Intramolecular Radical Cyclization−Ring-Closing Metathesis Approach to Fused Polycyclic Ethers. Convergent Synthesis and Conformational Analysis of the (E)FGH Ring System of Ciguatoxin

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A convergent synthetic route to the (E)FGH ring system **4** of ciguatoxins, the causative toxins for ciguatera fish poisoning, has been developed. The synthesis features convergent coupling to form dioxane acetal, regioselective acetal cleavage by diethylaluminum phenylthiolate or diisobutylaluminum phenylselenolate followed by intramolecular radical cyclization to construct the oxepane ring G, and a ring-closing metathesis reaction to form the hexahydrooxonine ring F. The hexahydrooxonine ring F of tetracyclic model system **4** existed as a 5:1 equilibrium mixture of two conformers (UP and DOWN conformers), with the UP one predominating. This is the first illustration that reproduces the preference for the UP conformer over the DOWN one, which preference was observed for natural ciguatoxins.

Introduction

Ciguatera is a seafood poisoning prevalent in circum tropical areas with more than 20 000 victims annually and continues to be a serious public health problem.[1] The causative toxins originate in the epiphytic dinoflagellate *Gambierdiscus toxicus*[2] and are accumulated in fish through the food chain, thus causing human intoxication. These dinoflagellate toxins undergo oxidative changes in fish, yielding the principal toxin, ciguatoxin (CTX, **1**) and a number of congeners.

Ciguatoxin (**1**) was first isolated from the moray eel, *Gymnothorax javanicus*, by Scheuer's group in 1980.[3] The structure of **1**, except for the absolute configuration and relative configuration at C2, was finally elucidated using a purified sample of only 0.35 μg by Yasumoto and co-workers in 1989.[4,5] The ciguatoxin molecule consists of 12 trans-fused polycyclic ethers, ranging from six- to nine-membered, and a spirally attached five-membered cyclic ether at one end. The prime characteristic feature of the structure is that the hexahydrooxonine ring F in the central region of the molecule undergoes a slow conformational change in solution.[4b,5a] So far, 22 ciguatoxin congeners, including CTX3C (**2**)[6] and 51-hydroxy-CTX3C (**3**),[7] have been identified from toxic fish and/or *G. toxicus*, and the structures were elucidated by extensive NMR analysis and/or CID FAB/MS/MS experiments using minute amounts of samples.[8] More recently, the absolute configuration of **1** was successfully determined, as shown in Figure 1, by Yasumoto and co-workers.[9]

These toxins are extremely potent neurotoxins that bind to voltage-sensitive Na^+ channels (VSSC) and inhibit depolarization to allow inward Na^+ influx to continue;[10] however, the mechanism for ciguatoxins in binding to VSSC has not yet been clarified. The binding site on VSSC was reported to be shared by brevetoxins, another class of structurally related marine toxins.[11] It is noteworthy that the binding affinity of **1** was shown to be some 10 times more potent than that of brevetoxins, despite their structural similarity.[11b,12] However, the precise location of the receptor site of ciguatoxins and brevetoxins on VSSC has not been fully identified.[13] The common structural feature of these polycyclic ether toxins

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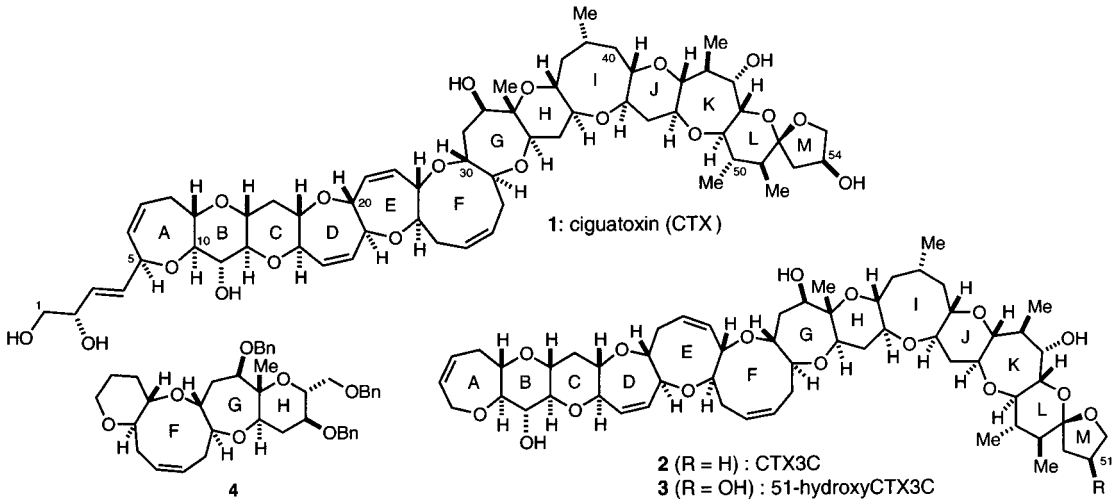

Figure 1. Structures of ciguatoxin (CTX, **1**), its congeners (CTX3C (**2**) and 51-hydroxyCTX3C (**3**)), and (E)FGH ring compound **4**.

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 channel proteins.[5a] However, the scarcity of ciguatoxins from natural sources has also precluded further investigations on their interactions with VSSC. Thus, a practical total synthesis is currently the only potential source of these intriguing molecules. In addition, structure−activity relationship studies of structural analogues not accessible by degradation or functionalization of the natural toxins may provide useful information for understanding the detailed structural basis necessary for their high-affinity binding to and activation of VSSC.

The complex molecular architecture and their potential as tools for biological studies of the ciguatoxins, as well as their limited availability from natural sources, make these compounds attractive targets for total synthesis, and thus a number of synthetic efforts, including ours,[14] have been reported to date.[15−17] In the course of our synthetic efforts toward ciguatoxins and their nonnatural analogues, we have engaged in the development of convergent and efficient methods for the assembly of large polycyclic ether arrays.[18] In particular, construction of the fused hexahydrooxonine ring system, corresponding to the F ring of ciguatoxins, was a formidable challenge in the synthesis of ciguatoxins. A series of analogues that preserves the central EFGH ring domain of **1** would be useful for probing the role of the conformational flexible part of ciguatoxins in binding to VSSC.

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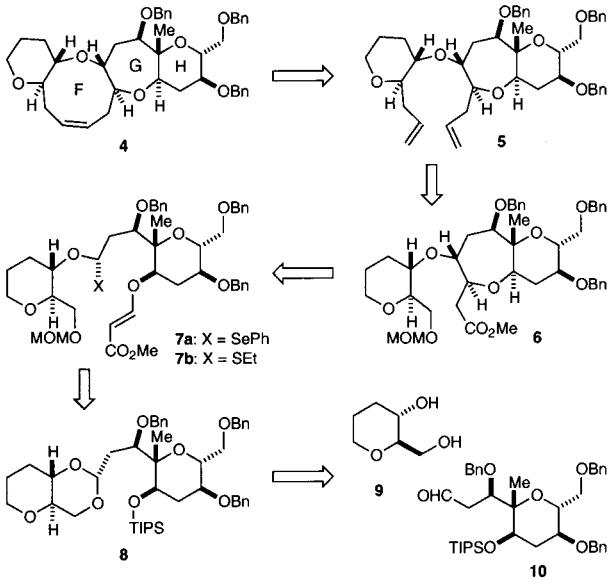
Scheme 1. Retrosynthetic Analysis of (E)FGH Ring System 4

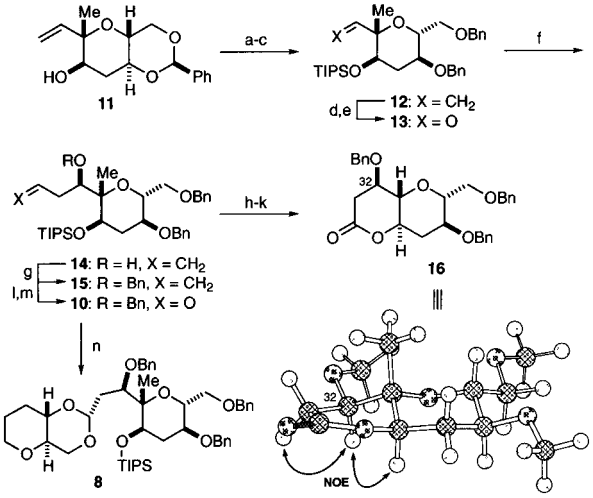


We have already reported that a trans-fused hexahydrooxonine ring system could be assembled via an SmI_2-mediated Reformatsky-type reaction of an O-linked oxacyclic ring system, which was constructed by an intramolecular reaction of (γ-alkoxyallyl)silane with acetal.[14c,d,h,k] However, an O-linked oxepane ring system with the correct trans-syn-trans stereochemistry could not be obtained by this method. To circumvent this problem, we have developed an alternative method for the construction of an O-linked oxepane ring system based on an intramolecular radical cyclization.[14e] In this paper, we describe in detail a convergent and efficient synthetic route to the (E)FGH ring system **4** of ciguatoxins via the intramolecular radical cyclization methodology combined with a ring-closing metathesis reaction[19] and also a conformational analysis of the hexahydrooxonine ring F of **4** by dynamic NMR studies.[20]

Results and Discussion

Synthesis Plan. A retrosynthetic analysis of the (E)-FGH ring system **4** of ciguatoxins is outlined in Scheme 1. In our earlier synthesis of model compounds furnished with the hexahydrooxonine F ring, we employed an intramolecular SmI_2-mediated Reformatsky-type reaction to construct the fused hexahydrooxonine ring system.[14c,d,h,k] However, this synthesis necessitated a multistep sequence of reactions, and thus a more efficient route to construct the F ring from a precursor O-linked oxacyclic system was sought. Hence, we planned to construct the hexahydrooxonine ring F in **4** from the precursor diene **5** by a ring-closing metathesis (RCM) reaction,[21] which has been successfully used in the synthesis of a medium-sized ether ring system.[16,22] The diene **5** should be readily obtained from the O-linked oxepane ring system **6**.

