Pergamon

Tetrahedron 54 (1998) 1–20

TETRAHEDRON

Synthetic Studies on Ciguatoxin [1]; Construction of the Spiro Acetal Part (C46-C55)

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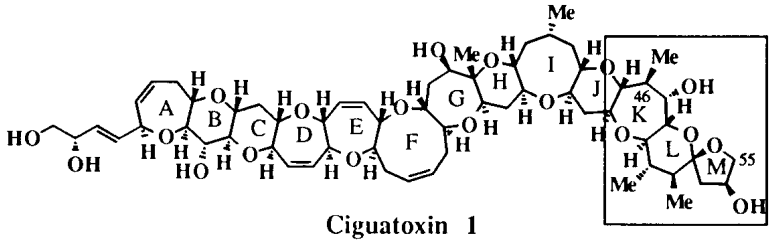
Received 17 September 1997; accepted 23 October 1997

Abstract: The spiro acetal part (C46-C55) of ciguatoxin was synthesized stereoselectively.

INTRODUCTION

Ciguatoxin **1** is the principal marine toxin from moray eel *Gymnothorax javanicus* which causes ciguatera. The structure of **1** determined by Yasumoto *et al.* has a characteristic polycyclic system consisting of 13 medium sized cyclic ethers.[1] Its interesting biological activities and limited availability from natural sources have made **1** one of the most challenging synthetic target molecules.[2] The L,M-ring part of **1** consists of a 6/5 cyclic spiro acetal. It is one of the synthetic problems how the spiro acetal system could be constructed stereochemically. Recently, Tachibana group has reported the first construction of the K,L,M-ring system of **1**.[2i,2k] Their publication has prompted us to submit our own results on the corresponding ring moiety. We reported the synthesis of the spiro acetal part (C46-C55) of **1** including all the correct chiral centers in rather short steps[2j] and the details are described in this paper.

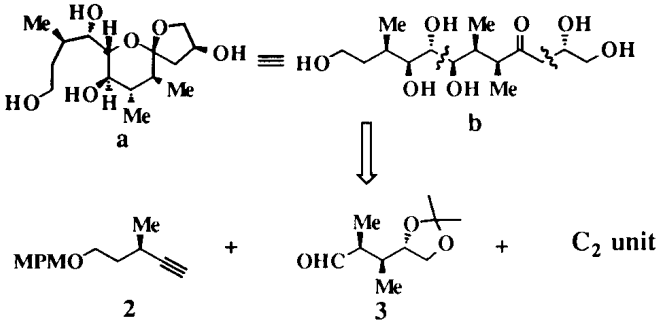


Ciguatoxin **1**

0040-4020/98/$19.00
PII: S0040-4020(97)10253-8

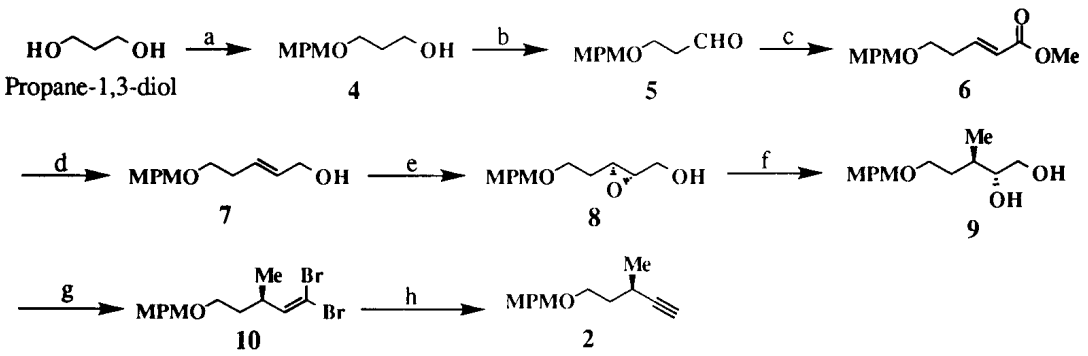
RESULTS AND DISCUSSION

In order to synthesize the L,M-ring system including the necessary functional groups of the K-ring part stereoselectively, we planned to synthesize the compound **a** equivalent synthetically to the spiro acetal part of **1** as follows (Scheme 1). The compound **b** corresponding to **a** could be constructed through stepwise coupling reactions of the compounds **2**, **3**, and a C_2 unit.



Scheme 1.

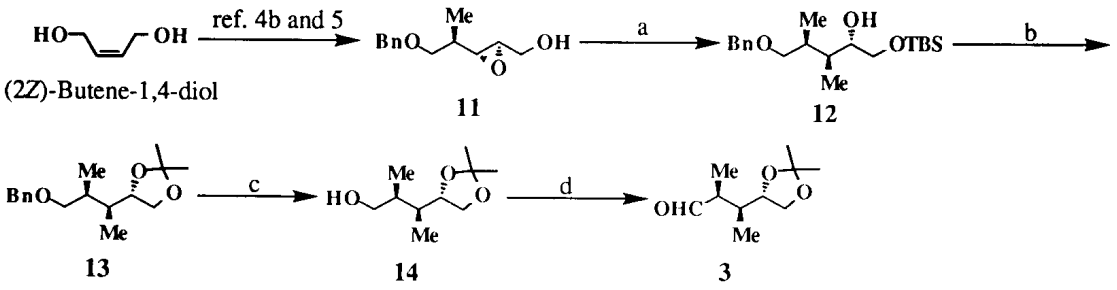
The preparation of the alkyne **2** commenced with a mono-MPM ether protection of the readily available propane-1,3-diol to afford **4** (Scheme 2). The hydroxy group of **4** was oxidized to the aldehyde **5** under Swern conditions, followed by Wittig reaction with $Ph_3P{=}CHCO_2Me$ to give *E*-olefin **6** as a sole product. Reduction of the ester group in **6** with DIBAL afforded the allylic alcohol **7** in a good yield. Compound **7** was oxidized under Sharpless conditions using L-(+)-DET[3] to afford the epoxy alcohol **8** in good yield (94%) and selectivity (>95% ee, determined by MTPA ester method), which further led to the methylated 1,2-diol **9** using Me_3Al.[4] The diol part in **9** was cleaved with $NaIO_4$ and the crude aldehyde was treated immediately with CBr_4 and PPh_3 to yield the dibromo-olefin **10**, which was converted smoothly with BuLi to the alkyne **2**.



Reagents and Conditions: a) MPMCl, NaH, THF-DMF (3:1), r.t., 18 h (69%); b) Swern oxid. (99%); c) $Ph_3P{=}CHCO_2Me$, PhH, r.t., 15 h (80%); d) DIBAL, CH_2Cl_2, -78 °C, 1 h (99%); e) L-(+)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, TBHP, MS4Å, CH_2Cl_2, -20 °C, 20 h (94%, >95% ee); f) Me_3Al, CH_2Cl_2-hexane (1:2), 0 °C, 16 h (77%); g) $NaIO_4$, THF-H_2O (1:1), r.t., 10 min; CBr_4, PPh_3, CH_2Cl_2, 0 °C, 20 min (97% for 2 steps); h) BuLi, THF, -78 °C, 30 min (87%).

Scheme 2.

The aldehyde **3** was prepared as depicted in Scheme 3. Epoxy alcohol **11** was prepared in 12 steps in 18% overall yield starting from (2Z)-butene-1,4-diol according to the Kishi procedure on the enantiomer of **11**.[4b,5] The compound **11** (>95% ee) was also treated with Me_3Al[4] to give a 6:1 mixture of the 3,4-dimethyl-1,2-diol and an unknown by-product. After the selective silylation of the primary hydroxy groups in the mixture with TBSCl, the products were separated by silica gel column chromatography to yield mono-TBS ether **12** in pure form in a total yield of 66% from **11**. Treatment of **12** with acetone and PTS·H_2O detached the TBS group and led to the acetonide derivative of the corresponding 1,2-diol to afford compound **13**, which provided **14** after hydrogenolysis with Pd/C. The resulting hydroxy group was then oxidized under Swern conditions to the crude aldehyde **3**.

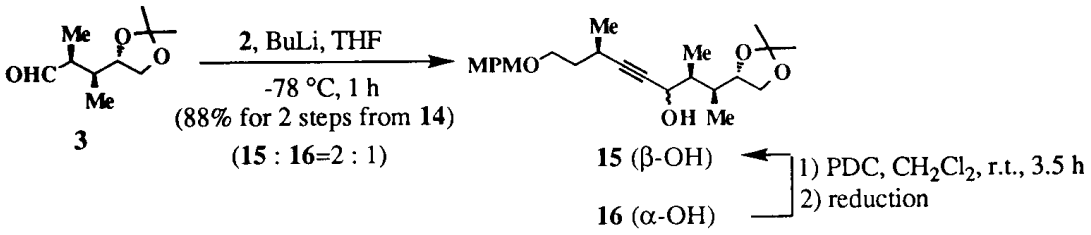


Reagents and Conditions: a) Me_3Al, CH_2Cl_2-hexane (1:2), 0 °C, 17 h; TBSCl, NEt_3, DMAP, CH_2Cl_2, r.t., 17 h; separation by silica gel column chromatography (66% for 2 steps); b) PTS·H_2O, acetone, r.t., 36 h (93%); c) H_2, Pd/C, EtOH, r.t., 24 h (98%); d) Swern oxid.

Scheme 3.

The crude aldehyde **3** was immediately treated with a solution of **2** and BuLi (Table 1). The coupling reaction proceeded smoothly to afford a 2:1 mixture of the acetylene alcohol **15** (β-OH) and its diastereomer **16** (α-OH). The stereochemistry of the introduced hydroxy group was deduced by applying the improved Moscher procedure[6] to both the MTPA esters of **15** (Figure 1). While the fact that compound **15** was preferable had been expected on the basis of the Cram rule,[7] the relative ratio of **15** to **16** was rather low. Therefore, the compounds were oxidized with PDC and then reduced with several agents (Table 1). DIBAL reduction afforded a 1:2 mixture of **15** and **16** (entry 1). Reaction with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ produced a 4:1 mixture of **15** and **16** (entry 2). Finally, reduction with $LiAlH(Ot\text{-}Bu)_3$ yielded an 8:1 mixture of **15** and **16** (entry 3). These selectivities were explained as follows (Figure 2); in the cases of $NaBH_4$ and $LiAlH(Ot\text{-}Bu)_3$, the carbonyl oxygen coordinated by Na^+ or Li^+ would be attacked by the hydride agents {BH_4^- or $[AlH(Ot\text{-}Bu)_3]^-$} from the less hindered side (*si*-face) (**A**). On the other hand, in the case of DIBAL, the carbonyl oxygen is directly coordinated by DIBAL. The alkoxide, that is formed by hydride attack, will occupy the less hindered side (α-face) because of its bulkiness as shown in **B**. Therefore, the hydride attack to the *re*-face is preferred.

Table 1.



entry	reagents and conditions	15 : 16[a]	total yield (for 2 steps)[b]
1	DIBAL, CH_2Cl_2, -78 °C, 10 min	1 : 2	78%
2	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, r.t., 20 min	4 : 1	86%
3	$LiAlH(Ot\text{-}Bu)_3$, ether, 0 °C, 5 h	8 : 1	80%

a) The ratios were determined by ^{1}H-NMR (400 MHz); b) Isolated yield of the mixture of diastereoisomers.

