STUDIES TOWARD THE SYNTHESIS OF THE KEMPANE DITERPENE RING SYSTEM, AND SOME CASCADE RADICAL CYCLIZATIONS

GUANGLIN BAO

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by

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Abstract

Kempane diterpenes such as **1** and **2**, which are isolated from the defense secretions of nasute termite soldiers, are attractive and challenging targets for total synthesis. We have developed a highly stereoselective route, which is referred to as the Dithiane Route, to the kempane diterpene ring system that possesses all of the required stereogenic centers and sufficient functionality to allow for its conversion to the natural products. Our strategy took advantage of a highly regio- and endo-selective Diels-Alder reaction to construct the benzo-indane ring system. 2-[1-[(*tert*-Butyldimethylsilyl)oxy]vinyl]-6,10-dithia-spiro[4,5]-dec-2-ene reacted with 2,6-dimethyl-1,4-benzoquinone to produce a cyclo-addition adduct. The diene was prepared through a sequence that involved an alkylation of a dithiane compound with 2-methyl-2-(2-iodoethyl)-1,3-dioxolane, followed by an acid-catalyzed intramolecular aldol condensation. During the course of assembling the seven-membered ring cyclization precursor, a remarkably regioselective acetylide addition to a seemly more hindered carbonyl group was observed. In subsequent steps, a γ-hydroxyl group in an α,β-unsaturated ketone was cleaved by zinc reduction, followed by epimerization of a resulting decalin ring junction and double-bond isomerization catalyzed by *p*-toluene-sulfonic acid. In order to introduce the required double bond in the seven-membered ring at a later stage of the synthesis, a four-carbon side chain required for the target molecule was designed to be installed in two steps.

Despite the failures of our "First Route" and "Diether Route", the Dithiane Route proved to be promising enough for construction of the kempane diterpene ring skeleton and elaboration to the natural products.

To explore the possibility of introducing a methyl group at C-4 of kempane diterpenes, we investigated an electrophilic reaction of a silyl enol ether with 1,3-dithienium tetrafluoroborate and a cyclopropanation of a silyl enol ether. Model studies showed that indirect methylation of the TBS enol ether was successful, but that the subsequent acetylide addition step gave poor regio- and stereo-selectivity.

During the study of a cascade radical cyclization, a 5-*exo-dig*, 5-*exo-trig* tandem process and a 5-*exo-dig*, 6-*exo-trig* tandem process were achieved, although in low yield. It had been anticipated that this tandem radical cyclization strategy could provide an efficient approach to polycyclic compounds in high stereoselectivity.

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List of Schemes

Glossary of Abbreviations

Ac	Acetyl
acac	Acetylacetonyl
AIBN	2,2'-azobis(isobutyronitrile)
APT	Attached proton test
Bp	Boiling point
Bn	Benzyl
t-Bu	*tert*-Butyl
conc.	Concentrated
COSY	^{1}H-^{1}H Correlation (NMR spectrum)
Cp	Cyclopentadienyl
m-CPBA	*meta*-Chloroperoxybenzoic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
e	Electron
eq.	Equivalent
Et	Ethyl
ERG	Electron releasing group

EWG	Electron withdrawing group
GC-MS	Gas chromatography-mass spectrometry
HETCOR	Heteronuclear correlation (NMR spectrum)
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrum
hν	Ultraviolet irradiation
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MEM	(2-Methoxyethoxy)methyl
MOM	Methoxymethyl
Mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser effect
Nu	Nucleophile

PCC	Pyridinium chlorochromate
Ph	Phenyl
PPTS	Pyridium *p*-toluenesulfonate
i-Pr	Isopropyl
Pyr.	Pyridine
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
SOMO	Singly occupied orbital
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	*para*-Toluenesulfonyl

Part I.

Stereoselective Synthesis of the Kempane Diterpene Ring System

1.1. Introduction

The soldiers of termites have both physical and chemical defense mechanisms, which can be used either separately or in combination, to protect their colonies.[1] Physical defense mechanisms are utilized by primitive termite soldiers, and these involve the use of their mandibles. These mandibles are large and powerful, and the termite soldiers can use them to cut and bite their enemies. Termite soldiers in some other species also use chemical defense mechanisms, which are a more highly evolved form of defense. They use their mandibles to capture their opponents firmly, and the soldiers then eject viscous and sticky secretions into the enemies' wounds.

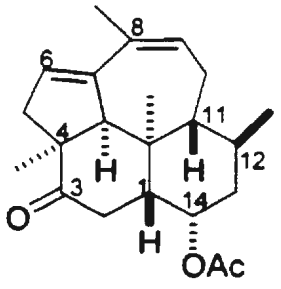
The soldiers of nasute termites have the most highly evolved chemical defense system. Nasute soldiers totally avoid contact with the enemy by ejecting a gluey, viscous secretion from an elongated rostrum called a nasus. The secretions can be thrown a distance of several centimeters and are able to immobilize their enemies. Even more impressively, many different organic compounds have been identified as components of the defense secretions of termites. The soldiers of the most advanced genera of nasute termites have

evolved a great ability to biosynthesize diterpenes in a gland that is unique in insects. A high concentration of hydrogen-bonded diterpenes in a monoterpene solvent is responsible for the stickiness of their defense secretions.

There has been much discussion on the role of the components of these secretions. It was proposed that the monoterpene hydrocarbons act as alarm pheromones, feeding deterrents, topical poisons and/or surface irritants, while the role of the diterpenes is to provide the high viscosity that is required of a good glue. The exact biological activity of these diterpenes however is not known, but it is believed that it is not reasonable that termite soldiers would make complex diterpenes without any specific purpose. If enough of these diterpenes were available, it would be possible to conduct further studies in order to determine the biological activities of these diterpenes.

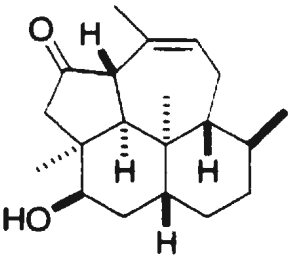
The kempenes form one class of diterpenoids isolated from the defense secretions of nasute soldiers. Two representative members of the kempene diterpenes, 14α-hydroxykempa-6,8-dien-3-one 14-acetate (**1**), which has the short name of "kempene-2", and 3β-hydroxy-7β-kemp-8(9)-en-6-one (**2**) with the trivial name of "kempenone", are shown in Figure 1.

Figure 1. Representative members of the kempane family of diterpenes



1

kempene-2



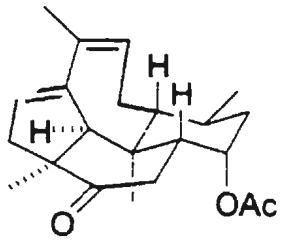
2

kempenone

In 1977, Prestwich and co-workers[2] first isolated kempene-2 (**1**) from the hexane extract of crushed heads of *Nasutitermes kempae* soldiers. using chromatography over Florisil, followed by HPLC on μ-Porasil. The structure of **1** was elucidated by single-crystal X-ray diffraction and NMR experiments in1979.[3]

Kempenone **2** was isolated by the same group from the soldier defense secretion of *Nasutitermes octopilis*, by chromatography over Florisil. The structure of kempenone **2** was established by single-crystal X-ray diffraction using the *p*-bromobenzoate derivative.[3] Crystal structures of these compounds also showed that they had bowl-like shapes, as shown for kempene-2 (**1**) in Figure 2, and that the diene system in **1** was not planar but twisted by about 20 degrees. The absolute configuration of kempane-2 (**1**) was obtained from the helicity of both diene and carbonyl chromophores.[4]

Figure 2. The shape of kempene-2 (**1**)

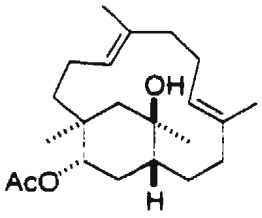


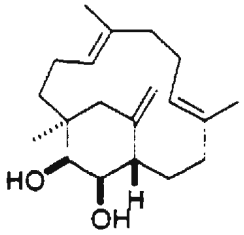
From the defense secretions of termite soldiers, a large number of structurally-related diterpenoids have been isolated. These include bicyclic secotrinervitenes,[5] tricyclic trinervitenes,[6] tetracyclic rippertenes,[7] and spiro-fused tetracyclic longipanes,[8] along with the tetracyclic kempenes. Examples of these diterpenoids are shown in Figure 3.

Investigations[5a 8] of the biosynthetic origins and the biosynthetic key intermediates have shown that all five classes of diterpenes are derived from the cyclization of farnesyl pyrophosphate, which, in turn, is derived from mevalonate, as shown in Scheme 1.

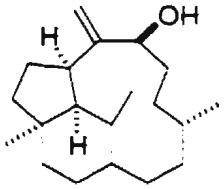
Figure 3. Examples of diterpenoids from the defense secretions of nasute termite soldiers

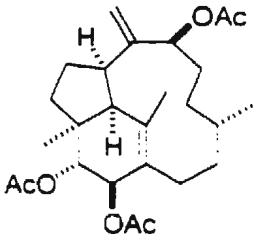
Secotrinervitenes

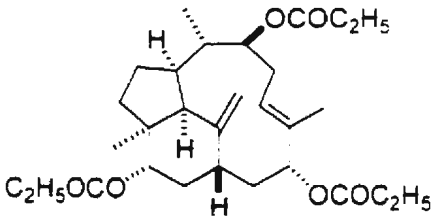




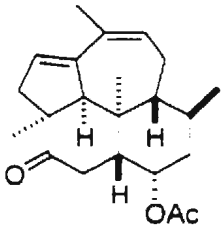
Trinervitenes

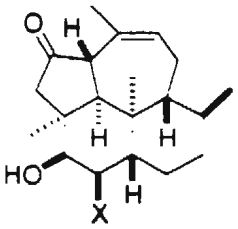




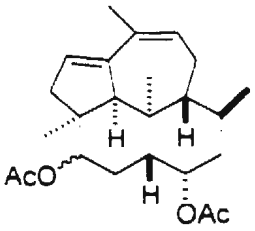


Kempanes

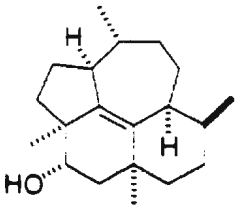




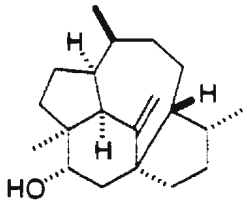
X = H, or OAc



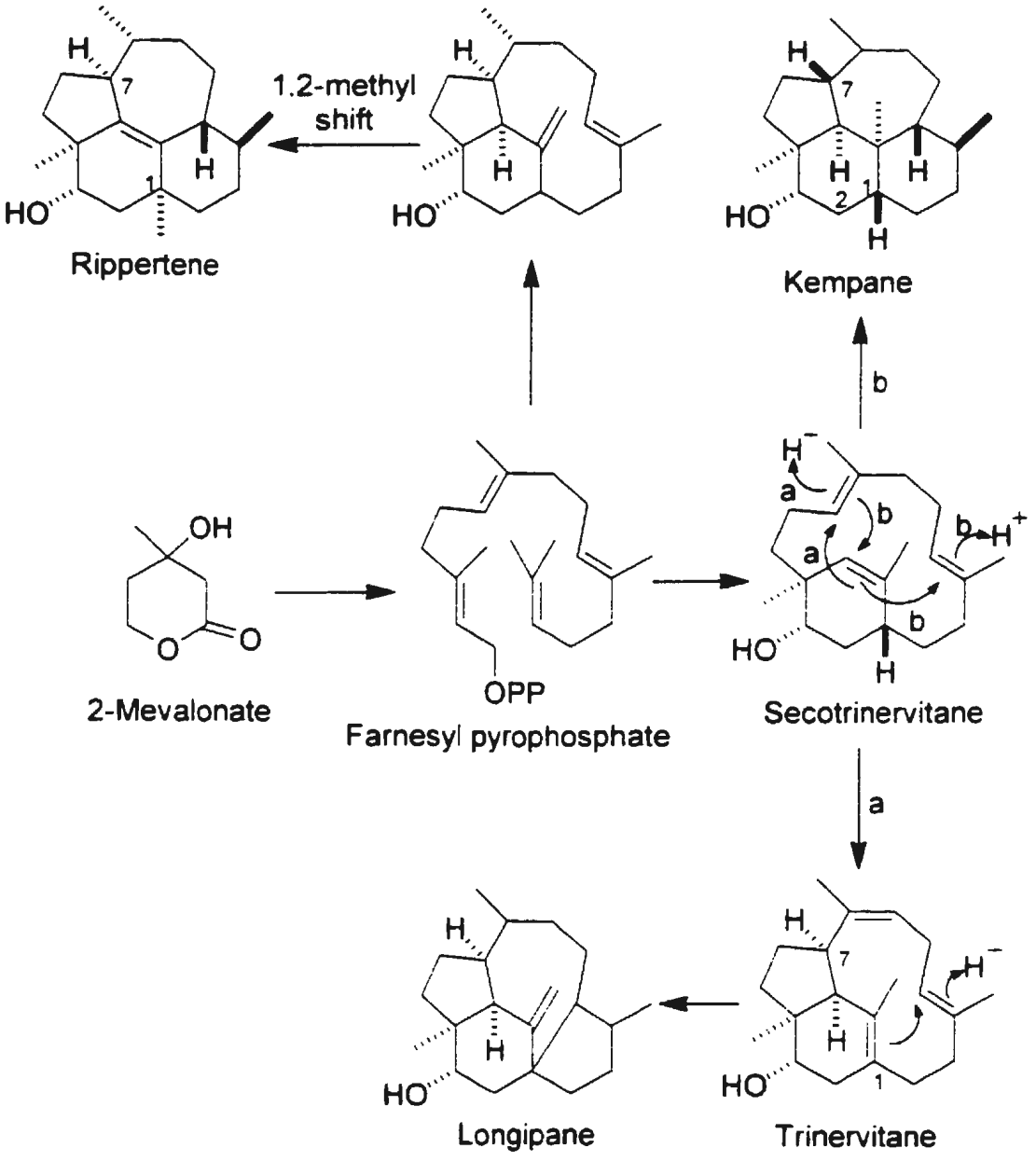
Rippertene



Longipane

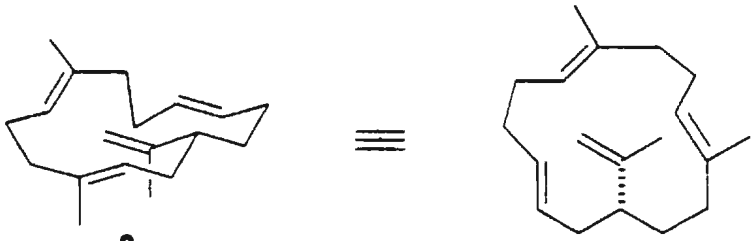


Scheme 1. Biogenesis of termite diterpenes



This biosynthetic proposal has been confirmed by both isotopic labeling experiments[9] and by the coexistence of trinervitene and secotrinervitene in *Nasutitermes princepts*.[5c] It seems reasonable that the secotrinervitane derivative

is an intermediate in the biosynthesis of the kempane and trinervitane diterpenes. Even though cembrene A (**3**) is a well-known trail pheromone of termite workers[10] and was suggested to be a common precursor to all of these diterpenes,[4,11] **3** has never been found in the defense secretions of nasute termite soldiers.



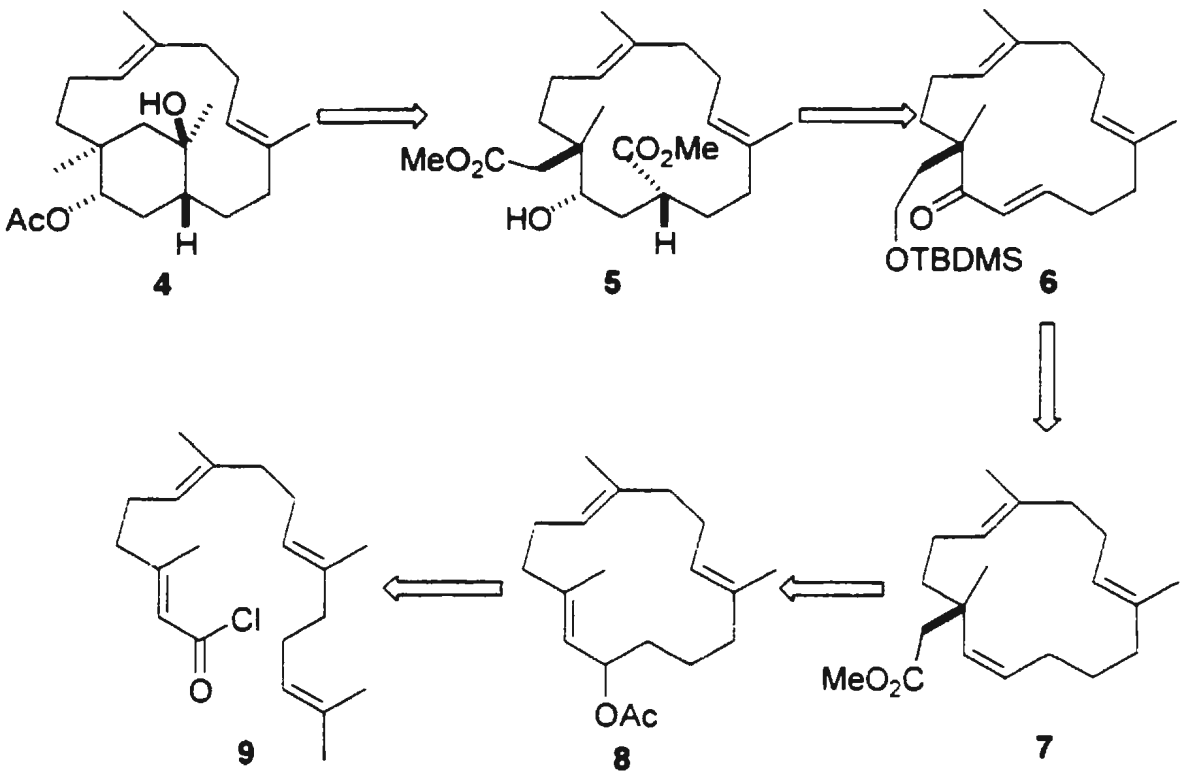
3

It is also obvious that the tetracyclic diterpenoids are not derived from the tricyclic ones, due to the opposite configurations of C-7 in trinervitenes with those in kempenes and rippertene.

Because of their biological interest and, especially, their unique carbon skeletons, the diterpenoids from the defense secretions of termite soldiers have been attractive and challenging targets for total synthesis. Up to now, there have been six synthetic endeavors in this area.

In 1987, T. Kato's group reported the first total synthesis of a defense substance from a termite soldier, the synthesis of (±)-3α-acetoxy-15β-hydroxy-7,16-secotrinervita-7,11-diene (**4**).[12] The strategy is outlined in Scheme 2.

Scheme 2: Kato's strategy in the synthesis of secotrinervitene **4**

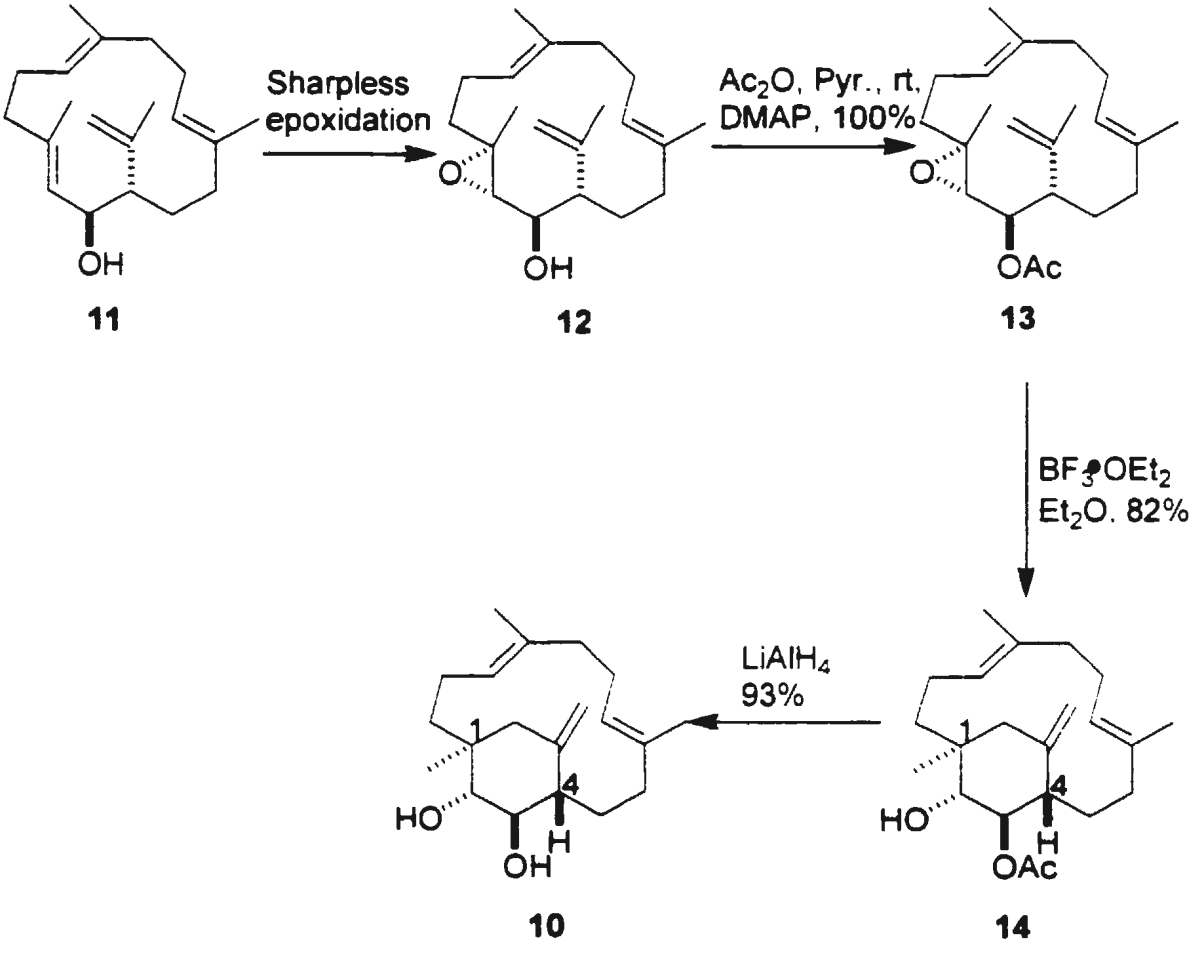


Kato used the macrocyclic allyl acetate **8**, which had been previously prepared from *trans*-geranyl geranoyl chloride **9** by a convenient, large-scale method developed in their laboratory.[13] In order to get the ester **7**, an Ireland-type Claisen rearrangement was used to introduce a two-carbon side chain. Regioselective epoxidation of the disubstituted double bond was achieved by Sharpless epoxidation. After protection, ring opening of the epoxide and oxidation, compound **7** was transformed into the enone **6**, from which a second side-chain was introduced by a Michael addition reaction. The cyclohexane ring in **4** was constructed by Dieckmann condensation of diester **5**. This strategy did

yield the racemic natural product **4**, but because of its poor stereoselectivity and the low yield in the final step, this synthesis was quite inefficient.

Almost at the same time, the same group reported an elegant biomimetic synthesis of (±) secotrinervitene-2β,3α-diol (**10**), as shown in Scheme 3.[14]

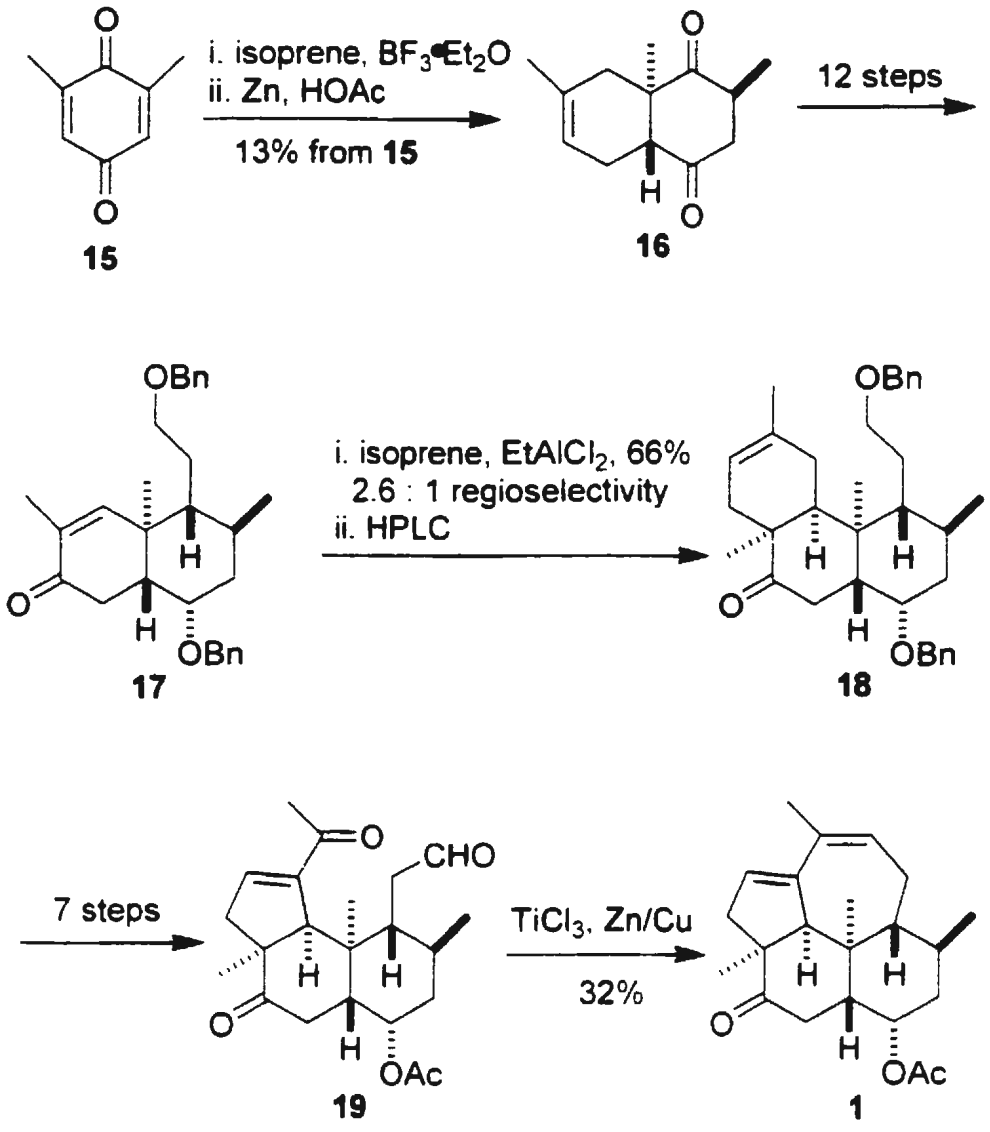
Scheme 3: Kato's biomimetic synthesis of secotrinervitene **10**



Based on biogenetic considerations, the natural product **10** was synthesized from acetyl epoxy-dehydromukulol **13**, which had been prepared in their laboratory from *trans*-dehydromukulol **11**,[15] by treatment with boron trifluoride etherate and lithium aluminum hydride From a biosynthetic point of view, it is of interest to note that all the natural products possessing the secotrinervitane and trinervitane skeletons have the *trans* orientation with respect to the C-1 and C-4 positions.

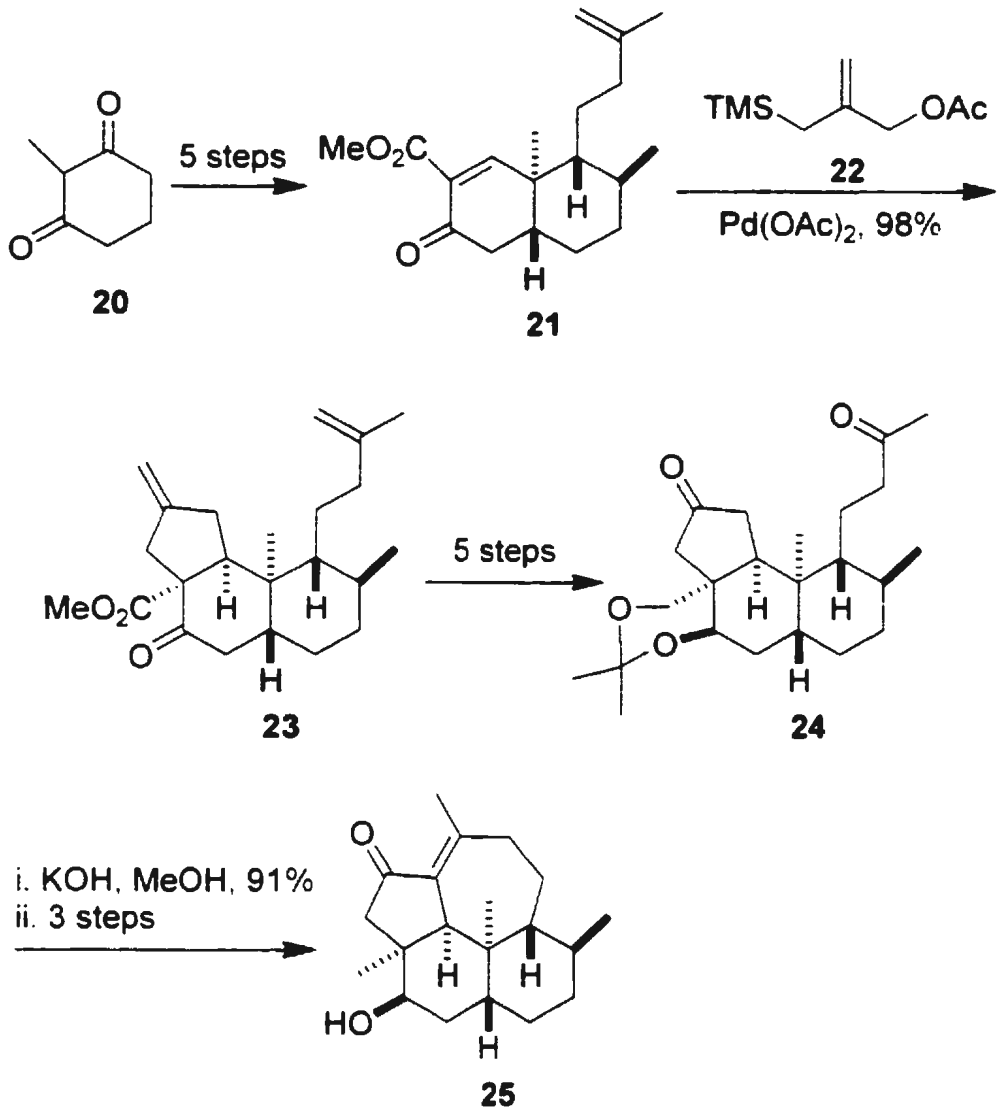
In 1991, Dauben's group reported the first total synthesis of the kempene diterpene **1** (Scheme 4).[16] In their synthetic scheme, the *trans*-decalin derivative of **16** was constructed by a Lewis acid-catalyzed Diels-Alder reaction of 2,6-dimethylbenzoquinone (**15**) with isoprene, followed by a zinc reduction of the Diels-Alder adduct in acetic acid, and a simultaneous epimerization of the product. The five-membered ring was stereoselectively constructed by a second Lewis acid-catalyzed Diels-Alder reaction of **17** with isoprene and subsequent operation on the resulting cyclohexene ring. The final seven-membered ring was cyclized from **19** to kempene-2 (**1**) by a McMurry coupling. A weakness in this strategy is the use of isoprene twice as a Diels-Alder diene. Diels-Alder reactions with isoprene as the diene usually give poor regioselectivity. The poor regioselectivity must contribute to the low yield (only 13%) in the first two steps. In addition, the regioselectivity in the second Diels-Alder reaction with isoprene was only 2.6 : 1 in favor of the desired regioisomer, and the two regioisomers had to be separated by HPLC, which was also inefficient, especially as this step was only the middle of the synthetic route.

Scheme 4. Dauben's synthesis of kempene-2 (**1**)



Paquette's group reported an approach towards kempenone **2** (Scheme 5).[17] A key feature in their approach is that they used a palladium-promoted [3+2] cycloaddition of the activated enone **21**, which was derived from 2-methyl-1,3-

Scheme 5. Paquette's approach to kempenone **2**

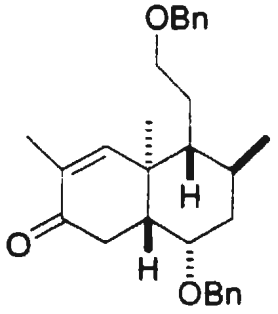


cyclohexanedione (**20**), with (2-acetoxymethyl)allyltrimethylsilane (**22**) to construct the five-membered ring. The last, seven-membered ring cyclization was achieved with a base-induced intramolecular aldol condensation of dione **24**. Unfortunately, the conjugated double bond in the final product **25** could not be

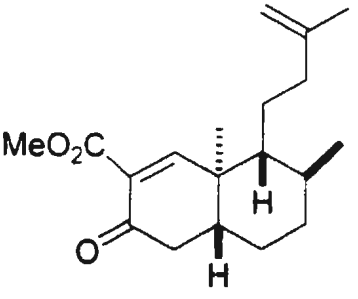
deconjugated to make the natural product **2**. This synthesis ended with several other regioisomers and stereoisomers of the naturally occurring kempane diterpene. Semi-empirical calculations showed that **25** is more stable than **2** by 1.6 kcal/mol.[18]

Both Dauben's synthesis of kempene-2 (**1**) and Paquette's approach toward kempenone **2** began with the construction of a *trans*-decalin ring system, and proceeded through very similar intermediates, **17** and **21** (Figure 4). Both of the syntheses then took advantage of cycloaddition reactions to install a third ring. The angular methyl groups in the *trans*-decalin systems made the cycloadditions occur from the side opposite the methyls to provide the desired relative stereochemistry.

Figure 4. Similar intermediates in Dauben's and Paquette's syntheses



17

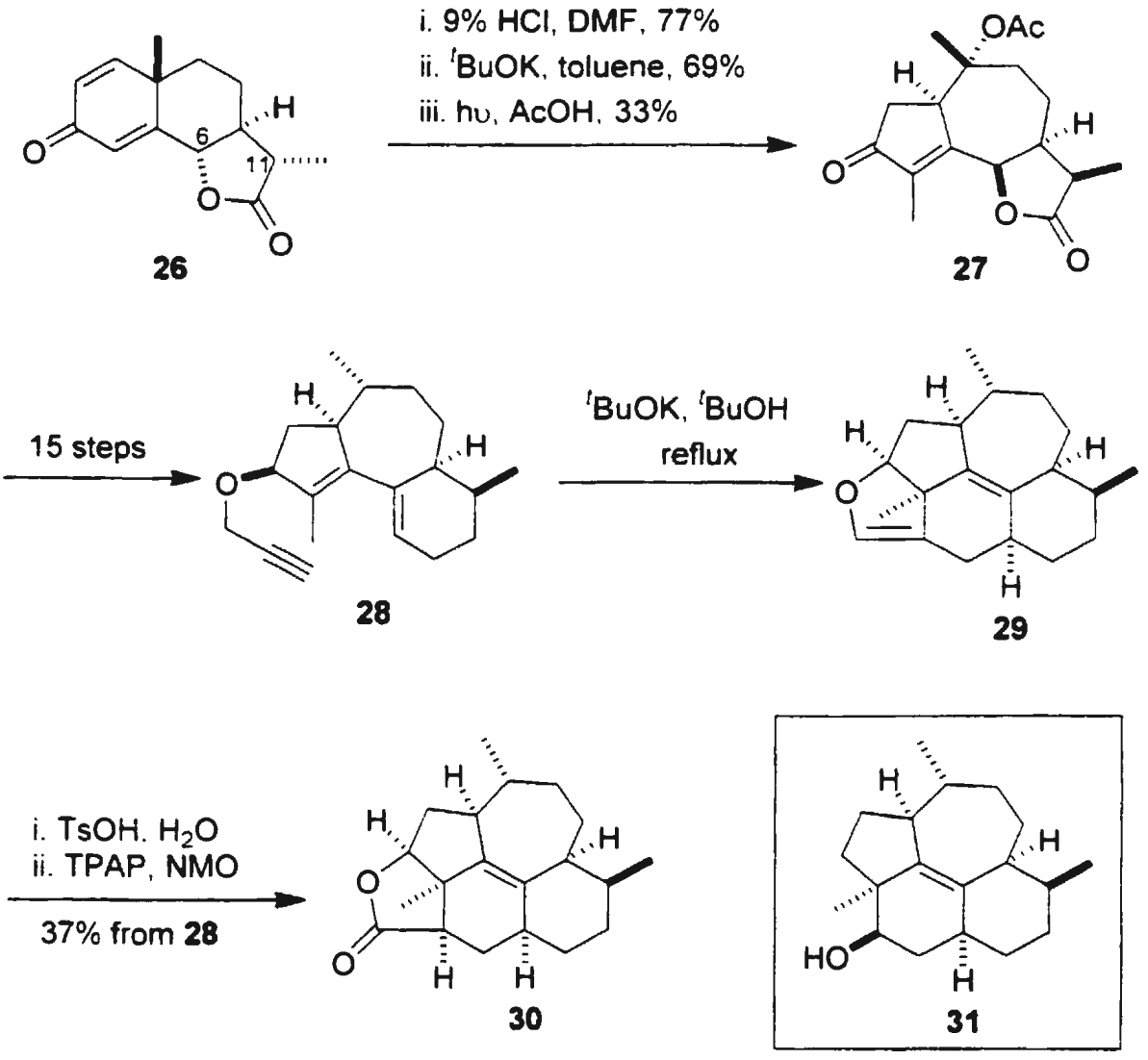


21

In 1993, Metz *et al.*[19] reported an enantioselective approach to the ring system of 3α-hydroxy-15-rippertene (**31**) (Scheme 6). This approach started from

the commercially available, enantiomerically pure eudesmanolide, (-)-α-santonin (**26**). After consecutive epimerizations at C-6 and C-11, effected by 9% HCl and

Scheme 6. Metz's synthesis of the rippertene ring system

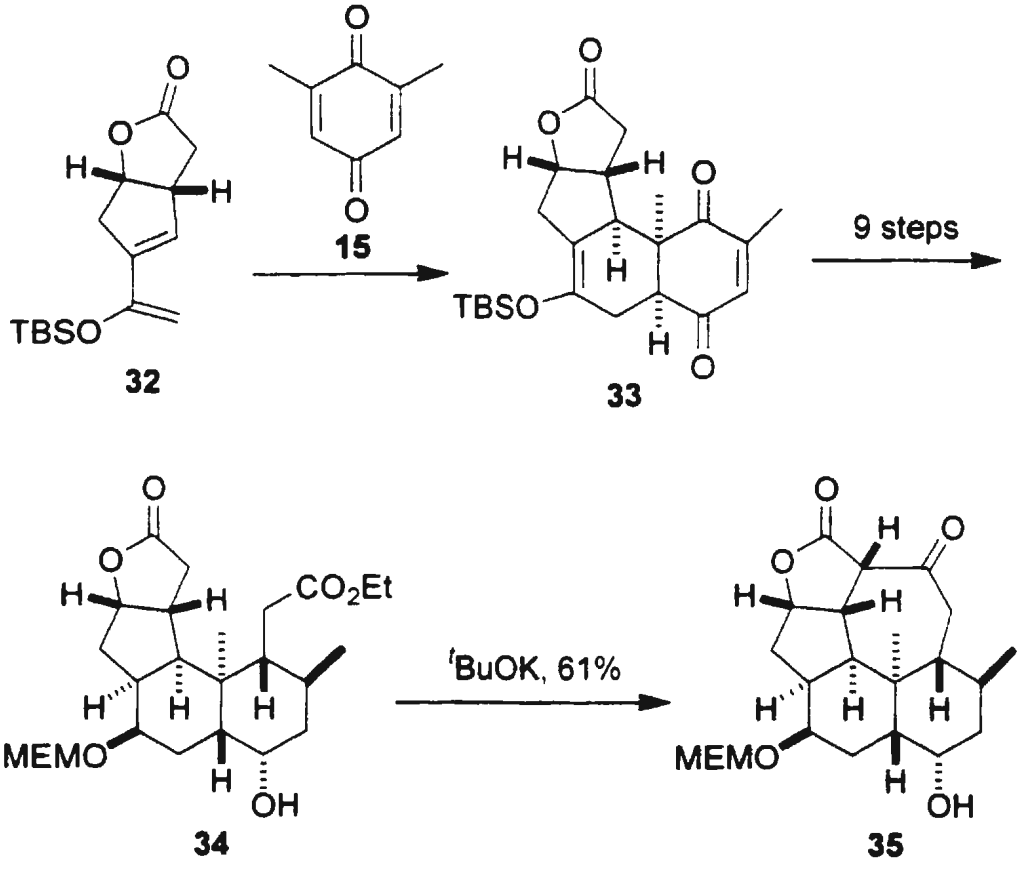


t-BuOK, respectively, **26** was converted into a hydrazulene **27** by photoisomerization.[20] The intramolecular Diels-Alder reaction to give **29** was effected by treatment of propargyl ether **28** with *t*-BuOK to generate the

corresponding allenyl ether as a dienophile. This was the key step to construct the tetracyclic ring system of rippertene. It seems that the ring system in this synthesis was not easily modified into the natural product **31**, because the total synthesis of rippertene **31** has still not been reported.

Intrigued by the compact carbon skeleton and the large number of stereogenic centers of kempane diterpenoids, our group developed a stereoselective approach to kempane ring system **35** in 1997 (Scheme 7).[22]

Scheme 7. Burnell's approach to the kempane ring system



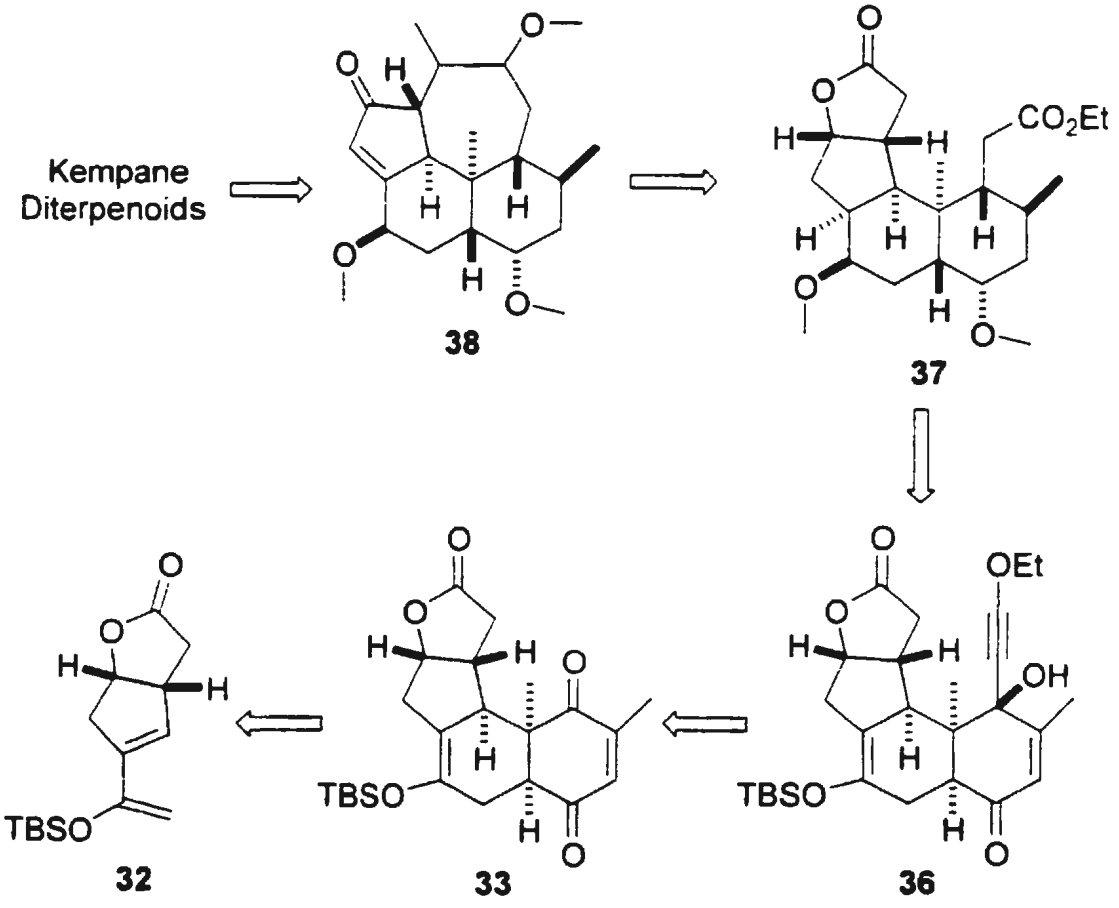
This strategy made use of a Diels-Alder reaction to construct a *cis*-decalin ring system in which three key stereogenic centers were all correct. The final seven-membered ring cyclization was realized by an intramolecular Dieckmann condensation. Compound **35** possessed all the required stereogenic centers for the kempane ring system and seemed to carry enough functionality in order to be converted to the natural products. This was the starting point for the original research described in Part I of this thesis.

1.2. First Route

1.2.1. Synthetic Analysis

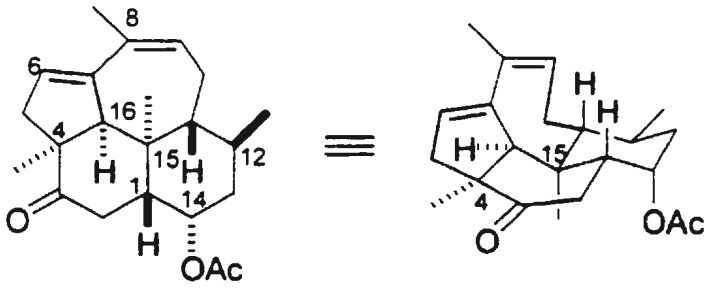
Our original strategy, which was evaluated and which will be referred to as the First Route, was based on Dr. Chunjian Liu's studies[22] in our group. The retrosynthetic analysis of the First Route is outlined in Scheme 8.

Scheme 8. Retrosynthetic analysis of the First Route



After a careful examination of the structures of these bowl-shaped diterpene systems, we realized that the concave conformational bias inherent to

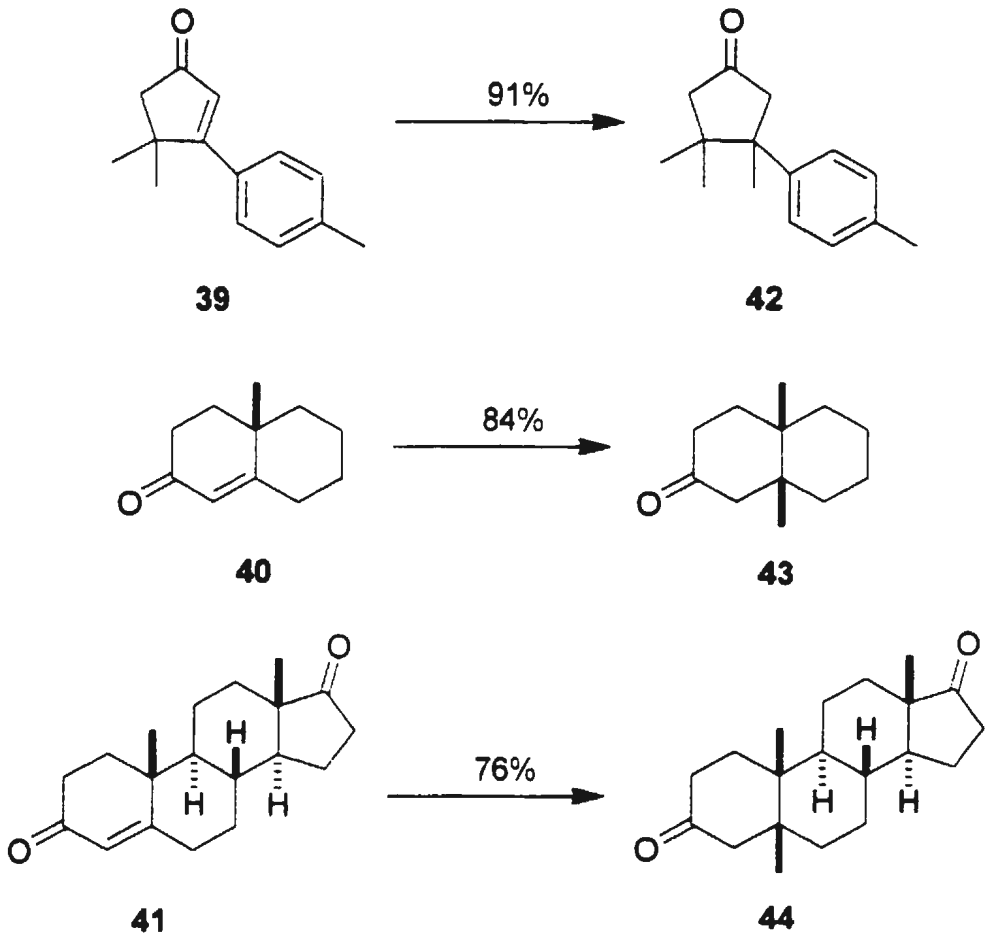
these molecules could prohibit their chemical interconversion. From a retro-synthetic perspective, it was expected that 1,4-addition to the α,β-unsaturated ketone **38** could install the last methyl group. We noticed in advance that the two methyl groups at C-4 and C-15 of **1** are not in a 1,3-diaxial relationship, even though they are on the same side of the molecule. Because of the concave shape of the molecules, the last methyl at C-4 should therefore be



1

introduced from the convex side, in the correct stereochemical manner. It was also noticed that the Michael acceptor **38** might be too congested, which could result in difficulty with the 1,4-addition. However, Fleming *et al.*[23] developed an efficient procedure that allowed 1,4-addition of a methyl group to very sterically hindered α,β-unsaturated ketones. The use of this procedure which employed trimethylaluminum as a Michael donor and nickel(II) acetylacetonate [$Ni(acac)_2$] as a catalyst, allowed the 1,4-addition to the sterically hindered α,β-unsaturated ketones **39**, **40** and **41** to occur very smoothly and efficiently to give **42**, **43** and **44** (Scheme 9).

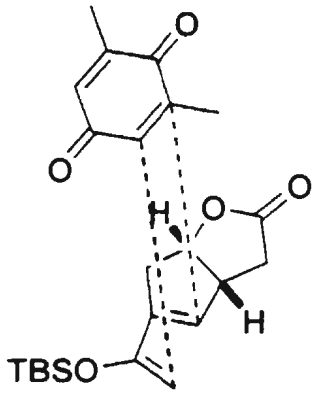
Scheme 9. $Ni(acac)_2$-catalyzed Michael additions of $AlMe_3$ to hindered enones



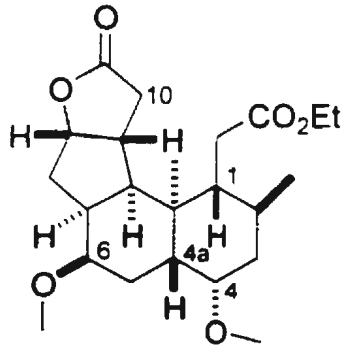
From a synthetic point of view, we can take advantage of a Diels-Alder reaction to construct the *cis*-decalin ring system. The Diels-Alder reaction of diene **32** with 2,6-dimethyl-1,4-benzoquinone (**15**) would construct the benzoindane ring system **33** with three correct stereogenic centers. It was believed that this Diels-Alder reaction would proceed in an *endo*-, regio- and

facially selective manner, as shown in Figure 5, to produce the desired adduct as the major product.

Figure 5. An *endo*-, regio- and facially selective Diels-Alder reaction



The final seven-membered ring was expected to be formed by an intramolecular Dieckmann condensation between the C-10 and the ester carbonyl in compound **37**.

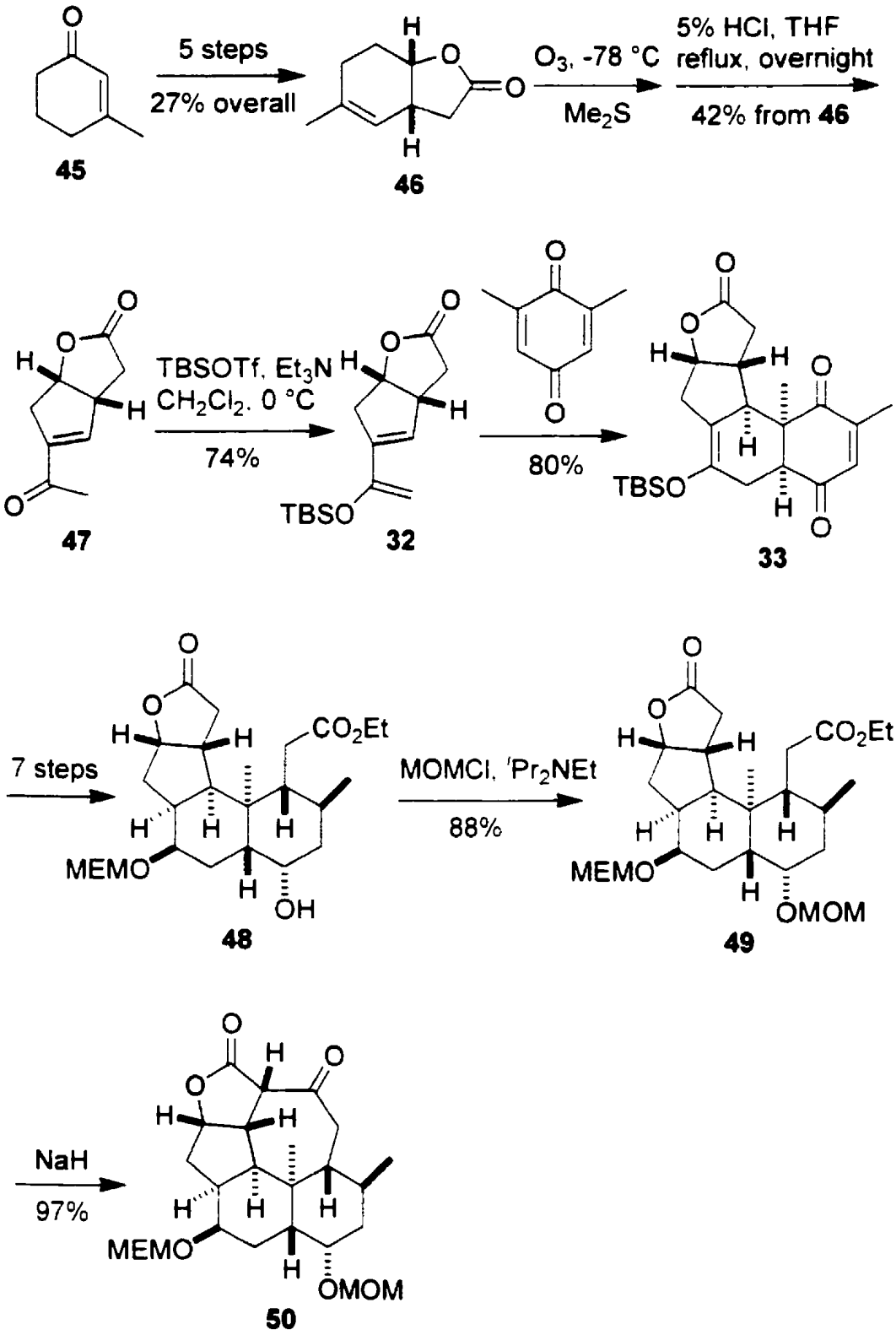


37

1.2.2. Synthesis of the Kempene Diterpene Ring System

The synthetic route to the kempene diterpene ring system was similar to that used in Dr. Liu's research (Scheme 10). It should be mentioned that simply increasing the reflux time from 3.5 hours to overnight increased the yield of enone **47** from 23% to 42%. Another significant improvement in this synthesis was the seven-membered ring cyclization step. After protection of the hydroxyl group in **48** as the MOM ether, the final cyclization was achieved by intramolecular Dieckmann condensation with NaH in 97% yield, instead of the 61% yield with an unprotected hydroxyl group. When KO^tBu/C_6H_6 was used to cyclize the seven-membered ring, a cyclization product, **50** was obtained in 68% yield.

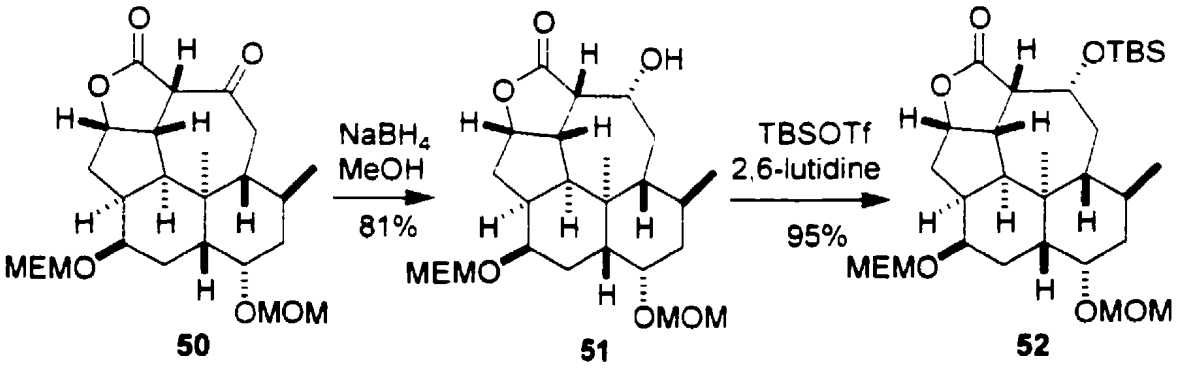
Scheme 10. Synthesis of kempane ring system in the First Route



1.2.3. Attempts to Reduce the Ketone in the Seven-Membered Ring

After the cyclized product **50** was obtained, what we intended to do was to reduce the carbonyl group in the newly-created seven-membered ring and then to protect the resulting hydroxyl group. At first, we attempted to reduce the ketone **50** with $LiAl(O^tBu)_3H$, but we failed to obtain the expected product. When **50** was stirred with L-Selectride, only the starting material was returned. The reason why we chose $LiAl(O^tBu)_3H$ and L-Selectride as reducing reagents was that we hoped the large groups on these reagents might help to stereoselectively reduce the ketone. We thought the difficulty in reducing this ketone might be due to the enolization, but an attempt to trap the enol form of this ketone as a TBS enol ether failed. Finally, we decided to use $NaBH_4$ to reduce the ketone **50**, and the reduction proceeded with high stereoselectivity to give compound **51** in 81% yield (Scheme 11).

Scheme 11. Reduction of the ketone of **50** and protection of the hydroxyl



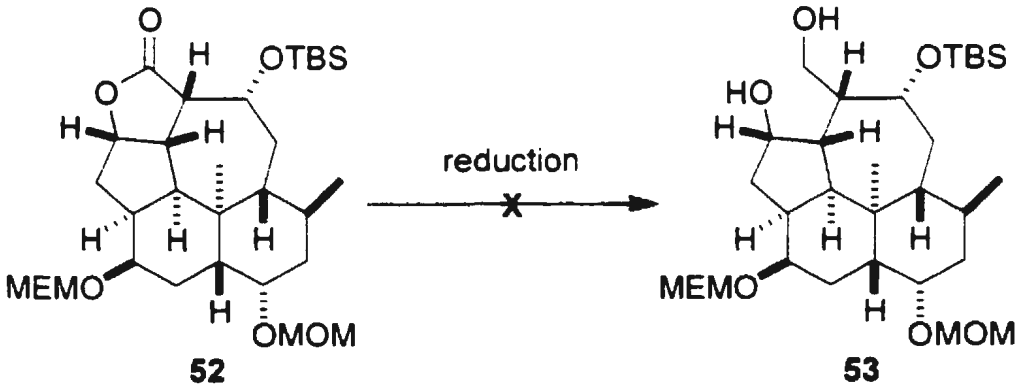
After reduction of the ketone, the resulting hydroxyl group was protected with TBSOTf and 2,6-lutidine in dichloromethane to give the expected product **52** in excellent yield.

1.2.4. Attempts to Open the Five-Membered Lactone

Now we were at the stage to open the five-membered lactone. It was anticipated that reduction of the lactone could provide us with a hydroxymethyl group, which would ultimately be reduced to afford the methyl group on the seven-membered ring, and a secondary alcohol, which would be oxidized to a ketone on the five-membered ring.

We tried many reducing reagents under various conditions, but none of them gave the expected product, diol **53** (Scheme 12). Most reductions ended

Scheme 12. Attempts to reduce the five-membered lactone

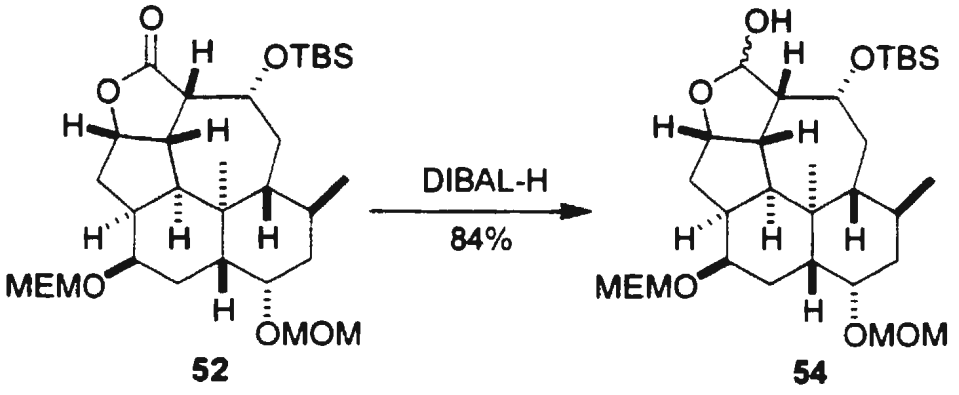


52 **53**

Reducing reagent: $LiAlH_4$, DIBAL-H, Red-Al, B_2H_6, Superhydride, Li/Et_2NH.

with a partially reduced product, identified as hemi-acetal **54**. The highest yield in this partial reduction was achieved with DIBAL (Scheme 13).

Scheme 13. Reduction of lactone **52** with DIBAL-H

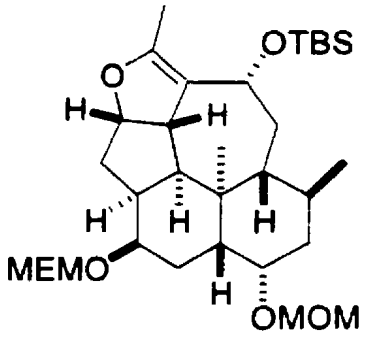


It is known that a hemi-acetal can react with a Wittig reagent to introduce a C=C bond.[24] However, when hemi-acetal **54** was treated with $Ph_3P=CH_2$, no reaction took place. Paquette's group[25] found that 1,2-ethanedithiol and titanium(IV) chloride reacted with hemi-acetals to produce dithiolane-protected aldehydes. However, when **54** was subjected to those reaction conditions, we obtained a complex mixture. The ^1H NMR spectrum showed that the TBS group was lost, but the hemi-acetal ring remained unchanged (Table 1).

Table 1. Attempts to transform hemi-acetal **54**

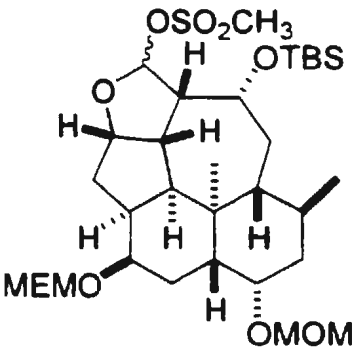
Substrate	Reagents and condition	Product
54	$Ph_3P=CH_2$, THF, -10 °C to rt	starting material
54	1,2-ethanedithiol, $TiCl_4$, CH_2Cl_2, -78 °C to rt	complex mixture with loss of TBS group
54	MsCl, Et_3N, CH_2Cl_2, -30 °C to rt; $EtN(i\text{-}Pr)_2$, CH_3CN, reflux	**56**
54	MsCl, Et_3N, CH_2Cl_2, rt; $EtN(i\text{-}Pr)_2$, toluene, reflux	**56**
54	MsCl, Et_3N, CH_2Cl_2, rt; Superhydride/THF 0 °C to rt to reflux	**56**
54	MsCl, Et_3N, CH_2Cl_2, rt; *t*-BuOK/*t*-BuOH	**56**
54	MsCl, Et_3N, CH_2Cl_2, rt; DABCO, toluene, reflux	**56**

We also used methyllithium to react with lactone **52** and obtained the methylated dihydrofuran compound **55**.



55

Even though compound **55** showed some promise that we might open the five-membered ring in a circuitous fashion, since the carbon-carbon double bond in this compound might be cleaved by ozonolysis, the low yield of the alkylation reaction made us curtail further studies with methyllithium. We thought we could make use of hemi-acetal **54** to introduce a carbon-carbon double bond in the five-membered ring by an elimination reaction, followed by cleavage of the double bond *exo* to the seven-membered ring to open the five-membered lactone. The hemi-acetal **54** reacted with mesyl chloride and triethylamine in dichloromethane to give the expected product **56**. However, numerous efforts, as shown in Table 1, to introduce a double bond in the five-membered ring by elimination failed.



56

Similarly, attempts at base-induced solvolysis (KOH/MeOH, or Et_2NH) of the lactone also failed to yield a desired reaction. Ultimately, our inability to open the five-membered lactone became a dead end for our First Route.

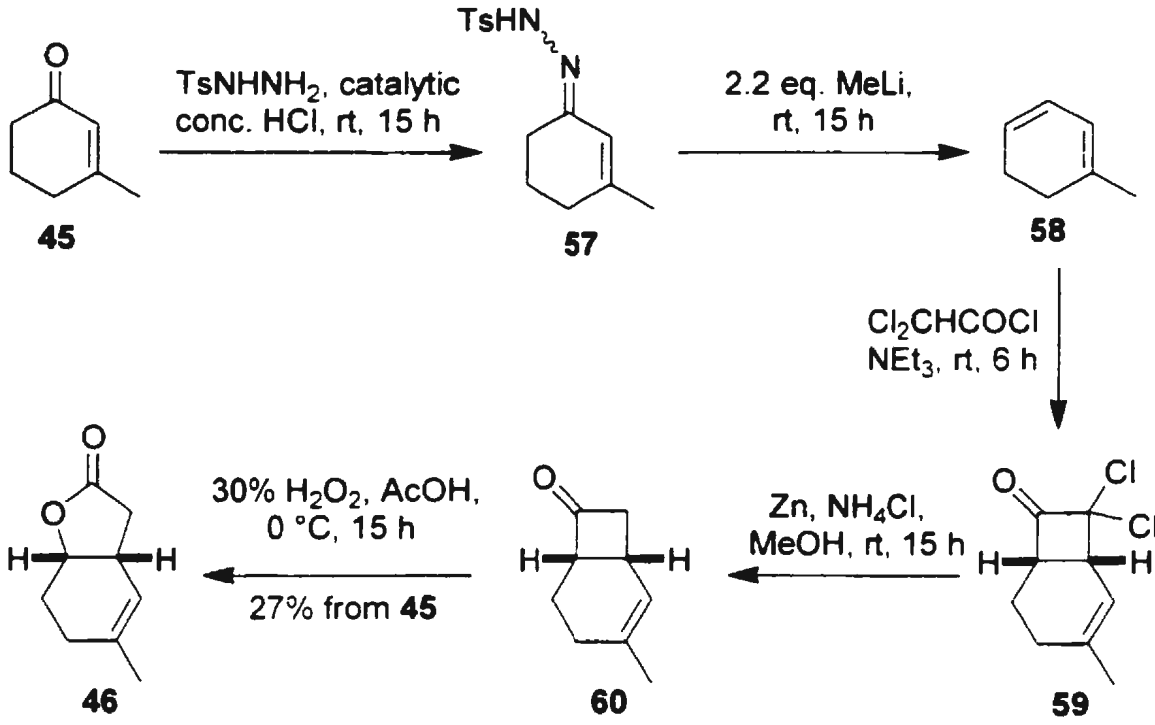
1.3. Diether Route

From the First Route, we knew that it is very difficult to open the five-membered lactone in an advanced intermediate. This difficulty forced us to consider other strategies for the total synthesis. It is known[26] that a simple five-membered lactone can be easily reduced to produce a diol. What would be the result if we reduced the lactone at the very beginning? This idea resulted in our Diether Route, which is described below.

1.3.1. Synthesis of the Diels-Alder Diene

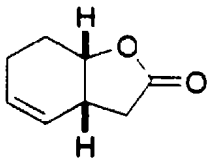
Just as in the First Route, the Diether Route started from commercially available 3-methyl-2-cyclohexen-1-one (**45**) (Scheme 14). The transformation of **45** to **58** by the Shapiro reaction is a well-known process. A 1:1 mixture of **45** and *para*-toluenesulfonyl hydrazide was stirred at room temperature in the presence of catalytic amount of concentrated hydrochloric acid to produce a mixture of the *syn* and *anti* hydrazones **57** in a ratio of 2:1. The hydrazone mixture was then treated with 2.2 equivalents of methyllithium at room temperature overnight to generate 1-methyl-1,3-cyclohexadiene (**58**). Because **58** is easily polymerized during distillation, the crude product of the Shapiro reaction was used directly in the next step. The solution of crude **58** was treated with dichloroketene, which was generated *in situ* from the reaction of dichloroacetyl chloride and triethylamine. The ketene thus generated underwent a highly regioselective [2+2] addition to the less substituted double bond of diene **58** to produce the bicyclic adduct **59**.

Scheme 14. Synthesis of lactone **46** from **45**



Dechlorination of **59** was achieved by zinc reduction[27] in methanol with ammonium chloride at room temperature over fifteen hours to afford cyclobutanone **60**. A regio- and stereoselective Baeyer-Villiger oxidation of cyclobutanone **60** with aqueous 30% hydrogen peroxide in glacial acetic acid at 0 °C afforded lactone **46**. From **45** to **46**, the overall yield over five steps was 27%, with no chromatographic separations being required.

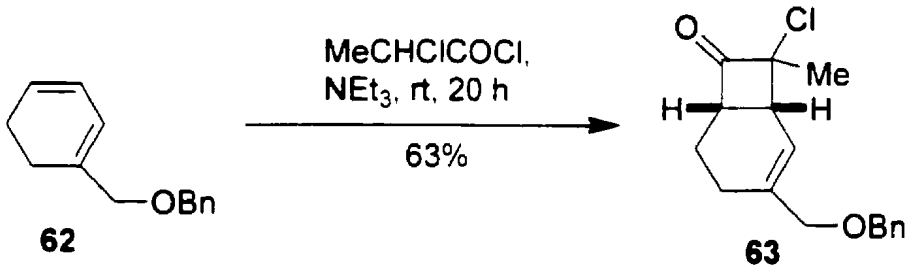
The synthetic process shown in Scheme 14 was similar to the transformation of Corey's lactone **61** from 1,3-cyclohexadiene,[28] but in our case the diene



61

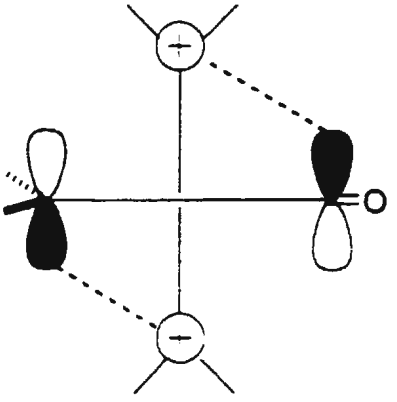
58 was unsymmetrical and the ketene addition took place at the less substituted double bond. Similar regioselectivity has been shown in the synthesis of sirenin (Scheme 15).[29]

Scheme 15. An example of regioselective ketene cycloaddition



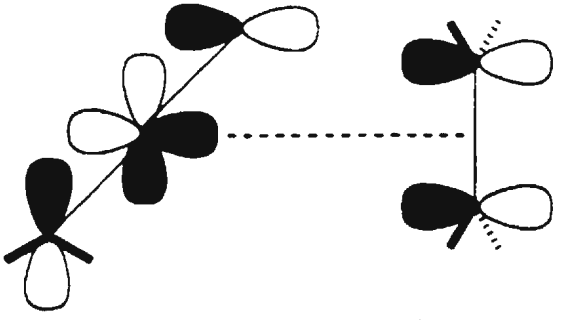
Regioselectivity in the ketene addition can be interpreted by steric and electronic interactions between the ketene and the diene. According to the principle of orbital symmetry, the reaction can be formulated as a ($\pi 2_s + \pi 2_a$) process, that is, one of the π orbitals is suprafacial and the other is antarafacial. The frontier orbital interaction between the HOMO of the alkene and the LUMO of the ethylenic portion of the ketene requires an orthogonal approach of the two reacting double bonds, as shown in Figure 6.[30]

Figure 6. Frontier orbital interaction in ketene addition



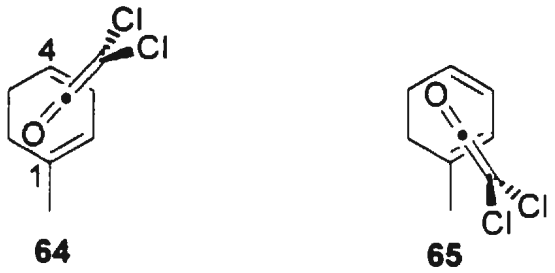
Self-Consistent Perturbation theory proposes that the stabilization through the interaction of the ketenophile π system with the carbonyl π bond is responsible for the orthogonal ($\pi 2_s + \pi 2_a$) approach of the two reactants and the addition at the carbon-carbon double bond rather than a reaction at the carbonyl group of ketene[31] (Figure 7).

Figure 7. Interaction of ketenophile π system with the carbonyl π bond



In our unsymmetrical case, there are two chemically distinct modes of addition for the "orthogonal" approach (Figure 8).

Figure 8. Two modes of ketene cycloaddition of **58**

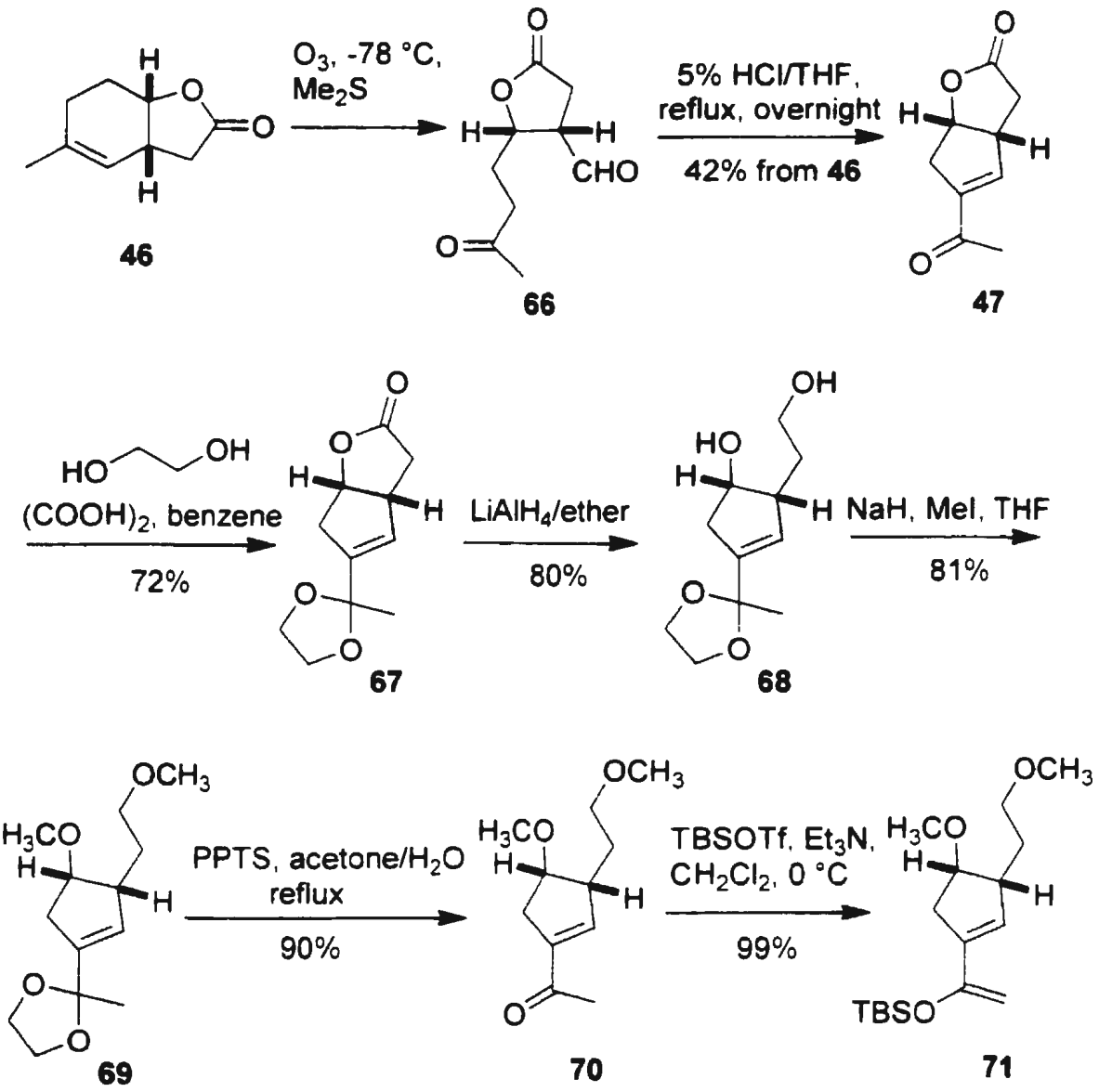


64 **65**

Due to a significant repulsion between the methyl group on the ketenophile and a chlorine atom on the ketene, obviously mode **65** is disfavored by steric hindrance. Electronic interactions also should make mode **64** more favorable. In the HOMO of the diene, the largest coefficient is at C-4 because of the electron-releasing methyl group at C-1 of the diene. On the other hand, the largest coefficient in the LUMO of the ketene is at C-1. The interactions between the centers having the largest coefficients make the strongest orbital interaction.

The preparation of the Diels-Alder diene from lactone **46** in the Diether Route is summarized in Scheme 16. The double bond in **46** was cleaved by ozonolysis[32] at –78 °C, followed by reductive work-up with dimethyl sulfide to form keto-aldehyde **66**, which was unstable during column chromatography. Therefore, without isolation, the crude reaction mixture was treated with 5% hydrochloric acid in THF under reflux to produce enone **47**, although the yield for

Scheme 16. Synthesis of diene **71** from **46**



this ozonolysis-aldol condensation step was usually low. For example, when the reaction mixture was heated with 5% hydrochloric acid for 3.5 hours, the yield was only 23%.[33] When the reflux time was lengthened to overnight. the yield for

this step reaction was significantly improved to 42%. An attempt to carry out the aldol condensation under basic conditions (KOH/methanol or Et_3N/MsCl) gave a very complex mixture, as shown by TLC. The protection of the enone carbonyl by ethylene glycol was catalyzed by oxalic acid without migration of the double bond. The expected enone acetal **67** was obtained in 72% yield.

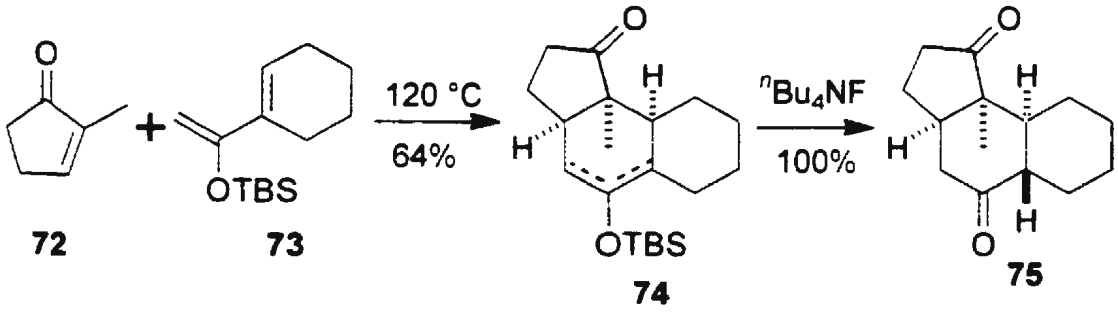
Now we had reached the stage to reduce the five-membered lactone. The lactone in **67** was reduced by lithium aluminum hydride in ether very smoothly to yield the corresponding diol **68**. Then the diol **68** was treated with sodium hydride and iodomethane in THF to produce the methyl ether **69**. When we had considered the protection of this diol, we had decided that the protective groups would have to be very stable because they were expected to survive until a late stage of the synthesis. The methyl ether is normally stable under both acidic and basic conditions (pH range 1-14).[34] After protection of the diol **68**, the acetal in **69** was removed with pyridinium *p*-tosylate (PPTS) in wet acetone[35] under reflux to produce the enone **70**, which still contained the two methyl ether side chains, in 90% yield. This enone acetal could also be cleaved by copper(II) chloride[36] in acetonitrile to give enone **70**, but in lower yield. The TBS-enol ether diene **71** was synthesized in very high yield by treating enone **70** with TBSOTf and triethylamine in dichloromethane at 0 °C.

1.3.2. Diels-Alder Reaction in the Diether Route

It is well known that TBS-enol ether dienes are excellent dienes for Diels-Alder reactions. Ireland *et al.*[37] showed that the reaction of 2-methylcyclo-

pentenone (**72**) and a TBS-enol ether cyclohexene (**73**) gave almost exclusively the *cis-syn* adduct, in keeping with the general preference for *endo* orientation in the Diels-Alder reaction (Scheme 17).

