Total Synthesis of (−)-Grayanotoxin

by

Toshiyuki Kan

Dissertation

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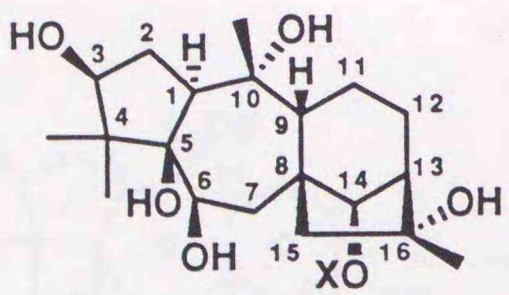
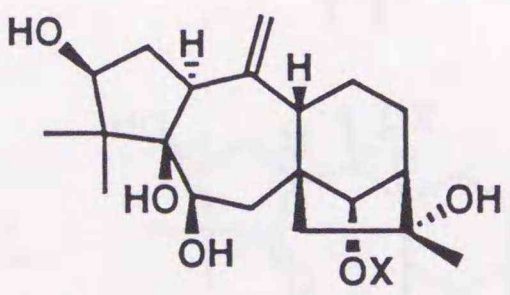
Contents

Chapter 1. Introduction

Grayanotoxins such as grayanotoxin I, II, III, IV (**1**, **2**, **3**, **4**), isolated as toxic principles from leaves of various plants of family *Ericaceae*,[1] have been shown to increase specifically membrane permeability to sodium cation in sodium-dependent excitable membranes resulting in a large depolarization.[2] Since the increase in resting sodium permeability caused by these toxins are due to modification of sodium channel, grayanotoxins are potential candidates for a pharmacological tool in examining the sodium channel. These diterpenes are characterized by the A-*nor*-B-*homo*-kaurane skeleton, unique tetracyclic carbon framework, and by the dense arrangement of hydroxyl groups. Their remarkable physiological activity and unique structure distinguish these molecules as very interesting targets for total synthesis. However, only one multi-step total synthesis of grayanotoxin II (**2**) has been hitherto reported.[3] The author started the program directed toward total synthesis of grayanotoxins with an aim to explore the general and flexible synthetic route to these novel diterpens. Eventually, the first total synthesis of grayanotoxin III (**3**) in an optically active form has been accomplished.

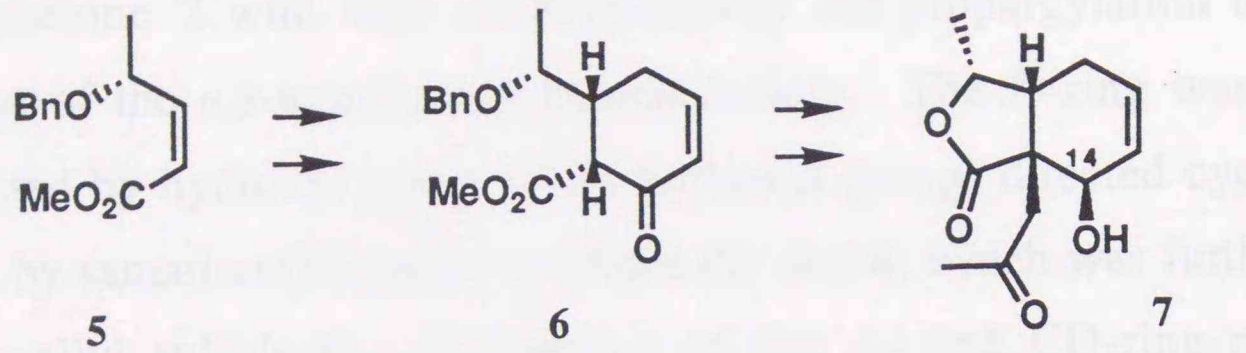


Grayanotoxin I (**1**) X=Ac
Grayanotoxin III (**3**) X=H

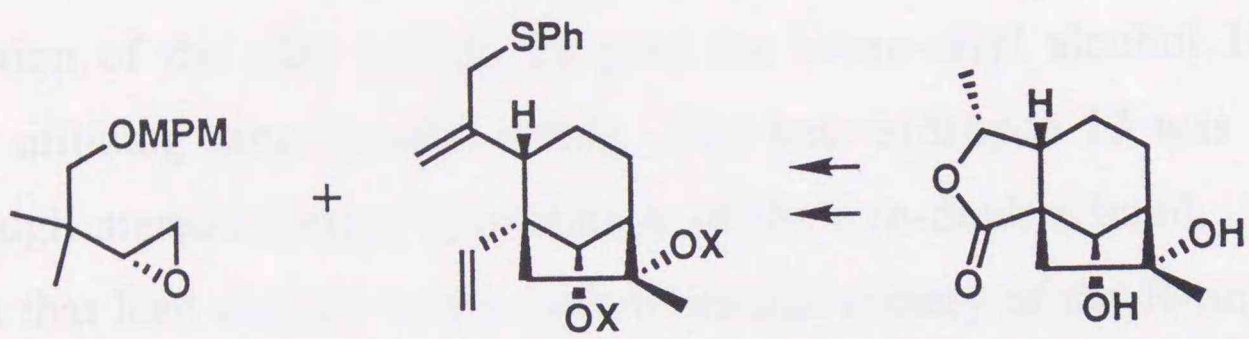


Grayanotoxin II (**2**) X=H
Grayanotoxin IV (**4**) X=Ac

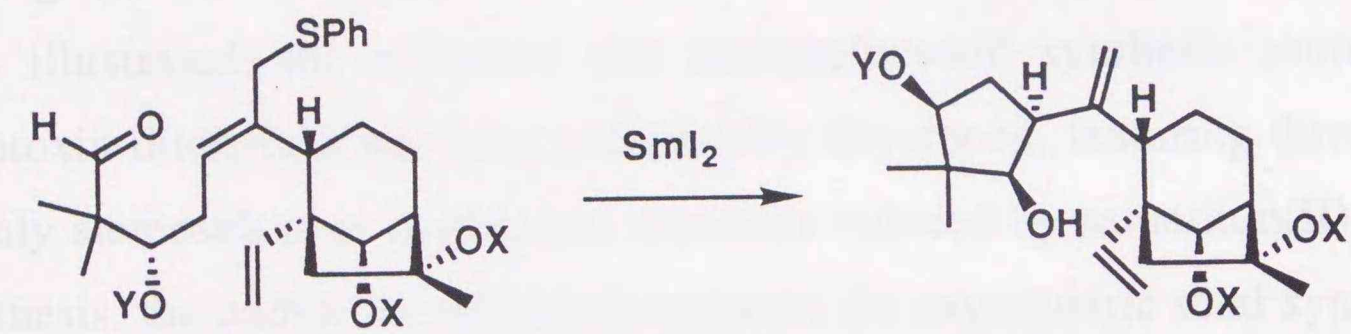
The synthetic route is outlined in **Scheme 1**. Diels-Alder reaction of the optically pure α,β-unsaturated ester **5**, prepared from ethyl (*S*)-lactate, occurred in a completely diastereoface-selective manner to achieve the formation of the C-ring. The β-keto ester **6** thus obtained, was further converted into the γ-



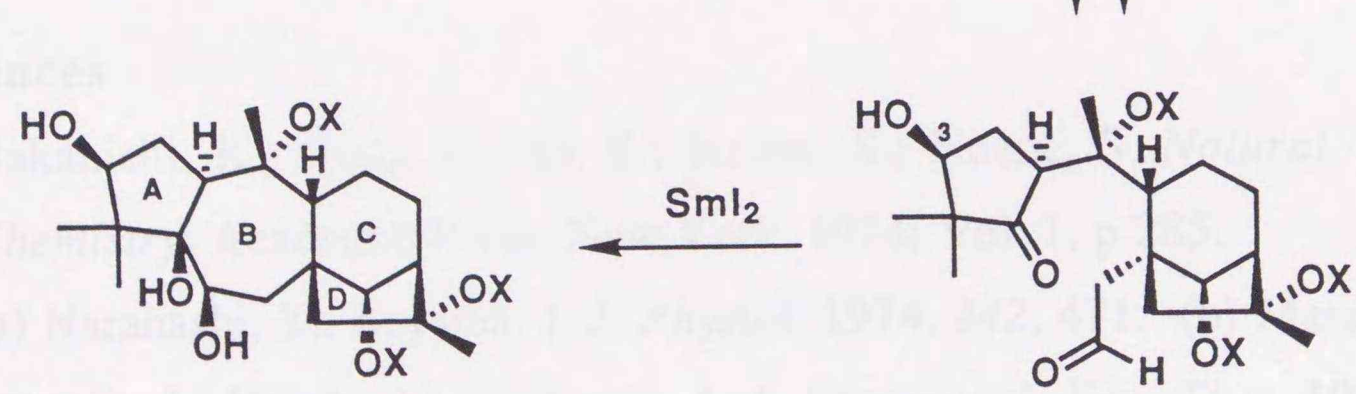
5 6 7



10 9 X=MOM 8



11 X=MOM, Y=Si^{t}BuMe$_2$ 12



14 X=MOM
3 X=H

13 X=MOM

Scheme 1

hydroxyketone **7** with high stereoselectivity *via* propargylation of **6** and 1,2-reduction of the α,β-unsaturated ketone moiety. The D-ring was exclusively constructed by hydroxyl group (C-14 hydroxyl group) directed cyclization of **7** induced by samarium(II) iodide to afford the diol **8**, which was further converted into the allyl sulfide **9**. Connection of the A- and CD-ring moieties was performed by alkylation of the anion generated from **9**, with the optically pure (*R*)-epoxide **10**, followed by allylic rearrangement of the phenyl sulfide group. Cyclization of the allyl sulfide **11** gave the *homo*-allyl alcohol **12** as the sole product utilizing samarium(II) iodide. The keto aldehyde **13** was derived from **12** through stereoselective epoxidation of the *exo*-double bond. Ring closure reaction that lead directly to the vicinal *cis*-diol moiety of the B-ring effected by samarium(II) iodide promoted pinacol coupling reaction of **13** stereocontrolled by the C-3 hydroxyl group, giving the triol **14** exclusively. Deprotection of **14** afforded grayanotoxin III (**3**).

As illustrated, the effective and straightforward synthetic route to the grayanotoxin diterpenes has been successfully developed, featuring three sort of the highly stereoselective cyclization reactions induced by samarium(II) iodide.[4] In this thesis, the author would like to mention the asymmetric total synthesis of **3**.

References

(1) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. *Natural Product Chemistry*; Academic Press: New York, 1974; Vol. 1, p 285.

(2) (a) Narahashi, T.; Seyama, I. *J. Physiol.* **1974**, *242*, 471. (b) Masutani, T.; Seyama, I.; Narahashi, T.; Iwasa, J. *J. Pharmacol. Exp. Ther.* **1981**, *217*, 812. (c) Seyama, I.; Narahashi, T. *J. Pharmacol. Exp. Ther.* **1981**, *219*, 614.

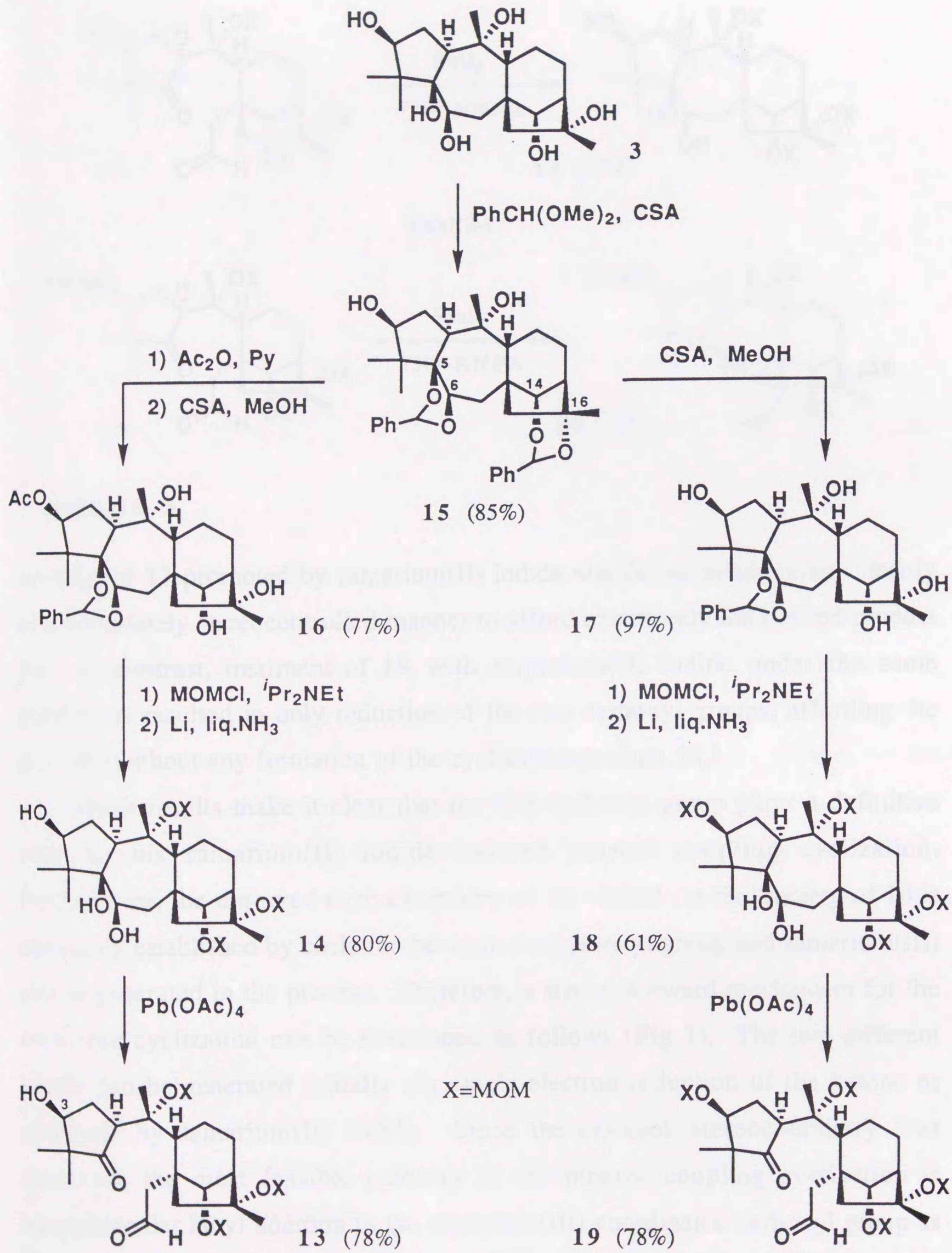
(3) (a) Hamanaka, N.; Matsumoto, T. *Tetrahedron Lett.* **1972**, 3087. (b) Gasa, S.; Hamanaka, N.; Matsunaga, S.; Okuno, T.; Takeda, N.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 553.

(4) (a) Inanaga, J. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 200. (b) Kagan, H.B. *New J. Chem.* **1990**, *14*, 453. (c) Molander, G.A. *Chem. Rev.* **1992**, *92*, 29.

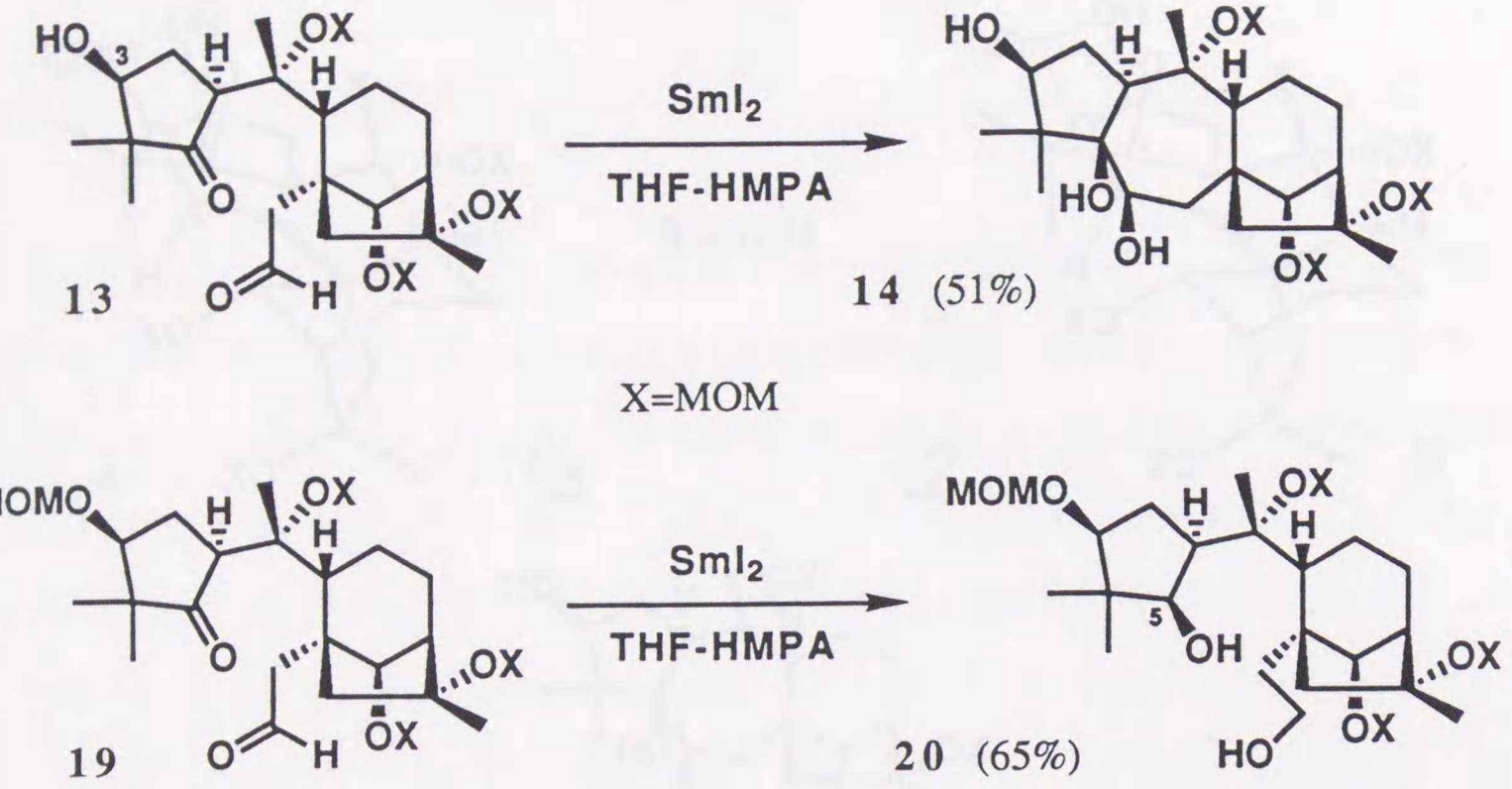
Chapter 2. Construction of the B-ring

At first, formation of the B-ring of grayanotoxins *via* pinacol coupling cyclization was attempted using the degradation products prepared from natural grayanotoxins. Two sort of the keto aldehydes **13** and **19**, which possess β-hydroxyl and β-methoxymethoxyl groups, respectively, at the C-3 position, were prepared from grayanotoxin III (**3**) to investigate the influence of the C-3 oxygen functionality to pathway of reductive coupling cyclization (**Scheme 2**). After selective benzylidenation of **3** with benzaldehyde dimethyl acetal, successive protection of the secondary hydroxyl group of the resulting di-benzylidene acetal **15**[1] in a form of acetate followed by selective cleavage of the 1,3-dioxane ring by mild acidic hydrolysis afforded the triol **16**. Protection of the three hydroxyl groups of **16** in a form of methoxymethyl ether and simultaneous removal of the C-3 acetyl and C-5,6 benzylidene groups under reductive conditions converted **16** into the triol **14**. On the other hand, the di-benzylidene acetal **15** was derived to the diol **18** by the same sequences of (1) selective removal of the C-14,16 benzylidene group, (2) protection of the four hydroxyl groups of the tetraol **17** as methoxymethyl ether, and (3) reductive cleavage of the 1,3-dioxolane ring. Oxidative cleavage of the vicinal diol parts of **14** and **18** readily produced the pinacol coupling substrates **13** and **19**, respectively.

For stereoselective formation of the 7-membered ring, reductive coupling reactions of **13** and **19** meditated by low valent transition metals were examined. Titanium induced carbonyl coupling reactions, explored by McMurry *et al.*,[2] were initially adopted to the cyclization of **13** and **19**, revealing that the starting materials were decomposed during the reactions because of their instability under the reaction conditions. Thus, samarium(II) iodide, which has recently been utilized to generate ketyl radicals from aldehydes or ketones under extremely mild conditions,[3] was employed (**Scheme 3**). Intramolecular pinacol coupling


3
PhCH(OMe)2, CSA
1) Ac2O, Py
2) CSA, MeOH
CSA, MeOH
15 (85%)
16 (77%)
17 (97%)
1) MOMCl, iPr2NEt
2) Li, liq.NH3
1) MOMCl, iPr2NEt
2) Li, liq.NH3
14 (80%)
18 (61%)
Pb(OAc)4
Pb(OAc)4
X=MOM
13 (78%)
19 (78%)

Scheme 2



Scheme 3

reaction of **13** promoted by samarium(II) iodide was found to take place cleanly in a completely stereocontrolled manner to afford exclusively the desired product **14**. In contrast, treatment of **19** with samarium(II) iodide under the same conditions resulted in only reduction of the two carbonyl groups, affording the diol **20**[4] without any formation of the cyclization product **18**.[5]

These results make it clear that the C-3 hydroxyl group plays a definitive role in this samarium(II) iodide induced pinacol coupling cyclization. Furthermore, the observed stereochemistry of the vicinal *cis*-diol moiety of **14** is obviously established by chelation between the hydroxyl group and samarium(III) cation generated in the process. Therefore, a straightforward mechanism for the reductive cyclization can be envisioned as follows (**Fig 1**). The two different ketyls can be generated initially *via* single-electron reduction of the ketone or aldehyde by samarium(II) iodide. Since the *cis*-diol stereochemistry was observed, the most feasible pathway of the pinacol coupling cyclization is intramolecular ketyl addition to the samarium(III)-coordinated carbonyl group as pointed out by Corey[6] and Molander.[7] Thus, in either of the resulting ketyl radicals, chelation of the samarium(III) cations attached to these intermediates

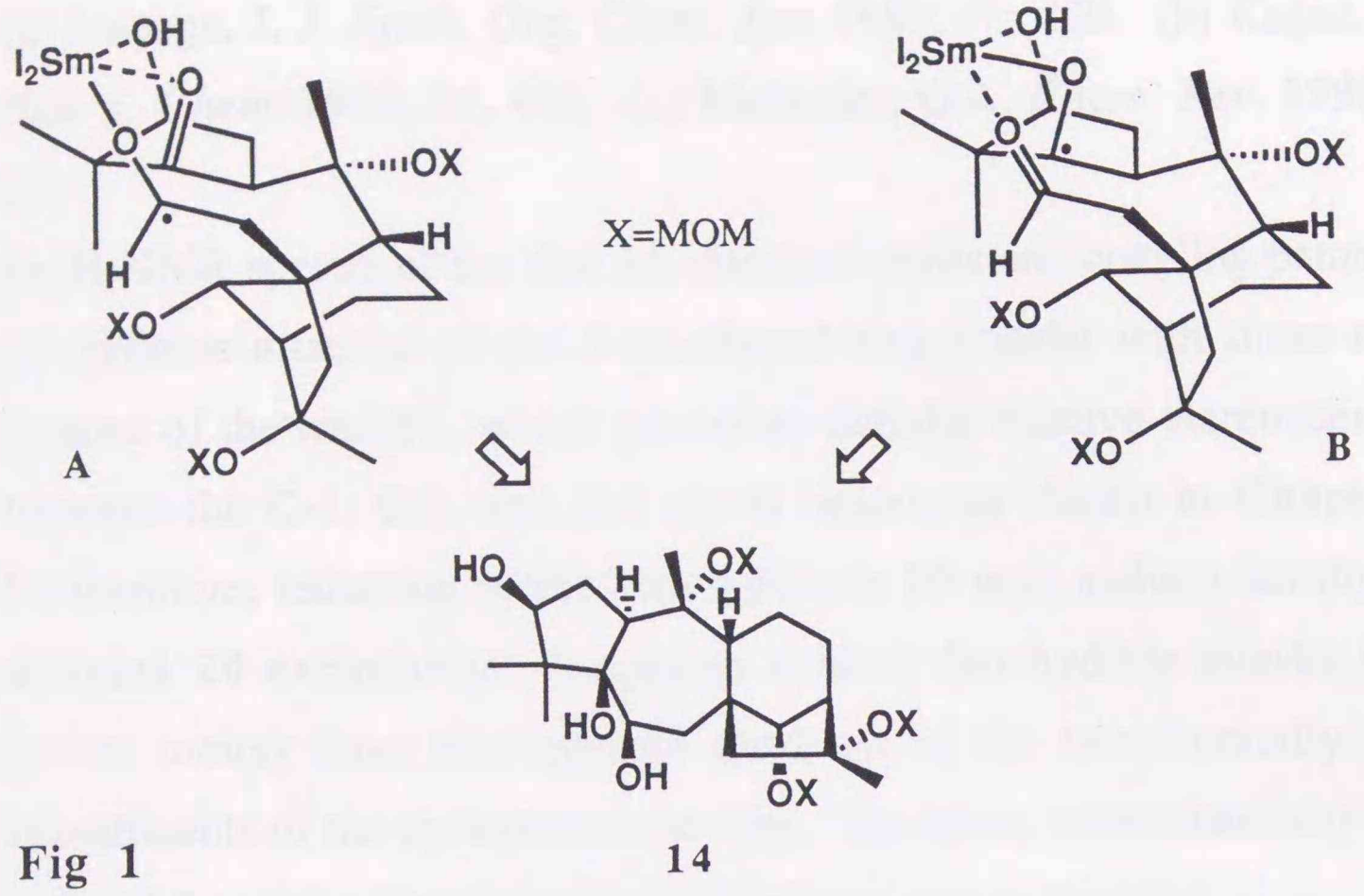


Fig 1

with the hydroxyl groups constructs the cyclic ketyls, which add through the transition states **A** and **B** to the unreduced aldehyde or ketone, respectively. This hydroxyl group directed cyclization using samarium(II) iodide provides an efficient entry into a powerful method of stereocontrol over various types of reductive coupling reactions promoted by samarium(II) iodide. Indeed, in the case of construction of the D-ring, stereochemical course of the intramolecular ketone-olefin coupling reaction mediated by samarium(II) iodide was also completely stereocontrolled by chelation of the samarium(III) cation with the hydroxyl group incorporated within the starting material as described in **Chapter 4.**

References and Notes

(1) The di-benzylidene acetal **15** turned out to consist of a single isomer with regard to the two benzylic positions. Stereochemistry of the phenyl groups has not been determined.

(2) (a) McMurry, J.E. *Chem. Rev.* **1989**, *89*, 1513. (b) McMurry, J.E.; Dushin, R.G. *J. Am. Chem. Soc.* **1990**, *112*, 6942.

(3) (a) Inanaga, J. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 200. (b) Kagan, H.B. *New J. Chem.* **1990**, *14*, 453. (c) Molander, G.A. *Chem. Rev.* **1992**, *92*, 29.

(4) In ^{1}H-NMR spectra of the diol **20**, chemical shifts and coupling patterns of the protons attached to the 5-membered ring consist with those of the protons of the triol **86**, which possesses definite relative stereochemistry between the C-1, C-3, and C-5 chiral centers as shown in **Chapter 6**. Furthermore, reduction of the keto aldehyde **19** with sodium borohydride afforded **20** exclusively. It appears evident that hydride attacks to the ketone moiety from the opposite direction of the two sterically bulky subsutituents of the cyclopentanone ring. Therefore, stereochemistry of **20** at the C-5 position was determined unambiguously as depicted.

