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A Convergent Synthesis of the *trans*-Fused Hexahydrooxonine Ring System and Reproduction of Conformational Behavior Shown by Ring F of Ciguatoxin

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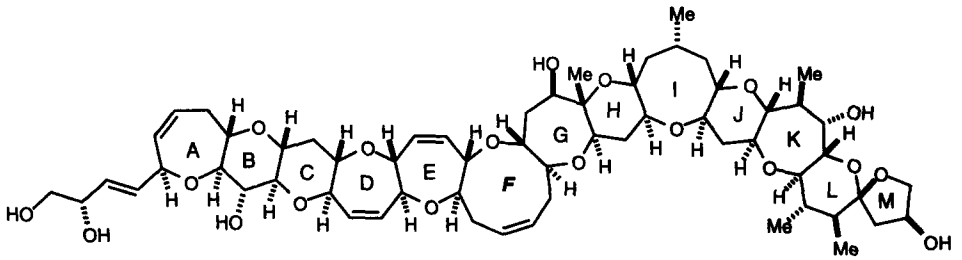
Abstract: A new strategy for the construction of the fused hexahydrooxonine ring system has been developed. The present synthesis involves an intramolecular reaction of γ-alkoxyallylsilane with acetal to form an *O*-linked oxacycle and a SmI_2-mediated intramolecular Reformatsky reaction for constructing an oxonane ring as the key steps. Thermodynamic behavior of the *trans*-fused hexahydrooxonine ring was clarified for the first time and the conformational alternation was reproduced in the 6-9-6 tricyclic model compound **1** as was observed for that in the ciguatoxin molecule (ring F).

Keywords: Conformation; Medium-ring heterocycles; Polyethers; Reformatsky reactions

INTRODUCTION

Ciguatoxin (CTX1B) and its congeners, naturally occurring polycyclic ethers originating in marine unicellular algae, are the principle toxins associated with ciguatera fish poisoning.[1,2] These toxins reportedly bind to the same site of voltage-sensitive sodium channels (VSSC) as brevetoxins, another class of structurally related marine toxins.[3] The ciguatoxin molecule consists of 12 *trans*-fused cyclic ethers ranging from six- to nine-members, where another five-membered oxacycle is spirally attached at one end. An important structural characteristic is the fact that the hexahydrooxonine ring (ring F) in ciguatoxin and its congeners undergoes a slow conformational change between at least two conformers in solution, which is suspected to play an important role in the high-affinity binding to VSSC and/or its activation.[2a]



Ciguatoxin (CTX1B)

Figure 1. Absolute Structure of Ciguatoxin (CTX1B)

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^{1}H NMR signals of the olefinic protons and their neighboring methylenes on the hexahydrooxonine ring F of ciguatoxin were severely broadened at room temperature.[1b,c] These signals became sharp when measured at -25 ℃ in CD_3CN. Since these sharpened peaks are thought to be derived from a single conformer, ring F is assumed to mostly exist as a dominant conformer at low temperature, and NOE experiments at low temperature indicated that the UP conformer was predominant in solution.[4] Molecular mechanics calculations suggested the existence of only two conformers, the UP and DOWN ones, which differ only in location of the olefinic bond with regard to the ring plane (Figure 2). However, an insufficient amount of material in addition to heavy crowding of the NMR signals prevented us from further investigating this unusual conformational behavior.

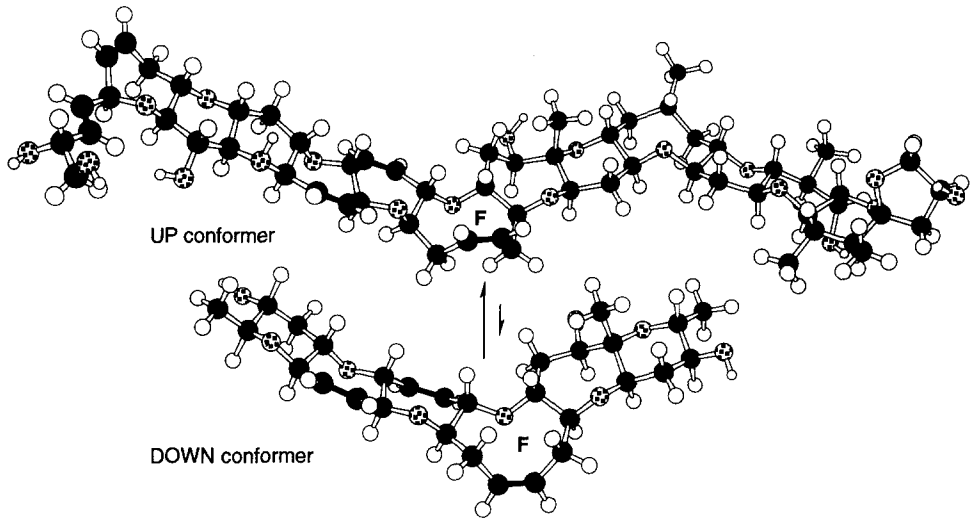


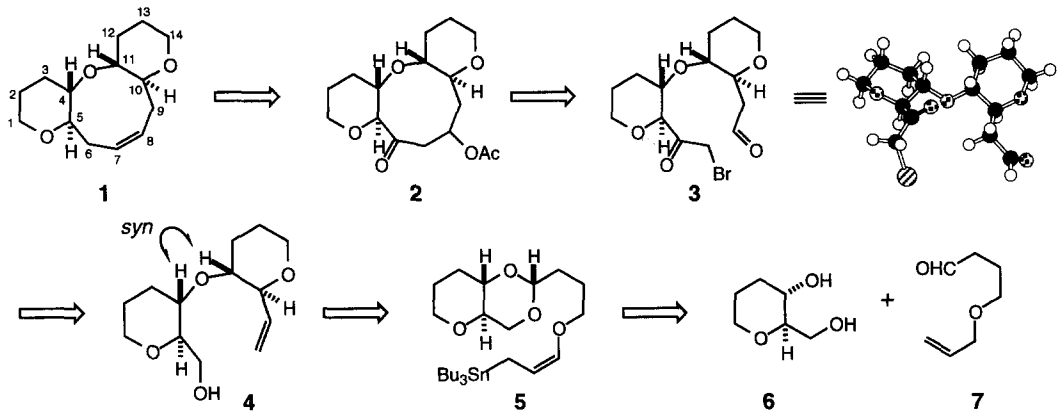
Figure 2. Possible Conformers of Ciguatoxin

From a synthetic point of view, construction of the *trans*-fused hexahydrooxonine ring system would be one of the most formidable and challenging problems for the total synthesis of ciguatoxins due to severe difficulties caused by unfavorable entropy factors as well as transannular interactions. In spite of the recent advances in the synthesis of cyclic ethers,[5] there is still no general and convergent method for the assembly of the fused nine-membered ether ring system at the outset of our studies.[6] As part of our studies directed toward the total synthesis of ciguatoxins, we initiated the development of a practical method for the synthesis of the fused nine-membered cyclic ether.[7-9] The synthesis of compounds containing ring F motif would also be useful for the thermodynamic analysis of its characteristic conformational behavior described earlier. Thus, we designed the 6-9-6 tricyclic system **1** as the simplest model compound of a fused hexahydrooxonine. Herein, we describe in detail the first achieved synthesis of **1** and also the conformational alteration of the constructed hexahydrooxonine ring based on dynamic NMR studies.[10]

RESULTS AND DISCUSSION

Synthetic Strategy. Our strategy for the construction of the fused hexahydrooxonine ring system **1** is outlined in Scheme 1. It was envisioned that the oxonane ring in **2** could be formed by the SmI_2-mediated intramolecular Reformatsky-type reaction of the *O*-linked bistetrahydropyranyl ether **3**. The SmI_2-mediated intramolecular Reformatsky reaction was first reported by Inanaga and co-workers.[11] Using this procedure, medium- as well as large-sized lactones could be prepared in high yields under mild conditions. However, there have been few reports concerning the synthesis of natural products based on this reaction.[12] Molecular mechanics calculations of **3** using Macromodel (version 5.5)[13] indicated that the reaction centers were in close proximity in the global minimum conformer. It was anticipated that the presence of the tetrahydropyran rings in **3** would make its conformation appropriate for the cyclization, thus making it entropically favorable to form the C-C bond. The *O*-linked bicyclic ether **3**, in turn, would be readily obtained from the known compound **4**, which was reported by Martín and co-workers in their synthesis of the 6-8-6 tricyclic ring system.[7r] They applied the intramolecular reaction of γ-alkoxyallylstannanes with acetals, which was originally developed by Yamamoto *et al.*[14] to the synthesis of **4**. Their synthesis was based on (a) acetalization between diol **6** and aldehyde **7**, and (b) the intramolecular cyclization reaction of **5**. The high convergency of this method allowed us to adopt their approach for the present synthesis. However, as discussed later, our results were not consistent with the reported stereostructure of **4**.

Scheme 1

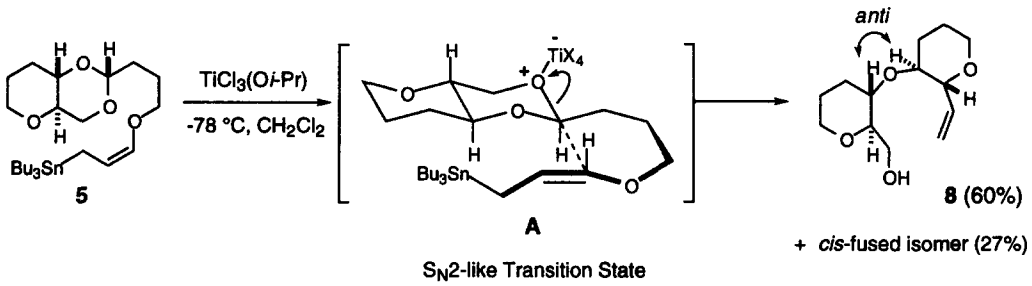


Intramolecular Reaction of γ-Alkoxyallylstannane with Acetal. According to Martín's procedure,[9e] γ-alkoxyallylstannane **5** was prepared from **6** and **7**. Contrary to their report, treatment of **5** with $TiCl_3(Oi\text{-}Pr)$ at -78 °C led to the undesired *O*-linked oxacycle **8** with eventual *trans-anti-trans* stereochemistry as the major product in 60% yield along with a 27% yield of the *cis*-fused isomer (Scheme 2). Martín *et al.* assigned the major product to be the desired **4** in their synthesis. However, as described later, the X-ray crystallographic analysis of the crystalline *p*-bromobenzoate derivative **22**, prepared from **8**, firmly established the *trans-anti-*

trans stereochemistry. The major product **8**, which had been believed to be the desired **4** until the X-ray crystallographic analysis of **22**, was utilized in the following experimentation of the crucial oxonane ring formation.

The stereochemical outcome of this cyclization can be rationalized as follows. The reactive allylstannane in **5** would react in an S_N2-like manner via the possible transition state **A**; breaking of a C-O bond of the acetal would take place simultaneously with the C-C bond formation between the γ-allylic and acetal carbons,[15] stereoselectively leading to the undesired **8**.