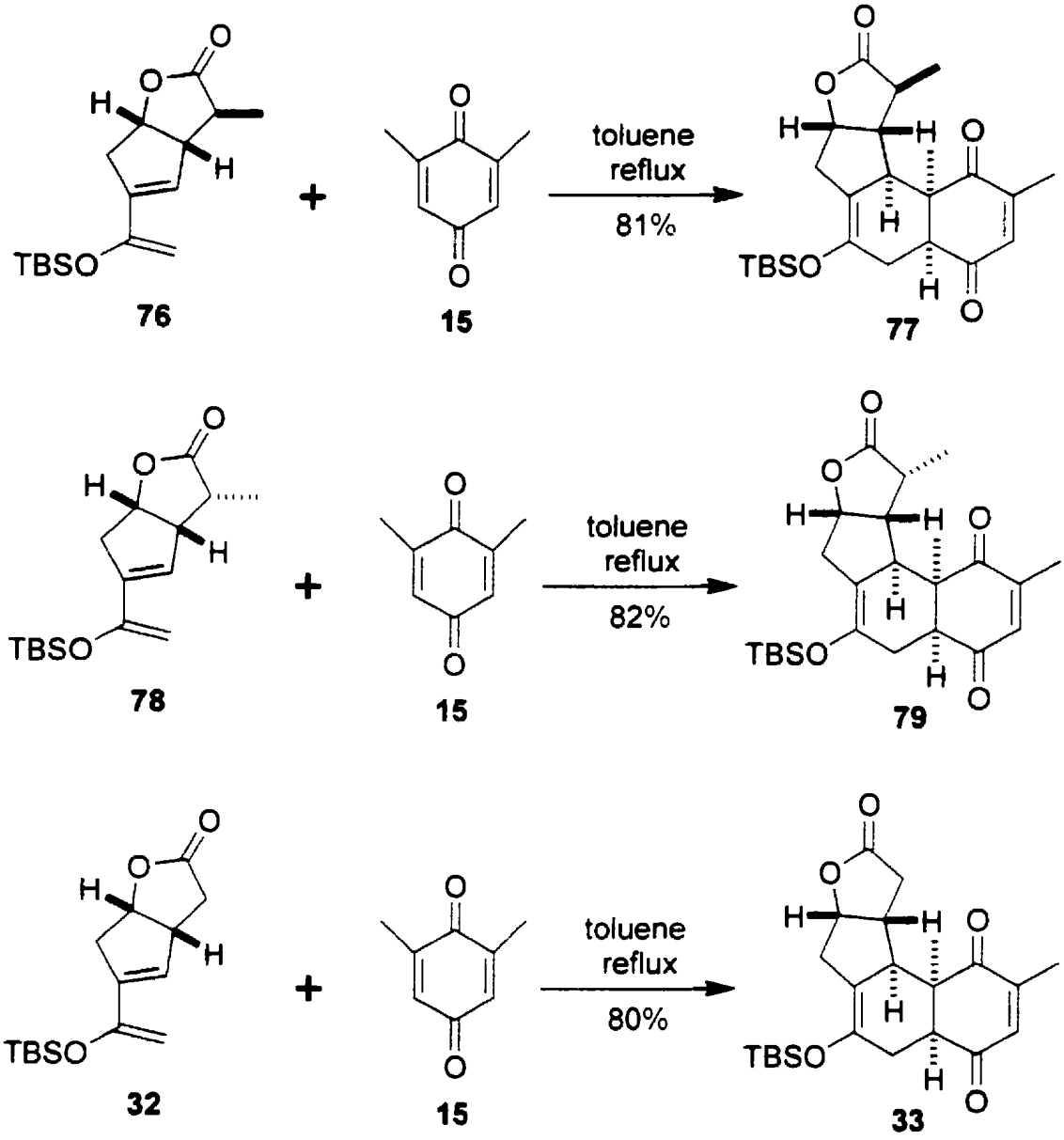
Scheme 17. An example of a Diels-Alder reaction with a TBS-enolate diene[37]



72 **73** **74** **75**

Studies on the Diels-Alder reaction of TBS-enolate diene with 2,6-dimethyl-benzoquinone (**15**) showed highly regio-, *endo*- and facial selectivity[38] (Scheme 18).

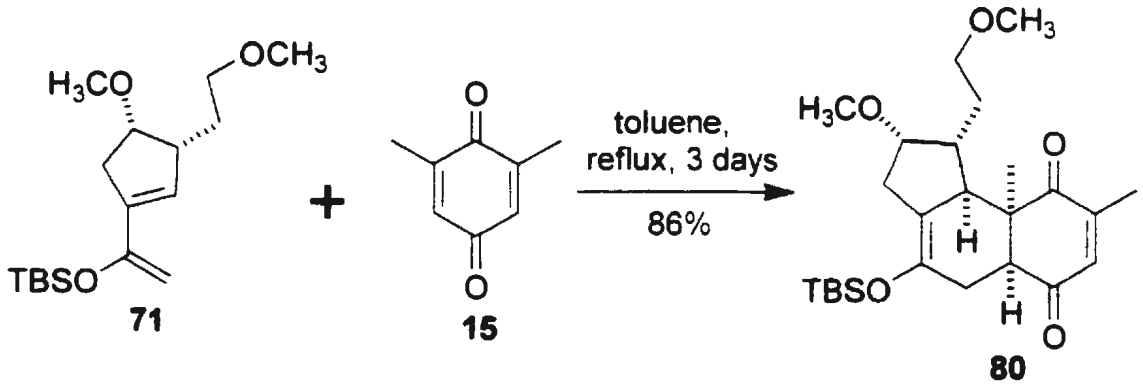
Scheme 18. Diels-Alder reactions of TBS-enolate dienes with **15**



With diene **71** in hand, its Diels-Alder cycloaddition with 2,6-dimethyl-1,4-benzoquinone (**15**) was performed in toluene under reflux for 3 days to produce the adduct enedione **80** in 86% yield. As expected, this Diels-Alder reaction

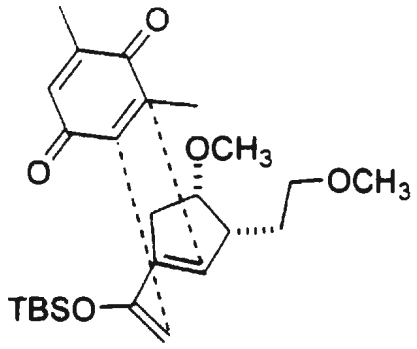
proceeded in a highly selective manner (Scheme 19), and **80** was isolated as a single isomer.

Scheme 19. Diels-Alder reaction of **71** in the Diether Route



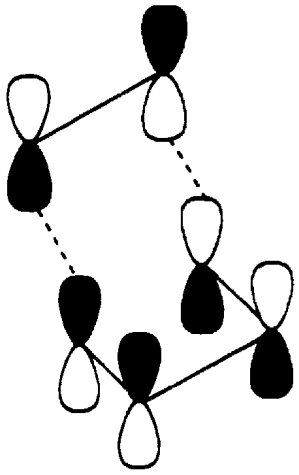
The highly regio-, *endo*- and facial selectivity in the Diels-Alder reaction of TBS-enolate diene **71** with 2,6-dimethylbenzoquinone (**15**) can be rationalized as follows, as shown in Figure 9.

Figure 9. An *endo*-, regio- and facially selective Diels-Alder reaction



The Diels-Alder reaction is a [$\pi 4_s + \pi 2_s$] cycloaddition. The diene and the dienophile approach each other in approximately parallel planes. The reaction involves the interaction of the LUMO of the dienophile with the HOMO of the diene (Figure 10).[39]

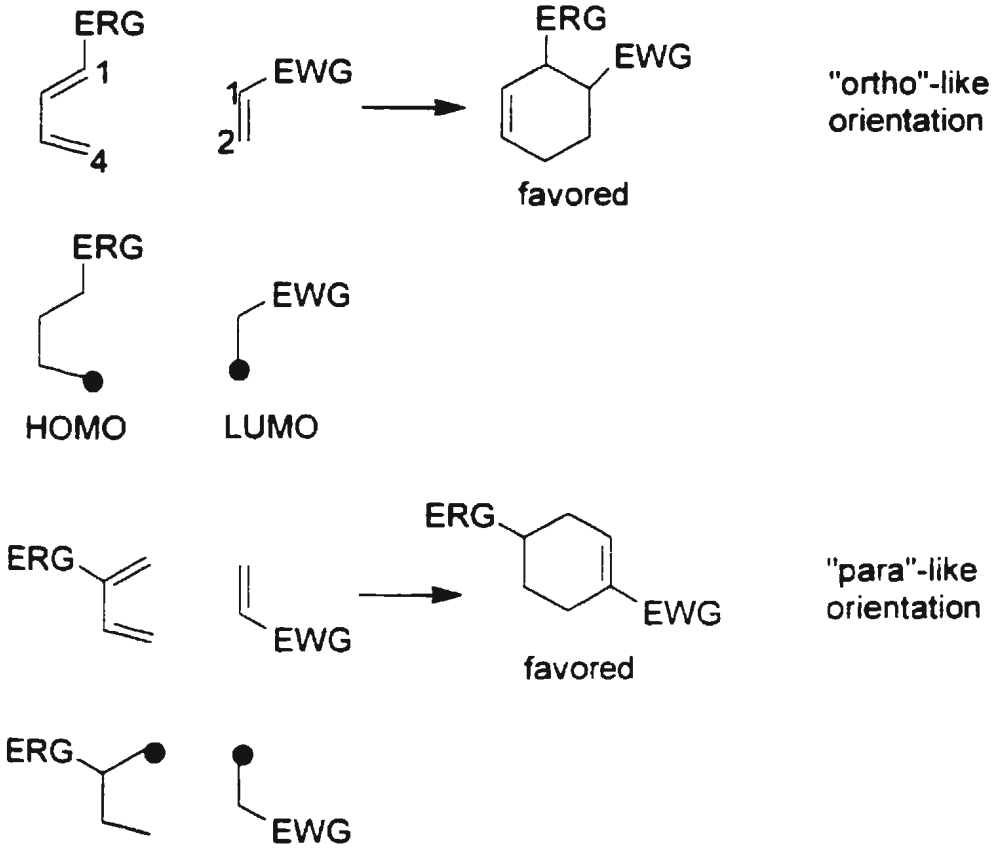
Figure 10. Interaction of LUMO of dienophile with HOMO of diene



In a Diels-Alder reaction, *endo* selectivity has been predicted classically by the "Alder Rule", which states that when an unsaturated substituent, such as one of the two carbonyl groups on **15**, is present on the dienophile, the *endo* transition state is favored over the *exo* transition state. That is, an unsaturated substituent on the dienophile is oriented toward π orbitals of the diene. According to Molecular Orbital Theory, a favorable secondary orbital interaction in the transition state between the π orbitals on the carbonyls and the developing double bond is responsible for *endo* selectivity.[39]

The regioselectivity of our Diels-Alder reaction can be understood in terms of the "*ortho-para*" rule.[39] When both the diene and dienophile are unsymmetrically substituted, it is generally predicted that the preferred product is the one in which the substituents have an *ortho* or a *para*-like relationship. Scheme 20 shows an interpretation for the regioselectivity of Diels-Alder

Scheme 20. Regioselectivity of the normal Diels-Alder reaction



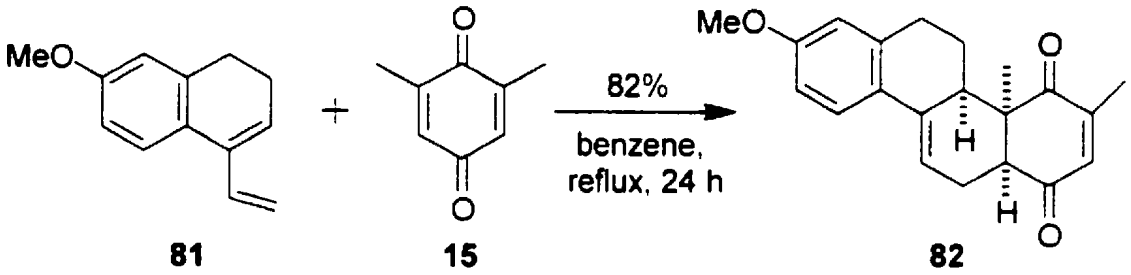
reactions. It is recognized that the strongest interaction between the HOMO of the diene and the LUMO of the dienophile is that given by matching carbon atoms having the largest coefficients in the frontier orbitals. For the first case in

Scheme 20, C-4 has the largest coefficient in the HOMO of the diene because of an electron-releasing group on C-1 of the diene. The LUMO of the dienophile has the largest coefficient at C-2 due to an electron-withdrawing group on C-1 of the dienophile. As a result, the "ortho" product will be produced because of a strong interaction between C-4 of the diene and C-2 of the dienophile. The "*para*" regioselectivity is similarly easily understood in terms of Frontier Molecular Orbital Theory.

When a diene bears more than one electron-releasing group at different positions, an electron-releasing group at C-1 will usually be dominant because of better conjugation with the π-system of the diene. On the other hand, when a dienophile contains EWG's at both ends of the reacting double bond, the stronger EWG will control the regioselectivity of the reaction. Of the three substituents on the part of diene **71**, the substituents at C-1 and C-3 both donate electron density into C-4 and this should provide a dominating effect creating the largest coefficient of HOMO of the diene at C-4. In the dienophile **15**, the electron-withdrawing ability of the carbonyl at C-4 is decreased by the electron-donating methyl groups at C-2 and C-6. Therefore, the regioselectivity in the Diels-Alder reaction should be dominated by the carbonyl at C-1, which has a strong electron-withdrawing ability. This analysis was confirmed by the Diels-Alder reaction in Scheme 19. The product in which the carbonyl at C-1 has the "*ortho*" relationship with the dominant substituent in the diene was obtained in

high yield. The regioselective Diels-Alder reaction in Scheme 21[40] also supported the above analysis.

Scheme 21. A literature example[40] of a regioselective Diels-Alder reaction with **15**



81 **15** **82**

The diene **81** reacted with the dienophile **15** in benzene under reflux to give the product **82** in good yield and with high selectivity.

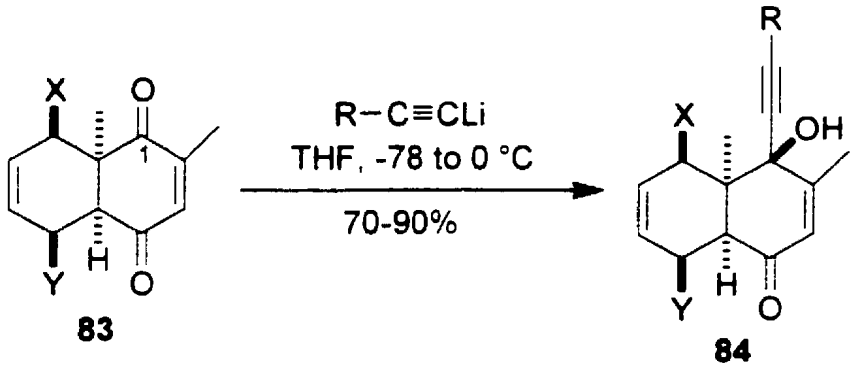
Diels-Alder cycloadditions are sensitive to steric effects.[39] The facial selectivity in our Diels-Alder reaction can be expected by consideration of steric interactions. It was anticipated that the two methyl ether side chains in diene **71** would make the dienophile approach the diene from the opposite side. This effect can also be seen in the Diels-Alder reaction in our First Route. In that case, it was the five-membered lactone in the diene that blocked one of the two faces of the diene.

1.3.3. Attemps to Cyclize the Seven-Membered Ring

After construction of the benzoindane ring system **80** with the Diels-Alder reaction, what was required was the introduction of a two-carbon side chain on right hand side of the molecule and then cyclization of the last seven-membered

ring. Liotta and co-workers[41] reported that additions of lithium acetylides to bicyclic enediones took place at the seemingly more sterically hindered carbonyl (C-1) with high regio- and stereoselectivity (Scheme 22).

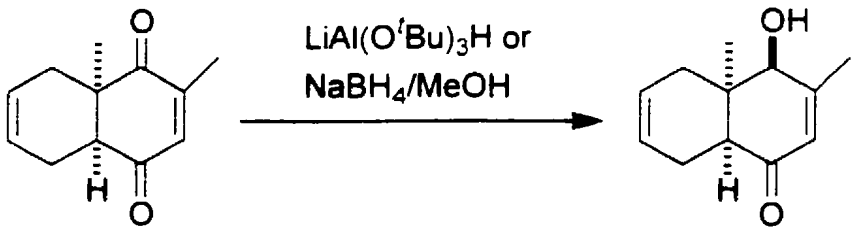
Scheme 22. An example of acetylide addition to bicyclic enedione **83**[41]



83 **84**

As shown in Scheme 22, the enedione **83** was treated with a number of different lithium acetylides to afford the carbinols **84** as the only isolated products in 70-90% yield. Our group[42] found that reduction of bicyclic enedione **85** with sodium borohydride or lithium tri-*tert*-butoxyaluminohydride also occurred at the C-1 carbonyl (Scheme 23).

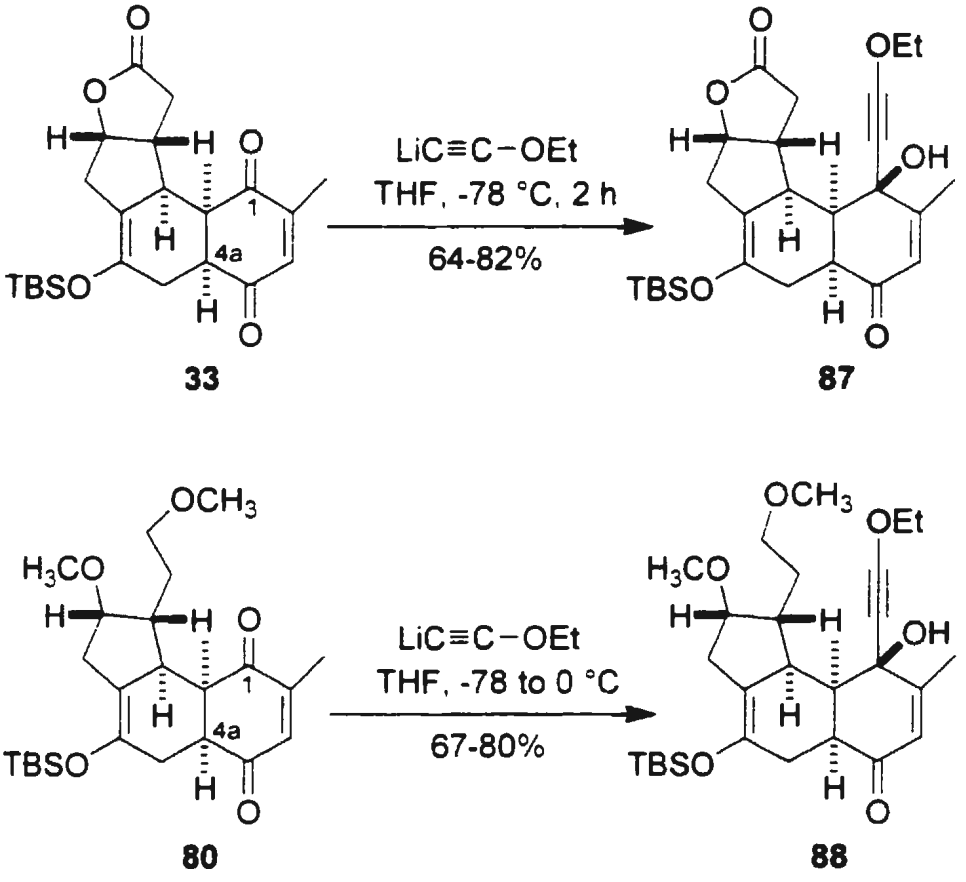
Scheme 23. Highly chemo- and stereoselective reduction of enedione **85**



85 **86**

The carbonyl at C-1 was reduced with nearly 100% chemo- and stereoselectivity. With this knowledge in mind, we anticipated the transformation from **80** to **88** in Scheme 24. In our First Route, the transformation of **33** to **87**

Scheme 24. Acetylide additions of enediones



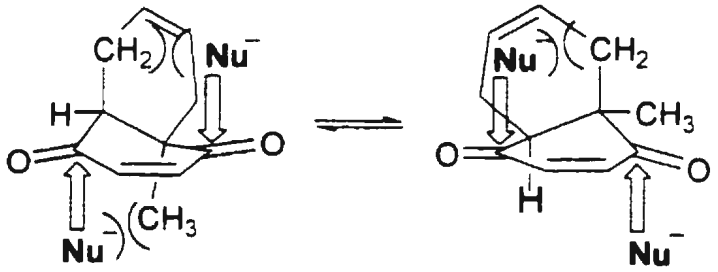
33 **87**

80 **88**

was achieved by acetylide addition in 64-82% yield with high selectivity.[22] When the Diels-Alder adduct **80** was treated with lithium ethoxyacetylide, prepared from ethyl ethynyl ether and *n*-butyllithium, the expected adduct was obtained in 67-80% yield. The nucleophilic addition was more sluggish than the one in the First

Route. Two equivalents of lithium acetylide had to be used and the reaction mixtures needed to be warmed to 0 °C. Double addition was not a problem, even though an excess of lithium ethoxyacetylide was used. This may correspond to the formation of an enolate at less sterically hindered carbonyl, because lithium ethoxyacetylide could also act as a base to deprotonate at C-4a. This explanation was confirmed by the recovery of some unreacted starting materials. The chemo- and stereoselectivity of the acetylide addition step is rationalized in Scheme 25.

Scheme 25. Axial attack on the cyclohexenedione

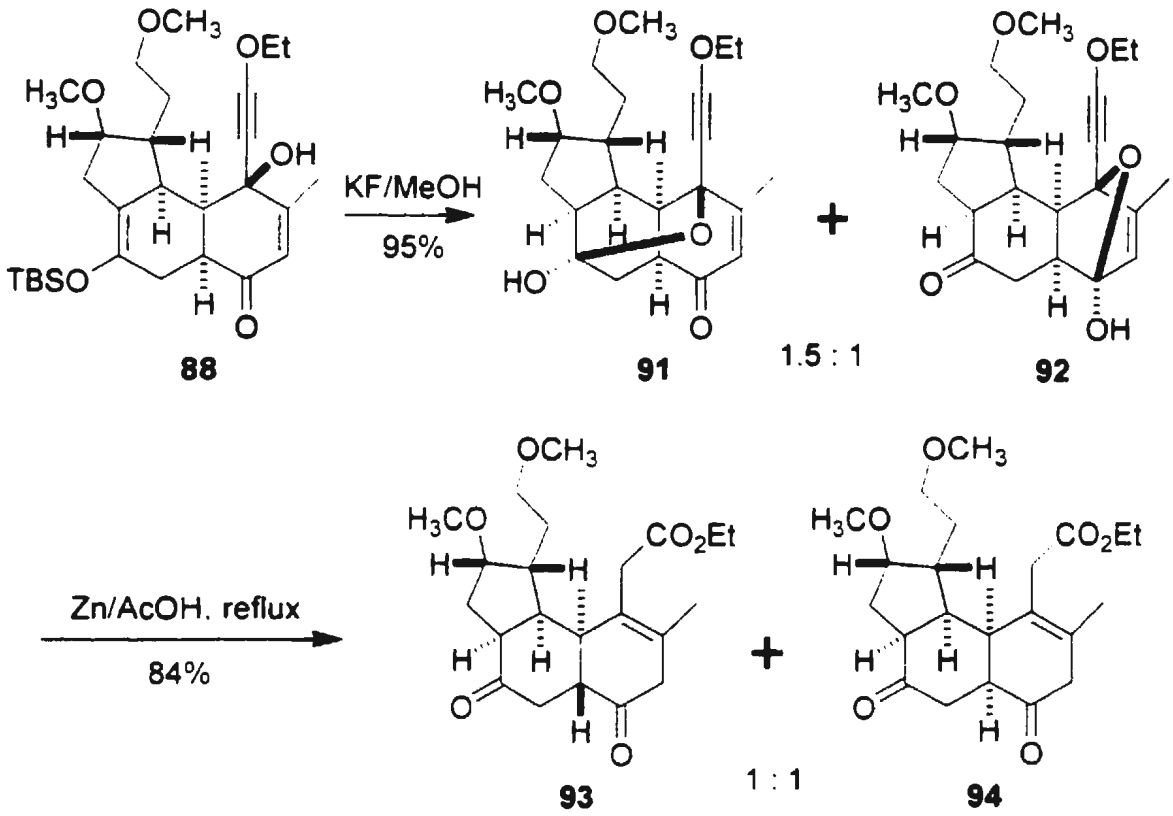


89 **90**

We believed that both of the chemo- and stereoselectivity in the acetylide addition step were due to a preference for axial attack. In Scheme 25, the two most stable conformers are shown as **89** and **90**, either of which can provide two approaches for axial attack. However, only one approach is not sterically hindered, the remaining approaches being impeded either by the β-axial methyl group or by a β-axial methylene group in the other six-membered ring.

The next step was to hydrolyze the silyl enol ether function of **88**. The acetylide addition product **88** was treated with potassium fluoride in methanol at room temperature overnight to form a mixture of two bridged hemi-acetals, **91** and **92** in a ratio of 1.5:1, in 95% combined yield (Scheme 26).

Scheme 26. Hydrolysis of TBS-enolate in **88** with KF and zinc reduction of the product

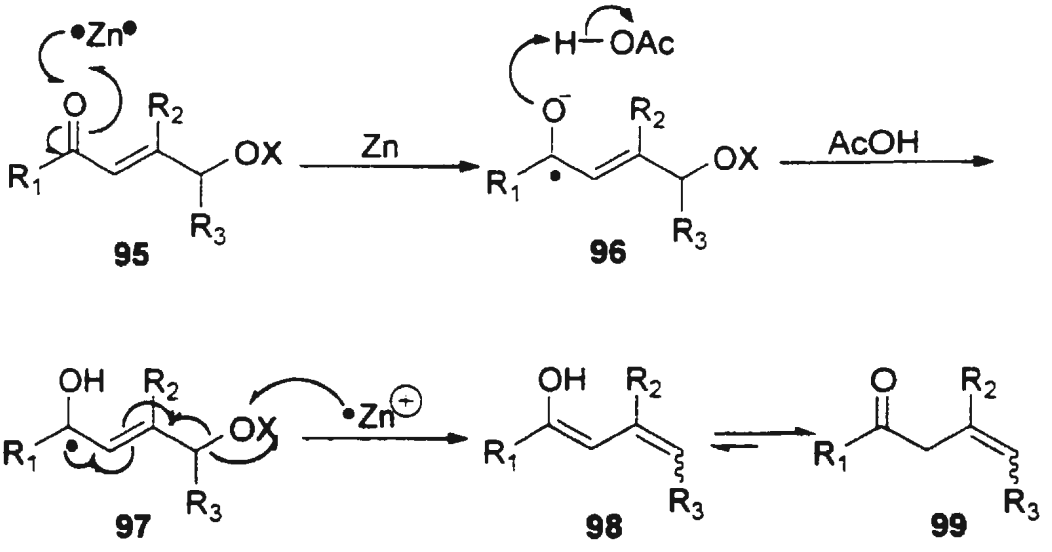


The formation of a mixture of bridged hemi-acetals **91** and **92** was unexpected but understandable. The formation of these compounds confirmed the stereochemistry of the acetylide addition step. These two bridged hemi-

acetals could be separated by flash chromatography, but the mixture was usually used without separation for the next step in our synthesis.

It was predicted that zinc reduction of the bridged hemi-acetals (**91** and **92**) could produce the β,γ-unsaturated ketone with the cleavage of the γ-oxygen substituent. Because both of the bridged hemi-acetals are γ-oxygen-substituted, α,β-unsaturated ketones, it was reasonable to speculate that the mechanism of zinc reduction might be similar to that of zinc reduction of α-oxygen-substituted ketones.[43] The proposed mechanism for the reduction of the γ-oxygen-substituted α,β-unsaturated ketone with zinc dust in acetic acid is shown in Scheme 27.

Scheme 27. Proposed mechanism for zinc reduction

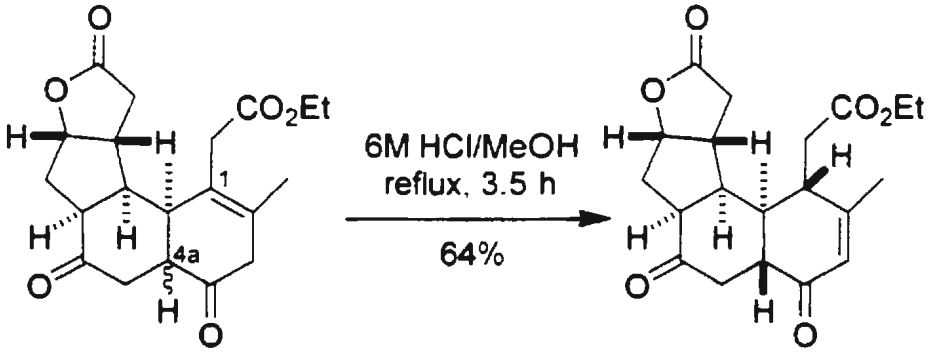


By obtaining an electron from zinc, the γ-oxygen-substituted enone **95** becomes a radical anion **96**. The radical anion **96** captures a proton from acetic

acid to form a radical alcohol **97**. By obtaining a second electron from zinc, the radical alcohol **97** is converted to an enol **98** by a single-electron transfer process and cleavage of the γ-oxygen substituent. Of course, the enol **98** then tautomerizes to the more stable form, a β,γ-unsaturated ketone **99**.

The mixture of **91** and **92** was reduced by zinc dust in hot acetic acid therefore to produce the 1:1 mixture of **93** and **94** in 84% yield. During the zinc reduction process, solvolysis of the ethyl ethynyl ether moiety to an ester group and partial epimerization of the *cis*-decalin ring junction also took place. To set the stage for the needed seven-membered ring cyclization, the isolated double bond had to be shifted into conjugation, and the *cis*-decalin ring system needed to be epimerized to *trans* in compounds **93** and **94**. In the First Route, the shifting of the double bond and the epimerization of the stereogenic center at C-4a were effected using methanolic hydrochloric acid in a single operation[22] (Scheme 28).

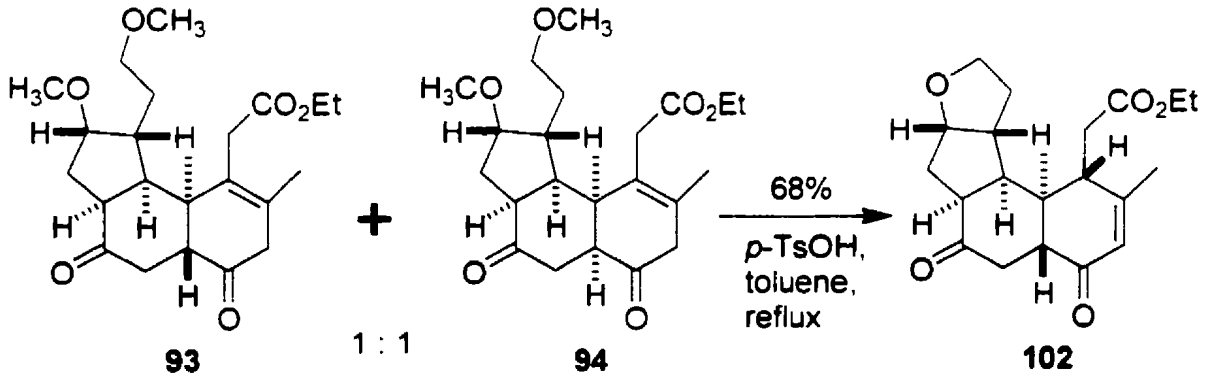
Scheme 28. Isomerization and epimerization of compound **100**



100 **101**

A mixture of **100** was treated with aqueous 6M HCl in methanol under reflux for 3.5 hours to afford the expected product **101** in which the ester side chain was in the equatorial position, and a *trans*-decalin ring system was obtained. In this one-step process, two stereogenic centers evolved with the correct relative stereochemistry. However, when the same reaction conditions were applied to the mixture of **93** and **94**, very complex mixtures were obtained, as shown by TLC. Several different acids were tested under different conditions, and eventually we found that only *para*-toluenesulfonic acid in toluene under reflux isomerized the double bond from the β,γ-position to the α,β-position, also changing the decalin ring junction from *cis* to *trans*. Unfortunately, at the same time, the two methyl ether side chains were cyclized to provide a tetra-hydrofuran derivative **102** (Scheme 29).

Scheme 29. Isomerization and epimerization of **93** and **94**



The structure of **102** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, which did not show the two methoxy groups and by the high-resolution mass spectrum. The relative stereochemistry of **102** was revealed by NOE measurements. After several attempts at ether cleavage[44] (BBr_3, Me_3SiI, etc.) failed, we decided to give up this strategy and to pursue another route for the synthesis of kempanes.

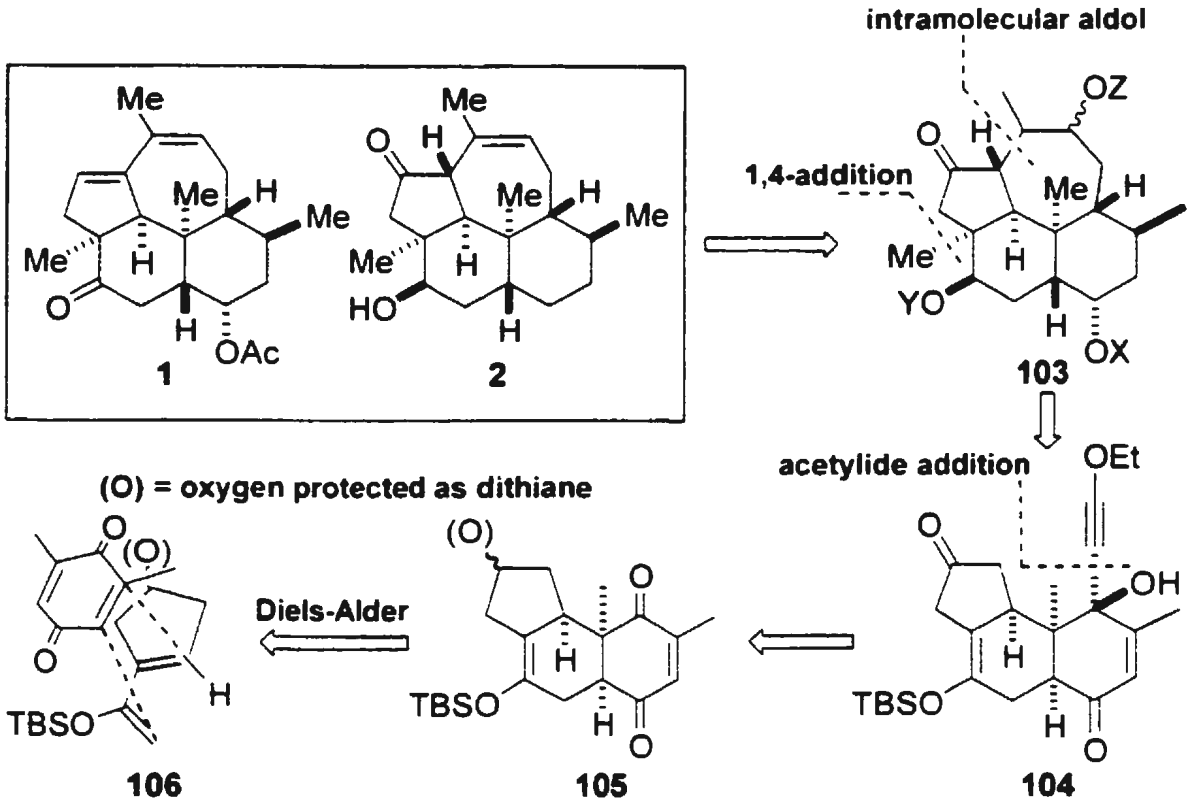
1.4. Dithiane Route

1.4.1. Retrosynthesis of the Dithiane Route

The failures of the First Route and the Diether Route forced us to consider yet another strategy, which will be referred to as the Dithiane Route. From our experience, it seemed that our tricyclic intermediates tended to form another five-membered ring in the left-hand side of the molecule, presumably because the existence of the extra five-membered ring added considerably to the conformational stability. In order to overcome this problem, the possibility of formation of this five-membered ring must be completely removed. The retrosynthetic analysis of our Dithiane Route is outlined in Scheme 30.

Kempane diterpenes **1** and **2** would both be derived from the advanced intermediate **103**. It was anticipated that the last methyl group could be introduced by 1,4-addition. We believed that the concave shape of the molecule should ensure 1,4-addition from the convex side to provide the correct relative stereochemistry. Intramolecular aldol condensation rather than the Dieckmann condensation of the First Route (Scheme 7) would be used for the seven-membered ring cyclization. This seven-membered ring cyclization would require the introduction of a four-carbon side chain on the right-hand side of the molecule, and we planned to do this in two steps. This would be essential for introduction of a hydroxyl group in the side chain, which would be eliminated to provide the double bond in the seven-membered ring. We hoped this would avoid the problem of the double bond position in Paquette's synthesis (Scheme 5).[17]

Scheme 30. Retrosynthetic analysis for the Dithiane Route



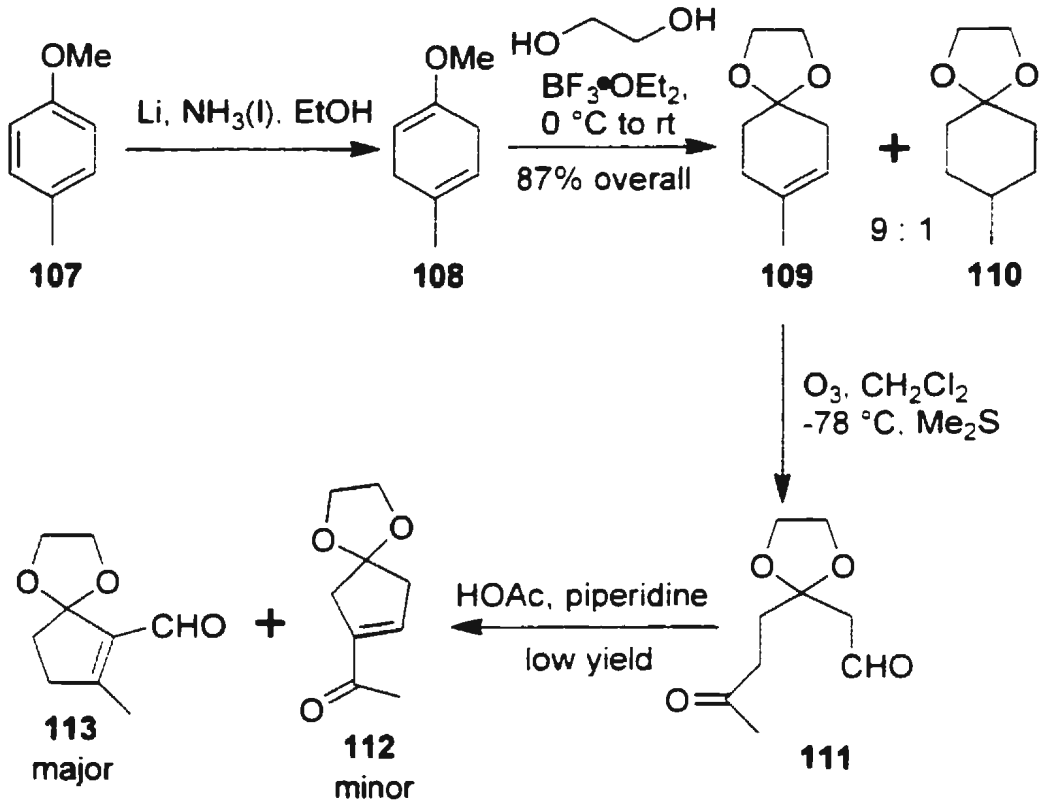
Central to the construction of intermediate **103** was the previously recognized efficiency and selectivity with which a lithium acetylide adds to the seemingly more congested carbonyl of an enedione. From this point, the strategy reduced itself to the preparation of **105** by a Diels-Alder reaction. Based on our studies in the First Route and the Diether Route, we expected that this Diels-Alder reaction would proceed as did the previous Diels-Alder reactions (Scheme 18 and Scheme19). The only difference in this Diels-Alder reaction was that the diene

106 in the Dithiane Route would carry only a protected carbonyl function on the five-membered ring.

1.4.2. Synthesis of the Diels-Alder Diene

An initial attempt for the synthesis of the required diene is outlined in Scheme 31.

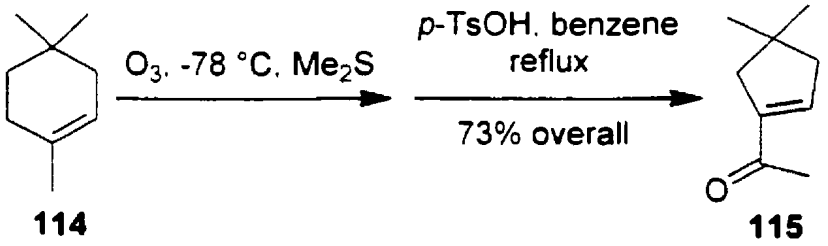
Scheme 31. Initial attempt in the synthesis of the diene



Birch reduction of 4-methylanisole (**107**) with lithium and ethanol in liquid ammonia[45] produced 4-methoxy-1-methylcyclohexa-1,4-diene (**108**). Reaction of the crude methoxy diene **108** with 1,2-ethanediol in the presence of $BF_3 \bullet OEt_2$[46]

yielded a mixture of cyclic ethylene acetals **109** and **110**, in a ratio of 9:1. The overall yield for these two steps was 87%. The subsequent ozonolysis and aldol condensation were very sluggish. The optimized conditions for aldol condensation involved the use of acetate salt of piperidene in acetic acid[47] as the catalyst, but the required diene was obtained as only a minor product. Aldol reaction under basic conditions (KOH/MeOH, K_2CO_3/MeOH, $NaOC_2H_5/C_2H_5OH$, 5% NaOH/ether,[48] etc.) and an amino acid catalyst (β-alanine[49]) was investigated, but no conditions were found which gave the required enone **112** as the major product. This was disappointing since there was a report[50] of a similar strategy that used an aldol condensation with acid to make the enone **115** in reasonable yield (Scheme 32). 1,4,4-Trimethylcyclohexene (**114**) was treated

Scheme 32. A literature example[50] of enone preparation



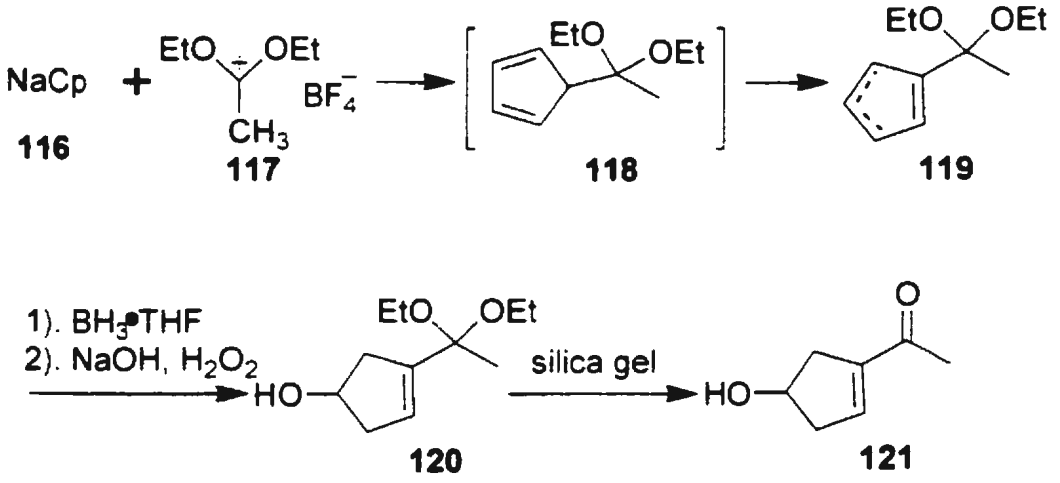
114 **115**

with ozone at –78 °C, followed by reductive work-up with dimethyl sulfide. The crude product was heated in benzene containing *p*-toluenesulfonic acid to produce the enone **115** in 73% yield from **114**. We felt that an acid-catalyzed aldol condensation might result in the formation of the required enone, but compound **109** contained an acid-sensitive acetal group. However, if the cyclic

acetal were replaced with a thio-acetal, the dithiane group would be oxidized during ozonolysis.

Another strategy for the preparation of the enone analogue was found in the literature (Scheme 33). Bartlett *et al.*[51] used the alkylation of sodium

Scheme 33. An alternative strategy of enone preparation[51]

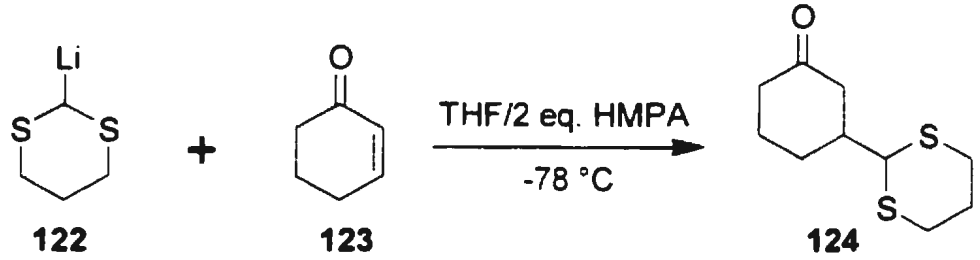


cyclopentadienide (**116**) with diethoxymethylcarbonium tetrafluoroborate to produce the 5-substituted compound **118**, which rearranged to a mixture of the 1- and 2-substituted cyclopentadienes (**119**) in 78% yield. Hydroboration and oxidation of this mixture yielded a single hydroxy ketal **120**, which was simultaneously purified and hydrolyzed through a silica gel column to afford the hydroxy enone **121** in 74% overall yield from **119**. The drawback of using enone **121** is that it has a stereogenic center. This would bring us diasteroisomers in later steps, which would make purification by chromatography tricky. Since we

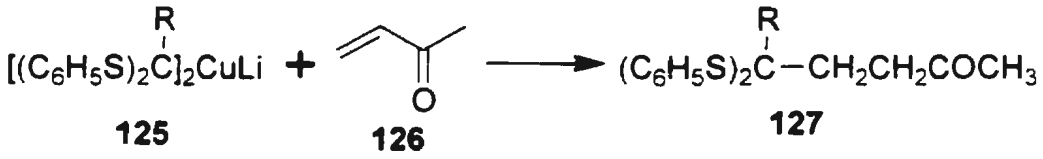
thought enone **121** would not be a suitable starting material in our synthesis, we did not pursue this strategy.

Next, we thought we should make a diene **106** with a dithiane-protected carbonyl. The literature shows that the dithiane anion **122** reacts with enone **123** in the presence of HMPA by 1,4-addition,[52] and the cuprate reagent **125**, made from diphenylthioacetal, reacts with a conjugated enone to yield the 1,4-addition product **127**[53] (Scheme 34).

Scheme 34. Literature examples of 1,4-addition of the dithiane anion and cuprate reagent with an enone[52, 53]



122 **123** **124**

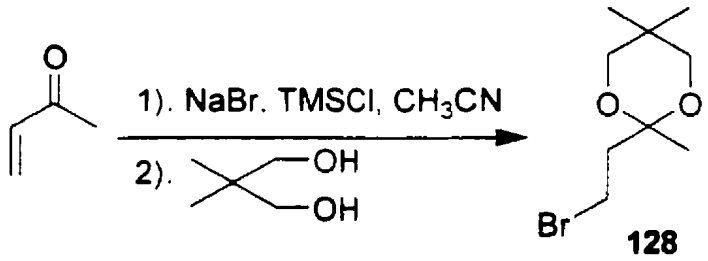


125 **126** **127**

In our hands, 1,4-addition of the mono-substituted dithiane anion with butenone **126** failed to give the expected product. Alkylation of the dithiane compound[54] was then considered.

First, we used the bromo-acetal **128** (made as shown in Scheme 35)[55] as the alkylating agent, but no reaction occurred. When bromo-acetal **128** was replaced by iodo-acetal **129**, the alkylation of the monosubstituted dithiane proceeded very smoothly to give the disubstituted dithiane in high yield.

Scheme 35. Preparation of bromo-acetal **128**

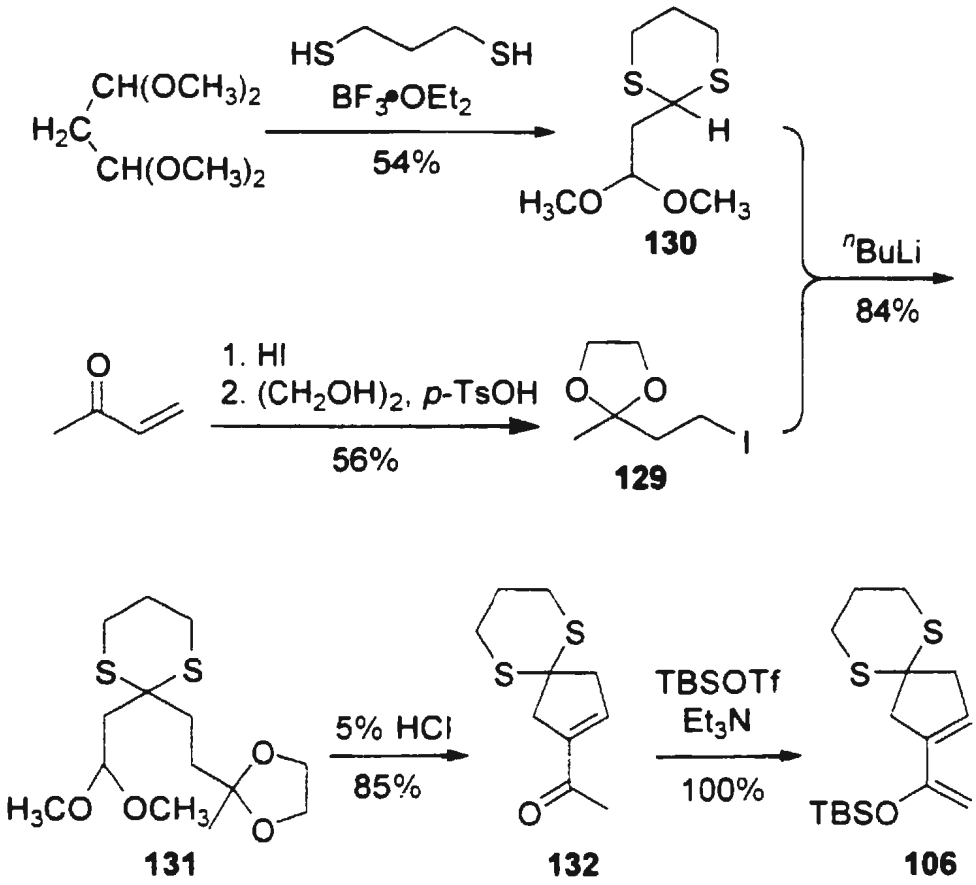


128

The synthesis of the required Diels-Alder diene in the Dithiane Route is summarized in Scheme 36. Malonaldehyde bis(dimethyl acetal) reacted with 1,3-propanedithiol in the presence of boron trifluoride etherate to produce the mono-substituted dithiane **130**.[56] Iodo-acetal **129** was prepared by reaction of butenone with hydroiodic acid by 1,4-addition, followed by protection of the carbonyl as an ethylene acetal.[57] Metalation of **130** was effected with *n*-butyllithium in THF at –20 to –30 °C for 2 hours. The product **131** was obtained in 84% yield by exposure of **129** to the above anion at –40 °C, then at 0 °C for 3 days. The disubstituted dithiane **131** contained three protected carbonyl functions. Then **131** was treated with aqueous 5% HCl in THF to afford the expected enone **132** as a single isomer in 85% yield. This aldol condensation took advantage of the fact that the aldehyde-acetal is more acid sensitive than the ketone-acetal. The

TBS-enolate diene **106** was synthesized in quantitative yield by treating enone **132** with TBSOTf and Et_3N.

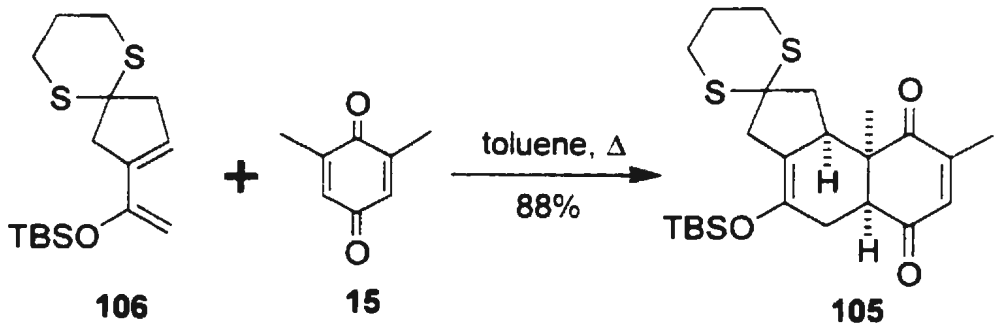
Scheme 36. Synthesis of diene **106** in the Dithiane Route



1.4.3. Attempts to Make the Kempane Ring System

As expected, the Diels-Alder reaction of the TBS-enol ether **106** with 2,6-dimethybenzoquinone (**15**) proceeded with highly regio- and *endo* selectivity to form a benzoindane system **105** in 88% yield (Scheme 37).

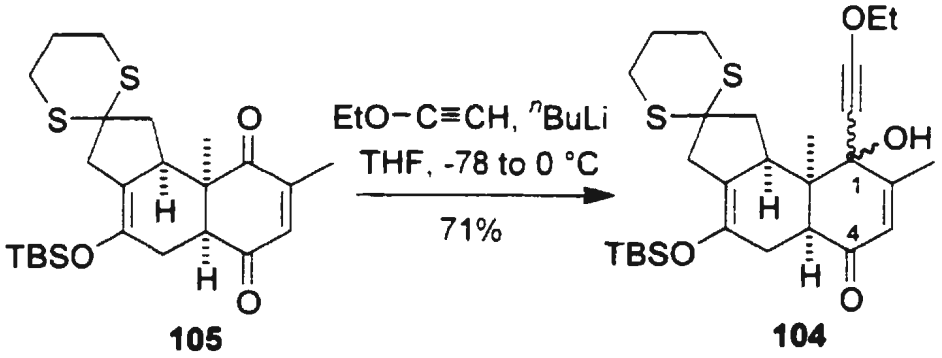
Scheme 37. Diels-Alder reaction of diene **106** with dienophile **15**



106 **15** **105**

Considering the high selectivity and good yields of this type of Diels-Alder reaction, we concluded that substituents on the five-membered ring of the diene had no significant effect on the reactivity and selectivity of this diene system. The stage was now set for introducing the side chain. Lithium ethoxyacetylide was chosen as the nucleophilic reagent in order to introduce the two-carbon chain first. The acetylide addition did take place at the seemingly more hindered carbonyl of the enedione, but with no stereoselectivity. The addition product **104** was obtained in 71% yield as a mixture of stereoisomers (Scheme 38).

Scheme 38. Acetylide addition of enedione **105**

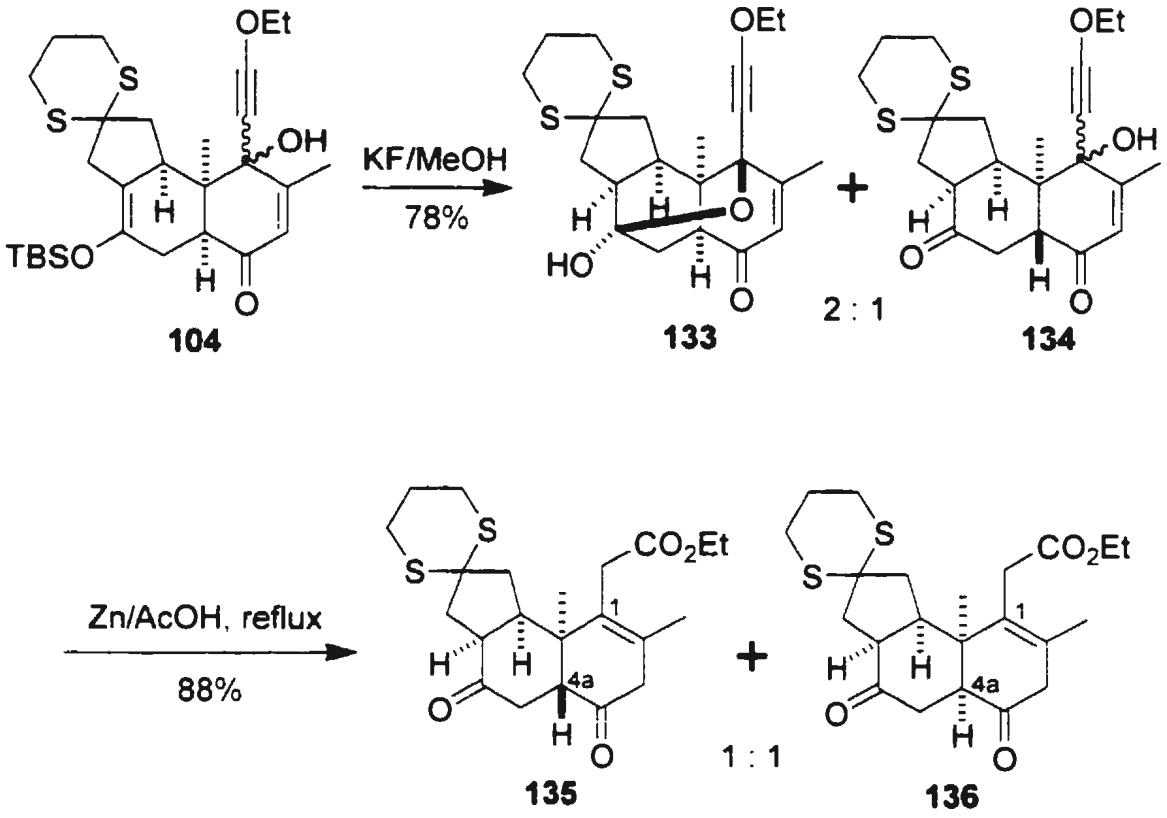


105 **104**

The reason for the loss of stereoselectivity remains unknown. It is reasonable to speculate that the six-membered ring of the 1,3-dithiane group made the conformation of the molecule change, which in turn influenced the stereoselectivity of the addition. It has been recognized that a zinc reduction step would form a β,γ-unsaturated ketone and the stereogenic center at C-1 would be destroyed. The loss of stereoselectivity in the acetylide-addition step should not affect the later synthetic sequences.

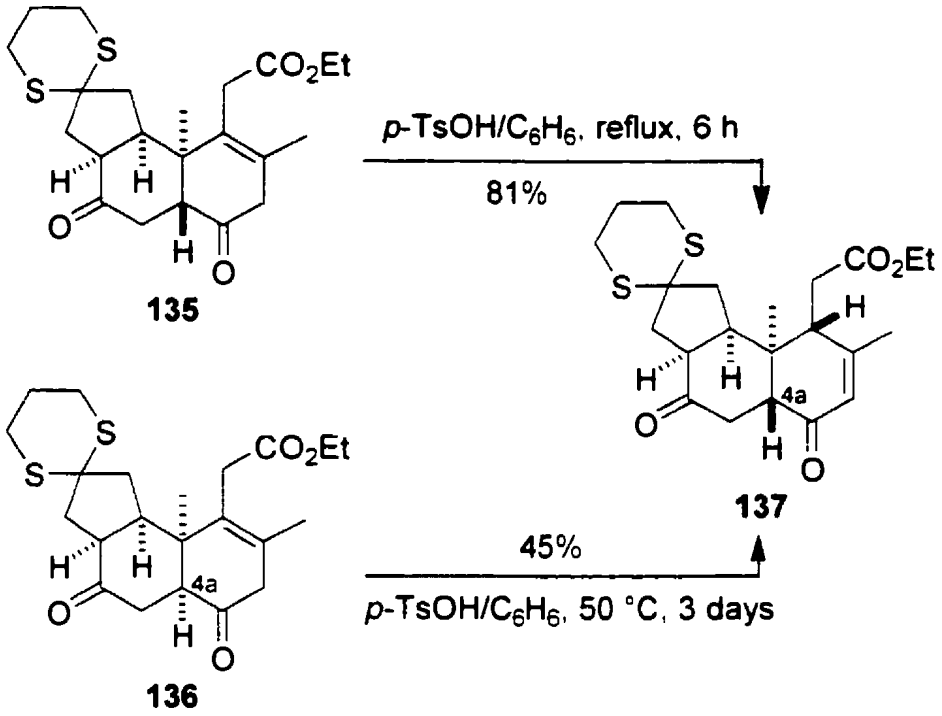
Just as in the First Route and the Diether Route, the acetylide-addition product **104** was treated with potassium fluoride in methanol to hydrolyze the TBS-enol ether (Scheme 39). A mixture of the bridged hemi-acetal **133** and carbinol **134** was obtained in 78% yield. This mixture was treated with zinc dust in hot acetic acid to generate the β,γ-unsatureted ketone. A 1:1 mixture of **135** and **136** was obtained in 80% yield. Again, in this zinc reduction step, solvolysis of the ethyl ethynyl ether and partial epimerization of the decalin ring junction also took place. The stereochemistry at the [6,6] ring junction of **135** and of **136** was determined by ^{1}H NMR analysis and nuclear Overhauser effect (NOE) measurements. The ^{1}H NMR spectra showed that **135** had an angular methyl group with a signal appearing at δ ~1.1 ppm, whereas **136**, which had a *cis* ring system, had the signal for the angular methyl group at δ ~1.5 ppm. NOE measurements showed that for **136** there were large enhancements that placed the angular methyl near the hydrogen at C-4a.

Scheme 39. Hydrolysis of TBS-enol ether and zinc reduction of the product



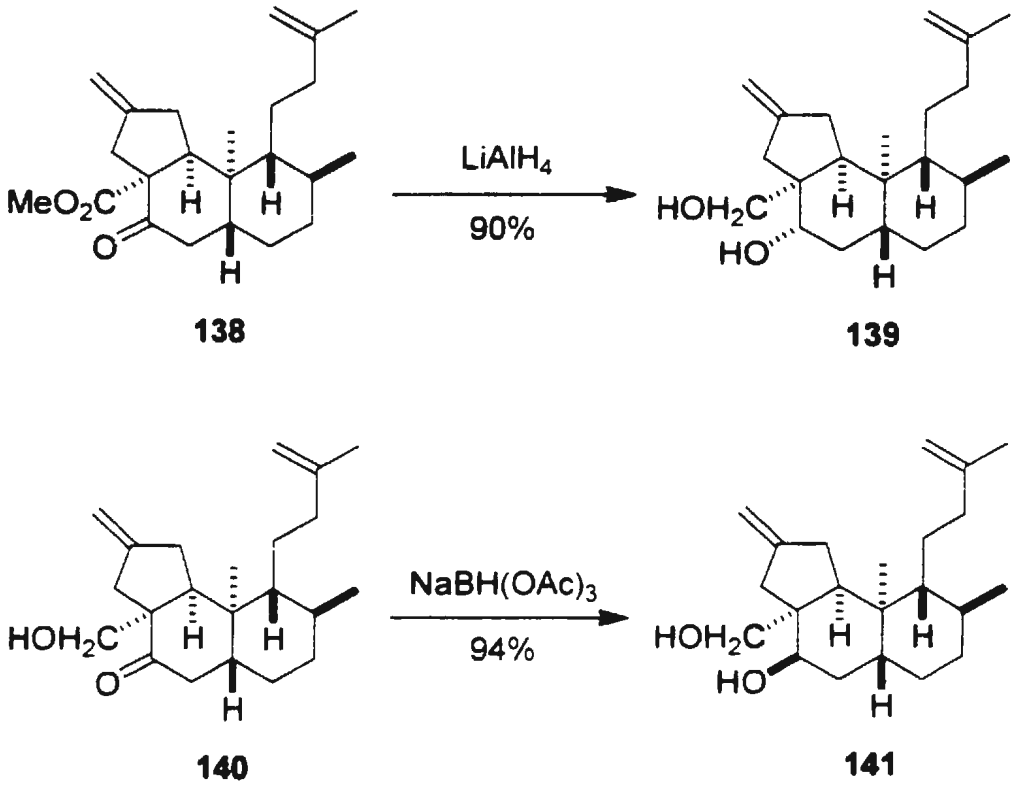
Isomerization of the double bond from the β,γ-position to the conjugated α,β-position and epimerization at C-4a were achieved by the action of *p*-toluene-sulfonic acid in benzene (Scheme 40). Exposure of **135** to *p*-TsOH in benzene under reflux for 6 hours gave the expected conjugated enone **137** in 81% yield. When **136** was treated with *p*-TsOH in benzene at 50 °C for 3 days, **137** was formed in 45% yield.

Scheme 40. Isomerization and epimerization of **135** and **136**



With compound **137** in hand, the selective reduction of the saturated carbonyl was evaluated. In Paquette's synthesis,[17] the overriding preference for kinetically controlled axial attack made the equatorial secondary alcohol **139** from **138**. The required axial alcohol **141** was obtained exclusively, by taking advantage of hydroxyl-directed hydride reduction of **140** (Scheme 41).

Scheme 41. Selective reduction of the carbonyl in Paquette's synthesis[17]



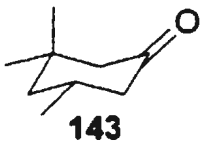
138 **139**

140 **141**

In our case, compound **137** contained an unconjugated and a α,β-unsaturated ketone. The chemoselective reduction of the former should not have been a problem, because the saturated carbonyl is usually more reactive than an α,β-unsaturated carbonyl toward the reduction. It was recognized that the size of the reducing reagent might affect the stereoselectivity of the reduction. Reductions with small reducing reagents, such as sodium borohydride, prefer axial attack to form the equatorial hydroxyl, and bulky reducing reagents would inhibit the axial addition and enhance the equatorial reaction. For example, the

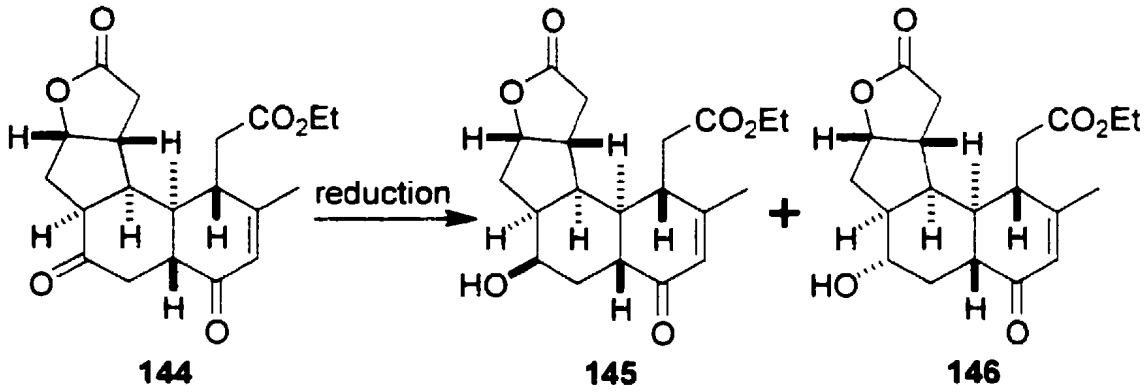
reduction of 4-*tert*-butylcyclohexanone (**142**) with sodium borohydride showed a preference for axial addition over equatorial, in a ratio of 86:14. However, when 3,3,4-trimethylcyclohexanone (**143**) was reduced by lithium tri-*tert*-butoxy-aluminohydride, the selectivity was reversed to 96:4 in favor of equatorial addition (Table 2).[58]

Table 2. Literature examples[58] of stereoselectivity in the reduction of cyclohexanones

Cyclohexanone	Reducing reagent and conditions	Ratio of axial addition to equatorial addition
 **142**	$NaBH_4$ 2-propanol, 25 °C	86 : 14
 **143**	$LiAl(O^tBu)_3H$ THF, 0 °C	4 : 96

In our First Route,[59] the reduction of the ketone with sodium borohydride gave poor stereoselectivity, but with lithium tri-*tert*-butoxyaluminohydride, the stereoselectivity was 8:1 in favor of equatorial addition (Scheme 42).

Scheme 42. Reduction of **144** with $NaBH_4$ and $LiAl(O^tBu)_3H$

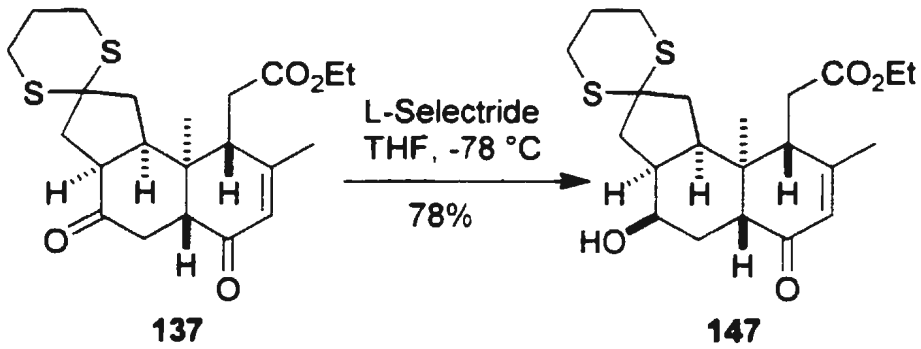


144 **145** **146**

Procedure	ratio of **145** to **146**
$NaBH_4$, -78 °C 1 : 1 $MeOH/CH_2Cl_2$	2 : 3
$LiAl(O^tBu)_3H$ -20 to 0 °C, 2 h	8 : 1

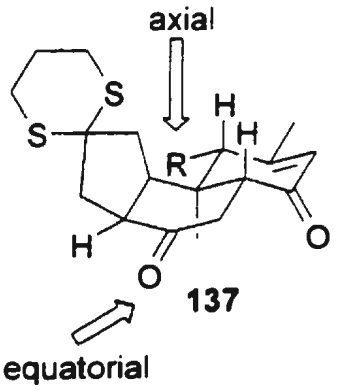
It was speculated that the reduction of **137** should be similar to that of **144**. The use of a bulky reducing reagent was expected to provide good chemo- and stereoselectivity in the reduction of the saturated ketone. When **137** was treated with lithium tri-*tert*-butoxyaluminohydride, an inseparable mixture (~1:1 ratio) of stereoisomers was obtained. However, when L-Selectride was used as the reducing reagent, the expected product of equatorial attack **147** was isolated as a single isomer (Scheme 43).

Scheme 43. Reduction of **137** with L-Selectride



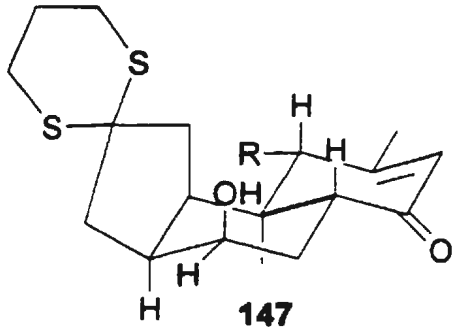
137 **147**

It can be argued that the shape of molecule **137** was responsible for the stereoselectivity of the reduction, because the six-membered ring with the saturated ketone might be in a boat conformation. The β-axial methylene group in the five-membered ring and the six-membered ring of dithiane group would then impede axial addition when a bulky reducing reagent was used.



The next task was the protection of the hydroxyl group in **147**. We realized that protection of this hydroxyl group might be difficult, because it was in an

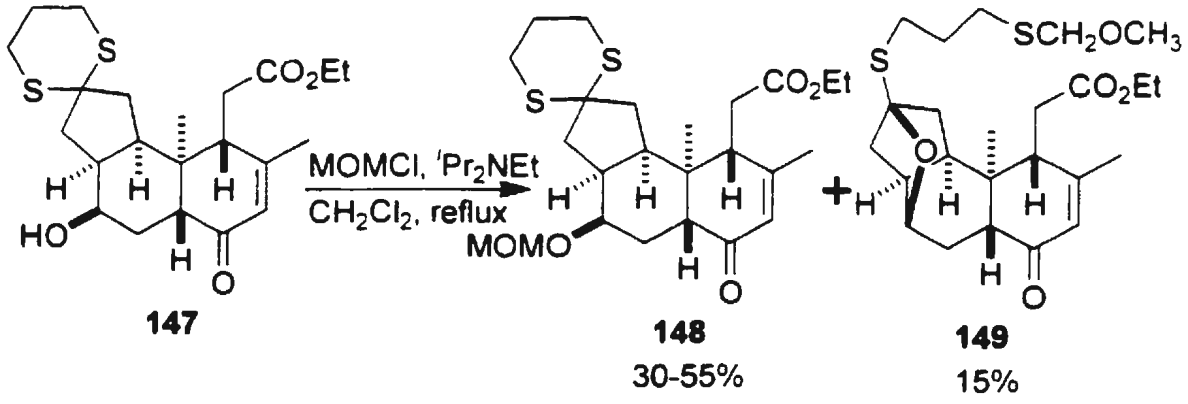
extremely sterically hindered environment. Three concerns had to be addressed in choosing the protecting group. First, the protecting group should not be too



147

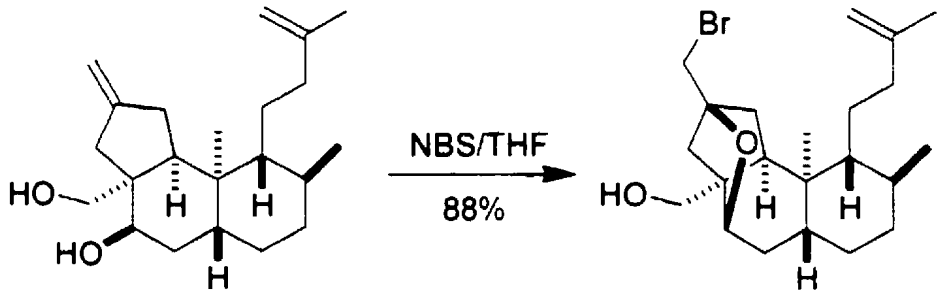
bulky, because of the sterically hindered environment. Secondly, the protecting group had to be fairly stable towards reduction, oxidation, and nucleophilic addition, because it was expected to be kept until the last stages of the synthesis. Thirdly, the conditions for introducing the protecting group should not be strongly basic, otherwise an undesired condensation might occur with the ester group in the molecule.[60] With these considerations in mind, a methoxymethyl (MOM) group was chosen as the protecting group (Scheme 44).

Scheme 44. Protection of the hydroxyl group in **147**



Compound **147** was treated with MOMCl and EtN(*i*-Pr)$_2$ in CH_2Cl_2 under reflux overnight, but the expected product **148** was obtained in only 30-55% yield. A significant amount (15%) of by-product **149** was unavoidable. The reason for forming **149** was that under the reaction conditions, MOMCl might associate with a sulfur atom in the dithiane group to form a sulfur cation, then the hydroxyl group attacked the dithiane-protected carbon, followed by rupture of the carbon-sulfur bond. The close proximity of the hydroxyl group in **147** to the dithiane group was likely responsible for the formation of **149**. A similar problem of proximity existed in Paquette's synthesis[17] (Scheme 45), leading to the formation of **150** from **141.**

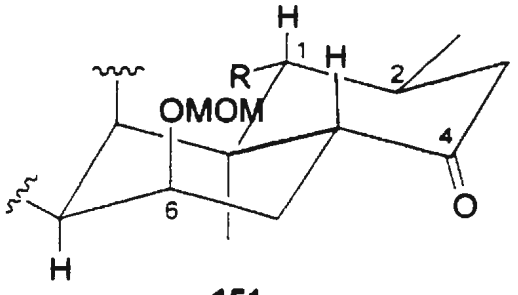
Scheme 45. Ether formation due to proximity in Paquette's synthesis[17]



141 **150**

At this point, the reduction of the C=C double bond in enone **148** and the correct establishment of the stereogenic center at C-2 were considered. There are many methods available for the reduction of a C=C double bond in an α,β-unsaturated ketone.[61] If we assume that the cyclohexanone ring in the desired

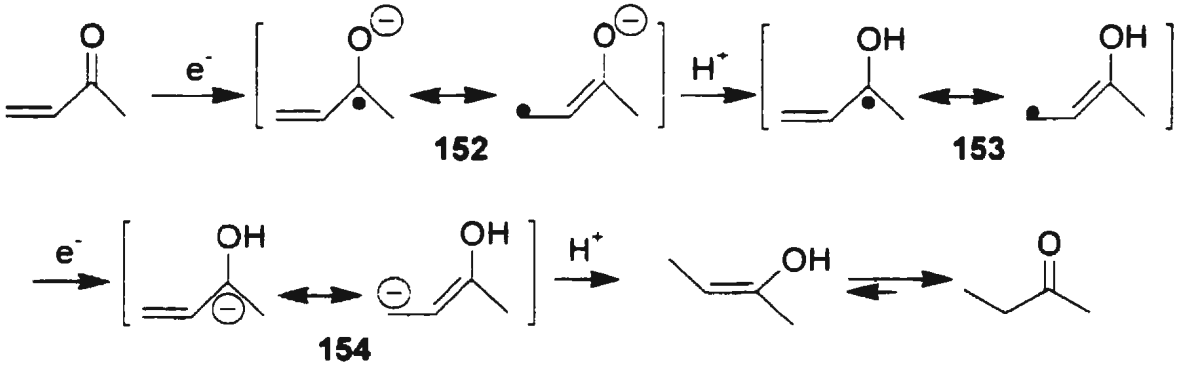
product **151** adopts a chair conformation, the methyl group at C-2 had to be *anti* to the ester side chain at C-1. In other words, the methyl group at C-2 in **151** is equatorial. Therefore, lithium in liquid ammonia was chosen as the reducing reagent.[63]



151

Conjugated ketones are reduced to give saturated ketones via 1,4-reduction, and this is rationalized by the ketyl mechanism[63] (Scheme 46).

Scheme 46. Mechanism for dissoving-metal reductions of conjugated ketones

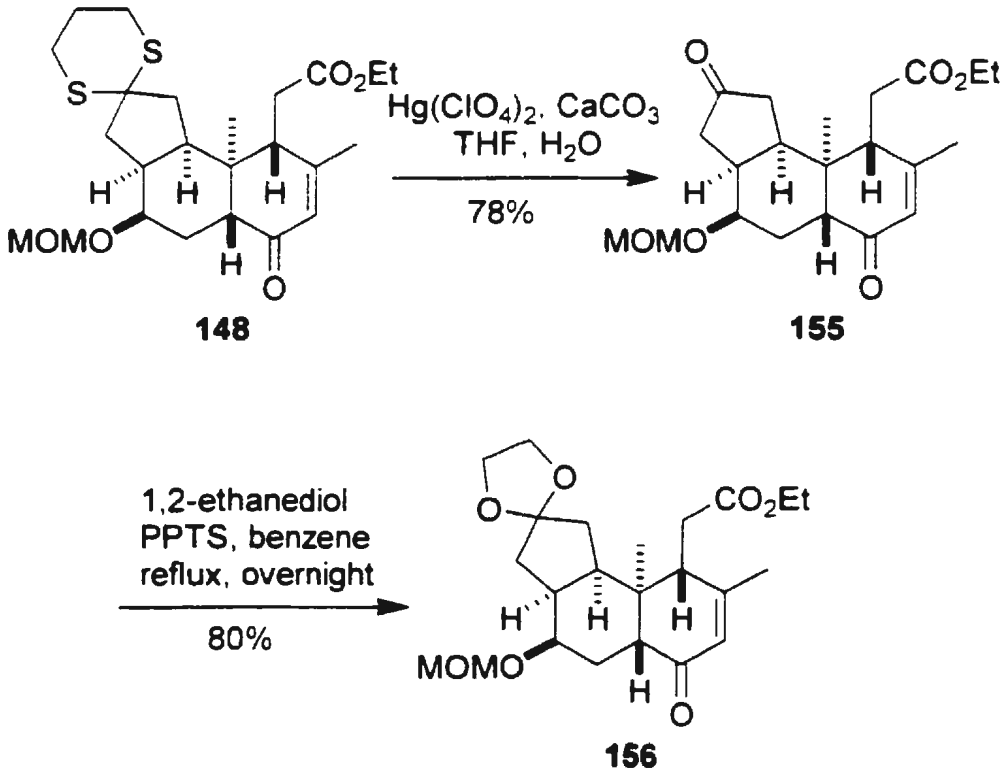


The conjugated ketone obtains an electron from the metal to give a relatively stable, resonance delocalized ketyl **152**. Protonation of **152** produces the allylic enol radical **153**, which captures a second electron to form **154**. Proton transfer

again generates the enol, followed by tautomerization to give the ketone. Because a dissolving-metal reduction of **148** would reduce the cyclic dithioacetal, we needed to convert the dithiane group to another protecting group before the lithium/ammonia reduction was executed.

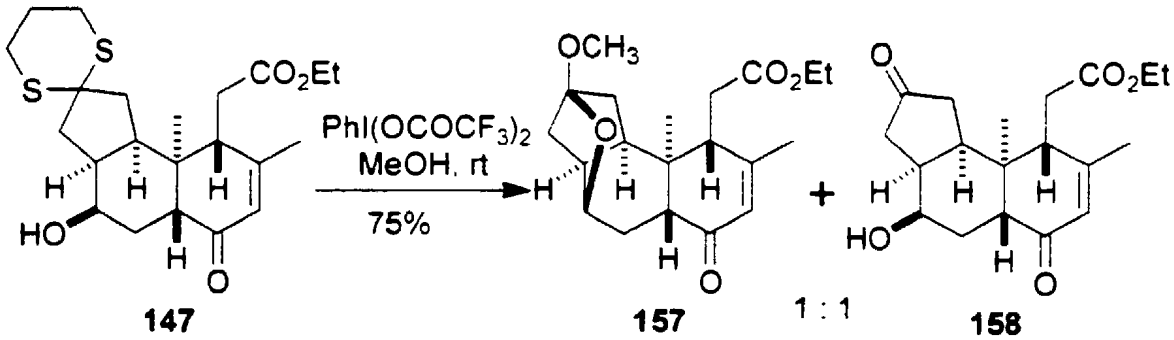
The thioacetal in **148** was deprotected by mercury perchlorate[65] in the presence of calcium carbonate to form **155**. Then the less hindered, saturated carbonyl in **155** was reprotected with 1,2-ethanediol, catalyzed by PPTS,[35] to form the corresponding acetal **156** in good yield (Scheme 47).

