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Convergent synthesis of the A–E ring segment of ciguatoxin CTX3C

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ABSTRACT

A convergent synthesis of the A–E ring segment of ciguatoxin CTX3C was achieved via the intramolecular allylation of an α-chloroacetoxy ether and subsequent ring-closing metathesis.

1. Introduction

Ciguatoxin CTX3C (**1**),[1] one of the causative toxin of 'ciguatera' seafood poisoning,[2] was isolated from cultured dinoflagellate *Gambierdiscus toxicus* (Fig. 1). The potent neurotoxicity and novel polycyclic ether framework including five- to nine-membered rings have attracted the attention of synthetic chemists.[3] In 2001, the first total synthesis of **1** was achieved by Hirama and co-workers.[4] In this paper, we describe a convergent synthesis of the A–E ring segment of ciguatoxin CTX3C (**1**).[5]

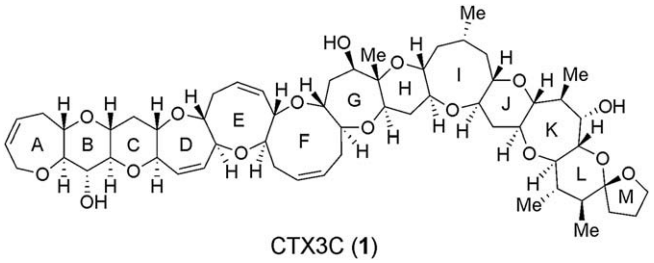
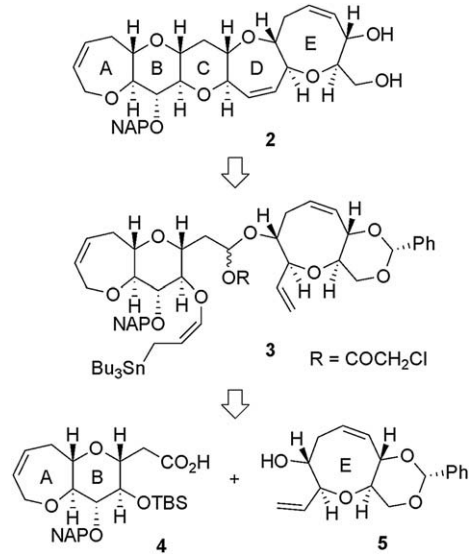


Figure 1. Structure of ciguatoxin CTX3C (**1**).

2. Results and discussion

Scheme 1 outlines our synthetic strategy. The A–E ring segment **2** would be synthesized from **3** via the intramolecular allylation followed by ring-closing metathesis.[6] The cyclization precursor **3** is retrosynthetically broken down into two segments, the AB ring **4** and the E ring **5**.



Scheme 1.

Synthesis of the carboxylic acid **4** is shown in Scheme 2. Treatment of the known triol **6**[5b] with $PhCH(OMe)_2$/*p*-TsOH gave **7** in 74% yield. Protection of the remaining secondary alcohol with NAPBr/NaH followed by deprotection of the benzylidene acetal afforded **8**

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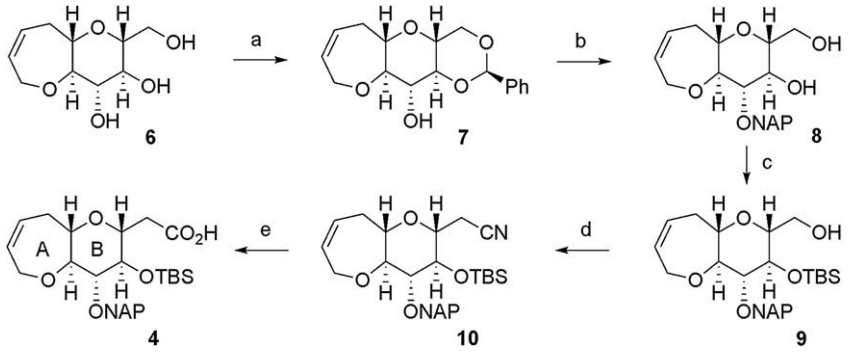
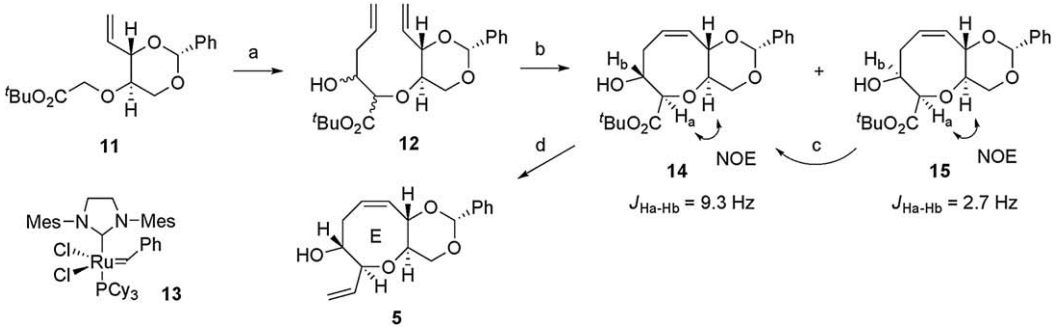


