Stereocontrolled Synthesis of the JKLM Ring Fragment of Ciguatoxin

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A highly stereocontrolled synthesis of the JKLM ring fragment of ciguatoxin has been achieved. The present synthesis starts with methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-altropyranoside, whose configurations and substituents at C2−C5 correspond to those at C46−C49 of ciguatoxin, and involves as the key step base-induced 7-*endo* selective cyclization of a hydroxy epoxide for the efficient construction of the fully substituted oxepane ring K. Construction of the spiroether ring M was achieved by introduction of an allyl group to the ring L lactone followed by asymmetric dihydroxylation to install the C54 stereogenic center and acid-induced spiroketalization to furnish the protected KLM ring system. Finally, ring J was constructed by the method of Nicolaou to complete the synthesis of the JKLM ring fragment. The synthesis of a carboxylic acid derivative and its conjugation to carrier proteins to give an artificial antigen for development of an immunoassay system for the parent toxin molecule are also reported.

Introduction

Ciguatoxin (CTX1B, **1**; Figure 1) and its congeners constitute the principal group of toxins for ciguatera, which is one of the most widespread seafood poisonings. These toxins are produced by the epiphytic dinoflagellate *Gambierdiscus toxicus*[1] and transferred through the food chain among coral biota and accumulated in carnivorous fish, thus causing human intoxication. It is estimated that roughly 20 000 people suffer annually from the poisoning, making it one of the largest-scale food poisonings of dinoflagellate origins.

Ciguatoxin (**1**) was first isolated from moray eel *Gymnothorax javanicus* by Scheuer and co-workers and characterized as a polycyclic ether compound in 1980.[2] In 1989, the structure of **1**, except for the absolute configuration and relative configuration at C2, was elucidated using a purified sample of only 0.35 mg by Yasumoto and co-workers.[3,4] The ciguatoxin molecule consists of 12 *trans*-fused cyclic ethers, ranging from six- to nine-membered, and a spirally attached five-membered cyclic ether at one end. The most characteristic feature of the structure is that the hexahydrooxonine ring F in the central region of the molecule undergoes a slow conformational change in solution.[3b,4a] So far, most of the ciguatoxin congeners have been isolated from *G. toxicus* and other toxic fish.[5] Only recently, the absolute configuration of **1** was successfully determined as shown in Figure 1 by Yasumoto and co-workers.[6] Pharmacological studies on **1** have disclosed the primary site of its action to be voltage-sensitive sodium channels (VSSC).[7] The binding site on VSSC was reported to be shared by brevetoxins, another class of structurally related marine toxins.[8] Despite their structural similarity, the binding affinity of **1** was shown to be 10 times more potent than that of brevetoxins.[7b] However, the precise location of the receptor site of ciguatoxins and brevetoxins on VSSC has not been fully identified.[9] Since ciguatoxins possess much higher affinity to VSSC than brevetoxins, the toxin molecule may be utilized as a tool to investigate the function of VSSC itself, and similarly, synthetic fragments and structurally simplified analogues may probe the interaction of **1** with VSSC and/or its activation. From the food hygienic point of view on the other hand, the development of highly specific assays for detection of

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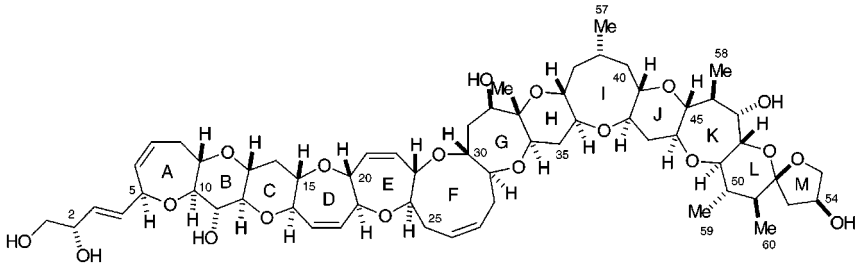
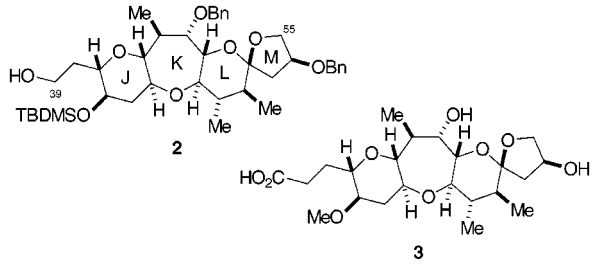


Figure 1. Structure of ciguatoxin (CTX1B; **1**).

minute amounts of these toxins in food sources has been urgently anticipated. Several different approaches to detect ciguateric fishes have been investigated during the past two decades.[10] Among them, antibody-based immunological assays appear to be the most promising approach for detecting the toxin molecules with high sensitivity. However, the extremely limited supply of ciguatoxins from natural sources and their highly complex molecular structure have prevented, in addition to the characterization of their interaction with VSSC, the development of a highly specific immunoassay for their detection in food sources. Thus, a synthetic supply is urgently needed, and considerable efforts have been devoted to the total synthesis of these polyether neurotoxins and the laboratory preparation of simplified models.[11−13]

In this vein, we became interested in the synthesis of a fragment of ciguatoxin not only as a piece in the total synthesis, but also as a hapten to raise antibodies that can recognize natural ciguatoxins. For the specific detection of ciguatoxins, the structural fragment used as a hapten must have a characteristic feature which is distinguishable from those of the many other polyether marine toxins. Thus, we chose the right-hand terminus of the ciguatoxin molecule, namely, the JKLM tetracyclic region where the density of asymmetric carbons is prominently heavy, as our synthetic target. Antibodies to the JKLM region, whose structure is relatively conserved among ciguatoxin congeners, were expected to recognize all of these congeners simultaneously. Similar attempts for the preparation of an anti-ciguatoxin antibody have already been carried out by Hirama and coworkers, and the ABC ring system, the left-hand terminus of **1**, has been synthesized as a hapten for the preparation of a monoclonal antibody.[14]

Herein, we describe in detail a stereocontrolled synthesis of the fully functionalized JKLM ring fragment **2**, representing the C39−C55 portion of ciguatoxin, as a potential precursor for total synthesis. We also report a synthesis of a carboxylic acid derivative **3** and its conjugation to appropriate carrier proteins for further immunological studies.



Results and Discussion

Synthetic Plan. The most critical issue in the synthesis of the JKLM ring system **2** is the construction of the fully substituted oxepane ring K. Recently, a number of strategies for the construction of oxepane ring systems

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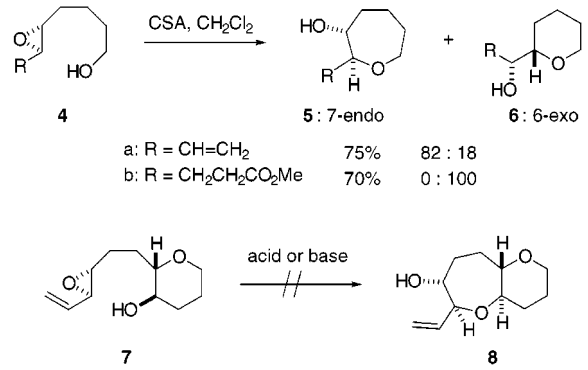
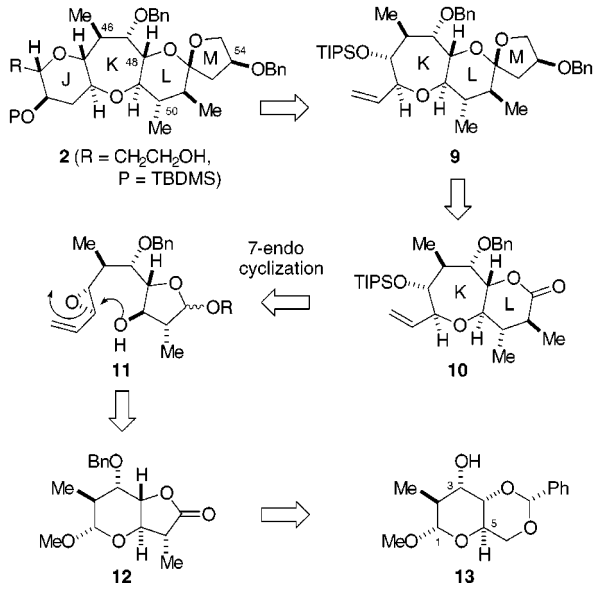
Scheme 1



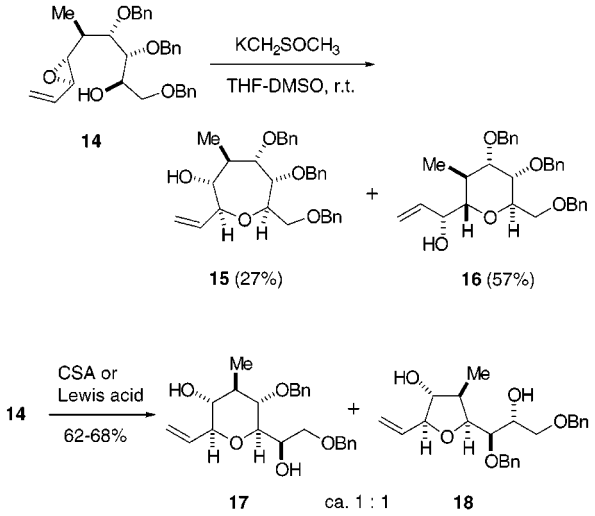
Scheme 2. Retrosynthetic Analysis of JKLM Ring Fragment 2



have been developed,[15] including one reported by Nicolaou and co-workers involving the acid-catalyzed 7-*endo* selective cyclization of hydroxy epoxides.[16] An olefinic bond adjacent to the epoxide in **4a** promoted the epoxide cleavage at the allylic position, leading to the predominant formation of oxepane **5a**, whereas its saturated derivative **4b** affords the tetrahydropyran system **6b** exclusively (Scheme 1). We first planned to apply this reaction to the construction of the hexasubstituted oxepane ring K; however, it has been reported that the 6/7-bicyclic ether system **8** could not be obtained by cyclization of hydroxy epoxide **7**.[16] In addition, to the best of our knowledge, there have been no examples of application of this reaction to the synthesis of highly substituted oxepanes.

Our initial synthetic plan for the target compound **2** is outlined in Scheme 2. Retrosynthetically, the tetrahydropyran ring J in **2** should be readily constructed by 6-*endo* selective cyclization of the hydroxy epoxide as demonstrated by Nicolaou,[17] a reaction which is well-precedented in the syntheses of related polyether compounds.[18] Tricyclic compound **9** was thus defined as a

Scheme 3



potential precursor to **2**. The five-membered spiroether ring M in **9**, which possesses the thermodynamically more stable configuration, was envisioned to be generated from lactone **10** by introduction of an allyl group as a three-carbon unit followed by asymmetric dihydroxylation to install the C54 stereogenic center,[19] and then subsequent acid-catalyzed spiroketalization. As mentioned earlier, the hexasubstituted oxepane ring in **10** was originally planned to be constructed by 7-*endo* cyclization of the precursor hydroxy epoxide **11**. In turn, compound **11** would be obtained from bicyclic lactone **12**, which can be traced back to the readily available starting material methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-altropyranoside (**13**),[20] whose configurations and substituents at C2−C5 in sugar numbering correspond to those at C46−C49 of ciguatoxin, respectively.

Synthesis of Epoxy Alcohol 29. Prior to the synthesis of **2**, we investigated a crucial cyclization reaction for the construction of hexasubstituted oxepane ring K using a model system (Scheme 3). Thus, hydroxy epoxide **14** was prepared from **13** and subjected to base- and acid-catalyzed cyclization. Treatment of **14** with potassium dimsylate in THF−DMSO provided a 27% yield of desired oxepane **15** along with a 57% yield of tetrahydropyran **16**, whereas acid treatment of **14** gave an approximately 1:1 mixture of diols **17** and **18** by the nucleophilic attack of the benzyl ether oxygen, rather than of the free hydroxyl, on the epoxide.[21] Although the regioselectivity of the acid-catalyzed cyclization of **14** was poor, we were encouraged by this result, which is in striking contrast to the cyclization of **7** and proceeded to undertake the synthesis of the JKLM ring system **2** according to the aforementioned synthetic plan incorporating this finding.

Alcohol **13** was protected as its benzyl ether **19**, and acid hydrolysis of the benzylidene acetal afforded diol **20**

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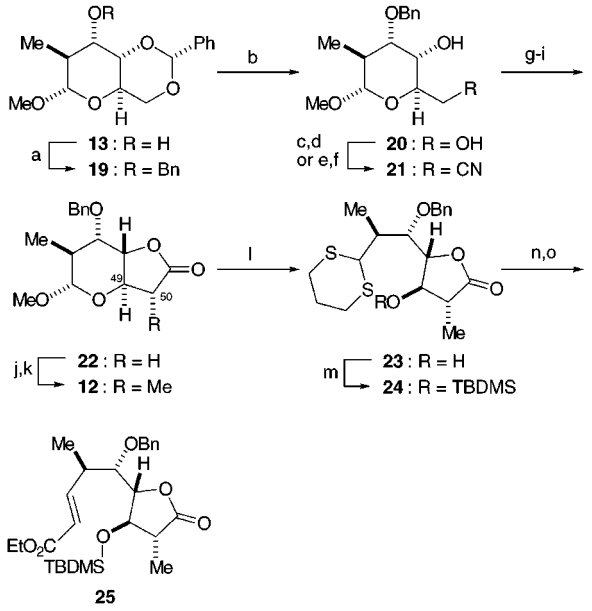
Scheme 4[a]

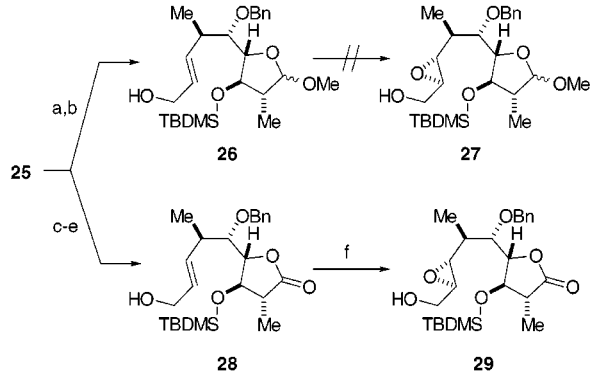


[a] Reagents and conditions: (a) NaH, BnBr, DMF, rt, 99%; (b) *p*-TsOH, MeOH, rt, 98%; (c) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (d) NaCN, DMSO, 70 °C, 65∼70% (two steps); (e) I_2, Ph_3P, imidazole, toluene, rt; (f) NaCN, DMSO, rt, 74% (two steps); (g) DIBALH, CH_2Cl_2, −78 °C; (h) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH−H_2O, rt; (i) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to rt, 51% (three steps); (j) LHMDS, THF, −78 °C, MeI; (k) LDA, THF, −78 °C, NH_4Cl, 71% (two steps); (l) $HS(CH_2)_3SH$, TMSOTf, CH_2Cl_2, 0 °C, 91%; (m) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 98%; (n) NIS, CH_3CN-H_2O, rt; (o) $(i\text{-PrO})_2POCH_2CO_2Et$, KO-*t*-Bu, THF, −78 to 0 °C, 90% (two steps).

in 98% overall yield (Scheme 4). Selective tosylation of the primary hydroxyl group followed by treatment with NaCN in DMSO at 70 °C provided nitrile **21** in 65−70% yield for the two steps. However, in large-scale operations (>20 g), the yield of this two-step sequence of reactions was quite low, presumably due to the instability of **21** under the reaction conditions. It became clear that an alternative method for the large-scale synthesis of **21** was necessary. After extensive experimentation, optimal results were obtained by selective iodination (I_2, Ph_3P, imidazole, toluene, room temperature) of the primary hydroxyl group in **20** and subsequent treatment with NaCN in DMSO at room temperature to afford **21** in 74% yield for the two steps in 50 g scale operations.

DIBALH reduction of **21** followed by sodium chlorite oxidation of the resulting aldehyde led to the hydroxy carboxylic acid, which was then activated with phenylsulfonyl chloride and triethylamine to give *trans*-fused bicyclic lactone **22** in 51% overall yield. At this stage, the α-oriented methyl group at the C50 position was introduced with complete stereocontrol by a two-step procedure. Namely, methylation of the lithium enolate derived from lactone **22** (LHMDS, THF, −78 °C) led exclusively to the kinetically favored *β*-methylated product. This methylated lactone was then treated with LDA, and the resulting enolate was kinetically protonated to furnish the desired α-methylated lactone **12** in 71% overall yield. The stereochemistry of the newly introduced C50 methyl group was confirmed by NOE between 49-H and 50-Me and $J_{49,50}$ = 11.7 Hz. Treatment of **12** with 1,3-propanedithiol in the presence of trimethylsilyl trifluoromethanesulfonate cleanly effected anomeric cleavage of the pyranose ring and provided the highly crystalline dithiane alcohol **23** in 91% yield.

Scheme 5[a]



[a] Reagents and conditions: (a) DIBALH, CH_2Cl_2, −78 °C; (b) $HC(OMe)_3$, catalytic PPTS, CH_2Cl_2, rt, 66% (two steps); (c) DIBALH, CH_2Cl_2, −78 °C; (d) PDC, 4 Å molecular sieves, CH_2Cl_2, rt; (e) $NaBH_4$, MeOH, 0 °C, 74% (three steps); (f) *t*-BuOOH, Ti(O-*i*-Pr)$_4$, (−)-diethyl tartrate, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 92%.

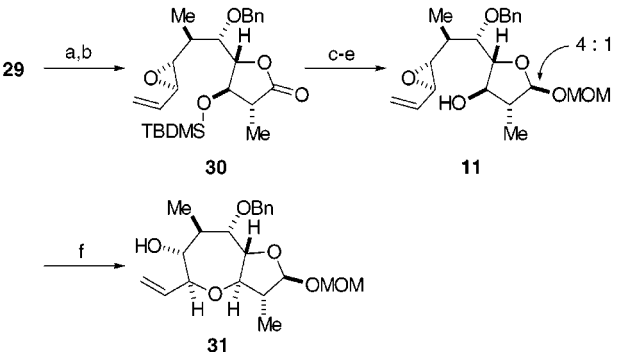
After protection of **23** as its TBDMS ether, hydrolysis of the thioacetal group in **24** to the corresponding aldehyde was investigated. A variety of reagents and conditions were tested for the oxidative hydrolysis of dithiane, among which *N*-iodosuccinimide (NIS) was found to give the most promising result with respect to both yield and reproducibility. Namely, treatment of **24** with 5 equiv of NIS in aqueous acetonitrile at room temperature gave the corresponding aldehyde, which was immediately subjected to Horner−Emmons olefination,[22] giving α,*β*-unsaturated ester **25** in 90% yield over the two steps.

