HETEROCYCLES, Vol. 82, No. 1, 2010, pp. 761 - 774. © The Japan Institute of Heterocyclic Chemistry
Received, 19th June, 1020, Accepted, 26th July, 2010, Published online, 27th July, 2010
DOI: 10.3987/COM-10-S(E)61

STEREOSELECTIVE SYNTHESIS OF CARIBBEAN CIGUATOXIN M-RING USING [2+2] PHOTOCYCLIZATION

Shuji Yamashita,[1,]* Naoya Iijima,[1] Takahiro Shida,[1] and Masahiro Hirama[1,2,]*

[1]Department of Chemistry, Graduate School of Science, Tohoku University, and [2]Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan. s-yamashita@m.tohoku.ac.jp; hirama@m.tohoku.ac.jp

Abstract – Ciguatoxins, the principal causative toxins of ciguatera seafood poisoning, are potent toxic polycyclic ethers. We report herein a stereoselective synthesis of the seven-membered M-ring moiety of Caribbean ciguatoxin C-CTX-1. The key features of the synthesis are the photo-induced [2+2] electrocyclization and enzymatic asymmetric hydrolysis to construct the congested oxepane ring.

This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

INTRODUCTION

Ciguatera seafood poisoning, an important medical issue in tropical and subtropical regions, causes gastrointestinal, cardiovascular and neurological disorders that may last for weeks or even years.[1] Ciguatoxins (CTXs), the principal causative toxins of ciguatera, are ladder-like polycyclic ethers.[2] To date, more than 20 ciguatoxin congeners have been structurally identified.[3] Caribbean ciguatoxin C-CTX-1 (**1**, Figure 1) was isolated by Lewis and co-workers from the carnivorous fish horse-eye jack (*Caranx latus*) as the main toxin of ciguatera in the Caribbean Sea.[4] In contrast to the typical Pacific ciguatoxin CTX3C (**2**, Figure 1), **1** possesses 14 ether rings with dissimilar functional group patterns. These structural differences are believed to cause the distinct ciguatera symptoms.

The very limited supply of ciguatoxins from natural sources has prevented chemical and biological studies of ciguatera. Thus, we have successfully synthesized three Pacific ciguatoxins[5,6] and developed a sandwich enzyme-linked immunosorbent assay (ELISA) for their detection.[7] Furthermore, we have reported the syntheses of ABCDE-[8] and LMN-ring[9] fragments of C-CTX-1 (**1**). Unfortunately, the large scale preparation of LMN-ring moiety was hampered, due to the low yield of the sterically congested seven-membered M-ring.[10] This prompted us to improve the synthetic route to the M-ring moiety of **1**.

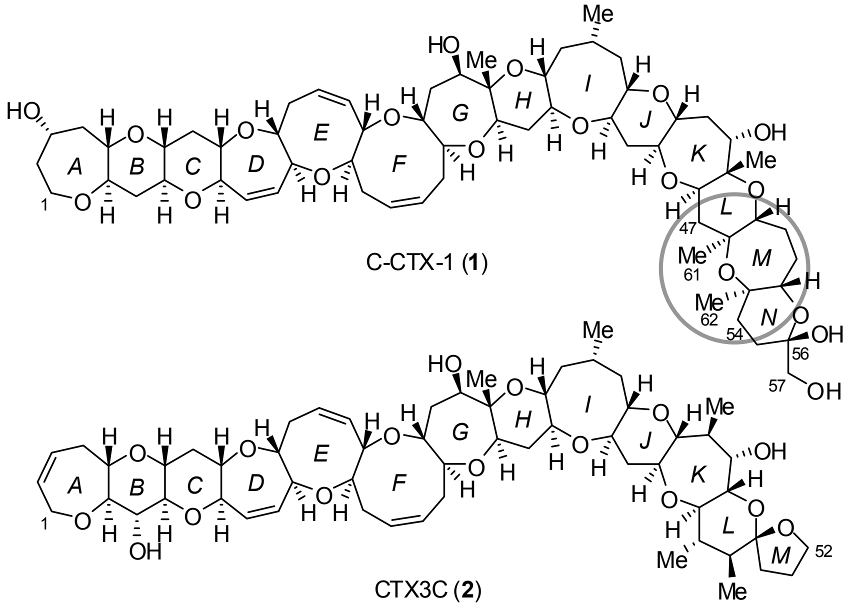
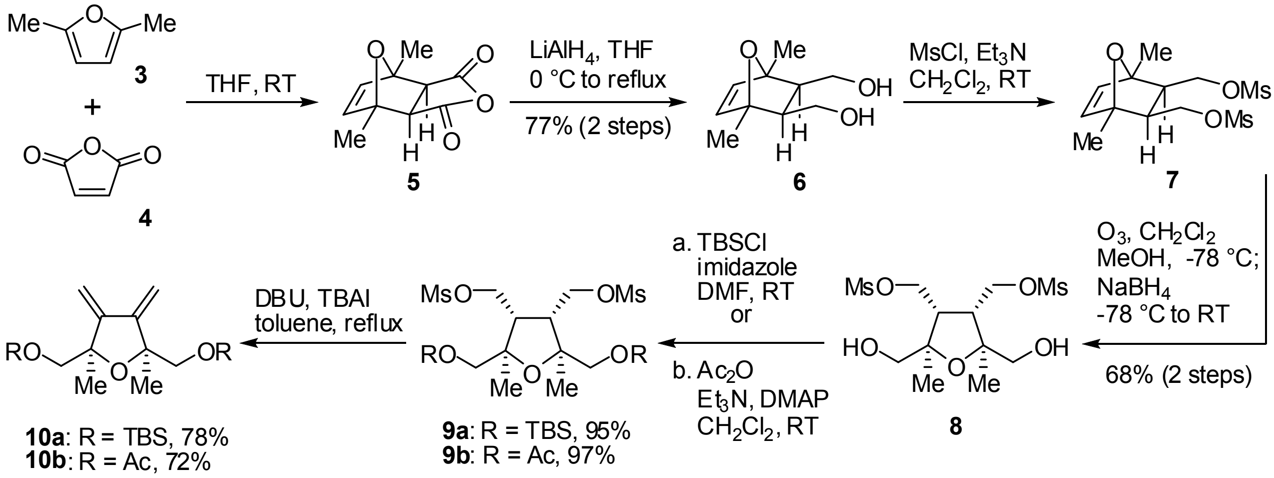