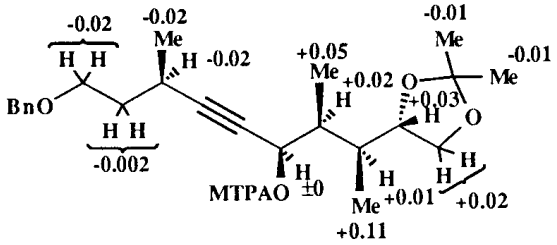


Figure 1. Δδ Values (= $\delta_S - \delta_R$, in ppm) obtained for (*S*)- and (*R*)-MTPA esters of **15**. (The data were obtained from the ^{1}H-NMR spectra measured using $CDCl_3$ as a solvent.)

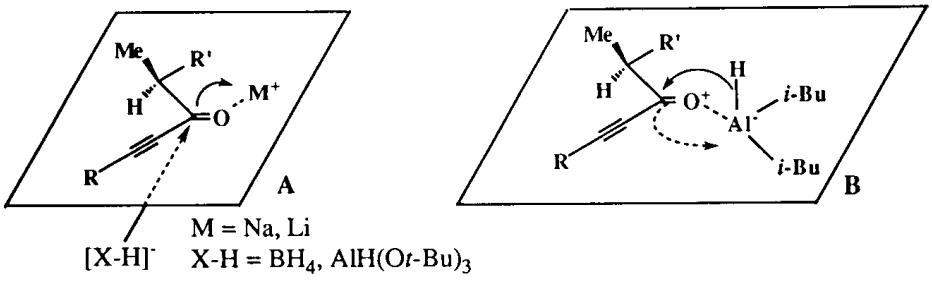
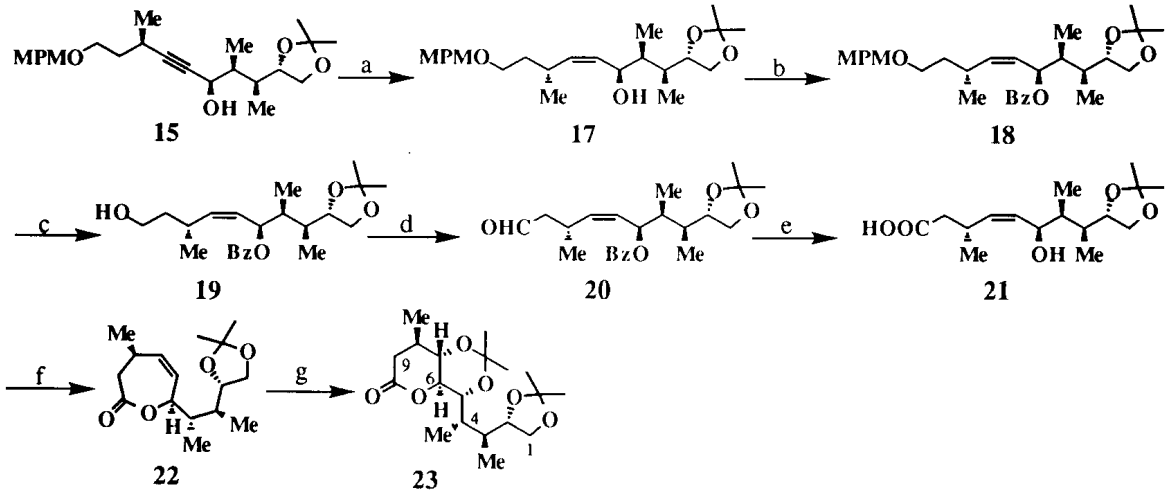


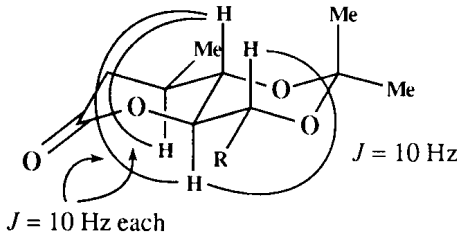
Figure 2.

The compound **15** (an 8:1 mixture of β-OH and α-OH) was then hydrogenated with Lindlar catalyst to afford *Z*-allylic alcohol **17** (an 8:1 mixture of β-OH and α-OH), which led to the benzoate **18** (an 8:1 mixture of β-OBz and α-OBz) (Scheme 4). The MPM ether in **18** was detached with DDQ, and the product **19** (a pure form) was oxidized to the corresponding aldehyde **20**. Further oxidation of **20** with $NaClO_2$ followed by saponification of the benzoyl group provided the hydroxy carboxylic acid **21**. Compound **21** was cyclized internally to the lactone **22** by the Yamaguchi procedure[8] in a high yield. Successive treatment of **22** with OsO_4 (a stoichiometric amount), with H_2S, and with conc. HCl in acetone gave rise to the thermodynamically more stable lactone **23** exclusively in good yield. The stereochemistry of the introduced 1,2-diol was determined by the respective coupling constants (10 Hz each) between the four successive protons in the ^{1}H-NMR spectrum of **23** (Figure 3). The direction of the dihydroxylation was achieved completely by α-side attack.[9] The attempted dihydroxylation reactions of **17** and **18** did not occur because of the steric hindrance of their double bonds.



Reagents and Conditions: a) H_2, Lindlar cat., MeOH, r.t., 48 h (98%); b) BzCl, NEt_3, DMAP, CH_2Cl_2, r.t., 15 h (quant.); c) DDQ, CH_2Cl_2-H_2O (10:1), 0 °C, 1.5 h (63% as a single isomer); d) PDC, MS4Å, CH_2Cl_2, r.t., 2 h (90%); e) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, *t*-BuOH-H_2O (15:4), 0 °C, 1.5 h; KOH (1 M soln in H_2O), MeOH, r.t., 24 h (75% for 2 steps); f) 2,4,6-trichlorobenzoyl chloride, NEt_3, toluene, r.t., 18 h, then DMAP, r.t., 1 h (81%); g) OsO_4, THF-pyridine (4:1), r.t., 2 h, then H_2S, MeOH, r.t., 1 h; conc. HCl, acetone, r.t., 3 h (67% for 2 steps).

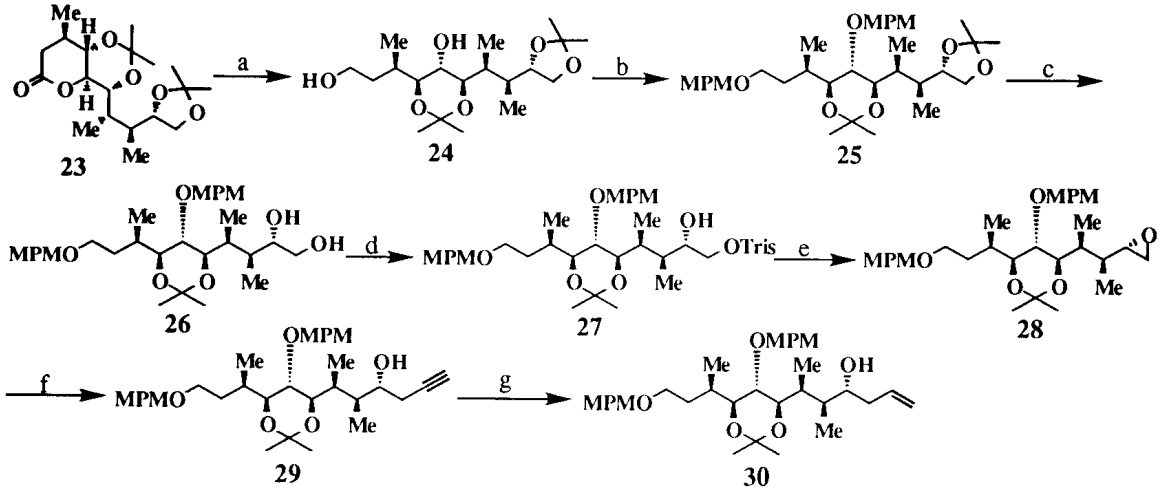
Scheme 4.



23

Figure 3.

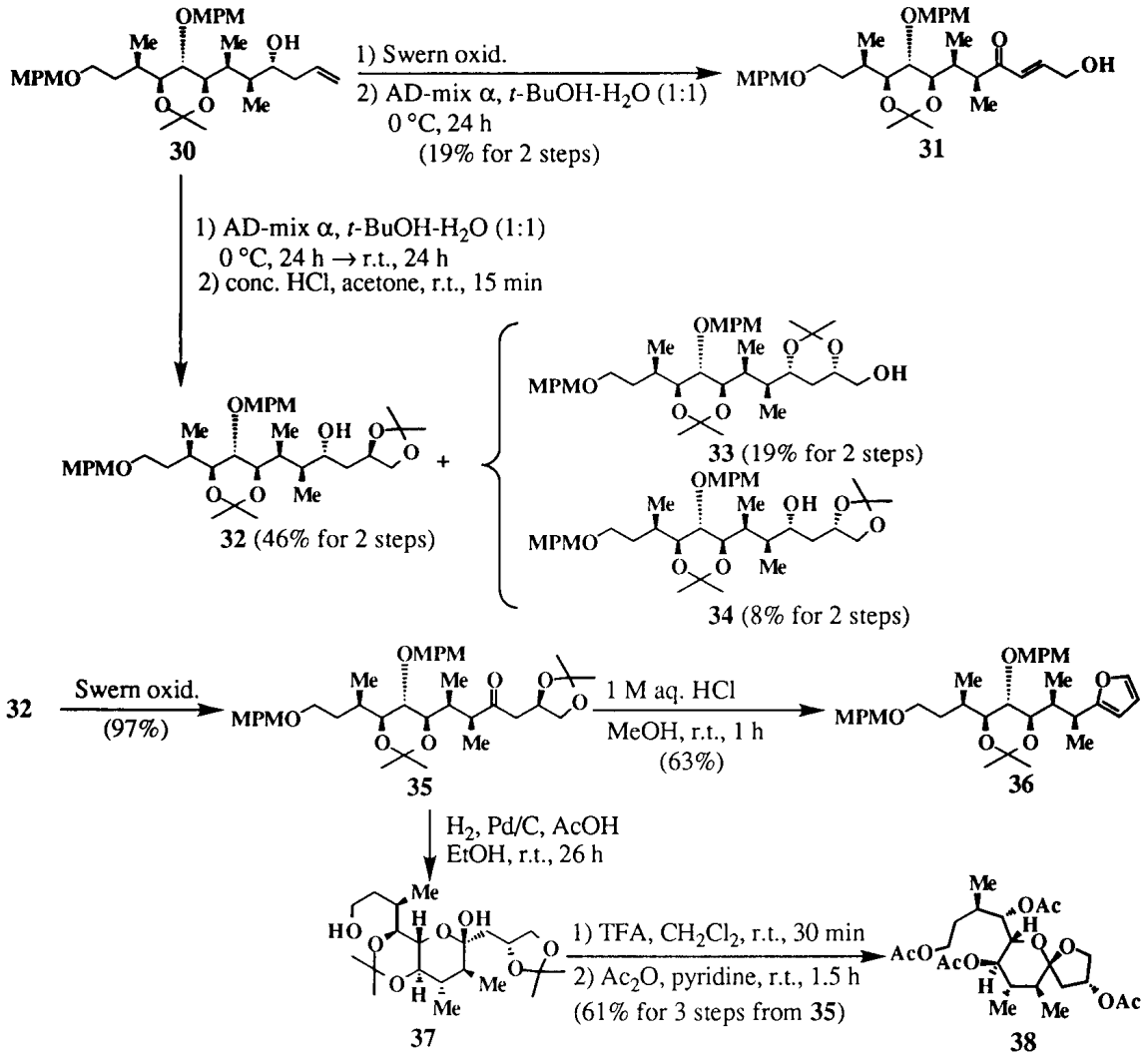
The compound **23** was reduced with $LiAlH_4$ to diol **24**, which was protected with MPMCl and KH to afford the bis-MPM ether **25** (Scheme 5). Treatment of **25** with MeOH and 1 M aqueous HCl cleaved selectively the terminal acetonide part to yield *vic*-diol **26**. Selective sulfonylation of the primary hydroxy group in **26** with TrisCl obtained compound **27**, which led to the terminal epoxide **28** with K_2CO_3 in MeOH in good yields. The coupling reaction of **28** with lithium acetylide-EDA complex proceeded smoothly to give the acetylene alcohol **29**, which was hydrogenated with Lindlar catalyst in PhH to the homo-allylic alcohol **30**.



