SYNTHESIS OF THE KEMPANE DITERPENE RING SYSTEM, AND REGIO-AND STEREOSELECTIVITY IN THE REDUCTIONS OF CYCLIC ENEDIONES

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Abstract

Kempane diterpenes such as **1** and **2**, which are a class of compact tetracyclic compounds isolated from the defense secretions of nasute soldier termites, have been challenging synthetic targets. We have achieved a highly stereoselective synthesis of the kempane diterpene ring system that possesses all the required stereogenic centers and sufficient functionality to allow elaboration to **1** and **2**. A key step of our synthesis of the ring system is the highly regio- and facially-selective Diels-Alder cycloaddition of *cis*-5-(1-((*tert*-butyldimethylsilyl)oxy)vinyl)-3,3a,6,6a-tetrahydro-*2H*-cyclopenta[*b*]furan-2-one (**78**) and 2,6-dimethyl-1,4-benzoquinone (**13**) to establish the benzoindane ring system **79**. The diene **78** was prepared through a sequence that contained a regiospecific [2 + 2] cycloaddition of 1-methyl-1,3-cyclohexadiene (**38**) with dichloroketene, generated *in situ* from dichloroacetyl chloride and triethylamine. Though attempts to cyclize the seven-membered ring in hemi-acetal **72** by aldol reaction were unsuccessful due to the difficulty in opening the five-membered hemi-acetal ring, the seven-membered ring was constructed by a regiospecific Dieckmann condensation in 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-hydroxy-6-(2-methoxyethoxy)methoxy-2,10c-dimethyl-9-oxo-1*H*-benz[6,7]indeno-[2,1-*b*]furan-1-methylcarboxylate (**131**). The transformation of the benzoindane ring system **79** to carboxylate **131** involved a remarkably regio- and stereoselective addition of an acetylide to the apparently more hindered carbonyl in **79**, a reductive cleavage of a γ-hydroxy group in an α,β-enone system, and a one-pot acid-

promoted epimerization and double-bond isomerization.

To explore the possibility of modifying our synthesis of the kempane diterpene ring system to an asymmetric approach, we investigated the asymmetric [2 + 2] cycloadditions of enantiopure, *L*-menthoxy- and 1,2:5,6-di-*O*-isopropyllidene-a-*D*-glucofuranoxy-substituted ketenes **174** and **185** with cyclopentadiene (**175**).

In the course of the synthetic study towards kempane diterpenes, an extremely regio- and stereoselective reduction of the seemingly more hindered carbonyl in enedione **56** with lithium tri-*tert*-butoxyaluminohydride or sodium borohydride was observed. Systematic study proved this observation to be general with non-bridged cyclic enediones. Both the regio- and stereoselectivities are due to a preference for axial attack by the reducing reagents. Among possible axial additions to the two carbonyls, only one approach is sterically allowed. It was also found that the combination of sodium borohydride and cerium trichloride, the Luche reagent, was a useful alternative reducing reagent. It either improved or completely reversed the regioselectivity.

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Glossary of abbreviations

Ac	Acetyl
acac	Acetylacetonate
APT	Attached proton test
bp	Boiling point
Bn	Benzyl
t-Bu	*tert*-Butyl
conc.	Concentrated
COSY	^{1}H-^{1}H Correlation (spectroscopy)
m-CPBA	*meta*-Chloroperoxybenzoic acid
CSA	Camphorsulfonic acid
de	Diastereomeric excess
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
ee	Enantiomeric excess
eq.	Equivalent
ERG	Electron releasing group
Et	Ethyl
EWG	Electron withdrawing group
GC-MS	Gas chromatography-mass spectrometry
h	Hours

HET-COR	Heteronuclear correlation (spectrum)
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrum
$h\nu$	Ultraviolet irradiation
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MEM	(2-Methoxyethoxy)methyl
min	Minutes
mp	Melting point
Ms	Methanesulphonyl
MS	Mass spectrometry
NMO	*N*-Methyl morpholine-*N*-oxide
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser effect enhancement
PCC	Pyridinium chlorochromate
PLC	Preparative layer chromatography
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride

TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl triflate
Tf_2O	Triflic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	*para*-Toluenesulphonyl
UV	Ultraviolet

Part I

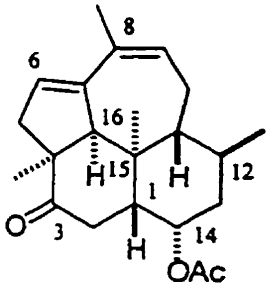
STEREOSELECTIVE SYNTHESIS OF THE KEMPANE DITERPENE RING SYSTEM

1. 1. Introduction

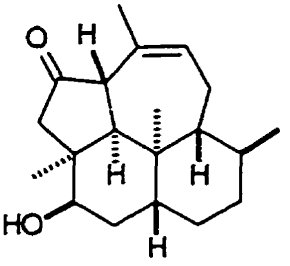
Termite soldiers adopt both physical and chemical defense mechanisms either separately or in combination.[1] The soldiers of primitive termite species usually employ physical defense involving the use of their mandibles, which are big and powerful, to cut and bite their opponents. Chemical defense is a more evolved form of defense. Instead of physical contact, it involves the ejection of viscous and sticky secretions upon the opponents. The secretions can cover a distance of several centimeters and are able to immobilize the opponents. When physical defense and chemical defense are used in combination, the opponents are captured physically and then treated with chemical defense secretions.

The most highly evolved chemical defense system belongs to non-mandibulate nasute soldiers. After a long evolution process, these soldiers have degenerated mandibles, but instead, they have developed an elongated rostrum called a nasus for their defense secretion. More impressively, they have developed a great ability to biosynthesize a large number of complex organic compounds, many of which have now been identified, to constitute their defense secretions. Kempene is one class of novel diterpenoids isolated from the defense secretions of nasute soldiers. 14α-Hydroxykempa-

Figure 1. Representative members of the kempane diterpenes



1



2

6,8-dien-3-one 14-acetate (**1**) and 3β-hydroxy-7β-kemp-8(9)-en-6-one (**2**) are two representative members of the kempane diterpenoids (Figure 1). They were first isolated from the defense secretions of *Nasutitermes kempae* and *Nasutitermes octopilis* in 1977[2] and 1979,[3] respectively, by G. D. Prestwich and coworkers. Their relative stereochemistry was solved by single-crystal x-ray diffraction analysis. Crystal structures also showed that these molecules had dome-like shapes, as shown for kempane diterpene **1** in Figure 2, and that the diene system in **1** was not planar but twisted by about 20°. The absolute configuration of **1** was obtained from the helicity of both the diene and carbonyl chromophores.[4]

Figure 2. The shape of kempane diterpene **1**

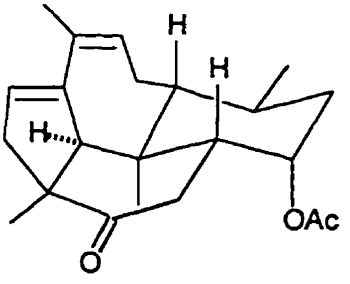
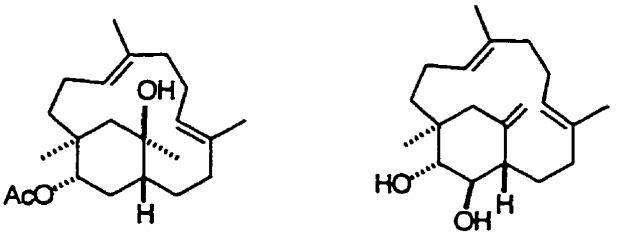
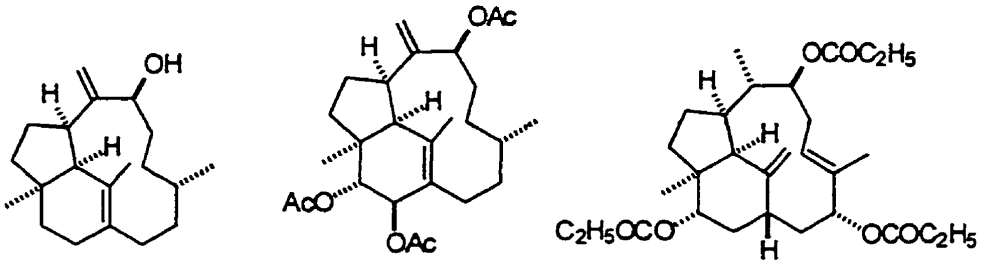


Figure 3. Diterpenoids from the defense secretions of nasute termite soldiers

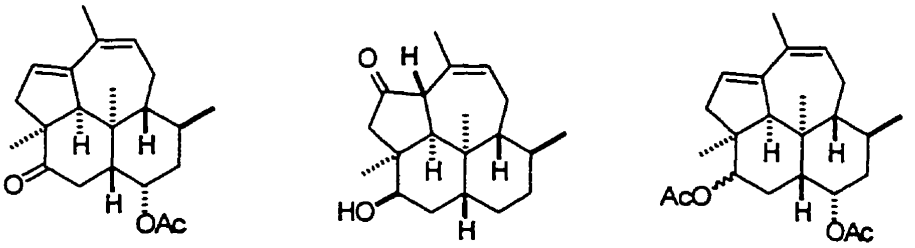
Secotrinervitenes



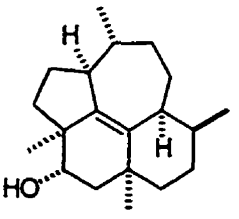
Trinervitenes



Kempanes



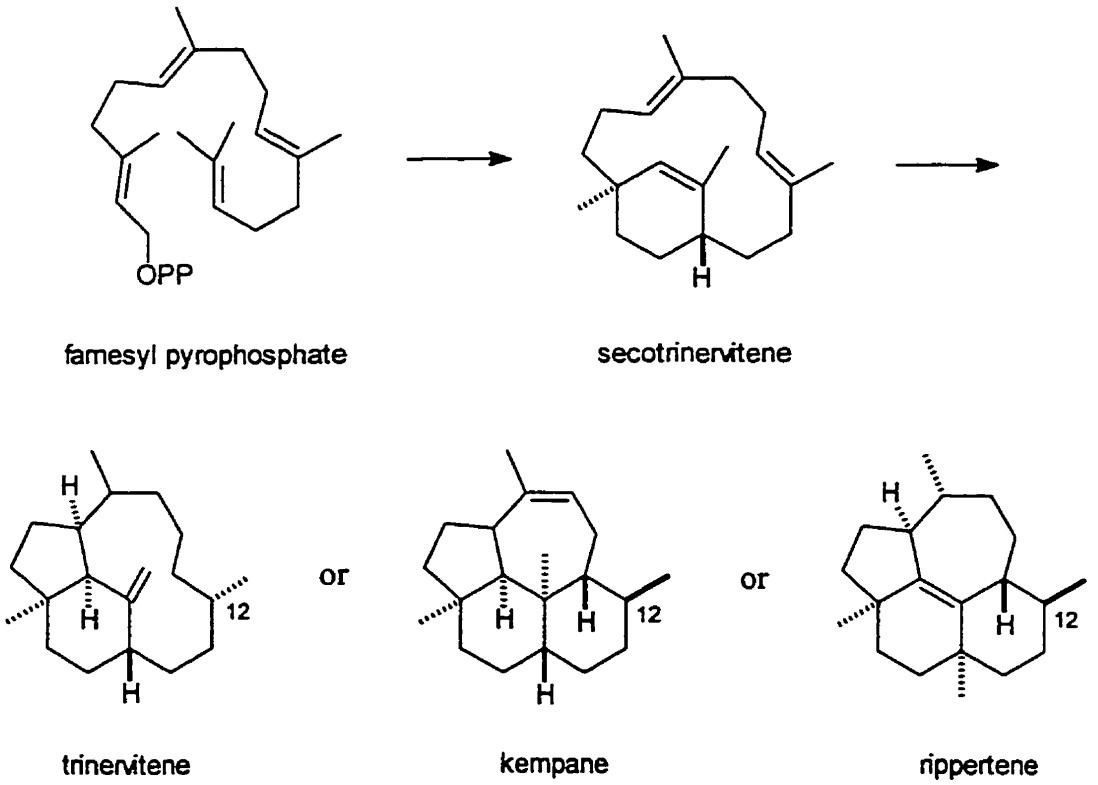
Rippertenes



Besides kempenes, a variety of other structurely related diterpenoids have been isolated from the defense secretions of soldier termites. These are bicyclic secotrinervitenes,[5,6] tricyclic trinervitenes,[7] and tetracyclic rippertenes.[8] Representatives of these diterpenoids, along with those of the kempanes, are arranged in Figure 3.

It was proposed[9] that all four classes of diterpenes are derived biogenetically from the cyclizations of farnesyl pyrophosphate, as shown in Scheme 1. (Scheme 1 has been slightly modified from the original.) This proposal has been supported by isotopic labeling experiments.[10] It is also supported by the demonstration of the coexistence of

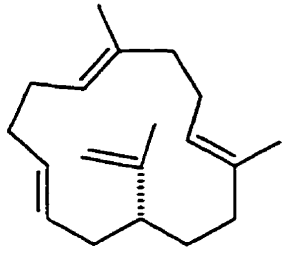
Scheme 1. Biogenesis of secotrinervitene, trinervitene, kempene, and rippertene from farnesyl pyrophosphate



farnesyl pyrophosphate secotrinervitene

trinervitene kempane rippertene

trinervitene and secotrinervitene in *Nasutitermes princepts*.[6] The formation of rippertene appears to involve the migration of a methyl group, a commonly occurring process in the course of biosynthesis. Some literature[4, 11] suggested that cembrene A (**3**) be a common precursor to all of the four classes of diterpenes. However, **3** has never been found in the defense secretions of nasute termite soldiers, though it is a well known trail pheromone of termite workers.[12] It is also unlikely that the tetracyclic diterpenoids are derived from the tricyclic ones, since the configurations of C-12 in trinervitenes are always found to be opposite to that in kempenes and rippertene.

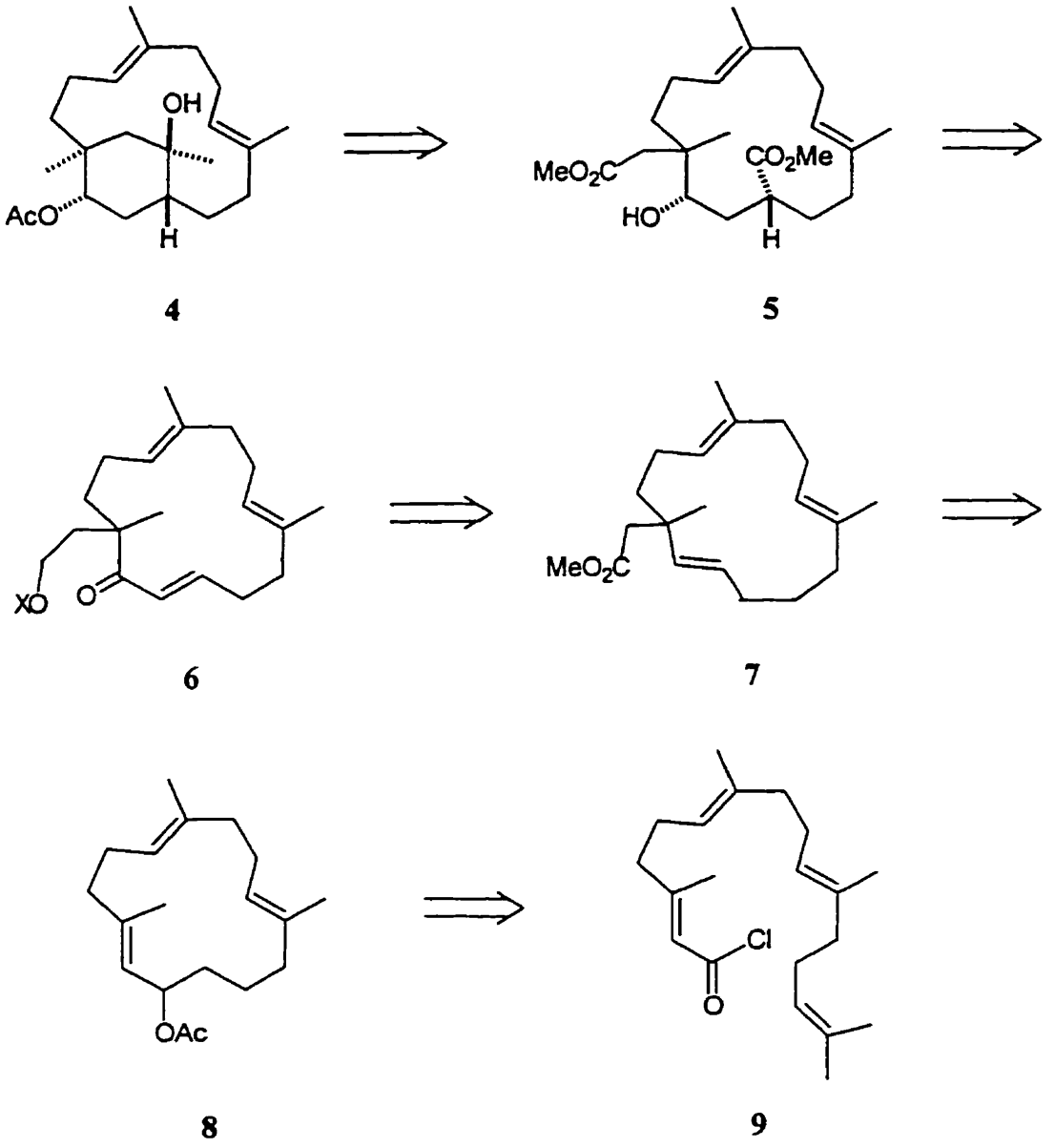


3

Due to their biological activity and particularly their unique structures, the termite defensive diterpenoids have attracted interest as targets for total synthesis. So far, five synthetic endeavors have been reported. Two members of the secotrinervitene class and kempane **1** have been synthesized. One approach resulted in the formation of an isomer of kempene **2,** and the other prepared the ring system of rippertene.

The first total synthesis in this area was the synthesis of (±)-3α-acetoxy-15β-hydroxy-7,16-secotrinervita-7,11-diene (**4**), reported by T. Kato's group in 1987.[13] The strategy is outlined in Scheme 2. Macrocyclic allyl acetate **8,** which was previously

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



4 **5**

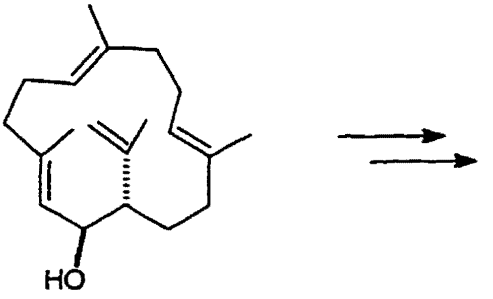
6 **7**

8 **9**

prepared in their laboratory from *trans* geranyl geranoyl chloride (**9**),[14] was used as the starting material. A two-carbon side-chain was introduced by an Ireland-type Claisen rearrangement to give an ester **7**, and **7** was converted to an enone **6**, from which a second side-chain was introduced by Michael addition. Dieckmann condensation of diester **5**

then constructed the cyclohexane ring in **4**. The strategy did yield **4**, but since a macrocyclic compound was chosen as a starting material and the six-membered ring was constructed in the last stage, there was no controlling element for the stereochemistry. As a result, the synthesis turned out to be very inefficient.

Scheme 3. Kato's biomimetic route to **12**



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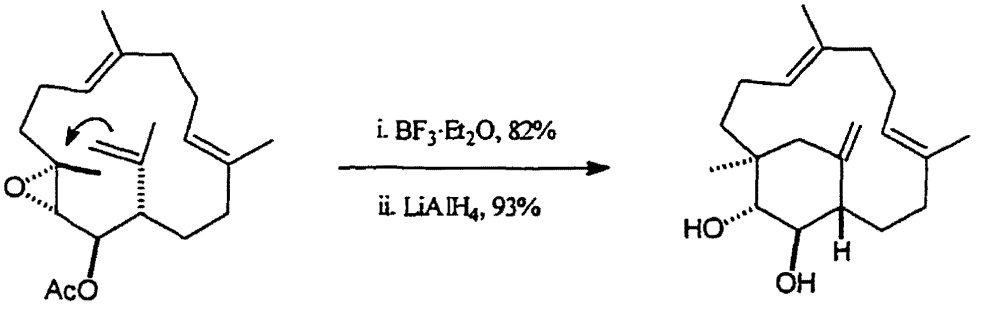
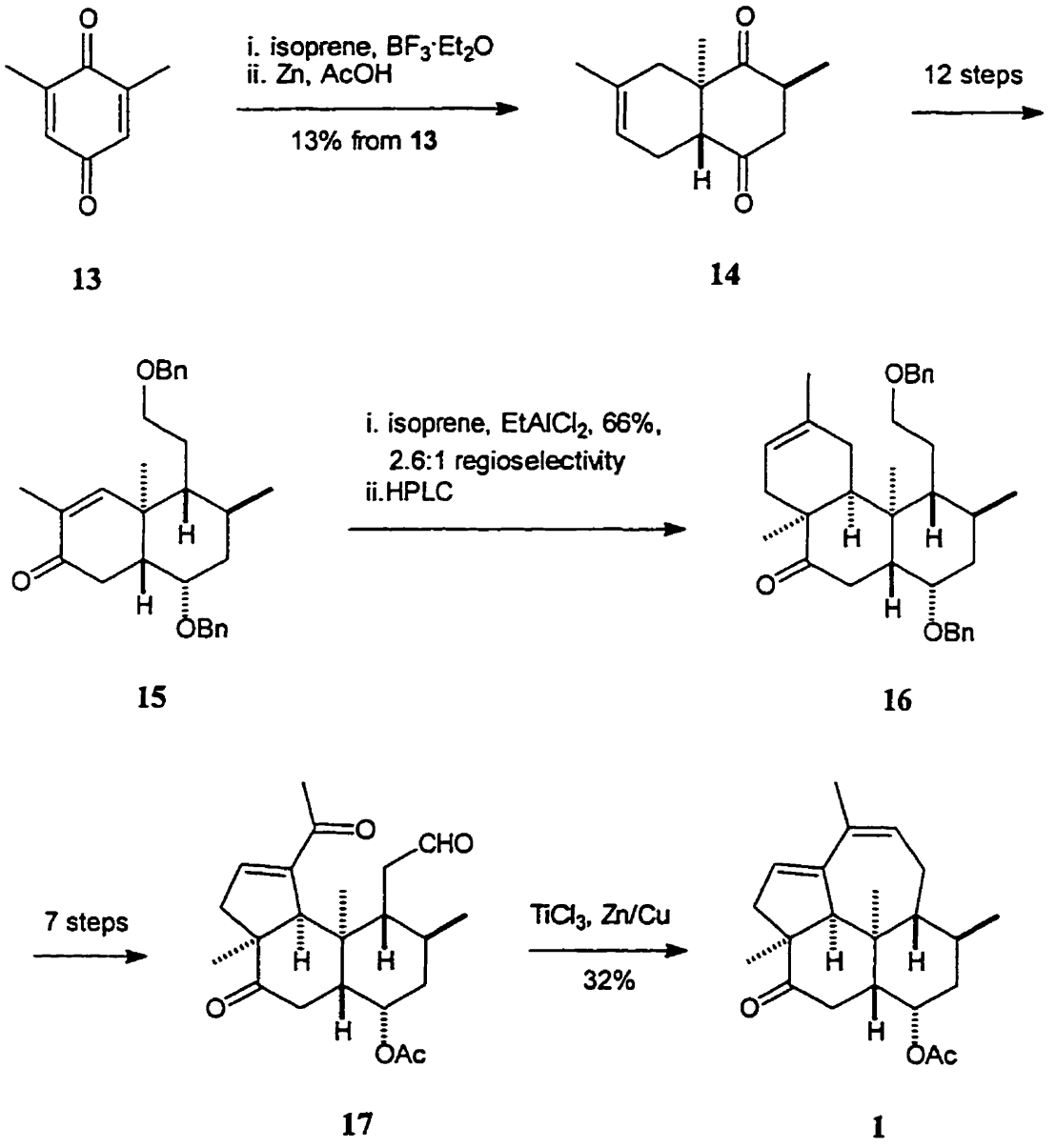


11 **12**

At almost the same time, the same group reported an elegant biomimetic route to (±)-secotrinervitene-2β,3α-diol (**12**) (Scheme 3).[15] Treatment of epoxide **11**, which had been previously made in the their laboratory from *trans*-dehydromukulol (**10**),[16] with BF_3·Et_2O afforded an 82% yield of the desired cyclization product, which was smoothly converted to the natural product **12** by $LiAlH_4$ reduction.

In 1991, Dauben's group achieved the total synthesis of kempene **1** (Scheme 4).[17] They started with a Lewis acid-catalyzed Diels-Alder reaction of 2,6-dimethylbenzo-quinone (**13**) with isoprene, followed by a reduction of the Diels-Alder adduct with zinc in glacial acetic acid and a simultaneous epimerization of the product, to construct the

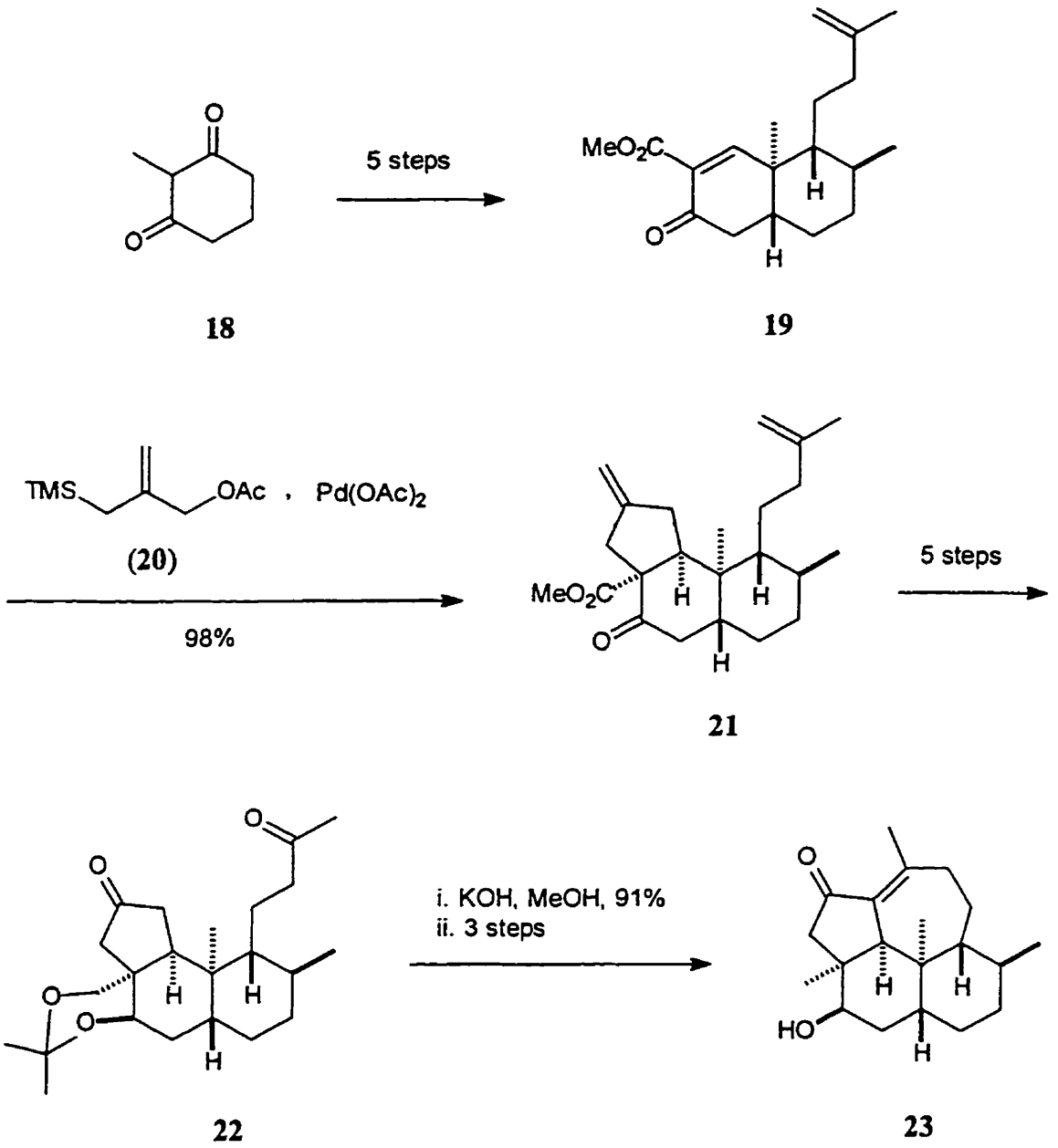
Scheme 4. Dauben's synthesis of kempene **1**



trans-decalin skeleton **14**. The five-membered ring was stereoselectively constructed with a second Lewis acid-catalyzed Diels-Alder reaction of **15** with isoprene and the subsequent operations on the resulting cyclohexene ring. The seven-membered ring was formed with **17** by a Ti^0-induced McMurry coupling. A weakness in this strategy is the use of isoprene twice as a Diels-Alder diene. Diels-Alder reactions with isoprene have very poor regioselectivity. This significantly affected the synthetic efficiency. For example, the overall yield of the first two steps was extremely low (13%). One reason must be the poor regioselectivity in the Diels-Alder reaction, though it was not pointed out in their paper. In our hands a Diels-Alder reaction of **13** with isoprene in a sealed tube resulted in nearly no regioselectivity. Again, the regioselectivity in Dauben's 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 preparative HPLC.

The next year Paquette's group reported an approach towards kempene **2**.[18] The strategy is summarized in Scheme 5. A key feature in this strategy is an extremely efficient palladium-promoted [3 +2] cycloaddition of the activated enone **19**, which was derived from 2-methyl-1,3-cyclohexanedione (**18**), with (2-(acetoxymethyl)allyl)trimethylsilane (**20**) to construct the five-membered ring. The final cyclization was realized by a base-catalyzed aldol condensation of dione **22**. Unfortunately, the conjugated double bond in **23** could not be deconjugated to make the naturally occurring kempane diterpene **2**. Otherwise, this approach would be a concise synthesis. Semi-empirical calculations have been carried out with **23** and **2**.[19] The results suggested that **23** is more stable than **2** by 1.6 kcal/mol.

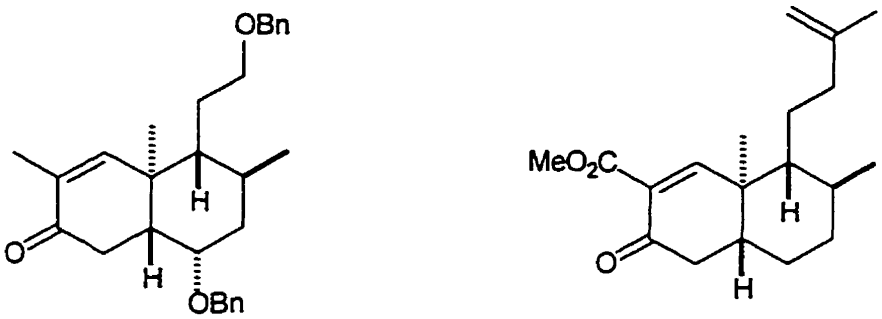
Scheme 5. Paquette's approach to kempane diterpene **2**



A common feature in Dauben's synthesis of kempene **1** and Paquette's approach towards kempene **2** is that both began with the construction of a *trans*-decalin ring system. As a result, the two syntheses passed through the very similar intermediates **15**

and **19** (Figure 4). Both approaches then utilized cycloaddition reactions to install a third ring. The angular methyl group in the *trans*-decalins ensured that the cycloadditions occurred from the opposite side to provide the desired stereochemistry.

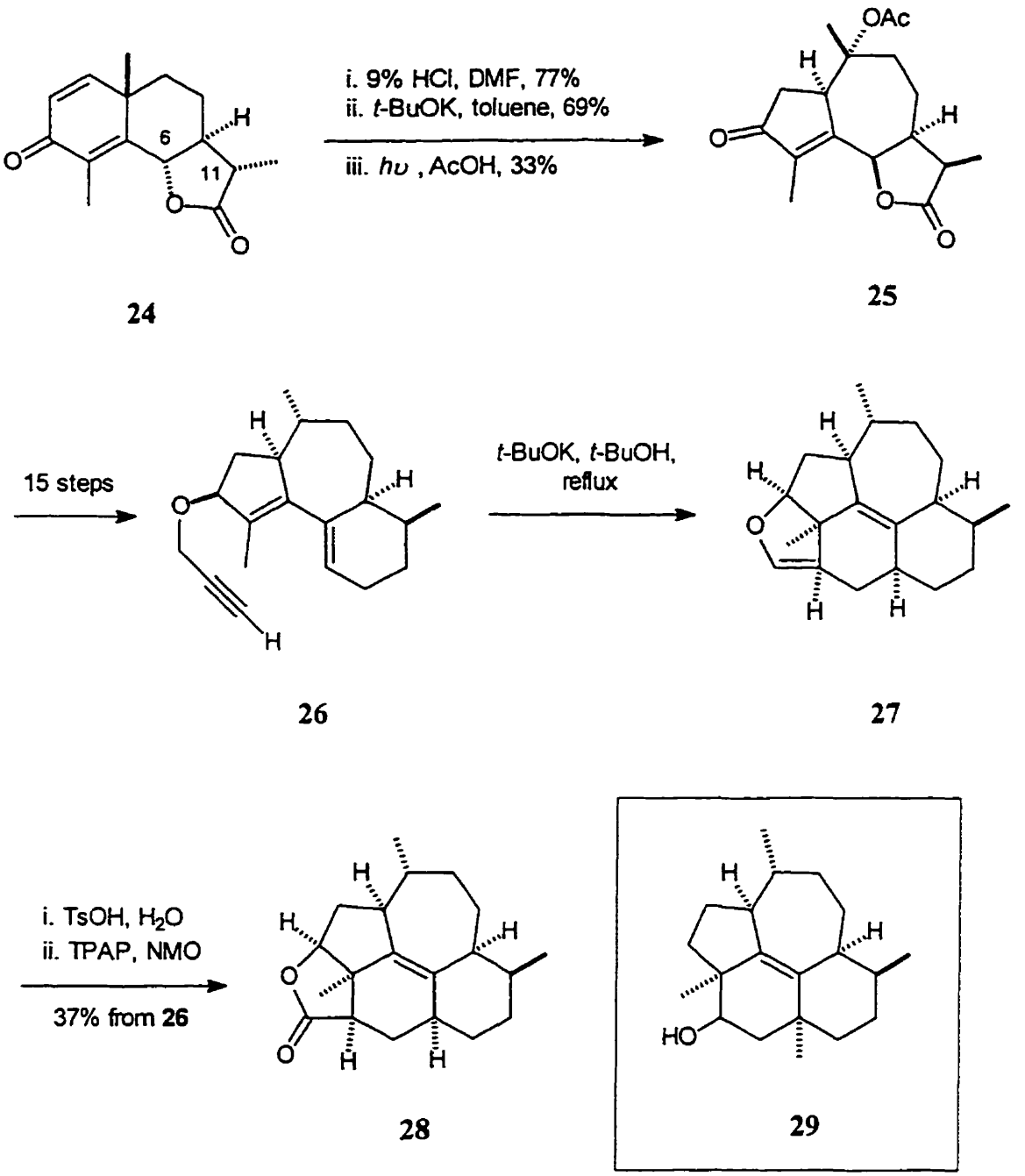
Figure 4. Similar intermediates in Dauben's and Paquette's syntheses



15 **19**

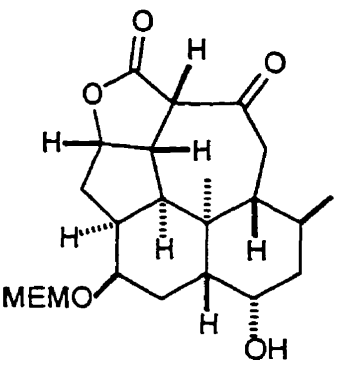
The only enantioselective approach to a termite defensive compound is the preparation of the ring system of 3α-hydroxy-15-rippertene (**29**), reported by Metz *et al.* in 1993 (Scheme 6).[20] This approach took advantage of the commercial availability of a relatively complex and enantiopure eudesmanolide, (−)-α-santonin (**24**). After consecutive epimerizations at C-6 and C-11, effected with 9% HCl and *t*-BuOK respectively, **24** was transformed into a hydrazulene **25** by photoisomerization.[21] A key step in this approach to construct the tetracyclic ring system of rippertene was the intramolecular Diels-Alder reaction which was effected by treatment of propargyl ether **26** with *t*-BuOK to generate the corresponding allenyl ether as a dienophilic moiety.[22] Though Metz's approach led to the rippertene ring system, it seems that the ring system will not easily be modified into the natural product **29**.

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



Intrigued by the very compact carbon skeleton and the large number of stereogenic centers of kempane diterpenoids, we have developed a stereoselective approach to the

kempane diterpene ring system **30**.[23] Compound **30** possesses all the required stereogenic centers for **1** and **2**. It also contains sufficient functionality to allow elaboration to the natural products. Our approach features a highly regio-, facial selective Diels-Alder cycloaddition and a highly regio-, stereoselective acetylide monoaddition to a cyclic enedione.



30

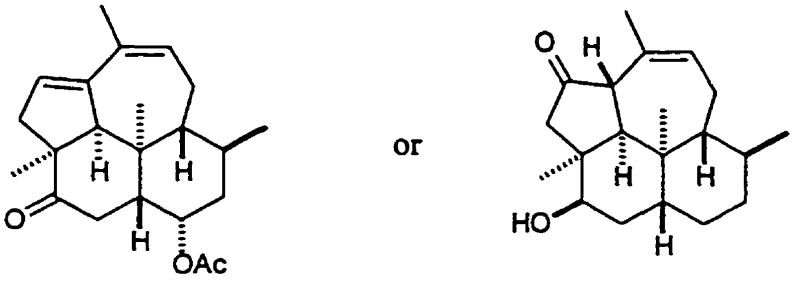
1. 2. Strategy One

1. 2. 1. Retrosynthetic Analysis

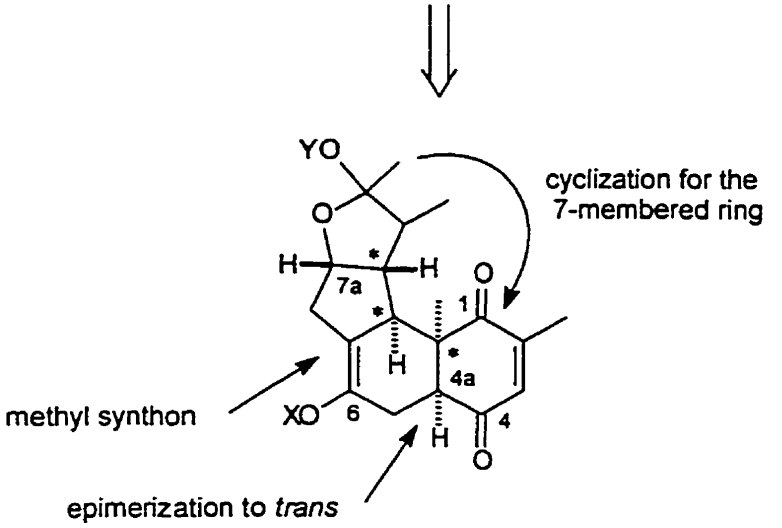
Our original retrosynthetic analysis of the kempane diterpenoids is displayed in Scheme 7. We assumed that tetracyclic enedione **31**, in which X could be an acetyl or a silyl group and Y could be a hydrogen or an alkyl group, would be an excellent common precursor to both kempene **1** and **2**. This enedione possesses a benzoindane ring system, three key stereogenic centers (indicated by asterisks), and all the annular carbons required for **1** and **2**. The correct stereochemistry of C-4a could be obtained by epimerization of the *cis*-decalin ring conjunction to the *trans*. The enol ether structural unit was expected to provide an opportunity to introduce the last methyl group. Opening the five-membered hemi-acetal ring would produce a methyl ketone, which would undergo the final cyclization to construct the seven-membered ring. The oxygen at C-7a could be eliminated to generate the double bond in **1** or be oxidized to the carbonyl in **2**.

The enedione **31** could be prepared by the Diels-Alder cycloaddition of diene **32** with 2,6-dimethyl-1,4-benzoquinone (**13**). Although theoretically this reaction might produce eight isomeric adducts, it is reasonable to expect that it would proceed in an *endo*-, regio-, and facially selective manner, as illustrated in Figure 5, to produce the desired adduct as the major product. *Endo* selectivity, which is sometimes called the "Alder Rule", is a well known phenomenon in Diels-Alder reactions. This rule states that in the preferred transition state an unsaturated substituent on a dienophile (two carbonyls on **13** in the currently discussed case) should be oriented towards the newly developing double bond. The origin of this selectivity, according to the molecular orbital theory, is

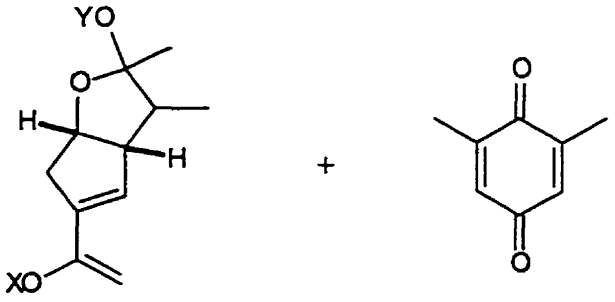
Scheme 7. Retrosynthetic analysis leading to Strategy One



1 **2**

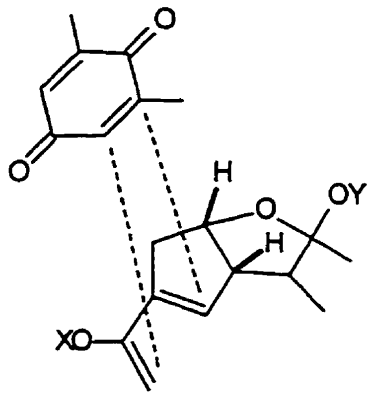


31



32 **13**

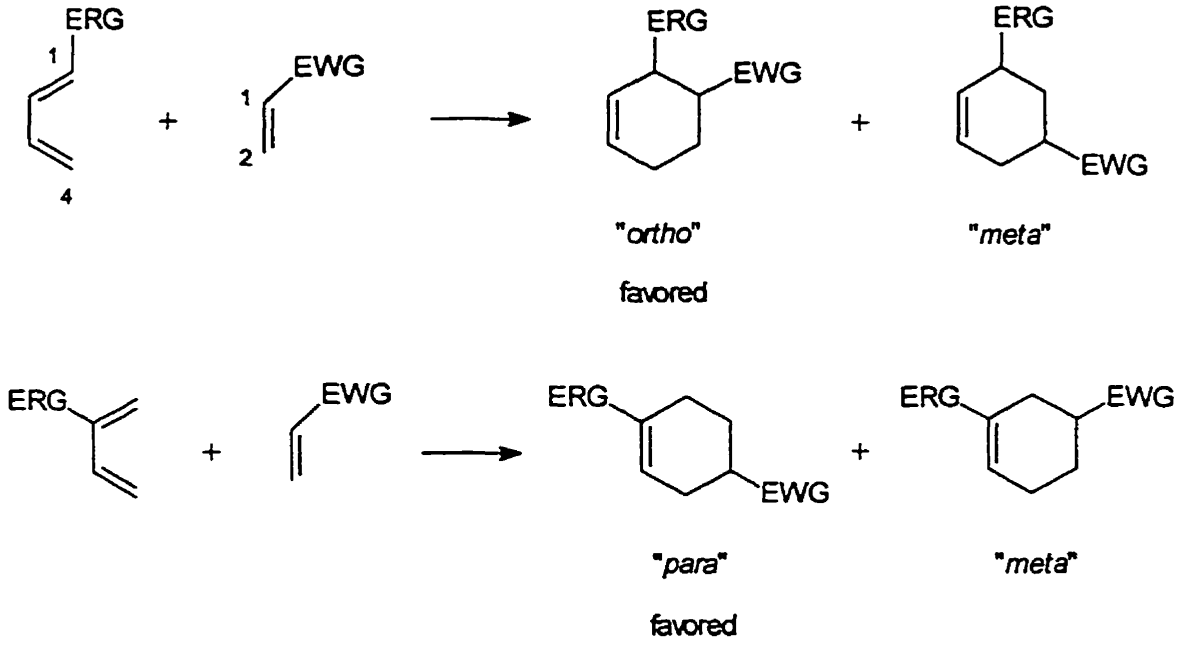
Figure 5. An *endo*-, regio-, and facially selective Diels-Alder reaction



the favorable secondary orbital interaction in the transition state between the π orbitals on the carbonyls and the developing double bond.[24]

The regioselectivity of our Diels-Alder reaction is expected on the basis of another generalization of Diels-Alder reaction, which is sometimes called the "*ortho-para*" rule. This rule addresses that when both the diene and the dienophile bear substituents, the preferred transition state, and subsequently the preferred product, is the one in which the subsitituents have an *ortho* or a *para* relationship. The two simplest cases in the normal Diels-Alder reaction are depicted in Scheme 8, where ERG and EWG represent an electron-releasing group and an electron-withdrawing group, respectively. The "ortho-para" rule can be interpreted by the frontier molecular orbital theory.[25] Normal Diels-Alder reactions occur by orbital interactions between the HOMO of dienes and the LUMO of dienophiles. The strongest interaction is between the centers having the largest orbital coefficients in the frontier orbitals. For the first case in Scheme 8, an ERG on C-1 of the diene will cause the HOMO of the diene to have the largest coefficient at C-4. An

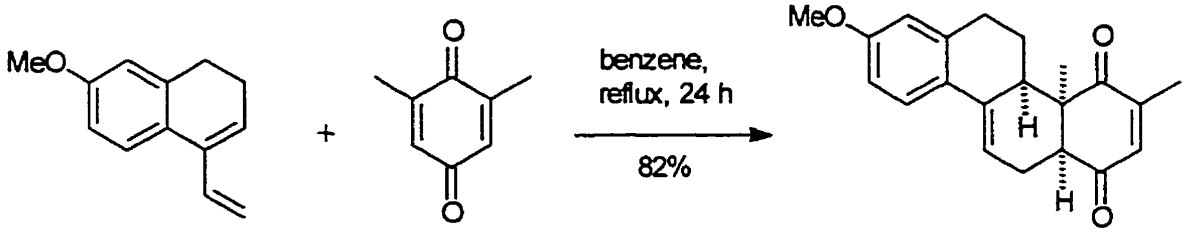
Scheme 8. Regioselectivity of the normal Diels-Alder reaction



EWG on C-1 of the dienophile will result in the LUMO of the dienophile having the largest coefficient at C-2. As a result, C-4 of the diene will interact most strongly with C-2 of the dienophile, which will regioselectively produce an "*ortho*" product. A similar analysis of the second case in Scheme 8 will account for the "*para*" regioselectivity. When a diene has more than one ERG at different positions, an ERG at the 1-position will dominate over an ERG at the 2-position if the two ERG's have similar electron-releasing capabilities. On the other hand, when a dienophile has EWG's at both ends of the reacting double bond, the regioselectivity will be dominated by the one having the greater ability to withdraw electrons. In our case, diene **32** bears three substituents, at the 1-, 2-, and 3-positions. The effects of the 1-substituent and 3-substituent are consistent and should be dominant over that of the 2-substituent. In the dienophile **13**, the two electron-

donating methyl groups at C-2 and C-6 will repress the electron-demand of the carbonyl at C-4 through a conjugative effect. Therefore, the carbonyl at C-1 will have more electron-withdrawing ability and should control the regioselectivity in the Diels-Alder reaction. In other words, in the major product this carbonyl should have the "*ortho-para*" relationship with the dominant substituents in the diene. This is exactly the situation shown in Figure 5. This analysis of regioselectivity was supported by a literature example. Valenta *et al.* showed that heating diene **33** with quinone **13** afforded adduct **34** as the exclusive product in 82% yield (Scheme 9).[26]

Scheme 9. A literature example of a regioseletive Diels-Alder rection with **13**[26]

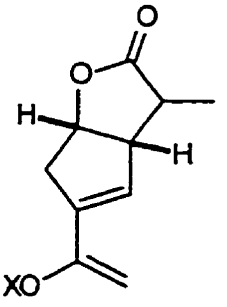


33 **13** **34**

The expectation of facial selectivity in our Diels-Alder reaction was based on steric interactions. We believed that the (hemi-)acetal ring in diene **32** would block one of the two faces of the diene and make the dienophile approach the the diene from the other face. We also anticipated that the methyl groups in the (hemi-)acetal ring were far enough away from the reacting site to have little influence on the reactivity and selectivity of the diene.

1. 2. 2. Syntheses of Dienes and Examination of Their Diels-Alder Reactions

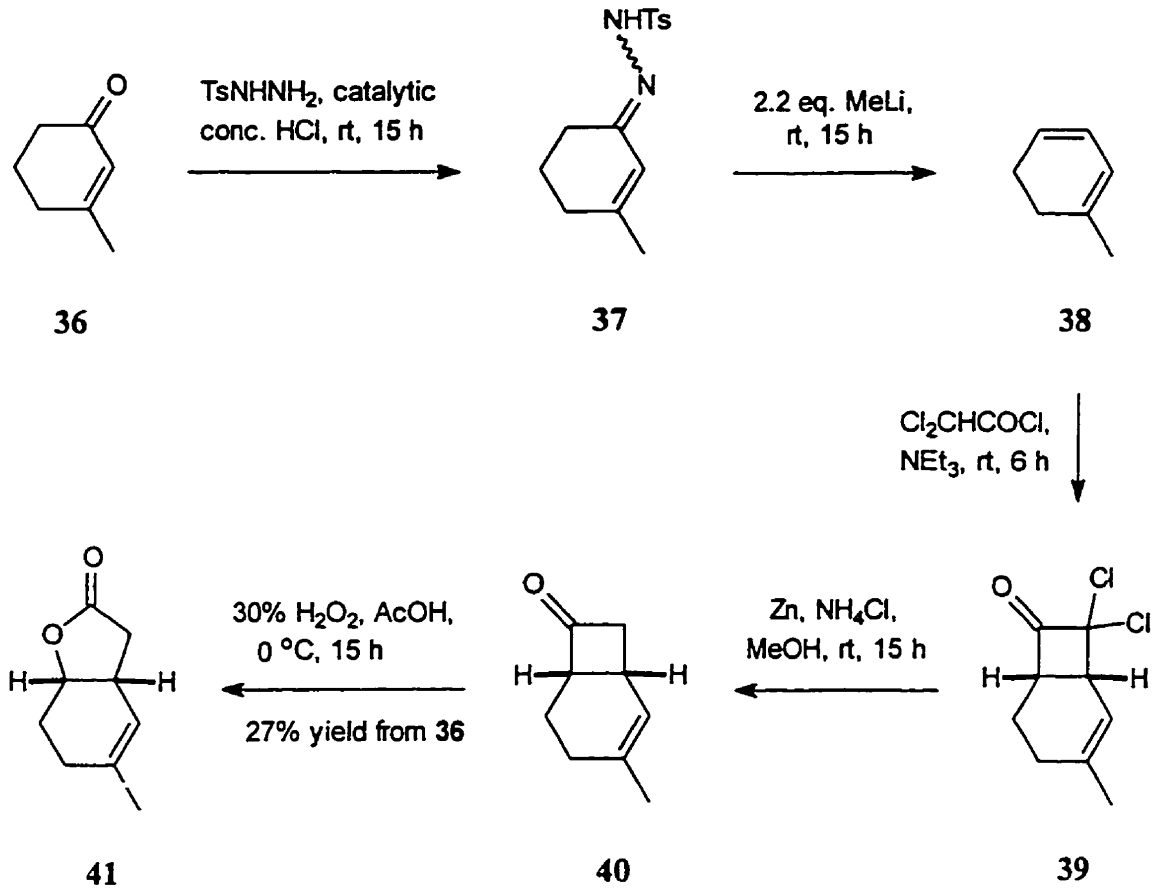
To execute the strategy discussed above, it was first desirable to examine the Diels-Alder cycloaddition to see if it would occur and, if so, to assess the extent of the *endo*-, regio-, and facial selectivities. For this purpose, we initially chose to use diene **35** instead of **32**, since the former is easier to handle.



35

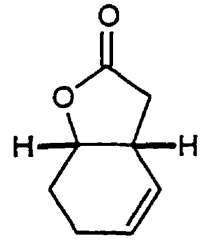
Our synthesis of diene **35** started with the Shapiro reaction of commercially available 3-methyl-2-cyclohexen-1-one (**36**) (Scheme 10). Stirring a 1:1 mixture of **36** and *p*-toluenesulfonylhydrazide in the presence of a catalytic amount of concentrated hydrochloric acid at room temperature overnight produced a mixture of *syn* and *anti* hydrazones **37** in a ratio of 2:1. This crude hydrazone was then treated with 2.2 equivalents of methyllithium at room temperature overnight, to provide 1-methyl-1,3-cyclohexadiene (**38**). The conversion of **36** to **38** by the Shapiro reaction is a known transformation. However, the literature yields are only moderate or poor: 62% and 22% were reported by Gregson *et al.*[27] and Eilbracht *et al.*,[28] respectively. Following their procedures, we obtained even lower yields (< 10%). When we attempted to isolate diene **38** by distillation, we noticed that the residue in the distillation flask turned more and

Scheme 10. Synthesis of lactone **41** from **36**



more viscous and non-volatile upon heating. Consequently, very little product was distilled. Therefore, we speculated that diene **38** was not stable under heating and it might have dimerized or polymerized during the attempts at distillation. Eventually, this problem was solved by avoiding the isolation of **38**. After workup of the Shapiro reaction, a solution of the crude **38** in diethyl ether and pentane was first dried over anhydrous Na_2SO_4 and then over solid KOH. To this solution was directly introduced triethylamine and then dichloroacetyl chloride at room temperature. Dichloroketene was generated *in situ* from the reaction of dichloroacetyl chloride and triethylamine, and the

ketene underwent a highly regioselective [2 + 2] addition to the less substituted double bond of diene **38** to give the bicyclic adduct **39**. Dechlorination of **39** with zinc dust in a slightly acidic medium, supplied by ammonium chloride in methanol,[29] at room temperature over fifteen hours afforded cyclobutanone **40**. The dechlorination could also be effected by zinc in refluxing glacial acetic acid. It was noticed that the zinc dust used for the latter procedure had to be of analytical grade (>98%). Less pure zinc dust (96%) resulted in incomplete reduction, producing a considerable amount of monodechlorinated product, as detected by GC-MS. Cyclobutanone **40** was converted to lactone **41** by a regio- and stereoselective Baeyer-Villiger oxidation with 30% aqueous hydrogen peroxide in glacial acetic acid at 0 °C. From **36** to **41** no chromatography was necessary except to obtain analytical samples, and the overall yield was 27%, amounting to an average yield of 77% for each step.

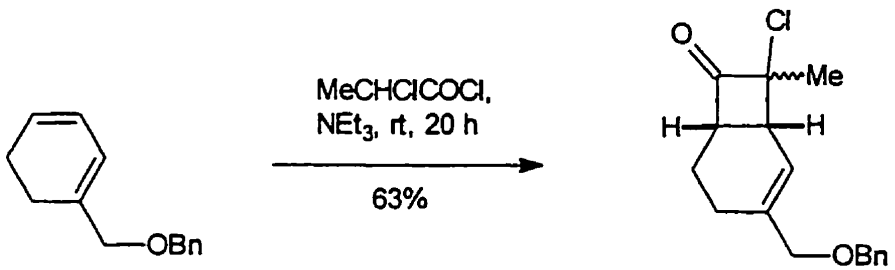


42

The transformation sequence from **38** to **41** was reminiscent of the preparation of Corey's lactone **42** from 1,3-cyclohexadiene.[30] A distinct difference in our case was that our diene **38** was unsymmetrical. We showed that the ketene addition could proceed regiospecifically to the less substituted double bond. A similar example of this

regiospecificity was recently seen in K. E. Harding's synthesis of sirenin (Scheme 11).[31] Reaction of diene **43** with 2-chloropropanoyl chloride and triethylamine regiospecifically gave a 63% yield of adduct **44** as a mixture of *endo*-methyl and *exo*-methyl isomers in a ratio of 3.6:1 favoring the *endo*-methyl isomer. Harding *et al.* mentioned that when the benzyl group was replaced by 2-methoxyethylmethyl (MEM) group in **43**, the yield of the cycloaddition dropped to less than 10%.

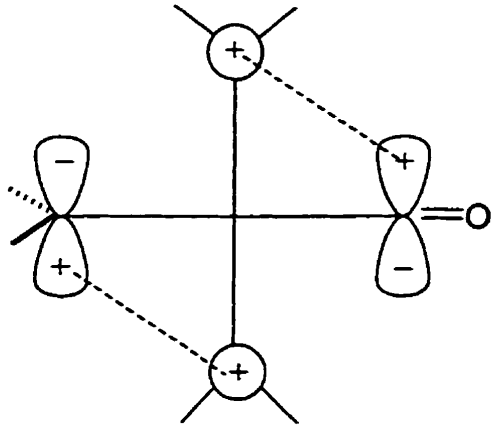
Scheme 11. A literature example of regiospecific ketene cycloaddition[31]



43 **44**

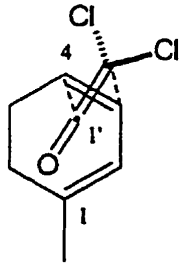
Regiospecificity in the ketene addition can be rationalized by steric and electronic interactions between ketene and diene. If we assume that the mechanism is that of a [2π + 2π] cycloaddition, according to the orbital symmetry principle, the reaction must be antarafacial for one of the π orbitals. That is, in the transition state, the two reacting double bonds must be orthogonal, as shown as Figure 6.[32] Figure 6 also represents the frontier orbital interaction between the HOMO of the alkene and the LUMO of the ethylenic portion of the ketene. When the "orthogonal" requirement is applied to our case, two modes of regiochemistry are possible (Figure 7). Sterically, mode **46** should be less favored because of a significant interaction between the methyl group on the diene

Figure 6. Frontier orbital interaction in ketene addition

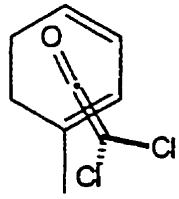


component and a chlorine on the ketene. With regard to electronic factors, the electron donating methyl group at C-1 of the diene will make C-4 have the largest coefficient in the HOMO of the diene. On the other hand, in the LUMO of the ethylenic portion of the ketene, the carbonyl will make C-1' have the largest coefficient. Frontier molecular orbital theory holds that the strongest orbital interaction should be between the centers having the largest coefficients on the frontier orbitals. That is, mode **45** is electronically more favorable for the orbital development in the formation of addition product. In

Figure 7. Two modes of ketene cycloaddition of **38**



45

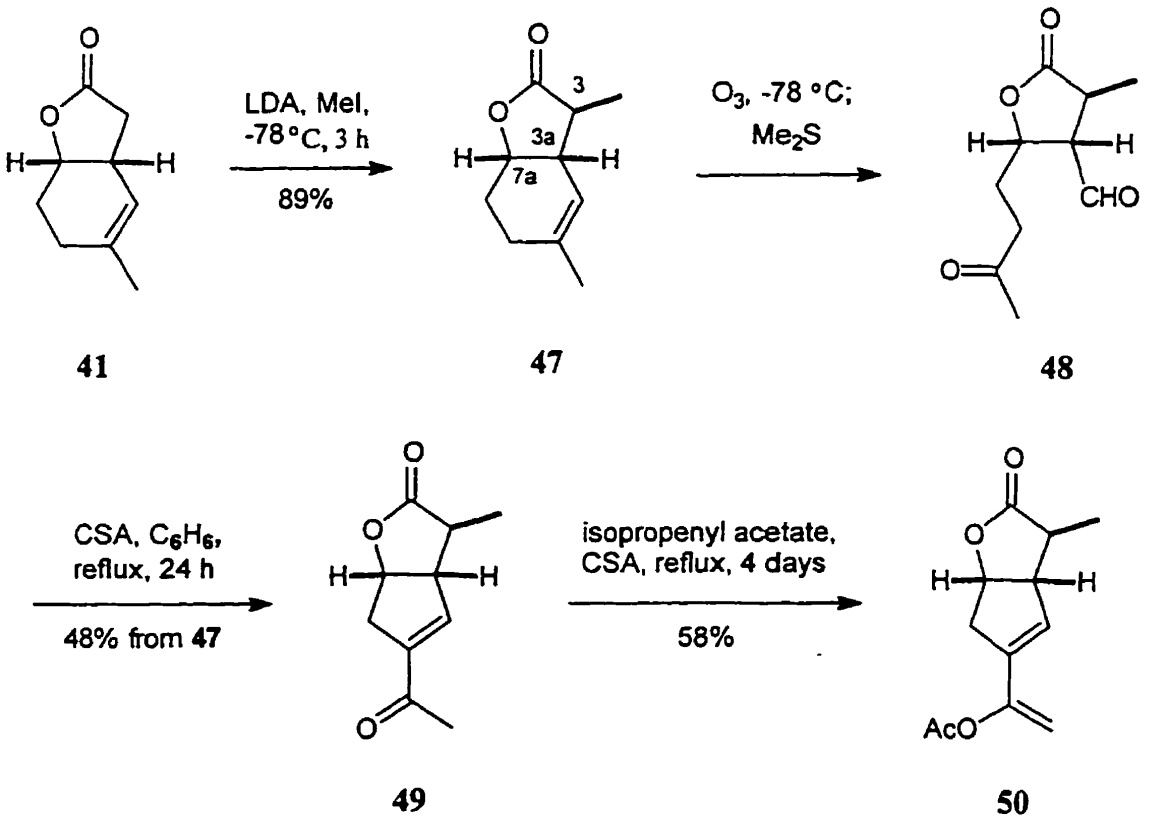


46

conclusion, both steric and electronic factors can account for the observed regiospecificity in the [2 + 2] ketene cycloaddition.

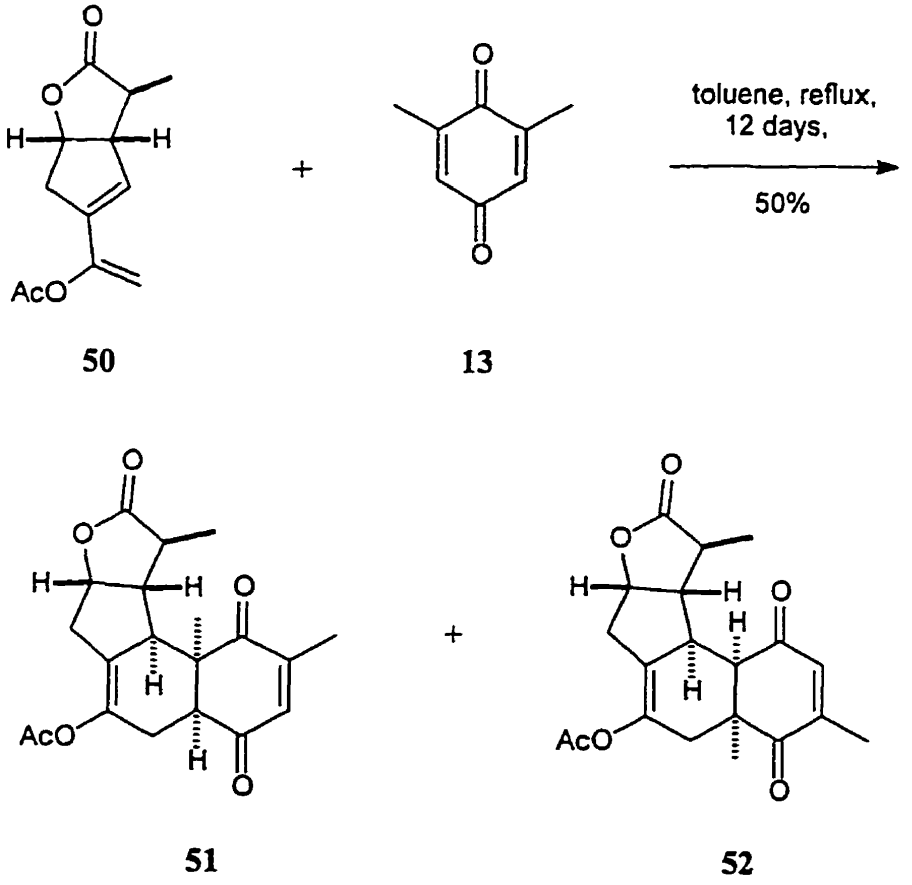
Scheme 12 summarizes the preparation of our first Diels-Alder diene **50** from lactone **41**. Treatment of **41** with lithium diisopropylamide (LDA), followed by iodomethane, at -78 °C [33] for three hours stereoselectively afforded **47** in 89% yield. The relative stereochemistry in **47** was confirmed by a nuclear Overhauser effect (NOE) experiment. Enhancements of 3% and 2% on H-3a were observed, respectively, when the signals for the 3-methyl and H-7a were irradiated. The high stereoselectivity (> 20:1) in this methylation was predicted by the geometry of the *cis*-fused ring system. The six-

Scheme 12. Synthesis of diene **50** from **41**



membered ring obstructed iodomethane from approaching the concave face. Ozonolysis[34] of the double bond in **47** at -78 °C and subsequent reductive workup with dimethylsulfide gave ketoaldehyde **48**. Without isolation, **48** underwent acid catalyzed intramolecular aldol condensation, when heated in the presence of (±)-camphorsulfonic acid with a Dean-Stark apparatus, to provide enone **49** in 48% yield from **47**. When the aldol cyclization was attempted in basic media (KOH/methanol or $Et_3N/MsCl$[35]), very complex mixtures were produced, as shown by TLC. With **49** I first prepared diene **50** in a

Scheme 13. Diels-Alder reaction of diene **50** with **13**



50 **13**

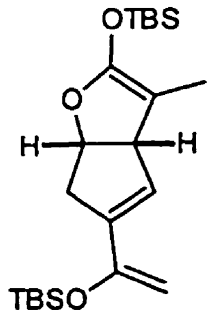
51 **52**

51:52 = 4:1

moderate yield (58%) simply by refluxing it with isopropenyl acetate in the presence of (±)-camphorsulfonic acid.[36]

As soon as diene **50** was obtained, its Diels-Alder cyclization with 2,6-dimethyl-1,4-benzoquinone (**13**) was examined. It was found that no reaction occurred between **50** and **13** in refluxing benzene, the conditions employed by Valenta *et al.*[26] However, a sluggish reaction was observed in refluxing toluene (Scheme 13). After 12 days at reflux, a mixture of two products in a 4:1 ratio was obtained in 50% yield. The two products proved to be inseparable by flash chromatography, but their structures were tentatively assigned as **51** and **52**, with **51** being the major. The reasoning for these assignments will appear later.

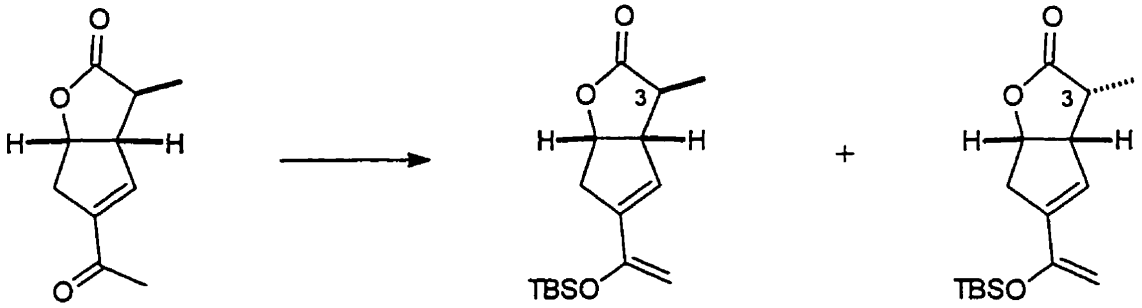
The results of the Diels-Alder reaction of diene **50** and quinone **13** indicated that diene **50** was not sufficiently reactive and regioselective, though the *endo*- and facial selectivities of the reaction were good. In order to increase the reactivity and regioselectivity of the diene **50**, we decided to replace the acetoxy group in **50** with a silyloxy group. To do so, we needed a base to generate an enolate. Initially we thought a commonly used base like LDA might show poor selectivity between a proton α to an enone carbonyl and a proton α to a lactone carbonyl. Furthermore, even though the methyl group α to the lactone carbonyl in enone **49** might engender steric hindrance and make LDA or other bulky base selective to the proton α to the enone carbonyl, an aldol side reaction between the generated enolate and the lactone carbonyl might be a problem. Therefore, we thought it would be a good idea to use two equivalents of LDA and two equivalents of tri-*tert*-butyldimethylsilyl chloride (TBSCl) to make ketene acetal diene **53**.