Figure 1. Structures of ciguatoxins

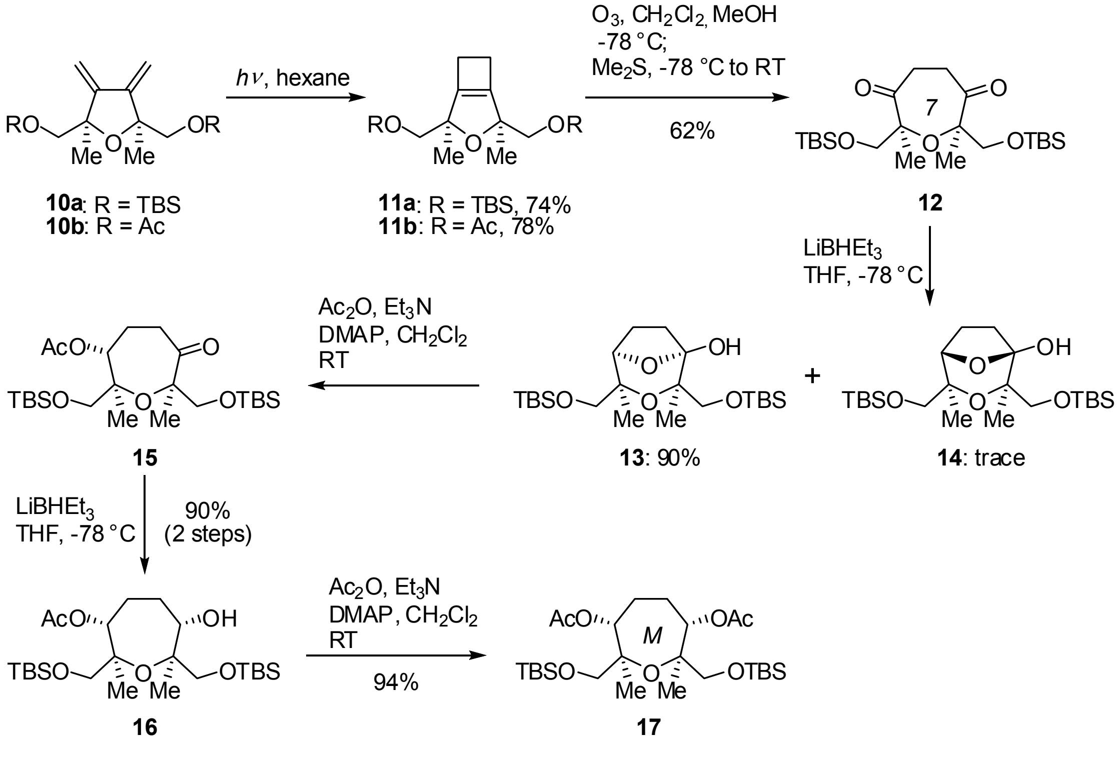


Scheme 1. Synthesis of dienes **10a** and **10b**

RESULTS AND DISCUSSION

Our new synthesis commenced with commercially available 2,5-dimethylfuran **3** and maleic anhydride **4** (Scheme 1). Diels-Alder reaction between **3** and **4** afforded the thermodynamically favored exo-adduct **5**,[11] which was successively reduced to the corresponding diol **6** in 77% overall yield. Treatment of **6** with methanesulfonyl chloride and triethylamine gave bis-mesylate **7**.[12] Ozonolysis of **7** followed by $NaBH_4$ reduction produced oxolane diol **8** in 68% yield from **6**. After the protection of **8** as its bis-TBS ether, β-elimination of the bis-mesylate was realized by treatment with DBU under reflux in toluene in the presence of tetrabutylammonium iodide (TBAI), leading to the required diene **10a** (74% from **8**). Following the same procedure, bis-acetate **10b** was prepared in 70% yield from **8**.

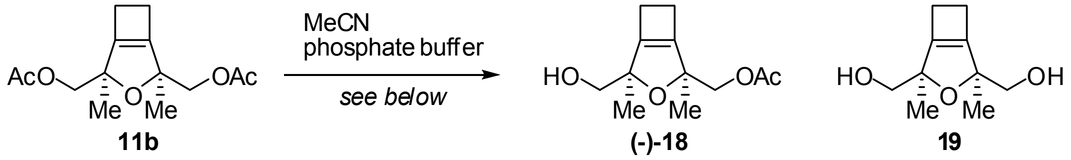
Next, we examined the [2+2] photocyclization of diene **10** (Scheme 2). Exposure of **10a** and **10b** to a low pressure mercury lamp in a quartz vessel led to formation of oxa-bicyclo[3.2.0]heptene **11a** and **11b**, respectively, in good yields.[13] Ozonolysis of the internal olefin of **11a** afforded the desired seven-membered diketone **12** in 62% yield, which has a bis-trisubstituted alkyl ether structure. With the requisite oxepane **12** in hand, stereoselective reduction of the diketone was pursued. After a considerable number of attempts, it was found that treatment of **12** with $LiBHEt_3$ at low temperature accomplished the desired β-face reduction, although the reaction stopped at the reduction of a single ketone to form hemiacetal **13** in 90% yield. Due to the stability of the hemiacetal structure of **13**, further reduction to the corresponding diol was not realized even at higher temperature. Other reducing reagents [$NaBH_4$, $LiAlH_4$, DIBAL, Al(O*i*-Pr)$_3$, and SmI_2] did not provide **13** as a major product. Fortunately, we found that the acetylation of **13** occurred at the secondary alcohol formed via the hemiacetal-ring opening, and the resulting ketone **15** could be reduced by $LiBHEt_3$ stereoselectively. Acetylation of alcohol **16** furnished *meso*-M-ring moiety **17** in 14% overall yield (12 steps) from the starting material **4**.



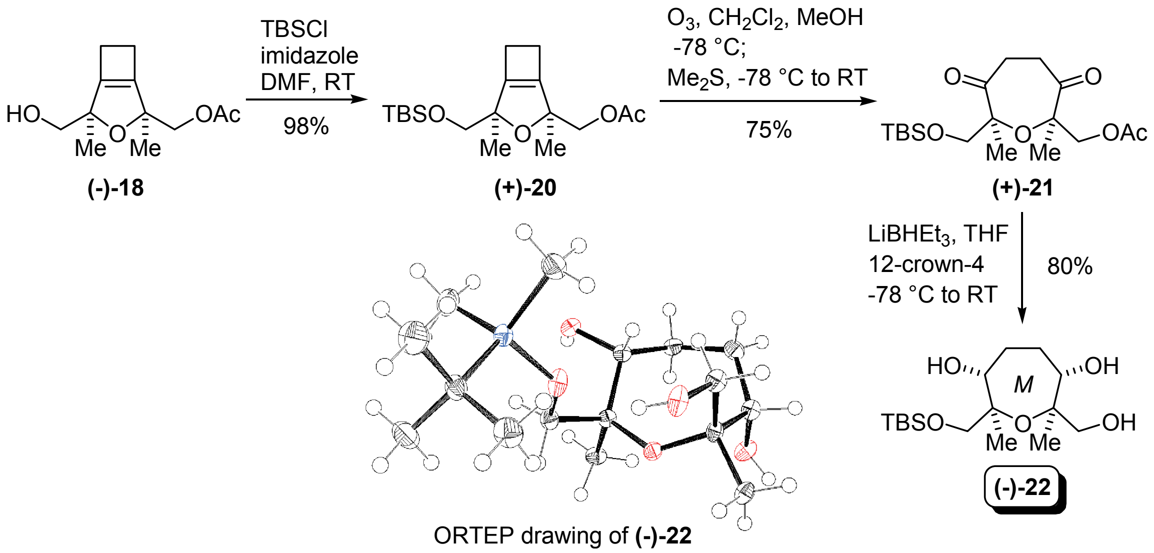
Scheme 2. Synthesis of the *meso*-M-ring of C-CTX-1

