TOWARD THE TOTAL SYNTHESIS OF THE KEMPANES

by

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ABSTRACT

The kempanes (e.g. kempene-2 and kempenone) are diterpenes that were isolated from the defense secretions of nasute termites. Due to their potential biological interest and their unique carbon skeleton with a large number of stereogenic centers, attempts have been made to achieve their total synthesis, but only one total synthesis of a kempane has been reported so far.

The research described in the this thesis was aimed at using ring-closing-metathesis (RCM) as the key step for the generation of the tetracyclic skeleton. Initial efforts were focused on the construction of a diene bearing an isopropylidene unit on a five-membered ring. An initial aldol approach to this diene gave none of expected product. An alternate route began with a previously prepared lactone. Dehydration was attempted to give the double-bond of the isopropylidene, but a mild selenation and oxidation protocol delivered a tetrafuran as the major product and the expected alkene as a very minor product. Finally, the diene was made using a Mannich route to introduce the isopropylidene unit in high overall yield. An endo-, regio-, and facially selective Diels-Alder reaction of the diene gave a compound with three of the four rings of the kempanes with the key central stereochemistry established. Diastereoselective allylation was tested in a model. Following cerium-mediated, regioselective reduction, Grignard allylation, and Dess–Martin oxidation, the RCM worked well to generate the final seven-membered ring. The construction of the tetracyclic skeleton of the kempanes via the RCM reaction was accomplished in 24 steps from commercially available starting materials. Further work to complete the total syntheses of all kempanes is under investigation in this laboratory.

This thesis also reports the relative proportions of the products of axial and equatorial 1,2-addition of allylindium, allyl Grignard, and allylbismuth reagents on α,β–conjugated ketones. The diastereoselectivity of allyl Grignard additions was the most selective, favoring axial addition, of the three reagents.

LIST OF ABBREVIATIONS AND SYMBOLS USED

Ac	acetyl
acac	acetylacetonyl
AIBN	2,2'-azobis(isobutyronitrile)
APT	attached proton test
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEN	5,5',6,6'-tetramethyl-3,3'-di-*tert*-butyl-1,1'-biphenyl-2,2'-diol
Boc	*t*-butoxycarbonyl
BP	boiling point
Bn	benzyl
Bs	phenylsulfonyl
t-Bu	*tert*-butyl
Bz	benzoyl
conc.	concentrated
COSY	^{1}H–^{1}H correlation (spectrum)
Cp	cyclopentadienyl
CSA	(1*S*)-(+)-camphorsulfonic acid
DBN	1,5-diazabicyclo[3.4.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
Dess–Martin (periodinane)	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one

DET	L-(+)-diethyl tartrate
DHP	3,4-dihydro-2*H*-pyran
Dibal-H	diisobutylaluminum hydride
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
e	electron
ee	enantiomeric excess
eq.	equivalent
Et	ethyl
ERG	electron-releasing group
EWG	electron-withdrawing group
GC–MS	gas chromatography-mass spectrometry
GGPP	geranyl geranyl pyrophosphate
h	hour(s)
HETCOR	heteronuclear correlation (NMR)
HMBC	heteronuclear multiple bond correlation (NMR)
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation (NMR)
HOMO	highest occupied molecular orbital

HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum correlation (NMR)
hν	ultraviolet irradiation
Im	imidazole
IR	infrared (spectroscopy or spectrum)
K-Selectride®	potassium tris(*sec*-butyl)borohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Lindlar's catalyst	Pd, $CaCO_3$, $Pd(OAc)_2$
L-Selectride®	litium tri-*sec*-butylborohydride
LS-Selectride®	lithium tri(isobut-2-yl)borohydride
LUMO	lowest unoccupied molecular orbital
MAD	methyl aluminum bis-(2,6-di-*tert*-butyl)-4-methylphenoxide
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	(2-methoxyethoxy)methyl
min	minute(s)
MOM	methoxymethyl
MP	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide

NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance (spectroscopy or spectrum)
NOE	nuclear Overhauser effect
Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PLC	preparative layer chromatography
PP	pyrophosphate
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	isopropyl
psi	pounds per square inch
py	pyridine
rac	racemic
RCM	ring-closing metathesis
Red-Al®	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
Sia	siamyl (3-methyl-2-butyl)
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMM	trimethylenemethane
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl
UV	ultraviolet (spectroscopy or spectrum)

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CHAPTER 1. INTRODUCTION

1.1 NATURAL PRODUCTS FROM TERMITE DEFENSIVE SECRETIONS

Defensive behavior in termites has evolved over a long period of time to ensure the survival of termite colonies. Termite soldiers can utilize physical and chemical forms of defense, either separately or in combination. As physical defense, termite soldiers' mandibles have evolved into powerful weapons for cutting and biting. On the other hand, the termite families *Rhinotermitidae* and *Termitidae* also use chemical forms of defense. At least two strategies are employed by specialized termite soldiers that are armed with chemical secretions. Some types of soldiers bite their foes and let an oily, toxic or irritating secretion from a frontal gland reservoir flow into the enemy's wound. Secondly, the most highly evolved "nasute" soldiers totally avoid any contact with their enemies. They eject at their enemies, from several centimeters away, a glue-like, viscous secretion through an elongated, syringe-like rostrum. [1]

A variety of compounds from the defensive secretions of termite soldiers have been identified. [2] (*E*)-1-Nitro-1-pentadecene has been reported as the major component of the secretion from *Prorhinotermes simplex*. [3] Straight-chain ketones (e.g. 1-tetradecen-3-one) were found as the major constituents of the secretion from the frontal gland of *Schedorhinotermes putorius*. [4] The aqueous, brown secretions from *Odontotermes badius* and *O. stercorivrovs* soldiers were found to be a mixture of benzoquinone and proteins. [5] Straight-chain and isoalkanes (C_{22}–C_{34}) from *Macrotermes goliath* [6] and olefins (e.g. (*Z*)-9-heptacosene) from *Macrotermes subhyalinus* [7] were also documented.

Besides the substances mentioned above, many terpenes have also been found in the termite defensive secretions. [2]

1.1.1 MONOTERPENES

Many monoterpene hydrocarbons from termite soldier species were already well known from plant sources. A few examples are shown in Figure 1.1. α-Thujene (**1**) and β-phellandrene (**2**) have been isolated from an extract of the soldiers of *Nasutitermes sp.*, while terpinolene (**3**) and α-phellandrene (**4**) were reported in the secretion of *Amitermes herbertensis* soldiers. [2] Limonene (**5**) and α-pinene (**6**) have also been found in the emission of *A. laurensis* soldiers. [8] The soldiers of *A. vitosus* can produce monoterpenes **3**, **4**, **5**, **6**, β-pinene (**7**), and myrcene (**8**). [8] The soldiers from several species of the sub-family *Termiternae* can produce varied defense compounds. For example, camphene (**9**) was found together with a few monoterpenes (**3**, **5**, **6**, **7**) and diterpenes in the soldiers of *Trinervitermes gratiosus*. [9] The frontal gland secretion from the soldiers of *N. rippertii* contains the monoterpenes α-terpinene (**10**) and Δ-carene (**11**), as well as some diterpene compounds. [10] A minor component of the frontal gland of the West African termite *Amitermes evuncifer* soldiers is *cis*-β-ocimene (**12**), although the major components are sesquiterpenes. [11]

1.1.2 SESQUITERPENES

Many sesquiterpene compounds have been identified from termite soldiers' secretions (Figure 1.2). Soldiers of *Ancistrotermes cavithorax* secrete ancistrofuran (**13**), with small amounts of α- and β-cyclogeraniolenes, while a small number of

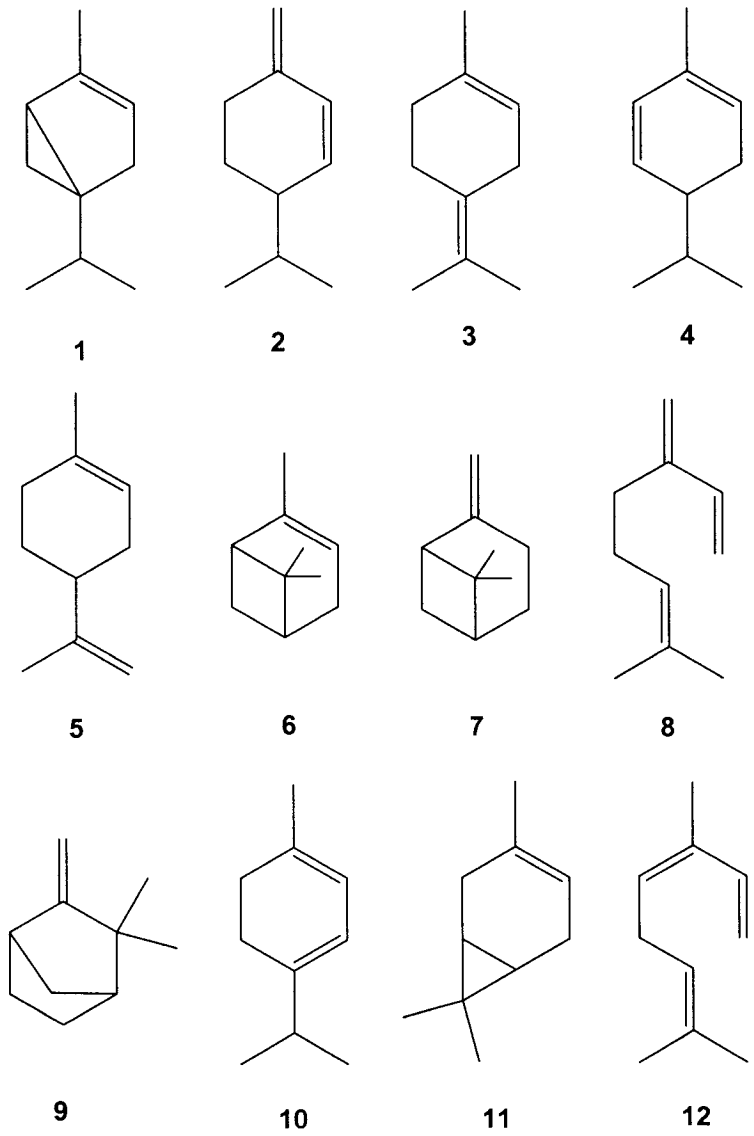


Figure 1.1 Examples of monoterpenes from the defense secretions of termite soldiers

soldiers emit (*R*)-ancistrodial (**14**) as the main constituent of their volatile secretion. [12] 10-*epi*-Eudesma-3,11-diene (**15**), 8-*epi*-cararrapi oxide (**16**), cararrapi oxide (**17**), [11] and a sesquiterpene ether, 4,11-epoxy-*cis*-eudesmane (**18**), [13] have also been isolated from soldiers' frontal gland secretion of the West African termite *Amitermes evuncifer*. Prestwich found that ether **18** is also present in the soldiers of termite *Amitermes messinae*. [14]

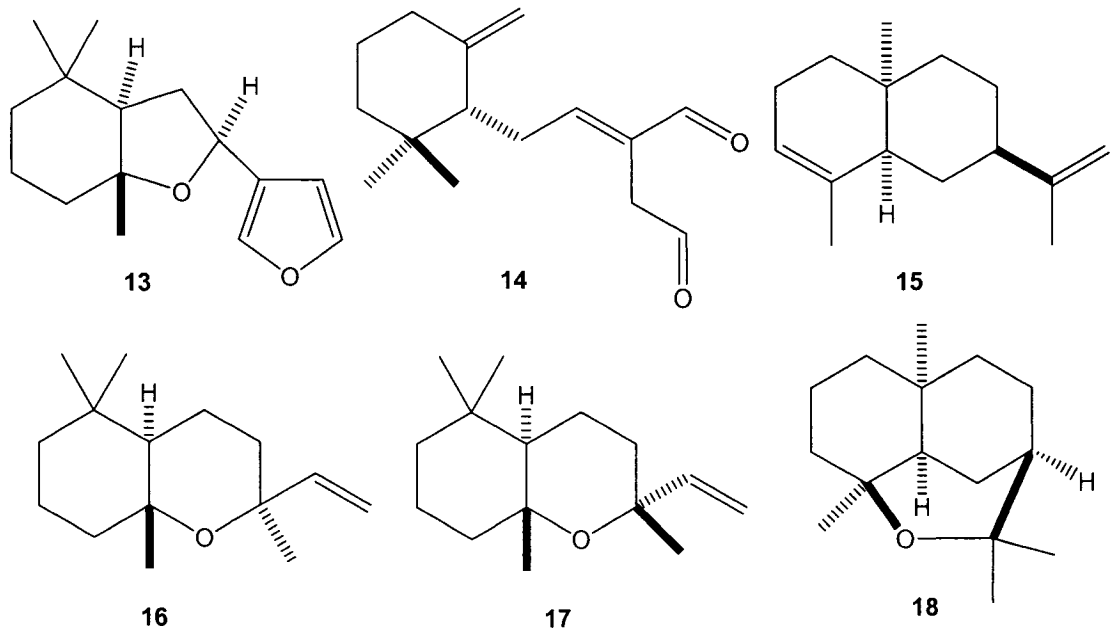


Figure 1.2 Examples of sesquiterpenes from the defense secretions of termite soldiers

1.1.3 DITERPENES

Compared with monoterpenes, which are widely distributed throughout termite subfamilies, diterpenes are known in only two groups of the more highly evolved termite genera. [1]

The first group is the two closely related genera of humivorous African termites, *Cubitermes* and *Crenetermes*, which have biting soldiers that have diterpene hydrocarbons in their cephalic reservoirs. Four diterpene hydrocarbons, which are the major constituents of the frontal gland secretion of soldiers of the East African termite, *Cubitermes umbratus*, have been isolated. The most abundant diterpene is cubitene (**19**) (Figure 1.3), which has a 12-membered ring with a skeleton composed of an irregular arrangement of isoprene units. [15] The other diterpenes found in this secretion are the macrocyclic diterpenes, cembrene A (**20**) and (3*Z*)-cembrene A (**21**), [16] and the bicyclic

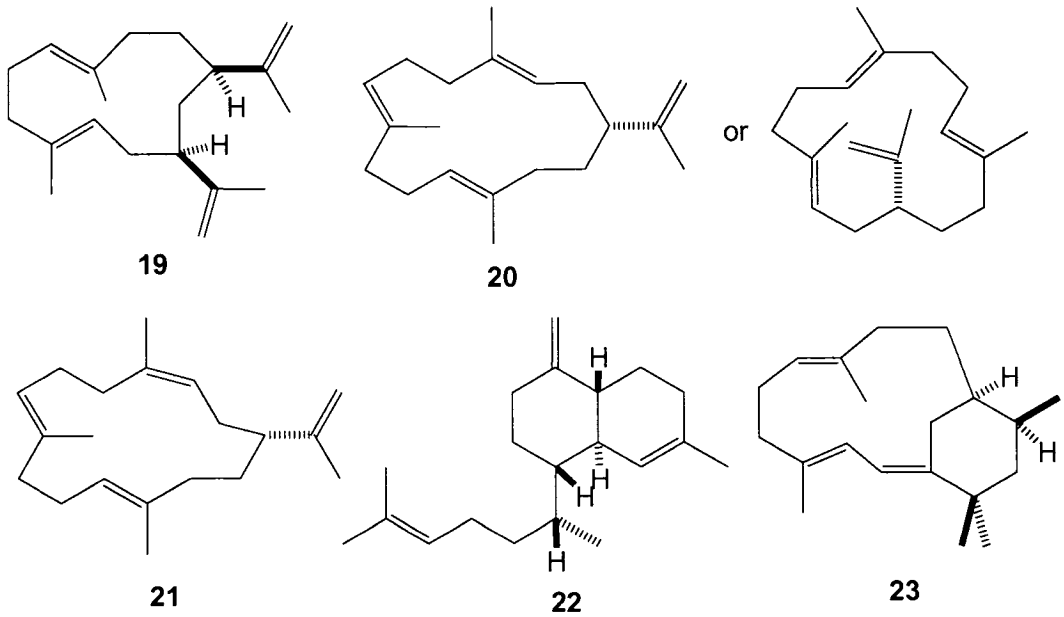


Figure 1.3 Examples of diterpenes from the defense secretions of *Cubitermes* and *Crenetermes* species

diterpene, biflora-4,10(19),15-triene (**22**), which has a skeletal resemblance to some quinone antibiotics, the biflorins. [17] An unstable bicyclic diterpene, cubugene (**23**), which is formally related to the irregular diterpene cubitene (**19**), was isolated from the secretion of termite soldier, *Cubitermes ugandensis*. [18]

The second group of diterpene-containing termites is made up of the pantropical nasute termites (*Termitidae*, *Nasutitermitinae*), which are the most advanced, abundant, and diverse subfamily of termites. Nasute soldiers have vestigial mandibles and rely entirely on secreted chemicals for defense. Upon attack, the soldiers eject at their enemies viscous, lipophilic solutions containing diterpenes dissolved in monoterpenes.

Approximately 50 derivatives of five diterpene skeletons are currently known from this source. [1] The first skeletal type is the bicyclic secotrinervitane. 3α-Acetoxy-15β-hydroxy-7,16-secotrinervita-7,11-diene (**24**, Figure 1.4) [19] has been isolated from

the soldier secretion of *Nasutitermes princeps*. Its structure was elucidated by an X-ray diffraction study. Secotrinervita-7,11,15(17)-trien-3α-ol (**25**) and secotrinervita-7,11, 15(17)-triene-2β,3α-diol (**26**) have been found in the defensive secretions of both *Nasutitermes princeps* [20a] and *Longipeditermes longipes* from the lowland Malaysian rainforests. [20b] A fourth secotrinervitane, 3,10-diacetoxy-7,16-secotrinervita-7,11, 15(17)-triene (**27**), was isolated from the Madagascan termite *Nasutitermes canaliculatus*, and the structure of **27** was also determined by X-ray crystallographic analysis. [21]

The second skeletal type is the tricyclic trinervitane, for example, trinervita-1(15),8(19)-diene-2β,3α-diol (**28**), [22] trinervita-1(15),8(19)-diene-2α,3α-diol (**29**), [23] and 3α,9β,13α-trihydroxy-11,15(17)-trinervitadiene tripropionate (**30**) [24] (Figure 1.4). Both the secotrinervitanes and the trinervitanes retain the absolute stereochemistry and olefin geometry found in the diterpene cembrene-A (**20**).

The third skeletal type comprises the tetracyclic kempanes (Figure 1.4). 3α,14β-Dihydroxy-6,8-kempadiene diacetate ("kempene-1") (**32**) and 14α-hydroxy-6,8-kempadien-3-one acetate ("kempene-2") (**33**), together with the trinervi-2β,3α,9α-triol-9-*O*-acetate (**31**) as the primary component, are produced by African *Nasutitermes kempae* soldiers, along with monoterpenes. These diterpenes were first isolated by Prestwich and co-workers in 1977. [25] The structure of kempene-2 (**33**), a dome-shaped, tetracyclic array of five-, six-, six- and seven-membered rings, was solved by single-crystal X-ray diffraction experiments. [25] Most of the substituents are on the convex surface, except the methyl group at C-12. The diene system is twisted approximately 20 degrees out of planarity. These two kempenes, along with 3β,14α-dihydroxy-6,8-kempadiene-3,14-

diacetate (**34**), were also found in the secretion of the Malaysian termite *Bulbitermes singaporensis*. [26] Two β,γ-unsaturated ketones based on the kempane skeleton, 3β-hydroxy-7β-kemp-8-en-6-one (**35**) and 2β-acetoxy-3β-hydroxy-7β-kemp-8-en-6-one (**36**) (the "kempenones"), found in the soldier defense secretion of *Nasutitermes octopilis*, were reported in 1979. [27] The structure of kempenone **35** was determined by single-crystal X-ray diffraction using its *p*-bromobenzoate derivative.

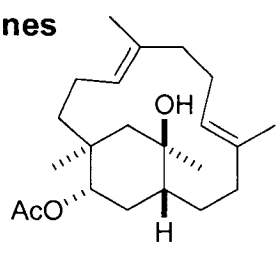
The fourth diterpene skeletal type is the tetracyclic rippertene skeleton. *Nasuti-termes rippertii* soldiers produce a secretion containing monoterpene hydrocarbons together with trinervitadienes and 3α-hydroxy-15-rippertene (**37**). This tetracyclic compound is obviously related to the kempenes, but with a 1,2-shifted angular methyl group. [28] The structure of **37**, which contains two six-membered rings in boat-like conformations, was established by single crystal X-ray diffraction experiments on its 3α-acetate-15,16-epoxide derivative.

The fifth carbon skeleton is longipane. Longipenol (**38**) is the only known example of this type of diterpene. [20b] Higher terpenes have not been isolated from termite soldiers so far.

1.2 BIOSYNTHESIS OF KEMPANES AND RELATED DITERPENES

Although many of the details of terpene biosynthesis in plants are well understood, much less is known generally about the processes in insects. However, the biological origin of the kempanes and related diterpenes has been investigated.

Secotrinervitenes



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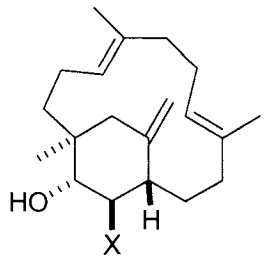
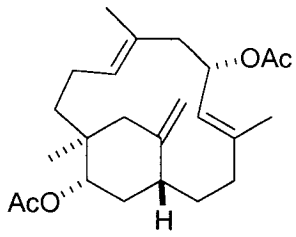
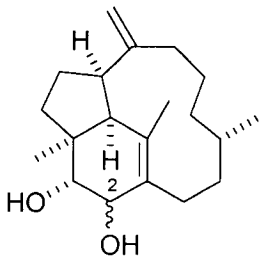


25 X = H
26 X = OH

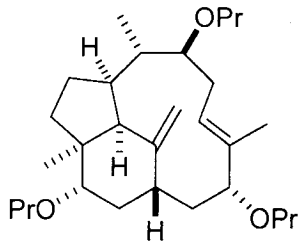


27

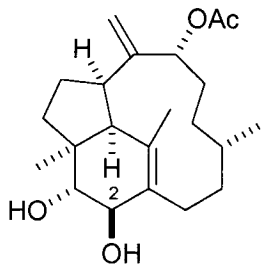
Trinervitenes



28 2β OH
29 2α OH

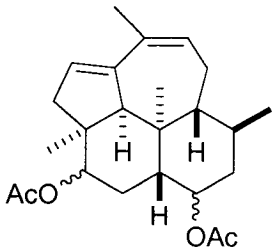


30

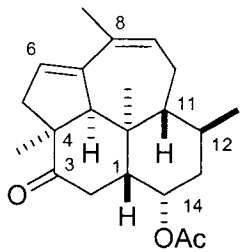


31

Kempanes



32 3α-OAc, 14β-OAc
34 3β-OAc, 14α-OAc



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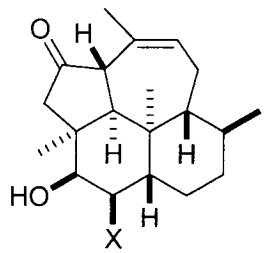
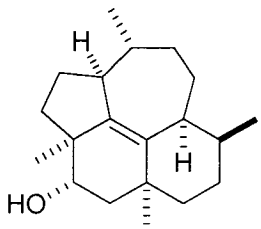


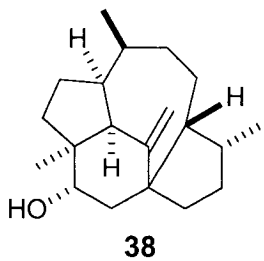
35 X = H
36 X = OAc

Rippertene



37

Longipene

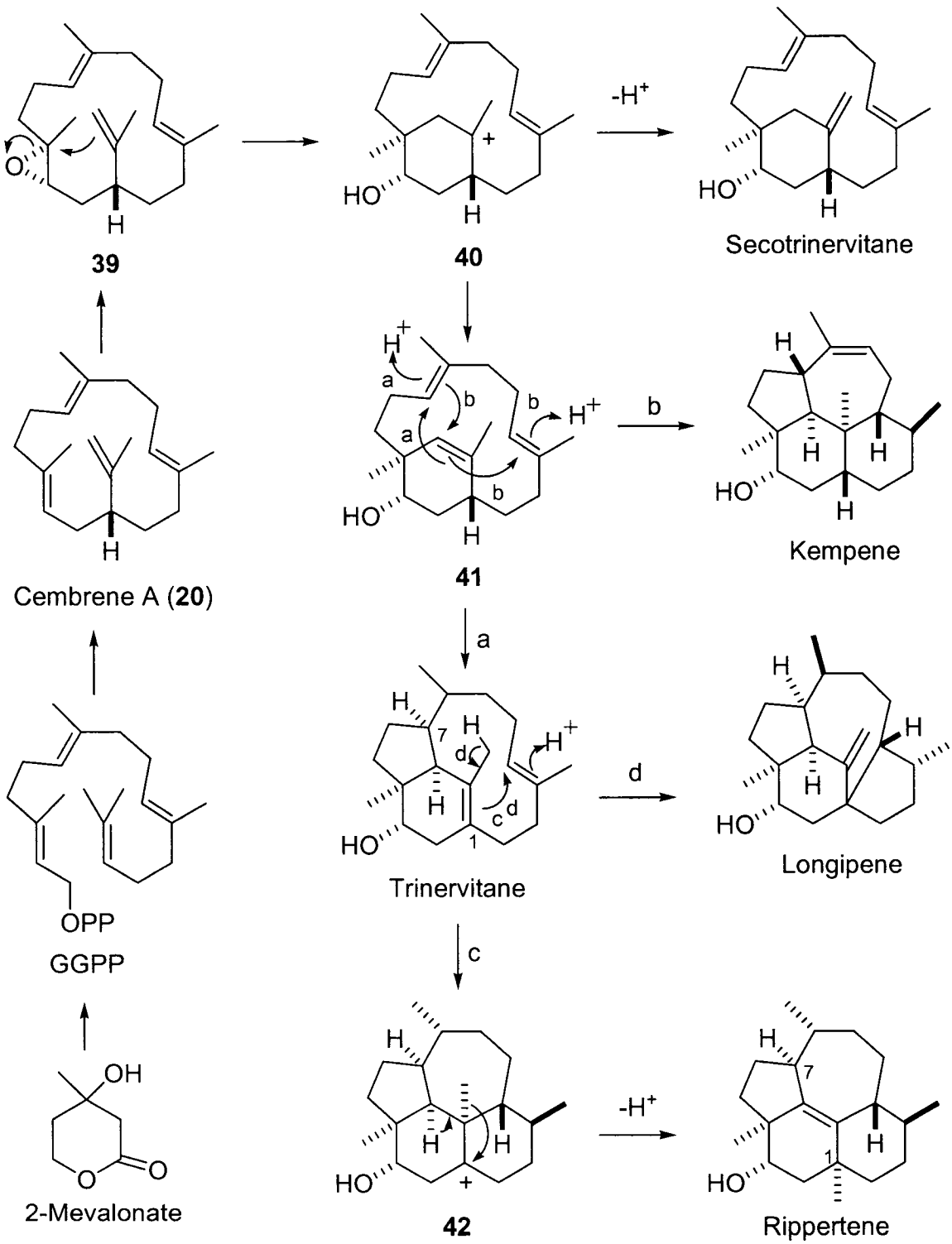


38

Figure 1.4 Diterpenes of *Nasutitermes* and related genera

It has been proposed that all five skeletal types of diterpenes isolated from termite soldiers are derived from the cyclization of geranylgeranyl pyrophophate (GGPP), which is in turn produced from 2-mevalonate [29–31] (Scheme 1.1). Four mevalonate units are assembled to give geranylgeranyl pyrophosphate, which undergoes cyclization to (*R*)-cembrene A (**20**), which was suggested as a common precursor to all of the termite diterpenes. [20b] Cyclization of (*R*)-cembrene-*trans*-3,4-epoxide (**39**), which is an immediate derivative of cembrene A, would directly yield a secotrinervitane skeleton via the carbocation intermediate **40**. After deprotonation of **40** to intermediate **41**, trans-annular cyclizations leads to the kempanes and trinervitanes. Further transannular cyclizations of trinervitanes would give longipane and the carbocation intermediate **42**, which finally lead to the methyl-shifted rippertene. This step-wise cyclization proposal for termite defensive diterpene biosynthesis suggests that the monocyclic cembrene A, the bicyclic secotrinervitatrienols and tricyclic trinervitadienols are all likely intermediates in the biosynthesis of the tetracyclic diterpenes.

This proposal has been supported by the following findings. Cembrene A has been isolated as a defensive compound from *Cubitermes*, [16] and it has been identified as a trail pheromone of the termite workers from *N. exitiosus*. [32] The coexistence in *N. princeps* of 7,16-secotrinervitane and trinervitane derivatives was also reported. [19] Furthermore, the discovery of compounds such as the bicyclic secotrinervitane and the tricyclic trinervitane, which retain the 1*R* configuration and the 7*E* and 11*E* olefinic bonds of cembrene A, strongly supports this biogenetic hypothesis. This proposal was also supported by isotopic labeling experiments with *in vivo* incorporation of mevalonate in termite soldiers. [31]



Scheme 1.1 Proposed biosysthesis of defensive diterpenes

CHAPTER 2. TOTAL SYNTHESIS OF KEMPANES AND RELATED DITERPENES

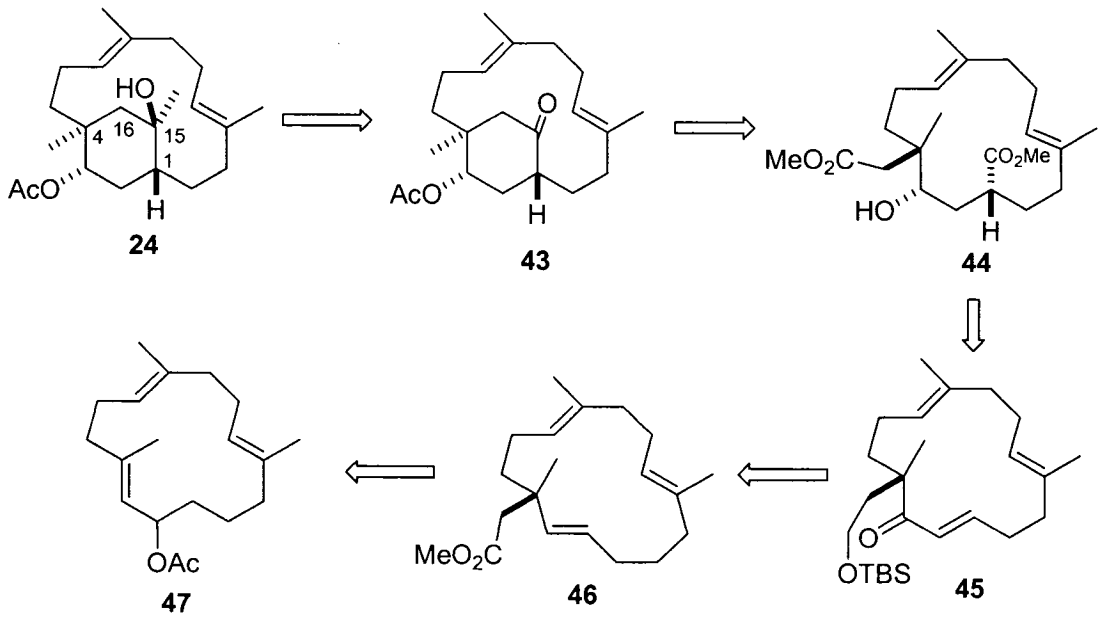
The functions of termite diterpenes are not understood. It is generally believed that the diterpenes may serve as a solute to retard the rate of the evaporation of the monoterpenes, which may be relatively more toxic.[33] However, the biological activities of these diterpenes have not been studied because of their scarcity from natural sources.

Due to their unique structures, the termite diterpenes are of interest as challenging targets for total synthesis. A few synthetic endeavors have been documented so far. Kato's research group reported the syntheses of two seconervitenes [34,35] and one trinervitane. [36] Although the construction of the ABD carbocyclic framework of the longipenol by Mehta's group [37] and an asymmetric approach to the rippertene ring system by Metz's group [38] have been reported, total syntheses of longipenol **38** and rippertene **37** and have not been achieved yet. Considering the total synthesis of kempanes, Dauben completed the first total synthesis of a kempene diterpene, kempene-2 (**32**), in 1991, and this is still the only complete total synthesis of a kempane. [39] In 1992, Paquette reported a more concise approach to kempenone (**34**), but, unfortunately, the conjugated double bond of their final advanced intermediate could not be deconjugated to the natural product. [40] In 1997, Burnell's group developed a stereoselective approach to the kempane ring system, [41,42] but attempts to complete the total synthesis of the natural products also failed. Most recently, in 2004, a synthetic leading model of the kempanes, 14-deacetoxy-kempa-6,8-dien-3-ol, was prepared by Kato's research group. [43] Previous synthetic efforts are presented in detail in this section.

2.1 KATO'S SYNTHESES OF SECOTRINERVITENES AND TRINERVITANES

2.1.1 KATO'S SYNTHESES OF SECOTRINERVITENES

The first total synthesis of a defensive diterpene from termite soldiers, which was of 3α-acetoxy-15β-hydroxy-7,16-secotrinervita-7,11-diene (**24**), was reported by Kato's group in 1987. [34] Their retrosynthetic analysis is shown in Scheme 2.1. It was hoped that acetoxy ketone **43** would be a convenient intermediate for **24**. Retrosynthetic cleavage of the C15–C16 bond in **43** furnishes intermediate **44** as a potential precursor. In the forward sense, a Dieckmann cyclization [44] of diester **44** could form the cyclohexane ring in **43**. Functional group transformations and Michael addition would lead to intermediate **45**, which could be created from compound **46** by a regioselective epoxidation, [45] ring-opening and oxidation of the hydroxy group. Finally, **46** could be generated by an Ireland-type Claisen rearrangement [46] from **47**, which had been prepared previously in large scale by the same laboratory. [47]



Scheme 2.1 Kato's strategy in the synthesis of secotrinervitene **24** [34]

The total synthesis of **24** is shown in Scheme 2.2. Treatment of the lithium enolate of **47** with TBSCl at low temperature gave a ketene silyl acetal, which was smoothly rearranged (Ireland-Claisen) into the desired γ,δ-unsaturated carboxylic acid, with the newly formed double bond *trans*, by warming to room temperature. Desilylation and subsequent esterification gave the methyl ester **46**, which was then reduced to alcohol **48**. Regioselective epoxidation of the disubstituted double bond using vanadyl acetylacetonate and *tert*-butylhydroperoxide gave the desired epoxide **49** as a 1:1 mixture of diastereomers. After protection of the hydroxy group, ring-opening of the epoxide (**50**) was achieved by a conventional procedure to give compound **51**, which was oxidized by Collins reagent to enone **45**. Michael addition of diethyl aluminum cyanide to enone **45** gave cyanide **52** as a 1:1 mixture of diastereomers. Deprotection of the silyl group of both isomers, oxidation of the resulting primary alcohol, and esterfication of the resulting carboxylic acid gave cyanide **53**. It was surprising that reduction the carbonyl group using tri(*tert*-butyloxy)aluminum hydride proceeded with high stereoselectivity to produce the cyano-lactone **54**. After separation of the diastereomers, the "right" isomer was subjected to hydrolysis and subsequent methylation to afford the hydroxy-ester (**44**), which was not stable and was converted to its corresponding TMS ether (**55**). The next step was the key step, a Dieckmann condensation. Treatment of the diester **55** with a large excess of potassium *tert*-butoxide produced the expected keto ester **56** without any epimerization at C-1. After deprotection of the TMS protecting group with acid, demethoxycarbonylation of the resulting hydroxy-ketoester with sodium chloride in refluxing DMSO yielded the corresponding hydroxy-ketone, which was subjected to acetylation to yield the acetate **43**. Treatment of ketone **43** with methyllithium gave only

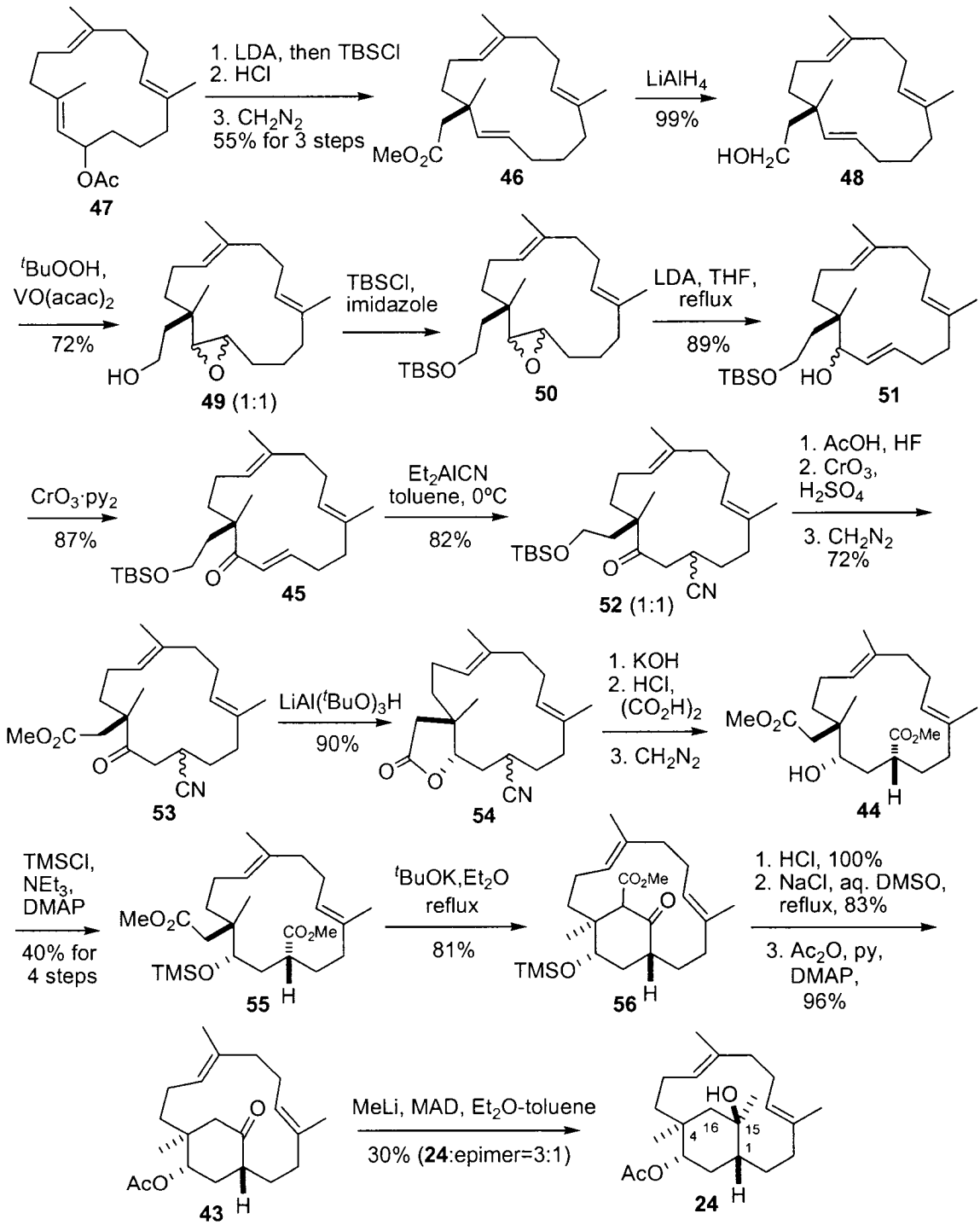
the epimer of **24** at C-15. In order to reverse the facial selectivity, Yamamoto's bulky Lewis acid "MAD" (methyl aluminum bis-(2,6-di-*tert*-butyl-4-methylphenoxide)) [48] was applied to shield the less hindered β-side during the nucleophilic addition. This method gave a mixture of the desired secotrinervitane **24** and its epimer in a 3:1 ratio in 30% yield together with 51% of the recovered ketone **43**.

This was an inefficient total synthesis because of the long sequence, the poor stereoselectivity, and the low yield at the last step. Nevertheless, the racemic natural product was produced, and this route also made other stereoisomers of **24** available.

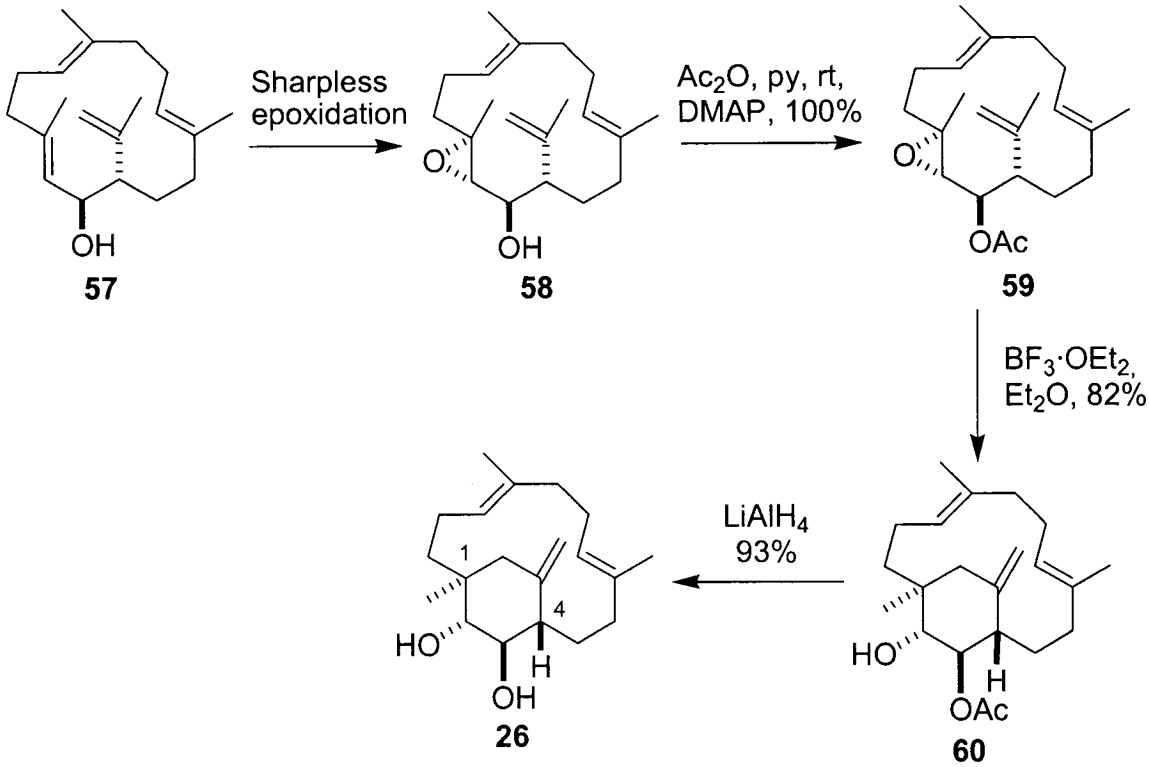
At about the same time, Kato's group [35] also reported an elegant biomimetic synthesis of (±)-secotrinervitene-2β,3α-diol (**26**) (Scheme 2.3). The secotrinervitenes are biogenetically related to cembrene A (**20**) and are believed to arise from epoxy-cembrene. [20b, 33] The selected starting material, epoxy alcohol **58**, had been efficiently prepared by the same group from *trans*-dehydromukulol (**57**) via epoxidation. [45] The alcohol **58** was first protected as the corresponding acetate **59** by the action of acetic anhydride in pyridine at room temperature in quantitative yield. Then, the key step, the cyclization, was achieved by treating **59** with boron trifluoride etherate to afford the bicyclic hydroxy-acetate in 82% yield. Finally, deprotection by reduction of **60** with lithium aluminum hydride gave the (±)-secotrinervitene-2β,3α-diol (**26**) in 93% yield.

2.1.2 KATO'S SYNTHESES OF TRINERVITENES

Kato's group has succeeded in the total syntheses of 2,3-dihydroxytrinervitanes **28** and **29** in *dl*-form from the secotrinervitane-type allyl chloride (**61**) [36] (Scheme 2.4). Compound **61** had been prepared by the same group. [49, 50a] Treatment of **61** with

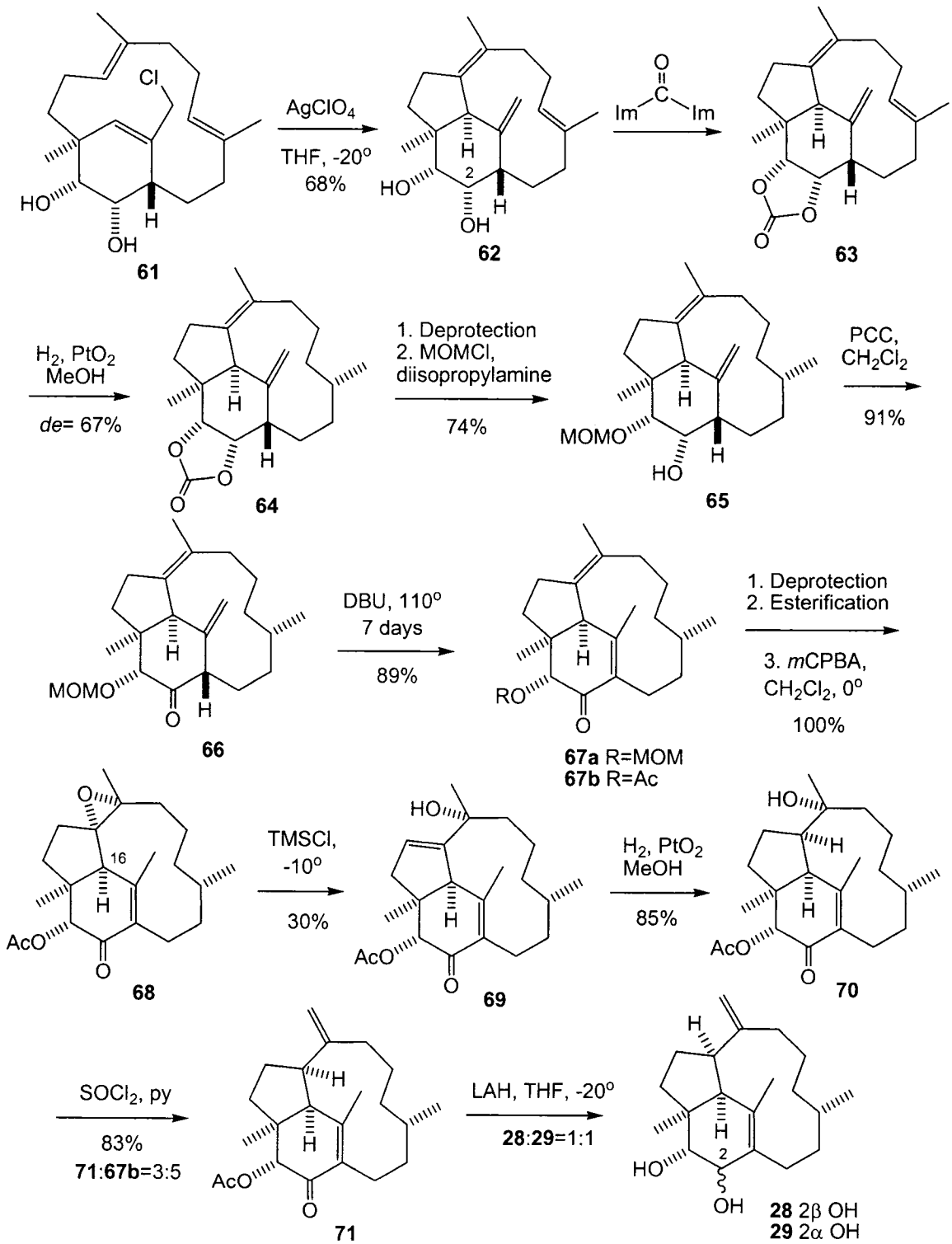


Scheme 2.2 Kato's total synthesis of secotrinervitene **24** [34]



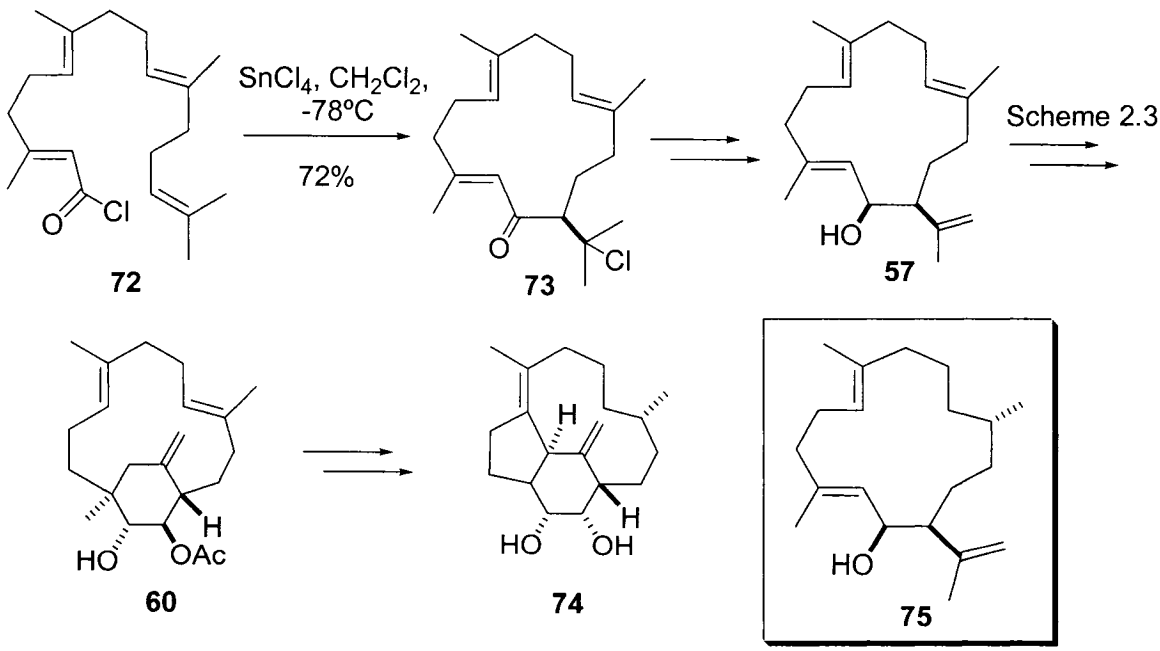
Scheme 2.3 Kato's biomimetic synthesis of secotrinervitene **26** [35]

$AgClO_4$ gave trinervitane-diol **62**, which was protected with carbonyldiimidazole as the carbonate to yield **63**. Regioselective and facially selective PtO_2-catalyzed hydrogenation afforded **64** as the major product. Removal the carbonyl group in **64** released the free diol, which was subsequently selectively protected as the 3-MOM ether **65**. PCC oxidation of the 2-hydroxy group in **65** gave the corresponding ketone **66** in excellent yield. DBU in refluxing toluene was applied for the isomerization of **66** to the conjugated enone **67a**. After changing the protecting group of the 3-hydroxy from a MOM ether to the corresponding acetate **67b**, selective epoxidation onto the convex face of the more nucleophilic alkene afforded epoxide **68** in quantitative yield. Ring-opening of the epoxide was quite restricted since the 16-proton was labile under both acidic and basic conditions. Finally, use of TMSCl was found to be the only reasonable choice of



Scheme 2.4 Kato's total synthesis of 2,3-dihydrooxytrinervitanes **28** and **29** [36]

reagent to afford **69**, but the yield was poor. Hydrogenation of **69** gave a single product **70**, as expected. Dehydration of the tertiary alcohol **70** with thionyl chloride and pyridine furnished **71**, which was isolated from a 3:5 mixture of **71** and **67b**, respectively. Finally, **71** was reduced with $LiAlH_4$ to give an easily separable 1:1 mixture of 2,3-dihydroxy-trinervitanes **28** and **29**, accomplishing the first total synthesis of a trinervitane. Kato's group also reported the efficient construction of the trinervitane skeleton in racemic form on the basis of biogenetic considerations, in which the formation of cembrene skeleton **73** from acyclic acid chloride **72**, followed by subsequent ring closure to the secotrinervitane **60** through the hydroxyneocembrene **57**, constituted the crucial steps to the tricyclic trinervitane skeleton **74** [50] (Scheme 2.5). Their recent preparation of the enantio-merically pure intermediate **75**, [51] which possess the correct absolute configuration for the synthesis of trinervitanes **28** and **29**, may enable them to perform the enantiospecific



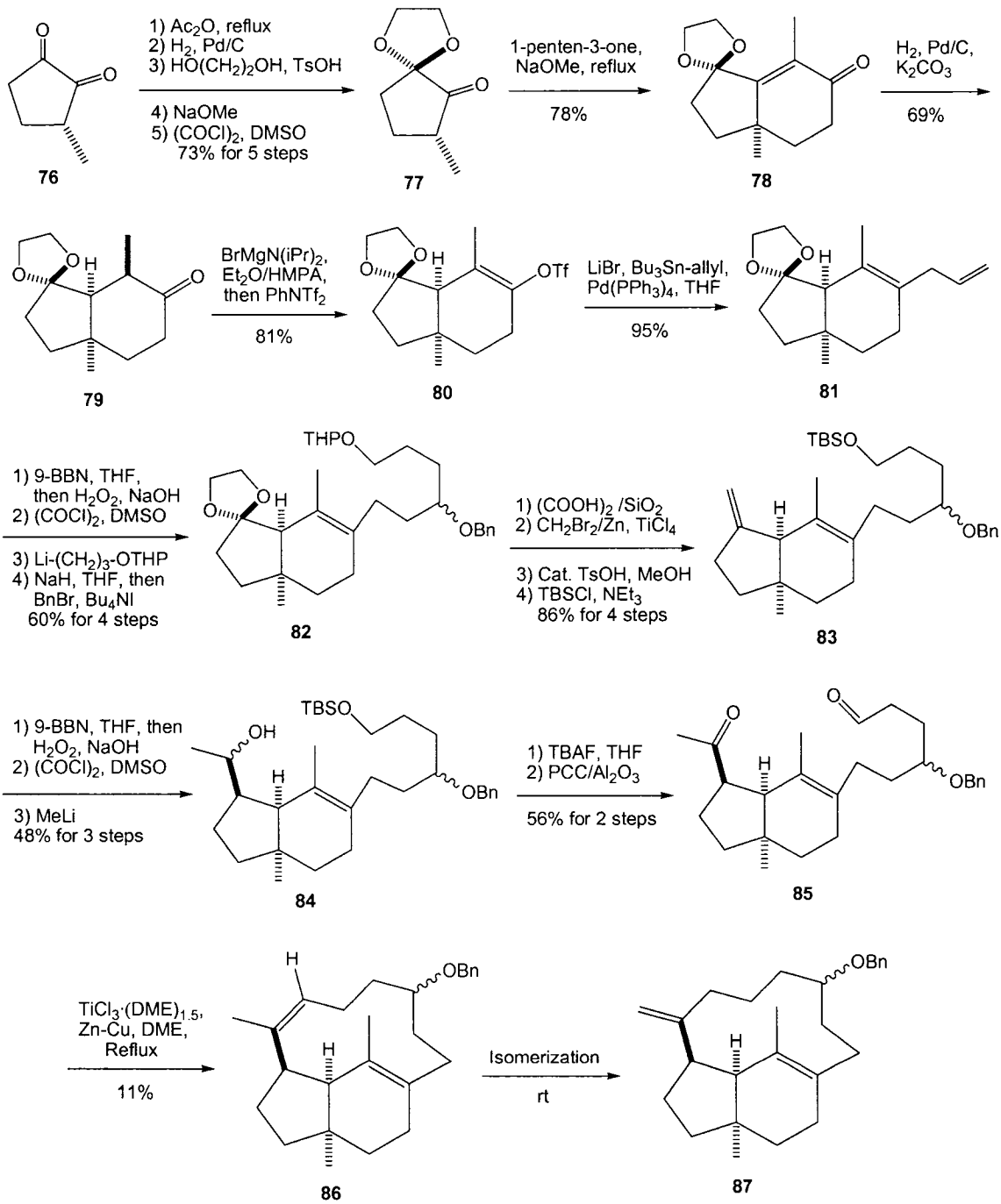
Scheme 2.5 Kato's construction of the trinervitane skeleton and the structure of **75**

total synthesis of the trinervitanes. Their recent synthetic efforts on these targets have been published. [50d-f]

2.2 DAUBEN'S SYNTHESIS OF THE TRINERVITENE SKELETON

In 1998, Dauben's group reported a synthesis of the basic skeleton of the trinervitane diterpenes in racemic form by means of a Robinson annulation and a McMurry coupling [52] (Scheme 2.6). The starting material was 3-methyl-1,2-cyclopentanedione (**76**), which was obtained from the flavor industry. This was efficiently transformed into intermediate **77** in five steps. Acylation to trap the enol gave a conjugated ketone, which was hydrogenated to an α-acetyloxy ketone. The ketone was then protected as an acetal, and the acetyloxy group was hydrolyzed and transformed to ketone **77** by Swern oxidation. [53] Robinson annulation of **77** with 1-penten-3-one gave the unsaturated ketone **78**, which was then catalytically hydrogenated to **79**. Compound **81** was prepared in excellent yield via a Stille coupling [54] of the stable triflate enol ether **80** and tri-*n*-butylallyltin. Hydroboration of the terminal double bond in **81** with 9-BBN followed by Swern oxidation [53] and condensation with Li-$(CH_2)_3$-OTHP afforded, after protection of the resulting alcohol as the benzyl ether, compound **82** as a 1:1 mixture of epimers at the side-chain center. After deacetalization of **82**, methylenation of the resulting ketone proceeded smoothly using non-basic conditions consisting of CH_2Br_2/Zn with $TiCl_4$ [55] after standard Wittig conditions failed. Subsequent deprotection and reprotection gave the *t*-butyldimethylsilyl ether **83**. Hydroboration with 9-BBN occurred almost exclusively from the less hindered, convex face, and then Swern oxidation [53] of the primary alcohol and treatment of the resulting aldehyde with methyl lithium yielded

intermediate **84**. Removal of the silyl ether gave a diol, which was then oxidized to keto-aldehyde **85**. $TiCl_3 \cdot (DME)_{1.5}$ and Zn/Cu in refluxing DME was used for the final McMurry coupling, [56] which produced, in very low yield, the expected product **86** as an



Scheme 2.6 Dauben's synthesis of the trinervitene skeleton [52]

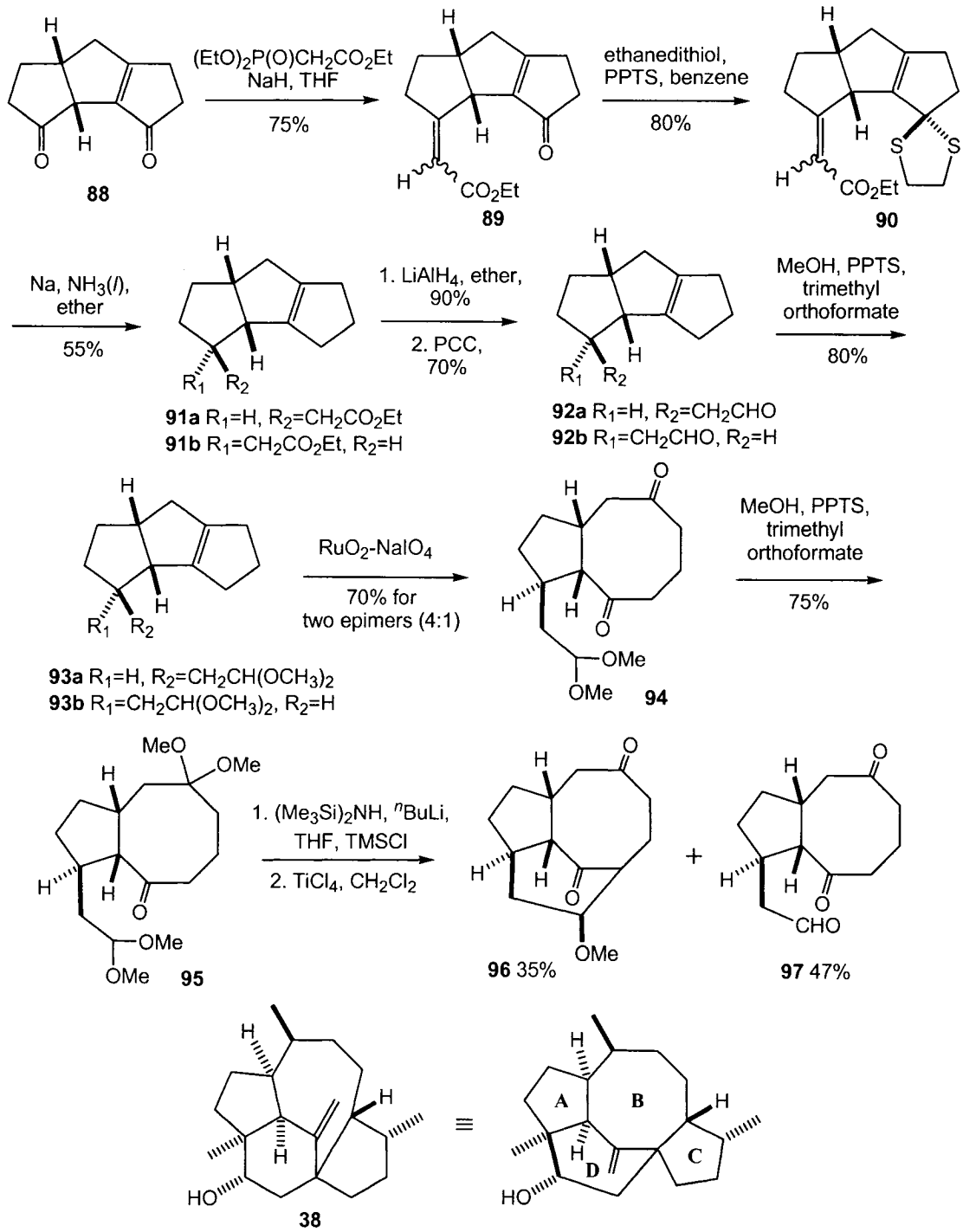
inseparable mixture of diastereomeric benzyl ethers. But, as they studied a sample of compound **86** by NMR at room temperature, it isomerized slowly, but completely, into **87** with the less strained, exocyclic double bond. Thus, they succeeded in the synthesis of the trinervitane skeleton with the correct relative stereochemistry about the hydrindane and the correct positioning of the unsaturation.

2.2 MEHTA'S CONSTRUCTION OF THE ABD RING FRAMEWORK OF LONGIPENOL

Mehta's group developed a general synthetic strategy to form the [5.8] ring-system from the more strained [5.5.5] ring-system, [57] and they applied this process to the construction of the ABD tricarbocyclic framework of the longipenol **38** (Scheme 2.7).[37]

The synthesis began with the readily available, triquinane-based enedione **88** [58] as the starting material (Scheme 2.6). A chemoselective Horner-Wadsworth-Emmons reaction on **88** gave the unsaturated ester **89**, as a mixture of *E*/*Z* isomers. The ketone was protected as its thioacetal **90**. Dissolving metal reduction of **90** furnished **91a** and **91b** as inseparable diastereomers, which were transformed into **92** by $LiAlH_4$ reduction and PCC oxidation. Protection of the aldehyde function in **92** as the dimethyl acetal **93**, and catalytic RuO_2 oxidation delivered two diastereomers (4:1), from which epimer **94** was separated by column chromatography. In order to effect an intramolecular Mukaiyama reaction, [59] the less hindered carbonyl was selectively protected as its dimethyl acetal **95**. Finally, treatment of the trimethylsilyl enol ether derived from **95** with $TiCl_4$ yielded the expected tricyclic compound **96** together with uncyclized **97**. Although they

succeeded in the synthesis of a tricyclic portion of longipenol **38**, no further endeavors toward the total synthesis of **38** have been reported by Mehta's group.

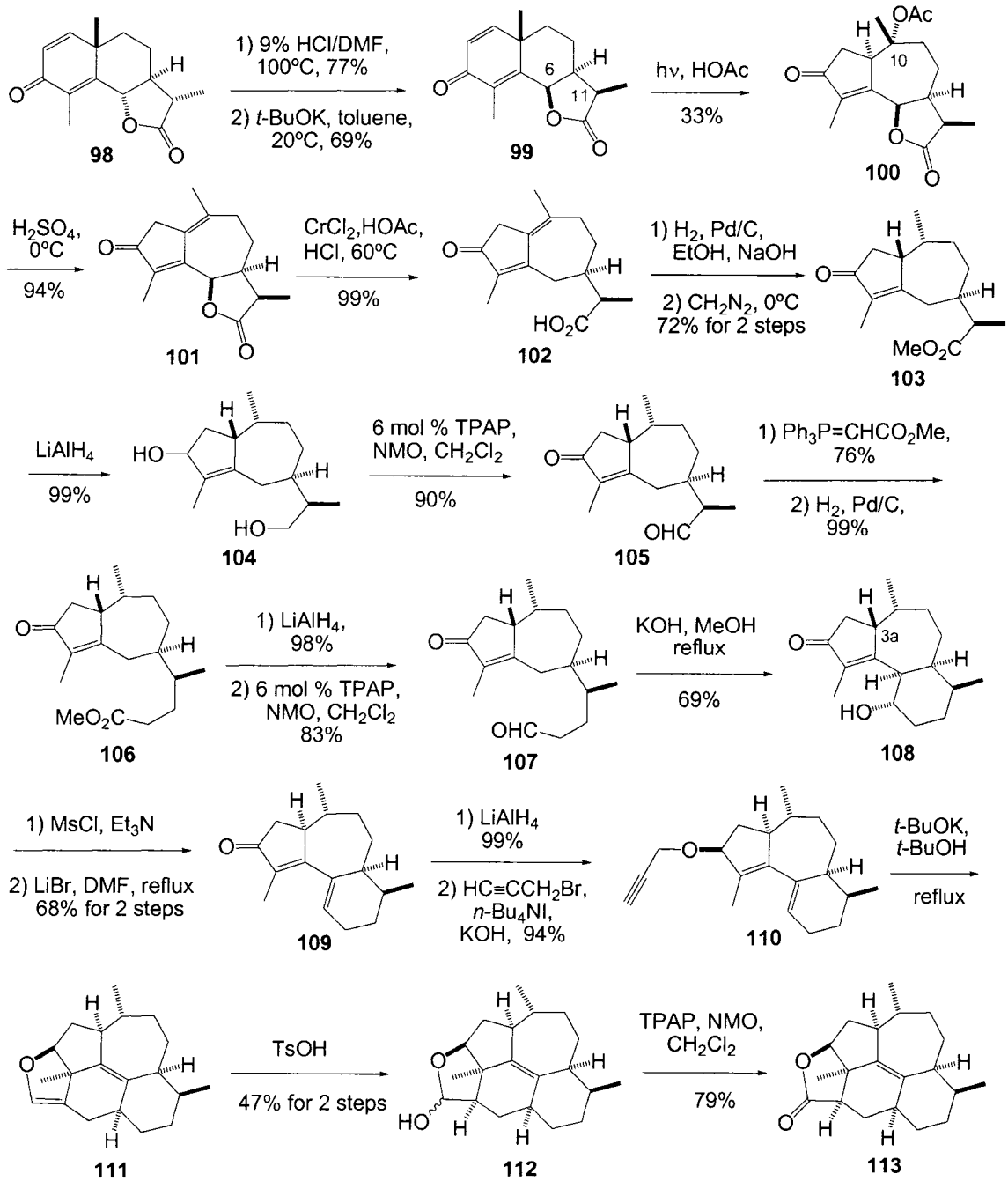


Scheme 2.7 Mehta's construction of the ABD ring framework of longipenol (**38**) [37]

2.4 METZ'S APPROACH TO THE RIPPERTENE RING SYSTEM

Metz's group developed a route to the ring system of 3α-hydroxy-15-rippertene (**37**) in enantiomerically enriched form. [38] A commercially available eudesmanolide, (-)-α-santonin (**98**), was cleverly selected as the chiral starting material (Scheme 2.8). The key steps in this route included a photoisomerization, an intramolecular vinylogous aldol, and an intramolecular Diels–Alder reaction.

The transformation of α-santonin (**98**) into 6-*epi*-β-santonin (**99**) by acid-catalyzed epimerization at C-6, equilibration at C-11 under basic conditions, and subsequent photolysis to hydroazulene (**100**) was a known process, first reported by Barton. [60] Next, Büchi's stereoselective deoxygenation strategy [61] was applied to produce dienone carboxylic acid **102** *via* the dienone lactone **101** by hydrogenolysis through the action of chromous chloride in acetic acid. Hydrogenation occurred predominantly from the β-face (86:14) to yield **103** as the major product after esterification. Reduction of **103** with lithium aluminum hydride delivered a diol **104**, which was oxidized to the ketoaldehyde **105** with tetra-*n*-propylammonium perruthenate/*N*-methylmorpholine *N*-oxide. Chemoselective Wittig reaction and subsequent chemoselective hydrogenation gave **106**. After adjustment of the oxidation levels, a clean and stereoselective cyclization gave **108** by an intramolecular vinylogous aldol reaction, which was effected by treatment of **107** with potassium hydroxide. The elimination of the mesylate derived from **108** yielded **109** with epimerization at C-3a. Reduction of **109** gave an alcohol, from which the propargyl ether **110** was produced. Base-induced isomerization to the corresponding allenyl ether and subsequent intramolecular Diels-Alder reaction delivered the pentacyclic enol ether **111**. Addition of



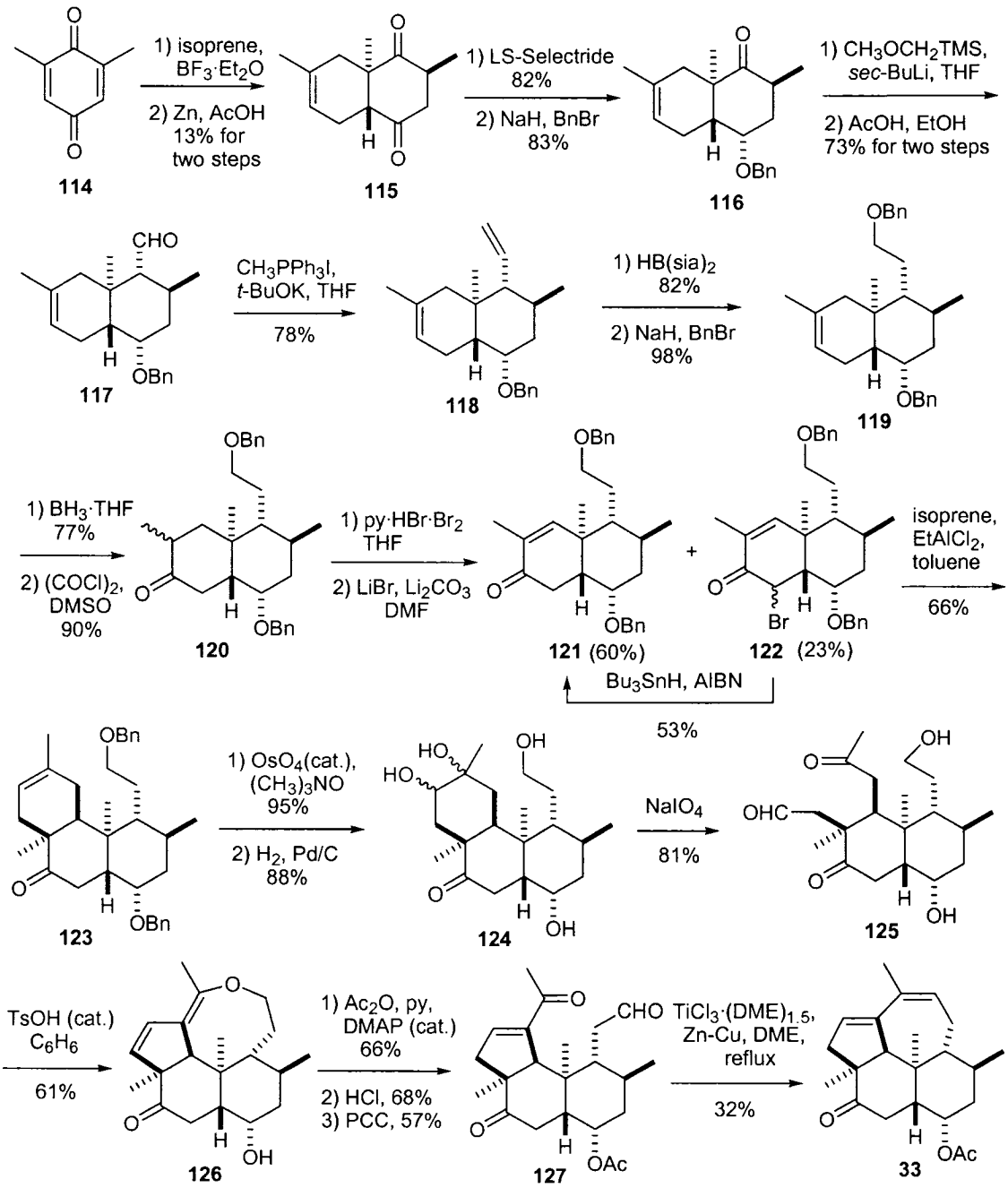
Scheme 2.8 Metz's approach to the rippertene ring system [38]

water to the enol ether of **111** led to diastereomeric lactols **112**, which were oxidized to lactone **113**. Unfortunately, the ring system produced by this synthesis cannot be easily transformed into the natural product **37**. A complete synthesis of rippertene has not been reported by this, or any other, approach.

2.5 DAUBEN'S TOTAL SYNTHESIS OF KEMPENE-2

Dauben's group reported the first total synthesis of kempene-2 (**32**), [39] which is still the only total synthesis of a kempane. This synthesis featured two Diels–Alder reactions and a McMurry coupling [56] (Scheme 2.9).

The total synthesis started with a Lewis acid-catalyzed Diels–Alder reaction between 2,6-dimethyl-*para*-benzoquinone (**114**) and isoprene, and the subsequent reduction of the remaining quinone double bond gave **115** in very low yield. This was not a good start for a total synthesis. Selective reduction of the less hindered carbonyl group and protection of the resulting alcohol gave benzyl ether **116**. Peterson-type homologation [62] converted **116** to the aldehyde **117,** and a Wittig reaction delivered the diene **118**. Selective hydroboration of the terminal alkene and protection of the resulting primary alcohol yielded the dibenzyl ether **119**. Hydroboration of the remaining disubstituted alkene and Swern oxidation gave a diastereomeric mixture **120**, which was subjected to bromination and elimination to furnish a mixture, favoring the expected compound **121**. The by-product, bromoketone **122**, could also be transformed into **121** by dehalogenation with Bu_3SnH. A second Diels–Alder reaction between **122** and isoprene proved to be difficult, but finally catalysis by Et_2AlCl led to **123** and its regioisomer in a ratio of 2.6:1, respectively. Separation of these isomers required HPLC,



Scheme 2.9 Dauben's total synthesis of kempene-2 [39]

which was a second shortcoming in this total synthesis. Compound **123** was now ready for the construction of the five-membered ring. Dihydroxylation of the double bond in compound **123** was achieved by osmium tetroxide-catalyzed trimethylamine *N*-oxide oxidation, and, following deprotection of the benzyl ether, tetraol **124** was obtained as a diastereomeric mixture. Glycol cleavage of **124** with sodium periodate gave a labile ketoaldehyde **125**, which cyclized to the enone with a catalytic amount of *para*-toluene-sulfonic acid. The enone spontaneously produced the dienol ether **126**. Although attempts to isolate the initially formed enone failed, the enol ether was exploited to block the primary alcohol. Acylation of the secondary alcohol in **126**, followed by hydrolysis of the enol ether, and oxidation of the liberated primary alcohol provided the advanced intermediate **127**. Finally, McMurry coupling in 32% yield between the carbonyls in **127** completed the first total synthesis of (±)-kempene-2.

This is an excellent example of well-designed synthesis of a complicated natural product, although the low yields of the Diels–Alder reactions and of the McMurry coupling, and low regionselectivity in the Diels–Alder reactions, left considerable room for improvement.

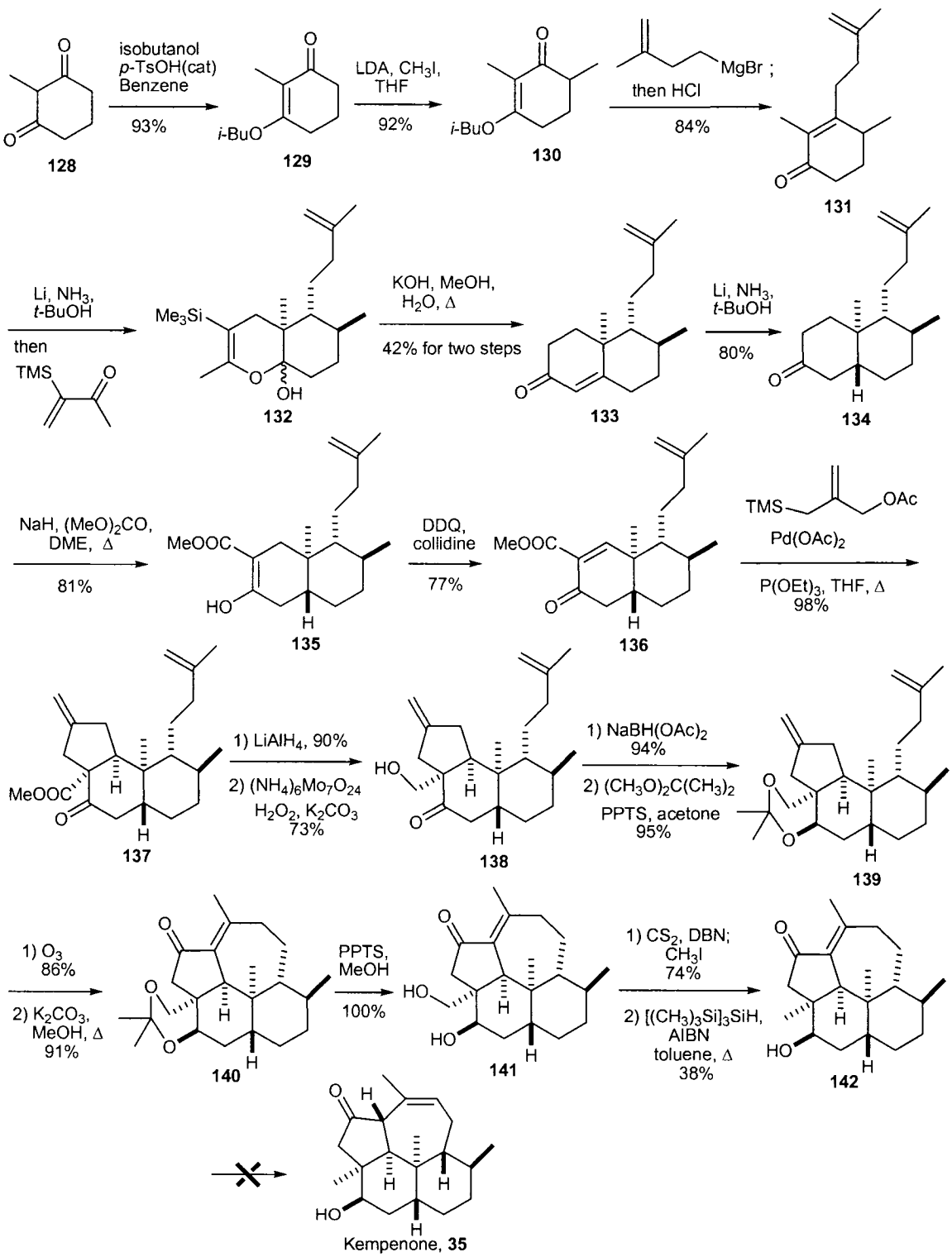
2.6 PAQUETTE'S APPROACH TO KEMPENONE

In 1992, Paquette's group published an approach to the total synthesis of kempenone (**35**). [40] The key feature of this approach was a palladium-mediated [3+2] cycloaddition to construct the five-membered ring in kempenone (**35**) (Scheme 2.10).

In Paquette's approach, regiospecific α′ deprotonation of 3-alkoxycyclohex-2-enone [63] was applied first for the monomethylation of **129**, which was prepared from 2-

methyl-1,3-cyclohexanone (**128**), to provide **130**. Reaction between **130** and the Grignard reagent derived from 4-bromo-2-methyl-1-butene and treatment of the product with acid generated the desired enone **131**. Dissolving metal reduction of **131**, followed by a Michael reaction with α-(trimethylsilyl)vinyl methyl ketone furnished enol hemiacetal **132** as the major product. Base-induced aldol reaction of **132** gave enone **133**, which was transformed to **134** by a second dissolving metal reduction. Deprotonation of **134** with a base and condensation with dimethyl carbonate provided ester **135**, which was oxidized efficiently to **136** by DDQ.

The key step in this approach from **136** to **137**, the palladium(II)-mediated [3+2] cycloaddition of trimethylenemethane (TMM), [64] took place with high stereoselectivity and in virtually quantitative yield. Both the ketone and the ester group in **137** were reduced by lithium aluminum hydride, but the secondary alcohol was *cis* to the hydroxymethyl group. Efforts were made to invert the stereochemistry of the secondary alcohol, but these failed. Therefore, the secondary alcohol was selectively oxidized by hydrogen peroxide and ammonium molybdate [65] to **138**, and subsequent reduction of the *β*-hydroxyketone with sodium triacetoxyborohydride [66] exclusively delivered the secondary alcohol *trans* to the hydroxymethyl group. The diol was then protected as its acetonide **139**. Ozonolysis and base-directed aldol cyclization gave **140**, which was deprotected to regenerate diol **141**. A modified Barton–McCombie reaction [67] was applied for the deoxygenation of the hydroxymethyl group to give **142**. Finally, all efforts to deconjugate the double bond of **142**, to make the natural product kempenone **35**, failed. Semi-empirical calculations by Taber [68] later showed that kempenone **35** is less stable than **142** by 1.6 kcal/mol.



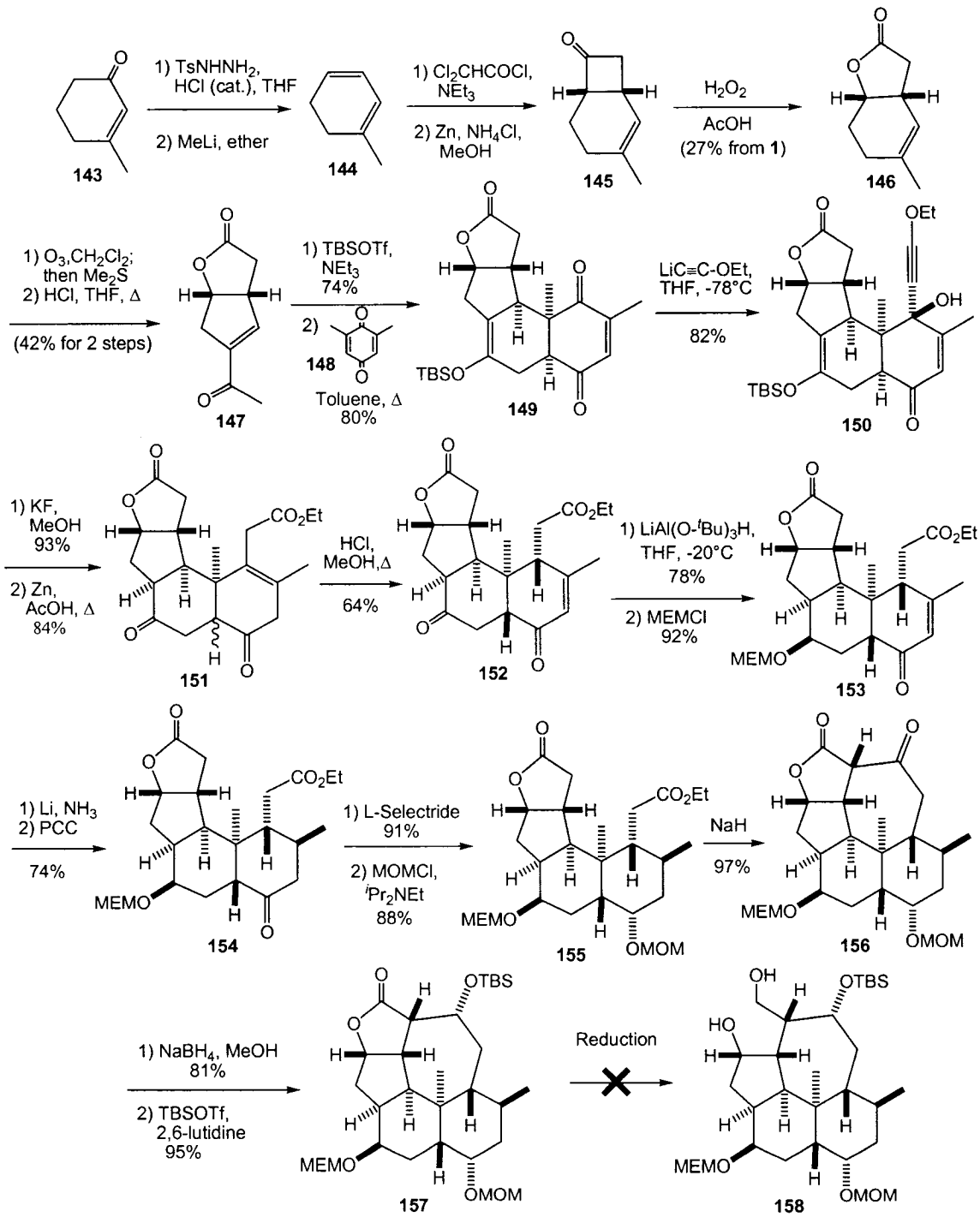
Scheme 2.10 Paquette's approach to kempenone [40]

2.7 BURNELL'S APPROACH TO THE KEMPANE RING SYSTEM

2.7.1 BURNELL'S LACTONE ROUTE

Our group developed a stereoselective approach to the kempane ring system in 1997. [41,42a] In this "lactone approach," three of the stereogenic centers in the *cis*-decalin ring system were assembled by a Diels–Alder reaction and the final, seven-membered ring was cyclized by an intramolecular Dieckmann condensation (Scheme 2.11).