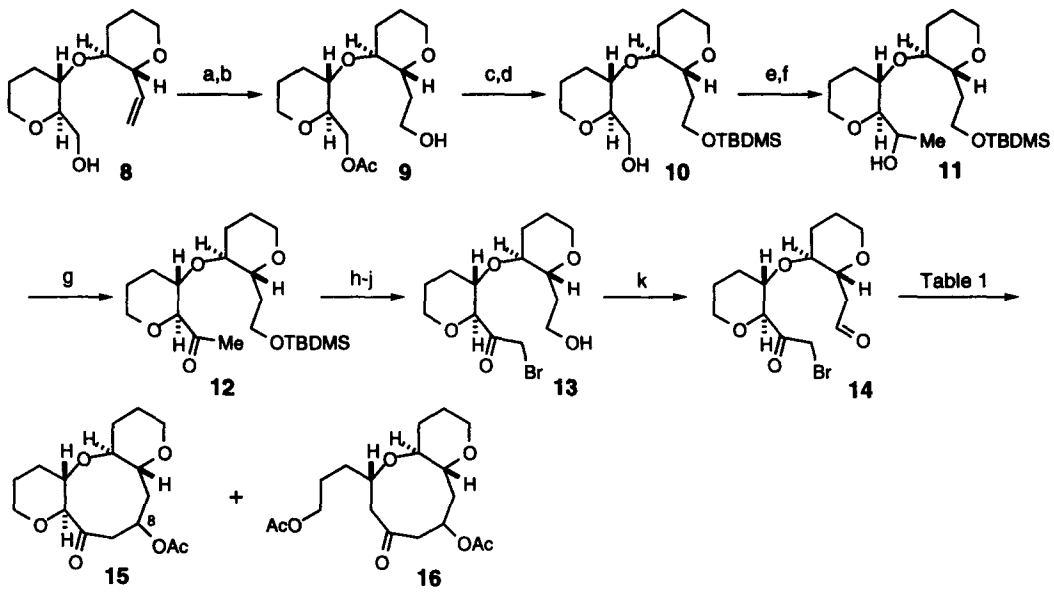
Scheme 2



Construction of Nine-membered Ring via SmI_2-mediated Reformatsky Reaction. The elaboration of **8** to the α-bromoketo aldehyde **14**, a precursor of the Reformatsky reaction, is summarized in Scheme 3. Protection of the primary hydroxyl group in **8** as the acetate followed by hydroboration gave alcohol **9**. The newly generated primary alcohol was protected as the TBDMS ether and the acetyl group was removed by DIBALH reduction to give alcohol **10** in 63% overall yield from **8**. Oxidation of **10** with SO_3·pyridine and DMSO gave an aldehyde, which was reacted with methylmagnesium bromide to afford secondary alcohol **11** as a 4:1 mixture of diastereomers in 81% yield for the two steps. Oxidation of **11** under Swern conditions then furnished methyl ketone **12** in 84% yield. Treatment of **12** with trimethylsilyl trifluoromethanesulfonate and *i*-Pr_2NEt, followed by bromination with *N*-bromosuccinimide (NBS), and removal of the TBDMS protecting group provided alcohol **13** in 92% overall yield from **12**. Finally, SO_3·pyridine oxidation of **13** led to the requisite α-bromoketo aldehyde **14**, which was ready for the crucial SmI_2-mediated Reformatsky reaction.

When **14** was added to a solution of SmI_2 in THF over 3 h at 0 °C and the resulting mixture was treated *in situ* with excess Ac_2O and DMAP, the desired cyclization product **15**[16] was obtained in only 3% yield (Table 1, entry 1). Reductive cleavage of the C-O bond at the α-position of the ketone occurred to give the undesired bicyclic product **16** as the major product. The formation of **16** was avoided by carrying out the reaction at a lower temperature (-78 °C), but the yield of **15** was still low (22%, entry 2). The yield of **15** was further improved by increasing the rate of addition of **14**; thus, the best result was obtained by adding **14** to a solution of SmI_2 over 10 min at -78 °C, giving **15** in 49% yield as a single diastereomer (entry 3).

Scheme 3



Reagents and conditions: (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C; (b) 9-BBN, THF, r.t., then H_2O_2, $NaHCO_3$, r.t.; (c) TBDMSCl, imidazole, DMF, r.t.; (d) DIBALH, CH_2Cl_2, -78 °C, 63% (4 steps); (e) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (f) MeMgBr, THF, -78 °C, 81% (2 steps); (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t., 84%; (h) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, -10 °C; (i) NBS, THF, 0 °C; (j) CSA, CH_2Cl_2-MeOH, 0 °C, 92% (3 steps); (k) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C, 81%.

Table 1. SmI_2-mediated intramolecular Reformatsky reactions

entry	SmI_2	temperature	concentration	addition time	yield
1	6 eq.	0 °C	2 mM	3 h	3%
2	5 eq.	-78 °C	10 mM	2 h	22%
3	5 eq.	-78 °C	10 mM	10 min	49%

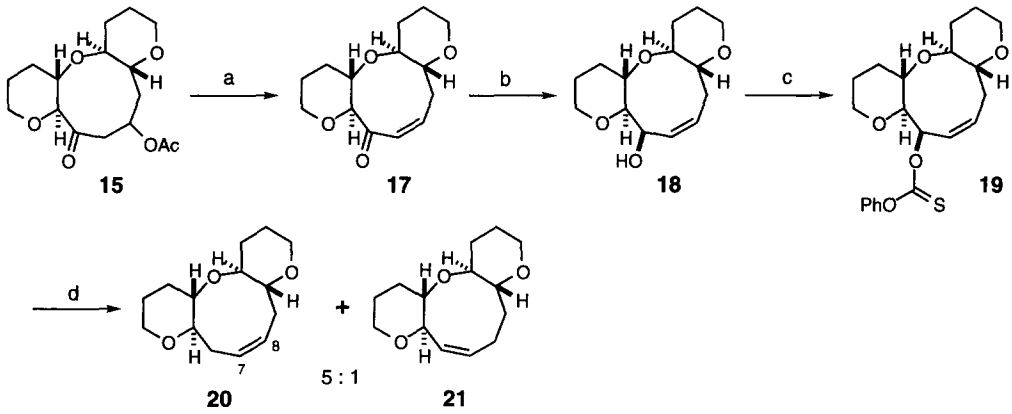
Introduction of C-C Double Bond. With the oxonane ring **15** in hand, attention was next focused on the introduction of the *cis*-double bond to the oxonane ring. To this end, we envisioned that β-elimination of the acetoxyl group followed by deoxygenation would lead to the desired hexahydrooxonine with the favorable regiospecificity (Scheme 4). Treatment of **15** with DBU in THF at 60 °C afforded α,β-unsaturated ketone **17** albeit in low yield (27%). When **15** was treated with BF_3·Et_2O in CH_2Cl_2 at room temperature, a more promising result was obtained. Finally, the optimal conditions were realized by treatment of **15** with BF_3·OEt_2 in acetonitrile at room temperature, and thus **17** was obtained in 84% yield.

Deoxygenation of the ketone in **17** was carried out in a straightforward manner. DIBALH reduction of **17** produced alcohol **18** as a single stereoisomer in 97% yield, which upon treatment with chlorophenyl

thiocarbonate and DMAP furnished phenyl thiocarbonate **19** (93%). Subsequent radical reduction using *n*-Bu_3SnH and AIBN furnished an inseparable 5:1 mixture of the desired hexahydrooxonine **20** ($J_{7,8}$ = 10.7 Hz) and its regioisomer **21** in 86% combined yield.

For the structural confirmation of **20**, *p*-bromobenzoate **22** was prepared from alcohol **18** (*p*-BrBzCl, DMAP, Et_3N, CH_2Cl_2, 93%). The recrystallization of **22** from diethyl ether-hexane gave a single crystal, which was subjected to an X-ray crystallographic analysis. As shown in Figure 3, the ORTEP drawing of **22** revealed the *anti* relationship between the C4 and C11 protons, indicating that bicyclic ether **8** had the incorrect stereochemistry. Thus, an alternative method for the synthesis of the desired bicyclic ether **4** is required.

Scheme 4



Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, CH_3CN, r.t., 84%; (b) DIBALH, CH_2Cl_2, -78 °C, 79%; (c) PhOC(S)Cl, DMAP, CH_3CN, r.t., 93%; (d) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 86%.

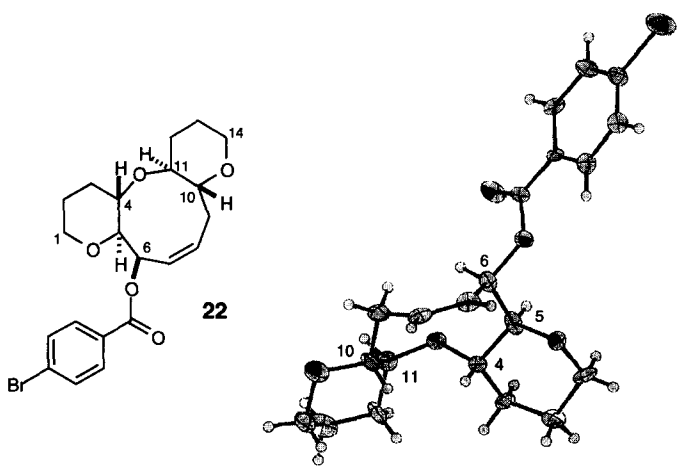
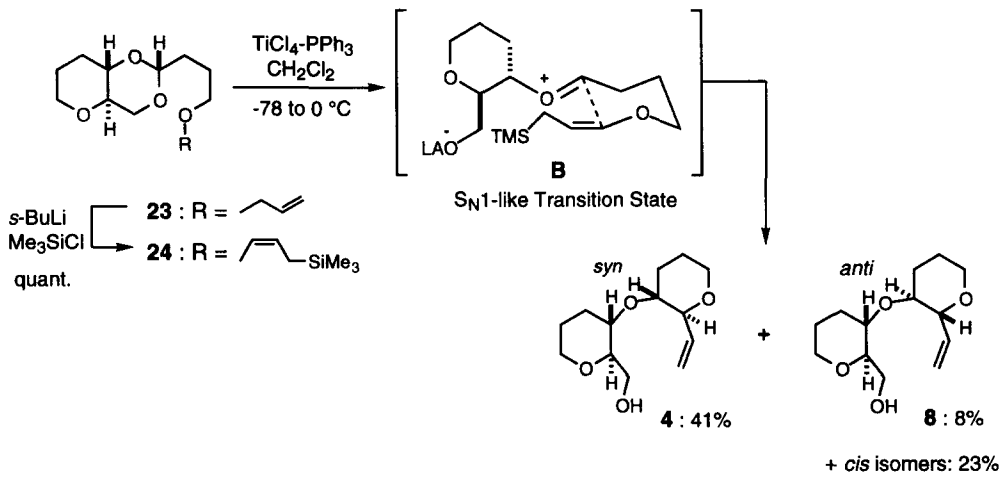


Figure 3. ORTEP drawing of *p*-bromobenzoate **22**

Intramolecular Reaction of γ-Alkoxyallylsilane with Acetal. In the case of cyclization of γ-alkoxyallylstannane **5**, the reactive allylstannane attacked the acetal carbon in an S_N2 manner to yield the *trans-anti-trans* product **8**. On the other hand, allyltrialkylsilanes are known to have significantly lower nucleophilicity than the corresponding stannanes. The addition of an allyltrimethylsilane to various electrophiles has been shown to be 10^3-10^4 times slower than that of the allyltributylstannane.[17] Therefore, it was assumed that an alternative use of less reactive γ-alkoxyallylsilane would enable the reaction to take place via an S_N1-like pathway to give the desired product.[18] In this pathway, the memory of the chirality of the acetal carbon would disappear to give an oxonium cation, which would react with the allylsilane to minimize the unfavorable steric interactions in the transition state.

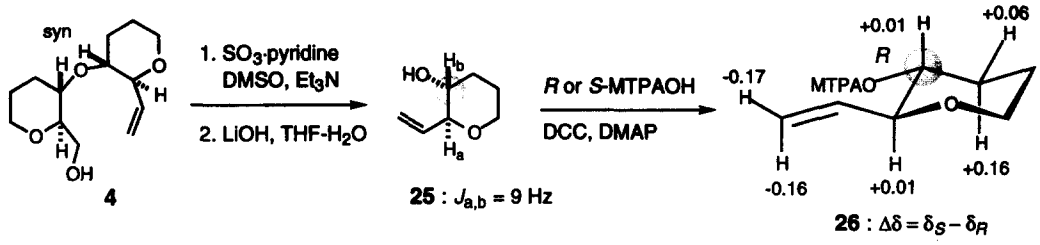
Formation of the alkoxy-substituted allylic anion from the known **23**[9e] with *sec*-BuLi, followed by trapping with Me_3SiCl, afforded γ-alkoxyallylsilane **24** in a quantitative yield (Scheme 5). As expected, the treatment of **24** with $TiCl_4$-PPh_3 (CH_2Cl_2, -78 to 0 °C)[19] led to the diastereoselective reversal and the desired **4** was obtained as the major product in 41% yield along with **8** (8%) and *cis*-fused isomers (23%). The predominant formation of **4** may be explained by the less congested approach of the γ-alkoxyallylsilane to the oxocarbenium ion through an S_N1-like transition state structure **B**.