In order to prepare the chiral M-ring, we focused on the desymmetrization of *meso*-intermediates **12** and **17**. Attempts at enantioselective reduction of diketone **12** and enzymatic asymmetric hydrolysis of bis-acetate **17** were unsuccessful. After examining various enzymes (Table 1), we eventually found that treatment of bis-acetate **11b** with lipoprotein lipase in MeCN/pH 8.0 phosphate buffer at 45 °C gave rise to mono-acetate **(-)-18** (85% ee)[14] in 72% yield along with a small amount of diol **19** (5%) and recovered **11b** (16%) (Entry 4).

Table 1. Enzymatic asymmetric hydrolysis of bis-acetate **11b**



Entry	Enzyme	pH	Conditions	**(-)-18**	**19**	Recovery of **11b**
1	lipase AS	7.0	RT, 14 h	55% ((**+**)-**18**; 70% ee)	5%	29%
2	lipase AY	7.0	40 °C, 12 h	46% (20% ee)	27%	17%
3	lipase type II	7.0	30 °C, 5 d	23% ((**+**)-**18**; 75% ee)	trace	51%
4	lipoprotein lipase	8.0	45 °C, 16 h	72% (85% ee)	5%	16%



Scheme 3. Synthesis of the M-ring triol **(-)-22**

The M-ring triol **22** was synthesized from the obtained mono-acetate **(-)-18** (Scheme 3). TBS-protection of **(-)-18**, followed by oxidative cleavage of cyclobutene **(+)-20** afforded diketone **(+)-21** in 74% overall yield. Stereoselective reduction of **(+)-21** was achieved using $LiBHEt_3$ in the presence of 12-crown-4 to give triol **(-)-22** in 80% yield.[15] The absolute configuration of **(-)-22** was confirmed by X-ray crystallographic analysis.[16, 17]

In conclusion, we have developed a secure and stereocontrolled synthetic route to the optically active M-ring of **1**. The key intermediate **(-)-22** was prepared in 11 steps from the commercially available compounds. The synthesis features (1) photo-induced [2+2] cyclization to construct the cyclobutene structure; (2) enzymatic desymmetrization of bis-acetate **11b**; and (3) stereoselective reduction of diketone **21**. The strategy described herein will accelerate our synthetic study of Caribbean C-CTX-1, which is being actively investigated in our laboratory.

EXPERIMENTAL

All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF was distilled from sodium/benzophenone. Toluene, dichloromethane (CH_2Cl_2), triethylamine (Et_3N), acetonitrile (MeCN) and hexane were distilled from calcium hydride. DMF was distilled under reduced pressure from calcium hydride. All other reagents were used as supplied unless otherwise stated.

Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Column chromatography was performed using 100-210 μm Silica Gel 60N (Kanto Chemical Co., Inc.), and for flash column chromatography 40-50 μm Silica Gel 60N (Kanto Chemical Co., Inc.) was used.

^{1}H- and ^{13}C-NMR spectra were recorded on Varian 400 (400 MHz), or Varian INOVA 500 (500 MHz) spectrometers. Chemical shifts are reported in δ (ppm) down field from tetramethylsilane (TMS) with reference to solvent signals [^{1}H-NMR: $CHCl_3$ (7.26); ^{13}C-NMR: $CDCl_3$ (77.0)]. Signal patterns are indicated as s, singlet; d, doublet; m, multiplet; br, broad peak. IR spectra were recorded on Perkin Elmer Spectrum BX FT-IR spectrometer. High resolution ESI-FT mass spectra were measured on Thermo Fisher Scientific Orbitrap Discovery (ESI LTQ Orbitrap). Optical rotations were recorded on JASCO P-2200 polarimeter. The carbon numbers of all compounds are corresponding with C-CTXs.

Diol 6. 2,5-Dimethylfuran (6.5 mL, 61 mmol) and maleic anhydride (5.1 g, 52 mmol) were dissolved with THF (10 mL) and stirred for 21 h at room temperature. The resulting crude mixture of adduct **5** was used for the next step without any purification.

To a suspension of $LiAlH_4$ (3.0 g, 79 mmol) in THF (100 mL) at 0 °C was added dropwise the above mixture in THF (60 mL). After being stirred for 2 h at room temperature, the mixture was warmed to reflux and stirred for 20 h. The reaction mixture was quenched at 0 °C by slow addition of saturated aqueous Na_2SO_4. The resulting inorganic salts were filtered and washed with EtOAc, then the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel (hexane/EtOAc 1:1-0:1) gave diol **6** (7.29 g, 39.6 mmol) in 77% yield over 2 steps: colorless oil; IR (film) ν 3443, 2932, 1731, 1714, 1650, 1454, 1383, 1033, 865 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52 (6H, s, Me61, Me62), 2.06 (2H, m, H49, H52), 3.86 (2H, m, H50, H51), 3.94 (2H, dd, *J* = 11.4, 3.5 Hz, H50, H51), 6.16 (2H, s, H47, H54); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.2 (Me61, Me62), 46.3 (C49, C52), 60.8 (C50, C51), 86.7(C48, C53), 140.2(C47, C54); HRMS (ESI), calcd for $C_{10}H_{16}O_3Na$ 207.0992 (M+Na$^+$), found 207.0994.

Diol 8. To a solution of **6** (7.03 g, 38.2 mmol) and Et_3N (17.5 mL, 126 mmol) in CH_2Cl_2 (80 mL) was added MsCl (6.5 mL, 84 mmol) at 0 °C. After being stirred for 1 h at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was passed through a short pad of silica gel (hexane/EtOAc 1:1-0:1), and the resulting bis-mesylate **7** was used for the next step without further purification. **[Caution!]** Bis-mesylate **7** underwent decomposition in high concentration.

