one (42)



$AlCl_3$ (57 mg, 0.42 mmol) was added to a solution of enone **41** (50 mg, 0.21 mmol) in ether (5 mL) at 0°C. The reaction mixture was stirred for 2 h and then water (1 x 10 mL) was added. The resulting mixture was extracted with ether (3 x 15 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Preparative thick layer chromatography of the residue using ethyl acetate/hexane (1:10) as a developing sovent gave compound **42** (28 mg, 50%): ir (CH_2Cl_2 cast) 3350 (OH, enol), 1720 (C=O, ester), 1655 (C=O, ketone and enol ester) and 1615 (C=C, enol) cm^{-1}; ^1H nmr (200 MHz) two enol isomers in a ratio of 2:1: δ 12.25, 12.15 (s, 1H, OH), 5.65, 4.05 (m, 1H, CHCl), 3.82, 3.75 (s, 3H, OCH_3), 2.00-2.40 (m, 4 H), 1.80-2.00 (m, 2 H), 1.20-1.80 (m, 7 H), 0.95, 0.85 (s, 3H, CH_3); hrms M^+ 272.1176, 274.1150 (calcd. for $C_{14}H_{21}ClO_3$: 272.1179, 274.1150).

3-Butenylmagnesium bromide and 4-pentenylmagnesium bromide

A solution of 4-bromo-1-butene (958 mg, 0.7 mL, 7 mmol) was added to a mixture of magnesium turnings (516 mg, 21 g/atom) in THF (10 mL) at 0°C under an argon atmosphere. After being stirred for 30 min, the mixture was allowed to warm up to room temperature and stirred for another 30 min. Then, the mixture was sonicated. After 1 h, the solution was titrated with menthol-

phenanthroline according to Paquette's procedure[40] to determine the concentration (0.38 mol/L; 55% yield).

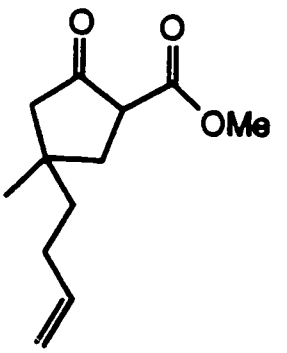
4-Pentenylmagnesium bromide was prepared using the same procedure described above.

3-(3-Butenyl)-3-methylcyclopentanone (44)

A mixture of manganese dichloride tetrahydrate (181 mg, 0.92 mmol) and lithium chloride (52 mg, 1.2 mmol) was dried at 200°C under vacuum (0.5 mm Hg) for 12 h. Copper(I) chloride (9 mg, 0.1 mmol) was added, and the mixture of salts was suspended in dry THF (10 mL) and stirred under argon at room temperature. 3-Methyl-2-cyclopentenone (300 mg, 0.3 mL, 3.13 mmol) was added dropwise, and the mixture was stirred for 3 h under the same conditions. Then the mixture was cooled to 0°C, and the freshly prepared 3-butenylmagnesium bromide solution (11.4 mL, 0.24 M, 2.8 mmol) was added dropwise during a period of 20 min. The mixture turned red at the first contact with the Grignard reagent and then changed to a green-black suspension. After 3 h, 1 N hydrochloric acid (15 mL) was added. The organic layer was taken up with diethyl ether and separated. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed sequentially with hydrochloric acid and a 1:1 mixture of saturated ammonium chloride

solution and 2 N ammonium hydroxide (2 x 15 mL) and then dried over sodium sulfate. After filtration, the solvents were removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/ hexane (25:75) as an eluent to give ketone **44** (470 mg, 99%): ir ($CDCl_3$ cast) 1742 (C=O, ketone) and 1640 (C=C) cm^{-1}; ^1H nmr (400 MHz) δ 5.80 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.01 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.93 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 2.28 (m, 2H, CH_2C=O), 2.08 (d, J=18 Hz, 1H, CCH**H**C=O), 2.06 (m, 2H, CH_2CH=CH_2), 2.01 (d, J=18 Hz, 1H, CC**H**HC=O), 1.79 (m, 2H, CH_2CH_2C=O), 1.50 (dd, J=9, 8 Hz, 2H, CH_2), 1.10 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 220.7 (p), 138.7 (a), 114.5 (p), 52.2 (p), 40.9 (p), 39.4 (p), 36.9 (p), 35.3 (p), 29.2 (p), 24.9 (a); hrms M^+ 152.1192 (calcd. for $C_{10}H_{16}O$: 152.1201). Anal. calcd. for $C_{10}H_{16}O$: C 78.89, H 10.60; found: C 78.84, H 10.75.

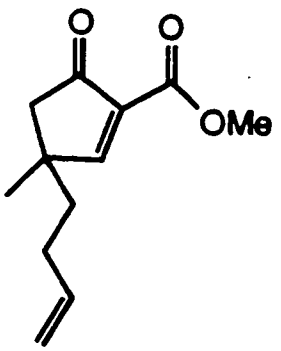
4-(3-Butenyl)-2-carbomethoxy-4-methylcyclopentanone (45)



Compound **45** was prepared according to the general procedure for carbomethoxylation. Treatment of **44** (1.58 g, 10.4 mmol) with dimethyl carbonate (7 mL) and sodium hydride (656.8 mg, 95%, 26 mmol) for 5 h, afforded keto ester **45** (1.66 g, 76%): ir ($CHCl_3$ cast) 1756 (C=O, ketone) and 1729 (C=O, ester) cm^{-1}; ^1H nmr (400 MHz) a mixture of two epimers in a ratio of

1.5:1: δ 5.80 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.05 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.99 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 3.76 (s, 3H,OCH_3), 3.36 (m, 1H, COC**H**COOCH_3), 1.95-2.50 (m, 5H), 1.30-1.65 (m, 3H), 1,10, 1.05 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 211.1 (p), 169.8 (p), 138.4 (a), 138.1 (a), 114.8 (p), 114.7 (p), 53.5 (a), 53.6 (a), 52.5 (a), 41.6 (a), 39.4 (p), 38.7 (p), 37.5 (p), 29.1 (p), 25.9 (a), 24.7 (a); hrms M^+ 210.1254 (calcd. for $C_{12}H_{18}O_3$: 210.1256). Anal. calcd. for $C_{12}H_{18}O_3$: C 68.55; H 8.63; found: C 68.55, H 8.92.

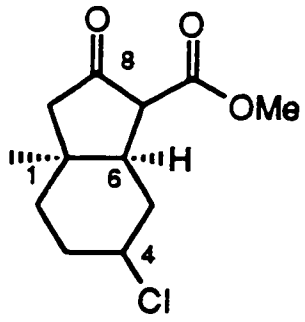
4-(3-Butenyl)-2-carbomethoxy-4-methyl-2-cyclopentenone (46)



Compound **46** was prepared according to the general procedure for DDQ oxidation using THF. Oxidation of keto ester **45** (400 mg, 1.9 mmol) with DDQ (833 mg, 1.9 mmol) in THF for 30 min gave enone ester **46** (284 mg, 72%): ir ($CDCl_3$ cast) 1753 (C=O, ketone) and 1723 (C=O, ester) cm^{-1}; ^1H nmr (400 MHz) δ 8.16 (s, 1H, CHCCOOMe), 5.75 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.00 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.96 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 3.82 (s, 3H, OCH_3), 2,51 (d, J=18.5 Hz, 1H, C**H**HC=O), 2.31 (d, J=18.5 Hz, 1H, CH**H**C=O), 2.01 (m, 2H, CH_2CH=CH_2), 1.64 (m, 2H, CH_2), 1,26 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 202.1 (p), 179.4 (a), 162.3 (p), 137.4 (a), 134.6 (p), 115.4 (p), 52.1 (a), 49.2 (p), 42.3

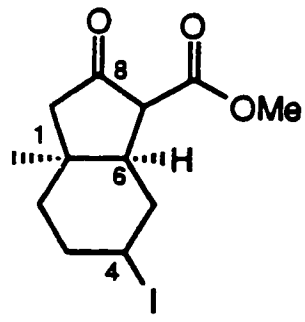
(p), 39.2 (p), 29.2 (p), 25.7 (a); hrms M^+ 208.1098 (calcd. for $C_{12}H_{16}O_3$: 208.1099).

(1S*, 6R*)-7-Carbomethoxy-4-chloro-1-methylbicyclo[4.3.0]nonan-8-one (47)



Compound **47** was prepared according to the general procedure for polyene cyclization using $ZnCl_2$ as reagent. Enone ester **46** (80 mg, 0.38 mmol) was treated with zinc chloride (106 mg, 0.78 mmol) for 4 h to give compound **47** (86 mg, 92%): ir ($CHCl_3$ cast) 1754 (C=O, ketone) and 1727 (C=O, ester) cm^{-1}; ^1H nmr (300 MHz) four isomers: δ 4.40 (m, 0.4H), 4.13 (m, 0.6H), 3.76, 3.75, 3.74, 3.71 (s, 3H, OCH_3), 3.63 (d, J= 7 Hz, 0.5H), 3.25 (d, J=12 Hz, 0.5H), 1.30-2.70 (m, 9H), 1.25, 1.20, 1.10, 1.05 (s, 3H, CH_3); hrms M^+ 244.0866, 246.0830 (calcd. for $C_{12}H_{16}ClO_3$: 244.0866, 246.0837).

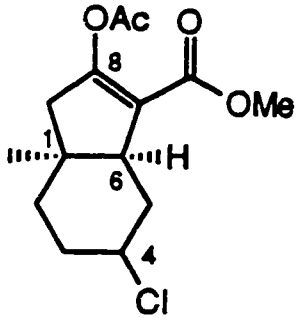
(1S*, 6R*)-7-Carbomethoxy-4-iodo-1-methylbicyclo[4.3.0]nonan-8-one (48)



Compound **48** was prepared according to the general procedure for polyene cyclization using ZnI_2 as reagent. Enone ester **46** (52 mg, 0.25 mmol) was treated with zinc iodide (166 mg, 0.52 mmol) for 24 h to give compound **48** (61 mg, 72%): ir ($CHCl_3$ cast) 1754 (C=O, ketone) and 1727 (C=O, ester) cm^{-1}; ^1H nmr (300 MHz) four isomers: δ 4.41 (m, 0.25H), 3.95-4.22 (m, 0.75H), 3.90 (d, J=7 Hz, 0.33H), 3.73, 3.71, 3.69 (s, 3H, OCH_3), 3.59 (d, J=7 Hz, 0.33H), 3.30 (d, J=11 Hz, 0.33H), 2.50-2.75 (m, 1H), 2.15-2.50 (m, 3H), 1.80-2.15 (m, 3H), 1.30-1.80 (m, 2H), 1.10, 1.05, 0.98 (s, 3H, CH_3); hrms M^+ 336.0225 (calcd. for $C_{12}H_{17}IO_3$: 336.0222).

$AlCl_3$, $SnCl_4$ and AlI_3 were also used as reagents for cyclization of compound **46**. These results can be found in Table 6.

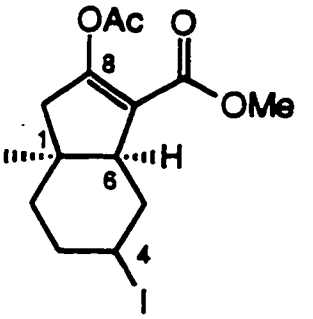
(1S*, 6S*)-8-Acetoxy-7-carbomethoxy-4-chloro-1-methylbicyclo-[4.3.0]non-7-ene (49)



The general procedure for acetylation was used for the preparation of compound **49**. Acetylation of **47** (44 mg, 0.18 mmol) with acetic anhydride and pyridine afforded acetate **49** (46 mg, 89%): ir (CH_2Cl_2 cast) 1771 (CH_3COO) and 1714 ($COOCH_3$) cm^{-1}; ^1H nmr (500 MHz) two isomers in 4.5:1 ratio; major: δ 3 .83 (m, 1H, **CH**Cl), 3.71 (s, 3H, OCH_3), 2.82 (d, J=17 Hz, 1H, **CH**HCO), 2.56 (m, 1H, **H5e**), 2.53 (ddd, J=11.5, 5.5, 1 Hz, 1H, ring junction proton), 2.22 (s, 3H, CH_3CO), 2.09 (m, 1H, **H3e**), 2.04 (d, J=17 Hz, 1H, CH**H**CO), 1.82 (ddd, J=14, 4,

4 Hz, **H2e**), 1.72 (m, 1H, **H5a**), 1.54 (m, 1H, **H3a**), 1.40 (ddd, J=14, 12, 4 Hz, **H2a**), 1.11 (s, 3H, CH_3); minor: δ 4.60 (m 1H, CHCl), 3.72 (s, 3H, OCH_3), 2.82 (d, J=17 Hz, 1H, CHHCO), 2.56 (m, 1H, **H5e**), 2.29 (ddd, J=12, 2, 1 Hz, ring junction proton), 2.20 (s, 3H, CH_3CO), 2.09 (m, 1H, **H3e**), 2.04 (d, J=17 Hz, 1H, CHHCO), 1.82 (ddd, J=14, 4, 4 Hz, 1H, **H2e**), 1.72 (m, 1H, **H5a**), 1.54 (m, 1H, **H3a**), 1.40 (ddd, J=14, 12, 4 Hz, **H2a**), 1.18 (s, 3H, CH_3); ^{13}C nmr (75 MHz) major: δ 167.6 (p), 163.7 (p), 159.2 (p), 122.3 (p), 57.1 (a), 51.4 (a), 48.6 (a), 44.6 (p), 42.7 (p), 39.7 (p), 34.1 (p), 33.7 (a), 29.3 (a), 20.9 (a); hrms M^+-42 244.0867, 246.0835 (calcd. for $C_{12}H_{17}O_3Cl$: 244.0866, 246.0837). Anal. calcd. for $C_{14}H_{19}ClO_3$: C 58.64, H 6.68; found: C 58.73, H 6.69.

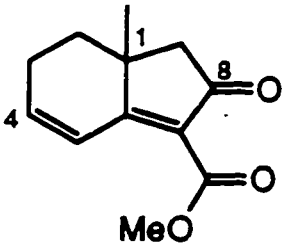
(1S*, 6S*)-8-Acetoxy-7-carbomethoxy-4-iodo-1-methylbicyclo-[4.3.0]-non-7-ene (50)



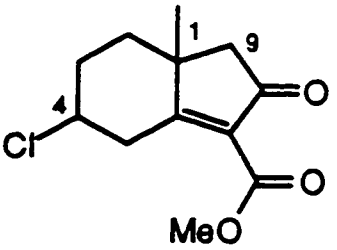
The general procedure for acetylation was used for the preparation of compound **50**. Acetylation of **48** (44 mg, 0.13 mmol) with acetic anhydride and pyridine afforded acetate **50** (45 mg, 91%): ir (CH_2Cl_2 cast) 1771 (CH_3COO) and 1714 ($COOCH_3$) cm^{-1}; ^1H nmr (500 MHz) two isomers; major: δ 4.00 (dddd, J=12, 6.5, 3.5, 3.5 Hz, 1H, CHI), 3.70 (s, 3H, OCH_3), 2.87 (d, J=17 Hz, 1H, CHHCO), 2.82 (m, 1H, **H5e**), 2.50 (ddd, J=10, 5, 1 Hz, 1H, ring junction proton), 2.30 (m, 1H, **H3e**), 2.22 (s, 3H, CH_3CO), 2.03 (m, 1H, **H2e**), 2.00 (d,

J=17 Hz, 1H, CH**H**CO), 1.82 (m, 1H, **H5a**), 1.62 (m, 1H, **H3a**), 1.41 (m, 1H, **H2a**), 1.07 (s, 3H, CH_3); minor: δ 4.45 (m 1H, C**H**I), 3.72 (s, 3H, OCH_3), 2.87 (d, J=17 Hz, 1H, C**H**HCO), 2.82 (m, 1H, **H5e**), 2.52 (dd, J=13, 6 Hz, ring junction proton), 2.30 (m, 1H, **H3e**), 2.20 (s, 3H, CH_3CO), 2.03 (m, 1H, **H2e**), 2.00 (d, J=17 Hz, 1H, CH**H**CO), 1.82 (m, 1H, **H5a**), 1.62 (m, 1H, **H3a**), 1.41 (m, 1H, **H2a**), 1.19 (s, 3H, CH_3); ^{13}C nmr (75 MHz) major: δ 167.7 (p), 163.8 (p), 159.6 (p), 120.1 (p), 51.4 (a), 50.3 (a), 45.1 (p), 43.3 (p), 42.3 (p), 37.3 (p), 36.5 (p), 30.1 (a), 25.7 (a), 25.7 (a); hrms M^+ 378.0344 (calcd. for $C_{14}H_{19}IO_4$: 378.0328). Anal. calcd. for $C_{14}H_{19}IO_4$: C 44.47, H 5.06; found: C 44.37, H 4.93.

7-Carbomethoxy-1-methylbicyclo[4.3.0]nona-4,6-dien-8-one (51) and 7-carbomethoxy-4-chloro-1-methylbicyclo[4.3.0]non-6-en-8-one (52)



51

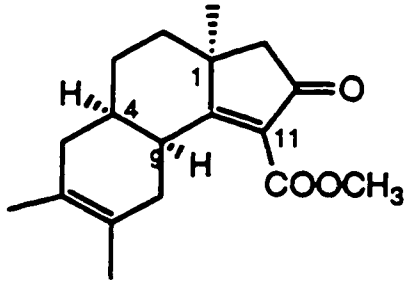


52

To a solution of keto ester **47** (100 mg, 0.41 mmol) in THF at room temperature under argon, was added DDQ (186 mg, 0.41 mmol). The mixture was stirred for 1 h and then refluxed for 5 h. The reaction mixture was cooled and evaporated to dryness. The precipitate was removed by filtration after chloroform (15 mL) was added to the residue. The filtrate was concentrated and the residue was subjected to flash chromatography using ethyl acetate/hexane (25:75) as an eluent to give compounds **51** (61 mg, 72%) and **52** (5 mg, 5%). Compound **51**:

ir (CH_2Cl_2 cast) 1740 (C=O) and 1708 (C=O) cm^{-1}; ^1H nmr (CD_3OD, 200 MHz) δ 7.21 (ddd, J=10, 2, 2 Hz, 1H, $CH_2CH=CH$), 6.66 (ddd, J=10, 4, 4 Hz, 1H, $CH_2CH=CH$), 3.75 (s, 3H, OCH_3), 2.45 (m, 2H, $CH_2CH=CH_2$), 2.42 (d, J=17 Hz, 1H, CHHCO), 2.32 (d, J=17 Hz, 1H, CHHCO), 1.98 (m, 1H, $CHHCH_2CH=CH_2$), 1.80 (m, 1H, $CHHCH_2CH=CH_2$), 1.10 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 201.7 (p), 181.7 (p), 163.6 (p), 144.2 (a), 123.9 (p), 122.9 (a), 51.9 (p), 51.8 (a), 38.8 (p), 33.7 (p), 25.4 (a), 24.6 (p); hrms M^+ 206.0947 (calcd. for $C_{12}H_{14}O_3$: 206.0943). Compound **52**: ir (CH_2Cl_2 cast) 1746 (C=O) and 1721 (C=O) cm^{-1}; ^1H nmr (200 MHz) a mixture of two isomers: δ 3.80-3.95 (m, 4H, CHCl and OCH_3), 2.70 (m, 1H), 2.00-2.50 (m, 5H), 1.40-1.70 (m, 2H), 1.35, 1.30 (s, 3H, CH_3); hrms M^+ 242.0712, 244.0752 (calcd. for $C_{12}H_{15}ClO_3$: 242.0710, 244.0753).

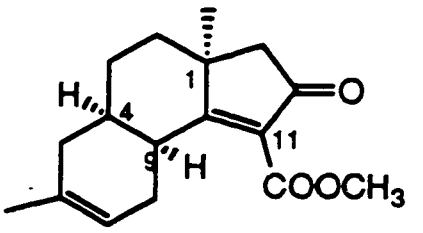
(1S*, 4R*, 9S*)-11-Carbomethoxy-1,6,7-trimethyltricyclo[8.3.0.0.^{4,9}] trideca-6,10-dien-12-one (53)



To a solution of **51** (75 mg, 0.36 mmol) and 2,3-dimethylbutadiene (212 mg, 3.6 mmol) in ether (15 mL) at room temperature under an atmosphere of argon, was added $SnCl_4$ (0.1 mL, 0.86 mmol). After stirring for 3 h, a saturated aqueous sodium bicarbonate solution (15 mL) was added. The mixture was extracted with diethyl ether (3 x 30 mL). The extracts were washed with water, dried

($MgSO_4$), filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (20:80) gave compound **53** (30 mg, 62% based on the consumed starting material): mp 110-112°C; ir (CH_2Cl_2 cast) 1734 (C=O) and 1705 (C=O) cm^{-1}; ^1H nmr (300 MHz); δ 3.73 (s, 3H, OCH_3), 3.07 (dd, J=5, 5 Hz, 1H, **H9**), 2.40 (d, J=18 Hz, **H8b**), 2.30 (m, 2H, **H4** and **H8a**), 2.20-2.30 (m, 2H), 1.40-2.10 (m, 6H), 1.55 (br s, 2 x CH_3), 1.35 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 203.1 (p), 183.9 (p), 165.6 (p), 133.6 (p), 125.5 (p), 122.8 (p), 51.9 (a), 51.4 (a), 43.9 (p), 37.2 (p), 36.9 (p), 366.6 (a), 31.7 (p), 30.5 (p), 26.6 (p), 24.1 (a), 18.9 (a), 18.2 (a); hrms M^+ 288.1735 (calcd. for $C_{18}H_{24}O_3$: 288.1726).

(1S*, 4R*, 9S*)-11-Carbomethoxy-1,6-dimethyltricyclo[8.3.0.0.^{4,9}]-trideca-6,10-dien-12-one (54)



To a solution of **51** (70 mg, 0.34 mmol) and isoprene (149.6 mg, 3.4 mmol) in ether (15 mL) at room temperature under an atmosphere of argon, was added $SnCl_4$ (0.1 mL, 0.85 mmol). After stirring for 3 h, a saturated aqueous sodium bicarbonate solution (15 mL) was added. The mixture was extracted with diethyl ether (3 x 30 mL), and the extracts were washed with water, dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (20:80) gave compound **54** (28 mg, 58% based on the consumed starting material): ir (CH_2Cl_2 cast) 1734 (C=O) and 1705 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ 5.19 (m, 1H, C=C**H**), 3.75 (s, 3H, OCH_3), 3.07 (dd, J=5, 5 Hz, 1H, **H9**), 2.58 (dd, J=17,.5 Hz, 1H, **H8b**), 2.30 (m, 2H, **H4** and **H8a**), 2.20-

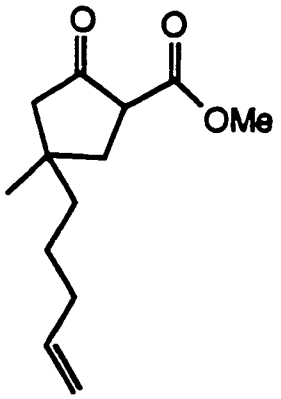
2.30 (m, 4H), 1.58 (s, 3H, CH_3), 1.50-1.75 (m, 4H), 1.35 (s, 3H, CH_3); hrms M+ 274.1566 (calcd. for $C_{17}H_{22}O_3$: 274.1569).