53

The use of trimethylsilyl chloride (TMSCl) was excluded since trimethylsilyl enol ethers are known to be too labile to isolate by chromatography. Nevertheless, diene **53** was never obtained. Instead, diene **54** and its epimer **55** were produced (Scheme 14). Obviously, a carbanion next to the lactone carbonyl had been generated, but the ketene

Scheme 14. Preparation of diene **54** and diene **55**



49 **54** **55**

contions	workup	yield	ratio of product
2 eq. LDA, 2 eq. TBSCl	"wet" pentene	56%	1:6
2 eq. LDA, 2 eq. TBSCl	water	53%	1:1
1 eq. LDA, 1.2 eq TBSOTf	"wet" hexane	85%	6:1

acetal diene **53** could not form, probably due to an interaction between the coplanar methyl and TBSO group in the transition state to **53**. Epimers **54** and **55** could be completely separated by preparative layer chromatography (PLC) or by short flash column chromatography. An interesting observation was that when the reaction was quenched with technical grade pentane, which is referred to as "wet" pentane in Scheme 14, the ratio of **54** to **55** was 1:6, while when quenched with water, the ratio was 1:1. This suggests that when the reaction was quenched with water, both the convex and concave sides of the molecule were surrounded with a large number of water molecules. Rapid quenching of the carbanion with water from both sides would give the 1:1 mixture of diene **54** and **55**. In contrast, when the reaction was treated with technical grade pentane, only a small amount of proton source could be present. The proton source selectively approached and reacted with the carbanion from the less hindered convex side to give diene **55** as a major product. The process in the latter case can be referred to as kinetic protonation, which was used to convert a thermodynamically more stable stereoisomer to its less stable epimer in the synthesis of podophyllotoxin.[37] Theoretically, both diene **54** and diene **55** could be utilized in our synthesis, because the stereogenic center at C-3 will not be present in the final product. However, the combined yields of **54** and **55** in both cases were not satisfactory. Eventually, it was found that diene **54** and **55** could be obtained in 85% yield and in a ratio of 6:1 favoring diene **54** by using one equivalent of LDA and *tert*-butyldimethylsilyl triflate (TBSOTf) as the silylating reagent. The problem of aldol side reactions was solved by introducing LDA to enone **49** in the presence of TBSOTf, so that as soon as a carbanion was generated it was trapped by TBSOTf.

Scheme 15. Diels-Alder cycloadditions of **54**, **55** with **13**

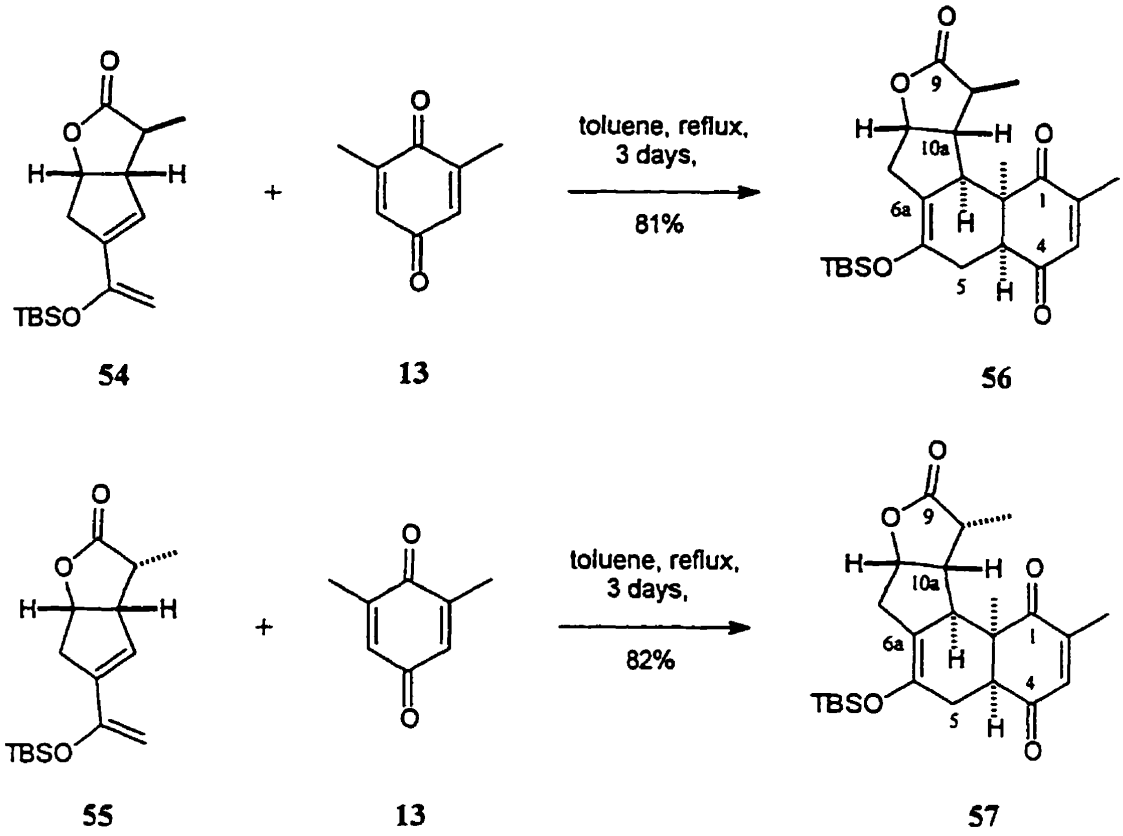
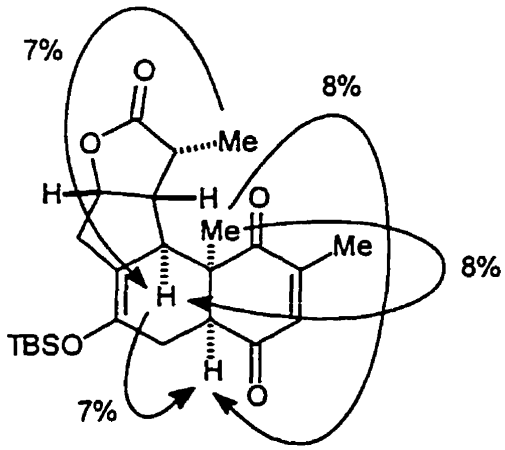


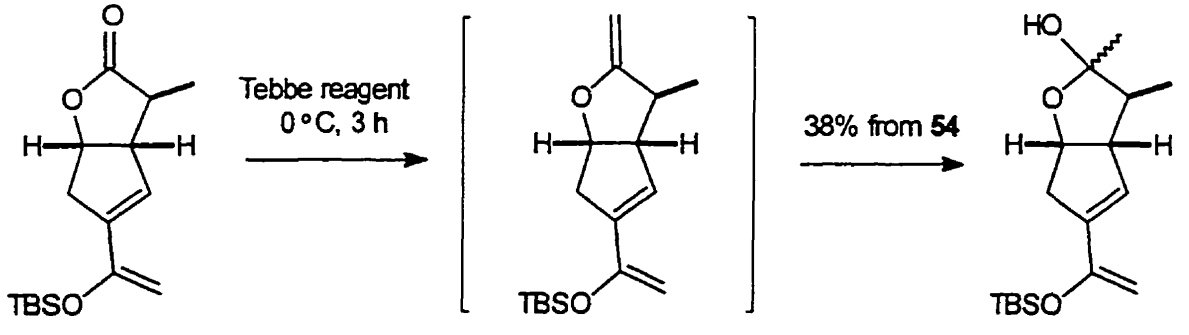
Figure 8. NOE results for **57**



As expected, the silyloxy-substituted dienes were much better than the acetoxy analogue for the Diels-Alder reaction. Both diene **54** and diene **55** gave the desired adducts **56** and **57**, respectively, in over 80% yields by heating with 2,6-dimethyl-1,4-benzoquinone (**13**) in toluene for three days (Scheme 15). The relative stereochemistry of the methyl group in the lactone ring had no effect on the reactivity and selectivities of the dienes. The structures of both **56** and **57** were assigned by 1D and 2D NMR, and they were also confirmed by high resolution MS. NOE results for adduct **57**, which completely verified the stereochemistry of the assigned structure, are shown in Figure 8. In both cases, a small amount of an isomeric by-product was detected by TLC and NMR, but these by-products could not be isolated in pure form. Hence, their structures were not be determined. The ^{1}H NMR spectrum of the crude product from the reaction of **54** with **13** revealed that the ratio of the desired adduct to the isomeric by-product was about 10:1.

After the model Diels-Alder cycloadditions succeeded in high yield and good

Scheme 16. Reaction of **54** with Tebbe reagent

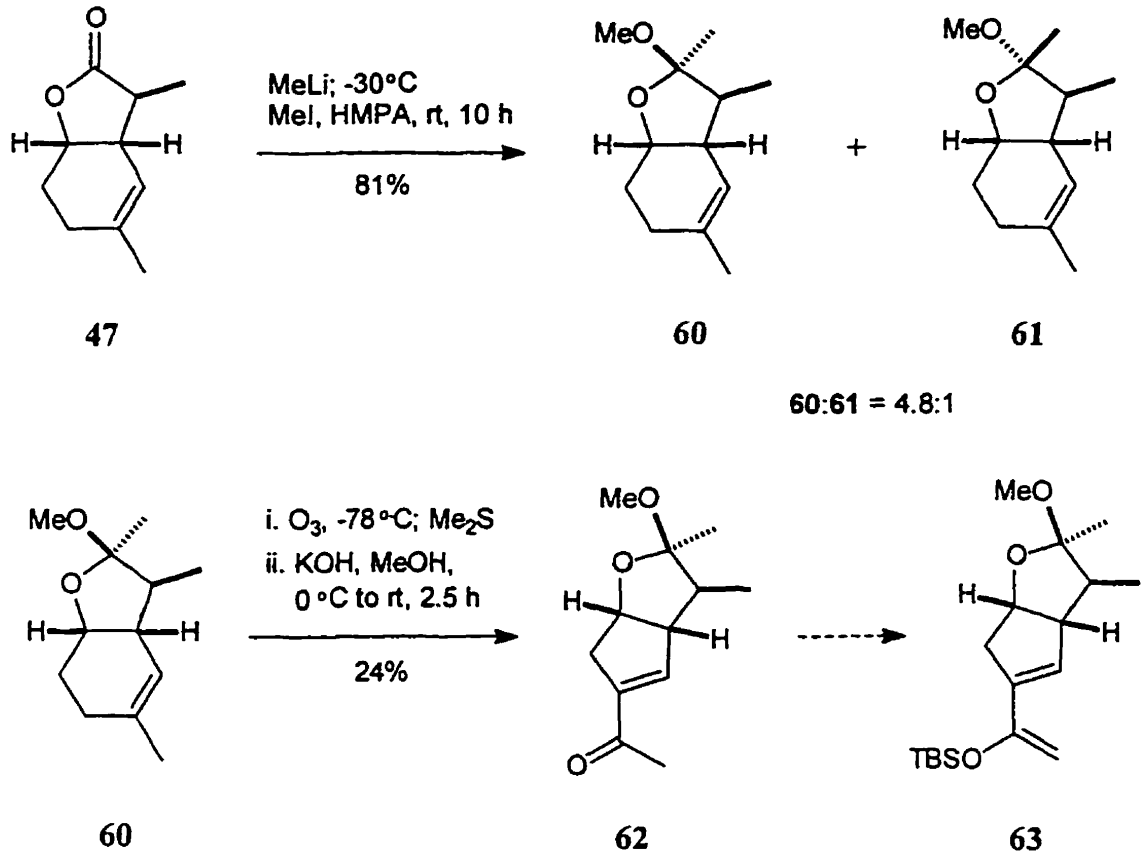


54 **58** **59**

selectivity (Scheme 15), we proceeded to prepare the more complex diene **59**. An initial idea was to convert diene **54** to **58** with the Tebbe reagent, $Cp_2TiCH_2 \cdot AlClMe_2$,[38] as shown in Scheme 16. However, **58** was too unstable to isolate. As a result, a 2:1 epimeric mixture **59** was obtained even after non-aqueous workup and preparative TLC. Diene **59** could play the same role as **58** in our synthesis, but the yield of **59** was only 38%. The low yield of the reaction was probably due to the incompatibility of the Tebbe reagent and silyl enol ether structure in **59**. Tebbe's reagent is a Lewis acid, and it could therefore induce cleavage of the TBSO group.

Our second attempt was to prepare diene **63** from lactone **47** (Scheme 17). This began with an investigation of the addition of methyllithium to **47**. We wondered if it would be possible to add only one equivalent of methyllithium to **47** to provide a cyclic hemi-acetal without ring opening. This proved to be practicable. Treatment of **47** with methyllithium at -30 °C, followed by iodomethane with hexamethylphosphoramide (HMPA) at room temperature for ten hours, afforded acetal **60** and its epimer **61** in 81% combined yield and in a ratio of 4.8:1 in favor of **60**. The relative stereochemistry of **61** was determined by NOE experiments, and that of **60** was assigned by deduction. It was noticed that the addition of methyllithium to **47** was very sluggish below -30 °C. Epimers **60** and **61** could be easily separated by flash column chromatography. It was then intended to convert acetal **60** to diene **63** by the same sequence that was used to prepare **54** and **55** from **47** (Scheme 12 and 14). Unfortunately, this was not successful. Ozonolysis of the double bond in **60** and treatment of the resulting keto-aldehyde with (±)-camphorsulfonic acid did not afford any enone **62**. Base-catalyzed aldol condensation

Scheme 17. Attempts to prepare **63** from lactone **47**



47 **60** **61**

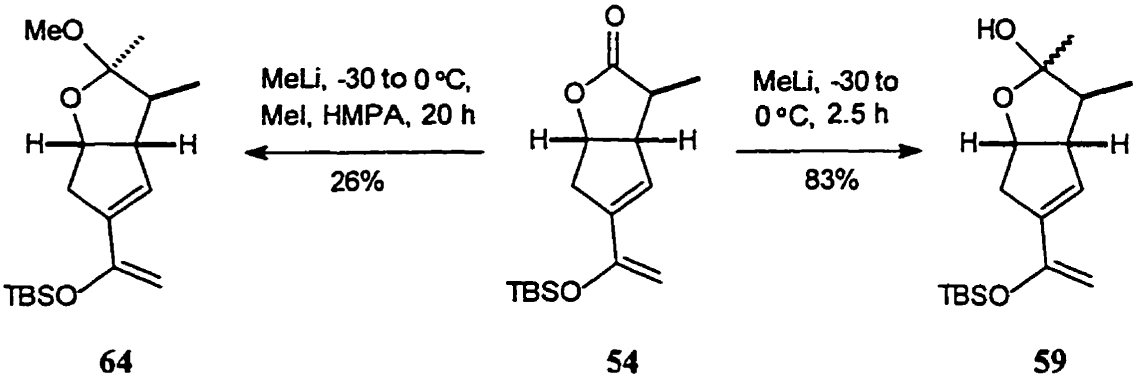
60:61 = 4.8:1

60 **62** **63**

with KOH/MeOH following the ozonolysis of **60** provided **62** in only 24% yield. Hence, this idea was abandoned without attempting to change **62** into **63**.

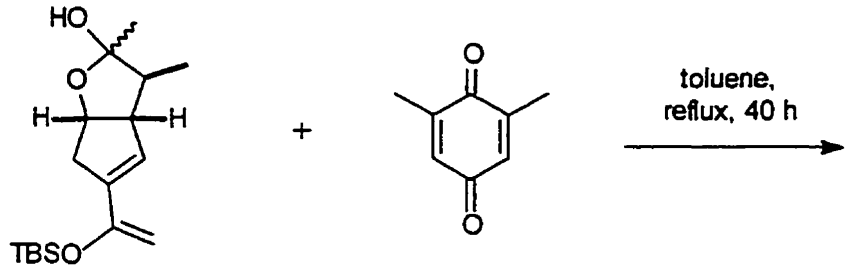
Eventually, it was found that a 2.2:1 epimeric mixture of diene **59** could be prepared in 83% yield from diene **54** by simple addition of methyllithium (Scheme 18). This was somewhat surprising. Methyllithium is commonly employed to generate carbanions from silyl enol ethers,[39] but in our case even though two equivalents of methyllithium were used, the silyl enol ether structure in **55** was not disturbed. The epimers of **59** were chromatographically inseparable, and the stereochemistry at C-2 was

Scheme 18. Preparation of diene 59 and its Diels-Alder reaction with 13

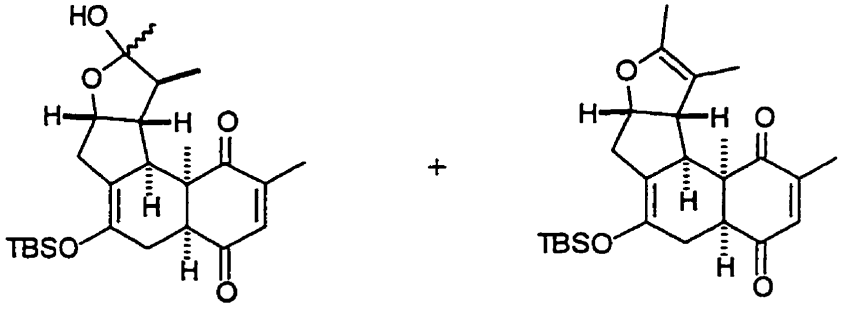


64 54 59

2.2:1 epimeric mixture



59 13



65 (31%) 66 (37%)

not determined in either epimer. Attempts to trap the resulting oxygen anion from the addition of methyllithium to **54**, with iodomethane in the presence of HMPA, as was done very successfully with **47** (Scheme 17), were disappointing. The major methylated

product **64** was obtained in only 26% yield.

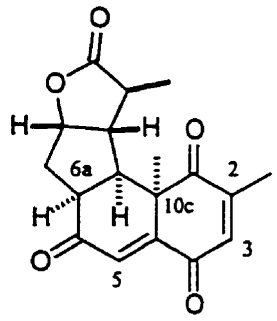
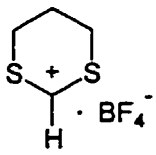
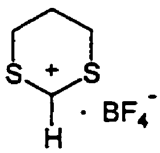
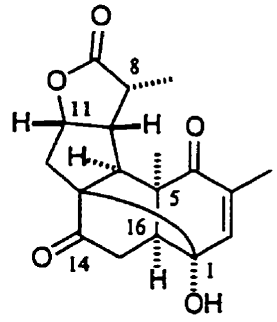
Both of the epimers of **59** were expected to be utilized in our synthesis. Their Diels-Alder cycloaddition with 2,6-dimethyl-1,4-benzoquinone (**13**) was shown to proceed in the same selective manner as dienes **54** and **55**, though two products **65** and **66** were isolated in a ratio of approximately 1:1. Compound **66** might have been produced from **65** by elimination of water by heat. It was also possible that the elimination of water from **59** occurred first and then the resulting diene reacted with **13** to give **66**.

1. 2. 3. Attempts to Methylate Diels-Alder Adducts 56 and 57

Diels-Alder adducts **65** and **66** possess all the annular carbons for the kempane diterpenoids. What was needed to elaborate **65** and **66** into the natural products was to epimerize the stereogenic center at C-4a, to install a methyl group at C-6a, and to cyclize the seven-membered ring. Since **65** and **66** contain a silyl enol ether structural unit, we hoped that it would provide a chance to introduce the 6a-methyl group for the synthesis of kempane **1**. For the synthesis of kempane **2**, the introduction of the 6a-methyl group at this stage would make it difficult to achieve the correct stereochemistry at C-6.[18] For the same reason that we initially used diene **35** instead of **32** to examine the desired Diels-Alder cycloaddition, we now used **56** and **57** to investigate direct or indirect methylation of the silyl enol ether. We attempted a number of methods, but, unfortunately, none of them worked. The results are summarized in Table 1.

Direct methylation of **56** with iodomethane and silver trifluoroacetate[40] gave starting material **56** back after overnight reflux in dichloromethane. The use of the

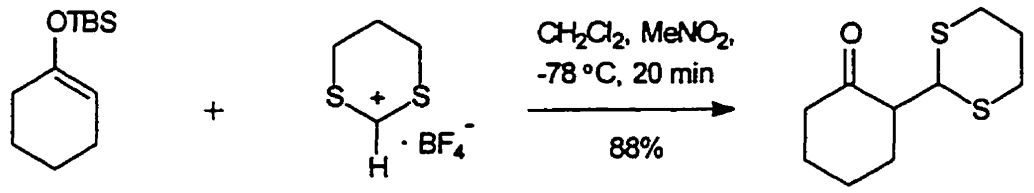
Table 1. Attempts to methylate the silyl enol ether in **56** and **57**

Substrate	Reagents and Conditions	Products
56	MeI, CF_3CO_2Ag, CH_2Cl_2, reflux, 12 h	starting material
56	CH_2I_2, Et_2Zn, THF, 50°C, 10 h, or CH_2Cl_2, reflux, 10 h	mainly starting material
56	$MeOCH_2Cl$, $TiCl_4$, rt, 12 h	very complex mixture
56	$PhSCH_2Cl$, $TiCl_4$, -15°C, 2 h, rt, 1.5 h	 **67**
56	 **68** CH_2Cl_2, $MeNO_2$, -78°C, 20 min	one major initial product, but too unstable to characterize
57	 **68** CH_2Cl_2, $MeNO_2$, -78°C, 20 min	 **71**

Simons-Smith reaction, followed by a cyclopropane ring opening, as an indirect method to methylate enol ethers has been well documented.[41] However, **56** was found to be inert to CH_2I_2, Et_2Zn either in THF at 50 °C or in dichloromethane at reflux. Another indirect methylation of silyl enol ethers involves the use of an activated methylating reagent in combination with a Lewis acid. Thus, **56** was treated with methoxymethyl chloride in the presence of titanium tetrachloride[42] at room temperature for twelve hours. None of the desired product was obtained, but a very complex mixture was produced. After **56** was exposed to phenylthiomethylchloride with titanium tetrachloride[43] at -15 °C for two hours and then at room temperature for one and half hours, a yellow crystalline product **67** was isolated in 51% yield. The structure of **67** was assigned by the analysis of NMR spectra. Its ^1H NMR spectrum (CH_2Cl_2) presented two alkenic protons at δ 7.10 and 6.40. In its COSY spectrum a long range coupling from 2-methyl indicated the proton resonating at δ 6.40 was H-3. The ^{13}C NMR spectrum (CD_3COCD_3) showed **67** contained three conjugated carbonyls, at δ 199.6, 198.9, and 186.3, along with the lactone carbonyl at δ 180.3. It was also apparent that **67** contained four alkenic carbons. The stereochemistry of the newly generated stereogenic center C-6a was revealed by NOE experiments. A NOE of 10% on H-6a was observed when the ^1H signal of the 10c-methyl was irradiated. The formation of **67** was probably a consequence of the cleavage of the silyl enol ether structure in **57** with titanium tetrachloride, followed by an aerial oxidation of the resulting 1,4-dione.

1, 3-Dithienium tetrafluoroborate (**68**) is an excellent electrophile, first prepared in Corey's group.[44] It usually reacts with silyl enol ethers at low temperature to give very

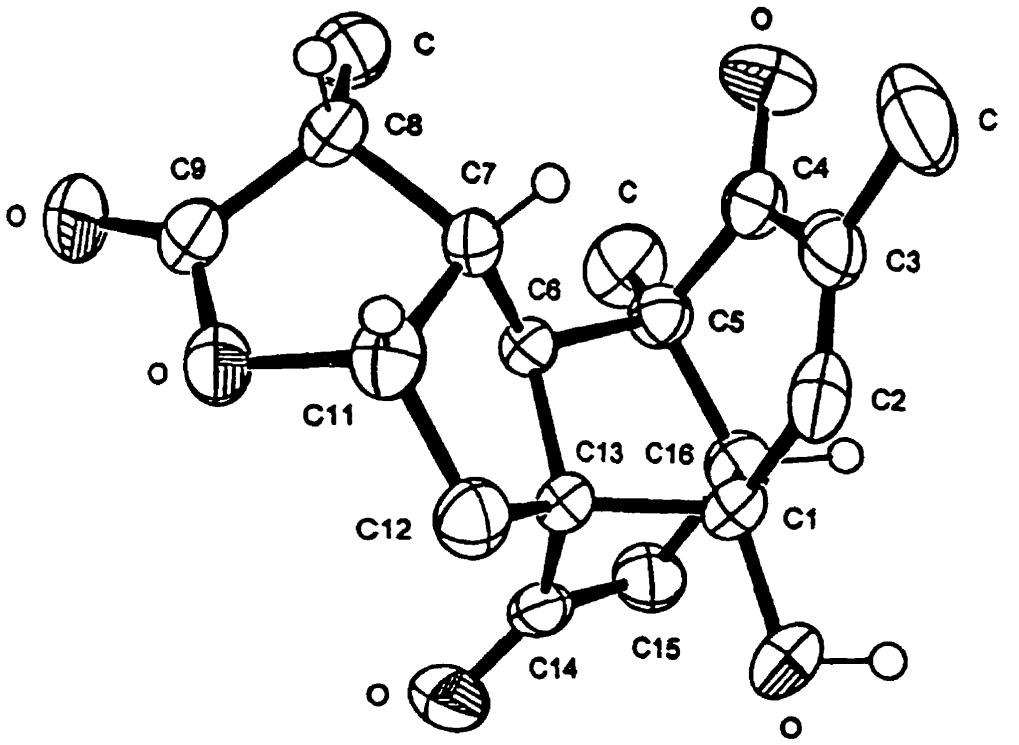
Scheme 19. Reaction of 1,3-dithienium fluoroborate (68) with 69



69 68 70

high yields of products.[45] For instance, as a test of the quality of the **68** that we prepared, it was reacted with silyl enol ether **69** at -78 °C for 20 minutes and it provided **70** in 88% yield (Scheme 19). However, when **68** was applied to **57** under the same conditions, none of the desired product was detected. Instead, an unexpected pentacyclic compound **71** was isolated in 48% yield. The structure of **71** was revealed by an x-ray crystallographic study (Figure 9). The formation of **71** could be regarded as a consequence of an intramolecular Mukaiyama reaction of **57**. This reaction was probably promoted by the 1,3-dithienium by activation of the carbonyl at C-4. In contrast, when **68** was reacted with **56**, TLC indicated that one major product was formed, but this initial major product was too unstable to isolate and characterize. During workup and PLC it decomposed into many components. The difference in behavior to 1,3-dithienium fluoroborate (**68**) between **56** and **57** is probably due to a difference in their conformations. In order to avoid a steric interaction between the 10-methyl and the 10c-methyl groups, **57** may have to assume a more "folded" conformation, in which the silyl enol structure is close to the carbonyl at C-4. On the other hand, the 10-methyl in **56** would impede the approach of C-6a to C-4.

Figure 9. X-ray crystal structure of compound 71

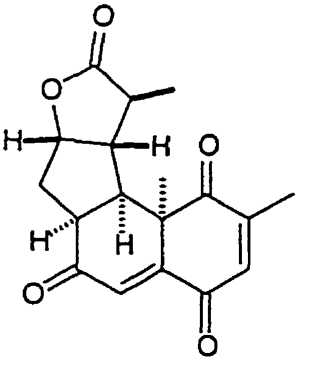


1. 2. 4. Epimerization of the *cis*-Decalin Ring System to the *trans*

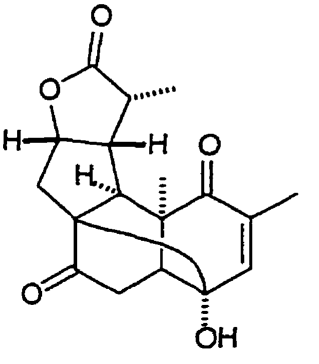
Though the attempts to introduce a methyl group at C-6a in the Diels-Alder adducts **56** and **57** by taking advantage of the presence of silyl enol ether structures failed, the methyl group might still be installed at a later stage. Therefore, Strategy One proceeded with an investigation of the possibility of converting the *cis* ring junction of the Diels-Alder adducts to the *trans* by epimerization at C-4a.

Since the Diels-Alder adducts bear silyl enol ether structures, which are not stable in either acidic or basic media, it was decided that the TBS group should be removed first. It was also envisaged that after the silyl enol ether was hydrolyzed, the energy difference

between the *cis* and *trans* ring systems would be more favorable for the desired epimerization to occur. However, this hydrolysis turned to be unexpectedly difficult. With **56** and **57**, we first tried tetrabutylammonium fluoride (TBAF) in THF,[46] 49% aqueous hydrofluoric acid in 1:1 THF and methanol,[47] and $BF_3 \cdot Et_2O$ in dichloromethane,[48] but none of them gave a clean reaction. The products that were isolated and characterized were the pentacyclic compound **71** and the oxidation product **67**, again. Compound **71** was isolated in 30% yield from the reaction of **57** with aqueous hydrofluoric acid. The reaction of **56** with $BF_3 \cdot Et_2O$ provided **67** in 46% yield. Nevertheless, it was found that treatment of **56** with 5% aqueous hydrochloric acid could afford **67** in moderate yield (61%).



67



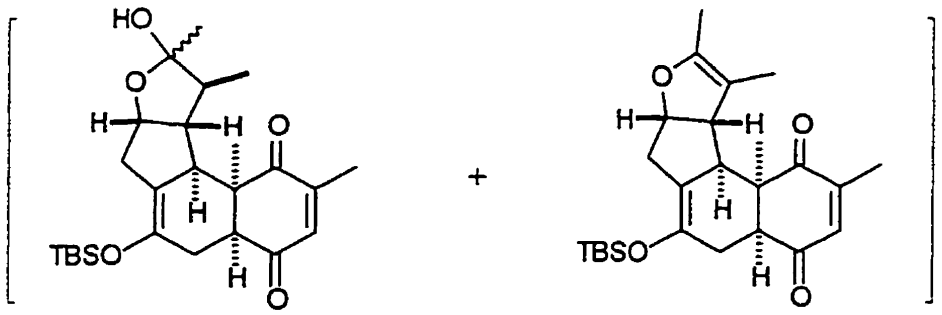
71

Similarly, when the crude mixture of **65** and **66**, produced from the Diels-Alder reaction of diene **59** and 2,6-dimethyl-1,4-benzoquinone (**13**) (Scheme 18), was treated with 5% aqueous hydrochloric acid, compound **72** was isolated as a mixture of stereoisomers at C-9 and C-10 in 52% yield based on diene **59**. The stereoisomers at C-10 have resulted from facially indiscriminate hydration of the double bond between C-9

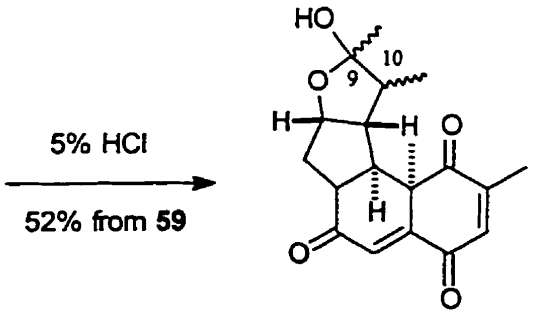
and C-10 in **66**. Though the mixture was inseparable by flash chromatography, the NMR spectroscopic analysis clearly indicated that a double bond had formed between C-4a and C-5 in the components of the mixture. For example, in the ^{13}C NMR spectrum ($CDCl_3$) the major isomer displayed three conjugated carbonyls at δ 200.3, 197.6, and 185. 5, which were consistent with δ 199.6, 198.9, and 186.3 in the ^{13}C NMR spectrum of **67**. The ^{13}C NMR spectrum also showed all the isomers having four alkenic carbons, and their chemical shifts were similar to those in **67**.

Since the anticipated product **73** was never obtained from **56** or **57**, we decided to

Scheme 20. Reaction of **65** and **66** with 5% aqueous HCl

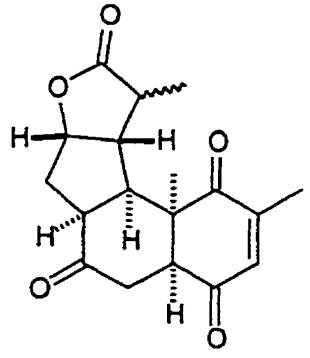


65 **66**

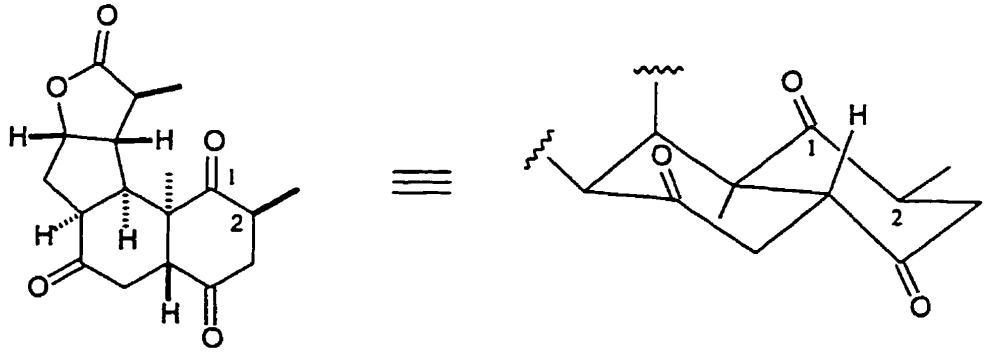


72

employ **72** to carry out our synthesis and to utilize **67** to examine the epimerization. It was believed that the two C=C double bonds could be reduced in one pot and the resulting saturated trione might be epimerized. After this process an imagined thermodynamically stable product **74**, in which the *trans*-decalin ring system assumed a chair-chair conformation and the methyl group at C-2 was in the equatorial position, was expected. In other words, after this process two new desired stereogenic centers at C-2 and C-4a could be obtained. It was also hoped that the reduction of the C=C double bonds in **67** might directly produce **74** and a separate epimerization step might be unnecessary.



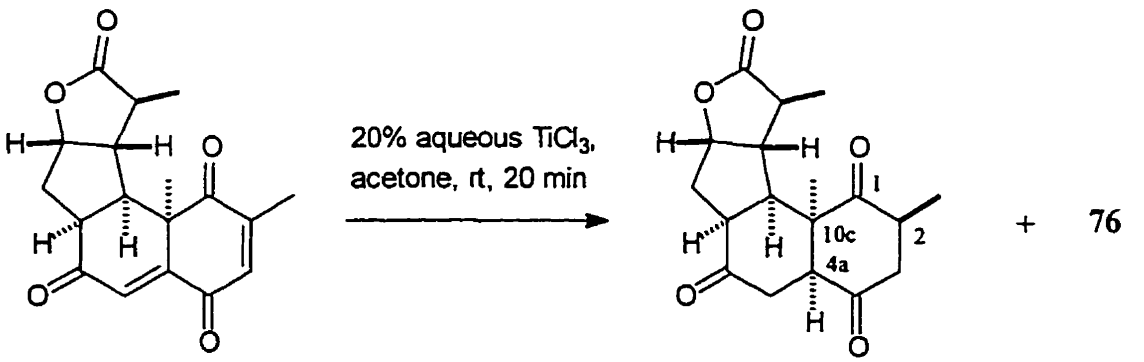
73



74

Thus, compound **67** was treated with 20% aqueous $TiCl_3$ solution.[49] The reaction took place smoothly. After 20 minutes of stirring at room temperture, **67** was completely consumed to give two products, as shown by TLC. Neither was UV active. The more polar, major product was isolated in 50% yield, and its structure was established as **75**, in which the decalin ring system was still *cis*-fused while the stereochemistry at the other newly generated stereogenic center at C-2 was correct. The stereochemistry of the structure was assigned on the basis of NOE measurements, as follows. When the ^1H NMR signal for the 10c-methyl group was irradiated, the signals for H-2 and H-4a were enhanced by 3% and 8%, respectively. The structure of the minor product was not determined at this point because of its small amount and a lack of purity. (However, it was later confirmed to be **76**.)

Scheme 21. Reduction of **67** with $TiCl_3$

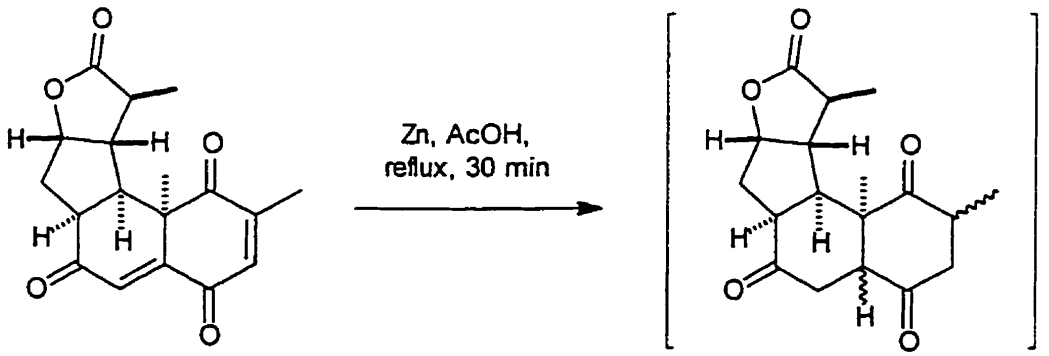


67 **75** (50%) + **76**

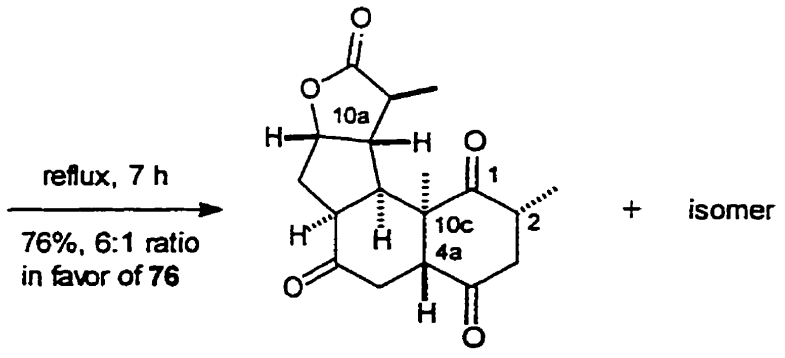
Reduction of **67** with zinc in refluxing glacial acetic acid[50] led to a similar result. However, after the reaction mixture was refluxed for seven hours, the initial major product was changed into the initial minor product. This product was isolated by

chromatography in 76% yield based on **67**, but it was revealed by ^{1}H and ^{13}C NMR spectroscopy to contain two isomers in a ratio of 6:1. An analytical sample of the major isomer was obtained by recrystallization from 4:1 dichloromethane and ethyl acetate. A homogenous sample of the minor product was not obtained. Careful analysis of the NMR spectra of the major isomer indicated that it was **76**. The *trans*-decalin ring system was obvious by NOE measurements between H-4a and H-10a. Each of them received an enhancement of 9% when the other proton was irradiated. ^{1}H NMR spectroscopy was also very indicative. In the case of *cis*-isomer **75**, the ^{1}H NMR signal for the 10c-methyl

Scheme 22. Reduction of **67** with Zn/AcOH and subsequent epimerization



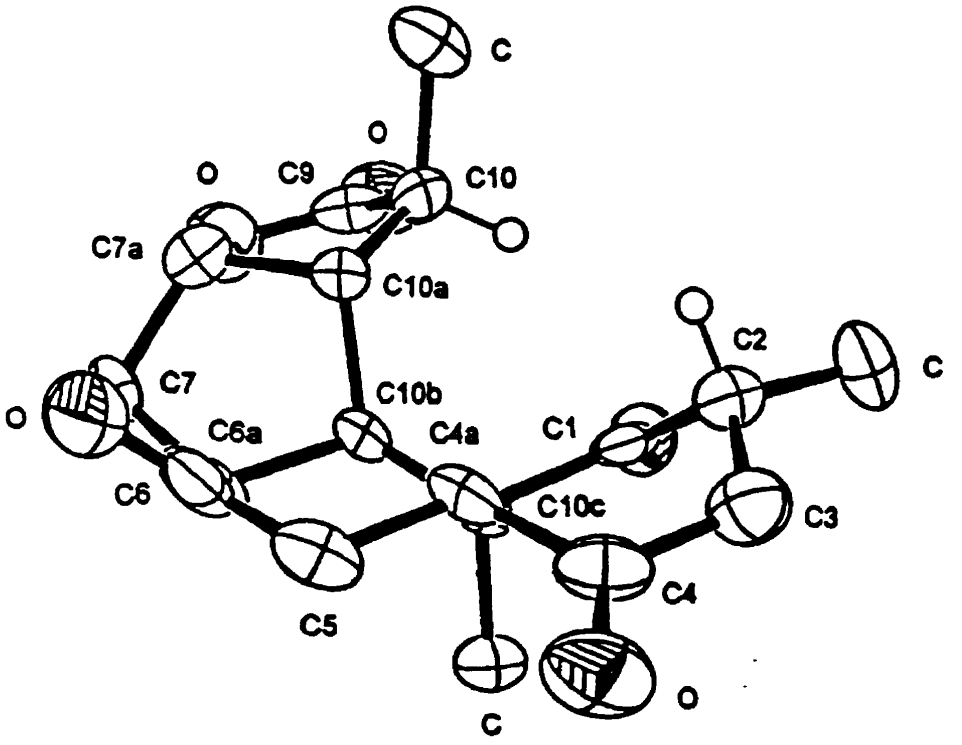
67



76

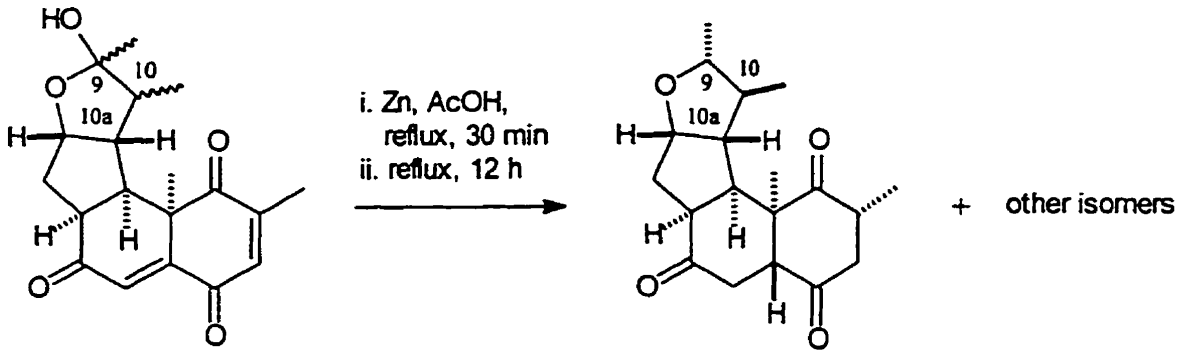
appears at unusually low field: δ 1.68. This is probably because the *cis*-junction is flexible and the 10c-methyls can assume the equatorial position. When the 10c-methyl is in the equatorial position, it is approximately coplanar with the carbonyl group at C-1. Consequently, the anisotropic effect of the carbonyl, albeit not very strong due to the distance, caused the 10c-methyl group to move downfield. However, after the *cis* ring junction was epimerized to the *trans*, the *trans*-junction is rigid so that the 10c-methyl group can only take the axial position and will experience less or no anisotropic effect of the carbonyl at C-1. In addition, when it is in the axial position, the 10c-methyl group is right beneath the *trans*-decalin ring system and it is shielded. Both the absence of the anisotropic effect and the shielding will shift the 10c-methyl in the *trans*-isomer upfield. In fact, the 10c-methyl in **76** appears at δ 1.30. The structure of **76** was verified by x-ray crystallography (Figure 10). Obviously, during reflux in acetic acid an epimerization process occurred. However, contrary to our expectation, the methyl group at C-2 is *syn* to the axial methyl at C-10c, even though the decalin ring junction is *trans*. X-ray crystallography showed that the cyclohexanedione ring in **76** does not adopt a chair but a boat conformation, in which the methyl group at C-2 is placed in the *pseudo*-equatorial position that is, nevertheless, *syn* to the C-10c methyl. The cyclohexanedione ring in **76** adopts the boat conformation presumably because in a chair conformer, the carbonyl at C-1 is situated in the same plane as the cyclopentane ring, and this will engender a serious steric interaction. The boat conformation of the cyclohexanedione ring allows **76** to assume a spiral shape, in which the steric interaction between the carbonyl at C-1 and the cyclopentane ring is much reduced, as seen in Figure 10.

Figure 10. X-ray crystal structure of compound **76**



When the same sequence, zinc reduction in refluxing glacial acetic acid and the subsequent epimerization, was applied to the stereoisomeric mixture **72**, it gave three products, as shown by TLC. The major product was isolated in 33% yield and was assigned structure **77**, in which the decalin ring system has a *trans*-junction and the methyl group at C-2 is *syn* to the C-10c methyl, just as in **76**. During the transformation of **72** to **77**, the 9-hydroxy group in **72** was reductively cleaved. It could also be deduced from **77** that the major component in mixture **72** had its 10-methyl group *syn* to H-10a. The structures of the two minor products were not determined because pure samples were not obtained.

Scheme 23. Reduction of 72 with Zn/AcOH and subsequent epimerization



72 77 (33%)

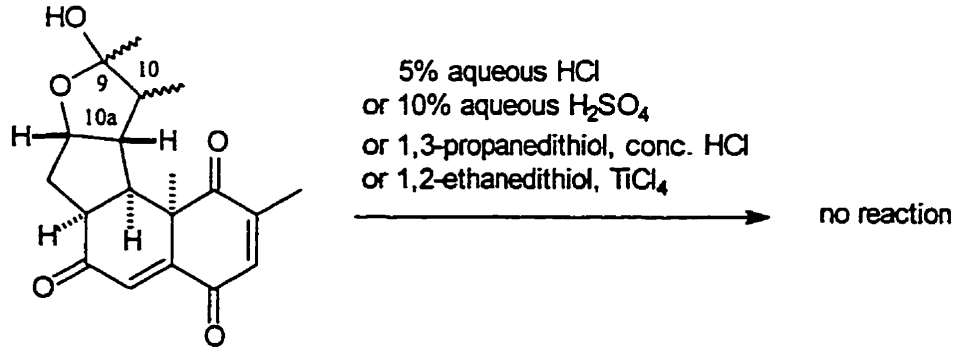
The results presented in schemes 22 and 23 successfully demonstrated that the *trans* decalin ring system in kempane diterpenes could be obtained from a *cis*-ring junction by epimerization. However, two unexpected concerns were revealed. One was that during the reduction of **72** with zinc in refluxing acetic acid, the 9-hydroxy group was cleaved to give a tetrahydrofuran ring, which would be difficult to open in order to provide a chain for the final cyclization of the seven-membered ring. This problem might be solved by reduction of **72** with aqueous $TiCl_3$, which could be conducted at room temperature. The other concern was the stereochemistry at C-2 in **76** and **77**, which was opposite to what was desired. It was considered that if the final cyclization were accomplished with a molecule like **77**, the stereogenic center at C-2 might be very difficult to correct later. One possible solution to this problem was to open the hemi-acetal ring and cyclize the final seven-membered ring before any reduction and epimerization. It was hoped that after this final cyclization a tetracyclic product might be easier to modify to the natural skeleton of the kempane diterpenes. Accordingly, Strategy

One moved to another stage: the cyclization of **72** to form the seven-membered ring.

1. 2. 5. Attempts to Cyclize the Seven-membered Ring in 72

In order to cyclize the seven-membered ring in **72**, we first needed to open the five-membered hemi-acetal ring. It was realized that a five- or six-membered hemi-acetal is sometimes very stable. To open such rings, one generally is required to trap irreversibly the resulting carbonyl from the ring opening in a protected form. It was hoped that when **72** was treated with dilute aqueous acid, the five-membered hemi-acetal ring would be opened at least reversibly, and the resulting methyl ketone would undergo the final cyclization by an aldol condensation under the same conditions. If the aldol condensation would also be accompanied by the elimination of water, the whole process would be irreversible. However, hemi-acetal **72** proved to be very stable. No change was detected after heating it in either 5% aqueous hydrochloric acid or 10% aqueous sulfuric acid at 80-90 °C for twelve hours.

Scheme 24. Attempts to open the five-membered hemi-acetal ring in **72**



72

Corey's group employed 1,3-propanedithiol and concentrated hydrochloric acid to open a six-membered hemi-acetal in the synthesis of (−)-*N*-methylmaysenine.[51] Paquette's group found that five-membered hemi-acetals were even more difficult to open than six-membered hemi-acetals, and they developed a procedure in which 1,2-ethanedithiol and titanium tetrachloride were used to surmount this difficulty.[52] Unfortunately, neither of these procedures worked in our case, and only starting material **72** was recovered (Scheme 24).

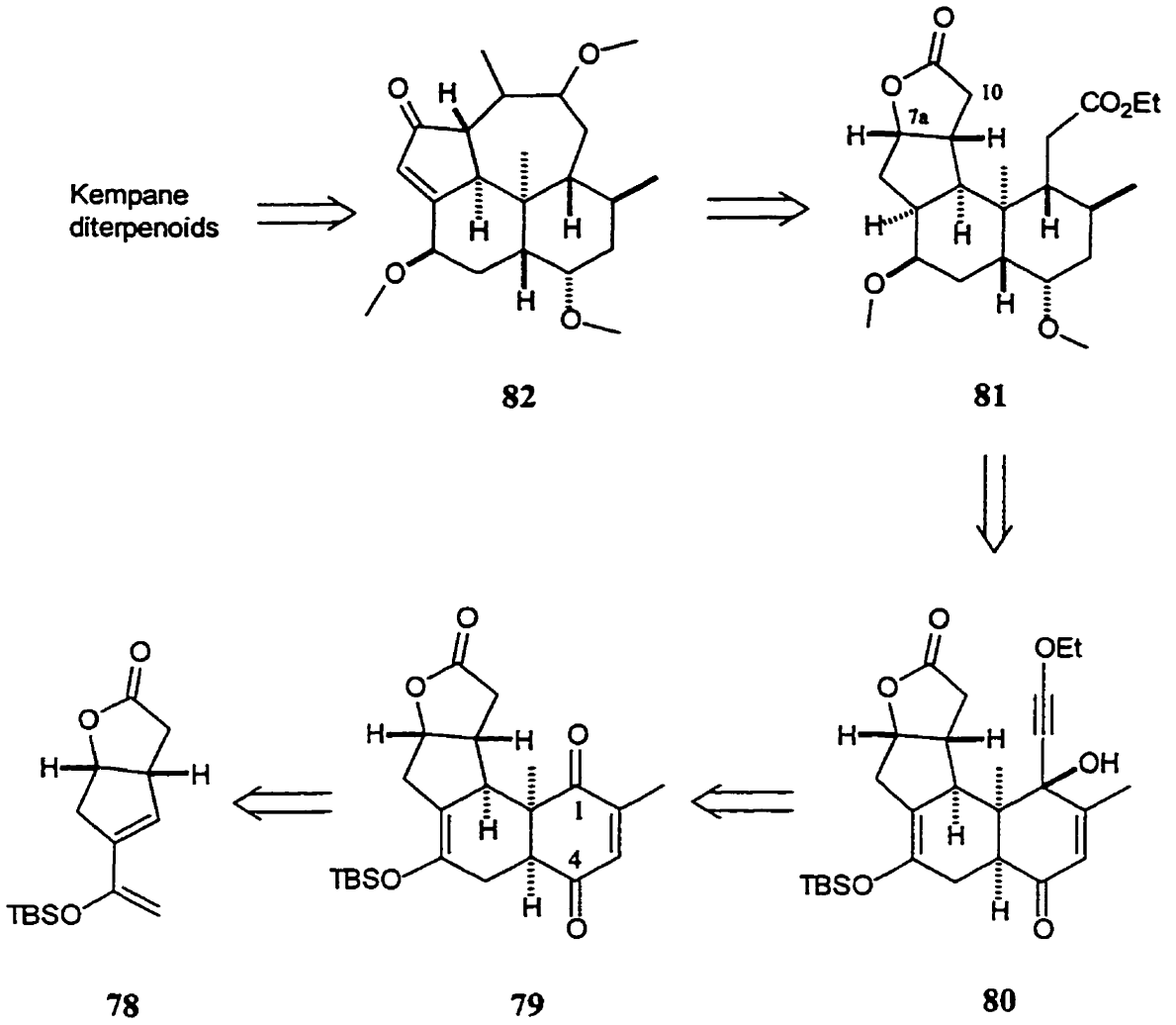
Strategy One was composed of four main ideas: the Diels-Alder reaction to establish the benzoindane ring system, the methylation of the resulting enol ether to introduce an angular methyl group, the epimerization to change the *cis*-decalin ring junction to the *trans*, and the aldol cyclization to construct the seven-membered ring. The following conclusions can be drawn from our efforts with Strategy One: The Diels-Alder reaction proceeded in high yield with high *endo*-, regio-, and facial selectivities under the conditions of refluxing in toluene for three days when the enol portion of the diene was trapped as a silyl enol ether (Scheme 15 and 18). The epimerization of the *cis*-decalin system could be achieved with acid (Scheme 22 and 23). However, the methylation was not feasible (Table 1), and the aldol cyclization could not be carried out because of the difficulty in opening the five-membered hemi-acetal ring in **72**.

1. 3. Strategy Two

1. 3. 1. Retrosynthetic Analysis

Our modified strategy, which will be referred to as Strategy Two, was based on our experience with Strategy One, and it is outlined in Scheme 25. The Diels-Alder reaction of diene **78** with 2,6-dimethyl-1,4-benzoquinone (**13**) would be employed as an early key step to construct the benzoindane ring system **79**. We believed that this Diels-Alder reaction would occur in the same manner as did the Diels-Alder reaction of diene **54** or **55** with **13** (Scheme 15). The only difference between diene **78** and **54** or **55** was that dienes **54** and **55** each had a methyl group α to the lactone carbonyl. However, we had already shown that the methyl group α to the lactone carbonyl had no significant effect on the reactivity and selectivity of the dienes (Scheme 15). Instead of an aldol cyclization for the formation of the seven-membered ring, a regiospecific Dieckmann condensation between the C-10 and the ester carbonyl was planned with molecule **81**. The regiospecificity of this Dieckmann condensation was expected based on the fact that the lactone carbonyl could not be reached by the carbon α to the ester carbonyl due to the rigidity of the molecule. After reductive opening of the lactone, the resulting hydroxy group at C-7a would be oxidized to a carbonyl, and the latter would be utilized to generate an enone system in molecule **82**. Then, the last methyl group was expected to be installed by 1,4-addition. The dome-like shape of the molecule should ensure that the addition would take place from the convex side. It was realized that the Michael acceptor **82** may be a little congested, but it was noticed that Flemming *et al.* had developed a procedure that allowed 1,4-addition of a methyl group to very sterically hindered α,β-

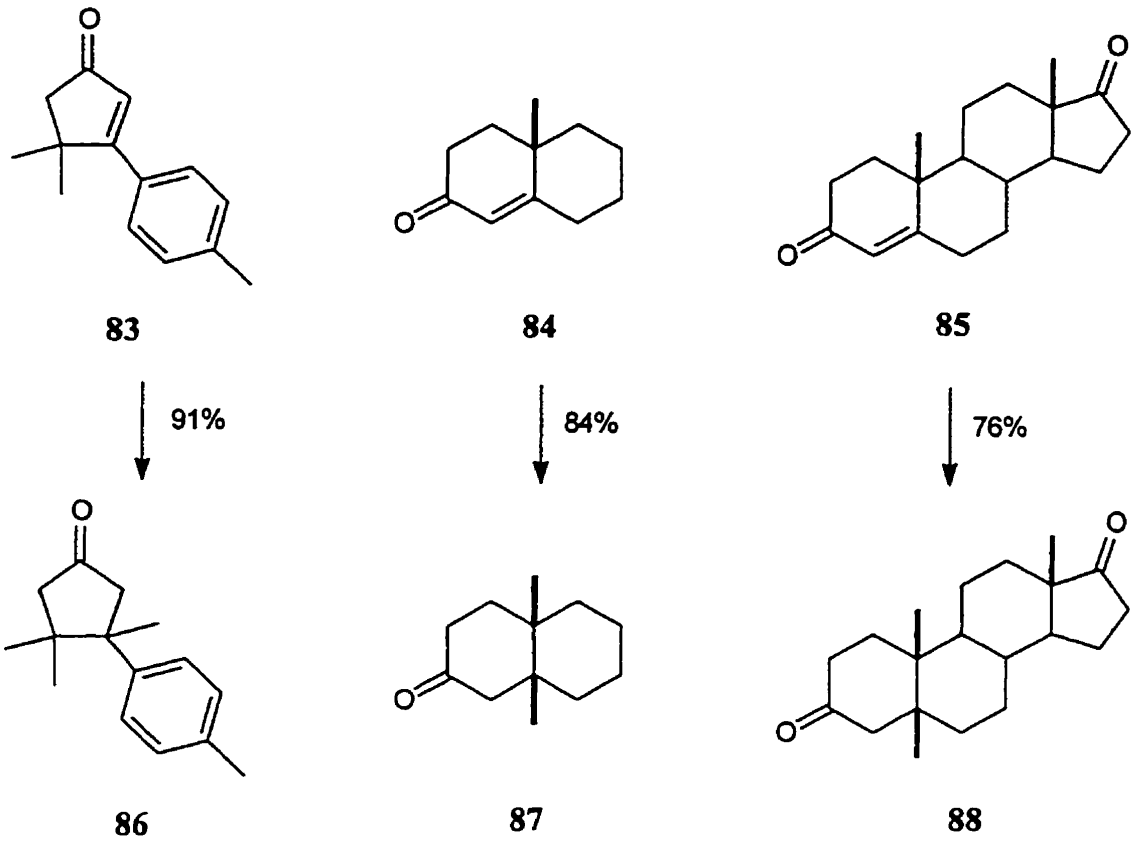
Scheme 25. Retrosynthetic analysis leading to Strategy Two



unsaturated ketones.[53] This procedure used trimethylaluminum as a Michael donor and nickel(II) acetylacetonate [$Ni(acac)_2$] as a catalyst. For example, when α,β-unsaturated ketones **83**, **84**, and **85** were treated with trimethylaluminum in the presence of $Ni(acac)_2$ at 0 °C, Michael adducts **86**, **87**, and **88** were produced in 91%, 84%, and 76% yields, respectively (Scheme 26).

A very daring aspect of Strategy Two was that we wanted to add a two-carbon unit

Scheme 26. $Ni(acac)_2$-catalyzed Michael additions of $AlMe_3$ to hindered enones[53]

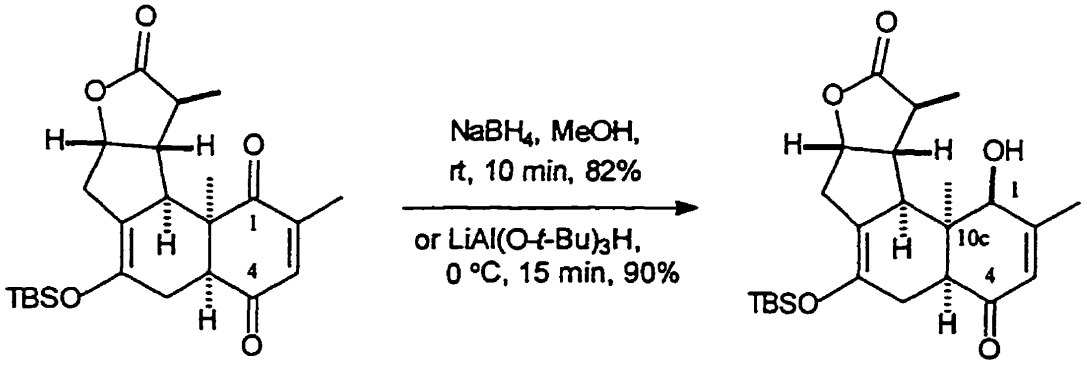


regio- and stereoselectively to the carbonyl at C-1 of enedione **79**. This carbonyl certainly looked much more hindered than the carbonyl at C-4. A high level of stereoselectivity in this addition was not imperative for our synthesis, but it was desired. Precedence for this step was based on both our own reductive experiments[54] during the work with Strategy One and the observations of Liotta and coworkers.[55]

In Strategy One, methylation or hydrolysis of the silyl enol ether **56** or **57** was extremely troublesome. The undesired reactions that occurred were the intramolecular Mukaiyama reaction and the aerial oxidation (Section 1. 2. 3 and 1. 2. 4). We once thought that if the carbonyl at C-4 in **56** or **57** was modified, those undesired reactions

should not take place. We attempted to protect the carbonyl at C-4 in **56** with 1,2-bis[(trimethylsilyl)oxy]ethane in the presence of trimethylsilylmethanesulfonate at -78 °C,[56] but no reaction occurred, and the starting material **56** was recovered. The other way we considered to change the carbonyl was by reduction. We anticipated that the carbonyl at C-4 could be reduced selectively because it seemed much less congested. However, when enedione **56** was treated with sodium borohydride or lithium tri-*tert*-butoxyaluminohydride, the carbonyl at C-1 was reduced with 100% regio- and stereoselectivity, giving **89** as the single product (Scheme 27). The regiochemistry in the reduction was obvious by the chemical shift of H-3, which was at δ 5.83, in the ^{1}H NMR spectrum of the product. If the carbonyl at C-4 were reduced, the signal of H-3 should have appeared around δ 6.5. The stereochemistry in the reduction was determined by NOE measurements. An enhancement of 2% on the 10c-methyl group was detected when the signal for H-1 was saturated. This regio- and stereoselectivity in the reductions of cyclic enediones proved to be general (Part Two).

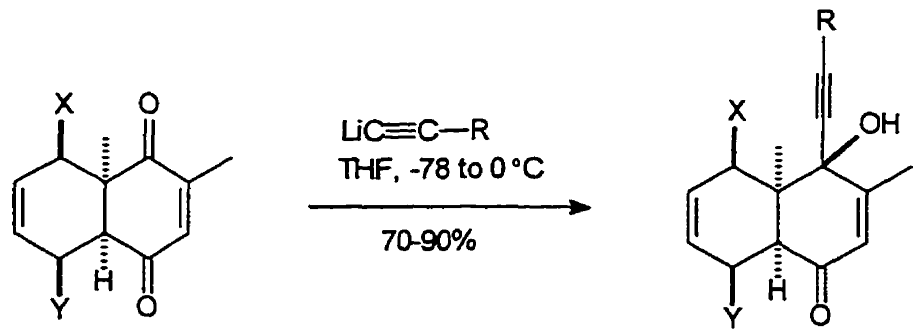
Scheme 27. Highly regio- and stereoselective reduction of **56**



56 **89**

While we wondered if the observed regio- and stereoselective reduction could be extended to nucleophilic addition of acetylide, we found Liotta and coworkers' report[55] that additions of lithium acetylides to bicyclic enediones displayed the same regio- and stereoselectivities as we had observed in our reductions. As shown in Scheme 28, a number of different lithium acetylides reacted with enedione **90** to give carbinols **91** as the sole isolated products in 70-99% yields. Accordingly, the transformation of **79** to **80** in Scheme 25 was designed. Ethoxyacetylide was chosen as the two-carbon nucleophile because the product could be solvolyzed to the ester that would be required for the Dieckmann condensation to form the seven-membered ring.

Scheme 28. Literature example of monoaddition of acetylides to bicyclic enedione **90**[56]



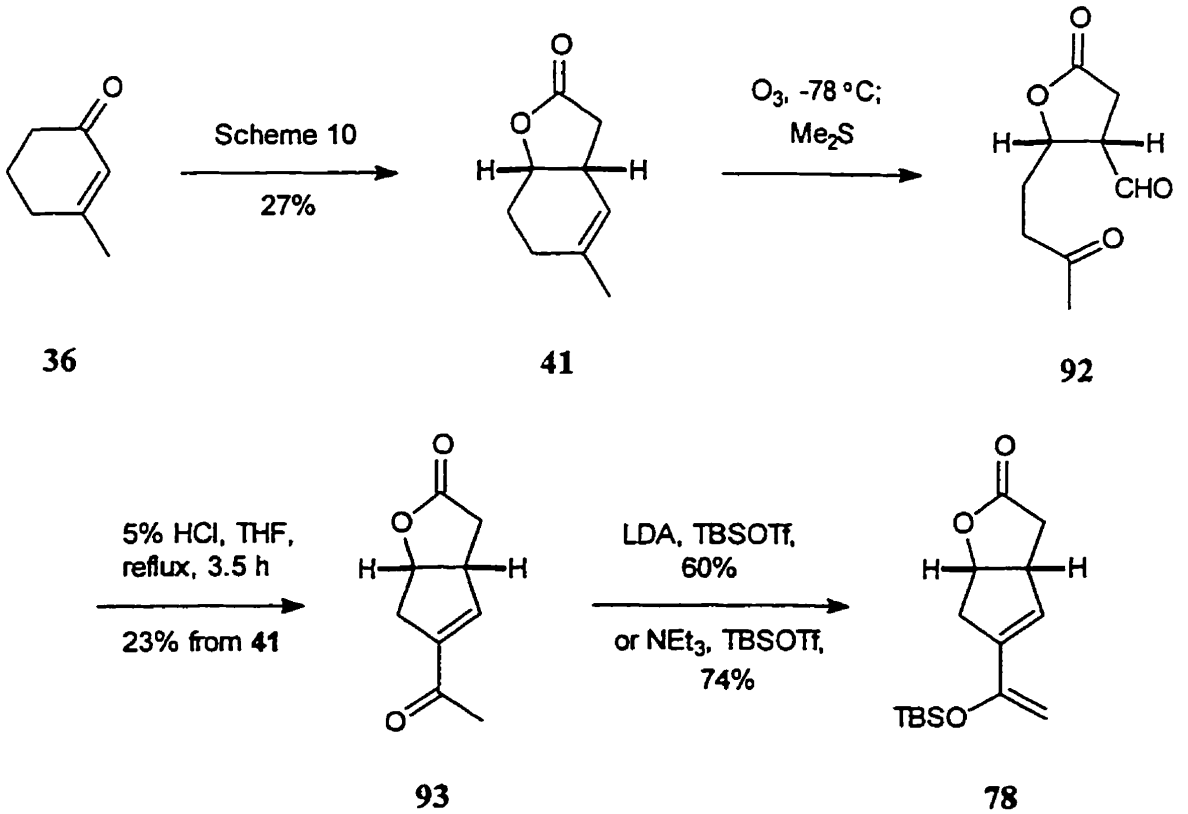
90 **91**

1. 3. 2. Synthesis of the Kempane Diterpene Ring System

The synthetic route to the benzoindane derivative **79** was the same as was used to synthesize **56** and **57** (Schemes 10, 12, 14 and 15), except that the methylation of lactone **41** was omitted. However, this small adjustment proved to be an unforeseen problem in

the application of the previous procedures to transform lactone **41** to diene **78** (Scheme 29). Firstly, when the crude keto-aldehyde **92**, obtained from the ozonolysis of lactone **41** and the subsequent reductive workup, was heated in benzene with a catalytic amount of (±)-camphorsulfonic acid for 24 hours, enone **93** was isolated in only 4% yield based on lactone **41**. It was noticed that even under heating, keto-aldehyde **92** did not dissolve in benzene. Therefore, the reaction was repeated by heating **92** and (±)-camphorsulfonic acid in a 1:2 mixture of 1,2-dimethoxyethane (DME) and benzene. The solubility of **92** was much better in the mixed solvent, but the yield of enone **93** was only slightly improved (7%). This was probably because DME is a Brönsted base, and its presence in

Scheme 29. Synthesis of diene **78** from enone **36**

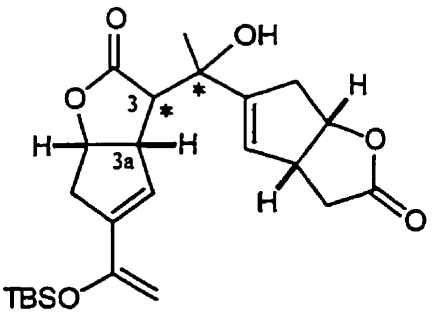


36 **41** **92**

93 **78**

large quantity prevented the camphorsulfonic acid from protonating reactant **92** efficiently. This speculation was confirmed by the replacement of DME with glacial acetic acid in the solvent system for the aldol cyclization. The yield of enone **93** was 21% after **92** was heated with (±)-camphorsulfonic acid in 1:2 glacial acetic acid and benzene for eight hours. A slightly better result (23% yield) was obtained when **92** was heated with 5% HCl in THF for 3.5 hours.[26b]

The second problem encountered was that when enone **93** was treated with LDA in the presence of TBSOTf at -78 °C, the conditions that were successfully used to convert enone **49** to dienes **54** and **55** in 82% combined yield, diene **78** was obtained in only 60% yield. The yield of **78** was even lower (43%) when the reaction was run in a more concentrated solution. It was found that in the absence of a methyl group α to the lactone carbonyl, undesired intermolecular aldol condensations between the carbon α to the lactone carbonyl and the enone carbonyl occurred to a significant extent. One of the by-products was isolated, and its spectra allowed its identification as **94**. Compound **94** was a single stereoisomer, but the relative stereochemistry at both the newly produced stereogenic centers, at C-3 and the carbinol center, was not determined.