To a solution of **7** in CH_2Cl_2 (300 mL) and MeOH (75 mL) was bubbled O_3 at -78 °C for 70 min. After the color of solution turned to blue, the excess O_3 was removed with a stream of air for 10 min. $NaBH_4$ (1.58 g, 41.8 mmol) was added to the resulting mixture at -78 °C, and then allowed to warm to room temperature. After being stirred for 3 h, the mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (EtOAc/MeOH 1:0-10:1) gave diol **8** (9.84 g, 26.1 mmol) in 68% yield over 2 steps: colorless solid; mp 116-117 °C; IR (film) ν 3389, 2939, 1351, 1172, 1048, 954, 848, 773 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (6H, s, Me61, Me62), 3.08 (6H, s, Ms x 2), 3.11 (2H, m, H49, H52), 3.46 (2H, d, *J* = 11.4 Hz, H47, H54), 3.56 (2H, d, *J* = 11.4 Hz, H47, H54), 4.33 (2H, ddd, *J* = 10.2, 4.9, 2.0 Hz, H50, H51), 4.44 (2H, ddd, *J* = 10.2, 5.1, 1.5 Hz, H50, H51); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1 (Me61, Me62), 37.6 (Ms x 2), 43.7 (C49, C52), 66.5 (C50, C51), 69.4 (C47, C54), 84.0 (C48, C53); HRMS (ESI), calcd for $C_{12}H_{24}O_9S_2Na$ 399.0754 (M+Na$^+$), found 399.0757.

Bis-TBS ether 9a. To a solution of **8** (129 mg, 343 μmol) in DMF (3.4 mL) were added imidazole (98.0 mg, 1.44 mmol) and TBSCl (170 mg, 1.13 mmol). After being stirred for 6 h at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 4:1-3:1) gave bis-TBS ether **9a** (197 mg, 326 μmol) in 95% yield: colorless solid; mp 74-75 °C; IR (film) ν 2930, 2857, 1471, 1359, 1255, 1176, 1095, 953, 836, 777 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.06 (12H, s, TBS x 2), 0.90 (18H, s, TBS x 2), 1.20 (6H, s, Me61, Me62), 2.96 (2H, m, H49, H52), 3.05 (6H, s, Ms x 2), 3.34 (2H, d, *J* = 9.8 Hz, H47, H54), 3.49 (2H, d, *J* = 9.8 Hz, H47, H54), 4.35 (2H, ddd, *J* = 10.2, 5.3, 2.2 Hz, H50, H51), 4.43 (2H, ddd, *J* = 10.2, 4.9, 1.0 Hz, H50, H51); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.6 (TBS x 2), -5.4 (TBS x 2), 18.2 (TBS x 2), 21.3 (Me61, Me62), 25.9 (TBS x 2), 37.3 (Ms x 2), 44.5 (C49, C52), 66.9 (C50, C51), 70.7(C47, C54), 83.4 (C48, C53); HRMS (ESI), calcd for $C_{24}H_{52}O_9S_2Si_2Na$ 627.2483(M+Na$^+$), found 627.2485.

Diene 10a. To a solution of **9a** (10.8 g, 17.9 mmol) in toluene (75 mL) were added TBAI (3.45 g, 9.34 mmol) and DBU (11.0 mL, 73.2 mmol) at room temperature, then warmed to reflux. After being stirred for 20 h, the mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (hexane/EtOAc 50:1-20:1) gave diene **10a** (5.76 g, 14.0 mmol) in 78% yield: colorless oil; IR (film) ν 2927, 2855, 1471, 1255, 1092, 836, 775 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.02 (6H, s, TBS x 2), 0.03 (6H, s, TBS x 2), 0.88 (18H, s, TBS x 2), 1.31 (6H, s, Me61, Me62), 3.47 (2H, d, *J* = 9.8 Hz, H47, H54), 3.50 (2H, d, *J* = 9.8 Hz, H47, H54), 4.91 (2H, s, H50, H51), 5.40 (2H, s, H50, H51); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.5 (TBS x 2), -5.4 (TBS x 2), 18.3 (TBS x 2), 25.85 (Me61, Me62), 25.92 (TBS x 2), 70.0 (C47, C54), 83.9 (C48, C53), 104.0 (C50, C51), 150.9 (C49, C52); HRMS (ESI), calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 (M+Na$^+$), found 435.2719.

Bis-acetate 9b. To a mixture of **8** (9.71 g, 25.8 mmol), Et_3N (18.0 mL, 129 mmol) and DMAP (1.54 g, 12.6 mmol) in CH_2Cl_2 (200 mL) was added Ac_2O (7.5 mL, 79.3 mmol). After being stirred for 14 h at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (hexane/EtOAc 2:1-0:1) gave bis-acetate **9b** (11.5 g, 25.0 mmol) in 97% yield: colorless solid; mp 73-74 °C; IR (film) ν 2941, 1731, 1359, 1242, 1173, 1045, 956, 824, 734 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (6H, s, Me61, Me62), 2.12 (6H, s, Ac x 2), 2.88 (2H, m, H49, H52), 3.09 (6H, s, Ms x 2), 3.89 (2H, d, *J* = 11.3 Hz, H47, H54), 4.08 (2H, d, *J* = 11.3 Hz, H47, H54), 4.36 (2H, ddd, *J* = 10.4, 4.5, 1.8 Hz, H50, H51), 4.41 (2H, ddd, *J* = 10.4, 5.1, 2.1 Hz, H50, H51); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.9 (Ac x 2), 21.2 (Me61, Me62), 37.6 (Ms x 2), 44.5 (C49, C52), 65.5 (C50, C51), 69.6 (C47, C54), 82.2 (C48, C53), 170.6 (Ac x 2); HRMS (ESI), calcd for $C_{16}H_{28}O_{11}S_2Na$ 483.0965 (M+Na$^+$), found 483.0965.

Diene 10b. To a solution of **9b** (11.5 g, 25.0 mmol) in toluene (125 mL) were added TBAI (2.52 g, 6.82 mmol) and DBU (11.5 mL, 76.5 mmol) at room temperature, then warmed to reflux. After being stirred for 20 h, the mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (hexane/EtOAc 8:1-2:1) gave diene **10b** (4.81 g, 17.9 mmol) in 72% yield: colorless oil; IR (film) ν 2979, 1743, 1372, 1243, 1103, 1044, 996, 901 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.38 (6H, s, Me61, Me62), 2.08 (6H, s, Ac x 2), 4.03 (2H, d, J = 11.3 Hz, H47, H54), 4.08 (2H, d, J = 11.3 Hz, H47, H54), 4.90 (2H, s, H50, H51), 5.51 (2H, s, H50, H51); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.9 (Ac x 2), 25.8 (Me61, Me62), 69.9 (C47, C54), 83.0 (C48, C53), 105.5 (C50, C51), 149.0 (C49, C52), 170.9 (Ac x 2); HRMS (ESI), calcd for $C_{14}H_{20}O_5Na$ 291.1203 ($M+Na^+$), found 291.1205.

