# A Convergent Synthesis of the Decacyclic Ciguatoxin Model Containing the F−M Ring Framework

Masayuki Inoue,[†,§] Makoto Sasaki,*[,†,‡] and Kazuo Tachibana*[,†,‡]

*Department of Chemistry, School of Science, The University of Tokyo, and CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

*Received June 21, 1999*

A highly convergent synthesis of the decacyclic ciguatoxin model **2**, which contains the F−M ring framework of the natural product, has been achieved through the assembly of pentacyclic oxonane **4** and JKLM ring fragment **5**. The two key steps in the synthesis of the former compound are (i) a Lewis acid-mediated intramolecular reaction of a $\gamma$-alkoxyallylsilane with an acetal group to form an *O*-linked oxacycle and (ii) a $SmI_2$-mediated intramolecular Reformatsky reaction leading to construction of the annelated oxonane ring system. Preliminary biological investigations revealed that model compound **2** did not inhibit the binding of tritium-labeled dihydrobrevetoxin B to voltage-sensitive sodium channels at micromolar concentrations.

## Introduction

Ciguatoxin (CTX1B, **1**) and its congeners, naturally occurring polycyclic ethers originating from marine unicellular algae, are the principle toxins for 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 common structural feature of these polyether toxins is that they possess conformationally flexible medium-sized ether rings in the middle region of the molecules. It is speculated that the conformational flexibility of these marine toxins plays an important role in their high-affinity binding to VSSC and leads to alteration of the gating mechanism (or the inactivation mechanism) of the channels.[2a] However, the scarcity of ciguatoxins from natural sources has prevented further investigations on their interactions with VSSC. Thus, the total synthesis of these toxins and the construction of more accessible model compounds are necessary for additional studies. In addition, structure−activity relationship studies of well-designed synthetic models may provide useful topochemical information for the identification of the common structural features necessary for the toxic effect.

In light of these demands, ciguatoxins have attracted a great deal of attention from synthetic organic chemists, and thus a wide variety of new synthetic methods and strategies have been developed for their synthesis.[4,5] At first glance, construction of the hexahydrooxonine ring F would appear to be one of the most formidable and challenging problems for their synthesis. Recently, we disclosed a convergent approach to the fused hexahydrooxonine ring system, featuring an intramolecular reaction of a $\gamma$-alkoxyallylsilane with an acetal group to form an *O*-linked oxacycle and a $SmI_2$-mediated intramolecular Reformatsky reaction for constructing a fused oxonane ring system.[4c,h] To understand the structural requirements of ciguatoxins for their specific and high-affinity binding to VSSC, we set out to synthesize structurally simplified model compounds. Since the left-hand portion, the A−E ring system, of ciguatoxin is considered to form a rigid backbone, we anticipated that this portion could be replaced with a *trans*-fused polytetrahydropyran unit. In addition, synthetically problematic substituents on rings G and I seemed irrelevant to the total shape of the molecule. In the course of our studies to synthesize a biologically active model compound as well as to execute the strategy for the total synthesis, we designed a decacyclic ciguatoxin model **2**, containing the F−M ring framework of the natural product, in which the conformationally rigid DE ring

* To whom correspondence should be addressed. E-mail: msasaki@chem.s.u-tokyo.ac.jp (M.S.), ktachi@chem.s.u-tokyo.ac.jp (K.T.). Fax/phone: +81-3-5841-8380.

† The University of Tokyo.

‡ CREST, Japan Science and Technology Corp. (JST).

§ Present address: Laboratory of Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Ave., New York, NY 10021-6007.

(1) (a) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929. (b) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380. (c) Murata, M.; Legrand, A.-M.; Scheuer, P. J.; Yasumoto, T. *Tetrahedron Lett.* **1992**, *33*, 525. (d) Lewis, R. J.; Sellin, M.; Poli, M. A.; Norton, R. S.; MacLeod, J. K.; Sheil, M. M. *Toxicon* **1991**, *29*, 1115. (e) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975. (f) Lewis, R. J.; Norton, R. S.; Brereton, I. M.; Eccles, C. D. *Toxicon* **1993**, *31*, 637. (g) Satake, M.; Ishibashi, Y.; Legrand, A.-M.; Yasumoto, T. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 2103. (h) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11325. (i) Satake, M.; Fukui, M.; Legrand, A.-M.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 1197. (j) Lewis, R. J.; Vernoux, J.-P.; Brereton, I. M. *J. Am. Chem. Soc.* **1998**, *120*, 5914.

(2) For reviews on ciguatoxins and related compounds, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3.

(3) (a) Bidard, J.-N.; Vijverberg, H. P. M.; Frelin, C.; Chungue, E.; Legrand, A.-M.; Bagnis, R.; Lazdanski, M. *J. Biol. Chem.* **1984**, *259*, 8353. (b) Lombet, A.; Bidard, J. N.; Lazdanski, M. *FEBS Lett.* **1987**, *219*, 355.

(4) For our synthetic studies on ciguatoxins, see: (a) Sasaki, M.; Hasegawa, A.; Tachibana, K. *Tetrahedron Lett.* **1993**, *34*, 8489. (b) Sasaki, M.; Inoue, M.; Tachibana, K. *J. Org. Chem.* **1994**, *59*, 715. (c) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **1997**, *38*, 1611. (d) Inoue, M.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 965. (e) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 2783. (f) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (g) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, 40 1337. (h) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron* **1999**, *55*, 10949. (i) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075. (j) Sasaki, M.; Inoue, M.; Takamatsu, K.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9399.

10.1021/jo990989b CCC: $18.00 
Published on Web 12/03/1999

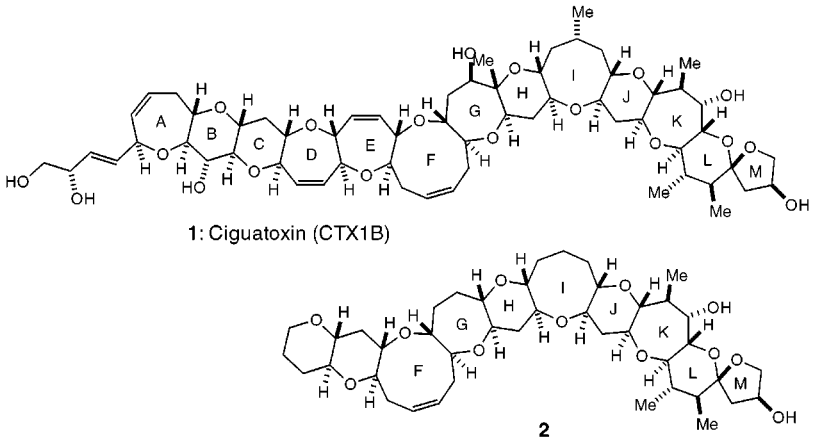



**Figure 1.** Structure of ciguatoxin (CTX1B, **1**) and decacyclic ciguatoxin model compound **2**.

system of ciguatoxin was replaced with a 1,5-dioxadecalin unit (Figure 1).

In this paper, we describe in detail the highly convergent synthesis of the decacyclic ciguatoxin model **2** which features the construction of the fused hexahydrooxonine ring system based on our previously described strategy.[4c,d,h]

## Results and Discussion

**Synthetic Plan.** The retrosynthetic analysis of decacyclic compound **2** is shown in Scheme 1. The *cis* double bond in the hexahydrooxonine ring of **2** was to be introduced in the final stage of the synthesis, because it causes severe broadening in the NMR.[1a−c,4c,h] The construction of the tetrahydrooxocine ring in **2** was envisioned to occur via silver salt-mediated hydroxydithioketal cyclization developed by Nicolaou and co-workers[6] from **3**, which would be formed from aldehyde **4** and phosphonium salt **5** by a Wittig coupling reaction. The latter compound, corresponding to the JKLM ring system, could be easily derived from alcohol **7**.[4j] Construction of the oxonane ring in **4** would be feasible from the *O*-linked oxacycle **6** by our previously developed $SmI_2$-mediated Reformatsky reaction. *O*-Linked oxacycle **6** in turn could be derived via route A or route B through intramolecular reaction of $\gamma$-alkoxyallylsilane with acetal. Route A involves the cyclization to yield oxepane, while route B involves tetrahydropyran formation similar to the previous report.[4c,h]

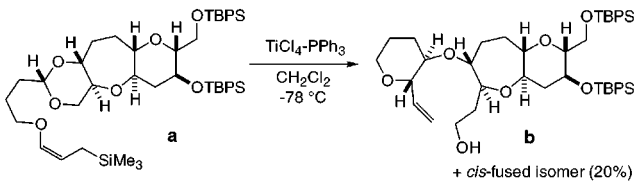
To investigate the feasibility of route A, $\gamma$-alkoxyallylsilanes **12** and **14** were prepared by conventional methods, and each was subjected to Lewis acid-mediated cyclization (Scheme 2). Unfortunately, treatment of **12** and **14** with $TiCl_4-PPh_3$ did not give the desired products **13** and **15** at all. Only oxepanes with the *cis* stereochemistry were obtained in quite low yield (ca. 10%); thus, alternate route B was adopted. Preliminary model experiments revealed that a six-membered acetal ring fused to an oxepane was so stable under acidic conditions that its cyclization with a $\gamma$-alkoxyallylsilane in the presence of Lewis acid would proceed via an $S_N2$ mechanism, leading predominantly to the undesired *anti* product.[7] Thus, seven-membered acetal **9** was defined as the possible precursor for **6**, and the former compound was further traced back to aldehyde **10** and diol **11**.

**Synthesis of the *O*-Linked Oxacycle.** The synthesis of diol **11** began with the known alcohol **16** (Scheme 3), which was obtained from methyl α-D-glucopyranoside in eight steps.[8] Routine protecting group manipulations allowed for its conversion to allyl ether **17** in 68% overall yield through the seven steps. Formation of the alkoxy-substituted allylic anion of **17** using *sec*-BuLi, followed by trapping with $Bu_3SnCl$, gave $\gamma$-alkoxyallylstannane **18** in 88% yield, which was oxidized with $SO_3$·pyridine and DMSO to provide aldehyde **19** (92%). Treatment of

(5) For synthetic work from other laboratories, see: (a) Alvarez, E.; Díaz, M. T.; Pérez, R.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2241. (b) Alvarez, E.; Zurita, D.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2245. (c) Zárraga, M.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2249. (d) Alvarez, E.; Rodríguez, M. L.; Zurita, D.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2253. (e) Suzuki, T.; Sato, O.; Hirama, M.; Yamamoto, Y.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron Lett.* **1991**, *32*, 4505. (f) Sato, O.; Hirama, M. *Synlett* **1992**, 705. (g) Alvarez, E.; Rico, M.; Rodríguez, R. M.; Zurita, D.; Martín, J. D. *Tetrahedron Lett.* **1992**, *33*, 3385. (h) Ravelo, J. L.; Regueiro, A.; Martín, J. D. *Tetrahedron Lett.* **1992**, *33*, 3389. (i) Soler, M. A.; Palazón, J. M.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5471. (j) Tanaka, S.; Isobe, M. *Tetrahedron* **1994**, *50*, 5633. (k) Oka, T.; Murai, A. *Chem. Lett.* **1994**, 1611. (l) Hosokawa, S.; Isobe, M. *Synlett* **1995**, 1179. (m) Oguri, H.; Hishiyama, S.; Oishi, T.; Hirama, M. *Synlett* **1995**, 1252. (n) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1996**, *52*, 12091. (o) Oishi, T.; Shoji, M.; Maeda, K.; Kumahara, N.; Hirama, M. *Synlett* **1996**, 1165. (p) Alvarez, E.; Delgado, M.; Díaz, M. T.; Hanxing, L.; Pérez, R.; Martín, J. D. *Tetrahedron Lett.* **1996**, *37*, 2865. (q) Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.* **1996**, 473. (r) Alvarez, E.; Díaz, M. T.; Hanxing, L.; Martín, J. D. *J. Am. Chem. Soc.* **1995**, *117*, 1437. (s) Atsuta, H.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 307. (t) Oishi, T.; Maeda, K.; Hirama, M. *Chem. Commun.* **1997**, 1289. (u) Oguri, H.; Hishiyama, S.; Sato, O.; Oishi, T.; Hirama, M.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron* **1997**, *53*, 3057. (v) Oishi, T.; Shoji, M.; Kumahara, N.; Hirama, M. *Chem. Lett.* **1997**, 845. (w) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1997**, *38*, 8053. (x) Ami, E.; Kishimoto, H.; Ohrui, H.; Meguro, H. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 2019. (y) Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1. (z) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1998**, *54*, 21. (aa) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1359. (bb) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665. (cc) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37. (dd) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911 and references therein. (ee) Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405. (ff) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Chem. Commun.* **1999**, 1063.

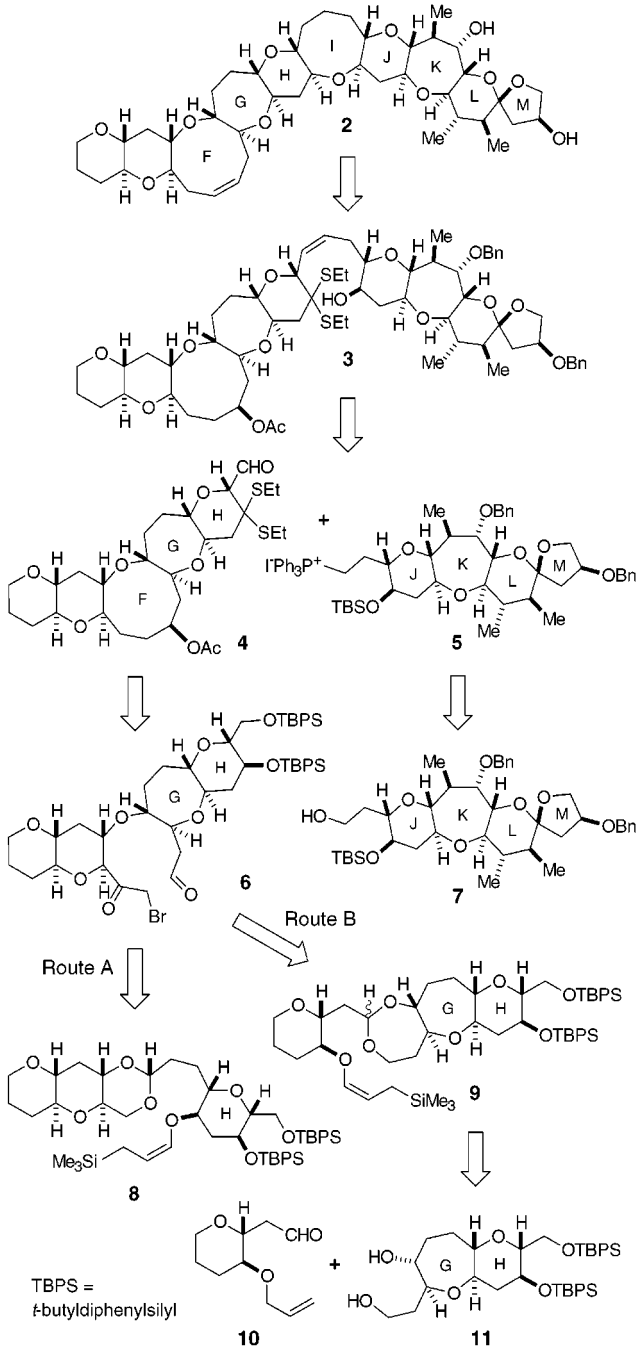
(6) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.

(7) Reaction of $\gamma$-alkoxyallylsilane **a** with $TiCl_4-PPh_3$ ($CH_2Cl_2$, −78 to 0 °C) yielded *O*-linked tricycle **b** with the undesired *anti* stereochemistry in 42% yield together with the *cis*-isomer (20%).

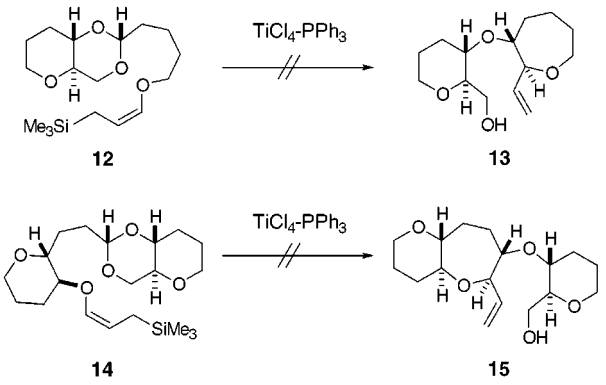



(8) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946.

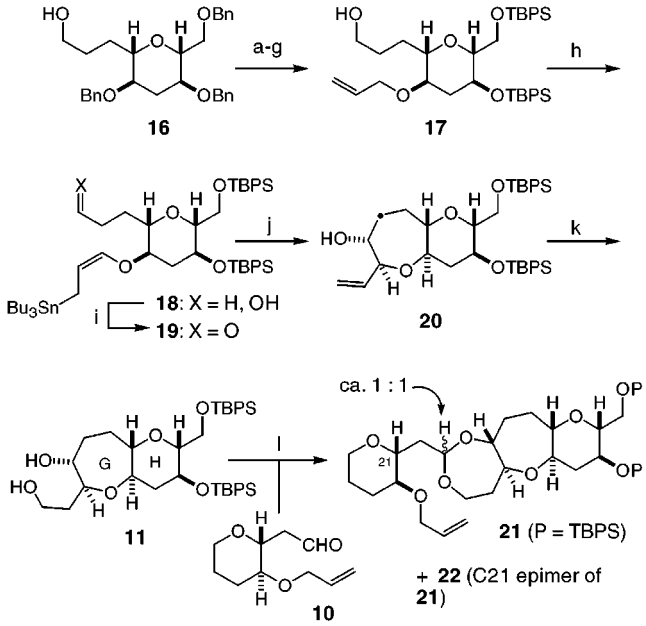
**Scheme 1. Retrosysnthetic Analysis of Decacyclic Ciguatoxin Model 2**




**Scheme 2. Attempts To Construct the Seven-Membered Ring via γ-Alkoxyallylsilane−Acetal Cyclization**




**Scheme 3**[a]




[a] Reagents and conditions: (a) *t*-BuCOCl, DMAP, $Et_3N$, $CH_2Cl_2$, rt, quantitative; (b) $H_2$, $Pd(OH)_2$/C, EtOAc−MeOH; (c) $Me_2C(OMe)_2$, CSA, $CH_2Cl_2$−DMF, 88% (two steps); (d) NaHMDS, allyl bromide, THF−DMF (4:1), 0 °C to rt, 91%; (e) CSA, MeOH; (f) TBPSCl, imidazole, DMF, 65 °C, 91% (two steps); (g) DIBALH, $CH_2Cl_2$, −78 °C, 93%; (h) *sec*-BuLi, $Bu_3SnCl$, THF, −78 °C, 88%; (i) $SO_3$·Pyr, $Et_3N$, DMSO, $CH_2Cl_2$, rt, 92%; (j) $BF_3$·$OEt_2$, $CH_2Cl_2$, −90 °C; (k) 9-BBN−H, THF, rt, then $H_2O_2$, $NaHCO_3$, 94% (two steps); (l) CSA, benzene, 80 °C, 73%.