Scheme 2[a]



[a] Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, room temperature; (b) CSA, CH_2Cl_2/MeOH (1:1), room temperature; (c) NaH, BnBr, DMF, 0 °C → room temperature, 89% (three steps); (d) OsO_4 (cat.), NMO, acetone/H_2O (5:1), room temperature; (e) $NaIO_4$, THF/H_2O (5:1), room temperature; (f) *n*-$Bu_3SnCH_2CH{=}CH_2$, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −78 → 0 °C, 81% (three steps); (g) NaH, BnBr, DMF, 0 °C → room temperature, quant; (h) TBAF, THF, room temperature, 92%; (i) OsO_4 (cat.), NMO, acetone/H_2O (4:1), room temperature; (j) $NaIO_4$, THF/H_2O (2:1), room temperature; (k) PDC, 4 Å molecular sieves, CH_2Cl_2, room temperature, 57% (three steps); (l) OsO_4 (cat.), NMO, acetone/H_2O (4:1), room temperature; (m) $NaIO_4$, THF/H_2O (2:1), room temperature; (n) **9**, $Sc(OTf)_3$, benzene, room temperature, 80% (three steps).

Construction of the oxepane ring G in **6** would be accessible from the precursor mixed thio- or selenoacetal **7** with the aid of our radical cyclization strategy, which has been already reported to proceed in a highly stereoselective manner in a simple model system.[14e] In turn, the mixed thio- or selenoacetal moiety in **7** would be introduced by regioselective cleavage of the acetal ring in **8**, which should be easily derived from diol **9**[23] and aldehyde **10**.

Synthesis of Acetal 8. The synthesis of acetal **8** commenced with the known alcohol **11**,[24] which was converted into triisopropylsilyl (TIPS) ether **12** by a three-step procedure in 89% overall yield (Scheme 2). Oxidative cleavage of the double bond of **12** provided aldehyde **13**. Subsequent chelation-controlled addition of

(19) Part of this work has been communicated.[14g]

(20) Very recently, the first total synthesis of CTX3C was reported by Hirama and co-workers; see: Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904−1907. They utilized our radical cyclization−ring-closing metathesis strategy for the critical step to complete their total synthesis.

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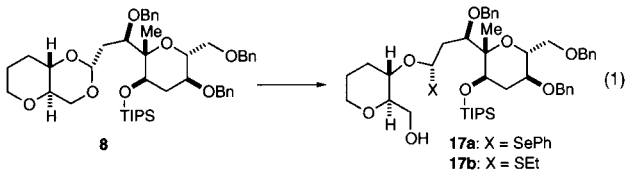
(24) Compound **11** is available in nine steps from 2-deoxy-D-ribose; see: Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517−4552.

Table 1. Regioselective Cleavage of Dioxane Acetal 8[a]



entry	reagent	conditions	yield, %
1	*i*-$Bu_2AlSePh$	toluene, −20 °C, 6 h	NR[b]
2	*i*-$Bu_2AlSePh$	CH_2Cl_2/hexane (1:2), 0 °C, 21 h	62[c]
3	*i*-$Bu_2AlSePh$	CH_2Cl_2/hexane (1:2), room temp, 2 h	70[d]
4	Et_2AlSPh	CH_2Cl_2/hexane (1:2), room temp, 2 h	79

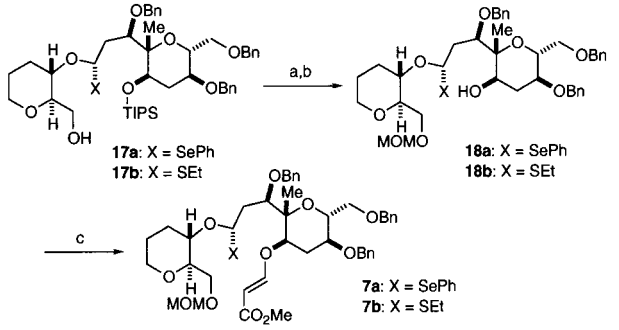
[a] Reactions were carried out using 6 equiv of *i*-$Bu_2AlSePh$ or Et_2AlSPh in 7 mM solution. [b] NR = no reaction. [c] Starting material was recovered in 21% yield. [d] Starting material was recovered in 5% yield.

allyltributyltin[25] afforded the homoallylic alcohol **14** as the sole product in 81% overall yield, which was protected as the benzyl ether **15**. The stereochemistry of the newly generated stereocenter at C32[26] was confirmed by its conversion to lactone **16** and its ^1H NMR analysis. Thus, removal of the silyl group of **15** (92%) followed by oxidative cleavage of the double bond and further oxidation of the derived hemiacetal with pyridinium dichromate gave lactone **16** in 57% yield for the three steps. NOE experiments on **16** unambiguously established the stereochemistry as shown.

Oxidative cleavage of the double bond of **15** produced *β*-benzyloxyaldehyde **10**, which was then treated with diol **9**[23] in the presence of scandium triflate ($Sc(OTf)_3$)[27] to afford the desired acetal **8** as a single stereoisomer in 80% overall yield.

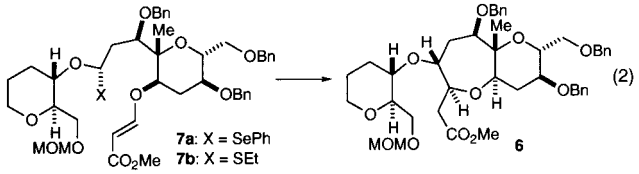
Synthesis of *β*-Alkoxyacrylate 7. With the desired **8** in hand, we investigated regioselective cleavage of the acetal ring; the results are summarized in Table 1. Treatment of **8** with diisobutylaluminum benzeneselenolate (*i*-$Bu_2AlSePh$),[28] generated in situ from diphenyl diselenide and DIBALH, under the previously reported conditions[14e] resulted in no reaction (entry 1). The use of CH_2Cl_2/hexane (1:2) as a solvent effected regioselective cleavage of the acetal C−O bond, leading to the desired mixed selenoacetal **17a** as a single stereoisomer (entries 2 and 3). However, the yield of **17a** was moderate (60−70% yield), and the starting material was recovered (5−20% yield). Prolonged reaction time to improve the yield resulted in formation of a significant amount of debenzylated byproducts. On the other hand, the use of diethylaluminum benzenethiolate (Et_2AlSPh)[28] instead of *i*-Bu_2-AlSePh resulted in a higher yield of product and better reproducibility (entry 4). Thus, treatment of **8** with Et_2-AlSPh, generated in situ from triethylaluminum and benzenethiol, produced the mixed thioacetal **17b** in 79% yield. The stereochemistry at the acetal carbon was tentatively assigned as shown in structure **17** on the basis of the proposed reaction mechanism.[29] Presumably, this reaction proceeds by a tight ion paired S_N1-like mechanism, which involves regioselective complexation of the organoaluminum reagent to the more sterically accessible dioxane oxygen followed by intramolecular attack of the phenylselenide anion syn to the cleaved C−O bond.

Scheme 3[a]



[a] Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, room temperature; (b) TBAF, THF, room temperature; (c) methyl propiolate, *N*-methylmorpholine, CH_2Cl_2, room temperature, 88% from **17a**, 87% from **17b**.

Table 2. Intramolecular Radical Cyclization To Construct the Oxepane Ring G



entry	substrate	conditions	yield, % (recovered **7**, %)
1[a]	**7a**	*n*-Bu_3SnH (2.5 equiv), AIBN (cat.), toluene (10 mM), 80 °C	76 (0)
2	**7a**	*n*-Bu_3SnH (2.5 equiv), Et_3B (cat.), benzene (1 mM), room temp	75 (0)
3	**7b**	*n*-Bu_3SnH (10 equiv), Et_3B (cat.), benzene (1 mM), room temp	14 (76)
4[a]	**7b**	*n*-Bu_3SnH (2 equiv), AIBN (cat.), toluene (10 mM), 80 °C	45 (44)
5[a]	**7b**	*n*-Bu_3SnH (10 equiv), AIBN (cat.), toluene (10 mM), 80 °C	85 (0)

[a] Dropwise addition of *n*-Bu_3SnH by syringe pump over 4−5 h.

Protection of the primary alcohol of **17a** and **17b** as their methoxymethyl (MOM) ethers followed by removal of the silyl group provided alcohols **18a** and **18b** (Scheme 3). Subsequent treatment with methyl propiolate and *N*-methylmorpholine[30] provided the requisite *β*-alkoxyacrylates **7a** and **7b** in high overall yield, setting the stage for radical cyclization to construct the G ring.

Radical Cyclization for the Construction of the G Ring. With the desired **7a** and **7b** in hand, we next attempted the crucial intramolecular radical cyclization reaction (Table 2). Treatment of a solution of mixed selenoacetal **7a** and a catalytic amount of 2,2′-azobis-(isobutyronitrile) (AIBN) in toluene with *n*-Bu_3SnH (2.5 equiv) at 80 °C provided the desired O-linked seven-membered-ring system **6** in 76% yield (entry 1). In this

(25) Charette, A. B.; Mellon, C.; Pouillard, L.; Malenfant, E. *Synlett* **1993**, 81−82.