Scheme 47. Deprotection and reprotection of the carbonyl in **148**

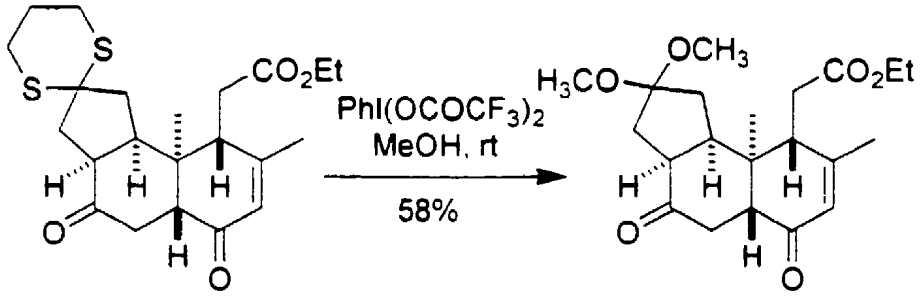


Because of the low yield in the protection of hydroxyl in **147** (Scheme 44), we decided to examine deprotection of the thioacetal without protection of the hydroxyl group. Stork's group[66] had developed a procedure for the conversion of a dithiane group to a dimethyl acetal in one pot with bis(trifluoroacetoxy)iodo-benzene in the presence of methanol. When Stork's conditions were employed with compound **147**, a 1:1 mixture of **157** and **158** was obtained (Scheme 48).

Scheme 48. Transformation of the dithiane to the dimethyl acetal by Stork's conditions



147 **157** **158**



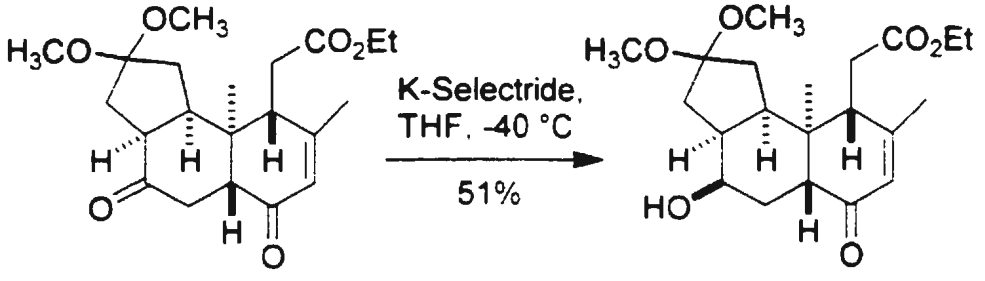
137 **159**

The product **158** arose by simple deprotection of the dithiane without protection of the carbonyl. Compound **157** is an acetal, but one alcohol unit has been provided via an intramolecular mechanism. The proximity of the hydroxyl group in

147 to the dithiane made the formation of this acetal possible. Obviously, the free hydroxyl group in **147** had a significant impact on this reaction. This suggested that changing the protecting group should take place before the reduction of the ketone. When compound **137** was treated with bis(trifluoroacetoxy)iodobenzene in methanol, the expected product **159** was produced in moderate yield.

Selective reduction of the saturated carbonyl was the next task. K-Selectride was chosen as the reducing reagent. K-Selectride is known to be a weaker reducing reagent than L-Selectride,[67] and we hoped that it might therefore maintain the selectivity but give higher yields than L-Selectride. Our experiments (Scheme 49) only partially met our expectations.

Scheme 49. Selective reduction of saturated ketone in **159** by K-Selectride

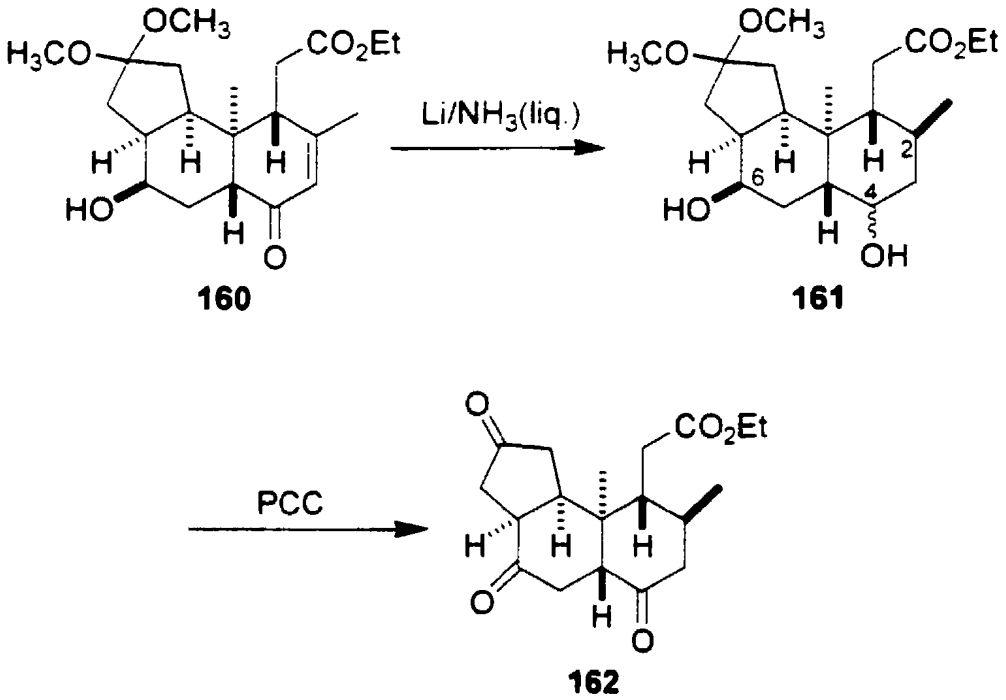


159 **160**

When **159** was exposed to K-Selectride in THF at –40 °C for three hours, the desired product **160** was obtained in 51% yield. Compared to the reduction of **137** by L-Selectride, the selectivity was same, even though the reduction had to be performed at a higher temperature. However, the yield was significantly lower.

With **160** in hand, we faced the protection of the axial hydroxyl group again. It was recognized that the methoxyl group on the five-membered ring made the hydroxyl an extremely sterically hindered environment. As expected, this protection was very difficult. All of the attempts for the protection failed. The protecting groups we tested included methyl, MOM, MEM, TBS, and Bn. Considering the trouble we were having in trying to protect this group, we thought that the hydroxyl might be also inert to other transformations. We decided to use **160**, which contains the free hydroxyl group, directly in the lithium/liquid ammonia reduction step (Scheme 50).

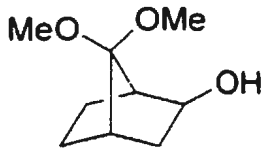
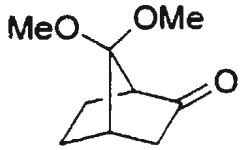
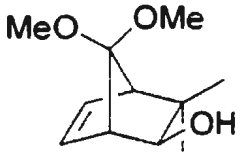
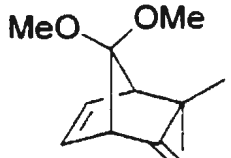
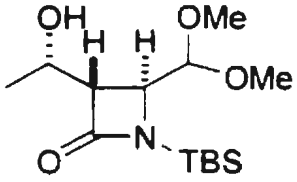
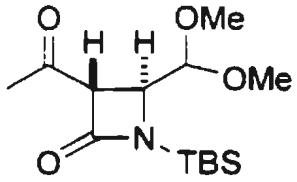
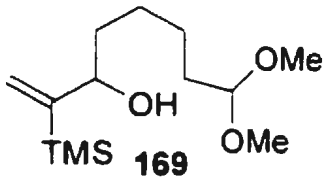
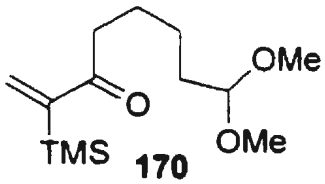
Scheme 50. Reduction of enone in **160** by lithium in liquid ammonia



160 **161** **162**

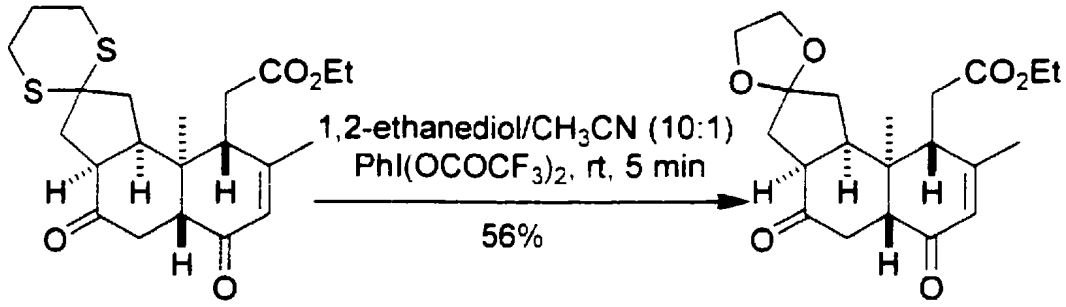
Enone **160** was treated with lithium in dry liquid ammonia at –50 °C for five minutes. After evaporation of ammonia and work-up, the crude product **161** was oxidized with PCC to afford **162**. The reduction of the enone did occur to provide the correct stereochemistry at C-2. However, because of some over-reduction of the ketone to alcohol at C-4, PCC was used to oxidize the hydroxyl at C-4 and C-6 to the carbonyl. Unfortunately, it not only oxidized those hydroxyl groups, but also deprotected the dimethyl acetal to the ketone. There are examples in the literature which show that a dimethyl acetal should be stable to PCC oxidation (Table 3).[68] We must presume that it was the steric hindrance in **160** that resulted in this unusually low stability of a dimethyl acetal with PCC.

Table 3. Literature examples of PCC oxidation of alcohols in the presence of a dimethyl acetal[68]

Substrate	Conditions	Product	Yield
 **163**	PCC (1.4 eq.) CH_2Cl_2, rt, 2 h	 **164**	95%
 **165**	PCC CH_2Cl_2, rt	 **166**	75%
 **167**	PCC (1.5 eq.) NaOAc, CH_2Cl_2 rt, 6 h	 **168**	63%
 **169**	PCC $NaHSO_4$ CH_2Cl_2, rt	 **170**	65%

In order to solve this problem, we had to go back to the dithiane deprotection step. This time we used 1,2-ethanediol as the solvent instead of methanol (Scheme 51). Compound **137** in acetonitrile reacted with bis(trifluoroacetoxy)iodobenzene in the presence of 1,2-ethanediol at room temperature for five minutes to give the cyclic acetal **171** in 56% yield.

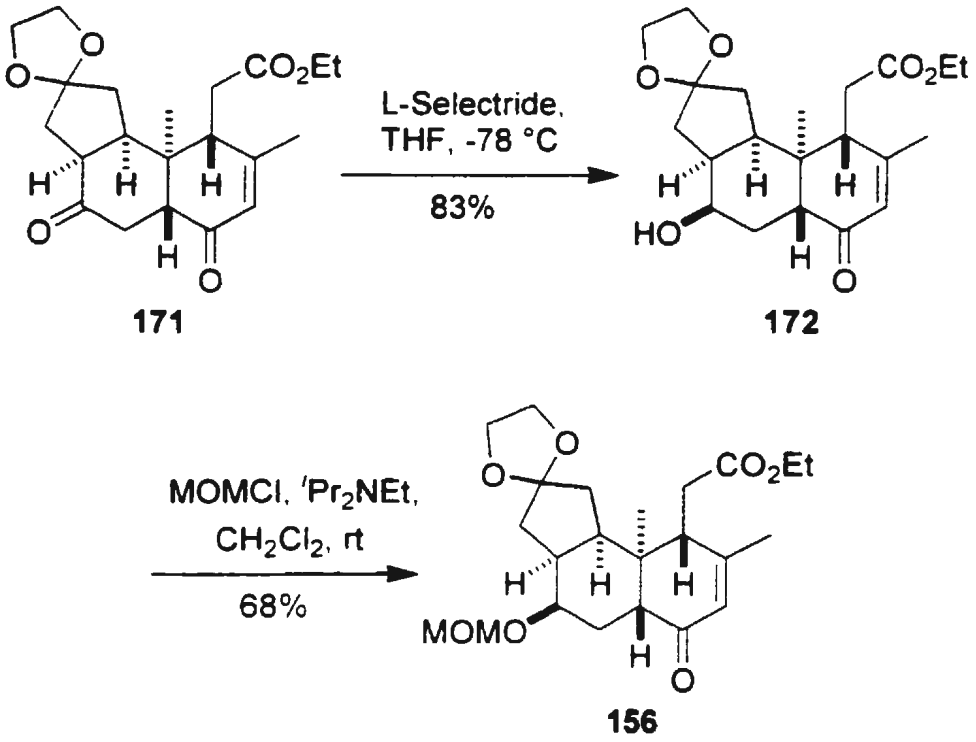
Scheme 51. Transformation of the dithiane to a cyclic acetal by Stork's conditions



137 **171**

Next, the saturated ketone in **171** was selectively reduced by L-Selectride to form **172**, followed by protection of the hydroxyl in **172** by MOMCl and $EtN(i\text{-}Pr)_2$ at room temperature in dichloromethane to produce **156** (Scheme 52).

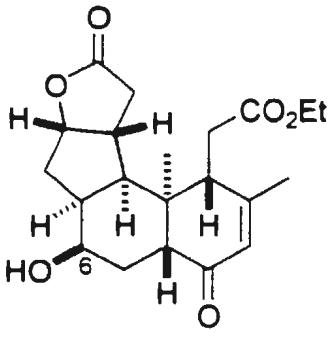
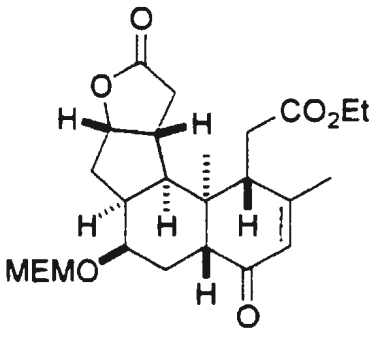
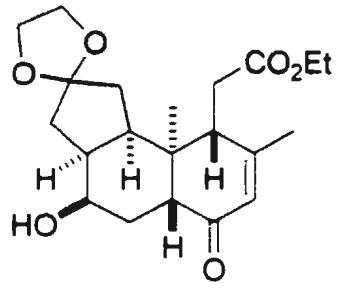
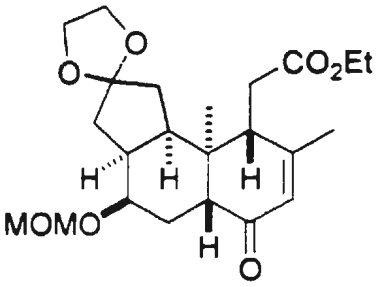
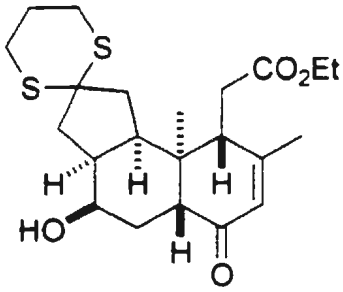
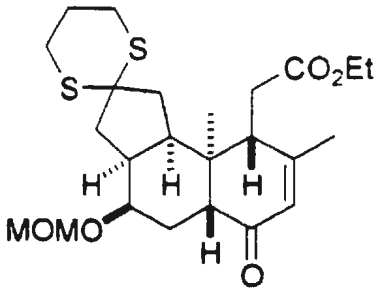
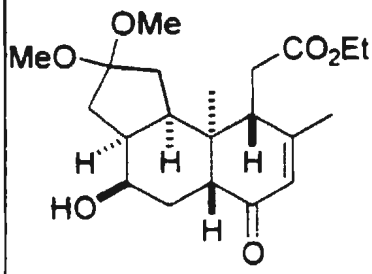
Scheme 52. Reduction and protection in **171**



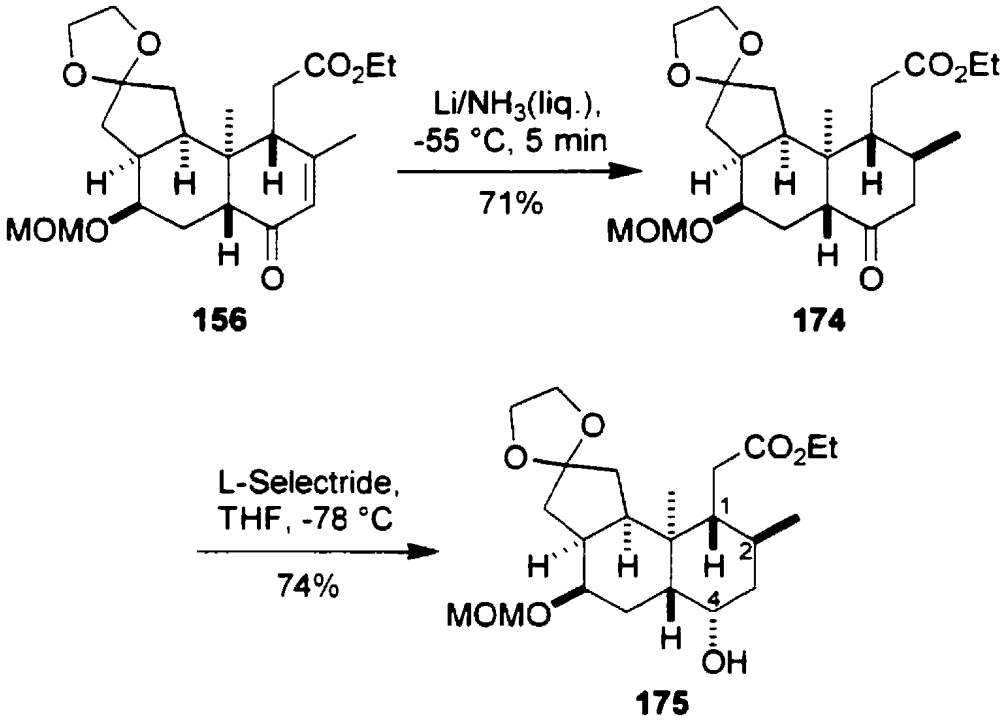
171 **172** **156**

The protection of the hydroxyl in **172** proceeded very smoothly and in high yield considering our previous problems. We believed that the lesser steric hindrance around the hydroxyl group in **172** made the protection easier to achieve (Table 4). The ease of the protection decreased in the order of **145** > **172** > **147** > **160**. After protection of **172** as the MOM ether, the enone double bond in **156** was reduced by lithium in liquid ammonia to give the expected product **174**. Next, the saturated ketone in **174** was stereoselectively reduced with L-Selectride to yield the axial alcohol **175** (Scheme 53). This provided the correct relative stereochemistry at C-4 for elaboration into kempene-2 (**1**).

Table 4. Comparison of protection of the C-6 hydroxyl group

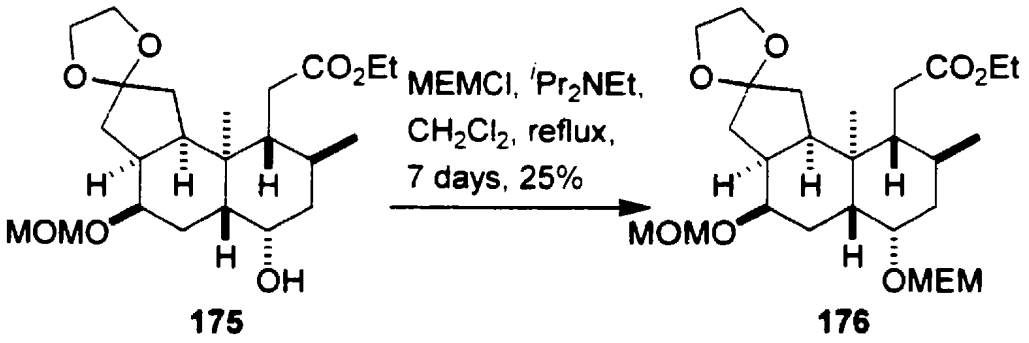
Substrate	Conditions	Product	Yield
 **145**	MEMCl, $^{i}Pr_2NEt$, CH_2Cl_2, reflux	 **173**	92%[22]
 **172**	MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, rt	 **156**	68%
 **147**	MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, reflux	 **148**	30-55%
 **160**	MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, reflux	no reaction	0%

Scheme 53. Reduction of **156**



It was surprisingly difficult to protect the axial hydroxyl group in **175**. This secondary hydroxyl group could not be protected as a methyl ether, a benzyl ether, or a TBS ether under various conditions. When **175** was treated with MEMCl and EtN(*i*-Pr)$_2$ in CH_2Cl_2 for 7 days, the corresponding MEM ether **176** was produced in low yield (Scheme 54).

Scheme 54. Protection of the hydroxyl in **175**

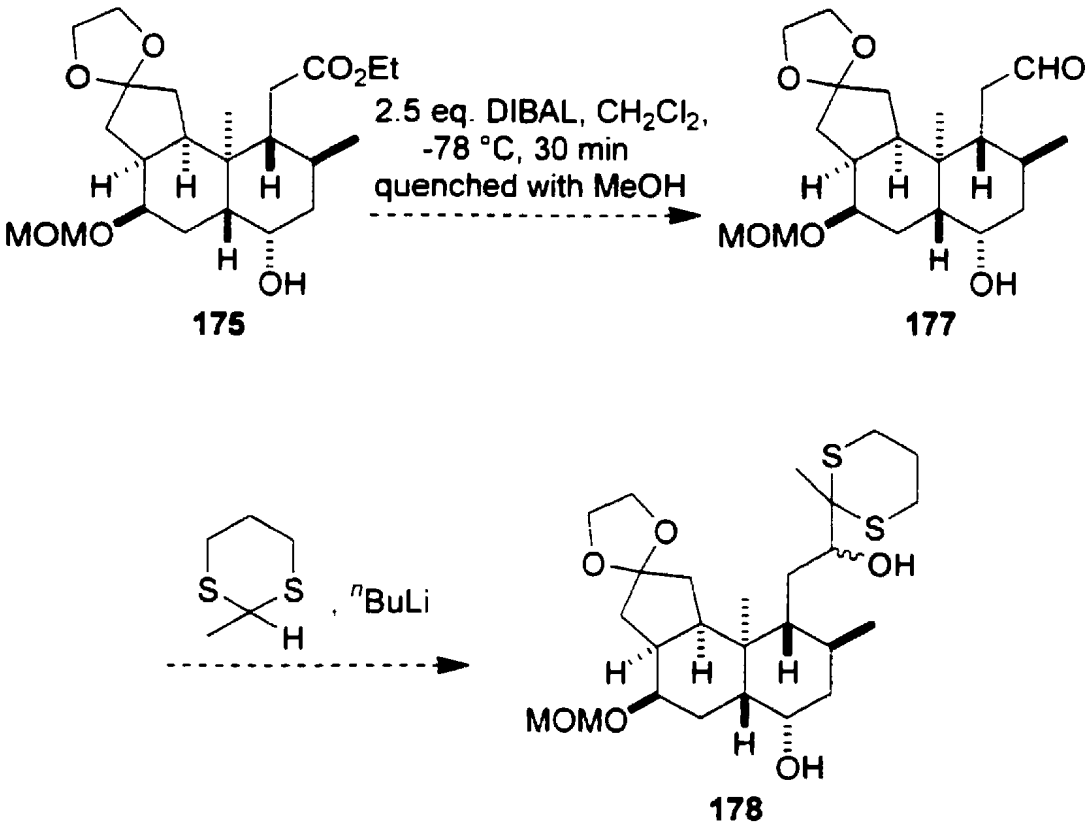


175 **176**

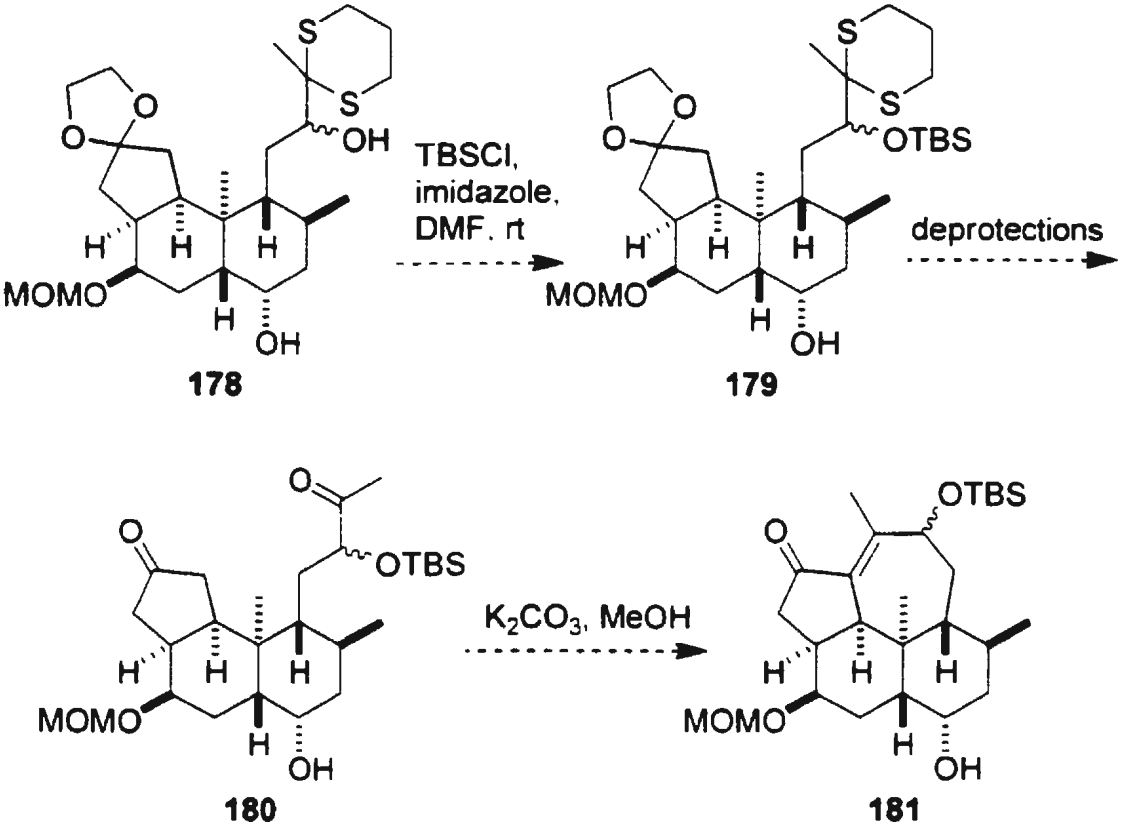
This is the point that has been reached in this synthesis. Due to the difficulty in the protection of **175**, it might be feasible for the secondary axial hydroxyl group of **175** to remain as a free hydroxyl group during the subsequent step (Scheme 55). In order to set up the four-carbon side chain, the ester group must be reduced to an aldehyde group, followed by a nucleophilic addition onto the aldehyde carbonyl with a dithiane anion, which can be generated from 2-methyl-1,3-dithiane and *n*-butyllithium. DIBAL is well known as the best reducing reagent for the reduction of an ester group to an aldehyde at –78 °C.[69] It is also possible that the reduction of the ester by DIBAL would give a primary alcohol, however there are many good methods for the oxidation of a primary alcohol to the aldehyde, so this would not be a problem. The secondary hydroxyl in the side chain of **178** should be more easily protected than the annular hydroxyl, which has shown itself to be fairly unreactive. Then, after deprotection of the acetal and

the thio-acetal, the intramolecular aldol condensation should afford the kempane ring system **181** (Scheme 56).

Scheme 55. Planned preparation of the four-carbon side chain



Scheme 56. Planned final stages in the synthesis of the kempane ring system

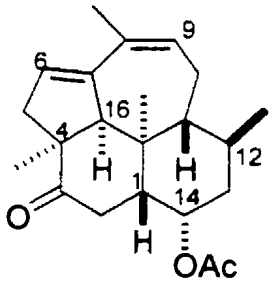


178 **179** **180** **181**

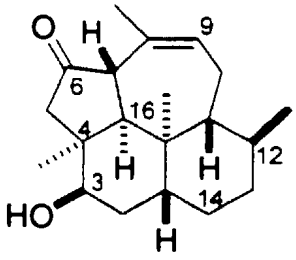
The kempane ring skeleton **181** possesses all of the required stereogenic centers and enough functional groups for elaboration of both of the kempane diterpenoids **1** and **2**. It is expected that the hydroxyl group in the seven-membered ring will ensure a carbon-carbon double bond in the correct position. A plan for completing the total synthesis will be found in a subsequent section.

1.5. Model Studies for the Introduction of the Methyl Group at C-4

In our synthetic plan outlined in Scheme 30, the methyl group at C-4 has to be installed very late in the synthesis. There may be some difficulty in introducing this methyl by 1,4-addition, because the conjugated ketone in the advanced intermediate is sterically hindered. If we could introduce this methyl at an earlier stage and preset all of the stereogenic centers, then cyclize the seven-membered ring, the synthesis might be more efficient.



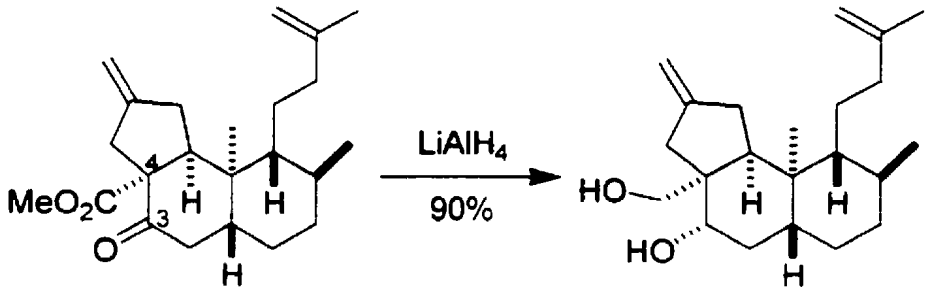
1



2

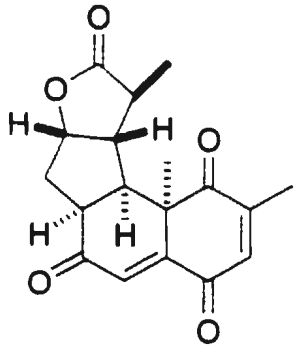
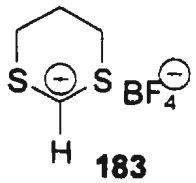
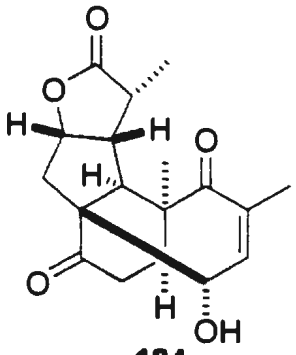
In Paquette's approach toward kempenone **2**, an ester group at C-4 influenced the reduction of the ketone at C-3, and gave the hydroxyl group with the incorrect stereochemistry (Scheme 57).[17] Similarly, the presence of a methyl group at C-4 might have the same effect on the reduction of the C-3 ketone. However, this strategy could be beneficial for the synthesis of kempane **1**, which contains a carbonyl at C-3.

Scheme 57. Reduction in Paquette's approach[17]



Diels-Alder adducts **33** and **80** possess all the annular carbons for both of the kempane diterpenoids. Since **33** and **80** contain a silyl enol ether unit, we expected that they might be good points to introduce the C-4 methyl group. The electron-rich carbon-carbon double bond of a silyl enol ether is extremely susceptible to attack by electrophiles[70] and electrophilic carbenes. During Dr. Liu's[71] research, a number of methods were investigated for the direct or indirect methylation of the silyl enol ether (Table 5), but none of those methods worked. We re-examined some of these methods, and found that the electrophilic reaction of a silyl enol ether with 1,3-dithienium tetrafluoroborate (**183**) and cyclopropanation of the silyl enol ether by a Simmons-Smith reaction were able to introduce a carbon at C-4 indirectly, which could then be convertible to a methyl group.

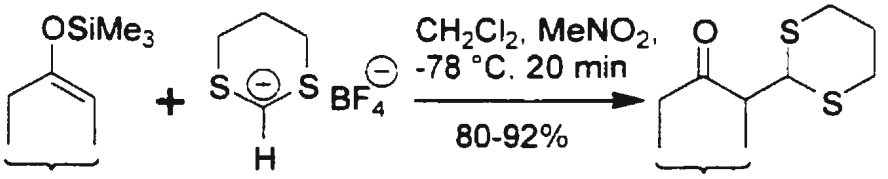
Table 5. Attempted methylation of the silyl enol ether in the research of Dr. Chunjian Liu[71]

Substrate	Reagents and conditions	Product	Reference for method
77	MeI, CF_3CO_2Ag, CH_2Cl_2, reflux, 12 h	starting material	72
77	CH_2I_2, Et_2Zn, THF, 50 °C, 10 h or CH_2Cl_2, reflux, 10 h	mainly starting material	73
77	$MeOCH_2Cl$, $TiCl_4$, rt, 12 h	very complex mixture	74
77	$PhSCH_2Cl$, $TiCl_4$, -15 °C, 2 h, rt, 1.5 h	 **182**	75
79	 **183** CH_2Cl_2, $MeNO_2$, -78 °C, 20 min	 **184**	76

1.5.1. Electrophilic Reaction of a Silyl Enol Ether with 1,3-Dithienium Tetrafluoroborate

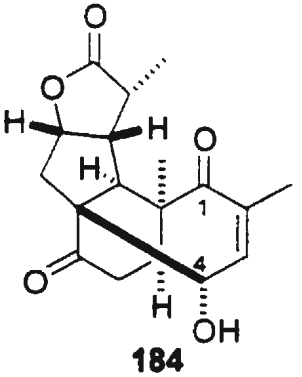
Corey's group[77] first prepared 1,3-dithienium tetrafluoroborate (**183**) in 1972. It was found that **183** is an excellent electrophile and reacts with silyl enol ethers at low temperature to produce high yields of products (Scheme 58).[76]

Scheme 58. Electrophilic reaction of a silyl enol ether with **183**



185 **183** **186**

In Dr. Liu's research,[71] when Diels-Alder adduct **79** was subjected to the same reaction conditions, **184** was obtained (Table 5). It was believed that the formation of **184** was due to an intramolecular Mukaiyama reaction of **79**. The



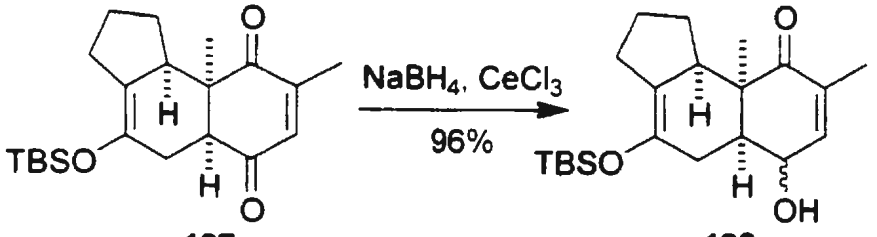
184

reaction was promoted by F^-, which just removed the TBS group, then the enolate attacked the C-4 carbonyl. This also provided us with a clue to make the

reaction proceed in the desired direction. If we reduce the carbonyl at C-4 in advance, the intramolecuar Mukaiyama reaction might be avoided.

We used a simpler Diels-Alder adduct to test this idea. The carbonyl at C-4 of the model compound **187** was selectivity reduced by sodium borohydride and cerium trichloride[78] to give a 1:1 mixture of epimers **188** (Scheme 59).

Scheme 59. Chemoselective reduction of enedione **187**

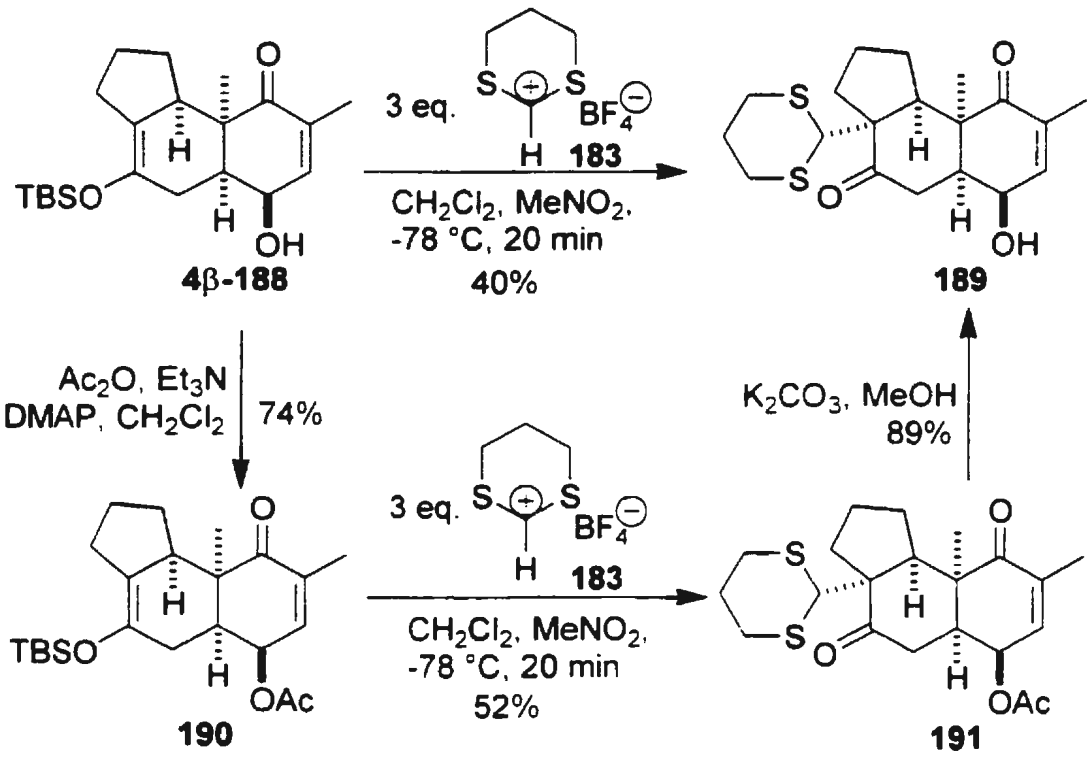


187 **188**

1 : 1 mixture

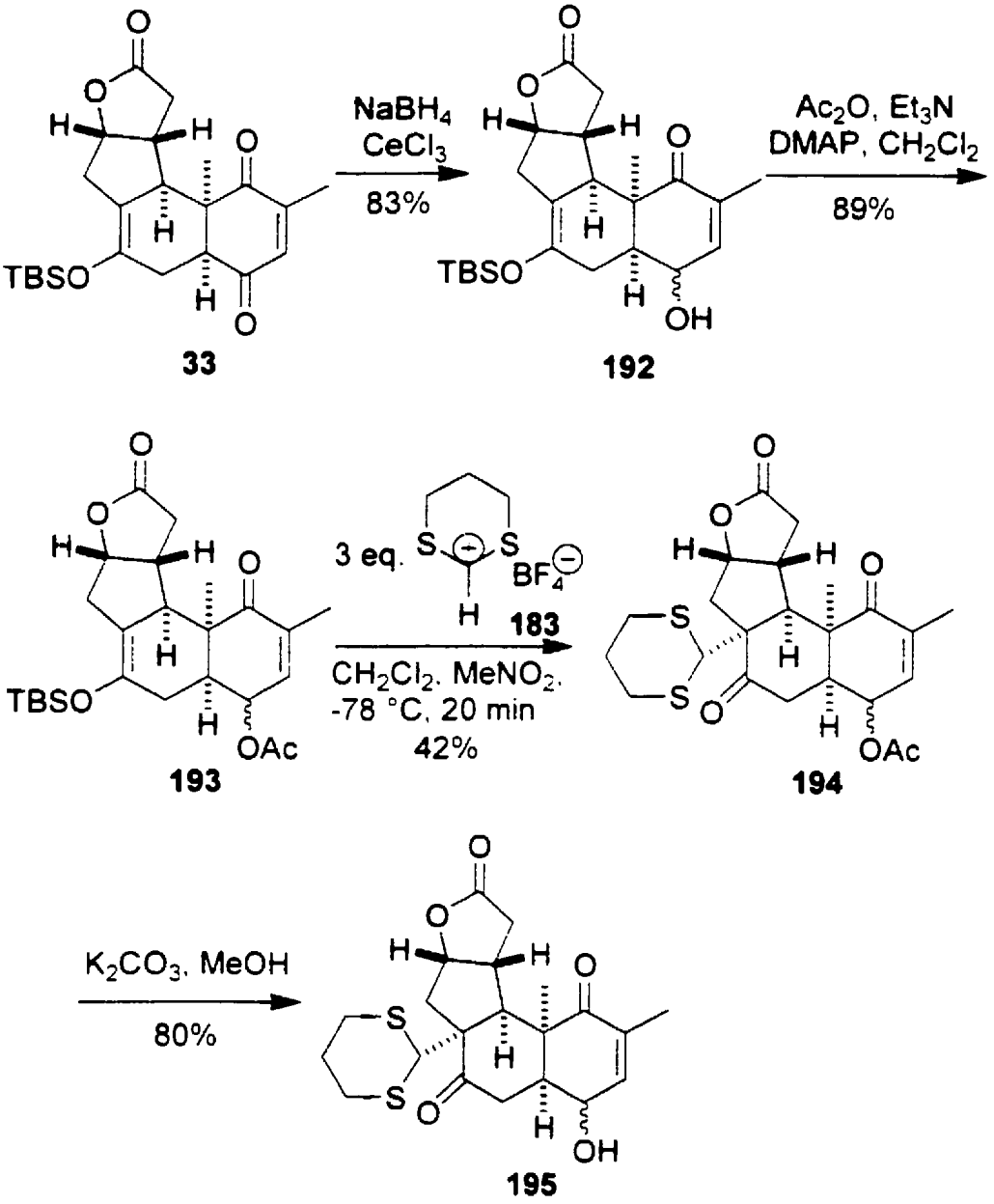
To the 4β-**188** was added 3 equivalents of 1,3-dithienium tetrafluoroborate (**183**) at –78 °C for 20 minutes to afford the expected product **189** (Scheme 60). The 1,3-dithiane group was expected to be reduced in a later step to provide a methyl group in the correct stereochemical manner. We also tried the protection of the hydroxyl group with acetate **190**, and then treated this with **183** to give **191**. Deprotection of **191** generated **189** in good yield.

Scheme 60. Electrophilic reaction of silyl enol ether with **183**



We applied this strategy to the Diels-Alder adduct **33** from the First Route (Scheme 61). The Diels-Alder product **33** was reduced[78] to **192** and the hydroxyl group was protected as the acetate **193**. Compound **193** reacted with 1,3-dithienium tetrafluoroborate (**183**) to yield **194**. The by-product was the hydrolysis product of the TBS-enol ether. Compound **194** was treated with K_2CO_3 in MeOH to produce **195**.

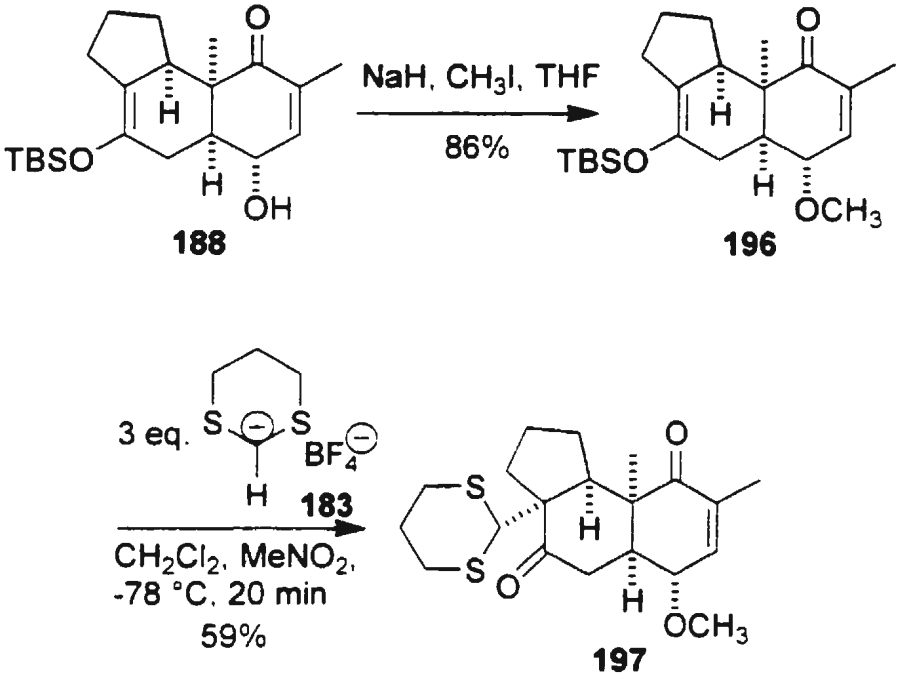
Scheme 61. Reaction of **193** with **183**



Another example we tried for this type of reaction was the methyl ether **196**. This was subjected to the same reaction conditions, and **197** was obtained

in 59% yield (Scheme 62). The relative stereochemistry of **197** was confirmed by X-ray analysis.

Scheme 62. Reaction of **196** with **183**



Because of the difficulty of protecting the hydroxyl as the methyl ether in the real system, we did not investigate the methyl ether further.

1.5.2. Cyclopropanation of the Silyl Enol Ether

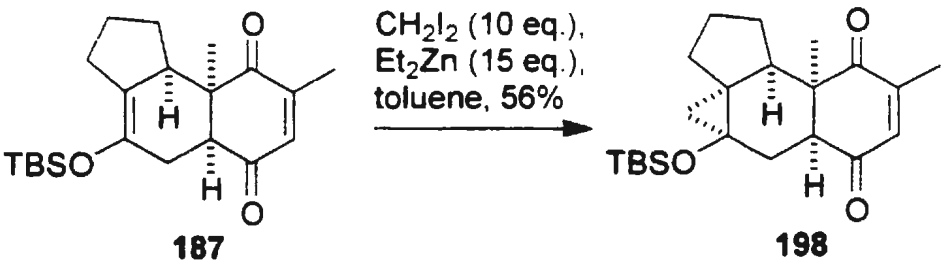
Simmons-Smith reaction[79] of the electron-rich C-C double bond of trimethylsilyl enol ethers provides an alternative method for the indirect introduction of the required methyl group. The original reagent for Simmons-Smith reaction was diiodomethane and zinc-copper couple.[79] The more reactive zinc-silver couple[80] was developed to replace zinc-copper couple, and diethyl

zinc[81] has been used more often in recent years. It was expected that the TBS enol ether has similar reactivity as the TMS enol ether for cyclopropanation. Ragauskas' study[80] showed that the increased stability of *tert*-butyldimethylsilyl derivatives relative to their trimethylsilyl counterparts leads to much more efficient conversion to allylic products resulting from cleavage of the cyclopropyl ring. Very few examples[80,82] can be found in the literature for cyclopropanation of a TBS enol ether.

We wondered if a Simmons-Smith reaction could be applied to our Diels-Alder adducts which contained a TBS enol ether unit, to produce a cyclopropyl ring in the molecule. The *cis*-decalin ring junction in the Diels-Alder adducts would ensure that the reaction took place from the convex side of the molecule. Thus, the correct stereochemistry of cyclopropane ring was expected. Also, it is known that trimethylsilyloxycyclopropanes can be converted to methyl and ketone regiospecifically by NaOH/MeOH[73] or *p*-TsOH/$CHCl_3$ [82]

Again, the model Diels-Alder adduct **187** was chosen to test this idea. It was treated with 10 equivalents CH_2I_2 and 15 equivalents Et_2Zn in toluene at room temperature to form the expected product **198** in 56% yield (Scheme 63). This reaction was highly stereoselective and the reagents for this reaction must be in considerable excess. The relative stereochemistry was indicated by NOE experiments between the angular methyl and a hydrogen in the cyclopropane ring.

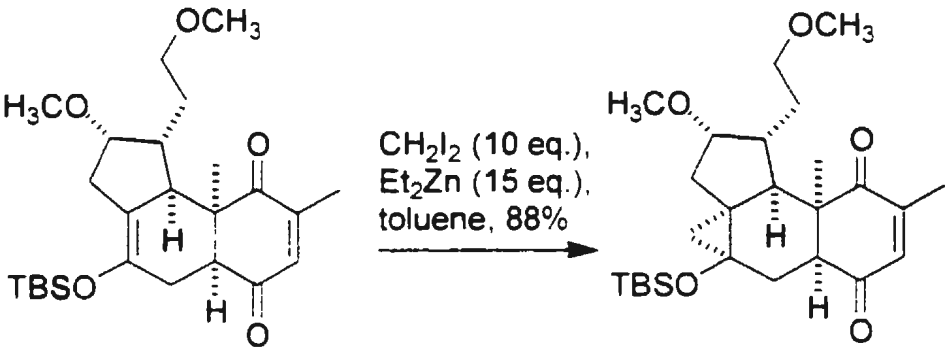
Scheme 63. Cyclopropanation of model compound **187**



187 **198**

This strategy was applied to Diels-Alder adduct **80** from the Diether Route (Scheme 64). Simmons-Smith reaction of **80** under the same conditions generated the expected product **199** in 88% yield.

Scheme 64. Cyclopropanation of **80**



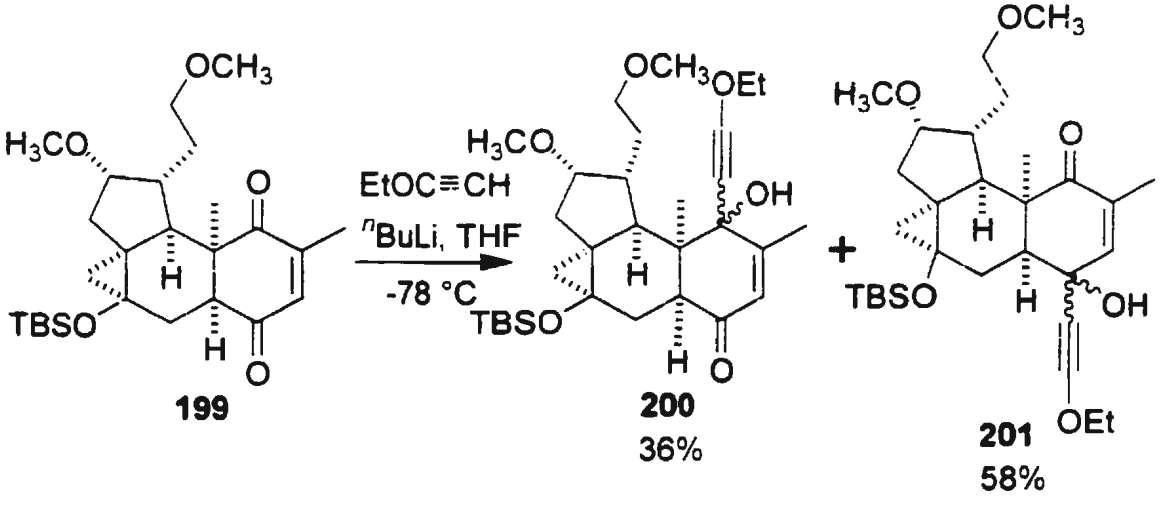
80 **199**

1.5.3. Acetylide Additions in Model Studies

After the success of the electrophilic reaction with **183** and the cyclopropanation of the Diels-Alder adducts in our model studies, the nucleophilic additions of lithium ethoxyacetylide to the enedione compounds (**198**, **199**, and

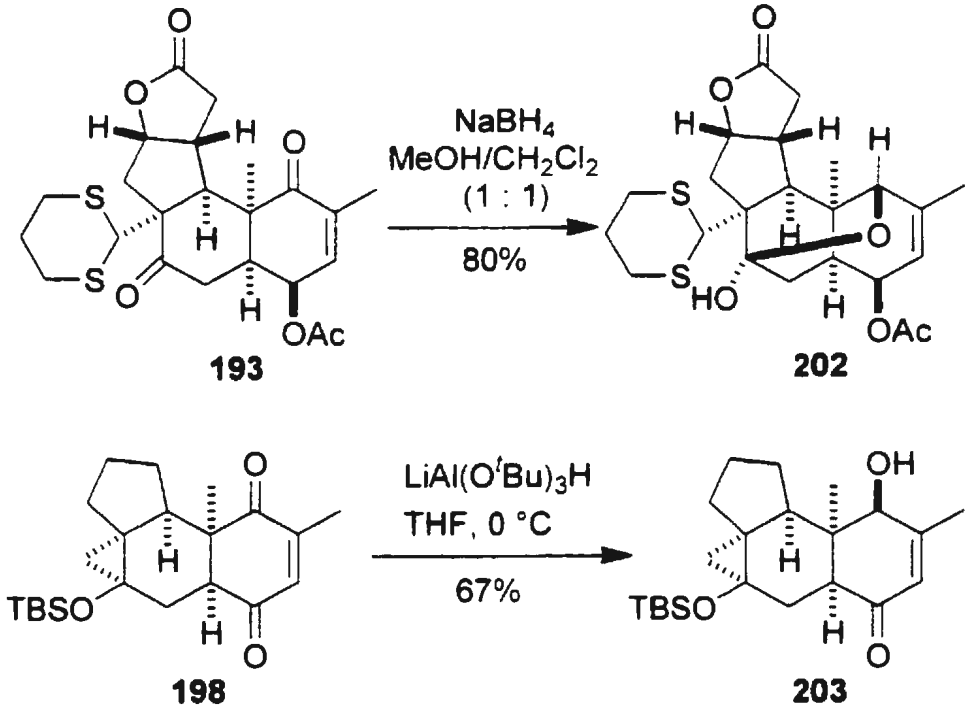
oxidation products of **189** and **195**) were examined. From our previous experience, we knew that acetylide additions of enedione compounds (**33**, **80** and **105**) occurred at the seemingly more hindered carbonyl position because of the preference of axial attack. Unfortunately, acetylide additions to the model compounds (**198**, **199**, and enediones from oxidation of **189** and **195**,) gave poor chemo- and stereoselectivity. For example, when enedione **199** was treated with lithium ethoxyacetylide at –78 °C, a mixture of regioisomers **200** and **201** was obtained and the undesired regioisomer **201** was the major product (Scheme 65). The reason for the loss of selectivity in the acetylide additions is not clear. One interpretation is that the model compounds had a strong preference for the non-selective conformation similar to **89**, which was shown in Scheme 25. In other words, the introduction of a dithiane group or cyclopropane ring in Diels-Alder adducts resulted in a compound with the "wrong" conformation.

Scheme 65. Acetylide addition to **199**



We also tried reductions of indirect-methylated products (Scheme 66). When compound **193** was treated with sodium borohydride in 1:1 mixture of methanol and dichloromethane, reduction took place at C-1 and bridged hemi-acetal **202** was obtained. The formation of bridged hemi-acetal **202** showed that this reduction is chemo- and stereoselective. Similarly, reduction of enedione **198** by lithium tri-*tert*-butoxyaluminohydride produced **203** in a highly chemo- and stereoselective manner.

Scheme 66. Reduction of indirectly methylated products



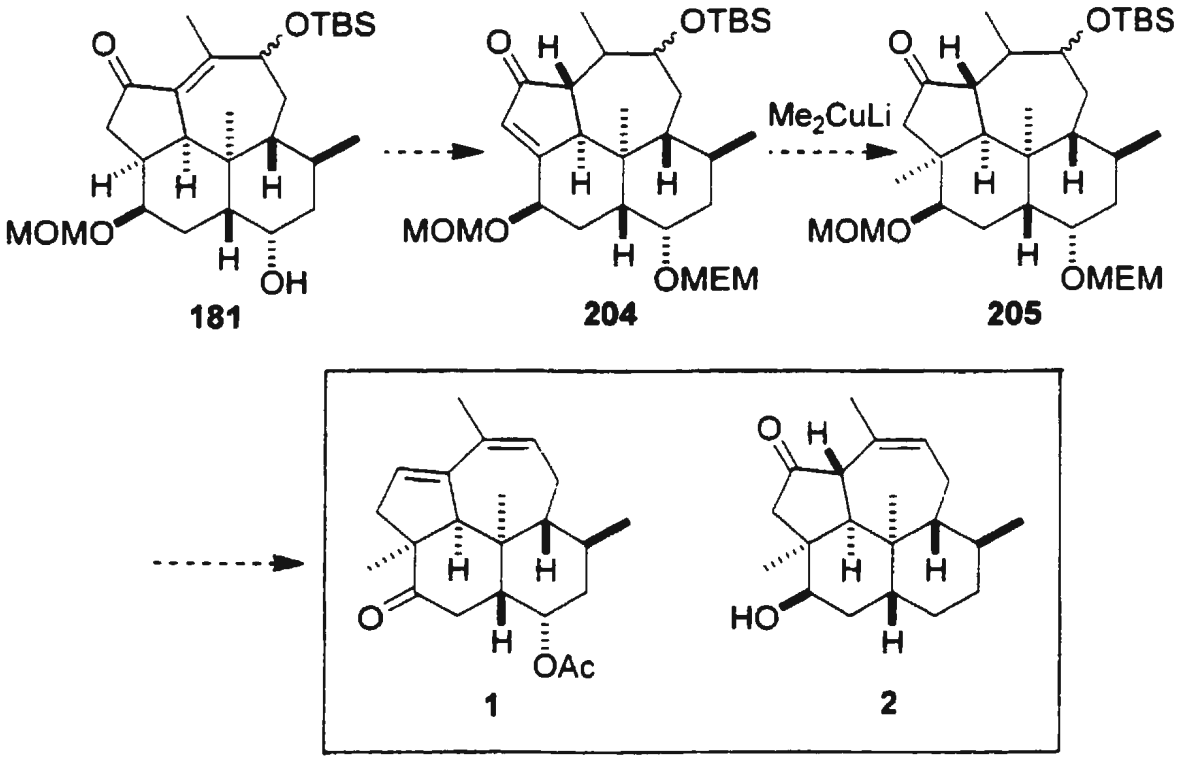
In conclusion, the model studies showed that indirect methylation of the TBS enol ether is possible, but poor regio- and stereoselectivity in the subsequent acetylide addition step made this strategy impractical.

1.6. Future Work

1.6.1. Completion of the Total Synthesis of Kempane Diterpenes (1 and 2)

Future work for finishing the total synthesis of both kempane diterpenes (**1** and **2**) from kempane ring system **181** is outlined in Scheme 67.

Scheme 67. Strategy to finish the total synthesis of kempane diterpenes



After completion of the kempane ring skeleton **181**, protection of the hydroxyl as the MEM ether will be required. It is expected that this protection will be easier after construction of the seven-membered ring. Reduction of the α,β-unsaturated ketone to the saturated ketone will be achieved by a dissolving metal

reduction, such as with lithium in liquid ammonia. The reduction with dissolving metal will in all likelihood give the thermodynamic product, with the correct relative stereochemistry in **204**.

In order to install the last methyl group, an α,β-unsaturated ketone must be introduced into the five-membered ring. Several methods to effect this operation have been developed over the years.[83] Most of the protocols depend on highly toxic selenium reagents in one- or two-step procedures.[84] Very recently, Nicolaou's group developed a one-step method for conversion of alcohols, ketones, and aldehydes to α,β-unsaturated carbonyl compounds with the use of IBX (*o*-iodoxybenzoic acid).[85] Another popular tactic involves palladium-catalyzed oxidation of the enol ether derived from the carbonyl compound.[86] It is expected that treating the carbonyl compound with LDA and TMSCl in the cold solution will trap the kinetic enolate. Oxidation of the silyl enol ether with palladium diacetate should produce the desired enone **204**.

With enone **204** in hand, the installation of the last methyl group will be expected by 1,4-addition. It is possible that the steric hindrance of Michael acceptor **204** will cause some difficulty in the 1,4-addition. However, the use of trimethylaluminum and nickel(II) acetylacetonate as the catalyst[23] should be able to make the reaction proceed as expected. The Michael donor would approach the α,β-unsaturated ketone from the opposite side of the MOM ether group at C-3 to provide an angular methyl with the correct stereochemistry.

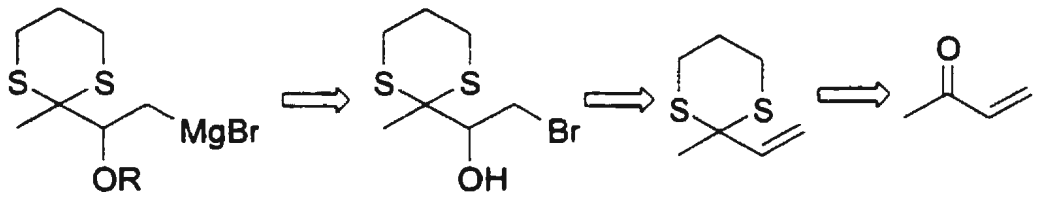
Now we will have set all of the stereogenic centers for both of kempane diterpenes. The rest of the transformations will involve manipulations of the protecting groups and introduction of a C-C double bond in the seven-membered ring. The alcohol function on the seven-membered ring will install the double bond in the desired position and will definitely avoid the problem in Paquette's synthesis.[17] For the conversion of **205** to kempane **1**, the conjugated diene system should be constructed first. Deprotection of the MEM group and reprotection with acetate, followed by deprotection of MOM group and oxidation of the resulting secondary alcohol should produce the naturally occurring kempane **1**. For the transformation to kempane **2** from **205**, the hydroxylation of MEM ether should be implemented before the introduction of C-C double bond in the seven-membered ring. Kempane **2** will be synthesized after deprotection of the MOM group.

1.6.2. Optimization Required for Some Steps

In the Dithiane Route, some steps need to be optimized by further studies. One weakness in this synthesis is the preparation of the side chain for the seven-membered ring cyclization in the advanced intermediate. If an appropriate nucleophilic reagent can be made in advance, nucleophilic addition of the Diels-Alder adduct will give a product, which is ready for final cyclization. Obviously, this strategy will be more efficient for the total synthesis. Two problems have to be resolved for this strategy. First, a Grignard reagent **206** will be used for nucleophilic addition. A proposed preparation of **206** is shown in Scheme 68. It is

reasonable to expect that **206** might be synthesized from butenone in a three-step sequence. More importantly, the regioselectivity of the nucleophilic addition of enedione with **206** needs to be investigated. The regioselectivity of nucleophilic addition at seemly more sterically hindered carbonyl would be the key to proceed with the synthesis. A model study may be necessary to assess the regioselectivity.

Scheme 68. Proposed synthesis of nucleophilic reagent



206

For the step of conjugation and epimerization of the β,γ-unsaturated ketones (**135** and **136**), *trans* **135** gave a good yield of expected product, but *cis* **136** gave the expected product in very low yield. It is quite possible that appropriate conditions might be found for the latter transformation.

1.7. 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 nitrogen or argon. Tetrahydrofuran (THF) 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. *N*, *N*-Dimethylformamide (DMF) was dried over anhydrous $MgSO_4$. Dry 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 thin-layer chromatography (TLC) when possible. TLC was performed on Polygram Sil G/UV_{254} plates, visualized under ultraviolet (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 an aqueous solution of HCl, $NaHCO_3$, NaCl, *etc.*

Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Mattson Polaris FT-IR spectrometer. The units in the infrared spectra are cm^{-1}. Nuclear magnetic resonance (NMR) spectra were obtained on a General Electric GE-300-NB (300 MHz) instrument or a Bruker Avance (500 MHz) instrument. ^1H NMR and ^{13}C NMR spectra were recorded on GE-300-NB at 300 MHz and 75 MHz,

respectively, in deuterated solvents. Low and high-resolution mass spectra (MS, HRMS) were obtained on a V. G. Micromass 7070HS instrument. GC-MS analyses were performed on Hewlett Packard 5890 instrument with a 12.5 m fused silica capillary column using crosslinked dimethylsilicone as the liquid phase. X-ray crystallographic data were collected by Dr. J. N. Bridson and Mr. D. Miller on a Rigaku AFC6S diffractometer. They are responsible for the structure solutions.

Spectroscopic data are reported in the order of IR, ^{1}H NMR, NOE (nuclear Overhauser effect enhancement), ^{13}C NMR, MS, and HRMS or combustion analysis. Media used for the acquisition of spectra are indicated in parentheses, where applicable. IR data are followed in parentheses by the following descriptors: s: strong, m: medium, w: weak, br: broad. ^{1}H NMR data are reported in the following form: chemical shift (number of protons, multiplicity, coupling constant, assignment). Chemical shifts are in ppm units relative to an internal standard, tetramethylsilane (TMS). Multiplicity is represented by the following designations: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: double doublet, br: broad. Assignments are based on COSY, HETCORR, APT, 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 as: chemical shift (number of protons attached to the carbon, assignment). MS data are reported as *m/z* (intensity relative to the largest peak in %). Molecular ions of less than 1% are generally not reported.

Ethyl (1α,2β,4α,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-2,3,4,4a,5,6,6a,7,7a,10,10a,10b,10c-tridecahydro-4-(methoxy)methoxy-6-(2-methoxyethoxy)methoxy-2,10c-dimethyl-9-oxo-1*H*-benz[6,7]indeno-[2,1-*b*]furan-1-methylcarboxylate (49)

To a solution of **48** (751 mg, 1.60 mmol) in dry CH_2Cl_2 (100 mL) was successively added chloromethyl methyl ether (1.22 mL, 16.0 mmol) and *N,N*-diisopropylethylamine (3.63 mL, 20.8 mmol). The solution was heated at reflux for 15 h before it was diluted with CH_2Cl_2 (100 mL), and then washed with 0.5% HCl (2 x 50 mL) and brine (50 mL). The resulting organic solution was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (95% EtOAc/hexane) to afford **49** (720 mg, 88%) as a white solid: mp 71-73 °C. IR (Nujol) 1721 (s), 1302 (s), 1169 (s), 1094 (s), 1036 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.11 (1H, dd, *J*=14.2, 7.7 Hz, H7a), 4.75 (1H, d, *J*=6.8 Hz, OCH_2O), 4.64 (1H, d, *J*=6.8 Hz, OCH_2O), 4.62 (1H, d, *J*=6.9 Hz, OCH_2O), 4.51 (1H, d, *J*=6.9 Hz, OCH_2O), 4.14 (2H, m, OCH_2CH_3), 3.73 (1H, m, H4), 3.69 (2H, dd, *J*=11.6, 4.9 Hz, $OCH_2CH_2OCH_3$), 3.61 (1H, m, H6), 3.55 (2H, t, *J*=4.0 Hz, $OCH_2CH_2OCH_3$), 3.39 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 2.89-2.76 (2H, m, H10β+H10a), 2.44-2.34 (2H, m, H6a and CH_2CO_2Et), 2.28 (1H, d, *J*=5.3 Hz, H10α), 2.24 (1H, dd, *J*=13.5, 7.8 Hz, H7β), 2.10 (1H, dd, *J*=16.9, 9.5 Hz, CH_2CO_2Et), 1.97-1.85 (2H, m, H2+H5α), 1.82-1.74 (4H, m), 1.68 (1H, dd, *J*=15.4, 7.7 Hz), 1.58 (1H, m), 1.27 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.24 (1H, m), 1.02 (3H,

s, 10c-methyl), 0.82 (3H, d, *J*=6.1 Hz, 2-methyl). NOE data 5.11 (2.89-2.76, 8%), 0.82 (1.82-1.74, 7%; 1.68, 4%). ^{13}C NMR ($CDCl_3$) δ 178.2 (0, C9), 173.6 (0, **C**O_2Et), 95.6 (2, OCH_2O), 94.2 (2, OCH_2O), 86.5 (1, C7a), 77.7 (1, C6), 75.2 (1, C4), 71.7 (2, CH_3O**C**H_2CH_2O), 67.5 (2, CH_3OCH_2**C**H_2O), 60.6 (2, O**C**H_2CH_3), 59.1 (3, OCH_3), 55.4 (3, OCH_3), 55.3 (1), 45.2 (1), 42.0 (1, C6a), 39.4 (2), 39.0 (0, C10c), 38.4 (1, C10a), 37.2 (2, C7), 35.5 (2, C10), 34.9 (1), 34.7 (2), 29.8 (1, C2), 29.7 (2), 20.0 (3, 2-methyl), 18.3 (3, 10c-methyl), 14.1 (3, OCH_2**C**H_3). MS *m/z* 423 (1), 391 (2), 373 (3), 363 (3), 361 (8), 345 (4), 315 (3), 299 (3), 269 (3), 257 (5), 256 (3), 197 (3), 195 (4), 167 (4), 119 (7), 105 (6), 93 (5), 89 (81), 59 (84), 45 (100). HRMS calcd. for $C_{27}H_{44}O_9$ 512.2983, found 512.2977.

(2aα,4aα,5α,7β,7aα,9α,9aβ,10aα,10bα,10cβ,10dβ)-2a,4,4a,5,6,7,7a,8,9,9a,10,10a,10b,10c,10d-Tetradecahydro-7-(methoxy)methoxy-9-(2-methoxyethoxy)methoxy-5,10d-dimethylnaphth[2,1,8-*cde*]-2*H*-azuleno[1,8-*bc*]furan-2,3-dione (50)

To a solution of **49** (81.5 mg, 0.159 mmol) in dry benzene (50 mL) was added NaH (40 mg, 1.6 mmol). The mixture was heated at reflux for 60 h before it was cooled to rt and washed with ice-cold 0.5% aqueous HCl (2 x 30 mL). The aqueous layer was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column

chromatography (95% EtOAc/hexane) to provide **50** (71.5 mg, 97%) as a white solid: mp 88-89 °C. IR (Nujol) 1776 (s), 1710 (s), 1159 (s), 1086 (m), 1043 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.89 (1H, m, H10a), 4.73 (1H, d, *J*=6.9 Hz, OCH_2O), 4.65 (2H, d, *J*=6.9 Hz, OCH_2OCH_3 and $OCH_2OCH_2CH_2OCH_3$), 4.52 (1H, d, *J*=6.9 Hz, OCH_2O), 3.79 (1H, br s), 3.73-3.66 (5H, m), 3.56 (2H, t, *J*=4.5 Hz, $CH_3OCH_2CH_2$), 3.40 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.23 (1H, m, H10b), 2.59 (1H, dd, *J*=16.8, 3.8 Hz, H3α), 2.49-2.36 (3H, m), 2.28 (1H, dd, *J*=14.3, 7.9 Hz), 2.06-2.00 (2H, m), 1.89-1.71 (3H, m), 1.67-1.53 (2H, m), 1.31-1.21 (2H, m), 1.12 (3H, s, 10d-methyl), 0.91 (3H, d, *J*=6.8 Hz, 5-methyl). NOE data 4.89 (3.23, 5%; 2.28, 4%), 3.23 (4.89, 6%; 3.73-3.66, 3%; 1.67-1.53, 6%), 0.91 (1.89-1.71, 7%; 2.59, 5%). ^{13}C NMR ($CDCl_3$) δ 203.1 (0, C3), 172.4 (0, C2), 95.6 (2, OCH_2O), 94.4 (2, OCH_2O), 83.3 (1, C10a), 77.3 (1, C9), 75.2 (1, C7), 71.7 (2, $CH_3OCH_2CH_2$), 67.6 (2, $CH_3OCH_2CH_2O$), 59.1 (3, OCH_3), 55.4 (3, OCH_3), 55.1 (1, C2a), 53.3 (1), 49.8 (1), 42.8 (2), 41.7 (1), 40.7 (2), 40.1 (1), 37.1 (0, C10d), 36.9 (2), 36.6 (1), 28.6 (2), 26.7 (1), 20.0 (3, 5-methyl), 17.7 (3, 10d-methyl). MS *m/z* 390 (9), 377 (5), 360 (4), 359 (5), 328 (6), 316 (5), 315 (13), 299 (9), 298 (9), 297 (5), 283 (6), 239 (6), 197 (6), 181 (5), 159 (5), 157 (5), 143 (5), 131 (6), 119 (6), 105 (9), 91 (12), 89 (87), 59 (100). HRMS calcd. for $C_{25}H_{38}O_8$ 466.2564, found 466.2542.

(2aα,3β,4aα,5α,7β,7aα,9α,9aβ,10aα,10bα,10cβ,10dβ)-2a,3,4,4a,5,6,7,7a,8,9,9a,10,10a,10b,10c,10d-Pentadecahydro-3-hydroxy-7-(methoxy)methoxy-9-(2-methoxyethoxy)methoxy-5,10d-dimethylnaphth[2,1,8-*cde*]-2*H*-azuleno[1,8-*bc*]furan-2-one (51)

To a solution of **50** (40 mg, 0.086 mmol) in methanol (10 mL) was added $NaBH_4$ (33 mg, 0.086 mmol) at rt. The reaction mixture was stirred at rt for 2h before it was quenched with water (10 mL). This mixture was extracted with EtOAc (4 x 20 mL), and the combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected column chromatography (95% EtOAc/hexane) to afford **51** (32 mg, 81%) as a viscous oil. IR (Nujol) 3434 (br s), 1710 (s), 1169 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.83 (1H, m, H10a), 4.72 (1H, d, *J*=7.3 Hz, OCH_2O), 4.65 (1H, d, *J*=7.3 Hz, OCH_2O), 4.63 (1H, d, *J*=6.8 Hz, OCH_2O), 4.51 (1H, d, *J*=6.8 Hz, OCH_2O), 3.90 (1H, br s, H3), 3.70-3.64 (4H, m, H7 and H9 and $CH_3OCH_2CH_2O$), 3.55 (2H, br t, *J*=4.3 Hz, $CH_3OCH_2CH_2O$), 3.39 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.20 (1H, t, *J*=7.0 Hz, H2a), 2.88 (1H, m, H10b), 2.44 (1H, br m), 2.17-2.08 (2H, m), 2.04 (1H, m), 1.99 (1H, dd, *J*=3.8, 2.2 Hz), 1.90 (1H, d, *J*=3.0 Hz), 1.85 (1H, d, *J*=3.6 Hz), 1.80 (2H, br t, *J*=6.4 Hz), 1.75-1.72 (2H, m), 1.69-1.53 (3H, m), 1.17 (1H, dd, *J*=14.5, 3.7 Hz), 1.09 (3H, s, 10d-methyl), 0.95 (3H, d, *J*=6.6 Hz, 5-methyl), 0.65 (1H, dd, J=10.7, 7.0 Hz). NOE data 3.90 (3.20, 11%; 0.65, 10%), 2.88 (4.83, 6%), 2.44 (3.70-3.64, 5%), 1.09 (1.75-1.72, 12%). ^{13}C NMR ($CDCl_3$) δ 178.7 (0, C2), 95.6 (2, OCH_2O), 94.7 (2, OCH_2O), 85.9 (1, C10a), 77.7 (1, C7),

76.2 (1, C9), 73.5 (1, C3), 71.7 (2, $CH_3O\mathbf{C}H_2CH_2O$), 67.5 (2, $CH_3OCH_2\mathbf{C}H_2O$), 59.1 (3, OCH_3), 55.4 (3, OCH_3), 52.0 (1), 49.6 (1), 46.3 (1, C2a), 43.8 (1), 41.3 (1), 41.2 (2), 38.0 (1), 36.2 (0, C10d), 33.4 (2), 30.5 (2), 29.2 (2), 27.3 (1), 20.0 (3, 5-methyl), 18.6 (3, 10d-methyl).

(2aα,3β,4aα,5α,7β,7aα,9α,9aβ,10aα,10bα,10cβ,10dβ)-2a,3,4,4a,5,6,7,7a,8,9,9a,10,10a,10b,10c,10d-Pentadecahydro-3-(*tert*-butyldimethylsilyl)oxy-7-(methoxy)methoxy-9-(2-methoxyethoxy)methoxy-5,10d-dimethylnaphth[2,1,8-*cde*]-2*H*-azuleno[1,8-*bc*]furan-2-one (52)

To a solution of **51** (17 mg, 0.036 mmol) in dry CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.064 mL, 0.54 mmol) and *tert*-butyldimethylsilyl triflate (TBSOTf) (0.085 mL, 0.36 mmol) at rt. The reaction mixture was stirred at rt for 6 h before it was diluted with CH_2Cl_2 (100 mL). This mixture was washed with 0.5% aqueous HCl (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (40% EtOAc/hexane) to afford **52** (20 mg, 95%) as a white solid: mp 145-146 °C. IR (CH_2Cl_2) 1775 (s), 1422 (s), 1155 (m), 1037 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.82 (1H, m, H10a), 4.71 (1H, d, *J*=7.0 Hz, OCH_2O), 4.65 (1H, d, *J*=6.9 Hz, OCH_2O), 4.63 (1H, d, *J*=7.0 Hz, OCH_2O), 4.58 (1H, dd, *J*=7.9, 4.2 Hz, H3), 4.52 (1H, d, *J*=6.9 Hz, OCH_2O), 3.75 (1H, m), 3.72-3.65 (2H, m), 3.65 (1H, d, *J*=3.3 Hz), 3.55 (2H, t, *J*=4.5 Hz), 3.39 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.34 (1H, dd, *J*=12.5, 6.8 Hz), 2.93 (1H, dd, *J*=12.3, 9.0 Hz), 2.74 (1H, dd, *J*=10.8, 3.9 Hz), 2.33 (1H,

m), 2.23 (1H, dd, *J*=13.9, 7.8 Hz), 2.19 (1H, dd, *J*=12.0, 3.9 Hz), 1.96 (2H, br dd, *J*=12.0, 1.8 Hz), 1.87-1.73 (5H, m), 1.54 (1H, m), 1.13 (3H, s, 10d-methyl), 1.04 (1H, m), 0.86 (3H, d, *J*=3.2 Hz, 5-methyl), 0.85 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) 178.3 (0, C2), 95.6 (2, OCH_2O), 94.3 (2, OCH_2O), 83.4 (1, C10a), 78.1 (1), 75.6 (1), 71.7 (2, $CH_3OCH_2CH_2O$), 70.4 (1, C3), 67.3 (2, $CH_3OCH_2CH_2O$), 59.1 (1), 55.3 (3, OCH_3), 52.1 (3, OCH_3), 47.2 (1), 46.2 (1), 41.7 (1), 41.4 (2), 41.0 (1), 37.3 (2), 37.1 (1), 36.2 (0, C10d), 34.3 (2), 29.1 (2), 27.4 (1), 25.8 (3, $SiC(CH_3)_3$), 20.5 (3, 5-methyl), 17.8 (0, $SiC(CH_3)_3$), 17.5 (3, 10d-methyl), -3.6 (3, $SiCH_3$), -5.9 (3, $SiCH_3$). MS *m/z* 378 (1), 377 (2), 376 (2), 363 (2), 334 (3), 333 (8), 317 (4), 315 (5), 299 (3), 257 (5), 209 (2), 197 (2), 191 (3), 167 (5), 157 (3), 151 (3), 143 (2), 131 (4), 107 (5), 93 (5), 89 (89), 59 (93), 45 (100). HRMS calcd. for $C_{31}H_{54}O_8Si$ 582.3585, found (to be determined).

(2aα,3β,4aα,5α,7β,7aα,9α,9aβ,10aα,10bα,10cβ,10dβ)-2,2a,3,4,4a,5,6,7,7a,8,9,9a,10,10a,10b,10c,10d-Hexadecahydro-3-(*tert*-butyldimethylsilyl)oxy-7-(methoxy)methoxy-9-(2-methoxyethoxy)methoxy-5,10d-dimethylnaphth[2,1,8-*cde*]-2*H*-azuleno[1,8-*bc*]furan-2-ol (54)

To a solution of **52** (62 mg, 0.11 mmol) in THF (10 mL) was added diisobutylaluminum hydride (DIBAL) (0.35 mL, 1.5 M solution in toluene, 0.53 mmol) at –78 °C. The resulting mixture was allowed to warm to rt and kept at rt

with stirring for 4 h. The reaction mixture was quenched with methanol (1 mL), diluted with EtOAc (100 mL), and washed with 0.5% aqueous HCl solution (20 mL) and brine (20 mL). The resulting organic solution was dried with anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane) to provide the mixture of epimers **54** (52 mg, 84%). ^{1}H NMR ($CDCl_3$) 5.51 (1H, d, *J*=5.1 Hz, H2), 5.48 (1H, d, *J*=4.8 Hz, H2), 4.74 (1H, m, H10a), 4.70 (1H, d, *J*=6.9 Hz, OCH_2O), 4.65 (1H, d, *J*=6.9 Hz. OCH_2O), 4.61 (1H, d, *J*=6.8 Hz, OCH_2O), 4.51 (1H, d, *J*=6.8 Hz, OCH_2O), 4.08-4.39 (2H, m), 3.70-3.62 (m), 3.56-3.53 (m), 3.39 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.10 (1H, s, OH), 2.77-2.50 (m), 2.41-2.35 (m), 2.13 (1H, dd, *J*=12.9, 7.0 Hz), 2.50-1.50 (m), 1.16 (1H, m), 1.07 (3H, s, 10d-methyl), 0.91 (3H, d, *J*=7.3 Hz, 5-methyl), 0.90 (9H, s, $SiC(CH_3)_3$), 0.74 (1H, m), 0.10 (6H, s, $Si(CH_3)_2$, 0.09 (3H. s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) 102.1 (1, C2), 100.0 (1, C2), 95.6 (2, OCH_2O), 94.7 (2, OCH_2O), 94.5 (2, OCH_2O), 88.9 (1, C10a), 85.3 (1, C3), 78.0 (1), 76.8 (1), 74.5 (1), 73.8 (1), 71.7 (2, $CH_3O\mathbf{C}H_2CH_2O$), 67.2 (2. $CH_3OCH_2\mathbf{C}H_2O$), 67.1 (2. $CH_3OCH_2\mathbf{C}H_2O$), 59.1 (3, OCH_3), 55.3 (3, OCH_3), 52.6 (1), 51.5 (1), 50.6 (1), 49.2 (1), 49.0 (1), 48.5 (1), 46.4 (1), 44.3 (1), 42.6 (1), 42.1 (1), 41.4 (2), 37.7 (1), 37.6 (2), 37.2 (1), 36.2 (2), 34.9 (2), 31.7 (2), 30.8 (2), 29.5 (2), 29.1 (2), 27.3 (1), 27.0 (1), 25.9 (3, $SiC(\mathbf{C}H_3)_3$), 25.8 (3, $SiC(\mathbf{C}H_3)_3$), 20.6 (3, 5-methyl), 20.2 (3, 5-methyl), 18.5 (3, 10d-methyl), 18.4 (3, 10d-methyl), 18.0 (0, $Si\mathbf{C}(CH_3)_3$), -4.4 (3H, $SiCH_3$), -4.8 (3, $SiCH_3$), -4.9 (3, $SiCH_3$), -5.2 (3, $SiCH_3$).