**19** with $BF_3$·$OEt_2$ provided 6/7-bicyclic alcohol **20** as a single stereoisomer in high yield.[9] Hydroboration of the olefin in **20** using 9-BBN−H, followed by oxidative workup, afforded the desired diol **11** in 94% yield from **19**.

Acetal formation between β-alkoxy aldehyde **10**[10] and diol **11** was carried out in the presence of a catalytic amount of camphorsulfonic acid (CSA; 0.05 equiv) at 80 °C to produce acetal **21** in 73% yield as a 1:1 mixture of diastereomers at the acetal. In this reaction a small amount of the C-21 stereoisomer **22** was also obtained. Epimerization at C-21 indicated that the ring opening of **10** by β-elimination and subsequent ring closure by hetero-Michael addition before acetalization occurred under the reaction conditions.

Having successfully prepared acetal **21**, the intramolecular γ-alkoxyallylsilane−acetal cyclization was next explored (Scheme 4). Metalation of **21** (a 1:1 mixture of diastereomers) with *sec*-BuLi followed by treatment with $Me_3SiCl$ gave γ-alkoxyallyltrimethylsilane **9** as a mixture of diastereomers in 79% yield, along with recovered pure α-H isomer **21α** (16%). Treatment of **9** with $TiCl_4$−$PPh_3$ provided *O*-linked oxacycle **23** with the desired stereochemistry (23*S*,24*R*) as the major product albeit in

(9) (a) Yamada, J.-i.; Asano, T.; Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 6066. (b) Yamamoto Y.; Yamada J.; Kadota I. *Tetrahedron Lett.* **1991**, *32*, 7069. (c) Gevorgyan, V.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 1313. (d) Kadota, I.; Matsukawa, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1638. (e) Kadota, I.; Yamamoto, Y. *Main Group Met. Chem.* **1994**, *17*, 269.

(10) Aldehyde **10** was prepared from tri-*O*-acetyl-D-glucal in 13 steps by a standard sequence of reactions, which is included in the Supporting Information.

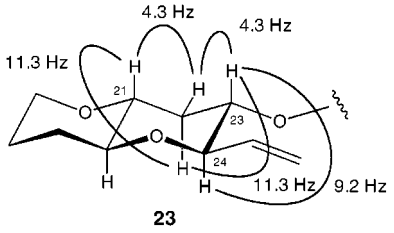



**Figure 2.** Stereochemical assignment of *O*-linked oxacycle **23** based on the proton−proton coupling constants. The stereochemistry at C21 is derived from the chiral center of D-glucose.

**Scheme 4**

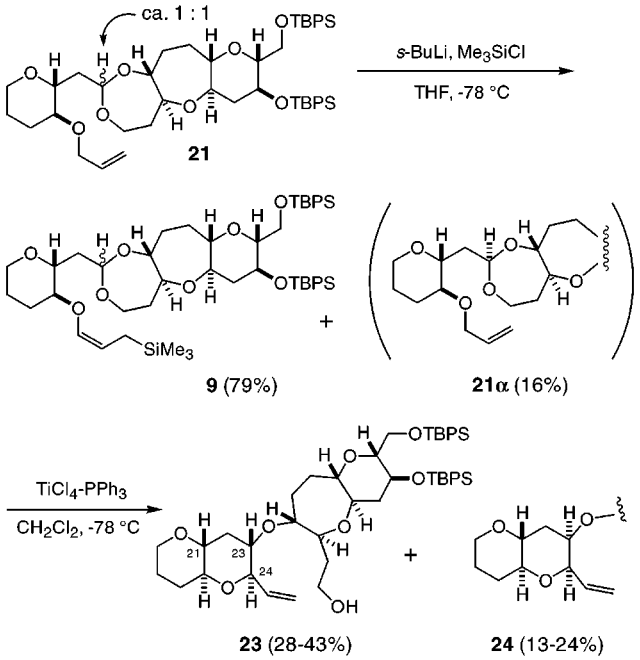



**Table 1. Acetal Formation between Aldehyde 10 and Diol 11**

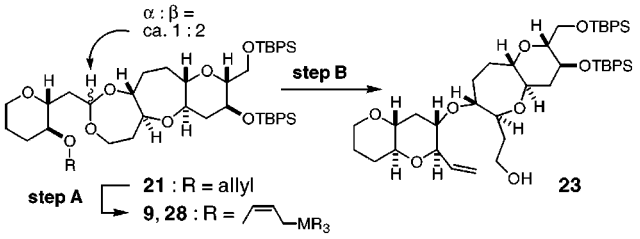
| entry | acid catalyst (equiv) | solvent | temperature | time (h) | % yield | α:β |
|---|---|---|---|---|---|---|
| 1 | CSA (0.05) | benzene | 80 °C | 16 | 73 | 1:1 |
| 2 | CSA (1.0) | $CH_2Cl_2$ | rt | 5 | 75 | 2:3 |
| 3[a] | $Me_3SiOTf$ (1.0) | $CH_2Cl_2$ | −78 °C | 1 | 80 | 1:1 |
| 4 | $Sc(OTf)_3$ (0.1) | benzene | rt | 3 | 90 | 1:2 |

[a] The bis(trimethylsilyl ether) of **11** was used.

modest and variable yields (28−43%), together with the 23*R*,24*R* diastereoisomer **24** (13−24%) and trace amounts of two other stereoisomers. The newly generated stereocenters of the major product **23** were unambiguously determined to be 23*S*,24*R* on the basis of proton−proton coupling constants as illustrated in Figure 2.

To evaluate the difference in the stereoselectivity of this cyclization between the two diastereomers at the acetal position, each isomer was separately subjected to the Lewis acid-mediated reaction (Scheme 5). Sequential treatment of the pure α-H isomer **21α**, obtained as the recovered starting material in the allylsilylation reaction, with *sec*-BuLi and $Me_3SiCl$ produced a mixture of the desired γ-alkoxyallylsilane **9α** (32%), α-alkoxyallylsilane **25** (15%), and a significant amount of the starting material **21α** (25%). This result indicates that the allyl ether portion of **21α** was much more sterically hindered than that of the corresponding β-H isomer. Allylsilane **9α** was separated by column chromatography on silica gel and subjected to $TiCl_4-PPh_3$, yielding the desired **23** in only 29% yield together with three other stereoisomers, **24** (23*R*,24*R*), **26** (23*R*,24*S*), and **27** (23*S*,24*S*), in 28%, 27%, and 13% yields, respectively. Consequently, in the case of the α-H isomer, the desired *O*-linked oxacycle **23** was obtained in only 9% overall yield from allyl ether **21α**. On the other hand, the corresponding β-H isomer **9β**, which was obtained in approximately 75% purity by careful chromatographic separation of the diastereomeric mixture, was subjected to Lewis acid-promoted cyclization to produce the desired **23** in 42% yield as the major product together with a 30% yield of **24**. The significant difference in the diastereoselectivity observed for these isomers, **9α** and **9β**, is not easily understood, but these results indicate that these reactions do not proceed through a complete $S_N1$ mechanism via the oxocarbenium ion intermediate. Unusual steric congestion of the allylsilane moiety in **9α** might have unfavorable effects on the formation of the desired isomer **23**.

**Table 2. γ-Alkoxyallylmetal−Acetal Condensation**




| entry | $MR_3$ | step A[a] % yield | step B[b] % yield |
|---|---|---|---|
| 1 | $SiMe_3$ | 79 (16) | 28 (24) |
| 2 | $SiMe_2Ph$ | 77 (26) | 11 (11) |
| 3 | $Si(i\text{-}Pr)_3$ | 35 (30) | 0 (25) |
| 4 | $SiEt_3$ | 87 (12) | 36 (16) |
| 5[c] | $SnBu_3$ | 67 (20) | 0 (0) |

[a] Numbers in parentheses represent the % yield of recovered **21α**. [b] Numbers in parentheses represent the % yield of *cis*-isomer **23**. [c] $TiCl_3$(O-*i*-Pr) was used as a Lewis acid in step B.

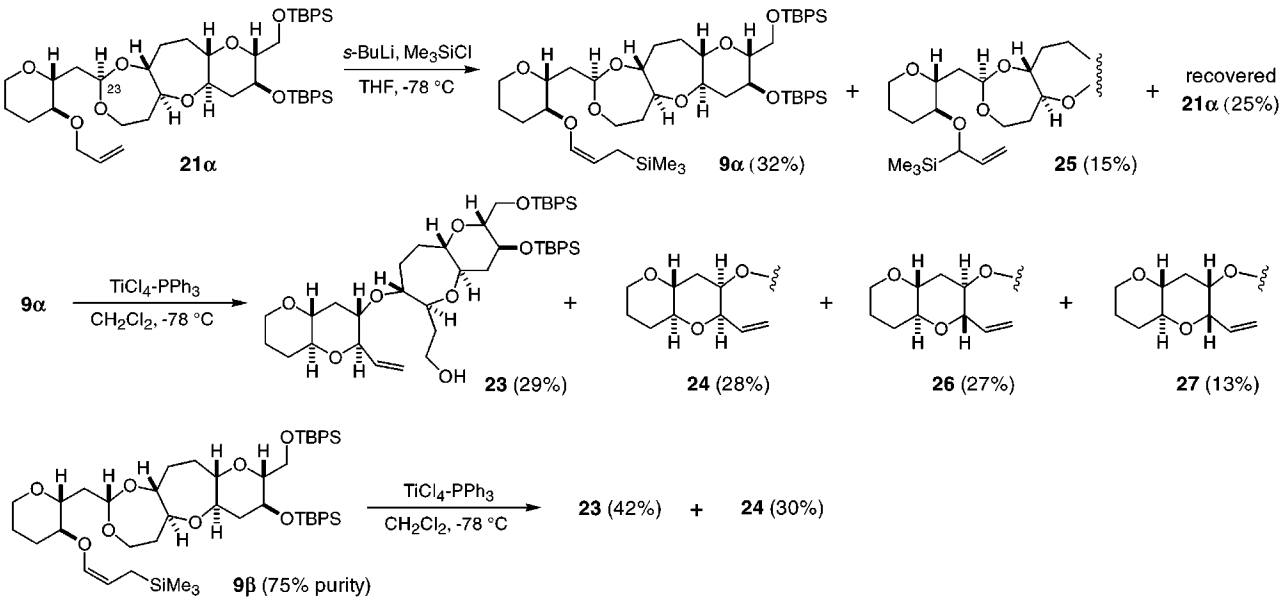
To improve the yield of **23**, selective formation of the more favorable β-H isomer **21β** was next examined (Table 1). Whereas conventional acetalization conditions led to approximately 1:1 mixtures of the acetal isomers (entries 1−3), use of scandium trifluoromethanesulfonate[11] as an acid catalyst enhanced the formation of the β-H isomer (α:β = ca. 1:2, 90% combined yield, entry 4). Moreover, under the reaction conditions in this case, acid-catalyzed epimerization of **10** at the C-21 position due to the ring opening−reclosure was not observed (vide supra).

Next, we investigated the influence of the trialkylmetal groups on this cyclization reaction (Table 2). Allyl anion derived from **21** (α:β = 1:2) was treated with several trialkylmetal chlorides (step A), and the resulting γ-alkoxyallylmetals were subjected to $TiCl_4-PPh_3$-promoted cyclization (step B). A change from trimethylsilane to dimethylphenylsilane decreased the yield of the desired allylsilane, presumably due to the lower nucleophilicity of allyldimethylphenylsilane relative to allyltrimethylsilane (entry 2).[12] In the case of triisopropylsilane and

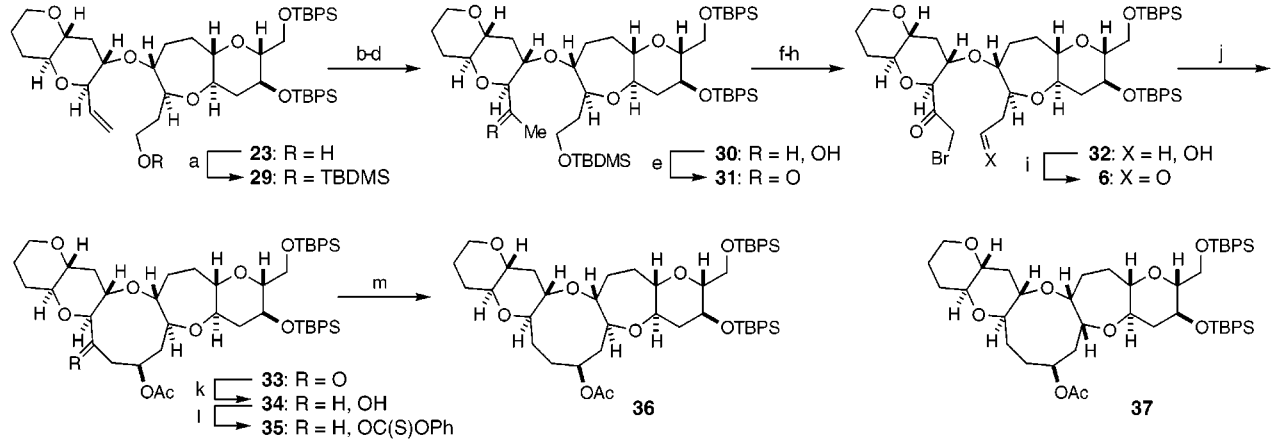
(11) (a) Fukuzawa, S.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077. (b) Ishihara, K.; Karumi, Y.; Kubota, M.: Yamamoto, H. *Synlett* **1996**, 839.

(12) Kadota, I.; Miura, K.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 823 and references therein.

**Scheme 5**




**Scheme 6**[a]




[a] Reagents and conditions: (a) TBDMSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 95%; (b) $OsO_4$, NMO, *t*-BuOH−$H_2O$; (c) $Pb(OAc)_4$, benzene; (d) MeMgBr, THF, −78 to 0 °C, 91% (three steps); (e) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C to rt, 94%; (f) LDA, TMSCl, THF, −78 °C; (g) NBS, THF, 0 °C; (h) CSA, MeOH, rt, 83% (three steps); (i) $SO_3$·Pyr, $Et_3N$, DMSO, $CH_2Cl_2$, 0 °C; (j) $SmI_2$, THF, −78 °C, then $Ac_2O$, DMAP, 0 °C; (k) $NaBH_4$, $CH_2Cl_2$−MeOH, 0 °C; (l) PhOC(S)Cl, DMAP, $CH_3CN$, rt, 66% (five steps); (m) $Bu_3SnH$ (20 equiv), $Et_3B$ (0.2 equiv), benzene, rt, 80%.

tributylstannane, the yields of step A were modest, and none of the desired product was obtained in step B (entries 3 and 5). These results indicate that both the size and nucleophilicity of the trialkylmetal play a significant role in steps A and B. Use of a triethylsilyl group in step A resulted in the formation of allyltriethylsilane **28** ($MR_3$ = $SiEt_3$) in 87% yield (entry 4). Furthermore, in the subsequent step B, allyltriethylsilane **28** ($MR_3$ = $SiEt_3$) afforded the desired **23** as the major product in better yield and reproducibility than in the case of the original γ-allyltrimethylsilane.

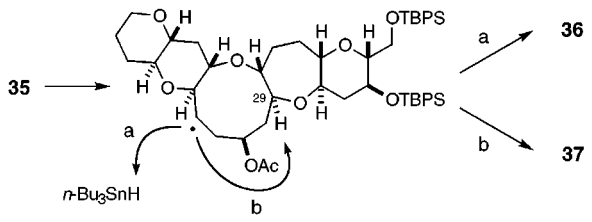
**Synthesis of the FGH Ring Fragment.** With the desired *O*-linked oxacycle **23** in hand, our attention was next focused on the construction of the oxonane ring, which corresponds to ring F of ciguatoxin (Scheme 6). Elaboration of **23** to aldehyde **6**, the requisite cyclization precursor, was carried out in a manner similar to that of the previous report.[4c,d,h] Protection of **23** as its TBDMS ether **29** and oxidative cleavage of the double bond [(1) $OsO_4$(cat.), NMO, acetone−$H_2O$; (2) $Pb(OAc)_4$, benzene] gave an aldehyde, which reacted with methylmagnesium bromide to afford alcohol **30** as a mixture of diastereomers. Swern oxidation of **30** furnished methyl ketone **31** in 81% overall yield from **29**. Enolization of **31** with LDA and subsequent trapping of the enolate with trimethylsilyl chloride provided the silyl enol ether, which was treated with NBS and then desilylated under acidic conditions to provide alcohol **32** in 83% yield for the three steps.