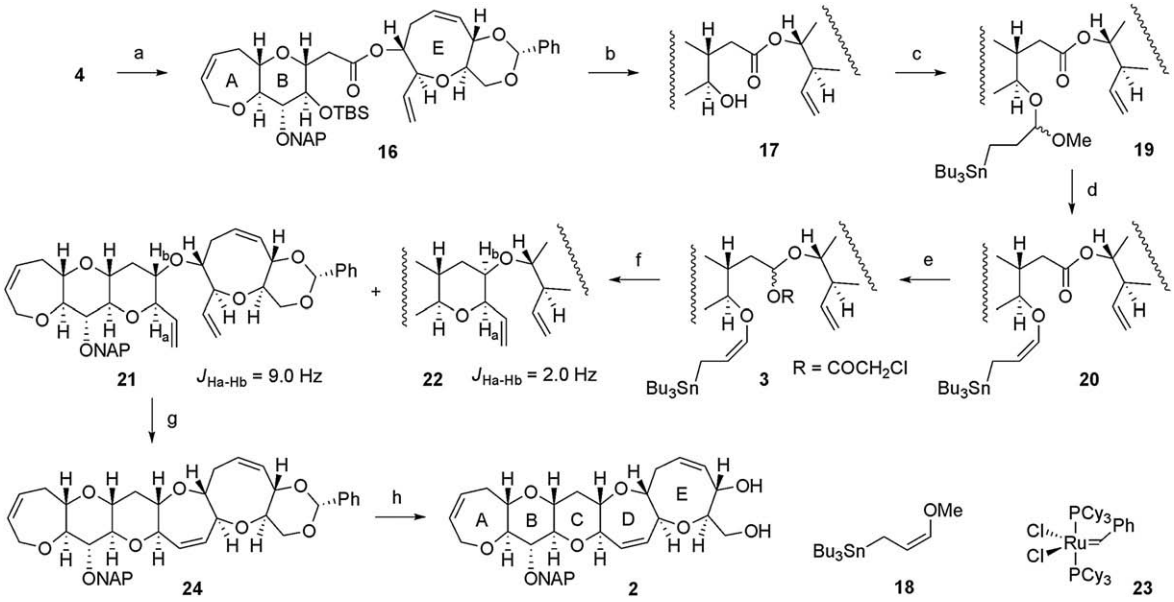
Scheme 2. Reagents and conditions: (a) $PhCH(OMe)_2$, *p*-TsOH·H_2O, DMF, rt, 74%; (b) (i) NAPBr, NaH, TBAI, THF, 40 °C, (ii) CSA, MeOH, reflux, 95% (two steps); (c) (i) TBSCl, imidazole, DMF, 70 °C, (ii) CSA, MeOH, 0 °C, 90% (two steps); (d) (i) I_2, PPh_3, imidazole, benzene/Et_2O, 40 °C, (ii) NaCN, DMSO, 70 °C, 94% (two steps); (e) (i) DIBAL-H, CH_2Cl_2, −78 °C, (ii) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, *t*-BuOH/H_2O, 0 °C.

in 95% overall yield. Conversion of the diol **8** to the corresponding bis-TBS ether followed by selective deprotection of the primary TBS group furnished **9** in 90% overall yield. Treatment of the alcohol **9** with I_2/PPh_3/imidazole followed by NaCN provided the nitrile **10** in 94% overall yield. Reduction of **10** with DIBAL-H, and subsequent oxidation of the resulting aldehyde with $NaClO_2$ furnished the carboxylic acid **4** in quantitative yield.