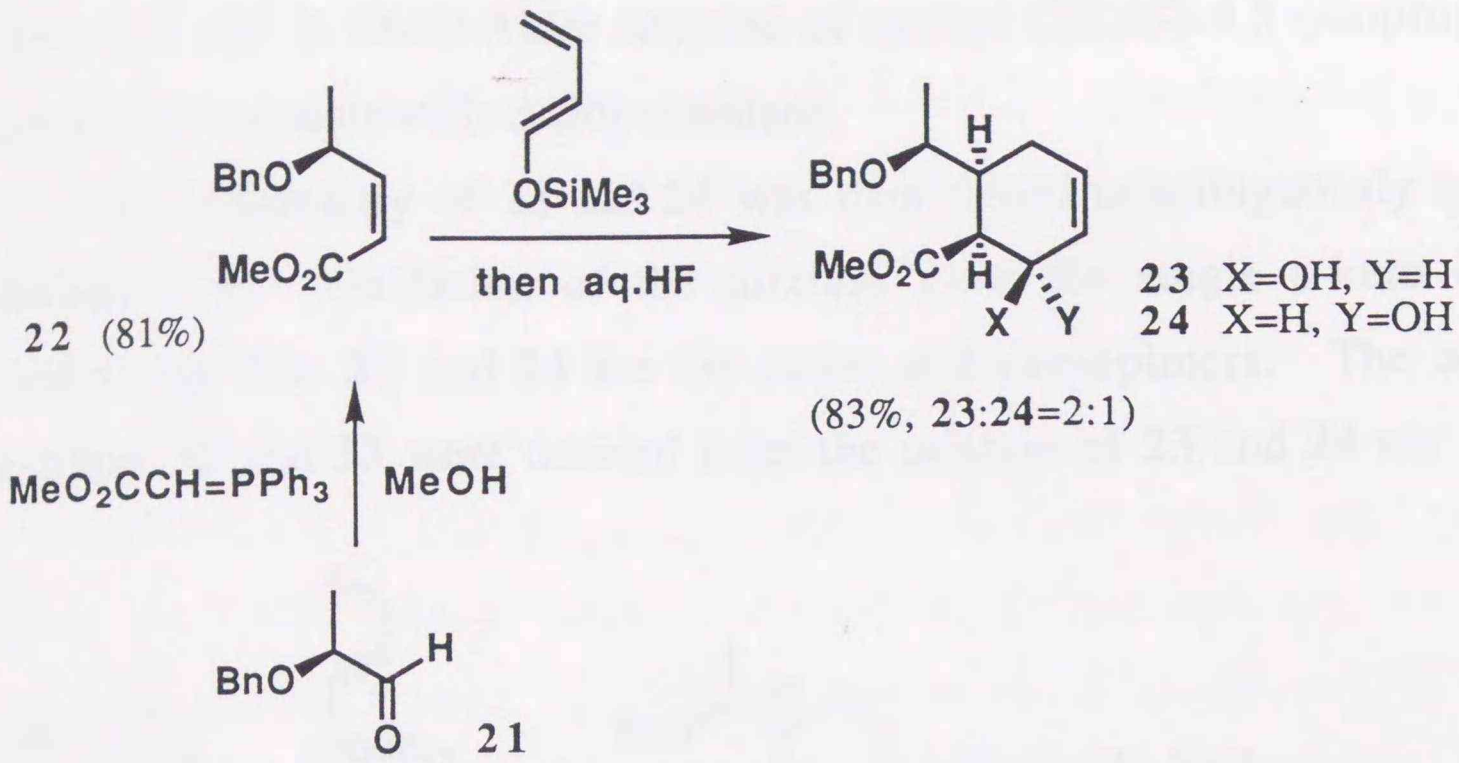
(5) Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391.

(6) Corey, E.J.; Danheiser, R.L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.

(7) Molander, G.A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.

Chapter 3. Construction of the C-ring

From retrosynthetic perspective, formation of the C-ring of grayanotoxins by diastereoface-selective Diels-Alder reaction was anticipated to hold promise as one of the most convenient synthetic route. After preliminary experiments,[1] it was found that Diels-Alder reaction of acyclic methyl (Z)-4-benzyloxy-2-butenoate carrying the chiral center at the allylic position occurred with high diastereofacial selectivity and furthermore, the cycloadducts thus obtained, were quite suitable for the formation of the CD-ring system of grayanotoxins as mentioned in **Chapter 4**. As shown in **Scheme 4**, and methyl (2*Z*,4*S*)-4-benzyloxy-2-butenoate (**22**) and methyl (2*E*,4*S*)-4-benzyloxy-2-butenoate (**25**), the Diels-Alder dienopiles, were synthesized readily through stereoselective olefination of (*S*)-2-benzyloxypropionaldehyde (**21**), which was prepared from ethyl (*S*)-lactate according to the method explored by Terashima *et al.*[2] Wittig reactions of **21** with methyl triphenylphosphoranylideneacetate yielded **22** and **25** in the ratios of 10:1 and 1:5, carrying out the reactions in methanol[3] or toluene, respectively. Purification of the major isomers of the mixtures by silica gel chromatography afforded the pure samples of **22** and **25**. Diels-Alder reaction of **22** with 1-(trimethylsilyloxy)-1,3-butadiene took place in a completely diastereoface-selective manner to give the epimeric mixture of **23** and **24** (2:1).[4] On the other hand, **25** gave the mixture containing the four cycloadducts **26–29** (4:1:1:1) by performing the reaction under the same conditions. The notable diastereoface-selectivity of the Diels-Alder reaction of **22** can be rationalized as illustrated in **Fig 2**. Thus, considering dipole-dipole and non-bonded steric interactions, the plausible transition state of the reaction is depicted as partially eclipsed **C**, which avoids unfavorable interactions and offers an open face to the attacking diene. Similar diastereoselectivity was reported by



Scheme 4

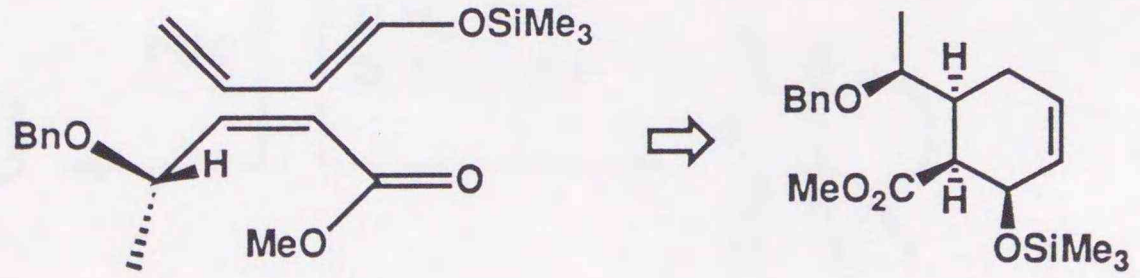
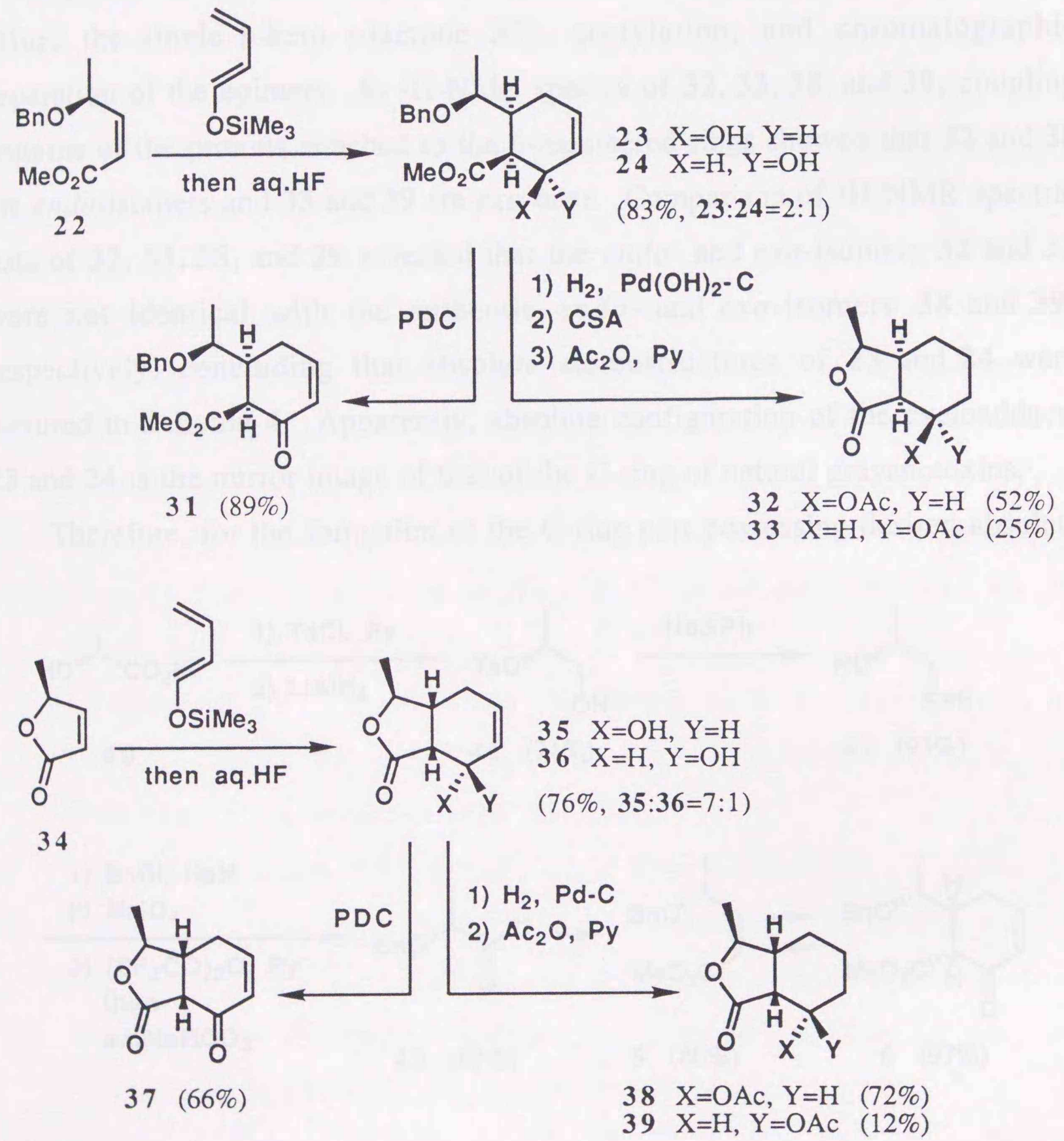


Fig 2 C 30

Mulzer *et al.*[5] in Diels-Alder reaction of methyl (2*Z*,4*S*)-4,5-(isopropylidene-dioxy)-2-pentenoate with cyclopentadiene.

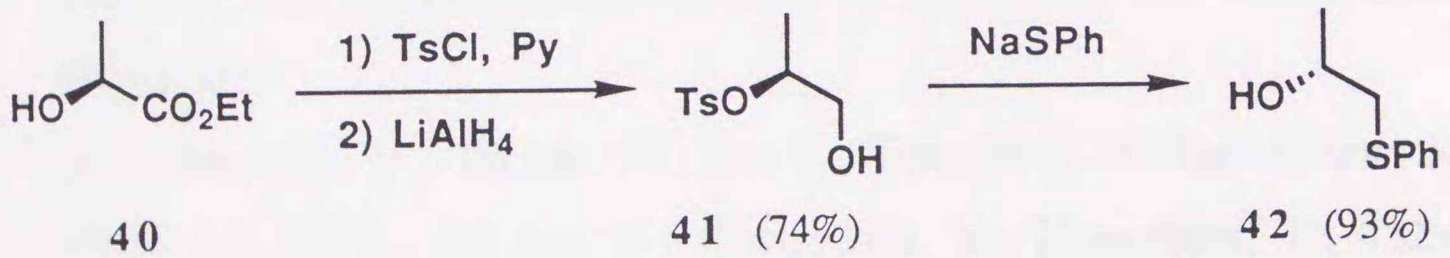
Stereochemistry of **23** and **24** was determined unambiguously as follows (**Scheme 5**). Oxidation of the mixture gave the single β-keto ester **31**, confirming that **23** and **24** are the *endo*- and *exo*-epimers. The acetoxy-γ-lactones **32** and **33** were derived from the mixture of **23** and **24** *via* reductive



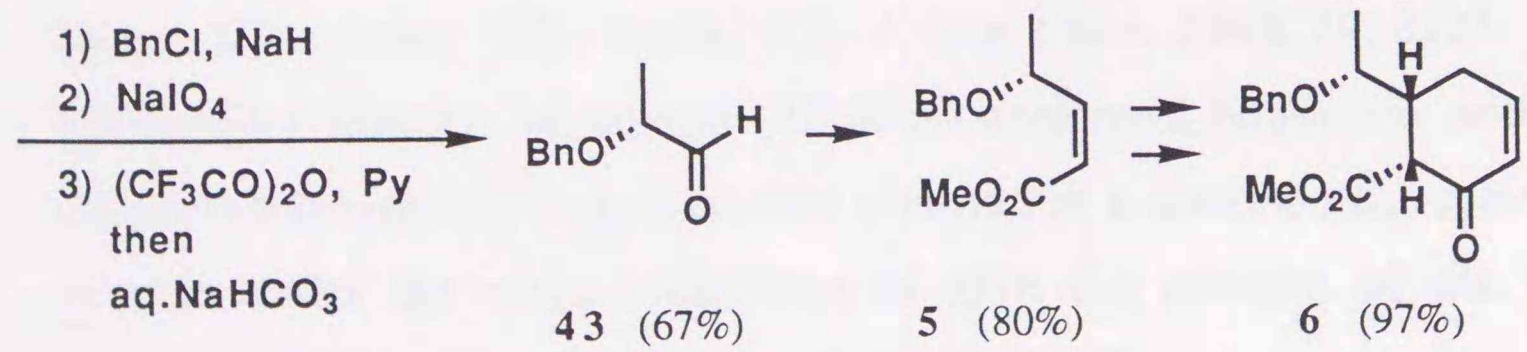
Scheme 5

removal of the benzyl ether groups, lactonization, acetylation, and separation of the epimers by silica gel chromatography. It had been reported that Diels-Alder reactions of (*S*)-5-methyl-2(5*H*)-furanone (**34**) take place from the opposite direction of the methyl group.[6] Thus, the authentic acetoxy-γ-lactones **38** and **39** bearing definite absolute stereochemistry, were synthesized by Diels-Alder reaction of **34** with 1-(trimethylsilyloxy)-1,3-butadiene, hydrogenation of the resulting mixture of the two adducts **35** and **36** (7:1) (which was oxidized to afford the single β-keto γ-lactone **37**), acetylation, and chromatographic separation of the epimers. In ^{1}H-NMR spectra of **32, 33, 38**, and **39**, coupling patterns of the protons attached to the 6-membered rings showed that **32** and **38** are *endo*-isomers and **33** and **39** are *exo*-ones. Comparison of ^{1}H-NMR spectral data of **32, 33, 38**, and **39** revealed that the *endo*- and *exo*-isomers **32** and **33** were not identical with the authentic *endo*- and *exo*-isomers **38** and **39**, respectively, concluding that absolute stereostructures of **23** and **24** were pictured in **Scheme 4**. Apparently, absolute configuration of the cycloadducts **23** and **24** is the mirror image of that of the C-ring of natural grayanotoxins.

Therefore, for the formation of the C-ring part possessing desired absolute



40 **41** (74%) **42** (93%)



43 (67%) **5** (80%) **6** (97%)

Scheme 6

configuration, a practical synthetic scheme for (*R*)-1-benzyloxypropionaldehyde (**43**), the antipode of **21**, starting from ethyl (*S*)-lactate (**40**) was developed (**Scheme 6**).[7] Tosylation of the hydroxyl group of **40** and subsequent reduction of the ester part gave the alcohol **41**. The phenyl sulfide ether **42** was obtained by treating **41** with sodium thiophenoxide through *in situ* formation of (*R*)-propylene oxide and successive opening of the epoxide ring. After protection of the hydroxyl group of **42** in a form of benzyl ether, oxidation of the phenylthio ether group, followed by Pummerer rearrangement of the resulting sulfoxide, afforded **43**. Following to exactly same procedure as that described for the β-keto ester **31**, **43** was led to the desired β-keto ester **6** by way of methyl (2*Z*,4*R*)-4-benzyloxy-2-butenotate (**5**).

References and Notes

(1) At first, elaboration of the CD-ring system from the β-keto γ-lactone **37**, which was obtained through the Diels-Alder reaction of (*S*)-5-methyl-2(5*H*)-furanone (**34**) with 1-(trimethylsilyloxy)-1,3-butadiene as described in text, was examined. Attempted alkylation of **37** with 2-bromoallyl bromide met failure due to liability of **37** under the conditions for the alkylation.

(2) (a) Kobayashi, Y.; Takase, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3038. (b) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767.

(3) House, H.O.; Jones, V.K.; Frank, G.A. *J. Org. Chem.* **1964**, *29*, 3327.

(4) Diels-Alder reaction of methyl (2*E*,4*S*)-4-acetoxy-2-butenoate with 1-(trimethylsilyloxy)-1,3-butadiene also occurred in a diastereoface-selective manner under the same conditions to give the mixture of the four cycloadducts in a ratio of 17:3:3:1 and in 34% yield.

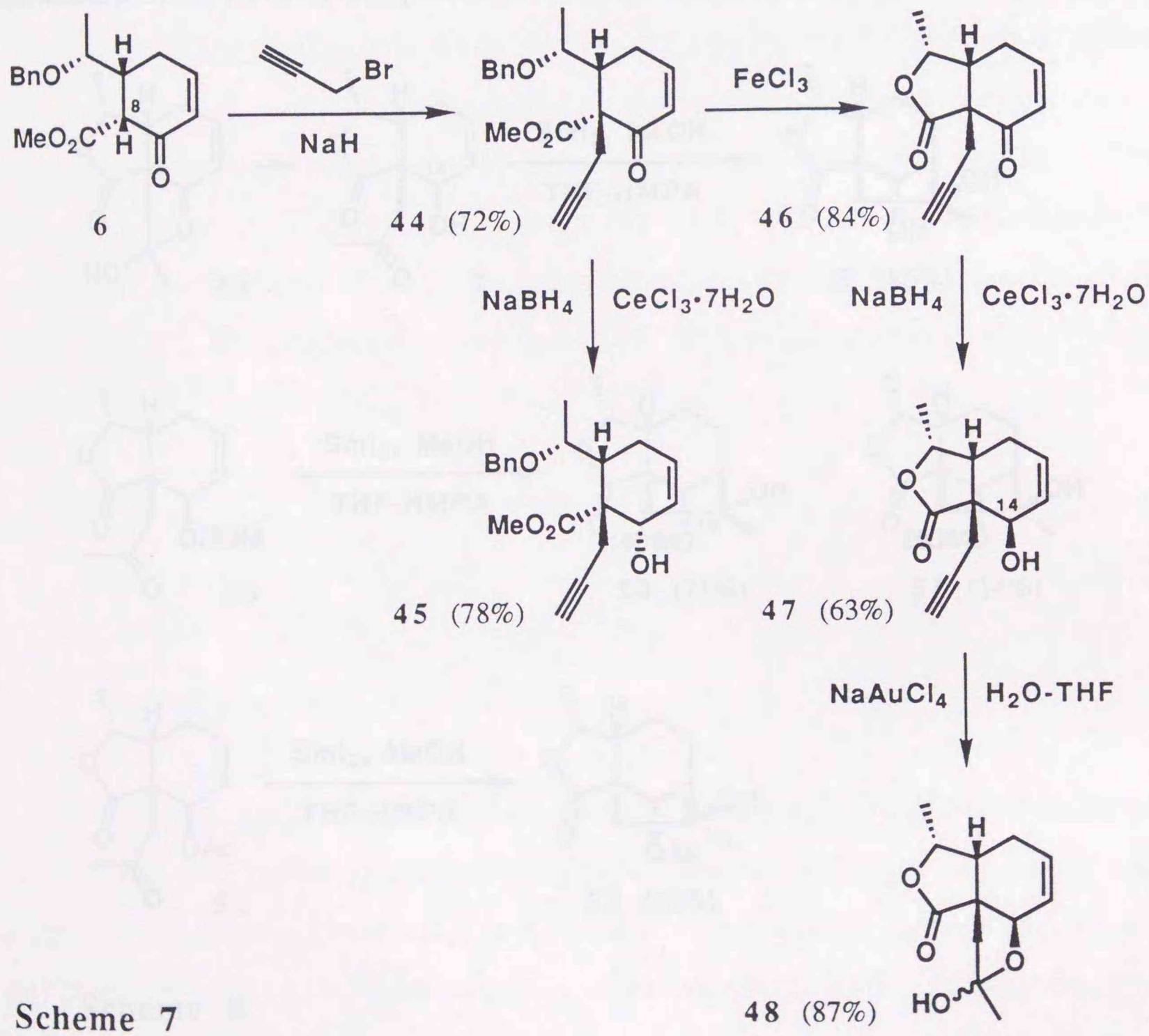
(5) Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Tetrahedron Lett.* **1985**, *26*, 1631.

(6) (a) Ortuno, R.M.; Ballesteros, M.; Corbera, J.; Sanchez-Ferrando, F.; Font, J. *Tetrahedron* **1988**, *44*, 1711. (b) Batllori, R.; Font, J.; Monsalvatje, M.; Ortuno, R.M.; Sanchez-Ferrando, F. *Tetrahedron* **1989**, *45*, 1833.

(7) Yanagiya, M.; Shirahama, H.; Matsutmoto. T. In *28th The Chemistry of Natural Products Symposium Paper* 1986; p 325.

Chapter 4. Construction of the D-ring

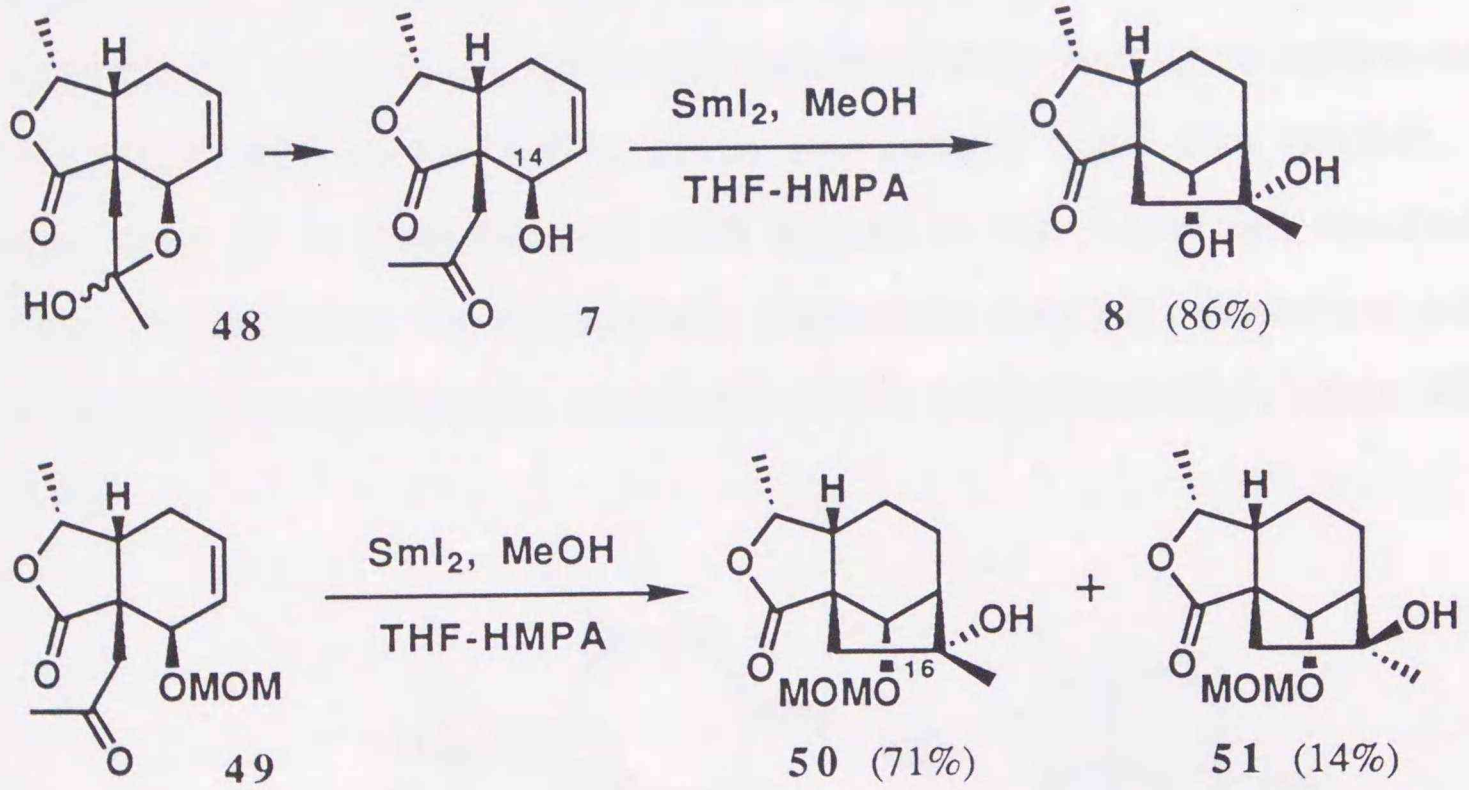
In order to construct the D-ring, stereoselective introduction of C_3-carbon chain into the C-8 position of the C-ring system **6** was achieved by performing stereocontrolled alkylation of **6** with propargyl bromide to afford the β-keto ester **44** as the sole product. The β-keto ester **44** was reduced with sodium borohydride in the presence of cerium(III) chloride[1] giving the undesired α-alcohol **45**.[2] On the other hand, similar reduction of the β-keto γ-lactone **46**, prepared *via* cleavage of the benzyl ether group of **44** with iron(III) chloride[3] and simultaneous lactone closure, took place in a completely regioselective and



Scheme 7

stereoselective manner to yield the desired β-alcohol **47**.[4] It seems apparent that the conformation of the cyclohexenone ring of **46** is fixed by constructing the γ-lactone ring and consequently, the propargyl group takes axial like orientation. Therefore, the hydride may approach the ketone moiety of **46** from the direction opposite to the sterically congested propargyl group. The ketol **48**[5] was derived from **47** cleanly by using sodium tetrachloroaurate(III), which was explored as effective catalyst for hydration of terminal acetylene groups by Uchimoto *et al.*[6]

As expected from the results described in **Chapter 2**, hydroxyl group (C-14 hydroxyl group) directed cyclization of **48** took place in a completely stereocontrolled manner by treatment with samarium(II) iodide to afford the diol **8** exclusively. It is apparent that the corresponding γ-hydroxyketone **7** must be generated in an equilibrium process before ketone-olefin reductive coupling. On



Scheme 8

the other hand, samarium(II) iodide mediated cyclizations of the protected derivatives, methoxymethy ether **49**[7] and acetate **52**,[8] yielded the mixture of the α-alcohol **50** and β-alcohol **51** (**50**:**51**=5:1),[9] and the β-alcohol **53**,[9] respectively. Obviously, the observed stereochemistry on the reaction product **8** is established by chelation between the γ-hydroxyl group and samarium(III) cation generated during the reduction. Therefore, similar to the pinacol coupling reaction induced by samarium(II) iodide mentioned in **Chapter 2**, after single-electron reduction of the ketone functionality of the γ-hydroxyketone **7**, the 7-membered ring ketyl intermediate was formed due to chelation of the samarium(III) cation attached to the resulting ketyl radical, with the γ-hydroxyl group (**Fig 3**). The chelated ketyl radical thus constructed, adds to the olefin through the transition state **D**. As pointed out by Beckwith,[10] in ketone-olefin reductive coupling *via* ketyl radical, the oxygen of the nucleophilic ketyl and the developing methylene radical center both carry partial negative charge in the transition state leading to carbon-carbon bond formation and consequently, these two centers repel one another. The transition state **D** is also favored with regard to the important electrostatic repulsion. Furthermore, the electrostatic interaction may play important roles in the stereoselective cyclization reactions of the methoxymethyl ether **49** and acetate **52**.