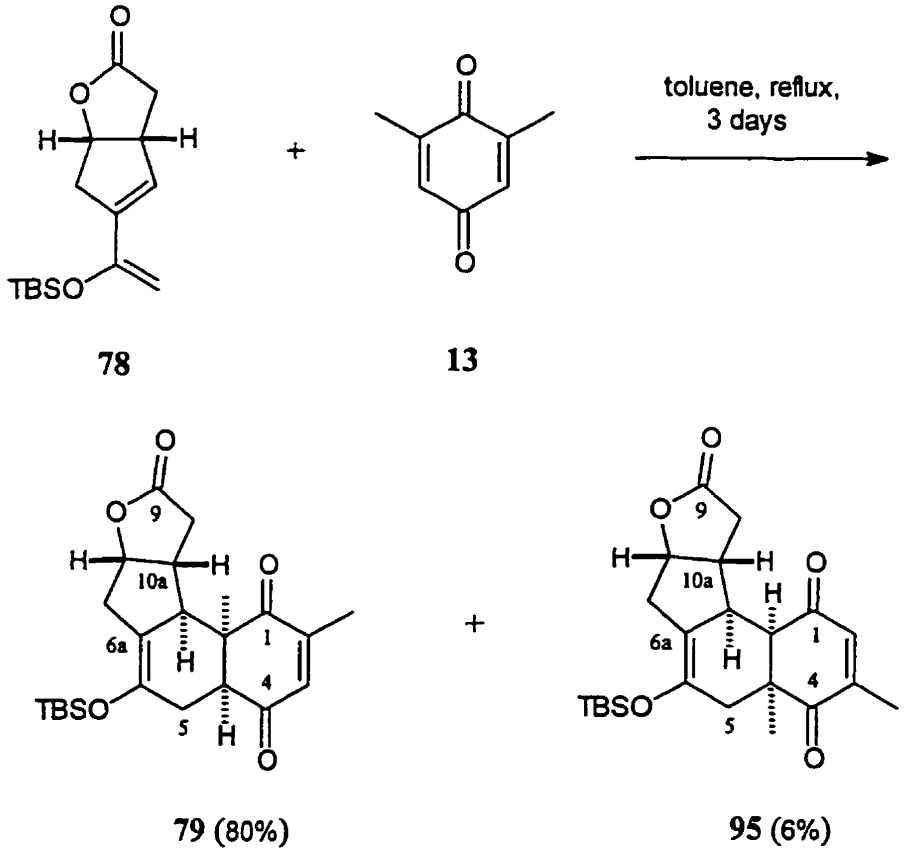


94

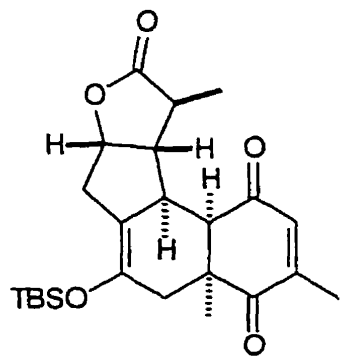
It was likely that when the enolate of lactone **78** reacted with enone **93**, the enolate would approach the enone carbonyl by the convex face, and therefore leave the H-3 *anti* to H-3a in **94**. The problem of the undesired aldol reactions was somewhat diminished by employing a weaker base. A 74% yield of diene **78** was obtained when triethylamine was used at 0 °C for 15 minutes.[57]

As expected, the Diels-Alder cycloaddition of diene **78** with 2,6-dimethyl-1,4-benzoquinone (**13**) proceeded in exactly the same manner as did dienes **54** or **55**. After a mixture of **78** and **13** in toluene was refluxed for three days, the benzoindane system **79**

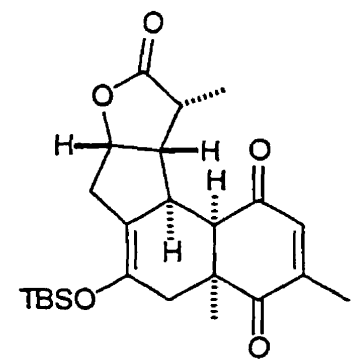
Scheme 30. Diels-Alder reaction of diene **78** and quinone **13**



was isolated in 80% yield (Scheme 30). In this case, however, a homogenous by-product was obtained in 6% yield, and it was assigned as the regioisomeric adduct **95** as follows. In the COSY spectrum of **95** the proton-proton correlation between the H-10b and H-10c was clear, and the H-10c appeared at δ 3.03 as a doublet (J = 5.3 Hz). The stereochemistry of structure **95** was consistent with NOE experiments. The structure was also supported by its high resolution mass analysis. As mentioned in Section 1. 2. 2, a small amount of by-product was also detected in the Diels-Alder reaction of diene **54** or **55** with **13**, but the structures of the by-products were not determined because pure samples were not obtained. By analogy we could now presume that the by-products in the reactions of **54** and **55** with **13** might be **96** and **97**, respectively.



96



97

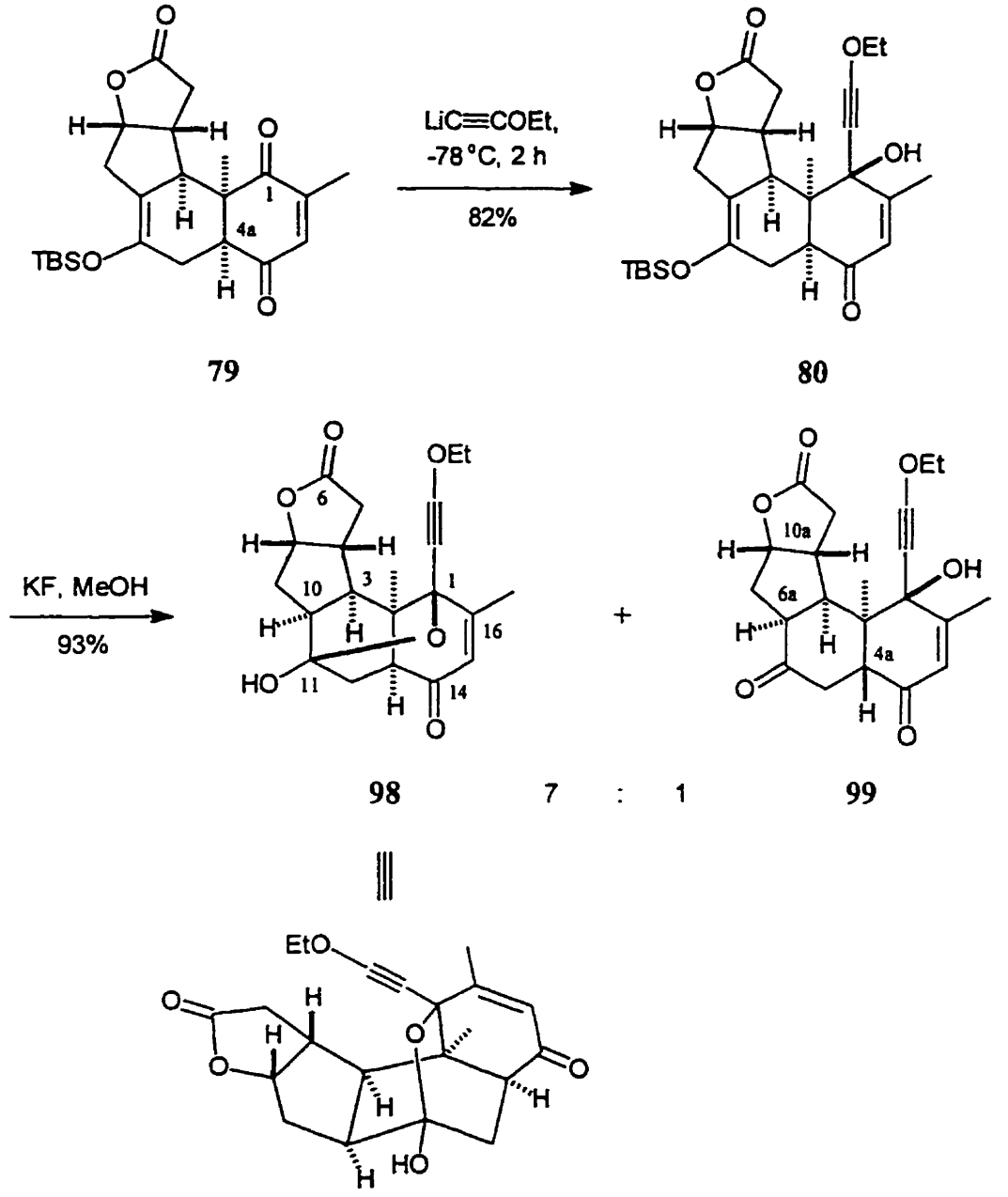
By analogy with the results obtained from the Diels-Alder reaction of diene **78** with **13**, the structures of adducts **51** and **52**, produced in the Diels-Alder reaction of diene **50** with **13** (Scheme 13), could also be tentatively assigned. The difference between diene **50** and **78**, other than the presence of a methyl group α to the lactone carbonyl in **50**, was that the former was an acetoxy-substituted diene whereas the latter was a *tert*-

butyldimethylsilyloxy- (TBSO) substituted one. An acetoxy group should be smaller than a TBSO group, and therefore, a change of TBSO group to acetoxy in the diene should not change the *endo*- and facial selectivities of the Diels-Alder reaction. However, because an acetoxy group had less electron-donating ability, diene **50** could be less reactive and less regioselective to **13**. It was reasonable that the Diels-Alder reaction of diene **78** with **13** afforded 13:1 (80%:6%) regioselectivity in favor of adduct **78**, whereas diene **50** gave only 4:1 regioselectivity in favor of adduct **51**.

Just as for the reduction of enedione **56** with $NaBH_4$ or $LiAl(O\text{-}t\text{-}Bu)_3H$ (Scheme 27) and similar to Liotta and coworkers' observation,[55] the addition of lithium ethoxyacetylide, prepared from ethyl ethynyl ether and *n*-butyllithium, to the benzoindane ring system **79** occurred at the seemingly more hindered carbonyl at C-1 in a highly regio- and stereoselective manner. The desired adduct **80** was isolated as the only product in 82% yield (Scheme 31). Double addition was not a problem under the conditions employed, but a small amount of starting material **79** was detected after workup of the reaction, even though ethoxyacetylide was used in excess. This was probably because lithium ethoxyacetylide could also act as a base, and it might deprotonate **79** at C-4a to generate an enolate. The carbonyl at C-1 in the resulting enolate would much less reactive than that in **79** towards a nucleophile and it might not react with the acetylide. During workup the enolate would be converted back to the starting material **79**.

The next step was to hydrolyze the enol silyl ether function of **80**. Thus, compound **80** was treated with potassium fluoride in methanol at room temperature for seven hours. Two unexpected, but understandable, products **98** and **99**, in a ratio of 7:1 in

Scheme 31. Acetylide addition to **79** and hydrolysis of the enol silyl ether in **80** with KF

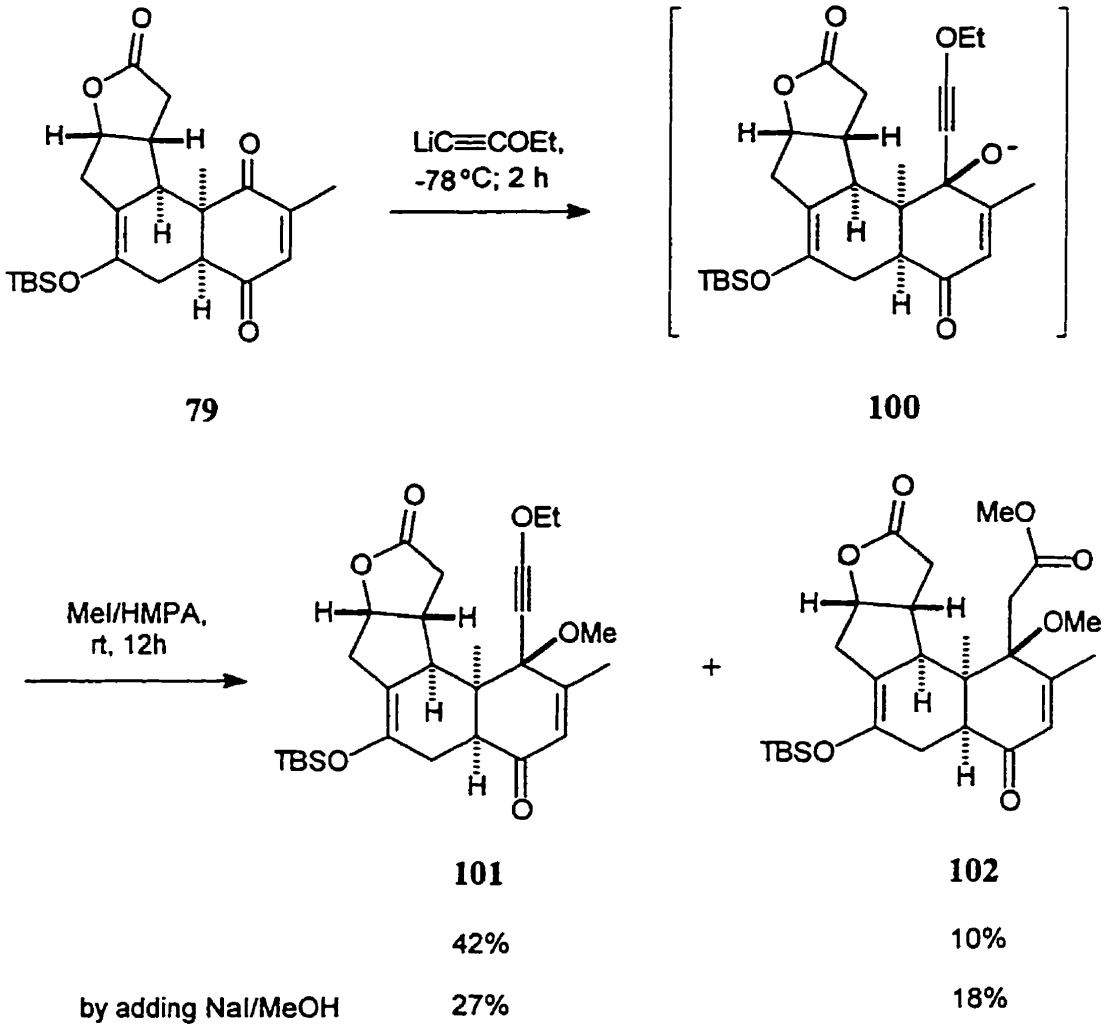


favor of **98**, were obtained in a 93% combined yield (Scheme 31). Tetrabutylammonium fluoride (TBAF) in THF could also be used, but the combined yield was lower (80%). Obviously, the major product **98** resulted by intramolecular hemi-acetalization of the

immediate TBS cleavage product, and the minor product **99** was produced from the epimerization at C-4a of the immediate product. Both the hemi-acetalization and the epimerization might be promoted by fluoride ion, which is a weak base in methanol. The formation of the bridged hemi-acetal **98** confirmed the stereochemistry of the acetylide addition to **79** in the previous step. The *trans*-decalin ring system in **99** was revealed by NOE measurements between H-4a and H-10a. When the signal due to H-4a was saturated, the signal for H-10a was enhanced by 15%. The relative stereochemistry at C-10 in **98** and at C-6a in **99** was also confirmed by NOE experiments. The two products could be completely separated by flash chromatography, but, as seen later, both products were used in our synthesis without separation.

At first, it was thought that the bridged hemi-acetal **98** would be problematic for our synthesis, because we were concerned that the hemi-acetal bridge might be difficult to break, just as we had encountered in Strategy One. To avoid the formation of the bridged hemi-acetal **98**, a logical idea was the protection of the hydroxy group in carbinol **80** before the hydrolysis of the silyl enol ether. The easiest way to do this seemed to be to trap alkoxide **100**, resulting from the addition of ethoxyacetylide to **82** (Scheme 32). Thus, after the completion of the acetylide addition, the reaction mixture was treated with iodomethane in the presence of HMPA at room temperature for twelve hours. Two products were isolated, in 42% and 10% yield. The major one was the expected product **101**. However, the IR spectrum of the minor product showed no absorption for the triple bond, and its ^{13}C NMR spectrum indicated that besides a lactone carbonyl (δ 178.2) it contained an ester carbonyl (δ 170.7). Also, in the ^{1}H NMR spectrum two three-proton

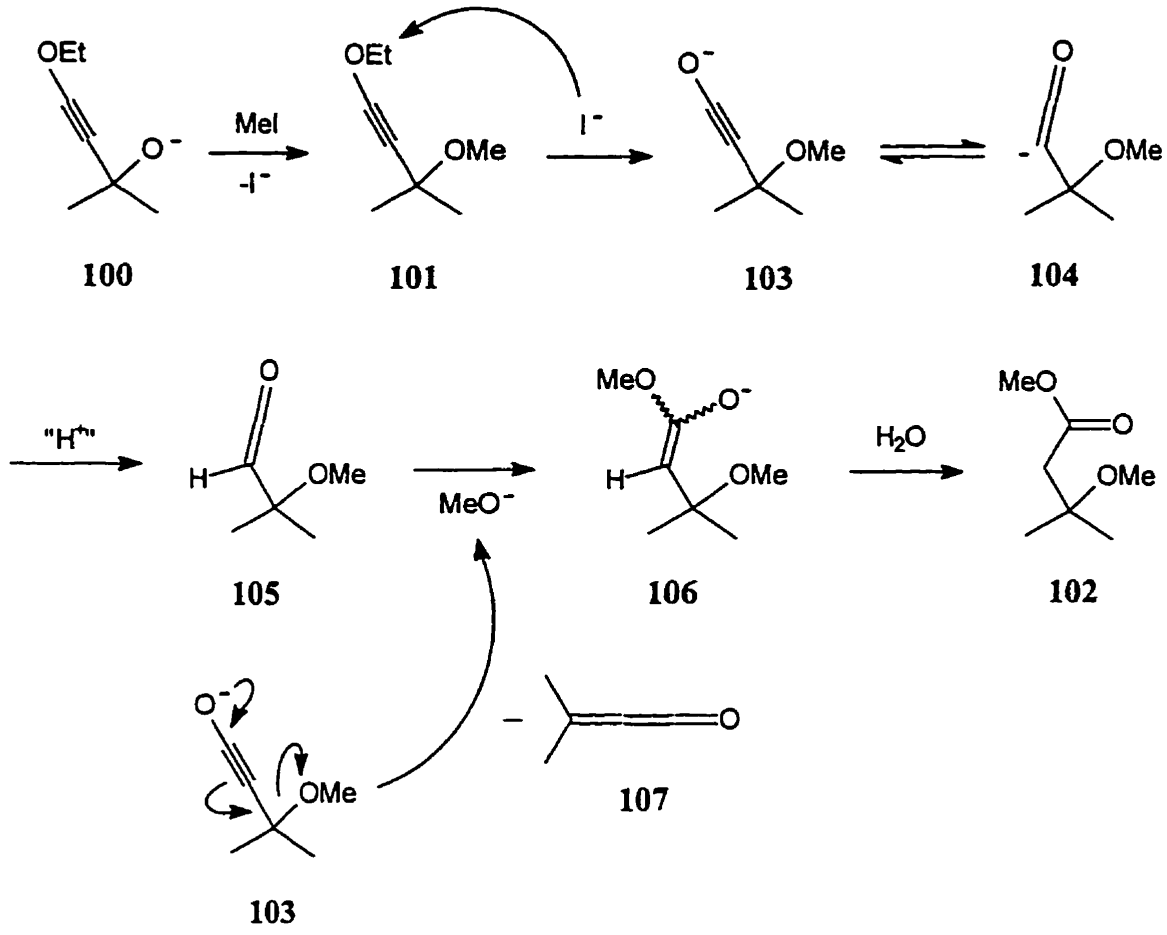
Scheme 32. Trapping alkoxide **100** with MeI



singlets appeared at δ 3.70 and 3.65, indicating that two methoxy groups were present. Accordingly, the minor product was assigned structure **102**, and this was supported by its high resolution MS spectrum. Obviously, the unexpected minor product could be used in our synthesis.

Scheme 33 is our proposed mechanism for the formation of the minor product **102**. When alkoxide **100** reacted with iodomethane to produce the major product **101**, an

Scheme 33. Proposed mechanism for the formation of **102**

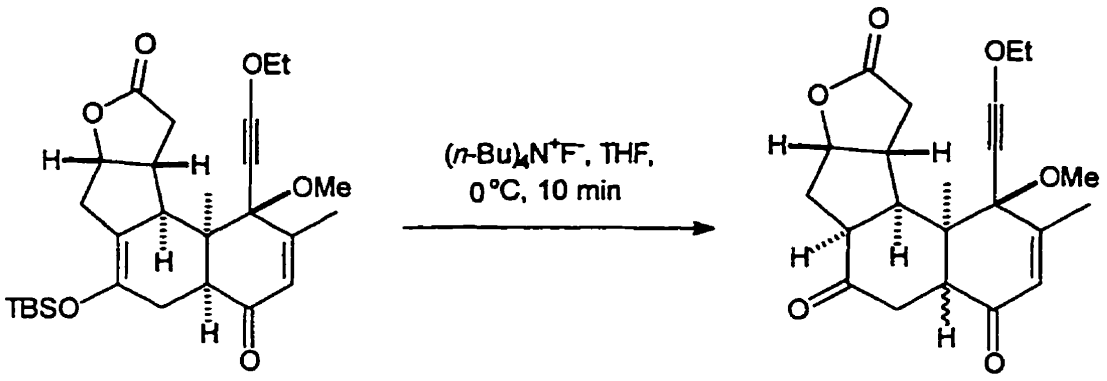


iodide anion was generated. Iodide is an excellent nucleophile, and its attack on the ethyl group in **101** would release ynolate **103**. The latter could tautomerize to carbanion **104**. This type of tautomerization has been demonstrated by Shindo very recently.[58] Carbanion **104** could obtain a proton from carbons α to the carbonyls in molecule **104** itself or from another molecule like **101** to provide the ketene intermediate **105**. On the other hand, ynolate **103** could transform to **107** by losing methoxide. The methoxide could react with the ketene intermediate **105** to produce enolate **106**, which was protonated to lead to the

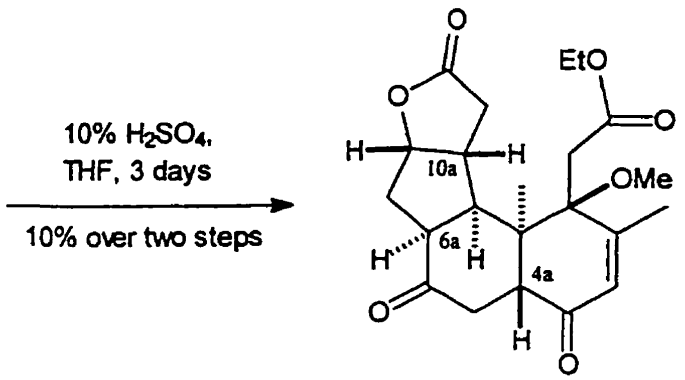
isolated minor product **102** during workup. It was also possible that the HMPA that was used, which was from an old bottle, contained some water. Water could protonate carbanion **104** to provide ketene **105** and hydroxide. The hydroxide could react with **105** to produce a carboxylate, which might react with iodomethane to give **102**. A piece of evidence for the proposed mechanism was that addition of sodium iodide to the reaction medium increased the yield of the ester product **102** from 10% to 18%, while the yield of **101** decreased from 42% to 27%. This result implied that the minor product **102** was derived from the expected product **101** with the participation of iodide anion.

When carbinol **80** was protected as the methyl ether, hydrolysis of the enol silyl ether with TBAF in THF at 0 °C for ten minutes afforded **108** as an epimeric mixture in a ratio of 5:1 favoring the *cis*-isomer (Scheme 34). This mixture was then treated with 10% H_2SO_4 in THF at room temperature, conditions commonly used for the hydrolysis of an ethyl ethynyl ether.[59] However, the reaction turned out to be very sluggish and messy. After a period of three days, the starting material **108** was essentially consumed, but a complex mixture of products was produced. One isolated product was shown to be ester **109**. Again, a *trans*-decalin ring system was clearly evident as a result of the NOE measurements observed between H-4a and H-10a. An 8% enhancement of the signal for H-10a was observed when H-4a was saturated. This NOE experiment could also be used to assign the stereochemistry of C-6a. Compound **109** was almost ready for the final cyclization for the seven-membered ring, but the yield of **109** was unacceptably low. The difficulty in hydrolyzing **108** was probably a consequence of steric hindrance. The reactive site was next to a quaternary carbon, and it was also congested by the 10c-methyl

Scheme 34. Conversion of compound **101** to **109**



101 **108** (5:1 *cis/trans*)



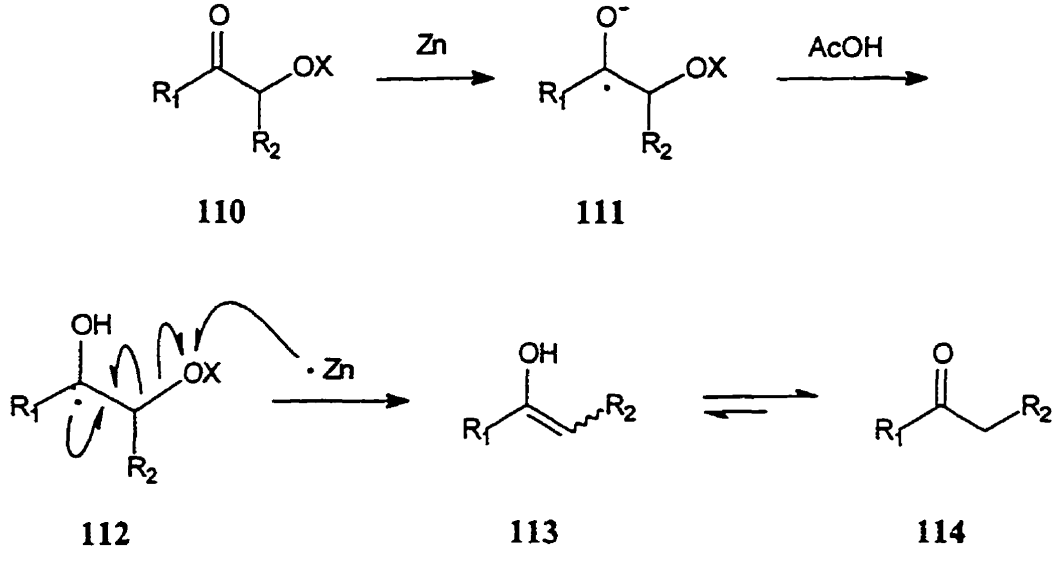
109

group and the cyclopenta[b]furanone ring system in the molecule. On the other hand, a protonated methoxy group might eliminate and generate a carbocation, which could then undergo eliminations and/or rearrangements to lead to a complex mixture of products.

Given this poor yield, we reconsidered how to exploit the bridged hemi-acetal **98** and carbinol **99**, the products in the hydrolysis of enol silyl ether **80** with KF in methanol (Scheme 31). It is known that a hydroxy group or other oxygen substituents α to a carbonyl can be reductively cleaved with zinc dust in glacial acetic acid.[60] The

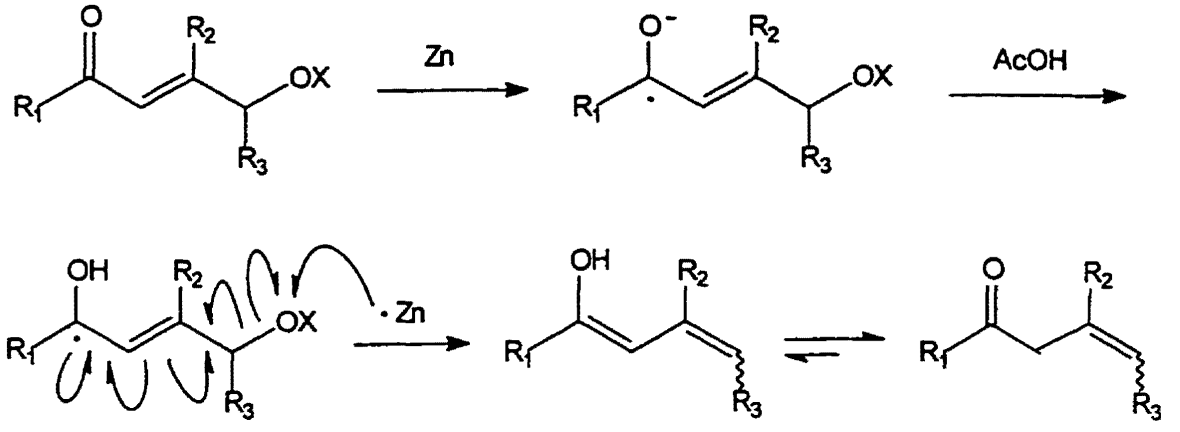
mechanism of this reduction could be described as in Scheme 35. By obtaining an electron from zinc, the α-oxygen-substituted ketone **110** becomes a radical anion **111**, which captures a proton from acetic acid to lead to radical alcohol **112**. Obtaining a second electron from zinc, the α-oxygen-substituent is cleaved by a single-electron-transfer process to produce enol **113**, which tautomerizes to ketone **114**, the reduced product.

Scheme 35. Proposed mechanism of the reduction of α oxygen-substituted ketones with Zn



We wondered if we could apply the same sort of reduction to the bridged hemacetal **98** and carbinol **99**, both of which were γ-oxygen-substituted α,β-unsaturated ketones. Extrapolation of the mechanism in Scheme 35 to a γ-oxygen-substituted α,β-unsaturated ketone system allowed us to predict that a reduction should occur, and the product would be a β,γ-unsaturated ketone (Scheme 36). It was also anticipated that after the γ-oxygen substituent was cleaved, the hydrolysis of the ethyl ethynyl ether could be

Scheme 36. Prediction for the reduction of a γ-oxygen-substituted enone with Zn

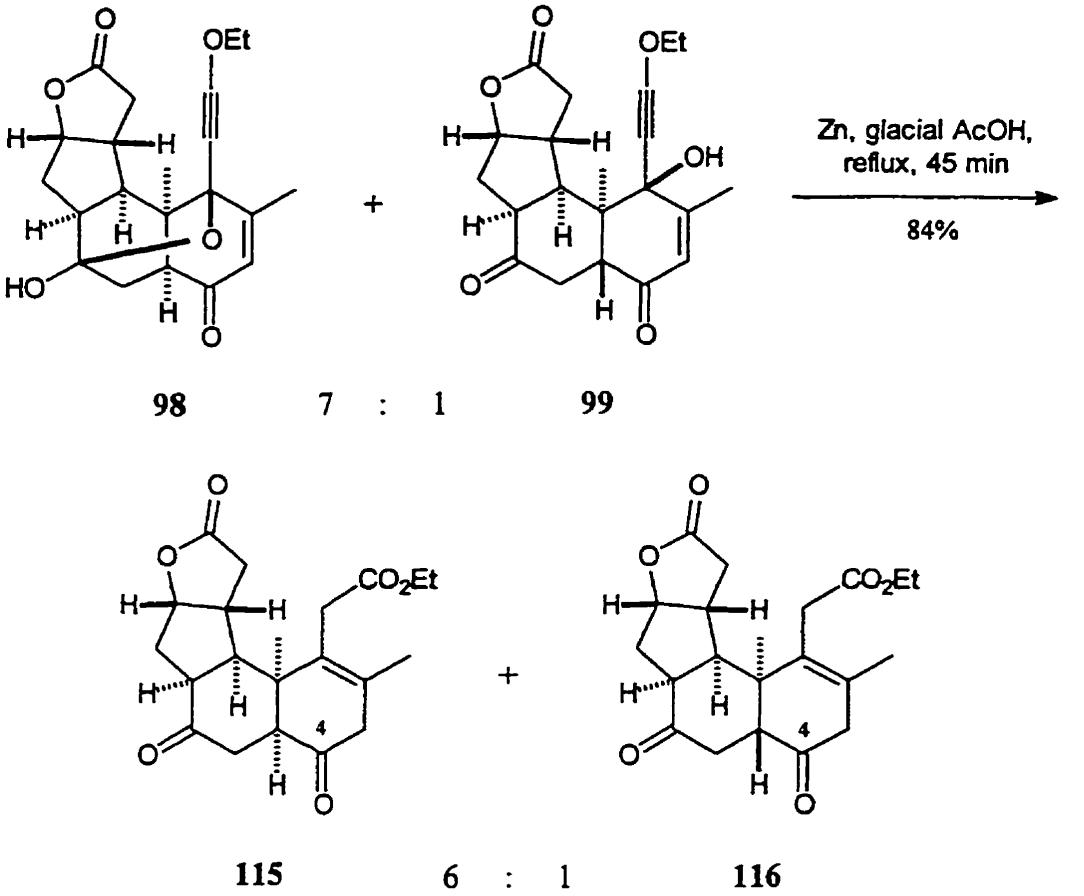


easier and cleaner.

As shown in Scheme 37, our predictions were entirely correct. Both **98** and **99**, when treated with zinc dust in refluxing glacial acetic acid, underwent the expected reduction and gave products **115** and **116** in 84% yield. The β,γ-unsaturated ketone structural unit in the products was confirmed by the following facts: (a) Neither **115** nor **116** was UV active. (b) The ^{1}H NMR spectra revealed that neither of the products had an alkenic proton. (c) The ^{13}C NMR spectra showed that the chemical shifts for the two alkenic carbons in **115** and in **116** were very similar, but distinct from those of a C=C double bond conjugated with a carbonyl. (d) ^{13}C resonances due to the carbonyls at C-4 in both **115** and **116** were consistent with unconjugated ketones.

In addition, during the reduction the ethyl ethynyl ether moieties were very cleanly solvolyzed to ester groups. This was indicated by the lack of a triple bond absorption in the IR spectra and the presence of an additional ester carbonyl at δ 171.3 for **115** and at δ 171.0 for **116** in the ^{13}C NMR spectra (CD_2Cl_2). This was also confirmed by high

Scheme 37. Reduction of hemi-acetal **98** and carbinol **99** with Zn

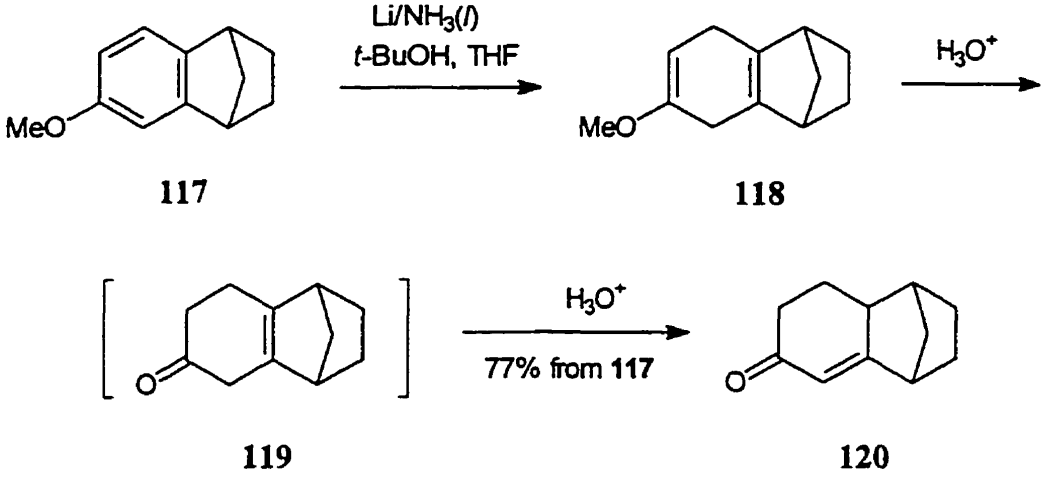


resolution MS analysis. Though intermediates were not detected, we speculated that the solvolysis was preceded by the reduction, because, as shown earlier (Scheme 34), prior to reduction the ethyl ethynyl ether had been very difficult to hydrolyze cleanly.

What we needed to do with **115** and **116** was to shift the isolated C=C double bond to conjugate it with the carbonyl at C-4 and to change the *cis*-decalin ring system to the *trans* by epimerization at C-4a. The C=C double bonds in **115** and **116** might be reduced by catalytic hydrogenation at this point, but the stereochemistry of the reduction would not be controlled. It was expected that the desired isomerization of the double

bond and epimerization of the stereogenic center at C-4 could be completed in the same pot with acid. We had earlier shown that with glacial acetic acid and 10% sulphuric acid, respectively, the epimerization of the *cis*-decalin ring junction to the *trans* in **75** and **108** could be achieved. Acid-catalyzed isomerization of a β,γ-enone to an α,β-enone is well documented in the preparation of α,β-enones from anisole derivatives by Birch reduction, followed by acid hydrolysis.[61] For instance, when 1,4-diene **118**, the Birch reduction product of anisole **117**, was treated with dilute hydrochloric acid, the isolated product was α,β-enone **120**,[62] which must have resulted from acid-promoted isomerization of α,β-enone **119**, the initial hydrolysis product (Scheme 38).

Scheme 38. An example of acid-catalyzed isomerization of β,γ-enone to α,β-enone[62]



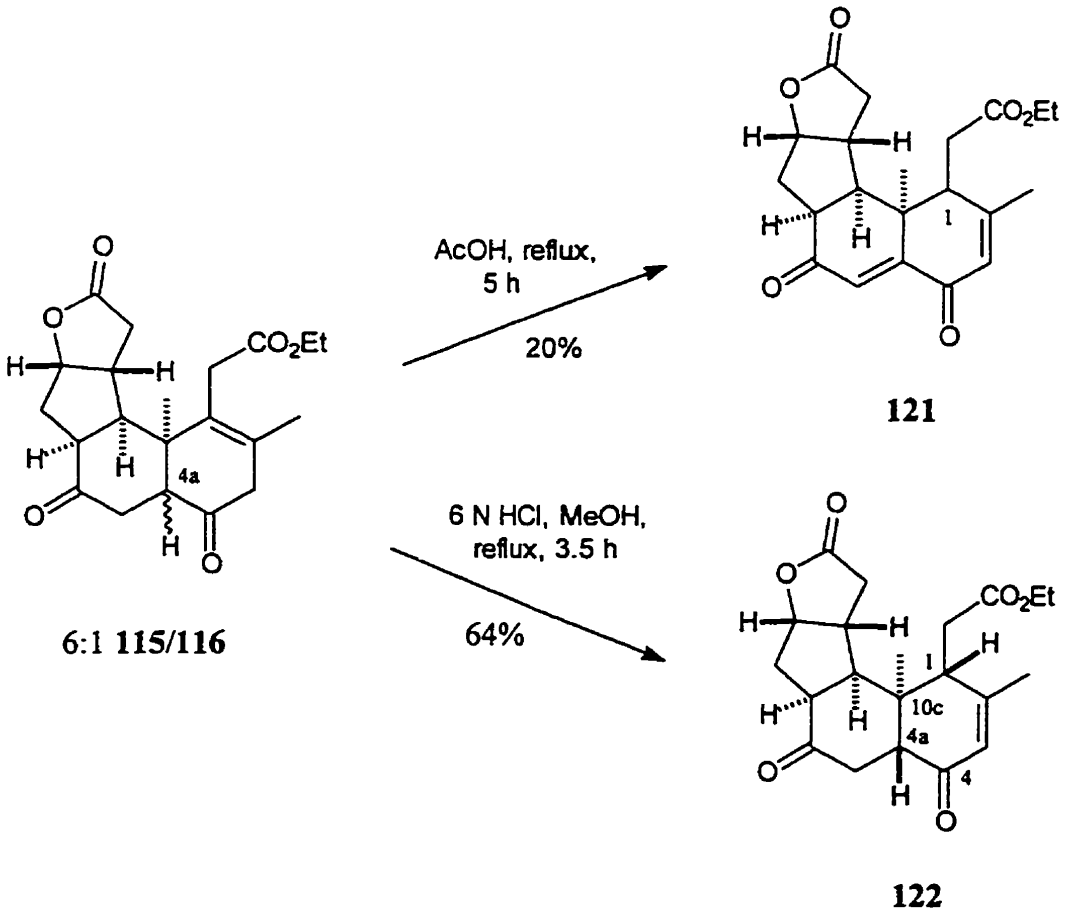
117 **118** **119** **120**

Thus, a mixture of **115** and **116**, in an initial ratio of 6:1, was heated with glacial acetic acid for five hours. However, a complex mixture of products, along with remaining starting materials, was produced. One isolated product, in 20% yield, was tentatively assigned as **121** (Scheme 39), an oxidation product, by comparing its ^{1}H and

^{13}C NMR spectra with those of compound **67**. The stereochemistry at C-1 in **121** was not determined because the sample was not sufficient for NOE experiments.

Eventually, the desired isomerization and epimerization was succeeded with 6 N aqueous HCl in methanol. After three and half hours of reflux, the 6:1 mixture of **115** and **116** was converted, in 64% yield, to the desired product **122**, in which the C=C double bond was brought into conjugation with the carbonyl at C-4, the ester side chain was at the equatorial position, *syn* to the 10c-methyl group as required, and the decalin

Scheme 39. Acid-catalyzed isomerization and epimerization of **115** and **116**



6:1 **115/116**

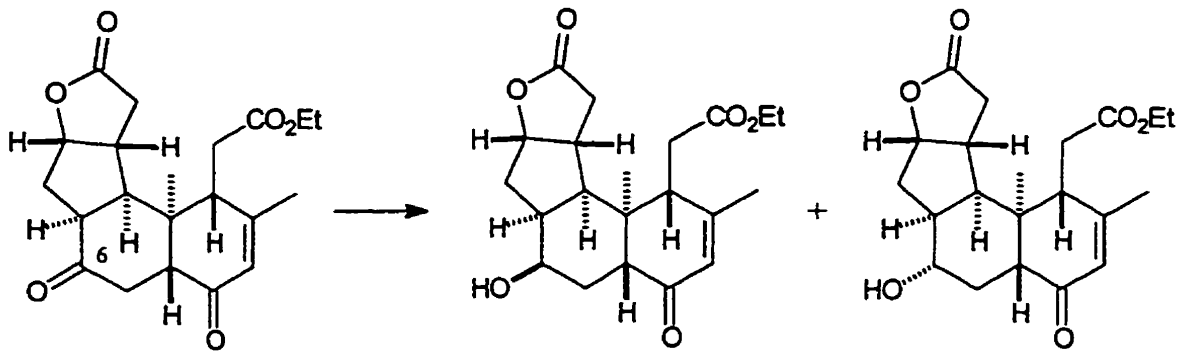
121

122

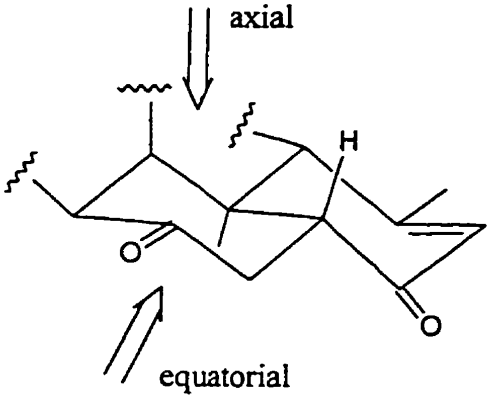
ring system was completely *trans*. The position of the double bond was very clear from the H-3 signal at δ 5.90 in the ^{1}H NMR spectrum (CD_3COCD_3) and the C-4 (carbonyl) signal at δ 197.9 in the ^{13}C NMR spectrum (CD_3COCD_3). The relative stereochemistry between C-1 and C-4a in **122** was revealed by NOE measurements. A 3% enhancement of the signal for H-1 was observed when the signal for H-4a was saturated. Since signals in the ^{1}H NMR spectrum of **122** were heavily overlapped, and consequently useful NOE information was not available to determine the relative stereochemistry between C-1 and C-10c or between C-4a and C-10c, the *trans*-decalin ring junction was assigned on the basis of the NOE measurements between H-4a and H-10a in the product of next step.

With compound **122** in hand, we could attempt to cyclize the seven-membered ring, but the cyclization might occur between the ester carbonyl and the methyl group at C-2.[63] We could also attempt to reduce the C=C double bond, but the product would have two unconjugated carbonyls, and it could be difficult to conduct a selective reaction with them. Therefore, it was decided that the saturated carbonyl at C-6 should be chemo- and stereoselectively reduced at this point. Thus, **122** was first treated with sodium borohydride in 1:1 mixture of methanol and dichloromethane at -78 °C, a published procedure for chemoselective reductions of unconjugated carbonyls in the presence of conjugated carbonyls.[64] This reaction did display 100% chemoselectivity, though a significant amount (28%) of starting material remained after the reaction had proceeded for one hour. However, the stereoselectivity was poor (Scheme 40). The ratio of the two stereoisomeric products **123** and **124** was 2:3 in favor of the undesired isomer **124**, as determined by the ^{1}H NMR analysis of the crude product. Nevertheless, this result

Scheme 40. Reduction of **122** with $NaBH_4$ and $LiAl(O\text{-}t\text{-}Bu)_3H$



122 **123** **124**

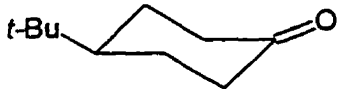
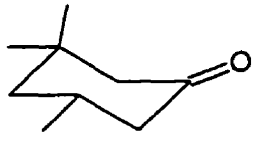
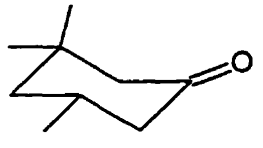


procedure	ratio of **123** to **124**
$NaBH_4$, -78 °C, 1:1 $MeOH/CH_2Cl_2$	2 : 3
$LiAl(O\text{-}t\text{-}Bu)_3H$, -20 to 0 °C, 2 h	8 : 1

provided very useful information. The two stereoisomeric products resulted from two different modes of attack by sodium borohydride. The equatorial addition of hydride to the carbonyl at C-6 led to **123**, and the axial addition led to **124**. It is well known that the reductions of cyclohexanones with small reducing reagents, like sodium borohydride, display significant axial selectivity, and that an axial substituent at the 3-position to the carbonyl or/and a bulky reducing reagent would inhibit the axial addition and improve the equatorial selectivity.[65] For example, the reduction of 4-*tert*-butylcyclohexanone (**125**) with sodium borohydride in isopropyl alcohol at 25 °C presented a selectivity of 86:14

favoring the axial addition over the equatorial. However, the selectivity in the reduction of 3,3,4-trimethylcyclohexanone (**126**), where a 3-axial methyl group was present, was dramatically changed to 48:52, slightly in favor of the equatorial addition. When **126** was reduced with lithium tri-*tert*-butoxyaluminohydride, which is bulkier than sodium borohydride, the equatorial selectivity over axial improved to 96:4.

Table 2. Literature examples of stereoselectivity in the reductions of cyclohexanones[65]

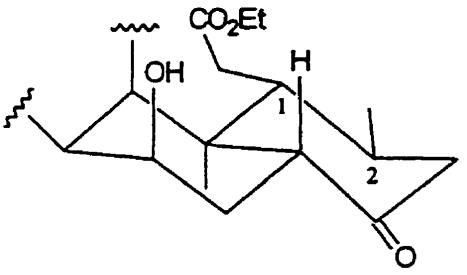
cyclohexanone	reducing reagent and conditions	ratio of axial addition to equatorial addition
 **125**	$NaBH_4$, 2-propanol, 25 °C	86:14
 **126**	$NaBH_4$, 2-propanol, 25 °C	48:52
 **126**	$LiAl(O\text{-}t\text{-}Bu)_3H$ THF, 0 °C	4:96

In our more elaborate case with **122**, sodium borohydride only displayed a small preference for axial attack. This suggested that fairly good equatorial selectivity might be obtained by employing a bulkier reducing reagent. Thus, **122** was then treated with

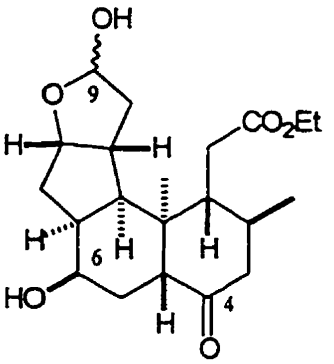
$LiAl(O\text{-}t\text{-}Bu)_3H$ at -20 °C to room temperature for two hours. The same two products **123** and **124** were obtained in 78% and 10% yield, respectively. The reduction of the conjugated carbonyl was not detected. In other words, $LiAl(O\text{-}t\text{-}Bu)_3H$ also had complete chemoselectivity for the unconjugated carbonyl over the conjugated carbonyl, and the equatorial selectivity was 8:1 favoring the desired product **123**. The epimer **124** could be oxidized back to **122** to be recycled, although we did not do this.

At this point, we were anxious to know if we could reduce the C=C double bond in enone **123** and correctly establish the stereogenic center at C-2. A large number of methods were available for the reduction of a C=C double bond in an α,β-unsaturated ketone,[66] but the desired reduction must leave the methyl group at C-2 *anti* to the ester side chain at C-1 in the product. Though x-ray diffraction analysis had revealed that the cyclohexanedione ring in **76** adopted a boat conformation in the solid state, presumably due to the steric interaction between the carbonyl at C-1 and the cyclopentane ring in the molecule, we assumed that the cyclohexanone ring in the desired product **127** would adopt a chair conformation in which both the methyl group at C-2 and the ester side chain at C-1 would be in equatorial positions, i.e. we assumed that **127** would be the thermodynamically most stable product of the reduction. Therefore, lithium in liquid ammonia was chosen to be the reducing reagent.[67] However, a preliminary examination of the reduction of enone **123** with lithium in liquid ammonia at -50 °C for five minutes showed that the product was a mixture of several over-reduced products, with a 4:1 epimeric mixture of hemi-acetals **128** being the major component. The formation of **128** was revealed by the examination of its ^1H and ^{13}C NMR spectra. In the ^1H spectrum

(CD_3OD), epimeric mixture **128** exhibited a doublet (J = 4.6 Hz) at δ 5.50 and a doublet of doublets (J = 7.9, 4.6 Hz) at δ 5.36, corresponding to the anomeric protons H-9 in the major and minor epimers, respectively. In the ^{13}C NMR spectrum (CD_3OD), the signals at δ 102.9 and 102.5 were attributed to C-9 in the two epimers of **128**. The presence of the carbonyls at C-4 in the epimers was indicated by signals at δ 215.8 and 215.7 ppm. The reason why the carbonyl at C-4 survived while the lactone carbonyl was reduced in the formation of **128** was that the carbonyl at C-4 existed as an enolate before the reaction was quenched.



127

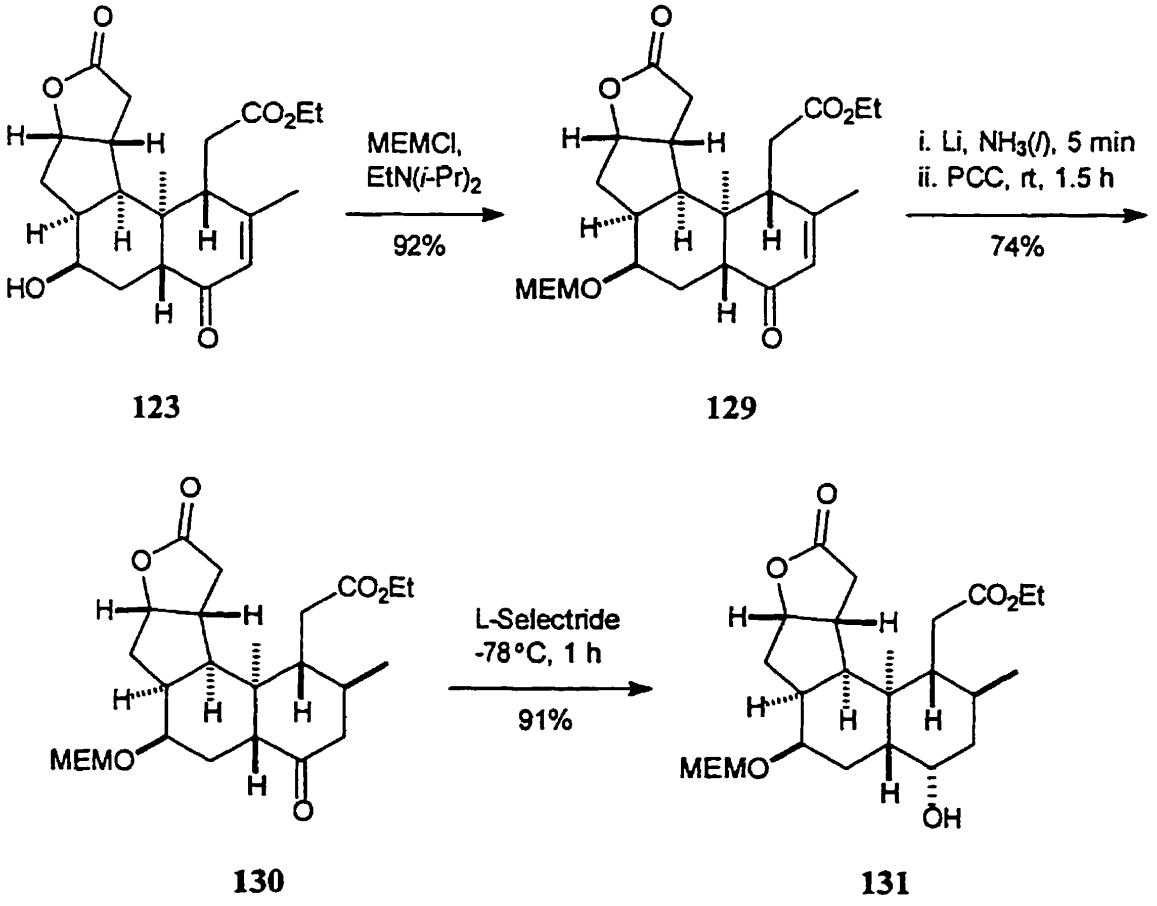


128

The hemi-acetal **128** might be converted to a lactone by oxidation, but the hydroxy group at C-6 could also be oxidized. This meant that the hydroxy group should be protected before the reduction step. Regarding the protection of the hydroxy group in alcohol **123**, three concerns were considered. First, the protecting group should be fairly stable, because it might be needed until the last stage of the synthesis. Second, the conditions employed to introduce the protecting group should not be strongly basic, otherwise the undesired condensation between the ester carbonyl and the methyl group at

C-2 might occur.[63] Third, the protecting group should not be too large, otherwise it might impede the 1,4-addition of enone **82** during the introduction of the last angular methyl group. Therefore, the first attempt was to protect the hydroxy group as a methoxy group with iodomethane and silver(I) oxide,[68] a nearly neutral procedure. However, alcohol **123** was found to be inert to this procedure. After a mixture of **123**, iodomethane, and silver(I) oxide was refluxed in acetonitrile overnight, no reaction was detectable, and **123** was quantitatively recovered. Eventually, protection of the hydroxy group was

Scheme 41. Transformation of compound **123** to **131**

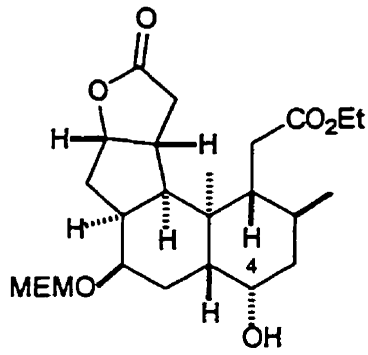


accomplished with a (2-methoxyethoxy)methyl (MEM) group by a method developed by Corey and coworkers.[69] After twelve hours of heating with (2-methoxyethoxy)methyl chloride (MEM chloride) in dichloromethane in the presence of Hünig's base (diisopropylethylamine), alcohol **123** was converted to **129** in 92% yield (Scheme 41).

Just as with the reduction of **123** with lithium in liquid ammonia, when **129** was treated with lithium in ammonia at -50 °C for five minutes, several over-reduced products, together with the desired product **130**, were produced. However, when this crude mixture was stirred with pyridinium chlorochromate (PCC) at room temperature for one and a half hours, ketone **130** was obtained in 74% yield based on **129**. The stereochemistry at C-2 in **130** was confirmed by NOE measurements between signals between the H-2 and the 10c-methyl group. When the signal for the 10c-methyl was saturated, the signal for the H-2 was enhanced by 6%. Then, **130** was stereospecifically reduced by the equatoral attack of L-Selectride in THF at -78 °C, the axial alcohol **131** was obtained in 91% yield. It is well documented that L-Selectride is an excellent selective reducing reagent for equatorial reductions of cyclohexanones, even in the absence of an axial substituent β to the carbonyl to be reduced.[17, 70]

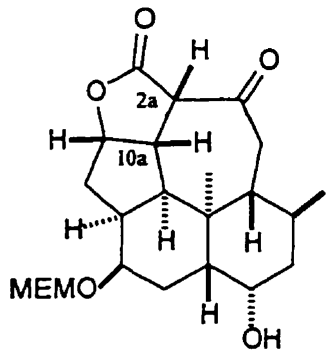
The Dieckmann cyclization of the seven-membered ring in **131** was attempted with potassium *tert*-butoxide in refluxing benzene.[71] (Scheme 42). After four hours of heating, ^{1}H NMR analysis of the crude product indicated that two products had been produced and some starting material **131** still remained. The ratio of the two products and the remaining starting material was approximately 5:1:1. The major product was isolated in 61% yield, and its characterization showed it to be the desired product **30**. The relative

Scheme 42. The Dickmann condensation of **131**

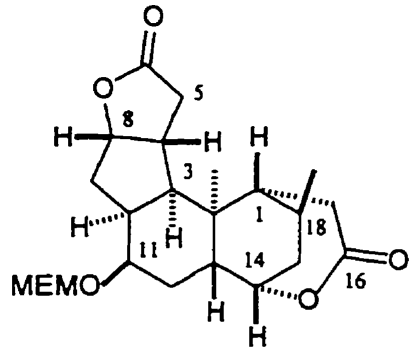


KO-*t*-Bu, C_6H_6,
reflux, 4 h

131



+



30 (61% isolated yield)

132

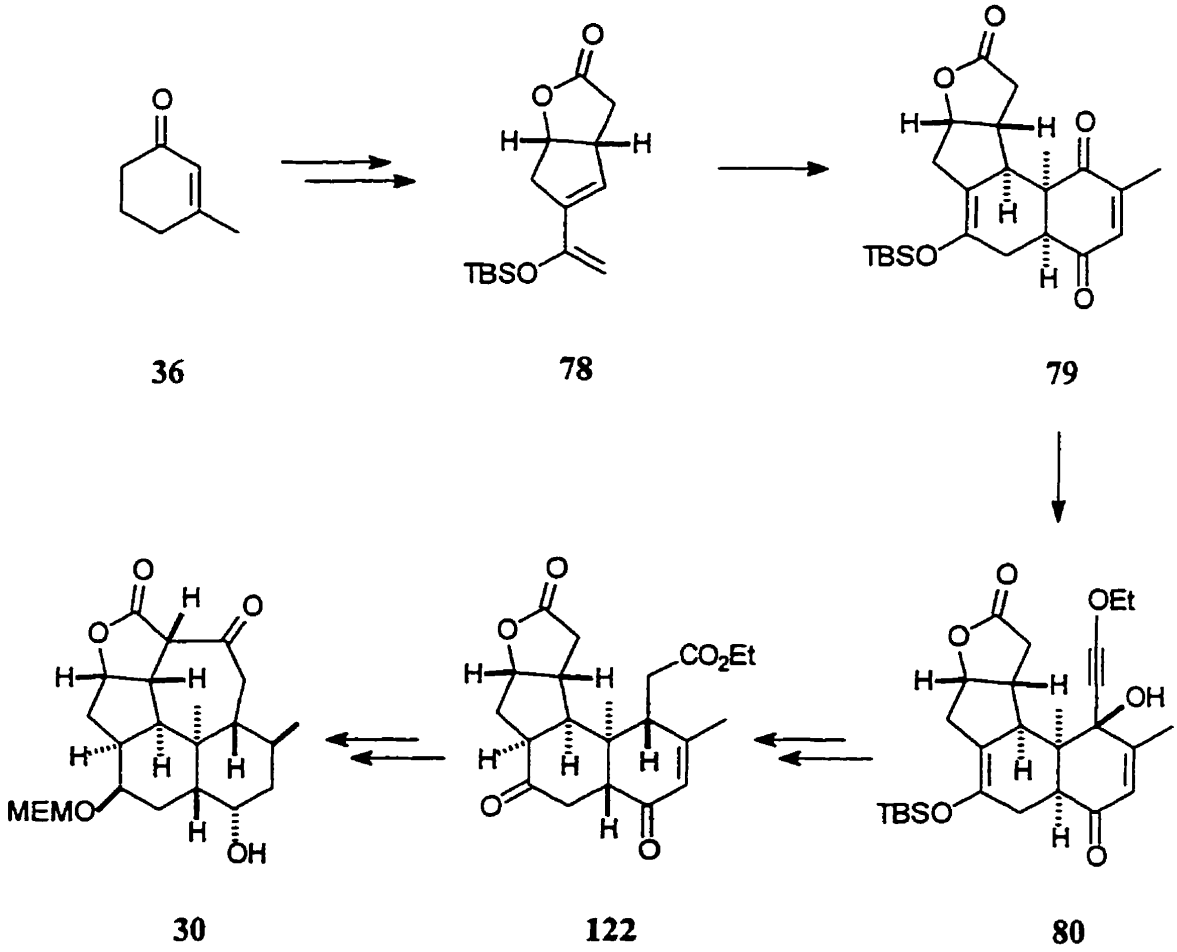
Ratio of **30** to **132** by ^{1}H NMR: 5:1

stereochemistry at the newly generated stereogenic center at C-2a was determined by NOE experiments. When the signal for H-10a was saturated, the signal for H-2a was enhanced by 4%. The minor product was assigned as **132** based on the fact that **132** had the same molecular mass as **30**, and that it had two lactone carbonyls appearing at δ 181.4 and 178.0 but had no ketone signal in its ^{13}C NMR spectrum (CD_3OD). The formation of **132** undoubtedly confirmed the stereochemistry of the previous reduction step. The final cyclization was not optimized. The formation of the minor product **132** suggests that in

future work the 4-hydroxy group in **131** should be protected or removed before the Dieckmann cyclization.

Scheme 43 is used to summarize the synthesis of the kempane diterpene ring system **30**. This synthesis featured the highly regio- and stereoselective Diels-Alder reaction of diene **78** with 2,6-dimethyl-1,4-benzoquinone (**13**) to construct the benzoindane ring system **79** and three key stereogenic centers. Diene **78** was derived from commercially available 3-methyl-2-cyclohexen-1-one (**36**) through a sequence

Scheme 43. Outline of the synthesis of the kempane diterpene ring system **30**



36 **78** **79**

30 **122** **80**

including a regiospecific [2 + 2] ketene cycloaddition. The remaining annular carbons for the kempane diterpene ring system in **79** were introduced by the extremely regio- and stereoselective nucleophilic addition of an acetylide to the seemingly more hindered carbonyl in the enedione system to provide carbinol **80**. Carbinol **80** was then efficiently converted to **122** by reductive expulsion of γ-oxygen-sustituent in the α,β-unsaturated ketone and a one-pot, acid-promoted epimerization and double-bond isomerization. The remaining stereogenic centers were produced by stereoselective reductions of **122**. The final cyclization of the seven-membered ring was achieved by a Dieckmann condensation. The ring system **30** possesses all the stereogenic centers required by kempane diterpenes, and it also contains sufficient functionality to allow modification to kempanes **1** and **2**.

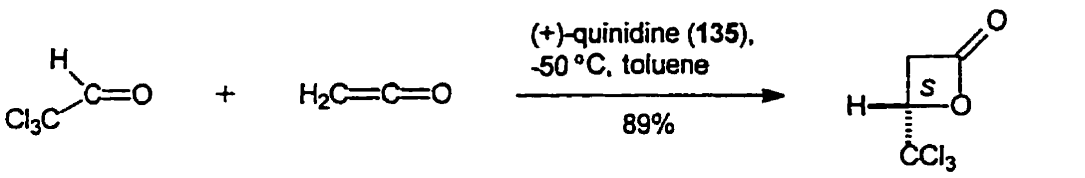
1. 4. Preliminary Study of Asymmetric [2 + 2] Ketene Cycloadditions

1. 4. 1. Introduction

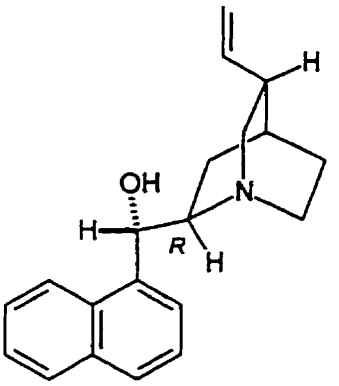
The first step in which stereochemistry was involved in our approach to the kempane diterpenes was the cycloaddition of dichloroketene with 1-methyl-1,3-cyclohexadiene (**38**) to provide cyclobutanone **39**. Therefore, for an asymmetric synthesis of the kempane diterpenes by a very similar route, an asymmetric [2 + 2] ketene cycloaddition would be a potential key step. In spite of the versatility of [2 + 2] ketene cycloadditions in organic synthesis[72] and rapid advances in asymmetric synthetic methodology,[73] the asymmetric ketene addition has not been extensively investigated. Only a few of examples were found in the literature. These included the use of chiral catalysts and the use of chiral auxiliaries.

In 1982, Wynberg and Staring[74] found that by using 1-2 mol % of optically pure quinidine (**135**) as a catalyst, addition of ketene **134** to chloral **133** could occur in an asymmetric manner to afford β-lactone **136** in 98% enantiomeric excess (ee) and in 89% chemical yield (Scheme 44). Other Cinchona alkaloids could also be used, though their chiral inductions were somewhat lower. Either enantiomer of **136** could be obtained when diastereomers of catalysts were used. The absolute configuration of the β-carbon in **136** was found to be predictable on the basis of a knowledge of the absolute stereochemistry of the catalyst. When the carbon adjacent to the tertiary nitrogen in the catalyst was *R*, the absolute configuration of the β-carbon in **136** would be *S*, as exemplified in Scheme 44. Wynberg and Staring's work would appear to provide an ideal method for asymmetric ketene addition, but to date the reported examples are

Scheme 44. Catalytic asymmetric addition of ketene (134) to chloral (133)



133 134 136 ee = 98%

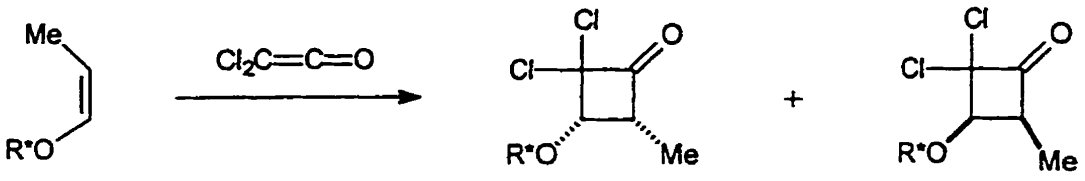


135

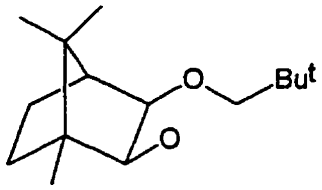
restricted to the reactions of ketene **134** with chloral **133**, α,α-dichloroaldehydes, and a couple of trichloromethyl ketones.[74, 75]

The use of chiral auxiliaries in the cycloadditions of ketenes to alkenes can be classified into two groups, based on whether the alkene or the ketene bears the chiral auxiliary. The use of a chiral auxiliary in the alkene component was investigated by Greene's group with chiral enol ethers and dichloroketene, prepared *in situ* from trichloroacetyl chloride and zinc-copper couple (Scheme 45).[76] A number of chiral auxiliaries were examined, and the best results were obtained when *R** were camphor-derived auxiliaries. When the enol ether carried auxiliaries **139** and **140**, respectively, diastereoisomers **137** and **138** were both produced in 80% diastereoisomeric excess (de).