Preparation of the E ring segment **5** was carried out primarily based on a Hirama's procedure (Scheme 3).[5b] Thus, treatment of **11**, prepared from D-glucose, with NaHMDS followed by 3-butenal gave **12** as an inseparable mixture of diastereoisomers in 95% yield. Ring-closing metathesis of **12** was carried out using the second generation Grubbs catalyst **13**[7] to afford a 1:1 mixture of **14** and **15** in 68% yield.[8] These stereoisomers were easily separated by



Scheme 3. Reagents and conditions: (a) NaHMDS, THF, −78 °C, then 3-butenal, 95%; (b) **13**, CH_2Cl_2, 30 °C, 68% (**14**/**15**=1:1); (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 95%, (ii) L-Selectride, THF, −78 °C, 88% (**14**/**15**=2:1); (d) (i) TBSCl, imidazole, DMF, 30 °C, 77%; (ii) DIBAL-H, CH_2Cl_2, −78 °C; (iii) $Ph_3PCH_3^+Br^-$, NaHMDS, THF, 0 °C to rt; (iv) TBAF, THF, rt, 91% (three steps).



Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then **5**, DMAP, toluene, 64% from **10**; (b) TBAF, THF, 40 °C, 82%; (c) **18**, CSA, CH_2Cl_2, rt, 87%; (d) TMSI, HMDS, CH_2Cl_2, 0 °C, 85%; (e) DIBAL-H, −78 °C, CH_2Cl_2, then $(CH_2ClCO)_2O$, DMAP, pyridine, −78 to −20 °C; (f) BF_3·OEt, 4 Å MS, CH_3CN/CH_2Cl_2 (10:1), −40 °C, 60% (two steps), **21**/**22**=4:1); (g) **23**, benzene, 70 °C, 74%; (h) CSA, CH_2Cl_2/MeOH (1:2), 40 °C, 92%.

chromatography, and the stereochemistries were confirmed by ^{1}H NMR analysis and NOE experiments as shown in Scheme 3. The undesired stereoisomer **15** was subjected to Swern oxidation followed by L-Selectride reduction to give a 2:1 mixture of **14** and **15** in 88% overall yield.[9] Protection of **14** with TBSCl/imidazole, DIBAL-H reduction of the ester, Wittig reaction of the resulting aldehyde, and removal of the TBS group with TBAF furnished the E ring segment **5**.

Scheme 4 describes the key segment coupling. Thus, esterification of the carboxylic acid **4** and the alcohol **5** under Yamaguchi conditions gave the ester **16** in 64% overall yield.[10] Removal of the TBS protective group with TBAF afforded **17** in 82% yield. Acetalization of **17** with γ-methoxyallylstannane **18** in the presence of CSA provided the acetal **19** as a mixture of diastereoisomers in 87% yield. Treatment of **19** with TMSI/HMDS gave allylic stannane **20** in 85% yield.[11] Modified Rychnovsky acetylation of the ester **20** provided the α-chloroacetoxy ether **3**.[12,13] Intramolecular allylation of **3** was carried out with $BF_3\cdot OEt_2$ to give a 4:1 mixture of the desired product **21** and its stereoisomer **22** in 60% overall yield. The trans relationship between Ha and Hb of **21** was confirmed by the large coupling constant, J_{Ha-Hb}=9.0 Hz. The small J value, J_{Ha-Hb}=2.0 Hz, for **22** clearly indicates the cis relationship of these protons. Ring-closing metathesis of **21** with the Grubbs' catalyst **23** furnished the pentacyclic ether **24** in 74% yield.[14] Treatment of **24** with catalytic CSA in MeOH provided the diol **2** in 92% yield. The spectroscopic data of **2** obtained are identical with those reported previously.[5d]

3. Conclusions

We have achieved a convergent synthesis of the A–E ring segment of ciguatoxin CTX3C via the intramolecular allylation of an α-chloroacetoxy ether and ring-closing metathesis. Further studies toward the total synthesis of ciguatoxin CTX3C are in progress in our laboratories.

4. Experimental section

4.1. General

Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. All other solvents were used as purchased. Reactions requiring anhydrous conditions were performed under an argon atmosphere. The NMR spectra were recorded on JEOL JNM-AL400 (^{1}H, ^{13}C NMR). Chemical shifts were reported in delta units (δ) relative to chloroform (7.24), benzene (7.15). IR spectra were recorded on a JASCO FT/IR-460 plus. Optical rotations were measured by a JASCO DIP-1000. Mass spectra were measured by Micromass LCT (ESI TOF-MS). Thin layer chromatography (TLC) was performed on Merck silica gel 60F-254 plates. Column chromatography was performed with Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral) or Fuji Silysia silica gel BW-300 (200–400 mesh).