DIBALH reduction of **25** followed by selective protection of the resulting hemiacetal (catalytic PPTS, $HC(OMe)_3$, CH_2Cl_2) gave methyl acetal **26** in 66% yield (Scheme 5). Sharpless asymmetric epoxidation of **26** using (−)-diethyl tartrate as the chiral auxiliary provided an unexpectedly complex mixture of products, from which the desired epoxy alcohol **27** was obtained only in poor yield. Oxidation of **26** with *m*-CPBA yielded a mixture of epoxides consisting of predominantly the undesired diastereomer. On the suspicion that the acetal moiety participates in titanium complexation in Sharpless epoxidation, epoxidation of lactone **28** was pursued. DIBALH reduction of **25** followed by PDC oxidation led to an aldehyde which was reduced with $NaBH_4$ to give allylic alcohol **28** in 74% overall yield for the three steps. Sharpless asymmetric epoxidation of **28** using (−)-diethyl tartrate as the chiral auxiliary proceeded smoothly in this case, giving epoxide **29** in 92% yield.

Construction of Fully Substituted Oxepane Ring K. With epoxy alcohol **29** in hand, attention was turned to the synthesis and cyclization of vinyl epoxide **11**. Conversion of **29** to olefin **30** proved to be problematic, though, due to the instability of the lactone moiety in **29** under basic conditions. Usual Wittig methylenation of the aldehyde obtained by SO_3·pyridine oxidation of **29** resulted in a complex mixture of products including the α,*β*-unsaturated lactone resulting from *β*-elimination. After some experimentation, Takai−Nozaki methylenation[23] was found to give **30** albeit in a low yield (Scheme

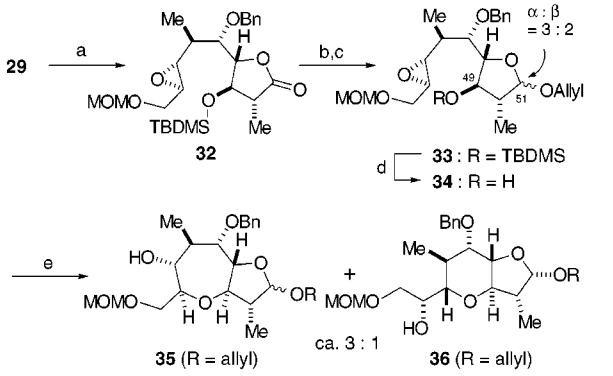
(22) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

Scheme 6[a]



[a] Reagents and conditions: (a) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (b) CH_2I_2, Zn, Ti(O-*i*-Pr)$_4$, THF, rt, 30−40% (two steps); (c) DIBALH, CH_2Cl_2, −78 °C; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt; (e) Bu_4NF, THF, rt, 83% (three steps); (f) $NaCH_2SOCH_3$, DMSO−THF, rt, 86%.

Scheme 7[a]



[a] Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 95%; (b) DIBALH, CH_2Cl_2, −78 °C; (c) allyl ethyl carbonate, Pd_2(dibenzylideneacetone)$_3$·$CHCl_3$, 1,4-bis(diphenylphosphino)butane, THF, 65 °C, 91% (two steps); (d) Bu_4NF, THF, rt, 94%; (e) $NaCH_2SOCH_3$, DMSO−THF, rt, 80%.

6). DIBALH reduction of **30** followed by protection of the resulting hemiacetal as its MOM ether and desilylation provided hydroxy epoxide **11** (R = MOM) in 83% overall yield as an approximately 4:1 mixture of anomers, with the *β*-anomer predominating. Treatment of **11** (R = MOM) with potassium dimsylate in THF−DMSO effected 7-*endo* selective cyclization to give oxepane **31** in good yield. Comparing this result with that obtained for cyclization of **14** (vide supra), the high 7-*endo* selectivity observed for **11** (R = MOM) is presumably due to the presence of the *trans*-fused five-membered ring, which restricts rotation along the C48−C49 bond.

However, the low yield of one-carbon homologation from **29** remained a serious problem in this sequence. Considering the high *endo* selectivity observed for the cyclization of **11** (R = MOM), we next attempted to construct the oxepane ring K without a directing functionality, such as a double bond, adjacent to the epoxide. Thus, the primary hydroxyl in **29** was protected as its MOM ether to give **32** in 95% yield (Scheme 7). DIBALH reduction of **32** and protection of the resulting hemiacetal under neutral conditions using a palladium(0) catalyst by the method of Sinou[24] provided allyl ether **33** as a 3:2 anomeric mixture, with the α-anomer predominating, in

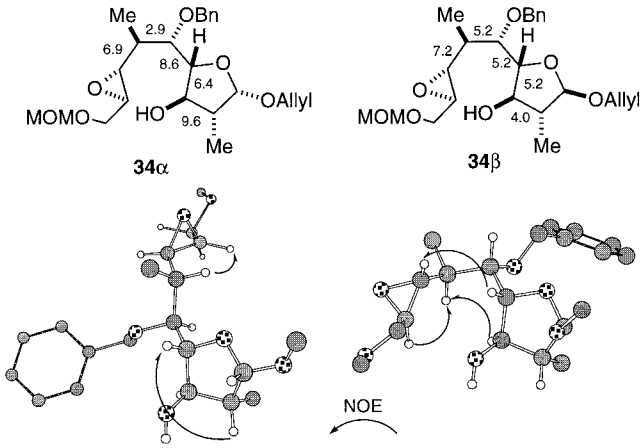


Figure 2. Possible conformations on the basis of ^{1}H NMR data of epoxy alcohols **34**α and **34***β*. Numbers indicate the vicinal coupling constants.

91% overall yield. After removal of the silyl group (94%), treatment of the resulting hydroxy epoxide **34** with potassium dimsylate in THF−DMSO at room temperature for 3 h resulted in the formation of the fully substituted oxepane **35** accompanied by tetrahydropyran **36** (**35**:**36** = ca. 3:1, 80% combined yield). It is noteworthy that 7-*endo* cyclization proceeded preferentially despite the absence of the olefin.

Interestingly, differences in the regioselectivity of the cyclization were observed between the two diastereomers at C51. A part of the anomeric mixture **34** was separated by HPLC, and each diastereomer was separately subjected to the cyclization reaction. Base treatment of 51*β* allyl ether **34***β* provided only the desired oxepane **35***β*, whereas the 51α allyl ether **34**α produced an inseparable 1.7:1 mixture of oxepane **35**α and tetrahydropyran **36**.

To rationalize the regiochemical outcome of the cyclization reaction, conformational analysis of each of the diastereomers **34**α and **34***β* was carried out with ^{1}H NMR and molecular mechanics calculations. The ^{1}H NMR coupling constants and NOE data indicated that the C43−C48 carbon chain of **34**α preferentially adopts an extended conformation (Figure 2). On the other hand, the ^{1}H NMR coupling constants of **34***β* indicated that it exists as a mixture of conformers, and the NOE data also strongly suggested that one of the conformers, in which the C49 hydroxy group is in close proximity to C44, is suitably preorganized for cyclization. The conformational analysis studies were also supported by molecular mechanics calculations (Monte Carlo conformational search using the MM2* force field in MacroModel version 5.5).[25−27]

Although a route to the key intermediate **35** had been secured, the overall selectivity of the crucial cyclization to obtain oxepane **35** was modest due to the formation of **34**α. Thus, we next focused our attention on the selective synthesis of 51*β* allyl ether **34***β*. The poor selectivity observed in the allylation of the hemiacetal derived from **32** was considered to be due to the steric repulsion

(23) Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5581.

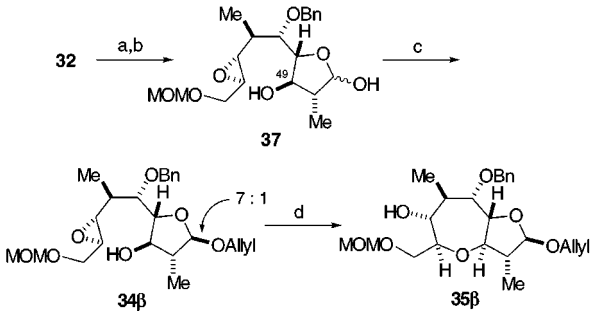
(24) Lakhmiri, R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1989**, *30*, 4669.

(25) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(26) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

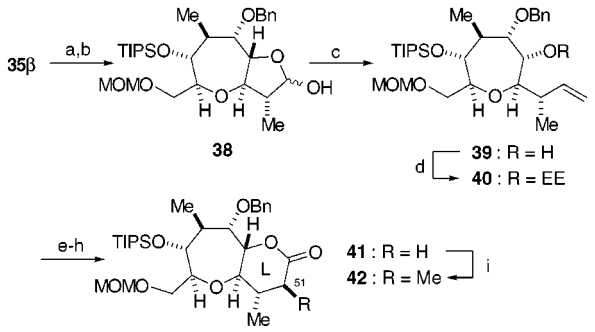
(27) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Scheme 8[a]



[a] Reagents and conditions: (a) $Bu_4NF-AcOH$ (1:1), THF, rt; (b) DIBALH, CH_2Cl_2, −78 °C; (c) allyl ethyl carbonate, Pd_2(dibenzylideneacetone)$_3$·$CHCl_3$, 1,4-bis(diphenylphosphino)butane, THF, 65 °C, 71% (three steps); (d) $NaCH_2SOCH_3$, DMSO−THF, rt, 94% (ca. 83% purity).

Scheme 9[a]



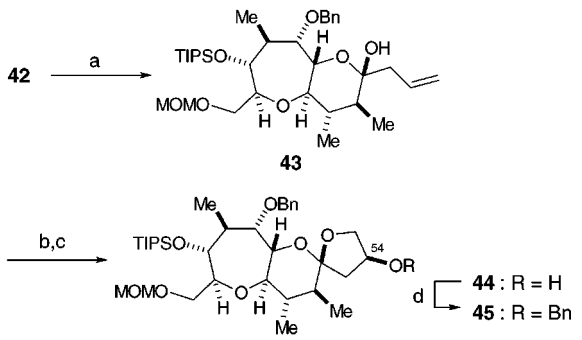
[a] Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt; (b) $[Ir(COD)(PMePh_2)_2]PF_6$, THF, H_2, rt, then I_2, THF−H_2O, rt, 78% from **34*β***; (c) $Ph_3P^+CH_3I^-$, NaHMDS, THF, 0 °C, 71%; (d) ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 98%; (e) 9-BBN−H, THF, rt, then H_2O_2, NaOH, rt; (f) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (g) THF−AcOH−H_2O (3:3:1), rt; (h) PDC, 4 Å molecular sieves, CH_2Cl_2, rt, 83% (four steps); (i) LHMDS, THF, MeI, −78 °C, 92%.

between the β-silyloxy group at C49 and the sterically bulky π-allylpalladium complex, generated from palladium(0) and allyl ethyl carbonate. We therefore anticipated that, without the TBDMS protecting group at C49, approach of the allylating reagent from the β-face would be kinetically favored due to the α-oriented methyl group at C50, leading to the selective formation of 51β allyl ether **34*β***. Thus, removal of the silyl group from base-labile **32** with Bu_4NF−acetic acid (1:1) followed by DIBALH reduction of the lactone gave hydroxy hemiacetal **37** (Scheme 8). As expected, allylation of the hydroxy hemiacetal in **37** under the same conditions described earlier produced a 7:1 mixture of anomers, with the desired **34*β*** predominating, in 71% combined yield for the three steps. Treatment of this product with base provided oxepane **35*β*** in 94% yield, which ^{1}H NMR analysis showed to be 83% pure.[28] Thus, an efficient route for the preparation of multigram quantities of the key intermediate **35** had been established.

Construction of Ring L. Having successfully constructed a fully substituted oxepane ring K, the next stage of our synthesis called for the construction of ring L, requiring one-carbon homologation of **35**. The hydroxy group in **35** was protected as its TIPS ether (Scheme 9), and selective removal of the allyl group was carried out

(28) The 17% impurity consisted of a mixture of the corresponding tetrahydropyran **36** and other unidentified products.

Scheme 10[a]



[a] Reagents and conditions: (a) AllylMgBr, THF, −78 °C, 79%; (b) OsO_4, *N,N′*-bis(2,4,6-trimethylbenzyl)-(*S,S*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, −90 °C, then aqueous $NaHSO_3$−THF, reflux, 85%; (c) CSA, benzene, rt, 86%; (d) NaH, BnBr, DMF, rt, 83%.

using an iridium complex by the method of Oltvoort et al.,[29] giving hemiacetal **38** in 78% yield from **34*β*** (7:1). Wittig methylenation of **38** provided hydroxy olefin **39** (71% yield), which was protected as the ethoxyethyl (EE) ether **40** in 98% yield. Hydroboration with 9-BBN−H, followed by oxidative workup, gave the corresponding primary alcohol, which was then converted to lactone **41** in 83% overall yield by a three-step sequence of reactions: (i) oxidation to the corresponding aldehyde with SO_3·pyridine, (ii) selective removal of the EE group with THF−AcOH−H_2O to yield the corresponding hemiacetal, and (iii) PDC oxidation to the lactone.

Methylation of the lithium enolate derived from **41** (LHMDS, THF, −78 °C) led exclusively to β-methyl lactone **42** with the desired configuration at the C51 position in 92% yield, where the stereochemistry at C51 was established by the ^{1}H NMR coupling constant of $J_{50,51}$ = 10.8 Hz.

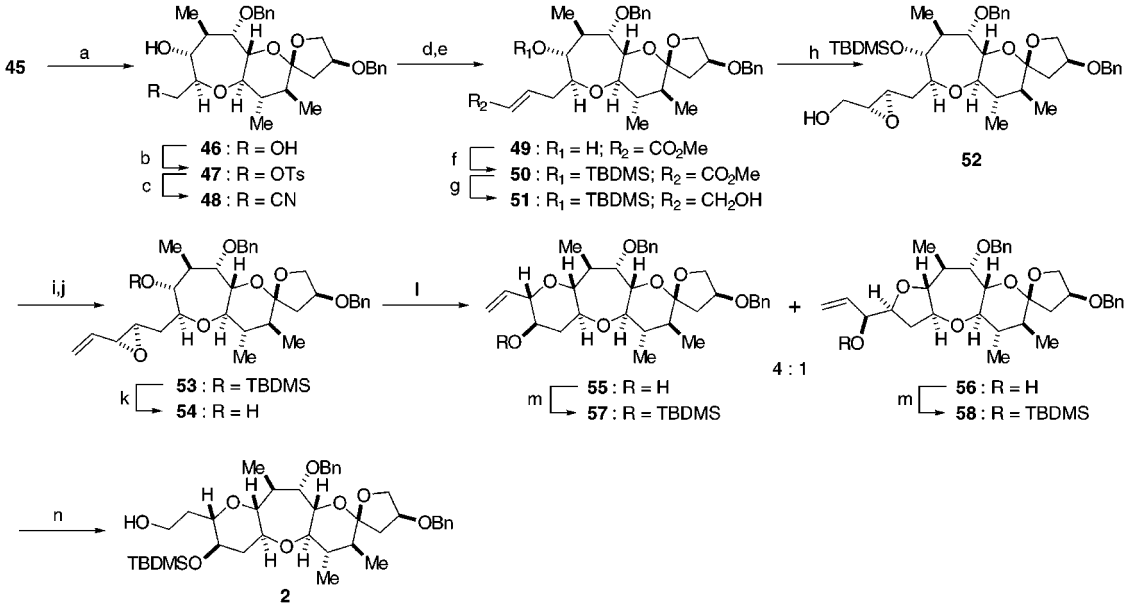
Construction of Spiroketal Ring M. The next stage of the synthesis involved construction of the spiro-fused ring M. Toward this end, an allyl group was introduced as a three-carbon unit (Scheme 10). Thus, treatment of **42** with allylmagnesium bromide furnished hemiketal **43** as a single diastereomer in 79% yield. Application of Corey's asymmetric dihydroxylation using *N,N′*-bis(2,4,6-trimethylbenzyl)-(*S,S*)-1,2-diphenyl-1,2-diaminoethane as a chiral ligand[30] to the terminal olefin in **43** gave the corresponding triol as the only product in 85% yield. The stereochemistry at the newly generated stereogenic center at C54 was tentatively assigned on the basis of literature precedent. Treatment of the triol with camphorsulfonic acid (CSA) in benzene at room temperature gave the thermodynamically more stable spiroketal **44** in 86% yield, which was subsequently benzylated to give the protected KLM ring fragment **45** in 83% yield. The stereochemistries at the C52 and C54 positions in **44** were unambiguously assigned by differential NOE experiments.

Construction of Ring J. With the desired KLM ring fragment in hand, all that remained was the construction of ring J, which was to be based on the acid-catalyzed epoxide opening−ring closure reaction of hydroxy epoxide developed by Nicolaou.[17] Since all attempts to deprotect

(29) Olvoort, J. J.; VanBoeckel, C. A. A.; DeKoning, J. H.; VanBoom, J. H. *Synthesis* **1981**, 305.

(30) Corey, E. J.; Jardine, D. P.; Virgil, S.; Yuen, P.-W.; Connel, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.

Scheme 11[a]

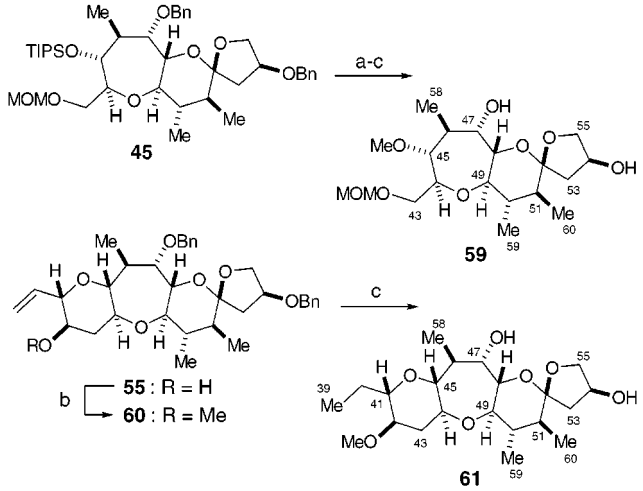


[a] Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2, 0 °C, 77%; (b) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 93%; (c) NaCN, DMSO, 70 °C, 89%; (d) DIBALH, CH_2Cl_2, −78 °C; (e) $Ph_3P{=}CHCO_2Me$, benzene, 80 °C, 80% (two steps); (f) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 97%; (g) DIBALH, CH_2Cl_2, −78 °C, 89%; (h) *t*-BuOOH, Ti(O-*i*-Pr)$_4$, (−)-diethyl tartrate, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 75%; (i) $SO_3{\cdot}$Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (j) $Ph_3PCH_3{}^+Br^-$, NaHMDS, THF, 0 °C, 91% (two steps); (k) Bu_4NF, THF, rt; (l) CSA, CH_2Cl_2, −40 to 0 °C, 93% (two steps, inseparable 4:1 mixture); (m) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 87%; (n) 9-BBN−H, THF, rt, then H_2O_2, $NaHCO_3$, 78%.

the MOM group in **45** selectively in the presence of the TIPS group were unsuccessful, we decided to remove both protective groups. Thus, treatment of **45** with dimethyl sulfide and boron trifluoride etherate[31] provided diol **46** in good yield (Scheme 11). Selective monotosylation of the primary hydroxyl in **46** (93% yield) followed by treatment of the resulting tosylate **47** with NaCN in DMSO afforded nitrile **48** in 89% yield. DIBALH reduction of **48** followed by Wittig homologation of the resultant hemiacetal furnished α,β-unsaturated ester **49** in 80% yield for the two steps. Protection of the secondary hydroxyl of **49** as its TBDMS ether **50** and subsequent reduction with DIBALH yielded allylic alcohol **51** in 86% overall yield. Sharpless asymmetric epoxidation of **51** using (−)-diethyl tartrate as the chiral auxiliary gave epoxide **52** in 75% yield. Oxidation of the primary hydroxyl in **52** to the aldehyde with $SO_3{\cdot}$pyridine complex and subsequent Wittig methylenation gave rise to olefin **53** in 91% overall yield. Removal of the silyl protecting group with Bu_4NF provided alcohol **54**, which was then submitted to acid-catalyzed ring closure. Treatment of **54** with camphorsulfonic acid in CH_2Cl_2 at 0 °C provided a 4:1 mixture of the desired tetracyclic product **55** and tetrahydrofuran **56** in 93% combined yield from **53**. Protection of this mixture using *tert*-butyldimethylsilyl trifluoromethansulfonate and 2,6-lutidine gave the TBDMS ethers **57** and **58** in 87% combined yield. When this mixture was subjected to hydroboration conditions, a notable difference in the reactivity between **57** and **58** was observed. Thus, treatment of a 4:1 mixture of **57** and **58** with 9-BBN−H followed by oxidative workup (H_2O_2 and $NaHCO_3$) furnished alcohol **2** in pure form in 78% yield, together with its regioisomer (7%) and recovered **58** (10%).

