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TOTAL SYNTHESES OF (±)-LONGIFOLENE, (+)-QINGHAOSU, AND (-)-QINGHAOSU IV AND DIELS-ALDER REACTIONS OF 2-CARBALKOXY-2-CYCLOHEXEN-1-ONES

BY

WEN-LUNG YEH

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

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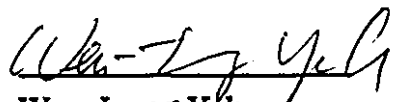

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Date: Nov. 15, 1993

To my wife Esther

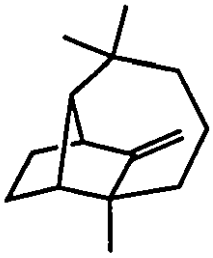
Abstract

The first chapter of this thesis describes the total synthesis of (±)-longifolene (**1**), a tricyclic sesquiterpene which occupies a significant position in natural product chemistry. A formal synthesis of this compound was achieved *via* Johnson intermediate **21**. The synthesis is based on an intermolecular Diels-Alder approach using 6,6-dimethylfulvene and maleic anhydride as the counterparts. Other key steps include cyclodehydration (**50**→**44**), conjugate methylation (**44**→**43**), ring expansion (**43**→**54**+**55**), and Baeyer-Villiger oxidation (**83**→**84**).

The second chapter deals with the total synthesis of (+)-qinghaosu (**89**). This sesquiterpene, which contains some of the most unusual oxygen functionalities among natural products, has been shown to be both fast acting and effective against malaria and to be superior to conventional antimalarial agents such as quinine and chloroquine. The synthesis involves dienone **131** as a key intermediate. This compound, which contains all the carbon units present in qinghaosu, was derived in fourteen steps from the facially selective intermolecular Diels-Alder reaction of enone **133** and isoprene. Dienone **131** was elaborated to give the target molecule *via* several major operations. These include hydrogenolysis to remove the enone oxygen (**131**→**168**), hydroboration to stereoselectively introduce (R)-1-carbomethoxyethyl side chain at C-10 (**169**→**170**), and the final photooxygenation (**168**→**89**).

In the third chapter of the thesis, the total synthesis of (-)-qinghaosu IV (**171**), a natural isomer of qinghaosu, is discussed. Benzoyloxy ester **170**, which was prepared in the previous synthesis, serves as a key compound to promote the synthesis of qinghaosu IV. After exploring several possible routes, the synthesis was accomplished *via* the intermediacy of dihydropyran **173**. This compound was prepared in four steps from acid **193**. Epoxidation and ruthenium tetroxide-oxidation of compound **173** afforded the natural product.

The last chapter is focused on the Diels-Alder chemistry of 2-carbalkoxy-2-cyclohepten-1-ones **254**. The purpose of this work is to develop a facile general approach to the synthesis of polycyclic natural products containing a seven-membered ring. Several compounds of type **254** have been successfully prepared and their Diels-Alder characteristics examined. Substitution pattern on the seven-membered ring was found to greatly effect the Diels-Alder behavior. In addition, some extraordinary facial stereoselectivities were observed.



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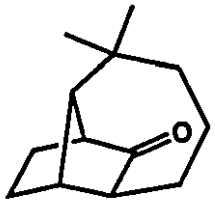

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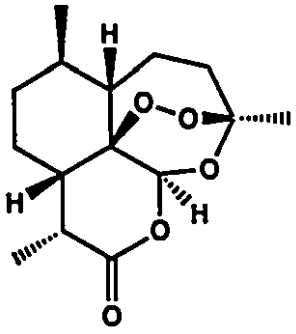

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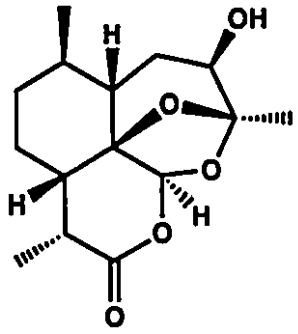

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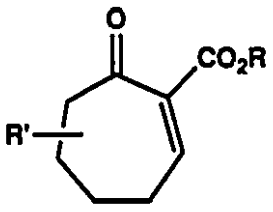

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List of Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
APT	Attached Proton Test
ax	axial
9-BBN	9-Borabicyclo[3.3.1]nonane
Bu	Butyl
Bz	Benzoyl
C	Celsius
c.	concentration
CIMS	Chemical Ionization Mass Spectra
d	doublet
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
e	equatorial
eq.	equivalent
Eq.	Equation
Et	Ethyl
FPP	Farnesyl pyrophosphate
FTIR	Fourier Transform Infrared Spectroscopy
gem	geminal
h	hour
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphorous triamide
i	iso
IR	Infrared
LCIA	Lithium cyclohexylisopropylamide
LDA	Lithium diisopropylamide
m	multiplet

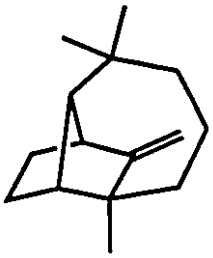
MCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
min	minute
mp	melting point
MS	Mass Spectrum
Ms	Methanesulfonyl
NMMNO	*N*-Methylmorpholine *N*-oxide monohydrate
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
p	para
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
pp	pyrophosphate
Pr	Propyl
p.s.i.	pound per square inch
Py	Pyridine
q	quartet
Ra-Ni	Raney-Nickel
s	singlet
t	triplet
t	tertiary
TFA	Trifluoroacetic acid
TfOTMS	Trimethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPP	Tetraphenylporphine
Ts	*p*-Toluenesulfonyl

Chapter 1

Formal Synthesis of (±)-Longifolene

Introduction

Longifolene (**1**), a tricyclic sesquiterpene, occupies a significant position in natural product chemistry.[1] It is known to occur to the extent of 5-10% in the Indian turpentine oil produced from the oleoresin of *Pinus longifolia* Roxb.[2] In fact, it exists widely in higher plants, mainly in the family Pinaceae. In 1953, the structure of (+)-longifolene was revealed by Moffett's X-ray crystallographic study[3] on the formulation of the hydrochloride derivative (**2**). This was further confirmed by Ourisson's independent chemical studies,[4,5] from which it was recognized that the addition of hydrochloric acid induces a Wagner-Meerwein rearrangement that converts longifolene to its hydrochloride derivative. In the past few decades after its structural elucidation, longifolene continues to attract a great deal of attention, especially on the wide variety of skeletal rearrangements[2,6-9] which give rise to a host of interesting derivatives including isolongifolene (**3**), its natural enantiomer (-)-longifolene,[10] and its congener, longicyclene (**4**). Some of the rearrangements have been applied in the syntheses to be discussed later.



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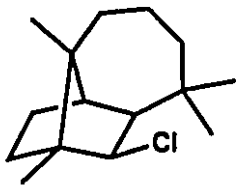

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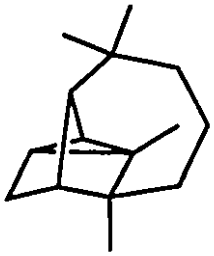

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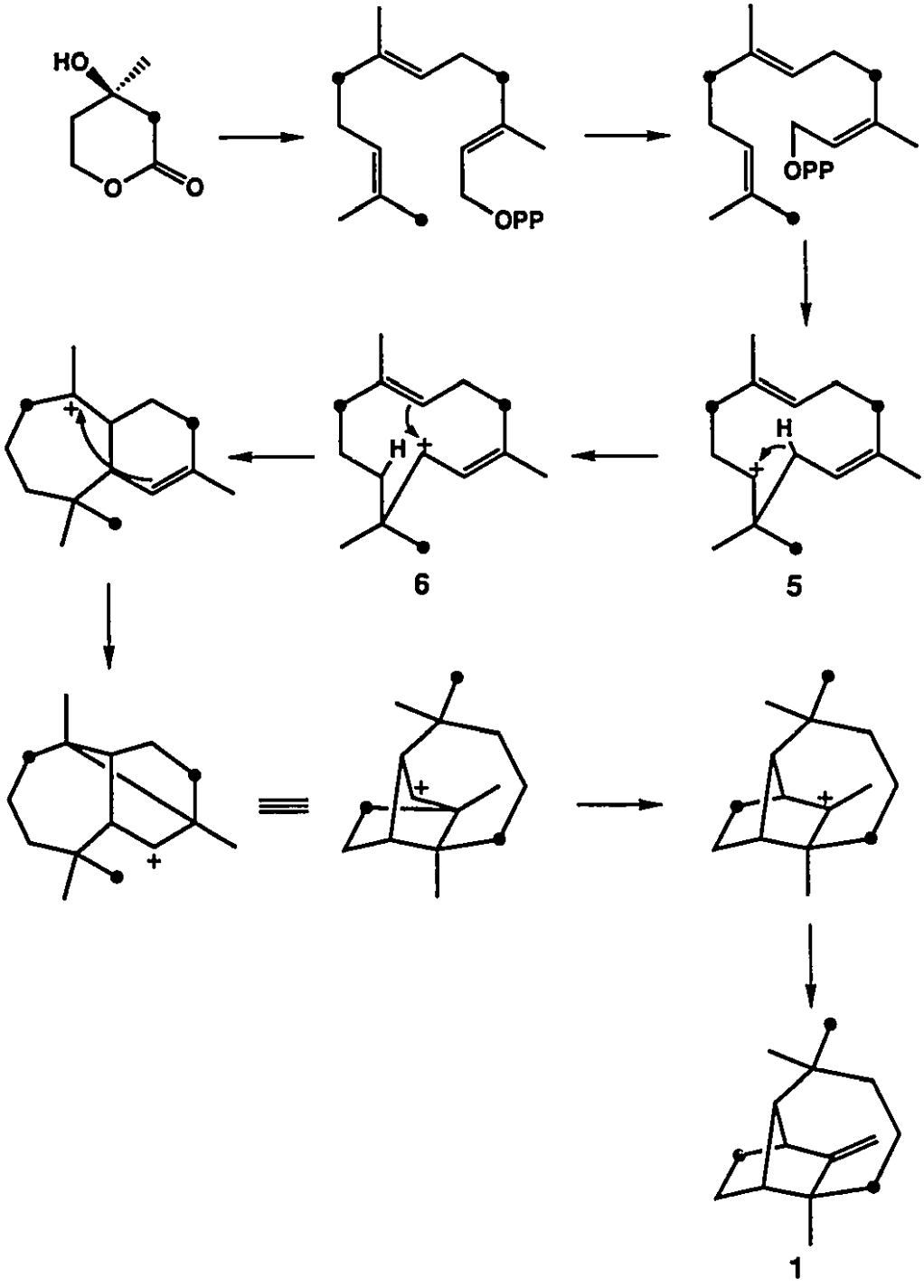
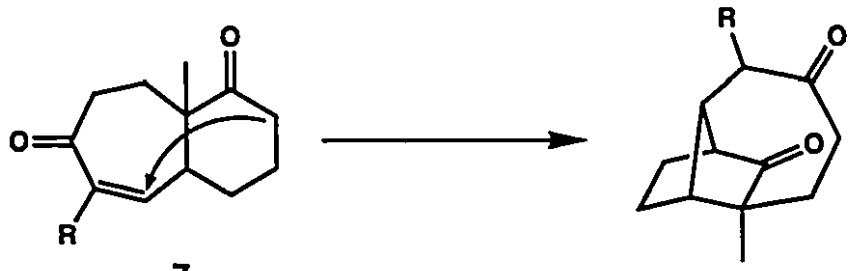
Scheme 1



In the biosynthetic study, the biosynthetic pathway of (+)-longifolene outlined in **Scheme 1** was initially verified by Arigoni's experiment.[11,12] He obtained radioactive longifolene (0.1-0.2% incorporation) when [2-^{14}C]-mevalonate was administered to fresh cuttings of the *Pinus ponderosa* tree. Feeding of specifically tritiated mevalonates resulted in an interesting fact that it is the mevalonoid (5-*pro*-R)-hydrogen which migrates during the 1,3-hydrogen shift (**5**→**6**). However, in the biosynthesis of (-)-longifolene, it is the mevalonoid (5-*pro*-S)-hydrogen which migrates.

Longifolene, containing an intricate tricyclic carbon framework, provides a challenging course in the development of various annelation methodologies. Several groups have been attracted to demonstrate their unique skill and ingenuity to achieve this interesting synthetic task.

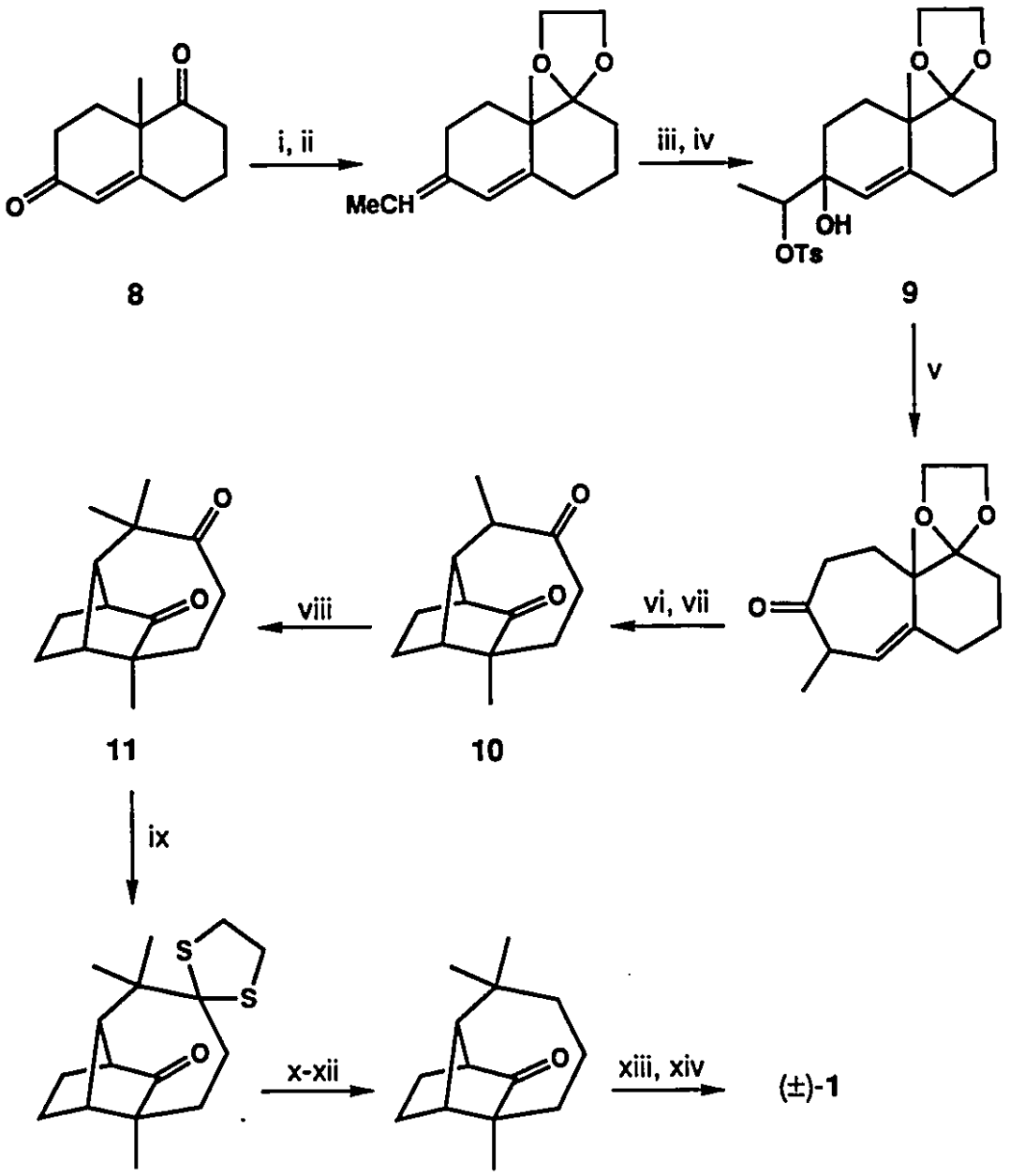
Scheme 2



7

Corey and co-workers[13] accomplished the first total synthesis of racemic longifolene in 1961 by using intramolecular Michael addition of a homodecalin system (**7**) to construct the tricyclic framework (**Scheme 2**). The homodecalin was introduced by a pinacol rearrangement of a decalin derivative **9**, that was readily prepared from the known Wieland-Miescher ketone (**8**) in four steps (**Scheme 3**). The Michael addition was carried out in ethylene glycol containing triethylamine at 225°C for 24 hours. However, the expected tricyclic compound **10** was only obtained in 10-20% yield along with a number of degradation products. After discrete α-

Scheme 3

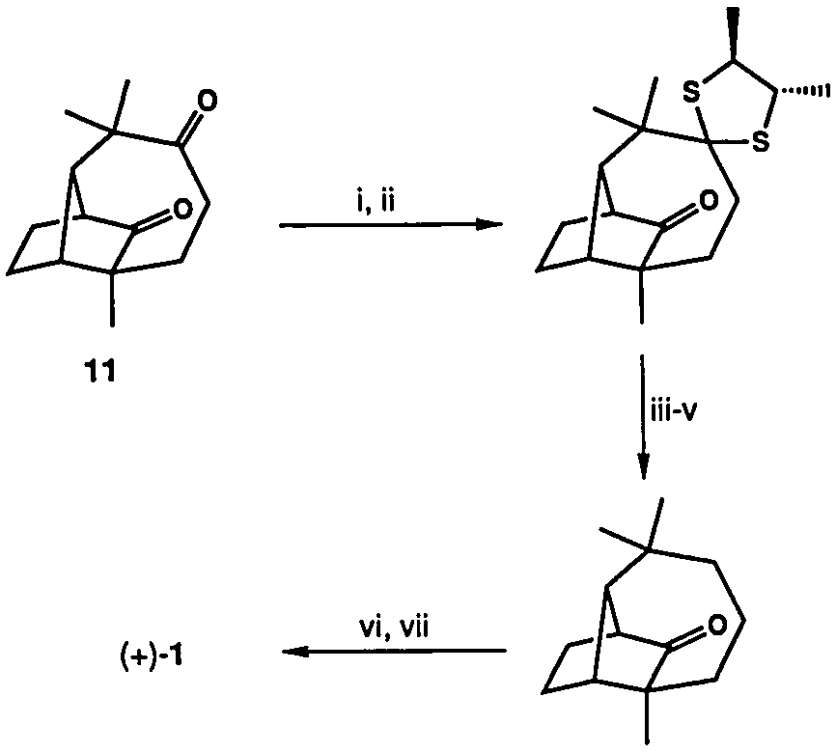


i. $(CH_2OH)_2$, *p*-TsOH; ii. $MeCH{=}PPh_3$; iii. OsO_4; iv. TsCl, Py; v. $LiClO_4$, $CaCO_3$; vi. 2 N HCl; vii. Et_3N, $(CH_2OH)_2$, 225°C; viii. Ph_3CNa, MeI; ix. $(CH_2SH)_2$; x. $LiAlH_4$; xi. Na, $(CH_2OH)_2$, H_2NNH_2; xii. H_2CrO_4; xiii. MeLi; xiv. $SOCl_2$, Py

methylation (**10**→**11**) to provide the desired geminal dimethyl group, the less hindered carbonyl group was thioketalized and ready for removal. The unsuccessful desulfurization, however, forced them to combine the carbonyl reduction and the subsequent Wolff-Kishner reduction to afford the desired product.

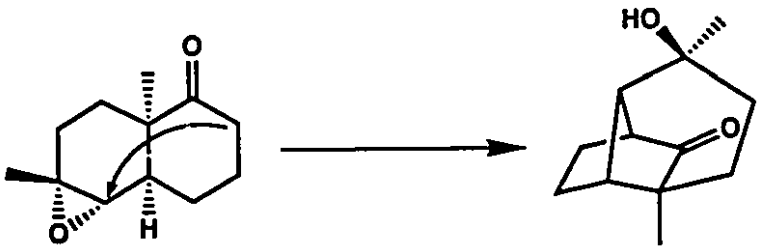
In an extension of this effort, Corey *et al.* further resolved diketone **11** by utilizing L-(+)-2,3-butanedithiol as a protecting group and achieved the total synthesis of optically pure longifolene using the same operations (**Scheme 4**).[14]

Scheme 4



i. L-(+)-2,3-butanedithiol; ii. separation, alumina; iii. $LiAlH_4$; iv. Na, H_2NNH_2, $(CH_2OH)_2$; v. RuO_4; vi. MeLi; vii. $SOCl_2$, Py

Scheme 5



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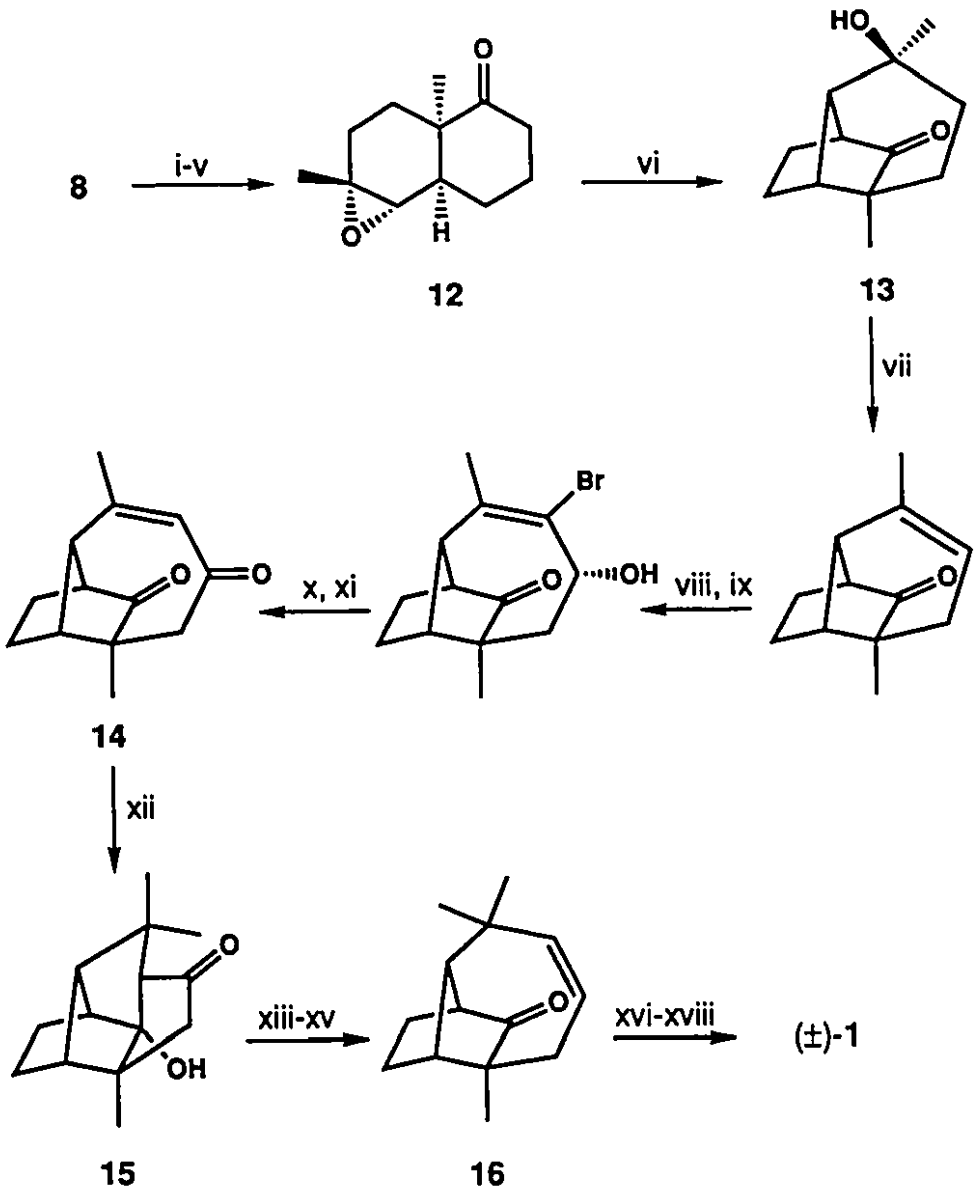
Corey's synthetic strategy was later modified by McMurry and Isser.[15] They improved the yield of the cyclization step to 93% by utilizing intramolecular alkylation of the keto epoxide **12** (**Scheme 5**) and postponed the ring expansion stage. The key intermediate **12** was generated by a five-step sequence, shown in **Scheme 6**, from the same ketone **8** used before. After dehydration of the tricyclic compound **13**, addition of dibromocarbene to the resulting olefin and subsequent solvolysis assisted by silver ion induced the required ring expansion. However, to remove the unwanted bromo and hydroxyl groups required additional steps. Reductive elimination of bromine followed by oxidation of the allylic alcohol afforded the enone **14**, which was ready for the construction of the geminal dimethyl group by 1,4-addition. The resulting tetracyclic intermediate **15** was subjected to a 1,3-glycol cleavage process to give ketone **16**, which was converted to (±)-longifolene without incident.

In 1975, Johnson and co-workers observed the formation of tricyclic alcohols **18** as side products when they examined the stannic chloride-catalyzed cyclization of the heptynylmethylcyclopentenol **17**, in an attempt to develop a new hydroazulene synthesis (**Scheme 7**). Recognizing that **18** possessed the basic carbon skeleton of longifolene, they elaborated an elegant synthesis[16] illustrated in **Scheme 8**.

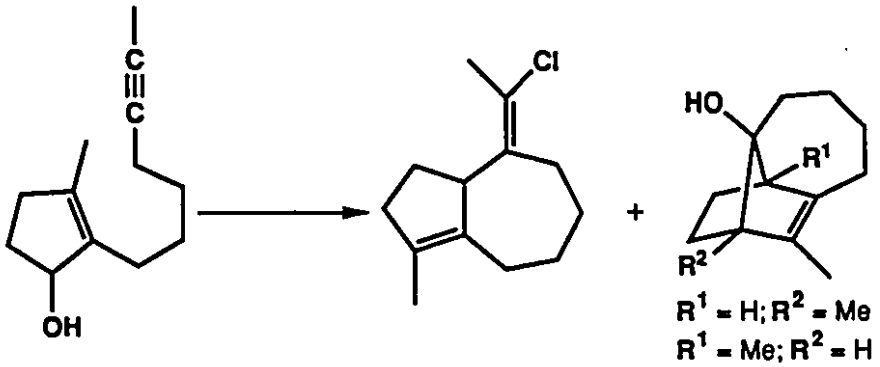
Scheme 6



i. $(CH_2OH)_2$, *p*-TsOH; ii. H_2, Pd; iii. MeMgI; iv. 50% aq. H_2SO_4; v. MCPBA; vi. NaH, DMSO; vii. 50% aq. H_2SO_4; viii. $CHBr_3$, *t*-BuOK; ix. $AgClO_4$, aq. Me_2CO; x. Na, MeOH-NH_3; xi. CrO_3, Py; xii. Me_2CuLi; xiii. $NaBH_4$; xiv. MsCl, Et_3N; xv. *t*-BuOK; xvi. H_2, $(Ph_3P)_3RhCl$; xvii. MeLi; xviii. $SOCl_2$, Py

The appropriately designed enynol **19** cyclized to give the desired bridged-ring carbinol **20** in 75% yield using trifluoroacetic acid as a catalyst. Reduction of the hydroxyl group, isomerization of the double bond due to the relief of strain, and oxidative cleavage gave rise to ketone **21**. This compound, which was later called Johnson intermediate, served as a target for a number of other synthetic approaches. Introduction of the missing angular methyl group followed by modification of the carbonyl group completed a proficient synthesis in 21% overall yield from **19**.

Scheme 7

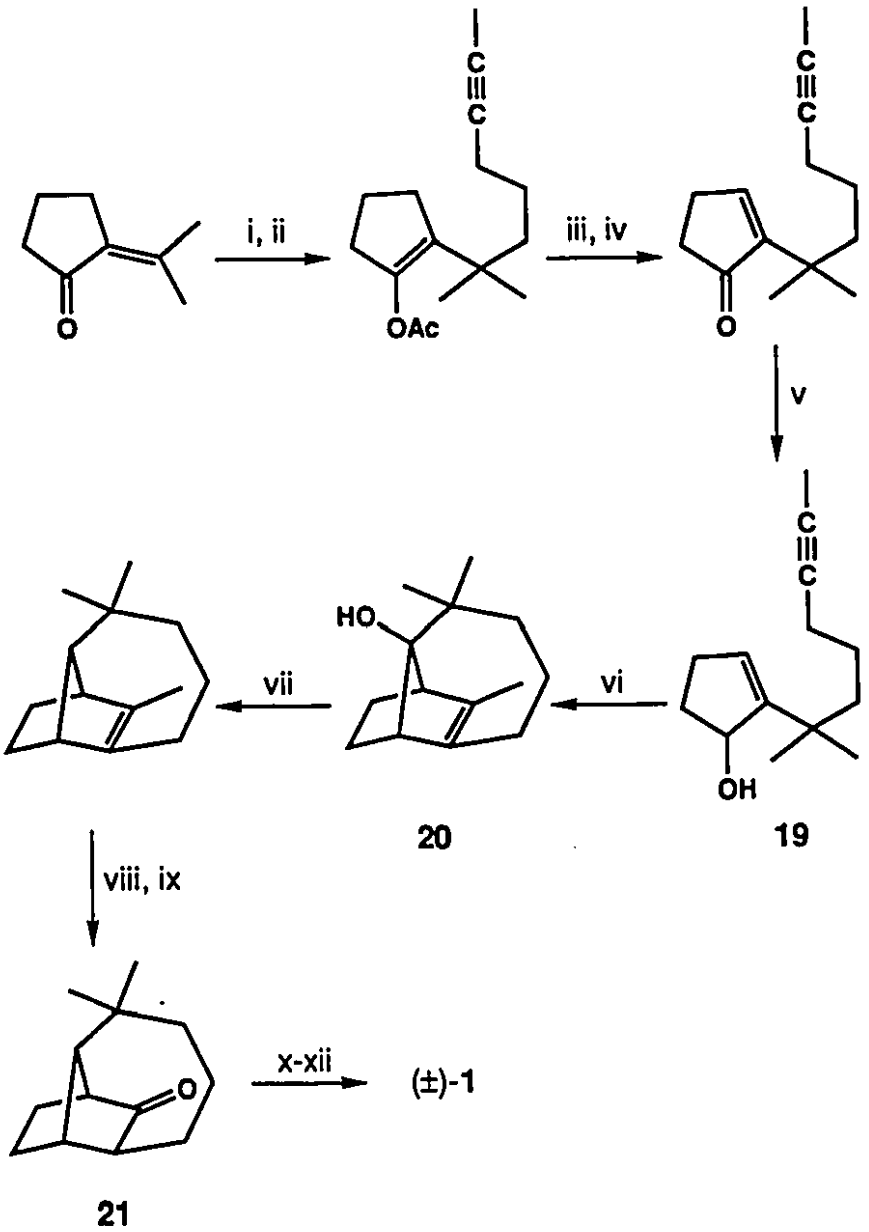


17 **18**

In Oppolzer and Godel's approach,[17] an efficient bimolecular photoaddition-retroaldol reaction sequence (de Mayo reaction) was utilized as an entry to assemble the carbon network of longifolene as depicted in **Scheme 9**. Irradiation of the enol derivative **23**, prepared from the acid chloride **22**, followed by cleavage of the resulting strained tetracyclic adduct furnished (83% yield each) the diketone **24** possessing the required tricyclic framework. The geminal dimethyl group was achieved by a combination of Simmons-Smith cyclopropanation and hydrogenolysis of the olefin **25** that was obtained from the Wittig methylenation of **24**. Applying the reaction sequence used before, (±)-longifolene was produced in an overall yield of 25% from **22** (**Scheme**

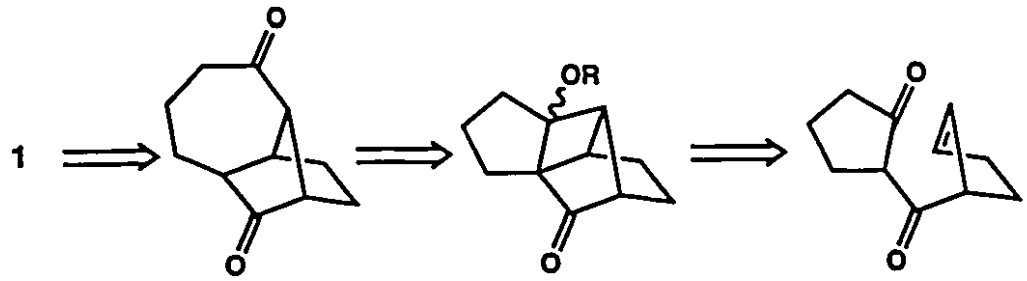
10). This synthetic sequence provides the most efficient route to longifolene in the literature.

Scheme 8



i. $CuLi[-(CH_2)_3C{\equiv}CMe]_2$; ii. MeCOCl; iii. MeLi, Br_2; iv. 2,4,6-$Me_3C_6H_2CO_2NMe_4$; v. $LiAlH_4$; vi. CF_3CO_2H; vii. $ZnBr_2$, $NaBH_3CN$; viii. *p*-TsOH; ix. RuO_2, H_5IO_6-$NaIO_4$; x. LDA, MeI; xi. MeLi; xii. $SOCl_2$, Py

Scheme 9

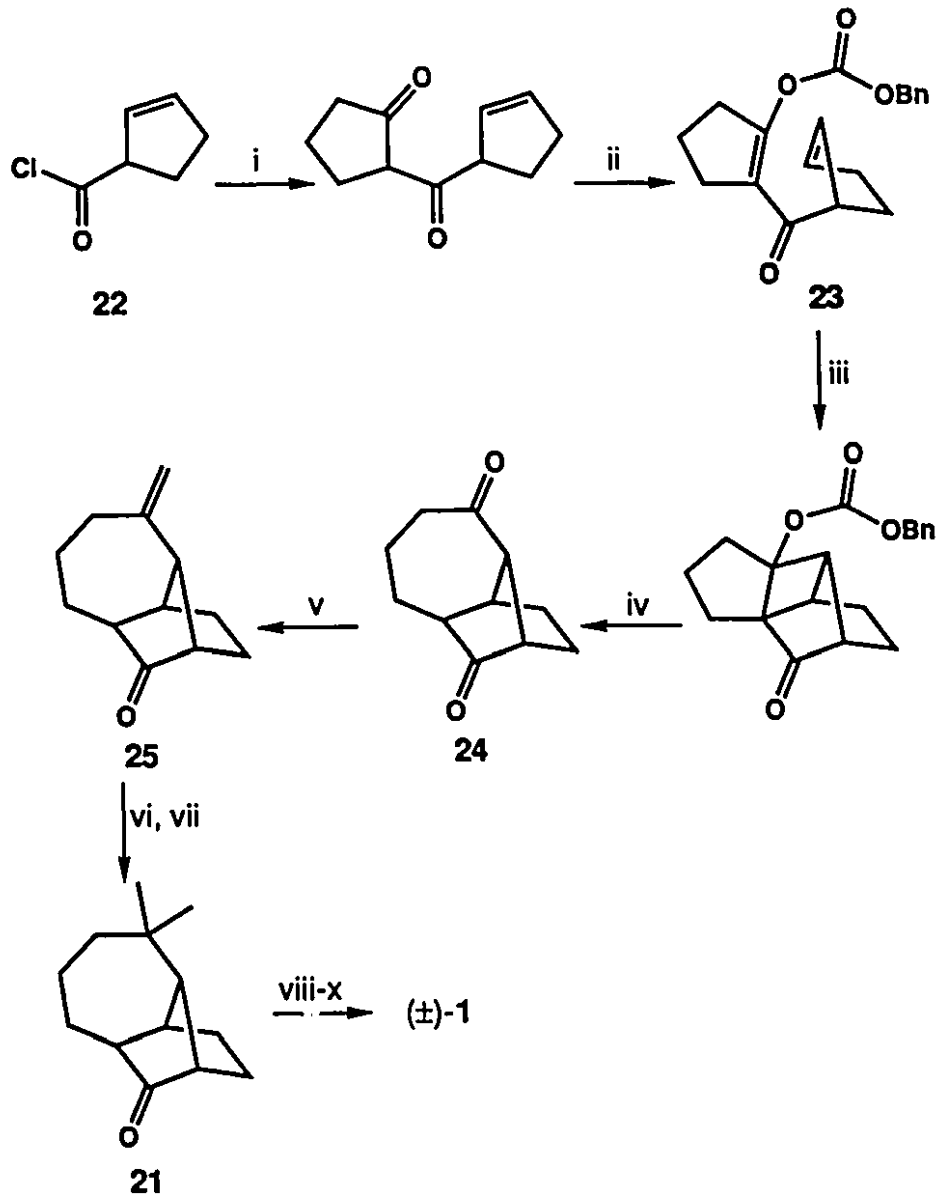


Oppolzer further envisaged the considerable promise of producing enantiomerically pure (+)-longifolene by employing optically pure acid (-)-**26** to make the starting acid chloride.[18] (+)-Longifolene was thus obtained based on the same strategy (**Scheme 11**).

A new approach for the construction of the desired tricyclic ring system was demonstrated by Schultz and Puig[19] in 1985. They considered the synthetic equivalence of an intramolecular cycloaddition between a diene and a carbene (**Scheme 12**) as a key feature to build up the carbon framework. Birch reduction-alkylation of methyl 2-methoxybenzoate gave the cyclohexadiene **27**, which was then converted to the key dienone aldehyde **28** in three steps (**Scheme 13**). With compound **28** in hand, preparation of the corresponding aziridinyl imine and subsequent thermolysis in refluxing xylene were performed to generate the tricyclic ketone **29** in 40% overall yield. Johnson intermediate **21** was achieved from **29** by hydrogenation, saponification, and decarboxylation.

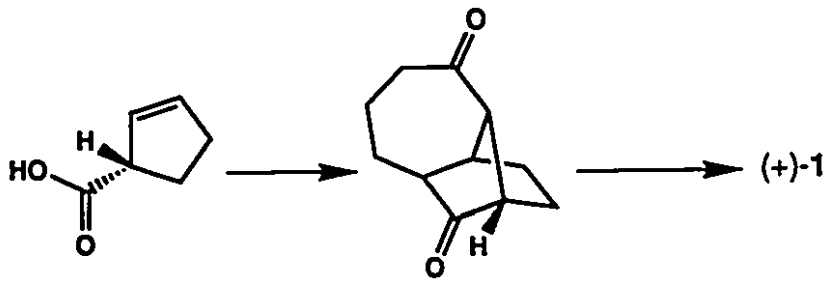
Schultz was also able to provide the first enantiospecific synthesis of (-)-longifolene by using chiral benzoxazepenone **30** as a starting material. However, the conversion of **30** to the enantiomerically pure **27** required somewhat long operation. This is illustrated in **Scheme 14**.

Scheme 10



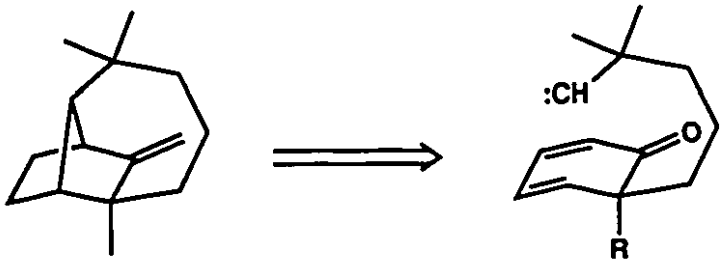
i. 1-morpholino-1-cyclopentene; ii. $ClCO_2CH_2Ph$, Py; iii. light; iv. H_2, Pd/C, HOAc; v. Ph_3PCH_3Br, $MeCH_2C(Me)_2ONa$; vi. CH_2I_2, Zn-Ag; vii. H_2, PtO_2; viii. LCIA, MeI; ix. MeLi; x. $SOCl_2$, Py

Scheme 11

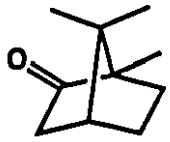


(-)-26 (+)-24

Scheme 12



1

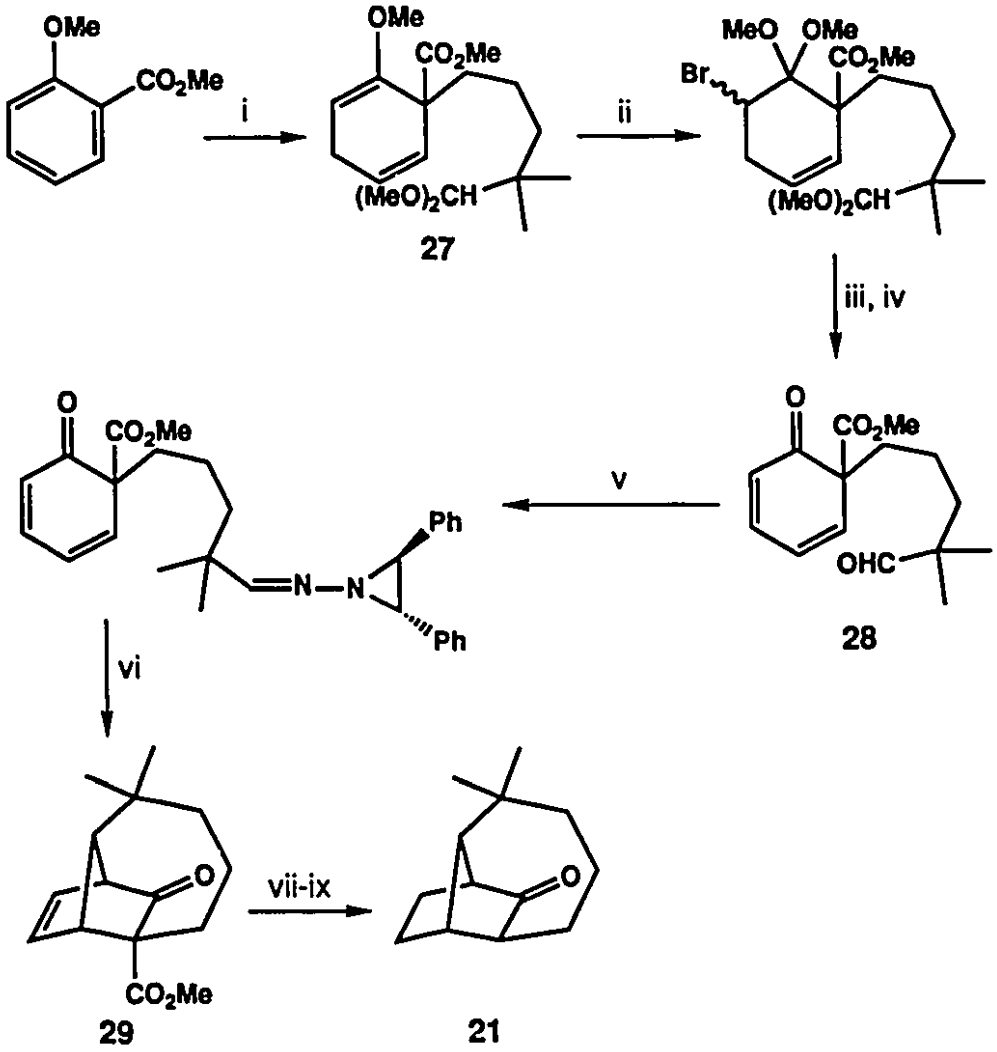


31

In continuation of the synthetic investigations on a series of structrually related sesquiterpenoids using (+)-camphor (**31**) as a chiral starting material, Kuo and Money developed a synthetic route[20,21] to (+)-longifolene by constructing the seven-membered ring with an intramolecular Mukaiyama reaction. (+)-8-Bromocamphor (**32**), readily derived from **31**, was converted to the chiral enol ether acetal **33** by a series of transformations as shown in **Scheme 15**. Intramolecular cyclization of **33** was promoted by titanium tetrachloride to provide, in

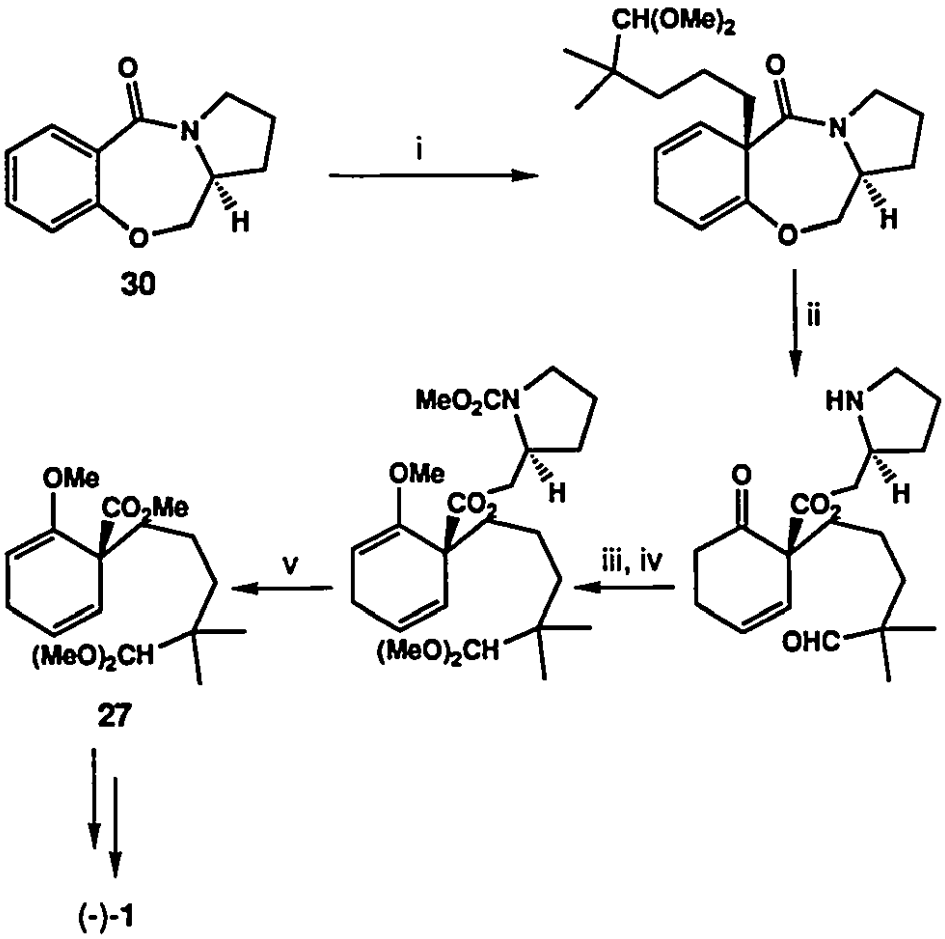
85% yield, the tricyclic intermediate **34** which holds the required functionality at the specific position for the introduction of the geminal dimethyl group (**34**→**35**). Deprotection of **35** gave a natural sesquiterpene, (+)-longiborneol (**36**), that was then inverted to its diastereomer **37**. Conversion of **37** to the mesylate induced a Wagner-Meerwein rearrangement to directly provide (+)-longifolene.

Scheme 13



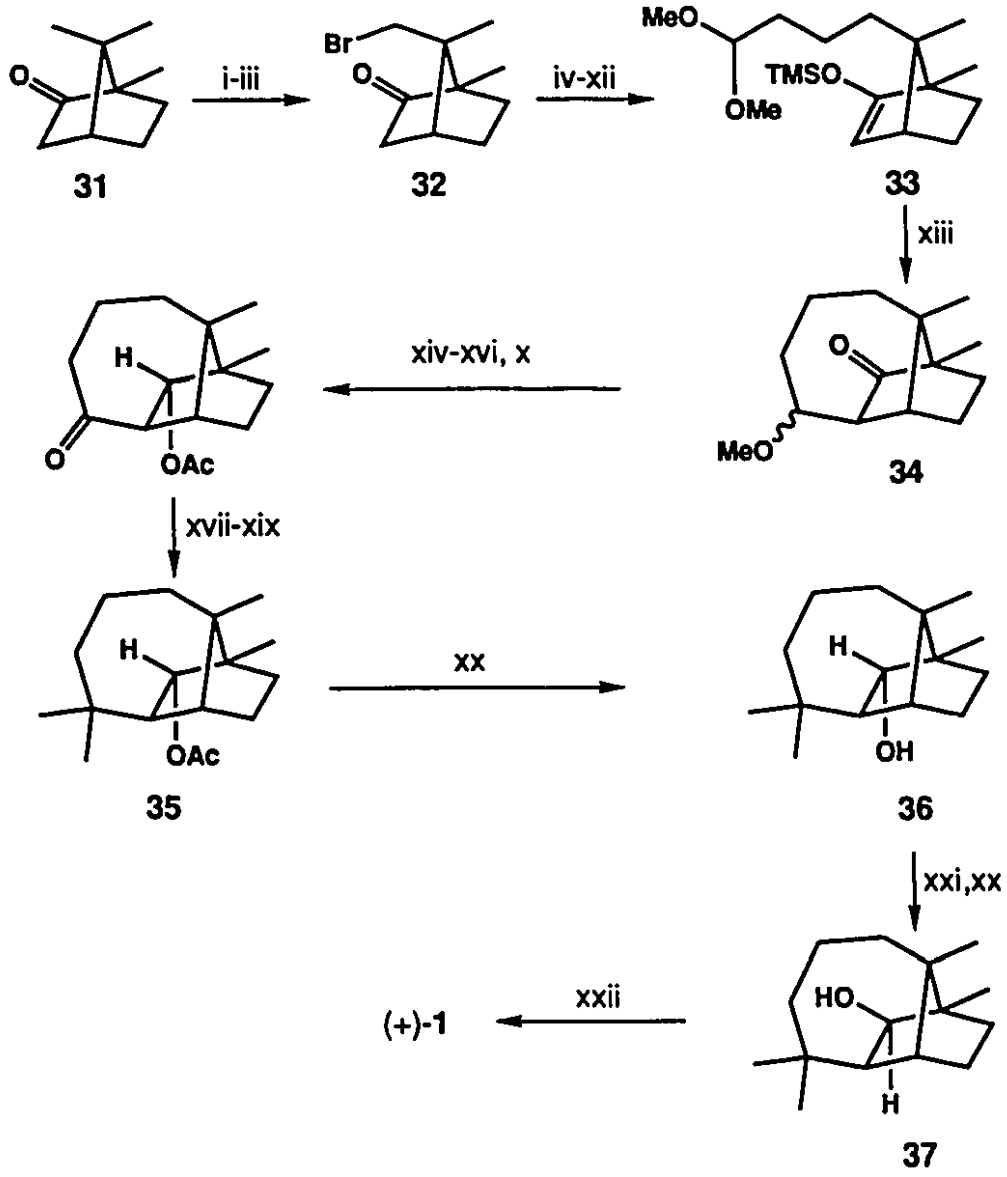
i. K, NH_3(l), *t*-BuOH, dimethyl acetal of 2,2-dimethyl-5-iodopentanal; ii. MeCONHBr, MeOH; iii. DBN; iv. *p*-TsOH, Me_2CO; v. 1-amino-*trans*-2,3-diphenylaziridine; vi. xylene, reflux; vii. H_2, Pd/C; viii. KOH; ix. PhMe, reflux

Scheme 14



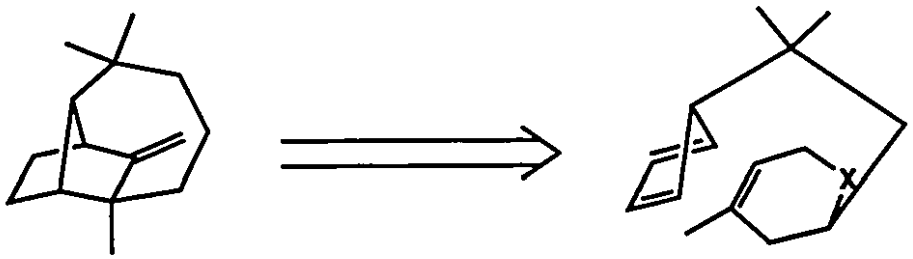
i. K, NH_3(l), *t*-BuOH, dimethyl acetal of 2,2-dimethyl-5-iodopentanal; ii. HCl, MeOH; iii. $ClCO_2Me$, Na_2CO_3; iv. $CH(OMe)_3$, MeOH, HCl; v. NaOMe, MeOH

Scheme 15



i. Br_2, HBr, HOAc; ii. Br_2, $ClSO_3H$; iii. Zn, HOAc; iv. KI; v. $(CH_2OH)_2$, Me_3SiCl; vi. NaCN; vii. LDA, *t*-$BuMe_2SiO(CH_2)_3Br$; viii. K, HMPA; ix. HCl; x. PDC; xi. $HC(OMe)_3$, $CeCl_3$, MeOH; xii. LDA, Me_3SiCl; xiii. $TiCl_4$; xiv. Ca, $NH_3(l)$; xv. Ac_2O, DMAP, Py; xvi. BBr_3; xvii. BuLi, Ph_3PMeBr; xviii. Et_2Zn, CH_2I_2; xix. H_2, Pt, HOAc; xx. $LiAlH_4$; xxi. PCC; xxii. $MeSO_2Cl$, DMAP, Py

Scheme 16

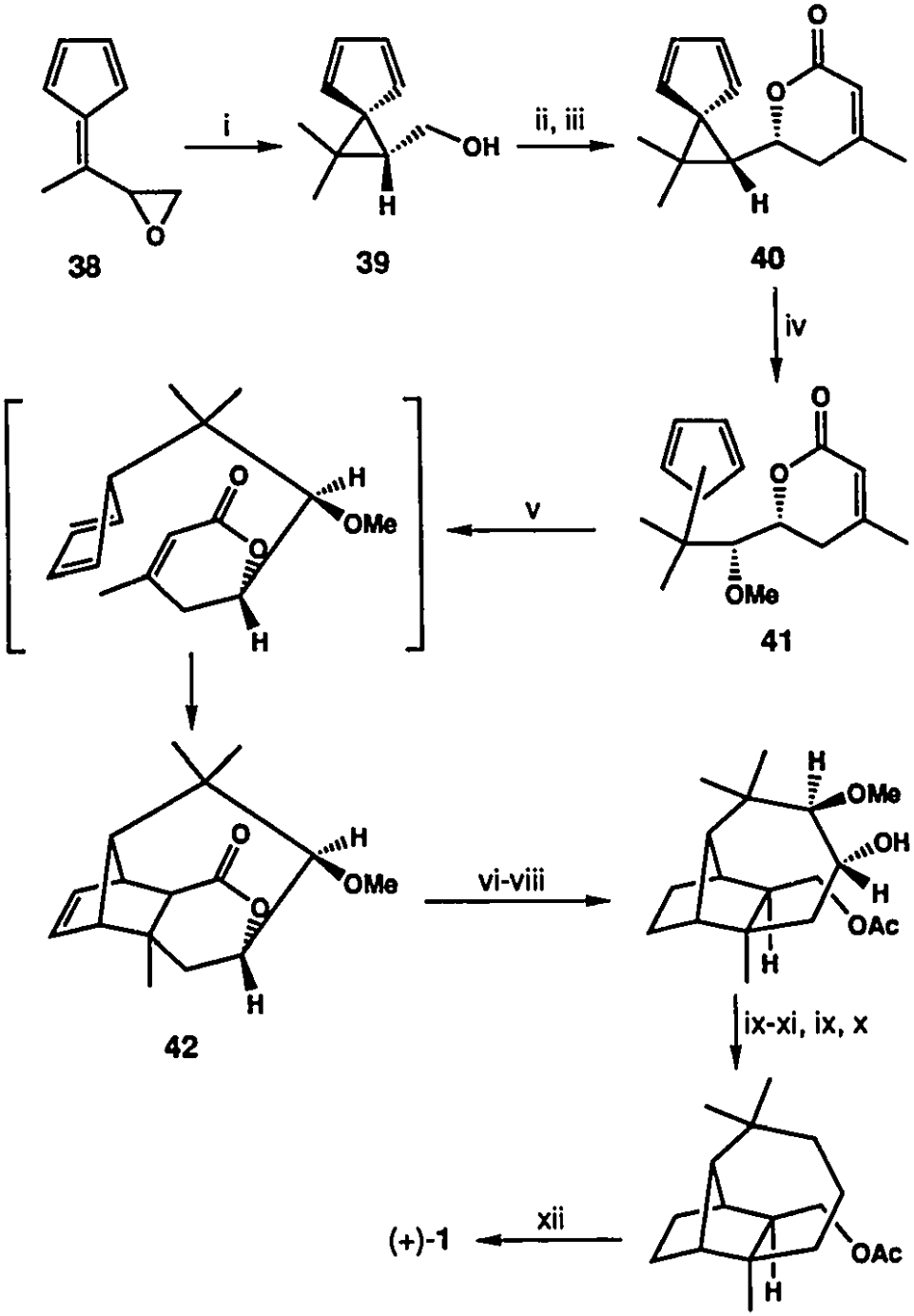


1

The most recent total synthesis of (+)-longifolene, disclosed by Lei and Fallis,[22] utilized an intramolecular Diels-Alder reaction as a strategy to form the required skeleton (**Scheme 16**). Starting with fulvene **38**, the racemic spiro alcohol **39** was generated and resolved to give the R-(+)-isomer. Oxidation and condensation of the resulting aldehyde with crotonate from the less hindered side provided the lactone **40** containing a strained cyclopropane ring. Acidic cleavage of the cyclopropane ring gave rise to a mixture of diene isomers **41** which were ready for cycloaddition. The Diels-Alder reaction was carried out in a microwave oven to give the desired adduct **42** as a single product, suprisingly, in 97% yield. A series of functional group manipulation was then carried out to conclude the synthesis (**Scheme 17**).

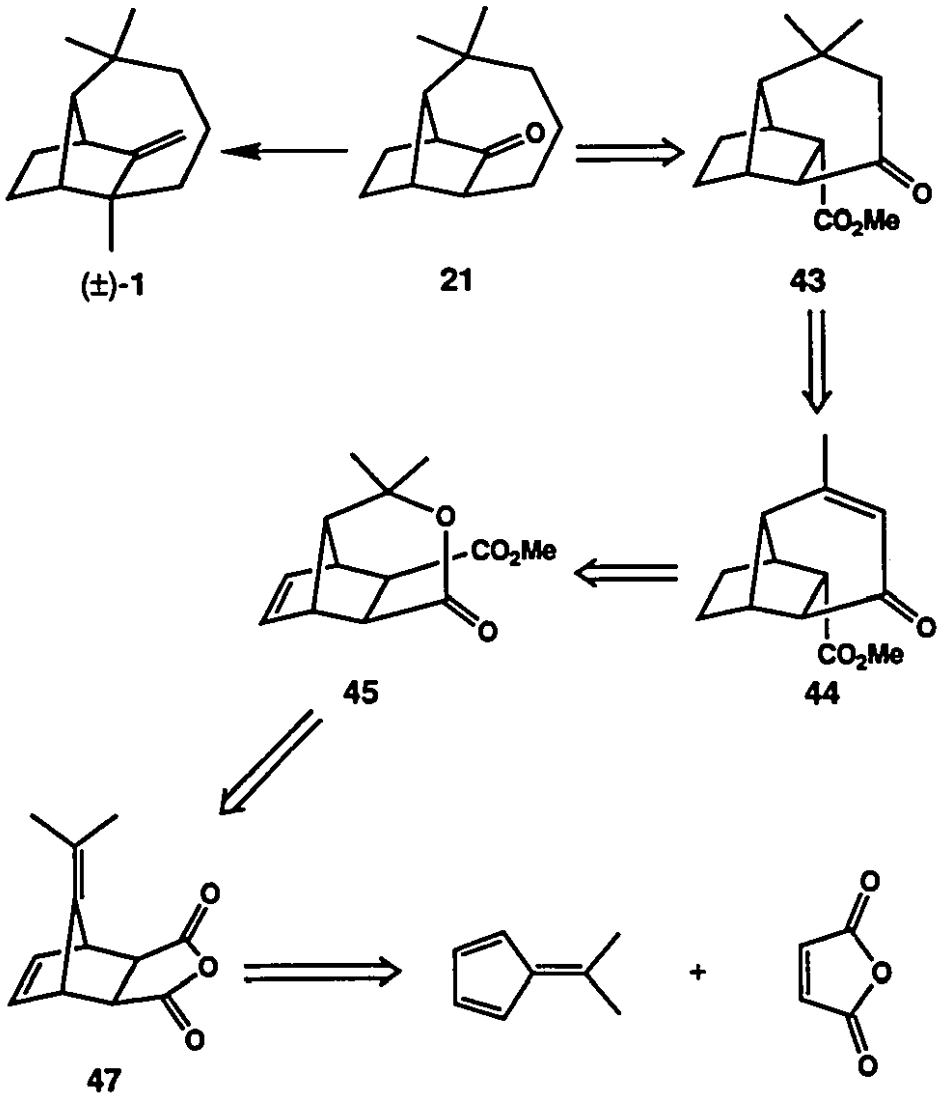
In our investigation directed towards the synthesis of longifolene, Johnson intermediate **21** was chosen as the final goal. The seven-membered ring was considered to be expanded from a suitably functionalized cyclohexanone moiety existing in the tricyclic compound **43**, in which the geminal dimethyl group could be easily achieved by a 1,4-addition of the tricyclic enone **44**. As a consequence, **44** was derived from lactone **45** *via* a three-step operation including hydrogenation, dehydration, and epimerization. We were aware that **45** is similar to the known dihydrolactone acid **46** reported by Alder.[23] According to Alder's procedure, **45** could be thus produced from the cycloadduct **47** of 6,6-dimethylfulvene and maleic anhydride. The retrosynthetic analysis is summarized in **Scheme 18**.

Scheme 17



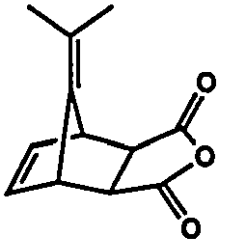
i. MeLi; resolution; ii. MnO_2; iii. LDA, $Me_2C{=}CHCO_2Me$; iv. $BF_3{\cdot}OEt_2$, MeOH; v. sealed tube, microwave; vi. H_2, Pd/C; vii. $LiAlH_4$; viii. Ac_2O, Py; ix. ClC(=S)OPh, Py; x. Bu_3SnH, AIBN; xi. NaI, Me_3SiCl, Et_3N; xii. pyrolysis

Scheme 18

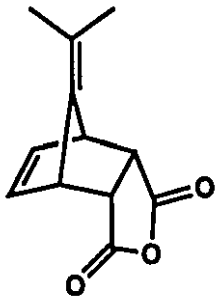


Results and Discussion

As mentioned previously, Alder and Ruhlmann[23] obtained cycloadduct **47** as the thermodynamically favored product from the cycloaddition of 6,6-dimethylfulvene[24] and maleic anhydride. Following their procedure, we repeated the same Diels-Alder reaction in refluxing benzene to generate **47** in 67% yield, along with a minute amount of the *endo* isomer **48** (0.25% yield).



47

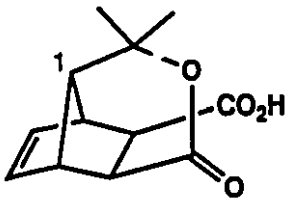


48

High resolution mass spectrometry of the *exo* adduct **47** yielded a molecular ion peak at m/z 204.0779, consistent with the molecular formula $C_{12}H_{12}O_3$. The infrared spectrum showed an anhydride absorption at 1771 cm^{-1}. The ^1H NMR spectrum displayed the two vinylic protons at δ 6.45 as a doublet of doublets (J = 2, J' = 2 Hz) and the two allylic protons at δ 3.87 also as a doublet of doublets (J = 2, J' = 2 Hz). The two *endo* protons attached to the ring junction carbons (C-2 and C-6) were displayed at δ 3.04 as a singlet, due to the 90° dihedral angle between these *endo* protons and their respective neighboring proton. This further confirmed the stereochemistry of **47**. A sharp singlet was observed for the methyl groups at δ 1.60. Compound **47** was recryst llized from petroleum ether and ether to afford a white crystalline solid with a melting point of 138-140°C.

The ^1H NMR spectrum of the *endo* isomer **48** displayed a similar pattern except for two notable changes. The first change was the downfield shift of the two allylic protons to a multiplet at δ 3.94 on account of their position in the deshielding zone of the anhydride functionality. The other was the more significant downfield shift of the two *exo* protons to δ 3.40 as a multiplet because these protons are in the deshielding zone of the exocyclic double bond. These two changes are in agreement with the *endo* stereochemistry of **48**. The other two sets of peaks at δ 6.46 (multiplet) and 1.61 (singlet) corresponded to the two vinylic protons and the geminal methyl groups respectively. The infrared spectrum showed an anhydride absorption at 1783 cm^{-1} and the molecular peak at m/z 204.0788 supported the molecular formula $C_{12}H_{12}O_3$.

The fact that the *exo* isomer **47** predominated as the thermodynamically favored product was further confirmed by the cycloaddition of 6,6-dimethylfulvene and maleic anhydride at room temperature. The reaction proceeded smoothly and the ^1H NMR spectrum of the crude material displayed the existence of the two isomeric cycloadducts **47** and **48** in a ratio of 1 : 1, determined by integration of ^1H NMR signals.

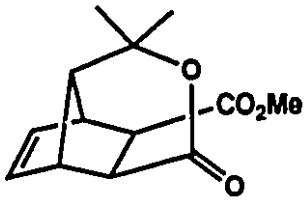


49

Cyclization of the exocyclic olefin and the anhydride moieties in **47** was performed by treatment with 50% aqueous sulfuric acid at room temperature for 48 hours. The resulting crude material was purified by recrystallization to give a white crystalline solid **49** with a melting point of 174-176.5°C in 53% isolated yield. Acid **49** showed a broad absorption in the infrared spectrum at 3440 cm^{-1} indicating the presence of a carboxy group. A strong carbonyl absorption for the carboxy and the

lactone was observed at 1721 cm^{-1}. The ^1H NMR spectrum displayed a broad singlet at δ 7.13 for the carboxylic proton. The two vinylic protons were displayed as a pair of doublets of doublets of doublets (J = 6, J' = 3, J'' = 1 Hz) at δ 6.63 and 6.15. The two allylic protons appeared at δ 3.41 and 3.26, each as a multiplet. The two protons α to carbonyls were observed at δ 2.87 (ddd, J = 8, J' = J'' = 1.5 Hz) and 2.49 (dd, J = 8, J' = 1.5 Hz). A multiplet at δ 1.98 was assigned to the bridgehead proton at C-1. Two methyl singlets were displayed at δ 1.40 and 1.35. The molecular formula $C_{12}H_{14}O_4$ was confirmed by the molecular ion peak at m/z 222.0877 in the high resolution mass spectrum.

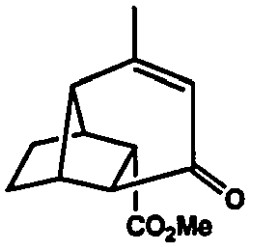
Many methods are available for the esterification of carboxylic acids. We first investigated the method using potassium carbonate to deprotonate the carboxylic proton, and then treating the resulting carboxylate with methyl iodide. However, ester **45** was produced in only 20% yield.



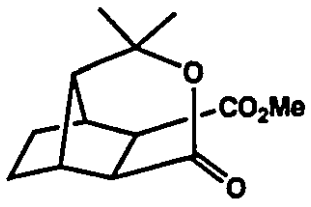
45

On the other hand, esterification of lactone acid **49** was readily accomplished at room temperature in methanol containing a catalytic amount of concentrated sulfuric acid to produce quantitatively ester **45** with a melting point of 159-160°C after 16 hours. The presence of two carbonyl absorptions at 1748 and 1731 cm^{-1} in the infrared spectrum supported the existence of the lactone and the ester functionalities. The ^1H NMR spectrum of **45** is quite similar to that of **49** except for the presence of a characteristic methyl singlet at δ 3.70 due to the methyl ester. High resolution mass spectrometry gave a molecular ion peak at m/z 236.1047 in accordance with the molecular formula $C_{13}H_{16}O_4$.

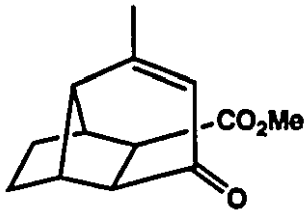
During the separation of cycloadducts **47** and **48** by flash chromatography, the retention of material in the column sometimes resulted in dramatic reduction of yield. This was due to the hydrolysis of the anhydride functionality in the column. Thus we examined the possibility of converting the mixture of **47** and **48** to ester **45** directly without separating them. A mixture of **47** and **48**, containing 28% **47**, was treated with 50% aqueous sulfuric acid to give a crude product, which was then esterified directly by using the above procedure without further purification. Purification of the resulting mixture by flash chromatography gave the desired **45** in 38% yield based on the starting *exo* anhydride **47**.



44



50



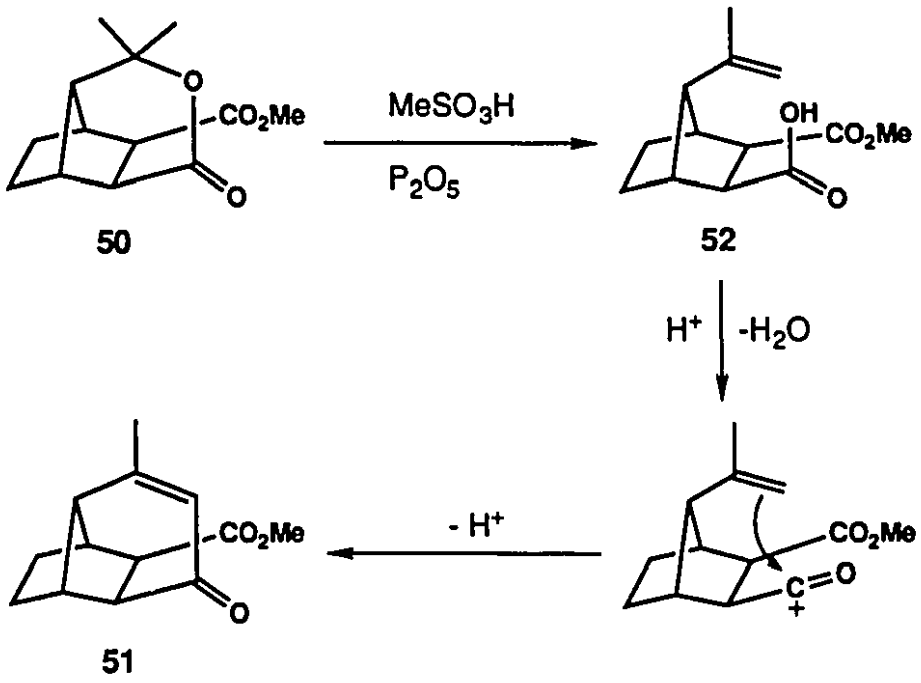
51

In order to prepare compound **44**, it was decided to proceed with hydrogenation prior to other operations in order to prevent any side reactions resulting from the double bond. Hydrogenation was carried out in ethyl acetate under 20 p.s.i. of hydrogen with 5% palladium on carbon as a catalyst to produce lactone ester **50**, a white crystalline solid with a melting point of 118-120°C, in 98% yield after 6 hours. The ^{1}H NMR spectrum, which did not display any vinylic protons, confirmed the saturation of the double bond. The methyl singlet of the ester was displayed at δ 3.68. A multiplet at δ 2.97, two protons by integration, was assigned to the protons α to the carbonyls. The other two methyl singlets were observed at δ 1.46 and 1.39. In the ^{13}C NMR APT spectrum, two carbonyl signals appeared at δ 171.97 and 171.77. The infrared spectrum of **50** had a broad band at 1650-1800 cm^{-1}, indicating the ester and the lactone. The high resolution mass spectrum showed a

molecular ion peak at m/z 238.1209, consistent with the molecular formula $C_{13}H_{18}O_4$.

With lactone ester **50** in hand, the next operation involved the cyclodehydration to generate the desired tricyclic system. Sacrifice of one methyl group in this process would not be detractive, because restoring the substitution pattern by conjugate methylation should be rather straightforward in the following step. When **50** was subjected to treatment with phosphorus pentoxide-methanesulfonic acid reagent[25] at 65°C for 40 hours, the epimeric enones **51** and **44** were produced in a ratio of 3 : 1 and a combined yield of only 37%.

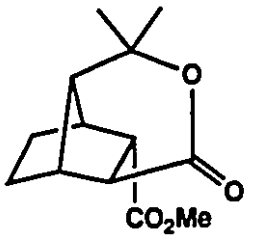
Scheme 19



The low yield of this cyclodehydration reaction was thought to be caused by the intervention of the *exo* ester group. This can be rationalized by the mechanism shown in **Scheme 19**. When the lactone ring is cleaved under the influence of phosphorus pentoxide-methanesulfonic acid

reagent, the resulting intermediate **52** then undergoes recyclization to generate the desired enone **51**. On the other hand, this recyclization process can be interrupted by the participation of the neighbouring *exo* ester, leading to the other side reactions. In principle, a potential remedy to this problem is to epimerize the *exo* ester group to the *endo* position, which is distant from the reaction center.

exo Ester **50** was thus epimerized for 8 hours under basic conditions using sodium methoxide in refluxing methanol to give the *endo* ester **53** in 93% yield. A melting point of 91-93°C was observed for this white solid. In the ^1H NMR spectrum of **53**, the methyl singlet of the ester had shifted downfield to δ 3.74 from δ 3.68 observed for **50**. Also, the two protons α to the carbonyls had been split from δ 2.97 into δ 3.10 and 2.88, each as a multiplet. The other two methyl singlets were displayed at δ 1.48 and 1.44. The infrared spectrum showed a strong absorption attributed to the carbonyls of ester and lactone at 1737 cm^{-1}. In the high resolution mass spectrum, the required molecular ion peak at m/z 238.1193 for the molecular formula $C_{13}H_{18}O_4$ was observed.



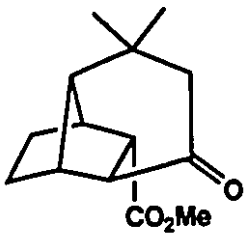
53

Gratifyingly, much improved results emerged when the *endo* ester **53** was treated under the same cyclodehydration conditions. In this case, a high yield (82%) of **44** was produced along with a minute amount (1%) of **51**.

Compound **44** was recrystallized from skelly B to give a white solid with a melting point of 39-40°C. Its infrared spectrum showed an ester absorption at 1739 cm^{-1} and an absorption band at 1676 cm^{-1} which

confirmed the presence of the enone moiety. In the ^1H NMR spectrum of **44**, the enone moiety displayed the vinylic proton at δ 5.75 as a multiplet, the allylic proton at δ 3.02 as a multiplet, and the vinylic methyl group at δ 2.03 as a doublet (J = 1.5 Hz). The methyl singlet of the ester was shown at δ 3.71. Two multiplets at δ 2.78 and 2.70 were assigned to the protons α to carbonyls. The ^{13}C NMR APT spectrum displayed signals for ketone carbonyl, ester carbonyl, and two olefinic carbons at δ 202.07, 173.21, 161.79, and 124.30, respectively. The molecular formula $C_{13}H_{16}O_3$ was confirmed by the molecular ion peak at m/z 220.1098 in the high resolution mass spectrum.

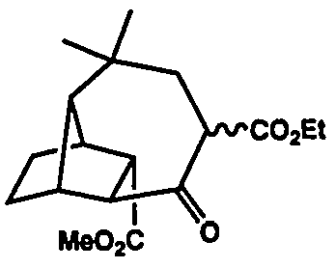
On the other hand, in the ^1H NMR spectrum of **51**, a pair of broad doublets (J = 8.5 Hz) displayed at δ 2.93 and 2.89 were assigned to the two protons α to carbonyls. The vinylic and the allylic protons appeared at δ 5.64 and 2.98, each as a multiplet. The singlet of the methyl ester and the doublet (J = 2 Hz) of the vinylic methyl group had shifted upfield to δ 3.54 and 1.99, respectively, compared to those of **44**. The ^{13}C NMR APT spectrum showed carbonyl signals at δ 201.00 (ketone) and 176 (ester), together with signals at δ 163.44 and 124.65 for the olefinic carbons. In the infrared spectrum, absorptions at 1733 and 1681 cm^{-1} were shown for the ester and the enone. High resolution mass spectrometry showed a molecular ion peak at m/z 220.1098, in agreement with the molecular formula $C_{13}H_{16}O_3$.



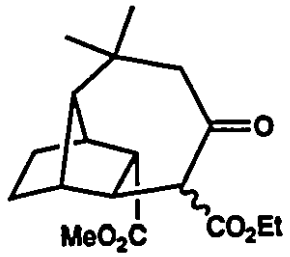
43

The geminal dimethyl group was restored by treatment of enone **44** with lithium dimethylcuprate in ether at 0°C. This 1,4-addition reaction generated the desired dimethyl ketone **43** with a melting point of 93-

93.5°C in nearly quantitative yield after 2 hours. The ^{1}H NMR spectrum of **43** showed the disappearance of the vinylic signal and the presence of the geminal dimethyl singlets at δ 1.13 and 1.02, indicating a conjugate addition to the enone. Moreover, a pair of doublets (J = 18 Hz) at δ 2.35 and 2.23 were observed due to the methylene protons adjacent to the ketone carbonyl. The methyl singlet of ester was displayed at δ 3.68. The ^{13}C NMR APT spectrum displayed carbonyl signals at δ 212.22 (ketone) and 173.09 (ester) and the absence of signals for the olefinic carbons. Two strong carbonyl absorptions at 1736 (ester) and 1714 cm^{-1} (ketone) were present in the infrared spectrum of **43**. The molecular ion peak at m/z 236.1413 in the high resolution mass spectrum was consistent with the molecular formula $C_{14}H_{20}O_3$.



54

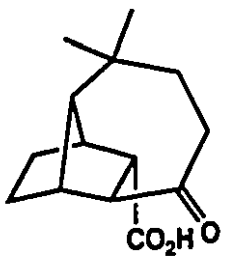


55

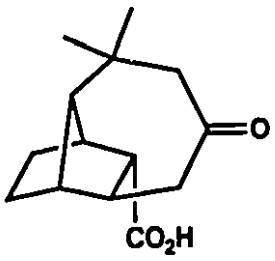
Once keto ester **43** was obtained, it set the stage for the construction of the ring skeleton of longifolene (**1**) *via* ring expansion. Towards this goal, **43** was treated with ethyl diazoacetate in the presence of boron trifluoride etherate.[26] The reaction proceeded smoothly to produce, in 100% yield, a mixture of the desired homologation products, which likely contained all of the six possible isomers (regioisomers **54** and **55** and their respective stereoisomers and enols). The ^{1}H NMR spectrum of this mixture is very complex and only some signals could be identified: δ 13.10, 12.95 (enolic), 4.25-4.05 (methylene of ethyl ester), and 3.70 (methyl of methyl ester). However, a small amount of **54** was isolated during the flash chromatography. It consisted of a pair of epimers (10% each) and the corresponding enol form (80%) as observed in the ^{1}H NMR spectrum. A singlet appeared at δ 13.1 characteristic of a chelated enolic

proton. The methylene protons of the ethyl ester group appeared as a quartet (J = 6.5 Hz) at δ 4.20 due to coupling with the adjacent methyl protons at δ 1.29 (t, J = 6.5 Hz). The two epimeric protons adjacent to both ketone carbonyl and ethoxycarbonyl, corresponding to two epimers, were observed at δ 3.12 and 3.09, each as a multiplet. The methyl singlet of the methoxycarbonyl group was shown at δ 3.70. The infrared spectrum further supported the coexistence of the keto and enol forms with absorption bands at 1739 (ester), 1704 (ketone), 1636 (enol ester), and 1608 cm^{-1} (enol). In the high resolution mass spectrum, a molecular ion peak at m/z 322.1779 is consistent with the molecular formula $C_{18}H_{26}O_5$.

It is believed that the regioselectivity of the ring expansion reaction of unsymmetrical cyclic ketones with ethyl diazoacetate and boron trifluoride etherate is controlled by steric effects.[27-29] The regioselectivity of our ring expansion reaction of **43** followed this general rule as verified after the subsequent transformations. For our synthetic purpose, however, the generation of two regioisomers was not detrimental because the functionalities in the seven-membered ring were to be removed immediately.



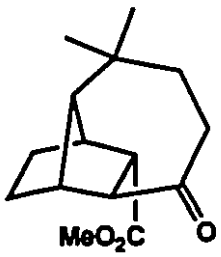
56



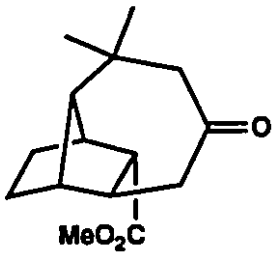
57

Consequently, the decarbethoxylation of the mixture **54** and **55** was carried out by using moist lithium iodide in refluxing collidine for 3 hours to give an inseparable mixture of regioisomeric acids **56** and **57** in 90% crude yield. The absence of the methyl singlets of the methyl esters in the ^1H NMR spectrum of the crude mixture confirmed that the hydrolysis

of the methyl esters also occurred during the reaction. The ester groups were subsequently restored using potassium carbonate and methyl iodide. It is noteworthy that the reaction proceeded sluggishly at room temperature and only a 31% yield of the products was formed after 20 hours. On the other hand, the yield was improved to 95% after 12 hours in refluxing acetone. At this stage, the ratio of the resulting inseparable esters was determined to be 2.5 : 1 (based on the integration of ^{1}H NMR spectrum).



58

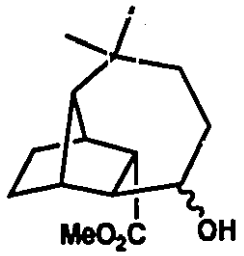


59

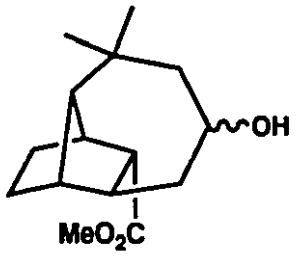
However, at this stage, it was not known which isomer was predominating since the complexity of the spectrum made the assignment of the key signals for each isomer impossible. On the other hand, the structural assignments were achieved based on the following chemical transformation. The isomeric ketones **58** and **59** could be separated in their corresponding alcohol forms. The subsequent oxidation of these separated alcohols individually re-established the original keto esters **58** and **59**, respectively. Comparing the spectral data, **58** was shown to be predominating.

The reduction of the mixture of **58** and **59** was simply achieved by using sodium borohydride. The resulting alcohols **60** and **61**, in a combined yield of 82%, were separated by flash chromatography. Alcohol **60** showed a broad absorption in the infrared spectrum at 3450 cm^{-1}, indicating the presence of a hydroxyl group, and an ester absorption at 1736 cm^{-1}. The ^{1}H NMR spectrum indicated that **60** exists as a 1 : 1 epimeric pair. Two doublets of doublets at δ 4.12 (J = 11, J' = 4 Hz) and

3.63 ($J = J' = 8$ Hz) were assigned to the epimeric protons adjacent to the hydroxyl groups. The protons next to the ester groups were observed at δ 3.32 (m) for one epimer, and δ 2.78 (ddd, $J = J' = 5$, $J'' = 2.5$ Hz) for the other. Methyl singlets were displayed at δ 3.71, 3.68 (ester), 1.02, 1.01, 0.98, 0.97 (*gem*-dimethyl). High resolution mass spectrometry showed a molecular ion peak at m/z 252.1719, in agreement with the molecular formula $C_{15}H_{24}O_3$.



60



61

Alcohol **61**, on the other hand, exists as a 3 : 2 epimeric pair, as displayed by its ^1H NMR spectrum. Signals for the protons next to hydroxyl groups appeared as two multiplets at δ 3.94 and 3.81, in contrast to those of **60** as simpler doublets of doublets. These different coupling patterns were crucial for the structural assignment of **60** and **61**. Since the proton adjacent to the hydroxyl group in each epimer of **61** can be coupled to five neighboring protons in theory, it should show a more complicated pattern than that of **60**, which has only four protons nearby. The protons α to esters of the epimeric mixture of **61** were displayed at δ 2.87 (ddd, $J = J' = 5$, $J'' = 2$ Hz) and 2.64 (ddd, $J = J' = 5$, J'' = 3 Hz). Methyl singlets were observed at δ 3.67 (ester), 1.08, 1.06, 1.00, and 0.99 (*gem*-dimethyl). The infrared spectrum of **61** displayed a broad hydroxyl absorption at 3370 cm^{-1} and an ester absorption at 1735 cm^{-1}. The high resolution mass spectrum gave a molecular ion peak at m/z 252.1727 in accordance with the molecular formula $C_{15}H_{24}O_3$.

Alcohols **60** and **61** were individually oxidized back to keto esters **58** and **59** respectively using pyridinium chlorochromate on alumina.[30]

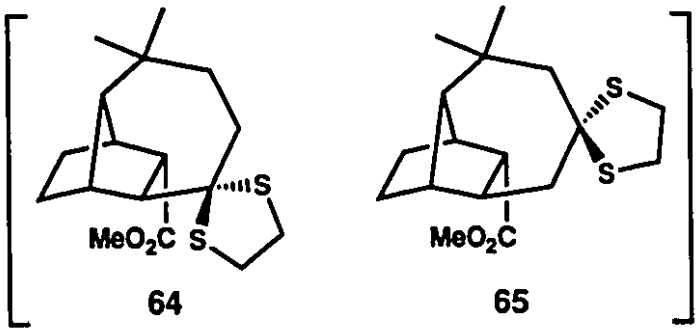
Compound **58** was obtained in 95% yield as a white crystalline solid with a melting point of 97-99°C. Its infrared spectrum showed the ester absorption at 1738 cm^{-1} and the ketone absorption at 1697 cm^{-1}. In the ^1H NMR spectrum, the methyl singlet of the ester appeared at δ 3.68. The proton adjacent to the ester was displayed at δ 3.13 (ddd, $J = J' = 5$, $J'' = 2.5$ Hz). It was coupled to the bridgehead proton next to the ketone carbonyl at δ 2.93 (d, $J = 5$ Hz). The methylene protons α to the ketone carbonyl were observed at δ 2.61 (ddd, $J = J' = 16$, $J'' = 3$ Hz) and 2.32 (ddd, $J = 16$, $J' = 5$, $J'' = 1$ Hz). The recognition of these three α protons was essential for the determination of regiochemistry of **58**. The geminal methyls showed a sharp singlet at δ 1.06. The ^{13}C NMR APT spectrum displayed signals for two carbonyl carbons at δ 212.50 (ketone) and 173.25 (ester). The presence of ester and ketone functionalities were also confirmed by the infrared spectrum, showing absorptions at 1738 and 1697 cm^{-1} respectively. The molecular peak at m/z 250.1564 in the high resolution mass spectrum supported the molecular formula $C_{15}H_{22}O_3$.

Similarly, keto ester **59** with a melting point of 101-103°C was produced in a yield of 90%. The regiochemistry of **59** was confirmed by pinpointing the methylene protons flanked by both the ketone carbonyl and geminal dimethyl group in the ^1H NMR spectrum. These protons appeared as a pair of doublets ($J = 12$ Hz) at δ 2.76 and 2.18. The other pair of α methylene protons of the ketone carbonyl were located at δ 2.65 as a multiplet, and δ 2.31 as a doublet of doublets ($J = 16$, $J' = 3$ Hz). The proton next to the ester appeared at δ 3.18 (ddd, $J = J' = 5$, $J'' = 2.5$ Hz), while the three methyl singlets were observed at δ 3.70 (ester), 1.11, and 1.00 (*gem*-dimethyl). In the ^{13}C NMR APT spectrum, the carbonyl carbons of ketone and ester were displayed at δ 210.61 and 174.58, respectively. The infrared spectrum showed two carbonyl absorptions at 1726 (ester) and 1687 cm^{-1} (ketone). The high resolution mass spectrum displayed a molecular ion peak at m/z 250.1565 in accordance with the molecular formula $C_{15}H_{22}O_3$.

The ketone carbonyls of **58** and **59** had to be removed in order to achieve Johnson intermediate **21**. Much effort was directed towards this supposedly trivial deoxygenation. Attempts to reduce the ketone by a

modified Wolff-Kishner reduction[31] led to complete decomposition. Another good method for the reduction of a ketone carbonyl to the corresponding methylene group involves thioketalization and subsequent desulfurization. Unexpectedly, attempted thioketalizations of keto esters **58** and **59** using 1,2-ethanedithiol and boron trifluoride etherate resulted in the formation of products whose spectral data were inconsistent with those predicted.

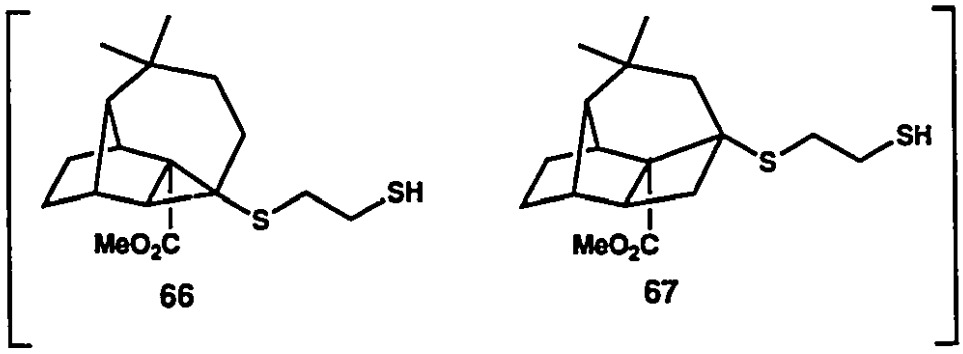
Thioketalization of **58** produced, in 70% yield, a major product **62** as a yellowish solid with a melting point of 92-94°C. The infrared spectrum of **62** showed an ester absorption at 1736 cm^{-1} and the absence of ketone absorption. In the ^1H NMR spectrum, a complex multiplet for four protons was displayed between δ 3.44 and 3.15, characteristic of protons at sulfur-bearing carbons. Two methyl singlets were also observed at δ 3.69 (ester) and 1.00 (*gem*-dimethyl). The molecular ion peak at m/z 326.1370 in the high resolution mass spectrum supported the molecular formula $C_{17}H_{26}O_2S_2$. All of the above spectral data agree with the expected structure **64**. However, the disagreement stemmed from the ^{13}C NMR APT spectrum. Compound **62** should display 9 in-phase and 8 out-of-phase signals, if it possessed the expected structure **64**. However, 10 in-phase and 6 out-of-phase signals were obtained repeatedly. Two out-of-phase signals presumably overlapped.