Oxidation of **32** with $SO_3$·pyridine and DMSO led to aldehyde **6**, which was subjected to $SmI_2$-mediated intramolecular Reformatsky reaction under the previously reported optimal conditions.[4c,d,h] Thus, treatment of **6** with 5 equiv of $SmI_2$ in THF at −78 °C gave, after in situ acetylation using $Ac_2O$ and DMAP, β-acetoxy ketone **33** in high yield as a single stereoisomer. When **33** was purified by column chromatography on silica gel, partial β-elimination of the acetoxyl group was observed, giving the *trans*-α,β-unsaturated ketone; therefore, the crude product was immediately reduced with sodium borohy-

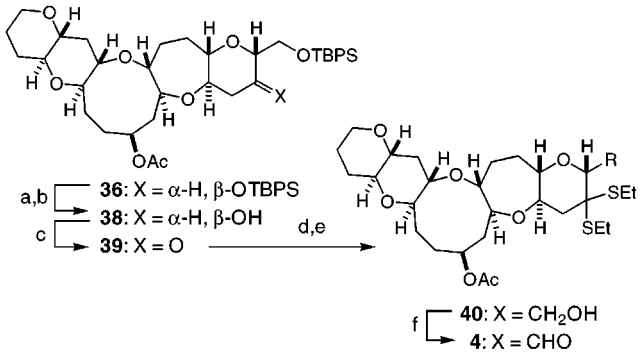
**Table 3. Radical Reduction of Phenylthiocarbonate 35**

| entry | reagents and conditions | % yield of **36** | % yield of **37** |
|---|---|---|---|
| 1 | $Bu_3SnH$ (5 equiv), AIBN (0.2 equiv), benzene, rt to 80 °C | 33 | 36 |
| 2 | $Bu_3SnH$ (5 equiv), AIBN (0.2 equiv), toluene, 80 °C | 26 | 53 |
| 3 | $Bu_3SnH$ (3 equiv), $Et_3B$ (0.2 equiv), benzene, rt | 70 | 24 |
| 4 | $Bu_3SnH$ (20 equiv), $Et_3B$ (0.2 equiv), benzene, rt | 80 | 0 |

**Scheme 7. Radical Reduction of Phenylthiocarbonate 35**




**Scheme 8**[a]




[a] Reagents and conditions: (a) $Bu_4NF$, THF, rt; (b) TBPSCl, imidazole, DMF, 0 °C, 82% (two steps); (c) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C to rt, 94%; (d) EtSH, $TiCl_4$, $CH_2Cl_2$, −78 °C; (e) $Bu_4NF$, THF, rt, 97% (two steps); (f) $SO_3$·Pyr, $Et_3N$, DMSO, $CH_2Cl_2$, 0 °C.

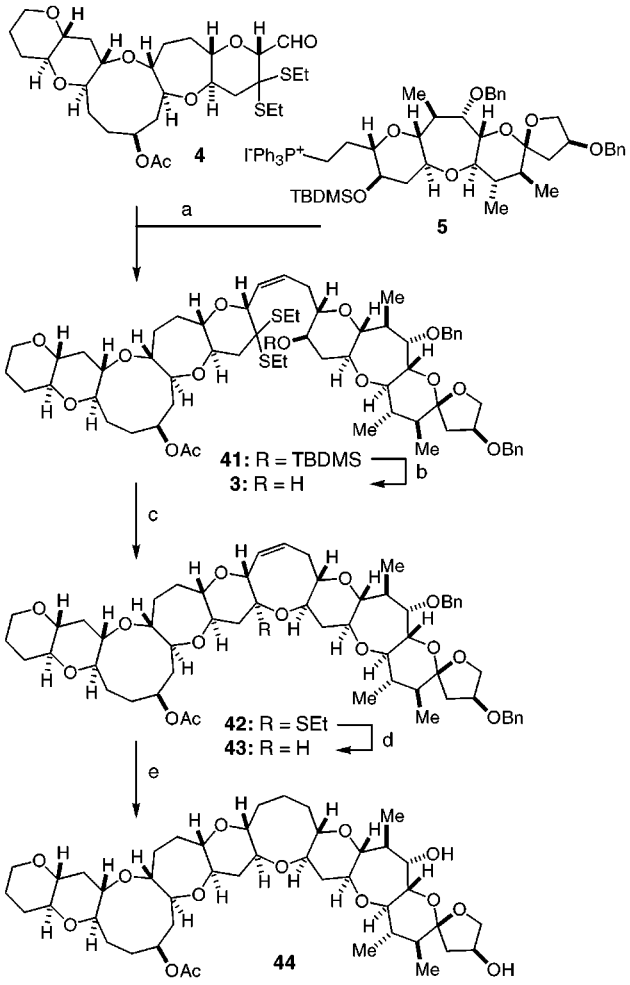
dride to afford **34** as a mixture of diastereomers. The resulting alcohol **34** was then converted to phenyl thiocarbonate **35** in 66% overall yield from **30**.

Subsequent radical reduction of **35** proved to be problematic (Table 3). When the reduction was performed using $Bu_3SnH$ (5 equiv) and AIBN (0.2 equiv) in benzene or toluene at 80 °C, a mixture of the desired product **36** and its C29 isomer **37** was obtained, with the latter being the predominant product (Table 3, entries 1 and 2). Formation of the undesired isomer **37** was presumably due to transannular hydrogen abstraction as shown in Scheme 7. The yield of the desired **36** was improved by carrying out the reaction at room temperature with triethylborane[13] as a radical initiator (entry 3). An optimal result was obtained using a large excess of $Bu_3SnH$ (20 equiv) in the presence of triethylborane (0.2 equiv) in benzene at room temperature (entry 4). It is believed that the higher concentration of $Bu_3SnH$ prevented the competitive intramolecular radical abstraction of the transannular hydrogen. By this method, an 80% yield of acetate **36** was obtained.

**Completion of the Synthesis of Decacyclic Model Compound 2.** Elaboration of bis(silyl ether) **36** to aldehyde **4** is summarized in Scheme 8. Desilylation of **36** using $Bu_4NF$ and selective protection of the hydroxyl

(13) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2578.

**Scheme 9**[a]



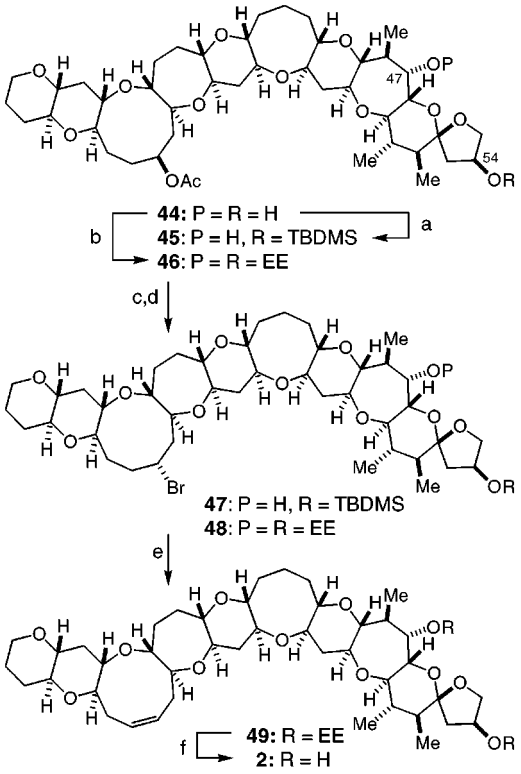

[a] Reagents and conditions: (a) BuLi, THF−HMPA, −78 °C to rt, 63%; (b) $Bu_4NF$, THF, rt, 91%; (c) AgOTf, $NaHCO_3$, 4 Å molecular sieves, silica gel, $CH_3NO_2$, rt, 76% (70% conversion); (d) $Ph_3SnH$ (10 equiv), AIBN(cat.), toluene, 110 °C, then *m*-CPBA, $CH_2Cl_2$, 0 °C, 86%; (e) $H_2$, $Pd(OH)_2$/C, EtOAc−MeOH−AcOH, rt.

group as the *tert*-butyldiphenylsilyl (TBPS) ether provided monosilyl ether **38** (82% yield for the two steps), which was then subjected to Swern oxidation to give ketone **39** in 94% yield. Dithioketal formation from **39** proceeded smoothly in the presence of excess EtSH and $TiCl_4$ to afford, after desilylation with $Bu_4NF$, alcohol **40** in 97% yield for the two steps. Finally, oxidation of the primary hydroxyl group in **40** with $SO_3$·pyridine and DMSO led to the desired aldehyde **4**.

Phosphonium salt **5** was easily prepared from alcohol **7**[4j] by sequential treatment with $I_2$, $PPh_3$, and imidazole followed by excess $PPh_3$ in $CH_3CN$ at 70 °C.

With the requisite aldehyde **4** and phosphonium salt **5** in hand, the stage was then set to couple these fragments and further elaborate toward the target molecule **2** (Scheme 9). Generation of the ylide from phosphonium salt **5** using BuLi in the presence of HMPA in

**Scheme 10**[a]




[a] Reagents and conditions: (a) TBDMSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 84% from **43**; (b) ethyl vinyl ether, PPTS, $CH_2Cl_2$, rt, 99% from **43**; (c) DIBALH, $CH_2Cl_2$, −78 °C; (d) $Ms_2O$, LiBr, *i*-$Pr_2NEt$, $CH_2Cl_2$, 0 °C to rt; (e) KO-*t*-Bu, DMSO, rt, 52% from **46**; (f) PPTS, MeOH, rt, quantitative.

THF followed by addition of aldehyde **4** resulted in the formation of (*Z*)-olefin **41** in 63% yield, which upon treatment with $Bu_4NF$ furnished hydroxy dithioketal **3** in 91% yield. Ring closure of **3** induced by silver trifluoromethanesulfonate gave rise to mixed thioketal **42** in 76% yield (based on 70% conversion), from which the ethylthio group was reductively removed under radical conditions using $Ph_3SnH$−AIBN, leading to decacyclic polyether compound **43** in 86% yield.[6] Subsequent hydrogenation and hydrogenolysis of **43** to obtain diol **44** did not proceed at all, probably due to the contaminant sulfur-containing materials including a trace amount of starting **42**, which might have deactivated the catalyst. As expected, treatment of compound **43** with *m*-CPBA for 1 h at 0 °C prior to hydrogenation led to smooth conversion of **43** to **44**. Hydrogenation of the double bond and simultaneous hydrogenolysis of the benzyl group in **43** were achieved using Pearlman's catalyst in EtOAc−MeOH containing 1% AcOH to give **44** in excellent yield.

With the entire polycyclic ether framework in place, all that remained for the completion of the synthesis of **2** was introduction of a *cis* double bond on the oxonane ring. Since protection of the C47 hydroxyl group (e.g., pivaloyl, *p*-bromobenzoyl, and TBDMS) turned out to be difficult due to its steric hindrance, the selective protection of the C54 hydroxyl group over the one at C47 before introduction of the double bond was attempted (Scheme 10). Selective silylation using TBDMSOTf and 2,6-lutidine at −78 °C gave monosilyl ether **45** in 84% yield from **43**. Deprotection of the acetyl group in **45** with DIBALH, followed by treatment with methanesulfonic anhydride in the presence of lithium bromide and $Et_3N$, smoothly afforded bromide **47**. Unexpectedly, upon exposure to KO-*t*-Bu in DMSO, only trace amounts of the desired compound **2** were obtained presumably due to decomposition of **47** under the basic reaction conditions.[14] This result suggested that a protecting group for both hydroxyl groups at C47 and C54 other than silyl ethers was necessary for the final introduction of the double bond on the oxonane ring. Thus, **44** was protected as its bis(ethoxyethyl ether) **46** under the standard conditions in a quantitative yield. After deacetylation of **46** with DIBALH, the resultant alcohol was treated with methanesulfonic anhydride in the presence of lithium bromide and *i*-$Pr_2NEt$ to give bromide **48** as a single stereoisomer. As expected, exposure of **48** to KO-*t*-Bu in DMSO at room temperature afforded the desired hexahydrooxonine **49** in 52% overall yield for the three steps.[15] Finally, removal of the ethoxyethyl (EE) groups in **49** with PPTS furnished the targeted compound **2** in a quantitative yield.

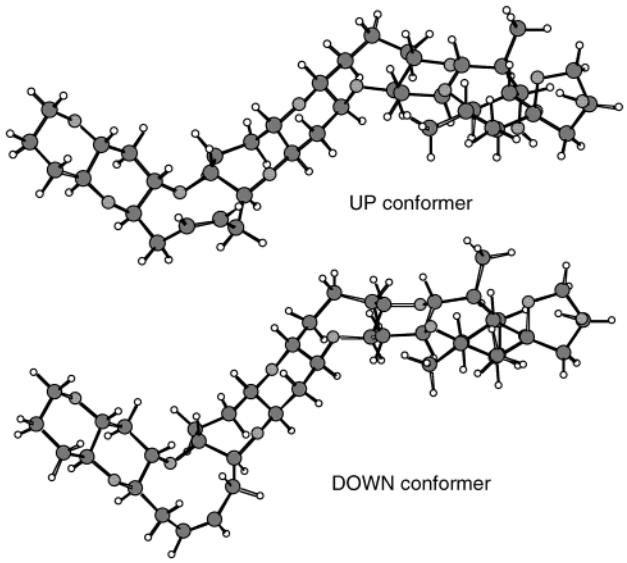
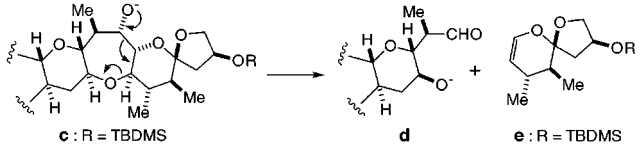



**Figure 3.** UP and DOWN conformers of decacyclic ciguatoxin model compound **2**.

**Conformational Behavior of the Model Compounds Possessing a Hexahydrooxonine Ring.** As was the case with the previous reported 6/9/6-tricyclic system,[4c,h] the $^1H$ and $^{13}C$ NMR signals on the hexahydrooxonine ring in **2** were severely broadened at room temperature, which also closely mimics the ring F of ciguatoxin.[1a−c] The dynamic NMR studies showed that **2** existed as an approximately 1:1 mixture of two conformers. The structures of these two conformers were unambiguously assigned to be UP and DOWN (Figure 3) by virtue of proton−proton coupling constants in pyridine-$d_5$, an observation consistent with that of the tricyclic model.[4c,h] The free energy of activation for this confor-

(14) Alkoxide **c** may suffer from Grob fragmentation to yield another alkoxide **d** and dihydropyran **e**, which lead to further decomposition; see: Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.




(15) The corresponding olefin regioisomer could not be isolated in this reaction.

mational change was estimated to be approximately 14.6 kcal/mol at the coalescence temperature (30 °C) in pyridine-$d_5$ from the chemical shift difference of olefin signals between two conformers. It is worth noting that the deduced conformation of the oxepane ring in **2** agrees well with that of ring G in ciguatoxin, which indicates that the entire shape of decacyclic model **2** would correspond to that of the natural product except for its molecular length.

**Biological Studies.** The biological activity of decacyclic model compound **2** was evaluated. The binding affinity of **2** to VSSC was examined using a competitive inhibition assay with tritiated dihydrobrevetoxin B ([$^3$H]PbTx-3).[16] The model compound **2** did not inhibit the binding of [$^3$H]PbTx-3 to rat brain synaptosomes or VSSC reconstructed in liposome even at concentrations of up to 100 $\mu$M, whereas ciguatoxin inhibits the binding of PbTx-3 at the 100 pM level under similar conditions. Assays at higher levels proved impractical owing to the low solubility of **2** in aqueous media.

Next, to evaluate the action of **2** upon VSSC, [$^{14}$C]guanidinium influx assay using neuroblastoma NB14 cells was carried out.[17] [$^{14}$C]Guanidinium has often been used as a valid model for $^{23}Na^+$ influx, replacing radioisotope $^{23}Na^+$, which is a $\gamma$-light emitter and very difficult to handle in pharmacological experiments. Compound **2** did not stimulate [$^{14}$C]guanidinium ion influx through VSSC at concentrations up to 30 $\mu$M.

Compared with ciguatoxin, the hydroxyl groups in **2** exist only in the right-hand portion of the molecule, which make this molecule detergent-like in structure with an amphiphilic dipole along the longitudinal direction. This amphiphilic nature of **2** may result in its low solubility in membranes due to micelle formation in aqueous media and/or prevent **2** from binding to VSSC with appropriate orientation when bound within membranes. Due to these problems, it appears necessary to devise another assay that efficiently evaluates the biological activity of **2**. Evaluation of noncompetitive binding, a procedure which has not yet been highly studied, is a potential method currently under investigation. Derivatization of **2** at the left side to improve the solubility will also be investigated in the future.

## Conclusion

In conclusion, a convergent synthesis of the decacyclic ciguatoxin model **2**, containing the F−M ring framework of the natural product, has been achieved. The described synthesis demonstrates the power of our strategy for constructing the fused hexahydrooxonine ring system through (i) Lewis acid-mediated intramolecular condensation of $\gamma$-alkoxyallylsilane with acetal to yield *O*-linked oxacycles and (ii) $SmI_2$-mediated intramolecular Reformatsky-type reaction to construct the oxonane ring. The importance of the molecular length and/or the hydrophilicity of the left-hand portion of ciguatoxins for biological activity was also demonstrated. This work will provide the basis for the total synthesis of ciguatoxins as well as their simplified model compounds for further biological evaluation.

(16) Rein, K. S.; Lynn, B.; Gawley, R. E.; Baden, D. G. *J. Org. Chem.* **1994**, *59*, 2107 and references therein.

(17) Tas, P. W. L.; Kress, H-.G.; Koschel, K. *FEBS Lett.* **1985**, *182*, 269.