3-Methyl-3-(4-pentenyl)cyclopentanone (55)

A mixture of manganese dichloride tetrahydrate (118 mg, 0.92 mmol) and lithium chloride (52 mg, 1.2 mmol) was dried at 200°C under vacuum (0.5 mm Hg) for 12 h. Copper(I) chloride (9 mg, 0.1 mmol) was added, and the mixture of salts was suspended in dry THF (10 mL) and stirred under argon at room temperature. 3-Methyl-2-cyclopentenone (300 mg, 3.13 mmol) was added dropwise, and the mixture was stirred for 2 h under the same conditions. Then the mixture was cooled to 0°C, and the freshly prepared 4-pentenylmagnesium bromide solution (4.5 mL, 0.71 mmol/mL, 3.2 mmol) was added dropwise during a period of 20 min. The mixture turned red at the first contact with the Grignard reagent and then changed to a green-black suspension. After 2 h, 1 N hydrochloric acid (15 mL) was added. The organic layer was taken up with diethyl ether and separated. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed sequentially with hydrochloric acid and a 1:1 mixture of saturated ammonium chloride solution and 2 N ammonium hydroxide (2 x 15 mL) and then dried over sodium

sulfate. After filtration, the solvents were removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (25:75) as an eluent to give ketone **55** (451 mg, 87%): ir (CH_2Cl_2 cast) 1731 (C=O, ketone) cm^{-1}; ^1H nmr (300 MHz) δ 5.74 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 4.95 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.90 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 2.20 (m, 2H), 1.90-2.10 (m, 4H), 1.65-1.85 (m, 2H), 1.35-1.45 (m, 4H), 1.00 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 219.5 (p), 138.5 (a), 114.6 (p), 52.2 (p), 41.2 (p), 39.4 (p), 36.7 (p), 35.2 (p), 34.2 (p), 24.9 (a), 24.0 (p); hrms M^+ 166.1354 (calcd. for $C_{11}H_{18}O$: 166.1358). Anal. calcd. for $C_{11}H_{18}O$: C 79.46, H 10.91; found: C 79.50, H 10.83.

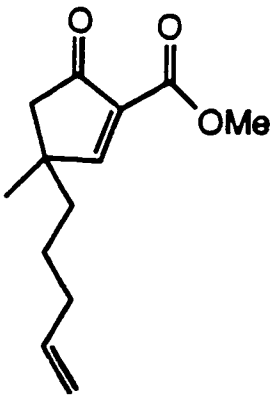
2-Carbomethoxy-4-methyl-4-(4-pentenyl)cyclopentanone (56)



The general procedure for carbomethoxylation was used for the preparation of compound **56**. Carbomethoxylation of **55** (258 mg, 1.6 mmol) with dimethyl carbonate (10 mL) and sodium hydride (98 mg, 3.9 mmol) gave keto ester **56** (278 mg, 80%): ir (CH_2Cl_2 cast) 1756 (C=O, ketone) and 1731 (C=O, ester) cm^{-1}; ^1H nmr (300 MHz) a mixture of two epimers in a ratio of 1.5:1: δ 5.80 (dddd, , J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.03 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 5.00 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 3.75, 3.74 (s, 3H, OCH_3), 3.30-3.42 (m, 1H, COC**H**COOMe), 2.00-2.30 (m, 6H), 1.20-1.60 (m,

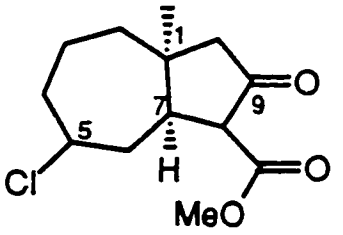
4H), 1.15, 1.10 (s, 3H, CH_3); hrms M^+ 224.1413 (calcd. for $C_{13}H_{20}O_3$: 224.1408).

2-Carbomethoxy-4-methyl-4-(4-pentenyl)-2-cyclopentenone (57)



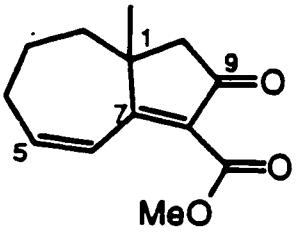
Compound **57** was prepared according to the general procedure for DDQ oxidation using THF as solvent. Oxidation of **56** (136 mg, 0.61 mmol) with DDQ (167 mg, 0.74 mmol) in refluxing THF for 1h afforded enone ester **57** (105 mg, 78%): ir (CH_2Cl_2 cast) 1754 (C=O, ketone) and 1723 (C=O, ester) cm^{-1}; ^1H nmr (300 MHz) δ 8.12 (s, 1H, CH=CCOOMe), 5.74 (dddd, , J=17, 10, 6.5, 6.5 Hz, 1H, $CH=CH_2$), 4.95 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CHH), 4.90 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CHH), 3.85 (s, 3H, OCH_3), 2.49 (d, J=19 Hz, 1H, CHHCO), 2.30 (d, J=19 Hz, 1H, CHHCO), 2.05 (m, 2H, $CH_2CH=CH_2$), 1.20-1.60 (m, 4H), 1.00 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 202.3 (p), 179.8 (a), 162.4 (p), 137.8 (a), 134.5 (p), 115.3 (a), 52.1 (a), 49.3 (p), 42.4 (p), 39.5 (p), 33.9 (p), 25.7 (a), 24.2 (p); hrms M^+ 222.1254 (calcd. for $C_{13}H_{18}O_3$: 222.1256).

(1S*, 7R*)-8-Carbomethoxy-5-chloro-1-methylbicyclo[5.3.0]decan-9-one (58)



$SnCl_4$ (0.1 mL, 0.3 mmol) was added to a solution of enone **57** (43 mg, 0.2 mmol) in ether (5 mL) at room temperature. The reaction mixture was stirred for 2 h and then water (1 x 10 mL) was added. The resulting mixture was extracted with ether (3 x 15 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (5:95) as an eluent gave compound **58** (35 mg, 71%): ir (CH_2Cl_2 cast) 3410 (OH, enol), 1760 (C=O, ketone), 1730 (C=O, ester), 1660 (C=O, enol ester) and 1620 (C=C, enol) cm^{-1}; ^1H nmr (300 MHz) two enol isomers in a ratio of 1:1: δ 10.52, 10.45 (s, 1H, OH), 4.45, 3.85 (m, 1H, CHCl), 3.35, 3.34 (s, 3H, OCH_3), 3.00 (ddd, J=10, 1.5, 1.5 Hz, 0.5H, ring conjuction proton), 2.36 (ddd, J=11, 1.5, 1.5 Hz, 0.5H, ring conjuction proton), 2.50 (d, J=17 Hz, 0.5 H, CHHCO), 2.00-2.30 (m, 3.5H), 1.40-2.00 (m, 5H), 1.10-1.35 (m, 2H), 1.10, 1.09 (s, 3H, CH_3); hrms M^+ 258.1010, 260.0986 (calcd. for $C_{13}H_{19}ClO_3$: 258.1023, 260.0993)

8-Carbomethoxy-1-methylbicyclo[5.3.0]deca-5,7-dien-9-one (59)



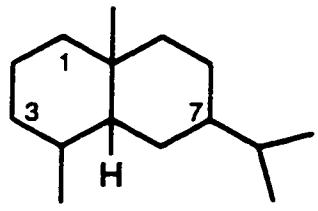
DDQ (70 mg, 0.18 mmol) was added to a solution of **58** (30 mg, 0.12 mmol) in THF (10 mL) at room temperature under an argon atmosphere. After the reaction mixture was stirred for 30 min, THF was removed under reduced pressure. The residue was subjected to flash chromatography using ethyl acetate/hexane (25:75) as an eluent to afford **59** (21 mg, 78%): ir (CH_2Cl_2) 1742 (C=O), 1712 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ 6.89 (ddd, J=12, 1, 1 Hz, 1H, CCH=CH), 6.32 (ddd, J=12, 6.5, 4.5 Hz, 1H, CH=CHCH$_2$), 3.85 (s, 3H, OCH$_3$), 2.30-2.60 (m, 4H), 1.85-2.00 (m, 3H), 1.75 (m, 1H), 1.30 (s, 3H, CH$_3$); ^{13}C nmr (75 MHz) δ 208.0 (p), 185.1 (p), 157.3 (p), 142.7 (a), 127.0 (p), 124.3 (a), 53.2 (p), 52.0 (a), 45.0 (p), 40.0 (p), 31.7 (p), 28.2 (a), 22.8 (p); hrms M^+ 220.1097 (calcd. for $C_{13}H_{16}O_3$: 220.1099)

Chapter Two

Total Synthesis of (±)-Dehydrochamaecynenol and (±)-Occidentalol

Introduction

Sesquiterpenes of the eudesmane family with carbon skeleton **60** occur widely in nature and have been further divided into the *cis* and *trans* series of compounds based on the nature of the ring fusion.

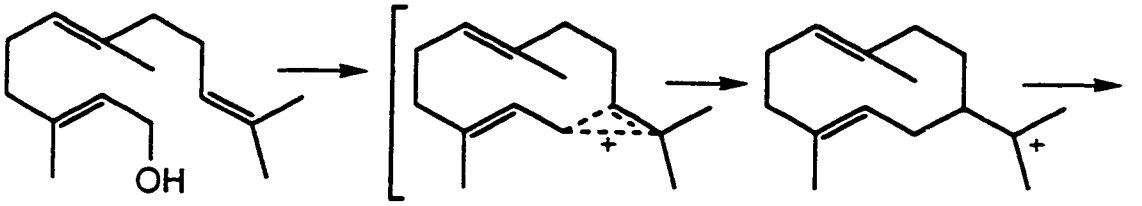


60

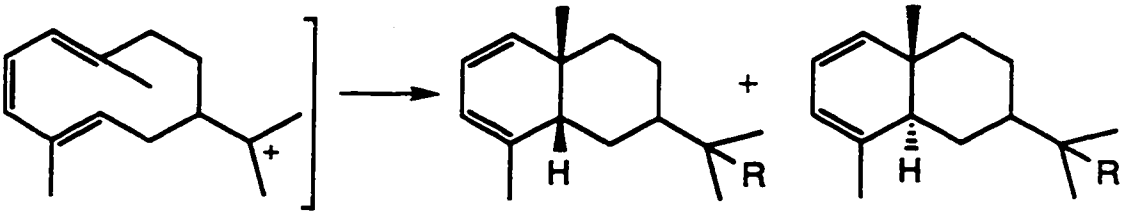
From a biosynthetic point of view, these *cis* and *trans*-fused eudesmane compounds arise from a valence tautomerism of 1,3,5-*trans*, *cis*, *trans*-cyclodecatriene derived from acyclic farnesol (Scheme 30).[42-45] Although this represents a simplification of the overall biogenetic route, it involves many parallel pathways to yield a multitude of eudesmane natural products.

(+)-Occidentalol is a *cis*-fused eudesmane sesquiterpene first isolated from the wood of Eastern white cedar (*Thuja occidentalis L.*) in 1966.[46] Initially, (+)-occidentalol was assigned structure **62**,[47] but it was later confirmed to be incorrect and revised to structure **61** by Hortman, on the basis of the ^{1}H nmr spectrum as well as the ORD curve.[48]

Its intriguing combination of a *cis*-fused decalin system and a homoannular 1,3-diene unit has prompted several total syntheses of (±)- and (+)-occidentalol as well as one total synthesis of (-)-occidentalol.[49-54]

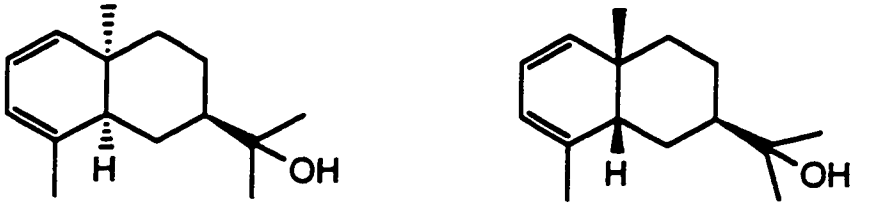


trans-farnesol



cis-fused *trans*-fused

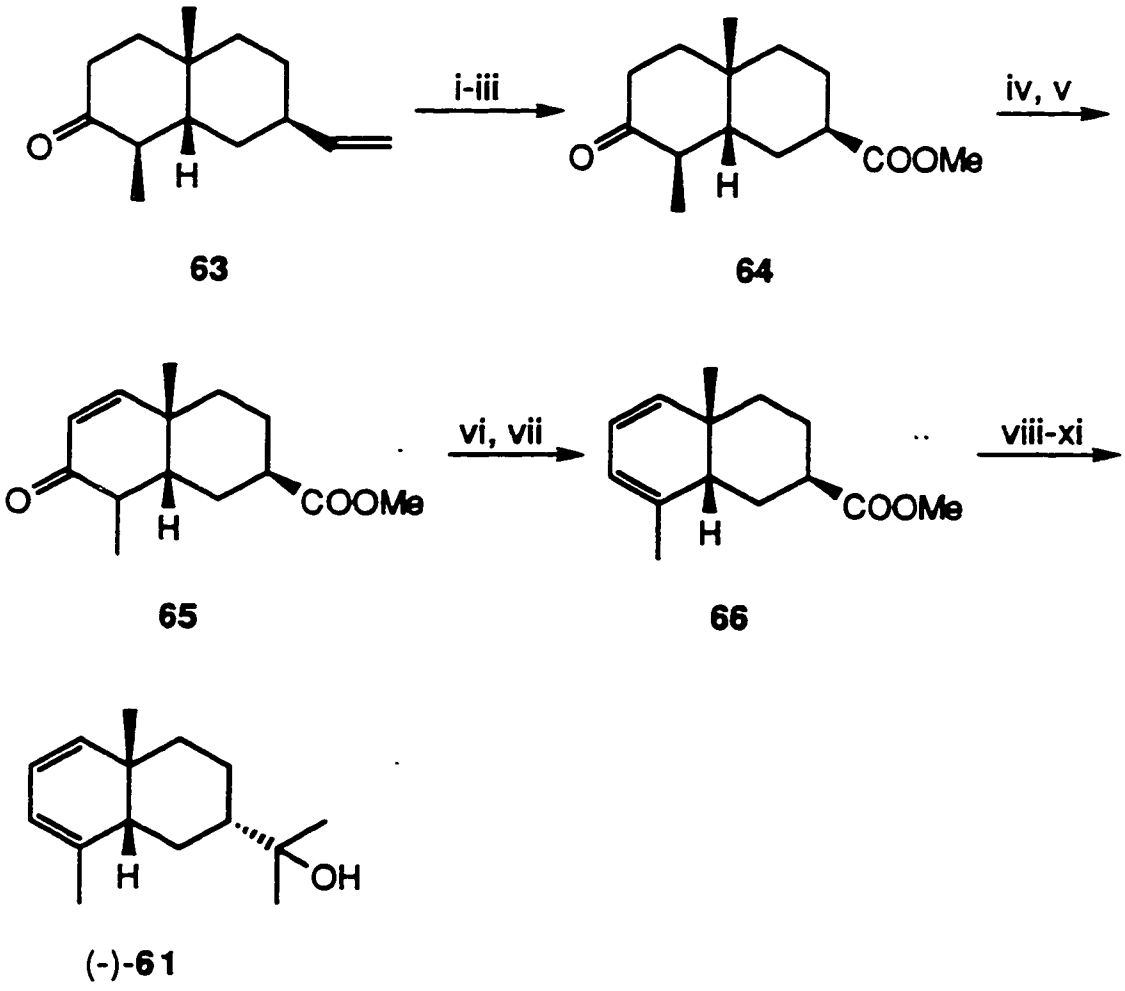
Scheme 30



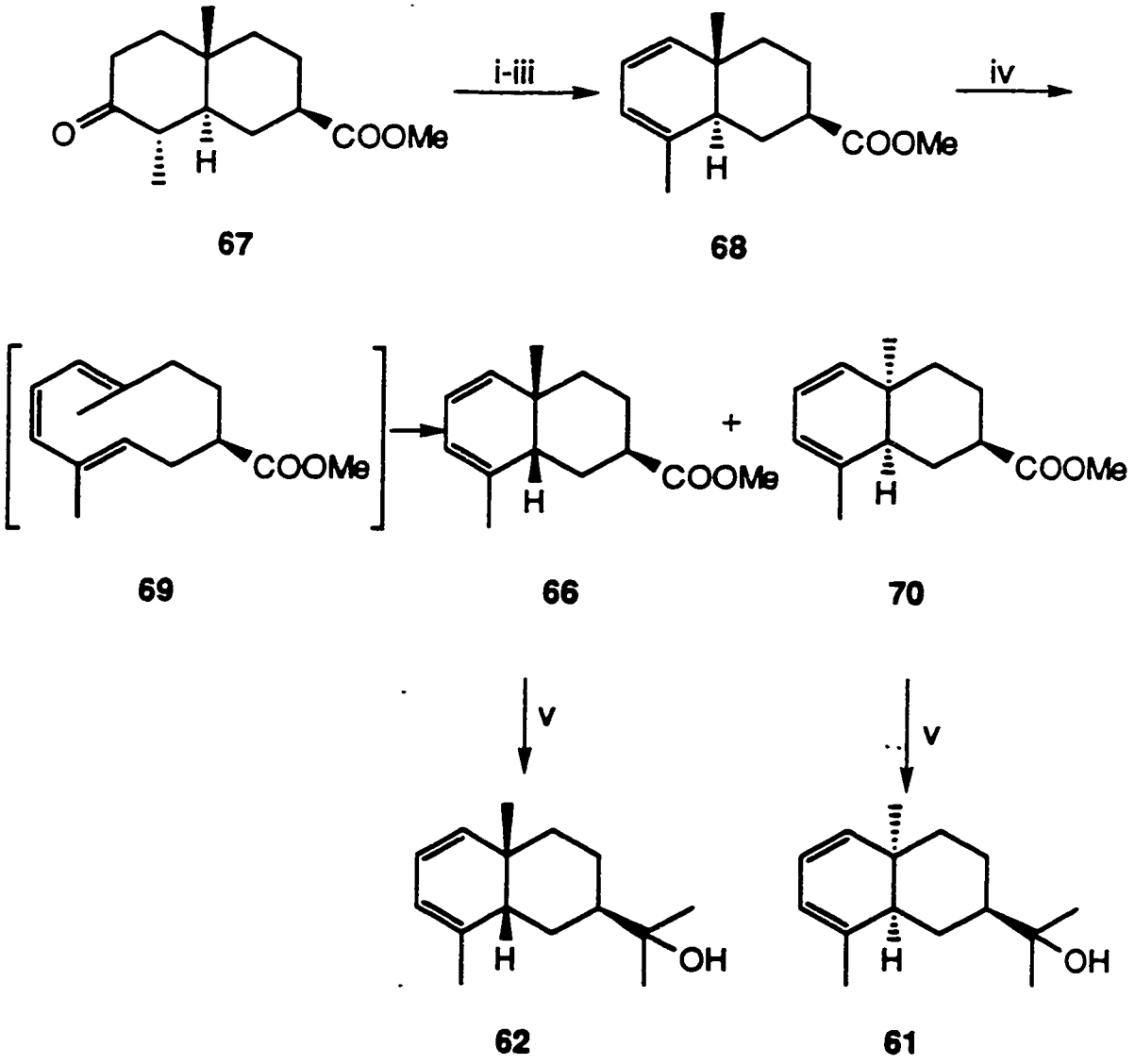
61 **62**

In 1970, Ando *et al.* [49] reported a total synthesis of (-)-occidentalol, the antipode of the naturally occurring (+)-occidentalol (Scheme 31). The key intermediate **63** in this synthesis, obtained from α-santonin, was converted to **64** by sequential oxidation with sodium *meta*-periodate-osmium tetroxide and silver oxide, followed by esterfication with diazomethane. The introduction of the carbon-carbon double bond was accomplished by a bromination-dehydrobromination process. Enone **65** was then subjected to a selective reduction of the ketone carbonyl, followed by dehydration to form the diene

ester **66**. The inversion of the configuration of the ester group was achieved by treatment of **66** with potassium *t*-butoxide. In the final step, the resulting C_7 epimer of **66** was treated with methylmagnesium bromide to produce (-)-occidentalol, which had ir and nmr spectra identical to (+)-occidentalol, but showed the opposite sign in the CD curve.



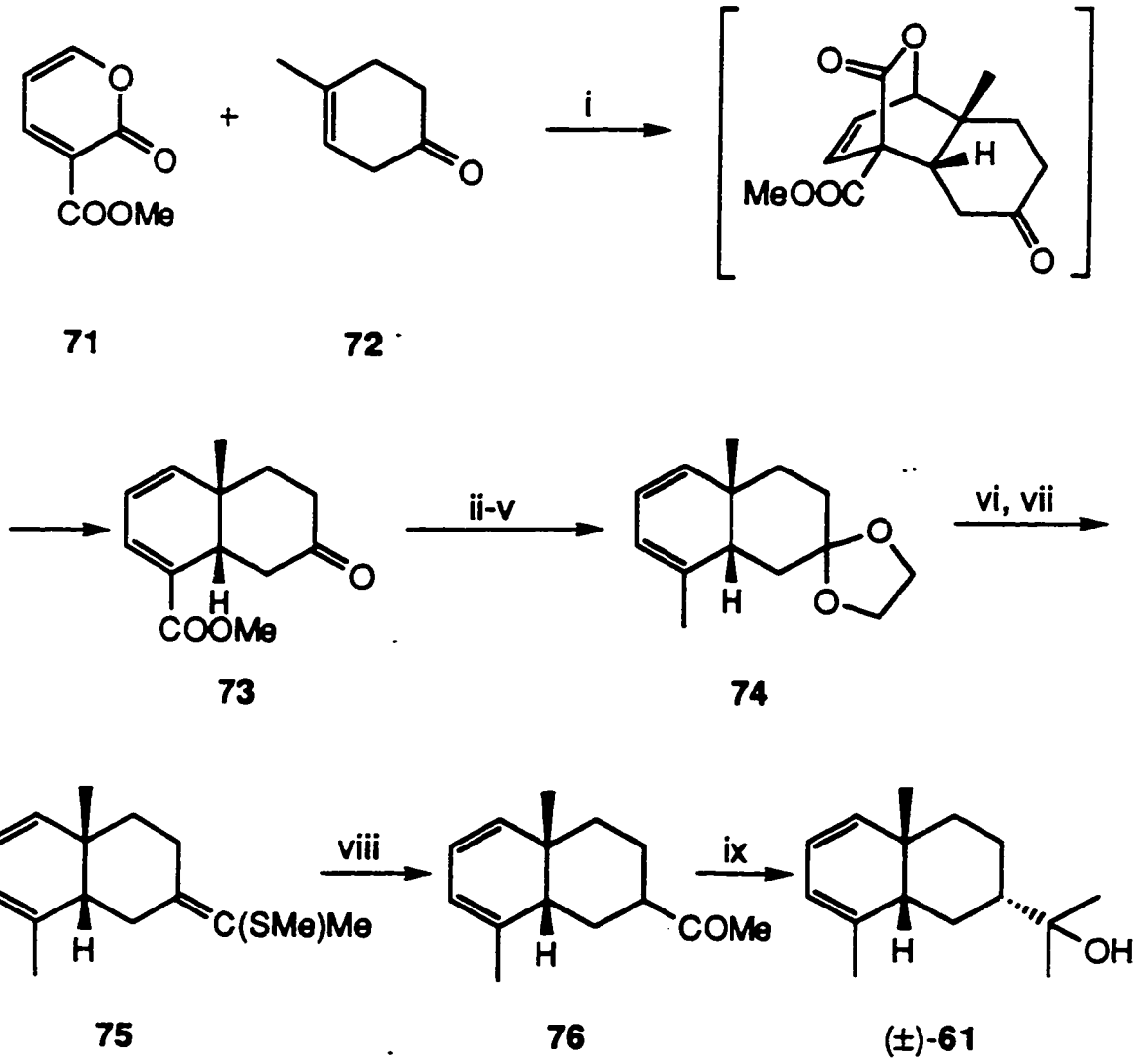
Scheme 31. reagents: i, $NaIO_4$-OsO_4; ii, Ag_2O; iii, CH_2N_2; iv, Br_2, AcOH-HCl; v, LiBr-$LiCO_3$, DMF, 140°C; vi, $NaBH_4$; vii, Alumina-pyridine, 210°C; viii, $KOBu^t$, reflux; ix, OH^-; x, CH_2N_2; xi, MeMgBr.