64 65

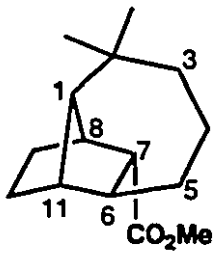
Like **62**, the major product **63**, obtained in 55% yield from the thioketalization of keto ester **59**, repeatedly displayed a ^{13}C NMR APT spectrum which is inconsistent with that of the desired thioketal **65**. The

observed 10 in-phase and 7 out-of-phase signals in the ^{13}C NMR APT spectrum of **63** differed from the expected 9 in-phase and 8 out-of-phase signals for **65**. The infrared spectrum of **63** showed a single carbonyl absorption at 1733 cm^{-1}, while the ^{1}H NMR spectrum displayed a multiplet at δ 3.17-3.37 for the four protons next to sulfurs, along with three methyl singlets at δ 3.68 (ester), 1.25, and 1.07 (*gem*-dimethyl). The high resolution mass spectrum showed the molecular ion peak at m/z 326.1373, also supporting the molecular formula $C_{17}H_{26}O_2S_2$.



According to the ^{13}C NMR APT spectra, we proposed structures **66** and **67** for the thioketalization products **62** and **63**, because they fit the spectral data well. In order to confirm this proposal, **62** and **63** were subjected to acetylation reaction in order to produce the corresponding thioacetates for further identification. However, under a variety of conditions, only the starting materials were recovered intact. Based on this result, the proposed structures **66** and **67** appeared to be very unlikely.

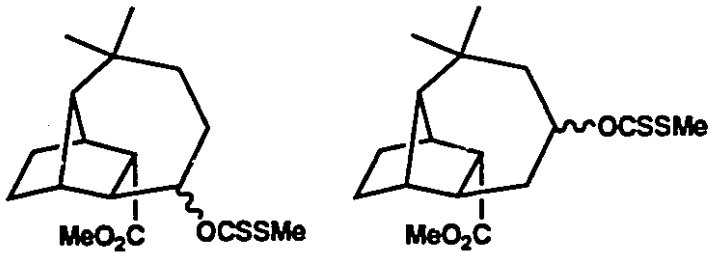
Another method to identify the structures of **62** and **63** was to remove the thioketal functionalities. Surprisingly, treatment of a mixture of **62** and **63** with Raney-nickel for 19 hours produced, in 61% yield, the desired deoxygenated compound **68** as a white solid with a melting point of 59-61°C.



68

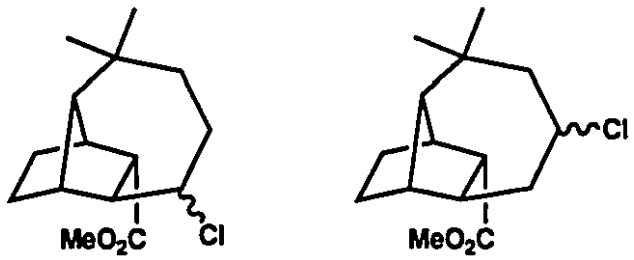
The infrared spectrum of **68** showed a carbonyl absorption at 1736 cm^{-1}. The high resolution mass spectrum gave a molecular ion peak at m/z 236.1777 corresponding to the molecular formula $C_{15}H_{24}O_2$. In the ^1H NMR spectrum, the methyl singlet of the ester was observed at δ 3.67. The α proton (C-7) of the ester was displayed at δ 2.76 (ddd, J = 5, J' = 4, J'' = 2 Hz) coupled to two neighboring bridge protons. One at C-8 appeared at δ 2.39 as a doublet of doublets ($J = J'$ = 4 Hz), while the other one at C-6 connected to the seven-membered ring was displayed at δ 2.18 as a doublet of doublets (J = 6, J' = 5 Hz). The other bridgehead proton at C-11 was shown at δ 2.03 as a doublet (J = 4.5 Hz). The six protons of the geminal dimethyl group were displayed at δ 0.92 as a sharp singlet. In the ^{13}C NMR APT spectrum, the carbonyl carbon displayed a signal at δ 175.83 and the numbers of in-phase and out-of-phase signals were in agreement with the presented structure.

Longifolene and its derivatives are well known to undergo skeletal rearrangements resulting in a variety of compounds.[1,2,6-9] Presumably, during the thioketalization, keto esters **58** and **59** undergo concomitant skeletal rearrangement catalyzed by boron trifluoride etherate, giving rise to **62** and **63** with unknown structures. Once **62** and **63** are treated with Raney-nickel, the intermediates containing free radicals induce another rearrangement to afford the single compound **68**.



69 70

While we were attempting to identify the structures of **62** and **63**, we were also searching for other less direct but more promising approaches to deoxygenate keto esters **58** and **59**. Starting with a mixture of alcohols **60** and **61**, an inseparable mixture of the corresponding xanthates **69** and **70** was obtained easily, in 95% yield, by successive treatment with sodium hydride, carbon disulfide, and methyl iodide. The infrared spectrum of the mixture showed a carbonyl absorption at 1738 cm^{-1} along with the characteristic thiocarbonyl absorption at 1048 cm^{-1}. In the ^1H NMR spectrum, the protons adjacent to the xanthate groups appeared at δ 5.92, 5.80, 5.46, and 5.02, each as a multiplet. Methyl singlets were displayed at δ 3.60 (ester), 2.53, 2.52 (xanthate), 1.17, and 1.07 (*gem*-dimethyl). In the high resolution mass spectrum, the molecular ion peak at m/z 341.1328 was in accordance with the molecular formula $C_{17}H_{26}O_3S_2$.

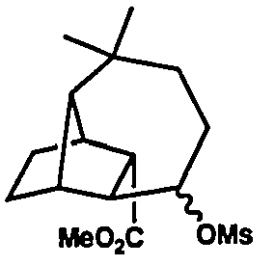


71 72

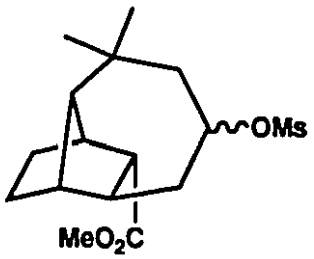
Disappointedly, attempted reduction of the xanthates **69** and **70** using tri-*n*-butyltin hydride with a catalytic amount of azobisisobutyronitrile in

refluxing toluene failed to give any of the desired product **68**. Another similar method was to convert the alcohols **60** and **61** to the corresponding chlorides. A mixture of **60** and **61** was thus treated with thionyl chloride and pyridine at 0°C to give a mixture of products in 65% yield after 1.5 hours. However, when these products were hydrogenated using platinum(IV) oxide as a catalyst, the original alcohols **60** and **61** were recovered quantitatively. This result indicated that the above chlorination products were not the expected chlorides, but the oxygen-containing intermediates, such as chlorosulfinates. As a result, more drastic conditions were required to force the chlorination to completion. We consequently carried out the chlorination reaction in refluxing dichloromethane for 13 hours. The desired chlorides **71** and **72** were thus produced in 64% yield.

The ^{1}H NMR spectrum of the mixture of **71** and **72** displayed the protons at the chlorine-bearing carbons at δ 4.39 and 4.16 as two multiplets. Signals at δ 3.21 (m) and 2.83 (ddd, $J = J' = 5$, $J'' = 3$ Hz) were assigned to the α protons of esters. Four methyl singlets were displayed at δ 3.63, 3.62 (ester), 1.03, and 0.98 (*gem*-dimethyl). The infrared spectrum showed an ester absorption at 1736 cm^{-1}, while the high resolution mass spectrum gave molecular ion peaks at m/z 270.1379 and 272.1361, corresponding to the molecular formula $C_{15}H_{23}O_2Cl$.



73

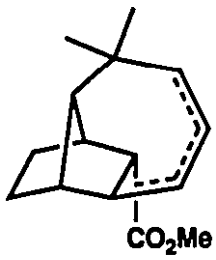


74

Although the chlorides could be obtained successfully, this method was abandoned partly due to the modest yield. Moreover, the corresponding mesylates **73** and **74**, serving the same purpose, could be prepared easily

in 85% yield by treatment with methanesulfonyl chloride, pyridine, and triethylamine. The ^1H NMR spectrum of this inseparable mixture displayed the protons next to the mesylate groups at δ 5.01, 4.90, 4.79, and 4.48, each as a multiplet. Nine methyl singlets were assigned to the esters (δ 3.69 and 3.67), the mesylates (δ 3.04, 2.56, 2.54), and the geminal methyl groups (δ 1.09, 1.07, 1.02, and 0.98). Although the molecular ion peak corresponding to the molecular formula ($C_{16}H_{26}O_4S$) was not observed in the high resolution mass spectrum, a fragment at m/z 299.1314 ($C_{15}H_{23}O_4S$) resulting from the loss of a methyl unit was displayed.

Towards the desired deoxygenated ester **68**, the mesylate functionalities of **73** and **74** were removed by reductive elimination using sodium iodide and zinc dust in refluxing tetrahydrofuran for 15 hours.[32] Under these conditions, a mixture of the desired **68** and the elimination product **75** was produced in a combined yield of 90%. Subsequent hydrogenation of this inseparable mixture using 5% palladium on carbon as a catalyst resulted in only recovery of the starting materials. On the other hand, when the hydrogenation was catalyzed by platinum(IV) oxide in methanol for 24 hours, a yield of 98% of the desired **68** was generated.

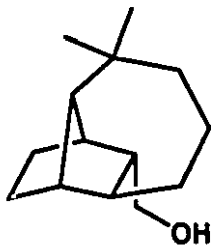


75

With ester **68** in hand, the introduction of a double bond conjugated to the ester group *via* selenation-oxidative elimination[33-35] was attempted in light of the prospect that it would permit conjugate addition of the required angular methyl group. Unfortunately, the maneuver proved to be unfruitful. Under no conditions examined could a phenylselenenyl

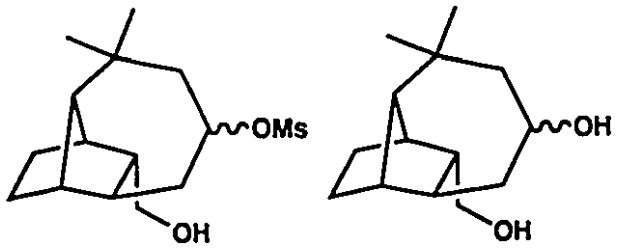
group be incorporated. We were unable to deuterate ester **68** by consecutive treatment with lithium diisopropylamide and deuterium oxide. This inertness towards deprotonation probably was due to the steric hindrance, caused by the seven-membered ring surrounding the α proton of the ester.

At this stage, the conversion of **68** into Johnson intermediate **21** was initiated. Accordingly, ester **68** was reduced by lithium aluminum hydride at room temperature to give rise to alcohol **76** in 100% yield. The infrared spectrum of **76** displayed a broad band at 3310 cm^{-1}, characteristic of a hydroxyl group. In the ^1H NMR spectrum, methylene protons adjacent to the hydroxyl group appeared as a pair of doublets of doublets at δ 3.65 (J = 11, J' = 7 Hz) and 3.51 (J = 11, J' = 9 Hz). Two methyl singlets were observed at δ 0.98 and 0.97. High resolution mass spectrometry showed a molecular ion peak at m/z 208.1826, in agreement with the molecular formula $C_{14}H_{24}O$.



76

We also attempted to synthesize alcohol **76** directly from the mesylates **73** and **74** with lithium aluminum hydride, but this short cut turned out to be disappointing. Reduction of mesylate **74** with lithium aluminum hydride at room temperature resulted in hydroxymesylate **77** (68% yield) along with a small amount of diol **78** (11% yield). On the other hand, when the reduction was performed in refluxing tetrahydrofuran, only **78** was produced in 82% yield without any of the desired **76**.

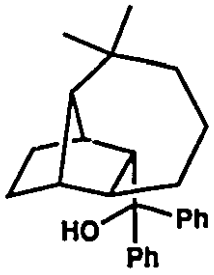


77 78

In the infrared spectrum of **77**, a broad absorption at 3400 cm^{-1} indicated the presence of a hydroxyl group. In the ^1H NMR spectrum, the protons next to the mesylate functionalities were displayed at δ 4.92 as a multiplet, while the methylene protons adjacent to the hydroxyl group appeared as a pair of doublets of doublets at δ 3.68 (J = 11, J' = 8 Hz) and 3.53 ($J = J'$ = 11 Hz). Three methyl singlets were observed at δ 2.98 (mesylate), 1.14, and 1.04 (*gem*-dimethyl). High resolution mass spectrometry gave a fragment ion peak at m/z 284.1439 which confirmed the formula $C_{15}H_{24}O_3S$ resulting from the loss of a water unit from compound **77**.

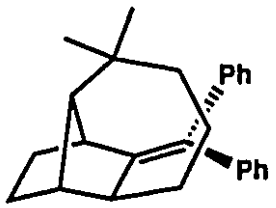
Diol **78** also showed a broad absorption at 3340 cm^{-1} in the infrared spectrum. The ^1H NMR spectrum showed the disappearance of the methyl singlet of the mesylate and an upfield shift of the methine protons at the oxygen-bearing carbons to δ 3.94 as a multiplet, owing to the conversion of mesylate to hydroxyl group. The rest of the spectrum was similar to that of **77**. The high resolution mass spectrum gave a molecular ion peak at m/z 224.1767 corresponding to the molecular formula $C_{14}H_{24}O_2$.

Alcohol **76** was thought to be able to form the corresponding selenide, which could then be converted into an exocyclic methylene group *via* selenoxide pyrolysis.[36,37] However, attempts to produce the selenide by using *N*-phenylselenophthalimide (N-PSP) and tri-*n*-butylphosphine[38,39] led to either complete decomposition or recovery of the starting material. Presumably, the β branching of the hydroxyl group prevents the occurrance of the displacement reaction.

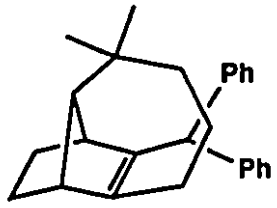


79

Another possible route towards Johnson intermediate **21** involves an application of the Barbier-Wieland degradation. Reaction of ester **68** with phenyllithium in refluxing tetrahydrofuran resulted in the required diphenylalcohol **79** in quantitative yield after 4.5 hours.[40] The infrared spectrum of **79** showed a broad band at 3600 cm^{-1}, indicating the presence of a hydroxyl group. The ^1H NMR spectrum further confirmed the presence of two phenyl groups by displaying ten phenyl protons between δ 7.13-7.63. Two methyl singlets appeared at δ 1.08 and 0.99. The high resolution mass spectrum gave a molecular ion peak at m/z 360.2451, consistent with the molecular formula $C_{26}H_{32}O$.



80

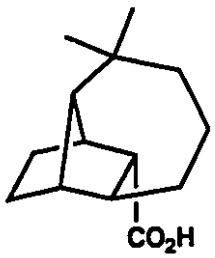


81

Dehydration of alcohol **79** proceeded smoothly with copper(II) sulfate on silica gel[41-43] in refluxing carbon tetrachloride for 0.5 hour to give the desired exocyclic olefin **80** (92% yield) along with a small amount of endocyclic olefin **81** (8% yield). In the ^1H NMR spectrum of **80**, ten phenyl protons appeared between δ 7.11-7.35, while two allylic protons were displayed at δ 2.88 (d, J = 6 Hz) and 2.82 (d, J = 4 Hz). Two methyl

singlets were shown at δ 1.01 and 0.97. The infrared spectrum showed a phenyl absorption at 1600 cm^{-1}. High resolution mass spectrometry of **80** provided a molecular ion peak at m/z 342.2345, consistent with the molecular formula $C_{26}H_{30}$. In the high resolution mass spectrum of **81**, a molecular ion peak at m/z 342.2363 also supported the same molecular formula. Its infrared spectrum again showed a phenyl absorption at 1600 cm^{-1}. In the ^1H NMR spectrum, other than a complex multiplet due to ten phenyl protons, a downfield broad singlet at δ 4.20 was displayed and assigned to the allylic proton adjacent to the phenyl groups. Two other allylic protons appeared at δ 3.57 (d, J = 11 Hz) and 3.00 (d, J = 11 Hz). The remaining allylic protons moved upfield to δ 1.95 and 1.74, each as a multiplet. The methyl singlets also moved upfield slightly to δ 0.94 and 0.92.

Although olefin **80** could be readily prepared, the ensuing ozonolysis did not give any detectable amount of the required ketone **21**. Again, the seven-membered ring surrounding the double bond presumably played an important role to prevent the attack of ozone.

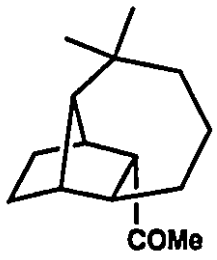


82

Eventually, the conversion of ester **68** into Johnson intermediate **21** was achieved *via* the following synthetic sequence involving Baeyer-Villiger oxidation as the key step. Saponification of **68** with aqueous potassium hydroxide in refluxing tetrahydrofuran for 39 hours generated, in quantitative yield, acid **82** as a white solid with a melting point of 156-157°C. The infrared spectrum displayed the characteristic absorption of a carboxylic acid in the 2400-3200 cm^{-1} region, along with a strong

carbonyl absorption at 1698 cm^{-1}. The ^1H NMR spectrum showed the α proton of the carboxy group at δ 2.90 (ddd, J = 5, J' = 4, J'' = 2 Hz) and the geminal dimethyl group at δ 1.00 as a sharp singlet. The carboxylic proton was not observed. The carbonyl carbon appeared at δ 181.15 in the ^{13}C NMR APT spectrum. The high resolution mass spectrum gave a molecular ion peak at 222.1619, in agreement with the molecular formula $C_{14}H_{22}O_2$.

Acid **82** was treated with excess methyllithium at room temperature in tetrahydrofuran for 16 hours, followed by quenching the reaction mixture with trimethylsilyl chloride to give the required methyl ketone **83** in 87% yield.[44] The appearance of a singlet at δ 2.10 in the ^1H NMR spectrum indicated the formation of the methyl ketone. The methine proton neighboring the carbonyl shifted upfield slightly to δ 2.84 (ddd, $J = J' = 5$, $J'' = 2$ Hz) and the geminal dimethyl singlets were observed at δ 1.01 and 0.98. In the ^{13}C NMR APT spectrum of **83**, the carbonyl signal moved downfield to δ 210.00, further supporting the ketone functionality. The infrared spectrum showed a ketone absorption at 1708 cm^{-1}, while the high resolution mass spectrum displayed a molecular ion peak at 220.1825, consistent with the molecular formula $C_{15}H_{24}O$.

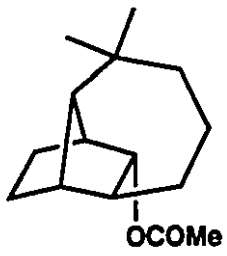


83

Once ketone **83** was prepared, it set the stage for the Baeyer-Villiger oxidation. Based on the previous experiences we realized that more drastic conditions or more active reagents were required in order to overcome the steric barrier. We first tried the normal Baeyer-Villiger conditions using *m*-chloroperoxybenzoic acid and, as expected, **83**

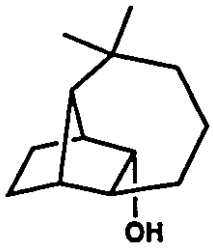
remained intact. However, when **83** was treated with trifluoroperoxyacetic acid and disodium hydrogen phosphate in refluxing dichloromethane, the desired acetate **84** was produced in 48% yield after 5 hours.[45,46]

The infrared spectrum of **84** displayed a typical absorption of ester at 1737 cm^{-1}. In the ^1H NMR spectrum, the proton at C-7 had shifted downfield to δ 5.09 as a doublet of doublets ($J = J' = 4$ Hz), representative of the α proton of an acetoxy group. The methyl singlet of the acetoxy group appeared at δ 2.03, while the geminal dimethyl group was displayed as a sharp singlet at δ 0.98. The ^{13}C NMR APT spectrum also confirmed the production of the acetate **84** by displaying the carbonyl carbon signal at δ 171.38. In the high resolution mass spectrum, the molecular ion peak at m/z 236.1763 was consistent with the molecular formula $C_{15}H_{24}O_2$.



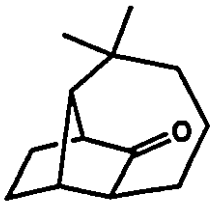
84

Subsequent hydrolysis of acetate **84** at room temperature with aqueous sodium hydroxide afforded, in 93% yield, alcohol **85** with a melting point of 68-70°C. The infrared spectrum of **85** showed the broad band of a hydroxyl group at 3320 cm^{-1}. The ^1H NMR spectrum displayed the proton neighboring the hydroxyl group at δ 4.23 as a doublet of doublets ($J = J' = 4.5$ Hz). Two singlets for the geminal dimethyl group were observed at δ 0.91 and 0.88. The molecular ion peak at m/z 194.1672 in the high resolution mass spectrum supported the molecular formula $C_{13}H_{22}O$.



85

The target molecule, Johnson intermediate **21**, was subsequently obtained in 86% yield by oxidation of alcohol **85** with pyridinium chlorochromate on alumina in dichloromethane at room temperature for 1.5 hours. Ketone **21** thus generated was identified by direct comparision of its IR, MS, ^{1}H NMR, and ^{13}C NMR spectra with those of an authentic sample kindly provided by Prof. Oppolzer of Université de Genève. Accordingly, a formal synthesis of (±)-longifolene (**1**) was completed.

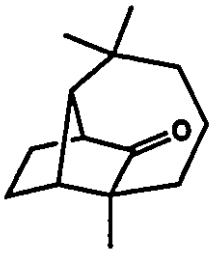


21

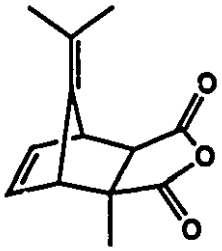
In conclusion, the formal synthesis of (±)-longifolene (**1**) has been accomplished by synthesizing Johnson intermediate **21** from 6,6-dimethylfulvene in *ca.* 5% overall yield, using a Diels-Alder approach as outlined in **Scheme 20**.[47]

It is noteworthy that the same synthetic sequence starting with citraconic anhydride and 6,6-dimethylfulvene could, in principle, lead to the production of ketone **86**. This alternative approach had been explored in our laboratory.[48] Unfortunately, it was found that the Diels-Alder

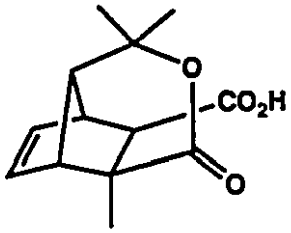
reaction of citraconic anhydride and 6,6-dimethylfulvene gave only 30% yield of the *exo* adduct **87**. Furthermore, the subsequent lactonization resulted in the formation of the desired lactone acid **88** in only 18% yield at best. This approach was thus proved to be ineffective.



86

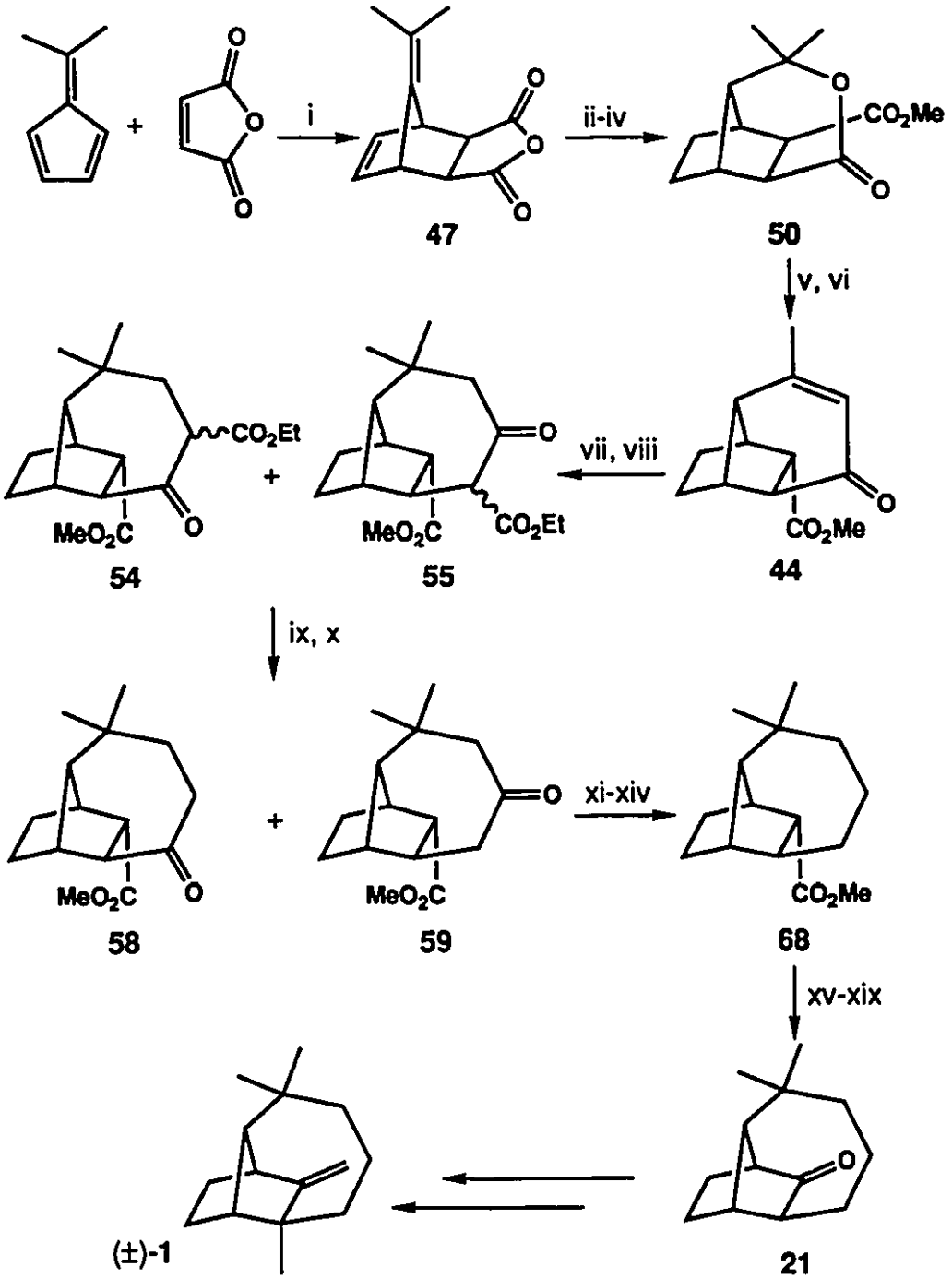


87



88

Scheme 20



i. PhH, reflux; ii. 50% H_2SO_4; iii. H_2SO_4, MeOH; iv. H_2, Pd/C; v. NaOMe, MeOH; vi. P_2O_5, $MeSO_3H$; vii. Me_2CuLi; viii. N_2CHCO_2Et, $BF_3{\cdot}OEt_2$; ix. LiI, H_2O, collidine; x. K_2CO_3; MeI; xi. $NaBH_4$; xii. MsCl, Et_3N, Py; xiii. NaI, Zn; xiv. H_2, PtO_2; xv. KOH; xvi. MeLi; xvii. CF_3CO_3H, Na_2HPO_4; xviii. 1 N NaOH; xix. PCC-Al_2O_3

Experimental

General

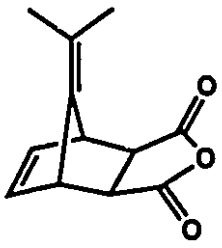
Melting points were recorded on a Köfler hot stage apparatus and are uncorrected. Infrared spectra (IR) were recorded using Nicolet 7-199, Nicolet MX-1, or Perkin-Elmer FTIR spectrometers. High resolution mass spectra (MS) were obtained using a Kratos AEI MS-50 high resolution mass spectrometer. Chemical ionization mass spectra (CIMS) were obtained using an AEI MS-12 mass spectrometer with ammonia as the reagent gas. Elemental analyses were carried out by the microanalytical laboratory of this department. Optical rotations were determined in a Perkin-Elmer 241 polarimeter. Specific rotation, $[\alpha]_D$, is reported in degrees at the specified temperature and concentration (c.) is given in grams per 100 mL in the specified solvent. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded using the following spectrometers: Bruker WH-200 (200 MHz), Bruker AM-300 (300 MHz), Bruker WH-400 (400 MHz), and Varian 500 (500 MHz). Coupling constants are reported to within ±0.5 Hz. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker WH-200 (50 MHz), Bruker AM-300 (75 MHz), and Bruker WH-400 (100 MHz). Carbon-13 mutiplicities were derived from off-resonance or Carr-Purcel-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test). Methylene groups and quaternary carbons appear as signals in-phase with respect to the deuteriochloroform signal while the signals out-of-phase to that of deuteriochloroform are for the methyl and methine groups. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a reference (undecoupled) spectrum was computer-subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing antiphase with respect to the irradiated signal.

Products were purified either by flash chromatography using silica gel 60 (230-400 mesh), distillation using a bulb-to-bulb Kugelrohr apparatus, or by fractional crystallization. All reactions were monitored by analytical thin-layer chromatography (TLC) performed on aluminum-backed plates precoated with silica gel 60 F_{254} as supplied by Merck. The visualization of the chromatograms was performed by dipping in either an ethanol solution of vanillin (5%, w/v) or an aqueous solution of phosphomolybdic acid (3%, w/v). Solvents were removed under reduced pressure on a rotary evaporator.

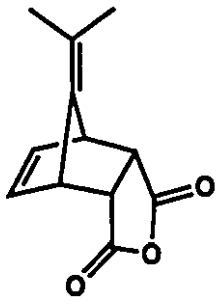
Materials

Skellysolve B refers to Skelly Oil Company light petroleum, bp 62-70°C. Skellysolve B (skelly B) was distilled prior to use. Pyrrolidine was distilled from barium oxide. Triethylamine was distilled from calcium hydride under an argon atmosphere. Solvents were dried as follows: benzene by distillation from lithium aluminum hydride or calcium hydride; diethyl ether, tetrahydrofuran, toluene, and xylene by distillation from a blue or purple solution of sodium and benzophenone under an argon atmosphere; dichloromethane, pyridine, and acetonitrile by distillation from calcium hydride under an argon atmosphere; acetone by distillation first over potassium permanganate and then potassium carbonate under an argon atmosphere; methanol by distillation from magnesium and a trace amount of carbon tetrachloride; chloroform by distillation from potassium carbonate under an argon atmosphere; dimethylformamide by distillation under reduced pressure from magnesium sulfate or barium oxide; carbon tetrachloride by simple distillation. Anhydrous magnesium sulfate was used for drying organic solutions.

(1R*,2R*,6S*,7S*)-10-Isopropylidene-4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (47) and (1R*,2S*,6R*,7S*)-10-isopropylidene-4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (48)



47



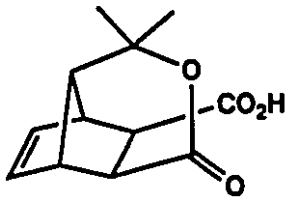
48

Diels-Alder reaction in refluxing benzene: A solution of 6,6-dimethylfulvene (8.82 g, 0.083 mol) and maleic anhydride (10.58 g, 0.108 mol) in dry benzene (76 mL) was heated under reflux under an argon atmosphere for 48 hours. Cooling this solution to room temperature produced a large amount of yellow-white solid that was filtered and recrystallized from petroleum ether-ether to produce the white crystalline anhydride **47**. The filtrate and mother liquor were combined, concentrated, and recrystallized to give more of **47**. The remaining filtrate and mother liquor were then combined, concentrated, and subjected to flash chromatography (5-33% ether in petroleum ether) to give starting fulvene (1.1 g, 12% recovery), followed by *endo* isomer **48** (37 mg, 0.25% based on consumed fulvene): IR ($CHCl_3$, cast): 1783 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 6.46 (m, 2H, -**H**C=C**H**-), 3.94 (m, 2H, 2 × =CC**H**-), 3.40 (m, 2H, 2 × -C**H**CO-), 1.61 (s, 6H, 2 × -C**H**$_3$); MS m/z (M^+) for $C_{12}H_{12}O_3$: calcd. 204.0787, found 204.0788. Continued elution gave *exo* isomer **47**: mp 138-140°C; IR ($CHCl_3$, cast): 1771 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 6.45 (dd, J = 2, 2 Hz, 2H, -**H**C=C**H**-), 3.87 (dd, J = 2, 2 Hz, 2H, 2 × =CC**H**-), 3.04 (s, 2H, 2 × -C**H**CO-), 1.60 (s, 6H, 2 × -C**H**$_3$); MS m/z (M^+) for $C_{12}H_{12}O_3$: calcd. 204.0787, found 204.0779. The *exo*

product **47** obtained by recrystallization and chromatography gave a combined yield of 10 g (67% based on consumed fulvene).

Diels-Alder reaction at room temperature: A solution of 6,6-dimethylfulvene (85 mg, 0.80 mmol) and maleic anhydride (97 mg, 0.99 mmol) in dry benzene (5 mL) was stirred at room temperature under an argon atmosphere for 48 hours. The solution was then concentrated to give a crude product (0.17 g) that contained a mixture of **47** and **48** in a ratio of 1 : 1 (based on ^{1}H NMR integration).

(1S*,5S*,6R*,7S*,10R*)-6-Carboxy-2,2-dimethyl-3-oxatricyclo-[5.3.0.0^{5,10}]dec-8-en-4-one (49)

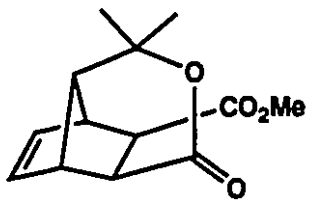


49

The Diels-Alder adduct **47** (9.25 g, 45.3 mL) was dissolved in 50% sulfuric acid (45 mL). The solution was stirred at room temperature under an argon atmosphere for 48 hours. The resulting dark red-brown solution was then diluted with water (50 mL) and filtered through Celite. The filtrate was extracted with ethyl acetate (4 × 20 mL). The combined extracts were dried, concentrated, and recrystallized from ethyl acetate to give acid **49** (5.3 g, 53% yield) as a white crystalline solid: mp 174-176.5°C; IR ($CHCl_3$, cast): 3440 (br, COOH), 1721 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (br s, 1H, -COO**H**), 6.63 (ddd, *J* = 6, 3, 1 Hz, 1H, =C**H**-), 6.15 (ddd, *J* = 6, 3, 1 Hz, 1H, =C**H**-), 3.41 (m, 1H, =CC**H**-), 3.26 (m, 1H, =CC**H**-), 2.87 (ddd, *J* = 8, 1.5, 1.5 Hz, 1H, -C**H**CO-), 2.49 (dd, *J* = 8, 1.5 Hz, 1H, -C**H**CO-),

1.98 (m, 1H, -C(CH_3)$_2$C**H**-), 1.40 (s, 3H, -C**H**$_3$), 1.35 (s, 3H, -C**H**$_3$); MS m/z (M^+) for $C_{12}H_{14}O_4$: calcd. 222.0892, found 222.0877.

(1S*,5S*,6R*,7S*,10R*)-6-Carbomethoxy-2,2-dimethyl-3-oxatricyclo-[5.3.0.0^{5,10}]dec-8-en-4-one (45)

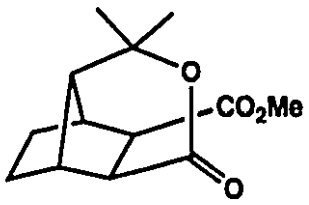


45

From acid 49: Acid **49** (4.4 g, 19.7 mmol) was dissolved in dry methanol (25 mL). Concentrated sulfuric acid (*ca.* 20 mg) was added. The resulting solution was stirred at room temperature for 16 hours. At the end of this time, the reaction flask was filled with a white solid. Fitration gave white crystalline ester **45** (2.5 g). The filtrate was concentrated and then dissolved in chloroform. The chloroform solution was washed with water, 5% aqueous sodium bicarbonate solution, and saturated sodium chloride solution. The organic solution was then dried and concentrated to give more of ester **45** (2.1 g). The combined yield of ester **45** was 4.6 g (100% yield). This material was used in the following step without further purification: mp 159-160°C; IR ($CHCl_3$, cast): 1748, 1731 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (ddd, *J* = 6, 3, 1 Hz, 1H, =C**H**-), 6.14 (ddd, *J* = 6, 3, 1 Hz, 1H, =C**H**-), 3.70 (s, 3H, -COOC**H**$_3$), 3.45 (m, 1H, =CC**H**-), 3.24 (m, 1H, =CC**H**-), 2.85 (ddd, *J* = 8, 1.5, 1.5 Hz, 1H, -C**H**CO-), 2.43 (d, *J* = 8 Hz, 1H, -C**H**CO-), 1.97 (dd, *J* = 1.5, 1.5 Hz, 1H, -C(CH_3)$_2$C**H**-), 1.39 (s, 3H, -C**H**$_3$), 1.34 (s, 3H, -C**H**$_3$); MS m/z (M^+) for $C_{13}H_{16}O_4$: calcd. 236.1049, found 236.1047; Analysis for $C_{13}H_{16}O_4$: calcd. C: 66.08%, H: 6.83%, found C: 65.87%, H: 6.76%.

From a mixture of anhydrides 47 and 48: A solution of a mixture of anhydrides **47** and **48** (8.95 g, 28% for **47** based on ^{1}H NMR integration) in 50% sulfuric acid (50 mL) was stirred at room temperature under an argon atmosphere for 45 hours. The resulting dark solution was then diluted with water and filtered through Celite. The filtrate was extracted with ethyl acetate (3 × 20 mL). The extracts were combined, dried, concentrated, and then dissolved in dry methanol (22 mL). Concentrated sulfuric acid (*ca.* 15 mg) was added and the resulting solution was stirred at room temperature for 16 hours. The solution was then concentrated and dissolved in chloroform. The chloroform solution was washed with water, 5% aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The organic layer was then dried, concentrated, and recrystallized from ethyl acetate to give a white crystalline solid **45** (0.92 g). The mother liquor was concentrated and subjected to flash chromatography (25% ethyl acetate in skelly B) to give more of ester **45** (0.40 g). The combined yield of **45** for two steps was 1.32 g (38% yield based on starting *exo* anhydride **47**).

(1S*,5S*,6R*,7S*,10R*)-6-Carbomethoxy-2,2-dimethyl-3-oxatricyclo-[5.3.0.0^{5,10}]decan-4-one (50)

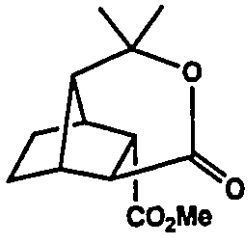


50

Ester **45** (5.53 g, 23.4 mmol) was dissolved in ethyl acetate (50 mL). 5% Palladium on carbon (100 mg) was added. The mixture was hydrogenated under 20 p.s.i. (1 p.s.i. = 6.9 kPa) of hydrogen for 6

hours using a Parr hydrogenation apparatus. The mixture was then filtered and concentrated to give *exo* ester **50** (5.47 g, 98% yield) as a white solid: mp 118-120°C; IR ($CHCl_3$, cast): 1800-1650 cm^{-1} (br, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, -COOC**H**$_3$), 2.97 (m, 2H, 2 × -C**H**CO-), 2.63 (br d, *J* = 5.5 Hz, 1H), 2.58 (d, *J* = 7.5 Hz, 1H), 1.87 (m, 2H), 1.68 (m, 1H), 1.50-1.42 (m, 2H), 1.46 (s, 3H, -C**H**$_3$), 1.39 (s, 3H, -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 171.97 (p), 171.77 (p), 82.60 (p), 54.33 (a), 52.10 (a), 49.07 (a), 48.60 (a), 39.96 (a), 38.87 (a), 31.96 (p), 31.14 (a), 26.36 (a), 25.33 (p); MS m/z (M^+) for $C_{13}H_{18}O_4$: calcd. 238.1205, found 238.1209; Analysis for $C_{13}H_{18}O_4$: calcd. C: 65.53%, H: 7.61%, found C: 65.19%, H: 7.55%.

(1S*,5S*,6S*,7S*,10R*)-6-Carbomethoxy-2,2-dimethyl-3-oxatricyclo-[5.3.0.0^{5,10}]decan-4-one (53)

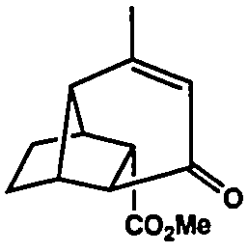


53

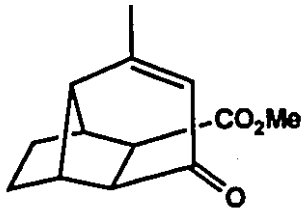
A solution of sodium methoxide in methanol was prepared by dissolving sodium metal (0.49 g, 21.3 mmol) in dry methanol (25 mL). *exo* Ester **50** (4.59 g, 19.3 mmol) was added and the resulting solution was heated under reflux under an argon atmosphere for 8 hours. The solution was then acidified with 1 N hydrochloric acid and extracted with chloroform (3 × 30 mL). The combined extracts were dried and concentrated to give *endo* ester **53** (4.28 g, 93% yield) as a white solid: mp 91-93°C; IR ($CHCl_3$, cast): 1737 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 3.74 (s, 3H, -COOC**H**$_3$), 3.10 (m, 1H, -C**H**CO-), 2.88 (m, 1H, -C**H**CO-), 2.73 (m, 1H), 2.50 (d, *J* = 5 Hz, 1H), 2.06 (dd, *J* = 3, 1.5

Hz, 1H), 1.78 (m, 1H), 1.62-1.47 (m, 3H), 1.48 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3); MS m/z (M^+) for $C_{13}H_{18}O_4$: calcd. 238.1205, found 238.1193; Analysis for $C_{13}H_{18}O_4$: calcd. C: 65.53%, H: 7.61%, found C: 65.39%, H: 7.77%.

(1R*,5S*,6S*,7S*,10R*)-6-Carbomethoxy-2-methyltricyclo-[5.3.0.0^{5,10}]dec-2-en-4-one (44) and (1R*,5S*,6R*,7S*,10R*)-6-carbomethoxy-2-methyltricyclo[5.3.0.0^{5,10}]dec-2-en-4-one (51)



44



51

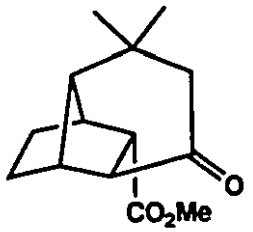
Preparation of P_2O_5-$MeSO_3H$ reagent: Phosphorus pentoxide (9 g) was added to freshly distilled methanesulfonic acid (95 g). The mixture was stirred at room temperature under an argon atmosphere overnight. The resulting clear solution was stored at room temperature.

From *exo* ester 50: A solution of *exo* ester **50** (0.20 g, 0.84 mmol) in dry dichloromethane (1 mL) was added to the P_2O_5-$MeSO_3H$ reagent (2.01 g) and the resulting solution was then stirred at 65°C under an argon atmosphere for 40 hours. At the end of this time the dark brown solution was diluted with dichloromethane and poured into water (10 mL). The organic layer was then removed and washed with water, 5% aqueous sodium bicarbonate solution, and water. The organic solution was dried and concentrated to give a brown oil. Flash chromatography (50% ether in skelly B) gave *endo* enone **44** (16 mg, 9% yield) as a white solid: mp 39-40°C (skelly B); IR ($CHCl_3$, cast):

1739 (C=O, ester), 1676 cm^{-1} (C=O, enone); ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (m, 1H, =C**H**-), 3.71 (s, 3H, -COOC**H**$_3$), 3.02 (m, 1H, =C(CH_3)C**H**-), 2.78 (m, 1H, -C**H**CO-), 2.70 (m, 1H, -C**H**CO-), 2.61 (m, 1H), 2.51 (m, 1H), 2.03 (d, J = 1.5 Hz, 3H, -C**H**$_3$), 1.73-1.54 (m, 3H), 1.39 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 202.07 (p), 173.21 (p), 161.79 (p), 124.30 (a), 54.76 (a), 54.10 (a), 51.88 (a), 50.43 (a), 47.07 (a), 42.28 (a), 28.18 (p), 24.89 (p), 23.73 (a); MS m/z (M^+) for $C_{13}H_{16}O_3$: calcd. 220.1100, found 220.1098; Analysis for $C_{13}H_{16}O_3$: calcd. C: 70.89%, H: 7.32%, found C: 70.98%, H: 7.37%. Continued elution gave *exo* enone **51** (52 mg, 28% yield) as a yellow oil: IR ($CHCl_3$, cast): 1733 (C=O, ester), 1681 cm^{-1} (C=O, enone); ^1H NMR (300 MHz, $CDCl_3$): δ 5.64 (m, 1H, =C**H**-), 3.54 (s, 3H, -COOC**H**$_3$), 2.98 (m, 1H, =C(CH_3)C**H**-), 2.93 (br d, J = 8.5 Hz, 1H, -C**H**CO-), 2.89 (d, J = 8.5 Hz, 1H, -C**H**CO-), 2.65 (m, 1H), 2.33 (s, 1H), 1.99 (d, J = 2 Hz, 3H, -C**H**$_3$), 1.88-1.63 (m, 3H), 1.27 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 201.00 (p), 176 (p), 163.44 (p), 124.65 (a), 57.51 (a), 53.49 (a), 51.72 (a), 51.51 (a), 49.15 (a), 42.16 (a), 32.12 (p), 25.78 (p), 23.58 (a); MS m/z (M^+) for $C_{13}H_{16}O_3$: calcd. 220.1100, found 220.1098.

From *endo* ester 53: A solution of *endo* ester **53** (4.23 g, 17.8 mmol) in dry dichloromethane (20 mL) was added to the P_2O_5-$MeSO_3H$ reagent (43 g) and the resulting solution was stirred at 65°C under an argon atmosphere for 40 hours. At the end of this time the dark brown solution was diluted with dichloromethane and poured into water (100 mL). The organic layer was then removed and washed with water, 5% aqueous sodium bicarbonate solution, and water. The organic solution was dried and concentrated to give a brown oil. Flash chromatography (50% ether in skelly B) gave enones **44** (3.21 g, 82% yield) and **51** (12 mg, 1% yield).

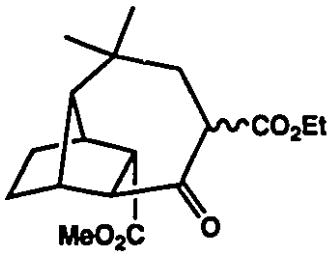
(1R*,5S*,6S*,7S*,10R*)-6-Carbomethoxy-2,2-dimethyltricyclo-[5.3.0.0^{5,10}]decan-4-one (43)



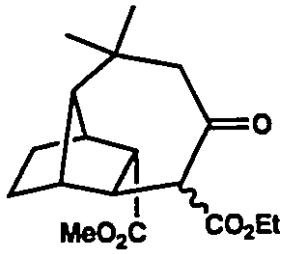
43

Purified copper(I) iodide (5.20 g, 27.3 mmol) was added to dry ether (160 mL) at 0°C. Methyllithium (1.6 M in ether, 34.1 mL, 54.6 mmol) was added dropwise to this stirred suspension and the mixture was stirred at 0°C under an argon atmosphere untill all the yellow-brown solid had dissolved (*ca.* 1 hour). A solution of **44** (2.00 g, 9.07 mmol) in dry ether (10 mL) was added dropwise to the lithium dimethylcopper reagent and the resulting solution was stirred at 0°C under an argon atmosphere for 2 hours. The reaction was then quenched by addition of 1 N hydrochloric acid. Chloroform was added and the mixture was filtered through Celite. The organic layer was removed and the aqueous layer was extracted with chloroform (2 × 50 mL). The combined organic extracts were then washed with water, dried, concentrated, and purified by flash chromatography (50% ether in skelly B) to give keto ester **43** (2.07 g, 96% yield) as a white solid: mp 93-93.5°C; IR ($CHCl_3$, cast): 1736 (C=O, ester), 1714 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H, -COOC**H**$_3$), 2.91 (s, 1H), 2.89 (m, 1H), 2.72 (m, 1H), 2.35 (d, *J* = 18 Hz, 1H, -C**H**HCO-), 2.31 (d, *J* = 5 Hz, 1H), 2.23 (d, *J* = 18 Hz, 1H, -CH**H**CO-), 1.71 (m, 2H), 1.48 (m, 2H), 1.27 (m, 1H), 1.13 (s, 3H, -C**H**$_3$), 1.02 (s, 3H, -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 212.22 (p), 173.09 (p), 59.50 (a), 55.86 (a), 51.86 (a), 49.50 (p), 45.37 (a), 43.61 (a), 42.03 (a), 34.04 (p), 32.37 (a), 29.64 (a), 27.21 (p), 25.82 (p); MS m/z (M^+) for $C_{14}H_{20}O_3$: calcd. 236.1413, found 236.1413; Analysis for $C_{14}H_{20}O_3$: calcd. C: 71.16%, H: 8.53%, found C: 70.85%, H: 8.64%.

(1S*,2S*,3S*,8R*,9R*)-5-Carbethoxy-2-carbomethoxy-7,7-dimethyltricyclo[6.3.0.0^{3,9}]undecan-4-one (54) and (1R*,6S*,7S*,8S*,11S*)-5-carbethoxy-7-carbomethoxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecan-4-one (55)



54

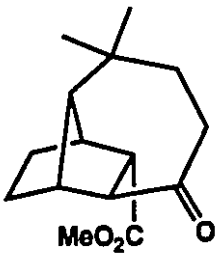


55

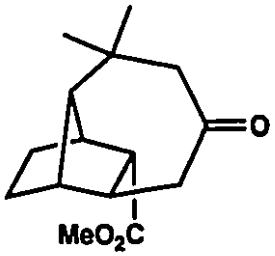
Boron trifluoride etherate (1.60 mL, 12.95 mmol) was added to a solution of keto ester **43** (2.00 g, 8.47 mmol) in dry ether (50 mL) at 0°C. Ethyl diazoacetate (1.36 mL, 12.95 mmol) was then added to this solution. The reaction mixture was allowed to warm up to room temperature and left to stir in the dark under an argon atmosphere for 17 hours. At the end of this time, the solution was neutralized with saturated aqueous sodium bicarbonate solution and then extracted with chloroform (3 × 50 mL). The combined extracts were washed with water, dried, concentrated, and purified by flash chromatography (50% ether in skelly B) to give a mixture of the desired ring expansion products (2.73 g, 100% yield) as a yellow oil. The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of this mixture was very complex due to the likely presence of all six possible isomers (regioisomers **54** and **55** and their respective stereoisomers and enols). Only the following few isolated signals could be clearly identified: δ 13.10, 12.95 (-C(COOEt)=C(O**H**)-), 4.25-4.05 (-COOC**H**$_2$CH$_3$), 3.70 (-COOC**H**$_3$). During the flash chromatography, a small amount of regioisomer **54** was isolated. This material was shown by the following spectral data to exist as a pair of epimers (10% each) and in the corresponding enol form (80%): IR ($CHCl_3$, cast): 1739 (C=O, ester), 1704 (C=O, ketone), 1636 (C=O, enol ester), 1608 cm^{-1} (C=C, enol); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.1 (s,

0.8H, =C(O**H**)-), 4.20 (q, J = 6.5 Hz, 2H, -COOC**H**$_2$CH$_3$), 3.70 (s, 3H, -COOC**H**$_3$), 3.47 (m, 1H, -C**H**(COOCH$_3$)-), 3.12 (m, 0.1H, -C**H**(C=O)(COOEt)-), 3.09 (m, 0.1H, -C**H**(C=O)(COOEt)-), 2.93 (d, J = 3.5 Hz, 1H), 2.65 (m, 1H), 2.44 (d, J = 18.5 Hz, 1H), 2.32 (d, J = 18.5 Hz, 1H), 2.32 (d, J = 5 Hz, 1H), 1.60 (m, 1H), 1.46 (m, 1H), 1.29 (t, J = 6.5 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.24-1.13 (m, 2H), 1.06 (s, 3H, -C**H**$_3$), 0.92 (s, 3H, -C**H**$_3$); MS m/z (M^+) for $C_{18}H_{26}O_5$: calcd. 322.1781, found 322.1779.

(1S*,2S*,3S*,8R*,9R*)-2-Carbomethoxy-7,7-dimethyltricyclo-[6.3.0.0^{3,9}]undecan-4-one (58) and (1R*,6S*,7R*,8S*,11S*)-7-carbomethoxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecan-4-one (59)



58



59

From carboxylic acids 56 and 57: A mixture of **54** and **55** (2.93 g, 9.10 mmol) was dissolved in collidine (40 mL) in a flask wrapped in aluminum foil. Lithium iodide (9.77 g, 73.0 mmol) and water (1.3 mL, 73.0 mmol) were added. The resulting mixture was heated under reflux for 3 hours. The resulting solution was cooled and poured into ice-cold 10% hydrochloric acid (100 mL). Ether (100 mL) was then added. The ether layer was removed, washed with 10% hydrochloric acid (2 × 100 mL), and water. The ether solution was then dried and concentrated to give a mixture of carboxylic acids **56** and **57** (1.94 g, 90% yield) as a brown oil. This mixture (1.94 g, 8.23 mmol) was then dissolved in dry acetone (45 mL) and potassium carbonate (2.85 g,

20.64 mmol) was introduced. After stirring at room temperature under an argon atmosphere for 2.5 hours, methyl iodide (2.6 mL, 41.29 mmol) was added and the resulting mixture was heated under reflux under an argon atmosphere for 12 hours. The reaction mixture was then acidified with 1 N hydrochloric acid and extracted with chloroform (3 × 50 mL). The combined extracts were washed with saturated sodium bisulfite and water, dried, and concentrated to give a yellow oil that was purified by flash chromatography (50% ether in skelly B) to give an inseparable mixture of esters **58** and **59** (1.96 g, 95% yield) in a ratio of 2.5 : 1 (based on 300 MHz ^1H NMR integration).

Keto ester 58 from alcohol 60: To a solution of alcohol **60** (37 mg, 0.147 mmol) in dry dichloromethane (1 mL), pyridinium chlorochromate on alumina (0.93 mmol/g, 246 mg, 0.221 mmol) was added. The resulting mixture was stirred at room temperature under an argon atmosphere for 17 hours and then filtered through Celite. The filtrate was concentrated and purified by flash chromatography (30% ether in skelly B) to give keto ester **58** (35 mg, 95% yield) as a white crystalline solid: mp 97-99°C (ether); IR ($CHCl_3$, cast): 1738 (C=O, ester), 1697 cm^{-1} (C=O, ketone); ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, -COOC**H**$_3$), 3.13 (ddd, J = 5, 5, 2.5 Hz, 1H, -C**H**(COOCH$_3$)-), 2.93 (d, J = 5 Hz, 1H, -C**H**CO-), 2.61 (ddd, J = 16, 16, 3 Hz, 1H, -C**H**HCO-), 2.60 (m, 1H), 2.39 (d, J = 5 Hz, 1H, -C**H**CH(COOCH$_3$)-), 2.32 (ddq, J = 16, 5, 1 Hz, 1H, -CH**H**CO-), 1.81 (dd, J = 14, 14 Hz, 1H), 1.70-1.57 (m, 2H), 1.51-1.12 (m, 4H), 1.06 (s, 6H, 2 × -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 212.50 (p), 173.25 (p), 63.65 (a), 58.32 (a), 52.02 (a), 48.43 (a), 41.41 (a), 40.00 (a), 38.56 (p), 35.58 (p), 33.60 (p), 31.01 (a), 29.63 (a), 29.12 (p), 25.97 (p); MS m/z (M^+) for $C_{15}H_{22}O_3$: calcd. 250.1570, found 250.1564; Analysis for $C_{15}H_{22}O_3$: calcd. C: 71.97%, H: 8.86%, found C: 71.24%, H: 8.96%.

Keto ester 59 from alcohol 61: To a solution of alcohol **61** (29 mg, 0.115 mmol) in dry dichloromethane (1 mL), was added pyridinium chlorochromate on alumina (0.93 mmol/g, 249 mg, 0.232 mmol). After stirring at room temperature under an argon

atmosphere for 11 hours, the mixture was filtered through Celite, concentrated, and purified by flash chromatography (30% ether in skelly B) to give keto ester **59** (26 mg, 90% yield) as a white solid: mp 101-103°C; IR ($CHCl_3$, cast): 1726 (C=O, ester), 1687 cm^{-1} (C=O, ketone); ^1H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 3H, -COOC**H**$_3$), 3.18 (ddd, J = 5, 5, 2.5 Hz, 1H, -C**H**(COOCH$_3$)-), 2.76 (d, J = 12 Hz, 1H, -C(CH$_3$)$_2$C**H**HCO-), 2.65 (m, 2H, -C**H**CH(COOCH$_3$)-, -CHC**H**HCO-), 2.42 (m, 1H, -C**H**CH$_2$CO-), 2.31 (dd, J = 16, 3 Hz, 1H, -CHCH**H**CO-), 2.18 (br d, J = 12 Hz, 1H, -C(CH$_3$)$_2$CH**H**CO-), 2.02 (d, J = 4.5 Hz, 1H, -C**H**CHCH$_2$CO-), 1.70-1.56 (m, 2H), 1.46 (m, 1H), 1.37-1.15 (m, 2H), 1.11 (s, 3H, -C**H**$_3$), 1.00 (s, 3H, -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 210.61 (p), 174.58 (p), 62.68 (a), 55.29 (p), 51.78 (a), 51.59 (a), 49.37 (p), 41.81 (a), 41.69 (a), 39.50 (a), 33.71 (p), 30.88 (a), 30.60 (a), 29.78 (p), 25.62 (p); MS m/z (M^+) for $C_{15}H_{22}O_3$: calcd. 250.1570, found 250.1565; Analysis for $C_{15}H_{22}O_3$: calcd. C: 71.97%, H: 8.86%, found C: 71.99%, H: 8.76%.

Thioketalization of a mixture of keto esters 58 and 59:

1,2-Ethanedithiol (76 μL, 0.899 mmol), followed by boron trifluoride etherate (22 μL, 0.180 mmol), was added to a solution of keto esters **58** and **59** (35 mg, 0.140 mmol) in dry dichloromethane (1 mL) at 0°C. The resulting solution was stirred at 0°C for 3 hours under an argon atmosphere. At the end of this time, the solution was poured into ice-cold 1 N aqueous sodium hydroxide solution (10 mL) and then extracted with dichloromethane. The extract was washed with water, dried, concentrated, and purified by flash chromatography (10% ether in skelly B) to give thioketal **63** (3 mg, 6% yield) as a yellow oil: IR ($CHCl_3$, cast): 1733 cm^{-1} (C=O, ester); ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, -COOC**H**$_3$), 3.37-3.17 (m, 4H, -SC**H**$_2$C**H**$_2$S-), 3.06 (m, 1H), 2.70-2.60 (m, 2H), 2.51 (dd, J = 4, 4 Hz, 1H), 2.42 (d, J = 15 Hz, 1H), 2.33-2.18 (m, 3H), 1.60-1.10 (m, 5H), 1.25 (s, 3H, -C**H**$_3$), 1.07 (s, 3H, -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 175.23 (p), 69.22 (p), 62.32 (a), 55.16 (p), 51.62 (a), 50.63 (p), 43.52 (a), 41.85 (a), 40.27 (a), 39.92 (p), 37.88 (p), 35.31 (p), 34.53 (a), 31.50

(a), 30.35 (p), 29.75 (p), 25.14 (p); MS m/z (M^+) for $C_{17}H_{26}O_2S_2$: calcd. 326.1376, found 326.1373. Continued elution gave a mixture of **62** and **63** (28 mg, 61% yield). The combined yield of **62** and **63** was 31 mg (67% yield).

Thioketalization of keto ester 58:

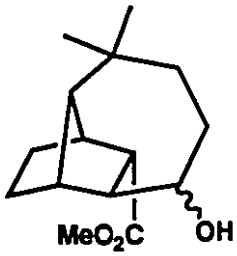
1,2-Ethanedithiol (48 μL, 0.580 mmol), followed by boron trifluoride etherate (16 μL, 0.130 mmol), was added to a solution of keto ester **58** (22 mg, 0.088 mmol) in dry dichloromethane (0.5 mL) at 0°C. The resulting solution was stirred at 0°C for 1.5 hours under an argon atmosphere. The reaction was then worked up as before and purified by flash chromatography (10-30% ether in skelly B) to give a yellow solid **62** (14 mg, 70% based on consumed starting material): mp 92-94°C; IR ($CHCl_3$, cast): 1736 cm^{-1} (C=O, ester); ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H, -COOC**H**$_3$), 3.44-3.15 (m, 4H, -SC**H**$_2$C**H**$_2$S-), 3.08 (m, 1H), 2.75 (d, J = 6 Hz, 1H), 2.47 (dd, J = 5, 5 Hz, 1H), 2.42-2.28 (m, 2H), 2.09 (dd, J = 15.5, 9 Hz, 1H), 1.69-1.57 (m, 2H), 1.48-1.08 (m, 5H), 1.00 (s, 6H, 2 × -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 175.08 (p), 73.75 (p), 62.48 (a), 58.79 (a), 52.27 (a), 51.71 (a), 42.41 (a), 41.15 (a), 39.19 (p × 2), 38.59 (p), 38.33 (p), 33.10 (p), 30.21 (p), 29.75 (p), 25.37 (p); MS m/z (M^+) for $C_{17}H_{26}O_2S_2$: calcd. 326.1376, found 326.1370. Continued elution gave starting keto ester **58** (6.7 mg, 30% recovery).

Thioketalization of keto ester 59:

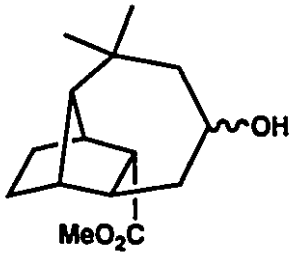
1,2-Ethanedithiol (44 μL, 0.525 mmol), followed by boron trifluoride etherate (15 μL, 0.125 mmol), was added to a solution of keto ester **59** (19.8 mg, 0.079 mmol) in dry dichloromethane (0.5 mL) at 0°C. The resulting solution was stirred at 0°C for 1.5 hours under an argon atmosphere. The reaction was then worked up as before and the residue subjected to flash chromatography (10-30% ether in skelly

B) to give thioketal **63** (7 mg, 55% based on consumed starting material) and starting keto ester **59** (10 mg, 51% recovery).

(1S*,2S*,3S*,8R*,9S*)-2-Carbomethoxy-7,7-dimethyltricyclo-[6.3.0.0^{3,9}]undecan-4-ol (60) and (1R*,6S*,7R*,8S*,11S*)-7-carbomethoxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecan-4-ol (61)



60

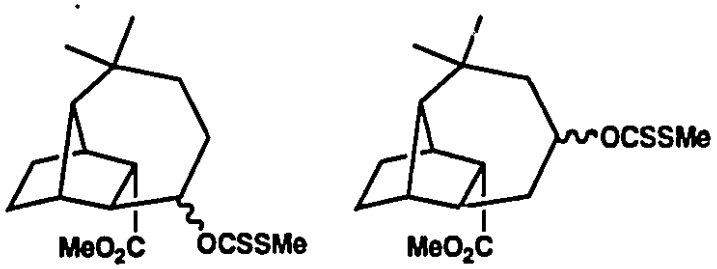


61

A mixture of keto esters **58** and **59** (33 mg, 0.132 mmol) was dissolved in methanol (1 mL). Sodium borohydride (10 mg, 0.264 mmol) was then added to this solution at 0°C and the resulting solution was stirred at 0°C under an argon atmosphere for 1 hour. The solution was then acidified with 1 N hydrochloric acid and extracted with ether (3 × 2 mL). The combined extracts were washed with water, dried, concentrated, and subjected to flash chromatography (70% ether in skelly B) to give a 1 : 1 mixture of epimeric alcohols **60** (4 mg, 12% yield) as a white solid: IR ($CHCl_3$, cast): 3450 (br, O-H), 1736 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (br dd, *J* = 11, 4 Hz, 0.5H, -C**H**(OH)-), 3.71 (s, 1.5H, -COOC**H**$_3$), 3.68 (s, 1.5H, -COOC**H**$_3$), 3.63 (br dd, *J* = 8, 8 Hz, 0.5H, -C**H**(OH)-), 3.32 (m, 0.5H, -C**H**(COOCH$_3$)-), 2.78 (ddd, *J* = 5, 5, 2.5 Hz, 0.5H, -C**H**(COOCH$_3$)-), 2.52 (dd, *J* = 4.5, 4.5 Hz, 0.5H), 2.46 (dd, *J* = 4.5, 4.5 Hz, 0.5H), 2.38 (d, *J* = 4.5 Hz, 0.5H), 2.35 (d, *J* = 6.5 Hz, 0.5H), 2.25 (br d, *J* = 6.5 Hz, 0.5H), 2.07 (d, *J* = 4.5 Hz, 0.5H), 1.94-1.70 (m, 2H), 1.67-1.51 (m, 3H), 1.49-1.39 (m, 2H), 1.35-1.07 (m, 3H), 1.02 (s, 1.5H, -C**H**$_3$), 1.01

(s, 1.5H, -C**H**$_3$), 0.98 (s, 1.5H, -C**H**$_3$), 0.97 (s, 1.5H, -C**H**$_3$); MS m/z (M^+) for $C_{15}H_{24}O_3$: calcd. 252.1726, found 252.1719. Continued elution gave a mixture of **60** and **61** (19 mg, 58% yield) and then an epimeric mixture of alcohols **61** (4 mg, 12% yield) in a ratio of 3 : 2 as a white solid: IR ($CHCl_3$, cast): 3370 (br, O-H), 1735 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 3.94 (m, 0.4H, -C**H**(OH)-), 3.81 (m, 0.6H, -C**H**(OH)-), 3.67 (s, 3H, -COOC**H**$_3$), 2.87 (ddd, J = 5, 5, 2 Hz, 0.4H, -C**H**(COOCH$_3$)-), 2.64 (ddd, J = 5, 5, 3 Hz, 0.6H, -C**H**(COOCH$_3$)-), 1.08 (s, 1.2H, -C**H**$_3$), 1.06 (s, 1.8H, -C**H**$_3$), 1.00 (s, 1.8H, -C**H**$_3$), 0.99 (s, 1.2H, -C**H**$_3$); MS m/z (M^+) for $C_{15}H_{24}O_3$: calcd. 252.1726, found 252.1727. The epimeric mixture of alcohols **61** was subjected to flash chromatography again to give the major epimer as a white solid: mp 83-85°C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (dddd, J = 11, 11, 5, 2.5 Hz, 1H, -C**H**(OH)-), 3.66 (s, 3H, -COOC**H**$_3$), 2.64 (ddd, J = 5, 5, 2.5 Hz, 1H, -C**H**(COOCH$_3$)-), 2.38 (dd, J = 4, 4 Hz, 1H), 2.30 (m, 1H), 2.07-1.98 (m, 2H), ..65 (m, 2H), 1.59-1.30 (m, 4H), 1.28-1.09 (m, 3H), 1.07 (s, 3H, -C**H**$_3$), 1.01 (s, 3H, -C**H**$_3$); Analysis for $C_{15}H_{24}O_3$: calcd. C: 71.39%, H: 9.59%, found C: 71.39%, H: 9.84%. The combined yield of **60** and **61** was 27 mg (82% yield).

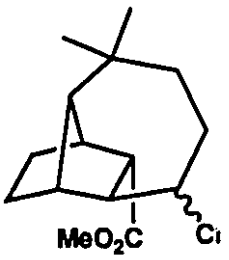
(1R*,6S*,7S*,8S*,11S*)-7-Carbomethoxy-2,2-dimethyl-5-(methylmercaptothiocarbonyloxy)tricyclo[6.3.0.0^{6,11}]undecane (69) and (1R*,6S*,7R*,8S*,11S*)-7-carbomethoxy-2,2-dimethyl-4-(methylmercaptothiocarbonyloxy)tricyclo[6.3.0.0^{6,11}]undecane (70)



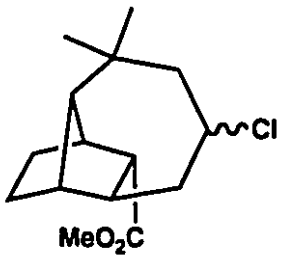
69 70

Sodium hydride (80% dispersion in mineral oil, 38 mg, 1.267 mmol) was added to a solution of alcohols **60** and **61** (44 mg, 0.174 mmol) in dry tetrahydrofuran (1 mL) at 0°C and the resulting solution was stirred at 0°C under an argon atmosphere for 30 minutes. At the end of this time, carbon disulfide (136 µL, 2.260 mmol) was added, followed by methyl iodide (70 µL, 1.130 mmol). After stirring at room temperature under an argon atmosphere for 4.5 hours, the solution was poured into ice-water (10 mL) and extracted with ether. The organic layer was washed with water, dried, concentrated, and purified by flash chromatography (5% ether in skelly B) to give an inseparable mixture of xanthates **69** and **70** (57 mg, 95% yield) as a yellow oil: IR ($CHCl_3$, cast): 1738 (C=O), 1048 cm^{-1} (C=S); ^1H NMR (300 MHz, $CDCl_3$): δ 5.92, 5.80, 5.46, 5.02 (4 × m, 1H, -C**H**(OCSS-)-), 3.60 (s, 3H, -COOC**H**$_3$), 2.53 (s, 1.5H, -SC**H**$_3$), 2.52 (s, 1.5H, -SC**H**$_3$), 1.17 (s, 1.5H, -C**H**$_3$), 1.07 (s, 1.5H, -C**H**$_3$); MS m/z (M^+) for $C_{17}H_{26}O_3S_2$: calcd. 342.1325, found 341.1328.

(1R*,6S*,7S*,8S*,11S*)-7-Carbomethoxy-5-chloro-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecane (71) and (1R*,6S*,7R*,8S*,11S*)-7-carbomethoxy-4-chloro-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecane (72)



71

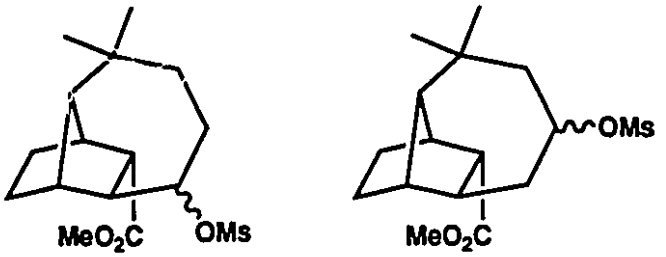


72

Pyridine (1 mL) was added to a solution of alcohols **60** and **61** (19 mg, 0.075 mmol) in dry dichloromethane (0.5 mL) and the

solution was kept at 0°C. To this solution thionyl chloride (55 μL, 0.750 mmol) was added and the resulting solution was heated under reflux for 13 hours under an argon atmosphere. At the end of this time, the dark mixture was diluted with ether (1 mL) and water (1 mL). The organic layer was removed and the aqueous layer was extracted with ether (3 × 1 mL). The combined organic portions were washed with 1 N hydrochloric acid and water, dried, concentrated, and purified by flash chromatography (skelly B) to give an inseparable mixture of chlorides **71** and **72** (13 mg, 64% yield) as a yellow solid: IR ($CHCl_3$, cast): 1736 cm^{-1} (C=O); ^1H NMR (300 NMR, $CDCl_3$): δ 4.39 (m, 0.5H, -C**H**Cl-), 4.16 (m, 0.5H, -C**H**Cl-), 3.63 (s, 1.5H, -COOC**H**$_3$), 3.62 (s, 1.5H, -COOC**H**$_3$), 3.21 (m, 0.5H, -C**H**(COOCH$_3$)-), 2.83 (ddd, *J* = 5, 5, 3 Hz, 0.5H, -C**H**(COOCH$_3$)-), 1.03 (s, 1.5H, -C**H**$_3$), 0.98 (s, 1.5H, -C**H**$_3$); MS m/z (M^+) for $C_{15}H_{23}O_2Cl$: calcd. 272.1358, 270.1388, found 272.1361, 270.1379.

(1R*,6S*,7S*,8S*,11S*)-7-Carbomethoxy-5-methanesulfonyloxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecane (73) and (1R*,6S*,7R*,8S*,11S*)-7-carbomethoxy-4-methanesulfonyloxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecane (74)

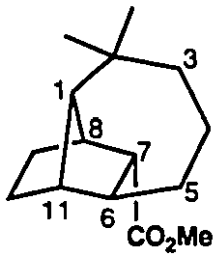


73 74

Pyridine (1.30 mL, 16.30 mmol), methanesulfonyl chloride (1.30 mL, 16.30 mmol), and triethylamine (2.3 mL, 16.30 mmol) were added sequentially to a solution of alcohols **60** and **61** (0.82 g, 3.26

mmol) in dry dichloromethane (30 mL) at 0°C. The resulting mixture was stirred at 0°C under an argon atmosphere for 30 minutes. Water was added and the resulting solution was diluted with ether (20 mL) and acidified with 1 N hydrochloric acid. The organic layer was removed and the aqueous layer was extracted with ether (2 × 30 mL). The combined organic portions were washed with 1 N hydrochloric acid and water, dried, concentrated, and purified by flash chromatography (30-50% ether in skelly B) to give an inseparable mixture of mesylates **73** and **74** (0.92 g, 85% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01, 4.90, 4.79, 4.48 (4 × m, 1H, -C**H**(OMs)-), 3.69, 3.67 (2 × s, 3H, -COOC**H**$_3$), 3.04, 2.56, 2.54 (3 × s, 3H, -SO_2C**H**$_3$), 1.09, 1.07, 1.02, 0.98 (4 × s, 6H, 2 × -C**H**$_3$); MS m/z (M^+ - CH_3) for $C_{15}H_{23}O_4S$: calcd. 299.1318, found 299.1314.

(1R*,6S*,7R*,8S*,11S*)-7-Carbomethoxy-2,2-dimethyltricyclo-[6.3.0.0^{6,11}]undecane (68)



68

From mesylates 73 and 74: Sodium iodide (2.07 g, 13.8 mmol) and zinc dust (30-mesh granular, 1.82 g, 27.8 g-atom) were added to a solution of mesylates **73** and **74** (0.92 g, 2.77 mmol) in dry tetrahydrofuran (25 mL). The resulting mixture was heated under reflux under an argon atmosphere for 15 hours. The mixture was then cooled and filtered through Celite. The filtrate was washed with water and saturated aqueous sodium chloride solution, dried, concentrated, and subjected to flash chromatography (5-50% ether in skelly B) to

give a mixture of **68** and **75** (0.50 g, 90% based on consumed starting mesylates) in a ratio of 1 : 1 (based on ^{1}H NMR integration). Continued elution gave starting mesylate **74** (0.13 g, 15% recovery).

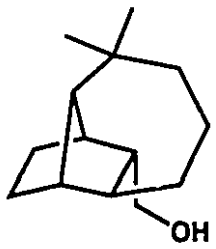
The mixture of **68** and **75** (0.50 g, 2.12 mmol) was dissolved in methanol (50 mL). Platinum(IV) oxide (44 mg) was added. The mixture was hydrogenated at room temperature under 30 p.s.i. (1 p.s.i. = 6.9 kPa) of hydrogen for 24 hours using a Parr apparatus. It was then filtered, concentrated, and purified by flash chromatography (2% ether in skelly B) to give ester **68** (0.49 g, 98% yield) as a white solid: mp 59-61°C; IR ($CHCl_3$, cast): 1736 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H, -COOC**H**$_3$), 2.76 (ddd, J = 5, 4, 2 Hz, 1H, **H**-7), 2.39 (dd, J = 4, 4 Hz, 1H, **H**-8), 2.18 (dd, J = 6, 5 Hz, 1H, **H**-6), 2.03 (d, J = 4.5 Hz, 1H, **H**-11), 1.75 (m, 1H, **H**-5), 1.55-1.01 (m, 10H), 0.92 (s, 6H, 2 × -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 175.83 (p), 62.86 (a), 53.32 (a), 51.44 (a), 43.42 (a), 41.71 (a), 40.27 (a), 40.07 (p), 33.22 (p), 32.66 (p), 32.08 (a), 30.16 (p), 29.91 (a), 25.55 (p), 21.29 (p); MS m/z (M$^+$) for $C_{15}H_{24}O_2$: calcd. 236.1777, found 236.1777; Analysis for $C_{15}H_{24}O_2$: calcd. C: 76.23%, H: 10.24%, found C: 76.29%, H: 10.33%.

Preparation of Raney-nickel (W-2 type): To a solution of sodium hydroxide (76 g) in water (300 mL) at 0°C, aluminum-nickel alloy powder (15 g) was added in small portions while stirring, ensuring that the temperature did not exceed 25°C. When the evolution of hydrogen had moderated to slow, the suspension was allowed to warm up to room temperature, and then heated on a steam bath until the evolution of hydrogen ceased (*ca.* 2 hours). The suspension was then washed with water until the washings had a pH of 7 (*ca.* 2 L water). Then the suspension was washed with isopropanol (3 × 200 mL) and 98% ethanol (3 × 200 mL). The resulting Raney-nickel was stored as a suspension in ethanol.

From thioketals 62 and 63: Raney-nickel (W-2 type in ethanol, 0.8 mL) was added to a solution of thioketals **62** and **63** (2.5 : 1, 45 mg, 0.138 mmol) in ethanol (98%, 1 mL) and the resulting mixture was stirred at room temperature under an argon atmosphere for 19

hours. The mixture was then filtered through Celite, concentrated, and purified by flash chromatography (3% ether in skelly B) to give ester **68** (20 mg, 61% yield).

(1R*,6R*,7R*,8R*,11S*)-7-Hydroxymethyl-2,2-dimethyltricyclo-[6.3.0.0^{6,11}]undecane (76)

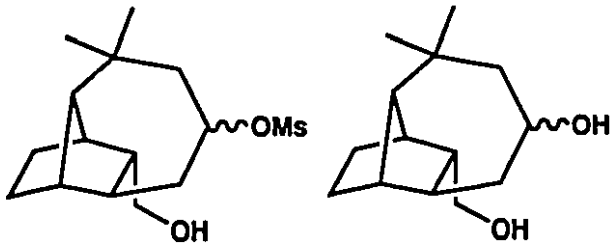


76

To a solution of ester **68** (22 mg, 0.093 mmol) in dry tetrahydrofuran (1 mL), lithium aluminum hydride (13 mg, 0.342 mmol) was added. The resulting mixture was stirred at room temperature for 20 minutes under an argon atmosphere. The mixture was then poured slowly into water (10 mL) and extracted with ether (3 × 10 mL). The extracts were combined and washed with 1 N hydrochloric acid and water. The organic solution was then dried and concentrated to give alcohol **76** (19 mg, 100% yield) as a white solid: IR ($CHCl_3$, cast): 3310 cm^{-1} (br, O-H); ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (dd, J = 11, 7 Hz, 1H, -C**H**HOH), 3.51 (dd, J = 11, 9 Hz, 1H, -CH**H**OH), 2.23 (dd, J = 4, 4 Hz, 1H), 2.12 (m, 1H), 2.04 (d, J = 4.5 Hz, 1H), 1.79 (m, 1H), 1.70-1.00 (m, 12H), 0.98 (s, 3H, -C**H**$_3$), 0.97 (s, 3H, -C**H**$_3$); MS m/z (M^+) for $C_{14}H_{24}O$: calcd. 208.1828, found 208.1826.

(1R*,6R*,7R*,8R*,11S*)-7-Hydroxymethyl-4-methanesulfonyloxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]undecane (77) and

(1R*,6R*,7R*,8R*,11S*)-7-hydroxymethyl-2,2-dimethyltricyclo-[6.3.0.0^{6,11}]undecan-4-ol (78)

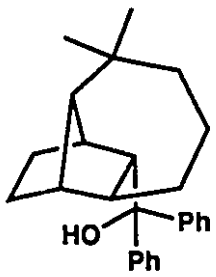


77 78

Reduction at room temperature: Lithium aluminum hydride (15 mg, 0.409 mmol) was added to a solution of mesylate **74** (27 mg, 0.082 mmol) in dry tetrahydrofuran (1 mL). The resulting mixture was then stirred at room temperature under an argon atmosphere for 10 minutes. At the end of this time, the solution was poured slowly into water (10 mL) and extracted with ether (3 × 10 mL). The extracts were combined, washed with 1 N hydrochloric acid and water, dried, and concentrated. Flash chromatography (70% ether in skelly B) gave a colorless oil **77** (17 mg, 68% yield) as a single stereoisomer: IR ($CHCl_3$, cast): 3400 cm^{-1} (br, O-H); ^1H NMR (300 MHz, $CDCl_3$): δ 4.92 (m, 1H, -C**H**(OMs)-), 3.68 (dd, *J* = 11, 8 Hz, 1H, -C**H**HOH), 3.53 (dd, *J* = 11, 11 Hz, 1H, -CH**H**OH), 2.98 (s, 3H, -OSO_2CH_3), 2.46 (dddd, *J* = 13.5, 13.5, 7, 2 Hz, 1H), 2.30 (m, 1H), 2.16 (m, 2H), 2.03 (d, *J* = 5 Hz, 1H), 1.74 (d, *J* = 12 Hz, 1H), 1.60 (m, 3H), 1.48-1.22 (m, 5H), 1.14 (s, 3H, -CH_3), 1.04 (s, 3H, -CH_3); MS m/z (M^+ - H_2O) for $C_{15}H_{24}O_3S$: calcd. 284.1447, found 284.1439. Continued elution with ethyl acetate gave a colorless oil **78** (2 mg, 11% yield) as a single stereoisomer: IR ($CHCl_3$, cast): 3340 cm^{-1} (br, O-H); ^1H NMR (300 MHz, $CDCl_3$): δ 3.94 (m, 1H, -C**H**(OH)-), 3.63 (dd, *J* = 10.5, 6.5 Hz, 1H, -C**H**HOH), 3.50 (dd, *J* = 10.5, 9 Hz, 1H, -CH**H**OH), 1.05 (s, 3H, -CH_3), 0.98 (s, 3H, -CH_3); MS m/z (M^+) for $C_{14}H_{24}O_2$: calcd. 224.1777, found 224.1767.

Reduction under reflux: Lithium aluminum hydride (11 mg, 0.290 mmol) was added to a solution of mesylate **74** (17 mg, 0.051 mmol) in dry tetrahydrofuran (1 mL). The resulting mixture was then heated under reflux under an argon atmosphere for 2.5 hours. At the end of this time, the solution was cooled, poured slowly into water (10 mL), and extracted with ether (3 × 10 mL). The extracts were combined, washed with 1 N hydrochloric acid and water, dried, and concentrated to give diol **78** (9 mg, 82% yield).

(1R*,6S*,7R*,8S*,11S*)-2,2-Dimethyl-7-(hydroxydiphenylmethyl)tricyclo[6.3.0.0^{6,11}]undecane (79)

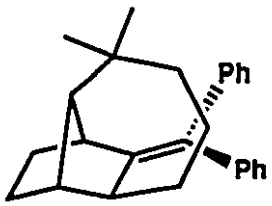


79

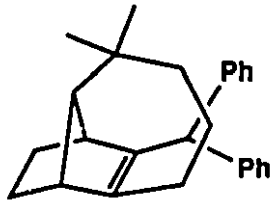
To a solution of phenyllithium (2.0 M in ether, 64 μL, 0.127 mmol) in dry tetrahydrofuran (1 mL) at 0°C, a solution of ester **68** (10 mg, 0.0423 mmol) in dry tetrahydrofuran (0.5 mL) was added dropwise. The resulting solution was stirred at room temperature for 1.5 hours and heated under reflux for 3 hours under an argon atmosphere. At the end of this time, the reaction was quenched with ice. The resulting mixture was extracted with ether (2 mL). The extract was washed with saturated aqueous sodium chloride solution, dried, concentrated, and purified by flash chromatography (5% ether in skelly B) to give alcohol **79** (15 mg, 100% yield) as a colorless oil: IR ($CHCl_3$, cast): 3600 cm^{-1} (O-H); ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 2H, phenyl), 7.52 (m, 2H, phenyl), 7.36 (m, 2H, phenyl), 7.23 (m,

3H, phenyl), 7.13 (m, 1H, phenyl), 3.15 (m, 1H, -C**H**(CPh_2OH)-), 2.44 (br s, 1H), 2.34 (dd, J = 4, 4 Hz, 1H), 2.11 (d, J = 5 Hz, 1H), 1.94-1.82 (m, 2H), 1.68-1.27 (m, 10H), 1.08 (s, 3H, -C**H**$_3$), 0.99 (s, 3H, -C**H**$_3$); MS m/z (M^+) for $C_{26}H_{32}O$: calcd. 360.2455, found 360.2451.

(1R*,6S*,8S*,11S*)-2,2-Dimethyl-7-(diphenylmethylidene)tricyclo-[6.3.0.0^{6,11}]undecane (80) and (1S*,8R*,9R*)-7,7-dimethyl-2-(diphenylmethyl)tricyclo[6.3.0.0^{3,9}]undec-2-ene (81)



80

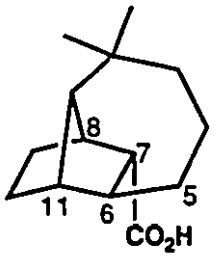


81

A mixture of alcohol **79** (14 mg, 0.039 mmol) and copper(II) sulfate on silica gel (1 mmol/g, 38 mg, 0.039 mmol) in dry carbon tetrachloride (1 mL) was heated under reflux for 30 minutes under an argon atmosphere. The resulting solution was then diluted with skelly B (2 mL), filtered, concentrated, and subjected to flash chromatography (skelly B) to give olefin **80** (12 mg, 92% yield) as a white solid: IR (CH_2Cl_2, cast): 1600 cm^{-1} (Ph); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.11 (m, 10H, phenyl), 2.88 (d, J = 6 Hz, 1H, =CC**H**-), 2.82 (d, J = 4 Hz, 1H, =CC**H**-), 2.24 (d, J = 4 Hz, 1H), 1.78 (dd, J = 12.5, 12.5 Hz, 1H), 1.70-1.15 (m, 10H), 1.01 (s, 3H, -C**H**$_3$), 0.97 (s, 3H, -C**H**$_3$); MS m/s (M^+) for $C_{26}H_{30}$: calcd. 342.2349, found 342.2345. Continued elution gave olefin **81** (1 mg, 8% yield) as a colorless oil: IR ($CHCl_3$, cast): 1600 cm^{-1} (Ph); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.10 (m, 10H, phenyl), 4.20 (br s, 1H, -C**H**Ph_2), 3.57 (d, J = 11 Hz, 1H, =CC**H**-), 3.00 (br d, J = 11 Hz, 1H, =CC**H**-), 1.95 (m, 1H), 1.74 (m,

1H), 1.64 (m, 1H), 1.50-1.10 (m, 8H), 0.94 (s, 3H, -C**H**$_3$), 0.92 (s, 3H, -C**H**$_3$); MS m/z (M$^+$) for $C_{26}H_{30}$: calcd. 342.2349, found 342.2363.

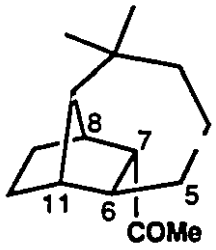
(1R*,6S*,7R*,8S*,11S*)-7-Carboxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]-undecane (82)



82

A 20% aqueous potassium hydroxide solution (15 mL) was added to a solution of ester **68** (76 mg, 0.322 mmol) in tetrahydrofuran (2 mL). The resulting mixture was heated under reflux for 39 hours. It was then cooled, poured into 1 N hydrochloric acid (100 mL), and extracted with ether (3 × 100 mL). The combined extracts were washed with water, dried, and concentrated to give acid **82** (73 mg, 100% yield) as a white solid: mp 156-157°C (skelly B); IR ($CHCl_3$, cast): 3200-2400 (COOH), 1698 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90 (ddd, J = 5, 4, 2 Hz, 1H, **H**-7), 2.51 (dd, J = 4, 4 Hz, 1H, **H**-8), 2.22 (br dd, J = 5, 5 Hz, 1H, **H**-6), 2.13 (d, J = 4.5 Hz, 1H, **H**-11), 1.84 (m, 1H, **H**-5), 1.76-1.21 (m, 10H), 1.00 (s, 6H, 2 × -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 181.15 (p), 62.86 (a), 53.20 (a), 43.31 (a), 41.66 (a), 40.32 (a), 40.31 (p), 33.23 (p), 32.59 (p), 32.09 (a), 30.16 (p), 29.90 (a), 25.49 (p), 21.26 (p); MS m/z (M$^+$) for $C_{14}H_{22}O_2$: calcd. 222.1621, found 222.1619; Analysis for $C_{14}H_{22}O_2$: calcd. C: 75.63%, H: 9.97%, found C: 75.93%, H: 10.08%.