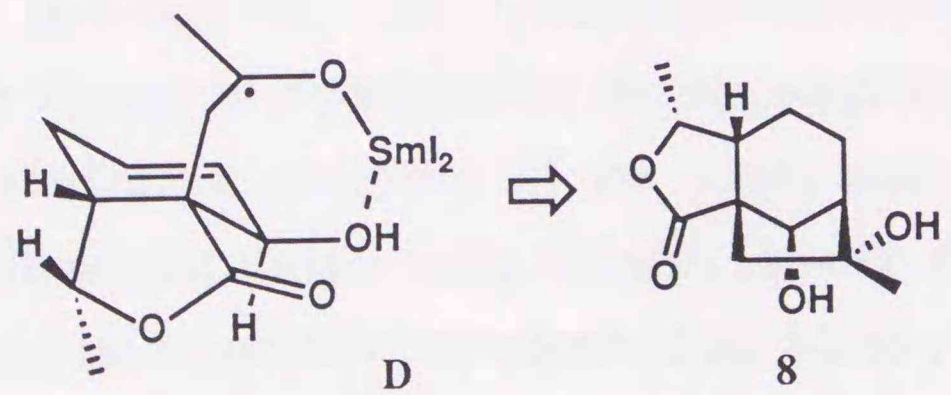
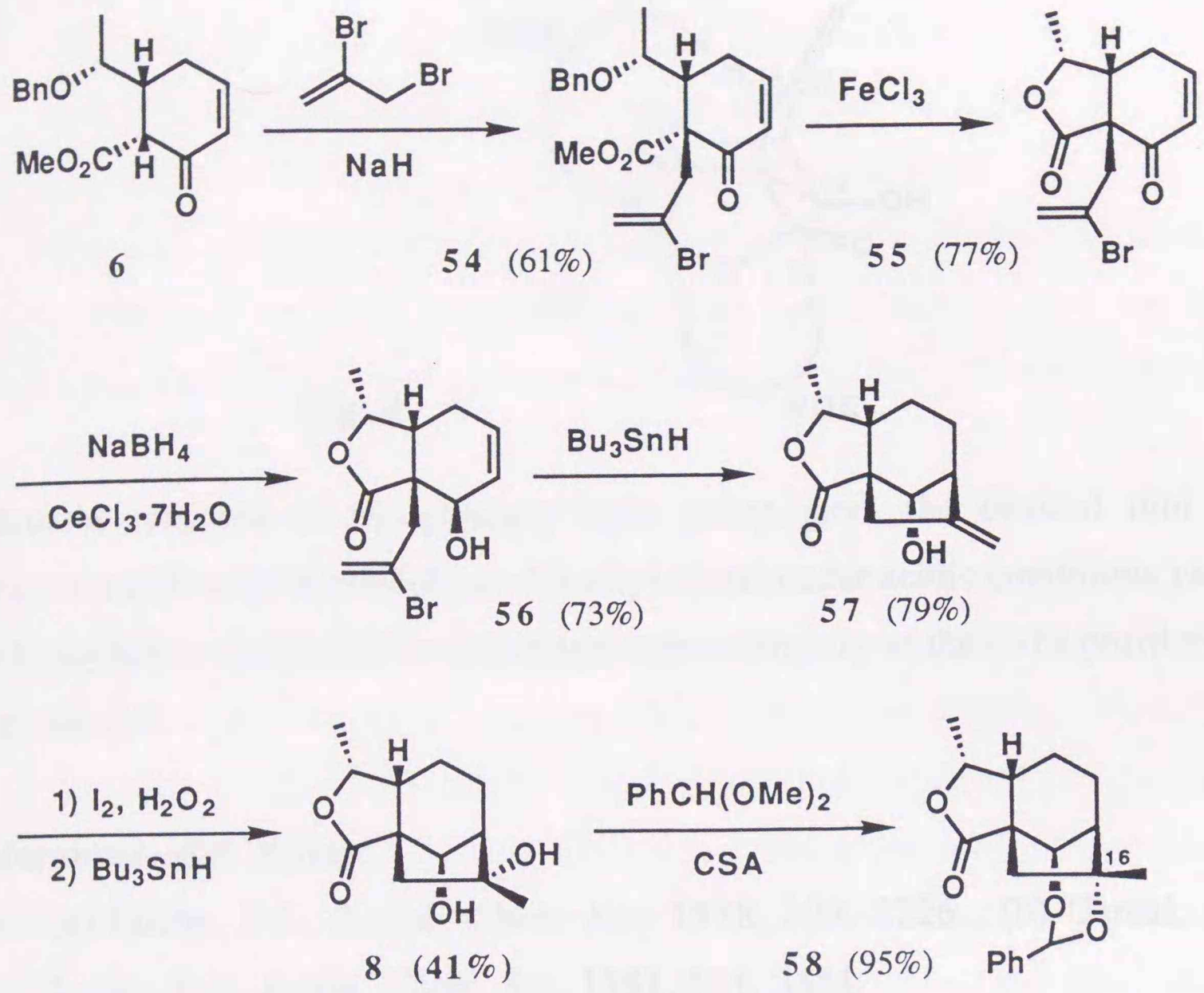


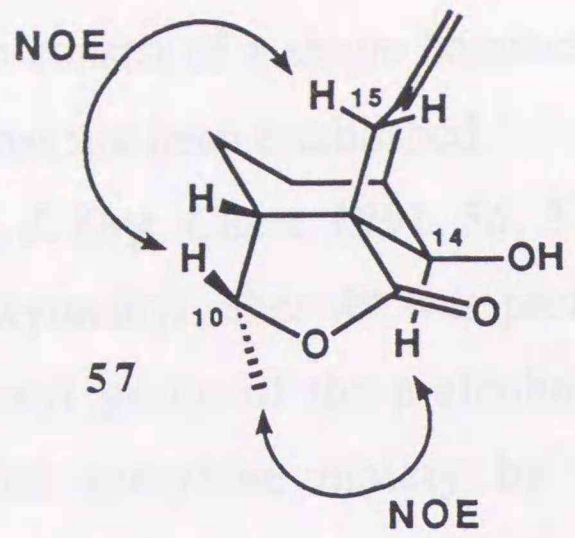
Fig 3 **D** **8**

The physical and spectral data of **8** were identical with those of the authentic sample carrying definite stereochemistry as shown in formula **8**, which was prepared employing vinyl radical cycliztion in the course of the preliminary experiments. Based on this result, the stereochemistry of **8** obtained *via* ketyl



Scheme 9

radical cyclization promoted by samarium(II) iodide, was determined without ambiguity. Synthesis and structure confirmation of the authentic **8** was performed as follows (**Scheme 9**). The 2-bromoallyl β-alcohol **56** was synthesized in the same manner as mentioned for the propargyl β-alcohol **47**. After completely stereoselective alkylation of the β-keto ester **6** with 2-bromoallyl bromide, lactone ring closure using iron(III) chloride followed by highly regioselective and stereoselective reduction[4] of the β-keto γ-lactone **55** afforded **56**. Vinyl radical cyclization of **56** occurred cleanly by treatment with tributyltin hydride to give the *homo*-allyl alcohol **57**. In 2D-NOESY spectrum of **57**, NOEs ($H_{15\beta} \leftrightarrow H_{10}$ and $H_{14} \leftrightarrow Me_{10}$) as shown in **Fig 4**, were observed. Therefore, stereochemistry of the bicyclic compound was determined to be depicted in formula **57**. Stereoselective formation of iodohydrine followed by



57

Fig 4

reductive removal of the primary iodo group gave the desired diol **8**.[11] Treatment of **8** with benzaldehyde dimethyl acetal under acidic conditions yielded the benzylidene acetal **58**[12] to determine stereochemistry at the C-16 position of **8** as pictured.[11]

References and Notes

(1) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Gemal, A.L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(2) Lactone ring closure of the α-alcohol **45** with iron(III) chloride under the same conditions as those described for **44** gave the C-14 epimer of the β-alcohol **47**. The epimer showed identical physical and spectral data with those of the authentic sample.[4] On the basis of the result, stereochemistry of **45** at the C-14 position was determined unambiguously.

(3) The facile removals of the benzyl ether groups of the β-keto esters **44** and **54** were carried by modifying the protocol reported by Ganem *et al.* See: Ganem, B.; Small, V.R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.

(4) Although the reduction of the β-keto γ-lactone **46** gave the β-alcohol **47** exclusively by lowering the reaction temperature at –78 °C, performing the reduction at 0 °C, the 5:1 mixture of **47** and the its C-14 epimer was obtained. On the other hand, the reduction of the β-keto γ-lactone **55** took place in a completely stereoselective manner even at 0 °C. This is because the 2-bromoallyl side chain is sterically more bulky than propargyl one.

(5) The ketol **48** turned out to consist of a single hemiacetal. Stereochemistry at the hemiacetal position has not been established.

(6) Fukuda, Y.; Uchimoto, K. *J. Org. Chem.* **1991**, *56*, 3729.

(7) Preparation of the methoxymethyl ether **49** was performed *via* methoxymethylation of the hydroxyl group of the β-alcohol **47** and successive hydration of the terminal acetylene moiety by sodium tetrachloroaurate(III).

(8) The acetate **52** was synthesized from the ketol **48** by acetylation.

(9) Separation of the C-16 epimers by silica gel chromatography and acidic cleavage of the methoxymethyl ether group converted each of the α-alcohol **50** and β-alcohol **51** into the diol **8** and its C-16 epimer, respectively. Furthermore, the C-16 epimer was also obtained *via* basic hydrolysis of the β-alcohol **53**. Physical and spectral data of the epimers thus obtained, were completely identical with those of the authentic samples.[11] Therefore, stereochemistry of **50**, **51**, and **53** at the C-16 position was established as pictured.

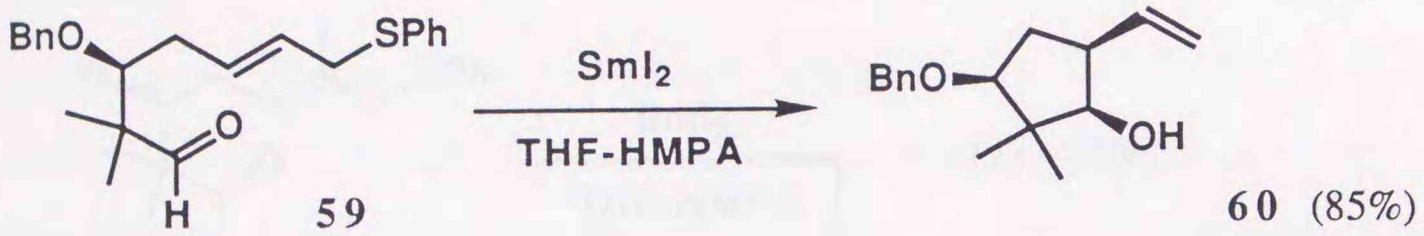
(10) (a) Beckwith, A.L.J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A.L.J.; Ingold, K.U. In *Rearrangements in Ground and Excited States* de Mayo, R., Ed.; Academic Press: New York, 1980; Vol. 1, p 161. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds* Pergamon Press: New York, 1986; p 147.

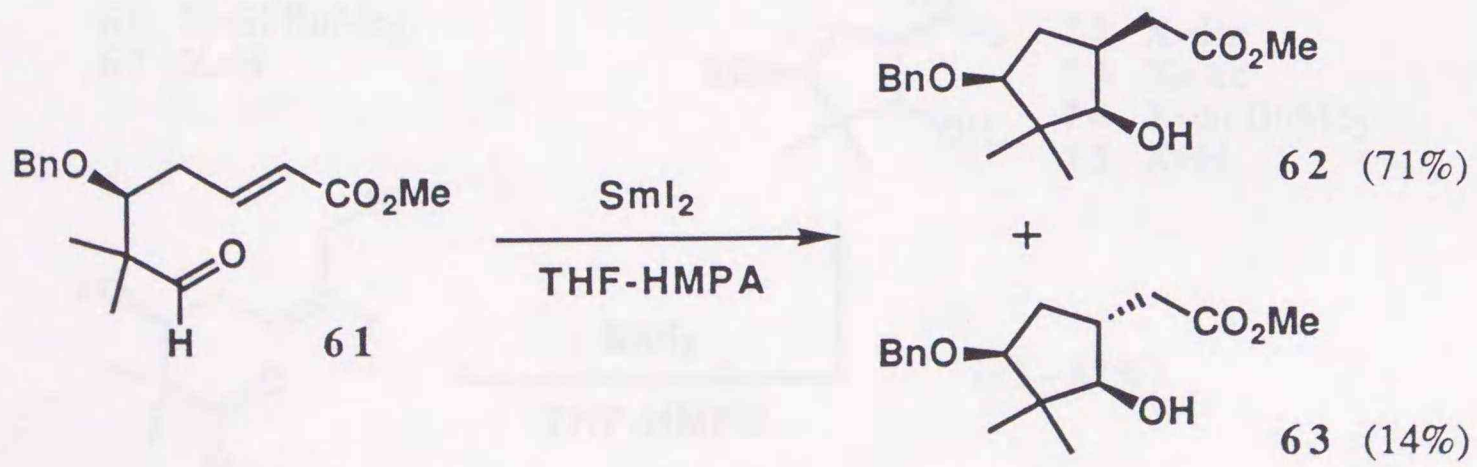
(11) Treatment of the *homo*-allyl alcohol **57** with *N*-bromosuccinimide followed by reductive debromination afforded the 1:1 mixture of the diol **8** and its C-16 epimer, which was separated by silica gel chromatography. Benzylidenation of the C-16 epimer under the same conditions as those described for **8** resulted in complete recovery of the starting material.

(12) The benzylidene acetal **58** consists of a single acetal whose stereostructure has not been determined.

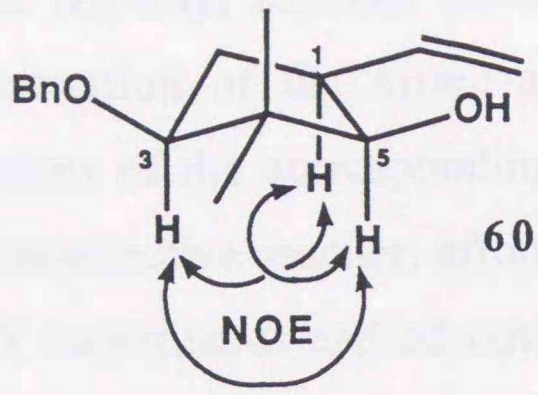
Chapter 5. Construction of the A-Ring

All attempts to attach the 5-membered precursors of the A-ring to the CD-ring systems were led to failure probably owing to steric hindrance.[1] Therefore, it was planed that the acyclic precursor of the A-ring and the CD-ring system were connected and the A-ring was elaborated at the later stage of the synthesis. For the total synthesis of grayanotoxins according to this synthetic plan, it was indispensable to explore an efficient and reliable synthetic method to produce the A-ring. Thus, at first, a model study on construction of the A-ring was performed by examining aldehyde-olefin reductive cyclization induced by samarium(II) iodide. Eventually, completely stereoselective cyclization occurred utilizing the allyl sulfide **59**[2] as the starting material to give the *homo*-allyl alcohol **60**, which possesses the desired functionalities and stereochemisty present in the A-ring of grayanotoxins, as the sole product (**Scheme 10**). Stereostructure of **60** was established by 2D-NOESY spectra of **60**, in which





Scheme 10

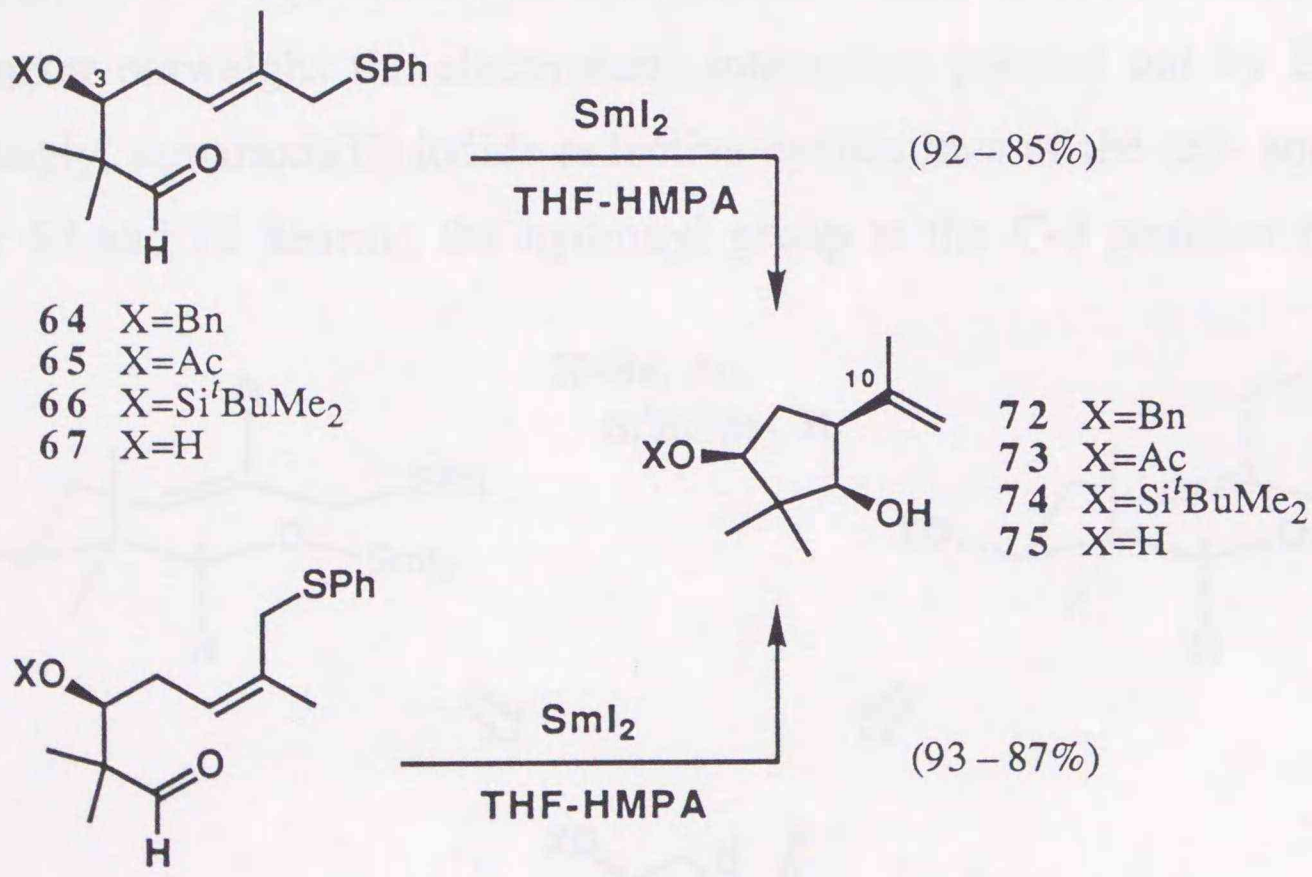


60

Fig 5

NOEs ($H_1 \leftrightarrow H_3$, $H_3 \leftrightarrow H_5$, and $H_1 \leftrightarrow H_5$) as shown in **Fig 5**, were observed. In contrast, similar reductive coupling of the α,β-unsaturated ester **61** afforded the hydroxyester **62** along with a considerable amount of the diastereomeric hydroxyester **63** (**62**:**63**=5:1). This result strongly suggested that ketyl radical cyclizations mediated by samarium(II) iodide takes place in a stereocontrolled manner by using allyl sulfides as the ketyl radical acceptor in stead of α,β-unsaturated esters in general.

Next, for the application of the samarium(II) iodide promoted coupling between aldehydes and allyl sulfides to the formation of the A-ring, reductive cyclizations of the various trisubstituted allyl sulfides **64**–**71**[2] were examined



64 X=Bn
65 X=Ac
66 X=Si^{t}BuMe$_2$
67 X=H

72 X=Bn
73 X=Ac
74 X=Si^{t}BuMe$_2$
75 X=H

68 X=Bn
69 X=Ac
70 X=Si^{t}BuMe$_2$
71 X=H

Scheme 11

(**Scheme 11**). Treatment of the (*E*)-allyl sulfides **64–67** with samarium(II) iodide resulted in exclusive formation of the *homo*-allyl alcohols **72–75**, respectively. Similarly, cyclizations of the corresponding (*Z*)-allyl sulfide **68–71**[2] occurred in a completely stereoselective manner, affording the same alcohols **72–75**, respectively. 2D-NOESY experiments carried out on **72–75**, determined that the stereochemistry of **72–75** was consistent with the stereochemistry determined for **60**. Therefore, stereochemical control at the three stereocenters was not affected by changing geometry of the olefinic part and the C-3 oxygen functionality. Obviously, the highly stereoselective cyclization explored is very suitable for construction of the A-ring and furthermore, for introduction of the C-10 hydroxyl group by oxidizing the *exo*-double bonds of the resulting *homo*-allyl alcohols. The remarkably high degree of stereoselectivity leading to **60** and **72–75** may be explained by assuming that the ketyl radicals generated from the (*E*)- and (*Z*)-allyl sulfides *via* single-electron reductions of the aldehyde parts, add to the olefin through the chair like transition states **E** and **F**, respectively, in which all the substituents attached to the 5-membered rings of the product *homo*-allyl alcohols take equatorial like orientation. Thus, in these transition states, steric factor outweighs the electrostatic interaction pointed out by Beckwith.[3] Interestingly, samarium(II) iodide reductive cyclizations of the (*E*)- and (*Z*)-allyl sulfides **67** and **71** bearing the hydroxyl group at the C-3 position took place

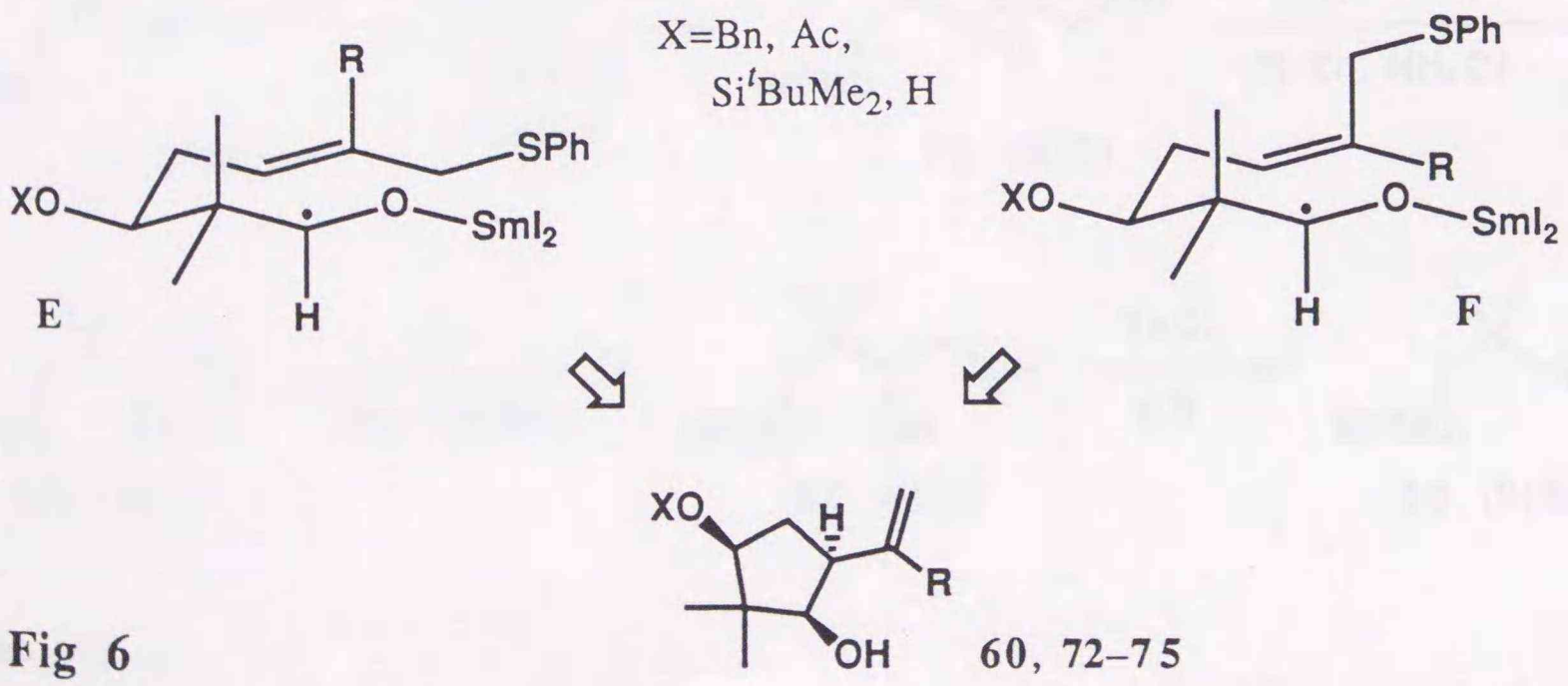
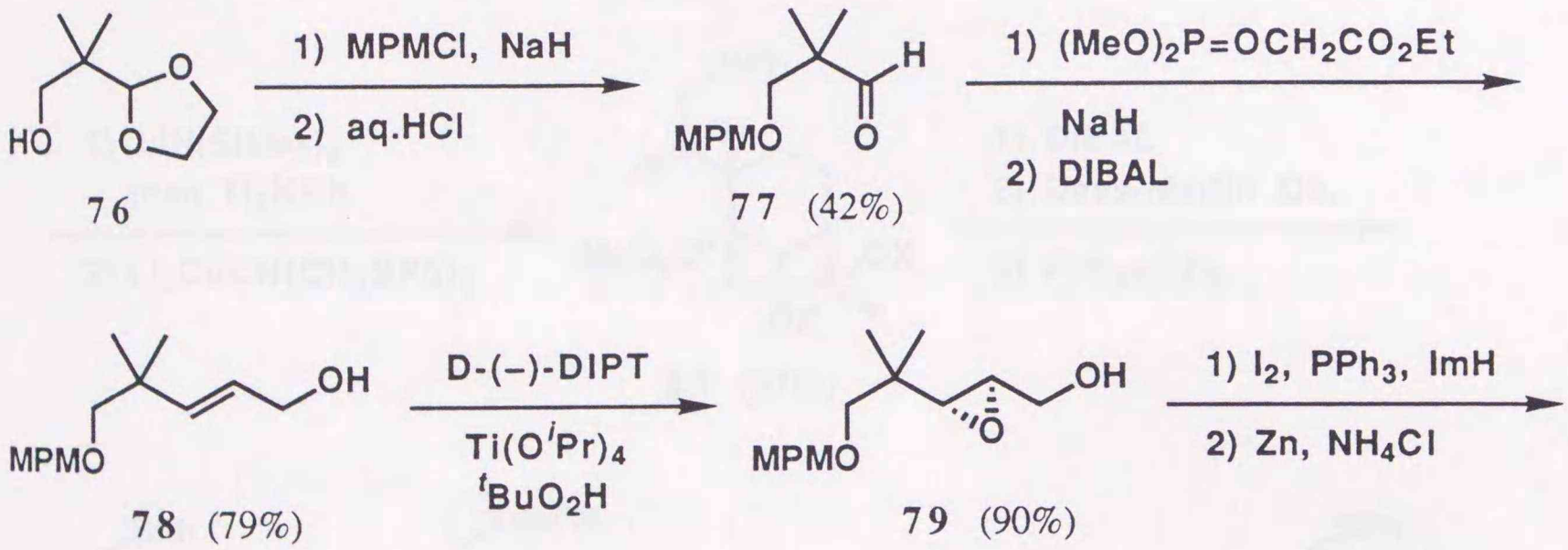
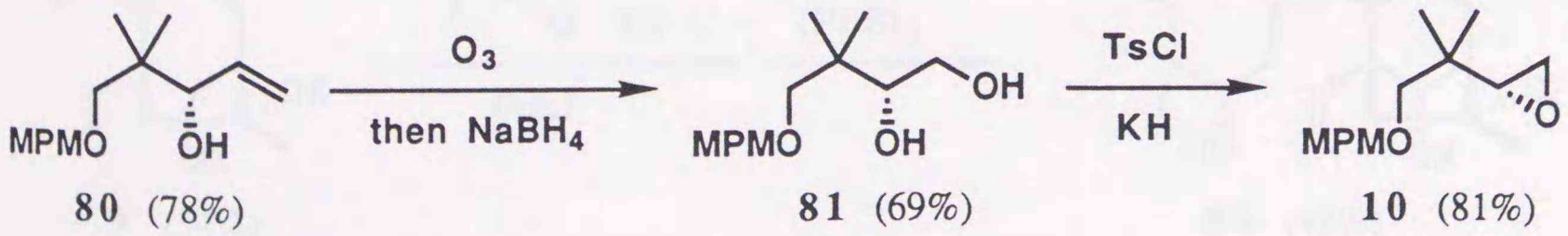


Fig 6

through the similar stereocourse to those of the coupling reactions of the other C-3 protected allyl sulfide, in contrast to the hydroxyl group directed cyclizations of the β-hydroxyketones described in **Chapter 2** and **Chapter 4**. In these aldehyde-olefin reductive couplings, the hydroxyl group may not be able to coordinate to the samarium(III) cation in transition state probably owing to serious steric repulsion between the allyl sulfide side chain and the *gem*-dimethyl group or the large chelated ring.