Reagents and Conditions: a) $LiAlH_4$, ether, 0 °C → r.t., 1.5 h (92%); b) MPMCl, KH, TBAI, THF, reflux, 4 h (95%); c) 1 M aq. HCl, MeOH, r.t., 3 h (75%); d) TrisCl, NEt_3, DMAP, CH_2Cl_2 (71%, recovery 26%); e) K_2CO_3, MeOH, r.t., 2.5 h (quant.); f) lithium acetylide-EDA complex, DMSO, r.t., 4 h (76%, recovery 6%); g) H_2, Lindlar cat., PhH, r.t., 30 min (quant.).

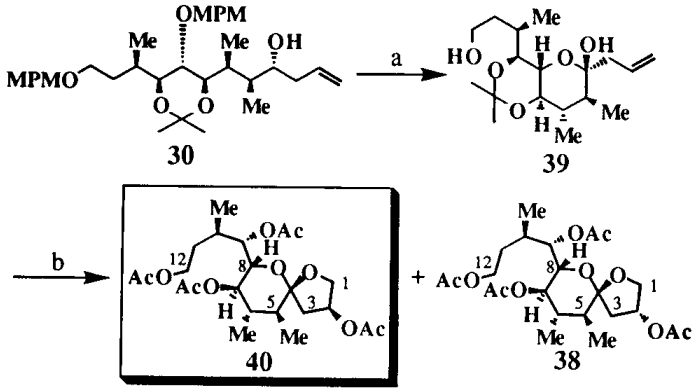
Scheme 5.

The construction of the spiro acetal system was examined as shown in Scheme 6. After oxidation of **30** under Swern conditions, the crude product was treated with AD-mix α.[10] However, the product was the α,β-unsaturated ketone **31** which was characterized by ^{1}H-NMR spectrum [δ 6.92 (1H, dt, J = 16, 4 Hz) and 6.32 (1H, dt, J = 16, 2 Hz)]. The compound **31** seemed to be formed by an elimination of the intermediate β-hydroxy ketone under basic conditions. Compound **30** was then treated with AD-mix α followed by acetonization to yield the corresponding undesired (2*R*)-triol acetonide **32** (46%), along with a mixture of the (2*S*)-triol acetonide **33** (19%) and (2*S*)-diol acetonide **34** (8%). The yield of the desired compound **34** was rather low. On the other hand, the following results were obtained by using the compound **32**. After oxidation of the hydroxy group in **32**, the ketone **35** was treated with HCl and gave furan **36**. The structure of **36** was determined by ^{1}H-NMR spectrum [δ 7.29 (1H, br t, J = 1 Hz), 6.25 (1H, br t, J = 2 Hz), and 5.94 (1H, br d, J = 3 Hz)]. On the other hand, the MPM groups in **35** could be detached by hydrogenolysis with Pd/C to yield the hemiacetal **37**, carrying no carbonyl groups according to the IR spectrum. Acidic hydrolysis of **37** followed by peracetylation led to the spiro acetal **38**. These results suggest that i) the stereochemistry of the spiro acetal system underlies stereoelectronic and thermodynamic control (anomeric effect); ii) the order of the ring closure reactions occurred from 6-membered ring (L-ring in ciguatoxin **1**) to 5-membered ring (M-ring in **1**).



Scheme 6.

Finally, the construction of the spiro acetal part of ciguatoxin **1** was achieved as shown in Scheme 7. Compound **30** was oxidized under Swern conditions and deprotected with DDQ to afford the hemiacetal **39**. Reaction of **39** with OsO_4 (a stoichiometric amount),[11] with TFA, and then with Ac_2O in pyridine produced the spiro acetal **40** and its diastereomer **38** in 22% and 15% overall yields from **39**. The respective structures of **40** and **38** were deduced from the comparison of the results of their NOE measurements (Figure 4). Alternatively, if the stereochemistries at C-4 in the products would take the unnatural configurations, the NOE data could not be rationalized for their alternate structures (**41** and **42**). Furthermore, our NOE results were not contradictory to the Tachibana's data.[2i] Consequently, the compound **40** thus obtained corresponds exactly to the spiro acetal part (C46-C55) fragment of natural ciguatoxin **1** with all the necessary functional groups.



Reagents and Conditions: a) Swern oxid.; DDQ, CH_2Cl_2-H_2O (10:1), r.t., 1.5 h (92% for 2 steps); b) OsO_4, CH_3CN-H_2O (2:1), r.t., 1 h; TFA, CH_2Cl_2, r.t., 1 h; Ac_2O, DMAP, pyridine, r.t., 3 h (**40**, 22% for 3 steps; **38**, 15% for 3 steps).

Scheme 7.

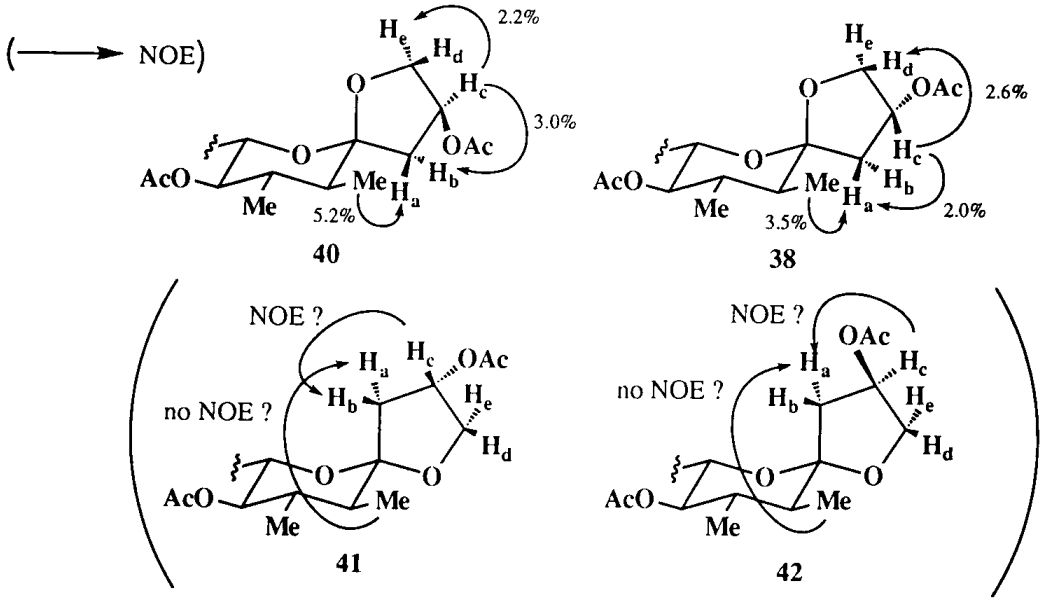


Figure 4.

EXPERIMENTAL

General: All reactions involving air- or moisture-sensitive reagents were conducted under argon atmosphere, and solvents and reagents were dried and distilled before use. Ether, tetrahydrofuran (THF), and toluene were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), hexane, and benzene (PhH) were distilled from calcium hydride (CaH_2). Molecular sieves 4Å (MS4Å) were finely powdered and activated at 220 °C for 3 h *in vacuo*. All reactions were monitored by thin-layer chromatography (TLC) with pre-coated silica gel (SiO_2) plates (E. Merck, Silica gel 60 F_{254} Art. 5554). Flash chromatography utilized silica gel (SiO_2) (E. Merck, Silica gel 60, 70-230 mesh ASTM, Art. 7734). Preparative thin-layer chromatography (PTLC) utilized pre-coated silica gel (SiO_2) plates (E. Merck, Silica gel 60 F_{254} Art. 5554). Infrared (IR) spectra were obtained on a Hitachi 270-30 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX-270 (270 MHz), JNM-EX-400 (400 MHz), and JNM-GX-400 (400 MHz) NMR spectrometers. Tetramethylsilane (δ 0.00) was used as an internal reference for spectra measured. Splitting patterns are designated as "s, d, t, q, m, and br," indicating "singlet, doublet, triplet, quartet, multiplet, and broad," respectively. High-resolution mass spectra (HR-MS) were obtained on a JEOL JMS-HX-110, a JMS-AX-500, or a JMS-SX-102A mass spectrometers. Optical rotations were recorded on JASCO DIP-360 digital polarimeter. Melting points were measured on YANAGIMOTO micro-melting point apparatus, and were not corrected.

3-*p*-Methoxybenzyloxy-1-propanol (4).

To a suspension of sodium hydride (NaH) (5.50 g, 229 mmol) in a 10:7 mixture of THF-dimethylformamide (DMF) (170 ml) was added dropwise a solution of propane-1,3-diol (17.0 g, 223 mmol) in THF (50 ml) at 0 °C, and the mixture was stirred at room temperature for 3 h. To the mixture was added dropwise *p*-methoxybenzyl chloride (MPMCl) (20.0 ml, 148 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water and extracted repeatedly with ether. The combined organic layers were dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 [hexane:ethyl acetate (EtOAc), 3:1] to afford **4** (19.9 g, 69% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.25 (2H, d, J = 9 Hz), 6.88 (2H, d, J = 9 Hz), 4.45 (2H, s), 3.80 (3H, s), 3.77 (2H, t, J = 5 Hz), 3.64 (2H, t, J = 5 Hz), 2.36-2.20 (1H, br s), and 1.85 (2H, qui, J = 5 Hz); IR (film), ν_{max} 3432, 2944, 1614, 1514, 1466, 1302, 1250, 1180, 1086, and 822 cm^{-1}; HR-EI-MS, calcd. for $C_{11}H_{16}O_3$ (M^+) 196.1100, found *m/z* 196.1086.

3-*p*-Methoxybenzyloxypropanal (5).

To a solution of oxalyl chloride (6.60 ml, 76.4 mmol) in CH_2Cl_2 (150 ml) was added dimethyl sulfoxide (DMSO) (9.10 ml, 125 mmol) in CH_2Cl_2 (30 ml) at -78 °C and the mixture was stirred at -78 °C for 30 min. A solution of **4** (10.0 g, 51.0 mmol) in CH_2Cl_2 (40 ml) was added and the mixture was stirred at -78 °C for 30 min. Triethylamine (NEt_3) (28.4 ml, 204 mmol) was added at -78 °C and the mixture was stirred at 0 °C for 10 min and then at room temperature for 30 min. The mixture was diluted with chloroform ($CHCl_3$), and then mixed with water. The organic layer was washed with 2 M aq. HCl, satd. aq. sodium bicarbonate ($NaHCO_3$), and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 4:1) to afford **5** (9.82 g, 99% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.79 (1H, t, J = 2 Hz), 7.24 (2H, d, J = 9 Hz), 6.88 (2H, d, J = 9 Hz), 4.46 (2H, s), 3.80 (3H, s), 3.78 (2H, t, J = 6 Hz), and 2.68 (2H, dt, J = 2, 6 Hz); IR (film), ν_{max} 3004, 2860, 2732, 1728, 1614, 1514, 1466, 1362, 1248, 1094, 1034, and 818 cm^{-1}; HR-EI-MS, calcd. for $C_{11}H_{14}O_3$ (M^+) 194.0943, found *m/z* 194.0941.