4.2. Benzylidene acetal 7

To a mixture of triol **6** (44.4 mg, 0.210 mmol) and $PhCH(OMe)_2$ (66.0 μL, 0.44 mmol) in DMF (1.0 mL) was added p-$TsOH\cdot H_2O$ (5.0 mg, 26.0 μmol) at room temperature. After the mixture was stirred for 23 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 4:1, 1:2) gave benzylidene acetal **7** (45.1 mg, 74%): colorless needle; mp 176 °C (hexane/EtOAc); R_f=0.46 (hexane/EtOAc, 1:1); $[\alpha]_D^{22}$ −7.9 (c 0.25, $CHCl_3$); IR (neat) 3464, 3030, 2979 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.24 (m, 5H), 5.94–5.88 (m, 1H), 5.84–5.78 (m, 1H), 5.54 (s, 1H), 4.34 (dd, J=15.0, 5.9 Hz, 1H), 4.30 (dd, J=9.5, 4.8 Hz, 1H), 4.04 (dq, J=15.0, 2.7 Hz, 1H), 3.84 (t, J=9.5 Hz, 1H), 3.68 (t, J=9.5 Hz, 1H), 3.56 (t, J=9.5 Hz, 1H), 3.46 (td, J=9.5, 4.8 Hz, 1H), 3.35 (td, J=9.5, 3.6 Hz, 1H), 3.29 (t, J=9.5 Hz, 1H), 2.72 (br s, 1H), 2.63 (ddd, J=15.9, 8.0, 3.6 Hz, 1H), 2.41–2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 129.1, 128.2, 127.2, 126.3, 101.8, 87.7, 80.8, 76.4, 73.7, 69.9, 68.9, 68.5, 34.4; HRMS (ESI TOF) calcd for $C_{17}H_{20}O_5Na$ $(M+Na)^+$ 327.1208, found 327.1208.

4.3. Diol 8

To a suspension of NaH (500 mg, 12.5 mmol, washed with hexane) in THF (32.0 mL) were added alcohol **7** (1.72 g, 5.66 mmol) in THF (15.0+5.0+5.0 mL), NAPBr (1.88 g, 8.49 mmol), and TBAI (1.05 g, 2.83 mmol) at 0 °C. After the mixture was stirred for 3 h at 40 °C, the reaction was quenched with MeOH. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration gave crude naphthylmethyl ether, which was used for the next step without further purification.

To a solution of naphthylmethyl ether obtained above in MeOH (57.0 mL) was added CSA (262 mg, 1.13 mmol) at room temperature. After the mixture was stirred for 2 h at reflux, the reaction was quenched with Et_3N. Concentration and column chromatography (hexane/EtOAc, 4:1, 2:1, 1:2) gave diol **8** (1.91 g, 95% in two steps): yellow oil; R_f=0.20 (hexane/EtOAc, 2:1); $[\alpha]_D^{27}$ −28.3 (c 0.21, $CHCl_3$); IR (neat) 3434, 3025, 2884, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.79 (m, 4H), 7.48–7.43 (m, 3H), 5.92–5.87 (m, 1H), 5.82–5.76 (m, 1H), 5.14 (d, J=12.0 Hz, 1H), 4.87 (d, J=12.0 Hz, 1H), 4.28 (dd, J=15.2, 6.0 Hz, 1H), 4.00 (dd, J=15.2, 2.6 Hz, 1H), 3.85–3.82 (m, 1H), 3.69–3.66 (m, 1H), 3.56–3.47 (m, 2H), 3.40 (t, J=8.7 Hz, 1H), 3.35–3.27 (m, 2H), 2.64 (ddd, J=16.2, 8.0, 4.0 Hz, 1H), 2.40–2.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 133.3, 132.9, 131.5, 128.4, 127.8, 127.7, 127.1, 126.5, 126.1, 125.9, 125.7, 87.8, 84.8, 78.3, 76.0, 75.2, 70.5, 67.9, 63.0, 34.6; HRMS (ESI TOF) calcd for $C_{21}H_{24}O_5Na$ $(M+Na)^+$ 379.1521, found 379.1520.

4.4. Alcohol 9

To a solution of diol **8** (330 mg, 0.930 mmol) in DMF (4.7 mL) were added imidazole (412 mg, 6.05 mmol) and TBSCl (560 mg, 3.72 mmol) at room temperature. After the mixture was stirred for 5 h at 70 °C, the reaction was quenched with MeOH. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 30:1, 10:1) gave crude bis-TBS ether, which was used for the next step without further purification.