In order to construct the A-ring employing the explored method mentioned above, it was necessary that the acyclic precursor of the A-ring was attached to the CD-ring system building up the allyl sulfide functionality at the appropriate position. For this purpose, application of alkylation reaction[4] of an anion generated from an allyl sulfide with an epoxide was attempted. Thus, the optically pure (*R*)-epoxide **10**, acyclic precursor of the A-ring, was prepared from the alcohol **76**.[5] As shown in **Scheme 12**, the allyl alcohol **78** was synthesized by the sequence of (1) protection of the hydroxyl group of **76** in a

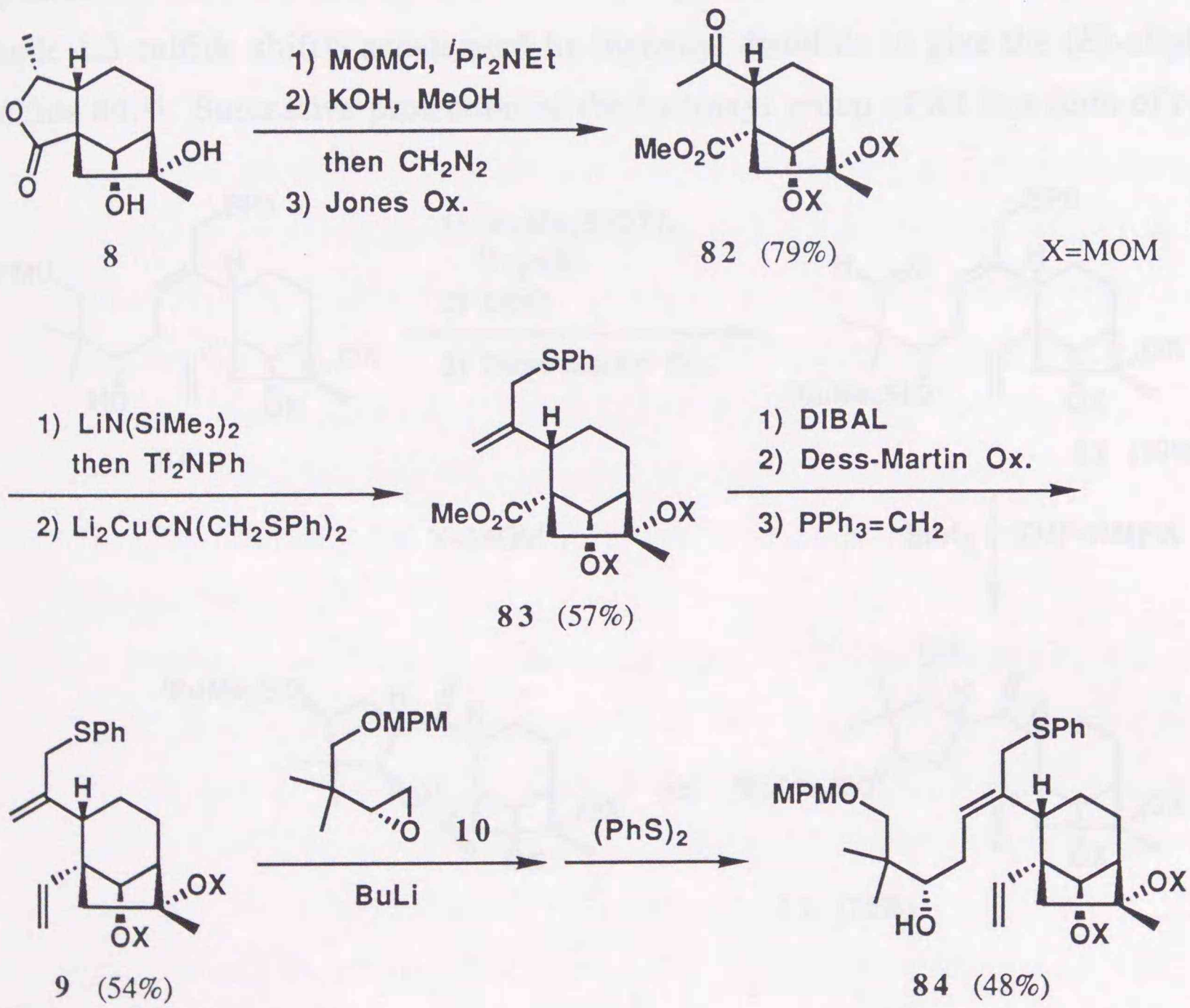




Scheme 12

form of (4-methoxyphenyl)methyl ether, (2) removal of the acetal group under the acidic conditions, (3) elongation of carbon chain by Horner-Emmons olefination of the aldehyde **77**, and (4) reduction of the ester moiety. Sharpless asymmetric epoxidation of **78** occurred cleanly to give the epoxy alcohol **79** in 98% e.e.[6] Iodination of **79** and successive reductive removal of the primary iodo group gave the allyl alcohol **80**. After ozonolysis of the double bond of **80** followed by reductive work-up, treatment of the diol **81** with tosyl chloride in the presence of excess potassium hydride resulted in the tosylation accompanied with epoxide ring closure to yield **10**.

On the other hand, the allyl sulfide **9**, CD-ring system, was derived from the



8 **82** (79%) X=MOM

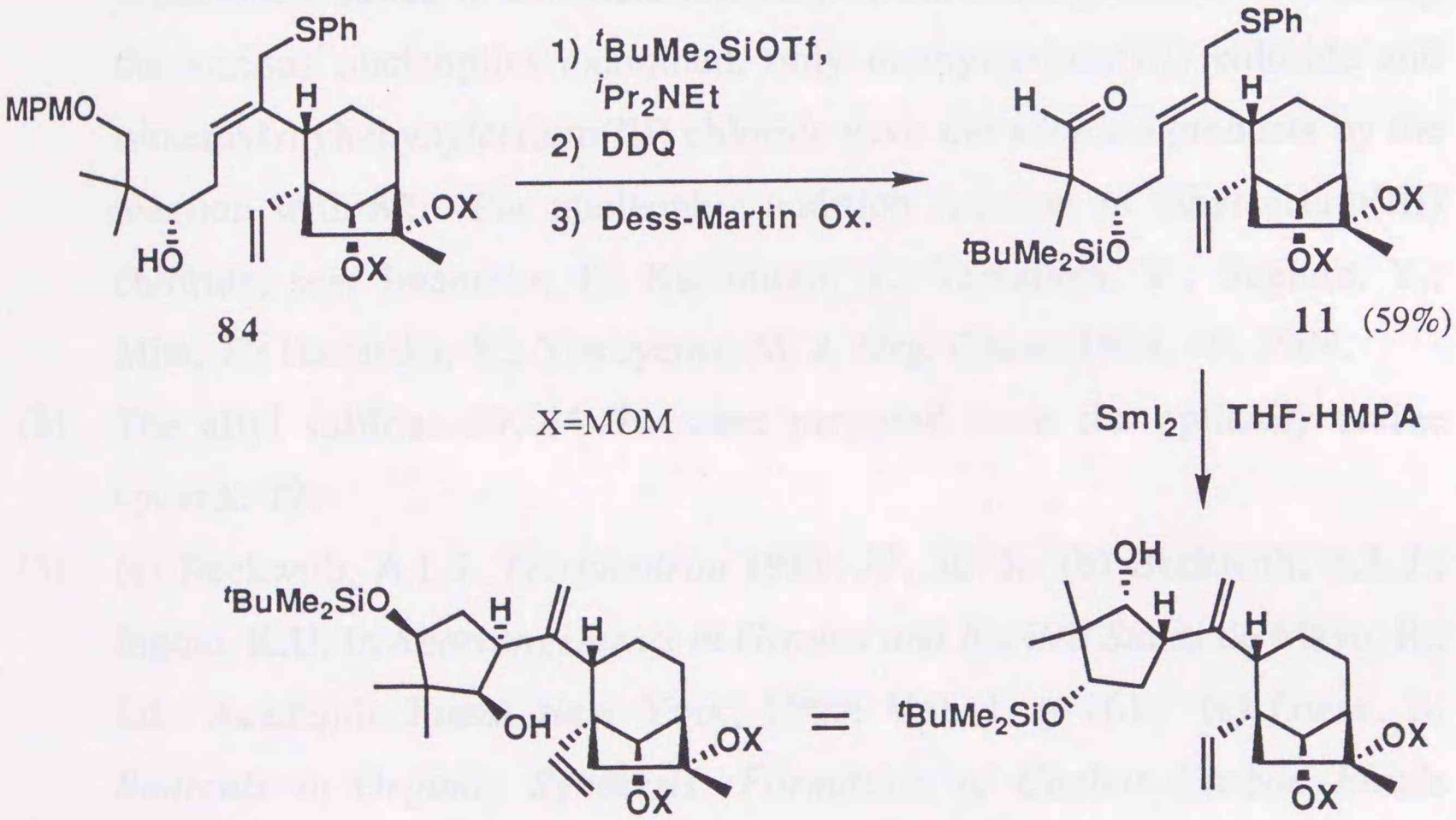
83 (57%)

9 (54%) **84** (48%)

Scheme 13

diol **8** (**Scheme 13**). At first, the allyl sulfide functionality was constructed by (1) protection of the two hydroxyl groups of **8** as methoxymethyl ether, (2) hydrolysis of the γ-lactone ring followed by successive esterification, (3) oxidation of the secondary hydroxyl group, (4) vinyl triflate formation through trapping the lithium enolate anion of the methyl ketone **82**, and (5) coupling reaction[7] of the triflate and the higher order organocupurate[8] prepared from phenylthiomethyllithium with copper(I) cyanide. After reduction of the ester moiety of the resulting allyl sulfide **83**, Dess-Martin oxidation[9] of the alcohol followed by Wittig olefination afforded **9**.

Coupling of the lithium anion generated from the allyl sulfide **9** and the epoxide **10** occurred cleanly and the coupling adduct was further subjected to facile 1,3-sulfide shift[10] accelerated by biphenyl disulfide to give the (*E*)-allyl sulfide **84**.[11] Successive protection of the hydroxyl group of **84** in a form of *t*-



84

X=MOM

11 (59%)

12 (78%)

Scheme 14

butyldimethylsilyl ether, oxidative removal of the (4-methoxyphenyl)methyl ether group, and oxidation of the primary hydroxyl group converted **84** into the aldehyde **11** (**Scheme 14**). As expected from the model study described above, samarium(II) iodide mediated cyclization of **11** also took place in a completely stereocontrolled manner, yielding the *homo*-allyl alcohol **12** as the sole product, achieving formation of the A-ring. In ^{1}H-NMR spectra of **12**, chemical shifts and coupling patterns of the protons attached to the 5-membered ring consist with those of the protons of the model A-ring systems **72–75**. Therefore, stereostructure of **12** was determined unambiguously as depicted.[12]

References and Notes

(1) For example, cross aldol reaction of the methylketone **82** with the lithium enolate prepared from (*S*)-3-(*t*-butyldimethylsilyloxy)-2,2-dimethylcyclopentanone resulted in complete recovery of the starting materials. Among the various nucleopiles examined, only methylcerium(III) chloride and trimethylsilylethynylcerium(III) chloride gave the addition products by the reaction with **82**. For nucleophic addition reaction of alkylcerium(III) chloride, see: Imamoto, T.; Kusumoto, T.; Tawaraya, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(2) The allyl sulfides **59**, **64–71** were prepared from the optically active epoxide **79**.

(3) (a) Beckwith, A.L.J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A.L.J.; Ingold, K.U. In *Rearrangements in Ground and Excited States* de Mayo, R., Ed.; Academic Press: New York, 1980; Vol. 1, p 161. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds* Pergamon Press: New York, 1986; p 147.

(4) Kodama, M.; Takahashi, T.; Kojima, T.; Ito, S. *Tetrahedron Lett.* **1982**, *23*, 3397.

(5) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1990**, *46*, 3469.

(6) Enatiomeric excess (e.e.) value of the epoxide **79** was estimated by measuring the ^{1}H-NMR spectrum of the corresponding MTPA ester derived from **79**.

(7) (a) McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* **1980**, *21*, 4313. (b) McMurry, J.E.; Mohanraj, S. *Tetrahedron Lett.* **1983**, *24*, 2723.

(8) Lipshutz, B.H.; Wilhelm, R.S.; Floyd, D.M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(9) Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155.

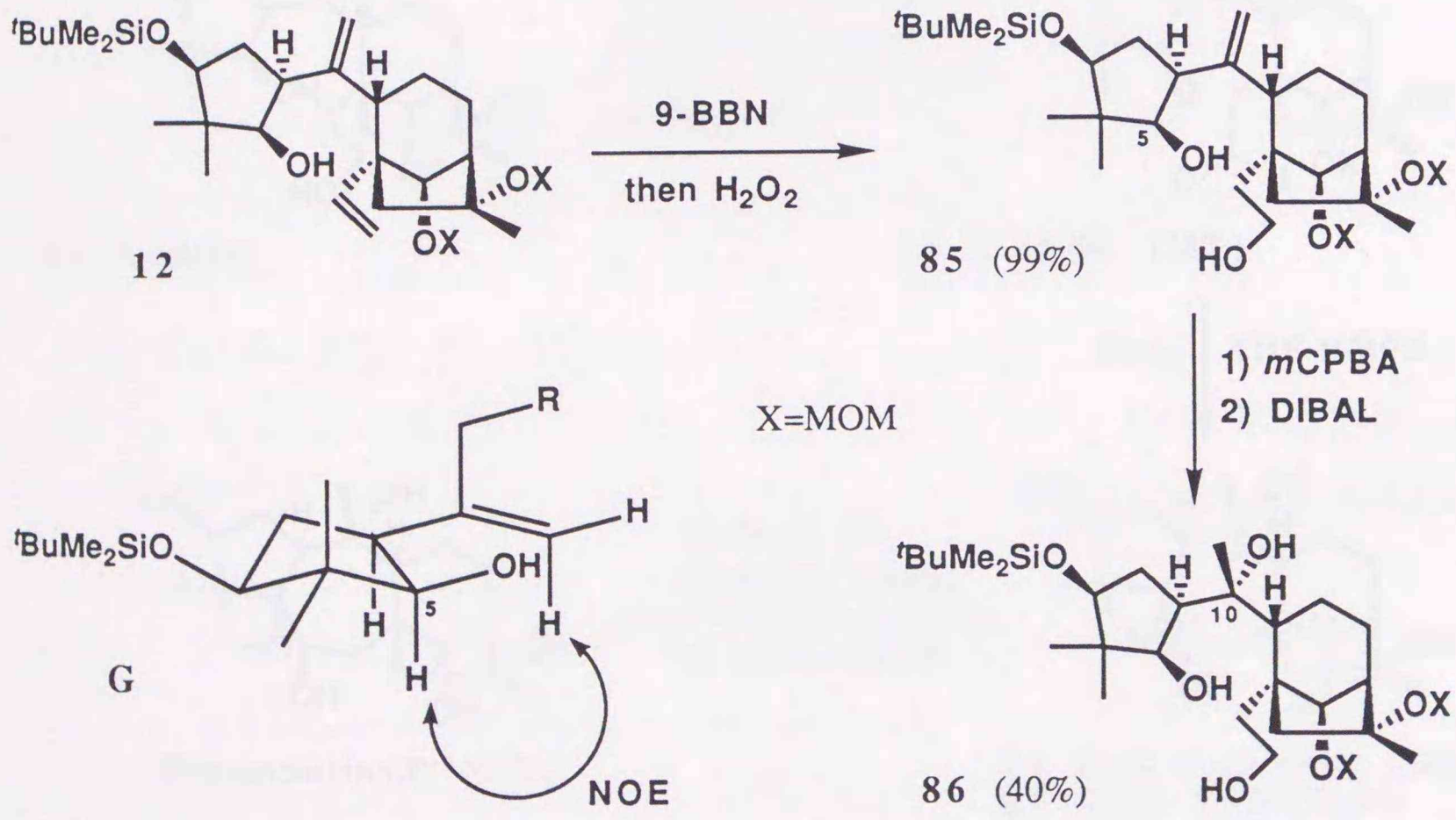
(10) (a) Kwart, H.; Johnson, N.A. *J. Am. Chem. Soc.* **1977**, *99*, 3441. (b) Kwart, H.; Johnson, N.A. *J. Org. Chem.* **1977**, *42*, 2855.

(11) Comparison of ^{1}H-NMR spectral data of the aldehyde **11** synthesized from the allyl sulfide **84**, with those of the (*E*)- and (*Z*)-model aldehydes **66** and **70** revealed that chemical shift of the olefinic proton of **11** rather consists with that of the olefinic proton of **66**. 2D-NOESY experiment carried out on the *t*-butyldimethylsilyl ether derived from **84**, showed that NOE was observed between the olefinic proton and one of the methylene protons attached to the phenylthiomethyl group. On the basis of these results, the geometry with regard to the olefinic bond of **84** was determined as pictured unambiguously.

(12) Furthermore, in 2D-NOESY spectrum of the diol **85**, synthesized from the *homo*-allyl alcohol **12** through regioselective hydroboration-oxidation as mentioned in **Chapter 6**, similar NOEs were observed between the C-1, C-3, C-5 protons as those observed in the model A-ring systems **60** and **72–75**.

Chapter 6. Total Synthesis of (–)-Grayanotoxin III

After regioselective hydroboration-oxidation of the mono-substituted olefin of the *homo*-allyl alcohol **12**, epoxidation of the resulting diol **85** was examined for the introduction of the C-10 hydroxyl group (**Scheme 15**). By treating **85** with *m*-chloroperbenzoic acid, epoxidation stereocontrolled by the C-5 hydroxyl group took place with high stereoselectivity and immediate reduction of the unstable α-epoxide yielded the desired triol **86**[1] exclusively. In 2D-NOESY spectra of **86**, NOE was observed between the peaks due to the C-5 proton and one of the olefinic protons as shown in the figure **G**.[2] This result suggests that the conformation **G** significantly distributes at grand state. Therefore, the high stereoselectivity of the hydroxyl group directed epoxidation reaction may be explained by assuming that the reaction proceeds without significant alternation in three-dimensional arrangement and the α-epoxide was derived from the reactive



Scheme 15

conformer **G**.

The triol **86** thus obtained, was converted into grayanotoxin III (**3**) as follows (**Scheme 16**). After oxidation of the primary and secondary hydroxyl groups of **86**, protection of the tertiary hydroxyl group in a form of methoxymethyl ether followed by removal of the silyl ether group gave the keto aldehyde **13**.[1] Samarium(II) iodide promoted cyclization of **13** afforded the triol **14** exclusively as mentioned in **Chapter 2**. Deprotection of **14** was carried out in a stepwise manner.[3] Acetylation of the two secondary hydroxyl groups of **14** and oxidation of the methylene moieties of the methoxymethyl ether groups afforded the mixture of the 3,6-*O*-acetyl-10,14,16-tris-*O*-(methoxycarbonyl)-grayanotoxin III (**87**) and 3,6-*O*-acetyl-14,16-*O*-carbonyl-10-(methoxycarbonyl)-grayanotoxin III (**88**), which were further subjected to hydrolysis under basic conditions to give grayanotoxin III (**3**). The synthetic sample was found to be identical with natural grayanotoxin III (**3**) in all respects.

86 X=MOM

13 X=MOM (38%)

Grayanotoxin (**3**) (81%)

14 X=H, Y=Z=MOM (54%)
87 X=Ac, Y=Z=CO_2Me
88 X=Ac, Y=CO_2Me, Z=CO

Scheme 16

As described in this thesis, the author was able to complete the chiral total synthesis of (–)-grayanotoxin III (**3**). It appears evident that the explored synthetic scheme is highly promising as one of the most convenient and flexible synthetic routes to various structural types of grayanotoxin diterpenes. The characteristic points of the total synthesis are the three sort of the highly stereocontrolled cyclization reactions induced by samarium(II) iodide. Samarium(II) iodide has been shown to be extremely useful reagent for promoting reductive coupling reactions, such as pinacol and ketone-olefin couplings, to accomplish carbon-carbon bond formation effectively under mild conditions.[4] However, a limited number of highly stereoselective reactions have been hitherto reported.[5] It is apparent that these highly stereoselective cyclization reactions including pinacol and ketone-olefin couplings, explored during the total synthesis of grayanotoxin III (**3**), provide efficient entries into powerful methods for control over various types of reductive coupling reactions promoted by samarium(II) iodide.[6]

References and Notes

(1) Stereochemistry of the triol **86** at the C-10 position was established by converting **86** into the keto aldehyde **13**, which showed identical physical and spectral data to those of the authentic sample prepared from grayanotoxin III (**3**) as described in **Chapter 2**.

(2) In each case of 2D-NOESY experiments carried out on the A-ring systems **72–75** (**Chapter 5**), the similar NOE between the one of the olefinic protons and the C-5 proton was always observed.

(3) Acidic removal of the three methoxymethyl ether group of the triol **14** afforded 14,16-*O*-methylenegraynotoxin III, which was further subjected to acidic hydrolysis, resulting in a simple recovery of the starting material.

(4) (a) Inanaga, J. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 200. (b) Kagan, H.B. *New J. Chem.* **1990**, *14*, 453. (c) Molander, G.A. *Chem. Rev.* **1992**, *92*, 29.

(5) (a) Enholm, E.J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463. (b) Molander, G.A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (c) Chiara, J.L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125.

(6) The hydroxyl group directed cyclization induced by samarium(II) iodide was successfully applied to stereoselective formation of *trans*-decalin and *cis*-decalin skeletons in this laboratory. See: Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158.

Experimental Section

General Methods.

Melting points are uncorrected. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. IR spectra were recorded on a JASCO IR-S spectrometer on NaCl cell. ^{1}H-NMR spectra were recorded on a Hitachi R-90H (90 MHz), a R-250H (250 MHz), and a JEOL Model JMN-FX-400 (400 MHz) spectrometers. Chemical shifts were reported in ppm down field from the peak of tetramethylsilane as an internal standard. Splitting patterns are designed as "s, d, t, q, and br"; these symbols indicate "singlet, doublet, triplet, quartet, and broad," respectively. Grayanotoxin numbering is used for assignments on all intermediate. Low and high resolution mass spectra were obtained on a JEOL Model JMS-DX 300, a JMS-DX 303, and a 01SG-2 spectrometers. Unless otherwise noted, nonaqueous reactions were carried out under an argon atmosphere. Ether and tetrahydrofuran (THF) were distilled from sodium metal/benzophenone ketyl. Benzene (PhH), dichloromethane (CH_2Cl_2), diisopropylethylamine ($^iPr_2NEt$), *N*,*N*-dimethylformamide (DMF), hexamethylphosphoramide (HMPA), hexane, pyridine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and triethylamine (Et_3N) were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide. Molecular sieves 4A (MS-4A) were finely powdered and activated at 180 °C for 10 h in vacuo. All other commercially obtained reagents were used as received. Analytical and preparative thin layer chromatographies were carried out by precoated silica gel plates (Macherey-Nagel DC-Fertigplatten SIL G-25 UV_{254}). Silica gel used for column chromatographies were Merck Kieselgel 60 Art 7734.

5,6:14,16-Di-*O*-benzylidenegrayanotoxin III (15).

To a solution of grayanotoxin III (**3**) (1.00 g, 2.70 mmol) and $PhCH(OMe)_2$ (2.06 g, 13.5 mmol) in CH_2Cl_2 (500 ml) at room temperature was added CSA (50.0 mg, 0.216 mmol). The mixture was stirred at room temperature for 20 h and neutralized with Et_3N. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (AcOEt/PhH, 1:4) to give **15** (1.25 g, 85%) as a colorless amorphous powder: $[\alpha]_D^{25}$ +26.4° (*c* 0.300, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1460, 1380, 1150, 1100, 1070, 1000, 910 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.92, 1.18, 1.20, 1.35 (each 3H, s, Me x 4), 3.70 (1H, dd, J = 1.0, 5.1 Hz, C_6-H), 4.43 (1H, dd, J = 3.9, 6.8 Hz, C_3-H), 4.65 (1H, brs, C_{14}-H), 5.83, 5.96 (each 1H, s, Ph*CH* x 2), 7.30 – 7.60 (10H, m, Ph x 2). Anal. Calcd for $C_{32}H_{42}O_6$: C, 74.68; H, 7.75. Found: C, 74.58; H, 7.56.

3-*O*-Acetyl-5,6:14,16-di-*O*-benzylidenegrayanotoxin III.

To a solution of **15** (1.25 g, 2.29 mmol) in pyridine (50 ml) at room temperature was added Ac_2O (10.0 ml, 10.6 mmol). The solution was stirred at room temperature for 15 h, poured into a mixture of ice and saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic extracts were washed with saturated aqueous $CuSO_4$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 1:9) afforded the acetate (1.30 g, 99%) as colorless crystals: mp 191 – 192 °C; $[\alpha]_D^{25}$ +25.8° (*c* 0.400, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1730, 1450, 1380, 1250, 1100, 1050, 1020, 950 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) 0.99, 1.10, 1.19, 1.37 (each 3H, s, Me x 4), 2.08 (3H, s, OCOMe), 4.46 (1H, dd, J = 1.0, 5.1 Hz, C_6-H), 4.66 (1H, brs, C_{14}-H), 4.85 (1H, dd, J = 3.9, 6.8 Hz, C_3-H), 5.78, 5.96 (each 1H, s, Ph*CH* x 2), 7.35 – 7.55 (10H, m, Ph x 2). Anal. Calcd for $C_{36}H_{44}O_7$: C, 73.43; H, 7.54. Found: C, 73.19; H, 7.54.

3-*O*-Acetyl-5,6-*O*-benzylidenegrayanotoxin III (16).

To a solution of the acetate (1.30 g, 2.21 mmol) in MeOH (100 ml) cooled at 0 °C was added CSA (50.0 mg, 0.216 mmol). After stirring at 0 °C for 1 h, the mixture was neutralized with Et_3N and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (AcOEt/PhH, 1:1) to give **16** (880 mg, 78%) as colorless crystals: mp 164 – 165 °C; $[\alpha]_D^{25}$ +14.3° (*c* 0.400, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1730, 1450, 1370, 1250, 1100, 1080, 1000 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.01, 1.08, 1.16, 1.37 (each 3H, s, Me x 4), 2.10 (3H, s, OCOMe), 4.41 (2H, m, C_{14}-H, C_7-H), 4.86 (1H, dd, J = 3.9, 6.8 Hz, C_3-H), 5.74 (1H, s, Ph*CH*), 7.35 – 7.45 (5H, m, Ph). Anal. Calcd for $C_{29}H_{40}O_7$: C, 68.56; H, 8.06. Found: C, 68.71; H, 8.24.

3-*O*-Acetyl-5,6-*O*-benzylidene-10,14,16-tris-*O*-(methoxymethyl)-grayanotoxin III.

To a solution of **16** (880 mg, 1.76 mmol), $^iPr_2NEt$ (4.60 ml, 26.4 mmol), and DMAP (50.0 mg, 0.409 mmol) in CH_2Cl_2 (100 ml) at room temperature was added MOMCl (1.34 ml, 17.6 mmol). The reaction mixture was stirred at room temperature for 36 h, poured into saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/PhH, 1:4) to yield the tris(methoxymethyl) ether (950 mg, 85%) as a colorless oil: $[\alpha]_D^{25}$ –32.4° (*c* 0.800, $CHCl_3$); IR (neat) 2950, 1450, 1370, 1250, 1130, 1020, 910 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.98, 1.03, 1.20, 1.37 (each 3H, s, Me x 4), 2.08 (3H, s, OCOMe), 3.35, 3.38, 3.39 (each 3H, s, OMe x 3), 4.37 (1H, dd, J = 1.0, 5.5 Hz, C_6-H), 4.50 – 4.77 (7H, m, C_{14}-H, OCH_2O x 3), 4.88 (1H, dd, J = 5.0, 6.4 Hz, C_3-H), 5.75 (1H, s, Ph*CH*), 7.35 – 7.45 (5H, m, Ph); FAB-MS m/z 632 (M^+), 631 (M^+–H); High-Resolution FAB-MS m/z 632.3592 (M^+, calcd for $C_{35}H_{52}O_{10}$ 632.3562).