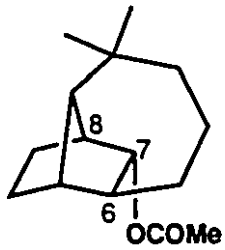
(1R*,6S*,7R*,8S*,11S*)-7-Acetyl-2,2-dimethyltricyclo[6.3.0.0^{6,11}]-undecane (83)



83

Methyllithium (0.9 M in ether, 1.3 mL, 1.116 mmol) was added to a solution of acid **82** (62 mg, 0.279 mmol) in dry tetrahydrofuran (10 mL) at 0°C and the resulting solution was stirred at room temperature under an argon atmosphere for 16 hours. At the end of this time the solution was cooled to 0°C and trimethylsilyl chloride (0.7 mL, 5.580 mmol) was added rapidly. The mixture was then warmed up to room temperature and 1 N hydrochloric acid (20 mL) was added. The resulting mixture was stirred for 30 minutes. The ether layer was removed and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic solutions were washed with water, dried, concentrated, and purified by flash chromatography (10% ether in skelly B) to give ketone **83** (53 mg, 87% yield) as a colorless oil: IR ($CHCl_3$, cast): 1708 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.84 (ddd, J = 5, 4.5, 2 Hz, 1H, **H**-7), 2.53 (dd, J = 4.5, 4.5 Hz, 1H, **H**-8), 2.32 (dd, J = 7, 5 Hz, 1H, **H**-6), 2.10 (s, 3H, -COC**H**$_3$), 2.09 (dd, J = 10.5, 4.5 Hz, 1H, **H**-11), 1.80 (m, 1H, **H**-5), 1.66-1.07 (m, 10H), 1.01 (s, 3H, -C**H**$_3$), 0.98 (s, 3H, -C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 210.00 (p), 63.16 (a), 65.47 (a), 41.60 (a), 40.59 (a), 40.38 (a), 40.18 (p), 33.23 (p), 32.81 (p), 32.04 (a), 30.14 (p), 30.01 (a), 29.66 (a), 25.11 (p), 21.35 (p); MS m/z (M^+) for $C_{15}H_{24}O$: calcd. 220.1828, found 220.1825.

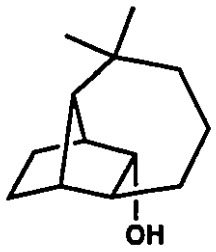
(1R*,6S*,7R*,8S*,11S*)-7-Acetoxy-2,2-dimethyltricyclo[6.3.0.0^{6,11}]-undecane (84)



84

Trifluoroacetic anhydride (0.4 mL, 2.925 mmol) was added dropwise to a solution of hydrogen peroxide (90%, 64 μL, 2.340 mmol) in dry dichloromethane (0.5 mL) at 0°C. After stirring at 0°C under an argon atmosphere for 15 minutes the solution was warmed up to room temperature and added to a mixture of ketone **83** (43 mg, 0.195 mmol) and disodium hydrogen phosphate (0.555 g, 3.900 mmol) in dry dichloromethane (0.5 mL). The resulting mixture was heated under reflux under an argon atmosphere for 5 hours. At the end of this time, the mixture was filtered through Celite and the filtrate was washed with 10% aqueous sodium sulfite solution, saturated aqueous sodium bicarbonate solution, and water. The organic layer was dried, concentrated, and purified by flash chromatography (5% ether in skelly B) to give acetate **84** (22 mg, 48% yield) as a yellow oil: IR (CH_2Cl_2, cast): 1737 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.09 (dd, J = 4, 4 Hz, 1H, **H**-7), 2.41 (m, 1H, **H**-8), 2.07 (br d, J = 4 Hz, 1H, **H**-6), 2.03 (s, 3H, -COC**H**$_3$), 1.82-1.15 (m, 12H), 0.98 (s, 6H, 2 × -C**H**$_3$); ^{13}C NMR APT (75 Mz, $CDCl_3$): δ 171.38 (p), 83.14 (a), 62.56 (a), 48.62 (a), 41.94 (a), 40.19 (p), 39.57 (a), 33.19 (p), 31.30 (p), 31.20 (a), 30.54 (p), 30.47 (a), 21.36 (a), 21.30 (p), 20.99 (p); MS m/z (M^+) for $C_{15}H_{24}O_2$: calcd. 236.1777, found 236.1763; Analysis for $C_{15}H_{24}O_2$: calcd. C: 76.23%, H: 10.24%, found C: 75.94%, H: 10.15%.

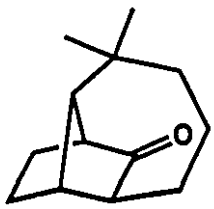
(1S*,2R*,3S*,8R*,9S*)-7,7-Dimethyltricyclo[6.3.0.0^{3,9}]undecan-2-ol (85)



85

A 1 N aqueous sodium hydroxide solution (0.5 mL) was added to a solution of ester **84** (12.7 mg, 0.0538 mmol) in methanol (0.5 mL) and the resulting solution was stirred at room temperature for 5 hours. The solution was then acidified with 1 N hydrochloric acid and extracted with ether (3 × 2 mL). The combined extracts were washed with water, dried, concentrated, and purified by flash chromatography (30% ether in skelly B) to give alcohol **85** (9.7 mg, 93% yield) as a white solid: mp 68-70°C; IR ($CHCl_3$, cast): 3320 cm^{-1} (br, O-H); ^1H NMR (300 MHz, $CDCl_3$): δ 4.23 (dd, J = 4.5, 4.5 Hz, 1H, -C**H**(OH)-), 2.17 (dd, J = 4.5, 3 Hz, 1H), 1.98 (d, J = 4.5 Hz, 1H), 1.77 (m, 2H), 1.61-1.15 (m, 11H), 0.91 (s, 3H, -C**H**$_3$), 0.88 (s, 3H, -C**H**$_3$); MS m/z (M^+) for $C_{13}H_{22}O$: calcd. 194.1672, found 194.1672.

(1S*,3S*,8R*,9R*)-7,7-Dimethyltricyclo[6.3.0.0^{3,9}]undecan-2-one (21)



21

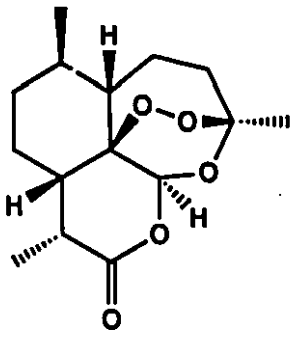
Pyridinium chlorochromate on alumina (0.9 mmol/g, 176 mg, 0.158 mmol) was added to a solution of alcohol **85** (9.6 mg, 0.0494 mmol) in dry dichloromethane (1 mL) and the mixture was stirred at room temperature under an argon atmosphere for 1.5 hours. The mixture was then filtered through Florisil, concentrated, and purified by flash chromatography (10% ether in skelly B) to give ketone **21** (8.2 mg, 86% yield) as a colorless oil: IR ($CHCl_3$, cast): 1739 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.57 (br d, J = 4 Hz, 1H, -C**H**CO-), 2.49 (m, 1H, -C**H**CO-), 2.02-1.05 (m, 12H), 1.01 (s, 3H, -C**H**$_3$), 0.91 (s, 3H, -C**H**$_3$); ^{13}C NMR APT ($CDCl_3$, 75 MHz): δ 223.80 (p), 60.90 (a), 51.33 (a), 50.47 (a), 38.75 (a), 37.17 (p), 33.56 (p), 30.94 (a), 29.67 (p), 29.30 (p), 28.89 (a), 24.28 (p), 20.32 (p); MS m/z (M^+) for $C_{13}H_{20}O$: calcd. 192.1515, found 192.1516. These spectral data are in good agreement with those provided by Prof. Oppolzer of Université de Genève.

Chapter 2

Total Synthesis of (+)-Qinghaosu

Introduction

Scientists have been examining traditional Chinese medicines, which are based on more than 2,000 years of trial and error, in an attempt to develop new therapeutic agents.[49] One of the most fascinating findings in recent years is the emergence of a therapy for malaria that is probably older than mankind.[50-52] Malaria continues to be one of the most widespread health hazards,[53] and the use of insecticides to kill mosquitos is always a key factor in control of this parasitic disease. Unfortunately, some so-called DDT-resistant mosquitos have appeared due to the indiscriminate use of the insecticides. To make matter worse, strains of *P. falciparum*, one of the four species of *Plasmodium* causing malaria, resistant to conventional quinoline and acridine based drugs have been detected in these mosquitos. In fact, there are an estimated 270 million people suffering from this increasingly drug-resistant strain of malaria and 150 million new cases are being reported every year. As a consequence, there is a serious demand for new antimalarial drugs.

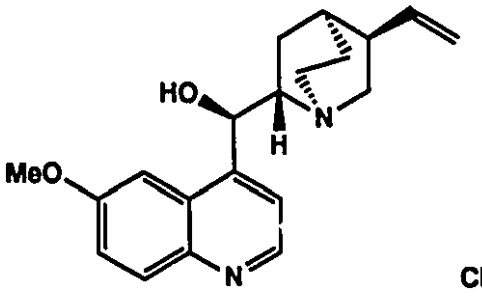


89

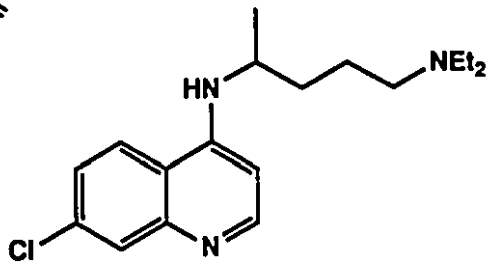
Since ancient times, Chinese people have been using a traditional herbal medicine, qinghao (*Artemisia annua* L.), for the treatment of fever and malaria. However, its active constituent was not isolated until 1972 by the Chinese research group led by Chou.[54-56] This colorless crystalline compound named qinghaosu (**89**) (component of qinghao), dubbed

artemisinin or arteannuin in the West, is a modified cadinane sesquiterpene lactone bearing the only known 1,2,4-trioxane functionality in nature. Moreover, it lacks any nitrogen-containing heterocyclic ring system that is found in most of the antimalarial drugs. The structure and the absolute configuration of (+)-qinghaosu have also been determined unambiguously by X-ray diffraction.[57]

(+)-Qinghaosu was found to be superior to the conventional antimalarial drugs, such as quinine (**90**) and chloroquine (**91**), against strains of malaria, especially the most serious drug-resistant cerebral malaria caused by *P. falciparum* mentioned before. For instance, administration of (+)-qinghaosu has been revealed to revive comatose patients suffering from cerebral malaria in the extensive clinical tests in China. The cure rate was averaged up to 90%. Moreover, only approximately 21 hours were required for the recovery of patients from coma, compared to about 47 hours using quinine. (+)-Qinghaosu also showed relatively low toxicity. Neither obvious adverse reactions nor noticeable side effects were observed in the patients after treatment. Thus (+)-qinghaosu is expected to become a leading compound for the new class of antimalarial drugs developed since World War II.



90

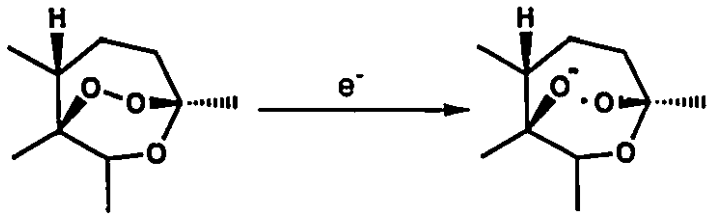


91

The action of (+)-qinghaosu on the malaria parasites appears to be fundamentally different from that of the other antimalarial agents. This may explain why (+)-qinghaosu acts against drug-resistant parasites. There is evidence that malaria parasites grab amino acids by proteolytic

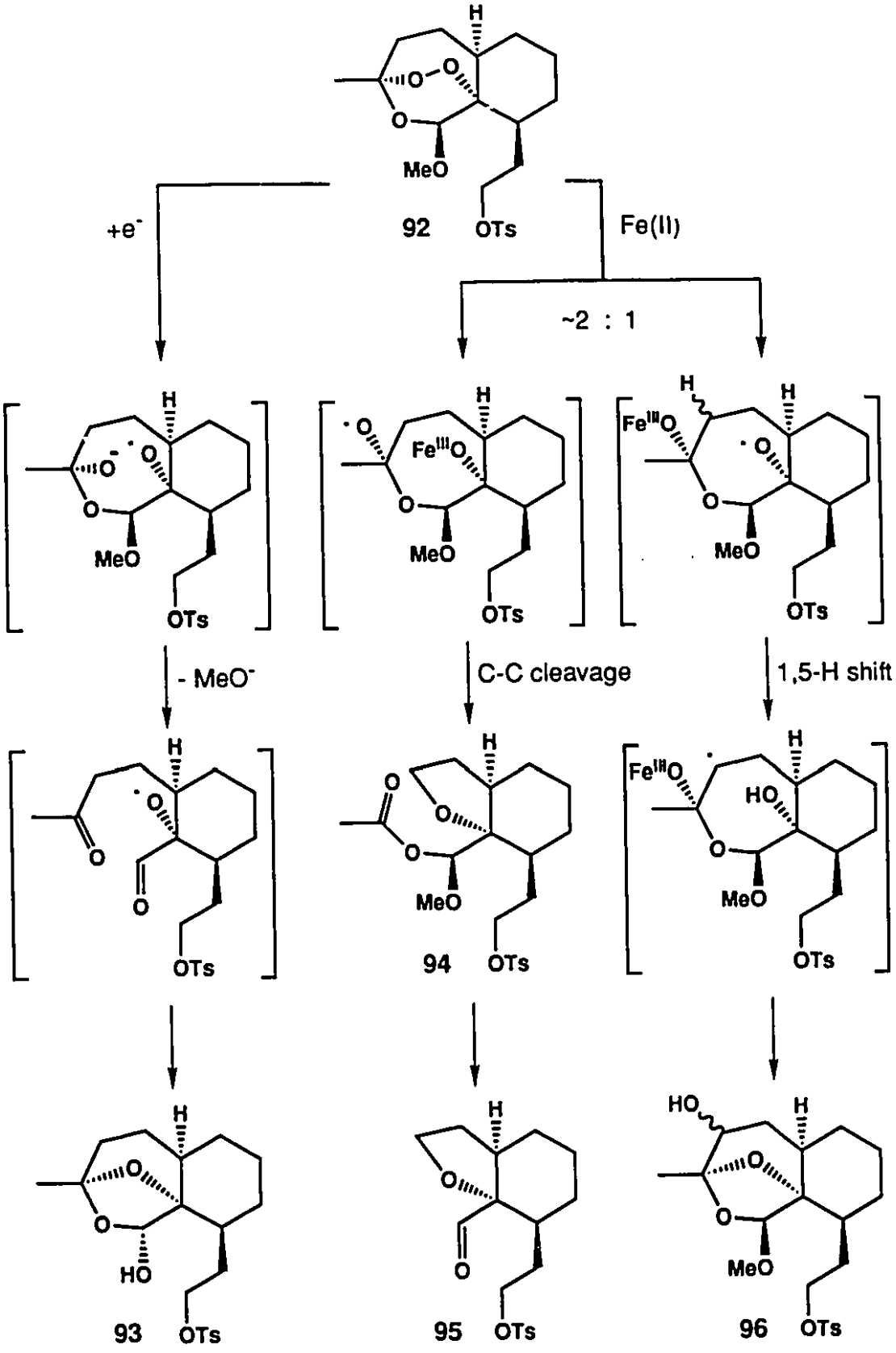
decomposition of host-cell hemoglobin. Therefore, one mode of action of conventional antimalarial agents might be to depress the decomposition by acting as hemoglobinase inhibitors. However, the primary target of (+)-qinghaosu may be the prevention of constructing the proteins needed by the malaria parasites, as suggested by Gu.[58] Other evidence further pointed to the possibility that the drug may be localized in the membranes of the parasites so that the changes in its membrane integrity might precede the early depression of protein synthesis by an oxidative mechanism.[59,60] At the molecular level it is possible that a hemin-catalyzed electron transfer results in the cleavage of the oxygen-oxygen bond of the peroxide bridge with the generation of an oxygen-centered radical, which could be responsible for the destruction of the membranes of the malaria parasites (**Scheme 21**).

Scheme 21



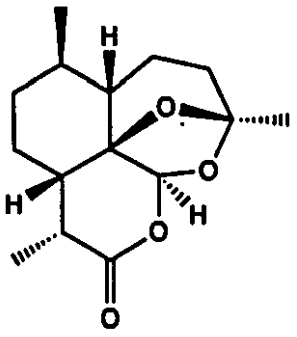
Recently, Posner and Oh[61] utilized a simple chemical mode system to probe the antimalarial activity of activated (+)-qinghaosu at the molecular level and, for the first time, reported mechanistic evidence for the reductive cleavage of a 1,2,4-trioxane to 1,3-dioxolane. Formation of a 1,3-dioxolane has physiological relevance because malarial parasites are known to operate on trioxanes to deliver the corresponding dioxolanes. As shown in **Scheme 22**, when trioxane tosylate **92** (an antimalarial compound) was treated separately with several reducing agents, such as samarium diiodide, zinc, Ph_3CLi, and Bu_3SnH/AIBN, all produced 1,3-dioxolane tosylate **93** within 4 hours in good to excellent yields. On the other hand, when **92** was treated with two different sources of ferrous ions, ferrous bromide and hemin/$PhCH_2SH$, to mimic the biologically

Scheme 22

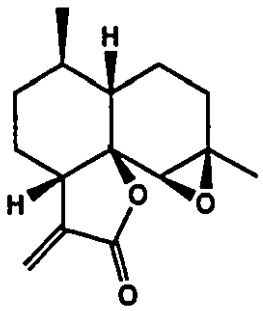


erythrocyte hemin-catalyzed cleavage of the trioxane unit in (+)-qinghaosu, products acetal **94**, aldehyde **95**, and hydroxy dioxolane **96** were generated in good yields. Compounds like **94**, **95**, and **96** are typical metabolites formed from trioxanes such as (+)-qinghaosu in the presence of rat liver microsomes.

The other evidence for this mechanism is the essentiality of the peroxide bridge for the antimalarial activity of (+)-qinghaosu. All of the other related sesquiterpenoids isolated from qinghao without this particular functionality, such as deoxyartemisinin (**97**), artemisinin B (**98**), and artemisinin F (**99**), are devoid of antimalarial activity. Conversely, some compounds not obviously related to (+)-qinghaosu but containing a peroxide group, such as ascaridole (**100**),[62] are antimalarial active. However, these compounds were found to be active *in vitro* against *P. falciparum* but inactive *in vivo*. It was thus suggested that the remainder of the (+)-qinghaosu molecule is responsible for preserving the activity of the drug during the delivery to the infected erythrocyte where it can manipulate its toxicity towards the parasite. In addition, it also plays a role in the potency of the drug. For example, the ether derivative of 2-hydroxy-2-deoxoartemisinin (**101**),[63] generally called arte-ether, shows an increased antimalarial activity compared to (+)-qinghaosu itself and is the form of qinghaosu which is currently under commercial development. This increase may be a consequence of different solubilities in lipids.



97



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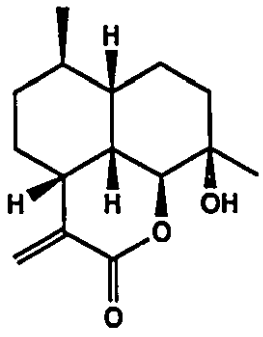
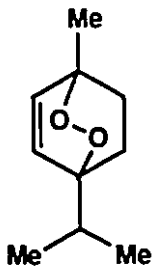
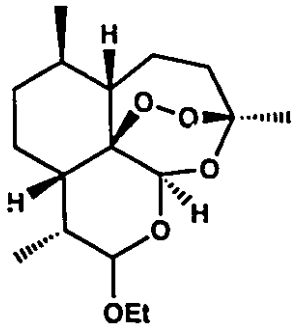


99



100

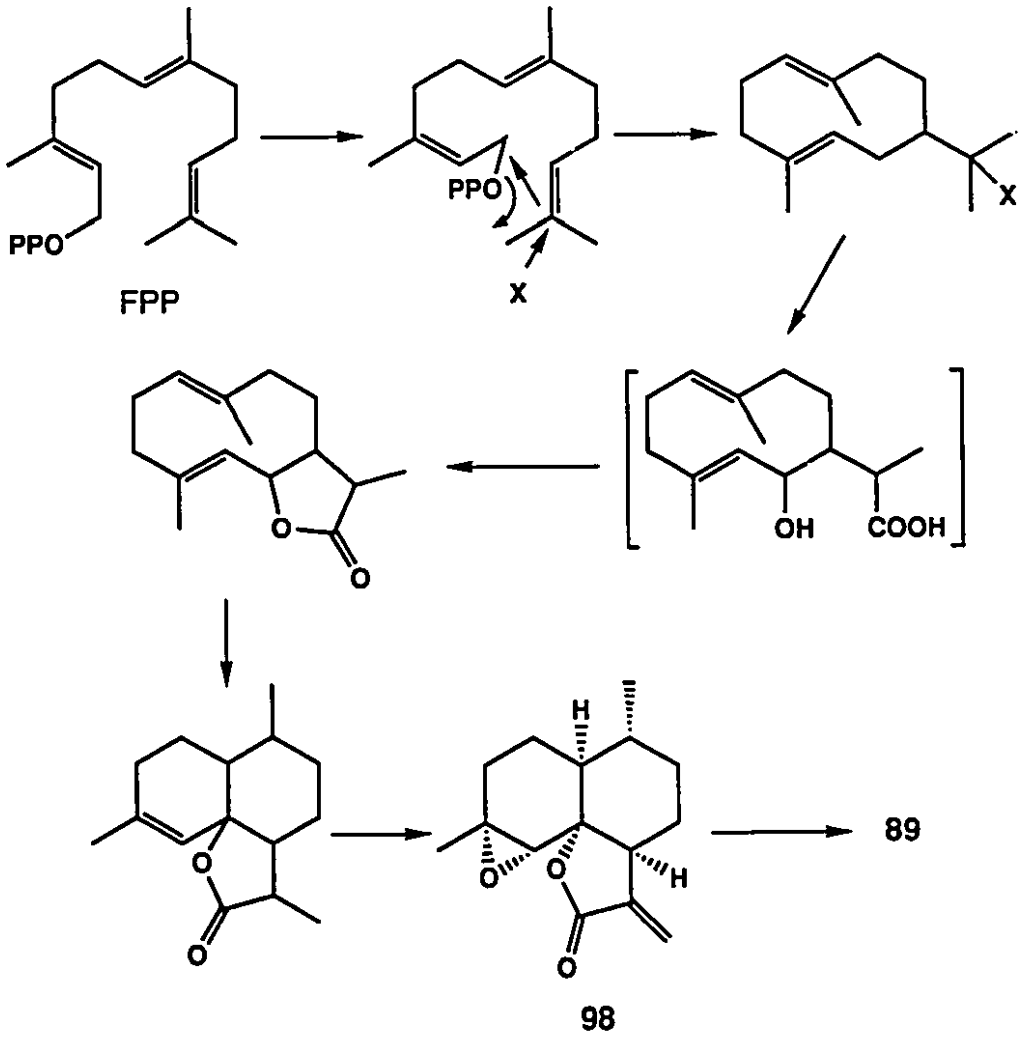


101

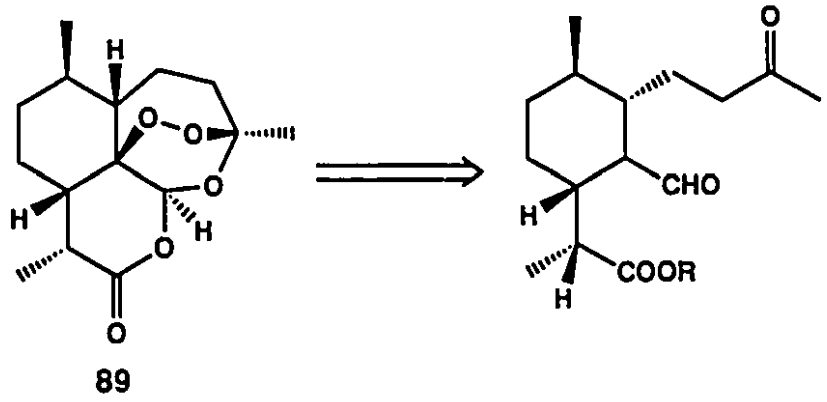
The biosynthetic pathway of (+)-qinghaosu has already been investigated by Akhila and co-workers.[64] Feeding the plant with appropriately labelled ($^3H/^{14}C$) mevalonic acids, they were able to isolate the labelled artemisinin B (**98**) and (+)-qinghaosu. By the determination of their isotope ratios (^3H : ^{14}C), a preliminary biosynthetic sequence was postulated as outlined in **Scheme 23**.

Because of the intriguing chemical structure, the promising medicinal application, and the low natural content (up to 0.1%), (+)-qinghaosu (**89**) has been the subject of extensive synthetic efforts and four total syntheses have been reported during the past decade. The strategies to achieve the 1,2,4-trioxane moiety were all derived from the visualization of a peroxyketal-acetal-lactone system which can be constructed by the oxidation of a keto-aldehyde-ester system (**Scheme 24**). The first total synthesis was accomplished in 1983 by Schmid and Hofheinz[65] using (-)-isopulegol (**102**) as starting material (**Scheme 25**). This compound was converted to benzoyloxymenthone **103** and the required stereogenic center on the isopropyl sidechain was created by stereoselective hydroboration. Compound **103** was then elaborated to the key intermediate **104** in six steps including the first two stereoselective operations: kinetic alkylation to attach the four-carbon sidechain and addition of the organolithium reagent to the carbonyl. Photooxygenation of **104** in methanol at -78°C using methylene blue as photosensitizer followed by treatment with formic acid gave rise to (+)-**89** in 30% yield. Hydroperoxide **105** was assumed to be the intermediate.

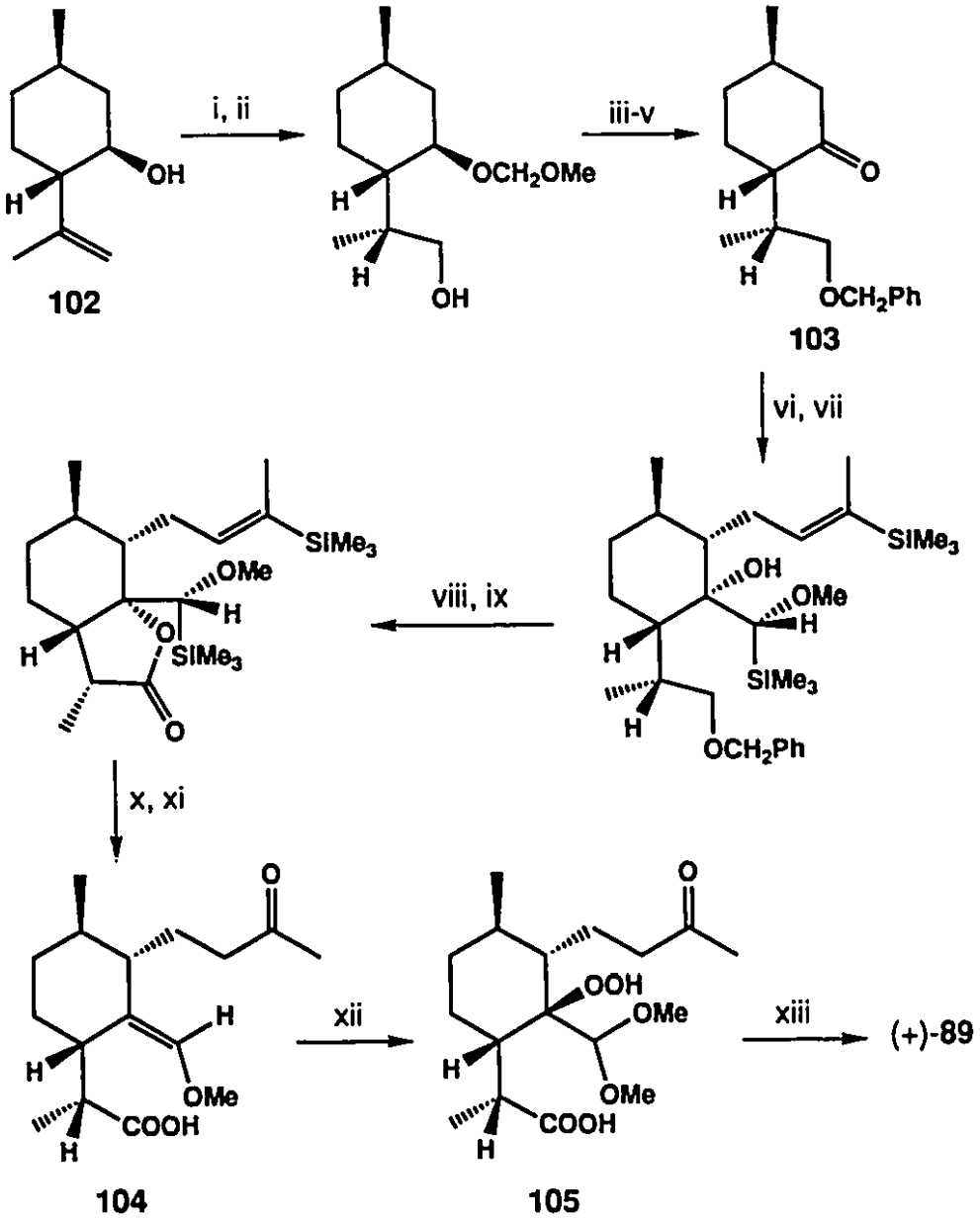
Scheme 23



Scheme 24



Scheme 25



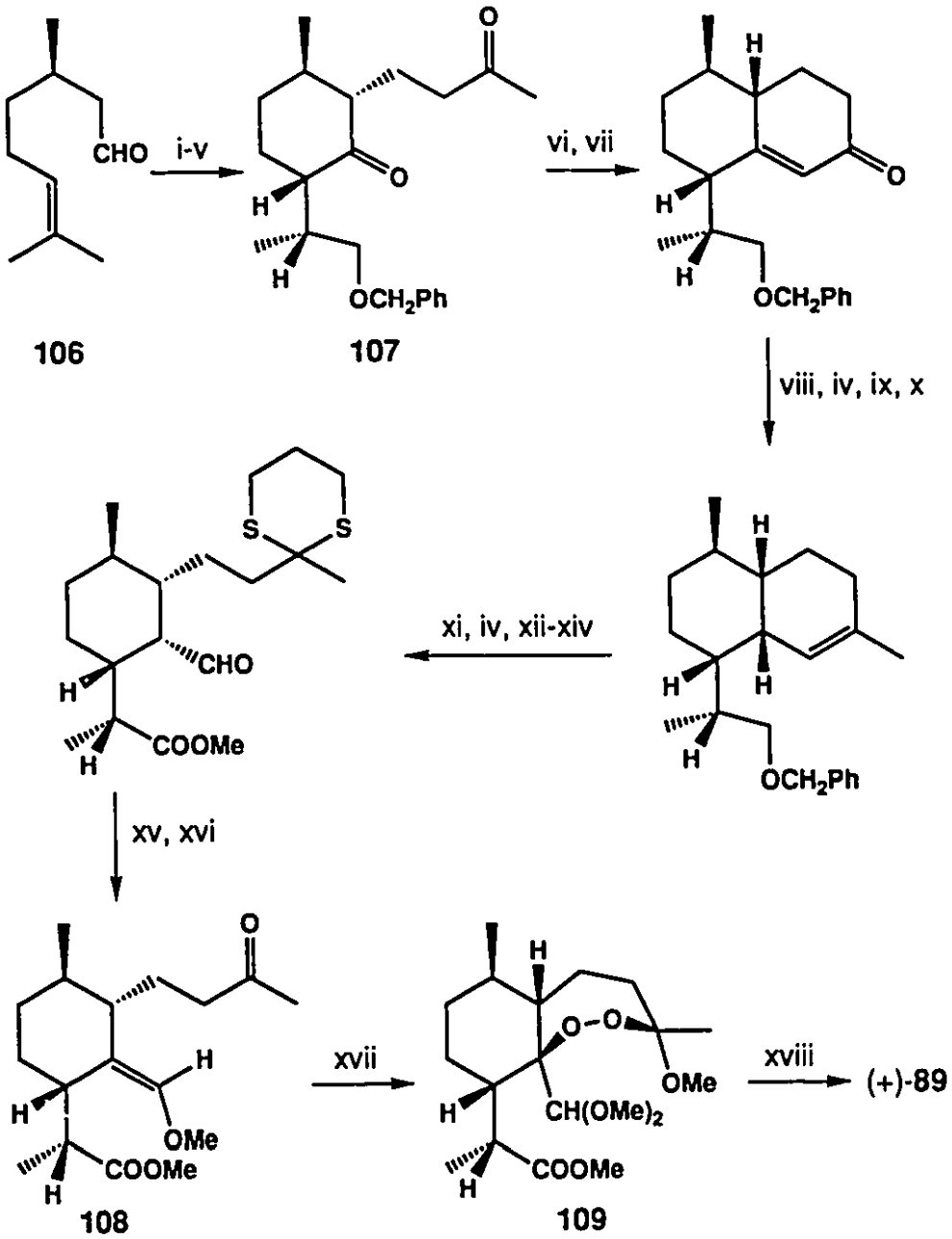
i. $ClCH_2OMe$, $PhNMe_2$; ii. B_2H_6; HO^-, H_2O_2; iii. $PhCH_2Br$, KH; iv. MeOH, HCl; v. PCC; vi. LDA, (*E*)-$ICH_2CH{=}C(SiMe_3)Me$; vii. $MeOCH(Li)SiMe_3$; viii. Li, NH_3; ix. PCC; x. MCPBA; TFA; xi. Bu_4NF; xii. $^1O_2$, MeOH, -78°C; xiii. HCO_2H

Three years later, Chou and co-workers[66,67] reported a similar concept to approach (+)-qinghaosu (**Scheme 26**). Starting with (R)-(+)-citronellal

(**106**), benzoyloxy diketone **107** was obtained in five steps including the same hydroboration and kinetic alkylation used by Hofheinz. The second ring was introduced by Robinson annelation using barium hydroxide as a base to induce cyclization in order to prevent epimerization. It was then cleaved by ozonolysis after a series of functional group transformations to construct the required intermediate **108** (ester version of **104**) for photooxygenation. Irradiation of a methanol solution of **108** in the presence of Rose Bengal at -78°C using a high pressure mercury lamp followed by acid treatment afforded the intermediate **109**, which was then cyclized by treatment with 70% aqueous perchloric acid to give (+)-qinghaosu in 28% yield in two steps.

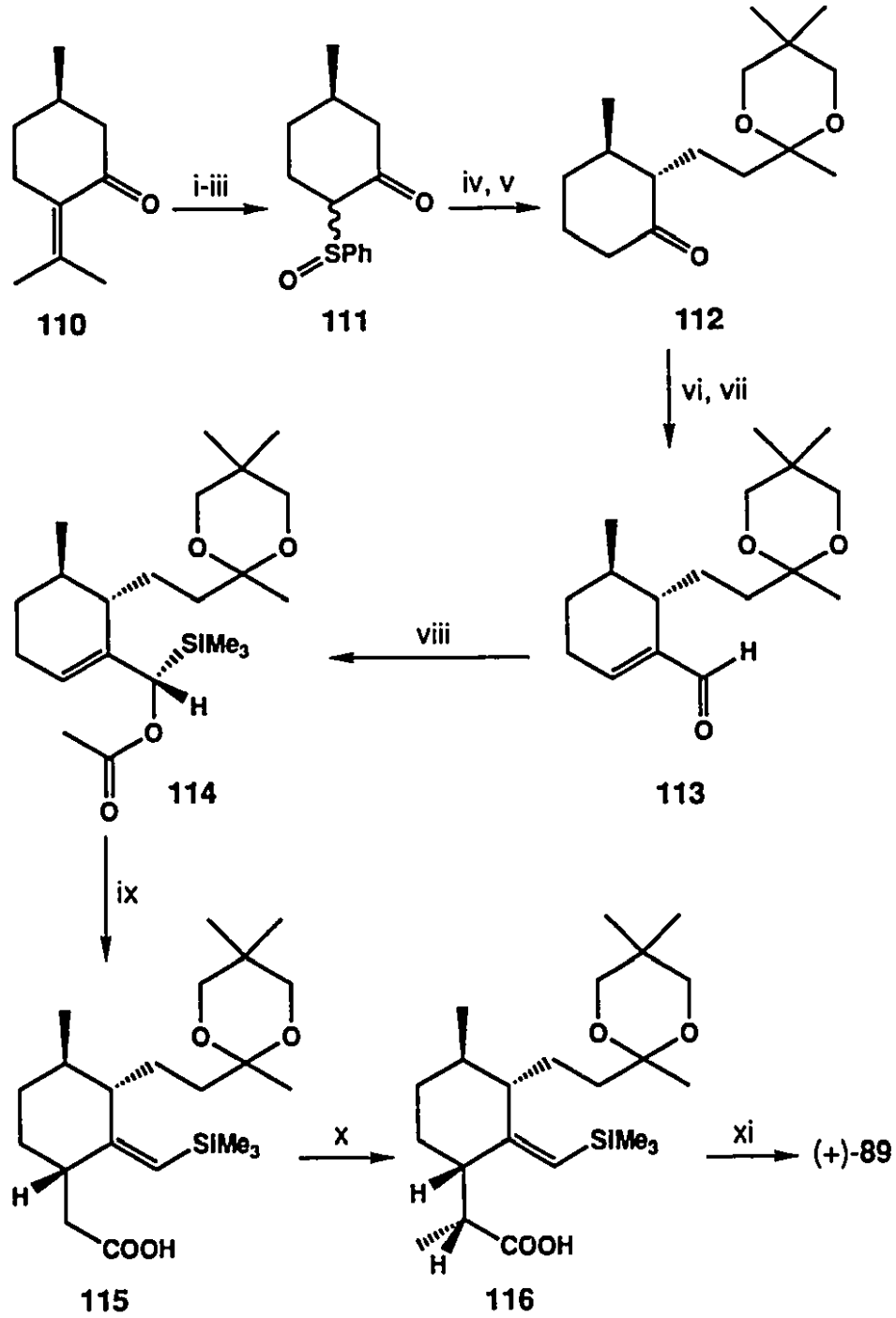
A different strategy to achieve the synthesis of (+)-qinghaosu was demonstrated by Avery and co-workers.[68,69] The key steps involved the creation of the isopropyl moiety by a tandem Claisen ester-enolate rearrangement and the constitution of the 1,2,4-trioxane moiety by using an abnormal course of reaction of vinylsilanes with ozone. This is illustrated in **Scheme 27**. (R)-(+)-Pulegone (**110**) served as a starting material to prepare sulfoxide **111**, which was converted to its dianion with lithium diisopropylamide. The subsequent alkylation and desulfurization furnished the ketone **112**. The homologation of **112** to aldehyde **113** was accomplished by Shapiro reaction with dimethylformamide as the acylating agent. Diastereoselective silyl anion addition gave the corresponding alcohol which was then acetylated to produce **114**. With this key compound in hand, the rearrangement was optimized by using lithium diethylamide (LDEA) as a base to give the desired compound **115** in 63% yield. The missing methyl group α to carboxyl was introduced by methylation of the corresponding dianion (**115**→**116**). At the final stage, the abnormal ozonolysis followed by successive addition of aqueous sulfuric acid and silica gel concluded the synthesis of (+)-qinghaosu in a yield of 33-39%.

Scheme 26



i. $ZnBr_2$; ii. B_2H_6; H_2O_2, OH^-; iii. $PhCH_2Cl$, NaH; iv. Jones oxidation; v. LDA, $CH_2=C(SiMe_3)COMe$; vi. $Ba(OH)_2$; vii. $(COOH)_2$; viii. $NaBH_4$, Py; ix. MeMgI; x. *p*-TsOH; xi. Na, NH_3; xii. CH_2N_2; xiii. O_3; Me_2S; xiv. $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$; xv. $HC(OMe)_3$, *p*-TsOH; xylene, reflux; xvi. $HgCl_2$; xvii. $^1O_2$, MeOH, -78°C; HCl; xviii. 70% $HClO_4$

Scheme 27

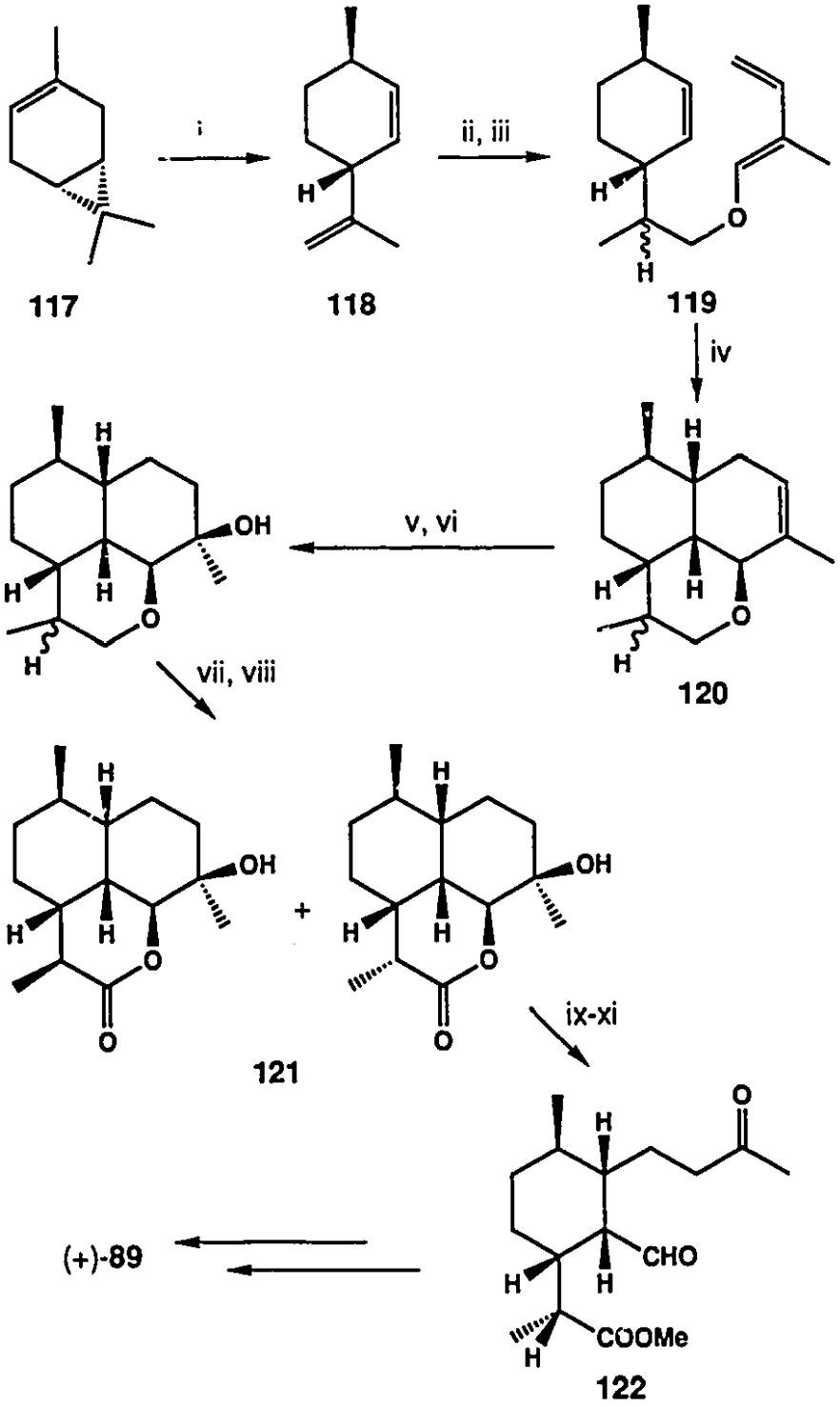


i. H_2O_2, HO^-; ii. NaSPh; iii. MCPBA; iv. LDA, HMPT, 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane; v. Al(Hg); vi. *p*-$MePhSO_2NHNH_2$; vii. *n*-BuLi, TMEDA; DMF; viii. $(Me_3Si)_3Al{\cdot}OEt_2$; Ac_2O; ix. LDEA; x. LDA, MeI; xi. O_3/O_2; H_2SO_4, SiO_2

The last synthesis of (+)-qinghaosu was claimed by Ravindranathan and co-workers[70] to achieve Chou's intermediate **122** (aldehyde version of **108**) utilizing an intramolecular Diels-Alder reaction as a key step to construct the tricyclic ring system with stereochemical control (**Scheme 28**). The precursor **119** of the Diels-Alder reaction was assembled from (+)-isolimenene (**118**), which was in turn easily derived from (+)-3-carene (**117**). Diels-Alder reaction of **119** was carried out in toluene in a sealed tube at 210°C to give an epimeric mixture of ethers **120** in 25-30% yield. This mixture was not separated until the stage of hydroxylactones **121** and the ratio was determined to be 6 : 4 with the undesired isomer predominating. Periodate cleavage of the corresponding carboxylate and subsequent methylation yielded Chou's intermediate **122** to complete the formal synthesis.

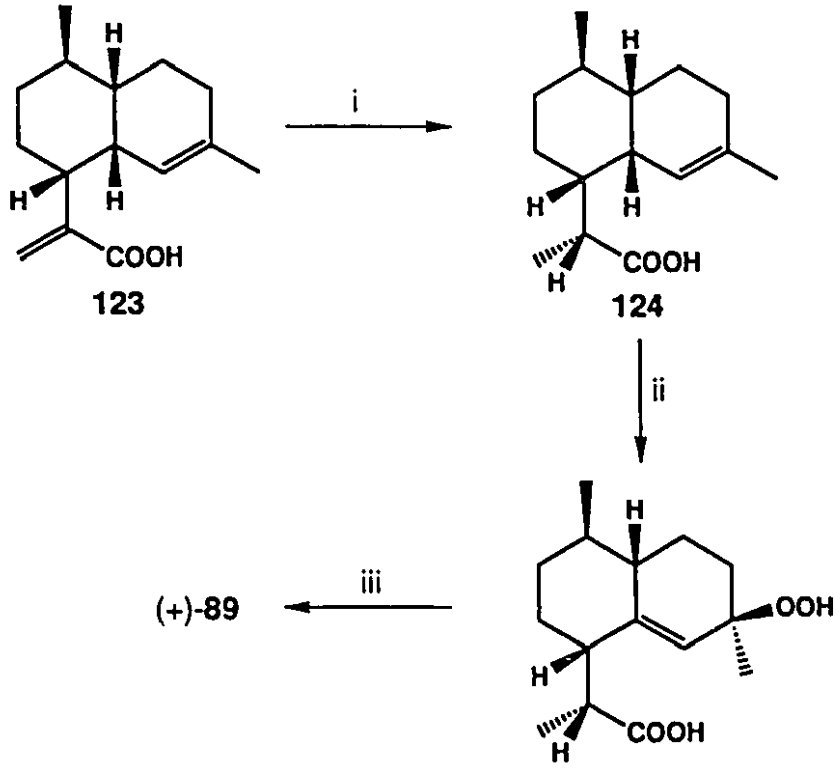
Beside the aforementioned total syntheses, researchers continue to investigate more efficient routes to produce (+)-qinghaosu. Four facile semisyntheses based on qinghao acid (**123**) have been published. Qinghao acid (**123**), also called arteannuic acid or artemisinic acid, is eight to ten times more abundant than (+)-qinghaosu in the same plant and can be isolated without chromatography.[56] Biosynthetic studies have also shown that **123** is the biogenetic precursor of (+)-qinghaosu.[71] Roth and Acton[72,73] first successfully carried out the conversion of **123** to (+)-qinghaosu in 30% isolated yield *via* a sequence of reduction, photooxygenation, and acid treatment (**Scheme 29**). The operations were relatively simple. For example, the photooxygenation with methylene blue as photosensitizer could be carried out either by passing oxygen gas through an acetone solution at 0°C while irradiation with a streep lamp, or outdoors on a sunny day in an open beaker containing the acetone solution. As suggested by Acton and Roth,[74] the peroxide bridge oxygens of (+)-qinghaosu are introduced during the triplet oxygen (air) oxidation step as shown in **Scheme 30**.

Scheme 28



i. heat; ii. 9-BBN; H_2O_2, NaOH; iii. $EtOCH=CMeCH=CH_2$, $Hg(OAc)_2$, NaOAc; iv. sealed tube, PhMe, 210°C; v. MCPBA; vi. $LiAlH_4$; vii. $RuCl_3$, $NaIO_4$; viii. NaOMe; ix. NaOH; x. $NaIO_4$; xi. CH_2N_2

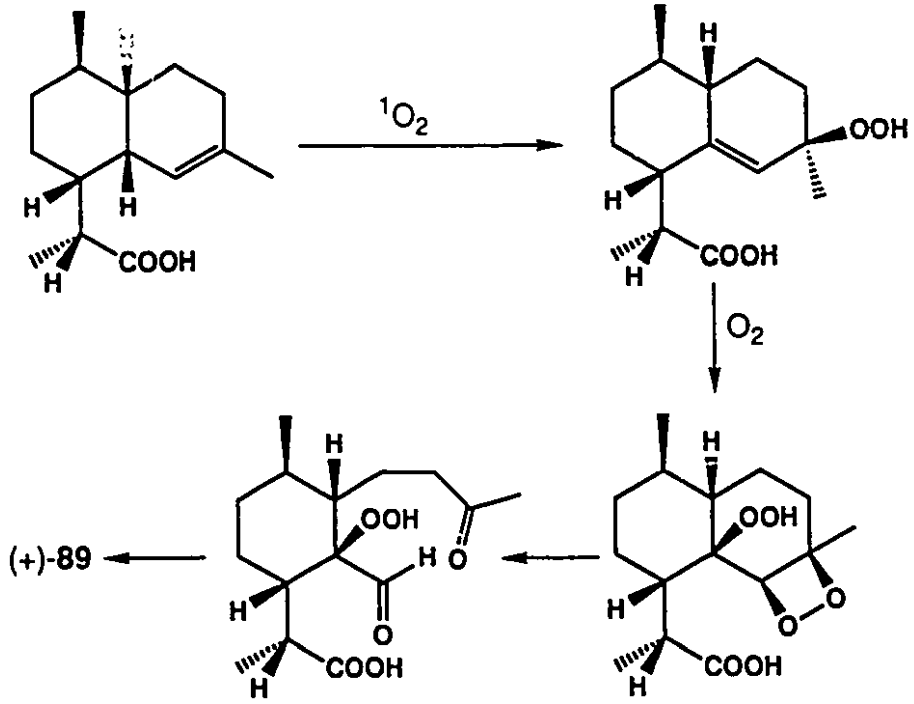
Scheme 29



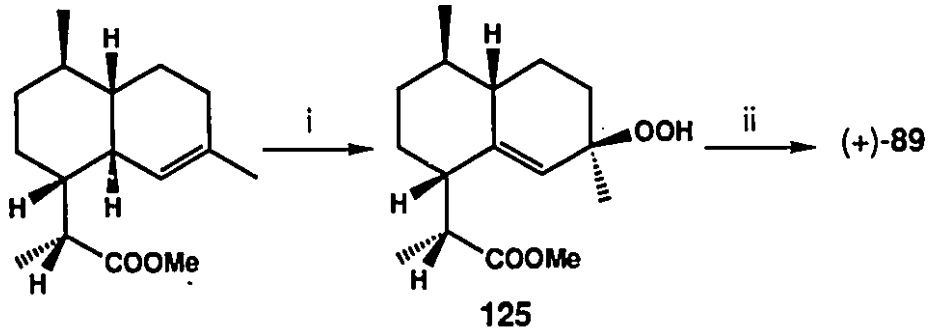
i. $NaBH_4$, $NiCl_2$; ii. hv, O_2, Methylene Blue; iii. air, TFA, pet. ether

In 1990 Haynes and Vonwiller,[75] unaware of Acton and Roth's work, also described a similar sequence using different conditions. As illustrated in **Scheme 31**, the hydroperoxide **125** was prepared from the ester of dihydroqinghao acid (from CH_2N_2 and **124**) by photooxygenation (Rose Bengal, 500 W tungsten lamp) in 70% yield. The conversion from **125** to (+)-qinghaosu was accomplished by a redox reaction catalyzed by copper(II) trifluoromethanesulfonate in 29% yield.

Scheme 30



Scheme 31



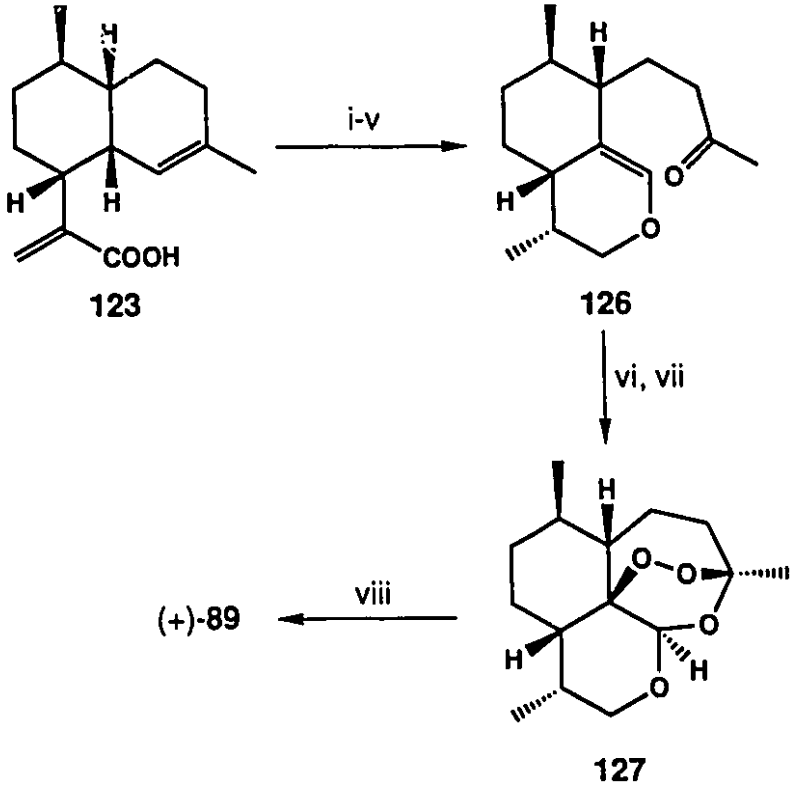
125

i. hv, O_2, Rose Bengal, MeCN, -30°C; ii. $Cu(OSO_2CF_3)_2$

In the same year, Ye and Wu reported[76] a less direct approach, but the yield of the formation of the 1,2,4-trioxane moiety was much improved (**Scheme 32**). The key intermediate, cyclic enol ether **126**, was prepared

in five straightforward steps from qinghao acid (**123**). Photooxygenation of **126** followed by treatment with trimethylsilyl trifluoromethanesulfonate (TfOTMS) yielded the desired deoxoqinghaosu (**127**) in 62% yield. It was found to be more active against malaria than (+)-qinghoasu.[77] The subsequent oxidation gave (+)-qinghaosu. The overall yield for this semisynthesis was increased to 37%.

Scheme 32

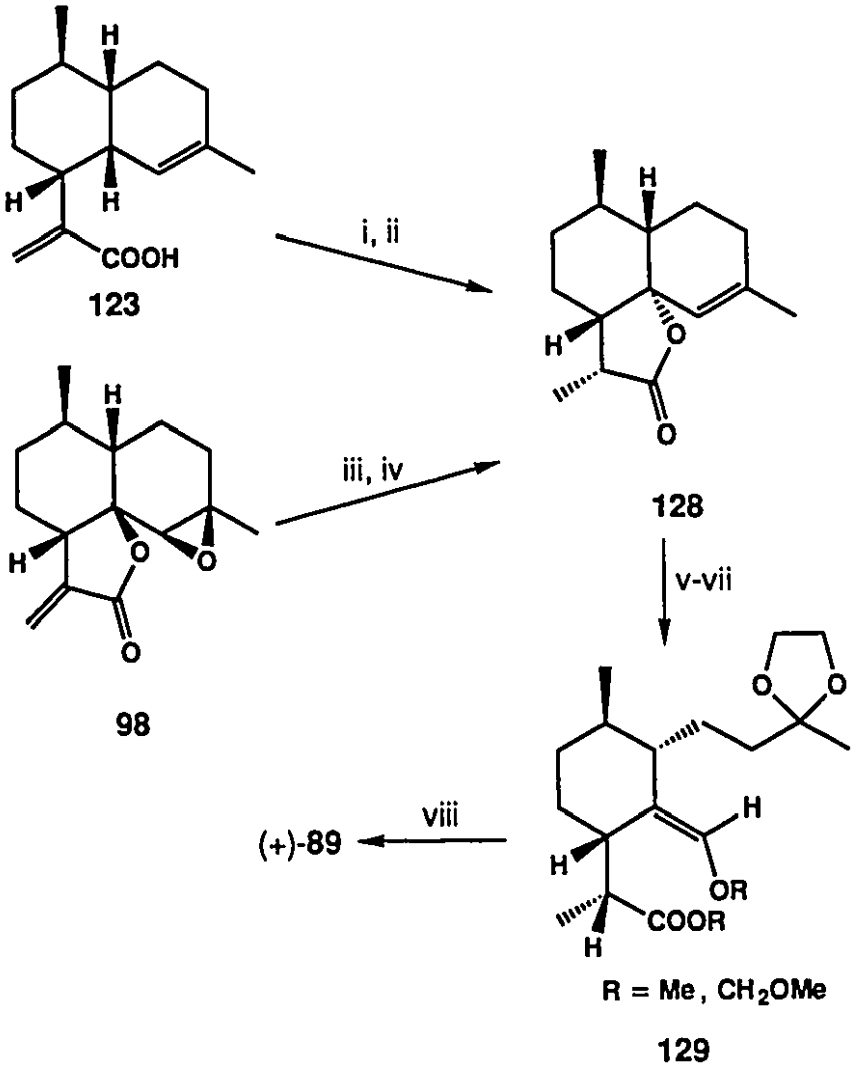


i. CH_2N_2; ii. $NiCl_2$, $NaBH_4$; iii. $LiAlH_4$; iv. O_3; Me_2S; v. *p*-TsOH; vi. hv, Methylene Blue, O_2; vii. TfOTMS; viii. $RuCl_3$-$NaIO_4$

Recently, a different approach was published by Lansbury and Nowak[78] starting with qinghao acid (**123**) and artemisinin B (**98**), respectively. As depicted in **Scheme 33**, **123** was converted into the common intermediate lactone **128** by hydrogenation and allylic oxidation. This

compound could also be obtained from **98** by hydrogenation over modified Wilkinson's catalyst and then reduction with concomitant isomerization. Ozonolysis of **128** followed by ketalization and reductive cleavage afforded ketal **129**, which was in turn photooxygenated without deprotection to generate (+)-qinghaosu in 30-35% yield.

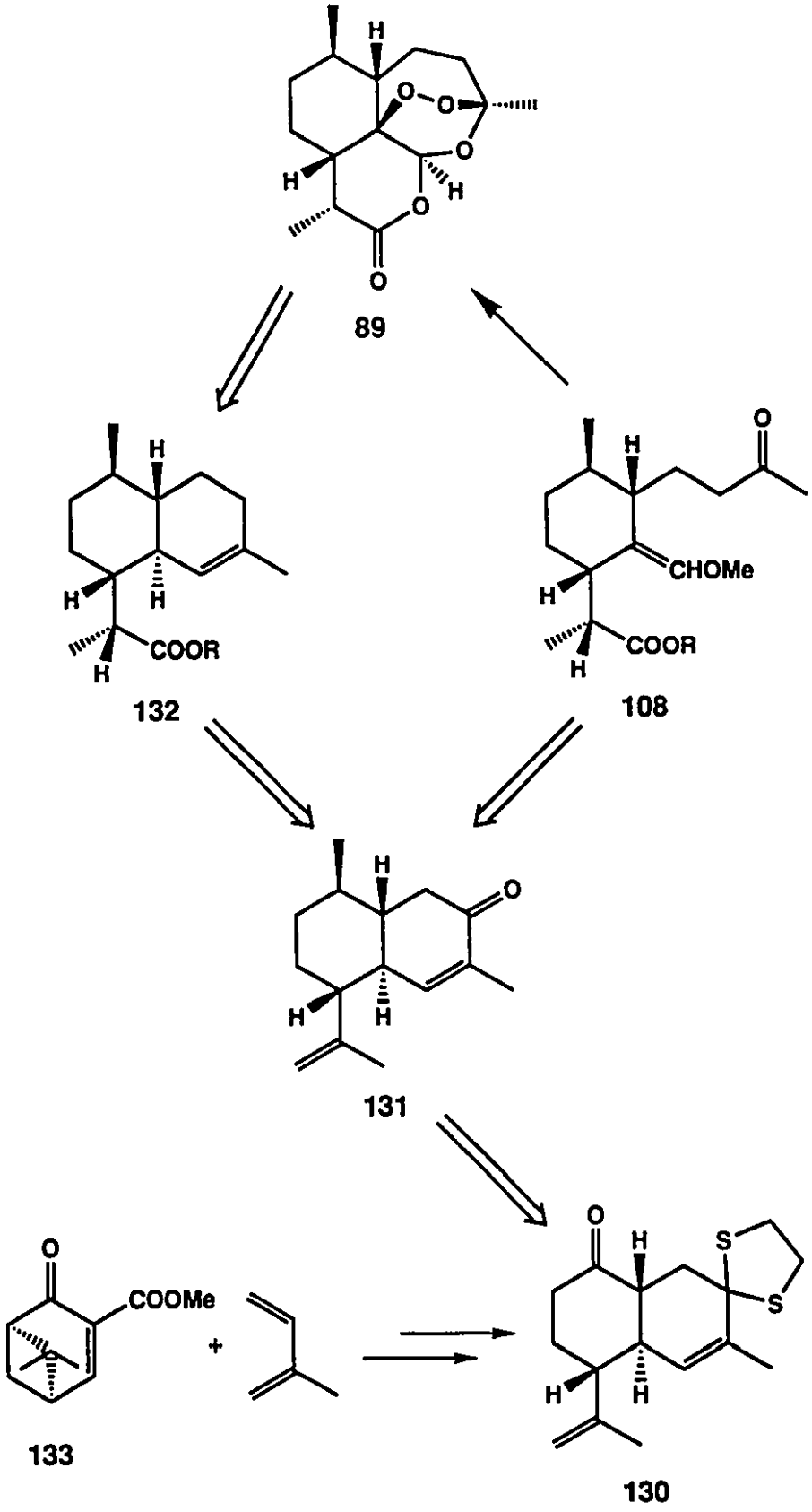
Scheme 33



i. $NiCl_2$, $NaBH_4$; ii. CrO_3, 3,5-dimethylpyrazole; iii. H_2, Wilkinson's catalyst; iv. *n*-BuLi, WCl_6; v. ozonolysis; vi. 1,2-bis(trimethylsilyloxy)ethane, TMS triflate; vii. Na naphthalenide; MeI or $MeOCH_2Cl$; viii. hv, O_2, Rose Bengal; camphorsulfonic acid

We have been interested in utilizing a fundamentally different strategy to approach the synthesis of (+)-qinghaosu. In the synthesis recently developed in our laboratory,[79,80] thioketal **130**, readily prepared *via* a facially stereoselective intermolecular Diels-Alder reaction, was envisaged as a key intermediate because it contains virtually all the carbon units present in (+)-qinghaosu. After incorporation of the missing methyl group and deprotection of the thioketal, the resulting dienone **131** could, in principle, be transformed to the target molecule by two routes (**Scheme 34**). In one approach, **131** could be converted to ester **132** which is similar to Acton and Roth's intermediate **124** except for the configuration of the ring junction. Therefore, photooxygenation could be applied to conclude the total synthesis. Alternatively, **131** might be directed to Chou's intermediate **108** and a formal synthesis of (+)-qinghaosu could then be achieved. These synthetic routes were investigated culminating in the total synthesis of (+)-qinghaosu described in this chapter.

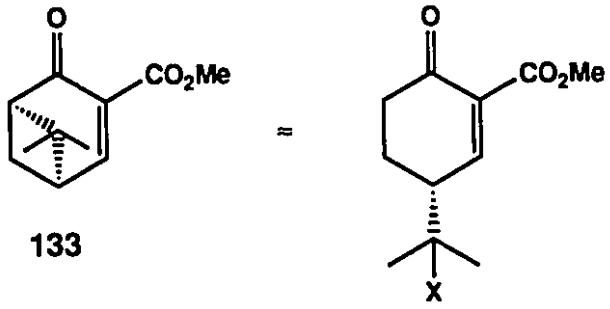
Scheme 34



Results and Discussion

Chiral 5,5-dimethyl-4,6-methano-2-methoxycarbonyl-2-cyclohexenone (**133**), readily prepared in optically active form (≥ 92% ee) from (-)-β-pinene, is a potentially useful starting material for the synthesis of natural products.[79] It has been shown to undergo Diels-Alder reaction with high facial selectivity because of its conformational rigidity and profound stereofacial difference. Furthermore, the present cyclobutane ring can be easily cleaved due to the ring strain and being α to the ketone carbonyl. Thus, **133** can serve as an excellent synthetic equivalent of a 2-carbomethoxy-2-cyclohexenone derivative possessing a functionalized isopropyl group at C-4 (**Scheme 35**).

Scheme 35



133

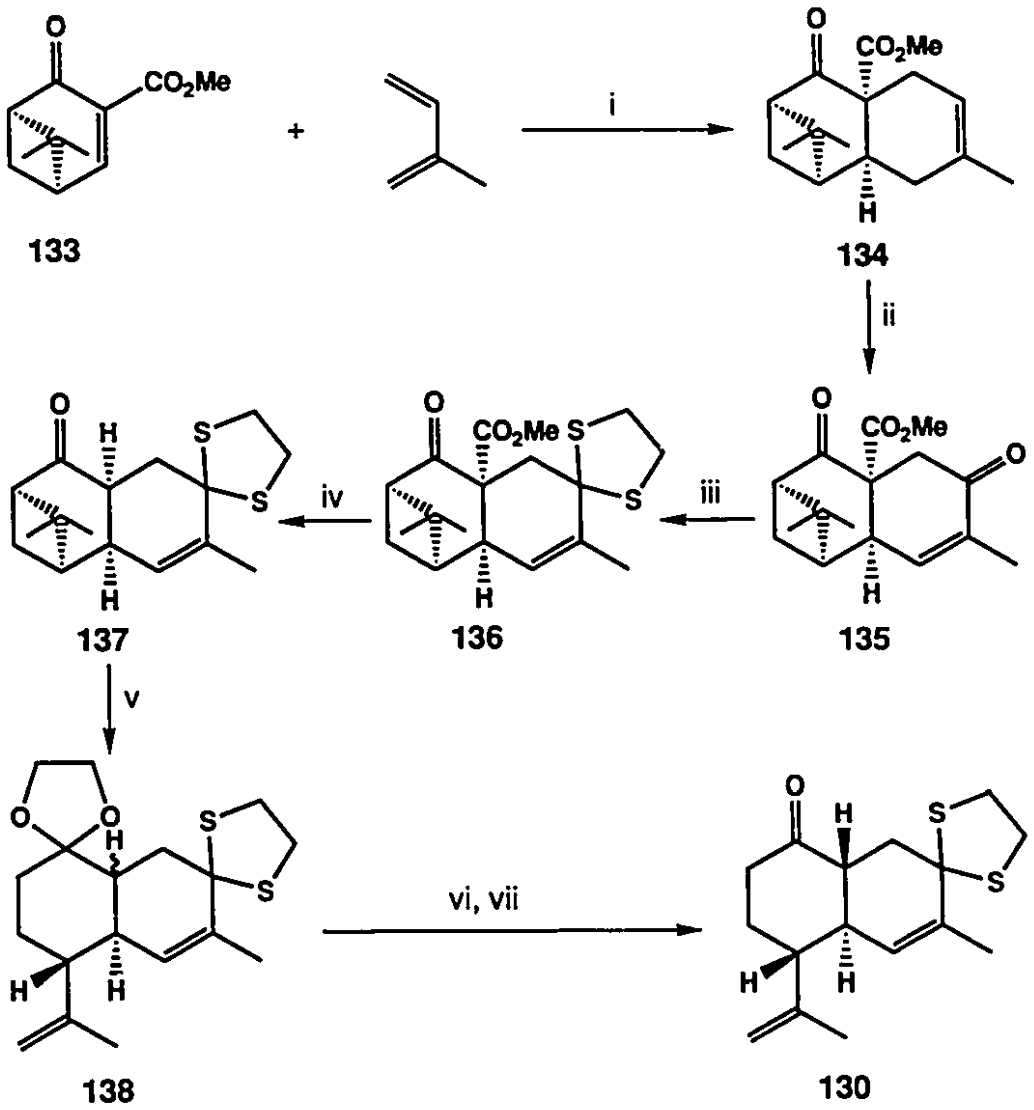
Recently in our laboratory, Chew has succeeded in the syntheses of "methyl zafronate" and "methyl ledesmate" using **133** as a starting material. In the syntheses, which disproved the structural assignments of these natural products,[80] ketone **130** served as a key intermediate. Chew has also introduced the synthetic project directed towards the synthesis of (+)-qinghaosu (**89**) making use of **130** as an intermediate.

As outlined in **Scheme 36**, the zinc chloride-catalyzed Diels-Alder reaction of enone ester **133** and isoprene gave adduct **134** in 95% yield

with complete regioselectivity and facial selectivity. In order to migrate the double bond to the adjacent position to provide a handle for the eventual incorporation of the peroxy moiety, a photochemical process was carried out. Irradiation of a dichloromethane solution of **134**, tetraphenylporphine and oxygen in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine[81] resulted in enedione **135** with the double bond at the required position. The less hindered enone carbonyl group was consequently protected selectively, in 98% yield, by thioketalization with 1,2-ethanedithiol and boron trifluoride etherate at low temperature. The carbomethoxy group of the thus formed thioketal **136** was then removed, in a yield of 91%, using lithium iodide monohydrate in refluxing collidine. With keto thioketal **137** in hand, subsequent ketalization with *p*-toluenesulfonic acid and ethylene glycol in refluxing benzene with removal of water induced concomitant cleavage of the cyclobutane ring, generating a mixture of epimeric ketals **138** quantitatively. Successive treatment of **138** with *p*-toluenesulfonic acid in refluxing acetone and sodium hydroxide in refluxing aqueous methanol gave rise to dienone **130** in *ca.* 80% overall yield.

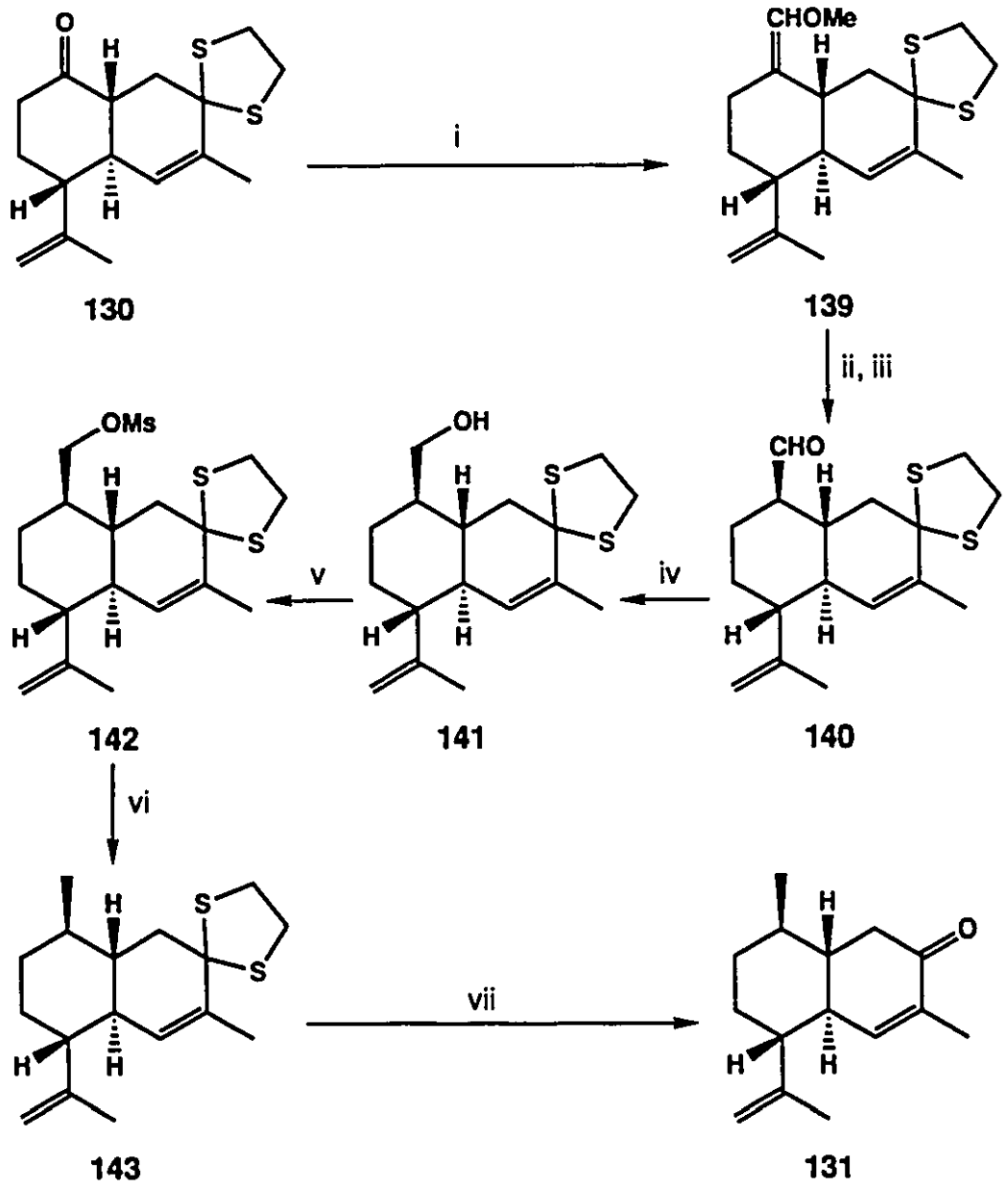
For the purpose of controlling the stereochemistry, the missing methyl group at C-7 was incorporated in an indirect manner as illustrated in **Scheme 37**. Wittig reaction of dienone **130** with methoxymethyltriphenylphosphorane in dimethyl sulfoxide gave enol ether **139** in 94% yield. Compound **139** was then hydrolyzed with *p*-toluenesulfonic acid in refluxing aqueous acetone. This was followed by epimerization using sodium hydroxide in aqueous methanol at room temperature giving rise to the thermodynamically more stable aldehyde **140** in 92% yield. Lithium aluminum hydride reduction of **140** generated alcohol **141**, which was mesylated with methanesulfonyl chloride and triethylamine. The resulting mesylate **142** was produced in 92% overall yield. Reductive cleavage of the mesylate **142** using lithium aluminum hydride in refluxing tetrahydrofuran resulted in thioketal **143**, in 92% yield, bearing the required methyl group. Subsequent dethioketalization with mercuric chloride in aqueous acetonitrile produced dienone **131** in 89% yield.

Scheme 36



i. $ZnCl_2$, ether, -20°C, 95%; ii. hv, O_2, TPP, Ac_2O, Py, DMAP, CH_2Cl_2, 20°C, 90%; iii. $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -10°C, 98%; iv. $LiI{\cdot}H_2O$, collidine, reflux, 91%; v. $(CH_2OH)_2$, *p*-TsOH, PhH, reflux, 98%; vi. *p*-TsOH, aq. Me_2CO, reflux; vii. aq. NaOH, MeOH, 80% (two steps)

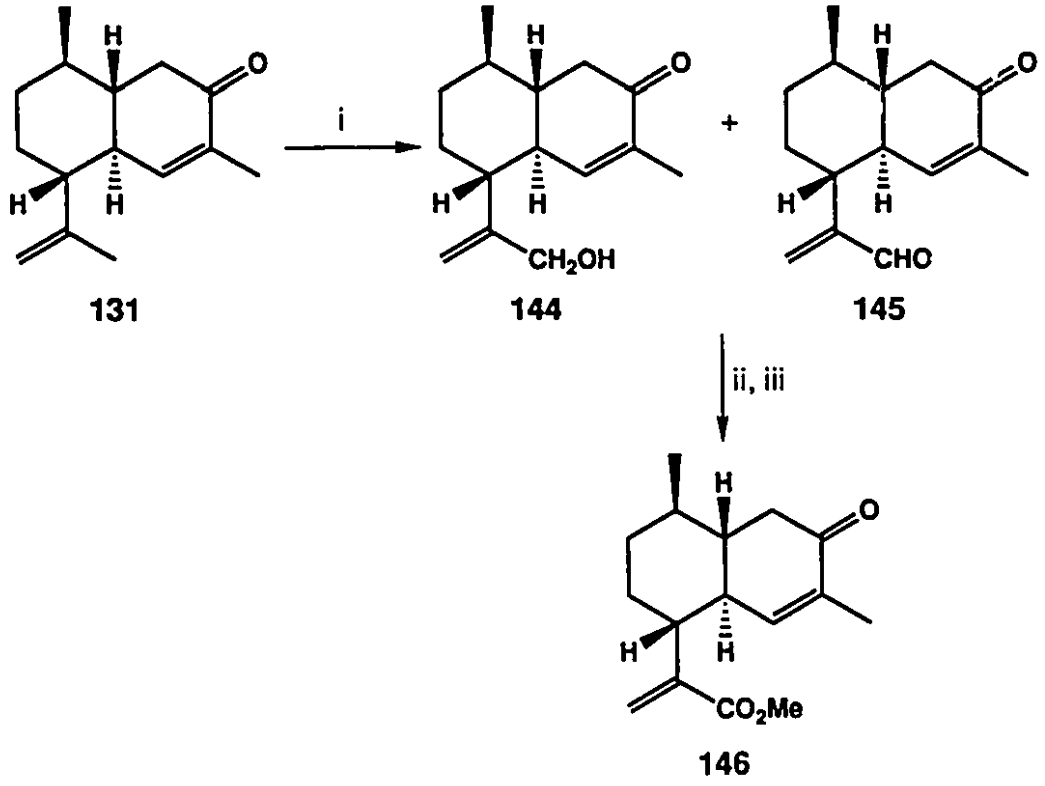
Scheme 37



i. KH, $Ph_3P^+CH_2OMeCl^-$, DMSO, 20°C, 94%; ii. *p*-TsOH, aq. Me_2CO, reflux; iii. NaOH, aq. MeOH, 20°C, 92% (two steps); iv. $LiAlH_4$, THF, reflux; v. Et_3N, MsCl, CH_2Cl_2, 0°C, 92% (two steps); vi. $LiAlH_4$, THF, reflux, 92%; vii. $HgCl_2$, aq. MeCN, 20°C, 89%

Several routes were investigated to remove the enone carbonyl and to functionalize the isopropenyl side chain present in dienone **131**. Although the results were somewhat disappointing, these preliminary studies provided us with useful information for the further investigation. The previous results are summarized in **Schemes 38-40**.[80]

Scheme 38

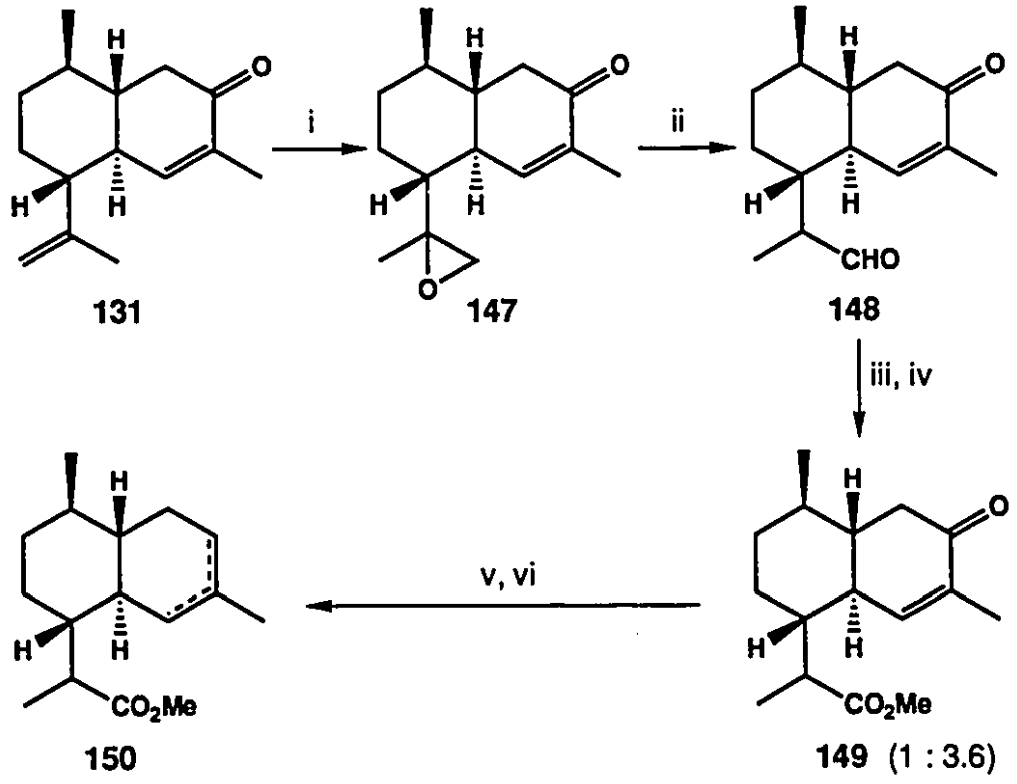


i. SeO_2, *t*-BuO_2H, CH_2Cl_2, 20°C, 73%; ii. H_2CrO_4, Me_2CO, 20°C; iii. K_2CO_3; MeI, Me_2CO, 20°C, 50% (two steps)

In the first approach (**Scheme 38**), allylic oxidation of **131** was carried out smoothly by employing selenium dioxide and *t*-butyl hydroperoxide in dichloromethane[82] at room temperature to give a mixture of alcohol **144** and aldehyde **145** in 73% yield. This mixture, without separation, was then converted to the corresponding ester **146** *via* a two-step sequence.

Jones oxidation with chromic acid in acetone, followed by treatment of the resulting acid with potassium carbonate and then methyl iodide in acetone gave rise to ester **146** in 50% overall yield. Although ester **146** could be obtained in this manner, it was still necessary to selectively reduce the α,β-unsaturated ester to the saturated ester. Hence, this approach was suspended.

Scheme 39



131 **147** **148** **150** **149** (1 : 3.6)

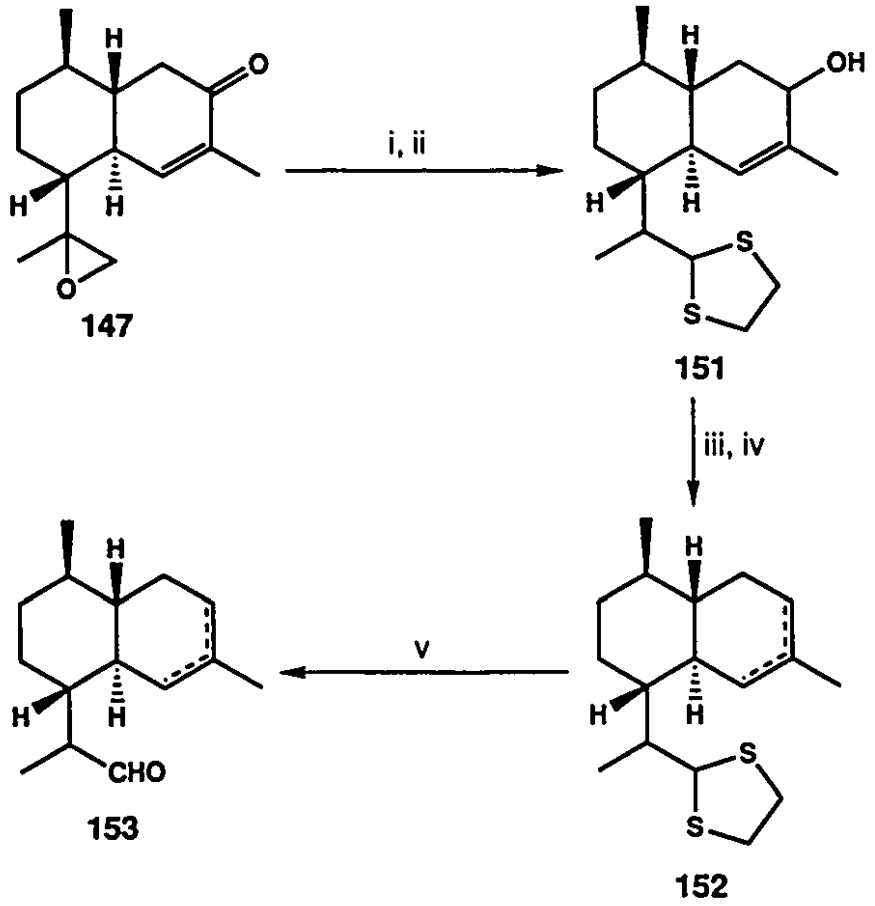
i. MCPBA, CH_2Cl_2, 0°C, 91%; ii. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 81%; iii. H_2CrO_4, Me_2CO, 20°C; iv. K_2CO_3; MeI, Me_2CO, 69% (two steps); v. $(CH_2SH)_2$, *p*-TsOH, PhH, reflux, 65%; vi. Ra-Ni, EtOH, 20°C, 60%

Another method involving a different strategy to introduce the oxygen functionality is outlined in **Scheme 39**. Dienone **131** was epoxidized with *m*-chloroperoxybenzoic acid in dichloromethane at 0°C to give a

mixure of epoxides **147** in 91% yield. Rearrangement of the epoxides **147** was induced by boron trifluoride etherate in dichloromethane at 0°C to give a 81% yield of an epimeric mixture of aldehydes **148**. Conversion of **148** to the corresponding esters **149** was subsequently accomplished by the above mentioned Jones oxidation and esterification method. The ratio of this inseparable epimeric mixture of esters **149**, obtained in 69% overall yield, was determined to be 1 : 3.6. The major epimer was purified by successive recrystallization and then analyzed by X-ray diffraction study. Unfortunately, this predominating component was clearly unveiled to bear a wrong configuration (S) at the α position of the ester group. In addition, removal of the oxygen functionality of the enone moiety again encountered difficulties. Esters **149** were first subjected to thioketalization with 1,2-ethanedithiol and *p*-toluenesulfonic acid in refluxing benzene (65% yield). Subsequent desulfurization with Raney-nickel in ethanol produced a mixture of four isomeric esters **150** (60% yield), caused by partial double bond migration. The lack of stereochemical control and unexpected double bond migration forced us to abandon this alternative sequence.

The plan of the last attempt which Chew carried out (**Scheme 40**) was based on a different mechanism, a nucleophilic displacement, to eliminate the oxygen atom of the enone unit. Starting with epoxides **147**, the epoxide group was converted directly to a protected form (thioacetal) of aldehyde by treatment with 1,2-ethanedithiol in the presence of boron trifluoride etherate in dichloromethane at 0°C. The resulting keto thioacetals were subsequently reduced with sodium borohydride and cerium(III) chloride[83,84] to generate a mixture of alcohols **151** in 57% overall yield. The hydroxyl group was removed by converting to the corresponding mesylate using methanesulfonyl chloride and triethylamine, followed by reducing the resulting mesylates with lithium aluminum hydride in refluxing tetrahydrofuran. Partial double bond migration again occurred during the reduction to give a 76% yield of thioacetals **152** containing at least three components. Moreover, restoration of the aldehyde functionality by treating **152** with mecuric chloride in aqueous acetonitrile gave rise to aldehydes **153** in only 24% yield.

Scheme 40



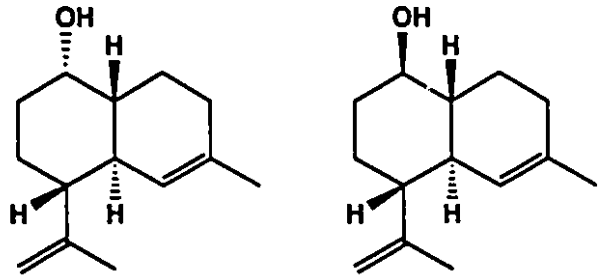
i. $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C; ii. $NaBH_4$, $CeCl_3$, MeOH, 0°C, 57% (two steps); iii. MsCl, Et_3N, CH_2Cl_2, 0°C; iv. $LiAlH_4$, THF, reflux, 76% (two steps); v. $HgCl_2$, aq. MeCN, 20°C, 24%

At this stage, two main problems existing in this whole synthetic plan towards (+)-qinghaosu (**89**) had to be overcome. The first one was to remove the enone carbonyl oxygen without the migration of the double bond. The second problem was the stereochemical control during the conversion of the isopropenyl group into the carbomethoxyethyl moiety possessing the correct configuration (R) at the stereogenic center.

It was assumed that, in the present case, the course of the migration of the double bond was related to the three-dimensional structure of the

molecule. In other words, the double bond would prefer to stay at the position which makes the molecule thermodynamically more stable. Based on this assumption, we examined the behaviors of the desulfurizations of several thioketals obtained in the previous synthetic scheme, including **130**, **136**, and **140-143**. However, this effort turned out to be unfruitful as detailed below.

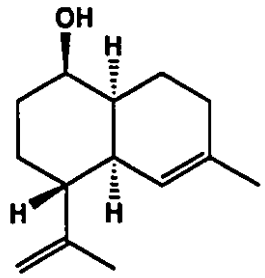
Desulfurization of thioketal **136** using Raney-nickel in ethanol at room temperature resulted in a messy mixture of desulfurized products which was determined to contain at least three olefins based on ^{1}H NMR spectrum. To make matter worse, the yield was only 33%.