This lactone approach started with the construction of an enone-lactone **147** from enone **143** by a process similar to Corey's prostaglandin synthesis. [69] Diene **144** was prepared from enone **143** by a Shapiro reaction. [70] Then, [2+2] cycloaddition of dichloroketene to diene **144** took place with complete chemo- and regiochemical control. Reductive removal of chlorine provided the ketone **145**. Baeyer–Villiger reaction [71] of **145** afforded exclusively the lactone **146**, which was subjected to ozonolysis and immediate aldol cyclization to give enone-lactone **147**. Treatment of the silyl enol ether derived from **147** with 2,6-dimethyl-*para*-benzoquinone (**148**) resulted in a Diels–Alder reaction to provide adduct **149** with good regioselectivity and excellent *endo* and facial selectivity. Addition of lithium ethoxyacetylide to **149** gave **150** as the only product. Potassium fluoride was applied to deliver the ketone from the silyl enol ether **150**, and deoxygenation by zinc and acetic acid provided an epimeric mixture **151**. Both reconjugation of the β,γ-double bond and epimerization were done in a single operation with methanolic HCl to afford **152**. Chemoselective reduction of the carbonyl at C-6 of **152** with $LiAl(O^tBu)_3H$ and protection as the MEM ether gave **153**. Dissolving metal reduction was applied to **153** followed immediately by treatment with PCC (to re-oxidize some over-reduced product) to provide compound **154**. Stereoselective reduction of the



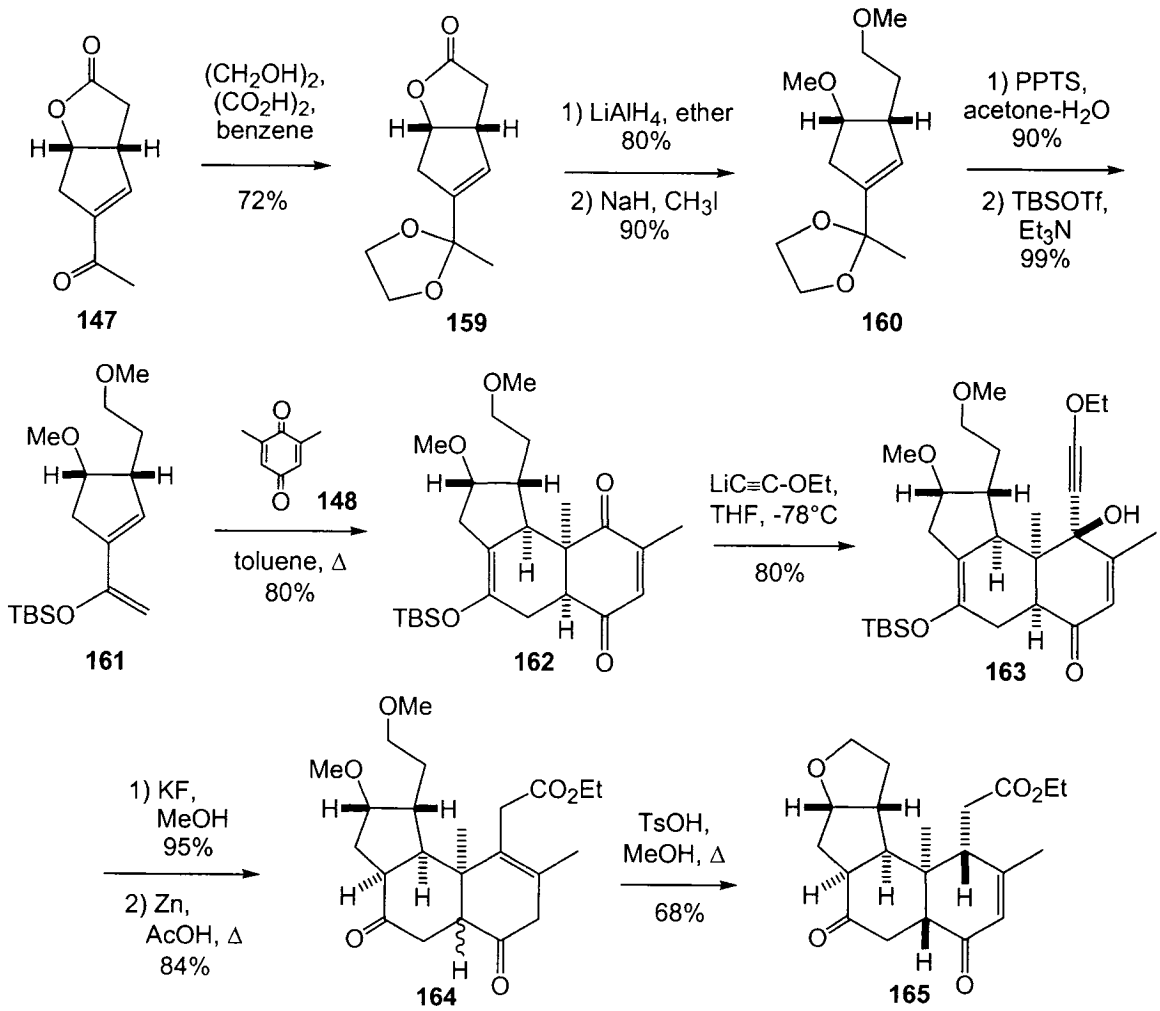
Scheme 2.11 Burnell's lactone approach to the kempanes [41]

ketone **154** was achieved with bulky L-Selectride and, following protection of the alcohol as a MOM ether, gave **155**. As one of the key steps, NaH-mediated intramolecular Dieckmann condensation of **155** provided ketone **156**, which was stereoselectively reduced by sodium borohydride and then protected as the silyl ether **157**. In order to achieve the total synthesis of the kempanes, the lactone group in **157** needed to be reduced to the corresponding diol **158**, and then deoxygenation of the primary alcohol should have provided the methyl group of the natural product. Unfortunately, all efforts to reduce that lactone to diol **158** failed. This problem might have been avoided simply by reduction of the lactone at an earlier stage, and this was explored in our second approach, the "diether route."

2.7.2 BURNELL'S DIETHER ROUTE

It has been reported that a simple five-membered lactone can be easily reduced to a diol. [72] This route is similar to the lactone route except opening the lactone ring took place at an earlier stage. The diether route [42b, 42c] started with the protection of the carbonyl in the lactone ketone **147** as its acetal **159**. Reduction of the lactone with lithium aluminum hydride gave a diol, which was treated with sodium hydride and iodomethane to provide methyl ether **160**. Deprotection of the carbonyl in **160** and subsequent treatment with TBSOTf and Et_3N furnished the diene **161**, which underwent a Diels–Alder reaction with 2,6-dimethyl-*para*-benzoquinone to give **162**. Treatment with lithium ethoxyacetylide (**163**), release of the ketone, and deoxygenation with zinc in acetic acid (**164**) went very well, but, unfortunately, an unexpected tetrahydrofuran ring (**165**) formed in the reconjugation step with *para*-toluenesulfonic acid. After several

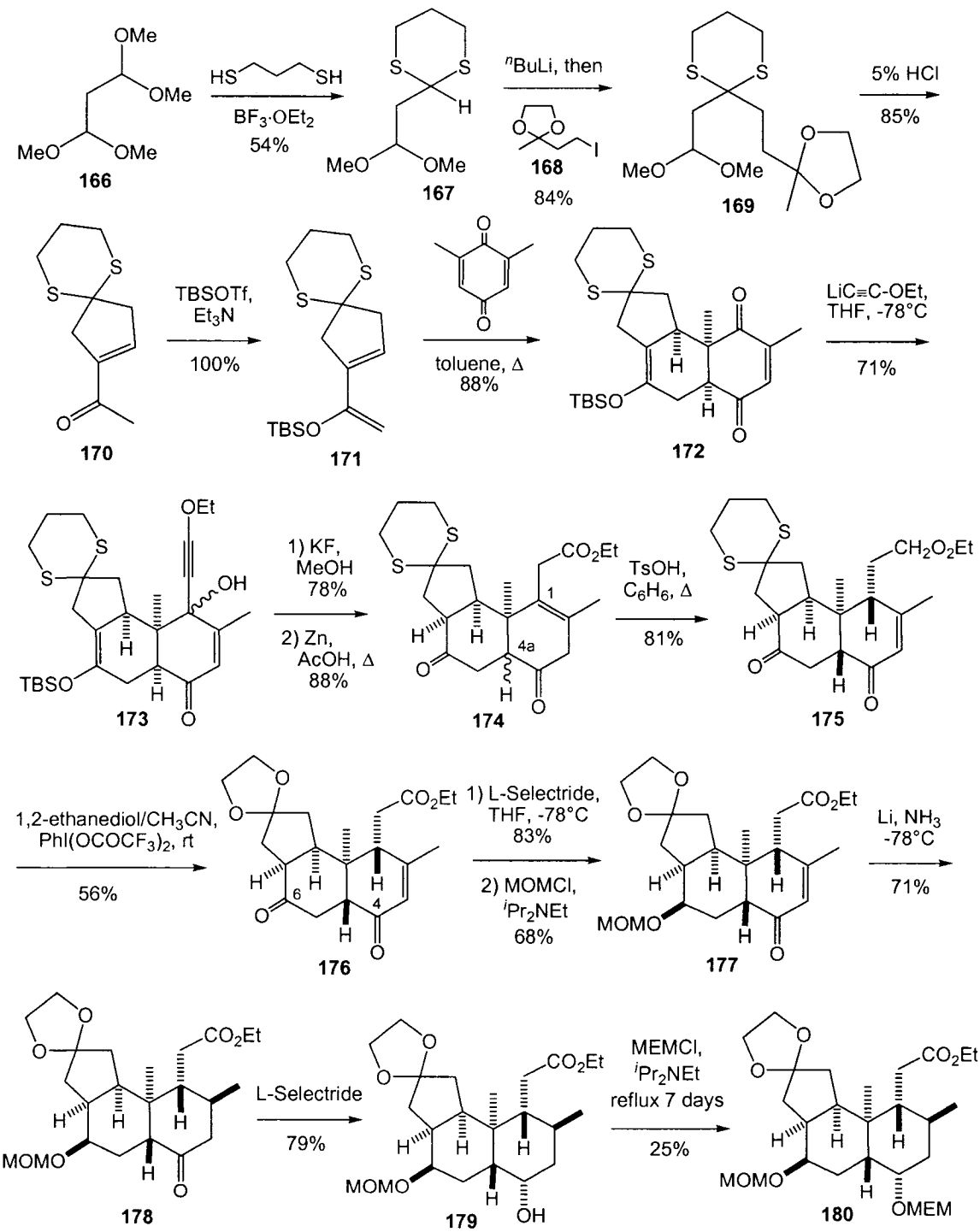
attempts to reconjugate by alternative methods and also to cleave the ether ring failed, this strategy had to be given up and other approaches to avoid any "extra" cyclizations were undertaken.



Scheme 2.12 Burnell's diether approach to the kempanes [42]

2.7.3 BURNELL'S DITHIANE ROUTE

In order to overcome the problems of the "extra" five-membered ring in the previous two routes, the "dithiane route" was initiated [42c] (Scheme 2.13). Malonaldehyde bis(dimethyl acetal) **166** was reacted with 1,3-propanedithiol in the presence of a Lewis acid to afford the monosubstituted dithiane **167**, which was metalated by *n*-butyllithium and then reacted with iodo-acetal **168** to provide **169**. When **169** was treated with dilute HCl, the expected enone **170** was obtained in high yield. The enone was used to make diene **171,** and its Diels–Alder adduct **172** was obtained under conditions similar to those of the lactone route. Also, a similar acetylide addition gave **173**. Release of the ketone, and deoxygenation by zinc and acetic acid furnished a mixture of C-4a epimers (**174**). Reconjugation of the double bond from the β,γ-position and epimerization at C-4a of **174** to **175** were achieved in the same step by *p*-toluenesulfonic acid. Reduction of the cyclic dithiane-protecting group was prevented in the next, dissolving metal reduction step by conversion of the dithiane to an acetal **176**. In order to differentiate the carbonyl at C-6 from the one at C-4 after the dissolving metal reduction, the former was selectively reduced by the equatorial attack of L-Selectride, and subsequent protection as the MOM ether afforded **177**. Dissolving metal reduction of **177** gave ketone **178**, which was stereoselectively reduced to alcohol **179** by L-Selectride. But, unfortunately, the protection of the alcohol as a MEM ether **180** was not very effective, with only a 25% yield of the product. Although this fairly unreactive alcohol might have been left unprotected in the continuation of this approach, this approach was halted at this point [42c] in favor of a more novel route outlined below. However, some work towards the improvement of aspects of this dithiane approach is presented in more detail below.



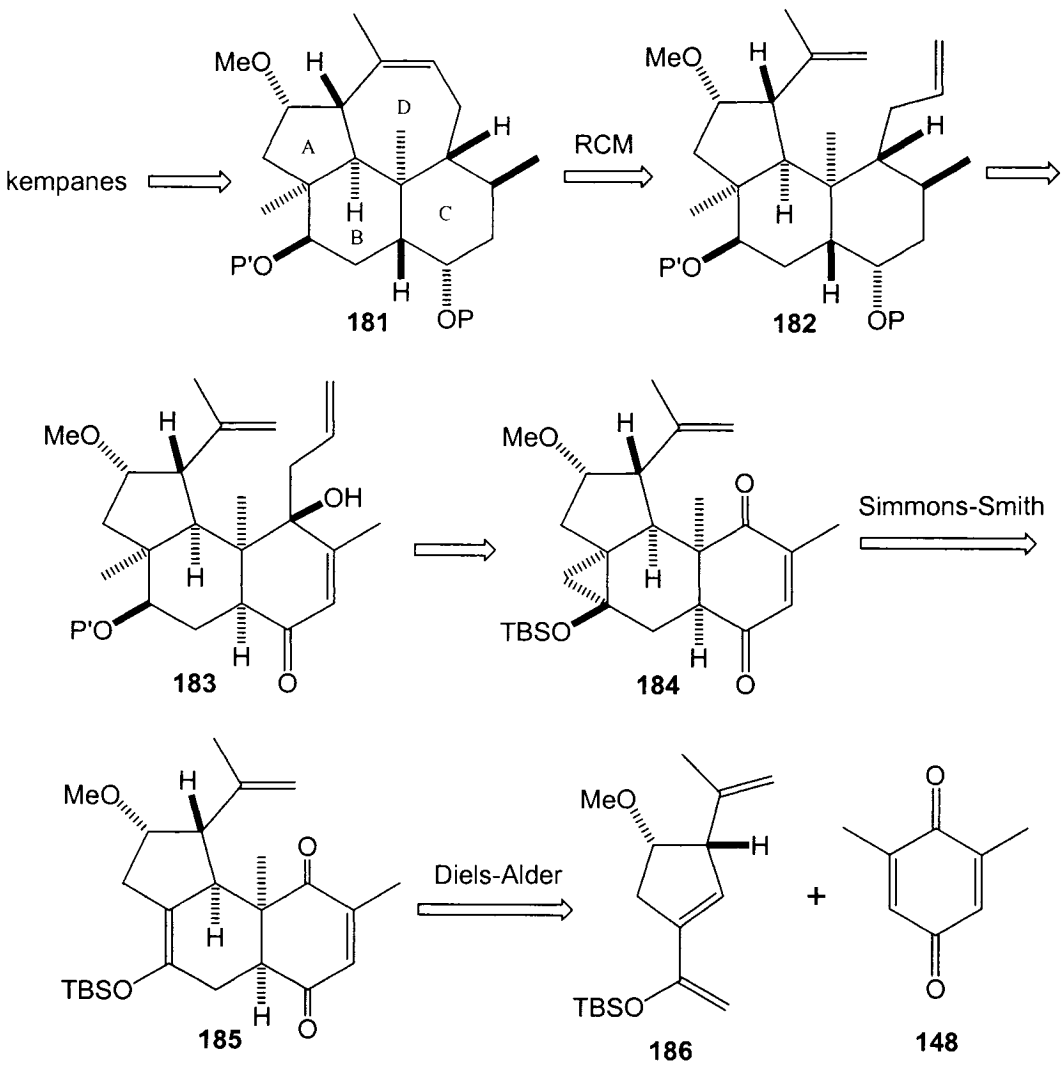
Scheme 2.13 Burnell's dithiane approach to the kempanes [42c]

CHAPTER 3. RETROSYNTHETIC ANALYSIS OF THE KEMPANES

A strategy that is amenable to the preparation of all of the known kempanes was sought. New methodologies needed to be considered due to problems with the three previous routes. The new retrosynthetic analysis is shown in Schemes 3.1 and 3.2.

Kempanes **33**-**36** could be derived from the advanced intermediate **181**, which has all of the correct stereochemistry and all of the required functionality for transformation into the natural products (Scheme 3.1). The new key step, ring-closing metathesis (RCM), [73] was chosen for the cyclization of the seven-membered ring D from the terminal alkenes in **182**. RCM has been developed for the construction of medium-sized rings, such as five- to seven-membered rings, but when this work began there were only a few examples of RCM in the total synthesis of complicated natural products. [74] There were very few examples of an RCM step for the construction of a seven-membered ring in natural product synthesis. [75] Compound **182** might be obtained from compound **183** via reductive deoxygenation, reconjugation, dissolving metal reduction and epimerization under acidic conditions, in a manner similar to the lactone route (Scheme 2.11). Compound **183** might be made *via* ring-opening of the cyclopropane in compound **184** by fluoride, reduction of the resulting carbonyl, protection of the secondary alcohol and regioselective and facially selective allylation. The cyclopropane ring in **184** might be inserted by a stereoselective Simmons–Smith reaction [76] on the electron-rich silyl enol ether double bond in **185**. In order to obtain **185**, a regio-, *endo*- and facially selective Diels–Alder reaction between diene **186** and 2,6-dimethyl-*para*-benzoquinone **148**,

making rings B and C and generating three core stereogenic centers in the kempane skeleton at the same time, is probably the best choice based on our experience. [41,42]

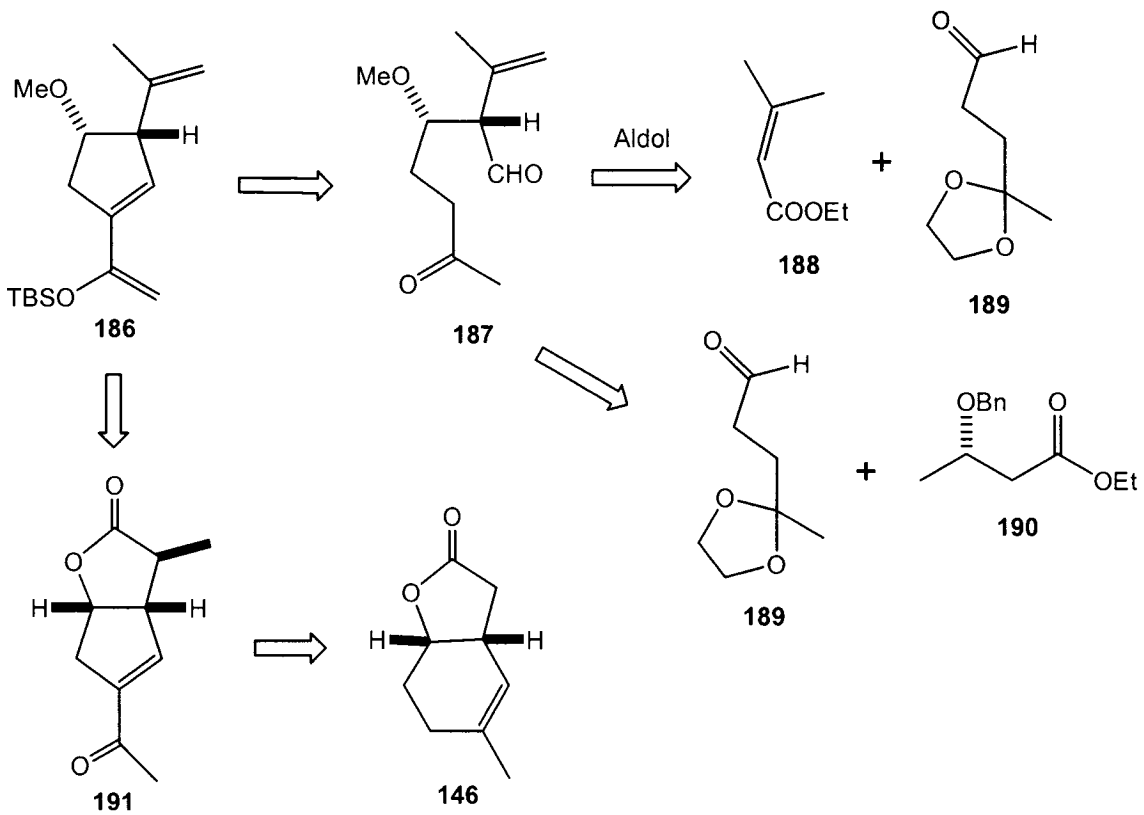


Scheme 3.1 Retrosynthetic analysis of kempanes

The initial target was thus diene **186** (Scheme 3.2). First of all, **186** (ring A in the kempane skeleton) might be obtained by an intramolecular aldol condensation from keto-aldehyde **187**, which might be also prepared by an aldol reaction between **188** and **189**, or between **189** and **190**, and Wittig olefination, although the relative stereochemistry of the

aldol products would be difficult to predict. However, it seems possible that some control might be derived from an Evans' chiral auxiliary on a compound similar to **188** or from the stereogenic center in **190**.

On the other hand, should these routes fail, it was felt that the preparation of **186** might be achieved from **191** by ring-opening of the lactone, dehydration of the primary alcohol and formation of a silyl enol ether from the methyl ketone. Lactone **191** is a known compound, and it can be prepared from **146** via ozonolysis, aldol cyclization and methylation, as shown in previous work from our group. [41b]

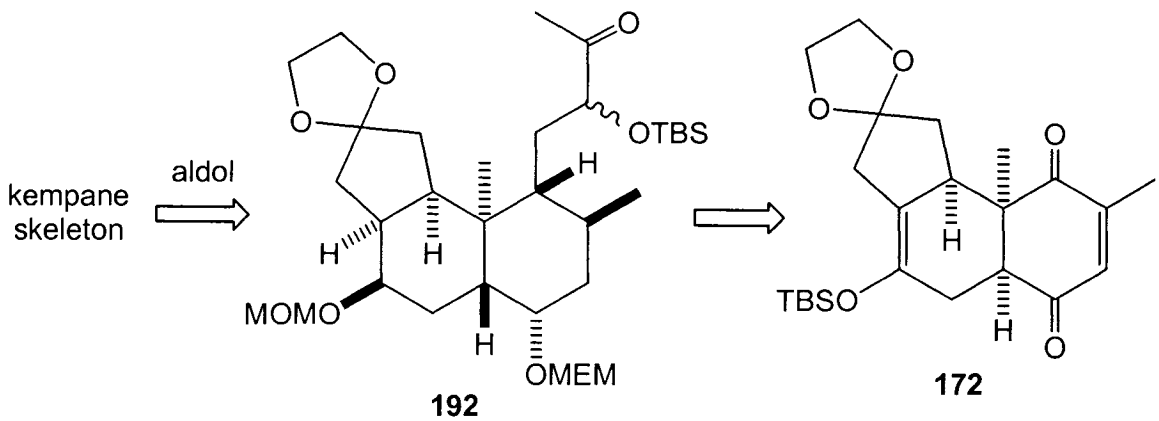


Scheme 3.2 Retrosynthetic analysis of diene **186**

CHAPTER 4. RESULTS AND DISCUSSION

4.1 ATTEMPTS TO IMPROVE THE DITHIANE ROUTE

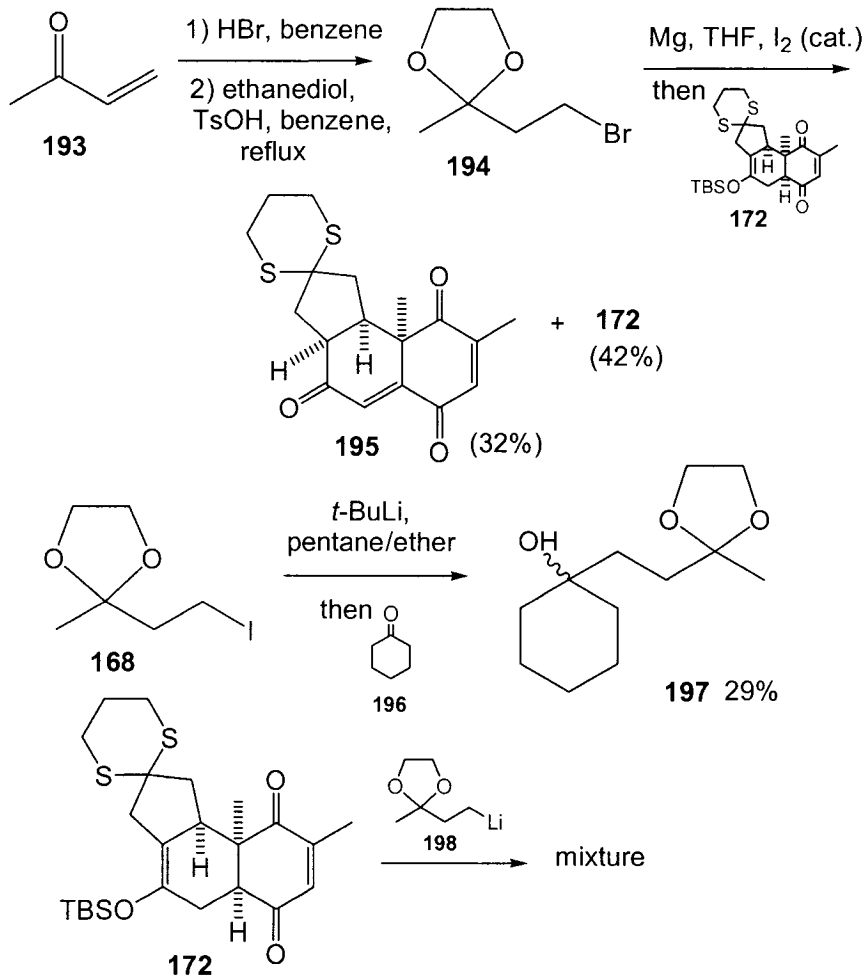
In Burnell's dithiane route, a four-carbon side-chain is required for addition to **172**, in order to obtain the compound **192** to complete the final, seven-membered ring *via* an aldol reaction, at a point beyond what is shown in Scheme 2.13. The retrosynthetic analysis is shown in Scheme 4.1. An intramolecular aldol reaction of a diketone after deprotection of the acetal in **192** might deliver the kempane skeleton, while the addition of a four-carbon side-chain on the top right carbonyl in **172** regioselectively and diastereoselectively, would be required.



Scheme 4.1 Retrosynthetic analysis of the final stage of the dithiane route

Some additions of appropriate four-carbon units were tested with simpler model compounds, and then additions to **172** were attempted. The results are summarized in Scheme 4.2. Bromo-acetal **194** was prepared by addition of hydrobromic acid to 3-butenone **193**, followed by protection of the carbonyl as an ethylene acetal using a procedure based on the preparation of iodo-acetal **168**. [77a] Addition of the Grignard

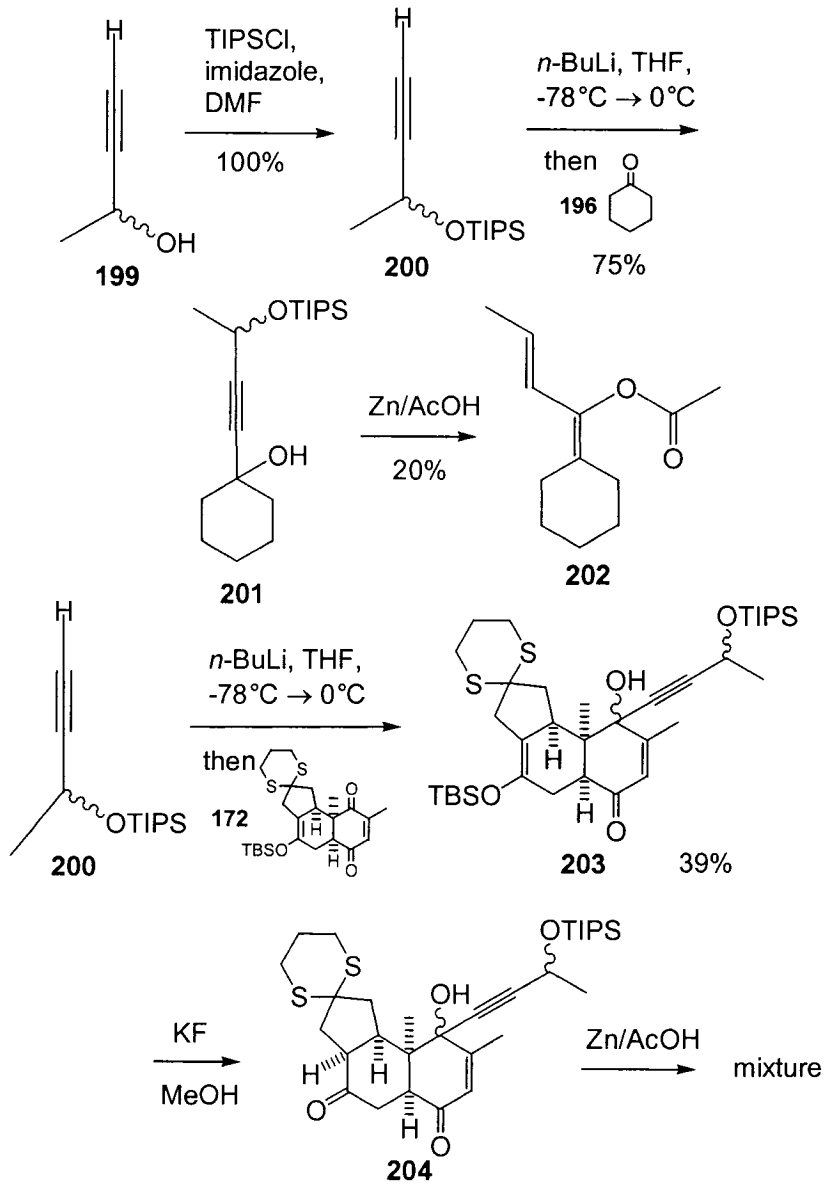
reagent derived from **194** to compound **172** was then attempted (Scheme 4.2). Unfortunately, none of the expected product was obtained, but an oxidized product **195** was isolated, and a significant amount of the starting material **172** was recovered. Compound **172** is obviously very susceptible to oxidation; the oxidant might have been some molecular iodine (used to promote the formation of the Grignard reagent) or it might have been oxygen in the air during work-up. Similar problems had also been reported in our group's lactone route to kempanes. [42a]



Scheme 4.2 Experiments with four-carbon synthons

The lithium reagent derived from iodo-acetal **168** was then examined (Scheme 4.2). Addition of this lithium reagent **198** to cyclohexanone **196** resulted in formation of the alcohol **197**, [77b] but in low yield. Furthermore, when this lithium reagent **198** was reacted with compound **172** it gave a complicated mixture, and none of the desired product was isolated following chromatography.

In other experiments, the four-carbon synthon **200** was evaluated (Scheme 4.3). This was similar to the lithium ethoxyacetylide that had worked very well for us in the past. [41] The alkyne **200** was easily prepared from commercially available 3-butyn-2-ol (**199**). The alcohol was protected as the tri(isopropyl)silyl (TIPS) ether in quantitative yield, and the acetylenic proton was removed with *n*-butyllithium. Reaction of this lithium acetylide to cyclohexanone **196** gave the alcohol **201** in an encouraging 75% yield, and a deoxygenation product **202** was formed when **201** was treated with zinc in refluxing acetic acid. Addition of the lithium acetylide to compound **172** resulted the expected product alcohol as an epimeric mixture **203**, although the yield was modest. The collapse of TBS silyl enol ether with potassium fluoride led to the ketone **204**, but the TIPS protecting group remained. It was disappointing that none of the desired deoxygenation product was detected in the reaction mixture after **204** was treated with zinc in acetic acid. At this point work on this route was suspended in favor of the "RCM route."

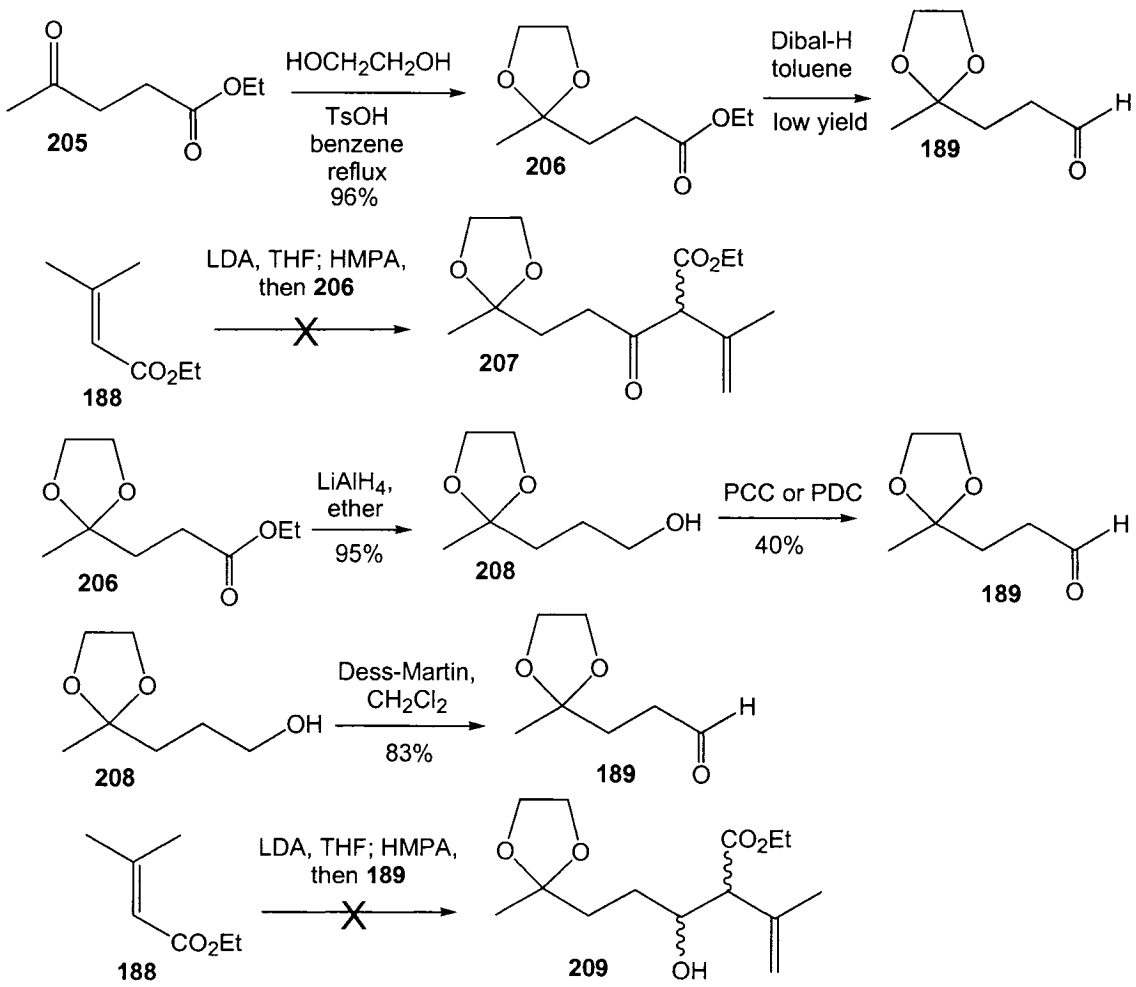


Scheme 4.3 Experiments with four-carbon synthons

4.2 INITIAL ATTEMPTS AT THE PREPARATION OF DIENE 186

In initial attempts to prepare diene **186** (Scheme 4.4), an unusual crossed-Claisen condensation using the enolate of ethyl 3-methyl-2-butenoate **188** was envisaged. Alkylation of **188** has been reported recently, [78] though no Claisen condensation was documented. Protection of the ketone moiety in **205** gave acetal ester **206** in 96% yield.

The unsaturated ester **188** was treated with LDA, and then the enolate was mixed with ester **206**. This gave no detectable amount of product **207**; only the starting materials were recovered.

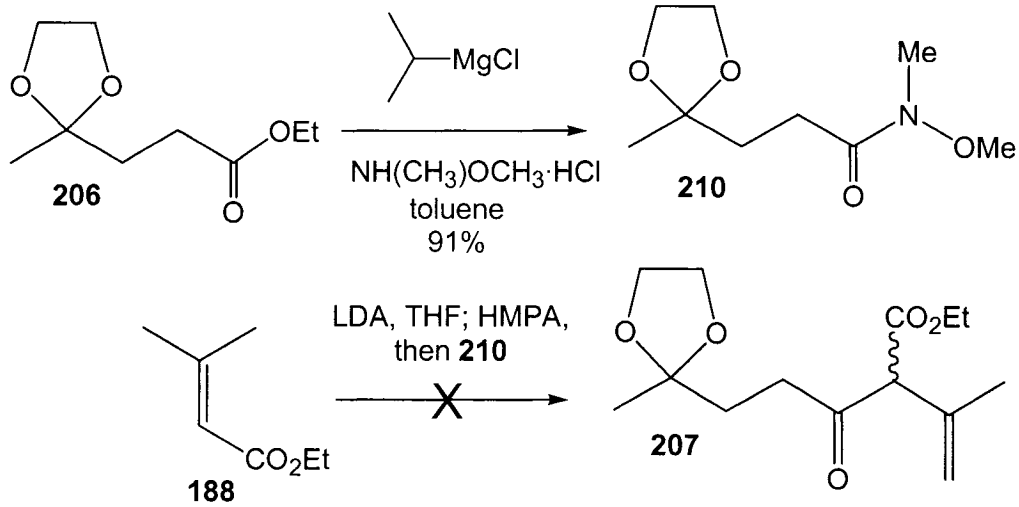


Scheme **4.4** Attempts at the preparation of diene **186** via an ester or an aldehyde

The reaction between the enolate of ester **188** and the more reactive aldehyde **189** was attempted. Ester **206** can be reduced to its corresponding aldehyde **189** by Dibal-H directly, but the low yield prevented its application. Ester **206** was easily reduced with lithium aluminum hydride to its corresponding alcohol **208** in high yield. Oxidation of the alcohol **208** with either PCC or PDC gave the expected aldehyde **189**, again in low

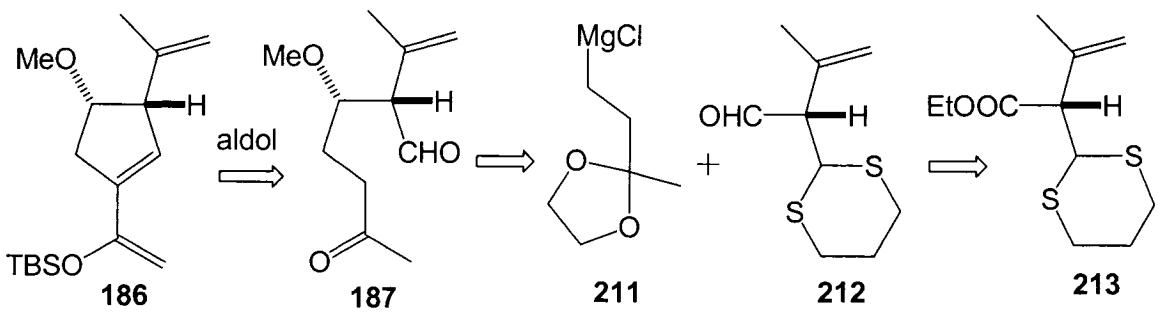
yield, but the treatment of **208** with Dess–Martin periodinane [79] delivered the aldehyde **189** in high yield. However, when the enolate of **188** (generated with LDA) was mixed with aldehyde **189** none of the expected alcohol **209** was detected. This might have been due to a retro-aldol reaction during the aqueous work-up process.

In one last attempt, a Weinreb amide [80] was considered instead of an aldehyde (Scheme 4.5). Since the initial report of Nahm and Weinreb [81] on the use of *N*-methoxy-*N*-methylamides as reactive carbonyl equivalents, this synthon has become more and more popular because of its ease of preparation and the few side reactions encountered during nucleophilic additions. This advantage can be explained by the stability of the tetrahedral intermediate formed by addition of a nucleophile (e.g. an organometallic reagent) to *N*-methoxy-*N*-methylamides due to chelation. [81] The tetrahedral intermediate resists collapse to form the ketone under the reaction conditions thereby preventing the subsequent reaction of ketone and an organometallic reagent. The *N*-methoxy-*N*-methylamide is generally prepared from the ester using an aluminum-based reagent. [82] Using trimethyl aluminum, the normal procedure was followed with ester **206** and *N*,*O*-dimethylhydroxylamine·HCl as the starting materials, but the Weinreb amide **210** was not obtained. Again, just the starting material **206** was recovered. A research group at Merck reported a new, general method for the preparation of Weinreb amides using organomagnesium reagents. [83] This procedure did work well in this case; using isopropylmagnesium chloride, Weinreb amide **210** was obtained in 91% yield. The result was once again disappointing when an attempted aldol reaction between **188** and **210** furnished none of the expected product, keto-ester **207**.



Scheme 4.5 Attempts for the preparation of diene **186** via a Weinreb amide

Next, attention turned to the reactions of 1,3-dithienium tetrafluoroborate **216**. [84] This bulky methyl equivalent has been used in total syntheses of natural products, [84c, 84d] after its regioselective alkylation onto *O*-silylated enolates was reported. [84b]



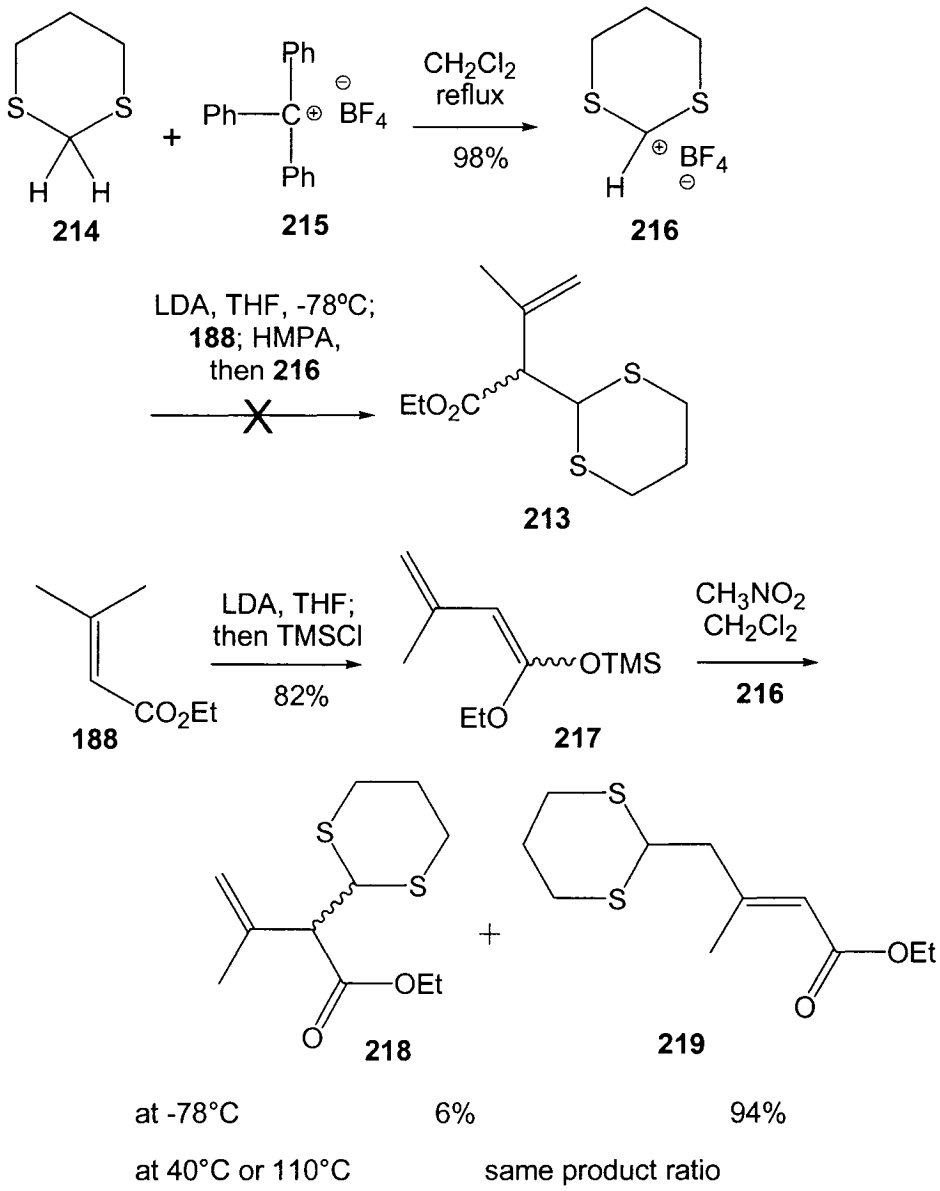
Scheme 4.6 Retrosynthetic analysis using 1,3-dithienium tetrafluoroborate

As already mentioned in the retrosynthetic analysis section, diene **186** might be obtained via an aldol reaction from dicarbonyl compound **187**. Retrosynthetic analysis of

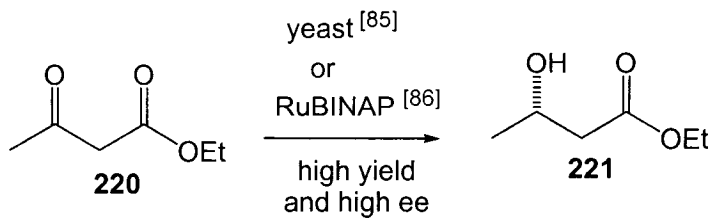
187 is shown in Scheme 4.6. Intermediate **187** could be prepared from the addition organometallic **211** to aldehyde **212**, which could be obtained by reduction of ester **213**.

An attempt was made to synthesize ester **213** using 1,3-dithienium tetrafluoroborate **216** (Scheme 4.7). Compound **216** was prepared from 1,3-dithiane (**211**) and trityl tetrafluoroborate (**212**) in 98% yield following Corey's procedure. [84a] However, the reaction between 1,3-dithienium tetrafluoroborate (**216**) and the enolate of **188** at –78 °C failed to give any the desired product **213**; instead an intractable mixture was obtained. Then attention turned to Paterson's work with **216**. In his original work, the ratio of α-alkylated product (**218**) to γ-alkylated product (**219**) was 6:94. [84b] It was hoped that a higher temperature might change the product ratio, with an increase in the proportion of the desired α-alkylated product (**218**). Unfortunately, experiments at 40 °C and 110 °C did not change the product ratio.

As it has been already mentioned in the retrosynthetic analysis (Scheme 3.1), an alternative for the construction of diene **186** would be to use **221** as the starting material *via* **190**, in which the stereochemistry of the hydroxy group might be used to control the stereochemistry in subsequent aldol reaction products. One more reason to choose **221** as the starting material is that this chiral compound can be easily obtained *via* the reduction of the keto-ester **220** by yeast (68%, 78% *ee*) [85] or by Noyori's catalyst, RuBINAP, in both higher yield and with higher *ee* (100%, 98% *ee*) [86] (Scheme 4.8).

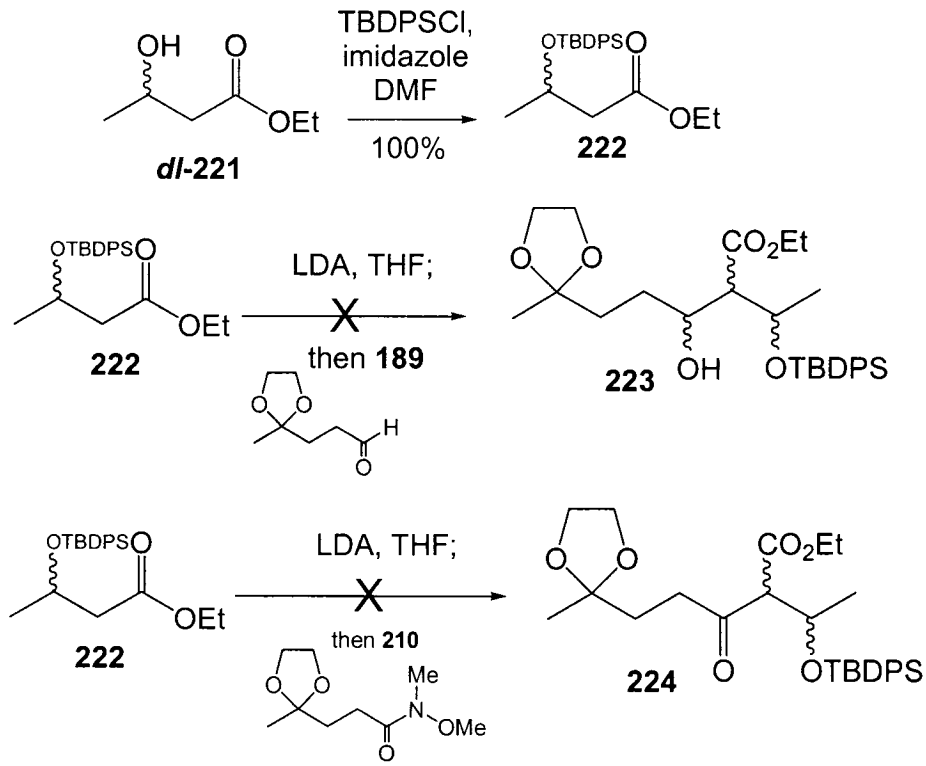


Scheme 4.7 Attempted preparation of **186** via 1,3-dithienium tetrafluoroborate



Scheme 4.8 Enantioselective reduction to make chiral ester **221**

As shown in Scheme 4.9, although TBDPS-protection of the hydroxy group was successful in quantitative yield to give ester **222**, attempted aldol reactions between **222** and either aldehyde **189** or Weinreb amide **210** failed to deliver the desired products, **223** or **224**. In both cases, ester **222** lost its silyl-protecting group. This result suggested that in this type aldol reaction silyl protection group might not be hardy enough to survive in the LDA solution.

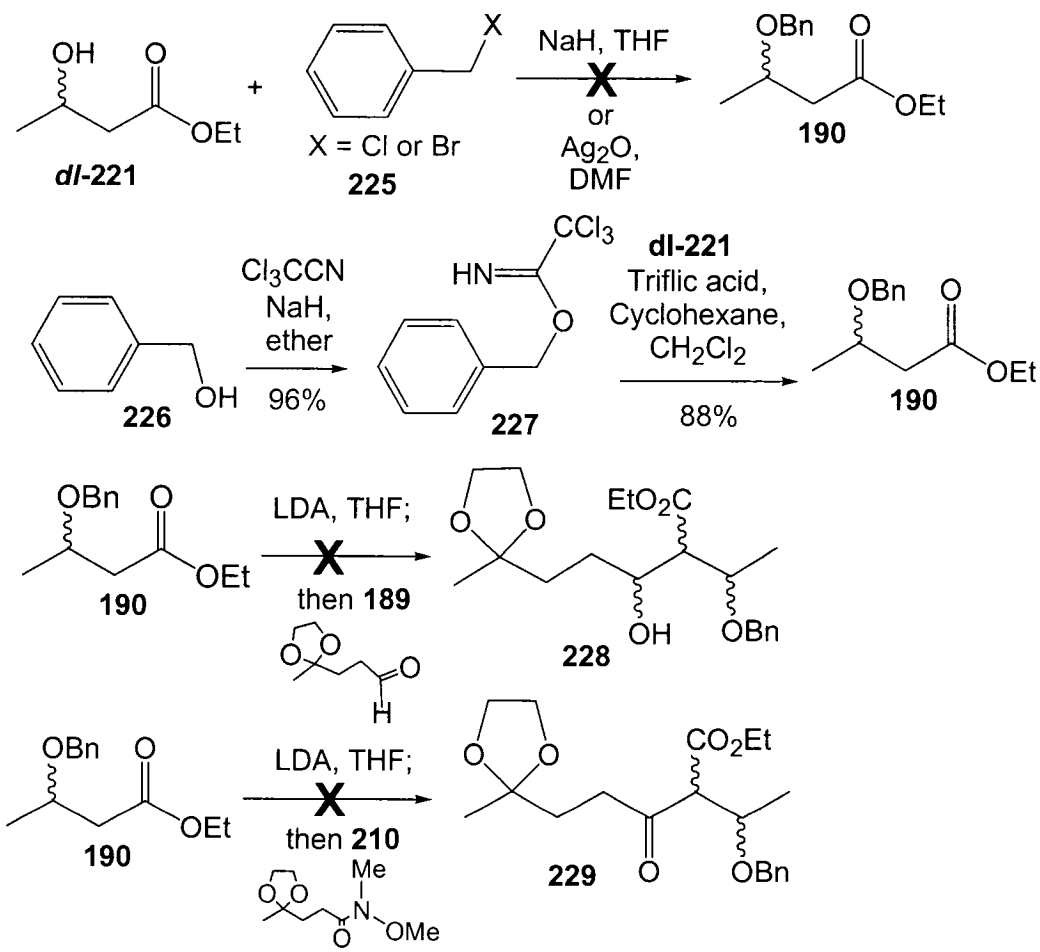


Scheme 4.9 Attempted aldol reactions using ester **222**

A further attempt was made to protect the hydroxy group in **221** as its benzyl ether **190** (Scheme 4.10). The normal sodium hydride or silver oxide conditions for protection the hydroxy group as a benzyl ether did not work here with either benzyl bromide or chloride. Keck [87] has succeeded in the benzyl ether protection of **221** using

the Iversen reagent, 2,2,2-trichloroacetimidate, [88a-88c] according to the general procedure of Widmer. [88c] Following Keck's procedure, we succeeded in the preparation of benzyl ether-protected ester **190** via 2,2,2-trichloroacetimidate **227** from benzyl alcohol **226**, but reactions between ester **190** and either aldehyde **189** or Weinreb amide **210** failed to give the desired products, alcohol **228** or ketone **229.**

Further attempts using aldol methodology were abandoned following these disappointing results. It was hoped that the existing compound **146**, from the previous lactone route (Scheme 2.11), might be used to generate diene **186**.



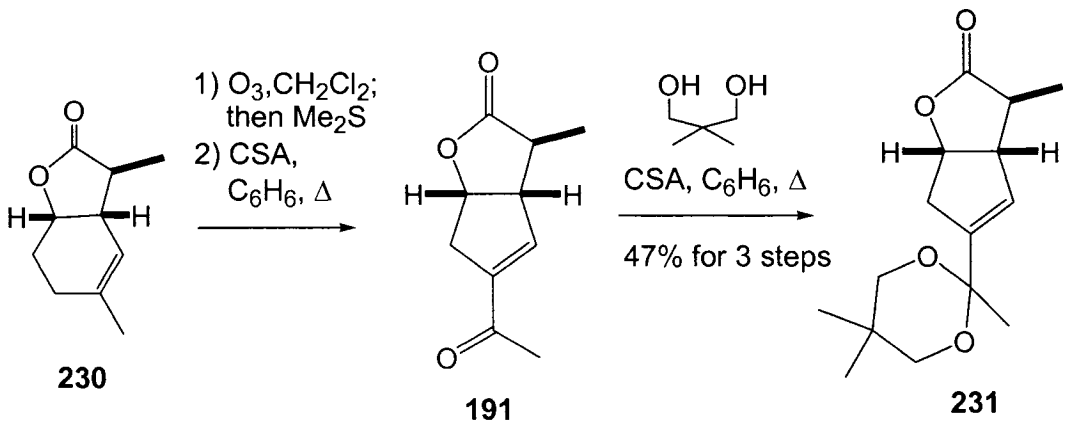
Scheme 4.10 Attempted aldol reactions using ester **190**

4.3 SYNTHESIS OF DIENE 186

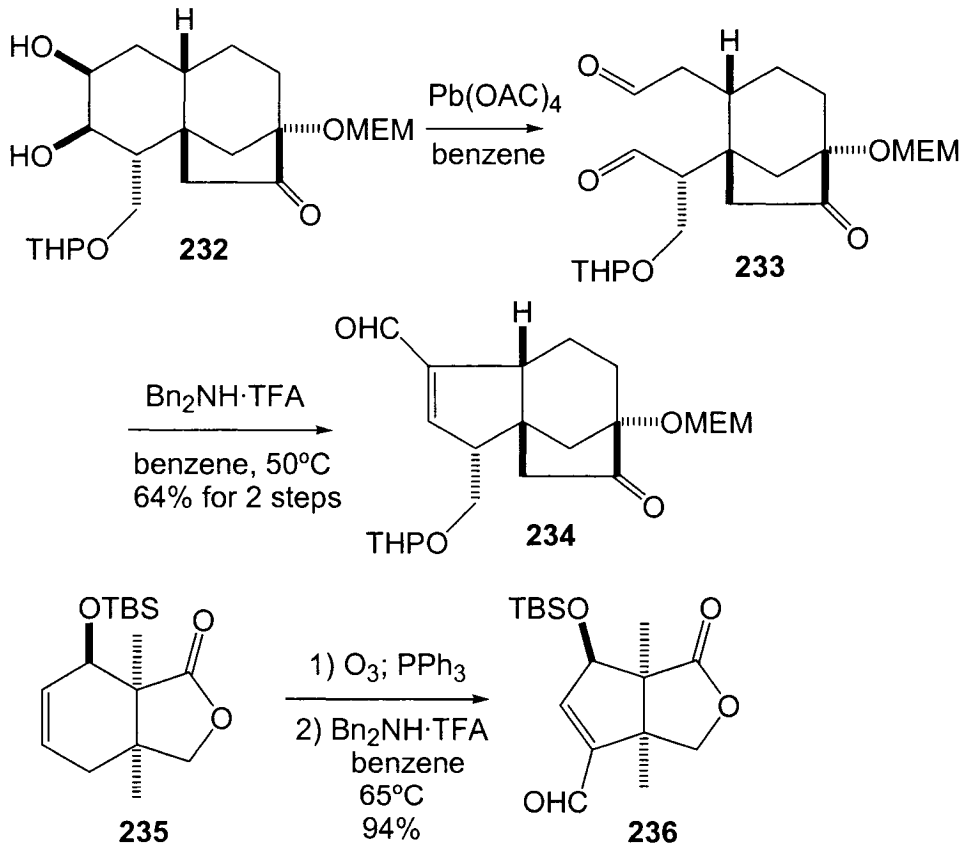
4.3.1 DEHYDRATION ROUTE TO DIENE 186

From the previous lactone route (Scheme 2.11), **146** had been prepared from commercially available 3-methylcyclohex-2-en-1-one in five steps. [42a] Stereoselective methylation of **146** to **230** had also been achieved in 89%. [42a] The present synthesis started with **230** (Scheme 4.11). Ozonolysis of **230** and reductive work-up gave a keto-aldehyde intermediate. In order to improve the yield of the subsequent cyclization, new procedures were tried to make the known compound **191**. [41b] First, this aldol condensation was tried under Corey's almost neutral, aprotic conditions [89a,b] (dibenzylammonium trifluoroacetate), which have been successfully applied to the preparation of compounds **234** [89b] and **236** [89c] (Scheme 4.12). Unfortunately, this reagent did not work in this instance.

Camphorsulfonic acid was tested as a catalyst for the aldol cyclization reaction. The use of this acid increased the yield and simplified the operation (Scheme 4.11). All the three steps could be carried out in one pot, i.e., after ozonolysis, the solvent and the excess dimethylsulfide were removed under vacuum, the residue was refluxed in benzene containing a catalytic amount of camphorsulfonic acid overnight, and finally 2,2-dimethyl-1,3-propanol was added to the mixture, which was refluxed overnight again to furnish compound **231** in 47% yield over three steps, after flash column chromatography.

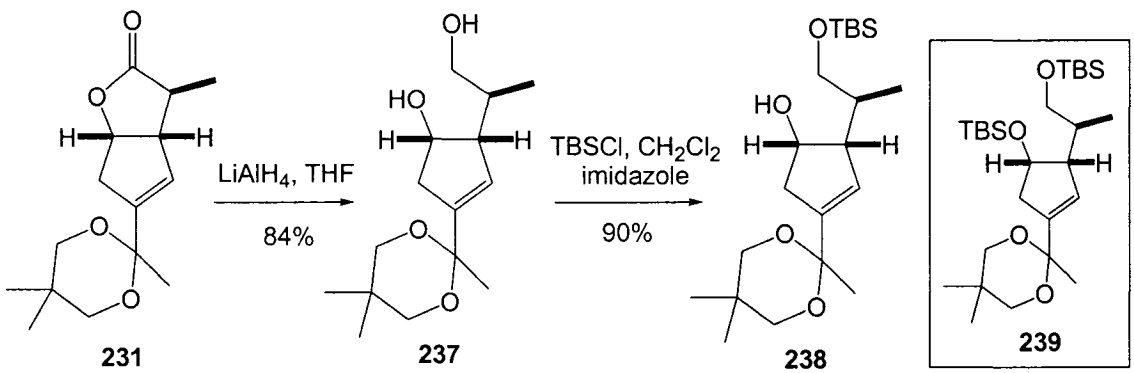


Scheme 4.11 Construction of the A ring in the kempane skeleton



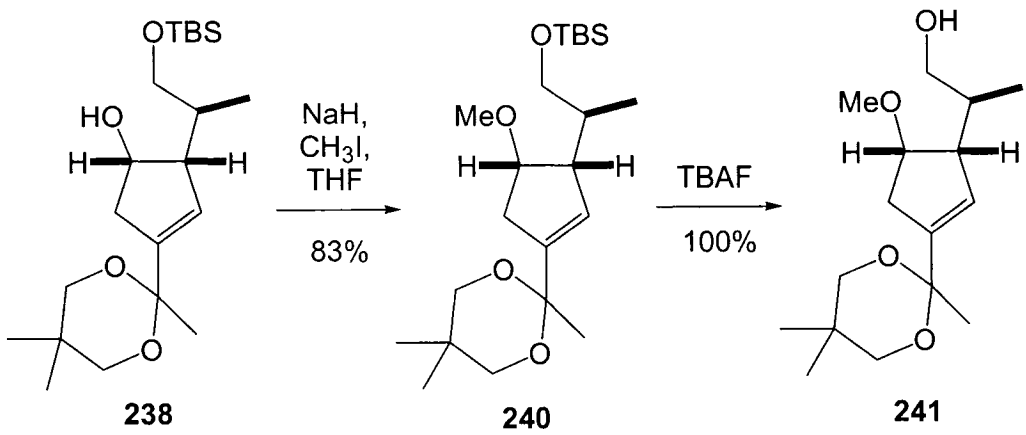
Scheme 4.12 Two examples of Corey's aldol conditions

The reduction of lactone **231** gave the diol **237**. The secondary alcohol was to be retained while the primary alcohol needed to be eliminated. Distinguishing the alcohols was accomplished in the following way. The protection of the primary alcohol as the *tert*-butyldimethylsilyl ether **238** was very selective (Scheme 4.13), along with very little disubstituted silyl ether **239,** which could be recycled.



Scheme 4.13 Selective protection of the primary alcohol

For the subsequent protection of the secondary alcohol, the extremely stable methyl ether was chosen since this protecting group had to be kept until the very end of the synthesis. Methylation on the secondary alcohol in **238** using sodium hydride and iodomethane furnished compound **240** in 83% yield (with 16% **238** being recovered). Then, deprotection of the silyl ether provided the free primary alcohol **241** in quantitative yield (Scheme 4.14).

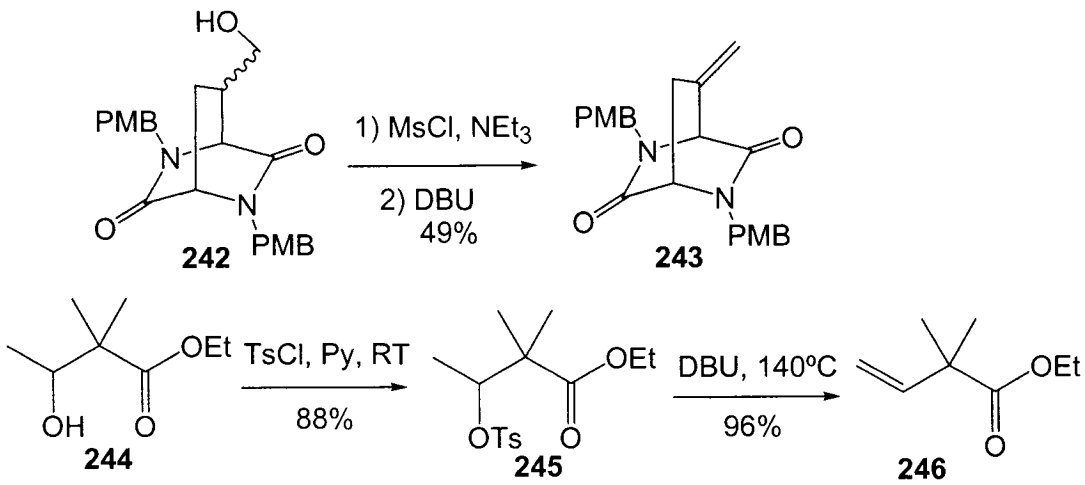


Scheme 4.14 Preparation of alcohol **241**

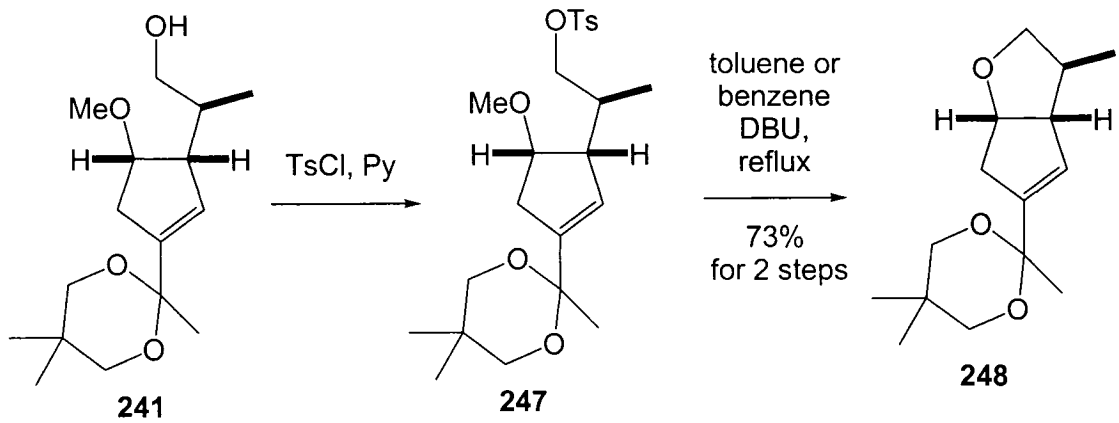
Now the dehydration of the primary alcohol in intermediate **241** was required to provide the terminal alkene **186**. The normal, harsh dehydration conditions [90] could not be employed due to the vulnerable functional groups in compound **241**. Tosylation of a primary alcohol and elimination using DBU in refluxing toluene had been reported to make olefin **243** in modest yield [91a] (Scheme 4.15). The same sequence on a secondary alcohol **244** had resulted a terminal alkene (**246**) in high yield [91b] (Scheme 4.15).

A literature procedure [91] was followed in an attempt to form the tosylate **247** from compound **241** (Scheme 4.16). Experiments using triethylamine or using a mixture of triethylamine and a catalytic amount of dimethylaminopyridine (DMAP) resulted in slow tosylation of compound **241**. However, pyridine was much superior s the base when it was used as the solvent in this tosylation reaction. When the tosylate **247** was subjected to DBU in refluxing toluene, the cyclized ether ring **248** was the only product without any expected dehydration alkene product **186**. The same result was obtained when the reaction was carried out in refluxing benzene. It is believed that the lone pair on the oxygen atom of the methoxy group attacked the primary carbon in a S_N2 fashion,

then the free tosylate anion picked up the methyl group on the resulting oxonium ion, giving the stable tetrahydrofuran ring **248**. Even milder reaction conditions for the dehydration needed to be considered due to this unforeseen, disappointing result.



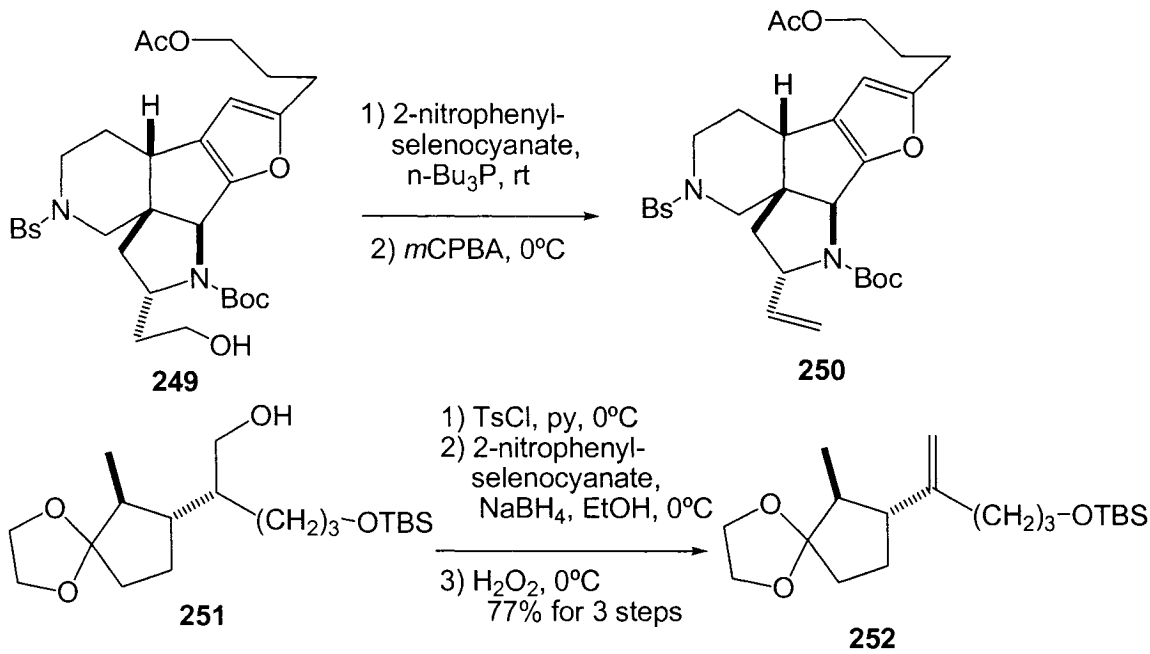
Scheme 4.15 Examples of terminal alkene formation via tosylates [91a, 91b]



Scheme 4.16 Unsuccessful dehydration route to diene **186** via tosylate **247**

Attention turned to a selenation and oxidation protocol. [92a] Nagata *et al.* applied this methodology to the preparation of terminal alkene **250** from primary alcohol **249**

under very mild reaction conditions in the total synthesis of nakadomarin A [92b] (Scheme 4.17). Unfortunately, a slow reaction and a low yield were encountered when 2-nitrophenylselenocyanate and tri-*n*-butylphosphine were used with the primary alcohol **241**. However, Mash reported a selenation and oxidation protocol from the tosylate of a primary alcohol to prepare a terminal alkene **252** in 77% yield over three steps in the synthesis of (-)-chokol A [92c] (Scheme 4.17).

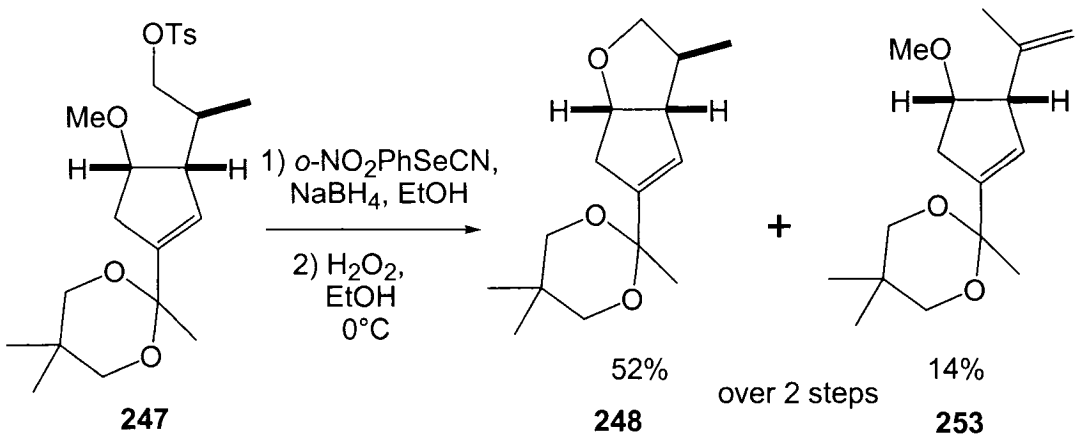


Scheme 4.17 Examples of terminal alkene formation via selenocyanates [92b, 92c]

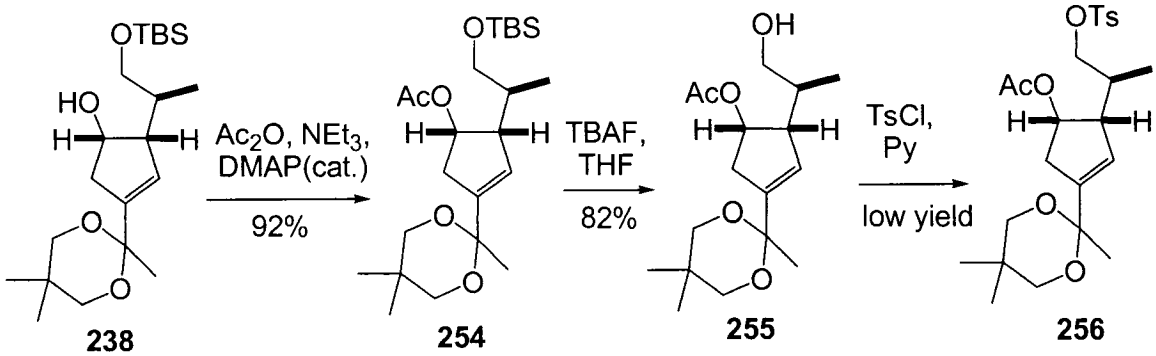
The selenation of tosylate **247** was successful using Mash's protocol. However, oxidation of the resulting selenide furnished tetrahydrofuran **248** as the major product once again, but the desired terminal alkene **253** was a minor product (Scheme 4.18).

Methyl is an electron-donating group, so theoretically it would enhance the nucleophilicity of the oxygen in this S_N2 process. An electron-withdrawing group (*e.g.* acetate) should restrain the nucleophilicity of the oxygen. Thus, an acetate **254** of the

secondary alcohol **241** was made (Scheme 4.19). Smooth deprotection of the TBS silyl ether gave the primary alcohol **255**, and this was subjected to the same tosylation conditions, but the yield was very low. Further attempts to produce a diene in this way were prevented by the low yield of the tosylation.



Scheme 4.18 Selenation and oxidation route to terminal alkene **253**

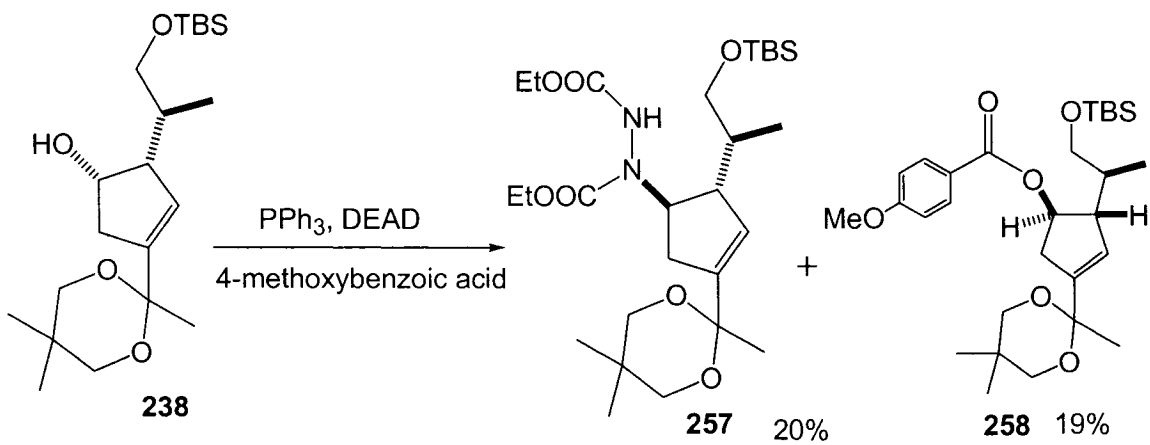


Scheme 4.19 Unsuccessful acetate protecting group route to terminal alkene

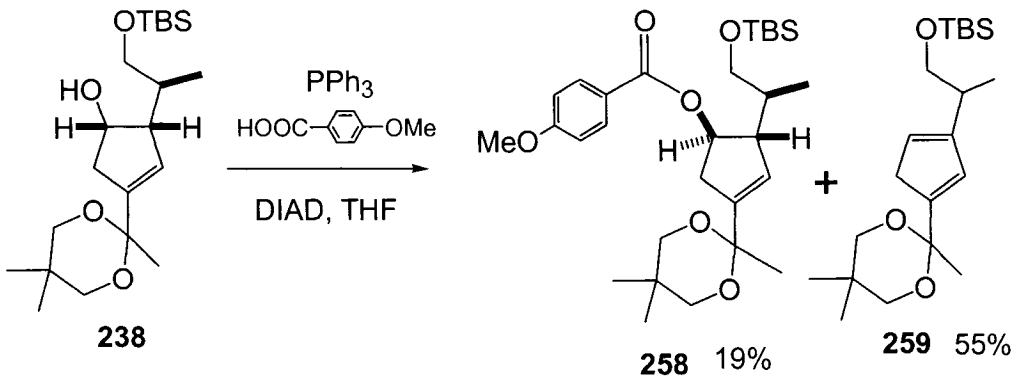
The above results suggested that the problem of "extra" cyclization might be overcome by inverting the stereochemistry of the methoxy-protecting group. In order to

invert the configuration, a Mitsunobu reaction [93] was required. When compound **238** was tested with excess DEAD as the reagent, compound **257** was isolated in 20% yield along with 19% of the expected product **258** (Scheme 4.20). When DIAD was used under the Mitsunobu conditions, it gave mainly the elimination product **259** and the expected product **258** in a minor amount (Scheme 4.21). The structure of diene **259** was confirmed by a Diels–Alder reaction between **259** and the dienophile **260** to give adduct **261** in 31% yield (Scheme 4.22). The observation of elimination under Mitsunobu conditions is not novel. An example of this type of reaction [94] is the formation of alkene **263** in high yield shown in Scheme 4.23. [94a]

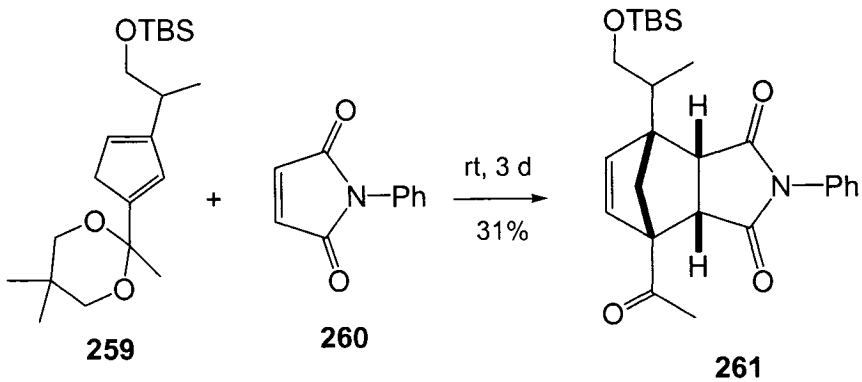
A different process to make the terminal alkene, other than dehydration, was required.



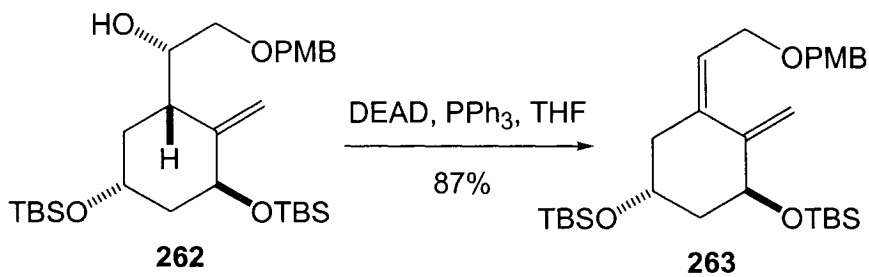
Scheme 4.20 Mitsunobu conditions giving the unexpected product **257**



Scheme 4.21 Mitsunobu conditions furnishing the product **258** in a minor amount



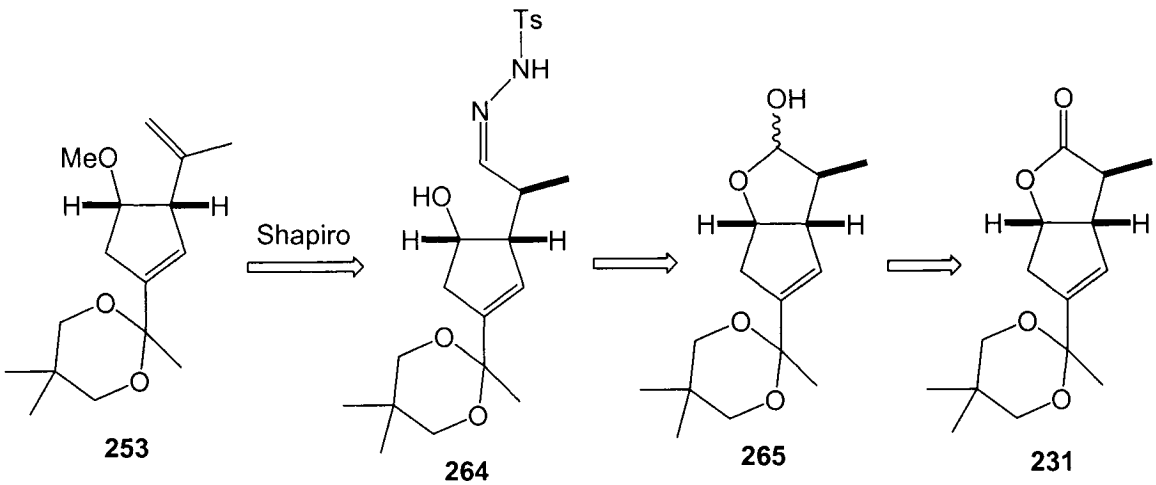
Scheme 4.22 Diels-Alder reaction between diene **259** and dienophile **260**



Scheme 4.23 Example of alkene formation under Mitsunobu conditions [94a]

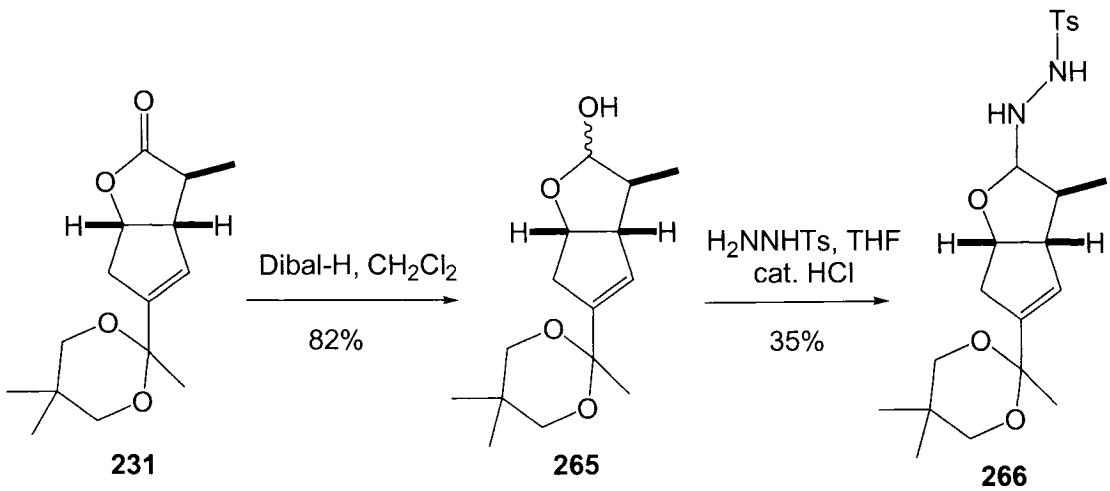
4.3.2 UNSUCCESSFUL SHAPIRO REACTION ROUTE TO DIENE 186

The Shapiro reaction provides a convenient method to convert ketones simply and in high yield into olefinic substances. [70a-c] This reaction was utilized in the previous lactone route [41] (Scheme 2.11, from **143** to **144**). However, few examples have been reported using aldehydes. [70d] Is it possible to utilize this type of reaction again to generate a terminal alkene? The retrosynthetic analysis is shown in Scheme 4.24. Terminal alkene **253** might be obtained via a Shapiro reaction from hydrazone **264** after selective protection of the secondary alcohol. Hydrazone **264** might be prepared under acidic conditions from lactol **265**, which could be produced by reduction of the known lactone **231**.