Scheme 32. reagents: i, Br_2 then $LiBr\text{-}LiClO_4$; ii, $Al(i\text{-}PrO)_3$; iii, Δ, Al_2O_3, Py; iv, hv, -78°C; v, MeLi.

Hortmann and coworkers[50] reported a biogenetically patterned synthesis of (+)-occidentalol using a photolysis-recyclization process as a key step (Scheme 32). Irradiation of **68** at -78°C led to an equilibrium between **68** and the unstable cyclodecatriene **69**, which underwent a thermally induced cyclization at low temperature to yield the *cis*-fused dienes **66** and **70** in a 1:2 ratio.

Eventually, this synthesis was accomplished by treatment of **70** and **66** with methyllithium to afford (+)-occidentalol and the corresponding C_7 epimer **62**, respectively. Compound **68** was prepared in three steps from keto ester **67**, which was readily obtained from (+)-carvone.

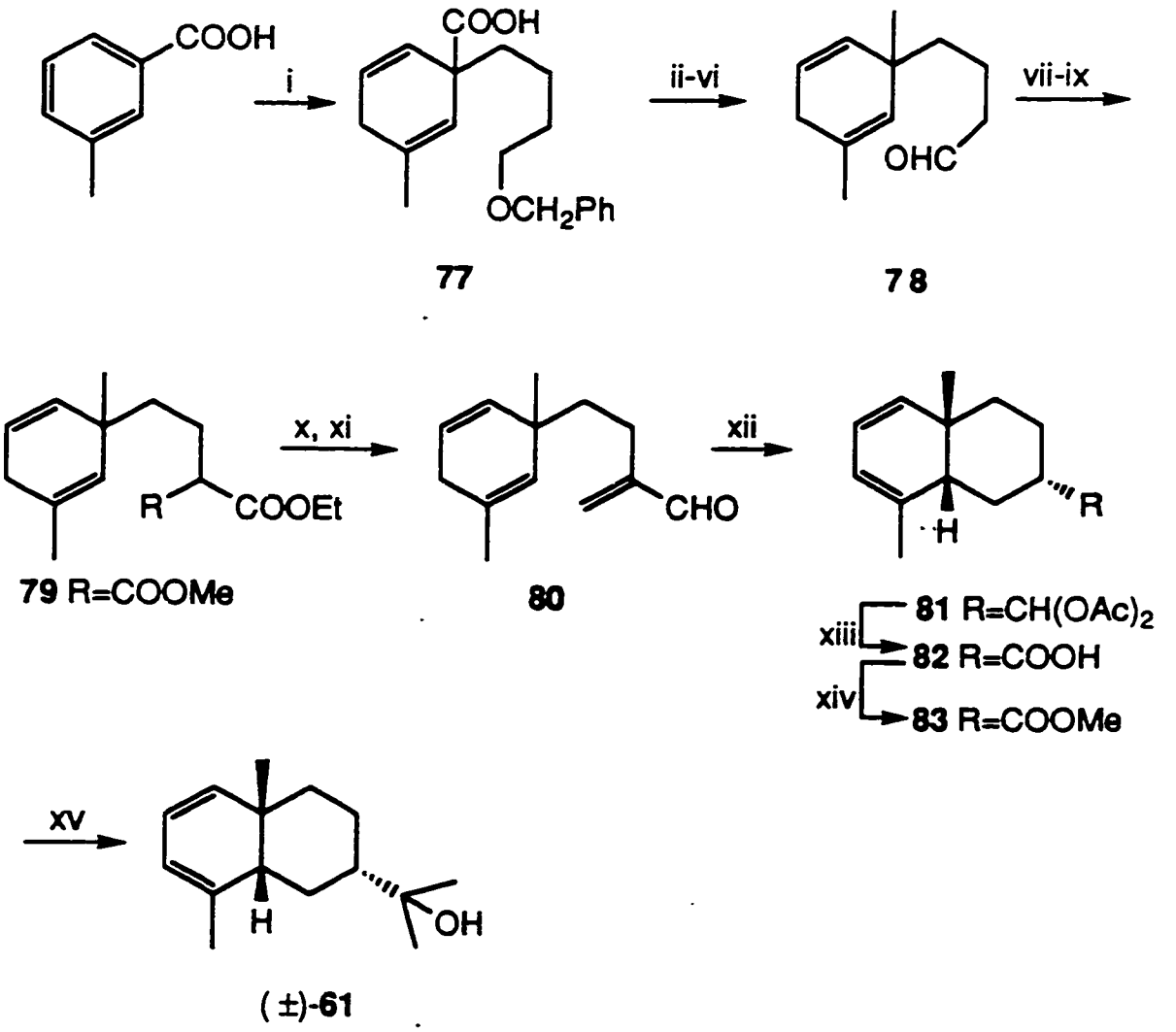


Scheme 33. reagents: i, 150°C; ii, ethylene glycol, *p*-TsOH, benzene, 80°C; iii, $LiAlH_4$, ether; iv, pyridine-SO_3, THF, 0°C; v, $LiAlH_4$, THF; vi, 1 M HCl-HOAc; vii, diethyl 1-(methylthio)ethylphosphonate, *n*-BuLi, HMPA-DME; viii, $HgCl_2$, aqueous CH_3CN; ix, MeLi, ether, -78°C.

Corey and Watt[51] reported a different approach to the total synthesis of (±)-occidentalol (Scheme 33). In their synthesis, a Diels-Alder reaction was used for the construction of the *cis*-fused decalin skeleton. The Diels-Alder reaction of pyrone **71** and cyclohexenone **72** at 150°C provided stereoselectively the keto ester **73** with the required *cis*-fused decalin system and homoannular 1,3-diene unit. Starting from adduct **73**, synthetic operations towards occidentalol, in the racemic form, consisted of the conversion of the carbomethoxy function to a methyl group and the installation of a tertiary alcohol group at C_7. After ketalization of the ketone carbonyl in **73**, reduction of the resulting ketal ester provided the corresponding ketal alcohol. This intermediate was then converted to the corresponding pyridinium sulfate derivative, which readily underwent reduction to furnish the ketal diene **74**. Hydrolysis of **74** gave the keto diene. This diene was elaborated by a Wadsworth-Emmons reaction to the vinyl thioether **75** which was subjected to treatment with aqueous mercuric chloride to afford acetyl diene **76** as a 2.9:1 mixture of two epimers (7α and 7β). These epimeric ketones were separated by preparative thick layer chromatography on silica gel. In the final step, (±)-occidentalol was obtained by treatment of the 7α-acetyl diene **76** with methyllithium.

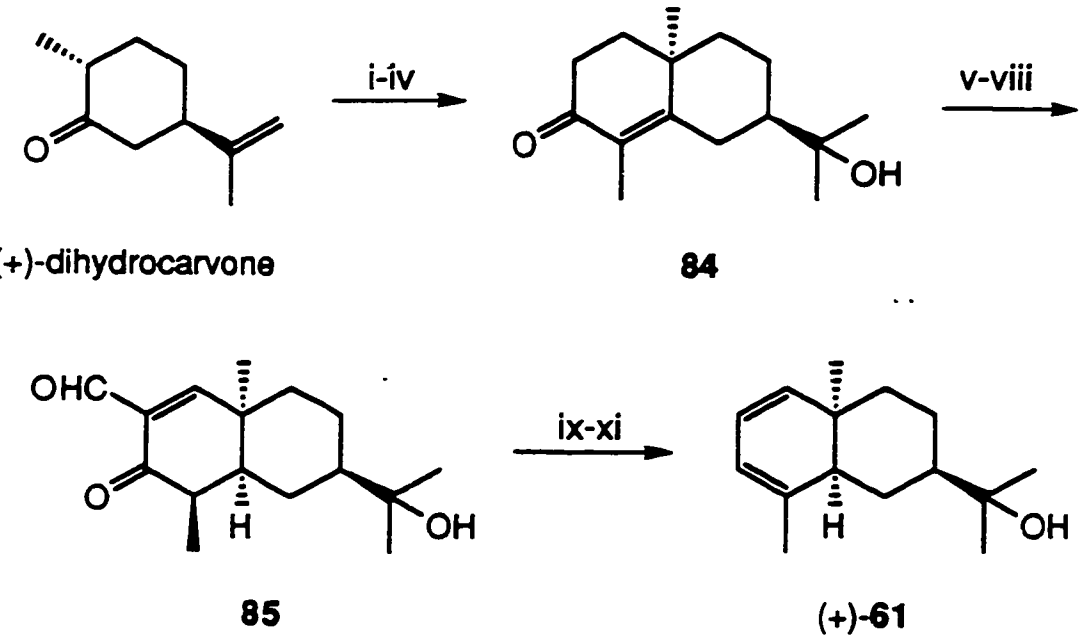
Marshall and Wuts[52] have also developed a total synthesis of (±)-occidentalol using a different approach for generating the *cis*-decalin skeleton. Their approach involved a stereocontrolled cyclization of the unsaturated aldehyde **80** using perchloric acid as a catalyst, affording the required *cis*-fused diene **81** (Scheme 34). The key intermediate **80** was prepared from *m*-toluic acid in eleven steps *via* compounds **77-79**. Further transformation of diene **81** gave

(±)-occidentalol in three steps involving the intermediacy of acid **82** and ester **83**.



Scheme 34. reagents: i, Li, NH_3; $Br(CH_2)_4OCH_2Ph$; HCl; ii, $LiAlH_4$; H_2O; iii, *p*-TsCl, pyridine; iv, $LiB(Et)_3H$, HMPA; v, Li, NH_3, *t*-BuOH; vi, NCS, Me_2S, CH_3Ph; vii, Ag_2O; viii, CH_3OH, H_2SO_4; ix, $LiNR_2$; ClCOOEt; x, NaH; $LiAlH_4$; ethyl formate; xi, MnO_2; xii, Ac_2O, $HClO_4$; xiii, NaOH, Ag_2O; HCl; xiv, CH_2N_2; xv, CH_3Li.

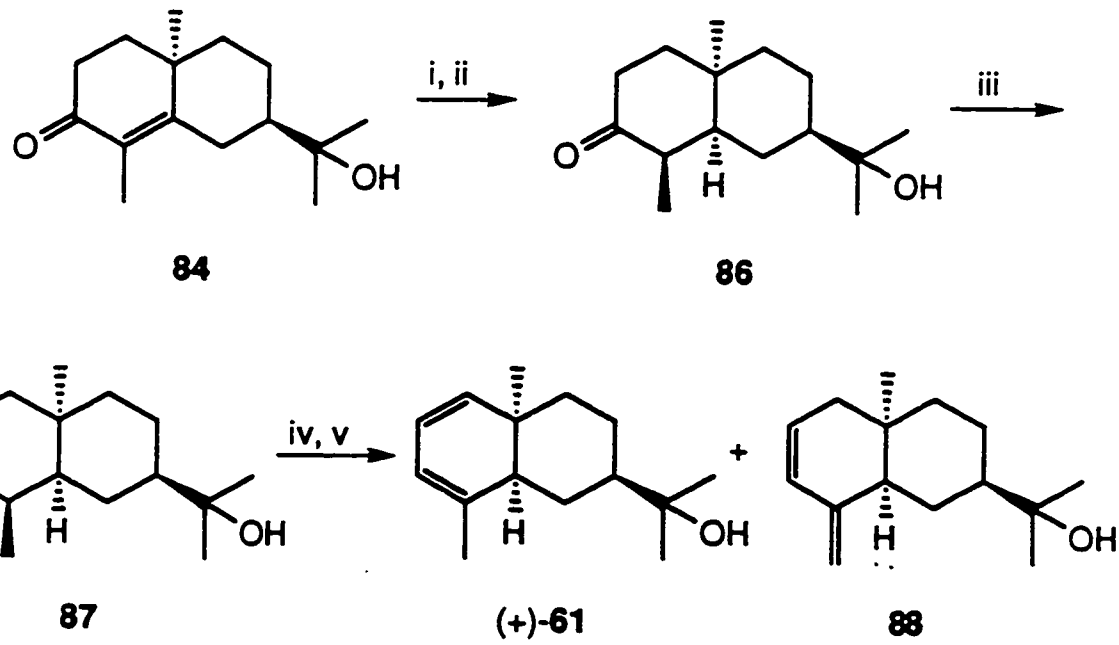
Two other total syntheses of (+)-occidentalol have been reported by Deslongchamps[53] (Scheme 35) and Heathcock[54] (Scheme 36). These syntheses confirmed the absolute stereochemistry of (+)-occidentalol. Both groups commenced the synthesis with (+)-dihydrocarvone and used a Robinson annulation for the preparation of the key intermediate **84**. This compound and (+)-occidentalol have the same carbon skeleton and the same absolute stereochemistry at C_7 and C_{10}.



Scheme 35. reagents: i, $Hg(OAc)_2$, THF; ii, $NaBH_4$, OH^-; iii, $CH_3CH_2COCH{=}CH_2$, OH^-; iv, con. HCl, THF; v, H_2, Pd/C, MeOH; vi, HCOOEt, NaH, benzene; vii, Br_2, OH^- $CHCl_3$; viii, LiCl, DMF, 125°C; ix, $(Ph_3P)_3RhCl$, CH_2Cl_2, reflux; x, $LiAlH_4$, ether, 0°C; xi, *p*-TsOH, benzene.

In Deslongchamps' approach, catalytic hydrogenation of **84** followed by formylation furnished the corresponding hydroxy methylene derivative, which was then converted into the intermediate **85** by a bromination-

dehydrobromination process. Compound **85** was subjected to a series of reactions including deformylation, reduction and dehydration to afford (+)-**61**.



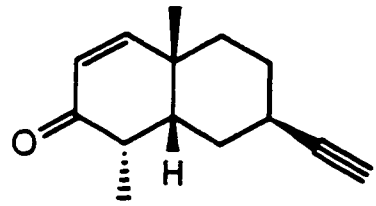
84 **86** **87** (+)-**61** **88**

Scheme 36. reagents: i, H_2, Pd/C, MeOH; ii, OH^-; iii, *p*-toluenesulfonylhydrazide, THF, reflux; MeLi; iv, Br_2/CCl_4, 0°C; v, 2,6-lutidine, 135°C.

In Heathcock's approach, compound **86** obtained from hydrogenation of **84** was subjected to a modified Bamford-Stevens reaction to afford compound **87**. Subsequent bromination and dehydrobromination provided (+)-**61** along with compound **88**.

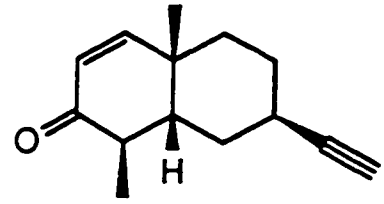
In 1966, chamaecynone **89**, a nor-sesquiterpene with a *cis*-decalin skeleton, along with three other closely related nor-sesquiterpenoids (isochamaecynone **90**, hydroxychamaecynone **91** and dihydroisochamaecynone **92**), was

isolated from the essential oil of the Benihi tree (*Chamaecyparis formosensis* Matsum., Cupressaceae).[55]



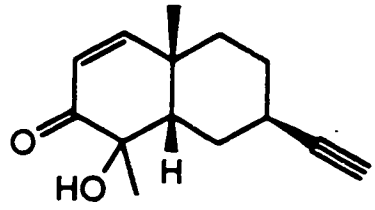
89

chamaecynone



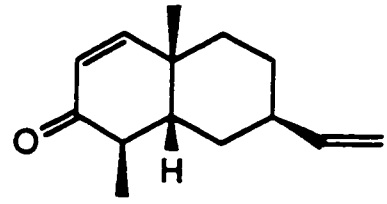
90

Isochamaecynone



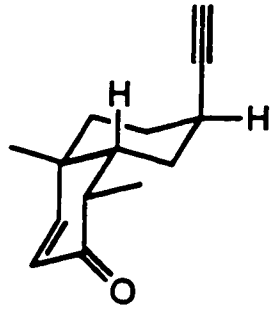
91

hydroxychamaecynone

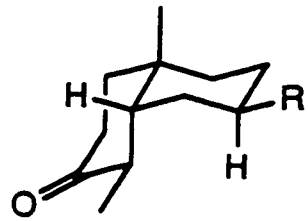


92

dihydroisochamaecynone



89b



90a R=C≡CH

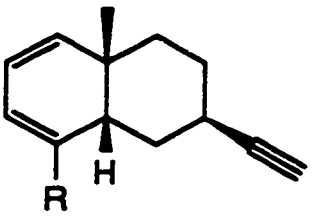
92a R=CH=CH$_2$

Figure 12

Chamaecynone has been shown to have a novel non-steriod *cis*-decalin conformation (**89b** in Figure 12) and to be one of the first examples of a natural acetylenic compound of terpenoid origin. On the other hand, isochamaecynone

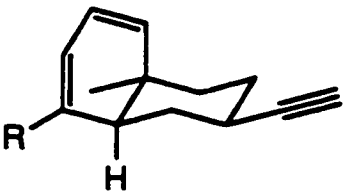
(the C_4 epimer of chamaecynone) and dihydroisochamaecynone exist in a steroidal conformation (**90a** and **92a**, respectively, in Figure 12). Hydroxychamaecynone also has the *cis*-decalin skeleton with the steroid conformation, except for the configuration of the hydroxyl group at C_4.

Two years later, two acetylenic sesquiterpenes, dehydrochamaecynenol **93** and dehydrochamaecynenal **94** were isolated as minor constituents from the same source by the same group.[56] Both compounds have the *cis*-decalin skeleton existing in a non-steriodal conformation (**93b** and **94b** in Figure 13). The structures of these natural compounds were assigned by a combination of spectral evidence and chemical correlation with known compounds as well as ORD measurements.



93 R=CH_2OH

94 R=CHO



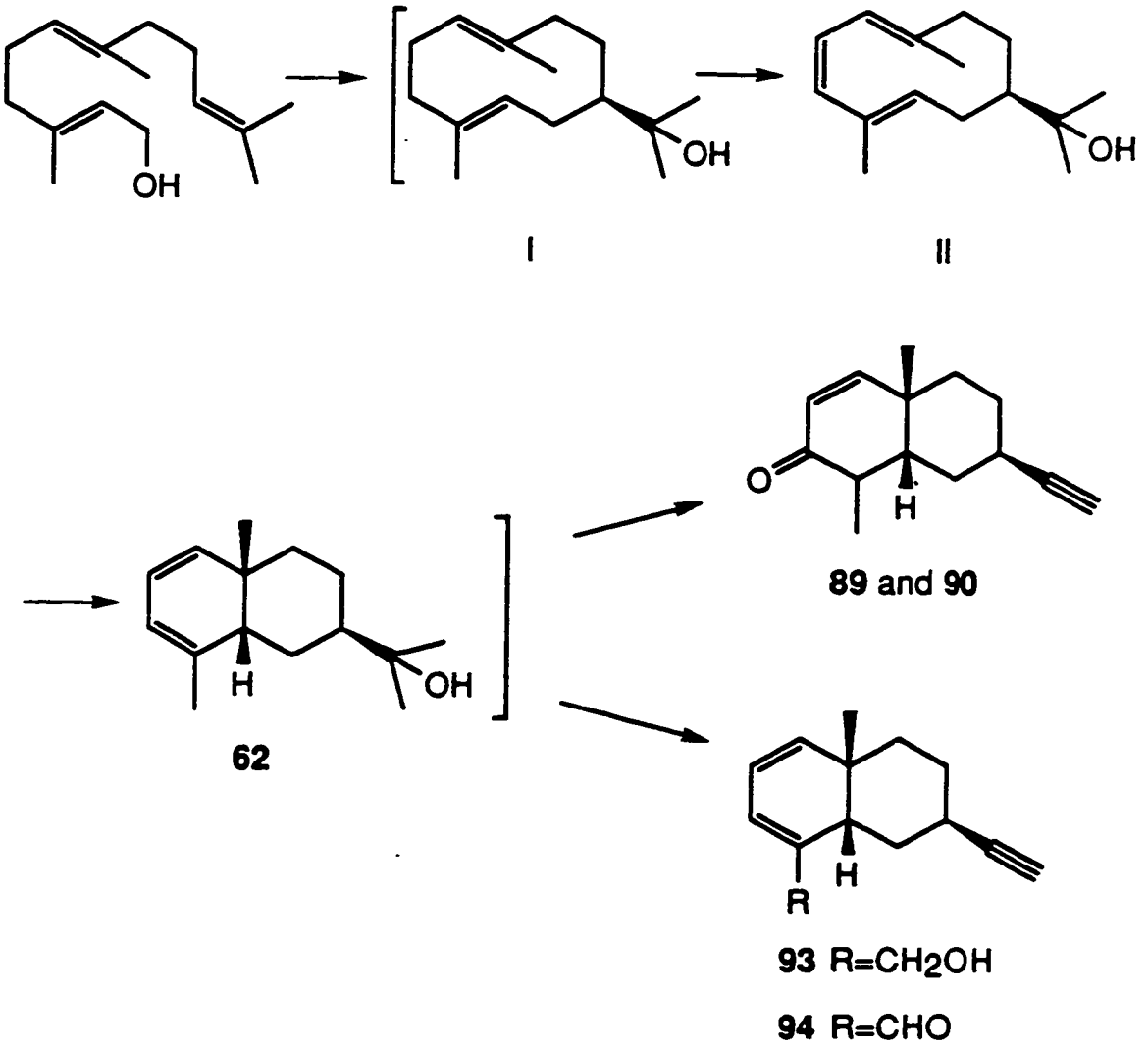
93b R=CH_2OH

94b R=CHO

Figure 13

The biogenesis of these *cis*-fused nor-sesquiterpenes is believed to involve intermediates **I**, **II** and **62** (Scheme 37).[45, 57] Either enzymatic hydroxylation-dehydration or direct dehydrogenation of **I** gives rise to *trans*, *cis*, *trans*-cyclodecatriene **II**, which undergoes enzymatically-controlled or non-enzymatically-controlled valence tautomerism to give the C_7 epimer of occidentalol **62**. Oxidation of **62** at C_3 and C_{15} provides the natural compounds **89**, **90**, **93** and **94**.