(31) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662.

Scheme 12[a]



[a] Reagents and conditions: (a) Bu_4NF, THF, rt; (b) NaH, MeI, THF, rt; (c) H_2, $Pd(OH)_2$/C, MeOH, rt.

Comparison of ^{1}H NMR Spectra between Synthetic Fragments and Ciguatoxin. For the purpose of comparison between synthetic fragments and natural ciguatoxin by ^{1}H NMR spectra, compounds **45** and **55** were converted to their deprotected derivatives **59** and **61**, respectively (Scheme 12). Desilylation of **45** with Bu_4NF followed by methylation under standard conditions and debenzylation provided **59**. Treatment of a 4:1 mixture of **55** and **56** with sodium hydride and iodomethane gave a mixture of methyl ethers, from which **60** was separated by HPLC. Simultaneous hydrogenolysis and hydrogenation of **60** provided **61**.

The ^{1}H NMR data in pyridine-d_5 of both **59** and **61** were compared to those of the corresponding spectra of ciguatoxin (Table 1). As seen from Table 1, introduction

Table 1. Comparison of ^{1}H NMR Spectra between Ciguatoxin and Synthetic Fragments 59 and 61[a]

position	CTX1B	59	61
39	1.90 (−)		1.05 (t, 7.5)
40	1.72 (−)		1.52 (m)
	2.03 (−)		1.98 (m)
41	3.21 (ddd, 10, 10, 3)		3.10 (ddd, 8.7, 8.7, 2.5)
42	3.35 (−)		2.99 (ddd, 11.1, 9.0, 4.3)
43	1.77 (q, 12)		1.48 (q, 11.4)
		2.59 (−)	2.68 (m)
44	4.45 (ddd, 11, 9, 5)	4.56 (ddd, 9.1, 6.9, 2.1)	4.36 (ddd, 11.1, 9.3, 5.1)
45	3.21 (dd, 9, 5)	3.24 (dd, 9.1, 1.6)	3.13 (dd, 9.3, 5.0)
46	2.59 (−)	2.71 (m)	2.55 (m)
47	4.21 (−)	4.36 (br d, 5.5)	4.17 (m)
48	4.06 (dd, 10, 1)	4.10 (dd, 9.8, 1.3)	4.03 (br d, 9.4)
49	3.96 (dd, 10, 10)	3.80 (dd, 10.0, 10.0)	3.92 (dd, 9.7, 9.7)
50	2.01 (−)	1.99 (qdd, 6.3, 10.8, 10.8)	1.98 (m)
51	1.67 (−)	1.63 (qd, 6.6, 10.7)	1.65 (qd, 6.5, 11.3)
53	2.40 (dd, 13, 8)	2.40 (dd, 13.5, 7.0)	2.39 (dd, 13.5, 6.9)
	2.35 (dd, 13, 5)	2.30 (dd, 13.5, 3.4)	2.32 (dd, 13.6, 3.6)
54	4.86 (m)	4.86 (m)	4.86 (m)
55	4.18 (10, 2)	4.15 (dd, 9.0, 1.7)	4.17 (m)
	4.19 (10, 5)	4.20 (dd, 9.1, 4.9)	
58	1.30 (d, 8)	1.17 (d, 7.7)	1.26 (d, 7.9)
59	1.32 (d, 6)	1.31 (d, 6.3)	1.25 (d, 7.3)
60	1.24 (d, 7)	1.20 (d, 6.7)	1.21 (d, 6.7)

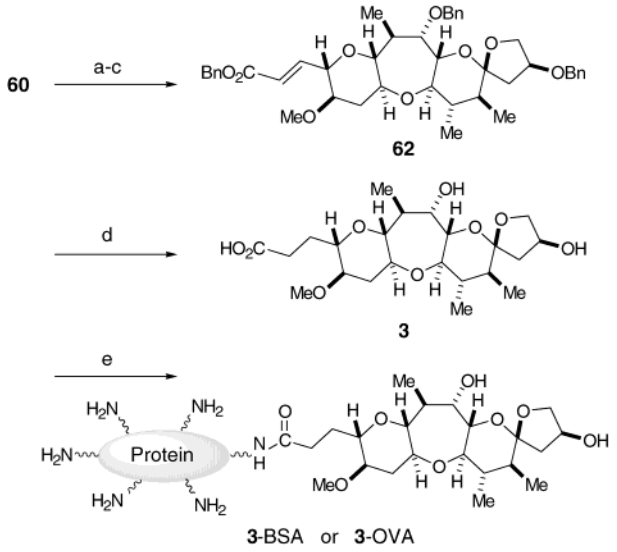
[a] All NMR spectra were measured in pyridine-d_5.

of ring J dramatically improved the correlation of the chemical shifts and coupling constants for the C44−C49 protons. These data indicate that the presence of ring J influences the conformation of the oxepane ring K, which is rather flexible. The close agreement in the conformational behavior of ring K in **61** with that in ciguatoxin strongly suggests that the JKLM ring system may become a possible candidate for a haptenic epitope in an anti-ciguatoxin antibody.

Preparation of the JKLM Fragment−Albumin Conjugate. For the preparation of carboxylic acid **3**, oxidative cleavage of the double bond in **60** was followed by Wittig homologation to give α,β-unsaturated benzyl ester **62** quantitatively (Scheme 13). Simultaneous hydrogenolysis and hydrogenation using $Pd(OH)_2$/C catalyst provided carboxylic acid **3** (98% yield), which was then ready to be conjugated to an appropriate carrier protein. Conjugation of **3** to carrier proteins, bovine serum albumin (BSA) and ovalbumin (OVA), was respectively carried out by the method of Kitagawa.[32] Thus, carboxylic acid **3** was activated as its *N*-hydroxy succinimidate, and subsequent treatment with BSA or OVA gave, after purification by dialysis, the **3**−BSA or **3**−OVA conjugate, respectively. For the BSA conjugate, about 16 hapten molecules per protein were introduced, compared to about 10 haptens for OVA.[33]

Preliminary immunological experiments in collaboration with Drs. A.-M. Legrand and S. Pauillac at the Institute Territorial de Recherches Médicales Louis Malardé clearly demonstrated that the polyclonal antibody raised by the **3**−BSA conjugate exhibited high cross-

Scheme 13[a]



[a] Reagents and conditions: (a) OsO_4, NMO, acetone−H_2O (4:1), rt; (b) $NaIO_4$, THF−H_2O (2:1), rt; (c) $Ph_3P{=}CHCO_2Bn$, benzene, rt, quantitative (three steps); (d) H_2, $Pd(OH)_2$/C, EtOH, rt, 98%; (e) *N*-hydroxysuccinimide, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate, dioxane−H_2O, rt, then BSA or OVA, pH 7.3 phosphate buffer−pyridine, 4 °C.

reactivity to natural ciguatoxin.[34] This is the first example of the production of a specific polyclonal antibody to ciguatoxin using the synthetic fragment as a hapten. Further studies toward development of the ELISA system for the detection of ciguatoxin are now in progress.

Conclusion. A stereocontrolled synthesis of the JKLM ring fragment **2** has been achieved starting from readily obtainable D-glucose derivative **13**. The synthetic route developed herein has the potential to provide adequate amounts of **2** (over 300 mg of **2** could be prepared using this strategy). The tetracyclic fragments **2** and **3** may serve not only as potential precursors for total synthesis of the ciguatoxins and their model compounds, but also as haptens of antigens to raise antibodies that could recognize the natural toxins for immunological studies.

Experimental Section

General Methods. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Diethyl ether (Et_2O) and THF were distilled from sodium/benzophenone, acetonitrile (MeCN), benzene, dichloromethane (CH_2Cl_2), diisopropylamine, *N*,*N*-diisopropylethylamine, pyridine, triethylamine, and toluene from calcium hydride, and DMF and DMSO from calcium hydride under reduced pressure. All other reagents were used as supplied unless otherwise stated.

Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm thickness). Column chromatography was performed using 70−230 mesh E. Merck silica gel 60, and for flash column chromatography 230−400 mesh E. Merck silica gel 60 was used.

NMR chemical shift values are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent [^{1}H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), C_5HD_4N (8.50), CHD_2CN (1.93); ^{13}C NMR, $CDCl_3$ (77.0); C_6D_6 (128.0), C_5D_5N (149.8), CD_3CN (1.30)]. Coupling constants (*J*)

(32) Kitagawa, T.; Miura, T.; Taniyama, H. *Chem. Pharm. Bull.* **1972**, *20*, 2176.

(33) The number of hapten molecules per protein was estimated by the trinitrophenylation method; see: Habeeb, A. F. S. A. *Anal. Biochem.* **1966**, *14*, 328.

(34) Pauillac, S.; Sasaki, M.; Inoue, M.; Naar, J.; Branaa, P.; Chinain, M.; Tachibana, K.; Legrand, A.-M. *Toxicon*, in press.

are reported in hertz (Hz). Carbon numbers of synthetic compounds correspond to those of ciguatoxin.

Benzyl Ether 19. A solution of alcohol **13** (21.49 g, 76.67 mmol) and Bu_4NI (2.84 g, 7.69 mmol) in THF (100 mL) and DMF (25 mL) was cooled to 0 °C and treated with sodium hydride (60% dispersion in mineral oil, 4.64 g, 116 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 45 min. The mixture was recooled to 0 °C and treated with benzyl bromide (12 mL, 101 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into ice−water (300 mL) and extracted with EtOAc (700 and 300 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a pale yellow solid. The solid was recrystallized from ether and hexane to afford 23.67 g of benzyl ether **19** in two crops. The mother liquor was purified by flash chromatography on silica gel (20% EtOAc−hexane) to afford 4.47 g of additional product. The total yield of **19** was 28.14 g (99%): mp 110.8−111.8 °C; $[\alpha]^{26}_D = +52.9°$ (*c* 1.00, $CHCl_3$); IR (KBr) 2906, 1614, 1456, 1384 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.20−7.55 (10H, m), 5.55 (1H, br s), 4.83 (1H, d, $J = 12.9$ Hz), 4.77 (1H, d, $J = 12.9$ Hz), 4.45 (1H, ddd, $J = 10.3$, 9.7, 5.3 Hz), 4.42 (3H, s), 4.32 (1H, dd, $J = 10.3$, 5.3 Hz), 3.82 (1H, dd, $J = 9.7$, 2.7 Hz), 3.73 (1H, dd, $J = 10.3$, 10.3 Hz), 3.69 (1H, dd, $J = 2.7$, 2.2 Hz), 2.37 (1H, dq, $J = 2.2$, 7.8 Hz), 1.10 (3H, d, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.2, 137.8, 129.0, 128.2, 128.1, 127.4, 127.1, 126.3, 103.2, 102.3, 77.4, 76.1, 72.3, 69.6, 58.5, 55.5, 38.9, 16.7. Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.27; H, 7.00.

Diol 20. A solution of benzyl ether **19** (21.66 g, 58.47 mmol) in MeOH (500 mL) was treated with *p*-toluenesulfonic acid monohydrate (2.22 g, 11.7 mmol), and the resulting mixture was stirred at room temperature for 90 min. The reaction was quenched with triethylamine (3.0 mL, 21.5 mmol), and evaporation of the solvent and purification by chromatography on silica gel (1:1−2:1 EtOAc−hexane) afforded diol **20** (16.24 g, 98%), which solidified on standing: mp 89.0−90.2 °C; $[\alpha]^{25}_D = +130.2°$ (*c* 1.63, $CHCl_3$); IR (KBr) 3390, 3369 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25−7.40 (5H, m), 4.77 (1H, d, $J = 11.4$ Hz), 4.42 (1H, s), 4.41 (1H, d, $J = 11.4$ Hz), 3.82−3.92 (2H, m), 3.75−3.80 (2H, m), 3.55 (1H, dd, $J = 3.6$, 3.6 Hz), 3.36 (3H, s), 2.40 (1H, m), 1.04 (3H, d, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.8, 128.3, 127.7, 102.6, 78.2, 70.7, 69.0, 64.3, 63.0, 55.2, 34.5, 15.2. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.81; H, 7.80.

Nitrile 21. Method A. Via Tosylate. A solution of diol **20** (28.84 g, 0.102 mol), DMAP (0.71 g, 5.81 mmol), and triethylamine (57 mL, 0.41 mol) in CH_2Cl_2 (550 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (23.38 g, 0.123 mol), and the resulting mixture was stirred at 0 °C for 4 h. The solution was diluted with EtOAc (1.5 L) and washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on silica gel (20−40% EtOAc−hexane) to afford monotosylate as a colorless oil (47.10 g, quantitative): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.24 (9H, m), 4.71 (1H, d, $J = 11.3$ Hz), 4.33 (1H, d, $J = 11.3$ Hz), 4.32 (1H, s), 4.31 (1H, d, $J = 1.9$ Hz), 4.17 (1H, dd, $J = 10.6$, 6.1 Hz), 3.99 (1H, m), 3.60 (1H, dd, $J = 9.7$, 3.3 Hz), 3.51 (1H, dd, $J = 3.4$, 3.4 Hz), 3.27 (3H, s), 2.38 (3H, s), 0.96 (3H, d, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 129.6, 128.4, 127.7, 102.3, 77.9, 70.6, 70.1, 67.3, 63.6, 55.1, 34.3, 21.4, 15.3.

A solution of the above tosylate (7.82 g, 17.9 mmol) in DMSO (50 mL) was treated with NaCN (1.76 g, 35.9 mmol), and the resulting mixture was stirred at 70 °C for 1.5 h. The mixture was cooled to room temperature, poured into saturated aqueous NH_4Cl (100 mL), and extracted with EtOAc (300 mL). The organic extract was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (30% EtOAc−hexane) afforded nitrile **21** as a pale yellow oil (3.66 g, 70%): $[\alpha]^{29}_D = +124.7°$ (*c* 1.12, $CHCl_3$); IR (film) 3539, 2931, 2700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.25 (5H, m), 4.79 (1H, d, $J = 11.2$ Hz), 4.43 (1H, s), 4.36 (1H, d, $J = 11.2$ Hz), 4.05 (1H, m), 3.58 (1H, dd, $J = 3.0$, 3.0 Hz), 3.53 (1H, m), 3.40 (3H, s), 2.79 (1H, dd, $J = 16.8$, 3.4 Hz), 2.65 (1H, d, $J = 10.5$ Hz), 2.55 (1H, dd, $J = 16.8$, 7.9 Hz), 2.44 (1H, m), 1.04 (3H, d, $J = 7.5$ Hz); ^{13}C NMR δ 137.5, 128.3, 127.8, 127.7, 117.4, 102.4, 77.8, 70.5, 66.4, 65.0, 55.3, 34.3, 20.8, 15.0; HRMS (FAB) calcd for $C_{16}H_{21}O_4NNa$ [$(M + Na)^+$] 314.1368, found 314.1369.

Method B. Via Iodide. To a solution of diol **20** (69.53 g, 0.246 mol) in toluene (2 L) were added sequentially imidazole (50.3 g, 0.739 mol), triphenylphosphine (96.8 g, 0.369 mol), and iodine (87.5 g, 0.345 mol). After 4 h at room temperature, the reaction was quenched with saturated aqueous Na_2SO_3 (500 mL). The mixture was diluted with EtOAc (2 L) and washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (10−20% EtOAc−hexane) afforded the iodide as a colorless oil (98.92 g): $[\alpha]^{25}_D = +78.8°$ (*c* 1.23, $CHCl_3$); IR (film) 3534, 2928, 1497, 1456, 741, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.28 (5H, m), 4.77 (1H, d, $J = 11.3$ Hz), 4.45 (1H, s), 4.36 (1H, d, $J = 11.3$ Hz), 3.70 (1H, m), 3.58 (1H, dd, $J = 10.5$, 2.5 Hz), 3.54 (2H, m), 3.42 (3H, s), 3.31 (1H, dd, $J = 10.5$, 7.5 Hz), 2.59 (1H, d, $J = 9.7$ Hz), 2.41 (1H, m), 1.04 (3H, d, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 128.4, 127.9, 127.8, 102.7, 78.2, 70.7, 68.5, 67.7, 55.5, 34.6, 15.1, 8.6.

A solution of the above iodide (98.92 g, 0.252 mol) in DMSO (500 mL) was treated with NaCN (24.8 g, 0.596 mol), and the resulting mixture was stirred at room temperature for 16 h. The mixture was poured into saturated aqueous NH_4Cl (1 L) and extracted with EtOAc (3 L). The organic extract was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (20−30% EtOAc−hexane) gave nitrile **21** as a pale yellow oil (53.51 g, 74% for the two steps). This material was identical to a sample prepared via method A.

Lactone 22. To a solution of nitrile **21** (8.98 g, 30.82 mmol) in CH_2Cl_2 (170 mL) was added DIBALH (0.93 M solution in hexane, 83 mL, 77.2 mmol) at −78 °C. After 1 h, the reaction was quenched with 1 N aqueous HCl (130 mL), and the cooling bath was removed. The mixture was vigorously stirred at room temperature for 15 min and diluted with EtOAc (750 mL). The organic layer was washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (20−40% EtOAc−hexane) afforded the aldehyde as a pale brown oil (12.38 g), which was used in the next reaction without further purification: IR (film) 3500, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.79 (1H, dd, $J = 2.9$, 1.4 Hz), 7.40−7.25 (5H, m), 4.77 (1H, d, $J = 11.3$ Hz), 4.39 (1H, ddd, $J = 9.6$, 3.4, 3.4 Hz), 4.37 (1H, d, $J = 11.3$ Hz), 4.34 (1H, s), 3.55 (1H, dd, $J = 3.3$, 3.3 Hz), 3.50 (1H, m), 3.34 (3H, s), 2.66 (1H, ddd, $J = 16.5$, 3.4, 1.4 Hz), 2.63 (1H, d, $J = 10.0$), 2.54 (1H, ddd, $J = 16.3$, 9.4, 3.0 Hz), 2.42 (1H, m), 1.02 (1H, d, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.0, 137.9, 128.5, 128.0, 127.9, 102.5, 78.1, 70.8, 67.1, 64.5, 55.5, 46.2, 34.6, 15.4.