(26) The numbering of carbon atoms of all compounds in this paper corresponds to that of ciguatoxin (CTX).

(27) (a) Fukuzawa, S.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077−1078. (b) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839−841.

(28) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831−2843.

(29) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595−4612.

(30) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952−1958.

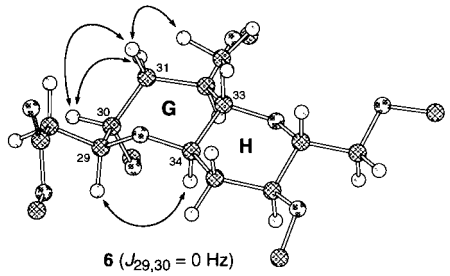


Figure 2. NOE experiments on compound **6**. Benzyl groups and the six-membered-ring portion are omitted for clarity.

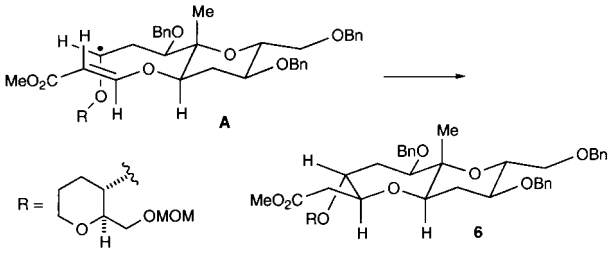
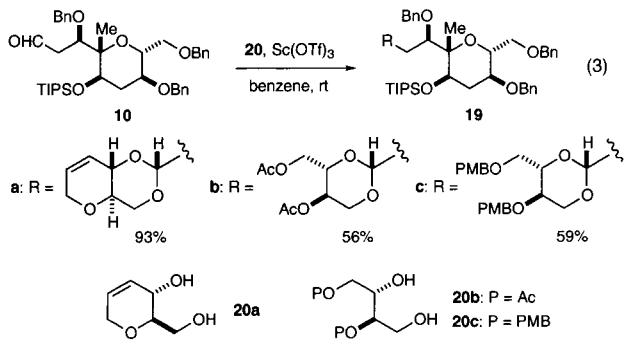


Figure 3. Mechanistic rationale for the radical cyclization to form O-linked oxepane.

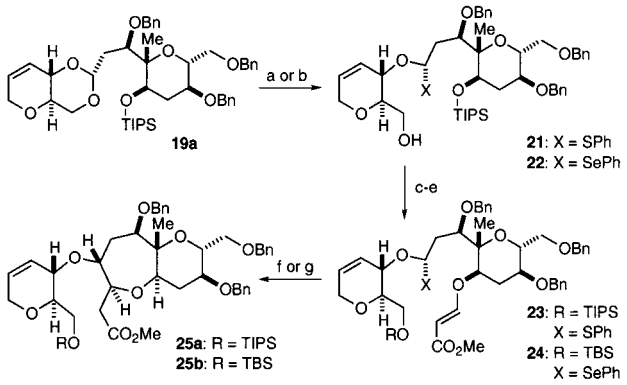
reaction, to avoid formation of the reduction product, it was required that the *n*-Bu_3SnH concentration be kept low by slow addition via a syringe pump over a 4−5 h period. When the reaction was carried out with triethylborane[31] in place of AIBN at room temperature, a comparable yield of **6** was obtained (entry 2). On the other hand, radical cyclization of mixed thioacetal **7b** under the conditions described in entry 3 resulted in a low yield of **6**, although an excess amount of *n*-Bu_3SnH was used. The yield of **6** was improved by carrying out the reaction under thermal conditions (entry 4). Finally, the best result was realized when excess *n*-Bu_3SnH was used, and the desired **6** was obtained reproducibly in 85% yield (entry 5). The stereochemistry of **6** was confirmed on the basis of the coupling constant, $J_{26,27} = 0$ Hz, and NOE data as shown in Figure 2. The stereochemical outcome of these radical reactions may be rationalized by the transition state conformer **A**, in which steric congestion between the bulky alkoxy group attached to the radical center and the acrylate unit is avoided (Figure 3).

To ascertain the scope of this radical cyclization reaction, acetals **19a**−**c** were prepared by condensation between **10** and **20a**−**c** following the same method as described before (eq 3) and allowed to react with *i*-Bu_2-



(31) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2578−2583.

Scheme 4[a]



[a] Reagents and conditions: (a) Et_2AlSPh (6 equiv), CH_2Cl_2/hexane (1:2, 7 mM), room temperature, 6.5 h, 64% for **21**; (b) *i*-$Bu_2AlSePh$ (3 equiv), CH_2Cl_2-hexane (1:2, 30 mM), room temperature, 3 h, 89% for **22**; (c) TBAF, THF, room temperature; (d) TIPSCl or TBDMSCl, imidazole, DMF, room temperature; (e) methyl propiolate, *N*-methylmorpholine, CH_2Cl_2, room temperature, 78% (three steps) for **23**; 77% (three steps) for **24**; (f) *n*-Bu_3SnH (10 equiv), AIBN (cat.), toluene (10 mM), 80 °C, 90% for **25a**; (g) *n*-Bu_3SnH (1.5 equiv), AIBN (cat.), toluene (10 mM), 65 °C, 89% for **25b**.

AlSePh or Et_2AlSPh. Treatment of **19a** with Et_2AlSPh or *i*-$Bu_2AlSePh$ under the similar conditions used to generate **7a** and **7b** produced the mixed thioacetal **21** or selenoacetal **22**, respectively, in good yield (Scheme 4). However, reactions of **19b** and **19c** with Et_2AlSPh or *i*-$Bu_2AlSePh$ failed to provide the desired products and were complicated by undesired side products, including deprotected compounds and dithio- or diselenoacetal. These results clearly show that the presence of a ring structure that restricts the acetal moiety is necessary to effect regioselective acetal cleavage.

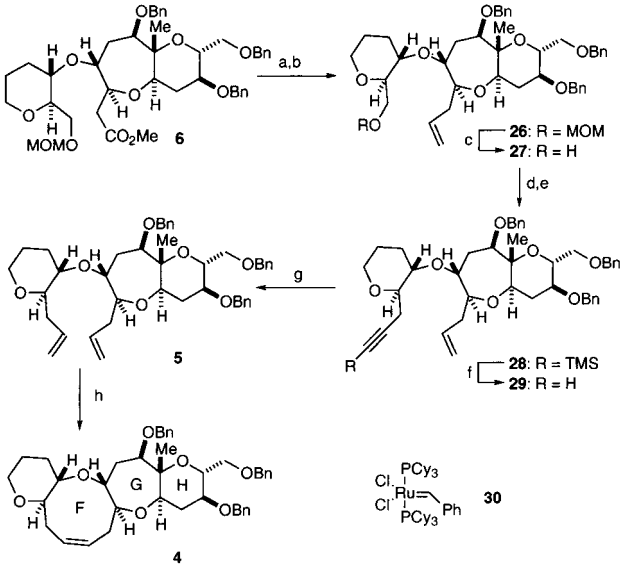
Mixed acetals **21** and **22** were readily converted to β-alkoxyacrylates **23** and **24**, respectively, as shown in Scheme 4. Removal of the silyl group followed by selective protection of the primary alcohol and subsequent treatment with methyl propiolate and *N*-methylmorpholine afforded **23** and **24**, respectively. Radical cyclization of **23** and **24** proceeded smoothly in the presence of the dihydropyran ring system to afford O-linked oxepane **25** in 90% and 89% yield from the respective precursors.

Synthesis of the (E)FGH Ring System of Ciguatoxin. Elaboration of the O-linked oxacycle **6** thus obtained to the ciguatoxin (E)FGH ring system **4** is outlined in Scheme 5. DIBALH reduction of **6** and Wittig methylenation of the resultant aldehyde gave olefin **26** in 77% yield for the two steps. Selective removal of the MOM group was accomplished with dimethyl sulfide and $BF_3{\cdot}OEt_2$[32] to give alcohol **27** in 83% yield. Activation of the primary alcohol by triflate formation and subsequent displacement with lithium (trimethylsilyl)acetylide provided silylacetylene **28** in 61% yield (two steps).[33] Removal of the TMS group (K_2CO_3, MeOH) afforded alkyne **29** (90%), which was then subjected to partial hydrogenation with Lindlar catalyst to furnish diene **5** in 86% yield, setting the stage for RCM reaction to form the hexahydrooxonine ring. Finally, treatment of **5** with Grubbs

(32) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662−3664.

(33) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *31*, 4609−4612.