Cyclobutene 11a. A solution of **10a** (5.76 g, 14.0 mmol) in hexane (700 mL) in quartz vessel was irradiated by low pressure mercury lamps (20 W x 4) for 60 h at room temperature. The resulting solution was concentrated in vacuo, purified by column chromatography on silica gel (hexane/EtOAc 50:1) to give cyclobutene **11a** (4.28 g, 10.4 mmol) in 74% yield: colorless oil; IR (film) ν 2956, 2928, 2857, 1472, 1255, 1096, 836, 775 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 0.02 (12H, s, TBS x 2), 0.87 (18H, s, TBS x 2), 1.27 (6H, s, Me61, Me62), 2.61 (4H, s, H50 x 2, H51 x 2), 3.50 (2H, d, J = 9.6 Hz, H47, H54), 3.52 (2H, d, J = 9.6 Hz, H47, H54), ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.5 (TBS), -5.4 (TBS), 18.2 (TBS), 23.5 (Me61, Me62), 25.8 (TBS), 26.5 (C50, C51), 69.7 (C47, C54), 87.9 (C48, C53), 150.0 (C49, C52); HRMS (ESI), calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 ($M+Na^+$), found 435.2719.

Cyclobutene 11b. A solution of **10b** (4.81 g, 17.9 mmol) in hexane (700 mL) in quartz vessel was irradiated by low pressure mercury lamps (20 W x 4) for 13 h at room temperature. The resulting solution was concentrated in vacuo, purified by column chromatography on silica gel (hexane/EtOAc 8:1-1:1) to give cyclobutene **11b** (3.75 g, 14.0 mmol) in 78% yield: colorless oil; IR (film) ν 2930 1745, 1454, 1371, 1233, 1148, 1039, 906, 858 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, s, Me61, Me62), 2.07 (6H, s, Ac x 2), 2.57-2.66 (4H, m, H50 x 2, H51 x 2), 4.05 (2H, d, J = 11.3 Hz, H47, H54), 4.07 (2H, d, J = 11.3 Hz, H47, H54); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.9 (Ac x 2), 23.3 (Me61, Me62), 26.2 (C50, C51), 68.9 (C47, C54), 86.4 (C48, C53), 149.6 (C49, C52), 170.8 (Ac x 2); HRMS (ESI), calcd for $C_{14}H_{20}O_5Na$ 291.1203 ($M+Na^+$), found 291.1202.

Diketone 12. To a solution of **11a** (2.23 g, 5.40 mmol) in CH_2Cl_2 (40 mL) and MeOH (10 mL) was bubbled O_3 at -78 °C for 20 min. After the color of solution turned to blue, the excess O_3 was removed with a stream of air for 10 min. Me_2S (600 μl, 8.10 mmol) was added to the resulting mixture at -78 °C, and then allowed to warm to room temperature. After being stirred for 1 h, the mixture was concentrated in vacuo. Purification by column chromatography on silica gel (hexane/EtOAc 50:1-20:1) gave diketone **12** (1.48 g, 3.33 mmol) in 62% yield: colorless oil; IR (film) ν 2954, 2929, 2857, 1724, 1471, 1256, 1112, 838, 777 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS x 2), 0.06 (6H, s, TBS x 2), 0.88 (18H, s, TBS x 2), 1.28 (6H, s, Me61, Me62), 2.45 (2H, m, H50, H51), 3.27 (2H, m, H50, H51), 3.67 (2H, d, *J* = 10.1 Hz, H47, H54), 3.78 (2H, d, *J* = 10.1 Hz, H47, H54); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.6 (TBS x 2), -5.5 (TBS x 2), 18.3 (TBS x 2), 21.3 (Me61, Me62), 25.8 (TBS x 2), 36.8 (C50, C51), 70.6 (C47, C54), 86.8 (C48, C53), 213.3 (C49, C52); HRMS (ESI), calcd for $C_{22}H_{44}O_5Si_2Na$ 467.2619 ($M+Na^+$), found 467.2615.

Hemiacetal 13. To a solution of **12** (430 mg, 967 μmol) in THF (10 mL) was added $LiBHEt_3$ (1.0 M in THF, 4.84 mL, 4.84 mmol) at -78 °C. After being stirred for 30 min at the same temperature, the mixture was quenched with 2N NaOH and 35% aqueous H_2O_2. After being stirred for 1 h at room temperature, the excess H_2O_2 was quenched with aqueous $Na_2S_2O_3$. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 60:1-40:1) gave hemiacetal **13** (390 mg, 875 μmol) in 90% yield: colorless solid; mp 80-81 °C; IR (film) ν 3406, 2954, 2929, 2884, 2857, 1471, 1463, 1255, 1106, 837, 776 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s, TBS), 0.01 (3H, s, TBS), 0.07 (6H, s, TBS x 2), 0.85 (9H, s, TBS), 0.89 (9H, s, TBS), 1.44 (3H, s, Me61), 1.48 (3H, s, Me62), 1.66 (1H, ddd, *J* = 12.9, 12.9, 4.5 Hz, H51), 1.88 (1H, ddd, *J* = 13.5, 9.8, 4.5 Hz, H50), 2.00 (1H, m, H50), 2.28 (1H, ddd, *J* = 12.9, 9.8, 5.7 Hz, H51), 3.26 (1H, d, *J* = 9.4 Hz, H47), 3.34 (1H, d, *J* = 9.6 Hz, H54), 3.38 (1H, d, *J* = 9.4 Hz, H47), 3.57 (1H, d, *J* = 9.6 Hz, H54), 3.87 (1H, s, OH), 4.14 (1H, d, *J* = 7.0 Hz, H49); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.72 (TBS), -5.69 (TBS x 2), -5.64 (TBS), 18.0 (TBS), 18.1 (TBS), 19.9 (Me62), 23.1 (C50), 23.2 (Me61), 25.7 (TBS), 25.8 (TBS), 30.8 (C51), 68.3 (C47), 69.1 (C54), 75.1 (C48), 76.7 (C53), 80.0 (C49), 105.3 (C52); HRMS (ESI), calcd for $C_{22}H_{46}O_5Si_2Na$ 469.2776 ($M+Na^+$), found 469.2779.

Acetate 15. To a mixture of **13** (768 mg, 1.72 mmol), Et_3N (1.2 mL, 8.6 mmol) and DMAP (215 mg, 1.76 mmol) in CH_2Cl_2 (17 mL) was added Ac_2O (500 μL, 5.29 mmol). After being stirred for 17 h at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 50:1-25:1) gave acetate **15** (826 mg, 1.69 mmol) in 98% yield: colorless oil; IR (film) ν 2954, 2930, 2857, 1747, 1721, 1472, 1373, 1234, 1115, 1033, 838, 777 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s, TBS), 0.01 (3H, s, TBS), 0.03 (3H, s, TBS), 0.04 (3H, s, TBS), 0.85 (9H, s, TBS), 0.88 (9H, s, TBS), 1.16 (3H, s, Me61), 1.37 (3H, s, Me62), 1.73 (1H, dddd, *J* = 13.8, 11.7, 8.5, 5.1 Hz, H50), 2.00 (3H, s, Ac), 2.08 (1H, m, H50), 2.29 (1H, ddd, *J* = 11.7, 5.1, 5.1 Hz, H51), 3.07 (1H, ddd, *J* = 11.7, 11.7, 6.1 Hz, H51), 3.43 (1H, d, *J* = 10.0 Hz, H54), 3.45 (1H, d, *J* = 10.0 Hz, H47), 3.50 (1H, d, *J* = 10.0 Hz, H47), 3.60 (1H, d, *J* = 10.0 Hz, H54), 5.02 (1H, dd, *J* = 8.5, 4.0 Hz, H49); ^{13}C-NMR (100 MHz,