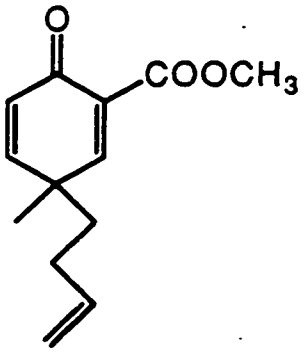
Efficient termiticidal activity without any significant toxicity on humans or domestic animals[58] and the intriguing chemical structure of chamaecynone have prompted two total syntheses of this compound.[59-61] However, its congener **93** has not been synthesized previously.



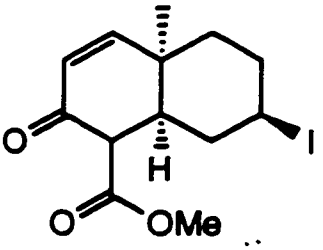
Scheme 37

Our interests in the synthesis of *cis*-fused eudesmane sesquiterpenes and nor-sesquiterpenes stemmed from the results acquired from our newly developed polyene cyclization process as described in Chapter 1 of this thesis. It was discovered that the cross conjugated α-carbomethoxy enone system could

serve as a highly effective promoter for cationic cyclization, which occurred readily with high regio- and stereoselectivity, and also with an unusual termination process involving halogen incorporation when a metal halide was used as the reagent. In essence, this cyclization process allows for expeditious construction of *cis*-fused polycyclic compounds with a high level of functionalization.



10

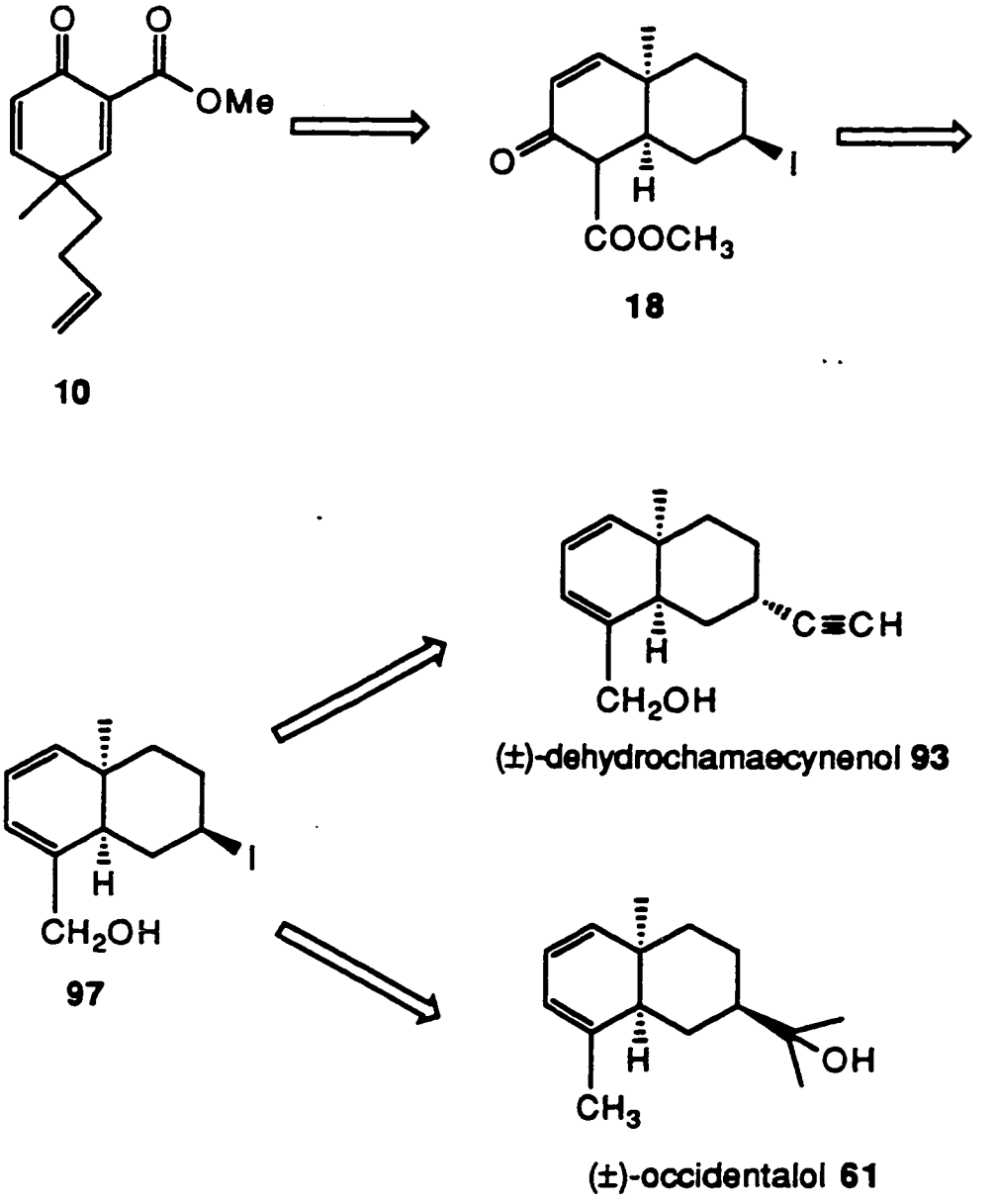


18

When enone ester **10** was treated with zinc iodide in ether at room temperature, iodide **18**, which contains suitable functional groups at strategic positions for rapid construction of the natural products **93** and **61**, in racemic form, was formed in good yield. Application of this facile polyene cyclization process has led to the first total synthesis, in racemic form, of dehydrochamaecynenol and a new synthesis of (±)-occidentalol. Details are discussed in the following sections.

Results and Discussion

As shown by the retrosynthetic analysis outlined in Scheme 38, the cyclization product **18** was envisioned as a good precursor for the synthesis of dehydrochamaecynenol **93** and occidentalol **61** for the following obvious reasons.



Scheme 38

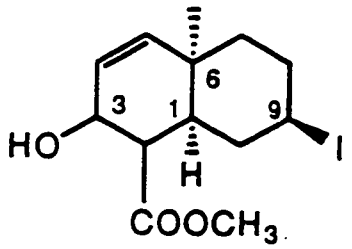
Firstly, this compound possesses the same *cis*-fused decalin system present in the natural products. As well, the established stereochemistry of its ring junction would serve to confirm the relative stereochemistry proposed for **93**. Secondly, the keto ester moiety of **18** could, in principle, be easily transformed into an allyl moiety or an allylic alcohol. Finally, the iodo group presents itself as an appropriate functionality to facilitate the incorporation of the required C_7 side chain in each case with stereocontrol.

1. The total synthesis of (±)-dehydrochamaecynenol (93)

The synthesis began with a modification of the β-keto ester moiety of **18**. Conversion of the β-keto ester into an allylic alcohol was effected in three steps. Treatment of **18** with sodium borohydride in methanol at 0°C for 1 h led cleanly to a chromatographically separable mixture of two isomeric hydroxy esters **95** in a ratio of 1.6:1. The less polar major isomer obtained in 58% yield showed characteristic absorptions at 3515 cm^{-1} for the hydroxyl group and 1737 cm^{-1} for the ester carbonyl. The ^1H nmr spectrum showed two vinylic protons at δ 5.86 (dd, J=10, 5.5 Hz) and 5.55 (ddd, J=10, 1, 1 Hz). The methyl ester singlet appeared at δ 3.80, while the angular methyl singlet appeared at δ 1.00. The spectrum also showed a signal at δ 4.00 (dddd, J=12, 12, 4, 4 Hz) for H_9. The ^{13}C nmr spectrum displayed a signal for the carbonyl carbon at δ 174.4 and two signals for the vinylic carbons at δ 137.4 and 126.8. The mass spectrum did not show a molecular ion peak. Instead, a fragment was observed at m/z 223.1334 ($C_{13}H_{19}O_3$) due to the loss of an iodine atom.

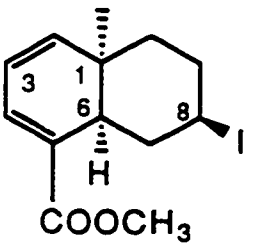
The more polar minor isomer obtained in 37% yield displayed a molecular ion peak at m/z 350.0377 in agreement with the formula $C_{13}H_{19}IO_3$. The ir spectrum

showed absorptions at 3211 cm^{-1} for the hydroxyl group and 1731 cm^{-1} for the ester carbonyl. The ^1H nmr spectrum displayed two vinylic protons at δ 5.70 (dd, J=10, 3 Hz) and 5.45 (ddd, J=10, 2, 2 Hz). A signal at δ 4.02 (dddd, J=12, 12, 3.5, 3.5 Hz) was attributed to H_9. The methoxy and methyl singlets were found at δ 3.75 and 1.10, respectively.



95

A dehydration of the isomeric hydroxy esters was required at this stage. It was found that the desired dehydration could be easily accomplished by treating the mixture of **95** with *p*-toluenesulfonic acid in refluxing benzene. The conjugated ester **96** was obtained in 91% yield. This product showed a molecular ion peak at m/z 332.0271 ($C_{13}H_{17}IO_2$) and an ir absorption at 1707 cm^{-1} for the conjugated ester carbonyl group. The ^1H nmr spectrum displayed the methoxy and methyl singlets at δ 3.80 and 0.85, respectively. The vinylic protons appeared at δ 6.95 (dd, J=5.5, 1 Hz), 6.10 (dd, J=9, 5.5 Hz) and 5.85 (ddd, J=9, 1, 1 Hz). The spectrum also showed signals at δ 4.05 (dddd, J=12, 12, 4, 4 Hz) for H_8 and 2.55 (ddd, J=12, 4, 1 Hz) for the ring junction proton. The ^{13}C nmr spectrum confirmed the presence of a carbonyl group by a signal at δ 167.3 and four vinylic carbons by signals at δ 143.1, 131.3, 130.1 and 123.2.



96

The *cis* ring junction was substantiated by NOE experiments. As shown in Figure 14, irradiation of the C_1 methyl signal at δ 0.85 resulted in a 7.4% enhancement of H_6.

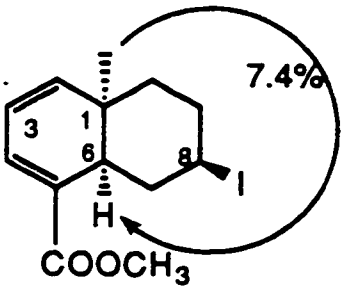
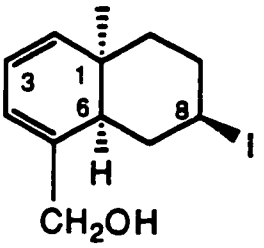


Figure 14. NOE data of compound **96**

Conversion of the ester group into an allylic alcohol was achieved with DIBAL. Treatment of an ethereal solution of ester **96** at -78°C with DIBAL gave the allylic alcohol **97** in 94% yield.

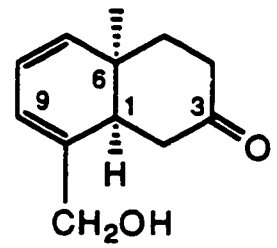


97

The ir spectrum of this product showed the presence of the hydroxy group by an absorption at 3328 cm^{-1}. In the ^1H nmr spectrum, the disappearance of the methoxy singlet indicated that the reduction had taken place. The methylene protons adjacent to the hydroxyl group and the angular methyl group appeared at δ 4.15 and 0.87, respectively, each as a singlet. A molecular ion peak at m/z 304.0326 in the mass spectrum indicated a molecular formula of $C_{12}H_{17}IO$ for the product. The ^{13}C nmr spectrum confirmed the presence of four vinylic carbons by signals at δ 140.2, 135.9, 123.5 and 117.9.

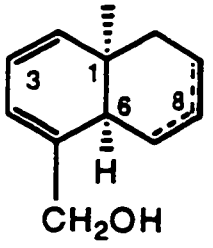
Having converted the β-keto ester group into the required allylic alcohol, the next operation was to install the acetylene unit at C8. Unfortunately, treatment of either allylic alcohol **97** or the corresponding *t*-butyldimethylsilyl ether with lithium (trimethylsilyl)acetylide resulted in only recovery of the starting material. The unexpected difficulties led us to explore an alternative route for effecting the required transformation of the iodo group to an acetylene unit.

Iodo alcohol **97** was directly oxidized to the corresponding ketone **98** (55% yield) using a combination of dimethyl sulfoxide, silver tetrafluoroborate and triethylamine.[62] A 35% yield of the isomeric trienes **99** was also obtained from this reaction. Attempts to suppress the formation of this byproduct by varying the reaction conditions met with little success.



98

The ir spectrum of compound **98** showed absorptions at 3411 cm^{-1} for the hydroxyl group and 1713 cm^{-1} for the ketone carbonyl. In the ^1H nmr spectrum, the vinylic protons resonated at δ 6.06 (dd, J=9.5, 5.5 Hz), 5.91 (dddd, J=5.5, 1, 1, 1 Hz) and 5.68 (dd, J=9.5, 1 Hz). The protons adjacent to the hydroxy group and the angular methyl group were observed at δ 4.12 and 1.05, respectively, each as a singlet. The ^{13}C nmr spectrum confirmed the presence of a carbonyl carbon by a signal at δ 210.0 and four vinylic carbons by signals at δ 140.7, 134.7, 124.3 and 117.7. The mass spectrum showed a molecular ion peak at m/z 192.1145, corresponding to the expected molecular formula $C_{12}H_{16}O_2$.

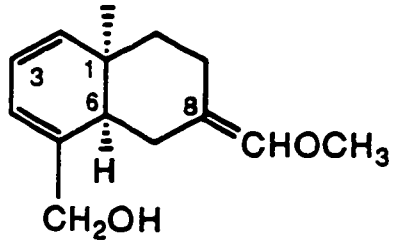


99

The ir spectrum of compound **99** displayed a hydroxyl absorption at 3341 cm^{-1}. A molecular ion peak at m/z 176.1204, in agreement with the molecular formula $C_{12}H_{16}O$, was observed in the mass spectrum. In the ^1H nmr spectrum, five vinylic protons were observed between δ 5.36 and 5.86. The protons adjacent to the hydroxy group appeared at δ 4.17 and 4.16 as singlets, while the angular methyl singlets were observed at δ 1.24 and 1.20, indicating that compound **99** was a mixture of two isomeric trienes.

To install the acetylene unit, ketone **98** was subjected to a Wittig reaction with methoxymethylenetriphenylphosphorane (prepared from the reaction of *n*-BuLi and methoxymethyltriphenylphosphonium chloride)[63] at room temperature to

give an 81% yield of enol ether **100** as a mixture of two isomers in a ratio of 3:2. These isomers were not separated since the newly generated stereogenic center would be destroyed in the subsequent step. The presence of the enol ether functionality was indicated by the methoxy signals at δ 3.53 for the major isomer and at δ 3.52 for the minor one. The absence of a ketone carbonyl absorption in the ir spectrum confirmed that the desired transformation had taken place. The mass spectrum showed a molecular ion peak at m/z 220.1461, which was in agreement with the expected formula $C_{14}H_{20}O_2$.

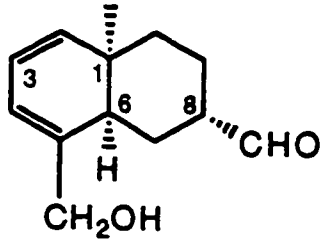


100

Initially, hydrolysis of enol ethers **100** was attempted using perchloric acid in aqueous THF. Under these conditions, the product decomposed before all the starting material had been consumed. Milder reaction conditions were then employed. Treatment of enol ethers **100** with 1 N HCl at room temperature for 4.5 h afforded a mixture of aldehyes in a ratio of 2.2:1. The desired kinetic product **101** was found to be the major isomer. Aldehyde **102** was formed in increasing amount at the expense of **101** when the hydrolysis reaction was prolonged. Aldehyde **101** was found to undergo complete epimerization upon treatment with sodium hydroxide in methanol at room temperature for 24 h, resulting in the exclusive formation of aldehyde **102**.

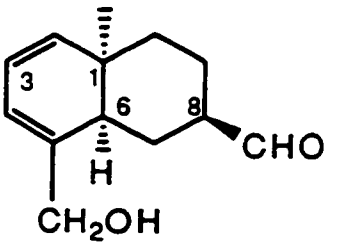
The ir spectrum of aldehyde **101** displayed absorptions at 3397 cm^{-1} for the hydroxyl group and at 2858, 2713 and 1725 cm^{-1} for the aldehyde group. In the

^1H nmr spectrum, the aldehyde proton appeared as a singlet at δ 9.75, indicating that the enol ether had been hydrolyzed. The vinylic protons appeared at δ 5.95 (dd, J=9.5, 5.5 Hz), 5.83 (dddd, J=5.5, 1, 1, 1 Hz) and 5.45 (dd, J=9.5, 1 Hz). The protons adjacent to the hydroxyl group and the angular methyl group were observed at δ 4.17 and 0.85, respectively, each as a singlet. The presence of the aldehyde group was confirmed by a signal at δ 205.5 in the ^{13}C nmr spectrum which also showed four vinylic carbon signals at δ 141.8, 135.4, 123.4 and 117.2. The molecular ion peak of this compound was found in the mass spectrum at m/z 206.1305, which was in agreement with the molecular formula $C_{13}H_{18}O_2$.



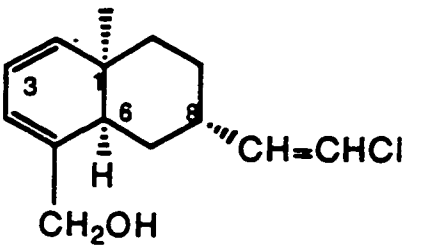
101

Aldehyde **102** displayed absorptions at 3386 cm^{-1} for the hydroxy group, 2854, 2720 and 1723 cm^{-1} for the aldehyde moiety in the ir spectrum, and a molecular ion peak at m/z 206.1302 in the mass spectrum, consistent with the formula $C_{13}H_{18}O_2$. In the ^1H nmr spectrum, the aldehyde proton appeared as a doublet at δ 9.65 (J=1.5 Hz). The vinylic protons appeared at δ 5.91 (dd, J=9.5, 5.5 Hz), 5.83 (dddd, J=5.5, 1, 1, 1 Hz) and 5.44 (dd, J=9.5, 1 Hz). The protons adjacent to the hydroxyl group and the angular methyl group were observed at δ 4.15 and 0.95, respectively, each as a singlet. The ^{13}C nmr spectrum confirmed the presence of an aldehyde group by a signal at δ 204.1 and four vinylic carbons by signals at δ 141.2, 135.5, 123.3 and 117.8.



102

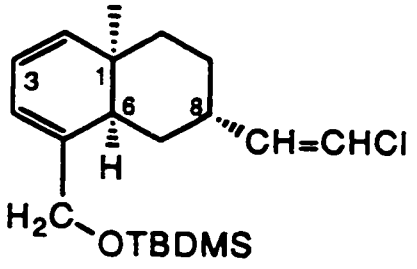
To complete the synthesis of (±)-dehyochamaecynenol, aldehyde **101** was first converted to vinyl chloride **103** using a Wittig reaction. Treatment of **101** with chloromethylenetriphenylphosphorane (prepared from the reaction of chloromethyltriphenylphosphonium chloride with *t*-BuOK)[64] in THF at -78°C for 1.5 h resulted in the formation of vinyl chloride **103** in 74% yield. The ir spectrum of this compound showed a hydroxyl absorption at 3348 cm^{-1}. In the ^1H nmr spectrum, the protons adjacent to the hydroxyl group appeared at δ 4.10 as a broad singlet, while the two vinylic protons of the vinyl chloride moiety were observed between δ 6.10 and 6.00. Three additional vinylic protons appeared at δ 5.92 (dd, J=9, 5 Hz), 5.82 (ddd, J=5, 1, 1 Hz) and 5.45 (br d, J=9 Hz). A molecular ion peak at m/z 238.0910 observed in the mass spectrum was consistent with the molecular formula $C_{14}H_{19}ClO_2$.



103

Direct transformation of **103** into (±)-**93** was attempted using potassium *t*-butoxide[64] and *n*-butyllithium.[65] However, in each case, a complex mixture was

produced, apparently due to complications caused by the presence of the hydroxyl group. Consequently, the hydroxyl group was protected by treatment of **103** with *t*-butyldimethylsilyl chloride and imidazole. Silyl ether **104** was obtained in 96% yield. In the ir spectrum of this compound, the disappearance of the hydroxyl absorption indicated that the protection had taken place. The ^1H nmr spectrum confirmed the presence of the *t*-butyldimethylsilyl group by singlets at δ 0.90 (3 x CH_3) and 0.05 (2 x CH_3). The mass spectrum showed a molecular ion peak at m/z 352.1990, in accordance with the formula $C_{20}H_{33}ClOSi$.

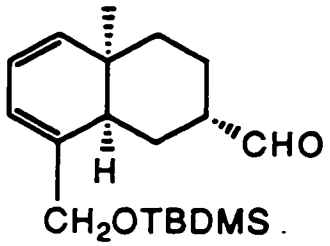


104

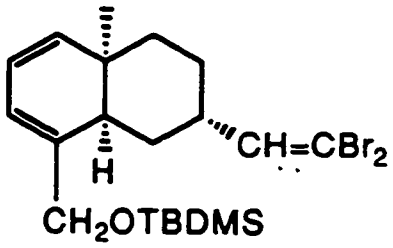
The conversion of silyl ether **104** into the target molecule was carried as follows. Compound **104** was subjected to dehydrochlorination with potassium *t*-butoxide in THF at room temperature, and the racemic dehydrochamacynenol **93** was isolated in 61% yield following the removal of the silyl protecting group using tetra-*n*-butylammonium fluoride. The ir spectrum of this compound showed absorptions at 3390 (OH), 3308 (≡CH) and 2120 (C≡C) cm^{-1}. In the ^1H nmr spectrum, the protons adjacent to the hydroxyl group and the angular methyl group appeared at δ 4.15 and 0.95, respectively, each as a singlet. The vinylic protons appeared at δ 5.92 (dd, J=9, 5 Hz), 5.85 (br d, J=5 Hz) and 5.45 (br d, J=9 Hz). A molecular ion peak at m/z 202.1361, consistent with the expected molecular formula $C_{14}H_{18}O_2$, was observed in the mass spectrum.

These spectral data of the synthetic material were found to be in good agreement with those reported for the naturally occurring compound (-)-**93**.[56]

In another approach to **93**, compound **101** was first converted (TBDMSCl, imidazole, THF) to the corresponding *t*-butyldimethylsilyl ether **105**. This was followed by a Wittig reaction (triphenylphosphine, carbon tetrabromide) to give dibromide **106**, which was transformed into (±)-**93** by sequential treatment with *n*-butyllithium and tetra-*n*-butylammonium fluoride. This approach was inferior in terms of overall yield (5% from **101**).



105



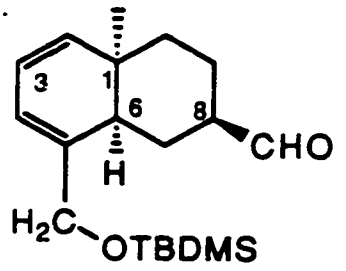
106

2. A total synthesis of (±)-occdentalol (61)

Our synthesis began with hydroxy aldehyde **102**. This compound and (±)-occidentalol have the same *cis*-fused ring system with a homoannular 1,3-diene and the same relative stereochemistry. The conversion of **102** to the target molecular **61** required only two major operations: deoxygenation of the hydroxy group and transformation of the aldehyde into an isopropyl alcohol unit. The latter requirement was examined first.