Scheme 4.24 Retrosynthetic analysis via a Shapiro reaction

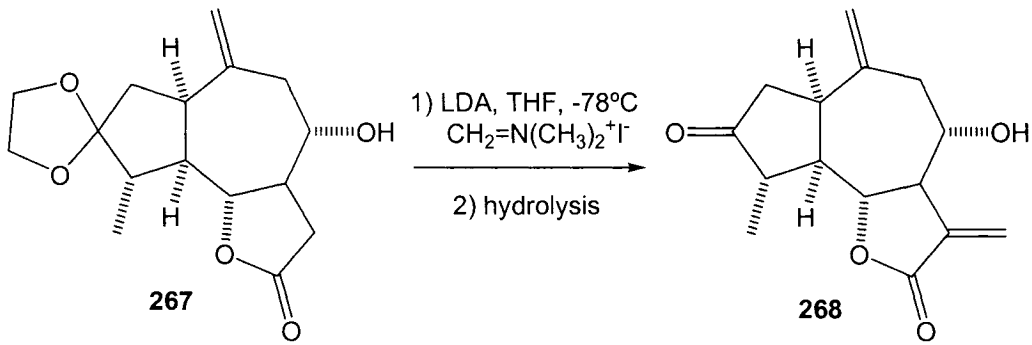
Reduction of **231** with Dibal-H successfully delivered lactol **265** (a mixture of diastereomers) in 82% yield (diastereomeric ratio 2:1), but the subsequent reaction of sulfonylhydrazine with lactol **265** did not give sulfonyl-hydrazone **264**. Instead, compound **266** was obtained in 35% yield (Scheme 4.25).



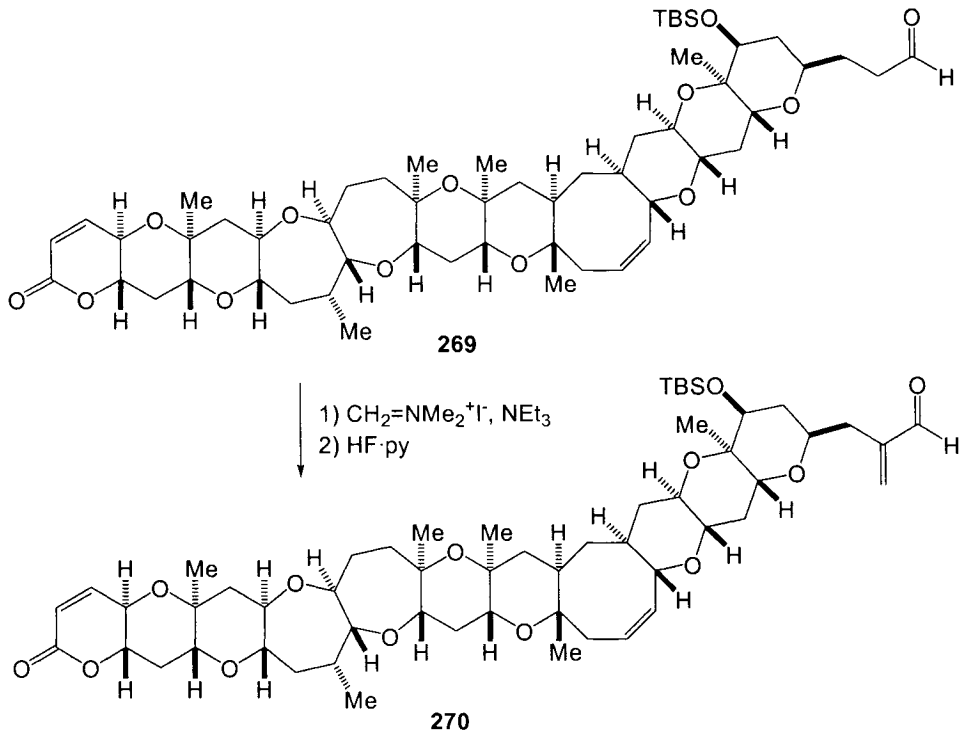
Scheme 4.25 Unsuccessful Shapiro reaction route

4.3.3 MANNICH REACTION ROUTE TO DIENE 186

To achieve the goal of making diene **186** (Scheme 3.1), a famous reagent came to mind, Eschenmoser's salt ($H_2C{=}NMe_2^+I^-$) [95] and its Mannich-type reaction to introduce the methylene group onto a lactone, [96] aldehyde [97] or ketone. [98] Schemes 4.26 and 4.27 show examples of Mannich reactions of Eschenmoser's salt onto a lactone **268** [96] and an aldehyde **270**, [97] respectively.

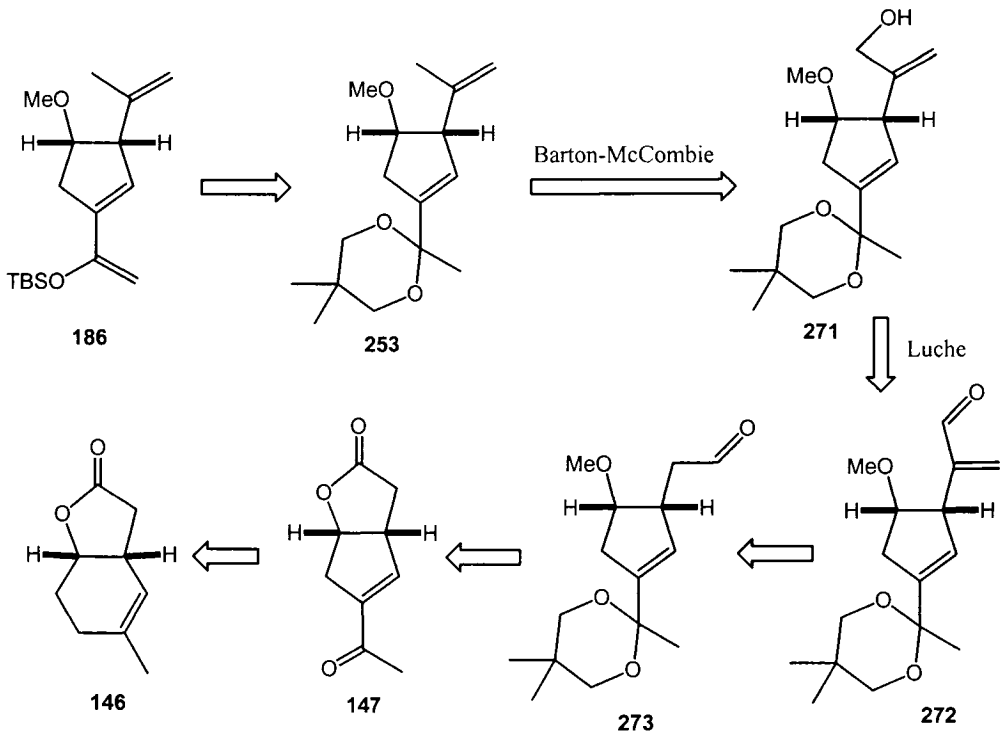


Scheme 4.26 Example of a Mannich reaction of Eschenmoser's salt with a lactone [96]



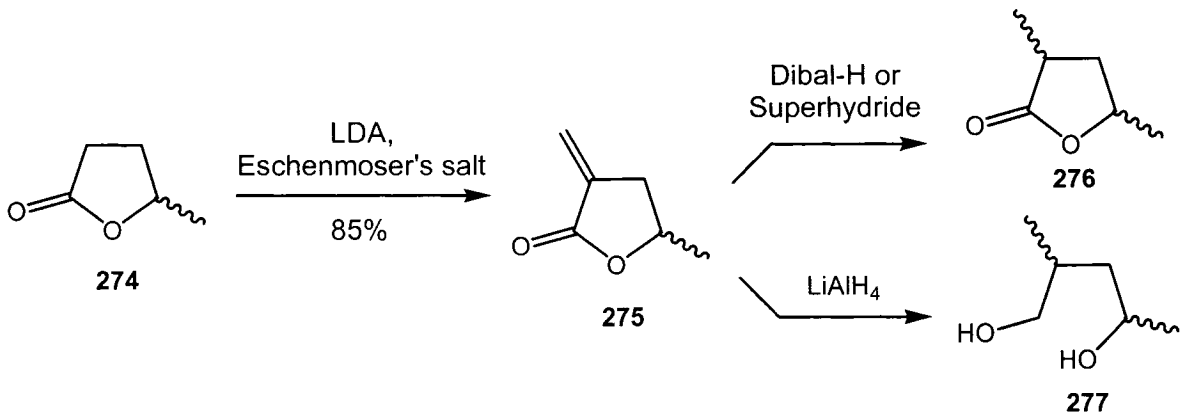
Scheme 4.27 Example of a Mannich reaction of Eschenmoser's salt onto an aldehyde [97]

The retrosynthetic analysis via a Mannich route is shown in Scheme 4.28. In order to obtain the desired alkene **186** from the Mannich product **272**, reduction of the aldehyde using Luche conditions was envisaged, to give alcohol **271**, followed by a Barton-McCombie deoxygenation, to provide **253**. Deprotection of the latent ketone and subsequent capture of the enolate with TBSOTf should give **186**. Initially, compound **273** should be available by oxidation of a primary alcohol, which could be prepared by reduction of the lactone ring of **147**, which had been prepared from the readily accessible lactone **146**.



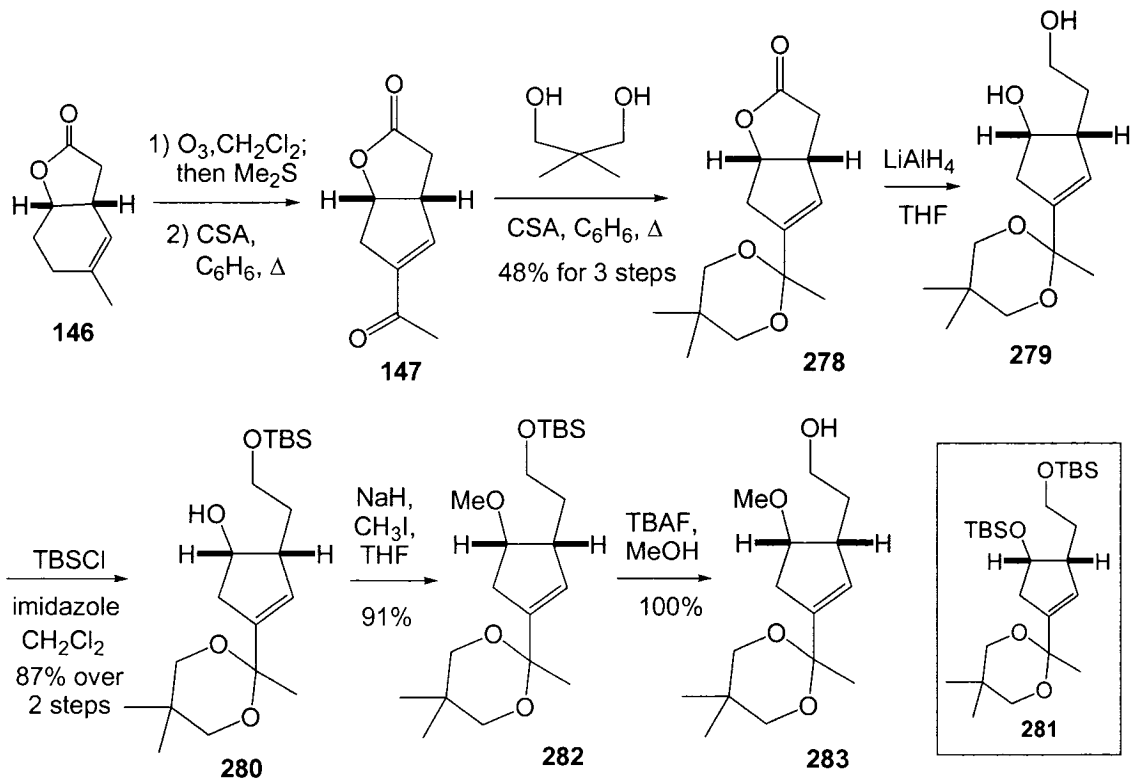
Scheme 4.28 Retrosynthetic analysis of diene **186** via a Mannich reaction

As usual, a model was studied first (Scheme 4.29). LDA was used to form the enolate of the simple lactone **274**, and then it was reacted with Eschenmoser's salt to deliver the terminal alkene **275** in 83% yield. At the beginning, it was hoped that the lactone ring could be chemoselectively reduced without touching the terminal alkene. Dibal-H and Superhydride reduced only the terminal double bond to give the same product **276**, without reducing the lactone, whereas $LiAlH_4$ reduced both the double bond and lactone to produce diol **277**. It was quite clear that a direct methodology would not lead to the intermediate bearing an aldehyde and a free secondary alcohol, so protection and deprotection were required to make compound **273** (Scheme 4.28).



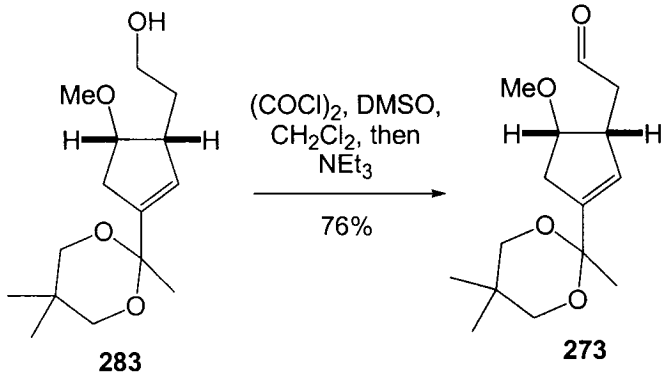
Scheme 4.29 Model study for the Mannich route

The synthetic route to intermediate **283** is shown in Scheme 4.30. Starting from the known compound **146**, ozonolysis and CSA-catalyzed aldol cyclization delivered the expected ketone **147**, which was protected as an acetal with 2,2-dimethyl-1,3-propanediol to give **278** in 48% over three steps. Reduction of **278** with lithium aluminum hydride furnished the diol **279**, and selective protection of the primary alcohol in **279** as the TBS ether **280** was achieved in 87% yield over two steps, although 2% of the disubstituted TBS ether **281** was also produced and has been recycled. Methylation of the secondary alcohol in **280** gave **282** in 91% yield, and the removal of the silyl group with TBAF led to the free primary alcohol **283** in quantitative yield.

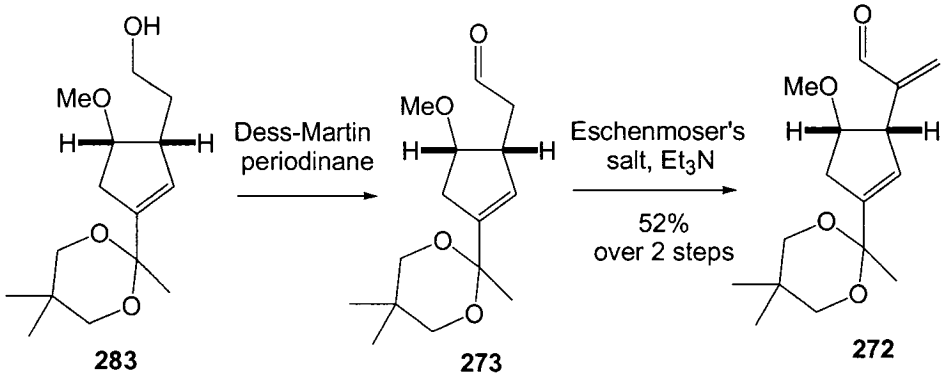


Scheme 4.30 Construction of alcohol **283** for diene **186**

Oxidation of the primary alcohol to aldehyde **273** was the next step. Swern oxidation [53] of alcohol **283** was attempted first (Scheme 4.31). Although the yield of the aldehyde **273** was acceptable, this reaction was not as clean as a Dess-Martin oxidation (Scheme 4.32). Mannich reaction of Eschenmoser's salt on aldehyde **273** worked smoothly to deliver the conjugated aldehyde **272** in 52% yield over two steps. It is worth mentioning that both aldehydes **272** and **273** were stable enough to be purified by column chromatography, and they could be stored in the refrigerator for a week without any observable decomposition.

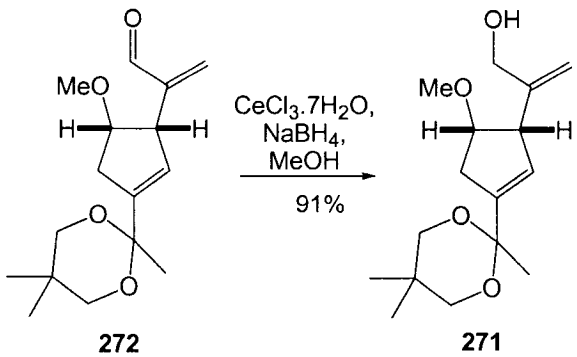


Scheme 4.31 Swern oxidation on alcohol **283**



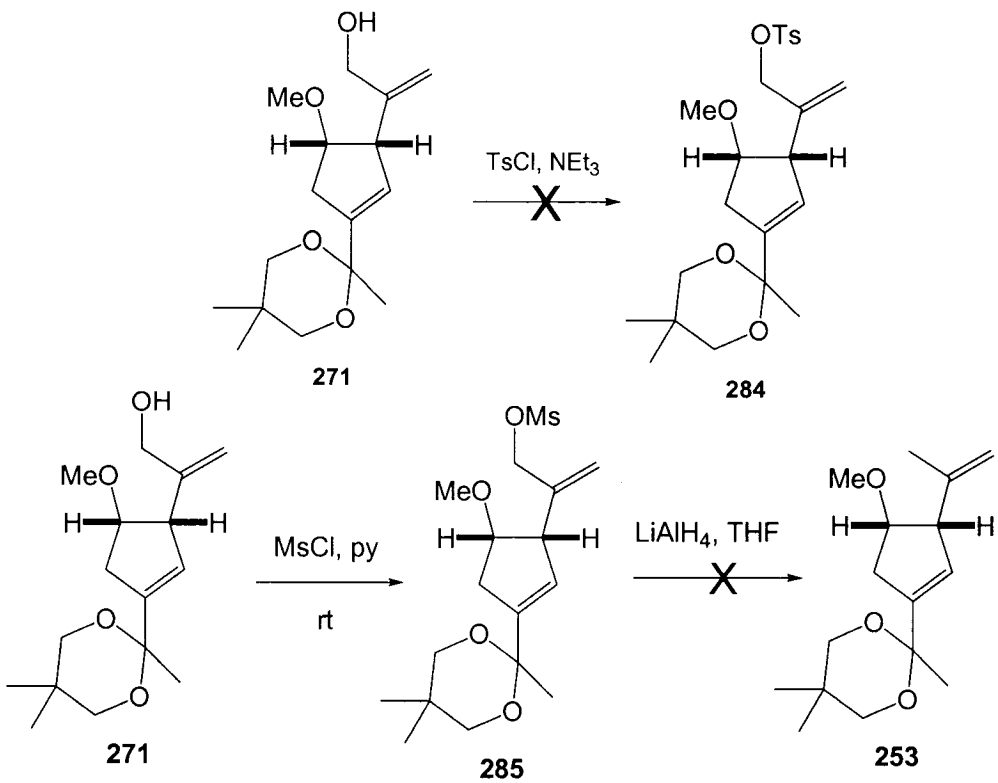
Scheme 4.32 Dess-Martin oxidation and Mannich reaction

In order to obtain terminal alkene **253**, a 1,2-reduction was first required on the conjugated aldehyde **272**. As expected, the Luche reduction worked well to give primary alcohol **271** in 91% yield (Scheme 4.33).



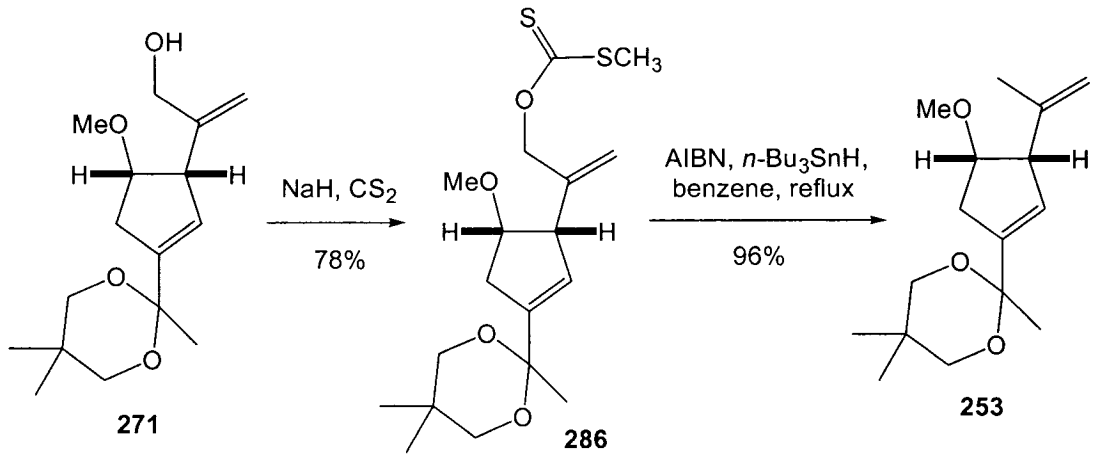
Scheme 4.33 Luche reduction of conjugated aldehyde **272**

With primary alcohol **271** in hand, deoxygenation by hydride reduction was tested first (Scheme 4.34). This methodology might be better than Barton-McCombie deoxygenation that uses toxic tributyltin hydride as a reagent. Treatment of alcohol **271** with tosyl chloride and triethyl amine failed to give tosylate **284**, but mesylate **285** was obtained by the reaction of **271** with mesyl chloride in pyridine. Without separation, the crude **285** was subjected to reduction with lithium aluminum hydride in THF, but none of the expected terminal alkene **253** was obtained. The Barton-McCombie deoxygenation, which was tried at the same time on alcohol **271**, seemed promising, so no more attempts were made to reduce sulfonic esters with hydride.



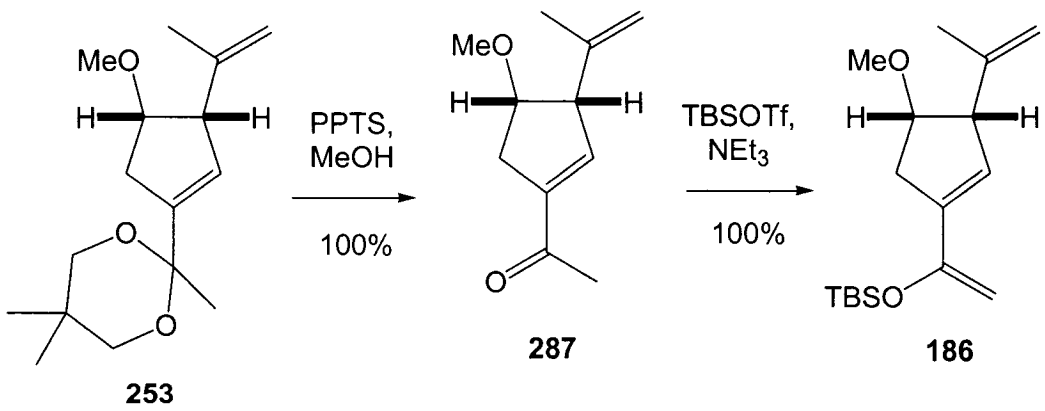
Scheme 4.34 Deoxygenation via hydride reduction

The two-step Barton-McCombie deoxygenation reaction on alcohol **271** gave the terminal alkene **253** cleanly and in good yield (Scheme 4.35).



Scheme 4.35 Barton-McCombie deoxygenation of alcohol **271**

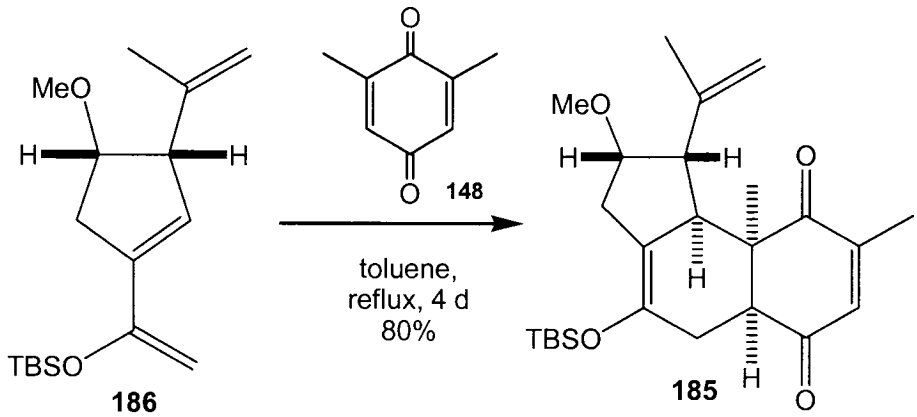
The next two steps to the key diene **186** were straightforward (Scheme 4.36). Removal of the acetal under very mild conditions, with pyridinium *para*-toluenesulfonate in methanol at room temperature, released the conjugated ketone **287** in quantitative yield. Then, **287** was treated with *tert*-butyldimethylsilyl triflate and excess triethyl amine in dichloromethane at 0 °C to generate diene **186**, also in quantitative yield.



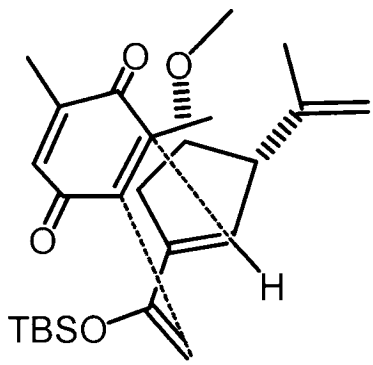
Scheme 4.36 Completion of the construction of key diene **186**

4.4 DIELS–ALDER REACTION AND RCM

Now one of the key reactions in this route, the Diels–Alder reaction, was ready to be tested. Following the reaction conditions previously employed in our group, [41,42] a solution of diene **186** and 2,6-dimethyl-*para*-benzoquinone **148** in dry toluene was heated at reflux for four days. This provided the key compound **185**, possessing the A, B, and C rings of the kempane skeleton (Scheme 4.37). The gross structure of **185** was confirmed by HMBC, while evidence for the stereochemistry in **185** came from NOE measurements and from subsequent synthetic work. It is worth mentioning that this Diels–Alder reaction gave only one of the eight possible diastereomers, thus with very high regioselectivity, *endo* stereoselectivity and facial selectivity (Scheme 4.38). It is also interesting to note that a model reaction between a similar diene, Danishefsky's diene, [99] and 2,6-dimethyl-*para*-benzoquinone **148** did not work under these conditions. Even though the reactants and dry toluene were maintained in a sealed tube at 110 °C overnight, the starting materials were recovered unchanged.

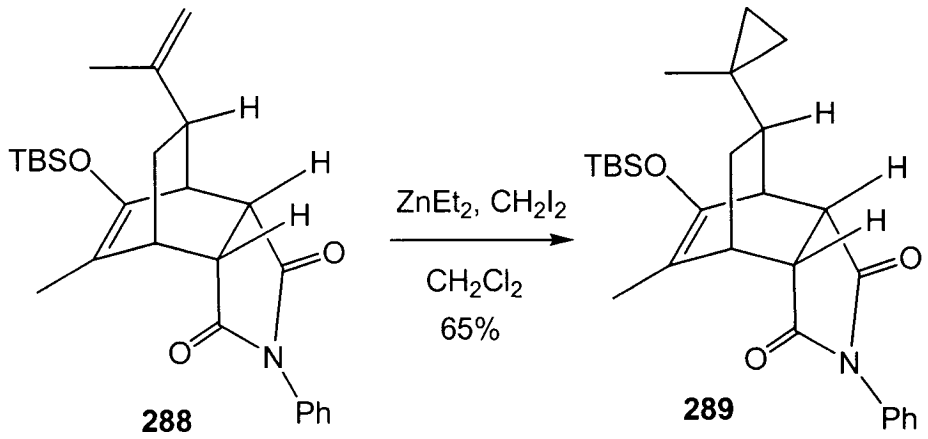


Scheme 4.37 Diels–Alder reaction to deliver key compound **185**



Scheme 4.38 Regio-, endo- and facial selectivities in the Diels–Alder reaction

At this point a decision had to be made regarding the installation of the methyl group at C-4 (Figure 1.4, compound **33**). Compound **185** had three very different double bonds, and it was decided to test the selectivity of the Simmons–Smith reaction in a similar case. The idea was that if the most electron rich, but also most sterically hindered, double bond reacted preferentially, then it would have been the opportune moment to introduce the remaining carbon via cyclopropanation and ring opening, as suggested in compound **183** and **184** in Scheme 3.1. A model compound **288** was available from another study. [100] It was tested under the common Simmons–Smith conditions (2.5 equivalents of diethylzinc and 3.0 equivalents of diiodomethane), but only compound **289**, with cyclopropanation of the less sterically hindered alkene was obtained in 65% yield, and 35% of the starting material **288** was recovered. The Simmons–Smith reaction on compound **185** was still carried out on very small scale, but this resulted in none of expected product **184** being observed.

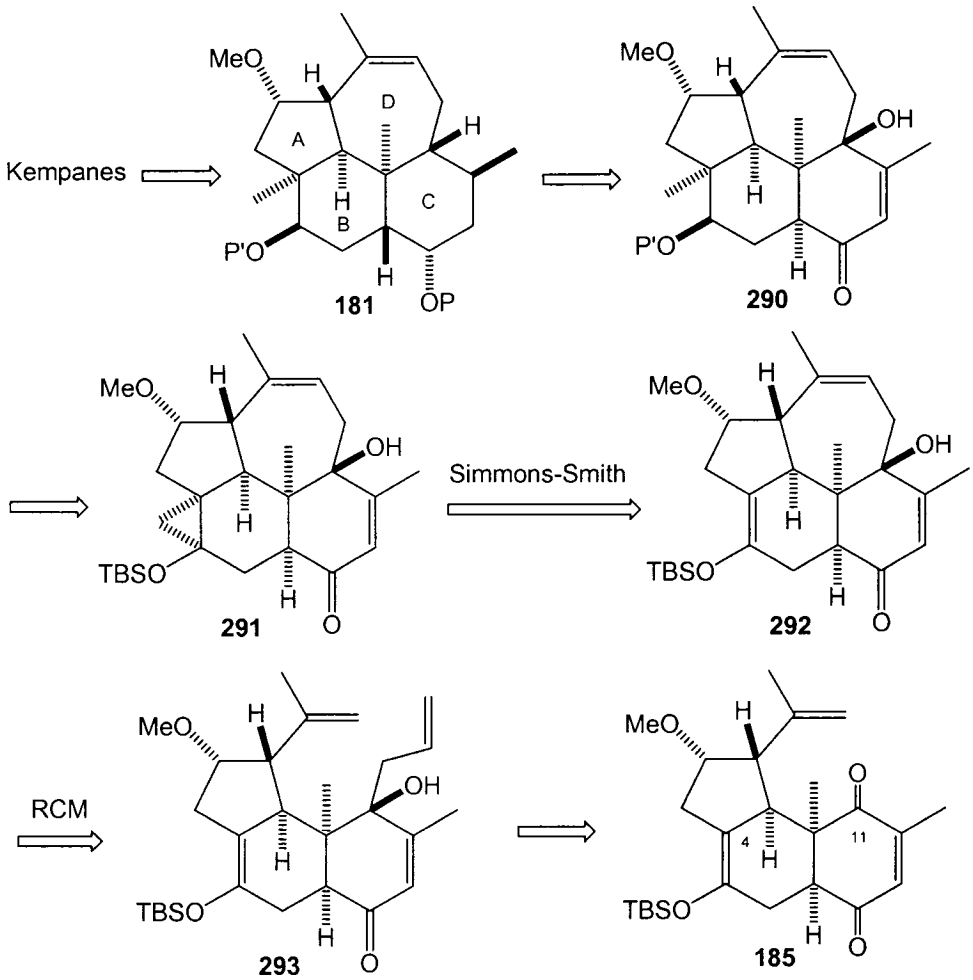


Scheme 4.39 Selectivity test for the Simmons-Smith reaction

The sequence of synthetic operations needed to be changed due to the results of the Simmons–Smith reactions. (See Scheme 4.40 for the revised retrosynthetic analysis.) Compound **292** would be the next key compound. It was anticipated that in the absence of a terminal alkene, the Simmons–Smith reaction would have the desired selectivity, i.e., the most electron-rich double bond, the silyl enol ether would react faster than the other two double bonds. The shape of molecule **292** would be expected to control the facial selectivity to make the Simmons–Smith reaction take place *syn* to the angular methyl.

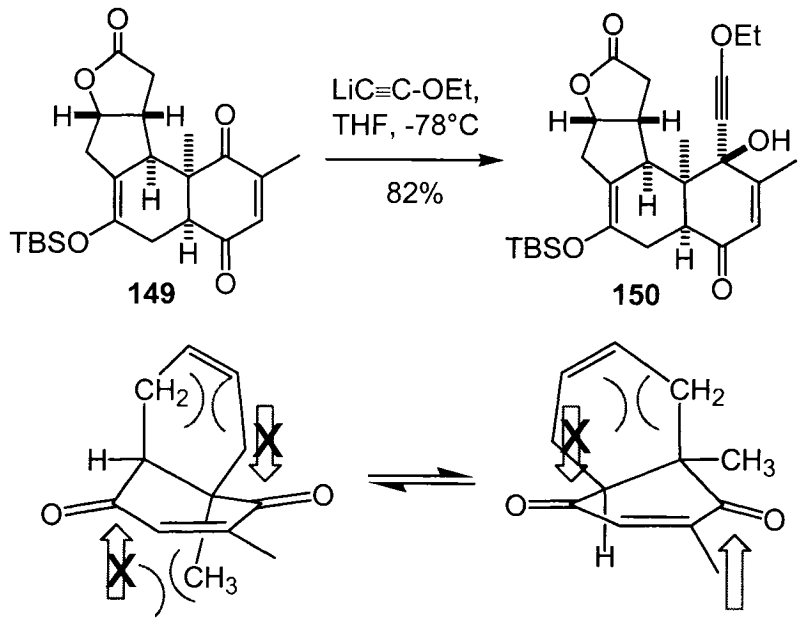
In order to obtain compound **292**, addition of an allyl group was required at C-11 (following the numbering of kempane) of **185**. The question was whether this compound (**293**) could be formed directly from **185**. The regioselectivity and facial selectivity of the addition of lithium acetylide on unsymmetrical cyclohexendiones have been studied in our group [41,42] (An example is shown in Scheme 4.41.) The previous results (high regioselectivity and facial selectivity) were explained by an axial attack on the enedione [101, 41b] (Scheme 4.41, bottom). Compared to acetylide anion, the allyl anion would be larger, and larger nucleophiles tend to add equatorially. Would the addition of allyl anion

to an enedione be axial or equatorial? (The details of a model study are presented on Part II in the thesis.)



Scheme 4.40 Revised retrosynthetic analysis of the kempanes from **185**

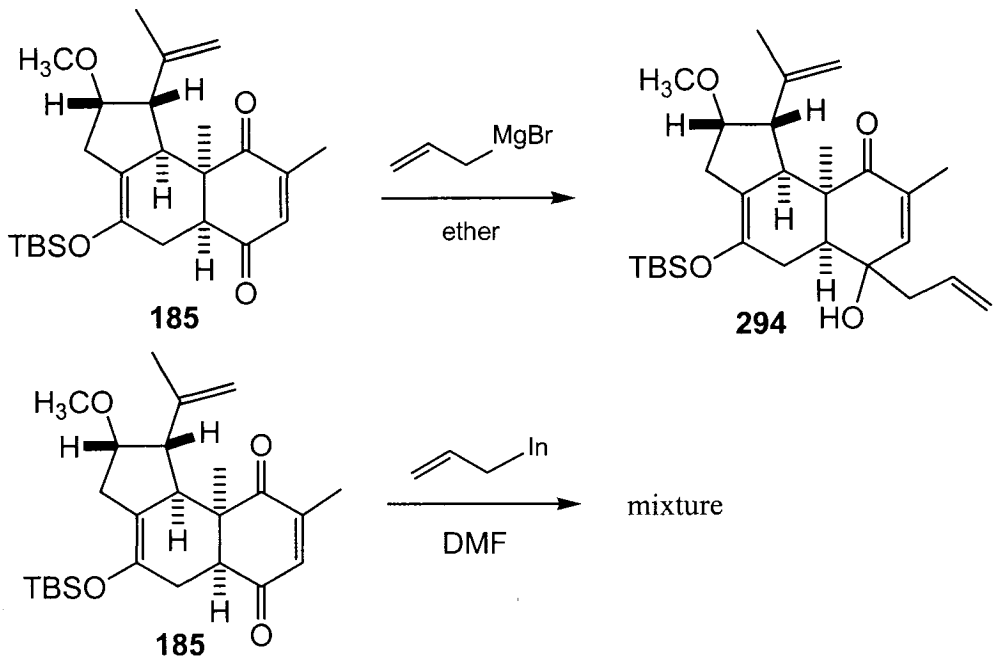
Model studies showed that allyl Grignard reagent attacked the enones mainly from the axial direction, giving a 5:1 ratio of axial-attack-product to equatorial-attack-product in a simple case. Allylindium reacted with no selectivity, i.e., with a 1:1 ratio of axial- to equatorial-attack-products. So the allyl Grignard reagent was tried first with compound **185** in ether, but the unwanted regioisomer **294** was the only isolated product



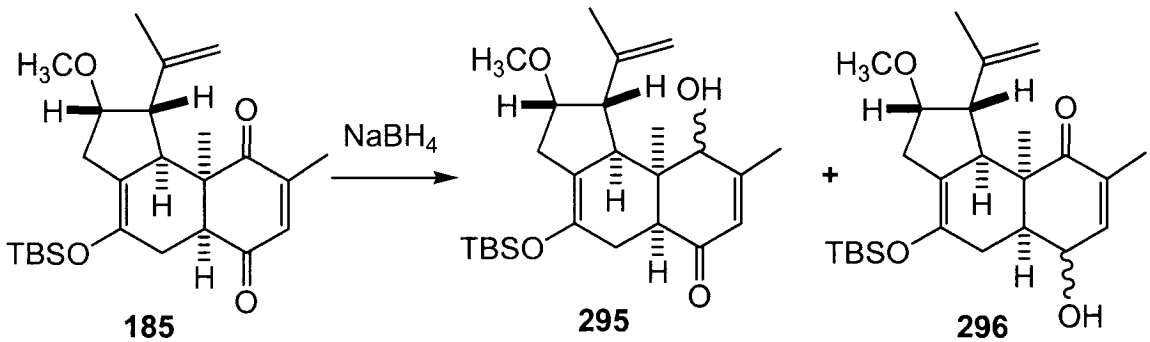
Scheme 4.41 An example of a facial and regioselective addition of acetylide to an enedione and a rationale for the selectivity [41]

(Scheme 4.42). The reason for this result was likely that the allyl anion was too large to attack the more steric-hindered "top" carbonyl, and so it reacted with the "bottom" carbonyl instead. Allylindium in DMF reacting with **185** produced a mixture of allylation products.

It was clear that the two carbonyls needed to be differentiated before allylation. Allylindium would tolerate a hydroxyl group on the substrate, [102] so the allyl group might be delivered to the "top" carbonyl, if the "bottom" carbonyl could be reduced regioselectively. Sodium borohydride reduction of compound **185** occurred with no regioselectivity at all (Scheme 4.43).



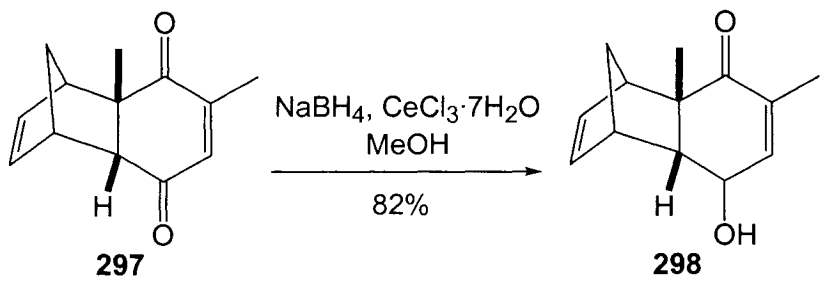
Scheme 4.42 Allylation of compound **185**



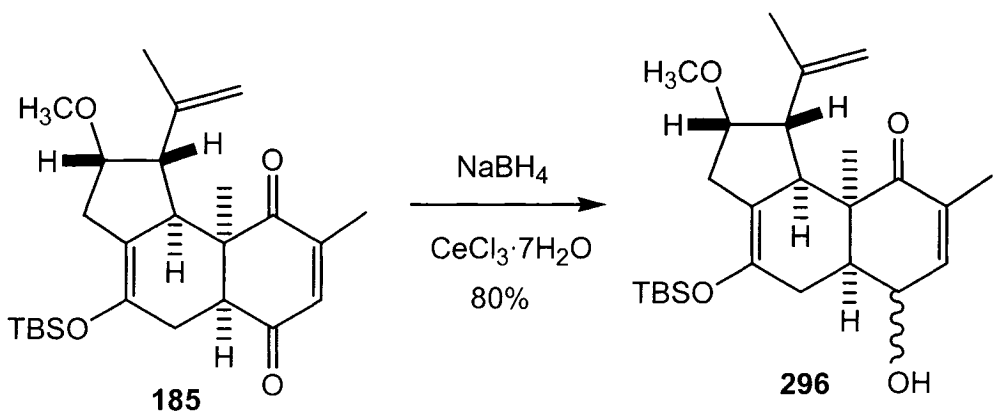
Scheme 4.43 Reduction of **185** with sodium borohydride

Model compound **297** [103] was reduced with sodium borohydride in the presence of cerium chloride in methanol at 0 °C to generate **298** as the only product (Scheme 4.44).

Reduction of **185** under the same Luche conditions, yielded the desired product **295**, but as a mixture of diastereomers (Scheme 4.45). These two diastereomers were not separated, and the mixture was subjected to the next step directly.

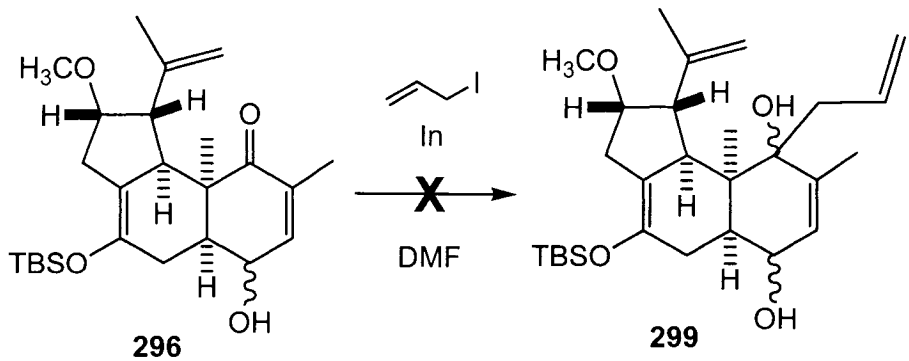


Scheme 4.44 Luche reduction on a model compound **297**



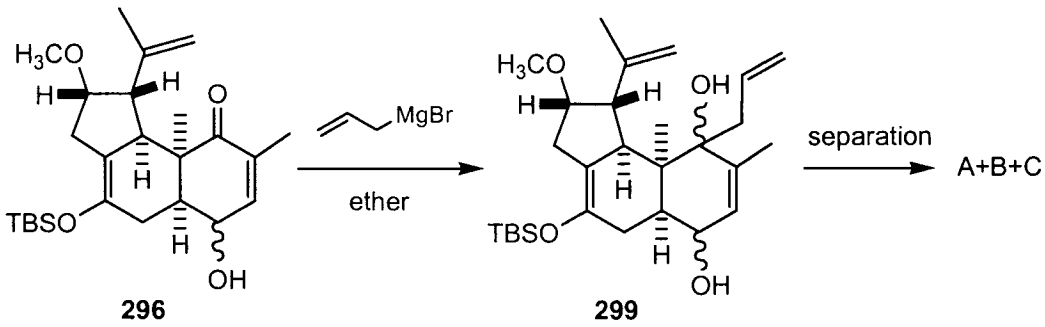
Scheme 4.45 Luche reduction of compound **185**

It was hoped that allylindium, which tolerates hydroxyl groups in substrates, could be applied to make compound **299**. Unfortunately, only starting material was recovered even when an excess of allyl indium reagent was used (Scheme 4.46).



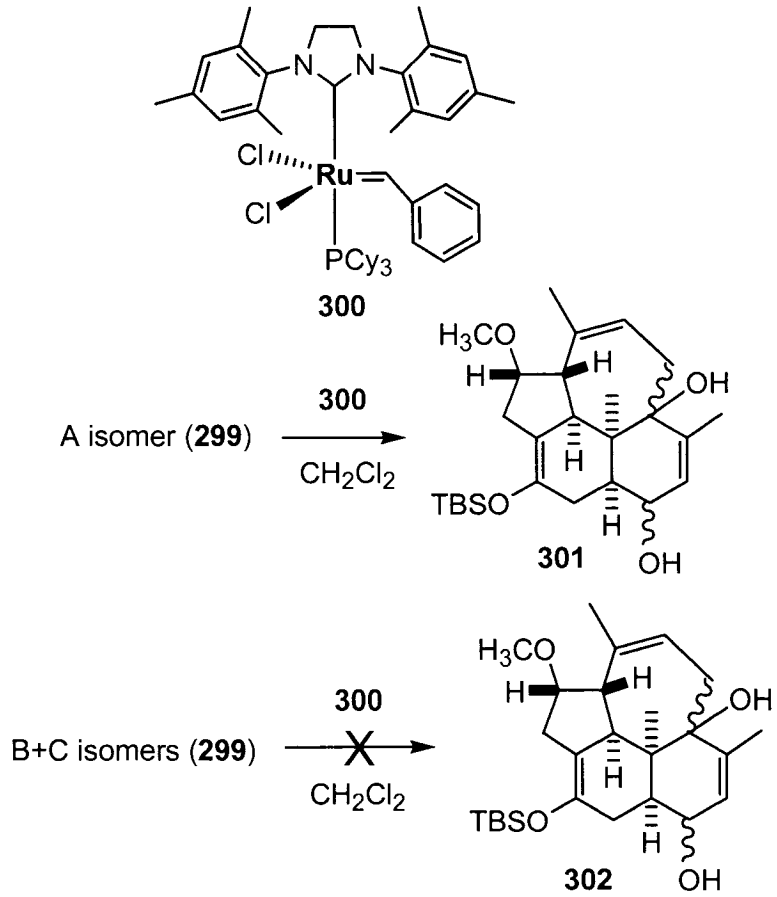
Scheme 4.46 Attempted reaction of allyl indium with compound **296**

An excess of allyl magnesium bromide was successful in reacting with compound **296** in ether to generate compound **299** without any 1,4-addition products being observed (Scheme 4.47). Two diastereomers of **296** were used, so four diastereomers of product should have been present, theoretically. However, only three diastereomers of **299** were obtained after separation by preparative TLC.



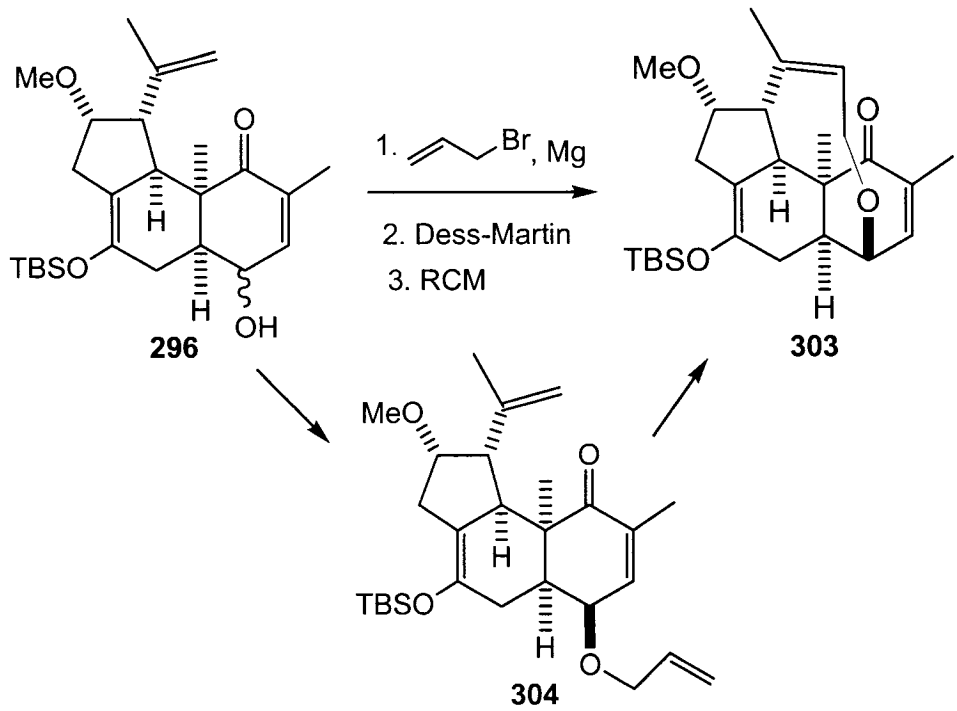
Scheme 4.47 Reaction of allyl Grignard reagent with compound **296**

Diastereomer A of **299** was tried first in the RCM reaction. Diastereomer A, in the presence of Grubbs' second-generation catalyst (**300**), gave a product **301**, which was strongly supported by crude NMR, which shows a new doublet at 5.51 ppm and paeks at 5.77 ppm, 5.00 ppm, 4.91 ppm in the starting material disappeared. (Scheme 4.48). However, when a mixture of diastereomers B and C was subjected to the same RCM conditions, no product **302** was observed. It was not known which isomer underwent the RCM reaction and which ones did not and why neither B nor C is reactive. In order to solve this problem, the structure of compound **299** needed to be simplified. One way to simplify its structure was to oxidize the secondary hydroxyl group to a ketone, thereby reducing the number of possible diastereomers from four to two.



Scheme 4.48 Grubbs' catalyst and the RCM reaction of the diastereomers of **299**

Allyl Grignard reagent reacted with compound **296** in ether, then, without any separation, the crude product was oxidized with Dess-Martin periodinane in CH_2Cl_2. The resulting product was subjected to the RCM conditions using catalyst **300** (Scheme 4.49). The surprising result was compound **303**, which was fully characterized by NMR. This result was rationalized in the following way. Allyl Grignard reacted initially with **296** as a base, deprotonating the secondary alcohol. The resulting anion attacked the excess allyl bromide that was in the reaction mixture to produce allyl ether **304**, and the RCM reaction between the two terminal alkenes in **304** delivered **303** as the major product.



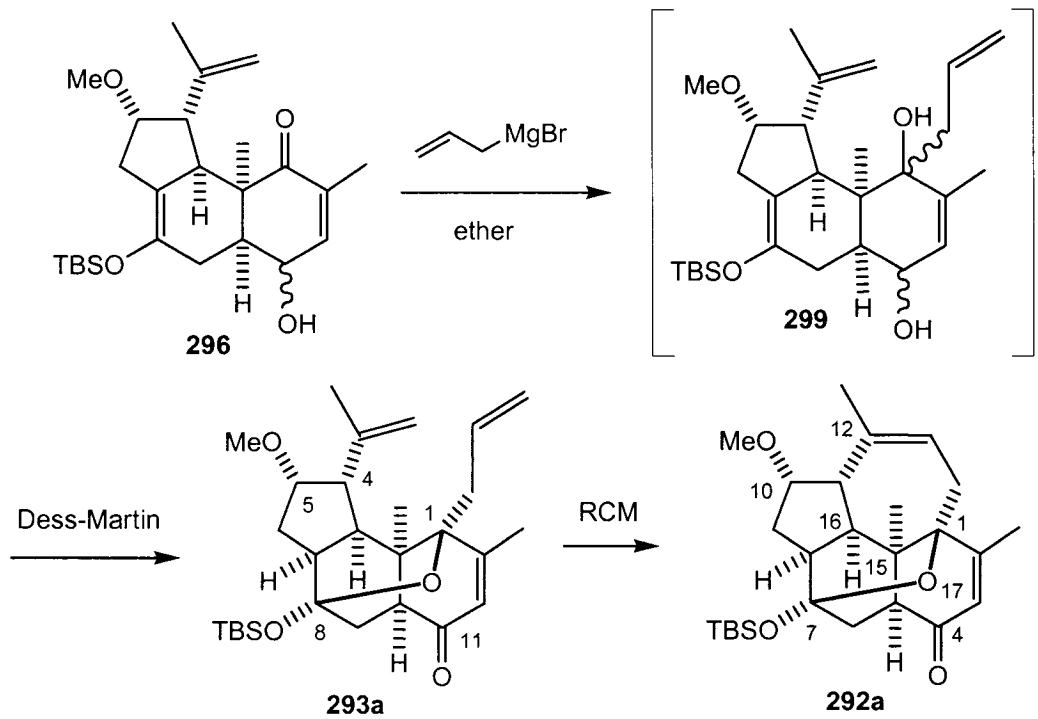
Scheme 4.49 The RCM reaction that gave **303**

In order to solve this problem, an excess of magnesium was used in the next experiment, and this delivered compound **299** successfully. The resulting crude product was subjected, without separation, to oxidation by Dess-Martin periodinane, but this generated compound **293a** instead the expected compound **293**. The ^{1}H NMR spectrum included one "extra" C–H signal, which the COSY spectrum was found coupled with the signals for the hydrogens at C3 and C9b. The ^{13}C NMR spectrum contained signals for only two olefinic carbons, but it included a signal for an "extra" sp^3-carbon and a signal at δ 99.4 that pointed to an acetal. After addition of the allyl group, the new tertiary alcohol at C9 had closed onto the double bond of the silyl enol ether to form **293a**. Transannular hemiacetal formation involving a tertiary alcohol at C9 had been seen previously in kempane chemistry.[41,42] The formation of the acetal was fortuitous proof of

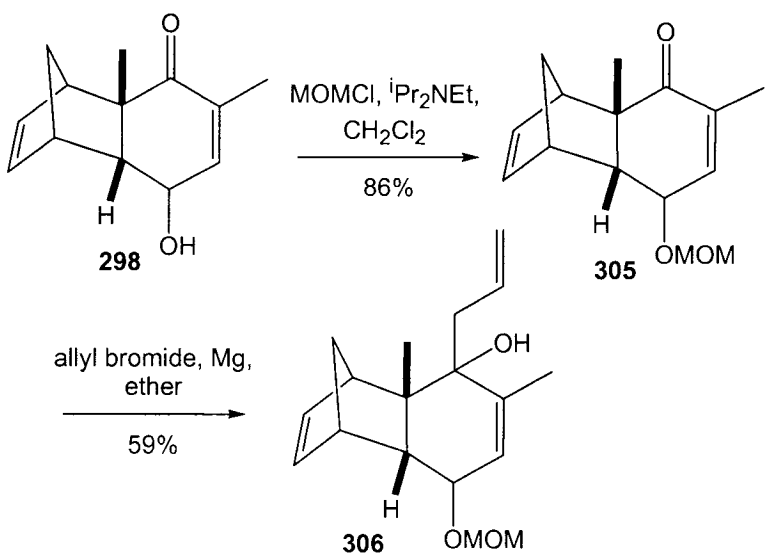
the relative stereochemistry at C9 as the tertiary alcohol of opposite configuration cannot form an oxygen bridge to C4.

Finally, the RCM reaction of compound **293a** in refluxing C_6D_6 gave compound **292a,** with the skeleton of all of the kempanes (Scheme 4.50), which was characterized by IR, NMR and HRMS. The relative stereochemistry of **292a** was confirmed by an NOE study. The most important proximities detected were the C5-hydrogen with the hydrogens on C8, C16, and the methyl on C15, as well as the C15-methyl with the hydrogens on C13, C16, and the C12-methyl. Compound **292a** includes the tetracyclic core of the kempane diterpenes, and it has a double bond in the seven-membered ring at the required position along with oxygen functions at the correct locations on the remaining rings.

The total yield for these three steps was low, which might have been due to the reactive dianion after Grignard reagent had reacted with the carbonyl group. Protection of the secondary alcohol was contemplated. A model compound **298** was tested (Scheme 4.51). Its MOM ether **305** was prepared by treatment with MOMCl in the presence of Hünig's base in CH_2Cl_2. Allyl Grignard reagent reacted with the compound **305** in ether to deliver only diastereomer **306**, but in moderate yield.



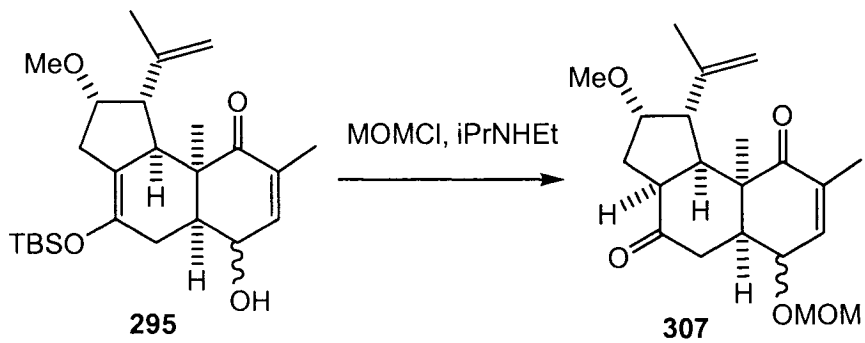
Scheme 4.50 Completion of the kempanes' tetracyclic skeleton **292a**



Scheme 4.51 Alcohol protection and allylation on model **298**

Allylindium was also tried with compound **305** in DMF at room temperature and at 60°C overnight, but without any sign of allylation. This was consistent with similar results of a failure of allylindium to react with compounds **185** and **295**. It can be presumed that the indium reagent is more sterically demanding or less reactive than the corresponding allylmagnesium. (See Schemes 4.42 and 4.46.)

An attempt was made to protect compound **295** as the MOM ether. The alcohol was protected, but not without removal of the silyl group, leading to compound **307**. The silyl enol ether was required for a Simmons–Smith reaction to generate the methyl group on the quaternary carbon center, so this result prevented further attempts to add a MOM group.



Scheme 4.52 MOM ether protection of the alcohol in **295**

Also, the idea of introducing a methyl thiomethyl group was abandoned when addition of the group to the model compound **298** failed.

CHAPTER 5. THE STEREOCHEMISTRY OF 1,2-ADDITIONS OF ALLYL ORGANOMETALLICS TO CYCLOHEXENONES

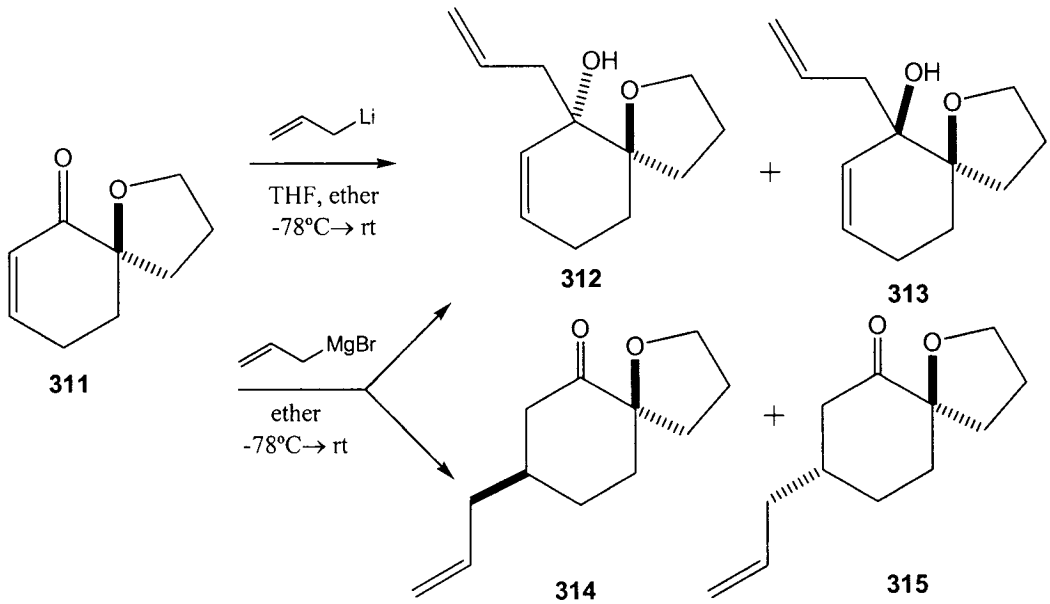
5.1 INTRODUCTION

In Chapter 4 of this thesis, compound **293** was to be obtained from enedione **185** (Scheme 4.40). Thus, a regioselective and facially selective allylation was required. Axial attack has been used to explain the regioselectivity and the facial selectivity of the products of 1,2-additions of lithium acetylide onto α,β-unsaturated ketones, particularly enediones [41,42] (Scheme 4.41). The question arose of the extent of facial selectivity in 1,2-additions of allyl organometallic reagents onto α,β-unsaturated ketones. There are some, but not many, examples in the literature where this phenomenon has been examined.

Paquette studied the addition of allyllithium and allyl Grignard reagents onto 6,6-disubstituted cyclohexenones (Scheme 5.1). [104] Although the addition of allyllithium onto ketone **311** took place only in a 1,2-fashion (in 56% yield), the ratio of the epimers **312** and **313** was 1:1. Allylmagnesium bromide also reacted with ketone **311** to furnish **312** (14%) and **313** (16%) via a 1,2-addition, but the two stereoisomeric 1,4-adducts **314** and **315** predominated (46% combined).

After indium was first reported in Barbier-type additions of allyl bromide to carbonyl compounds, [105] indium-mediated organometallic reactions attracted much attention because indium reagents are fairly stable under aqueous and even mildly acidic conditions and are compatible with many organic functional groups, e.g. hydroxyl

groups, in the substrates. [106] It should be mentioned here that indium was reported to be non-toxic and has considerable use in dental alloys. [106]

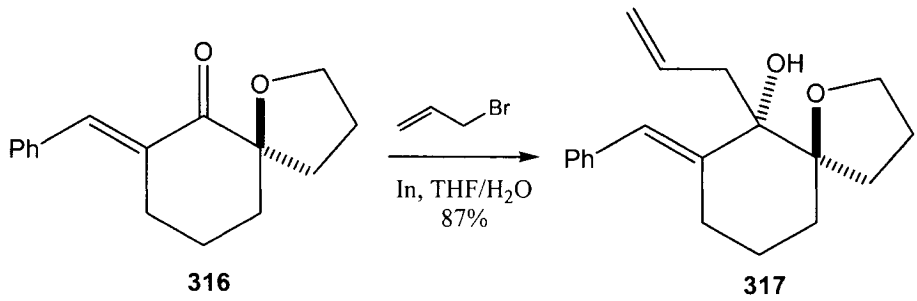


Scheme 5.1 Allyl lithium and Grignard addition to an α,β-unsaturated ketone **311** [104]

Compounds with the formula $R_3In_2X_3$ are formed when indium is treated with allyl halides, but only two of the three allyl moieties can be transferred to an electrophile. A molar ratio of 3:3:2 (indium: allyl iodide: 2-octanone) gave the best yields in allyl additions as long as the reactions were performed with the exclusion of water. [105,107] Chan and Yang found that an allylindium(I) seems to be the active substrate in water-containing solvents, and virtually all available allyl moieties are transferred to the substrate. [108]

Generally, a regioselective 1,2-attack on α,β-unsaturated aldehydes and ketones was observed in indium-mediated allyl additions (e.g. allylation of compound **316** to compound **317**, Scheme 5.2),[109, 110] though a 1,4-allyl addition is dominant with certain

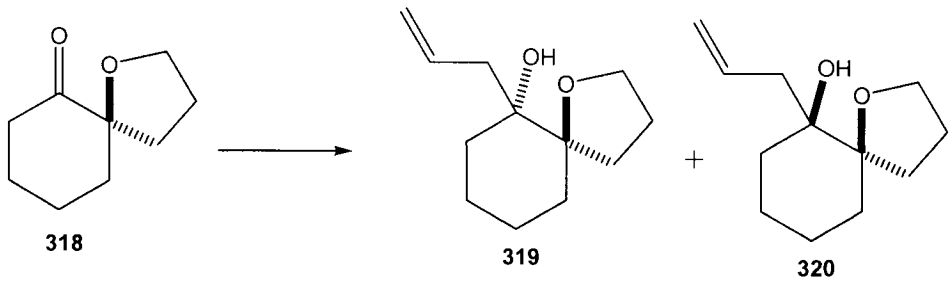
cyclic enones (e.g. 2-cyclohexen-1-one, (*R*)-carvone, and 2-cyclohepten-1-one) when chlorotrimethylsilane (TMSCl) was added.[111]



316 317

Scheme 5.2 1,2-Addition of allylindium to an α,β-unsaturated ketone **316** [110]

Similar to the reaction in Scheme 5.2, Paquette demonstrated stereoselectivity through chelation control of allyl reagents on ketone **318**, a situation in which allyl Grignard gave almost no selectivity [104] (Scheme 5.3). Scheme 5.4 shows an example of the excellent diastereoselectity of allylindium addition on the α,β-unsaturated ketone **321**.[109]

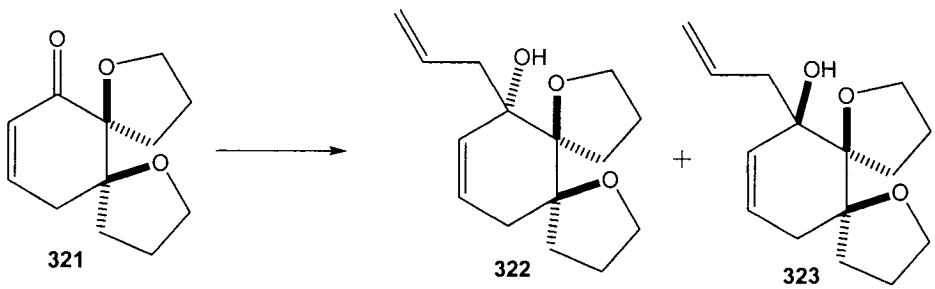


318 319 320

CH_2=$CHCH_2MgCl$, THF, 0°C	1.2 : 1	(88%)
CH_2=$CHCH_2MgCl$, $CeCl_3$, THF, 0°C	1 : 2.4	(96%)
CH_2=$CHCH_2Br$, In, THF, 25°C	5.6 : 1	(82%)
CH_2=$CHCH_2Br$, In, H_2O, 25°C	2.7 : 1	(81%)

Scheme 5.3 Stereoselectivity of allylindium via chelation control on ketone **318** [104]

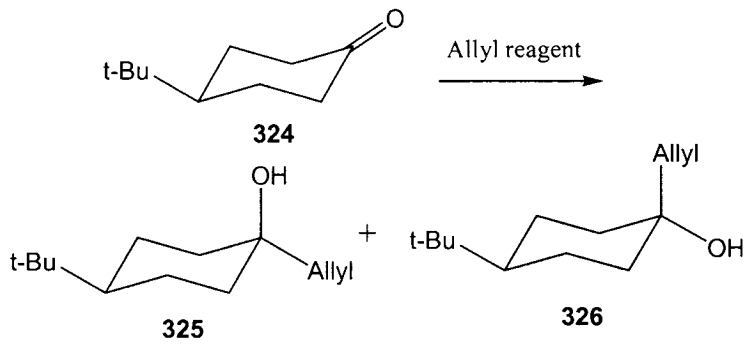
In the first report of indium-mediated allylation by Araki in 1988, 4-*tert*-butylcyclohexanone gave the axial alcohol predominantly (axial alcohol: equatorial alcohol, 8:2). [105] Similarly, Reetz reported later that when a preformed allylindium sesquibromide was reacted with 4-*tert*-butylcyclohexanone, preferential formation of the corresponding axial alcohol was observed (axial: equatorial, 82:18).[112] The diastereoselectivity could be improved to 90:10 by mixing the allylindium species with lithium neopentanoate (Scheme 5.5).



CH_2=$CHCH_2MgBr$, ether, 0°C	1 : 2.0	(73%)
CH_2=$CHCH_2MgBr$, $CeCl_3$, THF, 0°C	1 : 2.1	(57%)
CH_2=$CHCH_2Br$, In, THF, 0°C→rt	100 : 0	(50%)

Scheme 5.4 Excellent stereoselectivity via chelation control on α,β-unsaturated ketone **321** [109]

The effect of solvent on diastereoselectivity with additions of allylindium to 4-*tert*-butylcyclohexanone was also documented [113] (Scheme 5.5). Regardless of whether the reaction medium was pure water, dry THF or a 1:1 mixture of water and THF, the product of equatorial attack **326** (axial alcohol) was predominant. Though the diastereo-selectivity was improved with THF as the solvent, a prolonged reaction time was required to complete the reaction. Preferential equatorial attack was also observed with 2-methyl, 3-methyl, and 4-methylcyclohexanone.

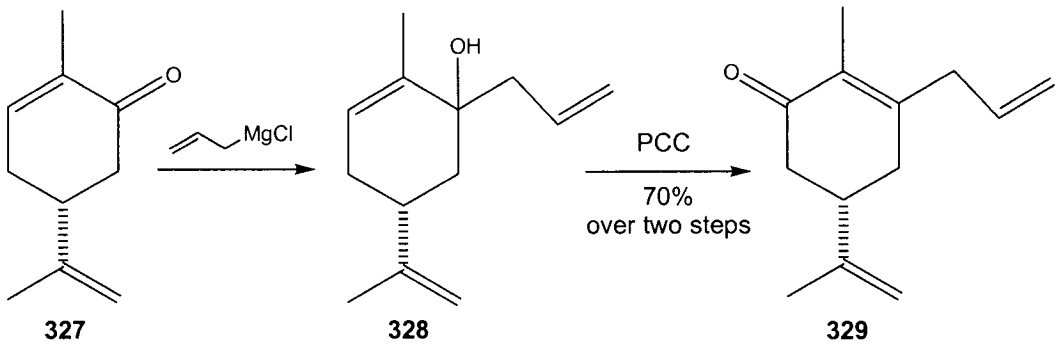


324 **325** **326**

allylMgCl	45:55 (>90%)
$allyl_3In_2Br_3$	82:18 (85%)
$allyl_3In_2Br_3$/ $4(CH_3)_3CCH_2OLi$	90:10 (99%)
CH_2=$CHCH_2Br$, In, H_2O, 3 h, rt	82:18 (75%)
CH_2=$CHCH_2Br$, In, THF/H_2O(1:1), 4 h, rt	84:16 (79%)
CH_2=$CHCH_2Br$, In, THF, 48 h, rt	91:9 (73%)

Scheme 5.5 Stereoselectivity in the additions of allylmetal reagents to 4-*tert*-butylcyclohexanone [112]

No work has been reported on the diastereoselectivity of the reaction between 4-*tert*-butyl-2-cyclohexen-1-one and allylindium or allyl Grignard reagents, although the stereochemistry of the 1,4-addition of allyl copper reagents on 4-*iso*propyl-2-cyclohexenone has been examined. [114] The reaction of (*R*)-carvone **327** and an allyl Grignard reagent has been reported in a model study (to **328** and then to **329**) towards the total synthesis of taxanes, [115] but the stereochemistry of **328** was not reported (Scheme 5.6).



Scheme 5.6 Allyl Grignard reagent with (*R*)-(-)-carvone in the literature [115]

5.2 RESULTS AND DISCUSSION

5.2.1 4-*TERT*-BUTYL-2-CYCLOHEXEN-1-ONE

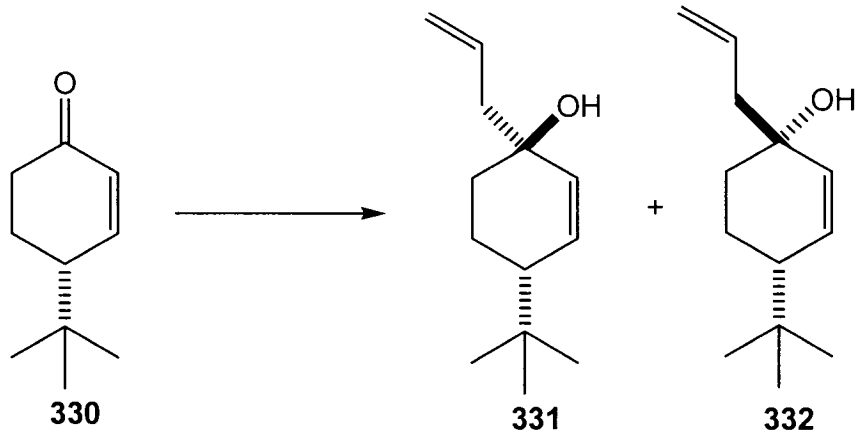
4-*tert*-Butyl-2-cyclohexen-1-one, [116] (*R*)-(-)-carvone and (+)-4-cholesten-3-one were selected as substrates for this study. Allyl Grignard, allylindium, and allylbismuth reagents [117] were the organometallics tested.

Allyl Grignard was found to generate a 5:1 ratio of epimeric 1,2-reaction products (83% yield) with 4-*tert*-butyl-2-cyclohexen-1-one. Addition of allylindium took place in a 1,2-fashion in good yield, but with no diastereoselectivity (1:1 ratio of epimers, 85% yield). The allylbismuth reagent was prepared by adding zinc powder to a mixture of allyl bromide and bismuth(III) chloride in the presence of 4-*tert*-butyl-2-cyclohexen-1-one. This led to the same the epimers in a ratio of 2.2:1.

No solvent effect was found on both reaction rate or product ratio with Grignard reagents using diethyl ether or THF. However, for the allylindium reagents, though no solvent effect on product ratio was found, the allylation reaction was fast in pure DMF (the reaction was complete in 6 hours), slower in 1:1 DMF/H_2O (one day) or pure water

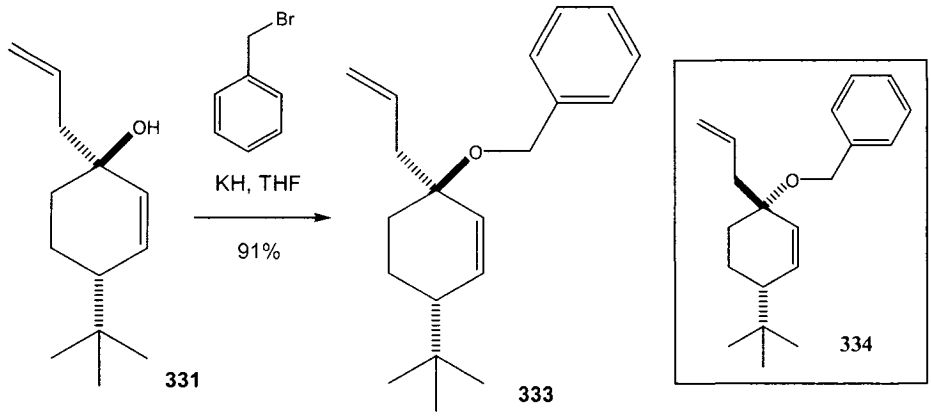
(two days) and slowest in pure THF (incomplete after 7 days), which was similar to the results reported before. [113]

Although the ratios of the 1,2-addition products had been easily determined by NMR, it was not obvious by NMR which epimer was which. The initial plan was then to determine the stereochemistry of one of the diastereomeric products by X-ray crystallography, but the products of allyl addition were liquids.



Scheme 5.7 Allylindium and allylmagnesium bromide reacted with 4-*tert*-butyl-2-cyclohexen-1-one (**330**)

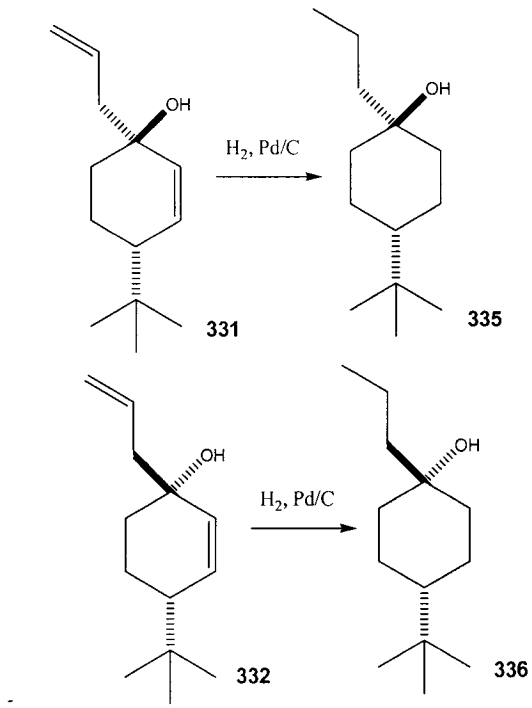
A benzyl ether **333** was made in 91% yield from compound **331**, which was the major epimer from the reaction with allyl Grignard, with benzyl bromide in the presence of potassium hydride in THF in excellent yield, but the product was a liquid. A similar procedure worked on the minor compound **332,** producing benzyl ether **334** in 88% yield, but this derivative was also a liquid (Scheme 58).



Scheme 5.8 A benzyl ether derived from compound **331**

A literature search revealed that (1*R**,4*R**)-4-*tert*-butyl-1-propylcyclohexanol is a known compound, [118] which had to be the hydrogenated product of **331** or **332**. Compounds **331** and **332** were subjected to catalytic hydrogenation, and the product **336** from compound **332** had NMR spectra that corresponded to the published data for (1*R**,4*R**)-4-*tert*-butyl-1-propylcyclohexanol.[118] Furthermore, **336** was a solid, and the stereochemistry of **336** was determined independently by an X-ray single crystal structure.

With the stereochemistry of the diastereomeric products no longer in question, it could be concluded that allyl Grignard generated mainly the axial-addition product (in a 5:1 ratio) with 4-*tert*-butyl-2-cyclohexen-1-one, while allylindium gave no diastereo-selectivity. The allylbismuth reagent gave a product ratio that slightly favored the axial-addition product (2.2:1).

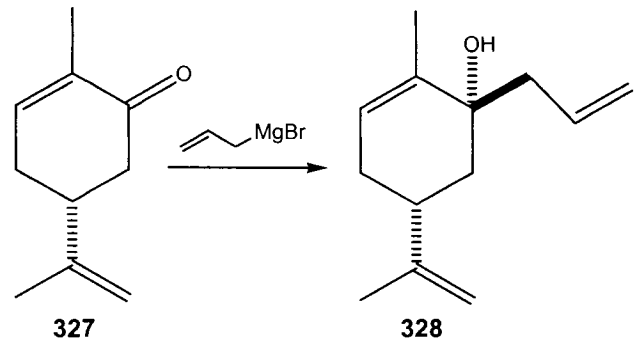


Scheme 5.9 Hydrogenation of compounds **331** and **332**

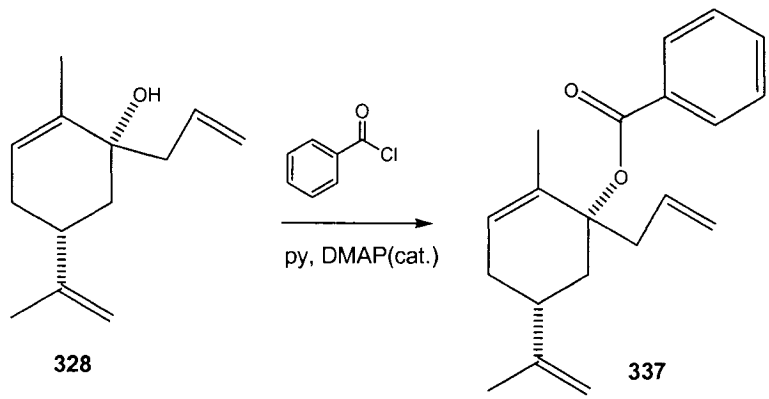
5.2.2 (*R*)-(-)-CARVONE (327)

Allyl Grignard reacted with (*R*)-(-)-carvone (**327**) to give only one diastereomer **328**, a liquid, in 86% yield (Scheme 5.10). Reaction of **327** with allylindium generated the same product. An attempt to determine the stereochemistry of this product by measurement of nuclear Overhauser enhancements gave inconclusive results. No significant reaction was observed with allylbismuth even after many days. Derivatives were prepared from **328** in order to obtain crystals for X-ray analysis.

The benzoate ester **337** was made from compound **328** with benzoyl chloride and pyridine and in the presence of a catalytic amount of DMAP, but **337** was an oil (Scheme 5.11). Hydrogenation of **337** resulted in the production of another oil.

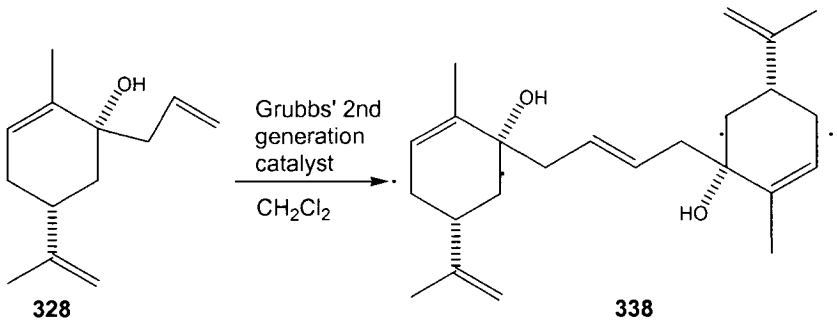


Scheme 5.10 Reaction of allyl Grignard with **327** generating **328**



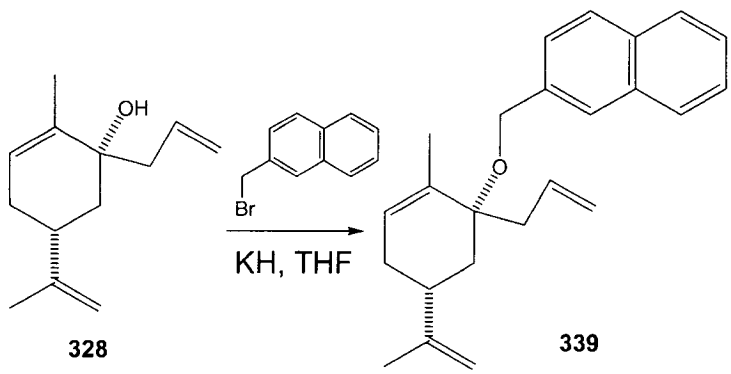
Scheme 5.11 Benzoate ester **337** formation from **328**

Next, it was thought that the presence of two alkenes in compound **328** might allow an intramolecular ring-closing metathesis (RCM) reaction to occur if the relative stereochemistry of the allyl and isopropenyl groups were *cis*. A dimeric compound **338** was produced in 93% yield instead of a bicyclic compound (Scheme 5.12). However, that a dimeric compound was produced did not prove that the relative stereochemistry of the allyl and isopropyl groups was *trans*. Compound **338** was a solid, but crystals of sufficient quality could not be obtained by recrystallization using various solvents and mixed solvents. The benzyl ether was made from **338**, but it was an oil.



Scheme 5.12 Dimer **338** formation from **328**

The β-methylnaphthyl ether **339** was made from compound **328** and 2-(bromomethyl)naphthalene (Scheme 5.13). The idea was once again to produce crystals suitable for X-ray analysis, but **339** was an oil. However, NOE data gathered with **339** showed that in **339** the allyl and the isopropenyl groups are *trans*. Thus, the attack of the organometallics on carvone had taken place by axial attack to give **328**.



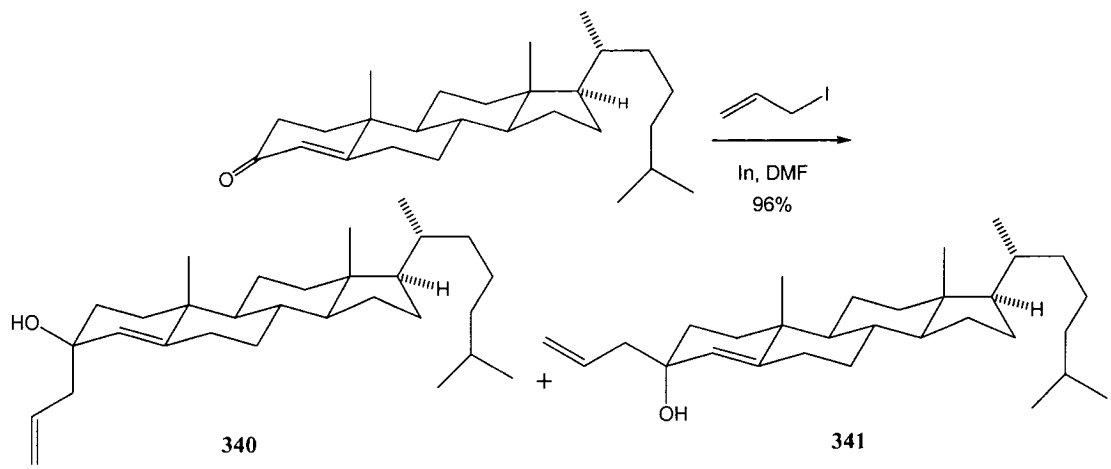
Scheme 5.13 β-Methylnaphthyl ether formation from **328**

5.2.3 (+)-4-CHOLESTEN-3-ONE

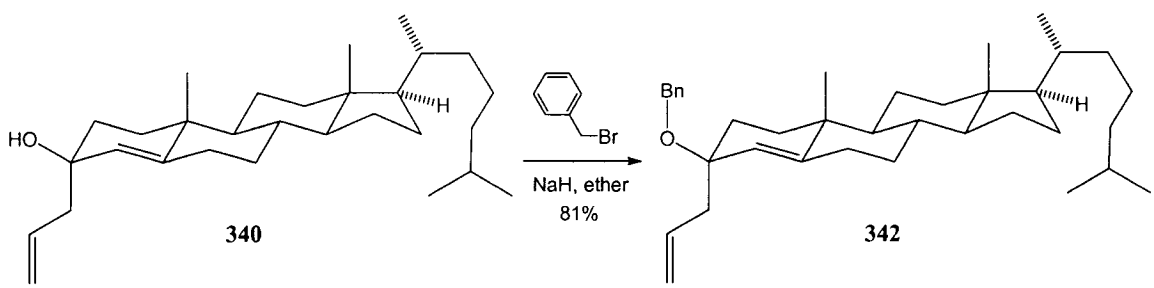
Allyl Grignard reacted with (+)-4-cholesten-3-one to provide epimeric 1,2-addition products in a ratio of 6.3:1. Allylindium reagent gave the same products in a ratio 4.5:1 ratio, and allylbismuth addition led to a 4.2:1 ratio of products (Scheme 5.14).