$CDCl_3$) δ -5.6 (TBS), -5.5 (TBS), -5.44 (TBS), -5.41 (TBS), 17.9 (Me61), 18.20 (TBS), 18.22 (TBS), 21.19 (Ac), 21.25 (Me62), 24.4 (C50), 25.7 (TBS), 25.8 (TBS), 36.4 (C51), 69.2 (C47), 71.0 (C54), 74.6 (C49), 81.0 (C48), 85.0 (C53), 169.6 (Ac), 214.1 (C52); HRMS (ESI), calcd for $C_{24}H_{48}O_6Si_2Na$ 511.2882 ($M+Na^+$), found 511.2881.

Alcohol 16. To a solution of **15** (728 mg, 1.49 mmol) in THF (15 mL) was added $LiBHEt_3$ (1.0 M in THF, 2.3 mL, 2.3 mmol) at -90 °C. After being stirred for 20 min at the same temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 50:1-20:1) gave alcohol **16** (673 mg, 1.37 mmol) in 92% yield: colorless solid; mp 93-94 °C; IR (film) ν 3499, 2929, 2857, 1745, 1472, 1363, 1250, 1105, 837, 776 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 0.02 (3H, s TBS), 0.03 (3H, s, TBS), 0.08 (6H, s, TBS x 2), 0.88 (9H, s, TBS), 0.89 (9H, s, TBS), 1.17 (3H, s, Me61), 1.46 (3H, s, Me62), 1.61-1.81 (3H, m, H50, H51 x 2), 1.86 (1H, m, H50), 2.10 (3H, s, Ac), 3.17 (1H, d, J = 9.7 Hz, H47), 3.30 (1H, d, J = 9.7 Hz, H47), 3.40 (1H, d, J = 9.4 Hz, H54), 3.57 (1H, d, J = 9.4 Hz, H54), 3.65 (1H, dd, J = 10.5, 3.8 Hz, H52), 4.06 (1H, brs, OH), 5.29 (1H, d, J = 5.9 Hz, H49); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.7 (TBS), -5.5 (TBS), 15.4 (Me62), 18.0 (TBS), 18.1 (TBS), 21.1 (Ac), 21.5 (Me61), 23.2 (C50), 25.7 (TBS), 25.8 (TBS), 26.4 (C51), 69.0 (C47), 73.8 (C49), 74.7 (C54), 78.0 (C53), 78.8 (C52), 80.8 (C48), 169.7 (Ac); HRMS (ESI), calcd for $C_{24}H_{50}O_6Si_2Na$ 513.3038 ($M+Na^+$), found 513.3036.

***Meso*-M-ring 17.** To a mixture of **16** (124 mg, 253 μmol), Et_3N (250 μL, 1.79 mmol) and DMAP (60 mg, 491 μmol) in CH_2Cl_2 (3.0 mL) was added Ac_2O (125 μL, 1.32 mmol). After being stirred for 16 h at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 30:1-20:1) gave *meso*-M-ring **17** (127 mg, 238 μmol) in 94% yield: colorless oil; IR (film) ν 2930, 2857, 1746, 1366, 1237, 1110, 1037, 837, 776 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 0.01 (6H, s, TBS x 2), 0.02 (6H, s, TBS x 2), 0.87 (18H, s, TBS x 2), 1.27 (6H, s, Me61, Me62), 1.70-1.89 (4H, m, H50 x 2, H51 x 2), 2.05 (6H, s, Ac x 2), 3.30 (2H, d, J = 10.0 Hz, H47, H54), 3.33 (2H, d, J = 10.0 Hz, H47, H54), 5.04 (2H, d, J = 7.6 Hz, H49, H52); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.5 (TBS x 2), 18.2 (Me61, Me62), 18.3 (TBS x 2), 21.2 (Ac x 2), 23.2 (C50, C51), 25.8 (TBS x 2), 69.7 (C47, C54), 74.4 (C49, C52), 80.2 (C48, C53), 169.6 (Ac x 2); HRMS (ESI), calcd for $C_{26}H_{52}O_7Si_2Na$ 555.3144 ($M+Na^+$), found 555.3148.

Mono-acetate (-)-18. To a solution of **11b** (75.4 mg, 281 μmol) in MeCN (500 μL) and 0.1 M phosphate buffer (pH 8.0, 4.5 mL) was added lipoprotein lipase (TOYOBO Co., Ltd., 12.0 mg), then warmed to 45 °C. After being stirred for 16 h, the mixture was extracted with EtOAc and the organic layer was washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 10:1-0:1) gave mono-acetate **(-)-18** (45.7 mg, 202 μmol, 85% ee) in 72% yield, diol **19** (2.6 mg, 14.1 μmol) in 5% yield, and starting material **11b** in 16%. Enantiomeric excess of **(-)-18** was determined by ^{1}H-NMR analysis of the corresponding MTPA ester. **(-)-18**: colorless oil; $[\alpha]_D^{21}$ -61.3 (*c* 0.85 $CHCl_3$, 85% ee); IR (film) ν 3484, 2971, 2929, 1744, 1370, 1235, 1042, 901 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, s, Me61), 1.33 (3H, s, Me62), 2.07 (3H, s, Ac), 2.59-2.71 (4H, m, H50 x 2, H51 x 2), 3.08 (1H, dd, *J* = 9.5, 2.4 Hz, OH), 3.50 (1H, dd, *J* = 11.5, 9.5 Hz, H47), 3.58 (1H, dd, *J* = 11.5, 2.4 Hz, H47), 3.85 (1H, d, *J* = 11.5 Hz, H54), 4.47 (1H, d, *J* = 11.5 Hz, H54); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.8 (Ac), 23.1 (Me61), 23.8 (Me62), 25.9 (C50 or C51), 26.1 (C50 or C51), 67.3 (C47), 68.2 (C54), 86.2 (C53), 89.4 (C48), 148.9 (C52), 150.7 (C49), 170.6 (Ac); HRMS (ESI), calcd for $C_{12}H_{18}O_4Na$ 249.1097 (M+Na$^+$), found 249.1096.