## Experimental Section[4j]

**Alcohol 17.** A solution of the known alcohol **16**[8] (13.91 g, 29.2 mmol), DMAP (347 mg, 2.84 mmol), and $Et_3N$ (14.0 mL, 100 mmol) in $CH_2Cl_2$ (200 mL) was cooled to 0 °C and treated with pivaloyl chloride (5.6 mL, 45.5 mmol). The mixture was stirred for 2 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (80 mL). The resulting solution was diluted with EtOAc (800 mL) and washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine. Drying ($Na_2SO_4$), filtration, concentration, and flash chromatography (silica gel, EtOAc) gave pivalate ester (17.14 g, quantitative): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.22−7.35 (15H, m), 4.51−4.63 (6H, m), 4.05 (2H, m), 3.73 (1H, dd, $J$ = 10.7, 1.8 Hz), 3.64 (1H, dd, $J$ = 10.7, 4.6 Hz), 3.46 (1H, ddd, $J$ = 11.0, 9.5, 4.6 Hz), 3.35 (1H, ddd, $J$ = 9.5, 4.6, 1.8 Hz), 3.20 (1H, ddd, $J$ = 9.2, 8.5, 2.4 Hz), 3.14 (1H, ddd, $J$ = 10.7, 9.2, 4.3 Hz), 2.69 (1H, ddd, $J$ = 11.3, 4.6, 4.3 Hz), 1.97 (1H, m), 1.84 (1H, m), 1.67 (1H, m), 1.44 (1H, m), 1.41 (1H, ddd, $J$ = 11.3, 11.0, 10.7 Hz), 1.16 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 178.6, 129.0, 128.9, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.7, 127.5, 126.9, 126.8, 80.3, 79.8, 76.1, 73.4, 72.5, 71.1, 70.9, 69.3, 64,6, 35.2, 28.3, 27.2, 27.1, 24.9; HRMS (FAB) calcd for $C_{35}H_{44}O_6Na$ [(M + Na)$^+$] 583.3036, found 583.3038.

To a solution of the above pivalate (17.13 g, 30.6 mmol) in EtOAc−MeOH (1:1, 150 mL) was added 20% $Pd(OH)_2$/C (1.68 g), and the mixture was stirred under hydrogen overnight. Additional 20% $Pd(OH)_2$/C (1.06 g) was added, and the stirring was continued overnight. The catalyst was filtered off, and the solvent was removed under vacuum to give triol, which was used in the following reaction without further purification.

A solution of the triol and 2,2-dimethoxypropane (24 mL, 0.195 mol) in $CH_2Cl_2$−DMF (3:1, 200 mL) was treated with camphorsulfonic acid (0.592 g, 2.55 mmol), and the solution was stirred at room temperature for 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ (300 mL), and the aqueous layer was extracted with EtOAc (500 mL × 2). The organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, 0−60% EtOAc−hexane) to give acetonide (8.47 g, 88% for the two steps): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 4.05 (2H, m), 3.85 (1H, dd, $J$ = 10.7, 5.2 Hz), 3.64 (1H, dd, $J$ = 10.7, 10.7 Hz), 3.54 (1H, ddd, $J$ = 11.3, 9.2, 4.3 Hz), 3.42 (1H, ddd, $J$ = 11.0, 9.2, 4.6 Hz), 3.13 (1H, ddd, $J$ = 10.7, 9.2, 5.2 Hz), 3.12 (1H, ddd, $J$ = 9.2, 6.7, 1.8 Hz), 2.28 (1H, ddd, $J$ = 11.3, 4.6, 4.3 Hz), 1.90 (1H, m), 1.82 (1H, m), 1.63−1.71 (2H, m), 1.48 (1H, ddd, 11.3, 11.3, 11.0 Hz), 1.46 (3H, s), 1.43 (1H, m), 1.38 (3H, s), 1.17 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 178.8, 99.1, 81.9, 74.2, 69.8, 68.9, 64.3, 62.7, 38.9, 38.7, 29.2, 28.1, 27.2, 24.7, 19.1; HRMS (FAB) calcd for $C_{17}H_{30}O_6Na$ [(M + Na)$^+$] 353.1940, found 353.1934.

A solution of the above acetonide (8.46 g, 25.6 mmol) in THF−DMF (4:1, 400 mL) was treated with NaHMDS (1.0 M solution in THF, 31 mL, 31 mmol) at 0 °C, and the mixture was stirred for 30 min at 0 °C. To this solution was added allyl bromide (3.6 mL, 42 mmol) at room temperature, and the solution was stirred for 1 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (100 mL), and the mixture was diluted with EtOAc (1200 mL). The organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (silica gel, 10−30% EtOAc−hexane) gave allyl ether (8.59 g, 91%): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 5.85 (1H, dddd, $J$ = 17.1, 10.4, 5.8, 5.5 Hz), 5.24 (1H, dd, $J$ = 17.1, 0.9 Hz), 5.15 (1H, dd, $J$ = 10.4, 0.9 Hz), 4.07 (1H, dd, $J$ = 12.5, 5.5 Hz), 4.03 (2H, t, $J$ = 6.4 Hz), 3.90 (1H, dd, $J$ = 12.5, 5.8 Hz), 3.85 (1H, dd, $J$ = 10.7, 5.2 Hz), 3.62 (1H, dd, $J$ = 10.7, 10.7 Hz), 3.49 (1H, ddd, $J$ = 11.3, 9.5, 4.3 Hz), 3.21 (1H, ddd, $J$ = 8.9, 8.9, 2.5 Hz), 3.14 (2H, m), 2.38 (1H, ddd, $J$ = 11.3, 4.3, 4.3 Hz), 1.92 (1H, m), 1.81 (1H, m), 1.66 (1H, m), 1.46 (3H, s), 1.41 (1H, ddd, $J$ = 11.3, 11.3, 11.3 Hz), 1.38 (3H, s), 1.36 (1H, m), 1.17 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 178.6, 134.6, 117.2, 99.1, 80.5, 76.3, 74.0, 69.9, 69.0, 64.4, 62.8, 38.7, 35.2, 29.2, 28.4, 27.2, 24.8, 19.1; HRMS (FAB) calcd for $C_{20}H_{34}O_6Na$ [(M + Na)$^+$] 393.2253, found 393.2228.

A solution of the above allyl ether (8.58 g, 23.2 mmol) in

MeOH (400 mL) was treated with camphorsulfonic acid (0.511 g, 2.20 mmol), the solution was stirred at room temperature for 50 min, and then the reaction was quenched with $Et_3N$ (1.0 mL). The mixture was evaporated, and the residue was diluted with EtOAc (1000 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried ($Na_2SO_4$). Filtration and concentration gave the crude diol, which was used in the next reaction without further purification.

A mixed solution of the above diol and imidazole (9.47 g, 139 mmol) in DMF (60 mL) was treated with *tert*-butyldiphenylsilyl chloride (TBPSCl) (18.5 mL, 71.3 mmol) at room temperature. The mixture was heated for 17 h at 65 °C. The resulting solution was poured into $H_2O$ (500 mL), and the aqueous layer was extracted with EtOAc (600 mL × 2). The combined organic layers were washed with brine and dried ($Na_2SO_4$). Filtration, concentration, and flash chromatography (silica gel, 5−20% $Et_2O$−hexane) gave diTBPS ether (18.31 g, 91% for the two steps): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.56−7.68 (8H, m), 7.22−7.41 (12H, m), 5.69 (1H, dddd, $J$ = 17.3, 10.4, 5.7, 5.6 Hz), 5.06 (1H, dddd, $J$ = 17.3, 2.9, 1.4, 1.3 Hz), 5.03 (1H, dddd, $J$ = 10.4, 2.9, 1.4, 1.3 Hz), 4.04 (2H, dd, $J$ = 6.4, 6.4 Hz), 3.99 (1H, dd, $J$ = 11.0, 1.8 Hz), 3.76 (1H, dddd, $J$ = 12.5, 5.8, 1.4, 1.3 Hz), 3.69 (1H, dd, $J$ = 11.0, 6.0 Hz), 3.58−3.64 (2H, m), 3.31 (1H, ddd, $J$ = 9.0, 6.0, 1.8 Hz), 3.09 (1H, ddd, $J$ = 9.2, 8.8, 1.6 Hz), 2.73 (1H, ddd, $J$ = 11.1, 9.2, 4.4 Hz), 2.05 (1H, ddd, $J$ = 11.8, 4.6, 4.4 Hz), 1.83−1.88 (2H, m), 1.66 (1H, m), 1.23−1.33 (2H, m), 1.16 (9H, s), 1.00 (9H, s), 0.95 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 178.6, 135.8, 135.8, 135.8, 135.7, 134.7, 134.3, 134.0, 133.8, 133.4, 129.7, 129.6, 129.6, 129.4, 129.4, 127.6, 127.5, 127.5, 117.0, 82.8, 79.7, 76.0, 69.7, 67.6, 64.5, 63.9, 39.0, 38.7, 31.6, 28.3, 27.2, 26.9, 26.8, 24.8, 22.6, 19.3, 19.2, 14.1; HRMS (FAB) calcd for $C_{49}H_{66}O_6Si_2Na$ [$(M + Na)^+$] 829.4296, found 829.4324.

A solution of the above diTBPS ether (19.01 g, 23.6 mmol) in $CH_2Cl_2$ (150 mL) was cooled to −78 °C and treated with DIBALH (1.0 M solution in toluene, 86 mL, 86 mmol). After being stirred at −78 °C for 3 h, the reaction was quenched with saturated aqueous sodium potassium tartrate (300 mL), and the mixture was vigorously stirred at room temperature until the layers were separated. The resulting solution was diluted with EtOAc (800 mL) and washed with brine. The combined organic layer was dried ($Na_2SO_4$), filtered, and concentrated. Purification by flash chromatography (silica gel, 10−30% EtOAc−hexane) gave alcohol **17** (15.87 g, 93%): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.14−7.62 (20H, m), 5.70 (1H, dddd, $J$ = 17.2, 10.4, 5.8, 5.7 Hz), 5.06 (1H, dd, $J$ = 17.2, 3.1 Hz), 5.05 (1H, dd, $J$ = 10.4, 3.1 Hz), 4.01 (1H, dd, $J$ = 11.0, 1.8 Hz), 3.76 (1H, dddd, $J$ = 12.5, 5.6, 1.2, 1.2 Hz), 3.57−3.67 (4H, m), 3.51 (1H, ddd, $J$ = 11.0, 9.2, 4.6 Hz), 3.38 (1H, ddd, $J$ = 9.2, 6.9, 1.8 Hz), 3.15 (1H, ddd $J$ = 11.1, 9.2, 2.0 Hz), 2.75 (1H, ddd, $J$ = 11.0, 9.2, 4.4 Hz), 2.05 (1H, ddd, $J$ = 11.6, 4.6, 4.4 Hz), 1.92 (1H, m), 1.63−1.74 (3H, m), 1.35 (1H, m), 1.30 (1H, ddd, $J$ = 11.6, 11.1, 11.0 Hz), 1.03 (9H, s), 0.90 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 135.8, 135.8, 135.7, 135.7, 134.7, 134.7, 133.8, 133.8, 129.7, 129.6, 129.5, 129.5, 128.3, 127.6, 127.5, 127.5, 117.1, 107.3, 82.8, 80.8, 75.8, 69.7, 67.8, 64.4, 62.8, 38.9, 29.2, 28.4; HRMS (FAB) calcd for $C_{44}H_{58}O_5Si_2Na$ [$(M + Na)^+$] 745.3721, found 745.3702.

**Oxepane 20.** A solution of alcohol **17** (12.85 g, 17.79 mmol) in THF (200 mL) was cooled to −78 °C and treated with *sec*-BuLi (52.0 mL, 1.03 M solution in cyclohexane, 53.6 mmol). After 20 min at −78 °C, $Bu_3SnCl$ (10.5 mL, 39.0 mmol) was added to this mixture. After being stirred for 1 h at −78 °C, the reaction was quenched with $H_2O$ (50 mL), and the mixture was diluted with EtOAc (600 mL). The organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated. Flash chromatography (silica gel, 10−20% EtOAc−hexane containing 1% $Et_3N$) gave allylstannane **18** (15.91 g, 88%).

A solution of allylstannane **18** (15.91 g, 15.75 mmol) and $Et_3N$ (11 mL, 78.9 mmol) in $CH_2Cl_2$−DMSO (220 mL, 10:1) was cooled to 0 °C and treated with sulfur trioxide·pyridine complex (10.25 g, 64.40 mmol). The mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature, and the stirring was continued for 1.5 h. The resulting solution was diluted with EtOAc (600 mL), washed with $H_2O$, saturated aqueous $NaHCO_3$, and brine, and dried ($Na_2SO_4$). Filtration, concentration, and flash chromatography (silica gel, 10−20% EtOAc−hexane containing 1% $Et_3N$) gave aldehyde **19** (14.63 g, 92%).

A solution of the aldehyde **19** (14.63 g, 14.51 mmol) in $CH_2Cl_2$ (200 mL) was cooled to −90 °C and treated with boron trifluoride etherate (2.2 mL, 17.9 mmol). After being stirred for 30 min at −90 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL) and allowed to warm to room temperature. To this mixture was added saturated aqueous KF (200 mL), and the resulting solution was vigorously stirred overnight. The aqueous layer was extracted with EtOAc (800 mL). The organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), filtered, and concentrated. Flash chromatography (silica gel, 20−30% EtOAc−hexane) gave oxepane **20** (12.74 g), which was used in the following reaction without further purification: $^1$H NMR ($C_6D_6$, 500 MHz) $\delta$ 7.92−7.87 (4H, m), 7.72−7.68 (4H, m), 7.27−7.12 (12H, m), 5.71 (1H, ddd, $J$ = 17.1, 10.7, 5.2 Hz), 5.15 (1H, ddd, $J$ = 17.1, 1.5, 1.5 Hz), 4.91 (1H, ddd, $J$ = 10.7, 1.5, 1.5 Hz), 4.22 (1H, dd, $J$ = 11.0, 1.8 Hz), 3.92 (1H, dd, $J$ = 11.0, 5.8 Hz), 3.84 (1H, ddd, $J$ = 11.0, 9.2, 4.9 Hz), 3.51 (1H, m), 3.49 (1H, m), 3.36 (1H, m), 3.02 (1H, ddd, $J$ = 9.2, 9.2, 4.9 Hz), 2.94 (1H, ddd, $J$ = 11.3, 9.2, 4.0 Hz), 2.33 (1H, ddd, $J$ = 11.6, 4.6, 4.6 Hz), 1.88−1.49 (5H, m), 1.21 (9H, s), 1.09 (9H, s); $^{13}$C NMR ($C_6D_6$, 125 MHz) $\delta$ 138.4, 136.4, 136.24 (x 2), 136.20, 134.6, 134.4, 134.3, 133.8, 130.02, 129.99, 129.8, 129.7, 128.5, 128.4, 128.3, 127.9, 114.6, 86.0, 83.3, 82.5, 79.6, 73.8, 68.3, 64.8, 41.6, 29.1, 27.2 (×2), 27.0, 19.7, 19.5.

**Diol 11.** A solution of oxepane **20** (12.74 g) in THF (120 mL) was cooled to 0 °C and treated with 9-BBN−H (110 mL, 0.5 M solution in THF, 55 mmol), and the mixture was stirred for 2 h at room temperature. The solution was recooled to 0 °C, and the reaction was quenched with $H_2O$ (10 mL). To the mixture were added saturated aqueous $NaHCO_3$ (80 mL) and 30% $H_2O_2$ (80 mL) at 0 °C. The resulting solution was stirred for 1 h at room temperature and diluted with EtOAc (700 mL). The organic layer was washed with $H_2O$, saturated aqueous $Na_2SO_3$, saturated aqueous $NaHCO_3$, and brine. Drying ($Na_2SO_4$), filtration, concentration, and flash chromatography (silica gel, 30−65% EtOAc−hexane) gave alcohol **11** (94% for two steps): $[\alpha]^{27}_D = +12.0°$ ($c$ 1.38, $CHCl_3$); IR (film) 3365 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.67−7.26 (20H, m, $Si(C_6H_5)_2$), 3.95 (1H, dd, $J$ = 11.3, 1.8 Hz, 38-H), 3.72 (1H, m, 30-H), 3.69−3.60 (5H, m, 27-$H_2$, 38-$H_2$, 36-H), 3.35 (1H, ddd, $J$ = 8.2, 6.4, 4.3 Hz, 29-H), 3.30 (1H, ddd, $J$ = 9.2, 5.8, 1.8 Hz, 37-H), 2.99 (1H, ddd, $J$ = 9.2, 8.9, 3.4 Hz, 33-H), 2.90 (1H, ddd, $J$ = 11.6, 9.2, 4.0 Hz, 34-H), 1.96 (1H, ddd, $J$ = 11.6, 4.6, 4.6 Hz, 35-H), 1.84−1.65 (6H, m, 28-$H_2$, 31-$H_2$, 32-$H_2$), 1.45 (1H, ddd, $J$ = 11.6, 11.6, 11.3 Hz, 35-H), 1.00 (9H, s, $SiC_4H_9$), 0.96 (9H, s, $SiC_4H_9$); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 135.88, 135.84, 135.80, 135.7, 134.1, 133.92, 133.88, 133.4, 129.70, 129.67, 129.4, 129.3, 127.7, 127.5, 127.42, 127.37, 85.4, 82.8, 81.6, 80.8, 74.6, 67.6, 64.0, 60.8, 40.8, 37.3, 29.9, 26.9, 26.8, 26.4, 19.3, 19.2; HRMS (FAB) calcd for $C_{44}H_{58}O_6Si_2Na$ [$(M + Na)^+$] 761.3670, found 761.3667.