Scheme 5



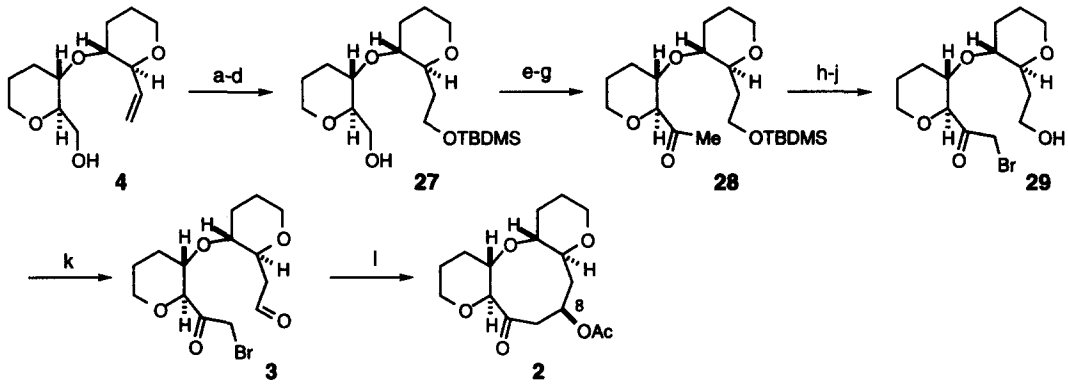
Configurations of the stereogenic centers within the newly generated tetrahydropyran ring in **4** was unambiguously determined by its conversion to alcohol **25** and application of modified Mosher's method[20] (Scheme 6). Oxidation of **4** with SO_3·pyridine and DMSO, followed by treatment with lithium hydroxide at 60 °C, resulted in β-elimination from the pre-existed tetrahydropyran ring, furnishing the alcohol **25**. The *trans* relationship between substituents on **25** was assigned by the proton-proton coupling constant ($J_{a,b}$ = 9 Hz). The alcohol **25** was then converted to the corresponding (*R*)- and (*S*)-MTPA esters **26**. By analyzing the COSY spectra of these MTPA esters, the chemical shifts of each proton (δ_S, δ_R) were obtained. The absolute configuration of the secondary hydroxyl group in **4** was determined to be *R* from $\Delta\delta$ (δ_S-δ_R) as illustrated in Scheme 6.

Scheme 6



Construction of Oxonane Ring. Having the desired bicyclic ether **4** in hand, the next task was to construct the oxonane ring by the SmI_2-mediated Reformatsky reaction developed as shown above. The conversion of **4** to α-bromoketo aldehyde **3** followed the same sequence of reactions as the preparation of **14** (Scheme 7). Acetylation of **4**, hydroboration with 9-BBN followed by oxidative workup, protection of the resulting hydroxyl as its TBDMS ether, and deacetylation in this sequence provided alcohol **27** in 76% overall yield. The alcohol **27** was converted by standard methods to methyl ketone **28**, which was then transformed into α-bromoketo alcohol **29** by trimethylsilyl enol ether formation, subsequent treatment with NBS, and removal of the TBDMS group. Finally, oxidation of **29** with SO_3·pyridine and DMSO provided the aldehyde **3**.

Scheme 7



Reagents and conditions: (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C; (b) 9-BBN, THF, r.t., then H_2O_2, $NaHCO_3$, r.t.; (c) TBDMSCl, imidazole, DMF, r.t.; (d) DIBALH, CH_2Cl_2, -78 °C, 76% (4 steps); (e) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (f) MeMgBr, THF, -78 °C, 87% (2 steps); (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t., 69%; (h) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, -10 °C; (i) NBS, THF, 0 °C; (j) CSA, CH_2Cl_2-MeOH, 0 °C, 92% (3 steps); (k) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (l) SmI_2, THF (10 mM), -78 °C, 0.5 h, then Ac_2O, DMAP, 62% from **29**.

Treatment of **3** with five equivalents of SmI_2 in THF (10 mM) at -78 °C effected oxonane formation to yield a tricyclic compound, which was directly acetylated with Ac_2O and DMAP in one pot giving β-acetoxy ketone **2**

as a single diastereomer in 62 % yield from **29**. The *syn*-relationship between angular protons, 4-H and 11-H, in **2** was confirmed by NOE experiments (Figure 4). The configuration of the newly generated secondary hydroxyl group at C8 was also assigned on the basis of the prominent NOEs due to 5-H/8-H and 8-H/10-H.

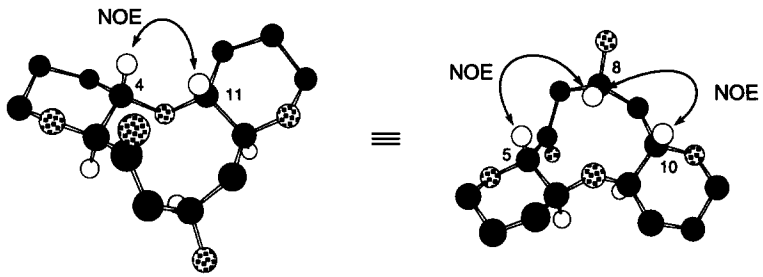
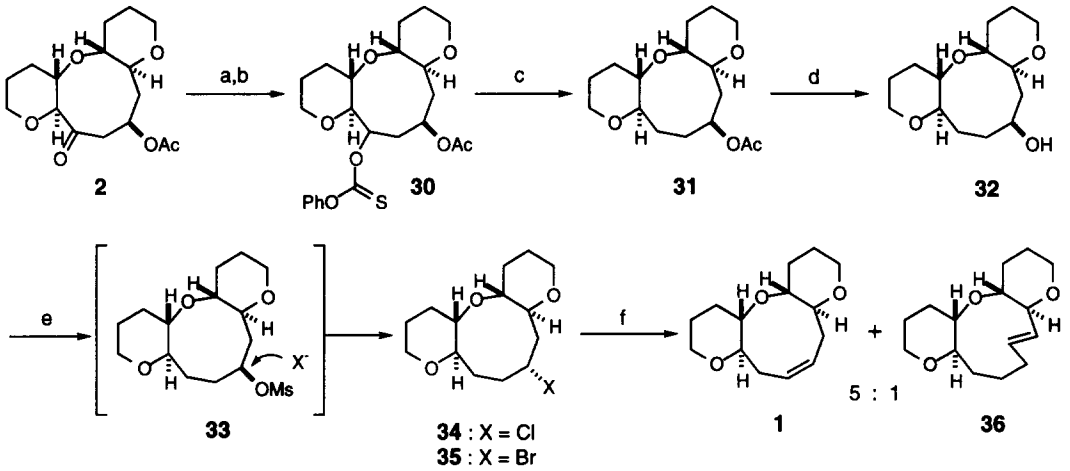


Figure 4. Energy-minimized structure (Macromodel, MM2* force field) and NOE data for compound **2**

Completion of Synthesis of 6-9-6 Tricyclic System 1. To complete the synthesis of the model compound **1**, we first attempted to introduce the *cis*-double bond according to the synthesis of **20** (vide supra). However, upon treatment of **2** under the conditions optimized for the synthesis of **17** ($BF_3 \cdot Et_2O$, acetonitrile), the corresponding α,β-unsaturated ketone was isolated in less than 10% yield. On the other hand, when **2** was treated with DBU, extensive decomposition of the starting material was observed and none of the desired product was obtained. Also, use of trifluoroacetyl or *p*-nitrobenzoyl instead of acetyl as a leaving group to accelerate the β-elimination of acyloxy group failed to improve the yield.

Thus, an alternative approach, which involved deoxygenation of the ketone moiety in **2** followed by an elimination reaction to introduce a double bond, was examined. Reduction of **2** with $NaBH_4$ followed by treatment of the resultant alcohol with PhOC(S)Cl and DMAP afforded phenyl thiocarbonate **30** as a mixture of diastereoisomers in 85% yield for the two steps (Scheme 8). Radical reduction of **30** with *n*-Bu_3SnH and AIBN smoothly proceeded to give acetate **31** in 78% yield, which was deprotected with DIBALH to afford alcohol **32**. We initially attempted to convert **32** into the corresponding mesylate **33** and introduce a double bond into the oxonane ring. However, mesylation of **32** using MsCl and Et_3N did not give **33**, but only chloride **34** was obtained through complete S_N2 inversion of the mesylate with a coexisting chloride ion. Upon treatment of **34** with KO*t*-Bu in DMSO,[21] the desired **1** was obtained in only 25% yield along with a significant amount of recovered starting material. Since these results indicated that the inversion of stereochemistry facilitates subsequent elimination, it was decided to change the leaving group to a bromide to improve the yield of the elimination reaction. Treatment of **32** with methanesulfonic anhydride in the presence of lithium bromide and *i*-Pr_2NEt provided bromide **35** as a single diastereomer, which must be used immediately in the next reaction because of the instability to chromatographic separation on silica gel. Exposure of **34** to KO*t*-Bu in DMSO led to a 5:1 mixture of the targeted hexahydrooxonine **1** and its regioisomer **35** (58% combined yield from **31**), which were easily separated by column chromatography on silica gel. Thus, the first synthesis of the fused hexahydrooxonine ring system **1** was achieved.

Scheme 8



Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C; (b) PhOC(S)Cl, DMAP, CH_3CN, r.t., 85% (2 steps); (c) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 78%; (d) DIBALH, CH_2Cl_2, -78 °C; (e) Ms_2O, LiBr, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to r.t.; (f) KO*t*-Bu, DMSO, r.t., 58% (3 steps).

Conformational Analysis of Fused Hexahydrooxonine Ring System. The ^1H and ^{13}C NMR signals due to the hexahydrooxonine ring of **1** were severely broadened at room temperature, which is consistent with the behavior of ring F in ciguatoxin. Dynamic NMR studies revealed that **1** exists as an approximate 1:1 equilibrium of two conformational states at the hexahydrooxonine ring in pyridine-d_5 solution.[22] The structure of these two conformers were unambiguously assigned to be the UP (**A**) and DOWN (**B**) ones by virtue of their proton-proton coupling constants at low temperature (-30 °C) (Figure 5). The olefin signals coalesced at 28 °C in pyridine-d_5. The free energy of activation ($\Delta G^{\ddagger}$) for this conformational change at 28 °C in pyridine-d_5 was estimated to be approximately 14 kcal/mol using the olefinic signal. Broadening of the NMR signals was also observed for **20**, but not for the synthetic intermediates that possess nine-membered cyclic ethers. Thus, conformational alternation between UP and DOWN conformers should be the characteristic property of the fused hexahydrooxonine ring system. Natural ciguatoxin, where the hexahydrooxonine ring F is flanked by two seven-membered ether rings, exhibits a preference for the UP conformation over the DOWN one, while in the model compound **1**, these two conformers are approximately equal in energy judging from their population. The relative energy between the UP and DOWN conformers may correlate with the torsion angles of the fused C-C bond which are determined by the adjacent ring sizes.

In conclusion, a convergent method for the synthesis of the fused hexahydrooxonine ring system has been developed. The synthetic strategy described herein provides a possible solution to the total synthesis of ciguatoxins and their designed analogues. Thermodynamic behavior of the fused hexahydrooxonine ring was clarified for the first time and we disclosed that conformational alternation of the 6-9-6 tricyclic model compound **1** closely mimicked that of ring F of the ciguatoxin molecule, except for the ratio of the two conformers.

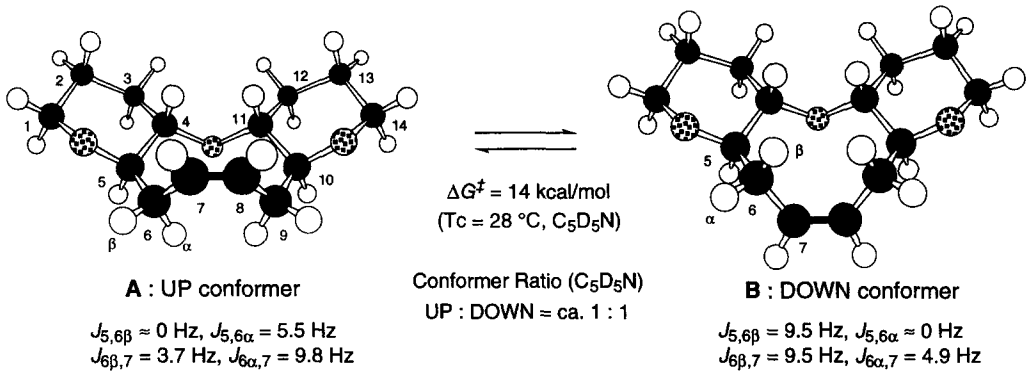


Figure 5. Conformational alteration of 6-9-6 tricyclic model compound **1**

EXPERIMENTAL

General Methods. Melting points were recorded on a Mel-temp capillary melting point apparatus (Laboratory Devices) and are uncorrected. NMR spectra were recorded on a Bruker AM-500 or JEOL A-500 spectrometer and the chemical shifts are reported in parts per million (ppm) down field from tetramethylsilane (TMS) with reference to solvent signals [^{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 (135.5), CD_3CN (1.30)]. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities of signals are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broadened (br). Carbon numbers of synthetic compounds in this paper were based on compound **1** (see Scheme 1). Infrared (IR) spectra were recorded on a Horiba FT-200 spectrometer. Low- and high-resolution mass spectra were recorded on a JEOL SX-102 mass spectrometer. Fast atom bombardment mass (FAB) spectrometry was performed on the same instrument with NBA as the matrix. Optical rotations were measured on a JASCO DIP-370 polarimeter. Elemental analyses were performed by the Analytical Laboratory at Department of Chemistry, The University of Tokyo.