Once again, NMR methods were not useful in determining the relative stereochemistry of either product, so suitable crystals were sought for X-ay analysis.

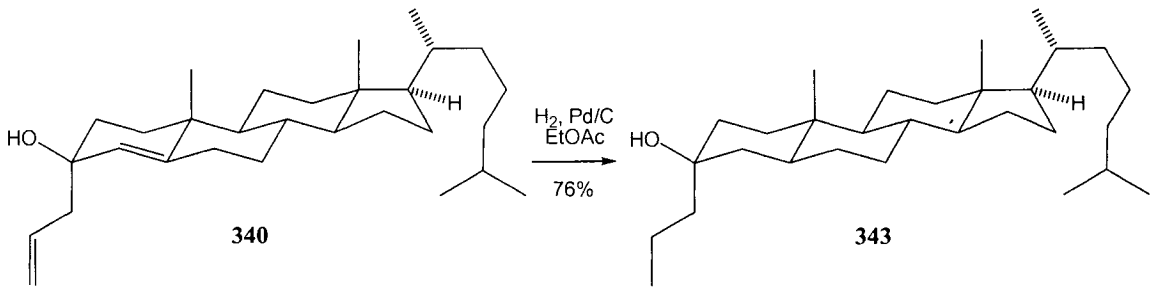
A benzyl ether **342** was made in 81% from the major product **340**, but it was an oil (Scheme 5.15). Hydrogenation of compound **340** gave a solid product **343** in 76% yield, which gave crystals by recrystallization (Scheme 5.16).



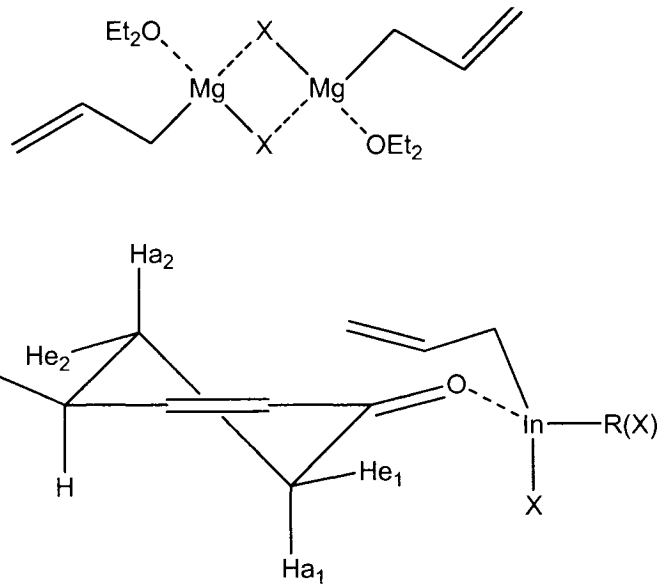
Scheme 5.14 Reaction of allylindium with (+)-4-cholesten-3-one



Scheme 5.15 The benzyl ether from compound **340**



Scheme 5.16 Hydrogenation of compound **340**



Schme 5.17 Possible structure of allyl organometallic intermediate and conformer of cyclic enone

In conclusion, when reacted with conjugated ketones, allyl Grignard gave higher stereoselectivity (mainly axial-attack-product) than either allylindium reagent or allylbismuth.

These results might be explained by the nature of the reation intermediates, as shown in Scheme 5.17. When reacting with carbonyls, allylindium prefers the γ-position and gives a rearrangement product, [102] while allyl Grignard reagents usually produce α-position coupled homoallylic alcohol. [119] When allylindium(III) reacts with an enone, as

a better Lewis acid than magnesium, indium bonds with the carbonyl oxygen first, then a 3,3-sigmatropic rearrangement-like reaction generates the product. Indium bonding to oxygen makes the little difference between axial H_{a1} and H_{a2}, and thus produces a 1:1 ratio of axial- and equatorial-attack products. In the case of Grignard reagents, their bigger dimeric structure and α-position-preferred attack on the carbonyl makes the steric effect of axial H_{a1}, which is closer to the carbonyl than H_{a2}, more than that in the case of a allylindium reaction with a conjugated ketone. Little is known regarding the nature of allylbismuth reagents. It seems that the selectivity of the allylbismuth reagent is between that of allylindium and allyl Grignard, but without an understanding of the structure and mechanism of the organobismuth reaction, it is difficult to hypothesize about the stereoselectivity.

CHAPTER 6. CONCLUSIONS

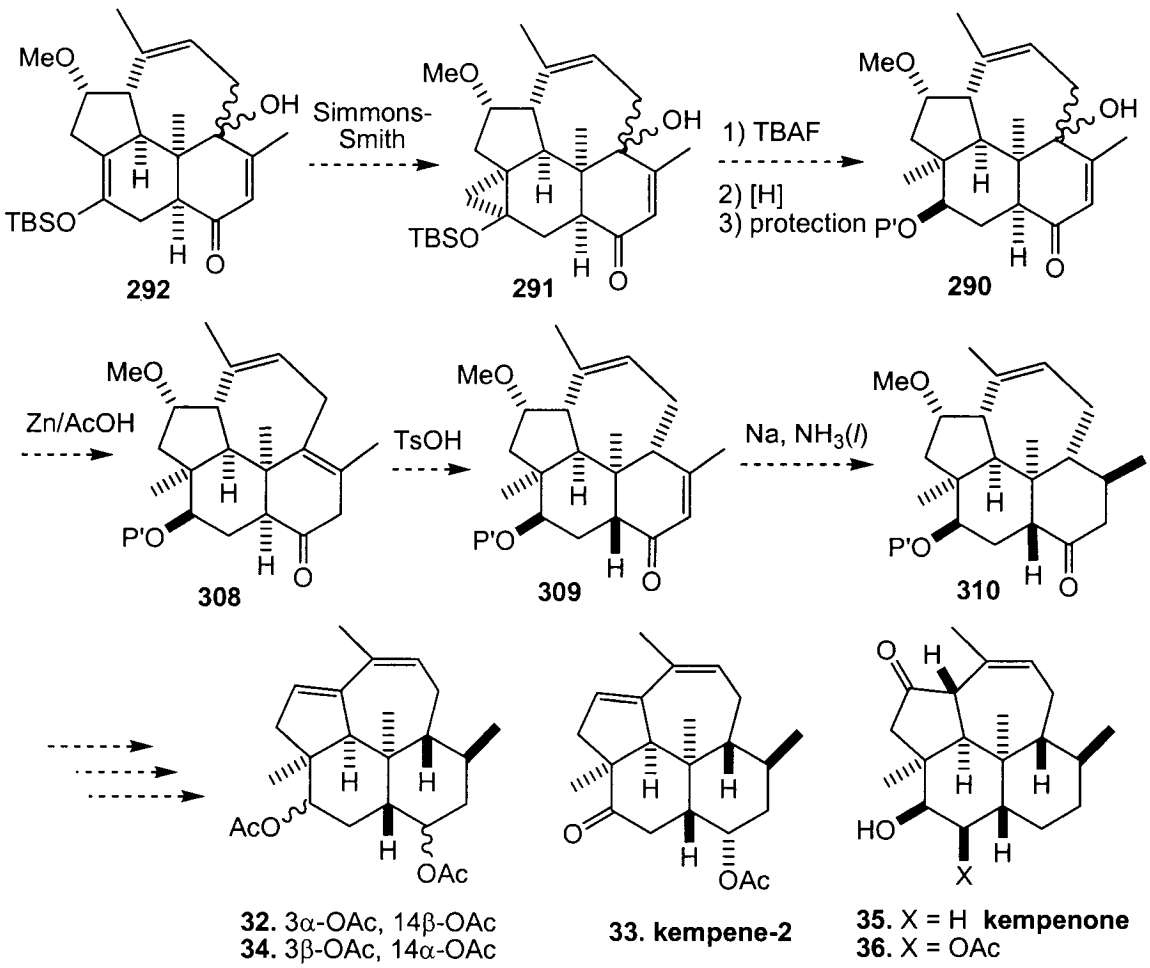
The viability of ring-closing-metathesis (RCM) as the key step for the generation of the tetracyclic skeleton of the kempanes has been demonstrated. The route to achieve this result was via the synthesis of an appropriately functionalized diene, which was made using a Mannich route to introduce the isopropylidene unit in high overall yield. This diene was employed in an endo-, regio-, and facially selective Diels-Alder reaction to gave an adduct with three of the four rings of the kempanes with the central stereochemistry established. The diastereoselectivity of 1,2-allylation with allylindium, allyl Grignard, and allylbismuth reagents on α,β–conjugated ketones was tested with simple conformationally restricted models. The diastereoselectivity of allyl Grignard additions was the most selective, favoring axial addition, of the three reagents. Following cerium-mediated, regioselective reduction, Grignard allylation, and Dess–Martin oxidation, the RCM step worked well to generate the final seven-membered ring. The construction of the tetracyclic skeleton of the kempanes via the RCM reaction was accomplished in 24 steps from commercially available starting materials.

The total synthesis of the kempane diterpenes may not be far away. If we use large excess solid sodium bicarbonate in the Dess-Martin oxidation reaction to prevent the formation of any acetal, we might obtain intermediate **293** in high yield. (See Schemes 4.40 and 4.50) If then compound **292** could be made in high yield from **293**, the Simmons–Smith reaction will be studied with this substrate. It is hoped that compound **291** can be obtained selectively. Compound **291** is the result of cyclo-propanation of only one of the three double bonds of **292**, but the desired product would result of

reaction of the most electron rich double bond where the steric differences between the double bonds are not large.

Once the cyclopropane has formed, the difficult part of the synthesis is likely to be over. Deprotection of the silyl ether and ring-opening of the cyclopropane by TBAF, reduction of the resulting ketone, and protection of the secondary alcohol as an ether would generate compound 290.

From this point on, the procedures described in this thesis can be followed. Zinc and acetic acid will deoxygenate to give compound 308, and subsequent treatment with *para*-toluenesulfonic acid will carry out both the reconjugation of the double bond and epimerization to deliver compound 309. Dissolving metal reduction will provide compound 310 with the right stereochemistry of the methyl group. Compound 310 has all the correct stereochemistry and required functional groups for the transformations to all three kempane compounds *via* routine deprotection steps and functional group interconversions.



Scheme 6.1 Future work (P' represents a protecting group)

CHAPTER 7. EXPERIMENTAL

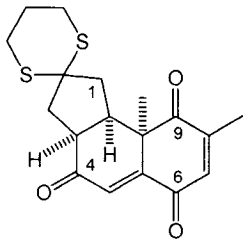
GENERAL METHODS

Reactions involving moisture- and/or air-sensitive reactants were conducted with pre-heated and nitrogen-flushed glassware and with dry solvents under an atmosphere of dry nitrogen or argon. THF, ether and 1,4-dioxane were dried over sodium with benzophenone as an indicator, *i.e.*, THF and 1,4-dioxane were heated gently under reflux with sodium in the presence of benzophenone until a dark blue color persisted, then they were distilled. DMF was dried over anhydrous $MgSO_4$. Hexane, pentane, benzene, toluene, dichloromethane, nitromethane and triethylamine were obtained by distillation over calcium hydride, and then stored over 4Å Molecular Sieves. Reactions were monitored by TLC when possible. TLC was performed on Polygram Sil G/UV_{254} plates, visualized under UV light and/or with a spray of phosphomolybdic acid in ethanol. All flash column chromatography was conducted on 230-400 mesh silica gel. Workup employed aqueous solutions of HCl, $NaHCO_3$, NaCl, *etc.*

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were obtained on a Mattson Polaris FT-IR spectrometer. NMR spectra were obtained on a General Electric GE-300-NB (300 MHz) instrument, a Bruker AC-250F (250 MHz) instrument, or a Bruker Avance (500 MHz) instrument. NMR spectra were recorded in $CDCl_3$, unless other solvents are shown. Chemical shifts (δ) are reported as parts per million (ppm) relative to tetramethylsilane internal standard. GC–MS analyses were performed on a Perkin-Elmer Autosystem XL instrument (controlled by a computer

with TurboMass and TurboChrom software) with a Turbomass detector and a flame ionization detector (both columns: Supelco 30 m / 0.25 mm MDN-5S 5% phenyl methylsiloxane, film thickness 0.50 μm; injection volume: 1 μL). MS were obtained on a Thermo Finnigan LCQ Duo ion trap instrument, and HRMS were obtained on a CEC 21-110B sector instrument. Optical rotations were measured on a Rudolph Instruments Digipol 781 automatic polarimeter.

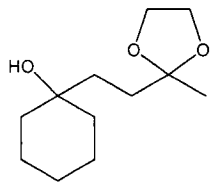
Spectroscopic data are reported in the order of IR, ^{1}H NMR, NOE, ^{13}C NMR, GC-MS, MS, and HRMS. Media used for the acquisition of spectra are indicated in parentheses, where applicable. ^{1}H NMR data are reported in the following order: chemical shift (number of protons, multiplicity, coupling constant, *J* in Hertz, assignment). Chemical shifts are in ppm units relative to an internal standard, tetramethylsilane. Multiplicity is represented by the following designations: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: double doublet etc., br: broad. Assignments are based on ^{1}H, ^{13}C, COSY, DEPT, HMQC or HSQC, HMBC, and NOE spectra. NOE data are reported as: saturated signal (enhanced signal, enhancement as determined by the difference method). ^{13}C NMR data are reported in this order: chemical shift (number of protons attached to the carbon, assignment). MS data are reported in units of mass over charge (*m/z*) with intensities relative to the largest peak in %. Molecular ions of less than 1% are generally not reported.



(3aα,9aα,9bα)-2,3,3a,4,9a,9b-Hexahydro-8,9a-dimethyl-1*H*-benz[*e*]indene-2,6,9-trione, 2-(propylene thioacetal) derivative (195)

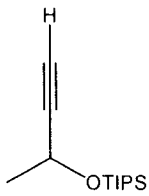
Magnesium turnings (50 mg, 2.0 mmol) were added under argon to dry benzene (10 mL), followed by iodine (25 mg, 0.10 mmol) and dry ether (0.1 mL). [120] The mixture was stirred until the iodine's color disappeared. The solvent was removed by distillation over an oil bath, and the residue was maintained at 150 to 160 °C for 5 min to ensure complete removal of the solvent. The activated magnesium was then cooled under argon. Dry THF (5 mL) and bromide **194** (42 mg, 0.22 mmol) were added to the activated magnesium, and the mixture was then stirred at rt for 2 h. Compound **172** (100 mg, 0.220 mmol) in THF (2.0 mL) was added dropwise to the above Grignard reagent at 0 °C, and the reaction mixture was stirred at rt overnight. The reaction was quenched with saturated NH_4Cl and extracted with ether (10 mL × 3). The organic layer was washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL) and dried over anhydrous $MgSO_4$. Flash column chromatography returned some of the starting material **172** (42 mg, 42%) and provided compound **195** as a colorless oil (R_f 0.24; 30% ethyl acetate/hexane, 24 mg, 32%). δ_H 6.92 (1 H, s, C=*CH*), 6.70 (1 H, s, C=*CH*), 3.31 (1 H, dt, J_1 7.1, J_2 11.2), 3.05 (2 H, m), 2.91 (2 H, m), 2.78 (2 H, ddd, J_1 3.4, J_2 7.8, J_3 14.7), 2.58 (1 H, dd, J_1 8.7, J_2 14.2), 2.42 (1 H, dd, J_1 8.1, J_2 14.2), 2.12 (3 H, s, C-CH_3), 1.97 (3 H, m), 1.58 (3 H, s, C-CH_3). δ_C 198.9 (*C*=O), 196.2 (*C*=O), 185.8 (*C*=O), 149.7, 149.1,

138.6, 128.6, 53.1, 50.3, 47.4, 46.5, 45.5, 45.3, 30.1, 29.0 (*CH*$_3$), 28.9, 24.8, 17.1 (*CH*$_3$). HRMS: Experimental, 348.0862 amu ($C_{18}H_{20}O_3S_2$, Calculated 348.0854).



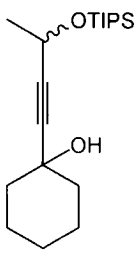
1-[2-(2-Methyl-[1,3]dioxolan-2-yl)ethyl]cyclohexanol (197)

The general lithium-halogen exchange procedure described by Negishi [121] was applied to this reaction. A flame-dried flask was charged with iodide **168** (600 mg, 2.47 mmol) and a mixture of 24 mL of dry pentane and 12 mL of dry ether under argon. The stirred solution was cooled to –78 °C. *t*-BuLi (1.7 M in pentane, 3.55 mL, 6.03 mmol) was added dropwise via an argon-flushed syringe. Stirring was continued at –78 °C for additional 5 min. The cooling bath was removed, and the mixture was allowed to warm to rt and to stand for 1 h. Argon flow was adjusted to a minimum to avoid the loss of solvent by evaporation. The solution was then recooled to –78 °C, and a solution of ketone **196** (242 mg, 2.47 mmol) in dry ether (5 mL) was added. The cooling bath was removed, and the mixture was allowed to warm to rt with stirring overnight. The reaction was quenched by addition of water (5 mL), and the aqueous layer was extracted with ether (5 mL × 3). The combined organic layers were washed with water (10 mL × 3) and brine (10 mL), and the solvent was removed under vacuum. Flash chromatography provided **197** as a colorless liquid (R_f 0.10; 20% ethyl acetate/hexane, 152 mg, 29%). δ_H 3.96 (4 H, m, O*CH*$_2$*CH*$_2$O), 1.87 (1 H, br s, OH), 1.76 (2 H, m), 1.52 (12 H, m), 1.34 (3 H, s, *CH*$_3$).



3-Triisopropylsilyloxybut-1-yne (200)

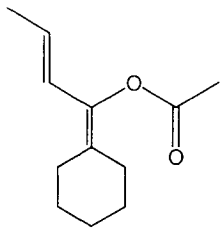
Chlorotriisopropylsilane (1.52 g, 7.88 mmol) was added to a solution of 3-butyn-2-ol (460 mg, 6.57 mmol) and imidazole (1.12 g, 16.5 mmol) in dry DMF (2.0 mL) under argon. The mixture was stirred at rt for 15 h before water (10 mL) was added, and then this was extracted with ethyl acetate (20 mL × 3). The combined organic solutions were washed with water (10 mL × 3) and brine (10 mL), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to flash column chromatography to give **200** as a colorless liquid (R_f 0.60; 1% ethyl acetate/hexane, 1.49 g, 100%). δ_H 4.60 (1 H, dq, J_1 2.2, J_2 6.4, O*CH*), 2.38 (1 H, d, J 2.2, *alkyne*), 1.46 (3 H, d, J 6.4, O-C-*CH*$_3$), 1.06 (21 H, m, *TIPS*). δ_C 86.6, 71.0, 58.8, 25.6, 18.0, 12.2. HRMS: Experimental, 226.1756 amu ($C_{13}H_{26}OSi$, Calculated 226.1756).



1-(3-Triisopropylsilyloxybut-1-ynyl)cyclohexanol (201)

n-BuLi (2.5 M in hexane, 0.23 mL, 0.57 mmol) was introduced to a solution of **200** (129 mg, 0.57 mmol) in dry THF (5 mL) at –78 °C over 5 min. The solution was stirred for 30 min before it was transferred with a double-headed needle to a solution of cyclohexanone **196** (56 mg, 0.57 mmol) in dry THF (10 mL) at –78 °C. The mixture was

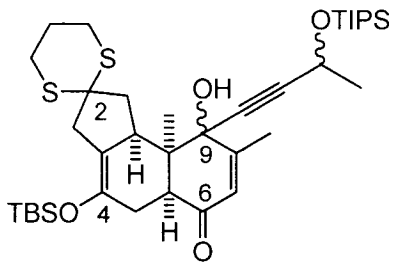
stirred at –78 °C for 2 h and then at 0 °C for 1 h. The reaction was quenched by addition of water (10 mL). Ether (100 mL) was added, and the organic solution was washed with water (20 mL × 3) and brine (20 mL). The resulting solution was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography to give **201** as a colorless liquid (R_f 0.21; 10% ethyl acetate/hexane, 117 mg, 75%). δ_H 4.64 (1 H, q, *J* 6.6, O*CH*), 2.04 (1 H, s, *OH*), 1.86 (2 H, m), 1.60 (8 H, m), 1.44 (3 H, d, *J* 6.6, CH_3), 1.09 (21 H, m, *TIPS*).



(*E*)-1-Acetoxy-1-cyclohexylindene-2-butene (202)

Compound **201** (55 mg, 0.17 mmol) was dissolved in glacial AcOH (10 mL). The solution was heated to reflux, and zinc dust (2.0 g, 31 mmol) was added in portions until TLC showed that **201** was completely consumed. The remaining solid was removed by filtration after the reaction mixture had cooled to rt. The filtrate was poured into ethyl acetate (30 mL) and water (30 mL), and solid Na_2CO_3 was added until CO_2-evolution ceased. The aqueous layer was re-extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to flash column chromatography to afford **202** as a colorless liquid (R_f 0.35; 5% EtOAc/hexane, 6.5 mg, 20%). δ_H 6.35 (1 H, dd, J_1 1.5, J_2 15.7, *CH*=CH-CH_3), 5.61 (1 H, m, C=C*H*-CH_3), 2.34 (2 H, t, *J* 6.3, CH_2), 2.25 (3 H, s, CH_3), 2.09 (2 H, t, *J* 6.2, CH_2), 1.81 (3 H,

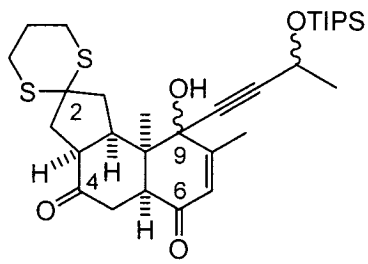
dd, J_1 1.3, J_2 6.4, CH=CH-CH_3), 1.59 (6 H, m, $CH_2CH_2CH_2$). δ_C 169.6, 137.9, 124.8, 122.1, 29.3, 28.9, 27.9, 26.9, 21.0, 18.6.



(5aα,9aα,9bα)-4-(*tert*-Butyldimethylsilyl)oxy-2,3,5,5a,6,9,9a,9b-octahydro-9-hydroxy-8,9a-dimethyl-9-[3-(triisopropylsilyl)oxybut-1-yn-1-yl]-1*H*-benz[*e*]indene-2,6-dione, 2-(propylene thioacetal) derivative (203)

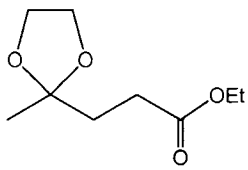
n-BuLi (2.5 M in hexane, 0.68 mL, 1.7 mmol) was introduced to a solution of **200** (386 mg, 1.70 mmol) in dry THF (20 mL) at –78 °C over 5 min. The solution was stirred for 30 min before it was transferred with a double-headed needle to a solution of enedione **172** (628 mg, 1.35 mmol) in dry THF (10 mL) at –78 °C. The mixture was stirred at –78 °C for 2 h and then at 0 °C for 1 h. This was quenched with water (20 mL), and ether (100 mL) was added. The aqueous layer was re-extracted with ether (20 mL × 3). The combined organic layers were washed with water (20 mL × 3) and brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by flash column chromatography to yield **203** as a yellow liquid (R_f 0.70; 30% EtOAc/hexane, 52 mg, 39%). IR (neat, cm^{-1}): 3405, 1675. δ_H 5.81 (1 H, s, *CH*=C), 4.70 (1 H, q, *J* 6.4, CH_3-*CH*-O), 3.30 (1 H, dt, J_1 4.0, J_2 13.0), 2.92 (2 H, q, *J* 7.0), 2.87 (2 H, q, *J* 6.6), 2.57 (1 H, m), 2.36 (4 H, m), 2.16 (3 H, s, CH_3), 2.02 (3 H, m), 1.69 (1 H, dd, J_1 4.3, J_2 14.4), 1.52 (6 H, m), 1.25 (1 H, br s), 1.00-1.16 (21 H, m, *TIPS*), 1.01 (3 H,

s, CH_3), 0.84 (9 H, s, *t*-butyl), 0.07 (3 H, s, CH_3 in TBS), 0.03 (3 H, s, CH_3 in TBS). δ_C 196.8, 159.3, 140.8, 125.4, 116.1, 81.7, 76.2, 59.2, 53.3, 52.5, 46.2, 39.9, 34.7, 31.8, 29.1, 28.3, 26.0, 25.9, 25.5, 22.8, 19.1, 18.1, 16.8, 12.3, –3.4, –3.5, –3.7.



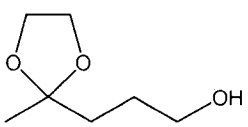
(3aα,5aα,9aα,9bα)-2,3,3a,5,5a,9,9a,9b-Octahydro-9-hydroxy-8,9a-dimethyl-9-[3-(triisopropylsilyl)oxybut-1-yn-1-yl]-1*H*-benz[*e*]indene-2,4,6-trione, 2-(propylene thioacetal) derivative (mixture of epimers at C-9) (204)

Potassium fluoride monohydrate (35 mg, 0.38 mmol) was added to the solution of **203** (52 mg, 0.75 mmol) in methanol (10 mL) at rt. The mixture was stirred at rt for 24 h. After most of the solvent was removed, the residue was diluted with water (5 mL), and extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent gave **204** as a colorless liquid (crude, 48 mg, 95%). δ_H 5.78 (1 H, s, *CH*=C), 4.71 (1 H, q, *J* 6.1, CH_3-*CH*-O), 3.30 (1 H, dt, J_1 9.0, J_2 9.7), 2.62 (9 H, m), 2.17 (3 H, CH_3), 2.05 (3 H, m), 1.70 (1 H, dd, J_1 4.9, J_2 14.2), 1.50 (3 H, m), 1.26 (2 H, m), 1.06 (24 H, m). GC-MS: 576 (20, M^+), 534 (16), 533 (41), 515 (10), 469 (2), 426 (6), 425 (13), 397 (4), 357 (6), 320 (6), 319 (19), 317 (7), 280 (6), 279 (20), 250 (3), 249 (7), 213 (20), 173 (20), 172 (60), 171 (15), 131 (54), 115 (24), 103 (54), 75 (100), 61 (47), 59 (38).



Ethyl 3-(2-methyl-[1,3]dioxolan-2-yl)propanoate (206)

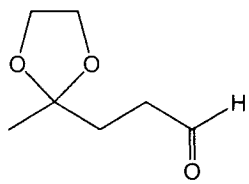
para-Toluenesulfonic acid (200 mg) was added to a mixture of ethyl levulinate (18.8 g, 0.130 mol) and 1,2-ethanediol (9.68 g, 0.156 mol) in dry benzene (200 mL). The mixture was refluxed overnight using a Dean–Stark apparatus. After cooling to rt, solid $NaHCO_3$ (1.0 g) was added to the solution, followed by saturated $NaHCO_3$ solution (100 mL). The organic layer was washed with brine and dried over anhydrous K_2CO_3. After evaporation of the solvent, flash column chromatography of the residue gave **206** as a colorless liquid (R_f 0.45; 30% ethyl acetate/hexane, 13.4 g, 55%). IR (neat, cm^{-1}): 1736. δ_H 4.13 (2 H, q, *J* 7.2, $COOCH_2$), 3.95 (4 H, m, OCH_2CH_2O), 2.39 (2 H, t, *J* 7.7, $C\text{-}CH_2\text{-}CH_2COO$), 2.02 (2 H, t, *J* 7.7, $C\text{-}CH_2\text{-}CH_2\text{-}COO$), 1.35 (3 H, s, CH_3-C), 1.26 (3 H, t, *J* 7.2, $COOCH_2CH_3$). δ_C 173.6 (*C*=O), 109.2 ($C(OCH_2CH_2O)$, 64.9 ($COOCH_2CH_3$), 60.3 ($C(OCH_2\text{-}CH_2O)$, 34.0 (CH_2CH_2COO), 29.1 (CH_2CH_2COO), 24.0 ($CH_3C(OCH_2CH_2)C$), 14.2 ($COOCH_2CH_3$). GC-MS: 173 (58, $M^+\text{-}CH_3$), 158 (4), 143 (65), 129 (20), 115 (12), 101 (27), 99 (83), 97 (12), 88 (27), 87 (100), 85 (45), 73 (20), 71 (46). HRMS: Experimental, 173.0809 amu ($M^+\text{-}CH_3 = C_8H_{13}O_4$, Calculated 173.0814).



3-(2-Methyl-[1,3]dioxolan-2-yl)propan-1-ol (208)

Lithium aluminum hydride (160 mg, 4.20 mmol) was added to a solution of acetal-ester **206** (760 mg, 4.00 mmol) in dry ether (20 mL) at 0 °C. The mixture was

warmed to rt and left overnight. Ethyl acetate (5 mL) was added, followed by 10% NaOH solution (20 mL). The aqueous solution was extracted with ether (10 mL × 2), and the combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous K_2CO_3. Evaporation of the solvent and flash column chromatography of the residue gave **208** as a colorless liquid (R_f 0.11; 30% ethyl acetate/hexane, 583 mg, 95%). IR (neat, cm^{-1}): 3414. δ_H 3.96 (4 H, m, O*CH*$_2$*CH*$_2$O), 3.66 (2 H, t, *J* 6.1, *CH*$_2$OH), 2.62 (1 H, br s, CH$_2$-*OH*), 1.75 (2 H, m, *CH*$_2$-*CH*$_2$-CH$_2$OH), 1.67 (2 H, m, *CH*$_2$-*CH*$_2$-CH$_2$OH), 1.34 (3 H, s, *CH*$_3$-C). δ_C: 110.1 (O-*C*-O), 64.7 (O*CH*$_2$*CH*$_2$O), 62.9 (*CH*$_2$OH), 35.8 (*CH*$_2$CH$_2$CH$_2$OH), 27.3 (CH$_2$*CH*$_2$CH$_2$OH), 23.8 (*CH*$_3$). GC-MS: 101 (2, M^+-C_2H_5O), 85 (7, M^+-$C_2H_5O_2$), 84 (100), 83 (51), 71 (8), 69 (20), 68 (6), 55 (36). HRMS: Experimental, 131.0707 amu (M^+-CH_3 = $C_6H_{11}O_3$, Calculated 131.0708).

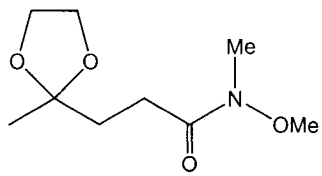


3-(2-Methyl-[1,3]dioxolan-2-yl)propanal (189)

a) With PCC. Celite (*ca.* 1.0 g) and PCC (193 mg, 0.902 mmol) was added to the solution of alcohol **207** (100 mg, 0.694 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at rt overnight. The Celite was removed by filtration, and the organic solution was washed with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to flash column chromatography to provide **189** as a colorless liquid (R_f 0.32; 10% ethyl acetate/hexane, 40 mg, 40%).

b) With Dess–Martin periodinane. Dess–Martin periodinane (510 mg, 1.20 mmol) was added to a solution of alcohol **207** (140 mg, 1.00 mmol) in CH_2Cl_2 (20 mL).

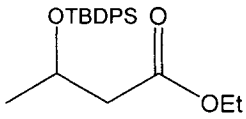
The mixture was stirred at rt overnight. The solution was washed with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. After the solvent was removed, flash column chromatography of the residue provided aldehyde **189** as a colorless liquid (R_f 0.32; 10% ethyl acetate/hexane, 120 mg, 83%). IR (neat, cm^{-1}): 1724. δ_H 9.72 (1 H, t, *J* 2.0, *CHO*), 3.92 (4 H, m, O*CH*$_2$*CH*$_2$O), 2.48 (2 H, dt, J_1 2.0, J_2 7.1, CH_2*CH*$_2$-CHO), 2.07 (2 H, t, *J* 7.1, *CH*$_2$$CH_2$-CHO), 1.34 (3 H, s, *CH*$_3$-C). δ_C 202.3 (*CHO*), 109.3 (O-*C*-O), 64.9 (O*CH*$_2$*CH*$_2$O), 38.6 (CH_2*CH*$_2$CHO), 32.0 (*CH*$_2$$CH_2$CHO), 24.3 (*CH*$_3$). GC-MS: 129 (69, M^+-CH_3), 116 (4), 99 (11), 87 (100), 85 (64), 84 (32), 73 (33), 71 (23), 57 (27). HRMS: Experimental, 144.0779 amu ($C_7H_{12}O_3$, Calculated 144.0786).



***N*-Methoxy-*N*-methyl-3-(2-methyl-[1,3]dioxolan-2-yl)propionamide (210)**

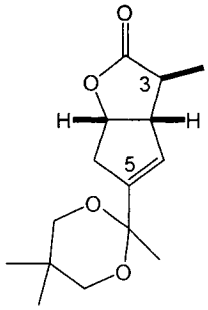
Isopropyl magnesium chloride (2 M in THF, 3.8 mL, 7.6 mmol) was added to a solution of ester **206** (512 mg, 2.72 mmol) and *N*,*O*-dimethylhydroxy-amine·HCl (42 mg, 4.4 mmol) in dry toluene (30 mL) dropwise at –10 °C over 2 h. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with saturated NH_4Cl solution (10 mL). The organic layer was separated, and the aqueous layer was re-extracted with toluene (10 mL × 2). The combined organic layers were washed with saturated $NaHCO_4$, dried over $MgSO_4$ and concentrated under vacuum. Flash column chromatography gave a pale yellow liquid **210** (R_f 0.30; 65% EtOAc/hexane, 510 mg, 91%). IR (neat, cm^{-1}): 1664. δ_H 3.96 (4 H, m, O*CH*$_2$*CH*$_2$O), 3.69 (3 H, s, O*CH*$_3$), 3.18 (3 H, s, N*CH*$_3$), 2.52 (2 H, t, *J* 8.0, CH_2-*CH*$_2$C=O), 2.02 (2 H, t, *J* 8.0, *CH*$_2$-CH_2C=O), 1.35 (3 H, s, *CH*$_3$-C). δ_C 174.4

(*C*=O), 109.5 (O-*C*-O), 64.7 (O*CH*$_2$*CH*$_2$O), 61.2, 33.4, 32.4, 26.6, 23.9. GC-MS: 204 (3, M+1), 188 (26, M^+-CH_3), 158 (2), 144 (21), 143 (97), 128 (2), 127 (7), 113 (12), 112 (58), 111 (6), 100 (24), 99 (100), 87 (93), 71 (67). HRMS: Experimental, 203.1157 amu ($C_9H_{17}NO_4$, Calculated 203.1158).



Ethyl 3-((*tert*-butyldiphenylsilyl)oxy)butanoate (222)

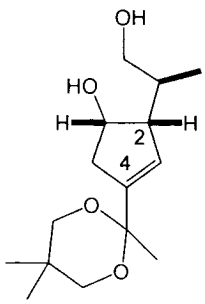
TBDPSCl (3.02 g, 11.0 mmol) was added to a solution of ethyl 3-hydroxybutanoate (*dl*-**221**) (1.32 g, 10.0 mmol) and imidazole (1.70 g, 25.0 mmol) in 5 mL of dry DMF under argon. The mixture was stirred under argon for 6 h. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with water (20 mL) and brine (20 mL) and dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to afford **222** as a colorless liquid (R_f 0.78; 10% EtOAc/hexane, 3.70 g, 100%). IR (neat, cm^{-1}): 1737. δ_H 7.69 (4 H, m, *Ph*), 7.37 (6 H, m, *Ph*), 4.32 (1 H, m, Si-O-*CH*), 4.05 (2 H, m, O*CH*$_2$CH$_3$), 2.54 (1 H, dd, J_1 6.9, J_2 14.4, *CH*$_2$COO), 2.38 (1 H, dd, J_1 5.8, J_2 14.4, *CH*$_2$COO), 1.19 (3 H, t, *J* 6.9, O-CH$_2$-*CH*$_3$), 1.11 (3 H, d, *J* 6.3, *CH*$_3$-CH), 1.04 (9 H, s, *^{t}Bu*). δ_C 171.5 (*C*=O), 136.02, 136.00, 134.5, 134.1, 129.8, 129.7, 127.7, 127.6, 67.1, 60.4, 44.9, 27.1, 23.8, 19.4, 14.3. GC-MS: 325 (5, M^+-OCH_2CH_3), 314 (24), 313 (92), 285 (6), 269 (6), 241 (6), 227 (82), 207 (8), 200 (22), 199 (100), 183 (41), 167 (28), 140 (8), 139 (81), 135 (29), 123 (15), 105 (24), 78 (15), 77 (51), 69 (18). HRMS: Experimental, 325.1624 amu (M^+-OCH_2CH_3 = $C_{20}H_{25}O_2Si$, Calculated 325.1624).



(3*R,3a*R**,6a*R**)-3,3a,6,6a-Tetrahydro-3-methyl-5-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopenta[*b*]furan-2-one (231)**

Ozone was introduced into a solution of **230** [41b,42a] (5.54 g, 33.3 mmol) in dichloromethane (200 mL) at –78 °C until a blue color persisted. Excess ozone was removed by bubbling nitrogen through the solution until the blue color disappeared. Dimethyl sulfide (27.2 mL, 350 mmol) was added. The mixture attained rt while stirring overnight. The solvent and excess dimethyl sulfide were evaporated under reduced pressure to give a yellow oil, which was immediately redissolved in benzene (350 mL). Camphorsulfonic acid (0.39 g, 1.7 mmol) was added, and the mixture was heated under reflux in a Dean–Stark apparatus for 24 h. 2,2-Dimethyl-1,3-propanediol was added, and the mixture was heated under reflux for an additional 24 h using a Dean–Stark apparatus. The cooled solution was washed with 5% aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography of the residue provided **231** as a pale yellow oil (R_f 0.72; 20% ethyl acetate/hexane, 4.12 g, 47% from **230** over three steps). δ_H 5.62 (1 H, s, *CH*=C), 5.18 (1 H, t, *J* 5.3, O*CH*), 3.36 (5 H, m, O*CH*$_2$C*CH*$_2$O and *CH*-CH=C), 2.65 (3 H, m, *CH*$_2$-C=CH and O=C-*CH*), 1.41 (3 H, s, CH=C-C-*CH*$_3$), 1.38 (3 H, d, *J* 7.7, CH*CH*$_3$), 1.14 (3 H, s, CH_3-C-*CH*$_3$), 0.69 (3 H, s, *CH*$_3$–C-CH_3). δ_C 179.8 (*C*=O), 143.0 (*C*=CH), 128.8 (C=*CH*), 97.9 (O-*C*-O), 81.5 (CH_3O*CH*), 71.7 (O*CH*$_2$CCH_2O), 71.6

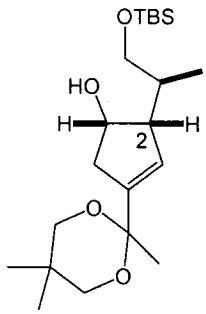
($OCH_2C\mathit{CH_2}O$), 53.9 (C=CH-*CH*), 40.2 (O=C-*CH*), 39.0 (*CH_2*-C=CH), 29.7 ($OCH_2\mathit{C}CH_2O$), 27.2 (CH=C-C-*CH_3*), 22.6 (*CH_3*–C-CH_3), 22.0 (CH_3-C-*CH_3*), 17.3 ($CH\mathit{CH_3}$). GC-MS: 251 (53, M^+-CH_3), 181 (26), 180 (2), 166 (7), 165 (68), 137 (8), 135 (28), 129 (87), 121 (9), 109 (13), 93 (39), 91 (18), 81 (13), 77 (19), 69 (100), 56 (59). HRMS: Experimental, 266.1518 amu ($C_{15}H_{22}O_4$, Calculated 266.1517).



(1*R,2*R**,6*R**)-2-(2-Hydroxy-1-methylethyl)-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-3-en-1-ol (237)**

$LiAlH_4$ (1.36 g, 34.1 mmol) was added to a solution of **231** (3.63 g, 13.7 mmol) in dry THF (100 mL) at 0 °C. The mixture was allowed to warm to rt, and it was stirred for 15 h. The reaction was quenched with 0.5 mL of water, and 15% aqueous NaOH (0.5 mL) was added followed by 1.5 mL of water. The white solid was removed by filtration and washed with ether (20 mL × 3). The combined organic solutions were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to afford **237** (R_f 0.11 50% EtOAc/hexane, 3.10 g, 84%) as a colorless oil. IR (neat, cm^{-1}): 3380, 1658. δ_H 5.71 (1 H, s, C=*CH*), 4.54 (1 H, s, *CH*OH), 4.10 (2 H, br s, *OH*), 3.62 (1 H, d, *J* 10.4, HO*CH_2*), 3.56 (2 H, d, *J* 11.0, OCH_2), 3.50 (1 H, m, HO*CH_2*), 3.35 (2 H, d, *J* 11.0, OCH_2), 2.58 (1 H, dd, J_1 2.5, J_2 17.0, *CH_2*CHOH), 2.52 (1 H, s, *CH*), 2.32 (1 H, d, *J*

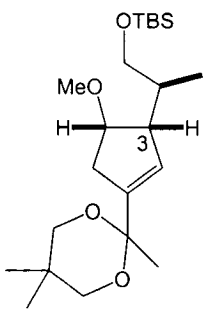
17.0), 2.05 (1 H, s, *CH*), 1.44 (3 H, s, CH=C-C-*CH*$_3$), 1.16 (3 H, s, *CH*$_3$–C-CH$_3$), 1.02 (3 H, d, *J* 6.6, CH*CH*$_3$), 0.72 (3 H, s, CH$_3$-C-*CH*$_3$). δ_C 141.4 (*C*=CH), 129.3 (C=*C*H), 98.6 (O-*C*-O), 72.5 (*C*HOH), 71.8 (*C*H$_2$O), 71.6 (*C*H$_2$O), 68.0 (*C*H$_2$OH), 56.5 (*C*H), 41.4 (*C*H$_2$), 34.2 (*C*HCH$_3$), 29.7 (*C*(CH$_3$)$_2$), 27.1 (CH=C-C-*CH*$_3$), 22.7 (*CH*$_3$–C-CH$_3$), 22.1 (CH$_3$-C-*CH*$_3$), 16.5 (CH*CH*$_3$). HRMS: Experimental, 270.1824 amu ($C_{15}H_{26}O_4$, Calculated 270.1831).



(1*R,2*R**,6*R**)-2-[2-((*tert*-Butyldimethylsilyl)oxy)-1-methylethyl]-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-3-en-1-ol (238)**

TBSCl (744 mg, 4.79 mmol) in CH_2Cl_2 (20 mL) was added to a mixture of diol **237** (1.29 g, 4.79 mmol) and imidazole (0.977 g, 14.4 mmol) in CH_2Cl_2 (30 mL) dropwise at rt over 3 h. The mixture was then stirred at rt for 15 h. After water (50 mL) was added, the organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to afford **238** as pale yellow oil (R_f 0.49; 20% EtOAc/hexane, 1.66 g, 90%). IR (neat, cm^{-1}): 3388, 1659. δ_H 5.70 (1 H, s, C=*CH*), 4.49 (1 H, s, *CH*OH), 3.67 (1 H, d, *J* 2.4, *OH*), 3.63 (1 H, dd, J_1 3.0, J_2 10.2, *CH*$_2$OSi), 3.56 (2 H, d, *J* 11.4, O*CH*$_2$), 3.44 (1 H, apparent t, *J* 10.2, *CH*$_2$OSi), 3.33 (2 H, d, *J* 11.4, O*CH*$_2$), 2.57 (1 H, dt, J_1 2.7, J_2 17.0, *CH*$_2$CHOH), 2.43 (1 H, dd, J_1 4.9, J_2

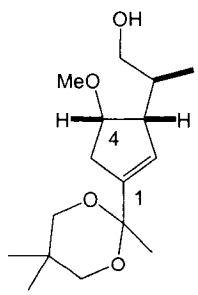
8.8, *CH*-CHOH), 2.34 (1 H, d, *J* 17.0, *CH*$_2$CHOH), 2.09 (1 H, m, *CH*CH$_3$), 1.43 (3 H, s, CH=C-C-*CH*$_3$), 1.16 (3 H, s, *CH*$_3$–C-CH$_3$), 0.99 (3 H, d, *J* 6.6, CH*CH*$_3$), 0.92 (9 H, s, Si-C(*CH*$_3$)$_3$), 0.70 (3 H, s, CH$_3$-C-*CH*$_3$), 0.10 (3 H, s, Si*CH*$_3$), 0.09 (3 H, s, Si*CH*$_3$). δ_C 141.7 (*C*=CH), 129.2 (C=*CH*), 98.8 (O-*C*-O), 72.3 (*CH*OH), 72.0 (*C*H$_2$O), 71.8 (*C*H$_2$O), 69.9 (*CH*$_2$OTBS), 58.0 (*CH*-CHOH), 41.2 (*CH*$_2$CHOH), 34.4 (*C*HCH$_3$), 31.1 (*C*(CH$_3$)$_2$), 29.9 (*C*(CH$_3$)$_2$), 27.6 (CH=C-C-*CH*$_3$), 26.1 (C*(CH*$_3$*)*$_3$), 22.9 (*CH*$_3$–C-CH$_3$), 22.3 (CH$_3$-C-*CH*$_3$), 18.4 (*C*(CH$_3$)$_3$), 16.6 (CH*CH*$_3$), –5.5 (Si-*CH*$_3$). GC-MS: 385 (18, M+1), 368 (28), 367 (100, M+1-CH$_3$), 211 (2), 151 (2), 149 (3), 121 (4), 105 (4), 93 (8), 91 (12), 77 (17), 75 (100), 73 (31), 65 (7), 57 (69). HRMS: Experimental, 384.2660 amu ($C_{21}H_{40}O_4Si$, Calculated 384.2696).



(3*R,4*R**,6*R**)-3-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-4-methoxy-1-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-1-ene (240)**

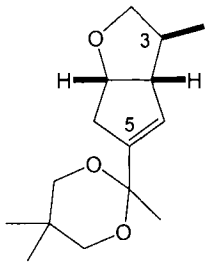
NaH (60% in mineral oil, 158 mg, 3.95 mmol) was suspended in dry THF (10 mL) for 10 min, and the solid was left to sink to the bottom of the flask after the stirrer was turned off. The solvent layer was then removed by pipette. More dry THF (10 mL) was added, and this suspension was cooled to 0 °C. Compound **238** (756 mg, 1.97 mmol) in THF (10 mL) was added dropwise at 0 °C, followed by HMPA (0.70 mL, 3.9 mmol). Finally, iodomethane (838 mg, 5.91 mmol) was added. The solution was left to

warm to rt while stirring overnight (15 h). The reaction was quenched with water (2 mL), and much of the solvent was removed under vacuum. The residue was mixed with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with water (10 mL × 2) and brine (10 mL). The solvent was removed under vacuum. The residue was subjected to flash column chromatography to give **240** (R_f 0.85; 20% ethyl acetate/hexane, 654 mg, 83%) as a pale yellow oil, and 120 mg (16%) of **238** was recovered. For **240**, δ_H 5.70 (1 H, s, C=*CH*), 4.03 (1 H, m, *CH*OCH$_3$), 3.59 (1 H, d, *J* 11.0, O*CH*$_2$), 3.44-3.55 (3 H, m, O*CH*$_2$), 3.34 (2 H, apparent s, O*CH*$_2$), 3.32 (3 H, s, O*CH*$_3$), 2.88 (1 H, t, *J* 6.1, C=CH-*CH*), 2.42 (1 H, dd, J_1 6.7, J_2 16.3, *CH*$_2$-CH-OCH$_3$), 2.32 (1 H, dd, J_1 5.0, J_2 16.3, *CH*$_2$-CH-OCH$_3$), 2.02 (1 H, m, *CH*CH$_3$), 1.42 (3 H, s, CH=C-C-*CH*$_3$), 1.18 (3 H, s, *CH*$_3$–C-CH$_3$), 0.94 (3 H, d, *J* 6.3, CH*CH*$_3$), 0.90 (9 H, s, Si-C(*CH*$_3$)$_3$), 0.70 (3 H, s, CH$_3$-C-*CH*$_3$), 0.05 (6 H, s, Si*CH*$_3$). δ_C 141.1 (*C*=CH), 129.7 (C=*CH*), 98.9 (O-*C*-O), 82.4 (*CH*-OCH$_3$), 71.93 (O*CH*$_2$), 71.88 (O*CH*$_2$), 67.5 (*CH*$_2$OTBS), 57.4(O*CH*$_3$), 49.8 (*CH*-CHOH), 37.7 (CH=C-*CH*$_2$), 34.7 (*CH*-CH$_2$-OH), 29.9 (OCH$_2$-*C*-CH$_2$O), 27.8 (CH=C-C-*CH*$_3$), 26.2 (Si-C*(CH*$_3$*)*$_3$), 22.9 (*CH*$_3$-C-CH$_3$), 22.3 (CH$_3$-C-*CH*$_3$), 18.6 (Si-*C*(CH$_3$)$_3$), 14.9 (*CH*$_3$-CH-CH$_2$OH), –4.9 (Si*CH*$_3$), –5.1 (Si*CH*$_3$).



(3*R,4*R**,6*R**)-3-(2-Hydroxy-1-methylethyl)- 4-Methoxy-1-(2,5,5-trimethyl-[1,3]-dioxan-2-yl)cyclopent-1-ene (241)**

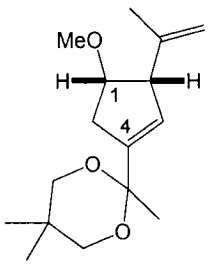
Solid TBAF (1.86 g, 7.10 mmol) was added to a solution of **240** (942 mg, 2.37 mmol) in THF (20 mL) at rt. The mixture was stirred at rt for 15 h before water (5 mL) was added to the solution. The solvent was removed under vacuum, and the residue was extracted with ethyl acetate (10 mL × 3). The combined organic solutions were washed with water (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to yield a pale yellow oil, **241** (R_f 0.10; 20% ethyl acetate/hexane, 670 mg, 100%). IR (neat, cm^{-1}): 3431, 1646. δ_H 5.72 (1 H, s, C=*CH*), 4.11 (1 H, m, CH_3OCH), 3.57 (1 H, d, *J* 11.0, OCH_2), 3.54 (2 H, apparent s, OCH_2), 3.50 (1 H, d, *J* 11.0, OCH_2), 3.34 (3 H, s, OCH_3), 3.32 (2 H, m, OCH_2), 2.84 (1 H, m, C=CH-*CH*), 2.67 (1 H, br s, OH), 2.45 (1 H, dd, J_1 6.0, J_2 16.5, CH_2-C=CH), 2.39 (1 H, d, *J* 16.5, CH_2-C=CH), 2.08 (1 H, m, $CHCH_3$), 1.42 (3 H, s, CH=C-C-CH_3), 1.18 (3 H, s, CH_3-C-CH_3), 1.00 (3 H, d, *J* 6.8, CH-CH_3), 0.70 (3 H, s, CH_3-C-CH_3). δ_C 141.0 (*C* =CH), 129.6 (C=*CH*), 98.5 (O-*C*-O), 82.1 (*CH*-OCH_3), 71.7 (OCH_2-C-CH_2O), 71.6 (OCH_2-C-CH_2O), 67.4 (CH_2OH), 56.8 (OCH_3), 52.0 (*CH*-CH=C), 36.9 (CH=C-CH_2), 34.9 (*CH*-CH_2-OH), 29.7 (OCH_2-*C*-CH_2O), 27.4 (CH=C-C-CH_3), 22.7 (CH_3-C-CH_3), 22.1(CH_3-C-CH_3), 15.4 (CH_3-CH-CH_2OH). GC-MS: 285 (M+1), 270 (3), 269 (14, M-CH_3), 237 (9), 181(14), 167 (4), 151 (4), 149 (13), 133 (5), 129 (26), 123 (8), 99 (12), 95 (16), 91 (18), 77 (17), 71 (23), 69 (100). HRMS: Experimental, 284.1979 amu ($C_{16}H_{28}O_4$, Calculated 284.1988).



(3*R,3a*R**,6a*R**)-3,3a,6,6a-Tetrahydro-3-methyl-5-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-2*H*-cyclopenta[*b*]furan (248)**

Tosyl chloride (32 mg, 0.17 mmol) was added to the solution of **241** (40 mg, 0.14 mmol) in pyridine (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and at rt overnight. The mixture was diluted with ether (20 mL), washed with water (10 mL × 3), saturated $NaHCO_3$ (10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was dissolved in dry toluene (10 mL). DBU (106 mg, 0.70 mmol) was added to the toluene solution and the solution was refluxed for 4 h. The mixture was then cooled and poured into ether (20 mL) at 0 °C. The mixture was washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to yield **248** (R_f 0.64; 20% ethyl acetate/hexane, 26 mg, 73%) as a colorless liquid. IR (neat, cm^{-1}): 1646. δ_H 5.60 (1 H, s, C=*CH*), 4.73 (1 H, t, *J* 5.9, CH_3OCH), 3.79 (1 H, dd, J_1 5.3, J_2 8.1, OCH_2CHCH_3), 3.52 (1 H, d, *J* 10.5, OCH_2CCH_2O), 3.48 (1 H, d, *J* 10.5, OCH_2CCH_2O), 3.43 (1 H, dd, J_1 3.5, J_2 8.1, $OCH_2CH\text{-}CH_3$), 3.34 (2 H, d, *J* 10.7, OCH_2CCH_2O), 2.99 (1 H, d, *J* 5.7, C=CH-*CH*), 2.57 (1 H, dd, J_1 5.5, J_2 17.7, CH_2-C=CH), 2.39 (1 H, d, *J* 17.7, CH_2-C=CH), 2.10 (1 H, m, *CH*-CH_3), 1.41 (3 H, s, CH_3-C-C=CH), 1.17 (3 H, s, CH_3-C-CH_3), 1.08 (3 H, d, *J* 7.2, CH-CH_3), 0.69 (3 H, s, CH_3-C-CH_3). δ_C 142.6 (*C*=CH), 130.1 (C=*CH*), 98.3 (O-*C*-O), 81.1 (*CH*-OCH_3), 73.8 (OCH_2-CH-CH_3), 71.8 (OCH_2-C-CH_2O),

71.7 (OCH_2-C-CH_2O), 58.5 (CH-CH-CH_3), 40.4 (CH_2-C=CH), 39.2 (CH-CH_3), 29.7 (OCH_2CCH_2O), 27.4 (CH=C-C-CH_3), 22.6 (CH_3-C-CH_3), 22.1 (CH_3-C-CH_3), 18.7 (O-CH_2-CH-CH_3). GC-MS: 252 (3, M^+), 238 (32), 237 (100), 207 (2), 195 (3), 193 (4), 179 (4), 167 (28), 151 (69), 149 (12), 137 (26), 129 (87), 121 (16), 109 (26), 107 (20), 95 (45), 93 (55), 91 (27), 79 (24), 77 (29), 69 (82). HRMS: Experimental, 252.1729 amu ($C_{15}H_{24}O_3$, Calculated 252.1725).



(1*R,2S*)-1-Methoxy-2-isoprenyl-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-3-ene (253)**

A) DEHYDRATION

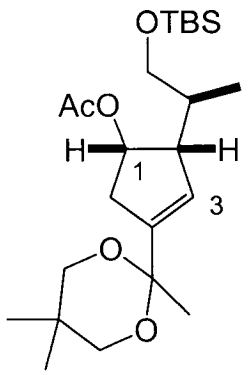
Tosyl chloride (74 mg, 0.39 mmol) was added to a solution of **241** (92 mg, 0.32 mmol) in pyridine (3 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and at rt overnight. The mixture was diluted with ether (20 mL), washed with water (10 mL × 3), saturated $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was used immediately for the next step.

Sodium borohydride (25 mg, 0.64 mmol) was added to a well-stirred suspension of *o*-nitrophenylselenylcyanate (147 mg, 0.64 mmol) in absolute EtOH (10 mL) under argon at 0 °C. After 1 h at 0 °C and 1 h at rt, a solution of the tosylate in EtOH (3 mL) was added to the mixture at 0 °C. After 72 h at 0 °C, THF (5 mL) was added, followed by aqueous 30% H_2O_2 (0.15 mL). After another 48 h at 0 °C, the mixture was poured

into saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to yield **248** (R_f 0.62; 20% ethyl acetate/hexane, 42 mg, 52%) as a colorless liquid and **253** (R_f 0.48; 20% ethyl acetate/ hexane, 12 mg, 14%) as a colorless liquid.

B) BARTON–MCCOMBIE REACTION

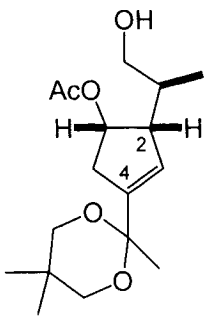
AIBN (42 mg, 0.25 mmol) and tributyltin hydride (751 mg, 0.70 mL, 2.58 mmol) was added to a solution of **283** (480 mg, 1.29 mmol) in deoxygenated benzene (25 mL) at rt. The mixture was refluxed over night before it was cooled to rt. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to yield **253** (R_f 0.46; 20% ethyl acetate/hexane, 329 mg, 96%) as a colorless liquid. IR (neat, cm^{-1}): 1616. δ_H 5.66 (1 H, d, *J* 2.0, C=*CH*), 4.88 (1 H, s, C=*CH*$_2$), 4.83 (1 H, s, C=*CH*$_2$), 4.16 (1 H, m, CH_3O*CH*), 3.60 (1 H, d, *J* 11.2, O*CH*$_2$CCH_2O), 3.49-3.54 (2 H, m, O*CH*$_2$CCH_2O and C=CH-*CH*-C=CH_2), 3.33-3.38 (2 H, m, OCH_2C*CH*$_2$O), 3.34 (3 H, s, O*CH*$_3$), 2.51 (1 H, ddd, J_1 16.5, J_2 7.1, J_3 1.3, *CH*$_2$C=CH), 2.38 (1 H, m, *CH*$_2$C=CH), 1.81 (3 H, s, *CH*$_3$-C=CH_2), 1.44 (3 H, s, CH=C-C*CH*$_3$), 1.18 (3 H, s, *CH*$_3$-C-CH_3), 0.70 (3 H, s, CH_3-C-*CH*$_3$). δ_C 144.7 (CH_2=*C*), 142.1 (*C*=CH), 130.1 (C=*CH*), 112.6 (C=*CH*$_2$), 98.7 (O-*C*-O), 82.5 (*CH*OCH_3), 72.0 (O*CH*$_2$-C-CH_2O), 71.9 (OCH_2C*CH*$_2$O), 57.9 (O*CH*$_3$), 56.0 (*CH*-CH=C), 37.5 (*CH*$_2$C=CH), 29.9 (*CH*$_3$C-C=CH), 22.9 (OCH_2*C*CH_2), 27.7 (CH_3-*C*-*CH*$_3$), 22.3 (*CH*$_3$-*C*-CH_3), 22.0 (*CH*$_3$-C=CH_2). GC-MS: 210 (6, M^+-C_4H_8), 195 (4), 165 (2), 139 (3), 129 (16), 126 (3), 111 (48), 110 (15), 95 (14), 83 (78), 81 (8), 69 (57), 55 (100). HRMS: Experimental, 266.1876 amu ($C_{16}H_{26}O_3$, Calculated 266.1882).



(1*R,2*R**,6*R**)-2-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-3-en-1-ol, acetate ester (254)**

Acetic anhydride (1 mL) was added to the solution of **238** (57 mg, 0.15 mmol) and a catalytic amount of DMAP (5 mg) in triethylamine (1 mL), and the mixture was stirred overnight at rt. The solvent was then removed under vacuum, and the residue was subjected to flash column chromatography to yield **254** (R_f 0.74; 20% ethyl acetate/hexane, 58 mg, 92%) as a colorless liquid. IR (neat, cm^{-1}): 1737, 1620. δ_H 5.72 (1 H, d, *J* 1.4, C=*CH*), 5.47 (1 H, m, *CH*-OAc), 3.30-3.60 (6 H, m, O*CH*$_2$O*CH*$_2$O and *CH*$_2$OTBS), 3.60 (1 H, d, *J* 11.2, O*CH*$_2$CCH$_2$O), 3.49-3.54 (2 H, m, O*CH*$_2$CCH$_2$O and C=CH-*CH*-C=CH$_2$), 3.00 (1 H, t, *J* 5.9, *CH*CHCH$_3$), 2.65 (1 H, dd, J_1 6.7, J_2 16.8, *CH*$_2$C=CH), 2.30 (1 H, dd, J_1 3.8, J_2 16.8, *CH*$_2$C=CH), 2.05 (3 H, s, *CH*$_3$-C=O), 1.90 (1 H, m, *CH*-CH$_3$), 1.42 (3 H, s, CH=C-C-*CH*$_3$), 1.18 (*CH*$_3$-C-CH$_3$), 0.98 (3 H, d, *J* 6.7, CH-*CH*$_3$), 0.90 (9 H, s, TBS), 0.70 (3 H, s, CH$_3$-C-*CH*$_3$), 0.044 (3 H, s, TBS), 0.041 (3 H, s, TBS). δ_C 170.9 (C=O), 141.5 (CH=*C*), 129.2 (C=*CH*), 98.6 (O-*C*-O), 75.6 (*CH*-OAc), 72.0 (O*CH*$_2$CCH$_2$O), 71.9 (OCH$_2$C*CH*$_2$O), 67.4 (*CH*$_2$OTBS), 49.6 (C=CH-*CH*), 39.4 (*CH*$_2$C=CH), 38.4 (*CH*-CH$_3$), 29.9 (CH$_3$-*C*-CH$_3$), 27.6 (*CH*$_3$C-C=CH), 26.2 (methyl in *t*-butyl), 22.9 (CH$_3$-*C*-*CH*$_3$), 22.3 (*CH*$_3$-*C*-CH$_3$), 21.7 (CH-*CH*$_3$), 21.4 (*CH*$_3$-C=O), 18.6 (*C*

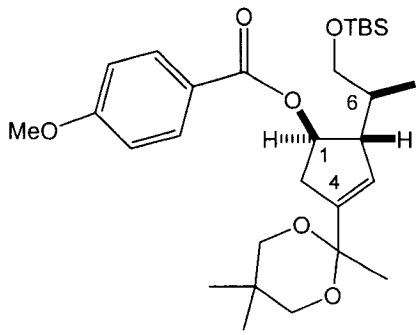
in *t*-butyl), -5.17 (Si-CH_3), -5.2(Si-CH_3). HRMS: Experimental, 426.2791 amu ($C_{23}H_{42}O_5Si$, Calculated 426.2802).



(1*R,2*R**,6*R**)-2-(2-Hydroxy-1-methylethyl)-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-3-en-1-ol, acetate ester (255)**

TBAF (2.47 g, 9.44 mmol) was added to the solution of **254** (0.804 g, 1.88 mmol) in THF (50 mL) at rt, and the mixture was stirred overnight. Water (30 mL) was added, and THF was removed under vacuum. The residue was extracted with ethyl acetate (10 mL × 3). The combined organic solutions were washed with water (20 mL) and brine (20 mL), and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum, and the residue was subjected to flash column chromatography to yield **255** (R_f 0.10; 20% ethyl acetate/hexane, 482 mg, 82%) as a colorless liquid. IR (neat, cm^{-1}): 1737, 1617. δ_H 5.71 (1 H, s, C=*CH*), 4.51 (1 H, dt, J_1 1.7, J_2 5.5, *CH*OAc), 4.19 (1 H, dd, J_1 5.0, J_2 10.6, CH_2OH), 3.95 (1 H, dd, J_1 6.5, J_2 10.8, CH_2OH), 3.53 (1 H, t, *J* 11.2, OCH_2CCH_2O), 3.36 (2 H, d, *J* 11.1, OCH_2CCH_2O), 2.54-2.63 (2 H, m, CH_2C=CH and *CH*-CH-CH_3), 2.31 (1 H, m, CH_2C=CH), 2.17 (1 H, m, *CH*-CH_3), 2.08 (3 H, s, CH_3-C=O), 1.43 (3 H, s, CH_3-C-C=CH_2), 1.17 (3 H, s, CH_3-C-CH_3), 1.10 (3 H, d, *J* 6.5, CH_3CH), 0.72 (3 H, s, CH_3-C-CH_3). δ_C 171.3 (*C*=O), 142.2 (*C*=CH), 128.1 (C=*CH*), 98.5 (O-*C*-O), 72.7 (*CH*-OAc), 71.8 (OCH_2CCH_2O), 71.7 (OCH_2CCH_2O), 69.1

(CH_2OH), 53.5 (CHCHCH$_3$), 42.0 (CH_2C=CH), 31.3 (CHCH$_3$), 29.8 (O-C-O), 27.2 (CH-C-C-CH$_3$), 22.7 (CH$_3$-C-CH_3), 22.1 (CH_3-C-CH$_3$), 21.0 (CH_3-C=O), 16.3 (CH-CH_3). HRMS: Experimental, 297.1734 amu (M^+-CH$_3$ = $C_{16}H_{25}O_5$, Calculated 297.1702).

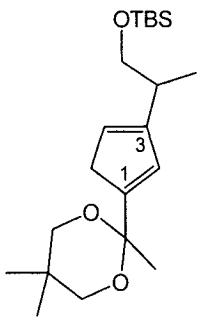


(1*R,2*S**,6*S**)-2-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-3-en-1-ol, 4-methoxybenzoyl ester (258)**

A solution of **238** (115 mg, 0.30 mmol), triphenylphosphine (315 mg, 1.20 mmol), and 4-methoxybenzoic acid (182 mg, 1.20 mmol) in THF (10 mL) was cooled to –10 °C. Diisopropyl azodicarboxylate (DIAD, 243 mg, 1.20 mmol) was then added dropwise. The resulting mixture was then allowed to warm to rt, and it was stirred for 12 h. The reaction was quenched with $NaHCO_3$ solution (20 mL), extracted into ethyl acetate (20 mL × 3), and dried over Na_2SO_4. After removal of the solvent under vacuum, the residue was subjected to flash column chromatography to yield compound **258** as a white solid (R_f 0.75; 20% ethyl acetate/hexane, 30 mg, 19%) and compound **259** (mixture of double bond isomers) (R_f 0.90; 20% ethyl acetate/hexane, 60 mg, 55%) as a colorless liquid.

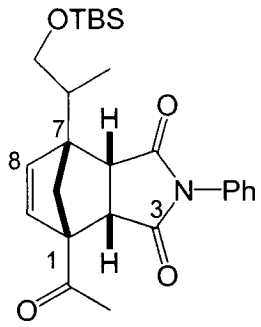
For **258**: IR (cm^{-1}, neat) 1718, 1607, 1511, 1471. δ_H 7.99 (2 H, d, *J* 9.3, phenyl), 6.91 (2 H, d, *J* 9.4, phenyl), 5.74 (1 H, , d, *J* 1.5, C=CH), 5.36 (1 H, m, Ar-COO-CH), 3.87 (3 H, s, Ph-OCH_3), 3.48-3.63 (4 H, m, OCH_2CCH_2O and TBSOCH_2), 3.31-3.42 (2

H, m, OCH_2CCH_2O), 3.07 (1 H, br s, C=CH-*CH*), 2.87 (1 H, dd, J_1 6.7, J_2 17.6, CH_2-C=CH), 2.36 (1 H, br d, J 17.5, CH_2-C=CH), 1.93 (1 H, m, *CH*-CH_3), 1.46 (3 H, s, CH=C-C-CH_3), 1.20 (3 H, s, CH_3-C-CH_3), 0.92 (3 H, d, J 6.9, CH-CH_3), 0.89 (9 H, s, $C(CH_3)_3$), 0.72 (3 H, s, CH_3-C-CH_3), 0.048 (3 H, s, Si-CH_3), 0.038 (3 H, s, Si-CH_3). δ_C 166.3 (*C*=O), 163.6 (phenyl), 141.8 (*C*=CH), 131.8 (*CH*, phenyl), 129.0 (C=*CH*), 123.2 (phenyl), 113.8 (*CH*, phenyl), 98.4 (O-*C*-O), 78.6 (*CH*-O-C=O), 72.07 (OCH_2CCH_2O), 72.03 (OCH_2CCH_2O), 67.0 (CH_2-OTBS), 55.7 (OCH_3), 54.6 (C=CH-*CH*), 39.4 (CH_2-C=CH), 38.4 (*CH*-CH_3), 29.9 (CH_3-*C*-CH_3), 27.8 (CH=C-C-CH_3), 26.2 ($C(CH_3)_3$), 22.9 (CH_3-C-CH_3), 22.4 (CH_3-C-CH_3), 18.6 ($C(CH_3)_3$),13.8 (CH-CH_3), -5.3 (Si-CH_3), -5.4 (Si-CH_3). HRMS: Experimental, 518.3068 amu ($C_{29}H_{46}O_6Si$, Calculated 518.3064).



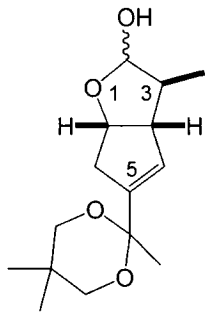
3-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-1-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-1,3-cyclopentadiene (mixture of double bond isomers) (259)

IR (neat, cm^{-1}): 1614. δ_H 6.45 (s), 6.37 (s), 6.31 (s), 6.15 (d, J 1.2), 6.12 (s), 6.00 (s), 3.61-3.68 (m), 3.50-3.60 (m), 3.33-3.39 (m), 2.64-2.76 (m), 2.85-3.10 (m), 1.51 (s), 1.48 (s), 1.19 (s), 1.48 (s), 1.19 (d, J 6.2), 1.15 (d, J 6.1), 0.88 (br s), 0.69 (s), 0.66 (s), 0.02 (br s). δ_C 153.3, 152.1, 149.1, 146.8, 145.2, 132.4, 130.8, 127.4, 126.1, 125.6, 125.5, 99.3, 98.7, 72.1, 72.0, 68.8, 68.1, 42.3, 41.7, 40.5, 38.2, 37.4, 30.1, 30.0, 29.3, 26.1, 23.1, 22.9, 22.2, 21.5, 18.5, 17.3, 17.2, 16.5, -5.1, -5.2.



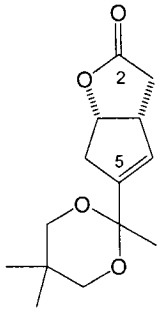
1-Acetyl-7-[2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-4-phenyl-4-azatricyclo-[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (261)

N-Phenylmaleimide (**260**) solution (28 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **259** (60 mg, 0.16 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 3 days. After removal of the solvent under vacuum, the residue was subjected to flash column chromatography to yield compound **261** (R_f 0.22; 20% ethyl acetate/hexane, 25 mg, 31%) as white solid. IR (cm^{-1}, neat): 1775, 1714, 1598, 1500, 1470. δ_H 7.42 (2 H, t, *J* 7.0, *meta phenyl*), 7.35 (1 H, t, *J* 7.0, *para phenyl*), 7.14 (2 H, d, *J* 7.6, *ortho phenyl*), 6.37 (2 H, d, *J* 4.5, *CH*=*CH*), 3.87 (1 H, d, *J* 7.8, *CH*-C=O), 3.72 (1 H, dd, J_1 4.7, J_2 10.2, CH_2-OTBS), 3.67 (1 H, dd, J_1 14.7, J_2 4.7, CH_2-OTBS), 3.58 (1 H, d, *J* 7.8, *CH*-C=O), 2.53 (1 H, br d, *J* 6.1, *CH*-CH_3), 2.42 (3 H, s, CH_3-C=O), 1.91 (1 H, d, *J* 8.8, C-CH_2-C), 1.87 (1 H, d, *J* 8.5, C-CH_2-C), 1.15 (3 H, d, *J* 6.7, CH_3), 0.89 (9 H, s, *tert*-butyl), 0.04 (6 H, CH_3-Si-CH_3). δ_C 206.4 (CH_3-*C*=*O*), 175.7 (*O*=*C*-N), 175.3 (N-*C*=*O*), 139.8 (*CH*=*CH*), 132.5 (*CH*=*CH*), 131.9 (*C*-N, phenyl), 129.2 (*CH, meta*, phenyl), 128.8 (*CH, para*, phenyl), 126.7 (*CH*, *ortho*, phenyl), 67.5 (*C*-C(O)-CH_3), 66.3 (C-CH_2-C), 62.6 (*C*-CH-CH_3), 56.3 (C-CH_2-C), 49.6 (*CH*-C(O)-N), 48.1 (*CH*-C(O)-N), 35.3 (*CH*-CH_3), 28.8 (O=C-CH_3), 26.1 (C$(CH_3)_3$), 18.4 (*C*$(CH_3)_3$), 13.6 (CH-CH_3), -5.2 (CH_3-Si), -5.3 (Si-CH_3). MS: 454 (M^++1).



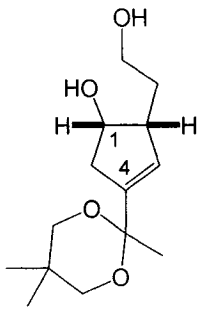
(3*R,3a*R**,6a*R**)-3,3a,6,6a-Tetrahydro-3-methyl-5-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopenta[*b*]furan-2-ol (mixture of epimers at C-2) (265)**

DibalH (1.0 M in THF, 2.0 mmol, 2.0 mL) was added to the solution of **231** (231 mg, 0.868 mmol) in CH_2Cl_2 (5 mL) at –78°C dropwise. The reaction was monitored by TLC. When the reaction was complete, it was quenched with methanol (20 mL) at –78°C. After removal of the solvent under vacuum, the residue was subjected to flash column chromatography to yield an inseparable mixture of epimers at C-2 **265** (R_f 0.72; 50% ethyl acetate/hexane, 192 mg, 82%, diastereomeric ratio, 2:1 from ^{1}H NMR) as a colorless liquid. δ_H 5.75 (s, C=*CH*), 5.72 (s, C=*CH*), 5.07 (d, *J* 6.4, *CH*OH), 4.95 (t, *J* 6.8, O*CH*), 4.91 (t, *J* 5.6, O*CH*), 3.63 (d, *J* 11.2, O*CH*$_2$C*CH*$_2$O), 3.53 (d, *J* 10.7, O*CH*$_2$C*CH*$_2$O), 3.49 (d, *J* 4.2), 3.35 (d, *J* 10.9), 3.31 (d, *J* 2.3), 3.04 (d, *J* 4.7), 2.97 (d, *J* 3.5), 2.74 (d, *J* 6.7, CH*OH*), 2.54-2.68 (m), 2.27 (q, *J* 7.2), 1.92-1.99 (m), 1.42 (s, *CH*$_3$), 1.16 (s, *CH*$_3$), 1.13 (d, *J* 7.3), 1.05 (d, *J* 6.9, CH-*CH*$_3$), 0.71 (s), 0.69 (s, *CH*$_3$). δ_C 142.7, 141.4, 131.4, 130.4, 105.3, 100.4, 98.3, 82.7, 80.8, 71.9, 71.8, 57.2, 56.5, 45.9, 45.0, 41.5, 39.3, 29.9, 27.4, 27.3, 22.8, 22.3, 22.2, 18.4. HRMS: Experimental, 268.1683 amu ($C_{15}H_{24}O_4$, Calculated 268.1675).



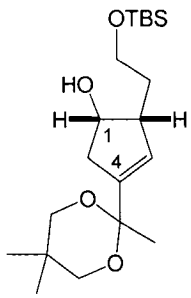
(3a*R,6a*R**)-3,3a,6,6a-Tetrahydro-5-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopenta-[*b*]furan-2-one (278)**

A procedure very similar to that for compound **231** was applied to make **278**; quantities: **146** (5.82 g, 38.3 mmol), CH_2Cl_2 (200 mL), Me_2S (29.3 mL, 24.8 g, 400 mmol); then benzene (500 mL), CSA (0.50 g), and 2,2-dimethylpropane-1,3-diol (7.97 g, 76.6 mmol). Flash column chromatography provided **278** (R_f 0.38; 50% ethyl acetate/ hexane, 4.67 g, 48% from **146**) as a colorless oil. IR (cm^{-1}, neat): 1736, 1641. δ_H 5.60 (1 H, s, C=*CH*), 5.15 (1 H, t, *J* 5.5, COO*CH*), 3.61(1 H, m, *CH*CH_2COO), 3.47 (1 H, d, *J* 11.0, O*CH*$_2$C*CH*$_2$O), 3.43 (1 H, d, *J* 11.0, O*CH*$_2$C*CH*$_2$O), 3.37 (2 H, d, *J* 11.3 O*CH*$_2$C*CH*$_2$O), 2.79 (1 H, dd, J_1 9.4, J_2 18.1, *CH*$_2$COO), 2.72 (1 H, dm, *J* 18.3, *CH*$_2$C=CH), 2.66 (1 H, d, *J* 18.3, *CH*$_2$C=CH), 2.48 (1 H, d, *J* 17.9, *CH*$_2$COO), 1.43 (3 H, s, C=C-C-*CH*$_3$), 1.15 (3 H, s, *CH*$_3$), 0.71 (3 H, s, *CH*$_3$). δ_C 176.5 (O=*C*-O), 143.6 (*C*=CH), 129.1 (C=*CH*), 97.9 (CH=C-*C*-CH_3), 83.4 (O=C-O-*CH*), 71.9 (O*CH*$_2$CCH_2O), 71.8 (OCH_2C*CH*$_2$O), 45.9 (*CH*-CH_2-C=O), 39.3 (*CH*$_2$-CH-O-C=O), 33.6 (*CH*$_2$-C=O), 29.8 (CH_3-*C*-CH_3), 27.2 (*CH*$_3$-C-C=CH), 22.7 (*CH*$_3$-C-CH_3), 22.2 (CH_3-C-*CH*$_3$). GC-MS: 237 (27, M^+-CH_3), 167 (36), 151 (81), 129 (100), 121 (29), 107 (17), 95 (32), 91 (16), 79 (58), 77 (30), 69 (97), 56 (63). HRMS: Experimental, 252.1366 amu ($C_{14}H_{20}O_4$, Calculated 252.1361).



(1*R,2*S**)-2-(2-Hydroxyethyl)-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-3-en-1-ol (279)**

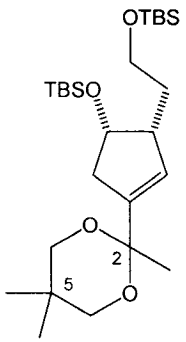
A procedure similar to that for compound **237** was used to make **279**; quantities: **278** (314 mg, 1.25 mmol), $LiAlH_4$ (97 mg, 2.5 mmol), in THF (20 mL). This yielded 297 mg (93%) of **279** (R_f 0.06; 50% ethyl acetate/ hexane) as a pale yellow liquid, which was taken immediately to the next step. IR (cm^{-1}, neat): 3384, 1641. δ_H 5.57 (1 H, s, C=*CH*), 4.51 (1 H, dt, J_1 2.5, J_2 7.8, HO*CH*), 3.80 (1 H, m, CH_2OH), 3.74 (2 H, br, 2 OH), 3.68 (1 H, m, CH_2OH), 3.54 (2 H, m, OCH_2CCH_2O), 3.35 (2 H, d, *J* 10.9, OCH_2CCH_2O), 2.87 (1 H, m, *CH*CH=C), 2.61 (1 H, ddt, J_1 1.8, J_2 6.7, J_3 17.0, CH_2C=CH), 2.32 (1 H, dt, J_1 1.5, J_2 16.5, CH_2C=CH), 1.91 (1 H, m, CH_2CH_2OH), 1.78 (1 H, m, CH_2CH_2OH), 1.43 (3 H, s, CH_3), 1.16 (3 H, s, CH_3), 0.72 (3 H, s, CH_3). δ_C 141.0 (*C*=CH), 131.0 (C=*CH*), 98.6 (O-*C*-O), 72.5 (*CH*OH), 71.9 (OCH_2CCH_2O), 71.8 (OCH_2CCH_2O), 61.6 (CH_2OH), 49.6 (*CH*C=C), 41.2 (CH_2C=CH), 30.5 (CH_2CH_2OH), 29.9 (CH_3-*C*-CH_3), 27.2 (CH_3-C=CH), 22.8 (CH_3-C-CH_3), 22.2 (CH_3-C-CH_3). GC-MS: 256 (3, M^+), 241 (64, M^+-CH_3), 238 (13), 223 (24), 211 (4), 205 (6), 170 (22), 155 (9), 153 (25), 152 (28), 139 (38), 137 (40), 129 (66), 119 (35), 109 (38), 95 (18), 93 (37), 81 (36), 79 (33), 77 (26), 69 (100).



(1*R,2*S**)-2-[2-*tert*-Butyldimethylsilyloxyethyl]-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-3-en-1-ol (280)**

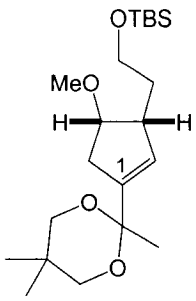
A procedure analogous to that for compound **238** was applied to make **280**; quantities: crude **279** (297 mg, 1.16 mmol), imidazole (237 mg, 3.48 mmol), TBSCl (175 mg, 1.16 mmol), CH_2Cl_2 (20 mL). Flash column chromatography provided compound **280** (R_f 0.80; 20% ethyl acetate/hexane, 402 mg, 87% from **278**) as a pale yellow liquid and compound **281** (R_f 0.95; 20% ethyl acetate/hexane, 12 mg, 2% from **278**) as a pale yellow liquid. For compound **280**: IR (cm^{-1}, neat): 3448, 1654. δ_H 5.51 (1 H, s, C=*CH*), 4.48 (1 H, m, *CH*OH), 3.83 (1 H, m, *CH*$_2$OTBS), 3.66 (1 H, dt, J_1 2.3, J_2 10.0, *CH*$_2$OTBS), 3.59 (1 H, d, *J* 9.8, O*CH*$_2$C*CH*$_2$O), 3.57 (1 H, d, *J* 9.8, O*CH*$_2$C*CH*$_2$O), 3.51 (1 H, d, *J* 2.7, CH*OH*), 3.34 (2 H, d, *J* 10.9, O*CH*$_2$C-*CH*$_2$O), 2.82 (1 H, m, *CH*CH=C), 2.59 (1 H, dd, J_1 6.0, J_2 16.7, *CH*$_2$C=CH), 2.34 (1 H, d, *J* 16.5, *CH*$_2$COO), 1.95 (1 H, m, *CH*$_2$CH$_2$OTBS), 1.77 (1 H, m, *CH*$_2$CH$_2$OTBS), 1.43 (3 H, s, *CH*$_3$), 1.16 (3 H, s, *CH*$_3$), 0.92 (9 H, s, *tert*-butyl), 0.70 (3 H, s, *CH*$_3$), 0.11 (3 H, s, Si*CH*$_3$), 0.10 (3 H, s, Si*CH*$_3$). δ_C 141.2 (*C*=CH), 131.0 (C=*CH*), 98.7 (O-*C*-O), 72.5 (*CH*OH), 72.0 (O*CH*$_2$CCH$_2$O), 71.9 (OCH$_2$C*CH*$_2$O), 63.4 (*CH*$_2$OTBS), 50.9 (*CH*C=C), 41.3 (*CH*$_2$C=CH), 30.8 (*CH*$_2$CH$_2$OTBS), 29.9 (CH$_3$-*C*-CH$_3$), 27.6 (*CH*$_3$C-C=CH), 26.1 (SiC*(CH*$_3$*)*$_3$), 22.9 (*CH*$_3$-*C*-CH$_3$), 22.3 (CH$_3$-*C*-*CH*$_3$), 18.4 (Si*C*(CH$_3$)$_3$), -5.36 (Si*CH*$_3$), -5.40 (Si*CH*$_3$). GC-MS:

370 (3, M^+), 313 (9), 299 (7), 227 (4), 225 (12), 209 (11), 185 (4), 183 (6), 161 (13), 153 (18), 145 (62), 129 (10), 127 (11), 115 (42), 101 (14), 93 (12), 83 (78), 75 (100), 69 (74).