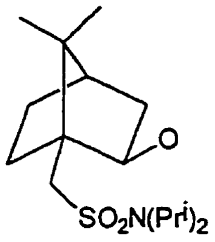
Scheme 45. Cycloaddition of dichloroketene with chiral enol ethers



137 **138**

when R*O =  **137:138** = 9:1

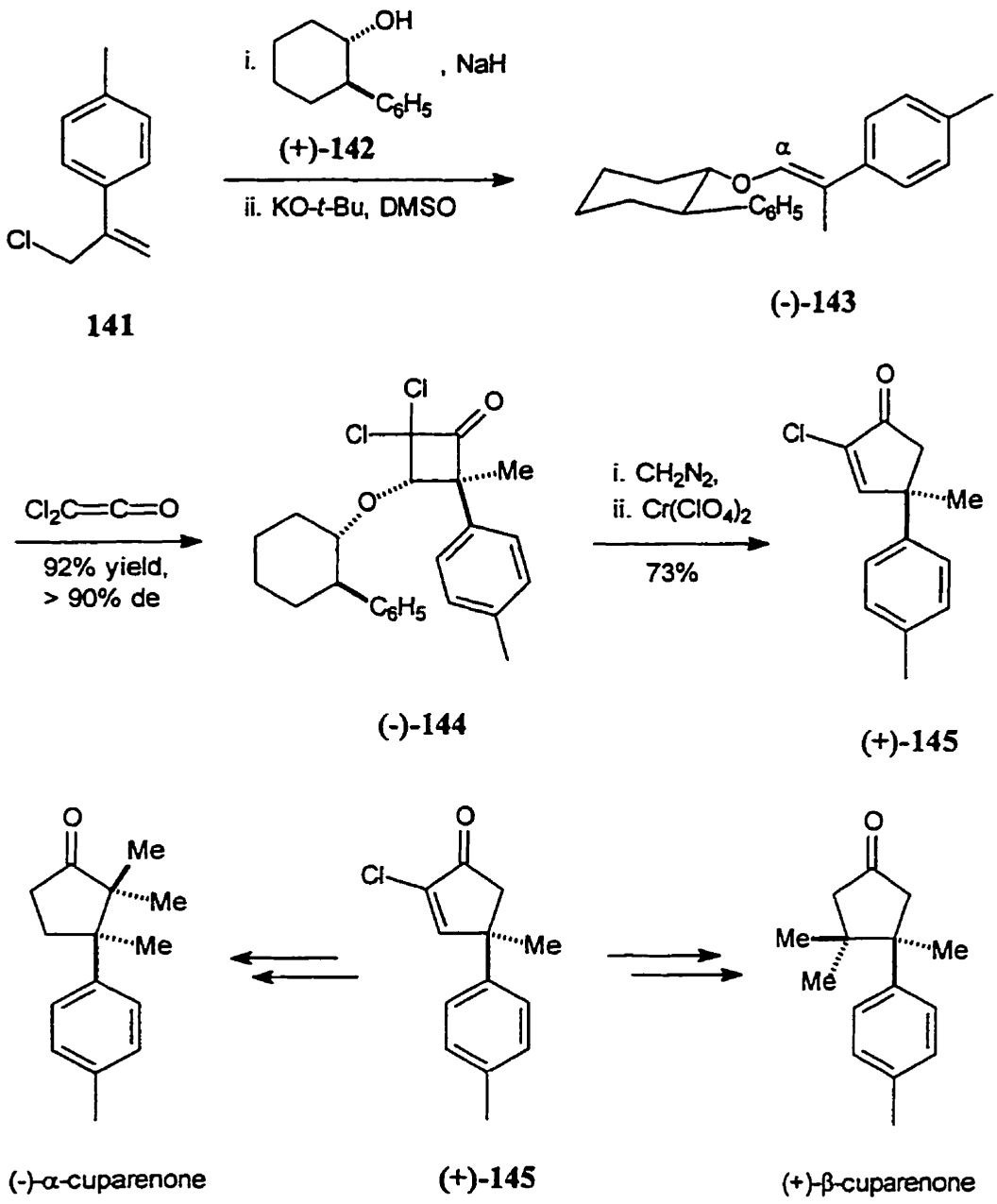
139

when R*O =  **137:138** = 1:9

140

Application of this chiral enol ether-ketene diastereofacial differentiation approach allowed the same group to complete enantioselective syntheses of α- and β-cuparenones (Scheme 46).[77] In the synthesis, however, optically pure (1*S*,2*R*)-(+)-2-phenylcyclohexanol (**142**) was used as a chiral auxiliary, and a better chiral induction (greater than 90% de) was achieved in the cycloaddition of dichloroketene with chiral enol ether (−)-**143**. The high diastereofacial selectivity was explained as follows. Enol ether (−)-**143** adopted an s-*trans* or nearly s-*trans* conformation, as depicted in Scheme 46. This would bare the C_α-*re* face of the enol ether for dichloroketene to attack, while

Scheme 46. Asymmetric ketene cycloaddition approach to α- and β-cuparenone

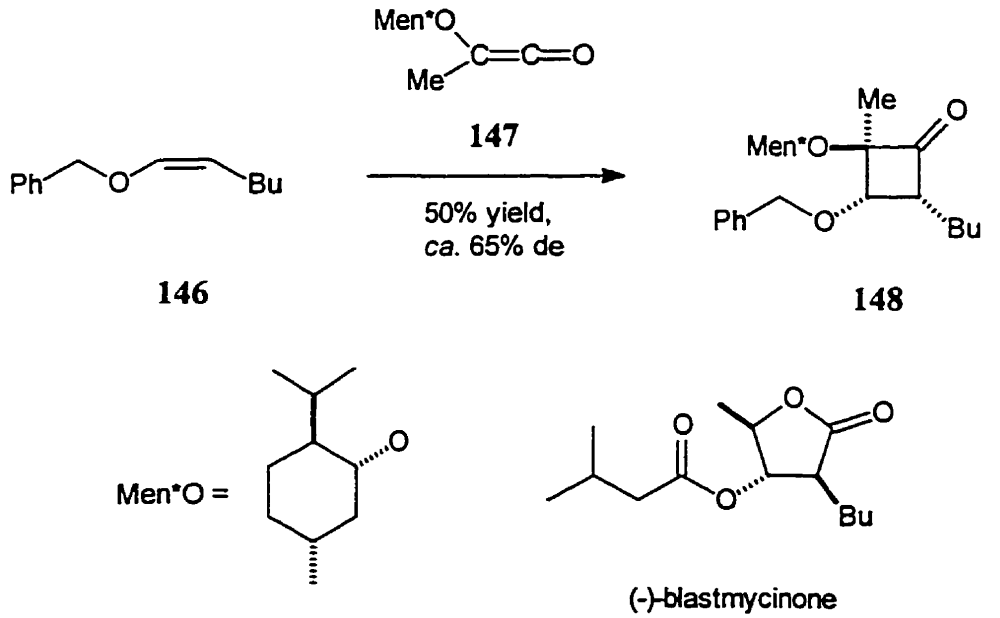


the C_α-*si* face would be sterically shielded by the phenyl group of the chiral auxiliary. Ring expansion of cyclobutanone (−)-**144** with diazomethane and reductive release of the chiral auxiliary with chromous perchlorate furnished optically pure α-chloroenone (+)-

145, which was transformed into (−)-α- and (+)-β-cuparenone.

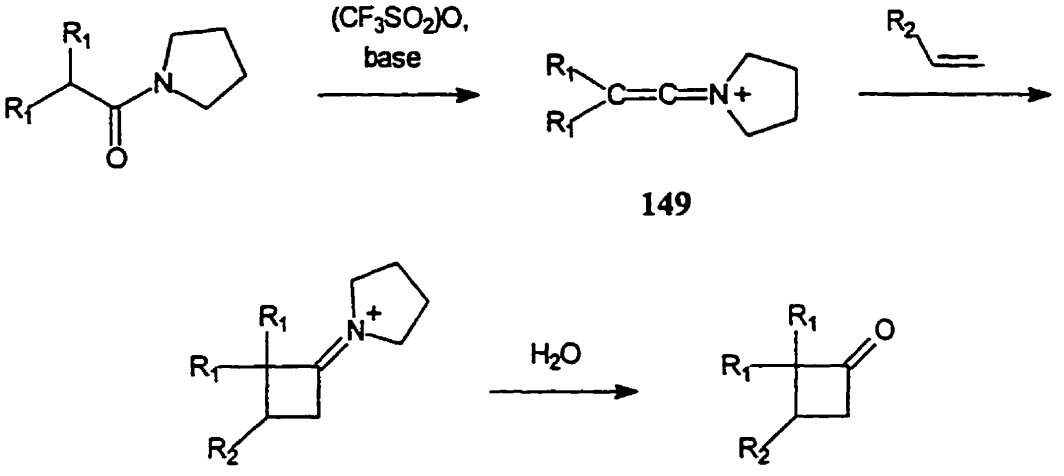
Fráter and coworkers studied the asymmetric [2 + 2] ketene cycloaddition by attaching the chiral auxiliary onto the ketene component.[78] They reported that optically pure menthyloxymethylketene (**147**), prepared *in situ* from 2-menthyloxypropanoyl chloride and triethylamine, could diastereoselectively react with *cis*-enol ether **146** to give cyclobutanone **148** in approximately 65% de. The absolute stereochemistry of the product was determined by converting **148** to (−)-blastmycinone (Scheme 47).

Scheme 47. Cycloaddition of chiral ketene with enol ether



Another way to attach a chiral auxiliary to the enophile component for a [2 + 2] cycloaddition is by the the use of a keteniminium salt. Keteniminium salts are the equivalents of ketenes with regard to [2 + 2] cycloadditions for the formation of cyclobutanones, but they are more electrophilic than ketenes and they do not dimerize.[79]

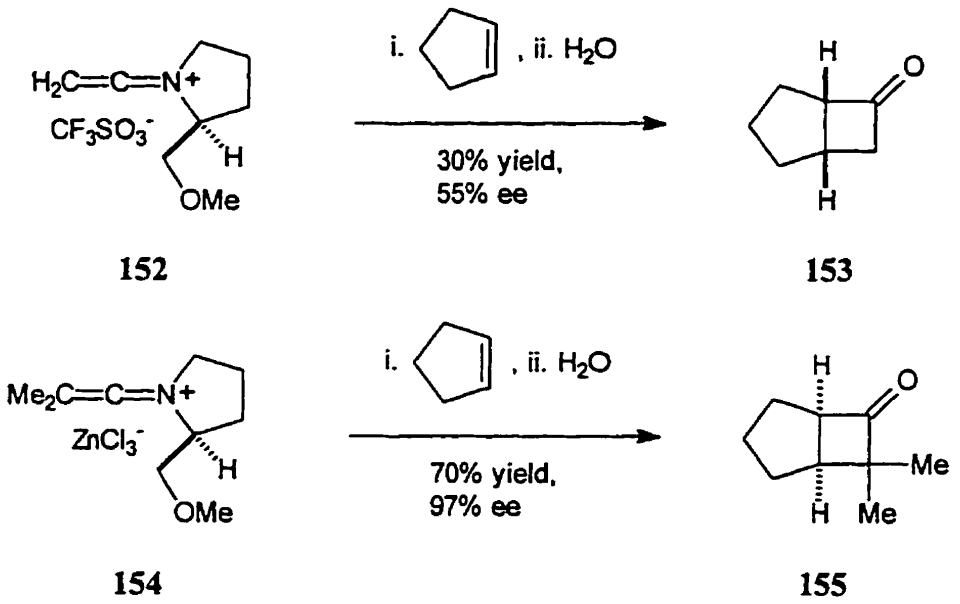
Scheme 48. Generation of a keteniminium salt and its cycloaddition with an alkene

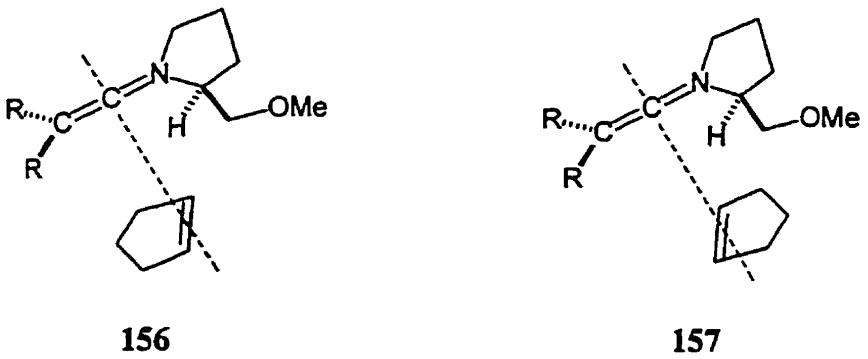


A keteniminium salt like **149** is usually generated *in situ* by the treatment of an amide with triflic anhydride in the presence of a base (usually an amine). Cycloaddition of the keteniminium salt with an alkene initially gives cyclobutanimium salt **150**, which is then hydrolyzed to cyclobutanone **151** without isolation (Scheme 48). It was shown that keteniminium salts are more general for intramolecular cycloadditions, and they could afford very successful results where the corresponding ketenes failed to undergo cycloadditions.[79] Another potential advantage of keteniminium salts over ketenes is that they may provide a convenient scaffold for asymmetric [2 + 2] cycloaddition due to the fact that an optically pure amine can be easily introduced and it is also easy to remove. Also, since the chiral auxiliary would be attached by a double bond, it is closer to the reacting site and higher chiral inductions might be anticipated. This potential was investigated by Ghosez's group. In 1982, they reported the first examples of asymmetric

[2 + 2] cycloadditions of keteniminium salts bearing optically pure 2-(methoxymethyl)pyrrolidine as a chiral auxiliary (Scheme 49).[80] Though the unsubstituted keteniminium salt **152**, when reacted with cyclopentene followed by the hydrolysis of the resulting cyclobutanimium salt, gave cyclobutanone **153** in only 55% enantiomeric excess (ee) and in 30% yield, the β-disubstituted ketenimium salt **154** afforded **155** in 97% ee and in 70% yield. The chiralities of the two products **153** and **155**

Scheme 49. Asymmetric [2 + 2] cycloadditions with enantiopure ketenimium salts

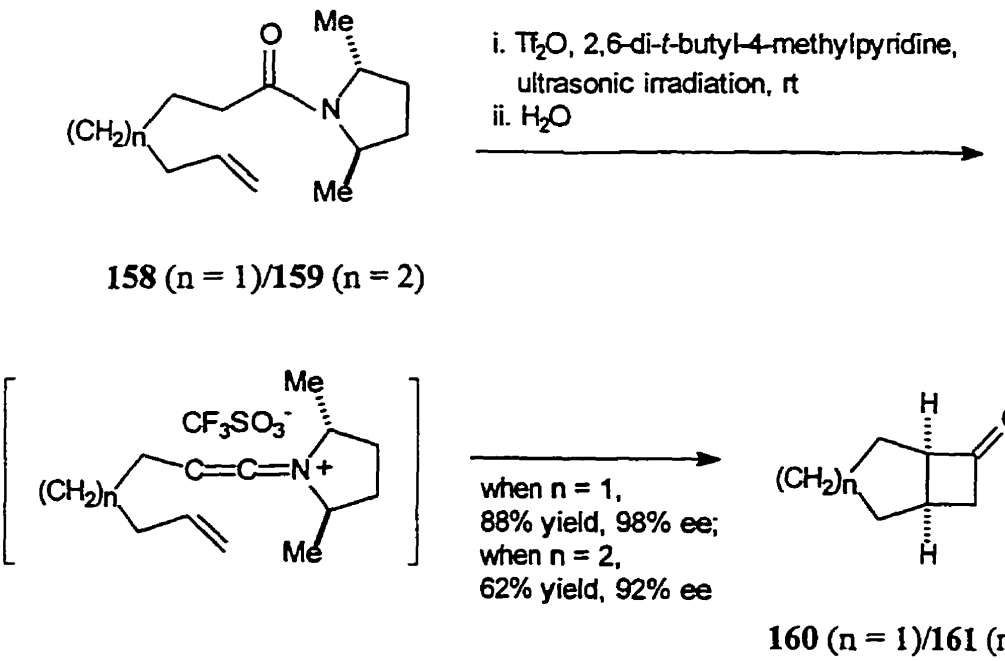




were found to be opposite, though the same chiral auxiliary was used in the reactions to produce them. The difference in chiral induction between **152** and **154** was explained by steric consideration in the two possible orthogonal transition states in the reactions. When R was hydrogen, transition state **156** might be favored, and therefore **153** was the major product in the reaction of **152** with cyclopentene. When R was methyl, the steric interaction between the methyl group and the methylenes in cyclopentene might make **156** relatively unfavored, and therefore **157** might become the favored transition state that led to the product **155**.

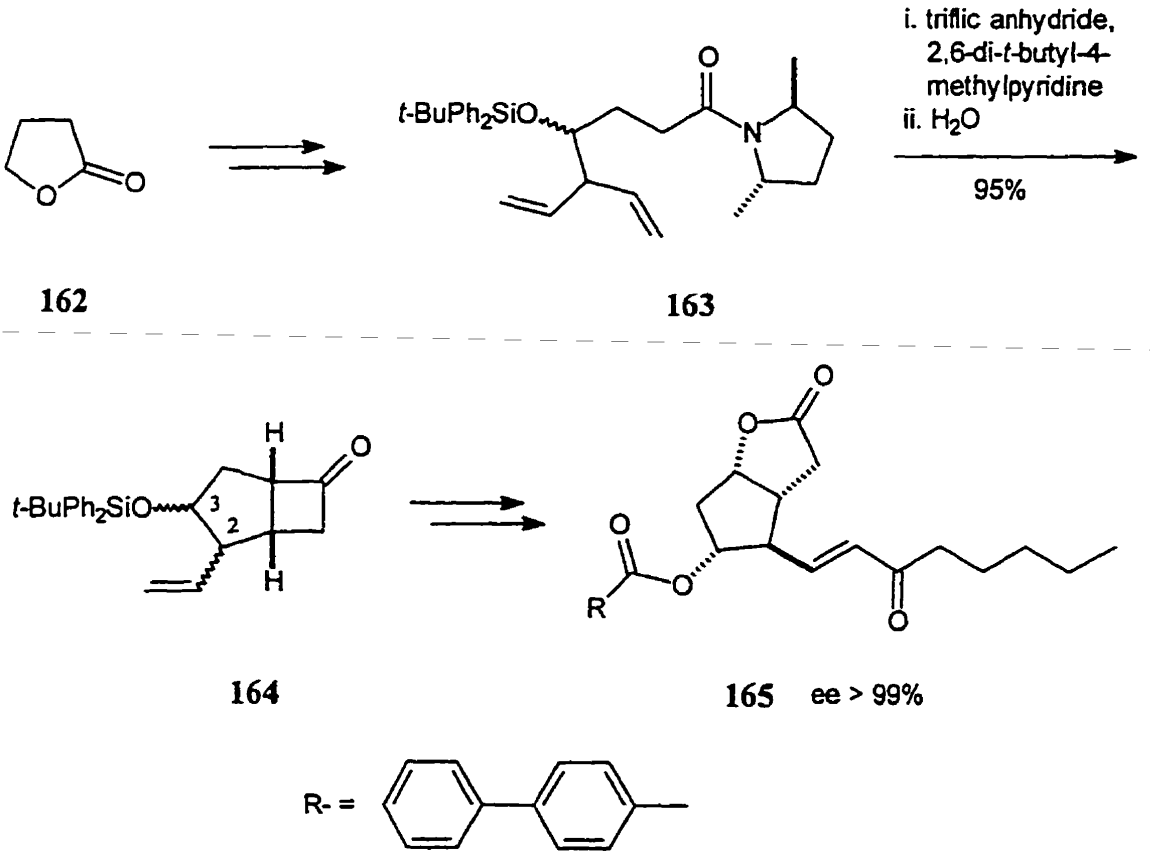
The asymmetric [2 + 2] cycloaddition of an optically pure keteniminium salt to an alkene has also been extended to an intramolecular version.[81] However, the chiral auxiliary has to have C_2 symmetry in order to avoid the formation of two possible

Scheme 50. Intramolecular asymmetric cycloadditions with enantiopure ketenimium salts



diastereoisomeric keteniminium salts, which would have opposite diastereofacial selectivities, when the parent amide was treated with triflic anhydride and a base. Excellent chiral induction was observed when 2,5-dimethylpyrrolidine was used as a chiral auxiliary. As shown in Scheme 50, when enantiopure keteniminium salt **158** or **159** was treated with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine under ultrasonic activation, followed by hydrolysis, bicyclo[3.2.0]heptan-6-one (**160**) and bicyclo[4.2.0]optan-7-one (**161**) were obtained in 98% and 92% ee, respectively. Without ultrasonic activation, the cycloadditions had to be run at a higher temperature, and the

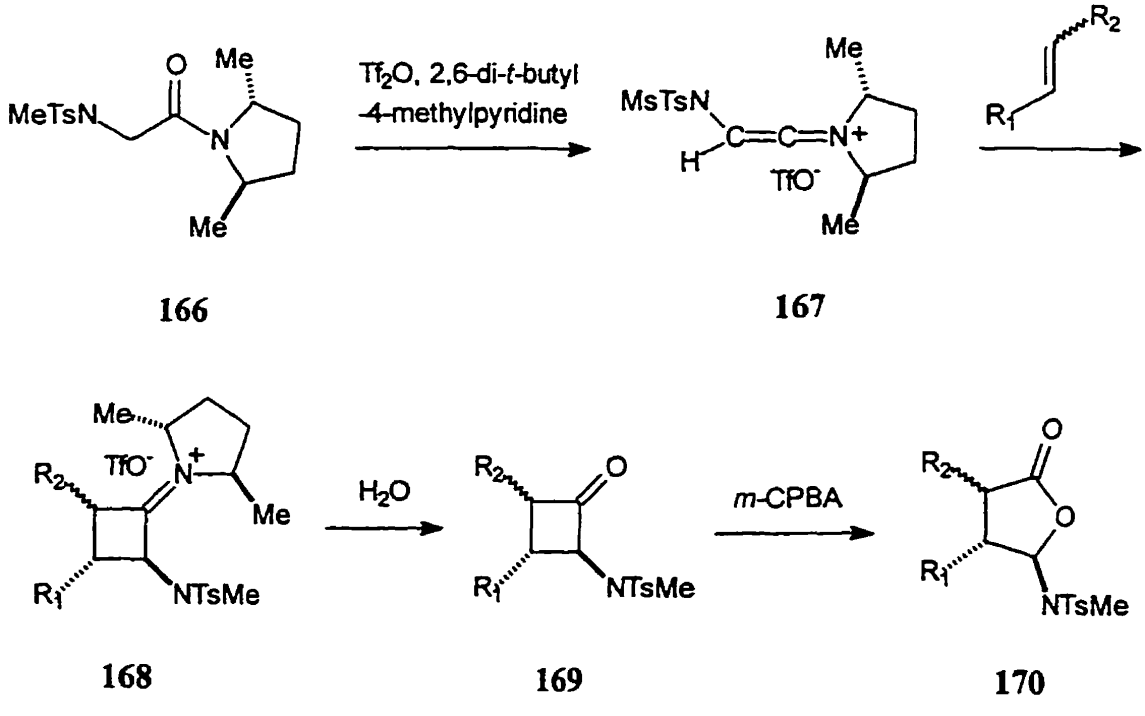
Scheme 51. Asymmetric formal synthesis of prostaglandins through ketenimium salt



diastereoselectivities were lower.

By employing the intramolecular asymmetric [2 + 2] cycloaddition as a key step, Ghosez's group achieved a short formal synthesis of enantiopure prostaglandins (Scheme 51).[82] Optically pure amide **163** was derived from γ-butyrolactone (**162**) and (2*S*,5*S*)-dimethylpyrrolidine. Treatment of **163** with triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine generated a keteniminium salt that underwent cycloaddition to provide, after hydrolysis, a 95% yield of cyclobutanone **164** as a mixture of four diastereoisomers, differing by the stereochemistry at C-2 and C-3. From **164**, lactone **165**, an advanced intermediate towards prostaglandins,[83] was then synthesized with greater than 99% enantiomeric purity.

Scheme 52. Asymmetric bis-acylation of alkenes through an enantiopure ketenimium salt

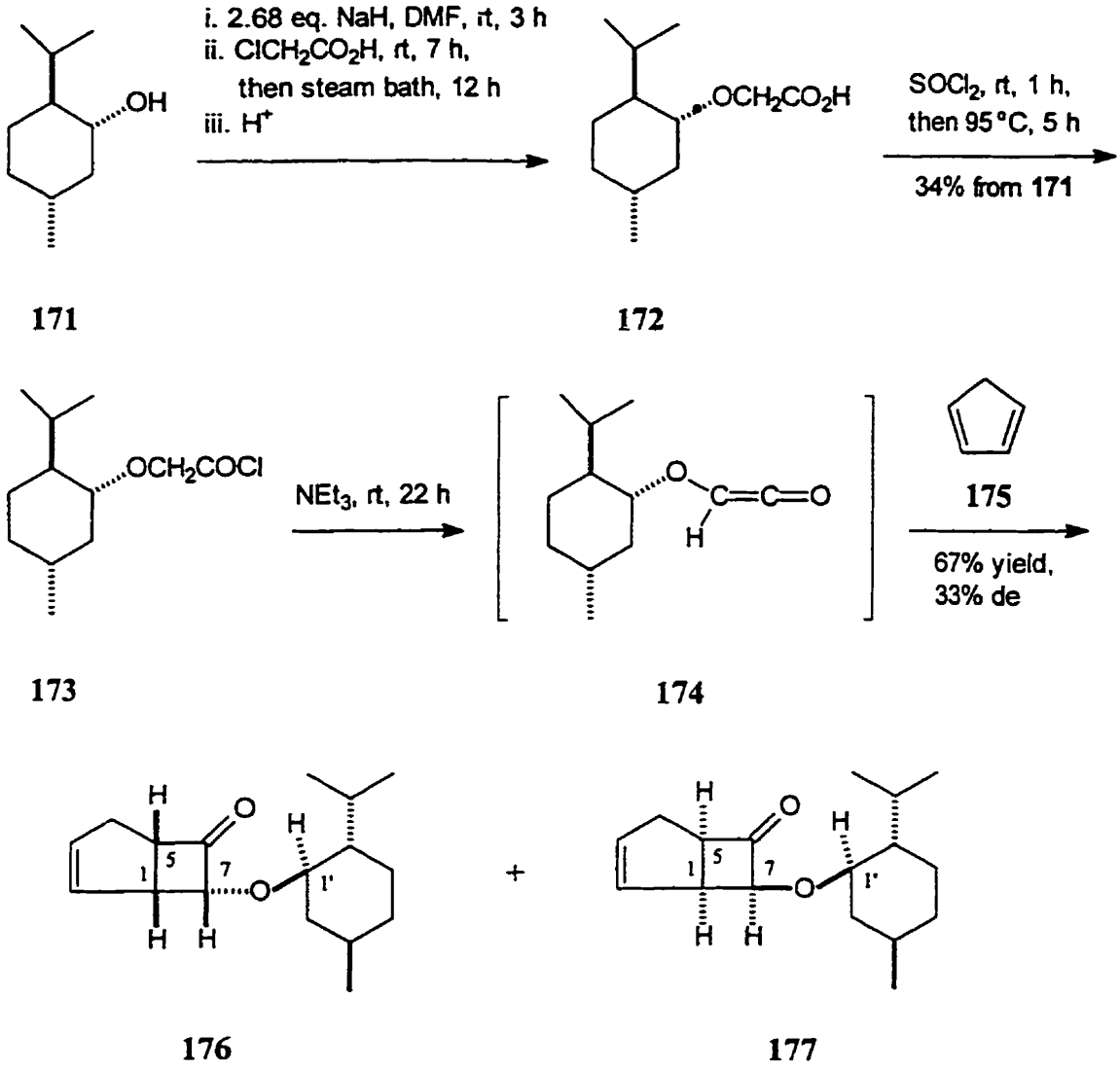


More recently, with the goal of developing chiral reagents for the "bis-acylation" of prochiral alkenes with high enantiofacial selectivities, Ghosez's group studied the asymmetric [2 + 2] cycloaddition of optically pure ketenimium salt **167**, generated from optically pure amide **166**, with a number of alkenes.[84] The results showed that the diastereofacial selectivities were generally good to excellent (86% to 96% de) in cycloadditions with cyclic and *cis*-1,2-disubstituted alkenes. However, with *trans*- and terminal alkenes, chiral induction was much lower. Baeyer-Villiger oxidation of the α nitrogen-substituted cyclobutanone **169** with *meta*-chloroperoxybenzoic acid (*m*-CPBA) regiospecifically afforded γ-lactone **170**, which was thought to be the equivalent of a bis-acylated product of an alkene.[85]

1. 4. 2. Preliminary Model Study of [2 + 2] Cycloaddition with Optically pure ketene

To explore the possibility of modifying our synthesis of the kempane diterpene ring system to an asymmetric approach, we first examined the asymmetric [2 + 2] cycloaddition of optically pure menthylketene **174** with cyclopentadiene (**175**) (Scheme 53). *l*-Menthoxyacetyl chloride (**173**) was prepared according to known procedures.[86] Treatment of *l*-menthol with excess sodium hydride in *N,N*-dimethylformamide (DMF) at room temperature for three hours, followed by chloroacetic acid, provided, after acidification, *l*-menthoxyacetic acid (**172**) in 48% yield. Then, **172** was converted to **173** in 72% yield with thionyl chloride at 95 °C for five hours. The reaction of **173** with triethylamine at room temperature generated *l*-menthoxyketene (**174**), which underwent cycloaddition to cyclopentadiene (**175**) to afford a 2:1 mixture of diastereoisomers **176**

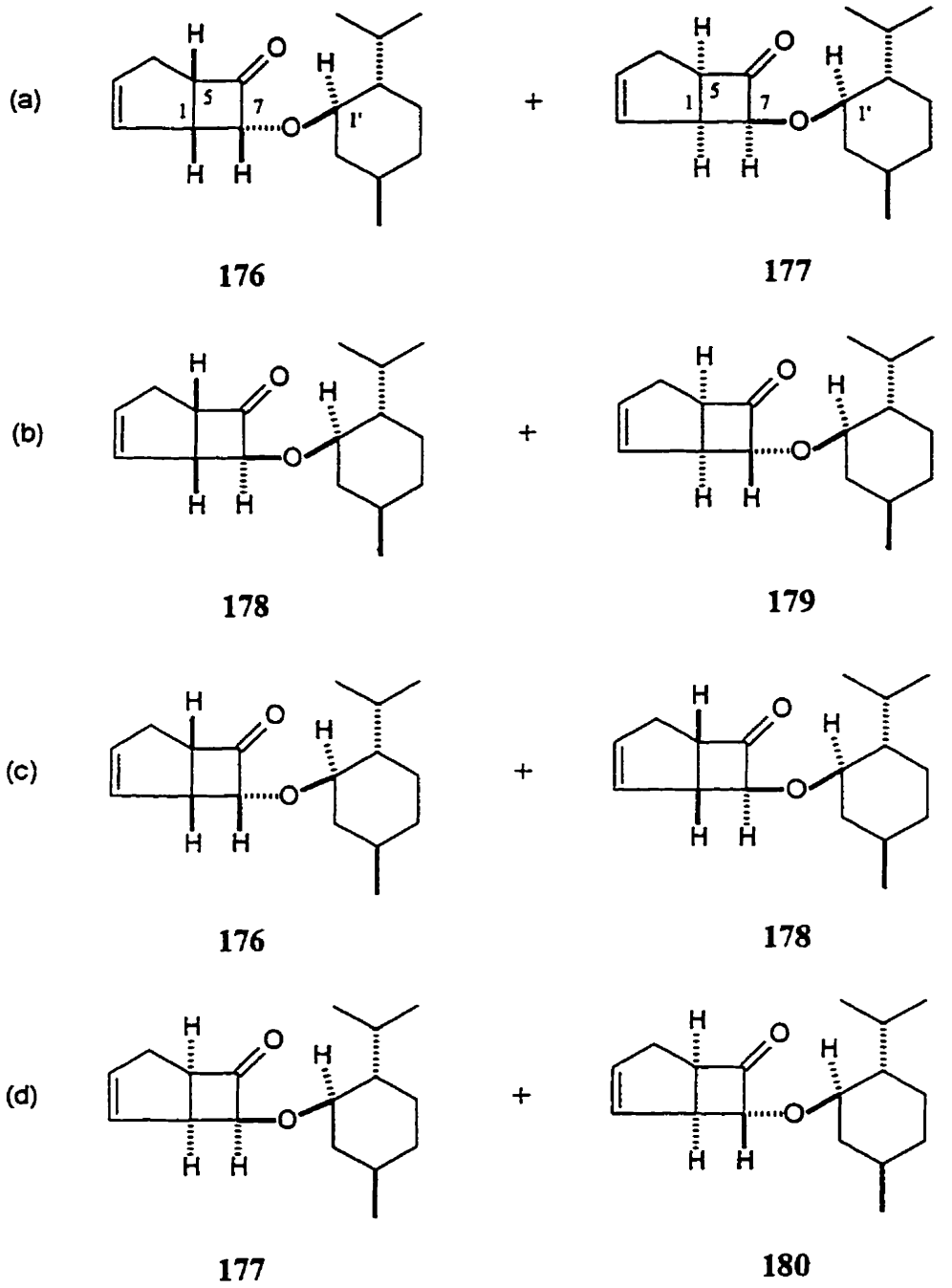
Scheme 53. Asymmetric cycloaddition of enantiopure ketene **174** to cyclopentadiene



and **177** in 67% yield. The menthoxy chiral auxiliary in ketene **174** did display chiral induction in the cycloaddition, but the diastereofacial selectivity was not good, as only a 33% de was obtained. The two diastereoisomers **176** and **177** were inseparable by flash chromatography, but their structures were suggested by the following rationale.

There were four likely combinations of the two products in the cycloaddition of

Scheme 54. Likely combinations of the two products in the reaction of **174** with **175**

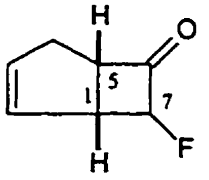
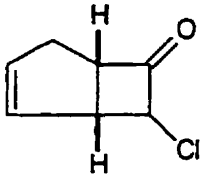
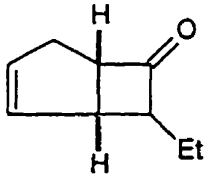
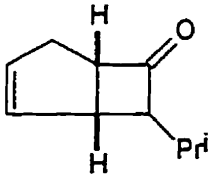
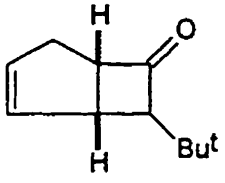


174 with **175**, as shown in Scheme 54. Composition (a), **176** and **177**, represented the diastereoisomers resulting from the menthoxy-*endo* addition of **174** to cyclopentadiene

(**175**) from both faces. Composition (b), **178** and **179**, would represent the diastereoisomers resulting from epimerization of the menthoxy-*endo* addition products **176** and **177**, or from the menthoxy-*exo* addition of **174** to **175** from both faces. Compositions (c), and (d) represented the possibilities that the menthoxy-*endo* addition of **174** to cyclopentadiene (**175**) proceeded with diastereofacial specificity to give **176** or **177**, but during the reaction, partial epimerization occurred leading to the formation of **178** and **180**.

For each isomer, the NMR signals for H-1, H-5, and H-7 were well separated and easily assigned using COSY spectra. However, the corresponding signals for these protons in the two isomers were almost identical. The signals that were well separated for the two products (and used to measure the ratio of the two products) were the signals corresponding to H-1', appearing at δ 3.17 as a doublet of triplets (J = 10.6, 4.2 Hz) for the major product and at δ 3.31 as a doublet of triplets (J = 10.6, 4.3 Hz) for the minor product. The fact that the pairs of the H-1, H-5, and H-7 signals for the two products appeared at the same chemical shift suggested that the two products had the same relative stereochemistry at C-1, C-5 and C-7. This was consistent with compositions (a) and (b). In addition, if one of the two products was the menthoxy-*endo* adduct, but the other was a menthoxy-*exo* adduct, as in the case of compositions (c) and (d), the pairs of H-1 and H-7 signals would be expected to have very different chemical shifts due to their distinct chemical environments. This could be corroborated by a large number of literature examples, [87] some of which are listed in Table 3. Finally, compositions (a) and (b) were distinguished by NOE experiments. When the signals for H-7 were saturated, the signals

Table 3. Chemical shifts of H-7 and H-1 in *endo* and *exo* 7-substituted bicyclo[3.2.0]hept-2-en-6-ones[87]

7-substituted-bicyclo[3.2.0]hept-2-en-6-one	H-7		H-1	
	endo-isomer	*exo*-isomer	*endo*-isomer	*exo*-isomer
	5.52	4.86	3.86	3.58
	5.08	3.88	3.84	3.02
	3.28	2.69	3.52	3.07
	3.02	2.53	3.50	3.14
	3.26	2.58	3.53	3.24

for H-1 were enhanced by 4%. Therefore, composition (a) was determined to be the products of the cycloaddition of **174** and **175**.

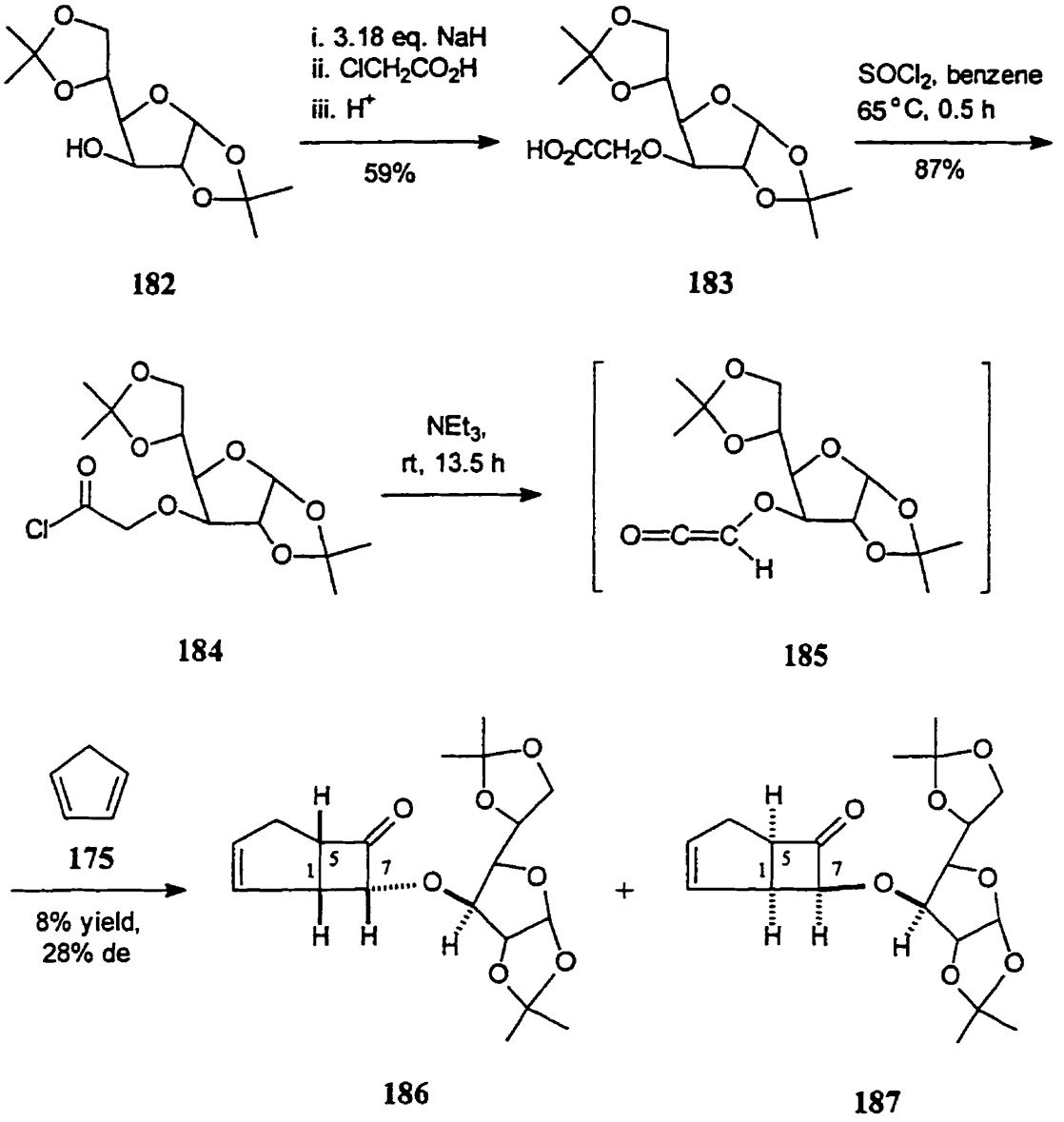
The absolute configurations of C-1, C-5, and C-7 in products **176** and **177** were

181

not determined, but they could be solved by reductive removal of the chiral auxiliary and measurement of the specifically optical rotation of the resulting bicyclo[3.2.0]hept-2-en-6-one (**181**). The specific rotations of both enantiomers of **181** are known.[88]

We also examined the cycloaddition of optically pure, (-)-diacetone-D-glucose derived ketene **185** with cyclopentadiene (**175**) (Scheme 55). (-)-Diacetone-D-glucose is readily available and has successfully been used as a chiral auxiliary to prepare enantiopure dimethylsulfoxide.[89] Treatment of (-)-diacetone-D-glucose (**182**) with excess sodium hydride in DMF at room temperature for one hour, and then with sodium chloroacetate, produced *in situ* from chloroacetic acid and the sodium hydride, afforded, after acidification, the carboxylic acid **183** in 59% yield. The conversion of **183** to **184** was initially attempted with neat thionyl chloride at reflux for five hours, the conditions that had successfully been used to convert menthoxyacetic acid (**172**) to **173**. However, it was found that the acetal functions were not sufficiently stable, and a complex mixture of products was produced. However, the acid chloride **184** was obtained in 87% yield, by reacting **183** with only a slight excess thionyl chloride in benzene at 65 °C for 30 minutes. Subjection of **184** to triethylamine in the presence of cyclopentadiene (**175**) at room temperature for twelve hours gave a mixture of two adducts **186** and **187** in only 8% yield. The structures of the products were assigned on the basis of their NMR spectra.

Scheme 55. Asymmetric cycloaddition of enantiopure ketene **185** to cyclopentadiene

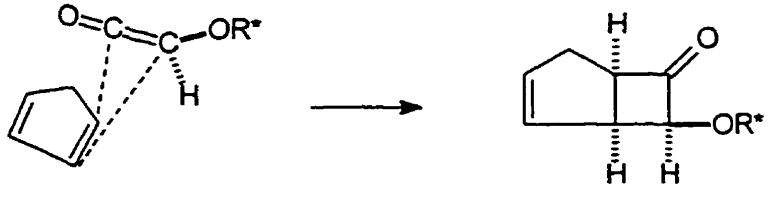


The COSY spectrum showed that the corresponding signals for H-1 and H-5 of the two adducts were completely overlapped, but the H-7 signals appeared separately, at δ 5.03 as a doublet of doublets (J = 8.4, 3.0 Hz) for the minor adduct and at δ 4.90 as doublet of doublets (J = 8.7, 2.8 Hz) for the major adduct. However, NOE experiments confirmed

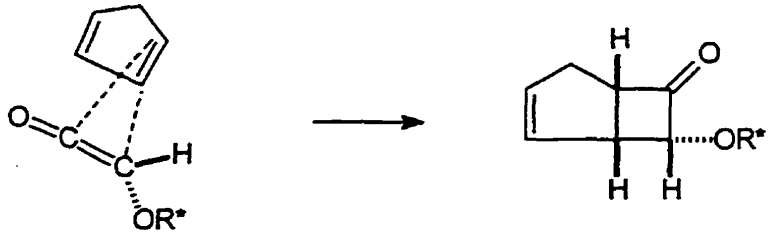
that in both adducts H-7 was *cis* to H-1 and H-5. The ratio of the two adducts was 1:1.8, as determined by the integration of the signals for the H-7. Therefore, the diastereomeric excess of the two products was only 28%.

The low chiral induction in the [2 + 2] cycloaddition of ketene **174** and **185** with cyclopentadiene (**175**) could be understood by consideration of the orthogonal transition state, which is required by the conservation of orbital symmetry (Section 1. 2. 2). The formation of oxygen-endo adducts in the cycloadditions revealed that the reactions were initiated by the approach of cyclopentadiene to the less hindered, unsubstituted side of the ketenes, as shown in Scheme 56. Since the chiral auxiliaries were behind the reacting side of the ketenes, it was reasonable that the two transition states **188** and **189** were close in energy and therefore the diastereofacial selectivities in the cycloadditions were low.

Scheme 56. Transition states in the asymmetric cycloadditions of **174** and **185** with **175**



188 **177 or 187**

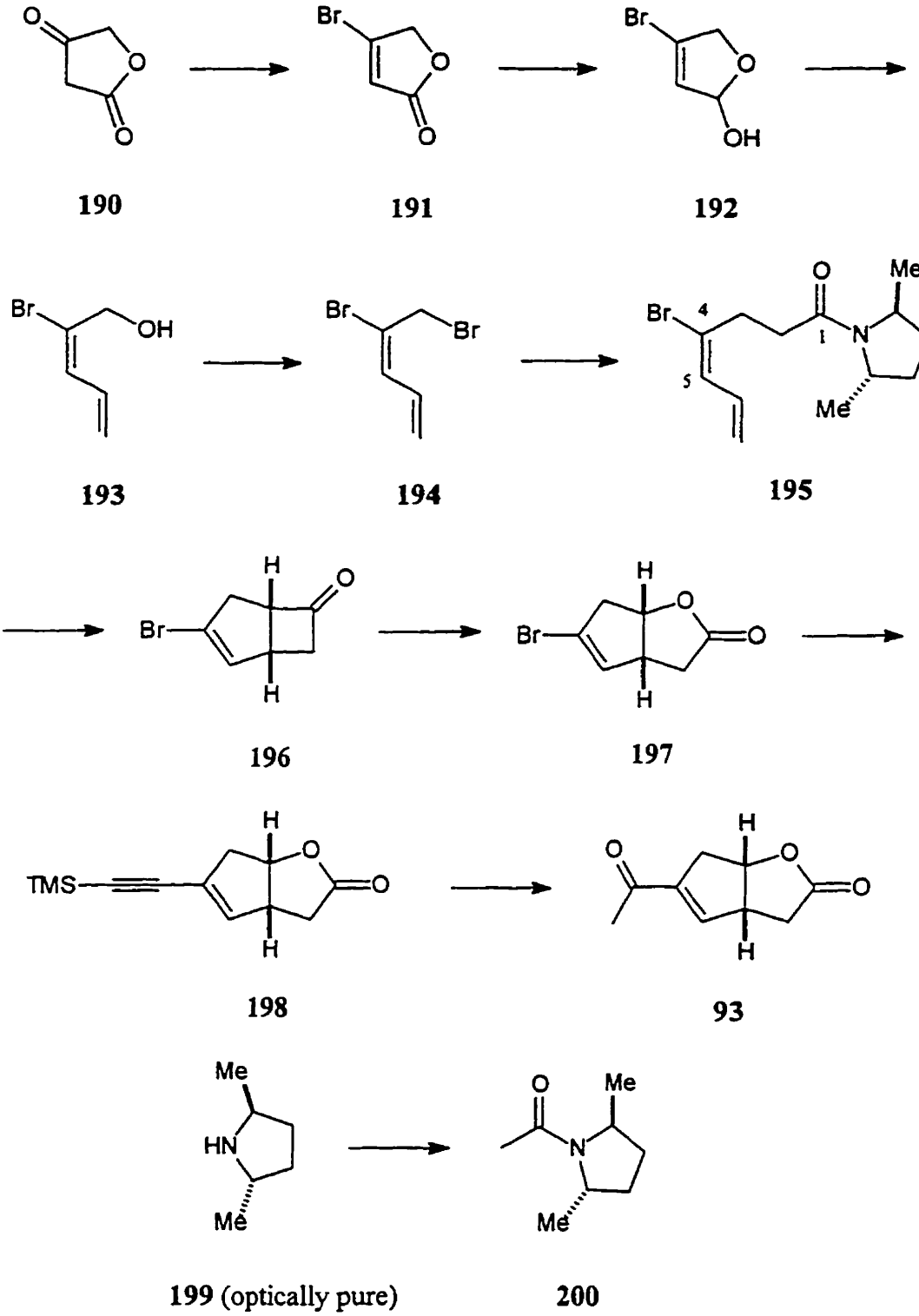


189 **176 or 186**

For further exploration of an efficient approach to asymmetric synthesis of kempane diterpenoids, a proposal of the preparation of enantiopure enone **93**, the racemic form of which was a key intermediate in our synthesis of the kempane diterpene ring system (Section 1. 2), is given in Scheme 57. The key step would be the conversion of enantiopure amide **195** to 3-bromobicyclo[3.2.0]hept-2-en-6-one (**196**) by the intramolecular asymmetric [2 + 2] cycloaddition of a keteniminium salt. An excellent degree of chiral induction in the reaction is expected according to Ghosez's reports.[81] Compared to Ghosez's amide **158**, the major difference in **195** is the extra double bond between C-4 and C-5. However, the *cis*-geometry of this extra double bond should make the keteniminium salt more favorable for the intramolecular cycloaddition. Baeyer-Villiger oxidation of **196** would provide lactone **197**, which could be converted to enyne **198** by a Heck reaction with trimethylsilylacetylene.[90] Removal of the trimethylsilyl group with fluoride and hydrolysis of the triple bond in **198** should furnish the optically pure intermediate **93**.

The enantiopure amide **195** would be prepared from commercially available tetronic acid (**190**). G. Jas has shown that reacting **190** with oxalyl bromide could afford 4-bromo-2(5*H*)-furanone (**191**) in 83% yield.[91] Reduction of **191** with diisobutylaluminum hydride (Dibal) should give hemi-acetal **192**, which would then be converted to diene **193** by Wittig reaction of triphenylphosphonium methylid.[92] Reaction of **193** with triphenylphosphine and bromine[93] should provide dibromide **194**. Enantiopure amide **195** would be obtained by treatment of enantiopure acetamide **200** with LDA, followed by dibromide **194**. Finally, acetamide **200** could be prepared from

Scheme 57. A proposal of the asymmetric approach to kempane diterpenoids



190 **191** **192**

193 **194** **195**

196 **197**

198 **93**

199 (optically pure) **200**

optically active 2,5-dimethylpyrrolidine and acetyl chloride. According to Ghosez's results,[81] it is most likely that we would need (2*S*,5*S*)-2,5-dimethylpyrrolidine as the chiral auxiliary to give the absolute stereochemistry of the kempane diterpenoids. Since there is only one step between the introduction and removal of the chiral auxiliary, the chiral auxiliary would be most efficiently utilized. This proposal also avoids the low yield transformation of lactone **41** to **93** in the racemic synthesis (Scheme 29).

1. 5. Experimental

General Methods.

All reactions involving moisture- or/and air-sensitive reactants were conducted with pre-heated and nitrogen-flushed glassware and using dry solvents under nitrogen. Tetrahydrofuran (THF) and 1,4-dioxane were dried over sodium with benzophenone as an indicator, i.e., THF and 1,4-dioxane were gently refluxed with sodium in the presence of benzophenone until a dark blue color persisted, then they were distilled. Dimethylformamide (DMF) was dried over anhydrous $MgSO_4$. Nitromethane was dried over 4Å Molecular Sieves. Dry hexane, pentane, benzene, toluene, dichloromethane, and triethylamine were obtained by distillation over calcium hydride. 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. Preparative layer chromatography (PLC) was carried out on E. Merck silica gel 60 F_{254} precoated plates.

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. Nuclear magnetic resonance (NMR) spectra were obtained on a General Electric GE-300-NB (300 MHz) instrument. ^1H NMR and ^{13}C NMR spectra were recorded 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 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 on a Rigaku AFC6S diffractometer.

Spectroscopic data are reported in the order of IR, ^{1}H NMR, NOE (nuclear Overhauser effect enhancements), ^{13}C NMR, MS, and HRMS or combustion analysis. Media used for the acquisition of spectra are indicated in parentheses, where applicable. For example, IR (Nujol) denotes that the sample for the IR spectrum was prepared in Nujol. 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: doublet of doublets, dt: doublet of triplets, dq: doublet of quartets, ddd: doublet of doublets of doublets, br: broad. Assignments are based on COSY, HET-CORR, APT, and NOE difference 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 %).

syn and _anti_ 3-Methyl-2-cyclohexen-1-one, _p_-toluenesulfonylhydrazone (37)

A mixture of 3-methyl-2-cyclohexen-1-one (**36**) (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 for 15 h. To the resulting red solution was added benzene (200 mL), and the mixture was concentrated under vacuum. This operation was repeated twice with 200 mL of benzene. The residue was solidified by trituration with Et_2O and dried in a desiccator over $CaCl_2$ under vacuum for 24 h to afford the crude hydrazone **37** (57.8 g) as a beige solid. The crude **37** was a 2:1 mixture of stereoisomers, otherwise, it was fairly pure, as shown by ^1H NMR. This mixture was used in the next step without purification.

^1H NMR ($CDCl_3$) data for the major isomer of **37** from the mixture: δ 7.85 (2H, d, J = 8.2 Hz), 7.31 (2H, d, J = 8.2 Hz), 5.94 (1H, q, J = 1.4 Hz, H2), 2.42 (3H, s, C_6H_4-CH_3), 2.24 (2H, t, J = 6.5 Hz), 2.05 (2H, t, J = 6.0 Hz), 1.81 (3H, d, J = 1.4 Hz, 3-methyl), 1.75 (2H, m, H5).

^1H NMR ($CDCl_3$) data for the minor isomer of **37** from the mixture: δ 7.86 (2H, d, J = 8.5 Hz), 7.31 (2H, d, J = 8.2 Hz), 6.13 (1H, q, J = 1.4 Hz, H2), 2.42 (3H, s, C_6H_4-CH_3), 2.32 (2H, t, J = 6.4 Hz), 2.15 (2H, t, J = 6.1 Hz), 1.87 (3H, d, J = 1.4 Hz, 3-methyl), 1.75 (2H, m, H5).

cis-8,8-Dichloro-3-methylbicyclo[4.2.0]oct-2-en-7-one (39)

To a mechanically stirred suspension of the crude hydrazone **37** (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 solution

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 (**38**) 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 filtration cake was extracted with pentane twice. The combined filtrates 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. Vacuum distillation of the residue provided crude **39** (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. An analytical sample was obtained by column chromatography (2% Et_2O/hexane) as a colorless oil: IR (neat) 1804 (s), 1444 (m), 1109 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.60 (1H, m, H2), 4.05 (1H, m, H6), 3.43 (1H, m, H1), 2.15 (1H, m, H5 *anti* to H6), 1.99-1.92 (2H, m, H4), 1.77 (3H, s, 3-methyl), 1.65 (1H, m, H5 *syn* to H6). NOE data 1.65 (4.05, 2%). ^{13}C NMR ($CDCl_3$) δ 197.0 (0, C7), 140.4 (0, C3), 117.1 (1, C2), 87.1 (0, C8), 52.4 (1, C6), 44.8 (1, C1), 25.9 (2, C4), 24.6 (3, 3-methyl), 19.4 (2, C5). MS *m/z* 206 (M^++2, 4), 204 (M^+, 5), 169 (6), 141 (6), 94 (22), 91 (10), 79 (29), 77 (22), 55 (100), 51 (12). HRMS calcd. for $C_9H_{10}{}^{35}Cl_2O$ 204.0109, found 204.0103.

cis-3-Methylbicyclo[4.2.0]oct-2-en-7-one (40)

To a mixture of **39** (11.4 g, approximately 55.4 mmol) and NH_4Cl (23.5 g, 44.7

mmol) in MeOH (300 mL) was added Zn dust (analytical grade, 47.9 g, 730 mmol) in portions with stirring at 0 °C over 1 h. The mixture was then stirred at rt for 10 h. Et_2O (150 mL) was added. The solid was removed by filtration, and 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. Vacuum distillation of the residue provided **40** (4.34 g) at 70-80 °C/5 mmHg as a colorless oil. This distilled product was fairly pure and was used in the next step without further purification. An analytical sample was obtained by column chromatography (15% Et_2O/hexane) as a colorless oil: IR (neat) 1778 (s), 1446 (m), 1071 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.63 (1H, q, J = 1.3 Hz, H2), 3.49 (1H, m, H6), 3.24 (1H, ddd, J =16.8, 9.2, 2.8 Hz, H8 *syn* to H1), 2.91 (1H, m, H1), 2.54 (1H, ddd, J = 16.8, 3.7, 2.6 Hz, H8 *anti* to H1), 2.05-1.94 (2H, m, H5 and H4), 1.80 (1H, m, H4), 1.57 (1H, m, H5 *syn* to H6). NOE data 3.49 (2.91, 2%; 1.57, 2%), 3.24 (2.91, 2%), 2.91 (5.63, 2%; 3.49, 2%). ^{13}C NMR ($CDCl_3$) δ 212.1 (0, C7), 135.8 (0, C3), 122.6 (1, C2), 56.3 (1, C6), 52.3 (2, C8), 26.2 (2, C4), 24.4 (3, 3-methyl), 23.4 (1, C1), 19.9 (2, C5). MS *m/z* 136 (M^+, 0.3), 94 (84), 93 (16), 91 (14), 79 (100), 77 (22), 55 (22). HRMS calcd. for $C_9H_{12}O$ 136.0888, found 136.0892.

cis-3a,6,7,7a-Tetrahydro-5-methyl-2(3*H*)-benzofuranone (41)

To a solution of **40** (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 column chromatography (55% Et_2O/hexane) to afford **41** (4.05 g, 27% overall yield from **36**) 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.

(3α,3aα,7aα)-3a,6,7,7a-Tetrahydro-3,5-dimethyl-2(3*H*)-benzofuranone (47)

To diisopropylamine (2.81 mL, 21.2 mmol) in dry THF (26 mL) was introduced *n*-BuLi (2.5 M in hexane, 7.72 mL, 19.3 mmol) at 0 °C over 20 min. The solution was stirred for 10 min and then cooled to -78 °C when lactone **41** (2.94 g, 19.3 mmol) in dry THF (26 mL) was introduced over 30 min. This solution was stirred for 30 min before MeI (3.04 g, 21.3 mmol) in hexamethylphosphoramide (HMPA) (4.16 g, 23.2 mmol) was

added over 20 min. After 3 h, the reaction mixture was allowed to warm to 0 °C. The reaction was quenched with dilute NH_4Cl solution (100 mL) and diluted with Et_2O (300 mL). The aqueous phase was removed. The organic layer was washed with water (3 x 80 mL) and brine (80 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was subjected to column chromatography (25% EtOAc/hexane) to afford **47** (2.87 g, 89% yield) as a colorless oil: IR (neat) 1773 (s), 1154 (m), 1012 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.32 (1H, m, H4), 4.67 (1H, ddd, J = 10.8, 6.8, 4.1 Hz, H7a), 2.58 (1H, m, H3a), 2.37 (1H, m, H3), 2.08-1.70 (4H, m, H6 and H7), 1.71 (3H, s, 5-methyl), 1.31 (3H, d, J = 7.5 Hz, 3-methyl). NOE data 4.67 (2.58, 2%), 1.31 (2.58, 3%). ^{13}C NMR ($CDCl_3$) δ 179.7 (0, C2), 136.0 (0, C5), 119.4 (1, C4), 75.9 (1, C7a), 42.7 (1, C3a), 41.6 (1, C3), 26.1 (2), 25.6 (2), 23.5 (3, 5-methyl), 14.4 (3, 3-methyl). MS *m/z* 166 (M^+, 23), 121 (9), 110 (17), 107 (28), 96 (14), 95 (17), 93 (81), 91 (20), 86 (17), 81 (17), 79 (100), 77 (18), 74 (100), 69 (24), 68 (22), 67 (18), 55 (12), 53 (13). HRMS calcd. for $C_{10}H_{14}O_2$ 166.0994, found 166.0996.

(3α,3aα,6aα)-5-Acetyl-3,3a,6,6a-tetrahydro-3-methyl-2*H*-cyclopenta[*b*]furan-2-one (49)

To a solution of **47** (3.05 g, 18.4 mmol) in CH_2Cl_2 (200 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. Then, dimethyl sulfide (15 mL, 205 mmol) was added, and the mixture was allowed to warm to rt while stirring overnight. The solvent and excess Me_2S were evaporated under vacuum to give the crude

ozonolysis product **48** as a yellow oil.

The crude product **48** was dissolved in benzene (350 mL) and a catalytic amount of (±)-camphorsulfonic acid (0.430 g, 1.85 mmol) was added. The solution was refluxed in a Dean-Stark apparatus for 25 h. After cooling to rt, this solution was washed with 5% $NaHCO_3$ (2 x 100 mL) and brine (2 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was subjected to column chromatography (70% EtOAc/hexane) to provide **49** (1.59 g, 48% yield from **47**) as a pale yellow oil: IR (neat) 1769 (s), 1670 (s), 1179 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.51 (1H, d, J = 1.7 Hz, H4), 5.20 (1H, apparent dt, J = 5.5, 1.6 Hz, H6a), 3.41 (1H, m, H3a), 2.98-2.82 (2H, m, H6), 2.65 (1H, dq, J = 7.6, 1.9 Hz, H3), 2.35 (3H, s, $COCH_3$), 1.42 (3H, d, J = 7.6 Hz, 3-methyl). NOE data 5.20 (3.41, 2%), 3.41 (5.20, 2%), 1.42 (5.20, 2%; 3.41, 4%). ^{13}C NMR ($CDCl_3$) δ 195.9 (0, $COCH_3$), 178.8 (0, C2), 143.6 (0, C5), 140.7 (1, C4), 80.6 (1, C6a), 54.6 (1, C3a), 39.3 (1, C3), 37.6 (2, C6), 26.7 (3, $COCH_3$), 17.4 (3, 3-methyl). MS *m/z* 180 (M^+, 18), 165 (20), 136 (14), 121 (16), 109 (14), 93 (13), 91 (11), 81 (14), 77 (16), 65 (11), 56 (18), 53 (10), 43 (100). HRMS calcd. for $C_{10}H_{12}O_3$ 180.0786, found 180.0781.

(3α,3aα,6aα)-5-(1-Acetoxyvinyl)-3,3a,6,6a-tetrahydro-3-methyl-*2H*-cyclopenta[*b*]furan-2-one (50)

A solution of enone **49** (180 mg, 1.00 mmol) and isopropenyl acetate (5.0 mL, 45 mmol) with a catalytic amount of (±)-camphorsulfonic acid (20 mg, 0.086 mmol) was heated at reflux for 4 days. The excess isopropenyl acetate was removed under vacuum.

The residue was subjected to PLC (60% EtOAc/hexane) to afford **50** (130 mg, 58% yield) as a pale yellow oil: IR (neat) 1765 (s), 1372 (m), 1196 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.64 (1H, d, J = 1.1 Hz, H4), 5.20 (1H, dt, J = 6.0, 1.2 Hz, H6a), 5.00 (1H, d, J = 2.0 Hz, CH_2=), 4.98 (1H, d, J = 2.0 Hz, CH_2=), 3.27 (1H, m, H3a), 2.88 (2H, m, H6), 2.57 (1H, dq, J = 7.6, 2.1 Hz, H3), 2.22 (3H, s, CH_3CO), 1.37 (3H, d, J = 7.6 Hz, 3-methyl). ^{13}C NMR ($CDCl_3$) δ 179.4 (0, C2), 168.7 (0, $COCH_3$), 149.0 (0), 136.3 (0), 127.7 (1, C4), 105.5 (2, CH_2=), 81.1 (1, C6a), 54.0 (1, C3a), 39.9 (1, C3), 38.8 (2, C6), 20.8 (3, CH_3CO), 17.3 (3, 3-methyl).

(4aα,7aβ,10β,10aβ,10bα,10cα)-6-Acetoxy-4a,5,7,7a,10,10a,10b,10c-octahydro-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,9-trione (51) and **(4aα,7aβ,10β,10aβ,10bα,10cα)-6-acetoxy-4a,5,7,7a,10,10a,10b,10c-octahydro-3,4a,10-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,9-trione (52)**

A solution of diene **50** (107 mg, 0.481 mmol) and 2,6-dimethyl-1,4-benzoquinone (**13**) (73 mg, 0.53 mmol) in dry toluene (5.0 mL) was heated at reflux. The product happened to have exactly the same R_f value by TLC as the starting diene **50**, so that the reaction could not be monitored in this way. After 4 days, the solvent was removed under vacuum. The residue was subjected to PLC (60% EtOAc) to afford material (120 mg) that was found by ^1H NMR to be a 2:1 mixture of products and starting diene **50**. Thus, this material was again heated at reflux with another portion of **13** (110 mg, 0.808 mmol) in dry toluene (5.0 mL) for 8 days. The solvent was removed under vacuum. PLC (60%

EtOAc/hexane) gave a 4:1 mixture of **51** and **52** (83 mg, 50% yield) as a pale yellow foam.

NMR data for **51** from the mixture: ^{1}H NMR ($CDCl_3$) δ 6.45 (1H, t, J = 1.4 Hz, H3), 5.19 (1H, m, H7a), 3.18 (1H, dd, J = 13.2, 5.8 Hz, H10a), 3.02 (1H, m, H4a), 2.90 (1H, m, H7β), 2.62 (1H, m), 2.51-2.39 (3H, m), 2.19 (1H, m), 2.10 (3H, s, CH_3CO), 1.99 (3H, d, J = 1.4 Hz, 2-methyl), 1.44 (3H, s, 10c-methyl), 1.32 (3H, d, J = 7.4 Hz, 10-methyl). NOE data 5.19 (3.18, 5%; 2.90, 3%), 3.18 (5.19, 6%), 1.44 (3.02, 8%), 1.32 (3.18, 7%). ^{13}C NMR ($CDCl_3$) δ 201.4 (0), 198.8 (0), 179.1 (0, C9), 168.4 (0, $COCH_3$), 148.1 (0, C2), 137.4 (0, C6), 133.8 (1, C3), 127.0 (0, C6a), 81.8 (1, C7a), 55.9, 52.8, 51.1, 48.9, 43.2, 34.4, 28.7, 24.4, 20.6, 16.5, 15.2.

Discernible ^{1}H NMR ($CDCl_3$) data for **52** from the mixture: δ 6.63 (1H, q, J = 1.4 Hz, H2), 4.94 (1H, m, H7a), 2.17 (3H, s, CH_3CO), 2.02 (3H, d, J = 1.4 Hz, 3-methyl), 1.40 (3H, d, J = 7.7 Hz, 10-methyl), 1.25 (3H, s, 10c-methyl).

(3α,3aα, 6aα)-5-((1-(*tert*-Butyldimethylsilyl)oxy)vinyl)-3,3a,6,6a-tetrahydro-3-methyl-2*H*-cyclopenta[*b*]furan-2-one (54) and **(3α,3aβ, 6aβ)-5-((1-(*tert*-butyldimethylsilyl)oxy)vinyl)-3,3a,6,6a-tetrahydro-3-methyl-2*H*-cyclopenta[*b*]furan-2-one (55)**

Method A: To a solution of diisopropylamine (0.14 mL, 1.00 mmol) in dry THF (4.0 mL) was introduced *n*-BuLi (2.5 M in hexane, 0.40 mL, 1.00 mmol) at 0 °C over 5 min. The solution was stirred for 20 min and then transferred by syringe to a solution of

enone **49** (0.180 g, 1.00 mmol) and *tert*-butyldimethylsilyl triflate (TBSOTf) (0.28 mL, 1.22 mmol) in dry THF (5.0 mL) at - 78 °C over 15 min. This mixture was stirred at -78 °C for 1 h before it was allowed to warm to rt. This was diluted with hexane (100 mL), washed with water (3 x 30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was subjected to PLC (25% EtOAc/hexane) to afford **54** (214 mg, 73% yield) and **55** (37 mg, 12% yield).

Method B: To a solution of diisopropylamine (0.23 mL, 1.75 mmol) in dry THF (5.0 mL) was introduced *n*-BuLi (2.5 M in hexane, 0.63 mL, 1.57 mmol) at 0 °C over 5 min. This solution was stirred for 10 min and then cooled to -78 °C when enone **49** (128 mg, 0.710 mmol) in dry THF (1.0 mL) was added over 10 min. After 30 min, HMPA (1.0 mL) was added, followed by *tert*-butyldimethylsilyl chloride (243 mg, 1.56 mmol) in dry THF (1.0 mL). The mixture was allowed to warm to rt, and it was stirred for 2 h before it was diluted with pentane (100 mL) then washed with water (2 x 30 mL) and brine (30 mL). The resulting solution was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was subjected to PLC (25% EtOAc/hexane) to afford **54** (16 mg, 8% yield) and **55** (100 mg, 48% yield).

Diene **54**: Colorless crystals: mp 75.0-76.5 °C. IR (CH_2Cl_2) 1772 (s), 1590 (m), 1472 (m), 1314 (m), 1253 (m), 1177 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.80 (1H, d, J = 1.4 Hz, H4), 5.19 (1H, apparent dt, J = 5.5, 1.7 Hz, H6a), 4.36 (1H, s, CH_2=), 4.33 (1H, s, CH_2=), 3.25 (1H, m, H3a), 2.88-2.73 (2H, m, H6), 2.58 (1H, dt, J = 7.6, 1.9 Hz, H3), 1.37 (3H, d, J = 7.6 Hz, 3-methyl), 0.96 (9H, s, $SiC(CH_3)_3$), 0.17 (6H, s, $SiMe_2$). NOE data

5.19 (3.25, 3%), 3.25 (5.19, 3%), 1.37 (3.25, 4%). ^{13}C NMR ($CDCl_3$) δ 179.8 (0, C2), 152.4 (0), 140.0 (0), 127.1 (1, C4), 94.8 (2, CH_2=), 81.7 (1, C6a), 53.8 (1, C3a), 40.2 (1, C3), 38.9 (2, C6), 25.7 (3, $C(CH_3)_3$), 18.2 (0, $C(CH_3)_3$), 17.4 (3, 3-methyl), -4.7 (3, 2 $Si(CH_3)_2$). MS *m/z* 294 (M^+, 0.9), 279 (1), 238 (8), 209 (18), 181 (14), 130 (18), 117 (18), 75 (100), 73 (18). HRMS calcad. for $C_{16}H_{26}O_3Si$ 294.1650, found 294.1646.

Diene **55**: Colorless oil: IR (neat) 1772 (s), 1590 (m), 1472 (m), 1306 (m), 1169 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.86 (1H, s, H4), 5.06 (1H, m, H6a), 4.37 (1H, s, CH_2=), 4.34 (1H, s, CH_2=), 3.64 (1H, apparent t, J = 6.8 Hz, H3a), 2.89-2.75 (3H, m, H3 and 2H6), 1.27 (3H, d, J = 7.4 Hz, 3-methyl), 0.96 (9H, s, $SiC(CH_3)_3$), 0.18 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$). NOE data 5.06 (3.64, 4%), 3.64 (5.06, 4%), 1.27 (5.86, 6%). ^{13}C NMR ($CDCl_3$) δ 178.6 (0, C2), 152.5 (0), 141.0 (0), 123.7 (1, C4), 94.8 (2, CH_2=), 81.1 (1, C6a), 50.6 (1, C3a), 39.2 (2, C6), 37.7 (1, C3), 25.7 (3, $SiC(CH_3)_3$), 18.2 (0, $C(CH_3)_3$), 12.0 (3, 3-methyl), -4.6 (3, $SiCH_3$), -4.8 (3, $SiCH_3$). MS *m/z* 294 (M^+, 0.4), 238 (5), 237 (5), 209 (10), 181 (12), 130 (17), 117 (15), 75 (100), 73 (15). HRMS calcd. for $C_{16}H_{26}O_3Si$ 294.1650, found 294.1651.