154 **155**

In the case of **130**, desulfurization under the standard conditions for 1 hour also gave a mixture. Separation by flash chromatography afforded alcohols **154** (19% yield) and **155** (24% yield), along with some other inseparable isomers. The infrared spectrum of **154** showed a typical hydroxyl absorption at 3380 cm^{-1} and the absence of the ketone band. In its ^{1}H NMR spectrum, the vinylic proton of the trisubstituted double bond was displayed at δ 5.29 as a broad singlet. The lack of coupling indicated the position of the double bond. An examination of the molecular model showed that the dihedral angle between this proton and the neighboring proton is very close to 90 degrees. Consequently, they are not coupled to each other efficiently. The other vinylic protons on the disubstituted double bond were observed at δ 4.80 (m) and 4.73 (br d, J = 2.5 Hz). The proton next to hydroxyl group was displayed at δ 3.89 as a doublet of doublets (J = 5, J' = 2 Hz), indicating its equatorial position.

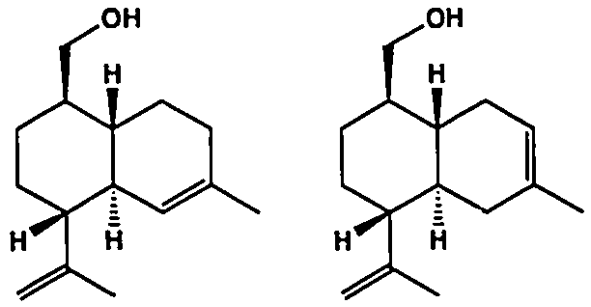
Two broad vinylic methyl singlets appeared at δ 1.68 and 1.61. The high resolution mass spectrum showed a molecular ion peak at m/z 206.1669, consistent with the molecular formula $C_{14}H_{22}O$. The ^1H NMR spectrum of **155** displayed a slightly different pattern. A broad singlet at δ 5.23, representing the vinylic proton of the endocyclic double bond, confirmed the position of the double bond. The other vinylic protons were displayed at δ 4.82 and 4.73, each as a broad singlet. The proton adjacent to hydroxyl group was shown as a multiplet at δ 3.33. The width of this multiplet suggested the axial orientation of this proton. The infrared spectrum showed a broad absorption at 3350 cm^{-1}, while a molecular ion peak at m/z 206.1677 in the high resolution mass spectrum was in agreement with the molecular formula $C_{14}H_{22}O$. Although we could isolate the desired olefins, the yield was unsatisfactory.



156

A 1 : 1 mixture of **130** and its *cis* isomer was also treated under desulfurization conditions for 1 hour. Alcohol **156** was isolated in 15% yield along with several unidentified compounds. The infrared spectrum displayed a broad hydroxyl band at 3350 cm^{-1}. The position of the double bond was indicated by the ^1H NMR spectrum, displaying a vinylic proton at δ 5.36 as a narrow multiplet. A broad multiplet at δ 3.85 was assigned to the axial proton at the hydroxyl-bearing carbon. The two vinylic protons on the terminal double bond were located at δ 4.72 and 4.66, each as a multiplet. The high resolution mass spectrum provided a

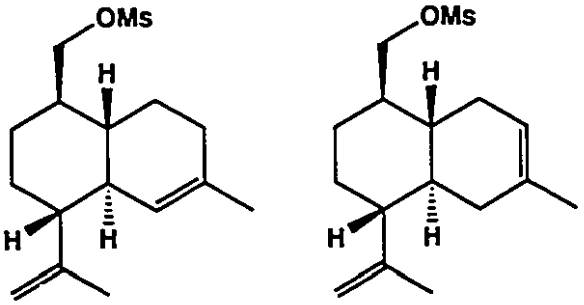
molecular ion peak at m/z 206.1671, consistent with the molecular formula $C_{14}H_{22}O$.



157a **157b**

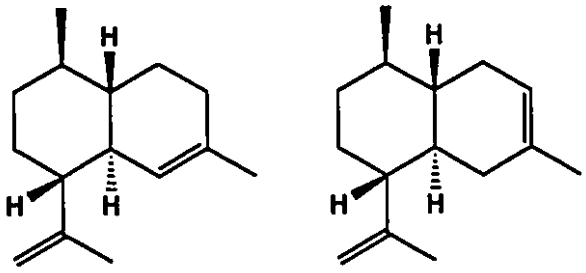
Reaction of aldehyde **140** with Raney-nickel resulted in an inseparable mixture of alcohols **157a** and **157b** in a ratio of 5 : 3 and in 61% yield. The infrared spectrum of this mixture displayed a broad hydroxyl absorption at 3350 cm^{-1}, indicating the reduction of the aldehyde. Two vinylic signals appeared at δ 5.33 (multiplet) and 5.26 (broad singlet) in a ratio of 3 : 5. According to the above principle of assignment, the broad singlet at δ 5.26 was assigned to the vinylic proton of the internal double bond in **157a** and the multiplet at δ 5.33 to the parallel proton in **157b** because this proton is next to two other protons, thus the coupling pattern should be more complex than that of the analogous proton in **157a**. The vinylic protons of the terminal double bond were displayed at δ 4.79 and 4.72, while the methylene protons adjacent to the hydroxyl group were observed at δ 3.75 and 3.57, all of these signals being multiplets. In the high resolution mass spectrum of this mixture, a molecular ion peak at m/z 220.1828 was in agreement with the molecular formula $C_{15}H_{24}O$.

Desulfurization of alcohol **141** gave rise to exactly the same result as that of **140**, except for the reaction time and the yield. Reduction of **141** took 2 hours to give products in 74% yield, compared to 1 hour and 61% yield for that of **140**.



158a **158b**

Treatment of mesylate **142** with Raney-nickel generated an inseparable 5 : 3 mixture of the corresponding mesylates **158a** and **158b** in 64% yield. In the infrared spectrum, a medium olefinic band appeared at 1644 cm^{-1}. The ^1H NMR spectrum of the mixture displayed the vinylic proton of the internal double bond in **158b** at δ 5.33 as a multiplet, while the corresponding proton in **158a** was observed at δ 5.25 as a broad singlet. Two multiplets at δ 4.80 and 4.72 were assigned to the protons on the terminal double bond. The methylene protons α to the mesylate functionalities appeared at δ 4.11-4.32 as a broad multiplet and the methyl singlets of the mesylate groups were shown at δ 3.02 and 3.01. The high resolution mass spectrometry gave a molecular ion peak at m/z 298.1605, supporting the molecular formula $C_{16}H_{26}O_3S$.



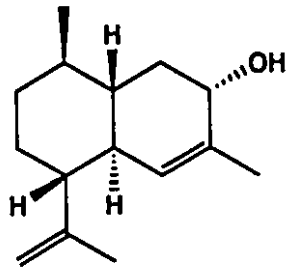
159a **159b**

The last desulfurization was performed on thioketal **143**. The reaction proceeded for 1 hour and produced a 52% yield of an inseparable mixture of dienes **159a** and **159b** in a ratio of 4 : 3. The high resolution

mass spectrum displayed a molecular ion peak at m/z 204.1876, corresponding to the molecular formula $C_{15}H_{24}$, and the infrared spectrum showed an olefin absorption at 1644 cm^{-1}. In the ^1H NMR spectrum of the mixture, a multiplet at δ 5.35 was assigned to the vinylic proton of the trisubstituted double bond in the minor isomer (**159b**), while a doublet of doublets ($J = J' = 1.5$ Hz) at δ 5.25 belonged to the parallel proton in the major isomer (**159a**). The other two vinylic protons were displayed at δ 4.78 and 4.70 as two multiplets.

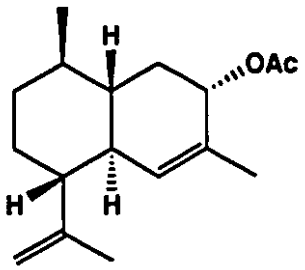
Concurrent to the above investigation, we also paid attention to the reduction of the allylic mesylate. A mixture of enones **149** was reduced with sodium borohydride and cerium(III) chloride in methanol at room temperature for 30 minutes to produce the corresponding allyic alcohols, which were directly subjected to mesylation using sodium hydride and then methanesulfonyl chloride. Unfortunately, a complete decomposition occurred. The allylic mesylate was too unstable to be isolated.

It has been reported[85,86] that a combination of palladium(0) complex and a potent nucleophilic reagent (such as super hydride $LiBHEt_3$) can reduce allylic acetates, or even the less reactive allylic ethers, to alkenes. In point of mechanism, palladium(0) and allylic substrate form an intermediate π-allyl complex, which is rapidly attacked by an effective nucleophilic hydride source at the less hindered terminal site before significant double bond migration. In light of these publications, we decided to investigate the applicability of this method to our system.

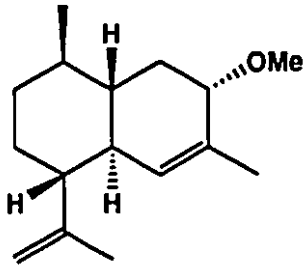


160

Dienone **131** was treated with sodium borohydride in the presence of cerium(III) chloride in methanol at -78°C for 1.5 hours to give alcohol **160** as a single isomer in 100% yield. Alcohol **160** displayed a specific rotation of -62.72° (c. 1.01, MeOH) and melted between 122.5-123.5°C. A hydroxyl absorption was observed at 3388 cm^{-1} in the infrared spectrum. In the ^1H NMR spectrum, three vinylic protons appeared at δ 5.37 (dd, $J = J' = 1.5$ Hz), 4.79 (m), and 4.71 (br d, $J = 1.5$ Hz). The proton at the hydroxyl-bearing carbon was displayed at δ 4.16 as a broad multiplet, indicating its axial position. A doublet of doublets of doublets ($J = 12.5$, $J' = 6$, $J'' = 2$ Hz) at δ 2.40 was assigned to the allylic proton at the ring junction. Two vinylic methyl groups were shown at δ 1.73 as a broad singlet and at δ 1.65 as a quintet ($J = 1$ Hz). The other methyl group appeared at δ 0.92 as a doublet ($J = 6$ Hz). The ^{13}C NMR APT spectrum displayed four olefinic signals at δ 148.27, 136.14, 127.61, and 111.50, along with the allylic carbon bearing the hydroxyl group at δ 71.53. The high resolution mass spectrum provided a molecular ion peak at m/z 220.1824, in agreement with the molecular formula $C_{15}H_{24}O$.



161

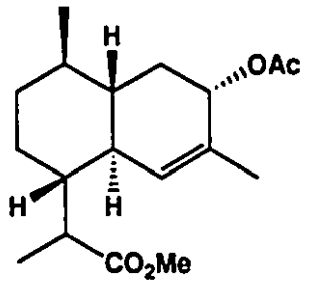


162

Alcohol **160** was treated with acetic anhydride, pyridine, and 4-dimethylaminopyridine in dichloromethane at room temperature to generate allylic acetate **161** in 82% yield. However, treatment of allylic acetate **161** with tetrakis(triphenylphosphine)palladium(0), triphenylphosphine, and super hydride only restored enol **160**.

The same reaction with the corresponding allylic methyl ether was attempted, too. Allylic ether **162** was prepared, in 67% yield, from **160** by treatment with sodium hydride, and then methyl iodide in tetrahydrofuran. The disapperance of the hydroxyl absorption in the infrared spectrum indicated the completeness of the methylation. In the ^{1}H NMR spectrum, three vinylic protons were displayed at δ 5.38 (br d, J = 1 Hz), 4.78 (m), and 4.70 (br d, J = 2 Hz). A multiplet at δ 3.82 was assigned to the allylic proton at the methoxy-bearing carbon. Four methyl groups were shown at δ 3.33 (methoxy), 1.66, 1.63 (br s, vinylic methyl, each), and 0.92 (d, J = 6 Hz, C-7 methyl). A molecular ion peak at m/z 234.1988 in the high resolution mass spectrum was consistent with the molecular formula $C_{16}H_{26}O$. Disappointingly, when **162** was treated under the same reduction conditions at room temperature, only starting material was intact. When the temperature was increased to *ca.* 65°C, complete decomposition occurred.

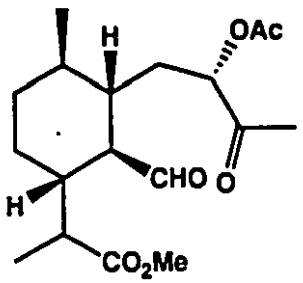
As a result of these failures encountered for the removal of the oxygen functionality, a different approach was considered. In this approach, it was attempted to cleave the double bond of the cyclohexene ring prior to the deoxygenation process. Similar operation has been previously applied by Chou and co-workers in the synthesis of (+)-qinghaosu.[66] Once the double bond is cleaved, the oxygen functionality, which is now located at the α positon of a ketone carbonyl, could be removed by the widely used reducing agents, such as samarium diiodide,[87,88] zinc-acetic acid,[89] and calcium-liquid ammonia.[90]



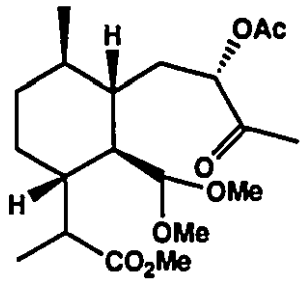
163

Reduction of an epimeric mixture of enones **149** with sodium borohydride and cerium(III) chloride followed by acetylation with acetic anhydride, pyridine, and 4-dimethylaminopyridine gave rise to a 1 : 2 epimeric mixture of acetates **163** in 43% overall yield. The infrared spectrum of this mixture displayed an ester carbonyl absorption at 1734 cm^{-1}. In the ^1H NMR spectrum, vinylic protons were shown at δ 5.72 (d, J = 1.5 Hz, major) and 5.58 (d, J = 1 Hz, minor). The protons next to the acetoxy groups overlapped at δ 5.38 as a multiplet. Two methyl singlets of the esters were displayed at δ 3.65 (major) and 3.62 (minor), while the α protons of the esters overlapped at δ 2.90 as a multiplet. The methyl groups of the acetoxy functionalities also overlapped at δ 2.06 as a singlet. The rest of the methyl groups were observed at δ 1.63 (br s, vinylic methyl), 1.22 (d, J = 7.5 Hz, α methyl of the ester, minor), 1.13 (d, J = 7 Hz, α methyl of the ester, major), 1.01 (d, J = 7 Hz, C-7 methyl, minor), and 0.88 (d, J = 6.5 Hz, C-7 methyl, major). The high resolution mass spectrum displayed a fragment at m/z 277.1804 due to the loss of a methoxy unit, supporting the required formula $C_{17}H_{25}O_3$.

Ozonolysis of the mixture of allylic acetates **163** was performed in dichloromethane and methanol at -78°C and then reductively worked up by adding dimethyl sulfide. However, the desired keto aldehydes **164** and keto acetals **165** were only isolated in 15% and 7% yields, respectively.



164

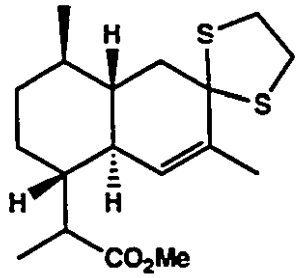


165

The four carbonyl groups present in **164** displayed a broad absorption at 1732 cm^{-1} in the infrared spectrum. In the ^1H NMR spectrum of **164**, two doublets were observed at δ 9.73 (J = 5 Hz, major) and 9.53 (J = 5.5 Hz, minor), characteristic of aldehydic protons. The α methine protons of the ketones overlapped as a multiplet at δ 4.91. All the protons α to the esters and aldehydes were shown at δ 2.40 as a multiplet. The methyls of the esters were observed at δ 3.68 as a singlet, while the methyl singlets of the acetoxy and ketone groups appeared at δ 2.19, 2.17, and 2.12. The high resolution mass spectrometry of **164** provided a molecular ion peak at m/z 340.1879, consistent with the molecular formula $C_{18}H_{28}O_6$. On the other hand, the ^1H NMR spectrum of **165** did not show any aldehydic signal, but six methyl singlets at δ 3.53, 3.52, 3.50, 3.49, 3.45, and 3.42, representing two sets of geminal methoxy and ester methyl groups. The methine protons adjacent to the dimethoxy groups were observed at δ 5.37 as a doublet (J = 2.5 Hz). The α methine protons of the ketones overlapped at δ 5.00 as a doublet of doublets (J = 11, J' = 2.5 Hz), while the ketone methyl and acetoxy methyl singlets were observed at δ 2.18 and 2.13, respectively. The infrared spectrum showed a strong absorption at 1742 cm^{-1} and the high resolution mass spectrum provided a fragement at m/z 341.1955 owing to the loss of a methoxy and a methylene units, consistent with the required formula $C_{18}H_{29}O_6$. Although these two ozonolyzed compounds were obtained, the poor yield diminished the usefulness of this alternative synthetic sequence.

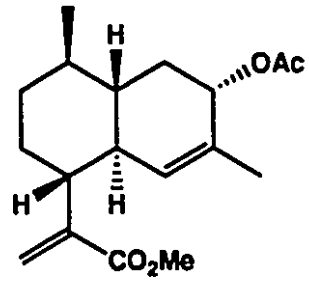
In another approach to (+)-qinghaosu, the installation of the carbomethoxyethyl side chain with the correct stereochemistry was examined. During the course of this investigation, a breakthrough emerged which led eventually to the completion of the synthetic project.

Towards this end, thioketals **166**, prepared from enones **149**, were subjected to epimerization with sodium methoxide in refluxing methanol. However, the ratio of the two epimers remained unchanged after prolonged treatment, as indicated by the ^1H NMR spectrum of the recovered material.



166

Previous work related to the semisynthesis of (+)-qinghaosu from qinghao acid has shown that nickel boride (P-2)[91] is an effective catalyst for the stereoselective conversion of acrylate moiety to the required propionate.[72,73,75,76,78] In order to examine this procedure, enone **146** was reduced with sodium borohydride and cerium(III) chloride. Subsequently acetylation of the crude product with acetic anhydride, pyridine, and 4-dimethylaminopyridine produced acetate **167** in 57% overall yield.

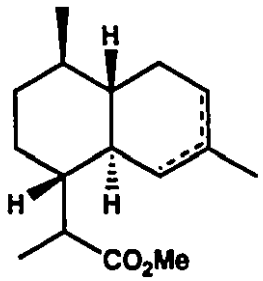


167

The infrared spectrum of **167** showed two carbonyl absorptions at 1734 (acetoxy) and 1722 cm^{-1} (carbomethoxy). In the ^1H NMR spectrum, the vinylic protons were displayed at δ 6.27 (d, J = 1 Hz, internal olefinic), 5.53 (br s, terminal olefinic), and 5.37 (m, terminal olefinic). The proton next to the acetoxy group overlapped with one of the vinylic protons at δ 5.37. One allylic proton, shown at δ 2.41 (ddd, J = 12, J' = 7, J'' = 2 Hz), coupled to the other allylic proton at δ 2.30 (ddd, J = J' = 12, J'' = 3 Hz)

with a coupling constant of 12 Hz. Four methyl groups were found at δ 3.75 (s, ester), 2.06 (s, acetate), 1.56 (br s, vinylic), and 0.91 (d, J = 6.5 Hz, C-7). A molecular ion peak at m/z 306.1837 was displayed in the high resolution mass spectrum, in agreement with the required molecular formula $C_{18}H_{26}O_4$.

Ester **167** was treated with nickel chloride and excess sodium borohydride (5 eq.), generating nickel boride *in situ*, in methanol at 0°C for 1.5 hours to afford a mixture of esters **163** in 63% yield. Based on the ^1H NMR spectrum, the major component of this epimeric mixture (2 : 1) possessed the desired configuration (R) at α carbon of the ester. Moreover, in addition to these esters **163**, we also isolated an inseparable mixture of hydrogenolyzed esters **168** from this hydrogenation reaction in 29% yield. Apparently, more drastic conditions should drive all the regular reduction products **163** further to hydrogenolyzed products **168**. Indeed, treatment of **163** with nickel chloride and a large excess of sodium borohydride (20 eq.) in methanol at room temperature for 29.5 hours resulted in **168** in 73% yield.

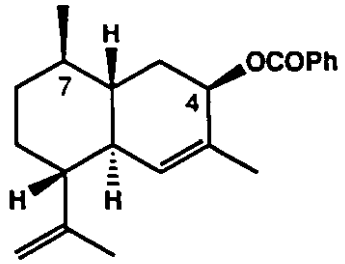


168

Although the degree of double bond migration was still to the extent of 50%, we were delighted with these results. For the first time, a simple synthetic route was recognized experimentally for achieving the desired advanced synthetic intermediate. Furthermore, the efficiency of this synthetic approach could, in principle, be improved with the replacement of the acetoxy group present in **167** with a better leaving group, such as a benzoyloxy group.

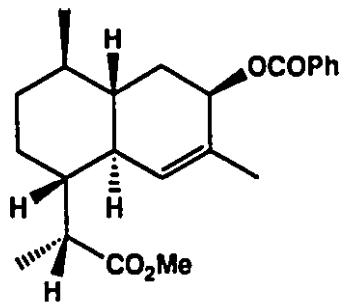
Meanwhile, we were aware of the similarity between **168** and Roth and Acton's key intermediate **124** (**Scheme 29**).[72,73] Acid **124** (an acid version of an isomer of **168** with a *cis*-fused ring system) was readily converted to (+)-qinghaosu (**89**) *via* a photooxygenation process.[72,73,92-94] According to their proposed mechanism,[74] this photooxygenation procedure should also work with our *trans*-fused ring system. To our delight, when the mixture **168** was subjected to photooxygenation at room temperature for 20 hours in dichloromethane using methylene blue as photosensitizer followed by treatment of the crude hydroperoxides with trifluoroacetic acid in petroleum ether under an oxygen atmosphere for 69 hours, (+)-qinghaosu (**89**) was produced in 7% overall yield. However, the net yield based on the major isomer of the mixture **168**, which was responsible for the production of (+)-qinghaosu, was not determined at this stage. The synthetic qinghaosu was found to be identical in every respect with an authentic sample of the natural product except slightly lower in the magnitude of the optical rotation (+63.3° *vs.* +64.53°).

After the completion of the total synthesis of (+)-qinghaosu, we further explored some modifications in order to improve the efficiency of the synthetic route. For the purpose of incorporating the carbomethoxyethyl unit more effectively, we investigated the possibility of employing the hydroboration process.[95,96] Thus alcohol **160** was converted to benzoate **169** with the inversion of stereochemistry using a Mitsunobu reaction[97] which was carried out at room temperature for 26 hours in tetrahydrofuran with triphenylphosphine, diethyl azodicarboxylate, and benzoic acid. Compound **169**, with an optical rotation of +46.00° (c. 0.75, $CHCl_3$), was obtained in 92% yield. The formation of **169** served for two purposes. First, the installation of the more reactive benzoyloxy group at the allylic position should promote its removal at the later stage by hydrogenolysis. Secondly, it is conceivable that **169** could also serve as an intermediate for the synthesis of qinghaosu IV (**171**), an isomer of qinghaosu. This synthetic aspect will be discussed in the next chapter.



169

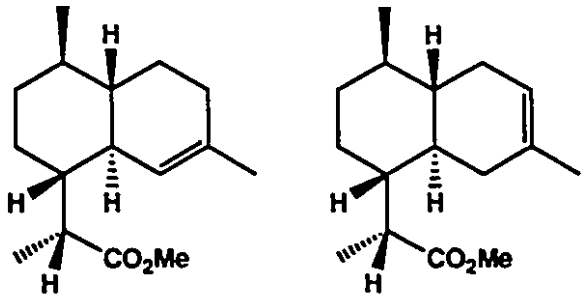
In the ^{1}H NMR spectrum of **169**, five phenyl protons were displayed at δ 7.45-8.08 and three vinylic protons appeared at δ 5.66 (br s, internal olefin), 4.84 (m, terminal olefin), and 4.78 (m, terminal olefin). A broad singlet at δ 5.66 was assigned to the allylic proton at the benzoyloxy-bearing carbon (C-4). The other two allylic protons were shown at δ 2.24 (dt, J = 10.5, J' = 1.5 Hz) and 1.91 (td, J = 8, J' = 2.5 Hz). Two vinylic methyl groups were observed at δ 1.71 and 1.69, each as a broad singlet, while the methyl group at C-7 appeared as a doublet (J = 4.5 Hz) at δ 0.86. In the ^{13}C NMR APT spectrum, a carbonyl signal was shown at δ 166.42 (ester) and four olefinic carbons were displayed at δ 148.07, 131.25, 128.28, and 111.77. The phenyl carbons were shown as four signals at δ 132.70, 131.07, 131, and 129.63. The benzoyloxy-bearing carbon signal was at δ 91.08. The infrared spectrum showed a carbonyl absorption at 1716 cm^{-1}. An observed molecular ion peak at m/z 324.2091 in the high resolution mass spectrum was consistent with the molecular formula $C_{22}H_{28}O_2$.



170

Subsequent hydroboration of **169** was carried out with 9-borabicyclo[3.3.1]nonane giving rise to a crude borane after 3 hours, which was readily converted to ester **170** by treatment with Jones reagent[98,99] at room temperature in ether for 8 hours and then with potassium carbonate and methyl iodide. The ester **170**, thus obtained in 66% overall yield, was the only isomer observed in the ^{1}H NMR spectrum and displayed an optical rotation of +14.58° (c. 0.78, $CHCl_3$). Its infrared spectrum showed two carbonyl absorptions at 1733 (carbomethoxy) and 1716 cm^{-1} (benzoyloxy). The five phenyl protons appeared at δ 7.45-8.07 and the vinylic proton was displayed at δ 5.93 as a broad singlet in the ^{1}H NMR spectrum of **170**. A methyl singlet at δ 3.69 indicated the formation of the methyl ester. The proton next to this carbomethoxy group was shown at δ 2.99 as a quartet of doublets (J = 7, J' = 4 Hz). A doublet of doublets of doublets (J = 15, J' = J'' = 2 Hz) at δ 2.22 was assigned to the allylic proton at the ring junction. The vinylic methyl group was shown at δ 1.75 as a doublet of doublets (J = J' = 1.5 Hz), while the other two methyl groups appeared at δ 1.19 (d, J = 7 Hz) and 0.84 (d, J = 6 Hz). In the ^{13}C NMR APT spectrum, the two carbonyl signals were shown at δ 175.60 and 166.39. Two olefinic carbons appeared at δ 131.91 and 128.30, while the phenyl carbons were displayed as four signals at δ 132.73, 131, 129.70, and 129.62. The signal at δ 70.96 was assigned to the allylic carbon bearing the benzoyloxy group. The molecular ion peak at m/z 370.2143 in the high resolution mass spectrum supported the molecular formula $C_{23}H_{30}O_4$.

With ester **170** in hand, the next stage was to remove the benzoyloxy group by hydrogenolysis. Treatment of **170** with nickel chloride and a large excess of sodium borohydride for 5 hours gave rise to an inseparable mixture of deoxygenated compounds **168a** and **168b** in 70% yield and with an improved ratio of 1.8 : 1. It was also attempted to further improve the ratio by carrying out the hydrogenolysis reaction under a hydrogen atmosphere. Under these conditions, the ratio of **168a** and **168b** could be slightly improved to 2.1 : 1. Hydrogenation over P-1 catalyst (prepared from sodium borohydride and nickel acetate in water)[100] was also attempted, but only starting material **170** was recovered.



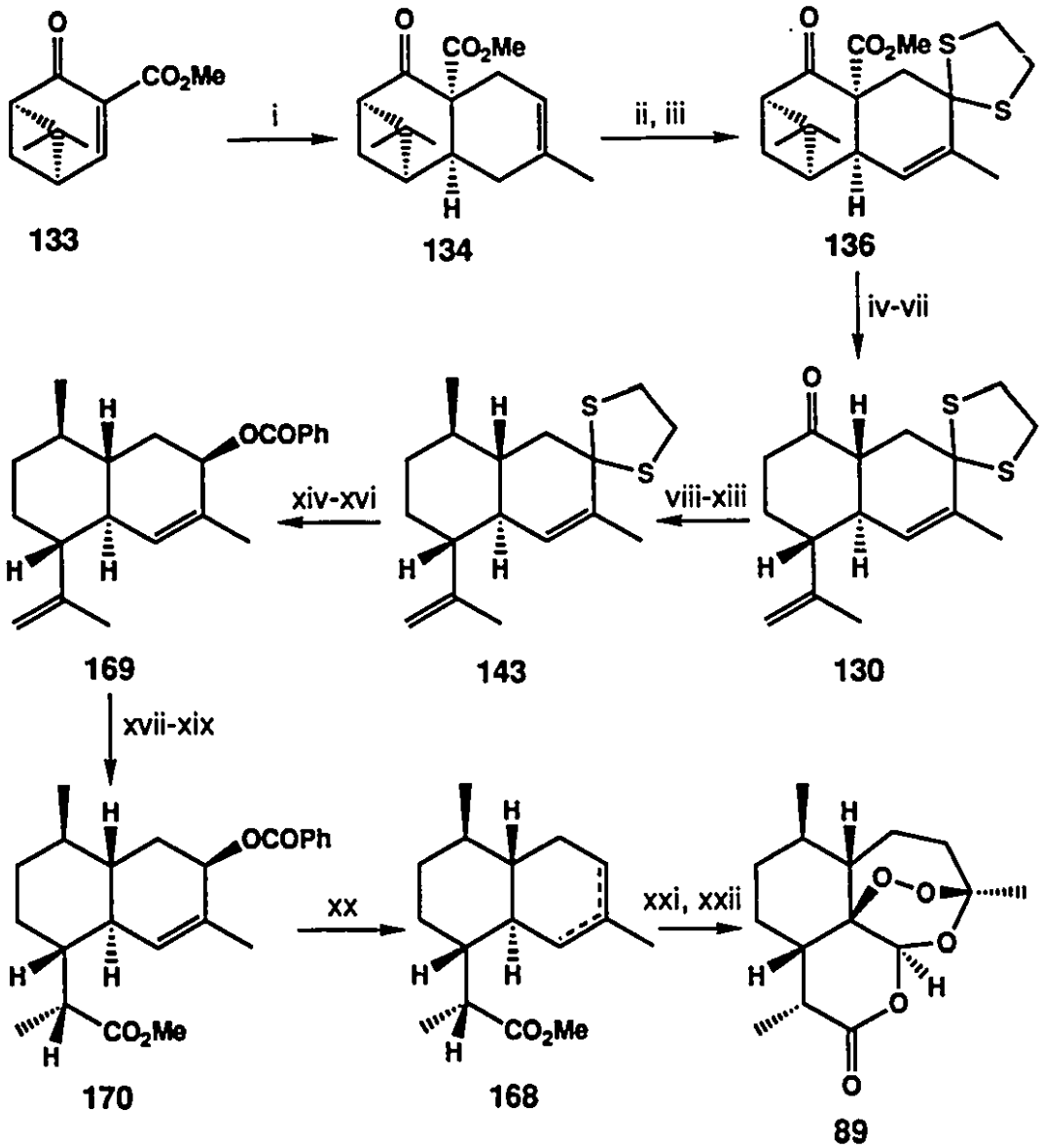
168a **168b**

The infrared spectrum of the mixture **168a** and **168b** showed an ester absorption at 1736 cm^{-1}. In the ^1H NMR spectrum, the vinylic protons were displayed at δ 5.50 (br s, major) and 5.35 (m, minor). Two ester methyl singlets were shown at δ 3.64 (major) and 3.63 (minor), while the protons next to these esters appeared at δ 2.90 (major) and 2.76 (minor), each as a quartet of doublets with the same large coupling constant (J = 7 Hz) and slightly different small coupling constants (J' = 2.5 for the major and 2 Hz for the minor). The vinylic methyl groups overlapped at δ 1.64 as a broad singlet. Two other overlapped methyl doublets at δ 1.14 (J = 7 Hz) and 0.89 (J = 6 Hz) were assigned to the methyl groups at the ester-bearing side chain and C-7. In the high resolution mass spectrum, a molecular ion peak at m/z 250.1931 was in agreement with the molecular formula $C_{16}H_{26}O_2$.

Eventually, the epimeric mixture of **168a** and **168b** was converted to the final compound (+)-qinghaosu (**89**), in 30% yield based on **168a**, using the above mentioned procedures involving a photooxygenation reaction. It was also attempted to trap the photooxygenation product by direct treatment with sodium borohydride after photooxygenation. However, a mixture of unidentified alcohols was obtained.

In conclusion, the antimalarial agent (+)-qinghaosu (**89**) has been successfully synthesized in optically active form from chiral 5,5-dimethyl-4,6-methano-2-methoxycarbonyl-2-cyclohexenone (**133**) in *ca.* 4% overall yield, using a facially stereoselective Diels-Alder approach as outlined in **Scheme 41**.[101,102]

Scheme 41



i. $ZnCl_2$, isoprene, ether, -20°C, 95%; ii. hv, O_2, TPP, Ac_2O, Py, DMAP, CH_2Cl_2, 20°C, 90%; iii. $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -10°C, 98%; iv. $LiI{\cdot}H_2O$, collidine, reflux, 91%; v. $(CH_2OH)_2$, *p*-TsOH, PhH, reflux, 98%; vi. *p*-TsOH, aq. Me_2CO, reflux; vii. aq. NaOH, MeOH, 80% (two steps); viii. KH, $Ph_3P^+CH_2OMeCl^-$, DMSO, 20°C, 94%; ix. *p*-TsOH, aq. Me_2CO, reflux; x. NaOH, aq. MeOH, 20°C, 92% (two steps); xi. $LiAlH_4$, THF, reflux; xii. Et_3N, MsCl, CH_2Cl_2, 0°C, 92% (two steps); xiii. $LiAlH_4$, THF, reflux, 92%; xiv. $HgCl_2$, aq. MeCN, 20°C, 89%; xv. $NaBH_4$, $CeCl_3$, MeOH, -78°C, 100%; xvi. Ph_3P, DEAD, $PhCO_2H$, THF, 20°C, 92%; xvii. 9-BBN, THF, 20°C; xviii. H_2CrO_4, ether, 20°C; xix. K_2CO_3; MeI, Me_2CO, 20°C, 66% (three steps); xx. $NiCl_2$, $NaBH_4$, MeOH, 20°C, 70% (9 : 5); xxi. hv, O_2, Methylene Blue, CH_2Cl_2, 20°C; xxii. CF_3CO_2H, O_2, pet. ether, 20°C

Experimental

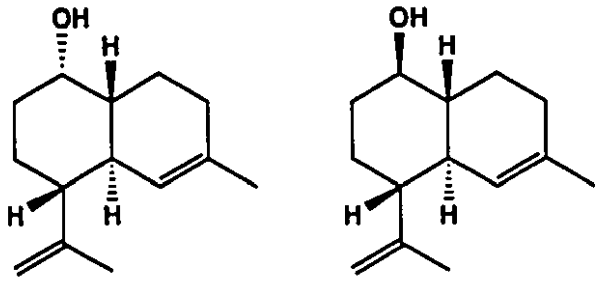
General Procedures and Materials

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

General procedure for desulfurization:

Raney-nickel (W-2 type in ethanol) was added to a solution of thioketal in 98% ethanol (1 mL) and the mixture was stirred at room temperature under an argon atmosphere for 1-2 hours. The mixture was then filtered through Celite and the residue washed with ether. The filtrate was concentrated and purified by flash chromatography.

(1R,2S,5R,6R)-8-Methyl-5-(1-methylethenyl)bicyclo[4.4.0]dec-7-en-2-ol (154) and (1R,2R,5R,6R)-8-methyl-5-(1-methylethenyl)bicyclo-[4.4.0]dec-7-en-2-ol (155)

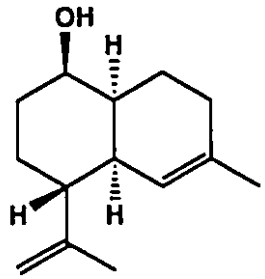


154 155

Thioketal **130** (25 mg, 0.085 mmol) was treated under standard desulfurization conditions with Raney-nickel (0.5 mL) for 1 hour. Flash

chromatography (20-25% ether in skelly B) gave a mixture of unidentified alcohols (2.4 mg) as a colorless oil: IR ($CHCl_3$, cast): 3380 cm^{-1} (O-H); ^1H NMR (200 MHz, $CDCl_3$): δ 5.57, 5.40, 5.29 (3 × m, 1H), 4.80, 4.73, 4.67 (3 × m, 1H), 3.84 (m, 1H); MS m/z (M^+) for $C_{14}H_{22}O$: calcd. 206.1672, found 206.1670. Further elution gave a colorless oil **154** (3.2 mg, 19% yield): IR ($CHCl_3$, cast): 3380 cm^{-1} (O-H); ^1H NMR (200 MHz, $CDCl_3$): δ 5.29 (br s, 1H, =C**H**-), 4.80 (m, 1H, =C**H**H), 4.73 (br d, J = 2.5 Hz, 1H, =CH**H**), 3.89 (dd, J = 5, 2 Hz, -C**H**(OH)-), 1.68 (br s, 3H, =C(C**H**$_3$)-), 1.61 (br s, 3H, =C(C**H**$_3$)-); MS m/z (M^+) for $C_{14}H_{22}O$: calcd. 206.1672, found 206.1669. This was followed by a white solid **155** (4.0 mg, 24% yield): IR ($CHCl_3$, cast): 3350 cm^{-1} (O-H); ^1H NMR (200 MHz, $CDCl_3$): δ 5.23 (br s, 1H, =C**H**-), 4.82 (br s, 1H, =C**H**H), 4.73 (br s, 1H, =CH**H**), 3.33 (m, 1H, -C**H**(OH)-); MS m/z (M^+) for $C_{14}H_{22}O$: calcd. 206.1672, found 206.1677.

(1S,2R,5R,6R)-8-Methyl-5-(1-methylethenyl)bicyclo[4.4.0]dec-7-en-2-ol (156)

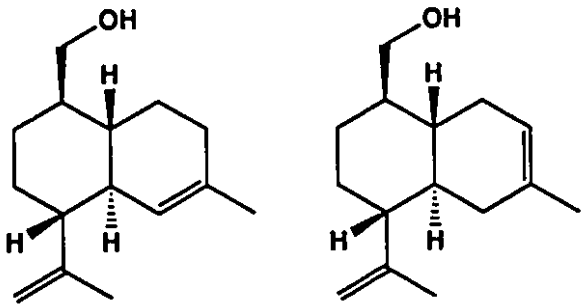


156

Thioketal **130** and its *cis* isomer (11.3 mg, 0.038 mmol) were treated under the standard desulfurization conditions with Raney-nickel (0.2 mL) for 1 hour. Flash chromatography (20-30% ether in skelly B) gave a mixture of unidentified alcohols (2.5 mg) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$): δ 5.51, 5.36, 5.31, 5.22 (4 × m, 1H), 4.81, 4.72, 4.68 (3 × m, 2H), 3.82, 3.75 (2 × m, 1H). Continued elution gave a colorless oil **156** (1.2 mg, 15% yield): IR ($CHCl_3$, cast): 3350 cm^{-1} (O-H);

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.36 (m, 1H, =C**H**-), 4.72 (m, 1H, =C**H**H), 4.66 (m, 1H, =CH**H**), 3.85 (m, 1H, -C**H**(OH)-); MS m/z (M^+) for $C_{14}H_{22}O$: calcd. 206.1672, found 206. 1671.

(1R,6S,7S,10R)-7-Hydroxymethyl-3-methyl-10-(1-methylethenyl)bicyclo[4.4.0]dec-2-ene (157a) and (1R,6S,7S,10R)-7-hydroxymethyl-3-methyl-10-(1-methylethenyl)bicyclo[4.4.0]dec-3-ene (157b)

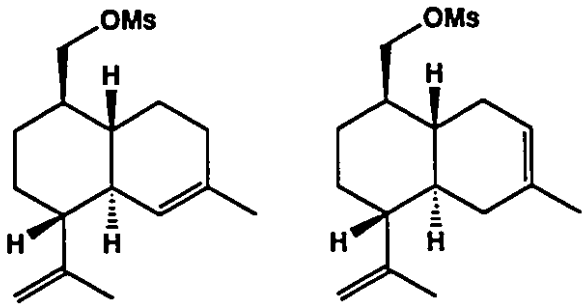


157a **157b**

From thioketal 140: Thioketal **140** (12 mg, 0.039 mmol) was treated under the standard desulfurization conditions with Raney-nickel (0.3 mL) for 1 hour. Flash chromatography (25% ether in skelly B) gave an inseparable mixture of **157a** and **157b** (5.2 mg, 61% yield) in a ratio of 5 : 3 (based on ^{1}H NMR integration) as a colorless oil: IR ($CHCl_3$, cast): 3350 cm^{-1} (O-H); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.33 (m, 0.38H, =C**H**-), 5.26 (br s, 0.62H, =C**H**-), 4.79, 4.72 (2 × br s, 2H, =C**H**H), 3.75 (m, 1H, -C**H**HOH), 3.57 (m, 1H, -CH**H**OH); MS m/z (M^+) for $C_{15}H_{24}O$: calcd. 220.1828, found 220.1828.

From thioketal 141: Thioketal **141** (7.9 mg, 0.025 mmol) was treated under the standard desulfurization conditions with Raney-nickel (0.2 mL) for 2 hours. Flash chromatography (50% ether in skelly B) gave an inseparable mixture of **157a** and **157b** (4.1 mg, 74% yield) in a ratio of 5 : 3 (based on ^{1}H NMR integration) as a colorless oil.

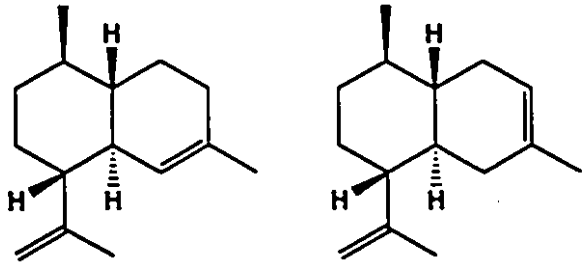
(1R,6S,7S,10R)-7-Methanesulfonyloxymethyl-3-methyl-10-(1-methylethenyl)bicyclo[4.4.0]dec-2-ene (158a) and (1R,6S,7S,10R)-7-methanesulfonyloxymethyl-3-methyl-10-(1-methylethenyl)bicyclo-[4.4.0]dec-3-ene (158b)



158a 158b

Thioketal **142** (10 mg, 0.026 mmol) was treated under the standard desulfurization conditions with Raney-nickel (0.3 mL) for 2 hours. Flash chromatography (20% ether in skelly B) gave an inseparable mixture of **158a** and **158b** (5 mg, 64% yield) in a ratio of 5 : 3 (based on ^{1}H NMR integration) as a colorless oil: IR ($CHCl_3$, cast): 1644 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33 (m, 0.38H, =C**H**-), 5.25 (br s, 0.62H, =C**H**-), 4.80, 4.72 (2 × m, 2H, =C**HH**), 4.32-4.11 (m, 2H, -C**H**$_2$OMs), 3.02, 3.01 (2 × s, 3H, -OSO$_2$C**H**$_3$); MS m/z (M^+) for $C_{16}H_{26}O_3S$: calcd. 298.1604, found 298.1605.

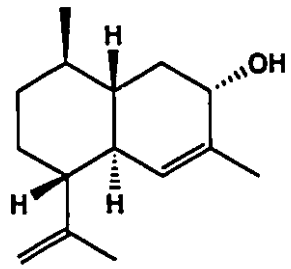
(1R,6S,7R,10R)-3,7-Dimethyl-10-(1-methylethenyl)bicyclo[4.4.0]dec-2-ene (159a) and (1R,6S,7R,10R)-3,7-dimethyl-10-(1-methylethenyl)bicyclo[4.4.0]dec-3-ene (159b)



159a 159b

Thioketal **143** (12.5 mg, 0.042 mmol) was treated under the standard desulfurization conditions with Raney-nickel (0.4 mL) for 1 hour. Flash chromatography (skelly B) gave an inseparable mixture of **159a** and **159b** (4.5 mg, 52% yield) in a ratio of 4 : 3 (based on ^{1}H NMR integration) as a colorless oil: IR ($CHCl_3$, cast): 1644 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (m, 0.43H, =C**H**-), 5.25 (dd, J = 1.5, 1.5 Hz, 0.57H, =C**H**-), 4.78, 4.70 (2 × m, 2H, =C**HH**); MS m/z (M^+) for $C_{15}H_{24}$: calcd. 204.1879, found 204.1876.

(1S,3S,6R,7R,10R)-(-)-4,10-Dimethyl-7-(1-methylethenyl)bicyclo-[4.4.0]dec-4-en-3-ol (160)

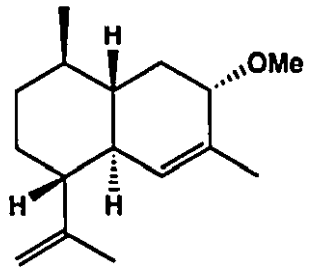


160

Cerium(III) chloride heptahydrate (4.70 g, 12.6 mmol) was added to a solution of dienone **131** (0.55 g, 2.52 mmol) in methanol (25 mL), and the resulting mixture was kept at -78°C. Sodium borohydride (0.47 g,

12.4 mmol) was then added slowly and the mixture was stirred at -78°C under an argon atmosphere for 1.5 hours. At the end of this time, the mixture was poured into saturated aqueous ammonium chloride solution and extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with water, dried, concentrated, and purified by flash chromatography (40% ether in skelly B) to give alcohol **160** (0.56 g, 100% yield) as a white crystalline solid: mp 122.5-123.5°C (skelly B); $[\alpha]_D^{22}$ = -62.72° (c. 1.01, MeOH); IR (CH_2Cl_2, cast): 3388 cm^{-1} (O-H); ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (dd, *J* = 1.5, 1.5 Hz, 1H, =C**H**-), 4.79 (m, 1H, =C**H**H), 4.71 (br d, *J* = 1.5 Hz, 1H, =CH**H**), 4.16 (m, 1H, -C**H**(OH)-), 2.40 (ddd, *J* = 12.5, 6, 2 Hz, 1H, =CC**H**-), 1.82-1.70 (m, 3H), 1.73 (br s, 3H, =C(C**H**$_3$)-), 1.65 (quintet, *J* = 1 Hz, 3H, =C(C**H**$_3$)-), 1.60 (m, 1H), 1.44 (m, 1H), 1.38 (d, *J* = 7 Hz, 1H, -O**H**), 1.25 (m, 1H), 1.15 (dddd, *J* = 12.5, 12.5, 12.5, 2 Hz, 1H), 1.10 (ddddd, *J* = 11.5, 11.5, 11.5, 4, 1 Hz, 1H), 0.94 (m, 1H), 0.92 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)-); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 148.27 (p), 136.14 (p), 127.61 (a), 111.50 (p), 71.53 (a), 50.91 (a), 46.31 (a), 43.54 (a), 37.45 (p), 35.99 (a), 35.51 (p), 32.48 (p), 19.48 (a), 19.05 (a), 18.91 (a); MS m/z (M^+) for $C_{15}H_{24}O$: calcd. 220.1828, found 220.1824; Analysis: calcd. C: 81.76%, H: 10.98%, found C: 81.54%, H: 11.09%.

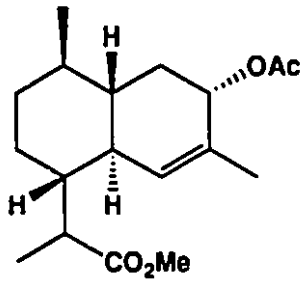
(1R,4S,6S,7R,10R)-4-Methoxy-3,7-dimethyl-10-(1-methylethenyl)bicyclo[4.4.0]dec-2-ene (162)



162

Sodium hydride (60% dispersion in mineral oil, 15 mg, 0.375 mmol) was added to a solution of alcohol **160** (14 mg, 0.0635 mmol) in dry tetrahydrofuran (1 mL) at 0°C and the resulting solution was stirred at 0°C under an argon atmosphere for 30 minutes. At the end of this time, methyl iodide (40 μL, 0.635 mmol) was added. After stirring at room temperature for 6 hours, the solution was poured into ice-water (10 mL) and extracted with ether (2 × 5 mL). The combined extracts were washed with water, dried, concentrated, and purified by flash chromatography (5% ether in skelly B) to give a colorless oil **162** (10 mg, 67% yield): IR ($CHCl_3$, cast): 1093 cm^{-1} (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ 5.38 (br d, J = 1 Hz, 1H, =C**H**-), 4.78 (m, 1H, =C**H**H), 4.70 (br d, J = 2 Hz, 1H, =CH**H**), 3.82 (m, 1H, -C**H**(OCH_3)-), 3.33 (s, 3H, -O**CH**$_3$), 2.39 (ddd, J = 12, 6.5, 2 Hz, 1H, =CC**H**-), 2.10-1.03 (m, 9H), 1.66 (br s, 3H, =C(C**H**$_3$)-), 1.63 (br s, 3H, =C(C**H**$_3$)-), 0.92 (d, J = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{16}H_{26}O$: calcd. 234.1985, found 234.1988.

(1R,4R,6S,7R,10R)-4-Acetoxy-10-(1-carbomethoxyethyl)-3,7-dimethylbicyclo[4.4.0]dec-2-ene (163)



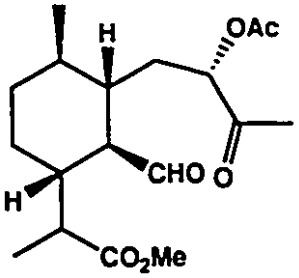
163

To a solution of ketones **149** (24 mg, 0.0908 mmol) in methanol (2 mL) was added cerium(III) chloride heptahydrate (0.17 g, 0.0454 mmol), followed by sodium borohydride (18 mg, 0.476 mmol). The resulting solution was stirred at room temperature for 30 minutes. At the end of this time, the solution was poured into saturated aqueous ammonium

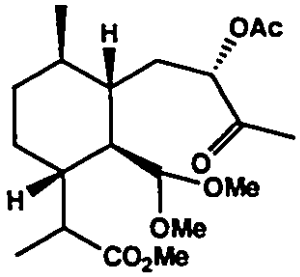
chloride solution (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water, dried, and concentrated to give a crude alcohol (21 mg) as a white solid. This crude material was used in the following reaction without further purification.

Acetic anhydride (85 μL, 0.908 mmol), pyridine (75 μL, 0.908 mmol), and 4-dimethylaminopyridine (5 mg, 0.041 mmol) were added sequentially to a solution of the crude alcohol (21 mg) in dry dichloromethane (2 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 14 hours. The solution was then acidified with 1 N hydrochloric acid. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (10 mL). The combined dichloromethane layers were washed with 1 N hydrochloric acid and water, dried, concentrated, and purified by flash chromatography (30% ether in skelly B) to give acetates **163** (12 mg, 43% yield) as a yellowish oil: IR (CH_2Cl_2, cast): 1734 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 5.72 (br d, J = 1.5 Hz, 0.67H, =C**H**-), 5.58 (br d, J = 1 Hz, 0.33H, =C**H**-), 5.38 (m, 1H, -C**H**(OAc)-), 3.65 (s, 2H, -COOC**H**$_3$), 3.62 (s, 1H, -COOC**H**$_3$), 2.90 (m, 1H, -C**H**COOCH$_3$), 2.35 (m, 1H, =CC**H**-), 2.06 (s, 3H, C**H**$_3$CO-), 1.85-1.60 (m, 4H), 1.63 (br s, 3H, =C(C**H**$_3$)-), 1.43-0.95 (m, 5H), 1.22 (d, J = 7.5 Hz, 1H, -CH(C**H**$_3$)-), 1.13 (d, J = 7 Hz, 2H, -CH(C**H**$_3$)-), 1.01 (d, J = 7 Hz, 1H, -CH(C**H**$_3$)-), 0.88 (d, J = 6.5 Hz, 2H, -CH(C**H**$_3$)-); MS m/z (M^+ - CH_3O) for $C_{17}H_{25}O_3$: calcd. 277.1804, found 277.1804.

(1R,2S,3R,4R)-2-((S)-2-Acetoxy-3-oxobutyl)-4-(1-carbomethoxyethyl)-3-formyl-1-methylcyclohexane (164) and (1R,2S,3R,4R)-2-((S)-2-acetoxy-3-oxobutyl)-4-(1-carbomethoxyethyl)-3-dimethoxymethyl-1-methylcyclohexane (165)



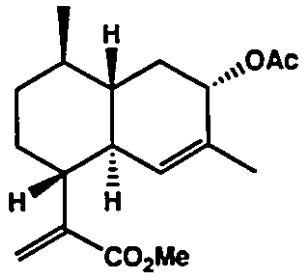
164



165

Ozone was passed through a solution of acetates **163** (12 mg, 0.0389 mmol) in dichloromethane (2 mL) and methanol (1 mL) at -78°C for 40 minutes. Dimethyl sulfide (0.1 mL) was then added and the resulting solution was warmed up to room temperature gradually while stirring. After 25 hours, the solution was concentrated and subjected to flash chromatography (70% ether in skelly B) to give a colorless oil **164** (2 mg, 15% yield): IR (CH_2Cl_2, cast): 1732 cm^{-1} (br, C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 9.73 (d, J = 5 Hz, 0.67H, -C**H**O), 9.53 (d, J = 5.5 Hz, 0.33H, -C**H**O), 4.91 (m, 1H, -C**H**(OAc)-), 3.68 (s, 3H, -COOC**H**$_3$), 2.40 (m, 2H, -C**H**CHO, -C**H**COOCH$_3$), 2.19 (s, 2H, C**H**$_3$CO-), 2.17 (s, 1H, C**H**$_3$CO-), 2.12 (s, 3H, C**H**$_3$CO-); MS m/z (M^+) for $C_{18}H_{28}O_6$: calcd. 340.1886, found 340.1879. Continued elution gave a colorless oil **165** (1 mg, 7% yield): IR (CH_2Cl_2, cast): 1742 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 5.37 (d, J = 2.5 Hz, 1H, -C**H**(OCH$_3$)$_2$), 5.00 (dd, J = 11, 2.5 Hz, 1H, -C**H**(OAc)-), 3.53, 3.52, 3.50, 3.49, 3.45, 3.42 (6 × s, 9H, 3 × -OC**H**$_3$), 2.18 (s, 3H, C**H**$_3$CO-), 2.13 (s, 3H, C**H**$_3$CO-); MS m/z (M^+ - C_2H_5O) for $C_{18}H_{29}O_6$: calcd. 341.1965, found 341.1955.

(1R,4S,6S,7R,10R)-4-Acetoxy-10-(1-carbomethoxyethenyl)-3,7-dimethylbicyclo[4.4.0]dec-2-ene (167)

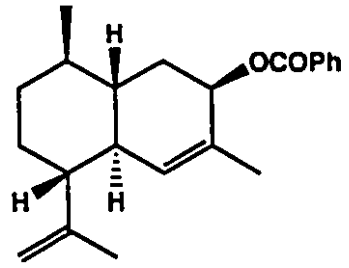


167

To a solution of ketone **146** (20 mg, 0.0762 mmol) in methanol (2 mL) was added cerium(III) chloride heptahydrate (0.14 g, 0.38 mmol), followed by sodium borohydride (14 mg, 0.381 mmol). The resulting mixture was stirred at room temperature for 30 minutes. At the end of this time, the solution was poured into saturated aqueous ammonium chloride (10 mL) and then extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water, dried, and concentrated to give a crude alcohol (18 mg, 90% yield) as a colorless oil. This material was used in the following reaction without further purification.

Acetic anhydride (0.1 mL, 1.25 mmol), pyridine (0.1 mL, 1.25 mmol), and 4-dimethylaminopyridine (6 mg, 0.049 mmol) were sequentially added to a solution of the above alcohol (33 mg, 0.125 mmol) in dry dichloromethane (1.5 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 19 hours and then acidified with 1 N hydrochloric acid. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic portions were washed with 1 N hydrochloric acid and water, dried, concentrated, and purified by flash chromatography (30% ether in skelly B) to give a colorless oil **167** (24 mg, 63% yield): IR ($CHCl_3$, cast): 1734 (C=O, acetoxy), 1722 cm^{-1} (C=O, carbomethoxy); ^1H NMR (200 MHz, $CDCl_3$): δ 6.27 (d, J = 1 Hz, 1H, =C**H**-), 5.53 (br s, 1H, =C**H**H), 5.37 (m, 2H, =CH**H**, -C**H**(OAc)-), 3.75 (s, 3H, -COOC**H**$_3$), 2.41 (ddd, J = 12, 7, 2 Hz, 1H, =CC**H**-), 2.30 (ddd, J = 12, 12, 3 Hz, 1H, =CC**H**-), 2.06 (s, 3H, C**H**$_3$CO-), 1.86-1.55 (m, 3H), 1.56 (br s, 3H, =C(C**H**$_3$)-), 1.45-0.95 (m, 5H), 0.91 (d, J = 6.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{18}H_{26}O_4$: calcd. 306.1832, found 306.1837.

(1R,4R,6S,7R,10R)-(+)-4-Benzoyloxy-3,7-dimethyl-10-(1-methylethenyl)bicyclo[4.4.0]dec-2-ene (169)

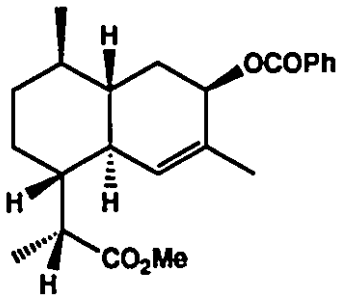


169

To a solution of alcohol **160** (426 mg, 1.933 mmol) and triphenylphosphine (557 mg, 2.126 mmol) in dry tetrahydrofuran (10 mL), a solution of benzoic acid (260 mg, 2.126 mmol) in dry tetrahydrofuran (4 mL) was added. A solution of diethyl azodicarboxylate (0.34 mL, 2.126 mmol) in dry tetrahydrofuran (4 mL) was then added dropwise and the resulting solution was stirred at room temperature under an argon atmosphere. After 23 hours, additional triphenylphosphine (710 mg, 2.706 mmol), benzoic acid (331 mg, 2.706 mmol), and diethyl azodicarboxylate (0.42 mL, 2.706 mmol) were added sequentially to accelerate the reaction to completion. After 3 hours, the solution was concentrated and subjected to flash chromatography (0-5% ether in skelly B) to give benzoate **169** (575 mg, 92% yield) as a colorless oil: $[\alpha]_D^{22}$ = +46.00° (c. 0.75, $CHCl_3$); IR ($CHCl_3$, cast): 1716 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (m, 2H, phenyl *ortho*), 7.57 (m, 1H, phenyl *para*), 7.45 (m, 2H, phenyl *meta*), 5.66 (br s, 1H, =C**H**-), 5.45 (br d, *J* = 4.5 Hz, 1H, -C**H**(OBz)-), 4.84 (m, 1H, =CH**H**), 4.78 (m, 1H, =CH**H**), 2.24 (dt, *J* = 10.5, 1.5 Hz, 1H, =CC**H**-), 1.91 (td, *J* = 8, 2.5 Hz, 1H, =CC**H**-), 1.79-1.65 (m, 3H), 1.71 (br s, 3H, =C(C**H**$_3$)-), 1.69 (s, 3H, =C(C**H**$_3$)-), 1.52-1.42 (m, 2H), 1.26-1.02 (m, 3H), 0.86 (d, *J* = 4.5 Hz, 3H, -CH(C**H**$_3$)-); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 166.42 (p), 148.07 (p), 132.70 (a), 131.25 (p), 131.07 (a), 131 (p), 129.63 (a), 128.28 (a), 111.77 (p), 91.08 (a), 71.30 (a), 50.54 (a), 43.20 (a), 41.42 (a), 35.88 (a), 35.54 (p), 33.45 (p), 32.53 (p), 20.57 (a), 19.43 (a), 19.15 (a); MS m/z (M^+) for $C_{22}H_{28}O_2$:

calcd. 324.2090, found 324.2091; Analysis: calcd. C: 81.44%, H: 8.70%, found C: 81.27%, H: 8.53%.

(1R,4R,6S,7R,10R)-(+)-4-Benzoyloxy-10-((R)-1-carbomethoxyethyl)-3,7-dimethylbicyclo[4.4.0]dec-2-ene (170)



170

The reaction flask, syringes, and needles were all flame-dried before use. 9-Borabicyclo[3.3.1]nonane (dimer, 0.22 g, 0.9 mmol) was added to a solution of benzoate **169** (534 mg, 1.646 mmol) in dry tetrahydrofuran (10 mL). After stirring at room temperature under an argon atmosphere for 2 hours, additional 9-borabicyclo[3.3.1]nonane (0.24 g, 0.98 mmol) was added to complete the reaction. After 1 hour, the solution was concentrated and the residue redissolved in ether (5 mL) for the subsequent reaction.

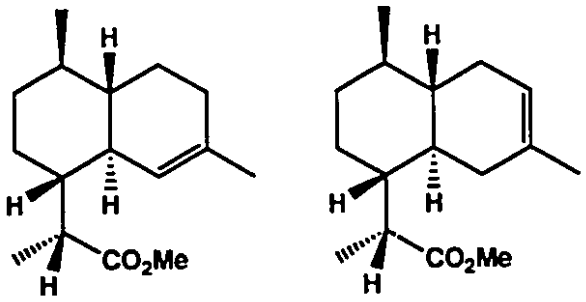
Preparation of Jones reagent:[99] Sodium dichromate dihydrate (11 g, 36.9 mmol) was dissolved in water (30 mL). To this solution was then added concentrated sulfuric acid (8.25 mL, 147.4 mmol) slowly. The solution was diluted to a total volume of 45 mL and stored at room temperature.

Both the ether solution of the crude hydroboration product and Jones reagent were kept at 0°C for 30 minutes before use. Jones reagent (10 mL) was then added to the ether solution over a period of 5 minutes

and the resulting mixture was stirred at room temperature for 8 hours. At the end of this time, the solution was diluted with water and extracted with dichloromethane (3 × 20 mL). The extracts were combined, washed with water (4 × 50 mL), dried, and concentrated to give a crude acid (0.87 g) as a yellowish oil. This material was used in the following reaction without further purification.

Potassium carbonate (0.67 g, 4.88 mmol) was added to a solution of the above crude acid in dry acetone (15 mL) and the resulting solution was stirred at room temperature under an argon atmosphere for 30 minutes. At the end of this time, methyl iodide (1.5 mL, 24.4 mmol) was added. After stirring for 13 hours, the mixture was filtered. The filtrate was then concentrated and purified by flash chromatography (5% ether in skelly B) to give a colorless oil **170** (400 mg, 66% yield in three steps): $[\alpha]_D^{22}$ = +14.58° (c. 0.78, $CHCl_3$); IR ($CHCl_3$, cast): 1733 (C=O, carbomethoxy), 1716 cm^{-1} (C=O, benzoyloxy); ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (m, 2H, phenyl *ortho*), 7.57 (m, 1H, phenyl *para*), 7.45 (m, 2H, phenyl *meta*), 5.93 (br s, 1H, =C**H**-), 5.44 (br d, *J* = 4 Hz, 1H, -C**H**(OBz)-), 3.69 (s, 3H, -COOC**H**$_3$), 2.99 (qd, *J* = 7, 3 Hz, 1H, -(CH_3)C**H**COOCH_3), 2.22 (ddd, *J* = 15, 2, 2 Hz, 1H, -C**H**C=C(CH_3)-), 1.85 (dddd, *J* = 13, 2, 2, 2 Hz, 1H), 1.77 (m, 1H), 1.75 (dd, *J* = 1.5, 1.5 Hz, 3H, =C(C**H**$_3$)-), 1.69 (m, 1H), 1.44 (m, 2H), 1.19 (d, *J* = 7 Hz, 3H, -CH(C**H**$_3$)COOCH_3), 1.27-1.03 (m, 4H), 0.84 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)-); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 175.60 (p), 166.39 (p), 132.73 (a), 131.91 (p), 131 (p), 129.70 (a), 129.62 (a), 128.30 (a), 70.96 (a), 51.23 (a), 45.11 (a), 43.78 (a), 41.86 (a), 39.49 (a), 35.66 (a), 35.55 (p), 33.27 (p), 28.04 (p), 20.99 (a), 19.51 (a), 14.63 (a); MS m/z (M^+) for $C_{23}H_{30}O_4$: calcd. 370.2145, found 370.2143; Analysis: calcd. C: 74.56%, H: 8.16%, found C: 74.76%, H: 8.03%.

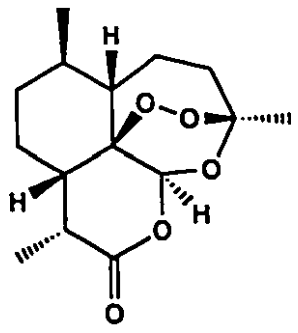
(1R,6S,7R,10R)-10-((R)-1-Carbomethoxyethyl)-3,7-dimethylbicyclo-[4.4.0]dec-2-ene (168a) and (1R,6S,7R,10R)-10-((R)-1-carbomethoxyethyl)-3,7-dimethylbicyclo[4.4.0]dec-3-ene (168b)



168a 168b

Nickel(II) chloride hexahydrate (22 mg, 0.092 mmol) was added to a solution of ester **170** (34 mg, 0.092 mmol) in methanol (2 mL). Sodium borohydride (35 mg, 0.92 mmol) was then added and the resulting mixture was stirred at room temperature for 2 hours. At the end of this time, additional sodium borohydride (35 mg, 0.92 mmol) was added. After stirring for 3 hours, the mixture was acidified with 1 N hydrochloric acid and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water, dried, concentrated, and purified by flash chromatography (4% ether in skelly B) to give an inseparable mixture of **168a** and **168b** (16 mg, 70% yield) in a ratio of 9 : 5 (based on ^{1}H NMR integration) as a colorless oil: IR ($CHCl_3$, cast): 1736 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.50 (br s, 0.64H, =C**H**-), 5.35 (m, 0.36H, =C**H**-), 3.64 (s, 1.92H, -COOC**H**$_3$), 3.63 (s, 1.08H, -COOC**H**$_3$), 2.90 (qd, *J* = 7, 2.5 Hz, 0.64H, -(CH_3)C**H**COOCH_3), 2.76 (qd, *J* = 7, 2 Hz, 0.36H, -(CH_3)C**H**COOCH_3), 1.64 (br s, 3H, =C(C**H**$_3$)-), 1.14 (d, *J* = 7 Hz, 3H, -CH(C**H**$_3$)COOCH_3), 0.89 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M$^+$) for $C_{16}H_{26}O_2$: calcd. 250.1934, found 250.1931.

(+)-Qinghaosu (89)



89

A solution of a mixture of esters **168a** and **168b** (15.5 mg, 0.0619 mmol) and methylene blue (3 mg) in dry dichloromethane (0.8 mL) was irradiated with a fluorescent lamp (15 W) at room temperature under an oxygen atmosphere for 22 hours. The solution was then concentrated, taken up in ether (10 mL), and filtered through Celite to remove the dye. The filtrate was again concentrated to give a colorless oil (20 mg).

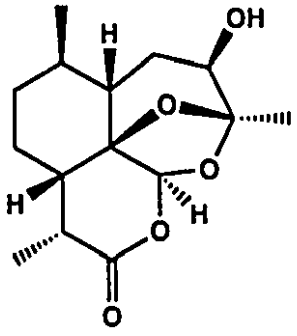
This colorless oil was mixed with trifluoroacetic acid (5 μL, 0.0619 mmol) in petroleum ether (1 mL). The resulting solution was stirred at room temperature under an oxygen atmosphere for 90.5 hours. The solution was then concentrated and subjected to flash chromatography (30% ether in skelly B) to give a white crystalline solid **89** (3.2 mg, 30% yield based on ester **168a**): mp 152-153°C (skelly B); $[\alpha]_D^{22}$ = +63.3° (c. 0.06, $CHCl_3$); IR ($CHCl_3$, cast): 1740 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 1H, -OC**H**O-), 3.40 (qd, *J* = 7.5, 5.5 Hz, 1H, -(CH_3)C**H**C(=O)O-), 2.44 (ddd, *J* = 14.5, 13, 4 Hz, 1H, -C**H**HC(CH_3)(O-)(OO-)), 2.03 (m, 2H), 1.88 (m, 1H), 1.78 (m, 2H), 1.50-1.37 (m, 3H), 1.45 (s, 3H, -C(C**H**$_3$)(O-)OO-), 1.21 (d, *J* = 7.5 Hz, 3H, -CH(C**H**$_3$)C(=O)O-), 1.09 (m, 2H), 1.00 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{15}H_{22}O_5$: calcd. 282.1468, found 282.1466. The physical properties and spectral data of an authentic sample: mp 153-154°C; $[\alpha]_D^{22}$ = +64.5° (c. 1.02, $CHCl_3$); IR ($CHCl_3$, cast): 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 1H), 3.40 (qd, *J* = 7, 5.5 Hz, 1H), 2.44 (m, 1H), 2.03 (m, 2H), 1.88 (m, 1H), 1.78 (m, 2H), 1.50-1.36 (m, 3H), 1.44 (s, 3H), 1.21 (d, *J* = 7 Hz, 3H), 1.07 (m, 2H), 1.01 (d, *J* = 6 Hz, 3H); MS m/z (M^+) for $C_{15}H_{22}O_5$: 282.1475.

Chapter 3

Total Synthesis of (-)-Qinghaosu IV

Introduction

In addition to (+)-qinghaosu (**89**), sixteen closely related compounds have also been found in qinghao (*A. annua*), a traditional Chinese herbal medicine.[51] Among these constituents, qinghaosu IV (**171**) (also called artemisinin D or arteannuin D), bearing a unique structural feature, attracted our attention. Qinghaosu IV, first isolated in 1982 by Liang and co-workers,[103] served as a clue in the investigation of the metabolic pathway of (+)-qinghaosu in humans. In the microbial metabolism study published by Hufford and co-workers,[104] qinghaosu IV was identified as one of the two major metabolites, the other one being deoxyartemisinin (**97**). Furthermore, heating of (+)-qinghaosu at 190°C for 10 minutes resulted in qinghaosu IV in 10% yield along with two other products.[105] The proposed mechanism involving the homolytic cleavage of the peroxy bridge is depicted in **Scheme 42**. It is noteworthy that an ionic process instead of the free radical process could well be involved in the latest stage of the mechanistic pathway.

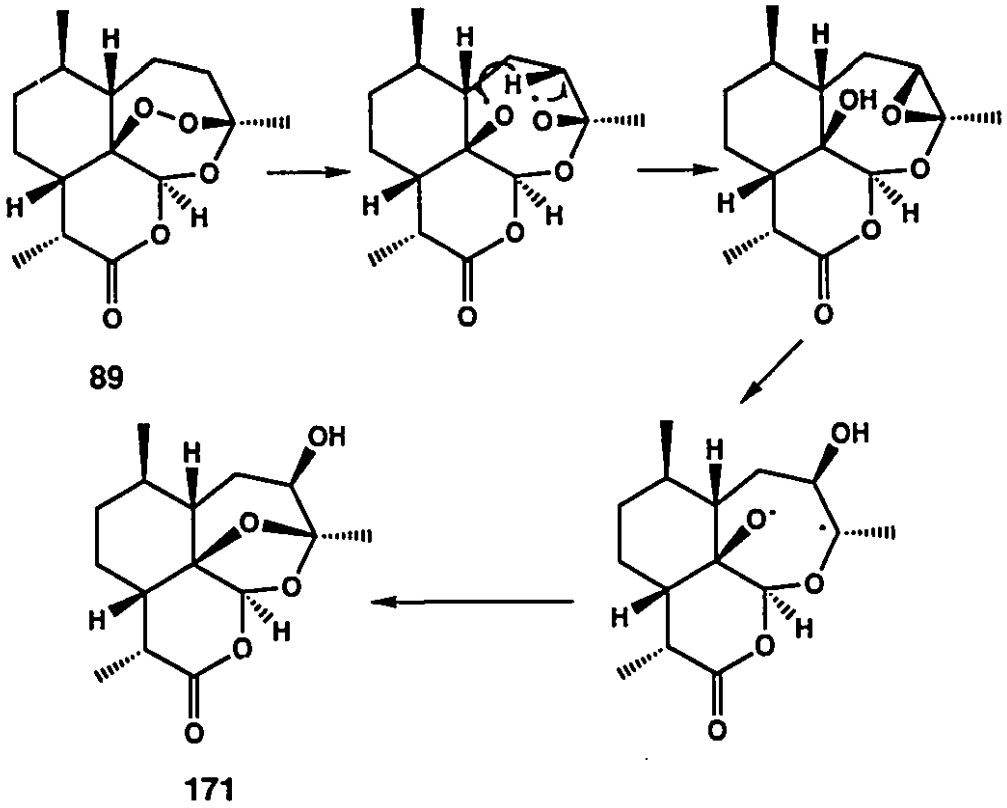


171

So far, there is only one synthesis of qinghaosu IV reported by Chou and co-workers based on their original plan towards (+)-qinghaosu.[106] Starting with qinghao acid (**123**), the common intermediate ketone **108** was obtained in five known steps (**Scheme 43**). The required hydroxyl group was introduced nonstereoselectively by hydroxylation of the

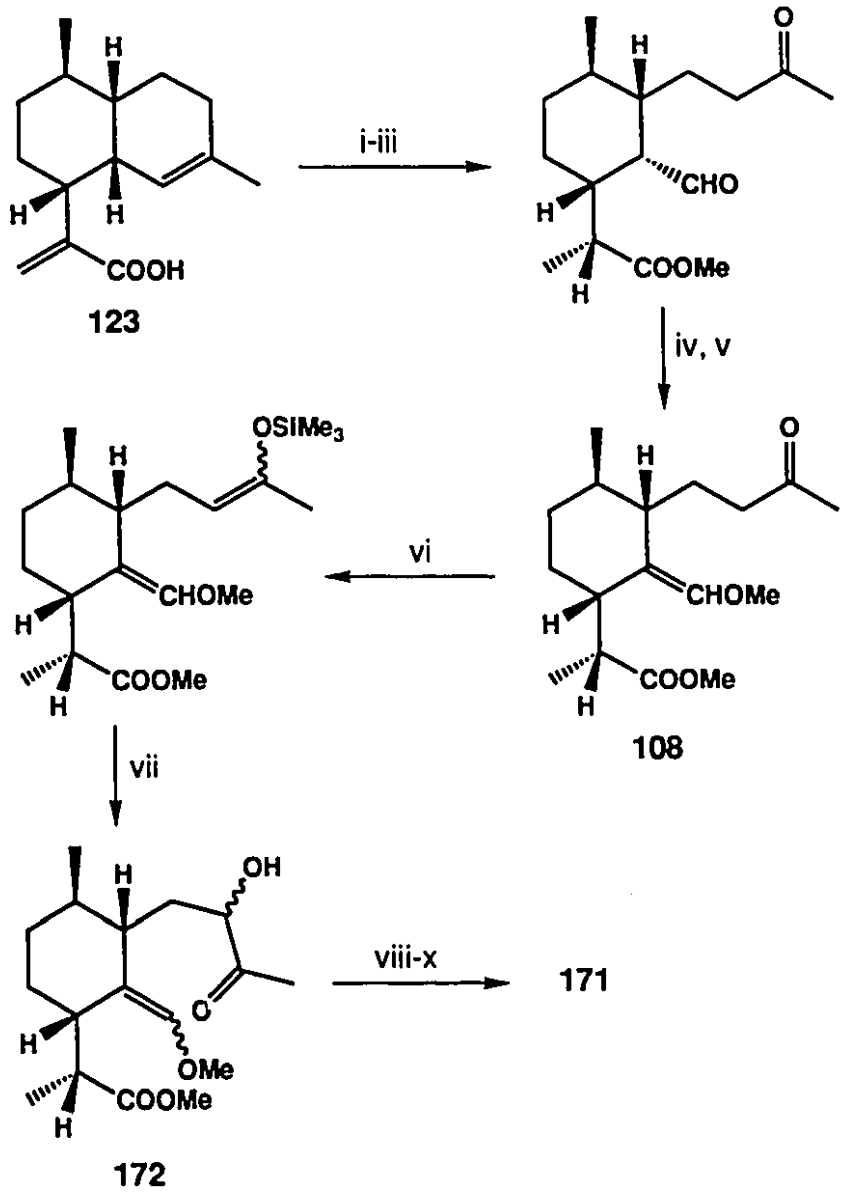
corresponding silyl enol ether of **108** (**108→172**). The construction of the 1,3-dioxolane moiety was initiated by the hydroxylation of the enol ether function present in **172**. After deprotection and separation, qinghaosu IV was thus produced.

Scheme 42



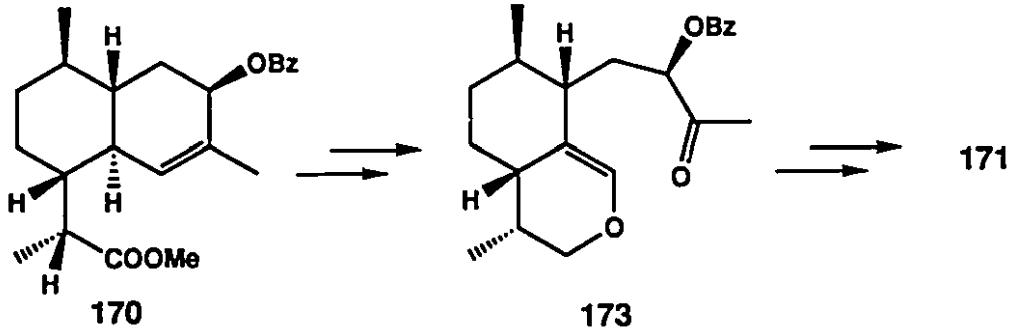
During the course of our synthesis towards (+)-qinghaosu, we envisaged that benzoyloxy ester **170** could be utilized as a key compound to promote the synthesis of qinghaosu IV because **170** possesses a hydroxyl group at the correct position with the desired configuration. After extensive studies, the total synthesis of qinghaosu IV (**171**) was achieved *via* the intermediacy of dihydropyran **173** (**Scheme 44**). Results are described in this chapter.

Scheme 43



i. CH_2N_2; ii. $NaBH_4$, $NiCl_2$; iii. O_3; Me_2S; iv. $HC(OMe)_3$, *p*-TsOH; aq. HCl; v. *p*-TsOH; vi. Me_3SiI, $(Me_3Si)_2NH$; vii. OsO_4, NMMNO; viii. Ac_2O, Py; ix. OsO_4; x. aq. K_2CO_3

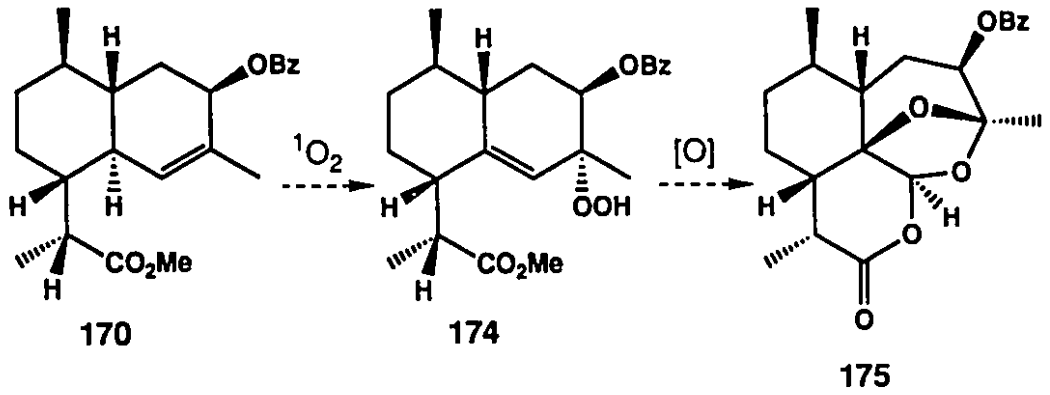
Scheme 44



Results and Discussion

It is deemed that one of the difficuties in the synthesis towards qinghaosu IV (**171**) is the stereochemical installation of the β-hydroxyl group at C-3 position. For the duration of the synthetic study of qinghaosu, we were able to prepare ester **170** possessing a β-benzoyloxy group which was envisaged to be an equivalence of the β-hydroxyl group of qinghaosu IV (**171**). As a consequence, **170** should be readily elaborated to qinghaosu IV (**171**) without the stereochemical problem regarding this hydroxyl group. With a total amount of *ca.* 1 g useful compounds left from the previous synthesis, we decided to pursue this synthetic work. However, the whole work turned out to be an arduous endeavor encountering many unexpected difficulties.

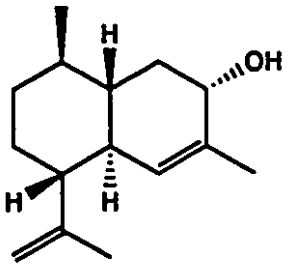
Scheme 45



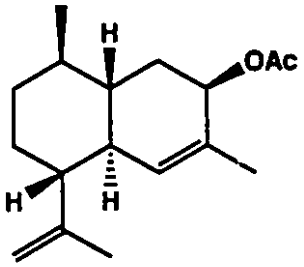
170 **174** **175**

Hypothetically, ester **170** should be able to be converted to qinghaosu IV (**171**) using a similar strategy as the conversion from **170** to qinghaosu. As explained in **Scheme 45**, photooxygenation of **170** yields hydroperoxide **174**, which then rearranges to benzoyloxy qinghaosu IV (**175**) using an epoxidation reaction. Unfortunately, it has been noted

that an allylic benzoate system does not undergo photooxygenation reaction due to the deactivation of the olefin caused by the electron-withdrawing benzoyloxy group.[107,108] This was proved to be so in our system. Ester **170** remained intact after prolonged photooxygenation in the presence of different photosensitizers.

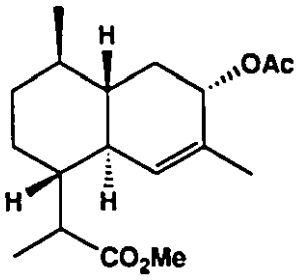


160



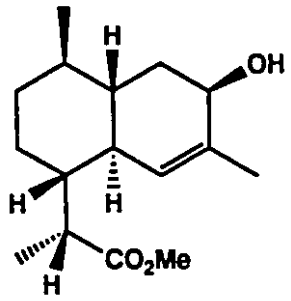
176

On the other hand, allylic acetates[109] and allylic alcohols[107,110,111] have been shown to undergo photooxygenation readily. Therefore, we proceeded to prepare the corresponding acetate, which could then be photooxygenated. Starting with dienol **160**, a Mitsunobu reaction at room temperature with triphenylphosphine, diethyl azodicarboxylate, and acetic acid in tetrahydrofuran was carried out. This reaction was sluggish and produced the desired acetate **176** in only 7% yield after prolonged stirring. The infrared spectrum of **176** showed an ester absorption at 1737 cm^{-1} and a molecular ion peak at 262.1931 in the high resolution mass spectrum was consistent with the molecular formula $C_{17}H_{26}O_2$. In the ^1H NMR spectrum, a methyl singlet at δ 2.07 confirmed the conversion to acetate. The allylic proton at the acetoxy-bearing carbon shifted downfield to δ 5.20 as a broad doublet (J = 4 Hz). The vinylic protons were found at δ 5.62 (br s), 4.82 (m), and 4.73 (br d, J = 2.5 Hz), while the two vinylic methyl groups appeared as a broad singlet at δ 1.65. The methyl group at C-7 was displayed as a doublet (J = 5.5 Hz) at δ 0.88.



163

Concurrent with the preparation of the desired acetate **176**, we also examined the photooxygenation of the epimeric allylic acetates **163** which were available. These compounds were shown to be unreactive under a variety of reaction conditions.



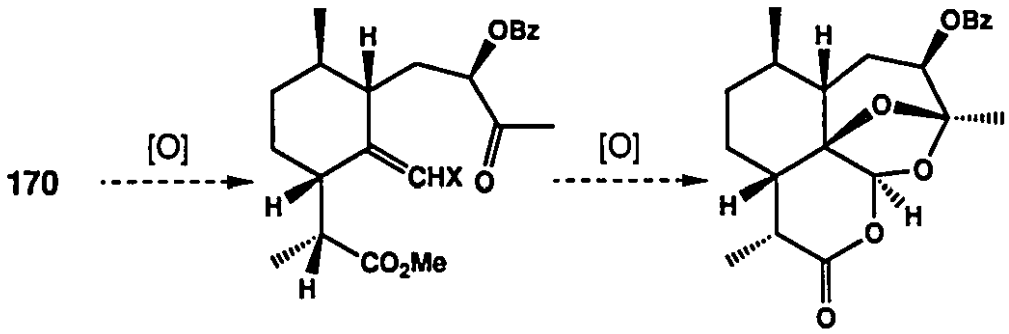
177

The other possibility for the photooxygenation approach was utilizing an allylic alcohol. Alcohol **177** was produced, in 87% yield, from the transesterification of **170** using anhydrous potassium carbonate in methanol. The infrared spectrum of **177** displayed a typical hydroxyl absorption at 3560 cm^{-1}. The production of the alcohol was further confirmed by the disapperance of the phenyl signal and the upfield shift of the allylic proton at the oxygen-bearing carbon to δ 3.93 as a broad singlet in its ^1H NMR spectrum. Four methyl groups were displayed at δ 3.63 (s, ester), 1.79 (dd, J = 2, J' = 1.5 Hz, vinylic), 1.14 (d, J = 7 Hz, adjacent to ester), and 0.90 (d, J = 5 Hz, C-7). The α proton of the ester

appeared at δ 2.91 as a quartet of doublets, with a large coupling constant (7 Hz) due to the adjacent methyl group (δ 1.14) and a small one (3 Hz) induced by the neighboring methine proton. The high resolution mass spectrum gave a fragment at m/z 248.1773, in agreement with the loss of a water unit from the molecular formula $C_{16}H_{26}O_3$.

Although the allylic alcohol should work well in the photooxygenation step because of the absence of the electron-withdrawing ester group, the subsequent oxidative cleavage and cyclization might still be troublesome. The unprotected hydroxyl group could interfere with the desired cyclization process resulting in extensive side reactions. Indeed, epoxidation of the crude product from the photooxygenation of **177** with *m*-chloroperoxybenzoic acid afforded a mixture of unidentifiable alcohols without the formation of qinghaosu IV.

Scheme 46

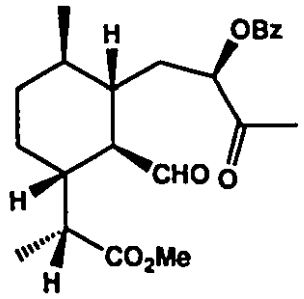


178 **175**

X = OR, OCOR, $OSiR_3$, SR, NR_2

Consequently, we explored a less direct synthetic sequence involving cleavage of the double bond. As outlined in **Scheme 46**, ester **170** could be converted to a monocyclic intermediate **178** containing a heteroatom-bearing olefin moiety *via* an oxidative cleavage and some functional group transformations. The resulting olefin **178**, which might be either an enol ether (X = OR), enol ester (X = OCOR), enol silyl ether (X = $OSiR_3$), enol

thioether (X = SR), or an enamine (X = NR_2), could yield **175** upon oxidation.



179

One of the methods for oxidative cleavage of olefins is ozonolysis. Ester **170** was ozonolyzed at -78°C in dichloromethane and methanol followed by reductive work-up with dimethyl sulfide to give the desired keto aldehyde **179**, with an optical rotation of -34.13° (c. 0.92, $CHCl_3$), in 70% yield. In the ^1H NMR spectrum of **179**, a doublet (J = 6 Hz) at δ 9.52, characteristic of an aldehydic proton, along with a methyl ketone singlet at δ 2.15, clearly indicated the cleavage of the double bond. The proton at the benzoyloxy-bearing carbon had a downfield shift to δ 5.28, as a doublet of doublets (J = 11, J' = 2 Hz), due to being α to a ketone carbonyl. The phenyl protons were displayed at δ 7.47-8.06 and the methyl singlet of the methoxycarbonyl group appeared at δ 3.64. The signals at δ 2.41 (qd, J = 8, J' = 3 Hz) and 2.31 (ddd, $J = J'$ = 12, J'' = 6 Hz) were assigned to the α protons of the ester and the aldehyde respectively. The remaining methyl groups were found at δ 1.12 (d, J = 8 Hz, adjacent to ester) and 1.10 (d, J = 6 Hz, C-1). Although the molecular ion peak was not found in the high resolution mass spectrum of **179**, a fragment (m/z 374.2108) due to the loss of carbon monoxide was present, consistent with the formula $C_{22}H_{30}O_5$. The infrared spectrum showed a strong carbonyl sbsorption at 1720 cm^{-1}.

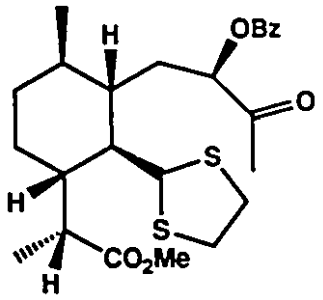
With **179** in hand, the next step was the conversion of its aldehyde moiety to an olefin linked with a heteroatom (**179**→**178**). There are a

number of methods regarding this type of conversion in the literature. However, the reagents and the conditions had to be carefully chosen in our case in order to differentiate the relatively hidden aldehyde group and the exposed ketone group which was further activated by an electron-withdrawing benzoyloxy group.

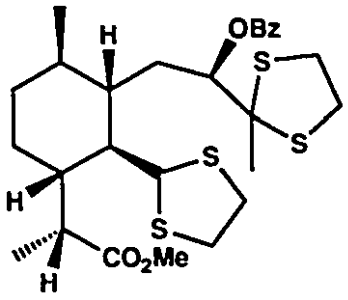
The preparation of the corresponding enol silyl ether was first attempted using *t*-butyldimethylsilyl chloride as a reagent. No matter how harsh the conditions were applied (e.g. diisopropylethylamine as a base at 100°C), only the starting **179** was recovered. We then turned our attention to synthesize the corresponding enamine. A simple and mild method for preparing enamines was reported[112,113] using molecular sieves as both a drying agent and a catalyst. This method was tried with morpholine in the presence or absence of alumina without success. On the other hand, the traditional preparative method using pyrrolidine and camphorsulfonic acid yielded a complex mixture. For the synthesis of enol acetates, a number of procedures starting from ketones are known, but few involve aldehydes. We tried a method dealing specifically with aldehydes using acetic anhydride, triethylamine, and 4-dimethylaminopyridine.[114] In our case, the reaction did not occur even in refluxing tetrahydrofuran.