Methyl (2*E*)-5-*p*-methoxybenzyloxy-2-pentenoate (6).

To a solution of **5** (9.70 g, 49.9 mmol) in PhH (150 ml) was added methyl (triphenylphosphoranylidene)acetate (Ph_3P=$CHCO_2Me$) (25.0 g, 74.8 mmol), and the mixture was stirred at room temperature for 15 h. The reaction mixture was purified by column chromatography on SiO_2 (hexane:EtOAc, 1:1, and hexane:EtOAc, 4:1) to afford **6** (10.7 g, 80% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.24 (2H, d, J = 9 Hz), 6.97 (1H, dt, J = 16, 7 Hz), 6.88 (2H, d, J = 9 Hz), 5.89 (1H, dt, J = 16, 1 Hz), 4.45 (2H, s), 3.80 (3H, s), 3.73 (3H, s), 3.55 (2H, t, J = 7 Hz), and 2.49 (2H, dq, J = 1, 7 Hz); IR (film), ν_{max} 3000, 2952, 2860, 1726, 1660, 1614, 1514, 1440, 1248, 1178, 1036, 980, and 822 cm^{-1}; HR-EI-MS, calcd. for $C_{14}H_{18}O_4$ (M^+) 250.1205, found *m/z* 250.1232.

(2*E*)-5-*p*-Methoxybenzyloxy-2-penten-1-ol (7).

To a solution of **6** (9.60 g, 38.4 mmol) in CH_2Cl_2 (230 ml) was added dropwise diisobutylaluminum hydride (DIBAL) (0.93 M solution in hexane, 118 ml, 110 mmol) at -78 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was diluted with ether (200 ml) and mixed with water (10 ml), and the mixture was stirred vigorously at room temperature until a white gel was generated. To the mixture were added 4 M aq. sodium hydroxide (NaOH) (10 ml) and water (20 ml), and the mixture was stirred vigorously at room temperature until a white solid was generated. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 3:2) to afford **7** (8.50 g, 99% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.25 (2H, d, J = 9 Hz), 6.87 (2H, d, J = 9 Hz), 5.78-5.67 (2H, m), 4.44 (2H, s), 4.10 (2H, br s), 3.81 (3H, s), 3.49 (2H, t, J = 7 Hz), and 2.40-2.30 (2H, m), and 1.62-1.50 (1H, br s); IR (film), ν_{max} 3416, 3004, 2936, 2860, 1614, 1516, 1466, 1362, 1302, 1250, 1176, 1098, 1032, 974, and 822 cm^{-1}; HR-EI-MS, calcd. for $C_{13}H_{18}O_3$ (M^+) 222.1256, found *m/z* 222.1275.

(2*S*,3*S*)-2,3-Epoxy-5-*p*-methoxybenzyloxy-1-pentanol (8).

To a cold (-40 °C) suspension of titanium tetraisopropoxide [Ti(O*i*-Pr)$_4$] (1.21 ml, 4.07 mmol) and MS4Å (7.0 g) in CH_2Cl_2 (1 ml) was added diethyl L-(+)-tartrate [L-(+)-DET] (1.05 ml, 4.07 mmol) and the mixture was stirred at -30 °C for 30 min. To the mixture was added *tert*-butyl hydroperoxide (TBHP) (4.73 M solution in toluene, 19.0 ml, 90.0 mmol) at -30 °C and the mixture was stirred at -30 °C for 30 min. To the mixture was added dropwise a solution of **7** (8.50 g, 38.2 mmol) in CH_2Cl_2 (50 ml) at -30 °C, and the mixture was stirred at -20 °C for 20 h. The solution was poured into a solution of tartaric acid (8.20 g) and iron(II) sulfate heptahydrate ($FeSO_4 \cdot 7H_2O$) (14.2 g) in water (82 ml) at 0 °C, and the mixture was stirred at 0 °C for 10 min. The water layer was extracted repeatedly with ether (3 × 50 ml). To the combined organic layers was added 30% NaOH brine solution (10 ml) at 0 °C, and the mixture was stirred vigorously at 0 °C for 1 h, and then mixed with water. The water layer was extracted repeatedly with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 2:1) to afford **8** [8.52 g, 94% yield, >95% ee (determined by its MTPA ester. not observed diastereomeric peaks)] as a colorless oil: $[\alpha]_D^{26}$ -25.3° (*c* 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.25 (2H, d, J = 9 Hz), 6.87 (2H, d, J = 9 Hz), 4.45 (2H, s), 3.90 (1H, br dd, J = 2, 12 Hz), 3.80 (3H, s), 3.63 (1H, br dd, J = 4, 12 Hz), 3.58 (2H, t, J = 7 Hz), 3.09 (1H, ddd, J = 2, 4, 6 Hz), 2.97 (1H, dt, J = 4, 2 Hz), 1.96-1.77 (2H, m), and 1.74-1.56 (1H, br s); IR (film), ν_{max} 3436, 2932, 2864, 1614, 1516, 1466, 1364, 1248, 1176, 1100, 1034, and 820 cm^{-1}; HR-EI-MS, calcd. for $C_{13}H_{18}O_4$ (M^+) 238.1205, found *m/z* 238.1210.

(2*R*,3*R*)-5-*p*-Methoxybenzyloxy-3-methylpentane-1,2-diol (9).

To a solution of **8** (8.50 g, 35.7 mmol) in CH_2Cl_2 (150 ml) was added dropwise trimethylaluminum (Me_3Al) (1.03 M solution in hexane, 152 ml, 157 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 h. After cooling to 0 °C, the reaction mixture was diluted with ether (150 ml) and then with

water (6.0 ml), and the mixture was stirred vigorously at room temperature until a white gel was generated. To the mixture were added 4 M aq. NaOH (6.0 ml) and water (12 ml), and the mixture was stirred vigorously at room temperature until a white solid was generated. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 2:3) to afford **9** (7.00 g, 77% yield) as a colorless oil: $[\alpha]_D^{24}$ +2.74° (*c* 1.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.24 (2H, d, *J* = 9 Hz), 6.87 (2H, d, *J* = 9 Hz), 4.46 (2H, s), 3.81 (3H, s), 3.67 (1H, dd, *J* = 3, 10 Hz), 3.58 (1H, ddd, *J* = 4, 6, 9 Hz), 3.51-3.41 (3H, m), 1.78-1.68 (3H, m), and 0.90 (3H, d, *J* = 6 Hz); IR (film), ν_{max} 3376, 2932, 2872, 1614, 1514, 1464, 1366, 1302, 1252, 1176, 1090, 1032, and 822 cm^{-1}; HR-EI-MS, calcd. for $C_{14}H_{22}O_4$ (M^+) 254.1519, found *m/z* 254.1532.

(3*R*)-1,1-Dibromo-5-*p*-methoxybenzyloxy-3-methyl-1-pentene (10).

To a solution of sodium periodate ($NaIO_4$) (3.03 g, 14.2 mmol) in a 1:1 mixture of THF-water (50 ml) was added dropwise a solution of **9** (3.01 g, 11.8 mmol) in THF (20 ml), and the mixture was stirred at room temperature for 10 min. To the reaction mixture was added a 2:1 mixture of PhH-ether (100 ml), and the organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude aldehyde (2.62 g) was obtained, and immediately used for the next reaction without further purification.

To a solution of carbon tetrabromide (CBr_4) (15.7 g, 47.2 mmol) in CH_2Cl_2 (50 ml) was added dropwise a solution of triphenylphosphine (Ph_3P) (24.8 g, 94.4 mmol) in CH_2Cl_2 (50 ml) at 0 °C, and the mixture was stirred at the same temperature for 10 min. To the solution was added dropwise a solution of the crude aldehyde (2.62 g) in CH_2Cl_2 (50 ml) at 0 °C, and the mixture was stirred at the same temperature for 20 min. The reaction mixture was washed with water, satd. aq. $NaHCO_3$, satd. aq. ammonium chloride (NH_4Cl), and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 2:1 and hexane:EtOAc, 4:1) to afford **10** (4.34 g, 97% yield for 2 steps) as a pale yellow oil: $[\alpha]_D^{26}$ -18.8° (*c* 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.26 (2H, d, *J* = 9 Hz), 6.88 (2H, d, *J* = 9 Hz), 6.20 (2H, d, *J* = 9 Hz), 4.24 (2H, s), 3.80 (3H, s), 3.58-3.37 (2H, m), 2.73-2.61 (1H, m), 1.74-1.55 (2H, m), and 1.02 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 2960, 2932, 2864, 1614, 1514, 1456, 1364, 1302, 1250, 1174, 1102, 1036, 820, 766, and 666 cm^{-1}; HR-EI-MS, calcd. for $C_{14}H_{18}O_2Br_2$ (M^+) 377.9452, found *m/z* 377.9438.

(3*R*)-1-*p*-Methoxybenzyloxy-3-methyl-4-pentyne (2).

To a solution of **10** (4.34 g, 11.5 mmol) in THF (30 ml) was added dropwise butyllithium (BuLi) (1.60 M solution in hexane, 15.5 ml, 26.4 mmol) at -78 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was diluted with ether and quenched with satd. aq. NH_4Cl at -78 °C, and warmed up to room temperature. The water layer was extracted repeatedly with ether. The combined organic layers were washed with satd. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:ether, 7:1) to afford **2** (2.18 g, 87% yield) as a colorless oil: $[\alpha]_D^{26}$ -51.2° (*c* 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.26 (2H, d, *J* = 9 Hz), 6.87 (2H, d, *J* = 9 Hz), 4.44 (2H, s), 3.80 (3H, s), 3.44 (2H, t, *J* = 8 Hz), 2.71-2.60 (1H, m), 2.02 (1H, d, *J* = 2 Hz), 1.80-1.65 (2H, m) and 1.19 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3300, 2936, 2864, 2112, 1614, 1514, 1466, 1366, 1302, 1248, 1174, 1096, 1038, and 824 cm^{-1}; HR-EI-MS, calcd. for $C_{14}H_{18}O_2$ (M^++H) 218.1314, found *m/z* 218.1314.

(2*S*,3*S*,4*S*)-5-Benzyloxy-1-*tert*-butyldimethylsilyloxy-3,4-dimethyl-2-pentanol (12).