(3*R,4*S**)-3-(2-*tert*-Butyldimethylsilyloxyethyl)-4-*tert*-butyldimethylsilyloxy-1-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-1-ene (281)**

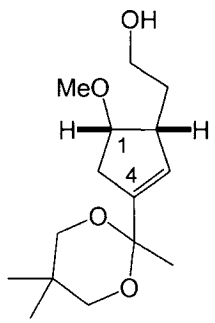
IR (cm^{-1}, neat): 1651. δ_H 5.72 (1 H, d, *J* 1.4, C=*CH*), 4.43 (1 H, m, *CH*-OTBS), 3.28-3.74 (6 H, m, CH_2-O), 2.76 (1 H, m), 2.42 (1 H, dd, J_1 5.4, J_2 15.7), 2.21 (1 H, dd, J_1 4.0, J_2 15.7), 1.86 (1 H, m), 1.73 (1 H, m), 1.39 (3 H, s, CH_3), 1.18 (3 H, s, CH_3), 0.90 (18 H, s, *tert*-butyl), 0.49 (3 H, s, CH_3), 0.05 (12 H, s, Si-CH_3). δ_C 140.2 (*C*=CH), 131.6 (C=*CH*), 98.8 (O-*C*-O), 74.2 (*CH*OTBS), 71.9 (OCH_2CCH_2O), 71.9 (OCH_2CCH_2O), 63.3 (CH_2OTBS), 47.0 (*CH*C=C), 41.3 (CH_2C=CH), 32.0 (CH_2CH_2OTBS), 29.6 (CH_3-*C*-CH_3), 27.8 (CH_3C-C=CH), 26.14 (SiC$(CH_3)_3$), 26.10 (SiC$(CH_3)_3$), 22.9 (CH_3-*C*-CH_3), 22.2(CH_3-*C*-CH_3), 18.56 (Si*C*$(CH_3)_3$), 18.54 (Si*C*$(CH_3)_3$), 1.4 (SiCH_3), 1.3 (SiCH_3), -5.06 (SiCH_3), -5.12 (SiCH_3). GC-MS: 187 (3), 163 (3), 162 (6), 161 (36), 143 (5), 120 (3), 119 (14), 105 (17), 88 (7), 76 (8), 75 (100), 73 (26), 61 (4), 59 (8), 57 (13). HRMS: Experimental, 484.3405 amu ($C_{26}H_{52}O_4Si_2$, Calculated 484.3404).



(3*R,4*S**)-3-(2-*tert*-Butyldimethylsilyloxyethyl)-4-methoxy-1-(2,5,5-trimethyl-[1,3]-dioxan-2-yl)cyclopent-1-ene (282)**

A procedure similar to that for compound **239** was used to make **282**; quantities: NaH (60% in mineral oil, 51 mg, 1.3 mmol), THF (20 mL), **280** (235 mg, 0.635 mmol), HMPA (342 mg, 1.91 mmol), CH_3I (270 mg, 1.91 mmol). Flash column chromatography provided **282** (R_f 0.50; 10% ethyl acetate/hexane, 221 mg, 91%) as a colorless liquid. IR (cm^{-1}, neat): 1646. δ_H 5.74 (1 H, d, *J* 2.1, C=*CH*), 3.97 (1 H, q, *J* 6.7, CH_3OCH), 3.70 (1 H, dt, J_1 1.1, J_2 6.8, CH_2OTBS), 3.52 (2 H, m, OCH_2CCH_2O), 3.33 (2 H, d, *J* 9.0, OCH_2C-CH_2O), 3.32 (3 H, s, OCH_3), 2.89 (1 H, q, *J* 6.7, *CH*CH=C), 2.43 (1 H, dd, J_1 6.6, J_2 16.1, CH_2C=CH), 2.32 (1 H, dd, J_1 6.1, J_2 16.1, CH_2C=CH), 1.87 (1 H, m, CH_2CH_2OTBS), 1.55 (1 H, m, CH_2CH_2OTBS), 1.40 (3 H, s, CH=C-CCH_3), 1.17 (3 H, s, CH_3-C-CH_3), 0.90 (9 H, s, (C$(CH_3)_3$), 0.70 (3 H, s, CH_3-C-CH_3), 0.06 (6 H, s, CH_3SiCH_3). δ_C 140.2 (*C*=CH), 131.9 (C=*CH*), 98.6 (O-*C*-O), 82.5 (*CH*OCH_3), 71.90 (OCH_2CCH_2O), 71.86 (OCH_2CCH_2O), 62.3 (CH_2OTBS), 57.3 (OCH_3), 44.8 (*CH*CH=C), 36.6 (CH_2C=CH), 31.6 (CH_2CH_2OTBS), 29.9 (CH_3-*C*-CH_3), 27.6 (CH_3C-C=CH), 25.2 (C$(CH_3)_3$), 22.9 (CH_3-*C*-CH_3), 22.3 (CH_3-*C*-CH_3), 18.6 (*C*$(CH_3)_3$), -5.1 (CH_3SiCH_3). GC-MS: 369 (5, M^+-CH_3), 352 (5), 338 (10), 337 (34), 328 (11), 327 (45), 295 (12), 241 (23), 227 (7), 211 (31), 209 (85), 193 (30), 181 (31), 167 (13), 165 (12), 137 (18), 135

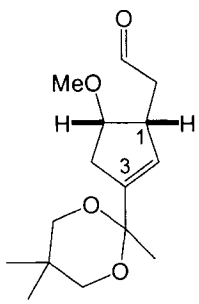
(92), 129 (69), 119 (86), 107 (84), 105 (26), 93 (53), 91 (58), 89 (100), 75 (73), 73 (79), 69 (84). HRMS: Experimental, 384.2710 amu ($C_{21}H_{40}O_4Si$, Calculated 384.2696).



(1*R,2*S**)-2-(2-Hydroxyethyl)-1-methoxy-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-3-ene (283)**

A procedure similar to that for compound **241** was used to make **283**; quantities: **282** (221 mg, 0.576 mmol), TBAF (752 mg, 2.88 mmol), THF (20 mL). Flash column chromatography provided **283** (R_f 0.20; 20% ethyl acetate/hexane, 155 mg, 100%) as a colorless liquid. IR (cm^{-1}, neat): 1640. δ_H 5.61 (1 H, d, *J* 1.5, C=*CH*), 4.01 (1 H, q, *J* 6.3, CH_3OCH), 3.53-3.67 (2 H, m, CH_2OH), 3.45 (2 H, m, OCH_2CCH_2O), 3.28 (3 H, s, OCH_3), 3.26 (2 H, d, *J* 11.1, OCH_2CCH_2O), 3.04 (1 H, br s, CH_2OH), 2.90 (1 H, q, *J* 6.7, *CH*CH=C), 2.40 (1 H, dd, J_1 6.7, J_2 16.4, CH_2C=CH), 2.29 (1 H, dd, J_1 5.6, J_2 16.4, CH_2C=CH), 1.82 (1 H, m, CH_2CH_2OH), 1.61 (1 H, m, CH_2CH_2OH), 1.33 (3 H, s, CH=C-C-CH_3), 1.09 (3 H, s, CH_3CCH_3), 0.64 (3 H, s, CH_3CCH_3). δ_C 140.2 (*C*=CH), 131.2 (C=*CH*), 98.4 (O-*C*-O), 82.0 (*CH*OCH_3), 71.69 (OCH_2CCH_2O), 71.67 (OCH_2C-CH_2O), 61.3 (CH_2OH), 57.1 (OCH_3), 46.0 (*CH*CH=C), 36.3 (CH_2C=CH), 31.2 (CH_2CH_2OH), 29.7 (CH_3-*C*-CH_3), 27.3 (CH_3C-C=CH), 22.7 (CH_3-C-CH_3), 22.1 (CH_3-C-CH_3). GC-MS: 255 (28, M^+-CH_3), 238 (9), 237 (5), 223 (17), 205 (7), 184 (18), 153 (59), 152 (24), 137 (34), 129 (63), 119 (39), 109 (36), 107 (23), 95 (31), 93 (53), 91 (58), 85 (18), 81

(28), 79 (53), 77 (48), 69 (100). HRMS: Experimental, 270.1824 amu ($C_{15}H_{26}O_4$, Calculated 270.1831).



(1'*R,5'*S**)-[5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-2-enyl]-acetaldehyde (273)**

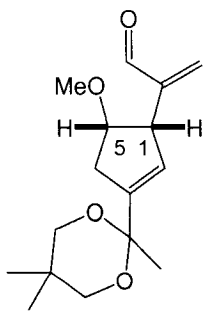
A) SWERN OXIDATION

DMSO (589 mg, 7.55 mmol) was added to a stirred solution of oxalyl chloride (479 mg, 3.77 mmol) in CH_2Cl_2 (10 mL) at –78 °C. The mixture was stirred for a further 15 min, then alcohol **283** (680 mg, 2.52 mmol) in CH_2Cl_2 (5 mL) was added over 15 min at –78 °C. After stirring for 60 min, triethylamine (1.15 g, 11.3 mmol) was added, and the mixture was allowed to warm to rt. The reaction was quenched with saturated $NaHCO_3$. The organic layer was washed with water (20 mL) and brine (20 mL) and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to flash column chromatography to give **273** (R_f 0.82; 50% ethyl acetate/hexane, 522 mg, 78%) as a pale yellow liquid.

B) DESS–MARTIN OXIDATION

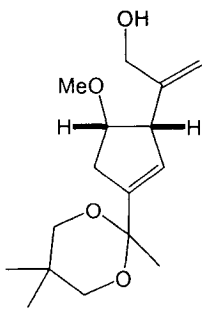
Dess–Martin periodinane (396 mg, 0.94 mmol) was added to a solution of **283** (210 mg, 0.78 mmol) and $NaHCO_3$ (0.5 g) in CH_2Cl_2 (10 mL) at rt under nitrogen. The resulting mixture was stirred at rt overnight. CH_2Cl_2 (20 mL) and water (20 mL) were

added. The organic layer was washed with 10% $Na_2S_2O_3$ solution (10 mL), saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), then dried over Na_2SO_4. After removal of the solvent, the residue was subjected to flash column chromatography to give **273** (R_f 0.82; 50% ethyl acetate/hexane, 190 mg, 91%) as a pale yellow liquid. IR (cm^{-1}, neat): 2721, 1722, 1671, 1621. δ_H 9.73 (1 H, s, *CHO*), 5.59 (1 H, d, *J* 2.6, C=*CH*), 4.01 (1 H, m, *CH*-OCH_3), 3.38-3.48 (2 H, m, OCH_2CCH_2O), 3.24-3.30 (2 H, m, OCH_2CCH_2O), 3.21 (3 H, s, OCH_3), 2.91 (1 H, m, C=CH-*CH*), 2.64 (1 H, ddd, J_1 2.0, J_2 7.9, J_3 17.0, CH_2C=CH), 2.34-2.46 (2 H, m, CH_2CHO), 2.29 (1 H, m, CH_2C=CH), 1.32 (3 H, s, CH=C-CCH_3), 1.08 (3 H, s, CH_3CCH_3), 0.64 (3 H, s, CH_3-C-CH_3). δ_C 201.9 (CHO), 141.5 (*C*=CH), 129.9 (C=*CH*), 98.2 (O-*C*-O), 81.2 (*CH*-OCH_3), 71.7 (OCH_2CCH_2O), 71.6 (OCH_2CCH_2O), 57.2 (OCH_3), 43.7 (CH_2-CHO), 42.7 (*CH*CH=C), 36.7 (CH_2C=CH), 29.7 (CH_3-*C*-CH_3), 27.2 (CH_3C-C=CH), 22.6 (CH_3-C-CH_3), 22.1 (CH_3-C-CH_3). GC-MS: 253 (68, M^+-CH_3), 236 (3), 225 (3), 221 (13), 209 (3), 193 (5), 179 (4), 167 (5), 153 (18), 151 (21), 150 (7), 139 (27), 135 (38), 129 (58), 121 (23), 109 (32), 107 (53), 97 (13), 95 (26), 93 (48), 91 (21), 79 (68), 77 (37), 69 (100). HRMS: Experimental, 268.1671 amu ($C_{15}H_{24}O_4$, Calculated 268.1675).



(1'*R,5'*R**)-2-[5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-2-enyl]-propenal (272)**

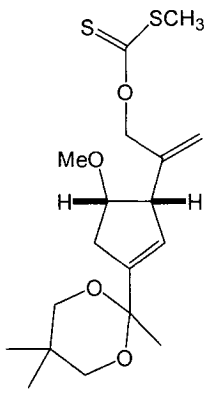
Eschenmoser's salt (methylenedimethyl- ammonium iodide, 510 mg, 2.76 mmol) was added to a solution of aldehyde **273** (148 mg, 0.55 mmol) and triethylamine (1.12 g, 11.0 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 15 h at rt. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography to give **272** (R_f 0.80; 50% EtOAc/ hexane, 80 mg, 52%) as a colorless oil. IR (cm^{-1}, neat): 1692. δ_H 9.62 (1 H, s, *CHO*), 6.22 (1 H, s, C=CH_2), 6.13 (1 H, s, C=CH_2), 5.67 (1 H, d, *J* 2.5, C=*CH*), 4.23 (1 H, m, CH_3OCH), 4.04 (1 H, d, *J* 7.5, *CH*CH=C), 3.55 (2 H, m, OCH_2CCH_2O), 3.38 (2 H, m, OCH_2CCH_2O), 3.19 (3 H, s, OCH_3), 2.55 (1 H, dd, J_1 6.7, J_2 17.4, CH_2C=CH), 2.39 (1 H, dt, J_1 1.9, J_2 16.7, CH_2C=CH), 1.46 (3 H, s, CH=C-CCH_3), 1.18 (3 H, s, CH_3CCH_3), 0.73 (3 H, s, CH_3-C-CH_3). δ_C 194.3 (*CHO*), 147.9 (CH_2=*C*-CHO), 143.8 (*C*=CH), 134.3 (C=CH_2), 127.9 (C=*CH*), 98.5 (O-*C*-O), 81.5 (*CH*OCH_3), 72.0 (OCH_2CCH_2O), 71.9 (OCH_2CCH_2O), 57.7 (OCH_3), 47.2 (*CH*CH=C), 37.6 (CH_2C=CH), 29.9 (CH_3-*C*-CH_3), 27.6 (CH_3C-C=CH), 22.8 (CH_3-*C*-CH_3), 22.3 (CH_3-*C*-CH_3). GC-MS: 265 (100, M^+-CH_3), 264 (47), 249 (4), 234 (10), 219 (13), 204 (4), 190 (33). HRMS: Experimental, 280.1688 amu ($C_{16}H_{24}O_4$, Calculated 280.1675).



(1'*R,5'*R**)-2-[5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-2-enyl]prop-2-en-1-ol (271)**

Solid $CeCl_3 \cdot 7H_2O$ (168 mg, 0.45 mmol) was added to a stirred solution of conjugated aldehyde **272** (63 mg, 0.23 mmol) in methanol (10 mL) at 0 °C. After 10 min, $NaBH_4$ (18 mg, 0.46 mmol) was added in portions. The reaction was monitored closely by TLC. After the reaction was complete, saturated NH_4Cl solution (1.0 mL) was added to quench the reaction. The methanol was removed under vacuum without any heating, and the residue was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to give compound **271** (R_f 0.40; 50% EtOAc/hexane, crude, 60 mg) as a colorless oil, which was used without further purification in the next step. IR (cm^{-1}, neat): 3452, 1643. δ_H 5.64 (1 H, d, *J* 1.7, C=*CH*), 5.21 (1 H, d, *J* 1.1, C=*CH*$_2$), 5.02 (1 H, s, C=*CH*$_2$), 4.23 (1 H, quartet, *J* 7.1, CH_3OCH), 4.14 (1 H, dd, J_1 2.9, J_2 12.3, *CH*$_2$OH), 4.06 (1 H, dd, J_1 4.6, J_2 12.6, *CH*$_2$OH), 3.71 (1 H, d, *J* 7.7, C=CH-*CH*-C=CH$_2$), 3.60 (1 H, d, *J* 11.2, O*CH*$_2$CCH$_2$O), 3.52 (1 H, d, *J* 11.0, OCH$_2$C*CH*$_2$O), 3.34-3.39 (2 H, m, O*CH*$_2$C*CH*$_2$O), 3.36 (3 H, s, O*CH*$_3$), 3.23 (1 H, t, *J* 8.9, CH$_2$*OH*), 2.55 (1 H, ddd, J_1 1.2, J_2 7.1, J_3 16.4, *CH*$_2$C=CH), 2.40 (1 H, ddt, J_1 2.0, J_2 6.2, J_3 16.4, *CH*$_2$C=CH), 1.45 (3 H, s, CH=C-C*CH*$_3$), 1.18 (3 H, s, *CH*$_3$CCH$_3$), 0.72 (3 H, s, CH$_3$-C-*CH*$_3$). δ_C 146.5 (CH$_2$=*C*-CH$_2$OH), 142.5 (*C*=CH), 129.4 (C=*CH*), 114.9 (C=*CH*$_2$), 98.5 (O-*C*-O), 82.7 (*CH*OCH$_3$), 72.0 (O*CH*$_2$CCH$_2$O), 71.9 (OCH$_2$C*CH*$_2$O), 66.1 (*CH*$_2$OH), 57.6 (O*CH*$_3$), 53.3 (*CH*CH=C), 36.7 (*CH*$_2$C=CH), 29.8 (CH$_3$-*C*-CH$_3$), 27.6 (*CH*$_3$C-C=CH), 22.8 (*CH*$_3$-*C*-CH$_3$), 22.3 (*CH*$_3$-*C*-CH$_3$). GC-MS: 282 (4, M^+), 267 (100, M^+-CH_3), 251 (12), 250 (15), 235 (27), 178 (11), 165 (48), 164 (19), 163 (13), 149 (23), 136 (16), 135 (50), 129 (62), 121 (36), 115 (42), 109 (60), 105 (41), 95 (13), 93

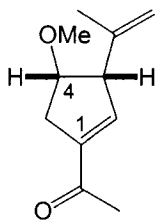
(29), 91 (78), 79 (40), 77 (48), 69 (93). HRMS: Experimental, 282.1826 amu ($C_{16}H_{26}O_4$, Calculated 282.1831).



***O*-{2-[(1*R**,5*R**)-5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-2-enyl]-allyl} *S*-methylthiocarbonate (286)**

Sodium hydride (60 % in mineral oil, 477 mg, 11.9 mmol) was washed free of mineral oil with dry THF. More THF (20 mL) was added to the sodium hydride, and the mixture was cooled to 0 °C. Alcohol **271** (672 mg, 2.38 mmol) in THF (5 mL) was added, and the mixture was allowed to warm to rt and was stirred for 30 min. The mixture was cooled to 0 °C again, and carbon disulfide (0.90 g, 11.9 mmol) was added. The mixture was allowed to warm to rt, and it was stirred at rt for 1 h. It was cooled to 0 °C again, and more carbon disulfide (0.90 g, 11.9 mmol) was added. After it had warmed to rt, iodomethane (1.69 g, 0.74 mL, 11.9 mmol) was added. The mixture was stirred at rt overnight. Water (5 mL) was added, and the organic solvent and any excess reagents were removed under vacuum. The residue was extracted with CH_2Cl_2 (20 mL × 3), and the combined organic layers were washed with water and brine, and then dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to give compound **286** (R_f 0.85; 50% EtOAc/hexane, 680 mg,

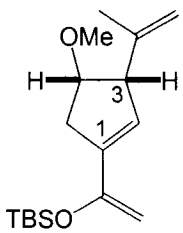
77%) as a pale yellow oil. IR (neat, cm^{-1}): 1671, 1649. δ_H 5.71 (1 H, d, *J* 2.3, C=*CH*), 5.28 (1 H, s, C=*CH*$_2$), 5.21 (1 H, d, *J* 13.5, *CH*$_2$OC=S), 5.13 (1 H, s, C=*CH*$_2$), 5.12 (1 H, d, *J* 14.2, *CH*$_2$OC=S), 4.17 (1 H, m, CH_3O*CH*), 3.66 (1 H, d, *J* 7.1, C=CH-*CH*-C=CH_2), 3.59 (1 H, d, *J* 11.1, O*CH*$_2$CCH_2O), 3.51 (1 H, d, *J* 10.6, OCH_2C*CH*$_2$O), 3.36 (2 H, m, O*CH*$_2$C-*CH*$_2$O), 3.32 (3 H, s, O*CH*$_3$), 2.58 (3 H, s, S*CH*$_3$), 2.53 (1 H, dd, J_1 6.8, J_2 16.6, *CH*$_2$C=CH), 2.38 (1 H, m, *CH*$_2$C=CH), 1.44 (3 H, s, CH=C-C*CH*$_3$), 1.18 (3 H, s, *CH*$_3$CCH_3), 0.71 (3 H, s, CH_3C*CH*$_3$). δ_C 215.8 (*C*=*S*), 143.1 (*C*=CH), 141.7 (CH_2=*C*-CH_2O), 128.8 (C=*CH*), 115.4 (C=*CH*$_2$), 98.6 (O-*C*-O), 82.2 (*CH*OCH_3), 75.9 (*CH*$_2$O-C=S), 72.1 (O*CH*$_2$CCH_2O), 72.0 (OCH_2C*CH*$_2$O), 57.7 (O*CH*$_3$), 52.9 (*CH*CH=C), 37.3 (*CH*$_2$C=CH), 29.9 (CH_3-*C*-CH_3), 27.7 (*CH*$_3$C-C=CH), 22.9 (*CH*$_3$-*C*-CH_3), 22.3 (*CH*$_3$-*C*-CH_3), 19.2 (S*CH*$_3$). GC-MS: 226 (4), 179 (5), 149 (6), 135 (8), 119 (7), 105 (9), 97 (4), 91 (23), 81 (4), 79 (13), 77 (24), 75 (100), 71 (4), 65 (15). HRMS: Experimental, 372.1418 amu ($C_{18}H_{28}O_4S_2$, Calculated 372.1429).



(3*R,4*R**)-1-Acetyl-3-isopropenyl-4-methoxycyclopent-1-ene (287)**

PPTS (7 mg, 0.027 mmol) was added to a solution of **253** (12 mg, 0.045 mmol) in methanol (5 mL) at rt. The mixture was stirred at rt overnight. The reaction was quenched with saturated $NaHCO_3$ solution (5 mL), and the solvent was removed under vacuum. The residue was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine, and then dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to

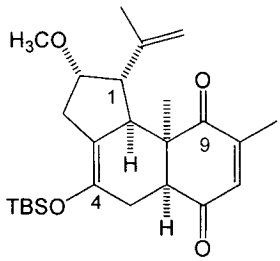
give compound **287** (R_f 0.38; 20% EtOAc/hexane, 8 mg, 100%) as a colorless oil. IR (neat, cm^{-1}): 1714, 1660, 1615. δ_H 6.66 (1 H, q, *J* 1.8, O=C-C=*CH*), 4.95 (1 H, s, CH_3-C=CH_2), 4.85 (1 H, s, CH_3-C=CH_2), 4.12 (1 H, m, MeO-*CH*), 3.59 (1 H, d, *J* 5.8, O=C-C=CH-*CH*), 3.31 (3 H, s, OCH_3), 2.64-2.76 (2 H, m, CH_2CH-OCH_3), 2.35 (3 H, s, CH_3-C=O), 1.81 (3 H, s, CH_3-C=CH_2). δ_C 196.6 (*C*=O), 143.8 (O=C-*C*=CH), 143.3 (O=C-C=*CH*), 142.5 (CH_3-*C*=CH_2), 112.7 (CH_3-C=CH_2), 81.4 (CH_3-O-*CH*), 57.4 (CH_3-O-CH), 35.8 (CH_3-O-CH-CH_2), 26.3 (CH_3-C=O), 22.3 (CH_3-C=CH_2). GC-MS: 165 (23, M^+-CH_3), 148 (6), 137 (9), 135 (18), 122 (100), 119 (21), 105 (95), 93 (16), 91 (66), 80 (20), 79 (75), 77 (86), 65 (52). HRMS: Experimental, 180.1149 amu ($C_{11}H_{16}O_2$, Calculated 180.1150).



(3*R,4*R**)-1-(1-*tert*-Butyldimethylsilyloxyvinyl)-3-isopropenyl-4-methoxycyclopent-1-ene (186)**

TBSOTf (15 mg, 0.05 mmol) was added to a solution of **287** (8 mg, 0.04 mmol) and triethylamine (14 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min before the solvent was removed under vacuum. The residue was subjected to flash column chromatography to give compound **186** (R_f 0.88; 20% EtOAc/hexane, 13 mg, 100%) as a colorless oil, which was used immediately for the next step. δ_H 5.88 (1 H, s, C=*CH*), 4.86 (1 H, s, CH_3-C=CH_2), 4.81 (1 H, s, CH_3-C=CH_2), 4.32 (2 H, s, CH_2=C-C=CH), 4.15 (1 H, m, CH_3O*CH*), 3.51 (1 H, d, *J* 7.1, *CH*C=CH_2), 3.34 (3 H, s, OCH_3), 2.64 (1 H, dd, J_1 7.1, J_2 15.7, CH_2CH-OCH_3), 2.53 (1

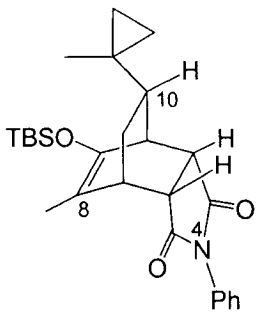
H, dd, J_1 5.4, J_2 15.7, CH_2CH-OCH_3), 1.78 (3 H, s, CH_3-C=CH_2), 0.96 (9 H, s, C(CH_3)$_3$), 0.18 (6 H, s, CH_3-Si-CH_3). δ_C 153.5 (CH_2=C-OTBS), 144.6 (CH_3-C=CH_2), 139.3 (CH_2-C=CH), 128.7 (TBSO-C-C=CH), 112.2 (CH_3-C=CH_2), 93.5 (TBSO-C-C=CH_2), 82.4 (CH_3-O-CH), 57.7 (CH_3-O-CH), 56.0 (CHC=CH_2), 37.4 (CH_3-O-CH-CH_2), 25.8 (C(CH_3)$_3$), 21.9 (CH_3-C=CH_2), 18.3 (C(CH_3)$_3$), -4.6 (Si-CH_3), -4.7 (Si-CH_3).



(1α,2α,5aα,9aα,9bα)-4-(*tert*-Butyldimethylsilyloxy)-2,3,5,5a,9a,9b-hexahydro-1-isopropenyl-2-methoxy-8,9a-dimethyl-1*H*-benz[*e*]indene-6,9-dione (185)

Compound **186** (13 mg, 0.04 mmol) was added to the solution of 2,6-dimethylbenzoquinone (12 mg, 0.09 mmol) in toluene (10 mL) at rt. The resulting mixture was refluxed for 4 days before the solvent was removed under vacuum, and the residue was subjected to flash column chromatography to give compound **185** (R_f 0.72; 20% EtOAc/hexane, 15 mg, 80%) as a yellow solid: mp 95-97 °C. IR (cm^{-1}, neat): 1709, 1683, 1625. δ_H 6.40 (1 H, s, CH_3-C=CH), 4.85 (1 H, s, C=CH_2), 4.82 (1 H, s, C=CH_2), 3.94 (1 H, m, CH_3OCH), 3.47 (1 H, m, CHC=CH_2), 3.30 (3 H, s, OCH_3), 2.91 (1 H, t, J 8.4, CH-C=O), 2.64 (2 H, m, CH_2CH-OCH_3 and CH-CH-C=CH_2), 2.32-2.42 (2 H, m, CH_2CH-OCH_3 and CH_2CH-C=O), 2.15 (1 H, m, CH_2CH-C=O), 1.97 (3 H, d, J 0.6, CH_3-C=CH_2), 1.82 (3 H, s, CH_3-C=CH_2), 1.36 (3 H, s, CH=C-C-C-CH_3), 0.90 (9 H, s, C(CH_3)$_3$), -0.06 (6 H, s, CH_3-Si-CH_3). δ_C 202.6 (CH_3-C=O), 200.4 (CH_3-C=C-C=O), 148.5 (CH_3-C=C-C=O), 145.9 (CH_3-C=CH_2), 138.9 (C=C-OTBS), 133.6 (CH_3-C=CH),

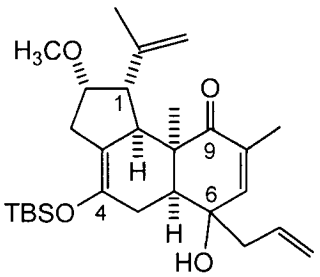
117.9 (*C*=C-OTBS), 113.8 (CH_3-C=*CH_2*), 83.5 (CH_3-O-*CH*), 57.4 (*CH_3*-O-CH), 57.4 (*CH*-C=O), 52.0 (*CH*-C=CH_2), 51.5 (CH_3-*C*-C=O), 48.8 (*CH*-CH-C=CH_2), 33.5 (CH_3-O-CH-*CH_2*), 31.6 (*CH_2*-CH-C=O), 25.7 (C*(CH_3)$_3$*), 24.6 (*CH_3*-C-C=O), 21.7 (*CH_3*-C=CH_2), 18.1 (*C*(CH_3)$_3$), 16.6 (*CH_3*-C=CH-C=O), -3.9 (Si-*CH_3*), -4.0 (Si-*CH_3*). GC-MS: 430 (7, M^+), 288 (17), 287 (76), 272 (9), 271 (56), 227 (13), 215 (24), 201 (6), 199 (14), 197 (73), 185 (11), 169 (5), 157 (13), 143 (6), 141 (37), 129 (100), 123 (18), 115 (12), 101 (16), 99 (38), 95 (18), 87 (7), 77 (8), 75 (59), 74 (44), 69 (81). HRMS: Experimental, 430.2550 amu ($C_{25}H_{38}O_4Si$, Calculated 430.2539).



(1*S,2*S**,6*R**,7*R**,10*S**)-9-(*tert*-Butyldimethylsilyloxy)-8-methyl-10-(1-methyl-cyclopropyl)-4-phenyl-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (289)**

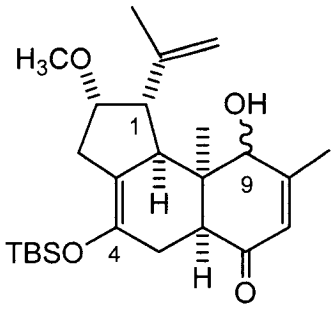
Diethyl zinc (1.0 M in hexane, 0.49 mL, 0.49 mmol) was added to a stirred solution of **288** (86 mg, 0.20 mmol) in dry CH_2Cl_2 (5 mL) at -20 °C under argon. After 10 min, diiodomethane (48 μL, 0.59 mmol) was added dropwise to the mixture. After 10 min, the solution turned cloudy and stirring was continued for 8 h, while the mixture was warmed to rt. A saturated NH_4Cl solution (5 mL) was added to the mixture, and the resulting mixture was extracted with CH_2Cl_2 (10 mL × 3). The extract was washed with brine (10 mL), dried over Na_2SO_4, and then concentrated under vacuum. The residue was purified by flash column chromatography to give **289** (R_f 0.45; 20 % AcOEt/hexane,

58 mg, 65%) as a white solid and **288** (30 mg, 35%) was recovered. IR (cm^{-1}, neat): 1774, 1711, 1673, 1599, 1499. δ_H 7.44 (2 H, t, *J* 8.0, *meta*-Ph), 7.36 (1 H, t, *J* 7.5, *para*-Ph), 7.20 (2 H, d, *J* 7.9, *ortho*-Ph), 3.05 (1 H, m, TBSO-C=C-*CH*), 3.02 (1 H, m, CH_3-C=C-*CH*), 2.95 (1 H, dd, J_1 3.5, J_2 8.3, CH-CH-*CH*-C=O), 2.89 (1 H, dd, J_1 3.3, J_2 8.4, CH_2-CH-*CH*-C=O), 1.64-1.71 (1 H, m, CH_2-CH-cyclopropane), 1.67 (3 H, s, CH_3-C=C), 1.42 (1 H, t, *J* 4.7, CH_2-*CH*-cyclopropane), 1.19 (1 H, ddd, J_1 3.0, J_2 6.0, J_3 9.1, CH_2-CH-cyclopropane), 0.97 (3 H, s, CH_3-cyclopropane), 0.89 (9 H, s, C$(CH_3)_3$)), 0.28-0.37 (2 H, m, cyclopropane), 0.13-0.23 (2 H, m, cyclopropane), 0.2 (3 H,s, SiCH_3), -0.1 (3 H,s, SiCH_3). δ_C 178.1 (CH_2-CH-CH-*C*=*O*), 177.3 (CH-CH-CH-*C*=*O*), 144.4 (C=C-OTBS), 132.3 (N-*C*(Ph)), 129.1 (*meta*-Ph), 128.5 (*ortho*-Ph), 126.7 (*para*-Ph), 111.8 (CH_3-*C*=C), 47.2 (CH-CH-*CH*-C=O), 45.9 (*CH*-cyclopropane), 44.5 (CH_2-CH-*CH*-C=O), 41.5 (TBSO-C=C-*CH*), 39.5 (CH_3-C=C-*CH*), 29.1 (CH_2-CH-cyclopropane), 25.8 (C$(CH_3)_3$)), 21.4 (CH_3-cyclopropane), 18.4 (*tertiary C* in cyclopropane), 18.3 (*C*$(CH_3)_3$), 14.0 (CH_3-C=C), 12.1 (CH_2 in cyclopropane)), 11.2 (CH_2 in cyclopropane)), -3.3 (SiCH_3), -3.8 (SiCH_3). HRMS: Experimental, 451.2549 amu ($C_{27}H_{37}NO_3Si$, Calculated 451.2543).



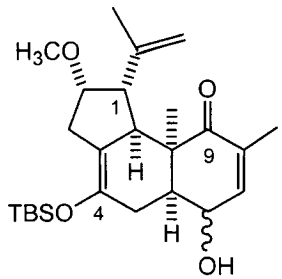
(1α,2α,5aα,9aα,9bα)-6-Allyl-4-(*tert*-Butyldimethylsilyloxy)-2,3,5,5a,6,9,9a,9b-octa-hydro-6-hydroxy-2-methoxy-8,9a-dimethyl-1-isopropenyl-1*H*-benz[*e*]indene-9-one (mixture of epimers at C-6) (294)

Allyl bromide (121 mg, 1.0 mmol) was added to the suspension of magnesium (29 mg, 1.2 mmol) in ether (10 mL) dropwise. The solution became cloudy while it was stirred at rt for 30 min. The mixture was then refluxed for 30 min. The Grignard reagent (0.39 mL, 0.039 mmol) was then added to a solution of **185** (14 mg, 0.033 mmol) in ether (1 mL) at –78 °C. The mixture was stirred at -78 °C for 1 h. It was allowed to warm to rt. The reaction was quenched with water (1 mL), and diluted with ether (5 mL). The aqueous layer was extracted with ether (5 mL × 3), and the combined organic layers were dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to give compound **294** (R_f 0.40; 20% EtOAc/hexane, 5 mg, 32%) as a pale yellow oil. δ_H 6.07 (1 H, s, C=*CH*-C=O), 5.84-6.02 (1 H, m, CH_2-*CH*=CH_2), 5.35 (1 H, dd, J_1 1.5, J_2 10.4, CH_2-CH=*CH_2*), 5.29 (1 H, dd, J_1 1.5, J_2 18.0, CH_2-CH=*CH_2*), 4.80-4.83 (2 H, m, CH_3-C-*CH_2*), 4.01 (1 H, q, *J* 6.6, CH_3-O-*CH*), 3.62 (1 H, t, *J* 7.1, CH_3-O-CH-*CH*), 3.33 (3 H, s, O-*CH_3*), 2.64-2.72 (1 H, m), 2.58-2.64 (1 H, m), 2.39-2.45 (1 H, m), 2.13-2.33 (4 H, m), 1.83 (3 H, s, CH_2=C-*CH_3*), 1.76-1.79 (4 H, m, CH=C-*CH_3* and *CH*), 1.49 (3 H, m, *CH_3*), 0.90 (9 H, s, Si-C(*CH_3*)$_3$), 0.54 (3 H, s, Si-*CH_3*), 0.50(3 H, s, Si-*CH_3*). δ_C 204.0 (*C=O*), 147.7 (C=*C*-OTBS), 139.3 (*CH*=C-CH_3), 138.7 (CH_2=*C*-CH_3), 134.4 (CH=*C*-CH_3), 131.3 (CH_2=*CH*-CH_2), 121.7 (*CH_2*=CH-CH_2), 116.8 (*C*=*C*-OTBS), 112.9 (*CH_2*=C-CH_3), 83.4 (*CH*-OCH_3), 72.2 (allyl-*C*-OH), 57.6 (O*CH_3*), 51.3 (*CH*), 50.5 (*CH*), 50.2 (*CH*), 49.4 (*C*-CH_3), 44.9 (*CH_2*), 33.6 (*CH_2*), 32.9 (*CH_2*), 25.7 (S-C(*CH_3*)$_3$), 25.6 (C=C-C(O)-C-*CH_3*), 21.7 (CH_2=C-*CH_3*), 16.4 (CH=C-*CH_3*), -4.0 (Si-*CH_3*), -3.9 (Si-*CH_3*). HRMS: Experimental, 472.3027 amu ($C_{28}H_{44}O_4Si$, Calculated 472.3009).



(1α,2α,5*a*α,9*,9*a*α,9*b*α)-4-(*tert*-Butyldimethylsilyloxy)-2,3,5,5*a*,9*a*,9*b*-hexahydro-9-hydroxy-1-isopropenyl-2-methoxy-8,9*a*-dimethyl-1*H*-benz[*e*]inden-9-one (295)

$NaBH_4$ (4.4 mg, 0.12 mmol) was dissolved in methanol (5.0 mL) at rt and the mixture was stirred for 10 min until the solid dissolved. 0.5 mL of the above solution was added to a solution of **185** (5.0 mg, 0.012 mmol) in methanol (0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. It was allowed to warm to rt. The reaction was quenched with five drops of water, and the solvent was removed under vacuum. The residue was extracted with CH_2Cl_2 (5 mL × 3), and the combined organic solutions were dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to PTLC to give compound **295** (R_f 0.12; 20% EtOAc/hexane, 1.0 mg, 20%) as a colorless oil and **296** (2.0 mg, R_f 0.10; 20% EtOAc/hexane, 40%). Compound **295**: δ_H 5.77 (1 H, s, CH_3-C=*CH*), 5.00 (1 H, s, C=*CH_2*), 4.91 (1 H, s, C=*CH_2*), 3.97 (1 H, d, *J* 6.5, *CH*-OH), 3.77 (1 H, m, CH_3O*CH*), 3.29 (3 H, s, O*CH_3*), 3.04 (1 H, dd, J_1 8.0, J_2 14.0, *CH_2*CH-OCH_3), 2.91 (1 H, m, *CH*-CH-C=CH_2), 2.70 (1 H, d, *J* 6.5), 2.54-2.64 (1 H, m), 2.33-2.42 (3 H, m), 2.05 (3 H, s, *CH_3*), 1.91 (3 H, s, *CH_3*), 1.04 (3H, s), 0.91 (9 H, s, C(*CH_3*)$_3$), 0.12 (3 H, s, *CH_3*-Si-CH_3) , 0.09 (3 H, s, *CH_3*-Si-CH_3).

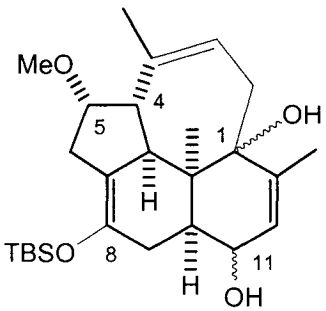


(1α,2α,5*a*α,6α,9*a*α,9*b*α)-4-(*tert*-Butyldimethylsilyloxy)-2,3,5,5*a*,9*a*,9*b*-hexahydro-6-hydroxy-1-isopropenyl-2-methoxy-8,9*a*-dimethyl-1*H*-benz[*e*]inden-9-one (296a) and (1α,2α,5*a*α,6β,9*a*α,9*b*α)-4-(*tert*-butyldimethylsilyloxy)-2,3,5,5*a*,9*a*,9*b*-hexahydro-6-hydroxy-1-isopropenyl-2-methoxy-8,9*a*-dimethyl-1*H*-benz[*e*]inden-9-one (296b)

$NaBH_4$ (13 mg, 0.35 mmol) was dissolved in methanol (5.0 mL) at rt and the mixture was stirred for 10 min until the solid dissolved. To a solution of **185** (15 mg, 0.035 mmol) and $CeCl_3 \cdot 7H_2O$ (26 mg, 0.070 mmol) in methanol (2 mL) was added some of the $NaBH_4$ solution (0.50 mL, 0.035 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. It was allowed to warm to rt. The reaction was quenched with five drops of water, and the solvent was removed under vacuum. The residue was extracted with CH_2Cl_2 (5 mL × 3), and the combined organic solutions were dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to give compound **296** (R_f 0.10; 20% EtOAc/hexane, 12 mg, 80%) as a colorless oil. One epimer of **296**: IR (cm^{-1}, neat), 1681. δ_H 6.40 (1 H, m, CH_3-C=*CH*), 4.86 (1 H, s, C=*CH*$_2$), 4.67 (1 H, s, C=*CH*$_2$), 4.26 (1 H, br s, *CH*-OH), 3.82 (1 H, m, CH_3O*CH*), 3.28 (3 H, s, O*CH*$_3$), 2.85 (1 H, dd, J_1 6.9, J_2 10.8, *CH*$_2$CH-OCH_3), 2.80 (1 H, dd, J_1 6.5, J_2 16.1, *CH*-CH-C=CH_2), 2.57 (1 H, d, J 10.6, *CH*$_2$CH-OCH_3), 2.35 (1 H, m, *CH*$_2$CH-C=O), 2.06-2.18 (3 H, m), 1.76 (3 H, t, J 1.5, *CH*$_3$-C=CH_2), 1.74 (3 H, s, *CH*$_3$-C=CH_2), 1.39 (3 H, s, CH=C-C-C-*CH*$_3$), 0.94 (9 H, s, C(*CH*$_3$)$_3$), 0.11 (3 H, s, *CH*$_3$-Si-CH_3) , 0.10 (3 H, s, *CH*$_3$-Si-CH_3). δ_C 202.6 (CH_3-*C*=*O*), 144.5 (CH_3-*C*=C-C-OH), 140.6

(CH_3-*C*=CH_2), 138.7 (C=*C*-OTBS), 135.8(CH_3-*C*=*CH*), 118.0 (*C*=C-OTBS), 114.5 (CH_3-C=*CH_2*), 83.1 (CH_3-O-*CH*), 67.8 (*CH*OH), 57.5 (*CH_3*-O-CH), 53.8, 49.8, 48.1, 46.8, 33.1, 30.9, 25.7 (C*(CH_3)$_3$*), 25.1 (*CH_3*-C-C=O), 21.7 (*CH_3*-C=CH_2), 18.1 (*C*(CH_3)$_3$), 16.4 (*CH_3*-C=CH-C=O), -3.9 (Si-*CH_3*), -4.1 (Si-*CH_3*). HRMS: Experimental, 432.2687 amu ($C_{25}H_{40}O_4Si$, Calculated 432.2696).

The other epimer of **296**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.34 (1H, s), 4.94 (1H, br m), 4.86 (1H, s), 4.83 (1H, s), 3.96 (1H, apparent q, J = 6 Hz), 3.73 (1H, t, J = 7 Hz), 3.32 (3H, s), 2.53–2.65 (3H, m), 2.37 (1H, m), 2.25 (1H, m), 2.01 (1H, m), 1.85 (3H, s), 1.76 (3H, s), 0.94 (3H, s), 0.91 (9H, s), 0.04 (6H, s).

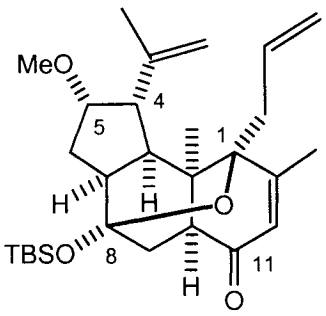


301

Compound 301

Allyl bromide (60 mg, 0.50 mmol) was added to magnesium (12 mg, 0.50 mmol) in ether (3.0 mL) dropwise. The mixture became cloudy while it was stirred at rt for 30 min. The mixture was then refluxed for 30 min. The above Grignard reagent was added to the solution of **296** (2.0 mg, 0.046 mmol) in ether (1 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and it was allowed to warm to rt. The reaction was quenched with water (1 mL), and it was diluted with ether (5 mL). The aqueous layer was extracted with ether (5 mL × 3), and the combined organic layers were dried over Na_2SO_4. The residue was subjected to RCM directly.

Grubbs' catalyst **300** (0.2 mg, 2.4 $\times 10^{-4}$ mmol) was added to a solution of the above residue in $CDCl_3$ (0.4 mL), and the mixture was stirred at rt for 20 h. The solvent was removed under vacuum, and the residue was subjected to NMR. Crude ^1H NMR shows a new doublet at 5.51 ppm and paeks at 5.77 ppm, 5.00 ppm, 4.91 ppm in the starting material disappeared.



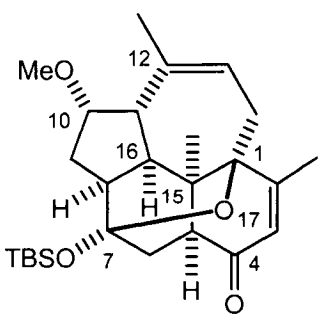
293a

(1*R,2*S**,3*S**,4*R**,5*S**,7*R**,8*R**,10*R**)-1-Allyl-8-(*tert*-butyldimethylsilyloxy)-4-isopropenyl-5-methoxy-2,13-dimethyl-14-oxatetracyclo[6.5.1.$0^{2,10}$.$0^{3,7}$]tetradec-12-en-11-one (293a)**

Allyl bromide (90 mg, 0.74 mmol) was added to magnesium (18 mg, 0.74 mmol) in ether (10 mL) dropwise. The mixture became cloudy while it was stirred at rt for 30 min. The mixture was then refluxed for 30 min. Some of the above Grignard reagent (3.0 mL, 0.22 mmol) was added to the solution of **296** (21 mg, 0.049 mmol) in ether (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and it was allowed to warm to rt. The reaction was quenched with water (1 mL), and it was diluted with ether (5 mL). The aqueous layer was extracted with ether (5 mL × 3), and the combined organic layers were dried over Na_2SO_4. The residue was used in the next step without purification.

Dess–Martin reagent (63 mg, 0.15 mmol) was added to the above crude product and $NaHCO_3$ (0.5 g, 6.0 mmol) in CH_2Cl_2 (3 mL) at rt. The mixture was stirred

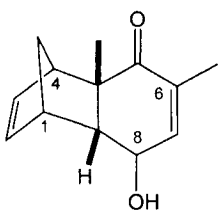
overnight before it was diluted with CH_2Cl_2 (10 mL). The mixture was washed with 10% $Na_2S_2O_3$ solution (5 mL), saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), and the organic layer was dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to give compound **293a** (R_f 0.72; 20% EtOAc/hexane, 4 mg, 17%) as a colorless oil and compound **185** (8 mg, 38%) recovered. For compound **293a:** δ_H 5.79 (1 H, s), 5.71 (1 H, m), 5.12 (1 H, d, *J* 17.3), 5.07 (1 H, d, *J* 10.2), 4.92 (1 H, s), 4.84 (1H, s), 3.87 (1 H, br t, *J* 3.8), 3.28 (3 H, s), 3.12 (1 H, dd, *J* = 4.5, 9.5), 2.88 (1 H, d of multiplets, *J* = 16.9), 2.77 (1 H, dd, *J* 8.8, 16.9), 2.50 (1 H, m), 2.42 (1 H, dd, *J* = 9.5, 12.0), 2.29 (1 H, dd, *J* 4.8, 11.0), 2.04 (3 H, s), 2.01–2.06 (2 H, m), 1.86 (1 H, m), 1.84 (3 H, s), 1.80 (1 H, dd, *J* 4.8, 13.8), 0.93 (3 H, s), 0.86 (9 H, s), 0.12 (3 H, s), 0.05 (3 H, s). Short distances identified by NOE/NOESY spectra: 2-C*H*$_3$–4-H, 2-C*H*$_3$–10-H, 2-C*H*$_3$–C*H*$_2$-CH=CH$_2$, 2-C*H*$_3$–CH$_2$-C*H*=CH$_2$, 3-H–10-H, 4-H–5-H, 4-H–C*H*$_2$-CH=CH$_2$ (δ 2.77), 6-αH–7-H, 13-C*H*$_3$–C*H*$_2$-CH=CH$_2$ and 13-C*H*$_3$–CH$_2$-C*H*=CH$_2$. δ_C 201.9 (0), 160.3 (0), 144.7 (0), 134.0 (1), 124.3 (1), 116.7 (2), 112.0 (2), 99.2 (0), 85.1 (1), 80.2 (0), 56.9 (3), 56.0 (1), 54.7 (1), 49.0 (1), 46.4 (1), 40.5 (2), 39.3 (0), 35.9 (2), 30.5 (2), 25.7 (3C, 3), 23.0 (3), 20.0 (3), 19.4 (3), 17.9 (3), –2.3 (3), –3.0 (3).



292a

(1*R,5*R**,7*R**,8*R**,10*R**,11*R**,15*S**,16*S**)-7-(*tert*-Butyldimethylsilyloxy)-10-methoxy-3,12,15-trimethyl-17-oxapentacyclo[6.6.2.$1^{1,7}$.$0^{5,15}$.$0^{11,16}$]heptadeca-2,12-dien-4-one (292a)**

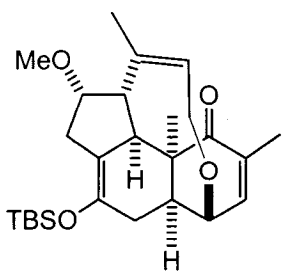
Grubbs' catalyst **300** (0.5 mg, 6 ×10^{-4} mmol) was added to a solution of **293a** (4 mg, 0.008mmol) in C_6D_6 (0.4 mL), and the mixture was maintained at 73 °C for 5 h. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to give compound **292a** (R_f 0.90; 20% EtOAc/hexane, 1 mg, 27%) as a colorless oil. IR: 1688 cm^{-1}. δ_H 5.57 (1 H, narrow m), 5.15 (1 H, br d, *J* 8.0), 3.73 (1 H, apparent t, *J* 3.5), 3.38 (1 H, br d, *J* 13.2), 2.69 (1 H, br d, *J* 17.8), 2.41 (1 H, dd, *J* 6.1, 10.5), 2.26 (1 H, dd, *J* 8.0, 17.8), 2.25 (1 H, dd, *J* 8.8, 13.2), 2.11 (1 H, td, *J* 8.8, 4.3), 2.01 (3 H, d, *J* 1.5), 1.96 (1 H, dd, *J* 6.1, 13.5), 1.90 (1 H, dd, *J* 4.3, 14.8), 1.84 (3 H, br s), 1.84 (1 H, overlapped), 1.76 (1 H, dd, *J* 8.8, 14.8), 1.06 (3 H, s), 0.86 (9 H, s), 0.14 (3 H, s), 0.07 (3 H, s). δ_C 202.3 (0), 159.4 (0), 139.3 (0), 121.8 (1), 102.0 (0), 80.7 (1), 79.5 (0), 56.1 (3), 54.2 (1), 49.9 (1), 46.7 (1), 43.4 (1), 39.6 (2), 39.0 (2), 37.3 (0), 29.7 (2), 25.7 (3), 20.0 (3), 18.6 (3), 18.0 (3), 18.0 (0), –2.2 (3), –2.9 (3). MS *m/z* 444.2692 (M^+, 444.2696 required for $C_{26}H_{40}O_4Si$).



(1α,4α,4aβ,8aβ)-1,4,4a,5,8,8a-Hexahydro-8-hydroxy-4a,6-dimethyl-1,4-methano-naphthalen-5-one (298)

$NaBH_4$ (154 mg, 4.07 mmol) was added to a solution of **297** (823 mg, 4.07 mmol) and $CeCl_3 \cdot 7H_2O$ (2.03 g, 5.45 mmol) in methanol (10 mL) and CH_2Cl_2 (10 mL) at 0 °C.

After the mixture had stirred at 0 °C for 2 h, the reaction was quenched with water (10 mL) at 0 °C and diluted with CH_2Cl_2 (50 mL). The aqueous layer was extracted CH_2Cl_2 (20 mL × 2), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to give compound **298** (R_f 0.32; 10% EtOAc/hexane, 680 mg, 82%) as a colorless oil. IR (cm^{-1}, neat): 3443, 1737, 1643. δ_H 6.28 (1 H, d, *J* 1.3, *CH*=CCH_3), 6.10 (1 H, m, CH=*CH*-CH-CH-CHOH), 5.82 (1 H, m, CH=*CH*-CH-C-CH_3), 4.83 (1 H, d, *J* 8.1, *CH*-OH), 3.16 (1 H, apparent s, *CH*-CH-CHOH), 2.89 (1 H, s, *CH*-C-CH_3), 2.67 (1 H, ddd, J_1 0.8, J_2 3.3, J_3 9.1, *CH*-CHOH), 2.24 (1 H, br s, *OH*), 1.66 (3 H, q, *J* 1.3, CH=C-*CH_3*), 1.55 (1 H, d, *J* 9.1, CH*CH_2*CH), 1.44 (3 H, s, O=C-C-*CH_3*), 1.42 (1 H, dt, J_1 1.8, J_2 9.1, CH*CH_2*CH). δ_C 204.0 (C=O), 144.8 (C=*CH*), 136.6 (O=C-*C*=CH), 136.0 (CH=*CH*-CH-CHOH), 135.5 (*CH*=CH-CH-CHOH), 65.3 (*CH*-OH), 56.8 (*CH*-C-CH_3), 51.2 (CH-*C*-CH_3), 50.6 (*CH*-CHOH), 47.2 (*CH_2*), 46.0 (*CH*-CH-CHOH), 25.5 (O=C-C-*CH_3*), 15.8 (CH=C-*CH_3*). GC-MS: 204 (11, M^+), 186 (19), 171 (28), 157 (14), 148 (48), 133 (34), 131 (100), 130 (80), 122 (76), 115 (23), 107 (37), 106 (58), 91 (88), 82 (19), 79 (90), 77 (88), 71 (70), 66 (57), 65 (47). HRMS: Experimental, 204.1152 amu ($C_{13}H_{16}O_2$, Calculated 204.1150).



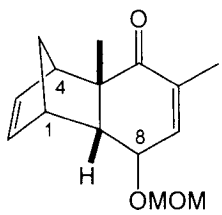
Compound 303

Allyl bromide (9 mg, 0.3 mmol) was added to magnesium (13 mg, 0.10 mmol) in ether (3 mL) dropwise. The mixture became cloudy while it was stirred at rt for 30 min. The mixture was then refluxed for 30 min. A solution of **296** (9 mg, 0.02 mmol) in ether (2 mL) was added to the above Grignard reagent at 0 °C. The mixture was stirred at 0 °C for 1 h before it was allowed to warm to rt. The reaction was quenched with water (1 mL), and the mixture was diluted with ether (5 mL). The aqueous layer was extracted with ether (5 mL × 3), and the combined organic layers were dried over Na_2SO_4. The residue was subjected to the next step immediately without any separation.

Dess–Martin reagent (18 mg, 0.042 mmol) was added to the crude product and $NaHCO_3$ (0.1 g) in CH_2Cl_2 (3 mL) at rt. The mixture was stirred overnight before it was diluted with CH_2Cl_2 (10 mL). The mixture was washed with 10% $Na_2S_2O_3$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL), and the organic layer was dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to the next RCM reaction without separation.

Grubbs' second generation catalyst **300** (0.5 mg, 6×10^{-4} mmol) was added to the product in benzene (5 mL), and the mixture was refluxed overnight. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to give compound **303** (R_f 0.55; 20% EtOAc/hexane, 1 mg, 11% over 3 steps) as a colorless oil. δ_H 5.71 (1 H, s, CH_3-C=*CH*-CH-O), 5.26 (2 H, t, *J* 4.0, *CH*OCH_2-CH=C and C=*CH*-CH_2-O), 4.29 (1 H, dd, J_1 4.5, J_2 7.0, C=CH-*CH_2*O), 4.11-4.18 (1 H, m, C=CH-*CH_2*O), 3.75 (1 H, dd, J_1 4., J_2 4.5, *CH*OCH_3), 3.29 (3 H, s, CHO*CH_3*), 2.80-3.00 (1 H, m), 2.63-2.70 (1 H, m), 2.44-2.56 (1 H, m), 2.20-2.36 (1 H, m), 2.00 (3 H, s, *CH_3*), 1.93 (3 H, s, *CH_3*), 1.44-1.64 (2 H, m), 1.20-1.40 (1 H, m), 1.26 (3 H, s, CH_3), 0.92 (9 H,

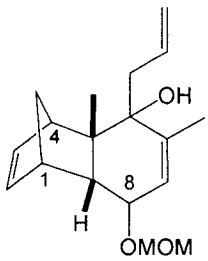
s, *tert*-butyl), 0.11 (3 H, s, CH_3-Si-CH_3), 0.09 (3 H, s, CH_3-Si-CH_3). δ_C 201.6 (C=O), 159.1, 138.8, 134.5, 129.8, 122.7, 118.7, 80.0, 75.9, 62.1, 55.6, 55.5, 49.2, 48.8, 40.4, 39.3, 34.1, 31.9, 29.7, 26.6, 24.9, 18.5, -3.7, -3.9.



(1α,4α,4aβ,8aβ)-1,4,4a,5,8,8a-Hexahydro-8-methoxymethoxy-4a,6-dimethyl-1,4-methanonaphthalen-5-one (305)

CH_3OCH_2Cl (118 mg, 1.46 mmol) was added to a solution of **298** (149 mg, 0.73 mmol) and $^iPr_2NEt$ (Hünig's base, 377 mg, 2.92 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was allowed to warm to rt and was stirred overnight. It was diluted with CH_2Cl_2 (20 mL), and water (20 mL) was added. The aqueous layer was extracted CH_2Cl_2 (20 mL × 2), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to give compound **305** (R_f 0.85; 50% EtOAc/hexane, 155 mg, 86%) as a colorless oil. IR (cm^{-1}, neat): 1738, 1694, 1660. δ_H 6.25 (1 H, d, *J* 1.2, *CH*=CCH_3), 6.05 (1 H, q, *J* 2.9, CH=*CH*-CH-CH-CHOH), 5.75 (1 H, q, *J* 2.9, CH=*CH*-CH-C-CH_3), 4.79 (1 H, d, *J* 6.5, OCH_2O-CH_3), 4.72 (1 H, d, *J* 6.6, OCH_2OCH_3), 4.68 (1 H, m, *CH*OMOM), 3.44 (3 H, s, OCH_2O-CH_3), 3.08 (1 H, d, *J* 1.2, *CH*-CH-CHOH), 2.86 (1 H, s, *CH*-C-CH_3), 2.66 (1 H, ddd, J_1 1.2, J_2 3.4, J_3 9.1, *CH*-CHOH), 1.65 (3 H, q, *J* 1.2, CH=C-CH_3), 1.55 (1 H, d, *J* 8.5, CHCH_2CH), 1.435 (3 H, s, O=C-C-CH_3), 1.39 (1 H, dt, J_1 1.7, J_2 8.7, CHCH_2CH). δ_C 203.6 (C=O), 143.1 (*CH*=C-CH_3), 136.9 (CH=*C*-CH_3), 136.5 (CH=*CH*-CH-CH-CHOH), 135.0 (*CH*=CH-CH-CH-

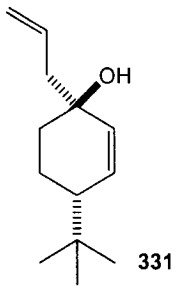
CHOH), 95.7 (O*CH*$_2$OCH$_3$), 70.0 (*CH*OH), 57.0 (O*CH*$_3$), 55.8 (*CH*-C-CH$_3$), 50.8 (CH$_3$-*C*-C=O), 48.3 (*CH*-CHOH), 47.1 (CH-*CH*$_2$-CH), 46.7 (*CH*-CH-CHOH), 25.2 (*CH*$_3$-C-C=O), 15.8 (CH=C-*CH*$_3$). GC-MS: 248 (3, M^+), 216 (2), 204 (14), 203 (100), 187 (4), 185 (5), 175 (9), 159 (15), 143 (11), 135 (12), 131 (13), 109 (16), 105 (31), 95 (18), 93 (22), 91 (49), 80 (17), 79 (44), 77 (50), 66 (50), 65 (27). HRMS: Experimental, 248.1407 amu ($C_{15}H_{20}O_3$, Calculated 248.1412).



(1α,4α,4aβ,8aβ)-5-Allyl-1,4,4a,5,8,8a-hexahydro-8-methoxymethoxy-4a,6-dimethyl-1,4-methanonaphthalen-5-ol (306)

Allyl bromide (78 mg, 0.65 mmol) was added to magnesium (15 mg, 0.74 mmol) in ether (5 mL) dropwise. The mixture became cloudy while it was stirred at rt for 30 min. The mixture was then refluxed for 30 min. A solution of **305** (32 mg, 0.13 mmol) in ether (3 mL) was added to the above Grignard reagent at rt. The mixture was stirred at rt overnight. The reaction was quenched with water (5 mL), and the solution was diluted with ether (10 mL). The aqueous layer was extracted with ether (5 mL × 3), and the combined organic layers were dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to give compound **306** (R_f 0.45; 20% EtOAc/hexane, 22 mg, 59%) as a colorless oil. IR (cm^{-1}, neat): 3501, 1636. δ_H (C_6D_6) 6.10 (1 H, s, *CH*=C), 6.00 (1 H, q, *J* 2.7, *CH*=C), 5.70 (1 H, m, CH=*CH*), 5.16 (1 H, s, *CH*=C), 4.90 (2 H, m, *CH*$_2$=CH), 4.58 (2 H, m, O*CH*$_2$O-CH$_3$),

4.49 (1 H, br s, *CH*OMOM), 3.22 (3 H, s, OCH_2OCH_3), 3.10 (1 H, s, *CH*), 2.73 (1 H, s, *CH*), 2.27 (1 H, dd, J_1 2.7, J_2 7.2), 2.12 (1 H, dd, J_1 7.9, J_2 14.5), 2.08 (1 H, dd, J_1 4.1, J_2 12.8), 1.57 (4 H, m, CH_3 + *CH*), 1.39 (1 H, d, *J* 8.7, $CHCH_2CH_2$), 1.19 (3 H, s, CH_3). δ_C ($CDCl_3$) 138.9 (*CH*=CH), 135.1 (CH_2=*CH*-CH_2), 132.4 (CH=*CH*), 123.1 (CH_3-*C*=CH), 118.8 (CH_2=CH-CH_2 and CH3-C=*CH*), 95.3 (OCH_2OCH_3), 77.4 (*C*-OH), 72.3 (*CH*-O-CH_2OCH_3), 55.7 (O-CH_2OCH_3), 54.5 (CH=CH-*CH*-C-CH_3), 51.3 (CH_3-*C*-C-OH), 51.2 (*CH*-CH-OMOM), 48.2 (CH-CH_2-CH), 46.4 (*CH*-CH-CH-OMOM), 45.0 (CH_2=CH-CH_2), 25.5 (CH_3), 19.7 (CH=C-CH_3). HRMS: Experimental, 290.1886 amu ($C_{18}H_{26}O_3$, Calculated 290.1882).



331

(1*R,4*S**)-1-Allyl-4-*tert*-butylcyclohex-2-en-1-ol (331)**

A) GRIGNARD REAGENT

Allyl bromide (60 mg, 0.5 mmol) was added to a suspension of magnesium metal (12 mg, 0.5 mmol) in ether (10 mL) dropwise. This mixture was stirred at rt for 1 h until most of the magnesium disappeared, resulting in a cloudy solution. A solution of 4-*tert*-butyl-2-cyclohexen-1-one [116] (76 mg, 0.50 mmol) in ether (5 mL) was added to the mixture over 10 min, and the resulting mixture was stirred at rt overnight. Water (10 mL) was added, and the organic layer was washed with water (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography to give **331** (R_f 0.76; 20% ethyl acetate/hexanes; 51 mg, 52%) as

a colorless liquid and **332** (R_f 0.68; 20% ethyl acetate/hexanes, 30 mg, 31%) as a colorless liquid (product ratio by ^{1}H NMR: 5:1 of **331**:**332**, respectively).

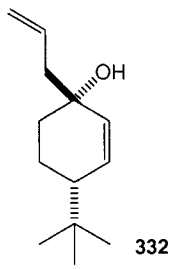
B) ALLYLINDIUM

Allyl iodide (126 mg, 0.75 mmol) was added to a suspension of indium metal (58 mg, 0.50 mmol) in DMF (2.0 mL) under argon. This mixture was stirred at rt for 1 h until most of the indium metal had dissolved to give a grey solution. 4-*tert*-Butyl-cyclohexen-2-one [116] (76 mg, 0.50 mmol) in DMF (1.0 mL) was then added dropwise to the solution. The mixture was stirred at rt for 6 hrs before the reaction was quenched with 5% HCl (5 mL), and water (10 mL) was added. The mixture was extracted with ether (3 × 5 mL). The combined organic layers were washed with water (3 ×10 mL) and saturated aqueous $NaHCO_3$, and then dried over $MgSO_4$. The solvent was removed under vacuum. The residue was subjected to flash column chromatography with to give **331** (52 mg, 54%) and **332** (30 mg, 31%) (product ratio by ^{1}H NMR: 1:1 of **331**:**332**).

C) ALLYLBISMUTH [117]

Zinc powder (80 mg, 1.3 mmol) was added to a mixture of 4-*tert*-butyl-2-cyclohexen-1-one (92 mg, 0.61 mmol), $BiCl_3$ (267 mg, 0.85 mmol), and allyl bromide (102 mg, 1.27 mmol) in THF (10 mL) while stirring at rt. The mixture was refluxed for 3 h and allowed to cool to rt. The solid was removed by filtration, and the solvent was removed under vacuum. The residue was diluted with ether (10 mL), and 0.5 M HCl (5 mL) was added. The organic layer was washed with water (2 × 5 mL) and saturated $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the crude residue was analysed by ^{1}H NMR to reveal a product ratio of 2.1:1 (**331**:**332**, respectively).

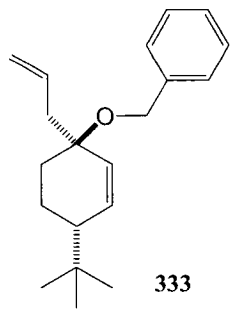
331: IR (cm^{-1}, neat): 3375, 1671, 1640. δ_H 5.89 (1 H, m, $CH_2CH{=}CH_2$), 5.74 (1 H, dt, J_1 10.7, J_2 1.8, CH=*CH*), 5.61 (1 H, dt, J_1 10.4, J_2 2.1, CH=*CH*), 5.07-5.19 (2 H, m, $CH_2CH{=}CH_2$), 2.34 (1 H, dd, J_1 13.7, J_2 7.2, $CH_2CH{=}CH_2$), 2.26 (1 H, dd, J_1 13.6, J_2 7.4, $CH_2CH{=}CH_2$), 1.20-2.00 (5 H, m, CH_2CH_2 and *CH*-*t*-Bu), 0.88 (9 H, s, *t*-Bu). δ_C 134.4, 133.9, 130.4, 118.9, 70.8, 46.0, 45.6, 35.2, 33.0, 27.4, 22.3. GC-MS: 176 (M^+-H_2O, 64), 161 (46), 153 (67), 135 (31), 120 (63), 119 (69), 117 (68), 105 (52), 97 (56), 91 (87), 83 (32), 79 (56), 65 (43), 57 (100). HRMS: Experimental, 194.1671 amu ($C_{13}H_{22}O$, Calculated 194.1671).



332

(1*R,4*R**)-1-Allyl-4-*tert*-butylcyclohex-2-en-1-ol (332)**

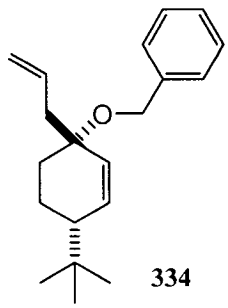
IR (cm^{-1}, neat): 3416, 1673, 1640. δ_H 5.80-5.86 (2 H, m, $CH_2CH{=}CH_2$ and *CH*=CH), 5.68 (1 H, dt, J_1 10.5, J_2 2.2, CH=*CH*), 5.07-5.16 (2 H, m, $CH_2CH{=}CH_2$), 2.22-2.34 (2 H, m, $CH_2CH{=}CH_2$), 1.20-1.82 (5 H, m, CH_2CH_2 and *CH*-*t*-Bu), 0.90 (9 H, s, *t*-Bu). δ_C 134.0, 133.2, 132.5, 118.5, 68.7, 47.3, 46.7, 35.7, 32.7, 27.5, 20.2. GC-MS: 176 (M^+-H_2O, 64), 161 (47), 135 (23), 133 (11), 120 (76), 119 (75), 117 (60), 105 (58), 91 (92), 79 (64), 65 (48), 57 (100). HRMS: Experimental, 194.1660 amu ($C_{13}H_{22}O$, Calculated 194.1671).



333

(1*R,4*S**)-1-Allyl-1-benzyloxy-4-*tert*-butylcyclohex-2-ene (333)**

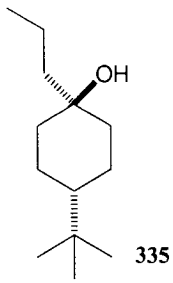
KH (30% in mineral oil) (12.4 mg, 0.93 mmol) was added to the solution of **331** (18.0 mg, 0.093 mmol) in THF (2.0 mL) at rt under an argon atmosphere. This mixture was stirred for 10 min, and benzyl bromide (16 mg, 0.093 mmol) was added dropwise. The mixture was then stirred overnight. TLC showed the reaction was complete, and it was quenched with water (2 mL), then diluted with ether (10 mL). The organic layer was dried with Na_2SO_4. After filtration, the organic solvent was removed under vacuum, and the residue was subjected to flash column chromatography to give **333** (R_f 0.92; 20% ethyl acetate/hexanes, 24 mg, 91%) as a colorless oil. IR (cm^{-1}, neat): 1639. δ_H 7.20-7.40 (5 H, m, phenyl), 6.00 (1 H, m, $CH_2CH{=}CH_2$), 5.90 (1 H, d, *J* 10.5, O-C-*CH*=CH), 5.66 (1 H, m, O-C-CH=*CH*-CH), 5.02-5.12 (2 H, m, $CH_2{=}CHCH_2$), 4.46 (2 H, d, *J* 3.5, CH_2Ph), 2.36-2.44 (2 H, m, $CH_2CH{=}CH_2$), 1.74-1.96 (4 H, m, CH_2CH_2 and *t*-Bu-*CH*), 1.30 (1 H, m, CH_2CH_2), 0.89 (9 H, s, *t*-Bu). δ_C 140.2 (tertiary, phenyl), 134.6 ($CH_2CH{=}CH_2$), 132.8, 132.6, 128.2, 127.0, 126.9 (phenyl), 117.0 (CH_2-CH=CH_2), 76.6 ($COCH_2Ph$), 64.0 ($COCH_2Ph$), 45.9 (*t*-Bu-*CH*), 44.6 (CH_2-CH=CH_2), 32.8 (CH_2-CH_2-CO), 30.8 ($C(CH_3)_3$), 27.2 ($C(CH_3)_3$), 22.4 (CH_2-CH_2-CO). GC-MS: 243 (14, M^+-allyl), 176 (26), 161 (16), 133 (4), 120 (33), 119 (48), 108 (40), 107 (31), 105 (22), 91 (100), 79 (63), 77 (57), 65 (28), 57 (68).



334

(1*R,4*R**)-1-Allyl-1-benzyloxy-4-*tert*-butylcyclohex-2-ene (334)**

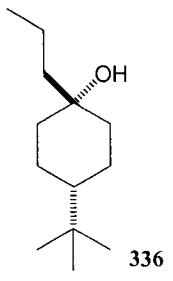
A similar procedure for making **333** (**332** (4 mg, 0.02 mmol), benzyl bromide (4 mg, 0.02 mmol), KH (30% in mineral oil, 3 mg, 0.2 mmol), THF (1 mL)) was applied to give **334** (R_f 0.92; 20% ethyl acetate/hexanes, 5 mg, 88%) as a colorless oil. δ_H 7.20-7.40 (5 H, m, phenyl), 6.02 (1 H, d, *J* 10.5, CH_2CH=CH_2), 5.86 (1 H, m, O-C-CH=*CH*-CH), 5.76 (1 H, d, *J* 10.5, O-C-*CH*=CH), 5.04-5.10 (2 H, m, CH_2=$CHCH_2$), 4.47 (2 H, s, CH_2Ph), 2.45 (1 H, dd, J_1 6.0, J_2 13.5, CH_2CH=CH_2), 2.35 (1 H, dd, J_1 6.0, J_2 13.5, CH_2CH=CH_2), 1.74-1.96 (4 H, m, CH_2CH_2 and *t*-Bu-*CH*), 1.30 (1 H, m, CH_2CH_2), 0.89 (9 H, s, *t*-Bu). δ_C 139.9 (tertiary, phenyl), 134.9 (CH_2CH=CH_2), 134.3, 130.5, 128.2, 127.6, 127.1 (phenyl), 117.4 (CH_2-CH=CH_2), 73.1 ($COCH_2$Ph), 64.9 (*C*OCH_2Ph), 46.5 (*t*-Bu-*CH*), 43.9 (CH_2-CH=CH_2), 31.9 (CH_2-CH_2-CO), 29.4 (*C*$(CH_3)_3$), 27.3 (C$(CH_3)_3$), 22.7 (CH_2-CH_2-CO). HRMS: Experimental, 284.2109 amu ($C_{20}H_{28}O$, Calculated 284.2140).



335

(1α,4β)-4-*tert*-Butyl-1-propylcyclohexanol (335)

Pd/C powder (catalytic amount) was added to the solution of **331** (axial-attack product, 14 mg, 0.072 mmol) in ethyl acetate (5 mL). The mixture was stirred under hydrogen gas at rt overnight. After removal of the solid by filtration, the residue was subjected to flash column chromatography to give **335** (R_f 0.38 (20% ethyl acetate/hexanes), 9 mg, 63%, mp 77-78°C) as a white solid. IR (cm^{-1}, cast): 3293, 2940, 2867. δ_H 1.76-1.84 (2 H, m), 1.63-1.71 (2 H, m), 1.44-1.51 (2 H, m), 1.29-1.41 (4 H, m), 1.18-1.23 (1 H, br s, OH), 1.00-1.12 (3 H, m), 0.94 (3 H, t, *J* 7.0), 0.86 (9 H, s, *t*-Bu). δ_C 72.5, 47.8, 39.1, 39.0, 32.5, 27.9, 24.7, 16.1, 15.0. GC-MS: 180 (14, M^+-H_2O), 165 (3), 155 (34), 137 (12), 124 (18), 123 (24), 122 (21), 109 (20), 99 (37), 95 (23), 82 (32), 81 (83), 79 (27), 68 (20), 67 (49), 57 (100).

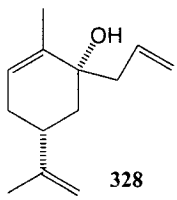


336

(1α,4α)-4-*tert*-Butyl-1-propylcyclohexanol (336)

Pd/C powder (catalytic amount) was added to the solution of **332** (59 mg, 0.072 mmol) in ethyl acetate (5 mL). The mixture was stirred under hydrogen gas at rt overnight. After removal of the solid by filtration, the residue was subjected to flash

column chromatography with to give **336** ((R_f 0.74; 20% ethyl acetate/hexanes, 54 mg, 92%, mp 71-73 °C) as a white solid. IR (cm^{-1}, cast): 3380, 2957, 2937. δ_H 1.62-1.68 (2 H, m), 1.56-1.61 (2 H, m), 1.36-1.42 (4 H, m), 1.25-1.35 (5 H, m), 0.88-0.96 (4 H, m), 0.86 (9 H, s, *t*-Bu). δ_C 70.9, 48.2, 46.9, 37.6, 32.6, 27.8, 22.7, 16.6, 15.0. GC-MS: 180 (28, M^+-H_2O), 165 (6), 155 (37), 141 (2), 137 (17), 124 (26), 123 (34), 109 (28), 99 (61), 95 (34), 81 (93), 79 (35), 67 (53), 57 (100). Literature [118] data: mp 73-74°C. δ_H (60 MHz, $CDCl_3$) 2.0-1.0 (m, aliphatic), 0.88 (s, *t*-Bu). δ_{13} (80 MHz, $CDCl_3$): 70.69, 48.11, 46.84, 37.49, 32.43, 27.62, 22.55, 16.44, 14.79.



328

(1*R*,5*R*)-1-Allyl-5-isopropenyl-2-methylcyclohex-2-en-1-ol (328)

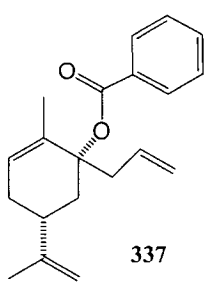
A) ALLYL GRIGNARD REAGENT

Allyl bromide (1.45 g, 12.0 mmol) was added to a suspension of magnesium metal (292 mg, 12.0 mmol) in ether (50 mL) dropwise. The mixture was stirred at rt for 1 h until most of the magnesium dissolved, resulting in a cloudy solution. (*R*)-(-)-Carvone (0.90 g, 6.0 mmol) was added dropwise over 10 min, and the resulting mixture was stirred at rt overnight. The reaction was quenched with water (20 mL), and the organic layer was washed with water (20 mL × 3) and dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to flash column chromatography to give **328** (R_f 0.43; 20% ethyl acetate /hexanes, 0.99 g, 86%) a colorless liquid. $[\alpha]_D^{25}$ = -57.5 (CH_2Cl_2, c=0.16). IR (cm^{-1}, neat): 3403, 1644. δ_H 5.87 (1 H, m, CH_2=*CH*CH_2), 5.48 (1 H, m, *CH*=C(CH_3)), 5.09-5.19 (2 H, m, *CH_2*=CH-CH_2),

4.73 (2 H, s, CH_2=C(CH_3)), 2.47 (1 H, ddd, J_1 1.1, J_2 7.3, J_3 14, CH_2=CHCH_2), 2.30-2.39 (2 H, m, CH_2=CHCH_2 and CH-C(CH_3)=CH_2)), 2.02-2.15 (2 H, m, CH_3C=CH-CH_2-CH and CH-CH_2-C(OH)), 1.96 (1 H, m, CH_3C=CH-CH_2-CH), 1.75 (3 H, m, CH=C-CH_3), 1.73 (3 H, s, isopropenyl), 1.50 (1 H, dt, J_1 12.5, J_2 0.9, CH-CH_2-C(OH)). δ_C 149.2 (tertiary, isopropenyl), 138.3 (CH=C(CH_3), ring), 133.9 (CH_2-CH=CH_2), 124.1 (CH=C(CH_3), ring), 118.8 (CH_2-CH=CH_2), 109.3 (terminal, isopropenyl), 73.8 (C(OH)), 43.1 (CH_2-CH=CH_2), 40.7 (CH_2-C(OH), ring), 39.4 (CH-isopropenyl), 31.0 (CH_2-CH=C(CH_3)), 21.0 (CH_3, isopropenyl), 17.2 (CH_3-C=CH). GC-MS: 174 (47, M^+-H_2O), 159 (18), 151 (42), 133 (100), 131 (88), 123 (37), 117 (78), 109 (98), 105 (87), 91 (79). HRMS: Experimental, 192.1512 amu ($C_{13}H_{20}O$, Calculated 192.1514).

B) ALLYLINDIUM REAGENT

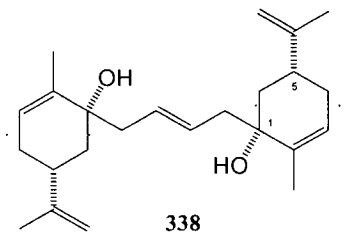
Allyl iodide (126 mg, 0.75 mmol) was added to the suspension of indium metal (58 mg, 0.50 mmol) in DMF (2.0 mL) under argon. The mixture was stirred at rt for 1 h until most of the indium metal was dissolved in DMF to give a grey solution. (*R*)-(-)-Carvone (75 mg, 0.50 mmol) in DMF (1.0 mL) was then added dropwise. The mixture was stirred at rt for 3 days before water (10 mL) was added. The mixture was then extracted with ether (5 mL × 3). The combined organic layers were then washed with water (10 mL × 3) and brine (5 mL), and then dried over $MgSO_4$. After removal of the solvent, the residue analyzed by NMR.



337

(1*R*,5*R*)-1-Allyl-5-isopropenyl-2-methylcyclohex-2-en-1-ol, benzoate ester (337)

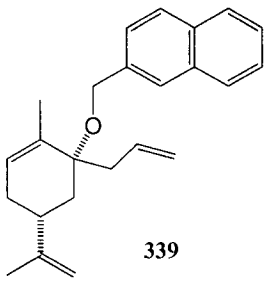
Benzoyl chloride (53 mg, 0.38 mmol) was added to a solution of **328** (66 mg, 0.34 mmol), pyridine (41 mg, 0.52 mmol) and DMAP (5 mg) in CH_2Cl_2 (3.0 mL) dropwise. The mixture was stirred overnight before it was diluted with CH_2Cl_2 (15 mL), and the reaction was quenched with water (10 mL). The organic layer was washed with water (10 mL), saturated $NaHCO_3$ solution and brine, and then dried over Na_2SO_4. After removal of the solvent under vacuum, the residue was subjected to flash column chromatography to give compound **337** as a colorless oil. (Rf 0.68; 20% ethyl acetate /hexanes, 91 mg, 91%). IR (cm^{-1}, neat): 1740. δ_H 8.16 (2 H, dd, J_1 8.0, J_2 1.4, *ortho* phenyl), 7.67 (1 H, tt, J_1 7.5, J_2 1.3, *para* phenyl), 7.52 (2 H, t, J 7.7, *meta* phenyl), 5.87 (1 H, m, CH_2=*CH*CH_2), 5.47 (1 H, m, *CH*=C(CH_3)), 5.07-5.18 (2 H, m, *CH_2*=$CHCH_2$), 4.73 (2 H, s, *CH_2*=C(CH_3)), 2.47 (1 H, ddd, J_1 14, J_2 7.4, J_3 0.8, CH_2=CH*CH_2*), 2.29-2.38 (2 H, m, CH_2=CH*CH_2* and *CH*-C(CH_3)=CH_2)), 2.03-2.13 (2 H, m, CH_3C=CH-*CH_2*-CH and CH-*CH_2*-C(OH)), 1.96 (1 H, m, CH_3C=CH-*CH_2*-CH), 1.73-1.75 (3 H, m, CH=C-*CH_3*), 1.73 (3 H, s, methyl isopropenyl), 1.50 (1 H, dt, J_1 12.3, J_2 1.4, CH-*CH_2*-C(OH)). δ_C 162.5 (O-C=O), 149.1 (tertiary, isopropenyl), 138.3 (tertiary, phenyl), 134.7 (*para*, phenyl), 133.9 (CH_2*CH*=CH_2), 130.7 (*ortho*, phenyl), 129.0 (*meta*, phenyl), 124.0 (CH_3-C=*CH*), 118.7 (CH_2CH=*CH_2*), 109.3 (terminal, isopropenyl), 73.7 (O-*C*-C=CH), 43.1 (*CH_2*CH=CH_2), 40.6 (O-C-*CH_2*), 39.4 (*CH*-isopropenyl), 31.0 (*CH_2*-CH=C-CH_3), 20.9 (*CH_3*, isopropenyl), 17.2 (CH=C-*CH_3*). GC-MS: 174 (29, M^+-PhCOOH), 159 (18), 151 (37), 145 (16), 133 (88), 131 (63), 117 (57), 109 (61), 105 (69), 91 (100), 79 (48), 77 (72). HRMS: Experimental, 296.1790 amu ($C_{20}H_{24}O_2$, Calculated 296.1776).



338

(1*R*,5*R*)-1-[4-((1*R*,5*R*)-1-Hydroxy-5-isopropenyl-2-methylcyclohex-2-enyl)but-2-*E*-enyl]-5-isopropenyl-2-methylcyclohex-2-en-1-ol (338)

A catalytic amount (0.5 mg) of Grubbs' second generation catalyst (**300**) was added to a solution of **328** (49 mg, 0.26 mmol) in CH_2Cl_2 (5.0 mL) under argon The mixture was stirred at rt overnight. After the removal of solvent, the residue was subjected to flash column chromatography to give compound **338** (R_f 0.15; 20% ethyl acetate/hexanes, 42 mg, 93%, mp 62-64°C) as colorless crystals. IR (cm^{-1}, cast): 3415, 1645. δ_H (C_6D_6) 5.63 (2 H, t, *J* 4.3, CH_2*CH*=*CH*CH_2), 5.30 (2 H, t, *CH*=C(CH_3)), 4.80 (2 H, s, *CH_2*=CCH_3), 4.77 (2 H, s, *CH_2*=CCH_3), 2.46 (2 H, dd, *J_1* 14.3, *J_2 4.2*, *CH_2*CH=CH*CH_2*), 2.21-2.32 (4 H, m, *CH*-C(CH_3)=CH_2 and *CH_2*CH =CH*CH_2*), 2.07 (2 H, dt, *J_1* 12.2, *J_2* 2.0, CH-*CH_2*-C(OH)), 1.93-2.00 (2 H, m, CH_3C=CH-*CH_2*-CH), 1.82-1.91 (2 H, m, CH_3C=CH-*CH_2*-CH), 1.78 (6 H, s, *CH_3*C=CH-CH_2-CH), 1.65 (6 H, s, isopropenyl), 1.39 (2 H, t, *J* 5.8, CH-*CH_2*-C(OH)). δ_C ($CDCl_3$) 148.9 (CH_3-*C*=CH_2), 138.2 (CH=*C*-CH_3), 129.3 (CH_2-*CH*=*CH*-CH_2), 123.8 (*CH*=C-CH_3), 109.2 (CH_3-C=*CH_2*), 73.7 (*C*(OH)), 41.7 (*CH_2*-CH=CH-*CH_2*), 40.4 (*CH_2*C(OH), ring), 39.3 (*CH*-isopropenyl), 30.9 (*CH_2*-CH=C(CH_3)), 20.7 (*CH_3*-C=CH), 17.0 (*CH_3*, isopropenyl). GC-MS: 133 (2), 131 (3), 129 (2), 118 (13), 117 (32), 115 (14), 105 (28), 92 (18), 91 (100), 80 (2), 79 (9), 77 (34), 67 (2), 65 (1), 55 (45).