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 E. Merck silica gel 60 (70-230 mesh) and, for flash column chromatography, E. Merck silica gel 60 (230-400 mesh) was used.

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

(2*R*,3*S*)-{3-[(2*R*,3*S*)-2-Vinyloxan-3-yloxy]oxan-2-yl}methanol (8). A solution of allylstannane **5**[7r] (216.0 mg, 0.407 mmol) in CH_2Cl_2 (5 mL) was cooled to -78 ℃ and treated dropwise with $TiCl_3$(O*i*-Pr) (1.33 M solution in toluene, 0.62 mL, 0.825 mmol) and the reaction mixture was then stirred at -78 ℃ for 15 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the mixture was allowed to warm to room temperature. Saturated aqueous KF (1 mL) was added to this mixture and the resulting solution was vigorously stirred for 2 h. The aqueous layer was extracted with EtOAc (30 mL) and the organic layer was washed with saturated aqueous KF (x 2) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (20-50% EtOAc-hexane) gave the bicyclic ether **8** (58.8 mg, 60%) along with the *cis*-fused isomers (26.3 mg,

27%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.95 (1H, ddd, J = 17.2, 10.7, 5.5 Hz 9-H), 5.31 (1H, ddd, J = 17.2, 1.5, 1.5 Hz, 8-H), 5.18 (1H, ddd, J = 10.7, 1.5, 1.4 Hz 8-H), 3.92 (1H, m, 1-H), 3.89 (1H, m, 14-H), 3.79 (1 H, m), 3.65 (1H, ddd, J = 11.0, 5.3, 5.3 Hz), 3.50 (1H, dd, J = 9.0, 5.6 Hz), 3.36 (1H, m), 3.34 (1H, m), 3.30 (1H, ddd, J = 10.6, 9.2, 4.5 Hz), 3.13 (1H, m), 3.12 (1H, ddd, J = 10.6, 9.0, 4.4 Hz), 2.21 (1H, m), 2.14 (1H, m), 2.03 (1H, m), 1.70-1.52 (3H, m), 1.33 (1H, m), 1.27 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.5, 116.4, 80.9, 80.4, 75.1, 71.8, 67.6, 67.4, 63.1, 29.7, 29.4, 25.21, 25.16; HRMS (FAB) calcd for $C_{13}H_{22}O_4Na$ [(M+Na)$^+$] 265.1416, found 265.1416.

(2*R*,3*S*)-(3-{(2*R*,3*S*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]oxan-3-yloxy}oxan-2-yl)methanol (10). A solution of the bicyclic ether **8** (313.9 mg, 1.297 mmol), DMAP (16.0 mg, 0.131 mmol) and Et_3N (0.75 mL, 5.38 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ℃ and treated with acetic anhydride (250 μL, 2.65 mmol). The reaction mixture was stirred for 30 min and diluted with EtOAc-Et_2O (6:1, 70 mL). The organic layer was washed with 1N aqueous HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give the crude acetate.

A solution of acetate in THF (7 mL) was cooled to 0 ℃ and treated with 9-BBN (0.5 M solution in THF, 7.5 mL, 3.7 mmol). After being stirred at room temperature for 2 h, the reaction mixture was cooled to 0 ℃ and the reaction was quenched with EtOH (0.5 mL). To the mixture was sequentially added saturated aqueous $NaHCO_3$ (5 mL) and 30 % H_2O_2 (2 mL) at 0 ℃. The resulting solution was stirred at room temperature for 30 min and diluted with EtOAc (80 mL). The organic layer was washed with H_2O, saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give the crude alcohol **9**.

A solution of the crude alcohol **9** and imidazole (265 mg, 3.89 mmol) in DMF (5 mL) was cooled to 0 ℃ and treated with TBDMSCl (294 mg, 1.95 mmol). The mixture was stirred at room temperature overnight and diluted with EtOAc (140 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (40% Et_2O-hexane) gave the TBDMS ether, which was used in the next reaction without further purification.

A solution of the above TBDMS ether in CH_2Cl_2 (18 mL) was cooled to -78 ℃, treated with DIBALH (3.2 mL, 1.01 M solution in toluene, 3.2 mmol) and the resulting mixture was stirred at -78 ℃ for 30 min. The reaction was quenched with saturated aqueous potassium sodium tartrate (5 mL) and the mixture was vigorously stirred at room temperature until the layers were separated. The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (30-40% EtOAc-hexane) gave the alcohol **10** (308.5 mg, 63% for the four steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.90 (1H, m), 3.83 (1H, m), 3.78 (1H, ddd, J = 11.3, 5.4, 5.2 Hz), 3.71 (2H, m), 3.64 (1H, ddd, J = 11.7, 6.8, 5.2 Hz), 3.35 (1H, ddd, J = 11.9, 11.9, 2.3 Hz), 3.31 (1H, ddd, J = 10.7, 9.3, 4.5 Hz), 3.26 (1H, ddd, J = 11.6, 11.6, 2.4 Hz), 3.14 (1H, m), 3.11 (1H, m) 3.07 (1H, ddd, J = 8.9, 8.9, 4.0 Hz), 2.20 (1H, m), 2.09 (1H, dddd, J = 13.7, 8.0, 8.0, 2.3 Hz), 2.02 (1H, dd, J = 6.6, 6.0 Hz), 1.70-1.54 (4H, m), 1.45 (1H, m), 1.32 (1H, m), 1.26 (1H, m), 0.87 (9H, s, *t*-Bu), 0.03 (6H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 80.3, 77.4, 74.5, 71.1, 67.7, 67.4, 63.2, 59.7, 35.5, 29.4, 29.2, 26.0, 25.4, 25.2, 18.4, -5.27, -5.30; HRMS (FAB) calcd for $C_{19}H_{38}O_5SiNa$ [(M+Na)$^+$] 397.2386, found 397.2414.

(2*S*,3*S*)-2-Acetyl-3-{(2*R*,3*S*)-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]oxan-3-yloxy}oxane (12). A solution of the alcohol **10** (811.7 mg, 2.166 mmol) and Et_3N (1.6 mL, 11.5 mmol) in CH_2Cl_2-DMSO (4:1, 25 mL) was cooled to 0 ℃ and treated with sulfur trioxide pyridine complex (1.40 g, 8.80 mmol). After being stirred at 0 ℃ for 30 min, the reaction mixture was diluted with EtOAc (150 mL), washed with H_2O, 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give the crude aldehyde, which was used in the following reaction without purification.

A solution of the above aldehyde in THF (20 mL) was cooled to -78 ℃ and treated with methylmagnesium bromide (3.0 M solution in Et_2O, 1.1 mL, 3.3 mmol), and the resulting mixture was stirred at -78 ℃ for 40 min. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was diluted with EtOAc (150

mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (30% EtOAc-hexane) gave alcohol **11** as a 4:1 mixture of diastereoisomers (680.9 mg, 81% for the two steps), which was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) of major isomer δ 3.97 (1H, m), 3.89 (1H, m), 3.82 (1H, m), 3.70 (2H, m), 3.44 (1H, ddd, *J* = 10.7, 9.2, 4.5 Hz), 3.32 (1H, ddd, *J* = 12.0, 12.0, 2.3 Hz), 3.25 (1H, ddd, *J* = 11.7, 11.7, 2.4 Hz), 3.11 (1H, m), 3.07 (1H, m) 2.88 (1H, dd, *J* = 9.1, 1.9 Hz), 2.27 (1H, m), 2.19 (1H, m), 2.10 (1H, m), 2.06 (1H, m), 1.65-1.50 (3H, m), 1.44 (1H, m), 1.28 (2H, m), 1.21 (3H, d, *J* = 6.7 Hz, Me), 0.84 (9H, s, *t*-Bu), 0.02 (6H, s SiCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) of major isomer δ 82.6, 77.4, 74.5, 70.2, 67.7, 67.5, 65.7, 59.8, 35.5, 29.4, 29.3, 26.0, 25.4, 25.2, 20 18.4, -5.28, -5.30.

A solution of oxalyl chloride (310 μl, 3.55 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 °C and treated with DMSO (500 μl, 7.05 mmol). The resulting solution was stirred at -78 °C for 10 min. To the solution was added dropwise via a cannula the alcohol **11** (680.9 mg, 1.752 mmol) in CH_2Cl_2 (14 mL). After being stirred at -78 °C for 50 min, the reaction mixture was treated with Et_3N (2.0 mL, 14.3 mmol) and allowed to warm to room temperature. The solution was stirred at room temperature for 15 min and diluted with EtOAc (150 mL). The organic layer was washed with H_2O, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (20% EtOAc-hexane) gave ketone **12** (569.6 mg, 84 %): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.91 (1H, m), 3.80 (1H, m), 3.70 (1H, d, *J* = 8.8 Hz), 3.69 (2H, m), 3.46 (1H, ddd, *J* = 10.1, 8.8, 4.2 Hz), 3.36 (1H, ddd, *J* = 11.3, 11.3, 2.8 Hz), 3.21 (1H, ddd, *J* = 11.8, 11.8, 2.4 Hz), 3.11 (1H, ddd, *J* = 9.2, 9.2, 2.4 Hz), 3.04 (1H, ddd, *J* = 10.3, 9.0, 4.3 Hz), 2.21 (3H, s, $COCH_3$), 2.18 (1H, m), 2.10 (1H, m), 2.04 (1H, m), 1.71-1.35 (6H, m), 1.13 (1H, m), 0.86 (9H, s, *t*-Bu), 0.02 (6H, s, SiCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.9, 84.6, 77.2, 74.5, 71.7, 67.44, 67.38, 59.6, 35.5, 29.14, 29.09, 29.06, 26.0, 25.2, 24.2, 18.3, -5.30, -5.34; HRMS (FAB) calcd for $C_{20}H_{38}O_5SiNa$ [(M+Na)$^+$] 409.2386, found 409.2343.

(2*S*,3*S*)-2-(Bromoacetyl)-3-[(2*R*,3*S*)-2-(2-hydroxyethyl)oxan-3-yloxy]oxane (13). A solution of the ketone **12** (157.3 mg, 0.408 mmol) and *i*-Pr_2NEt (0.22 mL, 1.26 mmol) in CH_2Cl_2 (7 mL) was cooled to -10 °C and treated with trimethylsilyl trifluoromethanesulfonate (160 μL, 0.828 mmol). After 45 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the mixture was extracted with Et_2O (60 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), concentrated to give the silyl enol ether, which was used in the next reaction without purification.

A solution of the silyl enol ether in THF (7 mL) was cooled to 0 °C and treated with *N*-bromosuccinimide (145 mg, 0.815 mmol). After being stirred at 0 °C for 20 min, the reaction mixture was diluted with EtOAc (60 mL), washed with saturated aqueous Na_2SO_3, H_2O, and brine, dried (Na_2SO_4), and concentrated to give the α-bromoketone, which was used in the next reaction without purification.