Since we could not find any effective method which could selectively convert aldehyde to enol ether in the presence of ketone in the literature, the protection of the ketone group of **179** became necessary before acetalization of the aldehyde. Based on the experience gained from the preceding unfruitful attempts, the aldehyde group of **179** was thought to be rather inert. It was hence considered that the selective protection of the ketone carbonyl was possible in the presence of the aldehyde group.

Thioketalization of **179** was carried out at room temperature using 1,2-ethanedithiol in the presence of boron trifluoride etherate in dichloromethane for 5 hours. Surprisingly, thioacetal **180** was produced in 67% yield along with dithioacetal **181** in 13% yield. Towards thioketalization under acidic conditions, the aldehyde group of **179** was more reactive than the ketone functionality.



180

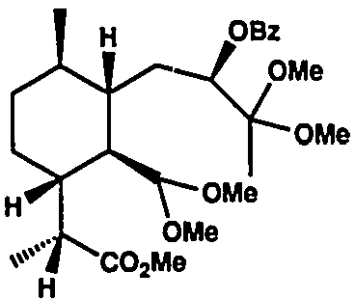


181

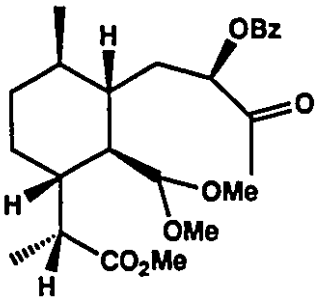
The infrared spectrum of thioacetal **180** showed a carbonyl absorption at 1721 cm^{-1} and a molecular ion peak was observed at m/z 478.1802 in the high resolution mass spectrum, in agreement with the molecular formula $C_{25}H_{34}O_5S_2$. In its ^1H NMR spectrum, thioketalization of the aldehyde group was confirmed by the absence of the aldehydic signal and the presence of a five-proton multiplet at δ 2.97-3.22, representing the four thioacetal protons along with the α proton of the ester. The proton next to the two sulfur atoms was shown as a doublet (J = 4.5 Hz) at δ 4.94. The intact ketone carbonyl was evident from its α proton at the benzoyloxy-bearing carbon slightly shifted to δ 5.33 (dd, J = 11, J' = 3 Hz), as well as its methyl singlet at δ 2.22. Five phenyl protons still remained at δ 7.44-8.11, while a methyl singlet appeared at δ 3.63 (ester) and two methyl doublets were displayed at δ 1.16 (J = 6 Hz, adjacent to ester) and 1.05 (J = 6 Hz, C-1). On the other hand, the ^1H NMR spectrum of **181** displayed eight acetal protons at δ 3.32 (5H), 3.00 (1H), 2.87 (1H), and 2.38 (1H), each as a multiplet. The proton next to the benzoyloxy appeared as a doublet of doublets (J = 11, J' = 1.5 Hz) at δ 5.48, while the proton next to the acetal sulfur atoms was shown at δ 4.87 (d, J = 3 Hz). A methyl singlet appeared at δ 1.83, further supporting the formation of the dithioacetal. The phenyl protons were shown at δ 7.42-8.02. The α proton of the ester overlapped with a ketal proton at δ 2.87 and the α methyl group was shown at δ 1.12 as a doublet (J = 6.5 Hz). Other methyl groups were observed at δ 3.66 (s, ester) and 1.11 (d, J = 7 Hz, C-1). In the infrared spectrum of **181**, a carbonyl band was displayed at 1725 cm^{-1}. The molecular ion peak was not observed in the high resolution mass spectrum, but a fragment (m/z

523.1451) due to the loss of a methoxy unit was in support of the formula $C_{26}H_{35}O_3S_4$.

In spite of the unexpected result from the thioketalization reaction, it might still be possible to convert the thioacetal group in **180** to an acetal group by a published method. It was reported that thioacetals could be transferred to acetals by a combination of mercury(II) oxide and boron trifluoride etherate in methanol.[115] This method was shown to work even in the presence of a ketone carbonyl.[116] In our case, however, application of the reported conditions to thioacetal **180** gave diacetal **182** as a major product in 49% yield, along with a small amount of the desired monoacetal **183** in 11% yield. Obviously, the presence of boron trifluoride etherate was responsible for the ketalization of the ketone. However, this reaction did not occur without boron trifluoride etherate.



182



183

In the ^{1}H NMR spectrum of **182**, four methoxy singlets were displayed at δ 3.28, 3.25, 3.16, and 3.04, representing two acetal functionalities, along with an ester methyl singlet at δ 3.63. The methyl group adjacent to the ketal was located at δ 1.38 as a singlet and the proton at the benzoyloxy-bearing carbon was observed as a doublet of doublets (J = 10.5, J' = 2 Hz) at δ 5.53. The proton next to the two methoxy groups was shown at δ 4.34 as a narrow doublet (J = 1.5 Hz). A multiplet at δ 3.19 was assigned to the α proton of the ester. Five phenyl protons appeared at δ 7.42-8.02 and two methyl doublets were displayed at δ 1.06 (J = 7 Hz, adjacent to ester) and 1.02 (J = 7 Hz, C-1). Despite the

fact that the molecular ion peak was not found in the high resolution mass spectrum of **182**, a fragment (m/z 431.2430) due to the loss of a methanol and a methoxy units was consistent with the formula $C_{25}H_{35}O_6$. The infrared spectrum showed a carbonyl absorption at 1724 cm^{-1}. The ^1H NMR spectral data of **183** were similar to those of **182** except the absence of two methoxy singlets and the downfield shift of a methyl singlet (δ 2.23) owing to the preservation of the ketone. The molecular formula $C_{25}H_{36}O_7$ was confirmed by the molecular ion peak (m/z 448.2472) in the high resolution mass spectrum.

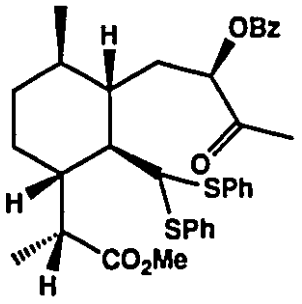
In Chou's synthesis of qinghaosu IV,[106] a diacetal compound was converted to the desired keto acetal by careful treatment of a methanol solution of the diacetal with 1 N hydrochloric acid (step iv in **Scheme 43**). With diacetal **182** in hand, we decided to check on this possibility. Some selectivity was observed under the applied conditions, but not to a desired extent. Invariably, a mixture containing **183** and **179** was formed.

We also examined the transformation of acetal **183** to the corresponding enol ether.[117-119] A toluene solution of **183** was heated under reflux in the presence of *p*-toluenesulfonic acid with removal of methanol.[119] This resulted in the formation of a complex mixture. It seems that the desired enol ether was unstable under the acidic conditions. This phenomenon occurred repeatedly in other related experiments.

The last attempt according to **Scheme 46** was the preparation of enol thioethers. Some good methods for this preparation exist in the literature, either involving a direct formation from ketones[120,121] or *via* the elimination of thioketals.[120,122-124] We first applied the direct method[120] using phosphorus pentoxide, which served as both an acid catalyst and a dehydrating agent, and thiophenol in dichloromethane. Under these conditions, the starting **179** was recovered in 49% yield along with some degree of decompositon.

Consequently, indirect methods involving thioacetal were explored. Phenyl thioacetal **184**, with an optical rotation of -47.65° (c. 1.42, $CHCl_3$), was produced in 83% yield after keto aldehyde **179** was treated

with boron trifluoride etherate and thiophenol in methylene chloride at room temperature for 38 hours. The production of **184** was supported by the ^{1}H NMR spectrum showing the absence of the aldehydic signal and the presence of a complex multiplet at δ 7.18-8.01 for a total of fifteen phenyl protons. The proton at the benzoyloxy-bearing carbon appeared as a doublet of doublets (J = 10, J' = 4 Hz) at δ 5.33, while the proton flanked by the two phenylthio groups was observed at δ 4.70 as a singlet. Two methyl singlets were displayed at δ 3.62 (ester) and 2.08 (ketone). The proton and the methyl group adjacent to the ester were shown at δ 3.21 (qd, J = 7, J' = 2 Hz) and 1.20 (d, J = 7 Hz), respectively. The other methyl doublet (J = 6.5 Hz) at C-1 was displayed at δ 1.01. A fragment (m/z 495.2214, $C_{29}H_{35}O_5S$) due to the loss of a phenylthio unit (PhS) was observed in the high resolution mass spectrum. A carbonyl absorption at 1722 cm^{-1} was displayed in the infrared spectrum.

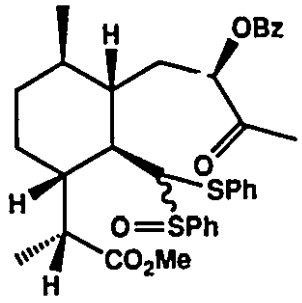


184

Among the methods for the elimination of thioketals, Trost's procedure[120] using mercuric trifluoroacetate in the presence of lithium carbonate was chosen because of its mildness and efficiency. Disappointingly, only aldehyde **179** and its C-3 epimer were isolated in 65% yield from the reaction of **184**. Eventually, the desired enol thioether was prepared in two steps *via* the pyrolysis of a sulfoxide.

Oxidation of thioketal **184** with magnesium monoperoxyphthalate in ethanol and water at 50°C for 2 hours generated a 4 : 1 mixture of sulfoxides **185** in 83% yield. In the ^{1}H NMR spectrum of **185**, fifteen

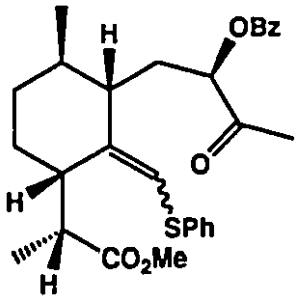
phenyl protons appeared at δ 7.17-8.20. The protons at the benzoyloxy-bearing carbons were shown at δ 5.71 (dd, J = 10, J' = 3.5 Hz, minor) and 5.66 (dd, J = 9, J' = 4.5 Hz, major), while the protons next to the sulfoxides appeared at δ 4.53 (d, J = 1 Hz, minor) and 4.41 (s, major). The methyl singlets of ester and ketone moieties were displayed at δ 3.78 (ester, major), 3.74 (ester, minor), 2.27 (ketone, minor), and 2.25 (ketone, major). A multiplet at δ 3.00 was assigned to the α protons of the esters, and methyl doublets were displayed at δ 1.28 (J = 7 Hz, next to ester, major), 1.11 (J = 6.5 Hz, next to ester, minor), 1.03 (J = 5.5 Hz, C-1, major), and 1.02 (J = 6 Hz, C-1, minor). The infrared spectrum of **185** showed a carbonyl absorption at 1721 cm^{-1}. In its high resolution mass spectrum, the molecular ion peak was not displayed, but a fragment at m/z 494.2128 due to the loss of a PhSOH unit was in agreement with the formula $C_{29}H_{34}O_5S$.



185

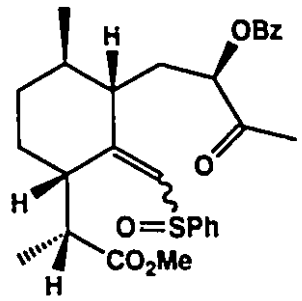
Upon refluxing in toluene for 2 hours, sulfoxides **185** were converted smoothly to the desired vinyl sulfides **186** in 83% yield. The production of vinyl sulfides was supported by the ^1H NMR spectrum displaying ten phenyl protons at δ 7.18-8.22 and the vinylic protons at δ 6.21 (major) and 6.17 (minor). The doublets of doublets due to the protons at the benzoyloxy-bearing carbons shifted upfield to δ 5.32 (J = 11, J' = 2 Hz, minor) and 5.26 (J = 10, J' = 3.5 Hz, major). The other important indication of the formation of the olefins was the appearance of the allylic protons at δ 3.23 (dd, J = 12, J' = 5 Hz, major) and 2.92 (d, J = 11 Hz, minor). The infrared spectrum of **186** showed a carbonyl band at 1722

cm^{-1}, while a molecular ion peak at m/z 494.2128 in the high resolution mass spectrum was consistent with the molecular formula $C_{29}H_{34}O_5S$.



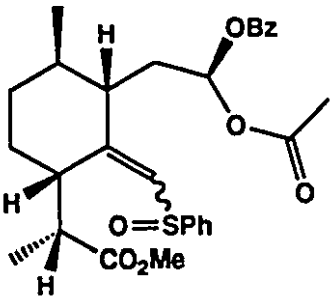
186

Having successfully prepared enol thioether **186**, the next stage required its elaboration to the tetracyclic compound **175**. Unfortunately, the effort in this direction turned out to be very disappointing. The simplest method to effect the conversion was epoxidation using *m*-chloroperoxybenzoic acid. However, in spite of activation by the sulfur atom, the double bond was still less reactive than the sulfur atom towards oxidation. Treatment of **186** with one equivalent of *m*-chloroperoxybenzoic acid at 0°C resulted in a mixture of four stereoisomeric vinyl sulfoxides **187** in 93% yield. The infrared spectrum of **187** showed a carbonyl absorption at 1721 cm^{-1}. The high resolution mass spectrum displayed a molecular ion peak at m/z 510.2086, supporting the molecular formula $C_{29}H_{34}O_6S$, and a fragment at m/z 385.2017 ($C_{23}H_{29}O_5$) due to the loss of a PhSO unit. The ^1H NMR spectrum of **187** was very complex and the crucial signals assisting the identification were the ones due to the downfield shifted phenyl protons (δ 7.35-8.35) and vinylic protons (δ 6.42, 6.38, 6.21, and 6.18).



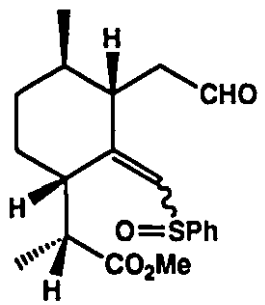
187

In order to induce the oxidation of the double bond, an excess of *m*-chloroperoxybenzoic acid was employed. Under these conditions, the Baeyer-Villiger product **188** was formed in 50% yield along with an equal amount of **187**. The ^{1}H NMR spectrum of **188**, containing two stereoisomers, showed the absence of the regular doublet of doublets for the proton at the benzoyloxy-bearing carbon. The diagnostic signal at δ 7.00, a multiplet, was assigned to the proton at the carbon bearing both the benzoyloxy and the acetoxy groups. The phenyl protons were shown at δ 7.40-8.30, while the vinylic protons appeared at δ 6.39 (minor) and 6.35 (major). The α protons and the α methyl groups of the carbomethoxy groups were located respectively at δ 4.01 (overlapped) as a multiplet, 1.22 (major), and 1.11 (minor), each as a doublet (J = 7 Hz). The methyl singlets of the carbomethoxy groups were observed at δ 3.72 (major) and 3.68 (minor), and those of the acetoxy groups were displayed at δ 2.12 (minor) and 2.07 (major). The C-1 methyl doublets (J = 7 Hz) appeared at δ 0.78 (major) and 0.52 (minor). The infrared spectrum of **188** displayed two carbonyl absorptions at 1759 and 1733 cm^{-1}. The molecular ion peak of **188** was not displayed in the high resolution mass spectrum, but the observed fragment at m/z 401.1973, resulting from the loss of a PhSO unit, was in agreement with the formula $C_{23}H_{29}O_6$.



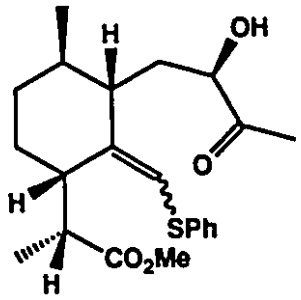
188

The formation of **188** was further confirmed by the hydrolysis of its acylal moiety. Treatment of a tetrahydrofuran solution of **188** with aqueous perchloric acid generated aldehydes **189** in 34% yield. A broad singlet at δ 9.70, characteristic of aldehydic protons, in the ^{1}H NMR spectrum of **189**, indicated the formation of aldehydes. Moreover, only five phenyl protons remained at δ 7.56-7.96, confirming the removal of one phenyl-containing substituent. The absence of the acetoxy group was also supported by the disapperance of its methyl singlet in the spectrum. The other signals corresponding to the ester side chain, the olefinic portion, and the C-1 methyl group remained nearly unchanged. The infrared spectrum of **189** showed a carbonyl absorption at 1732 cm^{-1}. As usual, a PhSO unit was lost in the high resolution mass spectrometry and a fragment at m/z 237.1493 was observed, consistent with the formula $C_{14}H_{21}O_3$.



189

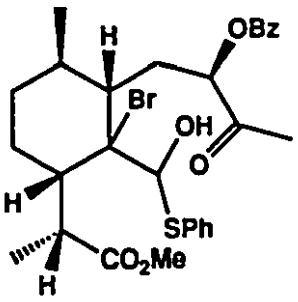
Due to the failures encountered using *m*-chloroperoxybenzoic acid, the use of other reagents which would not oxidize the sulfur atom became essential in order to achieve the desired oxidation. Trost reported a method employing lead tetraacetate for the hydroxylation of phenyl vinyl sulfides.[126] Although this strategy was thought to fit in our system, **186** did not react with lead tetraacetate even in refluxing tetrahydrofuran.



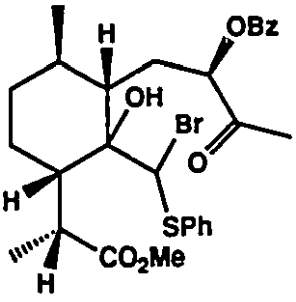
190

Another workable reagent for the hydroxylation of vinyl sulfides is osmium tetroxide.[127] When **186** was treated with osmium tetroxide in tetrahydrofuran, no reaction was detected. On the other hand, when pyridine[128] was added to the reaction mixture, a reaction did occur slowly, but the product was the unexpected alcohol **190** in 38% yield. Probably the benzoyl group was activated by coordination with osmium tetroxide and was able to depart upon attack by pyridine. The formation of alcohol was indicated by the infrared spectrum, showing a broad hydroxyl absorption at 3400 cm^{-1} along with a carbonyl absorption at 1730 cm^{-1}. The ^1H NMR spectrum of **190** indicated the presence of a single isomer. Only five phenyl protons were displayed at δ 7.18-7.32 and the proton at the oxygen-bearing carbon shifted upfield to δ 4.18 as a multiplet, due to the removal of the electron-withdrawing benzoyl group. The vinylic proton was displayed as a singlet at δ 6.24, while two methyl singlets were shown at δ 3.72 (ester) and 2.23 (ketone). A doublet (J = 5.5 Hz) at δ 3.38 was assigned to the hydroxyl proton and the α proton of the ester appeared at δ 3.19 as a multiplet. Two methyl doublets (J = 7 Hz) at δ 1.17 and 1.05 belonged to the α methyl group of

the ester and the C-1 methyl group. In the high resolution mass spectrum, the molecular ion peak was displayed at m/z 390.1869, in agreement with the molecular formula $C_{22}H_{30}O_4S$. The formation of alcohol **190** was further confirmed by the reformation of benzoate **186**, in 91% yield, when **190** was treated with benzoic anhydride, pyridine, and 4-dimethylaminopyridine.



191a

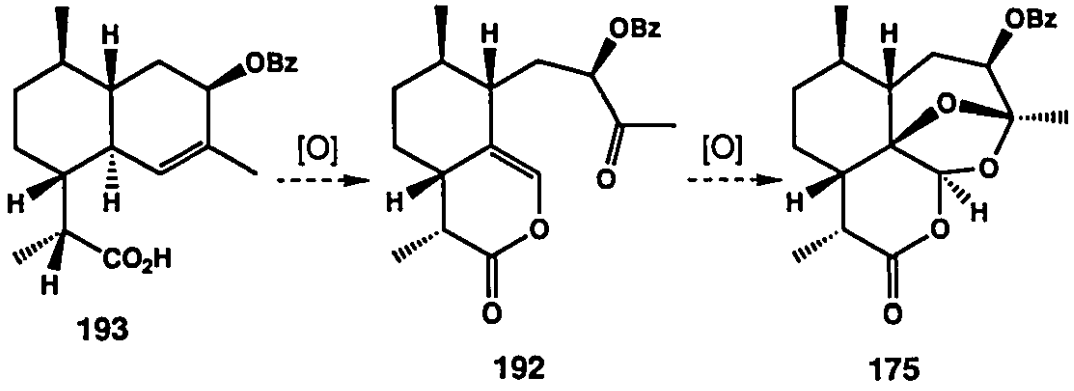


191b

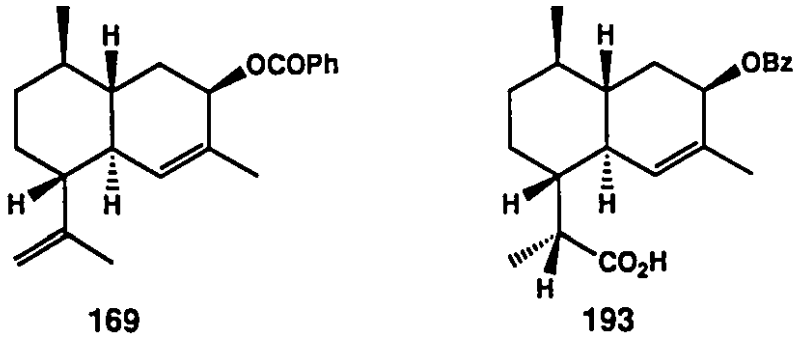
The last effort made on **186** was the preparation of bromohydrins.[129,130] The bromohydrin, possessing the same level of oxidation state as that of a diol, might be elaborated to the desired **175** in the presence of water. Treatment of an aqueous tetrahydrofuran solution of **186** with *N*-bromosuccinimide readily afforded a complex inseparable mixture quantitatively in 1 hour. This mixture was determined to contain regioisomers **191a** and **191b** and their individual stereoisomers. The infrared spectrum of this mixture displayed a hydroxyl absorption at 3450 cm^{-1} as well as a carbonyl band at 1722 cm^{-1}. The ^1H NMR spectrum was rather complex. However, the absence of the allylic protons indicated that the addition had occurred. The protons at carbons bearing two heteroatoms (sulfur and oxygen, or sulfur and bromine) were displayed at δ 6.37, 6.20, and 6.18, each as a singlet, indicating the absence of neighboring protons. The molecular ion peak was not found in the high resolution mass spectrum, but a fragment at m/z 511.2138, due to the loss of a bromine atom, was consistent with the formula $C_{29}H_{35}O_6S$.

In theory, these phenylthio bromohydrins **191a** and **191b** should be very labile and ready for reactions with slight promotion. In contrast, **191a** and **191b** proved to be extremely unreactive. Treatment of the mixture either with boron trifluoride etherate, mercury(II) chloride, or silver perchlorate failed to induce any reaction at all. Even the attempts made to acetylate them failed. This extraordinary behavior of bromohydrins **191a** and **191b** remains to be understood.

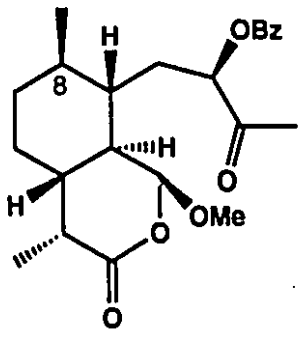
Scheme 47



The failure of all the efforts with vinyl sulfides **186** indicated that the synthetic sequence of **Scheme 46** was a fiasco. In further studies, a modified scheme was examined. As shown in **Scheme 47**, the essence of this modification was to prepare the cyclic enol lactone **192** *via* acid **193**, making use of the existing carboxyl group.



Acid **193** was readily prepared from benzoate **169** *via* a two-step sequence used previously. Hydroboration of **169** with 9-borabicyclo[3.3.1]nonane followed by treatment of the resulting crude borane with Jones reagent yielded the desired acid **193**, with an optical rotation of -10.94° (c. 6.2, $CHCl_3$), in 78% overall yield. The infrared spectrum of **193** displayed a typical broad carboxylic band in the region of 2500-3600 cm^{-1} as well as a carbonyl absorption at 1714 cm^{-1}. The ^1H NMR spectrum showed five phenyl protons at δ 7.44-8.05, along with a broad vinylic singlet at δ 5.96. The allylic proton at the benzoyloxy-bearing carbon appeared as a doublet (J = 4 Hz) at δ 5.43. The α proton and the α methyl group of the carboxy group were shown at δ 3.02 (qd, J = 7, J' = 3 Hz) and 1.21 (d, J = 7 Hz). The broad vinylic methyl singlet was shown at δ 1.74, while the methyl group at C-7 appeared as a doublet (J = 6 Hz) at δ 0.83. In the high resolution mass spectrum of **193**, a molecular ion peak was found at m/z 356.1974, in agreement with the molecular formula $C_{22}H_{28}O_4$.

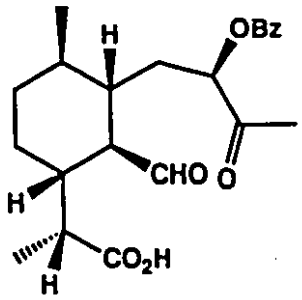


194

Ozonolysis of acid **193** at -78°C in dichloromethane and methanol resulted in only 25% yield of lactone **194**. The infrared spectrum displayed two carbonyl absorptions at 1740 and 1719 cm^{-1}. In its ^1H NMR spectrum, the methoxy lactone moiety was confirmed by a doublet (J = 3 Hz) at δ 5.29, representing the proton at methoxy-bearing carbon, and the methoxy singlet at δ 3.46. Five phenyl protons were shown at δ 7.50-8.08, while the proton at the benzoyloxy-bearing carbon appeared

as a doublet of doublets (J = 10, J' = 3 Hz) at δ 5.35. The α proton of the lactone carbonyl was displayed at δ 2.67 (qd, J = 7, J' = 1.5 Hz), coupled to its adjacent methyl group at δ 1.21 (d, J = 7 Hz). The methyl ketone singlet appeared at δ 2.22 and the methyl group at C-8 was shown at δ 1.05 as a doublet (J = 6 Hz). A fragment at m/z 371.1851 due to the loss of a methoxy unit was observed in the high resolution mass spectrum, supporting the formula $C_{22}H_{27}O_5$.

In addition to the poor production of lactone **194**, the subsequent elimination of a methanol unit from **194** also caused problems. Attempts to remove methanol from **194** using aluminium chloride and triethyl amine[117] resulted in decomposition. Compound **194** also decomposed rapidly at room temperature in the presence of 1 N hydrochloric acid.



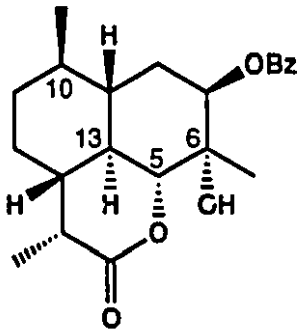
195

Since the removal of methanol is generally more difficult than that of water, it was thus decided to prepare the corresponding hydroxylactone. The simplest way was to ozonolyze acid **193** in dichloromethane in the absence of methanol. However, the result was highly unsatisfactory. Monocyclic acid **195** was obtained in only 16% yield. In the infrared spectrum of **195**, a typical broad carboxylic absorption was observed at 3450 cm^{-1}, along with a carbonyl absorption at 1718 cm^{-1}. Its ^1H NMR spectrum displayed a characteristic aldehydic signal at δ 9.67 as a singlet. Five phenyl protons appeared at δ 7.51-8.07 and the proton at the benzoyloxy-bearing carbon was shown at δ 5.27 as a doublet of doublets (J = 10, J' = 4 Hz). The α proton of the carboxy group was

displayed at δ 2.45 as a broad quartet (J = 6 Hz), coupled to the adjacent methyl group at δ 1.15 (d, J = 6 Hz). The proton next to the aldehyde group was shown at δ 2.21 as a multiplet. The methyl singlet of the ketone appeared at δ 2.17, while the methyl group at C-1 was displayed at δ 1.11 as a doublet (J = 7 Hz). In the high resolution mass spectrum, the molecular ion peak was not displayed. Instead, a fragment at m/z 386.1722 ($C_{22}H_{26}O_6$) appeared, due to the loss of two hydrogens.

Every exertion to cyclize between the carboxyl and aldehyde groups in **195** resulted in futility. Acid **195** remained intact either under both acidic conditions with *p*-toluenesulfonic acid or under basic conditions using methanesulfonyl chloride (or acetyl chloride), pyridine, and 4-dimethylaminopyridine, even in refluxing dichloromethane.

The other modification carried out regarding ozonolysis involved the use of methanol as a single solvent and the addition of *p*-toluenesulfonic acid along with dimethyl sulfide during the work-up, in order to induce the elimination reaction *in situ*.[131] When this procedure was performed on **193**, it produced a complex mixture of products. After tedious separation by flash chromatography, this mixture was shown to contain keto aldehyde **179** (15% yield), keto acid **195** (11% yield), a mixture of acetal **183** and diacetal **182** (11% yield), and methoxy lactone **194** (3% yield). None of them was useful for further reaction.

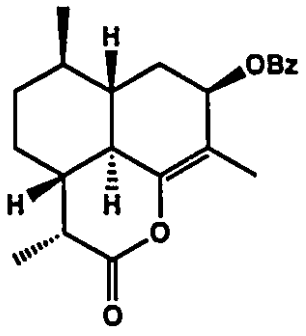


196

The other commonly used method for oxidative cleavage of olefins is the osmium tetroxide oxidation.[132] Treatment of **193** with sodium periodate and a catalytic amount of osmium tetroxide in aqueous dioxane for 1 hour generated unexpectedly alcohol **196** in 24% yield, whereas reaction of **193** with an equal amount of osmium tetroxide gave rise to extensive decomposition. The production of an alcohol was mainly indicated by the infrared spectrum of **196**, displaying a broad hydroxyl absorption at 3450 cm^{-1} along with a carbonyl absorption at 1719 cm^{-1}. The ^1H NMR spectrum of **196** showed an upfield shift of the proton at the benzoyloxy-bearing carbon to δ 5.23, as a doublet of doublets ($J = J' = 3$ Hz), suggesting that this proton was neither next to a double bond nor a carbonyl. Furthermore, a methyl singlet (C-6) also experienced an upfield shift to δ 1.41, demonstrating that it was no longer a vinylic or ketone methyl group. However, its low chemical shift, compared to the regular methyl group at C-10 (δ 0.85, d, $J = 6$ Hz), indicated that there was an electron-withdrawing group, such as a hydroxyl group, close to it. The α orientation of this hydroxyl group was tentatively proposed based on the formation of an osmium complex in the intermediate. The proton at the lactone oxygen-bearing carbon (C-5) was displayed at δ 4.18 as a doublet ($J = 10$ Hz), which indicated that this proton possessed a *trans* relationship with its adjacent proton (C-13). Five phenyl protons appeared within δ 7.47-8.00, while the α proton of the lactone carbonyl was shown at δ 2.80 as a quartet of doublets ($J = 7.5$, $J' = 1$ Hz), coupled to its neighboring methyl group at δ 1.27, a doublet with a coupling constant of 7.5 Hz. The molecular ion peak at m/z 372.1939 in the high resolution mass spectrum supported the molecular formula $C_{22}H_{28}O_5$.

The production of **196** and the orientation of its hydroxyl group were further confirmed by dehydration with phosphorus oxychloride in pyridine at room temperature. Under these conditions, olefin **197** was obtained in 29% yield after 45 hours. Its infrared spectrum displayed two carbonyl absorptions at 1757 and 1716 cm^{-1} along with two medium absorptions at 1675 and 1645 cm^{-1}, characteristic of an enol derivative. In the ^1H NMR spectrum, the disappearance of the typical signal for the proton at the lactone oxygen-bearing carbon (C-5) pointed out the position of the double bond. This position of the double bond was also

indicated by the downfield shift of the proton adjacent to the benzoyloxy group to δ 5.63 (br d, J = 4 Hz) as a result of being also allylic. The other allylic methine proton was displayed as a broad doublet (J = 14 Hz) at δ 2.24. The vinylic methyl group was shown at δ 1.74 as a doublet (J = 2 Hz). The rest of the spectrum remained similar to that of **196**. The molecular formula $C_{22}H_{26}O_4$ of **197** was confirmed by the observation of the molecular ion peak at m/z 354.1854 in the high resolution mass spectrum. It is known that dehydration with phosphorus oxychloride is favored by the *trans* elimination process. The formation of **197** as the only product suggested a *trans* relationship between the hydroxyl group and the benzoyloxy group in the starting compound. Otherwise, the exocyclic olefin would also be produced.



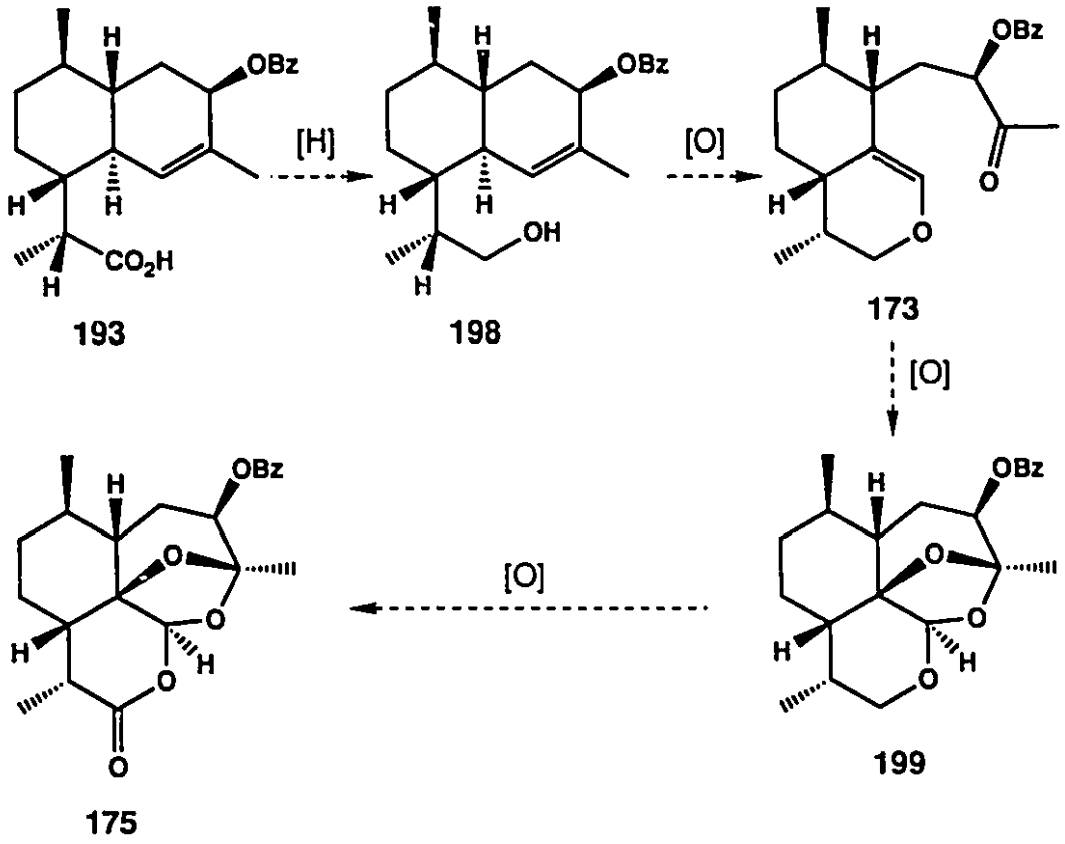
197

In light of the above results, it was felt that the participation of the neighboring carboxyl group made the cleavage of the double bond even less predictable. To circumvent this problem, it was intended to protect the carboxyl functionality, in the form of a *t*-butyl ester, which could be selectively removed in the later stage under acidic conditions in the presence of the base-labile benzoyloxy group. However, esterification of acid **193** with *t*-butanol induced by dicyclohexyl carbodiimide[133] always produced a messy mixture containing only a small amount of the desired ester.

Finally the conversion of **193** to the target qinghaosu IV (**171**) was achieved *via* the sequence displayed in **Scheme 48**. The carboxyl group

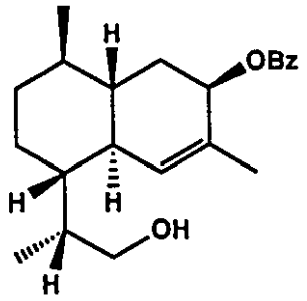
was first reduced (**193**→**198**), and the carbonyl was restored after assembling the tetracyclic skeleton (**199**→**175**).

Scheme 48



Selective reduction of a carboxylic acid to an alcohol in the presence of a benzoate and a double bond required careful selection of the reducing agent. Obviously, normal nucleophilic hydride reagents could not be employed directly. Hydroboration using diborane or 9-borabicyclo[3.3.1]nonane was a possible candidate but had its limitations. Diborane is known to be more reactive towards carboxylic acids than olefins, but the difference is small and these two functional groups are sometimes equally reactive.[134] Unlike diborane, 9-borabicyclo[3.3.1]nonane would not touch the internal double bond of

193 due to steric hindrance, but it could only reduce the carboxylic acid under drastic conditions, with which the benzoate group might also be reduced.[135] The other typical method to reduce selectively the carboxylic acid in the presence of other functional groups is *via* the corresponding acyl chloride which can be reduced by a mild metal hydride reducing reagent, such as sodium borohydride.[136] Unfortunately, the corresponding acyl chloride of **193** was too unstable to be observed on TLC plates. Without adequate means to monitor the reaction, the two-step sequence, involving treatment with oxalyl chloride and reduction with sodium borohydride, turned out to be an impractical try and error. After several unfruitful attempts, we decided to abandon this method.

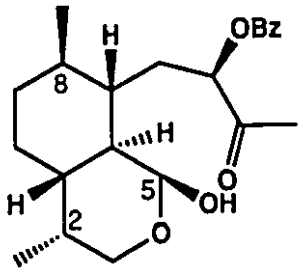


198

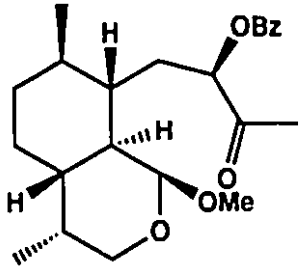
The successful conversion was based on the *in situ* preparation of a mixed carbonic-carboxylic acid anhydride, which was more stable than the acyl chloride and could be monitored by TLC plates.[137] Treatment of **193** with ethyl chloroformate and triethyl amine in tetrahydrofuran at 0°C for 2 hours produced the mixed anhydride intermediate, which was immediately reduced by sodium borohydride in aqueous tetrahydrofuran to give the desired alcohol **198**, with an optical rotation of +47.69° (c. 1.40, $CHCl_3$), in 87% yield. Its infrared spectrum showed a typical hydroxyl absorption at 3450 cm^{-1} along with a carbonyl absorption at 1715 cm^{-1}. In the ^1H NMR spectrum, the production of a primary alcohol was evident from the appearance of a pair of doublets of doublets at δ 3.73 (J = 10, J' = 5 Hz) and 3.43 (J = 10, J' = 9 Hz), each with a large geminal coupling constant of 10 Hz. Five phenyl protons were shown

within δ 7.43-8.05, while the vinylic proton and methyl group were displayed at δ 5.99 and 1.75, each as a singlet. The allylic proton at the benzoyloxy-bearing carbon appeared as a doublet (J = 4 Hz) at δ 5.43. Two methyl doublets were displayed at δ 1.02 (J = 7 Hz) and 0.83 (J = 6 Hz). The high resolution mass spectrum displayed a molecular ion peak at m/z 342.2216, consistent with the molecular formula $C_{22}H_{30}O_3$.

Normally the time used for reducing the ozonolysis products with dimethyl sulfide is not crucial as long as all the ozonides have been destroyed. But it became an important factor in the ozonolysis of alcohol **198**. When the ozonolysis products of **198** in dichloromethane and methanol was treated with dimethyl sulfide for 16.5 hours, cyclic hemiacetal **200** was obtained in 60% yield along with a 16% yield of cyclic acetal **201**. On the other hand, when the reduction time was decreased to 3 hours, the yield of **200** was improved to 77% and the byproduct **201** was produced in only 4% yield. The shorter time for the reductive work-up prevented the exchange between the reaction intermediates and methanol efficiently.



200



201

Hemiacetal **200** displayed an optical rotation of +67.19° (c. 1.47, $CHCl_3$). The infrared spectrum showed a broad hydroxyl band at 3400 cm^{-1} and a carbonyl absorption at 1718 cm^{-1}. In the ^1H NMR spectrum, five phenyl protons were shown within δ 7.47-8.08, while the proton at the benzoyloxy-bearing carbon was observed as a doublet of doublets (J = 10, J' = 4 Hz) at δ 5.35. A doublet at δ 5.34 was assigned to the proton at the hydroxy-bearing carbon. Its small coupling constant (J = 2 Hz) indicated

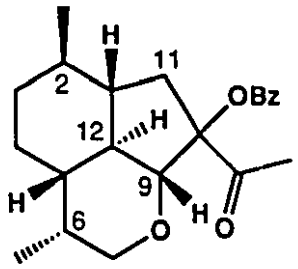
the *cis* relationship with its adjacent proton. The methylene protons next to the endocyclic oxygen were displayed as a pair of signals at δ 4.16 (dd, J = 11, J' = 3 Hz) and 3.33 (d, J = 11 Hz). The methyl ketone singlet at δ 2.21 provided further evidence for the cleavage of the double bond. The other two methyl groups were shown at δ 1.04 (d, J = 6 Hz, C-2) and 0.98 (d, J = 7 Hz, C-8). In the ^{13}C NMR APT spectrum of **200**, in addition to two carbonyl signals at δ 206 (ketone) and 166 (ester), and four benzene signals at δ 133, 130, 129, and 128, a diagnostic signal for the carbon (C-5) bearing two oxygen functionalities was displayed at δ 92. The high resolution mass spectrum displayed a molecular ion peak at m/z 374.2112, in agreement with the molecular formula $C_{22}H_{30}O_5$.

The infrared spectrum of **201** displayed only carbonyl absorption at 1719 cm^{-1} without the broad hydroxyl band. In its ^1H NMR spectrum, a methyl singlet at δ 3.35 indicated the presence of a methoxy group. The proton at the methoxy-bearing carbon was displayed at δ 4.74 as a doublet with a coupling constant of 3.5 Hz, suggesting the β orientation of the methoxy group. The methylene protons next to oxygen atom were shown at δ 3.90 (dd, J = 11, J' = 3 Hz) and 3.64 (m). The rest of the spectrum was similar to that of **200**. The molecular ion peak was not found in the high resolution mass spectrum of **201**. Instead, a fragment (m/z 357.2075) due to the loss of a methoxy unit was observed, corresponding to the formula $C_{22}H_{29}O_4$.

With hemiacetal **200** in hand, the rest of the synthesis seemed to be rather straightforward, requiring only four operations: dehydration, oxidative cyclization, oxidation, and deprotection. In practice, however, a large number of experiments were designed and carried out due to the high sensitivity of the dehydration product **173** towards acid.

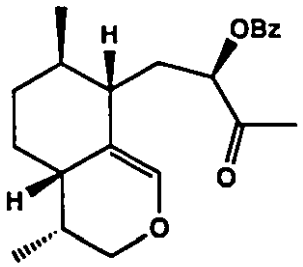
Prior to the dehydration of **200**, we examined the behavior of **201** under acidic conditions. When a xylene solution of **201** was heated under reflux in the presence of *p*-toluenesulfonic acid for 2 hours, a tricyclic compound **202** was obtained in 56% yield. The high resolution mass spectrum of **202** displayed a molecular ion peak at m/z 356.1999, supporting the molecular formula $C_{22}H_{28}O_4$. In the ^1H NMR spectrum, the absence of the signal within δ 4-5, corresponding to the proton at the

benzoyloxy-bearing carbon, was consistent with the formation of the third ring. The ring junction proton at C-9 (adjacent to the ether oxygen) was displayed at δ 3.67 as a doublet of doublets with a large coupling constant of 11.5 Hz, indicating the *trans* relationship with the adjacent proton (C-12), and a small coupling constant of 2.5 Hz. The methylene protons next to the ethereal oxygen atom were shown at δ 3.85 (dd, J = 11.5, J' = 1 Hz) and 3.65 (d, J = 11.5 Hz). The other methylene protons (C-11) next to the carbon possessing both benzoyloxy and acetyl groups were displayed at δ 2.74 (dd, J = 15, J' = 10.5 Hz) and 1.92 (dd, J = 15, J' = 7.5 Hz). Five phenyl protons appeared at δ 7.48-8.12, while the acetyl methyl singlet was shown at δ 2.15. Two methyl doublets were observed at δ 0.88 (J = 7 Hz, C-6) and 0.85 (J = 6.5 Hz, C-2). The infrared spectrum of **202** displayed a carbonyl absorption at 1721 cm^{-1}.



202

Tricyclic ether **202** was likely formed from the acid-catalyzed cyclization of the desired enol ether **173**. In light of this, it was felt that strong acid conditions should be avoided for the dehydration of **200**. When **200** was treated with phosphorus oxychloride in pyridine at room temperature, it afforded a major product as indicated by TLC analysis. This product was found to decompose during flash chromatography and only a tiny amount was isolated. Its spectral data supported the generation of **173**. The infrared spectrum displayed enol ether absorptions at 1600 and 1670 cm^{-1}. The high resolution mass spectrum provided a molecular ion peak at m/z 356.1986, supporting the molecular formula $C_{22}H_{28}O_4$. Moreover, the ^1H NMR spectrum displayed a vinylic singlet at δ 6.55.

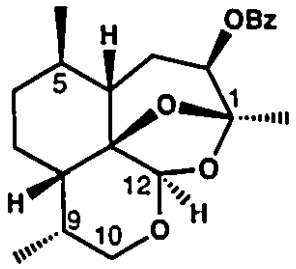


173

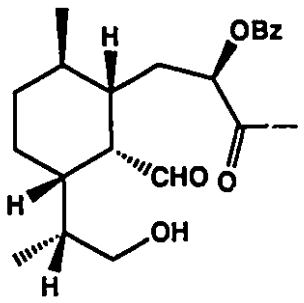
Owing to the production of this highly acid-sensitive intermediate **173**, the subsequent oxidation process clearly had to be performed on the crude material. The immediate concern was to improve the dehydration reaction and to minimize the loss of product during the work-up. After considerable experimentation using different reagents and solvents, some promising results were realized using the following procedure. Hemiacetal **200** was treated with phosphorus oxychloride in pyridine. The reaction was worked up under basic conditions by addition of aqueous sodium bicarbonate solution. The crude product thus obtained was immediately subjected to epoxidation with *m*-chloroperoxybenzoic acid in dichloromethane at room temperature. After flash chromatography, three products were isolated: the desired tetracyclic compound **199** (14% yield), monocyclic alcohol **203** (11% yield), and an addition product **204** (6% yield).

Benzoate **199**, a solid with a melting point of 133-135°C, was identified by the following spectral analysis. The infrared spectrum showed a carbonyl absorption at 1721 cm^{-1}. The hydroxyl absorption was absent. In the ^1H NMR spectrum, five phenyl protons appeared at δ 7.46-8.10. The acetal proton at C-12 was displayed as a singlet at δ 5.27. The upfield shift of the proton at the benzoyloxy-bearing carbon at δ 4.97 (br d, J = 4 Hz) indicated the participation of the ketone carbonyl in cyclization. The cyclization was further supported by the upfield shift of the C-1 methyl group to δ 1.25 as a singlet. The methylene protons at C-10 were shown at δ 3.93 (dd, J = 11.5, J' = 7 Hz) and 3.35 (dd, J = 11.5, J' = 5 Hz). Two methyl doublets were displayed at δ 0.94 (J = 7 Hz, C-9) and 0.86 (J = 6.5 Hz, C-5). The molecular ion peak of **199** was not

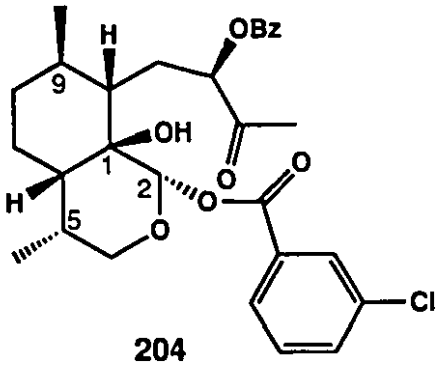
displayed in the high resolution mass spectrum. Instead, a fragment (m/z 251.1623) due to the loss of a benzoyloxy unit was found, corresponding to the formula $C_{15}H_{23}O_3$.



199



203



204

In the infrared spectrum of **203**, a broad hydroxyl absorption was displayed at 3400 cm^{-1} along with a carbonyl absorption at 1721 cm^{-1}. The high resolution mass spectrum displayed a fragment at m/z 357.2061 due to the loss of a hydroxyl unit, corresponding to the formula $C_{22}H_{29}O_4$. The ^1H NMR spectrum of **203** was very similar to that of **195**. However, these two spectra were clearly different in chemical shifts and coupling constants of some signals. For instance, the aldehydic proton of **203** was displayed at δ 9.45 as a doublet (J = 6 Hz), while that of **195** was shown at δ 9.67 as a singlet. The appearance of the aldehydic proton as a doublet indicated the presence of an α-proton. It also suggested that this compound and acid **195** possessed opposite stereochemistry at the carbon center bearing the formyl group. The

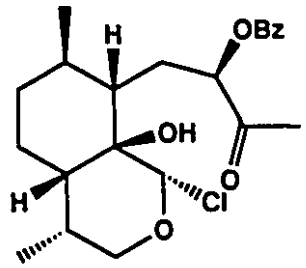
production of **203** could be rationalized by involving hydration of the intermediate **173** initiated by protonation from the *Re* face of the olefin followed by ring opening. Interestingly, all attempts to cyclize **203** failed. Unchanged **203** was recovered even after treatment with camphorsulfonic acid in refluxing toluene.

The structure of **204** was primarily confirmed by the observation of nine phenyl protons displayed within δ 7.34-8.14 in its ^{1}H NMR spectrum. The acetal proton (C-2) had a downfield shift to δ 6.29 as a singlet due to the inductive effect of the chlorobenzoyloxy group. This singlet pattern further indicated that the adjacent carbon (C-1) did not bear any proton. The methylene protons next to the ether oxygen were displayed at δ 3.76 (dd, J = 11.5, J' = 5 Hz) and 3.62 (dd, $J = J'$ = 11.5 Hz). The observation of the proton at the benzoyloxy-bearing carbon at δ 5.25 (dd, J = 11, J' = 3.5 Hz) and a methyl singlet at δ 2.11 indicated the intact ketone carbonyl. Two methyl doublets were observed at δ 1.03 (J = 6 Hz, C-5) and 0.81 (J = 6.5 Hz, C-9). The infrared spectrum of **204** displayed a hydroxyl absorption at 3450 cm^{-1} along with a carbonyl absorption at 1721 cm^{-1}. In the high resolution mass spectrum, a fragment at m/z 250.1578, due to the loss of a benzoic acid and a chlorobenzoic acid units, supported the formula $C_{15}H_{22}O_3$. Since **204** was the result of the attack of *m*-chlorobenzoate on the protonated epoxide, formed by epoxidation likely from the less hindered side, the hydroxyl group was assigned a β orientation.

Two valuable pieces of information emerged from the preceding experiment. First, aldehyde **203** had been produced in the dehydration reaction, indicating that pyridine was not sufficiently basic to remove irreversibly all hydrogen chloride derived from phosphorus oxychloride. Secondly, *m*-chlorobenzoic acid, acting as both a proton source and a nucleophilic agent, was responsible for the production of **204**. Removal of this compound might inhibit the formation of **204**.

In order to remove hydrogen chloride more effectively, diisopropylethylamine was added to the dehydration reaction. Keeping the other conditions the same, **203** was not produced any more and the desired **199** was obtained in 12% yield, along with **204** (4% yield) and a

mixture of the starting hemiacetal **200** and its C-5 epimer (30% yield). According to this result, the dehydration reaction was improved by the involvement of diisopropylethylamine. The poor production of **199** was mainly caused by the unsatisfactory conditions used for the subsequent oxidation step.

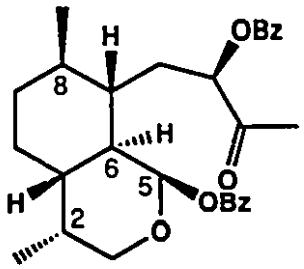


205

In order to improve the oxidation process, a number of experiments were carried out. We first performed osmium tetroxide-hydroxylation instead of epoxidation, but only decomposition of the intermediate **173** was observed.

Two reagents are known to serve as good substitutes for *m*-chloroperoxybenzoic acid because of their mild chemical properties. One is magnesium monoperoxyphthalate[125] and the other is a combination of dibenzoyl peroxide and hexamethyldisilazane.[138] These reagents were explored. Treatment of **173**, prepared *in situ* from dehydration of **200**, with magnesium monoperoxyphthalate in dimethylformamide at room temperature produced alcohol **205** in 35% yield as well as the epimeric mixture of starting **200** in 52% yield. None of the desired **199** was found. The infrared spectrum of **205** showed a typical hydroxyl absorption at 3400 cm^{-1} and two carbonyl absorptions at 1736 (ester) and 1720 cm^{-1} (ketone). In its ^1H NMR spectrum, a singlet at δ 6.15 was assigned to the proton at the chlorine-bearing carbon. The singlet pattern further indicated that the adjacent carbon did not bear any protons. Basically, the spectrum was quite similar to that of **204** except for the appearance of a total of five phenyl protons instead of nine

observed for **204**. In the high resolution mass spectrum, a fragment at m/z 356.1978, due to the loss of a hydroxyl group and a chlorine atom, was consistent with the formula $C_{22}H_{28}O_4$. The formation of **205** could be rationalized by the same mechanism as the production of **204**. Based on the result of this experiment, it was concluded that proper acidic conditions were essential for the transformation of the epoxide intermediate to cyclic **199**.



206

Epoxidation of **173** with a combination of benzoyl peroxide and hexamethyldisilazane repeatedly yielded undesired products. Stirring the reaction mixture in dichloromethane for four days produced dibenzoate **206** in 23% yield along with a 28% recovery of the starting material **200**. Under these conditions involving a weaker oxidant, protonation and benzoate addition occurred preferentially. In the ^1H NMR spectrum of **206**, ten phenyl protons were displayed within δ 7.50-8.17. The acetal proton (C-5) was shown at δ 6.43 as a doublet with a small coupling constant of 1 Hz, suggesting its *cis* relationship with the adjacent proton at C-6. The methine proton at the benzoyloxy-bearing carbon appeared as a doublet of doublets (J = 11.5, J' = 2.5 Hz) at δ 5.38. The methylene protons next to the ether oxygen were displayed at δ 3.65 (dd, $J = J'$ = 11.5 Hz) and 3.54 (dd, J = 11.5, J' = 4.5 Hz). The methyl singlet of the ketone was shown at δ 2.19, while two other methyl signals were displayed at δ 1.03 (d, J = 6 Hz, C-2) and 0.85 (d, J = 7 Hz, C-8). The infrared spectrum of **206** showed a carbonyl band at 1732 cm^{-1}. In the high resolution mass spectrum of **206**, a fragment at m/z 355.1908 due

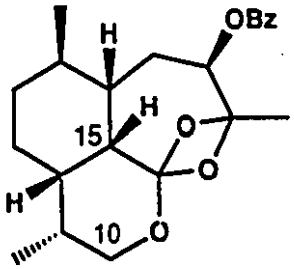
to the loss of a benzoic acid unit and a hydrogen atom was in agreement with the formula $C_{22}H_{27}O_4$.

At this point, a likely mechanism for the conversion of **173** to **199** emerged. This transformation proceeded in two stages: epoxidation and intramolecular acetalization. In the epoxidation, a powerful epoxidizing agent is required in order to form the epoxide effectively. Otherwise, **173** would be protonated by any proton source present in the reaction medium and then react with nucleophiles to give byproducts like **206** or the starting alcohol **200** and its epimer. Once the epoxide is formed, the next intramolecular acetalization has to be induced by a sufficiently strong acid in order to compete with the side reactions with nucleophiles to form products like **204** and **205**. Apparently, these two requirements are somewhat contradictory in nature. For example, the strong acid needed for the second acetalization stage would cause **173** to decompose more readily.

Under the aforementioned considerations, a reagent which fulfills the dual requirements more properly emerged. This was trifluoroperoxyacetic acid.[45,46] Trifluoroperoxyacetic acid itself is a strong epoxidizing agent and a weak acid. After epoxidation, it is converted to trifluoroacetic acid, which is a strong acid and a weak nucleophile. Accordingly, the reaction of the *in situ* generated **173** with trifluoroperoxyacetic acid was carried out at 0°C in dichloromethane. The yield of the desired **199** was improved to 33%. An epimeric mixture of the starting alcohol **200** was also recovered in 7% yield. In additon to these two products, an interesting compound was isolated in 17% yield. By extensive spectral analysis including $^1H,^1H$ correlated 2D NMR and $^1H,^{13}C$ correlated 2D NMR spectral studies, this compound was unambiguously determined to be oxetane **207**, an isomer of **199**.

The infrared spectrum of **207** displayed a carbonyl absorption at 1724 cm^{-1}. Like **199**, the molecular ion peak of **207** was not found in the high resolution mass spectrum. Instead, a fragment at m/z 250.1570 ($C_{15}H_{22}O_3$), due to the loss of a molecule of benzoic acid, was observed. Generally speaking, the ^1H NMR spectrum of **207** was similar to that of **199** except for one crucial difference: the significant acetal bridge proton

singlet of **199** displayed at δ 5.27 was absent in the spectrum of **207**. The proton at the benzoyloxy-bearing carbon was displayed as a doublet of doublets (J = 4, J' = 2.5 Hz) at δ 5.07, indicating the participation of the neighboring carbonyl group in the reaction. Compared to **199**, the methylene protons (C-10) adjacent to the ether oxygen had a downfield shift to δ 4.47 (dd, J = 11, J' = 4 Hz) and 4.07 (dd, J = 11, J' = 8.5 Hz) due to the inductive effects of the two oxetane oxygens. The methyl group of the oxetane moiety was displayed as a singlet at δ 1.53. In the ^{13}C NMR APT spectrum of **207**, two unique in-phase signals at δ 111.19 and 106.37 were assigned to the two carbons of the oxetane. The $^{1}H,^{1}H$ correlated 2D NMR spectrum (**Figure 1**) and the $^{1}H,^{13}C$ correlated 2D NMR spectrum (**Figure 2**) were also essential for the determination of the structure of **207**. It was noteworthy that the assignment of the stereochemistry of the center carbon (C-15) in **207** could not be achieved without these two 2D NMR spectra. The $^{1}H,^{13}C$-2D NMR spectrum (**Figure 2**) showed a methine proton at δ 1.25, which did not show any coupling in the spectrum of the $^{1}H,^{1}H$-2D NMR. This proton, appearing as a broad singlet in the ^{1}H-1D NMR spectrum, was thus assigned to that at the center carbon (C-15) with a β orientation, *cis* to the adjacent protons. Based on the 2D NMR spectra, all the protons and carbons of **207** were assigned. Details are to be found in the experimental section.



207

Figure 1. $^{1}H,^{1}H$ correlated 2D NMR spectrum of **207**

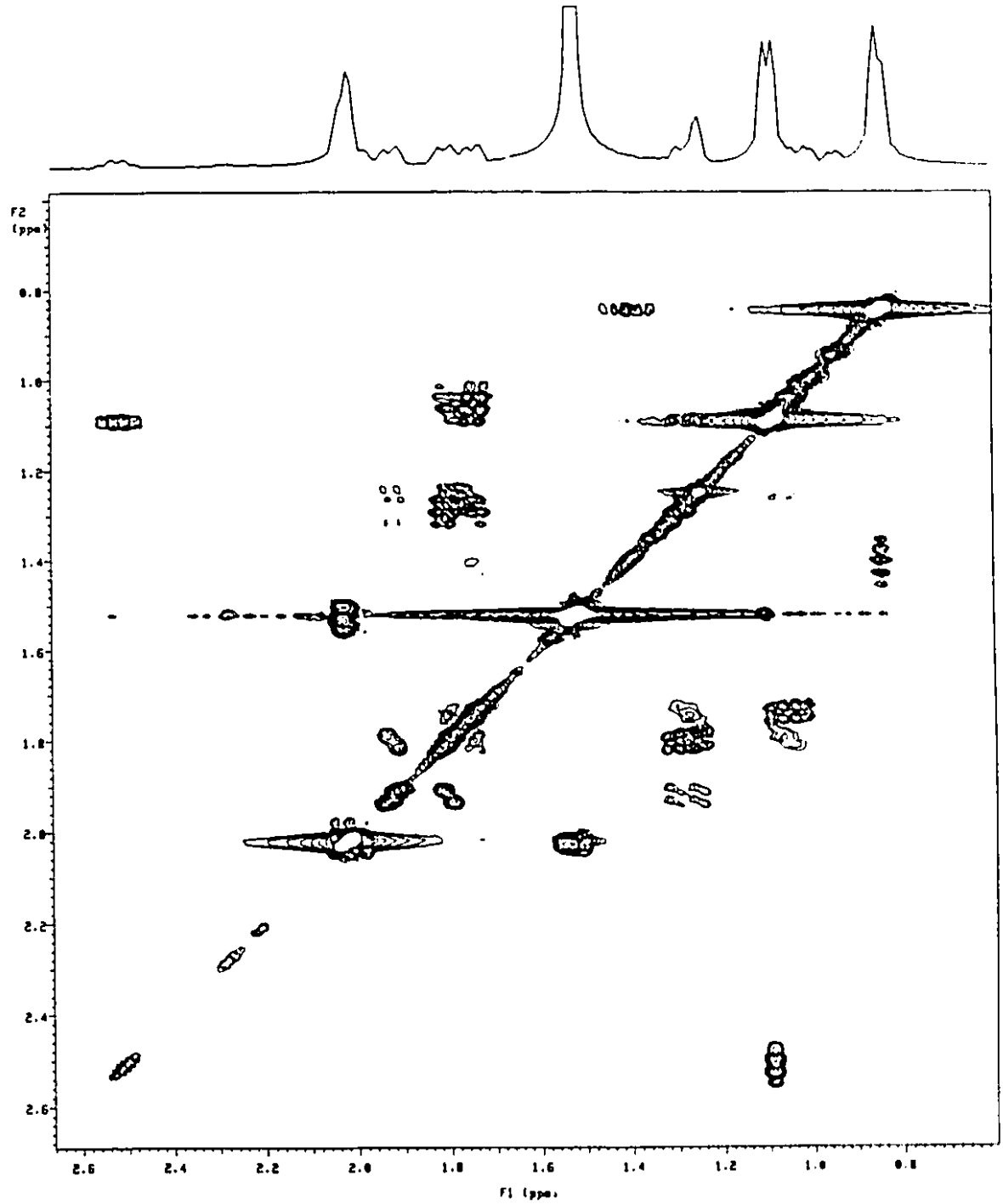
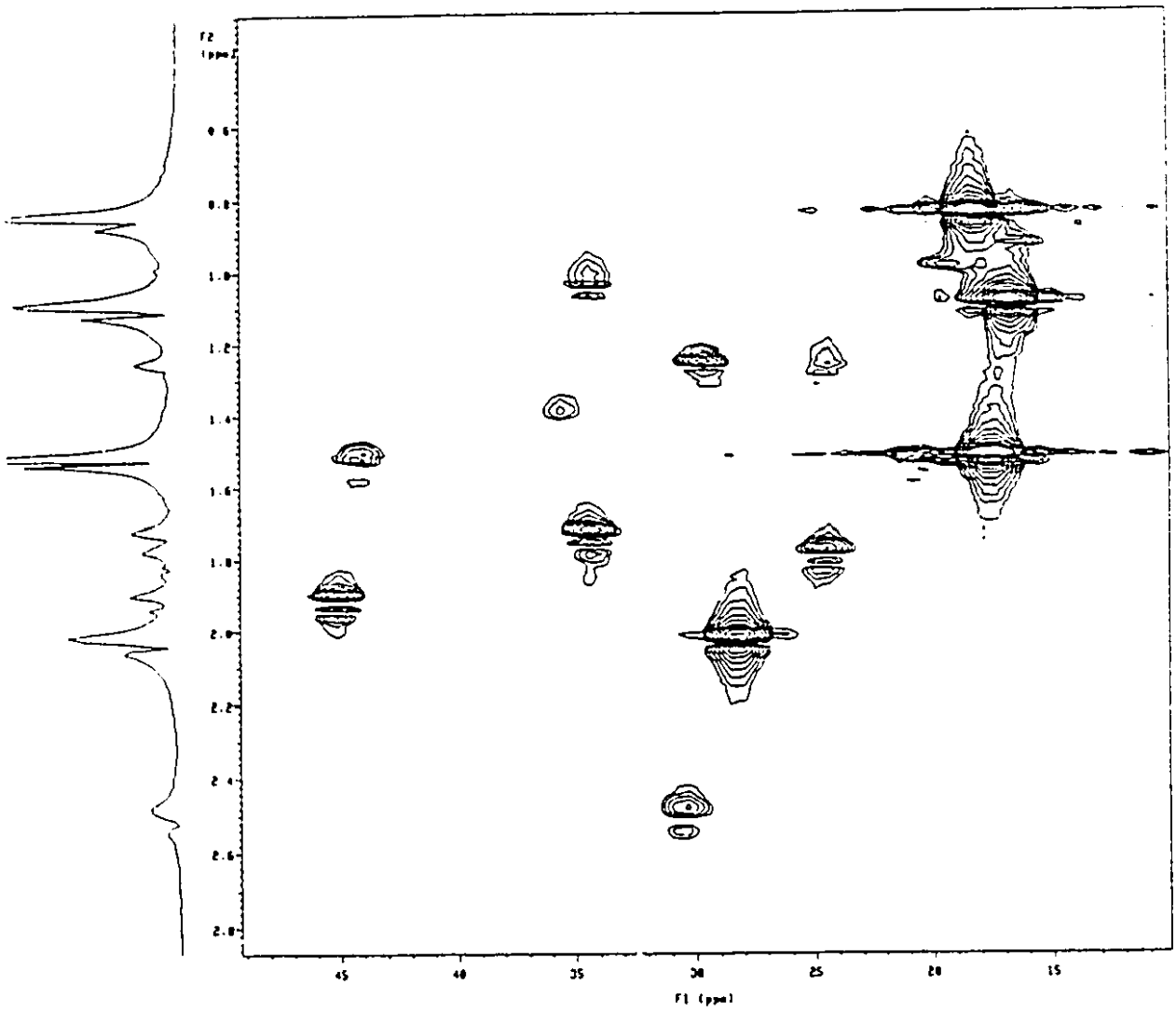
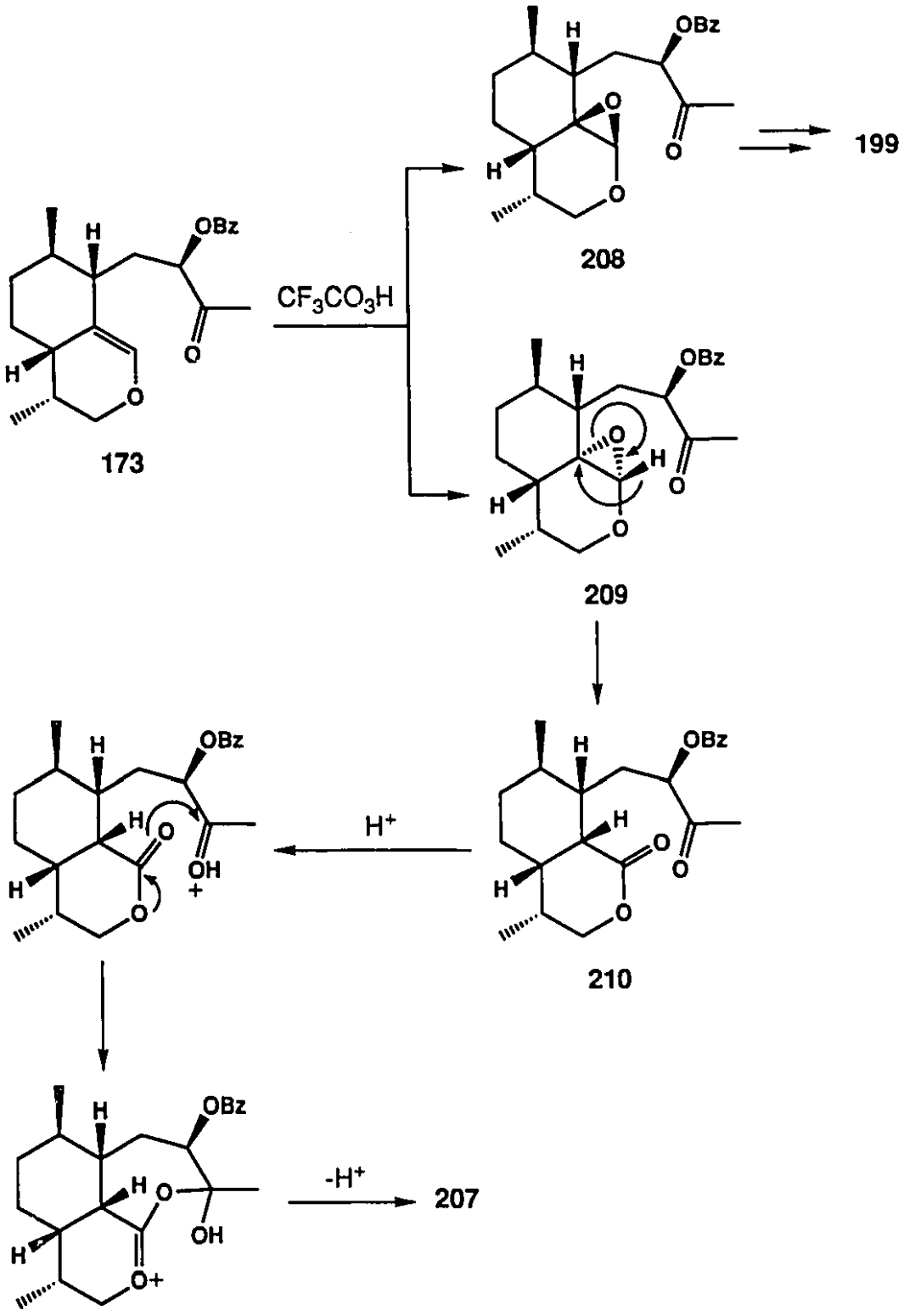


Figure 2. $^{1}H,^{13}C$ correlated 2D NMR spctrum of **207**

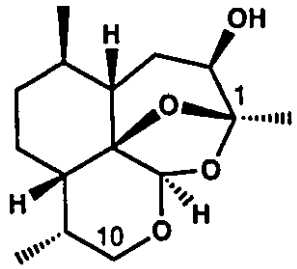


Scheme 49



The mechanism for the production of **207** is proposed in **Scheme 49**. Epoxidation of **173** with trifluoroperoxyacetic acid generates two isomeric epoxides **208** and **209**. Epoxide **208** rearranges to the desired compound **199** directly. In contrast, the sterically unfavored epoxide **209** undergoes rearrangement to give lactone **210**, which is then cyclized to produce oxetane **207**. The reason as to why epoxides **208** and **209** behave differently is not known. When *m*-chloroperoxybenzoic acid was used in the reaction, epoxide **209** could not be formed due to the bulkiness of the oxidant. Therefore, **207** was not found in that reaction.

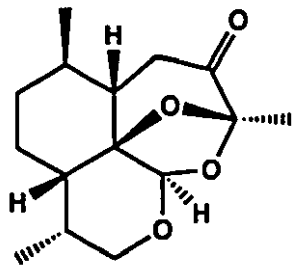
With the desired tetracyclic compound **199** in hand, the subsequent step was the installation of the oxo functionality. At this point, it had to be decided either to proceed with the oxidation or to carry out the debenzoylation first. Either process could suffer from some disadvantage. When the corresponding lactone was formed by the oxidation, the subsequent debenzoylation might induce the breakdown of the acetal structure by hydrolyzing the lactone moiety. On the other hand, if debenzoylation was carried out prior to oxidation, the resulting alcohol could also be oxidized under the oxidation conditions.



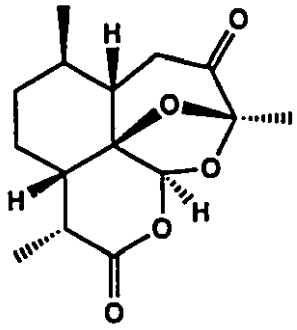
211

The sequence beginning with debenzoylation was first tested. Benzoate **199** was treated with 1 N aqueous sodium hydroxide solution in methanol. Unexpectedly, the desired alcohol **211** was obtained in only 40% yield. The infrared spectrum of **211** displayed a broad band at 3450 cm^{-1}, supporting the production of an alcohol. In the ^1H NMR spectrum, the significant acetal bridge proton singlet shifted upfield to δ 5.19. The

methylene protons at C-10 also had a upfield shift to δ 3.90 (dd, J = 11.5, J' = 6.5 Hz) and 3.33 (dd, J = 11.5, J' = 5 Hz). The proton at the hydroxy-bearing carbon was shown at δ 3.56 as a multiplet. The methyl singlet at C-1 was displayed at δ 1.55, while two methyl doublets appeared at δ 0.93 (J = 7 Hz) and 0.88 (J = 6 Hz). In the high resolution mass spectrum, a molecular ion peak at m/z 268.1671 was consistent with the molecular formula $C_{15}H_{24}O_4$.



212

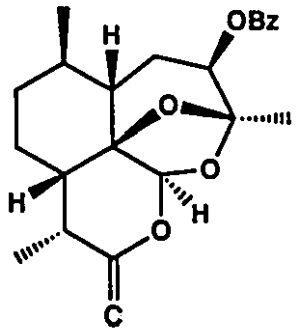


213

Oxidation of **211** was carried out using a combination of sodium periodate and ruthenium(III) chloride in a mixture of carbon tetrachloride, acetonitrile, and water, standard conditions for converting ethers into esters.[139,140] Oxidation of the hydroxyl group occurred and a mixture of ketones **212** and **213** were produced in a ratio of 3 : 2. The ^{1}H NMR spectrum of this mixture displayed two acetal bridge proton singlets at δ 5.89 (minor) and 5.47 (major). A pair of doublets of doublets at δ 3.98 (J = 12, J' = 7 Hz) and 3.37 (J = 12, J' = 5 Hz) were assigned to the methylene protons at C-10 of **212**, while a quartet of doublets at δ 3.22 (J = 7, J' = 4.5) was assigned to the α proton of the lactone carbonyl of **213**. The α methyl group of this lactone carbonyl of **213** was displayed at δ 1.25 as a doublet (J = 7 Hz). The formation of the ketone was indicated by a pair of doublets of doublets at δ 2.66 (J = 16, J' = 6 Hz) and 2.57 (J = 16, J' = 6.5 Hz), corresponding to the α methylene protons of ketone carbonyl of **212**. The parallel protons of **213** were believed to be buried in an unidentified broad multiplet. The oxidation of

the hydroxyl group to a ketone carbonyl was further confirmed by a strong absorption at 1738 cm^{-1} and the disapperance of the hydroxyl absorption in the infrared spectrum. In the high resolution mass spectrum of this mixture, the molecular formula $C_{15}H_{22}O_4$ of **212** was indicated by a molecular ion peak at m/z 266.1505. The molecular ion peak of **213** was not found. Instead, a fragment (m/z 252.1359) due to the loss of a carbon monoxide unit was in agreement with the formula $C_{14}H_{20}O_4$.

Having observed the incompatibility of the secondary hydroxyl group with the above oxidation conditions, we then proceeded with the oxidation of benzoate **199**. Oxidation of **199** using the *in situ* prepared ruthenium tetroxide under the same conditions produced, surprisingly, qinghaosu IV (**171**) in 8.5% yield in addition to the expected lactone **175** in 2.8% yield.



175

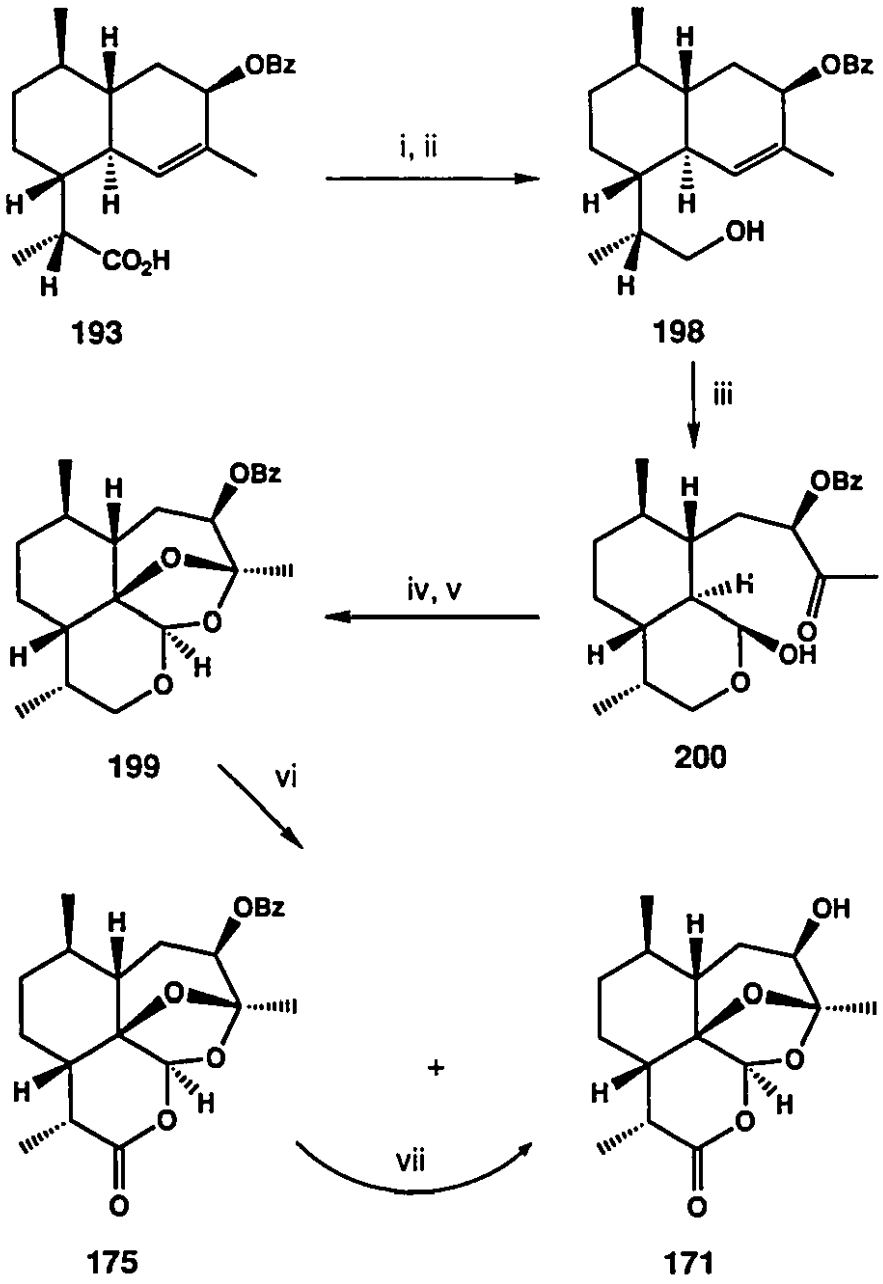
The infrared spectrum of **175** displayed two carbonyl bands at 1739 and 1724 cm^{-1}. In the ^1H NMR spectrum, the generation of a lactone was indicated by a quartet of doublets (J = 7, J' = 4.5 Hz) at δ 3.25, corresponding to the α proton of the lactone carbonyl group, and the absence of a significant pair of methylene protons next to the oxygen. The α methyl group of the lactone appeared as a doublet (J = 7 Hz) at δ 1.23. Five phenyl protons appeared at δ 7.48-8.09 and the proton at the benzoyloxy-bearing carbon was shown at δ 5.02 (dd, J = 4, J' = 2 Hz).

The acetal bridge proton was displayed at δ 5.72 and the methyl group at the ketal bridge carbon was shown at δ 1.56, each as a singlet. A methyl doublet was displayed at δ 0.91 (J = 6.5 Hz). The high resolution mass spectrum of **175** indicated a molecular ion peak at m/z 386.1705, corresponding to the molecular formula $C_{22}H_{26}O_6$.

The production of qinghaosu IV (**171**) was realized by the comparison of the spectral data of the synthetic product with those of an authentic natural product. The melting points were consistent, too. Regarding the optical rotation, the measurement of the synthetic compound was not precise due to insufficient material. Nevertheless, the direction of optical rotation of the synthetic product was in agreement with the reported one.

At this stage, we could not optimize the last oxidation step since all the material had been used up. Debenzoylation of benzoate **175** was attempted with anhydrous potassium carbonate in methanol. Although the production of qinghaosu IV (**171**) was detected on TLC analysis, the yield could not be determined owing to too small a scale. In conclusion, despite that the last oxidation was not satisfactory, it provided a good basis for further optimization. Anyhow, starting with only *ca.* 1 g of compounds and after more than one hundred reactions, it was a great pleasure indeed to obtain the final target qinghaosu IV (**171**). The successful synthetic sequence is summarized in **Scheme 50**.

Scheme 50



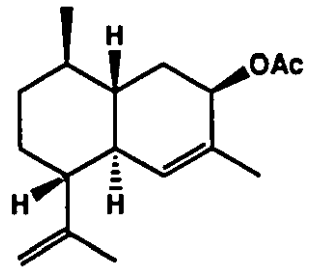
i. $ClCO_2Et$, Et_3N, THF, 0°C; ii. $NaBH_4$, aq. THF, 20°C, 87% (two steps); iii. O_3, CH_2Cl_2-MeOH, -78°C; Me_2S, 20°C, 77%; iv. $POCl_3$, $(i\text{-}Pr)_2NEt$, Py, 20°C; v. CF_3CO_3H, CH_2Cl_2, 0°C, 33% (two steps); vi. $RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O, 20°C, 8.5% of **171**; vii. K_2CO_3, MeOH, 20°C

Experimental

General Procedures and Materials

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

(1R,4R,6S,7R,10R)-4-Acetoxy-3,7-dimethyl-10-(1-methylethenyl)-bicyclo[4.4.0]dec-2-ene (176)

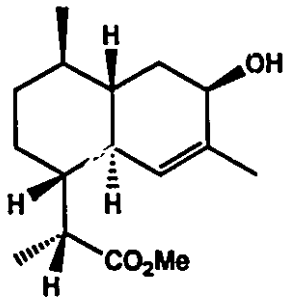


176

Alcohol **160** (19 mg, 0.086 mmol), triphenylphosphine (113 mg, 0.43 mmol), and acetic acid (glacial, 25 μL, 0.43 mmol) were dissolved in dry tetrahydrofuran (1.5 mL). A solution of diethyl azodicarboxylate (68 μL, 0.43 mmol) in dry tetrahydrofuran (0.5 mL) was added slowly and the resulting solution was stirred at room temperature under an argon atmosphere. After 54 hours, additional triphenylphosphine (225 mg, 0.86 mmol), acetic acid (glacial, 48 μL, 0.86 mmol), and diethyl azodicarboxylate (135 μL, 0.86 mmol) were added sequentially. After stirring for 16.5 hours, the solution was concentrated and subjected to flash chromatography (0-30% ether in skelly B) to give a colorless oil **176** (1.3 mg, 6.6% yield based on consumed starting alcohol): IR (CH_2Cl_2, cast): 1737 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 5.62 (br s, 1H, =C**H**-), 5.20 (br d, J = 4 Hz, 1H, -C**H**(OAc)-), 4.82 (m, 1H, =C**H**H), 4.73 (br

d, J = 2.5 Hz, 1H, =CH**H**), 2.38 (m, 1H, =CC**H**-), 2.09 (ddd, J = 15, 1.5, 1.5 Hz, 1H, =CC**H**-), 2.07 (s, 3H, C**H**$_3$CO-), 1.94-1.00 (m, 8H), 1.65 (br s, 6H, 2 × =C(C**H**$_3$)-), 0.88 (d, J = 5.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M$^+$) for $C_{17}H_{26}O_2$: calcd. 262.1934, found 262.1931. Continued elution gave the starting alcohol (2.8 mg, 15% recovery).

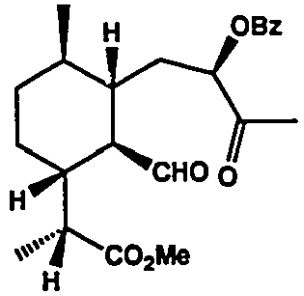
(1S,3R,6R,7R,10R)-7-((R)-1-Carbomethoxyethyl)-4,10-dimethylbicyclo[4.4.0]dec-4-en-3-ol (177)



177

Potassium carbonate (anhydrous, 67 mg, 0.485 mmol) was added to a solution of ester **170** (36 mg, 0.097 mmol) in dry methanol (2 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 23 hours. The solution was then acidified with 1 N hydrochloric acid and extracted with dichloromethane (3 × 5 mL). The combined extracts were washed with water, dried, concentrated, and purified by flash chromatography (50% ether in skelly B) to give alcohol **177** (22.5 mg, 87% yield) as a colorless oil: IR ($CHCl_3$, cast): 3560 (br, O-H), 1734 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.70 (dd, J = 1.5, 1.5 Hz, 1H, =C**H**-), 3.93 (br s, 1H, -C**H**(OH)-), 3.63 (s, 3H, -COOC**H**$_3$), 2.91 (qd, J = 7, 3 Hz, 1H, -(CH$_3$)C**H**COOCH$_3$), 2.09 (ddd, J = 14, 2, 1.5 Hz, 1H, -C**H**C=C(CH$_3$)-), 1.79 (dd, J = 2, 1.5 Hz, 3H, =C(C**H**$_3$)-), 1.78-0.94 (m, 10H), 1.14 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)COOCH$_3$), 0.90 (d, J = 5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M$^+$ - H_2O) for $C_{16}H_{24}O_2$: calcd. 248.1777, found 248.1773.

(1R,2S,3R,4R)-(-)-2-((R)-2-Benzoyloxy-3-oxobutyl)-4-((R)-1-carbomethoxyethyl)-3-formyl-1-methylcyclohexane (179)

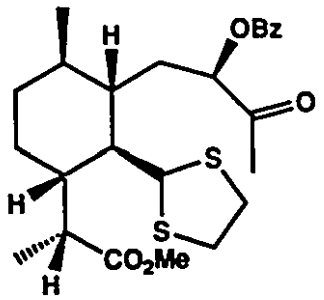


179

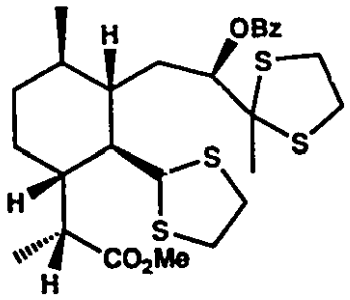
Ozone was passed through a solution of ester **170** (85 mg, 0.229 mmol) in dichloromethane (5 mL) and methanol (1 mL) at -78°C for 10 minutes. Dimethyl sulfide (0.5 mL) was then added and the resulting solution was warmed up to room temperature gradually while stirring. After 6.5 hours, the solution was concentrated and subjected to flash chromatography (40% ether in skelly B) to give aldehyde **179** (64 mg, 70% yield) as a colorless oil: $[\alpha]_D^{22}$ = -34.13° (c. 0.920, $CHCl_3$); IR ($CHCl_3$, cast): 1720 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, *J* = 6 Hz, 1H, -C**H**O), 8.06 (m, 2H, phenyl *ortho*), 7.60 (m, 1H, phenyl *para*), 7.47 (m, 2H, phenyl *meta*), 5.28 (dd, *J* = 11, 2 Hz, 1H, -C**H**(OBz)-), 3.64 (s, 3H, -COOC**H**$_3$), 2.41 (qd, *J* = 8, 3 Hz, 1H, -(CH$_3$)C**H**COOCH$_3$), 2.31 (ddd, *J* = 12, 12, 6 Hz, 1H, -C**H**(CHO)-), 2.15 (s, 3H, C**H**$_3$CO-), 2.00-1.87 (m, 2H), 1.83-1.70 (m, 3H), 1.43 (m, 1H), 1.35 (m, 1H), 1.16-0.99 (m, 2H), 1.12 (d, *J* = 8 Hz, 3H, -CH(C**H**$_3$)COOCH$_3$), 1.10 (d, *J* = 6 Hz, 3H -CH(C**H**$_3$)-); MS m/z (M^+ - CO) for $C_{22}H_{30}O_5$: calcd. 374.2094, found 374.2108.