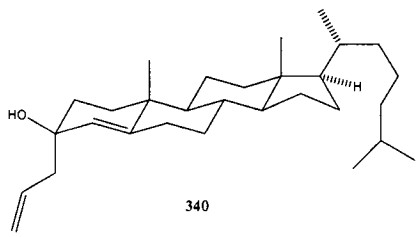


339

(1*R*,5*R*)-1-Allyl-5-isopropenyl-2-methyl-1-(2-naphthlymethoxy)cyclohex-2-ene (339)

Compound **328** (116 mg, 0.60 mmol) was added to a suspension of potassium hydride (133 mg, 0.60 mmol, 30% in mineral oil) in THF (3.0 mL) under argon. The mixture was stirred at rt for 1 h before 2-(bromomethyl)naphthylene (133 mg, 0.60 mmol) in THF (3.0 mL) was added dropwise. The mixture was stirred at rt overnight before it was diluted with ether (20 mL) and quenched with water (10 mL). The organic layer was dried over Na_2SO_4 before it was filtered. The organic solvent was then removed under vacuum, and the residue was subjected to flash column chromatography to give compound **339** (R_f 0.82; 20% ethyl acetate/hexanes, 75 mg, 38%) as a colorless oil. $[\alpha]_D^{25}$ = -0.61 (CH_2Cl_2, c=0.013). IR (cm^{-1}, neat): 1640, 1602, 1509, 1451. δ_H 7.77-7.83 (4 H, m, aromatic), 7.40-7.48 (3 H, m, aromatic), 6.03 (1 H, m, CH_2=*CH*CH_2), 5.74 (1 H, m, *CH*=C(CH_3)), 5.07-5.14 (2 H, m, *CH_2*=CHCH_2), 4.71 (2 H, d, *J* 6.0, *CH_2*=C(CH_3)), 4.62 (1 H, d, *J* 12.0, O*CH_2*), 4.37 (1 H, d, *J* 12.6, O*CH_2*), 2.67 (1 H, ddd, J_1 14.2, J_2 6.0, J_3 1.6, CH_2=CH*CH_2*), 2.44 (1 H, dd, J_1 14.6, J_2 8.8, CH_2=CH*CH_2*), 2.38 (1 H, m, *CH*-C(CH_3)=CH_2)), 2.09 (1 H, m, CH_3C=CH-*CH_2*-CH), 1.94-2.03 (2 H, m, CH-*CH_2*-C(OCH_2Ar) and CH_3C=CH-*CH_2*-CH), 1.82 (1 H, t, *J* 12.8, CH-*CH_2*-C(OCH_2Ar)), 1.73 (6 H, s, *CH_3* and *CH_3*). NOE: 4.71 (2.35-2.42, 0.2%; 1.94-2.03, 0.3%; 1.82, 0.1%; 1.73, 0.5%), 2.35-2.42 (2.67, 0.6%; 2.44, 0.7%; 2.06-2.14, 2%; 1.94-2.03, 1.3%; 1.72, 1%), and 1.82 (4.71, 0.5%; 4.62, 4%; 4.37, 0.7%; 1.98, 6%). δ_C 149.3 (tertiary,

isopropenyl), 137.7 (CH=*C*(CH_3), ring), 136.6 (CH_2-*CH*=CH_2), 135.2, 133.7, 132.9, 128.1, 128.0, 127.9, 127.8, 126.1, 125.7, 125.5, 125.4 (*CH*=C(CH_3), ring), 117.4 (CH_2-CH=*CH_2*), 109.0 (terminal, isopropenyl), 80.5 (*C*(OAr)), 64.1 (O*CH_2*Ar), 44.00 (*CH_2*-CH=CH_2), 39.7 (*CH_2*C(OCH_2Ar), ring), 34.7 (*CH*-isopropenyl), 31.2 (*CH_2*-CH=C(CH_3)), 21.1 (*CH_3*, isopropenyl), 17.6 (*CH_3*-C=CH). GC-MS: 174 (4, M^+-158 (naphyl-CH_2OH)), 159 (2), 145 (7), 133 (19), 131 (34), 129 (17), 117 (58), 115 (44), 105 (38), 103 (13), 91 (100), 89 (7), 79 (33), 77 (57), 67 (14), 65 (39). HRMS: Experimental, 174.1411 amu (M^+-(naphthyl-CH_2OH) = $C_{13}H_{18}$, Calculated 174.1409).



340

(+)-(3*R*)-3-Allyl-4-cholesten-3-ol (340)

A) ALLYL GRIGNARD

Allyl bromide (30 mg, 0.25 mmol) was added to a suspension of magnesium metal (8 mg, 0.3 mmol) in ether (5 mL) dropwise. The mixture was stirred at rt for 1 h until most of the magnesium dissolved, resulting in a cloudy solution. (+)-4-Cholesten-3-one (96 mg, 0.25 mmol) was added dropwise over 10 min, and the resulting mixture was stirred at rt overnight. The reaction was quenched with water (10 mL), and the organic layer was washed with water (10 mL × 3) and dried over Na_2SO_4. After the solvent was removed under vacuum, the crude residue was analyzed by NMR (^{1}H NMR product ratio: **340**: **341** = 6.3:1).

B) ALLYLINDIUM REAGENT

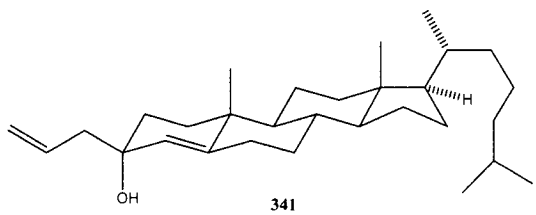
Allyl iodide (168 mg, 1.0 mmol) was added to a suspension of indium metal (115 mg, 1.0 mmol) in DMF (2.0 mL) under argon. The mixture was stirred at rt for 1 h until most of the indium metal was dissolved, to give a grey solution. (+)-4-Cholesten-3-one (96 mg, 0.25 mmol) in DMF (1.0 mL) was then added dropwise. The mixture was stirred at rt overnight before water (10 mL) was added. The mixture was extracted with ether (5 mL × 3). The combined organic layers were washed with water (10 mL × 3) and saturated $NaHCO_3$, and then dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was subjected to flash column chromatography with to give **340** as a white solid (R_f 0.52; 20% ethyl acetate/hexanes, 87 mg, 82%) and **341** (R_f 0.44; 20% ethyl acetate/hexanes, 15 mg, 14%) as a colorless oil (product ratio from ^{1}H NMR, **340**: **341** = 4.5:1).

C) ALLYLBISMUTH [117]

Zinc powder (33 mg, 0.53 mmol) was added to a mixture of (+)-4-Cholesten-3-one (96 mg, 0.25 mmol), $BiCl_3$ (110 mg, 0.35 mmol), and allyl bromide (42 mg, 0.35 mmol) in THF (5 mL) while stirring at rt. The mixture was refluxed for 3 h and allowed to cool to rt. The solid was removed by filtration, and the solvent was removed under vacuum. The residue was diluted with ether (5 mL), and 0.5 M HCl (3 mL) was added. The organic layer was washed with water (2 × 5 mL) and saturated $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the crude residue was analysed by ^{1}H NMR to reveal a product ratio of 4.2:1 (**340**:**341**, respectively).

Compound **340**: $[\alpha]_D^{25}$ = +75.7 (CH_2Cl_2, c=0.026). . IR (cm^{-1}, neat): 3348, 1638. δ_H 5.90 (1 H, m, CH_2=*C*HCH_2), 5.08-5.18 (3 H, m, *C*H_2=CHCH_2 and HO-C-*C*H=C), 2.33 (1

H, dd, J_1 13.7, J_2 6.9), 2.15-2.18 (2H, m), 1.70-1.84 (3 H, m), 1.20-1.68 (15 H, m), 1.05-1.16 (6 H, m), 1.04 (3 H, s, CH_3), 0.93-1.03 (2 H, m), 0.90 (3 H, d, J 6.8, CH_3), 0.86 (6 H, d, J 6.6, $CH(CH_3)_2$), 0.82 (1H, m), 0.73 (1 H, m), 0.68 (3 H, s, CH_3). δ_C 147.1, 134.2, 125.6, 118.7, 71.1, 56.5, 56.4, 54.4, 45.7, 42.7, 40.1, 39.7, 37.7, 36.4, 36.2, 36.0, 34.9, 33.5, 32.6, 32.5, 28.4, 28.2, 24.4, 24.1, 23.0, 22.8, 21.5, 19.2, 18.9, 12.2. GC-MS: 356 (44), 341 (4), 328 (23, M^+-C_3H_4-H_2O), 327 (100), 325 (11), 298 (4), 297 (8), 296 (14), 238 (3), 219 (9), 218 (37), 203 (31), 190 (14), 189 (83), 187 (7), 175 (16), 165 (18), 156 (19), 151 (26), 115 (13). HRMS: Experimental, 386.3545 amu (M^+-C_3H_4 = $C_{27}H_{46}O$, Calculated 386.3549).



341

(+)-(3*S*)-3-Allyl-4-cholesten-3-ol (341)

IR (cm^{-1}, neat): 3422, 1684, 1617. δ_H 5.86 (1 H, m, CH_2=$CH$$CH_2$), 5.24 (1 H, s, HO-C-C$H$=C), 5.08-5.14 (2 H, m, CH_2=CHCH_2), 2.15-2.32 (3 H, m), 1.96-2.04 (2 H, m), 1.82 (1 H, m), 1.70 (1 H, m), 1.47-1.66 (8 H, m), 1.30-1.46 (5 H, m), 1.20-1.28 (2 H, m), 0.98-1.19 (7 H, m), 0.96 (3 H, s, CH_3), 0.91 (3 H, d, J 6.8, CH_3), 0.86 (6 H, d, J 6.8, $CH(CH_3)_2$), 0.76-0.84 (2 H, m), 0.66 (3 H, s, CH_3). δ_C 149.6, 134.3, 124.1, 118.4, 69.3, 56.4, 56.3, 54.5, 47.6, 42.7, 40.1, 39.7, 37.8, 36.4, 36.1, 36.0, 33.5, 32.9, 32.7, 32.2, 28.4, 28.2, 24.5, 24.1, 23.0, 22.8, 21.7, 18.9, 18.1, 12.2. GC-MS: 356 (54), 328 (19), 327 (100), 325 (6), 312 (2), 297 (4), 296 (10), 222 (3), 219 (7), 218 (37), 203 (34), 190 (9), 189 (88), 178 (6), 174 (17), 165 (13), 156 (19), 151 (29), 135 (9), 128 (11), 77 (12).

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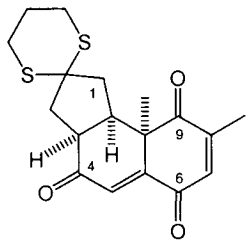
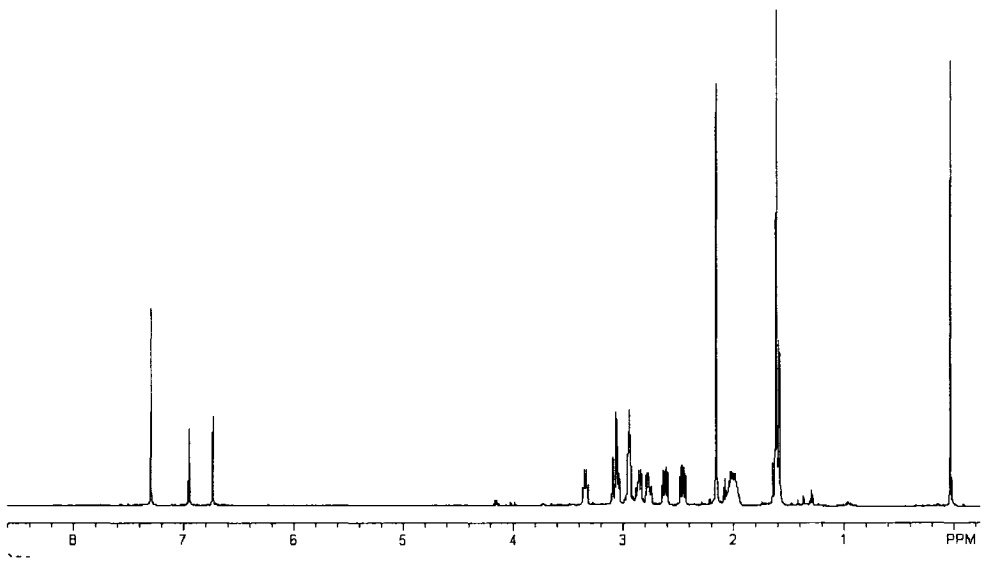
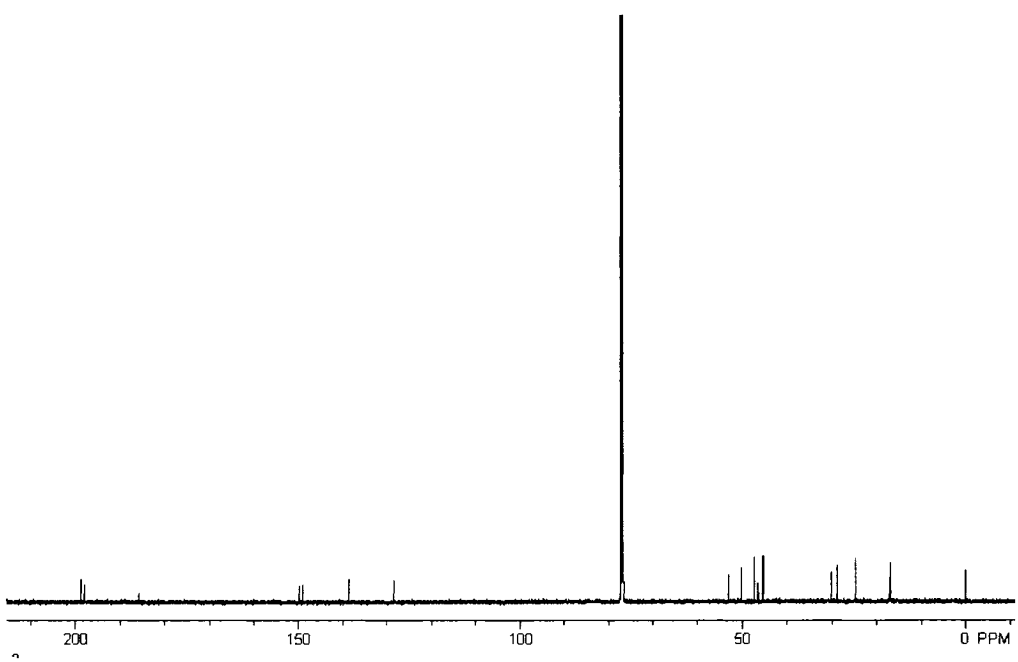
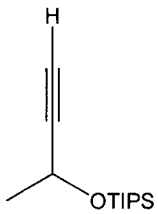
APPENDIX: NMR SPECTRA OF NEW COMPOUNDS



(3aα,9aα,9bα)-2,3,3a,4,9a,9b-Hexahydro-8,9a-dimethyl-1*H*-benz[*e*]indene-2,6,9-trione, 2-(propylene thioacetal) derivative (**195**)

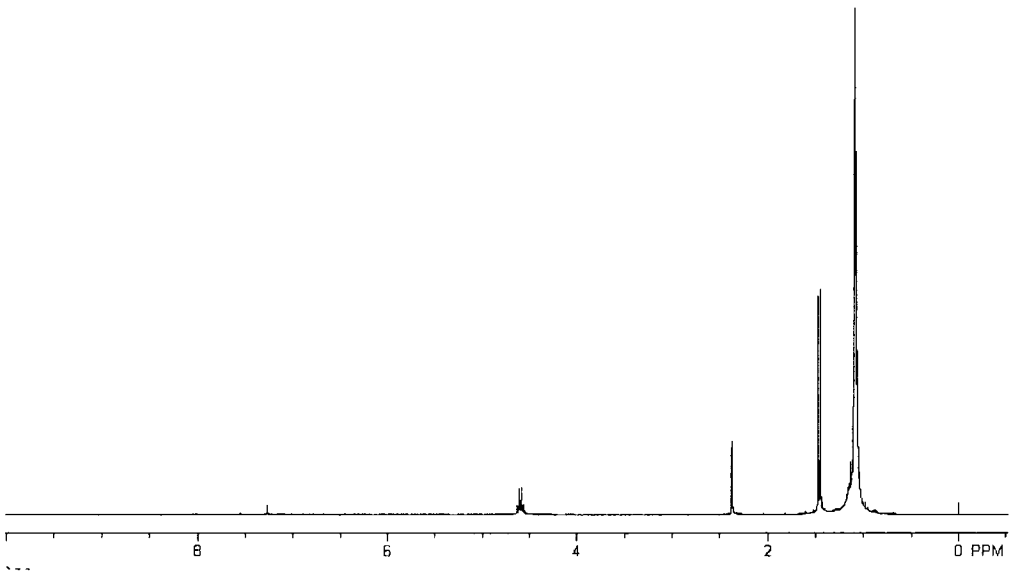


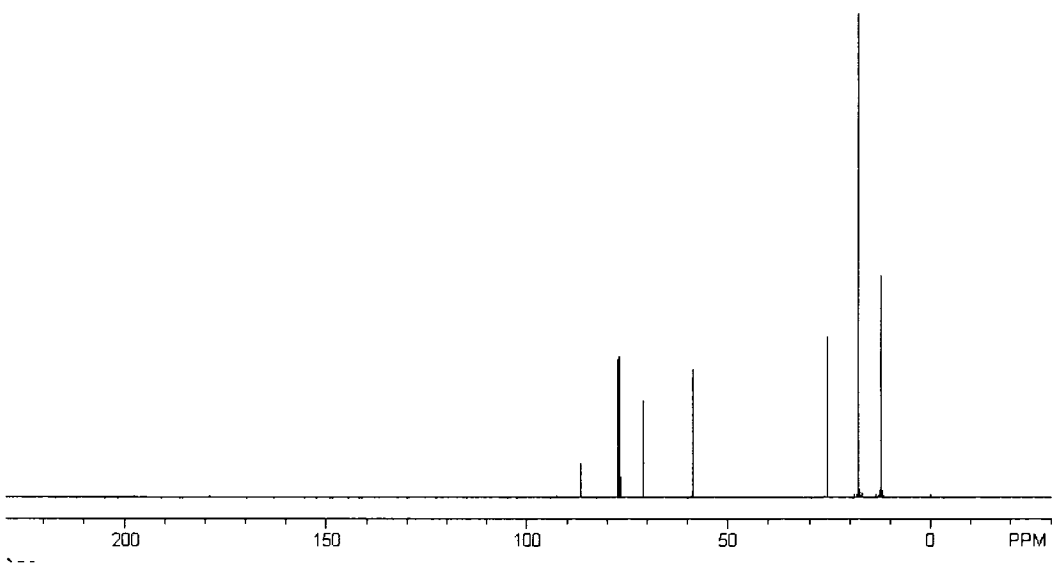


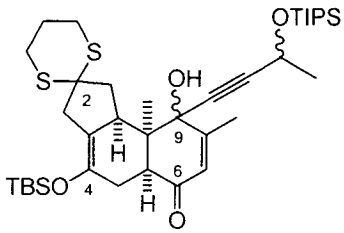


200

3-Triisopropylsilyloxybut-1-yne (**200**)

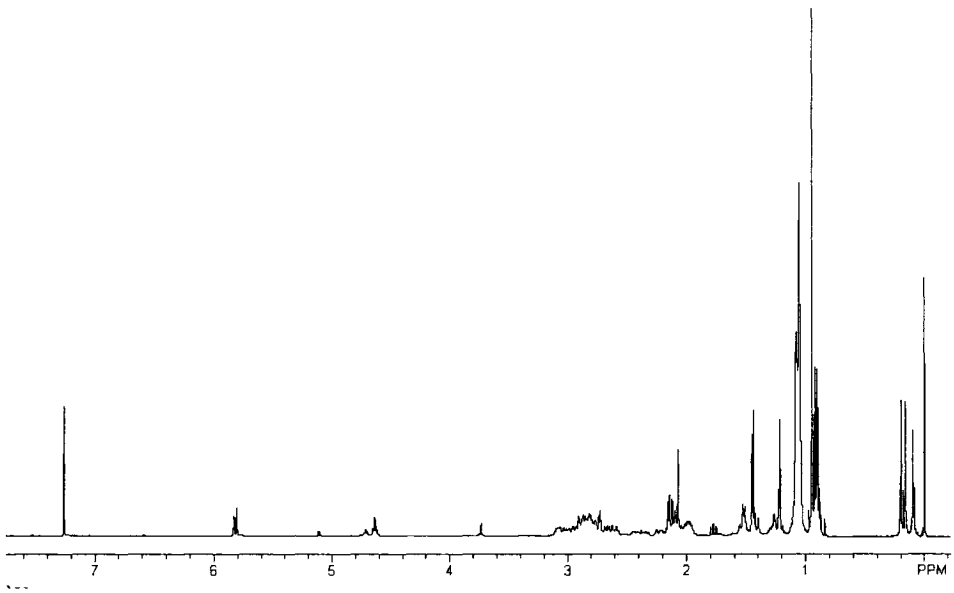


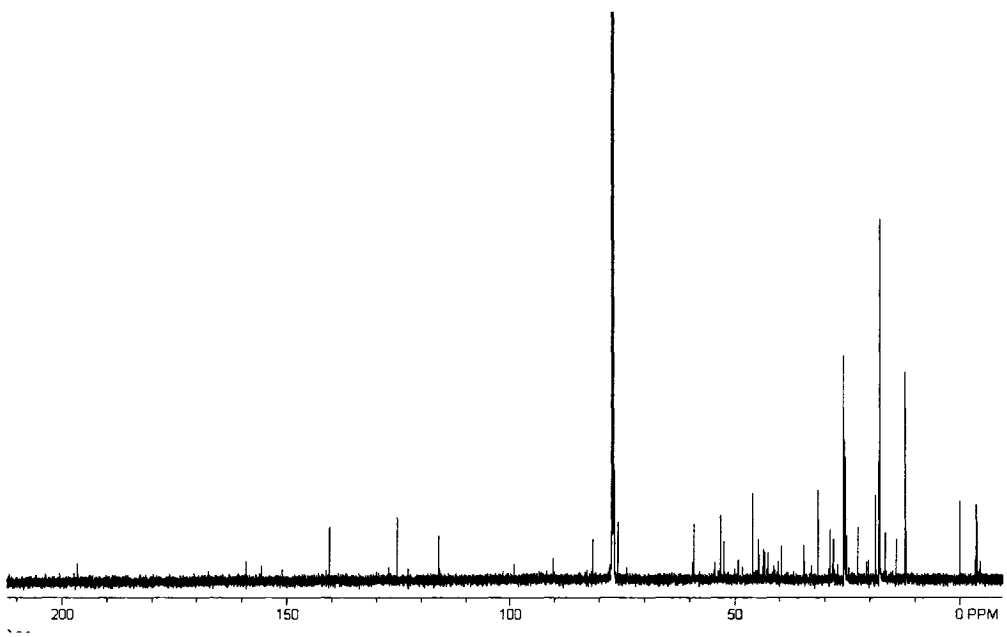


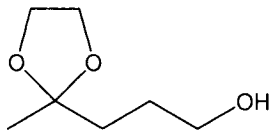


203

(5aα,9aα,9bα)-4-(*tert*-Butyldimethylsilyl)oxy-2,3,5,5a,6,9,9a,9b-octahydro-9-hydroxy-8,9a-dimethyl-9-[3-(triisopropylsilyl)oxybut-1-yn-1-yl]-1*H*-benz[*e*]indene-2,6-dione, 2-(propylene thioacetal) derivative (mixture of epimers at C-9) (**203**)

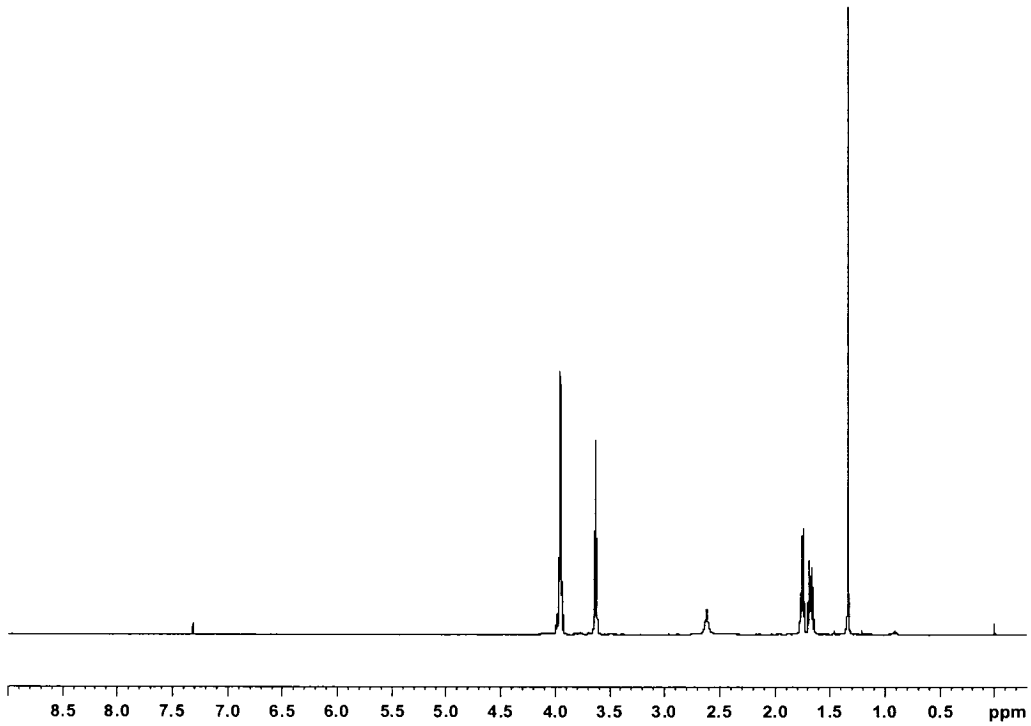


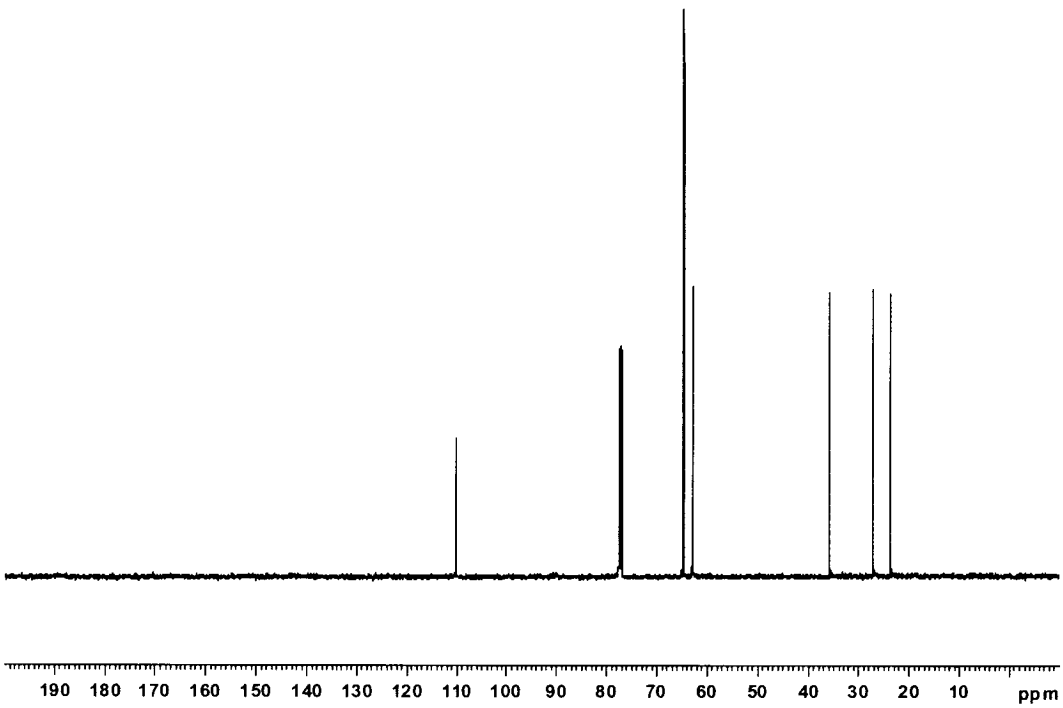


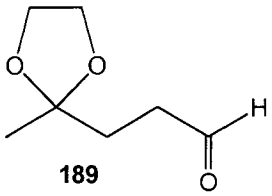


208

3-(2-Methyl-[1,3]dioxolan-2-yl)propan-1-ol (**208**)

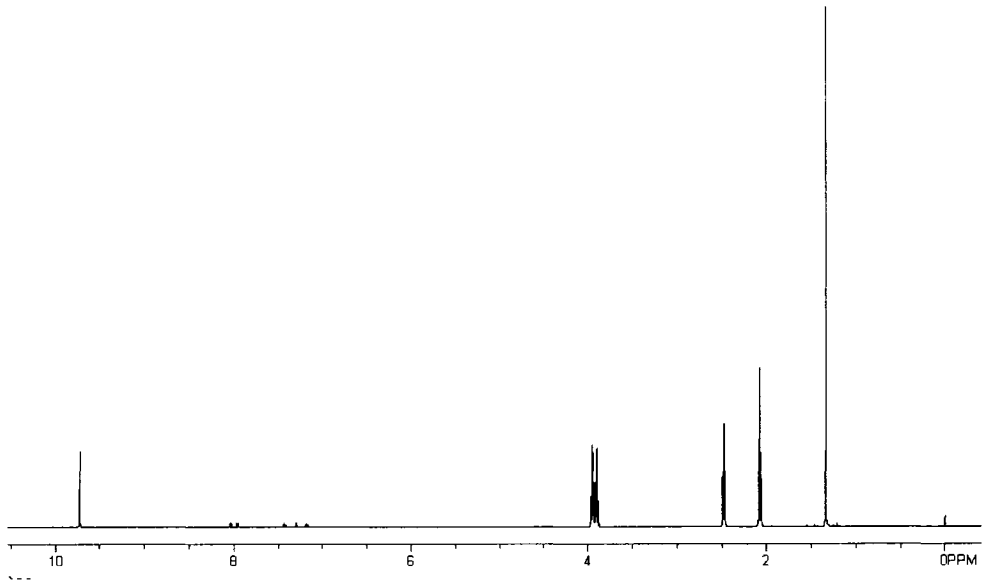


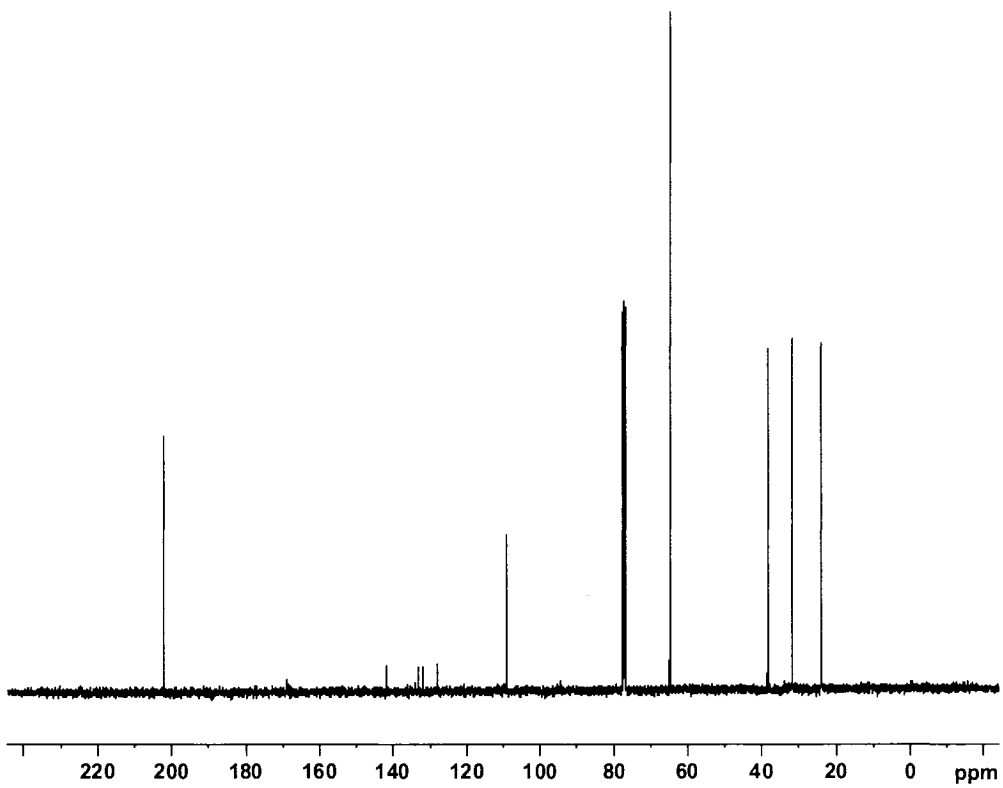


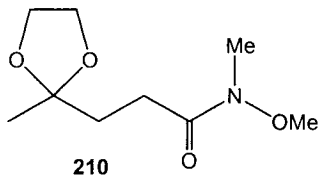


189

3-(2-Methyl-[1,3]dioxolan-2-yl)propionaldehyde (**189**)

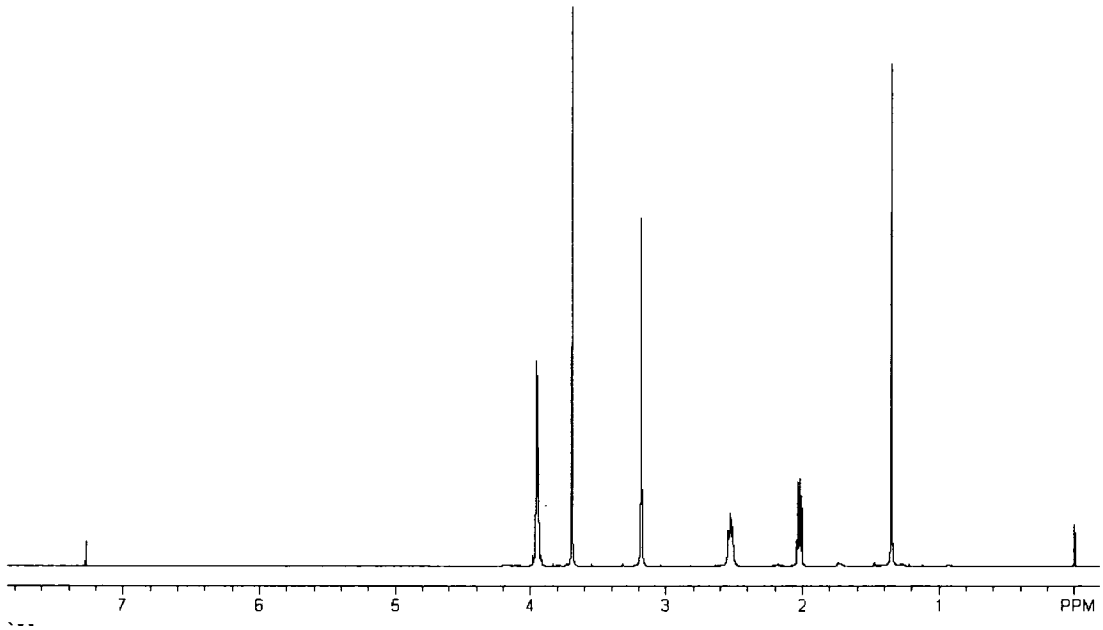


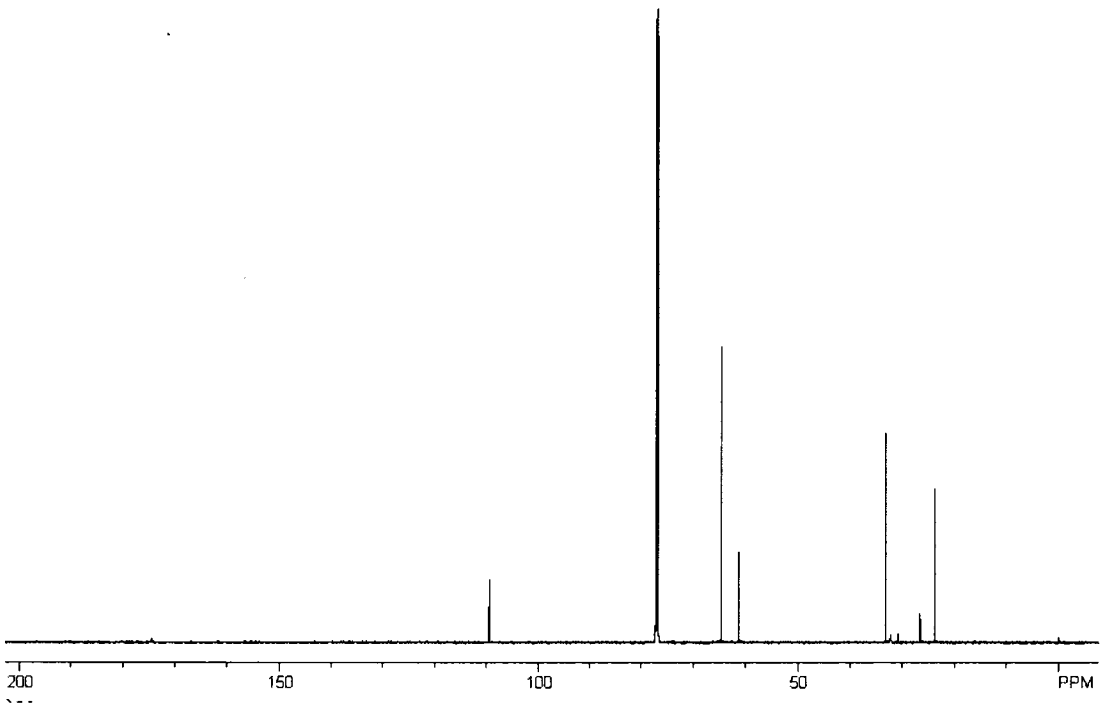


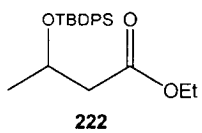


210

N-Methoxy-*N*-methyl-3-(2-methyl-[1,3]dioxolan-2-yl)-propionamide (**210**)

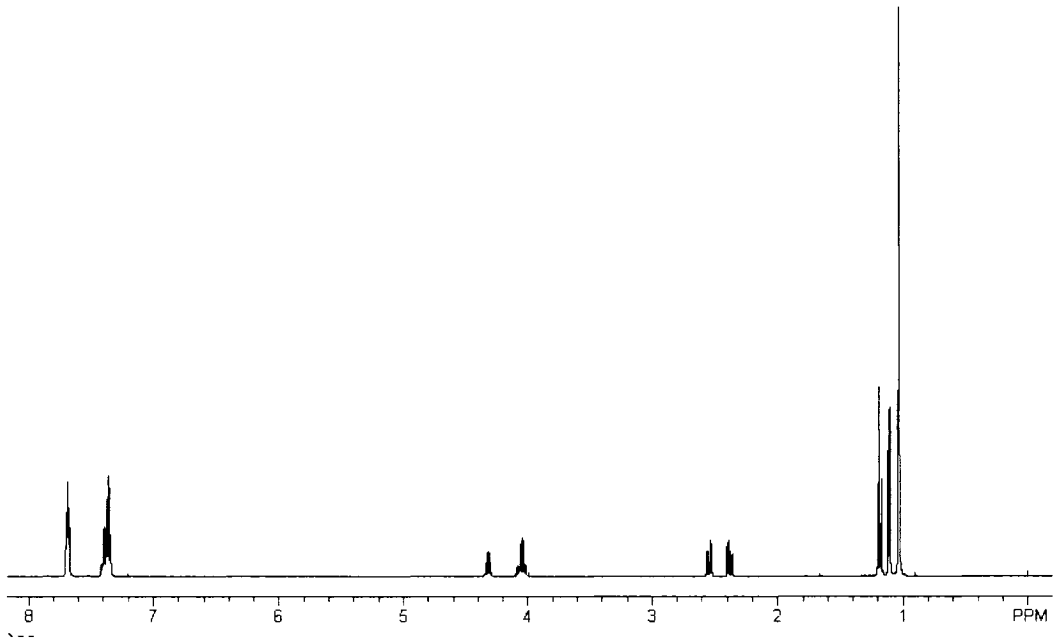


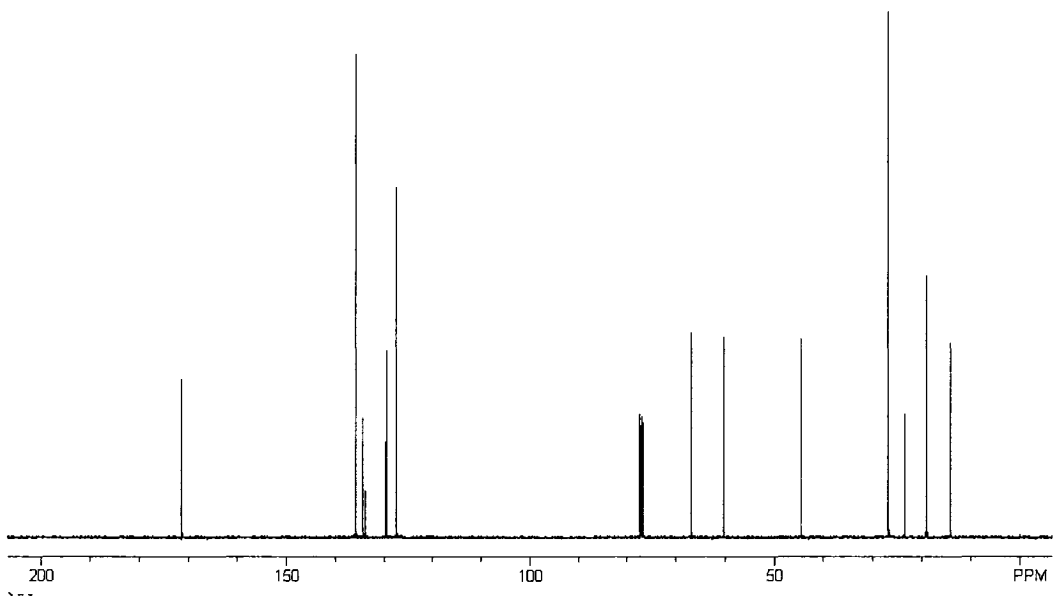


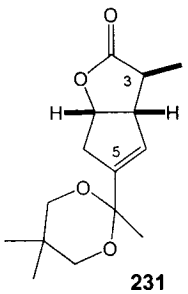


222

Ethyl 3-((*tert*-butyldiphenylsilyl)oxy)butanoate (**222**)

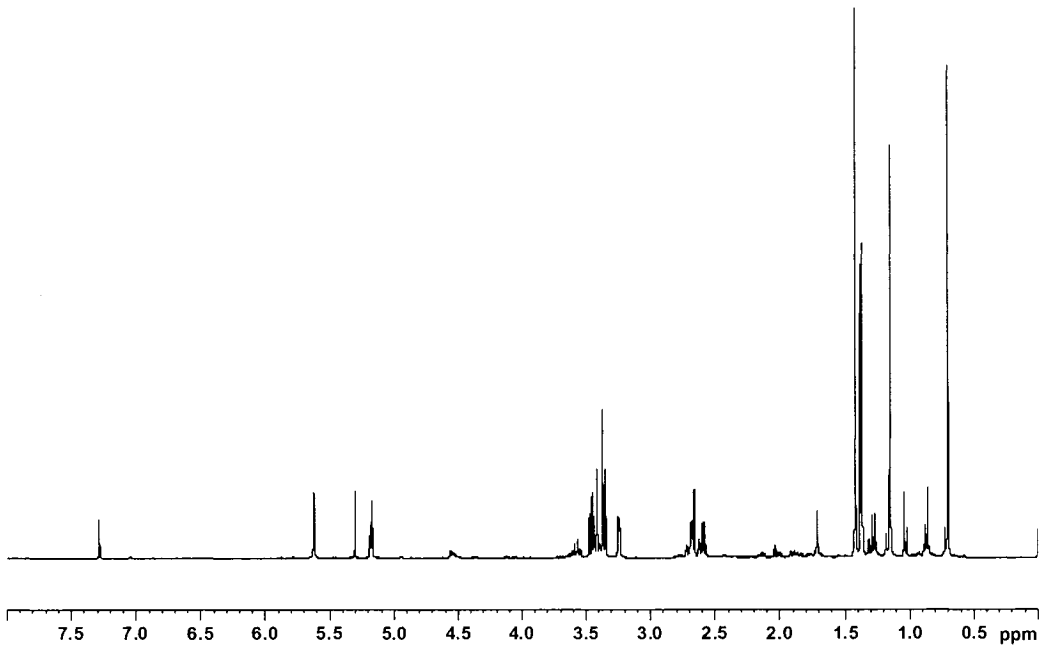


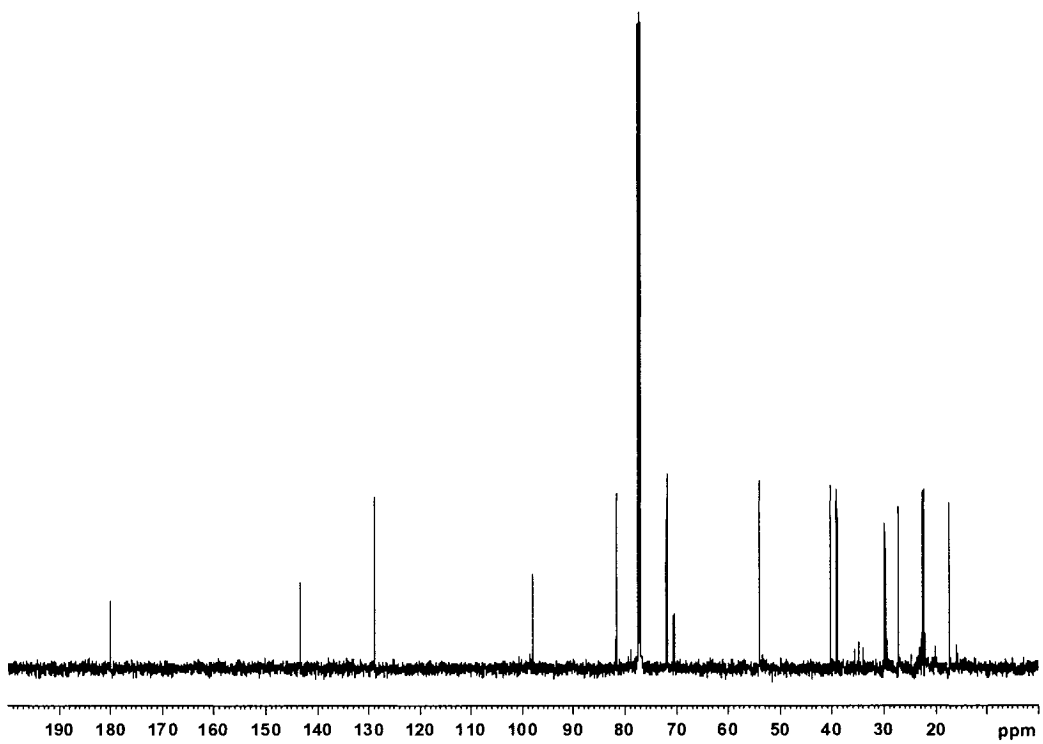


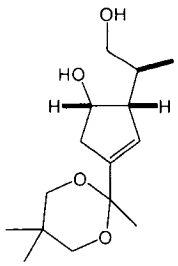


231

(3*R**,3a*R**,6a*R**)-3,3a,6,6a-Tetrahydro-3-methyl-5-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopenta[*b*]furan-2-one (**231**)

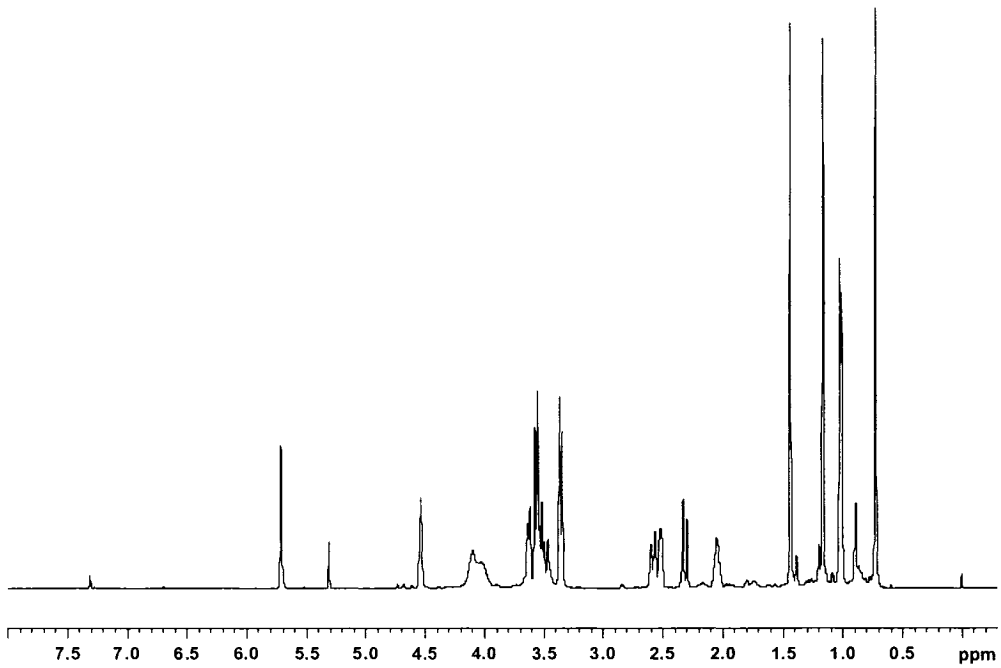


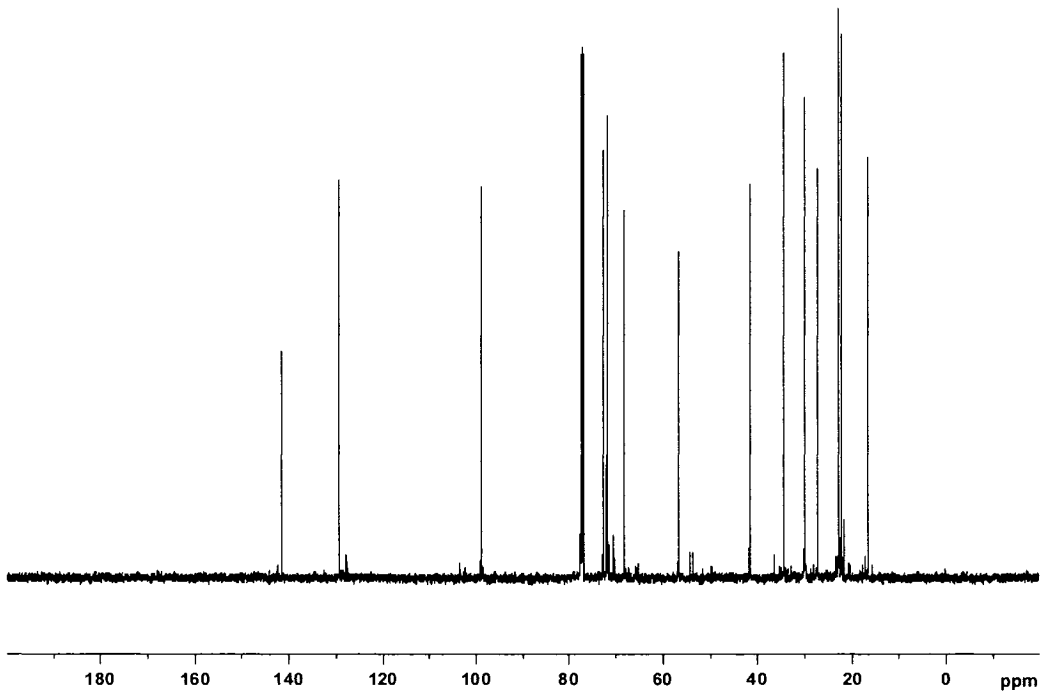


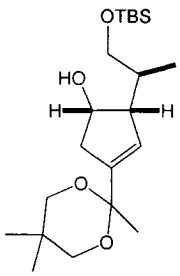


237

(1*R**,2*R**,6*R**)-2-(2-Hydroxy-1-methylethyl)-4-(2,5,5-trimethyl[1,3]dioxan-2-yl)cyclopent-3-en-1-ol (**237**)

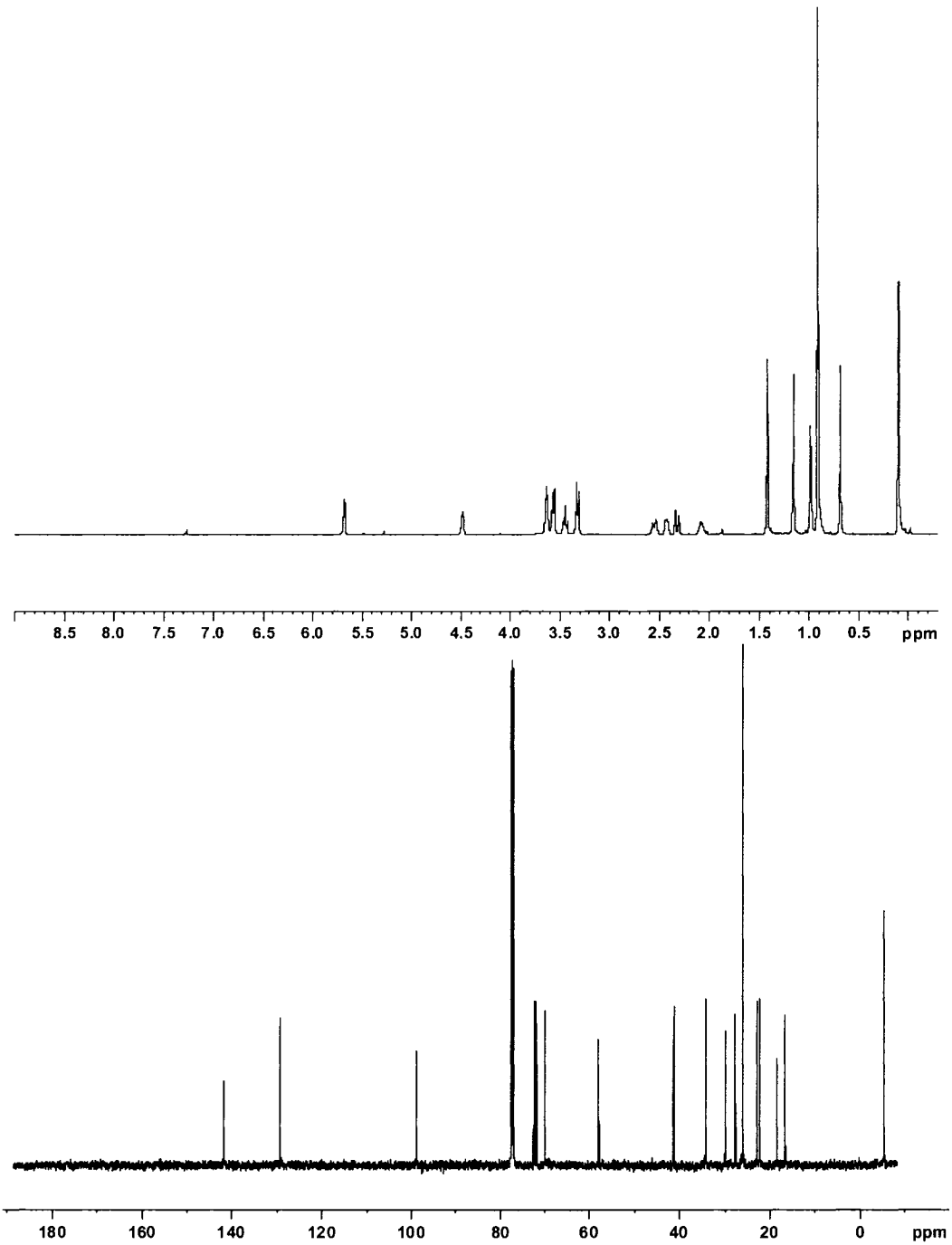


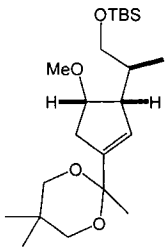




238

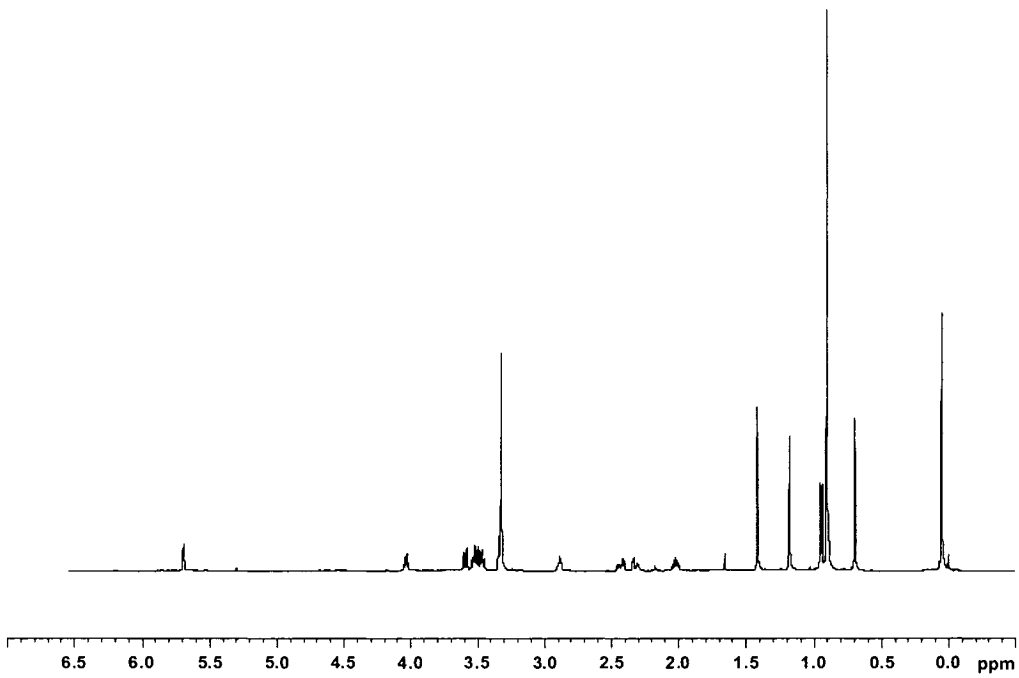
(1*R**,2*R**,6*R**)-2-[2-((*tert*-Butyldimethylsilyl)oxy)-1-methylethyl]-4-(2,5,5-trimethyl[1,3]dioxan-2-yl)cyclopent-3-en-1-ol (**238**)



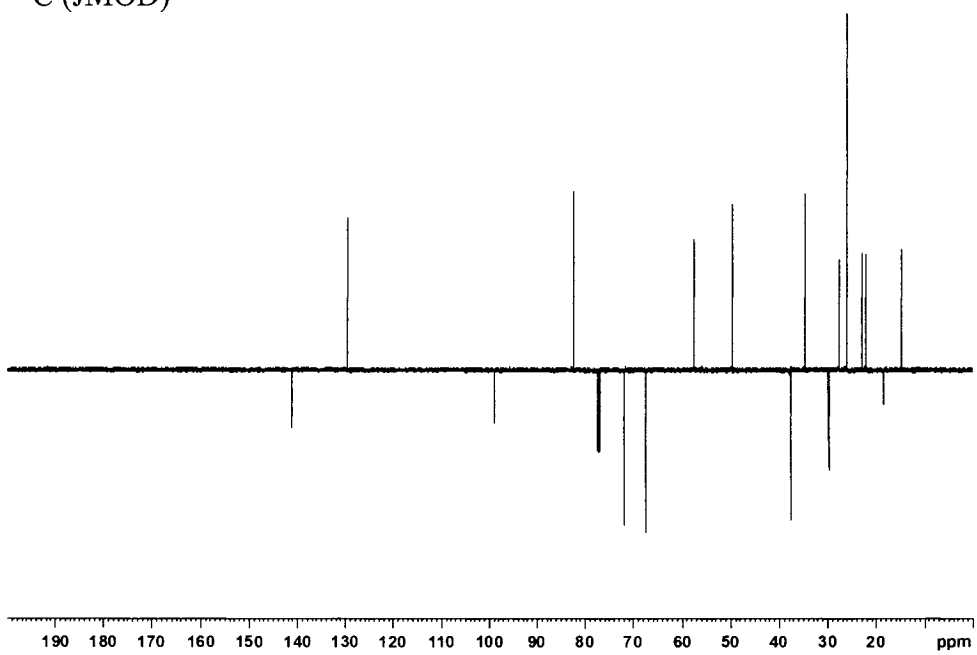


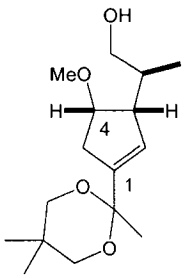
240

(3*R**,4*R**,8*R**)-3-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-4-methoxy-1-(2,5,5-trimethyl[1,3]dioxan-2-yl)-cyclopent-1-ene (**240**)

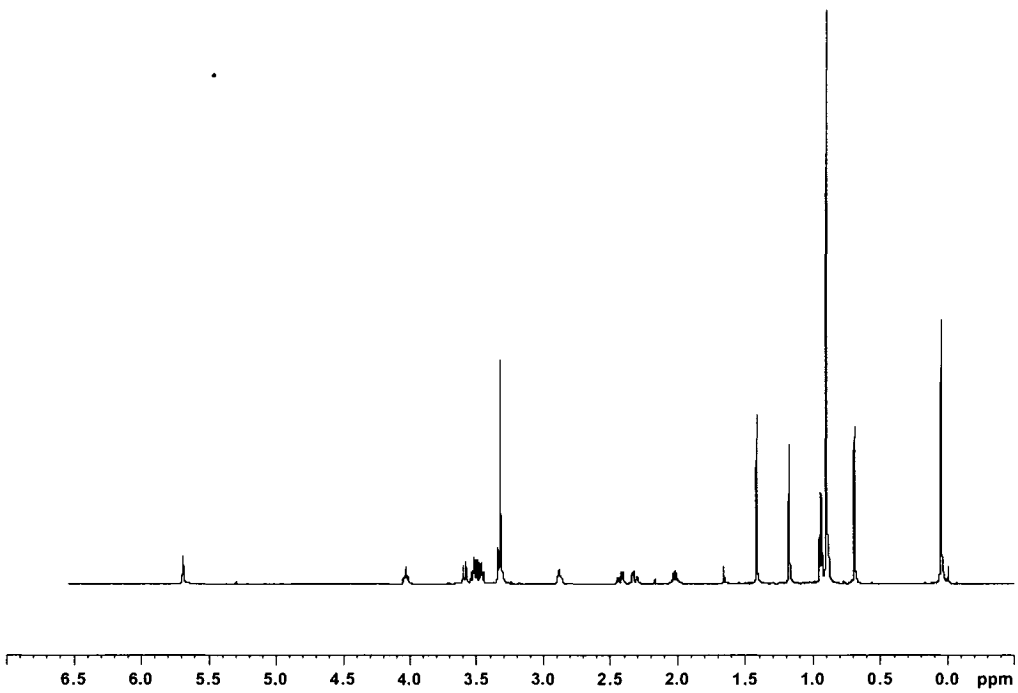


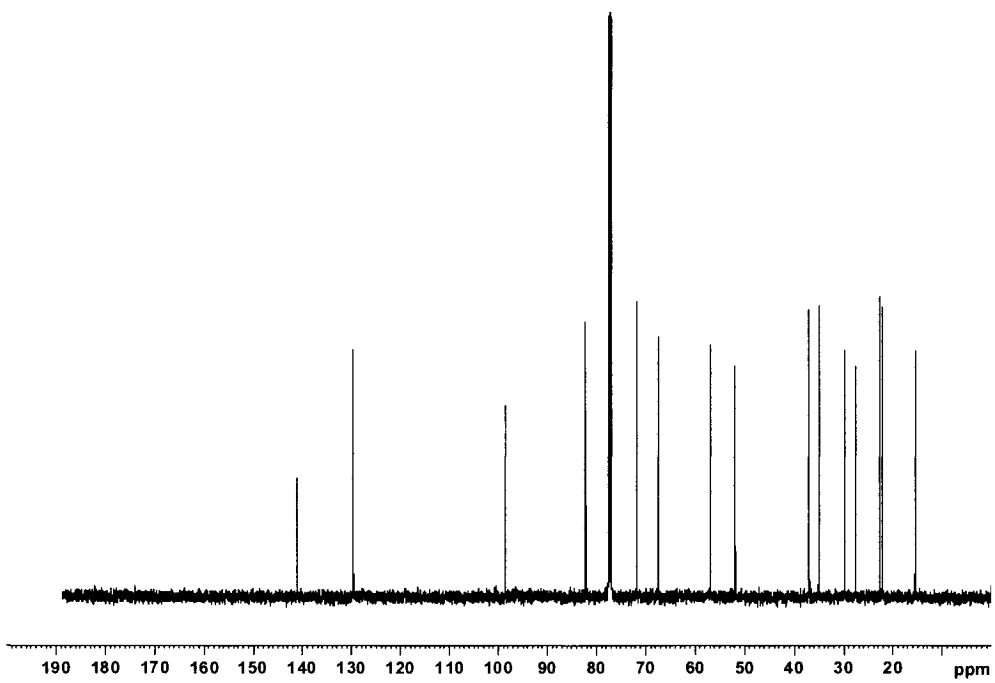
^{13}C (JMOD)

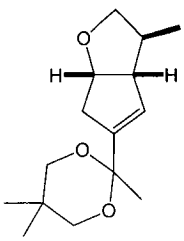




(3*R**,4*R**,6*R**)-4-Methoxy-3-(2-hydroxy-1-methylethyl)-1-(2,5,5-trimethyl-[1,3]-dioxan-2-yl)cyclopent-1-ene (**241**)

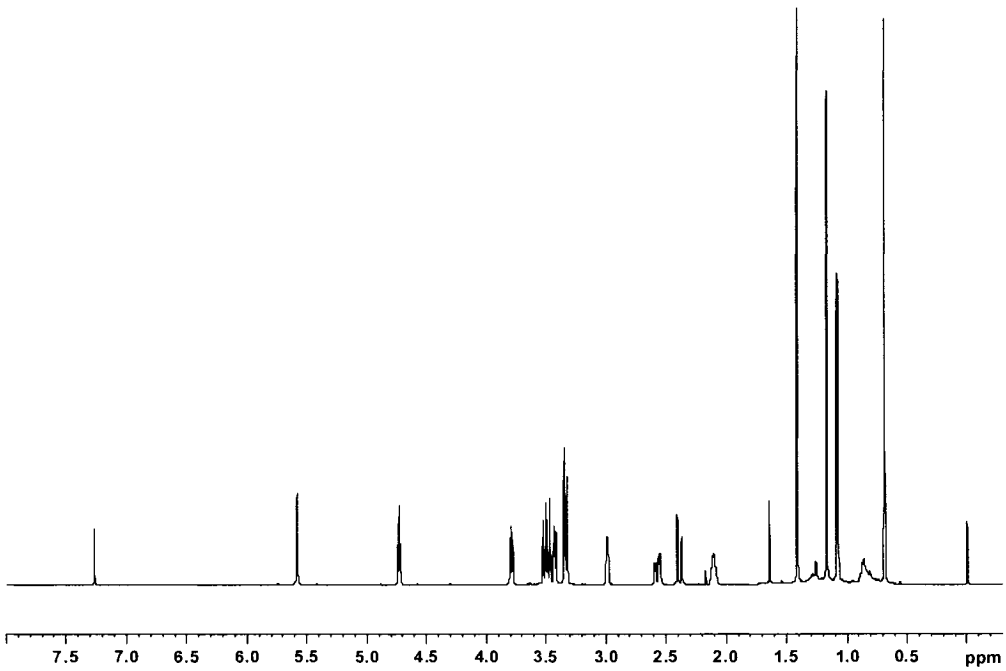


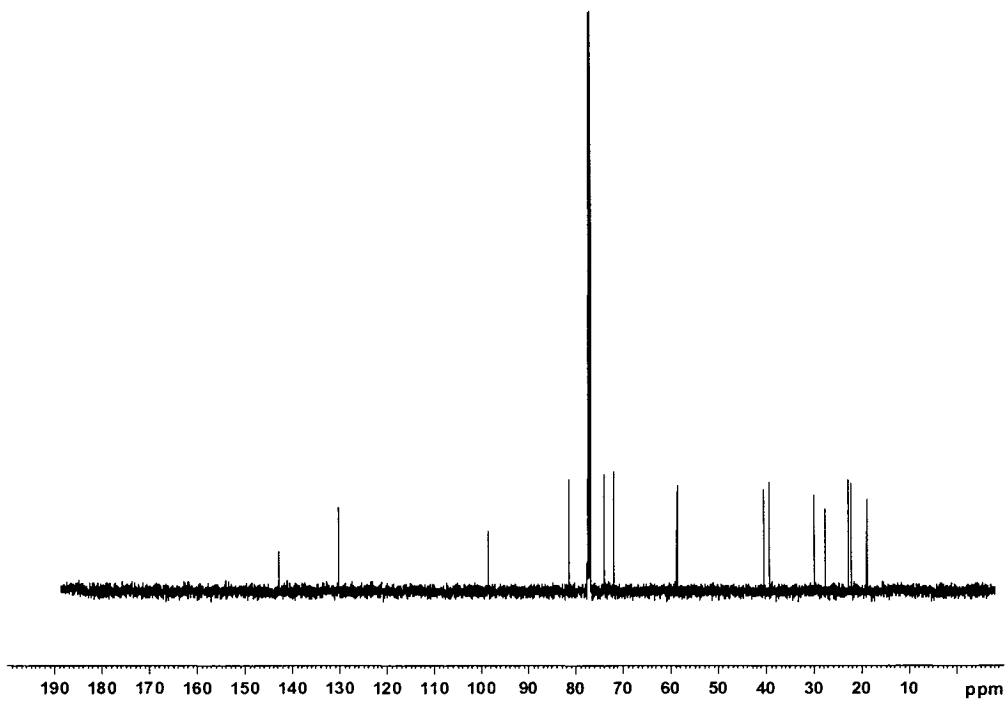


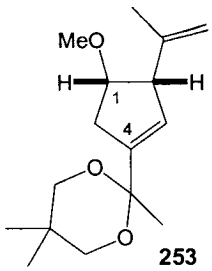


248

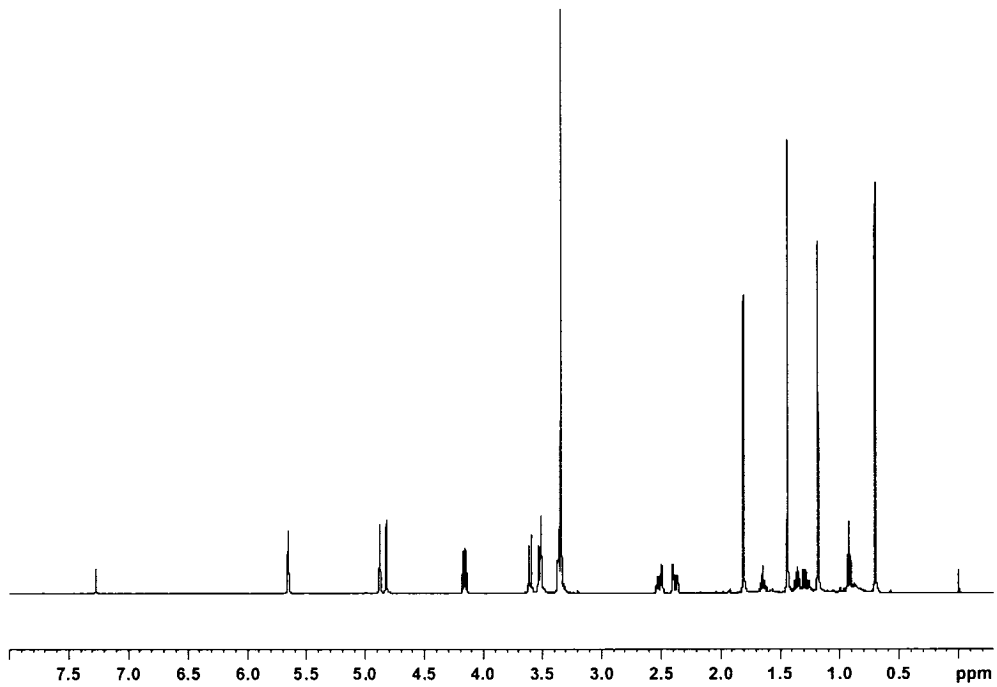
(3*R**,3a*R**,6a*R**)-3,3a,6,6a-Tetrahydro-3-methyl-5-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-2*H*-cyclopenta[*b*]furan (**248**)

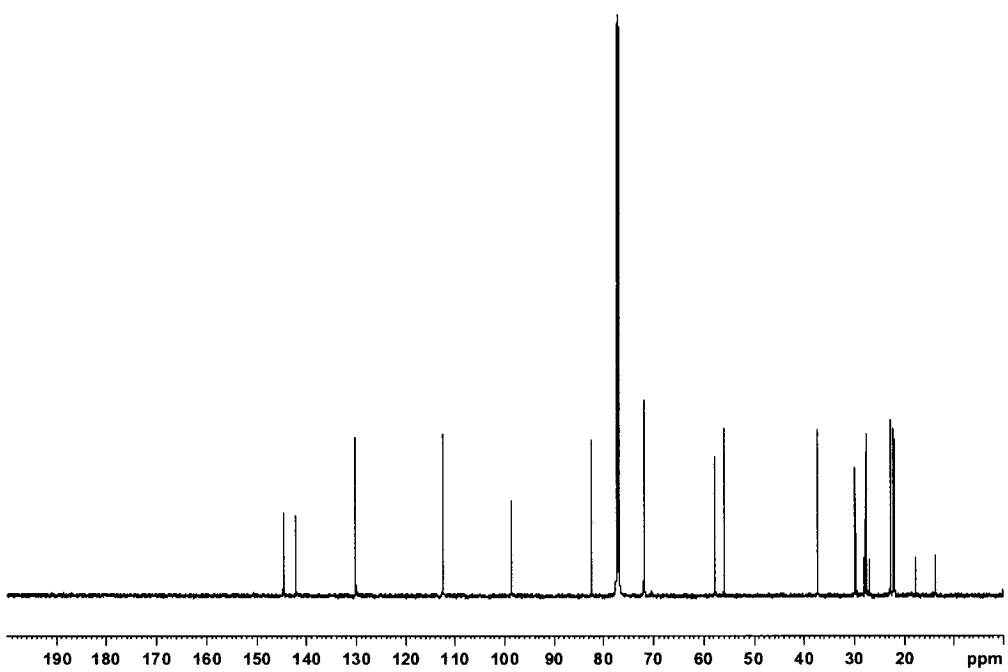


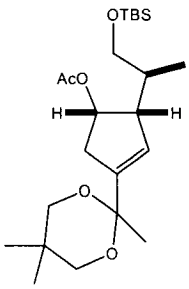




(1*R**,2S*)-1-Methoxy-2-isoprenyl-4-(2,5,5-trimethyl-[1,3]dioxan-2-yl)cyclopent-3-ene (**253**)

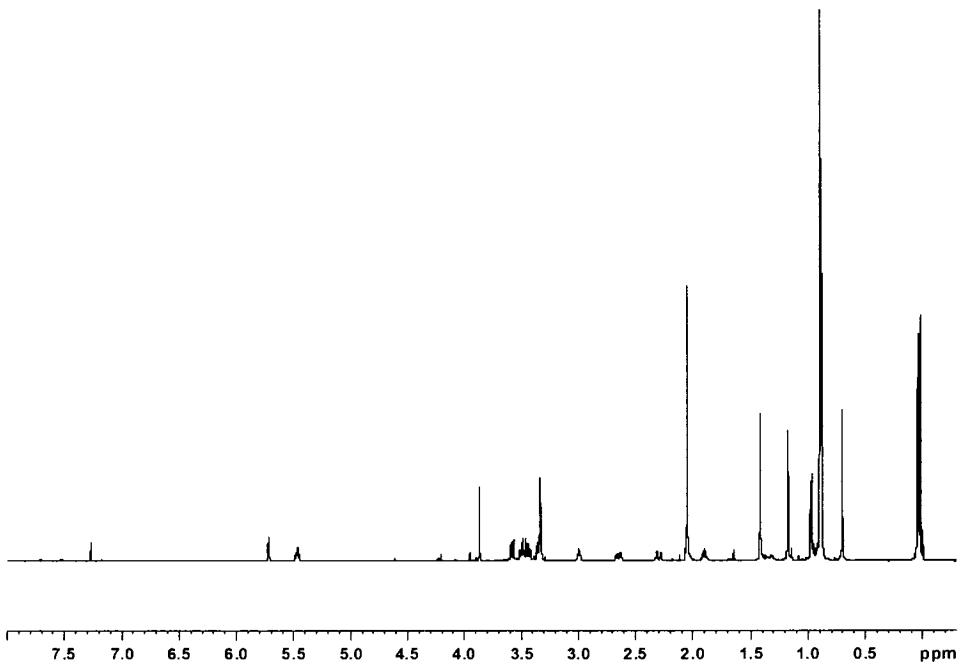


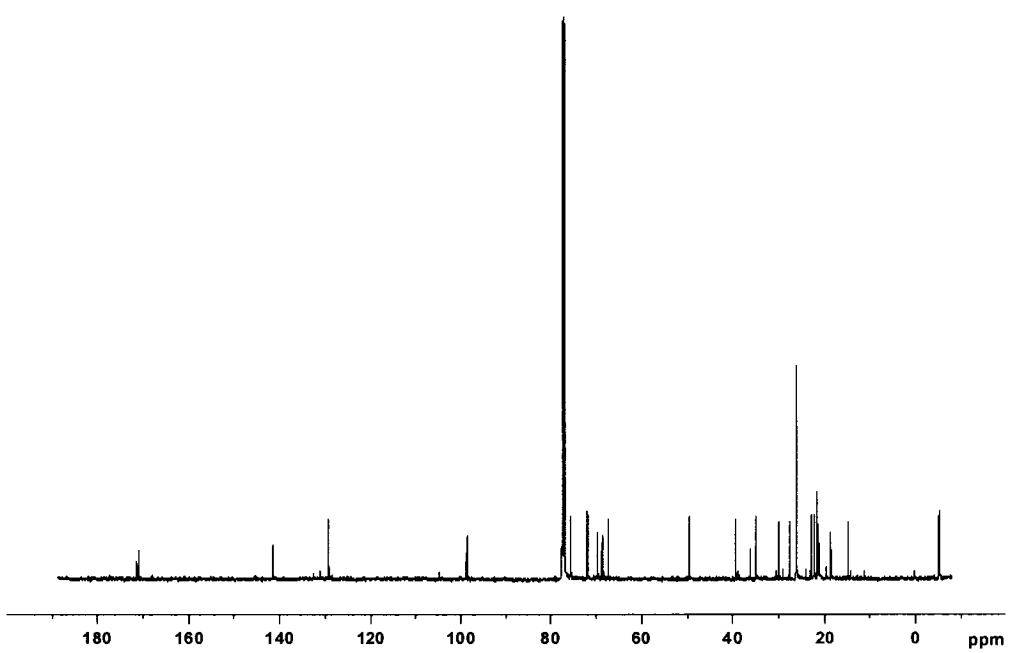


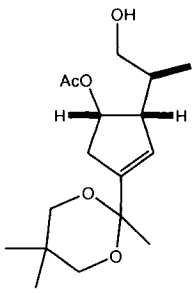


254

(1*R**,2*R**,6*R**)-2-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-4-(2,5,5-trimethyl[1,3]dioxan-2-yl)cyclopent-3-en-1-ol, acetic ester (**254**)

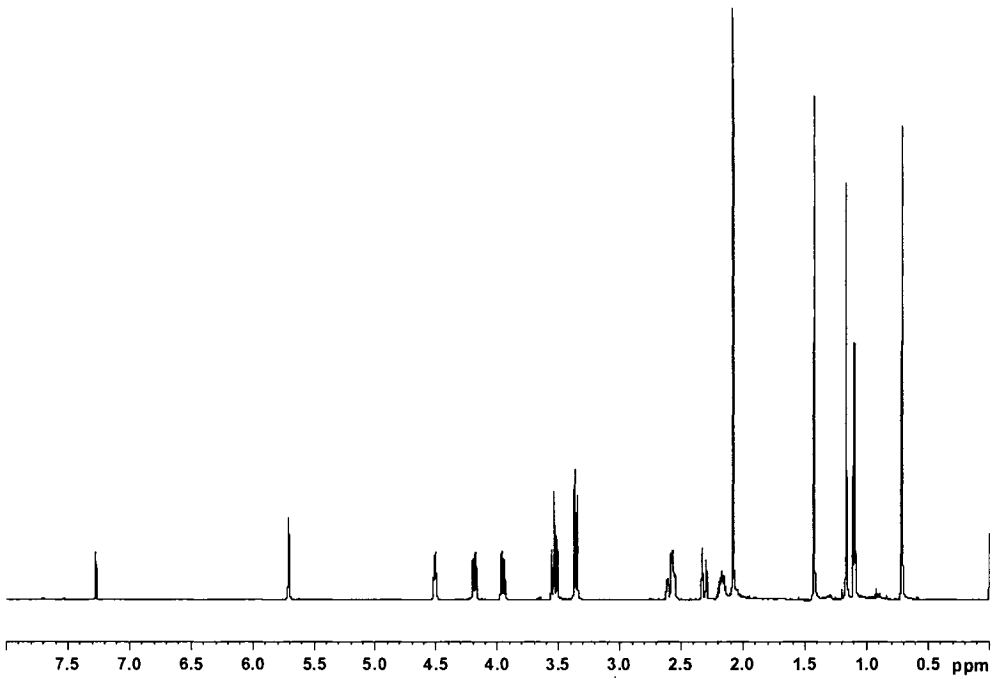


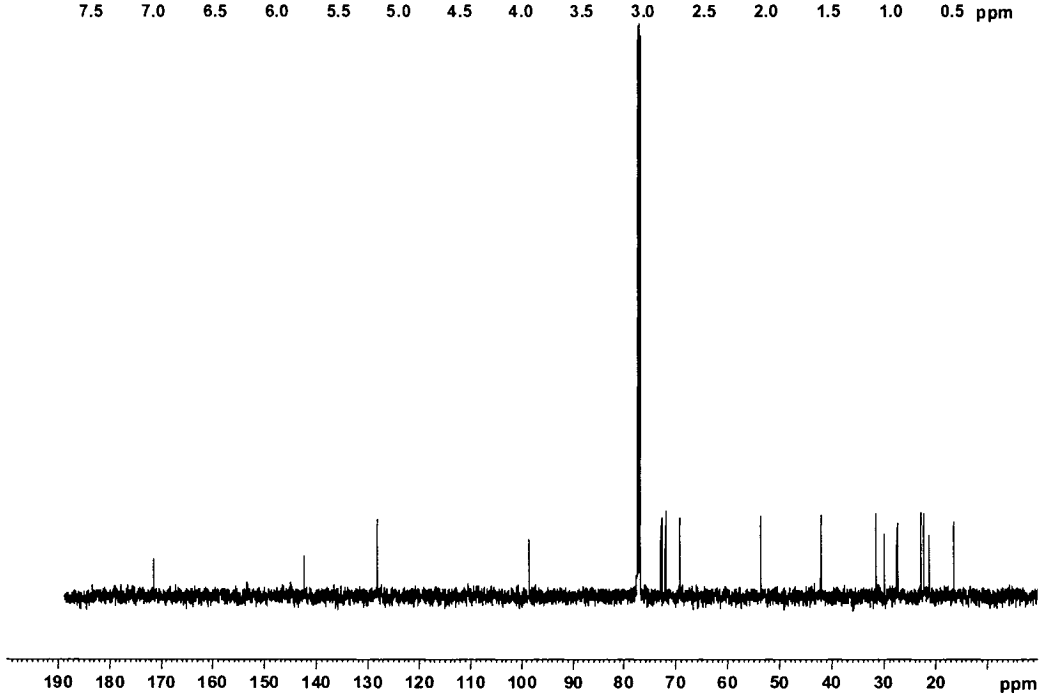


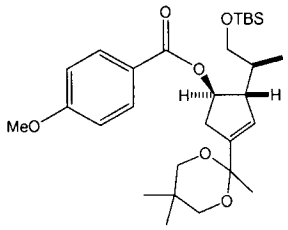


255

(1*R**,2*R**,6*R**)-2-(2-Hydroxy-1-methylethyl)-4-(2,5,5-trimethyl[1,3]dioxan-2-yl)cyclopent-3-en-1-ol, acetate ester (**255**)