To a solution of bis-TBS ether obtained above in MeOH (9.3 mL) was added CSA (21.6 mg, 0.09 mmol) at 0 °C. After the mixture was stirred for 2 h at 0 °C, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 10:1, 4:1) gave alcohol **9** (396 mg, 90% in two steps): colorless oil; R_f=0.30 (hexane/EtOAc, 4:1); $[\alpha]_D^{27}$ +0.10 (c 0.22, $CHCl_3$); IR (neat) 3470, 3024, 2856, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 4H), 7.50–7.41 (m, 3H), 5.84–5.73 (m, 2H), 5.08 (d, J=11.7 Hz, 1H), 4.89 (d, J=11.7 Hz, 1H), 4.12 (dd, J=15.2, 5.7 Hz, 1H), 3.87–3.82 (m, 2H), 3.64–3.55 (m, 2H), 3.47 (t, J=8.4 Hz, 1H), 3.37 (t, J=8.7 Hz, 1H), 3.33–3.27 (m, 2H), 2.64 (ddd, J=16.4, 7.9, 4.0 Hz, 1H), 2.34–2.28 (m, 1H), 1.90 (t, J=6.3 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 133.1, 132.7, 131.4, 127.8, 127.6, 127.6, 126.8, 125.8, 125.7, 125.5, 88.5, 85.6, 79.8, 75.8, 75.2, 70.9, 67.9, 62.5, 34.7, 26.0, 18.2, −3.7, −4.8; HRMS (ESI TOF) calcd for $C_{27}H_{38}O_5SiNa$ $(M+Na)^+$ 493.2386, found 493.2382.

4.5. Nitrile 10

To a solution of alcohol **9** (313 mg, 0.670 mmol) in benzene (3.4 mL) and Et_2O (3.4 mL) were added imidazole (246 mg, 3.62 mmol), PPh_3 (703 mg, 2.68 mmol), and I_2 (510 mg, 2.01 mmol) at room temperature. After the mixture was stirred for 1 h at 40 °C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration gave crude iodide, which was used for the next step without further purification.

To a solution of iodide obtained above in DMSO (6.7 mL) was added NaCN (49.5 mg, 1.01 mmol) at room temperature. The mixture was stirred for 1 h at 70 °C. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 20:1, 4:1) gave nitrile **10** (300 mg, 94% in two steps): colorless oil; R_f=0.34 (hexane/EtOAc, 7:1); $[\alpha]_D^{28}$ +23.4 (*c* 0.22, $CHCl_3$); IR (neat) 3025, 2929, 2252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.77 (m, 4H), 7.50–7.42 (m, 3H), 5.83–5.71 (m, 2H), 5.12 (d, *J*=12.0 Hz, 1H), 4.87 (d, *J*=12.0 Hz, 1H), 4.08 (d, *J*=15.4 Hz, 1H), 3.81 (dd, *J*=15.2, 2.6 Hz, 1H), 3.54–3.40 (m, 4H), 3.29 (dt, *J*=13.7, 4.7 Hz, 1H), 2.78 (dd, *J*=16.6, 3.4 Hz, 1H), 2.67 (ddd, *J*=16.3, 7.4, 4.0 Hz, 1H), 2.56 (dd, *J*=16.6, 6.3 Hz, 1H), 2.37–2.30 (m, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 133.2, 132.7, 131.1, 127.8, 127.7, 127.6, 126.7, 125.9, 125.5, 125.5, 125.4, 117.1, 88.2, 85.0, 76.1, 75.2, 75.0, 73.4, 67.9, 34.4, 26.0, 21.7, 18.2, −3.6, −4.6; HRMS (ESI TOF) calcd for $C_{28}H_{37}NO_4SiNa$ $(M+Na)^+$ 502.2390, found 502.2363.

4.6. Alcohol 12

To a solution of ester **11** (500 mg, 1.56 mmol) in THF (7.8 mL) was added NaHMDS (1.0 M in THF, 2.34 ml, 2.34 mmol) at −78 °C. After the mixture was stirred for 15 min at −78 °C, to the resulting mixture was added 3-butenal (6.24 mmol) at the same temperature. After the mixture was stirred for 20 min at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl/MeOH. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 10:1, 7:1, 5:1) gave alcohol **12** (384 mg, 95%) as a diastereomeric mixture.