To a solution of **11** (1.12 g, 5.04 mmol) in a 5:2 mixture of CH_2Cl_2-hexane (28 ml) was added dropwise Me_3Al (1.00 M solution in hexane, 17.0 ml, 17.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 17 h. After cooling to 0 °C, the reaction mixture was diluted with ether (100 ml) and then with water (1.0 ml), and the mixture was stirred vigorously at room temperature until a white gel was generated. To the mixture were added 4 M aq. NaOH (1.0 ml) and water (2.0 ml), and the mixture was stirred

vigorously at room temperature until a white solid was generated. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was passed over a column of SiO_2 (hexane:EtOAc, 2:3) to separate methylated compounds from the other products. To a solution of the methylated mixture, NEt_3 (1.50 ml, 10.6 mmol), and 4-dimethylaminopyridine (DMAP) (a cat. amount) in CH_2Cl_2 (30 ml) was added *tert*-butyldimethylsilyl chloride (TBSCl) (811 mg, 5.38 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with ether and quenched with satd. aq. $NaHCO_3$. The water layer was extracted repeatedly with ether. The combined organic layers were washed with satd. aq. NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:ether, 40:1) to afford **12** (1.18 g, 66% yield for 2 steps) as a colorless oil: $[\alpha]_D^{26}$ +4.33° (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 7.36-7.24 (5H, m), 4.53 (1H, d, *J* = 12 Hz), 4.48 (1H, d, *J* = 12 Hz), 3.75-3.72 (1H, m), 3.49-3.43 (2H, m), 3.35 (1H, t, *J* = 9 Hz), 3.32 (1H, dd, *J* = 7, 9 Hz), 2.54-2.53 (1H, br s), 2.42-2.35 (1H, m), 1.84-1.80 (1H, m), 0.91 (9H, s), 0.83 (3H, d, *J* = 7 Hz), 0.71 (3H, d, *J* = 7 Hz), and 0.08 (6H, s); IR (film), ν_{max} 3588, 3488, 3064, 3032, 2956, 2932, 2860, 1464, 1364, 1254, 1098, 838, 778, 736, and 736 cm^{-1}; HR-EI-MS, calcd. for $C_{20}H_{36}O_3Si$ (M^+) 352.2435, found *m/z* 352.2448.

(2*S*,3*S*,4*S*)-5-Benzyloxy-3,4-dimethyl-1,2-(dimethylmethylenedioxy)pentane (13).

To a solution of **12** (1.46 g, 4.15 mmol) in acetone (15 ml) was added *p*-toluenesulfonic acid monohydrate ($PTS{\cdot}H_2O$) (a cat. amount), and the mixture was stirred at room temperature for 36 h. The reaction mixture was diluted with EtOAc and then mixed with satd. aq. $NaHCO_3$. The water layer was extracted repeatedly with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:ether, 20:1) to afford **13** (1.07 g, 93% yield) as a colorless oil: $[\alpha]_D^{26}$ +15.4° (*c* 1.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 7.36-7.24 (5H, m), 4.53 (1H, d, *J* = 12 Hz), 4.47 (1H, d, *J* = 12 Hz), 4.01 (1H, dd, *J* = 5, 7 Hz), 3.94 (1H, dd, *J* = 7, 9 Hz), 3.59 (1H, t, *J* = 8 Hz), 3.36 (1H, t, *J* = 8 Hz), 3.31 (1H, dd, *J* = 6, 8 Hz), 2.32-2.22 (1H, m), 1.95-1.86 (1H, m), 1.40 (3H, s), 1.35 (3H, s), 0.84 (3H, d, *J* = 7 Hz), and 0.70 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3064, 3032, 2984, 2936, 2880, 1456, 1370, 1248, 1068, 864, 736, and 698 cm^{-1}; HR-EI-MS, calcd. for $C_{17}H_{26}O_3$ (M^+) 278.1883, found *m/z* 278.1904.

(2*S*,3*S*,4*S*)-2,3-Dimethyl-4,5-(dimethylmethylenedioxy)-1-pentanol (14).

A suspension of **13** (1.06 g, 3.82 mmol) and 10% palladium on carbon (Pd/C) (100 mg) in ethanol (EtOH) (20 ml) was stirred under H_2 atmosphere (ca. 1 atm) at room temperature for 24 h. The reaction mixture was filtered over Celite, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 5:1) to afford **14** (625 mg, 87% yield) as a colorless oil along with the recovered starting material (122 mg, 11% yield): $[\alpha]_D^{26}$ +24.3° (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 4.05 (1H, dd, *J* = 5, 7 Hz), 3.92 (1H, dd, *J* = 7, 9 Hz), 3.63-3.57 (1H, br m), 3.57 (1H, t, *J* = 8 Hz), 3.54-3.46 (1H, br m), 1.94-1.88 (1H, br s), 1.88-1.83 (1H, m), 1.76-1.71 (1H, m), 1.40 (3H, s), 1.37 (3H, s), 0.90 (3H, d, *J* = 7 Hz), and 0.76 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3440, 2984, 2936, 2880, 1458, 1382, 1248, 1218, 1162, 1068, and 862 cm^{-1}; HR-EI-MS, calcd. for $C_{10}H_{21}O_3$ (M^+) 189.1491, found *m/z* 189.1474.

(2*S*,3*S*,4*S*,5*R*,8*R*)-10-*p*-Methoxybenzyloxy-3,4,8-trimethyl-1,2-(dimethylmethylenedioxy)-6-decyn-5-ol (15).

To a solution of oxalyl chloride (135 μl, 1.55 mmol) in CH_2Cl_2 (15 ml) was added dropwise a solution of dimethyl sulfoxide (DMSO) (146 μl, 2.06 mmol) in CH_2Cl_2 (5 ml) at -78 °C and the mixture was stirred at -78 °C for 30 min. A solution of **14** (193 mg, 1.03 mmol) in CH_2Cl_2 (5 ml) was added dropwise and the mixture was stirred at -78 °C for 15 min. NEt_3 (717 μl, 5.15 mmol) was added at -78 °C and the mixture was stirred at 0 °C for 20 min. The reaction mixture was partitioned between a solution of PhH-ether (4:1) and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The

crude aldehyde **3** (190 mg) was obtained, and immediately used for the next reaction without further purification.

To a solution of **2** (263 mg, 1.20 mmol) in THF (10 ml) was added dropwise BuLi (1.56 M solution in hexane, 814 μl, 1.27 mmol) at -78 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture was added dropwise a solution of crude aldehyde **3** (190 mg) in THF (7 ml) at -78 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was diluted with ether and quenched with satd. aq. NH_4Cl at -78 °C, and warmed to room temperature. The water layer was extracted repeatedly with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 6:1) to afford the coupling products (413 mg, an α-OH:β-OH=1:2 mixture, 88% yield for 2 steps) as a pale yellow oil.

To a suspension of the coupling products (234 mg, 0.578 mmol) and MS4Å (100 mg) in CH_2Cl_2 (10 ml) was added pyridinium dichromate (PDC) (1.16 g, 3.08 mmol), and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was diluted with ether, filtered over Florisil®, and concentrated *in vacuo*. The crude ketone was obtained and immediately used for the next reaction without further purification.

To a solution of crude ketones in ether (10 ml) was added lithium tri-*tert*-butoxyaluminohydride [$LiAlH(O$*t*-$Bu)_3$] (an excess amount) at 0 °C, and the mixture was stirred at the same temperature for 5 h. Water (2 ml) was added to the reaction mixture, and the mixture was stirred vigorously at room temperature for 1 h and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude products were purified by column chromatography on SiO_2 (hexane:EtOAc, 10:1) to afford **15** (186 mg, an α-OH:β-OH=1:8 mixture, 80% yield for 2 steps) as a pale yellow oil: $[\alpha]_D^{26}$ -15.1° (*c* 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), (for β-OH), δ 7.26 (2H, d, *J* = 8 Hz), 6.88 (2H, d, *J* = 8 Hz), 4.43 (2H, s), 4.36 (1H, br dt, *J* = 2, 6 Hz), 4.05 (1H, dd, *J* = 6, 8 Hz), 3.91 (1H, br ddd, *J* = 6, 8, 9 Hz), 3.80 (3H, s), 3.62-3.54 (3H, m), 2.73-2.63 (1H, m), 1.92-1.83 (2H, m), 1.76-1.65 (2H, m), 1.40 (3H, s), 1.37 (3H, s), 1.18 (3H, d, *J* = 7 Hz), 1.00 (3H, d, *J* = 7 Hz), and 0.79 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3460, 2968, 2936, 2876, 2240, 1616, 1516, 1458, 1372, 1244, 1174, 1098, 1068, 862, 822, and 756 cm^{-1}; HR-FAB-MS, calcd. for $C_{24}H_{35}O_5$ (M^+-H) 403.2486, found *m/z* 403.2429.

(2*S*,3*S*,4*S*,5*R*,6*Z*,8*R*)-10-*p*-Methoxybenzyloxy-3,4,8-trimethyl-1,2-(dimethylmethylenedioxy)-6-decen-5-ol (17).

A suspension of **15** (186 mg, 460 μmol, an α-OH:β-OH=1:8 mixture) and Lindlar cat. (18.6 mg) in methanol (MeOH) (5.5 ml) was stirred under H_2 atmosphere (ca. 1 atm) at room temperature for 2 days. The reaction mixture was filtered over Celite, and concentrated *in vacuo*. The crude products were purified by column chromatography on SiO_2 (hexane:EtOAc, 3:1) to afford **17** (186 mg, an α-OH:β-OH=1:8 mixture, 98% yield) as a colorless oil: $[\alpha]_D^{24}$ +0.20° (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), (for β-OH), δ 7.26 (2H, d, *J* = 8 Hz), 6.87 (2H, d, *J* = 8 Hz), 5.45 (1H, dd, *J* = 9, 11 Hz), 5.20 (1H, t, *J* = 11 Hz), 4.44 (1H, d, *J* = 11 Hz), 4.40 (1H, d, *J* = 11 Hz), 4.24 (1H, t, *J* = 8 Hz), 4.01 (1H, dd, *J* = 6, 7 Hz), 3.90 (1H, dd, *J* = 7, 8 Hz), 3.80 (3H, s), 3.60-3.43 (3H, m), 2.80-2.74 (1H, m), 1.82-1.68 (2H, m), 1.66-1.58 (2H, m), 1.39 (3H, s), 1.36 (3H, s), 0.96 (3H, d, *J* = 7 Hz), 0.94 (3H, d, *J* = 7 Hz), and 0.69 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3476, 2960, 2932, 2872, 1616, 1516, 1460, 1372, 1252, 1064, 1036, 864, 822, and 758 cm^{-1}; HR-FAB-MS, calcd. for $C_{24}H_{39}O_5$ (M^++H) 407.2799, found *m/z* 407.2791.

(2*S*,3*S*,4*S*,5*R*,6*Z*,8*R*)-5-Benzoyloxy-10-*p*-methoxybenzyloxy-3,4,8-trimethyl-1,2-(dimethylmethylene-dioxy)- 6-decene (18).