A solution of the above aldehyde (12.38 g, 41.6 mmol), 2-methyl-2-butene (22.3 mL, 188 mmol), and $NaH_2PO_4 \cdot H_2O$ (6.56 g, 42.0 mmol) in *t*-BuOH (210 mL) and water (46 mL) was cooled to 0 °C and treated with $NaClO_2$ (86%, 15.03 g, 142.9 mmol) in portions. After being stirred at room temperature for 20 min, the reaction mixture was carefully acidified with 1 N aqueous HCl (200 mL) at 0 °C and extracted with CH_2Cl_2 (200 mL × 4). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (10% MeOH−$CHCl_3$) afforded carboxylic acid as a pale yellow oil (14.79 g), which was used in the next reaction without further purification: IR (film) 3400, 1714 cm^{-1}.

To a solution of the above hydroxy carboxylic acid (14.79 g) and triethylamine (19.9 mL, 142.8 mmol) in CH_2Cl_2 (200 mL) was added dropwise phenylsulfonyl chloride (9.12 mL, 71.3 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h and at room temperature for 1.5 h. The mixture was diluted with EtOAc (1 L), washed with water, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (10−30% EtOAc−hexane) afforded bicyclic lactone **22** as a pale

yellow solid (8.03 g, 51% for the three steps): mp 117.5−118.5 °C; $[\alpha]^{26}_D = +10.5°$ (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.25 (5H, m), 4.82 (1H, ddd, J = 12.2, 9.7, 7.3 Hz), 4.71 (1H, d, J = 12.5 Hz), 4.67 (1H, d, J = 12.5 Hz), 4.48 (1H, s), 4.11 (1H, dd, J = 9.7, 2.5 Hz), 3.98 (1H, br s), 3.39 (3H, s), 2.75 (1H, dd, J = 15.8, 7.3 Hz), 2.64 (1H, dd, J = 15.8, 12.2 Hz), 2.42 (1H, dq, J = 7.8, 2.0 Hz), 1.09 (3H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 138.0, 128.3, 127.5, 127.4, 104.7, 79.4, 74.7, 71.6, 63.1, 55.7, 38.6, 35.1, 16.7. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.73; H, 6.89. Found: C, 65.03; H, 6.83.

α-Methylated Lactone 12. To a solution of LHMDS (1.0 M solution in hexane, 136 mL, 0.136 mol) in THF (250 mL) was added dropwise a solution of lactone **22** (31.69 g, 0.1084 mol) in THF (200 and 50 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 30 min and treated with iodomethane (27 mL, 0.43 mol). After 30 min at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was allowed to warm to room temperature. The solution was diluted with EtOAc (2 L), washed with 1 N HCl, saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through a silica gel short column to give *β*-methylated lactone as a pale yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.23 (5H, m), 4.81 (1H, dd, J = 10.0, 8.1 Hz), 4.69 (1H, d, J = 12.6 Hz), 4.65 (1H, d, J = 12.6 Hz), 4.48 (1H, s), 4.26 (1H, dd, J = 10.0, 2.6 Hz), 3.89 (1H, m), 3.36 (3H, s), 2.83 (1H, dq, J = 8.1, 7.5 Hz), 2.39 (1H, dq, J = 2.1, 7.8 Hz), 1.27 (3H, d, J = 7.5 Hz), 1.07 (3H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.8, 138.1, 128.3, 127.5, 127.4, 104.7, 76.0, 75.1, 71.9, 64.4, 55.7, 38.6, 38.1, 16.7, 8.2.

To a solution of LDA, prepared from *i*-Pr_2NH (23 mL, 0.16 mol) and BuLi (1.66 M solution in hexane, 92 mL, 0.15 mol), in THF (250 mL) was added dropwise a solution of the above methylated lactone in THF (80 and 20 mL) at −78 °C. After 20 min at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl (125 mL) at the same temperature, and the mixture was diluted with EtOAc (1.5 L). The organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (20−30% EtOAc−hexane) afforded α-methylated lactone **12** as a pale yellow oil (23.46 g, 71% for the two steps): $[\alpha]^{23}_D = +43.1°$ (*c* 1.41, $CHCl_3$); IR (film) 1791, 1456, 939 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.24 (5H, m), 4.72 (1H, d, J = 12.7 Hz), 4.66 (1H, d, J = 12.7 Hz), 4.50 (1H, s), 4.37 (1H, dd, J = 9.7, 11.7 Hz), 4.05 (1H, dd, J = 9.7, 2.6 Hz), 3.87 (1H, br dd, J = 2.6, 2.1 Hz), 3.38 (3H, s), 2.69 (1H, dq, J = 11.7, 6.9 Hz), 2.41 (1H, dq, J = 2.1, 7.8 Hz), 1.33 (3H, d, J = 6.9 Hz), 1.09 (3H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 138.1, 128.3, 127.5, 127.4, 104.6, 77.3, 74.7, 71.9, 69.3, 55.5, 41.0, 38.8, 16.7, 12.0; LRMS (EI) *m*/*z* 306 (M^+, 8.5), 274 (61), 183 (6.5), 168 (17), 91 (100); HRMS (EI) calcd for $C_{17}H_{22}O_5$ (M^+) 306.1467, found 306.1450.

Dithiane Alcohol 23. A solution of **12** (23.46 g, 76.57 mmol) and 1,3-propanedithiol (16 mL, 0.16 mol) in CH_2Cl_2 (500 mL) was cooled to 0 °C and treated with TMSOTf (15 mL, 76.8 mmol). After 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (200 mL), and the resulting mixture was extracted with EtOAc (1.5 L) and ether (500 mL). The organic layer was washed with brine (400 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (40% EtOAc−hexane) afforded dithiane **23** as a white solid (26.52 g, 91%): mp 109.0−109.6 °C; $[\alpha]^{26}_D = +12.4°$ (*c* 1.17, $CHCl_3$); IR (KBr) 3425 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.24 (5H, m), 4.73 (1H, d, J = 10.8 Hz), 4.64 (1H, d, J = 10.8 Hz), 4.36 (1H, dd, J = 6.6, 5.4 Hz), 4.20 (1H, d, J = 5.5 Hz), 4.06 (1H, dd, J = 8.4, 6.6 Hz), 3.98 (1H, dd, J = 5.4, 5.4 Hz), 2.92−2.82 (4H, m), 2.62 (1H, dq, J = 8.4, 7.4 Hz), 2.26 (1H, m), 2.10 (1H, m), 1.87 (1H, m), 1.25 (3H, d, J = 7.4 Hz), 1.25 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.2, 137.5, 128.6, 128.1, 82.9, 80.4, 75.6, 75.0, 51.2, 43.4, 40.2, 30.7, 30.1, 25.9, 12.8, 12.7. Anal. Calcd for $C_{19}H_{26}O_4S_2$: C, 59.65; H, 6.85; S, 16.76. Found: C, 59.42; H, 6.84; S, 16.81.

Silyl Ether 24. A solution of dithiane **23** (33.01 g, 86.29 mmol) and 2,6-lutidine (31 mL, 0.27 mol) in CH_2Cl_2 (500 mL) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (28 mL, 0.12 mol). The solution was allowed to warm to room temperature and stirred for 2.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL), and the solution was extracted with EtOAc (1.5 L) and ether (300 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (20% Et_2O−hexane) afforded silyl ether **24** as a colorless oil (42.00 g, 98%), which solidified on standing. Recrystallization from Et_2O and hexane afforded colorless needles: mp 89.8−90.8 °C; $[\alpha]^{29}_D = -13.3°$ (*c* 0.93, $CHCl_3$); IR (KBr) 2936, 1782, 1254, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.24 (5H, m), 4.61 (1H, d, J = 10.6 Hz), 4.56 (1H, d, J = 10.6 Hz), 4.53 (1H, dd, J = 3.4, 2.7 Hz), 4.16 (1H, dd, J = 4.4, 3.4 Hz), 4.09 (1H, d, J = 4.4 Hz), 3.86 (1H, dd, J = 7.8, 2.7 Hz), 2.88−2.77 (4H, m), 2.51 (1H, dq, J = 4.4, 7.6 Hz), 2.14−2.05 (2H, m), 1.83 (1H, m), 1.24 (3H, d, J = 6.9 Hz), 1.19 (3H, d, J = 7.6 Hz), 0.88 (9H, s), 0.10 (3H, s), 0.07 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.0, 137.5, 128.4, 128.3, 127.8, 87.0, 79.9, 75.6, 74.9, 51.9, 45.1, 39.8, 30.9, 30.5, 25.9, 25.7, 17.7, 13.9, 13.0, −3.9, −4.7. Anal. Calcd for $C_{25}H_{40}O_4S_2Si$: C, 60.44; H, 8.12; S, 12.90. Found: C, 60.26; H, 7.96; S, 13.08.

α,*β*-Unsaturated Ester 25. A solution of silyl ether **24** (19.41 g, 39.08 mmol) in CH_3CN (440 mL) and water (110 mL) was treated with *N*-iodosuccinimide (NIS) (44.0 g, 0.195 mol). After 10 min, the reaction was quenched with saturated aqueous sodium sulfite (300 mL), and the mixture was extracted with EtOAc (1 L × 2). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to give crude aldehyde, which was immediately used in the next reaction without purification.

A solution of diisopropyl (ethoxycarbonylmethyl)phosphonate (43 mL, 0.181 mol) in THF (180 mL) was cooled to 0 °C and treated with KO-*t*-Bu (17.5 g, 0.156 mol). The resulting solution was allowed to warm to room temperature and stirred at that temperature for 45 min. The mixture was cooled to −78 °C, and a solution of the above aldehyde in THF (180 and 60 mL) was added. The mixture was stirred at −78 °C for 45 min and then allowed to warm to 0 °C over 30 min, and the reaction was quenched with saturated aqueous NH_4Cl (120 mL). The solution was extracted with EtOAc (1.5 L), washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (10−20% Et_2O−hexane) afforded α,*β*-unsaturated ester **25** as a colorless oil (30.5 g, 90%): $[\alpha]^{20}_D = +2.63°$ (*c* 2.25, $CHCl_3$); IR (film) 1734, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.25 (5H, m), 6.89 (1H, dd, J = 15.8, 8.0 Hz), 5.86 (1H, dd, J = 15.8, 1.0 Hz), 4.58 (1H, d, J = 10.9 Hz), 4.54 (1H, d, J = 10.9 Hz), 4.33 (1H, dd, J = 3.9, 2.9 Hz), 4.19 (1H, dd, J = 4.9, 3.9 Hz), 4.17 (2H, q, J = 7.2 Hz), 3.51 (1H, dd, J = 8.6, 2.9 Hz), 2.63 (1H, m), 2.49 (1H, dq, J = 4.9, 7.6 Hz), 1.26 (3H, t, J = 7.2 Hz), 1.18 (3H, d, J = 6.8 Hz), 1.17 (3H, d, J = 7.6 Hz), 0.85 (9H, s), 0.058 (3H, s), 0.050 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.8, 166.1, 149.0, 137.2, 128.46, 128.42, 128.1, 122.5, 86.4, 81.6, 75.3, 75.0, 60.4, 44.8, 38.2, 25.6, 17.7, 15.8, 14.2, 13.8, −3.9, −4.6; HRMS (FAB) calcd for $C_{26}H_{40}O_6SiNa$ [$(M + Na)^+$] 499.2492, found 499.2515.

Allylic Alcohol 28. A solution of α,*β*-unsaturated ester **25** (11.09 g, 23.3 mmol) in CH_2Cl_2 (250 mL) was cooled to −78 °C and treated with DIBALH (0.93 M solution in hexane, 125 mL, 116 mmol). After being stirred at −78 °C for 30 min, the reaction was quenched with saturated aqueous potassium sodium tartrate (200 mL), and the resulting mixture was vigorously stirred at room temperature for 1.5 h. The mixture was extracted with EtOAc (1 L), washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (230 mL) and treated with PDC (35.26 g, 93.72 mmol) and powdered 4 Å molecular sieves (19 g). After being stirred at room temperature for 2 h, the mixture was diluted with Et_2O, filtered through a florisil column, and washed thoroughly with EtOAc. The filtrate and washings were combined and concentrated to give a residue, which was dissolved in MeOH (180 mL) and treated with $NaBH_4$ (0.659 g, 17.4 mmol) portionwise at 0 °C. After being stirred at 0 °C

for 10 min, the reaction was quenched with saturated aqueous NH_4Cl (180 mL), and the solution was extracted with $CHCl_3$ (300 mL × 4). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (20% EtOAc−hexane) afforded allylic alcohol **28** as a colorless oil (7.49 g, 74% for the three steps): $[\alpha]^{28}_D = -6.27°$ (*c* 2.65, $CHCl_3$); IR (film) 3476 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.35−7.15 (5H, m), 5.56−5.76 (2H, m, 44-H), 4.57 (1H, d, J = 11.0 Hz), 4.54 (1H, d, J = 11.0 Hz), 4.43 (1H, dd, J = 4.0, 2.5 Hz), 4.22 (1H, dd, J = 4.0, 4.0 Hz), 4.09 (2H, m), 3.43 (1H, dd, J = 9.0, 2.5 Hz), 2.48 (2H, m), 1.16 (3H, d, J = 7.5 Hz), 1.12 (3H, d, J = 6.5 Hz), 0.85 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.2, 137.5, 133.3, 130.6, 128.4, 128.3, 127.9, 86.8, 82.6, 75.4, 75.0, 63.3, 45.0, 38.2, 25.6, 17.7, 16.9, 13.7, −3.9, −4.6; HRMS (FAB) calcd for $C_{24}H_{38}O_5SiNa$ [$(M + Na)^+$] 457.2386, found 457.2365.

Epoxy Alcohol 29. A solution of allylic alcohol **28** (1.92 g, 4.42 mmol) and activated powdered 4 Å molecular sieves (0.6 g) in CH_2Cl_2 (65 mL) was cooled to −20 °C and treated with D-(−)-diethyl tartrate (0.95 mL, 5.55 mmol). After the mixture was stirred at the same temperature for 10 min, titanium tetraisopropoxide (1.32 mL, 4.43 mmol) was added, and the resulting mixture was stirred at the same temperature for 30 min. *tert*-Butyl hydroperoxide (5.29 M solution in isooctane, 1.65 mL, 8.73 mmol) was added, and the resulting mixture was stirred at −20 °C for 3 h. Et_2O (10 mL) and saturated aqueous Na_2SO_4 (5 mL) were added to the solution, and the resulting mixture was vigorously stirred at room temperature for 1.5 h. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. Flash chromatography on silica gel (30% EtOAc−hexane) afforded epoxy alcohol **29** as a colorless oil (1.83 g, 92%): $[\alpha]^{24}_D = +5.23°$ (*c* 2.10, $CHCl_3$); IR (film) 3483 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50−7.10 (5H, m), 4.64 (1H, d, J = 10.9 Hz), 4.58 (1H, dd, J = 3.5, 2.9 Hz), 4.49 (1H, d, J = 10.9 Hz), 4.29 (1H, dd, J = 4.8, 3.5 Hz), 3.66 (1H, ddd, J = 12.0, 5.2, 3.3 Hz), 3.57 (1H, dd, J = 8.0, 2.9 Hz), 3.54 (1H, ddd, J = 12.0, 6.6, 4.1 Hz), 3.03 (1H, m), 2.86 (1H, dd, J = 6.8, 2.0 Hz), 2.49 (1H, m), 1.98 (1H, dd, J = 6.6, 5.2 Hz), 1.88 (1H, m), 1.25 (3H, d, J = 7.9 Hz), 1.23 (3H, d, J = 8.0 Hz), 0.95 (9H, s), 0.04 (3H, s), −0.02 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2, 138.4, 129.2, 129.0, 128.9, 86.6, 80.9, 76.0, 75.7, 62.1, 58.8, 58.0, 45.3, 37.8, 26.2, 18.3, 14.4, 13.2, −3.6, −4.1; HRMS (FAB) calcd for $C_{24}H_{39}O_6SiNa$ [$(M + Na)^+$] 451.2516, found 451.2514.

MOM Ether 32. A solution of epoxy alcohol **29** (1.465 g, 3.249 mmol) and *N*,*N*-diisopropylethylamine (2.9 mL, 16.6 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and treated with chloromethyl methyl ether (0.75 mL, 9.87 mmol). The resulting mixture was stirred at room temperature overnight. The solution was diluted with EtOAc (200 mL), washed with water, 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (20% EtOAc−hexane) afforded MOM ether **32** as a colorless oil (1.526 g, 95%): $[\alpha]^{28}_D = +4.72°$ (*c* 0.61, $CHCl_3$); IR (film) 2931, 2858, 1780, 1254, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (5H, m), 4.61 (1H, d, J = 6.6 Hz), 4.60 (1H, d, J = 6.6 Hz), 4.58 (1H, d, J = 10.9 Hz), 4.55 (1H, d, J = 10.9 Hz), 4.46 (1H, dd, J = 4.4, 3.5 Hz), 4.19 (1H, dd, J = 4.4, 4.4 Hz), 3.66 (1H, dd, J = 11.5, 3.5 Hz), 3.56 (1H, dd, J = 11.5, 3.5 Hz), 3.53 (1H, dd, J = 11.5, 5.3 Hz), 3.34 (3H, s), 3.06 (1H, m), 2.80 (1H, dd, J = 6.7, 2.2 Hz), 2.52 (1H, m), 1.77 (1H, m), 1.19 (3H, d, J = 7.6 Hz), 1.12 (3H, d, J = 6.9 Hz), 1.85 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.8, 137.3, 128.4 (×2), 128.0, 96.6, 86.6, 80.1, 75.2, 75.1, 67.3, 57.8, 56.4, 55.3, 44.9, 36.9, 25.6, 17.7, 13.9, 12.5, −3.9, −4.6; HRMS (FAB) calcd for $C_{26}H_{42}O_7SiNa$ [$(M + Na)^+$] 517.2598, found 517.2581.

Allyl Ether 33. A solution of MOM ether **32** (1.526 g, 3.086 mmol) in CH_2Cl_2 (30 mL) was cooled to −78 °C and treated with DIBALH (0.93 M solution in hexane, 3.9 mL, 3.6 mmol). After being stirred at −78 °C for 45 min, the reaction was quenched with saturated aqueous potassium sodium tartrate (10 mL). The cooling bath was removed, and the mixture was vigorously stirred at room temperature for 2 h. The resulting solution was diluted with EtOAc (200 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (30% EtOAc−hexane) afforded hemiacetal as a colorless oil (1.489 g), which was immediately used in the next reaction without further purification.