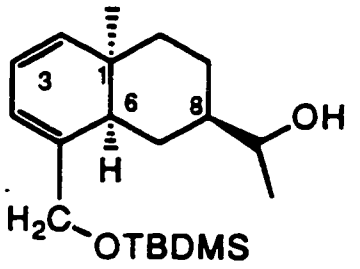
To prevent any complications which might arise due to the free hydroxyl group, hydroxy aldehyde **102** was first treated with *t*-butyldimethylsilyl chloride and imidazole in THF at room temperature to give the corresponding silyl ether **107**

in 95% yield. The ir spectrum of this compound showed the absence of a hydroxyl absorption, indicating that the protection had taken place. The ^1H nmr spectrum confirmed the presence of a *t*-butyldimethylsilyl group by two methyl singlets, one at δ 0.90 (3 x CH_3) and the other at δ 0.05 (2 x CH_3). The aldehyde proton appeared at δ 9.55 as a doublet, while the vinylic protons appeared at δ 5.92 (dd, J=9, 5 Hz), 5.81 (ddd, J=5, 1.5, 1.5 Hz) and 5.39 (br d, J=9, 1 Hz). The mass spectrum showed a molecular ion peak at m/z 320.2169, consistent with the molecular formula $C_{19}H_{32}O_2Si$.



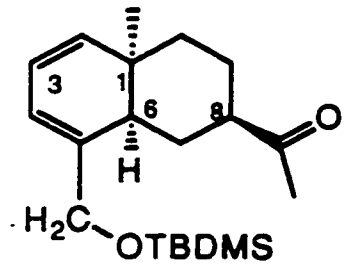
107

Treatment of **107** with methyllithium at -78°C afforded alcohol **108**, which showed a hydroxyl absorption at 3357 cm^{-1} in the ir spectrum. The ^1H nmr spectrum displayed a multiplet at δ 3.52 for the methine proton adjacent to the hydroxy group and a singlet at δ 4.16 for the protons attached to the carbon bearing the silyl ether. The newly introduced methyl group appeared at δ 1.16 and 1.15 as a pair of doublets (J=6.5 Hz each), indicating the presence of two epimers.



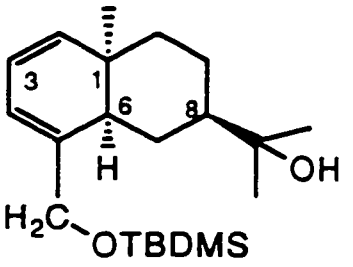
108

Transformation of alcohol **108** to the corresponding ketone was effected by treatment with excess pyridinium chlorochromate on alumina in methylene chloride for 3 h. Ketone **109** thus obtained in 82% yield showed a carbonyl absorption at 1710 cm^{-1} in the ir spectrum. The ^1H nmr spectrum displayed a singlet at δ 2.10 for the acetyl methyl group. The allylic protons adjacent to the silyl ether moiety and the angular methyl group appeared as singlets at δ 4.15 and 0.90, respectively. Three signals were observed at δ 5.89 (dd, J=9, 5 Hz), 5.77 (ddd, J=5, 1, 1 Hz) and 5.39 (br d, J=9 Hz) for the vinylic protons.



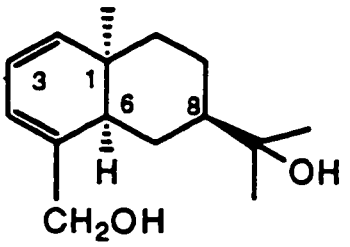
109

The isopropyl alcohol moiety found in the target molecule **61** was generated by treatment of ketone **109** with methyllithium at 0°C. Alcohol **110** was obtained in 85% yield. This compound showed a hydroxyl absorption at 3470 cm^{-1} in the ir spectrum and a molecular ion peak at 350.2638 ($C_{21}H_{38}O_2Si$) in the mass spectrum. The ^1H nmr spectrum showed a singlet at δ 1.15 for the methyl groups of the isopropyl alcohol moiety. The methylene protons adjacent to the silyl ether and the angular methyl group appeared as singlets at δ 4.16 and 0.90, respectively. The vinylic protons were shown at δ 5.89 (dd, J=9, 5 Hz), 5.77 (ddd, J=5, 1, 1 Hz) and 5.39 (br d, J=9 Hz).



110

With alcohol **110** in hand, the next stage of the synthesis was to remove the silyl protecting group and to deoxygenate the primary alcohol thus formed. Deprotection was achieved by treatment of **110** with tetra-*n*-butylammonium fluoride. The diol **111** was obtained in 85% yield. This diol showed a hydroxyl absorption at 3357 cm^{-1} in the ir spectrum and a molecular ion peak at m/z 236.1773 ($C_{15}H_{24}O_2$) in the mass spectrum. The disappearance of the *t*-butyldimethylsilyl group in the ^1H nmr spectrum indicated that the deprotection had taken place. Two methyl singlets were observed, one at δ 1.15 for the *gem*-dimethyl group of the isopropanol moiety and the other at δ 0.90 for the remaining methyl group. Another singlet appeared at δ 4.15 due to the protons attached to the carbon bearing the primary hydroxyl group.



111

Final transformation of diol **111** to (±)-occidentalol (**61**) was accomplished by selective mesylation of the primary alcohol followed by reduction. Treatment of **111** with methanesulfonyl chloride in pyridine at 0°C afforded the unstable

mesylate, which, without purification, was immediately reduced with sodium borohydride in DMSO[66] at room temperature for 3.5 h to furnish (±)-**61** in 65% yield.

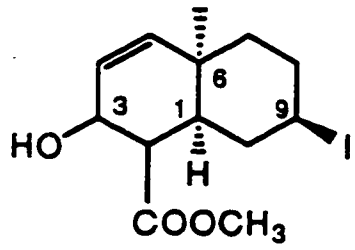
In conclusion, the newly developed polyene cyclization process has been successfully used for the expeditious construction of the *cis*-fused bicyclic compound **18**, which contains suitable functional groups at strategic positions for the synthesis of a variety of natural products. Modification of this compound has led to the first total synthesis, in racemic form, of dehydrochamaecynenol and a new synthesis of racemic occidentalol.

Experimental

General and materials

For general procedures and materials used in Chapter 2, refer to Chapter 1 of this thesis.

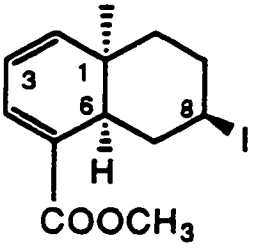
(1S*, 6S*, 9R*)-2-Carbomethoxy-9-iodo-6-methylbicyclo[4.4.0]dec-4-en-3-ol (95)



Sodium borohydride (1 g, 26.3 mmol) was added to a solution of keto ester **18** (1.05 g, 3 mmol) in methanol (40 mL) at 0°C under an argon atmosphere. The reaction mixture was stirred for 2 h. The reaction was followed by tlc. After most of the starting material was consumed, water (50 mL) was added. The resulting mixture was extracted with ether (3 x 50 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was subjected to flash chromatography using ethyl acetate/hexane (25:75) as an eluent to give the recovered starting material (160 mg) and then two diastereomeric hydroxy esters **95**. The less polar major isomer (523 mg, 58% based on the consumed starting material): ir (CH_2Cl_2) 3515 cm^{-1} (OH) and 1737 cm^{-1} (C=O, ester); ^1H nmr (200 MHz) δ 5.86 (dd, J=10, 5.5 Hz, 1H, H_4), 5.55 (ddd, J=10, 1, 1 Hz, 1H, H_5), 4.50 (m, 1H, CHOH), 4.00 (dddd, J=12, 12, 4, 4 Hz,

1H, CHI), 3.80 (s, 3H, OCH_3), 3.55 (d, J=3 Hz, 1H, OH), 2.97 (dd, J=4, 4 Hz, 1H, H_2), 1.85-2.75 (m, 4H), 1.30-1.65 (m, 3H), 1.00 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 174.4 (p), 137.4 (a), 126.8 (a), 62.5 (a), 52.1 (a), 44.8 (a), 42.9 (a), 42.2 (p), 38.4 (p), 37.3 (p), 35.6 (p), 29.4 (a), 28.4 (a); hrms M^+-I 223.1332 (calcd. for $C_{13}H_{19}O_3$: 223.1334). The more polar minor isomer (327 mg, 37% based on the consumed starting material): ir (CH_2Cl_2) 3211 cm^{-1} (OH) and 1731 cm^{-1} (C=O, ester); ^1H nmr (200 MHz) δ 5.70 (dd, J=10, 1.5 Hz, 1H, H_4), 5.45 (ddd, J=10, 1.5, 1.5 Hz, 1H, H_5), 4.62 (ddd, J=9.5, 1.5, 1.5 Hz, 1H, CHOH), 4.02(dddd, J=12, 12, 3.5, 3.5 Hz, 1H, CHI), 3.75 (s, 3H, OCH_3), 2.90 (dd, J=9.5, 3 Hz, 1H, H_2), 1.80-2.30 (m, 6H), 1.20-1.40 (m, 1H), 1.10 (s, 3H, CH_3); hrms M^+ 350.0377 (calcd. for $C_{13}H_{19}IO_3$: 350.0379).

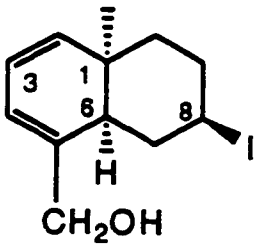
(1R*, 6R*, 8R*)-5-Carbomethoxy-8-iodo-1-methylbicyclo[4.4.0]deca-2,4-diene (96)



p-Toluenesulfonic acid (387 mg, 2.3 mmol) was added to a solution of hydroxy esters **95** (524 mg, 1.5 mmol) in benzene (30 mL) at room temperature, and the reaction mixture was refluxed for 2 h. Water (30 mL) was added and the resulting mixture was extracted with ether (3 x 50 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford the conjugated ester **96** (461 mg, 90%): ir (CH_2Cl_2)

1707 cm^{-1} (C=O, ester); ^1H nmr (400 MHz) δ 6.95 (dd, J=5.5, 1 Hz, 1H, H_4), 6.10 (dd, J=9, 5.5 Hz, 1H, H_3), 5.85 (ddd, J=9, 1, 1 Hz, 1H, H_2), 4.05 (dddd, J=12, 12, 4, 4 Hz, 1H, CHI), 3.80 (s, 3H, OCH_3), 2.55 (ddd, J=12, 4, 1 Hz, 1H, H_6), 2.30-2.45 (m, 2H), 1.80-2.00 (m, 2 H), 1.35-1.60 (m, 2H), 0.85 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 167.3 (p), 143.1 (a), 131.3 (a), 130.1 (p), 123.2 (a), 51.8 (a), 42.9 (a), 40.4 (p), 40.1 (p), 37.7 (p), 35.5 (p), 25.9 (a), 25.8 (a); hrms M^+ 332.0271 (calcd. for $C_{13}H_{17}IO_2$: 332.0273). Anal. calcd. for $C_{13}H_{17}IO_2$: C 47.01, H 5.16; found: C 47.07, H 5.19.

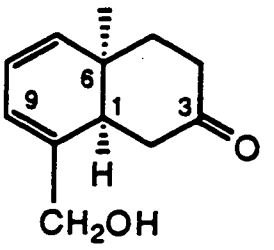
(1R*, 6R*, 8R*)-5-(Hydroxymethyl)-8-iodo-1-methylbicyclo[4.4.0]-deca-2,4-diene (97)



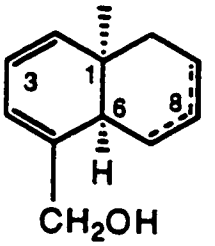
Diisobutylaluminum hydride (3.5 mL, 1 M in ether, 3.5 mmol) was added to a solution of ester **96** (461 mg, 1.4 mmol) in dry ether (30 mL) at -78°C under an argon atmosphere. After the reaction mixture was stirred for 2 h at -78°C and warmed up to room temperature, water (40 mL) was added and the resulting mixture was extracted with ether (3 x 50 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate/hexane (15:85) as an eluent to give the iodo alcohol **97** (397 mg, 94%): ir (CH_2Cl_2) 3328 cm^{-1} (OH); ^1H nmr (200 MHz) δ 5.95 (dd, J=9.5, 5.5 Hz, 1H, H_3), 5.85 (dddd, J=5.5, 1, 1, 1 Hz, 1H, H_4), 5.50 (dd, J=9.5, 1 Hz, 1H, H_2), 4.15 (s, 2H, CH_2OH), 4.00 (m, 1H,

H_8), 2.20-2.40 (m, 2H), 1.80-2.20 (m, 2H), 1.20-1.60 (m, 3H), 0.87 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 140.2 (p), 135.9 (a), 123.5 (a), 117.9 (a), 65.0 (p), 45.3 (a), 40.6 (p), 37.7 (p), 34.9 (p), 34.8 (p), 27.0 (a), 25.6 (a); hrms M^+ 304.0326 (calcd. for $C_{12}H_{17}IO$: 304.0324).

(1R*, 6R*)-10-(Hydroxymethyl)-6-methylbicyclo[4.4.0]deca-7,9-dien-3-one (98), (1R*, 6R*)-5-(Hydroxymethyl)-1-methylbicycl[4.4.0]deca-2,4,7-triene (99) and (1R*, 6R*)-5-(Hydroxymethyl)-1-methylbicycl[4.4.0]deca-2,4,8-triene (99)



98



99

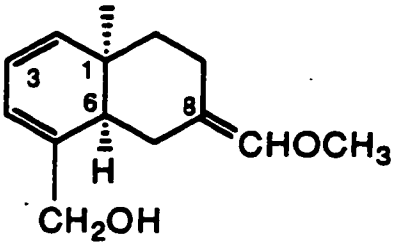
Iodo alcohol **97** (200 mg, 0.66 mmol) was added to a solution of silver tetrafluoroborate (153 mg, 0.8 mmol) in dry DMSO (5 mL) at room temperature under an argon atmosphere. After the reaction mixture was stirred for 1 h, triethylamine (1 mL) was added and the resulting mixture was stirred for 12 h. Water (10 mL) was added and the resulting mixture was extracted with ether (3 x 30 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate/hexane (25:75) as an eluent to give ketone **98** (more polar, 70 mg, 55%), along with a mixture of trienes **99** (less polar, 32.6 mg, 35%).

Ketone **98**: ir (CH_2Cl_2) 3411 (OH) and 1713 cm^{-1} (C=O); ^1H nmr (200 MHz) δ 6.06 (dd, J=9.5, 5.5 Hz, 1H, H_8), 5.91 (ddd, J=5.5, 1, 1 Hz, 1H, H_9), 5.68 (dd,

J=9.5, 1 Hz, 1H, H_7), 4.12 (s, 2H, CH_2OH), 2.55 (m, 1H), 2.10-2.30 (m, 3H), 1.75-2.05 (m, 3H), 1.05 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ 210.0 (p), 140.7 (p), 134.7 (a), 124.3 (a), 117.7 (a), 64.7 (p), 44.1 (a), 41.7 (p), 39.2 (p), 38.9 (p), 35.8 (p), 24.2 (a); hrms M^+ 192.1145 (calcd. for $C_{12}H_{16}O_2$: 192.1150).

Trienes **99**: ir (CH_2Cl_2) 3341 cm^{-1} (OH); ^1H nmr (200 MHz) two isomers in a ratio of 3:2: δ 5.86 (dd, J=9.5, 5 Hz, 1H, H_3), 5.74-5.82 (m, 2H, H_4 and CH=CH), 5.65 (m, 0.4H, CH=CH), 5.52 (d, J=9.5 Hz, 0.4H, H_2), 5.42 (m, 0.6H, CH=CH), 5.36 (d, J=9.5 Hz, 0.6H, H_2), 4.17 (s, 1.2H, CH_2OH), 4.16 (s, 0.8H, CH_2OH), 2.56 (m, 1H), 1.45-2.20 (m, 4H), 1.24 (s, 1.2H, CH_3), 1.20 (s, 1.8H, CH_3); hrms M^+ 176.1204 (calcd. for $C_{12}H_{16}O$: 176.1204).

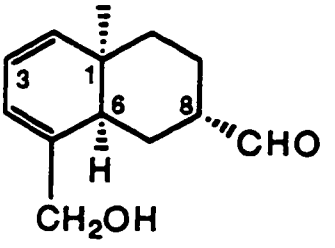
(1R*, 6R*)-5-(Hydroxymethyl)-8-(methoxymethylene)-1-methyl-bicyclo[4.4.0]deca-2,4-diene (100)



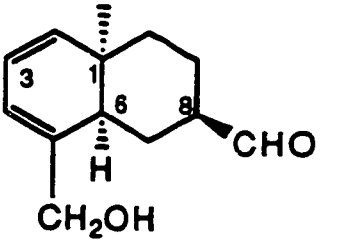
n-Butyllithium (0.7 mL, 2.5 M in hexane, 1.8 mmol) was added at -78°C to a suspension of methoxymethyltriphenylphosphonium chloride (684 mg, 2 mmol) in THF (10 mL) under an argon atmosphere. After stirring at room temperature for 30 min (solution turned homogeneous with a blood-red color), a solution of ketone **98** (80 mg, 0.42 mmol) in THF (5 mL) was added slowly. The reaction mixture was stirred at room temperature for 2 h, and then water was added to quench the reaction. The aqueous solution was extracted with ether (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and

concentrated. The crude product was subjected to flash chromatography using ethyl acetate/hexane (10:90) as an eluent to afford enol ethers **100** (60 mg, 70%) and then the starting material (5 mg). Enol ethers **100**: ir (CH_2Cl_2) 3395 cm^{-1} (OH); ^1H nmr (400 MHz) two isomers in a ratio of 3:2: δ 5.92 (dd, J=9.5, 5.5 Hz, 1H, H_3), 5.78-5.82 (m, 2H, H_4 and C=C**H**OCH3), 5.49 (d, J=9.5, 1Hz, 1H, H_2), 4.16 (s, 1.2H, CH_2OH), 4.12 (s, 0.8H, CH_2OH), 3.53 (s, 1.2H, OCH_3), 3.52 (s, 1.8H, OCH_3), 2.66 (m, 1H, H_6), 1.20-2.10 (m, 6H), 0.90 (s, 1.8H, CH_3), 0.84 (s, 1.2H, CH_3); hrms M^+ 220.1461 (calcd. for $C_{14}H_{20}O_2$: 220.1463).

(1R*, 6R*, 8S*)-8-Formyl-5-(hydroxymethyl)-1-methylbicyclo[4.4.0]-deca-2,4-diene (101) and (1R*, 6R*, 8R*)-8-formyl-5-hydroxy-1-methylbicyclo[4.4.0]deca-2,4-diene (102)



101

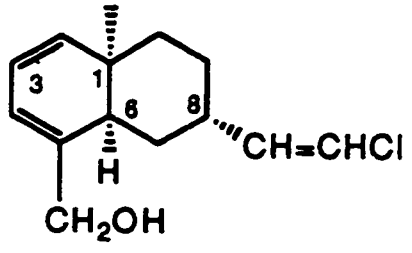


102

A mixture of enol ethers **100** (55 mg, 0.25 mmol) was dissolved in THF and 1 N HCl (1:1, 6 mL) at room temperature. The resulting solution was stirred for 4.5 h and then water (10 mL) was added. The aqueous solution was extracted with ether (3 x 50 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (20:80) afforded the recovered starting material (10 mg), and then aldehydes **101** (less polar, 27 mg, 65%) and **102** (more polar, 13 mg, 29%). Compound **101**: ir (CH_2Cl_2) 3397 (OH), 2858, 2713 and 1725 cm^{-1}

(CHO); ^{1}H nmr (200 MHz) δ 9.75 (s, 1H, CHO), 5.95 (dd, J=9.5, 5.5 Hz, 1H, **H$_3$**), 5.83 (ddd, J=5.5, 1, 1 Hz, 1H, **H$_4$**), 5.45 (dd, J=9.5, 1 Hz, 1H, **H$_2$**), 4.17 (s, 2H, **CH$_2$**OH), 2.40 (m, 1H, **H$_8$**), 2.10 (m, 2H), 1.15-1.90 (m, 5H), 0.85 (s, 3H, **CH$_3$**); ^{13}C nmr (75 MHz) δ 205.5 (a), 141.8 (p), 135.4 (a), 123.4 (a), 117.2 (a), 65.1 (p), 45.3 (a), 41.8 (a), 35.4 (p), 34.3 (p), 25.8 (a), 25.1 (p), 21.9 (p); hrms M$^+$ 206.1305 (calcd. for $C_{13}H_{18}O_2$: 206.1307). Compound **102**: ir (CH_2Cl_2) 3386 (OH), 2854, 2720 and 1723 cm^{-1} (CHO); ^{1}H nmr (200 MHz) δ 9.65 (d, J=1.5 Hz, 1H, CHO), 5.91 (dd, J=9.5, 5.5 Hz, 1H, **H$_3$**), 5.83 (ddd, J=5.5, 1, 1 Hz, 1H, **H$_4$**), 5.44 (dd, J=9.5, 1 Hz, 1H, **H$_2$**), 4.15 (s, 2H, **CH$_2$**OH), 1.70-2.20 (m, 4H), 1.10-1.60 (m, 4H), 0.95 (s, 3H, **CH$_3$**); ^{13}C nmr (75 MHz) δ 204.1 (a), 141.2 (p), 135.5 (a), 123.3 (a), 117.8 (a), 65.2 (p), 48.6 (a), 41.8 (a), 37.4 (p), 35.7 (p), 26.3 (a), 25.6 (p), 23.3 (p); hreims M$^+$ 206.1302 (calcd. for $C_{13}H_{18}O_2$: 206.1307).

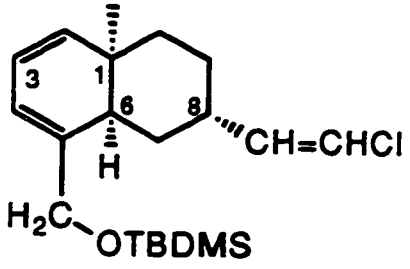
(1R*, 6R*, 8S*)-5-(Hydroxymethyl)-8-(2-chlorovinyl)-1-methyl-bicyclo[4.4.0]deca-2,4-diene (103)



t-BuOK (0.8 mL, 1 M in THF, 0.8 mmol) was added at -78°C to a solution of chloromethyltriphenylphosphonium chloride (348 mg, 1 mmol) in dry THF (10 mL) under an argon atmosphere. After stirring at -78°C for 1 h (solution turned yellow), a solution of aldehyde **101** (45 mg, 0.22 mmol) in THF (5 mL) was added slowly. After the reaction mixture was stirred at -78°C for 3 h and warmed to room temperature, water was added. The resulting mixture was extracted with

ether (3 x 30 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to give the vinyl chloride **103** (39 mg, 75%): ir (CH_2Cl_2) 3348 cm^{-1} (OH); ^1H nmr (200 MHz) δ 6.00-6.10 (m, 2H, C**H**=C**H**Cl), 5.92 (dd, J=9, 5 Hz, 1H, H_3), 5.82 (ddd, J=5, 1, Hz, 1H, H_4), 5.45 (br d, J=9 Hz, 1H, H_2), 4.10 (br s, 2H, CH_2OH), 2.90 (m, 1H, H_8), 2.00 (dd, J=11, 5 Hz, 1H, H_6), 1.10-1.80 (m, 6H), 0.95 (s, 3H, CH_3); hrms M^+ 238.0910, 240.1092 (calcd. for $C_{14}H_{19}ClO$: 238.1124, 240.1095).