To a solution of **17** (118 mg, 290 μmol, an α-OH:β-OH=1:8 mixture), NEt_3 (451 μl, 2.90 mmol), and DMAP (a cat. amount) in CH_2Cl_2 (5 ml) was added benzoyl chloride (BzCl) (168 μl, 1.45 mmol), and the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with EtOAc and quenched with satd. aq. $NaHCO_3$. The water layer was extracted repeatedly with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue

was purified by column chromatography on SiO_2 (hexane:EtOAc, 6:1) to afford **18** (148 mg, an α-OBz:β-OBz=1:8 mixture, 100% yield) as a pale yellow oil: $[\alpha]_D^{24}$ -9.10° (*c* 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), (for β-OBz), δ 8.04 (2H, d, *J* = 7 Hz), 7.54 (1H, t, *J* = 7 Hz), 7.43 (2H, t, *J* = 7 Hz), 7.17 (2H, d, *J* = 8 Hz), 6.80 (2H, d, *J* = 8 Hz), 5.74 (1H, t, *J* = 11 Hz), 5.43-5.34 (2H, m), 4.44 (1H, d, *J* = 12 Hz), 4.23 (1H, d, *J* = 12 Hz), 4.03 (1H, dd, *J* = 6, 8 Hz), 3.92 (1H, dt, *J* = 9, 6 Hz), 3.77 (3H, s), 3.59 (1H, t, *J* = 8 Hz), 3.46-3.34 (2H, m), 2.85-2.76 (1H, m), 2.36-2.27 (1H, m), 1.88-1.77 (1H, m), 1.68-1.50 (2H, m), 1.39 (3H, s), 1.35 (3H, s), 0.99 (3H, d, *J* = 7 Hz), 0.95 (3H, d, *J* = 7 Hz), and 0.75 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3064, 2964, 2872, 1720, 1614, 1516, 1456, 1370, 1250, 1110, 1070, 938, 850, 820, and 712 cm^{-1}; HR-FAB-MS, calcd. for $C_{31}H_{41}O_6$ (M^+) 509.2904, found *m/z* 509.2905.

(3*R*,4*Z*,6*R*,7*S*,8*S*,9*S*)-6-Benzoyloxy-3,7,8-trimethyl-9,10-(dimethylmethylenedioxy)-4-decen-1-ol (19).

To a solution of **18** (148 mg, 290 μmol, an α-OBz:β-OBz=1:8 mixture) in CH_2Cl_2 (10 ml) and water (1 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (98.7 mg, 435 μmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction was quenched with satd. aq. $NaHCO_3$ and the mixture was extracted repeatedly with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 10:1) to afford **19** (68.0 mg, a pure form, 63% yield) as a colorless oil: $[\alpha]_D^{18}$ -50.2° (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.05 (2H, d, *J* = 7 Hz), 7.56 (1H, t, *J* = 7 Hz), 7.43 (2H, t, *J* = 7 Hz), 5.68 (1H, t, *J* = 9 Hz), 5.39 (1H, dd, *J* = 9, 11 Hz), 5.34 (1H, t, *J* = 10 Hz), 4.04 (1H, dd, *J* = 6, 8 Hz), 3.92 (1H, dt, *J* = 9, 6 Hz), 3.60 (1H, t, *J* = 8 Hz), 3.62-3.51 (3H, m), 3.07-2.95 (1H, m), 2.37-2.27 (1H, m), 1.89-1.80 (1H, m), 1.80-1.70 (1H, m), 1.39 (3H, s), 1.37 (3H, s), 1.35-1.27 (1H, m), 1.01 (3H, d, *J* = 7 Hz), 0.99 (3H, d, *J* = 7 Hz), and 0.78 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3556, 3064, 2980, 2876, 1712, 1602, 1454, 1372, 1318, 1274, 1116, 1064, 934, 862, 754, and 714 cm^{-1}; HR-EI-MS, calcd. for $C_{22}H_{31}O_5$ (M^+-Me) 375.2172, found *m/z* 375.2144.

(3*R*,4*Z*,6*R*,7*S*,8*S*,9*S*)-6-Benzoyloxy-3,7,8-trimethyl-9,10-(dimethylmethylenedioxy)-4-decenal (20).

To a suspension of the **19** (65.0 mg, 174 μmol) and MS4Å (200 mg) in CH_2Cl_2 (7 ml) was added PDC (202 mg, 573 μmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether and filtered over Florisil®, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 4:1) to afford **20** (58.0 mg, 90% yield) as a colorless oil: $[\alpha]_D^{18}$ -56.8° (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.72 (1H, t, *J* = 2 Hz), 8.05 (2H, d, *J* = 7 Hz), 7.55 (1H, t, *J* = 7 Hz), 7.43 (2H, t, *J* = 7 Hz), 5.69 (1H, t, *J* = 9 Hz), 5.47 (1H, t, *J* = 11 Hz), 5.38 (1H, dd, *J* = 9, 10 Hz), 4.05 (1H, dd, *J* = 6, 8 Hz), 3.92 (1H, dt, *J* = 9, 6 Hz), 3.60 (1H, t, *J* = 8 Hz), 3.50-3.37 (1H, m), 2.55-2.30 (3H, m), 1.87-1.77 (1H, m), 1.40 (3H, s), 1.36 (3H, s), 1.06 (3H, d, *J* = 7 Hz), 0.98 (3H, d, *J* = 7 Hz), and 0.77 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3064, 2980, 2936, 2880, 2724, 1718, 1602, 1454, 1382, 1272, 1110, 1070, 938, 862, 714, and 682 cm^{-1}; HR-EI-MS, calcd. for $C_{23}H_{32}O_5$ (M^+) 388.2251, found *m/z* 388.2226.

(3*R*,4*Z*,6*R*,7*S*,8*S*,9*S*)-6-Hydroxy-3,7,8-trimethyl-9,10-(dimethylmethylenedioxy)-4-decenoic acid (21).

To a solution of **20** (56.0 mg, 151 μmol), 2-methyl-2-butene (57.0 μl, 678 μmol), and sodium dihydrogenphosphate dihydrate ($NaH_2PO_4 \cdot 2H_2O$) (24.0 mg, 527 μmol) in a 15:4 mixture of *tert*-butyl alcohol (*t*-BuOH)-water (7 ml) was added sodium chlorite ($NaClO_2$) (48.0 mg, 527 μmol) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. The reaction mixture was diluted with EtOAc, and the water layer was acidified to pH 1 with 1 M aq. HCl and extracted repeatedly with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude carboxylic acid was obtained, and immediately used for the next reaction without further purification.

To a solution of the crude carboxylic acid in MeOH (5 ml) was added 1 M aq. potassium hydroxide

(KOH) (1 ml), and the mixture was stirred at room temperature for 24 h. The reaction mixture was neutralized with 1 M aq. HCl and diluted with EtOAc. The water layer was acidified to pH 1 with 1 M aq. HCl and extracted repeatedly with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by PTLC on SiO_2 (hexane:EtOAc, 1:1, containing 0.5% of acetic acid) to afford **21** (34.0 mg, 75% yield for 2 steps) as a colorless oil: $[\alpha]_D^{22}$ -6.70° (*c* 0.045, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 5.41 (1H, t, *J* = 10 Hz), 5.23 (1H, t, *J* = 10 Hz), 4.37 (1H, t, *J* = 9 Hz), 4.01 (1H, dd, *J* = 6, 8 Hz), 3.90 (1H, dt, *J* = 8, 6 Hz), 3.57 (1H, t, *J* = 8 Hz), 3.15-3.07 (1H, m), 2.45 (1H, dd, *J* = 4, 17 Hz), 2.24 (1H, dd, *J* = 11, 17 Hz), 1.99-1.88 (1H, m), 1.75-1.65 (1H, m), 1.39 (3H, s), 1.35 (3H, s), 1.00 (3H, d, *J* = 7 Hz), 0.96 (3H, d, *J* = 7 Hz), and 0.66 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3440, 2984, 1724, 1458, 1380, 1214, 1062, 1004, 912, 864, and 780 cm^{-1}; HR-FAB-MS, calcd. for $C_{16}H_{29}O_5$ (M^++H) 301.2016, found *m/z* 301.2014.

(4*R*,5*Z*,7*R*,1'*S*,2'*S*,3'*S*)-4-Methyl-7-[1',2'-dimethyl-3',4'-(dimethylmethylenedioxy)butyl]-1-oxa-5-cyclohepten-2-one (22).

To a solution of **21** (33.0 mg, 110 μmol) and NEt_3 (21.0 μl, 151 μmol) in toluene (50 ml) was added 2,4,6-trichlorobenzoyl chloride (22.0 μl, 141 μmol), and the mixture was stirred at room temperature for 18 h. DMAP (55.2 mg, 452 μmol) was added to the mixture, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether, filtered, and concentrated *in vacuo*. The residue was purified by PTLC on SiO_2 (hexane:EtOAc, 2:1) to afford **22** (25.0 mg, 81% yield) as a colorless oil: $[\alpha]_D^{20}$ +61.9° (*c* 0.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 5.71 (1H, ddd, *J* = 1, 2, 11 Hz), 5.60 (1H, ddd, *J* = 2, 3, 11 Hz), 5.21-5.19 (1H, br m), 4.05 (1H, dd, *J* = 6, 8 Hz), 3.90 (1H, dt, *J* = 6, 8 Hz), 3.58 (1H, t, *J* = 8 Hz), 3.35 (1H, dd, *J* = 5, 13 Hz), 2.67-2.64 (1H, br m), 2.45 (1H, ddd, *J* = 2, 4, 13 Hz), 2.03-1.98 (1H, m), 1.84-1.79 (1H, m), 1.38 (3H, s), 1.35 (3H, s), 1.14 (3H, d, *J* = 7 Hz), 0.99 (3H, d, *J* = 7 Hz), and 0.84 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3018, 2968, 2932, 2876, 1739, 1659, 1460, 1369, 1256, 1175, 1064, 860, and 782 cm^{-1}; HR-FAB-MS, calcd. for $C_{16}H_{27}O_4$ (M^++H) 283.1910, found *m/z* 283.1930.

(1*S*,5*R*,6*S*,10*R*,1'*S*,2'*S*,3'*S*)-5,8,8-Trimethyl-10-[1',2'-dimethyl-3',4'-(dimethylmethylenedioxy)-butyl]-2,7,9-trioxabicyclo[4.4.0]decan-3-one (23).

To a solution of **22** (120 mg, 425 μmol) in a 4:1 mixture of THF-pyridine (10 ml) was added osmium tetroxide (OsO_4) (0.98 M solution in THF, 800 μl, 784 μmol). The mixture was stirred at room temperature for 2 h, and then diluted with MeOH (30 ml). Hydrogen sulfide (H_2S) gas was bubbled through the solution for 1 h, and the resulting black precipitate was removed by filtration over Celite. The clear filtrate was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 1:2) to afford the diols (134 mg, 100%) as a colorless oil.

To a solution of the diols (134 mg, 425 μmol) in acetone (5 ml) was added conc. HCl (a cat. amount), and the mixture was stirred at room temperature for 3 h, diluted with EtOAc, treated with satd. aq. $NaHCO_3$, and extracted repeatedly with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 6:1) to afford **23** (103 mg, 67% yield) as colorless needles: m.p. 152-153 °C; $[\alpha]_D^{20}$ +59.4° (*c* 0.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 3.99 (1H, br t, *J* = 7 Hz, H-1), 3.95 (1H, dt, *J* = 2, 7 Hz, H-2), 3.90 (1H, dd, *J* = 2, 10 Hz, H-5), 3.81 (1H, t, *J* = 10 Hz, H-6), 3.55 (1H, t, *J* = 7 Hz), 3.42 (1H, t, *J* = 10 Hz, H-7), 2.92 (1H, dd, *J* = 8, 18 Hz, H-9), 2.30-2.22 (2H, m, H-9 and 4), 2.15-2.03 (1H, m, H-8), 1.87-1.78 (1H, m, H-3), 1.50 (3H, s), 1.393 (3H, s), 1.388 (3H, s), 1.34 (3H, s), 1.05 (3H, d, *J* = 7 Hz, Me-8), 0.89 (3H, d, *J* = 7 Hz, Me-4), and 0.82 (3H, d, *J* = 7 Hz, Me-3); IR (film), ν_{max} 2984, 2936, 2884, 1758, 1466, 1382, 1246, 1200, 1074, 862, and 760 cm^{-1}; HR-FAB-MS, calcd. for $C_{19}H_{33}O_6$ (M^++H) 357.2278, found *m/z* 357.2251.