(4aα,7aβ,10β,10aβ,10bα,10cα)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5,7,7a,10,10a,10b,10c-octahydro-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,9-trione (56)

A solution of diene **54** (295 mg, 1.00 mmol) and 2,6-dimethyl-1,4-benzoquinone (**13**) (206 mg, 1.50 mmol) in dry toluene (10 mL) was heated at reflux for 3 days. The

solvent was removed under vacuum, and the residue was subjected to PLC (30% EtOAc/hexane) to afford **57** (347 mg, 81% yield) as a pale yellow foam, which was crystallized from Et_2O: mp 134.0-135.0 °C. IR (CCl_4) 1774 (s), 1682 (s), 1251 (m), 1178 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.44 (1H, q, J = 1.4 Hz, H3), 5.14 (1H, m, H7a), 3.14-3.00 (2H, m, H10a and H7β), 2.94 (1H, m, H4a), 2.45-2.34 (3H, m, H5β, H7α and H10), 2.32 (1H, m, H10b), 2.07 (1H, m, H5α), 1.97 (3H, d, J = 1.4 Hz, 2-methyl), 1.41 (3H, s, 10c-methyl), 1.31 (3H, d, J = 7.3 Hz, 10-methyl), 0.89 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$). NOE data 5.14 (3.14-3.00, 9%), 2.94 (2.32, 15%), 2.32 (2.94, 9%; 2.07, 5%), 1.41 (2.94, 9%; 2.32, 16%), 1.31 (3.14-3.00, 4%). ^{13}C NMR ($CDCl_3$) δ 201.8 (0), 199.6 (0), 179.5 (0, C9), 148.1 (0, C2), 139.6 (0, C6), 133.8 (1, C3), 116.8 (0, C6a), 82.0 (1, C7a), 56.5 (1, C4a), 52.8 (1, C10b), 51.0 (2, C5), 25.5 (3, $SiC(CH_3)_3$), 24.8 (3, 10c-methyl), 18.0 (0, $SiC(CH_3)_3$), 16.5 (3, 2-methyl), 15.2 (3, 10-methyl), -3.9 (3, $SiCH_3$), -4.1 (3, $SiCH_3$). MS *m/z* 430 (M^+, 10), 374 (15), 373 (45), 238 (21), 237 (22), 209 (32), 181 (18), 131 (20), 130 (32), 117 (28), 75 (100), 73 (81). HRMS calcd. for $C_{24}H_{34}O_5Si$ 430.2176, found 430.2157.

(4aα,7aβ,10β,10aβ,10bα,10cα)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5,7,7a,10,10a,10b,10c-octahydro-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,9-trione (57)

A solution of diene **55** (123 mg, 0.418 mmol) and 2,6-dimethyl-1,4-benzoquinone (**13**) (85 mg, 0.63 mmol) in dry toluene (5.0 mL) were heated at reflux for 3 days. The

solvent was removed under vacuum, and the residue was subjected to PLC (30% EtOAc/hexane) to afford **57** (147 mg, 82% yield) as a pale yellow foam, which was crystallized from Et_2O: mp 131.0-133.0 °C. IR (CCl_4) 1770 (s), 1681 (s), 1250 (m), 1179 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.45 (1H, t, J = 1.4 Hz, H3), 5.08 (1H, m, H7a), 3.70 (1H, m, H10a), 2.98-2.83 (3H, m, H4a, H7β, and H10), 2.57-2.47 (2H, m, H5 and H7α), 2.41 (1H, m, H10b), 2.03 (1H, m, H5), 1.95 (3H, d, J = 1.4 Hz, 2-methyl), 1.37 (3H, s, 10c-methyl), 1.25 (3H, d, J = 7.6 Hz, 10-methyl), 0.88 (9H, s, $SiC(CH_3)_3$), 0.05 (3H, $SiCH_3$), 0.04 (3H, $SiCH_3$). NOE data 5.08 (3.70, 5%), 2.41 (2.98-2.83, 8%), 1.37 (2.98-2.83, 8%), 1.25 (2.41, 7%). ^{13}C NMR ($CDCl_3$) δ 202.2 (0), 199.6 (0), 179.4 (0, C9), 147.9 (0, C2), 140.0 (0, C6), 133.9 (1, C3), 119.4 (0, C6a), 83.9 (1, C7a), 57.1 (1, C4a), 51.9 (0, C10c), 46.6 (1, C10b), 45.2 (1, C10a), 38.6 (1, C10), 35.5 (2, C7), 31.7 (2, C5), 25.5 (3, $SiC(CH_3)_3$), 25.5 (3, 10c-methyl), 18.0 (0, $SiC(CH_3)_3$), 16.5 (3, 2-methyl), 13.5 (3, 10-methyl), -4.0 (3, $Si(CH_3)_2$). MS *m/z* 430 (M^+, 10), 373 (17), 372 (48), 238 (25), 237 (22), 209 (29), 181 (17), 131 (26), 130 (28), 117 (34), 91 (21), 79 (21), 75 (96), 73 (100). HRMS calcd. for $C_{24}H_{34}O_5Si$ 430.2176, found 430.2177.

(2α,3α,3aα,6aα)- and (2α,3β,3aβ,6aβ)-5-((1-(*tert*-Butyldimethylsilyl)oxy)vinyl)-3,3a,6,6a-tetrahydro-2-hydroxy-2,3-dimethyl-*2H*-cyclopenta[*b*]furan (59)

To a solution of diene **54** (458 mg, 1.56 mmol) in anhydrous Et_2O (20 mL) was introduced MeLi (1.4 M in Et_2O, 1.28 mL, 1.79 mmol) at -30 °C over 6 min. The mixture was allowed to warm to 0 °C over 2.5 h, and then it was quenched with water (50 mL).

The aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to chromatography on a short column (50% Et_2O/hexane) to afford a 2.2:1 epimeric mixture **59** (403 mg, 83% yield) as a white solid. Discernible ^1H NMR ($CDCl_3$) signals for the major epimer of **59**: δ 5.94 (1H, d, J = 2.0 Hz, H4), 4.87 (1H, m, H6a), 4.29 (1H, s, CH_2=), 4.28 (1H, s, CH_2=), 3.06 (1H, H3a), 2.76-2.67 (2H, m), 2.51 (1H, m), 1.44 (3H, s, 2-methyl), 1.13 (3H, d, J = 7.0 Hz, 3-methyl), 0.97 (9H, s, $Si(CH_3)_3$), 0.18 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$).

Discernible ^1H NMR ($CDCl_3$) signals for the minor epimer of **59**: δ 6.04 (1H, d, J = 1.3 Hz, H4), 1.36 (3H, s, 2-methyl), 1.04 (3H, d, J = 7.2 Hz, 3-methyl), 0.96 (9H, s, $Si(CH_3)_3$), 0.17 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$).

(2α,3α,3aα,7aα)-2,3,3a,6,7,7a-Hexahydro-2-methoxy-2,3,5-trimethylbenzofuran (60) and (2α,3β,3aβ,7aβ)-2,3,3a,6,7,7a-hexahydro-2-methoxy-2,3,5-trimethylbenzofuran (61)

To a solution of lactone **47** (1.54 g, 9.25 mmol) in anhydrous Et_2O (75 mL) was introduced MeLi (1.4 M in ether, 7.60 mL, 10.6 mmol) at -30 °C over 15 min. The solution was allowed to warm to 0 °C over a period of 2 h before MeI (1.15 mL, 18.5 mmol) was added, followed by HMPA (15 mL). This mixture was stirred at rt for 11 h, and then it was quenched with 3% $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with 3% $NaHCO_3$ solution (2 x 40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4, and

concentrated under vacuum. The residue was subjected to chromatography on a short column (15% Et_2O/petroleum ether) to afford **60** (1.23 g, 67% yield) and **61** (0.251 g, 14% yield).

Hemi-acetal **60**: pale yellow oil. IR (neat) 3039 (w), 1453 (m), 1376 (m), 1070 (s), 1010 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.41 (1H, m, H4), 4.12 (1H, m, H7a), 3.23 (3H, s, OCH_3), 2.48 (1H, m, H3a), 1.94-1.87 (2H, m, H6), 1.83 (1H, m, H7α), 1.70 (3H, s, 5-methyl), 1.67-1.44 (2H, m, H3 and H7β), 1.33 (3H, s, 2-methyl), 1.03 (3H, d, J = 6.8 Hz, 3-methyl). NOE data 4.12 (2.48, 4%; 1.83, 3%), 1.03 (2.48, 3%). ^{13}C NMR ($CDCl_3$) δ 135.1 (0, C5), 121.3 (1, C4), 106.6 (0, C1), 74.7 (1, C7a), 50.1 (1, C3), 48.1 (3, OCH_3), 44.0 (1, C3a), 28.4 (2, C7), 27.5 (2, C6), 23.7 (3, 5-methyl), 19.8 (3, 2-methyl), 11.6 (3, 3-methyl). MS *m/z* 196 (M^+, 11), 165 (17), 164 (22), 122 (77), 121 (16), 107 (100), 93 (79), 91 (16), 79 (26), 77 (14). HRMS calcd. for $C_{12}H_{20}O_2$ 196.1463, found 196.1480.

Hemi-acetal **61**: colorless oil. IR (neat) 3038 (w), 1462 (m), 1378 (m), 1106 (s), 1029 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.37 (1H, m, H4), 4.12 (1H, m, H7a), 3.27 (3H, s, OCH_3), 2.28 (1H, m, H3a), 2.06 (1H, m, H3), 1.96-1.92 (2H, m, H6), 1.85-1.73 (2H, m, H7), 1.69 (3H, s, 5-methyl), 1.25 (3H, s, 2-methyl), 1.03 (3H, d, J = 7.0 Hz, 3-methyl). NOE data 3.27 (2.06, 5%), 2.28 (4.12, 3%), 1.25 (2.28, 3%), 1.03 (2.28, 3%). ^{13}C NMR ($CDCl_3$) δ 134.9 (0, C5), 120.9 (1, C4), 110.2 (0, C2), 75.2 (1, C7a), 48.9 (3, OCH_3), 46.1 (1, C3), 45.7 (1, C3a), 28.0 (2, C6), 27.6 (2, C7), 23.6 (3, 5-methyl), 20.6 (3, 2-methyl), 13.8 (3, 3-methyl). MS *m/z* 196 (M^+, 19), 165 (22), 164 (34), 123 (14), 122 (53), 121 (23), 107 (100), 93 (98), 91 (20), 79 (30), 77 (17). HRMS calcd. for $C_{12}H_{20}O_2$ 196.1463, found 196.1479.

(2α,3α,3aα,6aα)-5-((1-(*tert*-Butyldimethylsilyl)oxy)vinyl)-3,3a,6,6a-tetrahydro-2-methoxy-2,3-dimethyl-*2H*-cyclopenta[*b*]furan (62)

To a solution of **60** (361 mg, 1.84 mmol) in CH_2Cl_2 (40 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. Then, dimethyl sulfide (1.0 mL, 13.6 mmol) was added. The mixture was allowed to warm to rt, and it was stirred overnight. Evaporation of the solvent under vacuum gave the crude ozonolysis product (410 mg) as a yellow oil.

A portion of the crude ozonolysis product (180 mg) was dissolved in 0.5 M KOH/MeOH (20 mL). The solution was stirred 0 °C for 0.5 h and then at rt for 2 h. The mixture was diluted with Et_2O (150 mL) and washed with water (3 x 30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was subjected to column chromatography (2% MeOH/CH_2Cl_2) to provide **62** (40 mg, 24% yield) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.66 (1H, t, J = 2.0 Hz, H4), 4.61 (1H, m, H6a), 3.23 (3H, s, OCH_3), 3.14 (1H, m, H3a), 2.79 (1H, m, H6α), 2.64 (1H, ddd, J = 18.0, 3.9, 2.0 Hz, H6β), 23.2 (3H, s, $COCH_3$), 1.73 (1H, m, H3), 1.33 (3H, s, 2-methyl), 1.13 (3H, d, J = 7.0 Hz, 3-methyl). ^{13}C NMR ($CDCl_3$) δ 196.8 (0, $COCH_3$), 144.0 (1, C4), 142.6 (0, C5), 107.6 (0, C2), 78.9 (1, C6a), 58.6, 50.3, 47.9, 37.0, 26.6, 18.6, 13.3.

(4aα,7aβ,9ξ,10β,10aβ,10bα,10cα)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5,7,7a,9,10,10a,10b,10c-nonahydro-2,9,10,10c-tetramethylbenz[6,7]indeno[2,1-*b*]furan-1,4-dione (65) and **(4aα,7aβ,10aβ,10bα,10cα)-6-((*tert*-**

butyldimethylsilyl)oxy)-4a,5,7,7a,10a,10b,10c-heptahydro-2,9,10,10c-tetramethylbenz[6,7]indeno[2,1-*b*]furan-1,4-dione (66)

A solution of diene **59** (2.2:1 epimeric mixture) (111 mg, 0.357 mmol) and 2,6-dimethyl-1,4-benzoquinone (**13**) (97.2 mg, 0.714 mmol) in dry toluene (5.0 mL) was heated at reflux for 48 h. After the solvent was removed under vacuum, the residue was subjected to PLC (30% EtOAc/hexane) to afford **65** (50 mg, 31% yield), as an 8:1 epimeric mixture, and **66** (57 mg, 37% yield).

The major epimer of **65**: ^{1}H NMR ($CDCl_3$) δ 6.38 (1H, q, J = 1.3 Hz, H3), 4.89 (1H, dd, J = 15.1, 7.7 Hz, H7a), 3.05-2.83 (3H, m), 2.33 (1H, m), 2.18-2.01 (2H, m), 1.94 (3H, d, J = 1.3 Hz, 2-methyl), 1.67 (1H, m), 1.46 (3H, s), 1.38 (3H, s), 1.22 (1H, m), 1.03 (3H, d, J = 6.8 Hz, 10-methyl), 0.87 (9H, s, $SiC(CH_3)_3$), 0.035 (3H, s, $SiCH_3$), 0.018 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$) δ 201.5 (0), 200.4 (0), 148.4 (0, C2), 138.0 (0, C6), 133.3 (1, C3), 119.7 (0, C6a), 108.0 (0, C9), 81.3 (1, C7a), 56.9, 51.4, 49.8, 36.3, 31.7, 26.0, 25.6 (3, $SiC(\mathbf{C}H_3)_3$), 25.2, 18.0 (0, $Si\mathbf{C}(CH_3)_3$), 16.5, 12.4, -4.0 (3, $SiCH_3$), -4.2 (3, $SiCH_3$).

Discernible ^{1}H NMR ($CDCl_3$) signals for the minor epimer of **65**: 6.49 (1H, s, H3), 5.07 (1H, m, H7a), 0.97 (3H, d, J = 7.5 Hz, H10), 0.93 (9H, s, $SiC(CH_3)_3$), 0.19 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$).

Compound **66**: pale yellow solid: mp 128.0-129.5 °C. IR (CCl_4) 1681 (s), 1260 (m), 1178 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.38 (1H, s, H3), 5.06 (1H, dd, J = 16.7, 7.5 Hz, H7a), 3.68 (1H, d, J = 8.3 Hz, H10a), 3.12 (1H, dd, J = 15.3, 7.6 Hz, H7β), 2.94 (1H, apparent t, J = 8.9 Hz, H4a), 2.41-2.32 (2H, m, H5 and H10b), 2.19-2.00 (2H, m, H7α

and H5), 1.95 (3H, d, J = 1.3 Hz, 2-methyl), 1.72 (3H, s, 9-methyl), 1.56 (3H, s, 10-methyl), 1.43 (3H, s, 10c-methyl), 0.88 (9H, s, $SiC(CH_3)_3$), 0.05 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$). NOE data 5.06 (3.68, 7%; 2.12, 3%), 1.43 (2.94, 6%; 2.41-2.32, 4%). ^{13}C NMR ($CDCl_3$) δ 201.9 (0), 200.5 (0), 148.4 (0), 145.7 (0), 137.8 (0), 133.3 (1, C3), 118.1 (0), 104.6 (0, C6a), 82.5 (1, C7a), 57.2 (1, C4a), 53.5 (1, C10a), 51.5 (0, C10c), 50.5 (1, C10b), 36.9 (2, C7), 31.9 (2, C5), 25.6 (3, $C(CH_3)_3$), 11.8 (3, 9-methyl), 10.6 (3, 10-methyl), -3.9 (3, $SiCH_3$), -4.2 (3, $SiCH_3$). MS *m/z* 428 (M^+, 2), 332 (5), 291 (10), 275 (6), 247 (5), 179 (7), 109 (14), 75 (32), 73 (100), 59 (11). HRMS calcd. for $C_{25}H_{36}O_4Si$ 428.2383, found 428.2374.

(6aα,7aβ,10β,10aβ,10bα,10cα)-6a,7,7a,10,10a,10b,10c-Heptahydro-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,6,9-tetraone (67)

A solution of the Diels-Alder adduct **56** (0.335 g, 0.778 mmol) and 10% HCl (8.0 mL) in THF (16 mL) was stirred at rt for 24 h. This was diluted with EtOAc (80 mL), washed with water (3 x 25 mL) and brine (25 mL), and dried over anhydrous Na_2SO_4. After concentration under vacuum, the residue was subjected to column chromatography (50% EtOAC/hexane) to afford **67** (0.150 g, 61% yield) as yellow crystals: mp 180.0-182.0 °C. IR (CH_2Cl_2) 1767 (s), 1667 (s), 1624 (m), 1380 (m), 1265 (m) cm^{-1}. ^1H NMR (CD_3COCD_3) δ 7.10 (1H, q, J = 1.4 Hz, H3), 6.40 (1H, s, H5), 4.72 (1H, dd, J = 17.0, 7.8 Hz, H7a), 3.34 (1H, apparent t, J = 6.7 Hz, H6a), 3.23 (1H, dd, J = 8.8, 6.1 Hz, H10b), 2.84 (1H, m, H7β), 2.75 (1H, dq, J = 7.5, 4.8 Hz, H10), 2.33 (1H, apparent dt, J = 9.1, 4.7 Hz, H10a), 2.15 (3H, d, J = 1.4 Hz, 2-methyl), 1.91 (1H, m, H7α), 1.70 (3H, s, 10c-

methyl), 1.07 (3H, d, J = 7.5 Hz, 10-methyl). NOE data 4.72 (2.33, 6%), 3.23 (2.75, 12%), 1.91 (3.34, 4%), 1.70 (3.34, 10%; 3.23, 9%), 1.07 (2.33, 6%). ^{13}C NMR (CD_3COCD_3) δ 199.6 (0), 198.9 (0), 186.3 (0), 180.3 (0, C9), 152.1 (0), 150.5 (0), 139.9 (1, C3), 127.6 (1, C5), 81.8 (1, C7a), 53.6 (1, C10b), 51.5 (0, C10c), 48.84 (1, C6a), 48.80 (1, C10a), 42.5 (1, C10), 36.9 (2, C7), 30.5 (3, 10c-methyl), 17.9 (3, 10-methyl), 17.0 (3, 2-methyl). MS *m/z* 314 (M^+, 45), 296 (16), 286 (22), 268 (22), 253 (15), 241 (28), 217 (21), 213 (24), 188 (22), 176 (100), 48 (42), 120 (23), 96 (18), 94 (45), 91 (53), 81 (26), 79 (42), 77 (34). HRMS calcd. for $C_{18}H_{18}O_5$ 314.1154, found 314.1162.

1,3-Dithienium tetrafluoroborate (68)

This reagent was prepared by the procedure of Corey and Walinsky.[44] 1,3-Dithiane (496 mg, 4.00 mmol) and triphenylcarbenium tetrafluoroborate (1.32 g, 4.00 mmol) in dry CH_2Cl_2 (12 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 2 mL) and Et_2O (2 x 2 mL), and dried on a vacuum line to give **70** (655 mg, 79% yield) as a pale yellow solid.

(1*R,5*R**,6*S**,7*S**,8*R**,11*S**,13*R**,15*S**)-1-Hydroxy-3,5,8-trimethyl-10-oxapentacyclo[11.3.0.0^{5,16}.0^{6,13}.0^{7,11}]hexadec-2-ene-4,9,14-trione (71)**

To the Diels-Alder adduct **57** (50.0 mg, 0.116 mmol) in dry CH_2Cl_2 (3.0 mL) added 1,3-dithienium tetrafluoroborate (**68**) (24.0 mg, 0.116 mmol) in nitromethane (1.0 mL) at -78 °C over 2 min. The mixture was stirred for 20 min and then warmed to rt.

This was diluted with Et_2O (25 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL) and brine (2 x 10 mL), dried over anhydrous $NaSO_4$, and concentrated under vacuum. The residue was applied to PLC (85% EtOAc/hexane) to afford **71** (18 mg, 48% yield) as colorless crystals: mp > 220 °C (dec.). IR (Nujol) 3405 (s), 1748 (s), 1669 (s) cm^{-1}. ^1H NMR (CD_3COCD_3) δ 7.00 (1H, s, H2), 5.20 (1H, s, 1-OH), 4.90 (1H, t, J = 5.7 Hz), 2.80 (1H, m), 2.66-2.44 (3H, m), 2.35 (1H, d, J = 16.2 Hz), 2.08-2.01 (3H, m), 1.83 (3H, d, J = 1.4 Hz, 3-methyl), 1.35 (3H, s, 5-methyl), 0.98 (3H, d, J = 7.2 Hz, 8-methyl). ^{13}C NMR ($CDCl_3$) δ 209.0 (0, C14), 200.8 (0, C4), 178.0 (0, C9), 149.4 (1, C2), 138.3 (0, C3), 88.6 (1, C11), 83.5 (0, C1), 76.1 (0, C13), 59.6, 55.9, 54.7 (0, C5), 48.1, 39.3, 37.2, 26.6, 18.0, 15.1, 12.1. MS *m/z* 316 (M^+, 62), 288 (10), 205 (18), 178 (17), 165 (36), 151 (100), 137 (14), 123 (12), 91 (13), 79 (15). HRMS calcd. for $C_{18}H_{20}O_5$ 318.1310, found 318.1306. The structure of **71** was revealed by X-ray diffraction.

(2α,4aβ,6aβ,7aα,10α,10aα,10bβ,10cβ)-1,3,4a,5,6a,7,7a,10,10a,10b,10c-Undecahydro-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,6,9-tetraone (75)

To a solution of **67** (28 mg, 0.089 mmol) in acetone (2.0 mL) was added dropwise $TiCl_3$ (20% aqueous solution, 0.24 mL, 0.38 mmol) at rt. The solution was stirred for 20 min before it was poured into brine (25 mL). This was extracted with EtOAc (3 x 15 mL). The combined organic 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 (80% EtOAc/hexane) to afford **75** (14 mg, 50% yield) as a white solid: mp 178.0-180.0 °C. IR (Nujol) 1770 (s), 1710 (s) cm^{-1}. ^1H NMR

($CDCl_3$) δ 4.78 (1H, apparent q, J = 7.2 Hz, H7a), 3.49 (1H, m, H4a), 3.27 (1H, m, H2), 3.05-2.92 (4H, m), 2.74 (1H, dd, J = 9.6, 7.7 Hz, H10b), 2.53 (1H, m, H5β), 2.49 (1H, dq, J = 9.5, 5.0 Hz, H10), 2.26 (1H, dd, J = 19.6, 13.4 Hz, H3α), 1.71-1.53 (2H, m, H10a and H7β), 1.68 (3H, s, 10c-methyl), 1.20 (3H, d, J = 6.4 Hz, 2-methyl), 1.13 (3H, d, J = 7.5 Hz, 10-methyl). NOE data 3.49 (3.27, 6%), 1.68 (3.49, 8%; 3.27, 3%; 2.74, 10%), 1.20 (2.26, 2%). ^{13}C NMR ($CDCl_3$) δ 211.9 (0), 207.0 (0), 206 (0), 179.3 (0, C9), 81.6 (1, C7a), 55.4 (1, C10b), 54.1 (1, C4a), 49.6 (1, C6a), 47.9 (0, C10c), 47.9 (1, C10a), 42.3 (2, C3), 41.9 (1, C10), 39.0 (1, C2), 34.6 (2, C5), 31.9 (2, C7), 28.0 (3, 10c-methyl), 17.6 (3, 10-methyl), 13.6 (3, 2-methyl). MS *m/z* 318 (M^+, 44), 276 (17), 231 (22), 221 (18), 207 (100), 161 (22), 152 (46), 147 (20), 139 (22), 135 (29), 125 (21), 124 (22), 119 (22), 109 (36) 99 (32), 93 (37), 91 (32), 84 (22), 82 (23), 81 (21), 79 (42), 77 (32), 69 (51). HRMS calcd. for $C_{18}H_{22}O_5$ 318.1466, found 318.1447.

(2α,4aβ,6aα,7aβ,10β,10aβ,10bα,10cα)-2,3,4a,5,6a,7,7a,10,10a,10b,10c-Undecahydro-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,6,9-tetraone (76)

To a refluxing solution of **67** (80 mg, 0.25 mmol) in glacial AcOH (10 mL) was added analytical grade Zn dust (0.98 g, 15 mmol) in portions until the reaction solution turned colorless and TLC indicated that **67** was completely consumed. The mixture was then heated at reflux for 7 h. TLC showed that the initial major product had changed largely to what had initially been the minor product. The solid was removed by filtration, and the filtrate was poured into a mixture of EtOAc (100 mL) and water (40 mL). This was neutralized by adding solid Na_2CO_3 until CO_2 evolution ceased. The aqueous layer

was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with water (2 x 30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was subjected to column chromatography (70% EtOAc/hexane) to give material (62 mg, 76% yield) which contained **76** and the other isomer in a ratio of 6:1 in favor of **76**, as shown by ^{1}H NMR. An analytical sample of **76** was obtained by crystallization from CH_2Cl_2/EtOAc (4 : 1): mp > 220 °C (dec.). IR (Nujol) 1754 (s), 1705 (s) cm^{-1}. ^{1}H NMR (CD_2Cl_2) δ 4.80 (1H, dd, J = 16.2 , 7.5 Hz, H7a), 3.42 (1H, dd, J = 9.9, 7.1 Hz, H4a), 3.02-2.89 (3H, m, H6a, H2 and H7β), 2.85-2.80 (2H, m, H3β and H10b), 2.61-2.58 (2H, m, H5α and H5β), 2.26 (1H, dd, J = 19.0, 12.6 Hz, H3α), 1.98 (1H, apparent dt, J = 9.5, 3.6 Hz, H10a), 1.51 (1H, m, H7α), 1.30 (3H, s, 10c-methyl), 1.17 (3H, d, J = 6.2 Hz, 2-methyl), 1.11 (3H, d, J = 7.5 Hz, 10-methyl). NOE data 3.43 (1.98, 9%), 1.98 (4.80, 5%; 3.43, 9%), 1.30 (H6a, 5%; H10b, 8%; 2.26, 2%), 1.11 (1.98, 4%). ^{13}C NMR (CD_2Cl_2) δ 212.7 (0), 208.6 (0), 206.7 (0), 179.9 (0, C9), 81.7 (1, C7a), 56.3 (1, C10b), 50.5 (1, C6a), 49.5 (1, C4a), 48.0 (0, C10c), 57.2 (1, C10a), 42.4 (2, C3), 42.3 (1, C2), 42.2 (1, C10), 36.7 (2, C5), 32.5 (2, C7), 21.8 (3, 10c-methyl), 18.2 (3, 10-methyl), 13.8 (3, 2-methyl). MS *m/z* 318 (M^+, 22), 221 (7), 207 (100), 179 (12), 161 (27), 152 (19), 121 (14), 112 (15), 109 (17), 93 (16), 91 (16), 82 (13), 81 (11), 79 (20), 77 (17), 69 (20), 67 (11). HRMS calcd for $C_{18}H_{22}O_5$ 318.1466, found 318.1446. The stereochemistry of **76** was confirmed by X-ray analysis.

Selected NMR data for the other isomer: ^{1}H NMR (CD_2Cl_2) δ 3.16 (1H, dd, J = 12.5, 4.7 Hz, H4a), 1.30 (3H, s, 10c-methyl), 1.17 (3H, d, J = 7.4 Hz). ^{13}C NMR (CD_2Cl_2) δ 82.0 (1, C7a), 56.0 (1, C10b), 22.6 (3, 10c-methyl), 18.8 (3, 10-methyl), 16.1

(3, 2-methyl).

(2α,4β,6aα,7aβ,9α,10β,10aβ,10bα,10cα)-2,3,4a,5,6a,7,7a,9,10,10a,10b,10c-Dodecahydro-2,9,10,10c-tetramethylbenz[6,7]indeno[2,1-*b*]furan-1,4,6-trione (77)

A solution of diene **59** (a 2.2:1 epimeric mixture) (845 mg, 2.72 mmol) and 2,6-dimethyl-1,4-benzoquinone (**13**) in dry toluene (40 mL) was heated at reflux for 70 h. The solvent was removed under vacuum. The residue was dissolved in THF (40 mL) and combined with 5% aqueous HCl (20 mL). The resulting mixture was stirred at rt for 24 h and then diluted with EtOAc (160 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to provide **72** (472 mg, 52% yield) as an isomeric mixture.

Selected NMR data for a major isomer of **72** from the mixture: ^{1}H NMR ($CDCl_3$) δ 6.99 (1H, br s, H3), 6.58 (1H, s, H5), 2.15 (3H, br s, 2-methyl), 1.57 (3H, s), 1.44 (3H, s), 0.78 (3H, d, J = 6.7 Hz, 10-methyl). ^{13}C NMR ($CDCl_3$) δ 200.3 (0), 197.6 (0), 185.5 (0, C4), 109.5 (0, C9), 81.8 (1, C7a).

Selected NMR data for the second isomer of **72** from the mixture: ^{1}H NMR ($CDCl_3$) δ 6.98 (1H, br s, H3), 6.55 (1H, s, H5), 2.15 (3H, br s, 2-methyl), 1.60 (3H, s), 1.36 (3H, s), 0.72 (3H, d, J = 7.2 Hz, 10-methyl). ^{13}C NMR ($CDCl_3$) δ 201.4 (0), 197.3 (0), 195.5 (0), 186.0 (0, C4), 109.9 (0, C9), 83.0 (1, C7a).

To a refluxing solution of **72** (0.258 g, 0.781 mmol) in glacial AcOH was added Zn dust (1.45 g, 21.7 mmol) in portions until the solution turned to colorless and TLC

indicated that **72** was completely consumed. The mixture was heated at reflux overnight. After cooling to rt, the solid was removed by filtration. The filtrate was poured into a mixture of EtOAc (80 mL) and water (80 mL), and neutralized by adding solid Na_2CO_3 until CO_2-evolution ceased. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to provide **77** (50 mg, 10% yield from diene **59**) as a white solid: mp 179.0-181.0 °C. IR (Nujol) 1708 (s), 1152 (m), 1107 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.36 (1H, m, H7a), 3.52 (1H, dd, J = 10.4, 6.5 Hz, H4a), 3.42 (1H, dq, J = 8.8, 6.3 Hz, H9), 3.10-2.99 (2H, m, H2 and H6a), 2.86 (1H, dd, J = 9.6, 7.0 Hz, H3β), 2.81 (1H, dd, J = 12.6, 6.9 Hz, H10b), 2.74 (1H, dd, J = 13.6, 7.7 Hz, H7β), 2.59 (2H, m, H5α and H5β), 2.26 (1H, dd, J = 19.6, 13.4 Hz, H3α), 1.70 (1H, m, H10a), 1.57-1.49 (2H, m, H7α and H10), 1.30 (3H, s, 10c-methyl), 1.23 (3H, d, J = 6.0 Hz, 9-methyl), 1.20 (3H, d, J = 6.4 Hz, 2-methyl), 1.80 (3H, d, J = 6.7 Hz, 10-methyl). NOE data 4.36 (3.42, 4%; 2.74, 4%; 1.70, 3%), 3.52 (3.10-2.99, 3%; 1.70, 6%), 1.70 (4.36, 5%; 3.52, 10%), 1.30 (3.10-2.99, 4%; 2.81, 6%); 0.80 (3.42, 4%; 1.70, 3%). ^{13}C NMR ($CDCl_3$) δ 212.0 (0), 209.1 (0), 207.0 (0), 85.8 (1, C9), 83.1 (1, C7a), 55.7 (1, C10b), 53.2 (1, C10a), 53.1 (1, C6a), 48.9 (1, C4a), 47.5 (0, C10c), 47.4 (1, C10), 42.0 (2, C3), 41.4 (1, C2), 36.2 (2, C5), 30.2 (2, C7), 21.8 (3, 10c-methyl), 18.7 (3, 9-methyl), 17.0 (3, 10-methyl), 13.4 (3, 2-methyl). MS *m/z* 318 (M^+, 12), 207 (9), 178 (10), 161 (22), 152 (11), 136 (10), 121 (14), 112 (100), 109 (10), 97 (68), 97 (17), 77 (12), 69 (11), 67 (10). HRMS calcd. for $C_{19}H_{26}O_4$ 318.1831, found 318.1839.

(1α,4aβ,7aα,10α,10aα,10bβ,10cβ)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5,7,7a,10,10a,10b,10c-octahydro-1-hydroxy-2,10,10c-trimethyl-*1H*-benz[6,7]indeno[2,1-*b*]furan-4,9-dione (89)

Method A: To a solution of enedione **56** (100 mg, 0.232 mmol) in dry THF (5.0 mL) was introduced LiAl(O-*t*-Bu)$_3$H (1.0 M in THF, 0.30 mL, 0.30 mmol) at 0 °C over 5 min. The mixture was stirred at 0 °C for 15 min before it was quenched with water (30 mL) and extracted with EtOAc (4 x 20 mL). The combined extracts were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was subjected to column chromatography (50% EtOAc/hexane) to afford **89** (90 mg, 90% yield) as a white solid.

Method B: Enedione **56** (50.0 mg, 0.116 mmol) was dissolved in MeOH (2.0 mL) by warming. After the solution had cooled to rt, $NaBH_4$ (5.0 mg, 0.13 mmol) was added over 2 min. The mixture was stirred for 10 min before it was quenched with dilute NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was subjected to PLC (50% EtOAc/hexane) to provide **89** (41.3 mg, 82% yield) as a white solid.

Compound **89**: mp 171.0-172.0 °C. IR (Nujol) 3448 (s), 1740 (s), 1666 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.83 (1H, s, H3), 5.02 (1H, m, H7a), 3.91 (1H, s after D_2O shake, H1), 3.08 (1H, ddd, J = 17.4, 7.2, 1.6 Hz, H7), 2.77 (1H, m), 2.64 (1H, m), 2.60-2.17 (6H, m), 2.08 (3H, s, 2-methyl), 1.40 (3H, d, J = 7.5 Hz, 10-methyl), 1.10 (3H, s, 10c-methyl), 0.91(9H, s, $SiC(CH_3)_3$), 0.11(3H, s, $SiCH_3$), 0.089 (3H, s, $SiCH_3$). NOE data 3.91 (2.08,

2%; 1.10, 2%). ^{13}C NMR ($CDCl_3$) δ 200.3 (0, C4), 179.7 (0, C9), 155.9 (0, C2), 140.3 (0, C6), 123.3 (1, C3), 118.3 (0, C6a), 82.2 (1, C7a), 74.2 (1, C1), 53.3, 51.5, 47.7, 43.0, 38.7 (0, C10c), 33.7, 32.0, 27.0, 25.6 (3, $SiC(CH_3)_3$), 18.0 (0, $SiC(CH_3)_3$), 16.2 (3, 2-methyl), -3.8 (3, $SiCH_3$), -3.9 (3, $SiCH_3$); MS *m/z* 432 (M^+, 20), 376 (17), 375 (60), 238 (14), 237 (18), 209 (26), 195 (56), 193 (19), 181 (16), 135 (35), 131 (16), 130 (23), 117 (19), 91 (10), 75 (84), 73 (100). HRMS calcd. for $C_{24}H_{36}O_5Si$ 432.2330, found 432.2351.

cis-5-Acetyl-3,3a,6,6a-tetrahydro-2_H_-cyclopenta[_b_]furan-2-one (93)

To a solution of **41** (4.50 g, 29.6 mmol) in CH_2Cl_2 (300 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 (21.7 mL, 0.296 mol) 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 (150 mL) and combined with a 5% aqueous HCl solution (150 mL). The mixture was heated at reflux for 3 h. Most of 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 **93** (1.15 g, 23% yield) as a white solid: mp 109.0-111.0 °C. IR (CH_2Cl_2) 1751 (s), 1662 (s), 1426 (m), 1173 (s) cm^{-1}. ^{1}H 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 ($CDCl_3$) δ 195.8 (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-(1-((_tert_-Butyldimethylsilyl)oxy)vinyl)-3,3a,6,6a-tetrahydro-2_H_-cyclopenta[_b_]furan-2-one (78) and **_cis_-5-(1-((_tert_-Butyldimethylsilyl)oxy)vinyl)-3-(1-hydroxy-1-(_cis_-3,3a,6,6a-tetrahydro-2_H_-cyclopenta[_b_]furan-2-on-5-yl)ethyl)-3,3a,6,6a-tetrahydro-2_H_-cyclopenta[_b_]furan-2-one (94)**

Method A: To a mixture of enone **93** (0.548 g, 3.30 mmol) and *tert*-butyldimethylsilyl triflate (0.83 mL, 3.61 mmol) in dry CH_2Cl_2 was added dry triethylamine (0.60 mL, 4.30 mmol) at 0 °C over 5 min. The mixture was stirred at 0 °C for 10 min. The solvent was removed under vacuum, and the residue was subjected to column chromatography (silica gel, 30% dry EtOAc/hexane) to afford **78** (0.682 g, 74% yield).

Method B: To a solution of diisopropylamine (2.32 mL, 16.6 mmol) in dry THF (30 mL) was introduced *n*-BuLi (2.5 M in hexane, 5.75 mL, 14.4 mmol) at 0 °C over 10 min. The solution was stirred for 20 min and then transferred by a syringe to a solution of enone **93** (2.28 g, 13.7 mmol) and *tert*-butyldimethylsilyl triflate (3.62 mL, 15.8 mmol) in dry THF (80 mL) at -78 °C over 40 min. The solution was stirred at -78 °C for 1 h before it was allowed to warm to rt, quenched with water (100 mL), and extracted with Et_2O (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 (60% EtOAc/hexane) to afford **78** (1.65 g, 43% yield) and **94** (229 mg, 7% yield).

Diene **78**: a colorless oil: IR (neat) 1778 (s), 1590 (m), 1319 (m), 1259 (m), 1172 (m), 1014 (m), 831 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.77 (1H, apparent s, H4), 5.16 (1H, m, H6a), 4.36 (1H, s, CH_2=), 4.33 (1H, s, CH_2=), 3.61 (1H, m, H3a), 2.83-2.80 (2H, m, H6), 2.76 (1H, dd, J = 18.0, 9.6 Hz, H3 *syn* to H3a), 2.46 (1H, dd, J = 18.0, 1.5 Hz, H3 *anti* to H3a), 0.95 (9H, s, $SiC(CH_3)_3$), 0.17 (6H, s, $SiMe_2$). NOE data 5.16 (3.61, 3%), 2.76 (3.61, 2%). ^{13}C NMR ($CDCl_3$) δ 176.4 (0, C2), 152.4 (0), 140.2 (0), 127.3 (1, C4), 94.8 (2), 83.4 (1, C6a), 45.6 (1, C3a), 39.0 (2, C6), 33.5 (2, C3), 25.7 (3, $SiC(\mathbf{C}H_3)_3$), 18.2 (0, $SiC(CH_3)_3$), -4.7 (3, $SiMe_2$). MS *m/z* 280 (M^+, 0.6), 223 (11), 181 (10), 117 (12), 103 (9), 75 (100), 73 (14), 59 (7). HRMS calcd. for $C_{15}H_{24}O_3Si$ 280.1495, found 280.1496.

Compound **94**: white solid: mp 170.5-171.5. IR (Nujol) 3477 (s), 1766 (s), 1744 (s), 1579 (m), 1176 (s), 1013 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.73 (1H, br. s), 5.53 (1H, br. s), 5.14 (1H, t, J = 5.6 Hz), 5.09 (1H, t, J = 6.3 Hz), 4.36 (1H, s, CH_2=), 4.32 (1H, s, CH_2=), 3.58 (1H, m), 3.40 (1H, d, J = 6.1 Hz), 2.99 (1H, m), 2.82-2.63 (5H, m), 2.44 (1H, d, J = 17.6 Hz), 1.48 (3H, s), 0.97 (9H, s), 0.18 (6H, s). ^{13}C NMR ($CDCl_3$) δ 177.3 (0), 176.0 (0), 152.4 (0), 147.1 (0), 140.1 (0), 126.8 (1), 126.6 (1), 94.9 (2), 83.3 (1), 83.0 (1), 73.5 (0), 53.6 (1), 49.1 (1), 45.4 (1), 39.1 (2), 39.0 (2), 33.5 (2), 25.8 (3), 24.7 (1), 18.2 (0), -4.6 (3), -4.8 (0). MS *m/z* 389 (M^+- C_4H_9, 18), 224 (14), 223 (35), 195 (9), 181 (16), 151 (21), 117 (12), 103 (9), 77 (11), 75 (100), 73 (24). HRMS calcd. for $C_{24}H_{34}O_6Si$ - C_4H_9, 389.1419, found 389.1439.

(4aα,7aβ,10aβ,10bα,10cα)-6-(1-*tert*-Butyldimethylsilyl)oxy-4a,5,7,7a,10,10a,10b,10c-octahydro-2,10c-dimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,9-trione (79) and **(4aα,7aβ,10aβ,10bα,10cα)-6-(1-*tert*-butyldimethylsilyl)oxy-4a,5,7,7a,10,10a,10b,10c-octahydro-3,4a-dimethylbenz[6,7]indeno[2,1-*b*]furan-1,4,9-trione (95)**

A solution of diene **78** (1.65 g, 5.89 mmol) and 2,6-dimethyl-1,4-benzoquinone (**13**) (1.60 g, 11.8 mmol) in dry toluene (70 mL) was heated at reflux for 3 days. The solvent was removed under vacuum, and the residue was purified by column chromatography (75% anhydrous ether/hexane) to afford **79** (1.96 g, 80% yield) and **95** (0.141g, 6% yield). Both **79** and **95** were pale yellow foams. Attempts to obtain crystals by crystallization were unsuccessful.

Adduct **79**: IR (CCl_4) 1776 (s), 1681 (s), 1252 (m), 1163 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.44 (1H, t, J = 1.5 Hz, H3), 5.06 (1H, apparent dt, J = 6.5, 2.5 Hz, H7a), 3.61 (1H, ddd, J = 15.0, 8.2, 2.5 Hz, H10a), 2.98-2.89 (2H, m, H7β + H10b), 2.79 (1H, dd, J = 17.7, 8.4 Hz, H10β), 2.60 (1H, br d, J = 18.1 Hz, H7α), 2.45-2.32 (2H, m, H5α and H10α), 2.28 (1H, m, H4a), 2.13 (1H, m, H5β), 1.97 (3H, d, J = 1.4 Hz, 2-methyl), 1.42 (3H, s, 10c-methyl), 0.89 (9H, s, $SiC(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$). NOE data 3.61 (5.06, 6%; 2.79, 4%), 2.98-2.89 (5.06, 3%; 2.45-2.32, 5%; 2.28, 6%), 1.42 (2.98-2.89, 8%; 2.28, 10%). ^{13}C NMR ($CDCl_3$) δ 202.0 (0), 199.4 (0), 176.6 (0, C9), 148.2 (0, C2), 139.5 (0, C6), 133.8 (1, C3), 117.4 (0, C6a), 85.2 (1, C7a), 56.7 (1, C10b), 53.3 (1, C4a), 50.8 (0, C10c), 41.2 (1, C10a), 36.9 (2, C10), 34.4 (2, C7), 31.5 (2, C5), 25.5 (3, $SiC(CH_3)_3$), 24.4 (3, 10c-methyl), 18.0 (0, $SiC(CH_3)_3$), 16.5 (3, 2-methyl), -3.9 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 416 (M^+, 2), 360 (11), 359 (35), 224 (21), 223 (37), 195

(12), 181 (21), 117 (20), 103 (16), 75 (100), 73 (85), 59 (15). HRMS calcd. for $C_{23}H_{32}O_5Si$ 416.2019, found 416.1990.

Adduct **95**: IR (CCl_4) 1775 (s), 1684 (s), 1249 (s), 1162 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.49 (1H, d, *J* = 1.3 Hz, H2), 5.05 (1H, dt, *J* = 6.5, 1.9 Hz, H7a), 3.77 (1H, m, H10a), 3.03 (1H, d, *J* = 5.3 Hz, H10c), 2.98 (1H, m, H7β), 2.72 (1H, dd, *J* = 17.7, 8.2 Hz, H10β), 2.59 (1H, m, H7α), 2.52 (1H, m, H10b), 2.36 (1H, dd, *J* = 17.7, 2.1 Hz, H10α), 2.26 (1H, ddd, J = 17.2, 4.6, 2.8 Hz, H5β), 1.99 (3H, d, *J* = 1.3 Hz, 3-methyl), 1.78 (1H, ddd, *J* = 17.2, 4.4, 2.5 Hz, H5α), 1.37 (3H, s, 4a-methyl), 0.90 (9H, s, $SiC(CH_3)_3$), 0.08 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$). NOE data 5.05 (3.77, 11%; 2.98, 6%), 3.77 (5.05, 9%; 2.72, 5%), 2.52 (3.03, 11%), 1.37 (3.03, 14%; 2.52, 14%; 1.78, 7%). ^{13}C NMR ($CDCl_3$) δ 202.9 (0), 198.5 (0), 176.9 (0, C9), 146.6 (0, C3), 139.3 (0, C6), 136.9 (1, C2), 116.1 (0, C6a), 85.2 (1, C7a), 51.8 (1, C10c), 50.6 (0, C4a), 43.7 (1, C10b), 40.9 (1, C10a), 37.7 (2, C5), 35.4 (2, C10), 33.6 (2, C7), 25.5 (3, $SiC(CH_3)_3$), 21.2 (3, 4a-methyl), 17.9 (0, $SiC(CH_3)_3$), 16.4 (3, 3-methyl), -3.8 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 416 (M^+, 6), 360 (30), 359 (96), 331 (8), 251 (70), 223 (21), 195 (15), 194 (20), 181 (17), 117 (11), 77 (12), 75 (98), 73 (100). HRMS calcd. for $C_{23}H_{32}O_5Si$ 416.2019, found 416.2036.

(1α,4aβ,7aα,10aα,10bβ,10cβ)-6-((*tert*-Butyldimethylsilyl)oxy)-1-ethoxyethynyl-4a,5,7,7a,10,10a,10b,10c-octahydro-1-hydroxy-2,10c-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]furan-4,9-dione (80)

To a solution of ethyl ethynyl ether (50% wt % solution in hexane, 0.38 mL, 1.95 mmol) in dry THF (35 mL) was introduced *n*-BuLi (2.5 M in hexane, 0.58 mL, 1.45

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 **79** (0.506 g, 1.21 mmol) in dry THF (35 mL) at -78 °C over 30 min. This mixture was stirred for 2 h before it was allowed to warm to 0 °C. This was quenched with water (20 mL), diluted with Et_2O (200 mL), and washed with water (3 x 40 mL) and brine. The resulting solution was dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (40% anhydrous EtOAc/hexane) to provide **80** (0.481 g, 82% yield) as a pale yellow solid: mp 156.5-158.0 °C. IR (CCl_4), 3418 (br, m), 2258 (s), 1770 (s), 1672 (s), 1355 (m), 1246 (s) cm^{-1}. ^1H NMR (CD_2Cl_2, -85 °C, major conformer, signals were very broad at rt) δ 5.70 (1H, s, H3), 4.69 (1H, m, H7a), 4.06 (2H, q, J = 7.3 Hz, OCH_2CH_3), 3.49 (1H, br d, J = 18.6 Hz), 2.96-2.81 (2H, m), 2.62 (1H, br d, J = 16.6 Hz), 2.48-2.28 (2H, m), 2.15-1.92 (3H, m), 2.00 (3, s, 2-methyl), 1.34 (3H, s, 10c-methyl), 1.26 (3H, t, J = 7.3 Hz, OCH_2CH_3), 0.86 (9H, s, $SiC(CH_3)_3$), 0.050 (3H, s, $SiCH_3$), 0.043 (3H, s, $SiCH_3$). ^{13}C NMR (CD_2Cl_2, -85 °C, discernible signals for the major conformer) δ 197.9 (0, C4), 180.4 (0, C9), 163.0 (0, C2), 140.4 (0, C6), 125.0, 117.5, 94.0, 83.9, 75.0, 73.6, 49.5, 47.6, 46.3, 42.3, 41.1, 37.2, 32.7, 30.9, 25.0 (3, $SiC(CH_3)_3$), 19.1, 17.6, 14.1, -4.8 (3, $SiCH_3$), -5.0 (3, $SiCH_3$). MS *m/z* 486 (M^+, 0.6), 359 (14), 224 (21), 223 (33), 195 (12), 181 (19), 117 (18), 103 (13), 75 (97), 73 (100), 59 (16). HRMS calcd. for $C_{27}H_{38}O_6Si$ 486.2438, found 486.2412.

(1*R,2*R**,3*R**,4*R**,8*S**,10*S**,11*S**,13*S**)-1-Ethoxyethynyl-11-hydroxy-2,16-dimethyl-7,17-dioxapentacyclo[9.5.1.$0^{2,13}$.$0^{3,10}$.$0^{4,8}$]hexadec-15-ene-6,14-dione (98)** and

(1α,4aα,6aβ,7aα 10aα,10bβ,10cβ)-1-ethoxyethynyl-4a,5,6a,7,7a,10,10a,10b,10c-nonahydro-1-hydroxy-2,10c-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]furan-4,6,9-trione (99)

A solution of **80** (1.31 g, 2.67 mmol) in methanol (50 mL) and a solution of $KF{\cdot}2H_2O$ (1.26 g, 13.4 mmol) in methanol (40 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 (60 mL) and extracted with EtOAc (4 x 40 mL). The combined extracts were washed with water (40 mL) and brine (2 x 40 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was subjected to column chromatography (70% EtOAc/hexane) to provide **98** and **99** (0.924 g, 93% yield) in a ratio of 7:1 favoring the less mobile component **98**. Compounds **98** and **99** could be completely separated by column chromatography, but this was not necessary for our synthesis.

Compound **98**: White foam: attempts to obtain crystals by crystallization were unsuccessful. IR (Nujol) 3404 (br, s), 2260 (s), 1772 (s), 1674 (s), 1160 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.77 (1H, d, J = 1.3 Hz, H15), 5.04 (1H, apparent t, J = 4.5 Hz, H8), 4.19 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.93 (1H, dd, J = 5.8, 2.5 Hz, H4), 2.96 (1H, s, OH), 2.89 (1H, dd, J = 17.6, 8.2 Hz, H5 *syn* to H4), 2.68 (1H, m, H10), 2.51 (1H, m, H9 *syn* to H8), 2.41-2.33 (2H, m, H13 and H5 *anti* to H4), 2.18 (1H, dd, J = 13.9, 1.8 Hz, H12), 2.13 (3H, d, J = 1.3 Hz, 16-methyl), 1.95 (1H, dd, J = 11.9, 5.8 Hz, H3), 1.67 (1H, dd, J = 13.9, 4.2 Hz, H12), 1.42 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.08 (3H, s, 2-methyl). NOE data 5.04 (3.93, 6%; 2.51, 4%), 3.93 (5.04, 7%; 2.89, 3%), 2.68 (1.95, 5%), 1.08 (3.93, 7%; 2.41-2.33, 4%; 1.95, 3%). ^{13}C NMR ($CDCl_3$) δ 199.8 (0, C14), 176.7 (0, C6), 158.8 (0,

C16), 121.6 (1, C15), 98.2 (0), 97.1 (0, 2 C), 87.7 (1, C8), 75.0 (2, OCH_2CH_3), 56.9 (1, C3), 51.9 (1, C13), 45.7 (1, C10), 41.8 (1, C4), 38.6 (2, C5), 37.9 (0), 37.2 (0), 34.8 (2, C12), 32.6 (2, C9), 20.7 (3, 16-methyl), 18.9 (3, 2-methyl), 14.7 (3, OCH_2CH_3). MS *m/z* 343 (M^+-29, 13), 302 (16), 203 (18), 178 (19), 175 (42), 161 (27), 151 (34), 150 (39), 148 (23), 147 (24), 138 (34), 137 (72), 135 (20), 122 (20), 121 (19), 119 (18), 117 (19), 115 (16), 110 (44), 105 (32), 103 (21), 96 (20), 91 (71), 82 (22), 81 (21), 79 (64), 78 (20), 77 (72), 69 (64), 68 (46), 67 (34), 66 (18), 65 (34), 55 (95), 53 (57), 41 (100). HRMS calcd. for $C_{21}H_{24}O_6$-C_2H_5 343.1182, found 343.1182.

Compound **99**: white solid: mp > 180.0 °C (dec.). IR (Nujol) 3381 (s), 2266 (s), 1759 (s), 1702 (s), 1660 (s), 1173 (m), 1048 (m) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 5.83 (1H, d, *J* = 1.4 Hz, H3), 4.89 (1H, dd, *J* = 14.3, 8.6 Hz, H7a), 4.20 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.34 (1H, dd, *J* = 13.0, 4.8 Hz, H4a), 3.15-3.05 (2H, m, H6a and H10α), 2.94 (1H, dd, *J* = 13.5, 8.0 Hz, H7α), 2.92-2.77 (2H, m, H10β and H10a), 2.71 (1H, dd, *J* = 14.9, 5.1 Hz, H5α), 2.63 (1H, dd, *J* = 10.1, 6.2 Hz, H10b), 2.42 (1H, dd, *J* = 14.9, 3.1 Hz, H5β), 2.15 (3H, d, *J* = 1.4 Hz, 2-methyl), 1.47 (1H, m, H7β), 1.42 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.37 (3H, s, 10c-methyl). NOE data 4.89 (2.94, 4%), 3.34 (2.92-2.77, 15%; 2.71, 5%), 1.37 (2.63, 8%; 2.42, 5%). ^{13}C NMR (CD_2Cl_2) δ 210.0 (0, C6), 198.0 (0, C4), 178.3 (0, C9), 159.2 (0, C2), 124.7 (1, C3), 98.4 (0), 84.6 (1, C7a), 76.1 (2, OCH_2CH_3), 75.0 (0), 58.2 (1, C10b), 52.4 (1, C6a), 46.8 (0, C10c), 45.0 (1, C4a), 39.6 (1, C10a), 37.5 (2, C5), 37.4 (2, C10), 31.6 (2, C7), 22.1 (3, 10c-methyl), 21.3 (3, 2-methyl), 15.0 (3, OCH_2CH_3). MS *m/z* 344 (M^+-28, 2), 203 (14), 175 (22), 166 (32), 148 (13), 147 (14), 137 (100), 110 (35), 105 (14), 91 (24), 79 (21), 77 (21), 69 (19), 67 (12), 65 (12), 55 (25), 53 (17). Anal.

calcd. for $C_{23}H_{28}O_6$: C, 67.73; H, 6.50. Found: C, 67.61; H, 6.89.

(1α,4aβ,7aα,10aα,10bβ,10cβ)-6-(*tert*-Butyldimethylsilyl)oxy-1-ethoxyethynyl-4a,5,7,7a,10,10a,10b,10c-octahydro-1-methoxy-2,10c-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]furan-4,9-dione (101) and **methyl (1α,4aβ,7aα,10aα,10bβ,10cβ)-6-(*tert*-butyldimethylsilyl)oxy-4a,5,7,7a,10,10a,10b,10c-octahydro-1-methoxy-2,10c-dimethyl-4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (102)**

To a solution of ethyl ethynyl ether (50% wt % solution in hexane, 0.20 mL, 1.02 mmol) in dry THF (18 mL) was introduced *n*-BuLi (2.5 M in hexane, 0.30 mL, 0.75 mmol) at -78 °C over 3 min. The solution was stirred for 30 min and then transferred with a double-headed needle to a solution of **79** (0.258 g, 0.619 mmol) in dry THF (18 mL) at -78 °C over 30 min. The resulting solution was stirred for 2 h before iodomethane (0.19 mL, 3.05 mmol) in HMPA (7.0 mL) was added. The mixture was warmed to rt and then stirred for 12 h before it was quenched with water (60 mL) and extracted with EtOAc (4 x 25 mL). The combined extracts were washed with brine (3 x 40 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (40% EtOAc/hexane) to afford **101** (0.130 g, 40% yield) and **102** (30 mg, 10% yield).

Compound **101**: Pale yellow foam: attempts to obtain crystals by crystallization were unsuccessful. IR (CCl_4) 2257 (s), 1772 (s), 1672 (s), 1472 (m), 1244 (m), 1093 (m) cm^{-1}. ^1H NMR (CD_2Cl_2, -80 °C, signals are very broad at rt) δ 5.60 (1H, s, H3), 4.59 (1H,

m, H7a), 4.12 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.54 (3H, s, OCH_3), 3.25 (1H, m), 2.13-1.86 (3H, m), 1.98 (3H, s, 2-methyl), 1.31 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.23 (3H, s, 10c-methyl), 0.86 (9H, s, $SiC(CH_3)_3$), 0.04 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$). ^{13}C NMR (CD_2Cl_2, -80 °C) δ 197.6 (0, C4), 178.7 (0, C9), 163.2 (0, C2), 140.2, 125.0, 117.6 (0, C6a), 97.4 , 82.8, 80.6, 75.2, 56.7, 49.7, 48.3, 47.7, 42.2, 32.94, 32.89, 31.2, 25.3, 25.1, 24.9, 18.8, 17.7, 14.3, -4.8, -4.9. MS *m/z* 472 (M^+-C_2H_4, 4), 415 (10), 224 (21), 223 (31), 181 (16), 151 (13), 117 (18), 103 (12), 75 (79), 73 (100). HRMS calcd. for $C_{28}H_{40}O_6Si$ - C_2H_4 472.2281, found 472.2297.

Compound **102**: pale yellow solid: mp 145.0-147.0 °C. IR (Nujol) 1777 (s), 1727 (s), 1660 (s), 1213 (s), 1193 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.88 (1H, d, J = 1.2 Hz, H3), 4.62 (1H, m, H7a), 3.70 (3H, s, CO_2CH_3), 3.65 (1H, s, 1-methoxy), 3.08 (1H, d, J = 13.3 Hz, $CHHCO_2CH_3$), 3.02 (1H, d, J = 13.3 Hz, $CHHCO_2CH_3$), 3.09-2.86 (2H, m, H7α and H10α), 2.83 (1H, d, J = 17.6 Hz, H5), 2.61-2.53 (3H, m, H4a, H10β and H10a), 2.20-2.10 (2H, m, H5 and H10b), 2.00 (3H, d, J = 1.2 Hz, 2-methyl), 1.94 (1H, m, H7β), 1.38 (3H, s, 10c-methyl), 0.95 (9H, s, $SiC(CH_3)_3$), 0.18 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$). NOE data 4.62 (3.09-2.86, 3%; 2.61-2.53, 5%), 2.20-2.10 (2.61-2.53, 10%), 1.38 (3.70, 2%; 2.61-2.53, 13%; 2.20-2.10, 18%). ^{13}C NMR ($CDCl_3$) δ 196.0 (0, C4), 178.2 (0, C9), 170.7 (0, CO_2CH_3), 162.6 (0, C2), 141.4 (0, C6), 128.3 (1, C3), 115.6 (0, C6a), 82.5 (1, C7a), 82.3 (0, C1), 54.6 (3, CO_2CH_3), 52.6 (1, C10b), 52.3 (3, 1-methoxy), 49.1 (1, C10a), 48.8 (0, C10c), 42.0 (1, C4a), 37.0 (2, $CH_2CO_2CH_3$), 35.4 (2, C10), 32.2 (2, C7), 25.7 (3, $SiC(CH_3)_3$), 25.6 (2, C5), 24.9 (3, 10c-methyl), 20.4 (3, 2-methyl), 18.1 (0, $SiC(CH_3)_3$), -3.8 (3, $SiCH_3$), -4.3 (3, $SiCH_3$). MS *m/z* 504 (M^+, 3), 447 (10), 281 (8), 224 (26), 224

(39), 181 (19), 117 (26), 103 (13), 75 (80), 73 (100), 59 (15). HRMS calcd. for $C_{27}H_{40}O_7Si$ 504.2543, found 504.2536.

Ethyl (1α,4aα,6aβ,7aα,10aα,10bβ,10cβ)-4a,5, 6a,7,7a,10,10a,10b,10c-nonahydro-1-methoxy-2,10c-dimethyl-4,6,9-trioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (109)

To a solution of **101** (0.155 g, 0.130 mmol) in dry THF (8.0 mL) was added tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 0.50 mL, 0.50 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min before it was diluted with EtOAc (60 mL), washed with water (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was dissolved in THF (10 mL) and 5% aqueous H_2SO_4 (4.0 mL) was then added. The resulting solution was stirred at rt for 3 days before it was diluted with EtOAc (60 mL), washed with water (3 x 20 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue (**108**) was subjected to column chromatography (50% EtOAc/hexane) to afford **109** (13 mg, 10% yield from **101**) as a pale yellow solid: mp 181.0-183.0 °C. IR (Nujol) 1758 (s), 1738 (s), 1709 (s), 1662 (s), 1191 (s), 1089 (m), 1046 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.18 (1H, d, J = 1.6 Hz, H3), 4.88 (1H, m, H7a), 4.19 (2H, m, OCH_2CH_3), 3.37 (1H, dd, J = 12.4, 5.1 Hz, H4a), 3.32 (3H, s, OCH_3), 3.12 (1H, d, J = 15.7 Hz, $CHHCO_2Et$), 3.02-2.95 (2H, m, H6a and H7α), 2.82-2.75 (5H, m, H5α, H10α, H10β, H10a and $CHHCO_2Et$), 2.57 (1H, m, H10b), 2.48 (1H, dd, J = 16.2, 12.4 Hz, H5β), 2.31 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.24 (3H, s, 10c-methyl). NOE data 4.88 (3.02-2.95, 4%; 2.82-2.75, 4%), 3.37 (2.82-2.75, 8%), 1.24 (3.02-2.95,

10%; 2.57, 6%; 2.48, 9%). ^{13}C NMR ($CDCl_3$) δ 209.0 (0, C6), 197.4 (0, C4), 177.2 (0, C9), 169.7 (0, CO_2Et), 156.0 (0, C2), 130.0 (1, C3), 83.3 (1, C7a), 81.8 (0, C1), 61.3 (2, OCH_2CH_3), 57.1 (1, C10b), 53.4 (3, OCH_3), 51.5 (1, C6a), 49.9 (0, C10c), 45.2 (1, C4a), 39.0 (1, C10a), 37.1 (2, CH_2CO_2Et), 36.5 (2, C10), 36.2 (2, C5), 31.6 (2, C7), 23.7 (3, 2-methyl), 20.1 (3, 10c-methyl), 19.0 (3, OCH_2CH_3). MS *m/z* 372 (M^+-32, 29), 317 (11), 299 (19), 198 (100), 175 (12), 141 (25), 125 (59), 111 (35), 105 (12), 91 (14), 79 (13), 77 (10). HRMS calcd. for $C_{22}H_{28}O_7$ - CH_3OH 372.1573, found 372.1551.

Ethyl (4aα,6aα,7aβ,10aβ,10bα,10cα)-4a,5, 6a,7,7a,10,10a,10b,10c-nonahydro-2,10c-dimethyl-4,6,9-trioxo-3*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetate (115) and **ethyl (4aα,6aβ,7aα,10aα,10bβ,10cβ)-4a,5, 6a,7,7a,10,10a,10b,10c-nonahydro-2,10c-dimethyl-4,6,9-trioxo-3*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetate (116)**

A mixture of **98** and **99** (7:1 ratio favoring **98**) (0.920 g, 2.47 mmol,) was dissolved in glacial AcOH (35 mL). The solution was heated to boil, and then analytical grade Zn dust (6.4 g, 0.10 mol) was added in portions until **98** and **99** 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 (100 mL) and water (100 mL), and then neutralized by the adding solid Na_2CO_3 until CO_2-evolution ceased. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers 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 (65% EtOAc/hexane) to afford **115** and **116** (0.779 g, 84% yield

combined) in a ratio of 1:6 in favor of the less mobile component **115**. Compounds **115** and **116** could completely be separated by column chromatography, but the separation was not necessary for our synthesis.

Compound **115**: White solid: mp 188.0-190.0 °C. IR (Nujol) 1775 (s), 1740 (s), 1715 (s), 1179 (m), 1023 (m) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 4.66 (1H, m, H7a), 4.17 (2H, m, OCH_2CH_3), 3.31 (1H, d, J = 16.9 Hz, H3β), 3.20 (1H, d, J = 22.0 Hz, CH_2CO_2Et), 3.10 (1H, d, J = 6.8 Hz, H4a), 3.04-2.90 (4H, m), 2.81 (1H, d, J = 22.0 Hz, CH_2CO_2Et), 2.55 (1H, dd, J = 14.9, 6.7 Hz, H5α), 2.45 (1H, dd, J = 17.8, 9.6 Hz, H10β), 2.30 (1H, dd, J = 11.1, 6.8 Hz, H10b), 2.05-1.91 (2H, m, H10α and H10a), 1.75 (3H, s, 2-methyl), 1.60 (3H, s, 10c-methyl), 1.53 (1H, m, H7α), 1.27 (3H, t, J = 7.1 Hz, OCH_2CH_3). NOE data 2.55 (3.10, 3%), 2.05-1.91 (4.66, 6%; 3.31, 2%), 1.60 (3.10, 12%; 2.55, 2%; 2.30, 8%). ^{13}C NMR ($CDCl_3$) δ 208.8 (0), 207.3 (0), 176.5 (0, C9), 171.3 (0, CO_2Et), 131.6 (0), 128.7 (0), 83.7 (1, C7a), 61.6 (2, OCH_2CH_3), 56.9 (1, C10b), 55.1 (1, C4a), 50.4 (1, C6a), 46.2 (2, CH_2CO_2Et), 44.8 (0, C10c), 40.4 (1, C10a), 35.8 (2, C5), 35.2 (2, C3), 34.9 (2, C10), 32.2 (2, C7), 27.1 (3, 10c-methyl), 20.1 (3, 2-methyl), 14.5 (3, OCH_2CH_3). MS *m/z* 374 (M^+, 25), 301 (14), 249 (17), 222 (24), 221 (90), 208 (54), 180 (19), 175 (59), 149 (29), 148 (35), 135 (93), 134 (16), 121 (26), 119 (23), 107 (47), 106 (42), 105 (40), 93 (17), 91 (56), 79 (40), 77 (26), 67 (25), 65 (13), 55 (47), 53 (20), 43 (29), 41 (49), 29 (100). HRMS calcd. for $C_{21}H_{26}O_6$ 374.1729, found 374.1705.

Compound **116**: pale yellow solid, mp 184.5-187.0 °C. IR (Nujol) 1768 (s), 1736 (s), 1708 (s), 1179 (m), 1056 (m) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 4.76 (1H, dd, J = 14.3, 7.0 Hz, H7a), 4.13 (2H, m, OCH_2CH_3), 3.29 (1H, d, J = 17.0 Hz), 3.15 (1H, d, J = 20.4 Hz),

3.04-2.92 (3H, m), 2.85-2.59 (6H, m), 2.44 (1H, dd, J = 4.4, 1.2 Hz), 2.39 (1H, d, J = 4.8 Hz), 1.72 (1H, m, H7β), 1.67 (3H, s, 2-methyl), 1.24 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.11 (3H, s, 10c-methyl). ^{13}C NMR (CD_2Cl_2) δ 209.9 (0), 206.7 (0), 176.5 (0, C9), 171.0 (0, CO_2Et), 133.0 (0), 129.8 (0), 84.2 (1, C7a), 61.6 (2, OCH_2CH_3), 57.8 (1), 50.4 (1), 49.7 (1), 47.5 (0, C10c), 46.8 (2), 39.8 (1), 36.5 (2), 36.0 (2), 35.3 (2), 34.4 (2), 21.5 (3, 10c-methyl), 20.4 (3, 2-methyl), 14.5 (3, OCH_2CH_3). MS *m/z* 374 (M^+, 38), 328 (14), 301 (17), 285 (12), 222 (23), 221 (74), 208 (30), 203 (16), 175 (58), 149 (28), 148 (29), 147 (14), 135 (59), 121 (16), 119 (30), 107 (36), 106 (32), 105 (44), 93 (18), 91 (52), 79 (40), 77 (27), 67 (25), 55 (44), 53 (19), 43 (35), 41 (45), 29 (100). HRMS calcd. for $C_{21}H_{26}O_6$ 374.1729, found 374.1717.

Ethyl (1ξ,6aα,7aβ,10aβ,10bα,10cα)-6a,7,7a,10,10a,10b,10c-heptahydro-2,10c-dimethyl-4,6,9-trioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (121)

A mixture of **115** and **116** (6:1 ratio favoring **115**, 30 mg, 0.080 mmol) in glacial AcOH (8.0 mL) was heated at reflux for 5 h. After cooling to rt, this solution was poured into a mixture of EtOAc (30 mL) and water (30 mL), and neutralized by adding solid Na_2CO_3 until CO_2-evolution ceased. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (60% EtOAc/hexane) to afford **121** (6.0 mg, 20% yield) as yellow crystals: mp 142.0-142.5 °C. ^1H NMR (CD_2Cl_2) δ 6.65 (1H, s, H5), 6.21 (1H, s, H3), 4.77 (1H, m, H7a), 4.25 (2H, m,

OCH_2CH_3), 3.34 (1H, d, J = 9.4 Hz), 3.12-3.03 (2H, m), 2.95-2.77 (2H, m), 2.61-2.52 (3H, m), 2.38 (1H, dd, J = 18.1, 4.1 Hz), 2.00 (3H, s, 2-methyl), 1.82 (1H, m), 1.34 (3H, s, 10c-methyl), 1.31 (3H, t, J = 7.1 Hz, OCH_2CH_3). ^{13}C NMR (CD_2Cl_2) δ 199.3 (0, C6), 184.4 (0, C4), 176.7 (0, C9), 172.8 (0, CO_2Et), 163.3, 154.0, 128.0, 126.8, 83.3, 62.2, 55.8, 48.3, 43.2, 41.5, 39.4, 36.9, 35.4, 32.7, 25.2, 23.2, 14.4.