4.7. Alkene 14

To a solution of alcohol **12** (200 mg, 0.510 mmol) in CH_2Cl_2 (10.2 mL) was added **13** (21.6 mg, 25.5 μmol) at room temperature. The mixture was stirred for 4 h at 30 °C. Short column chromatography (hexane/EtOAc, 2:1) and concentration gave a mixture of crude products. Purification by column chromatography (hexane/EtOAc, 7:1, 4:1, 3:1) gave the desired alkene **14** (65.4 mg, 35%) and its diastereomer alkene **15** (61.6 mg, 33%).

*4.7.1. Compound **14**.* Colorless oil; R_f=0.58 (hexane/EtOAc, 2:1); $[\alpha]_D^{22}$ −51.2 (*c* 0.40, $CHCl_3$); IR (neat) 3502, 3035, 2976, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.34 (m, 5H), 5.92–5.83 (m, 2H), 5.48 (s, 1H), 4.46 (dd, *J*=9.9, 3.2 Hz, 1H), 4.34 (dd, *J*=9.9, 5.2 Hz, 1H), 4.16–4.13 (m, 1H), 3.86 (d, *J*=9.3 Hz, 1H), 3.67 (t, *J*=9.9 Hz, 1H), 3.53 (td, *J*=9.9, 5.2 Hz, 1H), 3.05 (brs, 1H), 2.69–2.65 (m, 1H), 2.45–2.40 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 137.3, 133.3, 129.0, 128.2, 126.7, 126.0, 100.9, 82.8, 80.8, 79.4, 76.5, 72.3, 69.2, 31.6, 28.1; HRMS (ESI TOF) calcd for $C_{20}H_{26}O_6Na$ $(M+Na)^+$ 385.1627, found 385.1665.

*4.7.2. Compound **15**.* Colorless oil; R_f=0.31 (hexane/EtOAc, 2:1); $[\alpha]_D^{22}$ +7.0 (*c* 0.40, $CHCl_3$); IR (neat) 3475, 3033, 2977, 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.33 (m, 5H), 5.83–5.70 (m, 2H), 5.49 (s, 1H), 4.57 (dd, *J*=10.1, 4.8 Hz, 1H), 4.42 (dd, *J*=10.1, 5.3 Hz, 1H), 4.25–4.21 (m, 1H), 4.20 (d, *J*=2.4 Hz, 1H), 3.80 (t, *J*=10.1 Hz, 1H), 3.42 (td, *J*=10.1, 5.3 Hz, 1H), 2.55–2.43 (m, 2H), 2.28 (brd, *J*=7.3 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 137.6, 134.2, 129.2, 128.5, 126.7, 126.4, 101.1, 82.6, 81.6, 79.7, 76.2, 73.7, 69.6, 33.7, 28.5; HRMS (ESI TOF) calcd for $C_{20}H_{26}O_6Na$ $(M+Na)^+$ 385.1627, found 385.1667.

4.8. Conversion of 15 to 14

To a solution of DMSO (85.2 μL, 1.20 mmol) in CH_2Cl_2 (4.0 mL) was added $(COCl)_2$ (68.8 μL, 0.800 mmol) at −78 °C. After the mixture was stirred for 15 min at −78 °C, to the resulting mixture was added alcohol **15** (145 mg, 0.400 mmol). After the mixture was stirred for 30 min at −78 °C, to the mixture was added Et_3N (0.33 mL, 2.40 mmol), and the mixture was allowed to warm up to room temperature. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 2:1) gave ketone and its corresponding enol as an equilibrated mixture (136 mg, 95%): R_f=0.50 (hexane/EtOAc, 4:1); HRMS (ESI TOF) calcd for $C_{20}H_{24}O_6Na$ $(M+Na)^+$ 383.1471, found 383.1485.

To a solution of ketone (23.7 mg, 65.8 μmol) in THF (1.0 mL) was added L-Selectride (1.0 M in THF, 0.13 mL, 0.130 mmol) at −78 °C. After the mixture was stirred for 30 min at the same temperature, the reaction was quenched with MeOH. Concentration and column chromatography (hexane/EtOAc, 7:1, 6:1, 3:1) gave alcohol **14** (7.6 mg, 32%, 57% based on recovery), alcohol **15** (4.2 mg, 18%, 31% based on recovery), and ketone (10.4 mg, 44% recovery).