(1R,2S,3R,4R)-2-((R)-2-Benzoyloxy-3-oxobutyl)-4-((R)-1-carbomethoxyethyl)-3-ethylenedithiomethyl-1-methylcyclohexane (180) and (1R,2S,3R,4R)-2-((R)-2-benzoyloxy-3,3-

ethylenedithiobutyl)-4-((R)-1-carbomethoxyethyl)-3-ethylenedithiomethyl-1-methylcyclohexane (181)



180

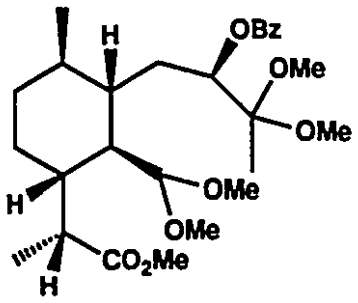


181

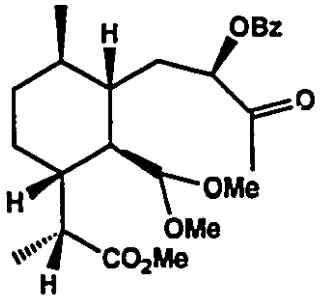
1,2-Ethanedithiol (3.4 μL, 0.041 mmol) was added to a solution of aldehyde **179** (15 mg, 0.0373 mmol) in dry dichloromethane (1 mL). Boron trifluoride etherate (2.3 μL, 0.0187 mmol) was then added and the resulting solution was stirred at room temperature under an argon atmosphere for 5 hours. At the end of this time, the solution was washed with 1 N aqueous sodium hydroxide solution and water, dried, and concentrated. Flash chromatography (40% ether in skelly B) gave dithioacetal **181** (2.6 mg, 13% yield) as a colorless oil: IR (CH_2Cl_2, cast): 1725 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (m, 2H, phenyl *ortho*), 7.53 (m, 1H, phenyl *para*), 7.42 (m, 2H, phenyl *meta*), 5.48 (dd, *J* = 11, 1.5 Hz, 1H, -C**H**(OBz)-), 4.87 (d, *J* = 3 Hz, 1H, -C**H**(SCH_2-)$_2$), 3.66 (s, 3H, -COOC**H**$_3$), 3.32 (m, 5H, 5 × -SC**H**-), 3.00 (m, 1H, -SC**H**-), 2.87 (m, 2H, -SC**H**-, -(CH_3)C**H**$COOCH_3$), 2.38 (m, 1H, -SC**H**-), 1.83 (s, 3H, C**H**$_3$C(SCH_2-)$_2$-), 1.12 (d, *J* = 6.5 Hz, 3H, -CH(C**H**$_3$)$COOCH_3$), 1.11 (d, *J* = 7 Hz, -CH(C**H**$_3$)-); MS m/z (M^+ - CH_3O) for $C_{26}H_{35}O_3S_4$: calcd. 523.1469, found 523.1451. Further elution gave thioacetal **180** (12 mg, 67% yield) as a colorless oil: IR (CH_2Cl_2, cast): 1721 cm^{-1} (br, C=O); ^1H NMR (400 HMz, $CDCl_3$): δ 8.11 (m, 2H, phenyl *ortho*), 7.58 (m, 1H, phenyl *para*), 7.44 (m, 2H, phenyl *meta*), 5.33 (dd, *J* = 11, 3 Hz, -C**H**(OBz)-), 4.94 (d, *J* = 4.5 Hz, 1H, -C**H**(SCH_2-)$_2$), 3.63 (s, 3H, -COOC**H**$_3$), 3.22-2.97 (m, 5H, -SC**H**$_2$C**H**$_2$S-, -(CH_3)C**H**$COOCH_3$), 2.22 (s, 3H, C**H**$_3$CO-), 2.05 (m, 2H), 1.88 (ddd, *J* = 15, 11, 1.5 Hz, 1H), 1.79-1.65 (m, 3H), 1.46 (m, 2H), 1.16

(d, J = 7 Hz, 3H, -CH(CH_3)$COOCH_3$), 1.11-1.00 (m, 2H), 1.05 (d, J = 6 Hz, 3H, -CH(CH_3)-); MS m/z (M^+) for $C_{25}H_{34}O_5S_2$: calcd. 478.1848, found 478.1802.

(1R,2S,3R,4R)-2-[(R)-2-Benzoyloxy-3,3-dimethoxybutyl)-4-((R)-1-carbomethoxyethyl)-3-dimethoxymethyl-1-methylcyclohexane (182) and (1R,2S,3R,4R)-2-((R)-2-benzoyloxy-3-oxobutyl)-4-((R)-1-carbomethoxyethyl)-3-dimethoxymethyl-1-methylcyclohexane (183)



182

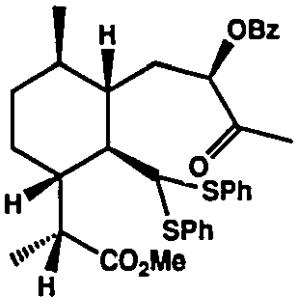


183

Mercury(II) oxide (red, 24 mg, 0.113 mmol) was added to a solution of thioketal **180** (10.8 mg, 0.0225 mmol) in dry methanol (2 mL). Boron trifluoride etherate (14 µL, 0.113 mmol) was then added and the resulting mixture was stirred at room temperature under an argon atmosphere for 4 hours. At the end of this time, the reaction mixture was filtered. The filtrate was then washed with saturated aqueous sodium bicarbonate solution and water, dried, and concentrated. Flash chromatography (30% ether in skelly B) gave acetal **182** (4.9 mg, 49% yield) as a colorless oil: IR ($CHCl_3$, cast): 1724 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (m, 2H, phenyl *ortho*), 7.53 (m, 1H, phenyl *para*), 7.42 (m, 2H, phenyl *meta*), 5.53 (dd, J = 10.5, 2 Hz, 1H, -C**H**(OBz)-), 4.34 (d, J = 1.5 Hz, 1H, -C**H**$(OCH_3)_2$), 3.63 (s, 3H, -$COOCH_3$), 3.28 (s, 3H, -OCH_3), 3.25 (s, 3H, -OCH_3), 3.19 (m, 1H, -(CH_3)C**H**$COOCH_3$), 3.16 (s, 3H, -OCH_3), 3.04 (s, 3H, -OCH_3), 1.38 (s, 3H, $CH_3C(OCH_3)_2$-), 1.06 (d, J = 7 Hz, 3H,

-CH(C**H**$_3$)COOCH$_3$), 1.02 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - CH_3OH - CH_3O) for $C_{25}H_{35}O_6$: calcd. 431.2434, found 431.2430. Continued elution gave a mixture of acetals **182** and **183** (1.6 mg) in a ratio of 1 : 2 as a colorless oil: IR ($CHCl_3$, cast): 1722 cm^{-1} (C=O). Acetal **183** (11% yield) showed the following spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 2H, phenyl *ortho*), 7.56 (m, 1H, phenyl *para*), 7.44 (m, 2H, phenyl *meta*), 5.43 (dd, J = 10.5, 2.5 Hz, 1H, -C**H**(OBz)-), 4.48 (d, J = 1.5 Hz, 1H, -C**H**(OCH$_3$)$_2$), 3.62 (s, 3H, -COOC**H**$_3$), 3.42 (s, 3H, -OC**H**$_3$), 3.40 (s, 3H, -OC**H**$_3$), 2.23 (s, 3H, C**H**$_3$CO-), 1.12 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)COOCH$_3$), 1.05 (d, J = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{25}H_{36}O_7$: calcd. 448.2462, found 448.2472.

(1R,2S,3R,4R)-(-)-2-((R)-2-Benzoyloxy-3-oxobutyl)-4-((R)-1-carbomethoxyethyl)-1-methyl-3-diphenylthiomethylcyclohexane (184)

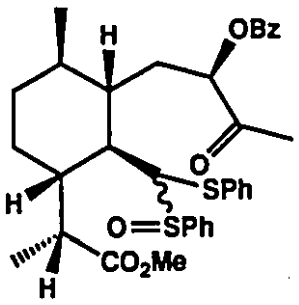


184

Thiophenol (19 μL, 0.184 mmol), followed by boron trifluoride etherate (6 μL, 0.042 mmol), was added to a solution of aldehyde **179** (33.6 mg, 0.0835 mmol) in dry dichloromethane (1.5 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 38 hours. The solution was then washed with 1 N aqueous sodium hydroxide solution and water, dried, concentrated, and subjected to flash chromatography (40% ether in skelly B) to give thioacetal **184** (23.9 mg, 83% yield based on consumed starting aldehyde) as a colorless oil: $[\alpha]_D^{22}$

= -47.65° (c. 1.425, $CHCl_3$); IR (CH_2Cl_2, cast): 1722 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (m, 2H, -COPh *ortho*), 7.55 (m, 1H, -COPh *para*), 7.38 (m, 6H, -COPh *para*, 2 × -SPh *ortho*), 7.24 (m, 2H, 2 × -SPh *para*), 7.18 (m, 4H, 2 × -SPh *meta*), 5.33 (dd, J = 10, 4 Hz, 1H, -C**H**(OBz)-), 4.70 (s, 1H, -C**H**$(SPh)_2$), 3.62 (s, 3H, -COOC**H**$_3$), 3.21 (qd, J = 7, 2 Hz, 1H, -(CH_3)C**H**COOCH_3), 2.48 (dd, J = 10, 10 Hz, 1H, -C**H**CH$(SPh)_2$), 2.08 (s, 3H, C**H**$_3$CO-), 1.95 (m, 1H), 1.78 (m, 2H), 1.63 (dq, J = 13, 3.5 Hz, 1H), 1.51 (m, 1H), 1.40 (m, 1H), 1.25-1.14 (m, 3H), 1.20 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)COOCH_3), 1.01 (d, J = 6.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - C_6H_5S) for $C_{29}H_{35}O_5S$: calcd. 495.2207, found 495.2214. Continued elution gave starting aldehyde **179** (14.4 mg, 43% recovery).

(1R,2S,3R,4R)-2-((R)-2-Benzoyloxy-3-oxobutyl)-4-((R)-1-carbomethoxyethyl)-1-methyl-3-(phenylsulfinylphenylthiomethyl)cyclohexane (185)

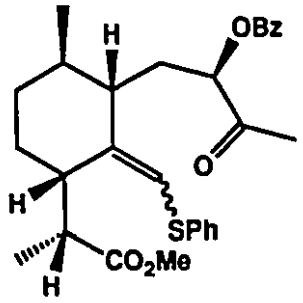


185

To a solution of thioketal **184** (21.4 mg, 0.0354 mmol) in ethanol (99.9%, 0.7 mL) was added a solution of magnesium monoperoxyphthalate hexahydrate (80%, 12 mg, 0.0195 mmol) in water (0.7 mL) and the resulting solution was stirred at 50°C. After 2 hours, the solution was extracted with dichloromethane (3 × 5 mL). The combined extracts were washed with water, dried, concentrated, and subjected to flash chromatography (60% ether in skelly B) to give starting

thioketal **184** (7.8 mg, 36% recovery). Continued elution gave sulfoxides **185** (11.7 mg, 83% yield based on consumed starting thioketal) in a ratio of 4 : 1 (based on ^{1}H NMR integration) as a colorless oil: IR ($CHCl_3$, cast): 1721 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20-7.17 (m, 15H, 3 × $C_6\mathbf{H}_5$), 5.71 (dd, J = 10, 3.5 Hz, 0.2H, -C**H**(OBz)-), 5.66 (dd, J = 9, 4.5 Hz, 0.8H, -C**H**(OBz)-), 4.53 (d, J = 1 Hz, 0.2H, -C**H**(SPh)(SOPh)), 4.41 (s, 0.8H, -C**H**(SPh)(SOPh)), 3.78 (s, 2.4H, -COOC$\mathbf{H}_3$), 3.74 (s, 0.6H, -COOC$\mathbf{H}_3$), 3.00 (m, 1H, -(CH_3)C**H**COOCH_3), 2.27 (s, 0.6H, C$\mathbf{H}_3$CO-), 2.25 (s, 2.4H, C$\mathbf{H}_3$CO-), 1.28 (d, J = 7 Hz, 2.4H, -CH(C$\mathbf{H}_3$)COOCH_3), 1.11 (d, J = 6.5 Hz, 0.6H, -CH(C$\mathbf{H}_3$)COOCH_3), 1.03 (d, J = 5.5 Hz, 2.4H, -CH(C$\mathbf{H}_3$)-), 1.02 (d, J = 6 Hz, 0.6H, -CH(C$\mathbf{H}_3$)-); MS m/z (M^+ - C_6H_5SOH) for $C_{29}H_{34}O_5S$: calcd. 494.2128, found 494.2128.

(1R,2S,4S)-2-((R)-2-Benzoyloxy-3-oxobutyl)-4-((R)-1-carbomethoxyethyl)-1-methyl-3-phenylthiomethylidenecyclohexane (186)



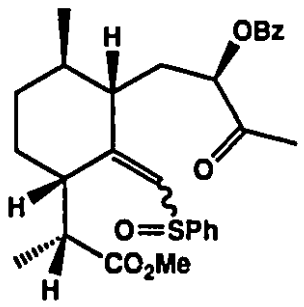
186

From sulfoxides 185: A solution of sulfoxides **185** (15 mg, 0.0242 mmol) in dry toluene (5 mL) was heated under reflux under an argon atmosphere for 2 hours. At the end of this time, the solution was concentrated and purified by flash chromatography (30% ether in skelly B) to give vinyl sulfides **186** (10 mg, 83% yield) in a ratio of 9 : 2 (based on ^{1}H NMR integration) as a colorless oil: IR ($CHCl_3$, cast): 1722 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (m, 0.36H, -COPh *ortho*), 8.07

(m, 1.64H, -COPh *ortho*), 7.60 (m, 1H, -COPh *para*), 7.45 (m, 2H, -COPh *meta*), 7.32-7.18 (m, 5H, -$SC_6\mathbf{H}_5$), 6.21 (s, 0.82H, =C**H**SPh), 6.17 (s, 0.18H, =C**H**SPh), 5.32 (dd, J = 11, 2 Hz, 0.18H, -C**H**(OBz)-), 5.26 (dd, J = 10, 3.5 Hz, 0.82H, -C**H**(OBz)-), 3.72 (s, 2.45H, -COOC**H**$_3$), 3.70 (s, 0.55H, -COOC**H**$_3$), 3.23 (br dd, J = 12, 5 Hz, 0.82H, =CC**H**-), 2.92 (br d, J = 11 Hz, 0.18H, =CC**H**-), 2.82 (q, J = 7 Hz, 0.82H, -(CH_3)C**H**COOCH_3), 2.78 (q, J = 7 Hz, 0.18H, -(CH_3)C**H**COOCH_3), 2.25 (s, 0.55H, C**H**$_3$CO-), 2.23 (s, 2.45H, C**H**$_3$CO-), 1.21 (d, J = 7 Hz, 2.45H, -CH(C**H**$_3$)COOCH_3), 1.12 (d, J = 7 Hz, 0.55H, -CH(C**H**$_3$)COOCH_3), 0.99 (d, J = 7 Hz, 2.45H, -CH(C**H**$_3$)-), 0.94 (d, J = 7 Hz, 0.55H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{29}H_{34}O_5S$: calcd. 494.2128, found 494.2128.

From alcohol 190: Benzoic anhydride (5 mg, 0.0225 mmol), pyridine (1.8 μL, 0.0225 mmol), and 4-dimethylaminopyridine (5 mg, 0.0409 mmol) were added sequentially to a solution of alcohol **190** (0.9 mg, 0.0023 mmol) in dry dichloromethane (1 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 11 hours. At the end of this time, the solution was washed with 1 N hydrochloric acid and water, dried, concentrated, and purified by flash chromatography (40% ether in skelly B) to give vinyl sulfides **186** (1.0 mg, 91% yield).

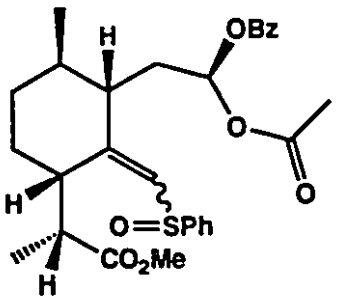
(1R,2S,4S)-2-((R)-2-Benzoyloxy-3-oxobutyl)-4-((R)-1-carbomethoxyethyl)-1-methyl-3-phenylsulfinylmethylidenecyclohexane (187)



187

To a solution of vinyl sulfides **186** (6.7 mg, 0.0135 mmol) in dry chloroform (1 mL) at 0°C was added *m*-chloroperoxybenzoic acid (70%, 3.7 mg, 0.0149 mmol) and the resulting solution was stirred at 0°C under an argon atmosphere for 1 hour. At the end of this time, the solution was washed with saturated aqueous sodium bicarbonate solution and water, dired, concentrated, and subjected to flash chromatography (70-100% ether in skelly B) to give a mixture of two stereoisomers of sulfoxides **187** (1.8 mg, 26% yield) in a ratio of 1 : 2 (based on ^{1}H NMR integration): IR ($CHCl_3$, cast): 1721 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.35-7.32 (m, 10H, 2 × $C_6\mathbf{H}_5$), 6.42 (s, 0.33H, =C**H**SOPh), 6.38 (s, 0.67H, =C**H**SOPh), 5.42 (m, 0.33H, -C**H**(OBz)-), 5.22 (dd, J = 10, 3 Hz, 0.67H, -C**H**(OBz)-), 3.73 (s, 2H, -COOC**H**$_3$), 3.69 (s, 1H, -COOC**H**$_3$), 2.81 (m, 1H, =CC**H**-), 2.27 (s, 1H, C**H**$_3$CO-), 2.21 (s, 2H, C**H**$_3$CO-), 1.22 (d, J = 7 Hz, 2H, -CH(C**H**$_3$)COOCH$_3$), 1.07 (d, J = 7 Hz, 1H, -CH(C**H**$_3$)COOCH$_3$), 0.76 (d, J = 7 Hz, 2H, -CH(C**H**$_3$)-), 0.49 (d, J = 7 Hz, 1H, -CH(C**H**$_3$)-); MS m/z (M$^+$ - SOPh) for $C_{23}H_{29}O_5$: calcd. 385.2016, found 385.2017. Continued elution gave a mixture of three stereoisomers of sulfoxides **187** (4.6 mg, 67% yield): IR ($CHCl_3$, cast): 1721 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.30-7.35 (m, 10H, 2 × $C_6\mathbf{H}_5$), 6.38, 6.21, 6.18 (3 × s, 1H, =C**H**SOPh), 5.45-5.15 (m, 1H, -C**H**(OBz)-), 3.73, 3.68 (2 × s, 3H, -COOC**H**$_3$), 3.61 (m, 1H, -(CH$_3$)C**H**COOCH$_3$), 2.81 (m, 1H, =CC**H**-), 2.27, 2.21, 2.18 (3 × s, 3H, C**H**$_3$CO-), 1.22, 1.14, 1.07 (3 × d, J = 7 Hz, 3H, -CH(C**H**$_3$)COOCH$_3$), 0.98, 0.85, 0.76 (3 × d, J = 7 Hz, -CH(C**H**$_3$)-); MS m/z (M$^+$) for $C_{29}H_{34}O_6S$: calcd. 510.2077, found 510.2086.

(1R,2S,4S)-2-((R)-2-Acetoxy-2-benzoyloxyethyl)-4-((R)-1-carbomethoxyethyl)-1-methyl-3-phenylsulfinylmethylidenecyclohexane (188)

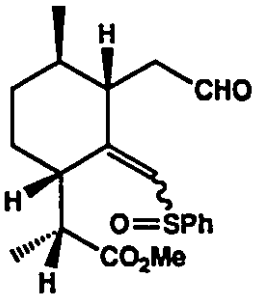


188

To a solution of vinyl sulfides **186** (4.1 mg, 0.00829 mmol) in dry chloroform (1.5 mL) was added *m*-chloroperoxybenzoic acid (70%, 10 mg, 0.0414 mmol) and the resulting solution was stirred at 0°C under an argon atmosphere for 1 h. At the end of this time, the reaction was quenched by addition of 10% aqueous sodium sulfite solution. The chloroform layer was separated, washed with saturated aqueous sodium bicarbonate solution and water, dried, concentrated, and subjected to flash chromatography (80% ether in skelly B) to give acetates **188** (2.6 mg, 50% yield) as an inseparable mixture of two stereoisomers in a ratio of 1 : 3 (based on ^{1}H NMR integration) as a colorless oil: IR ($CHCl_3$, cast): 1759, 1733 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-7.40 (m, 10H, 2 × $C_6\mathbf{H}_5$), 7.00 (m, 1H, -(OBz)C**H**(OAc)), 6.39 (s, 0.25H, =C**H**SOPh), 6.35 (s, 0.75H, =C**H**SOPh), 4.01 (m, 1H, -(CH_3)C**H**$COOCH_3$), 3.72 (s, 2.25H, -$COOC\mathbf{H}_3$), 3.68 (s, 0.75H, -$COOC\mathbf{H}_3$), 2.83 (m, 1H, =CC**H**-), 2.12 (s, 0.75H, $C\mathbf{H}_3COO$-), 2.07 (s, 2.25H, $C\mathbf{H}_3COO$-), 1.22 (d, *J* = 7 Hz, 2.25H, -CH($C\mathbf{H}_3$)$COOCH_3$), 1.11 (d, *J* = 7 Hz, 0.75H, -CH($C\mathbf{H}_3$)$COOCH_3$), 0.78 (d, *J* = 7 Hz, 2.25H, -CH($C\mathbf{H}_3$)-), 0.52 (d, *J* = 7 Hz, 0.75H, -CH($C\mathbf{H}_3$)-); MS m/z (M^+ - SOPh) for $C_{23}H_{29}O_6$: calcd. 401.1965, found 401.1973. Continued elution gave vinyl sulfoxides **187** (2.2 mg, 50% yield). This material was shown by the following spectral data to exist as a single stereoisomer: IR ($CHCl_3$, cast): 1726 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (m, 2H, -COPh *ortho*), 7.92 (m, 2H, -SOPh *ortho*), 7.67-7.47 (m, 6H, 2 × phenyl *para*, 2 × phenyl *meta*), 6.38 (s, 1H, =C**H**SOPh), 5.22 (dd, *J* = 10, 3 Hz, 1H, -C**H**(OBz)-), 4.00 (m, 1H, -(CH_3)C**H**$COOCH_3$), 3.73 (s, 3H, -$COOC\mathbf{H}_3$), 2.81 (m, 1H, =CC**H**-), 2.21 (s, 3H, $C\mathbf{H}_3CO$-), 1.22

(d, J = 7 Hz, 3H, -CH(C**H**$_3$)COOCH$_3$), 0.76 (d, J = 7 Hz, -CH(C**H**$_3$)-); MS m/z (M^+ - SOPh) for $C_{23}H_{29}O_5$: calcd. 385.2016, found 385.2016.

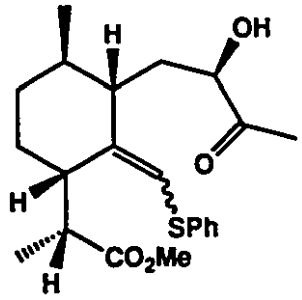
(1R,2S,4S)-4-((R)-1-Carbomethoxyethyl)-1-methyl-2-(2-oxoethyl)-3-phenylsulfinylmethylidenecyclohexane (189)



189

To a solution of acetates **188** (2.6 mg, 0.00494 mmol) in tetrahydrofuran (0.5 mL) was added 10% aqueous perchloric acid (0.5 mL). After stirring at room temperature for 4 days, the solution was extracted with ether (5 mL). The extract was then washed with water, saturated aqueous sodium bicarbonate solution, and water, dried, concentrated, and purified by flash chromatography (60% ether in skelly B) to give a mixture of aldehydes **189** (0.6 mg, 34% yield) in a ratio of 1 : 2 (based on ^{1}H NMR integration) as a colorless oil: IR (CH_2Cl_2, cast): 1732 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (br s, 1H, -C**H**O), 7.96 (m, 2H, phenyl *ortho*), 7.62 (m, 1H, phenyl *para*), 7.56 (m, 2H, phenyl *meta*), 6.48 (s, 0.67H, =C**H**SOPh), 6.45 (s, 0.33H, =C**H**SOPh), 4.03 (m, 1H, -(CH$_3$)C**H**COOCH$_3$), 3.73 (s, 2H, -COOC**H**$_3$), 3.70 (s, 1H, -COOC**H**$_3$), 2.82 (m, 2H, -C**H**$_2$CHO), 1.16 (d, J = 7 Hz, 2H, -CH(C**H**$_3$)COOCH$_3$), 1.08 (d, J = 7 Hz, 1H, -CH(C**H**$_3$)COOCH$_3$), 0.86 (d, J = 7 Hz, 2H, -CH(C**H**$_3$)-), 0.64 (d, J = 7 Hz, 1H, -CH(C**H**$_3$)-); MS m/z (M^+ - SOPh) for $C_{14}H_{21}O_3$: calcd. 237.1491, found 237.1493.

(1R,2S,4S)-4-((R)-1-Carbomethoxyethyl)-2-((R)-2-hydroxy-3-oxobutyl)-1-methyl-3-phenylthiomethylidenecyclohexane (190)

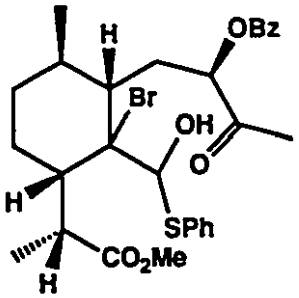


190

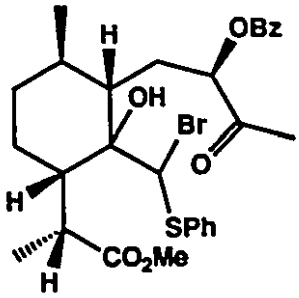
Pyridine (0.5 mL) was added to a solution of esters **186** (4 mg, 0.00809 mmol) in dry tetrahydrofuran (1 mL). Osmium tetroxide (*ca.* 0.05 g) was then added and the resulting solution was stirred at room temperature under an argon atmosphere for 42 hours. At the end of this time, the reaction was quenched by addition of saturated aqueous sodium sulfite solution. After stirring for 23 hours, the solution was extracted with dichloromethane (3 × 5 mL). The combined extracts were washed with 1 N hydrochloric acid and water, dried, concentrated, and purified by flash chromatography (50% ether in skelly B) to give alcohol **190** (1.2 mg, 38% yield) as a colorless oil: IR ($CHCl_3$, cast): 3400 (br, O-H), 1730 cm^{-1} (br, C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H, $-SC_6\mathbf{H}_5$), 6.24 (s, 1H, =C**H**SPh), 4.18 (m, 1H, -C**H**(OH)-), 3.72 (s, 3H, $-COOC\mathbf{H}_3$), 3.38 (d, J = 5.5 Hz, 1H, -O**H**), 3.19 (m, 1H, $-(CH_3)C\mathbf{H}COOCH_3$), 2.75 (dd, J = 12, 7 Hz, 1H, =CC**H**-), 2.45 (br d, J = 11 Hz, 1H, =CC**H**-), 2.23 (s, 3H, $C\mathbf{H}_3CO$-), 1.17 (d, J = 7 Hz, 3H, $-CH(C\mathbf{H}_3)COOCH_3$), 1.05 (d, J = 7 Hz, 3H, $-CH(C\mathbf{H}_3)$-); MS m/z (M^+) for $C_{22}H_{30}O_4S$: calcd. 390.1866, found 390.1869.

(1R,2S,4S)-2-((R)-2-Benzoyloxy-3-oxobutyl)-3-bromo-4-((R)-1-carbomethoxyethyl)-3-hydroxyphenylthiomethyl-1-methylcyclohexane (191a) and (2S,3R,6S)-2-((R)-benzoyloxy-3-

oxobutyl)-1-bromophenylthiomethyl-6-((R)-1-carbomethoxyethyl)-3-methylcyclohexan-1-ol (191b)



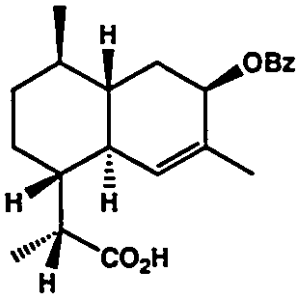
191a



191b

To a solution of vinyl sulfides **186** (4.1 mg, 0.00829 mmol) in 80% aqueous tetrahydrofuran (0.6 mL) was added *N*-bromosuccinimide (3 mg, 0.0166 mmol) and the resulting solution was stirred at room temperature for 1 hour. The solution was then diluted with water and extracted with ether (2 × 5 mL). The combined extracts were washed with water, dried, concentrated, and subjected to flash chromatography (ether) to give an inseparable mixture of compounds **191a** and **191b** (5 mg, 100% yield) as a colorless oil. This mixture was shown by the following spectral data to contain at least five isomers: IR (CH_2Cl_2, cast): 3450 (br, O-H), 1722 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 8.10-7.35 (m, 10H, 2 × -$C_6\mathbf{H}_5$), 6.37, 6.20, 6.18 (3 × s, 1H, -C**H**(SPh)-), 5.44-4.97 (m, 1H, -C**H**(OBz)-), 3.74, 3.68, 3.67 (3 × s, 3H, -COOC$\mathbf{H}_3$), 3.65 (m, 1H, -O**H**), 2.85 (m, 1H, -(CH_3)C**H**COOCH_3), 2.28, 2.27, 2.20, 2.17 (4 × s, 3H, C$\mathbf{H}_3$CO-), 1.39, 1.27, 1.23, 1.14, 1.08, 0.97, 0.86, 0.83, 0.77 (9 × d, J = 7 Hz, 6H, 2 × -C$\mathbf{H}_3$); MS m/z (M^+ - Br) for $C_{29}H_{35}O_6S$: calcd. 511.2156, found 511.2138.

(1R,4R,6S,7R,10R)-(-)-4-Benzoyloxy-10-((R)-1-carboxyethyl)-3,7-dimethylbicyclo[4.4.0]dec-2-ene (193)

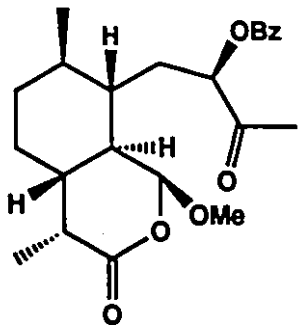


193

The reaction flask, syringes, and needles were all flame-dried before use. 9-Borabicyclo[3.3.1]nonane (dimer, 0.44 g, 1.803 mmol) was added to a solution of benzoate **169** (1.01 g, 3.113 mmol) in dry tetrahydrofuran (20 mL) and the resulting solution was stirred at room temperature under an argon atmosphere for 1 hour. The solution was then concentrated and the residue dissolved in ether (10 mL) for the following reaction.

Both the ether solution and Jones reagent were cooled at 0°C for 1 hour. Jones reagent (35 mL) was added to the ether solution over a period of 20 minutes and the resulting solution was stirred for 30 minutes at 0°C. At the end of this time, the solution was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with water (3 × 100 mL) and saturated aqueous sodium chloride solution (2 × 100 mL), dried, concentrated, and purified by flash chromatography (50-70% ether in skelly B) to give acid **193** (868 mg, 78% yield) as a colorless oil: $[\alpha]_D^{22}$ = -10.94° (c. 6.2, $CHCl_3$); IR ($CHCl_3$, cast): 3600-2500 (COOH), 1714 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (m, 2H, phenyl *ortho*), 7.56 (m, 1H, phenyl *para*), 7.44 (m, 2H, phenyl *meta*), 5.96 (br s, 1H, =C**H**-), 5.43 (d, *J* = 4 Hz, 1H, -C**H**(OBz)-), 3.02 (qd, *J* = 7, 3 Hz, 1H, -(CH_3)C**H**COOH), 2.21 (br d, *J* = 14.5 Hz, 1H, =CC**H**-), 1.74 (br s, 3H, =C(C**H**$_3$)-), 1.21 (d, *J* = 7 Hz, 3H, -CH(C**H**$_3$)COOH), 0.83 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{22}H_{28}O_4$: calcd. 356.1988, found 356.1974.

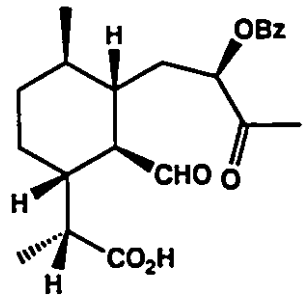
(1R,2R,5S,6R,7S,8R)-7-((R)-2-Benzoyloxy-3-oxobutyl)-5-methoxy-2,8-dimethyl-4-oxabicyclo[4.4.0]decan-3-one (194)



194

Ozone was passed through a solution of acid **193** (42 mg, 0.118 mmol) in dichloromethane (2 mL) and methanol (1 mL) at -78°C for 5 minutes. Dimethyl sulfide (0.5 mL) was then added and the resulting solution was warmed up to room temperature gradually while stirring. After 20 hours, the solution was concentrated and subjected to flash chromatography (60% ether in skelly B) to give lactone **194** (12 mg, 25% yield) as a colorless oil: IR ($CHCl_3$, cast): 1740 (C=O, ester), 1719 cm^{-1} (C=O, ketone); ^1H NMR (200 MHz, $CDCl_3$): δ 8.08 (m, 2H, phenyl *ortho*), 7.62 (m, 1H, phenyl *para*), 7.50 (m, 2H, phenyl *meta*), 5.35 (dd, J = 10, 3 Hz, 1H, -C**H**(OBz)-), 5.29 (d, J = 3 Hz, 1H, -C**H**(OCH_3)-), 3.46 (s, 3H, -OC**H**$_3$), 2.67 (qd, J = 7, 1.5 Hz, 1H, -(CH_3)C**H**COO-), 2.22 (s, 3H, C**H**$_3$CO-), 1.21 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)COO-), 1.05 (d, J = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - OCH_3) for $C_{22}H_{27}O_5$: calcd. 371.1859, found 371.1851.

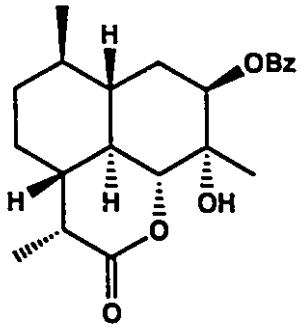
(1R,2S,3R,4R)-2-((R)-2-Benzoyloxy-3-oxobutyl)-4-((R)-1-carboxyethyl)-3-formyl-1-methylcyclohexane (195)



195

Ozone was passed through a solution of acid **193** (31.5 mg, 0.0884 mmol) in dichloromethane (3 mL) at -78°C for 10 minutes. Dimethyl sulfide (0.5 mL) was then added and the solution was warmed up to room temperature gradually while stirring. After 12 hours, the solution was concentrated and purified by flash chromatography (75% ether in skelly B) to give aldehyde **195** (5.5 mg, 16% yield) as a colorless oil: IR ($CHCl_3$, cast): 3450 (br, COOH), 1718 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H, -C**H**O), 8.07 (m, 2H, phenyl *ortho*), 7.63 (m, 1H, phenyl *para*), 7.51 (m, 2H, phenyl *meta*), 5.27 (dd, J = 10, 4 Hz, 1H, -C**H**(OBz)-), 2.45 (br q, J = 6 Hz, 1H, -(CH_3)C**H**COOH), 2.21 (m, 1H, -C**H**(CHO)-), 2.17 (s, 3H, C**H**$_3$CO-), 1.15 (d, J = 6 Hz, 3H, -CH(C**H**$_3$)COOH), 1.11 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - 2H) for $C_{22}H_{26}O_6$: calcd. 386.1730, found 386.1722.

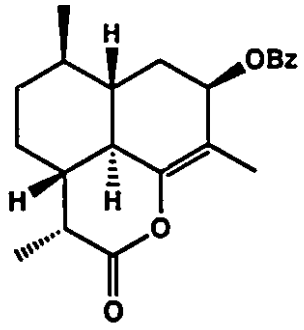
(1R,2R,5R,6R,7R,9S,10R,13R)-7-Benzoyloxy-6-hydroxy-2,6,10-trimethyl-4-oxatricyclo[7.3.1.0^{5,13}]tridecan-3-one (196)



196

A mixture of acid **193** (16.5 mg, 0.0463 mmol) and osmium tetroxide (5 mg, 0.0197 mmol) was stirred in 75% aqueous dioxane (2 mL) at room temperature for 10 minutes until the solution turned dark brown. Sodium periodate (30 mg, 0.139 mmol) was then added. After stirring for 1 hour, the mixture was diluted with ether and filtered through magnesium sulfate. The filtrate was dried, concentrated, and purified by flash chromatography (50-60% ether in skelly B) to give alcohol **196** (4.2 mg, 24% yield) as a colorless oil: IR ($CHCl_3$, cast): 3450 (O-H), 1719 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (m, 2H, phenyl *ortho*), 7.60 (m, 1H, phenyl *para*), 7.47 (m, 2H, phenyl *meta*), 5.23 (dd, J = 3, 3 Hz, 1H, -C**H**(OBz)-), 4.18 (d, J = 10 Hz, 1H, -C**H**OC(=O)-), 2.80 (qd, J = 7.5, 1 Hz, 1H, -(CH_3)C**H**COO-), 2.10 (ddd, J = 14, 3, 3 Hz, 1H), 2.00 (br s, 1H, -O**H**), 1.90-1.68 (m, 4H), 1.59 (m, 1H), 1.41 (s, 3H, C**H**$_3$C(OH)-), 1.36-1.19 (m, 2H), 1.27 (d, J = 7.5 Hz, 3H, -CH(C**H**$_3$)COO-), 1.11 (m, 2H), 0.85 (d, J = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{22}H_{28}O_5$: calcd. 372.1937, found 372.1939.

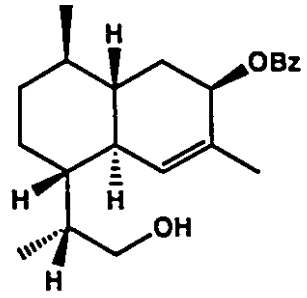
(1R,2R,7R,9S,10R,13R)-7-Benzoyloxy-2,6,10-trimethyl-4-oxatricyclo[7.3.1.$0^{5,13}$]tridec-5-en-3-one (197)



197

To a solution of alcohol **196** (3.5 mg, 0.0094 mmol) in pyridine (1 mL) was added phosphorus oxychloride (0.05 mL) and the resulting solution was stirred at room temperature under an argon atmosphere for 45 hours. At the end of this time, the solution was poured into ice-water (5 mL) and extracted with dichloromethane (4 × 5 mL). The combined extracts were washed with 2 N hydrochloric acid (2 × 10 mL) and water, dried, concentrated, and subjected to flash chromatography (40% ether in skelly B) to give a colorless oil **197** (0.6 mg, 29% based on consumed starting alcohol): IR (CH_2Cl_2, cast): 1757, 1716 (C=O), 1675, 1645 cm^{-1} (-C=C-O-); ^1H NMR (200 MHz, $CDCl_3$): δ 8.05 (m, 2H, phenyl *ortho*), 7.58 (m, 1H, phenyl *para*), 7.44 (m, 2H, phenyl *meta*), 5.63 (br d, J = 4 Hz, 1H, -C**H**(OBz)-), 2.83 (qd, J = 8, 4.5 Hz, 1H, -(C**H**$_3$)C**H**COO-), 2.24 (br d, J = 14 Hz, 1H, -C=CC**H**-), 1.74 (d, J = 2 Hz, 3H, =C(C**H**$_3$)-), 1.26 (d, J = 8 Hz, 3H, -CH(C**H**$_3$)COO-), 0.88 (d, J = 5.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{22}H_{26}O_4$: calcd. 354.1832, found 354.1854. Continued elution gave starting alcohol **196** (1.3 mg, 37% recovery).

(1R,4R,6S,7R,10S)-(+)-4-Benzoyloxy-10-((S)-2-hydroxy-1-methylethyl)-3,7-dimethylbicyclo[4.4.0]dec-2-ene (198)

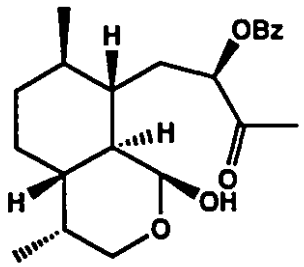


198

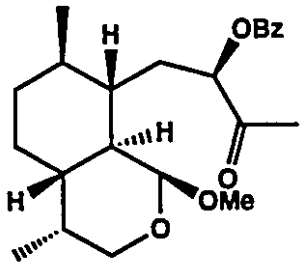
Triethylamine (0.30 mL, 2.180 mmol), followed by ethyl chloroformate (0.21 mL, 2.180 mmol), was added to a solution of acid **193** (259 mg, 0.727 mmol) in dry tetrahydrofuran (10 mL) at 0°C and the resulting solution was stirred at 0°C under an argon atmosphere for 2 hours. At the end of this time, the mixture was filtered to remove white precipitates and the filtrate was added to a solution of sodium borohydride (0.22 g, 5.816 mmol) in water (3 mL). After stirring at room temperature for 1 hour, the solution was poured into 1 N hydrochloric acid (40 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 × 10 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried, concentrated, and purified by flash chromatography (45% ether in skelly B) to give alcohol **198** (217 mg, 87% yield) as a colorless oil: $[\alpha]_D^{22}$ = +47.69° (c. 1.405, $CHCl_3$); IR ($CHCl_3$, cast): 3450 (O-H), 1715 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 8.05 (m, 2H, phenyl *ortho*), 7.55 (m, 1H, phenyl *para*), 7.43 (m, 2H, phenyl *meta*), 5.99 (s, 1H, =C**H**-), 5.43 (d, *J* = 4 Hz, 1H, -C**H**(OBz)-), 4.14 (br d, *J* = 3.5 Hz, 1H, -O**H**), 3.73 (dd, *J* = 10, 5 Hz, 1H, -C**H**HOH), 3.43 (dd, *J* = 10, 9 Hz, 1H, -CH**H**OH), 1.75 (s, 3H, =C(C**H**$_3$)-), 1.02 (d, *J* = 7 Hz, 3H, -CH(C**H**$_3$)CH_2OH), 0.83 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{22}H_{30}O_3$: calcd. 342.2196, found 342.2216.

(1R,2S,5S,6S,9R,10S)-(+)-10-((R)-2-Benzoyloxy-3-oxobutyl)-5,9-dimethyl-3-oxabicyclo[4.4.0]decan-2-ol (200) and

(1S,2S,5S,6R,7S,8R)-7-((R)-2-benzoyloxy-3-oxobutyl)-5-methoxy-2,8-dimethyl-4-oxabicyclo[4.4.0]decane (201)



200

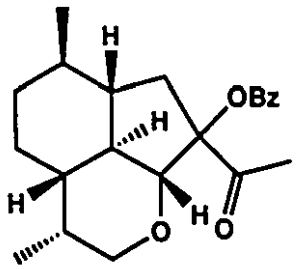


201

Ozone was passed through a solution of alcohol **198** (192 mg, 0.561 mmol) in dichloromethane (10 mL) and methanol (2 mL) at -78°C for 2 minutes. Dimethyl sulfide (1 mL) was then added and the resulting solution was stirred at -78°C for 1 hour and then at room temperature for 2 hours. The resulting solution was concentrated and subjected to flash chromatography (50% ether in skelly B) to give acetal **201** (8 mg, 4% yield) as a colorless oil: IR ($CHCl_3$, cast): 1719 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (m, 2H, phenyl *ortho*), 7.61 (m, 1H, phenyl *para*), 7.48 (m, 2H, phenyl *meta*), 5.31 (dd, *J* = 10, 3.5 Hz, 1H, -C**H**(OBz)-), 4.74 (d, *J* = 3.5 Hz, 1H, -OC**H**(OCH_3)-), 3.90 (dd, *J* = 11, 3 Hz, 1H, -C**H**HO-), 3.64 (m, 1H, -CH**H**O-), 3.35 (s, 3H, -OC**H**$_3$), 2.22 (s, 3H, C**H**$_3$CO-), 1.04 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)CH_2O-), 0.99 (d, *J* = 7 Hz, -CH(C**H**$_3$)-); MS m/z (M^+ - CH_3O) for $C_{22}H_{29}O_4$: calcd. 357.2067, found 357.2075. Continued elution gave hemiacetal **200** (161 mg, 77% yield) as a colorless oil: $[\alpha]_D^{22}$ = +67.19° (c. 1.475, $CHCl_3$); IR ($CHCl_3$, cast): 3400 (O-H), 1718 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (m, 2H, phenyl *ortho*), 7.60 (m, 1H, phenyl *para*), 7.47 (m, 2H, phenyl *meta*), 5.35 (dd, *J* = 10, 4 Hz, 1H, -C**H**(OBz)-), 5.34 (d, *J* = 2 Hz, 1H, -OC**H**(OH)-), 4.16 (dd, *J* = 11, 3 Hz, 1H, -C**H**HO-), 3.33 (d, *J* = 11 Hz, 1H, -CH**H**O-), 2.49 (br d, *J* = 3 Hz, 1H), 2.21 (s, 3H, C**H**$_3$CO-), 1.04 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)CH_2O-), 0.98 (d, *J* = 7 Hz, 3H, -CH(C**H**$_3$)-); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 206 (p), 166 (p), 133 (a), 130 (a), 129 (p), 128 (a), 92 (a),

78 (a), 66 (p), 42 (a), 41 (a), 37 (a), 36 (a), 35 (p), 33 (a), 30 (p), 29 (p), 27 (a), 21 (a), 12 (a); MS m/z (M^+) for $C_{22}H_{30}O_5$: calcd. 374.2094, found 374.2112.

(1S,2R,5S,6S,9R,12R)-10-Acetyl-10-benzoyloxy-2,6-dimethyl-8-oxatricyclo[7.2.1.0^{5,12}]dodecane (202)



202

A solution of *p*-toluenesulfonic acid monohydrate (22 mg, 0.116 mmol) in xylene (15 mL) was heated under reflux under an argon atmosphere with a Dean-Stark trap containing 4 Å molecular sieves for 1 hour. At the end of this time, xylene (*ca.* 10 mL) was distilled off and a solution of acetal **201** (4.3 mg, 0.0111 mmol) in xylene (6 mL) was then added. After refluxing for 2 hours, the solution was cooled and diluted with benzene. The resulting solution was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried, concentrated, and purified by flash chromatography (15% ether in skelly B) to give a colorless oil **202** (2.2 mg, 56% yield): IR ($CHCl_3$, cast): 1721 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (m, 2H, phenyl *ortho*), 7.59 (m, 1H, phenyl *para*), 7.48 (m, 2H, phenyl *meta*), 3.85 (dd, J = 11.5, 1 Hz, 1H, -C**H**HO-), 3.67 (dd, J = 11.5, 2.5 Hz, 1H, -OC**H**C($COCH_3$)(OBz)-), 3.65 (d, J = 11.5 Hz, 1H, -CH**H**O-), 2.74 (dd, J = 15, 10.5 Hz, 1H, -C**H**HC($COCH_3$)(OBz)-), 2.15 (s, 3H, C**H**$_3$CO-), 1.92 (dd, J = 15, 7.5 Hz, 1H, -CH**H**C($COCH_3$)(OBz)-), 0.88

(d, J = 7 Hz, 3H, -CH(C**H**$_3$)CH$_2$O-), 0.85 (d, J = 6.5 Hz, 1H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{22}H_{28}O_4$: calcd. 356.1988, found 356.1999.

Dehydration and Oxidation of Hemiacetal 200:

Dehydration without diisopropylethylamine and oxidation with *m*-chloroperoxybenzoic acid: Phosphorus oxychloride (0.18 mL, 1.896 mmol) was added to a solution of hemiacetal **200** (71 mg, 0.190 mmol) in pyridine (5 mL) at 0°C and the resulting solution was stirred at room temperature under an argon atmosphere for 4.5 hours. The solution was then diluted with dichloromethane and poured into ice-saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried, concentrated, and dissolved in dry dichloromethane (5 mL).

To the dichloromethane solution at 0°C was added *m*-chloroperoxybenzoic acid (70%, 0.14 g, 0.569 mmol) and the resulting solution was stirred at 0°C under an argon atmosphere for 30 minutes. The solution was then made basic with saturated aqueous sodium bicarbonate solution. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (10 mL). The combined dichloromethane layers were washed with saturated aqueous sodium chloride solution, dried, concentrated, and subjected to flash chromatography (20-40% ether in skelly B) to give compound **199** (10 mg, 14% yield) as a colorless oil. Continued elution gave an aldehyde **203** (8 mg, 11% yield) as a colorless oil, followed by a white solid **204** (17 mg, 6% yield).

Dehydration in the presence of diisopropylethylamine and oxidation with *m*-chloroperoxybenzoic acid: Phosphorus oxychloride

(7.5 mL, 0.08 mmol) was added to a solution of hemiacetal **200** (3.0 mg, 0.008 mmol) and diisopropylethylamine (14 μL, 0.08 mmol) in pyridine (0.5 mL) at 0°C and the resulting solution was stirred at room temperature under an argon atmosphere for 6 hours. The reaction was worked up as before to give a green oil that was dissolved in dry dichloromethane (0.5 mL).

To the dichloromethane solution at 0°C was added *m*-chloroperoxybenzoic acid (70%, 6 mg, 0.024 mmol) and the resulting solution was stirred at 0°C under an argon atmosphere for 30 minutes. The reaction was worked up as before to give the crude product, which was subjected to flash chromatography (20-50% ether in skelly B) to give compound **199** (0.35 mg, 12% yield) as a colorless oil. Continued elution gave compound **204** (1.1 mg, 4% yield), followed by an inseparable mixture of hemiacetal **200** and its C-5 epimer (0.9 mg, 30% recovery).

Dehydration in the presence of diisopropylethylamine and oxidation with magnesium monoperoxyphthalate hexahydrate: Phosphorus oxychloride (7.2 mL, 0.0774 mmol) was added to a solution of hemiacetal **200** (2.9 mg, 0.00774 mmol) and diisopropylethylamine (13.5 μL, 0.0774 mmol) in pyridine (0.5 mL) at 0°C and the resulting solution was stirred at room temperature under an argon atmosphere for 5 hours. The reaction was worked up as before to give a green oil that was dissolved in dry dimethylformamide (0.5 mL).

To the dimethylformamide solution was added magnesium monoperoxyphthalate hexahydrate (80%, 10 mg, 0.0155 mmol) and the resulting solution was stirred at room temperature under an argon atmosphere for 1 hour. The solution was then concentrated and dissolved in dichloromethane. The resulting solution was washed with water, dried, concentrated, and subjected to flash chromatography (40% ether in skelly B) to give compound **205** (1.1 mg, 35% yield) as a colorless oil. Continued elution gave an inseparable mixture of starting hemiacetal **200** and its C-5 epimer (1.5 mg, 52% recovery).

Dehydration in the presence of diisopropylethylamine and oxidation with benzoyl peroxide and hexamethyldisilazane: Phosphorus oxychloride (7.2 mL, 0.0774 mmol) was added to a solution of hemiacetal **200** (2.9 mg, 0.00774 mmol) and diisopropylethylamine (13.5 μL, 0.0774 mmol) in pyridine (0.5 mL) at 0°C and the resulting solution was stirred at room temperature under an argon atmosphere for 5 hours. The reaction was worked up as before to give a green oil that was dissolved in dry dichloromethane (0.7 mL).

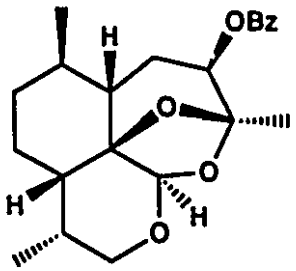
The dichloromethane solution was added to a solution of benzoyl peroxide (9.4 mg, 0.0387 mmol) and hexamethyldisilazane (8.2 μL, 0.0387 mmol) in dry dichloromethane (0.3 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 4 days. At the end of this time, the solution was washed with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium sulfite solution. The resulting solution was dried, concentrated, and subjected to flash chromatography (20-50% ether in skelly B) to give compound **206** (0.6 mg, 23% yield based on consumed starting hemiacetal). Continued elution gave the starting hemiacetal **200** (0.8 mg, 28% recovery).

Dehydration in the presence of diisopropylethylamine and oxidation with trifluoroperoxyacetic acid: Phosphorus oxychloride (0.14 mL, 1.549 mmol) was added to a solution of hemiacetal **200** (58 mg, 0.155 mmol) and diisopropylethylamine (0.27 mL, 1.549 mmol) in pyridine (5 mL) at 0°C and the resulting solution was stirred at room temperature under an argon atmosphere for 4.5 hours. The solution was then diluted with dichloromethane and poured into ice-saturated aqueous sodium bicarbonate solution (70 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried, and concentrated to give a crude enol ether as a brown oil.

Trifluoroacetic anhydride (0.22 mL, 1.549 mmol) was added dropwise to a solution of hydrogen peroxide (90%, 0.06 mL, 1.549 mmol) in dry dichloromethane (3 mL) at 0°C. After stirring at room temperature under an argon atmosphere for 30 minutes, the solution was added to a solution of the above crude enol ether in dry dichloromethane (2 mL) at 0°C and the resulting solution was stirred at 0°C under an argon atmosphere for 8.5 hours. The solution was then made basic with saturated aqueous sodium bicarbonate solution. The dichloromethane layer was separated, washed with saturated aqueous sodium sulfite solution, dried, concentrated, and subjected to flash chromatography (20-50% ether in skelly B) to give compound **207** (9.7 mg, 17% yield) as a yellowish oil. Continued elution gave compound **199** (19.4 mg, 33% yield), followed by an inseparable mixture of starting hemiacetal **200** and its C-5 epimer (4.1 mg, 7% recovery).

Compounds 199-207 showed the following spectral data:

(1R,2R,4S,5R,8S,9S,12R,13R)-2-Benzoyloxy-1,5,9-trimethyl-11,14,15-trioxatetracyclo[10.2.1.$0^{4,13}$.$0^{8,13}$]pentadecane (199)

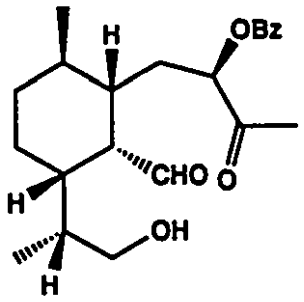


199

mp 133-135°C; IR ($CHCl_3$, cast): 1721 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (br d, J = 7.5 Hz, 2H, phenyl *ortho*), 7.58 (br t, J = 7 Hz, 1H, phenyl *para*), 7.46 (br t, J = 7.5 Hz, 2H, phenyl *meta*), 5.27 (s,

1H, -OC**H**(O-)-), 4.97 (br d, *J* = 4 Hz, 1H, -C**H**(OBz)-), 3.93 (dd, *J* = 11.5, 7 Hz, 1H, -C**H**HO-), 3.35 (dd, *J* = 11.5, 5 Hz, 1H, -CH**H**O-), 2.36 (m, 1H, -(CH_3)C**H**CH_2O-), 2.02 (m, 2H), 1.85-1.66 (m, 3H), 1.50 (m, 1H), 1.30 (m, 2H), 1.25 (s, 3H, -OC(C**H**$_3$)(O-)-), 1.05 (m, 1H), 0.94 (d, *J* = 7 Hz, 3H, -CH(C**H**$_3$)CH_2O-), 0.86 (d, *J* = 6.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - PhCOO) for $C_{15}H_{23}O_3$: calcd. 251.1648, found 251.1623.

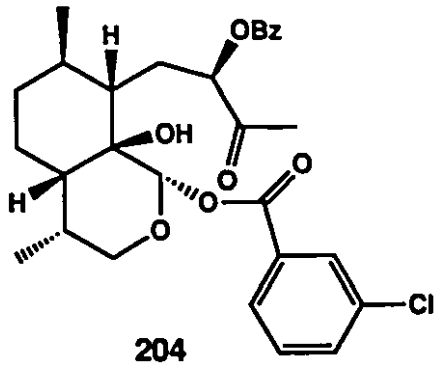
(1R,2S,3S,4S)-2-((R)-2-Benzoyloxy-3-oxobutyl)-3-formyl-4-((S)-2-hydroxy-1-methylethyl)-1-methylcyclohexane (203)



203

IR ($CHCl_3$, cast): 3400 (O-H), 1721 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 9.45 (d, *J* = 6 Hz, 1H, -C**H**O), 8.07 (m, 2H, phenyl *ortho*), 7.62 (m, 1H, phenyl *para*), 7.49 (m, 2H, phenyl *meta*), 5.30 (dd, *J* = 11, 2.5 Hz, 1H, -C**H**(OBz)-), 3.50 (dd, *J* = 11, 5.5 Hz, 1H, -C**H**HOH), 3.27 (dd, *J* = 11, 8.5 Hz, 1H, -CH**H**OH), 2.20 (m, 1H, -C**H**CHO), 2.18 (s, 3H, C**H**$_3$CO-), 1.97 (ddd, *J* = 16, 11, 3.Hz, 1H), 1.78 (m, 6H), 1.47 (ddd, *J* = 11, 5.5, 2.5 Hz, 1H), 1.37 (m, 1H), 1.25 (br s, 1H, -O**H**), 1.13 (d, *J* = 6.5 Hz, 3H, -CH(C**H**$_3$)CH_2O-), 1.09 (dd, *J* = 9, 2.5 Hz, 1H), 1.05 (d, *J* = 7 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - OH) for $C_{22}H_{29}O_4$: calcd. 357.2067, found 357.2061.

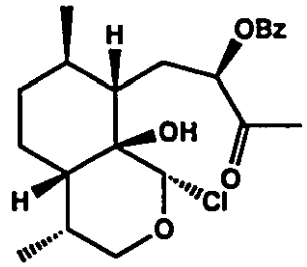
(1R,2S,5S,6S,9R,10S)-10-((R)-2-Benzoyloxy-3-oxobutyl)-2-(3-chlorobenzoyloxy)-5,9-dimethyl-3-oxabicyclo[4.4.0]decan-1-ol (204)



204

IR ($CHCl_3$, cast): 3450 (O-H), 1721 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (m, 2H, -COPh *ortho*), 8.02 (dd, *J* = 2, 2 Hz, 1H, -CO(Cl-Ph) **H**-2), 7.94 (br d, *J* = 8 Hz, 1H, -CO(Cl-Ph) *para*), 7.61 (m, 1H, -COPh *para*), 7.48 (m, 3H, -COPh *meta*, -CO(Cl-Ph) **H**-6), 7.34 (dd, *J* = 7, 7 Hz, 1H, -CO(Cl-Ph) *meta*), 6.29 (s, 1H, -OC**H**(O-)-), 5.25 (dd, *J* = 11, 3.5 Hz, 1H, -C**H**(OBz)-), 3.76 (dd, *J* = 11.5, 5 Hz, 1H, -C**H**HO-), 3.62 (dd, *J* = 11.5, 11.5 Hz, 1H, -CH**H**O-), 3.03 (s, 1H, -O**H**), 2.74 (ddd, *J* = 15, 10.5, 2.5 Hz, 1H), 2.58 (m, 1H), 2.11 (s, 3H, C**H**$_3$CO-), 1.03 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)CH_2O-), 0.81 (d, *J* = 6.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - PhCOOH - ClPhCOOH) for $C_{15}H_{22}O_3$: calcd. 250.1570, found 250.1578.

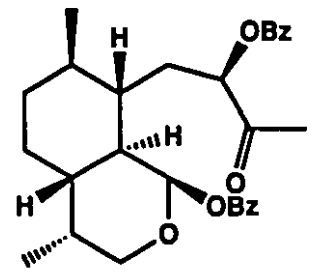
(1R,2S,5S,6S,9R,10S)-10-((R)-2-Benzoyloxy-3-oxobutyl)-2-chloro-5,9-dimethyl-3-oxabicyclo[4.4.0]decan-1-ol (205)



205

IR ($CHCl_3$, cast): 3400 (O-H), 1736 (C=O, ester), 1720 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (m, 2H, phenyl *ortho*), 7.61 (m, 1H, phenyl *para*), 7.48 (m, 2H, phenyl *meta*), 6.15 (s, 1H, -OC**H**Cl-), 5.43 (dd, J = 11.5, 2.5 Hz, 1H, -C**H**(OBz)-), 3.57 (dd, J = 11, 11 Hz, 1H, -C**H**HO-), 3.53 (dd, J = 11, 5 Hz, 1H, -CH**H**O-), 2.82 (m, 1H), 2.35 (dd, J = 13, 11.5 Hz, 1H), 2.22 (s, 3H, C**H**$_3$CO-), 1.10 (d, J = 6.5 Hz, 3H, -CH(C**H**$_3$)CH_2O-), 0.82 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+ - OH - Cl) for $C_{22}H_{28}O_4$: calcd. 356.1988, found 356.1978.

(1S,2S,5R,6R,7S,8R)-5-Benzoyloxy-7-((R)-2-benzoyloxy-3-oxobutyl)-2,8-dimethyl-4-oxabicyclo[4.4.0]decane (206)

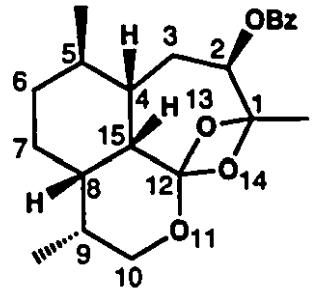


206

IR ($CHCl_3$, cast): 1732 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.17, 8.02 (2 × m, 2 × 2H, 2 × phenyl *ortho*), 7.62 (m, 2H, 2 × phenyl *para*), 7.50 (m, 4H, 2 × phenyl *meta*), 6.43 (d, J = 1 Hz, 1H, -OC**H**(OBz)-),

5.38 (dd, J = 11.5, 2.5 Hz, 1H, -C**H**(OBz)-), 3.65 (dd, J = 11.5, 11.5 Hz, 1H, -C**H**HO-), 3.54 (dd, J = 11.5, 4.5 Hz, 1H, -CH**H**O-), 2.90 (m, 1H), 2.46 (dd, J = 15, 11 Hz, 1H), 2.19 (s, 3H, C**H**$_3$CO-), 1.03 (d, J = 6 Hz, 3H, -CH(C**H**$_3$)CH$_2$O-), 0.85 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M$^+$ - PhCOOH - H) for $C_{22}H_{27}O_4$: calcd. 355.1910, found 355.1908.

(2R,4S,5R,8S,9S,15S)-2-Benzoyloxy-1,5,9-trimethyl-11,13,14-trioxatetracyclo[10.1.1.1^{4,12}.0^{8,15}]pentadecane (207)

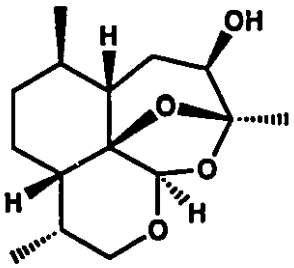


207

IR (CH_2Cl_2, cast): 1724 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (m, 2H, phenyl *ortho*), 7.60 (m, 1H, phenyl *para*), 7.48 (m, 2H, phenyl *meta*), 5.07 (dd, J = 4, 2.5 Hz, 1H, **H**-2), 4.47 (dd, J = 11, 4 Hz, 1H, **H**-10β), 4.07 (dd, J = 11, 8.5 Hz, 1H, **H**-10α), 2.52 (m, 1H, **H**-9), 2.03 (m, 2H, **H**-3α, **H**-3β), 1.93 (ddd, J = 13.5, 3.5, 3.5 Hz, 1H, **H**-8), 1.81 (dddd, J = 13.5, 3.5, 3.5, 3.5 Hz, 1H, **H**-7β), 1.75 (dddd, J = 13.5, 3.5, 3.5, 3.5 Hz, 1H, **H**-6α), 1.53 (s, 3H, 1-C**H**$_3$), 1.52 (m, 1H, **H**-4), 1.41 (m, 1H, **H**-5), 1.27 (ddd, J = 13.5, 13.5, 3.5 Hz, 1H, **H**-7α), 1.25 (br s, 1H, **H**-15), 1.10 (d, J = 7 Hz, 3H, 9-C**H**$_3$), 1.04 (m, 1H, **H**-6β), 0.85 (d, J = 7 Hz, 3H, 5-C**H**$_3$); ^{13}C NMR APT (100 MHz, $CDCl_3$): δ 165.60 (p, Ph**C**OO-), 133.35 (a, phenyl **C**-*p*), 129.90 (p, phenyl **C**-*i*), 129.80 (a, phenyl **C**-*o*), 128.51 (a, phenyl **C**-*m*), 111.19 (p, **C**-12), 106.37 (p, **C**-1), 70.18 (a, **C**-2), 67.28 (p, **C**-10), 45.06 (a, **C**-8), 43.97 (a, **C**-4), 35.50 (a, **C**-5), 34.26 (p, **C**-6), 30.25 (2 × a, **C**-9, **C**-15), 28.17 (p, **C**-3), 24.44 (p, **C**-7), 18.37 (a, 5-

CH_3), 17.64 (a, 1-CH_3), 16.87 (a, 9-CH_3); MS m/z (M^+ - PhCOOH) for $C_{15}H_{22}O_3$: calcd. 250.1570, found 250.1570.

(1R,2R,4S,5R,8S,9S,12R,13R)-1,5,9-Trimethyl-11,14,15-trioxatetracyclo[10.2.1.$0^{4,13}$.$0^{8,13}$]pentadecan-2-ol (211)

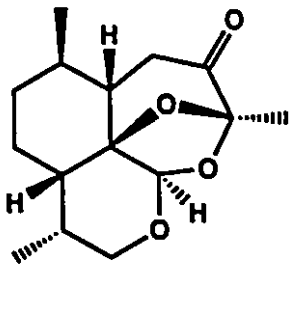


211

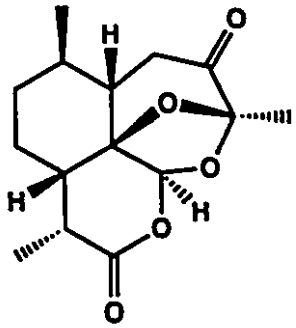
To a solution of benzoate **199** (5.8 mg, 0.0156 mmol) in methanol (0.5 mL) was added 1 N aqueous sodium hydroxide solution (0.5 mL) and the resulting solution was stirred at room temperature for 1 hour. The solution was then extracted with dichloromethane (3 × 5 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried, concentrated, and purified by flash chromatography (50% ether in skelly B) to give alcohol **211** (1.7 mg, 40% yield) as a colorless oil: IR ($CHCl_3$, cast): 3450 cm^{-1} (O-H); ^1H NMR (200 MHz, $CDCl_3$): δ 5.19 (s, 1H, -OC**H**(O-)-), 3.90 (dd, *J* = 11.5, 6.5 Hz, 1H, -C**H**HO-), 3.56 (m, 1H, -C**H**(OH)-), 3.33 (dd, *J* = 11.5, 5 Hz, 1H, -CH**H**O-), 2.31 (m, 1H, -(CH_3)C**H**CH_2O-), 1.55 (s, 3H, -OC(C**H**$_3$)(O-)-), 0.93 (d, *J* = 7 Hz, -CH(C**H**$_3$)CH_2O-), 0.88 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{15}H_{24}O_4$: calcd. 268.1675, found 268.1671.

(1R,4S,5R,8S,9S,12R,13R)-1,5,9-Trimethyl-11,14,15-trioxatetracyclo[10.2.1.$0^{4,13}$.$0^{8,13}$]pentadecan-2-one (212) and

(1R,4S,5R,8S,9R,12S,13R)-1,5,9-trimethyl-11,14,15-trioxatetracyclo[10.2.1.0^{4,13}.0^{8,13}]pentadecan-2,10-dione (213)



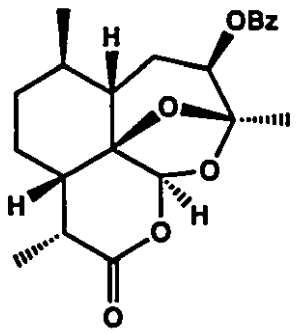
212



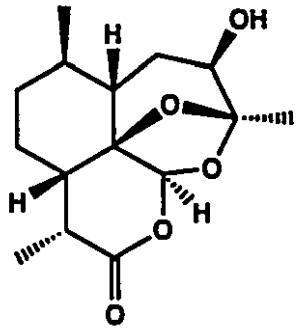
213

Sodium periodate (5 mg, 0.0224 mmol), followed by ruthenium(III) chloride (1 mg, 0.00447 mmol), was added to a solution of alcohol **211** (1.2 mg, 0.00447 mmol) in carbon tetrachloride (0.2 mL), acetonitrile (0.2 mL), and water (0.3 mL). The resulting solution was stirred at room temperature for 22 hours and then extracted with dichloromethane (3 × 5 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried, and concentrated. Ether (10 mL) was added and the resulting mixture was filtered to remove insoluble precipitates. Concentration and flash chromatography (80% ether in skelly B) gave an inseparable mixture of ketones **212** and **213** (1.1 mg) in a ratio of 3 : 2 (based on ^{1}H NMR integration): IR ($CHCl_3$, cast): 1738 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (s, 0.4H, -OC**H**(O-)-), 5.47 (s, 0.6H, -OC**H**(O-)-), 3.98 (dd, *J* = 12, 7 Hz, 0.6H, -C**H**HO-), 3.37 (dd, *J* = 12, 5 Hz, 0.6H, -CH**H**O-), 3.22 (qd, *J* = 7, 4.5 Hz, 0.4H, -(CH_3)C**H**COO-), 2.66 (dd, *J* = 16, 6 Hz, 0.6H, -C**H**HCO-), 2.57 (dd, *J* = 16, 6.5 Hz, 0.6H, -CH**H**CO-), 1.54 (br s, 3H, -OC(C**H**$_3$)(O-)-), 1.25 (d, *J* = 7 Hz, 1.2H, -CH(C**H**$_3$)COO-), 0.97 (d, *J* = 7 Hz, 1.8H, -CH(C**H**$_3$)CH_2O-), 0.95 (d, *J* = 6.5 Hz, 1.2H, -CH(C**H**$_3$)-), 0.90 (d, *J* = 6.5 Hz, 1.8H, -CH(C**H**$_3$)-); MS m/z [M$^+$ (**212**)] for $C_{15}H_{22}O_4$: calcd. 266.1519, found 266.1505, [M$^+$ (**213**) - CO] for $C_{14}H_{20}O_4$: calcd. 252.1362, found 252.1359.

(1S,4R,5S,8R,9S,11R,12R,14R)-11-Benzoyloxy-4,8,12-trimethyl-2,13,15-trioxatetracyclo[10.2.1.$0^{5,14}$.$0^{9,14}$]pentadecan-3-one (175) and (-)-qinghaosu IV (171)



175



171

Sodium periodate (244 mg, 1.141 mmol), followed by ruthenium(III) chloride (28 mg, 0.137 mmol), was added to a solution of benzoate **199** (17.0 mg, 0.0456 mmol) in carbon tetrachloride (0.6 mL), acetonitrile (0.6 mL), and water (0.9 mL). The resulting solution was stirred at room temperature for 22 hours and then extracted with dichloromethane (4 × 5 mL). The combined extracts were dried and concentrated. Ether (10 mL) was added and the resulting mixture was filtered to remove insoluble precipitates. Concentration and flash chromatography (30-60% ether in skelly B) gave lactone **175** (0.5 mg, 2.8% yield) as a white solid: IR ($CHCl_3$, cast): 1739 (C=O, lactone), 1724 cm^{-1} (C=O, ester); ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (m, 2H, phenyl *ortho*), 7.60 (m, 1H, phenyl *para*), 7.48 (m, 2H, phenyl *meta*), 5.72 (s, 1H, -OC**H**(O-)-), 5.02 (dd, J = 4, 2 Hz, 1H, -C**H**(OBz)-), 3.25 (qd, J = 7, 4.5 Hz, 1H, -(CH_3)C**H**COO-), 2.36 (m, 1H), 2.14 (m, 1H), 1.97 (dm, J = 13 Hz, 1H), 1.84 (dm, J = 13 Hz, 1H), 1.56 (s, 3H, -OC(C**H**$_3$)(O-)-), 1.23 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)COO-), 0.91 (d, J = 6.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{22}H_{26}O_6$: calcd. 386.1730, found 386.1705. Continued elution with chloroform gave qinghaosu IV (**171**) (1.1 mg, 8.5% yield) as a white solid: mp 189-190°C; IR ($CHCl_3$, cast): 3450 (O-H), 1745 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.64 (s, 1H, -OC**H**(O-)-), 3.63 (br d, J = 4 Hz, 1H, -C**H**(OH)-),

3.20 (qd, J = 7, 5 Hz, 1H, -(CH_3)C**H**COO-), 2.08 (ddd, J = 13, 4.5, 4.5 Hz, 1H), 2.00 (dddd, J = 9.5, 2, 2, 2 Hz, 1H), 1.94 (dddd, J = 13, 4.5, 4.5, 4.5 Hz, 1H), 1.82 (dddd, J= 12, 3, 3, 3 Hz, 1H), 1.58 (s, 3H, -OC(C**H**$_3$)(O-)-), 1.52 (m, 2H), 1.28 (m, 1H), 1.21 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)COO-), 1.13 (m, 1H), 1.00 (dd, J = 13.5, 3 Hz, 1H), 0.94 (d, J = 6.5 Hz, 3H, -CH(C**H**$_3$)-); MS m/z (M^+) for $C_{15}H_{22}O_5$: calcd. 282.1468, found 282.1455. [Lit.:[105] mp 190-192°C; IR: 3505, 1730 cm^{-1}; ^1H NMR: δ 5.63 (s, 1H), 3.63 (d, J = 7.2 Hz, 1H), 3.22 (m, 1H), 1.57 (s, 3H), 1.20 (d, J = 7.2 Hz, 3H), 0.94 (d, J = 5.4 Hz, 3H); MS m/z (M^+ + 1): 283.]

Chapter 4

Diels-Alder Reactions of 2-Carbalkoxy-2-cyclohepten-1-ones

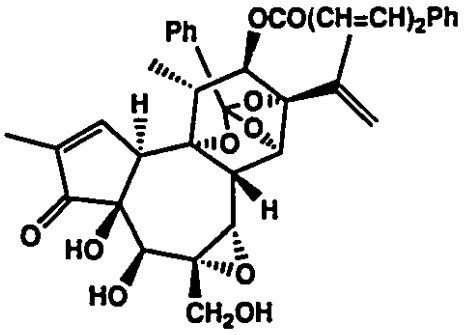
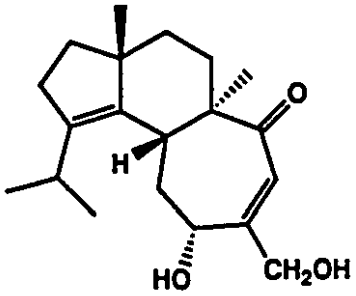
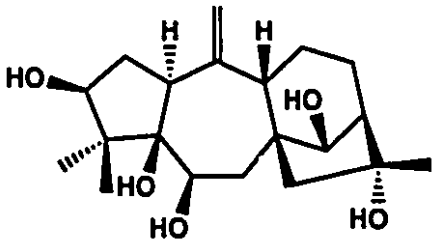
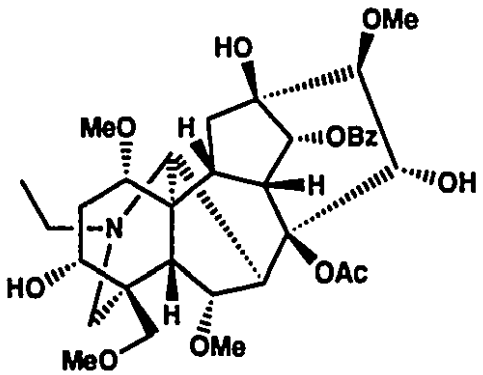
Introduction

Aided by increasingly effective techniques of separation and powerful spectroscopic methods, more and more polycyclic natural products, containing complex structures with a number of stereogenic centers, have been appearing at an overwhelming rate. Among them, the compounds possessing a six-membered ring fused with a seven-membered one are attractive in light of their structural complexity and interesting biological activities. Some examples are given in **Table 1**. Few successful synthetic approaches, however, have been directed toward them and their related compounds because the general synthetic tools available for the preparation of these systems bearing a seven-membered ring are limited in the literature.

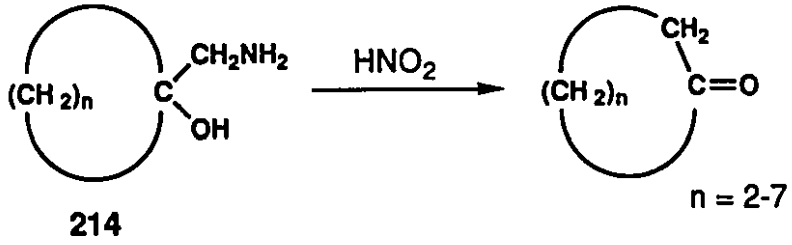
One of the sparse methods towards the synthesis of seven-membered rings is the carbocyclic ring expansion reaction. Several versatile procedures have been established for the homologation of six-membered ring to seven-membered ring. Many of these methods are particularly effective for the conversion of cyclohexanone to cycloheptanone with concomitant incorporation of specific functionalities.

The first method involves the application of diazoalkanes (diazomethane and diazoethane in particular). Taking diazoethane as an example, it has been noted[146-148] that the conversion of cyclohexanone into 2-methylcycloheptanone *via* ring expansion with ethereal diazoethane proceeds very slowly and in poor yield (38% yield after 4 days). The yields were improved, up to 95%, simply by the addition of ethanol into the reaction.[149] However, the necessity of using very active reagents like diazo compounds usually results in complex mixtures of mono- and polyhomologated products.

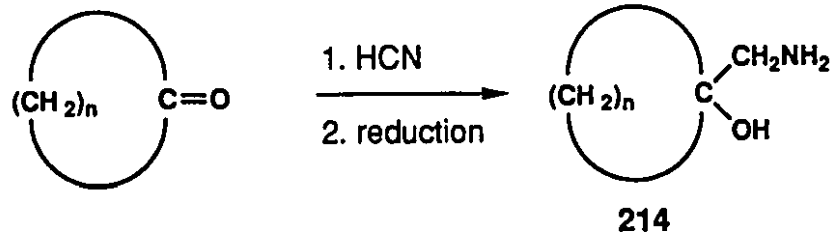
Table 1. Some polycyclic natural products possessing a six-membered ring fused with a seven-membered one

Example	Biological activity
 Mezerein [141]	Antileukemic activity [141]
 Cyathin-A_3 [142]	Antibiotic activity [143]
 Grayanotoxin-II [144]	Toxins [144]
 Aconitine [145]	Physiologically active constituent of several Chinese drugs [145]

One way to overcome this drawback is the utilization of the Tiffeneau-Demjanov ring expansion reaction. The Tiffeneau-Demjanov ring expansion,[150] as a highly useful extension of the Demjanov rearrangement, consists of the treatment of 1-aminomethylcycloalkanols **214** with nitrous acid, forming ring-enlarged ketones (**Eq. 1**). Since the amino alcohols **214** required for the expansion are usually produced by reduction of addition products of the ketones (**Eq. 2**), the Tiffeneau-Demjanov ring expansion can be used as the key step in the conversion of a cyclic ketone into its next higher ring homologue. All ring sizes from C_3 to C_8 have been successfully expanded but with a decrease in yield with increasing ring size. In addition, regioselectivity can not be easily predicted when this method is applied on an α-substituted or an α,β-unsaturated cyclic ketone.



214 **Eq. 1**

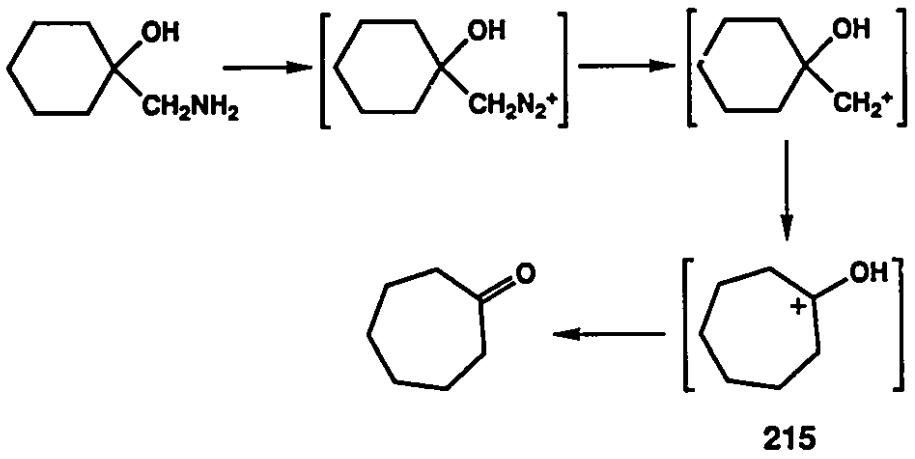


214 **Eq. 2**

The mechanism given in **Scheme 51** interprets why the Tiffeneau-Demjanov reaction favors ring expansion over other side reactions. First of all, there is no hydrogen atom in the position from which it could migrate in competition with a ring carbon atom. Moreover, the ion resulting from rearrangement bears its positive charge on a protonated carbonyl group (**215**), which has a much lower energy than a simple

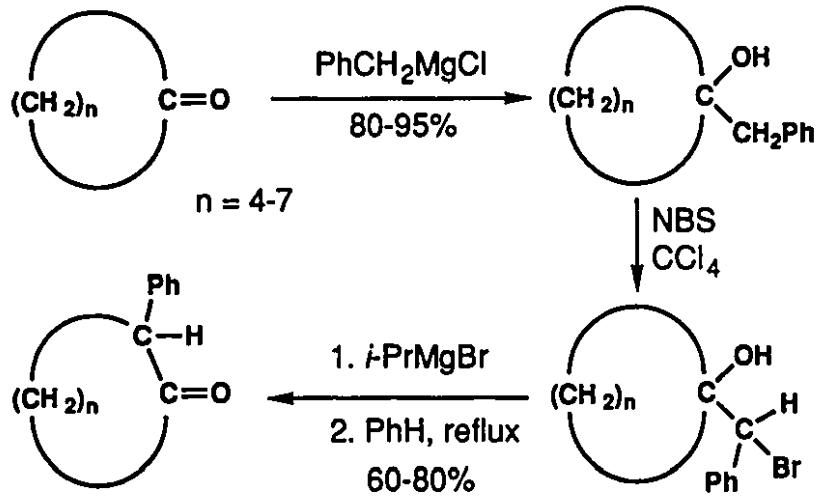
carbonium ion. Nevertheless, the required three-step operation (cyanohydrin formation, reduction to an amino alcohol, and nitrous acid deamination) and the unfavorable equilibria for the formation of cyanohydrins from ketones limit the applicability of the Tiffeneau-Demjanov procedure. In addition, the epoxide side product sometimes predominates.

Scheme 51



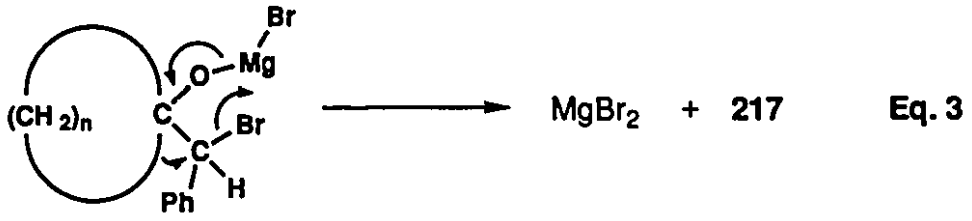
215

Scheme 52

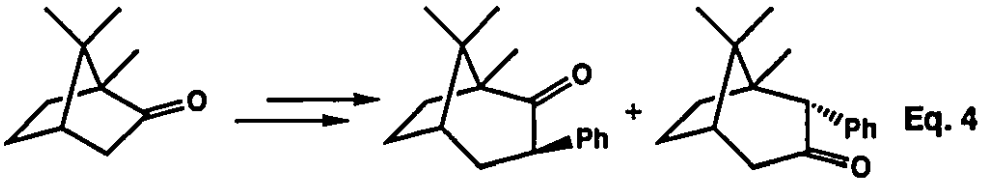


217 216

About three decades after the discovery the Tiffeneau-Demjanov ring expansion reaction, Sisti introduced[151,152] another ring enlargement strategy entailing the decomposition of the magnesium salts of appropriate halohydrins (**216**). As shown in **Scheme 52**, halohydrin **216**, easily prepared from a ketone by Grignard addition and bromination, is treated with isopropyl magnesium bromide and then in refluxing benzene to give the corresponding ring-enlarged 2-phenyl ketone **217**. The yield of the expansion of the halohydrin of cyclohexanone was ~70%. A concerted or an intimate ion pair mechanism is believed to be operating due to the effect of nonpolar solvents (**Eq. 3**). The rearrangement of the halohydrins of several unsymmetrical ketones was also studied.[153] As shown by the results summarized in **Eq. 4** and **Eq. 5**, electronic, steric, and conformational effects may all play a role in different cases.

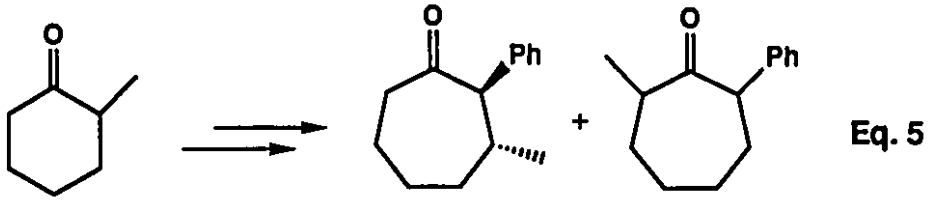


Eq. 3



52% 23%

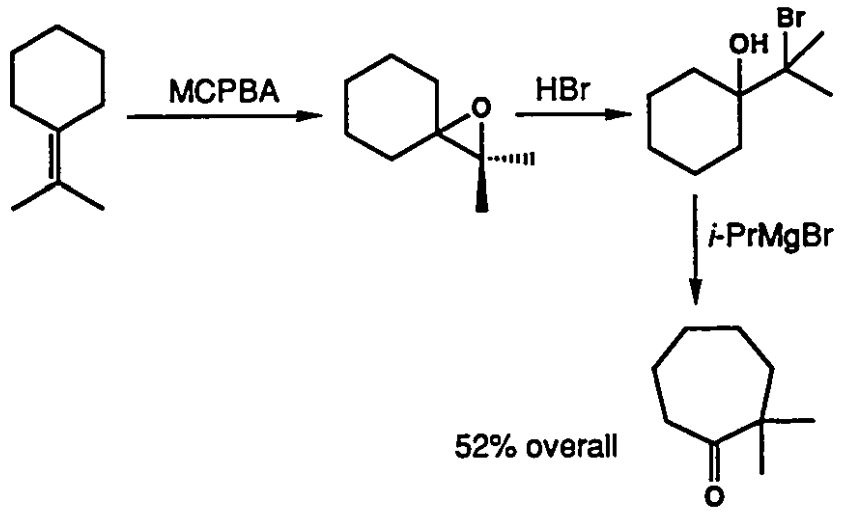
Eq. 4



32% 37%

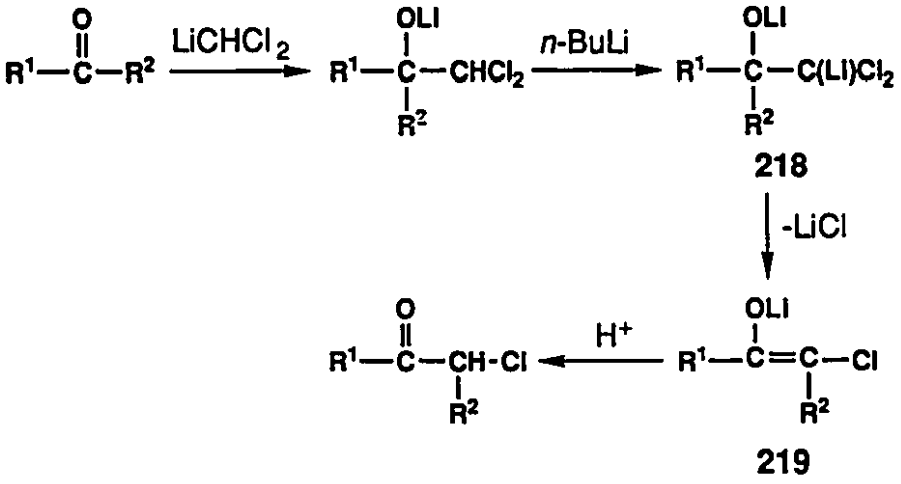
Eq. 5

Scheme 53

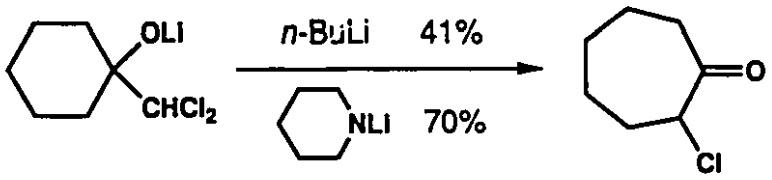


The enlarged cyclic ketones with substituent other than phenyl group were prepared by Sisti[154] using alternative approaches to synthesize halohydrins (**Scheme 53**). However, different methods for halohydrin formation had to be used for different systems, so that his effort was not proven to be particularly fruitful.

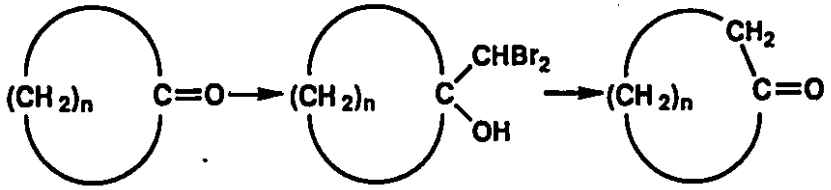
Scheme 54



This goal was achieved more efficiently some years later by two other groups independently based on the same concept.[155-157] As depicted in **Scheme 54**, the β-oxido carbenoid **218**, prepared readily from the corresponding ketone, can only undergo α-elimination and is than transposed effectively to an α-chloroenolate **219**, which gives the corresponding α-chloroketone upon workup. Application of different bases with cyclohexanone derivative may result in different yields as illustrated in **Eq. 6**. Unsubstituted cyclic ketones were also obtained by employing bromo-analogs and the yields were fairly good (**Eq. 7**). More importantly, this method, for the first time, displayed a high level of regioselectivity, especially for six-, twelve- and fourteen-membered rings. As demonstrated in **Scheme 55**, the regioselectivity is rationalized by steric effect.[157] This method has also been successfully applied to the regioselective ring enlargement of α,β-unsaturated cyclohexenone affording β,γ-unsaturated cycloheptenone in good yield.