Ethyl (1α,4aβ,6aα,7aβ,10aβ,10bα,10cα)-4a,5, 6a,7,7a,10,10a,10b,10c-nonahydro-2,10c-dimethyl-4,6,9-trioxo-1*H*-benz[6,7]indeno-[2,1-*b*]furan-1-methylcarboxylate (122)

A mixture of **115** and **116** (6:1 ratio favoring **115**, 0.245 g, 0.654 mmol) was dissolved in methanol (30 mL) by warming. The solution was combined with 6M aqueous HCl (10 mL) and heated at reflux for 3.5 h. After cooling to rt, the reaction mixture was diluted with EtOAc (150 mL), washed with water (2 x 40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatograghy (60% EtOAc/hexane) to provide **122** (0.156 g, 64%) as a pale yellow solid: mp 209.0-210.0 °C. IR (Nujol) 1764 (s), 1720 (s), 1702 (s), 1669 (s), 1172 (s), 1058 (m) cm^{-1}. ^1H NMR (CD_3COCD_3) δ 5.90 (1H, s, H3), 4.79 (1H, dd, J = 15.8, 7.7 Hz, H7a), 4.23 (2H, m, OCH_2CH_3), 3.29 (1H, d, J = 10.8 Hz, H1), 3.17-3.10 (2H, m, H4a and H6a), 2.96-2.81 (5H, m), 2.63-2.43 (4H, m), 1.91 (3H, s, 2-methyl), 1.48 (1H, m, H7α), 1.28 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.20 (3H, s, 10c-methyl). NOE data 3.29 (3.17-3.10, 2%), 3.17-3.10 (3.29, 3%), 1.48 (3.17-3.10, 3%), 1.20 (3.17-3.10, 9%). ^{13}C NMR (CD_3COCD_3) δ 210.3 (0, C6), 197.9 (0, C4), 177.3 (0, C9), 173.9 (0, CO_2Et),

160.3 (0, C2), 126.9 (1, C3), 83.4 (1, C7a), 61.7 (2, OCH_2CH_3), 58.1 (1), 50.8 (1), 49.9 (1), 44.8 (1), 43.0 (0, C10c), 37.9 (1), 37.2 (2), 35.2 (2), 33.4 (2), 33.2 (2), 22.2 (3, 2-methyl), 16.2 (3, 10c-methyl), 14.5 (3, OCH_2CH_3). MS *m/z* 374 (M^+, 39), 329 (11), 277 (10), 241 (10), 221 (24), 203 (14), 175 (100), 149 (13), 135 (28), 123 (14), 119 (14), 105 (19), 95 (51), 91 (30), 79 (26), 77 (17). HRMS calcd. for $C_{21}H_{26}O_6$ 374.1729, found 374.1717.

Ethyl (1α,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-4a,5,6,6a,7,7a,10,10a,10b,10c-decahydro-6-hydroxy-2,10c-dimethyl-4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (123) and **ethyl (1α, 4aβ,6α,6aα,7aβ,10aβ,10bα,10cα)-4a,5,6,6a,7,7a,10,10a,10b,10c-decahydro-6-hydroxy-2,10c-dimethyl-4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (124)**

To a solution of **122** (0.520 g, 1.39 mmol) in dry THF (55 mL) was introduced $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.0 M in THF, 2.10 mL, 2.10 mmol) at -20 °C over 5 min. The solution was slowly warmed to 0 °C over 1 h and then maintained at 0 °C with stirring for another 1 h before it was quenched with dilute NH_4Cl solution (100 mL) and extracted with EtOAc (4 x 50 mL). The combined 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 (70% EtOAc/hexane) to provide **123** (0.410 g, 78% yield) and **124** (51 mg, 10% yield).

Compound **123**: white solid: mp 221.5-223.0 °C. IR (Nujol) 3418 (m), 1764 (s), 1730 (s), 1665 (s), 1173 (m), 1044 (m) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 5.87 (1H, d, J = 1.3

Hz, H3), 5.19 (1H, m, H7a), 4.23 (2H, m, OCH_2CH_3), 3.95 (1H, m, H6), 3.17 (1H, d, J = 9.7 Hz, H1), 3.06 (1H, m, H10a), 2.86 (1H, dd, J = 18.6, 10.3 Hz, H10β), 2.80 (1H, dd, J = 12.2, 3.6 Hz, H4a), 2.56-2.33 (3H, m, CH_2CO_2Et and H7β), 2.30 (1H, m, H6a), 2.25 (1H, dd, J = 18.9, 3.8 Hz, H10α), 2.07 (1H, m, H5β), 1.91 (1H, dd, J = 10.8, 5.80 Hz, H10b), 1.86 (3H, apparent t, J = 1.1 Hz, 2-methyl), 1.83-1.74 (2H, m, H7α and 6-hydroxy), 1.65 (1H, m, H5α), 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3), 0.86 (3H, s, 10c-methyl). NOE data 3.95 (2.30, 6%), 3.17 (2.80, 2%), 3.06 (5.19, 7%; 2.80, 5%), 0.86 (2.30, 4%; 1.91, 4%; 1.65, 6%). ^{13}C NMR (CD_2Cl_2) δ 200.4 (0, C4), 178.1 (0, C9), 173.4 (0, CO_2Et), 159.5 (0, C2), 127.2 (1, C3), 86.7 (1, C7a), 68.3 (1, C6), 61.8 (2, OCH_2CH_3), 54.1 (1, C10b), 44.0 (1, C1), 42.4 (0, C10c), 42.2 (1, C4), 42.0 (1, C6a), 39.8 (1, C10a), 37.9 (2, C7), 36.0 (2, C10), 33.6 (2, CH_2CO_2Et), 29.4 (2, C5), 22.6 (3, 2-methyl), 16.4 (3, 10c-methyl), 14.4 (3, OCH_2CH_3). MS *m/z* 376 (M^+, 6), 358 (32), 340 (17), 271 (21), 269 (18), 234 (39), 221 (67), 211 (17), 196 (18), 177 (24), 161 (26), 149 (22), 147 (17), 135 (53), 123 (41), 122 (43), 121 (17), 119 (21), 107 (16), 105 (29), 95 (100), 93 (18), 91 (40), 79 (32), 77 (22). HRMS calcd. $C_{21}H_{28}O_6$ 376.1886, found 376.1878.

Compound **124**: white solid: mp 195.0-196.0 °C. IR (Nujol) 3512 (m), 1758 (s), 1732 (s), 1666 (s), 1173 (m), 1051 (m) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 5.87 (1H, d, J = 1.3 Hz, H3), 5.19 (1H, m, H7a), 4.23 (2H, m, OCH_2CH_3), 3.95 (1H, m, H6), 3.17 (1H, d, J = 9.7 Hz, H1), 3.06 (1H, m, H10a), 2.86 (1H, dd, J = 18.6, 10.3 Hz, H10β), 2.80 (1H, dd, J = 12.2, 3.6 Hz, H4a), 2.56-2.33 (3H, m, CH_2CO_2Et and H7β), 2.30 (1H, m, H6a), 2.25 (1H, dd, J = 18.9, 3.8 Hz, H10α), 2.07 (1H, m, H5β), 1.91 (1H, dd, J = 10.8, 5.8 Hz, H10b),

1.86 (3H, br s, 2-methyl), 1.83-1.74 (2H, m, H7α and 6-hydroxy), 1.65 (1H, m, H5α), 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3), 0.86 (3H, s, 10c-methyl). NOE data 3.95 (2.30, 6%), 3.17 (2.80, 2%), 3.06 (5.19, 7%; 2.80, 5%), 0.86 (2.30, 4%; 1.91, 4%; 1.65, 6%). ^{13}C NMR (CD_2Cl_2) δ 200.4 (0, C4), 178.1 (0, C9), 173.4 (0, CO_2Et), 159.5 (0, C2), 127.2 (1, C3), 86.7 (1, C7a), 68.3 (1, C6), 61.8 (2, OCH_2CH_3), 54.1 (1, C10b), 44.0 (1, C1), 42.4 (0, C10c), 42.2 (1, C4), 42.0 (1, C6a), 39.8 (1, C10a), 37.9 (2, C7), 36.2 (2, C10), 33.6 (2, CH_2CO_2Et), 29.4 (2, C5), 22.6 (3, 2-methyl), 16.4 (3, 10c-methyl), 14.4 (3, OCH_2CH_3). MS *m/z* 376 (M^+, 6), 358 (32), 340 (17), 270 (21), 269 (18), 234 (39), 221 (67), 211 (17), 196 (18), 177 (24), 161 (26), 149 (22), 147 (17), 135 (53), 123 (41), 122 (43), 119 (21), 105 (29), 95 (100), 91 (40), 79 (32), 77 (22). HRMS calcd. $C_{21}H_{28}O_6$ 376.1886, found 376.1889.

Ethyl (1α,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-4a,5,6,6a,7,7a,10,10a,10b,10c-decahydro-6-(2-methoxyethoxy)methoxy-2,10c-dimethyl-4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (129)

To a solution of **123** (0.160 g, 0.425 mmol) in dry CH_2Cl_2 (10 mL) was successively added (2-methoxyethoxy)methyl chloride (MEM chloride) (0.48 mL, 4.20 mmol) and *N,N*-diisopropylethylamine (0.95 mL, 5.45 mmol). The solution was heated at reflux for 12 h before it was diluted with CH_2Cl_2 (80 mL), and then washed with 1% HCl aqueous solution (2 x 30 mL) and brine (30 mL). The resulting organic solution was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography (70% EtOAc/hexane) to afford **129** (0.182 g, 92% yield) as a

white solid: mp 155.0-157.0 °C. IR (Nujol) 1769 (s), 1738 (s), 1661 (s), 1159 (m), 1041 (m) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 5.86 (1H, s, H3), 5.12 (1H, m, H7a), 4.72 (1H, d, J = 6.9 Hz, OCH_2O), 4.60 (1H, d, J = 6.9 Hz, OCH_2O), 4.22 (2H, m, OCH_2CH_3), 3.76 (1H, m, H6), 3.72-3.56 (2H, m, $CH_3OCH_2CH_2$), 3.49 (2H, t, J = 4.5 Hz, $CH_3OCH_2CH_2$), 3.32 (3H, s, CH_3O), 3.15 (1H, d, J = 10.4 Hz, H1), 2.98 (1H, m, H10a), 2.84 (1H, dd, J = 18.6, 10.9 Hz, H10β), 2.67 (1H, dd, J = 12.3, 3.1 Hz, H4a), 2.51 (1H, dd, J = 17.7, 1.8 Hz, CH_2CO_2Et), 2.44-2.23 (5H, m), 1.91 (1H, dd, J = 11.0, 5.8 Hz, H10b), 1.85 (3H, s, 2-methyl), 1.76 (1H, m, H7α), 1.44 (1H, m, H5α), 1.29 (3H, t, J = 7.2 Hz, OCH_2CH_3), 0.86 (3H, s, 10c-methyl). ^{13}C NMR (CD_2Cl_2) δ 200.0 (0, C4), 177.8 (0, C9), 173.4 (0, CO_2Et), 159.2 (0, C2), 127.2 (1, C3), 94.6 (2, OCH_2O), 86.5 (1, C7a), 74.1 (1, C6), 72.3 (2, $CH_3OCH_2CH_2$), 68.3 (2, $CH_3OCH_2CH_2$), 61.8 (2, OCH_2CH_3), 59.2 (3, CH_3O), 54.1 (1, C10b), 44.0 (1, C1), 42.7 (1, C4), 42.3 (0, C10c), 42.1 (1, C6a), 39.8 (1, C10b), 37.7 (2, C7), 35.8 (2, C10), 33.7 (2, CH_2CO_2Et), 24.7 (2, C5), 22.5 (3, 2-methyl), 16.6 (3, 10c-methyl), 14.4 (3, OCH_2CH_3). MS *m/z* 464 (M^+, 2), 388 (3), 359 (7), 358 (5), 285 (4), 221 (7), 159 (3), 95 (6), 89 (100), 59 (86). HRMS calcd. for $C_{25}H_{36}O_8$ 464.2408, found 464.2419.

Ethyl (1α,2β,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-2,3,4a,5,6,6a,7,7a,10,10a,10b,10c-dodecahydro-6-(2-methoxyethoxy)methoxy-2,10c-dimethyl-4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (130)

Liquid ammonia (about 150 mL) was collected in a 250 mL three-necked round-bottomed flask using a dry ice-acetone cold trap. To this liquid ammonia was added Na

shavings (about 1.0 g). The ammonia solution turned blue immediately. After 5 min, this ammonia solution was allowed to warm, and about 60 mL of dry ammonia was distilled into a dry 100 mL three-necked rounded-bottomed flask. To this dry liquid ammonia was added Li shavings (20 mg, 2.9 mmol) in one portion. The ammonia solution turned blue immediately. This blue solution was allowed to warm to -50 °C when enone **129** (0.177 g, 0.381 mmol) in 1:1 dry 1,4-dioxane/Et_2O (16 mL) was introduced over 1.5 min. The mixture was stirred for 4 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 (2 x 35 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum.

The residue was dissolved in CH_2Cl_2 (2.0 mL) and then added dropwise to a suspension of pyridinium chlorochromate (PCC) (0.210 g, 0.955 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 1.5 h and then filtered through Celite. The filtrate was concentrated, and the residue was subjected to column chromatography (70% EtOAc/hexane) to afford **130** (0.131 g, 74% yield) as a white solid: mp 154.0-155.0 °C. IR (Nujol) 1762 (s), 1720 (s), 1699 (s), 1188 (m), 1107 (m), 1039 (s) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 5.14 (1H, dd, J = 14.7, 7.7 Hz, H7a), 4.67 (1H, d, J = 7.2 Hz, OCH_2O), 4.57 (1H, d, J = 7.2 Hz, OCH_2O), 4.16 (2H, m, OCH_2CH_3), 3.72 (1H, m, H6), 3.69-3.56 (2H, m, $CH_3OCH_2CH_2$), 3.48 (2H, t, J = 4.7 Hz, $CH_3OCH_2CH_2$), 3.31 (3H, s, CH_3O), 3.00-2.81 (2H, m, H10β and H10a), 2.68 (1H, dd, J = 12.6, 2.5 Hz, H4a), 2.51 (1H, d, J = 16.4 Hz, CH_2CO_2Et), 2.38 (1H, m, H6a), 2.33-2.05 (6H, m), 1.96-1.88 (2H, m, H5β and

H10b), 1.85 (1H, m, H2), 1.72 (1H, m, H7α), 1.56 (1H, m, H5α), 1.27 (3H, t, J = 7.2 Hz, OCH_2CH_3), 0.94 (3H, d, J = 6.4 Hz, 2-methyl), 0.79 (3H, s, 10c-methyl). NOE data 3.72 (2.38, 6%; 1.56, 2%), 2.68 (3.00-2.81, 7%), 0.79 (2.38, 6%; 1.85, 6%; 1.56, 8%). ^{13}C NMR (CD_2Cl_2) δ 211.7 (0, C4), 178.1 (0, C9), 173.6 (0, CO_2Et), 94.6 (2, OCH_2O), 86.8 (1, C7a), 74.2 (1, C6), 72.3 (2, $CH_3OCH_2CH_2$), 68.3 (2, $CH_3OCH_2CH_2$), 61.4 (2, OCH_2CH_3), 59.2 (3, CH_3O), 54.5 (1, C10b), 50.1 (2, C3), 45.5 (1, C4a), 45.1 (1, C1), 44.6 (0, C10c), 42.3 (1, C6a), 39.0 (1, C10a), 38.0 (1, C2), 37.5 (2, C7), 36.0 (2, C10), 35.4 (2, CH_2CO_2Et), 24.8 (2, C5), 20.8 (3, 2-methyl), 16.8 (3, 10c-methyl), 14.5 (3, OCH_2CH_3). MS *m/z* 466 (M^+, 0.5), 390 (5), 377 (15), 359 (11), 331 (5), 313 (5), 273 (5), 89 (100), 59 (81).

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-hydroxy-6-(2-methoxyethoxy)methoxy-2,10c-dimethyl-9-oxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-methylcarboxylate (131)

To a solution of **130** (0.108 g, 0.231 mmol) in dry THF (20 mL) was introduced L-Selectride (0.28 mL, 0.28 mmol) at -78 °C over 2 min. The solution was stirred for 1 h before it was quenched with 5% aqueous NaOH (1.0 mL), followed by addition of 30% H_2O_2 (1.0 mL). After warming to rt, this mixture was diluted with EtOAc (100 mL), washed with 5% aqueous HCl (25 mL) and brine (2 x 25 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (95% EtOAc/hexane) to provide **131** (98.5 mg, 91% yield) as a white

solid: mp 112.5-113.5 °C. IR (Nujol) 3515 (m), 1761 (s), 1731 (s), 1194 (m), 1094 (m), 1042 (s) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 5.08 (1H, dd, *J* = 14.3, 7.6 Hz, H7a), 4.71 (1H, d, *J* = 7.1 Hz, OCH_2O), 4.61 (1H, d, *J* = 7.1 Hz, OCH_2O), 4.12 (2H, m, OCH_2CH_3), 3.80 (1H, br s, H4), 3.71 (1H, m, H6), 3.66 (1H, d, *J* = 4.2 Hz, $CH_3OCH_2CH_2$), 3.64 (1H, d, *J* = 4.2 Hz, $CH_3OCH_2CH_2$), 3.50 (2H, t, *J* = 4.4 Hz, $CH_3OCH_2CH_2$), 3.33 (3H, s, CH_3O), 2.83-2.71 (2H, m, H10β and H10a), 2.45-2.36 (2H, m, H6a and CH_2CO_2Et), 2.30 (1H, d, *J* = 15.7 Hz, H10α), 2.23 (1H, dd, *J* = 13.3, 7.4 Hz, H7β), 2.09 (1H, dd, *J* = 16.9, 9.8 Hz, CH_2CO_2Et), 1.93-1.82 (2H, m, H2 and H5α), 1.77-1.61(5H, m), 1.58 (1H, m, H5β), 1.46–1.36 (2H, m, H3β and 4-hydroxy). NOE data 3.80 (1.58, 3%; 1.46-1.36, 8%), 2.83-2.71 (5.08, 9%), 2.45-2.36 (3.71, 7%), 1.93-1.82 (3.71, 3%), 1.46-1.36 (3.80, 11%). ^{13}C NMR (CD_2Cl_2) δ 178.5 (0, C9), 174.3 (0, CO_2Et), 94.9 (2, OCH_2O), 87.0 (1, C7a), 75.9 (1, C6), 72.4 (2, $CH_3OCH_2CH_2$), 72.3 (1, C4), 68.1 (2, $CH_3OCH_2CH_2$), 61.0 (2, OCH_2CH_3), 59.2 (3, CH_3O), 55.8 (1), 45.8 (1), 43.5 (2, C3), 42.7 (1, C6a), 39.3 (0, C10c), 38.9 (1, C10a), 37.6 (2, C7), 36.0 (2, C10), 35.4 (2, CH_2CO_2Et), 35.3 (1), 30.3 (2, C5), 29.9 (1, C2), 20.4 (3, 2-methyl), 18.8 (3, 10c-methyl), 14.5 (3, OCH_2CH_3). MS *m/z* 392 (M^+-$CH_3OCH_2CH_2OH$, 1), 361 (8), 255 (6), 195 (5), 167 (6), 119 (6), 105 (6), 93 (6), 89 (77), 59 (100).

(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-hydroxy-9-(2-methoxyethoxy)methoxy-5,10d-dimethylnaphth[2,1,8-*cde*]-2*H*-azuleno[1,8-*bc*]furan-2,3-dione (30) and **(1*R**,2*S**,3*S**,4*R**,8*S**,10*S**,13*R**,14*S**,18*S**)-11-(2-**

methoxyethoxy)methoxy-2,18-dimethyl-7,15-dioxapentacyclo[12.3.2.$0^{2,13}$.$0^{3,10}$.$0^{4,8}$]nonadecane-6,16-dione (132)

To a solution of **131** (31 mg, 0.066 mmol) in dry benzene (15 mL) was added potassium *t*-butoxide (29 mg, 0.24 mmol) in one portion. The mixture was heated at reflux for 4 h before it was cooled to rt and washed with ice-cold 1% aqueous HCl (30 mL). The aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum to give the crude product, which consisted of **30**, **132** and the starting material **131** in a ratio of 5:1:1. The crude product was purified by column chromatography (40% acetone /hexane) to provide **30** (17 mg, 61% yield). By-product **132** was isolated in 8% yield in a separate 100 mg-scale reaction.

Compound **30**: white solid: mp 165-167.0 °C. IR (Nujol) 3534 (m), 1782 (s), 1693 (s), 1169 (s), 1036 (s) cm^{-1}. ^1H NMR (CD_2Cl_2) δ 4.86 (1H, m, H10a), 4.69 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.61 (1H, d, *J* = 7.0 Hz, OCH_2O), 3.91 (1H, br s, H7), 3.76 (1H, br s, H9), 3.70 (1H, d, *J* = 10.6 Hz, H2a), 3.65 (1H, *J* = 4.4 Hz, $CH_3OCH_2CH_2$), 3.63 (H, d, *J* = 4.4 Hz, $CH_3OCH_2CH_2$), 3.50 (2H, t, *J* = 4.6 Hz, $CH_3OCH_2CH_2$), 3.33 (3H, s, CH_3O), 3.24 (1H, m, H10b), 2.58 (1H, dd, *J* = 16.9, 3.9 Hz, H3α), 2.43-2.33 (2H, m, H3β and H9a), 2.27 (1H, dd, *J* = 14.4, 7.8 Hz, H10α), 1.91-1.66 (5H, m), 1.64-1.53 (3H, m), 1.49-1.38 (2H, m, 7-hydroxy and H6α), 1.14 (3H, s, H10d), 0.90 (3H, d, *J* = 6.2 Hz, 5-methyl). NOE data 3.76 (2.43-2.33, 6%), 3.24 (4.86, 5%; 3.70, 4%), 1.49-1.38 (3.91, 13%), 1.14 (2.43-2.33, 8%), 0.90 (2.58, 6%). ^{13}C NMR (CD_2Cl_2) δ 204.0 (0, C3), 172.9 (0, C2), 95.0 (2, OCH_2O), 83.9 (1, C10a), 75.9 (1, C9), 72.4 (2, $CH_3OCH_2CH_2$), 72.2 (1), 68.1 (2,

$CH_3OCH_2CH_2$), 59.3 (3, CH_3O), 55.8 (1, C2a), 54.7 (1), 50.2 (1), 44.7 (2, C6), 43.5 (2, C4), 42.4 (1, C9a), 40.6 (1, C10b), 37.5 (2, C10), 37.1 (1), 29.0 (2, C8), 27.0 (1), 20.2 (3, 5-methyl), 18.2 (3, 10d-methyl). MS *m/z* 422 (M^+, 1), 346 (4), 331 (13), 315 (6), 299 (8), 105 (4), 89 (65), 59 (100). HRMS calcd. for $C_{23}H_{34}O_7$ 422.2302, found 422.2270.

Compound **132**: white solid: mp 191.0-192.0 °C. IR (Nujol) 1759 (s), 1718 (s) cm^{-1}. ^1H NMR (CD_3OD) δ 5.16 (1H, dd, *J* = 14.3, 7.2 Hz, H8), 4.76 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.66 (1H, d, *J* = 7.0 Hz, OCH_2O), 3.76 (1H, d, *J* = 2.7 Hz), 3.72 (1H, m), 3.71-3.68 (2H, m, $CH_3OCH_2CH_2O$), 3.57-3.54 (2H, m, $CH_3OCH_2CH_2O$), 3.36 (3H, s, CH_3O), 2.87-2.77 (2H, m), 2.55 (1H, d, *J* = 17.7 Hz), 2.48-2.35 (2H, m), 2.25 (1H, dd, *J* = 13.3, 7.7 Hz), 2.06 (1H, dd, *J* = 17.7, 9.9 Hz), 1.99-1.85 (3H, m), 1.75-1.57 (5H, m), 1.39 (1H, m), 1.08 (3H, s, 2-methyl), 0.88 (3H, d, *J* = 7.0 Hz, 18-methyl). ^{13}C NMR (CD_3OD) δ 181.4 (0, C6), 178.0 (0, C16), 95.8, 88.9, 77.4, 73.1, 72.8, 68.8, 59.4, 56.5, 46.6, 44.1, 43.7, 40.2, 39.9, 38.2, 36.9, 36.5, 35.8, 31.2, 31.1, 20.8, 19.0. MS *m/z* 333 (M^+ - $C_4H_9O_2$, 11), 257 (6), 183 (5), 167 (7), 149 (13), 131 (7), 119 (10), 105 (12), 93 (10), 91 (12), 89 (68), 59 (100). HRMS calcd. for $C_{23}H_{34}O_7$ - $C_4H_9O_2$ 333.1203, found 333.1721.

(-)-Menthoxyacetic acid (172)

This compound was prepared by the procedure of Newton and Whitham.[86a] A solution of (-)-menthol (**171**) (7.90 g, 50.0 mmol) in dry DMF (140 mL) was added in one portion to NaH (60% oil dispersion, 5.45 g, 136 mmol, washed twice with petroleum ether). The mixture was mechanically stirred at rt for 3.5 h before chloroacetic acid (5.07 g, 534 mmol) in dry DMF (90 mL) was added over 50 min. The resulting mixture was

stirred at rt for 7 h and then at 100 °C for 14 h. After cooling to rt, the reaction was quenched with water (40 mL), and the solvent was removed by distillation at reduced pressure. The residue was dissolved in water (100 mL) and extracted with benzene (3 x 20 mL). The aqueous layer was acidified with concentrated HCl, and then extracted with benzene (4 x 40 mL). The combined extracts were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum gave reasonably pure **172** (5.13 g), which was used in the next step without further purification. An analytical sample was obtained by column chromatography (30% Et_2O/hexane) as a slightly yellow oil: IR (neat) 3150 (s, br), 1733 (s), 1128 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.7 (1H, br s, CO_2H), 4.20 (1H, d, J = 16.8 Hz, OCH_2CO), 2.10 (1H, d, J = 16.8 Hz, OCH_2CO), 3.20 (1H, dt, J = 10.6, 4.1 Hz, H1'), 2.24 (1H, m), 2.21 (1H, m), 1.68-1.61 (2H, m), 1.36-1.26 (2H, m), 0.96-0.87 (3H, m), 0.93 (3H, d, J = 5.9 Hz), 0.90 (3H, d, J = 6.8 Hz), 0.78 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 175.4 (0, C1), 80.3, 65.3, 47.8, 39.7, 34.2, 31.3, 25.4, 23.0, 22.1, 20.8, 16.0. MS *m/z* 155 (M^+ - CH_2CO_2H, 14), 139 (17), 138 (57), 129 (79), 123 (46), 109 (14), 96 (28), 95 (81), 83 (37), 82 (47), 81 (100), 71 (37).

(-)-Menthoxyacetyl chloride (173)

This compound was prepared by the procedure of Leffler and Calkins.[86b] To thionyl chloride (redistilled, 16.0 mL, 219 mmol) was added (-)-menthoxyacetic acid (**172**) (10.3 g, approximately 48.1 mmol) over 1 h. The solution was stirred at rt for 1h and then at reflux for 5 h. The excess thionyl chloride was removed under vacuum, and vacuum distillation of the residue gave **173** (8.02 g, 34% yield from **171**) as a colorless

oil: $[\alpha]_D$ -96.4° (benzene) (lit.[86b] -92.4°). IR (neat) 1808 (s), 1131 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.48 (1H, d, J = 18.5 Hz, OCH_2CO), 4.44 (1H, d, J = 18.5 Hz, OCH_2CO), 3.23 (1H, dt, J = 10.6, 6.4 Hz, H1'), 2.26 (1H, m), 2.04 (1H, m), 1.68-1.62 (2H, m), 1.41-1.22 (2H, m), 1.00-0.85 (3H, m), 0.93 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 7.1 Hz), 0.79 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 172.1 (0, C1), 80.8, 73.8, 48.1, 39.8, 34.2, 31.4, 25.3, 23.0, 22.2, 21.0, 16.1. MS *m/z* 155 (M^+ - CH_2COCl, 35), 139 (72), 138 (54), 137 (36), 123 (14), 97 (19), 95 (35), 83 (100), 81 (54), 69 (27).

(1*R*,5*S*,7*R*)-7-((1'*R*,2'*S*,5'*R*)-menthoxy)bicyclo[3.2.0]hept-2-en-6-one (176) and **(1*S*,5*R*,7*S*)-7-((1'*R*,2'*S*,5'*R*)-menthoxy)bicyclo[3.2.0]hept-2-en-6-one (177)**

To a solution of cyclopentadiene (**175**) (freshly cracked from dicyclopentadiene, 1.65 g, 25.0 mmol) and triethylamine (0.84 mL, 6.03 mmol) in anhydrous Et_2O (150 mL) was added (-)-menthoxyacetyl chloride (**173**) (1.16 g, 49.9 mmol) in anhydrous Et_2O (50 mL) at rt over 4 h. The resulting mixture was stirred for another 18 h. A solid was removed by filtration. The filtrate was washed with water (3 x 50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to column chromatography (15% Et_2O/hexane) to provide a 2:1 mixture of **176** and **177** (880 mg, 67% yield) as a pale yellow oil.

NMR data for the major diastereoisomer: ^1H NMR ($CDCl_3$) δ 5.89 (1H, m, H3), 5.78 (1H, m, H2), 4.82 (1H, dd, J = 8.8, 2.8 Hz, H7), 3.78 (1H, m, H1), 3.42 (1H, m, H5), 3.17 (1H, dt, J = 10.6, 4.2 Hz, H1'), 2.72 (1H, m, H4 *anti to* H5), 2.46 (1H, m, H4, *syn to* H5), 2.07 (1H, m), 1.66-1.59 (2H, m), 1.40-1.20 (2H, m), 1.01-0.86 (3H, m), 0.92 (3H, d,

J = 8.4 Hz), 0.90 (3H, d, J = 9.0 Hz), 0.81 (3H, d, J = 7.0 Hz). NOE data 4.82 (3.78, 4%; 3.42, 2%; 3.17, 3%), 2.46 (3.42, 2%). ^{13}C NMR ($CDCl_3$) δ 211.4 (0, C6), 135.1 (1), 128.5 (1), 89.8 (1), 80.5 (1), 53.1, 47.5, 46.4, 41.0, 34.7, 34.4, 31.6, 25.4, 23.2, 22.3, 20.8, 16.2.

Discernible NMR data for the minor diastereoisomer: ^{1}H NMR ($CDCl_3$) δ 3.31 (1H, dt, J = 10.6, 4.3 Hz, H1'), 0.93 (3H, d, J = 6.4 Hz), 0.87 (3H, d, J = 6.5 Hz), 0.77 (3H, d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 210.7 (0, C6), 134.9 (1), 129.0 (1), 89.6 (1), 80.7 (1), 53.9, 47.9, 47.6, 41.4, 34.8, 22.3.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranoxyacetic acid (183)

A solution of (-)-diacetone-D-glucose (**182**) (5.31 g, 20.0 mmol) in dry DMF (120 mL) was added in one portion to NaH (60% oil dispersion, 2.80 g, 70.0 mmol, washed twice with petroleum ether before use). This was stirred at rt for 1 h before chloroacetic acid (2.08 g, 22.0 mmol) in dry DMF (30 mL) was added over 50 min. The mixture was stirred at rt for 30 min and then at 110 °C for 15 h. After cooling to rt, the reaction was quenched with water (40 mL), and the solvent was removed by distillation at reduced pressure. The residue was dissolved in water (100 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The aqueous layer was neutralized with concentrated HCl, and then extracted with EtOAc (4 x 40 mL). The combined organic extracts were washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was subjected to column chromatography (5% MeOH/$CHCl_3$) to afford **183** (3.75 g, 59%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.58 (1H, br s, CO_2H), 5.95 (1H, d, J = 3.3 Hz, H1'), 4.60 (1H, d, J = 3.6 Hz), 4.38-4.32 (2H, m), 4.22-4.14 (3H, m), 4.04 (1H, m), 3.97 (1H, d,

J = 3.6 Hz), 1.50 (3H, s), 1.47 (3H, s), 1.39 (3H, s), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.8 (0, C1), 112.2 (0), 109.8 (0), 105.6 (1, C1'), 83.9, 82.3, 80.8, 73.0, 67.7, 67.1, 26.7 (3), 26.6 (3), 26.1 (3), 24.9 (3).

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranoxyacetyl chloride (184)

To a solution of **183** (980 mg, 3.08 mmol) in dry benzene (4.0 mL) was added thionyl chloride (430 mg, 3.61 mmol) in dry benzene (1.0 mL) at 60 °C over 10 min. The resulting solution was stirred at 65 °C for 30 min. Evaporation of the solvent and excess thionyl chloride gave crude **184** (1.00 g), which was a 9:1 mixture of **184** and starting material **183**, as shown by ^{1}H NMR. This product was used in the next step without further purification. : IR (neat) 1806 (s), 1381 (s), 1217 (s) cm^{-1}. For **184** (from the mixture): ^{1}H NMR ($CDCl_3$) δ 5.89 (1H, d, J = 3.6 Hz, H1'), 4.69 (1H, d, J = 3.6 Hz), 4.61 (2H, s, CH_2COCl), 4.23 (1H, m), 4.15-3.97 (4H, m), 1.49 (3H, s), 1.43 (3H, s), 1.36 (3H, s), 1.32 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.9 (0, C1), 112.1 (0), 109.3 (0), 105.1 (1, C1'), 84.1, 83.2, 81.0, 76.1, 72.3, 67.4, 26.8 (3), 26.7 (3), 26.2 (3), 25.3 (3).

(1*R*,5*S*,7*R*)-7-(1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranoxy)bicyclo[3.2.0]hept-2-en-6-one (186) and **(1*S*,5*R*,7*S*)-7-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoxy) bicyclo[3.2.0]hept-2-en-6-one (187)**

To a solution of cyclopentadiene (**175**) (freshly cracked from dicyclopentadiene, 900 mg, 13.6 mmol) and triethylamine (0.70 mL, 5.0 mmol) in dry Et_2O (100 mL) was added a 9:1 mixture of **184** and **183** (900 mg, 2.40 mmol of **184**) in dry Et_2O (25 mL) at rt

over 1.5 h. The mixture was stirred at rt for 12 h. A precipitate was removed by filtration. The filtrate was washed with a saturated $NaHCO_3$ solution (40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was subjected to column chromatography (40% EtOAc/hexane) to give a 1.8:1 mixture of **186** to **187** (70 mg, 8% yield) as a pale yellow oil.

Discernible NMR data for the major diastereoisomer from the mixture: ^{1}H NMR ($CDCl_3$) δ 5.87 (1H, d, J = 3.6 Hz, H1'), 4.90 (1H, dd, J = 8.7, 2.8 Hz, H7), 4.69 (1H, d, J = 3.6 Hz), 3.84 (1H, m, H1), 3.49 (1H, m, H5), 2.72 (1H, m, H4 *anti* to H5), 2.69 (1H, m, H4 *syn* to H5), 1.49 (3H, s), 1.48 (3H, s), 1.37 (3H, s), 1.31 (3H, s). NOE data 4.90 (3.84, 3%; 3.49, 3%), 3.84 (4.90, 3%; 3.49, 3%), 2.69 (3.49, 3%). ^{13}C NMR ($CDCl_3$) δ 209.0 (0, C6), 135.0 (1), 128.1 (1), 111.8 (0), 109.0 (0), 105.2 (1, C1'), 90.5, 82.7, 80.8, 72.2, 67.3, 53.4, 45.8, 34.8, 26.8, 26.2, 25.4.

Discernible NMR data for the minor diastereoisomer from the mixture: ^{1}H NMR ($CDCl_3$) δ 5.03 (1H, dd, J = 8.4, 3.0 Hz, H7), 4.55 (1H, d, J = 3.9 Hz), 3.84 (1H, m, H1), 3.49 (1H, m, H5), 1.49 (3H, s), 1.42 (3H, s), 1.33 (3H, s), 1.32 (3H, s). NOE data 3.84 (5.03, 2%). ^{13}C NMR ($CDCl_3$) δ 210.3 (0, C6), 135.6 (1), 127.8 (1), 112.4, 108.8, 105.1, 89.9, 83.1, 72.5, 66.7, 53.8, 46.2, 26.6, 25.3.

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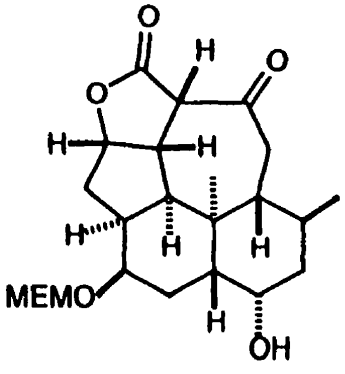
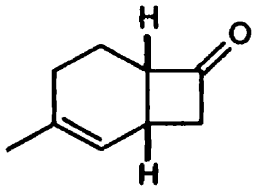
Appendix: Selected ^{1}H NMR Spectra

The ^{1}H NMR Spectra of the synthetic samples are arranged in the same order as they appear in the text.



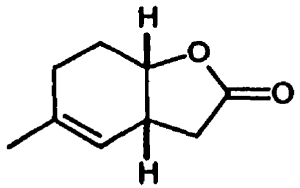
30

Solvent: CD_2Cl_2



40

Solvent: $CDCl_3$



41

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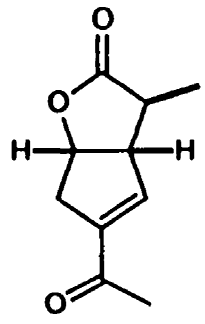

49

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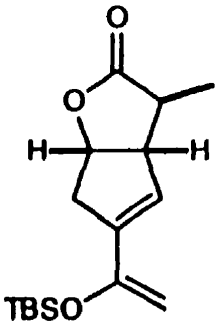

54

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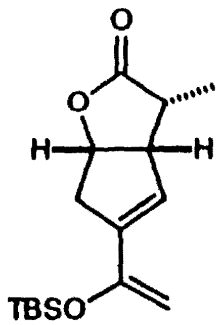

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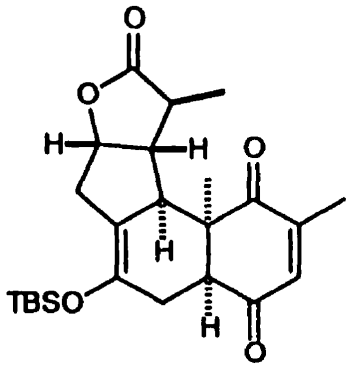

56

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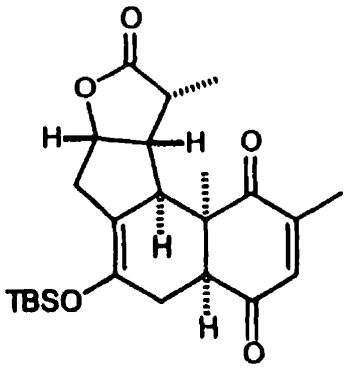

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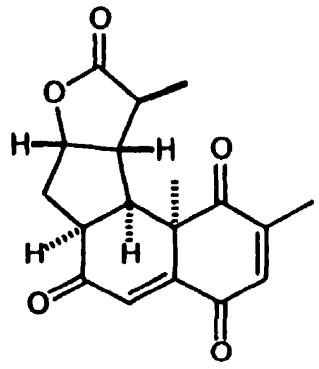
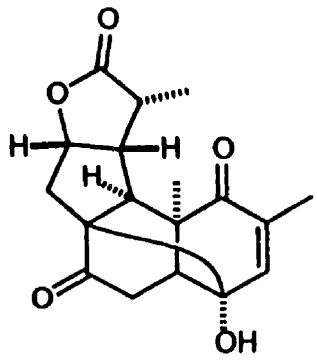


67

Solvent: CD_3COCD_3



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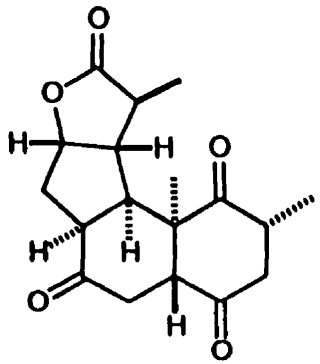
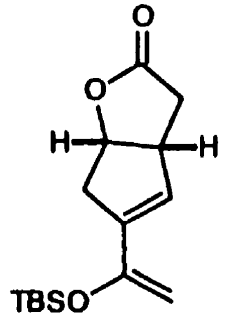
Solvent: $CDCl_3$



76

Solvent: CD_2Cl_2



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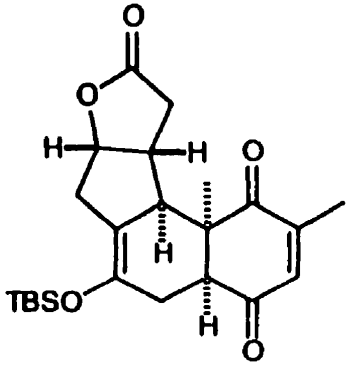
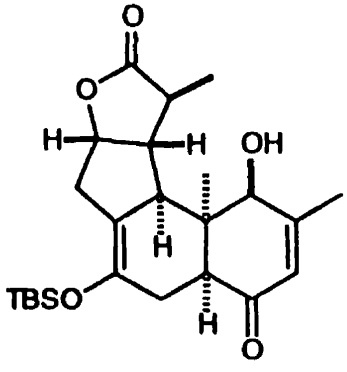
Solvent: $CDCl_3$



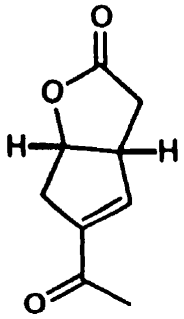
79

Solvent: $CDCl_3$



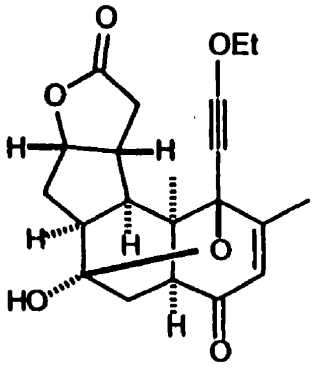
89

Solvent: $CDCl_3$



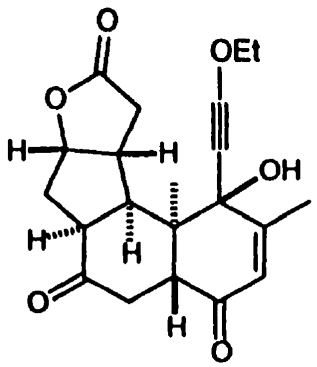
93

Solvent: $CDCl_3$



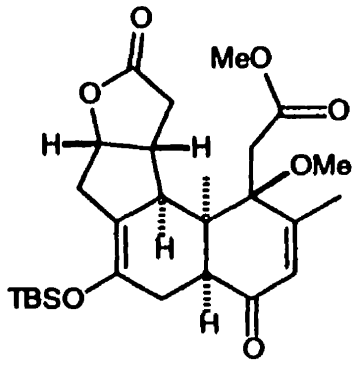
98

Solvent: $CDCl_3$



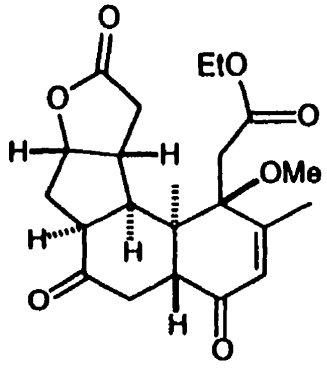
99

Solvent: CD_2Cl_2



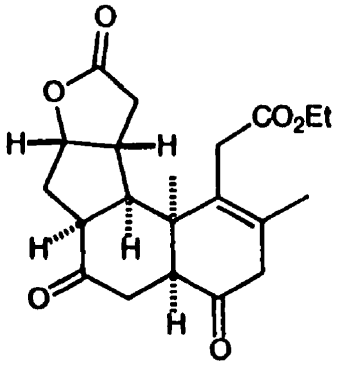
102

Solvent: $CDCl_3$



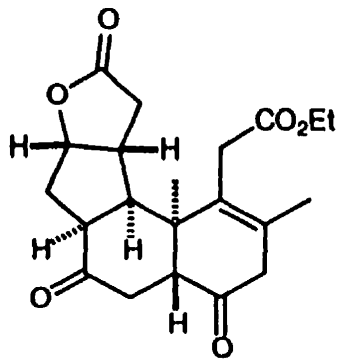
109

Solvent: $CDCl_3$



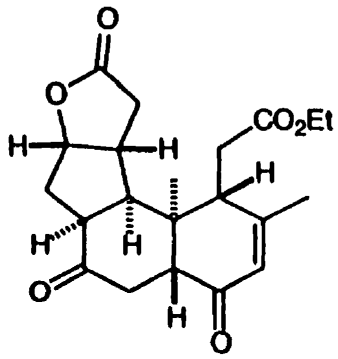
115

Solvent: CD_2Cl_2



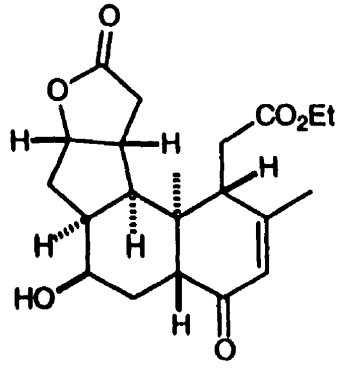
116

Solvent: CD_2Cl_2



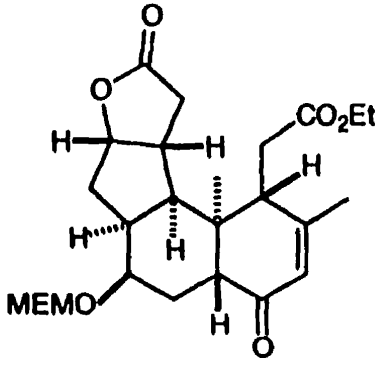
122

Solvent: CD_3COCD_3



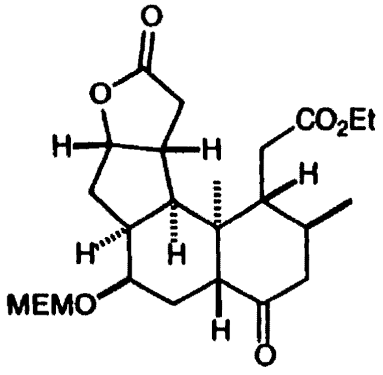
123

Solvent: CD_2Cl_2



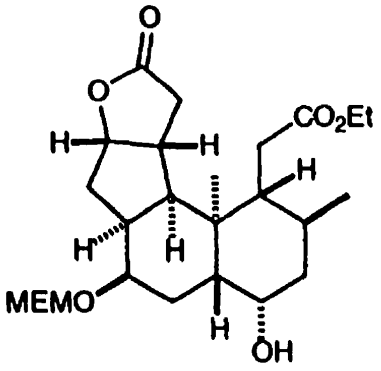
129

Solvent: CD_2Cl_2



130

Solvent: CD_2Cl_2



131

Solvent: CD_2Cl_2

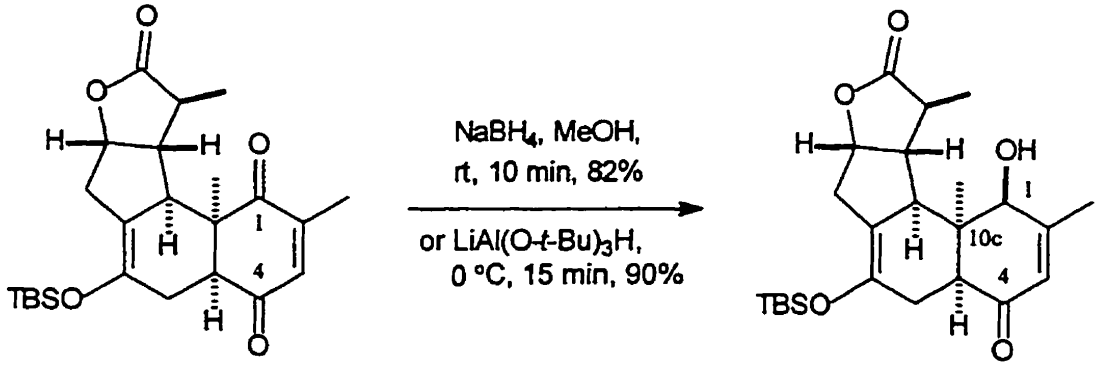
Part II

REGIO- AND STEREOSELECTIVITY IN THE REDUCTIONS OF CYCLIC ENEDIONES

2. 1. Introduction

Our study of regio- and stereoselective reductions of cyclic enediones arose from our observation that, as mentioned in Part I, the reduction of enedione **56** with sodium borohydride or lithium tri-*tert*-butoxyaluminohydride unexpectedly gave carbinol **89** as the single isolated product in 82% and 90% yield, respectively. The implausible, extreme regio- and stereoselectivity in this reduction was so intriguing to us that we decided to carry out a systematic investigation to see if the selectivity is general and to explore the origin of the selectivity. We believed that this study would be of theoretical and synthetic importance.

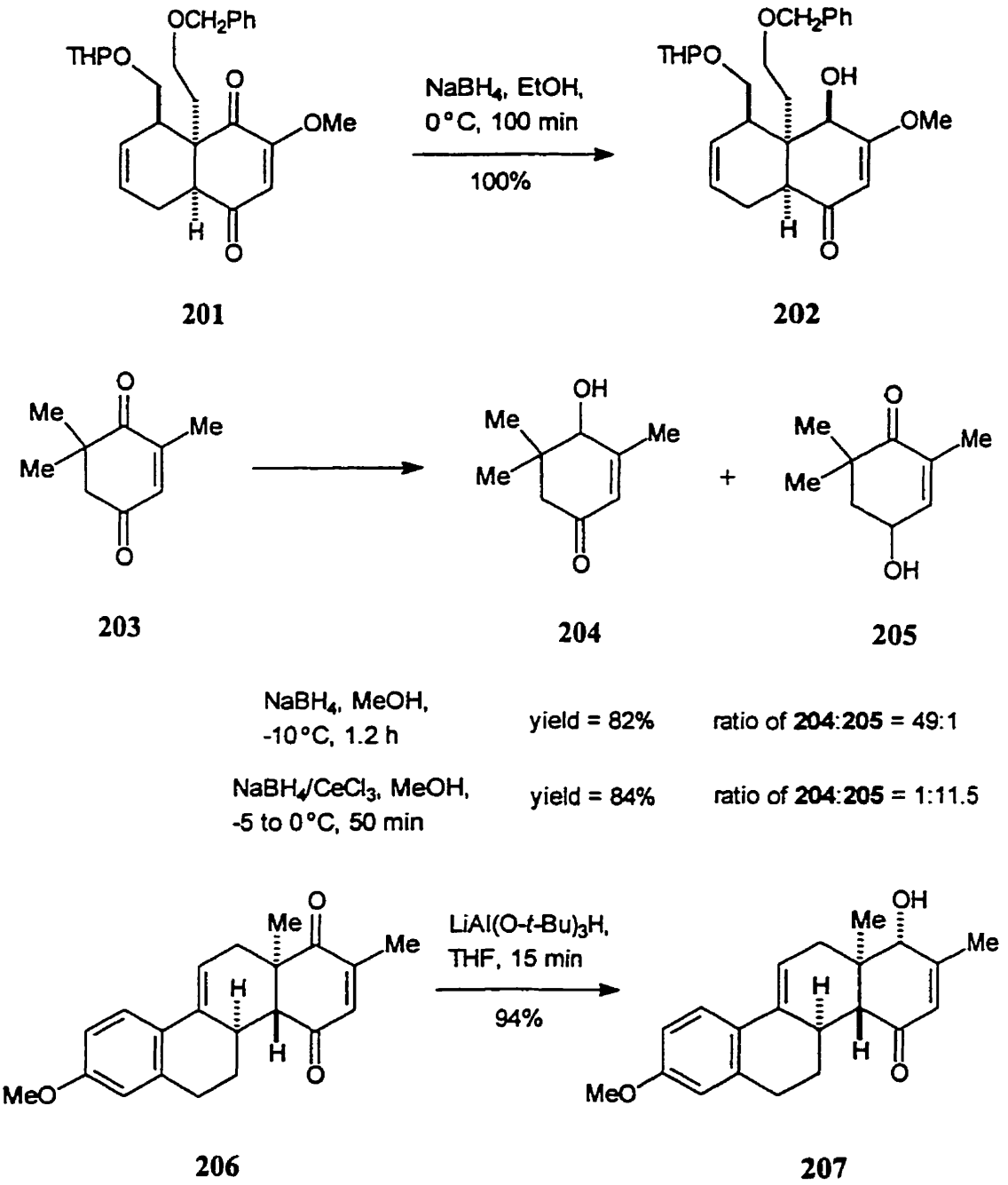
Scheme 27. Highly regio- and stereoselective reduction of **56**



56 **89**

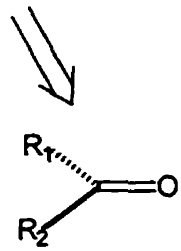
A perusal of literature revealed a couple of sporadic synthetic examples where reductions of cyclohex-2-ene-1,4-diones occurred regio- and stereoselectively at the

Scheme 58. Literature examples of regio- and stereoselective reductions of enediones



seemingly more hindered carbonyls, but the reason for the selectivity was not unearthed. These examples are presented Scheme 58. In the synthesis of gibberellic acid, Corey's group reduced enedione **201** with sodium borohydride in absolute ethanol at 0 °C to provide carbinol **202** in 100% yield.[1] Ishihara *et al.* reported that the reduction of 4-oxoisophorone (**203**) with 0.25 equivalents of sodium borohydride in methanol at -10 °C afforded alcohols **204** and **205** in 82% yield and in a 49:1 ratio in favor of **204**, whereas **203** was reduced with sodium borohydride in the presence of cerium trichloride to give **204** and **205** in 84% yield but in a 1:11.5 ratio favoring **205**.[2] However, no rationalization about the regio- and stereoselectivity in these reductions was mentioned, either by Corey or by Ishihara. An example of regio- and stereoselective monoreduction of the apparently more hindered carbonyl in a *trans*-fused cyclic enedione was noticed in a synthetic study of steroid compounds by Valenta's group.[3] When enedione **206** was treated with lithium tri-*tert*-butoxyaluminohydride at room temperature, alcohol **207** was obtained as the exclusive product in 94% yield. In this case, however, the hydride added to the carbonyl from the side opposite to the angular methyl group. Valenta speculated that the high regio- and stereoselectivity was due to the electronic difference between the two

Figure 11. The nonperpendicular nucleophilic attack to a carbonyl



carbonyls and /or the nonperpendicular, rearside attack of the reducing reagent. This angle for carbonyl reduction was initially proposed by Bürgi and coworkers,[4] who suggested that the preferred path for a nucleophile to attack a carbonyl was as shown in Figure 11.

Our observation was also reminiscent of the regioselective reduction of unsymmetrically substituted cyclic anhydrides to provide lactones, which was extensively studied by Kayser and coworkers.[5] Scheme 59 contains some of the examples, which can be classified into three groups. The first group, represented by examples (a) and (b),[5a] includes the reductions of flexible α,α-disubstituted succinic anhydrides. Reduction preferentially occurred at the seemingly more hindered carbonyl, the one adjacent to the substituents, with very high regioselectivity. The second group, represented by examples (c)[5b] and (d),[5f] consists of the reductions of α-substituted maleic anhydrides. In this group, reductions also displayed a preference for the carbonyls next to the substituent, but the extent of regioselectivity was dependent upon the nature of the substituent. When the substituent was an alkyl group, as in example (c), the regioselectivity (9:1) was much lower than that encountered in the first group. However, when the substituent was a methoxy group, as in example (d), the regioselectivity was 100%. The third group, represented by example (e),[5a] is composed of the reductions of bridged succinic anhydrides. Contrary to the first and second groups, these reductions very preferentially occurred to the carbonyls that were next to the less substituted sp^3 carbons.

To explain their observations, Kayser *et al.* put forward different rationalizations. For the first group, their main argument was the "antiperiplanar effect", after the theory of

Scheme 59. Regioselective hydride reductions of cyclic anhydrides[5]

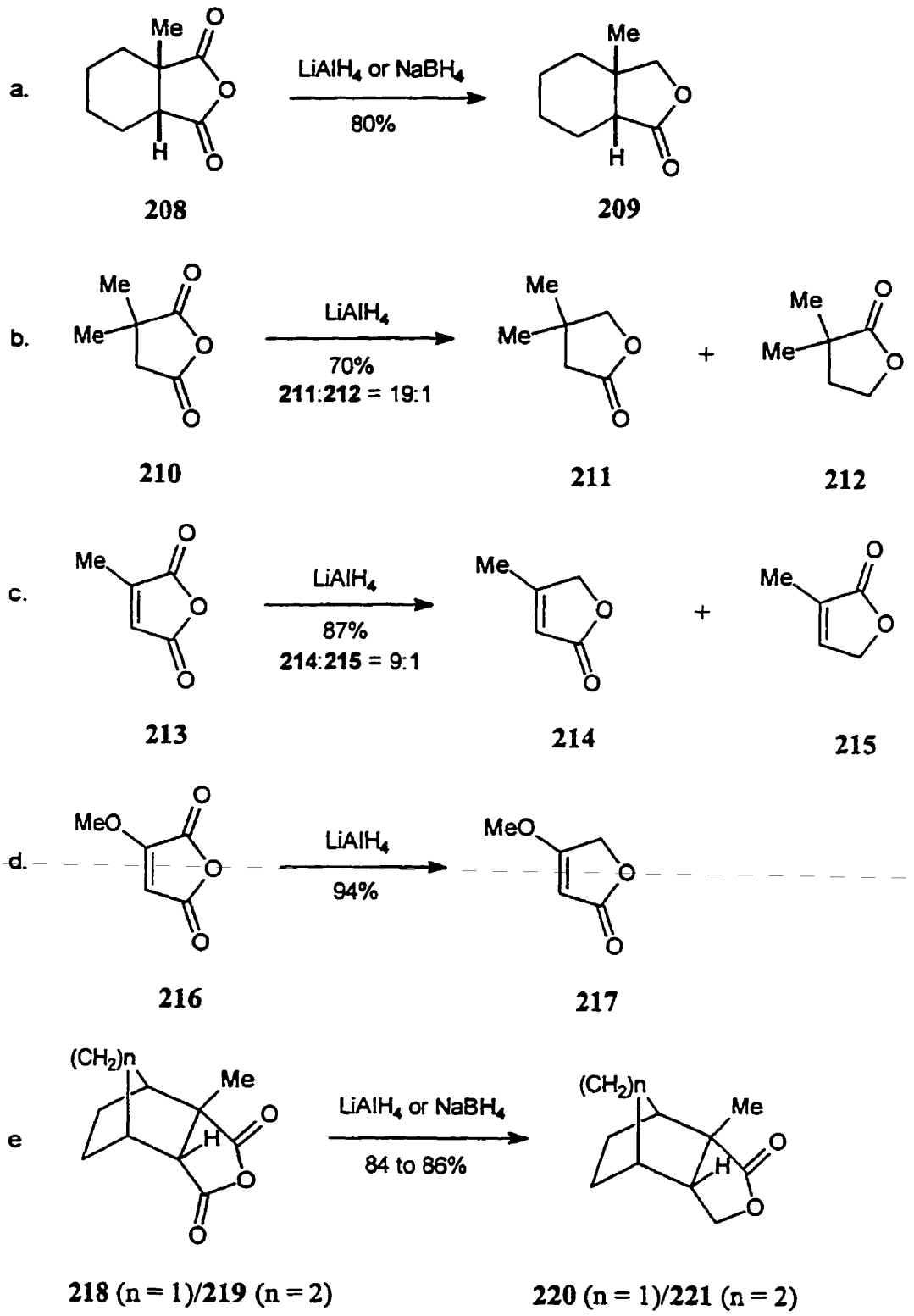
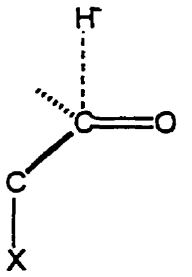
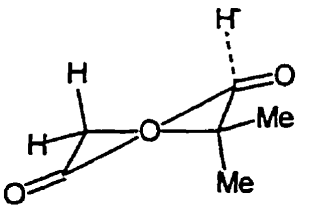


Figure 12. The antiperiplanar effect in the hydride addition to a carbonyl

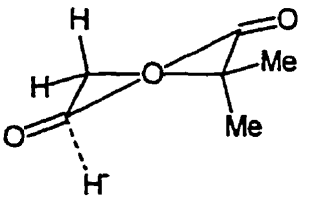


nonperpendicular, rearside attack was ruled out by a quantum mechanical study.[5d] The hypothesis of antiperiplanarity, originally proposed by Anh and coworkers,[6] suggested that in the hydride addition to a carbonyl, the transition state would be stabilized if there were a neighboring bond C-X antiperiplanar to the forming C-H bond, as shown in Figure 12. Applying Anh's theory, Kayser proposed that in the reductions of the substituted succinic anhydrides, the substrates assumed a quasi-chair conformation.[5d] This conformation could lead to two possible transition states in which antiperiplanarity could be achieved, as depicted in Figure 13 taking the reduction of α,α-dimethylsuccinic anhydride (**210**) as an example. In transition state **222**, the antiperiplanarity is achieved between the incipient C-H bond and a neighboring C-C bond, whereas in transition state

Figure 13. Antiperiplanar transition states in the reduction of anhydride **210**



222



223

223 antiperiplanarity is between the incipient C-H bond and a neighboring C-H bond. Anh's *ab initio* calculations suggested that an antiperiplanar C-C bond should be more efficient than an antiperiplanar C-H bond in stablizing the transition state. Therefore, transition state **222** should be more favorable than transition state **223**. Kayser and coworkers' calculations showed that transition **222** was more stable than transition state **223** by 3.3 kcal/mol.[5d] Both Anh's and Kayser's calculations were carried out with the STO-3G basis set. However, more recent, higher level *ab initio* calculations performed by Wu and Houk[7] indicated that an *anti* C-CH_3 bond should be disfavored compared to an *anti* C-H bond, because the former is a better electron donor and destablizes the electron-rich transition structure.

In the reductions of rigid bridged cyclic anhydrides, the quasi-chair conformation and subsquently the antiperiplanarity is not achievable. Kayser argued that the regioselectivity in these reductions is determined to a great extent by steric factors,[5e] which direct the reducing reagents to the less hindered carbonyl. For the second group, the reductions of α-substituted maleic anhydrides, the interpretation was that the intrinsic reactivities of the two carbonyls, expressed by the size of the LUMO coefficients, and chelating effects dominated the regioselectivity.[5c]

In short, according to Kayser and coworkers, in the reductions of flexible unsymmetrically substituted cyclic anhydrides, the regioselectivity in favor of the seemingly more hindered carbonyls being reduced is due to electronic factors, whereas the regioselectivity which leads to the less hindered carbonyls being reduced in rigid bridged anhydrides is the consequence of steric factors.

2. 2. Preparation of Cyclic Enediones

In order to carry out our study of the regio- and stereoselectivity in the reduction of cyclic enediones, we first needed to prepare a series of substrates. *cis*-Fused cyclohex-2-ene-1,4-diones were prepared by straightforward Diels-Alder reactions of commercially available dienes and dienophiles (Table 4). Most of the Diels-Alder reactions were conducted in toluene in sealed tubes at 120-130 ℃. In the preparation of enedione **227**, a mixture of *cis*- and *trans*-piperylene (**226**) was used, but only the *trans*-isomer reacted with 2,6-dimethyl-1,4-benzoquinone (**13**) under the conditions employed. Therefore, a single adduct was provided. The reaction of isoprene (**230**) with **13** was noticed to have nearly no regioselectivity, giving almost a 1:1 isomeric mixture **231**. The two regioisomers were inseparable by flash chromatography. The preparation of enediones **237** and **238** was according to the procedure of Alder *et al.*[8]

The *trans*-fused cyclohex-2-ene-1,4-diones **241-243** were obtained by epimerization of the corresponding *cis*-isomers **225**, **233**, and **235** (Scheme 60). Heating **225**, **233**, and **235** with glacial acetic acid, separately, for fifteen or sixteen hours produced the mixtures of the *cis*- and *trans*-isomers in a ratio of approximately 1:1, as revealed by GC-MS. The formation of the *trans*-isomers was also indicated by the ^{1}H NMR signals of the angular methyl groups of the products. As discussed in Section 1. 2. 4, the angular methyls in the *trans*-isomers appeared at a significantly higher field than those in the *cis*-isomers. The chemical shifts of the methyl groups in both the *cis*- and *trans*-isomers are shown in Scheme 60. Prolonging the heating period did not change the ratio of the isomers. Heating a solution of enedione **225** in methanol at reflux with

sodium bicarbonate for ten hours also gave a 1:1 mixture of the *cis*- and *trans*-isomers, but the reaction was less clean. The *cis*- and *trans*-enediones were inseparable by flash

Table 4. Preparation of cyclic enediones by Diels-Alder reactions

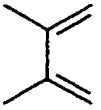
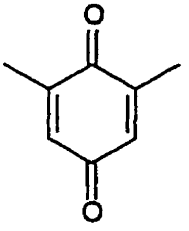
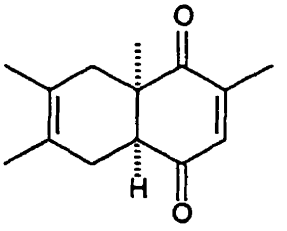
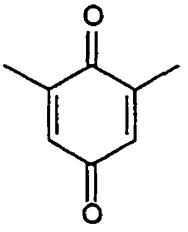
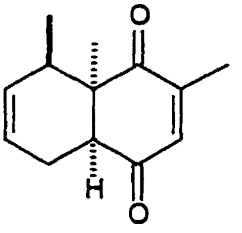
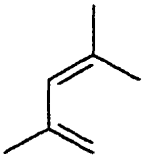
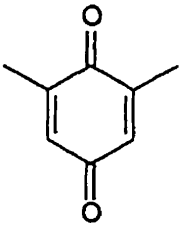
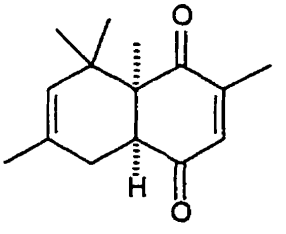
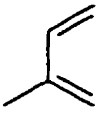
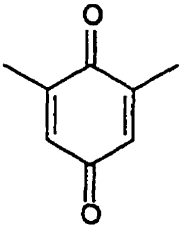
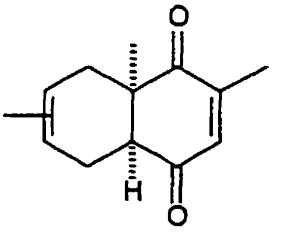
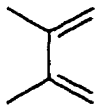
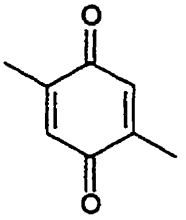
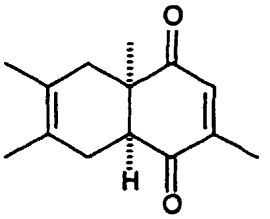
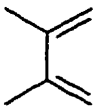
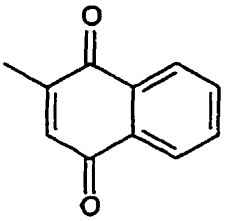
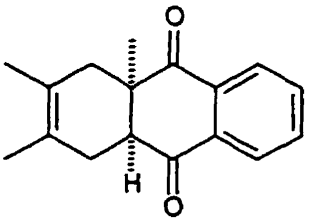
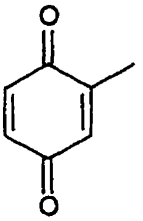
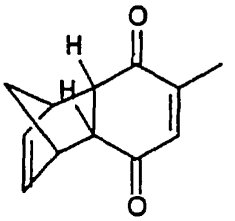
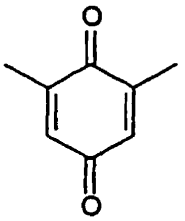
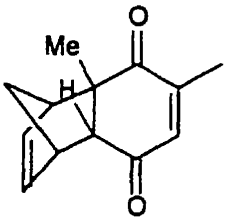
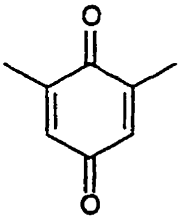
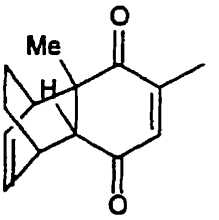
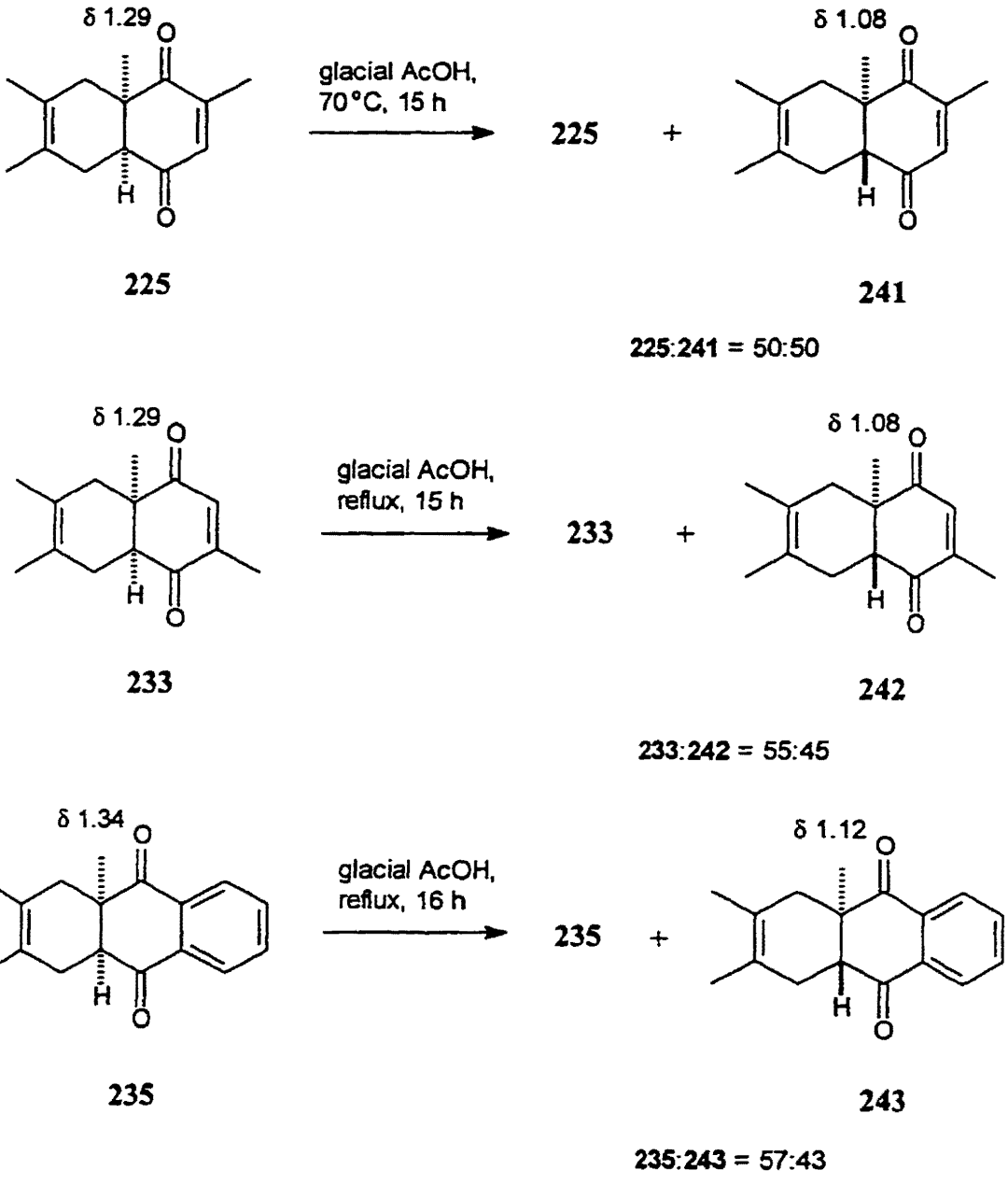
diene	dienophile	conditions	product	yield
		sealed tube, toluene, 120 °C, 27 h		94%
224	**13**		**225**	
		sealed tube, toluene, 120 °C, 11 h		77%
226	**13**		**227**	
		sealed tube, toluene, 145 °C, 4 days		45%
228	**13**		**229**	
		sealed tube, toluene, 120 °C, 36 h		88%
230	**13**		**231** (1:1 isomeric mixture)	

Table 4. Preparation of cyclic enediones by Diels-Alder reactions (continued)

diene	dienophile	conditions	product	yield
		sealed tube, toluene, 120 °C, 27 h		96%
224	**232**		**233**	
		sealed tube, toluene, 120 °C, 28 h		92%
224	**234**		**235**	
		methanol, rt, 1 h		94%
175	**236**		**237**	
		methanol, rt, 45 h		96%
175	**13**		**238**	
		sealed tube, toluene, 130 °C, 48 h		46%
239	**13**		**240**	

chromatography, but the mixtures could be used for our study of the regio- and stereoselectivity in the reductions of the *trans*-enediones.