A solution of the above hemiacetal (1.378 g, 2.774 mmol), tris(dibenzylideneacetone)dipalladium(0)·chloroform (73.5 mg, 0.0706 mmol), and 1,4-bis(diphenylphosphino)butane (121.3 mg, 0.279 mmol) in THF (12 mL) was treated with allyl ethyl carbonate (1.15 mL, 8.48 mmol), and the resulting mixture was heated at 65 °C for 3 h. Evaporation of the solvent and purification by flash chromatography on silica gel (10−20% EtOAc−hexane) afforded allyl ether **33** as an inseparable 3:2 anomeric mixture (1.363 g, 91% for the two steps): $[\alpha]^{26}_D = +9.98°$ (*c* 0.41, $CHCl_3$); IR (film) 2856, 1254, 777, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (α-isomer) δ 7.31−7.24 (5H, m), 5.84 (1H, m), 5.25 (1H, m), 4.93 (1H, d, J = 5.4 Hz), 4.01 (1H, dd, J = 6.9, 4.7 Hz), 3.31 (3H, s), 3.00 (1H, m), 2.82 (1H, dd, J = 7.1, 2.2 Hz), 1.83 (1H, m), 1.12 (3H, d, J = 6.9 Hz), 1.05 (3H, d, J = 7.2 Hz), 0.81 (9H, s), −0.02 (3H, s), −0.06 (3H, s); ^1H NMR ($CDCl_3$, 500 MHz) (β-isomer) δ 7.31−7.24 (5H, m), 5.92 (1H, m), 5.30 (1H, m), 4.74 (1H, d, J = 11.4 Hz), 3.51 (1H, dd, J = 7.4, 2.9 Hz), 3.33 (3H, s), 3.07 (1H, m), 2.78 (1H, dd, J = 7.2, 2.2 Hz), 1.68 (1H, m), 1.10 (3H, d, J = 6.9 Hz), 1.01 (3H, d, J = 7.5 Hz), 0.85 (9H, s), 0.05 (3H, s), −0.01 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) (diastereomixture at C51) δ 138.5, 138.3, 134.8, 134.4, 128.23, 128.21, 127.8, 127.7, 127.5, 116.2, 116.0, 108.4, 104.7, 96.5, 86.5, 85.7, 82.0, 80.4, 79.9, 78.6, 74.4, 73.4, 68.4, 67.73, 67.69, 67.5, 59.4, 58.5, 57.0, 56.5, 55.3, 55.2, 49.0, 47.3, 37.7, 37.5, 25.8, 25.7, 17.9, 17.8, 16.1, 12.9, 11.6, 11.2, −4.0, −4.4.

Alcohols 34. A solution of allyl ether **33** (1.471 g, 2.740 mmol) in THF (12 mL) was cooled to 0 °C and treated with Bu_4NF (1.0 M solution in THF, 4.2 mL, 4.2 mmol). The resulting mixture was stirred at room temperature for 2 h. Evaporation of the solvent and flash chromatography on silica gel (30% EtOAc−hexane) afforded a 3:2 anomeric mixture of alcohols **34** as a colorless oil (1.091 g, 94%). A part of the mixture was separated by HPLC (YMC A024 SIL column, 10 × 300 mm, eluent 25% EtOAc in hexane; UV 254 nm; flow rate 3.0 mL/min; t_R(**34**α) 23.6 min; t_R(**34**β) 24.7 min). Data for α-isomer **34**α: $[\alpha]^{30}_D = +100.1°$ (*c* 0.56, $CHCl_3$); IR (film) 3460 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.25 (5H, m), 5.84 (1H, m), 5.23 (1H, m), 5.13 (1H, m), 4.85 (1H, d, J = 5.0 Hz), 4.69 (1H, d, J = 11.0 Hz), 4.62 (2H, s), 4.34 (1H, d, J = 11.0 Hz), 4.10 (1H, m), 3.94 (1H, dd, J = 9.6, 6.4 Hz), 3.89 (1H, m), 3.73 (1H, dd, J = 8.7, 6.4 Hz), 3.71 (1H, dd, J = 11.6, 3.4 Hz), 3.55 (1H, dd, J = 11.6, 5.5 Hz), 3.48 (1H, dd, J = 8.7, 2.9 Hz), 3.33 (3H, s), 3.05 (1H, ddd, J = 5.5, 3.4, 2.3 Hz), 2.92 (1H, dd, J = 6.9, 2.3 Hz), 2.15 (1H, m), 1.68 (1H, m), 1.10 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 6.8 Hz). Data for β-isomer **34**β: $[\alpha]^{31}_D = -0.89°$ (*c* 0.75, $CHCl_3$); IR (film) 3458, 2931, 1454, 739, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.24 (5H, m), 5.89 (1H, m), 5.26 (1H, m), 5.16 (1H, m), 4.73 (1H, d, J = 2.0 Hz), 4.63 (2H, s), 4.62 (1H, d, J = 6.5 Hz), 4.61 (1H, d, J = 6.5 Hz), 4.18 (1H, m), 4.00 (1H, dd, J = 5.2, 5.2 Hz), 3.96 (1H, m), 3.76 (1H, m), 3.68 (1H, dd, J = 11.4, 3.5 Hz), 3.55 (1H, dd, J = 11.4, 5.4 Hz), 3.53 (1H, dd, J = 5.2, 5.2 Hz), 3.33 (3H, s), 3.11 (1H, ddd, J = 5.4, 3.5, 2.3 Hz), 2.88 (1H, dd, J = 7.2, 2.3 Hz), 2.18 (1H, m), 1.80 (1H, m), 1.10 (3H, d, J = 6.9 Hz), 1.01 (3H, d, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) (diastereomeric mixture at C51) δ 138.0, 137.9, 134.44, 134.35, 128.6, 128.4, 128.0, 127.9, 127.84, 127.79, 117.0, 116.1, 107.9, 104.0, 96.5, 85.3, 85.2, 83.3, 82.2, 79.6, 78.7, 74.1, 73.8, 68.2, 67.9, 67.7, 67.6, 58.9, 58.3, 56.6, 56.1, 55.3, 48.5, 45.3, 38.2, 38.1, 15.2, 12.4, 11.2, 10.7; HRMS (FAB) calcd for $C_{23}H_{34}O_7Na$ [$(M + Na)^+$] 445.2202, found 445.2227.

Oxepane 35 and Tetrahydropyran 36. A solution of hydroxy epoxide **34**α (10.9 mg, 0.0258 mmol) in THF (0.5 mL) was treated with dimsylpotassium (1.0 M solution in DMSO, 0.06 mL, 0.06 mmol). The resulting pale brown solution was stirred at room temperature for 2.5 h and diluted with EtOAc (30 mL). The solution was washed with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (40% EtOAc−hexane) afforded an inseparable 1.7:1 mixture of

oxepane **35α** and tetrahydropyran **36** (7.7 mg, 71%): IR (film) 3466 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) (**35α**) δ 7.50−7.10 (5H), 4.81 (1H, d, J = 5.9 Hz), 4.78 (1H, d, J = 11.9 Hz), 4.55 (1H, d, J = 11.9 Hz), 3.08 (3H, s), 1.11 (3H, d, J = 7.3 Hz); ^1H NMR (C_6D_6, 500 MHz) (**36**) δ 7.50−7.10 (5H), 4.87 (1H, d, J = 5.9 Hz), 4.84 (1H, d, J = 12.0 Hz), 4.64 (1H, d, J = 12.0 Hz), 4.15 (1H, dd, J = 10.4 Hz), 3.07 (3H, s), 2.84 (1H, m), 2.63 (1H, br d, J = 5.8 Hz), 0.96 (3H, d, J = 7.6 Hz).

β-Isomer **34*β*** (12.4 mg, 0.0293 mmol) was treated with dimesylpotassium following the same protocol as the conversion described above. Oxepane **35*β*** (8.0 mg, 65%) was obtained: $[\alpha]^{25}_D$ = −45.0° (*c* 0.50, $CHCl_3$); IR (film) 3467, 2929, 1454, 737, 698 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.45−7.05 (5H), 5.86 (1H, m), 5.24 (1H, m), 5.02 (1H, m), 4.74 (1H, d, J = 3.2 Hz), 4.64 (1H, d, J = 12.0 Hz), 4.57 (1H, d, J = 12.0 Hz), 4.40 (1H, d, J = 6.3 Hz), 4.37 (1H, d, J = 6.3 Hz), 4.32 (1H, m), 4.06 (2H, m), 3.97 (1H, m), 3.92 (1H, m), 3.80−3.73 (3H, m), 3.57 (1H, m), 3.09 (3H, s), 3.02 (1H, d, J = 5.0 Hz), 2.50 (1H, m), 2.22 (1H, m), 1.14 (3H, d, J = 7.0 Hz), 1.02 (3H, d, J = 7.2 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 139.8, 135.5, 129.0, 128.7, 128.1, 116.1, 108.8, 97.3, 82.1, 81.8, 81.4, 78.4, 73.5, 70.2, 69.6, 55.4, 46.5, 44.0, 19.2, 15.3; HRMS (FAB) calcd for $C_{23}H_{34}O_7Na$ [$(M + Na)^+$] 445.2202, found 445.2207.

A mixture of the α- and β-isomers (1.113 g, 2.63 mmol) was treated as above. An approximately 3:1 mixture of oxepane **35** and tetrahydropyran **36** (886.3 mg, 80%) was obtained.

Hydroxy Lactol 37. To a solution of MOM ether **32** (6.81 g, 13.8 mmol) in THF (120 mL) was added dropwise a 1:1 solution of Bu_4NF (1.0 M solution in THF) and acetic acid (27 mL). After being stirred at room temperature for 1 h, the mixture was diluted with EtOAc (600 mL), washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (50% EtOAc−hexane) afforded hydroxy lactone as a colorless oil (5.39 g), which was used in the next reaction without further purification: IR (film) 3458, 1780 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.30−7.00 (5H, m), 4.43 (1H, d, J = 10.8 Hz), 4.40 (2H, s), 4.33 (1H, d, J = 10.8 Hz), 4.17 (1H, dd, J = 6.1, 3.6 Hz), 3.98 (1H, dd, J = 7.5, 6.1 Hz), 3.45 (1H, dd, J = 11.5, 4.0 Hz), 3.41 (1H, dd, J = 11.5, 5.1 Hz), 3.38 (1H, dd, J = 7.0, 3.6 Hz), 3.11 (3H, s), 2.99 (1H, m), 2.68 (1H, dd, J = 6.6, 1.9 Hz), 2.36 (1H, m), 1.69 (1H, m), 1.13 (3H, d, J = 7.2 Hz), 0.96 (3H, d, J = 6.9 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 176.5, 138.5, 129.1, 128.9, 128.7, 97.1, 84.1, 81.9, 75.4, 75.1, 68.2, 57.9, 57.0, 55.4, 44.5, 37.8, 13.4, 13.0; HRMS (FAB) calcd for $C_{20}H_{28}O_7Na$ [$(M + Na)^+$] 403.1733, found 403.1741.

A solution of the above hydroxy lactone (5.39 g) in CH_2Cl_2 (100 mL) was cooled to −78 °C and treated with DIBALH (1.02 M solution in toluene, 30 mL, 30.6 mmol). After being stirred at −78 °C for 45 min, the reaction was quenched with saturated aqueous potassium sodium tartrate (25 mL), and the resulting solution was vigorously stirred at room temperature for 2 h. The mixture was diluted with EtOAc (600 mL), washed with brine, dried ($MgSO_4$), and concentrated to give crude hydroxy lactol **37**, which was used in the next reaction without purification.

Alcohol 34*β*. A solution of the above hydroxy lactol, tris(dibenzylideneacetone)palladium(0)·chloroform (337 mg, 0.326 mmol), and 1,4-bis(diphenylphosphino)butane (605 mg, 1.42 mmol) in THF (100 mL) was treated with allyl ethyl carbonate (2.2 mL, 16.7 mmol), and the resulting mixture was heated at 60 °C for 25 min. Evaporation of the solvent and purification by flash chromatography on silica gel (20−30% EtOAc−hexane) afforded **34*β*** as a pale yellow oil (7:1, 4.22 g, 71% for the three steps), the major isomer of which was identical to a sample prepared above.

Oxepane 35*β*. A solution of hydroxy epoxide **34*β*** (7: 1, 8.70 g, 20.6 mmol) in THF (150 mL) was treated with dimsylpotassium (1.0 M solution in DMSO, 42 mL, 42 mmol), and the resulting brown solution was stirred at 0 °C for 15 min and at room temperature for 1.5 h. The solution was diluted with EtOAc (1 L), washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (30% EtOAc−hexane) afforded oxepane **35*β*** as a colorless oil (8.21 g, 94%, ca. 83% purity by ^1H NMR), which was identical to a sample prepared as above.

Hydroxy Olefin 39. A solution of oxepane **35*β*** (ca. 83% purity, 11.49 g, 27.19 mmol) and 2,6-lutidine (13 mL, 112 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C and treated with TIPSOTf (14 mL, 50.5 mmol). The resulting mixture was stirred at 0 °C for 1.25 h and at room temperature for 1 h. The reaction was quenched with MeOH, and the solution was diluted with EtOAc (1 L), washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (5−10% EtOAc−hexane) afforded TIPS ether (16.64 g): $[\alpha]^{26}_D$ = −28.5° (*c*, 0.84, $CHCl_3$); IR (film) 2948, 2868, 1458, 1117, 1070, 920, 883, 679 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.50−7.00 (5H, m), 5.86 (1H, m), 5.24 (1H, m), 5.01 (1H, m), 4.75 (1H, d, J = 12.0 Hz), 4.75 (1H, d, J = 5.0 Hz), 4.68 (1H, d, J = 12.0 Hz), 4.68 (1H, d, J = 6.4 Hz), 4.66 (1H, d, J = 6.6 Hz), 4.34 (1H, m), 4.13 (2H, m), 4.05 (1H, dd, J = 10.6, 2.4 Hz), 3.93 (1H, m), 3.88−3.78 (3H, m), 3.24 (3H, s), 2.53 (1H, m), 2.42 (1H, m), 1.19 (3H, d, J = 6.9 Hz), 1.10 (21H, s), 0.91 (3H, d, J = 7.5 Hz); HRMS (FAB) calcd for $C_{32}H_{54}O_7SiNa$ [$(M + Na)^+$] 601.3537, found 601.3518.

A solution of the above TIPS ether (9.10 g, 15.7 mmol) in THF (160 mL) was deoxygenated with a stream of argon for 30 min and treated with $[Ir(COD)(Ph_2MeP)_2]PF_6$ (532 mg, 0.629 mmol). The mixture was stirred at room temperature for 5 min under hydrogen and then for 35 min under argon. The reaction mixture was treated with H_2O (40 mL) and then iodine (9.2 g). After being stirred for 5 min, the reaction was quenched with saturated aqueous Na_2SO_3 (150 mL) and diluted with EtOAc (30 mL). The organic layer was washed with saturated aqueous Na_2SO_3 and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography on silica gel (20−30% EtOAc−hexane) afforded hemiacetal **38** as a colorless oil (9.69 g, 78% for the three steps): $[\alpha]^{28}_D$ = −18.9° (*c* 0.71, $CHCl_3$); IR (film) 3429 cm^{-1}.

A suspension of methyltriphenylphosphonium bromide (18.1 g, 50.7 mmol) in THF (80 mL) was cooled to 0 °C and treated with NaHMDS (1 M solution in THF, 47 mL, 47 mmol). After being stirred at 0 °C for 30 min, a solution of the above hemiacetal **38** (9.69 g) in THF (80 and 30 mL) was added dropwise to the orange ylide solution, and the mixture was stirred at 0 °C for 30 min and at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the solution was diluted with EtOAc (700 mL), washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (5−30% EtOAc−hexane) afforded olefin **39** (6.83 g, 71%): $[\alpha]^{27}_D$ = −5.84° (*c* 0.85, $CHCl_3$); IR (film) 3460 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.40−7.05 (5H), 6.25 (1H, ddd, J = 17.3, 10.3, 7.5 Hz), 5.13 (1H, doublet of multiplets, J = 17.3 Hz), 5.08 (1H, doublet of multiplets, J = 10.3 Hz), 4.86 (1H, d, J = 11.3 Hz), 4.62 (1H, d, J = 6.4 Hz), 4.58 (1H, d, J = 6.4 Hz), 4.36 (1H, d, J = 11.3 Hz), 4.17 (1H, m), 3.94 (1H, m), 3.90 (1H, dd, J = 7.9, 1.3 Hz), 3.84 (1H, dd, J = 10.4, 2.9 Hz, 43-H), 3.75 (1H, dd, J = 6.9, 2.8 Hz, 47-H), 3.70 (1H, dd, J = 8.5, 3.3 Hz, 49-H), 3.64 (1H, dd, J = 10.4, 6.3 Hz), 3.22 (3H, s), 2.73 (1H, m), 2.59 (1H, m), 2.42 (1H, br d, J = 10.3 Hz), 1.20 (3H, d, J = 6.9 Hz), 1.13−1.02 (21H), 1.05 (3H, d, J = 7.6 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 143.4, 139.6, 128.9, 128.7, 128.3, 114.2, 97.4, 86.7, 85.4, 85.3, 76.8, 72.6, 70.2, 70.0, 55.4, 41.6, 41.2, 18.8, 18.4, 14.3, 13.6; HRMS (FAB) calcd for $C_{30}H_{52}O_6SiNa$ [$(M + Na)^+$] 559.3431, found 559.3419.

Bicyclic Lactone 41. To a solution of hydroxy olefin **39** (8.83 g, 15.5 mmol) in CH_2Cl_2 (150 mL) were added ethyl vinyl ether (15 mL, 157 mmol) and PPTS (780 mg, 3.12 mmol), and the mixture was stirred at room temperature for 2.5 h. The solution was diluted with EtOAc (600 mL) and washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (5−10% EtOAc−hexane) afforded ethoxyethyl ether **40** as a colorless oil (9.26 g, 98%): $[\alpha]^{25}_D$ = +5.03° (*c* 1.04, $CHCl_3$); HRMS (FAB) calcd for $C_{34}H_{60}O_7SiNa$ [$(M + Na)^+$] 631.4006, found 631.3980.

A solution of the above ethoxyethyl ether **40** (9.25 g, 15.2 mmol) in THF (100 mL) was cooled to 0 °C and treated with 9-BBN−H (0.5 M solution in THF, 61 mL, 30.5 mmol). After being stirred at 0 °C for 5 min, the mixture was allowed to warm to room temperature and stirred at that temperature for 3 h. The solution was cooled to 0 °C, and the reaction was quenched with water (5 mL). The mixture was sequentially treated with 3 M NaOH (20 mL) and 30% H_2O_2 (20 mL), and the resulting solution was stirred at room temperature for 1.5 h and diluted with EtOAc (600 mL). The organic layer was washed sequentially with H_2O (×2), saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on silica gel (30−40% EtOAc−hexane) afforded primary alcohol (9.90 g): $[\alpha]^{27}_D = +7.65°$ (*c* 1.47, $CHCl_3$); IR (film) 3446 cm^{-1}.

A solution of the above alcohol (9.89 g, 15.2 mmol) and triethylamine (11 mL, 78.9 mmol) in CH_2Cl_2−DMSO (4:1, 150 mL) was cooled to 0 °C and treated with SO_3·pyridine complex (9.70 g, 60.9 mmol). After being stirred at 0 °C for 30 min, the mixture was diluted with EtOAc (600 mL) and washed with water, 1 N aqueous HCl, water, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated to give crude aldehyde, which was used in the next reaction without purification.