***syn* and *anti* 3-Methyl-2-cyclohexen-1-one, *p*-toluenesulfonylhydrazone (57)**

A mixture of 3-methyl-2-cyclohexen-1-one (**45**) (22.5 g, 200 mmol) and *p*-toluenesulfonylhydrazine (38.4 g, 200 mmol) in THF (280 mL) with a catalytic amount of concentrated hydrochloric acid (1.5 mL) was stirred at rt overnight. To the resulting red solution was added benzene (200 mL), and the mixture was concentrated under vacuum. This operation was repeated three times with 200 mL of benzene. The residue was solidified by adding Et_2O, and the solid was dried in a desiccator over $CaCl_2$ under vacuum for 24 h to afford the crude hydrazone **57** (57.8 g) as a beige solid. The crude **57** was a 2:1 mixture of stereoisomers. This mixture was fairly pure, and used in the next step without purification.

***cis*-8,8-Dichloro-3-methylbicyclo[4.2.0]oct-2-en-7-one (59)**

To a mechanically stirred suspension of the crude hydrazone **57** (28.9 g, approximately 100 mmol) in anhydrous Et_2O (150 mL) was introduced MeLi (1.4 M in Et_2O, 157 mL, 220 mmol) at 0 °C over 3 h. The mixture was stirred at rt for 15 h before it was carefully quenched with water (200 mL). The organic layer was separated, and the aqueous layer was extracted with pentane (3 x 60 mL). The combined organic solutions were washed with 5% HCl (2 x 60 mL), saturated $NaHCO_3$ solution (60 mL) and brine (60 mL). This solution of 1-methyl-1,3-cyclohexadiene (**58**) was first dried over anhydrous Na_2SO_4 and then over solid KOH.

To the above solution was added dry triethylamine (26.8 mL, 193 mmol) and then dichloroacetyl chloride (26.0 g, 175 mmol) in dry pentane at rt with stirring over 3 h. The resulting mixture was stirred for a further 3.5 h. A precipitate was removed by suction filtration. The filter cake was extracted with pentane twice. The combined organic solutions were washed with water (200 mL), saturated $NaHCO_3$ solution (3 x 130 mL) and brine (2 x 130 mL). The organic solution was dried over anhydrous $MgSO_4$ and concentrated under vacuum. Distillation of the residue under vacuum provided crude **59** (11.4 g) at 75-91 °C/3 mm Hg. The bulk of the distilled product was used in the next step without further purification.

***cis*-3-Methylbicyclo[4.2.0]oct-2-en-7-one (60)**

To a mixture of **59** (11.4 g, approximately 55.4 mmol) and NH_4Cl (23.5 g, 44.7 mmol) in MeOH (300 mL) was added Zn dust (47.9 g, 730 mmol) in potions with stirring at 0 °C over 1 h. The mixture was then stirred at rt for 10 h. Et_2O (150 mL) was added to the mixture, and the solid was removed by filtration. The filtrate was concentrated under vacuum. The residue was dissolved in water (200 mL) and extracted with Et_2O (4 x 50 mL). The combined extracts were washed with water (40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. Distillation of the residue under vacuum provided **60** (4.34 g) at 70-80 °C/5 mm Hg as a colorless oil. This distilled product was fairly pure and was used in the next step without further purification.

***cis*-3a,6,7,7a-Tetrahydro-5-methyl-2(3*H*)-benzofuranone (46)**

To a solution of **60** (4.34 g, approximately 31.9 mmol) in glacial AcOH (30 mL) was added 30% H_2O_2 (9.00 g, 79.4 mmol) at 0 °C over 10 min. The solution was stirred at 0 °C for 15 h before it was poured into a mixture of CH_2Cl_2 (100 mL) and water (100 mL). This mixture was neutralized by adding solid Na_2CO_3 until CO_2 evolution ceased. After separation of the organic layer, the aqueous layer was re-extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to flash column chromatography (55% Et_2O/hexane) to afford **46** (4.05 g, 27% overall yield from **45**) as a colorless oil: IR (neat) 1779 (s), 1158 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.16 (1H, br s, H4), 4.73 (1H, m, H7a), 2.97 (1H, m, H3a), 2.75 (1H, dd, *J*=17.1, 8.5 Hz, H3 *syn* to H3a), 2.27 (1H, dd, *J*=17.1, 2.9 Hz, H3 *anti* to H3a), 2.18-2.07 (2H, m, H6 and H7), 1.90-1.71 (2H, m, H6 and H7), 1.67 (3H, s, 5-methyl). NOE data 4.73 (2.97, 2%), 2.75 (2.97, 2%). ^{13}C NMR ($CDCl_3$) δ 177.1 (0, C2), 136.1 (0, C5), 119.7 (1, C4), 77.6 (1, C7a), 36.3 (2, C3), 34.8 (1, C3a), 24.9 (2), 23.9 (2), 23.7 (3, 5-methyl). MS *m/z* 152 (M^+, 24), 110 (27), 109 (14), 102 (14), 95 (29), 93 (100), 92 (22), 91 (21), 88(14), 86 (51), 85 (19), 82 (17), 81 (26), 79 (22), 77 (21), 68 (31), 67 (29), 63 (18), 62 (17), 60 (34), 56 (18), 53 (19), 51 (15). HRMS calcd. for $C_9H_{12}O_2$ 152.0837, found 152.0845.

***cis*-5-Acetyl-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (47)**

To a solution of **46** (12.0 g, 79.0 mmol) in CH_2Cl_2 (750 mL) was introduced ozone at –78 °C until a blue color persisted. The excess ozone was removed by bubbling nitrogen through the solution until the blue color disappeared. Me_2S (45 mL) was added, and the mixture was allowed to warm to rt as it was stirred overnight. The solvent and excess Me_2S were removed under vacuum. The residue was dissolved in THF (350 mL) and combined with a 5% aqueous HCl solution (350 mL). The mixture was heated at reflux overnight (15-20 h). Most of the THF was removed under vacuum, and the remaining aqueous solution was extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (3% MeOH/$CHCl_3$) to provide **47** (5.60 g, 42%) as a white solid: mp 109.0-111.0 °C. IR (CH_2Cl_2) 1751 (s), 1662 (s), 1426 (m), 1173 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.46 (1H, d, *J*=1.3 Hz, H4), 5.18 (1H, apparent t, *J*=5.5 Hz, H6a), 3.77 (1H, m, H3a), 3.02-2.91 (2H, m, H6), 2.88 (1H, dd, *J*=18.0, 10.2 Hz, H3 *syn* to H3a), 2.56 (1H, dd, *J*=18.0, 2.0 Hz, H3 *anti* to H3a), 2.35 (3H, s, $COCH_3$). ^{13}C NMR ($CDCl_3$) δ195.8 (0, $COCH_3$), 175.5 (0, C2), 143.9 (0, C5), 141.0 (1, C4), 82.3 (1, C6a), 46.6 (1, C3a), 37.8 (2, C6), 32.4 (2, C3), 26.8 (3, $COCH_3$). MS *m/z* 166 (M^+, 8), 151 (25), 122 (11), 95 (20), 67 (29), 65 (10), 51 (11), 43 (100). HRMS calcd. for $C_9H_{10}O_3$ 166.0629, found 166.0628.

***cis*-5-(2-(2-Methyl-1,3-dioxolan-2-yl))-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (67)**

To a solution of **47** (2.28 g, 13.7 mmol) in benzene (150mL) was added 1,2-ethanediol (7.75 mL, 137 mmol) and a catalytic amount of oxalic acid (631 mg, 6.87 mmol). The mixture was heated at reflux in a Dean-Stark water separator for 15 h. The solvent was removed under vacuum. The residue was dissolved in EtOAc (300mL), and washed with saturated $NaHCO_3$ solution (2 x 50 mL), brine (50 mL), and dried over anhydrous $MgSO_4$. After removing the solvent under vacuum, the residue was subjected to column chromatography (60% EtOAc/hexane) to provide **67** (2.08 g, 72%) as a yellow oil: IR (Nujol) 1714 (s), 1660 (s), 1616 (m), 1293 (s), 1170 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.57 (1H, d, J=1.7 Hz, H4), 5.14 (1H, m, H6a), 4.00-3.95 (2H, m, OCH_2CH_2O), 3.87-3.83 (2H, m, OCH_2CH_2O), 3.55 (1H, m, H3a), 2.83 (1H, dd, J=18.0, 9.7 Hz, H3 *syn* to H3a), 2.76-2.72 (2H, m, H6), 2.45 (2H, dd, J=18.0, 1.7 Hz, H3 *anti* to H3a), 1.49 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 176.4 (0, C2), 144.7 (0, C5), 126.4 (1, C4), 106.4 (0, -OCO-), 83.4 (1, C6a), 64.7 (2, OCH_2CH_2O), 64.6 (2, OCH_2CH_2O), 45.3 (1, C3a), 38.5 (2, C6), 33.3 (2, C3), 23.8 (3, CH_3). MS *m/z* 195 (M^+-15, 1), 166 (11), 151 (40), 122 (9), 95 (23), 67 (23), 51 (8), 43 (100). HRMS calcd. for $C_{11}H_{14}O_4$ 210.0892, found 210.0893.

***cis*-2-((1-Hydroxy-2-(2-hydroxylethyl))cyclopenten-4-yl)-2-methyl-1,3-dioxolane (68)**

To a solution of **67** (125 mg, 0.590 mmol) in anhydrous Et_2O (10 mL) was added $LiAlH_4$ (45.0 mg, 1.18 mmol) at rt. The reaction mixture was allowed to stir at rt for 3 h. The reaction mixture was quenched with $NaHSO_4$ solution (0.28 M, 2 mL), and extracted with EtOAc (3 x 40 mL). The combined organic solution was washed with brine (40 mL), dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the residue was subjected to column chromatography (95% EtOAc/hexane) to afford **68** (100 mg, 80%) as a pale-yellow oil: IR (Nujol) 3408 (s), 1670 (s), 1242 (s), 1045 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.56 (1H, m, H3), 4.48 (1H, ddd, *J*=9.3, 6.3, 3.1 Hz, H1'), 3.98-3.95 (2H, m, OCH_2CH_2O), 3.93-3.88 (2H, m, OCH_2CH_2O), 3.80 (1H, m, CH_2OH), 3.67 (1H, m, CH_2OH), 2.80 (1H, m, H2'), 2.67 (1H, ddt, *J*=16.6, 7.0, 2.2 Hz, H5), 2.36 (1H, dm, *J*=16.6 Hz, H5), 1.94-1.70 (2H, m, CH_2), 1.49 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.2 (0, C4'), 128.5 (1, C3'), 107.0 (0, OCO), 72.6 (1, C1'), 64.6 (2, OCH_2CH_2O), 64.6 (2, OCH_2CH_2O), 61.6 (2, CH_2OH), 49.0 (1, C2'), 40.4 (2, C5'), 30.3 (2, CH_2CH_2OH), 23.7 (3, CH_3). MS *m/z* 199 (M^+-15, 1), 169 (1), 152 (2), 141 (1), 139 (4), 125 (2), 121 (3), 111 (3), 109 (4), 87 (23), 73 (11), 43 (100). HRMS calcd. for $C_{11}H_{18}O_4$ 214.1205. found 214.1223.

cis-2-((4-Methoxy-3-(2-methoxyethyl))cyclopenten-1-yl)-2-methyl-1,3-dioxolane (69)

To a solution of **68** (215 mg, 1.00 mmol) in THF (40 mL) was added NaH (120 mg, 5.00 mmol) and CH_3I (0.62 mL, 10 mmol) at rt. The reaction mixture

was allowed to stir at rt for 24 h, then the reaction was quenched with ice-cold water at 0 °C. The mixture was extracted with EtOAc (3 x 40 mL). The combined organic solutions were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. After the solvent was evaporated under vacuum, the residue was subjected to column chromatography (40% EtOAc/hexane) to afford **69** (196 mg, 81%) as a pale-yellow oil: IR (Nujol) 1672 (s), 1245 (s), 1046 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.71 (1H, dd, *J*=2.7, 1.8 Hz, H2'), 3.97 (1H, m, H4'), 4.00-3.85 (4H, m, OCH_2CH_2O), 3.44 (2H, t, *J*=5.9 Hz, CH_2O), 3.34 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 2.83 (1H, m, H3'), 2.49 (1H, ddm, *J*=15.8, 6.5 Hz, H5'), 2.36 (1H, ddt, *J*=15.8, 5.2, 1.7 Hz, H5'), 1.89 (1H, m, CH_2), 1.57 (1H, m, CH_2), 1.48 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 141.8 (0, C1'), 128.8 (1, C2'), 107.1 (0, OCO), 82.3 (1, C4'), 71.5 (2, CH_2O), 64.6 (2, OCH_2CH_2O), 64.6 (2, OCH_2CH_2O), 58.5 (3, OCH_3), 57.1 (3, OCH_3), 44.3 (1, C3'), 35.7 (2, C5'), 27.9 (2, CH_2), 23.6 (3, CH_3). MS *m/z* 197 (M^+-45, 1), 182 (2), 167 (2), 153 (3), 151 (3), 144 (2), 140 (2), 138 (6), 125 (10), 113 (5), 87 (23), 73 (17), 58 (9), 45 (100). HRMS calcd. for $C_{13}H_{22}O_4$ 242.1517, found (to be determined).

cis-1-Acetyl-4-methoxy-3-(2-methoxyethyl)-1-cyclopentene (70)

To a solution of **69** (605 mg, 2.50 mmol) in wet acetone (50 mL, acetone/H_2O 50:1) was added pyridinium *p*-toluenesulfonate (PPTS) (12.5 mg, 0.500 mmol) at rt. The reaction mixture was heated at reflux for 3 h. After the solvent was removed under vacuum, the residue was dissolved in EtOAc (100

mL), and washed with saturated $NaHCO_3$ solution (30 mL), brine (30 mL), then dried over anhydrous $MgSO_4$. After the solvent was evaporated under vacuum, the residue was subjected column chromatography (50% EtOAc/hexane) to afford **70** (445 mg, 90%) as a yellow oil: IR (Nujol) 1713 (s), 1673 (s), 1622 (m), 1239 (s), 1112 (s) cm^{-1}. ^1H NMR ($CDCl_3$) 6.67 (1H, m, H2), 3.95 (1H, ddd, *J*=11.3, 5.7, 2.8 Hz, H4), 3.50 (2H, ddd, *J*= 12.1, 6.1, 2.0 Hz, CH_2O), 3.36 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.05 (1H, m, H3), 2.70 (1H, dm *J*=16.7 Hz, H5), 2.59 (1H, ddt J=16.7, 5.7, 1.5 Hz, H5), 2.32 (3H, s, CH_3), 1.98 (1H, ddd, *J*=27.9, 14.0, 6.7 Hz, CH_2), 1.76 (1H, ddd, *J*=27.9, 14.1, 6.7 Hz, CH_2). ^{13}C NMR ($CDCl_3$) 196.7 (0, C=O), 146.0 (1, C2), 142.5 (0, C1), 81.4 (1, C4), 71.3 (2, CH_2O), 58.5 (3, OCH_3), 56.9 (3, OCH_3), 47.4 (1, C3), 35.2 (2, C5), 27.1 (2, CH_2), 26.2 (3, CH_3). MS *m/z* 198 (2), 182 (3), 170 (2), 166 (3), 153 (6), 138 (6), 127 (7), 125 (8), 111 (5), 97 (5), 85 (5), 83 (5), 79 (6), 58 (10), 45 (100). HRMS calcd. for $C_{11}H_{18}O_3$ 198.1255, found 198.1236.

cis-1-((_tert_-Butyldimethylsilyl)oxy)vinyl-4-methoxy-3-(2-methoxyethyl)-1-cyclopentene (71)

To a mixture of enone **70** (1.72 g, 8.66 mmol) and *tert*-butyldimethylsilyltriflate (2.23 mL, 9.52 mmol) in dry CH_2Cl_2 (100 mL) was added dry triethylamine (1.57 mL, 11.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. The solvent was removed under vacuum, and the residue was subjected to flash chromatography (30% dry EtOAc/hexane) to afford **71** (2.66 g,

98%) as an orange oil. Because **71** partially decomposed in the column, a pure sample was not obtained, and the above product was used for next step immediately.

(4aα,8β,9β,9aα,9bα)-6-(*tert*-Butyldimethylsilyl)oxy-8-methoxy-9-(2-methoxyethyl)-4a,5,7,8,9,9a,9b-heptahydro-2,9b-dimethylbenz[6,7]indeno[2,1*b*]-1,4-dione (80)

A solution of diene **71** (2.66 g, 8.51 mmol) and 2,6-dimethyl-1,4-benzoquinone (**15**) (2.34 g, 17.0 mmol) in dry toluene (180 mL) was heated at reflux for 3 days. The solvent was removed under vacuum, and the residue was purified by column chromatography (55% anhydrous ether/hexane) to afford **80** (3.28 g, 86%) as yellow solid: mp 67-69 °C. IR (Nujol) 1739 (s), 1712 (s), 1624 (s), 1257 (s), 1178 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.40 (1H, t, *J*=1.5 Hz, H3), 3.86 (1H, q, *J*=4.8 Hz, H8), 3.44 (2H, ddd, *J*=13.4, 6.9, 2.3 Hz, CH_2O), 3.33 (3H, OCH_3), 3.31 (3H, OCH_3), 2.99-2.87 (2H, m, H9+H4a), 2.40 (2H, m, H7), 2.27 (1H, d, *J*=8.8 Hz, H9a), 2.16-2.02 (2H, m, H5), 1.95 (3H, d, *J*=1.4 Hz, 2-methyl), 1.90 (1H, ddd, *J*=13.3, 7.0, 2.3 Hz, 9-CH_2), 1.69 (1H, m, 9-CH_2), 1.40 (3H, s, 9b-methyl), 0.89 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $SiCH_3$). NOE data 3.86 (2.99-2.87, 10%, 2.40, 6%), 1.40 (2.99-2.87, 12%, 2.27, 8%). ^{13}C NMR ($CDCl_3$) δ 202.4 (0), 200.8 (0), 148.2 (0, C2), 138.7 (0, C6), 133.4 (1, C3), 118.4 (0, C6a), 81.1 (1, C8), 71.4 (2, CH_2O), 58.5 (3, OCH_3), 57.6 (1, C4a), 56.6 (3, OCH_3), 51.6 (1, C9a), 50.9 (0, C9b), 41.5 (1, C9), 32.0 (2, C7), 31.9 (2, C5), 29.5 (2, C2-CH_2),

25.6 (3, $SiC(\mathbf{C}H_3)_3$), 25.6 (3, 9b-methyl), 18.0 (0, $Si\mathbf{C}(CH_3)_3$), 16.6 (3, 2-methyl), -4.0 (3, $SiCH_3$). MS *m/z* 448 (M^+, 2), 415 (13), 414 (11), 370 (12), 369 (11), 266 (6), 235 (6), 234 (5), 224 (9), 223 (12), 178 (12), 105 (5), 89 (34), 75 (26), 73 (100). HRMS calcd. for $C_{25}H_{40}O_5Si$ 448.2645, found 448.2638.

(1α,4aβ,8α,9α,9aβ,9bβ)-6-(*tert*-Butyldimethylsilyl)oxy-1-ethoxyethynyl-8-methoxy-9-(2-methoxy)ethyl-1,5,7,8,9,9a,9b-heptahydro-1-hydroxy-2,9b-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]-4-one (88)

To a solution of ethyl ethynyl ether (50 wt % solution in hexane, 0.88 mL, 4.50 mmol) in dry THF (30 mL) was introduced *n*-BuLi (2.5 M in hexane, 1.20 mL, 3.00 mmol) at –78 °C over 5 min. The solution was stirred for 30 min and then transferred with a double-headed needle to a solution of enedione **80** (673 mg, 1.50 mmol) in dry THF (30 mL) at –78 °C over 30 min. This mixture was stirred at –78 °C for 2 h and then at 0 °C for 1 h. This was quenched with water (20 mL), diluted with Et_2O (200 mL), and washed with water (3 x 40 mL) and brine (40 mL). The resulting solution was dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (30% dry EtOAc/hexane) to provide **88** (622 mg, 80%) as a pale yellow solid: mp 54-56 °C. IR (Nujol) 3368 (br, m), 2262 (s), 1712 (s), 1302 (m), 1166 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.74 (1H, d, *J*=0.8 Hz, H3), 4.19 (2H, q, *J*=7.7 Hz, $OC\mathbf{H}_2CH_3$), 3.67 (1H, t, *J*=3.9 Hz, H8), 3.65 (1H, s, OH), 3.54-3.38 (2H, m, CH_2O), 3.34 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 2.65 (1H, br m, H9), 2.61 (1H,

dd, *J*=10.6, 2.8 Hz, H4a), 2.50 (1H, br m, H9a), 2.36 (2H, m), 2.30 (1H, m), 2.25 (2H, dm, *J*=1.7 Hz), 2.14 (3H, d, *J*=1.2 Hz, 2-methyl), 1.95 (1H, m), 1.38 (3H, t, *J*=6.8 Hz, OCH_2CH_3), 1.29 (3H, s, 9b-methyl), 0.90 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 201.0 (0, C4), 156.5 (0), 141.2 (1, C3), 121.4 (0), 119.0 (0), 96.5 (0), 80.5 (1, C8), 74.4 (2, OCH_2CH_3), 74.3 (0), 71.8 (2, CH_2O), 58.5 (3, OCH_3), 56.2 (3, OCH_3), 54.5 (1, C4a), 52.0 (1), 44.5 (1), 42.4 (0, C1), 39.5 (0, C9b), 32.5 (2), 30.7 (2), 29.3 (2), 27.6 (3, 9b-methyl), 25.6 (3, $SiC(CH_3)_3$), 20.0 (3, 2-methyl), 18.0 (0, $SiC(CH_3)_3$), 14.7 (3, OCH_2CH_3), -3.6 (3, $SiCH_3$), -3.7 (3, $SiCH_3$). MS *m/z* 518 (M^+, 3), 505 (2), 489 (4), 461 (3), 428 (2), 427 (4), 280 (5), 261 (3), 147 (2), 119 (2), 91 (3), 77 (12), 76 (7), 75 (100). HRMS calcd. for $C_{29}H_{46}O_6Si$ 518.3063, found 518.3066.

(1*R,2*R**,3*R**,4*R**,5*S**,7*S**,8*S**,10*S**)-1-Ethoxyethynyl-8-hydroxy-5-methoxy-4-(2-methoxyethyl)-2,13-dimethyl-14-oxatetracyclo[6.5.1.$0^{2,10}$.$0^{3,7}$]tridec-12-ene-11-one (91) and (1*R**,2*R**,3*R**,4*R**,5*S**,7*S**,10*S**,11*S**)-1-ethoxyethynyl-11-hydroxy-5-methoxy-4-(2-methoxyethyl)-2,13-dimethyl-14-oxatetracyclo[9.2.1.$0^{2,10}$.$0^{3,7}$]tridec-12-ene-8-one (92)**

A solution of **88** (2.44 g, 4.70 mmol) in methanol (80 mL) and a solution of $KF•2H_2O$ (2.21 g, 23.5 mmol) in methanol (80 mL) were combined and stirred at rt for 7 h. After most of the solvent was removed under vacuum, the remaining solution was diluted with water (100 mL) and extracted with EtOAc (4 x 50 mL). The combined extracts were washed with water (50 mL) and brine (50 mL), dried

over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (70% EtOAc/hexane) to provide **91** and **92** (1.80 g, 95%) in a ratio of 1.5:1 favoring **91**. Compounds **91** and **92** could be completely separated by column chromatography, but this was not necessary for our synthesis.

Compound **91**: pale yellow solid, mp 125-127 °C. IR (Nujol) 3421 (br s), 2260 (s), 1712 (s), 1666 (s), 1167 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.72 (1H, t, *J*=1.1 Hz, H12), 4.18 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.81 (1H, t, *J*=3.4 Hz, H5), 3.47-3.37 (2H, m), 3.32 (3H, s, OCH_3); 3.30 (1H, m), 3.29 (3H, s, OCH_3), 2.48 (1H, ddd, *J*=23.0, 11.5, 7.0 Hz), 2.36 (1H, dd, *J*=11.8, 4.3 Hz), 2.13 (1H, dd, *J*=23.1, 1.9 Hz), 2.12 (3H, d, *J*=1.5 Hz, 13-methyl), 2.03 (1H, dd, *J*=8.1, 3.0 Hz), 1.97 (1H, t, *J*=2.7 Hz), 1.93 (1H, d, *J*=3.0 Hz), 1.89-1.78 (4H, m), 1.67 (1H, dd, *J*=13.5, 4.5 Hz), 1.39 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.11 (3H, s, 2-methyl). ^{13}C NMR ($CDCl_3$) δ 200.9 (0, C11), 159.3 (0), 121.1 (1, C12), 98.4 (0), 97.7 (0), 82.0 (1, C5), 76.8 (0), 74.6 (2, OCH_2CH_3). 71.6 (2, CH_2OCH_3), 58.3 (3, OCH_3), 56.1 (3, OCH_3), 53.1 (1), 52.5 (1), 44.7 (1), 41.9 (1), 38.6 (0), 37.6 (0), 34.9 (2), 30.2 (2), 28.9 (2), 20.6 (3, C13-methyl), 19.6 (3, C2-methyl), 14.7 (3, OCH_2CH_3). MS *m/z* 375 (M^+-29, 1), 345 (1), 343 (3), 325 (3), 203 (10), 175 (18), 147 (11), 137 (17), 123 (11), 109 (17), 93 (10), 91 (22), 81 (10), 77 (15), 71 (10), 69 (14), 55 (19), 53 (12), 45 (100). HRMS calcd. for $C_{23}H_{32}O_6$ 404.2199, found 404.2197.

Compound **92**: white solid, mp 142-143 °C. IR (Nujol) 3373 (br s), 2263 (s), 1712 (s), 1301 (m), 1247 (m), 1160 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.38 (1H, d, *J*=1.3 Hz, H12), 4.10 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.70 (1H, t, *J*=4.1 Hz, H5), 3.35 (1H, m), 3.32 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.25 (1H, dd, *J*=9.6, 5.3 Hz), 3.08 (1H, s, OH), 2.82 (1H, d, *J*=5.2 Hz), 2.57 (1H, dd, *J*=18.5, 5.1 Hz), 2.43 (1H, d, *J*=18.1 Hz), 2.30-2.22 (2H, m), 2.17 (1H, dd, *J*=14.8 Hz), 1.90 (3H, d, *J*=1.0 Hz, 13-methyl), 1.86 (2H, d, *J*=12.2 Hz, H9), 1.80 (1H, m), 1.37 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.33 (3H, s, 2-methyl), 1.30 (1H, d, *J*=4.3 Hz). ^{13}C NMR ($CDCl_3$) δ 211.7 (0, C8), 140.3 (0, C13), 126.3 (1, C12), 94.8 (0), 85.3 (1, C5), 82.6 (0), 74.6 (2, OCH_2CH_3), 72.9 (0), 71.3 (2), 58.4 (3, OCH_3), 57.3 (1), 56.2 (3, OCH_3), 54.3 (1), 50.3 (0), 42.1 (1), 40.6 (0), 35.8 (2), 26.3 (2), 22.6 (2), 20.8 (3, 2-methyl), 16.8 (3, 13-methyl), 14.4 (3, OCH_2CH_3). MS *m/z* 390 (1), 362 (2), 302 (6), 270 (5), 257 (8), 247 (4), 239 (5), 206 (5), 196 (21), 175 (12), 161 (9), 152 (7), 147 (16), 137 (14), 135 (19), 123 (12), 119 (34), 109 (11), 107 (12), 91 (28), 79 (15), 77 (18), 55 (15), 45 (100). HRMS calcd. for $C_{23}H_{32}O_6$ 404.2199, found 404.2191.

Ethyl (4aβ,6aα,8β,9β,9aα,9bα)-4a,5,6a,7,8,9a,9b-heptahydro-8-methoxy-9-(2-methoxy)ethyl-2,9b-dimethyl-4,6-dioxo-3*H*-benz[6,7]indeno[2,1-*b*]-1-acetate (93) and ethyl (4aα,6aα,8β,9β,9aα,9bα)-4a,5,6a,7,8,9a,9b-heptahydro-8-

methoxy-9-(2-methoxy)ethyl-2,9b-dimethyl-4,6-dioxo-3*H*-benz[6,7]indeno-[2,1-*b*]-1-acetate (94)

A mixture of **91** and **92** (1.5:1 ratio favoring **91**) (1.42 g, 3.51 mmol) was dissolved in glacial AcOH (120 mL). The solution was heated to boil, and then Zn dust (17 g, 0.26 mol) was added in portions until **91** and **92** was converted into products, monitored by TLC. The solid was removed by filtration after the reaction mixture had cooled to room temperature. The filtrate was poured into a mixture of EtOAc (300 mL) and water (300 mL), and then neutralized by adding solid Na_2CO_3 until CO_2-evolution ceased. The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane) to afford **93** and **94** (1.19 g, 84% combined) in a ratio of 1:1. These two compounds could not be separated by column chromatography, and the mixture of **93** and **94** was used in the next step.

A mixture of **93** and **94**: yellow viscous oil. IR (Nujol) 1712 (s), 1303 (s), 1168 (s), 1083 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.17 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.52 (1H, m, H8), 3.47 (1H, d, *J*=1.5 Hz), 3.27 (1H, m), 3.25 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 3.17-3.13 (2H, m, CH_2O), 3.03-3.00 (2H, m), 2.97 (1H, d, *J*=4.5 Hz, H4a), 2.96 (1H, m), 2.90 (1H, t, *J*=8.9 Hz, H6a), 2.33 (1H, dd, *J*=17.9, 9.3 Hz), 2.16 (1H, t, *J*=9.4 Hz, H9a), 1.97 (1H, dd, *J*=13.6, 7.9 Hz, H7), 1.76 (1H, dd,

J=23.4, 4.0 Hz, H7), 1.75 (3H, s, 2-methyl), 1.65-1.56 (2H, m), 1.51 (1H, m, H9), 1.30 (3H, s, 9b-methyl), 1.27 (3H, t, *J*=7.0 Hz, $OCH_2\mathbf{C}H_3$). ^{13}C NMR ($CDCl_3$) δ 213.0 (0), 208.5 (0), 171.3 (0, $\mathbf{C}O_2Et$), 130.7 (0), 129.0 (0), 81.5 (1, C8), 71.2 (2, CH_2O), 60.9 (2, $O\mathbf{C}H_2CH_3$), 58.6 (3, OCH_3), 56.2 (3, OCH_3), 53.6 (1, C4a), 52.1 (1, C9a), 48.1 (1, C6a), 45.8 (2), 44.9 (0, C9b), 44.1 (1, C9), 35.1 (2), 32.5 (2), 31.6 (2), 28.6 (2), 27.4 (3, 9b-methyl), 19.6 (3, 2-methyl), 14.2 (3, $OCH_2\mathbf{C}H_3$). MS *m/z* 406 (M^+, 3), 374 (10), 248 (11), 222 (12), 221 (21), 208 (16), 185 (12), 175 (26), 154 (10), 153 (27), 149 (11), 135 (44), 125 (22), 123 (12), 121 (17), 119 (14), 107 (17), 106 (14), 105 (18), 94 (15), 93 (43), 91 (30), 79 (21), 77 (17), 71 (16), 58 (25), 45 (100). HRMS calcd. for $C_{23}H_{34}O_6$ 406.2355, found 406.2360.

Ethyl (1α,4aβ,6aα,7aβ,10aβ,10bα,10cα)-4a,5,6a,7,7a,9,10,10a,10b,10c-decahydro-2,10c-dimethyl-4,6-dioxo-1*H*-benz[6,7]indeno-[2,1-*b*]furan-1-methylcarboxylate (102)

A 1:1 mixture of **93** and **94** (623 mg, 1.53 mmol) was dissolved in toluene (40 mL). To the solution was added *p*-toluenesulfonic acid (*p*-TsOH) (294 mg, 1.53 mmol), and it was heated at reflux for 4 h. After cooling to rt, the reaction mixture was diluted with EtOAc (150 mL), washed with saturated $NaHCO_3$ solution (2 x 40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane) to provide **102** (374 mg, 68%) as a yellow

solid: mp 219-221 °C. IR (Nujol) 1723 (s), 1703 (s), 1673 (s), 1623 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.96 (1H, s, H3), 4.45 (1H, dd, *J*=15.2, 7.5 Hz, H7a), 4.23 (2H, m, OCH_2CH_3), 3.93 (1H, m, H9), 3.75 (1H, m, H9), 3.33 (1H, d, *J*=9.6 Hz, H1), 2.95 (2H, dd, *J*=12.7, 4.7 Hz, H4a+H6a), 2.80 (1H, dd, *J*=12.8, 7.7 Hz, H7), 2.68 (2H, dd, *J*=15.8, 4.7 Hz), 2.55 (2H, d, *J*=26.0 Hz), 2.39 (1H, m, H10a), 2.34 (1H, dd, *J*=9.9, 6.0 Hz, H10b), 2.16 (1H, m, H10), 1.90 (3H, s, 2-methyl), 1.52 (1H, m, H10), 1.37 (1H, dd, *J*=13.1, 6.4 Hz, H7), 1.31 (3H, t, *J*=6.7 Hz, OCH_2CH_3), 1.11 (3H, s, 10c-methyl). NOE data 4.45 (2.39, 5%), 3.33 (2.95, 6%), 1.11 (2.95, 11%). ^{13}C NMR ($CDCl_3$) δ 210.2 (0, C6), 197.6 (0, C4), 172.6 (0, CO_2Et), 159.3 (0, C2), 126.5 (1, C3), 83.2 (1, C7a), 69.6 (2, C9), 61.2 (2, OCH_2CH_3), 57.7 (1, C10b), 52.5 (1, C4a), 49.3 (1, C6a), 43.7 (1, C1), 42.9 (1, C10a), 42.2 (0, C10c), 36.4 (2), 33.3 (2), 32.6 (2), 31.5 (2), 22.1 (3, 2-methyl), 16.2 (3, 10c-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 360 (M^+, 4), 276 (8), 273 (16), 231 (6), 221 (5), 213 (4), 203 (20), 189 (20), 185 (28), 175 (28), 161 (9), 135 (34), 123 (12), 121 (12), 119 (13), 109 (19), 107 (12), 105 (18), 95 (35), 93 (17), 91 (34), 85 (33), 84 (100). HRMS calcd. for $C_{21}H_{28}O_5$ 360.1937, found 360.1951.

2-Methyl-2-(2-iodoethyl)-1,3-dioxolane (129)

A solution of butenone (7.00 g, 100 mmol) in benzene (100 mL) was vigorously stirred with 57% aqueous HI solution (45.0 g, 200 mmol) for 2 h. The benzene layer was washed with saturated $NaHCO_3$ solution (3 x 40 mL) and

brine (40 mL) and dried with anhydrous $MgSO_4$. Ethylene glycol (6.20 g, 100 mmol) and *p*-toluenesulfonic acid monohydrate (0.5 g) were added to the dried solution. The mixture was heated at reflux with a Dean-Stark water separator for 2 h, and then the solution was washed with saturated aqueous $NaHCO_3$ solution (2 x 40 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The remaining oil was purified by passing it through a 2 x 14 cm column of neutral alumina, eluting with hexane, to afford **129** (15.4 g, 56%) as a pale yellow oil. The product **129** was pure enough for next step reaction, and was used in next step immediately.

2-(2,2-Dimethoxyethyl-1)-1,3-dithiane (130)

A 1 L. three-necked , round-bottomed flask with ground-glass fittings was charged with a mixture of boron trifluoride diethyl etherate (18 mL), glacial AcOH (36 mL), and chloroform (60 mL). The flask was equipped with a spiral reflux condenser, an efficient mechanical stirrer, and a dropping funnel. The chloroform solution was heated and maintained at reflux with vigorous stirring, and a solution of 1,3-propanedithiol (15 mL, 16 g, 0.15 mol) and malonaldehyde bis(dimethyl-acetal) (100 mL, 0.600 mol) in chloroform (350 mL) was added at a constant rate over 8 h. The mixture was allowed to cool to rt. It was washed successively with water (4 x 80 mL), 10% aqueous KOH solution (2 x 120 mL), and water (2 x 80 mL). The chloroform solution obtained was dried over anhydrous K_2CO_3 and

concentrated under reduced pressure. The residue was subjected to vacuum distillation to afford crude **130** as a yellow oil, bp 120-128/2 mm Hg. This crude product was purified by column chromatography (20% EtOAc/hexane) to provide **130** (17.0 g, 54%) as a pale yellow oil: IR (neat) 1737 (m), 1423 (s), 1382 (s), 1365 (s), 1277 (s), 1244 (s), 1169 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.67 (1H, t, *J*=5.8 Hz, C**H**$(OCH_3)_2$), 4.10 (1H, t, *J*=7.2 Hz, H2 in dithiane), 3.35 (6H, s, CH$(OCH_3)_2$), 2.95-2.79 (2H, m, C**H**$_2$CH$(OCH_3)_2$), 2.16-2.08 (2H, m, H4 or H6 in dithiane), 2.03 (2H, m, H5 in dithiane), 1.95-1.82 (2H, m, H6 or H4 in dithiane). ^{13}C NMR ($CDCl_3$) δ 101.0 (1, C**H**$(OCH_3)_2$), 52.9 (3, CH$(OCH_3)_2$), 42.5 (1, C2 in dithiane), 38.1 (2, C5 in dithiane), 29.8 (2, C4 and C6 in dithiane), 25.6 (2, C**H**$_2$CH$(OCH_3)_2$). MS *m/z* 208 (M^+, 1), 176 (34), 161 (10), 145 (12), 118 (40), 101 (21), 87 (12), 75 (100). HRMS calcd. for $C_8H_{16}O_2S_2$ 208.0592, found 208.0588.

2-[2-[2-(2,2-Dimethoxy)ethyl-1,3-dithian-2-yl]ethyl]-2-methyl-1,3-dioxolane (131)

To a solution of **130** (5.38 g, 25.3 mmol) in dry THF (130 mL) was added *n*-BuLi (2.5 M solution in hexane, 11.1 mL, 25.8 mmol) at –40 °C. The mixture was kept stirring at –20 °C for 2 h, followed by adding **129** (6.76 g, 27.9 mmol) at –40 °C. The resulting mixture was stored at 0 °C for 3 days. After most of solvents were removed under reduced pressure, the reaction was quenched with water (50 mL) and extracted with chloroform (4 x 50 mL). The combined extracts

were washed with water (50 mL), 7% aqueous KOH solution (50 mL), and brine (50 mL), and then dried over anhydrous K_2CO_3. The solvents were removed under reduced pressure, and the residue was subjected to column chromatography (30% EtOAc/hexane) to afford **131** (6.84 g, 84%) as a pale yellow oil: IR (neat) 1737 (s), 1444 (s), 1375 (s), 1243 (s), 859 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.66 (1H, t, *J*=4.6 Hz, $CH(OCH_3)_2$), 3.95 (4H, s, H4 and H5 in dioxolane), 3.35 (6H, s, $CH(OCH_3)_2$), 2.90-2.74 (4H, m, H4 and H6 in dithiane), 2.18 (2H, d, *J*=4.7 Hz, $CH_2CH(OCH_3)_2$), 2.07-1.83 (6H, m, CH_2CH_2 and H5 in dithiane), 1.34 (3H, s, 2-methyl). ^{13}C NMR ($CDCl_3$) δ 109.8 (0, C2 in dioxolane), 102.4 (1, $CH(OCH_3)_2$), 64.5 (2, C4 and C5 in dioxolane), 53.1 (3, OCH_3), 50.8 (0, C2 in dithiane), 41.5 (2, $CH_2CH(OCH_3)_2$), 33.2 (2), 33.1 (2), 26.0 (2, C4 and C6 in dithiane), 25.1 (2, C5 in dithiane), 23.9 (3, 2-methyl). MS *m/z* 322 (M^+, 2), 233 (3), 146 (1), 87 (21), 75 (100). HRMS calcd. for $C_{14}H_{26}O_4S_2$ 322.1272, found 322.1277.

2-Acetyl-6,10-dithiaspiro[4,5]dec-2-ene (132)

To a solution of **131** (2.31 g, 7.17 mmol) in THF (80 mL) was added 5% aqueous HCl solution (80 mL). The mixture was heated at reflux for 3 h. After the mixture was cooled to rt, most of THF was removed under reduced pressure. The residue was extracted with EtOAc (4 x 50 mL), and the combined extracts were washed with water (50 mL) and brine (50 mL), and then dried over

anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (40% EtOAc/hexane) to provide **132** (1.30 g, 85%) as a yellow solid: mp 68-69 °C. IR (Nujol) 1704 (s), 1655 (s), 1623 (s), 1300 (s), 1243 (s), 832 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.67 (1H, t, *J*=1.8 Hz, H3), 3.22 (2H, d, *J*=1.7 Hz, H1), 3.11 (2H, d, *J*=2.1 Hz, H4), 3.04 (1H, dd, *J*=8.8, 3.2 Hz, H7 or H9), 2.99 (1H, dd, *J*=8.1, 3.2 Hz, H7 or H9), 2.91 (1H, dd, *J*=7.1, 3.1 Hz, H7 or H9), 2.86 (1H, dd, *J*=7.0, 3.2 Hz, H7 or H9), 2.35 (3H, s, CH_3), 2.16-1.94 (2H, m, H8). ^{13}C NMR ($CDCl_3$) δ 195.9 (0, **C**OCH_3), 143.1 (0, C2), 140.0 (1, C3), 52.5 (0, C5), 50.4 (2, C4), 48.0 (2, C1), 28.4 (2, C7 and C9), 26.4 (3, CO**C**H_3), 25.0 (2, C8). MS *m/z* 214 (M^+, 36), 181 (4), 171 (12), 140 (19), 108 (6), 106 (9), 98 (9), 97 (15), 74 (6), 45 (17), 43 (100). HRMS calcd. for $C_{10}H_{14}OS_2$ 214.0486, found 214.0476.

2-[1-[(*tert*-Butyldimethylsilyl)oxy]vinyl]-6,10-dithiaspiro[4,5]dec-2-ene (106)

To a mixture of enone **132** (1.30 g, 6.07 mmol) and *tert*-butyldimethylsilyl triflate (1.57 mL, 6.68 mmol) in dry CH_2Cl_2 (50 mL) was added dry triethylamine (1.10 mL, 7.90 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. The solvent was removed under vacuum, and the residue was subjected to flash chromatography (10% dry EtOAc/hexane) to afford **106** (2.04 g, 100%) as an orange oil: IR (neat) 1636 (m), 1590 (s), 1471 (s), 1422 (s), 1362 (s), 1261 (s), 1106 (s), 1015 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.91 (1H, s, H3), 4.24 (2H, d, *J*=20.5

Hz, C=CH_2), 3.02 (4H, s, H1 and H4), 2.95-2.91 (4H, m, H7 and H9), 2.08-2.00 (2H, m, H8), 0.94 (9H, s, $SiC(CH_3)_3$), 0.16 (6H, s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 152.8 (0), 138.5 (0), 124.8 (1, C3), 93.2 (2, C=CH_2), 53.1 (0, C5), 50.1 (2, C1 or C4), 49.3 (2, C4 or C1), 28.5 (2, C7 and C9), 25.7 (3, $SiC(CH_3)_3$), 25.3 (2, C8), 18.1 (0, $SiC(CH_3)_3$), -4.7 (3, $Si(CH_3)_2$). MS *m/z* 329 (M^{+}+1, 9), 328 (M^{+}, 31), 272 (6), 271 (16), 253 (9), 221 (11), 198 (9), 197 (26), 166 (10), 165 (45), 149 (13), 140 (8), 107 (10), 91 (10), 77 (10), 75 (100). HRMS calcd. for $C_{16}H_{28}OS_2Si$ 328.1351, found 328.1339.

(4aα,9aα,9bα)-6-(*tert*-Butyldimethylsilyl)oxy-8-(spiro-1,3-dithian-2-yl)-4a,5,7,9,9a,9b-hexahydro-2,9b-dimethylbenz[6,7]indeno[2,1-*b*]-1,4-dione (105)

A solution of diene **106** (2.84 g, 8.65 mmol) and 2,6-dimethyl-1,4-benzoquinone (**15**) (2.38 g, 17.3 mmol) in dry toluene (100 mL) was heated at reflux for 3 days. The solvent was removed under vacuum, and the residue was purified by column chromatography (25% anhydrous ether/hexane) to afford **105** (3.53 g, 88%) as yellow solid: mp 162-164 °C. IR (Nujol) 1714 (s), 1692 (s), 1622 (s), 1311 (s), 1256 (s), 1181 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.42 (1H, t, *J*=1.6 Hz, H3), 3.03-2.68 (9H, m), 2.48 (1H, dd, *J*=12.2, 7.0 Hz), 2.38 (1H, dd, *J*=7.9, 2.5 Hz), 2.19-2.01 (3H, m), 1.96 (3H, d, *J*=1.7 Hz, 2-methyl), 1.38 (3H, s, 9b-methyl), 0.89 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$). NOE data 3.03-2.88 (2.70, 2%; 2.48, 7%), 2.85-2.75 (2.48, 9%), 1.38 (2.93, 4%; 2.85-2.75, 2%).

^{13}C NMR ($CDCl_3$) δ 202.2 (0), 200.1 (0), 148.6 (0), 138.8 (0), 133.4 (1, C3), 117.1 (0), 57.1 (1), 53.6 (0, C8), 50.0 (0, C9b), 47.3 (1), 44.2 (2), 41.4 (2), 32.1 (2), 28.7 (2), 27.8 (2), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 25.6 (2), 24.5 (3, 9b-methyl), 18.0 (0, $Si\mathbf{C}(CH_3)_3$), 16.6 (3, 2-methyl), -3.9 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 464 (M^+, 17), 389 (6), 366 (6), 358 (25), 357 (74), 328 (5), 301 (4), 197 (6), 130 (4), 115 (3), 107 (5), 97 (3), 75 (31), 73 (100). HRMS calcd. for $C_{24}H_{36}O_3S_2Si$ 464.1875, found 464.1874.

(4aα,9aα,9bα)-6-(*tert*-Butyldimethylsilyl)oxy-8-(spiro-1,3-dithian-2-yl)- 1-ethoxyethynyl-1,4a,5,7,9,9a-hexahydro-1-hydroxyl-2,9b-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]-4-one (104)

To a solution of ethyl ethynyl ether (50 wt% solution in hexane, 0.31 mL, 1.6 mmol) in dry THF (10 mL) was introduced *n*-BuLi (2.5 M in hexane, 0.43 mL, 1.1 mmol) at –78 °C over 5 min. The solution was stirred for 30 min and then transferred with a double-headed needle to a solution of enedione **105** (248 mg, 0.534 mmol) in dry THF (10 mL) at –78 °C. This mixture was stirred at –78 °C for 2 h and then at 0 °C for 1 h. This was quenched with water (10 mL), diluted with Et_2O (100 mL), and washed with water (3 x 20 mL) and brine (20 mL). The resulting solution was dried over anhydrous Na_2SO4, and concentrated under vacuum. The residue was purified by column chromatography (30% dry EtOAc/hexane) to provide the epimeric mixture **104** (202 mg, 71%) as a pale

yellow foam: IR (Nujol) 3413 (br, s), 2303 (s), 1692 (s), 1278 (s), 988 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.78 (1H, s, H3), 4.21-4.09 (2H, m, OCH_2CH_3), 3.59 (1H, s, OH), 3.14-2.73 (m), 2.64-2.56 (m), 2.49-2.31 (m), 2.22 (1H, m), 2.14 (3H, s, 2-methyl), 2.12 (3H, s, 2-methyl), 1.44 (2H, d, *J*=6.1 Hz), 1.38 (3H, t, *J*=6.7 Hz, OCH_2CH_3), 1.37 (3H, t, *J*=6.9 Hz, OCH_2CH_3), 1.20 (3H, s, 9b-methyl), 0.95 (9H, s, $SiC(CH_3)_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.20 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 200.8 (0), 196.7 (0), 162.0 (0), 156.7 (0), 141.0 (0), 139.8 (0), 125.9 (1, C3), 122.2 (1, C3), 116.3 (0), 115.8 (0), 97.1 (0, C1), 95.3 (0, C1), 75.0 (0), 74.5 (0), 74.2 (0), 73.8 (0), 54.4 (1), 53.4 (2), 52.0 (0, C8), 51.7 (1), 50.0 (1), 48.2 (1), 46.3 (0, C9b), 45.6 (0, C9b), 44.9 (1), 43.3 (2), 42.4 (2), 41.5 (2), 40.4 (2), 33.1 (2), 28.9 (2), 28.4 (2), 28.1 (2), 27.6 (2), 26.0 (2), 25.6 (3, $SiC(CH_3)_3$), 25.4 (2), 20.3 (3), 18.5 (3), 18.0 (0, $SiC(CH_3)_3$), 14.7 (3, OCH_2CH_3), 14.5 (3, OCH_2CH_3), -3.5 (3, $SiCH_3$), -3.6 (3, $SiCH_3$), -3.7 (3, $SiCH_3$), -3.9 (3, $SiCH_3$). MS *m/z* 534 (M^+, 4), 505 (1), 488 (2), 465 (2), 464 (5), 428 (4), 427 (11), 400 (2), 399 (6), 389 (2), 358 (6), 357 (17), 355 (4), 329 (3), 328 (8), 293 (3), 271 (4), 262 (4), 261 (17), 253 (2), 221 (3), 203 (3), 197 (5), 179 (3), 167 (2), 166 (4), 165 (10), 149 (5), 137 (4), 107 (7), 97 (3), 91 (5), 77 (5), 75 (61), 74 (8), 73 (100). HRMS calcd. for $C_{28}H_{42}O_4S_2Si$ 534.2294, found 534.2298.

(1*R,2*R**,3*R**,7*S**,8*S**,10*S**)-1-Ethoxyethynyl-8-hydroxy-5-(spiro-1,3-dithian-2-yl)- 2,13-dimethyl-14-oxatetracyclo[6.5.1.$0^{2,10}$.$0^{3,7}$]hexadec-12-en-11-one**

(133) and (4aα,6aβ,9aβ,9bβ)-1-ethoxyethynyl-4a,5,6a,7,9,9a-hexahydro-1-hydroxy-8-(spiro-1,3-dithian-2-yl)-2,9b-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]-4,6-dione (134)

A solution of **104** (2.67 g, 5.00 mmol) in methanol (130 mL) and a solution of $KF•2H_2O$ (2.35 g, 25.0 mmol) in methanol (130 mL) were combined and stirred at rt overnight. After most of the solvent was removed under vacuum, the remaining solution was diluted with water (100 mL) and extracted with EtOAc (4 x 100 mL). The combined extracts were washed with water (80 mL) and brine (2 x 80 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane) to provide **133** and **134** (1.64 g, 78%) as a white solid in a ratio of 2:1 favoring **133**. Compounds **133** and **134** could not be completely separated by column chromatography, and this mixture was used for next step.

Mixture of **133** and **134**: IR (Nujol) 3327 (br, s), 2264 (s), 1711 (m), 1666 (m), 1321 (s), 1163 (s) cm^{-1}.

Compound **133**: a pure sample was not obtained, and the NMR spectra data was assigned from the mixture of **133** and **134**. ^1H NMR ($CDCl_3$) δ 5.74 (1H, s, H12), 4.26 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.37 (1H, dd, *J*=13.3, 9.2 Hz), 3.01-2.77 (4H, m), 2.68 (1H, dd, *J*=11.1, 6.6 Hz), 2.65-2.58 (2H, m), 2.44 (1H, m), 2.38 (1H, dd, *J*=11.9, 3.8 Hz), 2.32 (1H, m), 2.13 (3H, d, *J*=1.3 Hz, 13-methyl), 2.05 (2H, m), 1.70 (2H, dd, *J*=13.5, 4.4 Hz), 1.40 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.05

(3H, s, 2-methyl). NOE data 3.37 (2.38, 3%; 2.32, 9%), 2.32 (3.37, 11%; 1.05, 6%), 1.05 (2.32, 7%). ^{13}C NMR ($CDCl_3$) δ 200.6 (0, C11), 159.2 (0, C13), 121.2 (1, C12), 99.1 (0), 97.6 (0), 74.7 (2, O**C**H_2CH_3), 60.4 (0), 55.2 (0, C5), 52.0 (1), 47.5 (1), 45.1 (1), 41.6 (2), 40.0 (2), 37.9 (2), 37.4 (0, C2), 35.3 (2), 28.7 (2), 27.5 (2), 25.7 (2), 20.5 (3, 13-methyl), 19.1 (3, 2-methyl), 14.8 (3, OCH_2**C**H_3). MS *m/z* 420 (M^+, 5), 392 (7), 391 (3), 374 (5), 363 (4), 350 (11), 348 (12), 272 (8), 257 (3), 244 (4), 225 (5), 214 (8), 213 (7), 199 (7), 185 (5), 179 (19), 178 (9), 177 (11), 175 (18), 173 (11), 172 (33), 171 (13), 161 (9), 151 (21), 147 (10), 145 (8), 139 (9), 137 (12), 135 (10), 115 (8), 107 (20), 106 (18), 105 (10), 98 (24), 97 (18), 91 (21), 79 (17), 77 (16), 75 (13), 74 (12), 73 (17), 69 (11), 65 (13), 55 (20), 53 (14), 47 (13), 45 (18), 44 (31), 43 (22), 41 (42), 39 (20), 29 (23), 28 (100). HRMS calcd. for $C_{22}H_{28}O_4S_2$ 420.1429, found 420.1425.

Compound **134**: a pure sample was not obtained, and the NMR spectra data was assigned from the mixture of **133** and **134**. ^{1}H NMR ($CDCl_3$) δ 5.74 (1H, s, H3), 4.12 (2H, q, *J*=7.1 Hz, O**C**H_2CH_3), 3.37 (1H, dd, *J*=13.3, 9.2 Hz), 3.01-2.77 (4H, m), 2.68 (1H, dd, *J*=11.1, 6.6 Hz), 2.65-2.58 (2H, m), 2.44 (1H, m), 2.38 (1H, dd, *J*=11.9, 3.8 Hz), 2.32 (1H, m), 2.10 (2H, m), 2.05 (3H, s, 2-methyl), 1.70 (2H, dd, *J*=13.5, 4.4 Hz), 1.26 (3H, t, *J*=7.1 Hz, OCH_2**C**H_3), 1.05 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 210.5 (0, C6), 200.6 (0, C4), 159.2 (0, C2), 121.2 (1, C3), 99.1 (0), 97.6 (0), 74.7 (2, O**C**H_2CH_3), 55.2 (0, C5), 52.0 (1), 47.5 (1), 45.1 (1), 41.6 (2), 40.0 (2), 37.9 (2), 37.4 (0, C2), 35.3 (2), 28.7 (2), 27.5 (2), 25.7 (2), 20.5 (3, 2-methyl), 19.1 (3, 9b-methyl), 14.1 (3, OCH_2**C**H_3). MS *m/z* 420 (M^+, 7),

392 (6), 351 (10), 350 (44), 348 (21), 272 (18), 247 (5), 244 (11), 241 (19), 214 (21), 213 (13), 201 (11), 200 (11), 199 (18), 179 (57), 178 (35), 177 (18), 175 (33), 174 (17), 173 (25), 172 (100), 171 (17), 161 (12), 152 (14), 151 (62), 150 (23), 139 (21), 135 (49), 125 (15), 107 (47), 106 (37), 98 (69), 77 (33), 45 (40). HRMS calcd. for $C_{22}H_{28}O_4S_2$ 420.1429, found 420.1424.

Ethyl (4aβ,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-8-(spiro-1,3-dithian-2-yl)-2,9b-dimethyl-4,6-dioxo-3*H*-benz[6,7]indeno[2,1-*b*]-1-acetate (135) and ethyl (4aα,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-8-(spiro-1,3-dithian-2-yl)-2,9b-dimethyl-4,6-dioxo-3*H*-benz[6,7]indeno[2,1-*b*]-1-acetate (136)

A mixture of **133** and **134** (2:1 ratio favoring **133**) (1.62 g, 3.86 mmol) was dissolved in glacial AcOH (120 mL). The solution was heated to reflux, and then Zn dust (18 g, 0.28 mol) was added in portions until **133** and **134** were converted into products, evidenced by TLC. The solid was removed by filtration after the reaction mixture had cooled to room temperature. The filtrate was poured into a mixture of EtOAc (300 mL) and water (300 mL), and then it was neutralized by adding solid Na_2CO_3 until CO_2-evolution ceased. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (55% EtOAc/hexane) to afford **135** and **136** (1.43 g, 88%

combined) in a ratio of about 1:1. Compound **135** and **136** could be separated by column chromatography.

Compound **135**: white solid, mp 161-163 °C. IR (Nujol) 1722 (s), 1714 (s), 1316 (s), 1261 (s), 1165 (s), 1928 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.16 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.33-3.00 (4H, m), 3.24 (1H, dd, *J*=11.9, 5.1 Hz), 2.95-2.71 (7H, m), 2.67-2.50 (3H, m), 2.22 (1H, m), 2.10 (2H, s), 2.06-1.91 (2H, m), 1.77 (1H, dd, *J*=14.3, 10.2 Hz), 1.71 (3H, s, 2-methyl), 1.27 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.07 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 209.9 (0), 207.4 (0), 171.2 (0, $COOCH_2CH_3$), 131.1 (0), 130.4 (0), 61.0 (2, OCH_2CH_3), 53.3 (0, C8), 49.1 (1), 48.5 (1), 48.5 (1), 46.1 (2), 44.7 (0, C9b), 43.5 (2), 35.3 (2), 33.5 (2), 28.8 (2), 28.7 (2), 28.4 (2), 24.9 (2), 21.3 (3, 9b-methyl), 19.8 (3, 2-methyl), 14.2 (3, OCH_2CH_3). MS *m/z* 422 (M^+, 71), 404 (5), 377 (8), 349 (5), 315 (9), 297 (5), 251 (9), 250 (9), 249 (23), 248 (10), 241 (7), 223 (9), 222 (17), 221 (35), 215 (9), 214 (41), 209 (8), 208 (17), 205 (12), 203 (12), 201 (20). 199 (10), 185 (13), 177 (19), 176 (17), 175 (84), 174 (21), 173 (100), 172 (56), 149 (22), 148 (13), 147 (13), 139 (16), 138 (14), 135 (58), 121 (15), 119 (17), 111 (12), 107 (37), 106 (28), 105 (25), 93 (21), 91 (41), 79 (26), 67 (26), 55 (29), 41 (69). HRMS calcd. for $C_{22}H_{30}O_4S_2$ 422.1585, found 422.1570.

Compound **136**: viscous yellow oil. IR (Nujol) 2249 (m), 1711 (s), 1666 (s), 1301 (m), 1240 (m), 1166 (s), 1025 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.23-4.15 (2H, m, OCH_2CH_3), 3.31-3.10 (3H, m), 3.18 (1H, dd, *J*=19.0, 12.2 Hz), 3.10-2.80 (2H, m),

3.03 (1H, d, *J*=6.9 Hz), 2.80-2.71 (4H, m), 2.78 (1H, m), 2.71 (1H, m), 2.65 (1H, d, *J*=5.0 Hz), 2.49 (1H, dd, *J*=16.6, 7.7Hz, H4a), 2.28 (1H, dd, *J*=14.4, 8.6 Hz), 2.07 (1H, m), 1.99-1.93 (2H, m), 1.77 (3H, s, 2-methyl), 1.51 (3H, s, 9b-methyl), 1.30 (3H, t, *J*=7.2 Hz, $OCH_2\mathbf{C}H_3$), 1.29 (1H, m). NOE data 2.49 (3.31-3.10, 5%; 1.51, 3%), 2.28 (2.80-2.71, 4%; 2.65, 9%), 1.51 (3.03, 3%; 2.78, 3%; 2.71, 4%; 2.49, 5%). ^{13}C NMR ($CDCl_3$) δ 208.5 (0), 208.0 (0), 171.3 (0, $\mathbf{C}OOCH_2CH_3$), 130.0 (0), 128.9 (0), 60.9 (2, $O\mathbf{C}H_2CH_3$), 53.5 (1), 52.5 (0, C8), 48.5 (1), 47.7 (1), 45.6 (2), 44.0 (2), 42.2 (2), 35.9 (0, C9b), 34.2 (2), 33.7 (2), 28.8 (2), 28.2 (2), 27.3 (3, 9b-methyl), 25.2 (2), 19.8 (3, 2-methyl), 14.1 (3, $OCH_2\mathbf{C}H_3$). MS *m/z* 422 (M^+, 9), 348 (3), 332 (6), 175 (8), 142 (5), 141 (6), 135 (10), 129 (6), 128 (7), 121 (11), 120 (9), 107 (12), 106 (27), 105 (17), 92 (12), 91 (29), 79 (11), 78 (11), 77 (13), 64 (10), 56 (12), 55 (16), 44 (24), 43 (33), 42 (25), 41 (100). HRMS calcd. for $C_{22}H_{30}O_4S_2$ 422.1585, found 422.1565.

Ethyl (1α,4aβ,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-8-(spiro-1,3-dithian-2-yl)-2,9b-dimethyl-4,6-dioxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (137)

Procedure 1:

To a solution of **135** (680 mg, 1.61 mmol) in benzene (80 mL) was added *p*-toluenesulfonic acid monohydrate (306 mg, 1.61 mmol). The mixture was

heated at reflux for 6 h. After cooling to rt, the reaction mixture was diluted with EtOAc (150 mL), washed with saturated $NaHCO_3$ solution (2 x 40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to provide **137** (560 mg, 81%).

Procedure 2:

To a solution of **136** (680 mg, 1.61 mmol) in benzene (80 mL) was added *p*-toluenesulfonic acid monohydrate (306 mg, 1.61 mmol). The mixture was heated at 60 °C for 2 days. After cooling to rt, the reaction mixture was diluted with EtOAc (150 mL), washed with saturated $NaHCO_3$ solution (2 x 40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to provide **137** (304 mg, 45%).

Compound **137**: yellow solid, mp 144-146 °C. IR (Nujol) 1712 (s), 1672 (s), 1619 (m), 1305 (s), 1241 (s), 1171 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.95 (1H, m, H3), 4.24 (2H, m, OCH_2CH_3), 3.26 (1H, d, *J*=10.0 Hz, H1), 3.02-2.91 (5H, m), 2.88 (1H, d, *J*=4.3 Hz), 2.83-2.70 (4H, m), 2.55-2.40 (3H, m), 2.05 (2H, s), 1.99 (1H, m), 1.91 (3H, t, *J*=1.3 Hz, 2-methyl), 1.77 (1H, m), 1.32 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.08 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 208.8 (0, C6), 197.5 (0, C4), 173.1 (0, COOEt), 159.3 (0, C2), 126.4 (1, C3), 61.3 (2, OCH_2CH_3), 51.7 (0, C8), 50.6 (1), 49.7 (1), 48.7 (1), 45.5 (1, C1), 42.2 (2), 41.3 (0, C9b), 40.5 (2),

35.9 (2), 31.5 (2), 29.0 (2), 28.8 (2), 25.0 (2), 21.8 (3, 2-methyl), 15.6 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 422 (M^+, 41), 249 (19), 248 (5), 222 (8), 221 (19), 214 (13), 201 (8), 196 (9), 177 (7), 176 (14), 175 (100), 173 (31), 172 (19), 149 (10), 148 (6), 147 (8), 135 (25), 107 (19), 106 (12), 99 (14), 98 (14), 95 (13), 91 (17), 79 (11), 73 (10), 67 (18), 55 (13), 43 (33), 41 (33). HRMS calcd. for $C_{22}H_{30}O_4S_2$ 422.1585, found 422.1566.

Ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-6-hydroxy-8-(spiro-1,3-dithian-2-yl)-2,9b-dimethyl-4-oxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (147)

To a solution of **137** (85 mg, 0.20 mmol) in dry THF (20 mL) was added L-Selectride (1.0 M solution in THF, 0.30 mL, 0.30 mmol) at –78 °C. The solution was stirred at –78 °C for 3 h before the reaction was quenched with 5% aqueous NaOH solution (2 mL). After warming to rt, the mixture was diluted with EtOAc (100 mL), washed by water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was subjected to column chromatography (50% EtOAc/hexane) to afford **147** (66 mg, 78%) as a white solid: mp 75-77 °C. IR (Nujol) 3427 (br, s), 1714 (s), 1670 (s), 1300 (s), 1243 (s), 1168 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.90 (1H, s, H3), 4.23 (2H, m, OCH_2CH_3), 3.97 (1H, m, H6), 3.24 (1H, d, *J*=10.2 Hz, H1), 3.07-2.81 (4H, m), 2.77 (1H, dd, *J*=6.4, 3.47 Hz), 2.53-2.47 (2H, m), 2.41-2.32 (2H, m), 2.28-2.17

(5H, m), 2.13 (2H, m), 1.87 (3H, 2-methyl), 1.56 (1H, m), 1.31 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 0.84 (3H, s, 9b-methyl). NOE data 3.97 (2.28-2.27, 12%; 2.13, 7%). 3.24 (3.07-2.81, 3%; 2.53-2.47, 4%). ^{13}C NMR ($CDCl_3$) δ 200.7 (0, C4), 173.3 (0, COOEt), 159.0 (0, C2), 126.7 (1, C3), 68.0 (1, C6), 61.0 (2, OCH_2CH_3), 52.8 (0, C8), 46.8 (1), 45.5 (2), 45.4 (1, C1), 43.6 (1), 43.0 (2), 41.2 (0, C9b), 40.4 (1), 31.5 (2), 29.2 (2), 29.0 (2), 27.4 (2), 25.1 (2), 21.8 (3, 2-methyl), 15.6 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 425 (M^++1, 8), 424 (M^+, 31), 391 (8), 317 (15), 259 (8), 252 (5), 251 (26), 250 (7), 243 (10), 235 (10), 225 (10), 223 (11), 222 (28), 221 (32), 214 (15), 211 (12), 201 (12), 198 (14), 197 (11), 196 (21), 187 (12), 185 (29), 178 (13), 177 (86), 175 (30), 174 (15), 173 (25), 172 (20), 165 (16), 161 (17), 159 (14), 149 (29), 148 (16), 147 (26), 135 (54), 123 (25), 107 (39), 106 (33), 105 (27), 98 (22), 95 (35), 91 (44), 79 (27), 77 (24), 67 (44), 65 (19), 57 (22), 55 (31), 45 (33), 43 (59), 41 (100). HRMS calcd. for $C_{22}H_{32}O_4S_2$ 424.1742, found 424.1735.

Ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-6-methoxymethoxy-8-(spiro-1,3-dithian-2-yl)-2,9b-dimethyl-4-oxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (148) and (1*R,3*S**,4*R**,5*S**,9*S**,11*R**,12*S**)-1-methoxythiomethoxythiopropyoxy-4,6-dimethyl-5-(2-oxo-2-ethoxyethyl)-14-oxatetracyclo[9.2.1.$0^{3,12}$.$0^{4,9}$]tridec-6-en-8-one (149)**

To a solution of **147** (100 mg, 0.236 mmol) in dry CH_2Cl_2 (10 mL) was added $(i\text{-Pr})_2NEt$ (0.54 mL, 3.1 mmol) and chloromethyl methyl ether (0.18 mL, 2.4 mmol) at rt. The mixture was heated at reflux for 2 days. After the mixture was cooled to rt, it was washed by 1% HCl (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The residue was subjected to column chromatography (40% EtOAc/hexane) to provide **148** (60 mg, 55%) and **149** (16 mg, 15%).

Compound **148**: IR 1713 (s), 1632 (m), 1167 (s), 974 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.90 (1H, m, H3), 4.71 (1H, d, *J*=6.9 Hz, OCH_2O), 4.55 (1H, d, *J*=6.9 Hz, OCH_2O), 4.24 (2H, m, OCH_2CH_3), 3.74 (1H, m, H6), 3.42 (3H, s, OCH_3), 3.25 (1H, d, *J*=10.3 Hz, H1), 3.10-2.90 (2H, m), 2.79 (1H, dd, *J*=12.1, 2.8 Hz, H4a), 2.73-2.66 (2H, m), 2.55-2.49 (4H, m), 2.40 (1H, m), 2.33 (1H, m, H6a or H9a), 2.26 (1H, H6a or H9a), 2.13 (2H, d, *J*=4.1 Hz), 2.05 (2H, d, *J*=1.4 Hz), 1.88 (3H, d, *J*=0.9 Hz, 2-methyl), 1.41 (1H, m), 1.32 (3H, t, *J*=6.6 Hz, OCH_2CH_3), 0.83 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 200.6 (0, C4), 173.4 (0, COOEt), 159.2 (0, C2), 126.7 (1, C3), 95.6 (2, OCH_2O), 73.5 (1, C6), 61.0 (2, OCH_2CH_3), 56.3 (3, OCH_3), 53.5 (0, C8), 46.9 (1, C6a or C9a), 45.5 (1, C1), 44.3 (1, C4a), 43.8 (2), 41.8 (2), 41.1 (0, C9b), 39.0 (1, C6a or C9a), 31.5 (2), 29.1 (2), 29.0 (2), 25.4 (2), 24.3 (2), 21.8 (3, 2-methyl), 15.7 (3, 9b-methyl), 14.2 (3, OCH_2CH_3). MS *m/z* 468 (M^+, 50), 438 (11), 437 (29), 436 (21), 424 (10), 423 (22), 233 (32), 222 (12), 221 (24), 215 (13), 196 (15), 185 (18), 177 (41), 135 (20), 119 (11), 107 (15), 106 (34), 105

(13), 95 (15), 91 (16), 79 (11), 73 (11), 67 (12), 45 (100). HRMS calcd. for $C_{24}H_{36}O_5S_2$ 468.2002, found 468.1995.

Compound **149**: IR (Nujol) 1713 (s), 1626 (m), 1301 (s), 1242 (s), 1167 (s), 1039 (s) 1082 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.90 (1H, m, H7), 4.63 (2H, s, SCH_2OCH_3), 4.30 (1H, m, H11), 4.34-4.14 (2H, m, OCH_2CH_3), 3.34 (3H, s, OCH_3), 3.23 (1H, d, *J*=7.6 Hz, H5), 2.86-2.76 (3H, m), 2.70 (2H, t, *J*=7.1 Hz), 2.43-2.36 (2H, m), 2.33 (1H, m, H3), 2.23 (1H, m, H10), 2.18 (1H, m, H12), 2.14 (1H, m, H2), 2.09-2.05 (2H, m, H13), 1.97 (2H, dd, *J*=14.7, 7.1 Hz), 1.88 (3H, s, 6-methyl), 1.77 (1H, d, *J*=9.7 Hz, H2), 1.61 (1H, m, H10), 1.29 (3H, t, *J*=7.1 Hz, OCH_2CH_3). 0.81 (3H, s, 4-methyl). NOE data 4.30 (2.33, 3%; 2.18, 2%; 1.61, 4%), 3.23 (2.86-2.76, 3%), 0.81 (2.33, 5%). ^{13}C NMR ($CDCl_3$) δ 200.1 (0, C8), 173.0 (0, COOEt), 158.6 (0, C6), 126.6 (1, C7), 91.2 (2, C1), 77.4 (1, C11), 75.3 (2, SCH_2OCH_3), 60.9 (2, OCH_2CH_3), 55.6 (3, OCH_3), 44.7 (1, C5), 44.6 (2, C2), 43.2 (1, C12), 42.4 (1, C9), 41.6 (0, C4), 39.5 (2, C13), 38.7 (1, C3), 31.2 (2, CH_2COOEt), 30.3 (2), 29.9 (2), 27.9 (2), 24.2 (2), 22.0 (3, 6-methyl), 14.1 (3, 4-methyl), 14.0 (3, OCH_2CH_3). MS *m/z* 468 (M^+, 1), 436 (10), 435 (7), 425 (9), 424 (19), 423 (61), 251 (16), 243 (9), 221 (17), 196 (12), 185 (14), 177 (52), 175 (19), 161 (10), 159 (10), 151 (14), 149 (14), 147 (13), 135 (28), 123 (13), 121 (16), 119 (14), 107 (19), 106 (28), 105 (16), 95 (21), 93 (11), 91 (23), 79 (17), 77 (13), 73 (14), 67 (21), 61 (14), 55 (17), 47 (11), 45 (100). HRMS calcd. for $C_{24}H_{36}O_5S_2$-45 423.1662, found 423.1648.

Ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-6-methoxymethoxy-2,9b-dimethyl-4,8-dioxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (155)

To a solution of **148** (25 mg, 0.053 mmol) in THF/H_2O (5:1, 6 mL) was added $CaCO_3$ (7 mg, 0.07 mmol), followed by adding a solution of $Hg(ClO_4)_2 \bullet xH_2O$ (26 mg, 0.065 mmol) in water (0.5 mL). The reaction mixture was stirred at rt overnight, then diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ solution (20 mL), and dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the residue was subjected to column chromatography (60% EtOAc/hexane) to afford **155** (15.5 mg, 78%) as a white solid: mp 133-134 °C. IR (Nujol) 1714 (s), 1666 (m), 1300 (s), 1244 (s), 1165 (s), 1027 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.92 (1H, m, H3), 4.61 (1H, d, *J*=7.0 Hz, OCH_2O), 4.43 (1H, d, *J*=7.0 Hz, OCH_2O), 4.20 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 3.93 (1H, m, H6), 3.32 (3H, s, OCH_3), 3.19 (1H, m, H1), 2.79 (1H, dd, *J*=11.9, 3.0 Hz, H4a), 2.59 (1H, dd, *J*=17.0, 13.2 Hz, H9), 2.48-2.40 (3H, m, H6a and CH_2COOEt), 2.37 (1H, t, *J*=3.3 Hz, H5), 2.33-2.24 (3H, m, H9a and H7), 2.19 (1H, m, H9), 1.88 (3H, s, 2-methyl), 1.48 (1H, m, H5), 1.30 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 0.90 (3H, s, 9b-methyl). NOE data 3.93 (2.48-2.40, 5%), 3.19 (2.79, 4%), 2.37 (3.93, 6%; 0.90, 9%). ^{13}C NMR ($CDCl_3$) δ 216.8 (0, C8), 200.0 (0, C4), 172.7 (0, COOEt), 159.3 (0, C2), 126.7 (1, C3), 95.2 (2, OCH_2O), 74.1 (1, C6), 61.2 (2, OCH_2CH_3), 56.2 (3, OCH_3), 45.4 (1, C9a), 45.1 (1, C1), 43.7 (2, C7),

43.0 (1, C4a), 41.7 (0, C9b), 38.8 (2, C9), 36.7 (1, C6a), 31.5 (2, CH_2COOEt), 24.3 (2, C5), 21.8 (3, 2-methyl), 15.0 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 378 (M^+, 3), 333 (3), 317 (3), 316 (5), 259 (5), 233 (6), 221 (6), 159 (5), 147 (4), 122 (4), 105 (4), 95 (10), 91 (6), 77 (3), 67 (6), 55 (4), 45 (100). HRMS calcd. for $C_{21}H_{30}O_6$ 378.2042, found 378.2042.

Ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6,6a,7,9,9a-octahydro-6-methoxy-methoxy-2,9b-dimethyl-4-oxo-8-(spiro-1,3-dioxolan-2-yl)-1*H*-benz[6,7]-indeno-[2,1-*b*]-1-methylcarboxylate (156)

To a solution of **155** (73.5 mg, 0.194 mmol) in benzene (20 mL) was added 1,2-ethanediol (0.11 mL, 1.9 mmol) and PPTS (10 mg, 0.039 mmol) at rt. The reaction mixture was heated at reflux for 16 h. After the mixture was cooled to rt, it was diluted with EtOAc (100 mL), washed by saturated $NaHCO_3$ solution (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane to provide **156** (65 mg, 80%) as a white solid: mp 91.5-93°C. IR (Nujol) 1713 (s), 1667 (s), 1626 (s), 1238 (s), 1169 (s), 1025 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.89 (1H, m, H3), 4.68 (1H, d, *J*=7.0 Hz, OCH_2O), 4.55 (1H, d, *J*=7.0 Hz, OCH_2O), 4.27-4.14 (2H, m, OCH_2CH_3), 3.97-3.80 (4H, m, OCH_2CH_2O), 3.78 (1H, m, H6), 3.42 (3H, s, OCH_3), 3.19 (1H, d, *J*=10.0 Hz, H1), 2.78 (1H, dd, *J*=12.1, 3.1 Hz, H4a), 2.55-2.35 (2H, m), 2.26 (1H, dd, *J*=12.8, 2.5 Hz, H5), 2.18-

2.07 (3H, H6a and H7), 2.02 (1H, m, H9a), 1.86 (3H, d, *J*=1.3 Hz, 2-methyl), 1.73 (2H, dd, *J*=11.5, 5.3 Hz, H9), 1.40 (1H, ddd, *J*=14.6, 12.3, 2.3 Hz, H5), 1.30 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.82 (3H, s, 9b-methyl). NOE data 3.78 (2.18-2.07, 5%), 3.19 (2.78, 5%). ^{13}C NMR ($CDCl_3$) δ 200.8 (0, C4), 173.2 (0, COOEt), 159.4 (0, C2), 126.7 (1, C3), 117.1 (0, C8), 95.7 (2, OCH_2O), 74.5 (1, C6), 64.5 (2, OCH_2CH_2O), 63.5 (2, OCH_2CH_2O), 60.9 (2, OCH_2CH_3), 55.9 (3, OCH_3), 46.7 (1, C9a), 45.4 (1, C1), 43.8 (1, C4a), 41.4 (0, C9b), 39.6 (2), 37.6 (1, C6a), 37.5 (2), 31.5 (2, CH_2COOEt), 24.6 (2, C5), 21.9 (3, 2-methyl), 15.3 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 422 (M^+, 16), 377 (14), 361 (15), 275 (5), 273 (9), 221 (9), 199 (8), 171 (6), 159 (7), 152 (11), 147 (9), 140 (6), 139 (8), 135 (8), 127 (11), 126 (13), 125 (11), 119 (6), 105 (5), 99 (20), 91 (7), 89 (19), 87 (31), 86 (46), 84 (40), 67 (8), 59 (9), 55 (8), 49 (7), 47 (10), 45 (100). HRMS calcd. for $C_{23}H_{34}O_7$ 422.2304, found 422.2309.

(1*S,3*S**,4*R**,5*S**,9*S**,11*R**,12*S**)-1-methoxy-4,6-dimethyl-5-(2-oxo-2-ethoxyethyl)tetracyclo[9.2.1.$0^{3,12}$.$0^{4,9}$]tridec-6-en-8-one (157) and ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-6-hydroxy-2,9b-dimethyl-4,8-dioxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (158)**

To a solution of **147** (81 mg, 0.19 mmol) in methanol (3 mL) was added [bis(trifluoroacetoxy)iodo]benzene (127 mg, 0.286 mmol) at rt and the reaction mixture was kept stirring for 4 h at rt. The mixture was diluted with EtOAc (100

mL), washed by saturated $NaHCO_3$ solution (20 mL). The organic layer was separated, dried with anhydrous $MgSO_4$, concentrated under reduced pressure. The residue was subjected to column chromatography (70% EtOAc/hexane) to afford **157** and **158** as a white solid in a ratio 1:1 and 75% combined yield. Compound **157** and **158** could be separated by column chromatography.

Compound **157**: IR (Nujol) 1713 (s), 1304 (s), 1169 (s), 973 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.90 (1H, m, H7), 4.30 (1H, m, H11), 4.23-4.14 (2H, m, OCH_2CH_3), 3.77 (3H, s, OCH_3), 3.23 (1H, m, H5), 2.95-2.77 (m), 2.43-2.32 (m), 2.29 (1H, dd, *J*=9.3, 4.3 Hz), 2.13-2.04 (m), 1.88 (3H, s, 6-methyl), 1.78 (1H, d, *J*=9.5 Hz), 1.67-1.55 (2H, m), 1.29 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.81 (3H, s, 4-methyl). ^{13}C NMR ($CDCl_3$) δ 200.2 (0, C8), 173.1 (0, COOEt), 158.7 (0, C6), 126.8 (1, C7), 91.3 (0, C1), 68.4 (1, C11), 61.1 (2, OCH_2CH_3), 55.4 (3, OCH_3), 44.8, 43.3, 42.5, 41.7 (0, C4), 39.6, 38.8, 31.4, 28.2, 24.3, 22.1 (3H, 6-methyl), 14.3 (3H, 4-methyl), 14.1 (3H, OCH_2CH_3). MS *m/z* 348 (M^+, 4), 335 (4), 334 (15), 317 (11), 316 (49), 301 (11), 298 (10), 243 (12), 229 (16), 227 (21), 222 (15), 221 (26), 185 (14), 177 (11), 161 (14), 149 (19), 148 (15), 147 (15), 135 (46), 123 (19), 122 (52), 121 (20), 119 (16), 108 (12), 107 (11), 106 (22), 105 (16), 95 (48), 94 (15), 93 (10), 91 (23), 86 (58), 84 (84), 79 (16), 77 (13), 74 (11), 73 (29), 67 (23), 55 (15), 47 (21), 46 (24), 45 (30), 41 (76), 32 (64), 31 (100). HRMS calcd. for $C_{20}H_{28}O_5$ 348.1935, found (to be determined).