Scheme 60. Preparation of **241-243** by the epimerization of **225, 233,** and **235**

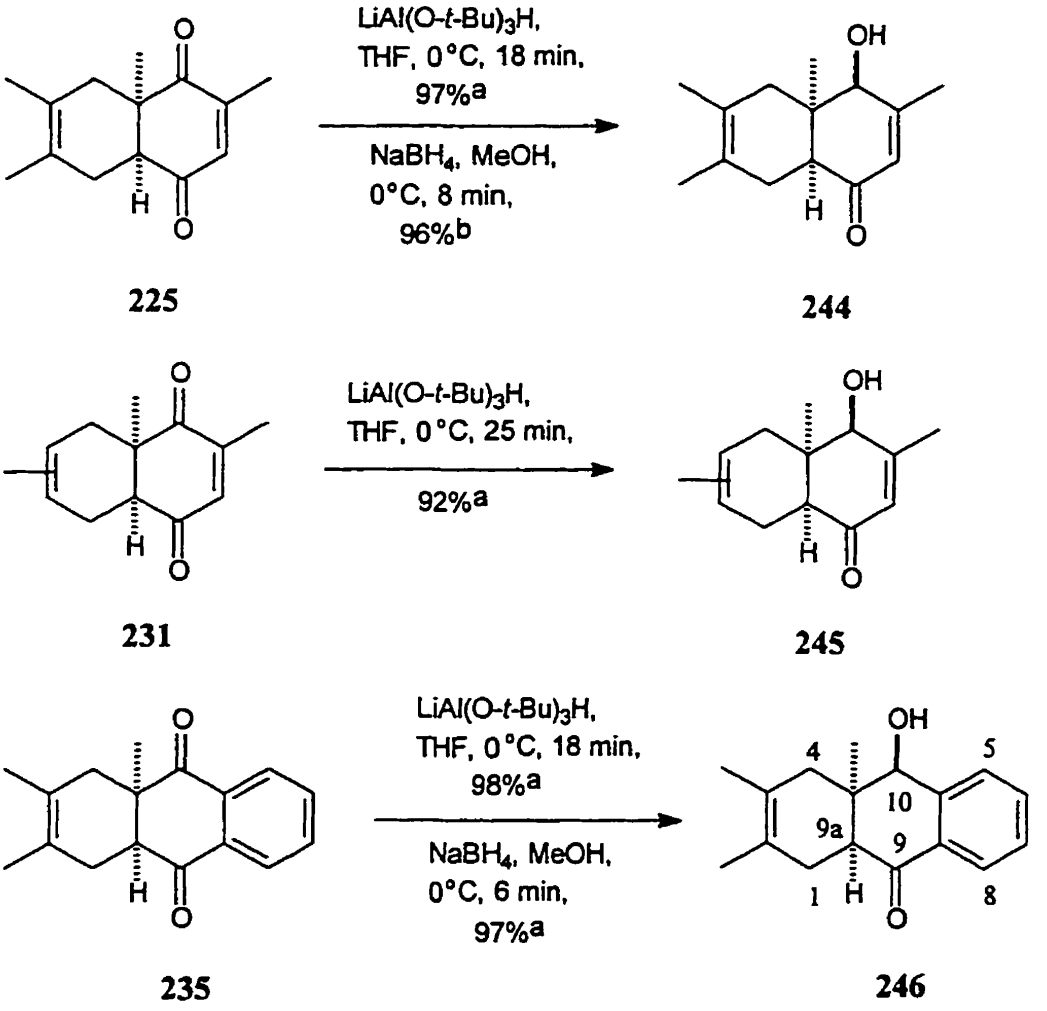


2. 3. Regio- and Stereoselectivity in the Reductions of Cyclic Enediones

2. 3. 1. Regio- and Stereoselectivity in the Reductions of *cis*, non-Bridged Enediones

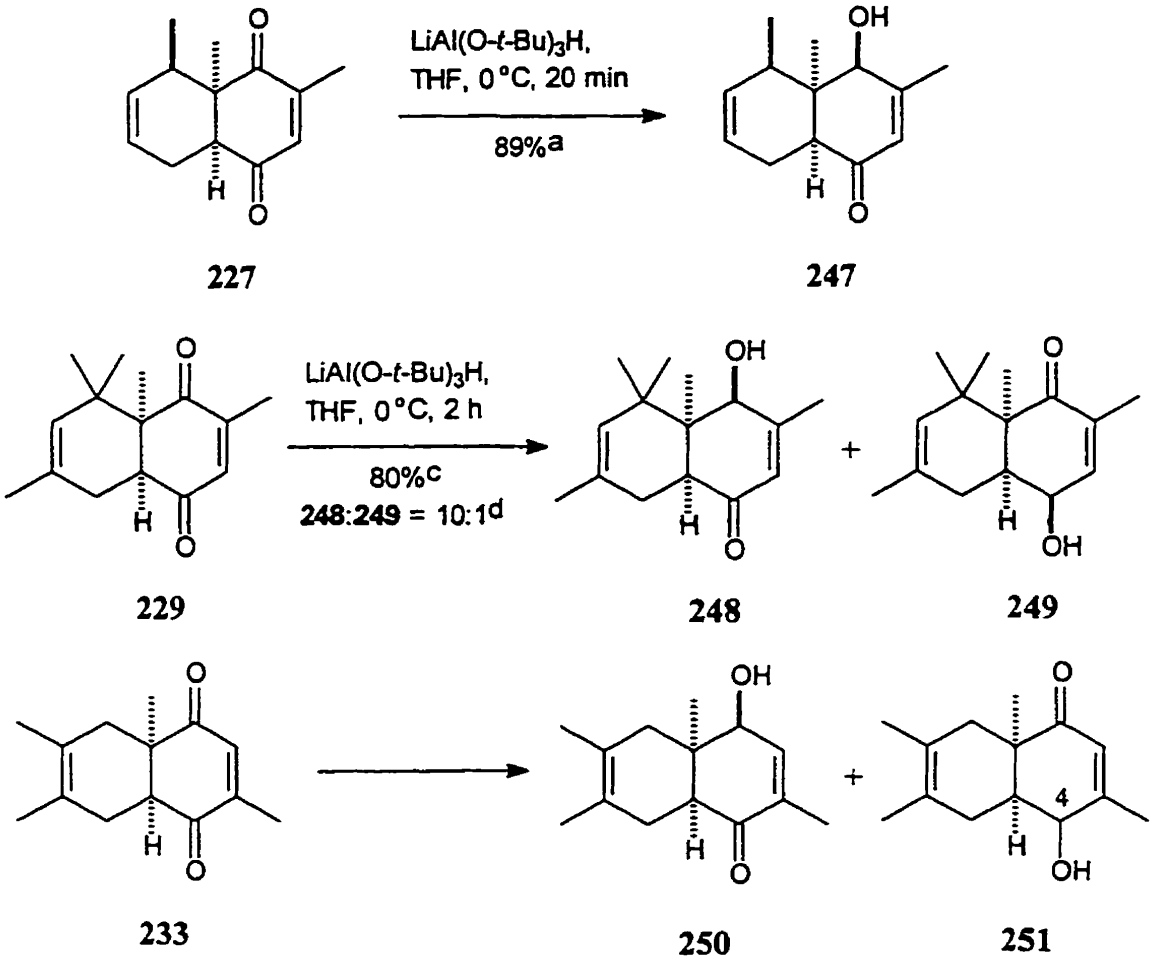
Our systematic examination of the reductions of the cyclic enediones, prepared in the previous section, with sodium borohydride and lithium tri-*tert*-butoxyaluminohydride revealed different regio- and stereoselectivities.[9] With *cis*, non-bridged enediones, the hydride consistently added to the seemingly more hindered carbonyl from the same side

Scheme 61. Regio- and stereoselectivity in the reduction of *cis*, non-bridged enediones



Scheme 61. Regio- and stereoselectivity in the reduction of *cis*, non-bridged enediones

(continued)



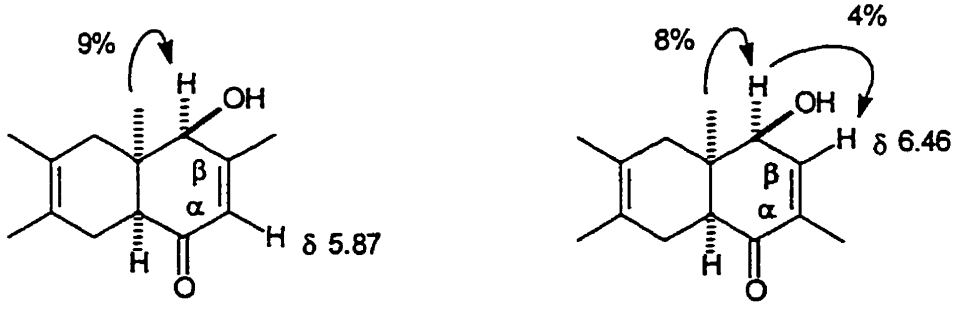
[a] isolated yields. [b] yields by GC-MS analysis. [c] isolated yield of **248**. [d] ratio by ^{1}H NMR analysis of crude product.

as the angular methyl group, as we had originally observed in the reduction of enedione **56** (Scheme 27). The reduction products were α or β substituted α,β-enones, except in

the case of enedione **235**. Therefore, the regiochemistry of the reductions could readily be diagnosed by the chemical shift of the vinyl proton in the α- or β- substituted α,β-enone product, since the α-proton and the β-proton in an α,β-enone system resonate at distinct fields, i.e., the signal for the α-proton appears at a significantly higher field. For example, in the reduction of enedione **225** the product had its vinyl proton appearing at δ 5.87, which implied that the proton was in the α-position of an α,β-enone, whereas in the reduction of **233** the vinyl proton of the major product appeared at δ 6.46, which indicated a proton in the β position of an α,β-enone. Therefore, the two products were assigned as **244** and **250**, respectively, both of them being produced by the reduction of the carbonyl next to the angular methyl group (Figure 14). In the reduction of **235**, the product **246** was not an α- or β- substituted α,β-enone but an aromatic ketone. The regiochemistry was assigned by analogy, and the assignment was supported by the fact that no coupling between H-9a and H-10 was observed in the COSY spectrum.

The stereochemistry of the reductions was clear by NOE measurements between

Figure 14. Assignment of the regio- and stereochemistry of **244** and **250** by NOE



244 **250**

the carbinol hydrogens and the angular methyl groups, as illustrated in Figure 14. The NOE experiments could also be used to corroborate the regiochemical assignments. For instance, a 4% of enhancement of the signal for the vinyl proton by irradiation of the carbinol hydrogen in **250** indicated that the carbonyl next to the alkenic hydrogen must have been reduced.

As seen in Scheme 61, the reductions were generally fast, clean, and highly efficient. In the reductions of enediones **225**, **227**, **231**, and **235**, only one monoreduction product was detected by ^{1}H NMR spectroscopy. With the more critical enedione **229** in which four methyl groups were around the carbonyl at C-1, the reduction with LiAl(O-*t*-Bu)$_3$H still preferentially occurred to the C-1 carbonyl, though more slowly, to give **248** as the major product, but the ^{1}H NMR spectrum of the crude product revealed a minor isomer that had discernible signals at δ 6.31, 5.25, and 4.80. By comparison with the ^{1}H NMR spectrum of an authentic sample, the minor product was confirmed to be **249**. The ratio of the major product to the minor was 10:1. In the reduction of enedione **233**, which differed from enedione **225** in that the vinyl methyl and the angular methyl group were not adjacent to the same carbonyl, a minor product was also detected both by GC-MS and by ^{1}H NMR spectroscopy. The minor product had a vinyl signal at δ 5.78 in its ^{1}H NMR spectrum, and therefore it was tentatively assigned as **251**. However, the stereochemistry at C-4 in **251** could not be determined. The ratios of the major product to the minor were 25:1 and 20:1, when enedione **233** was reduced with LiAl(O-*t*-Bu)$_3$H and NaBH$_4$, respectively.

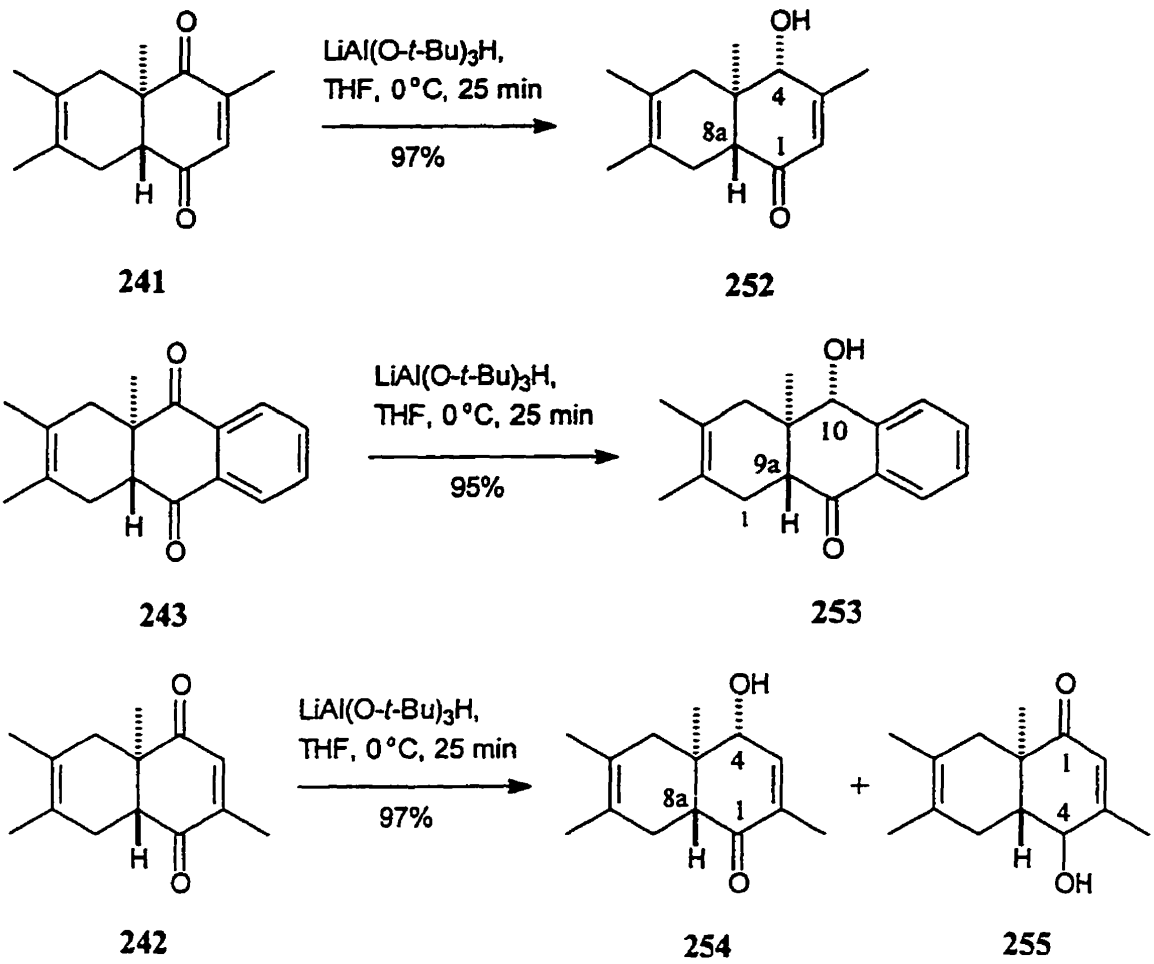
The reductions with lithium tri-*tert*-butoxyaluminohydride were typically

conducted at 0 °C for twenty minutues or so in THF, using 20 to 30% excess of the reducing reagent, whereas the typical conditions in the reductions with sodium borohydride were 0.8 equivalents of the reducing reagent, methanol as the solvent, 0 °C and six to ten minutes (including the time of addition of sodium borohydride). Usually, the reductions afforded slightly higher yields with $LiAl(O\text{-}t\text{-}Bu)_3H$ than with $NaBH_4$. This was because over-reductions occurred with $NaBH_4$, a very small amount of doubly and/or triply reduced products being detected by GC-MS. To prevent the over-reduction, it was important not to use excess $NaBH_4$ and to complete the reactions within minutes, except in the case of **229**.

2. 3. 2. Regio- and Stereoselectivity in the Reductions of *trans*-Fused Enediones

The *trans*-fused cyclohex-2-ene-1,4-diones **241-243** were obtained only as inseparable mixtures of approximately 1:1 of the *cis* and the *trans* isomers, by epimerization of the *cis* isomers, as mentioned earlier. Nevertheless, when the mixtures of the *cis* and the *trans* cyclic enediones were reduced with lithium tri-*tert*-butoxyaluminohydride, the regio- and stereoselectivity in the reactions of *trans*-fused isomers could be obtained by ^1H NMR spectroscopy and GC-MS without difficulty. These reductions gave the same regiochemistry as those of the *cis*-isomers (Scheme 62). However, the stereochemistry was opposite, namely, the hydride was delivered to the carbonyls from the side opposite the angular methyl groups. This was revealed by NOE experiments. When the signals for the H-4's in products **252** and **254** were irradiated, the signals for the H-8a's were enhanced by 5% and 7%, respectively. In product **253** an 8%

Scheme 62. Regio- and stereoseletivity in the reductions of *trans*-fused cyclic enediones



241 252

243 253

242 254 255

enhancement of the signal for the H-9a was observed by the irradiation of the H-10.

The reductions of enediones **241** and **243** each provided only one product. However, in the reduction of enedione **242** a minor product was indicated both by ^{1}H NMR spectroscopy and by GC-MS. The ^{1}H NMR spectrum of the crude product showed that the minor component had an vinyl signal at δ 5.84. Accordingly, the minor product was tentatively assigned to be **255**, without any attempt to determine its stereochemistry at C-4. The ratio of the major product to the minor was 8:1, by both ^{1}H NMR spectroscopy

and by GC-MS.

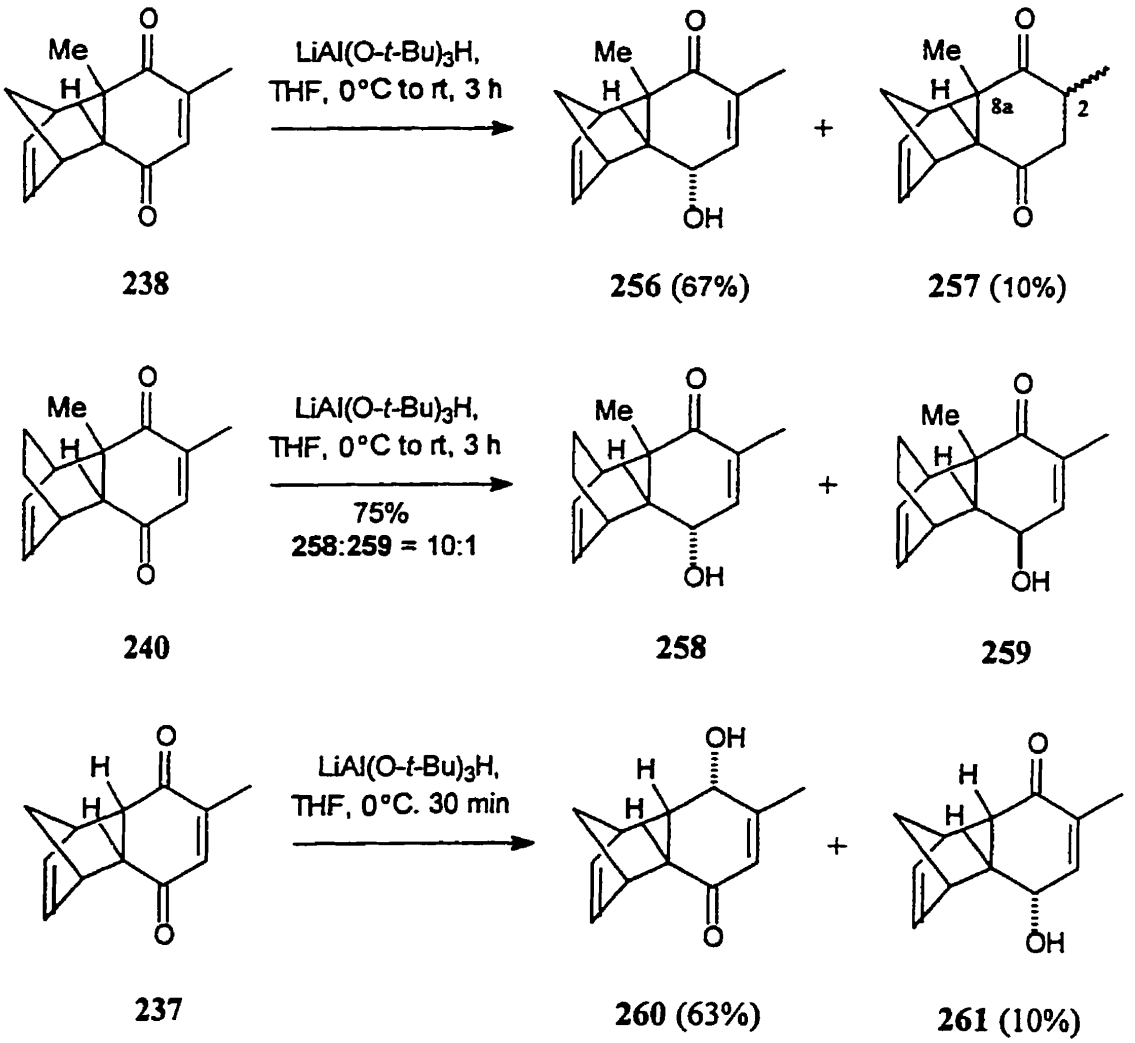
Since the reductions of enediones **241** to **243** were conducted by using a roughly 1:1 mixture of *cis*- and *trans*-isomers, the yields presented in Scheme 62 were, in fact, the yields of the mixture products. However, the numbers were very close to those obtained from the reductions of the homogeneous *cis*-isomers with $LiAl(O\text{-}t\text{-}Bu)_3H$ (Scheme 61). Therefore, the yields with the *cis-trans* mixtures should be similar to the yields in the reductions of *trans*-isomers.

2. 3. 3. Regio- and Stereoselectivity in the Reductions of Bridged Enediones

Scheme 63 presents the reductions of bridged enediones, which had different regioselectivities from the reductions of non-bridged enediones. The reduction of enedione **238** with lithium tri-*tert*-butoxyaluminohydride gave three isolated products. The major one, in 67% yield, was characterized as monoalcohol **256**, which was produced by the reduction from the convex side of the less hindered carbonyl. The two minor products, isolated as a 2.5:1 chromatographically inseparable epimeric mixture **257**, in 10% yield, were produced by 1,4-reduction. The major epimer of **257** was shown by NOE experiments to have the 2-methyl group *anti* to the 8a-methyl. Enedione **240** was similar to but slightly more flexible than **238**. Its reduction with lithium tri-*tert*-butoxyaluminohydride also occurred at the less hindered carbonyl to afford, in 75% yield, two stereoisomeric products **258** and **259** in a ratio of 10:1 favoring **258**. It was noticed that the reductions of **238** and **240** necessarily took three hours (one hour at 0 °C, and then two hours at room temperature) to complete. In other words, it seemed strange that

reductions of the seemingly sterically more hindered carbonyls in non-bridged enediones with LiAl(O-*t*-Bu)$_3$H only needed less than thirty minutes at 0 °C, but reductions of the less hindered carbonyls in bridged enediones **238** and **240** with the same reducing reagent required three hours at 0 °C to room temperature. Nevertheless, when bridged enedione **237**, where the angular methyl group was absent, was reduced with LiAl(O-*t*-Bu)$_3$H, the reduction occurred rapidly to give two regioisomers. The major product, in 63% yield,

Scheme 63. Regio- and stereoselectivity in the reductions of bridged enediones

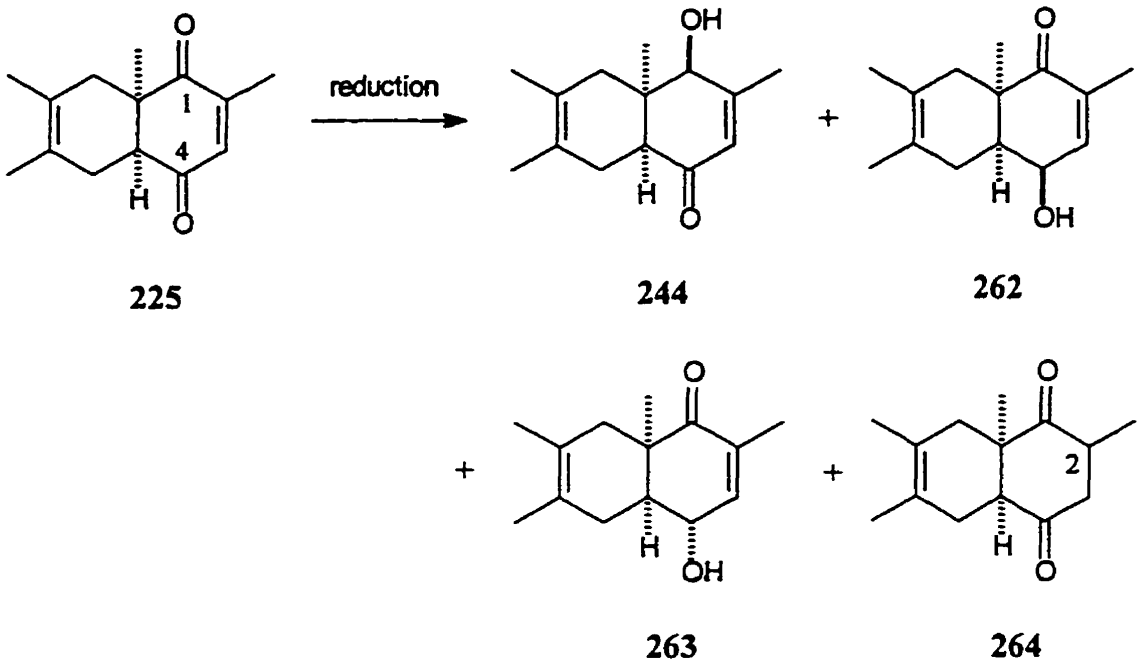


proved to be **260**, which was produced by the reduction of the carbonyl adjacent to the vinyl methyl group. The minor product, in 10% yield, was **261**.

2. 3. 4. Influences of Reducing Reagents in the Regio- and Stereoselectivity in the Reductions of Cyclic Enediones

With substrate **225**, which we considered to be typical of many of our substrates, we also examined the influence of reducing reagents on the regio- and stereoselectivity in the reductions of cyclic enediones (Table 5). As shown earlier, the reduction of enedione **225** with lithium tri-*tert*-butoxyaluminohydride and sodium borohydride gave monoalcohol **244** in 97% and 94% yield, respectively. The reduction of **225** with lithium borohydride also occurred regio- and stereoselectively at the apparently more hindered carbonyl at C-1, but in this case, over-reduction was significant, as shown by GC-MS analysis. The yield of **244** was only 80%. However, when L-Selectride, which is highly bulky, was used as the reducing reagent, the reduction of **225** gave three products. One was the 1,4-reduction product **264**, which was a single stereoisomer but the stereochemistry at C-2 could not be determined by NOE experiments. Another product was **244**, again. The major product was monoalcohol **262**, which was produced by the addition of hydride *syn* to the angular methyl group, but to the carbonyl at C-4 instead of the carbonyl at C-1. The ratio of the three products **244**, **262**, and **264** was 1:2.5:1, respectively. Lastly, enedione **225** was subjected to reduction by the Luche reagent,[10a] a combination of sodium borohydride and cerium trichloride. The major reduction also occurred at the carbonyl at C-4, though **244** was still a product. However, in this case the

Table 5. Reduction of enedione **225** with different reducing reagents



225 **244** **262**

263 **264**

reducing reagent and conditions	products	yield	ratio[d]
$LiAl(O\text{-}t\text{-}Bu)_3H$, THF, 0 °C, 18 min,	**244**	97%[a]	
$NaBH_4$, MeOH, 0 °C, 8 min,	**244**	96%[b]	
$LiBH_4$, THF, 0°C, 30 min,	**244**	80%[b]	
L-Selectride, THF, -78 °C, 1h	**244** + **262** + **264**	99%[c]	**244**:**262**:**264** = 1:2.5:1
$NaBH_4/CeCl_3$, MeOH, 0°C, 6 min,	**244** + **262** + **263**	90%[a]	**244**:**262**:**263** = 1:1.8:1

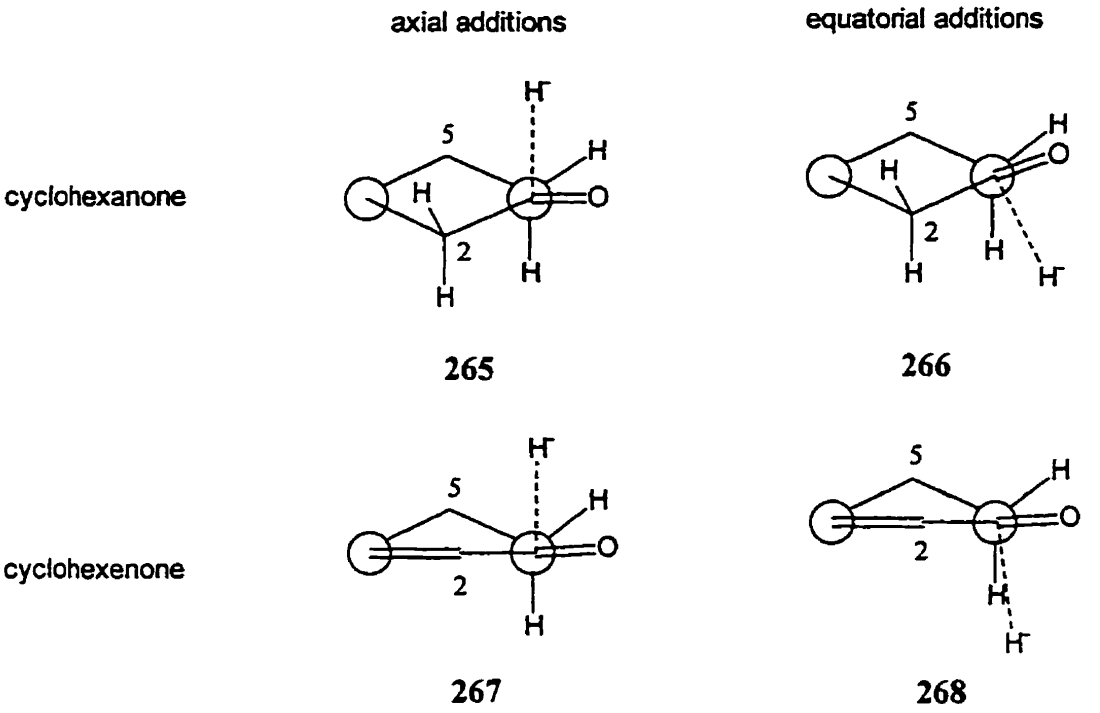
[a] isolated yields. [b] yields by GC-MS. [c] calculated yield based on 23% isolated yield of **264** and NMR ratio. [d] ratio by ^1H NMR.

delivery of hydride to the carbonyl at C-4 took place from both sides of the carbonyl, giving two stereoisomers **262** and **263**. The ratio of products **247**, **265**, and **276** in this reduction was 1:1.8:1.

2. 3. 5. Rationalization of the Selectivities in the Reductions of Cyclic Enediones

It was mentioned in Section 1. 3. 2 that reductions of cyclohexanones with small reducing reagents give predominantly equatorial alcohols through axial attack. This axial preference is significantly higher in the reductions and nucleophilic additions to 2-cyclohexenone. For example, Houk and Trost summarized[11a] that the addition of alkynyllithium to cyclohexanone typically shows about 6-8:1 axial addition over equatorial, but with 2-cyclohexenone the number is greater than 20:1. The origin of the axial selectivity and the difference in the extent of this selectivity between cyclohexanone and 2-cyclohexenone were quantitatively interpreted, using *ab initio* transition structures, to be due to torsional strain and poor orbital overlap in the equatorial transition state.[11] The torsional explanation for the axial selectivity in the nucleophilic additions to cyclohexanone was originally proposed by Felkin *et al.*[12] A pivotal difference between axial and equatorial addition resides in the fact that the transition structure for axial addition is staggered, whereas for equatorial addition it is eclipsed or nearly eclipsed (Figure 15). In the eclipsed transition state, significant torsional strain between the forming C-H bond and the axial C-H bond(s) α to the carbonyl exists, and therefore axial addition becomes the favorable process. Houk *et al.* calculated that transition structure **266** is 1.2 kcal/mol higher in energy than structure **265**. This implies that the axial

Figure 15. Newman projections of the transition structures for the axial and equatorial additions of hydride to cyclohexanone and 2-cyclohexenone



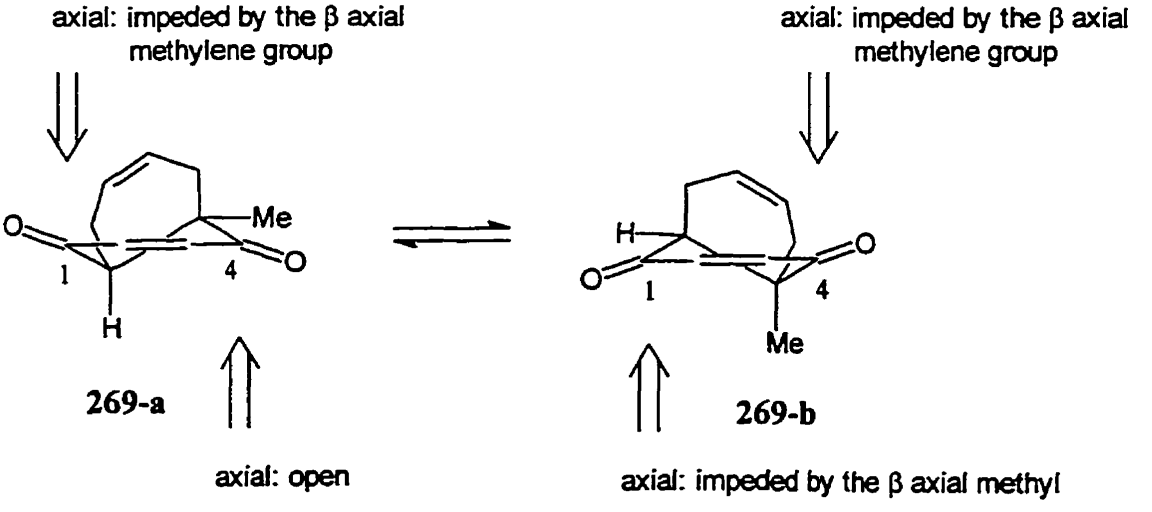
selectivity over equatorial for hydride reduction of simple cyclohexanones should be 7.3:1 at 25 °C.[11a] 2-Cyclohexenone is flatter than cyclohexanone because of the presence of the conjugated double bond. As a result, transition structure **268** for the equatorial addition is more eclipsed, and therefore the torsional strain in **268** is more serious though now only one α axial C-H bond is present. The axial transition structure **267** was found to be 2.0 kcal/mol more stable than **268**. At 25 °C, this corresponds to a 32:1 ratio of axial attack to equatorial.[11a]

The significance of orbital overlap was put forward originally by Toromanoff.[13] This assumption proposed that axial addition to the carbonyl in 2-cyclohexenone is

favored because in the course of axial addition the orbital overlap between the forming bond and the π bond in C_2=C_3 double bond can maximally, continuously be maintained. Houk and coworkers' calculations suggested that orbital overlap was possible in either axial transition structure **267** or equatorial transition structure **268**, but it was better in **267**.[11b]

We believe that both the regio- and stereoselectivities in the reductions of non-bridged enediones with lithium tri-*tert*-butoxyaluminohydride and sodium borohydride are due to the axial preference of the reductions, which has been proposed by Liotta *et al.* in their rationalization for the same selectivities in the addition of acetylide to bicyclic enediones.[14] AM-1[15] calculations with enedione **225**, using the Spartan, Version 4.1, indicated that there are two low-energy conformers for the *cis*-fused enediones. For enedione **225** the two conformers are within 0.5 kcal/mol of each other in energy, which implies that the two conformers are almost equally populated at 25 °C. This may not be

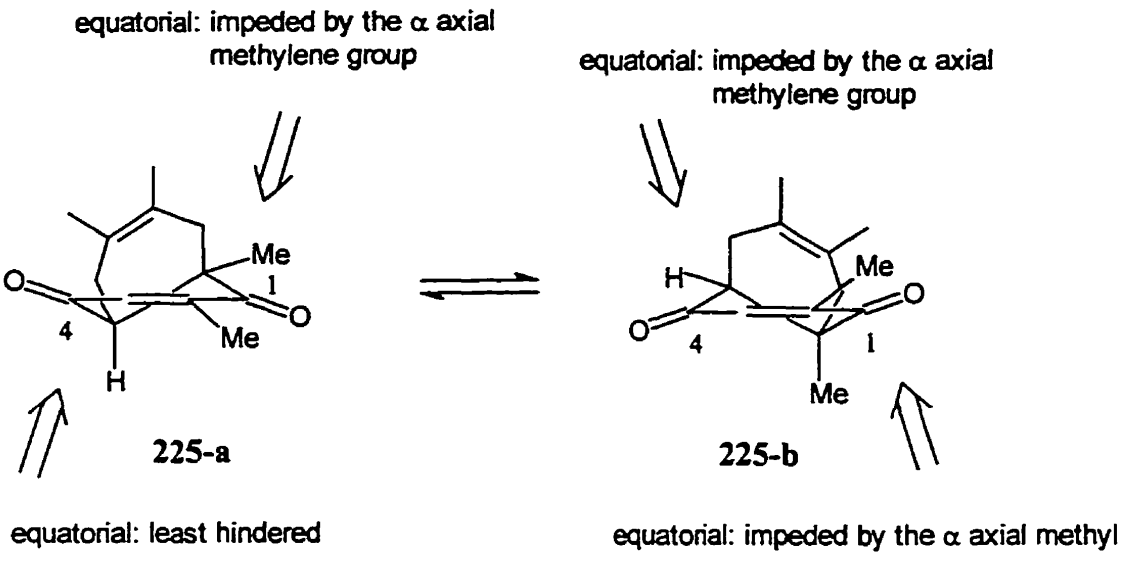
Figure 16. Regiochemical alternatives for axial addition on *cis* bicyclic enediones



quite true for the other *cis*-fused enediones, but it should not be very important with respect to our interpretation, because the Curtin-Hammett principle suggests that the ratio of products formed from conformational isomers is not dependent on conformer ratio as long as the barrier to their interconversion is not very high.[16] For the sake of simplicity and generality, these two conformers for all the *cis*-fused enediones are represented as **269-a** and **269-b** (Figure 16). Either of the two conformers provides two alternative approaches for axial addition, but among the four alternatives of the two conformers, only one is not sterically encumbered. This is the attack on carbonyl at C-4 in conformer **269-a**, in which the "angular" methyl group is in an equatorial position. It was this axial attack that led to the observed (exclusive or predominant) products in the reduction of *cis* bicyclic enediones. The other three alternatives are impeded either by a β-axial methyl group or by a β-axial methylene group in the other ring of the molecule, as shown in Figure 16.

It was also mentioned in Section 1. 3. 2 that axial selectivity would be suppressed in the reduction of cyclohexanones when the reducing reagents are sterically bulky, probably due to the steric interaction between the bulky reducing reagent and the axial hydrogens at C-3 and C-5 of cyclohexanone, and the equatorial addition could become dominant. This provides an explanation for the observation that when enedione **225** was reduced with L-Selectride, the regioselectivity was different from that in the reduction with lithium tri-*tert*-butoxyaluminohydride or sodium borohydride (Table 5). The major product in the reduction with L-Selectride was produced by equatorial addition. The alternative approaches for equatorial addition on enedione **225** are shown in Figure 17.

Figure 17. Regiochemical alternatives for equatorial addition on enediones **225**



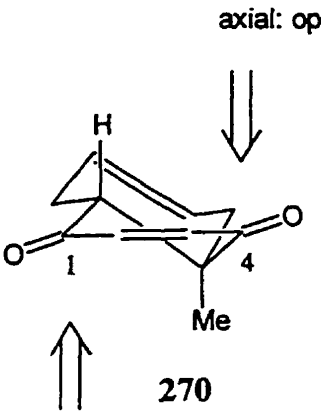
Similar to the situation of axial addition, conformers **225-a** and **225-b** provided four possibilities for equatorial addition. However, three of them are impeded either by an α-axial methylene group or by the α-axial methyl group. Only the attack to the carbonyl at C-4 in conformer **225-a** is relatively unencumbered. It was this equatorial attack that gave the major product **262** in the reduction of **225** with L-Selectride. L-Selectride usually effects exclusively equatorial reduction with a saturated cyclic ketone,[17] but it was not surprising that in our case the ratio of the equatorial attack at C-1 to the axial attack at C-4 in **225-a**, i.e., the ratio of product **262** to **263** was only 2.5:1. Cyclic enedione **225** has only one axial hydrogen at the 5-position to the carbonyl at C-1, and it is also flatter than a saturated cyclic ketone. Therefore, the steric interaction between the 5-axial hydrogen and the reducing reagent, L-Selectride, for the axial addition at the carbonyl at C-1 in **225-a** is less significant. On the other hand, the equatorial addition at C-4 in **225-a**

must be more difficult than in a saturated cyclic ketone, because the cyclic enedione system is closer to coplanar and the torsional strain between the forming C-H bond and the α-axial C-H bond should be enhanced.

With cerium trichloride and sodium borohydride, the major pathway for reduction of enedione **226** was also at the carbonyl at C-4, but the reason for this is probably not the issue of equatorial selectivity but selective complexation. It is well known that the Luche reagent is usually used to enhance 1,2-reduction over 1,4-reduction with an α,β-unsaturated ketone by virtue of the complexation of cerium(III) with the carbonyl oxygen.[10] Enedione **225** possesses two carbonyls, but the oxygen of the carbonyl at C-4 is less hindered. This carbonyl oxygen is also more basic, due to the presence of the electron-donating methyl group at C-2. After cerium(III) selectively complexes with this oxygen, the carbonyl at C-4 is activated and should be reduced preferentially. However, sterically, neither the axial approach nor the equatorial approach to reduce the carbonyl at C-4 was favored. Therefore, two stereoisomers **262** and **263** in a ratio of only 1.8:1 were produced.

The rigid *trans*-fused bicyclic enediones (**241-243**) have one distinct conformational preference, as represented by the simplified model **270** in Figure 18. Model **270** provides two axial addition alternatives. However, the approach to attack the carbonyl at C-1 would be impeded by the β axial methyl group, whereas the approach to attack the carbonyl at C-4 is encumbered by only a β hydrogen. The major products from the reductions of **241-243** with lithium tri-*tert*-butoxyaluminohydride were all consistent with the latter approach (Scheme 62).

Figure 18. Regiochemical alternatives for axial addition on *trans* bicyclic enediones



In the bridged tricyclic enediones (**237**, **238**, and **240**), the cyclohex-2-ene-1,4-dione ring cannot achieve a chair-like conformation but has to be planar. The facial selectivity in the reduction of the enediones would be determined by the pattern of substitution on the two sp^3 carbons next to the two carbonyls. That is, the less substituted face, or the convex face, would be attacked. With **238** and **240**, the regiochemistry would be governed by the angular methyl groups. The carbonyls which are not proximate to these methyls would be less shielded and therefore be reduced. This agrees with the experimental results. The fact that the reductions of **238** and **240** with lithium tri-*tert*-butoxyaluminohydride were significantly slower than the reductions of the non-bridged enediones also confirmed that the reduction of a carbonyl could indeed be impeded by a β axial methyl group, a factor that we have proposed to rationalize the regio- and stereoselectivity in the reductions of non-bridged enediones. With **237**, in which the angular methyl group is absent, the steric hindrance towards reducing reagents in

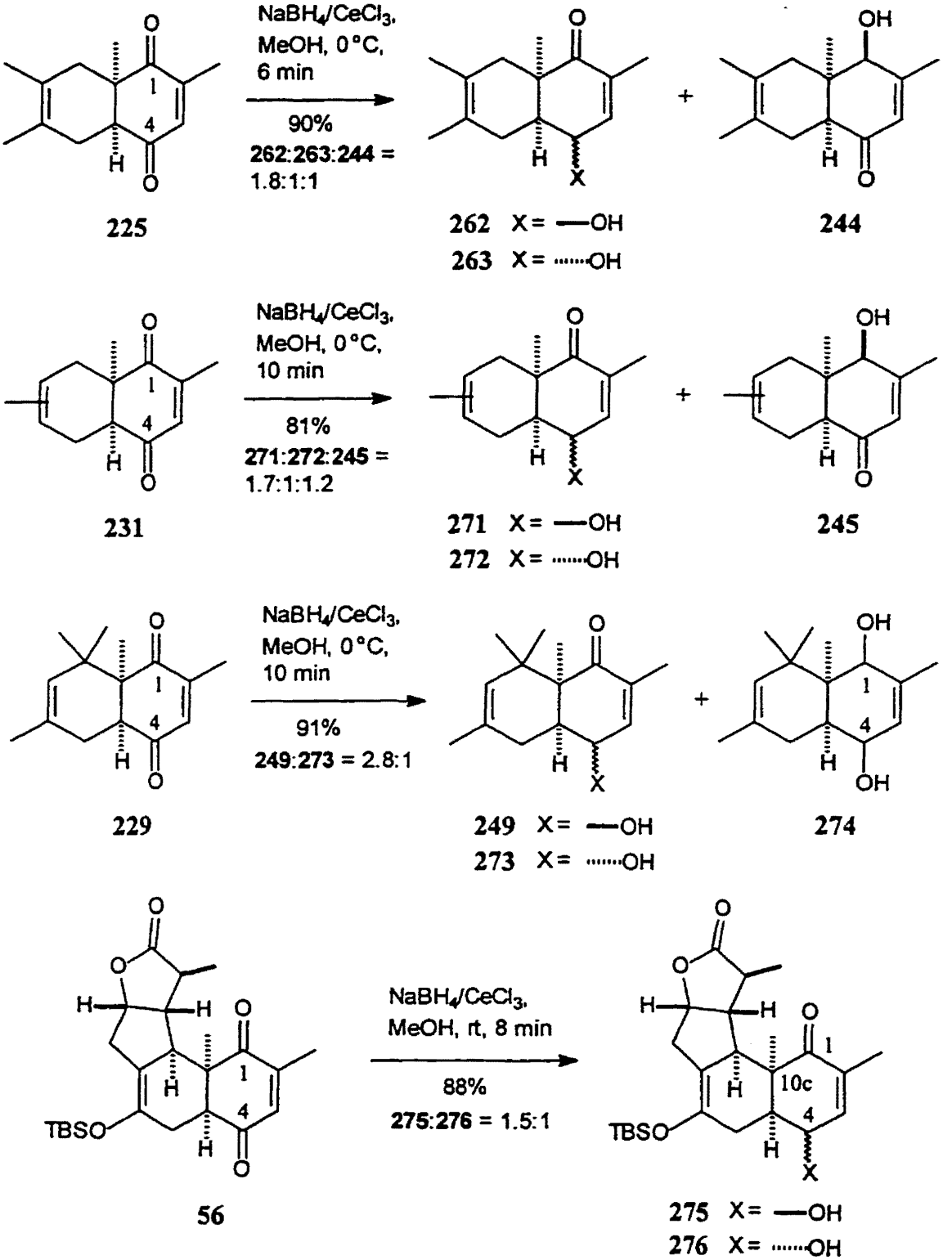
attacking the two carbonyls in the enedione system from the convex face should be almost same. However, the reduction of **237** with lithium tri-*tert*-butoxyaluminohydride furnished a 6:1 regioselectivity in favor of the carbonyl next to the allylic methyl group being reduced. This must be because of the electronic effect of the allylic methyl. The methyl group is an electron donor, and it would make the carbonyl at the other end intrinsically less reactive to nucleophiles. This electronic effect of an allylic methyl group also provides the interpretation to the fact that reductions of *cis* bicyclic enedione **233** and its *trans* isomer **242**, where the allylic methyl groups were "mismatched" to the angular methyls, gave small amounts of minor products resulting from the reductions of the carbonyls that were next to the allylic methyls, but not to the angular methyls, whereas the reductions of the other bicyclic enediones exclusively occurred to the carbonyls that were adjacent to the angular methyl groups.

2. 4. Regioselectivity in the Reductions of Cyclic Enediones with $NaBH_4/CeCl_3$[18]

So far, we have provided an excellent procedure for the regio- and stereoselective monoreduction of the seemingly more hindered carbonyl in a non-bridged enedione. However, as mentioned in Section 1. 3. 2, our original intent was to reduce the other carbonyl, the carbonyl at C-4, selectively in tetracyclic enedione **56**. In an attempt to find a general, alternative method to monoreduce cyclic enediones with the opposite regioselectivity, we examined the reductions of cyclic enediones with with $NaBH_4/CeCl_3$. Typically, these reductions were conducted in methanol at 0 °C for five or six minutes (including the period of addition of sodium borohydride), with 0.7 equivalents of sodium borohydride. The results are arranged in Scheme 64.

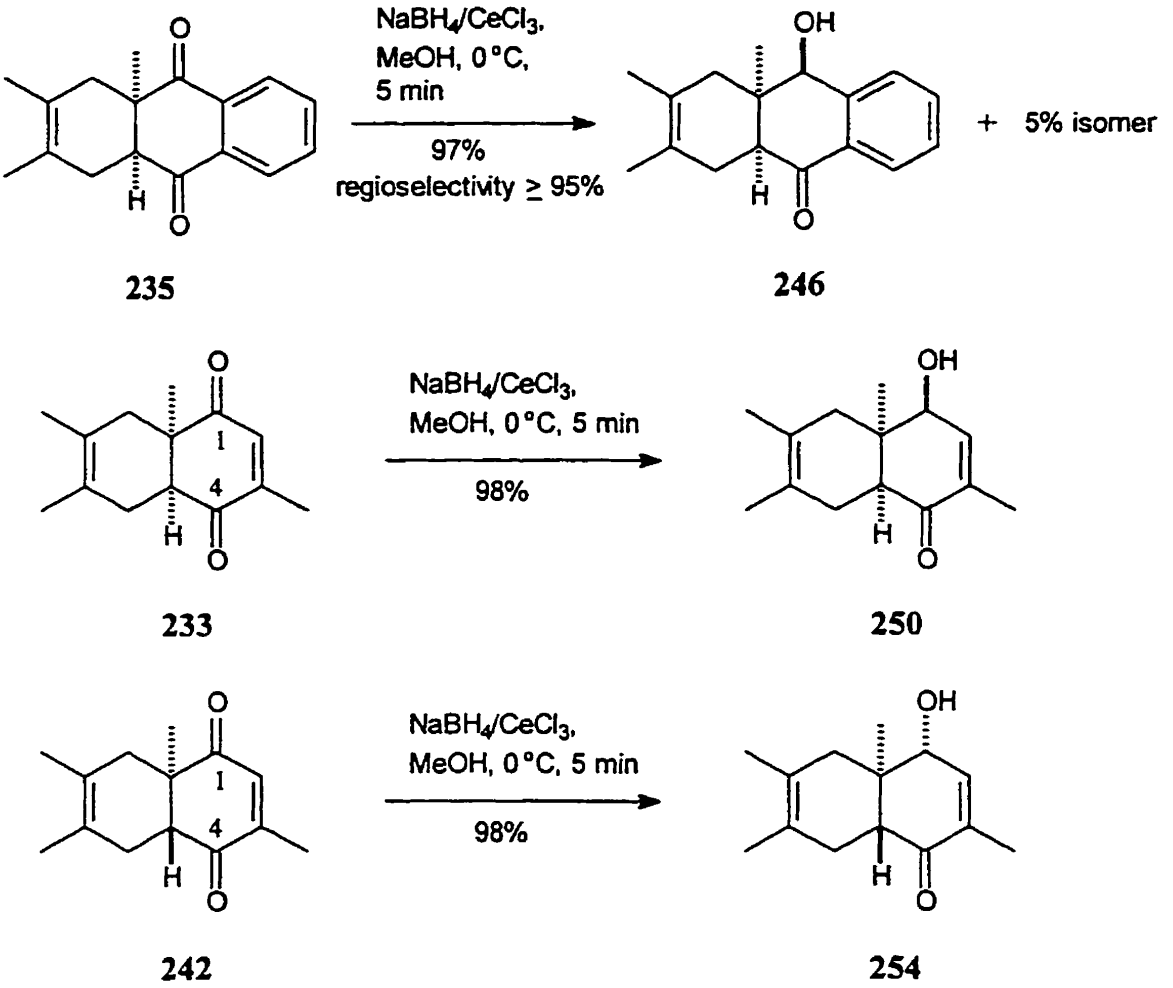
The reduction of enedione **225** with $NaBH_4/CeCl_3$ was discussed in Sections 2. 3. 4 and 2. 3. 5. Through the selective complexation of cerium trichloride with the less hindered carbonyl oxygen, the reduction occurred mainly to the carbonyl at C-4 with a regioselectivity of 74%, though with little stereoselectivity. With $NaBH_4$ alone or $LiAl(O\text{-}t\text{-}Bu)_3H$ the reduction took place exclusively at the carbonyl at C-1. In a similar manner, a 1:1 isomeric mixture **231** was reduced with $NaBH_4/CeCl_3$ to produce **271**, **272**, and **245** with 69% regioselectivity in favor of the carbonyl at C-4 being reduced. The selective complexation of cerium trichloride in **225** and **231** might be due to the difference in steric hindrance and/or in basicity between the two carbonyl oxygens, but the results from enediones **229** and **56** showed that the difference in steric hindrance must be the predominant factor. In **229** and **56**, the oxygens of the C-1 carbonyls are much

Scheme 64. Regioselectivity in the reductions of cyclic enediones with $NaBH_4/CeCl_3$



Scheme 64. Regioselectivity in the reductions of cyclic enediones with $NaBH_4/CeCl_3$

(continued)



more shielded than those of the C-4 carbonyls, but the basicity of the oxygens of the C-4 carbonyls cannot be significantly different from those in **225** and **231**. However, the monoreductions of **229** and **56** with $NaBH_4/CeCl_3$ occurred regiospecifically at the carbonyls at C-4. Enedione **229** gave epimeric alcohols **249** and **273** in a ratio of 2.8:1 and in a 76% combined yield. A minor amount (16%) of double-reduction product **274** was also detected by ^1H NMR spectroscopy, though its stereochemistry at C-1 and C-4

was not determined. Tetracyclic enedione **56** yielded epimers **275** and **276** in a 1.5:1 ratio and in an 88% combined yield. Thus, our original objective reducing the carbonyl at C-4 regioselectively in **56** was achieved.

In enedione **235**, the steric encumbrance between the two carbonyl oxygens is slightly different. Though the sp^3 carbon α to the carbonyl at C-10 is disubstituted whereas the sp^3 carbon α to the carbonyl at C-9 is monosubstituted, one of the two substituents on the carbon α to the carbonyl at C-10 has to be in axial position, which would be perpendicular to the carbonyl and would not provide steric encumbrance to the carbonyl oxygen. The reduction of **235** with $NaBH_4/CeCl_3$ gave two monoreduction products in a 20:1 ratio, as indicated by GC-MS, and in a 97% combined yield. The structure of the minor product was not determined, but the major product was found to be identical with the exclusive product from the reduction of **235** with $NaBH_4$ alone or $LiAl(O\text{-}t\text{-}Bu)_3H$. This may reasonably be rationalized as follows: cerium trichloride coordinated with the two carbonyl oxygens nearly without selectivity, and therefore the two carbonyls were almost equally activated. The regio- and stereoselectivities were then governed by the axial preference of the reduction.

Due to the minor electronic effect of the allylic methyl group, the reduction of enedione **233** with sodium borohydride alone gave 5% minor reduction at the carbonyl at C-1, which is next to the allylic methyl but not the angular methyl. However, with $NaBH_4/CeCl_3$, the reduction of **233** occurred exclusively at the carbonyl at C-1, giving carbinol **250** in 98% yield. This is understandable as both the steric and electronic factors would make the oxygen of the C-4 carbonyl more favorable to coordinate with

cerium(III). Similarly, the reduction of the *trans* isomer **242** with $NaBH_4/CeCl_3$ afforded exclusively carbinol **254** in 98% yield, whereas the regioselectivity with $LiAl(O\text{-}t\text{-}Bu)_3H$ was only 8:1 in favor of **254** being produced.

To summarize Part II, our systematic study has shown, for the first time, that in a non-bridged cyclic enediones, either with *cis* or *trans* junction, the seemingly sterically more hindered carbonyl can be reduced highly regio- and stereoselectively with relatively small reducing reagents. The overwhelming cause of both the regio- and stereoselectivities is the axial preference of the reduction. Only one axial approach is sterically allowed. A substituent on the double bond in enedione moieties may somewhat affect the regioselectivity by electron donation. The combination of sodium borohydride and cerium(III) chloride is a useful alternative reagent for the reduction of cyclic enediones. It can either completely reverse or greatly enhance the regioselectivity, depending on the structures of the enediones. With bridged enediones, the regio- and stereochemistry is also controlled by steric factors, but when the steric factors are absent, the regioselectivity will be determined by electronic factors. Benzoquinones are frequently used as excellent dienophiles in Diels-Alder reactions for the syntheses of natural or unnatural polycyclic compounds. We believe that our results from the study of regio- and stereoselectivies in the reductions of cyclic enediones, the Diels-Alder adducts of benzoquinones, can make this approach more versatile.

2. 5. Experimental

General procedure for the preparation of 225, 227, 229, 231, 233, 235, and 240 by sealed tube Diels-Alder reactions

A solution of 2,6-dimethyl-1,4-benzoquinone (**13**) or 2-methyl-1,4-naphthoquinone (**234**) (2-5 mmol) and 1,3-diene **224, 226, 228, 230,** or **239** (4-5 equivalents of the dienophiles) in dry toluene (5-10 mL) was degassed and sealed in a thick-walled (1.5 mm) glass tube (32 x 1.5 or 32 x 1.0 cm) on a vacuum line. The sealed tube was then heated in a oil bath for a certain period of time (detailed in the individual reports). After cooling to rt, the sealed tube was opened. The solvent and excess diene were removed under vacuum, and the residue was subjected to column chromatography (10-20% EtOAc/hexane) to afford the enedione.

***cis*-4a,5,8,8a-Tetrahydro-2,6,7,8a-tetramethyl-1,4-naphthalenedione (225)**

2,6-Dimethyl-1,4-benzoquinone (**13**) (688 mg, 5.00 mmol) and 2,3-dimethyl-1,3-butadiene (**224**) (2.80 mL, 24.3 mmol) in dry toluene (10 mL) in a sealed tube at 120-125 °C for 30 h afforded **225** (1.02 g, 94% yield) as a pale yellow oil: IR (neat) 1681(s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.50 (1H, q, J = 1.4 Hz, H3), 2.80 (1H, apparent t, J = 6.0 Hz, H4a), 2.49 (1H, dd, J = 18.4, 5.2 Hz, H5 *anti* to H4a), 2.43 (1H, d, J = 17.5 Hz, H8 *anti* to 8a-methyl), 2.08 (1H, dd, J = 18.4, 5.6 Hz, H5 *syn* to H4a), 1.99 (3H, d, J = 1.4 Hz, 2-methyl), 1.66 (1H, d, J = 17.5 Hz, H8, *syn* to 8a-methyl), 1.63 (3H, s), 1.58 (3H, s), 1.29 (3H, s, 8a-methyl); NOE data 1.29 (2.80, 6%; 2.08, 6%; 1.66, 1%). ^{13}C NMR ($CDCl_3$) δ 203.0 (0), 199.8 (0), 147.5 (0, C2), 135.5 (1, C3), 122.8 (0), 122.7 (0), 52.8 (1,

C4a), 48.2 (0, C8a), 38.8 (2, C8), 29.6 (2, C5), 22.8 (3, 8a-methyl), 18.9 (3), 18.6 (3), 16.6 (3, 2-methyl). MS *m/z* 218 (M^+, 59), 203 (41), 190 (34), 189 (18), 188 (37), 175 (100), 157 (18), 147 (15), 121 (16), 107 (28), 105 (27), 98 (19), 91 (45), 79 (26), 69 (39), 68 (19), 67 (19), 65 (14), 53 (19). HRMS calcd. for $C_{14}H_{18}O_2$ 218.1307, found 218.1311.

cis-4a,5,8,8a-Tetrahydro-2,8,8a-trimethyl-1,4-naphthalenedione (227)

2,6-Dimethyl-1,4-benzoquinone (**13**) (275 mg, 2.00 mmol) and piperylene (90%, mixture of *cis* and *trans* isomers, 1.60 mL, 14.4 mmol) in dry toluene (8.0 mL) in a sealed tube at 120 °C for 11 h afforded **227** (315 mg, 77% yield) as a pale yellow oil: IR (neat) 3024 (m), 1688 (s), 1628 (m), 1376 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.66 (1H, q, J = 1.4 Hz, H3), 5.65-5.58 (2H, m, H6 and H7), 2.93-2.84 (2H, m, H5 and H4a), 2.15-2.00 (2H, H5 and H8), 2.00 (3H, d, J = 1.4 Hz, 2-methyl), 1.42 (3H, s, 8a-methyl), 0.80 (3H, d, J = 7.3 Hz, 8-methyl). NOE data 1.42 (2.93-2.84, 5%; 2.15-2.00, 6%). ^{13}C NMR ($CDCl_3$) δ 203.8 (0), 198.8 (0), 149.6 (0, C2), 137.7 (1, C3), 130.0 (1), 122.5 (1), 50.5 (0, C8a), 50.3 (1, C4a), 39.3 (1, C8), 23.9 (3, 8a-methyl), 20.5 (2, C5), 19.5 (3, 8-methyl), 16.3 (3, 2-methyl). MS *m/z* 204 (M^+, 10), 189 (17), 176 (89), 161 (60), 96 (22), 93 (38), 91 (52), 79 (23), 77 (42), 69 (40), 68 (100). HRMS calcd. for $C_{13}H_{16}O_2$ 204.1150, found 204.1178.

cis-4a,5,8,8a-Tetrahydro-2,6,8,8,8a-pentamethyl-1,4-naphthalenedione (229)

2,6-Dimethyl-1,4-benzoquinone (**13**) (545 mg, 4.00 mmol) and 2,4-dimethyl-1,3-pentadiene (**228**) (2.60 mL, 19.7 mmol) in dry toluene (10 mL) in a sealed tube at 145 °C for 4 days afforded **229** (421 mg, 45% yield) as a pale yellow oil: IR (neat) 1680 (s), 1374

(m), 1206 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.69 (1H, s, H2), 5.01 (1H, s, H7), 2.91 (1H, d, *J* = 6.8 Hz, H4a), 2.80 (1H, d, *J* = 18.0 Hz, H5), 1.99 (3H, s, 2-methyl), 1.95 (1H, dd, *J* = 18.0, 6.8 Hz, H5), 1.70 (3H, s, 6-methyl), 1.32 (3H, s, 8a-methyl), 0.92 (3H, s, 8-methyl), 0.73 (3H, s, 8-methyl). NOE data 1.32 (2.91, 8%). ^{13}C NMR ($CDCl_3$) δ 202.7 (0), 198.6 (0), 149.7 (0, C2), 138.2 (1, C3), 130.1 (1, C7), 128.0 (0, C6), 53.0 (0, C8a), 52.8 (1, C4a), 38.1 (0, C8), 29.7 (3, 8-methyl), 24.9 (3, 8-methyl), 24.2 (2, C5), 23.2 (3, 6-methyl), 21.1 (3, 8a-methyl), 16.4 (3, 2-methyl). MS *m/z* 232 (M^+, 6), 204 (38), 189 (33), 161 (13), 121 (15), 105 (14), 96 (100), 91 (15), 83 (37), 81 (43), 79 (14), 77 (14), 69 (19). HRMS calcd. for $C_{15}H_{20}O_2$ 232.1463, found 232.1453.

cis-4a,5,8,8a-Tetrahydro-2,6 and 7,8a-trimethyl-1,4-naphthalenedione (231)

2,6-Dimethyl-1,4-benzoquinone (**13**) (275 mg, 2.00 mmol) and isoprene (**230**) (1.0 mL, 10 mmol) in dry toluene (8.0 mL) in a sealed tube at 120-125 °C for 36 h afforded **231** (361 mg, 88% yield) as an almost 1:1 isomeric mixture as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 6.52 (2H, overlapped narrow signals, H3), 5.38 (1H, m), 5.31 (1H, m), 2.86 (1H, dd, *J* = 6.6, 4.9 Hz, H4a), 2.79 (1H, t, *J* = 5.6 Hz, H4a), 2.64-2.37 (4H, m), 2.20-2.01 (2H, m), 2.00 (6H, overlapped narrow doublets, 2-methyl), 1.80-1.69 (2H, m), 1.69 (3H, s), 1.64 (3H, s), 1.32 (3H, s, 8a-methyl), 1.31 (3H, s, 8a-methyl). ^{13}C NMR ($CDCl_3$) (some signals are overlapped) δ 203.1 (0), 202.8 (0), 199.7 (0), 199.3 (0), 147.5 (0, C2), 135.5 (1, C3), 131.2 (0), 131.0 (0), 117.9 (1), 117.8 (1), 52.5 (1, C4a), 51.8 (1, C4a), 48.1 (0, C8a), 47.3 (0, C8a), 37.1 (2), 32.9 (2), 27.5 (2), 23.6 (2), 23.4 (3), 23.2 (3), 22.7 (3), 22.3 (3), 16.6 (3, 2-methyl).