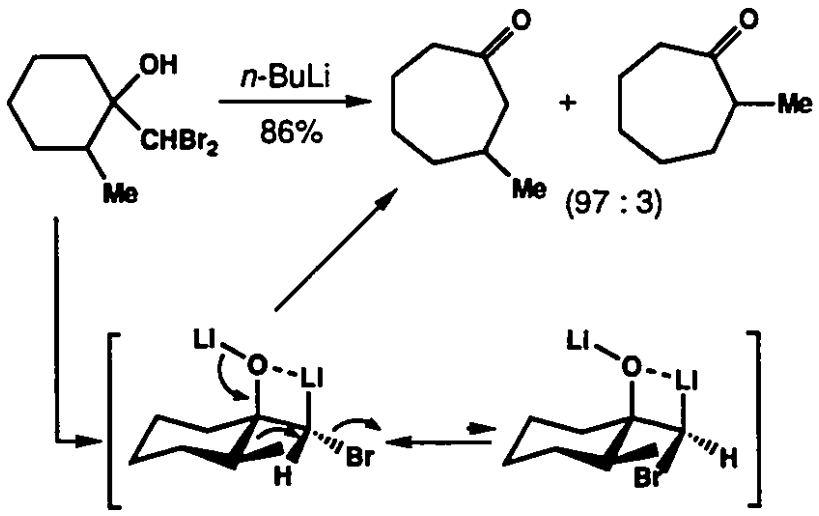
Eq. 6



Eq. 7

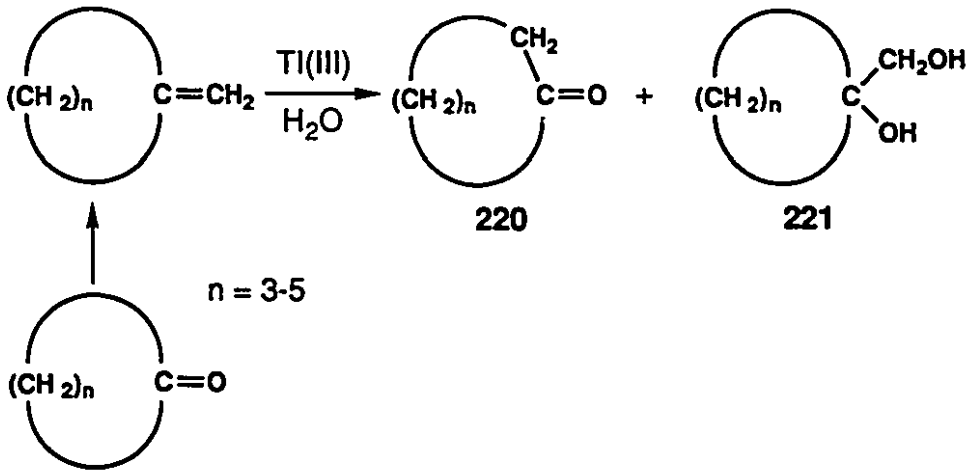
n = 4-7, 11

Scheme 55

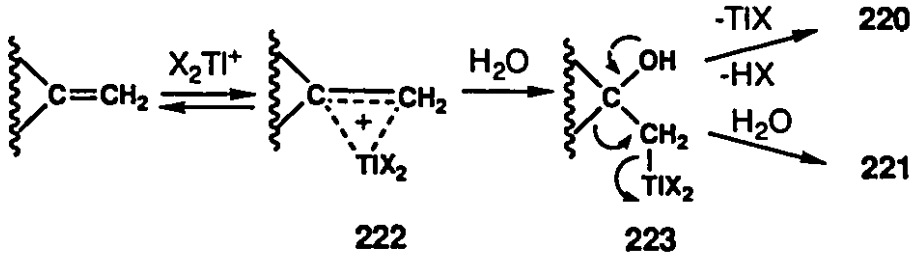


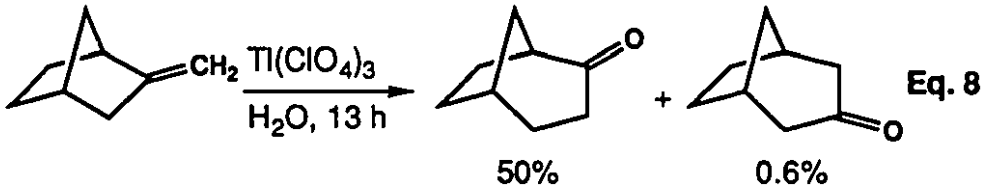
A common disadvantage of all the ring expansion methods discussed above is that too many steps are involved for a simple one-carbon ring enlargement of the cyclic ketone. A two-step homologation procedure was successfully explored based on the thallium(III) oxidation of exocyclic olefins (**Scheme 56**).[158] Since methylenecycloalkanes can be obtained readily from the corresponding cycloalkanones by the Wittig reaction, this process can serve as an alternative method for the ring enlargement of cyclic ketones. As outlined in **Scheme 57**, the mechanism generally involves the initial formation of a cyclic thallonium ion (**222**), followed by backside attack by water to give an intermediate **223** in which the thallium can function as a leaving group. Side product diol **221** is produced when nucleophilic displacement by water proceeds. This ring expansion method was found to be generally useful for cyclic systems in which a double bond is exocyclic to a four- or five-membered ring, but not to a six-membered ring. The only known example for six-membered ring expansion giving moderate yield is given in **Eq. 8**. This method was also reported to suffer from incomplete oxidation and the sensitivity of the ketone products towards further oxidation. As a consequence, it is deemed not to be a highly effective synthetic procedure.

Scheme 56



Scheme 57



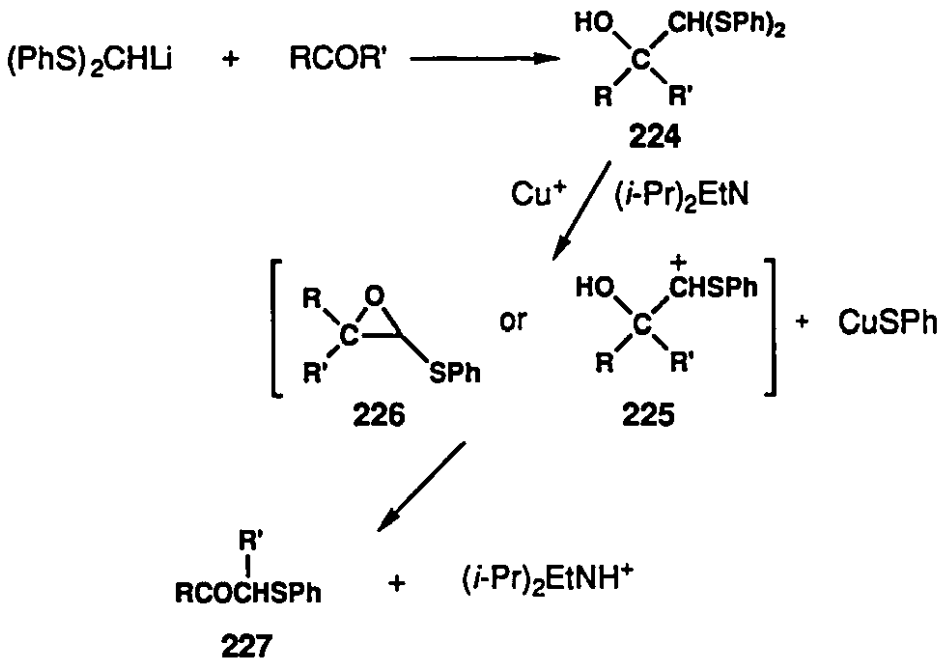


Eq. 8

The fifth main type of ring-expansion strategy deals with the rearrangement of the sulfur-stabilized intermediate. In 1975, Cohen's laboratory reported[159] a new expansion procedure based on the sequence outlined in **Scheme 58**. The hydroxydiphenylthioacetal **224**, obtained by addition of the lithio derivative of dithiophenoxymethane to

the ketone, reacts with cuprous trifluoromethanesulfonate in the presence of diisopropylethylamine to give the rearrangement product **227** in good yield, *via* either cation **225** or α-epoxy thioether **226**. As an example, applying the above ring homologation process to cyclohexanone, α-phenylthiocycloheptanone was obtained in 43% yield in two steps. As unsymmetrical cyclic ketones are concerned, the most highly substituted alkyl group migrates preferentially.

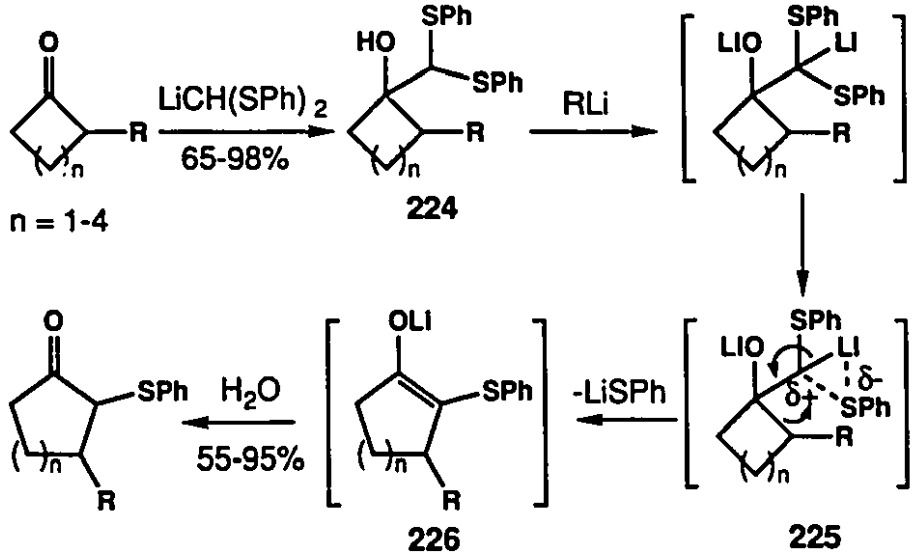
Scheme 58

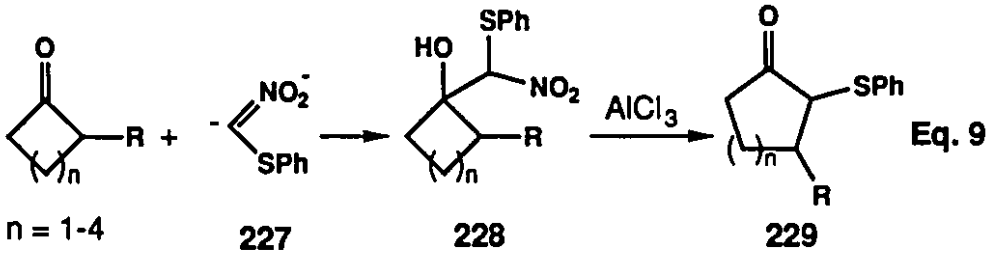


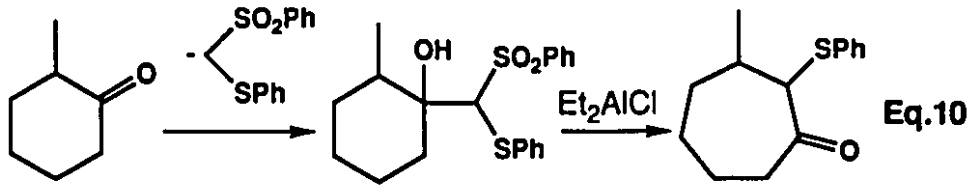
Twelve years later this method was further modified by the same research group[160] utilizing basic rather than acidic conditions to initiate the rearrangement of **224**. The mechanism is explained in **Scheme 59**. The hydroxydiphenylthioacetal **224** is deprotonated and then rearranged to the expanded enolate anion **226**, presumably through a carbenoid intermediate **225**. This procedure is superior to its predecessor in ease and generality. The regiochemical outcome is similar: the more substituted alkyl group migrates faster and a vinyl group migrates

preferentially over an alkyl group. Tris(methylthio)methyllithium ($(MeS)_3C^-Li^+$) has also been applied[161,162] to make the corresponding enlarged cyclic α,α-dimethylthioketone. However, the procedure was found to be ineffective for the homologation of cyclohexanone derivatives.

Scheme 59



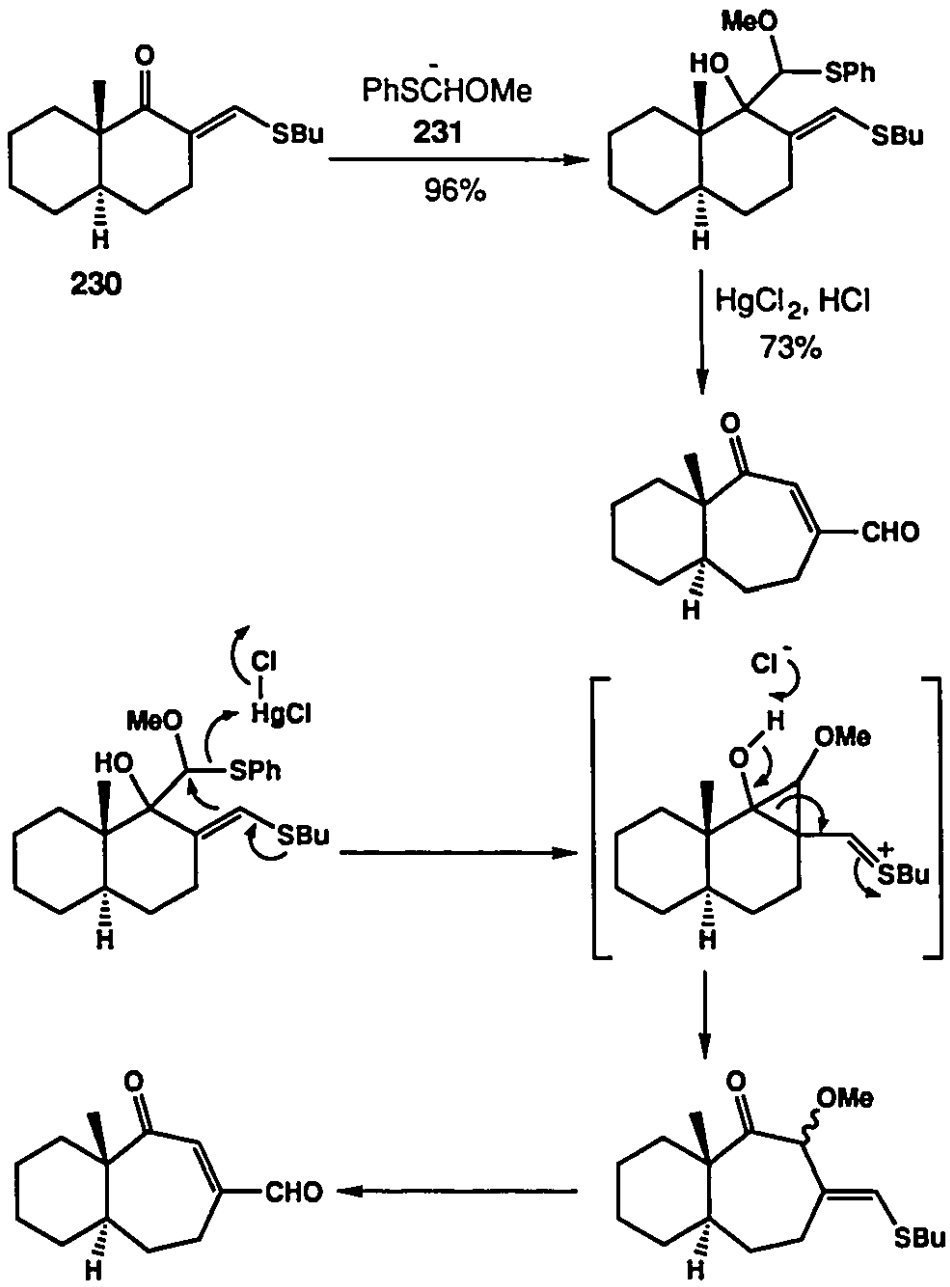


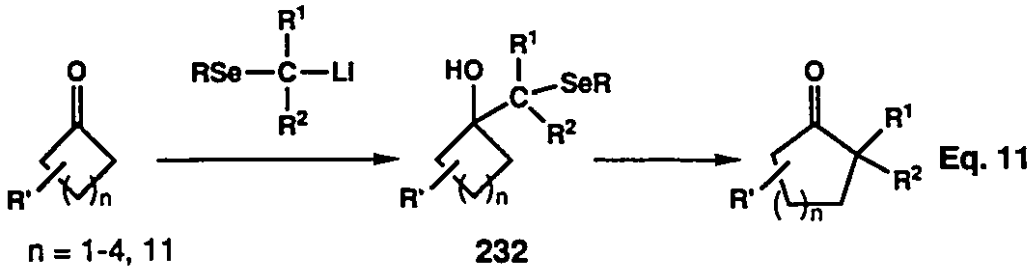


The use of other thio reagents to induce the ring expansion of cyclic ketone has also been carried out. The dianion of (phenylthio)nitromethane (**227**) is added to a ketone and the nitro compound **228** thus formed rearranges to give **229** with aluminum chloride (**Eq. 9**).[163] The overall yield of the expansion of cyclohexanone was 63%. Trost and Mikhail introduced[164] the sulfone functional group instead of the nitro group to accomplish the same purpose (**Eq. 10**). Guerrero and co-workers described[165] an expansion method to facilitate the preparation of 3-formyl-2-cyclohepten-1-ones, a class of compounds which would otherwise be difficult to prepare, by using the addition of methoxy(phenylthio)methyllithium (**231**) to non-enolizable cyclohexanones activated at the α position by a *n*-butylthiomethylene group (for example, **230**). A representative example is shown in **Scheme 60**. An anchimeric assistance of the *n*-butylthiomethylene to the departure of the phenylthio group was suggested for the facile transformation.

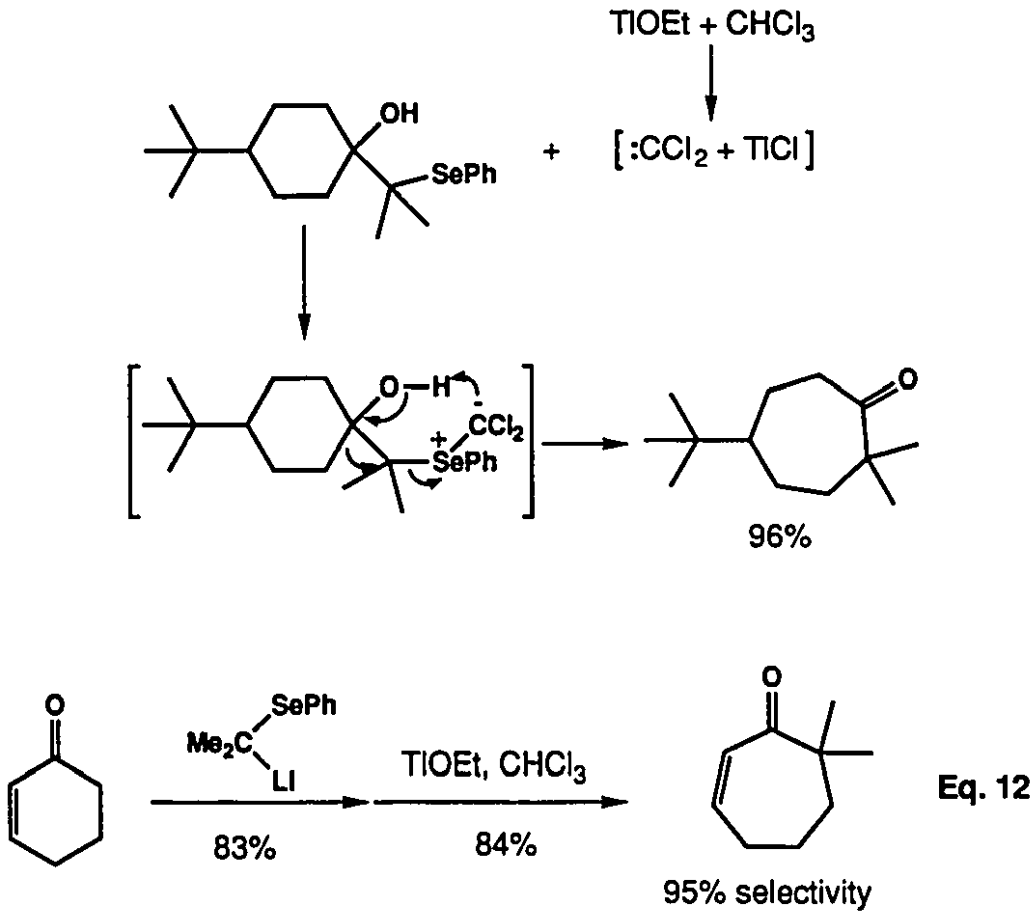
Replacing sulfur with selenium for this kind of ring expansion reactions was pioneered by Krief's group (**Eq. 11**).[166,167] They tried several metal salts under various conditions to increase the yield and the rate of the rearrangement of β-hydroxyselenides **232** and found that thallium ethoxide in chloroform is most suitable.[168] The requirement of chloroform as a solvent led them to believe that dichloro carbene, instead of thallium oxide, was responsible for the ring expansion. (**Scheme 61**). They further studied the regioselectivity of unsymmetrical ketones and reported[169] that the alkyl group migrates preferentially than the vinyl group, contrary to what was described in other related reactions (**Eq. 12**). Paquette and co-workers[170] evaluated the relative migratory abilities of the vinyl and the alkyl groups in a variety of structural contexts and concluded that the precise course of the ring expansion is dictated by a combination of electronic, steric, and conformational contributions. In some systems, vinyl migration can dominate. Regardless of the regiochemical outcome, the ring enlargement reaction involving selenium proceeds faster with better results than its sulfur analogues in general.

Scheme 60


O
SBu
H
230
PhSCHOMe
231
96%
MeO
HO
SPh
SBu
H
HgCl2, HCl
73%
O
CHO
H
Cl
HgCl
MeO
HO
SPh
SBu
H
Cl
H
O
OMe
+
SBu
H
O
OMe
SBu
H
O
CHO
H



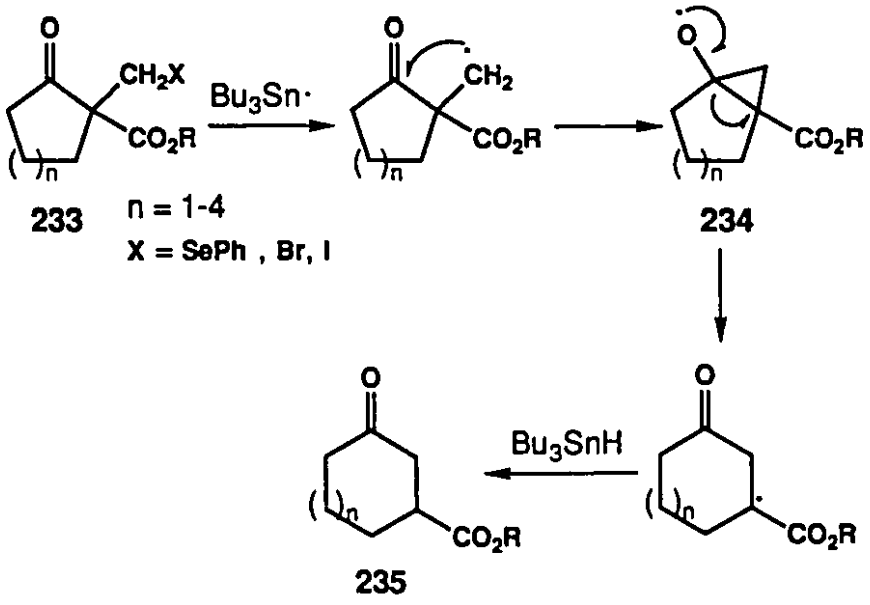
Scheme 61



As to the ring enlargement procedures discussed so far, all of them are based on the same type of mechanism: the carbonium or carbanion rearrangement. Considerable attention has been devoted to use a free radical rearrangement approach to provide a new route to the medium-

sized rings.[171,172] As described in **Scheme 62**, the suitable substrate **233**, readily prepared by the alkylation of a cyclic β-keto ester with halo(phenylseleno)methane or dihalomethane, is treated with tributyltin hydride in the presence of 2,2'-azobisisobutylnitrile to afford the corresponding γ-keto ester **235** *via* a cyclopropyloxy radical **234**. The ester functional group is crucial for the rearrangement. It facilitates the alkylation and activates the ketone toward the attack by the intermediate radical. Moreover, once the cyclopropane is formed, it provides the driving force for the ring cleavage. Generally, for ring expansion in the six-membered ring system, the bromo-substituted **233** proceeds better.

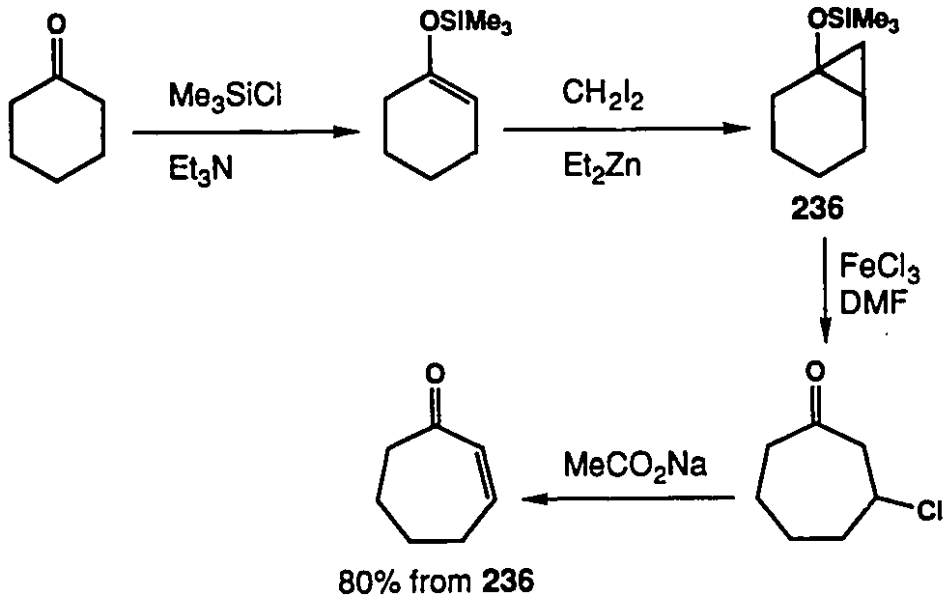
Scheme 62

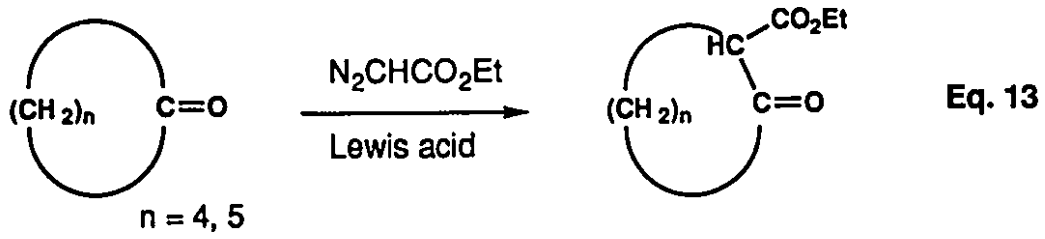


Scheme 63[173] shows a ring homologation plan that also involves the cleavage of the cyclopropane ring, but through a totally different route. The key step in the sequence is the iron(III) chloride induced cleavage of trimethylsilyloxycyclopropanes **236** that are prepared by the Simmons-Smith reaction of enol ethers. Although the mechanism of this step is not known with certainty, it is believed that an alkoxy radical is involved to initiate the cleavage of the cyclopropane ring. This cyclopropane

cleavage could also be promoted by a photo-induced single electron transfer process[174] but the yields were not satisfactory for five- and six-membered ring systems.

Scheme 63

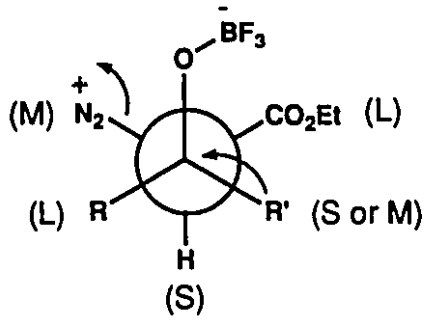




Eq. 13

The last ring expansion process discussed is the Lewis acid catalyzed ring expansion of cycloalkanones with ethyl diazoacetate (**Eq. 13**),[27-29,175] which is basically a variant of the diazoalkane method mentioned before. This method is very useful because it requires only one step to complete the conversion, generally in high yields, of a cycloalkanone to the enlarged homolog. The mechanistic study disclosed that the rate-

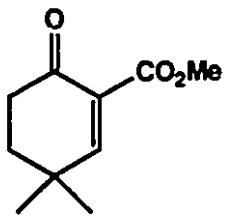
determining step involves the coordination between ketone and Lewis acid. As a result, the ring expansion product is protected from further homologation because its ketone carbonyl group is deactivated by the inductive effect of the carbethoxy group. Studies on the migratory aptitude indicated that, in general, the less substituted α-carbon migrates preferentially. The rationale behind this phenomenon is that the conformation of the resulting diazonium ion intermediate determines the products of the reaction. The favored conformation **237** should be the one minimizing gauche steric repulsions. From this conformation **237**, the preferred migration of the less bulky group (S or M) is predicted. This ring expansion procedure attracted our attention because the product, possessing simultaneously formed β-keto ester functionality, is highly suitable for elaboration to an activated dienophile for Diels-Alder reaction.



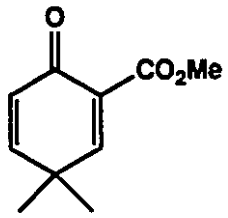
237

In theory, the Diels-Alder reaction of substituted cycloalkenones and substituted 1,3-butadiene is a versatile and facile method to assemble the basic skeleton of a variety of natural products containing polycyclic systems because of its high stereoselectivity and efficiency. Unfortunately, the thermal cycloaddition of dienes to cycloalkenones, such as cyclohexenone, is well known to proceed poorly even at elevated temperatures.[176-178] Over the last two decades, extensive efforts have been directed toward the improvement of the Diels-Alder reactivity of cycloalkenones, resulting in the development of two general solutions for

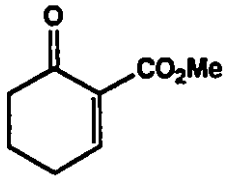
the enhancement of the dienophilicity.[179] One approach applies Lewis acid catalysis to increase the rate as well as the regio- and stereoselectivity of the addition. In the other approach, the rates and the yields are improved by placing an additional electron-withdrawing group on either the α- or the β-carbon of the dienophilic moiety as predicted by the Alder rule.[180,181]



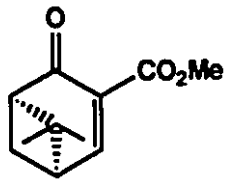
238



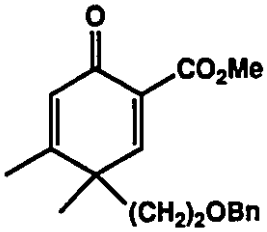
239



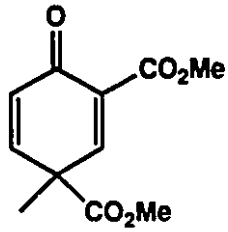
240



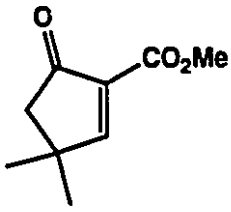
241



242



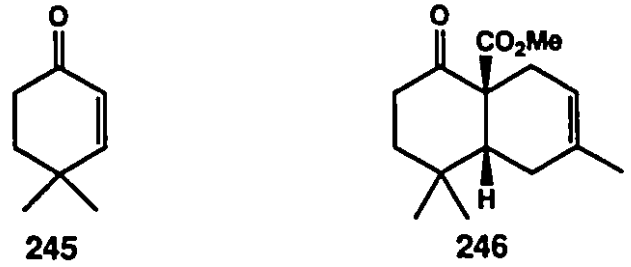
243



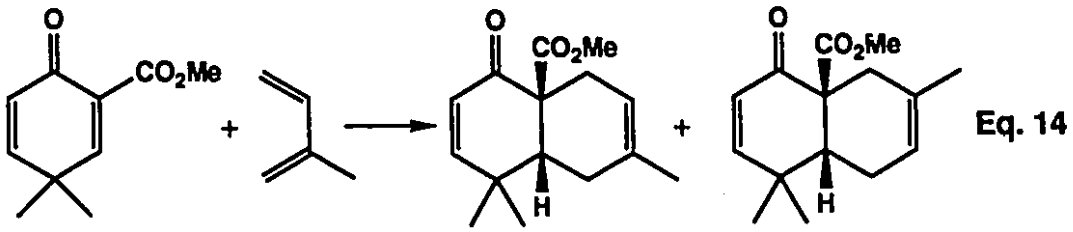
244

An extensive study of the Lewis acid catalyzed Diels-Alder reactions of 2-carbomethoxy-2-cycloalkenones **238-244** has been carried out in our laboratory. The outcomes of these additions, in terms of the stereochemistry and regiochemistry influenced by the unusual steric and electronic effects, are in general quite predictable. Their closely related enone **245** is a rather poor dienophile and the preliminary study

on its Diels-Alder reaction with isoprene and 1,3-butadiene using boron trifluoride etherate or aluminum chloride as a catalyst was unsuccessful.[182] Wenkert and co-workers[183] first made this reaction synthetically useful by adding the diene to the solution only after the appropriate complexation between **245** and aluminum chloride. Liu and co-workers[184] utilized an activated system **238** and discovered that the cycloaddition proceeded smoothly with isoprene in the presence of Lewis acid (such as tin(IV) chloride). This mild and fast reaction resulted in the *para*-addition adduct **246** exclusively in good yield.



245 **246**

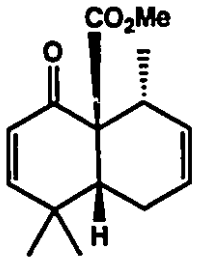


239 **247** **248** **Eq. 14**

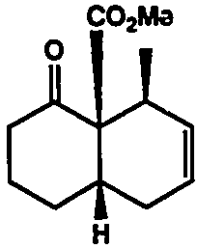
	$BF_3 \cdot OEt_2$	30 : 70
	$SnCl_4$	82 : 18

However, the study of the Diels-Alder reaction of dienone **239** with isoprene indicated that the regiochemical outcomes can be altered by using different Lewis acid catalysts.[185] As outlined in **Eq. 14**, the use of boron trifluoride etherate as a catalyst gave adducts **247** and **248** in a ratio of 30 : 70. On the contrary, tin(IV) chloride catalysis resulted in an 82 : 18 ratio of adducts **247** and **248**. This abnormal phenomena was

rationalized by different coordination capacities of different Lewis acids and a steric effect on the transition state. Addition of *trans*-piperylene to enone **239** gave rise to exclusively product **249** resulting from the transition state of keto-*endo* selectivity.

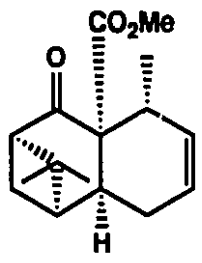


249

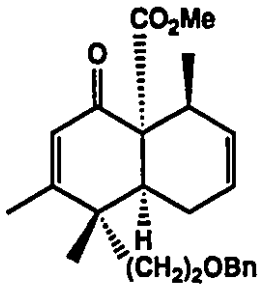


250

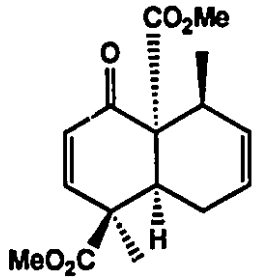
In both cases, the enone system is geminally disubstituted at the γ-position, blocking the facile enolization. The Diels-Alder characteristics of the enolizable analogue **240** was also studied.[186] It was found that the addition proceeded much faster but only in moderate yield and tin(IV) chloride gave better result among Lewis acids. Moreover, unlike **239**, addition of 1-substituted dienes to enone **240** favored the ester-*endo* addition product (such as **250**). This was realized as a combination of electronic and steric effects.



251



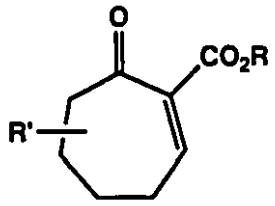
252



253

In addition to these facially symmetrical cyclohexenones, the Diels-Alder behaviors of the stereofacially differentiated cyclohexenones **241-243** have also been explored.[187,188] Zinc chloride catalyzed Diels-Alder reaction of **241** gave products (such as **251**) resulting from addition to the less-hindered face *via* the ester-*endo* transition state. On the other hand, the cycloaddition of **242** favored the addition to the less-hindered face but with the keto-*endo* transition state. The formation of **252** serves as an example. The facial selectivity of these two cases can be interpreted by steric effects. Interestingly, in the Diels-Alder reaction of enone **243**, *trans*-piperylene added to the ester face of **243** exclusively to afford adduct **253** in quantitative yield. This high degree of facial selectivity might be concluded from the different electron densities on both faces. The addition from the ester (electron poor) face was favored.

During the investigation on the Diels-Alder chemistry of 2-carbomethoxy-2-cyclohexen-1-ones, the behavior of their five-membered ring analogue **244** was also examined.[189] Basically, **244** is more reactive than its six-membered ring analogues and it undergos Diels-Alder reactions quite effectively even in the absence of Lewis acid catalyst. Nevertheless, tin(IV) chloride catalysis proved to be most effective in terms of yield and selectivity.

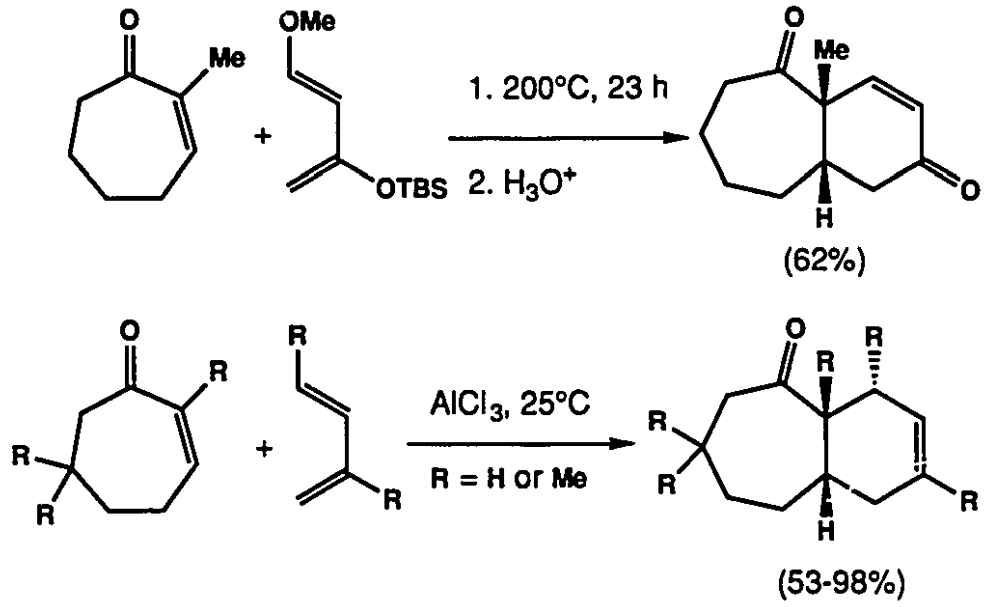


254

In continuation of our research in this area and in an attempt to find a facile synthetic approach towards the seven-membered ring-containing polycyclic natural products, such as the ones listed in **Table 1**, we became interested in the Diels-Alder reaction of various 2-carbalkoxy-2-cycloheptenones **254**. In spite of the apparent utility in this context and

the superior Diels-Alder reactivity of simple cycloheptenone, compared with cyclohexenone and cyclopentenone, there are only three examples of Diels-Alder reactions involving cycloheptenones in the literature (**Scheme 64**).[183,190-192] We have undertaken a systematic study on the Diels-Alder characteristics of several 2-carbalkoxy-2-cycloheptenones **254**. Preliminary results are described in this chapter.

Scheme 64



Results and Discussion

A general two-step approach has been developed for the preparation of various 2-carbalkoxy-2-cycloheptenones required for the present studies. This process begins with a Lewis acid, boron trifluoride etherate, catalyzed ring expansion of cyclohexanone with ethyl diazoacetate.[27-29] This reaction, which is highly reliable, allows the direct incorporation of the desired β-keto ester system. In addition, it is known to proceed with a high degree of regioselectivity with preferential migration of the less substituted α carbon, in case of unsymmetrically substituted cyclohexanones. Moreover, with symmetrical cyclohexanones such as 4,4-dimethylcyclohexanone, a single ring expansion product is expected.

For the incorporation of the conjugated double bond, the phenylselenenylation and oxidative elimination process was chosen due to its reliability.[193,194] In effect, this process has been successfully applied in many occasions for the transformation of β-keto ester systems to the corresponding α-carbalkoxy-α,β-unsaturated ketones.[187] With the exception of one compound, all of the 2-carbalkoxy-2-cycloheptenones used in this investigation were effectively prepared from the corresponding cyclohexanones by a combination of ring expansion, phenylselenenylation and oxidative elimination.

I. Preparations of 2-carbalkoxy-2-cycloheptenones:

All the 2-carbethoxycycloheptanones and 2-carbethoxy-2-cycloheptenones prepared according to the preceding procedures (except for **265** in entry 5) are listed in **Table 2**.

Table 2. Preparations of cycloheptanones and 2-cycloheptenones

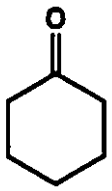
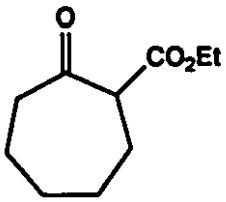
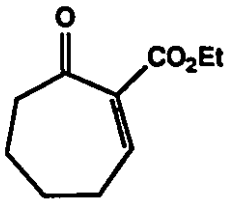
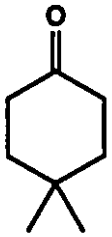
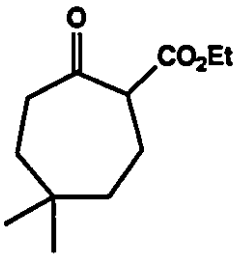
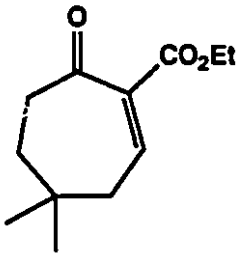
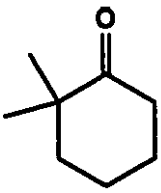
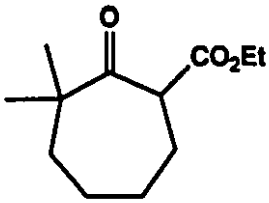
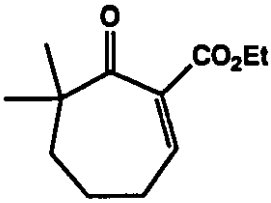
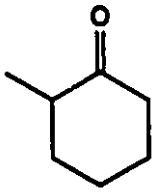
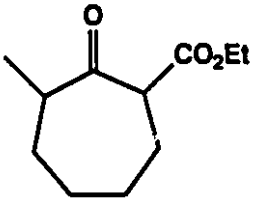
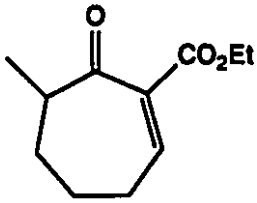
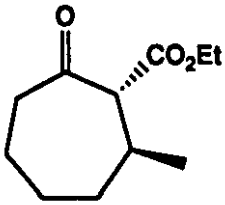
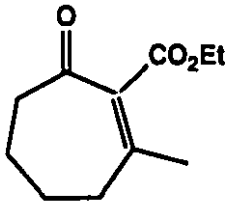
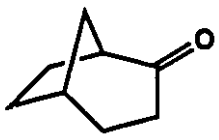
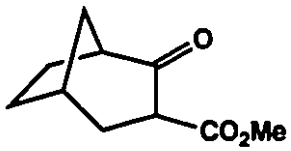
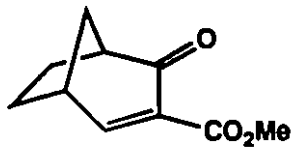
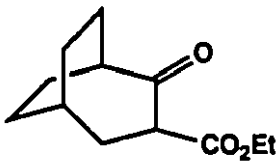
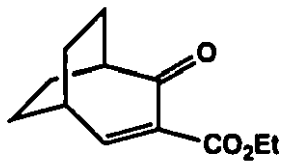
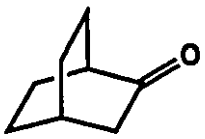
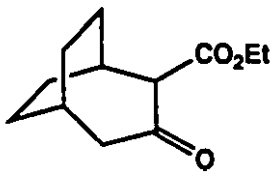
Entry	Starting material	Product	Time Yield	Product	Time Yield
1		 **255**	1 h 74%	 **256**	14.5 h 73%
2		 **257**	1 h 86%	 **258**	17 h 90%
3		 **259**	96 h 87%	 **260**	163 h 15%
4		 **261**	23 h 84%	 **263**	89 h 71%
		 **262**	9%	 **264**	3%

Table 2. Continued

Entry	Starting material	Product	Time Yield	Product	Time Yield
5		 **265**	2.5 h 95%	 **266**	25 h 31%
		 **268**	2 h 67%	 **270**	13 h 70%
6	 **267**	 **269**	25%	–	–

Ring expansion of cyclohexanone (entry 1) with ethyl diazoacetate and boron trifluoride etherate in ether at room temperature for 1 hour resulted in enlarged keto ester **255** in 74% yield. Compound **255** was shown to exist as a mixture of its keto form and enol form in a ratio of 3 : 1 by the ^{1}H NMR spectrum, which displayed the enolic proton at δ 12.75 as a singlet and the proton flanked by the carbonyl groups at δ 3.52 as a doublet of doublets (J = 10.5, J' = 4 Hz). For the ester moiety, the methylene protons were shown at δ 4.18, while two sets of methyl triplets (J = 7 Hz) were displayed at δ 1.30 (enol) and 1.26 (keto). The infrared spectrum confirmed the keto and enol forms at 1742 (ester), 1707

(ketone), and 1638 cm^{-1} (enol ester). In the high resolution mass spectrum, a molecular ion peak at m/z 184.1101 was consistent with the molecular formula $C_{10}H_{16}O_3$.

In the next oxidative elimination reaction, a dichloromethane solution of **255** was added to a stirring dichloromethane solution of phenylselenenyl chloride and pyridine at 0°C and the resulting mixture was stirred at room temperature overnight. When the selenated intermediate was formed completely, 30% hydrogen peroxide was added successively until the solution turned colorless. The pale color meant that all the selenenyl compounds have been oxidized. The desired enone **256** was thus obtained in 73% yield. The infrared spectrum of **256** showed two carbonyl absorptions at 1725 (ester) and 1694 cm^{-1} (ketone). In its ^1H NMR spectrum, the notable vinylic proton was displayed as a triplet (J = 6 Hz) at δ 7.36. The α' methylene protons were shown at δ 2.68 as a triplet (J = 6.5 Hz), while the allylic methylene protons were displayed as a doublet of triplets ($J = J'$ = 6 Hz) at δ 2.49. For the ester portion, the methylene protons were shown as a quartet at δ 4.22, coupled to the triplet of the methyl group at δ 1.28 with a coupling constant of 7 Hz.

The ring expansion reaction of 4,4-dimethylcyclohexanone and the oxidative elimination of its resulting ring enlarged product behaved similarly as cyclohexanone, but the yields were better (entry 2). In the ring expansion reaction, **257** was obtained as a single product in 86% yield due to the symmetrical starting material. Keto ester **257** was shown to exist as a mixture of 95% keto form and 5% enol form based on the ^1H NMR spectrum. A characteristic singlet at δ 12.70 was assigned to the enolic proton of the enol form. On the other hand, the keto form was supported by a triplet (J = 7.5 Hz) at δ 3.51 corresponding to the α proton of two carbonyl groups. The methylene protons of the ester group were displayed at δ 4.19 and 4.17, each as a quartet (J = 7 Hz), coupled to the adjacent methyl group at δ 1.26 (t, J = 7 Hz). The α' methylene protons of the keto form were found at δ 2.64 (ddd, J = 16.5, J' = 10, J'' = 5.5 Hz) and 2.45 (ddd, J = 16.5, J' = 6.5, J'' = 4 Hz). Two methyl singlets at δ 0.98 and 0.93 were in agreement with the geminal methyl groups. The infrared spectrum confirmed the keto and enol forms at 1743 (ester),

1707 (ketone), and 1640 cm^{-1} (enol ester). In the high resolution mass spectrum of **257**, a molecular ion peak at m/z 212.1413 was observed, corresponding to the molecular formula $C_{12}H_{20}O_3$.

Enone **258** was prepared from **257** in 90% yield (entry 2). Unlike enone **256**, which existed as a single keto form, **258** with additional geminal dimethyl group at C-5 possessed both keto form and enol form in a ratio of 9 : 1. In the ^1H NMR spectrum, the enol form displayed its enolic proton and two vinylic protons at δ 13.28 (s), 6.04 (d, J = 13.5 Hz), and 5.26 (d, J = 13.5 Hz), respectively. The conjugated vinylic protons of the keto form was displayed at δ 7.32 as a triplet (J = 7.5 Hz). The methylene protons of the ester group appeared as two quartets (J = 7 Hz) at δ 4.25 (enol) and 4.24 (keto), while their coupling methyl triplet (J = 7 Hz) was found at δ 1.29. The geminal methyl groups were displayed as a singlet at δ 1.03. In the infrared spectrum of **258**, the carbonyl absorptions were displayed at 1728 (ester), 1690 (ketone), and 1634 cm^{-1} (enol ester). A molecular ion peak was found at m/z 210.1259, consistent with the molecular formula $C_{12}H_{18}O_3$, in the high resolution mass spectrum.

Due to the steric hindrance of the neighboring geminal dimethyl group of the carbonyl group, ring expansion of 2,2-dimethylcyclohexanone took 4 days to complete (entry 3), compared to 1 hour required for each of the preceding cyclohexanones (entries 1 and 2). However, a 87% yield of the corresponding keto ester **259** was produced. Unlike **255** and **257**, possessing both keto and enol forms, **259** was shown by the ^1H NMR spectrum to be a single keto form. In this spectrum, a notable doublet of doublets (J = 12, J' = 3 Hz) at δ 3.86 was corresponding to the proton adjacent to both ketone carbonyl and ester moieties. The methylene and methyl groups of the ester group were shown at δ 4.14 as a quartet and δ 1.22 as a triplet, respectively, each with a coupling constant of 7 Hz. The geminal methyl groups appeared at δ 1.18 and 1.10, each as a singlet. The infrared spectrum of **259** displayed two carbonyl bands at 1748 (ester) and 1708 cm^{-1} (ketone). In its high resolution mass spectrum, a molecular ion peak at m/z 212.1415 supported the molecular formula $C_{12}H_{20}O_3$.

In contrast to the facile oxidative elimination in the previous two cases, the reaction of **259** was sluggish. After stirring for a week with phenylselenenyl chloride and pyridine, only 15% of enone **260** was obtained along with a 61% recovery of starting **259**. Other methods, including phenylselenenylation using sodium hydride as a base, *N*-bromosuccinimide bromination, and direct dichlorodicyanoquinone dehydrogenation, were attempted without success. The infrared spectrum of **260** showed bands at 1722 and 1695 cm^{-1}, corresponding to the carbonyl groups of ester and ketone, respectively. The ^1H NMR spectrum displayed only one set of signals, indicating the existence of keto form. The vinylic proton appeared as a triplet (J = 5 Hz) at δ 7.16, while the allylic methylene protons were shown at δ 2.42 as a triplet of doublets ($J = J'$ = 6 Hz). The methylene and the methyl groups of the ester moiety were displayed at δ 4.20 (quartet) and 1.25 (triplet), respectively, with a coupling constant of 7 Hz each. The geminal methyl groups were shown as a singlet at δ 1.18. In its high resolution mass spectrum, a molecular ion peak at m/z 210.1252 was in agreement with the molecular formula $C_{12}H_{18}O_3$.

Apparently, due to the steric effect, the ring expansion of 2-methylcyclohexanone (entry 4), which took *ca.* 1 day for completion, was found to be more rapid than 2,2-dimethylcyclohexanone and somewhat slower than the parent cyclohexanone. Furthermore, the steric difference between the two α carbons of carbonyl group was not enough to give complete regioselectivity. Therefore, an inseparable mixture of regioisomers **261** and **262** was obtained in a ratio of 9 : 1 and in a combined yield of 93%. This mixture displayed two carbonyl absorptions at 1743 (ester) and 1709 cm^{-1} (ketone). In the ^1H NMR spectrum, **261** appeared as a 7 : 2 mixture of stereoisomers. Two doublets of doublets at δ 3.67 (dd, J = 7.5, J' = 5 Hz, minor) and 3.48 (dd, J = 12, J' = 4.5 Hz, major) were consistent with the protons adjacent to two carbonyl groups of the two stereoisomers. The parallel proton of **262** was shown at δ 3.13 as a doublet with a large coupling constant of 10 Hz, indicating the *trans* relationship with the adjacent proton. The methylene protons of the ester were observed at δ 4.15 as a multiplet due to the three isomers, while the methyl groups were displayed at δ 1.25 and 1.23 as two triplets

with a coupling constant of 7 Hz each. Three methyl doublets (J = 6.5 Hz) for the two isomers of **261** and **262** were displayed at δ 1.12 (major), 1.11 (minor), and 1.01, respectively. In the high resolution mass spectrum, a molecular ion peak at m/z 198.1261 was observed, in agreement with the molecular formula $C_{11}H_{18}O_3$.

Phenylselenenylation and oxidative elimination of the mixture of **261** and **262** did not go to completion. After 89 hours, a 71% of enone **263** and 3 % of its isomer **264** were produced with a 7% recovery of **262** (entry 4). Fortunately, the desired conversion (**261**→**263**) was complete. At this stage, isomers **263** and **264** could be separated by flash chromatography.

In the ^{1}H NMR spectrum, **263** was shown to exist in both keto and enol forms in a ratio of 2 : 1. A singlet at δ 13.46, and two doublets of doublets of doublets at δ 6.22 (J = 12, J' = J'' = 2 Hz) and 5.65 (J = 12, J' = J'' = 5 Hz) were attributed to the enolic and two vinylic protons of the enol form, respectively. The vinylic proton of keto form was displayed at δ 7.32 as a doublet of doublets (J = 6, J' = 5.5 Hz). For the ester moieties, two sets of methylene protons were shown at δ 4.23 (enol) and 4.21 (keto), each as a quartet (J = 7 Hz), while the neighboring methyl groups were displayed at δ 1.32 (enol) and 1.27 (keto) as two triplets with the same coupling constant. A doublet (J = 6.5 Hz) was observed at δ 1.15 for the C-7 methyl group. The keto and enol forms of **263** were also confirmed by the infrared spectrum, displaying bands at 1724 and 1636 cm^{-1}, corresponding to the carbonyl groups of keto and enol forms, respectively. A molecular ion peak at m/z 196.1090 in the high resolution mass spectrum was consistent with the molecular formula $C_{11}H_{16}O_3$.

The high resolution mass spectrum of **264** also supported the same molecular formula showing a molecular ion peak at m/z 196.1100. The ^{1}H NMR spectrum displayed a broad singlet at δ 2.03, indicating the presence of a vinylic methyl group. The ester moiety displayed its methylene quartet and methyl triplet at δ 4.24 and 1.29, each with a coupling constant of 7 Hz. One broad absorption at 1729 cm^{-1} was observed in the infrared spectrum of **264**.

Bicyclic keto ester **265** (entry 5) was not prepared by a ring expansion reaction. Instead, commercially available bicyclo[3.2.2]octan-2-one (85% purity) was carbomethoxylated with dimethyl carbonate in refluxing tetrahydrofuran using sodium hydride as a base. After 2.5 hours, **265** was produced in 95% yield. Ester **265** existed mainly in the enol form (5 parts of enol *vs.* 2 parts of keto). The infrared spectrum of **265** displayed four characteristic bands at 1748 (ester), 1725 (ketone), 1655 (enol ester), and 1615 cm^{-1} (enolic olefin). In its ^1H NMR spectrum, the enolic proton was displayed at δ 11.91 as a singlet, while the proton flanked by two carbonyl groups was shown as a doublet of doublets (J = 12, J' = 8 Hz) at δ 3.47. Two methyl singlets appeared at δ 3.75 and 3.72, corresponding to the two forms. In the high resolution mass spectrum, a molecular ion peak was observed at m/z 182.0949, consistent with the molecular formula $C_{10}H_{14}O_3$.

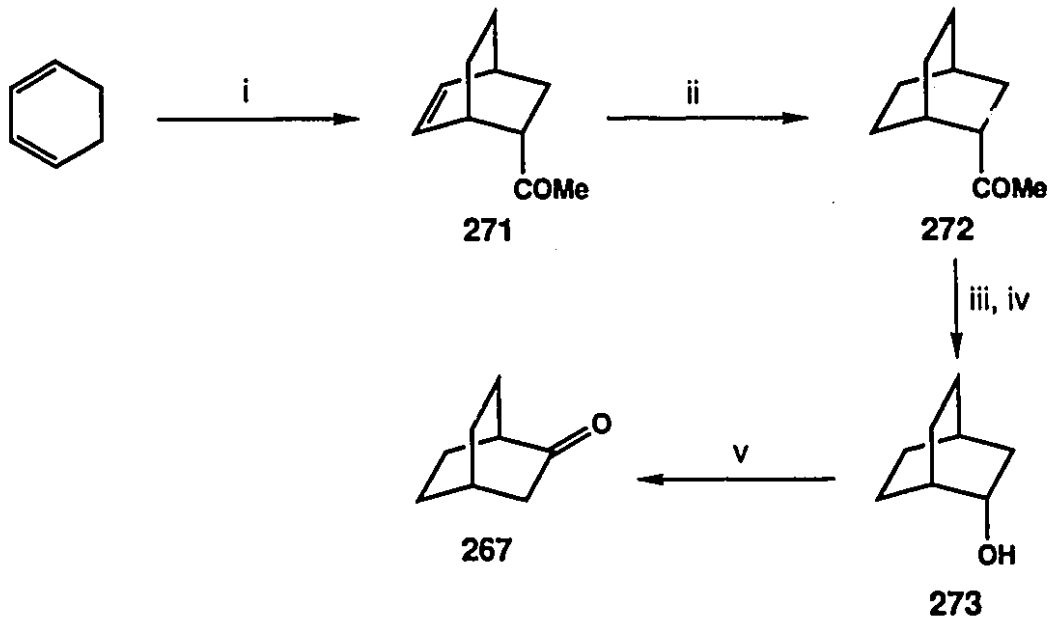
Phenylselenenylation-oxidative elimination of keto ester **265** produced the corresponding enone **266** in 31% yield (entry 5). In the infrared spectrum of **266**, two absorptions were displayed at 1743 and 1689 cm^{-1} corresponding to the ester and ketone carbonyls. The molecular formula $C_{10}H_{12}O_3$ was confirmed by the molecular ion peak at m/z 180.0790 in the high resolution mass spectrum. In the ^1H NMR spectrum, a vinylic proton was shown as a doublet of doublets (J = 7, J' = 1.5 Hz) at δ 8.01, indicating the production of an enone. The α' proton of the ketone and the allylic proton overlapped at δ 3.04 as a multiplet. The methyl singlet of the ester was shown at δ 3.78.

A method was reported by assembling cross-conjugated diene anions of 2-cyclohexenones and methyl acrylate to produce the corresponding bicyclo[2.2.2]octan-2-one derivatives in high yield.[195] In our hands, this method gave only unidentifiable mixtures. The synthesis of **267** was accomplished *via* a five-step operation starting from the Diels-Alder reaction of 1,3-cyclohexadiene and methyl vinyl ketone as shown in **Scheme 65**.

Diels-Alder reaction of 1,3-cyclohexadiene and methyl vinyl ketone was catalyzed by tin(IV) chloride and performed at 0°C in dichloromethane. After 1 hour, the cycloadduct **271** was obtained in 85% yield. A

molecular ion peak was observed at m/z 150.1043, confirming the molecular formula $C_{10}H_{14}O$. The infrared spectrum of **271** displayed a carbonyl absorption at 1709 cm^{-1}. In the ^1H NMR spectrum of **271**, a pair of doublets of doublets of doublets were displayed at δ 6.28 ($J = J' = 7$, $J'' = 1$ Hz) and 6.10 ($J = J' = 7$, $J'' = 0.5$ Hz), corresponding to the two vinylic protons. The methyl singlet of the acetyl group was observed at δ 2.10. The stereochemistry of this acetyl group, which would be destroyed in the later stage, was tentatively assigned based on *endo*-selectivity.

Scheme 65



i. methyl vinyl ketone, $SnCl_4$, CH_2Cl_2, 0°C, 1 h, 85%; ii. H_2, Pd/C, EtOAc, 20°C, 5 h, 97%; iii. MCPBA, Na_2HPO_4, CH_2Cl_2, 20°C, 25 h; iv. 1 N NaOH, MeOH, 20°C, 4.5 h, 100% (two steps); v. PCC-Al_2O_3, CH_2Cl_2, 20°C, 2 h, 76%

Olefin **271** was then hydrogenated in ethyl acetate using 5% palladium on carbon as a catalyst. After 5 hours under 20 p.s.i. of hydrogen pressure, the saturated ketone **272** was generated quantitatively. The disapperance of the vinylic signals in the ^1H NMR spectrum indicated the completion of the hydrogenation. The α proton of the ketone was

displayed at δ 2.63 (ddd, J = 10, J' = 6, J'' = 2.5 Hz) and its methyl singlet was shown at δ 2.13. The carbonyl absorption of **272** was observed at 1710 cm^{-1} in the infrared spectrum and the molecular formula $C_{10}H_{16}O$ was indicated by the molecular ion peak at m/z 152.1202 in the mass spectrum.

Baeyer-Villiger oxidation of ketone **272** was performed at room temperature using *m*-chloroperoxybenzoic acid buffered by disodium hydrogen phosphate in dichloromethane. The crude acetate thus obtained, without purification, was subjected to treatment with a mixture of 1 N aqueous sodium hydroxide solution and methanol. After stirring at room temperature for 4.5 hours, alcohol **273** was produced in 100% overall yield. Compound **273** was recrystallized from skelly B to give a white solid with a melting point of 88-89°C. A characteristic broad hydroxyl absorption was observed at 3293 cm^{-1} in the infrared spectrum of **273**. In the ^1H NMR spectrum, the proton at the hydroxy-bearing carbon was displayed at δ 3.95 (dddd, J = 9, J' = J'' = 4, J''' = 1.5 Hz). A molecular ion peak at m/z 126.1044 in the high resolution mass spectrum was consistent with the molecular formula $C_8H_{14}O$.

At last, the desired ketone **267** was formed by oxidizing alcohol **273** for 2 hours with pyridinium chlorochromate on alumina in dichloromethane. Ketone **267** was obtained as a volatile white solid in 76% yield. The absence of the hydroxyl absorption and the presence of a carbonyl absorption at 1727 cm^{-1} in the infrared spectrum indicated the formation of a ketone. The three α protons of the ketone were displayed as a broad singlet at δ 2.24 in the ^1H NMR spectrum. The molecular formula $C_8H_{12}O$ of **267** was confirmed by a molecular ion peak at m/z 124.0889 in the high resolution mass spectrum. Therefore ketone **267** was readily prepared *via* five steps in 63% overall yield.

Ring expansion of ketone **267** generated, after 2 hours, an inseparable mixture of **268** and **269**, in 92% yield (entry 6). The ^1H NMR spectrum of this mixture displayed four sets of signals due to two regioisomers and their corresponding enol forms. Although the formation of **268** would be more favorable than that of **269** in terms of the steric control, the ratio of these two isomers could not be determined merely based on this spectral

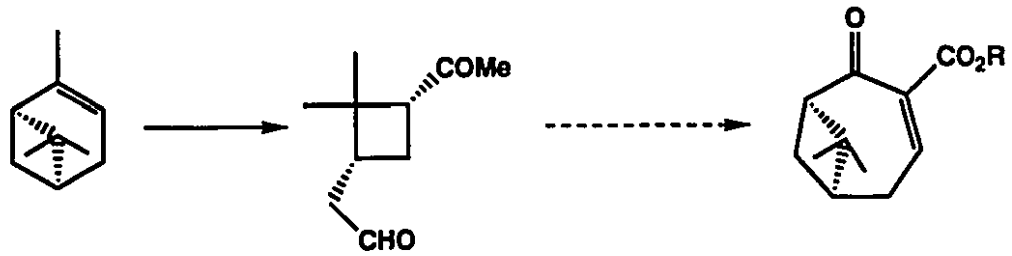
data. However, the determination became possible after the following transformation, since **269** could not be converted to the corresponding enone due to the structural restriction. In fact, **269** was recovered intact. With the isolation of this compound in pure form, the ratio of **268** (keto : enol = 5 : 6) and **269** (keto : enol = 1 : 1) was thus determined to be 11 : 4. The ^{1}H NMR spectrum of the mixture displayed two enolic protons at δ 12.72 (**269**) and 12.62 (**268**). The protons adjacent to both carbonyl groups were displayed at δ 3.80 (dd, J = 12, J' = 8.5 Hz, **268**) and 3.52 (ddd, J = 3, J' = J'' = 1 Hz, **269**). The large coupling constant (12 Hz) of the signal at δ 3.80 further confirmed the regiochemistry of **268**. The methylene and the methyl protons of the esters appeared as two multiplets at δ 4.20 and 1.29 respectively. The infrared spectrum of the mixture of **268** and **269** displayed bands at 1744 (ester), 1704 (ketone), and 1643 cm^{-1} (enol ester). In the high resolution mass spectrum, a molecular ion peak at m/z 210.2158 was in agreement with the molecular formula $C_{12}H_{18}O_3$.

After the phenylselenenylation-oxidative elimination process, **269** was recovered intact and **268** was converted to enone **270** in 70% yield. In the infrared spectrum of **270**, two carbonyl absorptions at 1736 (ester) and 1677 cm^{-1} (ketone) were observed. The ^{1}H NMR spectrum of **270** displayed a notable vinylic doublet (J = 9.5 Hz) at δ 7.82. The methylene quartet and the methyl triplet of the ester were shown at δ 4.26 and 1.32 respectively, with a coupling constant of 7 Hz each. A molecular ion peak at m/z 208.1104 in the high resolution mass spectrum was consistent with the molecular formula $C_{12}H_{16}O_3$.

It is noteworthy that the activated dienophiles (**256**, **258**, **260**, **263**, **266**, and **270**) thus prepared are more stable than their six-membered ring analogues and can be purified by flash chromatography without apparent decomposition. Although some of their enol forms were observed in the ^{1}H NMR spectra, no polymerization was detected. For example, 2 carbethoxy-2-cycloheptenone could be easily purified by flash chormatography. This is in sharp contrast to 2-carbomethoxy-2-cyclohexenone, which was found to decompose rapidly.[186]

Besides the dienophiles listed in **Table 2**, we also attempted to prepare a stereofacially differentiated dienophile **274** from (+)-α-pinene. The synthetic strategy is outlined in **Scheme 66**.

Scheme 66



275 **274**

Ozonolysis of (+)-α-pinene was first carried out in tetrahydrofuran according to a published procedure.[196] This resulted only in a 39% yield of keto aldehyde **275**. When tetrahydrofuran was replaced by a mixture of dichloromethane and methanol, the yield was improved to 89%. Compound **275** displayed an optical rotation of +75.47° (c. 1.9, $CHCl_3$). The two carbonyl groups of **275** showed absorptions at 1733 and 1706 cm^{-1} in the infrared spectrum. In the ^1H NMR spectrum, a triplet (J = 1 Hz) at δ 9.73 indicated the formation of the aldehyde. The α methine proton of ketone was displayed at δ 2.91 as a doublet of doublets (J = 10.5, J' = 8 Hz), while the methyl singlet of the ketone was shown at δ 2.03. The other two methyl singlets due to the geminal dimethyl group appeared at δ 1.33 and 0.87. In the high resolution mass spectrum, a fragment at m/z 167.1051 due to the loss of a hydrogen atom lent support to the required molecular formula $C_{10}H_{15}O_2$.

However, attempts to cyclize keto aldehyde **275** using piperidine and benzoic acid in refluxing xylene or toluene resulted invariably in poor yield of the desired cyclization product. This is propably due to the high volatility of the product causing material loss during the removal of

solvents. When benzene was used as a solvent instead of xylene or toluene, the cyclization process did not occur.

We also tried to prepare **274** *via* ring expansion of (+)-nopinone using our standard procedure. However, this reaction led to a complex mixture which did not contain the desired product.

II. Diels-Alder reactions of 2-carbalkoxy-2-cycloheptenones:

A. Diels-Alder reactions of enone 256:

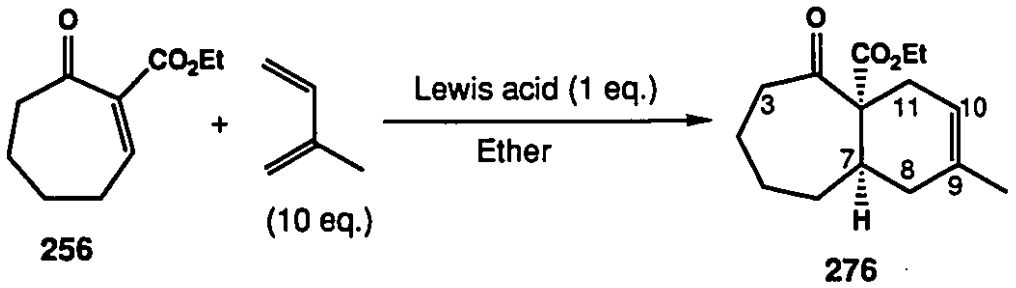
A variety of temperatures and Lewis acids were explored for the Diels-Alder reaction of enone **256** and isoprene in order to find the most suitable conditions. The particular Lewis acids (zinc chloride, ferric chloride, boron trifluoride etherate, and tin(IV) chloride) were chosen because they had been noted previously as appropriate catalysts for the reactions of the related dienophiles. The results are summarized in **Table 3**.

The experimental procedure for zinc chloride catalyzed reactions was slightly different from those using ferric chloride, boron trifluoride etherate, and tin(IV) chloride. The zinc chloride used in the Diels-Alder reactions was dried carefully by a flame before being dissolved in ether. To the resulting zinc chloride solution was then added an ether solution of the dienophile. After stirring for half an hour, allowing the complex formation, a diene was then added. It was reported that the progress of the reaction could be monitored by the disappearance of the white precipitate resulting from the complexation of zinc chloride and the starting enone.[80] This simple method proved to be inapplicable to the present system. In some cases, the cycloaddition was incomplete despite of the disappearance of the white precipitate.

The procedure for the Diels-Alder reactions catalyzed by the other Lewis acids was straightfoward. To a solution of dienophile and diene, the Lewis acid was simply added.

Table 3.

Lewis acid catalyzed Diels-Alder reaction of enone **256** and isoprene



256 **276**

Lewis acid	Temp. (°C)	Time (h)	Yield (%)
$ZnCl_2$	20	73	70
$FeCl_3$	0	1	47
$FeCl_3$	-40	1	47
$FeCl_3$	-78	78	54
$BF_3{\cdot}OEt_2$	20	15	23
$SnCl_4$	0	1	6

In the case of the addition of enone **256** to isoprene, zinc chloride catalyzed reaction required longer time (73 hours at room temperature). However, the yield (70%) of adduct **276** was the best among all trials. The reaction catalyzed by ferric chloride was rapid and a moderate yield (47%) of adduct **276** was obtained after 1 hour at 0°C. The reaction time and the yield were found unchanged when the temperature was lowered to -40°C. Lowering the temperature further down to -78°C, the reaction

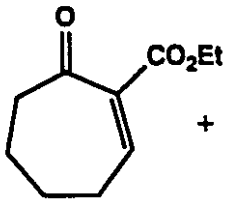
turned sluggish and the yield was only slightly improved. The addition catalyzed by boron trifluoride etherate was shown to be much less efficient than that by ferric chloride and yielded adduct **276** in only 23% yield after stirring at room temperature for 15 hours. When tin(IV) chloride was added to the reaction medium at 0°C, a rapid decomposition was observed and **276** was isolated in merely 6% yield. Due to the superiority of zinc chloride as a catalyst in this series, this Lewis acid was used as the catalyst in further investigations of the scope of Diels-Alder reactions of all our dienophiles.

The structure of adduct **276** was deduced as follows. The infrared spectrum of **276** displayed two carbonyl absorptions at 1743 (ester) and 1700 cm^{-1} (ketone). The high resolution mass spectrum showed a molecular ion peak at m/z 250.1568, corresponding to the molecular formula $C_{15}H_{22}O_3$. The ^{13}C NMR APT spectrum of **276** displayed only one set of signals, including two carbonyl signals at δ 209.72 (ketone) and 171.64 (ester) and two olefinic signals at δ 131.17 and 118.46, indicating the presence of a single compound. The assignment of the ^1H NMR spectrum of **276** was assisted by extensive ^1H decoupling experiments. The vinylic proton was displayed at δ 5.34 as a broad singlet, while the vinylic methyl group also appeared as a broad singlet at δ 1.61. The methylene protons of the ester group were shown as two quartets (J = 7 Hz) at δ 4.16 and 4.15. Its adjacent methyl group was displayed at δ 1.23 (t, J = 7 Hz). A pair of doublets of doublets of doublets corresponding to the α methylene protons of the ketone were shown at δ 2.98 (J = 14, J' = 9.5, J'' = 3 Hz) and 2.42 (J = 14, J' = 9, J'' = 4 Hz). The allylic methylene protons at C-11 were displayed at δ 2.65 (dq, J = 18, J' = 2 Hz) and 2.33 (br d, J = 18 Hz), while one of other allylic methylene protons at C-8 appeared as a broad doublet (J = 18 Hz) at δ 2.09. The proton at the ring juncture carbon (C-7) was observed as a multiplet at δ 2.68. The regiochemistry of adduct **276** (from *para*-rule) was also confirmed by the ^1H decoupling experiments. Irradiation of the vinylic signal at δ 5.34 resulted in change on the broad doublet at δ 2.33 due to one of the C-11 methylene protons. Conversely, irradiation of this doublet resulted in the change of the vinylic signal.

The results obtained for the zinc chloride catalyzed Diels-Alder reactions of enone **256** with isoprene and two other dienes are summarized in **Table 4**. When one equivalent of zinc chloride catalyst was applied, the cycloadditions with 2,3-dimethyl-1,3-butadiene and *trans*-piperylene proceeded faster than that with isoprene. However, the rates were generally slower than the rates of six-membered ring analogues. The yields in this series were moderate. In order to accelerate the reaction rate, the amount of the zinc chloride used was increased from one equivalent to two equivalents, but the results were less satisfactory. With isoprene, the reaction using two equivalents of zinc chloride did proceed faster (47 h *vs.* 73 h), however, the yield was lower (53% *vs.* 70%). It was even worse in the case of 2,3-dimethyl-1,3-butadiene, the reaction with two equivalents of zinc chloride did not display an enhancement in reaction rate. Meanwhile, the yield of cycloadduct **277** was lower (43% *vs.* 69%). With *trans*-piperylene, experiments using different amounts of zinc chloride gave almost the same results.

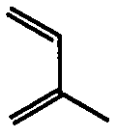
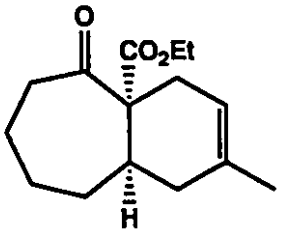
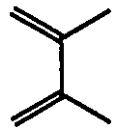
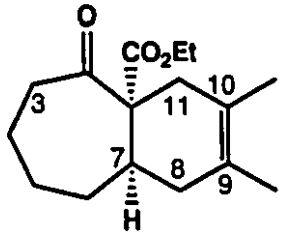
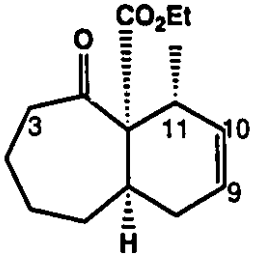
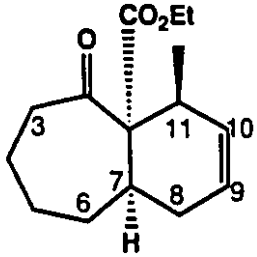
Diels-Alder cycloaddition of 2,3-dimethyl-1,3-butadiene to enone **256** carried out at room temperature with one equivalent of zinc chloride generated cycloadduct **277** in 69% yield after 22 hours. The infrared spectrum of **277** showed two carbonyl bands at 1742 (ester) and 1701 cm^{-1} (ketone). In the ^1H NMR spectrum, two vinylic methyl singlets appeared at δ 1.63 and 1.56, while the α methylene protons of the ketone were displayed at δ 2.96 (ddd, J = 14, J' = 10, J'' = 3.5 Hz) and 2.41 (ddd, J = 14, J' = 9, J'' = 3 Hz). A multiplet at δ 2.64 was assigned to the proton at ring juncture (C-7). The allylic methylene protons at C-11 were shown as a pair of broad doublets (J = 17.5 Hz) at δ 2.56 and 2.25, while one of the other allylic methylene protons H_8 was displayed at δ 2.10, also as a broad doublet (J = 17.5 Hz). The methylene quartet and the methyl triplet of the ester group were displayed at δ 4.14 and 1.22, each with a coupling constant of 7 Hz. These assignments were in agreement with the ^1H decoupling experiments. The ^{13}C NMR APT spectrum of **277** showed four characteristic signals at δ 209.94 (ketone), 199.57 (ester), 123.74 (olefin), and 122.76 (olefin). A molecular ion peak was found at m/z 264.1727, corresponding to the molecular formula $C_{16}H_{24}O_3$.

Table 4. Zinc chloride catalyzed Diels-Alder reaction of enone **256**



256

+ Diene (10 eq.) $\xrightarrow[\text{Ether, 20°C}]{ZnCl_2}$ Product(s)

Diene	L.A. eq.	Time (h)	Product(s)	Yield (%)
	1	73		70
	2	47		53
			276	
	1	22		69
	2	23		43
			277	
	1	44	 	62 (1 : 1)
	2	42		63 (1 : 1.1)
			278 **279**	

The Diels-Alder reaction of enone **256** and *trans*-piperylene catalyzed by zinc chloride did not afford any stereoselectivity. A 1 : 1 mixture of ester-

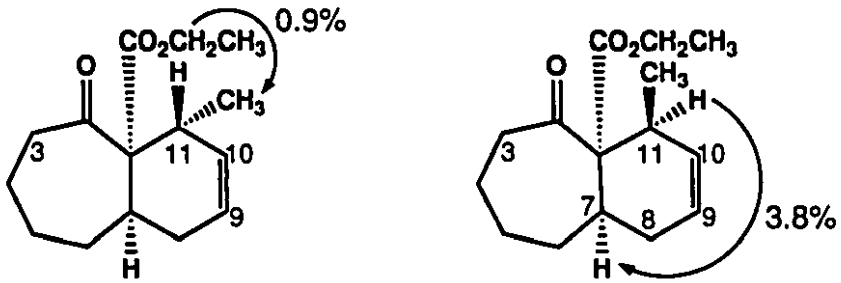
endo adduct **278** and keto-*endo* adduct **279** was produced in 62% combined yield. The ratio was not changed by employing two equivalents of zinc chloride. The stereoisomers were separated and identified by extensive spectroscopic studies, including ^1H decoupling and NOE experiments.

The infrared spectrum of **278** displayed two carbonyl absorptions at 1739 (ester) and 1702 cm^{-1} (ketone). Its high resolution mass spectrum showed a molecular ion peak at m/z 250.1569, indicating the molecular formula $C_{15}H_{22}O_3$. In the ^1H NMR spectrum, two vinylic protons were displayed at δ 5.64 (H_{10}) and 5.54 (H_9), each as a multiplet. The methylene protons of the ester appeared as a pair of doublets of quartets (J = 11, J' = 7 Hz) at δ 4.22 and 4.18, while the methyl group was observed at δ 1.27 as a triplet (J = 7 Hz). H_{11} overlapped with one of the α protons of the ketone at δ 2.83 as a multiplet. The methyl group at C-11 was displayed at δ 0.91 as a doublet (J = 7 Hz), coupled to H_{11}. The ^{13}C NMR APT spectrum displayed two carbonyl signals at δ 206.81 (ketone) and 170.69 (ester), and two olefinic signals at δ 131.65 and 123.13. The stereochemistry of **278** was confirmed by the NOE experiment. As shown in **Figure 3**, irradiation of the methylene signals of ester at δ 4.18-4.22 resulted in 0.9% enhancement on methyl doublet at δ 0.91.

In the case of **279**, two carbonyl bands were shown at 1720 (ester) and 1699 cm^{-1} (ketone) in its infrared spectrum. The molecular ion peak displayed at m/z 250.1569 in the high resolution mass spectrum supported the molecular formula $C_{15}H_{22}O_3$. In the ^{13}C NMR APT spectrum, two carbonyl signals and two olefinic signals were displayed at δ 205.95 (ketone), 172.45 (ester), 131.80 (olefin), and 123.05 (olefin). In the ^1H NMR spectrum of **279**, signals were quite well separated and could be assigned unambiguously. A multiplet at δ 5.55 corresponding to two protons were assigned to two vinylic protons. The methylene protons of the ester were displayed at δ 4.27 and 4.26 as two quartets (J = 7 Hz). The adjacent methyl was shown at δ 1.31 as a triplet (J = 7 Hz). A pair of complex signals at δ 2.88 (dddd, J = 18.5, J' = J'' = 4.5, J''' = 1.5 Hz) and 2.34 (ddd, J = 18.5, J' = 13, J'' = 5 Hz) were assigned to the α

methylene protons of the ketone. The ring juncture proton (H_7) was observed at δ 2.52 (ddd, J = 12, J' = 7.5, J'' = 4 Hz). The methyl group at C-11 appeared at δ 1.11 as a doublet (J = 7 Hz) which was coupled to the multiplet at δ 2.62 attributed to its neighboring proton (H_{11}). The allylic methylene protons at C-8 overlapped at δ 1.90 as a multiplet. In the NOE experiment, irradiation of the multiplet at δ 2.62 (H_{11}) resulted in 3.8% enhancement on H_7 (**Figure 3**), indicating the stereochemistry of the adduct.

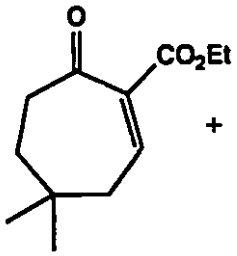
Figure 3



B. Diels-Alder reactions of enone 258:

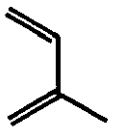
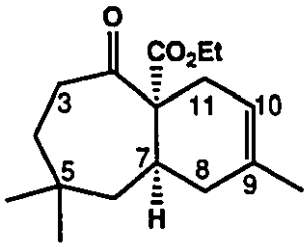
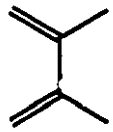
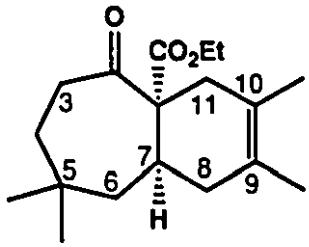
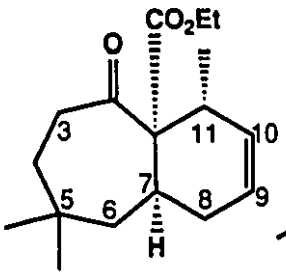
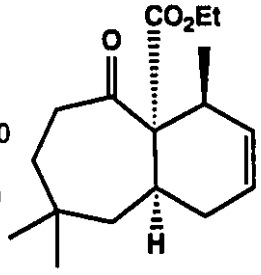
Zinc chloride catalyzed Diels-Alder reactions of enone **258** proceeded much less efficiently than those of enone **256**. As shown in **Table 5**, the required reaction times were doubled or even tripled, and the yields were generally poor. These results were likely due to the steric hindrance of the gem. al dimethyl grcup, interrupting the access of the diene. Ferric chloride, tin(IV) chloride, and aluminum chloride were also utilized as catalysts in the cycloadditon with isoprene in an attempt to improve the efficiency of the cycloadditons in this series. However, in every case, extensive decomposition was observed. Thus, zinc chloride still proved to be the most suitable Lewis acid catalyst.

Table 5. Zinc chloride catalyzed Diels-Alder reaction of enone **258**



258

+ Diene (10 eq.) $\xrightarrow[\text{Ether, 20°C}]{ZnCl_2}$ Product(s)

Diene	L.A. eq.	Time (h)	Product(s)	Yield (%)
	1	260	 **280**	28
	2	68		43
	3	43		39
	1	69	 **281**	52
	2	46		61
	1	148	 **282**	30 (10 : 1)
	2	94	 **283**	42 (7 : 5)

When one equivalent of zinc chloride was used in the Diels-Alder reaction of enone **258** and isoprene, the reaction took more than ten days to yield only 28% yield of adduct **280**. Increasing the amount of zinc chloride to two equivalents, the reaction rate was highly accelerated. Only 68 hours were required and it gave an improved yield of 43% of **280**. It was attempted to further improve the reaction using three equivalents of zinc chloride. The reaction time was reduced to 43 hours but the yield was slightly worse (39%).

The ^{13}C NMR spectrum of **280** displayed only one set of signals, including δ 183.88 (ketone), 170.98 (ester), 130.89 (olefin), and 118.31 (olefin), indicating a single isomer. The infrared spectrum showed two carbonyl absorptions at 1733 (ester) and 1694 cm^{-1} (ketone). A molecular ion peak at m/z 278.1885 in the high resolution mass spectrum was consistent with the molecular formula $C_{17}H_{26}O_3$. In the ^1H NMR spectrum of **280**, the vinylic proton was displayed as a broad singlet at δ 5.33 and the adjacent vinylic methyl group also appeared as a broad singlet at δ 1.62. A pair of doublets of doublets of doublets at δ 3.07 ($J = J' = 13$, $J'' = 2$ Hz) and 2.31 ($J = 13$, $J' = 8$, $J'' = 2$ Hz) were corresponding to the α methylene protons of the ketone. The allylic methylene protons at C-11 were displayed at δ 2.91 and 2.14 with a coupling constant of 18 Hz each, the former overlapped with the signal of H_7 to show a multiplet. One of the other allylic methylene protons (H_8) was observed at δ 2.29 as a multiplet. Singlets of the geminal dimethyl group were displayed at δ 1.12 and 0.93. For the ester moiety, the methylene protons were shown at δ 4.13 as a quartet ($J = 7$ Hz), coupled to the methyl triplet ($J = 7$ Hz) at δ 1.22. All of these assignments were in agreement with the ^1H decoupling experiments, which also confirmed the regiochemistry of **280**. When the broad vinylic singlet at δ 5.33 was irradiated, the coupling patterns of both protons at C-11 changed while those of the protons at C-8 remained intact.

Better results were obtained for 2,3-dimethyl-1,3-butadiene. When one equivalent of zinc chloride was used, the cycloaddition completed in 69 hours to give cycloadduct **281**, with a melting point of 62-63°C, in 52% yield. When two equivalents of zinc chloride were used, the reaction was

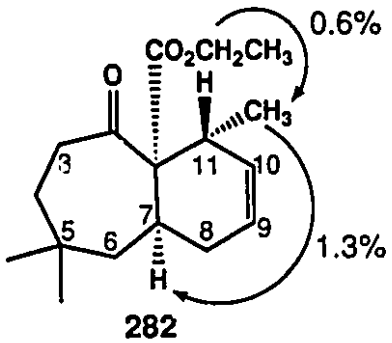
found to be complete in 46 hours and the yield was improved to 61%. Two carbonyl absorptions were observed at 1746 (ester) and 1702 cm^{-1} (ketone) in the infrared spectrum of **281**. In its ^1H NMR spectrum, the methylene group of the ester moiety was displayed as two quartets (J = 7 Hz each) at δ 4.14 and 4.13, and the adjacent methyl was displayed at δ 1.21 as a triplet (J = 7 Hz). A multiplet at δ 2.86 was assigned to the ring juncture proton (H_7). A notable pair of broad doublets (J = 18 Hz) at δ 2.73 and 2.10 were attributed to the allylic methylene protons at C-11. One of the other allylic protons (H_8) at δ 2.29 overlapped with an α proton of the ketone to show a multiplet. The other α proton appeared at δ 3.05 as a doublet of doublets of doublets ($J = J' = 14$, $J'' = 2$ Hz). Four methyl singlets were observed at δ 1.64 (C-10), 1.57 (C-9), 1.11 (C-5), and 0.92 (C-5). The ^1H decoupling experiments confirmed these assignments. The ^{13}C NMR APT spectrum displayed four signals at δ 211.35, 171.16, 123.05, and 122.66, corresponding to the carbonyl carbons of ester and ketone and two olefinic carbons, respectively. In the high resolution mass spectrum of **281**, a molecular ion peak at m/z 292.2040 corresponded to the molecular formula $C_{18}H_{28}O_3$.

In the cycloaddition of *trans*-piperylene to enone **258**, a good stereoselectivity was observed using one equivalent of zinc chloride as a catalyst. As shown in **Table 5**, a 10 : 1 mixture of stereoisomers **282** and **283** was produced in 30% yield with the *endo*-ester adduct **282** predominating. The less favorable *endo*-ketone transition state could be realized by invoking the steric effect due to the presence of the geminal dimethyl group at C-5. Increasing the amount of zinc chloride to two equivalents, the reaction time was shortened (94 h *vs.* 148 h), the yield was improved (42% *vs.* 30%), but the stereoselectivity was sacrificed to 7 : 5.