The above crude aldehyde was dissolved in THF−AcOH−H_2O (3:3:1, 140 mL). The resulting solution was stirred at room temperature overnight. The reaction was quenched with 1 N aqueous K_2CO_3 (300 mL) and diluted with Et_2O (600 mL), and the solution was cautiously treated with solid K_2CO_3 (160 g). The aqueous layer was extracted with Et_2O (500 mL), and the combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to afford crude hemiacetal, which was used in the next reaction without purification.

A solution of the above hemiacetal in CH_2Cl_2 (150 mL) was treated with PDC (17.5 g, 46.5 mmol) and powdered 4 Å molecular sieves (9 g), and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with Et_2O (150 mL), filtered through a florisil column, and washed with Et_2O. The eluent and washings were combined, washed sequentially with saturated aqueous $NaHCO_3$, saturated aqueous Na_2SO_3, 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (20% EtOAc−hexane) afforded lactone **41** (6.98 g, 83% for the four steps): $[\alpha]^{25}_D = -18.7°$ (*c* 1.10, $CHCl_3$); IR (film) 1750 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.55−7.05 (5H), 4.81 (1H, d, J = 11.5 Hz), 4.68 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 6.3 Hz, OCH_2O), 4.54 (1H, d, J = 6.3 Hz), 4.20 (1H, m), 3.88 (1H, dd, J = 10.6, 1.9 Hz), 3.86 (1H, dd, J = 9.8, 1.6 Hz), 3.79 (1H, m), ca. 3.78 (1H, d, overlapped), 3.58 (1H, dd, J = 10.6, 6.7 Hz), 3.46 (1H, dd, J = 10.1, 9.8 Hz), 3.19 (3H, s), 2.52 (1H, m), 2.35 (1H, dd, J = 18.0, 6.9 Hz), 1.74 (1H, dd, J = 18.0, 10.6 Hz), 1.51 (1H, m), 1.11−1.02 (21H), 0.86 (3H, d, J = 7.6 Hz), 0.81 (3H, d, J = 6.4 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 168.8, 139.2, 128.5, 128.3, 127.7, 96.9, 85.1, 82.5, 80.2, 79.7, 76.5, 73.3, 70.0, 54.9, 41.8, 36.8, 32.9, 18.7, 18.5, 17.8, 13.2; HRMS (FAB) calcd for $C_{30}H_{50}O_7SiNa$ [(M + Na)$^+$] 573.3224, found 573.3242.

α-Methylated Lactone 42. To a solution of LHMDS (1.0 M solution in hexane, 16 mL, 16 mmol) in THF (60 mL) was added a solution of lactone **41** (6.98 g, 12.8 mmol) in THF (70 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min and treated with iodomethane (4.0 mL, 64.3 mmol). The resulting mixture was stirred at that temperature for 30 min and then allowed to warm to 0 °C over 5 min, and the reaction was quenched with saturated aqueous NH_4Cl (25 mL). The solution was diluted with EtOAc (500 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (10−20% EtOAc−hexane) afforded compound **42** as a colorless oil (6.63 g, 92%): $[\alpha]^{27}_D = -37.4°$ (*c* 0.40, $CHCl_3$); IR (film) 1738 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.55−7.05 (5H), 4.82 (1H, d, J = 11.6 Hz), 4.69 (1H, d, J = 11.6 Hz), 4.61 (1H, d, J = 6.4 Hz), 4.56 (1H, d, J = 6.4 Hz), 4.22 (1H, m), 3.92 (1H, dd, J = 9.8, 1.6 Hz), 3.91 (1H, dd, J = 10.4, 1.9 Hz, 43-H), 3.80 (1H, d, J = 8.7 Hz), 3.79 (1H, dd, J = 5.8, 1.6 Hz), 3.61 (1H, dd, J = 10.4, 6.6 Hz), 3.52 (1H, dd, J = 10.2, 9.8 Hz), 3.21 (3H, s), 2.53 (1H, m), 1.70 (1H, m), 1.36 (1H, m, 50-H), 1.17 (3H, d, J = 7.1 Hz,), 1.14−1.02 (21H, 0.94 (3H, d, J = 6.3 Hz), 0.86 (3H, d, J = 7.7 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 171.9, 139.3, 128.5, 128.3, 127.7, 96.9, 85.3, 82.7, 79.7, 79.5, 76.5, 73.3, 70.0, 54.9, 42.0, 41.9, 40.5, 18.7, 18.5, 15.9, 15.7, 13.2; HRMS (FAB) calcd for $C_{31}H_{52}O_7SiNa$ [(M + Na)$^+$] 587.3380, found 587.3373.

Hemiketal 43. A solution of lactone **42** (6.63 g, 11.7 mmol) in THF (120 mL) was cooled to −78 °C and treated with allylmagnesium bromide (1.0 M solution in Et_2O, 14 mL, 14 mmol). After being stirred at that temperature for 45 min, the reaction was quenched with saturated aqueous NH_4Cl (25 mL). The mixture was diluted with EtOAc (500 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (15% EtOAc−hexane) afforded hemiketal **43** as a colorless oil (5.62 g, 79%): $[\alpha]^{27}_D = -9.7°$ (*c* 0.70, $CHCl_3$); IR (film) 3452 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.6−7.1 (5H), 5.98 (1H, m), 5.04 (1H, dd, J = 10.1, 2.1 Hz), 4.99 (1H, d, J = 6.3 Hz), 4.32 (1H, m), 4.13 (1H, dd, J = 9.8, 1.4 Hz), 4.01 (1H, dd, J = 10.3, 1.9 Hz), 3.91 (1H, d, J = 9.3 Hz), 3.79 (1H, dd, J = 5.9, 1.3 Hz), 3.71 (1H, dd, J = 10.4, 6.7 Hz), 3.50 (1H, dd, J = 10.1, 10.1 Hz), 3.25 (3H, s), 2.63 (1H, m), 2.31 (1H, br dd, J = 13.4, 6.7 Hz), 2.22 (1H, br dd, J = 13.4, 7.7 Hz), 1.91 (1H, m), 1.29 (1H, m), 1.22 (3H, d, J = 6.4 Hz), 1.16−1.11 (21H), 1.10 (3H, d, J = 7.7 Hz), 0.94 (3H, d, J = 6.7 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 140.2, 133.6, 128.3, 127.4, 127.3, 119.1, 98.5, 96.9, 85.1, 83.8, 82.4, 77.1, 72.9, 72.0, 70.3, 54.9, 44.8, 43.5, 43.0, 38.3, 19.3, 18.5, 15.3, 13.5, 13.3; HRMS (FAB) calcd for $C_{34}H_{58}O_7SiNa$ [(M + Na)$^+$] 629.3850 found 629.3831.

Spiroketal 44. A solution of hemiketal **43** (5.62 g, 9.26 mmol) and *N*,*N*′-bis(2,4,6-trimethylbenzyl)-(*S*,*S*)-1,2-diphenyl-1,2-diaminoethane (4.42 g, 9.27 mmol) in CH_2Cl_2 (100 mL) was cooled to −90 °C and treated with osmium tetroxide (2.36 g, 9.28 mmol). The resulting mixture was stirred at −90 °C for 2 h, and the solvent was evaporated. The residue was dissolved in THF (100 mL) and saturated aqueous $NaHSO_3$ (100 mL), and the resulting mixture was refluxed for 2 h. The aqueous layer was separated and extracted with EtOAc (300 mL × 2). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (40−60% EtOAc−hexane) afforded triol as a colorless oil (5.04 g, 85%): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (5H, m), 4.82 (1H, 44-H, 54-H), 3.96 (1H, dd, J = 9.9, 1.4 Hz), 3.81 (1H, dd, J = 10.3, 2.0 Hz), 3.73 (1H, d, J = 9.4 Hz), 3.66 (1H, dd, J = 5.8, 1.4 Hz), 3.61 (1H, dd, J = 11.3, 4.0 Hz), 3.57 (1H, dd, J = 11.3, 5.6 Hz), 3.49 (1H, dd, J = 10.3, 6.6 Hz), 3.33 (3H, s), 3.31 (1H, dd, J = 10.1, 9.9 Hz, 49-H), 2.62 (1H, m), 1.99 (1H, dd, J = 14.6, 3.6 Hz), 1.72 (1H, dd, J = 14.6, 8.0 Hz), 1.62 (1H, m), 1.32 (1H, m), 1.11 (3H, d, J = 7.8 Hz), 1.08−1.02 (24H, s), 0.94 (3H, d, J = 6.8 Hz).

A solution of the above triol (5.04 g, 7.86 mmol) in benzene (100 mL) was treated with camphorsulfonic acid (182.6 mg, 0.7863 mmol), and the resulting mixture was stirred at room temperature for 1.5 days. The reaction was quenched with triethylamine, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (30% EtOAc−hexane) to afford spiroketal **44** (4.22 g, 86%): $[\alpha]^{25}_D = -30.0°$ (*c* 0.97, $CHCl_3$); IR (film) 3466 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.60−7.10 (5H, m), 4.87 (2H, br s), 4.69 (1H, d, J = 6.4 Hz), 4.64 (1H, d, J = 6.4 Hz), 4.36 (1H, m), 4.10 (1H, m), 4.04 (1H, dd, J = 10.1, 1.5 Hz), 4.02 (1H, dd, J = 10.4, 1.9 Hz), 3.89 (1H, d, J = 9.2 Hz), 3.78 (1H, dd, J = 9.5, 4.5 Hz), 3.75 (1H, dd, J = 5.9, 1.5 Hz), 3.71 (1H, dd, J = 10.4, 6.7 Hz), 3.59 (1H, d, J = 9.5 Hz), 3.56 (1H, dd, J = 10.1, 10.1 Hz), 3.25 (3H, s), 2.63 (1H, m), 2.09 (1H, dd, J = 14.0, 7.0 Hz), 1.92 (1H, m), 1.82 (1H, dd, J = 14.0, 1.8 Hz), 1.35 (1H, m), 1.25 (3H, d, J = 6.3 Hz), 1.06−1.18 (21H), 1.08 (3H, d, J = 7.7 Hz), 1.01 (3H, d, J = 6.6 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 140.2, 128.3, 127.4, 127.3, 109.7, 97.0, 85.0, 84.3, 82.1, 77.1, 74.8, 72.9, 72.4, 71.7, 70.4, 54.9, 46.2, 42.8, 42.6, 39.7, 19.3, 18.5, 15.7, 13.7, 13.3; HRMS (FAB) calcd for $C_{34}H_{58}O_8SiNa$ [(M + Na)$^+$] 645.3799, found 645.3775.

Benzyl Ether 45. A solution of the spiroketal **44** (4.22 g, 6.77 mmol) in THF (60 mL) and DMF (20 mL) was cooled to 0 °C and treated with sodium hydride (60% dispersion in mineral oil, 541 mg, 13.5 mmol), and the mixture was stirred at room temperature for 30 min. The mixture was recooled to 0 °C and treated with benzyl bromide (1.2 mL, 10.1 mmol), and the resulting mixture was stirred at 0 °C for 1 h, at room temperature for 14 h, and then at 50 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl, and the solution was diluted with EtOAc (400 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (5−10% EtOAc−hexane) afforded benzyl ether **45** as a colorless oil (4.01 g, 83%): $[\alpha]^{27}_D = -25.9°$ (*c* 0.87, $CHCl_3$); IR (film) 2538, 1653, 1358, 1506, 940, 883, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42−7.15 (10H, m), 4.73 (1H, d, J = 12.4 Hz), 4.70 (1H, d, J = 12.4 Hz), 4.64 (1H, d, J = 6.5 Hz), 4.62 (1H, d, J = 6.5 Hz), 4.47 (1H, d, J = 11.9 Hz), 4.44 (1H, d, J = 11.9 Hz), 4.25 (1H, m), 4.07 (1H, m), 3.92 (1H, dd, J = 9.8, 1.7 Hz), 3.83 (1H, dd, J = 9.8, 5.1 Hz), 3.82 (1H, dd, J = 10.4, 2.0 Hz), 3.72 (1H, dd, J = 10.0, 1.5 Hz), 3.70 (1H, d, J = 9.5 Hz), 3.60 (1H, dd, J = 5.9, 1.5 Hz), 3.48 (1H, dd, J = 10.4, 6.8 Hz), 3.34 (3H, s), 3.31 (1H, dd, J = 10.0, 10.0 Hz), 2.52 (1H, m), 2.13 (1H, dd, J = 13.7, 7.0 Hz), 2.06 (1H, dd, J = 13.7, 3.6 Hz), 1.61 (1H, m), 1.50 (1H, m), 1.07 (3H, d, J = 6.3 Hz), 1.06−1.03 (21H), 1.04 (3H, m), 0.98 (3H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.7, 138.2, 128.4, 127.9, 127.59, 127.56, 127.0, 126.8, 109.3, 106.4, 103.6, 100.1, 96.8, 84.1, 83.5, 81.6, 81.3, 78.5, 76.4, 72.1, 71.52, 71.46, 71.4, 71.0, 70.2, 63.2, 60.4, 55.8, 55.1, 54.5, 42.6, 42.1, 41.0, 39.1, 35.1, 19.1, 18.4, 18.3, 15.3, 13.4, 13.1, 12.9, 10.3, 4.9; HRMS (FAB) calcd for $C_{41}H_{64}O_8SiNa$ [$(M + Na)^+$] 735.4268, found 735.4268.

Diol 46. A solution of benzyl ether **45** (4.01 g, 5.62 mmol) and dimethyl sulfide (10 mL) in CH_2Cl_2 (80 mL) was cooled to 0 °C and treated with boron trifluoride etherate (3.5 mL, 28.4 mmol). After being stirred at 0 °C for 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The solution was diluted with EtOAc (400 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (40% EtOAc−hexane) afforded diol **46** as a colorless oil (2.22, 77%): $[\alpha]^{25}_D = -36.2°$ (*c* 0.83, $CHCl_3$); IR (film) 3460 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.50−7.00 (10H, m), 4.77 (1H, d, J = 11.8 Hz), 4.58 (1H, d, J = 11.8 Hz), 4.18 (2H, s), 4.01 (1H, m), 3.95 (1H, dd, J = 9.6, 1.5 Hz), 3.92 (1H, dd, J = 9.8, 1.5 Hz), 3.86 (2H, m), 3.73−3.65 (3H, m), 3.49 (1H, m), 3.42 (1H, t, J = 10.0 Hz), 3.06 (1H, br d, J = 9.8 Hz), 2.43 (1H, m), 2.06 (2H, m), 1.85 (1H, m), 1.36 (1H, m), 1.03 (3H, d, J = 6.4 Hz), 1.02 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 7.6 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 139.4, 138.8, 128.7, 128.6, 128.3, 127.9, 127.8, 127.7, 109.4, 87.3, 84.8, 81.7, 78.8, 76.5, 74.0, 72.6, 71.7, 71.1, 65.8, 43.2, 42.3, 42.2, 39.5, 17.6, 15.8, 13.7; HRMS (FAB) calcd for $C_{30}H_{40}O_7Na$ [$(M + Na)^+$] 535.2672, found 535.2662.

Tosylate 47. A solution of diol **46** (2.20 g, 4.33 mmol), DMAP (1.00 g, 8.19 mmol), and triethylamine (6.0 mL, 43.0 mol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (0.99 g, 5.20 mmol), and the resulting mixture was stirred at 0 °C for 2 h. The solution was diluted with EtOAc (300 mL), washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (20−30% EtOAc−hexane) afforded monotosylate **47** as a colorless oil (2.68 g, 93%): $[\alpha]^{28}_D = -31.8°$ (*c* 0.413, $CHCl_3$); IR (film) 3535, 2972, 2924, 2881, 1363, 1176, 737, 698, 555 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.76 (2H, d, J = 8.3 Hz), 7.34−7.24 (12H, m), 4.83 (1H, d, J = 11.7 Hz), 4.55 (1H, d, J = 11.7 Hz), 4.47 (1H, d, J = 12.0 Hz), 4.44 (1H, d, J = 12.0 Hz), 4.25 (1H, m), 4.14 (1H, dd, J = 10.2, 2.3 Hz), 3.98 (1H, dd, J = 10.2, 7.9 Hz), 3.94 (1H, dd, J = 9.7, 1.9 Hz), 3.84 (1H, dd, J = 9.8, 5.1 Hz), 3.79 (1H, br d, J = 6.7 Hz), 3.76 (1H, m), 3.73 (1H, dd, J = 9.9, 1.6 Hz), 3.20 (1H, t, J = 10.0 Hz), 3.18 (1H, m), 2.87 (1H, br d, J = 10.2 Hz), 2.42 (1H, m), 2.41 (3H, s), 2.10 (2H, m), 1.56 (1H, m), 1.49 (1H, m), 1.00 (3H, d, J = 6.3 Hz), 0.99 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 7.6 Hz).

Nitrile 48. A solution of tosylate **47** (2.68 g, 4.02 mmol) in DMSO (40 mL) was treated with NaCN (591 g, 12.0 mmol), and the resulting mixture was heated at 70 °C for 5.5 h. The mixture was cooled to room temperature, poured into saturated aqueous NH_4Cl (100 mL), and extracted with EtOAc (300 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (30−50% EtOAc−hexane) afforded nitrile **48** as a pale yellow oil (1.86 g, 89%): $[\alpha]^{28}_D = -38.8°$ (*c* 0.393, $CHCl_3$); IR (film) 3501, 2927, 2253, 1456, 940, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30−7.20 (10H, m), 4.86 (1H, d, J = 11.7 Hz), 4.57 (1H, d, J = 11.7 Hz), 4.47 (1H, d, J = 12.0 Hz), 4.45 (1H, d, J = 12.0 Hz), 4.26 (1H, m), 3.96 (1H, dd, J = 9.7, 2.0 Hz), 3.86 (2H, m), 3.79 (2H, m), 3.34 (1H, t, J = 10.0 Hz), 2.73 (1H, m), 2.72 (1H, dd, J = 16.7, 3.0 Hz), 2.49 (1H, dd, J = 16.7, 8.8 Hz), 2.42 (1H, m), 2.13 (2H, m), 1.67 (1H, m), 1.54 (1H, m), 1.15 (3H, d, J = 6.3 Hz), 1.03 (3H, d, J = 7.6 Hz), 1.01 (3H, d, J = 6.6 Hz); HRMS (FAB) calcd for $C_{31}H_{39}O_6NNa$ [$(M + Na)^+$] 544.2675, found 544.2695.

α,β-Unsaturated Ester 49. A solution of nitrile **48** (1.76 g, 3.37 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C and treated with DIBALH (1.02 M solution in toluene, 8.2 mL, 8.36 mmol). After being stirred at −78 °C for 1 h, the reaction was quenched with 1 N aqueous HCl (15 mL), and the cooling bath was removed. The mixture was vigorously stirred at room temperature for 15 min and diluted with EtOAc (300 mL). The organic layer was washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by florisil column chromatography (30% EtOAc−hexane) afforded a mixture of hemiacetal as a colorless oil (1.721 g), which was used in the next reaction without further purification.