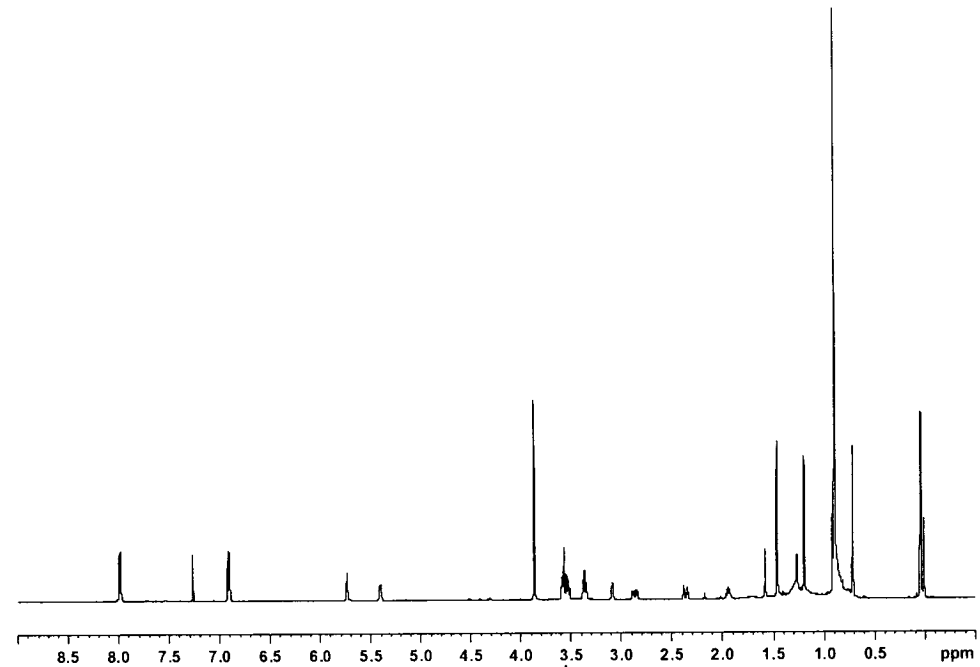


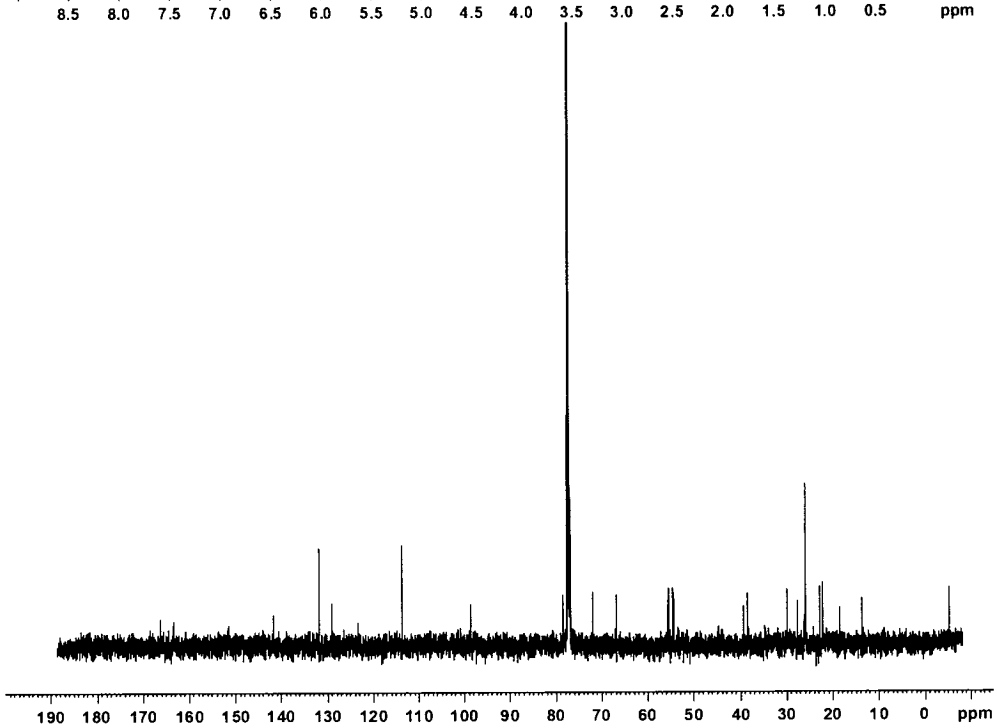


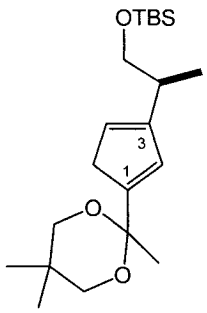


258

(1*R**,2*S**,6*S**)-2-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-4-(2,5,5-trimethyl[1,3]dioxan-2-yl)-cyclopent-3-en-1-ol, 4-methoxybenzoyl ester (**258**)

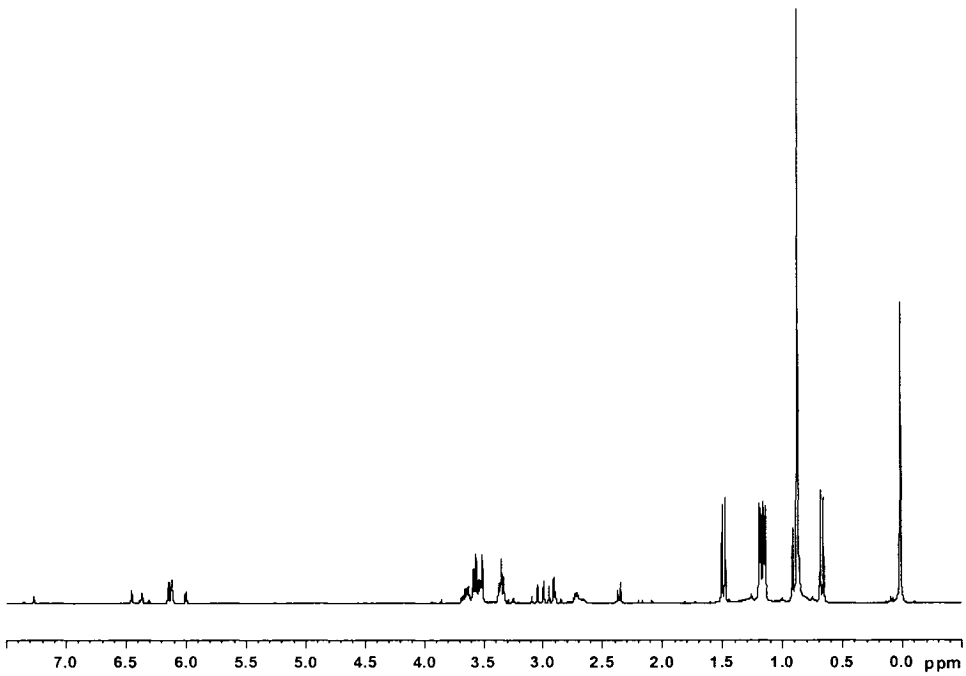


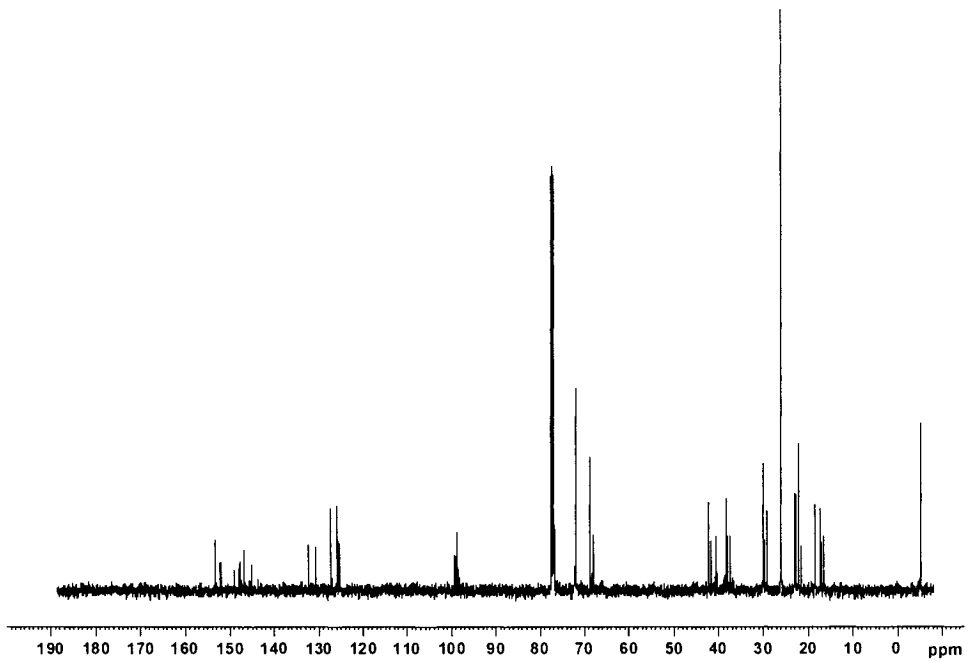


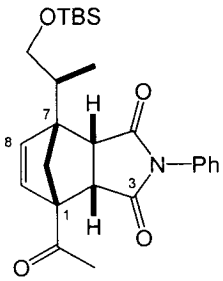


259

3-(2-*tert*-Butyldimethylsilyloxy-1-methylethyl)-1-(2,5,5-trimethyl[1,3]dioxan-2-yl)-1,3-cyclopentadiene (mixture of double bond isomers) (**259**)

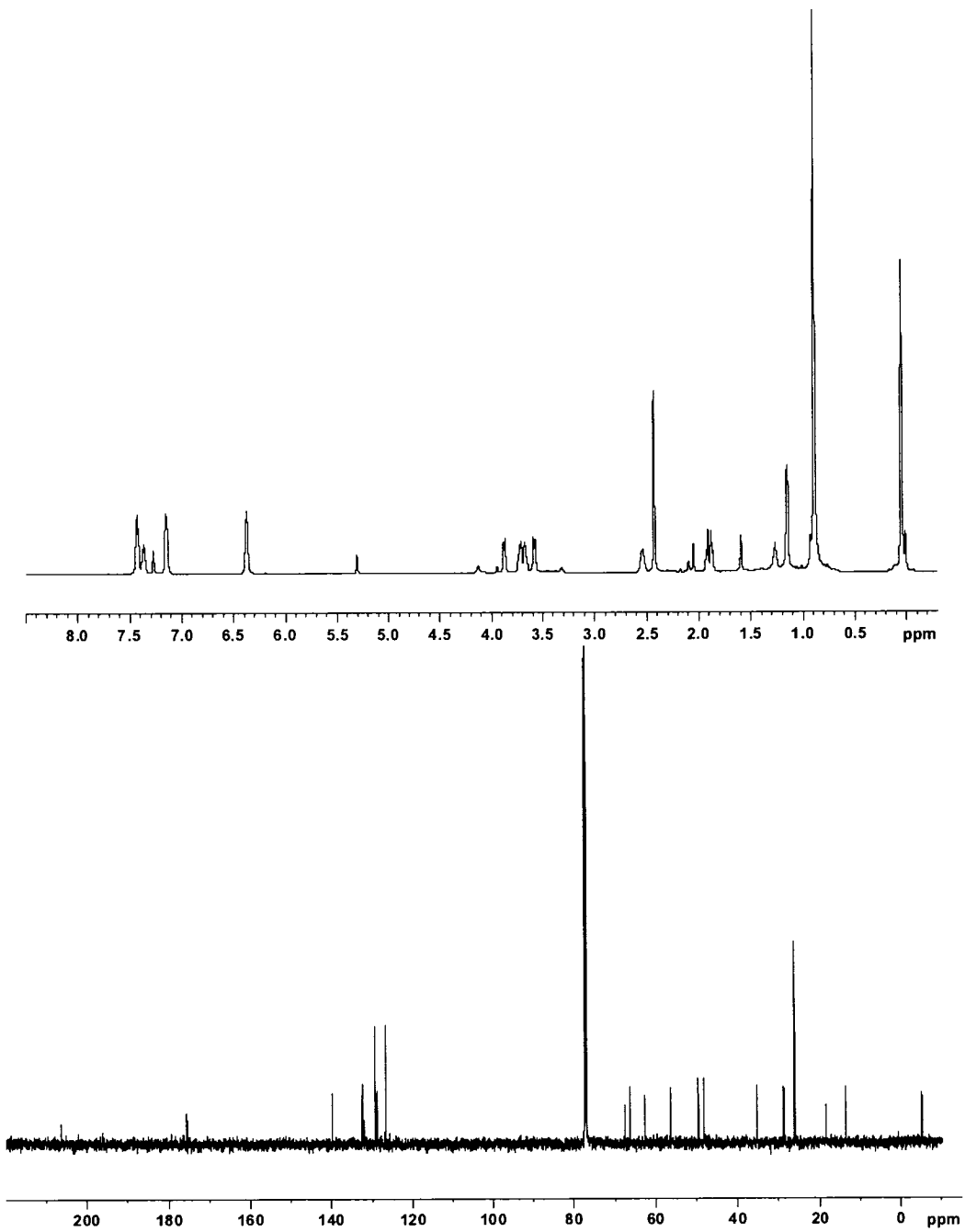


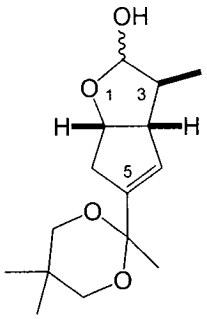




261

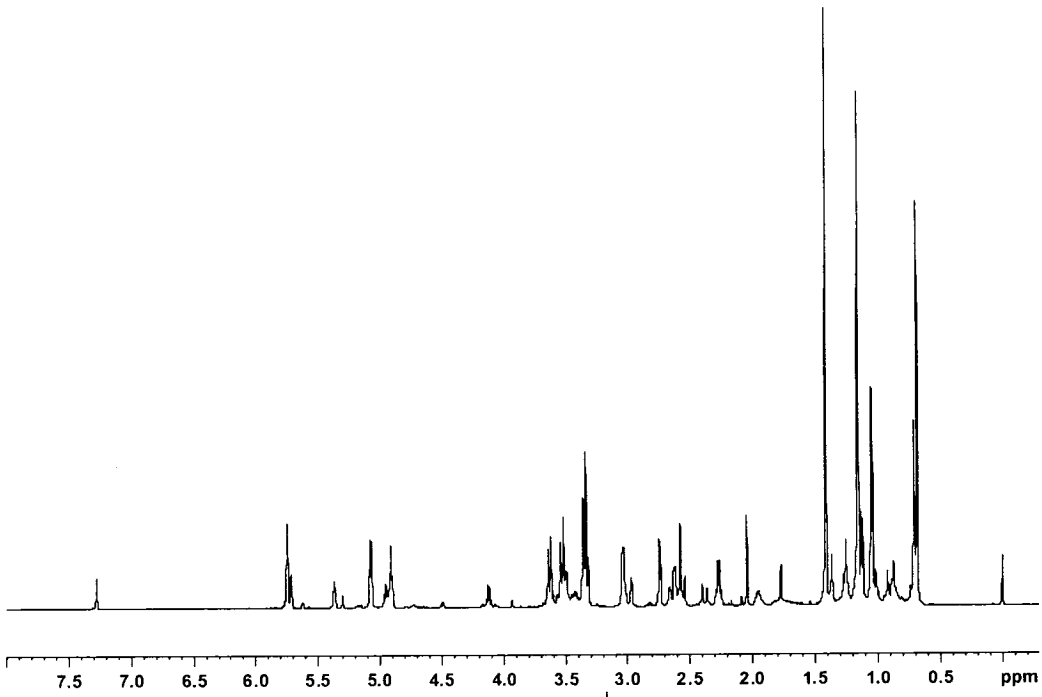
(1*R**,2*S**,6*S**,7*R**,10*S**)-1-Acetyl-7-[2-(tert-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-4-phenyl-4-aza-tricyclo[5.2.1.$0^{2,6}$]-dec-8-ene-3,5-dione (**261**)

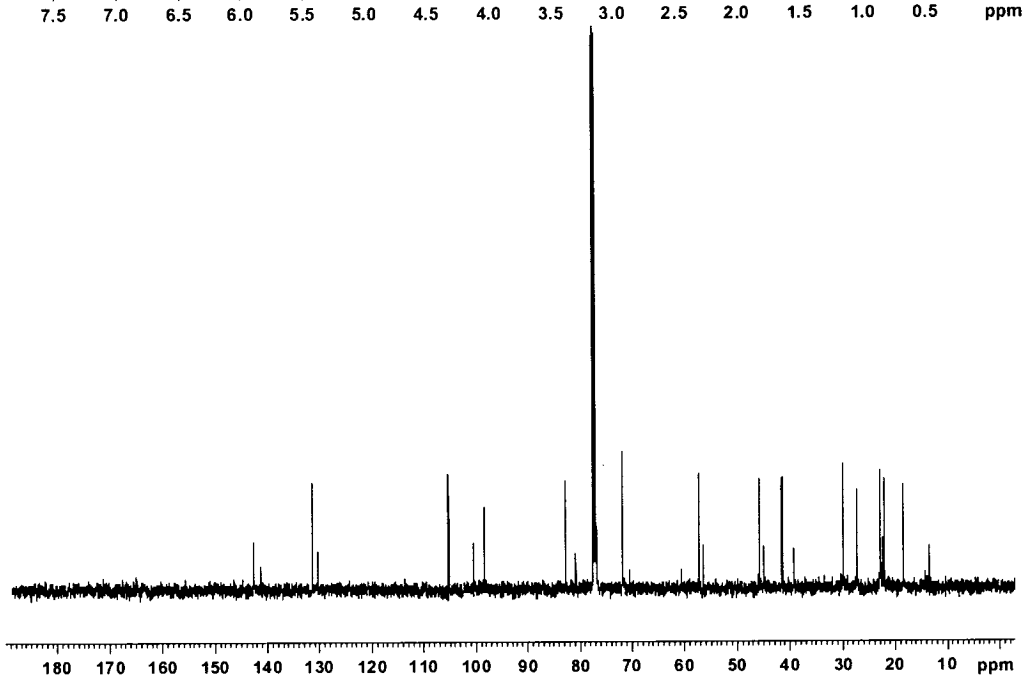


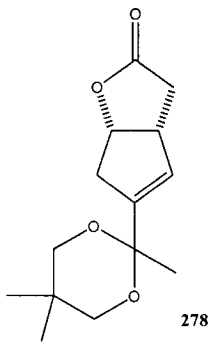


265

(3*R**,3a*R**,6a*R**)-3,3a,6,6a-Tetrahydro-3-methyl-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)-2*H*-cyclopenta[b]furan-2-ol (mixture of epimers at C-2) (**265**)

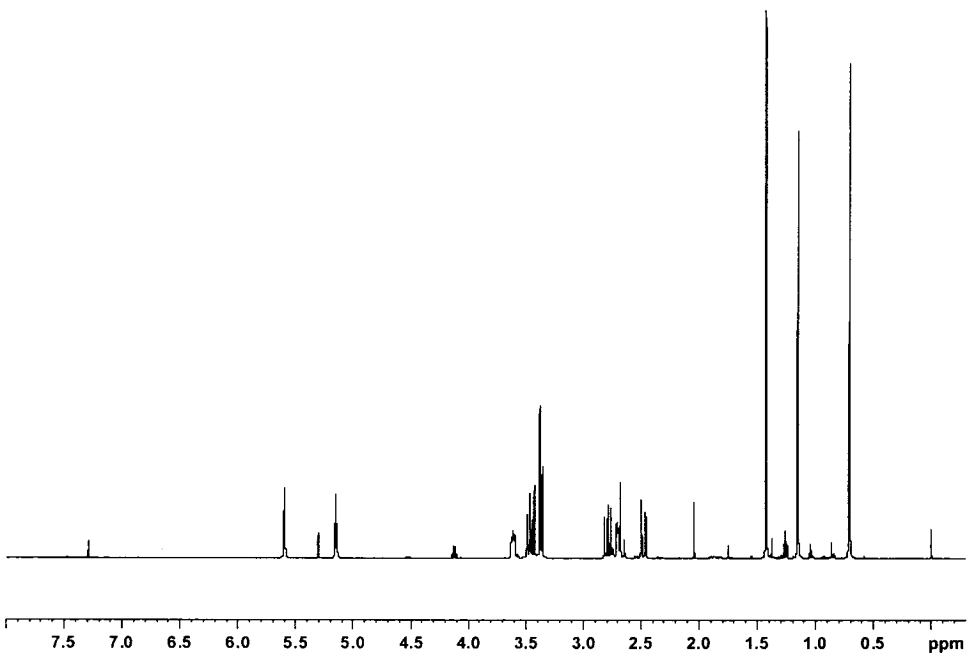


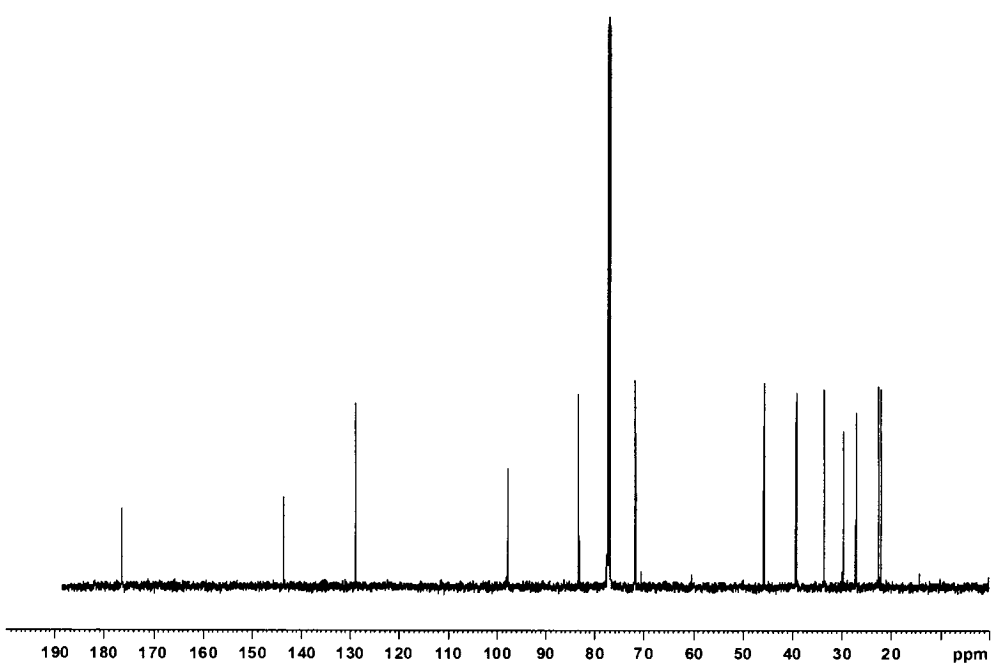


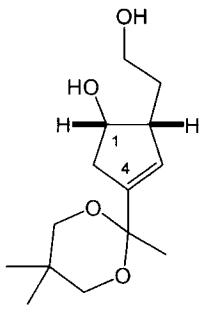


278

(3a*R**,6a*R**)-3,3a,6,6a-Tetrahydro-5-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopenta[*b*]furan-2-one (**278**)

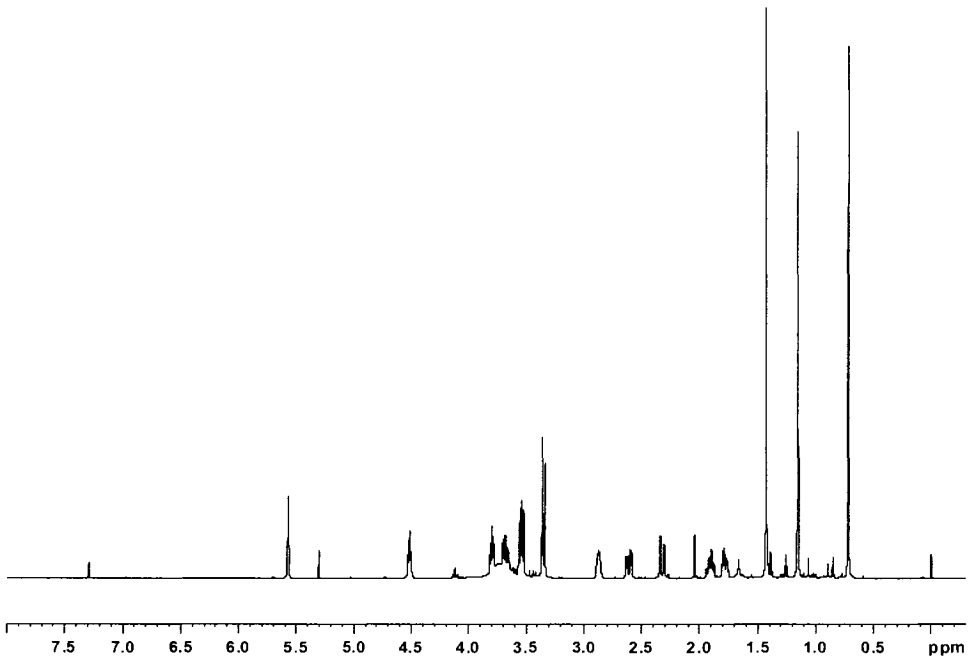


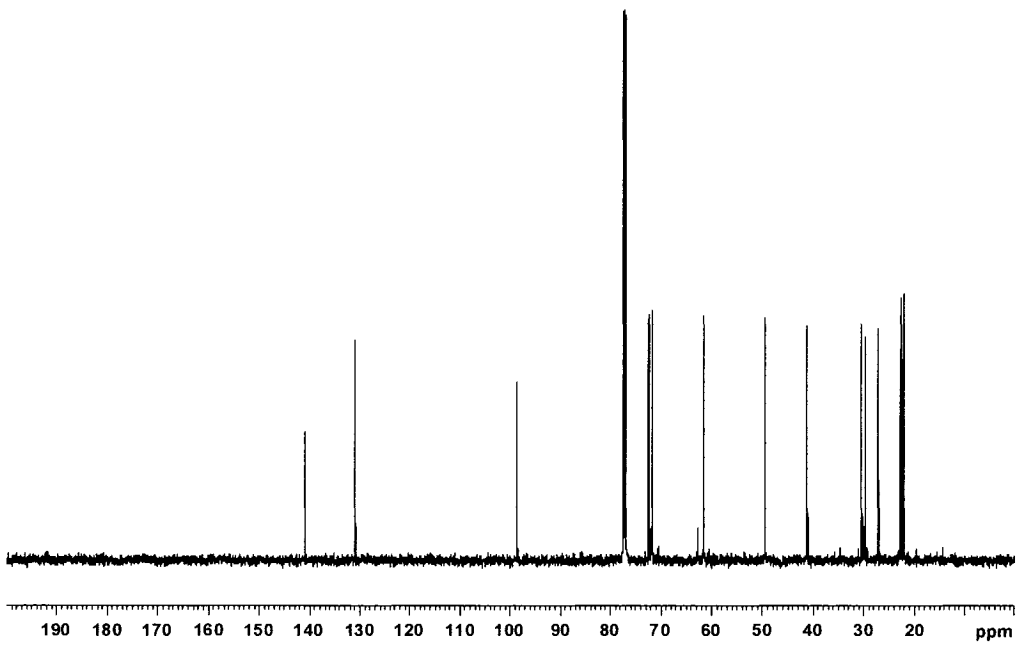


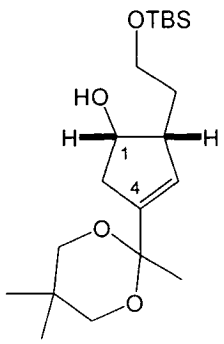


279

(1*R**,2*S**)-2-(2-Hydroxyethyl)-4-(2,5,5-trimethyl[1,3]dioxan-2-yl)cyclopent-3-en-1-ol (**279**)

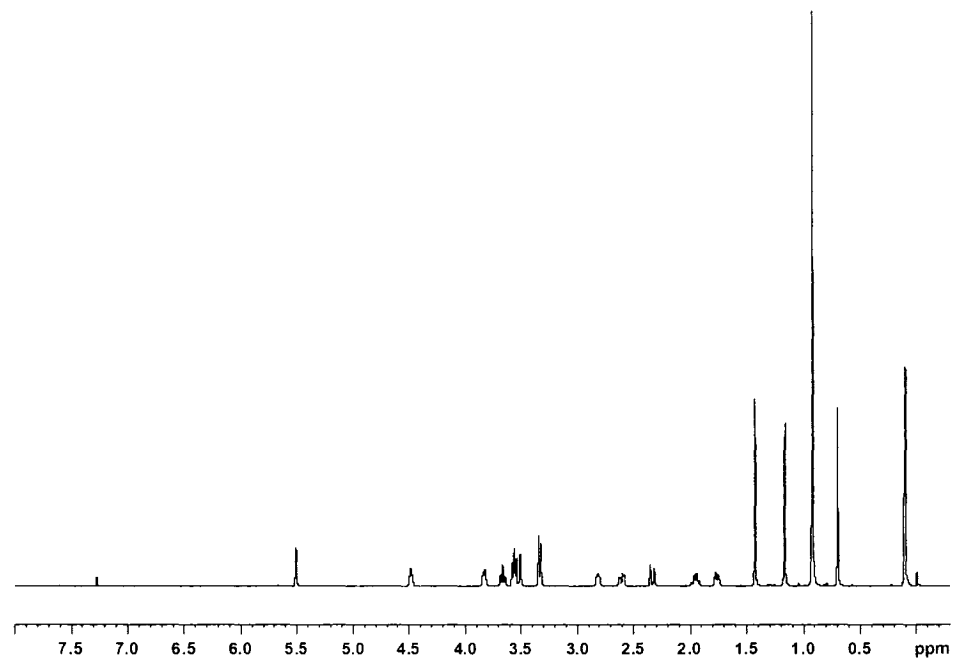


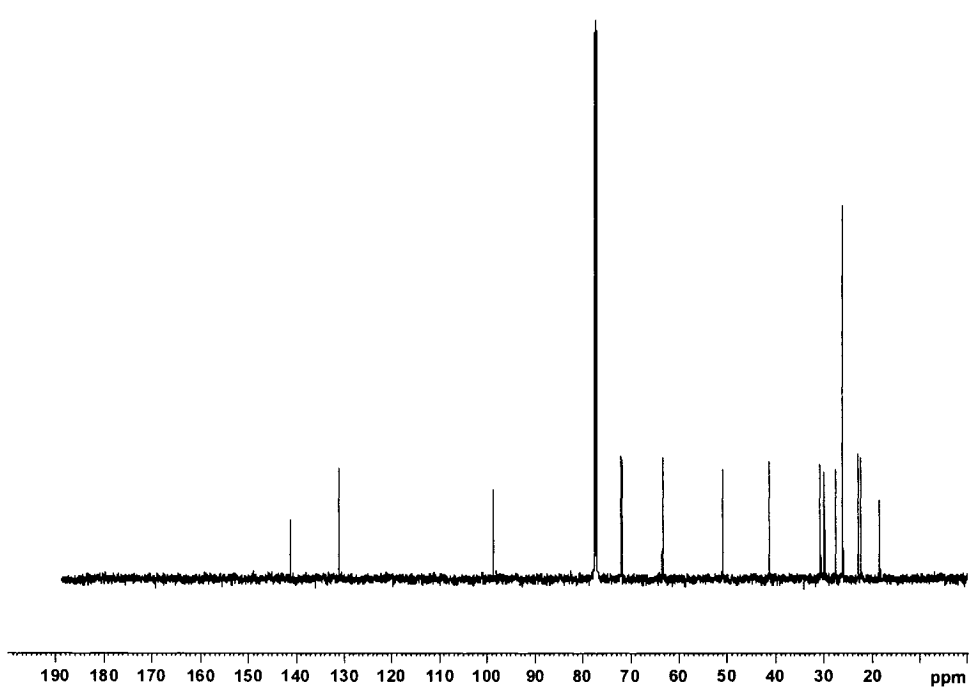


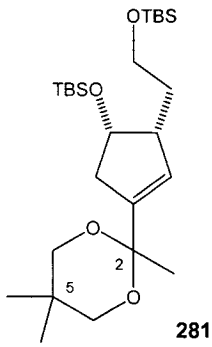


280

(1*R**,2*S**)-2-[2-(*tert*-Butyldimethylsilyl)oxyethyl]-4-(2,5,5-trimethyl-[1,3]-dioxan-2-yl)cyclopent-3-en-1-ol (**280**)

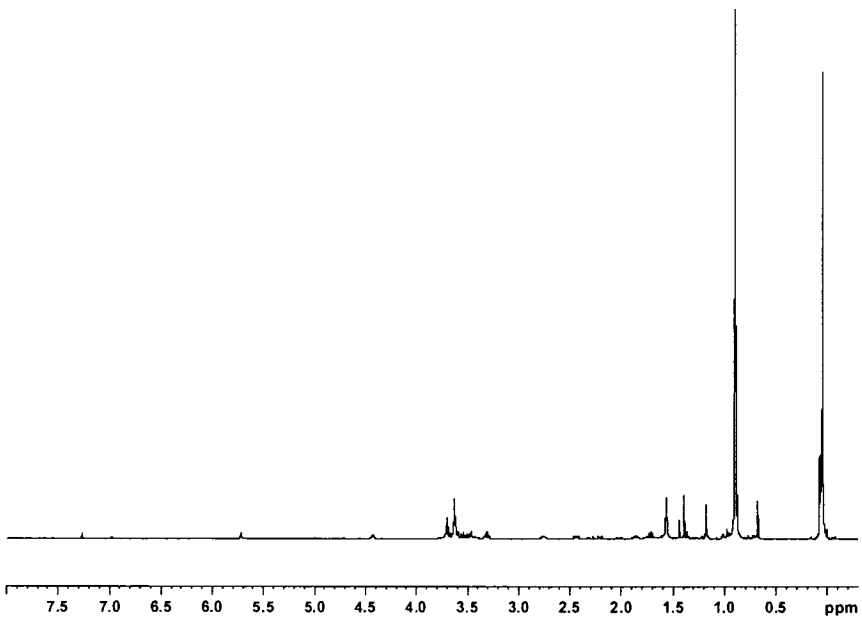


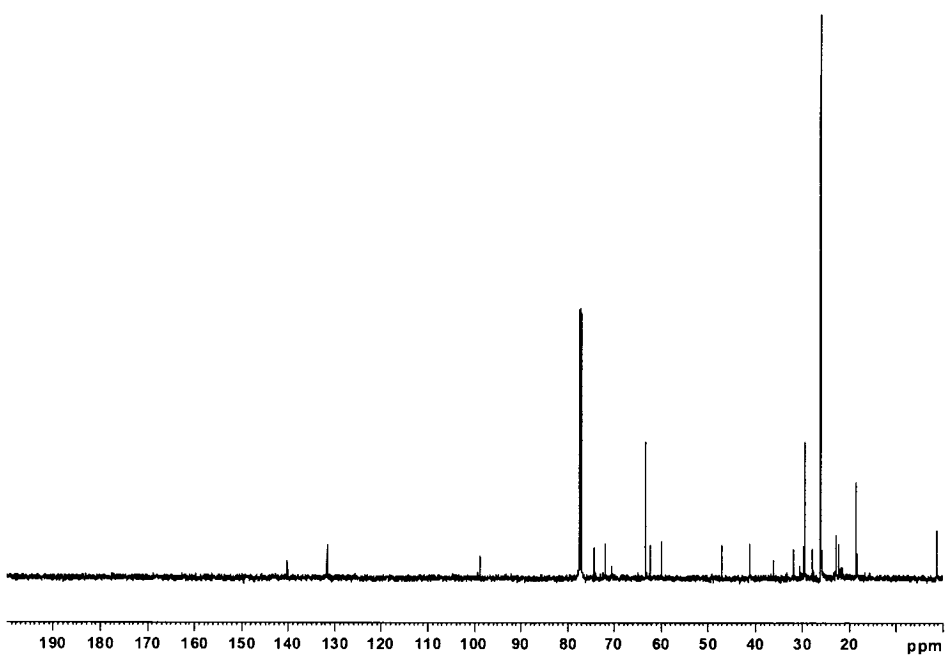


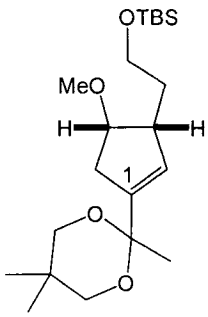


281

(3*R**,4*S**)-3-(2-*tert*-Butyldimethylsilyloxyethyl)-4-*tert*-butyldimethyl-silyloxy-1-(2,5,5-trimethyl[1,3]-dioxan-2-yl)cyclopent-1-ene (**281**)

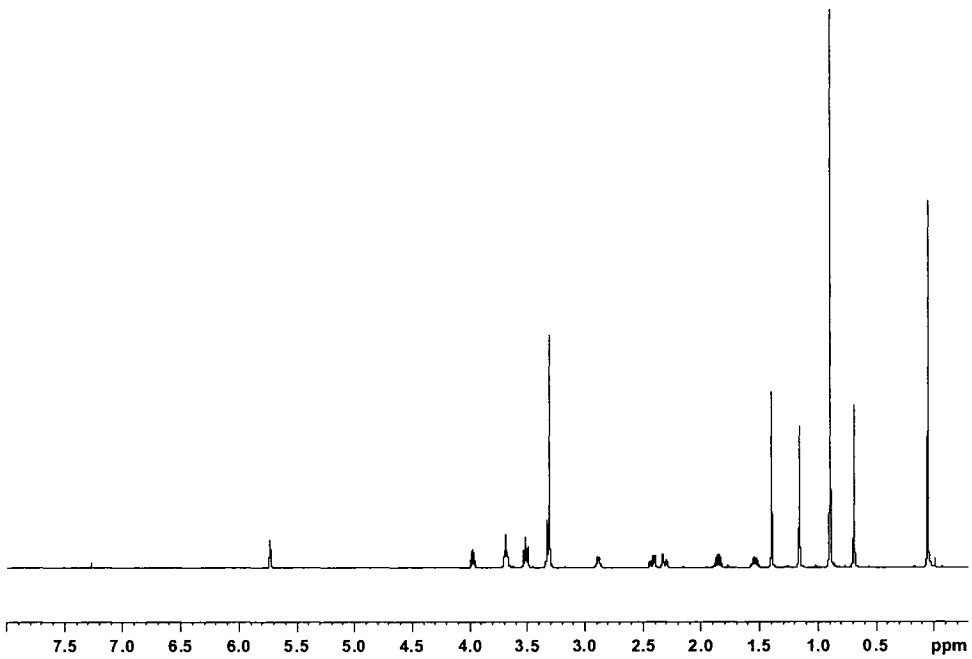


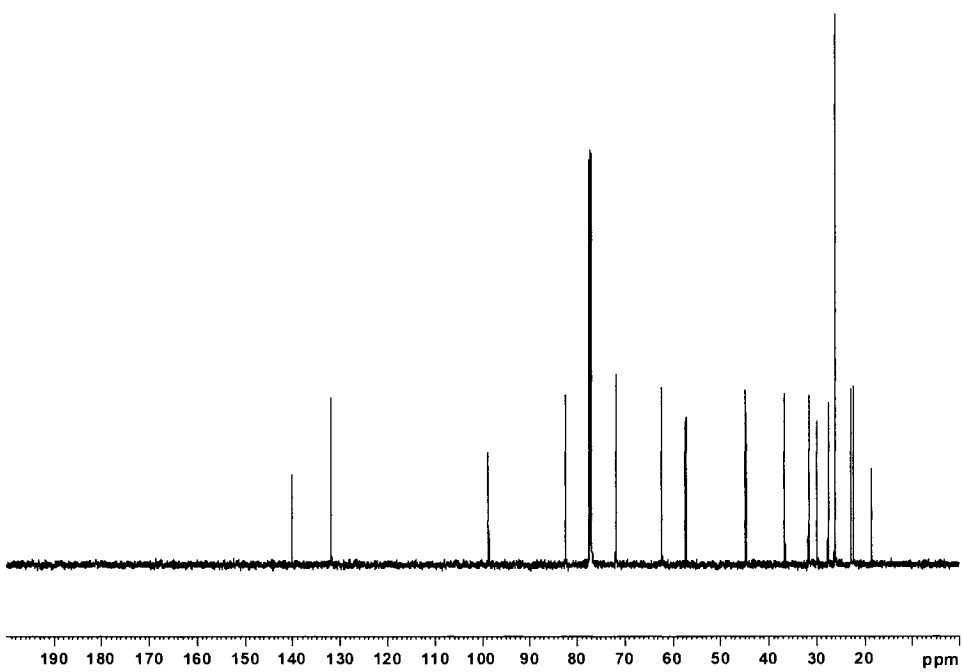


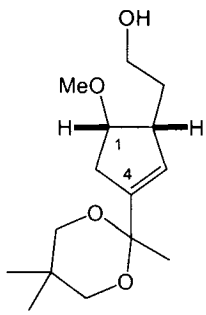


282

(3*R**,4*S**)-3-(2-*tert*-Butyldimethylsilyloxyethyl)-4-methoxy-1-(2,5,5-trimethyl[1,3]-dioxan-2-yl)cyclopent-1-ene (**282**)

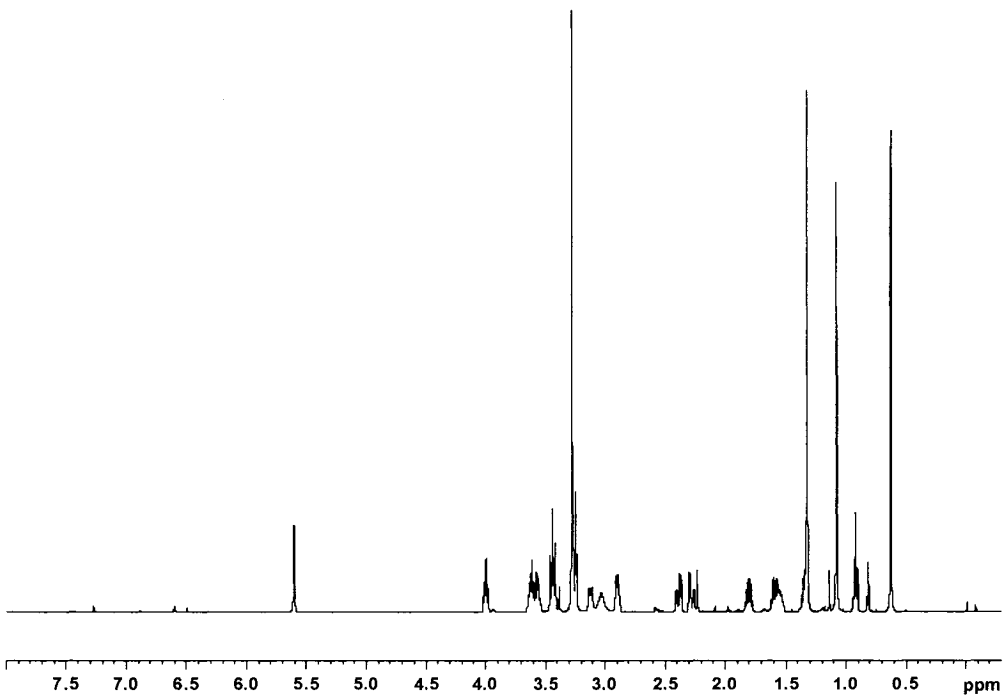


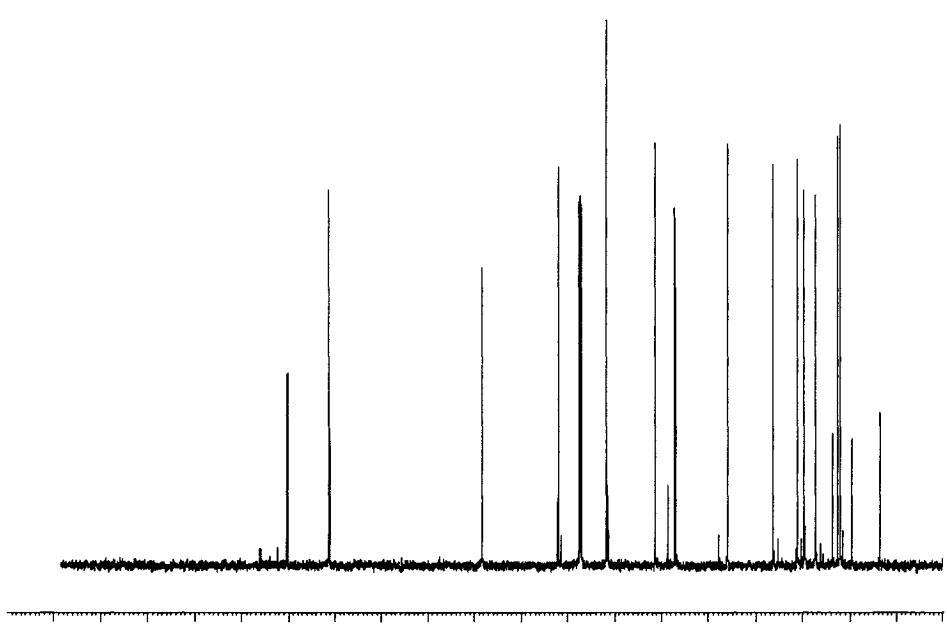


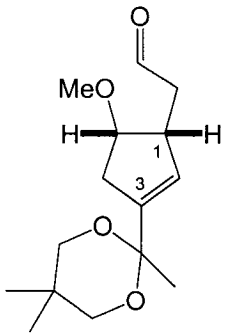


283

(1*R**,2*S**)-1-Methoxy-2-(2-hydroxyethyl)-4-(2,5,5-trimethyl-[1,3]-dioxan-2-yl)cyclopent-3-ene (**283**)

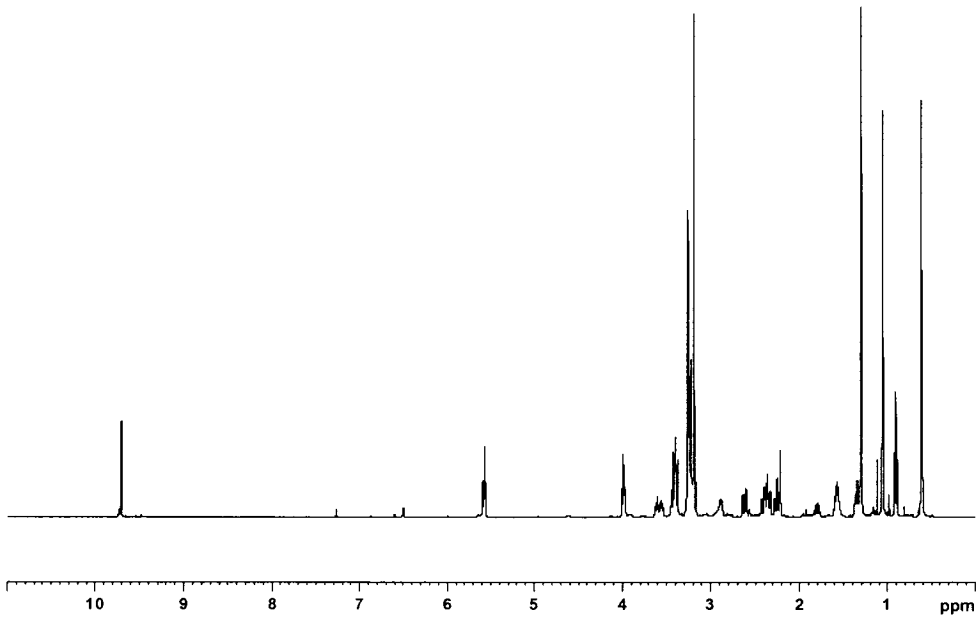


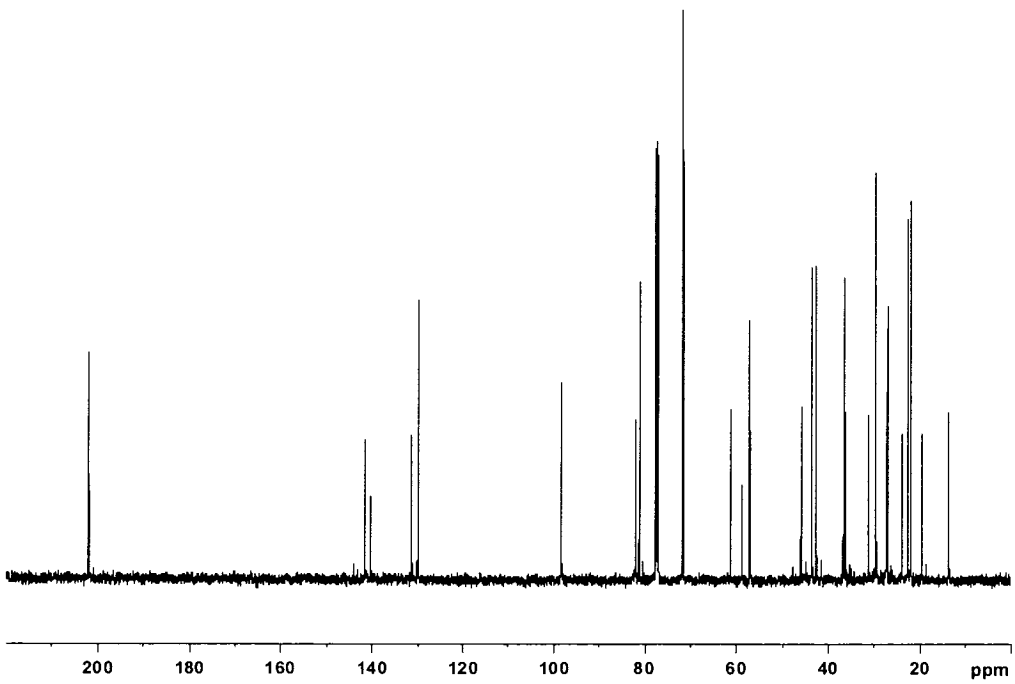


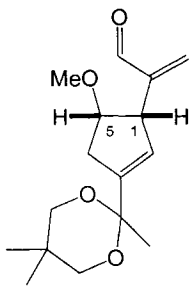


273

[(1*R**,5*S**)-5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-2-enyl]-acetaldehyde (**273**)

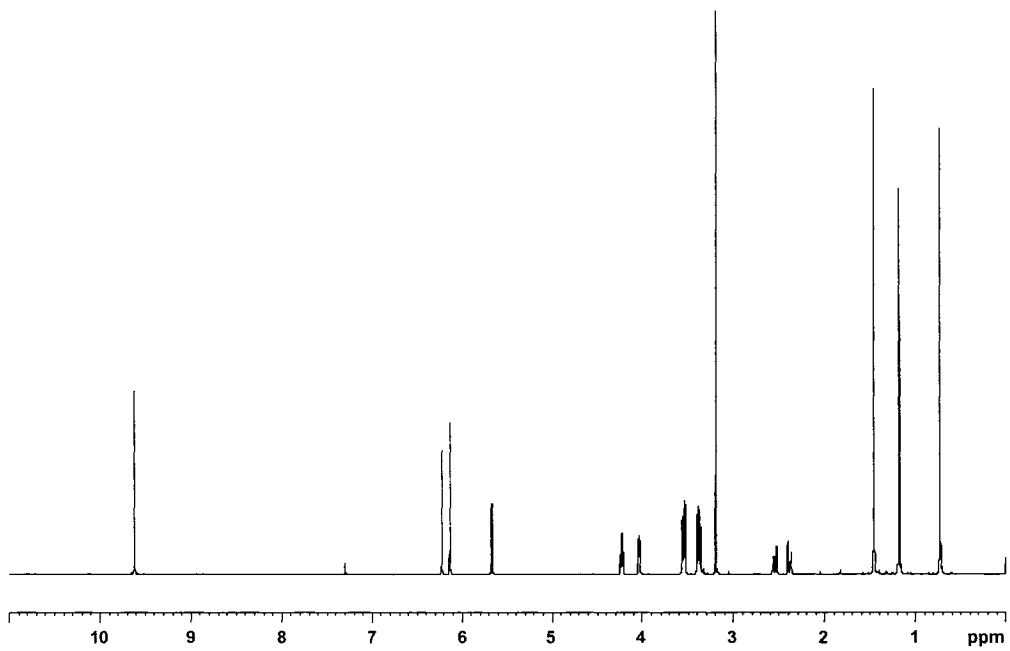


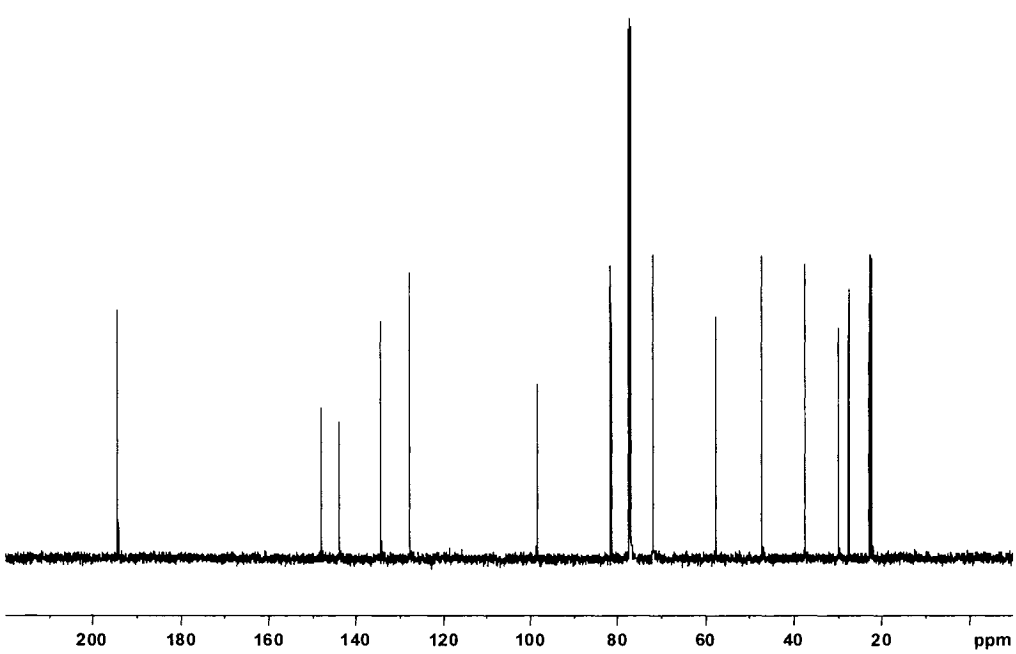


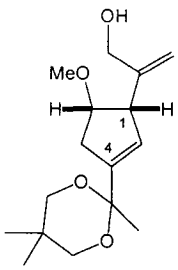


272

2-[(1*R**,5*R**)-5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-2-enyl]-propenal (**272**)

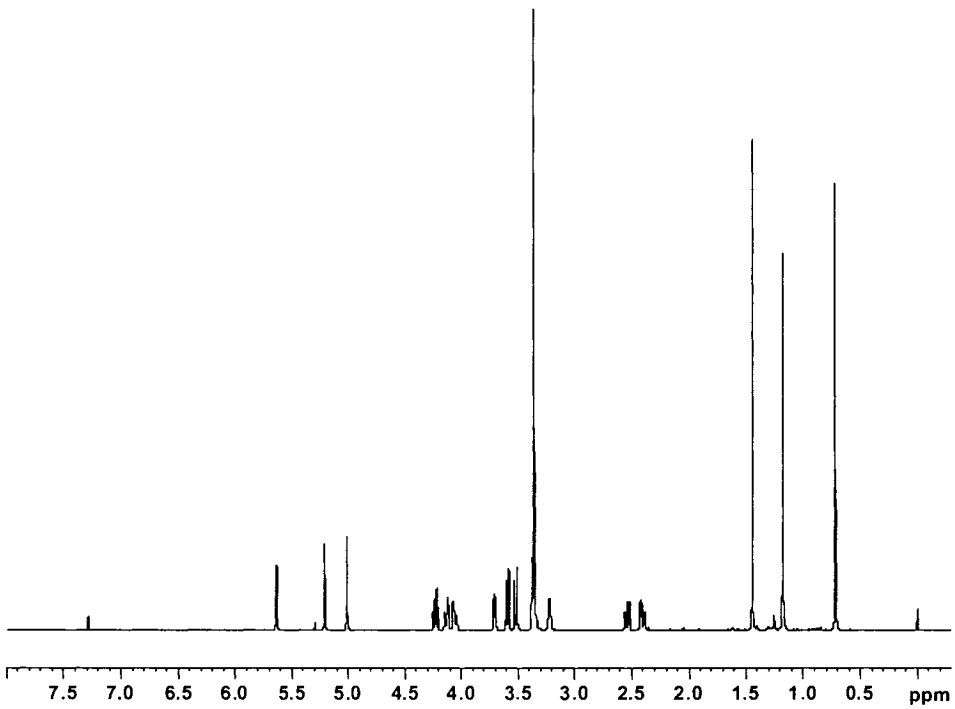


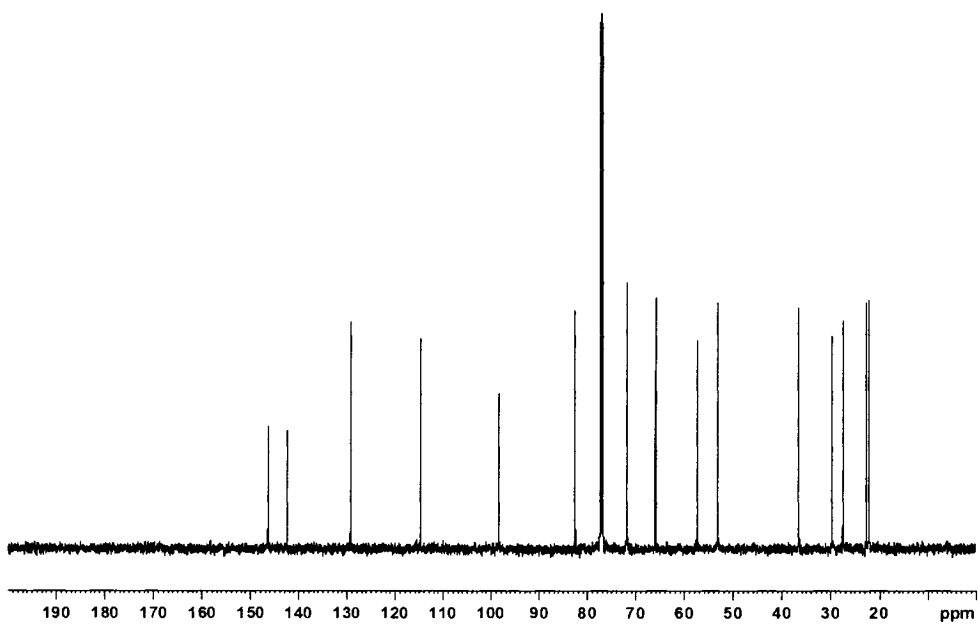


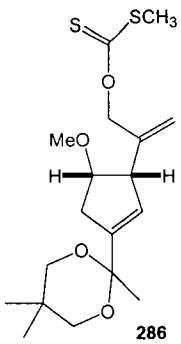


271

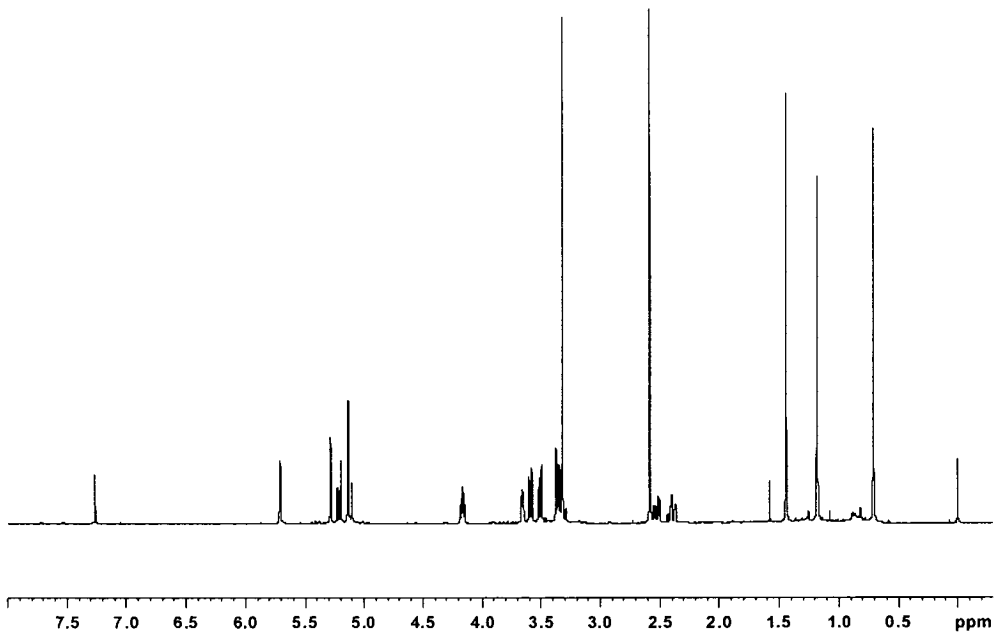
2-[(1*R**,5*R**)-5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-2-enyl]-prop-2-en-1-ol (**271**)

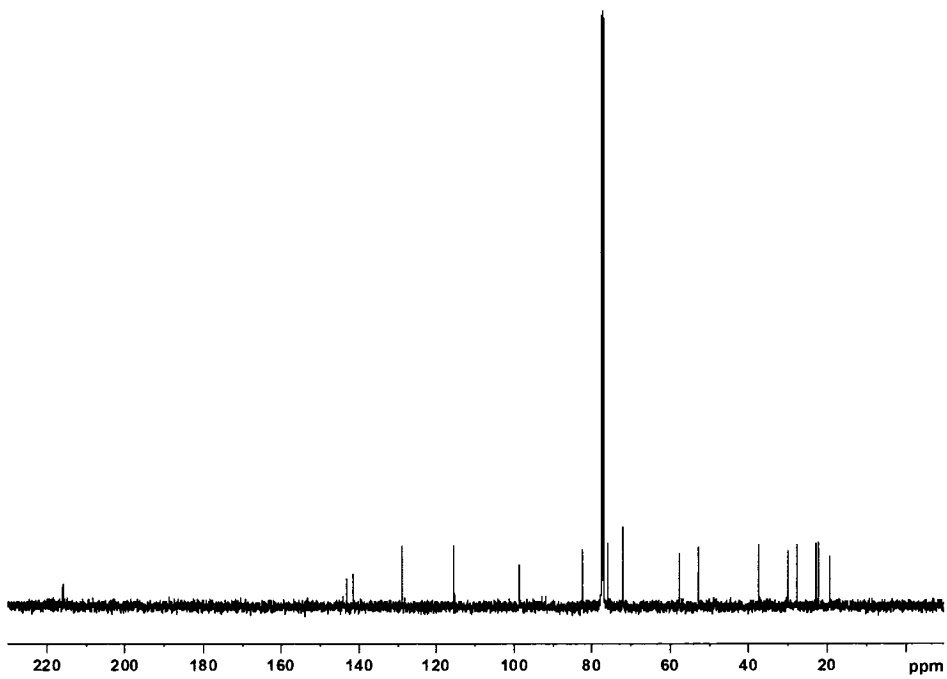


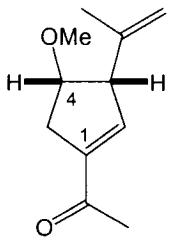




O-{2-[(1*R**,5*R**)-5-Methoxy-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-2-enyl]allyl}, dithiocarbonic acid ester, S-methyl ester (**286**)

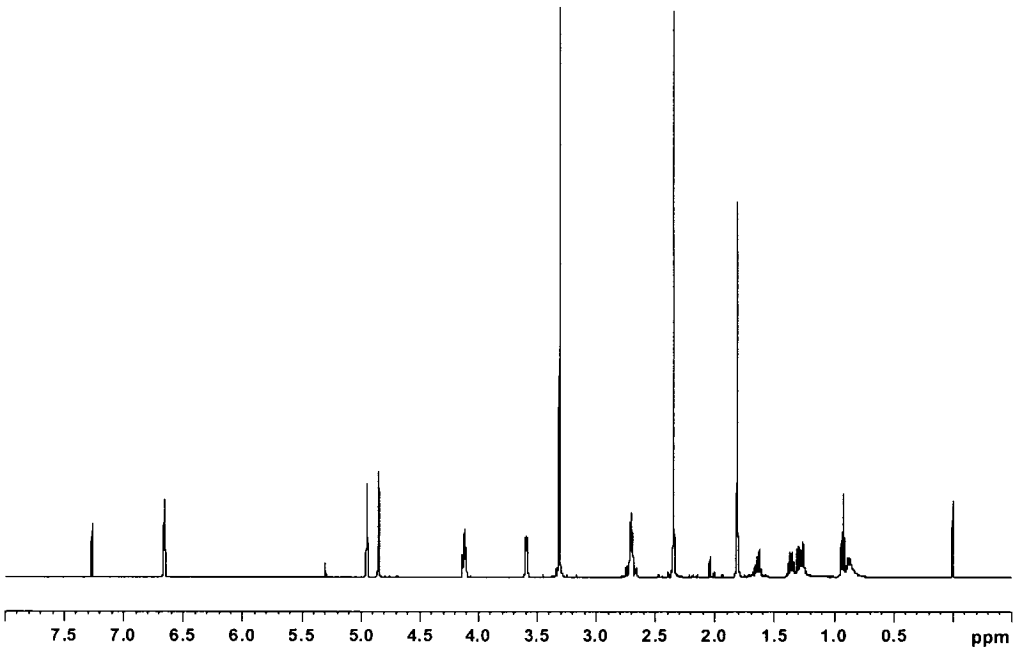


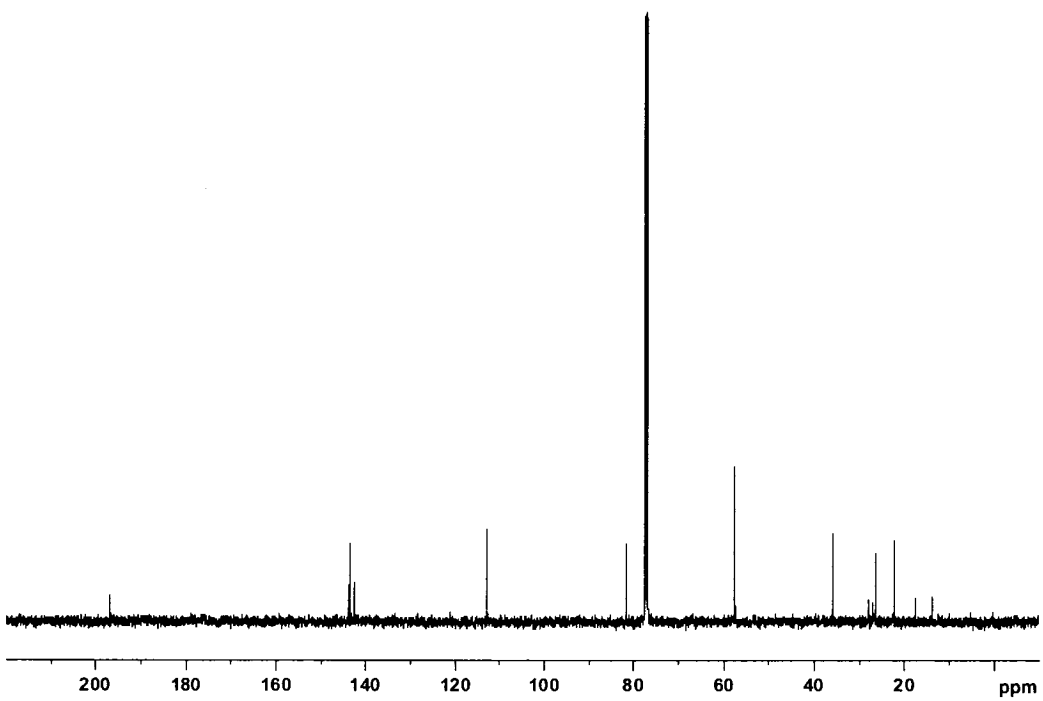


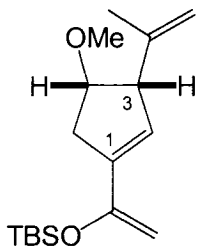


(3*R**,4*R**)-1-Acetyl-3-isopropenyl-4-methoxycyclopent-1-ene (**287**)

287

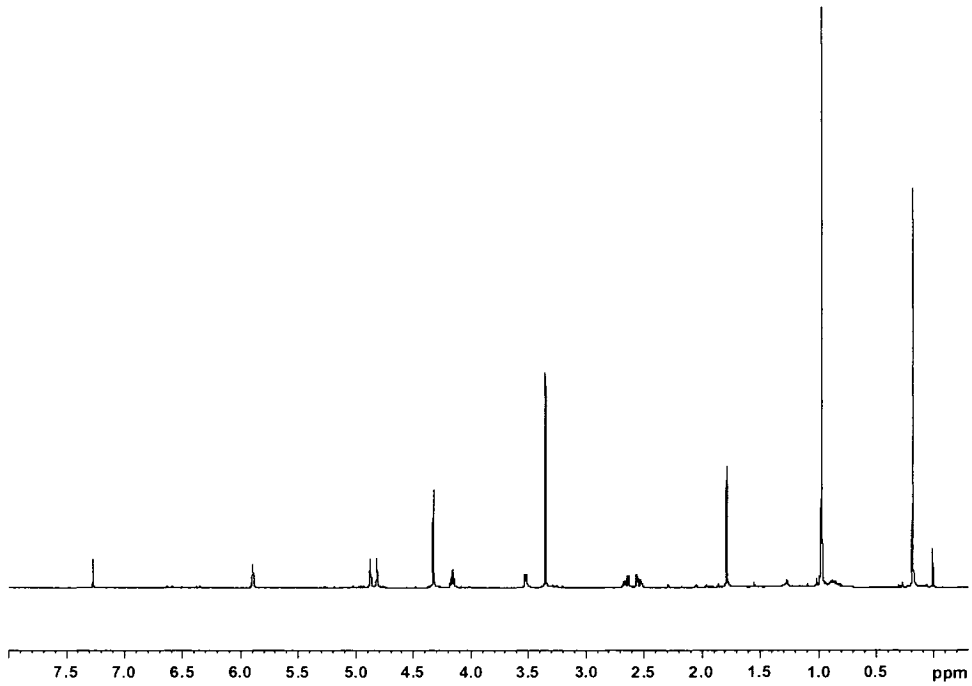


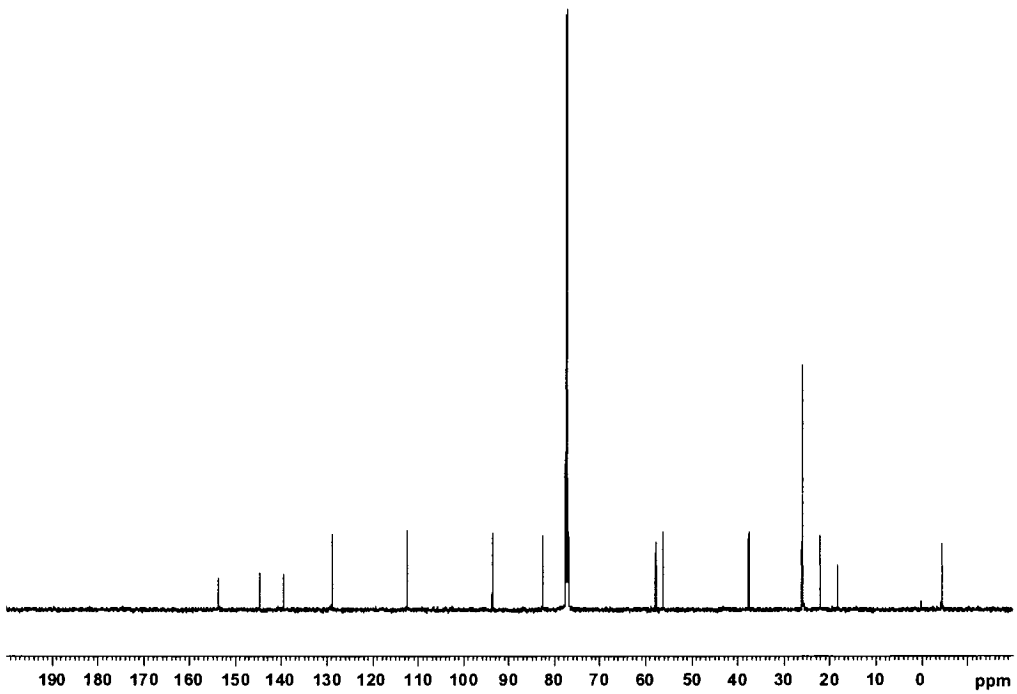


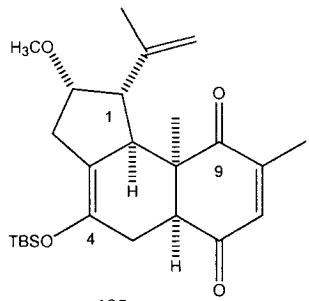


186

(3*R**,4*R**)-1-(1-*tert*-Butyldimethylsilyloxyvinyl)-3-isopropenyl-4-methoxycyclopent-1-ene (**186**)

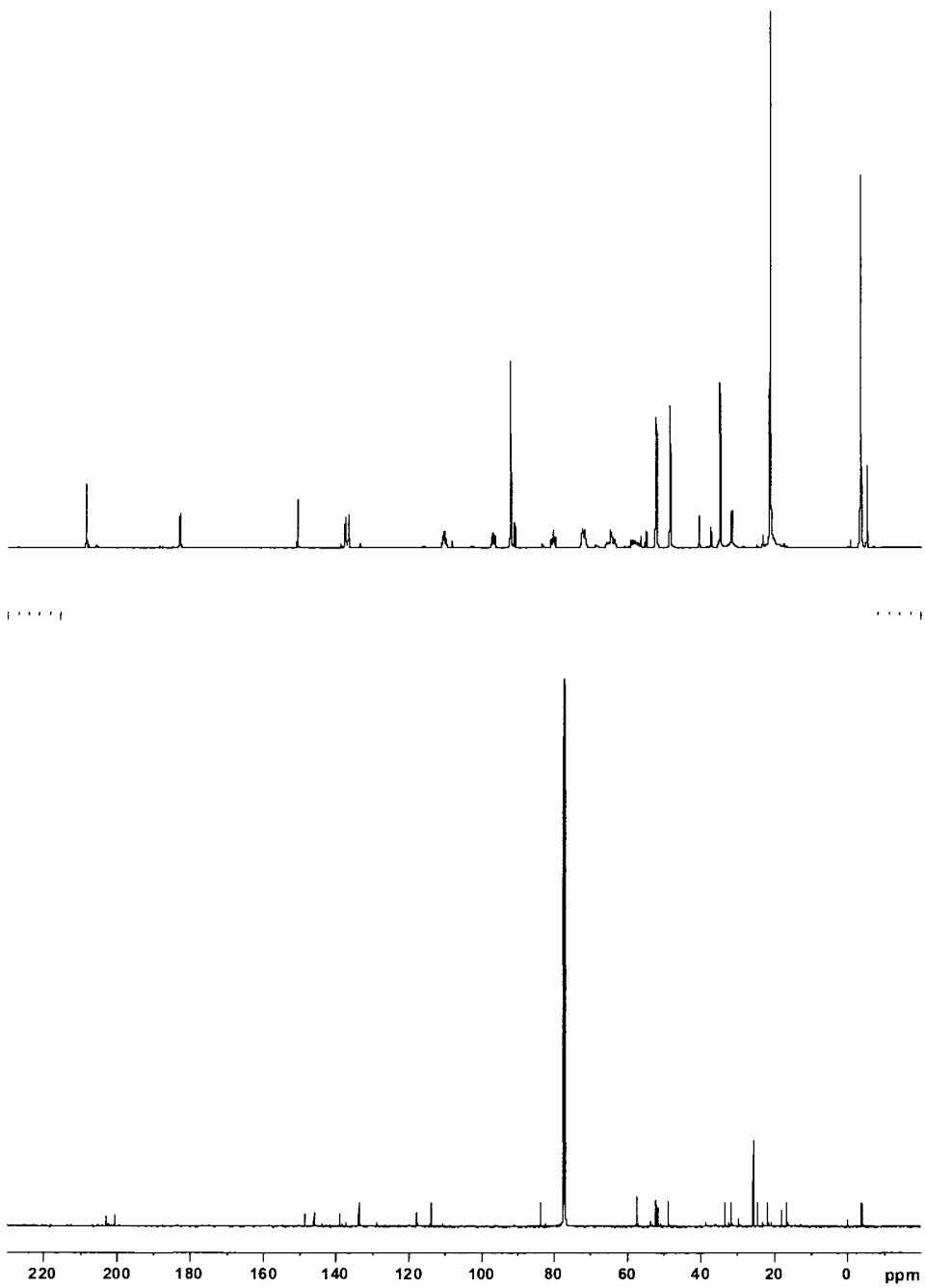


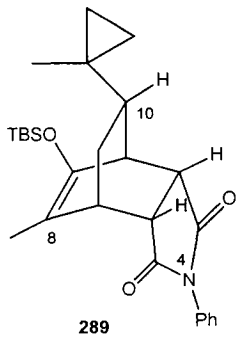




185

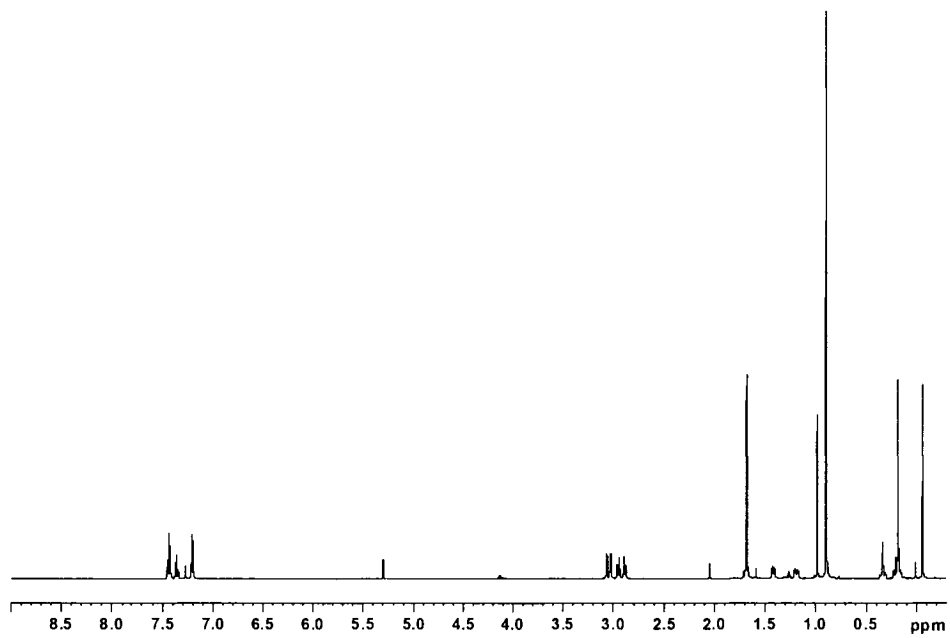
(1β,2β,5aα,9aα,9bα)-4-(*tert*-Butyldimethylsilanyloxy)-1-isopropenyl-2-methoxy-8,9a-dimethyl-2,3,5,5a,9a,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-6,9-dione (**185**)

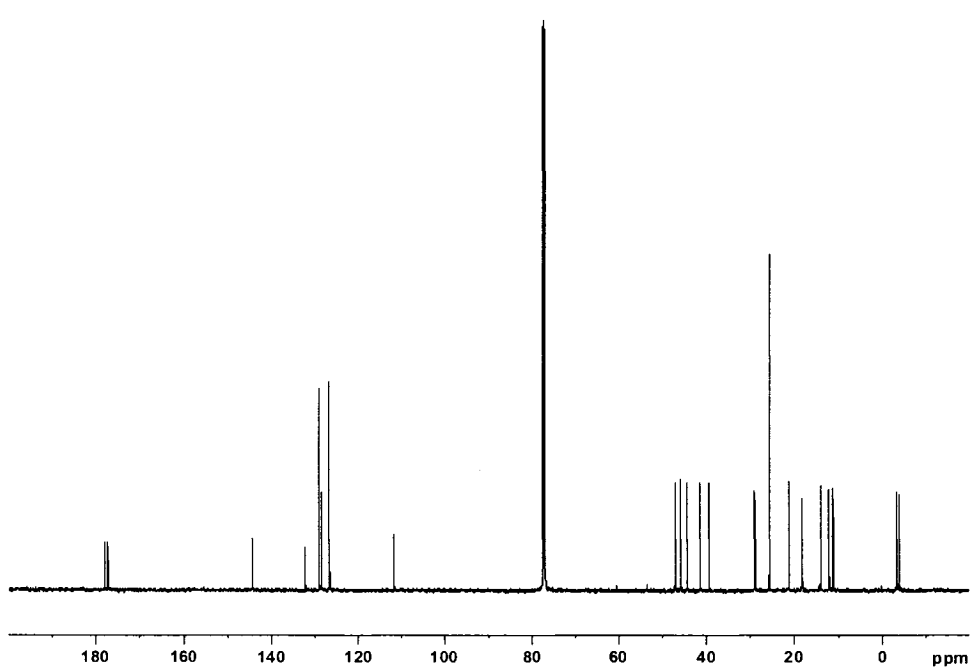


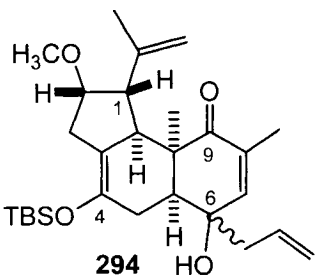


289

(1*S**,2*S**,6*R**,7*R**,10*S**)-9-(*tert*-Butyldimethylsilyloxy)-8-methyl-10-(1-methylcyclopropyl)-4-phenyl-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**289**)

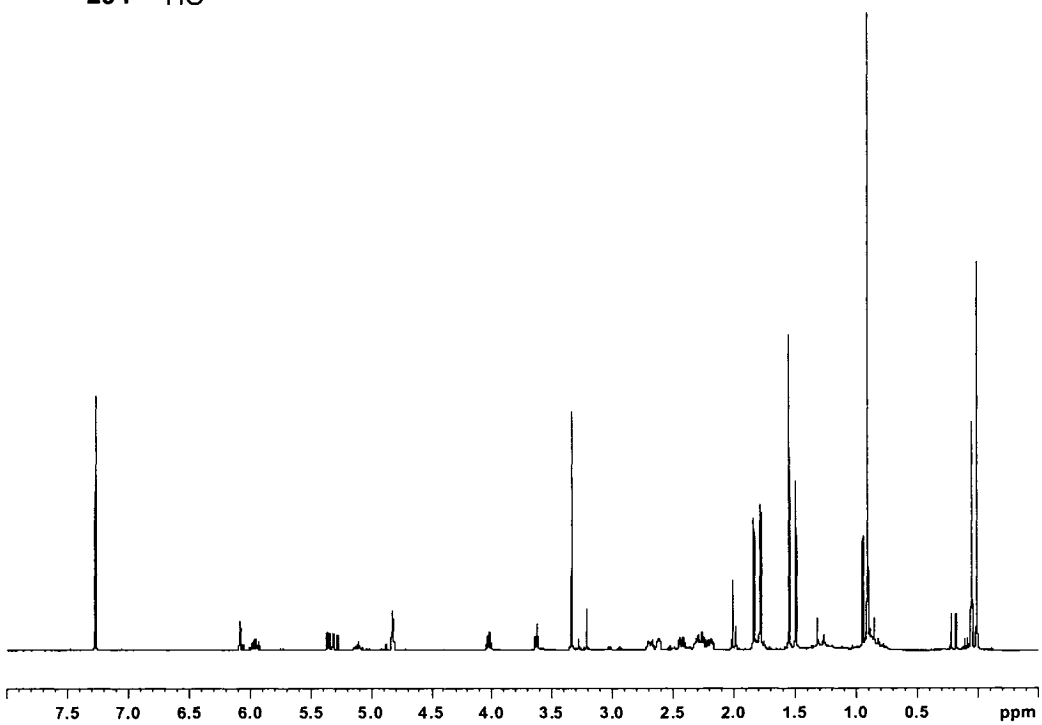


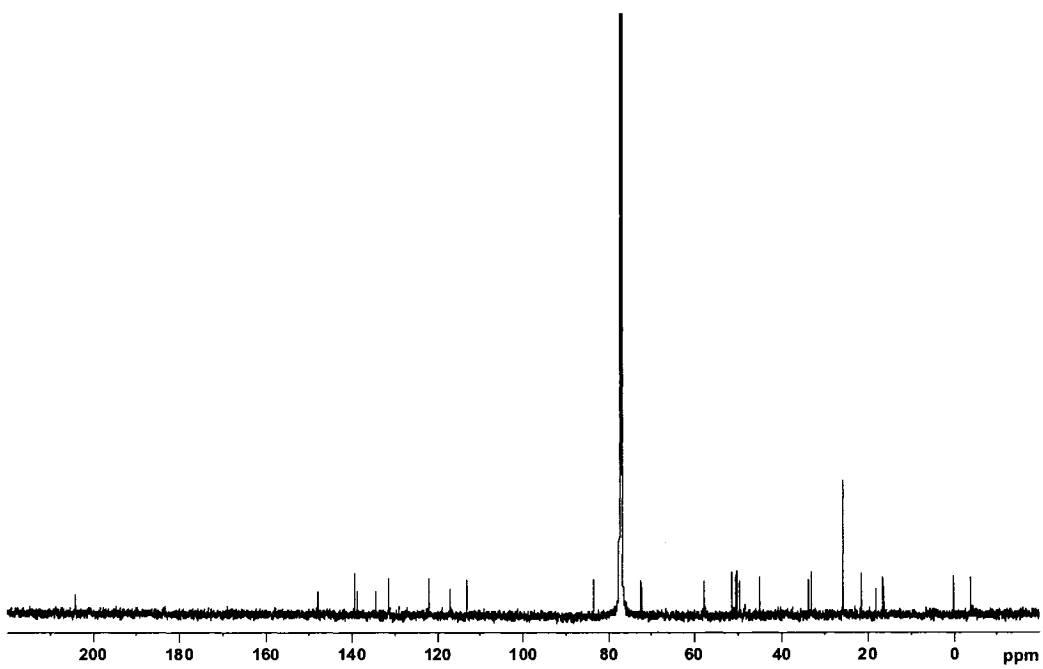


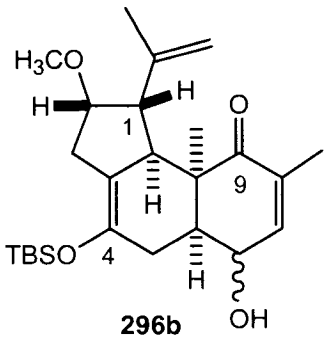


294

(1α,2α,5aα,9aα,9bα)-6-Allyl-4-(*tert*-butyldimethylsilyl-oxy)-2,3,5,5a,6,9,9a,9b-octahydro-6-hydroxy-2-methoxy-8,9a-dimethyl-1-isopropenyl-1*H*-benz[*e*]indene-9-one (mixture of epimers at C-6) (**294**)