TBS ether (+)-20. To a solution of **(-)-18** (27.1 mg, 120 μmol) in DMF (2.5 mL) were added imidazole (30 mg, 440 μmol) and TBSCl (38 mg, 250 μmol). After being stirred for 80 min at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 50:1) gave TBS ether **(+)-20** (40.1 mg, 118 μmol) in 98% yield: colorless oil; $[\alpha]_D^{21}$ 3.5 (*c* 1.04 $CHCl_3$, 85% ee); IR (film) ν 2929, 2857, 1746, 1368, 1249, 1098, 1040, 907, 837, 776 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.015 (3H, s, TBS), 0.020 (3H, s, TBS), 0.87 (9H, s, TBS), 1.29 (3H, s, Me61), 1.32 (3H, s, Me62), 2.06 (3H, s, Ac), 2.54-2.64 (4H, m, H50 x 2, H51 x 2), 3.51 (1H, d, *J* = 9.6 Hz, H47), 3.53 (1H, d, *J* = 9.6 Hz, H47), 4.05 (2H, s, H54 x 2); ^{13}C-NMR (100 MHz, $CDCl_3$)□ δ -5.6 (TBS), -5.5 (TBS), 18.2 (TBS), 20.9 (Ac), 23.2 (Me61), 23.3 (Me62), 25.8 (TBS), 26.2 (C50 or C51), 26.4 (C50 or C51), 69.4 (C47), 69.5 (C54), 85.9 (C53), 88.6 (C48), 147.9 (C52), 151.7 (C49), 170.8 (Ac); HRMS (ESI), calcd for $C_{18}H_{32}O_4SiNa$ 363.1962 (M+Na$^+$), found 363.1962.

Diketone (+)-21. To a solution of **(+)-20** (40.1 mg, 118 μmol) in CH_2Cl_2 (4.0 mL) and MeOH (1.0 mL) was bubbled O_3 at -78 °C for 20 min. After the color of solution turned to blue, the excess O_3 was removed with a stream of air for 10 min. Me_2S (26 μL, 350 μmol) was added to the resulting mixture at -78 °C, and then allowed to warm to room temperature. After being stirred for 3 h, the mixture was concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 30:1-5:1) gave diketone **(+)-21** (32.8 mg, 88.0 μmol) in 75% yield: colorless oil; $[\alpha]_D^{21}$ 1.6 (*c* 1.00 $CHCl_3$, 85% ee); IR (film) ν 2930, 2857, 1747, 1742, 1471, 1374, 1235, 1182, 1114, 1047, 839, 781 cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, TBS), 0.05 (3H, s, TBS), 0.86 (9H, s, TBS), 1.26 (3H, s, Me61), 1.37 (3H, s, Me62), 2.06 (3H, s, Ac), 2.51 (1H, ddd, J = 14.9, 6.0, 5.8 Hz, H51), 2.72 (1H, ddd, J = 14.9, 10.5, 5.8 Hz, H50), 2.96 (1H, ddd, J = 14.9, 6.8, 6.0 Hz, H50), 3.30 (1H, ddd, J = 14.9, 10.5, 6.8 Hz, H51), 3.69 (1H, d, J = 10.4 Hz, H47), 3.80 (1H, d, J = 10.4 Hz, H47), 4.24 (1H, d, J = 11.3 Hz, H54), 4.29 (1H, d, J = 11.3 Hz, H54); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.7 (TBS), -5.6 (TBS), 18.3 (TBS), 20.8 (Ac), 21.98 (Me61), 22.04 (Me62), 25.8 (TBS), 35.9 (C51), 36.7 (C50), 69.2 (C54), 70.3 (C47), 84.6 (C53), 87.3 (C48), 170.4 (Ac), 211.5 (C52), 212.8 (C49); HRMS (ESI), calcd for $C_{18}H_{32}O_6SiNa$ 395.1860 ($M+Na^+$), found 395.1863.

Triol (-)-22. To a solution of **(+)-21** (16.0 mg, 42.9 μmol) in THF (1.5 mL) were added 12-crown-4 (70 μL, 430 μmol) and $LiBHEt_3$ (1.0 M in THF, 440 μL, 440 μmol) at -78 °C. The reaction mixture was allowed to warm to room temperature over 16 h. The mixture was quenched with 2N NaOH and aqueous H_2O_2 at 0 °C. After being stirred for 1 h at room temperature, the excess H_2O_2 was quenched with aqueous $Na_2S_2O_3$. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/EtOAc 4:1-1:1) gave triol **(-)-22** (11.4 mg, 34.1 μmol) in 80% yield: colorless solid; mp 78-79 °C; $[\alpha]_D^{23}$ -8.8 (c 0.93 $CHCl_3$, 85% ee); IR (film) ν 3411, 2929, 2858, 1471, 1254, 1103, 1055, 837, 778 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.08 (6H, s, TBS), 0.90 (9H, s, TBS), 1.33 (6H, s, Me61, Me62), 1.63-1.75 (2H, m, H50, H51), 1.84 (1H, brs, OH49), 1.89-2.01 (2H, m, H50, H51), 2.60 (1H, brdd, J = 6.3, 5.3 Hz, OH54), 2.67 (1H, brs, OH52), 3.36 (1H, dd, J = 11.2, 6.3 Hz, H54), 3.48 (2H, s, H47 x 2), 3.51 (1H, dd, J = 11.2, 5.3 Hz, H54), 3.75 (1H, brd, J = 8.0 Hz, H52), 3.88 (1H, brd, J = 8.4 Hz, H49); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.60 (TBS), -5.58 (TBS), 18.2 (TBS), 18.6 (Me62), 19.5 (Me61), 25.8 (TBS), 26.3 (C50), 26.8 (C51), 70.2 (C54), 71.1 (C47), 73.0 (C52), 73.7 (C49), 80.7 (C48), 81.4 (C53); HRMS (ESI), calcd for $C_{16}H_{34}O_5SiNa$ 357.2068 ($M+Na^+$), found 357.2069.

X-Ray crystallographic analysis of (-)-22[17]

Single crystals of triol **(-)-22** suitable for X-ray crystallographic analysis was obtained by recrystallization from diethyl ether / hexane at room temperature. The single crystal coated by apiezon grease was mounted on the grass fiber and transferred to the cold gas stream of the diffractometer. X-ray data were collected on Bruker AXS APEXII diffractometer with graphite monochromated Mo-$K\alpha$ radiation (λ 0.71073 Å). The data were corrected for Lorentz and polarization effects. An empirical absorption correction based on the multiple measurement of equivalent reflections was applied using the program SADABS.[18] The structures were solved by direct methods and refined by full-matrix least squares against F^2 using all data (SHEXL-97).[19] The absolute structure was deduced based on Flack parameter, 0.01(13).[16]

Crystal data (100 K): $C_{16}H_{34}O_5Si$; Fw 334.52; monoclinic; space group $P2_1$, a = 7.4994(16) Å, b = 12.153(3) Å, c = 10.466(2) Å, β = 97.057(3)°, V = 946,7(4) Å^3, Z = 2, D_{calcd} = 1.174 Mg/m^3, R = 0.0364 ($I>2\sigma(I)$), $wR2$ = 0.0785 (all data), GOF = 1.044.