10,14,16-Tris-*O*-(methoxymethyl)grayanotoxin III (14).

A solution of the tris(methoxymethyl) ether (400 mg, 0.633 mmol) in a mixture of THF (50 ml) and EtOH (10 ml) was cooled to –78 °C. Ammonia (ca. 100 ml) was condensed into the solution and Li (300 mg, 432 mmol) was added. After stirring at –78 °C for 1 h, the reaction was quenched with NH_4Cl until the blue color disappeared. The mixture was warmed to ambient temperature and then the NH_3 was allowed to evaporate. The residue was dissolved in H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (acetone/CH_2Cl_2, 1:4) to give **14** (300 mg, 94%) as colorless crystals: mp 101 – 102 °C; $[\alpha]_D^{25}$ = –45.3° (*c* 0.100, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1470, 1450, 1380, 1140, 1100, 1030, 920 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.97, 1.20, 1.34, 1.46 (each 3H, s, Me x 4), 3.32, 3.36, 3.40, (each 3H, s, OMe x 3), 3.65 (1H, dd, J = 1.0, 5.5 Hz, C_6-H), 3.96 (1H, dd, J = 3.2, 10.5 Hz, C_3-H), 4.32 (1H, brs, C_{14}-H), 4.50, 4.78 (each 1H, d, J = 7.2 Hz, OCH_2O), 4.57, 4.74 (each 1H, d, J = 6.9 Hz, OCH_2O), 4.66, 4.74 (each 1H, d, J = 6.3 Hz, OCH_2O). Anal. Calcd for $C_{26}H_{46}O_9$: C, 62.11; H, 9.23. Found: C, 61.17; H, 9.32.

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(*R*)-1-[(1*S*,4*S*)-4-Hydroxy-3,3-dimethyl-2-oxocyclopent-1-yl]-1-(methoxymethoxy)ethyl]-6,8-bis(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-acetaldehyde (13).

To a solution of **14** (45.0 mg, 89.6 μmol) in PhH (2.0 ml) at room temperature were added K_2CO_3 (36.0 mg, 0.20 mmol) and $Pb(OAc)_4$ (50.0 mg, 98.6 μmol). The mixture was stirred at room temperature for 30 min, diluted with ether, filtered through a plug of Celite. The filtrate was concentrated in vacuo and the residue was subjected to alumina column chromatography (acetone/CH_2Cl_2, 1:4) to afford **13** (35.0 mg, 78%) as a colorless oil: $[\alpha]_D^{25}$ =

$-33.3°$ (*c* 0.700, $CHCl_3$); IR (neat) 3400, 2950, 1750, 1730, 1470, 1380, 1260, 1210, 1150, 980, 920, 800 cm^{-1}; ^1H-NMR (400 MHz, C_6D_6) δ 0.97, 1.06, 1.35, 1.83 (each 3H, s, Me x 4), 2.07, 2.63 (each 1H, d, J = 15.1 Hz, C_{15}-H_2), 2.42 (1H, d, J = 8.3 Hz, C_{13}-H), 2.91 (1H, d, J = 18.1 Hz, C_7-H), 3.01, 3.32, 3.34 (each 3H, s, OMe x 3), 3.49 (1H, t, J = 6.8 Hz, C_3-H), 3.59 (1H, dd, J = 1.4, 18.1 Hz, C_7-H), 4.31 (1H, brs, C_{14}-H), 4.45, 4.73 (each 1H, d, J = 5.8 Hz, OCH_2O), 4.55, 4.78 (each 1H, d, J = 6.3 Hz, OCH_2O), 4.68, 4.73 (each 1H, d, J = 8.3 Hz, OCH_2O), 9.88 (1H, brs, CHO); FI-MS m/z 501 (M^++H), 500 (M^+), 455 (M^+–CH_2OMe), 438 (M^+–$HOCH_2OMe$).

5,6-*O*-Benzylidenegrayanotoxin III (17).

To a solution of **15** (430 mg, 0.788 mmol) in MeOH (50 ml) cooled at 0 °C was added CSA (50.0 mg, 0.216 mmol). After stirring at 0 °C for 30 min, the reaction mixture was neutralized with Et_3N. The solvent was evaporated in vacuo and the product was purified by silica gel column chromatography (acetone/CH_2Cl_2, 3:7) to afford **17** (350 mg, 97%) as colorless crystals: mp 208 – 209 °C; $[\alpha]_D^{25}$ +62.0° (*c* 0.400, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1450, 1420, 1380, 1300, 1150, 1100, 1050, 1000 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.95, 1.18, 1.20, 1.35 (each 3H, s, Me x 4), 3.70 (1H, d, J = 5 Hz, C_6-H), 4.43 (2H, m, C_{14}-H, C_3-H), 5.80 (1H, s, Ph*CH*), 7.25 – 7.45 (5H, m, Ph). Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.70; H, 8.36. Found: C, 70.44; H, 8.52.

5,6-*O*-Benzylidene-3,10,14,16-tetrakis-*O*-(methoxymethyl)-grayanotoxin III.

To a solution of **17** (350 mg, 0.764 mmol), $^iPr_2NEt$ (1.33 ml, 7.64 mmol), and DMAP (50.0 mg, 0.400 mmol) in CH_2Cl_2 (5.0 ml) cooled at 0 °C was added MOMCl (0.500 ml, 6.58 mmol). The reaction mixture was stirred at room temperature for 48 h, poured into saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4,

filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 1:4) furnished the tetrakis(methoxymethyl) ether (400 mg, 83%) as a colorless oil: $[\alpha]_D^{25}$ –11.4° (*c* 0.800, $CHCl_3$); IR (neat) 2950, 1730, 1460, 1380, 1250, 1140, 1020, 960, 910 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.93, 1.13, 1.23, 1.36 (each 3H, s, Me x 4), 3.36, 3.37, 3.38, 3.39 (each 3H, s, OMe x 4), 3.65 (1H, dd, J = 5.5, 6.8 Hz, C_3-H), 4.38 (1H, dd, J = 1.0, 6.2 Hz, C_6-H), 4.53 – 4.76 (9H, m, C_{14}-H, OCH_2O x 4), 5.75 (1H, s, Ph*CH*), 7.30 – 7.50 (5H, m, Ph); FAB-MS m/z 633 (M^+–H), 589 (M^+–CH_2OMe); High-Resolution FAB-MS m/z 633.3654 (M^+–H, calcd for $C_{35}H_{53}O_{10}$ 633.3640).

3,10,14,16-Tetrakis-*O*-(methoxymethyl)grayanotoxin III (18).

A solution of the tetrakis(methoxymethyl) ether (400 mg, 631 mmol) in a mixture of THF (5.0 ml) and EtOH (1.0 ml) was cooled to –78 °C. Ammonia (ca. 50 ml) was condensed into the solution and Li (100 mg, 14.4 mmol) was added. The reaction mixture was stirred at –78 °C for 30 min, quenched with NH_4Cl, and warmed to ambient temperature. The NH_3 was allowed to evaporate and the residue was dissolved in H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (acetone/CH_2Cl_2, 1:4) gave **18** (250 mg, 73%) as a colorless oil: $[\alpha]_D^{25}$ –27.6° (*c* 2.00, $CHCl_3$); IR (neat) 3400, 2950, 1450, 1370, 1200, 1130, 1020, 910 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.05, 1.17, 1.32, 1.38 (each 3H, s, Me x 4), 3.30, 3.35, 3.40, 3.45 (each 3H, s, OMe x 4), 3.64 (1H, t, J = 6 Hz, C_3-H), 3.90 (1H, dd, J = 1.4, 6.8 Hz, C_6-H), 4.30 (1H, brs, C_{14}-H), 4.42 – 4.89 (8H, OCH_2O x 4).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(*R*)-1-[(1*S*,4*S*)-4-(Methoxymethoxy)-3,3-dimethyl-2-oxocyclopent-1-yl]-1-(methoxymethoxy)ethyl]-6,8-bis-(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-acetaldehyde (19).

To a solution of **18** (50.0 mg, 91.6 μmol) in PhH (2.0 ml) at room temperature were added K_2CO_3 (28.0 mg, 20.2 μmol) and $Pb(OAc)_4$ (60.0 mg, 0.110 mmol). After stirring at room temperature for 30 min, the reaction mixture was diluted with ether and filtered through a plug of Celite. The filtrate was concentrated in vacuo and the residue was purified by alumina column chromatography (acetone/CH_2Cl_2, 4:1) to afford **19** (38.0 mg, 78%) as a colorless oil: $[\alpha]_D^{25}$ –52.9 (*c* 2.00, $CHCl_3$); IR (neat) 2950, 1740, 1730, 1450, 1390, 1210, 1150, 1020, 920 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.95, 1.10, 1.42, 1.83 (each 3H, s, Me x 4), 3.23, 3.35, 3.40, 3.44 (each 3H, s, OMe x 4), 3.70 (1H, dd, J = 6, 10 Hz, C_3-H), 4.22 (1H, brs, C_{14}-H), 4.40 – 4.90 (8H, m, OCH_2O x 4), 9.75 (1H, brs, CHO).

10,14,16-Tris-*O*-(methoxymethyl)grayanotoxin III (14).

To a mixture of 0.100 M THF solution of SmI_2 (5.00 ml, 0.500 mmol), THF (1.0 ml), and HMPA (0.50 ml) cooled at –78 °C was added a solution of **13** (15.0 mg, 30.0 μmol) in THF (4.0 ml) by a cannula over 30 min. After stirring at –78 °C for 5 h, the reaction mixture was gradually warmed to ambient temperature over 10 h, poured into saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (acetone/CH_2Cl_2, 2:3) to give **14** (7.00 mg, 51%) as colorless crystals: mp 103 – 104 °C; $[\alpha]_D^{25}$ = –45.4° (*c* 0.100, $CHCl_3$). The spectral (IR, 250 MHz ^{1}H-NMR) data and chromatographic (TLC) behavior of this sample were identical with those of authentic **14**: mp 101 – 102 °C; $[\alpha]_D^{25}$ = –45.3° (*c* 0.100, $CHCl_3$), synthesized from grayanotoxin III (**3**) as described previously.

Chapter 3.

Methyl (2*Z*,4*S*)-4-Benzyloxy-2-pentenoate (22).

To a solution of (*S*)-2-benzyloxypropionaldehyde (**21**) (700 mg, 4.26 mmol) in MeOH (6.0 ml) cooled at 0 °C was added $Ph_3P{=}CHCO_2Me$ (1.65 g, 4.39 mmol). After stirring at 0 °C for 24 h, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (ether/hexane, 1:4) to afford **5** (760 mg, 81%) as a colorless oil: $[\alpha]_D^{25}$ = +49.7° (*c* 0.500, $CHCl_3$); IR (neat) 2950, 1730, 1645, 1440, 1200, 1100 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 6 Hz, CH*Me*), 3.71 (3H, s, CO_2Me), 4.44, 4.52 (each 1H, d, J = 15 Hz, PhCH_2), 5.16 (1H, ddq, J = 1, 8, 6 Hz, BnO*CH*), 5.86 (1H, dd, J = 1, 12 Hz, CH=*CH*CO), 6.25 (1H, dd, J = 8, 12 Hz, *CH*=CHCO), 7.2 – 7.4 (5H, m, Ph).

Methyl (1*S*,2*R*,6*S*)-6-[(*S*)-1-(Benzyloxy)ethyl]-2-hydroxycyclohex-3-ene-1-carboxylate (23) and Methyl (1*S*,2*S*,6*S*)-6-[(*S*)-1-(Benzyloxy)-ethyl]-2-hydroxycyclohex-3-ene-1-carboxylate (24).

A mixture of **22** (715 mg, 3.25 mmol), 1-(trimethylsilyloxy)-1,3-butadiene (630 mg, 6.50 mmol), and *p*-hydroquinone (3.00 mg, 94.0 μmol) was heated at 160 °C in a sealed tube for 48 h and cooled to room temperature. Purification by silica gel column chromatography (AcOEt/PhH, 1:4) afforded the adduct, which was dissolved in acetonitrile (20 ml). To the solution at room temperature was added 10% aqueous HF (1.0 ml). The reaction mixture was stirred at room temperature for 1 h and neutralized with Et_3N. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (AcOEt/PhH, 1:20 → 1:5), affording recovered **22** (300 mg, 42%) and the 2:1 mixture (250 MHz ^{1}H-NMR) of **23** and **24** (468 mg, 48%). Further purification of the mixture by preparative silica gel TLC (AcOEt/PhH, 1:5) afforded pure samples of **23** and **24** both as colorless oils.

(2*R*)-Isomer (*endo*-Isomer) 23: $[\alpha]_D^{25}$ = +16.1° (*c* 1.40, $CHCl_3$); IR (neat) 3400, 2950, 1730, 1430, 1380, 1200, 1150, 1050, 900 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.23 (3H, d, J = 6.2 Hz, C_{10}-Me), 2.16 – 2.38 (3H, m, C_9-H, C_{11}-H_2), 2.82 (1H, dd, J = 3.8, 4.5 Hz, C_8-H), 3.62 (3H, s, CO_2Me), 3.55 – 3.72 (1H, m, C_{10}-H), 4.37, 4.63 (each 1H, d, J = 11.5 Hz, Ph*C*H_2), 4.42 (1H, m, C_{14}-H), 5.64 – 5.83 (2H, m, CH=CH), 7.30 – 7.35 (5H, m, Ph); EI-MS m/z 273 (M^++H), 181 (M^+–Bn), 166 (M^+–BnOH).

(2*S*)-Isomer (*exo*-Isomer) 24: $[\alpha]_D^{25}$ = +8.36° (*c* 0.500, $CHCl_3$); IR (neat) 3400, 2950, 1730, 1430, 1380, 1200, 1050, 1060, 1040 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.27 (3H, d, J = 6.0 Hz, C_{10}-Me), 1.96 – 2.17 (2H, m, C_{11}-H_2), 2.38 (1H, dt, J = 17.5, 3.0 Hz, C_9-H), 3.08 (1H, dd, J = 3.2, 5.0 Hz, C_8-H), 3.60 (3H, s, CO_2Me), 3.58 – 3.68 (1H, m, C_{10}-H), 4.35, 4.62 (each 1H, d, J = 11.2 Hz, Ph*C*H_2), 4.42 (1H, brs, C_{14}-H), 7.27 – 7.30 (5H, m, Ph); EI-MS m/z 273 (M^++H), 181 (M^+–Bn), 166 (M^+–BnOH).

Methyl (2*E*,4*S*)-4-Benzyloxy-2-pentenoate (25).

To a solution of **21** (103 mg, 0.627 mmol) in PhMe (2.0 ml) at room temperature was added Ph_3P=$CHCO_2Me$ (231 mg, 0.690 mmol). After stirring at room temperature for 4 h, the solvent was removed in vacuo and purification by silica gel column chromatography (ether/hexane, 1:30) to afford **22** (21.0 mg, 15%) and **25** (81.0 mg, 59%) as a colorless oil: $[\alpha]_D^{25}$ = +31.2° (*c* 0.500, $CHCl_3$); IR (neat) 2950, 1730, 1645, 1440, 1200, 1100 cm^{-1}; ^1H-NMR (90 MHz, $CDCl_3$) δ 1.32 (3H, d, J = 6 Hz, CH*Me*), 3.74 (3H, s, CO_2Me), 4.16 (1H, ddq, J = 1, 7, 6 Hz, BnO*CH*), 4.38, 4.58 (each 1H, d, J = 11 Hz, Ph*C*H_2), 6.05 (1H, dd, J = 1, 16 Hz, CH=*CH*CO), 6.25 (1H, dd, J = 7, 16 Hz, *CH*=CHCO), 7.3 – 7.4 (5H, m, Ph).

Methyl 6-[(*S*)-1-(Benzyloxy)ethyl]-2-hydroxycyclohex-3-ene-1-carboxylate (26 – 29).

A mixture of **25** (48.0 mg, 0.218 mmol), 1-(trimethylsilyloxy)-1,3-butadiene (62.0 mg, 0.440 mmol), and *p*-hydroquinone (2.00 mg, 60.0 μmol) was heated at 160 °C in a sealed tube for 48 h and cooled to room temperature. Purification by silica gel column chromatography (AcOEt/PhH, 1:4) afforded the adduct, which was dissolved in acetonitrile (2.0 ml). To the solution at room temperature was added 10% aqueous HF (1.0 ml). The reaction mixture was stirred at room temperature for 1 h and neutralized with Et_3N. The solvent was removed in vacuo and purification by silica gel column chromatography (AcOEt/PhH, 1:20 → 1:5) gave the 4:1:1:1 mixture (250 MHz ^{1}H-NMR) of **26** – **29** (44.0 g, 75%) as a colorless oil: IR (neat) 3400, 2950, 1730, 1430, 1380, 1200, 1050, 1060, 1040 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.17, 1.18, 1.22, 1.24 (total 3H, each d, J = 6.8 Hz, C_{10}-Me), 3.55, 3.60, 3.66, 3.69 (total 3H, each s, CO_2Me), 4.26 – 4.59 (3H, m, Ph*C*H_2, C_{14}-H), 5.26 – 6.95 (2H, m, CH=CH); EI-MS m/z 273 (M^++H), 181 (M^+–Bn), 166 (M^+–BnOH).

Methyl (1*S*,6*S*)-6-[(*S*)-1-(Benzyloxy)ethyl]-2-oxocyclohex-3-ene-1-carboxylate (31).

To a suspension of PDC (170 mg, 0.444 mmol) and MS-4A (200 mg) in CH_2Cl_2 (2.0 ml) at room temperature was added a solution of the 2:1 mixture of **23** and **24** (43.0 g, 0.148 mmol) in CH_2Cl_2 (1.0 ml). After stirring at room temperature for 3 h, ether was added and the mixture was filtered through a plug of Celite. Filtrate was concentrated in vacuo and the residue was dissolved in ether. The ethereal solution was filtered through a plug of Florisil and filtrate was concentrated in vacuo to give almost pure **31** (38 mg, 89%) as a colorless oil: $[\alpha]_D^{25}$ +57.1° (*c* 1.00, $CHCl_3$); IR (neat) 2950, 1740, 1670, 1620, 1435, 1140 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.24 (3H, d, J = 7 Hz, C_{10}-Me), 2.5 – 2.7 (3H, m, C_9-H, C_{11}-H_2), 3.5 – 3.8 (2H, m, C_8-H, C_{10}-H), 3.73 (3H, s, CO_2Me), 4.32, 4.56 (each 1H, d, J = 12 Hz, Ph*C*H_2), 6.06 (1H, ddd, J = 1, 2, 10 Hz, CH=*CH*CO), 7.01 (1H, m, *CH*=CHCO), 7.20 – 7.40 (5H, m, Ph).

(1*S*,2*R*,6*S*,7*S*)-2-Acetoxy-7-methyl-8-oxabicyclo[4.3.0]nonan-9-one (32) and (1*S*,2*S*,6*S*,7*S*)-2-Acetoxy-7-methyl-8-oxabicyclo[4.3.0]-nonan-9-one (33).

A suspension of the 2:1 mixture of **23** and **24** (100 mg, 0.348 mmol) and $Pd(OH)_2$-C (2.0 mg) in MeOH (1.0 ml) was stirred at room temperature under an atmosphere of H_2 for 15 h, diluted with ether, and filtered through a plug of Celite. The filtrate was concentrated in vacuo and residue was dissolved in CH_2Cl_2 (1.0 ml). To the solution at room temperature was added CSA (5.00 mg, 21.6 μmol). The reaction mixture was stirred at room temperature for 1 h and neutralized with Et_3N. The solvent was removed in vacuo and the residual oil was purified by silica gel column chromatography (AcOEt/PhH, 1:4) to give the mixture of the hydroxy γ-lactones, which was dissolved in pyridine (1.0 ml). To the solution at room temperature was added Ac_2O (0.500 ml, 0.530 mmol). The mixture was stirred at room temperature for 15 h, poured into saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed with saturated aqueous $CuSO_4$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/PhH, 1:5) to give the 2:1 mixture (250 MHz ^{1}H-NMR) of **32** and **33**. Further purification of the mixture by preparative silica gel TLC (ether/hexane, 1:1) afforded **32** (38.0 mg, 52%) and **33** (18.0 mg, 25%) both as colorless oils.

(2*R*)-Isomer (*endo*-Isomer) 32: $[\alpha]_D^{25}$ –1.11° (*c* 3.00, $CHCl_3$); IR ($CHCl_3$) 2950, 1760, 1720, 1440, 1350, 1290, 1250, 1160, 1120, 1100, 950, 920 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.30 (3H, d, J = 6.5 Hz, C_{10}-Me), 2.09 (3H, s, OCOMe), 3.26 (1H, t, J = 5.5 Hz, C_8-H), 4.42 (1H, dq, J = 2.2, 6.5 Hz, C_{10}-H), 4.86 (1H, dt, J = 11.6, 5.5 Hz, C_{14}-H).

(2*S*)-Isomer (*exo*-Isomer) 33: $[\alpha]_D^{25}$ +35.9° (*c* 3.80, $CHCl_3$); IR ($CHCl_3$) 2950, 1760, 1720, 1440, 1350, 1290, 1250, 1160, 1120, 1100, 950, 920 cm^{-1}; ^{1}H-

NMR (250 MHz, $CDCl_3$) δ 1.32 (3H, d, J = 6.5 Hz, C_{10}-Me), 2.04 (3H, s, OCOMe), 2.92 (1H, dd, J = 3.1, 6.1 Hz, C_8-H), 4.45 (1H, dq, J = 5.0, 6.5 Hz, C_{10}-H), 5.38 (1H, dt, J = 2.0, 3.1 Hz, C_{14}-H).

(1*R*,2*S*,6*R*,7*S*)-2-Hydroxy-7-methyl-8-oxabicyclo[4.3.0]non-3-en-9-one (35) and (1*R*,2*R*,6*R*,7*S*)-2-Hydroxy-7-methyl-8-oxabicyclo[4.3.0]-non-3-en-9-one (36).

A mixture of (*S*)-5-methyl-2(5*H*)-furanone (**34**) (2.20 g, 20.0 mmol), 1-(trimethylsilyloxy)-1,3-butadiene (6.00 g, 40.0 mmol), and *p*-hydroquinone (32.0 mg, 1.00 mmol) was heated at 160 °C in a sealed tube for 48 h and cooled to room temperature. Purification by silica gel column chromatography (AcOEt/PhH, 1:5) afforded the adduct, which was dissolved in acetonitrile (30 ml). To the solution at room temperature was added 10% aqueous HF (10 ml). The reaction mixture was stirred at room temperature for 1 h and neutralized with Et_3N. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (AcOEt/PhH, 1:5) to give the 7:1 mixture (250 MHz ^{1}H-NMR) of **35** and **36** (2.80 g, 76%). Recrystallization from ether-hexane afforded pure sample of **35** as colorless crystals: mp 94 – 95 °C; $[\alpha]_D^{25}$ +68.8° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1750, 1370, 1300, 1270, 1070, 980 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.40 (3H, d, J = 6.5 Hz, C_{10}-Me), 3.05 (1H, dd, J = 6.2, 8.5 Hz, C_8-H), 3.43 (1H, brs, OH), 4.18 (1H, quintet, J = 6.8 Hz, C_{10}-H), 4.46 (1H, brs, C_{14}-H), 5.90, 6.10 (each 1H, m, CH=CH). Anal. found: C, 64.23; H, 7.37. Calcd for $C_9H_{12}O_3$: C, 64.26; H, 7.19.

(1*R*,6*R*,7*S*)-7-Methyl-8-oxabicyclo[4.3.0]non-3-ene-2,9-dione (37).

To a suspension of PDC (580 mg, 1.53 mmol) and MS-4A (600 mg) in CH_2Cl_2 (3.0 ml) at room temperature was added a solution of the 2:1 mixture of **35** and **36** (86.0 mg, 0.512 mmol) in CH_2Cl_2 (1.0 ml). After stirring at room temperature for 1 h, ether was added and the mixture was filtered through a plug

of Celite. Filtrate was concentrated in vacuo and the residue was dissolved in ether. The ethereal solution was filtered through a plug of Florisil and filtrate was concentrated in vacuo to give almost pure **37** (56 mg, 66%) as a colorless oil: $[\alpha]_D^{25}$ +106° (*c* 1.20, $CHCl_3$); IR (neat) 2950, 1770, 1670, 1430, 1340, 1300, 1250, 910 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.47 (3H, d, J = 7 Hz, C_{10}-Me), 2.3 –2.9 (3H, m, C_9-H, C_{11}-H_2), 3.53 (1H, d, J = 8 Hz, C_8-H), 4.47 (1H, dq, J = 1, 7 Hz, C_{10}-H), 6.20 (1H, d, J = 2, 10 Hz, CH=*CH*CO) 7.92 (1H, m, *CH*=CHCO).

(1*R*,2*S*,6*R*,7*S*)-2-Acetoxy-7-methyl-8-oxabicyclo[4.3.0]nonan-9-one (38) and (1*R*,2*R*,6*R*,7*S*)-2-Acetoxy-7-methyl-8-oxabicyclo[4.3.0]-nonan-9-one (39).

A suspension of the 7:1 mixture of **35** and **36** (200 mg, 1.19 mmol) and Pd-C (4.0 mg) in MeOH (2.0 ml) was stirred at room temperature under an atmosphere of H_2 for 15 h, diluted with ether, and filtered through a plug of Celite. The filtrate was concentrated in vacuo and residue was dissolved in pyridine (5.0 ml). To the solution at room temperature was added Ac_2O (0.500 ml, 0.530 mmol). The mixture was stirred at room temperature for 15 h, poured into saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed with saturated aqueous $CuSO_4$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/PhH, 1:5) to give the 7:1 mixture (250 MHz ^{1}H-NMR) of **38** and **39**. Further purification of the mixture by preparative silica gel TLC (ether/hexane, 1:1) afforded **38** (191 mg, 72%) and **33** (31.0 mg, 12%) both as colorless oils.

(2*S*)-Isomer (*endo*-Isomer) 38: $[\alpha]_D^{25}$ –13.6° (*c* 3.00, $CHCl_3$); IR ($CHCl_3$) 2950, 1760, 1720, 1440, 1350, 1290, 1250, 1160, 1120, 1100, 950, 920 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.39 (3H, d, J = 6.5 Hz, C_{10}-Me), 2.07 (3H, s, OCOMe), 2.95 (1H, dd, J = 6.0, 7.9 Hz, C_8-H), 4.47 (1H, quintet, J = 6.5 Hz, C_{10}-H), 5.23 (1H, dt, J = 2.9, 6.0 Hz, C_{14}-H).

(2*R*)-Isomer (*exo*-Isomer) 39: $[\alpha]_D^{25}$ –16.6° (*c* 3.60, $CHCl_3$); IR ($CHCl_3$) 2950, 1760, 1720, 1440, 1350, 1290, 1250, 1160, 1120, 1100, 950, 920 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.38 (3H, d, J = 6.5 Hz, C_{10}-Me), 2.05 (3H, s, OCOMe), 2.87 (1H, dd, J = 4.0, 6.9 Hz, C_8-H), 4.32 (1H, dq, J = 3.0, 6.5 Hz, C_{10}-H), 5.38 (1H, dt, J = 2.1, 4.0 Hz, C_{14}-H).

Ethyl (*S*)-*O*-*p*-Toluenesulfonyllactate.