A solution of the above α-bromoketone in CH_2Cl_2-MeOH (1:1, 7 mL) was cooled to 0 °C and treated with camphorsulfonic acid (19.0 mg, 0.082 mmol). After 40 min at 0 °C, the reaction was quenched with Et_3N and the mixture was concentrated. The residue was subjected to flash chromatography (2-4% MeOH-$CHCl_3$) to give the α-bromoketo alcohol **13** (126.3 mg, 92% for the three steps): ^{1}H NMR (C_6D_6, 500 MHz) δ 3.80 (2H, m), 3.77 (1H, d, *J* = 13.8 Hz), 3.72 (1H, d, *J* = 13.8 Hz), 3.57 (1H, d, *J* = 8.7 Hz), 3.48 (2H, m), 3.27 (1H, ddd, *J* = 10.0, 8.8, 4.4 Hz), 3.08 (1H, ddd, *J* = 8.9, 8.9, 3.0 Hz), 2.84 (1H, ddd, *J* = 11.1, 11.1, 2.6 Hz), 2.78 (1H, ddd, *J* = 10.6, 8.9, 4.4 Hz), 2.02 (1H, m), 1.77 (1H, m), 1.67-1.58 (2H, m), 1.22-1.05 (4H, m), 0.96 (1H, m), 0.88 (1H, m); ^{13}C NMR (C_6D_6, 125 MHz) δ 197.2, 82.4, 80.6, 74.7, 71.3, 67.4, 67.3, 61.0, 35.1, 34.1, 29.2, 28.9, 25.3, 24.3; HRMS (FAB) calcd for $C_{14}H_{23}O_5BrNa$ [(M+Na)$^+$] 373.0627, found 373.0637.

(1*S*,3*S*,8*S*,13*R*)-11-Acetoxy-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadecan-9-one (15). A solution of the α-bromoketo alcohol **13** (50.9 mg, 0.152 mmol) and Et_3N (110 μL, 0.789 mmol) in CH_2Cl_2-DMSO (2:1, 1.5 mL) was cooled to 0 °C and treated with sulfur trioxide pyridine complex (97 mg, 0.609 mmol). After being stirred at 0 °C for 40 min, the reaction mixture was diluted with EtOAc (30 mL), washed with H_2O, 1N aqueous

HCl, and saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give the crude aldehyde **14** (40.9 mg, 81%), which was used in the following reaction without purification.

To a solution of SmI_2 in THF (0.1 M, 6.0 mL, 0.60 mmol) was added dropwise over 10 min a solution of the above aldehyde **14** (40.9 mg, 0.123 mmol) in THF (12 mL) at -78 ℃. The reaction mixture was stirred at -78 ℃ for 1 h. Excess SmI_2 was quenched by exposure to dry oxygen until the deep blue solution turned to yellow. The mixture was directly treated with acetic anhydride (120 μL, 1.27 mmol) and DMAP (30.0 mg, 0.246 mmol) and allowed to warm to 0 ℃. After 40 min at 0 ℃, silica gel (3.0 g) and hexane (10 mL) was added to the solution. The resulting heterogeneous mixture was stirred at room temperature for 15 min and filtered through a short column of silica gel (2.0 g) and washed with Et_2O (70 mL). Concentration and flash chromatography (50% EtOAc-hexane) gave the β-acetoxy ketone **15** as a single diastereomer (19.0 mg, 49%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (1H, m, 8-H), 4.02 (1H, d, J = 9.2 Hz, 5-H), 3.93 (1H, m, 1-H), 3.75 (1H, m, 14-H), 3.60 (1H, ddd, J = 10.7, 9.2, 4.9 Hz, 4-H), 3.46 (1H, ddd, J = 11.0, 9.5, 4.3 Hz, 11-H), 3.30 (1H, ddd, J = 11.9, 11.9, 2.4 Hz, 1-H), 3.17 (1H, ddd, J = 11.6, 11.6, 2.1 Hz, 14-H), 3.14 (1H, ddd, J = 9.5, 9.5, 4.3 Hz, 10-H), 3.01 (1H, ddd, J = 13.1, 3.7, 0.9 Hz, 7-H), 2.70 (1H, dd, J = 13.1, 11.6 Hz, 7-H), 2.04 (3H, s, $COCH_3$), 1.98-1.87 (4H, m, 3-H, 12-H, 9-H_2), 1.79-1.51 (6H, m, 2-H_2, 3-H, 12-H, 13-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.3, 170.2, 84.1, 77.7, 77.0, 73.6, 70.0, 67.2, 66.4, 49.4, 41.3, 33.4, 27.2, 25.7, 24.8, 21.3; MS (EI) m/z 312 (M^+).

(1*S*,3*S*,8*S*,13*R*)-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadec-10-en-9-one (17). A solution of the β-acetoxy ketone **15** (22.6 mg, 0.0724 mmol) in acetonitrile (2 mL) was cooled to 0 ℃ and treated with boron trifluoride etherate (20 μL, 0.162 mmol). The resulting mixture was stirred at 0 ℃ for 30 min and allowed to warm to room temperature and the stirring was continued for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.5 mL) and the aqueous layer was extracted with $CHCl_3$ (10 mL x 4). The combined organic layers were dried (Na_2SO_4), and concentrated. Flash chromatography (2% MeOH-$CHCl_3$) gave the α,β-unsaturated ketone **17** (15.4 mg, 84%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.33 (1H, ddd, J = 12.2, 10.7, 8.6 Hz, 8-H), 3.12 (1H, d, J = 12.2 Hz, 7-H), 4.50 (1H, d, J = 10.4 Hz, 5-H), 4.06 (1H, m, 1-H), 3.87 (1H, m, 14-H), 3.64 (1H, ddd, J = 10.7, 8.9, 4.3 Hz, 11-H), 3.58 (1H, ddd, J = 11.6, 10.4, 4.9 Hz, 4-H), 3.37 (1H, ddd, J = 11.6, 11.6, 4.3 Hz, 1-H), 3.33 (1H, ddd, J = 11.3, 11.3, 3.7 Hz, 14-H), 3.14 (1H, ddd, J = 10.7, 8.9, 1.2 Hz, 10-H), 2.75 (1H, ddd, J = 13.1, 10.7, 10.7 Hz, 9-H), 2.46 (1H, ddd, J = 13.1, 8.6, 1.2 Hz, 9-H) 2.08 (1H, m, 3-H), 1.93 (2H, m, 3-H, 12-H), 1.78-1.65 (4H, m, 2-H_2, 13-H_2) 1.51 (1H, m, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.4, 139.2, 132.2, 82.9, 78.0, 75.8, 73.4, 68.1, 67.0, 36.9, 33.3, 28.0, 25.8, 25.1; MS (FAB) m/z 275 [(M+Na)$^+$].

(1*S*,3*S*,8*S*,9*R*,13*R*)-9-Hydroxy-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadec-10-ene (18). A solution of the α,β-unsaturated ketone **17** (15.4 mg, 0.0611 mmol) in CH_2Cl_2 (1.5 mL) was cooled to -78 ℃ and treated with DIBALH (1.0 M solution in toluene, 130 μL, 0.130 mmol). After 30 min at -78 ℃, the reaction was quenched with saturated aqueous potassium sodium tartrate (1 mL) and the mixture was vigorously stirred at room temperature until the layers were separated. The aqueous layer was then extracted with EtOAc (30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (50% EtOAc-hexane) gave the allyl alcohol **18** (12.3 mg, 79%) as a single diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.82 (1H, dddd, J = 11.0, 10.7, 7.6, 1.2 Hz, 8-H), 5.42 (1H, dd, J = 11.0, 8.5 Hz, 7-H), 4.87 (1H, brd, J = 8.5 Hz, 6-H), 3.91 (1H, m, 1-H), 3.83 (1H, m, 14-H), 3.39 (1H, ddd, J = 11.0, 9.2, 3.7 Hz, 11-H), 3.31 (1H, m, 1-H), 3.28 (1H, m, 14-H), 3.25 (1H, d, J = 9.2 Hz, 5-H), 3.24 (1H, m, 10-H), 3.10 (1H, ddd, J = 10.4, 9.2, 4.3 Hz, 4-H), 2.68 (1H, ddd, J = 13.4, 10.7, 7.0 Hz, 9-H), 2.07 (1H, m, 3-H), 2.04 (1H, dd, J = 13.4, 7.6 Hz, 9-H), 1.99 (1H, m, 12-H), 1.69-1.58 (5H, m, 2-H_2, 13-H_2, 12-H), 1.52 (1H, m, 3-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 130.7, 128.0, 83.2, 80.5, 79.7, 69.8, 68.6, 68.4, 67.0, 33.4, 32.7, 32.5, 27.1, 25.4; HRMS (FAB) calcd for $C_{14}H_{22}O_4Na$ [(M+Na)$^+$] 277.1416, found 277.1411.

(1*S*,3*S*,8*S*,9*R*,13*R*)-9-(Phenoxythiocarbonyloxy)-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadec-10-ene (19). A solution of the alcohol **18** (11.2 mg, 0.0441 mmol) and DMAP (27 mg, 0.221 mmol) in acetonitrile (1 mL) was treated with phenyl chlorothiocarbonate (15 μL, 0.108 mmol) at room temperature. After being stirred at room temperature for 4 h, the reaction mixture was diluted with EtOAc (20 mL). The organic layer was washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (20% EtOAc-hexane) gave the phenyl thiocarbonate **19** (16.0 mg, 93%), which was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.08 (5H, m), 6.52 (1H, dd, *J* = 9.1, 2.5 Hz), 6.06 (1H, ddd, *J* = 10.7, 10.7, 8.2 Hz), 5.62 (1H, dd, *J* = 10.7, 9.7 Hz), 3.98 (1H, m), 3.85 (1 H, m), 3.58 (1H, dd, *J* = 9.0, 3.1 Hz), 3.49 (1H, m), 3.89 (1H, ddd, *J* = 11.2, 11.2, 3.9 Hz), 3.31 (1H, m), 3.29 (1H, m), 3.21 (1H, ddd, *J* = 10.4, 10.4, 4.2 Hz), 2.89 (1H, ddd, *J* = 13.6, 10.3, 7.2 Hz), 2.16 (1H, dd, *J* = 13.7, 7.8 Hz), 2.11 (1H, m), 2.01 (1H, m), 1.70-1.55 (6H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.5, 153.5, 131.6, 129.4, 126.4, 124.4, 122.0, 81.1, 79.9, 79.8, 69.8 (x 2), 68.7, 68.4, 33.3, 32.9, 32.7, 27.1, 25.4.

(1*S*,3*S*,8*R*,13*R*)-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadec-10-ene (20). A solution of the phenyl thiocarbonate **19** (16.0 mg, 0.0410 mmol), 2,2'-azobis(isobutyronitrile) (AIBN, 2 mg, 0.0122 mmol) and tributyltin hydride (55 μL, 0.204 mmol) in toluene (1 mL) was heated at 80 ℃ for 3 h. After being cooled to room temperature, the reaction mixture was concentrated and the residue was subjected to flash chromatography (15-30% Et_2O-hexane) to give an inseparable 5:1 mixture of the hexahydrooxonine **20** and its regioisomer **21** (8.4 mg, 86%). **20**: ^{1}H NMR ($CDCl_3$, -40 ℃, 500 MHz) δ 5.89 (1H, ddd, *J* = 10.7, 10.4, 7.6 Hz, 7-H), 5.54 (1H, ddd, *J* = 10.7, 10.7, 6.1 Hz, 8-H), 3.85 (2H, m, 1-H, 14-H), 3.42 (1H, dd, *J* = 8.6, 8.6 Hz, 4-H), 3.36-3.27 (3H, m, 1-H, 5-H, 14-H), 3.16 (2H, m, 10-H, 11-H), 2.91 (1H, dd, *J* = 11.9, 10.7 Hz, 9-H), 2.81 (1H, ddd, *J* = 13.7, 10.4, 7.0 Hz, 6-H), 2.08 (1H, m, 9-H), 2.04-2.00 (2H, m, 3-H, 12-H), 1.94 (1H, dd, *J* = 13.7, 7.6 Hz, 6-H), 1.70-1.60 (5H, m, 2-H_2, 3-H, 13-H_2), 1.46 (1H, m, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz, -40 ℃) δ 129.9, 125.3, 80.6, 80.4, 79.6, 68.7, 68.5, 68.3, 33.2, 32.5, 31.4, 27.9, 26.9, 25.5; HRMS (FAB) calcd for $C_{14}H_{22}O_{13}Na$ [(M+Na)$^+$] 261.1467, found 261.1500.