The major component **282** was isolated and identified by the following spectroscopic methods. The infrared spectrum displayed two characteristic bands at 1746 (ester) and 1698 cm^{-1} (ketone). Its molecular formula $C_{17}H_{26}O_3$ was supported by the high resolution mass spectrum showing a molecular ion peak at m/z 278.1886. The ^{13}C NMR APT spectrum displayed carbonyl carbons at δ 209.37 (ketone) and

172.16 (ester), and olefinic carbons at δ 131.66 and 122.51. Assisted by the extensive ^1H decoupling experiments, all the signals in the ^1H NMR spectrum were assigned. Vinylic protons appeared as two multiplets at δ 5.62 (H_{10}) and 5.55 (H_9). The other two one-proton multiplets were assigned to H_{11} at δ 3.00 and H_7 at 2.81. The α methylene protons (H_3's) were displayed at δ 2.99 (ddd, J = 15, J' = 10.5, J'' = 3 Hz) and 2.40 (ddd, J = 15, J' = 9.5, J'' = 2.5 Hz). The allylic methylene protons (H_8's) were shown at δ 2.13 (dqdd, J = 17.5, J' = J'' = J''' = 3 Hz) and 1.92 (m), the latter overlapped with H_6. The other H_6 and two H_4's were shown together at δ 1.28-1.56 as a multiplet. A doublet (J = 7.5 Hz) at δ 1.11 coupled to H_{11} was attributed to the methyl group at C-11. Geminal methyl groups were shown at δ 1.05 and 0.93 as two singlets. The methylene quartet and the methyl triplet of the ester moiety were displayed at δ 4.16 and 1.24, each with a coupling constant of 7 Hz. The stereochemistry of **282** was indicated by the NOE experiments. As depicted in **Figure 4**, irradiation of the methylene quartet of the ester at δ 4.16 resulted in 0.6% enhancement on methyl group at C-11. When this methyl doublet at δ 1.11 was irradiated, an enhancement of 1.3% on H_7 was observed.

Figure 4



282

Compound **283** was not isolated in pure form. In the ^1H NMR spectrum of the mixture of **282** and **283**, the multiplets at δ 5.62 and 5.46 were attributed to the two vinylic protons of the minor component **283**. The

methyl group at C-11 and the geminal dimethyl group at C-5 of **283** were shown at δ 1.10 (d, J = 7 Hz), 1.01 (s), and 0.89 (s).

From the cycloadditions performed by enones **256** and **258**, it was concluded that using two equivalents of zinc chloride provided the best results with regard to reaction time and yield. Therefore, the following reactions with enones **260**, **263**, **266**, and **270** were carried out using two equivalents of zinc chloride.

C. Diels-Alder reactions of enone 260:

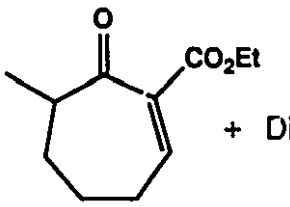
Somewhat expectedly, enone **260** was reluctant to undergo any Diels-Alder reaction with *trans*-piperylene under zinc chloride catalysis due to the serious steric hindrance caused by the geminal dimethyl group at C-7. When ferric chloride was used as a catalyst, extensive decomposition occurred.

D. Diels-Alder reactions of enone 263:

In the Diels-Alder reactions of enone **263**, some interesting and unexpected phenomena emerged. As shown in **Table 6**, all the reactions were completed in one day and the yields were extraordinarily high. Suprisingly, a high degree of facial selectivity was displayed with the addition of diene from the sterically more hindered methyl side. It appears that the methyl group plays a key role in directing the addition of the diene. The exact cause of this unusual stereoselectivity, however, remains to be determined.

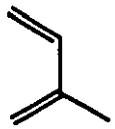
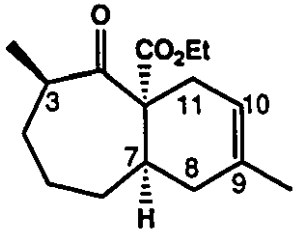
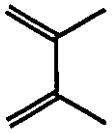
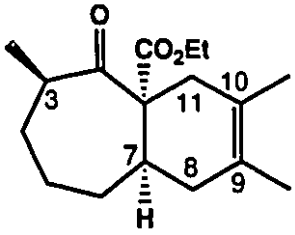
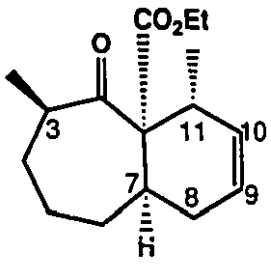
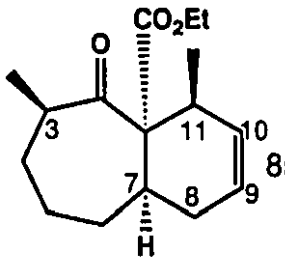
Cycloaddition of isoprene to enone **263** resulted in a single cycloadduct **284** quantitatively after 24 hours. The ^{13}C NMR APT spectrum displayed one set of signals which included four notable signals at δ 210.20 (ketone), 173.21 (ester), 132.21 (olefin), and 118.82 (olefin), supporting the generation of a single product. The infrared spectrum of **284** displayed two carbonyl bands at 1735 (ester) and 1697 cm^{-1} (ketone). In

Table 6. Zinc chloride catalyzed Diels-Alder reaction of enone **263**



263

+ Diene (10 eq.) $\xrightarrow[\text{Ether, 20°C}]{ZnCl_2\ (2\ eq.)}$ Product(s)

Diene	Time (h)	Product(s)	Yield (%)
	24	 **284**	98
	23	 **285**	93 (9 : 1)
	24	 **286**  **287**	85 (1 : 2)

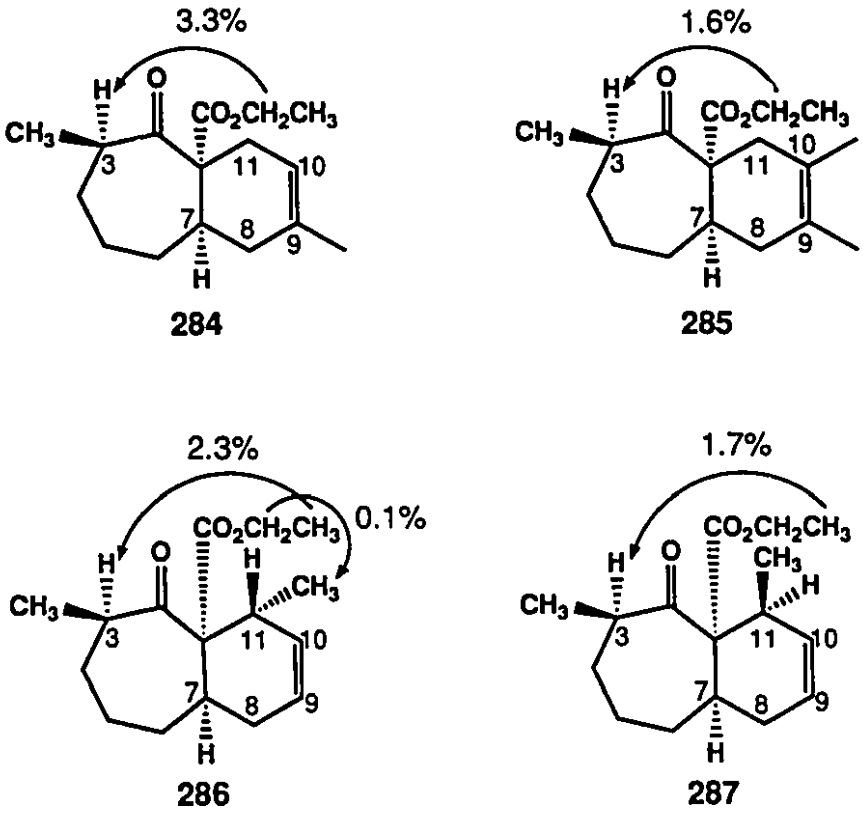
the high resolution mass spectrum, a molecular ion peak at m/z 264.1725 was consistent with the molecular formula $C_{16}H_{24}O_3$. The ^1H

NMR spectrum of **284** displayed the vinylic proton at δ 5.35 as a multiplet, while the vinylic methyl group was shown at δ 1.60 as a broad singlet. The methylene quartet and the methyl triplet of the ester group were observed at δ 4.18 and 1.26, respectively, with a coupling constant of 7 Hz each. A pair of signals corresponding to the allylic methylene protons at C-11 were shown at δ 2.72 (dddd, J = 16.5, J' = 3.5, J'' = J''' = 1.5 Hz) and 2.24 (dqd, J = 16.5, J' = J'' = 2.5 Hz). A multiplet at δ 2.54 was assigned to the ring juncture proton (H_7). The proton at C-3 appeared as a quartet of doublets of doublets (J = J' = 7, J'' = 3.5 Hz) at δ 2.38, coupled to a methyl doublet (J = 7 Hz) at δ 1.22, C-3 methyl group. One of the methylene protons at C-8 was shown as a multiplet at δ 2.01. On the basis of these spectral data, the regiochemistry of **284** was deduced. The stereochemistry was confirmed by the NOE experiments. Irradiation of the methylene quartet of the ester group at δ 4.18 resulted in 3.3% enhancement on H_3 as depicted in **Figure 5**.

In the cycloadditon with 2,3-dimethyl-1,3-butadiene, adduct **285** and its epimer were produced in a ratio of 9 : 1 and in 93% combined yield. The infrared spectrum of **285** showed two carbonyl absorptions at 1736 (ester) and 1697 cm^{-1} (ketone). The molecular formula $C_{17}H_{26}O_3$ of **285** was confirmed by the high resolution mass spectrum displaying a molecular ion peak at m/z 178.1882. The ^1H NMR spectrum displayed two characteristic broad methyl singlets at δ 1.63 and 1.54, corresponding to two vinylic methyl groups at C-10 and C-9, respectively. For the ester portion, the methylene and the methyl groups appeared at δ 4.18 (q, J = 7 Hz) and 1.26 (t, J = 7 Hz). A pair of doublets (J = 16 Hz) at δ 2.58 and 2.21 were corresponding to the two allylic protons (H_{11}'s). The other two allylic protons (H_8's) were shown at δ 2.51 (ddd, J = 16, J' = J'' = 5.5 Hz) and 1.85 (br d, J = 16 Hz). The α methine proton (H_3) of the ketone was displayed at δ 2.35 (dqd, J = 11, J' = 7, J'' = 4 Hz), while its coupling methyl group was shown at δ 1.22 (d, J = 7 Hz). The ring juncture proton (H_7) was observed as a multiplet at δ 2.00. The evidence of the stereochemistry regarding C-3 was provided by NOE experiments as shown in **Figure 5**. Irradiation of the methylene quartet of the ester at δ 4.18 resulted in 1.6% enhancement on H_3. The epimer of **285**, as the minor component of the mixture, displayed the methyl triplet (J = 7.5 Hz)

of the ester group at δ 1.18 and the methyl group at C-3 as a doublet (J = 6.5 Hz) at δ 1.13.

Figure 5



Zinc chloride catalyzed Diels-Alder cycloaddition of *trans*-piperylene to enone **263** generated a 1 : 2 mixture of enones **286** and **287** in a combined yield of 85%. This unusual selectivity favoring *endo*-keto **287**, contrast to those of the previous reactions, was probably again due to the inscrutable effect of the C-3 methyl group.

Enone **286**, with a melting point of 63-64°C, displayed two carbonyl bands at 1738 (ester) and 1697 cm^{-1} (ketone) in the infrared spectrum. The high resolution mass spectrum showed a molecular ion peak at m/z 264.1732, corresponding to the molecular formula $C_{16}H_{24}O_3$. In the ^1H

NMR spectrum of **286**, two vinylic protons were shown at δ 5.65 (H_{10}) and 5.50 (H_9) as two multiplets. Two characteristic methyl doublets appeared at δ 1.26 (J = 7 Hz, C-3) and 0.88 (J = 7.5 Hz, C-11), while their neighboring protons were found at δ 2.33 (H_3) and 2.93 (H_{11}), each as a multiplet. The ring juncture proton (H_7) was shown at δ 2.48 (dddd, J = J' = 13.5, J'' = J''' = 4 Hz) and a multiplet at δ 2.40 was assigned to H_8. The methylene protons of the ester appeared as a pair of doublets of quartets (J = 11, J' = 7 Hz) at δ 4.22 and 4.15. The methyl triplet was displayed at δ 1.28 (J = 7 Hz). All these assignments were consistent with the ^1H decoupling experiments. The stereochemistry of C-3 and C-11 was proven by the NOE experiments as shown in **figure 5**. Irradiation of the methylene signals of the ester group at δ 4.15-4.22 resulted in 0.1% enhancement on methyl group at C-11. On the other hand, when the methyl triplet of the ester at δ 1.28 was irradiated, a 2.3% enhancement on H_3 was displayed.

The spectral data of **287** are summarized as follows. The infrared spectrum displayed two diagnostic bands at 1733 (ester) and 1697 cm^{-1} (ketone), and the high resolution mass spectrum confirmed the molecular formula $C_{16}H_{24}O_3$ with a molecular ion peak at m/z 264.1728. Its ^{13}C NMR APT spectrum displayed the carbonyl carbons and the olefinic carbons at δ 208.47 (ketone), 172.69 (ester), 132.20 (olefin), and 123.03 (olefin). In the ^1H NMR spectrum, one of the vinylic protons (H_{10}) was displayed as a broad doublet (J = 10 Hz) at δ 5.57, while the other one (H_9) appeared as a multiplet at δ 5.51. The methylene protons of the ester group were observed at δ 4.30 and 4.24, each as a doublet of quartets (J = 11, J' = 7 Hz). The adjacent methyl was displayed at δ 1.32 as a triplet (J = 7 Hz). The protons at the stereogenic centers C-11 and C-3 were shown at δ 2.62 (m) and 2.25 (dqd, J = 11, J' = 7.5, J'' = 3 Hz), respectively. The methyl groups attached to these centers were displayed at δ 1.14 (C-11) and 1.28 (C-3), each as a doublet with a coupling constant of 7.5 Hz. One of the protons at C-8 was displayed at δ 2.52 (ddd, J = 9, J' = 4.5, J'' = 4 Hz), while the ring juncture proton H_7 appeared as a multiplet at δ 2.00. The ^1H decoupling experiments confirmed all these assignments. The stereochemistry of C-3 was indicated by the NOE experiment displaying a 1.7% enhancement on H_3

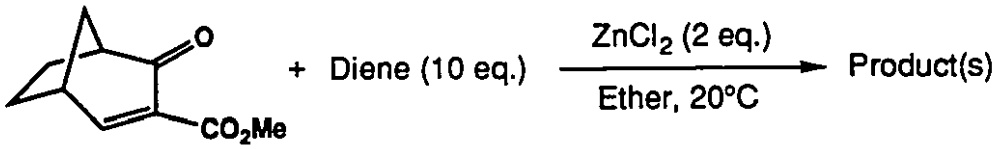
when the methyl triplet of the ester group at δ 1.32 was irradiated. This is shown in **Figure 5**. Although the NOE experiments could not confirm the stereochemistry at C-11, it must be as shown since the corresponding center of the isomer **286** was identified.

E. Diels-Alder reactions of enone 266:

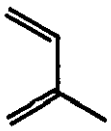
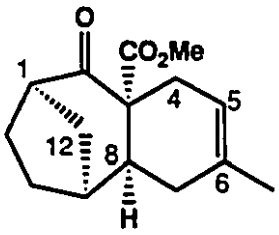
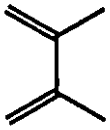
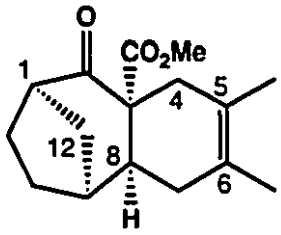
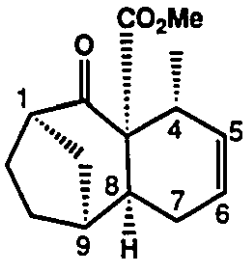
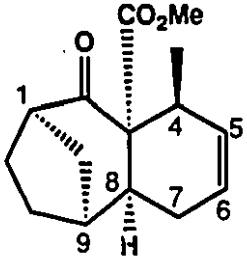
In this series, a complete facial selectivity favoring the addition of diene from the ethano bridge side was observed in every case as shown in **Table 7**. Apparently, this high selectivity cannot be explained by the steric effect alone. In 1976, Kobuke reported a similar facial stereoselectivity involving the diene system.[197] As depicted in **Scheme 67**, in the Diels-Alder reaction of isodicyclopentadiene and methyl propiolate, the addition occurred from the ethano bridge side of isodicyclopentadiene completely. Two possible explanations were given at that time. One was a greater steric attraction than steric repulsion by the ethano bridge which stablilizes the *syn* transition state. The other was based on a stereoelectronic effect resulting from a mixing of the unstable σ orbitals of the norbornane skeleton and the π orbitals. This mixing biased the spread of the π orbital in space above and below the cyclopentadiene plane and therefore favored the *syn* orientation of an attacking dienophile. However, Gleiter and Paquette later stressed that the σ/π interaction must be carefully evaluated in any rationalization of Diels-Alder stereoselectivity and implied a combined effect with other influences such as van der Waals forces (the first explanation above), induced dipole-dipole interactions, and steric effects.[198] In any event, none of the above explanations can be applied to demonstrate the stereoselectivity in our case completely.

Another feature of the Diels-Alder reactions of enone **266** is that these reactions proceeded to completion within the shortest period of reaction time among all the Diels-Alder reactions examined. The yields were fairly good.

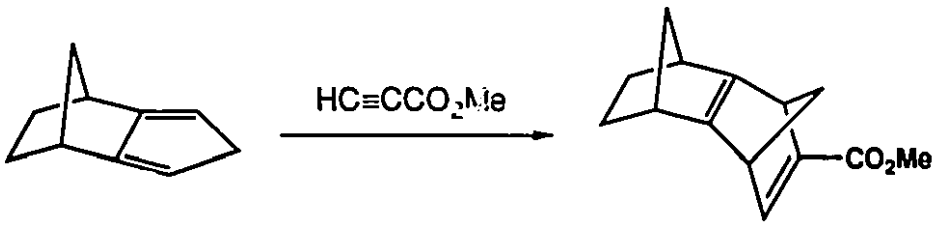
Table 7. Zinc chloride catalyzed Diels-Alder reaction of enone **266**



266

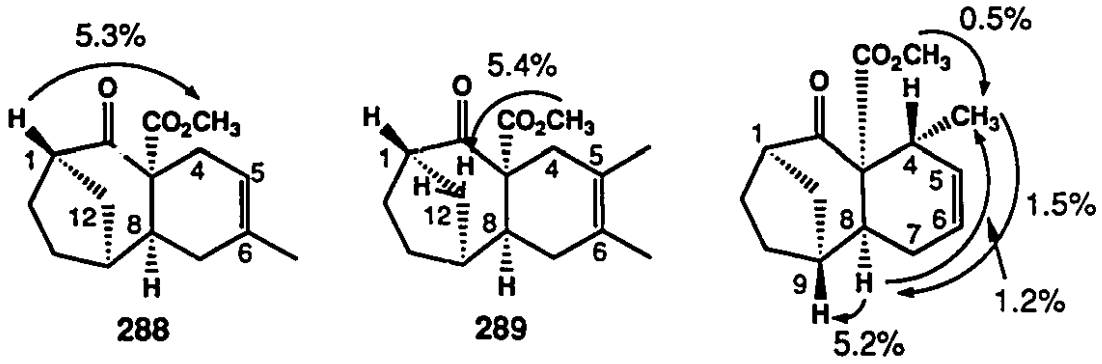
Diene	Time (h)	Product(s)	Yield (%)
	7.5	 **288**	72
	6	 **289**	76
	6	 **290**  **291**	65 (4 : 1)

Scheme 67



Zinc chloride catalyzed Diels-Alder cycloaddition of isoprene to enone **266** produced adduct **288** as a single product in 72% yield after 7.5 hours. The ^{13}C NMR APT spectrum of **288** displayed one set of signals, including δ 210.17 (ketone), 173.99 (ester), 136.36 (olefin), and 120.19 (olefin), confirming the formation of a single isomer. The infrared spectrum of **288** showed two carbonyl bands at 1733 (ester) and 1713 cm^{-1} (ketone). The molecular formula $C_{15}H_{20}O_3$ of **288** was confirmed by the molecular ion peak at m/z 248.1412 in the high resolution mass spectrum. The assignments of the ^1H NMR spectrum, assisted by the ^1H decoupling experiments, are shown below. The vinylic proton was displayed as a multiplet at δ 5.52, while the neighboring methyl group was shown as a singlet at δ 1.71. Another methyl singlet was observed at δ 3.68 (ester). A signal at δ 2.85 (dddd, $J = J' = 7$, $J'' = J''' = 2.5$ Hz) was assigned to H_8. The α proton of the ketone appeared at δ 2.79 as a doublet of doublets ($J = J' = 5$ Hz), which was coupled to the *syn* methano bridge proton (H_{12}) at δ 1.64 (dddd, $J = 12.5$, $J' = J'' = 5$, $J''' = 2.5$ Hz). One of the allylic methylene protons at C-4 was shown at δ 2.57 as a broad doublet of doublets ($J = 15$, $J' = 5.5$ Hz). The regiochemistry of *para*-orientation was also confirmed by the ^1H decoupling experiments. It displayed a changed pattern of the signal at δ 2.57 (H_4) and the unchanged pattern of the multiplet (δ 2.11-2.24) partly for H_7's when the vinylic multiplet was irradiated. The stereochemistry regarding the bridge head was indicated by the NOE experiment (**Figure 6**). Irradiation of H_1 at δ 2.79 resulted in 5.3% enhancement of the methyl singlet of the ester group.

Figure 6



Diels-Alder reaction of enone **266** with 2,3-dimethyl-1,3-butadiene gave the similar results. The corresponding adduct **289** was obtained in 76% yield. The infrared spectrum of **289** showed two carbonyl absorptions at 1733 (ester) and 1713 cm^{-1} (ketone). In the high resolution mass spectrum, a molecular ion peak was observed at m/z 262.1572, corresponding to the molecular formula $C_{16}H_{22}O_3$. The ^1H NMR spectrum of **289** displayed the methoxy singlet at δ 3.68, along with two vinylic methyl singlets at δ 1.70 (C-5) and 1.66 (C-6). A multiplet at δ 2.74 corresponding to two protons were assigned to H_1 and H_8. One of the protons at C-4 was shown at δ 2.42 as a doublet (J = 14 Hz) and the signal for the other one formed part of the multiplet at δ 2.18. The *syn* proton at the methano bridge (H_{12}), appearing at δ 1.62 (dddd, J = 12, J' = J'' = 4.5, J''' = 2 Hz), was crucial for the determination of the stereochemistry regarding the carbon bridge. As indicated in **Figure 6**, a 5.4% enhancement of this proton was observed when the methyl singlet of the ester group at δ 3.68 was irradiated.

When *trans*-piperylene was used as a diene, an inseparable mixture was obtained in a ratio of 4 : 1 and in 65% yield. This mixture showed two carbonyl absorptions at 1733 (ester) and 1714 cm^{-1} (ketone) in the infrared spectrum. In its high resolution mass spectrum, a molecular ion peak at m/z 248.1419 indicated the molecular formula $C_{15}H_{20}O_3$. The major component in this mixture was determined to be **290** based on the

assignment of the major set of the signals in the ^1H NMR spectrum. Two vinylic protons, H_5 and H_6, were displayed at δ 5.85 as a multiplet and 5.74 as a doublet of doublets of doublets (J = 9, J' = 5.5, J'' = 3 Hz), respectively. The methyl singlet of the ester group was shown at δ 3.78. The methine proton and the methyl group at C-4 were shown at δ 3.07 (qd, $J = J'$ = 7 Hz) and 0.83 (d, J = 7 Hz), respectively. H_8 appeared at δ 3.17 (dddd, J = 12.5, $J' = J''$ = 5.5, J''' = 3 Hz). H_1 was displayed as a doublet of doublets ($J = J'$ = 5 Hz) at δ 2.80, while the other bridge head proton H_9 appeared as a multiplet at δ 2.21. A signal at δ 2.38 (dddd, J = 17, J' = 9, $J'' = J'''$ = 3 Hz) was assigned to one of the allylic methylene protons (H_7). NOE experiments were again employed to determine the stereochemistry of **290** unambiguously. Irradiation of the methyl singlet of the ester group at δ 3.78 resulted in 0.5% enhancement on methyl doublet at δ 0.83, indicating the α orientation of the methyl group at C-4. This result was further confirmed by the following experiments. When methyl group at C-4 was irradiated, an enhancement of 1.5% on H_8 was observed. Conversely, when H_8 at δ 3.17 was irradiated, a 1.2% enhancement on the C-4 methyl group was found. The stereochemistry regarding the bridge head was indicated by the irradiation of H_8, resulting in 5.2% enhancement on H_9 was observed.

It was attempted to assign the minor set of signals in the ^1H NMR spectrum of this mixture by using extensive ^1H decoupling experiments. Only a few signals were identified. Unfortunately, this identification did not facilitate the stereochemical assignment using the NOE method since the recognized protons had nothing to do with the stereogenic centers. The structure of this minor component was tentatively proposed to be **291**, assuming that the Diels-Alder addition was completely facial selective. Consequently, the stereochemistry of the methyl group at C-4 must be opposite to that of **290**.

F. Diels-Alder reactions of enone 270:

Unlike the facile reactions of **266**, the Diels-Alder reactions of enone **270** were rather sluggish. When the cycloaddition of *trans*-piperylene to

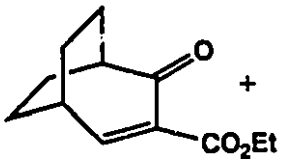
enone **270** was performed as usual using zinc chloride as a catalyst, **270** was still present in large quantity in the reaction medium after prolonged reaction time (272 hours), as indicated by TLC analysis. Only employing ferric chloride as a catalyst, these reactions became synthetically useful in terms of the reaction time and the yield (**Table 8**).

Ferric chloride catalyzed Diels-Alder reaction of **270** and isoprene at 0°C produced a 43% yield of adduct **292** after 19.5 hours. The ^{13}C NMR APT spectrum displayed one set of signals, which included δ 211.91 (ketone), 173.60 (ester), 134.58 (olefin), and 118.84 (olefin), indicating the presence of a single isomer. The infrared spectrum of **292** showed two carbonyl bands at 1740 (ester) and 1699 cm^{-1} (ketone). The molecular formula $C_{17}H_{24}O_3$ of **292** was supported by the molecular ion peak at m/z 276.1731 in the high resolution mass spectrum. In the ^1H NMR spectrum, the vinylic proton appeared as a broad singlet at δ 5.43, while the other broad singlet at δ 2.64 was assigned to the α proton of the ketone. H_8 was shown at δ 2.82 as a doublet of doublets of doublets (J = J' = 6, J'' = 2.5 Hz). The two allylic protons at C-4 were displayed as a pair of broad doublets (J = 18 Hz) at δ 2.55 and 2.38. A methyl singlet at δ 1.68 was corresponding to the vinylic methyl group. For the ester portion, the methylene protons were displayed at δ 4.16 and 4.15 as two quartets (J = 7 Hz), while the methyl triplet (J = 7 Hz) was observed at δ 1.22. The ^1H decoupling experiments were carried out to confirm the regiochemistry based on the working principle.

Cycloaddtion of 2,3-dimethyl-1,3-butadiene to enone **270** yielded adduct **293** in 49% yield. The molecular formula $C_{18}H_{26}O_3$ was confirmed by its high resolution mass spectrum, displaying a molecular ion peak at m/z 290.1882. Two carbonyl absorptions at 1738 (ester) and 1702 cm^{-1} (ketone) were observed in the infrared spectrum. The ^1H NMR spectrum of **293** displayed two vinylic methyl singlets at δ 1.68 (C-5) and 1.65 (C-6). The ring juncture proton H_8 was observed at δ 2.82 (ddd, J = J' = 6.5, J'' = 3 Hz). A multiplet at δ 2.64 was assigned to H_1 and the allylic methylene protons at C-4 were observed as a pair of doublets (J = 16 Hz) at δ 2.52 and 2.25. The methylene group of the ester moiety was displayed as a pair of doublets of quartets (J = 11, J' = 7 Hz) at δ 4.18

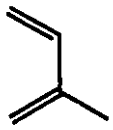
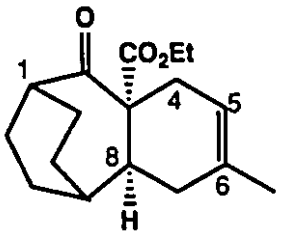
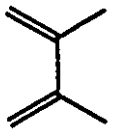
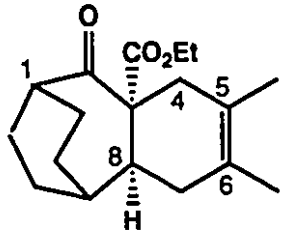
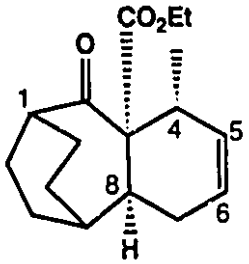
and 4.14, while the neighboring methyl group was shown at δ 1.23 as a triplet (J = 7 Hz).

Table 8. Ferric chloride catalyzed Diels-Alder reaction of enone **270**



270

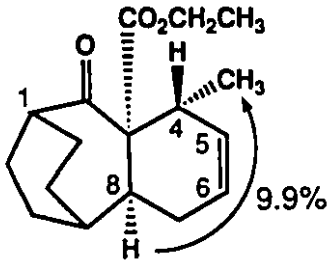
+ Diene (10 eq.) $\xrightarrow[\text{Ether, 0°C}]{FeCl_3\ (1\ eq.)}$ Product(s)

Diene	Time (h)	Product(s)	Yield (%)
	19.5	 **292**	43
	33	 **293**	49
	28	 **294**	45

A complete ester-*endo* selectivity was observed when *trans*-piperylene was added to enone **270** and the cycloadduct **294** was formed in 45% yield. The production of only one isomer was confirmed by the ^{13}C NMR APT spectrum displaying a single set of signals. This selectivity could be rationalized by the steric hindrance induced by the ethano bridge in the keto-*endo* transition state.

Four characteristic signals were observed in the ^{13}C NMR APT spectrum of **294** at δ 209.92 (ketone), 172.42 (ester), 133.58 (olefin), and 127.30 (olefin). The infrared spectrum of **294** showed two carbonyl bands at 1741 (ester) and 1702 cm^{-1} (ketone). In the high resolution mass spectrum, a molecular ion peak at m/z 276.1725 was found, consistent with the molecular formula $C_{17}H_{24}O_3$. The ^1H NMR spectrum of **294** displayed vinylic protons H_5 and H_6 at δ 5.85 as a multiplet and 5.75 as a doublet of doublets (J = 9.5, J' = 5 Hz), respectively. H_4 was shown at δ 2.99 as a broad quartet due to the coupling (J = 7 Hz) with the methyl group at the same carbon (δ 0.98, doublet). H_1 appeared as a multiplet at δ 2.64, and H_8 was displayed as a doublet of doublets of doublets (J = J' = 7, J'' = 4 Hz) at δ 2.93. For the ester group, the methylene protons appeared as a pair of doublets of quartets (J = 11, J' = 7 Hz) at δ 4.20 and 4.14, while the methyl protons were shown as a triplet (J = 7 Hz) at δ 1.26. The stereochemistry of **294** was supported by the NOE experiment (**Figure 7**). Irradiation of H_8 at δ 2.93 resulted in 9.9% enhancement on methyl doublet at δ 0.98 (C-4), indicating the proximity between these two units.

Figure 7



294

III. Conclusion:

Lewis acid catalyzed Diels-Alder reaction of 2-carbalkoxy-2-cycloheptenones displayed a promising and interesting aspect in terms of stereoselectivity and the unexpected high facial selectivity. In most cases the stereoselectivity favoring ester-*endo* adducts were exhibited due to the sterically unfavored keto-*endo* transition state. One exception with the keto-*endo* adduct favored was the cycloaddition with enone **263**. Likely, the extra methyl group of **263** played an important role in directing this unusual selectivity. The complete and extraordinary facial stereoselectivity was observed in the cycloadditions with enones **263** and **266**. However, further study is required to explore the reasons for this unusual phenomenon. In addition, the substitution pattern on the seven-membered ring also induced large effects on the rates and the yields of the reactions. A general trend is concluded as follows. In a related skeletal series, an unsymmetrically substituted enone reacts the fastest and gives the highest yield, followed by unsubstituted enone. The symmetrically substituted enone reacts slowly with poor yields. For instance, according to the rate and the yield of the corresponding Diels-Alder reactions, the order of **263** (unsymmetrically substituted) > **256** (unsubstituted) > **260** (symmetrically substituted) was observed. Similarly, **266** (unsymmetrically substituted) was found to be better than **270** (symmetrically substituted) as a dienophile. Accordingly, the study on the Diels-Alder chemistry of 2-carbalkoxy-2-cycloheptenones serves as a good basis for the stereoselective synthesis of various polycyclic natural products containing a six-membered ring fused with a seven-membered one.

Experimental

General Procedures and Materials

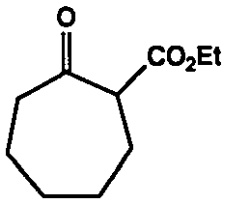
Refer to Chapter 1, Experimental Section for a detailed description of general procedures and materials.

General Procedure for the Ring Expansion Reactions:

Boron trifluoride etherate (15 mmol, 1.5 eq.) was added to a solution of ketone (10 mmol, 1.0 eq.) in dry ether (20 mL) at 0°C. A solution of ethyl diazoacetate (15 mmol, 1.5 eq.) in dry ether (5 mL) was then added over a period of 15 minutes and the resulting solution was stirred at room temperature under an argon atmosphere. When the reaction completed, it was cooled to 0°C and neutralized with saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with chloroform (3 × 20 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried, and concentrated. Purification by bulb-to-bulb distillation under reduced pressure gave the desired keto ester. Yields and times of the reactions can be found in **Table 2**.

The keto esters **255**, **257**, **259**, **261**, **262**, **268**, and **269** showed the following spectral data:

2-Carbethoxycycloheptanone (255)

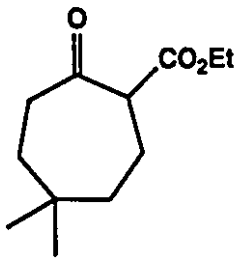


255

Keto ester **255** was shown by the following spectral data to exist as a mixture of 75% keto form and 25% enol form.

IR (CH_2Cl_2, cast): 1742 (C=O, ester), 1707 (C=O, ketone), 1638 cm^{-1} (C=O, enol ester); ^1H NMR (400 MHz, $CDCl_3$): δ 12.75 (s, 0.25H, =C(O**H**)-), 4.18 (m, 2H, -COOC**H**$_2$CH$_3$), 3.52 (dd, J = 10.5, 4 Hz, 0.75H, -COC**H**(COOEt)-), 2.65-1.40 (7 × m, 10H), 1.30 (t, J = 7 Hz, 0.75H, -COOCH$_2$C**H**$_3$), 1.26 (t, J = 7 Hz, 2.25H, -COOCH$_2$C**H**$_3$); MS m/z (M^+) for $C_{10}H_{16}O_3$: calcd. 184.1100, found 184.1101.

2-Carbethoxy-5,5-dimethylcycloheptanone (257)



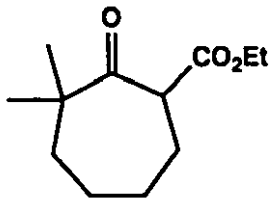
257

Keto ester **257** was shown by the following spectral data to exist as a mixture of 95% keto form and 5% enol form.

IR ($CHCl_3$, cast): 1743 (C=O, ester), 1707 (C=O, ketone), 1640 cm^{-1} (C=O, enol ester); ^1H NMR (400 MHz, $CDCl_3$): δ 12.70 (s, 0.05H, =C(O**H**)-), 4.19 (q, J = 7 Hz, 1H, -COOC**H**HCH$_3$), 4.17 (q, J = 7 Hz, 1H,

-COOCH**H**CH_3), 3.51 (t, J = 7.5 Hz, 0.95H, -COC**H**(COOEt)-), 2.64 (ddd, J = 16.5, 10, 5.5 Hz, 0.95H, -C**H**HCO-), 2.45 (ddd, J = 16.5, 6.5, 4 Hz, 0.95H, -CH**H**CO-), 2.35 (m, 0.1H), 1.97 (m, 2H), 1.65-1.55 (m, 3H), 1.38 (m, 1H), 1.26 (t, J = 7 Hz, 3H, -$COOCH_2C\mathbf{H}_3$), 0.98 (s, 3H, -$C\mathbf{H}_3$), 0.93 (s, 3H, -$C\mathbf{H}_3$); MS m/z (M^+) for $C_{12}H_{20}O_3$: calcd. 212.1413, found 212.1413.

2-Carbethoxy-7,7-dimethylcycloheptanone (259)

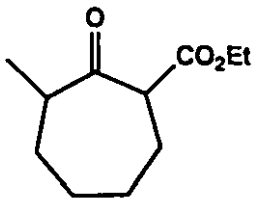


259

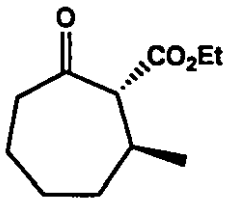
Keto ester **259** was shown by the following spectral data to exist completely in the keto form.

IR ($CHCl_3$, cast): 1748 (C=O, ester), 1708 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 4.14 (q, J = 7 Hz, 2H, -$COOC\mathbf{H}_2CH_3$), 3.86 (dd, J = 12, 3 Hz, 1H, -COC**H**(COOEt)-), 2.13 (br d, J = 14 Hz, 1H), 1.88 (br d, J = 14 Hz, 1H), 1.82-1.50 (m, 4H), 1.39 (br dd, J = 12, 12 Hz, 1H), 1.22 (t, J = 7 Hz, 3H, -$COOCH_2C\mathbf{H}_3$), 1.18 (s, 3H, -$C\mathbf{H}_3$), 1.14 (m, 1H), 1.10 (s, 3H, -$C\mathbf{H}_3$); MS m/z (M^+) for $C_{12}H_{20}O_3$: calcd. 212.1413, found 212.1415; Analysis for $C_{12}H_{20}O_3$: calcd. C: 67.89%, H: 9.50%, found C: 67.60%, H: 9.68%.

2-Carbethoxy-7-methylcycloheptanone (261) and *trans*-2-carbethoxy-3-methylcycloheptanone (262)



261

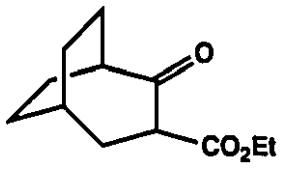


262

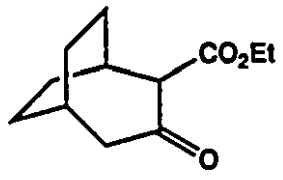
Ring expansion of 2-methylcyclohexanone gave a 9 : 1 mixture of regioisomers **261** (existing as a mixture of two stereoisomers in a ratio of 7 : 2) and **262**. All the isomers were shown to exist completely in the keto form.

IR (film): 1743 (C=O, ester), 1709 cm^{-1} (C=O, ketone); ^1H NMR (200 MHz, $CDCl_3$): δ 4.15 (m, 2H, -COOC**H**$_2$CH$_3$), 3.67 (dd, J = 7.5, 5 Hz, 0.2H, -COC**H**(COOEt)-), 3.48 (dd, J = 12, 4.5 Hz, 0.7H, -COC**H**(COOEt)-), 3.13 (d, J = 10 Hz, 0.1H, -COC**H**(COOEt)CH(CH$_3$)-), 1.25, 1.23 (2 × t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.12 (d, J = 6.5 Hz, 2.1H, -C**H**$_3$), 1.11 (d, J = 6.5 Hz, 0.6H, -C**H**$_3$), 1.01 (d, J = 6.5 Hz, 0.3H, -C**H**$_3$); MS m/z (M^+) for $C_{11}H_{18}O_3$: calcd. 198.1256, found 198.1261; Analysis for $C_{11}H_{18}O_3$: calcd. C: 66.64%, H: 9.15%, found C: 66.63%, H: 9.24%.

3-Carbethoxybicyclo[3.2.2]nonan-2-one (268) and 2-carbethoxybicyclo[3.2.2]nonan-3-one (269)



268

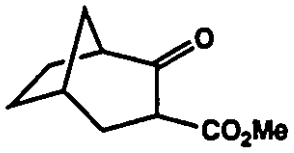


269

Ring expansion of bicyclo[2.2.2]octanone gave a 11 : 4 mixture of regioisomers **268** (keto form : enol form = 5 : 6) and **269** (keto form : enol form = 1 : 1).

IR ($CHCl_3$, cast): 1744 (C=O, ester), 1704 (C=O, ketone), 1643 (C=O, enol ester), 1610 cm^{-1} (-C=C-OH); ^1H NMR (400 MHz, $CDCl_3$): δ 12.72 (s, 0.13H, =C(O**H**)-), 12.62 (s, 0.4H, =C(O**H**)-), 4.20 (m, 2H, -COOC**H**$_2$CH$_3$), 3.80 (dd, J = 12, 8.5 Hz, 0.33H, -COC**H**(COOEt)-), 3.52 (ddd, J = 3, 1, 1 Hz, 0.13H, -COC**H**(COOEt)-), 1.29 (m, 3H, -COOCH$_2$C**H**$_3$); MS m/z (M^+) for $C_{12}H_{18}O_3$: calcd. 210.2156, found 210.1258; Analysis for $C_{12}H_{18}O_3$: calcd. C: 68.56%, H: 8.63%, found C: 68.28%, H: 8.82%.

(1S*,5R*)-3-Carbomethoxybicyclo[3.2.1]octan-2-one (265)



265

Dimethyl carbonate (4.30 mL, 50.73 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 1.01 g, 25.37 mmol) in dry tetrahydrofuran (15 mL). The resulting mixture was heated under reflux under an argon atmosphere. A solution of bicyclo[3.2.1]octan-2-one (85%, 1.05 g, 8.455 mmol) in dry tetrahydrofuran (15 mL) was then added. After refluxing for 2.5 hours, the solution was cooled, neutralized with 10% acetic acid, and extracted with ether (3 × 30 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried, concentrated, and purified by bulb-to-bulb distillation (85°C/1 mm-Hg) to give keto ester **265** (1.24 g, 95% yield based on 85% purity of the ketone; keto form : enol form = 2 : 5) as a colorless oil: IR ($CHCl_3$, cast): 1748 (C=O, ester),

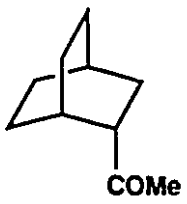
1725 (C=O, ketone), 1655 (C=O, enol ester), 1615 cm^{-1} (-C=C-OH); ^1H NMR (400 MHz, $CDCl_3$): δ 11.91 (s, 0.71H, =C(O**H**)-), 3.75 (s, 0.86H, -COOC**H**$_3$), 3.72 (s, 2.14H, -COOC**H**$_3$), 3.47 (dd, *J* = 12, 8 Hz, 0.29H, -COC**H**(COOCH$_3$)-); MS m/z (M^+) for $C_{10}H_{14}O_3$: calcd. 182.0943, found 182.0949.

(1S*,4S*,5S*)-5-Acetylbicyclo[2.2.2]oct-2-ene (271)

271

To a solution of 1,3-cyclohexadiene (5.02 g, 62.65 mmol) and methyl vinyl ketone (26.1 mL, 313.24 mmol) in dry dichloromethane (40 mL) at 0°C, tin(IV) chloride (7.3 mL, 62.65 mmol) was slowly added. The resulting solution was stirred at 0°C under an argon atmosphere for 1 hour. The solution was then neutralized with saturated aqueous sodium bicarbonate solution. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (30 mL). The combined dichloromethane solutions were washed with water, dried, concentrated, and purified by flash chromatography (20% ether in skelly B) to give the adduct **271** (8.0 g, 85% yield) as a colorless oil: IR ($CHCl_3$, cast): 1709 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 6.28 (ddd, *J* = 7, 7, 1 Hz, 1H, =C**H**-), 6.10 (ddd, *J* = 7, 7, 0.5 Hz, 1H, =C**H**-), 2.89 (m, 1H), 2.66 (ddd, *J* = 9, 7, 2 Hz, 1H, -C**H**(COCH$_3$)-), 2.60 (m, 1H), 2.10 (s, 3H, C**H**$_3$CO-), 1.65 (m, 2H), 1.60 (m, 1H), 1.49 (m, 1H), 1.32 (m, 1H), 1.25 (m, 1H); MS m/z (M^+) for $C_{10}H_{14}O$: calcd. 150.1045, found 150.1043.

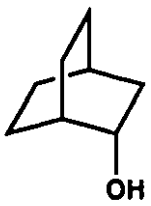
2-Acetylbicyclo[2.2.2]octane (272)



272

Ketone **271** (7.88 g, 52.46 mmol) was dissolved in ethyl acetate (70 mL). 5% Palladium on carbon (0.45 g) was added. The mixture was hydrogenated under 20 p.s.i. (1 p.s.i. = 6.9 kPa) of hydrogen for 5 hours using a Parr hydrogenation apparatus. The mixture was then filtered and concentrated to give ketone **272** (7.77 g, 97% yield) as a colorless oil: IR (CH_2Cl_2, cast): 1710 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 2.63 (ddd, J = 10, 6, 2.5 Hz, 1H, -C**H**($COCH_3$)-), 2.17-1.90 (m, 3H), 2.13 (s, 3H, C**H**$_3$CO-), 1.70-1.35 (m, 9H); MS m/z (M^+) for $C_{10}H_{16}O$: calcd. 152.1202, found 152.1202.

Bicyclo[2.2.2]octan-2-ol (273)



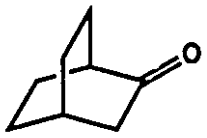
273

To a mixture of ketone **272** (4.59 g, 30.15 mmol) and disodium hydrogen phosphate (12.84 g, 90.45 mmol) in dry dichloromethane (50 mL) was added *m*-chloroperoxybenzoic acid (70%, 14.87 g, 60.30 mmol). The resulting solution was stirred at room temperature under an argon atmosphere for 25 hours. At the end of this time, the solution was neutralized with saturated sodium bicarbonate solution. The

dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined dichloromethane solutions were washed with saturated aqueous sodium sulfite solution, dried, and concentrated. The residue was dissolved in methanol (50 mL).

The methanol solution was mixed with 1 N aqueous sodium hydroxide solution (50 mL). After stirring at room temperature for 4.5 hours, the solution was acidified with 1 N hydrochloric acid and extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with water, dried, concentrated, and purified by flash chromatography (40-50% ether in skelly B) to give alcohol **273** (3.80 g, 100% yield) as a white solid: mp 88-89°C (skelly B); IR (CH_2Cl_2, cast): 3293 cm^{-1} (O-H); ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (dddd, J = 9, 4, 4, 1.5 Hz, 1H, -C**H**(OH)-), 2.01 (dddd, J = 14, 9.5, 3, 2.5 Hz, 1H), 1.88 (m, 1H), 1.60 (m, 4H), 1.50-1.30 (m, 7H); MS m/z (M^+) for $C_8H_{14}O$: calcd. 126.1045, found 126.1044.

Bicyclo[2.2.2]octanone (267)

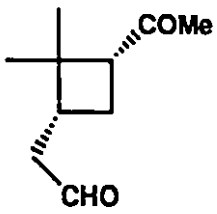


267

Pyridinium chlorochromate on alumina (0.9 mmol/g, 50.18 g, 45.16 mmol) was added to a solution of alcohol **273** (3.80 g, 30.11 mmol) in dry dichloromethane (70 mL) and the resulting mixture was stirred at room temperature under an argon atmosphere for 2 hours. The mixture was then filtered through Florisil, concentrated, and purified by flash chromatography (20% ether in skelly B) to give ketone **267** (2.86 g, 76% yield) as a volatile white solid: IR (CH_2Cl_2, cast): 1727 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 2.24 (br s, 3H), 2.15 (m, 1H), 1.80 (m, 4H),

1.73-1.55 (m, 4H); MS m/z (M^+) for $C_8H_{12}O$: calcd. 124.0888, found 124.0889.

(1R,3R)-(+)-1-Acetyl-2,2-dimethyl-3-(2-oxoethyl)cyclobutane (275)



275

Ozone was passed through a solution of (+)-α-pinene (1.27 g, 9.32 mmol) in dichloromethane (20 mL) and methanol (2 mL) at -78°C for 1 hour. At the end of this time, dimethyl sulfide (15 mL) was added and the resulting solution was warmed up to room temperature gradually while stirring. After 11 hours, the solution was concentrated and purified by flash chromatography (50% ether in skelly B) to give keto aldehyde **275** (1.39 g, 89% yield) as a colorless oil: $[\alpha]_D^{22}$ = +75.47° (c. 1.9, $CHCl_3$); IR (film): 1733, 1706 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, J = 1 Hz, 1H, -C**H**O), 2.91 (dd, J = 10.5, 8 Hz, 1H, -C**H**$COCH_3$), 2.51-2.38 (m, 3H), 2.03 (s, 3H, C**H**$_3$CO-), 1.95 (m, 2H), 1.33 (s, 3H, -C**H**$_3$), 0.87 (s, 3H, -C**H**$_3$); MS m/z (M^+ - H) for $C_{10}H_{15}O_2$: calcd. 167.1073, found 167.1051; Analysis for $C_{10}H_{16}O_2$: calcd. C: 71.39%, H: 9.59%, found C: 70.94%, H: 9.52%.

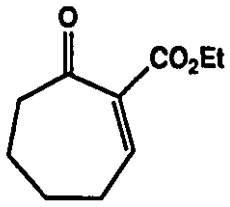
General Procedure for Phenylselenenylation and Oxidative Elimination Reactions:

To a solution of phenylselenenyl chloride (12.0 mmol, 3 eq.) in dry dichloromethane (20 mL) at 0°C, pyridine (12.0 mmol, 3 eq.) was slowly

added. After stirring at 0°C under an argon atmosphere for 15 minutes, a solution of keto ester (4.0 mmol, 1 eq.) in dry dichloromethane (10 mL) was then added. The resulting dark red solution was stirred at room temperature under an argon atmosphere. When the reaction completed, it was cooled to 0°C. Aqueous 30% hydrogen peroxide (1 mL each) was then added at intervals of 10 minutes until the solution turned colorless (*ca.* 5-10 times). At the end of this time, the mixture was diluted with water. The dichloromethane layer was separated, washed with saturated aqueous sodium bicarbonate solution, 1 N hydrochloric acid, and saturated aqueous sodium sulfite solution, dried, and concentrated. Purification by either flash chromatography or bulb-to-bulb distillation gave the desired carbethoxy enone. Yields and times of the reactions can be found in **Table 2**.

The keto esters **256**, **258**, **260**, **263**, **264**, **266**, and **270** showed the following spectral data:

2-Carbethoxy-2-cyclohepten-1-one (256)



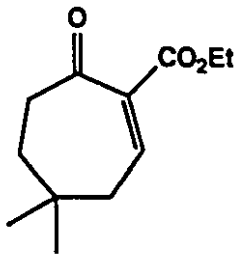
256

Keto ester **256** was shown by the following spectral data to exist completely in the keto form.

IR ($CHCl_3$, cast): 1725 (C=O, ester), 1694 cm^{-1} (C=O, ketone); ^1H NMR (200 MHz, $CDCl_3$): δ 7.36 (t, J = 6 Hz, 1H, -**H**C=CCO-), 4.22 (q, J = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 2.68 (t, J = 6.5 Hz, 2H, -C**H**$_2$CO-), 2.49(dt, J = 6

Hz, 2H, -C**H**$_2$CH=CCO-), 1.92-1.70 (m, 4H), 1.28 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$); MS m/z (M$^+$) for $C_{10}H_{14}O_3$: calcd. 182.0943, found 182.0944.

2-Carbethoxy-5,5-dimethyl-2-cyclohepten-1-one (258)

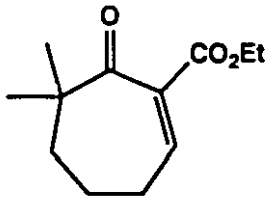


258

Keto ester **258** was shown by the following spectral data to exist as a mixture of 90% keto form and 10% enol form.

IR ($CHCl_3$, cast): 1728 (C=O, ester), 1690 (C=O, ketone), 1634 cm^{-1} (C=O, enol ester); ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.28 (s, 0.1H, =C(O**H**)-), 7.32 (t, J = 7.5 Hz, 0.9H, -**H**C=CCO-), 6.04 (d, J = 13.5 Hz, 0.1H, -**H**C=CH-), 5.26 (d, J = 13.5 Hz, 0.1H, -HC=C**H**-), 4.25 (q, J = 7 Hz, 0.2H, -COOC**H**$_2$CH$_3$), 4.24 (q, J = 7 Hz, 1.8H, -COOC**H**$_2$CH$_3$), 2.52 (dd, J = 2.5, 2.5 Hz, 1H), 2.51 (d, J = 12 Hz, 1H), 2.20 (d, J = 7 Hz, 2H), 1.64 (dd, J = 2.5, 2.5 Hz, 1H), 1.64 (d, J = 12 Hz, 1H), 1.29 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.03 (s, 6H, 2 × -C**H**$_3$); MS m/z (M$^+$) for $C_{12}H_{18}O_3$: calcd. 210.1256, found 210.1259.

2-Carbethoxy-7,7-dimethyl-2-cyclohepten-1-one (260)

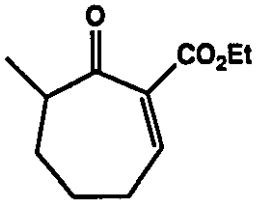


260

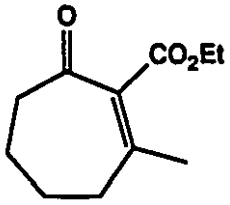
Phenylselenenylation-oxidative elimination of keto ester **259** did not proceed to completion. A 61% of **259** was recovered. Keto ester **260** was shown by the following spectral data to exist completely in the keto form.

IR (CH_2Cl_2, cast): 1722 (C=O, ester), 1695 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, J = 5 Hz, 1H, -**H**C=CCO-), 4.20 (q, J = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 2.42 (td, J = 6, 6 Hz, 2H, -C**H**$_2$CH=CCO-), 1.71-1.60 (m, 4H), 1.25 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.18 (s, 6H, 2 × -C**H**$_3$); MS m/z (M^+) for $C_{12}H_{18}O_3$: calcd. 210.1256, found 210.1252.

2-Carbethoxy-7-methyl-2-cyclohepten-1-one (263) and 2-carbethoxy-3-methyl-2-cyclohepten-1-one (264)



263



264

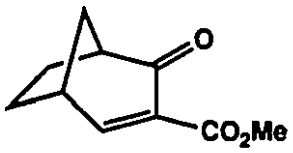
Phenylselenenylation-oxidative elimination of the inseparable 9 : 1 mixture of keto esters **261** and **262** did not proceed to completion. A 7% of **262** was recovered. Carbethoxy enones **263** (keto form : enol form = 2

: 1) and **264** (keto form only) were separated by flash chromatography and obtained in a ratio of 24 : 1.

263: IR (film): 1724 (br, C=O), 1636 cm^{-1} (C=O, enol ester); ^1H NMR (200 MHz, $CDCl_3$): δ 13.46 (s, 0.33H, =C(O**H**)-), 7.32 (dd, *J* = 6, 5.5 Hz, 0.67H, -**H**C=CCO-), 6.22 (ddd, *J* = 12, 2, 2 Hz, 0.33H, -**H**C=CH-), 5.65 (ddd, *J* = 12, 5, 5 Hz, 0.33H, -HC=C**H**-), 4.23 (q, *J* = 7 Hz, 0.67H, -COOC**H**$_2$CH$_3$), 4.21 (q, *J* = 7 Hz, 1.33H, -COOC**H**$_2$CH$_3$), 2.84, 2.46, 2.25, 1.91, 1.75, 1.50 (6 × m, 6.34H), 1.32 (t, *J* = 7 Hz, 1H, -COOCH$_2$C**H**$_3$), 1.27 (t, *J* = 7 Hz, 2H, -COOCH$_2$C**H**$_3$), 1.15 (d, *J* = 6.5 Hz, 3H, -C**H**$_3$); MS m/z (M^+) for $C_{11}H_{16}O_3$: calcd. 196.1100, found 196.1090; Analysis for $C_{11}H_{16}O_3$: calcd. C: 67.32%, H: 8.22%, found C: 66.84%, H: 8.48%.

264: IR (film): 1729 cm^{-1} (br, C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 4.24 (q, *J* = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 2.61 (m, 2H), 2.43 (m, 2H), 2.03 (s, 3H, =C(C**H**$_3$)-), 1.81 (m, 4H), 1.29 (t, *J* = 7 Hz, 3H, -COOCH$_2$C**H**$_3$); MS m/z (M^+) for $C_{11}H_{16}O_3$: calcd. 196.1100, found 196.1100.

(1S*,5R*)-3-Carbomethoxybicyclo[3.2.1]oct-3-en-2-one (266)

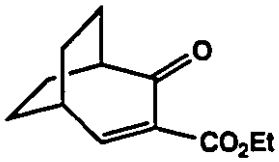


266

Keto ester **266** showed the following spectral data:

IR (film): 1743 (C=O, ester), 1689 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 7, 1.5 Hz, 1H, -**H**C=CCO-), 3.78 (s, 3H, -COOC**H**$_3$), 3.04 (m, 2H, -C**H**CO-, =CC**H**-), 2.16 (m, 1H), 2.06 (br d, *J* = 12 Hz, 1H), 2.01 (m, 1H), 1.76 (m, 1H), 1.66 (dddd, *J* = 12, 5, 5, 1.5 Hz, 1H), 1.59 (m, 1H); MS m/z (M^+) for $C_{10}H_{12}O_3$: calcd. 180.0787, found 180.0790.

3-Carbethoxybicyclo[3.2.2]non-3-en-2-one (270)



270

Keto ester **270** showed the following spectral data:

IR ($CHCl_3$, cast): 1736 (C=O, ester), 1677 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 9.5 Hz, 1H, -**H**C=CCO-), 4.26 (q, J = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 2.90 (m, 2H), 1.82 (m, 4H), 1.67 (m, 4H), 1.32 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$); MS m/z (M^+) for $C_{12}H_{16}O_3$: calcd. 208.1099, found 208.1104; Analysis for $C_{12}H_{16}O_3$: calcd. C: 69.21%, H: 7.74%, found C: 69.39%, H: 7.88%.

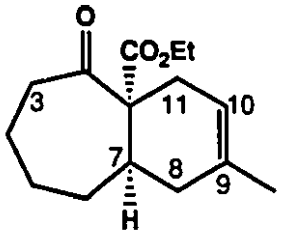
General Procedure for $ZnCl_2$ Catalyzed Diels-Alder Reactions:

Zinc chloride (1-3 eq.) was fused in a reaction flask under an argon atmosphere and then dissolved in dry ether (5 mL). A solution of carbalkoxy enone (0.3 mmol, 1 eq.) in dry ether (3 mL) was added. After stirring at room temperature under an argon atmosphere for 30 minutes, diene (3.0 mmol, 10 eq.) was then added. The resulting mixture was stirred at room temperature under an argon atmosphere. When the reaction completed, it was neutralized with saturated aqueous sodium bicarbonate solution. The ether layer was separated and the aqueous layer was extracted with ether (10 mL). The combined ether solutions were washed with saturated aqueous sodium chloride solution, dried, concentrated, and purified by flash chromatography (ether - skelly B) to give the desired adduct(s). Yields and times of the reactions as well as the quantities of zinc chloride relative to carbalkoxy enone can be found in **Tables 3-8**.

General Procedure for $FeCl_3$, $AlCl_3$, $SnCl_4$, and BF_3·OEt_2 Catalyzed Diels-Alder Reactions:

To a solution of carbalkoxy enone (0.5 mmol, 1 eq.) in dry ether (10 mL), diene (5.0 mmol, 10 eq.) was added. Lewis acid (0.5 mmol, 1 eq.) was then added and the resulting solution was stirred under an argon atmosphere. When the reaction completed, it was neutralized with saturated aqueous sodium bicarbonate solution. The ether layer was separated and the aqueous layer was extracted with ether (10 mL). The combined ether solutions were washed with saturated sodium chloride solution, dried, concentrated, and purified by flash chromatography (ether - skelly B) to give the desired adduct(s). Yields, times, and temperatures of the reactions can be found in **Tables 3** and **8**.

(1R*,7R*)-1-Carbethoxy-9-methylbicyclo[5.4.0]undec-9-en-2-one (276)

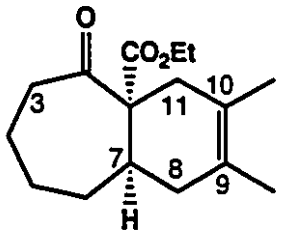


276

IR ($CHCl_3$, cast): 1743 (C=O, ester), 1700 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.34 (br s, 1H, **H**-10), 4.16 (q, *J* = 7 Hz, 1H, -COOC**H**HCH$_3$), 4.15 (q, *J* = 7 Hz, 1H, -COOCH**H**CH$_3$), 2.98 (ddd, *J* = 14, 9.5, 3 Hz, 1H, **H**-3), 2.68 (m, 1H, **H**-7), 2.65 (dq, *J* = 18, 2 Hz, 1H, **H**-11), 2.42 (ddd, *J* = 14, 9, 4 Hz, 1H, **H**-3), 2.33 (br d, *J* = 18 Hz, 1H, **H**-11), 2.09 (br d, *J* = 18 Hz, 1H, **H**-8), 1.82-1.50 (m, 7H), 1.61 (br s, 3H, 9-C**H**$_3$), 1.23 (t, *J* = 7 Hz, 3H, -COOCH$_2$C**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 209.72 (p), 171.64 (p), 131.17 (p), 118.46 (a), 61.60 (p), 61.24 (p), 42.67

(p), 36.58 (a), 35.47 (p), 33.12 (p), 29.81 (p), 27.65 (p), 25.27 (p), 23.35 (a), 14.00 (a); MS m/z (M^+) for $C_{15}H_{22}O_3$: calcd. 250.1570, found 250.1568; Analysis for $C_{15}H_{22}O_3$: calcd. C: 71.97%, H: 8.86%, found C: 71.51%, H: 8.65%.

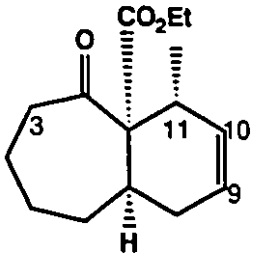
(1R*,7R*)-1-Carbethoxy-9,10-dimethylbicyclo[5.4.0]undec-9-en-2-one (277)



277

IR ($CHCl_3$, cast): 1742 (C=O, ester), 1701 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 4.14 (q, J = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 2.96 (ddd, J = 14, 10, 3.5 Hz, 1H, **H**-3), 2.64 (m, 1H, **H**-7), 2.56 (br d, J = 17.5 Hz, 1H, **H**-11), 2.41 (ddd, J = 14, 9, 3 Hz, 1H, **H**-3), 2.25 (br d, J = 17.5 Hz, 1H, **H**-11), 2.10 (br d, J = 17.5 Hz, 1H, **H**-8), 1.82-1.60 (m, 7H), 1.63 (s, 3H, 10-C**H**$_3$), 1.56 (s, 3H, 9-C**H**$_3$), 1.22 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 209.94 (p), 199.57 (p), 123.74 (p), 122.76 (p), 62.67 (p), 61.19 (p), 42.71 (p), 37.10 (p), 36.80 (a), 35.53 (p), 33.13 (p), 27.73 (p), 25.34 (p), 18.86 (a), 18.53 (a), 14.01 (a); MS m/z (M^+) for $C_{16}H_{24}O_3$: calcd. 264.1726, found 264.1727; Analysis for $C_{16}H_{24}O_3$: calcd. C: 72.69%, H: 9.15%, found C: 72.75%, H: 9.08%.

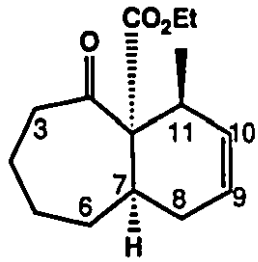
(1S*,7R*,11R*)-1-Carbethoxy-11-methylbicyclo[5.4.0]undec-9-en-2-one (278)



278

IR ($CHCl_3$, cast): 1739 (C=O, ester), 1702 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.64 (m, 1H, **H**-10), 5.54 (m, 1H, **H**-9), 4.22 (dq, J = 11, 7 Hz, 1H, -COOC**H**HCH_3), 4.18 (dq, J = 11, 7 Hz, 1H, -COOCH**H**CH_3), 2.83 (m, 2H, **H**-3, **H**-11), 2.40 (m, 2H), 2.30 (m, 1H), 1.92 (m, 1H), 1.85-1.67 (m, 4H), 1.42 (m, 2H), 1.27 (t, J = 7 Hz, 3H, -$COOCH_2C$**H**$_3$), 0.91 (d, J = 7 Hz, 3H, 11-C**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 206.81 (p), 170.69 (p), 131.65 (a), 123.13 (a), 64.94 (p), 60.79 (p), 43.66 (p), 34.66 (a), 31.87 (a), 31.69 (p), 28.81 (p), 24.91 (p), 23.34 (p), 17.27 (a), 14.05 (a); MS m/z (M^+) for $C_{15}H_{22}O_3$: calcd. 250.1570, found 250.1569.

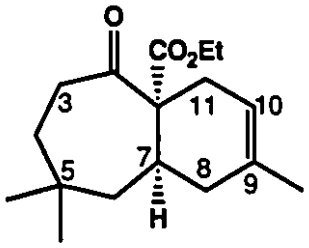
(1S*,7R*,11S*)-1-Carbethoxy-11-methylbicyclo[5.4.0]undec-9-en-2-one (279)



279

IR ($CHCl_3$, cast): 1720 (C=O, ester), 1699 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.55 (m, 2H, **H**-9, **H**-10), 4.27 (q, J = 7 Hz, 1H, -COOC**H**HCH$_3$), 4.26 (q, J = 7 Hz, 1H, -COOCH**H**CH$_3$), 2.88 (dddd, J = 18.5, 4.5, 4.5, 1.5 Hz, 1H, **H**-3), 2.62 (m, 1H, **H**-11), 2.52 (ddd, J = 12, 7.5, 4 Hz, 1H, **H**-7), 2.34 (ddd, J = 18.5, 13, 5 Hz, 1H, **H**-3), 1.96 (ddd, J = 15, 3, 3 Hz, 1H, **H**-6), 1.90 (m, 2H, 2 × **H**-8), 1.74 (m, 3H), 1.42 (m, 2H), 1.31 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.11 (d, J = 7 Hz, 3H, 11-C**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 205.95 (p), 172.45 (p), 131.80 (a), 123.05 (a), 65.67 (p), 60.97 (p), 44.70 (p), 40.87 (a), 38.52 (a), 32.63 (p), 28.26 (p), 23.96 (p), 23.37 (p), 16.48 (a), 14.12 (a); MS m/z (M^+) for $C_{15}H_{22}O_3$: calcd. 250.1570, found 250.1569; Analysis for $C_{15}H_{22}O_3$: calcd. C: 71.97%, H: 8.86%, found C: 72.03%, H: 9.11%.

(1R*,7R*)-1-Carbethoxy-5,5,9-trimethylbicyclo[5.4.0]undec-9-en-2-one (280)

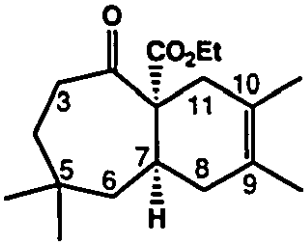


280

mp 98-99°C (skelly B); IR ($CHCl_3$, cast): 1733 (C=O, ester), 1694 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.33 (br s, 1H, **H**-10), 4.13 (q, J = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 3.07 (ddd, J = 13, 13, 2 Hz, 1H, **H**-3), 2.91 (m, 2H, **H**-7, **H**-11), 2.31 (ddd, J = 13, 8, 2 Hz, 1H, **H**-3), 2.29 (m, 1H, **H**-8), 2.14 (br d, J = 18 Hz, 1H, **H**-11), 1.65-1.52 (m, 3H), 1.62 (br s, 3H, 9-C**H**$_3$), 1.38 (m, 1H), 1.22 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.16 (m, 1H), 1.12 (s, 3H, 5-C**H**$_3$), 0.93 (s, 3H, 5-C**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 183.88 (p), 170.98 (p), 130.89 (p), 118.31 (a), 61.32 (2 × p), 46.60 (p), 39.07 (p), 38.16 (p), 37.60 (p), 33.04 (p), 32.83 (a), 31.18 (a),

27.21 (p), 25.50 (a), 23.58 (a), 13.99 (a); MS m/z (M^+) for $C_{17}H_{26}O_3$: calcd. 278.1883, found 278.1885; Analysis for $C_{17}H_{26}O_3$: calcd. C: 73.34%, H: 9.41%, found C: 73.16%, H: 9.20%.

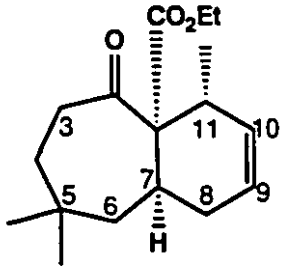
(1R*,7R*)-1-Carbethoxy-5,5,9,10-tetramethylbicyclo[5.4.0]-undec-9-en-2-one (281)



281

mp 62-63°C (skelly B); IR ($CHCl_3$, cast): 1746 (C=O, ester), 1702 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 4.14 (q, J = 7 Hz, 1H, -COOC**H**HCH$_3$), 4.13 (q, J = 7 Hz, 1H, -COOCH**H**CH$_3$), 3.05 (ddd, J = 14, 14, 2 Hz, 1H, **H**-3), 2.86 (m, 1H, **H**-7), 2.73 (br d, J = 18 Hz, 1H, **H**-11), 2.29 (m, 2H, **H**-3, **H**-8), 2.10 (br d, J = 18 Hz, 1H, **H**-11), 1.64 (s, 3H, 10-C**H**$_3$), 1.60 (m, 2H), 1.57 (br s, 3H, 9-C**H**$_3$), 1.51 (dd, J = 15.5, 11 Hz, 1H, **H**-6), 1.38 (dd, J = 14, 14 Hz, 1H, **H**-4), 1.21 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.12 (dd, J = 15, 2.5 Hz, 1H), 1.11 (s, 3H, 5-C**H**$_3$), 0.92 (s, 3H, 5-C**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 211.35 (p), 171.16 (p), 123.05 (p), 122.66 (p), 62.63 (p), 61.27 (p), 46.71 (p), 39.32 (p), 39.04 (p), 38.15 (p), 33.08 (p), 32.94 (p), 32.79 (a), 31.43 (a), 25.58 (a), 19.05 (a), 18.25 (a), 14.00 (a); MS m/z (M^+) for $C_{18}H_{28}O_3$: calcd. 292.2039, found 292.2040; Analysis for $C_{18}H_{28}O_3$: calcd. C: 73.93%, H: 9.65%, found C: 73.98%, H: 10.05%.

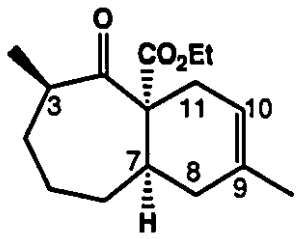
(1S*,7S*,11R*)-1-Carbethoxy-5,5,11-trimethylbicyclo[5.4.0]-undec-9-en-2-one (282)



282

IR ($CHCl_3$, cast): 1746 (C=O, ester), 1698 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (m, 1H, **H**-10), 5.55 (m, 1H, **H**-9), 4.16 (q, J = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 3.00 (m, 1H, **H**-11), 2.99 (ddd, J = 15, 10.5, 3 Hz, 1H, **H**-3), 2.81 (m, 1H, **H**-7), 2.40 (ddd, J = 15, 9.5, 2.5 Hz, 1H, **H**-3), 2.13 (dqdd, J = 17.5, 3, 3, 3 Hz, 1H, **H**-8), 1.92 (m, 2H, **H**-6, **H**-8), 1.56-1.28 (m, 3H, 2 × **H**-4, **H**-6), 1.24 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.11 (d, J = 7.5 Hz, 3H, 11-C**H**$_3$), 1.05 (s, 3H, 5-C**H**$_3$), 0.93 (s, 3H, 5-C**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 209.37 (p), 172.16 (p), 131.66 (a), 122.51 (a), 65.54 (p), 61.32 (p), 45.57 (p), 40.06 (p), 35.50 (p), 35.21 (a), 33.58 (a), 33.34 (p), 32.16 (p), 30.98 (a), 28.45 (a), 17.61 (a), 13.97 (a); MS m/z (M^+) for $C_{17}H_{26}O_3$: calcd. 278.1883, found 278.1886.

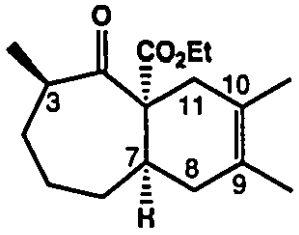
(1R*,3R*,7R*)-1-Carbethoxy-3,9-dimethylbicyclo[5.4.0]undec-9-en-2-one (284)



284

IR ($CHCl_3$, cast): 1735 (C=O, ester), 1697 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.35 (m, 1H, **H**-10), 4.18 (q, *J* = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 2.72 (dddd, *J* = 16.5, 3.5, 1.5, 1.5 Hz, 1H, **H**-11), 2.54 (m, 1H, **H**-7), 2.38 (qdd, *J* = 7, 7, 3.5 Hz, 1H, **H**-3), 2.24 (dqd, *J* = 16.5, 2.5, 2.5 Hz, 1H, **H**-11), 2.01 (m, 1H, **H**-8), 1.84 (br d, *J* = 7 Hz, 2H), 1.73 (m, 3H), 1.60 (br s, 3H, 9-C**H**$_3$), 1.55-1.40 (m, 2H), 1.26 (t, *J* = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.22 (d, *J* = 7 Hz, 3H, 3-C**H**$_3$); ^{13}C NMR APT (100 MHz, $CDCl_3$): δ 210.20 (p), 173.21 (p), 132.21 (p), 118.82 (a), 68.19 (p), 61.11 (p), 48.47 (a), 36.74 (a), 34.06 (p), 33.25 (p), 31.78 (p), 31.73 (p), 24.43 (p), 23.02 (a), 20.79 (a), 14.16 (a); MS m/z (M^+) for $C_{16}H_{24}O_3$: calcd. 264.1726, found 264.1725; Analysis for $C_{16}H_{24}O_3$: calcd. C: 72.69%, H: 9.15%, found C: 72.62%, H: 9.45%.

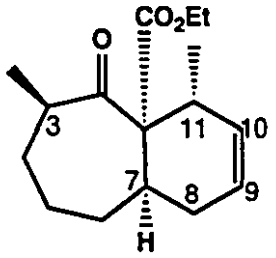
(1R*,3R*,7R*)-1-Carbethoxy-3,9,10-trimethylbicyclo[5.4.0]-undec-9-en-2-one (285)



285

IR (CH_2Cl_2, cast): 1736 (C=O, ester), 1697 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 4.18 (q, *J* = 7 Hz, 2H, -COOC**H**$_2$CH$_3$), 2.58 (d, *J* = 16 Hz, 1H, **H**-11), 2.51 (ddd, *J* = 16, 5.5, 5.5 Hz, 1H, **H**-8), 2.35 (dqd, *J* = 11, 7, 4 Hz, 1H, **H**-3), 2.21 (dm, *J* = 16 Hz, 1H, **H**-11), 2.00 (m, 1H, **H**-7), 1.85 (br d, *J* = 16 Hz, 1H, **H**-8), 1.83 (m, 1H), 1.72 (m, 3H), 1.63 (s, 3H, 10-C**H**$_3$), 1.55 (m, 1H), 1.54 (s, 3H, 9-C**H**$_3$), 1.44 (m, 1H), 1.26 (t, *J* = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.22 (d, *J* = 7 Hz, 3H, 3-C**H**$_3$); MS m/z (M^+) for $C_{17}H_{26}O_3$: calcd. 278.1883, found 278.1882; Analysis for $C_{17}H_{26}O_3$: calcd. C: 73.34%, H: 9.41%, found C: 72.97%, H: 9.58%.

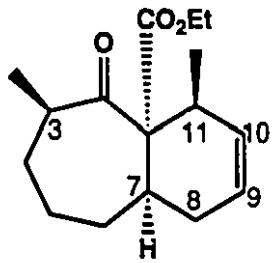
(1S*,3R*,7R*,11R*)-1-Carbethoxy-3,11-dimethylbicyclo[5.4.0]-undec-9-en-2-one (286)



286

mp 63-64°C (skelly B); IR ($CHCl_3$, cast): 1738 (C=O, ester), 1697 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.65 (m, 1H, **H**-10), 5.50 (m, 1H, **H**-9), 4.22 (dq, J = 11, 7 Hz, 1H, -COOC**H**HCH$_3$), 4.15 (dq, J = 11, 7 Hz, 1H, -COOCH**H**CH$_3$), 2.93 (m, 1H, **H**-11), 2.48 (dddd, J = 13.5, 13.5, 4, 4 Hz, 1H, **H**-7), 2.40 (m, 1H, **H**-8), 2.33 (m, 1H, **H**-3), 1.81 (m, 3H), 1.70 (m, 3H), 1.45 (m, 1H), 1.28 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.26 (d, J = 7 Hz, 3H, 3-C**H**$_3$), 0.88 (d, J = 7.5 Hz, 3H, 11-C**H**$_3$); MS m/z (M^+) for $C_{16}H_{24}O_3$: calcd. 264.1726, found 264.1732; Analysis for $C_{16}H_{24}O_3$: calcd. C: 72.69%, H: 9.15%, found C: 72.46%, H: 9.25%.

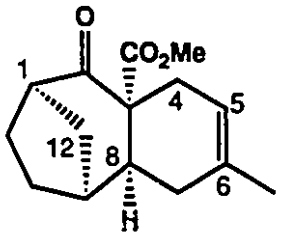
(1S*,3R*,7R*,11S*)-1-Carbethoxy-3,11-dimethylbicyclo[5.4.0]-undec-9-en-2-one (287)



287

IR (CH_2Cl_2, cast): 1733 (C=O, ester), 1697 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.57 (br d, J = 10 Hz, 1H, **H**-10), 5.51 (m, 1H, **H**-9), 4.30 (dq, J = 11, 7 Hz, 1H, -COOC**H**HCH$_3$), 4.24 (dq, J = 11, 7 Hz, 1H, -COOCH**H**CH$_3$), 2.62 (m, 1H, **H**-11), 2.52 (ddd, J = 9, 4.5, 4 Hz, 1H, **H**-8), 2.25 (dqd, J = 11, 7.5, 3 Hz, 1H, **H**-3), 2.00 (m, 1H, **H**-7), 1.92 (m, 2H), 1.73 (m, 2H), 1.63 (m, 1H), 1.40 (m, 2H), 1.32 (t, J = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 1.28 (d, J = 7.5 Hz, 3H, 3-C**H**$_3$), 1.14 (d, J = 7.5 Hz, 3H, 11-C**H**$_3$); ^{13}C NMR APT (100 MHz, $CDCl_3$): δ 208.47 (p), 172.69 (p), 132.20 (a), 123.03 (a), 66.10 (p), 60.87 (p), 49.76 (a), 42.51 (a), 39.54 (a), 31.77 (p), 31.59 (p), 27.99 (p), 23.85 (p), 21.71 (a), 16.87 (a), 14.25 (a); MS m/z (M^+) for $C_{16}H_{24}O_3$: calcd. 264.1726, found 264.1728; Analysis for $C_{16}H_{24}O_3$: calcd. C: 72.69%, H: 9.15%, found C: 72.90%, H: 9.36%.

(1R*,3R*,8S*,9S*)-3-Carbomethoxy-6-methyltricyclo[7.2.1.0^{3,8}]-dodec-5-en-2-one (288)

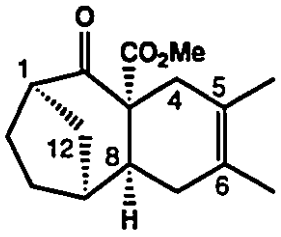


288

IR ($CHCl_3$, cast): 1733 (C=O, ester), 1713 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.52 (m, 1H, **H**-5), 3.68 (s, 3H, -COOC**H**$_3$), 2.85 (dddd, J = 7, 7, 2.5, 2.5 Hz, 1H, **H**-8), 2.79 (dd, J = 5, 5 Hz, 1H, **H**-1), 2.57 (br dd, J = 15, 5.5 Hz, 1H, **H**-4), 2.24-2.11 (m, 3H), 1.92-1.73 (m, 6H), 1.71 (s, 3H, 6-C**H**$_3$), 1.64 (dddd, J = 12.5, 5, 5, 2.5 Hz, 1H, **H**-12*syn*); ^{13}C NMR APT (100 MHz, $CDCl_3$): δ 210.17 (p), 173.99 (p), 136.36 (p), 120.19 (a), 57.80 (p), 52.66 (a), 51.13 (a), 43.33 (a), 42.42 (a), 34.93 (p), 33.14 (p), 31.80 (p), 28.54 (p), 26.85 (p), 23.02 (a); MS m/z (M^+) for

$C_{15}H_{20}O_3$: calcd. 248.1413, found 248.1412; Analysis for $C_{15}H_{20}O_3$: calcd. C: 72.55%, H: 8.12%, found C: 72.73%, H: 8.41%.

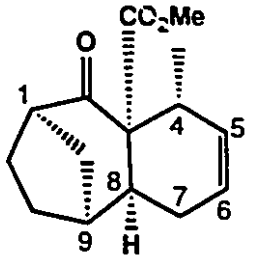
(1R*,3R*,8S*,9S*)-3-Carbomethoxy-5,6-dimethyltricyclo-[7.2.1.0^{3,8}]dodec-5-en-2-one (289)



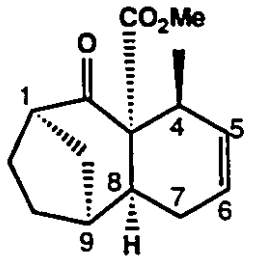
289

IR (CH_2Cl_2, cast): 1733 (C=O, ester), 1713 cm^{-1} (C=O, ketone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H, -COOC**H**$_3$), 2.74 (m, 2H, **H**-1, **H**-8), 2.42 (d, *J* = 14 Hz, 1H, **H**-4), 2.18 (m, 3H), 1.90-1.72 (m, 6H), 1.70 (s, 3H, 5-C**H**$_3$), 1.66 (s, 3H, 6-C**H**$_3$), 1.62 (dddd, *J* = 12, 4.5, 4.5, 2 Hz, 1H, **H**-12*syn*); MS m/z (M$^+$) for $C_{16}H_{22}O_3$: calcd. 262.1569, found 262.1572; Analysis for $C_{16}H_{22}O_3$: calcd. C: 73.25%, H: 8.45%, found C: 73.18%, H: 8.66%.

(1R*,3S*,4R*,8S*,9S*)-3-Carbomethoxy-4-methyltricyclo-[7.2.1.0^{3,8}]dodec-5-en-2-one (290) and (1R*,3S*,4S*,8S*,9S*)-3-carbomethoxy-4-methyltricyclo[7.2.1.0^{3,8}]dodec-5-en-2-one (291)



290

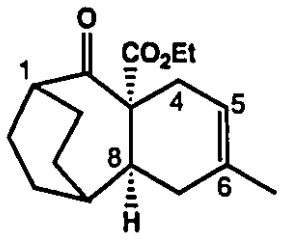


291

Adducts **290** and **291** were obtained as an inseparable mixture in a ratio of 4 : 1 (based on ^{1}H NMR integration).

IR (film): 1733 (C=O, ester), 1714 cm^{-1} (C=O, ketone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (m, 0.2H, **H**-5), 5.85 (m, 0.8H, **H**-5), 5.84 (m, 0.2H, **H**-6), 5.74 (ddd, *J* = 9, 5.5, 3 Hz, 0.8H, **H**-6), 3.78 (s, 2.4H, -COOC**H**$_3$), 3.71 (s, 0.6H, -COOC**H**$_3$), 3.17 (dddd, *J* = 12.5, 5.5, 5.5, 3 Hz, 0.8H, **H**-8), 3.07 (qd, *J* = 7, 7 Hz, 0.8H, **H**-4), 2.86 (m, 0.2H), 2.80 (dd, *J* = 5, 5 Hz, 0.8H, **H**-1), 2.68 (dd, *J* = 6.5, 4.5 Hz, 0.2H, **H**-4), 2.45 (m, 0.2H), 2.38 (dddd, *J* = 17, 9, 3, 3 Hz, 0.8H, **H**-7), 2.32 (m, 0.2H), 2.21 (m, 1H, **H**-9), 1.97-1.70 (m, 5H), 1.65 (m, 1H), 1.57 (m, 1H), 1.20 (d, *J* = 7 Hz, 0.6H, 4-C**H**$_3$), 0.83 (d, *J* = 7 Hz, 2.4H, 4-C**H**$_3$); MS m/z (M$^+$) for $C_{15}H_{20}O_3$: calcd. 248.1413, found 248.1419; Analysis for $C_{15}H_{20}O_3$: calcd. C: 72.55%, H: 8.12%, found C: 72.54%, H: 8.18%.

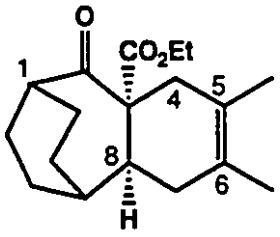
(3R*,8S*)-3-Carbethoxy-6-methyltricyclo[7.2.2.0^{3,8}]tridec-5-en-2-one (292)



292

IR ($CHCl_3$, cast): 1740 (C=O, ester), 1699 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.43 (br s, 1H, **H**-5), 4.16 (q, *J* = 7 Hz, 1H, -COOC**H**HCH$_3$), 4.15 (q, *J* = 7 Hz, 1H, -COOCH**H**CH$_3$), 2.82 (ddd, *J* = 6, 6, 2.5 Hz, 1H, **H**-8), 2.64 (br s, 1H, **H**-1), 2.55 (br d, *J* = 18 Hz, 1H, **H**-4), 2.38 (br d, *J* = 18 Hz, 1H, **H**-4), 2.03 (m, 2H), 1.81-1.60 (m, 9H), 1.68 (s, 3H, 6-C**H**$_3$), 1.22 (t, *J* = 7 Hz, 3H, -COOCH$_2$C**H**$_3$); ^{13}C NMR APT (100 MHz, $CDCl_3$): δ 211.91 (p), 173.60 (p), 134.58 (p), 118.84 (a), 61.39 (p), 60.87 (p), 46.02 (a), 39.51 (a), 37.21 (a), 35.23 (p), 30.40 (p), 25.81 (p), 23.71 (p), 23.26 (a), 21.49 (p), 20.80 (p), 14.14 (a); MS m/z (M^+) for $C_{17}H_{24}O_3$: calcd. 276.1726, found 276.1731.

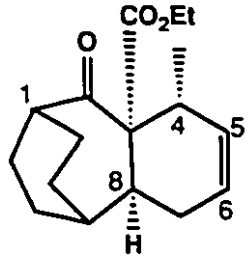
(3R*,8S*)-3-Carbethoxy-5,6-dimethyltricyclo[7.2.2.0^{3,8}]tridec-5-en-2-one (293)



293

IR (film): 1738 (C=O, ester), 1702 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 4.18 (dq, *J* = 11, 7 Hz, 1H, -COOC**H**HCH$_3$), 4.14 (dq, *J* = 11, 7 Hz, 1H, -COOCH**H**CH$_3$), 2.82 (ddd, *J* = 6.5, 6.5, 3 Hz, 1H, **H**-8), 2.64 (m, 1H, **H**-1), 2.52 (d, *J* = 16 Hz, 1H, **H**-4), 2.25 (d, *J* = 16 Hz, 1H, **H**-4), 2.02 (m, 2H), 1.83-1.50 (m, 9H), 1.68 (s, 3H, 5-C**H**$_3$), 1.65 (s, 3H, 6-C**H**$_3$), 1.23 (t, *J* = 7 Hz, 3H, -COOCH$_2$C**H**$_3$); MS m/z (M^+) for $C_{18}H_{26}O_3$: calcd. 290.1882, found 290.1882.

(3S*,4R*,8S*)-3-Carbethoxy-4-methyltricyclo[7.2.2.0^{3,8}]tridec-5-en-2-one (294)



294

IR (CH_2Cl_2, cast): 1741 (C=O, ester), 1702 cm^{-1} (C=O, ketone); ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (m, 1H, **H**-5), 5.75 (dd, *J* = 9.5, 5 Hz, 1H, **H**-6), 4.20 (dq, *J* = 11, 7 Hz, 1H, -COOC**H**HCH$_3$), 4.14 (dq, *J* = 11, 7 Hz, 1H, -COOCH**H**CH$_3$), 2.99 (br q, *J* = 7 Hz, 1H, **H**-4), 2.93 (ddd, *J* = 7, 7, 4 Hz, 1H, **H**-8), 2.64 (m, 1H, **H**-1), 2.15 (ddd, *J* = 16, 6, 6 Hz, 1H), 2.05 (br s, 1H), 1.83-1.45 (m, 9H), 1.26 (t, *J* = 7 Hz, 3H, -COOCH$_2$C**H**$_3$), 0.98 (d, *J* = 7 Hz, 3H, 4-C**H**$_3$); ^{13}C NMR APT (100 MHz, $CDCl_3$): δ 209.92 (p), 172.42 (p), 133.58 (a), 127.30 (a), 65.26 (p), 61.12 (p), 46.08 (a), 41.58 (a), 36.66 (a), 33.69 (a), 28.95 (p), 24.90 (p), 23.74 (p), 21.25 (p), 20.28 (p), 16.17 (a), 14.20 (a); MS m/z (M^+) for $C_{17}H_{24}O_3$: calcd. 276.1726, found 276.1725.

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