ACKNOWLEDGEMENTS

This work was supported financially by a Grant-in-Aid for Specially Promoted Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in Japan. We are grateful to Prof. T. Iwamoto and Prof. S. Ishida at Graduate School of Science, Tohoku University for their assistance of X-ray crystallographic analysis and helpful discussions.

REFERENCES AND NOTES

1. P. J. Scheuer, *Tetrahedron*, 1994, **50**, 3; R. J. Lewis, *Toxicon*, 2001, **39**, 97; T. Yasumoto and M. Murata, *Chem. Rev.*, 1993, **93**, 1897; T. Yasumoto, *Chem. Rec.*, 2001, **1**, 228.
2. M. Murata, A.-M. Legrand, Y. Ishibashi, M. Fukui, and T. Yasumoto, *J. Am. Chem. Soc.*, 1990, **112**, 4380; M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hirama, N. Harada, and T. Yasumoto, *J. Am. Chem. Soc.*, 1997, **119**, 11325; M. Satake, M. Murata, and T. Yasumoto, *Tetrahedron Lett.*, 1993, **34**, 1975; M. Satake, M. Fukui, A.-M. Legrand, P. Cruchet, and T. Yasumoto, *Tetrahedron Lett.*, 1998, **39**, 1197.
3. T. Yasumoto, T. Igarashi, A.-M. Legrand, P. Cruchet, M. Chinain, T. Fujita, and H. Naoki, *J. Am. Chem. Soc.*, 2000, **122**, 4988.
4. R. J. Lewis, J.-P. Vernoux, and I. M. Brereton, *J. Am. Chem. Soc.*, 1998, **120**, 5914.
5. M. Hirama, T. Oishi, H. Uehara, M. Inoue, M. Maruyama, H. Oguri, and M. Satake, *Science*, 2001, **294**, 1904; M. Inoue, H. Uehara, M. Maruyama, and M. Hirama, *Org. Lett.*, 2002, **4**, 4551; M. Inoue, K. Miyazaki, H. Uehara, M. Maruyama, and M. Hirama, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 12013; M. Inoue and M. Hirama, *Acc. Chem. Res.*, 2004, **37**, 961; M. Hirama, *Chem. Rec.*, 2005, **5**, 240; M. Inoue, K. Miyazaki, Y. Ishihara, A. Tatami, Y. Ohnuma, Y. Kawada, K. Komano, S. Yamashita, N. Lee, and M. Hirama, *J. Am. Chem. Soc.*, 2006, **128**, 9352; M. Inoue, S. Yamashita, Y. Ishihara, and M. Hirama, *Org. Lett.*, 2006, **8**, 5805.
6. For recent total synthesis and synthetic studies from other groups, see: A. Hamajima and M. Isobe, *Angew. Chem., Int. Ed.*, 2009, **48**, 2941; H. Fuwa, S. Fujikawa, K. Tachibana, H. Takakura, and M. Sasaki, *Tetrahedron Lett.*, 2004, **45**, 4795; K. Fujiwara, A. Goto, D. Sato, Y. Ohtaniuchi, H. Tanaka, A. Murai, H. Kawai, and T. Suzuki, *Tetrahedron Lett.*, 2004, **45**, 7011; D. Domon, K. Fujiwara, A. Murai, H. Kawai, and T. Suzuki, *Tetrahedron Lett.*, 2005, **46**, 8285; A. Takizawa, K. Fujiwara, E.

Doi, A. Murai, H. Kawai, and T. Suzuki, *Tetrahedron*, 2006, **62**, 7408; A. Hamajima and M. Isobe, *Org. Lett.*, 2006, **8**, 1205; A. Nonoyama, A. Hamajima, and M. Isobe, *Tetrahedron*, 2007, **63**, 5886; J. S. Clark, J. Conroy, and A. J. Blake, *Org. Lett.*, 2007, **9**, 2091; A. Goto, K. Fujiwara, A. Kawai, H. Kawai, and T. Suzuki, *Org. Lett.*, 2007, **9**, 5373; I. Kadota, T. Abe, M. Uni, H. Takamura, and Y. Yamamoto, *Tetrahedron Lett.*, 2008, **49**, 3643; I. Kadota, T. Abe, M. Uni, H. Takamura, and Y. Yamamoto, *Tetrahedron*, 2009, **65**, 7784.

7. H. Oguri, M. Hirama, T. Tsumuraya, I. Fujii, M. Maruyama, H. Uehara, and Y. Nagumo, *J. Am. Chem. Soc.*, 2003, **125**, 7608; T. Tsumuraya, I, Fujii, M. Inoue, A. Tatami, K. Miyazaki, and M. Hirama, *Toxicon*, 2006, **48**, 287.
8. M. Inoue, F. Saito, M. Iwatsu, Y. Ishihara, and M. Hirama, *Tetrahedron Lett.*, 2007, **48**, 2171.
9. K. Yoshikawa, M. Inoue, and M. Hirama, *Tetrahedron Lett.*, 2007, **48**, 2177.
10. For synthesis of the structurally similar O-ring of gymnocin-B, see: C. Tsukano and M. Sasaki, *Tetrahedron Lett.*, 2005, **46**, 4617.
11. O. Diels and K. Alder, *Ber. Deutsch. Chem. Ges. B.*, 1929, **62B**, 554; D. J. Brickwood, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1398; T. Imagawa, K. Matsuura, N. Murai, T. Akiyama, and M. Kawanisi, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3020; M. E. Jung and G-Y. J. Im, *J. Org. Chem.*, 2009, **74**, 8739.
12. Bis-mesylate **7** underwent exothermic decomposition in high concentration.
13. T. Oishi, M. Shoji, K. Maeda, N. Kumahara, and M. Hirama, *Synlett*, 1996, 1165; T. Oishi, M. Maruyama, M. Shoji, K. Maeda, N. Kumahara, S. Tanaka, and M. Hirama, *Tetrahedron*, 1999, **55**, 7471.
14. Enantiomeric excess of **18** was determined by ^{1}H-NMR analyses of the diastereomer ratio of the corresponding (*R*)- or (*S*)-MTPA esters.
15. Addition of 12-crown-4 was essential for the reduction of the diketone. In contrast, in the case of the reduction of **12** (vide supra), the addition of crown ether gave no effects.
16. H. D. Flack, *Acta Cryst.*, 1983, **A39**, 876; for a recent example of the absolute structure determination using X-ray crystallographic analysis, see: E. Canales and E. J. Corey, *Org. Lett.*, 2008, **10**, 3271.
17. CCDC 779930 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
18. G. M. Sheldrick, SADABS, Empirical Absorption Correction Program; Göttingen, Germany, 1996.
19. G. M. Sheldrick, SHELX-97, Empirical Absorption Correction Program; Göttingen, Germany, 1997.