To a solution of *p*-toluenesulfonyl chloride (194 g, 1.02 mol) in pyridine (690 ml) cooled at 0 °C was added (*S*)-ethyl lactate (**40**) (105 g, 890 mmol) dropwise over 20 min. The reaction mixture was stirred at 0 °C for 36 h, poured into a mixture of ice and H_2O, and extracted with ether. The organic layers were washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in ether and the ethereal solution was filtered through a plug of silica gel. The solvent was removed in vacuo to afford the tosylate (213 g, 88%) as a colorless oil: $[\alpha]_D^{25}$ = –31.1° (*c* 1.00, $CHCl_3$); ^1H-NMR (90 MHz, $CDCl_3$) δ 1.18 (3H, t, J = 7 Hz, $CO_2CH_2\mathit{Me}$), 1.47 (3H, d, J = 7 Hz, $CH\mathit{Me}$), 2.41 (3H, s, $C_6H_4\mathit{Me}$), 4.06 (2H, q, J = 7 Hz, $CO_2\mathit{CH_2}Me$), 4.48 (1H, q, J = 7 Hz, TsO*CH*), 7.34, 7.84 (each 2H, d, J = 9 Hz, C_6H_4); EI-MS m/z 272 (M^+), 199 (M^+–CO_2Et); High-Resolution EI-MS m/z 272.0728 (M+, calcd for $C_{12}H_{16}O_5S$ 272.0719).

(*S*)-2-(Toluenesulfonyloxy)-1-propanol (41).

To a suspension of $LiAlH_4$ (28.0 g, 740 mmol) in ether (1.0 l) cooled at –78 °C was added a solution of the tosylate (100 g, 370 mmol) in ether (500 ml) dropwise over 30 min. The reaction mixture was stirred at –78 °C for 1 h and warmed to room temperature. Excess reagent was destroyed by addition of AcOEt, H_2O, and 2 N aqueous HCl. The resulting mixture was extracted with ether, and ethereal layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give **41** (271 g, 84%) as a colorless oil: $[\alpha]_D^{25}$ =

–21.2° (*c* 1.00, $CHCl_3$); ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.22 (3H, d, J = 7 Hz, CH*Me*), 1.84 (1H, s, OH), 2.40 (3H, s, C_6H_4*Me*), 3.58 (2H, d, J = 5 Hz, HO*CH*$_2$), 4.62 (1H, m, TsO*CH*), 7.30, 7.77 (each 1H, d, J = 8 Hz, C_6H_4).

(*R*)-1-(Phenylthio)-2-propanol (42).

Sodium (86.0 g, 37.4 mol) was added in portions over 10 min to MeOH (1.0 l) at room temperature and the mixture was stirring at room temperature for 2 h. To the solution of NaOMe at room temperature were added PhSH (91 g, 830 mmol) and a solution of **41** (191 g, 830 mmol) in MeOH (200 ml) dropwise over 10 and 30 min, respectively. After stirring at room temperature for 1 h, the solvent was removed in vacuo. The residue was dissolved in H_2O and extracted with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (AcOEt/PhH, 1:9) to yield **42** (130 g, 93%) as a colorless oil: $[\alpha]_D^{25}$ = –33.5° (*c* 1.00, $CHCl_3$); IR (neat) 3400, 2950, 2900, 1580, 1480, 1430, 1370, 1120, 1080, 1020, 930, 750 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.25 (3H, d, J = 6 Hz, CH*Me*), 2.29 (1H, s, OH), 2.82 (1H, dd, J = 8, 14 Hz, PhS*CH*), 3.08 (1H, dd, J = 5, 14 Hz, PhS*CH*), 3.86 (1H, m, HO*CH*), 7.25 (5H, m, Ph); EI-MS m/z 168 (M^+), 150 (M^+–H_2O); High-Resolution EI-MS m/z 168.0610 (M^+, calcd for $C_9H_{12}OS$ 168.0609).

(*R*)-2-(Benzyloxy)-1-(phenylthio)propane.

To a suspension of NaH (6.00 g, 250 mmol) in DMF (400 ml) cooled at 0 °C was added a solution of **42** (34.5 g, 205 mmol) in DMF (200 ml) dropwise over 10 min. Stirring was continued at 0 °C for 30 min and benzyl chloride (28.0 ml, 240 mmol) was added. After stirring at room temperature for 24 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with ether. The combined ethereal layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to silica

gel column chromatography (hexane/PhH, 1:1) to give the benzyl ether (50.5 g, 96%) as a colorless oil: $[\alpha]_D^{25}$ = –68.1° (*c* 1.00, $CHCl_3$); IR (neat) 2950, 2850, 1680, 1480, 1450, 1370, 1200, 1150, 1100, 1030 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.27 (3H, d, J = 7 Hz, CH*Me*), 2.93 (1H, dd, J = 7, 14 Hz, PhS*CH*), 3.19 (1H, dd, J = 6, 14 Hz, PhS*CH*), 3.66 (1H, m, BnO*CH*), 4.42, 4.65 (each 1H, d, J=14, PhCH_2), 7.25 – 7.50 (10H, m, Ph x 2); EI-MS m/z 258 (M^+), 151 (M^+–OBn), 135 (M^+–SPh); High-Resolution EI-MS m/z 258.1062 (M^+, calcd for $C_{16}H_{18}OS$ 258.1074).

(*R*)-2-(Benzyloxy)propionaldehyde (43).

To a solution of the benzyl ether (116 g, 450 mmol) in a mixture of MeOH (2.0 l) and H_2O (500 ml) at room temperature was added $NaIO_4$ (200 g, 940 mmol). After stirring at room temperature for 24 h, the reaction mixture was diluted with CH_2Cl_2 and filtered through a plug of Celite, and the filtrate was concentrated in vacuo. The residual oil was dissolved in H_2O and extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 1:4) furnished the sufoxide, which was dissolved in a mixture of CH_2Cl_2 (1.0 l) and pyridine (300 ml). To the solution cooled at 0 °C was added $(CF_3CO)_2O$ (260 ml, 1.84 mol) dropwise over 30 min. After stirring was continued at room temperature for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic layers were washed with saturated aqueous $CuSO_4$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residual oil was distilled under reduced pressure (80 °C, 1 mmHg) to give **43** (54.8 g, 70%) as a colorless oil: $[\alpha]_D^{25}$ = +67.3° (*l* 1, neat); IR (neat) 3450, 2950, 1740, 1500, 1480, 1450, 1370, 1210, 1100, 730 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 6.7 Hz, CH*Me*), 3.88 (1H, dq, J = 1.8, 6.7 Hz, BnO*CH*), 4.58, 4.64 (each 1H, d, J = 11.6 Hz, PhCH_2), 7.20 – 7.50 (5H, m, Ph), 9.67 (1H, d, J = 1.8 Hz, CHO). The

spectral (IR, 250 MHz ^{1}H-NMR) data and chromatographic (TLC) behavior of this sample were identical with those of **21**: $[\alpha]_D^{25}$ = –67.0° (*l* 1, neat), the antipodes of **43**.

Methyl (2*Z*,4*R*)-4-Benzyloxy-2-pentenoate (5).

To a solution of **43** (54.8 g, 293 mmol) in MeOH (1.0 l) cooled at 0 °C was added $Ph_3P{=}CHCO_2Me$ (175 g, 586 mmol) in portions over 20 min. After stirring at 0 °C for 24 h, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (ether/hexane, 1:4) to give the mixture of **5** and its (*E*)-isomer (10:1, by 90 MHz ^{1}H-NMR). The mixture was further purified by distillation under reduced pressure (125 °C, 1 mmHg), affording geometrically pure **5** (51.6 g, 80%) as a colorless oil: $[\alpha]_D^{25}$ = –49.2° (*c* 0.500, $CHCl_3$). The spectral (IR, 90 MHz ^{1}H-NMR) data and chromatographic (TLC) behavior of this sample were identical with those of **22**: $[\alpha]_D^{25}$ = +49.7° (*c* 0.500, $CHCl_3$), the antipode of **5**, prepared as described previously.

Methyl (1*R*,2*S*,6*R*)-6-[(*R*)-1-(Benzyloxy)ethyl]-2-hydroxycyclohex-3-ene-1-carboxylate (ent-23) and Methyl (1*R*,2*R*,6*R*)-6-[(*R*)-1-(Benzyloxy)ethyl]-2-hydroxycyclohex-3-ene-1-carboxylate (ent-24).

A mixture of **5** (9.98 g, 453 mmol), 1-(trimethylsilyloxy)-1,3-butadiene (14.8 g, 194 mmol), and *p*-hydroquinone (64.0 mg, 2.00 mmol) was heated at 160 °C in a sealed tube for 48 h and cooled to room temperature. Purification by silica gel column chromatography (AcOEt/PhH, 1:4) afforded the adduct, which was dissolved in acetonitrile (200 ml). To the solution at room temperature was added 10% aqueous HF (10 ml). The reaction mixture was stirred at room temperature for 1 h and neutralized with Et_3N. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (AcOEt/PhH, 1:20 → 1:5), affording recovered **5** (6.61 g, 32%) and the 2:1

mixture (250 MHz ^{1}H-NMR) of **ent-23** and **ent-24** (8.80 g, 68%). Further purification of the mixture by preparative silica gel TLC (AcOEt/PhH, 1:5) afforded pure samples of **ent-23** (*endo*-isomer): $[\alpha]_D^{25}$ = –16.6° (*c* 1.40, $CHCl_3$), and **ent-24** (*exo*-isomer): $[\alpha]_D^{25}$ = –8.40° (*c* 0.500, $CHCl_3$), both as colorless oils. The spectral (IR, 250 MHz ^{1}H-NMR, EI-MS) data and chromatographic (TLC) behavior of these samples were identical with those of **23**: $[\alpha]_D^{25}$ = +16.1° (*c* 1.40, $CHCl_3$), and **24**: $[\alpha]_D^{25}$ = +8.36° (*c* 0.500, $CHCl_3$), the antipodes of **ent-23** and **ent-24**, respectively, prepared as mentioned above.

Methyl (1*R*,6*R*)-6-[(*R*)-1-(Benzyloxy)ethyl]-2-oxocyclohex-3-ene-1-carboxylate (6).

To a suspension of PDC (200 g, 532 mmol) and MS-4A (200 g) in CH_2Cl_2 (1.0 l) at room temperature was added a solution of the 2:1 mixture of **26** and **27** (50.0 g, 184 mmol) in CH_2Cl_2 (500 ml) dropwise over 30 min. After stirring at room temperature for 3 h, ether was added and the mixture was filtered through a plug of Celite. Filtrate was concentrated in vacuo and the residue was dissolved in ether. The ethereal solution was filtered through a plug of Florisil and filtrate was concentrated in vacuo to give almost pure **6** (48.0 g, 97%) as a colorless oil: $[\alpha]_D^{25}$ –56.8° (*c* 1.00, $CHCl_3$). The β-keto ester **6** was used in next step without further purification. The spectral (IR, 250 MHz ^{1}H-NMR) data and chromatographic (TLC) behavior of these sample were identical with those of **31**: $[\alpha]_D^{25}$ +57.1° (*c* 1.00, $CHCl_3$), the antipodes of **6**, synthesized as described previously.

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Methyl (1*R*,6*R*)-6-[(*R*)-1-(Benzyloxy)ethyl]-2-oxo-1-propargylcyclohex-3-ene-1-carboxylate (44).

To a suspension of NaH (5.80 g, 242 mmol) in DMF (1.0 l) cooled at 0 °C was added a solution of **6** (48.0 g, 178 mmol) in DMF (50 ml) dropwise over 30 min. After stirring at 0 °C for 10 min, propargyl bromide (26.0 ml, 297 mmol) was added. The reaction mixture was stirred at 0 °C for 3 h, quenched with saturated aqueous NH_4Cl solution, and extracted with ether. The combined ethereal layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (ether/hexane, 1:4) furnished **44** (42.0 g, 72%) as colorless crystals: mp 74–75 °C; $[\alpha]_D^{25}$ = –57.1° (*c* 1.00, $CHCl_3$); IR (neat) 3300, 2950, 1740, 1670, 1440, 1400, 1280, 1150, 1080, 980, 910 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.39 (3H, d, J = 6.2 Hz, C_{10}-Me), 1.93 (1H, t, J = 2.6 Hz, C≡CH), 2.50, (1H, dt, J = 18.4, 5.4 Hz, C_{11}-H), 2.88, 3.35 (each 1H, dd, J = 2.6, 17.4 Hz, $CH_2C{\equiv}C$), 3.20 (3H, s, CO_2Me), 3.81 (1H, dq, J = 1.5, 6.2 Hz, C_{10}-H), 6.15 (1H, dd, J = 2.3, 10.0 Hz, CH=*CH*CO), 7.15 (1H, ddd, J = 2.3, 6.5, 10.0 Hz, *CH*=CHCO), 7.30 (5H, m, Ph); EI-MS m/z 326 (M^+), 267 (M^+–CO_2Me), 191 (M^+–MeCHOBn); High-Resolution EI-MS m/z 326.1523 (M^+, calcd for $C_{20}H_{22}O_4$ 326.1518).

(1*R*,6*R*,7*R*)-7-Methyl-8-oxa-1-propargylbicyclo[4.3.0]non-3-ene-2,9-dione (46).

To a solution of $FeCl_3$ (83.7 g, 516 mmol) in CH_2Cl_2 (2.0 l) at room temperature was added a solution of **44** (42.0 g, 129 mmol) in CH_2Cl_2 (50.0 ml) dropwise over 30 min. After stirring at room temperature for 2 h, the reaction mixture was quenched with 1 N aqueous HCl and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column

chromatography (AcOEt/hexane, 2:3) to give **46** (22.0 g, 84%) as colorless crystals: mp 108 – 109 °C; $[\alpha]_D^{25}$ = +19.2° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3300, 2950, 1780, 1670, 1390, 1330, 1250, 1170, 1130, 1050, 1040, 1000, 900 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.34 (3H, d, J = 6.8 Hz, C_{10}-Me), 2.07 (1H, t, J = 2.2 Hz, C≡CH), 2.45 (1H, dt, J = 4.8, 2.1 Hz, C_{11}-H), 2.75, 3.03 (each 1H, dd, J = 2.2, 16.4 Hz, $CH_2C{\equiv}C$), 3.36 (1H, dt, J = 4.5, 6.8 Hz, C_9-H), 4.82 (1H, quintet, J = 6.8 Hz, C_{10}-H), 6.22 (1H, dd, J = 2.1, 10.2 Hz, CH=*CH*CO), 7.04 (1H, dt, J = 10.2, 3.5 Hz, *CH*=CHCO); EI-MS, m/z 204 (M^+), 159 (M^+–CO_2H); High-Resolution EI-MS m/z 204.0799 (M^+, calcd for $C_{12}H_{12}O_3$ 204.0786).

(1*R*,2*R*,6*R*,7*R*)-2-Hydroxy-7-methyl-8-oxa-1-propargylbicyclo-[4.3.0]non-3-ene-9-one (47).

To a solution of **46** (22.0 g, 108 mmol) and $CeCl_3{\bullet}7H_2O$ (128 g, 343 mmol) in MeOH (1.0 l) cooled at –78 °C was added $NaBH_4$ (6.12g, 162 mmol) in portions over 5 min. The reaction mixture was stirred at –78 °C for 1 h, warmed to room temperature over 3 h, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/hexane, 1:1) furnished **47** (14.0 g, 63%) as colorless crystals: mp 114 – 115 °C; $[\alpha]_D^{25}$ = +1.66° (*c* 0.900, $CHCl_3$); IR ($CHCl_3$) 3600, 3300, 2950, 1770, 1490, 1360, 1230, 1190, 1100, 1050, 950 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.36 (3H, d, J = 6.8 Hz, C_{10}-Me), 2.01 (1H, t, J = 2.5 Hz, C≡CH), 2.50 (1H, brs, OH), 2.42, 2.95 (each 1H, dd, J = 2.5, 16.5 Hz, $CH_2C{\equiv}C$), 2.87 (1H, q, J = 7.4 Hz, C_9-H), 4.25 (1H, brs, C_{14}-H), 4.92 (1H, quintet, J = 6.8 Hz, C_{10}-H), 5.82 – 6.00 (2H, m, CH=CH); EI-MS m/z 206 (M^+), 167 (M^+–$CH_2C{\equiv}CH$); High-Resolution EI-MS m/z 206.0981 (M^+, calcd for $C_{12}H_{14}O_3$ 206.0943).

(1*R*,2*R*,6*R*,1'*R*)-2-Ethyl-8-hydroxy-8-methyl-7-oxabicyclo[4.3.0]non-4-ene-1,1'-carbolactone (48).

A solution of **47** (5.21 g, 25.3 mmol) and $NaAuCl_4 \cdot H_2O$ (10.0 mg, 25.3 μmol) in a mixture of THF (100 ml) and H_2O (10 ml) was heated at 60 °C for 20 min and cooled to room temperature. The solvent was removed in vacuo and the residue was subjected to silica gel column chromatography (AcOEt/PhH, 1:4) to afford **48** (4.93 g, 87%) as colorless crystals: mp 92–93 °C; $[\alpha]_D^{25}$ = –2.33° (*c* 0.900, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1750, 1450, 1400, 1350, 1190, 1000, 970, 960 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.40 (3H, d, J = 6.8 Hz, C_{10}-Me), 1.68 (3H, s, C_{16}-Me), 2.06, 2.48 (each 1H, d, J = 13.2 Hz, C_{15}-H_2), 2.22 (1H, q, J = 5.5 Hz, C_{11}-H), 4.74 (1H, brs, C_{14}-H), 4.80 (1H, dq, J = 6.8, 1.0 Hz, C_{10}-H), 5.88–6.02 (2H, m, CH=CH); EI-MS m/z 224 (M^+), 206 (M^+–H_2O); High-Resolution EI-MS m/z 206.0955 (M^+–H_2O, calcd for $C_{12}H_{14}O_3$ 206.0943). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.19. Found: C, 64.18; H, 7.21.

(1*R*,2*R*,5*R*,6*R*,8*R*,1'*R*)-2-Ethyl-6,8-dihydroxy-6-methylbicyclo-[3.2.1]octane-1,1'-carbolactone (8).

To 0.100 M THF solution of SmI_2 (100 ml, 10.0 mmol) cooled at –78 °C was added a solution of **48** (400 mg, 1.79 mmol) in a mixture of THF (10 ml), MeOH (5.0 ml), and HMPA (10 ml). The solution was warmed to 0 °C, stirred at 0 °C for 15 h, and diluted with ether and 1 N aqueous HCl. The mixture was extracted with AcOEt and the combined organic layers were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by silica gel column chromatography (AcOEt/PhH, 1:1) to give **8** (350 mg, 86%) as white crystals: mp 142–143 °C; $[\alpha]_D^{25}$ +21.4° (*c* 0.900, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 6.8 Hz, C_{10}-Me), 1.38 (3H, s, C_{16}-Me), 1.87, 2.72 (each 1H, d, J = 14.5 Hz, C_{15}-H_2), 2.23 (1H, d, J = 9.3 Hz, C_{13}-H), 2.63 (1H, q, J = 9.2 Hz, C_9-H), 4.33 (1H, s, C_{14}-H), 4.80 (1H, dq, J = 9.2, 6.6 Hz, C_{10}-H); EI-MS m/z 226 (M^+), 209 (M^+–$\dot{O}H$);

High-Resolution EI-MS m/z 226.1209 (M^+, calcd for $C_{12}H_{18}O_4$ 226.1205). The spectral (IR, 250 MHz ^{1}H-NMR, EI-MS) data and chromatographic (TLC) behavior of this sample were identical with those of authentic **8**: mp 141 – 142 °C; $[\alpha]_D^{25}$ +20.9° (*c* 0.900, $CHCl_3$), synthesized through vinyl radical cyclization as described below.

Methyl (1*R*,6*R*)-6-[(*R*)-1-(Benzyloxy)ethyl]-1-(2-bromoallyl)-2-oxocyclohex-3-ene-1-carboxylate (54).

To a suspension of NaH (125 mg, 5.21 mmol) in DMF (30 ml) cooled at 0 °C was added a solution of **6** (980 mg, 3.40 mmol) in DMF (20 ml) dropwise over 5 min. After stirring at 0 °C for 10 min, 2-bromoallyl bromide (0.720 ml, 6.81 mmol) was added. The reaction mixture was heated at 50 °C for 15 h, cooled to room temperature, quenched with saturated aqueous NH_4Cl, and extracted with ether. The combined ethereal extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ether/hexane, 3:7) to afforded **54** (850 mg, 61%) as a colorless oil: $[\alpha]_D^{25}$ +14.1° (*c* 1.30, $CHCl_3$); IR (neat) 2950, 1730, 1670, 1620, 1430, 1260, 1250, 1200, 1130, 1070, 890 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.26 (3H, d, J = 6.5 Hz, C_{10}-Me), 2.41 – 2.94 (3H, m, C_9-H, C_{11}-H_2), 3.17 (3H, s, CO_2Me), 3.34, 3.53 (each 1H, d, J = 15.5 Hz, C_{15}-H_2), 3.85 (1H, dq, J = 1.0, 6.5 Hz, C_{10}-H), 4.19, 4.51 (each 1H, d, J = 10.5 Hz, Ph*C*H_2), 5.53, 5.64 (each 1H, s, CBr=CH_2), 6.17 (1H, dd, J = 2.5, 10.5 Hz, CH=*C*HCO), 7.13 (1H, m, *C*H=CHCO), 7.22 – 7.34 (5H, m, Ph); EI-MS m/z 409 (M^+), 407 (M^+); High-Resolution EI-MS m/z 407.0887 (M^+, calcd for $C_{20}H_{23}O_4Br$ 407.0972).

(1*R*,6*R*,7*R*)-1-(2-Bromoallyl)-7-methyl-8-oxabicyclo[4.3.0]non-3-ene-2,9-dione (55).

To a solution of $FeCl_3$ (780 mg, 4.80 mmol) in CH_2Cl_2 (15 ml) at room temperature was added a solution of **54** (650 mg, 1.60 mmol) in CH_2Cl_2 (15 ml)

dropwise over 10 min. The mixture was stirred at room temperature for 1 h, quenched with 1 N aqueous HCl, and extracted with CH_2Cl_2. The combined organic layers were washed with brine dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 1:9) gave **55** (350 mg, 77%) as a colorless oil: $[\alpha]_D^{25}$ +37.3° (*c* 1.00, $CHCl_3$); IR (neat) 2950, 1770, 1670, 1620, 1430, 1390, 1330, 1220, 1170, 1120, 1050, 990, 900 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.30 (3H, d, J = 6.5 Hz, C_{10}-Me), 2.36 – 2.49, 2.70 – 2.84 (each 1H, m, C_{11}-H), 3.10, 3.34 (each 1H, d, J = 15.0 Hz, C_{15}-H_2), 3.34 (1H, dd, J = 1.7, 6.8 Hz, C_9-H), 4.79 (1H, dq, J = 6.7, 6.5 Hz, C_{10}-H), 5.61, 5.78 (each 1H, d, J = 1.8 Hz, CBr=CH_2), 6.18 (1H, dt, J = 10.4, 2.1 Hz, CH=*CH*CO), 7,01 (1H, dt, J = 10.4, 4.2 Hz, *CH*=CHCO); EI-MS m/z 287 (M^+), 285 (M^+); High-Resolution EI-MS m/z 285.0096 (M^+, calcd for $C_{12}H_{13}O_3Br$ 285.0126).

(1*R*,2*R*,6*R*,7*R*)-1-(2-Bromoallyl)-2-hydroxy-7-methyl-8-oxabicyclo-[4.3.0]non-3-ene-9-one (56).

To a solution of **55** (350 mg, 1.23 mmol) and $CeCl_3 \cdot 7H_2O$ (874 mg, 2.46 mmol) in MeOH (20 ml) cooled at 0 °C was added $NaBH_4$ (140 mg, 3.69 mmol). After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (AcOEt/PhH, 1:4) to afford **56** (256 mg, 73%) as a colorless oil; $[\alpha]_D^{25}$ +6.90° (*c* 1.10, $CHCl_3$); IR (neat) 3400, 2950, 1770, 1620, 1430, 1390, 1350, 1180, 1050, 900 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 6.8 Hz, C_{10}-Me), 2.58, 3.32 (each 1H, d, J = 15.0 Hz, C_{15}-H_2), 2.86 (1H, dt, J = 5.5, 7.2 Hz, C_9-H), 4.36 (1H, brs, C_{14}-H), 4.82 (1H, dt, J = 14.2, 6.8 Hz, C_{10}-H), 5.58, 5.70 (each 1H, brs, CBr=CH_2), 5.80 – 5.98 (2H, m, CH=CH);EI-MS m/z 288 (M^+–H), 286 (M^+–H), 271 (M^+–H_2O), 269 (M^+–

H_2O); High-Resolution EI-MS m/z 286.0204 (M^+–H, calcd for $C_{12}H_{14}O_3Br$ 286.0203).

(1*R*,2*R*,5*R*,8*R*,1'*R*)-2-Ethyl-8-hydroxy-6-methylenebicyclo[3.2.1]-octane-1,1'-carbolactone (57).

A solution of **56** (256 mg, 0.910 mmol) and AIBN (8.00 mg, 40.0 mmol) in PhH (10 ml) was heated at 80 °C and ^{n}Bu$_3$SnH (0.270 ml, 1.00 mmol) was added dropwise over 5 min. The reaction was heated at 80 °C for 1 h and cooled to room temperature. The solvent was removed in vacuo and purification by silica gel column chromatography (AcOEt/PhH, 1:4) furnished **57** (150 mg, 79%) as white crystals: mp 119 – 121 °C; $[\alpha]_D^{25}$ = +43.2° (*c* 0.900, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1730, 1650, 1350, 1260, 1150, 950, 850 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.36 (3H, d, J = 7.2 Hz, C_{10}-Me), 2.26 (1H, d, J = 16.5 Hz, C_{15}-H), 2.69 (1H, dt, J = 8.5, 8.9 Hz, C_9-H), 2.76 (1H, d, J = 7.2 Hz, C_{13}-H), 3.13 (1H, dt, J = 16.5, 2.5 Hz, C_{15}-H), 4.26 (1H, brs, C_{14}-H), 4.85 (1H, dq, J = 6.5, 7.2 Hz, C_{10}-H), 5.03, 5.12 (each 1H, brs, C=CH_2). Anal. Found: C, 69.11; H, 7.94. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75.

(1*R*,2*R*,5*R*,6*R*,8*R*,1'*R*)-2-Ethyl-6,8-dihydroxy-6-methylbicyclo-[3.2.1]octane-1,1'-carbolactone (8).

To a solution of **57** (150 mg, 0.728 mmol) in a mixture of acetone (1.0 ml) and H_2O (1.0 ml) at room temperature was added I_2 (220 mg, 0.728 mmol). After stirring at room temperature for 1 h, 30% aqueous H_2O_2 (0.50 ml) was added. The mixture was stirred at room temperature for 48 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 3:7) gave the almost pure iodohydrine. A solution of the iodohydrine and AIBN (1.00 mg, 5.00 μmol) in PhH (2.0 ml) was heated at

80 °C and $^{n}Bu_3SnH$ (0.220 ml, 730 mmol) was added dropwise over 10 min. The reaction was heated at 80 °C for 1 h and cooled to room temperature. The solvent was removed in vacuo and residual oil was purified by silica gel column chromatography (AcOEt/PhH, 1:1) to afford **8** (65.0 mg, 41%, 2 steps) as white crystals: mp 141 – 142 °C; $[\alpha]_D^{25}$ +20.9° (*c* 0.900, $CHCl_3$). The spectral (IR, 250 MHz ^{1}H-NMR, EI-MS) data and chromatographic (TLC) behavior of this sample were identical with those of **8**: mp 142 – 143 °C; $[\alpha]_D^{25}$ +21.4° (*c* 0.900, $CHCl_3$), synthesized *via* cyclization induced by SmI_2 as described previously.

(1*R*,2*R*,5*R*,6*R*,8*R*,1'*R*)-6,8-(Benzylidenedioxy)-2-ethyl-6-methyl-bicyclo[3.2.1]octane-1,1'-carbolactone (58).