(1*S*,3*S*,8*S*,9*R*,13*R*)-9-(*p*-Bromobenzoyloxy)-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadec-10-ene (22). A solution of the allyl alcohol **18** (12.3 mg, 0.0484 mmol), Et_3N (30 μL, 0.22 mmol) and DMAP (2.0 mg, 0.016 mmol) in CH_2Cl_2 (1 mL) was treated with *p*-bromobenzoyl chloride (22.0 mg, 0.100 mmol) at room temperature. After being stirred at room temperature for 2.5 h, the reaction mixture was diluted with EtOAc (30 mL). The organic layer was washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10-20% EtOAc-hexane) gave the *p*-bromobenzoate **22** (19.6 mg, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (2H, d, *J* = 8.9 Hz, Ar), 7.54 (1H, d, *J* = 8.9 Hz, Ar), 6.26 (1H, brdd, *J* = 10.7, 3.1 Hz, 6-H), 6.00 (1H, ddd, *J* = 10.7, 10.7, 8.2 Hz, 8-H), 5.60 (1H, dd, *J* = 10.7, 10.7 Hz, 7-H), 3.94 (1H, m, 1-H), 3.86 (1H, m, 14-H), 3.48 (1H, m, 11-H), 3.46 (1H, dd, *J* = 8.9, 3.1 Hz, 5-H), 3.33 (1H, ddd, *J* = 11.3, 11.3, 4.3 Hz, 1-H), 3.31 (1H, m, 10-H), 3.30 (1H, m, 14-H), 3.21 (1H, br, 4-H), 2.91 (1H, br, 9-H), 2.18 (1H, br, 9-H), 2.10 (1H, m, 3-H), 2.01 (1H, m, 12-H), 1.70-1.60 (5H, m, 2-H_2, 12-H, 13-H_2), 1.57 (1H, m, 3-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3, 131.6, 131.3, 130.4, 129.3, 128.0, 125.7, 81.6, 80.1, 79.8, 70.7, 69.9, 68.7, 68.3, 33.4, 32.8 (x 2), 27.1, 25.5; HRMS (FAB) calcd for $C_{21}H_{25}O_5BrNa$ [(M+Na)$^+$] 459.0783, found 459.0766.

(1*S*,3*R*,6*S*)-3-{3-[(*Z*)-3-trimethylsilyl-1-propenyloxy]propyl}-2,4,7-trioxabicyclo[4.4.0]decane (24). A solution of the acetal **23** (1.91 g, 7.89 mmol) in THF (70 mL) was cooled to -78 ℃ and treated with *s*-BuLi (1.05 M solution in cyclohexane, 9.0 mL, 9.45 mmol) and the resulting mixture was stirred at that temperature for 20 min. Trimethylsilyl chloride (1.20 mL, 9.45 mmol) was then added to the solution. After 20 min at -78 ℃, the reaction was quenched with H_2O (5 mL) and the reaction mixture was diluted with EtOAc (250 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10%

EtOAc-hexane) gave the γ-alkoxyallylsilane **24** (2.52 g, quant.), which was immediately used in the next reaction: ^{1}H NMR (C_6D_6, 500 MHz) δ 5.82 (1H, dt, *J* = 6.3, 1.2 Hz, C*H*=), 4.43 (1H, t, *J* = 4.7 Hz), 4.39 (1H, td, *J* = 8.6, 6.3 Hz, C*H*=), 4.10 (1H, dd, *J* = 10.2, 4.2 Hz), 3.57 (1H, m), 3.46 (2H, t, *J* = 6.5 Hz), 3.38 (1H, t, *J* = 9.9 Hz), 3.12-3.04 (2H, m), 2.97 (1H, ddd, *J* = 12.0, 12.0, 2.5 Hz), 1.83-1.71 (5H, m), 1.64 (2H, dd, *J* = 8.4, 1.0 Hz), 1.37 (3H, m), 0.07 (9H, s, SiC*H*$_3$).

(2*R*,3*S*)-{3-[(2*S*,3*R*)-2-Vinyloxan-3-yloxy]oxan-2-yl}methanol (4). A solution of triphenylphosphine (2.004 g, 7.648 mmol) in CH_2Cl_2 (40 mL) was cooled to -78 ℃, treated with $TiCl_4$ (0.84 mL, 7.66 mmol), and the resulting solution was stirred at that temperature for 10 min. To this solution was added dropwise over 10 min a solution of the γ-alkoxyallylsilane **24** (1.2033 g, 3.826 mmol) in CH_2Cl_2 (40 mL). The resulting mixture was stirred at -78 ℃ for 30 min, allowed to warm to 0 °C, and the stirring was continued for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the mixture was diluted with EtOAc-Et_2O (1:1, 200 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (40-60% EtOAc-hexane) gave the bicyclic ethers **4** and **8** as an inseparable 5:1 mixture (454.5 mg, 49%) and the *cis*-fused isomers (214.9 mg, 23%). **4**: $[\alpha]_D^{26}$ = +27.7° (*c* 0.93, $CHCl_3$); IR (film) 3479, 2939, 2854, 1647, 1126, 1088, 989, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.94 (1H, ddd, *J* = 17.1, 10.7, 6.4 Hz, 9-H), 5.35 (1H, ddd, *J* = 17.1, 1.8, 1.8 Hz, 8-H), 5.24 (1H, ddd, *J* = 10.7, 1.8, 0.9 Hz, 8-H), 3.93-3.86 (2H, m, 1-H, 14-H), 3.79 (1H, dd, *J* = 11.3, 3.4 Hz, 6-H), 3.62 (1H, dd, *J* = 11.3, 5.2 Hz, 6-H), 3.52 (1H, brdd, *J* = 8.6, 6.4 Hz, 10-H), 3.38-3.30 (2H, m, 1-H, 14-H), 3.28 (1H, ddd, *J* = 10.7, 9.2, 4.6 Hz, 4-H), 3.14-3.10 (2H, m, 5-H, 11-H), 2.13 (1H, m, 3-H), 2.07 (1H, m, 12-H), 1.67- 1.61 (4H, m, 2-H$_2$, 13-H$_2$), 1.48-1.35 (2H, m, 3-H, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136,4, 117.7, 81.6, 80.9, 76.8, 74.2, 67.6, 67.2, 63.1, 31.8, 31.0, 25.3, 25.2; HRMS (FAB) calcd for $C_{13}H_{22}O_4Na$ [(M+Na)$^+$] 265.1416, found 265.1417.

(2*S*,3*R*)-3-Hydroxy-2-vinyloxane (25). A solution of the bicyclic ether **4** (45.9 mg, 0.190 mmol) and Et_3N (135 μL, 0.969 mmol) in CH_2Cl_2-DMSO (3:1, 2.7 mL) was cooled to 0 ℃ and treated with sulfur trioxide pyridine complex (121 mg, 0.760 mmol). After being stirred at 0 ℃ for 30 min, the reaction mixture was diluted with EtOAc (30 mL), washed with H_2O (x 2) and brine, dried (Na_2SO_4), and concentrated to give the crude aldehyde.

A solution of the crude aldehyde in THF-H_2O (3:1, 2.7 mL) was treated with LiOH·H_2O (20.0 mg, 0.476 mmol) and the resulting mixture was heated at 60 ℃ for 1 h. After being cooled to room temperature, the mixture was diluted with EtOAc (30 mL), washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (40% EtOAc-hexane) gave the alcohol **25** (24.3 mg), which was used in the next reaction without further purification.

(*R*)-MTPA Ester *R*-26. A solution of the alcohol **25** (5.2 mg, 0.040 mmol), DCC (25.0 mg, 0.121 mmo and DMAP (5.0 mg, 0.041 mmol) in CH_2Cl_2 (0.5 mL) was treated with (*R*)-MTPAOH (30.0 mg, 0.128 mmol). After being stirred at room temperature for 20 h, the reaction mixture was concentrated and the residue was subjected to flash chromatography (10% EtOAc-hexane) to give the (*R*)-MTPA ester ***R*-26** (13.2 mg, contaminated with dicyclohexyl urea): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54-7.34 (5H, m, Ar), 5.80 (1H, ddd, *J* = 17.1, 10.7, 7.0 Hz, 9-H), 5.31 (1H, d, *J* = 17.1 Hz, 8-H), 5.24 (1H, d, *J* = 10.7 Hz, 8-H), 4.80 (1H, ddd, *J* = 10.7, 9.2, 4.9 Hz, 11-H), 3.95 (1H, m, 14-H), 3.74 (1H, dd, *J* = 9.2, 7.0 Hz, 10-H), 3.50 (3H, s, OC*H*$_3$), 3.39 (1H, ddd, *J* = 11.6, 11.6, 2.4 Hz, 14-H), 2.22 (1H, m, 12-H), 1.82-1.44 (3H, m, 12-H, 13-H$_2$); HRMS (FAB) calcd for $C_{17}H_{19}O_4F_3Na$ [(M+Na)$^+$] 367.1133, found 367.1140.

(*S*)-MTPA Ester *S*-26. Following the procedure for the preparation of the (*R*)-MTPA ester, the alcohol **25** (4.4 mg, 0.034 mmol) was converted to the (*S*)-MTPA ester ***S*-26** (12.4 mg), which was contaminated with dicyclohexyl urea: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54-7.34 (5H, m, Ar), 5.64 (1H, ddd, *J* = 17.1, 10.4, 6.7 Hz, 9-H), 5.15 (1H, d, *J* = 17.1 Hz, 8-H), 5.06 (1H, d, *J* = 10.7 Hz, 8-H), 4.80 (1H, ddd, *J* = 9.8, 9.8, 4.9

Hz, 11-H), 3.96 (1H, m, 14-H), 3.69 (1H, dd, J = 8.5, 6.7 Hz, 10-H), 3.52 (3H, s, OMe), 3.40 (1H, ddd, J = 11.6, 11.6, 2.8 Hz, 14-H), 2.27 (1H, m, 12-H), 1.84-1.43 (3H, m, 12-H, 13-H_2); HRMS (FAB) calcd for $C_{17}H_{19}O_4F_3Na$ [(M+Na)$^+$] 367.1133, found 367.1121.

(2*R*,3*S*)-(3-{(2*S*,3*R*)-2-[2-(*tert*-Butyldimethylsilyloxy)ethyl]oxan-3-yloxy}oxan-2-yl)methanol (27). A solution of the bicyclic ether **4** (440.4 mg, 1.891 mmol), DMAP (23.0 mg, 0.188 mmol) and Et_3N (1.0 mL, 7.17 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 ℃ and treated with acetic anhydride (350 μL, 3.71 mmol). The reaction mixture was stirred at that temperature for 30 min and diluted with EtOAc-Et_2O (4:1, 150 mL). The organic layer was washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give the crude acetate.

A solution of the above acetate in THF (10 mL) was cooled to 0 ℃, treated with 9-BBN (0.5 M solution in THF, 11 mL, 5.5 mmol) and the resulting mixture was stirred at room temperature for 2 h. The mixture was recooled to 0 ℃ and the reaction was quenched with EtOH (0.7 mL). To the mixture was sequentially added saturated aqueous $NaHCO_3$ (7 mL) and 30 % H_2O_2 (3 mL) at 0 ℃. The resulting solution was stirred at room temperature for 30 min and diluted with EtOAc (150 mL). The organic layer was washed with H_2O, saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give the crude alcohol.

A solution of the crude alcohol and imidazole (387 mg, 5.68 mmol) in DMF (10 mL) was cooled to 0 ℃ and treated with TBDMSCl (428 mg, 2.84 mmol). The reaction mixture was stirred at 0 ℃ for 30 min and diluted with EtOAc (140 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (40% Et_2O-hexane) gave the TBS ether, which was used in the next reaction without further purification.

A solution of the above TBDMS ether in CH_2Cl_2 (30 mL) was cooled to -78 ℃ and treated with DIBALH (1.0 M solution in toluene, 4.8 mL, 4.8 mmol) and the resulting mixture was stirred at -78 ℃ for 30 min. The reaction was quenched with saturated aqueous potassium sodium tartrate (10 mL) and the mixture was vigorously stirred at room temperature until the layers were separated. The aqueous layer was extracted with EtOAc (150 mL) and the organic layer was dried (Na_2SO_4), and concentrated. Flash chromatography (30-50% EtOAc-hexane) gave the alcohol **27** (521 mg, 76% for the four steps): $[\alpha]_D^{28}$ = +5.1° (*c* 0.71, $CHCl_3$); IR (film) 3500, 2933, 2854, 1471, 1254, 1099, 835, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.89 (1H, m, 1-H), 3.82 (1H, m, 6-H), 3.8 (1H, m, 14-H), 3.72-3.67 (3H, m, 6-H, 8-H_2), 3.34 (1H, m, 1-H), 3.32 (1H, m, 4-H), 3.25 (1H, ddd, J = 11.3, 11.3, 3.4 Hz, 14-H), 3.18 (1H, ddd, J = 8.9, 8.9, 2.4 Hz, 10-H), 3.14 (1H, m, 5-H), 3.08 (1H, ddd, J = 10.1, 8.6, 4.3 Hz, 11-H), 2.15-2.03 (3H, m, 3-H, 9-H, 12-H), 1.59 (4H, m, 2-H_2, 13-H_2), 1.5 (1H, m, 9-H), 1.38 (2H, m, 3, 12-H), 0.87 (9-H, s, *t*-Bu), 0.03 (6-H, s, SiCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 81.0, 77.6, 76.9, 73.5, 67.6, 67.2, 62.8, 59.5, 35.1, 31.6, 31.3, 26.0, 25.4, 25.3, 18.4, -5.3, -5.4; HRMS (FAB) calcd for $C_{19}H_{38}O_5SiNa$ [(M+Na)$^+$] 397.2386, found 397.2366.