Scheme 5[a]



[a] Reagents and conditions: (a) DIBALH, CH_2Cl_2, −78 °C; (b) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 77% (two steps); (c) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2, 0 °C, 83%; (d) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (e) (trimethylsilyl)acetylene, *n*-BuLi, THF/HMPA, −78 °C, 61% (two steps); (f) K_2CO_3, THF/MeOH (2:3), room temperature, 90%; (g) H_2, Lindlar catalyst, EtOAc, room temperature, 86%; (h) $RuCl_2(PCy_3)_2{=}CHPh$ (**30**), CH_2Cl_2 (4 mM), 35 °C, 4 days, 61%.

catalyst **30**[34] in CH_2Cl_2 (4 mM) at 35 °C for 4 days led to the formation of the hexahydrooxonine F ring and completed the synthesis of the targeted (E)FGH ring system **4** in 61% yield.[35]

Conformational Analysis of Tetracyclic Model System 4. It is recognized that the fused hexahydrooxonine ring system, representing the F ring of ciguatoxins, exists as an equilibrium mixture of two conformations, UP and DOWN conformers, in solution.[14c,d,h,k] In the case of ciguatoxins, the ^{1}H NMR signals of the olefinic protons and their neighboring methylenes on the hexahydrooxonine ring F were severely broadened at room temperature, and these signals became sharp when measured at low temperature.[4b,c] Since these sharpened peaks are thought to be derived from a single conformer, the F ring is assumed to mostly exist as a dominant UP conformer at low temperature, the structure of which was confirmed by NOE experiments at low temperature.[4b] Whereas natural ciguatoxins exhibit a preference for the UP conformation over the DOWN one, model compounds **31**[14c,h] and **32**,[14d,k] containing the hexahydrooxonoine ring F, existed as a 1:1 equilibrium mixture of the two conformers (Figure 4).

The ^{1}H and ^{13}C NMR signals around the hexahydrooxonine ring F within **4** were also broadened at room temperature due to slow conformational changes, as was observed for ciguatoxins and model compounds (**31** and **32**) furnished with the F ring. The dynamic NMR studies showed that **4** existed as a mixture of the two conformers UP and DOWN, in an approximately 5:1 ratio (pyridine-d_5, −30 °C). The stereostructure of the major conformer was unambiguously determined to be the UP conformer by virtue of spin-coupling constants, which were extracted from the E.COSY spectrum[36] at low temperature (Figure 5). This is the first illustration that reproduces the conformational behavior of the F ring of ciguatoxins, *including the energy difference between the two conformers*. Considering the previous studies,[14c,d,h,k] the present result clearly shows that the presence of hydroxyl and/or angular methyl substituents on the G ring have an important effect on the energy difference between the UP and DOWN conformers of a fused hexahydrooxonine ring system.

Most recently, Hirama and co-workers showed that the conformational behavior of the hexahydrooxonine ring F of model compound **33** (Figure 4) is more similar to that of natural products than **4**.[16f] Only a single set of ^{1}H NMR

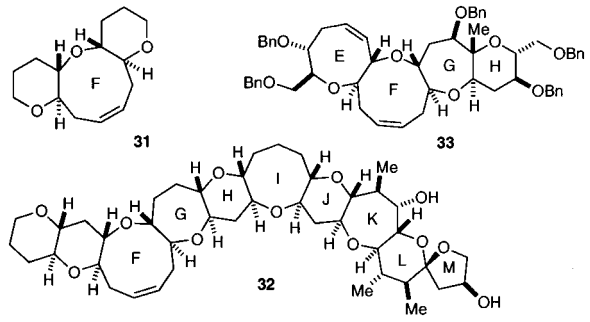


Figure 4. Model compounds containing the fused hexahydrooxonine ring system.

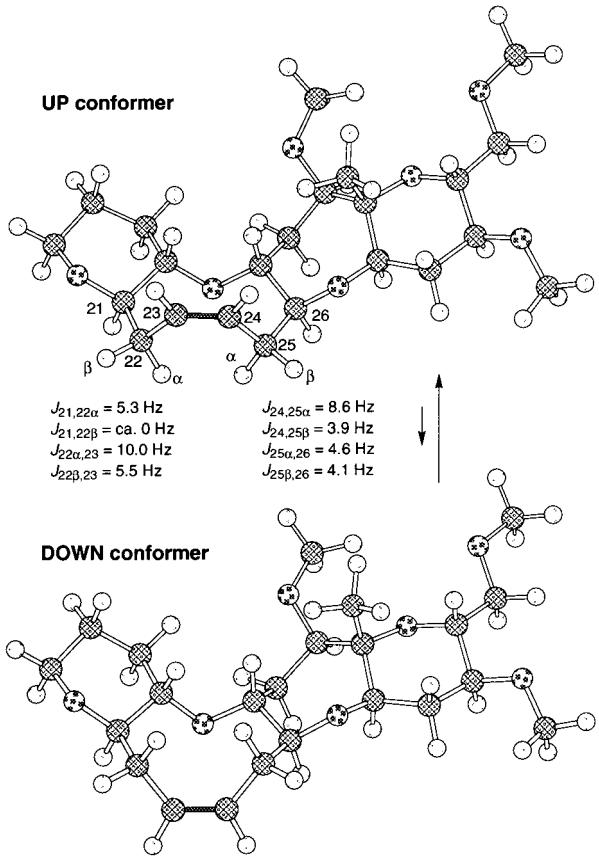


Figure 5. Two solution conformers (UP and DOWN) of compound **4** (pyridine-d_5, −30 °C) and selected coupling constants for the UP conformer.

(34) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(35) Use of other solvents, such as benzene or dichloroethane, resulted in a lower yield of **4**.

(36) Griesinger, C.; Sørensen, O. W.; Ernst, R. R. *J. Am. Chem. Soc.* **1985**, *107*, 6394−6395.

signals, presumably due to the UP conformer, was observed for **33** at −20 °C in pyridine. In addition to the G ring substituents, the ring size of the other adjacent E ring would be required for the reproduction of the conformational behavior of the hexahydrooxonine F ring of ciguatoxins.

Conclusion

A highly convergent and stereoselective synthetic route to the (E)FGH ring system **4** of ciguatoxins based on an intramolecular radical cyclization combined with a ring-closing metathesis reaction has been developed. The synthetic strategy described herein provides a possible solution to a convergent construction of the ciguatoxin framework at this position. Further synthetic studies toward ciguatoxins and their designed non-natural analogues are currently under way. The conformational behavior of the hexahydrooxonine ring of tetracyclic model system **4** reproduced that of the ring F of natural ciguatoxins, where the UP conformer was predominant over the DOWN one in solution. The result strongly suggests that the presence of substituents on the G ring may have an effect on the energy difference between the two conformers.

Experimental Section

General Methods. All reactions sensitive to air or moisture were carried out under an argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Anhydrous THF was used as supplied. Diethyl ether (Et_2O) was distilled under argon from sodium metal and benzophenone ketyl. Benzene, dichloromethane, hexane, 2,6-lutidine, methanol, pyridine, toluene, and triethylamine were distilled under nitrogen from calcium hydride. HMPA and DMSO were distilled from calcium hydride under reduced pressure. All other reagents were used as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F_{254} plates. Column chromatography was performed using silica gel 60 (70−230 mesh) or silica gel 60N (40−100 mesh, spherical, neutral), and for flash column chromatography silica gel 60 (230−400 mesh) or silica gel 60N (100−210 mesh, spherical, neutral) was used. IR spectra were recorded as thin films on NaCl plates. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in ppm relative to internal solvent (^1H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), C_5HD_4N (7.19); ^{13}C NMR, $CDCl_3$ (77.0); C_6D_6 (128.0), C_5D_5N (149.9)). Low- and high-resolution mass spectra were measured under fast atom bombardment (FAB) conditions with *m*-nitrobenzyl alcohol (NBA) as the matrix.

Bis(benzyl) Ether 12. To a solution of alcohol **11**[24] (21.03 g, 76.11 mmol) in CH_2Cl_2 (380 mL) at 0 °C were successively added 2,6-lutidine (27 mL, 230 mmol) and triisopropylsilyl chloride (27 mL, 100 mmol). The resultant solution was stirred at room temperature for 14 h before the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with ether (1 L), and the extracts were washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10−20% ethyl acetate/hexanes) to give TIPS ether.

To a solution of the above TIPS ether in methanol/CH_2Cl_2 (1:1, v/v. 500 mL) was added *p*-toluenesulfonic acid hydrate (4.45 g, 23.4 mmol). The resultant solution was stirred at room temperature for 19.5 h. Another portion of *p*-toluenesulfonic acid hydrate (2.87 g, 15.1 mmol) was added, and the stirring was continued for another 2 h. The reaction was quenched with triethylamine (20 mL), and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (20−80% ethyl acetate/hexanes) to give the diol.

To a solution of the above diol in DMF (150 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 12.34 g, 308.5 mmol). The resultant mixture was stirred at room temperature for 15 min. The mixture was recooled to 0 °C and treated with benzyl bromide (32 mL, 270 mmol). After 20 min, the resulting solution was cooled to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C. The mixture was extracted with ethyl acetate (1.5 L), and the extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2−10% ethyl acetate/hexanes) to give bis(benzyl) ether **12** (35.53 g, 89% for the three steps) as a colorless oil: $[\alpha]_D^{27}$ +13.5° (*c* 2.9, $CHCl_3$); IR (film) 3502, 3088, 3064, 2943, 1946, 1806, 1729, 1643, 1604, 1496, 1455, 1407, 1383, 1363, 1330, 1272, 1224, 1204, 1119, 1028, 996, 959, 922, 882, 818, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.24 (m, 10H), 6.09 (dd, J = 17.4, 10.9 Hz, 1H), 5.37 (dd, J = 17.4, 1.8 Hz, 1H), 5.11 (dd, J = 10.9, 1.8 Hz, 1H), 4.69 (d, J = 12,4 Hz, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 3.74 (d, J = 3.8 Hz, 2H), 3.68−3.64 (m, 2H), 3.46 (ddd, J = 11.8, 9.8, 4.7 Hz, 1H), 2.24 (ddd, J = 12.1, 4.7, 4.7 Hz, 1H), 1.67 (ddd, J = 12.1, 11.8, 11.8 Hz, 1H), 1.29 (s, 3H), 1.01 (s, 21H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 143.2, 138.7, 138.3, 128.4, 127.9, 127.7 (×2), 127.4, 112.8, 76.7, 73.4, 73.0, 72.6, 71.4, 69.8, 35.3, 18.1, 14.6, 12.7; HRMS (FAB) calcd for $C_{32}H_{48}O_4Si$ ((M + Na)$^+$) 547.3220, found 547.3223.