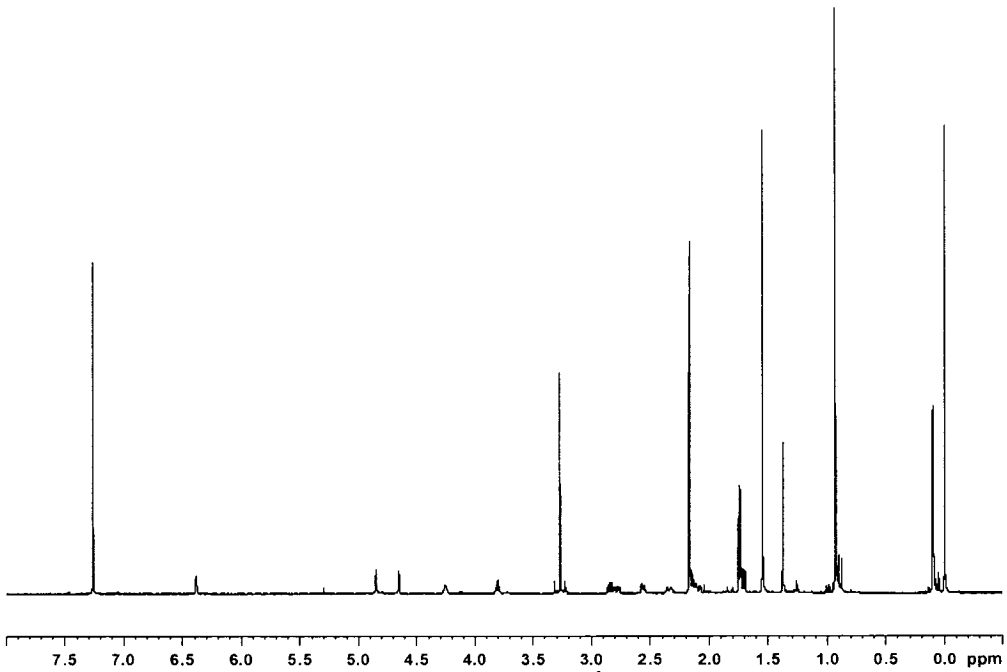


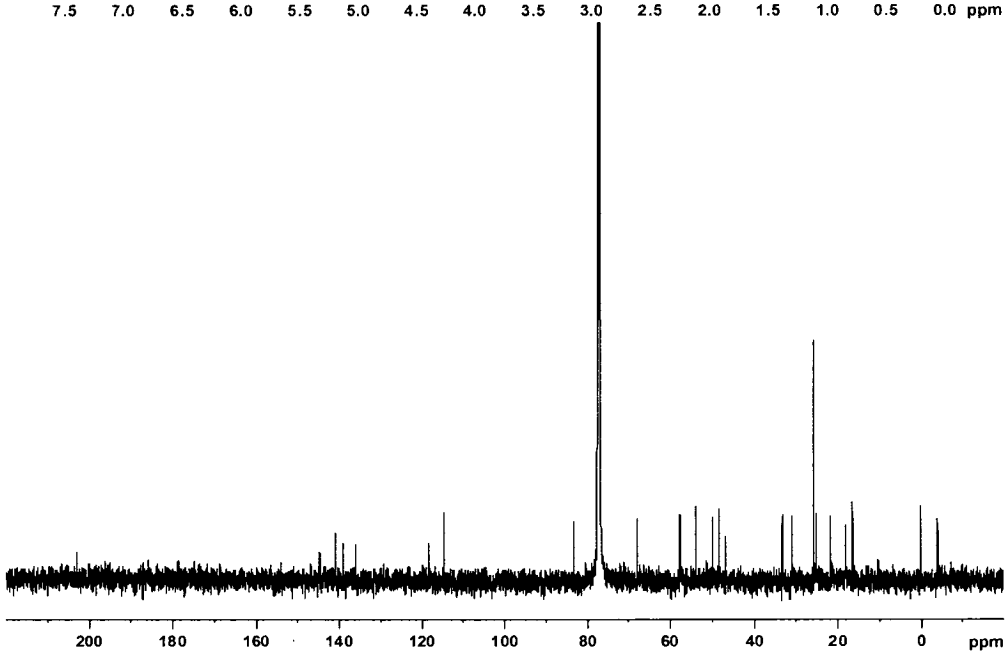


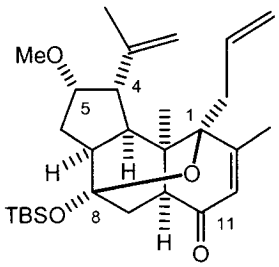


296b

(1α,2α,5aα,9aα,9bα)-4-(*tert*-Butyldimethylsilyloxy)-2,3,5,5a,6,9,9a,9b-octahydro-6-hydroxy-2-methoxy-8,9a-dimethyl-1-isopropenyl-1*H*-benz[*e*]indene-9-one (mixture of epimers at C-6) (**296b**)

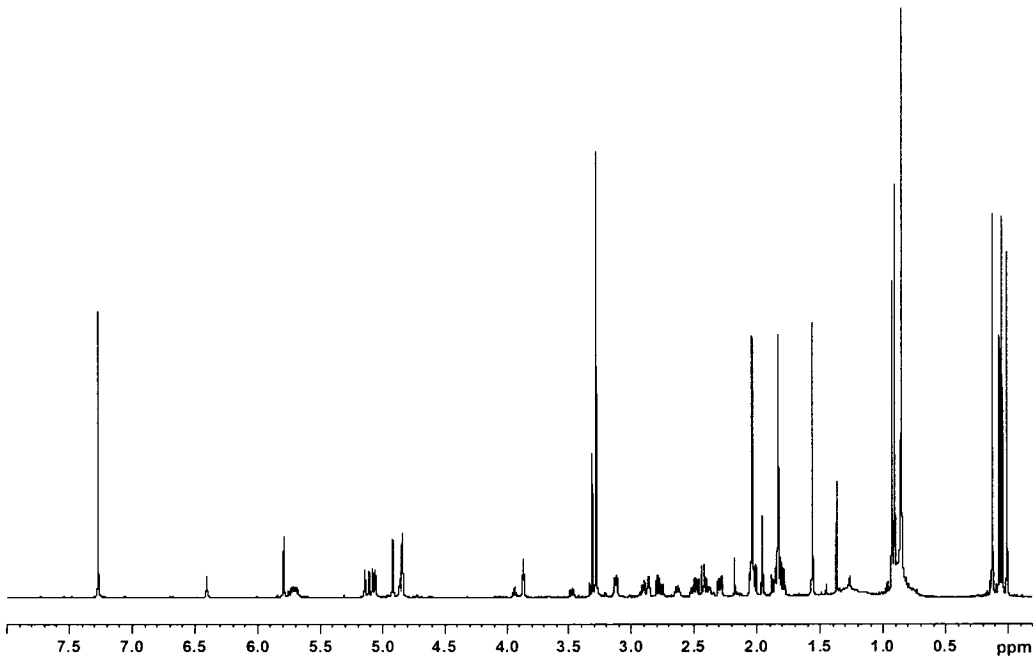


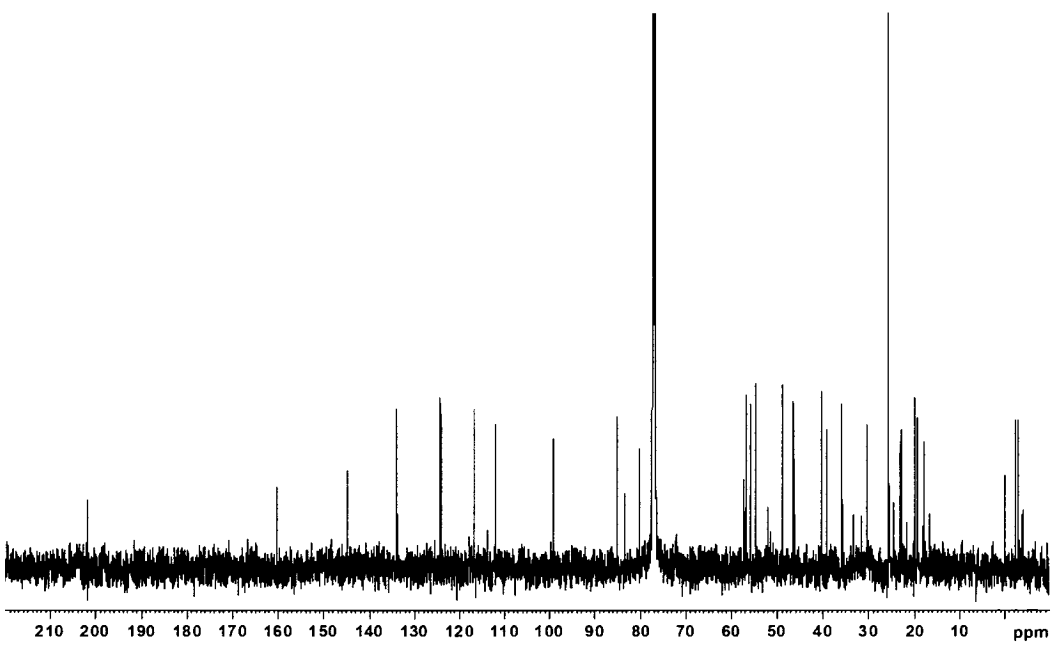


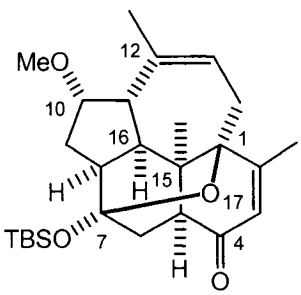


293a

(1*R**,2*S**,3*S**,4*R**,5*S**,7*R**,8*R**,10*R**)-1-Allyl-8-(*tert*-butyldimethylsilyloxy)-4-isopropenyl-5-methoxy-2,13-dimethyl-14-oxatetracyclo[6.5.1.$0^{2,10}$.$0^{3,7}$]tetradec-12-en-11-one (**293a**) and **185** (minor)

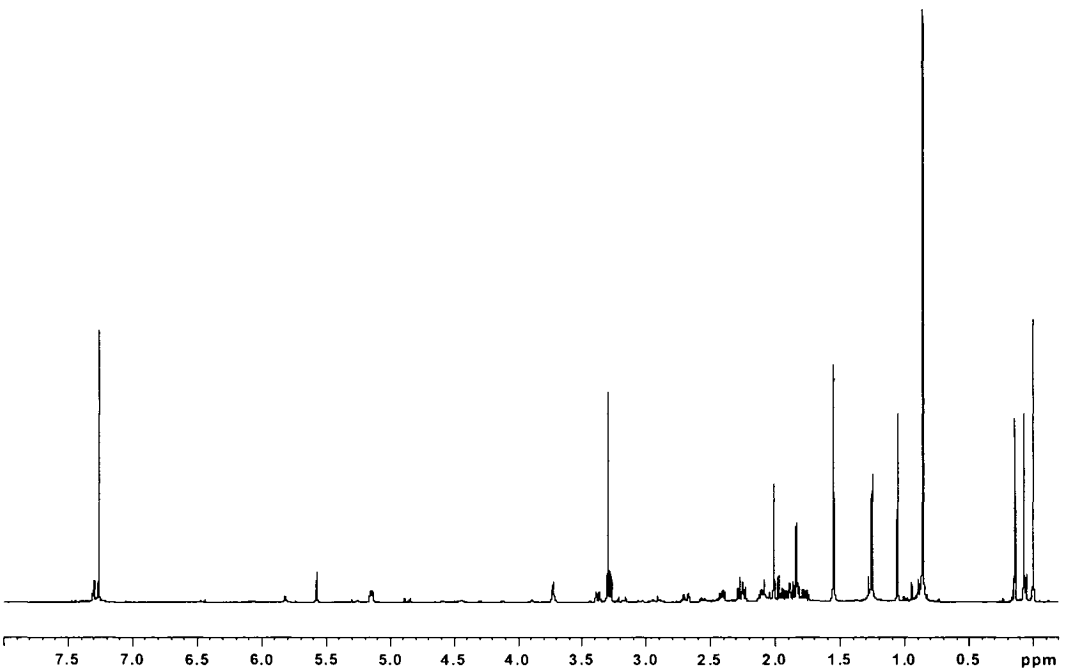




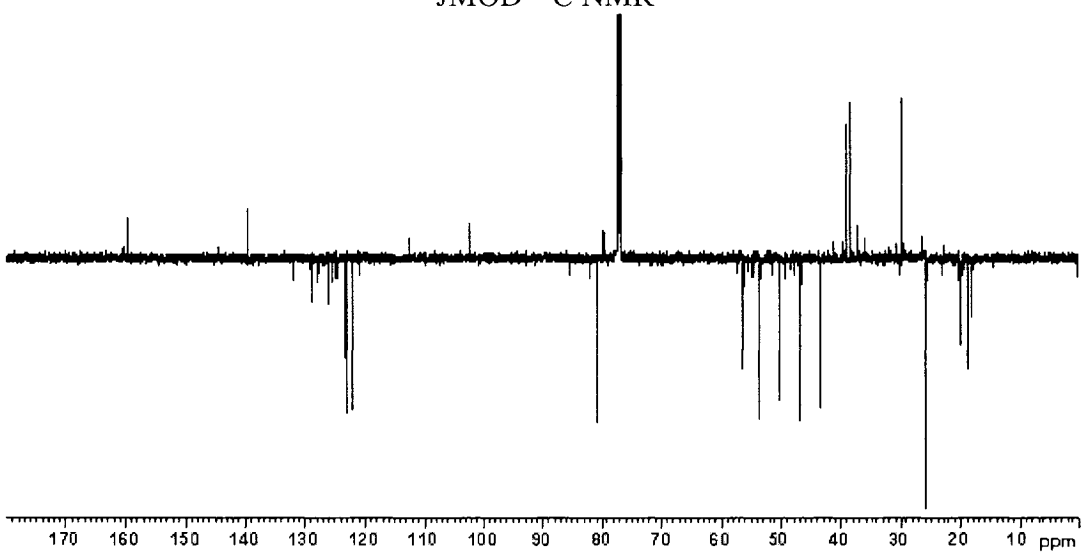


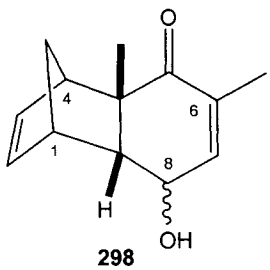
292a

(1*R**,5*R**,7*R**,8*R**,10*R**,11*R**,15*S**,16*S**)-7-(*tert*-Butyldimethylsilyloxy)-10-methoxy-3,12,15-trimethyl-17-oxapentacyclo[6.6.2.$1^{1,7}$.$0^{5,15}$.$0^{11,16}$]-heptadeca-2,12-dien-4-one (**292a**)



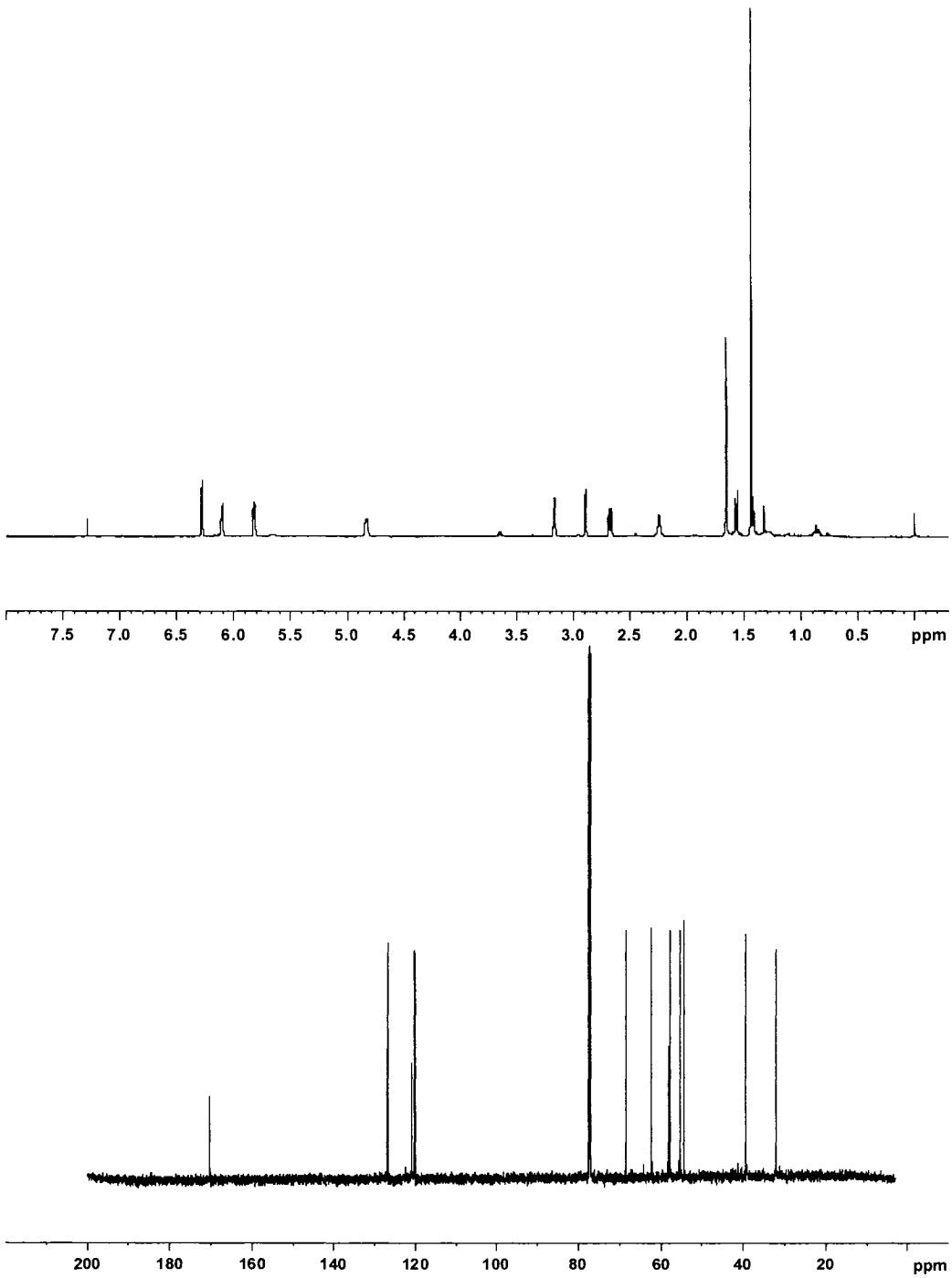
JMOD ^{13}C NMR

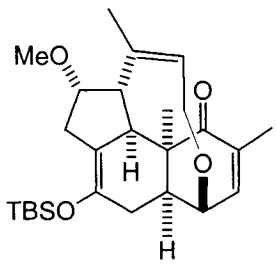




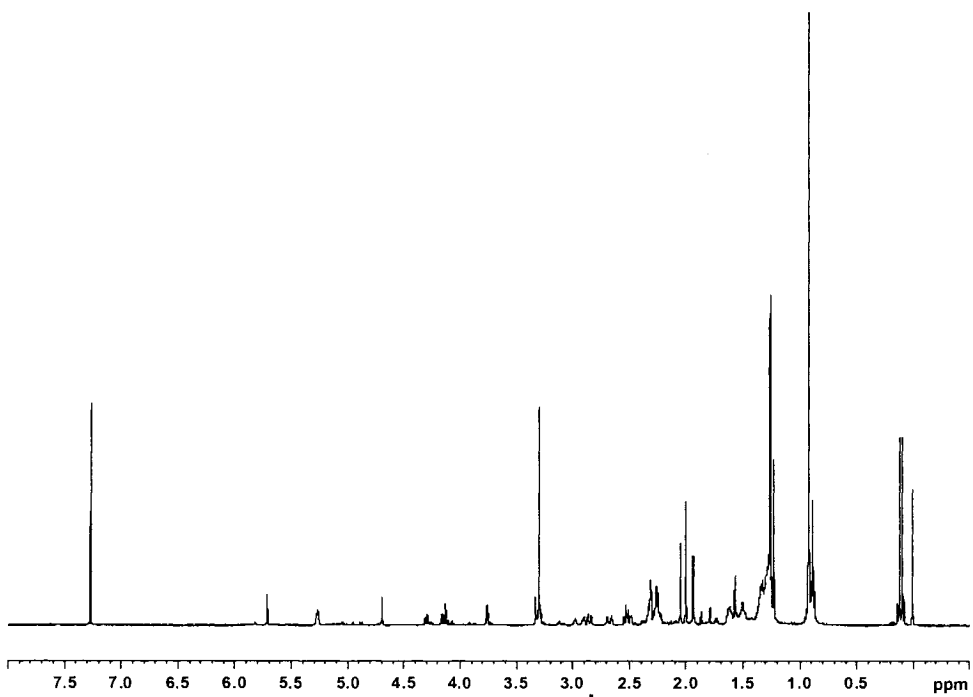
298

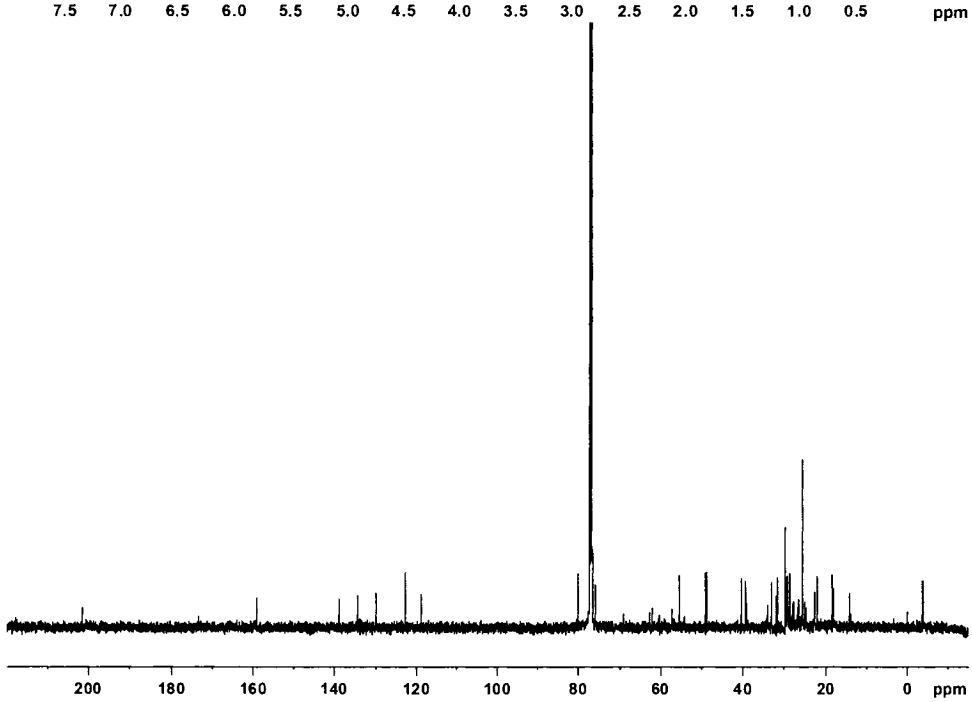
(1α,4α,4aβ,8aβ)-8-Hydroxy-4a,6-dimethyl-4,4a,8,8a-tetrahydro-1*H*-1,4-methanonaphthalen-5-one (**298**)

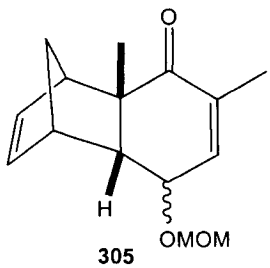



MeO
O
H
O
TBSO
H

303

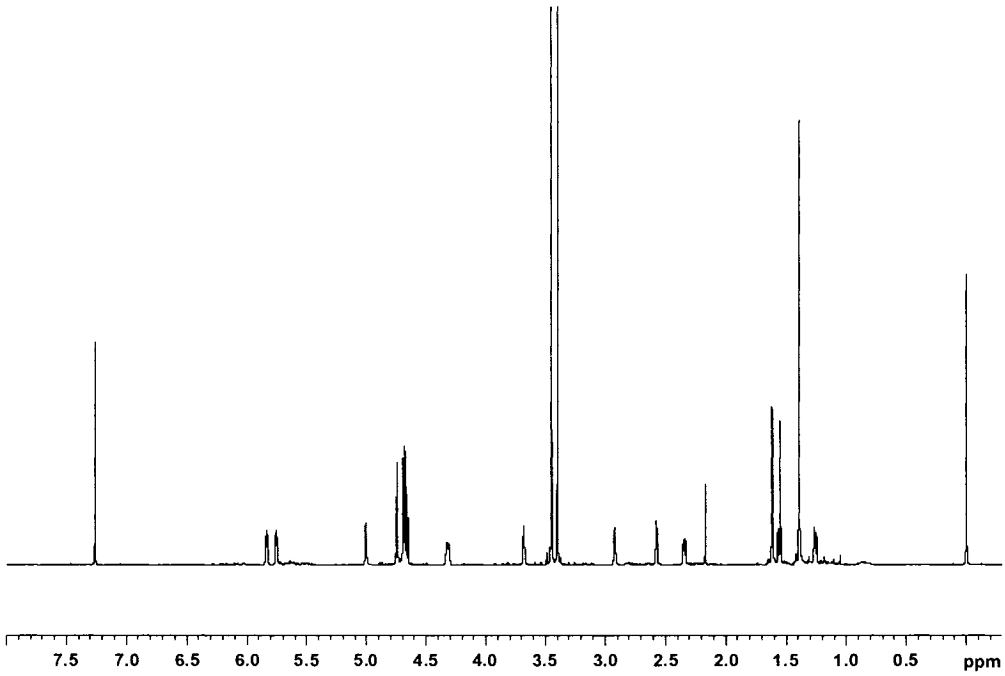

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

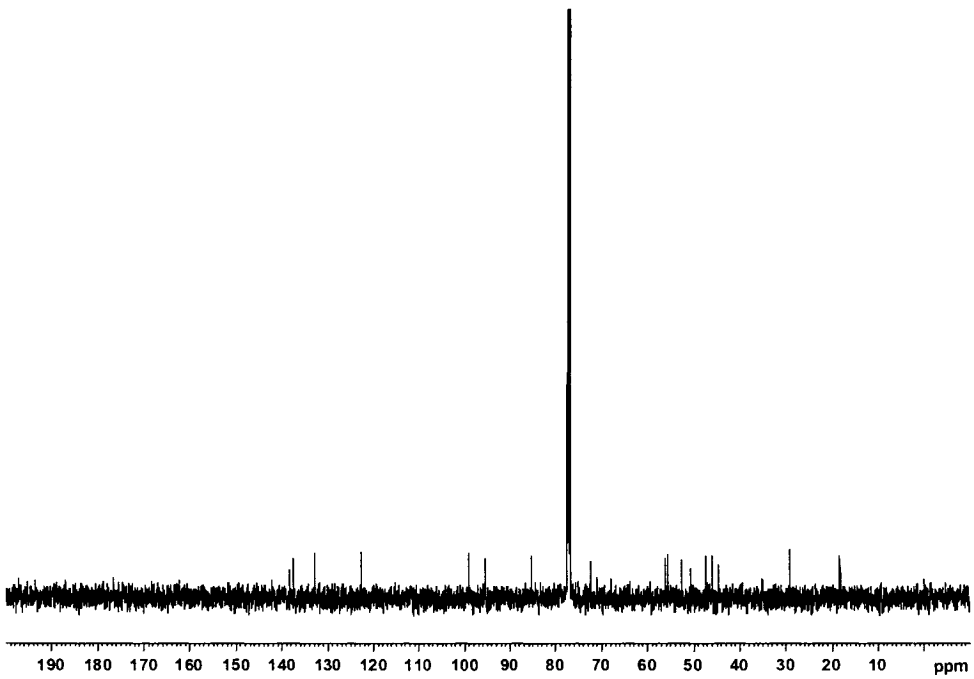

200
180
160
140
120
100
80
60
40
20
0
ppm

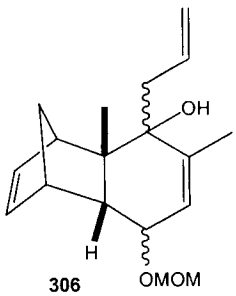


305

(1α,4α,4aβ,8aβ)-8-Methoxymethoxy-4a,6-dimethyl-4,4a,8,8a-tetrahydro-1*H*-1,4-methanonaphthalen-5-one (**305**)

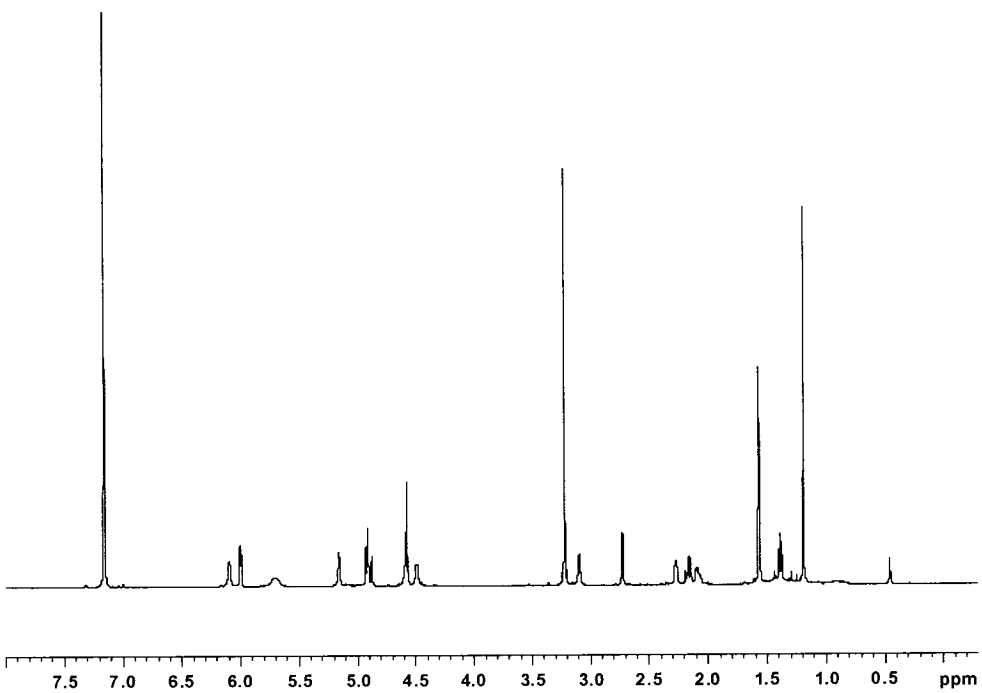


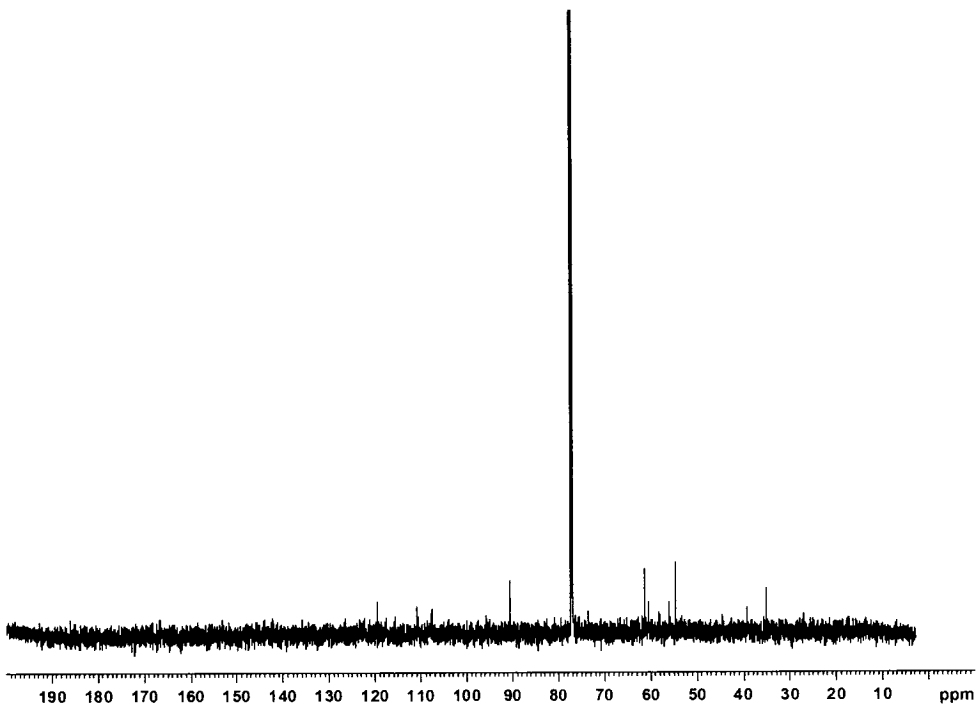


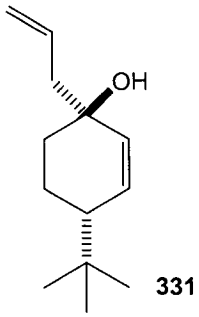


306

(1α,4α,4aβ,8aβ)-5-Allyl-8-methoxymethoxy-4a,6-dimethyl-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalen-5-ol (**306**)

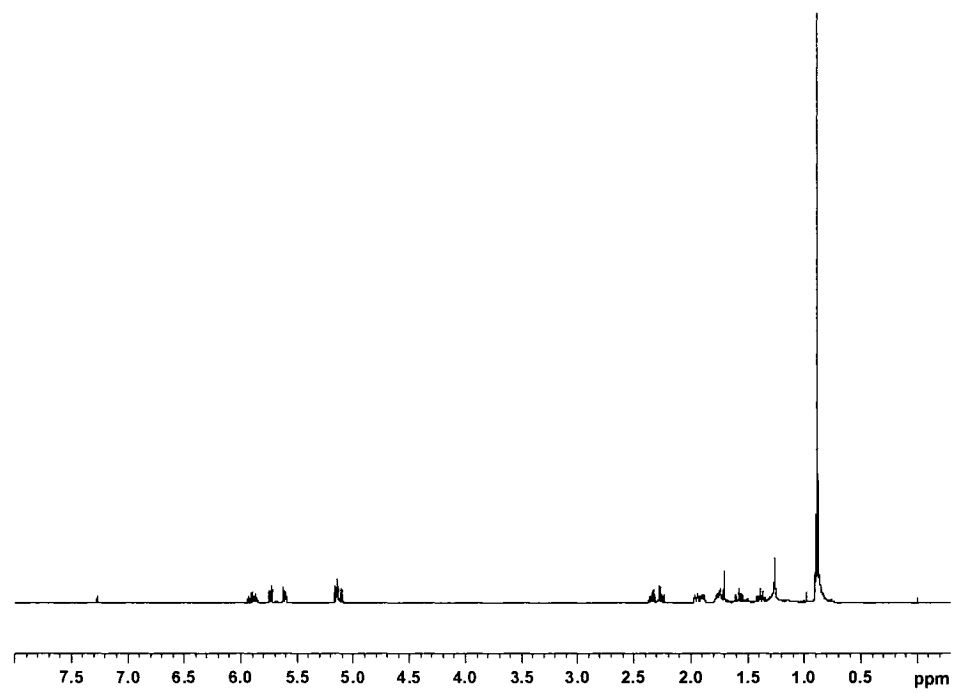


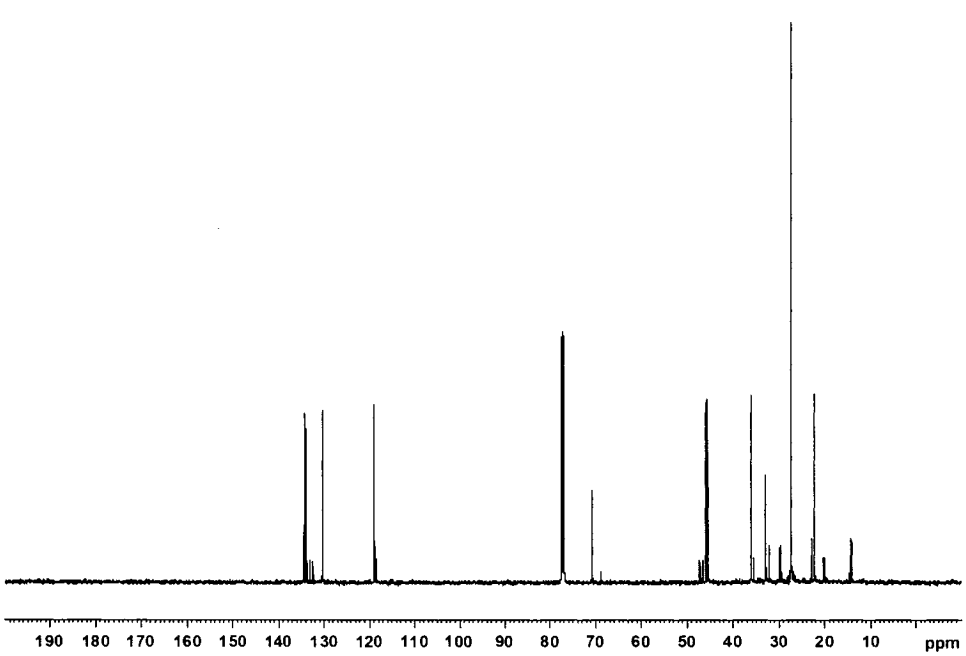


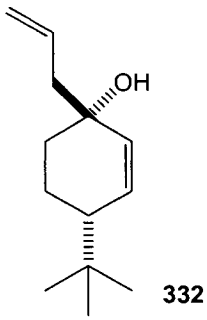


331

(1*R**,4*S**)-1-Allyl-4-*tert*-butylcyclohex-2-enol (**331**)

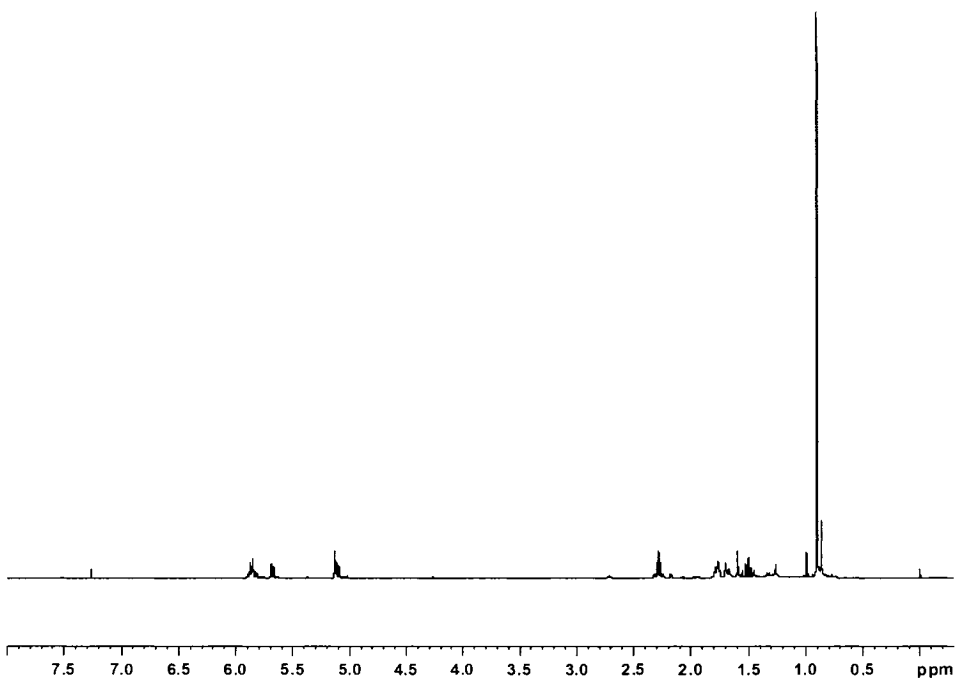


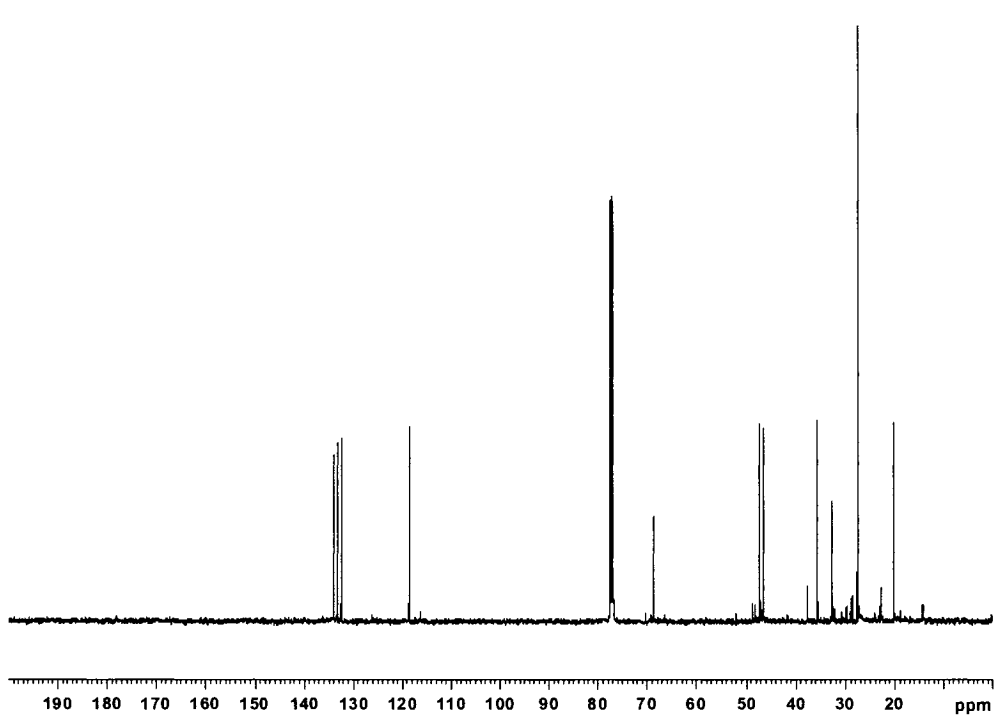


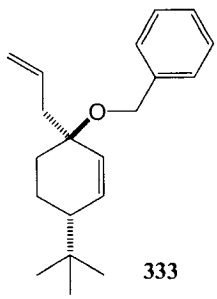


332

(1*R**,4*R**)-1-Allyl-4-*tert*-butylcyclohex-2-enol (**332**)



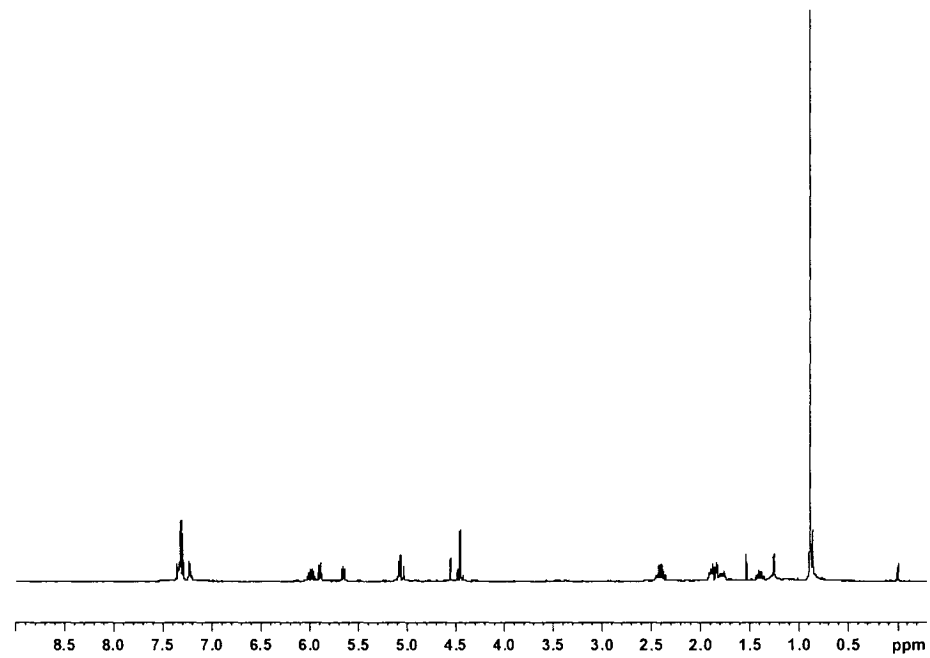


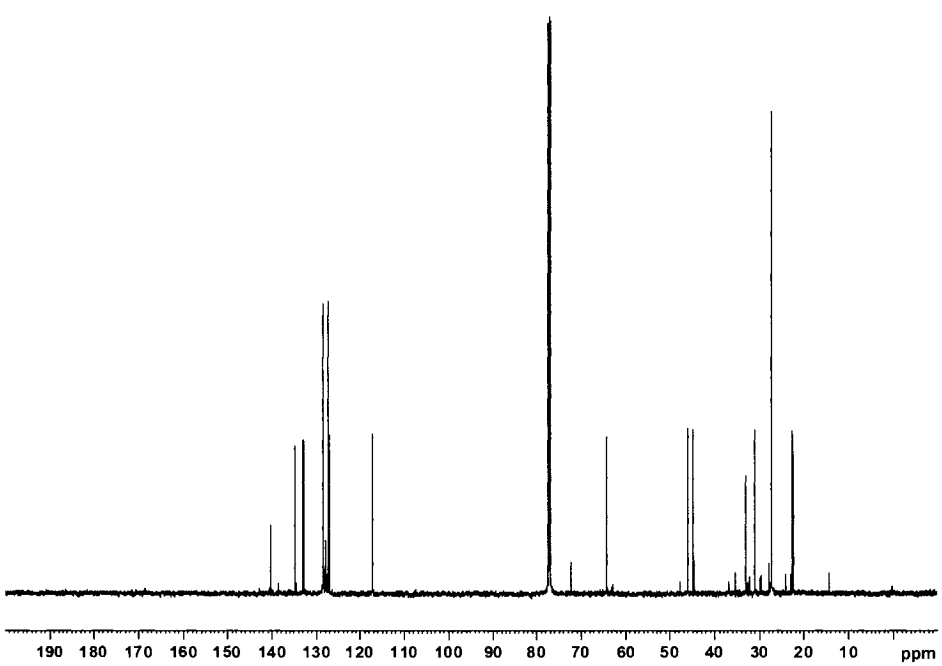


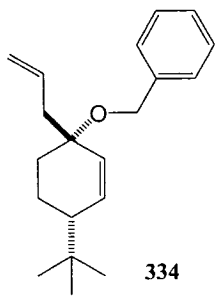
333

(1*R**,4*S**)-1-Allyl-1-benzyloxy-4-*tert*-butylcyclohex-2-ene

(333)

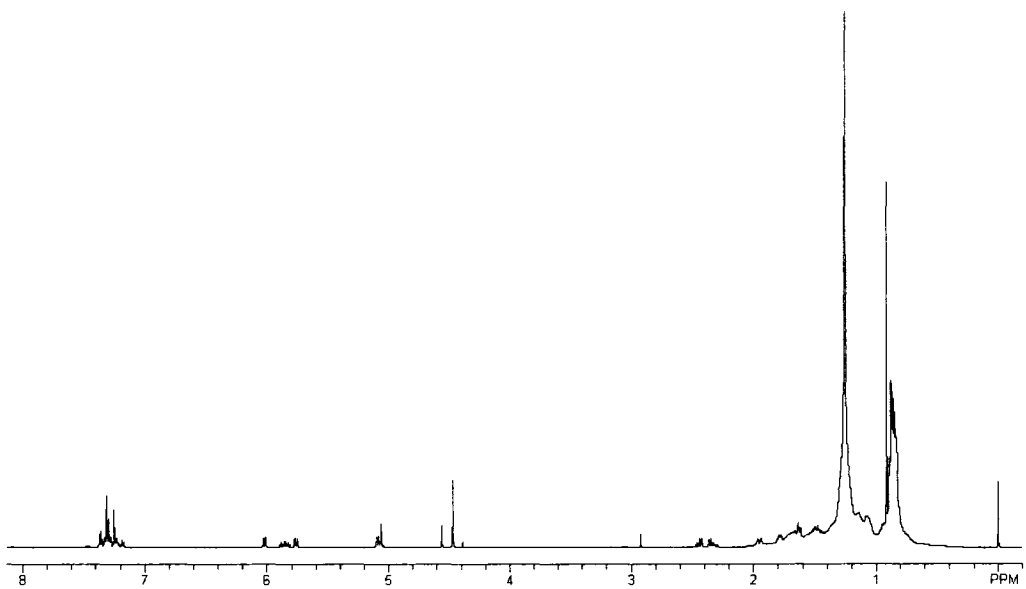


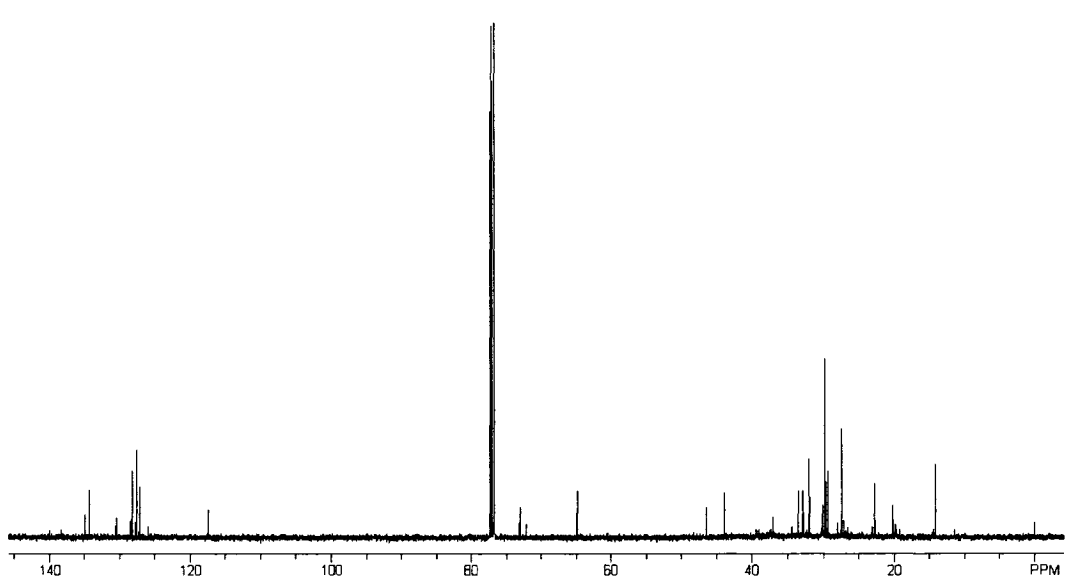


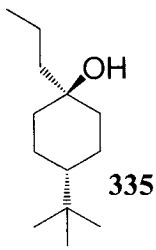


334

(1*R**,4*R**)-1-Allyl-1-benzyloxy-4-*tert*-butylcyclohex-2-ene (**334**)

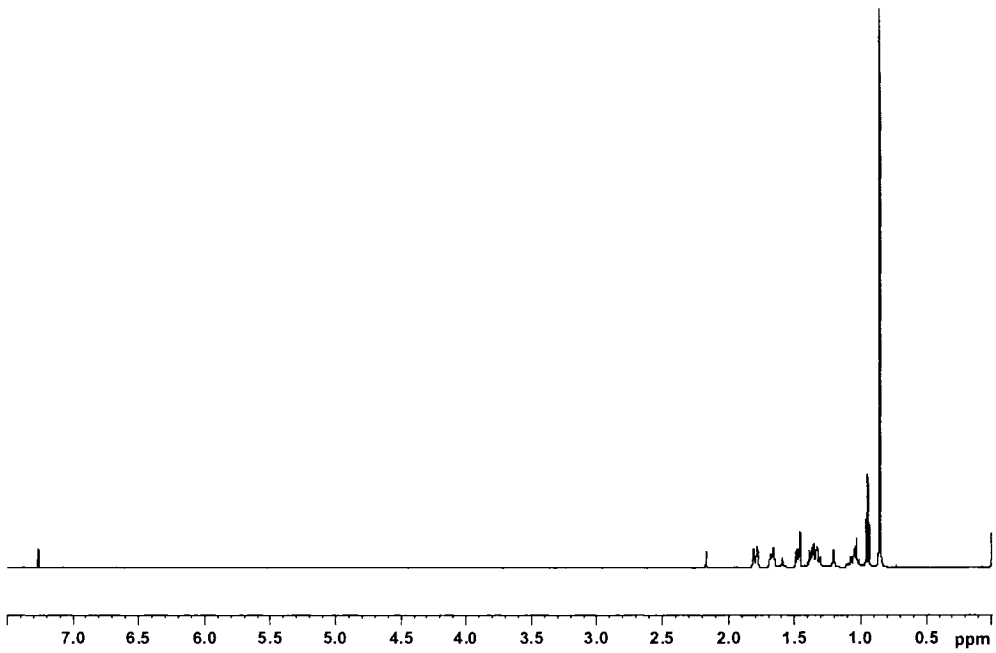


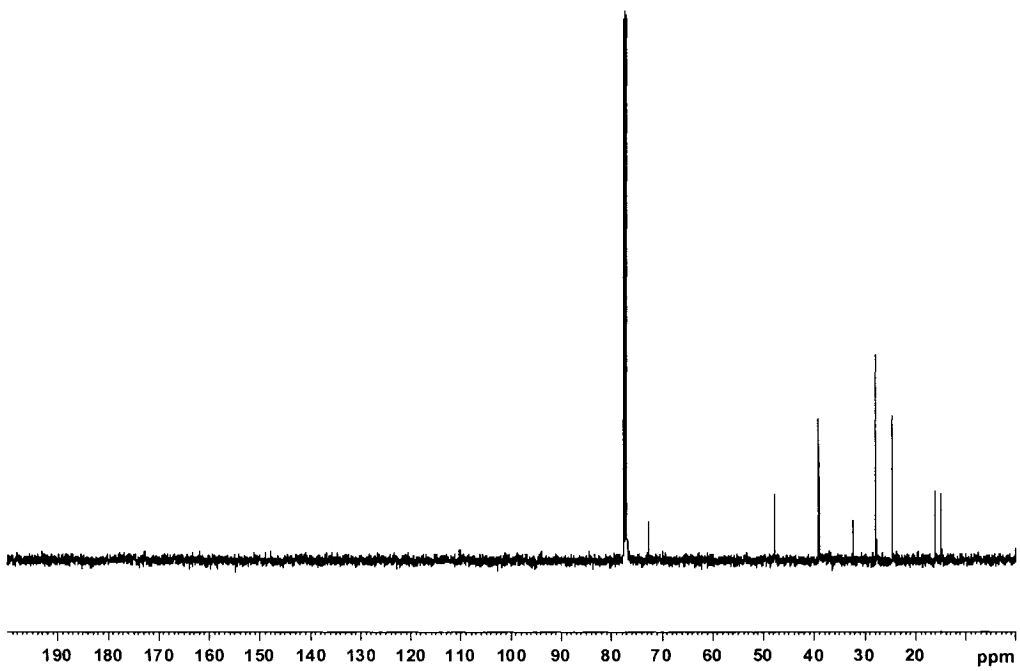


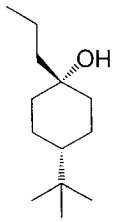


335

trans-4-*tert*-Butyl-1-propyl-cyclohexanol (**335**)

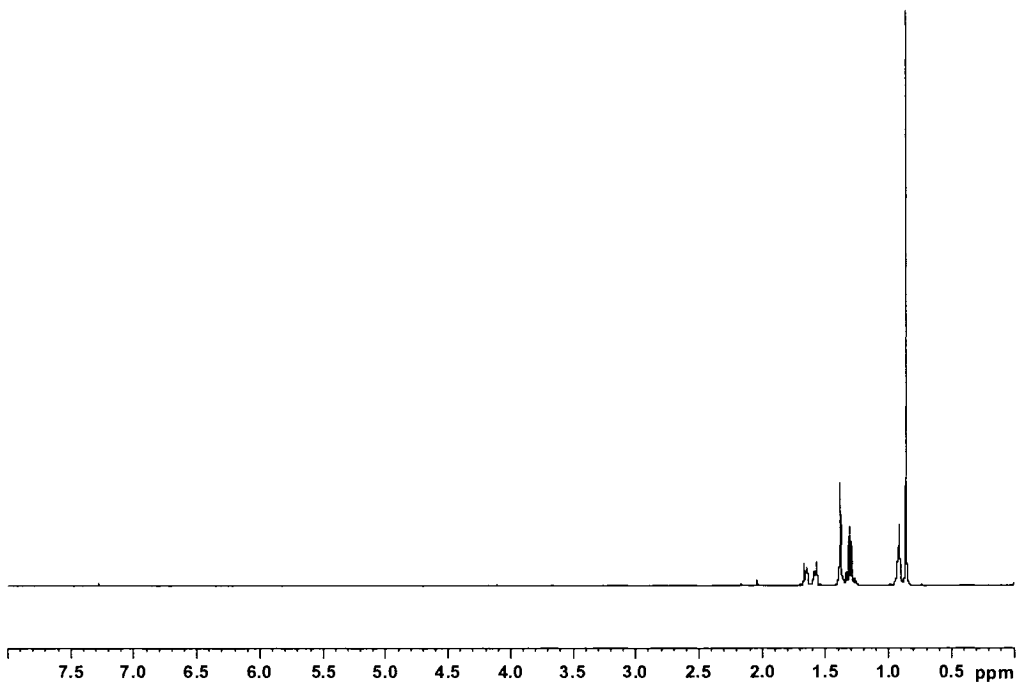


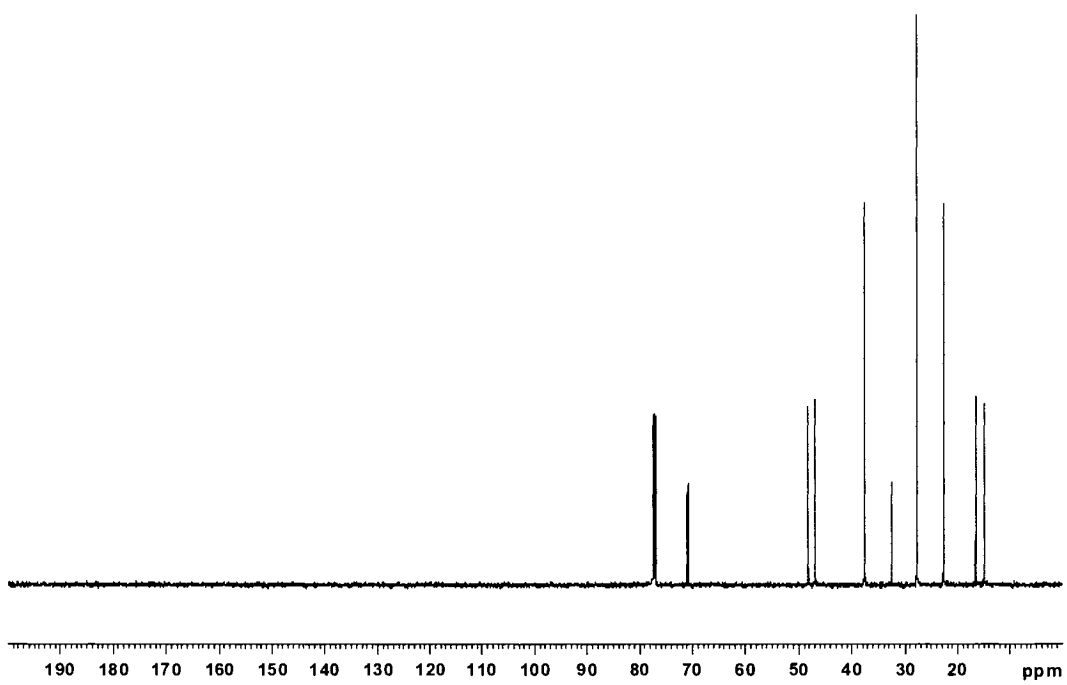


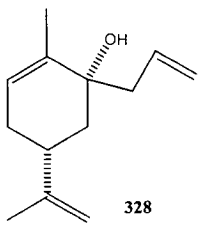


cis-4-*tert*-Butyl-1-propyl-cyclohexanol (**336**)

336

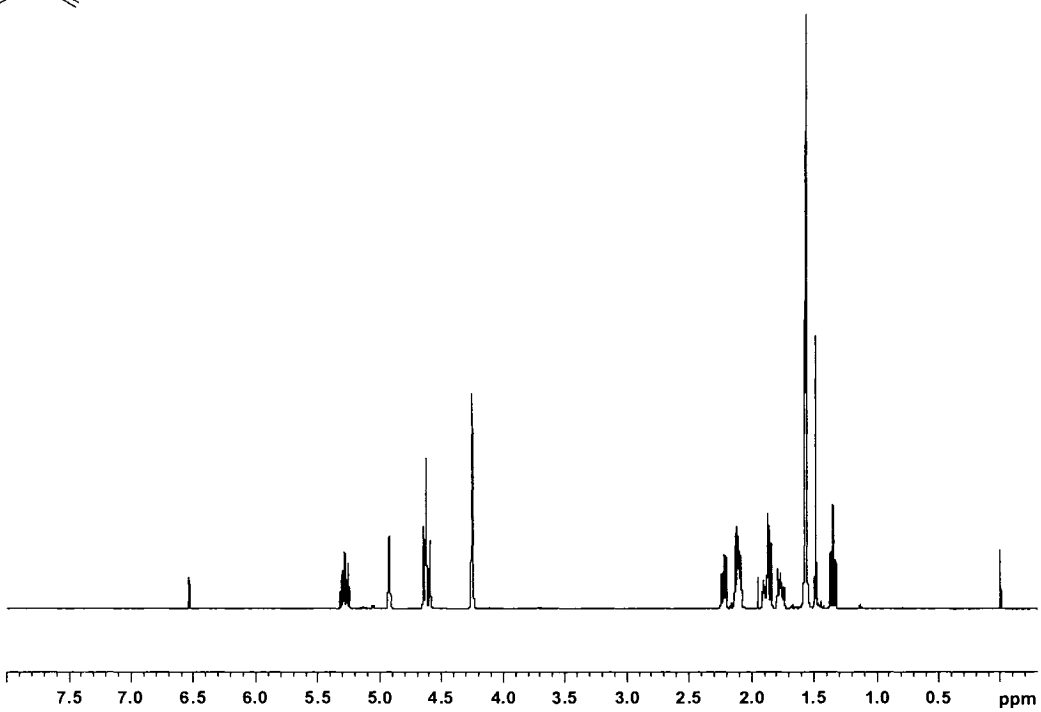


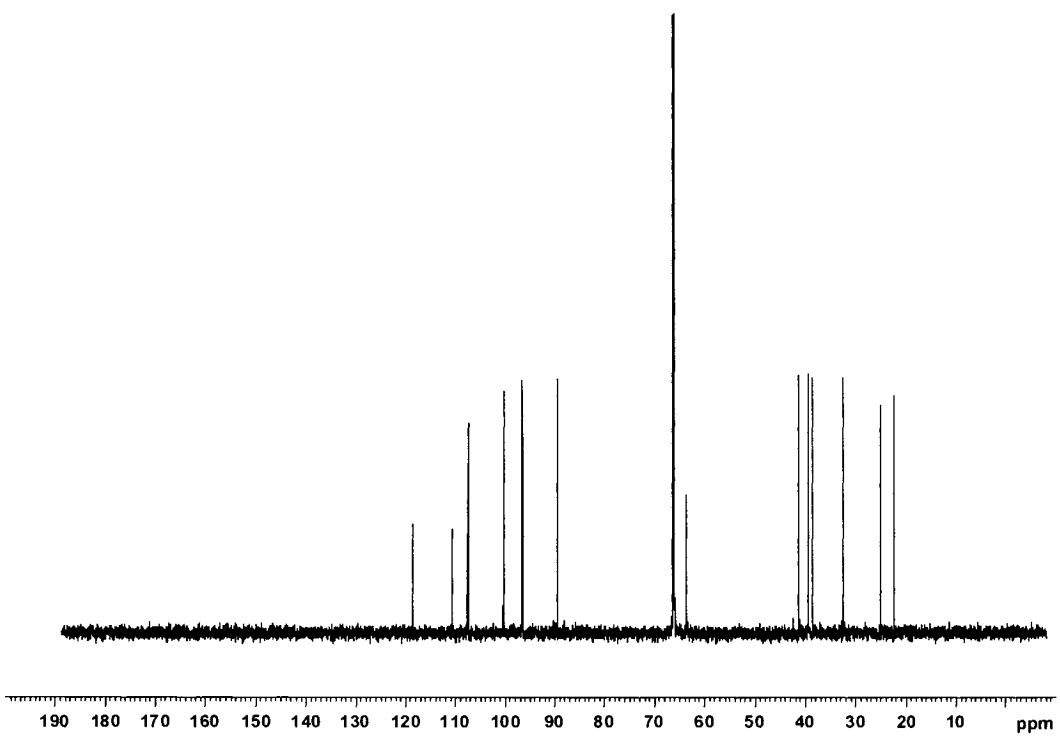


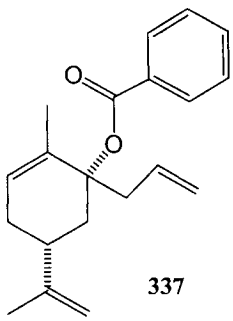


328

(1*R*,5*R*)-1-Allyl-5-isopropenyl-2-methyl-cyclohex-2-enol (**328**)

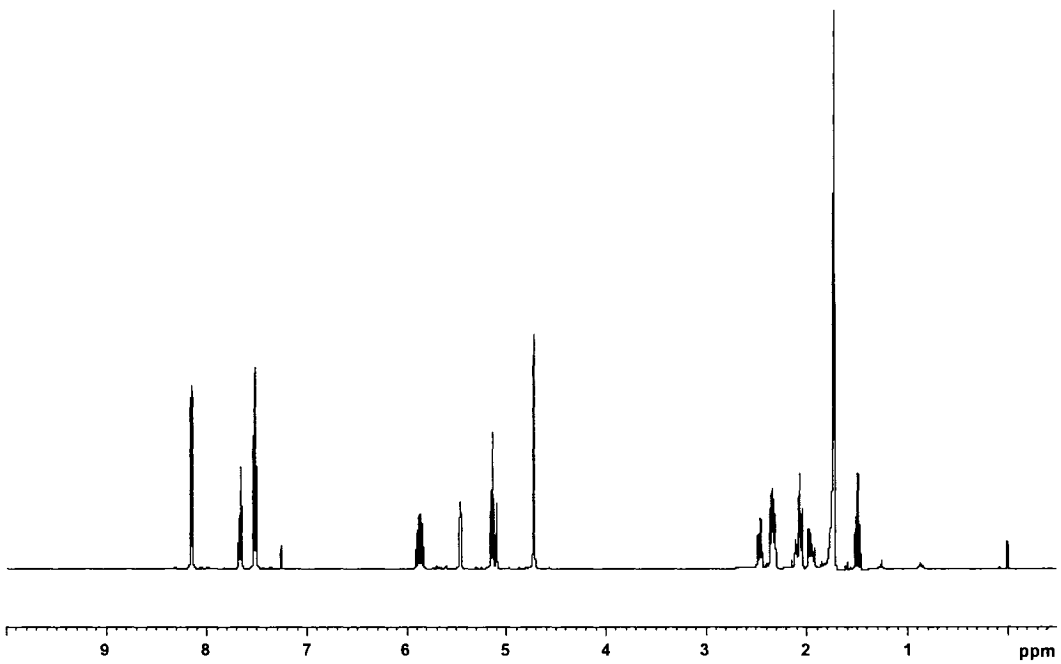


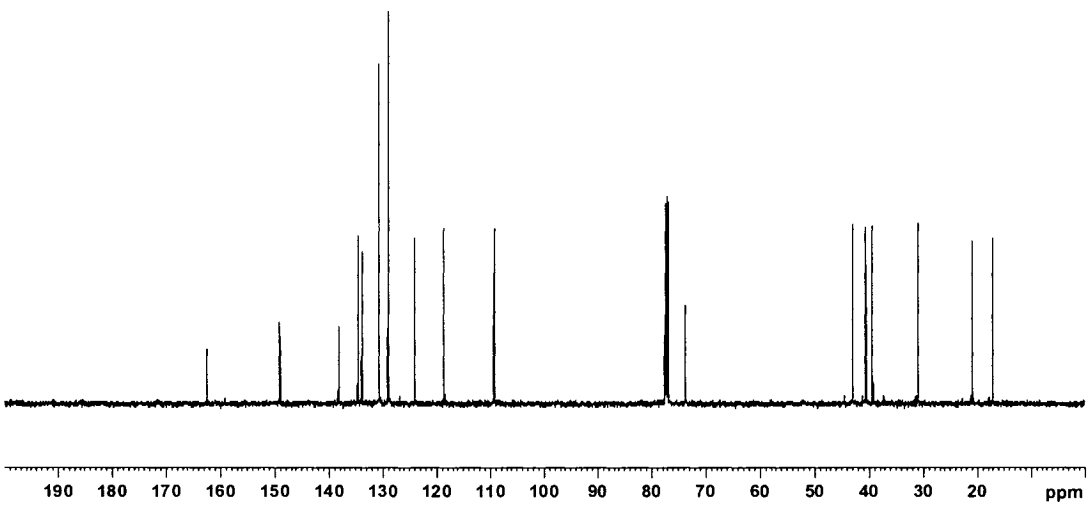


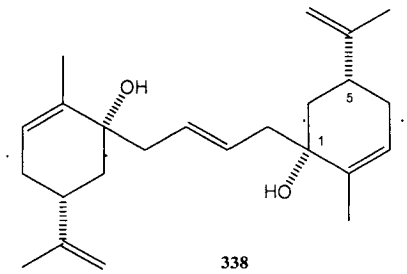


337

(1*R*,5*R*)- 1-Allyl-5-isopropenyl-2-methyl-cyclohex-2-en-1-ol, benzoic ester (**337**)

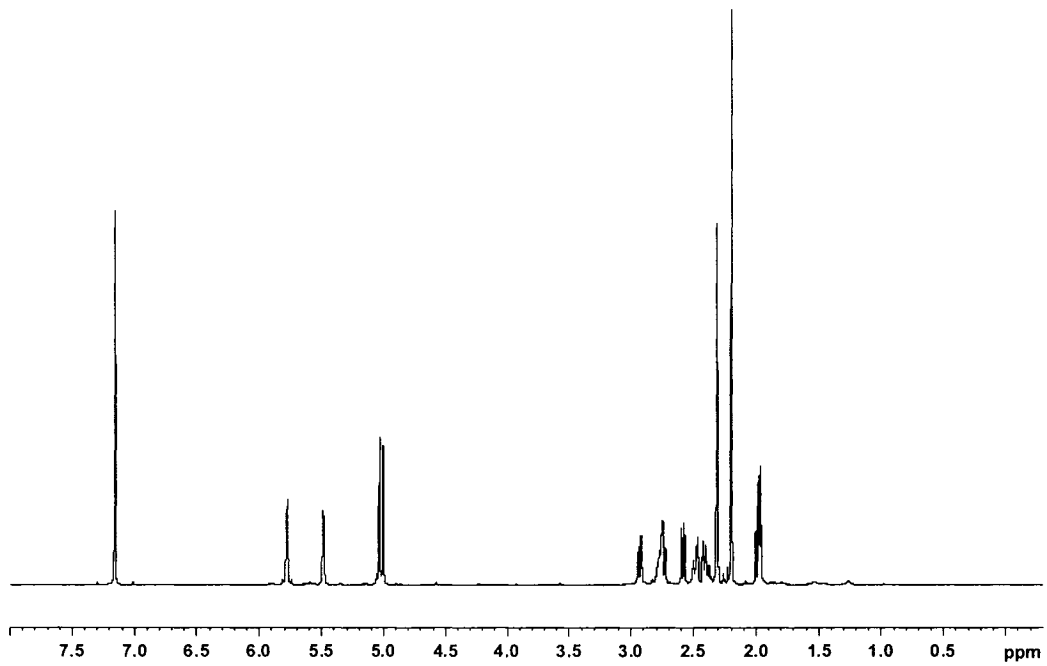


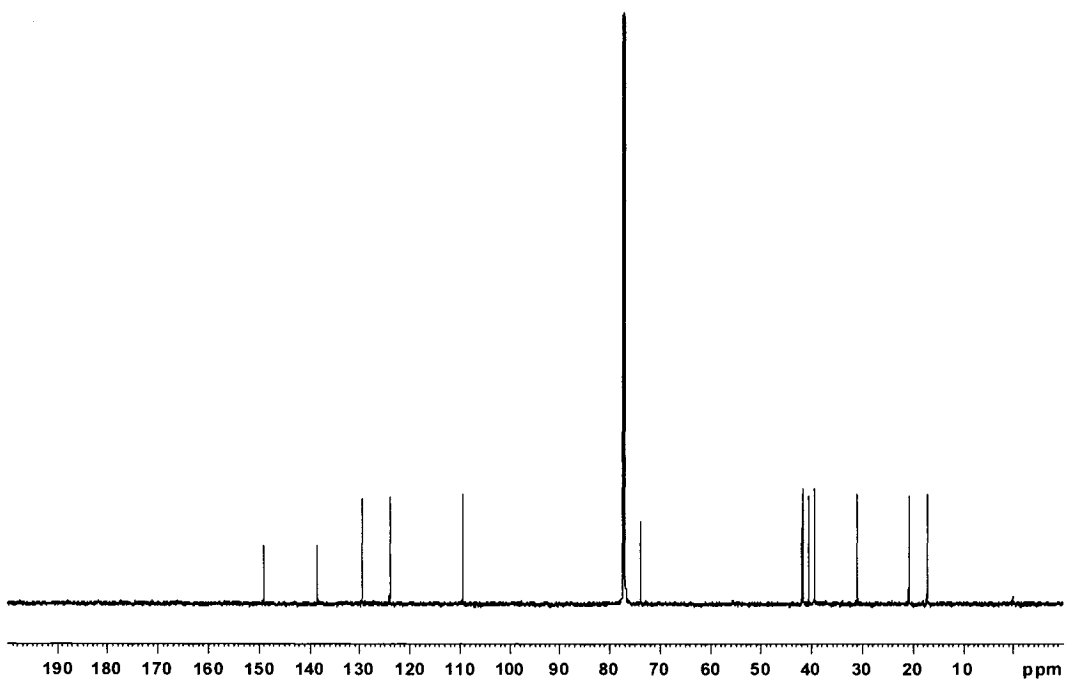


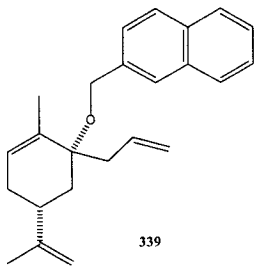


338

(1*R*,5*R*)-1-[4-((1*R*,5*R*)-1-Hydroxy-5-isopropenyl-2-methylcyclohex-2-enyl)but-2-enyl]-5-isopropenyl-2-methylcyclohex-2-enol (**338**)

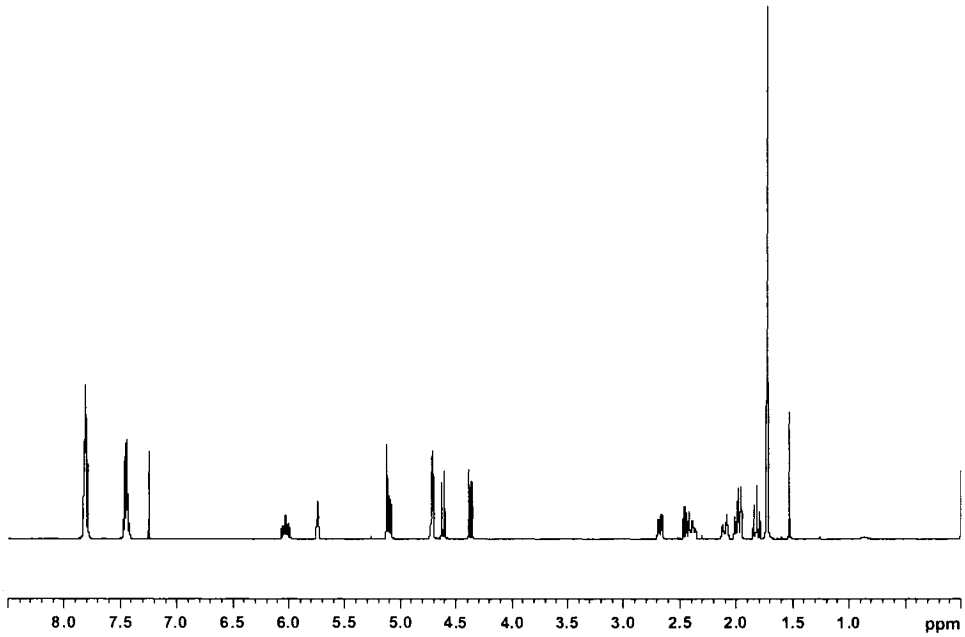


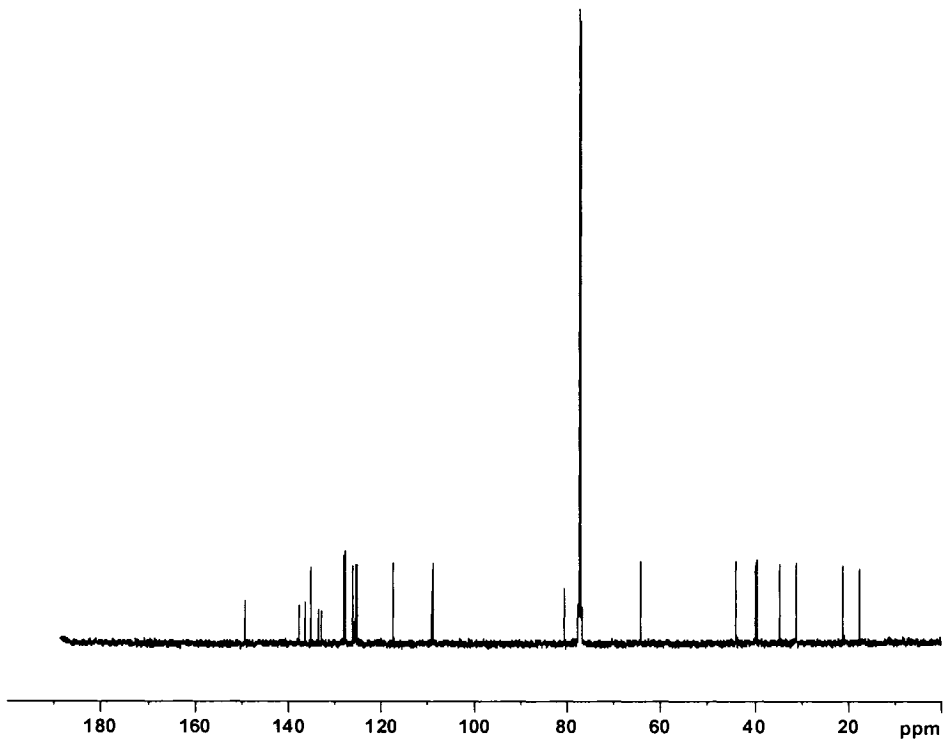


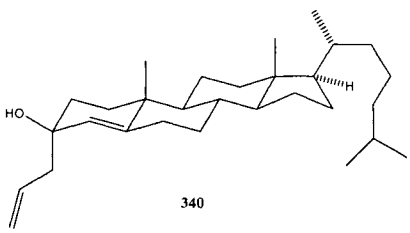


339

(1*R*,5*R*)-2-(1-Allyl-5-isopropenyl-2-methyl-cyclohex-2-enyloxymethyl)-naphthalene (**339**)

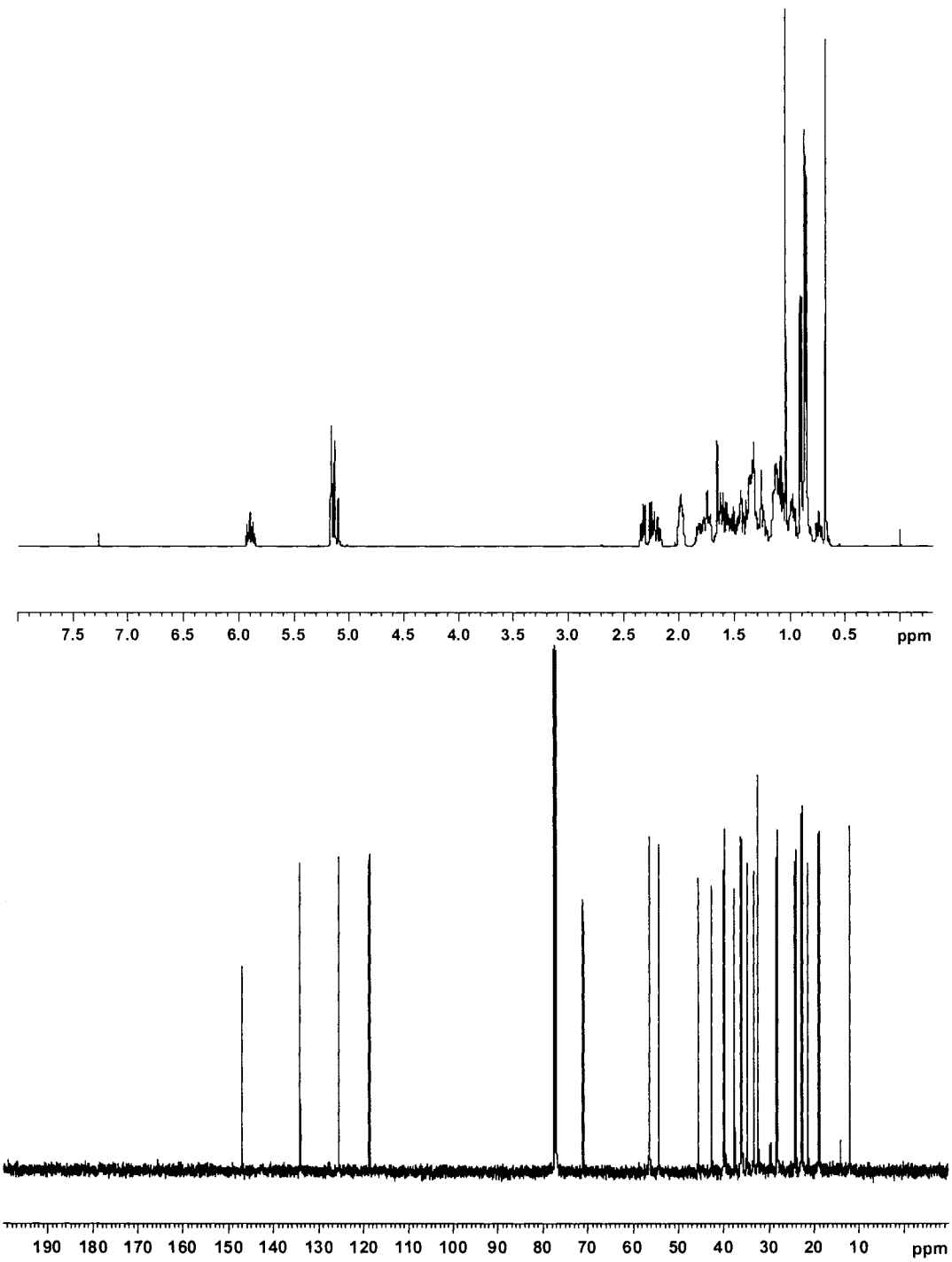


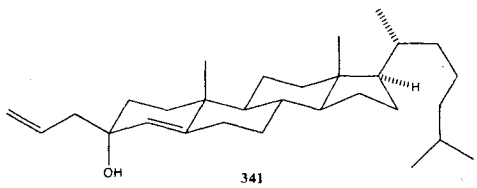




340

(+)-(3*R*)-3-allyl-4-Cholesten-3-ol (**340**)





341

(+)-(3*S*)-3-allyl-4-Cholesten-3-ol (**341**)