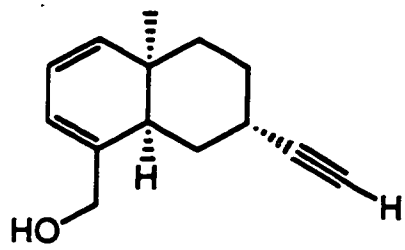
(1R*, 6R*, 8S*)-5-(*t*-Butyldimethylsiloxymethyl)-8-(2-chlorovinyl)-1-methylbicyclo[4.4.0]deca-2,4-diene (104)



Imidazole (21 mg, 0.3 mmol) was added to a solution of **103** (35 mg, 0.15 mmol) in THF (5 mL) under an argon atmosphere at -78°C. The reaction mixture was stirred at -78°C for 15 min before *t*-butyldimethylsilyl chloride (0.23 mL, 1 M in THF, 0.23 mmol) was added. The mixture was stirred at room temperature for 1.5 h, and water was added. The resulting mixture was extracted with ether (3 x 30 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate/hexane as an eluent to give the silyl ether **104** (50 mg, 96%): ^1H nmr (200 MHz) δ 5.97-6.07 (m, 2H, C**H**=C**H**Cl), 5.90 (dd, J=9, 5 Hz, 1H, H_3), 5.80 (ddd, J=5, 1.5, 1.5 Hz, 1H, H_4), 5.40 (br d, J=9 Hz, 1H,

H_2), 4.10 (s, 2H, $CH_2OTBDMS$), 2.90 (m, 1H, H_8), 1.85 (dd, J=11, 5 Hz, 1H, H_6), 1.20-1.80 (m, 6H), 0.90 (br s, 12H, 4 x CH_3), 0.05 (s, 6H, 2 x CH_3); hrms M^+ 352.1990, 354.1964 (calcd. for $C_{20}H_{33}ClOSi$: 352.1989, 354.1962).

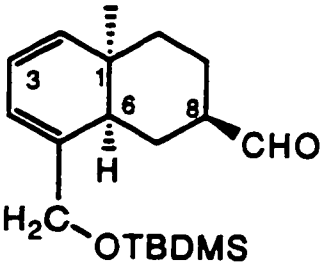
(±)-Dehydrochamacynenol (93)



Potassium *t*-Butoxide (0.3 mL, 1 M in THF, 0.3 mmol) was added to a solution of **104** (35 mg, 0.1 mmol) in THF (5 mL) under an argon atmosphere at 0°C. The reaction mixture was stirred at room temperature for 2.5 h, and then water was added to quench the reaction. The aqueous solution was extracted with ether (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in THF (5 mL) and tetra-*n*-butylammonium fluoride (0.15 mL, 1 M in THF, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 1h, and water was added. The aqueous solution was extracted with ether (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude product was subjected to flash chromatography using ethyl acetate/hexane (10:90) as an eluent to afford (±)-**93** (12 mg, 61%): ir (CH_2Cl_2) 3390 (OH), 3308 (≡CH) and 2120 cm^{-1} (C≡C); ^1H nmr (400 MHz) δ 5.92 (dd, J=9, 5 Hz, 1H, H_3), 5.85 (br d, J=5 Hz, 1H, H_4), 5.45 (br d, J=9 Hz, 1H, H_2), 4.15 (s, 2H, CH_2OH), 2.78 (m, 1H, H_8), 2.19 (ddd, J=11, 4.5, 1.5 Hz, 1H, H_6), 2.07 (d, J=2.5 Hz, 1H,

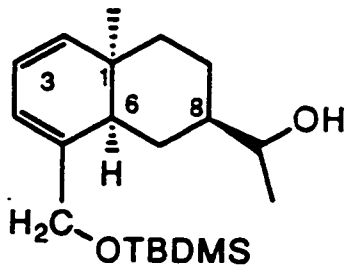
C≡CH), 1.00-1.95 (m, 6H), 0.95 (s, 3H, CH_3); hrms M^+ 202.1361 (calcd. for $C_{14}H_{18}O$: 202.1358).

(1R*, 6R*, 8R*)-5-(*t*-Butyldimethylsiloxymethyl)-8-formyl-1-methyl-bicyclo[4.4.0]deca-2,4-diene (107)



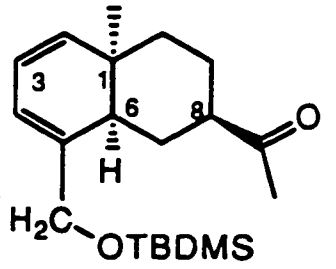
Imidazole (41 mg, 0.58 mmol) was added to a solution of **102** (60 mg, 0.29 mmol) in THF (5 mL) under an argon atmosphere at -78°C. The reaction mixture was stirred at -78°C for 15 min before *t*-butyldimethylsilyl chloride (0.44 mL, 1 M in THF, 0.44 mmol) was added. The mixture was stirred at room temperature for 1 h, and water was added. The resulting mixture was extracted with ether (3 x 30 mL). The extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate/hexane (3:97) as an eluent to give the silyl ether **107** (79 mg, 95%): ir (CH_2Cl_2) 1727, 2805 and 2706 cm^{-1} (CHO); ^1H nmr (200 MHz) δ 9.55 (d, J=2 Hz, 1H, CHO), 5.92 (dd, J=9, 5 Hz, 1H, H_3), 5.81 (ddd, J=5, 1.5, 1.5 Hz, 1H, H_4), 5.39 (br d, J=9 Hz, 1H, H_2), 4.15 (s, 2H, CH_2OTBDMS), 1.95-2.15 (m, 1H), 1.55-1.90 (m, 3H), 1.10-1.50 (m, 4H), 0.90 (br s, 9H, 3 x CH_3), 0.88 (s, 3H, CH_3), 0.05 (s, 6H, 2 x CH_3); hrms M^+ 320.2169 (calcd. for $C_{19}H_{32}O_2Si$: 352.1989).

(1R*, 6R*, 8R*)-5-(*t*-Butyldimethylsiloxymethyl)-8-(1-hydroxyethyl)-1-methylbicyclo[4.4.0]deca-2,4-diene (108)



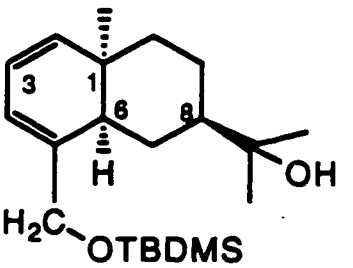
Silyl ether **107** (70 mg, 0.22 mmol) was dissolved in THF (10 mL) and cooled to -78°C. Methyllithium (0.69 mL, 1.6 M in THF, 1.1 mmol) was added. The reaction mixture was stirred at -78°C for 2 h, and warmed to room temperature. Ice-cold water was added to destroy the excess methyllithium. The resulting mixture was extracted with ether (3 x 30 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give the alcohol **108** (89 mg, 91%): ir (CH_2Cl_2) 3357 cm^{-1} (OH); ^1H nmr (200 MHz) δ 5.89 (dd, J=9, 5 Hz, 1H, H_3), 5.77 (ddd, J=5, 1, 1 Hz, 1H, H_4), 5.39 (br d, J=9 Hz, 1H, H_2), 4.16 (s, 2H, CH_2OTBDMS), 3.52 (m, 1H, CHOH), 1.15-1.85 (m, 8H), 1.16, 1.15 (d, J=6.5 Hz , 3H, CH_3), 0.95 (br s, 9H, 3 x CH_3), 0.90 (s, 3H, C_1-CH_3), 0.10 (s, 6H, 2 x CH_3); hrms M^+-TBDMSH 220.1457 (calcd. for $C_{14}H_{20}O_2$: 220.1463).

(1R*, 6R*, 8R*)-8-Acetyl-5-(*t*-Butyldimethylsiloxymethyl)-1-methyl-bicyclo[4.4.0]deca-2,4-diene (109)



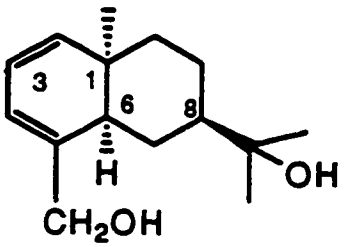
Pyridinium chlorochromate on basic alumina (774 mg, 10%, 0.36 mmol) was added to a solution of alcohol **108** (60 mg, 0.18 mmol) in methylene chloride (10 mL). After stirring under an argon atmosphere at room temperature for 3 h, the reaction mixture was filtered and the residue washed thoroughly with methylene chloride. The filtrate was concentrated and the residue was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give the ketone **109** (49 mg, 82%): ir (CH_2Cl_2) 1710 cm^{-1} (C=O); ^1H nmr (200 MHz) δ 5.89 (dd, J=9, 5 Hz, 1H, H_3), 5.77 (ddd, J=5, 1, 1 Hz, 1H, H_4), 5.39 (br d, J=9 Hz, 1H, H_2), 4.16 (s, 2H, $CH_2OTBDMS$), 2.10 (s, 3H, CH_3), 2.15 (m, 1H), 1.15-1.85 (m, 7H), 0.95 (br s, 9H, 3 x CH_3), 0.90 (s, 3H, CH_3), 0.10 (s, 6H, 2 x CH_3); hrms M^+-TBDMSH 218.1304 (calcd. for $C_{14}H_{18}O_2$: 218.1307).

(1R*, 6R*, 8R*)-5-(*t*-Butyldimethylsiloxymethyl)-8-(1-hydroxy-1-methylethyl)-1-methylbicyclo[4.4.0]deca-2,4-diene (110)



Ketone **109** (30 mg, 0.09 mmol) was dissolved in THF (5 mL) and cooled to 0°C. Methyllithium (0.28 mL, 1.6 M in THF, 0.45 mmol) was added. The reaction mixture was stirred at 0°C for 2 h, and warmed to room temperature. Ice-cold water was added to destroy the excess methyllithium. The resulting mixture was extracted with ether (3 x 30 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give the alcohol **110** (28 mg, 85%): ir (CH_2Cl_2) 3470 cm^{-1} (OH); ^1H nmr (200 MHz) δ 5.89 (dd, J=9, 5 Hz, 1H, H_3), 5.77 (ddd, J=5, 1, 1 Hz, 1H, H_4), 5.39 (br d, J=9 Hz, 1H, H_2), 4.16 (s, 2H, CH_2OTBDMS), 1.10-1.80 (m, 8H), 1.15 (s, 6H, 2 x CH_3), 0.95 (br s, 9H, 3 x CH_3), 0.90 (s, 3H, CH_3), 0.10 (s, 6H, 2 x CH_3); hrms M^+ 350.2638 (calcd. for $C_{21}H_{38}OSi$: 350.2641).

(1R*, 6R*, 8R*)-5-(Hydroxymethyl)-8-(1-hydroxy-1-methylethyl)-1-methylbicyclo[4.4.0]deca-2,4-diene (111)



Tetra-*n*-butylammonium fluoride (0.9 mL, 1 M in THF, 0.9 mmol) was added to a solution of **110** (20 mg, 0.06 mmol) in THF (5 mL). The reaction mixture was stirred for 0.5 h and ice-cold water was added. The resulting mixture was extracted with ether (3 x 30 mL). The extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate/hexane (5:95) as an eluent to afford

the diol **111** (11 mg, 65%): ir (CH_2Cl_2) 3357 cm^{-1} (OH); ^1H nmr (200 MHz) δ 5.75-5.95 (m, 2H, H_3 and H_4), 5.45 (br d, J=9 Hz, 1H, H_2), 4.15 (s, 2H, CH_2OH), 1.15-2.20 (m, 8H), 1.15 (s, 6H, 2 x CH_3), 0.88 (s, 3H, CH_3); hrms M^+ 236.1773 (calcd. for $C_{15}H_{24}O_2$: 236.1776).

(±)-Occidentalol (**61**)

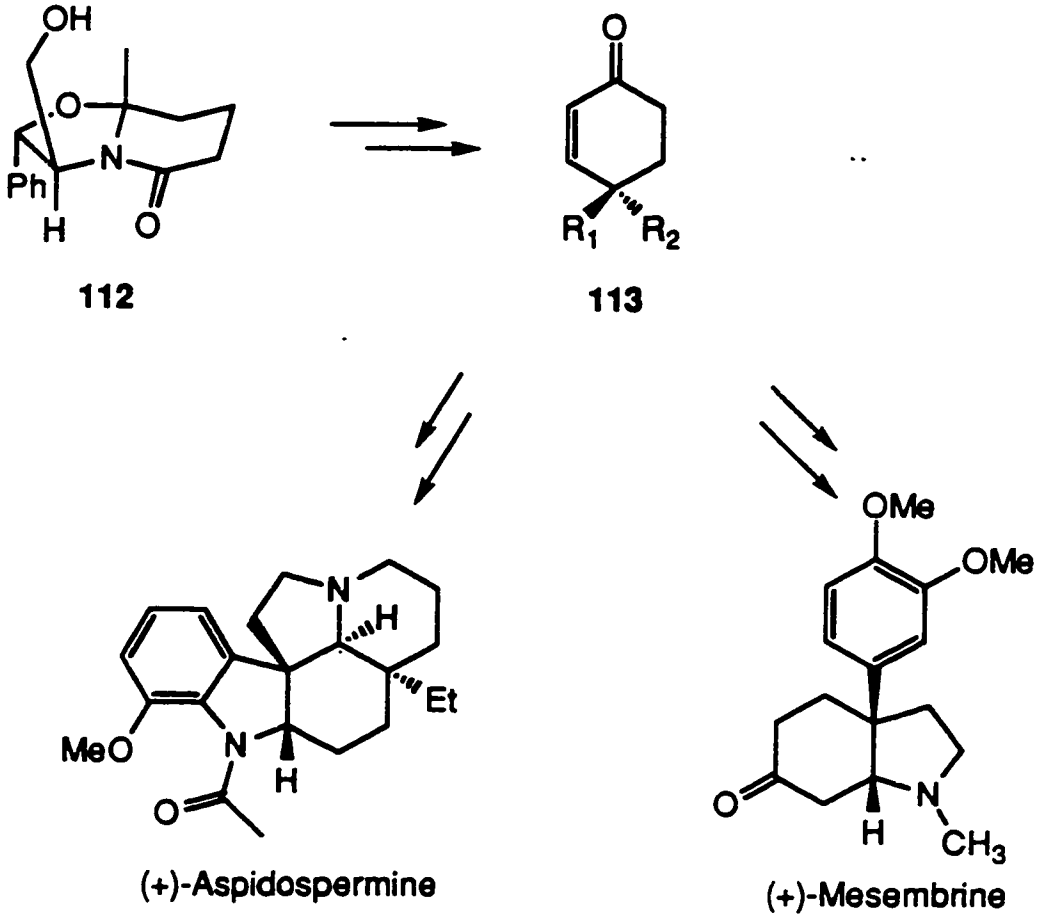
Diol **111** (8 mg, 0.03 mmol) was dissolved in pyridine (2 mL) and cooled to 0°C. Methanesulfonyl chloride (5 mg, 0.04 mmol) was added. After stirring under an argon atmosphere for 3 h, water was added. The aqueous solution was extracted with ether (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in DMSO (3 mL) and $NaBH_4$ (6 mg, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 3.5 h, and water was addeed. The aqueous solution was extracted with ether (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude product was subjected to flash chromatography using ethyl acetate/hexane (10:90) as an eluent to afford (±)-**61** (5 mg, 65%): ir (CH_2Cl_2) 3450 cm^{-1} (OH); hrms M^+ 220.1819 (calcd. for $C_{15}H_{24}O$: 220.1714).

Chapter Three

Formal Synthesis of (-)-Dehydrochamaecynenol

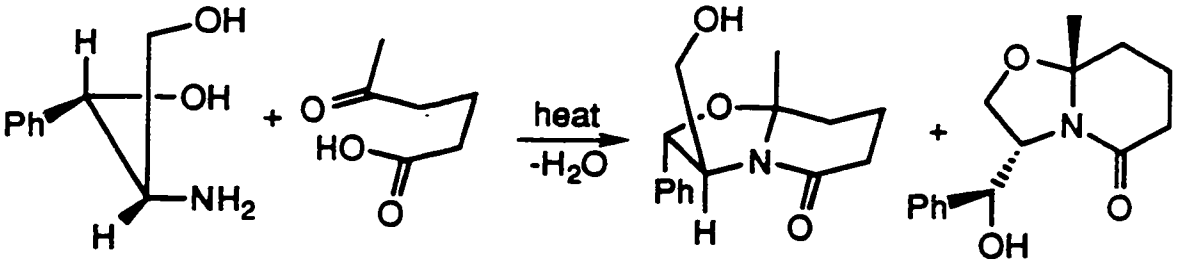
Introduction

Meyers and his coworkers have demonstrated that certain chiral bicyclic lactams, such as **112**, are extremely useful and versatile templates for the asymmetric synthesis of a variety of natural and unnatural products.[67] Bicyclic lactam **112**, containing a pendant hydroxyl group, has been used in the asymmetric synthesis of a number of natural and unnatural products, such as (+)-mesembrine[68] and (+)-aspidospermine[69], *via* cyclohexenones **113** (Scheme 39).



Scheme 39

Lactam **112** was prepared directly *via* a cyclodehydration reaction between (1S, 2S)-(+)-2-amino-1-phenyl-1,3-propanediol and 5-oxohexanoic acid.[70] This reaction provided lactam **112** as the sole diastereomer in good yield, along with a small amount of compound **114** (Scheme 40).



112 **114**

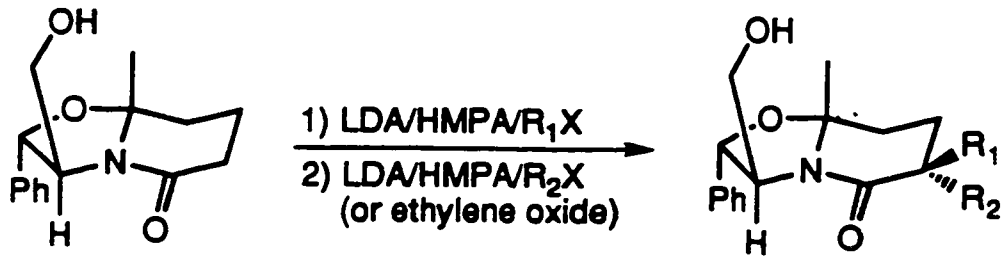
Scheme 40

A double alkylation of **112** gives the corresponding dialkylated lactam **115**. In this process, two equivalents of LDA are required to generate the corresponding enolate in each stage due to the presence of the hydroxyl group. The diastereoselectivity of the first alkylation is destroyed during the formation of the second enloate. However, the second alkylation proceeds with moderate to high diastereoselectivity and results in high *endo*/*exo* ratio in favor of the *endo* isomer (Table 8).[68, 72]

The order of alkylation is crucial to the extent of diastereoselectivity. In general, allyl and benzyl bromides give higher *endo* selectivity than methyl and ethyl. The results shown in Table 8 are consistent with the reactivity-selectivity principle[72] which states that the less reactive the substrate, the higher the selectivity. The change in order of alkylation also allows the preparation of either R or S stereoisomer. The *endo* and *exo* diastereomers can be easily separated by flash chromatography on silica gel. The assigned absolute

configurations of both isomers were confirmed by single crystal x-ray analysis of three different dialkylated lactams.[68, 71, 73] These results indicated that alkylation had occurred predominantly in an *endo* fashion. The major underlying reason for preferential *endo* alkylation of the lactams is not fully understood, although a number of studies have been performed. However, it is clear that more than a single factor is involved in giving preferential *endo* alkylation. It may be concluded that steric effect of the hydroxyl group makes some contribution to the diastereoselectivity observed.

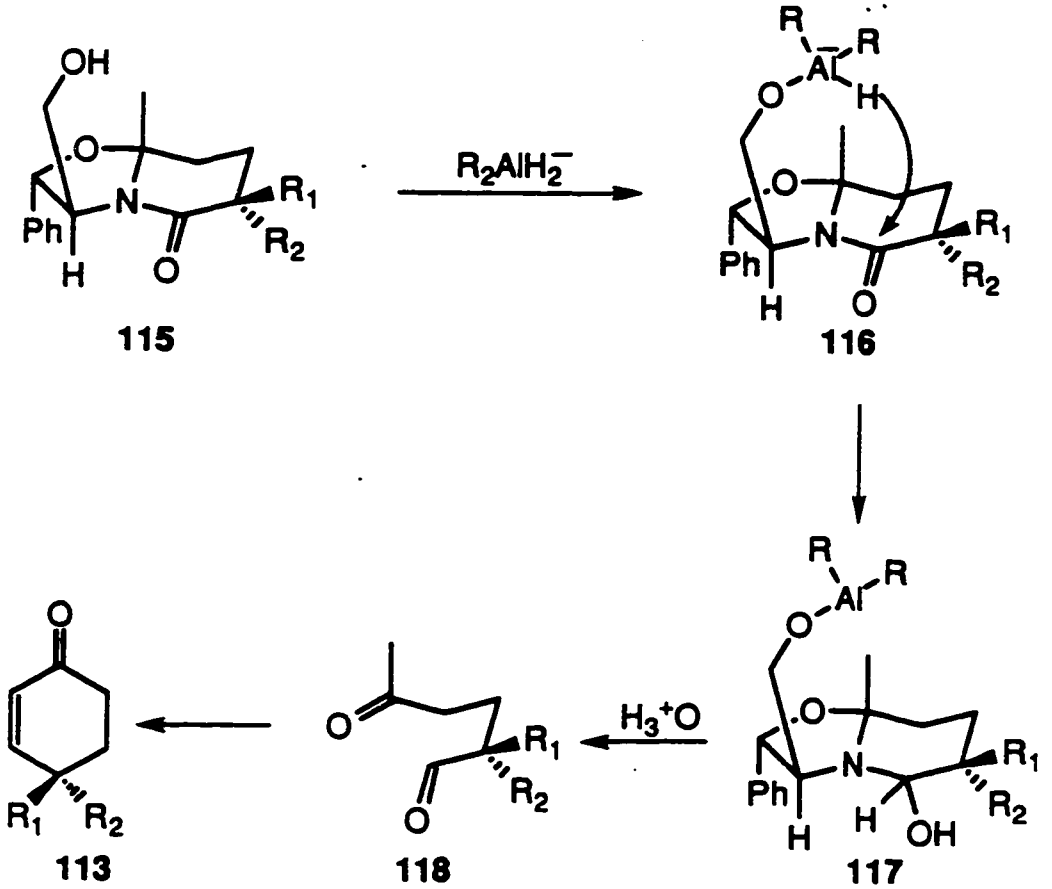
Table 8. Dialkylated lactam **115** from compound **112**



112 **115**

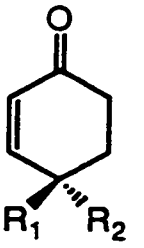
Entry	R_1	R_2	De (%)	Yield (%)
a	Me	$PhCH_2$	94	67
b	$PhCH_2$	Me	46	60
c	$PhCH_2$	allyl	64	72
d	Me	CH_2CH_2OH	72	90

Enantiomerically pure 4,4-dialkylcyclohexenones **113** were obtained from the dialkylated lactams by a three-step sequence, involving reduction of the lactam carbonyl group, hydrolysis of the bicyclic system and intramolecular aldol cyclization. The possible mechanism of the sequence was proposed as outlined in Scheme 41.[71] The first equivalent of hydride removes the alcohol proton of **115** to form an aluminum complex **116**, which is used as the "tether" to intramolecularly deliver a hydride to the lactam carbonyl group. Hydrolysis of the resulting intermediate **117** with $Bu_4NH_2PO_4$-H_2O-EtOH directly affords the optically pure 4,4-dialkylcyclohexenone **113**, presumably *via* an intramolecular aldol cyclization of intermediate **118** under the acidic conditions. A number of optically pure cyclohexenones prepared by this method are shown in Table 9.[68, 71]



Scheme 41

Table 9. 4,4-Disubstituted cyclohexenones **113** from lactams **115**



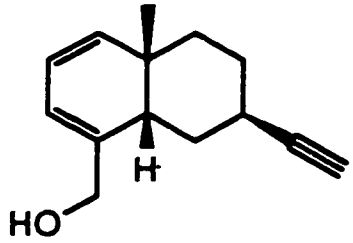
113

Entry	R_1	R_2	Overall yield (%)	$[\alpha]_D$ (°)	Configuration (C_4)
a	Me	$PhCH_2$	53	-65.6	R
b	$PhCH_2$	Me	68	+64.8	S
c	$PhCH_2$	allyl	47	+49.0	R
d	Me	CH_2CH_2OAc	71	-28.4	R

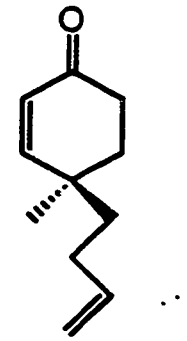
The absolute configuration of each cyclohexenone follows from that of the starting dialkylated lactam. On several occasions, the configurational assignment has been further verified by transforming the enone to a target compound with established absolute stereochemistry.