(2*S*,3*S*)-2-Acetyl-3-{(2*S*,3*R*)-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]oxan-3-yloxy}oxane (28). A solution of the alcohol **27** (332.1 mg, 0.887 mmol) and Et_3N (620 μL, 4.45 mmol) in CH_2Cl_2-DMSO (10:3, 13 mL) was cooled to 0 ℃ and treated with sulfur trioxide pyridine complex (565 mg, 3.55 mmol). After being stirred at 0 ℃ for 30 min, the reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (x 2) and brine, dried (Na_2SO_4) and concentrated to give the crude aldehyde, which was used in the following reaction without purification.

A solution of the crude aldehyde in THF (10 mL) was cooled to -78 ℃ and treated with methylmagnesium bromide (3.0 M solution in Et_2O, 0.6 mL, 1.8 mmol). The resulting mixture was stirred at -78 ℃ for 20 min, then allowed to warm to 0 ℃ and the stirring was continued for 30 min. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was diluted with EtOAc (80 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (30% EtOAc-hexane) gave the alcohol as a 5:1 mixture of diastereoisomers (300 mg, 87% for the two steps): ^{1}H NMR ($CDCl_3$, 500 MHz) of major isomer δ

4.04 (1H, br, 6-H), 3.90 (1H, m, 1-H), 3.81 (1H, m, 14-H), 3.71 (2H, m, 8-H_2), 3.45 (1H, ddd, J = 10.7, 8.9, 4.6 Hz, 4-H), 3.31 (1H, ddd, J = 11.0, 11.0, 3.7 Hz, 1-H), 3.26 (1H, ddd, J = 11.3, 11.3, 3.4 Hz, 14-H) 3.20 (1H, ddd, J = 8.9, 8.9, 2.4 Hz, 10-H), 3.13 (1H, ddd, J = 10.1, 8.9, 4.3 Hz, 11-H), 2.86 (1H, dd, J = 8.9, 1.5 Hz, 5-H), 2.15-2.05 (3H, m, 3-H, 9-H, 12-H), 1.59 (4H, m, 2-H_2, 13-H_2), 1.51 (1H, m, 9-H), 1.4 (2H, m, 3, 12-H), 1.22 (3H, d, J = 6.7 Hz, 7-H), 0.87 (9-H, s, t-Bu), 0.03 (6H, s, SiCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) of major isomer δ 83.3, 77.6, 76.7, 72.7, 67.7, 67.1, 65.0, 59.5, 35.1, 31.6, 31.5, 30.0, 26.0, 25.4, 25.3, 20.4, -5.3, -5.4.

A solution of oxalyl chloride (135 μL, 1.55 mmol) in CH_2Cl_2 (5 mL) was cooled to -78 ℃ and treated with DMSO (0.22 mL, 3.10 mmol) and the resulting solution was stirred at -78 ℃ for 10 min. To the solution was added dropwise via a cannula a solution of the above alcohol (300.0 mg, 0.7731 mmol) in CH_2Cl_2 (7 mL). After being stirred at -78 ℃ for 30 min, the reaction mixture was treated with Et_3N (0.87 mL, 6.24 mmol) and allowed to warm to room temperature. The solution was stirred at room temperature for 30 min and diluted with EtOAc (80 mL). The organic layer was washed with H_2O, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (10% EtOAc-hexane) gave the ketone **28** (205.2 mg, 69 %): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.85 (1H, m, 1-H), 3.80 (1H, m, 14-H), 3.71 (1H, d, J = 7.9 Hz, 5- H), 3.66 (2H, dd, J = 7.9, 4.9 Hz, 8-H_2), 3.54 (1H, ddd, J = 9.5, 7.9, 4.3 Hz, 4-H), 3.41 (1H, ddd, J = 10.7, 10.7, 2.8 Hz, 1-H 3.23 (1H, ddd, J = 11.0, 11.0, 3.4 Hz, 14-H), 3.14 (1H, ddd, J = 9.2, 9.2, 2.4 Hz, 10-H), 3.04 (1H, ddd, J = 10.1, 9.2, 4.3 Hz, 11-H), 2.25 (3H, s, COCH_3), 2.09 (1H, m, 3-H), 2.05 (1H, m, 12-H), 1.87 (1H, dddd, J = 10.4, 9.2, 7.9, 2.5 Hz, 9-H), 1.71 (1H, m, 2-H), 1.59 (2H, m, 13-H_2), 1.57 (1H, m, 2-H), 1.50 (1H, m, 3-H) 1.41 (1H, m, 12-H), 1.38 (1H, m, 9-H), 0.86 (9H, s, t-Bu), 0.016 (3H, s, SiCH_3), 0.013 (3H, s, SiCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.9, 84.2 (x 2), 77.3, 73.6, 67.2 (x 2), 59.2, 35.0, 31.5, 30.5, 28.5, 26.0, 25.5, 23.9, 18.3, -5.3, -5.4.

(2*S*,3*S*)-2-(Bromoacetyl)-3-[(2*S*,3*R*)-2-(2-hydroxyethyl)oxan-3-yloxy]oxane (29). A solution of the ketone **28** (210.4 mg, 0.545 mmol) and i-Pr_2NEt (290 μL, 1.50 mmol) in CH_2Cl_2 (8 mL) was cooled to -10 ℃ and treated with trimethylsilyl trifluoromethanesulfonate (210 μL, 1.09 mmol). After 45 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O (70 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated to give the silyl enol ether, which was used in the next reaction without purification.

A solution of the above silyl enol ether in THF (8 mL) was cooled to 0 ℃ and treated with N-bromosuccinimide (194 mg, 1.09 mmol). After being stirred at 0 ℃ for 20 min, the reaction mixture was diluted with EtOAc (70 mL). The organic layer was washed with saturated aqueous Na_2SO_3, H_2O and brine, dried (Na_2SO_4), and concentrated to give the α-bromoketone.

A solution of the α-bromoketone in CH_2Cl_2-MeOH (1:1, 8 mL) was cooled to 0 ℃ and treated with camphorsulfonic acid (26.0 mg, 0.112 mmol). After being stirred at 0 ℃ for 45 min, the reaction was quenched with Et_3N and the mixture was concentrated. The residue was subjected to flash chromatography (2-4% MeOH-$CHCl_3$) to give the α-bromoketo alcohol **29** (168.7 mg, 88% for the three steps): $[\alpha]_D^{28}$ = -7.5° (*c* 0.46, $CHCl_3$); IR (film) 3444, 2941, 2858, 1714, 1182, 1097, 943 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.15 (2H, s, 7-H_2), 3.91 (1H, d, J = 8.6 Hz, 5-H), 3.89 (1H, m, 1-H), 3.84 (1H, m, 14-H), 3.72 (2H, dd, J = 6.1, 4.0 Hz, 8-H_2), 3.56 (1H, ddd, J = 10.1, 8.6, 4.6 Hz, 4-H), 3.40 (1H, ddd, J = 11.3, 11.3, 3.1 Hz, 1-H), 3.29 (1H, ddd, J = 11.3, 6.7, 4.3 Hz, 14-H), 3.22 (1H, ddd, J = 8.9, 8.9, 3.1 Hz, 10-H), 3.15 (1H, ddd, J = 10.4, 8.9, 4.6 Hz, 11-H), 2.14 (1H, m, 3-H), 2.09 (1H, m, 12-H), 1.84 (1H, m, 9-H), 1.70 (1H, m, 2-H), 1.63 (3H, m, 2-H, 13-H_2), 1.57 (1H, m, 9-H), 1.49 (1H, m, 3-H), 1.39 (1H, m, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 81.8, 81.5, 76.7, 73.8, 67.7, 67.4, 61.4, 34.0, 33.6, 31.3, 31.0, 25.2, 24.1; HRMS (FAB) calcd for $C_{14}H_{23}O_5BrNa$ [(M+Na)$^+$] 373.0627, found 373.0649.

(1*R*,3*S*,8*S*,11*R*,13*S*)-11-Acetoxy-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadecan-9-one (2). A solution

of the α-bromoketo alcohol **29** (62.4 mg, 0.186 mmol) and Et_3N (130 μL, 0.933 mmol) in CH_2Cl_2-DMSO (3:1, 2.7 mL) was cooled to 0 ℃ and treated with sulfur trioxide pyridine complex (119 mg, 0.748 mmol). After being stirred at 0 ℃ for 40 min, the reaction mixture was diluted with EtOAc (30 mL), washed with H_2O (x 2) and brine, dried (Na_2SO_4) and concentrated to give the aldehyde **3**, which was used in the following reaction without purification.

To a solution of SmI_2 in THF (0.1 M, 9.3 mL, 0.93 mmol) was dropwise added over 10 min a solution of the above aldehyde **3** in THF (9 mL) at -78 ℃. After the reaction mixture was stirred at -78 ℃ for 1 h, the excess SmI_2 was quenched by exposure to dry oxygen until the deep blue solution turned yellow. The mixture was directly treated with acetic anhydride (180 μL, 1.90 mmol) and DMAP (46.0 mg, 0.377 mmol) and allowed to warmed to 0 ℃. After being stirred at 0 ℃ for 1 h, the solution was diluted with EtOAc (100 mL), washed with 1N aqueous HCl, saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (50% EtOAc-hexane) gave the β-acetoxy ketone **2** as a single diastereomer (34.3 mg, 62% for the three steps): $[\alpha]_D^{28}$ = +0.73° (*c* 0.10, $CHCl_3$); IR (film) 2935, 2856, 1732, 1716, 1236, 1132, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.46 (1H, m, 8-H), 3.94 (1H, m, 1-H), 3.93 (1H, d, *J* = 9.5 Hz, 5-H), 3.78 (1H, m, 14-H), 3.33 (1H, ddd, *J* = 11.3, 11.3, 4.6 Hz, 1-H), 3.31 (1H, ddd, *J* = 11.9, 9.5, 2.7 Hz, 4-H), 3.25 (1H, ddd, *J* = 11.3, 11.3, 4.0 Hz, 14-H), 3.18 (1H, ddd, *J* = 9.5, 9.5, 2.7 Hz, 10-H), 3.17 (1H, ddd, *J* = 12.2, 4.0 Hz, 7-H), 2.88 (1H, ddd, *J* = 10.4, 9.5, 4.6 Hz, 11-H), 2.60 (1H, dd, *J* = 12.2, 9.2 Hz, 7-H), 2.08 (1H, m, 3-H), 2.05 (3H, s, $COCH_3$), 2.00 (1H, m, 12-H), 1.92 (1H, ddd, *J* = 15.0, 2.7, 2.7 Hz, 9-H), 1.84 (1H, ddd, *J* = 15.0, 9.5, 7.0 Hz, 9-H), 1.72 (1H, m, 2-H), 1.66 (2H, m, 2-H, 3-H), 1.58 (2H, m, 13-H_2), 1.41 (1H, m, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.4, 170.5, 83.8, 83.7, 79.7, 77.6, 67.9, 67.5, 67.4, 49.2, 41.0, 32.8, 32.1, 25.2, 24.8, 21.3l; HRMS (FAB) calcd for $C_{16}H_{24}O_6Na$ [(M+Na)$^+$] 335.1471, found 335.1475.