4.9. Alcohol 5

To a solution of alcohol **14** (534 mg, 1.47 mmol) in DMF (10.0 mL) were added imidazole (300 mg, 4.41 mmol) and TBSCl (443 mg, 2.94 mmol) at room temperature. After the mixture was stirred for 5 h at 30 °C, the reaction was quenched with MeOH. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 40:1) gave silyl ether (545 mg, 77%): colorless crystal; mp 113 °C (MeOH); R_f=0.50 (hexane/EtOAc, 7:1); $[\alpha]_D^{22}$ −95.0 (*c* 0.37, $CHCl_3$); IR (neat) 3068, 2955, 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.33 (m, 5H), 5.87–5.76 (m, 2H), 5.46 (s, 1H), 4.43 (dd, *J*=7.9, 4.5 Hz, 1H), 4.30 (dt, *J*=9.2, 3.0 Hz, 1H), 4.24 (dd, *J*=9.8, 4.2 Hz, 1H), 3.73 (d, *J*=9.2 Hz, 1H), 3.66–3.55 (m, 2H), 2.63 (ddd, *J*=13.3, 9.7, 3.0 Hz, 1H), 2.28 (ddd, *J*=13.3, 6.0, 3.0 Hz, 1H), 1.45 (s, 9H), 0.85 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 137.7, 133.1, 129.2, 128.5, 127.3, 126.4, 101.2, 83.1, 81.5, 79.9, 76.7, 72.5, 69.8, 32.9, 28.4, 26.1, 18.3, −4.2, −4.6; HRMS (ESI TOF) calcd for $C_{26}H_{40}O_6SiNa$ $(M+Na)^+$ 499.2492, found 499.2484.

To a solution of ester (500 mg, 1.04 mmol) in CH_2Cl_2 (10.0 mL) was added DIBAL-H (1.0 M in hexane, 2.2 mL, 2.20 mmol) at −78 °C. After the mixture was stirred for 30 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl/MeOH. The mixture was diluted with EtOAc, washed with H_2O, saturated aqueous Rochelle salt and brine, and dried over Na_2SO_4. Concentration gave crude aldehyde, which was used for the next step without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (557 mg, 1.56 mmol) in THF (5.0 mL) was added NaHMDS (1.0 M in THF, 1.6 mL, 1.60 mmol) at 0 °C. After the mixture was stirred for 30 min at the same temperature, to the resulting mixture was added a solution of aldehyde obtained above in THF (3.0+1.0+1.0 mL) at 0 °C. After the mixture was stirred for 30 min at room temperature, the reaction was quenched with H_2O. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration gave crude alkene, which was used for the next step without further purification.

To a solution of crude silyl ether obtained above in THF (10.0 mL) was added TBAF (1.0 M in THF, 1.9 mL, 1.90 mmol) at room temperature. The mixture was stirred for 1 h at the same temperature. Concentration and column chromatography (hexane/EtOAc, 7:1, 4:1, 1:1) gave alcohol **5** (274 mg, 91% in three steps): colorless crystal; mp 90 °C (hexane/EtOAc); R_f=0.14 (hexane/EtOAc, 4:1); $[\alpha]_D^{24}$ −129.4 (*c* 0.25, $CHCl_3$); IR (neat) 3531, 3041, 2890 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.32 (m, 5H), 5.94–5.79 (m, 3H), 5.47 (s, 1H), 5.28 (dt, *J*=17.3, 1.5 Hz, 1H), 5.21 (dt, *J*=10.5, 1.5 Hz, 1H), 4.47–4.44 (m, 1H), 4.29 (dd, *J*=10.8, 5.2 Hz, 1H), 3.80 (dd, *J*=9.3, 6.1 Hz, 1H), 3.75–3.70 (m, 1H), 3.64 (t, *J*=10.8 Hz, 1H), 3.51–3.45 (m, 1H), 2.76 (ddd, *J*=13.6, 10.0, 3.4 Hz, 1H), 2.41 (ddd, *J*=13.6, 6.3, 2.5 Hz, 1H), 1.50 (br d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.9, 133.9, 128.9, 128.2, 126.1, 125.9, 116.7, 100.9, 83.4, 79.9, 75.1, 74.6, 69.9, 32.3; HRMS (ESI TOF) calcd for $C_{17}H_{20}O_4Na$ $(M+Na)^+$ 311.1259, found 311.1279.

4.10. Ester 16

To a solution of nitrile **10** (78.2 mg, 0.160 mmol) in CH_2Cl_2 (3.3 mL) was added DIBAL-H (1.0 M in hexane, 0.32 mL, 0.320 mmol) at −78 °C. After the mixture was stirred for 30 min at the same temperature, the reaction was quenched with MeOH. The mixture was diluted with EtOAc, washed with H_2O, saturated aqueous Rochelle salt and brine, and dried over Na_2SO_4. Concentration gave crude aldehyde, which was used for the next step without further purification.