As illustrated by the foregoing discussion, the elegant procedure developed by Meyers *et al.* provides an efficient general entry to chiral 4,4-disubstituted 2-cyclohexenones with a high level of stereocontrol and predictability. As described in the preceding chapter, the first total synthesis of the acetylenic nor-

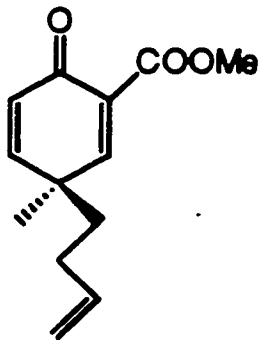
sesquiterpene dehydrochamaecynenol **93** in racemic form has been effected using a recently developed polyene cyclization process. In this synthesis, the racemic enone **16**, prepared from 3-ethoxy-6-methyl-2-cyclohexenone, was converted to enone ester **10**. Upon treatment with zinc iodide, this compound was found to undergo facile cyclization leading to the key synthetic intermediate **18**, which was subsequently transformed to (±)-**93** by an array of rather standard synthetic operations.



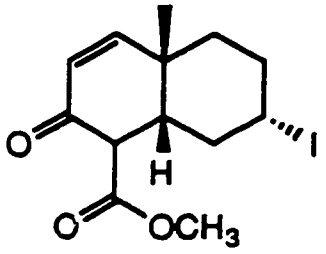
(-)-dehydrochamaecynenol **93**



(R)-**16**



10



18

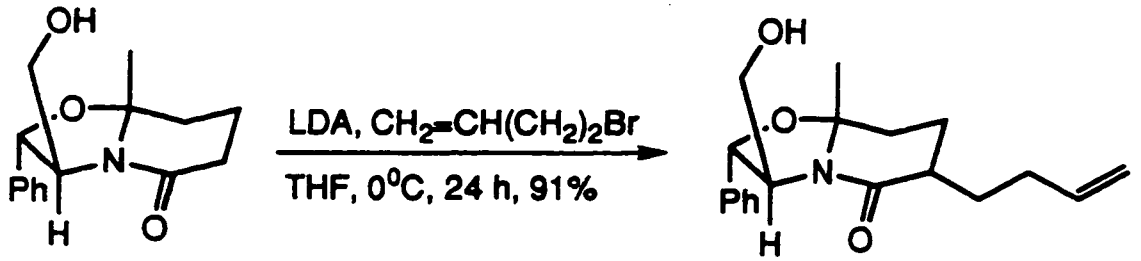
As far as the stereochemistry is concerned, the synthesis involves the overall transfer of the chiral center of enone **16** to the C_1 center of the target compound with retention of configuration. Accordingly, applying the same synthetic sequence with the (R)-enantiomer of enone **16** should result in the total

synthesis of dehydrochamaecynenol in the natural form. In this chapter, the successful preparation of the R enantiomer of enone **16**, using Meyers' general approach, and its transformation *via* polyene cyclization, to an advanced intermediate towards (-)-dehydrochamaecynenol are described.

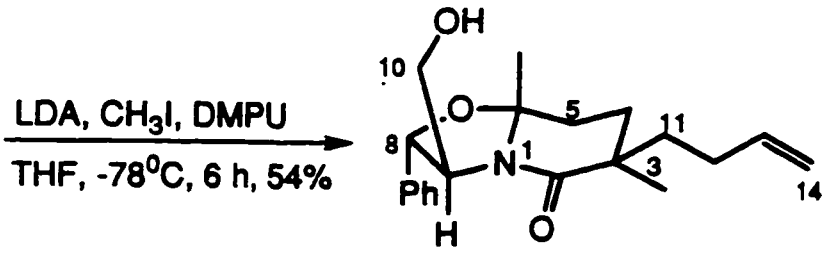
Results and Discussion

1. Preparation of (R)-(+)-4-(3-butenyl)-4-methyl-2-cyclohexenone [(+)-16)]

The preparation of the (R)-enantiomer of **16** started with a double alkylation of lactam **112** (Scheme 42). This lactam, which was obtained from the Aldrich Chemical Co., had an optical purity of 98%. Alkylation of **112** with LDA and 4-bromo-1-butene at 0°C for 24 h gave the monoalkylated lactam **119** as a mixture of two diastereomers in 91% yield. This mixture was subjected to a second alkylation with LDA and methyl iodide at -78°C for 6 h to afford the dialkylated lactam **120** as the only detectable diastereomer (*endo* isomer) in 54% yield. It was purified by flash chromatography on silica gel and displayed a specific rotation of $[\alpha]^{D}_{20}$ -9.5° (c 0.76, EtOH). The diastereoselectivity as indicated by the ^{1}H nmr spectrum was greater than 95%.



112 **119**



120

Scheme 42

Table 10. ^1H nmr Data of compound **120**

δ (ppm)	Multiplicity (J in Hz)	Proton
7.42-7.25	br s	5 x aromatic H
5.85	dddd (17, 10, 6.5, 6.5)	H_{13}
5.07	dddd (17, 1.5, 1.5, 1.5)	H_{14a}
4.98	dddd (10, 1.5, 1.5, 1.5)	H_{14b}
4.81	d (8.5)	H_8
4.39	br s	OH
4.11	ddd (8.5, 8.5, 2.5)	H_9
3.92	dd (11, 2.5)	H_{10a}
3.76	dd (11, 8.5)	H_{10b}
2.30-1.45	m	4 x CH_2
1.60	s	C_6-Me
1.25	s	C_3-Me

The ir spectrum of this compound showed absorptions at 3479 cm^{-1} for the hydroxyl group and 1641 cm^{-1} for the lactam. The mass spectrum displayed a

molecular ion peak at m/z 329.1995, which was in agreement with the expected molecular formula $C_{20}H_{27}O_3N$. The molecular composition was also confirmed by elemental analysis. To assign all the protons of compound **120** , a number of ^1H decoupling experiments were carried out. The ^1H nmr data of compound **120** is shown in Table 10. The ^{13}C APT nmr spectrum confirmed the presence of the lactam carbonyl group by a signal at δ 176.3 and eight *sp*^{2} carbons by signals between δ 138.1 and 114.9.

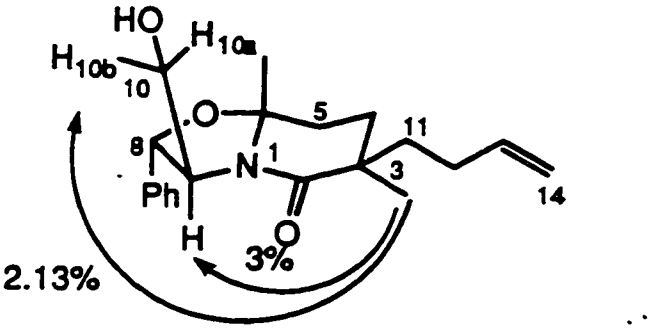


Figure 15. NOE data of compound **120**

NOE experiments were carried out in an attempt to verify the stereochemistry of the newly introduced chiral center. The results were, however, unclear. Irradiation of the C_3 methyl at δ 1.25 gave rise to a 3% enhancement of H_9 as expected. However, an enhancement of 2.13% was also observed for H_{10b} (Figure 15). Since these enhancements were independent of lactam concentration, this ambiguity might have arisen from intramolecular hydrogen bonding between the hydroxyl group and the lactam carbonyl. To suppress the hydrogen bonding, hydroxy lactam **120** was converted to the corresponding methyl ether **121** by treatment with methyl iodide and sodium hydride at room temperature overnight. Compound **121**, thus obtained in 95% yield, displayed a specific rotation of $[\alpha]^{20}_D$ -10.0^0 (c 0.76, EtOH) and a mp of 83-84^{0}C. The ir spectrum showed a lactam carbonyl absorption at 1641 cm^{-1}. A molecular ion

Table 11. ^1H nmr Data of compound **121**

δ (ppm)	Multiplicity (J in Hz)	Proton
7.42-7.25	br s	5 x aromatic H
5.82	dddd (17, 10, 6.5, 6.5)	H_{13}
5.25	d (8.5)	H_8
5.04	dddd (17, 1.5, 1.5, 1.5)	H_{14a}
4.96	dddd (10, 1.5, 1.5, 1.5)	H_{14b}
4.11	ddd (8.5, 4.5, 2.5)	H_9
3.74	dd (10, 4.5)	H_{10a}
3.65	dd (10, 3)	H_{10b}
3.48	s	OMe
2.30-1.45	m	4 x CH_2
1.61	s	C_6-Me
1.27	s	C_3-Me

peak at m/z 343.2156 was observed in the high resolution mass spectrum, corresponding to the molecular formula $C_{21}H_{29}O_3N$. The ^1H nmr spectrum exhibited a methoxy singlet at δ3.48, indicating that the protection had taken

place. To assign conclusively all protons of compound **121**, extensive ^{1}H decoupling experiments were carried out and a complete spectral assignment was achieved (Table 11). In the ^{13}C APT nmr spectrum, a signal due to the lactam carbonyl group was observed at δ 174.3 and eight *sp²* carbons appeared between δ 139.4 and 114.7.

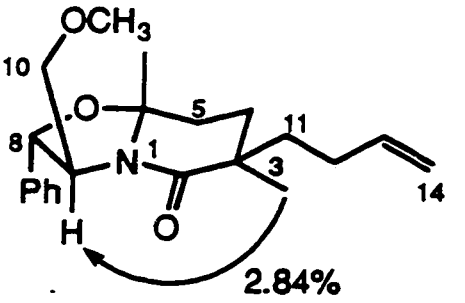
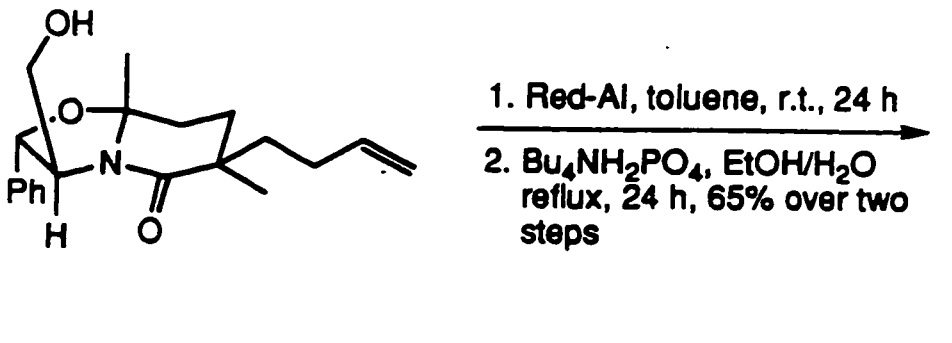


Figure 16. NOE data of compound **121**

In order to confirm the stereochemistry of compound **121**, NOE experiments were carried out. As shown in Figure 16, saturation of the signal at δ 1.27 (C_3-Me) resulted in an NOE enhancement of 2.84% for the signal at δ 4.11 (H_9). The signals at 3.74 (H_{10a}), 3.65 (H_{10b}) and 1.61 (C_6-Me) were unaffected. These results were in agreement only with the depicted stereochemistry.



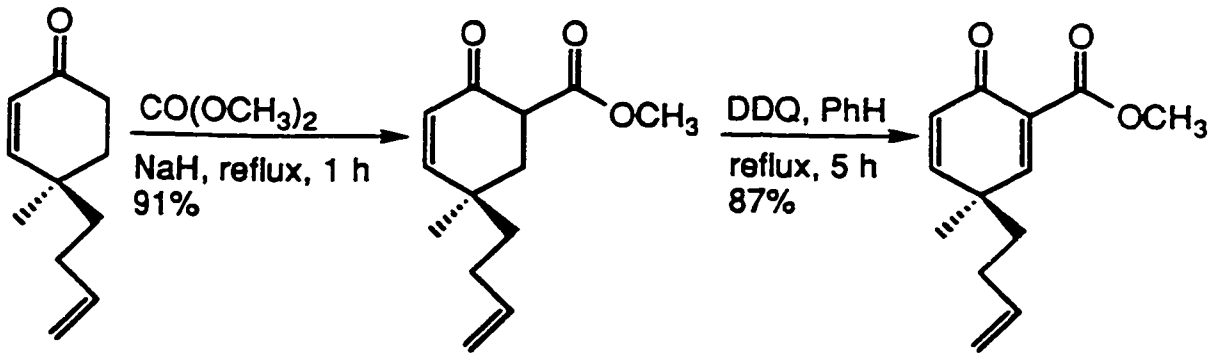
12 **(R)-16**

Scheme 43

With lactam **120** in hand, we were ready to prepare the non-racemic enone **16**. A two-step synthetic sequence was required, involving reduction of the lactam carbonyl group and hydrolysis of the bicyclic system with concomitant aldol condensation (Scheme 43). Reduction of **120** with Red-Al in toluene at room temperature for 24 h gave the α-hydroxy amine which, without purification, was subjected to treatment with $Bu_4NH_2PO_4$-H_2O-EtOH to afford the (R)-enantiomer of enone **16** in 65% overall yield . This compound displayed a specific rotation of $[\alpha]^{20}_D$ +75.7^0 (c 1.50, EtOH). Its spectral data (ir, hrms and ^{1}H nmr) were found to be identical to those reported for the corresponding racemate (Chapter 1).

2. Preparation of the key intermediate (-)-18

The optically active enone ester **10** required for the polyene cyclization was prepared by a two-step operation involving carbomethoxylation and oxidation (Scheme 44). The carbomethoxylation was effected by treating (+)-**16** with sodium hydride and dimethyl carbonate. After heating under reflux for 1 h, the non-racemic keto ester **17** was obtained in 91% yield. This compound showed a specific rotation of $[\alpha]^{20}_D$ +96.1^0 (c 1.80, EtOH). Its spectral data (ir, hrms and ^{1}H nmr) were shown to be identical to those reported in Chapter 1 for the corresponding racemic mixture. Dehydrogenation of (+)-**17** with DDQ in refluxing benzene afforded enone ester (+)-**10**, $[\alpha]^{20}_D$ +27.8^0 (c 1.60, EtOH), in 87% yield. Its structure was readily confirmed by comparison of its spectral data (ir, hrms, ^{1}H and ^{13}C APT nmr) with those obtained for the corresponding racemate (Chapter 1).

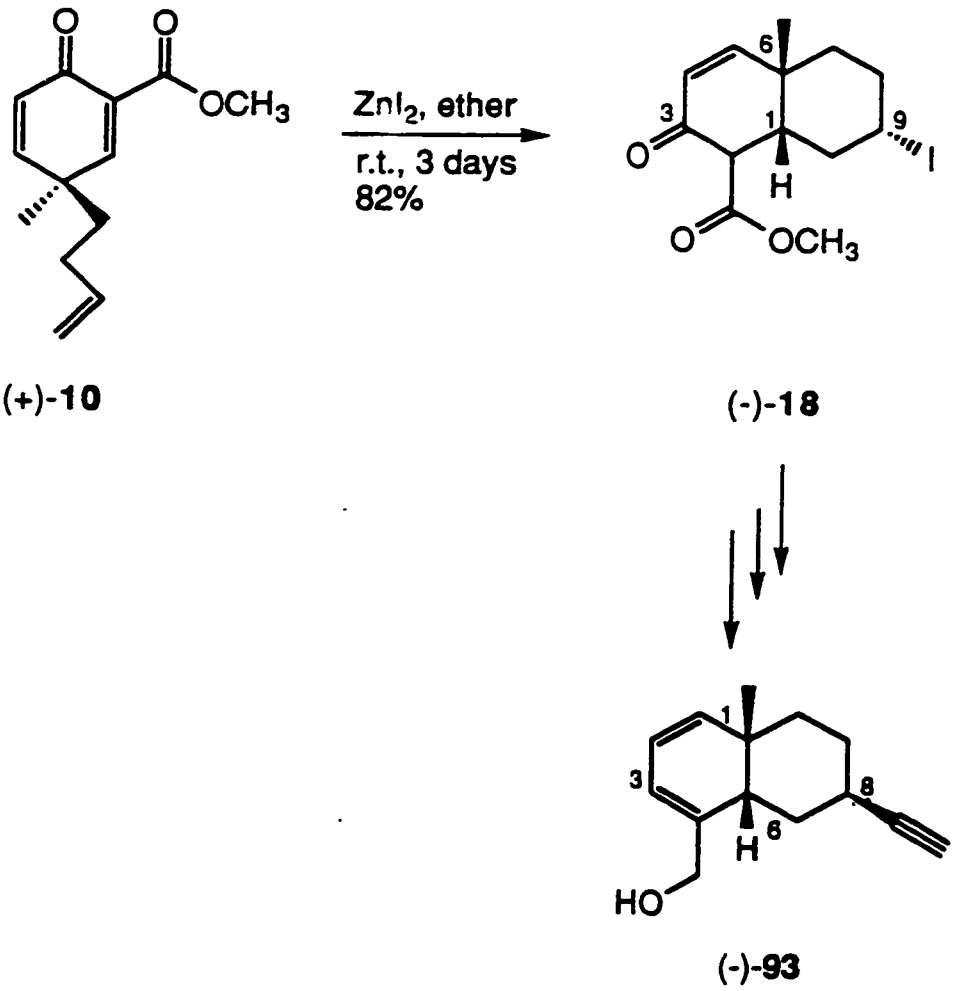


(+)-**16** (+)-**17** (+)-**10**

Scheme 44

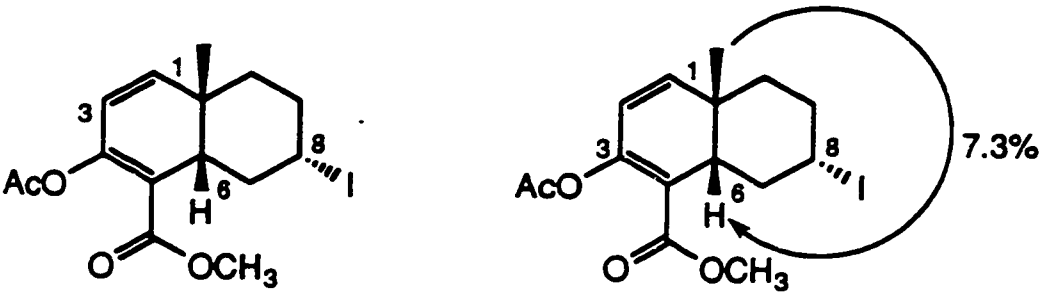
Having successfully prepared enone ester (+)-**10**, we were ready to carry out the polyene cyclization which was presented in the previous chapters. When (+)-**10** was treated with zinc iodide at room temperature for 3 days, it gave in 82% yield, the optically active iodide **18**, an advanced intermediate for the synthesis of (-)-dehydrochamaecynenol (Scheme 45). Iodide **18** displayed a specific rotation of $[\alpha]^{20}_{D}$ -142.4° (c 0.70, EtOH) and showed spectral data (ir, hrms, ^{1}H and ^{13}C APT nmr) in agreement with those observed for the corresponding racemic mixture (Chapter 1).

The structure of (-)-**18**, which is quite labile due to the presence of the β-keto ester moiety, was further confirmed as follows. Treatment of (-)-**18** with acetic anhydride in pyridine gave the corresponding enol acetate (-)-**21**, which showed spectral data (ir, hrms, ^{1}H and ^{13}C APT nmr) identical to those reported for the corresponding racemate (Chapter 1) and a specific rotation $[\alpha]^{20}_{D}$ -200.2° (c 2.60, EtOH). A NOE experiment performed on (-)-**21** provided evidence for the *cis* ring junction. As shown in Figure 17, irradiation of the signal at δ 0.95 resulted in an enhancement of 7.3% for the signal at δ 2.60 (H_6).



(+)-**10** (-)-**18** (-)-**93**

Scheme 45



(-)-**21** **Figure 17.** NOE data of (-)-**21**

In conclusion, the work presented in this chapter led to the successful preparation of (+)-enone **16** with high optical purity, making use of Meyers' general approach to optically active 4,4-disubstituted cyclohexenone. By the

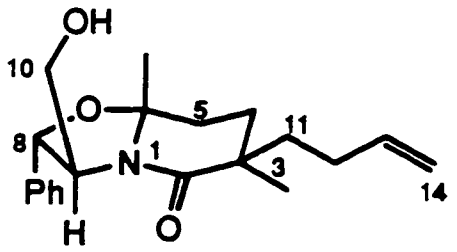
polyene cyclization process recently developed in our laboratory, (+)-**16** was further transformed to (-)-iodide **18**, the racemic modification of which had served as an advanced intermediate in the total synthesis of (±)-dehydrochamaecynenol **93** carried out also in our laboratory. Accordingly, a formal synthesis of the naturally occurring (-)-dehydrochamaecynenol has been effected.

Experimental

General and materials

For general procedures and materials used in Chapter 3, refer to Chapter 1 of this thesis.