A solution of the above hemiacetal (1.721 g) in dry benzene (40 mL) was treated with $Ph_3P{=}CHCOOMe$ (5.50 g, 16.5 mmol), and the resulting mixture was heated at 80 °C for 1 h. The solvent was evaporated, and the residue was directly subjected to flash chromatography on silica gel (30% EtOAc−hexane) to give α,β-unsaturated ester **49** as a colorless oil (1.574 g, 80% for the two steps): $[\alpha]^{28}_D = -21.0°$ (*c* 0.54, $CHCl_3$); IR (film) 3525, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33−7.24 (10H, m), 7.03 (1H, ddd, J = 15.6, 7.9, 6.5 Hz), 5.88 (1H, br d, J = 15.6 Hz), 4.85 (1H, d, J = 11.7 Hz), 4.58 (1H, d, J = 11.7 Hz), 4.47 (1H, d, J = 12.0 Hz), 4.44 (1H, d, J = 12.0 Hz), 4.26 (1H, m), 3.95 (1H, dd, J = 9.7, 2.0 Hz), 3.85 (1H, dd, J = 9.7, 5.2 Hz), 3.80 (1H, dd, J = 6.4, 1.8 Hz), 3.77 (1H, dd, J = 9.9, 1.8 Hz), 3.70 (3H, s), 3.63 (1H, ddd, J = 8.6, 8.6, 3.6 Hz), 3.29 (1H, br d, J = 8.6 Hz), 3.23 (1H, dd, J = 9.9, 9.9 Hz), 2.93 (1H, br d, J = 8.6 Hz), 2.61 (1H, m), 2.45 (1H, m), 2.39 (1H, m), 2.12 (2H, m), 1.62 (1H, m), 1.51 (1H, m), 1.02 (3H, d, J = 6.3 Hz), 1.00 (3H, d, J = 7.5 Hz), 0.99 (3H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.9, 146.8, 138.7, 138.1, 128.5, 128.4, 127.7, 127.6, 127.6, 127.6, 122.9, 109.2, 87.0, 84.3, 82.6, 79.3, 78.3, 74.3, 72.1, 71.6, 71.0, 51.3, 42.8, 42.1, 41.9, 39.3, 38.9, 17.3, 15.6, 13.4; HRMS (FAB) calcd for $C_{34}H_{44}O_8Na$ [$(M + Na)^+$] 603.2934, found 603.2944.

Silyl Ether 50. A solution of α,β-unsaturated ester **49** (1.574 g, 2.71 mmol) and 2,6-lutidine (1.0 mL, 8.59 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C and treated with TBDMSOTf (1.0 mL, 4.35 mmol), and the resulting solution was stirred at 0 °C for 40 min. The reaction mixture was partitioned between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (70 mL), and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica gel (15% Et_2O−hexane) afforded silyl ether **50** as a colorless oil (1.823 g, 97%): $[\alpha]^{28}_D = -17.5°$ (*c* 0.487, $CHCl_3$); IR (film) 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (10H, m), 7.05 (1H, ddd, J = 15.6, 8.2, 6.2 Hz), 5.87 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12.6 Hz), 4.63 (1H, d, J = 12.6 Hz), 4.47 (1H, d, J = 11.9 Hz), 4.44 (1H, d, J = 11.9 Hz), 4.24 (1H, m), 4.07 (1H, ddd, J = 9.3, 9.3, 2.4 Hz), 3.92 (1H, br d, J = 9.7 Hz), 3.81 (1H, dd, J = 9.7, 5.1 Hz), 3.70 (3H, s), 3.68 (1H, dd, J = 8.9, 1.6 Hz), 3.53 (1H, dd, J = 5.5, 1.6 Hz), 3.36 (1H, br d, J = 9.3 Hz), 3.27 (1H, dd, J = 9.8, 8.9 Hz), 2.62 (1H, m), 2.41 (1H, m), 2.20 (1H, m), 2.15 (1H, dd, J = 13.7, 7.0 Hz), 2.07 (1H, dd, J = 13.7, 3.6 Hz), 1.58 (1H, m), 1.52 (1H, m), 1.02 (3H, d, J = 7.8 Hz), 1.00 (3H, d, J = 6.2 Hz), 0.97 (3H, d, J = 6.5 Hz), 0.88 (9H, s), 0.10 (3H, s), 0.04

(3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.9, 147.6, 139.5, 138.2, 128.4, 128.0, 127.6, 127.6, 127.1, 127.0, 122.7, 109.3, 83.3, 82.8, 81.4, 79.9, 78.4, 71.5, 71.2, 71.0, 51.3, 42.6, 41.9, 41.3, 39.5, 37.7, 25.9, 19.1, 17.9, 15.6, 13.5, −3.7, −4.8; HRMS (FAB) calcd for $C_{40}H_{58}O_8SiNa$ [$(M + Na)^+$] 717.3799, found 717.3776.

Allyl Alcohol 51. A solution of silyl ether **50** (1.823 g, 2.622 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C and treated with DIBALH (1.02 M solution in hexane, 6.5 mL, 6.63 mmol), and the resulting solution was stirred at −78 °C for 30 min. The reaction was quenched with saturated aqueous potassium sodium tartrate (10 mL), and the solution was vigorously stirred at room temperature for 1.5 h. The mixture was extracted with EtOAc (300 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (20% EtOAc−hexane) afforded allyl alcohol **51** as a colorless oil (1.553 g, 89%): $[\alpha]^{27}_D = -23.2°$ (*c* 0.513, $CHCl_3$); IR (film) 3466 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50−7.10 (10H, m), 5.76 (1H, m), 5.68 (1H, m), 4.76 (1H, d, *J* = 12.7 Hz), 4.61 (1H, d, *J* = 12.7 Hz), 4.46 (1H, d, *J* = 12.0 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.24 (1H, m), 4.06 (1H, d, *J* = 5.8 Hz), 3.94 (1H, td, *J* = 9.2, 2.3 Hz), 3.91 (1H, br d, *J* = 10.1 Hz), 3.80 (1H, dd, *J* = 9.6, 5.1 Hz), 3.67 (1H, dd, *J* = 9.8, 1.6 Hz), 3.52 (1H, d, *J* = 5.7 Hz), 3.34 (1H, d, *J* = 8.9 Hz), 3.24 (1H, t, *J* = 10.0 Hz), 2.50 (1H, m), 2.41 (1H, m), 2.15 (1H, dd, *J* = 13.7, 7.1 Hz), 2.06 (1H, dd, *J* = 13.8, 3.5 Hz), 2.02 (1H, m), 1.59 (1H, m), 1.51 (1H, m), 1.03 (3H, d, *J* = 6.3 Hz), 1.01 (3H, d, *J* = 7.7 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 0.89 (9H, s), 0.09 (3H, s), 0.04 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.6, 138.2, 131.0, 130.8, 128.4, 128.0, 127.6, 127.6, 127.1, 127.0, 109.2, 83.7, 83.3, 81.3, 79.9, 78.5, 71.5, 71.3, 71.2, 71.0, 63.9, 42.6, 42.0, 41.2, 39.6, 37.8, 25.9, 19.1, 17.9, 15.8, 13.5, −3.7, −4.8; HRMS (FAB) calcd for $C_{39}H_{58}O_7SiNa$ [$(M + Na)^+$] 689.3850, found 689.3878.

Epoxy Alcohol 52. A solution of allylic alcohol **51** (1.553 g, 2.328 mmol) and activated powdered 4 Å molecular sieves (0.65 g) in CH_2Cl_2 (40 mL) was cooled to −20 °C and treated with D-(−)-diethyl tartrate (0.5 mL, 2.9 mmol). After the mixture was stirred at −20 °C for 10 min, titanium tetraisopropoxide (0.7 mL, 2.3 mmol) was added, and the resulting solution was stirred at the same temperature for 1 h. *tert*-Butyl hydroperoxide (5.5 M solution in isooctane, 1 mL, 5.5 mmol) was added, and the resulting mixture was stirred at −20 °C for 5 h. Et_2O (40 mL) and saturated aqueous Na_2SO_4 (5 mL) were added to the solution, and the resulting mixture was vigorously stirred at room temperature for 1.5 h. The reaction mixture was filtered through a pad of Celite and washed with EtOAc (600 mL). The filtrate and washings were combined and concentrated. Flash chromatography on silica gel (20% EtOAc−hexane) afforded epoxy alcohol **52** as a colorless oil (1.197 g, 75%): $[\alpha]^{23}_D = -23.2°$ (*c* 0.560, $CHCl_3$); IR (film) 3471 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 7.60−7.05 (10H, m), 4.89 (1H, d, *J* = 12.3 Hz), 4.72 (1H, d, *J* = 12.3 Hz), 4.32 (1H, dt, *J* = 10.8, 5.7 Hz), 4.18 (1H, d, *J* = 12.5 Hz), 4.16 (1H, d, *J* = 12.5 Hz), 4.04 (1H, m), 4.02 (1H, dd, *J* = 9.7, 1.3 Hz), 3.99 (1H, dd, *J* = 9.7, 4.9 Hz), 3.70 (1H, dd, *J* = 5.5, 1.3 Hz), 3.63 (1H, d, *J* = 9.1 Hz), 3.53 (1H, t, *J* = 10.0 Hz), 3.51 (1H, dd, *J* = 12.3, 2.5 Hz), 3.30 (2H, m), 2.70 (1H, ddd, *J* = 4.6, 2.5, 2.5 Hz), 2.51 (1H, m), 2.17 (1H, dd, *J* = 13.8, 7.0 Hz), 2.09 (1H, dd, *J* = 13.7, 3.2 Hz), 1.92 (3H, m), 1.42 (1H, m), 1.14 (3H, d, *J* = 6.4 Hz), 1.06 (3H, d, *J* = 6.8 Hz), 1.04 (3H, d, *J* = 7.7 Hz), 0.96 (9H, s), 0.10 (3H, s), 0.08 (3H, s); ^{13}C NMR (C_6D_6, 125 MHz) δ 140.0, 138.9, 128.6, 128.4, 128.3, 127.7, 127.6, 127.5, 109.7, 84.2, 82.7, 81.9, 80.0, 79.0, 72.2, 72.0, 71.7, 71.1, 61.9, 57.8, 53.5, 43.3, 42.4, 42.0, 39.8, 37.1, 26.1, 19.2, 18.2, 15.9, 13.8, −3.7, −4.6; HRMS (FAB) calcd for $C_{39}H_{58}O_8SiNa$ [$(M + Na)^+$] 705.3799, found 705.3823.

Olefin 53. A solution of epoxy alcohol **52** (1.174 g, 1.72 mmol) and triethylamine (1.3 mL, 9.33 mmol) in CH_2Cl_2−DMSO (4:1, 30 mL) was cooled to 0 °C and treated with sulfur trioxide·pyridine complex (1.20 g, 7.54 mmol), and the resulting solution was stirred at 0 °C for 30 min. The reaction mixture was diluted with EtOAc (200 mL) and washed with H_2O, 1 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to give aldehyde, which was used in the next reaction without purification.

A suspension of methyltriphenylphosphonium bromide (1.90 g, 5.32 mmol) in THF (10 mL) was cooled to 0 °C and treated with NaHMDS (1.0 M solution in THF, 5.3 mL, 5.3 mmol). After the orange ylide solution stirred at 0 °C for 30 min, a solution of the above crude aldehyde in THF (10 mL) was added via cannula, and the resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc (150 mL). The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (5−10% EtOAc−hexane) afforded olefin **53** as a colorless oil (1.081 g, 91%): $[\alpha]^{26}_D = -31.3°$ (*c* 0.447, $CHCl_3$); IR (film) 2927, 2858, 1456, 1257, 937, 835, 773, 735, 698, 669 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 7.54−7.10 (10H, m), 5.55 (1H, ddd, *J* = 17.9, 10.9, 7.9 Hz), 5.27 (1H, dd, *J* = 17.3, 1.1 Hz), 4.99 (1H, dd, *J* = 10.4, 1.4 Hz), 4.89 (1H, d, *J* = 12.2 Hz), 4.71 (1H, d, *J* = 12.2 Hz), 4.36 (1H, m), 4.17 (2H, br s), 4.04 (1H, m), 4.02 (1H, dd, *J* = 9.7, 1.5 Hz), 3.99 (1H, br d, *J* = 9.7 Hz), 3.79 (1H, dd, *J* = 9.7, 4.9 Hz), 3.70 (1H, dd, *J* = 5.6, 1.3 Hz), 3.65 (1H, dd, *J* = 9.0, 0.8 Hz), 3.53 (1H, t, *J* = 10.0 Hz), 3.27 (1H, td, *J* = 5.8, 2.0 Hz), 3.08 (1H, dd, *J* = 7.4, 1.9 Hz), 2.51 (1H, m), 2.16 (1H, dd, *J* = 13.8, 7.0 Hz), 2.08 (1H, dd, *J* = 13.7, 3.2 Hz), 1.93 (3H, m), 1.39 (1H, m), 1.11 (3H, d, *J* = 6.4 Hz), 1.05 (3H, d, *J* = 6.2 Hz), 1.04 (3H, d, *J* = 7.2 Hz), 0.96 (9H, s), 0.09 (3H, s), 0.08 (3H, s); ^{13}C NMR (C_6D_6, 125 MHz) δ 140.1, 138.9, 136.8, 128.6, 128.4, 128.3, 127.7, 127.6, 127.4, 118.0, 109.6, 84.2, 82.7, 81.9, 79.9, 79.0, 72.2, 72.0, 71.7, 71.1, 58.2, 57.8, 43.2, 42.4, 42.0, 39.8, 37.5, 26.1, 19.2, 18.2, 16.0, 13.8, −3.7, −4.6; HRMS (FAB) calcd for $C_{40}H_{58}O_7SiNa$ [$(M + Na)^+$] 701.3850, found 701.3867.

Tetrahydropyran 55. A solution of **53** (1.081 g, 1.58 mmol) in THF (30 mL) was cooled to 0 °C and treated with Bu_4NF (1.0 M solution in THF, 2.4 mL, 2.4 mmol), and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc (200 mL), and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by florisil column chromatography (20% EtOAc−hexane) afforded hydroxy epoxide **54** as a colorless oil, which was used directly for the next reaction: $[\alpha]^{27}_D = -31.7°$ (*c* 0.473, $CHCl_3$); IR (film) 3498 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 7.50−7.00 (10H, m), 5.42 (1H, ddd, *J* = 17.4, 10.3, 7.4 Hz), 5.21 (1H, dd, *J* = 17.2, 1.4 Hz), 4.97 (1H, dd, *J* = 10.3, 1.3 Hz), 4.72 (1H, d, *J* = 12.0 Hz), 4.61 (1H, d, *J* = 12.0 Hz), 4.17 (3H, m), 4.00 (1H, m), 3.97 (1H, d, *J* = 9.6 Hz), 3.92 (1H, dd, *J* = 9.7, 1.3 Hz), 3.72 (1H, dd, *J* = 9.7,4.9 Hz), 3.65 (1H, dd, *J* = 3.8, 1.0 Hz), 3.62 (1H, m), 3.56 (1H, t, *J* = 9.9 Hz), 3.32 (1H, br d, *J* = 7.1 Hz), 3.20 (1H, m), 2.80 (1H, dd, *J* = 7.5, 2.1 Hz), 2.43 (1H, m), 2.08 (2H, m), 1.99 (1H, dt, *J* = 14.6, 3.9 Hz), 1.92 (1H, m), 1.41 (1H, m), 1.10 (3H, d, *J* = 6.6 Hz), 1.08 (3H, d, *J* = 7.6 Hz), 1.06 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 136.2, 128.6, 128.6, 128.3, 127.9, 127.7, 127.7, 118.5, 109.3, 85.3, 81.8, 79.8, 79.4, 78.9, 73.5, 72.8, 71.6, 71.1, 58.5, 57.3, 43.2, 42.4, 42.2, 39.3, 37.0, 18.7, 16.1, 13.8; HRMS (FAB) calcd for $C_{34}H_{44}O_7Na$ [$(M + Na)^+$] 587.2985, found 587.3011.

A solution of the above hydroxy epoxide **54** in CH_2Cl_2 (30 mL) was cooled to −40 °C and treated with camphorsulfonic acid (37.0 mg, 0.159 mmol) in one portion. The resulting solution was stirred at −40 °C for 30 min and at 0 °C for 1 h. The reaction was quenched with triethylamine (0.50 mL), and the solvent was evaporated. Flash chromatography on silica gel (10−20% EtOAc−hexane) gave an inseparable 4:1 mixture of tetrahydropyran **55** and tetrahydrofuran **56** as a colorless oil (840.1 mg, 93%): $[\alpha]^{25}_D = -29.9°$ (*c* 0.447, $CHCl_3$); IR (film) 3456 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 7.50−7.10 (10H, m), 5.88 (1H, ddd, *J* = 17.1, 10.6, 5.3 Hz), 5.31 (1H, dt, *J* = 17.1, 1.7 Hz), 5.06 (1H, dd, *J* = 10.6, 1.7 Hz), 4.67 (1H, d, *J* = 12.1 Hz), 4.63 (1H, d, *J* = 12.1 Hz), 4.16 (2H, s), 4.11 (1H, ddd, *J* = 11.0, 9.3, 5.1 Hz), 4.00 (1H, m), 3.99 (1H, d, *J* = 9.4 Hz), 3.90 (1H, d, *J* = 9.3 Hz), 3.73 (1H, dd, *J* = 9.4, 4.7 Hz), 3.64 (1H, dd, *J* = 9.8, 9.3 Hz), 3.52 (1H, d, *J* = 2.9 Hz), 3.38 (1H, m), 3.12 (1H, m), 3.03 (1H, dd, *J* = 9.3, 4.9 Hz), 2.47 (1H, m), 2.33 (1H, ddd, *J* = 12.1, 5.1, 4.8 Hz), 2.10 (2H, m), 1.94 (1H, m), 1.50 (1H, ddd, *J* = 12.1, 11.5, 11.0 Hz), 1.45 (1H, m), 1.15 (3H,

d, J = 6.4 Hz), 1.07 (3H, d, J = 7.5 Hz), 1.06 (3H, d, J = 6.7 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 139.8, 138.9, 136.8, 128.6, 128.4, 128.3, 128.3, 127.9, 127.7, 117.1, 109.4, 87.3, 85.4, 83.3, 79.0, 78.3, 74.3, 72.7, 72.6, 71.6, 71.1, 69.2, 43.1, 42.1, 40.6, 39.0, 20.0, 16.1, 13.8; HRMS (FAB) calcd for $C_{34}H_{44}O_7Na$ [(M + Na)$^+$] 587.2985, found 587.3011.