Homoallylic Alcohol 14. To a solution of bis(benzyl) ether **12** (6.04 g, 11.5 mmol) and *N*-methylmorpholine *N*-oxide (50 wt % in water, 8.50 g, 36.3 nnol) in acetone/water (5:1, v/v, 168 mL) was added osmium tetroxide (147.4 mg, 0.580 mmol). The resultant solution was stirred at room temperature for 10 h. Another portion of *N*-methylmorpholine *N*-oxide (50 wt % in water, 2.85 g, 12.2 mmol) was added, and the stirring was continued for a further 9 h. The reaction was quenched with saturated aqueous Na_2SO_3 (70 mL), the mixture was extracted with ethyl acetate (500 mL), and the extracts were washed with water and saturated aqueous Na_2SO_3. The aqueous layers were combined and extracted with ethyl acetate (500 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (20−80% ethyl acetate/hexanes) gave the diol (5.53 g).

To a solution of the above diol (5.46 g, 9.77 mmol) in THF/water (2:1, v/v, 180 mL) was added $NaIO_4$ (10.45 g, 48.9 mmol). The resultant solution was stirred at room temperature for 9 h. The mixture was extracted with ethyl acetate (600 mL), and the extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give the aldehyde **13**.

To a solution of the above aldehyde **13** in CH_2Cl_2 (100 mL) at 0 °C was added magnesium bromide etherate (6.44 g, 28.0 mmol). After 30 min, the solution was cooled to −78 °C and treated with allyltributyltin (3.80 mL, 12.3 mmol). The resultant solution was warmed to room temperature over 1 h, and the stirring was continued at room temperature for a further 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), the mixture was extracted with ethyl acetate (600 mL), and the extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5−20% ethyl acetate/hexanes) to give the homoallylic alcohol **14** (5.24 g, 81% for the three steps) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (m, 10H), 5.95 (dddd, J = 17.1, 10.2, 3.2, 3.1 Hz, 1H), 5.09 (dd, J = 17.1, 1.7 Hz, 1H), 5.05 (dd, J = 10.2, 1.7 Hz, 1H), 4.57−4.45 (m, 4H), 4.15 (dd, J = 11.8, 4.8 Hz, 1H), 3.68−3.61 (m, 3H), 3.55 (ddd, J = 9.8, 4.3, 1.8 Hz, 1H), 3.34 (ddd, J = 11.2, 9.8, 4.7 Hz, 1H), 2.40−2.35 (m, 1H), 2.26−2.21 (m, 1H), 1.65−1.58 (m, 2H), 1.11 (s, 3H), 1.02 (s, 21H); MS (FAB) *m*/*z* 591 ((M + Na)$^+$).

Tris(benzyl) Ether 15. To a solution of homoallylic alcohol **14** (122.5 mg, 0.022 mmol) in DMF (1 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 3.5 mg, 0.088 mmol). The resultant solution was stirred at room temperature for 30 min and then cooled to 0 °C. Benzyl bromide (10 μL,

0.084 mmol) was added, and the mixture was stirred at 0 °C for 30 min. Another portion of benzyl bromide (10 μL, 0.084 nnol) was added, and the stirring was continued for a further 4 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL), the mixture was extracted with ethyl acetate (50 mL), and the extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5−10% ethyl acetate/hexanes) to give tris(benzyl) ether **15** (14.9 mg, quant.) as a colorless oil: $[\alpha]_D^{26} = +23.8°$ (*c* 1.3, $CHCl_3$); IR (film) 3064, 3030, 2943, 2865, 1724, 1639, 1496, 1454, 1362, 1255, 1206, 1093, 1028, 996, 910, 883, 816, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.22 (m, 15H), 5.96 (dddd, J = 17.2, 10.2, 3.2, 3.2 Hz, 1H), 5.10 (dd, J = 17.2, 1.9 Hz, 1H), 5.00 (dd, J = 10.2, 1.9 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 4.65 (d, J = 12.3 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.56 (d, J = 12.3 Hz, 1H), 4.18 (dd, J = 11.8, 4.8 Hz, 1H), 3.69 (m, 2H), 3.63 (dd, J = 7.2, 5.1 Hz, 1H), 3.55 (m, 1H), 3.39 (ddd, J = 11.3, 9.8, 4.6 Hz, 1H), 2.53 (m, 2H), 2.23 (ddd, J = 11.9, 4.8, 4.6 Hz, 1H), 1.65 (ddd, J = 11.9, 11.8, 11.3 Hz, 1H), 1.15 (s, 3H), 0.99 (s, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5, 138.7, 138.4, 138.3, 137.2, 128.7, 128.4, 128.2, 128.0, 127.8, 127.7, 127.4, 126.9, 115.8, 81.9, 80.6, 73.4, 73.1, 72.7, 72.1, 71.6, 69.8, 68.2, 35.3, 33.3, 18.3, 13.4, 13.3, 13.0; HRMS (FAB) calcd for $C_{41}H_{58}O_5SiNa$ ($(M + Na)^+$) 681.3951, found 681.3965.

Lactone 16. To a solution of tris(benzyl) ether **15** (21.4 mg, 0.0325 mmol) in THF (2 mL) was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 130 μL, 0.13 mmol), and the resultant solution was stirred at room temperature for 2.5 h. The mixture was extracted with ethyl acetate (50 mL), and the extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (15−35% ethyl acetate/hexanes) gave the alcohol (15.6 mg, 92%) as a colorless oil.

To a solution of the above alcohol (14.3, mg, 0.0284 mmol) and *N*-methylmorpholine *N*-oxide (50 wt % in water, 33.9 mg, 0.145 mmol) in acetone/water (4:1, v/v, 2 mL) was added osmium tetroxide (1.4 mg, 0.0055 mmol). The resultant solution was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous Na_2SO_3 (1 mL), the mixture was extracted with ethyl acetate (50 mL), and the extracts were washed with saturated aqueous Na_2SO_3 and brine. The combined aqueous layers were extracted with $CHCl_3$ (10 mL × 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, to give the crude diol.

To a solution of the above crude diol in THF/water (2:1, v/v, 2 mL) was added $NaIO_4$ (31.6 mg, 0.148 mmol). The resultant solution was stirred at room temperature for 1.5 h. The mixture was extracted with ethyl acetate (50 mL), and the extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (20−70% ethyl acetate/hexanes) gave the hemiacetal (10.7 mg) as a colorless oil.

To a suspension of the above hemiacetal (10.7 mg, 0.0211 mmol) and 4 Å molecular sieves (11.6 mg) in CH_2Cl_2 (1 mL) was added pyridinium dichromate (25.6 mg, 0.068 mmol). The resultant solution was stirred at room temperature overnight. Another portion of pyridinium dichromate (15.3 mg, 0.0407 mmol) was added, and the stirring was continued for a further 4.5 h. The mixture was diluted with ethyl acetate (10 mL), filtered through a pad of Florisil, and washed with ethyl acetate. The filtrate and washings were combined and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (20−30% ethyl acetate/hexanes) to give lactone **16** (8.1 mg, 57% for the three steps) as a colorless solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31−7. 24 (m, 15H), 4.84 (d, J = 11.9 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.59 (d, J = 11.3 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 11.3 Hz, 1H), 3.85 (dd, J = 12.5, 4.6 Hz, 1H), 3.77 (dd, J = 9.2, 7.6 Hz, 1H), 3.73−3.68 (m, 2H), 3.55 (ddd, J = 11.3, 9.5, 4.9 Hz, 1H), 3.03 (dd, J = 19.2, 9.2 Hz, 1H), 2.56 (dd, J = 19.2, 7.6 Hz, 1H), 2.46 (ddd, J = 12.2, 4.9, 4.6 Hz, 1H), 1.80 (ddd, J = 12.2, 11.9, 11.3 Hz, 1H), 1.30 (s, 3H); MS (FAB) *m*/*z* 525 ($(M + Na)^+$).

Acetal 8. To a solution of tris(benzyl) ether **15** (1.46 g, 2.22 mmol) and *N*-methylmorpholine *N*-oxide (50 wt % in water, 2.00 g, 8.53 mmol) in acetone/water (4:1, v/v, 60 mL) was added osmium tetroxide (47.2 mg, 0.186 mmol). The resultant solution was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous Na_2SO_3 (70 mL), the mixture was extracted with ethyl acetate (250 mL), and the extracts were washed with water and saturated aqueous Na_2SO_3. The combined aqueous layers were further extracted with ethyl acetate (50 mL × 2). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo, to give the crude diol.

To a solution of the above diol in THF/water (2:1, v/v, 70 mL) was added $NaIO_4$ (2.37 g, 11.1 mmol). The resultant solution was stirred at room temperature for 1 h. The mixture was extracted with ethyl acetate/ether (5:2, v/v, 350 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo, to give the crude aldehyde **10**.