(4*S*,5*S*,6*R*,1'*R*,1''*S*,2''*S*,3''*S*)-2,2-Dimethyl-5-hydroxy-4-(3'-hydroxy-1'-methylpropyl)-6-[1'',2''-dimethyl-3'',4''-(dimethylmethylenedioxy)butyl]-1,3-dioxane (24).

To a solution of **23** (156 mg, 440 μmol) in ether (15 ml) was added lithium aluminum hydride ($LiAlH_4$) (34.0 mg, 880 μmol) at 0 °C, the mixture was warmed to room temperature and stirring for 1.5 h. To the reaction mixture was added water (34 μl), and the mixture was stirred vigorously at room temperature until a white gel was generated. To the mixture were added 4 M aq. NaOH (34 μl) and water (68 μl), and the mixture was stirred vigorously at room temperature until a white solid was generated. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 1:1) to afford **24** (146 mg, 92% yield) as colorless needles: m.p. 145-147 °C; $[\alpha]_D^{20}$ +11.7° (*c* 0.73, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$), δ 4.03-3.90 (3H, m), 3.75-3.54 (4H, m), 3.45-3.35 (1H, m), 2.32-2.10 (2H, m), 1.90-1.60 (3H, m), 1.45 (3H, s), 1.39 (3H, s), 1.34 (3H, s), 1.33 (3H, s), 0.96 (3H, d, *J* = 7 Hz), 0.88 (3H, d, *J* = 7 Hz), and 0.82 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3396, 2984, 2936, 2880, 1460, 1382, 1254, 1204, 1174, 1066, 894, 864, and 756 cm^{-1}; HR-FAB-MS, calcd. for $C_{19}H_{37}O_6$ (M^++H) 361.2591, found *m/z* 361.2591.

(4*S*,5*S*,6*R*,1'*R*,1''*S*,2''*S*,3''*S*)-2,2-Dimethyl-5-*p*-methoxybenzyloxy-4-(3'-*p*-methoxybenzyloxy-1'-methylpropyl)-6-[1'',2''-dimethyl-3'',4''-(dimethylmethylenedioxy)butyl]-1,3-dioxane (25).

To a solution of **24** (140 mg, 388 μmol) in THF (20 ml) was added potassium hydride (KH) (in oil, an excess amount), and the mixture was stirred at room temperature for 10 min. To the suspension was added tetrabutylammonium iodide (TBAI) (a cat. amount) and MPMCl (150 μl, 1.11 mmol), and the mixture was heated under reflux for 2 h. After cooling at 0 °C, the reaction mixture was diluted with ether, and the reaction was quenched with water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 10:1) to afford **25** (221 mg, 95% yield) as a pale yellow oil: $[\alpha]_D^{20}$ +11.2° (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.27 (2H, d, *J* = 8 Hz), 7.24 (2H, d, *J* = 8 Hz), 6.84 (2H, d, *J* = 8 Hz), 6.82 (2H, d, *J* = 8 Hz), 4.49 (2H, s), 4.43 (2H, s), 4.02-3.95 (2H, m), 3.79 (6H, s), 3.67 (1H, br d, *J* = 9 Hz), 3.64 (1H, br d, *J* = 11 Hz), 3.56 (1H, t, *J* = 7 Hz), 3.49 (2H, t, *J* = 6 Hz), 3.21 (1H, t, *J* = 10 Hz), 2.41-2.32 (1H, br m), 2.16-2.07 (1H, m), 1.82-1.57 (3H, m), 1.39 (3H, s), 1.37 (3H, s), 1.35 (3H, s), 1.29 (3H, s), 0.96 (3H, d, *J* = 7 Hz), 0.90 (3H, d, *J* = 7 Hz), and 0.81 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 2984, 2936, 2876, 1516, 1466, 1302, 1252, 1174, 1096, 1066, 1036, and 822 cm^{-1}; HR-FAB-MS, calcd. for $C_{35}H_{53}O_8$ (M^++H) 601.3742, found *m/z* 601.3737.

(4*S*,5*S*,6*R*,1'*R*,1''*S*,2''*S*,3''*S*)-2,2-Dimethyl-5-*p*-methoxybenzyloxy-4-(3'-*p*-methoxybenzyloxy-1'-methylpropyl)-6-(1'',2''-dimethyl-3'',4''-dihydroxybutyl)-1,3-dioxane (26).

To a solution of **25** (219 mg, 365 μmol) in MeOH (10 ml) was added 1 M aq. HCl (10 drops *via* pipet), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc, and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (hexane:EtOAc, 1:1) to afford **26** (154 mg, 75% yield) as a pale yellow oil: $[\alpha]_D^{18}$ -2.22° (*c* 0.59, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$), δ 7.24 (2H, d, *J* = 8 Hz), 7.23 (2H, d, *J* = 8 Hz), 6.84 (4H, d, *J* = 8 Hz), 4.55 (1H, d, *J* = 11 Hz), 4.44 (1H, d, *J* = 11 Hz), 4.43 (2H, s), 3.80 (1H, d, *J* = 10 Hz), 3.79 (6H, s), 3.66 (1H, d, *J* = 10 Hz), 3.54-3.47 (5H, m), 3.25 (1H, t, *J* = 10 Hz), 2.67-1.99 (3H, m), 1.70-1.56 (2H, m), 1.40 (3H, s), 1.34 (3H, s), 1.06 (3H, d, *J* = 7 Hz), 0.96 (3H, d, *J* = 7 Hz), and 0.88 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3432, 2936, 2876, 1614, 1516, 1466, 1382, 1250, 1174, 1092, 1036, 892, 822, and 758 cm^{-1}; HR-FAB-MS, calcd. for $C_{32}H_{49}O_8$ (M^++H) 561.3429, found *m/z* 561.3420.

(4*S*,5*S*,6*R*,1'*R*,1''*S*,2''*S*,3''*S*)-2,2-Dimethyl-5-*p*-methoxybenzyloxy-4-(3'-*p*-methoxybenzyloxy-1'-methylpropyl)-6-[1'',2''-dimethyl-3''-hydroxy-4''-(2,4,6-triisopropylbenzenesulfonyloxy)butyl]-1,3-dioxane (27).

To a solution **26** (154 mg, 275 μmol), NEt_3 (100 μl, 717 μmol), and DMAP (a cat. amount) in CH_2Cl_2 (10 ml) was added 2,4,6-triisopropylbenzenesulfonyl chloride (TrisCl) (92.0 mg, 303 μmol), and the mixture was stirred at room temperature for 26 h. The reaction was quenched with satd. aq. $NaHCO_3$, and the water layer was extracted repeatedly with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 4:1) to afford **27** (160 mg, 71% yield) as a pale yellow oil and the starting material (28.5 mg, 19% yield): $[\alpha]_D^{19}$ +0.47° (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.24 (2H, d, *J* = 9 Hz), 7.21 (2H, d, *J* = 9 Hz), 7.18 (2H, s), 6.83 (2H, d, *J* = 8 Hz), 6.82 (2H, d, *J* = 8 Hz), 4.51 (1H, d, *J* = 10 Hz), 4.43 (1H, d, *J* = 10 Hz), 4.43 (2H, s), 4.23-4.11 (3H, m), 4.02 (1H, dd, *J* = 7, 10 Hz), 3.78 (6H, s), 3.71 (1H, br d, *J* = 10 Hz), 3.62 (1H, dd, *J* = 2, 10 Hz), 3.48 (1H, t, *J* = 7 Hz), 3.21 (1H, t, *J* = 10 Hz), 2.95-2.86 (2H, m), 2.23-2.17 (2H, m), 1.98-1.67 (3H, m), 1.34 (3H, s), 1.28 (3H, s), 1.26 (12H, d, *J* = 7 Hz), 1.25 (6H, d, *J* = 7 Hz), 0.94 (6H, d, *J* = 7 Hz), 0.87 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3472, 2960, 2872, 1614, 1516, 1466, 1380, 1348, 1200, 1178, 1092, 1038, 942, 890, 822, 756, and 666 cm^{-1}; HR-FAB-MS, calcd. for $C_{47}H_{69}O_{10}S$ (M^++H) 825.4620, found *m/z* 825.4587.

(4*S*,5*S*,6*R*,1'*R*,1''*S*,2''*S*,3''*S*)-2,2-Dimethyl-5-*p*-methoxybenzyloxy-4-(3'-*p*-methoxybenzyloxy-1'-methylpropyl)-6-(1'',2''-dimethyl-3'',4''-epoxybutyl)-1,3-dioxane (28).

To a solution of **27** (190 mg, 231 μmol) in MeOH (10 ml) was added sodium carbonate (K_2CO_3) (an excess amount), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with ether, and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 3:1) to afford **28** (125 mg, 100% yield) as a pale yellow oil: $[\alpha]_D^{19}$ +3.80° (*c* 0.21, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$), δ 7.24 (4H, d, *J* = 8 Hz), 6.84 (4H, d, *J* = 8 Hz), 4.54 (1H, d, *J* = 12 Hz), 4.48 (1H, d, *J* = 12 Hz), 4.43 (2H, s), 3.89 (1H, dd, *J* = 2, 10 Hz), 3.79 (6H, s), 3.64 (1H, dd, *J* = 2, 10 Hz), 3.49 (2H, t, *J* = 7 Hz), 3.25 (1H, t, *J* = 10 Hz), 2.86 (1H, ddd, *J* = 3, 4, 6 Hz), 2.68 (1H, dd, *J* = 5, 6 Hz), 2.42 (1H, dd, *J* = 3, 5 Hz), 2.19-2.07 (1H, m), 2.07-1.94 (1H, m), 1.78-1.55 (2H, m), 1.51-1.38 (1H, m), 1.37 (3H, s), 1.29 (3H, s), 0.98 (3H, d, *J* = 7 Hz), 0.95 (3H, d, *J* = 7 Hz), and 0.92 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 2932, 1614, 1516, 1250, 1204, 1174, 1096, and 1038 cm^{-1}; HR-FAB-MS, calcd. for $C_{32}H_{45}O_7$ (M^+-H) 541.3167, found *m/z* 541.3185.

(4*S*,5*S*,6*R*,1'*R*,1''*S*,2''*S*,3''*S*)-2,2-Dimethyl-5-*p*-methoxybenzyloxy-4-(3'-*p*-methoxybenzyloxy-1'-methylpropyl)-6-(1'',2''-dimethyl-3''-hydroxy-5''-hexynyl)-1,3-dioxane (29).