TBDMS Ether 57. A solution of a 4:1 mixture of tetrahydropyran **55** and tetrahydrofuran alcohol **56** (379.7 mg, 0.6724 mmol) and 2,6-lutidine (190 μL, 1.63 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and treated with TBDMSOTf (190 μL, 0.827 mmol). After 30 min at 0 °C, the reaction was quenched with MeOH. The mixture was diluted with EtOAc (80 mL) and Et_2O (20 mL), washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10% EtOAc−hexane) gave a 4:1 mixture of TBDMS ether **57** and **58** (397.5 mg, 87%): $[\alpha]^{28}_D$ = −35.2° (*c* 0.81, $CHCl_3$); IR (film) 2929, 2858, 1454, 1254, 1078, 1028, 937, 837, 777, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.23 (10H, m), 5.85 (1H, ddd, J = 17.5, 11.0, 6.0 Hz), 5.31 (1H, ddd, J = 17.5, 2.0, 1.0 Hz), 5.17 (1H, ddd, J = 11.0, 2.0, 1.5 Hz), 4.69 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 12.5 Hz), 4.46 (1H, d, J = 11.5 Hz), 4.44 (1H, d, J = 11.5 Hz), 4.23 (1H, m), 3.94 (1H, dd, J = 9.5, 1.5 Hz), 3.84 (1H, m), 3.81 (1H, dd, J = 9.5, 5.0 Hz), 3.61 (1H, dd, J = 9.0, 0.5 Hz), 3.40 (3H, m), 3.30 (1H, m, 42-H), 2.94 (1H, dd, J = 9.5, 4.5 Hz), 2.25 (1H, m), 2.20 (1H, m), 2.10 (2H, m), 1.56 (1H, m), 1.51 (1H, m), 1.41 (1H, ddd, J = 11.0, 11.0, 11.0 Hz), 1.10 (3H, d, J = 7.5 Hz), 1.04 (3H, d, J = 6.0 Hz), 0.99 (3H, d, J = 6.5 Hz), 0.85 (9H, s), 0.07 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.4, 138.2, 136.6, 128.4, 128.1, 127.59, 127.55, 127.46, 127.2, 116.8, 108.9, 86.7, 84.7, 82.5, 78.5, 77.9, 73.9, 72.0, 71.9, 71.4, 71.0, 70.3, 42.5, 41.6, 41.4, 40.0, 38.5, 25.8, 20.0, 17.9, 15.9, 13.5, −4.2, −4.5; HRMS (FAB) calcd for $C_{40}H_{58}O_7SiNa$ [(M + Na)$^+$] 701.3850, found 701.3851.

Alcohol 2. A solution of a 4:1 mixture of TBDMS ether **57** and **58** (385.4 mg, 0.5676 mmol) in THF (10 mL) was cooled to 0 °C and treated with 9-BBN−H (0.5 M solution in THF, 3.5 mL, 1.75 mmol), and the resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C, and the reaction was quenched with EtOH (0.3 mL). To this mixture were added saturated aqueous $NaHCO_3$ (2.5 mL) and 30% H_2O_2 (1 mL) at 0 °C. The resulting solution was stirred at room temperature for 1 h, diluted with EtOAc (100 mL), washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10−20% EtOAc−hexane) gave pure alcohol **2** (309.9 mg, 78%) and tetrahydrofuran alcohol (27.9 mg, 7%) along with recovered **58** (38.9 mg, 10%). Data for **2**: $[\alpha]^{27}_D$ = −36.8° (*c* 0.49, $CHCl_3$); IR (film) 3444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (10H, m), 4.64 (1H, d, J = 12.2 Hz), 4.59 (1H, d, J = 12.2 Hz), 4.46 (1H, d, J = 12.2 Hz), 4.43 (1H, d, J = 12.2 Hz), 4.23 (1H, m), 3.94 (1H, dd, J = 9.7, 1.8 Hz), 3.84−3.78 (4H, m), 3.57 (1H, d, J = 9.4 Hz), 3.38 (1H, dd, J = 9.6, 9.4 Hz), 3.37 (1H, d, J = 3.6 Hz), 3.32 (1H, m), 3.17 (1H, td, J = 9.2, 2.5 Hz), 2.92 (1H, dd, J = 9.4, 5.0 Hz), 2.19 (1H, dt, J = 12.1, 4.7 Hz), 2.10 (3H, m), 2.00 (1H, m), 1.59 (1H, m), 1.66−1.49 (2H, m), 1.35 (1H, ddd, J = 12.1, 11.3, 11.3 Hz), 1.10 (3H, d, J = 7.6 Hz), 1.03 (3H, d, J = 6.1 Hz), 0.99 (3H, d, J = 6.3 Hz), 0.85 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.2, 138.2, 128.4, 128.1, 127.6, 127.54, 127.46, 127.3, 108.9, 87.2, 84.6, 83.1, 78.5, 77.6, 73.4, 72.3, 72.0, 71.5, 71.0, 69.8, 62.0, 42.5, 41.5, 41.0, 40.6, 38.4, 33.6, 25.7, 19.9, 17.9, 15.9, 13.5, −4.0, −4.7; HRMS (FAB) calcd for $C_{40}H_{60}O_8SiNa$ [(M + Na)$^+$] 719.3955, found 719.3971.

Diol 59. A solution of benzyl ether **45** (11.3 mg, 0.0158 mmol) in THF (1 mL) was treated with Bu_4NF (1.0 M solution in THF, 0.025 mL, 0.025 mmol), and the resulting mixture was stirred at room temperature for 2 h. Evaporation of the solvent and purification by flash chromatography on silica gel (30% EtOAc−hexane) afforded alcohol (8.6 mg, 98%).

To a suspension of potassium hydride (35% dispersion in mineral oil, 5.8 mg, 0.051 mmol) in THF (0.5 mL) was added a solution of the above alcohol (8.6 mg, 0.015 mmol) in THF (0.5 mL) at 0 °C. The mixture was stirred at room temperature for 0.5 h, recooled to 0 °C, and treated with iodomethane (2 mL, 0.032 mmol). The resulting mixture was stirred at 0 °C for 0.5 h and at room temperature for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C, and the solution was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (20% EtOAc−hexane) afforded methyl ether (8.3 mg, 94%).

A solution of the above methyl ether (8.3 mg, 0.015 mmol) in EtOH (1 mL) was treated with 20% $Pd(OH)_2$/C (6.5 mg) and stirred at room temperature under a hydrogen atmosphere for 2 h. The catalyst was filtered, and the solvent was evaporated. Flash chromatography on silica gel (5% MeOH−$CHCl_3$) afforded diol **59** (3.8 mg, 67%): $[\alpha]^{27}_D$ = −42.0° (*c* 0.14, $CHCl_3$); IR (film) 3332 cm^{-1}; ^{1}H NMR (pyridine-d_5, 500 MHz) δ 4.84 (1H, m), 4.79 (1H, d, J = 6.3 Hz), 4.77 (1H, d, J = 6.3 Hz), 4.54 (1H, ddd, J = 9.1, 6.9, 2.1 Hz), 4.34 (1H, br d, J = 5.5 Hz), 4.18 (1H, dd, J = 9.1, 4.9 Hz), 4.13 (1H, dd, J = 9.1, 1.7 Hz), 4.08 (1H, dd, J = 9.8, 1.3 Hz), 3.91 (1H, dd, J = 10.4, 2.1 Hz), 3.81 (1H, dd, J = 10.4, 6.9 Hz), 3.78 (1H, dd, J = 10.8, 9.8 Hz), 3.37 (3H, s), 3.31 (3H, s), 3.22 (1H, dd, J = 9.1, 1.6 Hz), 2.69 (1H, m), 2.38 (1H, dd, J = 13.5, 7.0 Hz), 2.28 (1H, dd, J = 13.5, 3.4 Hz), 1.97 (1H, qt, J = 6.3, 10.8 Hz), 1.61 (1H, qd, J = 6.7, 10.8 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.18 (3H, d, J = 6.7 Hz), 1.15 (3H, d, J = 7.7 Hz); HRMS (FAB) calcd for $C_{19}H_{34}O_8Na$ [(M + Na)$^+$] 413.2151, found 413.2174.

Methyl Ether 60. A solution of a 4:1 mixture of tetrahydropyran **55** and tetrahydrofuran **56** (22.8 mg, 0.040 mmol) in DMF (1 mL) was cooled to 0 °C and treated with sodium hydride (60% dispersion in mineral oil, 7.0 mg, 0.18 mmol), and the resulting mixture was stirred at room temperature for 30 min. The mixture was recooled to 0 °C and treated with iodomethane (15 μL, 0.24 mmol), and the resulting solution was stirred at 0 °C for 30 min and at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) at 0 °C and diluted with EtOAc (30 mL). The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel (10% EtOAc−hexane) afforded a 4:1 mixture of methyl ethers as a colorless oil (21.3 mg, 91%), which was separated by HPLC (YMC A024 SIL column, 10 × 300 mm, eluent 10% EtOAc−hexane; UV 254 nm; flow rate 3 mL/min; t_R(major) 12.6 min; t_R(minor) 15.6 min) to give methyl ether **60** as a pure form: $[\alpha]^{25}_D$ = −41.8° (*c* 0.762, $CHCl_3$); IR (film) 2926, 2872, 1456, 937, 735, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (10H, m), 5.93 (1H, dt, J = 17.3, 1.5 Hz), 5.37 (1H, br d, J = 9.3 Hz), 5.21 (1H, ddd, J = 16.8, 10.7, 5.9 Hz), 4.67 (1H, d, J = 12.2 Hz), 4.60 (1H, d, J = 12.2 Hz), 4.46 (1H, d, J = 12.1 Hz), 4.44 (1H, d, J = 12.1 Hz), 4.23 (1H, m), 3.94 (1H, dd, J = 9.7, 1.7 Hz), 3.87 (1H, ddd, J = 11.2, 9.5, 4.9 Hz), 3.81 (1H, dd, J = 9.7, 5.0 Hz), 3.63 (1H, d, J = 9.7 Hz), 3.47 (1H, dd, J = 9.0, 5.9 Hz), 3.40 (1H, d, J = 3.4 Hz), 3.37 (1H, t, J = 9.7 Hz), 3.32 (3H, s), 2.97 (1H, dd, J = 9.4, 4.3 Hz), 2.93 (1H, ddd, J = 11.3, 9.1, 4.4 Hz), 2.47 (1H, dt, J = 12.1, 4.7 Hz), 2.27 (1H, m), 2.10 (1H, dd, J = 13.7, 6.8 Hz), 2.07 (1H, dd, J = 13.7, 3.9 Hz), 1.56 (1H, m), 1.53 (1H, m), 1.28 (1H, q, J = 11.5 Hz), 1.11 (3H, d, J = 7.6 Hz), 1.04 (3H, d, J = 6.1 Hz), 0.98 (3H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.3, 138.1, 136.2, 128.3, 128.0, 127.5, 127.5, 127.3, 127.1, 116.9, 108.9, 86.7, 84.6, 80.6, 78.4, 78.4, 78.1, 74.0, 71.9, 71.8, 71.3, 70.9, 56.7, 42.4, 41.5, 39.8, 38.4, 36.7, 19.8, 15.7, 13.4; HRMS (FAB) calcd for $C_{35}H_{46}O_7Na$ [(M + Na)$^+$] 601.3141, found 601.3145.

Tetracyclic Diol 61. A solution of the above methyl ether **60** (3.5 mg, 6.1 μmol) in EtOH (0.5 mL) was treated with a catalytic amount of 20% $Pd(OH)_2$/C, and the resulting mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was filtered, and the solvent was evaporated. Flash chromatography on silica gel (40% EtOAc−hexane) gave diol **61** as a colorless oil (2.365 mg, 98%): $[\alpha]^{25}_D$ = −83.2° (*c* 0.93, $CHCl_3$); IR (film) 3437 cm^{-1}; ^{1}H NMR (C_5D_5N, 500 MHz) δ 4.84 (1H, m), 4.34 (1H, ddd, J = 11.1, 9.3, 5.1 Hz), 4.15 (3H, m), 4.01 (1H, d, J = 9.4 Hz), 3.90 (1H, dd, J = 9.7, 9.4 Hz), 3.28 (3H, s), 3.11 (1H, dd, J = 9.3, 5.0 Hz), 3.08 (1H, ddd, J = 9.0, 8.7, 2.5 Hz), 2.97 (1H, ddd, J = 11.1, 9.0, 4.3 Hz), 2.66 (1H, m), 2.53 (1H, m), 2.37 (1H, dd, J = 13.5, 6.9 Hz), 2.30 (1H, dd, J = 13.5, 3.6 Hz), 1.96 (3H, m), 1.63 (1H, dq, J = 11.3, 6.7 Hz), 1.46 (1H, ddd, J = 11.4, 11.1, 11.1 Hz),

1.24 (3H, d, J = 7.9 Hz), 1.23 (3H, d, J = 7.3 Hz), 1.19 (3H, d, J = 6.7 Hz), 1.03 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.3, 86.3, 81.8, 78.3,. 78.1, 77.1, 75.7, 74.5, 74.1, 71.8, 56.5, 45.8, 42.2, 41.9, 38.4, 36.6, 24.8, 19.6, 15.8, 13.5, 10.0; HRMS (FAB) calcd for $C_{21}H_{36}O_7Na$ [(M + Na)$^+$] 423.2359, found 423.2377.

α,β-Unsaturated Ester 62. A solution of methyl ether **60** (13.0 mg, 0.022 mmol) and *N*-methylmorpholine *N*-oxide (50% in H_2O, 26.7 mg, 0.114 mmol) in acetone−H_2O (4:1, 1 mL) was treated with a catalytic amount of OsO_4, and the resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (30 mL), washed with saturated aqueous Na_2SO_3, 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to give crude diol, which was used in the next reaction without purification.

A solution of the above crude diol in THF−H_2O (2:1, 1 mL) was treated with $NaIO_4$ (23 mg, 0.070 mmol) and stirred at room temperature for 30 min. The mixture was diluted with EtOAc (30 mL), washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated to give crude aldehyde, which was used in the next reaction without purification.

A solution of the above crude aldehyde in benzene (1 mL) was treated with $Ph_3P{=}CHCOOBn$ (28.0 mg, 0.068 mmol), and the resulting solution was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was directly subjected to flash chromatography on silica gel (30% EtOAc−hexane) to give α,β-unsaturated ester **62** as a colorless oil (16.1 mg, quantitative, for the three steps): $[\alpha]^{25}_D = -42.7°$ (c 0.568, $CHCl_3$); IR (film) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (10H, m), 7.14 (1H, dd, J = 15.8, 4.0 Hz), 6.18 (1H, dd, J = 15.8, 1.7 Hz), 5.21 (1H, d, J = 12.4 Hz), 5.17 (1H, d, J = 12.4 Hz), 4.65 (1H, d, J = 12.2 Hz), 4.62 (1H, d, J = 12.2 Hz), 4.46 (1H, d, J = 12.1 Hz), 4.45 (1H, d, J = 12.2 Hz), 4.24 (1H, m), 3.95 (1H, br d, J = 9.7 Hz), 3.87 (1H, m), 3.82 (1H, dd, J = 9.6, 5.0 Hz), 3.66 (1H, ddd, J = 9.3, 4.0, 1.7 Hz), 3.62 (1H, br d, J = 9.4 Hz), 3.41 (1H, d, J = 3.3 Hz), 3.37 (1H, t, J = 9.6 Hz), 3.31 (3H, s), 2.98 (1H, dd, J = 9.4, 4.4 Hz), 2.92 (1H, m), 2.50 (1H, dt, J = 12.1, 4.7 Hz), 2.25 (1H, m), 2.10 (2H, m), 1.57 (1H, m), 1.52 (1H, m), 1.30 (1H, q, J = 11.5 Hz), 1.10 (3H, d, J = 7.6 Hz), 1.04 (3H, d, J = 6.1 Hz), 0.99 (3H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 145.8, 139.2, 138.0, 135.9, 128.4, 128.3, 128.1, 128.0, 128.0, 127.5, 127.4, 127.3, 127.1, 120.7, 108.8, 86.7, 84.5, 78.4, 78.2, 78.1, 78.0, 73.5, 72.1, 71.7, 71.3, 70.9, 66.0, 56.6, 42.4, 41.5, 39.9, 38.3, 36.8, 19.7, 15.7, 13.4; HRMS (FAB) calcd for $C_{43}H_{52}O_9Na$ [(M + Na)$^+$] 735.3509, found 735.3480.

Carboxylic Acid 3. A solution of α,β-unsaturated ester **62** (16.1 mg, 0.023 mmol) in EtOH (1 mL) was treated with a catalytic amount of 20% $Pd(OH)_2$/C, and the resulting mixture was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was filtered, and the solvent was evaporated. Flash chromatography on silica gel (20% MeOH−$CHCl_3$) gave carboxylic acid **3** as a white form (10.3 mg, 98%): $[\alpha]^{25}_D = -68.2°$ (c 1.09, $CHCl_3$); IR (film) 3456, 3350, 2927, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.49 (1H, m), 3.87 (1H, dd, J = 9.8, 4.3 Hz), 3.78 (1H, d, J = 9.8 Hz), 3.71 (1H, m), 3.68 (1H, m), 3.61 (1H, dd, J = 9.5, 1.5 Hz), 3.32 (3H, s), 3.26 (1H, t, J = 9.8 Hz), 2.99 (1H, td, J = 9.1, 2.7 Hz), 2.90 (1H, ddd, J = 11.1, 9.2, 4.3 Hz), 2.88 (1H, dd, J = 9.3, 4.9 Hz), 2.53−2.39 (3H, m), 2.18 (1H, dd, J = 14.3, 6.9 Hz), 2.15 (1H, m), 2.02 (1H, m), 1.96 (1H, br d, J = 14.3 Hz), 1.66 (1H, m), 1.59 (1H, m), 1.48 (1H, m), 1.22 (1H, q, J = 11.4 Hz), 1.11 (3H, d, J = 7.5 Hz), 1.03 (3H, d, J = 6.3 Hz), 0.98 (3H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.5, 109.2, 86.4, 79.4, 78.1, 78.0, 77.0, 75.1, 74.4, 71.9, 71.6, 56.4, 45.5, 42.0, 41.7, 38.2, 36.3, 30.4, 26.9, 19.6, 15.6, 13.3; MS (FAB) m/z 577 [(M + Cs)$^+$].

3−BSA Conjugate. A solution of carboxylic acid **3** (3.7 mg, 8.3 μmol) in 95% dioxane (2 mL) was treated with *N*-hydroxysuccinimide (26.0 mg, 226 μmol) and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (43 mg, 102 μmol), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was poured into H_2O, and the aqueous layer was extracted with EtOAc (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in pH 7.3 phosphate buffer (2.5 mL) and pyridine (2.5 mL), and the mixture was cooled to 4 °C. Bovine serum albumin (BSA; 25.0 mg, 0.362 μmol) was added to the solution, and the resulting mixture was stirred at 4 °C overnight. The reaction mixture was dialyzed four times against H_2O (1 L), and lyophilized for preservation to give the **3**−BSA conjugate (13.2 mg).

3−OVA Conjugate. Following the procedure for preparation of the **3**−BSA conjugate, carboxylic acid **3** (2.35 mg, 5.29 μmol) and OVA (17 mg, 0.378 μmol) were converted to the **3**−OVA conjugate (10.7 mg).

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Supporting Information Available: A synthetic scheme and experimental procedures for compound **14**, ^{1}H NMR spectra for compounds **3**, **12**, **25**, **28**, **32**, **34β**, **35β**, **39**, **41**−**43**, and **45**−**62**, and ^{13}C NMR spectra for compounds **3**, **12**, **25**, **28**, **35β**, **39**, **41**−**43**, **46**, **49**−**58**, **61**, and **62**. This material is available free of charge via the Internet at http://pubs.acs.org.

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