To a solution of the above aldehyde **10** and diol **9**[23] (392.2 mg, 297 mmol) in benzene (40 mL) was added scandium trifluoromethanesulfonate (108.0 mg, 0.219 mmol). The resultant solution was stirred at room temperature overnight. The mixture was poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with ethyl acetate (300 mL), and the extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10−20% ethyl acetate/hexanes) to give acetal **8** (1.33 g, 77% for the three steps) as a colorless oil: $[\alpha]_D^{26} = +48.8°$ (*c* 1.3, $CHCl_3$); IR (film) 3030, 2943, 2865, 1948, 1605, 1496, 1455, 1385, 1363, 1291, 1273, 1206, 1094, 1033, 984, 963, 917, 882, 815, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30−7.22 (m, 15H), 4.69 (d, J = 11.9 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.62 (d, J = 12.5 Hz, 1H), 4.62 (dd, J = 3.7, 3.7 Hz, 1H), 4.51 (d, J = 12.5 Hz, 1H), 4.10 (dd, J = 11.9, 4.9 Hz, 1H), 4.01 (dd, J = 10.1, 4.9 Hz, 1H), 3.87 (m, 1H), 3.81 (dd, J = 9.8, 3.1 Hz, 1H), 3.71 (dd, J = 10.7, 4.0 Hz, 1H), 3.64 (dd, J = 10.7, 1.8 Hz, 1H), 3.50 (ddd, J = 9.5, 4.0, 1.8 Hz, 1H), 3.45−3.36 (m, 2H), 3.34 (dd, J = 10.1, 10.1 Hz, 1H), 3.14−3.04 (m, 2H), 2.23 (ddd, J = 11.9, 4.9, 4.6 Hz, 1H), 2.05 (ddd, J = 14.6, 9.8, 3.1 Hz, 1H), 1.73−1.68 (m, 2H), 1.64 (ddd, J = 11.9, 11.9, 11.3 Hz, 1H), 1.49 (dddd, J = 12.3, 11.9, 11.9, 5.2 Hz, 1H), 1.12 (s, 3H), 0.99 (s, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.6, 138.7, 138.5, 128.4, 128.3 (×2), 128.1, 127.9, 127.7, 127.5, 127.4, 127.1, 100.9, 80.5, 78.7, 77.6, 74.4, 73.5, 73.1, 72.6, 72.0, 71.6, 69.7, 69.0, 68.4, 69.0, 35.4, 34.3, 28.7, 25.5, 18.3 (×2), 13.1; HRMS (FAB) calcd for $C_{46}H_{66}O_8SiNa$ ($(M + Na)^+$) 797.4425, found 797.4424.

Mixed Thioacetal 17b. To a solution of triethylaluminum (0.91 M solution in toluene, 1.7 mL, 1.55 mmol) in hexane (24 mL) at 0 °C was added benzenethiol (165 μL, 1.61 mmol). After 30 min, the solution was added to a solution of acetal **8** (203.6 mg, 0.263 mmol) in CH_2Cl_2 (12 mL), and the resultant solution was stirred at room temperature for 4.5 h. The reaction was quenched with saturated aqueous potassium sodium tartrate (5 mL), and the mixture was diluted with ethyl acetate (70 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10−40% ethyl acetate/hexanes) to give the mixed thioacetal **17b** (183.5 mg, 79%) as a colorless oil: $[\alpha]_D^{27} = +47.2°$ (*c* 0.55, $CHCl_3$); IR (film) 3482, 3061, 3030, 2943, 2865, 1583, 1496, 1454, 1361, 1261, 1208, 1102, 882, 804, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 (m, 2H), 7.31−7.16 (m, 18H), 5.06 (dd, J = 10.4, 2.0 Hz, 1H), 4.66 (d, J = 11.9 Hz, 2H), 4.63 (d, J = 12.5 Hz, 1H), 4.58 (d, J = 12.5 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.51 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.07 (dd, J = 11.6, 4.4 Hz, 1H), 3.87 (dd, J = 11.6, 5.0 Hz, 1H), 3.82−3.77 (m, 2H), 3.74−3.66 (m, 4H), 3.49 (ddd, J = 9.8, 3.5, 2.6 Hz, 1H), 3.38 (ddd, J = 11.6, 9.8, 5.0 Hz, 1H), 3.27 (ddd, J = 11.6, 11.6, 2.0 Hz, 1H), 3.12 (ddd, J = 9.2, 5.3, 2.9 Hz, 1H), 2.41 (ddd, J = 14.9, 10.4, 2.0 Hz, 1H), 2.24−2.17 (m, 3H), 1.93 (m, 1H), 1.62 (ddd, J = 11.9, 11.6, 11.6 Hz, 1H), 1.51 (m, 1H), 1.42 (m, 1H), 1.15 (m, 1H), 1.06 (s, 3H), 0.99 (s, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.8, 138.6, 138.4, 133.9, 133.0, 128.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 126.91, 126.86, 83.7, 81.0, 80.5, 78.8, 73.4,

72.9, 72.5, 71.5, 70.9, 69.82, 69.77, 68.4, 67.7, 63.0, 36.6, 35.3, 27.7, 25.0, 18.31, 18.27, 13.0; HRMS (FAB) calcd for $C_{52}H_{72}O_8SiSNa$ *m/z* 907 ((M + Na)$^+$) 907.4615, found 907.4629.

Alcohol 18b. To a solution of mixed thioacetal **17b** (141.8 mg, 0.160 mmol) in CH_2Cl_2 (10 mL) were added diisopropylethylamine (140 μL, 0.804 mmol) and chloromethyl methyl ether (40 μL, 0.53 mmol). The resultant solution was stirred at room temperature for 22 h. The mixture was diluted with ethyl acetate (50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in THF (10 mL) and treated with TBAF (1.0 M solution in THF, 0.65 mL, 0.65 mmol), and the resultant solution was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (35−60% ethyl acetate/hexanes) to give alcohol **18b** (123.1 mg, 99% for the two steps) as a colorless oil: IR (film) 3499, 3061, 3030, 2942, 2878, 1718, 1583, 1496, 1454, 1439, 1362, 1328, 1281, 1211, 1102, 966, 918, 866, 787, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (m, 2H), 7.35−7.19 (m, 18H), 5.24 (dd, J = 7.3, 6.1 Hz, 1H), 4.66 (d, J = 9.0 Hz, 2H), 4.58 (d, J = 11.2 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 4.50 (m, 2H), 4.47 (d, J = 12.1 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 3.87 (m, 3H), 3.78−3.72 (m, 2H), 3.68 (dd, J = 10.6, 1.6 Hz, 1H), 3.61−3.54 (m, 3H), 3.37 (ddd, J = 11.5, 9.7, 4.6 Hz, 1H), 3.35 (s, 3H), 3.33 (ddd, J = 9.4, 7.0, 2.5 Hz, 1H), 3.26 (ddd, J = 10.9, 8.2, 2.2 Hz, 1H), 3.10 (s, 1H), 2.39 (ddd, J = 14.8, 7.3, 6.1 Hz, 1H), 2.34 (ddd, J = 12.1, 4.9, 4.6 Hz, 1H), 2.21 (ddd, J = 14.8, 6.5, 6.1 Hz, 1H), 1.98 (m, 1H), 1.57 (ddd, J = 12.1, 11.5, 11.5 Hz, 1H), 1.47−1.38 (m, 2H), 1.32 (s, 3H), 1.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.4, 138.1, 137.8, 134.5, 132.4, 128.9, 128.49, 128.47, 128.4, 128.3, 127.9, 127.72, 127.69, 127.6, 127.5, 127.2, 96.9, 84.2, 84.0, 79.7, 73.5, 73.3, 72.7, 72.4, 70.9, 70.6, 69.9, 67.9, 67.6, 67.0, 55.2, 37.5, 33.2, 27.9, 24.8, 14.8; HRMS (FAB) calcd for $C_{45}H_{56}O_9SNa$ ((M + Na)$^+$) 795.3543, found 795.3553.

***β*-Alkoxyacrylate 7b.** To a solution of alcohol **18b** (108.5 mg, 0.140 mmol) in CH_2Cl_2 (6 mL) were added methyl propiolate (40 μL, 0.45 mmol) and *N*-methylmorpholine (25 μL, 0.23 mmol). The resultant solution was stirred at room temperature for 19.5 h. Additional methyl propiolate (25 μL, 0.28 mmol) and *N*-methylmorpholine (8 μL, 0.07 mmol) were added, and the stirring was continued for a further 19 h. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (20−60% ethyl acetate/hexanes) to give β-alkoxyacrylate **7b** (105.0 mg, 88%): $[\alpha]_D^{26}$ = +47.1° (*c* 1.7, $CHCl_3$); IR (film) 3030, 2947, 1713, 1642, 1623, 1496, 1454, 1438, 1362, 1329, 1285, 1191, 1140, 1102, 1045, 918, 836, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42−7.20 (m, 21H), 5.22 (d, J = 12.5 Hz, 1H), 5.08 (dd, J = 10.4, 2.6 Hz, 1H), 4.68 (d, J = 8.0 Hz, 2H), 4.61 (d, J = 11.9 Hz, 1H), 4.58−4.55 (m, 3H), 4.51 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.0 Hz, 1H), 4.19 (dd, J = 11.9, 5.0 Hz, 1H), 3.90 (m, 1H), 3.85 (dd, J = 11.0, 2.0 Hz, 1H), 3.78 (ddd, J = 10.4, 9.5, 4.1 Hz, 1H), 3.70 (s, 3H), 3.70−3.54 (m, 5H), 3.46 (ddd, J = 11.6, 9.5, 4.7 Hz, 1H), 3.37 (s, 3H), 3.34−3.28 (m, 2H), 2.45 (ddd, J = 11.9, 5.0, 4.7 Hz, 1H), 2.31 (ddd, J = 14.9, 9.5, 2.6 Hz, 1H), 2.08 (ddd, J = 14.9, 10.4, 2.0 Hz, 1H), 1.95 (m, 1H), 1.66 (ddd, J = 11.9, 11.9, 11.6 Hz, 1H), 1.49 (m, 2H), 1.16 (s, 3H), 1.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9, 160.8, 138.8, 138.4, 137.8, 133.5, 133.3, 128.8, 128.4, 128.30, 128.27, 128.25, 127.8, 127.7, 127.6, 127.54, 127.47, 127.3, 127.1, 98.2, 96.9, 82.6, 79.8, 78.8, 77.0, 73.4, 73.0, 72.0, 71.9, 71.3, 70.4, 69.4, 67.7, 67.6, 53.2, 51.0, 37.8, 30.8, 27.7, 24.8, 13.1; HRMS (FAB) calcd for $C_{49}H_{60}O_{11}SNa$ ((M + Na)$^+$) 879.3754, found 879.3751.