Compound **158**: white solid, mp 143-145 °C. IR (Nujol) 1714 (s), 1660 (m), 1299 (s), 1242 (s), 1166 (s), 1039 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.92 (1H, m, H3), 4.20 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 4.15 (1H, m, H6), 3.21 (1H, m, H1), 2.91 (1H, dd, *J*=12.2, 3.2 Hz, H4a), 2.66 (1H, dd, *J*=16.8, 12.6 Hz), 2.45-2.36 (5H, m), 2.31 (1H, m), 2.23 (1H, m, H5), 2.18 (1H, m), 1.88 (3H, s, 2-methyl), 1.67 (1H, ddd, *J*=14.6, 12.2, 2.4 Hz, H5), 1.29 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.90 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 217.6 (0, C8), 200.3 (0, C4), 172.7 (0, COOEt), 159.4 (0, C2), 126.6 (1, C3), 68.4 (1, C6), 61.2 (2, OCH_2CH_3), 45.4 (1), 45.1 (1, C1), 43.7 (2), 42.4 (1, C4a), 41.8 (0, C9b), 39.1 (2), 36.8 (1), 31.5 (2), 28.4 (2, C5), 21.9 (3, 2-methyl), 14.9 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 334 (M^+, 31), 317 (21), 316 (100), 301 (24), 298 (21), 289 (11), 243 (26), 235 (16), 234 (11), 229 (33), 228 (17), 227 (46), 222 (32), 221 (48), 213 (10), 209 (12), 208 (14), 201 (12), 193 (17), 185 (26), 177 (15), 161 (24), 159 (15), 149 (35), 148 (34), 147 (28), 135 (88), 123 (33), 122 (51), 121 (21), 108 (26), 105 (30), 91 (44), 79 (27), 67 (38), 55 (22), 41 (48). HRMS calcd. for $C_{19}H_{26}O_5$ 334.1779, found 334.1784.

Ethyl (1α,4aβ,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-8,8-dimethoxy-2,9b-dimethyl-4,6-dioxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (159)

To the mixture of **137** (153 mg, 0.362 mmol) in methanol (5 mL) was added [bis(trifluoroacetoxy)iodo]benzene (321 mg, 0.724 mmol) at rt, and the

mixture became clear immediately. After the solution was stirred at rt for 10 min, it was poured into saturated $NaHCO_3$ solution (20 mL), then extracted with EtOAc (4 x 20 mL). The combined extracts were washed by brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to afford **159** (79 mg, 58%) as a pale yellow solid: mp 156-158 °C. IR (Nujol) 1713 (s), 1666 (m), 1292 (s), 1238 (s), 1169 (s), 1023 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.94 (1H, m, H3), 4.27-4.20 (2H, m, OCH_2CH_3), 3.22 (1H, m, H1), 3.16 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 2.88 (1H, dd, *J*=12.9, 4.7 Hz, H4a), 2.80 (1H, d, *J*=1.7 Hz), 2.75 (1H, d, *J*=2.2 Hz), 2.70 (1H, m, H6a or H9a), 2.60-2.46 (3H, m), 2.42 (1H, m), 2.13 (1H, dd, *J*=13.0, 6.8 Hz), 1.90 (3H, s, 2-methyl), 1.74 (1H, dd, *J*=13.9, 8.4 Hz), 1.49 (1H, t, *J*=13.0 Hz), 1.31 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.04 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 209.3 (0, C6), 197.8 (0, C4), 172.8 (0, COOEt), 159.5 (0, C2), 126.4 (1, C3), 109.1 (0, C8), 61.2 (2, OCH_2CH_3), 49.4 (3, OCH_3), 48.9 (3, OCH_3), 48.7 (1, C4a), 48.7 (1), 47.5 (1), 45.0 (1, C1), 41.5 (0, C9b), 35.8 (2, C5), 35.2 (2), 34.2 (2), 31.7 (2), 21.9 (3, 2-methyl), 15.1 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 378 (M^+, 1), 346 (1), 279 (1), 205 (3), 204 (42), 175 (3), 167 (3), 149 (10), 138 (3), 135 (3), 127 (3), 113 (3), 97 (6), 96 (6), 86 (15), 85 (5), 84 (25), 78 (3), 77 (47), 71 (10), 57 (17), 51 (15), 43 (12), 41 (12), 32 (75), 31 (100). HRMS calcd. for $C_{21}H_{30}O_6$ 378.2041, found (to be determined).

Ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6,6a,7,9,9a-octahydro-6-hydroxy-8,8-dimethoxy-2,9b-dimethyl-4-oxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methyl-carboxylate (160)

To a solution of **159** (105 mg, 0.278 mmol) in dry THF (20 mL) was added K-Selectride (1.0 M solution in THF, 0.34 mL, 0.34 mmol) at –78 °C. After it was stirred at –78 °C for 3 h, the mixture was allowed to warm to 0 °C over 4 h. Then the reaction was quenched with 5% NaOH solution (5 mL), extracted with EtOAc (4 x 20 mL). The combined organic layers were washed by brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (60% EtOAc/hexane) to provide **160** (54 mg, 51%) as a white solid: mp 93-95 °C. IR (Nujol) 3438 (br s), 1714 (s), 1625 (m), 1301 (s), 1247 (s), 1167 (s), 1044 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.89 (1H, m, H3), 4.28-4.14 (2H, m, OCH_2CH_3), 4.03 (1H, m, H6), 3.23 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 3.16 (1H, m, H1), 2.95 (1H, dd, *J*=12.0, 3.5 Hz, H4a), 2.52-2.35 (2H, m), 2.31 (1H, m, H9), 2.26 (1H, m, H5), 2.22-2.05 (4H, H6a and H9a and H7), 1.88 (1H, m, H9), 1.85 (3H, s, 2-methyl), 1.50 (1H, ddd, *J*=14.6, 12.4, 2.3 Hz, H5), 1.30 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 0.82 (3H, s, 9b-methyl). NOE data 3.16 (2.95, 9%), 2.22-2.05 (4.03, 6%, 0.82, 3%). ^{13}C NMR ($CDCl_3$) δ 200.8 (0, C4), 173.1 (0, COOEt), 158.8 (0, C2), 126.8 (1, C3), 111.5 (0, C8), 68.5 (1, C6), 61.0 (2, OCH_2CH_3), 49.4 (3, OCH_3), 48.9 (3, OCH_3), 46.3 (1), 44.8 (1, C1), 43.1 (1, C4a), 41.6 (0, C9b), 40.0 (2, C7), 39.9 (1), 37.5 (2, C9), 31.6 (2, CH_2COOEt),

27.1 (2, C5), 21.8 (3, 2-methyl), 15.4 (3, 9b-methyl), 14.1 (3, $OCH_2\mathbf{C}H_3$). MS *m/z* 380 (M^+, 13), 349 (18), 348 (42), 316 (14), 303 (22), 275 (19), 261 (21), 260 (20), 259 (17), 243 (10), 229 (15), 222 (13), 221 (65), 208 (13), 201 (24), 187 (27), 186 (10), 185 (22), 177 (41), 161 (14), 159 (13), 149 (18), 148 (10), 147 (37), 135 (70), 133 (11), 129 (10), 123 (22), 122 (19), 121 (21), 119 (23), 111 (29), 107 (22), 105 (27), 97 (51), 96 (23), 95 (42), 91 (41), 81 (21), 79 (27), 77 (22), 67 (40), 55 (31), 53 (22), 43 (30), 41 (59), 32 (26), 31 (41), 29 (100). HRMS calcd. for $C_{21}H_{32}O_6$ 380.2197, found (to be determined).

Ethyl (1α,2β,4aβ,6aα,9aα,9bα)-1,2,3,4a,5,6,6a,7,9,9a-decahydro-2,9b-dimethyl-4,6,8-trioxo-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (162)

Liquid ammonia (approximately 200 mL) was collected in a 500 mL three-necked round-bottomed flask using a dry ice-acetone cold trap. To this liquid ammonia were added Na shavings (approximately 0.5 g). The ammonia solution turned blue immediately. After 5 min, this ammonia solution was allowed to warm, and about 160 mL of dry ammonia was distilled into a dry 500 mL three-necked round-bottomed flask. To this dry liquid ammonia were added Li shavings (55 mg, 7.9 mmol) and the ammonia solution turned blue immediately. This blue solution was allowed to warm to –50 °C when enone **160** (427 mg, 1.12 mmol) in 1:1 dry 1,4-dioxane/Et_2O (50 mL) was introduced over 2 min. The mixture was stirred for 5 min before sufficient anhydrous NH_4Cl was added to discharge the

blue color. This was allowed to warm up to evaporate ammonia. The remainder was diluted with water (100 mL) and extracted with EtOAc (4 x 20 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum.

The residue was dissolved in CH_2Cl_2 (2 mL) and then added dropwise to a suspension of pyridinium chlorochromate (PCC) (2.5 eq.) in CH_2Cl_2 (20 mL). The mixture was stirred at rt for 3 h and then filtered through Celite. The filtrate was concentrated, and the residue was subjected to column chromatography (60% EtOAc/hexane) to afford **162** (50 mg) as white solid: mp 186-188 °C. IR (Nujol) 1741 (s), 1263 (s), 1216 (s), 1155 (s), 1010 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.21-4.13 (2H, m, OCH_2CH_3), 3.18-3.09 (2H, m), 2.89 (1H, dd, *J*=13.0, 3.3 Hz, H4a), 2.80-2.64 (2H, m), 2.54-2.40 (4H, m), 2.24-1.92 (6H, m), 1.28 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.11 (3H, s, 9b-methyl), 1.00 (3H, d, *J*=6.2 Hz, 2-methyl). ^{13}C NMR ($CDCl_3$) δ 213.9 (0, C8), 209.1 (0), 207.9 (0), 172.7 (0, COOEt), 61.1 (2, OCH_2CH_3), 51.7 (1, C4a), 50.1 (1), 49.1 (2), 46.6 (1), 46.3 (1), 42.5 (0, C9b), 38.2 (2), 37.7 (2), 36.4 (2), 36.2 (1), 33.7 (2), 19.7 (3, 2-methyl), 15.3 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 334 (M^+, 14), 289 (7), 253 (13), 211 (12), 182 (14), 165 (5), 164 (5), 163 (6), 149 (8), 137 (9), 136 (14), 135 (12), 123 (11), 121 (12), 110 (10), 109 (14), 108 (11), 107 (17), 105 (12), 95 (17), 93 (20), 91 (26), 88 (14), 86 (12), 84 (19), 81 (32), 79 (32), 77 (23), 69 (30), 67 (21), 55 (81), 54 (24), 53 (37), 43 (26), 42 (15), 41 (72), 39 (33), 29 (100). HRMS calcd. for $C_{19}H_{26}O_5$ 334.1779, found 334.1792.

Ethyl (1α,4aβ,6aα,9aα,9bα)-1,4a,5,6a,7,9,9a-heptahydro-2,9b-dimethyl-4,6-dioxo-8-(spiro-1,3-dioxolan-2-yl)-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methyl-carboxylate (171)

To a solution of **137** (115 mg, 0.272 mmol) in acetonitrile (1 mL) was added 1,2-ethanediol (5 mL) and [bis(trifluoroacetoxy)iodo]benzene (181 mg, 0.408 mmol) at rt. After the mixture was stirred at rt for 10 min, it was poured into saturated $NaHCO_3$ solution. This was extracted with EtOAc (4 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane) to afford **171** (57 mg, 56%) as a white foam: IR (Nujol) 1713 (s), 1667 (s), 1626 (s), 1236 (s), 1169 (s), 1025 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.94 (1H, s, H3), 4.28-4.17 (2H, m, OCH_2CH_3), 3.96-3.88 (3H, m, OCH_2CH_2O), 3.80 (1H, m, OCH_2CH_2O), 3.18 (1H, d, *J*=10.0 Hz, H1), 2.87 (1H, dd, *J*=11.5, 3.0 Hz, H4a), 2.85 (1H, m), 2.77 (1H, m), 2.75 (1H, dd, *J*=13.0, 4.0 Hz), 2.59-2.53 (2H, m), 2.46 (1H, dd, *J*=9.5, 3.5 Hz), 2.43 (1H, dd, *J*=13.0, 6.0 Hz), 1.98 (1H, dd, *J*=13.0, 6.0 Hz), 1.89 (3H, s, 2-methyl), 1.85 (1H, dd, *J*=14.3, 8.8 Hz), 1.57 (1H, apparent t, *J*=13.5 Hz), 1.31 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.08 (3H, s, 9b-methyl). NOE data 3.18 (2.87, 3%, 1.57, 4%), 1.85 (2.85, 6%), 1.08 (2.77, 3%). ^{13}C NMR ($CDCl_3$) δ 209.2 (0, C6), 197.6 (0, C4), 172.8 (0, COOEt), 159.4 (0, C2), 126.4 (1, C3), 115.1 (0, C8), 64.6 (2, OCH_2CH_2O), 64.0 (2, OCH_2CH_2O), 61.2 (2, OCH_2CH_3), 50.1 (1, C4a), 49.3 (1), 47.7 (1), 45.3 (1, C1), 41.5 (0, C9b), 37.1 (2), 36.0 (2), 35.96 (2), 31.6 (2), 21.8 (3, 2-methyl), 15.1 (3,

9b-methyl), 14.1 ($OCH_2\mathbf{C}H_3$). MS *m/z* 376 (M^+, 52), 361 (6), 303 (29), 289 (6), 287 (14), 221 (14), 175 (15), 168 (19), 141 (13), 135 (20), 127 (31), 126 (62), 125 (20), 112 (21), 105 (12), 99 (76), 95 (21), 91 (21), 87 (27), 86 (100), 67 (17), 55 (37), 41 (29). HRMS calcd. for $C_{21}H_{28}O_6$ 376.1884, found 376.1883.

Ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6,6a,7,9,9a-octahydro-6-hydroxy-2,9b-dimethyl-4-oxo-8-(spiro-1,3-dioxolan-2-yl)-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (172)

To a solution of **171** (466 mg, 1.24 mmol) in dry THF (50 mL) was added L-Selectride (1.0 M solution in THF, 1.49 mL, 1.49 mmol) at –78 °C. The solution was stirred at –78 °C for 3 h before the reaction was quenched with 5% aqueous NaOH solution (5 mL). After warming to rt, the mixture was diluted with EtOAc (200 mL), washed by water (40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was subjected to column chromatography (70% EtOAc/hexane) to afford **172** (387 mg, 83%) as a white solid: mp 95-97 °C. IR (Nujol) 3467 (br, s), 1722 (s), 1673 (s), 1628 (s), 1299 (s), 1168 (s), 1042 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.88 (1H, s, H3), 4.27-4.16 (2H, m, $O\mathbf{C}H_2CH_3$), 4.04 (1H, d, *J*=2.5 Hz, H6), 4.0-3.94 (2H, m, OCH_2CH_2O), 3.90-3.85 (2H, m, OCH_2CH_2O), 3.19 (1H, d, *J*=10.5 Hz, H1), 2.94 (1H, dd, *J*=11.8, 2.8 Hz, H4a), 2.49 (1H, m), 2.35 (1H, dd, *J*=9.5, 3.0 Hz), 2.32 (1H, dd, *J*=11.5, 2.5 Hz), 2.23 (1H, dt, *J*=15.0, 3.0 Hz, H5), 2.17-2.09 (3H, m),

2.04 (1H, m, H6a or H9a), 1.88 (1H, m), 1.85 (3H, s, 2-methyl), 1.53 (1H, ddd, *J*=14.8, 12.0, 3.0 Hz, H5), 1.30 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.83 (3H, s, 9b-methyl). NOE data 4.04 (2.17-2.09, 4%), 3.19 (2.94, 6%), 1.53 (4.04, 2%, 0.83, 2%), 0.83 (1.53, 6%). ^{13}C NMR ($CDCl_3$) δ 200.8 (0, C4), 173.2 (0, **C**OOEt), 159.0 (0, C2), 126.8 (1, C3), 117.1 (0, C8), 68.6 (1, C6), 64.3 (2, $O\mathbf{C}H_2CH_2O$), 64.2 (2, $OCH_2\mathbf{C}H_2O$), 61.0 (2, $O\mathbf{C}H_2CH_3$), 46.8 (1), 45.1 (1, C1), 43.1 (1, C4a), 41.6 (2), 41.1 (0, C9b), 39.2 (1), 38.7 (2), 31.6 (2, $\mathbf{C}H_2COOEt$), 27.6 (2, C5), 21.8 (3, 2-methyl), 15.4 (3, 9b-methyl), 14.1 ($OCH_2\mathbf{C}H_3$). MS *m/z* 378 (M^+, 46), 333 (21), 316 (15), 291 (14), 287 (11), 273 (14), 243 (10), 230 (9), 229 (51), 227 (12), 221 (31), 211 (10), 201 (21), 199 (11), 187 (21), 185 (26), 183 (14), 182 (42), 177 (42), 169 (13), 168 (49), 165 (26), 161 (14), 159 (15), 155 (20), 152 (38), 149 (20), 148 (15), 147 (36), 141 (20), 140 (27), 139 (18), 135 (73), 128 (25), 127 (85), 126 (63), 107 (22), 105 (25), 99 (94), 95 (65), 91 (37), 87 (67), 86 (100), 79 (29), 67 (40), 55 (46), 45 (36), 43 (61). HRMS calcd. for $C_{21}H_{30}O_6$ 378.2041, found 378.2036.

Ethyl (1α,4aβ,6β,6aα,9aα,9bα)-1,4a,5,6,6a,7,9,9a-octahydro-6-methoxy-methoxy-2,9b-dimethyl-4-oxo-8-(spiro-1,3-dioxolan-2-yl)-1*H*-benz[6,7]-indeno-[2,1-*b*]-1-methylcarboxylate (156)

To a solution of **172** (255 mg, 0.674 mmol) in dry CH_2Cl_2 (20 mL) was added (i-Pr)$_2$NEt (0.88 mL, 5.0 mmol) and chloromethyl methyl ether (0.26 mL,

3.4 mmol) at rt. The mixture was stirred at rt for 24 h. After the mixture was cooled to rt, it was diluted with CH_2Cl_2 (100 mL), washed by water (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The residue was subjected to column chromatography (60% EtOAc/hexane) to provide **156** (193 mg, 68%) as a white solid: mp 91.5-93 °C. IR (Nujol) 1713 (s), 1667 (s), 1626 (s), 1238 (s), 1169 (s), 1025 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.89 (1H, m, H3), 4.68 (1H, d, *J*=7.1 Hz, OCH_2O), 4.55 (1H, d, *J*=6.9 Hz, OCH_2O), 4.27-4.14 (2H, m, OCH_2CH_3), 3.97-3.80 (4H, m, OCH_2CH_2O), 3.78 (1H, m, H6), 3.42 (3H, s, OCH_3), 3.19 (1H, d, *J*=10.0 Hz, H1), 2.78 (1H, dd, *J*=12.1, 3.1 Hz, H4a), 2.55-2.35 (2H, m), 2.26 (1H, dd, *J*=12.8, 2.5 Hz, H5), 2.18-2.07 (3H, H6a and H7), 2.02 (1H, m, H9a), 1.86 (3H, d, *J*=1.3 Hz, 2-methyl), 1.73 (2H, dd, *J*=11.5, 5.3 Hz, H9), 1.40 (1H, ddd, *J*=14.6, 12.3, 2.3 Hz, H5), 1.30 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.82 (3H, s, 9b-methyl). NOE data 3.78 (2.18-2.07, 5%), 3.19 (2.78, 5%). ^{13}C NMR ($CDCl_3$) δ 200.8 (0, C4), 173.2 (0, COOEt), 159.4 (0, C2), 126.7 (1, C3), 117.1 (0, C8), 95.7 (2, OCH_2O), 74.5 (1, C6), 64.5 (2, OCH_2CH_2O), 63.5 (2, OCH_2CH_2O), 60.9 (2, OCH_2CH_3), 55.9 (3, OCH_3), 46.7 (1, C9a), 45.4 (1, C1), 43.8 (1, C4a), 41.4 (0, C9b), 39.6 (2), 37.6 (1, C6a), 37.5 (2), 31.5 (2, CH_2COOEt), 24.6 (2, C5), 21.9 (3, 2-methyl), 15.3 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 422 (M^+, 16), 377 (14), 361 (15), 360 (4), 275 (5), 273 (9), 266 (4), 221 (9), 199 (8), 171 (6), 159 (7), 152 (11), 147 (9), 140 (6), 139 (8), 135 (8), 127 (11), 126 (13), 125 (11), 119 (6), 105 (5), 99 (20), 91 (7), 89 (19), 87

(31), 86 (46), 84 (40), 67 (8), 59 (9), 55 (8), 49 (7), 47 (10), 45 (100). HRMS calcd. for $C_{23}H_{34}O_7$ 422.2304, found 422.2309.

Ethyl (1α,2β,4aβ,6β,6aα,9aα,9bα)-1,2,3,4a,5,6,6a,7,9,9a-decahydro-6-methoxymethoxy-2,9b-dimethyl-4-oxo-8-(spiro-1,3-dioxolan-2-yl)-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (174)

Liquid ammonia (approximately 100 mL) was collected in a 250 mL three-necked round-bottomed flask using a dry ice-acetone cold trap. To this liquid ammonia were added Na shavings (approximately 0.2 g). The ammonia solution turned blue immediately. After 5 min, this ammonia solution was allowed to warm, and about 60 mL of dry ammonia were distilled into a dry 250 mL three-necked round-bottomed flask. To this dry liquid ammonia were added Li shavings (14.5 mg, 2.07 mmol) and the ammonia solution turned blue immediately. This blue solution was allowed to warm to –50 °C when enone **156** (125 mg, 0.296 mmol) in 1:1 dry 1,4-dioxane/Et_2O (14 mL) was introduced over 1 min. The mixture was stirred for 5 min before sufficient anhydrous NH_4Cl was added to discharge the blue color. This was allowed to warm up to evaporate ammonia. The remainder was diluted with water (100 mL) and extracted with EtOAc (4 x 20 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to afford **174** (89 mg, 71%) as a

white solid: mp 151-152 °C. IR (Nujol) 1714 (s), 1338 (s), 1278 (s), 1218 (s), 1150 (s), 1104 (s), 1018 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.64 (1H, d, *J*=7.0 Hz, OCH_2O), 4.54 (1H, d, *J*=7.0 Hz, OCH_2O), 4.22-4.10 (2H, m, OCH_2CH_3), 3.95-3.84 (3H, m, OCH_2CH_2O), 3.78 (1H, m, OCH_2CH_2O), 3.75 (1H, m, H6), 3.41 (3H, s, OCH_3), 2.80 (1H, d, *J*=11.0 Hz, H4a), 2.54 (1H, d, *J*=16.5 Hz), 2.32 (1H, dd, *J*=14.0, 4.5 Hz), 2.20-2.10 (4H, m), 2.08-1.93 (4H, m), 1.91-1.84 (2H, m), 1.52 (1H, ddd, *J*=14.3, 12.5, 1.8 Hz, H5), 1.27 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 0.95 (3H, d, *J*=6.5 Hz, 2-methyl), 0.73 (3H, s, 9b-methyl). NOE data 3.75 (3.95-3.90, 11%), 3.95-3.90 (3.75, 6%; 2.80, 7%; 0.95, 6%), 0.95 (2.32, 3%; 3.95-3.90, 7%; 3.89-3.84, 9%). ^{13}C NMR ($CDCl_3$) δ 212.5 (0, C4), 173.6 (0, COOEt), 117.4 (0, C8), 95.8 (2, OCH_2O), 74.6 (1, C6), 64.5 (2, OCH_2CH_2O), 63.5 (2, OCH_2CH_2O), 60.6 (2, OCH_2CH_3), 55.9 (3, OCH_3), 49.8 (2), 47.2 (1), 46.6 (1), 46.1 (1, C4a), 42.1 (0, C9b), 39.2 (2), 37.8 (1), 36.5 (2), 36.4 (1, C2), 33.5 (2), 24.9 (2, C5), 20.0 (3, 2-methyl), 15.8 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 424 (M^++2, 6), 380 (6), 379 (24), 276 (2), 275 (2), 255 (3), 253 (5), 226 (3), 212 (12), 200 (4), 199 (36), 171 (4), 153 (5), 152 (4), 140 (8), 139 (14), 126 (19), 125 (22), 112 (5), 107 (5), 99 (30), 89 (12), 87 (36), 86 (62), 69 (8), 59 (7), 55 (11), 45 (100). HRMS calcd. for $C_{23}H_{36}O_7$ 424.2459, found 424.2432.

Ethyl (1α,2β,4α,4aβ,6β,6aα,9aα,9bα)-1,2,3,4,4a,5,6,6a,7,9,9a-undecahydro-4-hydroxy-6-methoxymethoxy-2,9b-dimethyl-8-(spiro-1,3-dioxolan-2-yl)-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (175)

To a solution of **174** (68 mg, 0.16 mmol) in dry THF (10 mL) was added L-Selectride (1.0 M solution in THF, 0.24 mL, 0.24 mmol) at –78 °C. The solution was kept stirring at –78 °C for 2 h before the reaction was quenched with 5% aqueous NaOH solution (1 mL). After warming to rt, the mixture was diluted with EtOAc (100 mL), washed by water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to column chromatography (60% EtOAc/hexane) to afford **175** (53 mg, 79%) as a white solid: mp 105-106 °C. IR (Nujol) 1722 (s), 1299 (s), 1215 (s), 1165 (s), 1040 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.69 (1H, d, *J*=7.5 Hz, OCH_2O), 4.60 (1H, d, *J*=7.0 Hz, OCH_2O), 4.19-4.06 (2H, m, OCH_2CH_3), 3.93-3.82 (4H, m, H4 and OCH_2CH_2O), 3.78-3.75 (2H, m, H6 and OCH_2CH_2O), 3.42 (3H, s, OCH_3), 2.44 (1H, d, *J*=16.5 Hz), 2.22 (1H, m), 2.13 (1H, d, *J*=14.0 Hz), 2.05-1.99 (2H, m), 1.95 (1H, m), 1.88-1.82 (3H, m), 1.79 (1H, dd, *J*=10.7, 4.2 Hz), 1.75 (1H, m), 1.64-1.56 (2H, m), 1.40 (1H, ddd, *J*=14.8, 14.3, 3.3 Hz), 1.25 (3H, t, *J*=8.0 Hz, OCH_2CH_3), 1.03 (3H, s, 9b-methyl), 0.83 (3H, d, *J*=7.0 Hz, 2-methyl). NOE data 3.93-3.82 (1.88-1.82, 2%; 1.64-1.56, 4%), 3.78-3.75 (2.22, 6%), 2.22 (3.78-3.75, 4%; 1.03, 3%), 1.03 (2.44, 8%; 1.88-1.82, 3%), 0.83 (1.95, 7%). ^{13}C NMR ($CDCl_3$) δ 174.5 (0, COOEt), 117.7 (0, C8), 96.3 (2, OCH_2O), 76.5 (1, C6), 72.5

(1, C4), 64.4 (2, O**C**H_2CH_2O), 63.4 (2, OCH_2**C**H_2O), 60.2 (2, O**C**H_2CH_3), 55.7 (3, OCH_3), 48.8 (1), 47.4 (1), 43.3 (2), 39.3 (0, C9b), 38.3 (2), 37.4 (1), 36.5 (2), 35.5 (1), 33.4 (2), 30.4 (2), 29.1 (1), 19.6 (3, 2-methyl), 17.5 (3, 9b-methyl), 14.1 (3, OCH_2**C**H_3). MS *m/z* 426 (M^+, 1), 381 (3), 366 (2), 320 (2), 319 (2), 276 (1), 215 (2), 210 (2), 199 (28), 195 (3), 172 (3), 171 (3), 153 (3), 139 (5), 127 (7), 126 (7), 125 (12), 119 (8), 107 (9), 99 (23), 87 (14), 86 (29), 81 (7), 79 (6), 67 (6), 55 (12), 45 (100). HRMS calcd. for $C_{23}H_{38}O_7$ 426.2615, found 426.2647.

Ethyl (1α,2β,4α,4aβ,6β,6aα,9aα,9bα)-1,2,3,4,4a,5,6,6a,7,9,9a-undecahydro-4-(2-methoxyethoxy)methoxy-6-methoxymethoxy-2,9b-dimethyl-8-(spiro-1,3-dioxolan-2-yl)-1*H*-benz[6,7]indeno-[2,1-*b*]-1-methylcarboxylate (176)

To a solution of **175** (50 mg, 0.12 mmol) in dry CH_2Cl_2 (10 mL) was added $^iPr_2NEt$ (0.30 mL, 1.8 mmol) and MEM chloride (0.13 mL, 1.2 mmol) at rt. The mixture was heated at reflux for 7 days. After the mixture was cooled to rt, it was diluted with CH_2Cl_2 (100 mL), washed by water (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (60% EtOAc/hexane) to provide **176** (15 mg, 25%) and starting material **175** (25 mg, 50%).

Compound **176**: IR (CH_2Cl_2) 1730 (s), 1423 (s), 1373 (s), 1266 (s), 1160 (s), 1105 (s), 1042 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.73 (1H, d, *J*=7.0 Hz, OCH_2O),

4.68 (1H, d, *J*=7.0 Hz, OCH_2O), 4.62 (1H, d, *J*=7.0 Hz, OCH_2O), 4.58 (1H, d, *J*=7.0 Hz, OCH_2O), 4.18-4.05 (2H, m, OCH_2CH_3), 3.92-3.82 (3H, m, OCH_2CH_2O), 3.76 (1H, dd, *J*=13.5, 7.0 Hz, OCH_2CH_2O), 3.72-3.69 (2H, m, H6 and $OCH_2CH_2OCH_3$), 3.68-3.64 (2H, m, H4 and $OCH_2CH_2OCH_3$), 3.54 (2H, t, *J*=4.8 Hz, $OCH_2CH_2OCH_3$), 3.42 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 2.44 (1H, d, *J*=17.0 Hz), 2.19 (1H, m), 2.12 (1H, m), 2.04-1.96 (m), 1.94-1.77 (m), 1.62-1.53 (2H, m), 1.25 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.21 (1H, m), 0.97 (3H, 9b-methyl), 0.81 (3H, d, *J*=6.5 Hz, 2-methyl). ^{13}C NMR ($CDCl_3$) δ 174.6 (0, COOEt), 117.8 (0, C8), 96.1 (2, OCH_2OCH_3), 94.5 (2, $OCH_2OCH_2CH_2OCH_3$), 78.2 (1, C4), 76.4 (1, C6), 71.8 (2, $OCH_2CH_2OCH_3$), 66.8 (2, $OCH_2CH_2OCH_3$), 64.4 (2, OCH_2CH_2O), 63.4 (2, OCH_2CH_2O), 60.2 (2, OCH_2CH_3), 59.1 (3, OCH_3), 55.7 (3, OCH_3), 48.7 (1), 47.4 (1), 39.8 (2), 39.3 (2). 38.2 (1), 37.6 (0, C9b), 36.5 (2), 35.6 (1), 33.5 (2), 30.6 (2), 29.5 (1), 19.6 (3, 2-methyl), 17.2 (3, 9b-methyl), 14.1 (3, OCH_2CH_3). MS *m/z* 425 (M^+-$CH_3OCH_2CH_2OCH_2$, 1), 381 (2), 365 (3), 332 (2), 320 (4), 319 (8), 304 (2), 303 (9), 302 (4), 275 (3), 274 (2), 257 (2), 245 (2), 232 (3), 231 (3). 215 (5), 199 (3), 195 (4), 173 (3), 147 (4), 135 (4), 133 (5), 119 (8), 105 (6), 93 (6), 89 (57), 59 (76), 45 (100). HRMS calcd. for $C_{27}H_{46}O_9$ 514.3139, found (to be determined).

6-(*tert*-Butyldimethylsilyloxy)-2,9b-dimethyl-4aα,5,7,8,9,9aα,9b-heptahydro-1*H*-cyclopenta[*a*]naphthalene-1,4-dione (187)

1-Acetyl-1-cyclopentene was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine in CH_2Cl_2 at 0 °C to produce the diene 1-[(*tert*-butyldimethylsilyloxy)vinyl]-1-cyclopentene. The procedure is same as the preparation of **71**, which was described previously in this thesis.

The mixture of the above diene (3.64 g, 16.2 mmol) and 2,6-dimethylbenzoquinone (**15**) (4.46 g, 32.4 mmol) in dry toluene (200 mL) was heated at reflux for 3 days. After the solvent was removed under reduced pressure, the residue was subjected to flash column chromatography (10% dry EtOAc/hexane) to afford **187** (4.86 g, 83%) as a viscous orange oil: IR (Nujol) 1683 (s), 1624 (s), 1260 (s), 1216 (s), 1172 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.41 (1H, s, H3), 2.87 (1H, t, *J*=8.0 Hz, H4a), 2.42-2.10 (5H, m), 1.95 (3H, d, *J*=0.8 Hz, 2-methyl), 1.92-1.85 (2H, m), 1.79-1.70 (2H, m), 1.39 (3H, s, 9b-methyl), 0.89 (9H, s, $SiC(CH_3)_3$), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$). NOE data 1.39 (2.87, 4%). ^{13}C NMR ($CDCl_3$) δ 202.4 (0), 200.5 (0), 148.7 (0), 137.3 (0), 133.5 (1, C3), 120.8 (0), 57.1 (1, C4a), 50.4 (0, C9b), 49.4 (1, C9a), 31.8 (2), 28.0 (2), 27.8 (2), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 24.8 (3, 9b-methyl), 24.5 (2), 17.9 (0, $Si\mathbf{C}(CH_3)_3$), 16.5 (3, 2-methyl), -4.1 (3, $Si(CH_3)_2$). MS *m/z* 360 (M^+, 2), 345 (1), 303 (3), 244 (2), 211 (3), 205 (1), 195 (4), 177 (4), 176 (4), 168 (8), 167 (7), 150 (3), 132 (2), 121 (1), 120 (1), 105 (1), 91 (4), 84 (3), 83 (2), 79 (2), 77 (7), 76 (10), 75 (100). HRMS calcd. for $C_{21}H_{32}O_3Si$ 360.2119, found 360.2134.

(4α,4aα,9aα,9bα)-6-(*tert*-Butyldimethylsilyloxy)-2,9b-dimethyl-4-hydroxy-4,4a,5,7,8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalen-1-one and (4β,4aα,9aα,9bα)-6-(*tert*-butyldimethylsilyloxy)-2,9b-dimethyl-4-hydroxy-4,4a,5,7,8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalen-1-one (188)

To a solution of **187** (360 mg, 1.00 mmol) and $CeCl_3 \bullet 7H_2O$ (373 mg, 1.00 mmol) methanol (10 mL) was added sodium borohydride (26.6 mg, 0.70 mmol) at 0 °C over 5 min. The resulting mixture was stirred at the same temperature for another 2 min before it was quenched with dilute NH_4Cl solution (40 mL) and extracted with EtOAc (4 x 25 mL). The combined extracts were washed with water (2 x 25 mL), brine (25 mL), and dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the residue was subjected to column chromatography (30% dry EtOAc/hexane) to provide **188** (347 mg, 96% combined yield) as a 1:1 mixture of epimers. These two epimers were separated by column chromatography.

Compound **4α-188**: pale-yellow viscious oil. IR (Nujol) 3393 (br s), 1712 (s), 1306 (s), 1251 (s), 1171 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.51 (1H, d, *J*=2.1 Hz, H3), 4.32 (1H, m, H4), 2.46-2.23 (m), 2.16-1.98 (m), 1.79 (3H, d, *J*=0.9 Hz, 2-methyl), 1.66 (1H, dd, *J*=9.2, 3.5 Hz), 1.55-1.41 (m), 1.34 (3H, s, 9b-methyl), 1.24 (1H, m), 0.93 (9H, s, $SiC(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 202.7 (0, C1), 144.7 (1, C3), 137.7 (0), 135.2 (0), 121.1 (0), 66.7 (1, C4), 49.5 (1), 49.0 (1), 45.3 (0, C9b), 30.2 (2), 29.9 (2), 25.7 (3, $SiC(CH_3)_3$),

25.2 (3, 9b-methyl), 25.1 (2), 22.5 (2), 18.1 (0, Si**C**$(CH_3)_3$), 16.1 (3, 2-methyl), -4.0 (3, $SiCH_3$), -4.2 (3, $SiCH_3$). MS *m/z* 362 (M^+, 1), 307 (2), 280 (1), 265 (4), 264 (16), 225 (4), 205 (5), 168 (3), 167 (3), 149 (10), 148 (5), 138 (14), 135 (7), 98 (13), 91 (6), 77 (7), 76 (8), 75 (100), 73 (23). HRMS calcd. for $C_{21}H_{34}O_3Si$ 362.2275, found (to be determined).

Compound **4β-188**: colorless viscious oil. IR (Nujol) 3421 (br s), 1713 (s), 1306 (s), 1167 (s), 958 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.34 (1H, d, *J*=1.2 Hz, H3), 4.93 (1H, m, H4), 2.53-2.43 (m), 2.33-2.19 (m), 2.06-1.95 (m), 1.91-1.78 (m), 1.74 (3H, s, 2-methyl), 1.43 (1H, m), 1.28 (3H, s, 9b-methyl), 0.90 (9H, $SiC(CH_3)_3$), 0.04 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$). NOE data 4.93 (6.34, 4%; 1.28, 7%), 1.28 (4.93, 8%). ^{13}C NMR ($CDCl_3$) δ 202.7 (0, C1), 144.1 (1, C3), 138.1 (0), 134.2 (0), 121.4 (0), 67.9 (1, C4), 50.9 (1), 50.2 (1), 47.9 (0, C9b), 28.9 (2), 28.5 (2), 28.0 (2), 25.7 (3, $SiC(CH_3)_3$), 25.0 (2), 22.0 (3, 9b-methyl), 18.0 (0, Si**C**$(CH_3)_3$), 15.9 (3, 2-methyl), -4.0 (3, $SiCH_3$), -4.1 (3, $SiCH_3$). MS *m/z* 317 (M^+-45, 2), 305 (2), 262 (4), 245 (4), 244 (8), 229 (6), 228 (5), 216 (5), 215 (6), 203 (6), 202 (6), 201 (6), 189 (6), 188 (4), 187 (5), 177 (6), 175 (11), 165 (9), 164 (6), 163 (8), 161 (7), 151 (10), 150 (15), 149 (100), 147 (26), 137 (27), 135 (19), 121 (30), 98 (68), 91 (23), 75 (27), 55 (28), 43 (34). HRMS calcd. for $C_{21}H_{34}O_3Si$ 362.2275, found (to be determined).

1,3-Dithienium tetrafluoroborate (183)

This reagent was prepared by the procedure of Corey and Walinsky.[77] A mixture of 1,3-dithiane (1.21 g, 9.79 mmol) and triphenylcarbenium tetrafluoroborate (3.23 g, 9.79 mmol) in dry CH_2Cl_2 (25 mL) was heated at reflux for 2 h, during which period a yellow precipitate was produced. After the solvent was decanted, the precipitate was washed with cold dry CH_2Cl_2 (3 x 5 mL) and Et_2O (2 x 5 mL), and dried under vacuum to give **183** (1.77 g, 88%) as a pale yellow solid.

(4β,4aα,6aα,9aα,9bα)-6a-(1,3-Dithian-2-yl)-4-hydroxy-2,9b-dimethyl-4,4a,5,7,8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalene-1,6-dione (189)

To solution of **4β-188** (101 mg, 0.279 mmol) in dry CH_2Cl_2 (3 mL) was added a solution of 1,3-dithienium tetrafluoroborate (**183**) (172 mg, 0.836 mmol) in dry CH_3NO_2 (1 mL) at –78 °C under argon over 5 min. The solution was stirred at –78 °C for 20 min. After warming to rt, the reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (60% EtOAc/hexane) to afford **189** (34 mg, 40%) as a white solid: mp 171-172 °C. IR (Nujol) 3407 (br, s), 1712 (s), 1306 (s), 1236 (s),

1170 (s), 1050 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.34 (1H, d, *J*=1.5 Hz, H3), 4.86 (1H, t, *J*=2.2 Hz, H4), 4.34 (1H, s, H2 in dithiane), 2.91-2.77 (m), 2.66 (1H, dd, *J*=9.0, 5.7 Hz), 2.29 (1H, dd, *J*=17.8, 9.2 Hz), 2.14-2.05 (m), 1.97-1.79 (m), 1.75 (3H, s, 2-methyl) 1.68 (m), 1.40 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 211.6 (0, C5), 201.8 (0, C1), 140.6 (1, C3), 136.1 (0, C2), 67.1 (1, C4), 63.5 (0, C6a), 58.1 (1, C2 in dithiane), 53.0 (1), , 48.5 (0, C9b), 47.6 (1), 36.9 (2), 33.5 (2), 31.8 (2), 31.6 (2), 28.7 (2), 25.7 (2), 24.2 (2), 23.4 (3, 9b-methyl), 15.9 (3, 2-methyl). MS *m/z* 366 (6), 349 (7), 348 (21), 291 (5), 230 (10), 229 (11), 228 (17), 227 (9), 213 (9), 149 (7), 135 (6), 121 (10), 120 (13), 119 (100), 93 (6), 91 (9), 79 (6), 77 (6), 65 (5). HRMS calcd. for $C_{19}H_{26}O_3S_2$ 366.1322, found 366.1330.

(4β,4aα,9aα,9bα)-4-Acetoxy-6-(*tert*-butyldimethylsilyloxy)-2,9b-dimethyl-4,4a,5,7,8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalene-1-one (190)

To a solution of **4β-188** (544 mg, 1.50 mmol) in dry CH_2Cl_2 (15 mL) was added Ac_2O (0.71 mL, 7.5 mmol), Et_3N (1.05 mL, 7.50 mmol) and 4-(dimethylamino)pyridine (DMAP) (36.7 mg, 0.30 mmol) at rt. The resulting solution was stirred at rt for 24 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed by brine (2 x 20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (20% anhydrous Et_2O/hexane) to provide **190** (478 mg, 74%) as a yellow oil: IR (Nujol) 1736 (s), 1674 (s), 1234 (s), 1025 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.44 (1H, s, H3),

5.92 (1H, t, *J*=2.5 Hz, H4), 2.98 (1H, m), 2.90 (1H, m), 2.73 (1H, m), 2.57-2.53 (2H, m), 2.40 (1H, dd, *J*=17.3, 12.9 Hz), 2.12 (3H, s, CH_3COO), 2.08 (m), 1.94 (1H, m), 1.84 (3H, 2-methyl), 1.67 (1H, m), 1.50 (3H, 9b-methyl), 0.92 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 198.5 (0, C1), 170.1 (0, CH_3COO), 139.6 (1, C3), 138.0 (0), 137.4 (0), 136.8 (0), 68.2 (1, C4), 49.1 (0, C9b), 46.5 (1), 36.0 (2), 35.7 (2), 29.3 (2), 25.7 (3, $SiC(CH_3)_3$), 21.7 (2), 21.4 (3, 9b-methyl), 21.0 (3, CH_3COO), 18.1 (0, $SiC(CH_3)_3$), 15.9 (3, 2-methyl), -3.6 (3, $Si(CH_3)_2$). MS *m/z* 404 (M^+, 2), 363 (1), 327 (1), 304 (2), 303 (6), 287 (2), 285 (5), 270 (2), 262 (2), 257 (2), 246 (2), 245 (2), 244 (4), 230 (4), 229 (4), 228 (2), 223 (7), 213 (4), 212 (3), 211 (5), 206 (3), 205 (14), 191 (9), 189 (3), 185 (4), 184 (4), 183 (6), 177 (2), 169 (3), 165 (5), 163 (7), 159 (3), 150 (11), 149 (100), 148 (11), 147 (21), 121 (21), 98 (79), 91 (11), 75 (32), 73 (22), 43 (85). HRMS calcd. for $C_{23}H_{36}O_4Si$ 404.2381, found 404.2372.

(4β,4aα,6aα,9aα,9bα)-4-Acetoxy-6a-(1,3-dithian-2-yl)-2,9b-dimethyl-4,4a,5,7,8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalene-1,6-dione (191)

To solution of **4β-190** (415 mg, 1.10 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of 1,3-dithienium tetrafluoroborate (**183**) (600 mg, 2.91 mmol) in dry CH_3NO_2 (2 mL) at –78 °C under argon over 5 min. The solution was stirred at –78 °C for 20 min. After warming up to rt, the reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (3 x 40 mL). The

combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (40% EtOAc/hexane) to afford **191** (233 mg, 52%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.26 (1H, s, H3), 5.83 (1H, t, *J*=2.4 Hz, H4), 4.30 (1H, s, C2 in dithiane), 2.99 (1H, m), 2.92-2.82 (2H, m), 2.71 (1H, dd, *J*=14.6, 8.0 Hz), 2.66 (1H, dd, *J*=5.9, 3.6 Hz), 2.32 (1H, dd, *J*=18.8, 10.1 Hz), 2.26 (1H, m), 2.17-2.08 (4H, m), 2.05 (3H, s, CH_3COO), 1.95-1.79 (3H, m), 1.76 (3H, s, 2-methyl), 1.66 (1H, m), 1.46 (3H, s, 9b-methyl). NOE data 4.30 (2.99, 3%; 2.71 and 2.66, 12%), 1.46 (5.83, 12%; 4.30, 2%; 2.99, 3%; 2.71 and 2.66, 17%). ^{13}C NMR ($CDCl_3$) δ 210.5 (0, C6), 201.2 (0, C1), 170.2 (0, CH_3**C**OO), 137.4 (0, C2), 136.5 (1, C3), 69.4 (1, C4), 63.3 (0, C6a), 57.8 (1, C2 in dithiane), 52.6 (1), 48.5 (0, C9b), 44.8 (1), 37.2 (2), 33.4 (2), 31.7 (2), 31.5 (2), 28.6 (2), 25.6 (2), 24.1 (2), 23.4 (3, 9b-methyl), 20.9 (3, **C**H_3COO), 15.9 (3, 2-methyl).

(4β,4aα,6aα,9aα,9bα)-6a-(1,3-Dithian-2-yl)-4-hydroxy-2,9b-dimethyl-4,4a,5,7,8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalene-1,6-dione (189)

To a solution of **191** (197 mg, 0.480 mmol) in methanol (10 mL) was added a solution of K_2CO_3 (335 mg, 2.40 mmol) in water (2 mL) at rt. The mixture was stirred at rt for 2 h. The reaction mixture was quenched with 1% HCl solution (5 mL), extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under

vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane) to afford **189** (158 mg, 89%) as a white solid: mp 171-172 °C. IR (Nujol) 3407 (br, s), 1712 (s), 1306 9s), 1236 (s), 1170 (s), 1050 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.34 (1H, d, *J*=1.5 Hz, H3), 4.86 (1H, t, *J*=2.2 Hz, H4), 4.34 (1H, s, H2 in dithiane), 2.91-2.77 (m), 2.66 (1H, dd, *J*=9.0, 5.7 Hz), 2.29 (1H, dd, *J*=17.8, 9.2 Hz), 2.14-2.05 (m), 1.97-1.79 (m), 1.75 (3H, s, 2-methyl) 1.68 (m), 1.40 (3H, s, 9b-methyl). ^{13}C NMR ($CDCl_3$) δ 211.6 (0, C5), 201.8 (0, C1), 140.6 (1, C3), 136.1 (0, C2), 67.1 (1, C4), 63.5 (0, C6a), 58.1 (1, C2 in dithiane), 53.0 (1), 48.5 (0, C9b), 47.6 (1), 36.9 (2), 33.5 (2), 31.8 (2), 31.6 (2), 28.7 (2), 25.7 (2), 24.2 (2), 23.4 (3, 9b-methyl), 15.9 (3, 2-methyl). MS *m/z* 366 (6), 349 (7), 348 (21), 291 (5), 230 (10), 229 (11), 228 (17), 227 (9), 213 (9), 149 (7), 135 (6), 121 (10), 120 (13), 119 (100), 93 (6), 91 (9), 79 (6), 77 (6), 65 (5). HRMS calcd. for $C_{19}H_{26}O_3S_2$ 366.1322, found 366.1330.

(4α(β),4aα,7aβ,10aβ,10bα,10cα)-6-(1-*tert*-Butyldimethylsilyl)oxy-4-hydroxy-4,4a,5,7,7a,10,10a,10b,10c-nonahydro-2,10c-dimethylbenz[6,7]indeno[2,1-*b*]furan-1,9-dione (192)

To a solution of **33** (858 mg, 2.06 mmol) and $CeCl_3 \bullet 7H_2O$ (775 mg, 2.06 mmol) methanol (20 mL) was added sodium borohydride (55.7 mg, 1.44 mmol) at 0 °C over 5 min. The resulting mixture was stirred at the same temperature for

another 2 min before it was quenched with dilute NH_4Cl solution (40 mL) and extracted with EtOAc (4 x 40 mL). The combined extracts were washed with water (2 x 40 mL), brine (40 mL), and dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the residue was subjected to column chromatography (60% dry EtOAc/hexane) to provide **192** (712 mg, 83% combined yield) as a 1:1 mixture of isomers. These two epimers were separated by column chromatography.

Compound **4α-192**: white solid, mp 128-130 °C. IR (Nujol) 3416 (s), 1746 (s), 1708 (s), 1665 (s), 1269 (s), 1167 (s) 1017 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.54 (1H, t, *J*=1.7 Hz, H3), 4.91 (1H, dt, *J*=7.1, 2.6 Hz, H7a), 4.25 (1H, m, H4), 3.03 (1H, dd, *J*=15.7, 7.1 Hz, H10a), 2.86 (1H, apparent q, *J*=8.6 Hz), 2.58 (1H, dd, *J*=18.2, 8.3 Hz), 2.38-2.29 (m), 2.26-2.17 (m), 2.14-2.02 (m), 1.80 (3H, s, 2-methyl), 1.41 (3H, s, 10c-methyl), 0.93 (9H, s, $SiC(CH_3)_3$), 0.11 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$). NOE data 4.91 (3.03, 4%; 2.86, 5%), 4.25 (2.86, 5%), 2.86 (4.91, 7%; 4.25, 5%), 1.41 (2.14-2.02, 10%). ^{13}C NMR ($CDCl_3$) δ 201.8 (0, C1), 176.9 (0, C9), 142.9 (1, C3), 140.0 (0), 135.3 (0), 117.1 (0), 83.9 (1, C7a), 67.0 (1, C4), 51.9 (1), 48.8 (1), 45.6 (0, C10c), 42.0 (1), 35.2 (2), 33.1 (2), 30.4 (2), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 25.2 (3, 10c-methyl), 18.0 (0, $Si\mathbf{C}(CH_3)_3$), 16.1 (3, 2-methyl), -4.0 (3, $SiCH_3$), -4.1 (3, $SiCH_3$). MS *m/z* 418 (M^+, 5), 359 (9), 281 (13), 224 (7), 223 (13), 209 (5), 195 (7), 181 (9), 179 (6), 139 (12), 138 (100), 121 (5), 117 (10), 105 (7), 103 (6), 91 (7), 77 (9), 75 (61), 73 (50), 59 (9). HRMS calcd. for $C_{23}H_{34}O_5Si$ 418.2174, found 418.2198.

Compound **4β-192**: pale yellow solid, mp 100-102 °C. IR (Nujol) 3422 (br. s), 1712 (s), 1305 (s), 1257 (s), 1169 (s), 1041 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.38 (1H, s, H3), 5.05 (1H, dt, *J*=6.2, 2.6 Hz, H7a), 4.96 (1H, m, H4), 3.89 (1H, m), 2.90 (1H, dd, *J*=6.3, 2.7 Hz), 2.82 (1H, dd, *J*=17.7, 9.0 Hz), 2.64 (1H, br s), 2.57-2.45 (m), 2.41 (1H, d, *J*=2.7 Hz), 2.35 (1H, d, *J*=2.4 Hz), 2.31-2.21 (m), 2.05-1.97 (1H, m), 1.75 (3H, s, 2-methyl), 1.29 (3H, s, 10c-methyl), 0.90 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$). NOE data 3.89 (5.05, 7%; 2.82, 4%), 1.29 (4.96, 12%; 3.89, 5%). ^{13}C NMR ($CDCl_3$) δ 202.3 (0, C1), 177.4 (0, C9), 142.1 (1, C3), 140.6 (0), 133.9 (0), 117.3 (0), 86.0 (1, C7a), 67.5 (1, C4), 54.9 (1), 49.7 (1), 48.3 (0, C10c), 41.2 (1), 37.6 (2), 34.4 (2), 28.6 (2), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 21.4 (3, 10c-methyl), 17.9 (0, $Si\mathbf{C}(CH_3)_3$), 15.8 (3, 2-methyl), -3.8 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 418 (M^+, 5), 281 (8), 225 (6), 224 (15), 223 (25), 205 (6), 195 (9), 181 (14), 179 (9), 165 (5), 151 (8), 149 (7), 139 (12), 138 (100), 135 (9), 129 (5), 121 (20), 117 (18), 116 (5), 105 (12), 103 (11), 91 (12), 79 (6), 77 (13), 76 (7), 75 (95), 74 (8), 73 (97), 69 (8), 59 (17), 57 (15), 55 (5), 53 (5). HRMS calcd. for $C_{23}H_{34}O_5Si$ 418.2174, found 418.2191.

(4α,4aα,7aβ,10aβ,10bα,10cα)-4-Acetoxy-6-(1-*tert*-butyldimethylsilyl)oxy-4,4a,5,7,7a,10,10a,10b,10c-nonahydro-2,10c-dimethylbenz[6,7]indeno[2,1-*b*]furan-1,9-dione (193)

To a solution of **4α-192** (20 mg, 0.048 mmol) in dry CH_2Cl_2 (5 mL) was added Ac_2O (0.045 mL, 0.48 mmol), Et_3N (0.066 mL, 0.48 mmol) and 4-(dimethylamino)pyridine (DMAP) (1.2 mg, 0.01 mmol) at rt. The resulting solution was stirred at rt for 24 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed by brine (2 x 20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (20% anhydrous Et_2O/hexane) to provide **4α-193** (19.5 mg, 89%) as a white solid: mp 114-116 °C. IR (Nujol) 1713 (s), 1254 (s), 1167 (s), 1034 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.42 (1H, d, *J*=4.5 Hz, H3), 5.16 (1H, m, H4), 5.00 (1H, dt, *J*=6.8, 2.6 Hz, H7a), 3.37 (1H, dq, *J*=9.0, 2.4 Hz), 2.95 (1H, ddd, *J*=17.7, 3.6, 1.7 Hz), 2.71 (1H, dd, *J*=18.2, 8.3 Hz), 2.49 (1H, d, *J*=17.4 Hz), 2.40-2.34 (m), 2.29 (1H, d, *J*=2.1 Hz), 2.21 (1H, d, *J*=9.0 Hz), 2.12 (3H, s, CH_3COO), 1.80 (3H, s, 2-methyl), 1.42 (3H, s, 10c-methyl), 0.90 (9H, $SiC(CH_3)_3$), 0.07 (3H, $SiCH_3$), 0.05 (3H, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 202.1 (0, C1), 176.9 (0, C9), 170.3 (0, $CH_3\mathbf{C}OO$), 139.3 (0), 136.8 (0), 135.3 (1, C3), 117.2 (0), 84.9 (1, C7a), 69.5 (1, C4), 53.1 (1), 46.3 (0, C10c), 45.0 (1), 41.8 (1), 36.5 (2), 33.8 (2), 31.8 (2), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 24.6 (3, 10c-methyl), 21.1 (3, $\mathbf{C}H_3COO$), 17.9 (0, $Si\mathbf{C}(CH_3)_3$), 16.2 (3, 2-methyl), -3.9 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 460 (M^+, 9), 401 (6), 400 (7), 398 (6), 385 (6), 343 (11), 299 (9), 283 (6), 282 (5), 281 (14), 269 (5), 259 (6), 227 (5), 225 (9), 224 (15), 223 (27), 209 (11), 205 (9), 197 (6), 195 (10), 181 (17), 180 (24), 179 (10), 165 (8), 139 (11), 138 (63), 117 (64), 105 (11), 103 (10), 91 (14), 77 (13),

75 (100), 73 (90), 60 (11), 59 (14), 57 (19), 55 (14). HRMS calcd. for $C_{25}H_{36}O_6Si$ 460.2279, found 460.2305.

(4α(β),4aα,6aα,7aβ,10aβ,10bα,10cα)-4-Acetoxy-6a-(1,3-dithian-2-yl)-4,4a,5,7,7a,10,10a,10b,10c-nonahydro-2,10c-dimethyl-1*H*-benz[6,7]indeno-[2,1-*b*]furan-1,6,9-trione (194)

To solution of **4β-193** (371 mg, 0.805 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of 1,3-dithienium tetrafluoroborate (**183**) (498 mg, 2.42 mmol) in dry CH_3NO_2 (2 mL) at –78 °C under argon over 5 min. The solution was stirred at –78 °C for 20 min. After warming to rt, the reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (60% EtOAc/hexane) to afford **4β-194** (157 mg, 42%) as white solid and some by-product, which was the product of hydrolysis of TBS-enol ether.

Compound **4β-194**: IR (Nujol) 1778 (s), 1708 (s), 1669 (s), 1240 (s), 1196 (s), 1041 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.29 (1H, s, H3), 5.87 (1H, m, H4), 5.14 (1H, t, *J*=6.4 Hz, H7a), 4.16 (1H, s, H2 in dithiane), 3.62 (1H, m), 3.15 (1H, m), 2.94-2.82 (6H, m), 2.77 (1H, m), 2.50 (1H, m), 2.38 (1H, ddd, *J*=20.7, 18.7, 1.4

Hz), 2.11 (3H, s, CH_3COO), 2.07 (1H, m), 1.78 (1H, m), 1.74 (3H, d, *J*=2.6 Hz. 2-methyl), 1.46 (3H, s, 10c-methyl). NOE data 5.87 (3.15, 8%; 1.46, 10%), 5.14 (3.62, 7%), 1.46 (5.87, 12%; 3.62, 8%; 2.77, 8%). ^{13}C NMR ($CDCl_3$) δ 208.0 (0, C6), 201.3 (0, C1), 176.6 (0, C9), 170.1 (0, CH_3COO), 137.9 (1, C3), 136.9 (0, C2), 86.0 (1, C7a), 69.7 (1, C4), 63.0 (0, C6a), 59.9 (1), 56.2 (1, C2 in dithiane), 49.3 (0, C10c), 44.6 (1), 42.2 (1), 38.7 (2), 38.3 (2), 37.8 (2), 32.2 (2), 31.5 (2), 25.3 (2), 22.1 (3, 10c-methyl), 20.9 (3, CH_3COO), 15.7 (2-methyl). MS *m/z* 241 (2), 135 (2), 121 (9), 120 (6), 119 (100), 106 (3), 98 (3), 91 (4), 79 (2), 77 (2), 75 (2), 73 (2), 45 (4), 43 (22). HRMS calcd. for $C_{23}H_{28}O_6S_2$ 464.1326, found 464.1307.

(4β,4aα,6aα,7aβ,10aβ,10bα,10cα)-6a-(1,3-Dithian-2-yl)-4,4a,5,7,7a,10,10a,10b,10c-nonahydro-4-hydroxy-2,10c-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]furan-1,6,9-trione (195)

Method 1: To a solution of **4β-194** (35 mg, 0.075 mmol) in methanol (2 mL) was added a solution of K_2CO_3 (105 mg, 0.753 mmol) in water (1 mL) at rt. The mixture was stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (100 mL), washed with 1% HCl solution (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (80% EtOAc/hexane) to afford **4β-195** (25.5 mg, 80%).

Method 2: To solution of **4β-192** (57.6 mg, 0.138 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of 1,3-dithienium tetrafluoroborate (**183**) (85 mg, 0.41 mmol) in dry CH_3NO_2 (1 mL) at –78 °C under argon over 5 min. The solution was stirred at –78 °C for 20 min. After warming to rt, the reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (80% EtOAc/hexane) to afford **4β-195** (19.5 mg, 34%).

Compound **4β-195**: white solid, mp 264-267 °C. IR (Nujol) 1713 (s), 1674 (s), 1274 (s), 1243 (s), 1186 (s), 1039 (s) cm^{-1}. ^1H NMR (DMSO-d6) δ 6.41 (1H, s, H3), 4.99 (1H, m, H7a), 4.66 (1H, br s, H4), 4.43 (1H, s, H2 in dithiane), 3.44 (1H, m), 2.94-2.70 (m), 2.62 (1H, d, *J*=5.1 Hz), 2.53 (1H, dd, *J*=15.6, 4.2 Hz), 2.48 (1H, m), 2.38 (1H, dd, *J*=18.0, 1.8 Hz), 2.25 (1H, d, *J*=15.0 Hz), 2.10 (1H, dd, *J*=17.1, 7.8 Hz), 2.01 (1H, m), 1.60 (3H, s, 2-methyl), 1.31 (3H, s, 10c-methyl). NOE data 4.99 (3.44, 7%; 2.48, 2%), 4.43 (2.94-2.70, 6%; 2.62, 4%), 1.31 (4.66, 7%; 3.44, 6%; 2.62, 6%). ^{13}C NMR (DMSO-d6) δ 208.5 (0, C6), 202.5 (0, C1), 177.0 (0, C9), 144.7 (1, C3), 133.7 (0, C2), 85.0 (1, C7a), 65.6 (1, C4), 63.2 (0, C6a), 60.5 (1), 56.0 (1, C2 in dithiane), 48.7 (0, C10c), 46.6 (1), 41.6 (1), 37.1 (2), 37.0 (2), 31.0 (2), 30.8 (2), 25.5 (2), 22.3 (3, 10c-methyl), 15.6 (3, 2-methyl). MS *m/z* 286 (1), 243 (1), 242 (2), 241 (4), 225 (1), 207 (2), 197 (2), 161 (3), 159 (2), 151 (3), 149 (2), 147 (3), 145 (3), 135 (6), 131 (2), 129 (3), 128 (2),

121 (10), 119 (100), 115 (3), 109 (3), 107 (3), 105 (4), 98 (6), 95 (4), 91 (7), 83 (6), 82 (3), 81 (6), 79 (6), 77 (6), 73 (6), 71 (5), 70 (5), 69 (8), 67 (6), 65 (3), 61 (4), 57 (12), 55 (12), 53 (4). HRMS calcd. for $C_{21}H_{26}O_5S_2$ 422.1220, found 422.1229.

(4α,4aα,9aα,9bα)-6-(*tert*-Butyldimethylsilyloxy)-4,4a,5,7,8,9,9a,9b-octahydro-4-methoxy-2,9b-dimethyl-1*H*-cyclopenta[*a*]naphthalen-1-one (196)

To a solution of **4α-188** (690 mg, 1.90 mmol) in THF was added NaH (235 mg, 9.50 mmol) and CH_3I (1.20 mL, 19.0 mmol) at rt. The resulting mixture was stirred at rt overnight. The reaction was quenched with ice-cold water (30 mL), and extracted with EtOAc (4 x 50 mL). The combined extracts were washed with brine (2 x 40 mL), dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was subjected to column chromatography (10% dry EtOAc/hexane) to afford **189** (614 mg, 86%) as a pale yellow oil: IR (Nujol) 1712 (s), 1672 (s), 1625 (s), 1254 (s), 1205 (s), 1099 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.58 (1H, s, H3), 3.76 (1H, m, H4), 3.43 (3H, s, OCH_3), 2.46-2.22 (m), 2.15-2.07 (m), 1.79 (3H, s, 2-methyl), 1.73 (1H, m), 1.56-1.41 (3H, m), 1.34 (3H, s, 9b-methyl), 0.93 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 203.0 (0, C1), 139.8 (1, C3), 137.8 (0), 135.4 (0), 120.8 (0), 76.1 (1, C4), 57.0 (3, OCH_3), 49.4 (1), 46.0 (1), 45.6 (0, C9b), 30.8 (2), 29.9 (2), 25.7 (3, $SiC(\mathbf{C}H_3)_3$),

25.2 (3, 9b-methyl), 23.1 (2), 18.1 (0, Si**C**$(CH_3)_3$), 16.2 (3, 2-methyl), -4.0 (3, $SiCH_3$), -4.1 (3, $SiCH_3$). MS *m/z* 361 (M^+-15, 1), 335 (1), 287 (1), 280 (3), 264 (2), 263 (2), 262 (2), 226 (3), 225 (13), 223 (4), 213 (2), 206 (2), 205 (11), 183 (4), 169 (3), 168 (10), 167 (11), 165 (3), 153 (15), 152 (100), 149 (6), 148 (6), 140 (4), 115 (4), 112 (26), 105 (4), 91 (10), 89 (6), 84 (4), 77 (8), 75 (46), 73 (35), 69 (10), 59 (9). HRMS calcd. for $C_{22}H_{36}O_3Si$ 376.2432, found 376.2444.

(4α,4aα,6aα,9aα,9bα)-6a-(1,3-Dithian-2-yl)-4,4a,5,7,8,9,9a,9b-octahydro-4-methoxy-2,9b-dimethyl-1*H*-cyclopenta[*a*]naphthalene-1,6-dione (197)

To solution of **196** (140 mg, 0.372 mmol) in dry CH_2Cl_2 (3 mL) was added a solution of 1,3-dithienium tetrafluoroborate (**183**) (153 mg, 0.744 mmol) in dry CH_3NO_2 (1 mL) at –78 °C under argon over 5 min. The solution was stirred at –78 °C for 20 min. After warming to rt, the reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (30% EtOAc/hexane) to afford **197** (83.5 mg, 59%) as a white solid: mp 226-228 °C. IR (Nujol) 1745 (s), 1710 (s), 1661 (s), 1244 (s), 1172 (s), 1086 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.69 (1H, s, H3), 4.84 (1H, s, H2 in dithiane), 3.65 (1H, dt, *J*=10.1, 2.0 Hz, H4), 3.49 (3H, s, OCH_3), 3.09 (1H, dd, *J*=13.8, 6.0 Hz), 2.95 (1H, dd, *J*=7.8, 3.1 Hz), 2.89 (1H, dt, *J*=6.6, 1.5 Hz), 2.84

(1H, m), 2.70 (1H, dd, *J*=13.6, 2.5 Hz), 2.59 (1H, dt, *J*=14.1, 8.7 Hz), 2.43 (1H, m), 2.13 (2H, dq, *J*=14.0, 3.3 Hz), 1.88 (1H, ddd, *J*=13.7, 10.3, 3.1 Hz), 1.81 (3H, t, *J*=1.6 Hz, 2-methyl), 1.70 (3H, s, 9b-methyl), 1.56 (1H, m), 1.43 (1H, dd, *J*=12.6, 6.5 Hz), 1.29 (1H, m), 0.96 (1H, m). NOE data 4.84 (3.09, 7%; 1.70, 9%), 1.70 (4.84, 11%; 3.09, 4%; 2.43, 5%). ^{13}C NMR ($CDCl_3$) δ 210.0 (0, C6), 201.0 (0, C1), 142.3 (1, C3), 135.7 (0, C2), 75.3 (1, C4), 63.3 (0, C6a), 57.8 (3, OCH_3), 56.5 (1, C2 in dithiane), 53.4 (1), 50.1 (1), 45.6 (0, C9b), 36.4 (2), 31.8 (2), 31.1 (2, 2C), 27.9 (2), 26.2 (3, 9b-methyl), 25.8 (2), 22.8 (2), 16.3 (3, 2-methyl). MS *m/z* 380 (M^+, 1), 262 (4), 247 (2), 230 (3), 221 (8), 189 (4), 188 (2), 187 (3), 175 (2), 173 (2), 166 (2), 165 (3), 161 (3), 159 (3), 152 (18), 149 (13), 136 (4), 135 (15), 134 (3), 133 (3), 123 (5), 121 (10), 120 (8), 119 (100), 112 (29), 111 (6), 105 (6), 95 (7), 91 (10), 79 (10), 77 (9), 69 (15), 67 (10), 55 (9), 53 (7). HRMS calcd. for $C_{20}H_{28}O_3S_2$ 380.1478, found 380.1484. The relative stereochemistry of **197** was confirmed by X-ray analysis.

(1aα,2aα,6aα,6bα,9aα)-1a-(*tert*-Butyldimethylsilyl)oxy-1,1a,2,2a,6a,6b,7,8,9,9a-decahydro-5,6a-dimethylcyclopropa-1*H*-cyclopenta[*a*]naphthalene-3,6-dione (198)

To a solution of **187** (117 mg, 0.325 mmol) in dry toluene (5 mL) was added Et_2Zn (1.0 M solution in hexane, 1.95 mL, 1.95 mmol) and CH_2I_2 (0.32 mL, 3.9 mmol) at rt. The reaction mixture was stirred at rt for 2 h before it was poured

into a saturated NH_4Cl solution (20 mL). The resulting mixture was extracted with diethyl ether (4 x 30 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (10% EtOAc/hexane) to provide **198** (68 mg, 56%) as a yellow oil: IR (Nujol) 1726 (s), 1697 (s), 1622 (s), 1257 (s), 1182 (s), 1112 (s), 1034 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.30 (1H, m, H4), 2.38-2.13 (4H, m), 1.97 (3H, d, *J*=1.6 Hz, 5-methyl), 1.94 (1H, m), 1.83 (1H, dd, *J*=12.6, 1.7 Hz), 1.77 (1H, dd, *J*=3.8, 1.2 Hz), 1.64 (1H, m), 1.41 (2H, m), 1.24 (3H, s, 6a-methyl), 0.79 (9H, s, $SiC(CH_3)_3$), 0.71 (1H, d, *J*=5.2 Hz, H1), 0.36 (1H, d, *J*=5.4 Hz, H1), 0.01 (3H, s, $SiCH_3$), 0.009 (3H, s, $SiCH_3$). NOE data 1.24 (0.36, 5%). ^{13}C NMR ($CDCl_3$) δ 202.7 (0), 201.1 (0), 150.6 (0, C5), 132.4 (1, C4), 58.2 (0, C1a), 57.4 (1), 53.0 (1), 50.2 (0), 34.8 (2), 33.3 (2), 31.0 (0), 28.3 (2), 27.7 (2, C1), 26.0 (2), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 24.7 (3, 6a-methyl), 17.7 (0, $Si\mathbf{C}(CH_3)_3$), 16.6 (3, 5-methyl), -3.2 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 374 (M^+, 2), 360 (2), 345 (2), 317 (7), 293 (5), 292 (4), 289 (4), 265 (5), 238 (3), 237 (6), 236 (2), 213 (3), 212 (4), 209 (3), 197 (2), 195 (3), 182 (7), 181 (33), 180 (2), 168 (6), 167 (9), 149 (18), 147 (2), 133 (2), 131 (3), 115 (11), 106 (3), 105 (11), 93 (3), 91 (8), 81 (5), 79 (7), 77 (7), 76 (5), 75 (71), 74 (8), 73 (100), 67 (11), 59 (14), 57 (13), 43 (7), 41 (16). HRMS calcd. for $C_{22}H_{34}O_3Si$ 374.2275, found 374.2273.

(1aα,2aα,6aα,6bα,7β,8β,9aα)-1a-(*tert*-Butyldimethylsilyl)oxy-1,1a,2,2a,6a,6b,7,8,9,9a-decahydro-8-methoxy-7-(2-methoxy)ethyl-5,6a-dimethylcyclopropa-1*H*-cyclopenta[*a*]naphthalene-3,6-dione (199)

To a solution of **80** (238 mg, 0.530 mmol) in dry toluene (15 mL) was added Et_2Zn (1.0 M solution in hexane, 5.30 mL, 5.30 mmol) and CH_2I_2 (0.86 mL, 10.6 mmol) at rt. The reaction mixture was allowed to stir at rt for 2 h before it was poured into a saturated NH_4Cl solution (40 mL). The resulting mixture was extracted with diethyl ether (4 x 40 mL). The combined extracts were washed with water (40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (10% EtOAc/hexane) to provide **199** (216 mg, 88%) as a yellow oil: IR (Nujol) 1703 (s), 1622 (s), 1256 (s), 1180 (s), 1033 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.32 (1H, t, *J*=1.2 Hz, H4), 4.05 (1H, q, *J*=4.5 Hz, H8), 3.41 (2H, dt, *J*=6.6, 3.6 Hz, CH_2OCH_3), 3.33 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 3.05 (1H, m, H7), 2.31-2.17 (3H, m, H2a and H2 or H9), 1.98 (3H, d, *J*=1.8 Hz, 5-methyl), 1.95 (1H, m, $CH_2CH_2OCH_3$), 1.79 (2H, dt, *J*=12.8, 1.3 Hz, H2 or H9), 1.62 (1H, m, $CH_2CH_2OCH_3$), 1.29 (3H, s, 6a-methyl), 1.27 (1H, m, H6b), 0.80 (9H, s, $SiC(CH_3)_3$), 0.75 (1H, d, *J*=5.7 Hz, H1), 0.46 (1H, d, *J*=5.7 Hz, H1), 0.01 (6H, s, $Si(CH_3)_2$). NOE data 4.05 (3.05, 5%), 0.46 (2.31-2.17, 2%; 1.29, 3%). ^{13}C NMR ($CDCl_3$) δ 202.5 (0), 201.1 (0), 150.1 (0, C5), 132.4 (0, C4), 82.0 (1, C8), 71.5 (2, CH_2OCH_3), 58.5 (3, OCH_3), 57.4 (1, C2a), 57.0 (0, C1a), 56.9 (3, OCH_3), 56.5 (1, C6b), 50.2 (0), 41.4 (1, C7), 34.9 (2, C2 and C9), 30.3 (2, $CH_2CH_2OCH_3$), 28.5

(0), 27.3 (2, C1), 25.9 (3, 6a-methyl), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 17.7 (0, $Si\mathbf{C}(CH_3)_3$), 16.6 (5-methyl), -3.3 (3, $SiCH_3$), -3.9 (3, $SiCH_3$). MS *m/z* 462 (M^+, 1), 447 (1), 431 (1), 405 (1), 373 (3), 345 (1), 341 (1), 325 (1), 315 (2), 294 (9), 293 (34), 292 (3), 279 (2), 266 (3), 265 (13), 249 (3), 239 (2), 237 (5), 235 (4), 213 (2), 212 (3), 195 (3), 193 (2), 179 (4), 175 (2), 165 (3), 151 (3), 138 (3), 137 (2), 123 (3), 121 (2), 119 (2), 117 (3), 115 (4), 105 (8), 91 (9), 89 (19), 75 (23), 73 (100), 59 (12), 45 (40), 41 (10). HRMS calcd. for $C_{26}H_{42}O_5Si$ 462.2801, found 462.2804.

(1aα,2aα,6aα,6bα,7β,8β,9aα)-1a-(*tert*-Butyldimethylsilyl)oxy-6-ethoxyethynyl-1,1a,2,2a,6a,6b,7,8,9,9a-decahydro-6-hydroxy-8-methoxy-7-(2-methoxy)ethyl-5,6a-dimethylcyclopropa-1*H*-cyclopenta[*a*]naphthalen-3-one (200) and (1aα,2aα,6aα,6bα,7β,8β,9aα)-1a-(*tert*-butyldimethylsilyl)oxy-3-ethoxyethynyl-1,1a,2,2a,6a,6b,7,8,9,9a-decahydro-3-hydroxy-8-methoxy-7-(2-methoxy)ethyl-5,6a-dimethylcyclopropa-1*H*-cyclopenta[*a*]naphthalen-6-one (201)

To a solution of ethyl ethynyl ether (50 wt % solution in hexane, 0.55 mL, 2.8 mmol) in dry THF (15 mL) was introduced *n*-BuLi (2.5 M in hexane, 0.56 mL, 1.4 mmol) at –78 °C over 5 min. The solution was stirred for 30 min and then transferred with a double-headed needle to a solution of enedione **199** (324 mg, 0.700 mmol) in dry THF (15 mL) at –78 °C. This mixture was stirred at –78 °C for 2 h and then at 0 °C for 1 h. This was quenched with water (10 mL), diluted with

Et_2O (200 mL), and washed with water (3 x 20 mL) and brine (20 mL). The resulting solution was dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (30% dry EtOAc/hexane) to provide **200** (135 mg, 36%) and **201** (215 mg, 58%).

Compound **200**: yellow oil, IR (CH_2Cl_2) 3424 (br, s), 2259 (s) 1712 (s). 1678 (s), 1473 (s), 1378 (s), 1252 (s), 1117 (s), 1092 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.72 (1H, m, H4), 4.22-4.09 (2H, m, OCH_2CH_3), 3.82 (1H, m, H8), 3.46 (1H, m, CH_2OCH_3), 3.34 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.12 (1H, m), 2.43 (1H, s, OH), 2.21 (1H, ddd, *J*=13.7, 12.5, 1.1 Hz), 2.16 (3H, t, *J*=1.1 Hz, 5-methyl), 2.11-1.96 (m), 1.87 (1H, dd, *J*=13.5, 5.6 Hz), 1.56 (1H, m), 1.38 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.25 (1H, m), 1.13 (3H, s, 6a-methyl), 0.81 (9H, $SiC(CH_3)_3$), 0.78 (1H, d, *J*=5.2 Hz, H1), 0.54 (1H, d, *J*=5.2 Hz, H1), 0.05 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 201.9 (0, C3), 156.9 (0, C5), 121.9 (1, C4), 97.1 (0), 82.0 (1, C8), 74.6 (2, OCH_2CH_3), 73.9 (0), 71.9 (2, CH_2OCH_3), 58.5 (3, OCH_3), 58.4 (0), 56.7 (1), 56.3 (3, OCH_3), 54.3 (1), 44.2 (1), 41.7 (0), 39.2 (0), 35.5 (2), 35.2 (2), 30.2 (2), 29.6 (0), 28.0 (3, 6a-methyl), 27.9 (2, C1), 25.6 (3, $SiC(CH_3)_3$), 19.7 (3, 5-methyl), 17.8 (0, $SiC(CH_3)_3$), 14.7 (3, OCH_2CH_3), -3.2 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 503 (M^+-29, 1), 485 (1), 345 (1), 339 (1), 325 (2), 294 (2), 293 (5), 279 (2), 263 (2), 239 (2), 237 (3), 231 (4), 203 (8), 179 (3), 175 (4), 173 (2), 165 (3), 162 (2), 149 (2), 147 (2), 137 (3), 135 (3), 121 (2), 119 (3), 115 (4), 105 (7), 93 (3), 91 (7), 89 (12), 75 (24), 74 (8), 73 (100), 59 (11), 45 (33). HRMS calcd. for $C_{30}H_{48}O_6Si$ 532.3220, found 532.3224.

Compound **201**: yellow oil. IR (Nujol) 3402 (br, s), 2259 (s), 1712 (s), 1248 (s), 1156 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.13 (1H, s, H4), 4.18 (1H, m, H8), 4.15-4.08 (2H, m, OCH_2CH_3), 3.43 (2H, t, *J*=6.6 Hz, CH_2OCH_3), 3.35 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 2.90 (1H, q, *J*=6.0 Hz), 2.67 (1H, dd, *J*=13.7, 3.8 Hz), 2.42 (1H, m), 2.25 (1H, dd, *J*=13.5, 5.3 Hz), 2.03 (1H, m), 1.78 (3H, t, *J*=1.6 Hz, 5-methyl), 1.64 (1H, dd, *J*=13.5, 6.1 Hz), 1.58 (2H, dd, *J*=13.5, 5.8 Hz), 1.49 (1H, dd, *J*=24.4, 12.9 Hz), 1.40 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.38 (3H, s, 6a-methyl), 1.26 (2H, t, *J*=7.2 Hz), 0.82 (9H, s, $SiC(CH_3)_3$), 0.64 (1H, d, *J*=5.2 Hz, H1), 0.44 (1H, d, *J*=5.2 Hz, H1), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 203.3 (0, C6), 137.8 (1, C4), 132.8 (0, C5), 96.1 (0), 82.1 (1, C8), 74.8 (2, OCH_2CH_3), 71.6 (2, CH_2OCH_3), 69.7 (0), 60.3 (0), 58.4 (3, OCH_3), 57.9 (2), 56.6 (3, OCH_3), 50.4 (1), 48.3 (0), 41.5 (1), 41.4 (0), 36.1 (2), 34.6 (2), 30.5 (2), 28.0 (0), 26.7 (2, C1), 26.5 (3, 6a-methyl), 25.6 (3, $SiC(CH_3)_3$), 17.8 (0, $SiC(CH_3)_3$), 16.0 (3, 5-methyl), 14.5 (3, OCH_2CH_3), -3.2 (3, $SiCH_3$), -3.8 (3, $SiCH_3$). MS *m/z* 488 (1), 487 (4), 357 (5), 327 (1), 325 (2), 295 (3), 294 (2), 293 (6), 265 (2), 263 (2), 249 (2), 237 (2), 235 (2), 223 (1), 209 (1), 179 (2), 165 (4), 163 (2), 161 (4), 149 (2), 147 (2), 137 (3), 135 (7), 115 (3), 105 (7), 93 (3), 91 (5), 89 (12), 75 (22), 74 (8), 73 (100), 59 (8), 45 (25). HRMS calcd. for $C_{30}H_{48}O_6Si$ 532.3220, found 532.3224.

(1*R,2*R**,3*R**,4*R**,8*S**,10*S**,11*S**,13*S**,14*R**)-14-Acetoxy-10-(dithian-2-yl)-11-hydroxy-2,16-dimethyl-7,17-dioxapentacyclo[9.5.1.$0^{2,13}$.$0^{3,10}$.$0^{4,8}$]hexadec-15-en-6-one (202)**

To a solution of **193** (34.5 mg, 0.0743 mmol) in 1:1 mixture of MeOH/CH_2Cl_2 (4 mL) was added $NaBH_4$ (4.3 mg, 0.11 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min, then warmed to rt and stirred for 2 h. The reaction mixture was poured into diluted NH_4Cl solution (10 mL), extracted with EtOAc (4 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The residue was subjected to column chromatography (80% EtOAc/hexane) to provide **202** (27.5 mg, 80%) as a white solid: mp 242-243.5 °C. IR (Nujol) 1765 (s), 1714 (s), 1302 (s), 1240 (s), 1167 (s), 1031 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.42 (1H, m, H14), 5.40 (1H, s, H15), 5.06 (1H, m, H8), 4.14 (1H, s, H2 in dithiane), 3.62 (1H, d, *J*=1.3 Hz, H1), 3.03-2.85 (3H, m), 2.83-2.72 (3H, m), 2.53-2.45 (2H, m), 2.38 (1H, m), 2.21-1.94 (4H, m), 2.09 (3H, s, CH_3COO), 1.86 (3H, 16-methyl), 0.93 (3H, 2-methyl). NOE data 2.53-2.45 (4.14, 8%; 0.93, 2%), 2.38 (5.42, 8%; 4.14, 7%), 0.93 (5.42, 12%; 3.62, 5%; 3.03-2.85, 5%; 2.53-2.45, 6%). ^{13}C NMR ($CDCl_3$) δ 176.6 (0), 170.8 (0), 138.4 (0, C16), 121.7 (1, C15), 98.2 (0, C11), 86.3 (1, C8), 74.5 (1, C1), 71.6 (1, C14), 58.8 (0, C10), 58.7 (1), 57.9 (1, C2 in dithiane), 41.1 (1), 37.3 (1), 36.2 (2), 35.3 (2), 31.8 (2), 31.3 (2), 25.5 (2), 21.5 (3, 16-methyl), 21.2 (3, CH_3COO), 18.2 (3, 2-methyl). MS *m/z* 466 (M^+, 2), 244 (2), 243 (11), 242 (3), 241 (3), 183 (3), 165 (6), 163 (2), 137 (2),

135 (3), 123 (4), 122 (2), 121 (9), 120 (13), 119 (100), 106 (3), 105 (2), 91 (4), 79 (3), 77 (2), 75 (5), 43 (21). HRMS calcd. for $C_{23}H_{30}O_6S_2$ 466.1484, found 466.1493.