**Acetal 21.** A solution of aldehyde **10** (3.00 g, 17.85 mmol) and diol **11** (10.14 g, 13.73 mmol) in dry benzene (150 mL) was treated with scandium trifluoromethanesulfonate (676 mg, 1.37 mmol) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was diluted with EtOAc (500 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated to afford an inseparable mixture of acetal and the recovered aldehyde **10**. This crude residue was dissolved in MeOH−$CH_2Cl_2$ (1:1, 150 mL), and the solution was treated with sodium borohydride (700 mg, 18.5 mmol) and stirred at 0 °C for 10 min. The reaction was quenched with saturated aqueous $NH_4Cl$ (100 mL), and the aqueous layer was extracted with $CHCl_3$ (120 mL × 4). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. Flash chromatography (20% EtOAc−hexane) gave acetal **21** (10.04 g, 82%) as an inseparable mixture of diastereomers ($\alpha$: $\beta$ = 1:2): IR (film) 3070, 2933, 2856, 1427, 1081, 741, 704, 507 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) ($\alpha$-isomer) $\delta$ 7.67−7.26 (20H, m), 5.86 (1H, dddd, $J$ = 17.1, 10.4,

5.5, 5.5 Hz), 5.23 (1H, dddd, $J$ = 17.1, 1.5, 1.5, 1.5 Hz), 5.13 (1H, dddd, $J$ = 10.4, 1.5, 1.5, 1.5 Hz), 4.88 (1H, dd, $J$ = 8.9, 2.5 Hz), 4.09 (1H, dddd, $J$ = 12.8, 5.5, 1.5, 1.5 Hz), 3.92 (1H, dd, $J$ = 11.0, 1.8 Hz), 3.88 (1H, dddd, $J$ = 12.8, 5.5, 1.5, 1.5 Hz), 3.81 (2H, m, 17-H), 3.79 (1H, m), 3.69 (1H, dd, $J$ = 11.0, 5.5 Hz), 3.66 (1H, m), 3.44 (1H, dd, $J$ = 11.6, 11.6 Hz), 3.31 (1H, ddd, $J$ = 11.6, 11.6, 2.4 Hz), 3.29 (1H, m), 3.27 (1H, m), 3.22 (1H, ddd, $J$ = 9.8, 9.8, 1.8 Hz), 3.00 (1H, ddd, $J$ = 9.2, 9.2, 4.3 Hz), 2.97 (1H, ddd, $J$ = 10.4, 9.8, 4.3 Hz), 2.89 (1H, ddd, $J$ = 11.6, 9.2, 3.7 Hz), 2.19 (1H, m), 2.12 (1H, ddd, $J$ = 14.3, 8.9, 1.8 Hz), 2.02 (1H, ddd, $J$ = 11.6, 4.3, 4.3 Hz), 1.89−1.44 (10H, m), 1.33 (1H, dddd, $J$ = 12.5, 12.5, 10.4, 4.9 Hz), 0.99 (9H, s), 0.95 (9H, s); $^1$H NMR ($CDCl_3$, 500 MHz) ($\beta$-isomer) $\delta$ 7.67−7.26 (20H, m), 5.86 (1H, m), 5.22 (1H, dddd, $J$ = 17.1, 1.8, 1.2, 1.2 Hz), 5.12 (1H, dddd, $J$ = 10.1, 1.8, 1.2, 1.2 Hz), 4.92 (1H, dd, $J$ = 8.6, 2.8 Hz), 4.06 (1H, m), 3.93 (1H, dd, $J$ = 11.0, 1.5 Hz), 3.88 (1H, m), 3.82 (1H, m), 3.71−3.62 (4H, m), 3.54 (1H, ddd, $J$ = 12.5, 4.0, 4.0 Hz), 3.34−3.26 (3H, m), 3.20 (1H, m), 3.00 (1H, m), 2.98 (1H, m), 2.89 (1H, m), 2.19 (1H, m), 2.13 (1H, m), 2.02 (1H, m), 1.88−1.47 (10H, m), 1.33 (1H, m), 0.99 (9H, s), 0.96 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) ($\alpha$-isomer) $\delta$ 135.94, 135.85, 135.81, 135.7, 135.0, 134.1, 134.0, 133.8, 133.3, 129.7, 129.6, 129.4, 129.3, 127.6, 127.5, 127.4, 127.36, 116.4, 99.1, 83.9, 82.9, 82.6, 80.9, 77.5, 77.1, 72.0, 69.7, 67.8, 67.5, 63.9, 63.7, 40.8, 36.3, 36.1, 29.7, 29.3, 27.8, 26.9, 26.8, 25.3, 19.3, 19.2; $^{13}$C NMR ($CDCl_3$, 125 MHz) ($\beta$-isomer) $\delta$ 135.9, 135.82, 135.80, 135.7, 135.1, 134.2, 134.0, 133.8, 133.3, 129.7, 129.6, 129.4, 129.3, 127.6, 127.48, 127.39, 127.34, 116.7, 99.7, 83.2, 82.8, 82.2, 80.7, 80.3, 77.2, 69.9, 67.7, 67.5, 63.9, 58.3, 40.8, 36.4, 36.2, 29.8, 29.4, 27.81, 27.77, 26.9, 26.8, 25.4, 19.3, 19.2; HRMS (FAB) calcd for $C_{54}H_{72}O_8Si_2Na$ [(M + Na)$^+$] 927.4663, found 927.4650.

**Allyltriethylsilane 28.** A solution of acetal **21** (9.22 g, 10.38 mmol, $\alpha$:$\beta$ = 1:2) in THF (150 mL) was cooled to −78 °C and treated with *sec*-BuLi (1.03 M solution in cyclohexane, 12.0 mL, 14.1 mmol). After 20 min at −78 °C, triethylsilyl chloride (2.0 mL, 11.9 mmol) was added to this mixture. After the reaction mixture was stirred at −78 °C for 20 min, the reaction was quenched with $H_2O$ (30 mL), and the mixture was diluted with EtOAc (500 mL). The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. Chromatography (10−20% EtOAc−hexane) gave allyltriethylsilane **28** (9.03 g, 87%) as an inseparable mixture of diastereomers ($\alpha$:$\beta$ = ca. 1:4) along with the recovered acetal **21α** (1.16 g, 12%). Data for the $\beta$-isomer of **28**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.67−7.26 (20H, m), 5.85 (1H, d, $J$ = 6.1 Hz), 4.93 (1H, dd, $J$ = 8.6, 3.1 Hz), 4.29 (1H, ddd, $J$ = 8.6, 8.6, 6.1 Hz), 3.92 (1H, dd, $J$ = 11.3, 1.8 Hz), 3.82 (1H, m), 3.67 (1H, dd, $J$ = 11.3, 5.5 Hz), 3.63 (3H, m), 3.52 (1H, ddd, $J$ = 12.8, 4.3, 4.3 Hz), 3.33−3.18 (5H, m), 2.99 (1H, ddd, $J$ = 8.2, 8.2, 4.3 Hz), 2.88 (1H, m), 2.12−1.23 (16H, m), 0.99 (9H, s), 0.95 (9H, s), 0.91 (9H, t, $J$ = 7.9 Hz), 0.49 (6H, q, $J$ = 7.9 Hz).

**Tetracyclic *O*-Linked Oxacycle 23.** A solution of triphenylphosphine (7.09 g, 27.1 mmol) in $CH_2Cl_2$ (100 mL) was cooled to −78 °C and treated with $TiCl_4$ (3.0 mL, 27.4 mmol), and the resulting mixture was stirred at −78 °C for 10 min. A solution of allyltriethylsilane **28** (9.03 g, 9.01 mmol) in $CH_2Cl_2$ (75 mL) was added dropwise over 10 min to this solution. The resulting mixture was stirred at −78 °C for 30 min and at 0 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc−$Et_2O$ (4:1, 500 mL). The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (30−60% EtOAc−hexane) gave tetracyclic ether **23** (2.09 g, 36%) and its diastereoisomer **24** (1.33 g, 16%). Data for **23**: $[\alpha]^{29}_D$ = +12.2° (*c* 0.81, $CHCl_3$); IR (film) 3475 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.67−7.26 (20H, m), 5.74 (1H, ddd, $J$ = 17.4, 10.7, 7.0 Hz), 5.26 (1H, d, $J$ = 17.4 Hz), 5.10 (1H, d, $J$ = 10.7 Hz), 3.94 (1H, dd, $J$ = 11.3, 1.8 Hz), 3.88 (1H, m), 3.65 (1H, dd, $J$ = 11.3, 6.1 Hz), 3.60−3.56 (4H, m), 3.45 (1H, m), 3.42 (1H, m), 3.34 (1H, ddd, $J$ = 11.6, 11.6, 4.6 Hz), 3.26 (1H, ddd, $J$ = 9.2, 6.1, 1.8 Hz), 3.10 (1H, ddd, $J$ = 11.0, 9.2, 4.3 Hz), 3.00 (1H, ddd, $J$ = 11.3, 8.9, 4.6 Hz), 2.95−2.89 (3H, m), 2.30 (1H, ddd, $J$ = 11.3, 4.3, 4.3 Hz), 2.04 (1H, m), 1.91 (1H, ddd, $J$ = 11.6, 4.3, 4.3 Hz), 1.81 (1H, m), 1.74 (2H, m), 1.69−1.64 (3H, m), 1.59 (1H, m), 1.53 (1H, m), 1.47 (1H, ddd, $J$ = 11.3, 11.3, 11.0 Hz), 1.40 (2H, m), 0.99 (9H, s), 0.95 (9H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 135.93, 135.89, 135.83, 135.79, 135.67, 134.1, 133.9, 133.8, 133.4, 129.69, 129.67, 129.4, 129.3, 127.6, 127.5, 127.43, 127.38, 118.7, 83.9, 82.5, 82.0, 81.8, 81.0, 79.2, 77.3, 76.5, 76.4, 67.8, 67.5, 63.9, 61.1, 40.8, 37.3, 37.1, 29.2, 26.9, 26.8, 26.0, 25.40, 25.36, 19.3, 19.2; HRMS (FAB) calcd for $C_{54}H_{72}O_8Si_2Na$ [(M + Na)$^+$] 927.4663, found 927.4665. Data for **24**: $[\alpha]^{29}_D$ = −5.1° (*c* 2.32, $CHCl_3$); IR (film) 3444 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.68−7.27 (20H, m), 5.90 (1H, ddd, $J$ = 17.4, 10.7, 6.7 Hz), 5.26 (1H, d, $J$ = 17.4 Hz), 5.15 (1H, d, $J$ = 10.7 Hz), 3.94 (1H, dd, $J$ = 11.3, 1.8 Hz), 3.91 (1H, br d), 3.87 (1H, m), 3.65 (1H, dd, $J$ = 11.3, 5.8 Hz), 3.62 (3H, m, 27-$H_2$), 3.54 (1H, br), 3.46 (1H, ddd, $J$ = 9.5, 6.7, 3.1 Hz), 3.39 (1H, m), 3.37 (1H, m), 3.27 (1H, ddd, $J$ = 9.2, 5.8, 1.8 Hz), 3.23 (1H, ddd, $J$ = 11.9, 9.2, 4.3 Hz), 3.07 (1H, ddd, $J$ = 11.0, 9.2, 4.3 Hz), 2.93 (1H, ddd, $J$ = 9.8, 9.8, 4.3 Hz), 2.86 (1H, ddd, $J$ = 11.3, 9.8, 4.3 Hz), 2.12 (1H, ddd, $J$ = 14.0, 7.0, 4.0 Hz), 2.02 (1H, m), 1.91 (1H, ddd, $J$ = 11.3, 4.3, 4.3 Hz), 1.83−1.44 (10H, m), 1.41 (1H, ddd, $J$ = 11.3, 11.3, 11.3 Hz), 0.99 (9H, s), 0.95 (9H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 135.9 (×2), 135.82, 135.78, 135.71, 134.1, 133.9, 133.8, 133.4, 127.9 (×2), 129.4, 129.3, 127.7, 127.6, 127.40, 127.35, 116.9, 84.3, 82.7, 81.9, 81.5, 81.3, 80.1, 78.3, 74.1, 74.0, 68.2, 67.7, 64.0, 61.1, 40.7, 36.9, 33.0, 29.2, 26.9, 26.8, 26.3, 25.7, 24.2, 19.3, 19.2; HRMS (FAB) calcd for $C_{54}H_{72}O_8Si_2Na$ [(M + Na)$^+$] 927.4663, found 927.4671.

**TBDMS Ether 29.** A solution of tetracyclic ether **23** (3.16 g, 3.56 mmol) in $CH_2Cl_2$ (40 mL) was cooled to 0 °C and treated sequentially with 2,6-lutidine (0.92 mL, 7.90 mmol) and TBDMSOTf (0.90 mL, 3.92 mmol). After the reaction mixture was stirred at 0 °C for 30 min, the reaction was quenched with MeOH (0.5 mL). The mixture was diluted with EtOAc (200 mL) and $Et_2O$ (40 mL), washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (10−20% EtOAc−hexane) gave TBDMS ether **29** (3.4578 g, 95%): $[\alpha]^{28}_D$ = +24.9° (*c* 0.36, $CHCl_3$); IR (film) 2931, 2856, 1427, 1257, 1111, 1007, 837, 704 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.67−7.25 (20H, m), 5.76 (1H, ddd, $J$ = 17.1, 10.4, 6.4 Hz), 5.24 (1H, d, $J$ = 17.1 Hz), 5.04 (1H, d, $J$ = 10.4 Hz), 3.93 (1H, dd, $J$ = 11.3, 1.8 Hz), 3.88 (1H, m), 3.68 (1H, dd, $J$ = 11.3, 5.5 Hz), 3.59 (1H, m), 3.58 (1H, m), 3.50 (2H, m), 3.40 (2H, m), 3.34 (1H, ddd, $J$ = 11.3, 11.3, 4.3 Hz), 3.26 (1H, ddd, $J$ = 8.9, 5.5, 1.8 Hz), 3.11 (1H, ddd, $J$ = 11.0, 8.9, 4.3 Hz), 3.00 (1H, ddd, $J$ = 11.0, 8.9, 4.3 Hz), 2.95−2.87 (3H, m), 2.32 (1H, ddd, $J$ = 11.6, 4.6, 4.3 Hz), 2.04 (1H, m), 1.96 (1H, ddd, $J$ = 11.6, 4.0, 4.0 Hz), 1.80−1.37 (11H, m), 0.99 (9H, s), 0.95 (9H, s), 0.81 (9H, s), −0.07 (3H, s), −0.11 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 135.94 (×2), 135.86, 135.78, 135.70, 134.2, 134.1, 133.8, 133.4, 129.7, 129.6, 129.4, 129.3, 127.6, 127.43 (×2), 127.37, 118.3, 82.5, 81.9, 81.6, 81.4, 79.9, 78.8, 77.3, 76.6, 76.5, 67.8, 67.6, 64.0, 59.5, 40.8, 38.2, 37.1, 29.3, 26.92, 26.85, 26.1, 25.9, 25.8, 25.4, 19.3, 19.2, 18.2, −5.4 (×2); HRMS (FAB) calcd for $C_{60}H_{86}O_8Si_3Na$ [(M + Na)$^+$] 1041.5528, found 1041.5521.

**Alcohol 30.** A solution of TBDMS ether **29** (2.972 g, 2.916 mmol) and *N*-methylmorpholine *N*-oxide (50% in $H_2O$, 2.05 g, 8.75 mmol) in *t*-BuOMe−*t*-BuOH−$H_2O$ (1:1:1, 66 mL) was treated with $OsO_4$ (75.0 mg, 0.295 mmol). The mixture was stirred at room temperature overnight and diluted with EtOAc (250 mL). The organic layer was washed with saturated aqueous $Na_2SO_3$, $H_2O$, and brine, dried ($Na_2SO_4$), and concentrated to give crude diol.

A solution of the crude diol in benzene (40 mL) was treated with $Pb(OAc)_4$ (1.94 g, 4.38 mmol), and the resulting mixture was stirred at room temperature for 30 min. The mixture was diluted with EtOAc (250 mL), washed with $H_2O$, saturated aqueous $Na_2SO_3$, saturated aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated to give crude aldehyde.

A solution of the crude aldehyde in THF (40 mL) was cooled to −78 °C and treated with methylmagnesium bromide (3.0 M solution in $Et_2O$, 3.0 mL, 9.0 mmol). The mixture was stirred at −78 °C for 20 min and then at 0 °C for 30 min. The reaction was quenched with saturated aqueous $NH_4Cl$ (10 mL), and the mixture was diluted with EtOAc (250 mL). The organic

layer was washed with brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (30% EtOAc−hexane) gave alcohol **30** as a 5:1 mixture of diastereoisomers (2.778 g, 91% for the three steps): $[\alpha]^{29}_D = +6.37°$ (*c* 1.55, $CHCl_3$); IR (film) 3479 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) (major isomer) $\delta$ 7.65−7.25 (20H, m), 3.94 (1H, m), 3.93 (1H, br d, $J$ = 11.0 Hz), 3.88 (1H, m), 3.64 (1H, dd, $J$ = 11.0, 5.8 Hz), 3.60 (1H, ddd, $J$ = 11.0, 9.2, 4.9 Hz), 3.54 (1H, m), 3.51−3.45 (3H, m), 3.40−3.20 (3H, m), 2.99−2.92 (3H, m), 2.87 (1H, ddd, $J$ = 11.3, 8.9, 4.0 Hz), 2.79 (1H, ddd, $J$ = 11.9, 9.2, 4.3 Hz), 2.35 (1H, ddd, $J$ = 11.3, 4.3, 4.3 Hz), 2.03−1.36 (13H, m), 1.20 (1H, d, $J$ = 6.4 Hz), 0.99 (9H, s), 0.96 (9H, s), 0.81 (9H, s), −0.06 (3H, s), −0.10 (3H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) (major isomer) $\delta$ 135.92, 135.87, 135.78, 135.69, 134.2, 134.0, 133.8, 133.5, 129.7, 129.6, 129.4, 129.3, 127.6, 127.5, 127.42, 127.38, 83.0, 82.7, 82.4, 81.9, 81.2, 80.7, 77.6, 76.7, 73.2, 67.8, 67.7, 64.7, 64.1, 59.6, 40.8, 38.4, 37.2, 29.2, 27.3, 26.93, 26.85, 26.4, 25.9, 25.4, 20.4, 19.3, 19.2, 18.2, −5.4, −5.5; HRMS (FAB) calcd for $C_{60}H_{88}O_9Si_3Na$ [$(M + Na)^+$] 1059.5634, found 1059.5643.