O-Linked Oxepane 6. To a solution of β-alkoxyacrylate **7b** (18.4 mg, 0.0215 mmol) and 2,2′-azobis(isobutyronitrile) (1.7 mg, 0.010 mmol) in toluene (1 mL) heated at 80 °C was added dropwise a solution of tri-*n*-butyltin hydride (55 μL, 0.20 mmol) in toluene (1 mL) via syringe pump over 3.5 h. After the addition, the resultant solution was stirred at the same temperature for a further 1 h. The mixture was cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography on silica gel (25−50% ethyl acetate/hexanes) gave oxepane **6** (13.7 mg, 85%) as a colorless oil: $[\alpha]_D^{26}$ = +69.9° (*c* 1.3, $CHCl_3$); IR (film) 3030, 2947, 1739, 1642, 1496, 1454, 1362, 1284, 1208, 1094, 918, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.21 (m, 15H), 4.85 (d, J = 11.3 Hz, 1H), 4.69−4.52 (m, 6H), 4.41 (d, J = 11.3 Hz, 1H), 4.03 (dd, J = 7.3, 6.7 Hz, 1H), 3.90 (m, 1H), 3.78−3.57 (m, 10H), 3.41−3.18 (m, 9H), 2.42 (dd, J = 15.3, 7.3 Hz, 1H), 2.32 (dd, J = 15.3, 6.7 Hz, 1H), 2.24 (ddd, J = 14.0, 6.4, 3.1 Hz, 1H), 1.79 (dd, J = 13.4, 11.3 Hz, 1H), 1.59−1.52 (m, 2H), 1.26 (s, 3H), 1.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 139.4, 138.5, 138.2, 128.3, 128.23, 128.21, 128.1, 127.7, 127.61, 127.56, 127.4, 127.2, 96.9, 80.4, 80.0, 79.8, 79.4, 78.6, 73.7, 73.6, 73.4, 73.3, 73.1, 72.0, 70.9, 70.4, 67.7, 67.5, 55.3, 51.6, 39.6, 32.7, 32.0, 29.8, 25.1, 9.3; HRMS (FAB) calcd for $C_{43}H_{56}O_{11}Na$ ((M + Na)$^+$) 771.3720, found 771.3733.

Olefin 26. To a solution of oxepane **6** (33.3 mg, 0.0445 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added diisobutylaluminum hydride (1.0 M solution in toluene, 70 μL, 0.070 mmol). The resultant solution was stirred at −78 °C for 1 h before the reaction was quenched with saturated aqueous potassium sodium tartrate (2 mL). The mixture was extracted with ethyl acetate (20 mL), and the extracts were washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered, and concentrated in vacuo, to give the crude aldehyde.

To a suspension of methyltriphenylphosphonium bromide (25.1 mg, 0.0703 mmol) in THF (0.5 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 65 μL, 0.065 mmol). After 30 min, to the ylide solution was added the above aldehyde in THF (0.2 mL). The resultant solution was stirred at 0 °C for 30 min before the reaction was quenched with acetone (1 mL). The mixture was extracted with ethyl acetate (20 mL), and the extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (20−40% ethyl acetate/hexanes) gave olefin **26** (24.5 mg, 77% for the two steps) as a colorless oil: IR (film) 3064, 3030, 2937, 2856, 1732, 1641, 1495, 1454, 1358, 1281, 1209, 1084, 918, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.19 (m, 15H), 5.75 (dddd, J = 17.0, 11.0, 8.0, 6.2 Hz, 1H), 5.04 (dd, J = 11.0, 1.1 Hz, 1H), 5.03 (dd, J = 17.0, 1.1 Hz, 1H), 4.86 (d, J = 11.9 Hz, 1H), 4.68 (d, J = 11.3 Hz, 1H), 4.65−4.59 (m, 4H), 4.54 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 11.3 Hz, 1H), 3.89 (m, 1H), 3.77−3.72 (m, 2H), 3.67−3.61 (m, 2H), 3.58 (dd, J = 10.4, 5.3 Hz, 1H), 3.38 (ddd, J = 11.3, 9.5, 5.0 Hz, 1H), 3.34 (s, 3H), 3.36−3.25 (m, 4H), 3.19 (ddd, J = 8.9, 5.3, 2.0 Hz, 1H), 3.13 (ddd, J = 11.3, 8.9, 4.4 Hz, 1H), 2.26 (ddd, J = 11.9, 5.0, 5.0 Hz, 1H), 2.18 (ddd, J = 14.6, 7.4, 6.2 Hz, 1H), 2.03 (ddd, J = 14.6, 8.0, 5.9 Hz, 1H), 1.93 (m, 1H), 1.86 (ddd, J = 14.3, 6.5, 2.9 Hz, 1H), 1.79 (ddd, J = 14.3, 11.0, 1.4 Hz, 1H), 1.63 (ddd, J = 11.9, 11.3, 11.3 Hz, 1H), 1.55 (m, 2H), 1.28 (s, 3H), 1.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5, 138.6, 138.3, 134.4, 128.4, 128.3, 128.2, 128.1, 127.7, 127.65, 127.60, 127.4, 127.2, 117.6, 96.9, 82.9, 80.6, 80.1, 79.7, 78.7, 73.7, 73.45, 73.43, 73.41, 73.2, 72.1, 70.9, 70.5, 67.8, 67.6, 55.3, 39.5, 32.8, 32.3, 29.9, 25.2, 9.4; HRMS (FAB) calcd for $C_{43}H_{56}O_9Na$ ((M + Na)$^+$) 739.3822, found 739.3803.

Alcohol 27. To a solution of olefin **26** (16.7 mg, 0.0233 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C were added dimethyl sulfide (0.15 mL, 2.0 mmol) and boron trifluoride etherate (10 μL, 0.079 mmol). The resultant solution was stirred at room temperature for 1 h before the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was extracted with ethyl acetate (20 mL), and the extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (20−40% ethyl acetate/hexanes) gave alcohol **27** (13.0 mg, 83%) as a colorless oil: $[\alpha]_D^{27}$ = +66.3° (*c* 0.27, $CHCl_3$); IR (film) 3468, 3063, 3030, 2938, 2862, 1641, 1496, 1453, 1361, 1281, 1209, 1088, 1029, 985, 914, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.19 (m, 15H), 5.75 (dddd, J = 17.4, 11.4, 8.1, 6.3 Hz, 1H), 5.05 (dd, J = 17.4, 1.8 Hz, 1H), 5.04 (dd, J = 11.4, 1.8 Hz, 1H), 4.86 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.1 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.42 (d, J = 11.1 Hz, 1H), 3.87 (m, 1H), 3.79−3.70 (m, 3H), 3.67−3.58 (m, 4H), 3.54 (dd, J = 6.6, 1.5 Hz, 1H), 3.38 (ddd, J = 11.4, 9.6, 4.8 Hz, 1H), 3.32−3.27 (m, 2H), 3.14−

3.10 (m, 2H), 2.27 (ddd, J = 12.0, 4.8, 4.5 Hz, 1H), 2.19 (ddd, J = 14.1, 6.3, 6.0 Hz, 1H), 2.03 (ddd, J = 14.1, 8.0, 7.8 Hz, 1H), 1.88 (m, 1H), 1.85 (ddd, J = 14.4, 6.6, 3.6 Hz, 1H), 1.79 (ddd, J = 14.4, 11.4, 1.5 Hz, 1H), 1.60 (ddd, J = 12.0, 11.4, 11.4 Hz, 1H), 1.57−1.49 (m, 2H), 1.28 (s, 3H), 1.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5, 138.6, 138.3, 134.3, 128.4, 128.28, 128.25, 128.1, 127.8, 127.7, 127.6, 127.4, 127.2, 117.7, 83.1, 80.60, 80.55, 79.6, 79.1, 74.1, 73.5, 73.42, 73.38, 73.2, 72.1, 70.9, 70.5, 67.6, 62.9, 39.5, 32.8, 32.2, 29.8, 25.3, 9.4; HRMS (FAB) calcd for $C_{41}H_{52}O_8Na$ ($(M + Na)^+$) 695.3560, found 695.3541.