(1aα,2aα,6aα,6bα,9aα)-1a-(*tert*-Butyldimethylsilyl)oxy-1,1a,2,2a,6,6a,6b,7,8,9,9a-undecahydro-6-hydroxy-5,6a-dimethylcyclopropa-1*H*-cyclopenta[*a*]naphthalen-3-one (203)

To a solution of **198** (68 mg, 0.18 mmol) in dry THF (5 mL) was added $LiAl(O^tBu)_3H$ (1.0 M solution in THF, 0.22 mL, 0.22 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2 h. The reaction mixture was quenched with water (2 mL), and diluted with EtOAc (100 mL), washed with brine (20 mL), dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the residue was subjected to column chromatography (30% EtOAc/hexane) to afford **203** (45.5 mg, 67%) as a mixture of isomers in favor of **6α-203**: white solid, mp 144-146 °C. IR (Nujol) 1712 (s), 1658 (s), 1255 (s), 1164 (s), 1054 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.77 (1H, s, H4), 3.82 (1H, d, *J*=8.8 Hz, H6), 2.33 (1H, dd, *J*=13.3, 5.6 Hz), 2.09 (3H, d, *J*=1.2 Hz, 5-methyl), 2.06-1.58 (m), 1.41 (1H, dd, *J*=12.4, 5.9 Hz), 1.11 (2H, m), 0.87 (3H, s, 6a-methyl), 0.82 (9H, $SiC(CH_3)_3$), 0.82 (1H, d, *J*=5.5 Hz, H1), 0.46 (1H, d, *J*=5.5 Hz, H1), 0.06 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 202.4 (0, C3), 157.4 (0, C5), 123.3 (1, C4), 73.8 (1, C6), 58.3 (0, C1a), 52.6 (1), 52.2 (1), 37.8 (0, C6a), 35.4 (2), 34.0 (2), 30.8 (0,

C9a), 27.9 (2, C1), 27.5 (2), 26.3 (3, 6a-methyl), 26.0 (2), 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 22.1 (3, 5-methyl), 17.7 (0, $Si\mathbf{C}(CH_3)_3$), -3.2 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 376 (M^+, 1), 319 (4), 301 (4), 277 (3), 249 (3), 244 (4), 239 (4), 238 (5), 237 (4), 227 (3), 226 (4), 225 (2), 213 (2), 212 (6), 199 (3), 198 (2), 197 (2), 182 (4), 181 (15), 163 (6), 162 (3), 147 (4), 145 (5), 139 (7), 138 (7), 135 (9), 123 (4), 115 (8), 109 (5), 105 (10), 93 (4), 91 (11), 81 (8), 79 (10), 77 (8), 75 (67), 74 (8), 73 (100), 67 (11), 59 (15), 55 (6), 41 (22). HRMS calcd. for $C_{22}H_{36}O_3Si$ 376.2434, found 376.2431.

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Part II

A Cascade Radical Cyclization

2.1. Introduction

Free-radical reactions are ubiquitous in nature, and they have been among the most widely used methods for the manufacture of various vinyl polymers for several decades. Nevertheless, applications of these reactions for the synthesis of complex organic molecules are of more recent origin.[1-9] Before the beginning of the 1980's, mainly due to a lack of selectivity, only a few important functional group transformations, such as the Barton-McCombie reaction,[10] had been used in the total synthesis of natural products. However, during the past two decades, free radical chemistry has evolved dramatically. Organic chemists have come to understand many issues of reactivity, regioselectivity, chemoselectivity and stereoselectivity in radical reactions. A number of synthetic advantages inherent to radical reactions have greatly increased the importance of such reactions to the point where they have become an integral part of synthetic strategies in many laboratories. The synthetic advantages[2] include:

1. Carbon-centered radicals are extremely reactive.
2. Radical additions to C=C bonds are usually exothermic and irreversible, with early, reactant-like transition states.
3. Radical intermediates are very well suited for the synthesis of crowded bonds.

4. Carbon-centered radicals are generally inert toward OH or NH groups.

5. Carbon-radicals are not subject to β-elimination of OR or NR_2 groups.

Recent progress in radical chemistry has shown that radical reactions can be as efficient as, or even better than their ionic counterparts in some cases.

2.1.1. Tin Hydride Method

Several methods, which include the tin hydride method, the mercuric hydride method, the fragmentation method, the atom/group transfer method, the reductive method and the oxidative method have been involved in radical reactions.[2] Of these general methods, the most popular one is the tin hydride method. The most commonly reagent used for conducting free-radical reactions is tri-*n*-butyltin hydride.[11] It has been noticed that organotin hydrides are capable of both radical generation and kinetically controlled radical trapping. Besides tri-*n*-butyltin hydride, triphenyltin hydride and di-*n*-butyltin dihydride are also used, and these offer some advantages in some special cases. The trialkyltin hydride-mediated reduction of various organic functional groups is presented in Scheme 69.

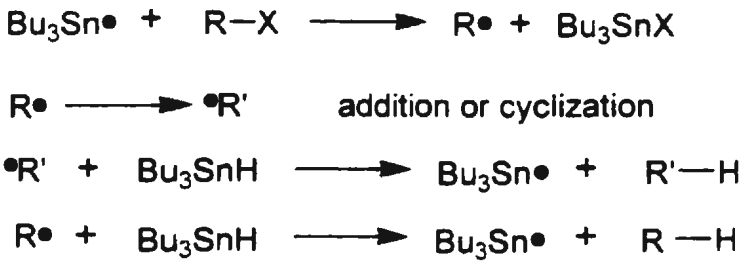
Radical reactions are usually initiated by the generation of tin radicals with azobisisobutyronitrile (AIBN). Other radical sources, such as benzoyl peroxide, UV light or heat, have also been used. The driving force for the overall reaction is the transformation of the Sn-H bond to a relatively strong Sn-X bond. The reactivity of different groups to tin radicals decreases in the order: I > Br > SePh ≈ OC(S)SMe > Cl > SPh.[12,13] The reactivity of various carbon radicals toward tin

hydride is in the order: aryl ≈ vinyl > alkyl > allyl ≈ benzyl. There is very little difference in the reactivity of primary, secondary, and tertiary radicals.

Scheme 69. Trialkyltin hydride-mediated radical reactions[2]

Initiation

Propagation



Addition of an alkyl radical to an alkene is a useful method for the formation of a C-C bond.[1] The substituent effects of these additions can be interpreted by FMO theory. The addition takes place due to the interaction of a singly occupied orbital (SOMO) of the radical with the lowest unoccupied orbital (LUMO) and/or the highest occupied orbital (HOMO) of the carbon-carbon multiple bond (Figure 11 and Figure 12). An electron-withdrawing substituent on the alkene lowers its LUMO energy. The energy difference between the SOMO and the LUMO is reduced, and the rate of the addition is increased. For a radical, which reacts like an electrophile, an electron-donating substituent on the alkene will increase the rate of reaction. The tin hydride method is extremely mild and

selective, so that carbonyl groups and alcohols do not usually need to be protected.

Figure 11. Orbital interaction between a nucleophilic radical and an electron-poor alkene

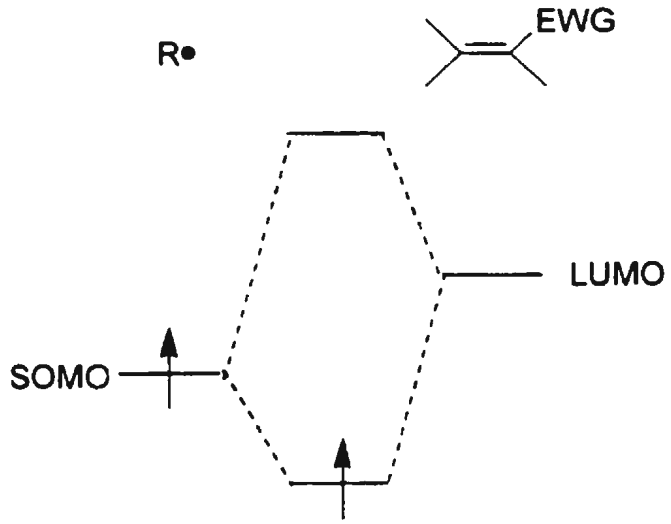
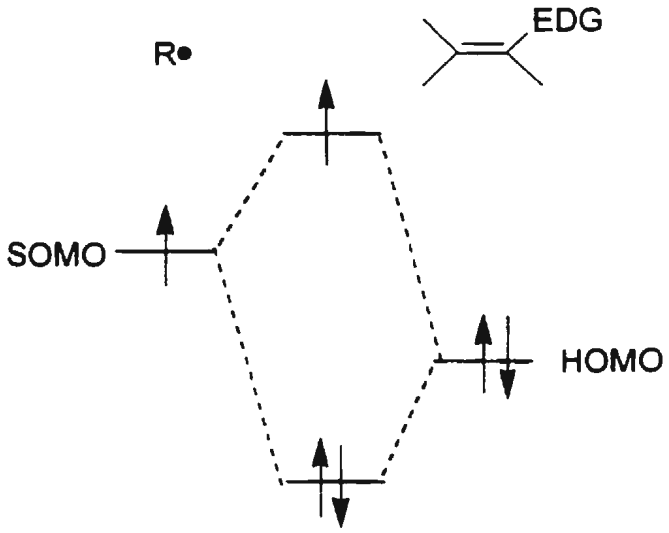


Figure 12. Orbital interaction between an electrophilic radical and an electron-rich alkene

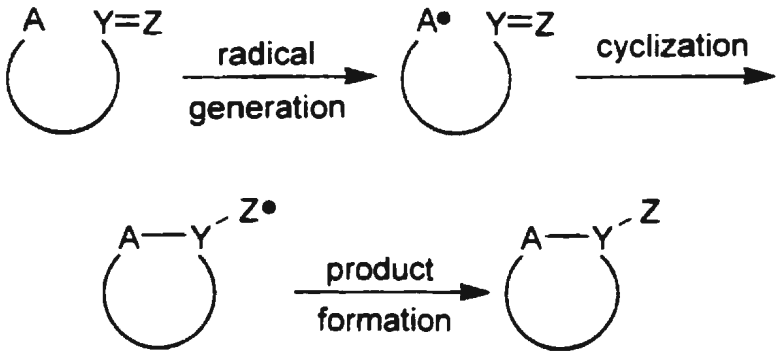


There are some limitations to the tin hydride method. First, tin hydride can act as a reducing reagent; both C-X functional groups and C-C π bonds can be reduced. Secondly, the initial radicals R• as well as product radicals R'• are susceptible to hydrogen atom transfer. Thirdly, it is frequently a problem that tin-containing by-products are hard to remove from the desired products.

2.1.2. Radical Cyclization with Tin Hydride

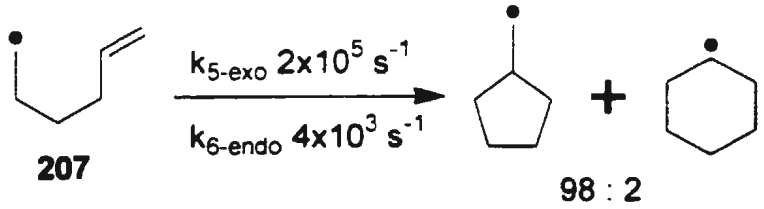
Radical cyclization is one of the most powerful and versatile methods for the construction of mono- and polycyclic systems. Radical cyclizations have been widely used in natural product synthesis because of their functional group tolerance and mild reaction conditions combined with high levels of chemo-, regio- and stereochemistry. In general, radical cyclizations involve three steps: selective radical generation, radical cyclization, and conversion of the cyclized intermediate to the product (Scheme 70).[9] The cyclization usually involves the intramolecular addition of a radical to a carbon-carbon multiple bond.

Scheme 70. General sequence for radical cyclization



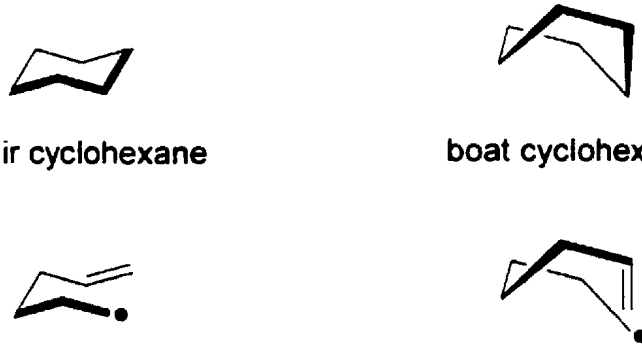
Of the carbocycles formed by radical cyclizations, five-membered ring cyclizations are most common. Five-membered ring cyclizations are usually faster than for any other ring size. For example, the simple 5-hexenyl radical cyclizes 20 times faster than does the 6-heptenyl radical.[14,15] 5-hexenyl radicals show outstanding regioselectivity in favor of 5-*exo* cyclization (Scheme 71).[9]

Scheme 71. Regioselectivity of 5-hexenyl radical **207**



Cyclization of the parent five-hexenyl radical **207** gave two cyclization products with the five-membered ring and the six-membered ring in a ratio of 98:2. The cyclizations are exothermic and irreversible with a preference of the smaller ring size by cyclization in the *exo* mode.[9] The stereoselectivity in five-membered ring radical cyclizations is usually high.[9] The predominant stereoisomer can be predicted by using the Beckwith-Houk transition state model.[16,17] This transition state model states that the hexenyl radical can accommodate the preferred tetrahedral-like approach of the radical to the alkene by folding into either of two conformations (Figure 13).

Figure 13. Transition structures for hexenyl radical cyclizations



chair cyclohexane

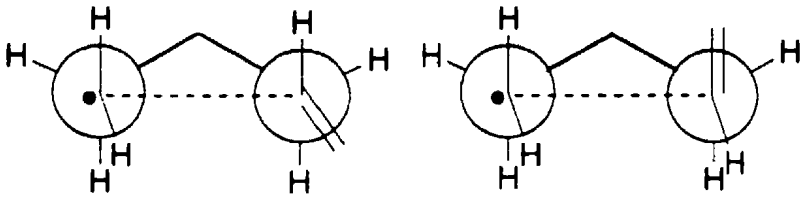
boat cyclohexane

"chair" transition state

"boat" transition state

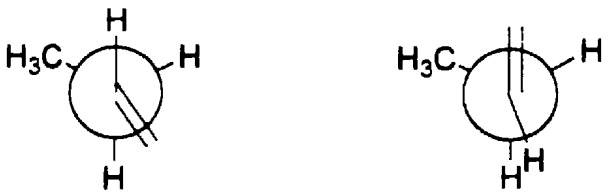
Newman projections for the hexenyl radical transition states are shown in Figure 14. Comparing the two low-energy conformations of 1-butene, gauche and skew, it is easy to understand why the chair transition state is 1 kcal/mol lower in energy than its boat counterpart.

Figure 14. Newman projection of hexenyl radical transition states



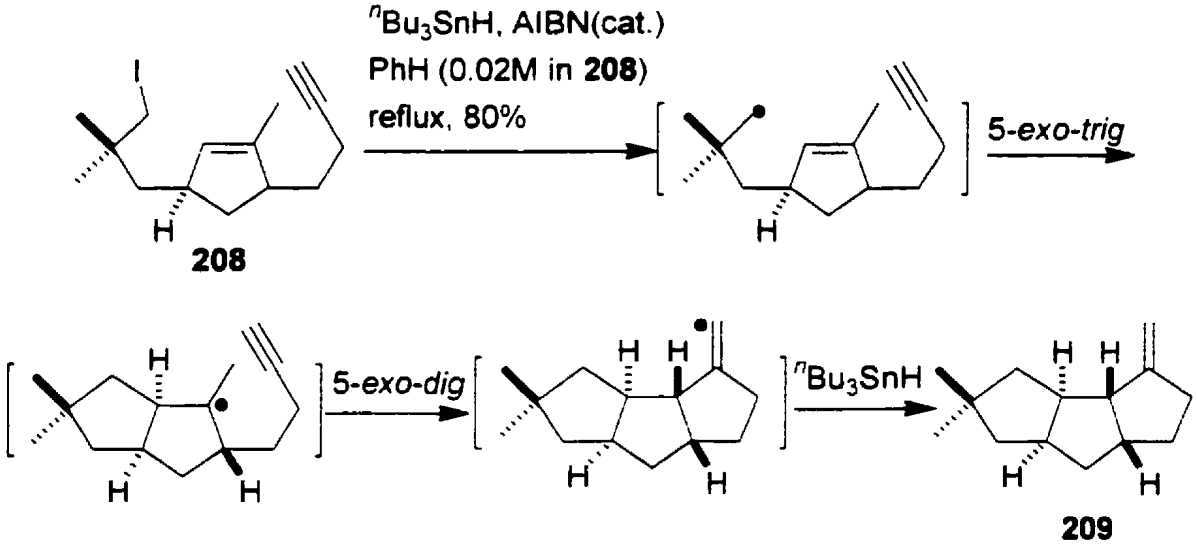
"chair" transition state resembles "skew" butene

"boat" transition state resembles "gauche" butene



In the past twenty years, cascade radical cyclizations have been applied to the synthesis of many natural products. The construction of fused five-membered rings (linear or angular polyquinanes) is the typical example. Curran's group used a "tandem radical cyclization" strategy to synthesize (±)-hirsutene [(±)**209**] from compound **208**[18] (Scheme 72).

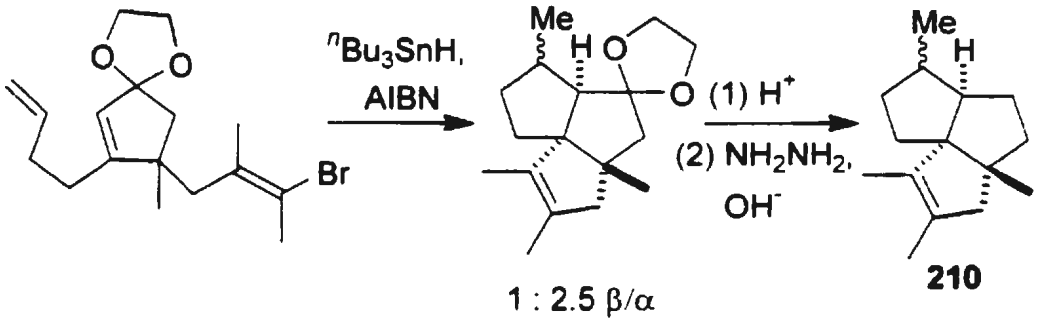
Scheme 72. Synthesis of hirsutene by tandem radical cyclization[18]

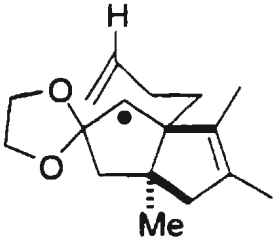


208 **209**

The angular triquinane silphiperfol-6-ene (**210**) has also been synthesized by a tandem radical cyclization process (Scheme 73).[19]

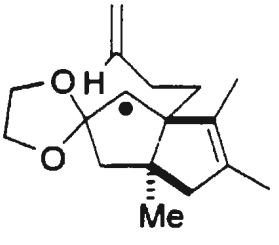
Scheme 73. Synthesis of silphiperfol-6-ene by tandem radical cyclization





chair-like

211



boat-like

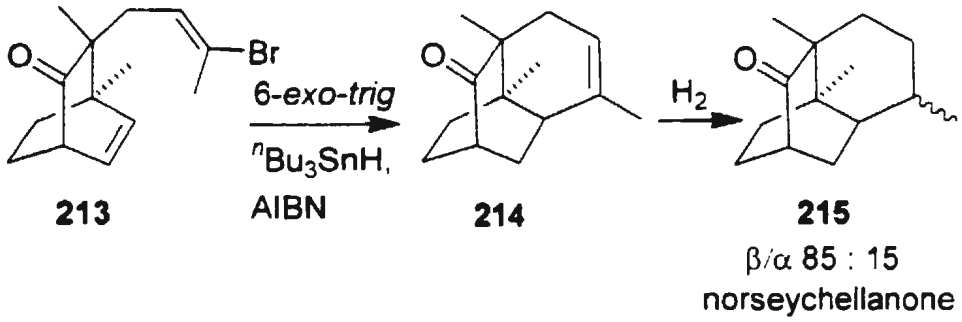
212

This synthesis consisted of two 5-*exo-trig* radical cyclizations. The stereochemistry of the second cyclization probably resulted from the boat-like geometry in the transition state **212**, in which the olefin terminus orients itself *exo* relative to the existing ring. Due to the steric hindrance of the cyclic acetal, the chair-like transition state **211** is not favored. This cyclization provided a 1:2.5 mixture of isomers, in favor of the desired α-methyl isomer. A vinyl radical was generated for the first radical cyclization.

Pioneering work from Stork's group[20] showed that vinyl radicals are much more reactive toward cyclization than alkyl radicals; 5-*exo* cyclizations by vinyl

radicals are about 1000 times faster than cyclizations involving analogous alkyl radicals. The reactivity of vinyl radicals toward tin hydride is also increased, but by a lesser amount. Six-membered ring radical cyclizations have also been used in the natural product synthesis, but these have been less popular than five-membered ring cyclizations. Six-heptenyl radical cyclizations have diminished reactivity, diminished chemoselectivity, diminished regioselectivity and diminished stereoselectivity[2] relative to their five-membered counterparts. Despite these limitations, a six-membered ring cyclization can be achieved by tin hydride. In 1985, Stork's group reported a 6-*exo-trig* cyclization of a vinyl radical in the synthesis of seychellene (Scheme 74).

Scheme 74. Stork's synthesis of seychellene



213 **214** **215**

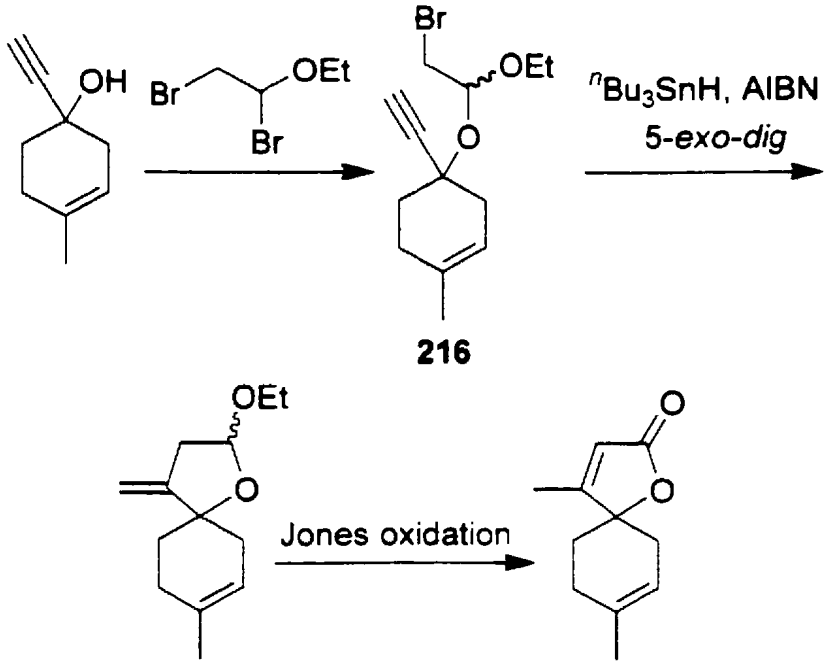
β/α 85 : 15

norseychellanone

The precusor **213** was treated with tri-*n*-butyltin hydride to form the cyclization product **214** by a 6-*exo-trig* radical cyclization. Hydrogenation of **214** provided norseychellanone (**215**β) predominantly, which was converted to seychellene.[21]

Besides C-C double bonds, C-C triple bonds can also act as radical acceptors to form vinyl radicals (Scheme 75). Even though radical additions to

Scheme 75. Radical cyclization with a C-C triple bond



216

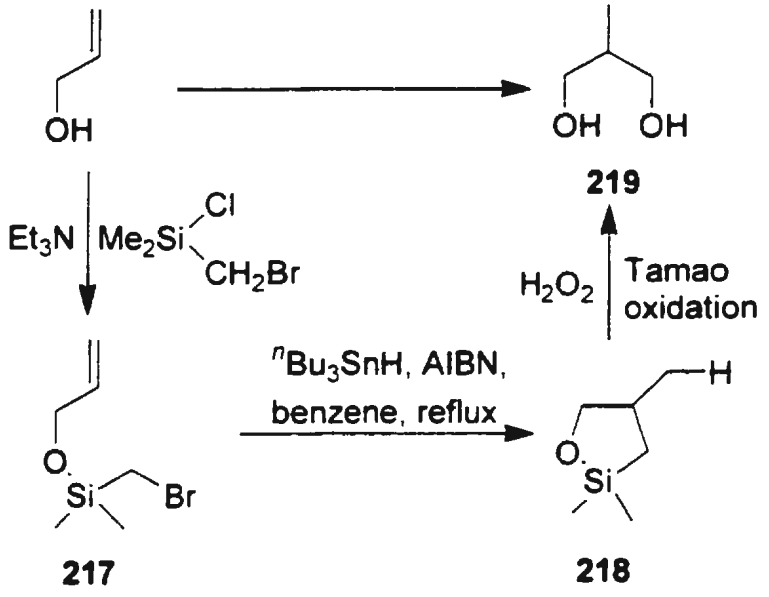
alkenes are faster than the comparable additions to alkynes, the rate of five- *versus* six-membered ring formation is a much more important consideration. Cyclization of **216** involved a 5-*exo-dig* cyclization onto an alkyne, rather than a 6-exo-trig cyclization onto an alkene.

2.1.3. The Propargyl Silyl Ether Approach

Nishiyama[23] and Stork[24,25] first developed the propargyl silyl ether approach for regio- and stereoselective 5-*exo-trig* cyclization of radicals generated from (bromomethyl)dimethylsilyl allyl ethers. Nishiyama[23] reported that silyl ether **217** was subjected to a radical reaction with tri-*n*-butyltin hydride (1.2 eq.) and AIBN (0.03 eq.) in benzene under reflux, affording the corresponding

cyclization product **218**, which gave 1,3-diol **219** predominantly by Tamao oxidation[26] (Scheme 76). The 5-*exo-trig* mode of cyclization predominated over the 6-*endo-trig* mode.

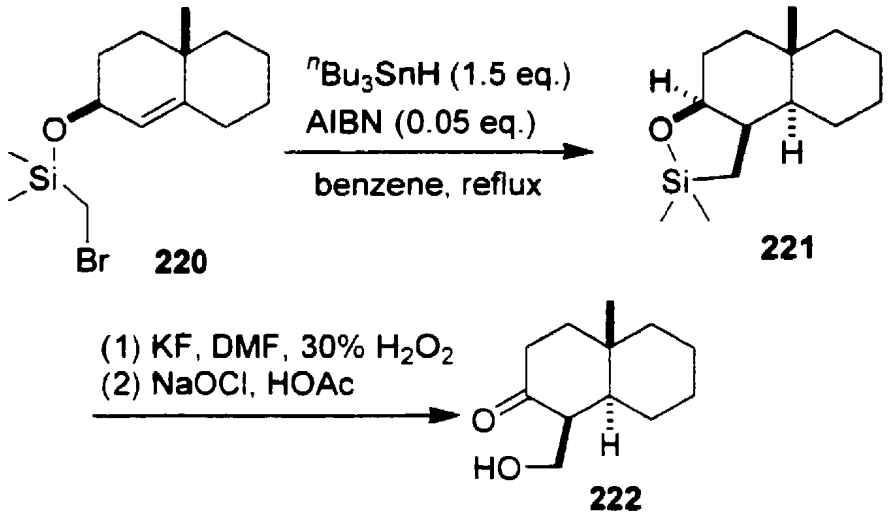
Scheme 76. Nishiyama's approach



Stork's seminal research[24,25] on radical cyclizations showed that the propargyl silyl ether could be cyclized by the 5-*exo-trig* mode in a regio- and stereochemically selective manner. This was the first time that the propargyl silyl ether in a cyclic compound was cyclized to an oxa-silacyclopentane ("siloxane"). This method appeared promising for the control of ring-junction stereochemistry (Scheme 77). Heating the silyl ether **220** in benzene with 1.5 equivalents of tri-*n*-butyltin hydride and 0.05 equivalents of AIBN for 30 minutes produced the cyclic siloxane **221** as a single isomer. The silicon was removed by Tamao oxidation,

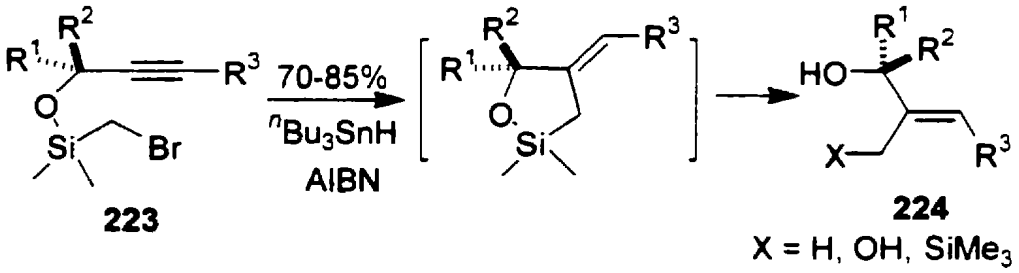
followed by oxidation of the resulting diol with NaOCl in acetic acid to the hydroxyketone **222**. The overall process achieved the operational equivalent of the *trans* addition of a functionalized alkane to the double bond of a cyclic allyl alcohol. Introducing a junction hydrogen *trans* to the original hydroxyl function of the allylic system generated the ring junction stereochemistry.

Scheme 77. Stork's approach



Based on a knowledge of the regio- and stereoselectivity of radical cyclizations with (bromomethyl)dimethylsilyl allyl ether, Malacria's group has undertaken extensive studies on the propargyl silyl ether approach (Scheme 78).

Scheme 78. Malacria's study on the propargyl silyl ether approach



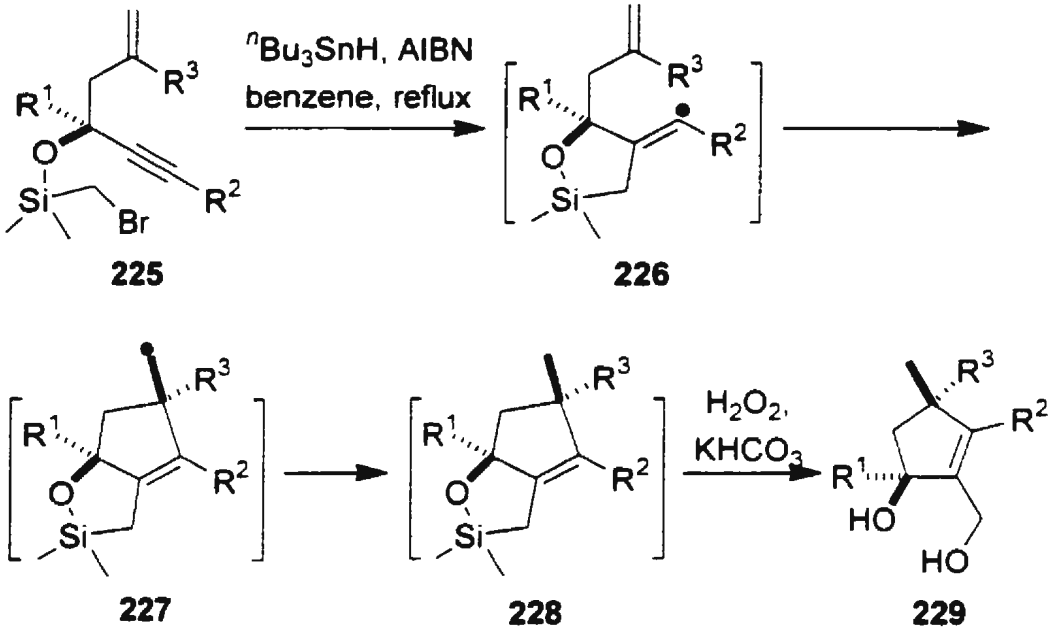
223 **224**

X = H, OH, $SiMe_3$

It was found that radical cyclization of bromomethylsilyl ether **223** in the 5-*exo-dig* mode is highly regio-, chemo-, and stereoselective, yielding di- and trisubstituted functionalized double bonds **224** under very mild conditions after simple *in situ* chemical transformation.[27-29]

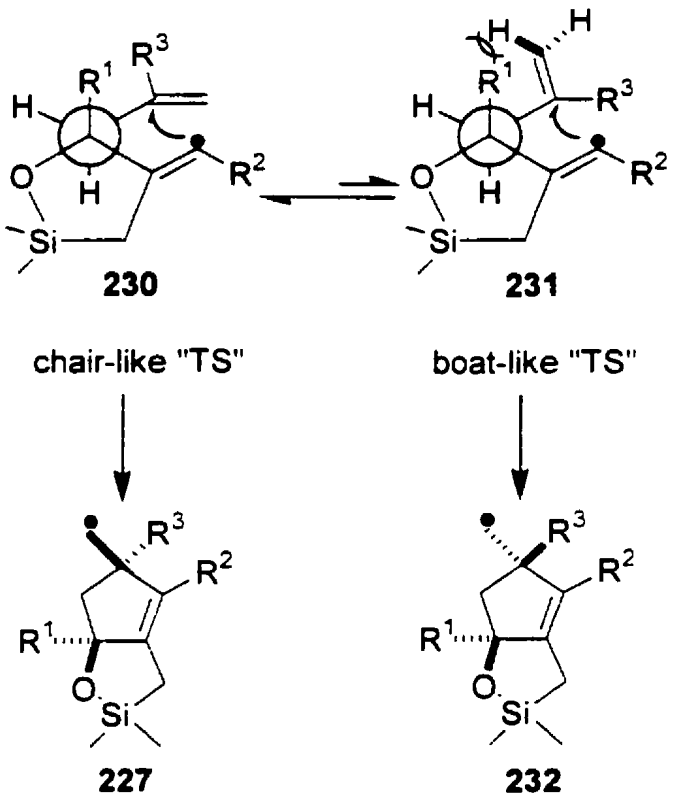
Because the intermediate exocyclic vinyl radical involved in this cyclization was very reactive, it could be trapped intramolecularly by a suitably located double bond or triple bond to form another unsaturated five-membered carbocycle (Scheme 79).[27b] Bromomethylsilyl ether **225** was subjected to radical cyclization conditions. A vinyl radical **226** was formed first in the 5-*exo-dig* mode, and then the resulting radical attacked another double bond intramolecularly to yield a five-membered ring in the molecule. After Tamao oxidation of the intermediate **228**, a fully functionalized 1,3-diol **229** could be obtained in high yield and with high stereoselectivity.

Scheme 79. Cascade radical cyclization of bromomethyl silyl ether



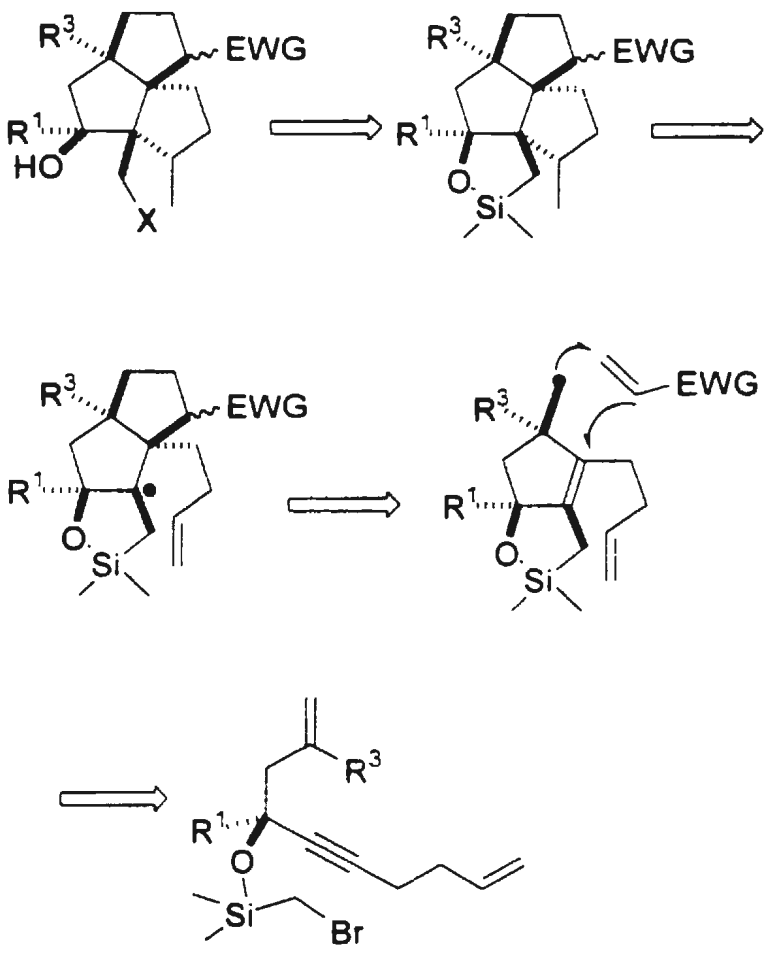
The high stereoselectivity in this radical cyclization can be rationalized by conformations of the vinyl radical intermediate (Scheme 80).[30]

Scheme 80. Transition state of radical **226**

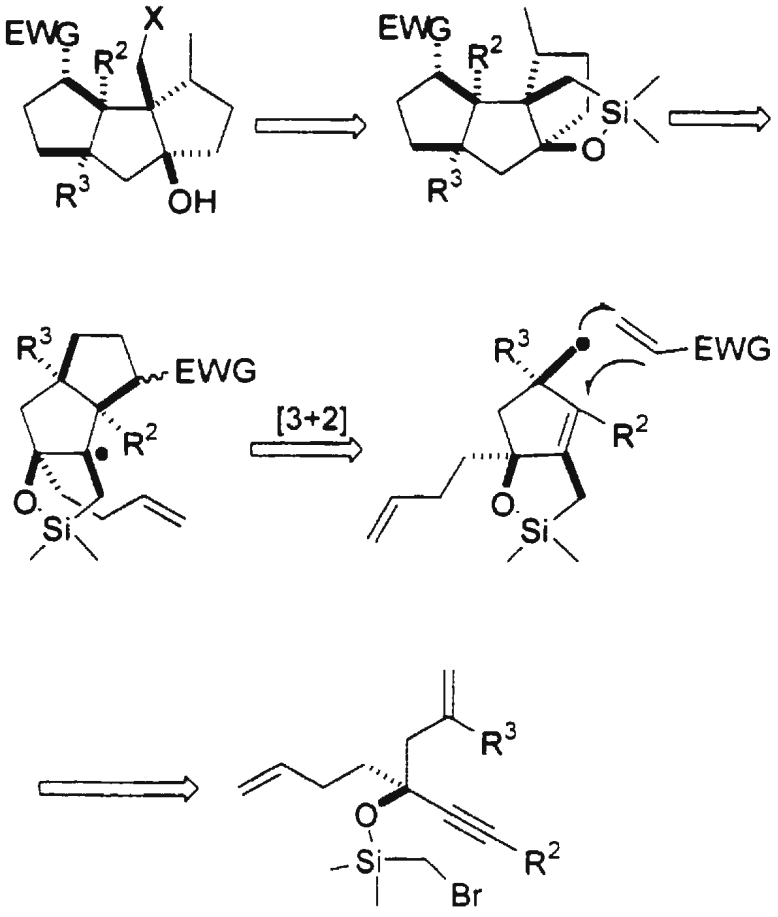


Of the two conformations, the chair-like transition state **230** is favored to predominately form the carbocycle **227**. Because of the interaction of R^1 with an H on the terminal double bond, the boat-like transition state **231** is disfavored and **232** is a minor product. In these radical cyclizations, both tri-*n*-butyltin hydride and triphenyltin hydride[28,29a] were used. Malacria believed that this strategy could be employed to make the highly functionalized angular triquinane skeletons (Scheme 81)[5] and linear triquinane skeletons (Scheme 82).[5]

Scheme 81. Proposed stereoselective access to angular triquinanes[5]

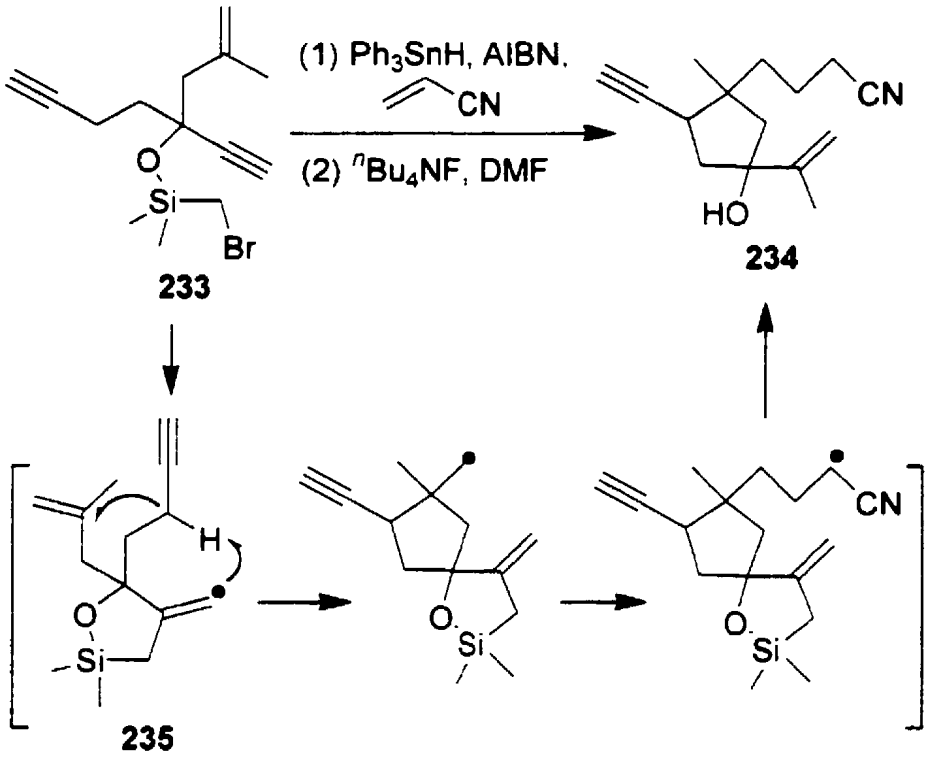


Scheme 82. Proposed stereoselective access to linear triquinanes[5]



Unfortunately, the attempts to make the angular triquinane skeletons in a one-pot synthesis using this strategy were not successful (Scheme 83).[31]

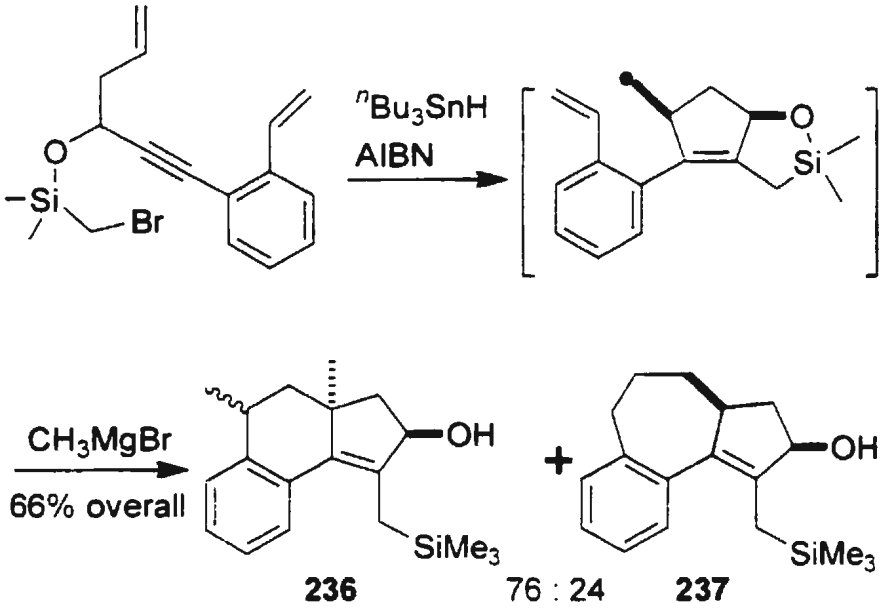
Scheme 83. Attempts to make an angular triquinane by cascade radical reactions[31]



The acyclic precursor **233** was subjected to conditions for radical cyclization with triphenyltin hydride in the presence of 10 equivalents of acrylonitrile followed by five equivalents of tetrabutylammonium fluoride (TBAF) in DMF at 70 °C. The highly substituted cyclopentane **234** was produced as a mixture of stereoisomers in 50% yield. This unexpected product resulted from a preference of the initially generated vinyl radical **235** to undergo a 1,5-hydrogen shift[32] involving the activated propargyl position rather than a 5-*exo*-*trig* cyclization.

Further studies in Malacria's group showed that the undesired 1,5-hydrogen migration was suppressed by the presence of an aromatic ring between the internal triple bond and the terminal unsaturation (Scheme 84).[32a,33] The by-product **237** was derived from a final 7-*endo-trig* cyclization.

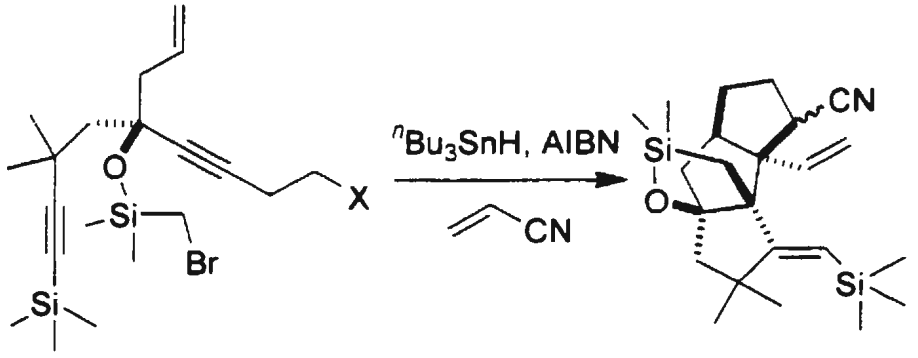
Scheme 84. Synthesis of **236** by radical cyclization



Construction of the linear triquinane framework from acyclic precursors was achieved by using a similar strategy (Scheme 85).[34] This study indicated that it is possible to synthesize diastereoselectively the functionalized linear triquinane frameworks from acyclic (bromomethyl)dimethylsilyl ethers through cascade radical reactions. When **238** was treated with tri-*n*-butyltin hydride and AIBN, the desired product **240** was obtained in 22% yield. The yield of the same reaction with **239** was 50%. A key feature is that this strategy used β-elimination

of a suitable leaving group to avoid telomerization of the last radical intermediate with acrylonitrile.[35]

Scheme 85. Construction of linear triquinane skeleton

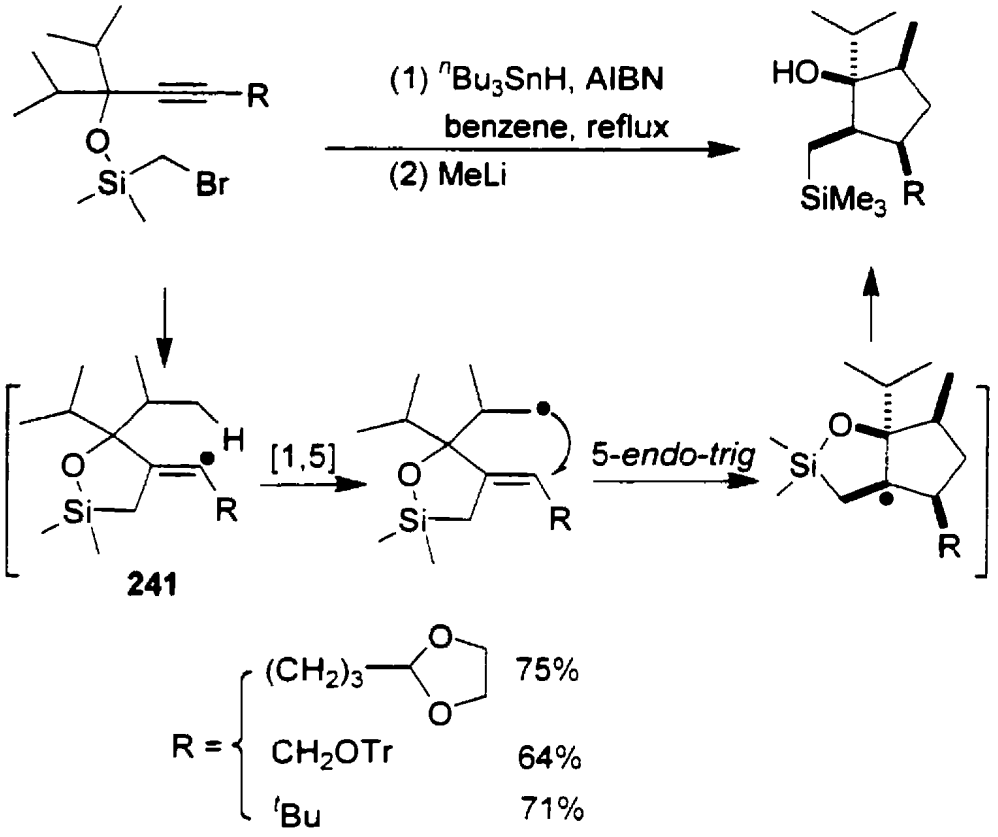


238, X = SOPh
239, X = SO_2Ph

240, 22%, α-CN:β-CN = 85:15
240, 50%, α-CN:β-CN = 90:10

An unusual 5-*endo-trig* radical cyclization[36] emerged from Malacria's outstanding research (Scheme 86). It provided a valuable new stereoselective synthesis of highly functionalized cyclopentanes and diquinanes. This example showed a totally different behavior of the vinyl radical intermediate **241**. Due to the steric hindrance resulting from the isopropyl group, it was impossible for a hydrogen shift from the acetal group to occur. Furthermore, this vinyl radical seemed to be reluctant to be reduced.

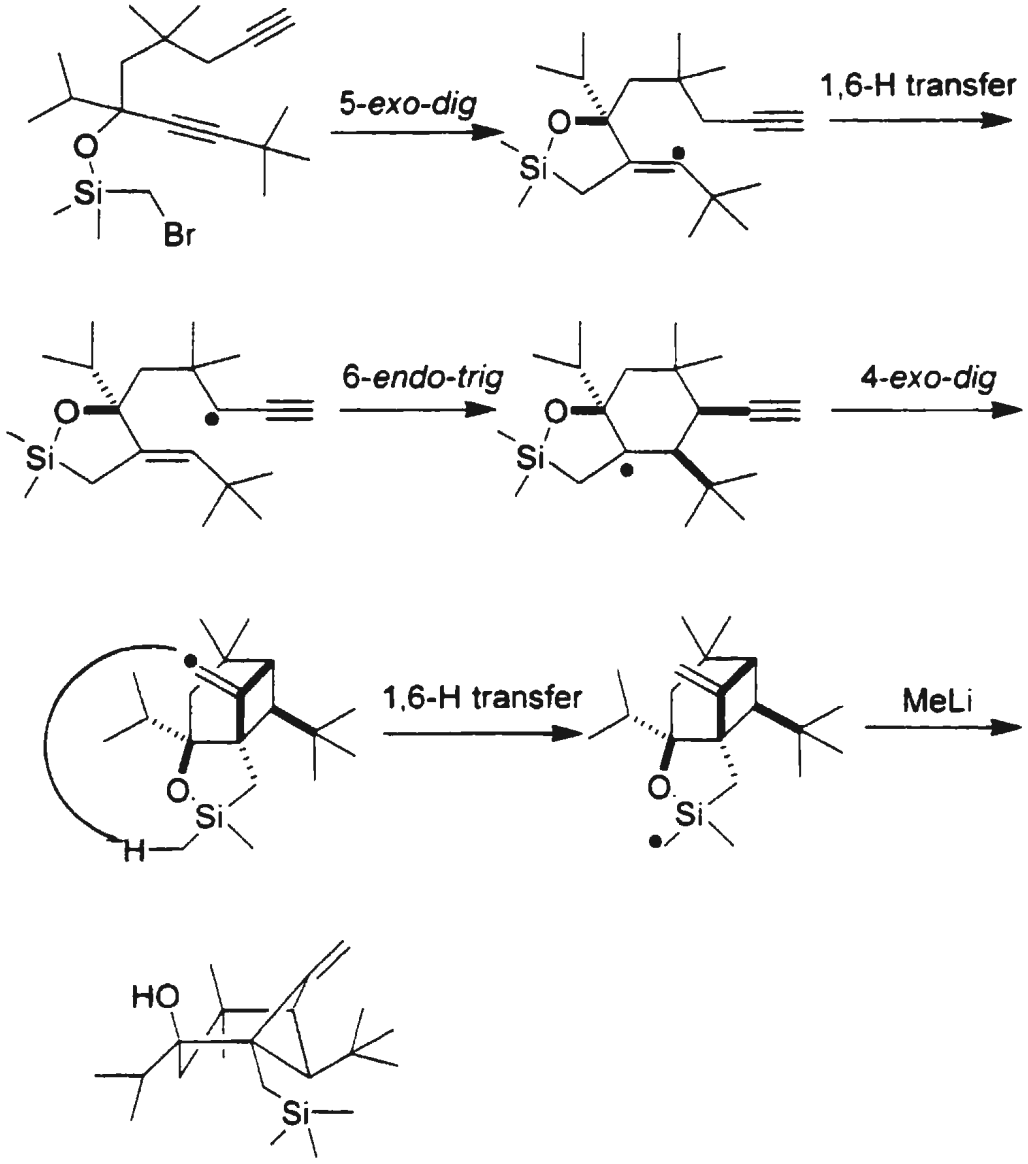
Scheme 86. A 5-*endo-trig* radical cyclization



Another interesting radical cascade involving a 5-*exo-dig* cyclization, a 1,6-H transfer, a 4-*exo-dig* cyclization, and a final 1,6-H transfer was reported by Malacria's group in 1999 (Scheme 87).[37]

In summary, radical cyclization has become a powerful tool for synthetic organic chemistry because of tremendous progress in the past two decades. Among the diverse methods for radical cyclization, the propargyl silyl ether approach, in which a radical is generated from (bromomethyl)dimethylsilyl ether,

Scheme 87. A cascade cyclization leading to bicyclo[3.1.1]heptanes

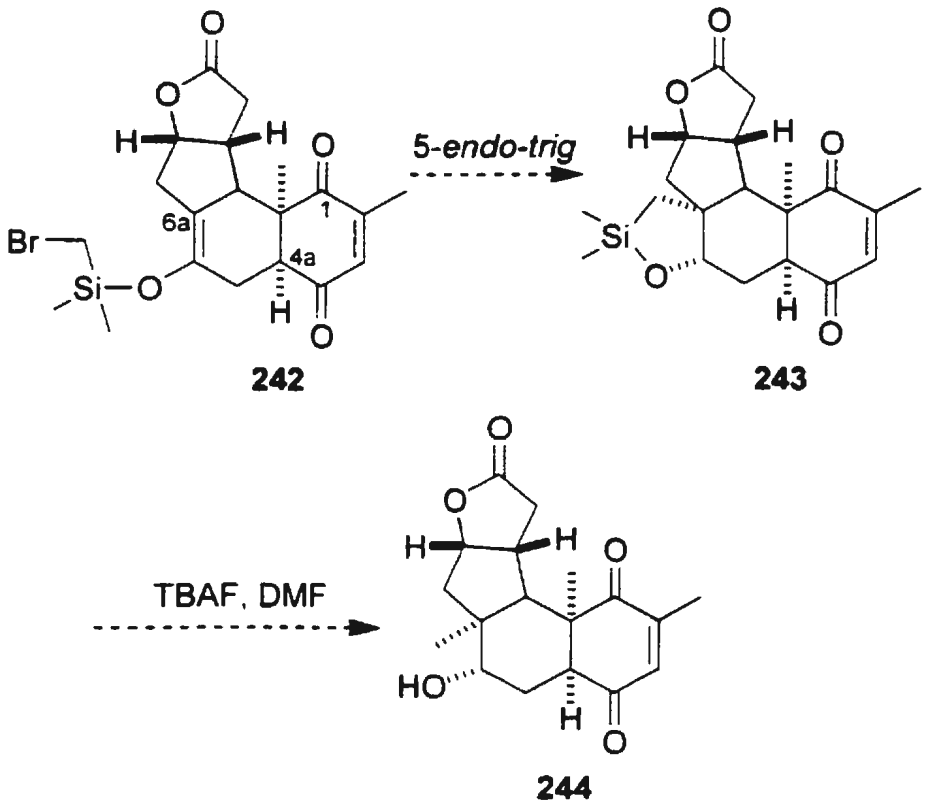


may provide a highly regio-, chemo- and stereoselective method for the synthesis of many polycyclic compounds.

2.2. Radical Cyclization with Silyl Enol Ether

Intrigued by the highly regio-, chemo- and stereoseletive radical cyclizations involving (bromomethyl)dimethylsilyl ethers,[23-37] we wondered if the silyl enol ether counterparts might engage in similar radical cyclizations. In the course of the kempane diterpene total synthesis, we wanted to introduce a methyl group at C-6a. If we could take advantage of a silyl enol ether radical cyclization, the methyl group would be installed in the correct stereochemical manner. In addition, because this position in the kempane system is sterically hindered, radical cyclization was expected to avoid other possible problems due to steric hindrance towards introducing the methyl group (Scheme 88).

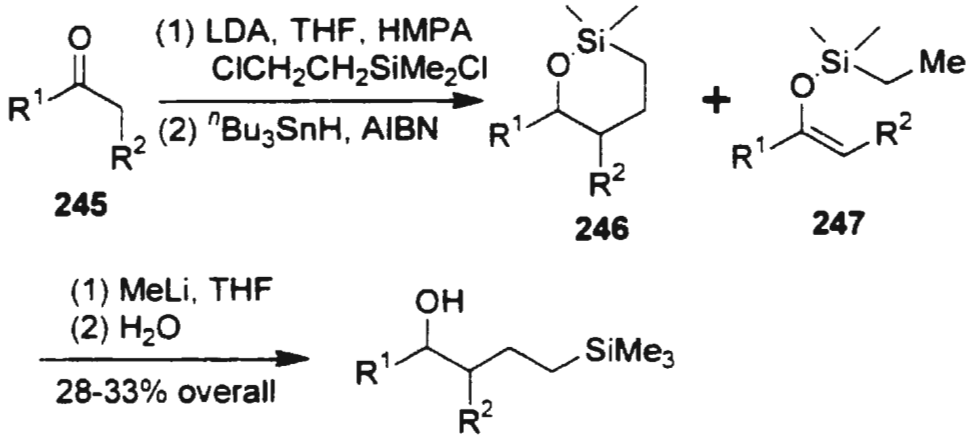
Scheme 88. Proposed introduction of methyl group by radical cyclization



In order to introduce the angular methyl group, a 5-*endo-trig* radical cyclization of **242** must be performed. Cyclization product **243** was to be treated with TBAF in DMF to yield **244**. The 5-*endo-trig* radical cyclization is a well-known "forbidden" process, but the process is not without some precedence.[36] Therefore we decided to investigate this radical cyclization with simple silyl enol ethers first. Since the forming ring contains a silicon atom, we felt that the longer bonds might overcome the geometrical shortcoming normally encountered in 5-*endo-trig* cyclizations of carbocyclic systems. Only a few radical cyclizations

involving a silyl enol ether[38] have been reported (Scheme 89), but these involved six-membered species.

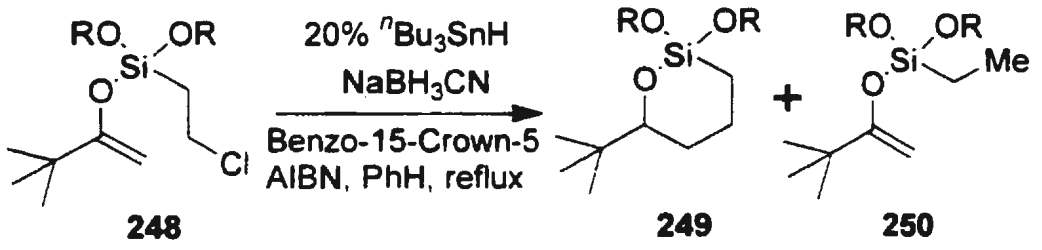
Scheme 89. Radical cyclization of a silyl enol ether



β-Chloroethyldimethylsilyl enol ether derivatives of ketones **245** were allowed to react with tri-*n*-butyltin hydride in the presence of AIBN to yield the products of "reductive α-alkylation," 1-oxa-2-silacyclohexanes **246**. This radical cyclization was in the 6-*endo-trig* mode, and the 5-*exo-trig* product was never detected. The by-product **247** resulted from the direct reduction of the radical intermediate.

Walkup's group also pursued the studies of alkoxy substituent effects upon radical cyclization of dialkoxy-2-chloroethylsilyl enol ethers (Scheme 90).[39]

Scheme 90. Radical cyclization of silyl enol ether **248**

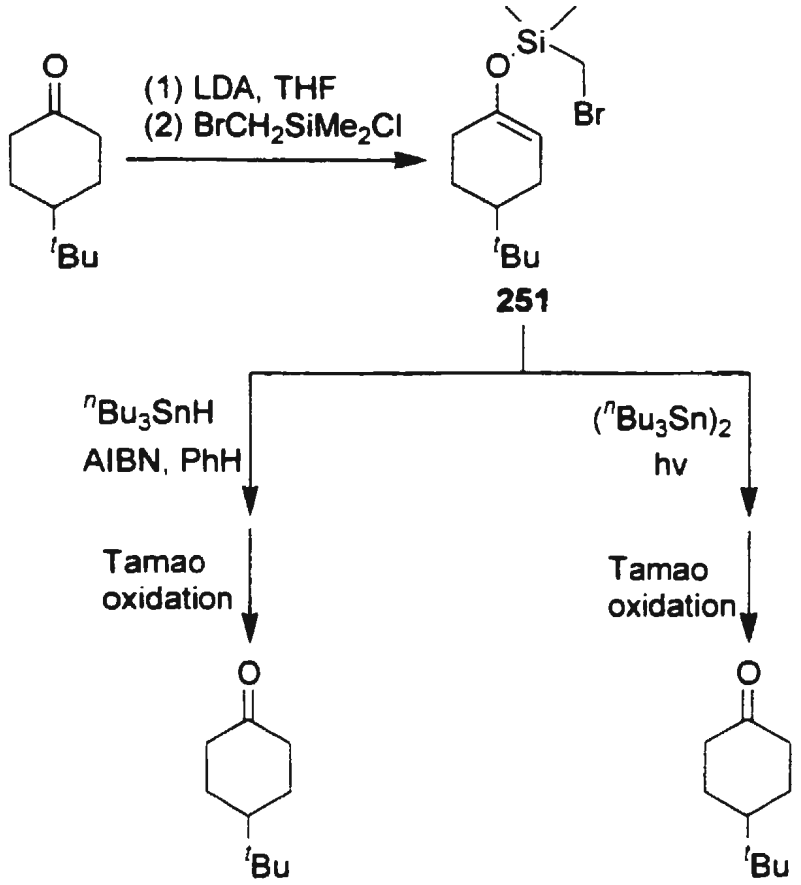


248 **249** **250**

Various dialkoxychloroethylsilyl enol ether derivatives of pinacolone **248** were subjected to radical cyclization conditions to yield **249** and the reduced product **250**. This study indicated that when the bulkiness of the alkoxy groups increased, the selectivity of the cyclization product over the directly reduced acyclic by-products improved. However, the yields of this 6-*endo-trig* cyclization of β-chloroethylsilyl ethers were consistently low. The reason for these low yields might have been the competing elimination of the β-chloroethylsilyl enol ethers to chlorosilanes and ethene. A precedented thermal decomposition reaction of β-chloroethylsilanes[40] under similar reaction conditions however, might also have been responsible for the low yields.

We used (bromomethyl)dimethylsilyl enol ether **251** to react with tri-*n*-butyltin hydride in the presence of AIBN. The crude product was subjected to Tamao oxidation, but none of the expected product was detected and most of the starting ketone was recovered (Scheme 91).

Scheme 91. Attempts at 5-*endo-trig* cyclization of a silyl enol ether



The recovery of the starting ketone demonstrated that the 5-*endo-trig* radical cyclization did not occur, and that only reduction of the radical took place. It is not surprising that this 5-*endo-trig* cyclization of silyl enol ether failed, because this process is disfavored according to Baldwin's rules[41] for ring closure. Even though the longer O-Si bond may lead to an easier process for cyclization, the silyl enol ether might not be stable enough to effect cyclization under the radical cyclization conditions.

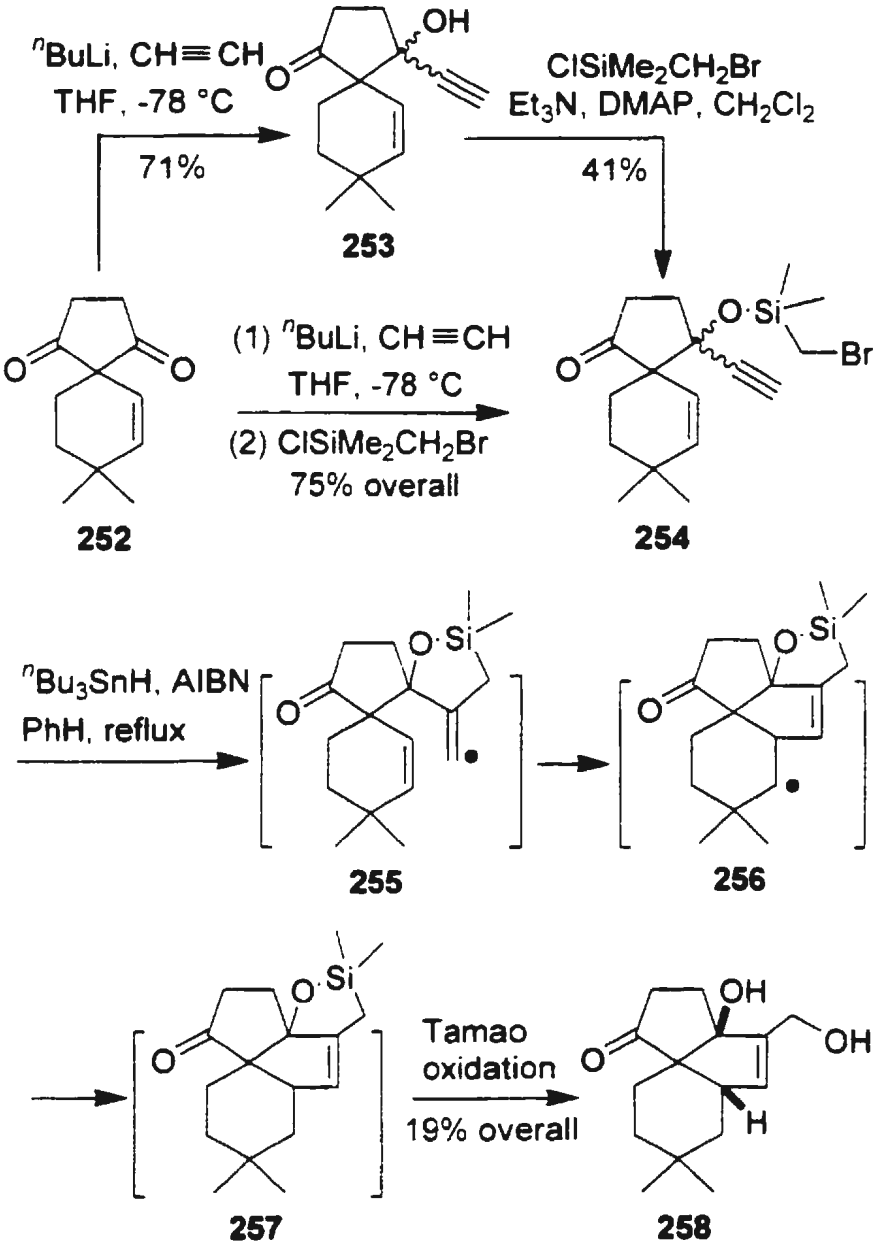
2.3. Cascade Radical Cyclizations

Next, we turned our attention to cascade radical cyclizations with a (bromomethyl)dimethylsilyl ether. In Malacria's extensive studies,[27-37] almost all of the unsaturated systems that were used to trap the initially generated exocyclic vinyl radical, were located on a flexible chain. We felt that such a vinyl radical should be able to cyclize onto unsaturation situated on a ring. It was believed that this strategy would provide an efficient approach to polycyclic compounds in high stereoselectivity.

2.3.1. A 5-*exo-dig* and 5-*exo-trig* Process in Spiro-1,3-diketone System

At first, a spiro-1,3-diketone was chosen to test this idea (Scheme 92). Spiro-1,3-diketone **252** reacted with lithium acetylide, which was generated from *n*-butyllithium and acetylene in THF at –78 °C, to produce **253** as a 1:1 mixture of two diastereoisomers. Compound **253** was treated with (bromomethyl)dimethyl-chlorosilane and triethylamine and 4-(dimethylamino)pyridine (DMAP) in dichloromethane to afford **254**. Compound **254** could also be prepared by trapping the resulting anion of acetylide addition with (bromomethyl)dimethyl-chlorosilane. Because the isomers of **254** were not separable by column chromatography, we decided to use the mixture **254** for the radical cyclization. This mixture **254** was treated with tri-*n*-butyltin hydride and a small amount of AIBN in benzene under reflux, followed by Tamao oxidation of the cyclized intermediate to afford **258** as a single isomer in 19% yield.

Scheme 92. A cascade cyclization of bromomethyl silyl ether from spiro-1,3-diketone



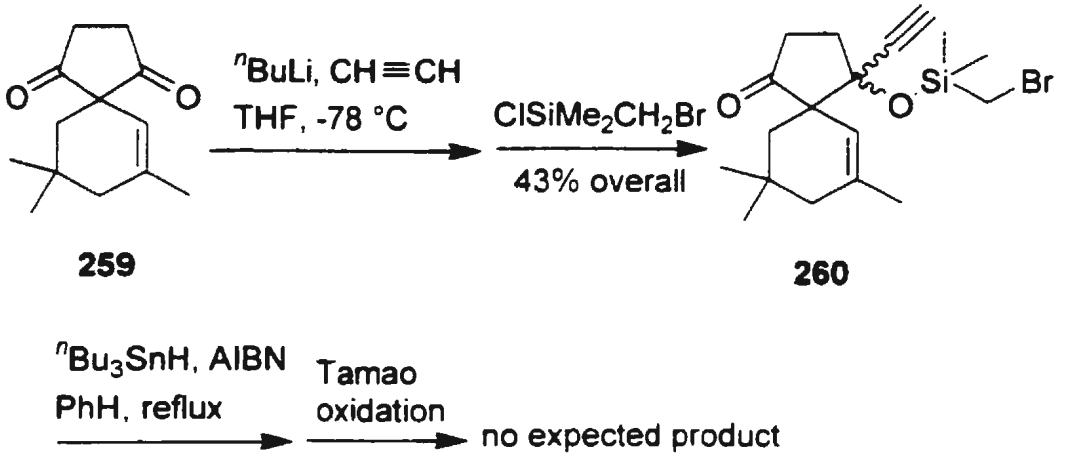
In this cascade radical cyclization, the first cyclization of (bromomethyl)-dimethylsilyl ether **254** involved a 5-*exo-dig* process and produced an exocyclic

vinyl radical **255**. Then, the vinyl radical **255** was trapped by the C-C double bond in the six-membered ring to undergo the second cyclization, by a 5-*exo-trig* mode. The radical **256** captured a hydrogen radical from tri-*n*-butyltin hydride to form the cyclized product **257**. This compound contained three carbon cycles and a siloxane-containing ring that was unstable in column chromatography. Tamao oxidation of **257** however replaced the carbon-silicon bond in **257** with the carbon-oxygen bond of **258** which was formed in 19% overall yield.

Several factors are responsible for the low yield of this cascade radical cyclization. First, acetylide addition to the spiro-1,3-diketone **252** produced two inseparable stereoisomers, but only one of the isomers had a geometry that would allow the second radical cyclization to take place. The vinyl radical **255** derived from the first cyclization, needs to be on the same side of the five-membered ring as the C-C double bond. In other words, only one of the two epimeric compounds **254** can participate in the second radical cyclization. Secondly, the double bond used to trap the vinyl radical was in a six-membered ring. The ring strain made the vinyl radical trapping process more difficult than in an acylic system. Thirdly, compound **257** had three five-membered rings and one six-membered ring. Therefore, the highly strained system in **257** might not be completely compatible with the Tamao oxidation conditions. It is also possible that competing decomposition of **257** in the final Tamao oxidation process took place.

A similar spiro-1,3-diketone **259** was also investigated for this radical process, but none of the expected product was obtained (Scheme 93). Acetylide

Scheme 93. Attempted cascade cyclization of **259**



259 **260**

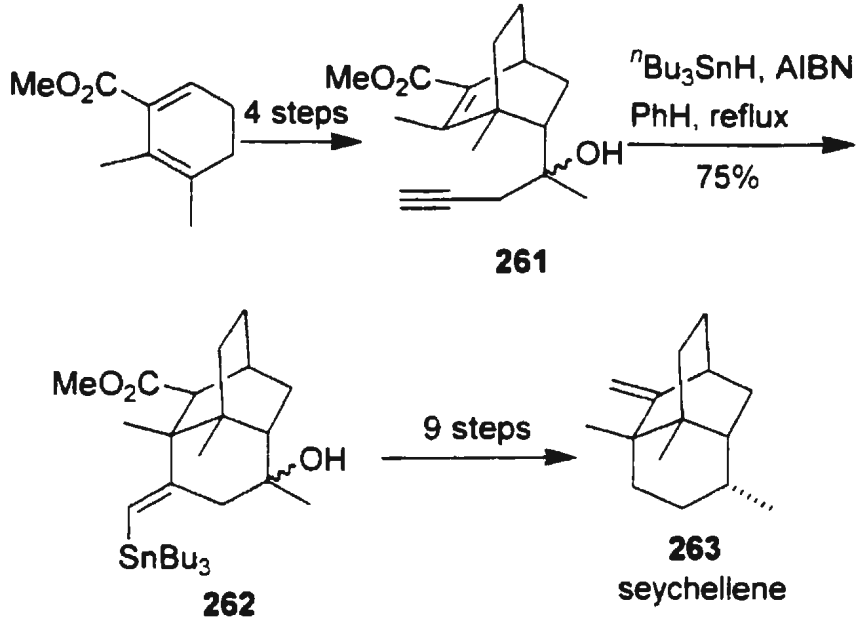
addition to spiro-1,3-diketone **259** did provide two stereoisomers, without selectivity, and these isomers were not separable by column chromatography. The mixture **260** was subjected to the cascade radical cyclization conditions. yet none of the expected product was isolated after Tamao oxidation. We also used triphenyltin hydride and AIBN to initiate the radical reaction, but the result was the same.

2.3.2. A 5-*exo-dig* and 6-*exo-trig* Process

Following the disappointing results obtained in our strategy of using spiro-1,3-diketone, we next turned our attention to the cascade radical reaction with 5-*exo-dig*, and 6-*exo-trig* modes. The 6-*exo-trig* radical cyclization process was used in the total synthesis of seychellene by Stork's group (Scheme 74) and

Subba Rao's group[42] (Scheme 94). The Subba Rao synthesis of seychellene **263** involved the closure of the final six-membered ring by the addition of a vinyl radical to an unsaturated ester (**261**→**262**).

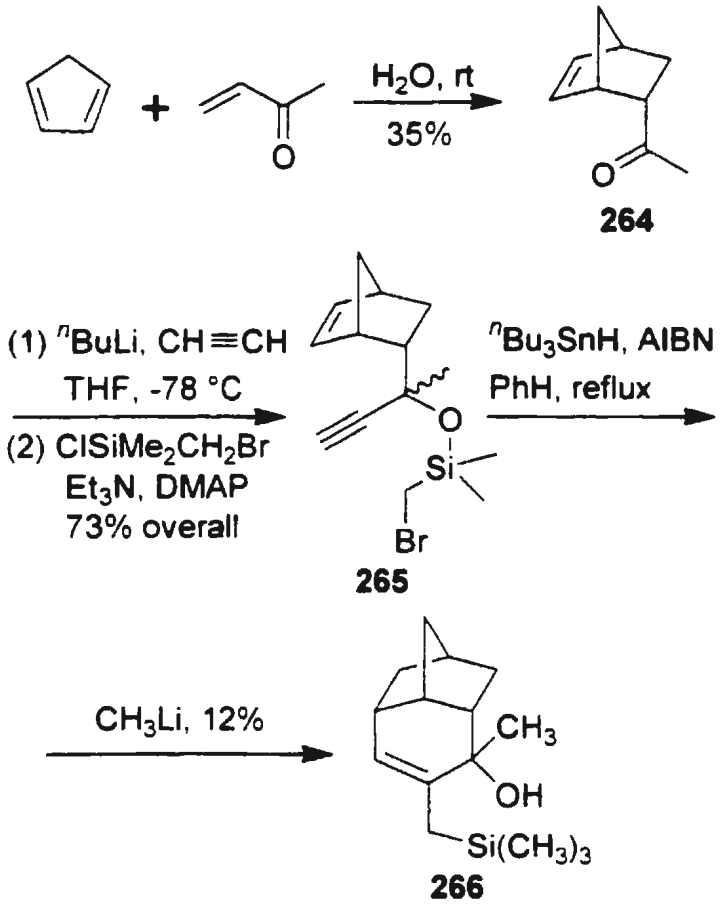
Scheme 94. Subba Rao's synthesis of seychellene **263**



Based on the application of a 6-*exo-trig* radical cyclization in natural product synthesis, a 5-*exo-dig*, 6-*exo-trig* tandem radical cyclization was designed (Scheme 95). The Diels-Alder adduct **264**, derived by *endo*-addition of butanone to cyclopentadiene, reacted with lithium acetylide, and the anion was trapped with (bromomethyl)dimethylchlorosilane to form the radical precursor **265** in good yield. The compound **265** was applied to regular radical cyclization conditions followed by treatment with methyllithium, to afford in low yield **266**, which was obviously the product of tandem radical cyclization. The difficulty for

the second 6-*exo-trig* cyclization may have been the result of the low accessibility of the exocyclic vinyl radical and the double bond in the ring.

Scheme 95. Attempted radical cyclization by 5-*exo-dig*, 6-*exo-trig* mode

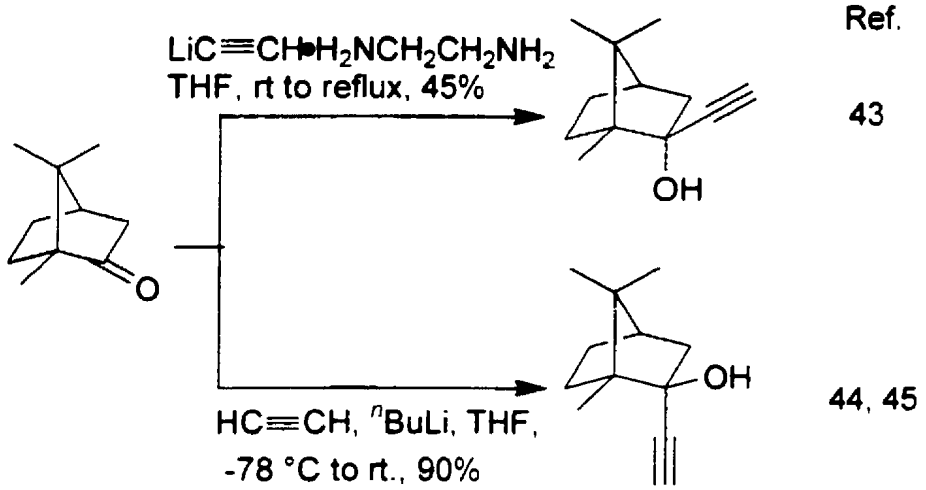


2.3.3. A 5-*exo-dig* and 5-*exo-trig* Process

Another tandem radical cyclization process that we tested was a cyclization of 5-*exo-dig*, 5-*exo-trig* modes. It is well known that 5-*exo-trig* cyclization is a faster and easier process relative to 6-*exo-trig* cyclization. There are some conflicting arguments about the stereoselectivity of addition of lithium

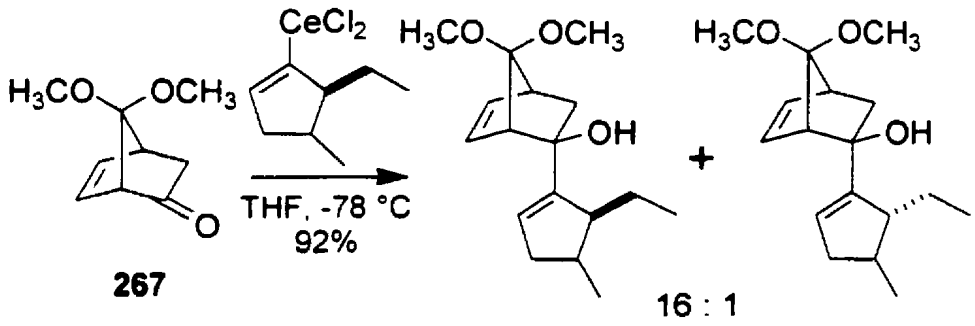
acetylide to camphor. It has been suggested that the *exo* adduct is produced,[43] but other authors[44,45] claim that acetylide addition to camphor gives predominantly the *endo* adduct (Scheme 96).