(3S, 6R, 8S, 9R)-1-Aza-3-(3-butenyl)-9-(hydroxymethyl)-3,6-dimethyl-8-phenyl-7-oxabicyclo[4.3.0]nonan-2-one (120)



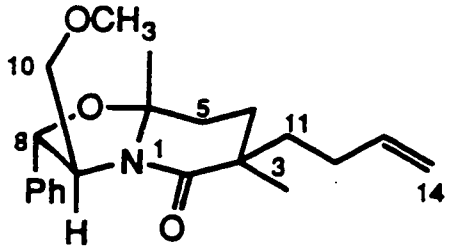
To a stirred solution of diisopropylamine (3.3 mL, 25.2 mmol) in dry THF (25 mL) under argon at 0°C, was added dropwise *n*-BuLi (8.8 mL, 2.5 M in hexane, 22 mmol). After being stirred for 20 min at 0°C, the solution was cooled to -78°C. A solution of lactam **112** (2 g, 7.8 mmol) in THF (5 mL) was added *via* syringe. The solution was immediately warmed to 0°C, stirred for 2 h and then cooled again to -78°C. 4-Bromo-1-butene (2.4 mL, 24.2 mmol) was added. After being stirred for 15 min at -78°C, the solution was warmed to 0°C and stirred at this temperature overnight. The reaction was quenched with 1 N HCl (20 mL) and the resulting mixture concentrated *in vacuo* to remove THF. The acidic aqueous layer was extracted with dichloromethane, and the combined organic solutions were then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil which was subjected to flash chromatography.

Elution with ethyl acetate/hexane (60:40) gave a mixture of two diastereomeric monoalkylated lactams (1.1 g, 91% yield based on the consumed starting material), which was used directly for the subsequent transformation. Further elution with the same solvent system gave the starting material (1 g).

To a stirred solution of diisopropylamine (1.7 mL, 12 mmol) in dry THF (20 mL) under argon at 0^0C, was added *n*-BuLi (4.4 mL, 2.5 M in hexane, 11 mmol). After being stirred at 0^0C for 15 min, DMPU (10 mL) was added. The solution was cooled to -78^0C, and a solution of the above monoalkylated lactams (1.1 g, 4 mmol) in THF (4 mL) was added. The reaction mixture was warmed to 0^0C, stirred for 3 h and then cooled to -78^0C. Iodomethane (0.75 mL, 12 mmol) was added. After being stirred for 20 min, the reaction mixture was warmed to room temperature, and stirred overnight. The reaction was quenched with 1 N HCl, and the resulting mixture concentrated *in vacuo* to remove THF. The aqueous layer was extracted with diethyl ether. The combined organic solutions were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow liquid. Flash chromatography of the liquid with ethyl acetate/hexane (50:50) gave lactam **120** as a white solid and then the starting material (200 mg). Recrystallization from ethyl acetate/hexane gave pure lactam **120** (0.5 g, 54% based on the consumed starting material): mp 169-171^{0}C; $[\alpha]_D^{20}$ = -9.5^0 (c 1.55, EtOH); ir (uscope) 3439 (OH) and 1641 (C=O) cm^{-1}; ^{1}H nmr (300 MHz) δ 7.42-7.25 (m, 5H, aromatic **H**), 5.85 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, C**H**=CH_2), 5.07 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.98 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=C**H**H), 4.81 (d, J = 8.5 Hz, 1H, H_8), , 4.39 (br s, 1H, O**H**), 4.11 (ddd, J = 8.5, 8.5, 2.5 Hz, 1H, H_9), 3.92 (dd, J = 11, 2.5 Hz, 1H, H_{10a}), 3.76 (dd, J = 11, 8.5 Hz, 1H, H_{10b}), 1.45-2.30 (m, 8H), 1.60 (s, 3H, C_6-C**H**$_3$), 1.25 (s, 3H, C_3-C**H**$_3$); ^{13}C nmr (300 MHz) δ 176.3 (p), 138.1 (a), 137.9 (p), 128.9 (a), 128.8 (a, 2 x **C**), 126.7 (a, 2 x **C**), 114.9 (p), 94.0 (p), 78.6

(a), 67.1 (a), 65.4 (p), 41.7 (p), 39.6 (p), 32.7 (p), 29.5 (p), 28.9 (p), 26.5 (a), 24.5 (a); hrms M^+ 329.1995 (calcd. for $C_{20}H_{27}O_3N$: 329.1991). Anal. calcd. $C_{20}H_{27}O_3N$: C 72.92, H 8.26; found: C 72.52, H 8.63.

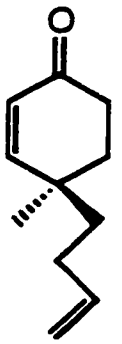
(3S, 6R, 8S, 9R)-1-Aza-3-(3-butenyl)-9-(methoxymethyl)-3,6-dimethyl-8-phenyl-7-oxabicyclo[4.3.0]nonan-2-one (121)



To a stirred suspension of bicyclic lactam **120** (165 mg, 0.5 mmol) in THF (10 mL) at 0°C under argon, were added NaH (25 mg, 95%, 1 mmol) and iodomethane (0.06 ml, 1 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was then quenched with saturated NH_4Cl. The aqueous solution was extracted with diethyl ether (3 x 30 mL). The combined organic solutions were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to afford lactam **121** (163 mg, 95%) as a white solid: mp 83-84°C; $[\alpha]_D^{20}$ = -10.0° (c 0.76, EtOH); ir (CH_2Cl_2) 1641 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ 7.42-7.25 (m, 5H, aromatic **H**), 5.82 (dddd, J=17, 10, 6.5, 6.5 Hz, 1H, $CH=CH_2$), 5.25 (d, J = 8.5 Hz, 1H, H_8), 5.04 (dddd, J=17, 1.5, 1.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 4.96 (dddd, J=10, 1.5, 1.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 4.11 (ddd, J = 8.5, 4.5, 3 Hz, 1H, H_9), 3.74 (dd, J = 10, 4.5 Hz, 1H, H_{10a}), 3.65 (dd, J = 10, 3 Hz, 1H, H_{10b}), 3.48 (s, 3H, OCH_3), 1.45-2.30 (m, 8H), 1.61 (s, 3H, C_6-CH_3), 1.27 (s, 3H, C_3-CH_3); ^{13}C

nmr (300 MHz) δ 174.3 (p), 139.4 (p), 138.4 (a), 128.6 (a), 128.3 (a, 2 x **C**), 126.7 (a, 2 x **C**), 114.7 (p), 93.7 (p), 78.8 (a), 71.0 (a), 63.3 (p), 59.3 (a), 41.9 (p), 40.1 (p), 33.0 (p), 29.6 (a), 28.9 (p), 26.4 (a), 24.2 (a); hrms M^+ 343.2156 (calcd. for $C_{21}H_{29}O_3N$: 343.2148).

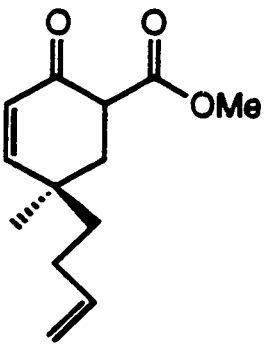
(R)-4-(3-Butenyl)-4-methyl-2-cyclohexenone (16)



To a stirred solution of the dialkylated lactam **120** (1.3 g, 3.9 mmol) in dry toluene (20 mL) at -78°C under argon, was added a 3.4 M solution of Red-Al in toluene (2.87 mL, 9.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 hr. Methanol was cautiously added with stirring to destroy excess Red-Al. The resulting solution was extracted with diethyl ether (3 x 100 mL). The combined organic solutions were washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was dissolved in ethanol (25 mL), a 1 M aqueous solution of tetra-*n*-butylammonium dihydrogen phosphate (15 mL) was added, and the resulting mixture was heated under reflux with stirring for 24 h. The solution was cooled and concentrated to remove most of the ethanol. The residue was extracted with diethyl ether (3 x 100 mL). The combined extracts were washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was subjected to flash chromatography using ethyl acetate/hexane (5:95) as an

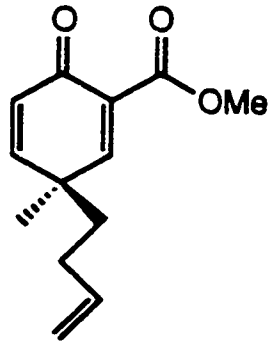
eluent to give (+)-**16** (0.42 g, 65%) as a colorless oil: $[\alpha]_D^{20}$ = + 75.7° (c 1.50, EtOH). Its spectral data (ir, hrms and ^{1}H nmr) are identical to those reported in Chapter 1 for the corresponding racemic mixture.

(4R)-(3-Butenyl)-6-carbomethoxy-4-methyl-2-cyclohexenone (17)



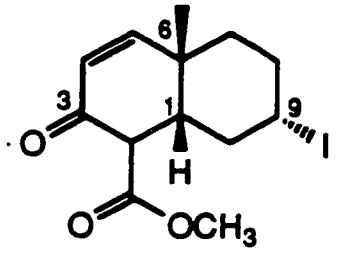
To a stirred suspension of sodium hydride (115 mg, 95%, 4.6 mmol) in dry dimethyl carbonate (7 mL) at room temperature under argon, was added a solution of (+)-**16** (300 mg, 1.83 mmol) in dimethyl carbonate (3 mL). The reaction mixture was refluxed for 1 h and then cooled to 0°C. A 1 N HCl solution (10 mL) was added cautiously to the mixture. The resulting mixture was extracted with diethyl ether (3 x 50 mL). The combined extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography with ethyl acetate/hexane (5:95) to afford (+)-**17** (368 mg, 91%) as a yellowish oil: $[\alpha]_D^{20}$ = + 96.1° (c 1.80, EtOH). Its spectral data (ir, hrms and ^{1}H nmr) are identical to those reported in Chapter 1 for the corresponding racemic mixture.

(S)-4-(3-Butenyl)-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (10)



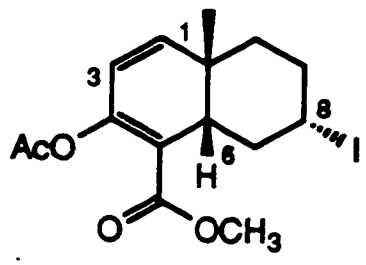
To a solution of (+)-**17** (200 mg, 0.9 mmol) in dry benzene (10 mL) at room temperature under argon, was added DDQ (407 mg, 1.8 mmol). The mixture was stirred for 15 min, and then refluxed for 5 h. The reaction mixture was cooled and concentrated. The precipitate was removed by filtration after chloroform (15 mL) was added to the residue. The filtrate was concentrated and the residue was subjected to flash chromatography with ethyl acetate/hexane (20:80) to give (+)-**10** (173 mg, 87%): $[\alpha]_D^{20}$ =+ 27.8^0 (c 1.60, EtOH). Its spectral data (ir, hrms, ^{1}H and ^{13}C APT nmr) are identical to those reported in Chapter 1 for the corresponding racemic mixture.

(1R, 6R, 9S)-2-Carbomethoxy-9-iodo-6-methylbicyclo[4.4.0]dec-4-en-3-one (18)



To a stirred suspension of anhydrous zinc iodide (80 mg, 0.26 mmol) in dry diethyl ether (10 mL) at room temperature under argon, was added a solution of (+)-**10** (46 mg, 0.21 mmol) in diethyl ether (5 mL). The reaction flask was protected from light. The reaction mixture was stirred for 3 days, A 1 N HCl solution (20 mL) was added. The resulting mixture was extracted with diethyl ether (3 x 50 mL). The extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (5:95) to afford the bicyclic iodide **18** (60 mg, 82%): $[\alpha]_D^{20}$ =-142.4^0 (c 0.70, EtOH). Its spectral data (ir, hrms, ^1H and ^{13}C APT nmr) are identical to those reported in Chapter 1 for the corresponding mixyure.

(1S, 6R, 8S)-4-Acetoxy-5-carbomethoxy-8-iodo-1-methylbicyclo-[4.4.0]deca-2,4-diene (21)



To a solution of (-)-**18** (50 mg, 0.14 mmol) in pyridine (2 mL) at room temperature under argon, was added acetic anhydride (0.5 mL). The reaction mixture was stirred overnight. Pyridine was removed under reduced pressure. The residue was extracted with diethyl ether (3 x 50 mL). The extracts were washed with 1N hydrochloric acid and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography of the residue with ethyl acetate/hexane (5:95) gave enol acetate **21** (49.9 mg, 89%): $[\alpha]_D^{20}$ =-200.2 ^{0} (c 2.60, EtOH). Its

spectral data (ir, hrms, ^{1}H and ^{13}C APT nmr) are identical to those reported in Chapter 1 for the corresponding racemic mixture.

References

1. Barlett, P. A. In *Asymmetric Synthesis*; J. D. Morrison, Ed.; Academic Press: Orlando, 1984; Vol. 3; pp.341-409.
2. Sutherland, J. K. In *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency*; I. Flemming, Ed.; Pergamon Press: Oxford, 1991; Vol. 3; pp. 341-377.
3. Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51-98.
4. Vandewalle, M.; Clerq, P. D. *Tetrahedron* **1985**, *41*, 1767.
5. Eschenmoser, A.; Ruzicka, L.; Jerger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
6. Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068.
7. Mann, J. *Secondary Metabolism*; 2nd ed.; Oxford University Press: Oxford, 1987, p. 374.
8. Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191.
9. Stadler, P. A.; Nechuatal, A.; Frey, J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373.
10. van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 1.
11. van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152.
12. Goldsmith, D. J.; Philips, F. *J. Am. Chem. Soc.* **1969**, *91*, 5862.
13. van Tamelen, E. E.; Freed, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 7206.
14. van der Gen, A.; Weidhaup, K.; Swoboda, J. J.; Dunathan, H.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 2656.
15. Majetich, G.; Khetani, V. *Tetrahedron Lett.* **1990**, *31*, 2243.
16. Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5873.

17. Marshall, J. A.; Wuts, P. G. A. *J. Org. Chem.* **1977**, *42*, 1794.

18. Cooper, J. L.; Harding, K. E. *Tetrahedron Lett.* **1977**, 3321.

19. Dastur, K. P. *J. Am. Chem. Soc.* **1974**, *96*, 2605.

20. Andersen, N. H.; Uh, H. S. *Tetrahedron Lett.* **1973**, 2079.

21. Naegeli, P. *Tetrahedron Lett.* **1978**, 2127.

22. Grutter, H.; Vogt, H. R.; Schinz, H. *Helv. Chim. Acta* **1954**, *37*, 1791.

23. Grutter, H.; Schinz, H. *Helv. Chim. Acta* **1952**, *35*, 1656.

24. Kappeler, H.; Schinz, H.; Eschenmoser, A.; Stauffacher, D. *Helv. Chim. Acta* **1954**, *37*, 957.

25, Semenovskii, A. V.; Smit, V. A.; Chernova, T. N.; Kucherov, V. F. *Izv. Akad. Nauk. SSSR, Ser. Kim.* **1965**, 1068.

26. Schinzer, D.; Ringe, K. *Synlett* **1994**, 463.

27. Kende, A. S.; Fludzinski, P. *Org. Synth.* **1985**, *64*, 68.

28. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

29. Orr, J. C.; de la Roz, A.; Bowers, A. *J. Org. Chem.* **1964**, *29*, 3300.

30. Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* **1978**, 3455.

31. Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.

32. Edwards, J. A.; Orr, J. C.; Bowers, A. *J. Org. Chem.* **1962**, *27*, 3378.

33. Mahoney, W. S.; Brestensky, D M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

34. Trost, B. M.; Ornstein, P. L. *J. Org. Chem.* **1983**, *48*, 1131.

35. Shubin, V. G.; Korchagina, D. V.; Borodkin, G. I.; Derendjaev, B. G.; Koptyug, V. A. *J. Chem. Soc. D* **1970**, 696.

36. Bachmann, W. E.; Ferguson, J. W. *J. Am. Chem. Soc.* **1934**, *56*, 2081.

37. Roa, F. Ph.D. Thesis, University of Alberta, **1997**.

38. Alami, M.; Marquais, S.; Cahiez, G. *Org. Synth.* **1995**, *72*, 135.

39. Nemoto, H.; Shikari, M.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 10391.

40. Lin, H. S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

41. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identication of Organic Compounds*; 4th ed.; John Wiley & Sons, Inc.; New York, 1981.

42. Ruzicka, L. *Experientia* **1953**, *9*, 357.

43. Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. chim. Acta.* **1955**, *38*, 1890.

44. Hendrickson, J. B. *Tetrahedron* **1959**, *7*, 82.

45. Hortmann, A. G. *Tetrahedron lett.* **1968**, 5785.

46. Nakatsaka, T.; Hirose, Y. *Bull. Agric. Chem. Soc. Jap.* **1956**, *20*, 215.

47. Ziffer, H.; Batterham, T. J.; Weise, V.; van Rudloff, E. *Tetrahedron* **1964**, *20*, 67.

48. Hortmann, A. G.; De Roos, J. B. *J. Org. Chem.* **1969**, *34*, 736.

49. Ando, M.; Nanaumi, K.; Nakagawa, T.; Asao, T.; Takase, K. *Tetrahedron Lett.* **1970**, 3891.

50. Hortmann, A. G.; Daniel, D. S.; Martinelli, J. E. *J. Org. Chem.* **1973**, *38*, 728.

51. Watt, D. S.; Corey, E. J. *Tetrahedron Lett.* **1972**, 4651.

52. Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794.

53. Sergent, M.; Mongrain, M.; Deslongchamps, P. *Can. J. Chem.* **1972**, *50*, 336.

54. Amano, Y.; Heathcock, C. H. *Can. J. Chem.* **1972**, *50*, 340.

55. Nozoe, T.; Cheng, Y. S.; Toda, T. *Tetrahedron Lett.* **1966**, 3663.

56. Asao, T.; Ibe, S.; Takase, K.; Cheng, Y. S.; Nozoe, T. *Tetrahedron Lett.* **1968**, 3639.

57. Corey, E. J.; Hortmann, A. G. *J, Am. Chem. Soc.* **1965**, *85*, 5736.

58. Saeki, I.; Sumimoto, M.; Kondo, T. *Holzforschung* **1973**, *27*, 93.

59. Nozoe, T.; Asao, T.; Ando, M.; Takase, K. *Tetrahedron Lett.* **1967**, 2821.

60. Harayama, T.; Cho, H.; Inubushi, Y. *Tetrahedron Lett.* **1977**, 3273.

61. Ando, M.; Asao, T.; Hiratsuka, N.; Takase, K.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1980**, 53, 1425.

62. Ganem, B.; Boeckman Jr, R.K. *Tetrahedron Lett.* **1974**, 917.

63. Danishefsky, S.; Nagasawa, K.; Wang, N. *J. Org. Chem.* **1975**, *40*, 1989.

64. Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, 4021.

65. Corey, E.J.; Achiwa, K.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* **1969**, *91*, 4318.

66. Lee, H.; Harvey, R. G. *J. Org. Chem.* **1986**, *51*, 3502.

67. Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.

68. Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776.

69. Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673.

70. Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 56663.

71. Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936.

72. Johnson, C. D. *Chem. Rev.* **1975**, *75*, 755.

73. Meyers, A. I.; Wanner, K. T. *Tetrahedron Lett.* **1985**, *26*, 2047.

IMAGE EVALUATION
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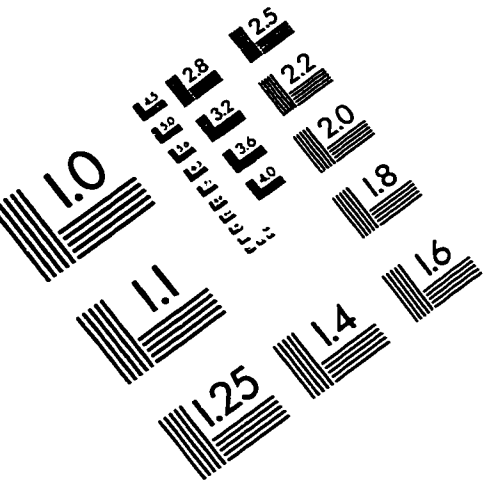

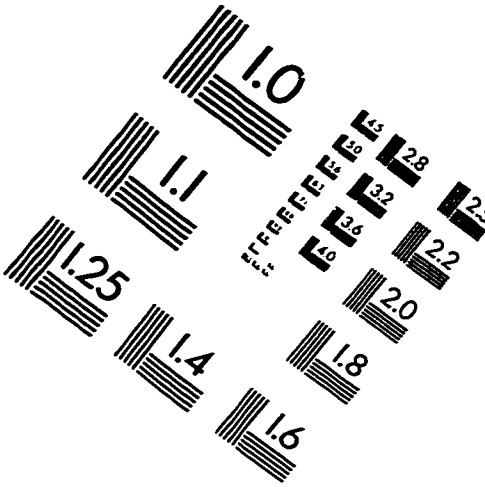

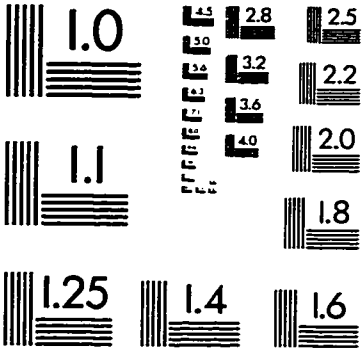

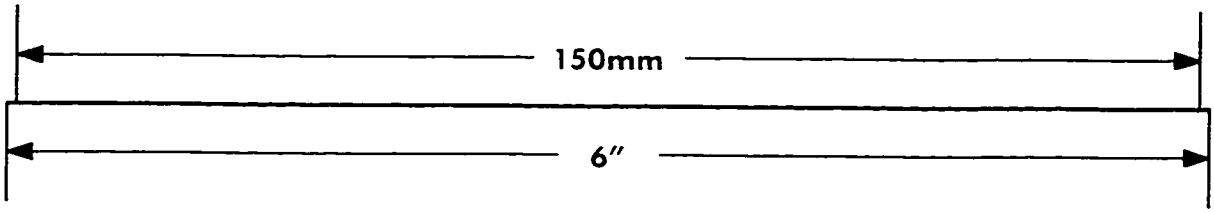

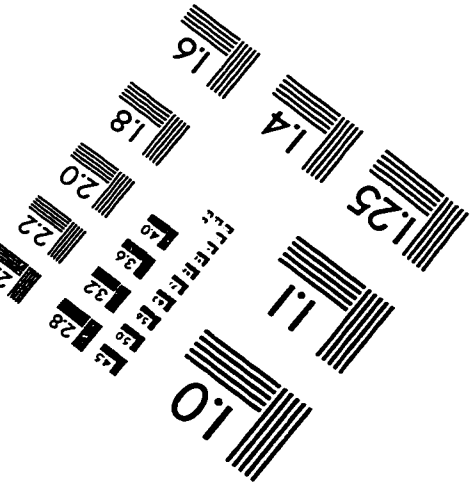

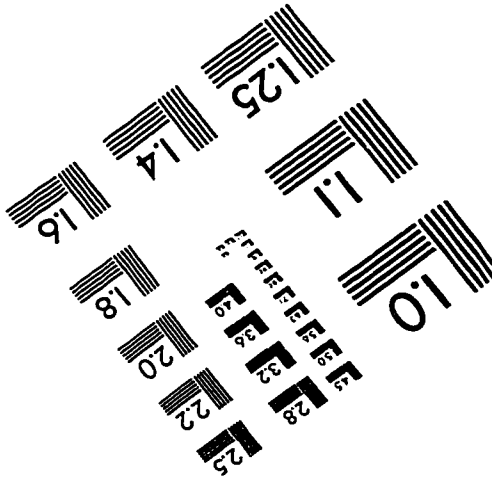

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