***cis*-4a,5,8,8a-Tetrahydro-2,4a,6,7-tetramethyl-1,4-naphthalenedione (233)**

2,5-Dimethylbenzoquinone (**232**) (362 mg, 2.66 mmol) and 2,3-dimethyl-1,3-butadiene (**224**) (1.50 mL, 13.2 mmol) in dry toluene (8.0 mL) in a sealed tube at 120-125 °C for 27 h provided **233** (558 mg, 96% yield) as a yellow oil: IR (neat) 1679 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.46 (1H, q, *J* = 1.5 Hz, H3), 2.83 (1H, t, *J* = 5.7 Hz, H8a), 2.49 (1H, dd, *J* = 17.7, 2.0 Hz, H8 *anti* to H8a), 2.40 (1H, d, *J* = 17.4 Hz, H5 *anti* to 4a-methyl), 2.08 (1H, dd, *J* = 17.7, 1.6 Hz, H8 *syn* to H8a), 1.98 (3H, d, *J* = 1.5 Hz, 2-methyl), 1.67 (1H, d, *J* = 17.4 Hz, H5 *syn* to 4a-methyl), 1.64 (3H, s), 1.58 (3H, s), 1.27 (3H, s, 4a-methyl). NOE data 1.27 (2.83, 7%; 2.08, 5%; 1.67, 1%). ^{13}C NMR ($CDCl_3$) δ 202.6 (0), 200.4 (0), 148.2 (0, C2), 135.0 (1, C3), 122.7 (0, C6 and C7), 52.8 (1, C8a), 48.5 (0, C4a), 38.8 (2, C5), 29.5 (2, C8), 22.7 (3, 4a-methyl), 18.9 (3), 18.6 (3), 16.1 (3, 2-methyl). MS *m/z* 218 (M^+, 60), 203 (36), 190 (23), 189 (17), 188 (38), 175 (100), 157 (18), 147 (19), 121 (16), 107 (30), 105 (25), 98 (18), 91 (42), 79 (24), 77 (26), 69 (35), 68 (22), 67 (20). HRMS calcd. for $C_{14}H_{18}O_2$ 218.1307, found 218.1304.

***cis*-1,4,4a,9a-Tetrahydro-2,3,4a-trimethyl-9,10-anthracenedione (235)**

2-Methyl-1,4-naphthoquinone (**234**) (703 mg, 4.00 mmol) and 2,3-dimethyl-1,3-butadiene (**224**) (1.85 mL, 16.0 mmol) in dry toluene (10 mL) in a sealed tube at 120-125 °C for 28 h gave **235** (0.936 g, 92% yield) as a colorless oil: IR (neat) 3068 (w), 1694 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.08-8.00 (2H, m), 7.76-7.29 (2H, m), 3.03 (1H, t, *J* = 6.86 Hz, H9a), 2.60 (1H, d, *J* = 16.5 Hz, H4a *anti* to 10a-methyl), 2.42 (1H, dd, *J* = 18.1, 7.2 Hz, H1a *anti* to H9a), 2.16 (1H, dd, *J* = 18.1, 7.2 Hz, H1a *syn* to H9a), 1.78 (1H, d, *J* = 16.5

Hz, H4a *syn* to 10a-methyl), 1.62 (6H, br s, 2-methyl and 3-methyl), 1.34 (3H, s, 4a-methyl). NOE data 3.03 (2.16, 3%), 1.34 (3.03, 7%; 1.78, 2%). ^{13}C NMR ($CDCl_3$) δ 200.3 (0), 198.6 (0), 134.2 (1), 134.0 (1), 133.5 (0), 132.9 (0), 127.2 (1), 126.5 (1), 123.4 (0), 122.6 (0), 53.6 (1, C9a), 48.4 (0, C4a), 38.6 (2, C4), 31.1 (2, C1), 23.8 (3, 4a-methyl), 18.9 (3), 18.5 (3). MS *m/z* 254 (M^+, 42), 239 (100), 226 (18), 225 (18), 224 (36), 221 (37), 211 (27), 193 (16), 134 (80), 133 (55), 119 (14), 106 (16), 105 (48), 104 (26), 91 (26), 79 (19), 77 (48), 76 (38), 67 (20). HRMS calcd. for $C_{17}H_{18}O_2$ 254.1307, found 254.1305.

(4aα,5α,8α,8aα)-4a,5,8,8a-Tetrahydro-2-methyl-5,8-methano-1,4-naphthalenedione (237)

A solution of 2-methyl-1,4-benzoquinone (**236**) (623 mg, 5.00 mmol) and cyclopentadiene (**175**) (992 mg, 15.0 mmol) in methanol (15 mL) was stirred at rt for 1h. The excess diene and solvent were removed under vacuum, and the residue was purified by column chromatography (30% EtOAc/hexane) to afford **237** (885 mg, 94% yield) as a pale yellow solid: mp 61.5-62.5 °C. IR (Nujol) 1672 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.48 (1H, q, J = 1.4 Hz, H3), 6.06 (1H, dd, J = 5.4, 2.8 Hz), 6.02 (1H, dd, J = 5.4, 2.8 Hz), 3.53-3.52 (2H, m, H5 and H8), 3.23-3.22 (2H, m, H4a and H8a), 1.92 (3H, d, J = 1.4 Hz, 2-methyl), 1.54 (1H, m, H9), 1.45 (1H, m, H9). ^{13}C NMR ($CDCl_3$) δ 199.6 (0), 199.1 (0), 151.6 (0, C2), 139.6 (1, C3), 135.4 (1), 134.8 (1), 49.0 (1), 48.9 (1), 48.8 (2, C9), 48.6 (1), 48.2 (1), 16.3 (3, 2-methyl). MS *m/z* 188 (M^+, 15), 123 (5), 91 (5), 66 (100), 65 (10). HRMS calcd. for $C_{12}H_{12}O_2$ 188.0836, found 188.0820.

(4aα,5α,8α,8aα)-4a,5,8,8a-Tetrahydro-2,8a-dimethyl-5,8-methano-1,4-naphthalenedione (238)

A solution of 2,6-dimethyl-1,4-benzoquinone (**13**) (275 mg, 2.00 mmol) and cyclopentadiene (**175**) (264 mg, 4.00 mmol) in methanol (5.0 mL) was stirred at rt for 45 h. The excess diene and solvent were removed under vacuum, and the residue was purified by column chromatography (15% AcOEt/hexane) to afford **238** (388 mg, 96% yield) as a pale yellow oil: IR (neat) 1664 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.49 (1H, q, J = 1.4 Hz, H3), 6.09 (1H, dd, J = 5.6, 2.9 Hz), 5.99 (1H, dd, J = 5.6, 2.8 Hz), 3.42 (1H, m, H5), 3.08 (1H, br s, H8), 2.82 (1H, d, J = 3.9 Hz, H4a), 1.94 (3H, d, J = 1.4 Hz, 2-methyl), 1.68 (1H, m, H9), 1.52 (1H, m, H9), 1.46 (3H, s, 8a-methyl). ^{13}C NMR ($CDCl_3$) δ 203.1 (0), 199.3 (0), 151.2 (0, C2), 139.0 (1), 137.7 (1), 134.9 (1), 57.7, 53.7, 52.4 (0), 48.9, 46.4, 26.6 (3, 8a-methyl), 16.6 (3, 2-methyl). MS *m/z* 202 (M^+, 4), 137 (15), 91 (3), 77 (3), 68 (5), 66 (100). HRMS calcd. for $C_{13}H_{14}O_2$ 202.0993, found 202.0990.

(4aα,5α,8α,8aα)-4a,5,8,8a-Tetrahydro-2,8a-dimethyl-5,8-ethano-1,4-naphthalenedione (240)

A solution of 2,6-dimethyl-1,4-benzoquinone (**13**) (275 mg, 2.00 mmol) and 1,3-cyclohexadiene (**239**) (0.29 mL, 3.0 mmol) in toluene (5.0 mL) in a sealed tube at 125-135 °C for 48 h. The excess diene and solvent were removed under vacuum, and the residue was subjected to column chromatography (10% AcOEt/hexane) to provide **240** (70 mg, 46% yield) as yellow oil, which solidified in the refrigerator to a pale yellow

solid: mp 43.5-44.0 °C: IR (CCl_4) 3048 (w), 1665 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.53 (1H, s, H3), 6.32 (1H, m, H7), 6.12 (1H, m, H6), 3.02 (1H, m, H5), 2.94 (1H, m, H8), 2.51 (1H, d, J = 1.8 Hz, H4a), 1.95 (3H, s, 2-methyl), 1.88 (1H, m, H9 *anti* to C6, C7 double bond), 1.73 (1H, H10 *anti* to C6, C7 double bond), 1.39-1.18 (2H, m, H9, H10 *syn* to C6, C7 double bond), 1.33 (3H, s, 8a-methyl). NOE data 2.51 (1.73, 3%), 1.33 (2.51, 8%; 1.88, 5%). ^{13}C NMR ($CDCl_3$) δ 203.2 (0), 199.5 (0), 151.1 (0, C2), 138.2 (1, C3), 136.0 (1, C7), 132.4 (1, C6), 58.8 (1, C4a), 50.5 (0, C8a), 39.3 (1, C8), 36.7 (1, C4), 26.2 (2, C10), 26.1 (3, 8a-methyl), 18.8 (2, C9), 16.9 (3, 2-methyl). MS *m/z* 216 (M^+, 0.6), 138 (11), 91 (6), 80 (100), 79 (22), 68 (9). HRMS calcd. for $C_{14}H_{16}O_2$ 216.1150, found 216.1152.

General procedure for the preparation of 241, 242, and 243 by epimerization of the corresponding *cis*-isomers 225, 233, and 235

cis-Fused enediones **225**, **233**, or **235** (approximately 2 mmol) were heated in glacial acetic acid (10 mL) at reflux overnight. The acetic acid was removed by vacuum distillation. The residue was dissolved in Et_2O (30 mL), and then washed with saturated $NaHCO_3$ solution (2 x 10 mL), water (10 mL), and brine (10 mL). The solution was dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography of the residue (when necessary) provided mixtures of the *cis* and *trans* isomers in ratios of approximately 1:1. These mixtures were used for the reduction study without separation.

***trans*-4a,5,8,8a-Tetrahydro-2,6,7,8a-tetramethyl-1,4-naphthalenedione (241)**

^{1}H NMR ($CDCl_3$) (discernible signals from a mixture of **225** and **241**) δ 6.58 (1H, q, J = 1.5 Hz, H3), 2.90 (1H, dd, J = 9.8, 7.2 Hz, H4a), 2.01 (3H, d, J = 1.5 Hz, 2-methyl), 1.08 (3H, s, 8a-methyl). ^{13}C NMR ($CDCl_3$) δ 204.3 (0), 199.7 (0), 147.9 (0, C2), 136.9 (1, C3), 123.0 (0), 122.6 (0), 50.6 (1, C4a), 47.7 (0, C8a), 39.6 (2), 28.1 (2), 20.0 (3), 19.1 (3), 18.6 (3), 16.5 (3, 2-methyl). MS (from GC-MS) *m/z* 218 (M^+, 64), 203 (100), 190 (14), 189 (35), 188 (71), 176 (16), 175 (52), 157 (39), 147 (20), 142 (14), 133 (62), 119 (20), 107 (40), 105 (39), 91 (75), 79 (55), 77 (55), 69 (62), 68 (36), 67 (30).

***trans*-4a,5,8,8a-Tetrahydro-2,4a,6,7-tetramethyl-1,4-naphthalenedione (242)**

^{1}H NMR ($CDCl_3$) (discernible signals from a mixture of **233** and **242**) δ 6.48 (1H, q, J = 1.5 Hz, H3), 2.91 (1H, dd, J = 10.8, 6.0 Hz, H8a), 2.01 (3H, d, J = 1.5 Hz, 2-methyl), 1.08 (3H, s, 4a-methyl). ^{13}C NMR ($CDCl_3$) δ 204.2 (0), 200.4 (0), 150.0 (0, C2), 135.3 (1, C3), 123.0 (0), 122.7 (0), 50.7 (1, C8a), 48.2 (0, C4a), 39.6 (2), 28.1 (2), 20.1 (3), 19.1 (3), 18.5 (3), 16.0 (3, 2-methyl). MS (from GC-MS) *m/z* 218 (M^+, 54), 203 (100), 189 (58), 188 (70), 175 (66), 157 (37), 147 (17), 142 (15), 133 (16), 119 (18), 107 (33), 105 (32), 93 (16), 91 (64), 79 (38), 77 (43), 69 (59).

***trans*-1,4,4a,9a-Tetrahydro-2,3,4a-trimethyl-9,10-anthracenedione (243)**

^{1}H NMR ($CDCl_3$) (discernible signals from a mixture of **235** and **243**) δ 8.11-8.00 (2H, m), 7.77-7.70 (2H, m), 3.13 (1H, dd, J = 10.6, 6.0 Hz, H9a), 1.71 (6H, s, 2-methyl and 3-methyl), 1.12 (3H, s, 4a-methyl). ^{13}C NMR ($CDCl_3$) δ 201.9, 198.2, 135.0, 134.1, 134.0, 133.2, 127.3, 126.0, 122.9, 122.6, 50.2, 47.6, 39.8, 28.4, 19.8, 19.1, 18.5. MS

(from GC-MS) *m/z* 254 (M^+, 29), 239 (100), 236 (12), 225 (13), 224 (35), 222 (14), 221 (47), 147 (10), 134 (10), 133 (49), 105 (29), 104 (16), 79 (13), 77 (33), 76 (28), 51 (13).

General procedure for the reduction of cyclic enediones with lithium tri-*tert*-butoxyaluminohydride (Method A)

To a solution of enediones (0.5-1.0 mmol) in dry THF (5.0-8.0 mL) was introduced lithium tri-*tert*-butoxyaluminohydride (1.2-1.5 equivalents of enediones) at 0 °C over 5 min. The resulting solution was stirred for a certain period of time (detailed in the individual reports) before it was poured into water (50 mL) and then extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were washed with water (2 x 30 mL), brine (30 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent and chromatography (when necessary) gave the monoreduction products.

General procedure for the reduction of cyclic enediones with sodium borohydride (Method B)

To a solution of enediones (0.5-1.0 mmol) in methanol (5.0-10 mL) was added sodium borohydride (approximately 0.8 equivalents of enediones) at 0 °C over 3-5 min. The resulting mixture was stirred at the same temperature for another 3-5 min before the reaction was quenched with dilute NH_4Cl solution (40 mL) and extracted with EtOAc (4 x 25 mL). The combined organic extracts were washed with water (2 x 25 mL), brine (25 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent and chromatography (if necessary) gave the products.

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-3,4a,6,7-tetramethylnaphthalen-1-one (244)

Method A: Enedione **225** (146 mg, 0.669 mmol) in dry THF (5.0 mL) was reduced with LiAl(O-*t*-Bu)$_3$H (0.80 mL, 0.80 mmol) at 0 °C over 18 min to give **244** (142 mg, 97% yield).

Method B: Enedione **225** (129 mg, 0.591 mmol) in methanol (5.0 mL) was reduced with $NaBH_4$ (18.8 mg, 0.472 mmol) at 0 °C over 8 min to give crude **244** (125 mg), which was contaminated by 4% of a triply reduced product by GC-MS.

Alcohol **244**: mp 129.0-131.0 °C. IR (Nujol,) 3451 (s), 1659 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.87 (1H, s, H2), 4.27 (1H, d, *J* = 6.8 Hz, H4), 2.69 (1H, d, *J* = 16.1 Hz), 2.23-2.05 (4H, m), 2.02 (3H, s, 3-methyl), 1.64 (3H, s), 1.61 (1H, d, *J* = 19.0 Hz), 1.55 (3H, s), 1.20 (3H, s, 4a-methyl). NOE data 1.20 (4.27, 9%). ^{13}C NMR ($CDCl_3$) δ 198.7 (0, C1), 160.1 (0, C3), 125.9 (1, C2), 123.5 (0), 122.8 (0), 78.0 (1, C4), 50.4 (1, C8a), 41.0 (0, C4a), 33.9 (2), 27.5 (2), 23.7 (3, 4a-methyl), 20.3 (3, 3-methyl), 19.4 (3), 18.8 (3). MS *m/z* 220 (M$^+$, 2), 202 (24), 187 (30), 174 (34), 172 (15), 159 (100), 121 (14), 107 (24), 105 (19), 98 (20), 91 (26), 79 (15), 77 (16), 71 (14), 69 (20). HRMS calcd. for $C_{14}H_{20}O_2$ 220.1463, found 220.1450.

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-3,4a,6 and-7-tetramethylnaphthalen-1-one (245)

Enedione **231** as 1:1 isomeric mixture (131 mg, 0.641 mmol) in dry THF (5.0 mL) was reduced with LiAl(O-*t*-Bu)$_3$H (0.90 mL, 0.90 mmol) at 0 °C over 25 min to give

245 (122 mg, 92% yield) as a colorless, viscous liquid: ^{1}H NMR ($CDCl_3$) δ 5.88 (2H, two overlapped singlets, H2), 5.36 (1H, m), 5.25 (1H, m), 4.32 (1H, s, H4a), 4.30 (1H, s, H4a), 2.81 (1H, br d, J = 17.0 Hz), 2.70 (1H, d, J = 17.1 Hz), 2.30-2.01 (8H, m), 2.02 (6H, two overlapped singlets, H2), 1.77-1.64 (2H, m), 1.69 (3H, s), 1.60 (3H, s), 1.22 (6H, two overlapped singlets, H4a). ^{13}C NMR ($CDCl_3$) (some signals are overlapped) δ 198.7, 198.6, 160.3, 132.0, 131.4, 125.9, 118.7, 118.4, 78.1, 78.0, 50.5, 49.7, 41.2, 40.4, 32.3, 27.7, 25.9, 23.9, 23.6, 23.5, 23.4, 21.3, 20.3.

(4aα,9aα,10β)-1,4,4a,9a,10-Pentahydro-10-hydroxy-2,3,4a-trimethylanthracen-9-one (246)

Method A: Enedione **235** (141 mg, 0.554 mmol) in dry THF (5.0 mL) was reduced with LiAl(O-*t*-Bu)$_3$H (0.66 mL, 0.66 mmol) at 0 °C over 18 min to give **246** (139 mg, 98% yield).

Method B: Enedione **235** (116 mg, 0.456 mmol) in methanol (4.0 mL) was reduced with $NaBH_4$ (14.5 mg, 0.364 mmol) at 0 °C over 6 min to give **246** (114 mg, 97% yield).

Alcohol **246**: white solid: mp 119.0-120.5 °C. IR (Nujol) 3466 (s), 1664 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, d, J = 7.8 Hz, H8), 7.98 (1H, d, J = 7.8 Hz, H5), 7.62 (1H, m, H6), 7.38 (1H, m, H7), 4.83 (1H, d, J = 8.0 Hz, H10), 2.89 (1H, d, J = 17.4 Hz, H1β), 2.43 (1H, m, H9a), 2.23-2.21 (2H, m, H1α, 10-hydroxy), 1.87 (1H, d, J = 17.4 Hz, H4a), 1.68 (3H, s), 1.60 (1H, d, J = 17.4 Hz, H4a), 1.49 (3H, s), 1.31 (3H, s, 4a-methyl). NOE 4.83 (7.98, 2%; 2.43, 5%), 1.31 (4.83, 9%; 2.43, 6%; 2.23-2.21, 4%). ^{13}C NMR ($CDCl_3$)

δ 197.5 (0, C9), 143.7 (0), 134.1 (1, C6), 130.5 (0), 127.7 (1, C7), 126.8 (1, C8), 126.5 (1, C5), 123.7 (0), 122.6 (0), 76.2 (1, C10), 50.9 (1, C9a), 41.0 (0, C4a), 33.7 (2, C4), 28.0 (2, C1), 23.6 (3, 4a-methyl), 19.4 (3), 18.9 (3). MS *m/z* 256 (M^+, 1), 238 (29), 223 (100), 208 (18), 195 (11), 158 (10), 134 (10), 133 (11), 121 (5), 118 (6), 105 (5). HRMS calcd. for $C_{17}H_{20}O_2$ 256.1463, found 256.1478.

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-3,4a,5-trimethylnaphthalen-1-one (247)

Enedione **227** (131 mg, 0.641 mmol) in dry THF (5.0 mL) was reduced with LiAl(O-*t*-Bu)$_3$H (0.80 mL, 0.80 mmol) at 0 °C over 20 min to give **247** (118 mg, 89% yield) as white solid: mp 111.5-112.5 °C. IR (CCl_4) 3503 (s), 1644 (s), 1072 (m) cm^{-1}. ^1H NMR ($C_6D_5CD_3$, 100 °C, signals are very broad at rt) δ 5.66 (1H, s, H2), 5.41 (2H, m), 3.74 (1H, d, J = 5.3 Hz, H4), 2.55 (1H, m, H8), 2.13-1.77 (4H, m), 1.72 (3H, s, 3-methyl), 0.94 (3H, d, J = 7.4 Hz, H5), 0.88 (3H, s, 4a-methyl). ^{13}C NMR (CD_2Cl_2, -85 °C, a total of 28 signals for two conformers) δ 203.6, 199.6, 163.9, 157.3, 133.6, 131.0, 125.8, 124.3, 122.3, 121.9, 76.7, 72.8, 49.6, 48.3, 45.1, 38.0, 37.6, 35.5, 27.8, 26.5, 25.2, 22.3, 20.9, 20.3, 19.8, 13.2. MS *m/z* 206 (M^+, 4), 188 (17), 173 (45), 160 (31), 159 (40), 145 (75), 122 (27), 109 (28), 98 (100), 93 (45), 91 (52), 77 (43), 70 (46), 69 (51). HRMS calcd. for $C_{13}H_{18}O_2$ 206.1307, found 206.1306.

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-3,4a,5,5,7-pentamethylnaphthalen-1-one (248)

Enedione **229** (149 mg, 0.641 mmol) in dry THF (5.0 mL) was reduced with $LiAl(O\text{-}t\text{-}Bu)_3H$ (0.95 mL, 0.95 mmol) at 0 °C over 2 h to give a mixture of **248** and **249** in a ratio of 10:1 favoring **248**, from the ^1H NMR spectrum of the crude product. Column chromatography gave **248** (125 mg, 83% yield) as white solid: mp 86.5-88.0 °C. IR (CCl_4) 3457 (m, br), 1659 (s), 1440 (m), 1374 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.80 (1H, s, H2), 5.42 (1H, s, H6), 3.84 (1H, m, H4), 3.16 (1H, d, J = 3.7 Hz, 4-hydroxy), 26.1 (1H, apparent t, J = 8.9 Hz, H8a), 2.16 (2H, apparent d, J = 8.9 Hz, H8), 2.06 (3H, s, 3-methyl), 1.67 (3H, s, 3-methyl), 1.20 (3H, s, 5-methyl), 0.95 (3H, s, 5-methyl), 0.91 (3H, s, 4a-methyl). NOE data 3.84 (0.91, 2%), 0.91 (3.84, 5%). ^{13}C NMR ($CDCl_3$) δ 202.3 (0, C1), 157.2 (0, C3), 133.8 (1, C6), 131.5 (0, C7), 122.7 (1, C2), 74.4 (1, C4), 47.2 (1, C8a), 40.6 (0, C4a), 36.4 (0, C5), 32.6 (2, C8), 27.7 (3, 5-methyl), 22.9 (3, 7-methyl), 22.4 (3, 3-methyl), 22.2 (3, 5-methyl), 20.4 (3, 4a-methyl). MS *m/z* 234 (M^+, 10), 201 (27), 173 (49), 139 (22), 137 (23), 136 (35), 135 (23), 121 (98), 105 (26), 98 (34), 96 (100), 91 (30), 81 (47), 79 (22), 77 (26), 69 (25). HRMS calcd. for $C_{15}H_{22}O_2$ 234.1620, found 234.1613.

Spectroscopic data for **249** are given on page of 248.

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-2,4a,6,7-tetramethylnaphthalen-1-one (250) and **(4ξ,4aα,8aα)-4,4a,5,8,8a-pentahydro-4-hydroxy-3,6,7,8a-tetramethylnaphthalen-1-one (251)**

Method A: Enedione **233** (206 mg, 0.944 mmol) in THF (7.0 mL) was reduced with $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.13 mL, 1.13 mmol) at 0 °C over 25 min to give **250** and **251** as a

mixture (203 mg, 98%) in a ratio of 25:1.

Method B: Enedione **233** (205 mg, 0.939 mmol) in methanol (8.0 mL) was reduced with $NaBH_4$ (37.4 mg, 0.939 mmol) at 0 °C over 9 min to give **250** and **251** as a mixture (195 mg, 94% yield) in a ratio of 25:1.

Alcohol **250**: white solid: mp 99.0-101.5 °C. IR (Nujol) 3460 (s), 1658 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.46 (1H, m, H3), 4.38 (1H, m, H4), 2.71 (1H, d, J = 17.6 Hz), 2.20 (1H, m, H8a), 2.13-2.07 (3H, m), 1.78 (3H, m, 2-methyl), 1.65 (3H, s), 1.57 (1H, d, J = 15.1 Hz), 1.55 (3H, s), 1.19 (3H, s, 8a-methyl). NOE data 4.38 (6.46, 4%; 2.20, 4%), 1.19 (4.38, 8%; 2.20, 5%). ^{13}C NMR ($CDCl_3$) δ 199.4 (0, C1), 144.8 (1, C3), 134.6 (0), 123.4 (0), 122.6 (0), 75.1 (1, C4), 50.1 (1, C8a), 42.1 (1, C4a), 33.3 (2), 27.3 (2), 23.5 (3, 4a-methyl), 19.4 (3), 18.8 (3), 15.6 (3, 2-methyl). MS *m/z* 220 (M^+, 2), 202 (23), 187 (41), 174 (64), 172 (16), 159 (100), 138 (14), 121 (14), 107 (27), 105 (19), 98 (27), 94 (15), 91 (28), 79 (17), 77 (18), 70 (18), 69 (21). HRMS calcd. for $C_{14}H_{20}O_2$ 220.1463, found 220.1488.

Alcohol **251**: ^1H NMR ($CDCl_3$, discernible signals from the mixture) δ 5.79 (1H, s, H2), 1.02 (3H, s, 8a-methyl). MS (from GC-MS) *m/z* 220 (M^+, 9), 159 (12), 150 (18), 138 (100), 121 (11), 107 (21), 105 (16), 98 (20), 91 (27), 79 (17), 77 (19), 69 (22).

(4α,4aα,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-3,4a,6,7-tetramethylnaphthalen-1-one (252)

A 1:1 epimeric mixture (146 mg, 0.669 mmol) of **225** and **241** in THF (5.0 mL) was reduced with $LiAl(O\text{-}t\text{-}Bu)_3H$ (0.80 mL, 0.80 mmol) at 0 °C over 25 min to give a 1:1

diastereoisomeric mixture (143 mg, 97% yield) of **244** and **252**.

Alcohol **252**: ^{1}H NMR ($CDCl_3$, discernible signals from the mixture) δ 5.87 (1H, s, H2), 4.33 (1H, d, J = 6.2 Hz, H4), 2.36 (1H, dd, J = 11.2, 5.8 Hz, H8a), 2.03 (3H, s, 3-methyl), 0.80 (3H, s, 4a-methyl). NOE data 4.33 (2.36, 5%). ^{13}C NMR ($CDCl_3$) δ 199.9, 161.6, 126.0, 123.4, 122.5, 79.4, 49.8, 44.4, 42.3, 28.2, 20.0, 19.0, 18.7, 11.5. MS (from GC-MS) *m/z* 220 (M^+, 48), 205 (25), 187 (40), 177 (24), 163 (23), 159 (24), 138 (53), 133 (19), 121 (20), 79 (28), 77 (30), 71 (67), 70 (20), 69 (43), 67 (20), 65 (21), 55 (25), 53 (26), 43 (47), 41 (100).

(4aα,9aβ,10α)-1,4,4a,9a,10-Pentahydro-10-hydroxy-2,3,4a-trimethyl-9-anthracenone (253)

A 57:43 epimeric mixture (139 mg, 0.546 mmol) of **235** and **243** in THF (5.0 mL) was reduced with LiAl(O-*t*-Bu)$_3$H (0.76 mL, 0.76 mmol) at 0 °C over 30 min to give a 57:43 diastereoisomeric mixture (133 mg, 95% yield) of **246** and **253**.

Alcohol **253**: ^{1}H NMR ($CDCl_3$, discernible signals from the mixture) δ 4.84 (1H, d, J = 7.6 Hz, H10), 2.58 (1H, dd, J = 11.0, 6.0 Hz, H9a), 0.72 (3H, s, 4a-methyl). NOE data 4.84 (2.58, 8%). ^{13}C NMR ($CDCl_3$) δ 198.7, 144.0, 134.0, 130.9, 127.4, 126.4, 125.6, 123.5, 122.6, 77.6, 50.2, 44.5, 41.9, 28.5, 19.1, 18.7, 11.2. MS (from GC-MS) *m/z* 256 (M^+, 82), 241 (18), 223 (100), 221 (15), 220 (27), 208 (45), 186 (22), 174 (12), 165 (13), 133 (23), 118 (35), 115 (17), 107 (13), 105 (86), 91 (29), 79 (22), 77 (69).

(4α,4aα,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-2,4a,6,7-tetramethylnaphthalen-1-

one (254) and **(4ξ,4aα,8aβ)-4,4a,5,8,8a-pentahydro-4-hydroxy-3,6,7,8a-tetramethylnaphthalen-1-one (255)**

A 55:45 epimeric mixture (136 mg, 0.523 mmol) of **233** and **242** in THF (5.0 mL) was reduced with $LiAl(O\text{-}t\text{-}Bu)_3H$ (0.75 mL, 0.75 mmol) at 0 °C over 25 min to give a mixture (133 mg, 97% yield) of **250, 251, 254,** and **255**. The ratio of **250** to **251** was 26:1 by GC-MS, and **254**:**255** was 8:1 by both GC-MS and ^1H NMR spectroscopy.

Alcohol **254**: ^1H NMR ($CDCl_3$, discernible signals from the mixture) δ 6.49 (1H, s, H3), 4.40 (1H, m, H4), 2.34 (1H, dd, J = 11.1, 5.9 Hz, H8a), 1.78 (3H, s, 2-methyl), 0.80 (3H, s, 4a-methyl). ^{13}C NMR ($CDCl_3$) δ 200.5, 145.6, 134.9, 123.4, 122.4, 77.1, 49.1, 44.5, 43.2, 28.2, 19.0, 18.6, 15.3, 11.5. NOE data 4.40 (2.34, 7%). MS (from GC-MS) *m/z* 220 (M^+, 36), 205 (27), 202 (13), 187 (59), 177 (16), 163 (17), 159 (28), 138 (36), 119 (14), 107 (53), 105 (31), 100 (63), 98 (45), 91 (53), 79 (33), 77 (35), 71 (78), 70 (37), 69 (50), 67 (21), 65 (22), 55 (27), 53 (27), 43 (54), 41 (100).

Alcohol **255**: ^1H NMR ($CDCl_3$, discernible signals from the mixture) δ 5.84 (1H, q, J = 1.4 Hz, H2), 4.03 (1H, m, H4). MS (from GC-MS) *m/z* 220 (M^+, 14), 205 (32), 187 (36), 177 (17), 172 (24), 159 (100), 144 (12), 133 (55), 119 (20), 107 (29), 105 (26), 91 (43), 79 (23), 77 (25), 71 (25), 69 (27).

(4α,4aβ,5β,8β,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-2,8a-dimethyl-5,8-methanonaphthalen-1-one (256) and **(2ξ,4aα,5α,8α,8aα)-2,3,4a,5,8,8a-hexahydro-2,8a-dimethyl-5,8-methanonaphthalen-1-one (257)**

Enedione **238** (150 mg, 0.742 mmol) in dry THF (8.0 mL) was reduced with

$LiAl(O\text{-}t\text{-}Bu)_3H$ (0.96 mL, 0.96 mmol) at 0 °C for 1 h and then at rt for 2 h to give **256** (102 mg, 67% yield) and a 2.5:1 epimeric mixture **257** (15 mg, 10% yield).

Alcohol **256**: white solid: mp 53.0-54.5 °C. IR (CCl_4) 3435 (s, br), 1641 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.28 (1H, m, H3), 6.10 (1H, dd, *J* = 5.6, 2.8 Hz, H6), 5.82 (1H, dd, *J* = 5.6, 2.9 Hz, H7), 4.83 (1H, m, H4), 3.16 (1H, br s, H5), 2.89 (1H, br s, H8), 2.67 (1H, m, H4a), 2.13 (1H, br s, 4-hydroxy), 1.66 (3H, dd, *J* = 2.4, 1.4 Hz, 2-methyl), 1.57 (1H, d, *J* = 8.8 Hz, H9 *anti* to C6,C7 double bond), 1.45 (3H, s, 8a-methyl), 1.43 (1H, m, H9 *syn* to C6, C7 double bond). NOE data 4.83 (2.67, 5%), 2.67 (4.83, 6%; 1.57, 3%), 1.57 (2.67, 4%). ^{13}C NMR ($CDCl_3$) δ 203.8 (0, C1), 144.8 (0, C2), 144.8 (1, C3), 135.7 (1, C6), 135.4 (1, C7), 65.2 (1, C4), 56.6 (1, C8), 51.0 (0, C8a), 50.4 (1, C4a), 47.1 (2, C9), 45.8 (1, C5), 25.3 (3, 8a-methyl), 15.6 (3, 2-methyl). MS *m/z* 204 (M^+, 1), 139 (28), 138 (9), 121 (5), 66 (100). HRMS calcd. for $C_{13}H_{16}O_2$ 204.1149, found 204.1132.

The major isomer of **257**: ^1H NMR ($CDCl_3$, from the epimeric mixture) δ 6.30 (1H, dd, *J* = 5.7, 3.0 Hz), 6.04 (1H, dd, *J* = 5.7, 2.9 Hz), 3.24 (1H, m, H5), 3.08 (1H, m, H8), 2.88 (1H, m, H2), 2.80 (1H, dd, *J* = 3.8, 1.7 Hz, H4a), 2.54 (1H, overlapped, H3), 2.04 (1H, dd, *J* = 16.0, 14.2 Hz, H3), 1.61 (1H, d, *J* = 8.5 Hz, H9), 1.50 (1H, d, *J* = 8.5 Hz), 1.43 (3H, s, 8a-methyl), 1.01 (3H, d, *J* = 6.6 Hz, 2-methyl). NOE data 1.43 (3.08, 5%; 2.88, 4%; 2.80, 8%). ^{13}C NMR ($CDCl_3$) δ 213.5 (0), 210.4 (0), 140.5 (1), 134.3 (1), 60.8, 57.1, 51.5, 49.2, 46.4, 45.9, 39.4, 28.0, 14.1.

The minor isomer of **260**: ^1H NMR ($CDCl_3$, from the epimeric mixture) δ 6.19 (1H, dd, *J* = 5.7, 2.9 Hz), 6.11 (1H, dd, *J* = 5.7, 2.9 Hz), 3.38 (1H, m), 2.99 (1H, m), 2.75 (1H, d, *J* = 3.7 Hz, H4a), 2.55 (1H, overlapped, H3), 2.43 (1H, dd, *J* = 13.7, 4.9 Hz), 2.23

(1H, m, H2), 1.65-1.50 (2H, overlapped, H9), 1.52 (3H, s, 8a-methyl), 1.16 (3H, d, J = 7.0 Hz, H2). NOE data 1.52 (2.75, 8%). ^{13}C NMR ($CDCl_3$) δ 215.1 (0), 208.9 (0), 137.8 (1), 136.8 (1), 60.7, 55.7, 53.8, 46.5, 46.2, 45.0, 43.1, 27.9, 16.6.

(4α,4aβ,5β,8β,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-2,8a-dimethyl-5,8-ethano naphthalenone (258) and **(4α,4aα,5α,8α,8aα)-4,4a,5,8,8a-pentahydro-4-hydroxy-2,8a-dimethyl-5,8-ethano naphthalenone (259)**

Enedione **240** (106 mg, 0.490 mmol) in dry THF (5.0 mL) was reduced with $LiAl(O\text{-}t\text{-}Bu)_3H$ (0.69 mL, 0.69 mmol) at 0 °C for 1 h and then at rt for 2 h to give **258** and **259** as a chromatographically inseparable mixture (80 mg, 75% yield) with a ratio of 10:1 in favor of **258**.

Alcohol **258**: IR (neat) 3444 (s), 3044 (w), 1658 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.30 (1H, m, H3), 6.24 (1H, m, H6), 5.96 (1H, m, H7), 4.74 (1H, m, H4), 2.90 (1H, m, H5), 2.70 (1H, m, H8), 2.36 (1H, br s, 4-hydroxy), 2.09 (1H, d, J = 7.1 Hz, H4a), 1.78 (1H, m, H9 *anti* to C6, C7 double bond), 1.66 (3H, dd, J = 2.2, 1.5 Hz, 2-methyl), 1.56 (1H, m, H10 *anti* to C6, C7 double bond), 1.28 (3H, s, 8a-methyl), 1.22-1.18 (2H, m, H9, H10 *syn* to C6, C7 double bond). NOE data 4.74 (6.30, 3%; 2.09, 4%), 1.28 (4.74, 3%; 2.09, 7%; 1.78, 4%). ^{13}C NMR ($CDCl_3$) δ 204.0 (0, C1), 143.3 (1, C3), 137.5 (0, C2), 135.8 (1, C6), 131.4 (1, C7), 65.2 (1, C4), 50.2 (1, C4a), 49.9 (0, C8a), 41.4 (1, C8), 29.1 (2, C10), 29.0 (1, C5), 21.8 (3, 8a-methyl), 18.4 (2, C9), 15.6 (3, 2-methyl). MS *m/z* 218 (M^+, 2), 139 (11), 122 (14), 98 (24), 96 (14), 91 (18), 80 (100), 79 (19), 77 (17), 69 (14). HRMS calcd. for $C_{14}H_{18}O_2$ 218.1307, found 218.1318.

Alcohol **259**: ^{1}H NMR ($CDCl_3$, discernible signals from the mixture) δ 6.40 (1H, q, J = 1.4 Hz, H3), 6.33 (1H, partially overlapped), 6.09 (1H, t, J = 7.5 Hz), 4.00 (1H, m, H4). MS *m/z* (from GC-MS) 218 (3), 190 (13), 138 (27), 110 (29), 98 (45), 91 (26), 80 (100), 79 (49), 77 (27).

(4α,4aβ,5β,8β,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-3-methyl-5,8-methanonaphthalen-1-one (260) and **(4α,4aβ,5β,8β,8aβ)-4,4a,5,8,8a-pentahydro-4-hydroxy-2-methyl-5,8-methanonaphthalen-1-one (261)**

Enedione **237** (153 mg, 0.813 mmol) in dry THF (6.0 mL) was reduced with $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.06 mL, 1.06 mmol) at 0 °C for 30 min to give **260** (98 mg, 63% yield) and **261** (16 mg, 10% yield).

Alcohol **260**: white solid: mp 93.0-94.5 °C. IR (Nujol) 3380 (s), 1618 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.14 (1H, dd, J = 5.6, 2.9 Hz), 5.83 (1H, dd, J = 5.6, 2.9 Hz), 5.68 (1H, br s, H2), 4.66 (1H, m, H3), 3.39 (1H, m), 3.24 (1H, m), 3.04-3.01 (2H, m, H4a and H8a), 2.36 (1H, d, J = 6.6 Hz, 4-hydroxy), 1.96(3H, s, 3-methyl), 1.45 (1H, m, H9 *syn* to C6, C7 double bond), 1.34 (1H, m, H9 *anti* to C6, C7 double bond). NOE data 4.66 (3.04-3.01, 3%), 3.04-3.01 (4.66, 7%; 1.34, 5%). ^{13}C NMR ($CDCl_3$) δ 200.3 (0, C1), 161.9 (0, C3), 135.6 (1), 134.7 (1), 127.5 (1, C2), 68.2 (1, C4), 50.5 (1), 48.9 (2, C9), 48.6 (1), 45.9 (1), 41.0 (1), 20.4 (3, 3-methyl). MS *m/z* 190 (M^+, 2), 125 (28), 124 (36), 123 (12), 66 (100), 65 (20). HRMS calcd. for $C_{12}H_{14}O_2$ 190.0993, found 190.0999.

Alcohol **261**: colorless, viscous oil: ^{1}H NMR ($CDCl_3$) δ 6.27 (1H, m, H3), 6.16

(1H, dd, J = 5.6, 2.9 Hz), 5.78 (1H, dd, J = 5.6, 2.9 Hz), 4.76 (1H, m, H4), 3.38 (1H, m), 3.22 (1H, m), 3.06-2.99 (2H, m, H4a and H8a), 1.92 (3H, br s, 4-hydroxy), 1.66 (3H, m, 2-methyl), 1.44 (1H, m, H9 *syn* to C6, C7 double bond), 1.33 (1H, d, J = 8.5 Hz, H9 *anti* to C6, C7 double bond). NOE data 4.76 (6.27, 3%; 3.06-2.99, 2%), 3.06-2.99 (4.76, 4%; 1.33, 4%). ^{13}C NMR ($CDCl_3$) δ 201.0 (0, C1), 145.6 (1, C3), 136.5 (0, C2), 135.7 (1), 134.1 (1), 65.4 (1, C4), 51.2 (1), 48.9 (2, C9), 47.9 (1), 45.8 (1), 40.9 (1), 15.6 (3, 2-methyl).

(2ξ,4aα,8aα)-2,3,4a,5,8,8a-Hexahydro-2,6,7,8a-tetramethyl-1,4-naphthalenedione (264)

To a solution of enedione **225** (101 mg, 0.463 mmol) in dry THF (5.0 mL) was introduced L-Selectride (1.0 M in THF, 0.56 mL, 0.56 mmol) at -78 °C over 5 min. This was stirred at -78 °C for 1 h before it was quenched with 5% aqueous NaOH solution (1.0 mL), followed by the addition of 30% H_2O_2 solution (1.0 mL). The mixture was then warmed to rt, diluted with EtOAc (50 mL), and washed with 5% aqueous HCl (2 x 20 mL). The resulting organic solution was dried over anhydrous $MgSO_4$ and concentrated under vacuum to give a mixture of **244**, **262**, and **264** in a ratio of 1:2.5:1. Column chromatography (20% EtOAc/hexane) of the mixture provided **264** (23 mg, 22% yield) as a white solid: mp 46.5-47.5 °C. IR (CCl_4) 1713 (s), 1452 (m), 1167 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.04 (1H, m, H2), 2.85 (1H, m, H4a), 2.78 (1H, dd, J = 19.0, 7.0 Hz, H3), 2.58 (1H, d, J = 17.9 Hz, H5), 2.30 (1H, dd, J = 19.0, 13.5 Hz, H3), 2.03 (1H, br d, J = 17.9 Hz, H5), 1.89 (1H, d, J = 17.3 Hz, H8), 1.79 (1H, d, J = 17.3 Hz, H8), 1.65 (3H, s), 1.55

(3H, s), 1.23 (3H, s, 8a-methyl), 1.15 (3H, d, J = 6.5 Hz, 2-methyl). NOE data 1.23 (2.85, 3%). ^{13}C NMR ($CDCl_3$) δ 214.0 (0), 208.5 (0), 122.9 (0), 121.4 (0), 51.4 (1, C4a), 45.3 (0, C8a), 42.7 (2, C3), 39.6 (1, C2), 37.7 (2, C8), 27.2 (2, C5), 22.5 (3, 8a-methyl), 19.0 (3), 18.6 (3), 14.0 (3, 2-methyl). MS *m/z* 220 (M^+, 27), 205 (17), 187 (19), 177 (16), 176 (14), 160 (25), 159 (29), 149 (29), 148 (21), 147 (28), 146 (31), 135 (55), 133 (58), 122 (29), 121 (65), 120 (21), 119 (17), 107 (100), 105 (43), 91 (67), 79 (29), 77 (33). HRMS calcd. for $C_{14}H_{20}O_2$ 220.1463, found 220.1464.

General procedure for the reduction of cyclic enediones with $NaBH_4/CeCl_3$

To a solution of enediones (0.5-1.0 mmol) and $CeCl_3 \cdot 7H_2O$ (1.0 equivalent) enediones in methanol (5.0-10 mL) was added sodium borohydride (approximately 0.7 equivalents) at 0 °C over 3-5 min. The resulting mixture was stirred at the same temperature for another 2-5 min before it was quenched with dilute NH_4Cl solution (40 mL) and extracted with EtOAc (4 x 25 mL). The combined organic extracts were washed with water (2 x 25 mL), brine (25 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent and chromatography (when necessary) gave the products.

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-2,6,7,8a-tetramethylnaphthalen-1-one (262) and **(4α,4aα,8aα)-4,4a,5,8,8a-pentahydro-4-hydroxy-2,6,7,8a-tetramethylnaphthalen-1-one (263)**

Enedione **225** (177 mg, 0.811 mmol) in methanol (8.0 mL) was reduced with $NaBH_4$ (22.3 mg, 0.560 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (302 mg, 0.811 mmol) at 0

°C over 6 min to give **244**, **262**, and **263** in a ratio of 1:1.8:1, respectively. Partial separation of the mixture by column chromatography (35% EtOAc/hexane) provided small amounts of homogeneous samples of **262** and **263**. The total mass of the fractions containing **244**, **262**, and **263** after the column was 161 mg (90% yield)

Alcohol **262**: colorless crystals: mp 67.5-69.0 °C. IR (Nujol) 3404 (s), 1651 (s), 1060 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.40 (1H, d, J = 1.5 Hz, H3), 4.92 (1H, m, H4), 2.62 (1H, d, J = 17.1 Hz, H8), 2.42 (1H, m, H4a), 2.03 (1H, dd, J = 17.5, 5.6 Hz, H5), 1.92 (1H, dd, J = 17.5, 11.7 Hz, H5), 1.83 (1H, d, J = 7.2 Hz, 4-hydroxy), 1.79 (3H, apparent t, J = 1.5 Hz, 2-methyl), 1.72 (1H, d, J = 17.1 Hz, H8), 1.62 (3H, s), 1.56 (3H, s), 1.18 (3H, s, 8a-methyl). NOE data 4.92 (2.42, 6%; 1.18, 2%), 1.18 (4.92, 9%; 2.42, 5%). ^{13}C NMR ($CDCl_3$) δ 202.2 (0, C1), 142.4 (1, C3), 133.7 (0, C2), 124.3 (0), 123.2 (0), 67.7 (1, C4), 46.2 (1, C4a), 45.9 (0, C8a), 39.8 (2, C8), 29.2 (2, C5), 24.2 (3, 8a-methyl), 18.8 (3), 18.7 (3), 16.0 (3, 2-methyl). MS (from GC-MS) *m/z* 220 (M^+, 2), 202 (11), 187 (22), 174 (44), 172 (16), 159 (100), 138 (23), 121 (14), 107 (28), 105 (21), 98 (18), 91 (34), 79 (21), 77 (26), 69 (28).

Alcohol **263**: colorless, viscous oil: IR (neat) 3434 (s), 1658 (s), 1440 (m), 1026 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.59 (1H, s, H3), 4.26 (1H, m, H4), 2.29 (1H, d, J = 17.0 Hz, H5), 2.19-2.09 (3H, m, H5, H8, and 4-hydroxy), 1.91 (1H, m, H4a), 1.78 (1H, apparent t, J = 1.5 Hz, 2-methyl), 1.65 (3H, s), 1.61 (3H, s), 1.51 (1H, d, J = 17.2 Hz, H8), 1.16 (3H, s, 8a-methyl). ^{13}C NMR ($CDCl_3$) δ 203.4 (0, C1), 146.1 (1, C3), 132.7 (0, C2), 123.9 (0), 122.0 (0), 67.4 (1, C4), 47.7 (1, C4a), 44.5 (0, C8a), 37.5 (2, C8), 29.8 (2, C5), 20.0 (3, 8a-methyl), 19.1 (3), 18.9 (3), 16.1 (3, 2-methyl). MS *m/z* 220 (M^+, 7), 175

(6), 159 (11), 138 (100), 121 (14), 107 (25), 105 (18), 98 (23), 91 (30), 79 (16), 77 (20), 69 (24). HRMS calcd. for $C_{14}H_{20}O_2$ 220.1463, found 220.1476.

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-2,6 and 7,8a-tetramethylnaphthalen-1-one (271) and **(4α,4aα,8aα)-4,4a,5,8,8a-pentahydro-4-hydroxy-2,6 or 7,8a-tetramethylnaphthalen-1-one (272)**

Enedione **231** (1:1 isomeric mixture) (138 mg, 0.676 mmol) in methanol (5.0 mL) was reduced with $NaBH_4$ (29.0 mg, 0.728 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (280 mg, 0.744 mmol) at 0 °C over 10 min to give **245**, **271**, and **272** as mixture (113 mg, 81% yield) in a ratio of 1.2:1.7:1, respectively.

Clearly discernible ^1H NMR ($CDCl_3$) signals for **271**: δ 6.41 (1H, br s, H3), 4.94 (1H, narrow m, H4).

Clearly discernible ^1H NMR ($CDCl_3$) signals for **272**: δ 6.59 (1H, br s, H3), 4.30 (1H, narrow m, H4).

(4α,4aβ,8aβ)-4,4a,5,8,8a-Pentahydro-4-hydroxy-2,6,8,8,8a-pentamethylnaphthalen-1-one (250), **(4α,4aα,8aα)-4,4a,5,8,8a-pentahydro-4-hydroxy-2,6,8,8,8a-pentamethylnaphthalen-1-one (273)** and **(2ξ,4ξ,4aα,8aα)-1,4,4a,5,8,8a-hexahydro-2,6,8,8,8a-pentamethyl-1,4-naphthalenediol (274)**

Enedione **229** (190 mg, 0.818 mmol) in methanol (8.0 mL) was reduced with $NaBH_4$ (40.0 mg, 1.04 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (308 mg, 0.818 mmol) at 0 °C over 45 min to give **249**, **273**, and **274** in a ratio of 4:1.4:1. Partial separation of the

mixture by column chromatography (25% EtOAc/hexane) provided small amounts of homogeneous samples of **249** and **273**. The total mass of the fractions containing **249**, **273**, and **274** after the column was 174 mg (91% yield).

Alcohol **249**: colorless oil: IR (neat) 3454 (s, br), 3016 (w), 1682 (s), 1441 (m), 1024 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.31 (1H, s, H3), 5.25 (1H, s, H7), 4.80 (1H, m, H4), 2.75 (1H, m, H4a), 2.08 (1H, dd, J = 18.1, 6.6 Hz, H5β), 1.89 (1H, dd, J = 18.1, 9.5 Hz, H5α), 1.76 (3H, s, 2-methyl), 1.59 (3H, s, 6-methyl), 1.34 (3H, s, 8-methyl *anti* to 8a-methyl), 1.23 (3H, s, 8a-methyl), 0.94 (3H, s, 8-methyl *syn* to 8a-methyl). NOE data 4.80 (6.31, 5%; 2.75, 6%), 2.75 (4.80, 5%; 2.08, 3%), 1.23 (4.80, 11%; 2.75, 3%), 0.94 (2.75, 12%). ^{13}C NMR ($CDCl_3$) δ 203.2 (0, C1), 140.0 (1, C3), 135.0 (0), 132.7 (1, C7), 128.4 (0), 68.1 (1, C4), 50.5 (0, C8a), 43.7 (1, C4a), 37.4 (0, C8), 28.1 (2, C5), 28.0 (3, 8-methyl *syn* to 8a-methyl), 25.1 (3, 8-methyl *anti* to 8a-methyl), 23.3 (3, 6-methyl), 17.2 (3, 8a-methyl), 16.4 (3, 2-methyl). MS *m/z* 234 (M^+, 10), 201 (5), 173 (6), 121 (33), 98 (12), 96 (100), 81 (15), 69 (5). HRMS calcd. for $C_{15}H_{22}O_2$ 234.1620, found 234.1605.

Alcohol **273**: white solid: mp 89.0-91.0 °C. IR (CCl_4) 3465 (s, br), 1664 (s), 1448 (m), 1374 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.60 (1H, s, H3), 5.06 (1H, s, H7), 4.32 (1H, m, H4), 2.28 (1H, d, J = 17.4 Hz, H5 *anti* to H4a), 2.14 (1H, dd, J = 17.4, 5.6 Hz, H5 *syn* to H4a), 2.06 (1H, dd, J = 9.7, 6.2 Hz, H4a), 1.95 (1H, br s, 4-hydroxy), 1.80 (3H, s, 2-methyl), 1.69 (3H, s, 6-methyl), 1.18 (3H, s, 8a-methyl), 0.91 (3H, s, 8-methyl *syn* to 8a-methyl), 0.79 (3H, s, 8-methyl *anti* to 8a-methyl). NOE data 4.32 (6.60, 4%; 0.79, 2%), 1.18 (2.14, 2%; 2.06, 6%), 0.91 (5.06, 8%; 1.18, 2%), 0.79 (5.06, 5%; 4.32, 11%). ^{13}C NMR ($CDCl_3$) δ 202.6 (0, C1), 145.9 (1, C3), 136.7 (0), 131.5 (1, C7), 127.2 (0, C2), 68.0

(1, C4), 50.2 (1, C4a), 48.4 (0, C8a), 36.3 (0, C8), 28.9 (3, 8-methyl *anti* to 8a-methyl), 27.8 (2, C5), 26.5 (3, 8-methyl *syn* to 8a-methyl), 23.7 (3, 6-methyl), 21.6 (3, 8a-methyl), 16.2 (3, 2-methyl). MS *m/z* 234 (M^+, 0.7), 138 (82), 121 (41), 98 (12), 96 (100), 81 (26), 69 (8). HRMS calcd. for $C_{15}H_{22}O_2$ 234.1620, found 234.1609.

Discernible ^1H NMR ($CDCl_3$) data for **274** from the crude mixture: δ 5.36 (1H, s), 5.34 (1H, s), 4.44 (1H, br s), 3.48 (1H, s), 1.82 (3H, s), 1.66 (3H, s), 1.16 (3H, s), 0.95 (3H, s), 0.84 (3H, s).

(4α,4aβ,7aα,10α,10aα,10bβ,10cβ)-6-((*tert*-Butyldimethylsilyl)oxy)-4,4a,5,7,7a,10,10a,10b,10c-nonahydro-4-hydroxy-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,9-dione (275) and **(4α,4aα,7aβ,10β,10aβ,10bα,10cα)-6-((*tert*-butyldimethylsilyl)oxy)-4,4a,5,7,7a,10,10a,10b,10c-nonahydro-4-hydroxy-2,10,10c-trimethylbenz[6,7]indeno[2,1-*b*]furan-1,9-dione (276)**

Enedione **56** (246 mg, 0.571 mmol) in methanol (10 mL) was reduced with $NaBH_4$ (15.9 mg, 0.399 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (215 mg, 0.571 mmol) at rt over 8 min to give **275** (128 mg, 52% yield) and **276** (90 mg, 36% yield).

Compound **275**: white solid: mp 148.5-150.0 °C. IR (CCl_4) 3463 (s), 1769 (s), 1677 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.38 (1H, s, H3), 5.10 (1H, m, H7a), 4.96 (1H, m, H4), 3.31 (1H, dd, J = 13.1, 6.0 Hz, H10a), 2.99 (1H, ddd, J = 16.8, 6.8, 1.8 Hz, H7α), 2.54 (1H, m, H4a), 2.44-2.35 (2H, m, H7β and H10), 2.30-2.22 (2H, m, H5 and H10b), 2.03-1.96 (2H, m, 4-hydroxy and H5), 1.75 (3H, s, 2-methyl), 1.31 (3H, d, J = 7.3 Hz, 10-

methyl), 1.30 (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 4.96 (6.38, 7%; 2.54, 7%), 2.54 (4.96, 8%), 1.30 (4.96, 15%; 2.54, 5%). ^{13}C NMR ($CDCl_3$) δ 202.0 (0, C1), 180.2 (0, C9), 142.1 (1, C3), 140.8 (0), 133.9 (0), 116.6 (0, C6a), 82.6 (1, C7a), 67.6 (1, C4), 54.4 (1, C10b), 49.4 (1, C4a), 49.0 (1, C10a), 48.8 (0, C10c), 43.6 (1, C10), 34.5 (2, C7), 28.6 (2, C5), 25.6 (3, $SiC(CH_3)_3$), 21.8 (3), 18.0 (3, $SiC(CH_3)_3$), 15.8 (3, 2-methyl), 15.1 (3), -3.8 (3, $SiCH_3$), -4.0 (3, $SiCH_3$). MS *m/z* 432 (M^+, 22), 414 (14), 238 (27), 237 (22), 209 (30), 181 (14), 165 (17), 135 (15), 131 (28), 130 (34), 121 (25), 117 (24), 91 (12), 77 (12), 75 (100), 73 (91). HRMS calcd. for $C_{24}H_{36}O_5Si$ 432.2330, found 432.2338.

Compound **276**: white solid: mp 150.0-151.5 °C. IR (CCl_4) 3456 (s), 1770 (s), 1667 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.54 (1H, s, H3), 4.98 (1H, m, H7a), 4.24 (1H, m, H4), 3.05 (1H, dd, J = 16.4, 7.2 Hz, H7β), 2.55 (1H, m, H10a), 2.39-2.01 (7H, m), 1.81 (3H, s, 2-methyl), 1.43 (3H, s, 10c-methyl), 1.20 (3H, d, J = 7.5 Hz, 10-methyl), 0.92 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$). NOE data 4.24 (6.54, 8%; 2.55, 7%), 2.55 (4.98, 10%; 4.24, 7%). ^{13}C NMR ($CDCl_3$) δ 202.0 (0, C1), 180.0 (0, C9), 142.3 (1, C3), 140.0 (0), 134.9 (0), 116.9 (0, C6a), 81.7 (1, C7a), 67.2 (1, C4), 52.0 (1), 49.9 (1, C10a), 48.5 (1), 45.9 (0, C10c), 42.2 (1), 33.3 (2, C7), 30.9 (2, C5), 25.6 (3, $SiC(CH_3)_3$), 25.5 (3, 10c-methyl), 16.1 (3), 16.0 (3), -3.9 (3, $SiCH_3$), -4.1 (3, $SiCH_3$). MS *m/z* 432 (M^+, 0.5), 334 (18), 295 (16), 252 (9), 165 (5), 138 (100), 130 (6), 117 (6), 91 (6), 75 (40), 73 (44).

Reduction of enedione 235 with $NaBH_4/CeCl_3$

Enedione **235** (153 mg, 0.602 mmol) in methanol (5.0 mL) was reduced with $NaBH_4$ (16.8 mg, 0.422 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (224 mg, 0.602 mmol) at 0 °C over 5 min to give **246** and an unidentified isomer as a mixture (149 mg, 97% yield) with a ratio of 20:1 favoring **246**.

Reduction of enedione 233 with $NaBH_4/CeCl_3$

Enedione **233** (188 mg, 0.861 mmol) in methanol (8.0 mL) was reduced with $NaBH_4$ (24.0 mg, 0.603 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (321 mg, 0.861 mmol) at 0 °C over 5 min to give **250** (149 mg, 97% yield) as the single product.

Reduction of enedione 242 with $NaBH_4/CeCl_3$

A 55:45 epimeric mixture (105 mg, 0.481 mmol) of **233** and **242** in methanol (4 mL) was reduced with $NaBH_4$ (11.3 mg, 0.284 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (179 mg, 0.481 mmol) at 0 °C over 5 min to give a 55:45 diastereoisomeric mixture (104 mg, 98% yield) of **250** and **254** as the only products.

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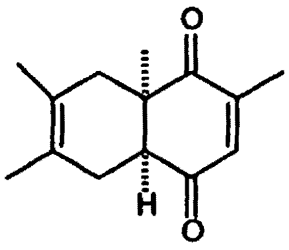
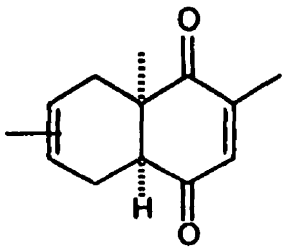
Appendix: Selected ^{1}H NMR Spectra

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



225



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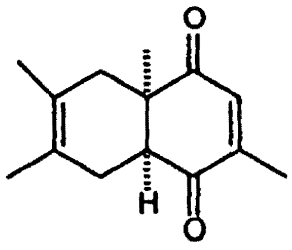

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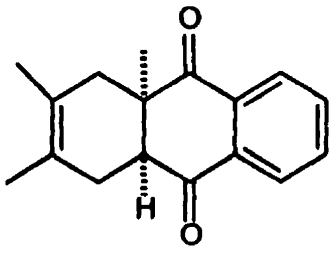

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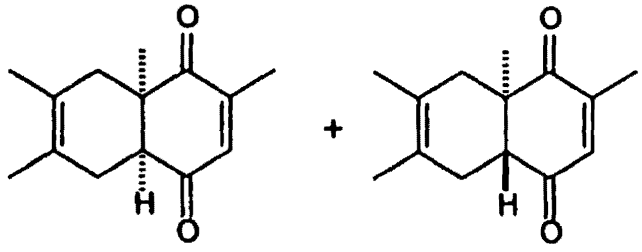

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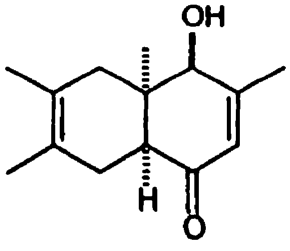

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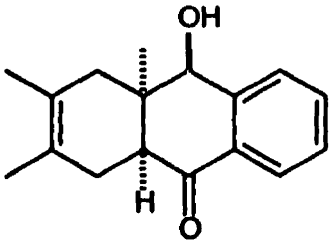

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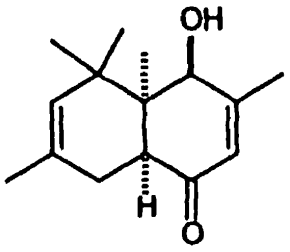

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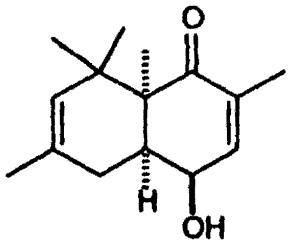

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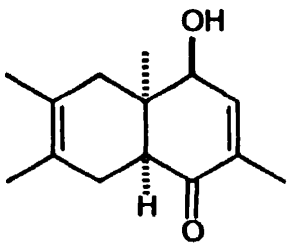

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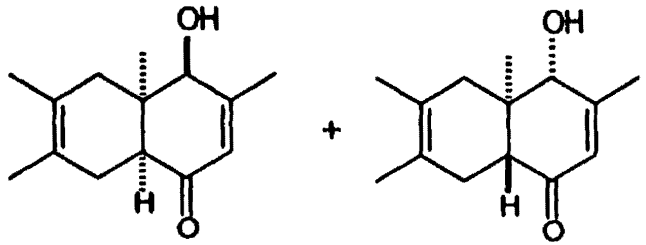

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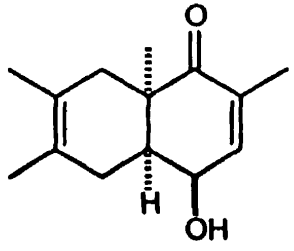
252



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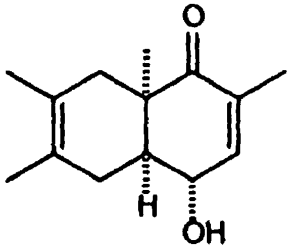

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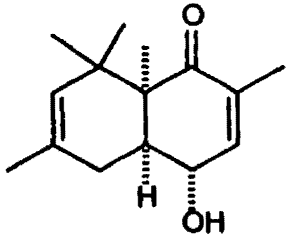

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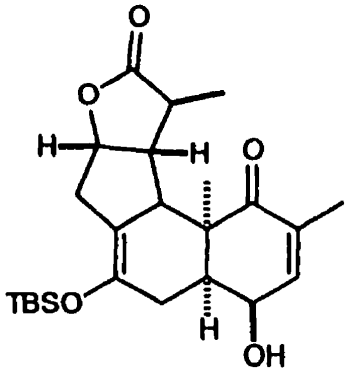

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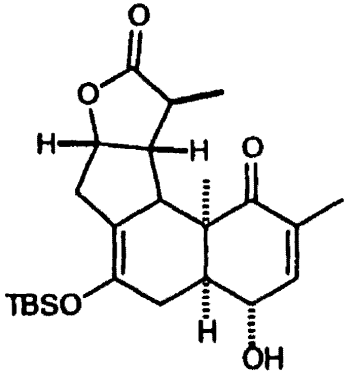

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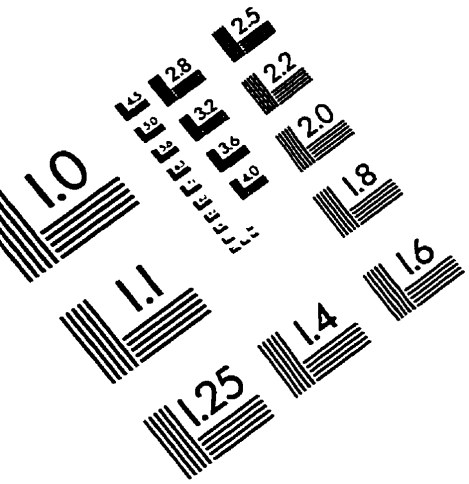
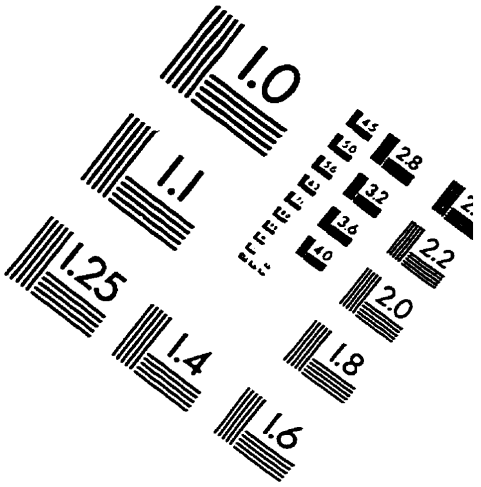
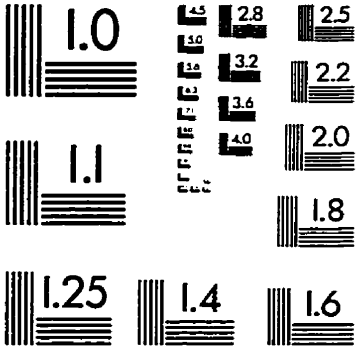
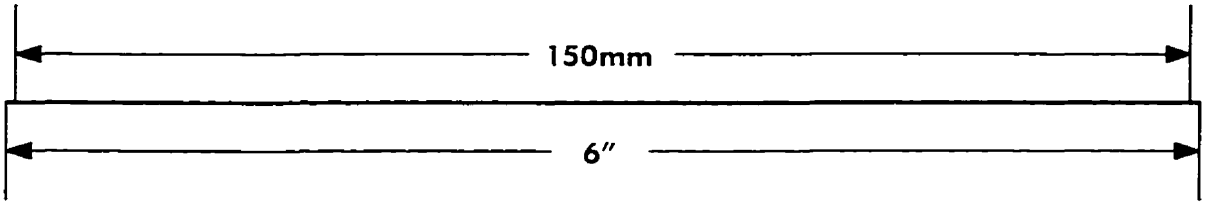
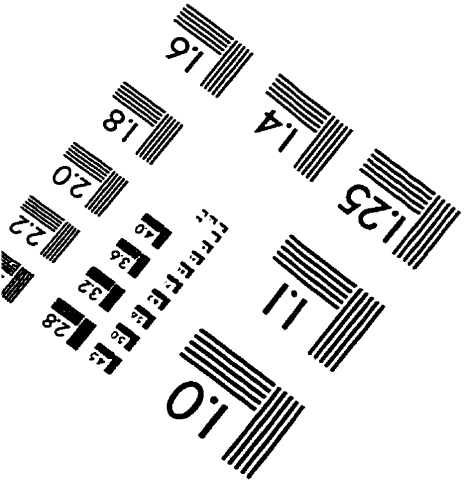
IMAGE EVALUATION TEST TARGET (QA-3)

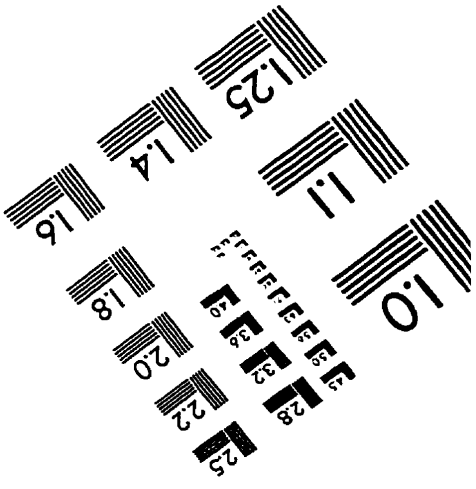












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