**Methyl Ketone 31.** A solution of oxalyl chloride (540 $\mu$L, 6.21 mmol) in $CH_2Cl_2$ (20 mL) was cooled to −78 °C and treated with DMSO (890 $\mu$L, 12.5 mmol). The resulting solution was stirred at −78 °C for 10 min. To the solution was added dropwise via cannula a solution of alcohol **30** (3.21 g, 3.09 mmol) in $CH_2Cl_2$ (20 mL). After being stirred at −78 °C for 30 min, the mixture was treated with $Et_3N$ (3.5 mL, 25.1 mmol) and allowed to warm to room temperature. The solution was stirred at room temperature for 30 min and diluted with EtOAc−$Et_2O$ (4:1, 250 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 methyl ketone **31** (3.02 g, 94%): $[\alpha]^{29}_D = +2.9°$ (*c* 0.98, $CHCl_3$); IR (film) 1730 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.67−7.25 (20H, m), 3.93 (1H, dd, $J$ = 11.0, 1.5 Hz), 3.88 (1H, br d, $J$ = 11.6 Hz), 3.72 (1H, d, $J$ = 9.2 Hz), 3.62 (1H, dd, $J$ = 11.0, 5.8 Hz), 3.57 (1H, ddd, $J$ = 11.0, 9.2, 4.6 Hz), 3.50 (1H, m), 3.45 (2H, m), 3.41 (1H, m), 3.34 (1H, ddd, $J$ = 11.6, 8.9, 6.4 Hz), 3.28 (2H, m), 3.01 (1H, ddd, $J$ = 10.7, 8.9, 4.3 Hz), 2.93 (2H, m), 2.76 (1H, ddd, $J$ = 11.6, 9.2, 4.3 Hz), 2.39 (1H, ddd, $J$ = 11.6, 4.6, 4.6 Hz), 2.17 (3H, s), 2.02 (1H, m), 1.99 (1H, ddd, $J$ = 11.6, 4.6, 4.3 Hz), 1.81 (1H, m), 1.75−1.62 (5H, m), 1.54−1.34 (5H, m), 0.99 (9H, s), 0.95 (9H, s), 0.80 (9H, s), −0.07 (3H, s), −0.12 (3H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 205.3, 139.5, 135.84, 135.76, 135.69, 134.1, 133.93, 133.86, 133.4, 129.64, 129.57, 129.4, 129.3, 127.6, 127.44, 127.42, 127.38, 83.7, 82.8, 82.6, 81.5, 80.5, 80.0, 77.9, 75.9, 74.4, 67.8, 67.6, 64.1, 59.3, 40.7, 38.0, 37.4, 29.5, 29.0, 26.9, 26.8, 26.5, 26.2, 25.9, 25.4, 19.3, 19.2, 18.2, −5.4, −5.5; HRMS (FAB) calcd for $C_{60}H_{86}O_9Si_3Na$ [$(M + Na)^+$] 1057.5477, found 1057.5459.

**α-Bromoketo Alcohol 32.** To a solution of LDA, prepared from *i*-$Pr_2NH$ (60 $\mu$L, 0.428 mmol) and BuLi (1.63 M solution in hexane, 230 $\mu$L, 0.375 mmol), in THF (2 mL) was added dropwise a solution of ketone **31** (125.3 mg, 0.1210 mmol) in THF (4 mL) at −78 °C. The mixture was stirred at −78 °C for 20 min and treated with TMSCl (50 $\mu$L, 0.39 mmol). After 20 min at −78 °C, the reaction was quenched with $H_2O$, and the solution was allowed to warm to room temperature. The solution was diluted with EtOAc (60 mL), washed with brine, dried ($Na_2SO_4$), and concentrated to give silyl enol ether, which was used immediately in the next reaction.

A solution of the silyl enol ether in THF (6 mL) was cooled to 0 °C and treated with *N*-bromosuccinimide (65.0 mg, 0.365 mmol). After being stirred at 0 °C for 45 min, the 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 α-bromoketone, which was used in the following reaction without purification.

A solution of the crude α-bromoketone in $CH_2Cl_2$−MeOH (1:1, 6 mL) was cooled to 0 °C and treated with camphorsulfonic acid (6.0 mg, 0.026 mmol). After the resulting mixture was stirred at 0 °C for 10 min and at room temperature for 45 min, the reaction was quenched with $Et_3N$, and the mixture was concentrated. The residue was subjected to flash chromatography (40−50% EtOAc−hexane) to give α-bromoketo alcohol **32** (101.0 mg, 83% for the three steps): $[\alpha]^{29}_D = +5.7°$ (*c* 0.97, $CHCl_3$); IR (film) 3473, 1732 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.66−7.25 (20H, m), 4.08 (1H, d, $J$ = 13.7 Hz), 4.05 (1H, d, $J$ = 13.7 Hz), 3.94 (1H, dd, $J$ = 11.0, 1.8 Hz), 3.93 (1H, d, $J$ = 9.2 Hz), 3.88 (1H, br d, $J$ = 11.9 Hz), 3.59 (1H, dd, $J$ = 11.0, 6.1 Hz), 3.56 (4H, m), 3.47 (1H, m), 3.37 (1H, ddd, $J$ = 8.9, 4.6, 4.6 Hz), 3.34 (1H, ddd, $J$ = 11.6, 9.2, 6.4 Hz), 3.28 (1H, ddd, $J$ = 8.9, 6.1, 1.8 Hz), 3.04 (1H, ddd, $J$ = 11.0, 8.9, 4.3 Hz), 2.94 (1H, m), 2.93 (1H, m), 2.81 (1H, ddd, $J$ = 11.3, 9.2, 4.3 Hz), 2.38 (1H, ddd, $J$ = 11.9, 4.3, 4.3 Hz), 2.03 (1H, m), 1.94 (1H, ddd, $J$ = 11.9, 4.3, 4.3 Hz), 1.83−1.53 (8H, m), 1.52 (1H, ddd, $J$ = 11.9, 11.6, 11.6 Hz), 1.41 (1H, m), 1.39 (1H, ddd, $J$ = 11.9, 11.6, 11.3 Hz), 0.99 (9H, s), 0.95 (9H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 197.8, 135.82 (×2), 135.78, 135.69, 134.1, 133.9, 133.8, 133.4, 129.7 (×2), 129.4, 129.3, 127.6, 127.5, 127.40, 127.38, 83.9, 83.1, 82.6, 81.4, 81.0, 79.9, 78.2, 75.6, 74.2, 67.8, 67.6, 64.1, 60.9, 40.7, 37.27, 37.24, 33.6, 29.0, 26.9, 26.8, 26.1, 26.0, 25.3, 19.3, 19.2; HRMS (FAB) calcd for $C_{54}H_{71}O_9BrSi_2Na$ [$(M + Na)^+$] 1021.3718, found 1021.3698.

**Phenylthiocarbonate 35.** A solution of α-bromoketo alcohol **32** (417.2 mg, 0.4172 mmol) and $Et_3N$ (300 $\mu$L, 2.15 mmol) in $CH_2Cl_2$−DMSO (3:1, 16 mL) was cooled to 0 °C and treated with sulfur trioxide•pyridine complex (270 mg, 1.70 mmol). After being stirred at 0 °C for 40 min, the mixture was diluted with EtOAc (100 mL) and $Et_2O$ (40 mL), washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated to give aldehyde **6**, which was used in the following reaction without purification.

To a solution of $SmI_2$ in THF (0.1 M, 21 mL, 2.10 mmol) was added dropwise over 10 min a solution of the above aldehyde **6** (0.4172 mmol) in THF (20 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 45 min. 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 (400 $\mu$L, 4.24 mmol) and DMAP (102 mg, 0.835 mmol) and allowed to warmed to 0 °C. After being stirred at 0 °C for 30 min, the solution was diluted with EtOAc (200 mL), washed with 1 N aqueous HCl, saturated aqueous $Na_2SO_3$, saturated aqueous $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated to give crude $\beta$-acetoxy ketone **33** (557 mg), which was used in the following reaction without purification. Analytically pure sample was purified by flash chromatography (30−60% EtOAc−hexane) to afford **33** as a single diastereomer: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.65−7.26 (20H, m), 5.46 (1H, br dd, $J$ = 10.4, 10.1 Hz), 4.08 (1H, d, $J$ = 9.5 Hz), 3.89 (1H, d, $J$ = 11.0 Hz), 3.87 (1H, br d, $J$ = 13.7 Hz), 3.59 (1H, dd, $J$ = 11.0, 5.5 Hz), 3.59 (1H, m), 3.41 (1H, ddd, $J$ = 11.6, 9.5, 4.6 Hz), 3.33 (1H, m), 3.28−3.25 (2H, m), 3.10 (1H, m), 3.06 (1H, dd, $J$ = 12.5, 2.8 Hz), 3.00 (2H, m), 2.90 (1H, m), 2.82 (1H, ddd, $J$ = 11.3, 9.2, 3.7 Hz), 2.60 (1H, dd, $J$ = 12.5, 10.4 Hz), 2.28 (1H, ddd, $J$ = 11.6, 4.0, 4.0 Hz), 2.04 (3H, s), 2.03−1.98 (3H, m), 1.78 (1H, ddd, $J$ = 15.0, 10.1, 7.6 Hz), 1.74−1.59 (7H, m), 1.47 (2H, ddd, $J$ = 11.3, 11.3, 11.3 Hz), 0.98 (9H, s), 0.94 (9H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 206.8, 170.4, 135.9 (×2), 135.8, 135.7, 134.1, 134.0, 133.8, 133.2, 129.7, 129.6, 129.4, 129.3, 127.7, 127.5, 127.4 (×2), 86.6, 83.0, 82.7, 82.2, 81.9, 80.5, 77.8, 77.4, 77.2, 76.0, 67.7, 66.9, 64.0, 51.9, 43.5, 40.8, 38.4, 28.9, 28.8, 26.9, 26.8, 26.5, 25.4, 21.3, 19.3, 19.2.

A solution of the above crude $\beta$-acetoxy ketone **33** in $CH_2Cl_2$−MeOH (1:1, 16 mL) was cooled to 0 °C and treated with $NaBH_4$ (32.0 mg, 0.846 mmol) portionwise. After 10 min at 0 °C, the reaction was quenched with saturated aqueous $NH_4Cl$ (16 mL), and the solution was extracted with $CHCl_3$ (30 mL × 4). The combined organic layers were dried ($Na_2SO_4$) and concentrated. Flash chromatography (2% MeOH−$CHCl_3$) afforded alcohol **34** (389.8 mg), which was used in the next reaction without further purification.

A solution of the above alcohol **34** (376.3 mg, 0.3911 mmol) and DMAP (478 mg, 3.912 mmol) in acetonitrile (10 mL) was treated with phenyl chlorothiocarbonate (270 $\mu$L, 1.951 mmol) at room temperature. After the mixture was stirred at room temperature for 23 h, most of the solvent was removed by evaporation, and the residue was diluted with EtOAc (100 mL). The organic layer was washed with 1 N aqueous HCl,

saturated aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (10−20% EtOAc−hexane) gave phenyl thiocarbonate **35** as a 1:1 mixture of diastereomers (300 mg, 66% for the five steps): $[\alpha]^{29}_D = +23.5°$ (*c* 0.59, $CHCl_3$); IR (film) 1732 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, a 1:1 mixture of diastereomers) $\delta$ 7.66−7.26 (23H, m), 7.09 (1H, d, *J* = 7.3 Hz), 7.04 (1H, d, *J* = 7.3 Hz), 5.75 (1/2H, m), 5.43 (1/2H, m), 5.19 (1H, m), 3.89 (2H, m), 3.63−3.49 (9/2H, m), 3.37−3.26 (7/2H, m), 3.00−2.82 (4H, m), 2.66 (1/2H, ddd, *J* = 16.8, 5.2, 5.2 Hz), 2.44 (1/2H, ddd, *J* = 12.2, 4.6, 4.6 Hz), 2.35 (1/2H, ddd, *J* = 11.6, 4.3, 4.3 Hz), 2.25 (1/2H, ddd, *J* = 15.0, 7.3, 7.3 Hz), 2.14 (1/2H, ddd, *J* = 15.0, 4.9, 4.9 Hz), 2.06−1.55 (23/2H, m), 2.02 (3/2H, s), 2.00 (3/2H, s), 1.49 (1H, ddd, *J* = 11.6, 11.6, 11.6 Hz), 1.37 (1H, m), 0.98 (9H, s), 0.96 (9/2H, s), 0.95 (9/2H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$, a 1:1 mixture of diastereomers) $\delta$ 194.4, 194.0, 170.5, 170.2, 153.4, 153.3, 136.0, 135.87, 135.85, 135.82, 135.79, 135.76, 135.69, 134.1, 134.0, 133.83, 133.79, 133.2, 133.1, 129.8, 129.7, 129.60, 129.57, 129.48, 129.45, 129.38, 129.33, 127.72, 85.2, 84.9, 84.8, 83.4, 83.0, 82.5, 82.3, 81.7, 81.3, 80.9, 80.7, 80.6, 80.4, 77.5, 77.2, 76.9, 76.2, 75.9, 75.6, 73.8, 69.3, 68.5. 67.8, 67.7, 67.6, 64.0, 63.9, 42.5, 41.6, 40.8, 39.13, 39.08, 36.9, 34.8, 29.9, 29.8, 29.2, 29.1, 26.91, 26.89, 26.84, 26.4, 25.3, 25.2, 21.4, 19.3, 19.2; HRMS (FAB) calcd for $C_{63}H_{78}O_{11}Si_2SNa$ [$(M + Na)^+$] 1121.4701, found 1121.4712.

**Acetate 36.** A solution of phenyl thiocarbonate **35** (121.1 mg, 0.1119 mmol) and triethylborane (1.04 M solution in hexane, 25 $\mu$L, 0.026 mmol) in benzene (5 mL) was treated with $Bu_3SnH$ (600 $\mu$L, 2.23 mmol) and stirred at room temperature for 2 h. The mixture was concentrated, and the residue was purified by flash chromatography (20−30% EtOAc−hexane) to give acetate **36** (85.3 mg, 80%): $[\alpha]^{28}_D = +21.2°$ (*c* 0.61, $CHCl_3$); IR (film) 1732 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.66−7.26 (20H, m), 5.03 (1H, m), 3.90 (1H, dd, *J* = 11.3, 1.8 Hz), 3.87 (1H, m), 3.60 (1H, m), 3.59 (1H, dd, *J* = 11.3, 5.8 Hz), 3.42 (1H, br dd, *J* = 9.2, 5.2 Hz), 3.36 (1H, m), 3.32 (1H, m), 3.27 (1H, ddd, *J* = 9.2, 5.8, 1.8 Hz), 3.11−3.05 (2H, m), 2.95 (1H, m), 2.94−2.87 (3H, m), 2.24 (1H, ddd, *J* = 11.6, 4.0, 4.0 Hz), 2.05 (1H, ddd, *J* = 11.3, 3.7, 3.7 Hz), 1.99 (3H, s), 1.99 (1H, m), 1.85−1.64 (12H, m), 1.52 (1H, ddd, *J* = 11.6, 11.3, 11.3 Hz), 1.47 (1H, ddd, *J* = 11.3, 11.3, 11.3 Hz), 1.35 (1H, m), 0.98 (9H, s), 0.95 (9H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 170.5, 135.9 (×2), 135.8, 135.7, 134.1, 134.0, 133.8, 133.2, 129.7, 129.6, 129.39, 129.36, 127.7, 127.5, 127.40, 127.36, 88.2, 83.0, 82.3, 81.3, 81.0, 80.9, 80.7, 77.7, 77.2, 71.7, 67.8 (×2), 64.0, 42.2, 40.9, 38.8, 32.5, 30.2, 29.3, 29.1, 27.0, 26.9, 26.8, 25.4, 21.4, 19.3, 19.2; HRMS (FAB) calcd for $C_{56}H_{74}O_9Si_2Na$ [$(M + Na)^+$] 969.4760, found 969.4752.

**Phosphonium Salt 5.** A solution of alcohol **7** (213.1 mg, 0.3061 mmol) in benzene (7 mL) was treated sequentially with triphenylphosphine (241 mg, 0.919 mmol), imidazole (63.0 mg, 0.925 mmol), and iodine (156 mg, 0.615 mmol), and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (100 mL), washed with saturated aqueous $Na_2SO_3$, $H_2O$, and brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (10% EtOAc−hexane) gave the corresponding iodide (239 mg, 97%): $[\alpha]^{28}_D = -51.1°$ (*c* 0.20, $CHCl_3$); IR (film) 2927, 2858, 1456, 1252, 1088, 1028, 837, 775, 735, 696 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.36−7.20 (10H, m), 4.64 (1H, d, *J* = 12.5 Hz), 4.60 (1H, d, *J* = 12.5 Hz), 4.46 (1H, d, *J* = 12.5 Hz), 4.44 (1H, d, *J* = 12.5 Hz), 4.23 (1H, m), 3.94 (1H, dd, *J* = 9.8, 1.8 Hz), 3.81 (1H, dd, *J* = 9.8, 5.2 Hz), 3.78 (1H, m), 3.58 (1H, d, *J* = 9.5 Hz), 3.38 (1H, dd, *J* = 9.5, 9.5 Hz), 3.36 (1H, d, *J* = 3.1 Hz), 3.29 (2H, m), 3.25 (1H, m), 2.99 (1H, ddd, *J* = 9.2, 9.2, 2.4 Hz), 2.86 (1H, dd, *J* = 9.2, 5.2 Hz), 2.27 (1H, m), 2.18 (1H, ddd, *J* = 12.2, 4.9, 4.9 Hz), 2.14−2.03 (3H, m), 1.73 (1H, m), 1.55 (1H, m), 1.51 (1H, m), 1.37 (1H, ddd, *J* = 12.2, 11.6, 11.6 Hz), 1.10 (3H, d, *J* = 7.3 Hz), 1.03 (3H, d, *J* = 6.1 Hz), 0.98 (3H, d, *J* = 6.4 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.02 (3H, s); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 139.4, 138.2, 128.4, 128.1, 127.6, 127.5, 127.4, 127.2, 108.8, 87.0, 84.7, 81.1, 78.5, 77.4, 73.6, 72.2, 72.0, 71.4, 71.0, 69.8, 42.5, 41.5, 41.2, 40.4, 38.4, 36.0, 25.7, 20.0, 17.9, 16.0, 13.5, 2.9, −4.0, −4.7; HRMS (FAB) calcd for $C_{40}H_{59}O_7SiNaI$ [$(M + Na)^+$] 829.2973, found 829.3000.