To a solution of **8** (45.0 mg, 0.199 mmol) and $PhCH(OMe)_2$ (36.0 mg, 0.237 mmol) in CH_2Cl_2 (1.0 ml) at room temperature was added CSA (5.00 mg, 21.6 μmol). The mixture was stirred at room temperature for 1 h and neutralized with Et_3N. The solvent was removed in vacuo and residue was purified by silica gel column chromatography (AcOEt/PhH, 1:9) to give **58** (57.0 mg, 95%) as colorless crystals: mp 119 – 121 °C; $[\alpha]_D^{25}$ = –5.61° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2950, 1770, 1450, 1390, 1350, 1310, 1270, 1110, 1070, 1020, 970 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.35 (3H, d, J = 6.8 Hz, C_{10}-Me), 1.43 (3H, s, C_{16}-Me), 1.85, 3.02 (each 1H, d, J = 15.2 Hz, C_{15}-H_2), 2.33 (1H, d, J = 10.8 Hz, C_{13}-H), 2.64 (1H, dt, J = 7.7, 10.2 Hz, C_9-H), 4.61 (1H, brs, C_{14}-H), 4.76 (1H, dq, 7.7, 6.8 Hz, C_{10}-H), 6.57 (1H, s, Ph*CH*), 7.28 – 7.54 (5H, m, Ph); EI-MS m/z 314 (M^+), 203 (M^+–PhCHO); High-Resolution EI-MS m/z 314.1516 (M^+, calcd for $C_{19}H_{22}O_4$ 314.1518).

Chapter 5.

2-[2-[(4-Methoxyphenyl)methoxy]-1,1-dimethylethyl]-1,3-dioxolane.

To a solution of NaH (12.2 g, 508 mmol) in DMF (750 ml) cooled at 0 °C was added a solution of 2-(2-hydroxy-1,1-dimethylethyl)-1,3-dioxolane (**76**) (50.0 g, 342 mmol) in DMF (250 ml). The reaction was stirred at room temperature for 30 min and cooled to 0 °C and MPMCl (63.4 g, 411 mmol) was added dropwise over 30 min. After stirring at room temperature for 2 h, the mixture was diluted with ether and saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (ether/hexane, 1:4) to yield the MPM ether (73.0 g, 80%) as a colorless oil: IR (neat) 2950, 1600, 1450, 1160, 1090, 1080, 820 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.90 (6H, s, Me x 2), 3.24 (2H, s, MPMO*CH*$_2$) 3.80 (3H, s, C_6H_4O*Me*), 3.92 (4H, m, OCH_2CH_2O), 4.45 (2H, s, C_6H_4*CH*$_2$), 4.73 (1H, s, OCHO), 6.85, 7.24 (each, 2H, d, J = 9 Hz, C_6H_4).

3-[(4-Methoxyphenyl)methoxy]-2,2-dimethylpropionaldehyde (77).

A solution of the MPM ether (73.0 g, 274 mmol) in a mixture of acetone (2.0 l) and 2 N aqueous HCl (100 ml) was heated at reflux for 1.5 h, cooled to room temperature, diluted with brine, and extracted with ether. The combined layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (ether/hexane, 1:4) to give **77** (32.0 g, 53%) as a colorless oil: ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.05 (6H, s, Me x 2), 3.40 (2H, s, MPMO*CH*$_2$), 3.78 (3H, s, C_6H_4O*Me*), 4.44 (2H, s, C_6H_4*CH*$_2$), 6.88, 7.24 (each 2H, d, J = 9 Hz, C_6H_4), 9.55 (1H, s, CHO).

Ethyl (*E*)-5-[(4-Methoxyphenyl)methoxy]-4,4-dimethyl-2-pentenoate.

To a suspension of NaH (3.00 g, 125 mmol) in THF (500 ml) at room temperature was added $(MeO)_2POCH_2CO_2Et$ (20.8 g, 115 mmol). After stirring at room temperature for 10 min, a solution of **77** (23.2 g, 104 mmol) in THF (100 ml) was added. The reaction was stirred at room temperature for 10 h, quenched with saturated aqueous NH_4Cl, and extracted with ether. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (ether/hexane, 1:4) gave the ester (25.4 g, 88%) as a colorless oil: IR (neat) 2950, 1710, 1610, 1590, 1450, 1300, 1250, 1170, 1080, 1030, 820 cm^{-1}; ^1H-NMR (90 MHz, $CDCl_3$) δ 1.04 (6H, s, Me x 2), 1.30 (3H, t, J = 8 Hz, $CO_2CH_2\mathit{Me}$), 3.20 (2H, s, MPMO$\mathit{CH_2}$), 3.80 (3H, s, $C_6H_4O\mathit{Me}$), 4.18 (2H, q, J = 8 Hz, O$\mathit{CH_2}$Me), 4.45 (2H, s, $C_6H_4\mathit{CH_2}$), 5.80 (1H, d, J = 15 Hz, CH=CHCO), 6.95 (1H, d, J = 15 Hz, CH=CHCO), 6.90, 7.22 (each, 2H, d, J = 9 Hz, C_6H_4).

(*E*)-5-[(4-Methoxyphenyl)methoxy]-4,4-dimethyl-2-penten-1-ol (78).

To a solution of the ester (25.4 g, 91.3 mmol) in hexane cooled at 0°C was added 1.00 M hexane solution of DIBAL (220 ml, 220 mmol) dropwise over 30 min. After stirring at 0 °C for 20 min, the reaction mixture was quenched with AcOEt (50 ml), MeOH (10 ml), and H_2O (16 ml), stirred at 0 °C for 1 h, diluted with AcOEt, and filtered through a plug of Celite. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (AcOEt/PhH, 3:7) to afford **78** (20.5 g, 90%) as a colorless oil: IR (neat) 3430, 2960, 2880, 1610, 1590, 1460, 1360, 1300, 1240, 1170, 1030, 870, 820 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.02 (6H, s, Me x 2), 3.15 (2H, s, C_5-H_2) 3.80 (3H, s, $C_6H_4O\mathit{Me}$), 4.10 (2H, d, J = 6.5 Hz, C_1-H), 4.44 (2H, s, $C_6H_4\mathit{CH_2}$), 5.60 (1H, dt, J = 15.2, 6.5 Hz, C_2-H), 5.72 (1H, d, J = 15.2 Hz, C_3-H), 6.86, 7.23 (each, 2H, d, J = 9.0 Hz, C_6H_4); EI-MS m/z 250 (M^+), 219 (M^+–OMe); High-Resolution EI-MS m/z 250.1561 (M^+, calcd for $C_{15}H_{22}O_3$ 250.1570).

(2*S*,3*R*)-2,3-Epoxy-5-[(4-methoxyphenyl)methoxy]-4,4-dimethyl-1-pentanol (79).

To a suspension of L-(+)-diisopropyl tartarate (1.48 g, 6.30 mmol), $Ti(O^iPr)_4$ (1.50 g, 5.04 mmol), and MS-4A (10.0 g) in CH_2Cl_2 (100 ml) cooled at –20 °C were added a solution of **78** (5.06 g, 20.2 mmol) in CH_2Cl_2 (10 ml) and 4.50 M CH_2Cl_2 solution of $^tBuO_2H$ (6.50 ml, 29.2 mmol). The mixture was stirred at –20 °C for 1 h, quenched with saturated aqueous tartaric acid (10 ml), stirred at ambient temperature for 30 min, diluted with CH_2Cl_2, and filtered through a plug of Celite. The solvent was removed in vacuo and residual oil was subject to silica gel column chromatography (AcOEt/PhH, 1:4) to afford **79** (4.85 g, 90%) as a colorless oil: $[\alpha]_D^{25}$ = +7.03° (*c* 1.28, $CHCl_3$); IR (neat) 3430, 2960, 2860, 1610, 1510, 1460, 1240, 1080, 1030, 890, 800 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.90, 0.89 (each 3H, s, Me x 2), 2.91 (1H, d, J = 2.4 Hz, C_3-H), 3.07 (1H, dt, J= 1.8, 3.5 Hz, C_2-H), 3.23, 3.18 (each 1H, d, J = 9.0 Hz, C_5-H_2), 3.58 (1H, dd, J = 3.5, 11.5 Hz, C_1-H), 3.80 (3H, s, C_6H_4OMe), 3.86 (1H, dd, J = 1.8, 11.5 Hz, C_1-H), 4.26 (2H, s, $C_6H_4CH_2$), 6.86, 7.23 (each 2H, d, J = 9.1 Hz, C_6H_4); EI-MS m/z 266 (M^+); High-Resolution EI-MS m/z 266.1515 (M^+, calcd. for $C_{15}H_{22}O_4$ 266.1519).

(*S*)-5-[(4-Methoxyphenyl)methoxy]-4,4-dimethyl-1-pentene-3-ol (80).

To a solution of **79** (2.26 g, 8.49 mmol) in PhH (50 ml) at room temperature were added imidazole (1.47 g, 21.6 mmol), Ph_3P (5.57 g, 21.2 mmol), and I_2 (4.32 g, 17.0 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 1:4) gave the crude iodide, which was dissolved in EtOH (50 ml). To the solution at room temperature were added powdered Zn (2.77 g, 42.5 mmol) and saturated aqueous NH_4Cl (2.0 ml).

The reaction mixture was stirred at room temperature for 1 h, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (AcOEt/hexane, 3:7) to give **80** (1.65 g, 78%) as a colorless oil: $[\alpha]_D^{25}$ = –24.7° (*c* 1.03, $CHCl_3$); IR (neat) 3430, 2960, 2880, 1610, 1510, 1585, 1460, 1240, 1080, 1030, 890, 800 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.94, 0.88 (each 3H, s, Me x 2), 3.25, 3.37 (each 1H, d, J = 8.5 Hz, C_5-H_2), 3.81 (3H, s, C_6H_4OMe), 3.93 (1H, d, J = 6.5 Hz, C_3-H), 4.44 (2H, s, $C_6H_4CH_2$), 5.15 (1H, dd, J = 1.1, 10.5 Hz, CH=*CH*H), 5.24 (1H, d, J = 1.1, 17.5 Hz, CH=*CH*H), 5.86 (1H, ddd, J = 6.5, 10.5, 17.5 Hz, *CH*=CH_2), 6.88, 7.24 (each, 2H, d, J = 8.9 Hz, C_6H_4); EI-MS m/z 250 (M^+); High-Resolution EI-MS m/z 250.1561 (M^+, calcd for $C_{15}H_{22}O_4$ 250.1570).

(*R*)-4-[(4-Methoxyphenyl)methoxy]-3,3-dimethyl-1,2-butanediol (81).

A solution of **80** (400 mg, 1.60 mmol) in a mixture of CH_2Cl_2 (20 ml), MeOH (20 ml), and pyridine (1.0 ml) containing Sudan III (1 drops) was cooled to –78 °C. Ozone was bubbled through the solution at –78 °C until the pink color turned a blue color, and $NaBH_4$ (300 mg, 8.00 mmol) was added. The mixture was diluted with 2 N aqueous HCl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 2:3) furnished **81** (280 mg, 69%) as a colorless oil: $[\alpha]_D^{25}$ = –5.72° (*c* 1.00, $CHCl_3$); IR (neat) 3420, 2960, 2880, 1610, 1590, 1510, 1460, 1340, 1290, 1240, 1170, 1080, 1030, 820 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.91, 0.94 (each 3H, s, Me x 2), 3.25, 3.37 (each 1H, d, J = 8.5 Hz, C_5-H_2), 3.48 (1H, dd, J= 4.2, 5.8 Hz, C_3-H), 3.57 (1H, dd, J = 5.8, 10.3 Hz, C_2-H), 3.63 (1H, dd, J = 4.2, 10.3 Hz, C_2-H), 3.80 (3H, s, C_6H_4OMe), 4.43 (2H, s, $C_6H_4CH_2$), 6.86, 7.23 (each, 2H, d, J = 8.8 Hz, C_6H_4); EI-MS m/z 254 (M^+); High-Resolution EI-MS m/z 254.1507 (M^+, calcd for $C_{14}H_{22}O_4$ 254.1519).

(*R*)-1,2-Epoxy-4-[(4-methoxyphenyl)methyl]-3,3-dimethylbutane (10).

To a solution of KH (2.10 g, 18.2 mmol) in THF (15 ml) at room temperature was added a solution of **81** (1.15 g, 4.52 mmol) in THF (10 ml). The reaction was heated at 40 °C for 10 min and *p*-TsCl (948 mg, 0.492 mmol) was added. The mixture was heated at 40 °C for 60 h, cooled to 0 °C, diluted with ether and saturated aqueous NH_4Cl, and extracted with ether. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to silica gel column chromatography (AcOEt/PhH, 1:7) to yield **10** (870 mg, 81%) as a colorless oil: $[\alpha]_D^{25}$ = –10.6° (*c* 1.42, $CHCl_3$); IR (neat) 2960, 2850, 1620, 1520, 1470, 1370, 1300, 1250, 1200, 1040, 920, 820 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.89, 0.91 (each 3H, s, Me x 2), 2.65 (2H, d, J = 5.6 Hz, C_2-H_2), 2.91 (1H, t, J = 5.6 Hz, C_3-H), 3.20, 3.26 (each 1H, d, J = 8.5 Hz, C_5-H_2), 3.81 (3H, s, C_6H_4OMe), 4.45 (2H, s, $C_6H_4CH_2$), 6.88 7.22 (each, 2H, d, J = 8.5 Hz, C_6H_4); EI-MS m/z 236 (M^+), 205 (M^+–OMe); High-Resolution EI-MS m/z 236.1416 (M^+, calcd for $C_{14}H_{20}O_3$ 236.1413).

(1*R*,2*R*,5*R*,6*R*,8*R*,1'*R*)-2-Ethyl-6,8-bis(methoxymethoxy)-6-methyl-bicyclo[3.2.1]octane-1,1'-carbolactone.

To 0.100 M THF solution of SmI_2 (400 ml, 40.0 mmol) cooled at –78 °C, was added a solution of **48** (2.20 g, 9.80 mmol) in a mixture of THF (50 ml) and HMPA (50 ml). The reaction mixture was warmed to 0 °C, stirred at 0 °C for 15 h, diluted with ether and 1 N aqueous HCl, and extracted with AcOEt. The combined organic layers were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated in vacuo, affording crude **8**, which was used in the next step without further purification. To a solution of crude **8** and ^{i}Pr$_2$NEt (30.0 ml, 313 mmol) in CH_2Cl_2 (50 ml) cooled at 0 °C was added MOMCl (6.50 ml, 86.0 mmol). The mixture was stirred at room temperature

for 48 h, poured into saturated aqueous NH_4Cl, and extracted with ether. The combined layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 1:4) to give the bis(methoxymethyl) ether (1.90 g, 85%, 2 steps) as a colorless oil: $[\alpha]_D^{25}$ = –40.2° (*c* 0.500, $CHCl_3$); IR (neat) 2950, 1770, 1450, 1390, 1350, 1000 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.40 (3H, d, J = 7.2 Hz, C_{10}-Me), 1.46 (3H, s, C_{16}-Me), 2.48 (1H, dd, J = 2.6, 5.8 Hz, C_{13}-H), 2.70 (1H, dt, J = 10.7, 7.7 Hz, C_9-H), 3.40 (1H, d, J = 13.5 Hz, C_{15}-H), 3.36, 3.38 (each 3H, s, OMe x 2), 4.20 (1H, brs, C_{14}-H), 4.60, 4.76 (each 1H, d, J = 6.9 Hz, OCH_2O), 4.62 (1H, dq, J = 6.8, 7.2 Hz, C_{10}-H), 4.65, 4.72 (each 1H, d, J = 7.5 Hz, OCH_2O); EI-MS m/z 314 (M^+), 269 (M^+–CO_2H), 253 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 314.1723 (M^+, calcd for $C_{16}H_{26}O_6$ 314.1729).

Methyl (1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(*R*)-1-Hydroxyethyl]-6,8-bis(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-carboxylate.

A solution of the bis(methoxymethyl) ether (1.50 g, 4.78 mmol) in a mixture of MeOH (50 ml) and 1 N aqueous KOH (20 ml) was heated at 80 °C for 1 h, poured into a mixture of ice and H_2O, acidified with 1 N aqueous HCl to pH 3, saturated with NaCl, and extracted with AcOEt. The extracts were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was treated with ethereal CH_2N_2 at room temperature until a yellow color persisted. Concentration in vacuo and purification by silica gel column chromatography (AcOEt/hexane, 1:3 → 1:1) afforded the hydroxyester (1.50 g, 91%) as a colorless oil: $[\alpha]_D^{25}$ = –0.660° (*c* 0.900, $CHCl_3$); IR (neat) 3450, 2950, 1730, 1440, 1380, 1300, 1250, 1200, 1140, 1030, 920 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.14 (3H, d, J = 6.2 Hz, C_{10}-Me), 1.47 (3H, s, C_{16}-Me), 1.80, 2.83 (each 1H, d, J = 14.8 Hz, C_{15}-H_2), 2.38 (1H, t, J = 2.7 Hz, C_{13}-H), 3.36, 3.39 (each 3H, s, OMe x 2), 3.69 (3H, s, CO_2Me), 4.18 (1H, quintet, J = 6.2 Hz, C_{10}-H), 4.60 (1H, s, C_{14}-H), 4.68,

4.77 (each 1H, d, J = 7.0 Hz, OCH_2O), 4.69 (2H, brs, OCH_2O); EI-MS m/z 346 (M^+), 315 (M^+–OMe), 301 (M^+–MeCHOH); High-Resolution EI-MS m/z 346.1971 (M^+, calcd for $C_{17}H_{30}O_7$ 346.1992).

Methyl (1*R*,2*R*,5*R*,6*R*,8*R*)-2-Acetyl-6,8-bis(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-carboxylate (82).

To a solution of the hydroxyester (1.50 g, 4.34 mmol) in acetone (50 ml) cooled at 0 °C was added Jones reagent until a faint red color persisted. After stirring was continued at 0 °C for 10 min, excess reagent was destroyed by addition of isopropanol. The resulting mixture was diluted with ether and filtered through a plug of Celite. The filtrate was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (AcOEt/PhH, 3:7) to give **82** (1.70 g, 88%) as a colorless oil: $[\alpha]_D^{25}$ = –23.9° (*c* 1.30, $CHCl_3$); IR (neat) 2950, 1740, 1715, 1450, 1360, 1300, 1255, 1235, 1150, 1100, 1070, 1040, 950 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.42 (3H, s, C_{16}-Me), 1.68, 3.08 (each 1H, d, J = 15.2 Hz, C_{15}-H_2), 2.12 (3H, s, COMe), 2.42 (1H, brt, J = 2.8 Hz, C_{13}-H), 2.92 (1H, d, J = 6.0 Hz, C_9-H), 3.32, 3.37 (each, 3H, s, OMe x 2), 3.68 (3H, s, CO_2Me), 4.56, 4.65 (each, 1H, d, J = 6.8 Hz, OCH_2O), 4.68, 4.78 (each, 1H, d, J = 9.6 Hz, OCH_2O), 4.74 (1H, brs, C_{14}-H); FI-MS m/z 344 (M^+), 313 (M^+–OMe), 283 (M^+–CH_2OMe); High-Resolution FI-MS m/z 344.1815 (M^+, calcd for $C_{17}H_{28}O_7$ 344.1735).

Methyl (1*R*,2*R*,5*R*,6*R*,8*R*)-6,8-Bis(methoxymethoxy)-2-[1-(trifluoromethanesulfonyloxy)vinyl]-6-methylbicyclo[3.2.1]octane-1-carboxylate.

To a solution of $(TMS)_2NH$ (1.20 ml, 5.69 mmol) in THF (20 ml) cooled at 0 °C was added 1.50 M hexane solution of ^{n}BuLi (3.60 ml, 5.39 mmol). After stirring at 0 °C for 10 min, the solution of $LiN(TMS)_2$ was cooled to –78 °C and a solution of **82** (1.00 g, 2.91 mmol) in THF (10 ml) was added. Stirring was

continued at –78 °C for 30 min and a solution of Tf_2NPh (1.30 g, 3.64 mmol) in THF (10 ml) was added. The reaction mixture was stirred at –78 °C for 3 h, quenched with MeOH (1.0 ml), diluted with AcOEt, and filtered through a plug of silica gel. The filtrate was concentrated in vacuo and the crude product was purified by silica gel column chromatography (AcOEt/PhH, 1:20 → 1:10) to yield the triflate (1.20 g, 87%) as a colorless oil: $[\alpha]_D^{25}$ = –17.8° (*c* 1.05, $CHCl_3$); IR (neat) 2950, 1740, 1650, 1420, 1300, 1250, 1220, 1150, 1050, 950 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.46 (3H, s, C_{16}-Me), 2.45 (1H, t, J = 2.7 Hz, C_{13}-H), 2.88 (1H, d, J = 7.5 Hz, C_9-H), 1.89, 2.93 (each 1H, d, J = 15.2 Hz, C_{15}-H), 3.35, 3.38 (each 3H, s, OMe x 2), 3.67 (3H, s, CO_2Me), 4.20 (1H, brs, C_{14}-H), 4.64, 4.69 (each 1H, d, J = 6.8 Hz, OCH_2O), 4.69, 4.75 (each 1H, d, J = 5.5 Hz, OCH_2O), 5.00, 5.24 (each 1H, d, J = 4.2 Hz, $C{=}CH_2$); FAB-MS m/z 477 (M^++H), 445 (M^+–OMe); High-Resolution FAB-MS m/z 477.1398 (M^++H, calcd for $C_{18}H_{27}O_9F_3S$ 477.1375).

Methyl (1*R*,2*R*,5*R*,6*R*,8*R*)-6,8-Bis(methoxymethoxy)-6-methyl-2-[3-(phenylthio)-1-propen-2-yl]bicyclo[3.2.1]octane-1-carboxylate (83).

To a solution of $^nBu_3SnCH_2SPh$ (8.40 g, 13.2 mmol) in THF (20 ml) cooled at 0 °C was added 1.50 M hexane solution of ^{n}BuLi (8.80 ml, 13.2 mmol). After stirring at room temperature for 10 min, the solution of $LiCH_2SPh$ was added to a solution of CuCN (600 mg, 6.70 mmol) and LiCl (284 mg, 6.70 mmol) in THF (10 ml) cooled at –78 °C. The resulting mixture was warmed to 0 °C over 10 min, and cooled to –20 °C. To the solution of $Li_2CuCN(CH_2SPh)_2$ was added a solution of the triflate (500 mg, 1.05 mmol) in THF (5.0 ml). After stirring at –20 °C for 5 h, the reaction was quenched with saturated aqueous NH_4Cl containing 10% NH_3. The mixture was extracted with ether and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/PhH, 1:4) afforded **83** (300 mg, 65%) as a colorless oil: $[\alpha]_D^{25}$ = +9.68° (*c*

0.950, $CHCl_3$); IR (neat) 2950, 1740, 1450, 1300, 1250, 1150, 1050, 950, 750 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.48 (3H, s, C_{16}-Me), 1.86, 2.87 (each 1H, d, J = 14.9 Hz, C_{15}-H_2), 2.42 (1H, t, J = 2.7 Hz, C_{13}-H), 2.83 (1H, d, J = 7.9 Hz, C_9-H), 2.88 (1H, d, J = 8 Hz, C_{15}-H), 3.12, 3.58 (each 1H, d, J = 13.6 Hz, PhS*C*H_2), 3.35, 3.37 (each 3H, s, OMe x 2), 3.60 (3H, s, CO_2Me), 4.21 (1H, brs, C_{14}-H), 4.64 (2H, s, OCH_2O), 4.68, 4.76 (each 1H, d, J = 7.2 Hz, OCH_2O), 5.00, 5.05 (each 1H, brs, C=CH_2), 7.22 – 7.30 (5H, m, Ph); FI-MS, m/z 451 (M^++H), 450 (M^+); High-Resolution FI-MS m/z 450.2051 (M^+, calcd for $C_{24}H_{34}O_6S$ 450.2077).

(1*R*,2*R*,5*R*,6*R*,8*R*)-6,8-Bis(methoxymethoxy)-6-methyl-2-[3-(phenylthio)-1-propen-2-yl]bicyclo[3.2.1]octane-1-methanol.

To a solution of **83** (320 mg, 0.711 mmol) in CH_2Cl_2 (50 ml) cooled at –78 °C was added 1.00 M hexane solution of DIBAL (3.30 ml, 3.30 mmol). After stirring at –78 °C for 1 h, the reaction mixture was warmed to 0 °C, quenched with MeOH (1.0 ml) and H_2O (0.25 ml), diluted by ether, filtered by a plug of Celite. The filtrate was concentrated in vacuo and the residue was subjected to silica gel column chromatography (AcOEt/PhH, 3:7) to afford the alcohol (220 mg, 73%) as a colorless oil: $[\alpha]_D^{25}$ = –4.25° (*c* 14.1, $CHCl_3$); IR (neat) 3400, 2950, 1450, 1210, 1100, 1050, 920, 750 cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.43 (3H, s, C_{16}-Me), 1.49, 2.83 (each 1H, d, J = 14.5 Hz, C_{15}-H_2), 2.38 (1H, brt, J = 2.7 Hz, C_{13}-H), 2.63 (1H, d, J = 7.8 Hz, C_9-H), 3.34, 3.35 (each, 3H, s, OMe x 2), 3.47, 3.63 (each 1H, d, J = 13.2 Hz, PhS*C*H_2), 3.58, 3.88 (each 1H, d, J = 10.6 Hz, C_7-H_2), 4.29 (1H, brs, C_{14}-H), 4.54, 4.71 (each 1H, d, J = 6.8 Hz, OCH_2O), 4.69 (2H, s, OCH_2O), 5.00, 5.03 (each 1H, brs, C=CH_2), 7.20 – 7.30 (5H, m, Ph); FI-MS m/z 423 (M^++H), 422 (M^+), 378 (M^+–CH_2OMe); High-Resolution FI-MS m/z 422.2122 (M^+, calcd for $C_{23}H_{34}O_5S$ 422.2128).

(1*R*,2*R*,5*R*,6*R*,8*R*)-6,8-Bis(methoxymethoxy)-6-methyl-2-[3-(phenylthio)-1-propen-2-yl]bicyclo[3.2.1]octane-1-carbaldehyde.

To a solution of the alcohol (220 mg, 520 mmol) in CH_2Cl_2 (20 ml) at room temperature was added Dess-Martin periodinane (550 mg, 1.29 mmol). After stirring at room temperature for 30 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was stirred at room temperature for 30 min and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/PhH, 1:9) to give the aldehyde (210 mg, 96%) as a colorless oil: $[\alpha]_D^{25}$ = –28.8° (*c* 2.00, $CHCl_3$); IR (neat) 2950, 1730, 1490, 1450, 1210, 1130, 1050, 920, 750 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.45 (3H, s, C_{16}-Me), 1.62, 2.85 (each 1H, d, J = 15.0 Hz, C_{15}-H), 2.50 (1H, t, J = 2.7 Hz, C_{13}-H), 2.82 (1H, d, J = 6.8 Hz, C_9-H), 3.30, 3.57 (each, 1H, d, J = 13.2 Hz, PhS*CH*$_2$), 3.32, 3.33 (each, 3H, s, OMe x 2), 4.53, 4.76 (each, 1H, d, J = 6.8 Hz, OCH_2O), 4.50 (2H, s, OCH_2O), 4.60 (1H, brs, C_{14}-H), 5.10 (2H, s, C=CH_2), 7.20 – 7.30 (5H, m, Ph), 9.80 (1H, s, CHO); FI-MS m/z 421 (M^++H), 420 (M^+), 376 (M^+–CH_2OMe); High-Resolution FI-MS m/z 420.1986 (M^+, calcd for $C_{23}H_{32}O_5S$ 420.1972).

(1*R*,2*R*,5*R*,6*R*,8*R*)-6,8-Bis(methoxymethoxy)-6-methyl-2-[3-(phenylthio)-1-propen-2-yl]-1-vinylbicyclo[3.2.1]octane (9).