(1*R*,3*S*,8*R*,11*S*,13*S*)-11-Acetoxy-9-(phenoxythiocarbonyloxy)-2,7,14-trioxatricyclo[11.4.0.0^{3,8}] heptadecane (30). A solution of the β-acetoxy ketone **2** (63.2 mg, 0.203 mmol) in MeOH (4 mL) was cooled to 0 ℃ and treated with $NaBH_4$ (12.0 mg, 0.317 mmol) in small portions. After 10 min at 0 ℃, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the resulting solution was extracted with $CHCl_3$ (10 mL x 4) The combined organic layers were dried (Na_2SO_4) and concentrated to afford the crude alcohol as a 4:1 mixture of diastereoisomers, which was used in the next reaction without purification: ^1H NMR ($CDCl_3$, 500 MHz) of major diastereomer δ 5.22 (1H, m, 8-H), 4.07 (1H, ddd, *J* = 9.8, 5.2, 4.3 Hz, 6-H), 3.86 (1H, m, 1-H), 3.79 (1H, m, 14-H), 3.39 (1H, m, 4-H), 3.34 (1H, m, 1-H), 3.28 (1H, m, 11-H), 3.25 (2H, m, 10-H, 14-H), 2.13 (1H, m, 3-H), 2.08 (1H, ddd, *J* = 14.7, 5.2, 5.2 Hz, 7-H), 2.08 (1H, m, 12-H), 1.96 (3H, s, $COCH_3$), 1.92 (2H, m, 9-H_2), 1.84 (1H, ddd, *J* = 14.7, 9.8, 4.3 Hz, 7-H), 1.58 (4H, m, 2-H_2, 13-H_2), 1.52 (1H, m, 3-H), 1.40 (1H, m, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) of major diastereomer δ 170.8, 80.2, 79.4, 77.6, 72.9, 69.6 68.6, 67.8, 67.5, 67.4, 41.7, 41.0, 32.9, 32.7, 25.0, 24.9.

A solution of the crude alcohol and DMAP (200 mg, 1.64 mmol) in acetonitrile (4 mL) was treated with phenyl chlorothiocarbonate (120 μL, 0.868 mmol) at room temperature. After the mixture was stirred at room temperature for 30 min, the reaction was quenched with 1N aqueous HCl (3 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL x 4) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. Flash chromatography (10-20% EtOAc-hexane) gave the phenyl thiocarbonate **30** as a 4:1 mixture of diastereoisomers (75 mg, 85% for the two steps): $[\alpha]_D^{28}$ = +11.1° (*c* 0.11, $CHCl_3$); IR (film) 2941, 2852, 1732, 1246, 1198, 1142, 1099, 1014, 752, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) of major diastereomer δ 7.42-7.12 (5H, m, C_6H_5), 5.73 (1H, dd, *J* = 5.5, 4.3 Hz, 6-H), 5.39 (1H, m, 8-H), 3.90 (1H, m, 1-H), 3.80 (1H, m, 14-H), 3.43 (1H, m, 4-H), 3.33-3.26 (4H, m, 1-H, 5-H, 10-H, 14-H), 3.22 (1H, ddd, *J* = 10.7, 9.2, 4.6 Hz, 11-H), 2.48 (1H, ddd, *J* = 15.6, 10.4, 5.5 Hz, 7-H), 2.09 (1H, m, 7-H), 2.07 (1H, m, 9-H), 2.03-1.97 (1H, m, 3-H, 12-H), 2.00 (3H, s, $COCH_3$), 1.84 (1H, ddd, *J* = 14.7, 2.1, 2.1 Hz, 9-H), 1.58 (4H, m, 2-H_2, 13-H_2), 1.53 (1H, m, 3-H), 1.43 (1H, m, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz)

of major diastereomer δ 194.1, 170.4, 153.3, 129.5, 126.5, 122.1, 85.0, 82.4, 82.0, 78.4, 75.4, 70.3, 68.0, 67.6, 41.8, 36.3, 33.1, 32.2, 25.4, 25.3, 21.4; HRMS (FAB) calcd for $C_{23}H_{30}O_7SNa$ [(M+Na)$^+$] 473.1610, found 473.1605.

(1*S*,3*R*,8*S*,10*S*,13*R*)-10-Acetoxy-2,7,14-trioxatricyclo[11.4.0.0^{3,8}]heptadecane (31). A solution of the phenyl thiocarbonate **30** (73.3 mg, 0.169 mmol), AIBN (5.7 mg, 0.035 mmol) and tributyltin hydride (230 μL, 0.855 mmol) in toluene (1.2 mL) was heated at 80 ℃ for 1.5 h. After being cooled to room temperature, the reaction mixture was concentrated and the residue was subjected to flash chromatography (20-30% EtOAc-hexane) to give the acetate **31** (39.3 mg, 78 %): $[\alpha]_D^{29}$ = +10.9° (*c* 0.11, $CHCl_3$); IR (film) 2937, 2856, 1732, 1250, 1103, 1012, 949 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.16 (1H, m, 8-H), 3.80 (2H, m, 1-H, 14-H), 3.31-3.23 (3H, m, 1-H, 10-H, 14-H), 3.09 (1H, ddd, *J* = 10.7, 9.2, 4.9 Hz, 11-H), 3.00 (1H, ddd, *J* = 9.2, 9.2, 4.6 Hz, 4-H), 2.97 (1H, dd, *J* = 9.2, 9.2 Hz, 5-H), 2.02 (2H, m, 3-H, 12-H), 1.99 (3H, s, $COCH_3$), 1.95 (1H, m, 9-H), 1.90 (1H, m, 7-H), 1.80 (1H, ddd, *J* = 15.0, 2.7, 2.7 Hz, 9-H), 1.77-1.69 (3H, m, 6-H_2, 7-H), 1.61 (4H, m, 2-H_2, 13-H_2), 1.43 (2H, m, 3-H, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 84.3, 83.1, 81.7, 78.1, 71.7, 67.8, 67.6, 40.3, 33.0, 32.32, 32.28, 30.2, 25.8, 25.5, 21.4; HRMS (FAB) calcd for $C_{16}H_{26}O_5Na$ [(M+Na)$^+$] 321.1678, found 321.1683.

(1*R*,3*S*,8*R*,13*S*)-2,7,14-Trioxatricyclo[11.4.0.0^{3,8}]heptadec-10-ene (1). A solution of the acetate **31** (36.8 mg, 0.123 mmol) in CH_2Cl_2 (3 mL) was cooled to -78 ℃ and treated with DIBALH (1.01 M solution in toluene, 400 μL, 0.404 mmol) and the resulting mixture was stirred at -78 ℃ for 40 min. The reaction was quenched with saturated aqueous potassium sodium tartrate (2 mL) and the mixture was vigorously stirred at room temperature until the layers were separated. The aqueous layer was extracted with EtOAc (30 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to give the crude alcohol **32** (32.0 mg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.11 (1H, m, 8-H), 3.82 (2H, m, 1-H, 14-H), 3.25 (2H, m, 1-H, 14-H), 3.09 (2H, m, 4-H, 11-H), 3.02 (1H, ddd, *J* = 8.9, 8.9, 1.8 Hz, 10-H), 2.99 (1H, m, 5-H), 2.02 (1H, m, 9-H), 2.00 (2H, m, 3-H, 12-H), 1.95 (1H, m, 7-H), 1.80 (1H, ddd, *J* = 14.7, 2.4, 1.8 Hz, 9-H), 1.74 (2H, m, 6-H_2, 7-H), 1.61 (4H, m, 2-H_2, 13-H_2), 1.40 (2H, m, 3-H, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 83.8, 83.7, 81.4, 78.6, 69.3, 67.7 (x 2), 42.2, 33.6, 32.9, 32.8, 29.1, 25.7, 25.6.

A solution of the crude alcohol **32** (8.7 mg, 0.034 mmol), LiBr (30.0 mg, 0.345 mmol) and *i*-Pr_2NEt (0.06 mL, 0.34 mmol) was cooled to 0 ℃ and treated with methanesulfonic anhydride (30.0 mg, 0.172 mmol). The resulting mixture was stirred at 0 ℃ for 1 h, allowed to warm to room temperature and the stirring was continued for 1.5 h. The mixture was diluted with EtOAc (30 mL), washed with water and brine, dried (Na_2SO_4), and concentrated to give crude bromide **35** (12.3 mg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.54 (1H, m, 8-H), 3.82 (2H, m, 1-H, 14-H), 3.26 (2H, m, 1-H, 14-H), 3.11 (1H, ddd, *J* = 10.7, 9.2, 4.6 Hz, 4-H), 3.07 (1H, ddd, *J* = 10.7, 9.2, 4.6 Hz, 11-H), 3.01 (1H, m, 5-H), 2.98 (1H, m, 10-H), 2.39-2.30 (3H, m, 7-H, 9-H_2), 2.18 (1H, m, 7-H), 2.02 (2H, m, 3-H, 12-H), 1.79 (2H, m, 6-H_2), 1.61 (4H, m, 2-H_2, 13-H_2), 1.41 (2H, m, 3-H, 12-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 84.2, 83.6, 80.5, 79.5, 67.9, 67.8, 51.8, 43.8, 35.3, 32.9 (x 2), 31.1, 25.7, 25.5.

A solution of the above crude bromide **35** in dry DMSO (0.6 mL) was treated with KO*t*-Bu (20.0 mg, 0.178 mmol). After the mixture was stirred at room temperature for 75 min, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (20 mL), and the organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (10-20% EtOAc-hexane) gave hexahydrooxonine **1** (4.0 mg, 49 %) and a 1:1 mixture of **1** and its regioisomer **36** (2.0 mg, 25 %). **1**: IR (film) 2927, 2852, 1109, 1086, 957, 835, 735 cm^{-1}; ^{1}H NMR (C_5D_5N, -20 ℃, 500 MHz, a 1:1 mixture of UP and DOWN conformers) δ 6.00 (1/2H, m, 7-H_{up}), 5.73 (1/2H, m, 7-H_{DOWN}), 3.86 (1H, m, 1-H), 3.34 (1H, m, 4-H_{DOWN}, 5-H_{UP}), 3.20 (1/2H, m, 4-H_{UP}), 3.19 (1H, m, 1-H), 3.07 (1/2H, ddd, *J* = 14.0, 9.8, 5.5 Hz, 6-H_{UP}), 3.04 (1/2H, dd, *J* = 9.5, 9.5 Hz, 5-H_{DOWN}), 2.95 (1/2H, ddd, *J* = 12.5, 9.5, 9.5 Hz, 6-H_{DOWN}), 2.30 (1/2H, dd, *J* = 12.8, 4.9 Hz, 6-H_{UP}), 2.19

(1/2H, dd, J = 14.0, 3.7 Hz, 6-H_{DOWN}), 2.00 (1/2H, m, 3-H_{UP}), 1.90 (1/2H, m, 3-H_{DOWN}), 1.67-1.41 (3H, m, 2-H, 3-H); ^{13}C NMR (C_5D_5N, -20 ℃, 125 MHz, a 1:1 mixture of UP and DOWN conformers) δ 129.3, 128.4, 87.6, 82.9, 82.4, 78.7, 68.1, 67.6, 34.6, 34.0, 33.5, 30.4, 26.4, 26.1; HRMS (FAB) calcd for $C_{14}H_{22}O_3Na$ [(M+Na)$^+$] 261.1467, found 261.1467. Regioisomer **36**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.65 (1H, ddd, J = 16.2, 10.7, 4.3 Hz, 8-H), 5.30 (1H, dd, J = 16.2, 8.9 Hz, 9-H), 3.89 (1H, m, 14-H), 3.82 (1H, m, 1-H), 3.61 (1H, dd, J = 8.9, 8.5 Hz, 10-H), 3.38 (1H, ddd, J = 11.6, 11.6, 3.4 Hz, 14-H), 3.31-3.23 (3H, m, 1-H, 4-H, 5-H), 2.70 (1H, ddd, J = 11.6, 8.5, 4.0 Hz, 11-H), 2.34 (1H, m, 7-H), 2.20 (1H, m, 7-H), 2.05 (1H, m, 12-H), 2.01 (1H, m, 3-H), 1.86 (1H, m, 6-H), 1.81 (1H, m, 6-H), 1.68-1.60 (4H, m, 2-H_2, 13-H_2), 1.50 (1H, m, 12-H), 1.34 (1H, m, 3-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.7, 125.4, 87.8, 81.3, 80.4, 78.9, 68.0, 67.9, 36.4, 32.0, 31.2, 27.1, 26.5, 25.7; HRMS (FAB) calcd for $C_{14}H_{22}O_3Na$ [(M+Na)$^+$] 261.1467, found 261.1437.

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