(Trimethylsilyl)acetylene 28. To a solution of alcohol **27** (13.7 mg, 0.0204 mmol) in CH_2Cl_2 (0.7 mL) at −78 °C were successively added 2,6-lutidine (10 μL) and trifluoromethanesulfonic acid anhydride (10 μL, 0.059 mmol). The resultant solution was stirred at −78 °C for 1 h before the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was extracted with ethyl acetate (15 mL), and the extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (20−40% ethyl acetate/hexanes) to give the corresponding triflate, which was used immediately in the next reaction without further purification.

To a solution of (trimethylsilyl)acetylene (15 μL, 0.11 mmol) in THF/HMPA (9:1, v/v, 0.35 mL) at −78 °C was added *n*-butyllithium (1.52 M solution in hexane, 60 μL, 0.091 mmol). The resultant solution was stirred at −78 °C for 20 min. To this solution was added dropwise a solution of the above triflate in THF (0.15 mL). The resulting mixture was stirred at −78 °C for 20 h before the reaction was quenched with saturated aqueous NH_4Cl (0.5 mL). The mixture was extracted with ethyl acetate (15 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10−20% ethyl acetate/hexanes) gave (trimethylsilyl)acetylene **28** (9.3 mg, 61%) as a colorless oil along with recovered triflate (3.5 mg, 21%). **28**: IR (film) 3030, 2945, 2175, 1647, 1496, 1454, 1358, 1250, 1207, 1092, 976, 916, 847, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.19 (m, 15H), 5.77 (dddd, J = 15.6, 11.6, 8.0, 6.9 Hz, 1H), 5.06 (dd, J = 15.6, 1.8 Hz, 1H), 5.05 (dd, J = 11.6, 1.8 Hz, 1H), 4.86 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.9 Hz, 1H), 4.62 (d, J = 11.3 Hz, 1H), 4.59 (d, J = 11.9 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 11.3, Hz, 1H), 3.88 (m, 1H), 3.79 (ddd, J = 7.7, 6.1, 1.0 Hz, 1H), 3.75−3.71 (m, 2H), 3.66−3.62 (m, 3H), 3.37 (ddd, J = 11.0, 9.5, 4.9 Hz, 1H), 3.34 (dd, J = 11.9, 4.9 Hz, 1H), 3.28 (ddd, J = 11.3, 9.7, 3.1 Hz, 1H), 3.21 (ddd, J = 10.4, 8.8, 4.3 Hz, 1H), 3.10 (ddd, J = 8.8, 4.3, 4.0 Hz, 1H), 2.56 (m, 2H), 2.30 (ddd, J = 11.9, 4.9, 4.9 Hz, 1H), 2.20 (ddd, J = 14.1, 6.9, 6.1 Hz, 1H), 2.07 (ddd, J = 14.1, 8.0, 7.7 Hz, 1H), 1.93 (m, 1H), 1.87 (ddd, J = 14.4, 6.7, 3.0 Hz, 1H), 1.80 (ddd, J = 14.4, 12.2, 1.5 Hz, 1H), 1.61 (ddd, J = 11.9, 11.9, 11.0 Hz, 1H), 1.54 (m, 2H), 1.29 (s, 3H), 1.13 (m, 1H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5, 138.6, 138.2, 134.2, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.4, 127.2, 117.7, 103.3, 86.6, 82.4, 80.6, 79.8, 78.38, 78.36, 75.3, 73.4, 73.39, 73.37, 73.1, 72.1, 70.8, 70.5, 67.8, 39.5, 32.7, 32.2, 29.6, 25.2, 23.7, 9.4, 0.2; HRMS (FAB) calcd for $C_{46}H_{60}O_7Na$ ($(M + Na)^+$) 775.4006, found 775.4016.

Alkyne 29. To a solution of (trimethylsilyl)acetylene **28** (17.5 mg, 0.0232 mmol) in methanol/THF (3:2, v/v, 1 mL) was added potassium carbonate (9.7 mg, 0.070 mmol). The resultant solution was stirred at room temperature for 10 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (20−40% ethyl acetate/hexanes) gave alkyne **29** (14.2 mg, 90%) as a colorless oil: $[\alpha]_D^{26} = +73.3°$ (*c* 0.4, $CHCl_3$); IR (film) 3290, 3063, 3030, 2941, 2860, 1641, 1496, 1453, 1361, 1281, 1208, 1092, 1029, 989, 914, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.21 (m, 15H), 5.77 (dddd, J = 15.0, 12.0, 7.5, 6.6 Hz, 1H), 5.07 (dd, J = 15.0, 1.8 Hz, 1H), 5.03 (dd, J = 12.0, 1.8 Hz, 1H), 4.85 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 11.7, Hz, 1H), 3.89 (m, 1H), 3.76−3.71 (m, 3Hm,), 3.68−3.61 (m, 3H), 3.40 (ddd, J = 11.7, 9.6, 4.5 Hz, 1H), 3.36 (dd, J = 12.0, 5.1 Hz, 1H), 3.30 (ddd, J = 11.4, 9.0, 4.5 Hz, 1H), 3.21 (ddd, J = 11.4, 9.0, 4.5 Hz, 1H), 3.12 (ddd, J = 9.0, 4.2, 4.2 Hz, 1H), 2.53−2.51 (m, 2H), 2.27 (ddd, J = 12.0, 5.1, 4.5 Hz, 1H), 2.20 (ddd, J = 12.6, 6.6, 5.4 Hz, 1H), 2.07−2.01 (m, 2H), 1.94 (m, 1H), 1.85 (ddd, J = 13.5, 6.6, 3.6 Hz, 1H), 1.80 (ddd, J = 13.5, 12.0, 1.5 Hz, 1H), 1.61 (ddd, J = 12.0, 12.0, 11.7 Hz, 1H), 1.55 (m, 2H), 1.29 (s, 3H), 1.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5, 138.6, 138.2, 134.3, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.4, 127.2, 117.7, 82.4, 80.8, 80.5, 79.7, 78.4, 78.3, 75.6, 73.43, 73.37, 73.34, 73.0, 72.1, 70.8, 70.4, 70.3, 68.00, 39.5, 32.8, 32.3, 29.6, 25.2, 22.3, 9.3; HRMS (FAB) calcd for $C_{43}H_{52}O_7Na$ ($(M + Na)^+$) 703.3611, found 703.3593.

(E)FGH Ring Model Compound 4. To a solution of alkyne **29** (10.1 mg, 0.0148 mmol) in ethyl acetate (0.7 mL) was added Lindlar catalyst (4.3 mg), and the mixture was stirred at room temperature under a hydrogen atmosphere for 13 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel (20−40% ethyl acetate/hexanes) gave diene **5** (8.7 mg, 86%) as a colorless oil.

To a solution of the above diene **5** (5.7 mg, 0.0083 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of Grubbs' catalyst **30** (1.5 mg, 0.0018 mmol) in CH_2Cl_2 (0.5 mL). The resultant solution was stirred at 35 °C for 20.5 h. Another portion of **30** (1.8 mg, 0.0022 mmol) in CH_2Cl_2 (1.0 mL) was added, and the stirring was continued for further 26.5 h. Since TLC analysis showed the starting material remained, another portion of **30** (1.4 mg, 0.0017 mmol) in CH_2Cl_2 (1.0 mL) was added. After 52 h at 35 °C, the solvent was removed in vacuo. Purification by flash chromatography on silica gel (5−15% ethyl acetate/hexanes) gave the (E)FGH ring model compound **4** (3.3 mg, 61%) as a pale brown oil: $[\alpha]_D^{27} = +43.9°$ (*c* 0.14, $CHCl_3$); IR (film) 3028, 2923, 2856, 1726, 1496, 1453, 1331, 1206, 1086, 1029, 840, 736 cm^{-1}; ^{1}H NMR (C_5D_5N, 25 °C, 500 MHz) δ 7.60−7.26 (m, 15H), 5.83 (br, 2H), 5.04 (d, J = 11.9 Hz, 1H), 4.82 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.67 (d, J = 11.9 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.6, Hz, 1H), 3.95 (d, J = 9.2 Hz, 1H), 3.89−3.79 (m, 5H), 3.63 (m, 2H), 3.33 (dd, J = 12.2, 4.6 Hz, 1H), 3.27 (br, 2H), 3.19 (ddd, J = 11.6, 11.6, 1.5 Hz, 1H), 2.93 (br, 2H), 2.50 (ddd, J = 12.2, 4.9, 4.6 Hz, 1H), 2.33 (m, 2H), 2.22 (br, 2H), 2.07 (m, 1H), 1.83 (ddd, J = 11.6, 11.6, 11.6 Hz, 1H), 1.58−1.40 (m, 6H); ^{13}C NMR (C_5D_5N, −25 °C, 125 MHz) δ 140.3, 139.3, 139.2, 128.9, 128.8, 128.7, 128.3, 128.2, 128.1, 127.9, 127.7, 85.9, 83.1, 82.4, 82.3, 81.5, 81.1, 79.4, 73.6, 73.3, 73.0, 72.4, 70.6, 70.5, 68.1, 40.2, 33.1, 32.7, 32.5, 31.3, 26.4, 11.2; HRMS (FAB) calcd for $C_{41}H_{50}O_7Na$ ($(M + Na)^+$) 677.3454, found 677.3431.

Supporting Information Available: Figures giving synthetic schemes for compounds **20b** and **20c**, text giving experimental procedures and characterization data for compounds **19a**, **22**, **24**, and **25**, and figures giving ^{1}H and ^{13}C NMR spectra for compounds **4**, **6**, **7b**, **8**, **12**, **14**, **15**, **17b**, **18b**, **19a**, **22**, and **24**−**29** and ^{1}H NMR spectra for compounds **5** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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