To a solution of $MePPh_3$•Br (70.0 mg, 0.200 mmol) in THF (2.0 ml) cooled at 0 °C was added a solution of $LiN(TMS)_2$ [prepared from $(TMS)_2NH$ (42.0 μl, 0.200 mmol) and 1.50 M THF solution of ^{n}BuLi (0.120 ml, 0.180 mmol) in THF (0.84 ml) as described above]. After stirring at 0 °C for 10 min, the solution of CH_2=PPh_3 was added to a solution of the aldehyde (55.0 mg, 0.130 mmol) in THF (1.0 ml) at room temperature. The reaction mixture was stirred at room temperature for 1 h, poured into brine, and extracted with ether. The combined ethereal layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column

chromatography (ether/hexane, 1:4) to afford **9** (42.0 mg, 77%) as a colorless oil: $[\alpha]_D^{25}$ = –23.3° (*c* 0.900, $CHCl_3$); IR (neat) 2950, 1490, 1480, 1450, 1150, 1130, 1050, 920, 750 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.48 (3H, s, C_{16}-Me), 1.82, 2.64 (1H, d, J = 14.5 Hz, C_{15}-H), 2.42 (1H, t, J = 2.8 Hz, C_{13}-H), 2.57 (1H, d, J = 6.8 Hz, C_9-H), 3.33, 3.34 (each 3H, s, OMe x 2), 3.53, 3.62 (each 1H, d, J = 13.2 Hz, PhS*CH*$_2$), 4.20 (1H, brs, C_{14}-H), 4.52, 4.61 (each 1H, d, J = 6.8 Hz, OCH_2O), 4.67, 4.72 (each 1H, d, J = 6.2 Hz, OCH_2O), 5.02 (1H, d, J = 11.1 Hz, CH=*CH*H), 5.03, 5.08 (each 1H, brs, C=CH_2), 5.10 (1H, d, J = 18.1 Hz, CH=*CH*H), 6.08 (1H, dd, J = 11.1, 18.1 Hz, *CH*=CH_2), 7.25 – 7.30 (5H, m, Ph); FI-MS m/z 419 (M^++H), 418 (M^+), 387 (M^+–OMe), 373 (M^+–CH_2OMe); High-Resolution FI-MS m/z 418.2196 (M^+, calcd for $C_{24}H_{34}O_4S$ 418.2179).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(2*E*,5*S*)-5-Hydroxy-7-[(4-methoxyphenyl)-methoxy]-6,6-dimethyl-1-(phenylthio)-2-hepten-2-yl]-6,8-bis-(methoxymethoxy)-6-methyl-1-vinylbicyclo[3.2.1]octane (84).

To a solution of **9** (18.0 mg, 43.0 μmol), **10** (40.0 mg, 0.169 mmol) TMEDA (20.0 μl, 0.130 mmol), and HMPA (40.0 μl, 0.220 mmol) in THF (2.0 ml) cooled at –78 °C was added 1.50 M THF solution of ^{n}BuLi (60.0 μl, 90.0 μmol). The reaction mixture was warmed to 0 °C, stirred at 0 °C for 1 h, poured into brine, and extracted with ether. The combined ethereal layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (ether/hexane, 1:9 → 1:1) gave the adduct (18.0 mg, 55%, 1:1 diastereomeric mixture by 250 MHz ^{1}H-NMR) as a colorless oil.

A solution of the adduct (15.0 mg, 24.0 μmol) and $(PhS)_2$ (50.0 mg, 229 mmol) in xylene (1.0 ml) was heated at 160 °C in a sealed tube for 1 h. Upon cooling, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (ether/hexane, 1:1) to afford **84** (12.0 mg, 88%) as a colorless oil: $[\alpha]_D^{25}$ = –58.6° (*c* 0.500, $CHCl_3$); IR (neat) 3400, 2950, 2850, 1615,

1590, 1520, 1470, 1450, 1300, 1250, 1150, 1050, 920, 830, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.88, 0.89, 1.25 (each 3H, s, Me x 3), 1.76, 2.64, (each 1H, d, J = 15.6 Hz, C_{15}-H_2), 2.16 (2H, m, C_2-H_2), 2.38 (1H, t, J = 3.2 Hz, C_{13}-H), 2.47 (1H, d, J = 7.1 Hz, C_9-H), 3.18, 3.36, (each 1H, d, J = 9.2 Hz, PhS*C*H_2), 3.38, 3.79 (each 1H, d, J = 13.6 Hz, C_5-H_2), 3.32, 3.34 (each 3H, s, OMe x 2), 3.80 (3H, s, C_6H_4O*Me*), 3.81 (1H, t, J = 2.5 Hz, C_3-H), 4.34 (1H, brs, 1H, C_{14}-H), 4.41 (2H, s, C_6H_4*C*H_2), 4.49, 4.71 (each 1H, d, J = 7.3 Hz, OCH_2O), 4.68, 4.72 (each 1H, d, J = 7.3 Hz, OCH_2O), 5.03 (1H, dd, J = 1.2, 17.6 Hz, CH=*CH*H), 5.12 (1H, dd, J = 1.2, 11.2 Hz, CH=*CH*H), 5.87 (1H, t, J = 7.8 Hz, C=CH), 5.95 (1H, dd, J = 11.2, 17.6 Hz, *CH*=CH_2), 6.84, 7.23 (each 1H, d, J = 8.3 Hz, C_6H_4), 7.18 – 7.32 (5H, m, Ph); FI-MS m/z 655 (M^++H), 654 (M^+), 592 (M^+–$HOCH_2OMe$); High-Resolution FI-MS m/z 654.3599 (M^+, calcd for $C_{38}H_{54}O_7S$ 654.5671).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(2*E*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-[(4-methoxyphenyl)methoxy]-6,6-dimethyl-1-(phenylthio)-2-hepten-2-yl]-6,8-bis(methoxymethoxy)-6-methyl-1-vinylbicyclo[3.2.1]octane.

To a solution of **84** (23.2 mg, 33.6 μmol) and ^{i}Pr_2NEt (20.0 μl, 67.2 μmol) in CH_2Cl_2 (1.0 ml) cooled at 0 °C was added ^{t}$BuMe_2SiOTf$ (8.00 μl, 37.0 μmol). The reaction mixture was stirred at 0 °C for 30 min, poured into brine, and extracted with ether. The combined ethereal layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (ether/hexane, 1:4) to give the *t*-butyldimethylsilyl ether (25.0 mg, 96%) as a colorless oil: $[\alpha]_D^{25}$ = –69.0° (*c* 0.400, $CHCl_3$); IR (neat) 2950, 2850, 1620, 1590, 1520, 1470, 1450, 1380, 1360, 1250, 1150, 1100, 1050, 910, 850, 780, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05, 0.06 (each 3H, s, $SiMe_2$), 0.88, 0.89, 1.25 (each 3H, s, Me x 3), 0.90 (9H, s, Si^{t}Bu), 1.73, 2.63 (each 1H, d, J = 14.7 Hz, C_{15}-H_2), 2.38 (1H, t, J = 3.2 Hz, C_{13}-H), 2.47 (1H, d, J = 7.1 Hz, C_9-H), 3.15, 3.23 (each 1H, d, J = 8.7 Hz, PhS*C*H_2), 3.29, 3.34 (each 3H, s, OMe x 2), 3.46, 3.78 (each 1H, d, J = 11.2 Hz, C_5-H_2),

3.74 (1H, dd, J = 2.9, 6.4 Hz, C_3-H), 3.80 (3H, s, C_6H_4OMe), 4.16 (1H, brs, C_{14}-H), 4.35, 4.43 (each 1H, d, J = 11.7 Hz, $C_6H_4CH_2$), 4.51, 4.67 (each 1H, d, J = 6.8 Hz, OCH_2O), 4.69, 4.72 (each 1H, d, J = 7.3 Hz, OCH_2O), 5.02 (1H, dd, J = 1.0, 17.6 Hz, CH=*CH*H), 5.05 (1H, dd, J = 1.0, 11.0 Hz, CH=*CH*H), 5.81 (1H, t, J = 6.5 Hz, C=CH), 6.04 (1H, dd, J = 11.0, 17.6 Hz, *CH*=CH_2), 6.83, 7.21 (each d, J = 8.8 Hz, C_6H_4), 7.24 – 7.28 (5H, m, Ph); FAB-MS m/z 768 (M^+), 737 (M^+–OMe); High-Resolution FAB-MS m/z 768.4427 (M^+, calcd for $C_{44}H_{68}O_7SSi$ 768.4457).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(2*E*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-6,6-dimethyl-1-(phenylthio)-2-hepten-2-yl]-6,8-bis-(methoxymethoxy)-6-methyl-1-vinylbicyclo[3.2.1]octane.

To a solution of the *t*-butyldimethylsilyl ether (25.0 mg, 32.5 μmol) in a mixture of CH_2Cl_2 (1.0 ml) and H_2O (0.05 ml) at room temperature was added DDQ (10.0 mg, 48.0 μmol). The reaction was stirred at room temperature for 30 min and quenched with saturated aqueous $NaHCO_3$. The resulting mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ether/hexane, 1:5) to afford the alcohol (15.0 mg, 71%) as a colorless oil: $[\alpha]_D^{25}$ = –49.5° (*c* 0.400, $CHCl_3$); IR (neat) 3400, 2950, 1590, 1470, 1450, 1360, 1250, 1100, 1050, 910, 850 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 0.07, 0.08 (each 3H, s, $SiMe_2$), 0.86, 0.98, 1.47 (each, 3H, s, Me x 3), 0.92 (9H, s, Si^{t}Bu), 1.74, 2.64 (each 1H, d, J = 14.2 Hz, C_{15}-H_2), 2.41 (1H, t, J = 2.4 Hz, C_{13}-H), 3.30, 3.60 (each 1H, d, J = 10.7 Hz, C_5-H_2), 3.33, 3.36 (each 3H, s, OMe x 2), 3.48, 3.81 (each 1H, d, J = 11.3 Hz, PhS*CH*$_2$), 3.72 (1H, dd, J = 2.0, 6.6 Hz, C_3-H), 4.16 (1H, brs, C_{14}-H), 4.51, 4.69 (each 1H, d, J = 6.8 Hz, OCH_2O), 4.68, 4.72 (each 1H, d, J = 7.3 Hz, OCH_2O), 5.03 (1H, dd, J = 0.9, 17.7 Hz, CH=*CH*H), 5.10 (1H, dd, J = 0.9, 10.8 Hz, CH=*CH*H), 5.81 (1H, t, J = 6.1 Hz, CH=CH), 5.97 (1H, dd, J = 10.8, 17.7 Hz, *CH*=CH_2), 7.24 – 7.36 (5H, m, Ph).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(2*E*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-6,6-dimethyl-7-oxo-1-(phenylthio)-2-hepten-2-yl]-6,8-bis(methoxymethoxy)-6-methyl-1-vinylbicyclo[3.2.1]octane (11).

To a solution of the alcohol (10.0 mg, 14.6 μmol) in CH_2Cl_2 (2.0 ml) at room temperature was added Dess-Martin periodinane (12.0 mg, 15.0 μmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_4, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in a 1:1 mixture of ether and hexane, and filtered through a plug of silica gel. Concentration of the filtrate in vacuo gave almost pure **11** (8.00 mg, 86%) as a colorless oil: $[\alpha]_D^{25}$ –32.4° (*c* 0.500, $CHCl_3$); IR (neat) 2950, 1730, 1450, 1360, 1250, 1080, 1020, 910, 830 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.07, 0.09 (each 3H, s, $SiMe_2$), 0.89 (9H, s, ^{t}Bu), 1.04, 1.06, 1.46 (each 3H, s, Me x 3), 1.74, 2.64 (each 1H, d, J = 15.2 Hz, C_{15}-H_2), 2.42 (1H, t, J = 2.5 Hz, C_{13}-H), 3.32, 3.35 (each 3H, s, OMe x 2), 3.47, 3.75 (each 1H, d, J = 11.2 Hz, PhS*C*H_2), 3.93 (1H, dd, J = 3.5, 7.0 Hz, C_3-H), 4.11 (1H, s, C_{14}-H), 4.52, 4.69 (each 1H, d, J = 6.8 Hz, OCH_2O), 4.68, 4.72 (each 1H, d, J = 7.2 Hz, OCH_2O), 5.02 (1H, dd, J = 1.2, 11.0 Hz, CH=*CH*H), 5.10 (1H, dd, J = 1.2, 17.5 Hz, CH=*CH*H), 5.62 (1H, t, J = 6.2 Hz, C=CH), 6.00 (1H, dd, J = 11.0, 17.5 Hz, *CH*=CH_2), 7.25 – 7.26 (5H, m, Ph), 9.52 (1H, s, CHO). The aldehyde **11** was used in next step without further purification.

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[1-[(1*S*,2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-3,3-dimethylcyclopent-1-yl]vinyl]-6,8-bis(methoxymethoxy)-6-methyl-1-vinylbicyclo[3.2.1]octane (12).

To a mixture of 0.100 M THF solution of SmI_2 (1.00 ml, 0.100 mmol) and HMPA (0.2 ml) cooled at –78 °C was added a solution of **11** (6.00 mg, 8.78

μmol) in THF (0.8 ml). After stirring at –78 °C for 3 h, the reaction mixture was warmed to ambient temperature, poured into saturated aqueous $NaHCO_3$, and extracted with ether. The combined ethereal extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (ether/hexane, 1:4) afforded **12** (4.00 mg, 78%) as a colorless oil: $[\alpha]_D^{25}$ = +0.500° (*c* 1.50, $CHCl_3$); IR (neat) 3400, 2950, 1590, 1470, 1450, 1360, 1250, 1100, 1050, 910, 840 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 0.05, 0.08 (each 3H, s, $SiMe_2$), 0.84, 1.06, 1.47 (each, 3H, s, Me x 3), 0.89 (9H, s, Si*t*Bu), 1.75, 2.66 (each 1H, d, J = 14.6 Hz, C_{15}-H_2), 2.27 (1H, d, J = 7.4 Hz, C_9-H), 2.44 (1H, t, J = 2.7 Hz, C_{13}-H), 3.49 (6H, s, MeO x 2), 3.44 (1H, dd, J = 1.0, 5.5 Hz, C_3-H), 3.71 (1H, d, J = 4.5 Hz, C_5-H), 4.28 (1H, brs, C_{14}-H), 4.54, 4.72 (each 1H, d, J = 7.0 Hz, OCH_2O), 4.69, 4.74 (each 1H, d, J = 7.3 Hz, OCH_2O), 5.02 (1H, dd, J = 1.0, 17.4 Hz, CH=*CH*H), 5.06 (1H, dd, J = 1.0, 10.7 Hz, CH=*CH*H), 5.13, 5.30 (each 1H, brs, $C=CH_2$), 6.00 (1H, dd, J = 10.7, 17.4 Hz, *CH*=CH_2); FI-MS m/z 539 (M^++H), 538 (M^+), 507 (M^+–OMe), 478 (M^+–OCH_2OMe); High-Resolution FI-MS m/z 538.3688 (M^+, calcd for $C_{30}H_{54}O_6Si$ 538.3691).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[1-[(1*S*,2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-3,3-dimethylcyclopent-1-yl]vinyl]-6,8-bis(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-ethanol (85).

To a solution of **12** (40.0 mg, 74.3 μmol) in THF (2.0 ml) at room temperature was added 9-BBN dimer (19.0 mg, 155 μmol). The reaction was stirred at room temperature for 3 h, quenched with H_2O (0.1 ml), 30% aqueous H_2O_2 (1.0 ml), and 2 N aqueous NaOH (1.0 ml). The mixture was stirred at room temperature for 5 h and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 1:9 → 3:7) to afford recovered **12** (30.0 mg, 72%) and **85** (12.0 mg, 29%) as a colorless oil: $[\alpha]_D^{25}$ = +2.77° (*c* 10.9, $CHCl_3$); IR (neat) 3400, 2950, 1470, 1450, 1100, 1050, 920, 840 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.06, 0.08 (each 3H, s, $SiMe_2$), 0.89 (9H, s, Si^{t}Bu), 0.92, 1.09, 1.42 (each 3H, s, Me x 3), 1.54, 2.42 (each 1H, d, J = 16.5 Hz, C_{15}-H_2), 2.35 (1H, d, J = 7.9 Hz, C_9-H), 2.41 (1H, t, J = 2.7 Hz, C_{13}-H), 2.95 (1H, m, C_1-H), 3.36, 3.37 (each 3H, s, OMe x 2), 3.54 (1H, dd, J = 5.2, 10.0 Hz, C_3-H), 3.71 – 3.75 (3H, m, C_5-H, C_6-H_2), 4.26 (1H, brs, C_{14}-H), 4.55, 4.75 (each, 1H, d, J = 6.4 Hz, OCH_2O), 4.67, 4.76 (each 1H, d, J = 7.2 Hz, OCH_2O), 5.14, 5.32 (each, 1H, brs, C=CH_2); FI-MS m/z 557 (M^++H), 556 (M^+), 525 (M^+–OMe), 495 (M^+–OCH_2OMe); High-Resolution FI-MS m/z 557.2857 (M^++H, calcd for $C_{30}H_{57}O_7Si$ 557.2875).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(*R*)-1-[(1*R*,2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,3-dimethyl-2-hydroxycyclopent-1-yl]-1-hydroxyethyl]-6,8-bis(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-ethanol (86).

To a solution of **85** (12.0 mg, 21.6 μmol) in CH_2Cl_2 (1.0 ml) cooled at 0 °C was added *m*CPBA (10.0 mg, 52.0 μmol). After stirring at room temperature for 2 h, the reaction was quenched with Me_2S (1.0 ml) and Et_3N (0.5 ml). The solvent was removed in vacuo and the residue was subjected to silica gel column chromatography (CH_2Cl_2/acetone/Et_3N, 5:1:0.1) to give the crude α-epoxide, which was dissolved in CH_2Cl_2 (1.0 ml). To the solution cooled at 0 °C was added 1.00 M hexane solution of DIBAL (0.100 ml, 0.100 mmol). The reaction mixture was stirred at 0 °C for 1 h, quenched with saturated aqueous NH_4Cl and brine, and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 1:1) to give **86** (5.00 mg, 40%) as a colorless oil: $[\alpha]_D^{25}$ = –26.8° (*c* 0.900, $CHCl_3$); IR (neat) 3400, 2950, 1470, 1450, 1380, 1250, 1100, 1020, 920, 880 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 0.15 (6H, s, $SiMe_2$), 0.90, 1.13, 1.29, 1.63 (each 3H, s, Me x 4), 0.93 (9H, s, Si*t*Bu), 1.89, 2.00 (each 1H, d, J = 14.5 Hz, C_{15}-H_2), 2.34 (1H, dt, J = 5.3, 9.2 Hz, C_1-H), 3.14 (1H, d, J = 8.9 Hz, C_9-H), 3.36, 3.39 (each 3H, s, OMe x 2), 3.56 (1H, dd, J = 2.9, 3.9 Hz, C_3-H), 3.64, 3.90 (each 1H, dt, J = 10.2, 8.2 Hz, C_6-H_2), 3.68 (1H, d, J = 4.9 Hz, C_5-H), 4.29 (1H, brs, C_{14}-H), 4.53, 4.66 (each, 1H, d, J = 6.9 Hz, OCH_2O), 4.79, 5.06 (each 1H, d, J = 5.2 Hz, OCH_2O); FAB-MS m/z 575 (M^++H), 513 (M^+–OCH_2OMe); High-Resolution FAB-MS m/z 575.3963 (M^++H, calcd for $C_{30}H_{59}O_8Si$ 575.3981).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(*R*)-1-[(1*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,3-dimethyl-2-oxocyclo-1-pentyl]-1-hydroxyethyl]-6,8-bis(methoxy-methoxy)-6-methylbicyclo[3.2.1]octane-1-acetaldehyde.

To a solution of Dess-Martin periodinane (48.0 mg, 0.110 mmol) and pyridine (10.0 μl, 0.420 mmol) in CH_2Cl_2 (2.0 ml) at room temperature was added a solution of **86** (15.0 mg, 26.1 μmol) in CH_2Cl_2 (1.5 ml). The reaction mixture was stirred at room temperature for 1 h, poured into a mixture of

saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (ether/hexane, 1:1) to afford the keto aldehyde (10.0 mg, 67%) as a colorless oil: $[\alpha]_D^{25}$ = –58.0° (*c* 0.500, $CHCl_3$); IR (neat) 3400, 2950, 1750, 1730, 1460, 1380, 1250, 1100, 920, 870, 840, 780 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.15, 0.17 (each 3H, s, $SiMe_2$), 0.91, 1.07, 1.33, 1.83 (each 3H, s, Me x 4), 0.92 (9H, s, Si^{t}Bu), 2.09, 2.72 (each 1H, d, J = 15.2 Hz, C_7-H_2), 2.59 (1H, d, J = 18.0, C_7-H), 3.25, 3.40 (each 3H, s, OMe x 2), 3.58 (1H, dd, J = 1.4, 18.0 Hz, C_7-H), 3.69 (1H, dd, J = 6.4, 10.8 Hz, C_3-H), 4.37 (1H, brs, C_{14}-H), 4.46, 4.67 (each 1H, d, J = 5.8 Hz, OCH_2O), 4.65, 4.76 (each 1H, d, J = 6.8 Hz, OCH_2O), 9.77 (1H, d, J = 1.4 Hz, CHO); FI-MS m/z 571 (M^++H), 570 (M^+), 552 (M^+–H_2O), 539 (M^+–OMe), 525 (M^+–CH_2OMe), 513 (M^+–^{t}Bu); High-Resolution FI-MS m/z 571.3685 (M^++H, calcd for $C_{30}H_{55}O_8Si$ 571.3668).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(*R*)-1-[(1*S*,4*S*)-4-(*tert*-Butyldimethylsiloxy)-3,3-dimethyl-2-oxocyclopent-1-yl]-1-(methoxymethoxy)ethyl]-6,8-bis(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-acetaldehyde.

To a solution of the keto aldehyde (10.0 mg, 17.5 μmol) and ^{i}Pr$_2$NEt (15.0 μl, 78.8 μmol) in CH_2Cl_2 (1.0 ml) cooled at 0 °C were added MOMCl (5.00 μl, 50.0 μmol). The mixture was stirred at ambient temperature for 15 h, poured into brine, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (ether/hexane, 3:7) gave the tris(methoxymethyl) ether (10.0 mg, 93%) as a colorless oil: $[\alpha]_D^{25}$ = –42.5° (*c* 0.300, $CHCl_3$); IR (neat) 2950, 1750, 1730, 1470, 1380, 1250, 1110, 1050, 980, 950, 880, 780 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.06, 0.09 (each 3H, s, $SiMe_2$), 0.91 (9H, s, Si^{t}Bu), 0.92, 1.07, 1.42, 1.83 (each 3H, s, Me x 4), 2.27, 2.36 (each 1H, d, J = 16.1 Hz, C_{15}-H_2), 2.64 (1H, d, J = 18.5 Hz, C_7-H), 3.25, 3.32, 3.40

(each 3H, s, OMe x 3), 3.44 (1H, dd, J = 1.5, 18.5 Hz, C_7-H), 3.70 (1H, dd, J = 6.3, 9.8 Hz, C_3-H), 4.26 (1H, brs, C_{14}-H), 4.48, 4.65 (each 1H, d, J = 5.9 Hz, OCH_2O), 4.63, 4.68 (each 1H, d, J = 10.7 Hz, OCH_2O), 4.66, 4.77 (each 1H, d, J= 6.8 Hz, OCH_2O), 9.78 (1H, d, J = 1.5 Hz, CHO); FI-MS m/z 615 (M^++H), 614 (M^+), 557 (M^+–^{t}Bu).

(1*R*,2*R*,5*R*,6*R*,8*R*)-2-[(*R*)-1-[(1*S*,4*S*)-4-Hydroxy-3,3-dimethyl-2-oxocyclopent-1-yl)-1-(methoxymethoxy)ethyl]-6,8-bis(methoxymethoxy)-6-methylbicyclo[3.2.1]octane-1-acetaldehyde (13).

To a solution of the tris(methoxymethyl) ether (10.0 mg, 16.3 mmol) in THF (1.0 ml) cooled at 0 °C was added 1.00 M THF solution of ^{n}Bu$_4$N•F (17.0 μl, 17.0 μmol). After stirring at 0 °C for 10 min, the mixture was poured into brine and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by alumina column chromatography (acetone/CH_2Cl_2, 1:1) to give **13** (5.00 mg, 61%) as a colorless oil: $[\alpha]_D^{25}$ = –33.8° (*c* 0.700, $CHCl_3$). The spectral (IR, 400 MHz ^{1}H-NMR, FI-MS) data and chromatographic (TLC) behavior of this sample were identical with those of authentic **13**: $[\alpha]_D^{25}$ –33.3° (*c* 0.700, $CHCl_3$), prepared from natural grayanotoxin III (**3**) as described in **Chapter 2**.

10,14,16-Tris-*O*-(methoxymethyl)grayanotoxin III (14).

To a mixture of 0.100 M THF solution of SmI_2 (10.0 ml, 1 mmol) and HMPA (2.5 ml) cooled at –78 °C was added a solution of **13** (50.0 mg, 0.100 mmol) in THF (2.0 ml) by a cannula over 30 min. After stirring at –78 °C for 5 h, the reaction mixture was gradually warmed to ambient temperature over 10 h, poured into saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (acetone/CH_2Cl_2, 2:3) to give **14** (27.0 mg,

54%) as colorless crystals: mp 102 – 103 °C; $[\alpha]_D^{25}$ = –45.0° (*c* 0.100, $CHCl_3$). The spectral (IR, 250 MHz ^{1}H-NMR) data and chromatographic (TLC) behavior of this sample were identical with those of authentic **14**: mp 101 – 102 °C; $[\alpha]_D^{25}$ = –45.3° (*c* 0.100, $CHCl_3$), synthesized from grayanotoxin III (**3**) as described in **Chapter 2.**

3,6-Di-*O*-acetyl-10,14,16-tris-*O*-(methoxymethyl)grayanotoxin III.

To a solution of **14** (20.0 mg, 39.8 mmol) and DMAP (5.00 mg, 39.0 μmol) in pyridine (0.5 ml) at room temperature was added Ac_2O (0.1 ml). The mixture was stirred at room temperature for 15 h, poured into a mixture of ice and saturated aqueous $NaHCO_3$, and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $CuSO_4$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (acetone/CH_2Cl_2, 1:9) to afford the diacetate (22.0 mg, 94%) as a colorless oil; $[\alpha]_D^{25}$ = –28.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 1750, 1470, 1450, 1380, 1250, 1150, 1100, 1030, 970, 950, 920 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.95, 1.05, 1.34, 1.42 (each 3H, s, Me x 4), 2.06 (6H, s, OCOMe x 2), 3.32, 3.37, 3.46, (each 3H, s, OMe x 3), 4.32 (1H, brs, C_{14}-H), 4.43, 4.74 (each 1H, d, J = 7.8 Hz, OCH_2O), 4,61, 4.74 (each 1H, d, J = 7.0 Hz, OCH_2O), 4.63, 4.88 (each, 1H, d, J = 7.8 Hz, OCH_2O), 4.83 (1H, dd, J = 1.0, 3.6 Hz, C_6-H), 5.12 (1H, dd, J = 4.2, 10.4 Hz, C_3-H); FAB-MS m/z 525 (M^++H–OCH_2OMe).

Grayanotoxin III (3).

To a solution of the diacetate (22.0 mg, 37.4 μmol) in a mixture of CCl_4 (0.5 ml), acetonitrile (0.5 ml), and H_2O (1.0 ml) were added $RuCl_3 \cdot nH_2O$ (1.00 mg, 4.82 μmol) and $NaIO_4$ (40.0 mg, 0.190 mmol). The reaction mixture was stirred at room temperature for 5 h, quenched with saturated aqueous $Na_2S_2O_3$, and filtered through a plug of Celite. The filtrate was extracted with CH_2Cl_2 and the

combined extracts were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in a mixture of MeOH (5.0 ml) and 1 N aqueous KOH (5.0 ml), and the mixture was heated at 80 °C for 15 h and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of by silica gel column chromatography (AcOEt) gave almost pure **3** (12.0 mg, 86%) as a white solid, which was further recrystallized from AcOEt to afforded a pure sample of **3** as white crystals: mp 213 – 214 °C; $[\alpha]_D^{25}$ = –17.5° (*c* 0.400, MeOH); ^{1}H-NMR (250 MHz, C_5D_5N) δ 1.12, 1.51, 1.65, 1.84 (each 3H, s, Me x 4), 3.89 (1H, dd, J = 1.0, 2.5 Hz, C_3-H), 4.52 (1H, dd, J = 4.0, 10.5 Hz, C_6-H), 5.00 (1H, brs, C_{14}-H). The spectral data (IR, 250 MHz ^{1}H-NMR) and chromatographic (TLC) behavior of this sample were identical with those of natural **3**: mp 211 – 212 °C; $[\alpha]_D^{25}$ = –17.0° (*c* 0.400, MeOH).

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inches 1 2 3 4 5 6 7 8

cm 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

Kodak Color Control Patches

Blue Cyan Green Yellow Red Magenta White 3/Color Black

Kodak Gray Scale

C Y M

A 1 2 3 4 5 6 **M** 8 9 10 11 12 13 14 15 **B** 17 18 19