To a solution of **28** (89.0 mg, 164 μmol) in DMSO (1 ml) was added lithium acetylide-ethylenediamine complex (an excess amount), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ether and the reaction was quenched with satd. aq. NH_4Cl, and the water layer was extracted repeatedly with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 3:1) to afford **29** (71.2 mg, 76% yield) as a pale yellow oil and the starting material (5.6 mg, 6% yield): $[\alpha]_D^{18}$ -2.61° (*c* 0.71, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$), δ 7.25 (4H, d, *J* = 9 Hz), 6.84 (4H, d, *J* = 9 Hz), 4.54 (1H, d, *J* = 10 Hz), 4.45 (1H, d, *J* = 10 Hz), 4.43 (2H, s), 3.79 (6H, s), 3.74 (1H, d, *J* = 10 Hz), 3.64 (1H, dd, *J* = 2, 10 Hz), 3.60-3.47 (1H, m), 3.49 (2H, t, *J* = 7 Hz), 3.24 (1H, t, *J* = 10 Hz), 2.86 (1H, d, *J* = 5 Hz), 2.51 (1H, ddd, *J* = 3, 4, 17 Hz), 2.33 (1H, ddd, *J* = 3, 6, 17 Hz), 2.24-2.07 (2H, m), 2.03 (1H, t, *J* = 3 Hz), 1.88-1.59 (3H, m), 1.38 (3H, s), 1.32 (3H, s), 0.99 (3H, d, *J* = 7 Hz), 0.96 (3H, d, *J* = 7 Hz), and 0.89 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3480, 3304, 2960, 2116, 1614, 1516, 1382, 1302, 1250, 1174, 1096, 1036, 892, and 822 cm^{-1}; HR-FAB-MS, calcd. for $C_{34}H_{47}O_7$ (M^+-H) 567.3323, found *m/z* 567.3298.

(4*S*,5*S*,6*R*,1'*R*,1''*S*,2''*S*,3''*S*)-2,2-Dimethyl-5-*p*-methoxybenzyloxy-4-(3'-*p*-methoxybenzyloxy-1'-methylpropyl)-6-(1'',2''-dimethyl-3''-hydroxy-5''-hexenyl)-1,3-dioxane (30).

A suspension of **29** (57.3 mg, 101 μmol) and Lindlar cat. (7.5 mg) in PhH (5.5 ml) was stirred under H_2 atmosphere (ca. 1 atm) at room temperature for 30 min. The reaction mixture was filtered over Celite, and concentrated *in vacuo*. **30** (54.6 mg 95% yield) was obtained as a pale yellow oil: $[\alpha]_D^{19}$ -4.15° (*c* 0.38, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$), δ 7.25 (2H, d, *J* = 9 Hz), 7.23 (2H, d, *J* = 9 Hz), 6.84 (2H, d, *J* = 9 Hz), 6.83 (2H, d, *J* = 9 Hz), 5.97-5.81 (1H, m), 5.20-5.08 (2H, m), 4.53 (1H, d, *J* = 11 Hz), 4.45 (1H, d, *J* = 11 Hz), 4.43 (2H, s), 3.79 (3H, s), 3.78 (3H, s), 3.75 (1H, d, *J* = 10 Hz), 3.64 (1H, dd, *J* = 2, 10 Hz), 3.49 (2H, t, *J* = 7 Hz), 3.51-3.46 (1H, m), 3.24 (1H, t, *J* = 10 Hz), 2.66 (1H, br d, *J* = 4 Hz), 2.43-2.32 (1H, br m), 2.19-2.02 (3H, br m), 1.38 (3H, s), 1.32 (3H, s), 1.01 (3H, d, *J* = 7 Hz), 0.95 (3H, d, *J* = 7 Hz), and 0.89 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3482, 3072, 2936, 2876, 1642, 1614, 1516, 1466, 1382, 1302, 1250, 1174, 1096, 1038, 892, and 822 cm^{-1}; HR-FAB-MS, calcd. for $C_{34}H_{49}O_7$ (M^+-H) 569.3480, found *m/z* 569.3499.

(1*S*,3*R*,4*S*,5*S*,6*R*,10*S*,1'*R*)-3-Allyl-3-hydroxy-4,5,8,8-tetramethyl-10-(3'-hydroxy-1'-methylpropyl)-2,7,9-trioxabicyclo[4.4.0]decane (39).

To a solution of oxalyl chloride (18.2 μl, 210 μmol) in CH_2Cl_2 (1 ml) was added dropwise a solution of DMSO (47.6 μl, 670 μmol) in CH_2Cl_2 (1 ml) at -78 °C and the mixture was stirred at -78 °C for 30 min. A solution of **30** (23.0 mg, 43.0 μmol) in CH_2Cl_2 (1.5 ml) was added dropwise and the mixture was stirred at -78 °C for 1 h. NEt_3 (100 μl, 712 μmol) was added at -78 °C and the mixture was stirred at 0 °C for 30 min. The mixture was treated with water, and the water layer was extracted repeatedly with ether. The combined organic layers were washed with satd. aq. NH_4Cl, satd. aq. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude ketone (29.6 mg) was obtained and immediately used for the next reaction without further purification: (a pure sample); $[\alpha]_D^{20}$ +3.13° (*c* 0.22, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$), δ 7.25 (4H, d, *J* = 9 Hz), 6.85 (2H, d, *J* = 9 Hz), 6.83 (2H, d, *J* = 9 Hz), 5.93 (1H, ddt, *J* = 11, 18, 6 Hz), 5.14 (1H, br dd, *J* = 1, 11 Hz), 5.07 (1H, br dd, *J* = 1, 18 Hz), 4.53 (1H, d, *J* = 10 Hz), 4.47 (1H, d, *J* = 10 Hz), 4.41 (2H, s), 3.79 (6H, s), 3.58 (1H, d, *J* = 10 Hz), 3.57 (1H, t, *J* = 10 Hz), 3.47 (2H, t, *J* = 7 Hz), 3.23 (1H, t, *J* = 10 Hz), 3.24-3.15 (2H, m), 2.74-2.60 (1H, m), 2.28-2.16 (1H, m), 2.16-2.02 (1H, m), 1.76-1.51 (2H, m), 1.28 (6H, s), 1.06 (3H, d, *J* = 7 Hz), and 0.92 (6H, d, *J* = 7 Hz); IR (film), ν_{max} 3076, 2964, 2940, 2880, 1714, 1614, 1516, 1464, 1382, 1302, 1250, 1204, 1174, 1098, 1036, 924, 892, 822, and 756 cm^{-1}; HR-FAB-MS, calcd. for $C_{34}H_{49}O_7$ (M^++H) 569.3480, found *m/z* 569.3450.

To a solution of the crude ketone (29.6 mg) in CH_2Cl_2 (2 ml) and water (0.2 ml) was added DDQ (94.0 mg, 417 μmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was treated with satd. aq. $NaHCO_3$ and extracted repeatedly with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane:EtOAc, 4:1) to afford **39** (12.2 mg, 92% yield for 2 steps) as a pale yellow oil: $[\alpha]_D^{19}$ -10.1° (*c* 0.60, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$), δ 5.97-5.78 (1H, m), 5.25 (1H, dd, *J* = 2, 11 Hz), 5.17 (1H, dd, *J* = 2, 17 Hz), 3.70-3.54 (4H, m), 3.15 (1H, br t, *J* = 10 Hz), 2.38 (1H, br d, *J* = 6 Hz), 2.27 (1H, br d, *J* = 2 Hz), 2.08-1.97 (1H, br m), 1.80-1.57 (4H, m), 1.47 (3H, s), 1.39 (3H, s), 0.98 (3H, d, *J* = 7 Hz), 0.94 (3H, d, *J* = 7 Hz), and 0.93 (3H, d, *J* = 7 Hz); IR (film), ν_{max} 3400, 3076, 2976, 2932, 2880, 1642, 1460, 1382, 1256, 1172, 1106, 1062, 988, and 896 cm^{-1}; HR-FAB-MS, calcd. for $C_{18}H_{33}O_5$ (M^++H) 329.2329, found *m/z* 329.2299.

(3*S*,5*R*,7*S*,8*R*,9*S*,10*S*,1'*S*,2'*R*)-3,8-Diacetoxy-9,10-dimethyl-7-(1',4'-diacetoxy-2'-methylbutyl)-1,6-dioxaspiro[4.5]decane (the spiro acetal part of ciguatoxin, 40).

To a solution of **39** (9.0 mg, 27.4 μmol) in a 2:1 mixture of acetonitrile (CH_3CN)-water (1 ml) was added OsO_4 (0.98 M in THF, 42.0 μl, 41.1 μmol), and the mixture was stirred at room temperature for 1 h. The mixture was poured into satd. aq. Na_2SO_3 and the mixture was extracted repeatedly with EtOAc. The

combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was obtained and immediately used for the next reaction without further purification.

A solution of the crude product and trifluoroacetic acid (TFA) (4 drops *via* pipet) in CH_2Cl_2 (1 ml) was stirred at room temperature for 1 h. The mixture was diluted with PhH, and concentrated *in vacuo*. The residue was dissolved with pyridine (1 ml). DMAP (a cat. amount) and acetic anhydride (Ac_2O) (0.5 ml) were added to the solution, and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with toluene, and concentrated *in vacuo*. The residue was purified by PTLC on SiO_2 (PhH:EtOAc, 7:1) to afford **40** (2.5 mg, 22% yield for 3 steps) and **38** (1.7 mg, 15% yield for 3 steps) as colorless oils, respectively.

40: $[\alpha]_D^{19}$ -58.5° (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 5.31-5.27 (1H, m, H-2), 4.85 (1H, t, *J* = 4 Hz, H-9), 4.65 (1H, t, *J* = 10 Hz, H-7), 4.13-4.01 (2H, m, H-12), 3.97 (1H, dd, *J* = 5, 11 Hz, H-1α), 3.91 (1H, br d, *J* = 10 Hz, H-8), 3.90 (1H, dd, *J* = 3, 11 Hz, H-1β), 2.28 (1H, dd, *J* = 7, 13 Hz, H-3α), 2.08 (1H, dd, *J* = 3, 13 Hz, H-3β), 2.08 (3H. s), 2.052 (6H, s), 2.050 (3H, s), 2.05-1.97 (1H, m, H-10), 1.88-1.59 (3H, m, H-6, 11, and 5), 1.48-1.38 (1H, m, H-11), 0.97 (3H, d, *J* = 7 Hz, Me-5), 0.95 (3H, d, *J* = 7 Hz, Me-10), and 0.88 (3H, d, *J* = 7 Hz, Me-6); IR (film), ν_{max} 2972, 2940, 1740, 1460, 1436, 1372, 1242, 1102, 1028, 982, and 948 cm^{-1}; HR-FAB-MS, calcd. for $C_{21}H_{33}O_8$ (M^+-OAc) 413.1448, found *m/z* 413.1469.

38: ^{1}H NMR (400 MHz, $CDCl_3$), δ 5.18-5.13 (1H, m, H-2), 4.89 (1H, t, *J* = 4 Hz, H-9), 4.65 (1H, t, *J* = 10 Hz, H-7), 4.25 (1H, dd, *J* = 7, 10 Hz, H-1β), 4.14-4.02 (2H, m, H-12), 3.93 (1H, dd, *J* = 4, 10 Hz, H-8), 3.76 (1H, dd, *J* = 5, 10 Hz, H-1α), 2.34 (1H, dd, *J* = 7, 13 Hz, H-3β), 2.13-2.05 (1H, m, H-10), 2.08 (3H, s), 2.053 (3H, s), 2.049 (3H, s), 2.045 (3H, s), 1.95 (1H, dd, J = 3, 14 Hz, H-3α), 1.88-1.65 (2H, m, H-6 and 11), 1.65-1.56 (1H, m, H-5), 1.52-1.40 (1H, m, H-11), 0.99 (3H, d, *J* = 7 Hz, Me-10), 0.89 (3H, d, *J* = 7 Hz, Me-5), and 0.87 (3H, d, *J* = 7 Hz, Me-6).

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