A solution of the above iodide (236 mg, 0.2928 mmol) and triphenylphosphine (768 mg, 2.93 mmol) in $CH_3CN$ (3 mL) was heated at 70−80 °C for 12 h. The mixture was cooled to room temperature and concentrated. The residue was subjected to flash chromatography (10% MeOH−EtOAc) to give phosphonium salt **5** (303 mg, 97%): $[\alpha]^{29}_D = -24.9°$ (*c* 0.55, $CHCl_3$); IR (film) 2927, 2858, 1439, 1084, 1028, 939, 837, 739, 692 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 500 MHz) $\delta$ 7.83−7.27 (25H, m), 4.68 (1H, d, *J* = 11.9 Hz), 4.58 (1H, d, *J* = 11.9 Hz), 4.45 (1H, d, *J* = 11.9 Hz), 4.42 (1H, d, *J* = 11.9 Hz), 4.24 (1H, m), 3.89 (1H, dd, *J* = 9.8, 1.5 Hz), 3.85−3.79 (2H, m), 3.60 (1H, dd, *J* = 9.5, 0.9 Hz), 3.48 (1H, dd, *J* = 3.4, 0.9 Hz), 3.45 (1H, m), 3.33 (1H, dd, *J* = 9.5, 9.5 Hz), 3.25−3.18 (2H, m), 3.00 (1H, br dd, *J* = 8.9, 8.9 Hz), 2.95 (1H, dd, *J* = 9.5, 4.6 Hz), 2.28 (1H, m), 2.22 (1H, ddd, *J* = 12.2, 4.9, 4.9 Hz), 2.08 (2H, m), 2.04 (1H, m), 1.52−1.42 (3H, m), 1.24 (1H, ddd, *J* = 12.2, 11.3, 11.3 Hz), 1.17 (3H, d, *J* = 7.3 Hz), 1.01 (3H, d, *J* = 6.1 Hz), 0.94 (3H, d, *J* = 6.4 Hz), 0.70 (9H, s), −0.03 (3H, s), −0.18 (3H, s); $^{13}C$ NMR ($CD_3CN$, 125 MHz) $\delta$ 140.4, 139.7, 136.10, 136.09, 134.6, 134.5, 131.3, 131.2, 129.3, 129.2, 128.64, 128.56, 128.4, 128.3, 119.5, 118.8, 109.8, 88.1, 85.6, 81.5, 79.6, 79.0, 74.8, 73.0, 72.9, 72.2, 71.4, 70.9, 43.3, 42.4, 41.8, 41.0, 39.5, 26.0, 20.4, 19.2, 18.9, 18.3, 16.2, 13.9, −3.9, −4.8; HRMS (FAB) calcd for $C_{58}H_{74}O_7SiP$ [$(M + I)^+$] 941.4941, found 941.4945.

**TBPS Ether 38.** A solution of acetate **36** (384.8 mg, 0.4068 mmol) in THF (15 mL) was treated with $Bu_4NF$ (1.0 M solution in THF, 1.3 mL, 1.3 mmol), and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was subjected to flash chromatography (5% MeOH−$CHCl_3$) to give diol, which was used in the following reaction without further purification.

A solution of the crude diol and imidazole (83.0 mg, 1.22 mmol) in DMF (6 mL) was cooled to 0 °C and treated with TBPSCl (130 $\mu$L, 0.506 mmol). The resulting mixture was stirred at 0 °C for 30 min and diluted with EtOAc (100 mL). The organic layer was washed with $H_2O$ (×2) and brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (30−50% EtOAc−hexane) gave TBPS ether **38** (236 mg, 82% for the two steps): $[\alpha]^{29}_D = +4.1°$ (*c* 0.55, $CHCl_3$); IR (film) 3444, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.66−7.12 (10H, m), 5.05 (1H, m), 3.87 (1H, dd, *J* = 10.4, 4.9 Hz), 3.86 (1H, m), 3.72 (1H, m), 3.71 (1H, dd, *J* = 10.4, 7.3 Hz), 3.54 (1H, ddd, *J* = 8.9, 8.9, 3.1 Hz), 3.47 (1H, ddd, *J* = 8.9, 4.3, 4.3 Hz), 3.31 (1H, m), 3.24 (1H, ddd, *J* = 8.9, 7.3, 4.9 Hz), 3.18 (1H, ddd, *J* = 11.9, 9.2, 4.0 Hz), 3.09 (2H, m), 2.97 (1H, ddd, *J* = 9.2, 6.4, 6.4 Hz), 2.91 (1H, m), 2.89 (1H, m), 2.36 (1H, ddd, *J* = 11.6, 4.3, 4.3 Hz), 2.21 (1H, ddd, *J* = 11.9, 3.7, 3.7 Hz), 2.02 (3H, s), 1.99 (1H, m), 1.95−1.64 (12H, m), 1.51 (1H, ddd, *J* = 11.9, 11.0, 11.0 Hz), 1.47 (1H, ddd, *J* = 11.6, 11.6, 11.6 Hz), 1.34 (1H, m), 1.04 (9H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 170.7, 135.6, 135.5, 132.53, 132.46, 129.93, 129.91, 127.8 (×2), 88.1, 82.5, 81.4, 81.3, 80.9, 80.8, 79.4, 77.7, 77.0, 71.8, 69.9, 67.7, 66.5, 42.5, 39.5, 38.8, 32.8, 30.0, 29.3, 29.1, 26.9, 26.8, 25.4, 21.4, 19.1; HRMS (FAB) calcd for $C_{40}H_{56}O_9SiNa$ [$(M + Na)^+$] 731.3591, found 731.3599.

**Ketone 39.** A solution of oxalyl chloride (55 $\mu$L, 0.633 mmol) in $CH_2Cl_2$ (3 mL) was cooled to −78 °C and treated with DMSO (95 $\mu$L, 1.34 mmol). The resulting solution was stirred at −78 °C for 10 min. To the solution was added dropwise via cannula a solution of alcohol **38** (228.1 mg, 0.3217 mmol) in $CH_2Cl_2$ (6 mL). After being stirred at −78 °C for 30 min, the mixture was treated with $Et_3N$ (360 $\mu$L, 2.56 mmol) and allowed to warm to room temperature. The solution was stirred at room temperature for 30 min and diluted with EtOAc (100 mL). The organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. Flash chromatography (40% EtOAc−hexane) gave ketone **39** (215.2 mg, 94%): $[\alpha]^{29}_D = +13.6°$ (*c* 0.55, $CHCl_3$); IR (film) 1728 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.69−7.33 (10H, m), 5.06 (1H, m), 3.97 (1H, dd, *J* = 11.3, 2.7 Hz), 3.90 (1H, dd, *J* = 11.3, 4.9 Hz), 3.86 (1H, m), 3.63 (1H, ddd, *J* = 11.3, 9.5, 5.5 Hz), 3.56 (1H, ddd, *J* = 8.9, 7.9, 4.9 Hz), 3.48 (1H, ddd, *J* = 8.9, 4.0, 4.0 Hz), 3.36−3.29 (3H, m), 3.12 (2H, m), 2.94 (1H, m), 2.92 (1H, m), 2.89 (1H, dd, *J* = 16.8, 5.5 Hz), 2.33 (1H, dd, *J* = 16.8, 11.3 Hz), 2.27 (1H, ddd, *J* = 11.9, 2.8, 2.8 Hz), 2.01 (1H, m), 2.00 (3H, s), 1.94−1.65

(12H, m), 1.56 (1H, m), 1.36 (1H, m), 1.01 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 205.9, 170.6, 135.7 (×2), 133.43, 133.36, 129.62, 129.59, 127.57, 127.56, 88.2, 83.9, 81.4, 81.3, 81.2, 81.0, 80.0, 77.7, 77.0, 71.7, 67.8, 63.4, 46.7, 42.2, 38.9, 32.6, 29.7, 29.3, 29.1, 26.9, 26.7, 25.4, 21.4, 19.2; HRMS (FAB) calcd for $C_{40}H_{54}O_9SiNa$ [$(M + Na)^+$] 729.3435, found 729.3448.

**Dithioketal 40.** A solution of ketone **39** (207 mg, 0.293 mmol) and EtSH (110 $\mu$L, 1.49 mmol) in $CH_2Cl_2$ (8 mL) was cooled to −78 °C and treated with $TiCl_4$ (60 $\mu$L, 0.547 mmol). After the mixture was stirred at −78 °C for 1.5 h, the reaction was quenched with aqueous $NaHCO_3$ (2 mL). The mixture was diluted with EtOAc (100 mL), washed with brine, dried ($Na_2SO_4$), and concentrated to give dithioketal, which was used in the next reaction without purification. Analytically pure sample was purified by chromatography (30% EtOAc−hexane): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.69−7.32 (10H, m), 5.07 (1H, m), 4.11 (1H, dd, $J$ = 11.3, 1.8 Hz), 3.88 (1H, m), 3.75 (1H, dd, $J$ = 11.3, 8.2 Hz), 3.67 (1H, ddd, $J$ = 11.0, 9.5, 4.0 Hz), 3.59 (1H, dd, $J$ = 8.2, 1.8 Hz), 3.51 (1H, ddd, $J$ = 8.9, 5.8, 5.8 Hz), 3.40 (1H, ddd, $J$ = 8.9, 4.6, 4.6 Hz), 3.32 (1H, ddd, $J$ = 11.3, 11.3, 4.3 Hz), 3.12 (2H, m), 2.98 (1H, m), 2.93 (1H, m), 2.91 (1H, m), 2.60−2.34 (4H, m), 2.32 (1H, dd, $J$ = 13.1, 4.0 Hz), 2.25 (1H, ddd, $J$ = 11.6, 3.7, 3.7 Hz), 2.00 (1H, m), 1.99 (3H, s), 1.95−1.64 (13H, m), 1.53 (1H, m), 1.35 (1H, m), 1.14 (3H, t, $J$ = 7.6 Hz), 1.09 (3H, t, $J$ = 7.6 Hz), 1.02 (9H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.4, 135.70, 135.68, 134.0, 133.8, 129.5, 129.4, 127.51, 127.48, 88.4, 86.5, 83.3, 81.4, 81.3, 81.2, 78.5, 77.7, 77.0, 71.9, 67.8, 64.1, 60.3, 42.8, 42.1, 38.8, 32.2, 30.4, 29.3, 29.0, 27.3, 26.8, 25.4, 23.4, 23.3, 21.4, 19.3, 14.24, 14.15.

A solution of the above dithioketal in THF (8 mL) was treated with $Bu_4NF$ (1.0 M solution in THF, 0.6 mL, 0.6 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was subjected to flash chromatography (2% MeOH−$CHCl_3$) to give dithioketal **40** (163.4 mg, 97% for the two steps): $[\alpha]^{26}_D$ = −13.0° (*c* 0.55, $CHCl_3$); IR (film) 3479 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 5.07 (1H, m), 3.93 (1H, dd, $J$ = 11.6, 2.7 Hz), 3.86 (1H, m), 3.74 (1H, ddd, $J$ = 11.0, 9.5, 4.0 Hz), 3.67 (1H, dd, $J$ = 11.3, 8.9 Hz), 3.60 (1H, dd, $J$ = 8.9, 2.7 Hz), 3.55 (1H, ddd, $J$ = 9.2, 6.4, 6.4 Hz), 3.40 (1H, ddd, $J$ = 9.2, 4.9, 4.9 Hz), 3.31 (1H, ddd, $J$ = 11.6, 11.6, 4.6 Hz), 3.10 (3H, m), 2.93 (1H, m), 2.90 (1H, m), 2.68−2.51 (4H, m), 2.37 (1H, dd, $J$ = 13.1, 4.0 Hz), 2.24 (1H, ddd, $J$ = 11.6, 4.0, 4.0 Hz), 2.00 (3H, s), 1.98 (1H, m), 1.95−1.63 (13H, m), 1.52 (1H, m), 1.34 (1H, m), 1.24 (3H, t, $J$ = 7.3 Hz), 1.19 (3H, t, $J$ = 7.6 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.5, 83.3, 85.4, 83.4, 81.6, 81.3, 81.2, 78.2, 77.7, 76.9, 71.8, 67.7, 62.1, 59.9, 42.5, 42.2, 38.8, 32.3, 30.3, 29.3, 29.1, 27.5, 25.4, 23.7, 23.4, 21.4, 14.3, 14.1; HRMS (FAB) calcd for $C_{28}H_{46}O_8S_2Na$ [$(M + Na)^+$] 597.2532, found 597.2538.

**Aldehyde 4.** A solution of dithioketal **40** (155.1 mg, 0.2698 mmol) and $Et_3N$ (190 $\mu$L, 1.36 mmol) in $CH_2Cl_2$−DMSO (3:1, 6 mL) was cooled to 0 °C and treated with sulfur trioxide•pyridine complex (172 mg, 1.08 mmol). After being stirred at 0 °C for 30 min, the mixture was diluted with EtOAc (100 mL), washed with $H_2O$ (×2), and brine, dried ($Na_2SO_4$), and concentrated to give crude aldehyde **3**, which was used in the following reaction without purification.

***(Z)*-Olefin 41.** A solution of phosphonium salt **5** (294.7 mg, 0.2759 mmol) in THF (4 mL) was cooled to −78 °C and treated with BuLi (1.63 M solution in hexane, 170 $\mu$L, 0.277 mmol). The mixture was allowed to warm to 0 °C and stirred at 0 °C for 30 min. After being cooled to −78 °C, the solution was treated with HMPA (150 $\mu$L, 0.862 mmol), and a solution of the above aldehyde **4** in THF (5 mL) was added dropwise via cannula. The resulting solution was stirred at −78 °C for 20 min and then warmed to room temperature and stirred at that temperature for 3.5 h. The mixture was concentrated, and the residue was directly subjected to flash chromatography (20−60% EtOAc−hexane) to give (*Z*)-olefin **41** (210.6 mg, 63% from **5**): $[\alpha]^{29}_D$ = −42.0° (*c* 0.29, $CHCl_3$); IR (film) 2931, 2868, 1732, 1456, 1250, 1086, 837, 775, 737, 698 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.55−7.22 (10H, m), 5.85 (1H, ddd, $J$ = 11.0, 9.2, 4.9 Hz), 5.58 (1H, dd, $J$ = 11.0, 8.9 Hz), 5.08 (1H, m), 4.65 (1H, d, $J$ = 12.5 Hz), 4.58 (1H, d, $J$ = 12.5 Hz), 4.45 (1H, d, $J$ = 12.8 Hz), 4.43 (1H, d, $J$ = 12.8 Hz), 4.23 (1H, d, $J$ = 8.9 Hz), 4.22 (1H, m), 3.93 (1H, dd, $J$ = 9.5, 1.5 Hz), 3.86 (1H, m), 3.80 (1H, dd, $J$ = 9.5, 4.9 Hz), 3.78 (1H, m), 3.76 (1H, m), 3.56 (1H, d, $J$ = 9.5 Hz), 3.53 (1H, m), 3.41−3.28 (4H, m), 3.25 (1H, ddd, $J$ = 11.3, 8.9, 4.6 Hz), 3.13−3.05 (3H, m), 2.94 (2H, m), 2.89 (1H, m), 2.82 (1H, dd, $J$ = 9.5, 5.2 Hz), 2.80 (1H, m), 2.68−2.56 (4H, m), 2.37 (1H, dd, $J$ = 13.1, 4.0 Hz), 2.24 (1H, m), 2.19−1.47 (22H, m), 2.00 (3H, s), 1.34 (2H, m), 1.25 (3H, t, $J$ = 7.3 Hz), 1.12 (3H, t, $J$ = 7.3 Hz), 1.06 (3H, d, $J$ = 7.3 Hz), 1.02 (3H, d, $J$ = 6.1 Hz), 0.97 (3H, d, $J$ = 6.4 Hz), 0.87 (9H, s), 0.07 (3H, s), 0.05 (3H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.4, 139.4, 138.2, 132.8, 128.4, 128.1, 127.6, 127.5, 127.4, 127.2, 126.4, 108.8, 88.4, 86.9, 84.7, 83.3, 81.7, 81.5, 81.4, 81.3, 81.2, 78.5, 78.2, 77.7, 77.4, 76.9, 73.8, 72.1, 72.0, 71.9, 71.4, 71.0, 70.4, 67.7, 63.3, 43.3, 42.5, 42.1, 41.5, 41.1, 40.3, 38.8, 38.4, 32.2, 31.0, 30.4, 29.3, 29.0, 27.6, 25.9, 25.4, 23.2, 23.0, 21.4, 20.0, 17.9, 16.0, 14.2, 14.1, 13.5, −4.0, −4.6; HRMS (FAB) calcd for $C_{68}H_{102}O_{14}SiS_2Na$ [$(M + Na)^+$] 1257.6378, found 1257.6400.