Scheme 96. Acetylide addition to camphor



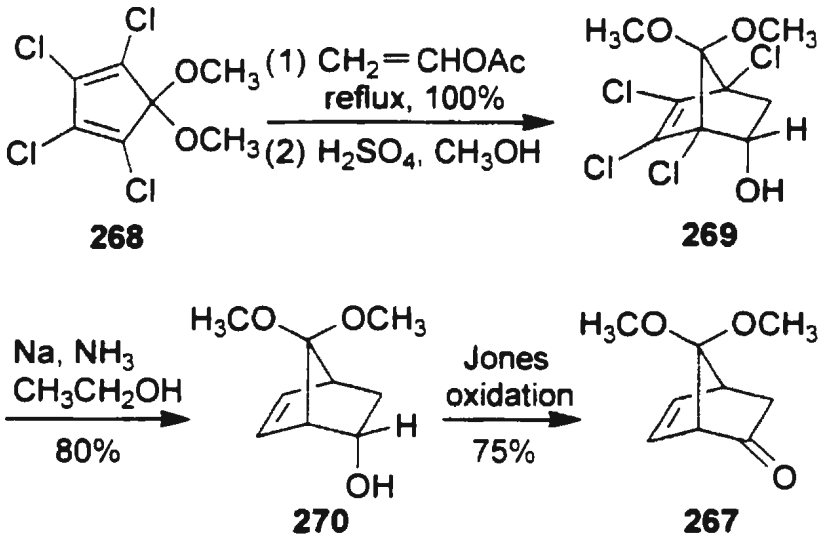
The addition of vinylcerium reagents to 7,7-dimethoxynorbornenone was reported to show good diastereoselectivity in favor of *endo* addition[46] (Scheme 97).

Scheme 97. Addition of vinylcerium reagents to 7,7-dimethoxynorbornenone



We speculated that acetylide addition to 7,7-dimethoxynorbornenone **267** would give the *endo* adduct. 7,7-Dimethoxynorbornenone **267** was prepared by the route originally reported by Jung[47] (Scheme 98). Diels-Alder cycloaddition of

Scheme 98. Synthesis of **267**

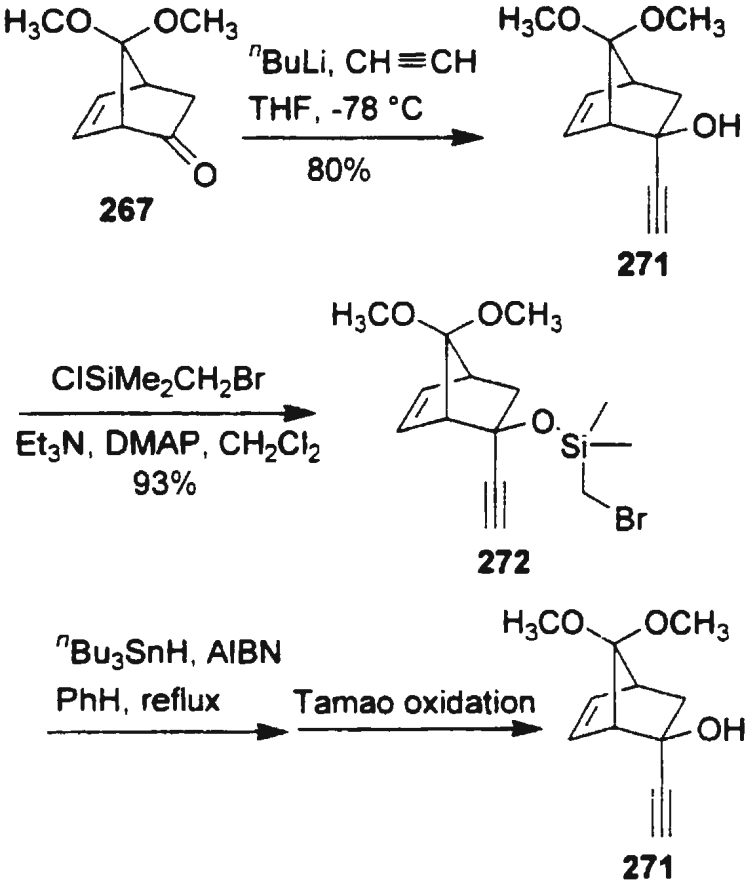


268 **269** **270** **267**

5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **268** with vinyl acetate furnished the desired acetate, which was subsequently hydrolyzed to give **269**. Reductive dechlorination was then achieved by sodium in liquid ammonia to form **270**. Finally, Jones oxidation of **270** was carried out to afford the desired product **267**. With **267** in hand, the tandem radical cyclization through the 5-*exo-dig* and 5-*exo-trig* modes was designed and tested (Scheme 99). Acetylide addition of **267** gave the expected *endo* product **271**. Treatment of **271** with (bromomethyl)dimethylsilylchlorosilane in the presence of triethylamine and a catalytic amount of DMAP in dichloromethane afforded the radical cyclization

precursor **272**. Again, the desired radical cyclization did not occur. After **272** was subjected to radical cyclization conditions and Tamao oxidation conditions, only **271** was recovered in a significant amount.

Scheme 99. Attempted tandem radical cyclization with **267**



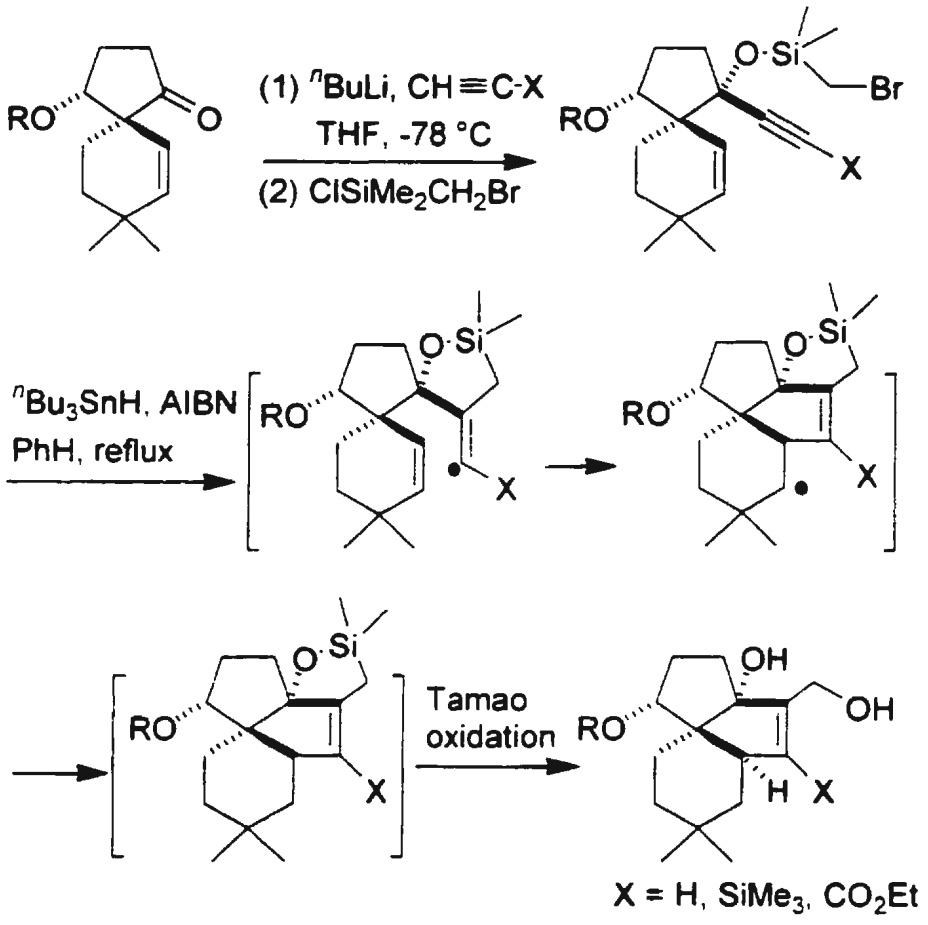
2.4. Future Work

From the preliminary results of our cascade radical cyclizations, it seemed to us that the second radical cyclization was reluctant to proceed. This could be because the C-C double bond that traps the vinyl radical was in a ring system and lacked flexibility. The low yield of radical cyclizations with the spiro-1,3-diketone indicated that more studies for this approach are necessary.

2.4.1. Further Studies for Radical Cyclization in a Spiro-1,3-diketone

One of the major reasons for the low yield in the cascade radical cyclization is that only one of the epimeric acetylide adducts is suitable for the second radical cyclization. If we reduce one of the carbonyl groups in the spiro-1,3-diketone and protect the resulting hydroxyl group, the selectivity of the acetylide addition should be higher. At least, one could expect to separate the two stereoisomers by column chromatography. It is anticipated that a cascade radical cyclization of the appropriate isomer would be more efficient (Scheme 100).

Scheme 100. Design for an improved cascade cyclization



Another strategy for improving the second radical cyclization is to increase the reactivity of the initially generated vinyl radical. Two reagents, LiC≡CTMS and LiC≡C-CO_2Et are recommended for acetylide addition. LiC≡CTMS is expected to be prepared from *n*-butyllithium and trimethylsilyl acetylene, and LiC≡C-CO_2Et is expected to be generated from *n*-butyllithium and ethyl propiolate.[48]

2.4.2. Tris(trimethylsilyl)silicon Hydride and Tri-*n*-butylgermanium Hydride

Besides tri-*n*-butyltin hydride, tris(trimethylsilyl)silicon hydride and tri-*n*-butylgermanium hydride are useful reagents for conducting radical reactions by the "metal hydride" method. Scheme 101 shows[6] a chain reaction involved for tri-*n*-butyltin hydride ($^{n}Bu_3SnH$). An analogus chain reaction can be written for tris(trimethylsilyl)silicon hydride [$(TMS)_3SiH$] or tri-*n*-butylgermanium hydride ($^{n}Bu_3GeH$).

Scheme 101. Radical chain reaction by metal hydride

Initiation

$$Bu_3SnH \xrightarrow{AIBN} Bu_3Sn\bullet$$

Propagation

$$Bu_3Sn\bullet + A{-}X \longrightarrow A\bullet + Bu_3SnX$$

$$A\bullet \xrightarrow{\text{reaction(s)}} \bullet B$$

$$\bullet B + Bu_3SnH \longrightarrow Bu_3Sn\bullet + B{-}H$$

Competing reaction

$$A\bullet + Bu_3SnH \longrightarrow Bu_3Sn\bullet + A{-}H$$

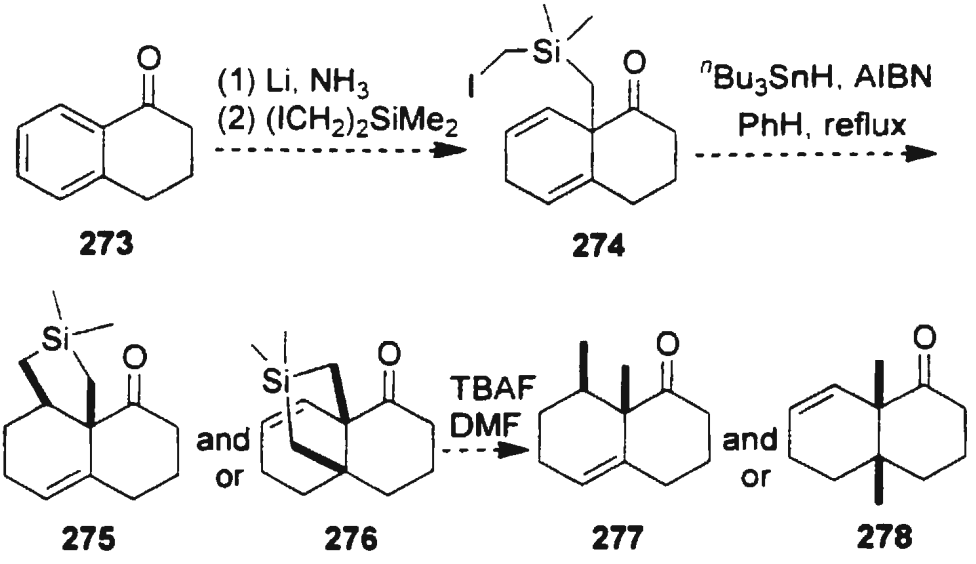
The competing reaction, a premature reduction of A• (or another intermediate radical) by the hydride reagent, is the standard problem in metal hydride radical reactions. If the rate of conversion of A• to B• is slow, then it is common to use low concentrations of the hydride reagent to reduce the rate of the competing

reduction. In this regard, the use of tris(trimethylsilyl)silicon hydride and tri-*n*-butylgermanium hydride can be advantageous, because they are less reactive hydrogen donors than tri-*n*-butyltin hydride.[1,6]

2.4.3. New Radical Cyclization

Bis(iodomethyl)dimethylsilane, which is easily generated from bis(chloromethyl)dimethylsilane by a Finkelstein reaction,[49] can be used for radical cyclization. A new design for a radical cyclization is presented in Scheme 102.

Scheme 102. Proposed radical cyclization



The precursor **274** for the radical cyclization can be prepared by reductive alkylation of α-tetralone **273**. Application of **274** to radical cyclization conditions should give cyclized product **275** and/or **276**. After treatment of the cyclized products with TBAF in DMF, **277** and/or **278** will be produced. This radical

cyclization should provide a method for introducing two *cis*-methyl groups in the decalin ring system and may be useful in natural product synthesis. Of course, α-tetralone can be replaced by α-indanone, and a similar radical cyclization should proceed.

It is possible that the reagent bis(iodomethyl)dimethylsilane can act as alkylating reagent and radical precursor. Investigation of the radical cyclization involving bis(iodomethyl)dimethylsilane will provide an interesting and useful method for stereoselectively introducing two *cis*-methyl groups in a one-pot reaction.

In conclusion, our preliminary study on cascade radical cyclization demonstrated that the vinyl radical by 5-*exo*-*dig* cyclization of (bromomethyl)dimethylsilyl ether can be trapped by a suitably located C-C double bond in the ring. This strategy can lead to a multifunctionalized polycyclic ring system in a highly stereoselective manner. Our studies also proved that 5-*endo*-*trig* cyclization cannot be easily made to work with a (bromomethyl)-dimethylsilyl enol ether. Further investigations on the cascade radical cyclization are needed.

2.5. Experimental

General methods: see pages 99-100.

4-Ethynyl-4-hydroxy-8,8-dimethylspiro[4,5]dec-6-en-1-one (253)

Purified acetylene (prepared by successively passing through a dry ice-acetone trap, concentrated sulfuric acid, and anhydrous $CaCl_2$) was passed through dry THF (30 mL) in a 100-mL, septum-capped, round-bottomed flask at –78 °C to produce a saturated solution. To this solution was added *n*-BuLi (2.5 M solution in hexane, 2.00 mL, 5.00 mmol) at –78 °C, and the resulting solution was stirred for 30 min. This lithium acetylide solution was transferred into a precooled solution of **252** (387 mg, 2.01 mmol) in dry THF (10 mL) by a double-ended needle at –78 °C. The resulting mixture was stirred at –78 °C for 2 h, then warmed to rt and stirred for 2 h. The reaction mixture was quenched with cold water (20 mL), and then extracted with diethyl ether (4 x 30 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography (10% Et_2O/petroleum ether) to afford **253** (231 mg, 75%) as a yellow oil: IR (Nujol) 3358 (s), 3263 (s), 1721 (s), 1269 (s), 1214 (s), 1171 (s), 1060 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.79 (1H, d, *J*=10.0 Hz), 5.28 (1H, d, *J*=10.0 Hz), 2.58 (1H, s, C≡CH), 2.50-2.26 (4H, m), 2.19 (1H, s, OH), 1.87-1.74 (2H, m), 1.66-1.59 (2H, m), 1.03 (3H, s, 8-methyl), 1.02 (3H, s, 8-methyl). ^{13}C NMR ($CDCl_3$) δ 215.3 (0, C1), 143.4 (1, C6 or C7), 120.3 (1, C7 or C6), 84.0 (0, **C**≡CH), 74.8 (1, C≡**C**H), 59.7 (0), 33.7 (2), 33.5 (2), 32.9 (2), 31.4

(0, C5 and C10), 29.5 (3, 8-methyl), 28.6 (3, 8-methyl), 20.3 (2). MS *m/z* 218 (M^+, 56), 203 (36), 175 (7), 161 (9), 159 (18), 157 (12), 150 (18), 147 (14), 145 (16), 143 (35), 142 (11), 131 (11), 129 (16), 128 (17), 121 (13), 119 (10), 117 (15), 109 (100), 107 (26), 105 (18), 93 (23), 91 (52), 81 (21), 79 (22), 78 (12), 77 (44), 67 (18), 65 (29), 63 (11), 55 (37), 53 (71), 51 (24), 43 (27). HRMS calcd. for $C_{14}H_{18}O_2$ 218.1306, found 218.1302.

4-[(Bromomethyl)dimethylsiloxy]-4-ethynyl-8,8-dimethylspiro[4,5]dec-6-en-1-one (254)

Method A: To a solution of **253** (189 mg, 0.865 mmol) and 4-(dimethylamino)pyridine (DMAP) (10.6 mg, 0.0865 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.18 mL, 1.3 mmol) and (bromomethyl)chlorodimethylsilane (0.15 mL, 1.0 mmol) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 30 min, then warmed to rt and stirred at rt for 24 h. The reaction mixture was quenched with water (10 mL), and the organic layer was separated. The aqueous layer was extracted with ether (3 x 20 mL). The combined organic solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography (10% Et_2O/petroleum ether) to afford **253** (129 mg, 41%) as a yellow oil.

Method B: Purified acetylene (prepared by successively passing through a dry ice-acetone trap, concentrated sulfuric acid, and anhydrous $CaCl_2$) was passed through dry THF (20 mL) in a 100-mL, septum-capped, round-bottomed

flask at –78 °C to produce a saturated solution. To this solution was added *n*-BuLi (2.5 M solution in hexane, 0.79 mL, 2.0 mmol) at –78 °C, and the resulting solution was stirred for 30 min. This lithium acetylide solution was transferred into a precooled solution of **252** (152 mg, 0.788 mmol) in dry THF (10 mL) by a double-ended needle at –78 °C. The resulting mixture was stirred at –78 °C for 2 h, then (bromomethyl)chlorodimethylsilane (0.42 mL, 3.0 mmol) was added and stirred at –78 °C for another 2h, at rt for 2 h. The reaction mixture was quenched with 10% $NaHCO_3$ solution (20 mL), extracted with diethyl ether (4 x 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography (10% Et_2O/petroleum ether) to afford **254** (217 mg, 75%) as a yellow oil: IR (Nujol) 1749 (s), 1255 (s), 1197 (s), 1171 (s), 1081 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ Major isomer: 5.76 (1H, d, *J*=9.9 Hz), 5.24 (1H, d, *J*=9.9 Hz), 2.65 (1H, s, C≡CH), 2.56 (2H, dd, *J*=20.3, 7.4 Hz), 2.44 (2H, s, $SiCH_2Br$), 2.42-2.28 (m), 1.83-1.74 (m), 1.69 (1H, dd, *J*=9.1, 4.5 Hz), 1.62 (1H, m), 1.02 (3H, s, 8-methyl), 1.00 (3H, s, 8-methyl), 0.25 (6H, $Si(CH_3)_2$). Minor isomer: 5.90 (1H, d, *J*=10.3 Hz), 5.40 (1H, d, *J*=10.3 Hz), 2.69 (1H, s, C≡CH), 2.41 (2H, s, $SiCH_2Br$), 2.42-2.28 (m), 1.83-1.72 (m), 1.57 (1H, m), 1.08 (3H, s, 8-methyl), 1.05 (3H, s, 8-methyl), 0.37 (3H, s, $SiCH_3$), 0.36 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ Major isomer: 215.4 (0, C1), 143.4 (1, C6 or C7), 120.3 (1, C7 or C6), 84.1 (0), 77.2 (0), 74.8 (1, C≡**C**H), 59.8 (0), 33.6 (2), 33.5 (2), 32.9 (2), 29.5 (3, 8-methyl), 28.6 (3, 8-methyl), 25.0 (0), 20.4 (2), 17.6 (2), -1.6 (3, $Si(CH_3)_2$).

Minor isomer: 215.1 (0, C1), 145.3 (1, C6 or C7), 118.1 (1, C7 or C6), 83.5 (0), 77.2 (0), 75.0 (1, C≡**C**H), 59.4 (0), 34.3 (2), 32.5 (2), 31.4 (2), 29.9 (3, 8-methyl), 29.1 (3, 8-methyl), 25.8 (0), 20.4 (2), 17.6 (2), -1.6 (3, $Si(CH_3)_2$). MS *m/z* 370 (41), 368 (M^+, 40), 356 (5), 355 (22), 354 (5), 353 (23), 314 (5), 313 (2), 312 (2), 301 (5), 300 (3), 299 (6), 275 (8), 263 (4), 261 (5), 233 (9), 231 (8), 185 (12), 177 (7), 173 (7), 172 (5), 159 (12), 158 (13), 157 (36), 153 (79), 151 (76), 143 (37), 142 (16), 141 (12), 135 (10), 131 (13), 130 (10), 129 (27), 128 (26), 127 (11), 125 (100), 123 (92), 121 (39), 115 (31), 109 (46), 107 (25), 105 (20), 93 (26), 91 (60), 83 (24), 79 (22), 77 (50), 75 (80), 65 (29), 55 (34), 53 (32), 45 (23), 43 (34), 41 (53). HRMS calcd. for $C_{17}H_{25}O_2SiBr$ 368.0806, found 368.0829.

(5*S,8*S**)-5-Hydroxy-6-hydroxymethyl-10,10-dimethyltricyclo[6.4.0^{1,5}.0^{1,8}]-dodec-6-en-2-one (258)**

To a solution of **254** (134 mg, 0.360 mmol) in dry benzene (30 mL) was added a solution of *n*-Bu_3SnH (0.15 mL, 0.54 mmol) and 2,2'-azobisisobutyronitrile (AIBN) (6.0 mg, 0.036 mmol) in dry benzene (10 mL) with a syringe pump over 8 h under reflux. After addition, the resulting solution was allowed to reflux for another 10 h. After the solution was cooled to rt, the solvent was removed under reduced pressure. The residue was dissolved in 1:1 THF/methanol (20 mL), then $KHCO_3$ (520 mg, 5.20 mmol) and 30% H_2O_2 (5.0 mL) was added to this solution. The mixture was heated at reflux for 4 h. The mixture was filtered through celite and extracted with diethyl ether (4 x 20 mL).

The combined extracts were washed with 10% $NaHSO_3$ solution (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. After the solvent was removed under vacuum, the residue was subjected to column chromatography (diethyl ether) to afford **258** (17 mg, 19%) as a white solid: mp 130-132 °C. IR (Nujol) 3405 (br, s), 1712 (s), 1306 (s), 1156 (s), 1076 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.00 (1H, s, H7), 4.33 (2H, s, CH_2OH), 2.73 (1H, ddd, *J*=6.6, 4.8, 1.4 Hz, H8), 2.40 (1H, m), 2.12 (1H, m), 2.03 (1H, dd, *J*=12.2, 7.3 Hz), 1.95 (1H, dd, *J*=9.0, 3.8 Hz), 1.85 (1H, dt, *J*=14.0, 3.9 Hz), 1.68 (1H, dd, *J*=13.0, 5.6 Hz, H9), 1.54 (1H, dd, *J*=13.9, 8.7 Hz), 1.37 (2H, dd, *J*=9.3, 4.3 Hz), 1.00 (3H. s, 10-methyl), 0.93 (1H, m, H9), 0.92 (3H, s, 10-methyl). ^{13}C NMR ($CDCl_3$) δ 223.0 (0, C2), 142.0 (0, C6), 139.5 (1, C7), 91.1 (0, C5), 59.4 (2, CH_2OH), 58.9 (0, C1), 44.3 (2, C9), 43.4 (1, C8), 36.5 (2), 35.7 (2), 32.2 (3, 10-methyl), 30.2 (0, C10), 28.9 (2), 23.4 (3, 10-methyl), 22.9 (2). MS *m/z* 250 (M^+, 8), 233 (4), 232 (9), 220 (3), 219 (3), 204 (4), 203 (3), 194 (7), 193 (5), 191 (15), 190 (4), 189 (4), 177 (20), 176 (100), 175 (12), 161 (11), 133 (14), 121 (19), 120 (48), 119 (12), 113 (11), 108 (30), 107 (18), 105 (20), 93 (13), 91 (46), 86 (21), 84 (34), 79 (22), 78 (15), 77 (32), 69 (32), 67 (14), 65 (18), 57 (29), 55 (39), 53 (21), 51 (10), 43 (34). HRMS calcd. for $C_{15}H_{22}O_3$ 250.1568, found 250.1579.

4-[(Bromomethyl)dimethylsiloxy]-4-ethynyl-7,9,9-trimethylspiro[4,5]dec-6-en-1-one (260)

Purified acetylene (prepared by successively passing through a dry ice-acetone trap, concentrated sulfuric acid, and anhydrous $CaCl_2$) was passed through dry THF (20 mL) in a 100-mL, septum-capped, round-bottomed flask at –78 °C to produce a saturated solution. To this solution was added *n*-BuLi (1.6 M solution in hexane, 2.95 mL, 4.73 mmol) at –78 °C, and the resulting solution was stirred for 30 min. This lithium acetylide solution was transferred into a precooled solution of **259** (390 mg, 0.788 mmol) in dry THF (10 mL) by a double-ended needle at –78 °C. The resulting mixture was stirred at –78 °C for 2 h, then (bromomethyl)chlorodimethylsilane (1.06 mL, 7.56 mmol) was added and stirred at –78 °C for another 2h, at rt for 2 h. The reaction mixture was quenched with 10% $NaHCO_3$ solution (20 mL), extracted with diethyl ether (4 x 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography (5% Et_2O/petroleum ether to afford **260** (311 mg, 43%) as a yellow oil: IR (Nujol) 1745 (s), 1255 (s), 1178 (s), 1082 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ Isomer 1: 5.33 (1H, s, H6), 2.62 (1H, s, C≡CH), 2.56 (2H, d, *J*=5.8 Hz, $SiCH_2Br$), 2.50-2.35 (m), 1.91-1.51 (m), 1.79 (3H, s, 7-methyl), 1.35 (1H, m), 1.01 (3H, 9-methyl), 0.96 (3H, 9-methyl), 0.34 (6H, $Si(CH_3)_2$). Isomer 2: 5.17 (1H, s, H6), 2.59 (1H, s, C≡CH), 2.54 (2H, d, *J*=6.8 Hz, $SiCH_2Br$), 2.50-2.35 (m), 1.91-1.51 (m), 1.74 (3H, s, 7-methyl), 1.30 (1H, m), 0.98 (3H, 9-

methyl), 0.87 (3H, 9-methyl), 0.34 (6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ Isomer 1: 215.1 (0, C1), 139.8 (0, C7), 115.6 (1, C6), 84.1 (0), 78.8 (0), 76.6 (1, C≡**C**H), 61.2 (0), 43.8 (2), 39.4 (2), 35.2 (0), 34.7 (2), 32.4 (3, 9-methyl), 32.0 (2), 31.2 (2), 26.5 (3, 9-methyl), 24.9 (3, 7-methyl), 17.0 (2, Si**C**H_2Br), -1.3 (3, $Si(CH_3)_2$). Isomer 2: 215.0 (0, C1), 140.1 (0, C7), 115.5 (1, C6), 83.4 (0), 80.0 (0), 76.2 (1, C≡**C**H), 62.4 (0), 43.3 (2), 39.4 (2), 35.2 (0), 35.1 (2), 32.8 (2), 31.4 (3, 9-methyl), 30.2 (2), 28.3 (3, 9-methyl), 24.8 (3, 7-methyl), 17.0 (2, Si**C**H_2Br), -1.3 (3, $Si(CH_3)_2$). MS *m/z* 384 (M^++2, 42), 382 (M^+, 42), 369 (4), 367 (4), 341 (2), 339 (2), 330 (2), 328 (3), 315 (3), 313 (2), 301 (1), 299 (2), 289 (6), 263 (3), 261 (4), 233 (4), 231 (4), 206 (5), 199 (8), 191 (3), 187 (2), 185 (1), 173 (7), 172 (4), 171 (15), 159 (4), 157 (19), 153 (37), 151 (36), 150 (12), 149 (13), 131 (16), 129 (9), 125 (42), 123 (100), 121 (21), 115 (11), 107 (26), 105 (15), 93 (10), 91 (27), 83 (14), 81 (10), 75 (38), 65 (11), 55 (16), 53 (14), 43 (17). HRMS calcd. for $C_{18}H_{27}O_2SiBr$ 382.0962, found 382.0988.

endo-5-Acetylbicyclo[2.2.1]hept-2-ene (264)

Cyclopentadiene (620 mg, 9.38 mmol) and methyl vinyl ketone (0.76 mL, 9.4 mmol) were added into water (60 mL) at rt, and the resulting mixture was stirred at rt for 5 h. The mixture was extracted with ether (4 x 20 mL), and the combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$. After the solvent was removed in vacuo, the residue was subjected to column chromatography (20% EtOAc/hexane) to provide **264** (445 mg, 35%) as

a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.15 (1H, m), 5.85 (1H, dd, *J*=5.3, 2.9 Hz), 3.24 (1H, m), 3.01 (1H, m), 2.89 (1H, m), 2.12 (3H, s, CH_3CO), 1.74 (1H, ddd, *J*=11.3, 8.7, 2.5 Hz), 1.52-1.42 (2H, m), 1.33 (1H, m). ^{13}C NMR ($CDCl_3$) δ 208.6 (0, **C**OCH_3), 137.6 (1), 131.0 (1), 52.0, 49.7, 45.6, 42.4, 29.0, 27.1.

***endo*-5-[(1-(Bromomethyl)dimethylsiloxy-1-ethynyl)ethyl]-bicyclo[2.2.1]hept-2-ene (265)**

To a saturated solution of acetylene in dry THF (30 mL), which was prepared by passing purified acetylene through dry THF, was added *n*-BuLi (2.5 M solution in hexane, 3.96 mL, 9.90 mmol) at –78 °C, and the solution was stirred at –78 °C for 30 min. Then a solution of **264** (674 mg, 4.95 mmol) in dry THF (10 mL) was added into the above lithium acetylide solution at –78 °C, and the resulting mixture was stirred at –78 °C for 2 h and at rt for 2h. The reaction mixture was quenched with water (20 mL), and extracted with ether (4 x 30 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to give the crude product (604 mg, 75%) as a yellow oil. This crude addition product was used in the next step without further purification.

To a solution of crude acetylide addition product (521 mg, 3.21 mmol) and 4-(dimethylamino)pyridine (DMAP) (39 mg, 0.32 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.54 mL, 3.9 mmol) and (bromomethyl)chlorodimethylsilane (0.54 mL, 3.9 mmol) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 30

min, then warmed to rt and stirred at rt for 2 h. The reaction mixture was quenched with water (10 mL), and the organic layer was separated. The aqueous layer was extracted with ether (3 x 40 mL). The combined organic solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (5% Et_2O/petroleum ether to afford **265** (992 mg, 98%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 6.01 (1H, dd, *J*=5.6, 2.8 Hz), 5.94 (1H, dd, *J*=5.3, 2.6 Hz), 2.96 (1H, m), 2.76 (1H, m), 2.56 (2H, d, *J*=1.6 Hz, $SiCH_2Br$), 2.44 (1H, s, C≡CH), 2.29 (1H, ddd, *J*=9.0, 5.6, 3.2 Hz), 1.81 (1H, ddd, *J*=11.8, 9.6, 4.2 Hz), 1.43 (3H, s, CH_3), 1.35 (1H, dq, *J*=8.3, 2.5 Hz), 1.23 (1H, m), 0.96 (1H, ddd, *J*=8.2, 6.0, 3.0 Hz), 0.33 (3H, s, $SiCH_3$), 0.32 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 135.4 (1), 132.7 (1), 87.3 (0), 74.4 (1, C≡**C**H), 71.2 (0), 51.3, 50.2, 44.2, 42.4, 31.6, 28.8, 17.5 (2, $SiCH_2Br$), -1.1 (3, $Si(CH_3)_2$).

4-Methyl-5-(trimethylsilyl)methyltricyclo[5.2.1.0^{3,8}]dec-5-en-4-ol (266)

To a solution of **265** (294 mg, 0.939 mmol) in dry benzene (40 mL) was added a solution of *n*-Bu_3SnH (0.15 mL, 0.54 mmol) and 2,2'-azobisisobutyronitrile (AIBN) (30.8 mg, 0.188 mmol) in dry benzene (10 mL) with a syringe pump over 8 h under reflux. After addition, the resulting solution was allowed to reflux for another 10 h. After the solution was cooled to 0 °C, CH_3Li (4.70 mmol) was added into the solution. The mixture was allowed to stir at 0 °C for 30 min, then at rt for 1 h. The reaction mixture was quenched with saturated

NH_4Cl solution (10 mL), extracted with ether (4 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (50% Et_2O/petro-ether) to afford **266** (27.8 mg, 12%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 5.51 (1H, d, J=5.7 Hz, H6), 2.30-2.21 (m), 2.03-1.96 (m), 1.78-1.60 (m), 1.49 (2H, s), 1.34-1.19 (m), 1.27 (3H, s, 4-methyl), 0.96 (1H, d, J=12.6 Hz), 0.83 (1H, dd, J=12.4, 6.1 Hz), 0.16 (6H, s, $Si(CH_3)_3$), 0.09 (3H, s, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 132.5 (0, C5), 129.9 (1, C6), 72.3 (0, C4), 49.8, 41.1, 39.6, 37.9, 36.7, 33.5, 31.7, 25.1, 24.0, -0.4 (3H, $Si(CH_3)_3$), -0.9 (3H, $Si(CH_3)_3$).

Compounds **269**, **270**, and **267** were prepared according to Jung's procedure.[47]

1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (269)

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (3.56 g, 13.5 mmol) was dissolved in vinyl acetate (50 mL), and the mixture was heated at reflux for 7 days. The volatiles were removed in vacuo at rt, and the residue was crystallized from methanol to afford 5-acetoxy-1,2,3,4-tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-2-ene (4.72 g, 100%) as a white solid: mp 83-85 °C (lit.[47] mp 81-82 °C).

To a stirred solution of the above product (4.72 g, 13.5 mmol) in methanol (60 mL) was added dry K_2CO_3 (186 mg, 1.35 mmol). The mixture was stirred at rt

for 30 min. The excess methanol was removed at rt, and the residue oil was taken up in diethyl ether and was washed with brine. The ethereal layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a small plug of silica gel (ether as eluent) to afford **269** (4.65 g, unpurified) as a pale yellow oil. This product was used in the next step without further purification.

7,7-Dimethoxybicyclo[2.2.1]hept-5-en-2-ol (270)

A solution of the crude **269** (1.83 g) and dry ethanol (1 mL) in 10 mL of anhydrous ether was added dropwise to a vigorously stirred solution of sodium (1.3 g, 57 mmol) in approximately 80 mL of dry ammonia at –78 °C under argon. A brilliant blue-green chemiluminescence was emitted during the addition. Following completion of this step, the reaction mixture was stirred at –78 °C for 5 min and treated in turn with isoprene, ether (200 mL), and saturated ammonium chloride solution (50 mL). The ammonia was allowed to evaporate and the residue was dissolved in water (100 mL), extracted with ether (4 x 40 mL). The combined extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum to give **270** (808 mg, 80%) as a red oil. This crude **270** was used in the next step without further purification.

7,7-Dimethoxybicyclo[2.2.1]hept-5-en-2-one (267)

Preparation of Jones reagent: Chromium trioxide (26.7 g, 267 mmol) was dissolved in water (40 mL), and concentrated sulfuric acid (23 mL) was added with cooling. The cold solution was diluted with water to 100 mL to form an 8 M solution of the reagent.

To a solution of **270** (808 mg, 4.75 mmol) in acetone (20 mL) was added Jones reagent (8 M solution) (3.00 mL, 24.0 mmol) at rt, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was diluted with water (50 mL), extracted with ether (4 x 40 mL). The combined extracts were washed with brine (2 x 40 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (30% EtOAc/hexane) to provide **267** (599 mg, 75%) as a yellow oil: IR (Nujol) 1758 (s), 1287 (s), 1224 (s), 1182 (s), 1140 (s), 1105 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.58 (1H, dd, J=5.9, 3.0 Hz), 6.05-6.01 (1H, m), 3.26 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.19-3.18 (2H, m), 2.31 (1H, dd, J=16.6, 3.7 Hz), 1.93 (1H, d, J=16.5 Hz). ^{13}C NMR ($CDCl_3$) δ 209.4 (0, C2), 141.3 (1), 126.6 (1), 120.6 (0, C7), 59.9, 52.1, 50.2, 44.7, 36.3. MS m/z 168 (M^+, 5), 140 (15), 137 (4), 110 (8), 109 (100), 108 (15), 101 (6), 97 (5), 95 (9), 94 (11), 93 (10), 79 (8), 77 (12), 66 (18), 65 (19), 59 (29), 41 (14). HRMS calcd. for $C_9H_{12}O_3$ 168.0786, found 168.0795.

exo-2-Ethynyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (271)

To a saturated solution of acetylene in dry THF (30 mL), which was prepared by passing purified acetylene through dry THF, was added *n*-BuLi (2.5 M solution in hexane, 2.06 mL, 5.15 mmol) at –78 °C, and the solution was stirred at –78 °C for 30 min. Then a solution of **267** (433 mg, 2.57 mmol) in dry THF (10 mL) was added into the above lithium acetylide solution at –78 °C, and the resulting mixture was stirred at –78 °C for 2 h and at rt for 2h. The reaction mixture was quenched with water (20 mL), and extracted with ether (4 x 30 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to provide **271** (400 mg, 80%) as a white solid: mp 87-89 °C. IR (Nujol) 3460 (s), 3275 (s), 1713 (s), 1663 (m), 1296 (s), 1122 (s), 1069 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.32 (1H, ddd, *J*=4.3, 3.6, 0.6 Hz), 6.18 (1H, dd, *J*=6.2, 3.5 Hz), 4.24 (1H, s, OH), 3.32 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 2.99 (1H, m), 2.92 (1H, m), 2.40 (1H, s, C≡CH), 2.03-1.90 (2H, m, H3). ^{13}C NMR ($CDCl_3$) δ 137.3 (1), 131.2 (1), 120.1 (0, C7), 86.5 (0), 73.3 (0), 71.1 (1, C≡**C**H), 55.5 (1), 52.6 (3, OCH_3), 49.6 (3, OCH_3), 45.5 (1), 43.6 (2, C3). MS *m/z* 164 (M^+-30, 3), 163 (21), 162 (3), 147 (1), 145 (1), 141 (2), 138 (5), 127 (12), 121 (5), 120 (3), 119 (3), 110 (9), 109 (100), 104 (4), 103 (6), 101 (2), 95 (7), 91 (25), 79 (5), 77 (9), 65 (8), 59 (11), 55 (6), 53 (15), 41 (10). HRMS calcd. for $C_{11}H_{14}O_3$ 194.0943, found 194.0943.

exo-2-[(Bromomethyl)dimethylsiloxy]-2-ethynyl-7,7-dimethoxy-bicyclo[2.2.1]hept-5-ene (272)

To a solution of **271** (375 mg, 1.92 mmol) and 4-(dimethylamino)pyridine (DMAP) (23.4 mg, 0.192 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.40 mL, 2.9 mmol) and (bromomethyl)chlorodimethylsilane (0.32 mL, 2.3 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then warmed to rt and stirred at rt for 12 h. The reaction mixture was quenched with water (10 mL), and the organic layer was separated. The aqueous layer was extracted with ether (3 x 40 mL). The combined organic solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography (30% Et_2O/petroleum ether) to afford **272** (615 mg, 93%) as a colorless oil: IR 1300 (s), 1253 (s), 1137 (s), 1078 (s) 1054 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.24-6.16 (2H, m, H5 and H6), 3.23 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 2.96 (1H, m, H1), 2.91 (1H, m, H4), 2.62 (2H, d, *J*=2.8 Hz, $SiCH_2Br$), 2.45 (1H, s, C≡CH), 2.28 (1H, dd, *J*=11.7, 3.7 Hz, H3), 1.87 (1H, d, *J*=12.1 Hz, H3), 0.38 (3H, $SiCH_3$), 0.37 (3H, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 134.5 (1), 133.8 (1), 119.2 (0, C7), 88.2 (0), 74.0 (0), 72.6 (1, C≡**C**H), 56.2 (1, C1), 51.3 (3, OCH_3), 50.6 (3, OCH_3), 45.3 (1, C4), 44.4 (2, C3), 17.4 (2, Si**C**H_2Br), -1.2 (3, $SiCH_3$), -1.3 (3, $SiCH_3$). MS *m/z* 329 (M^+-15, 8), 315 (9), 314 (7), 313 (10), 299 (20), 297 (18), 271 (4), 269 (3), 251 (6), 249 (2), 243 (16), 241 (15), 237 (12), 235 (12), 233 (19), 226 (13), 224 (14), 219 (7), 218 (3), 217 (3), 205 (2), 204 (4), 203 (2), 191 (7), 189 (5), 177 (19), 176 (8), 175 (7), 169 (6), 167 (6), 163 (6), 162 (7), 161

(42), 153 (99), 151 (100), 147 (33), 146 (13), 145 (23), 131 (20), 126 (23), 125 (70), 123 (66), 111 (60), 109 (27), 103 (32), 101 (16), 95 (62), 91 (25), 89 (71), 83 (25), 77 (31), 75 (52), 65 (18), 59 (39), 55 (19), 53 (23), 43 (20). HRMS calcd. for $C_{14}H_{21}O_3SiBr$ 344.0443, found 344.0445.

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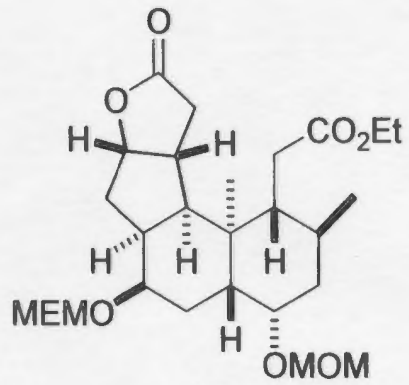
Appendix: Selected ^{1}H NMR Spectra

The ^{1}H NMR spectra of the synthetic compounds are arranged in the same order as they appear in the text. All the selected ^{1}H NMR spectra were recorded in $CDCl_3$



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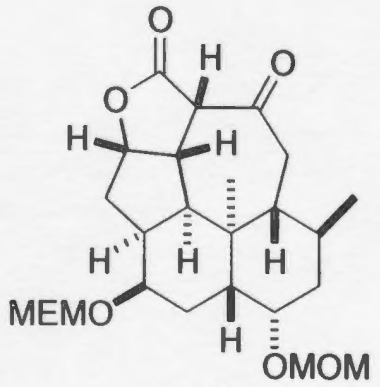

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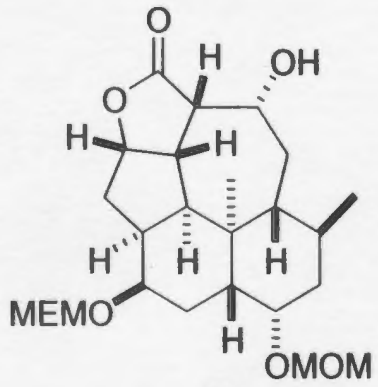

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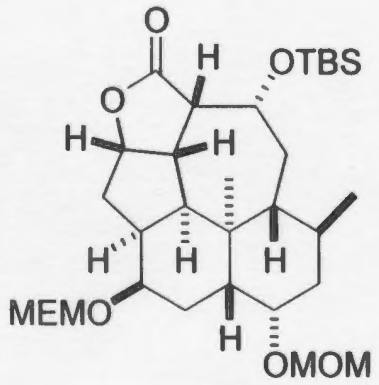

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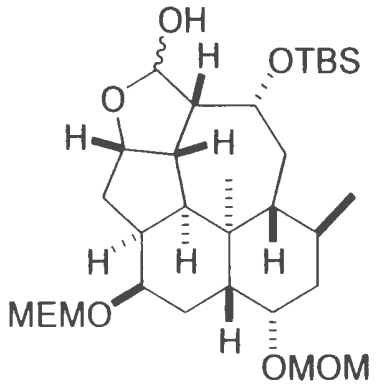

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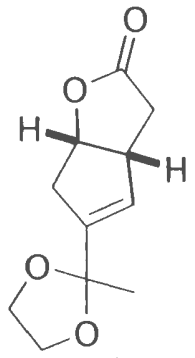

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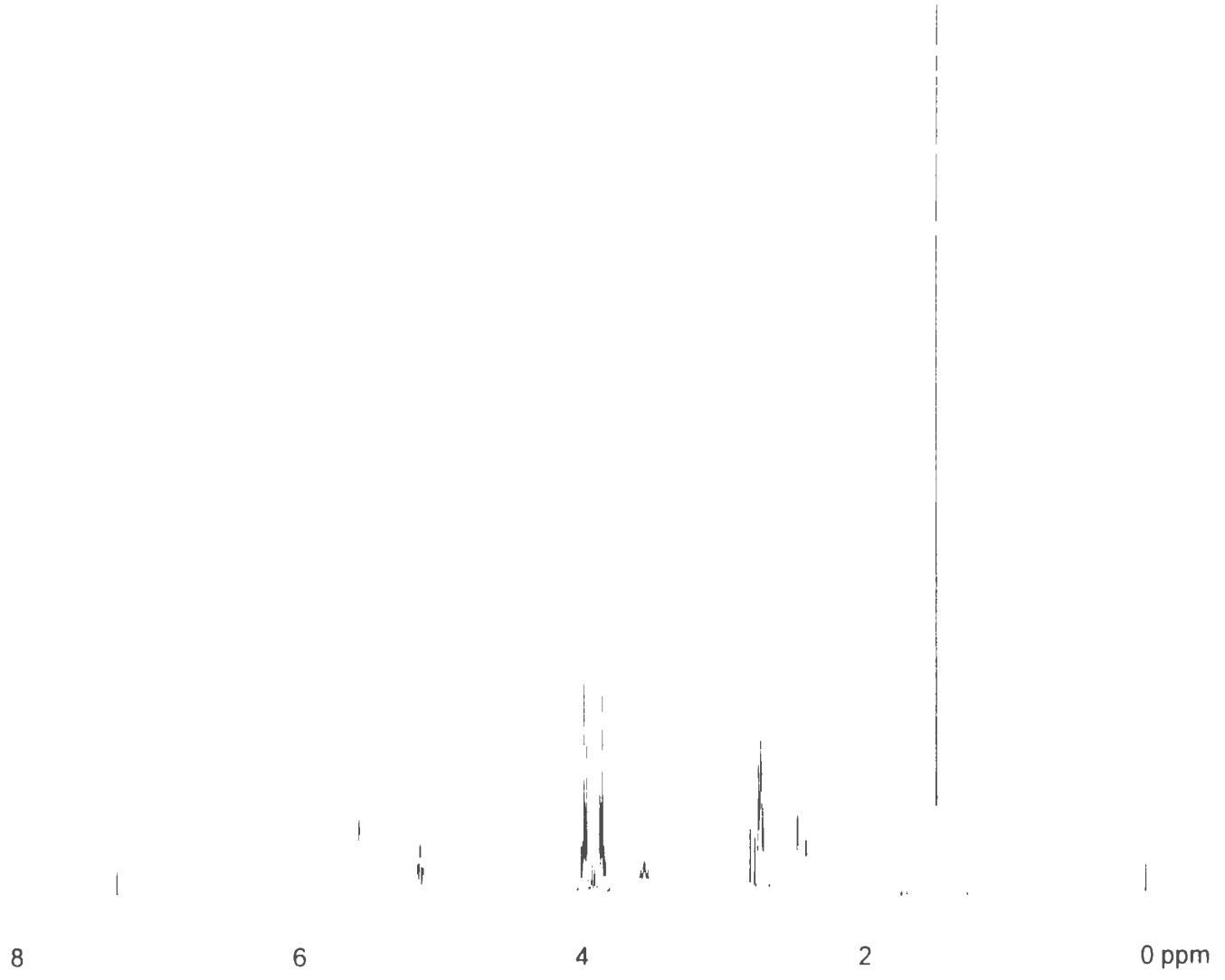

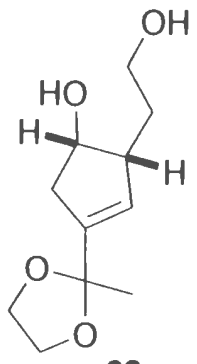

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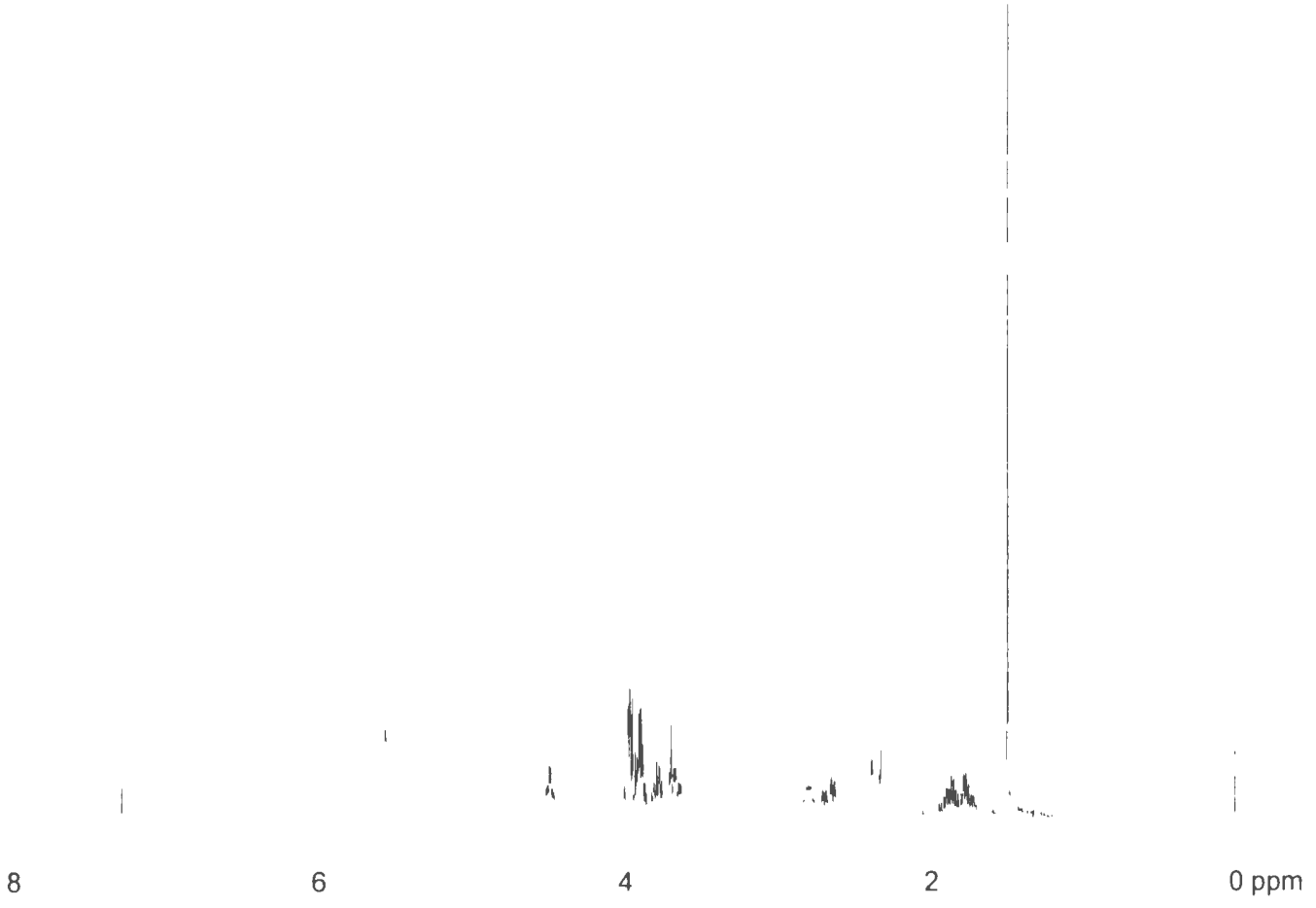

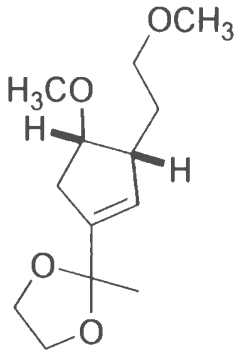

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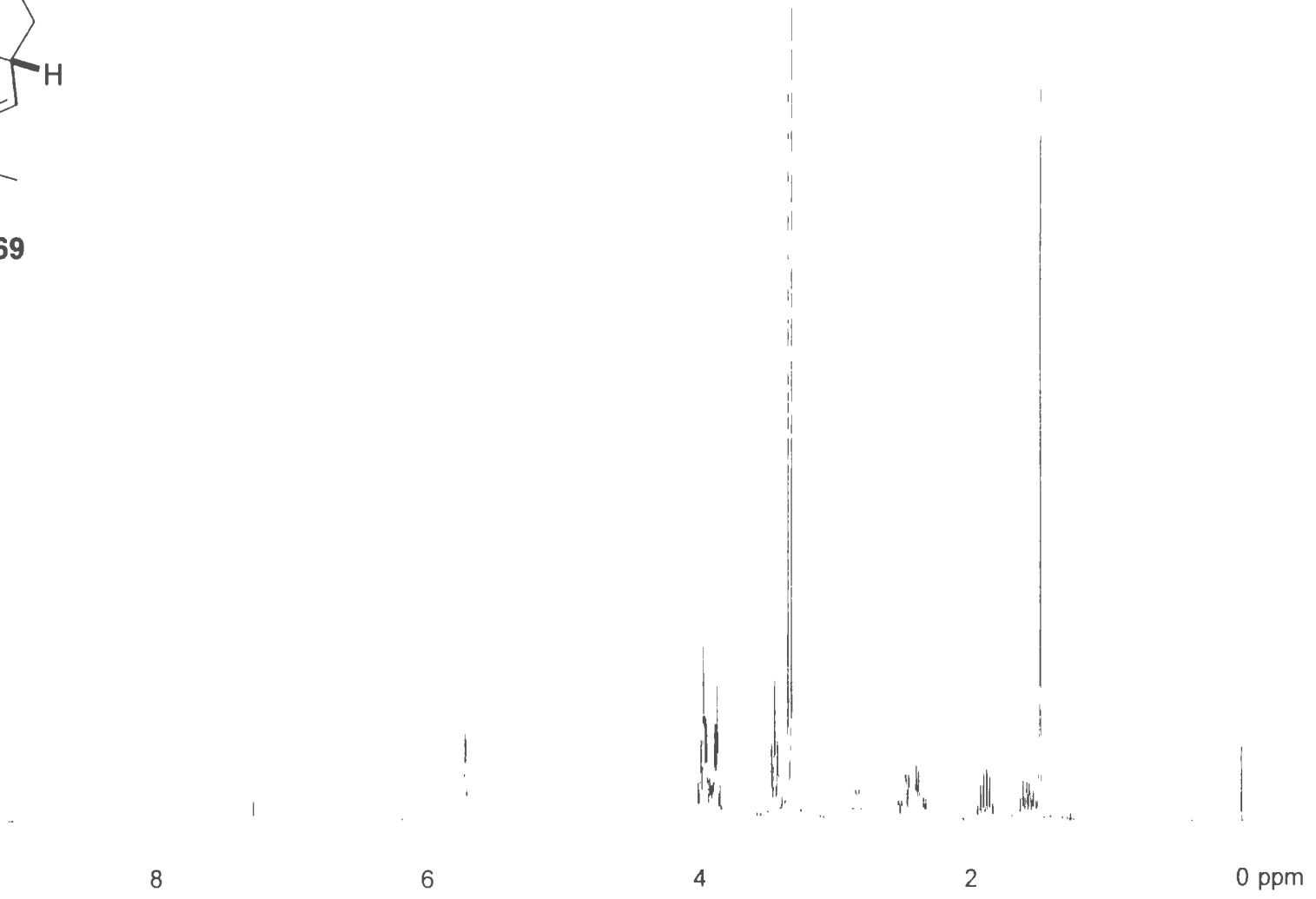

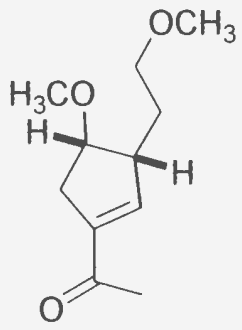

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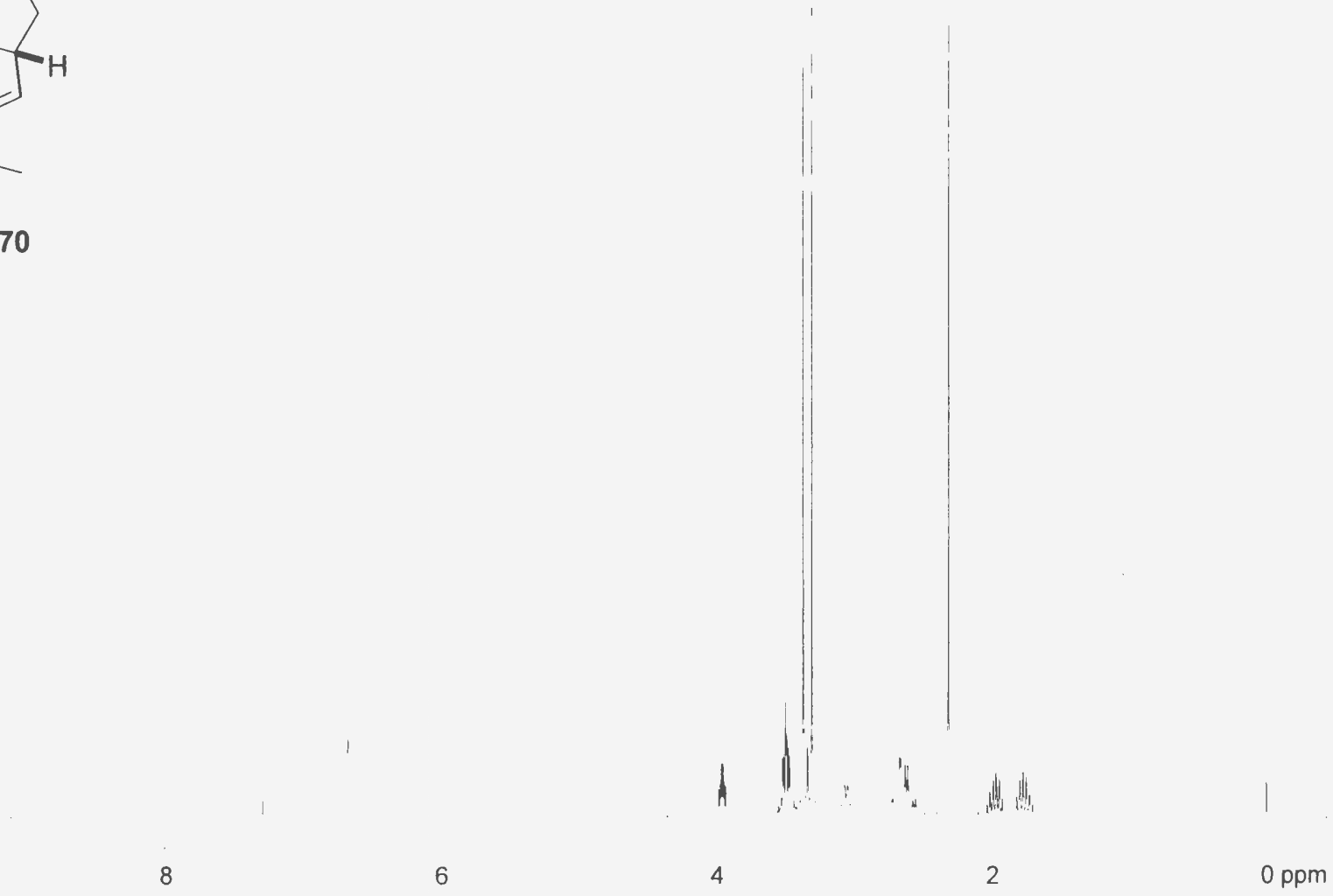

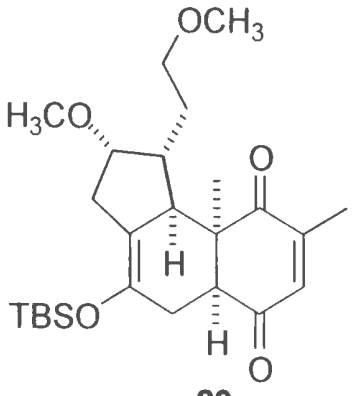

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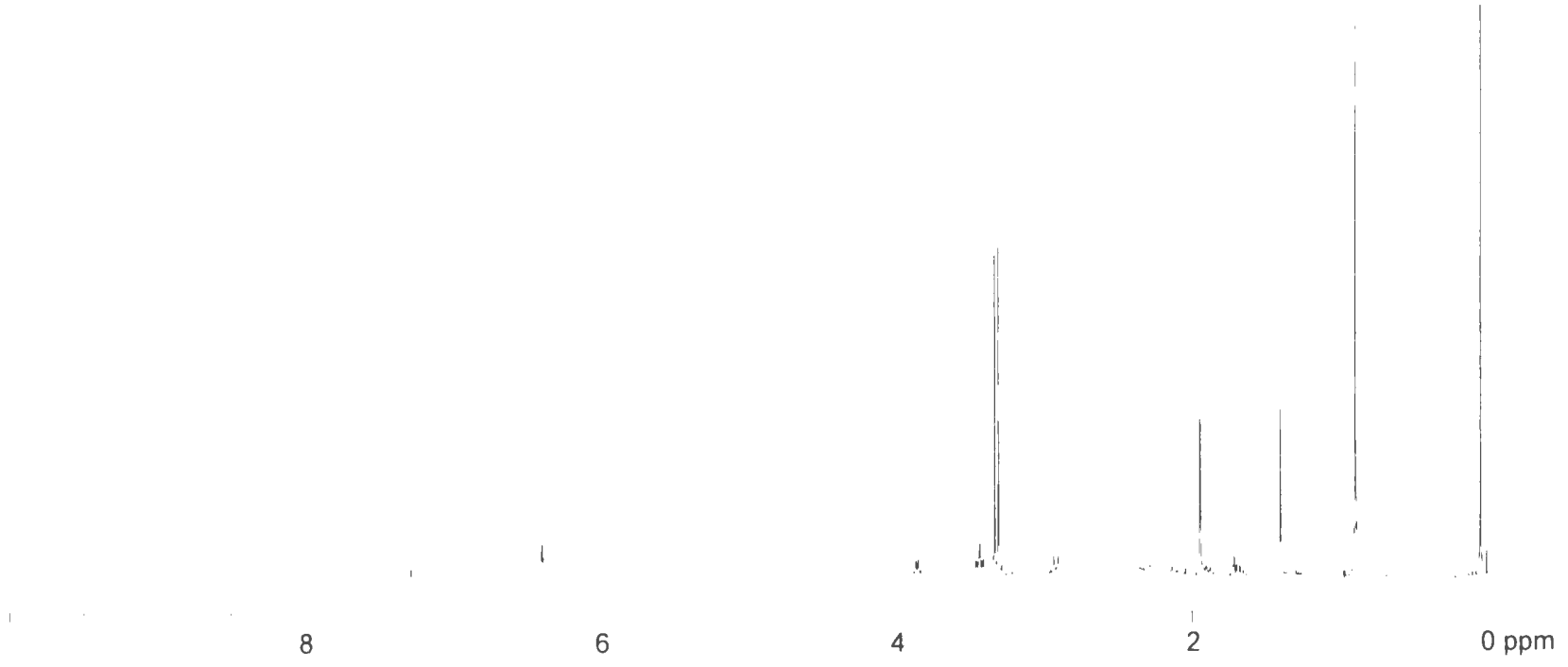

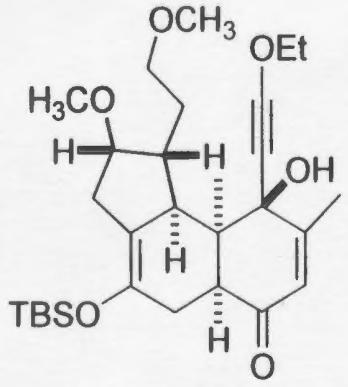

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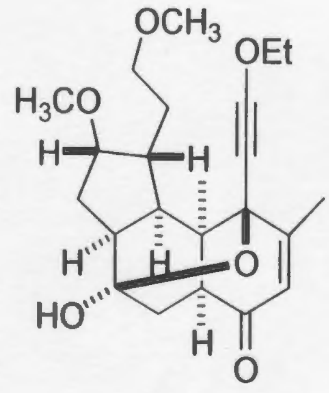

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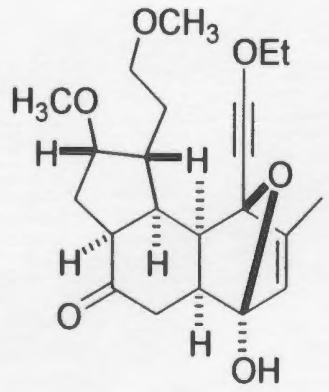

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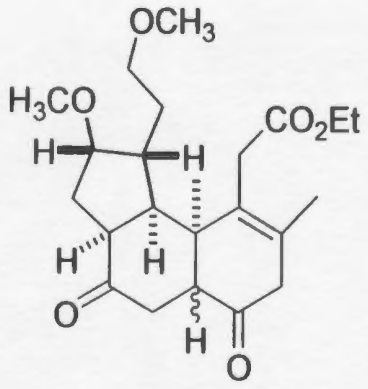

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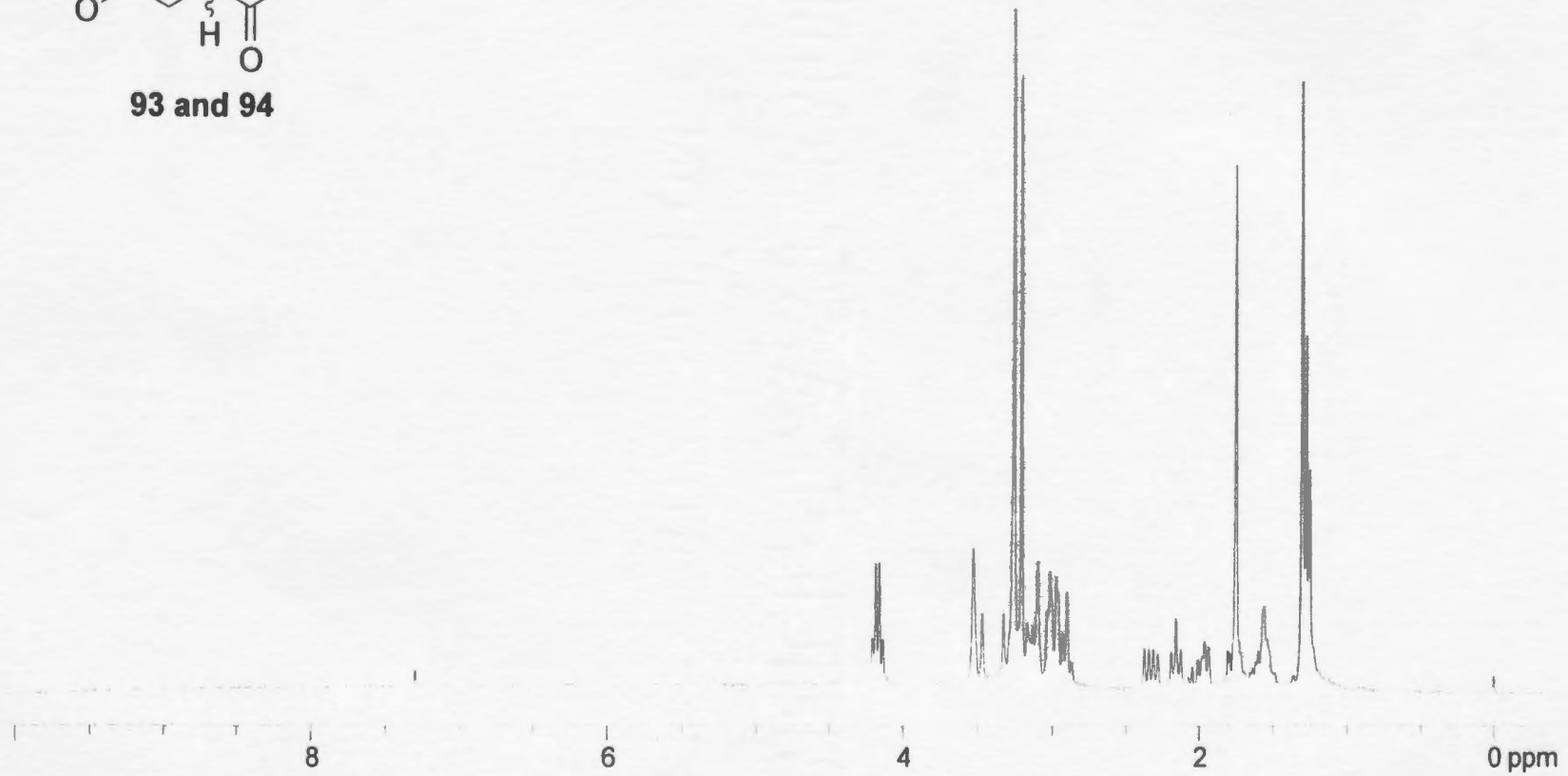

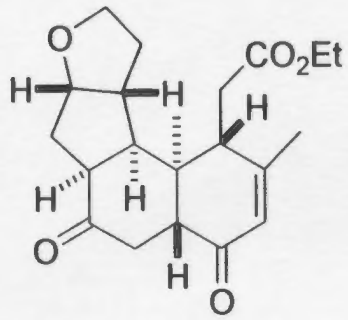

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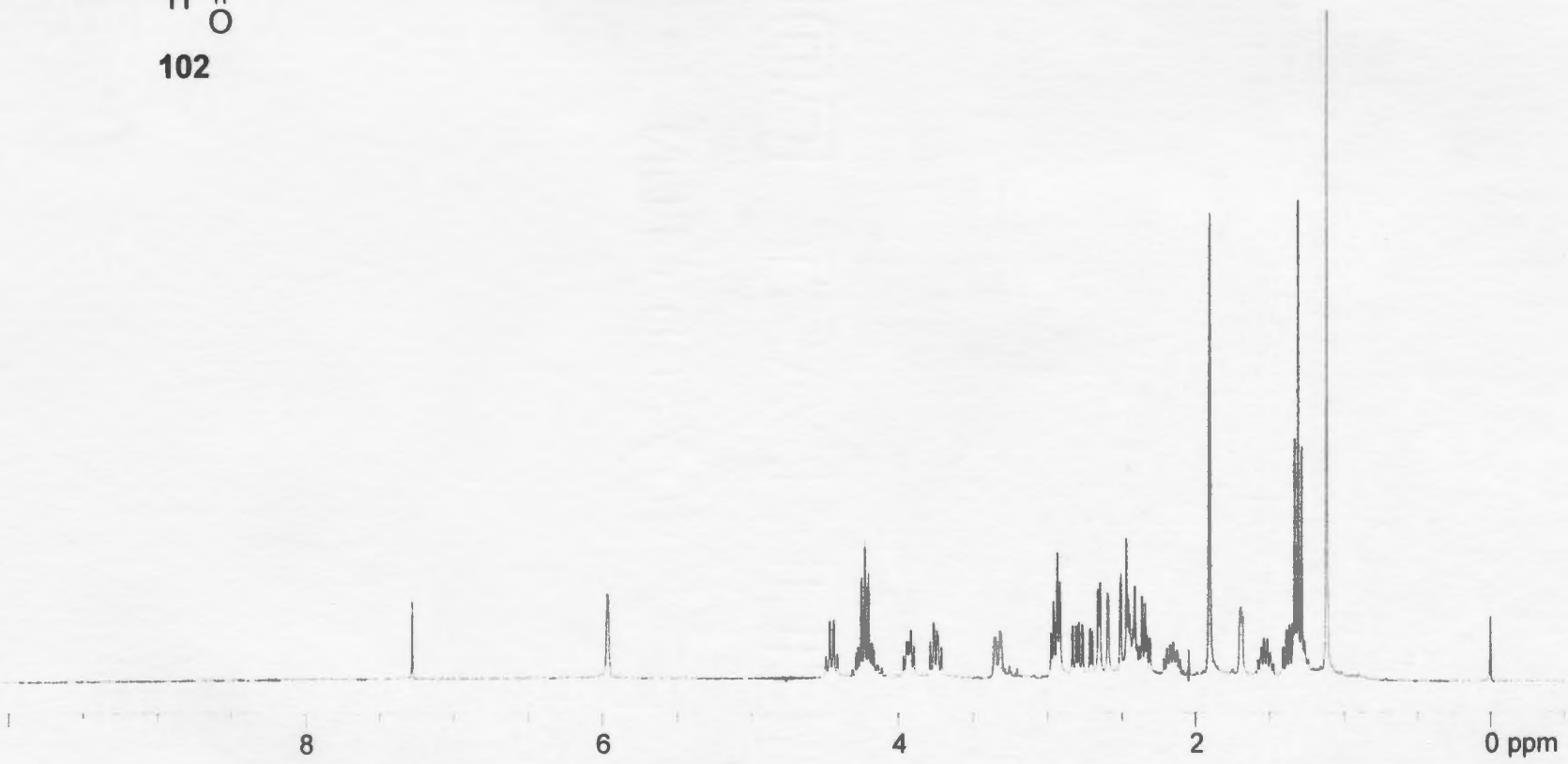

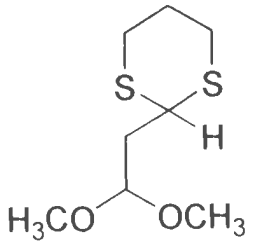

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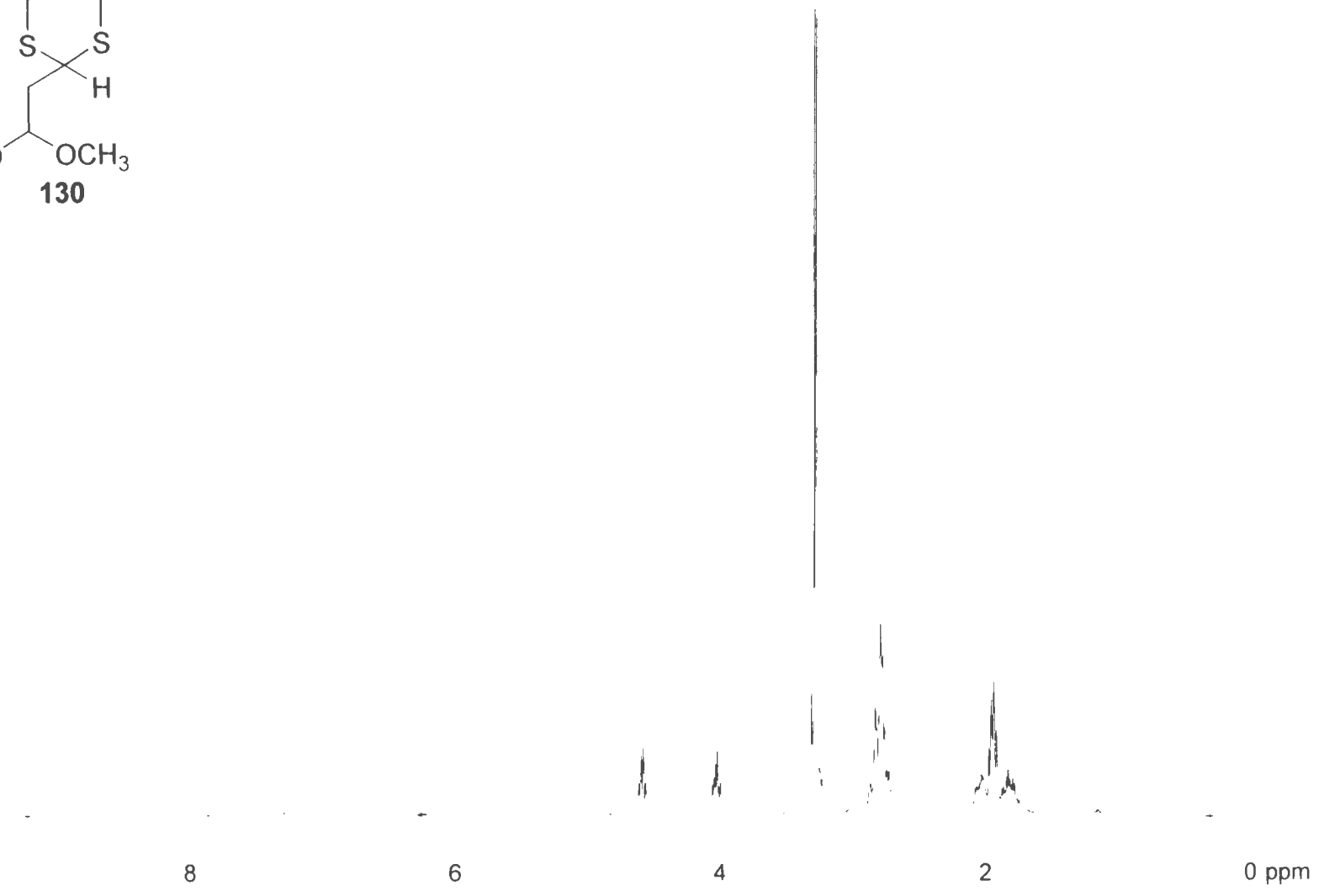

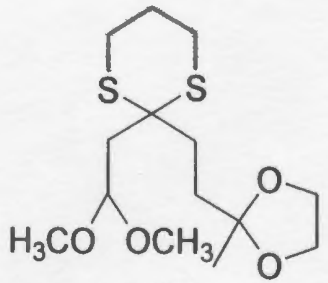

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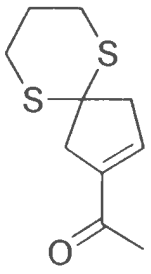

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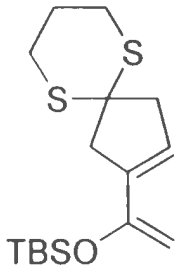

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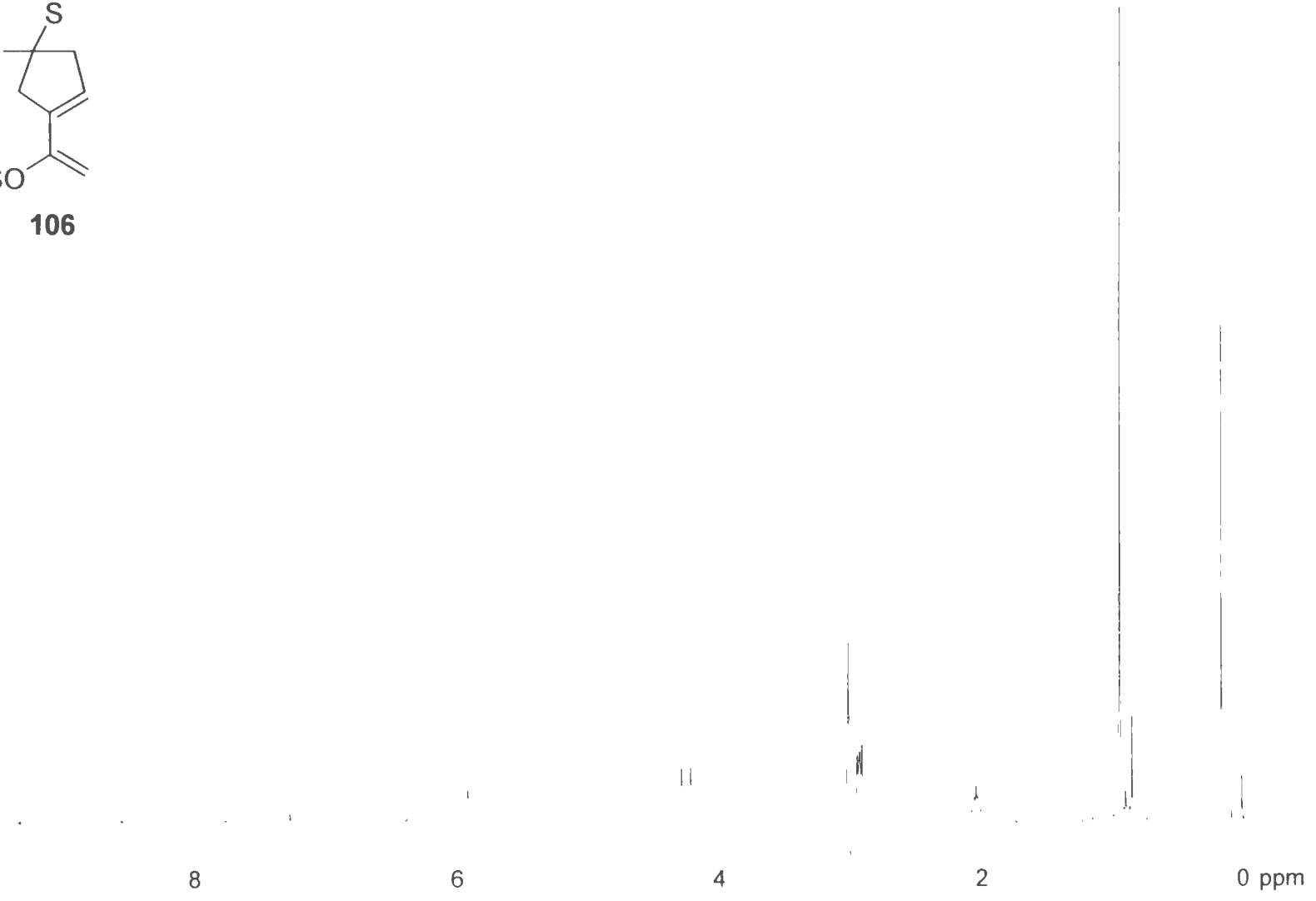