**Hydroxy Dithioketal 3.** A solution of olefin **41** (206.2 mg, 0.1668 mmol) in THF (7 mL) was treated with $Bu_4NF$ (1.0 M solution in THF, 340 $\mu$L, 0.34 mmol) at room temperature, and the mixture was stirred for 5 h. The solvent was evaporated, and the residue was subjected to flash chromatography (30−60% EtOAc−hexane) to give hydroxy dithioketal **3** (169.6 mg, 91%): $[\alpha]^{28}_D$ = −21.7° (*c* 0.83, $CHCl_3$); IR (film) 3444 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.35−7.26 (10H, m), 5.85 (1H, ddd, $J$ = 11.3, 7.9, 7.9 Hz), 5.67 (1H, dd, $J$ = 11.3, 8.2 Hz), 5.06 (1H, m), 4.65 (1H, d, $J$ = 12.2 Hz), 4.60 (1H, d, $J$ = 12.2 Hz), 4.45 (1H, d, $J$ = 12.2 Hz), 4.43 (1H, d, $J$ = 12.2 Hz), 4.28 (1H, d, $J$ = 8.2 Hz), 4.23 (1H, m), 3.93 (1H, dd, $J$ = 9.8, 1.5 Hz), 3.86 (1H, m), 3.83 (1H, m), 3.80 (1H, dd, $J$ = 9.8, 5.2 Hz), 3.78 (1H, m), 3.59 (1H, d, $J$ = 9.5 Hz), 3.53 (1H, m), 3.41−3.28 (5H, m), 3.16 (1H, ddd, $J$ = 9.5, 7.0, 7.0 Hz), 3.10 (2H, m), 3.02 (1H, ddd, $J$ = 8.9, 5.5, 5.5 Hz), 2.93 (1H, m), 2.89 (1H, m), 2.88 (1H, dd, $J$ = 9.5, 4.6 Hz), 2.67−2.58 (4H, m), 2.57 (1H, m), 2.42 (1H, m), 2.39 (1H, dd, $J$ = 13.1, 4.0 Hz), 2.29−1.47 (23H, m), 2.00 (3H, s), 1.32 (2H, m), 1.25 (3H, t, $J$ = 7.6 Hz), 1.14 (3H, t, $J$ = 7.6 Hz), 1.09 (3H, d, $J$ = 7.3 Hz), 1.01 (3H, d, $J$ = 6.1 Hz), 0.97 (3H, d, $J$ = 6.4 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.4, 139.4, 138.2, 132.7, 128.4, 128.1, 127.6, 127.5, 127.4, 127.2, 126.4, 108.9, 88.3, 87.0, 84.7, 83.5, 81.56, 81.53, 81.26, 81.23, 80.5, 78.5, 78.1, 77.9, 77.7, 76.9, 74.1, 72.1, 72.0, 71.9, 71.4, 71.0, 69.6, 67.7, 62.7, 42.9, 42.5, 42.2, 41.6, 40.1, 40.0, 38.8, 38.4, 32.3, 31.9, 30.3, 29.3, 29.0, 27.5, 25.4, 23.6, 23.0, 21.4, 20.2, 15.8, 14.2, 14.0, 13.5; HRMS (FAB) calcd for $C_{62}H_{88}O_{14}S_2Na$ [$(M + Na)^+$] 1143.5513, found 1143.5532.

**Mixed Thioketal 42.** A heterogeneous mixture of hydroxyl dithioketal **3** (175.2 mg, 0.1562 mmol), powdered 4 Å molecular sieves (350 mg), silica gel (350 mg), $NaHCO_3$ (131.2 mg, 1.561 mmol), and silver trifluoromethanesulfonate (160.6 mg, 0.6250 mmol) in dry nitromethane (1.6 mL) was stirred vigorously at room temperature for 10 h. The mixture was diluted with EtOAc (5 mL), filtered through Celite, and concentrated. Flash chromatography (30−50% EtOAc−hexane) gave mixed thioketal **42** (88.5 mg, 53%) along with the recovered **3** (51.9 mg, 30%): $[\alpha]^{29}_D$ = +42.9° (*c* 0.11, $CHCl_3$); IR (film) 2931, 2866, 1732, 1456, 1248, 1078, 737, 698 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.36−7.26 (10H, m), 5.81 (1H, dddd, $J$ = 10.7, 6.7, 6.7, 1.2 Hz), 5.62 (1H, dd, $J$ = 10.7, 6.4 Hz), 5.05 (1H, m), 4.66 (1H, d, $J$ = 12.2 Hz), 4.56 (1H, d, $J$ = 12.2 Hz), 4.45 (1H, d, $J$ = 12.2 Hz), 4.43 (1H, d, $J$ = 12.2 Hz), 4.25 (1H, ddd, $J$ = 11.9, 9.2, 4.3 Hz), 4.22 (1H, m), 4.02 (1H, dd, $J$ = 6.4, 1.2 Hz), 3.92 (1H, dd, $J$ = 9.5, 1.8 Hz), 3.86 (1H, m), 3.80 (1H, m), 3.79 (1H, dd, $J$ = 9.5, 4.9 Hz), 3.74 (1H, ddd, $J$ = 11.3, 9.2, 4.0 Hz), 3.56 (1H, m), 3.55 (1H, d, $J$ = 9.5 Hz), 3.41 (1H, ddd, $J$ = 8.9, 4.6, 4.6 Hz), 3.36−3.28 (4H, m), 3.10 (3H, m), 2.93 (1H, m), 2.89 (1H, m), 2.82 (1H, dd, $J$ = 9.2, 4.9 Hz), 2.57 (1H, m), 2.56 (1H, m), 2.46 (1H, m), 2.37 (1H, dd, $J$ = 13.1, 3.7 Hz), 2.25 (2H, m, 22-H), 2.13 (1H, m), 2.08−1.46 (20H, m), 1.99 (3H, s), 1.34 (2H, m), 1.25 (3H, t, $J$ = 7.6 Hz), 1.07 (3H, d, $J$ = 7.6 Hz), 0.99 (3H, d, $J$ = 5.8 Hz), 0.96 (3H, d, $J$ = 6.4 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.4, 139.3, 138.2, 131.0, 129.3, 128.4, 128.1, 127.59, 127.55, 127.51, 127.2, 108.9, 91.7, 88.5, 87.5, 84.5, 83.2, 83.20, 82.0, 81.7, 81.3, 81.2, 79.3, 78.5, 77.7, 77.6, 76.9, 74.3, 72.0, 71.9 (×2), 71.4, 71.0, 67.8, 67.3, 42.8, 42.4, 42.3, 41.5,

39.7, 39.3, 38.8, 38.4, 32.4, 30.8, 30.4, 29.3, 29.1, 27.4, 25.4, 21.4, 20.9, 19.9, 15.8, 14.7, 13.5; HRMS (FAB) calcd for $C_{60}H_{82}O_{14}SNa$ [(M + Na)$^+$] 1081.5323, found 1081.5320.

**Tetrahydrooxocine 43.** A solution of mixed thioketal **42** (60.6 mg, 0.056 mmol), AIBN (1 mg, 0.006 mmol), and $Ph_3SnH$ (197 mg, 0.561 mmol) in toluene (1.2 mL) was heated at 110 °C for 3 h. After being cooled to room temperature, the mixture was concentrated, and the residue was purified by flash chromatography (30−40% EtOAc−hexane) to give tetrahydrooxocine **43**, which was dissolved in $CH_2Cl_2$ (2 mL) and treated with *m*-CPBA (80%, 15 mg, 0.070 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with saturated aqueous $Na_2SO_3$. The mixture was extracted with EtOAc (25 mL), washed with saturated aqueous $NaHCO_3$ (×2), dried ($Na_2SO_4$), and concentrated. Flash chromatography (30−40% EtOAc−hexane) gave pure **43** (49 mg, 86%): $[\alpha]^{29}_D$ = +14.7° (*c* 0.17, $CHCl_3$); IR (film) 2935, 2869, 1730, 1454, 1373, 1250, 1082, 735, 698 cm$^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 7.43−7.08 (10H, m), 5.92 (1H, dd, *J* = 11.0, 5.2 Hz), 5.80 (1H, ddd, *J* = 11.3, 8.9, 1.8 Hz), 5.37 (1H, m), 4.65 (1H, d, *J* = 11.9 Hz), 4.62 (1H, d, *J* = 11.6 Hz), 4.17 (2H, s), 4.12 (1H, ddd, *J* = 11.0, 9.5, 5.2 Hz), 4.03 (1H, m), 4.00 (1H, d, *J* = 9.5 Hz), 3.90 (1H, dd, *J* = 9.5, 0.6 Hz), 3.88 (1H, m), 3.85 (1H, m), 3.76 (1H, dd, *J* = 9.5, 4.9 Hz), 3.70 (1H, br d, *J* = 11.3 Hz), 3.69 (1H, dd, *J* = 9.8, 9.8 Hz), 3.53 (1H, d, *J* = 3.1 Hz), 3.34 (1H, ddd, *J* = 12.2, 8.9, 4.0 Hz), 3.28 (1H, ddd, *J* = 8.6, 4.0, 4.0 Hz), 3.21 (2H, m), 3.09−3.04 (2H, m), 2.99 (1H, dd, *J* = 9.2, 4.9 Hz), 2.94−2.88 (2H, m), 2.84 (1H, ddd, *J* = 11.3, 8.9, 4.6 Hz), 2.79−2.72 (2H, m), 2.66 (1H, ddd, *J* = 14.7, 11.0, 4.9 Hz), 2.45 (1H, ddd, *J* = 7.3, 4.9, 3.1 Hz), 2.37−2.34 (3H, m), 2.28−2.23 (2H, m), 2.16−2.09 (2H, m), 2.00−1.62 (16H, m), 1.46 (1H, dq, *J* = 11.3, 6.7 Hz), 1.40 (1H, ddd, *J* = 12.8, 4.3, 4.3 Hz), 1.30 (1H, m), 1.21 (3H, d, *J* = 6.1 Hz), 1.19 (1H, m), 1.10 (3H, d, *J* = 7.3 Hz), 1.08 (3H, d, *J* = 6.7 Hz); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 170.1, 139.7, 138.9, 135.2, 128.6, 128.5, 128.3, 128.1, 127.69, 127.65, 126.3, 109.4, 88.8, 88.2, 85.3, 82.7, 82.6, 82.0, 81.9, 81.4, 81.2, 80.3, 79.0, 78.7, 78.4, 77.9, 77.5, 75.5, 75.0, 72.7, 72.6, 72.3, 71.6, 71.1, 67.6, 43.7, 43.1, 42.1, 40.4, 40.1, 39.5(x 2), 39.0, 33.6, 31.0, 30.5, 29.9, 29.8, 27.5, 25.8, 21.0, 20.0, 16.1, 13.8; HRMS (FAB) calcd for $C_{58}H_{78}O_{14}Na$ [(M + Na)$^+$] 1021.5289, found 1021.5271.

**Bis(ethoxyethyl ether) 46.** A solution of tetrahydrooxocine **43** (26.5 mg, 0.0280 mmol) in EtOAc−MeOH (1:2, 2 mL) and AcOH (25 $\mu$L) was treated with a catalytic amount of $Pd(OH)_2$/C, and the mixture was stirred at room temperature under hydrogen for 12 h. The catalyst was filtered, and the solvent was removed to give diol **44**, which was used in the following reaction without purification: $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 5.03 (1H, m), 4.48 (1H, m), 3.86 (1H, m), 3.86 (1H, dd, *J* = 9.8, 4.3 Hz), 3.77 (1H, d, *J* = 9.8 Hz), 3.67 (1H, dd, *J* = 3.7, 1.5 Hz), 3.66 (1H, m), 3.61 (1H, dd, *J* = 9.8, 1.5 Hz), 3.53 (1H, m), 3.43 (1H, m), 3.30 (1H, m), 3.23 (1H, dd, *J* = 9.8, 9.8 Hz), 3.18 (1H, m), 3.16 (1H, m), 3.13 (1H, m), 3.08 (2H, m), 3.00 (1H, ddd, *J* = 10.4, 10.4, 3.1 Hz), 2.96−2.87 (4H, m), 2.83 (1H, dd, *J* = 9.5, 4.6 Hz), 2.31−1.32 (31H, m), 2.00 (3H, s), 1.11 (3H, d, *J* = 7.6 Hz), 1.03 (3H, d, *J* = 6.1 Hz), 0.98 (3H, d, *J* = 6.7 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.7, 109.3, 88.4, 86.3, 84.0, 83.8, 82.1, 81.5, 81.45, 81.42, 81.38, 81.03, 80.98, 78.4, 77.7, 77.1, 77.0, 75.7, 74.5, 72.0, 71.9, 71.7, 67.7, 45.7, 42.5, 42.0, 41.9, 40.5, 40.4, 38.8, 38.3, 36.9, 36.7, 32.7, 30.1, 29.3, 29.1, 27.2, 25.3, 21.4, 20.4, 19.7, 15.6, 13.4; MS (FAB) *m*/*z* 843 [(M + Na)$^+$].

A solution of the above diol **44**, ethyl vinyl ether (110 $\mu$L, 1.15 mmol), and PPTS (10.0 mg, 0.0398 mmol) in $CH_2Cl_2$ (2 mL) was stirred at room temperature for 4 h and then directly subjected to flash chromatography (50% EtOAc−hexane) to give bis(ethoxyethyl) ether **46** (25.3 mg, 99%), which was used in the following reaction without further purification: IR (film) 2935, 2870, 1732, 1456, 1375, 1338, 1250, 1082, 951 cm$^{-1}$; HRMS (FAB) calcd for $C_{52}H_{84}O_{16}Na$ [(M + Na)$^+$] 987.5657, found 987.5670.

**Hexahydrooxonine 49.** A solution of bis(ethoxyethyl) ether **46** (25.3 mg, 0.0277 mmol) in $CH_2Cl_2$ (2 mL) was cooled to −78 °C and treated with DIBALH (1.0 M solution in $CH_2Cl_2$, 100 $\mu$L, 0.1 mmol). After the mixture was stirred at −78 °C for 30 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 (20 mL), and the combined organic layers were dried ($Na_2SO_4$) and concentrated to give crude alcohol, which was used in the next reaction without purification.

A solution of the above alcohol, LiBr (24.0 mg, 0.276 mmol), and *i*-$Pr_2NEt$ (75 $\mu$L, 0.431 mmol) in $CH_2Cl_2$ (2 mL) was treated with methanesulfonic anhydride (24.0 mg, 0.138 mmol). After being stirred at room temperature for 3 h, the mixture was diluted with EtOAc (30 mL), washed with water and brine, dried ($Na_2SO_4$), and concentrated to give crude bromide **48**.

A solution of the above bromide **48** in dry DMSO (1 mL) was treated with KO-*t*-Bu (16.0 mg, 0.143 mmol). After the mixture was stirred at room temperature for 75 min, the reaction was quenched with $H_2O$, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were dried ($Na_2SO_4$) and concentrated. Flash chromatography (40% EtOAc−hexane) gave hexahydrooxonine **49** (13.1 mg, 52%): IR (film) 2933, 2870, 1456, 1375, 1336, 1281, 972, 949 cm$^{-1}$; HRMS (FAB) calcd for $C_{50}H_{80}O_{14}Na$ [(M + Na)$^+$] 927.5446, found 927.5455.

**Decacyclic Compound 2.** A solution of hexahydrooxonine **49** (13.1 mg, 0.0144 mmol) in MeOH (2 mL) was treated with PPTS (3.0 mg, 0.012 mmol), and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with $Et_3N$, and the mixture was concentrated. The residue was purified by flash chromatography (5% MeOH−$CHCl_3$) to give decacyclic model compound **2** (11.0 mg, quantitative): $[\alpha]^{29}_D$ = −29.8° (*c* 0.17, $CHCl_3$); IR (film) 3446 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.74−5.61 (2H, br), 4.48 (1H, m), 3.86 (1H, dd, *J* = 10.1, 4.3 Hz), 3.85 (1H, m), 3.77 (1H, d, *J* = 10.1 Hz), 3.67 (1H, dd, *J* = 3.7, 1.5 Hz), 3.66 (1H, m), 3.61 (1H, dd, *J* = 9.8, 1.5 Hz), 3.55 (1H, br), 3.43 (1H, m), 3.31 (1H, m), 3.22 (1H, dd, *J* = 9.8, 9.8 Hz), 3.19−3.13 (3H, m), 3.07 (2H, m), 3.01 (1H, m), 2.94−2.89 (4H, m), 2.83 (1H, dd, *J* = 10.1, 5.2 Hz), 2.80−2.56 (2H, br), 2.34−1.35 (27H, m), 1.11 (1H, d, *J* = 7.6 Hz), 1.02 (3H, d, *J* = 6.4 Hz), 0.98 (3H, d, *J* = 6.7 Hz); HRMS (FAB) calcd for $C_{42}H_{64}O_{12}Na$ [(M + Na)$^+$] 783.4295, found 783.4285.

**Acknowledgment.** We thank Professor Emeritus T. Yasumoto of Tohoku University and Professor M. Murata of Osaka University for valuable discussions and advice throughout this work. We are grateful to Dr. K. Konoki for biological studies of our model compound and to Dr. M. Hentemann, Sloan-Kettering Institute for Cancer Research, for critical reading of the manuscript. This work was financially supported in part by a Grant-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan and a fellowship to M.I. from the Japan Society for the Promotion of Science for Young Scientists.

**Supporting Information Available:** A synthetic scheme for compound **10**, experimental procedures for compounds **12** and **14**, $^1$H NMR spectra for compounds **2**, **3**, **5**, **11**, **17**, **20**, **21**, **23**, **24**, **28**−**35**, **38**−**44**, **46**, and **49**, and $^{13}$C NMR spectra for compounds **3**, **5**, **11**, **21**, **23**, **24**, **28**, **29**, **31**−**33**, and **38**−**44**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990989B