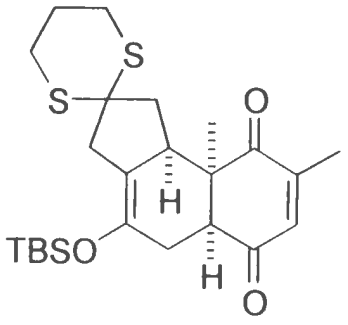

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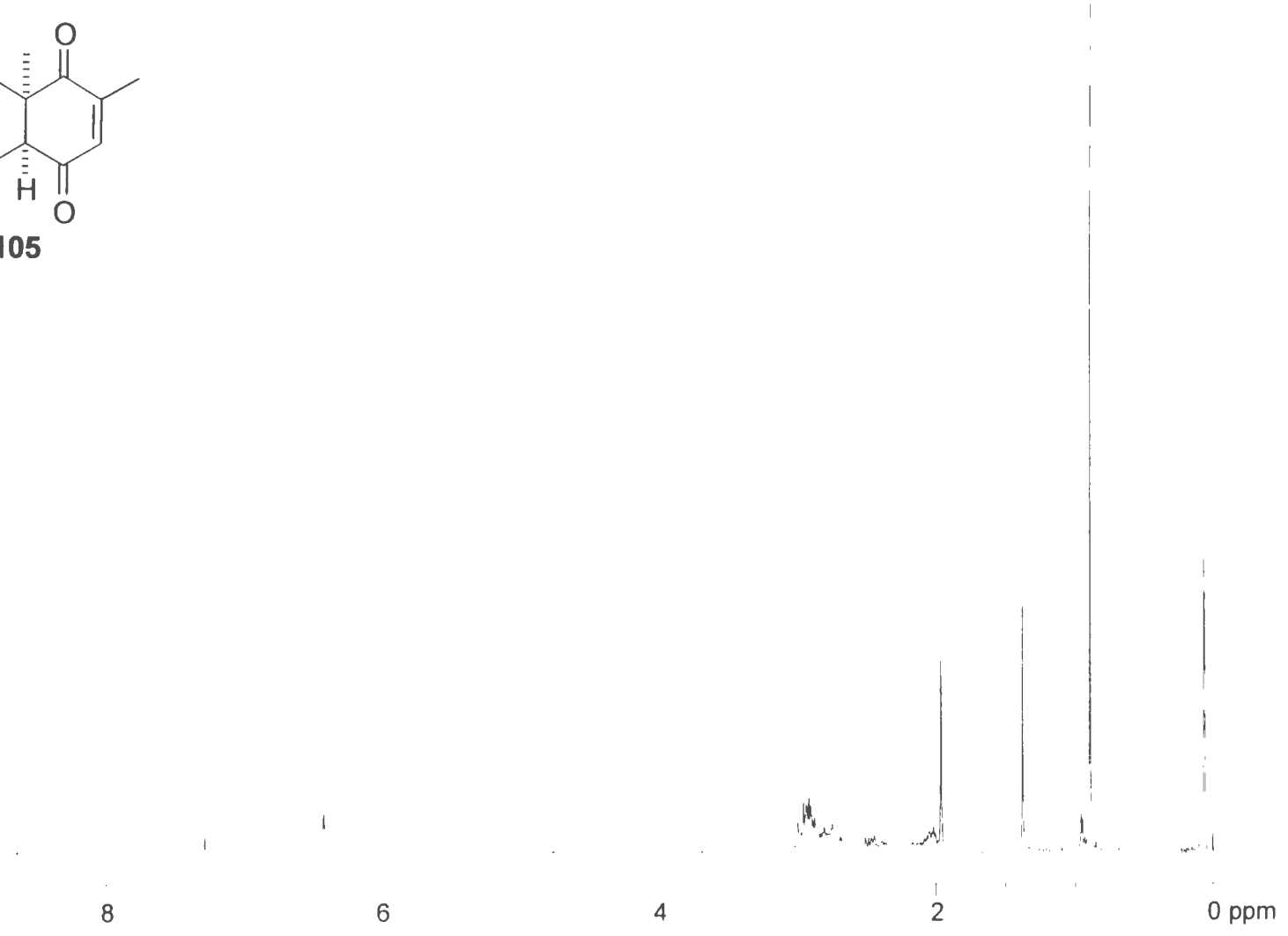

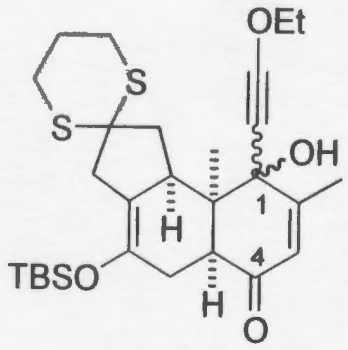

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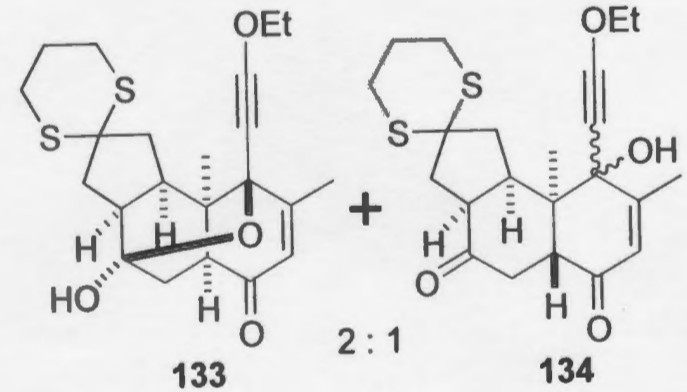
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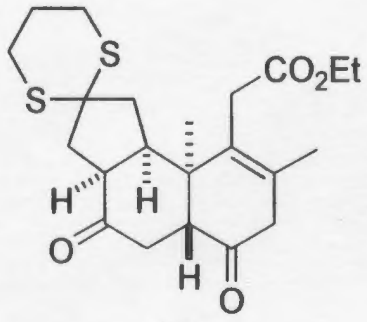

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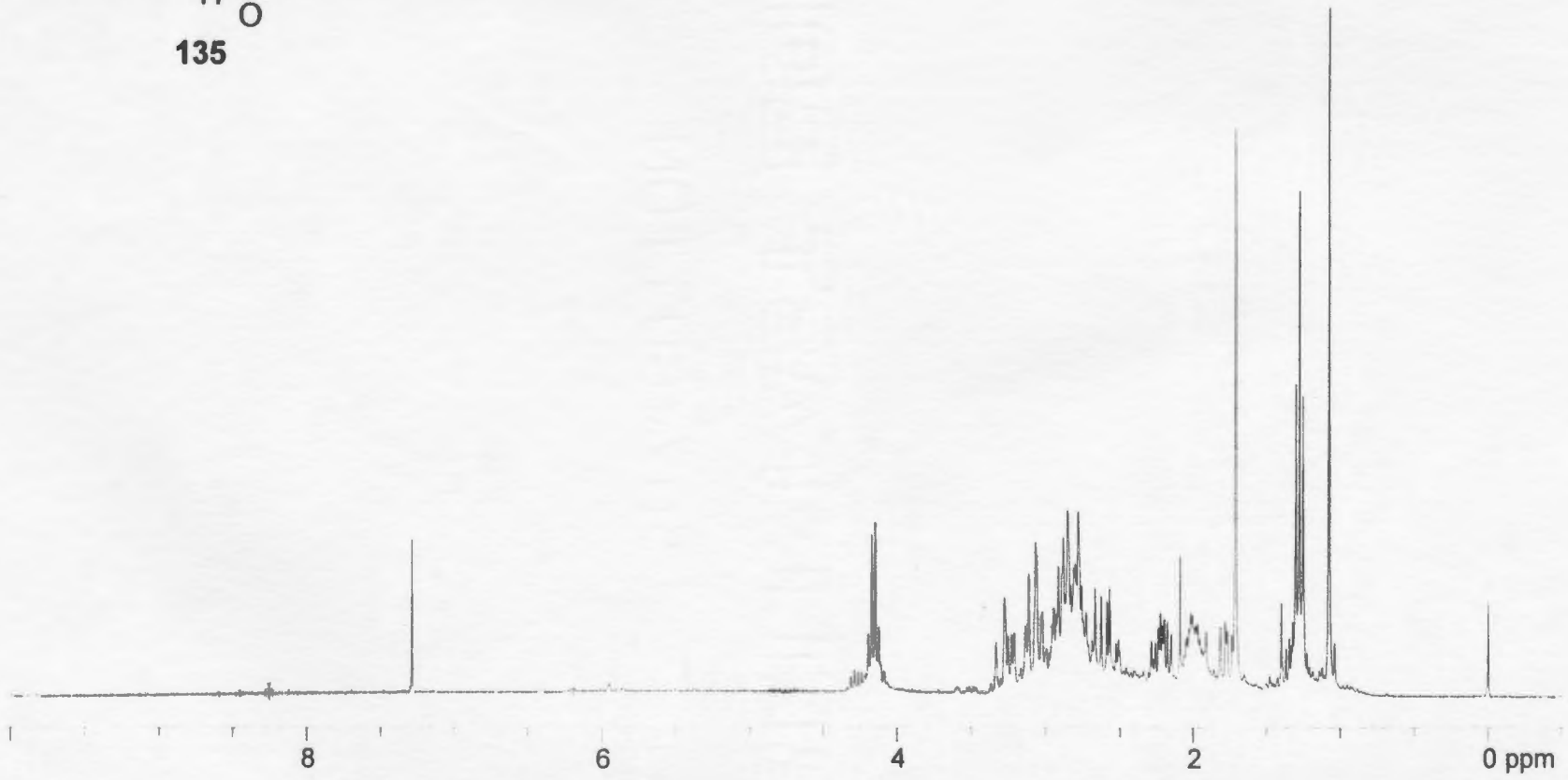

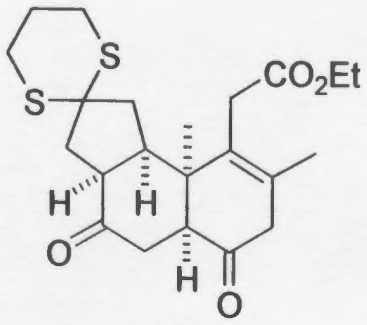

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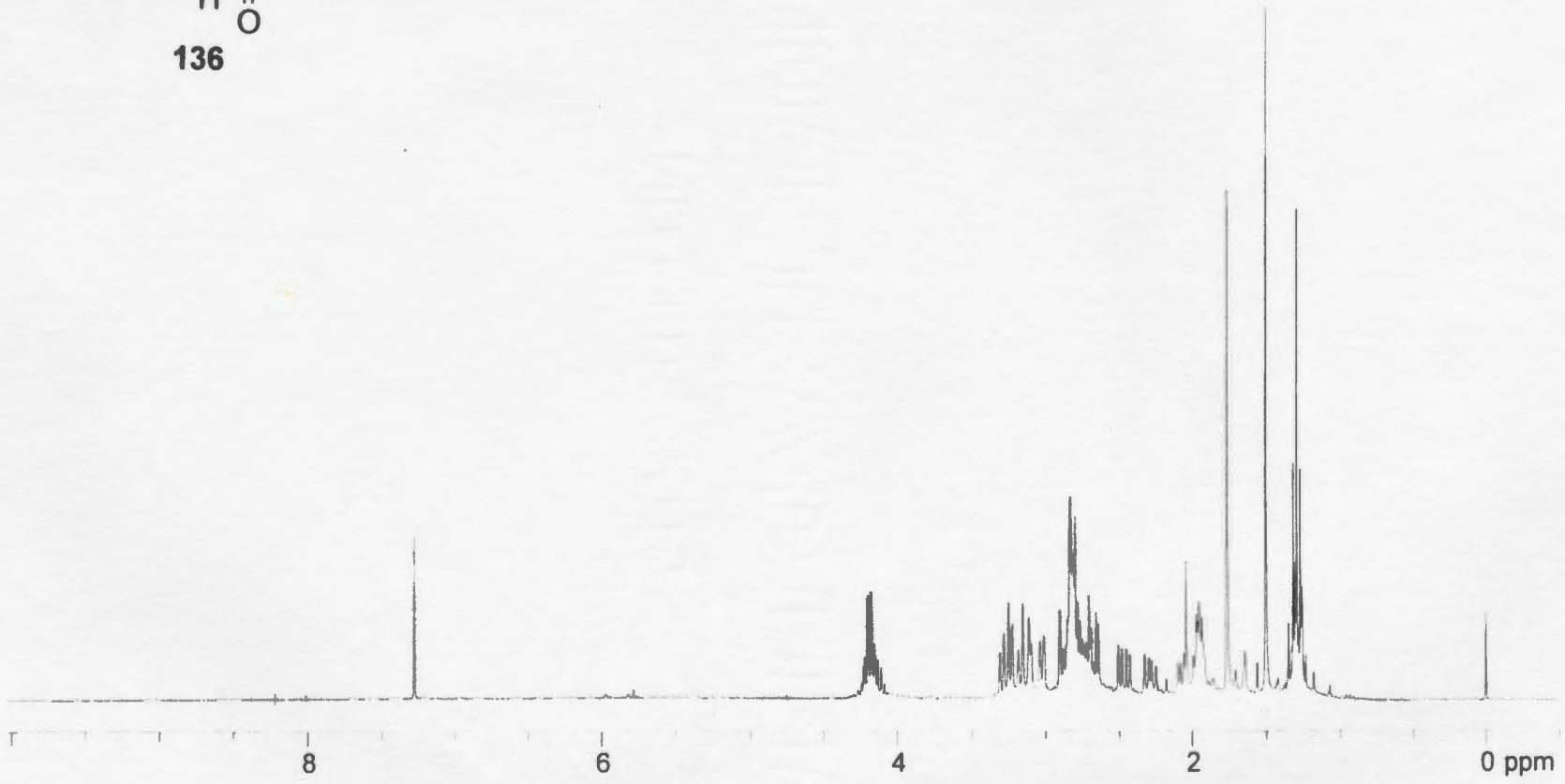

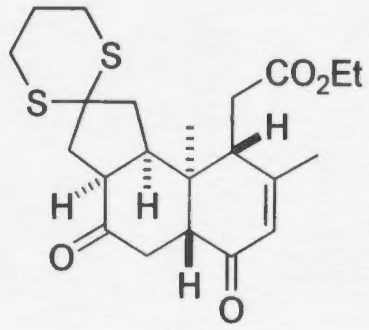

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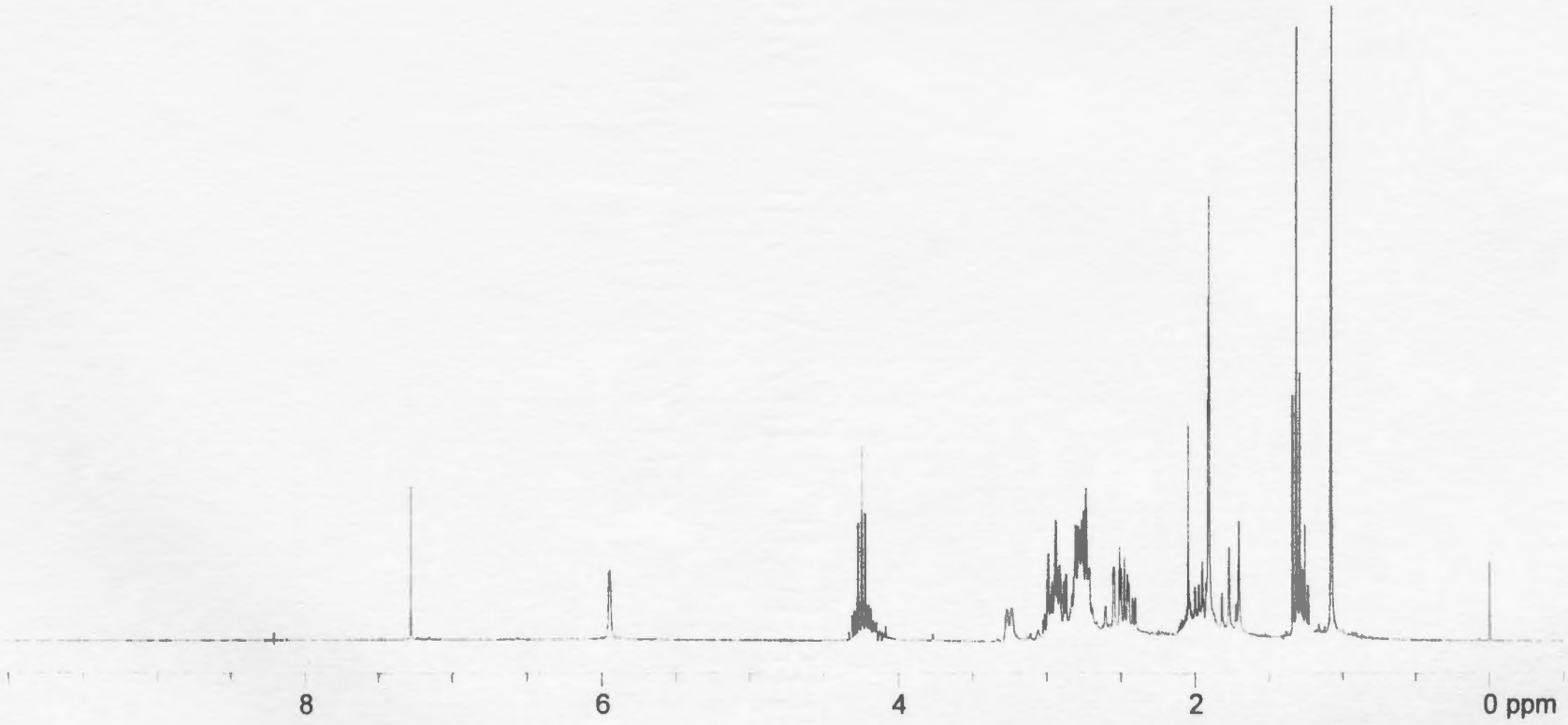

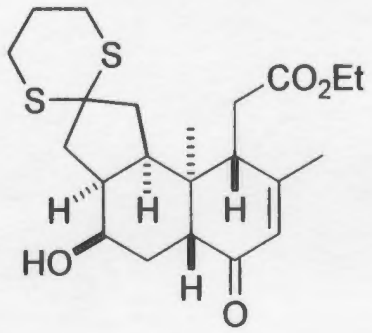

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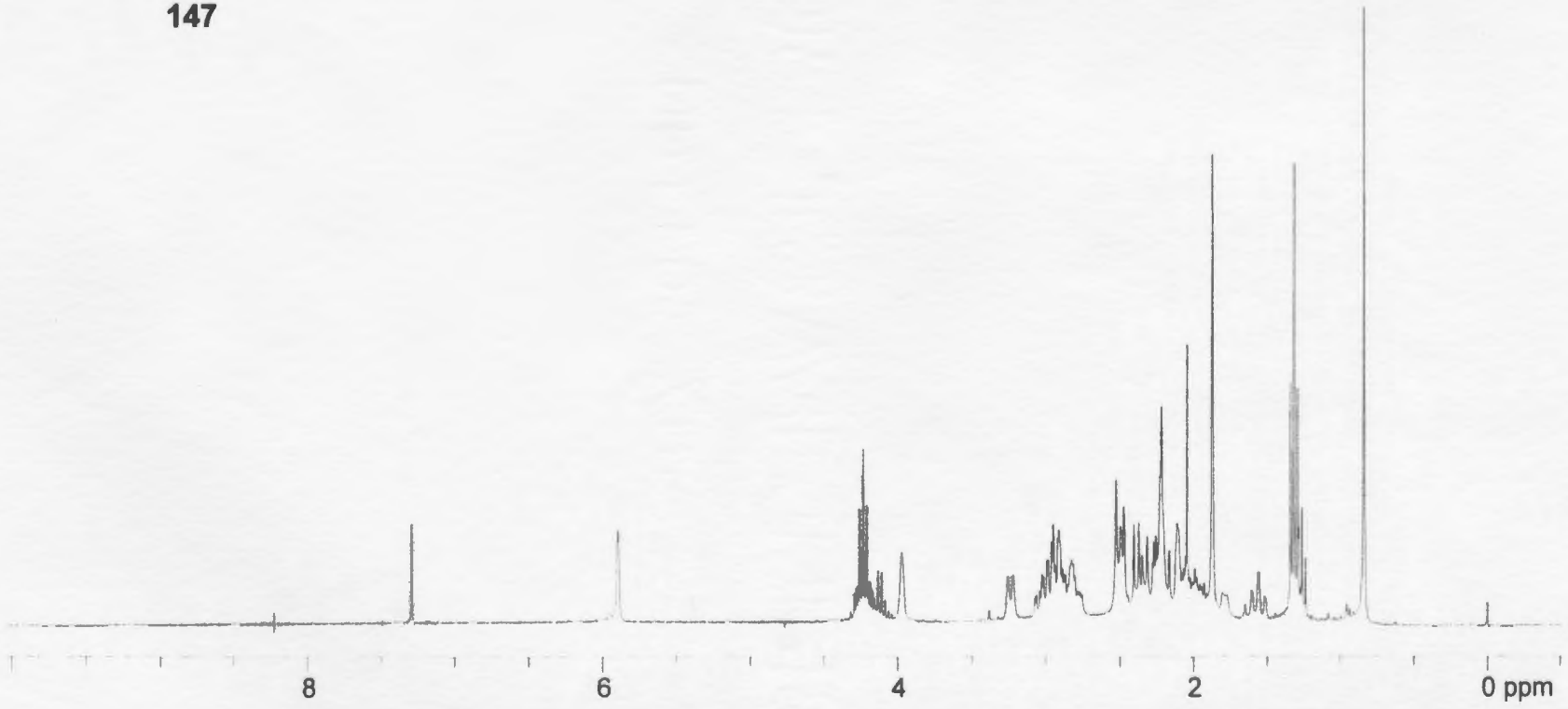

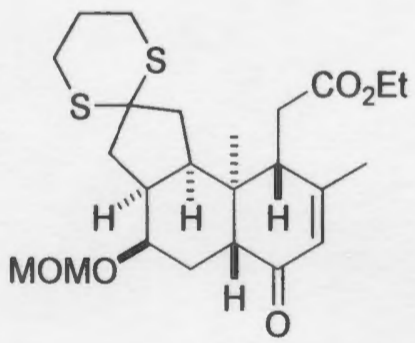

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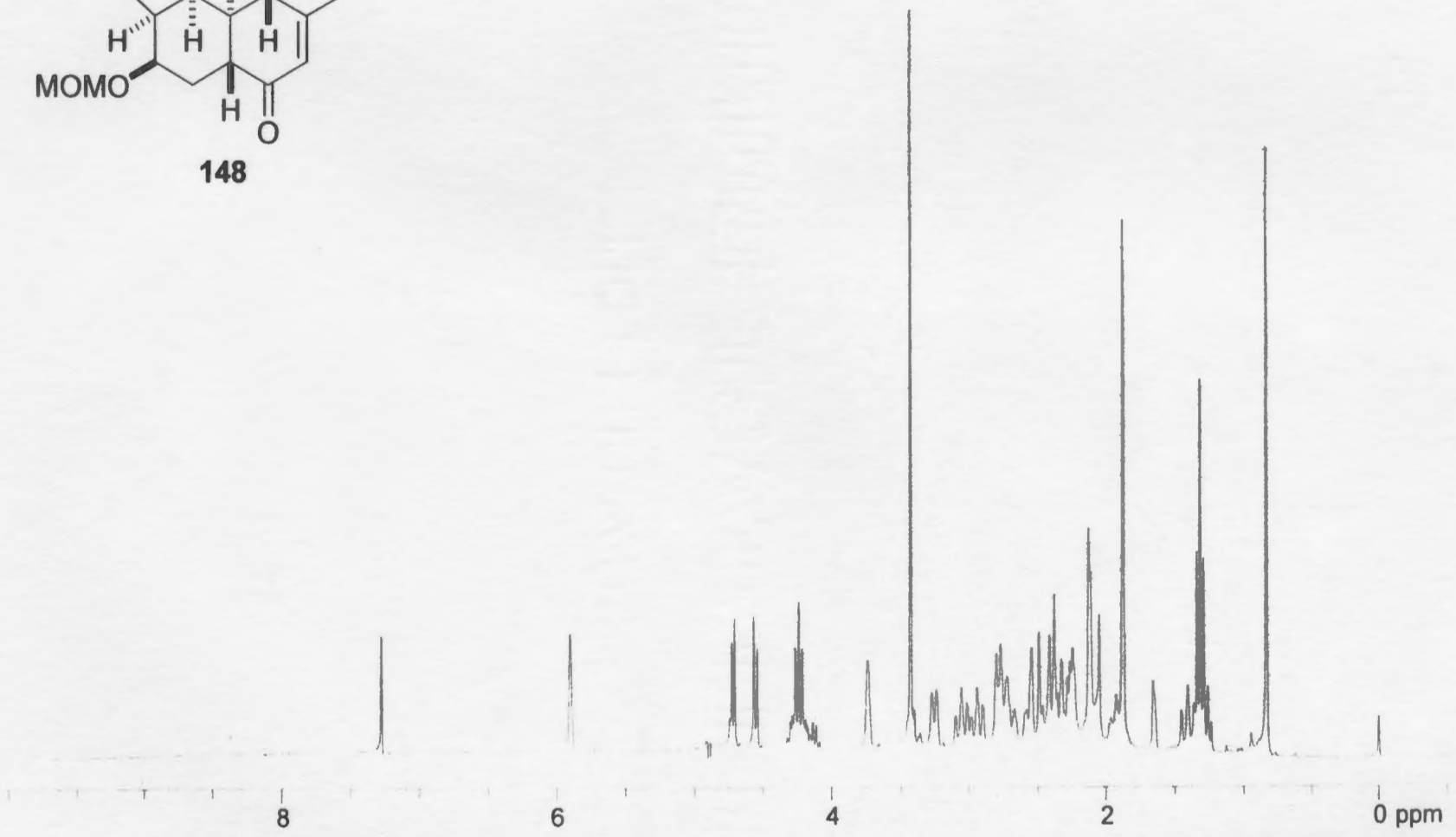

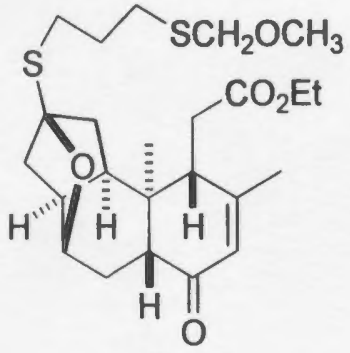

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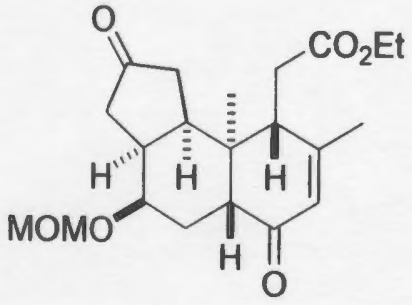

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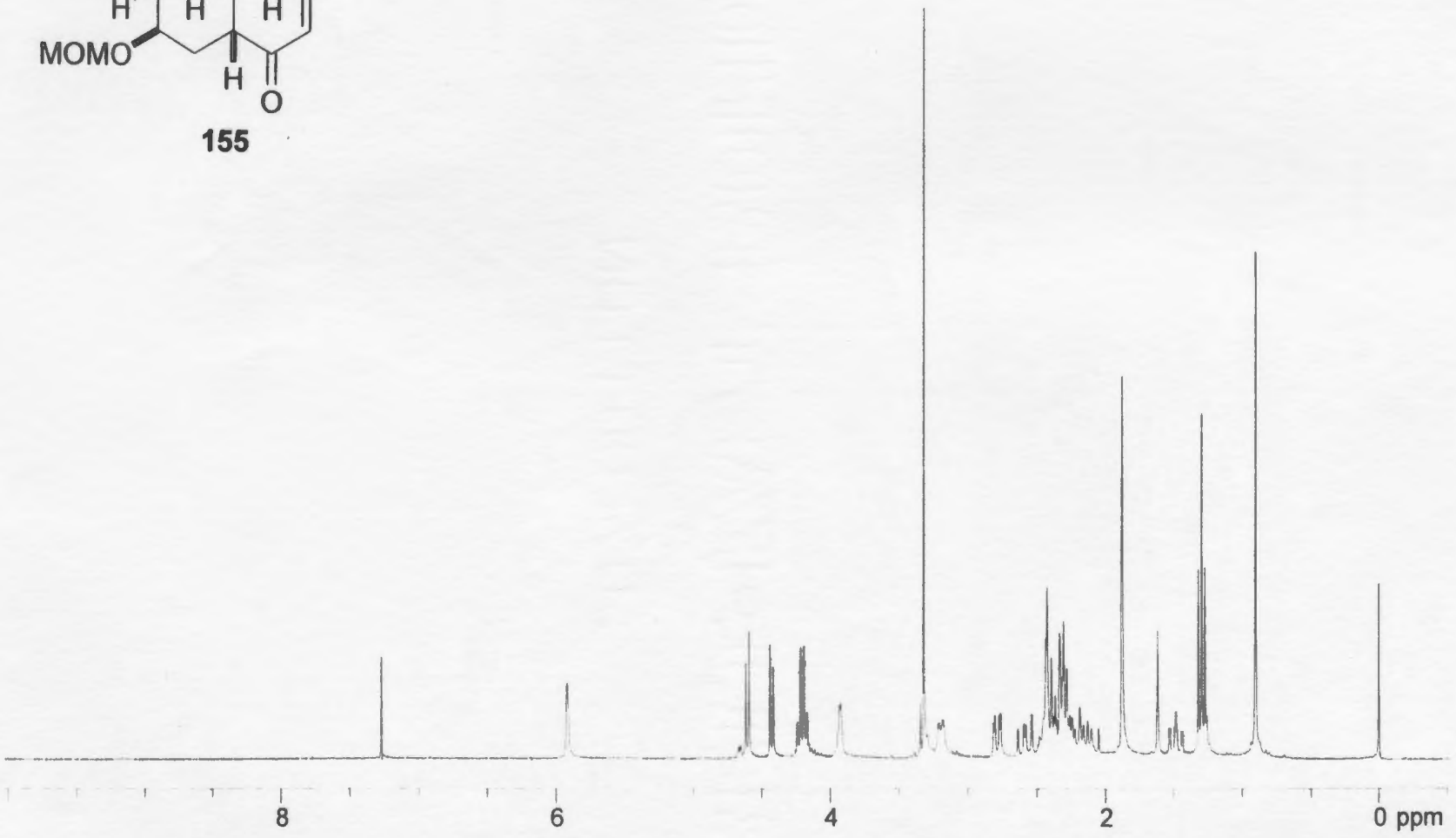

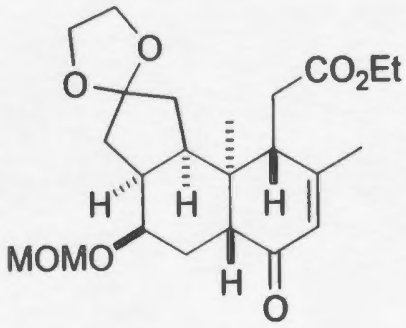

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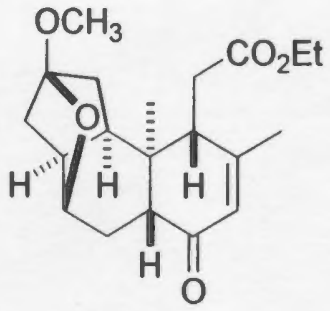

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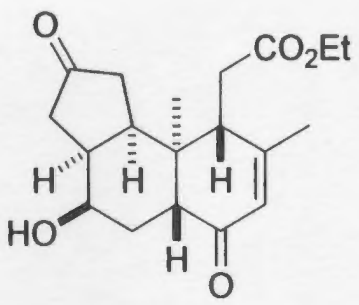

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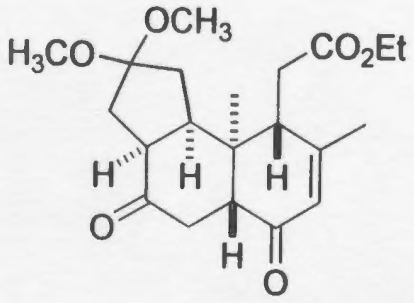

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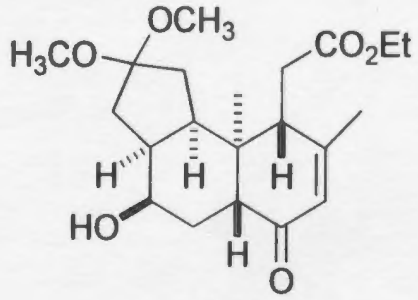

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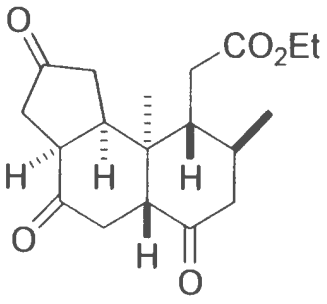

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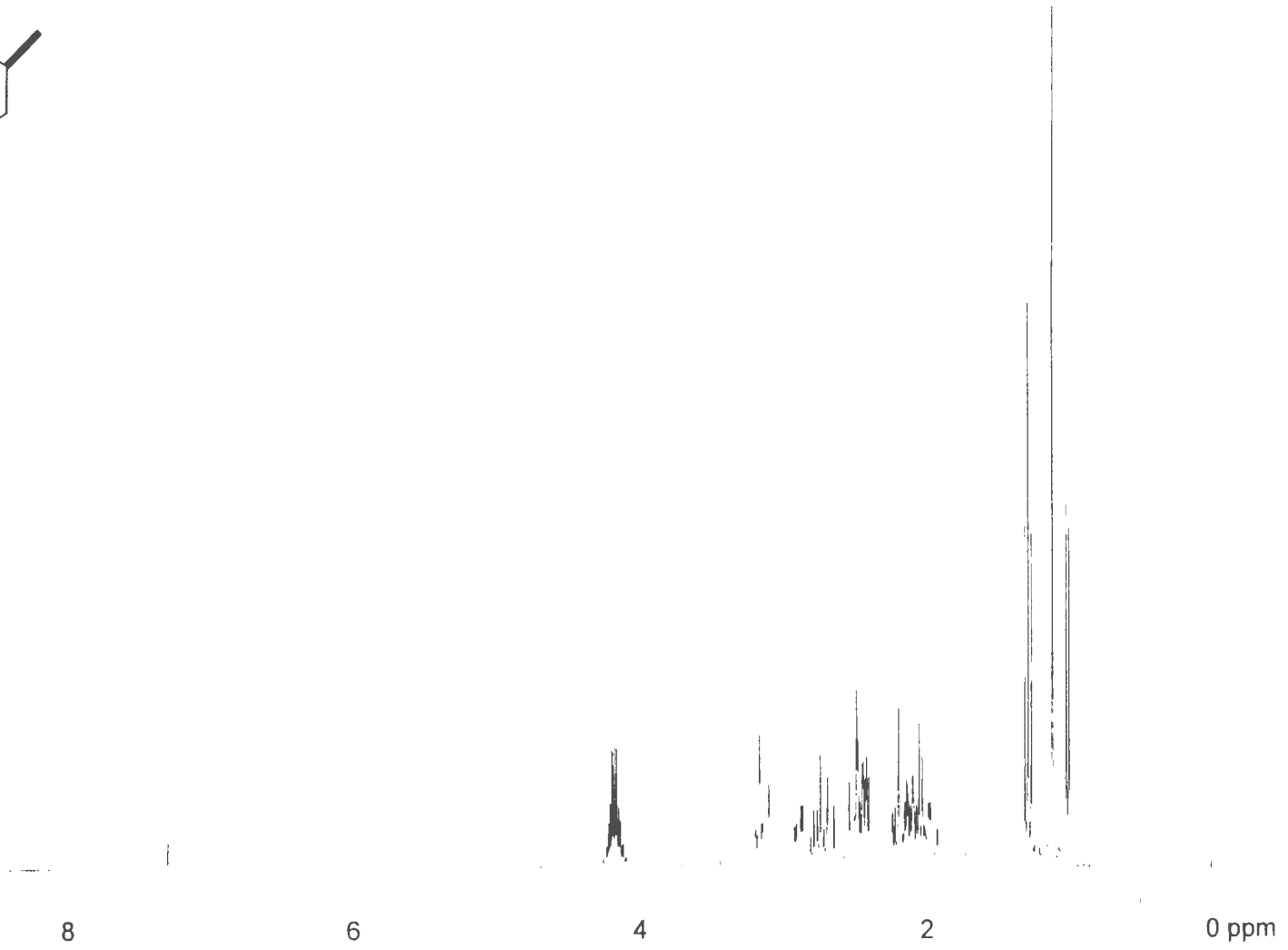
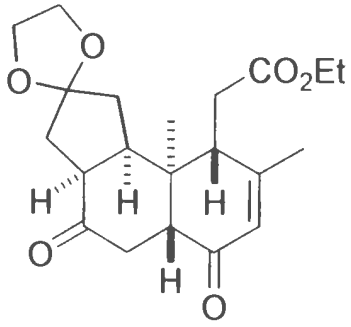
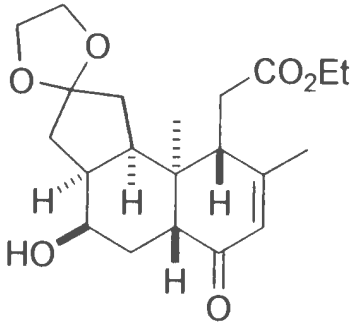
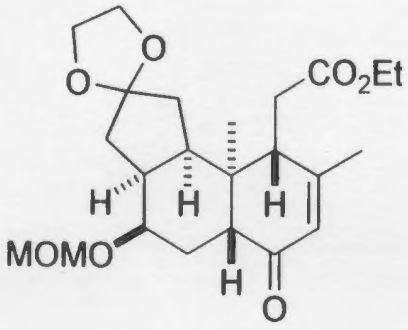




171
(in 500 MHz)



172
(in 500 MHz)



156
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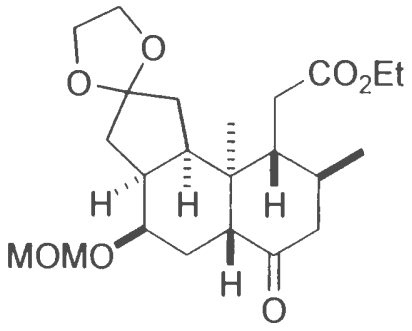

174
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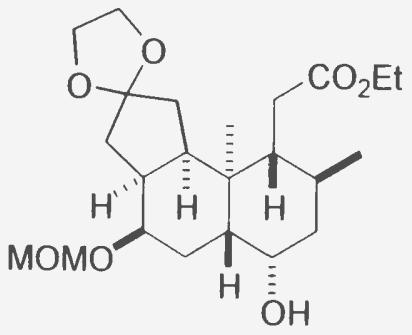
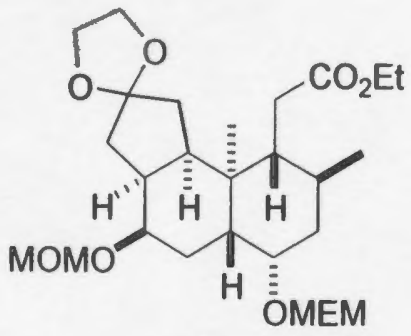
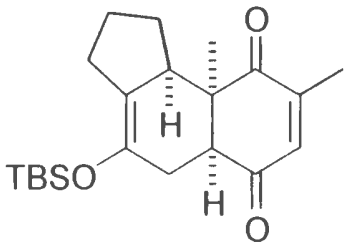


175
(in 500 MHz)



176
(in 500 MHz)



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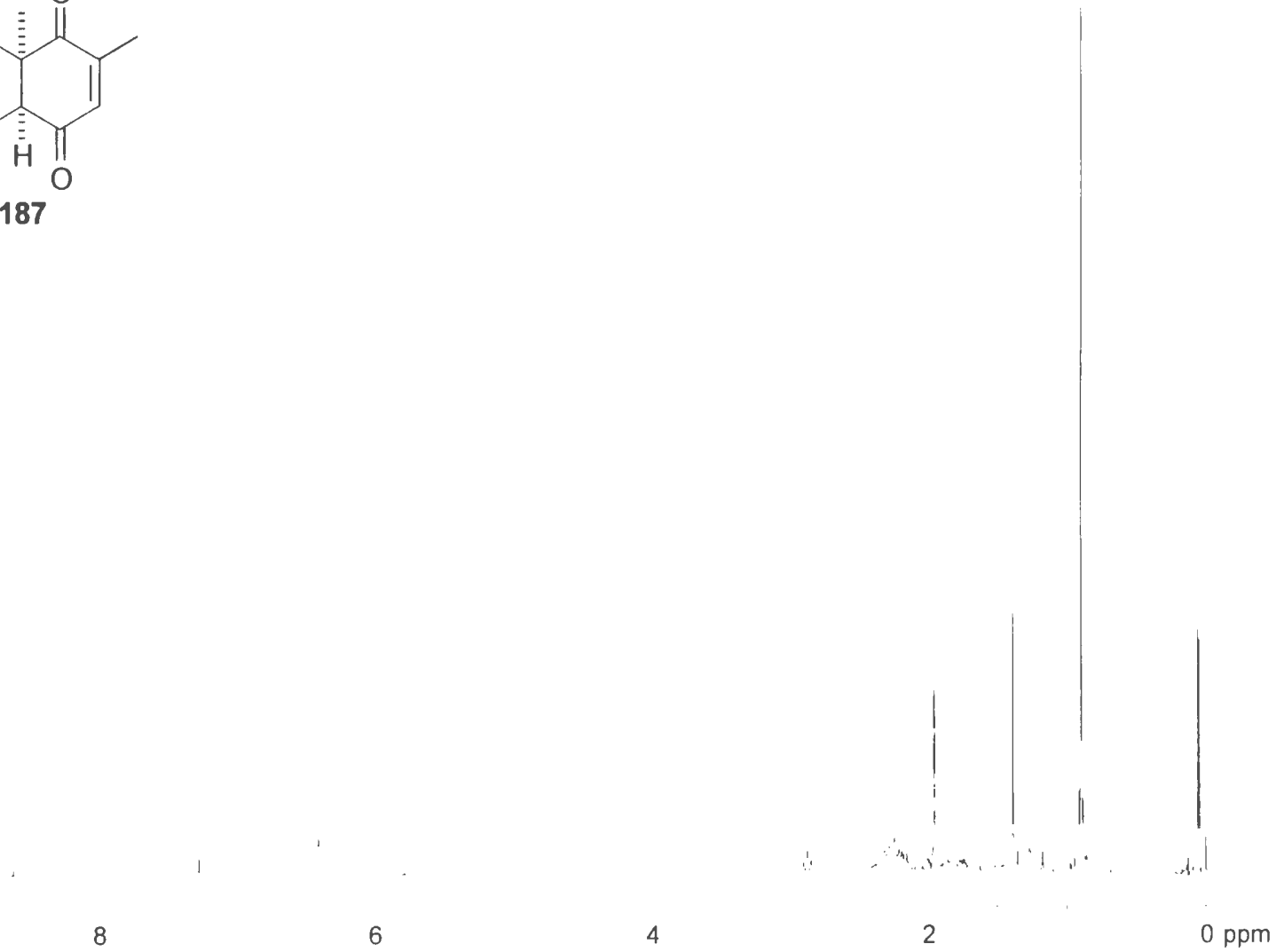
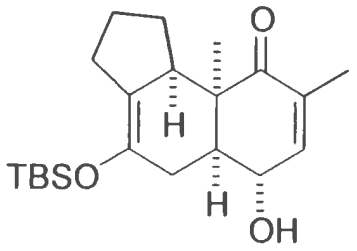
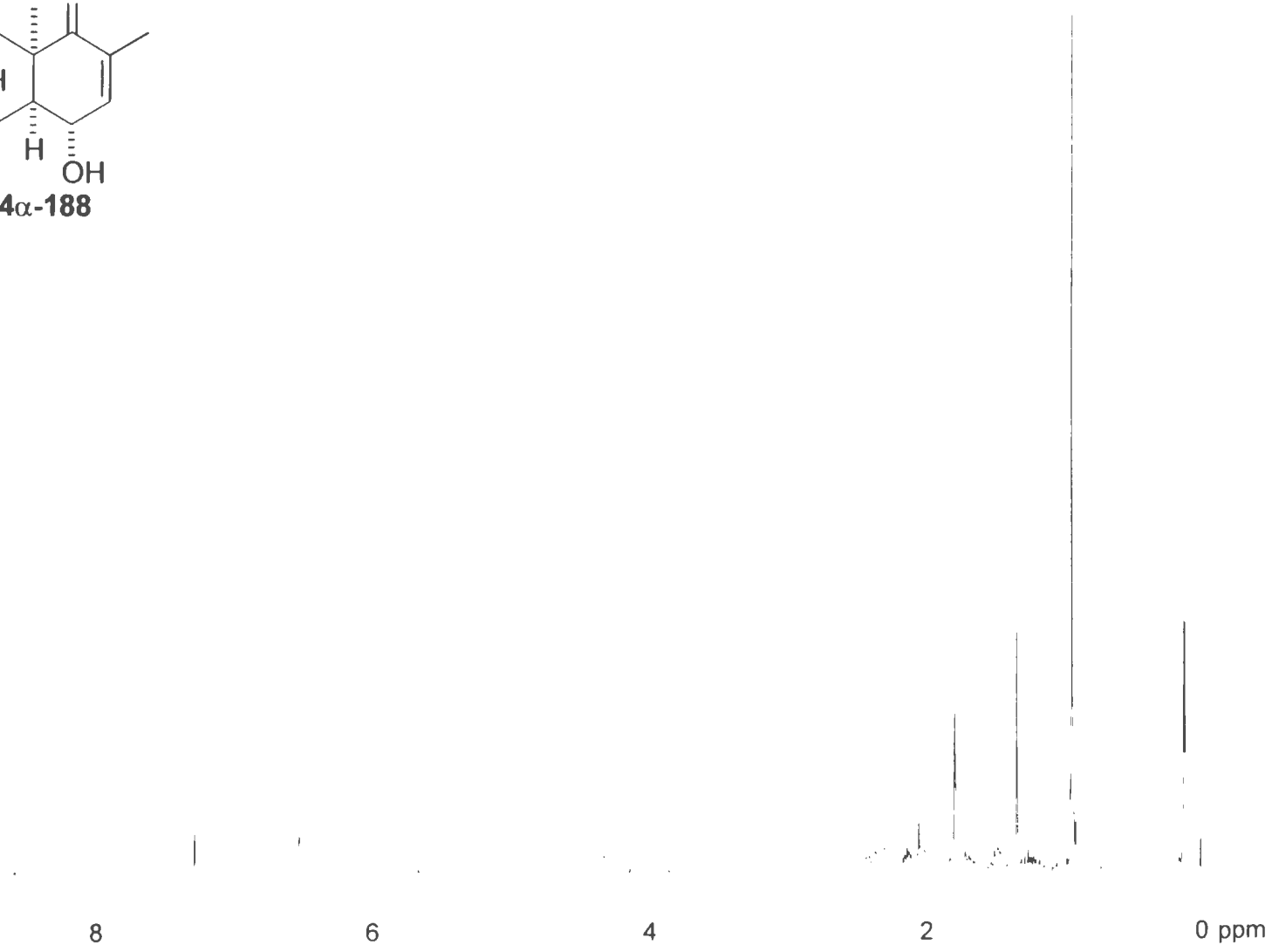
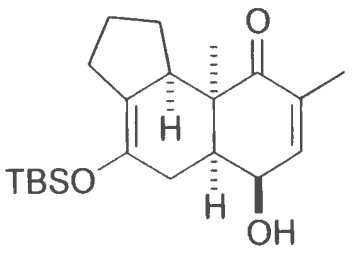


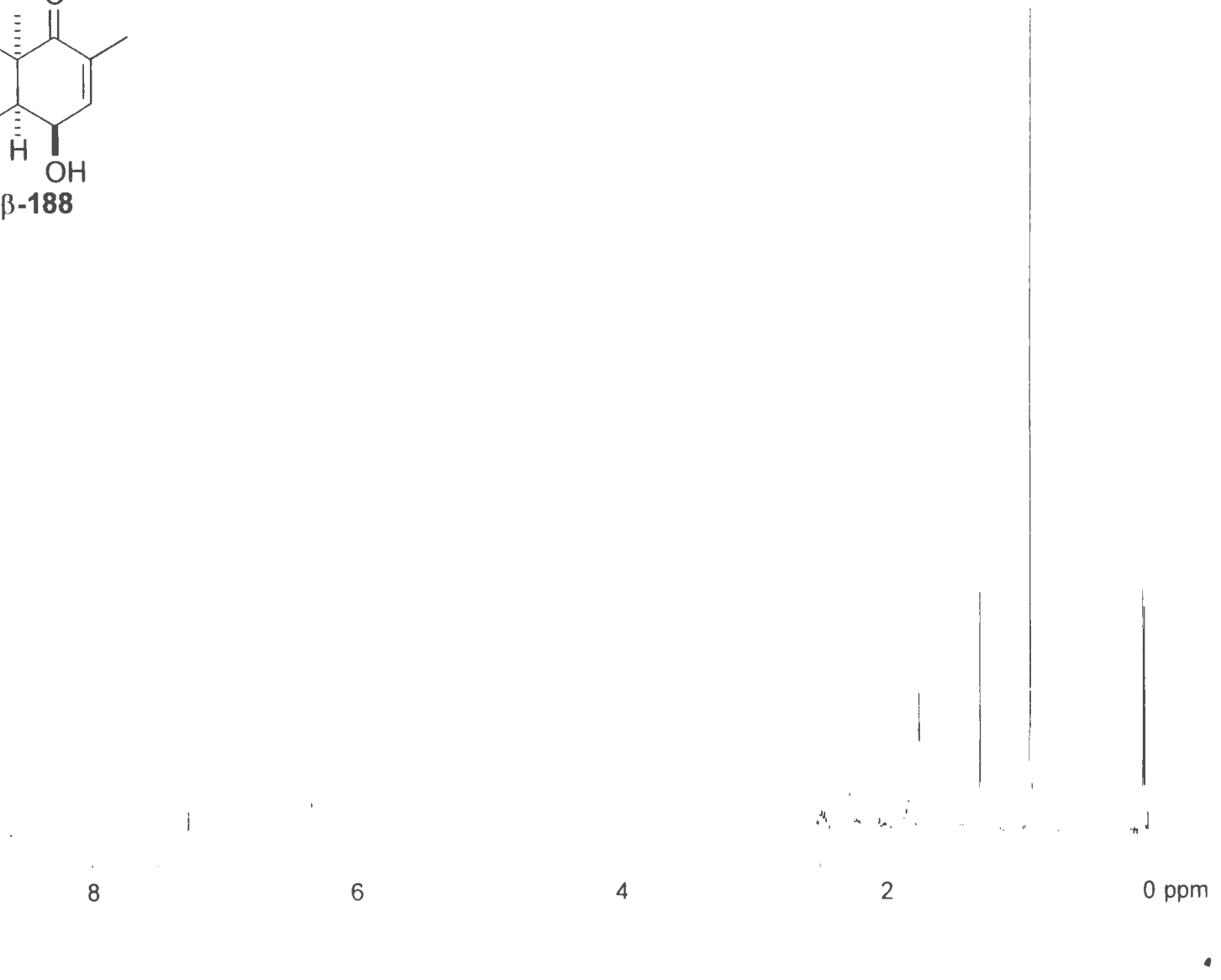


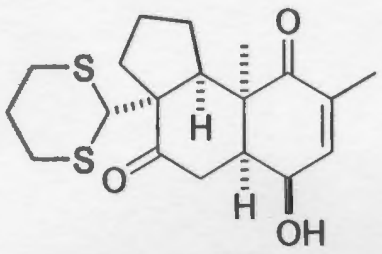
4α-188





4β-188





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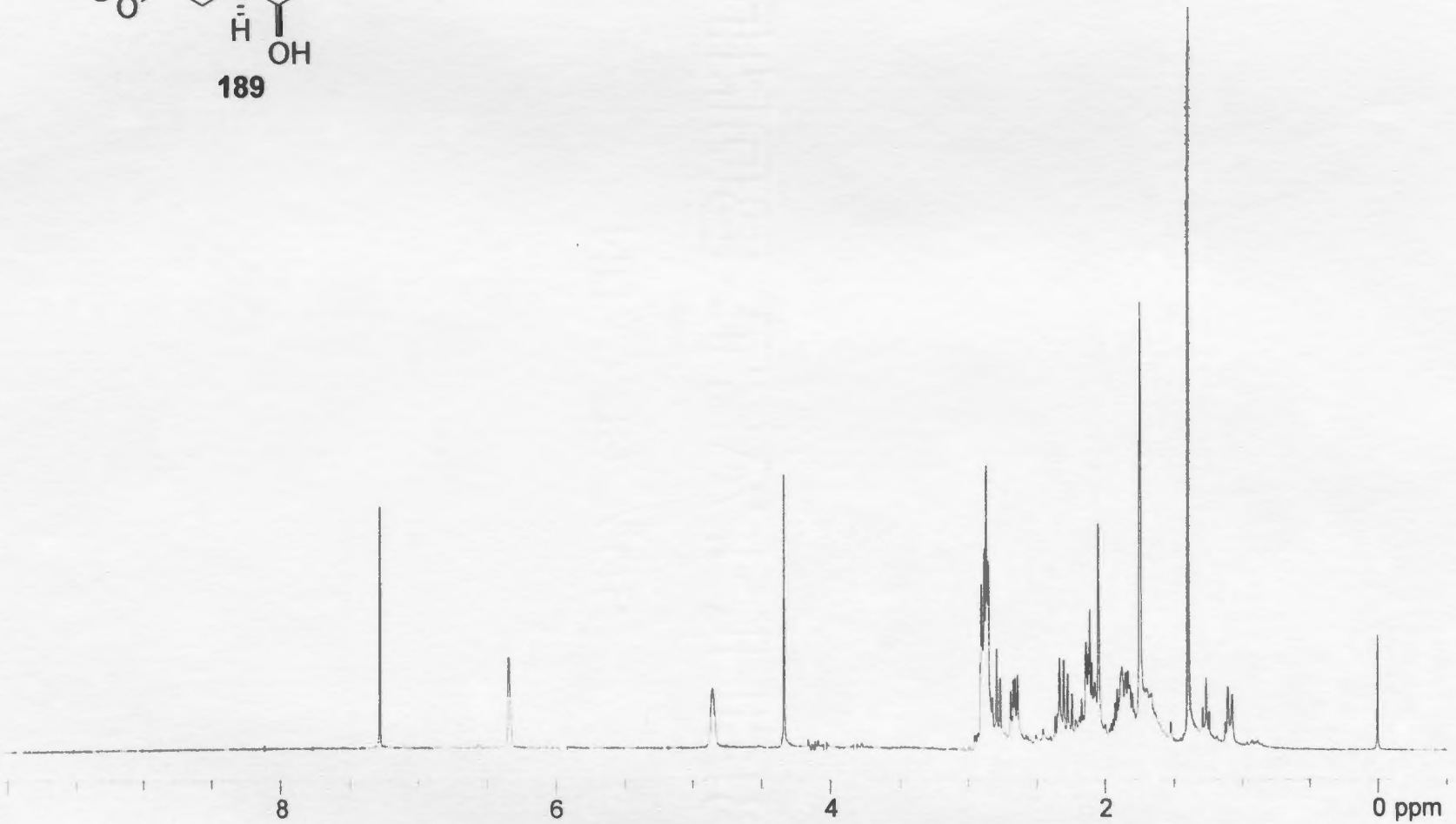
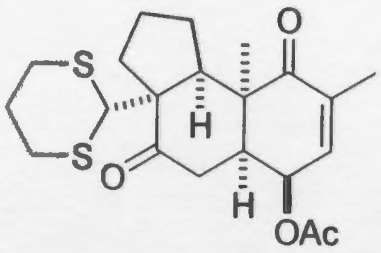
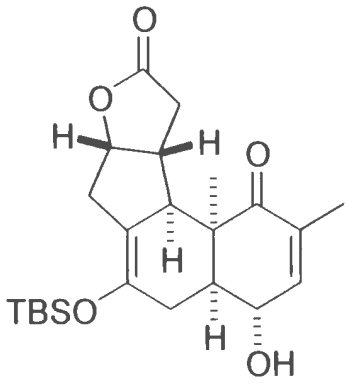


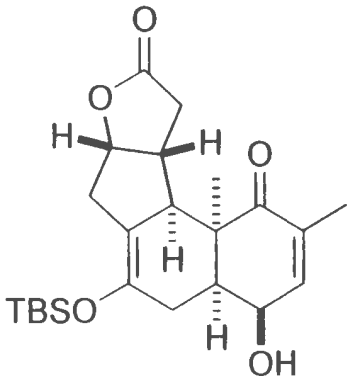


191

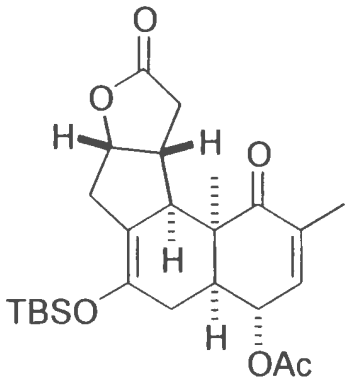
(containing $CH_3CO_2CH_2CH_3$)



4α-192



4β-192



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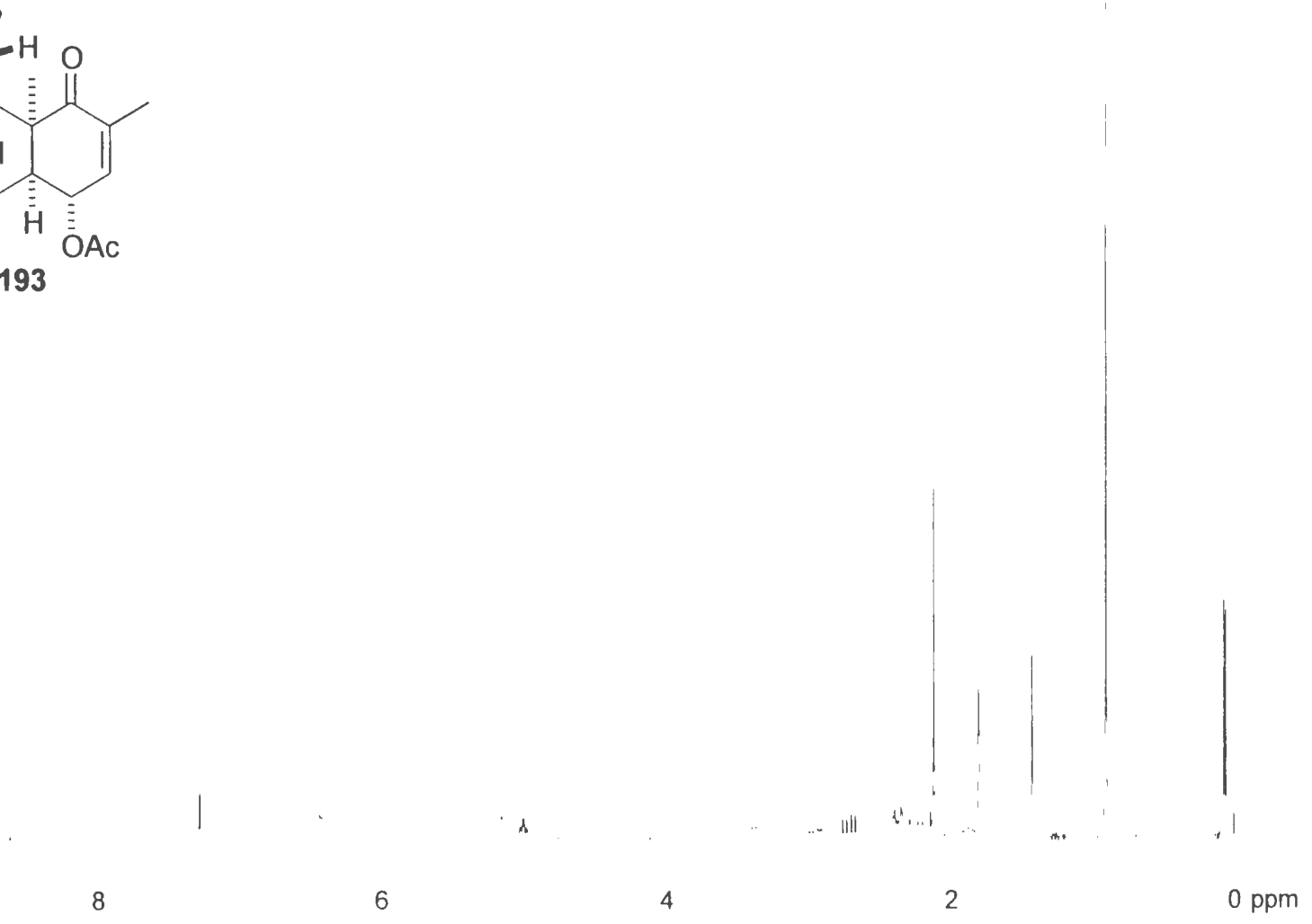
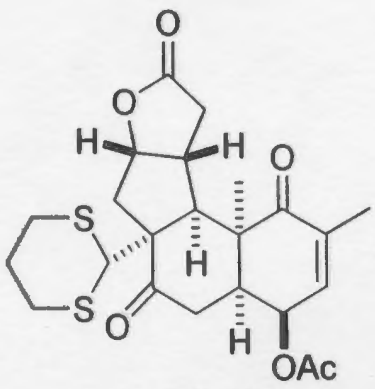
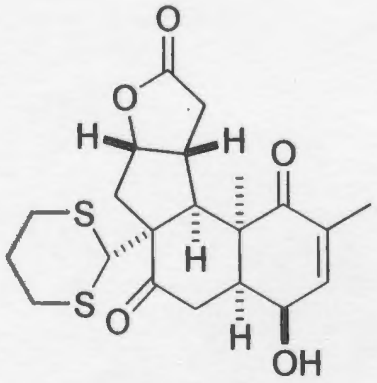
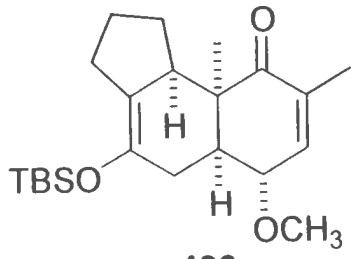




4β-194



4β-195
(in CD_3SOCD_3)



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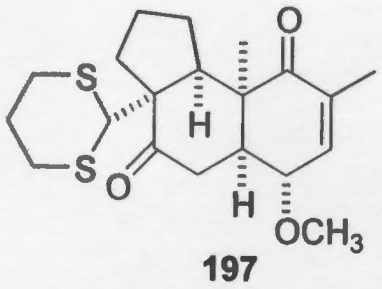

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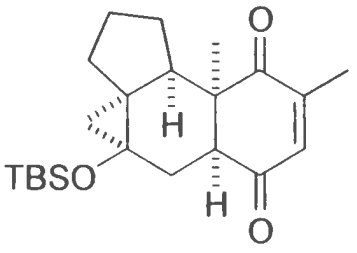

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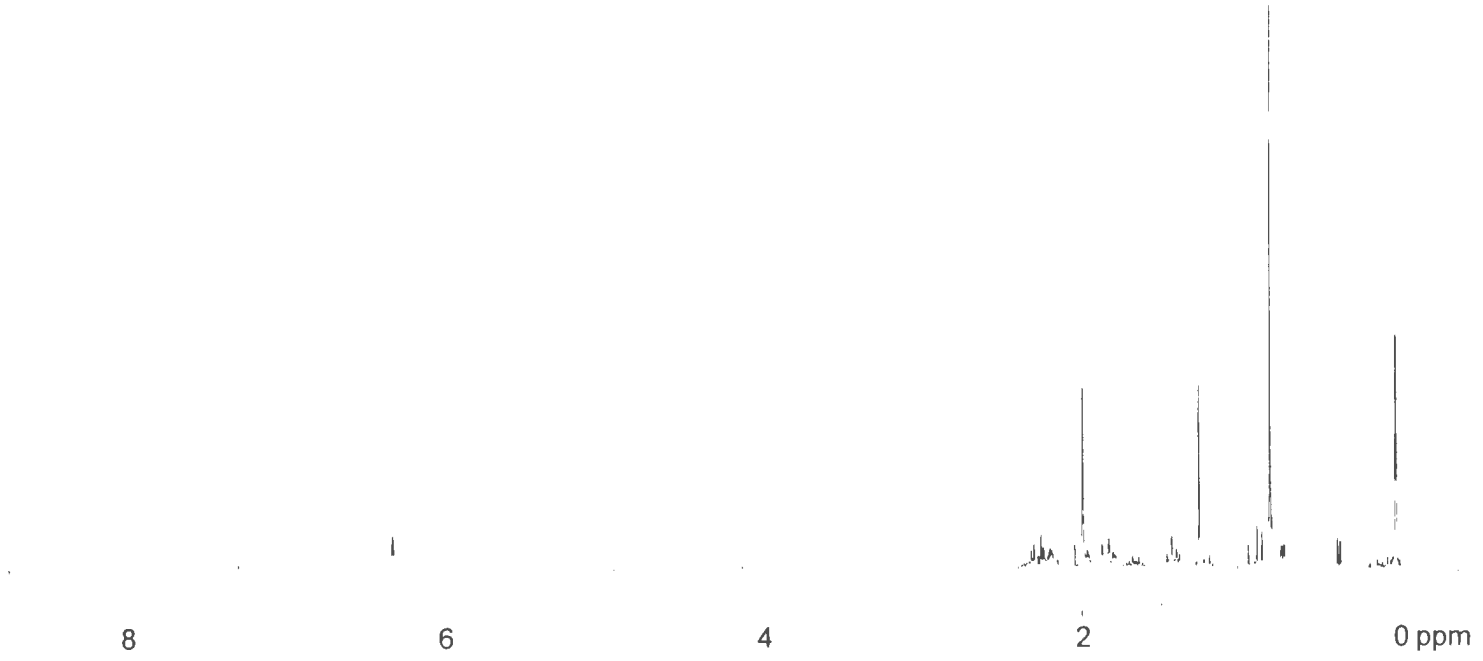

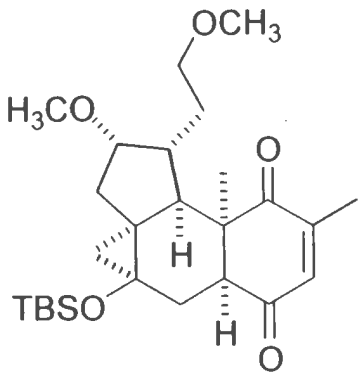

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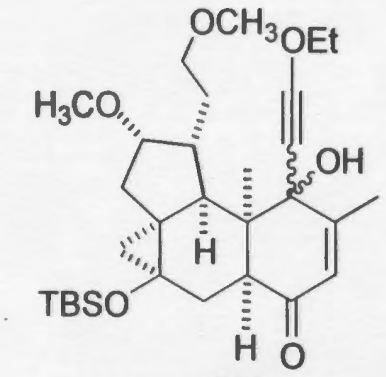
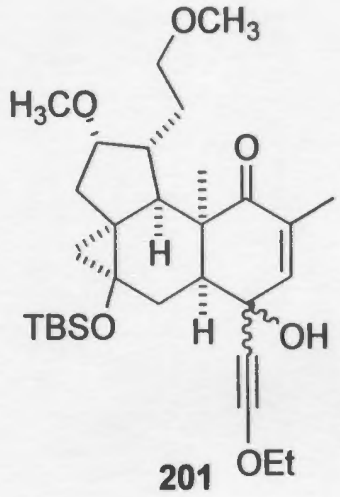


200



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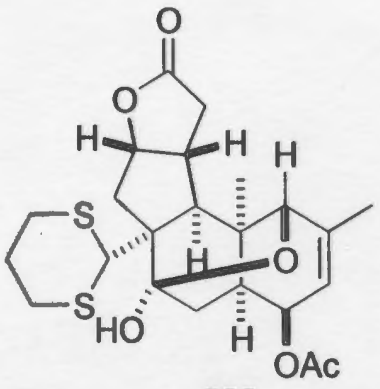

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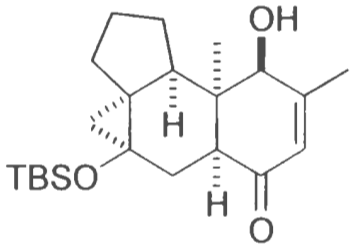
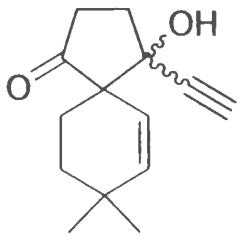


6α-203



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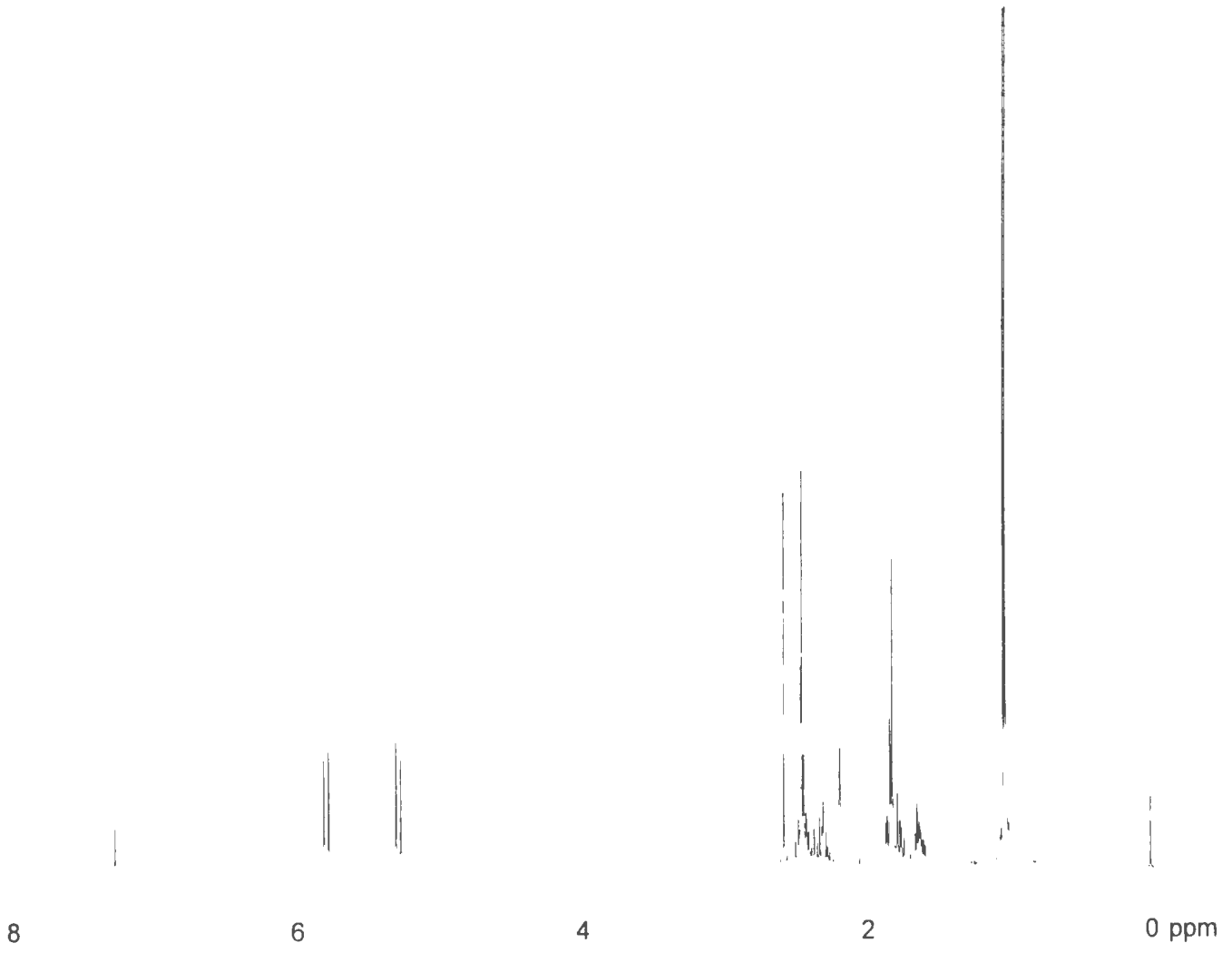

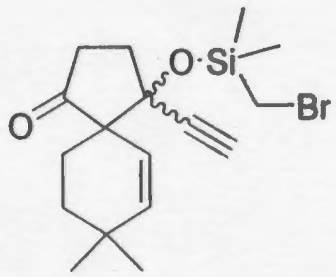

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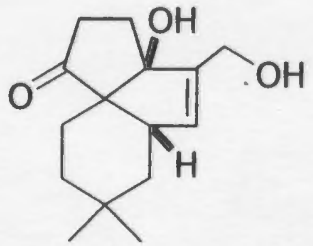
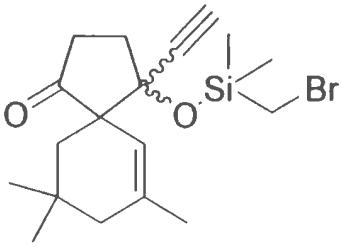


258



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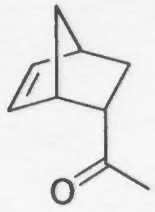

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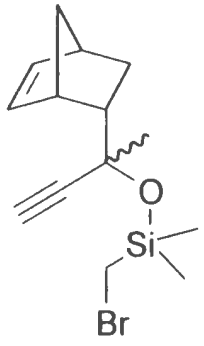

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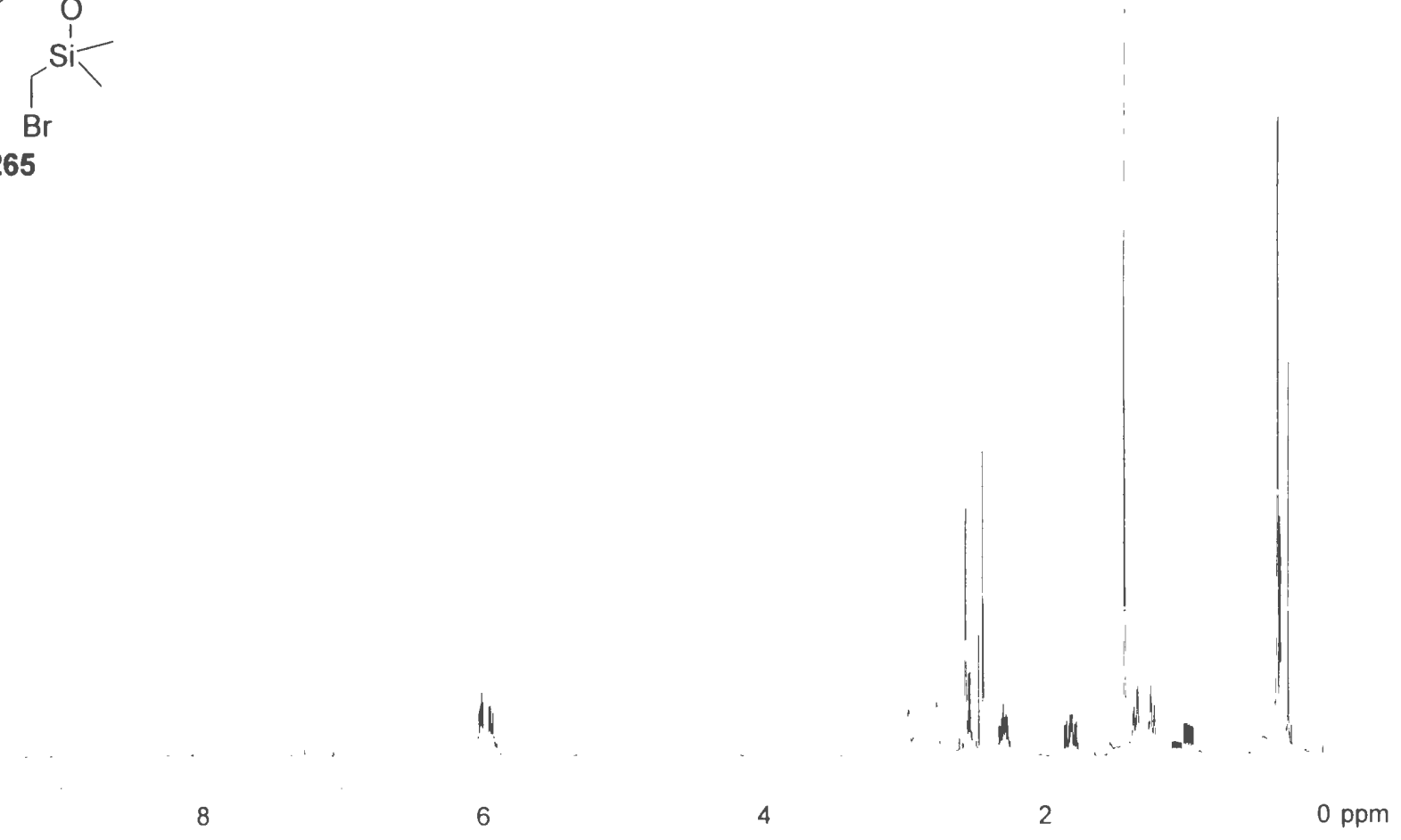

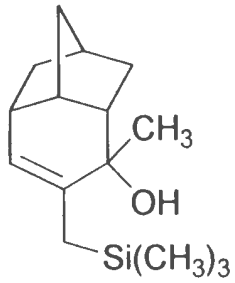

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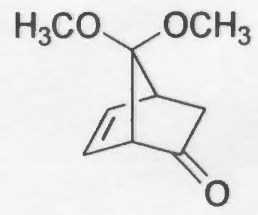

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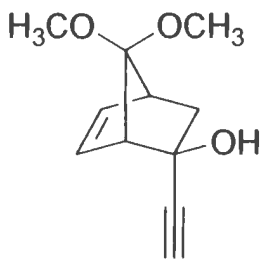

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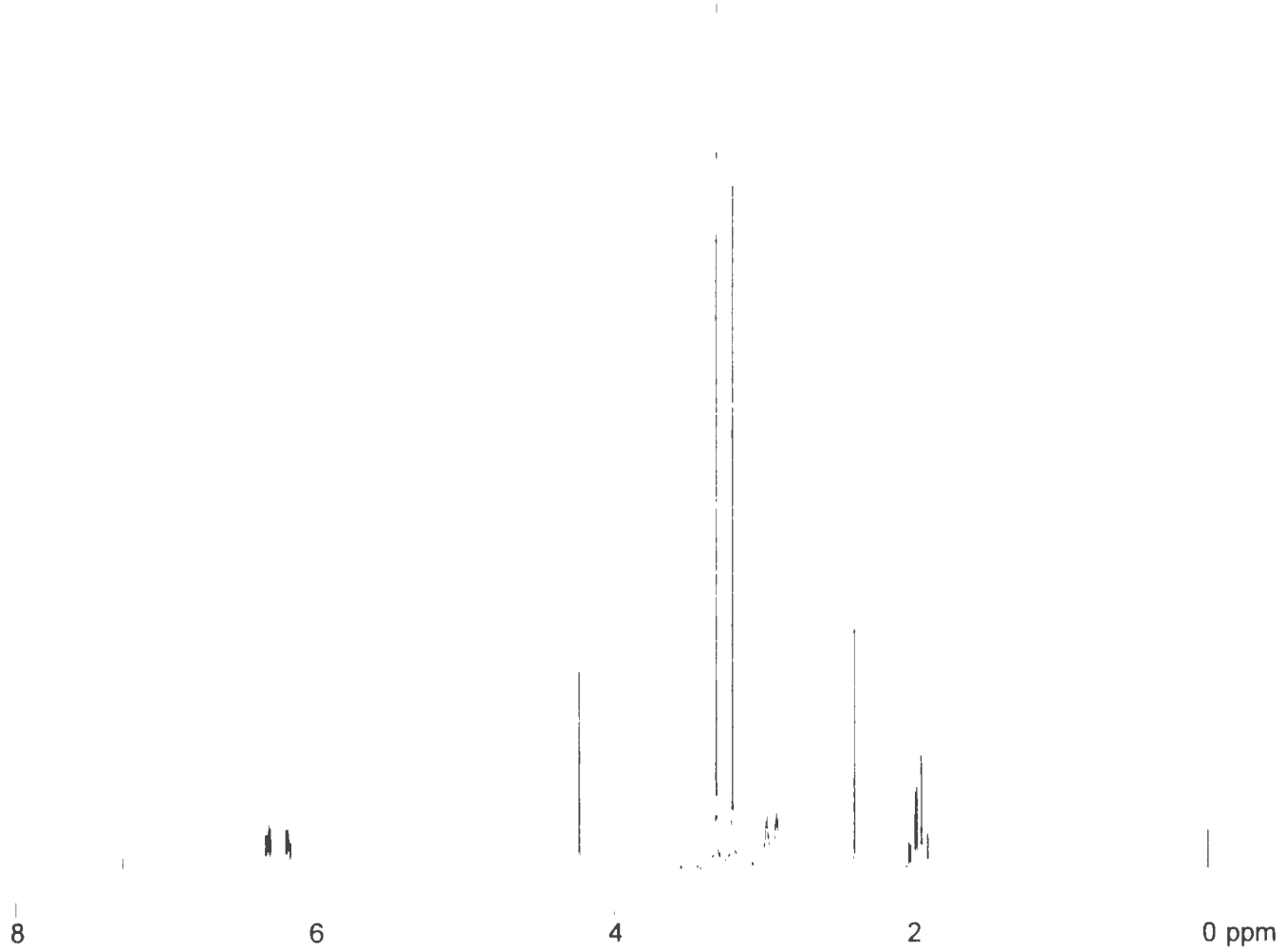

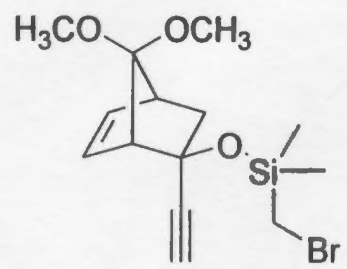

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