To a solution of aldehyde obtained above in *t*-BuOH (1.6 mL) and 2-methyl-2-butene (1.6 mL) were added 5% aqueous NaH_2PO_4 (1.6 mL) and $NaClO_2$ (50.6 mg, 0.560 mmol) at 0 °C. The mixture was stirred for 2 h at the same temperature. The mixture was diluted with EtOAc, washed with brine, and dried over Na_2SO_4. Concentration gave crude carboxylic acid **4**, which was used for the next step without further purification.

To a solution of **4** obtained above in THF (1.6 mL) were added Et_3N (66.9 μL, 0.480 mmol) and 2,4,6-trichlorobenzoyl chloride (37.5 μL, 0.240 mmol) at room temperature. The mixture was stirred for 1 h at the same temperature. After THF was removed under reduced pressure, toluene (1.2 mL) was added. To the resulting mixture was added a solution of alcohol **5** (60.6 mg, 0.210 mmol) and DMAP (35.4 mg, 0.290 mmol) in toluene (1.0+0.5+0.5 mL) at room temperature. After the mixture was stirred for 1 h at the same temperature, the insoluble material was filtered off through a Celite pad. Concentration and column chromatography (hexane/EtOAc, 15:1, 3:1, 1:1) gave ester **16** (80.4 mg, 64% from **10**): colorless oil; R_f=0.46 (hexane/EtOAc, 4:1); $[\alpha]_D^{26}$ −38.6 (*c* 0.26, $CHCl_3$); IR (neat) 2928, 2855, 1742, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.77 (m, 4H), 7.49–7.41 (m, 5H), 7.37–7.31 (m, 3H), 5.95 (dd, *J*=11.0, 5.1 Hz, 1H), 5.82–5.71 (m, 4H), 5.48 (s, 1H), 5.23 (d, *J*=17.1 Hz, 1H), 5.12–5.07 (m, 2H), 4.95 (dt, *J*=9.6, 2.8 Hz, 1H), 4.88 (d, *J*=11.7 Hz, 1H), 4.49–4.46 (m, 1H), 4.31 (dd, *J*=10.7, 5.1 Hz, 1H), 4.13–4.08 (m, 1H), 4.02 (dd, *J*=9.6, 5.5 Hz, 1H), 3.84 (brd, *J*=15.3 Hz, 1H), 3.70–3.62 (m, 2H), 3.51–3.35 (m, 4H), 3.23 (td, *J*=9.6, 3.7 Hz, 1H), 2.81–2.76 (m, 2H), 2.55–2.47 (m, 2H), 2.31–2.25 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 136.9, 135.7, 134.2, 133.5, 133.2, 132.7, 131.4, 131.3, 128.9, 128.1, 127.8, 127.7, 127.6, 127.0, 126.1, 125.8, 125.7, 125.5, 115.9, 88.6, 85.3, 81.3, 80.2, 79.7, 76.0, 75.8, 75.5, 74.0, 69.5, 67.9, 39.1, 38.2, 34.6, 25.8, 18.2, −3.5, −4.4; HRMS (ESI TOF) calcd for $C_{45}H_{56}O_9SiNa$ $(M+Na)^+$ 791.3591, found 791.3595.

4.11. Alcohol 17

To a solution of silyl ether **16** (130 mg, 0.170 mmol) in THF (1.7 mL) was added TBAF (1.0 M in THF, 1.7 mL, 1.70 mmol) at room temperature. The mixture was stirred for 1 h at 40 °C. Concentration and column chromatography (hexane/EtOAc, 10:1, 4:1, 2:1) gave alcohol **17** (91.5 mg, 82%): colorless solid; mp 118 °C (hexane/EtOAc); R_f=0.43 (hexane/EtOAc, 2:1); $[\alpha]_D^{24}$ −91.4 (*c* 0.30, $CHCl_3$); IR (neat) 3403, 3052, 2863, 1709, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.79 (m, 4H), 7.49–7.44 (m, 5H), 7.38–7.31 (m, 3H), 5.94–5.87 (m, 2H), 5.81–5.65 (m, 3H), 5.47 (s, 1H), 5.24–5.07 (m, 3H), 4.91 (dt, *J*=6.5, 3.3 Hz, 1H), 4.86 (d, *J*=12.0 Hz, 1H), 4.47–4.44 (m, 1H), 4.32–4.26 (m, 2H), 4.03–3.97 (m, 2H), 3.69–3.58 (m, 2H), 3.48–3.38 (m, 3H), 3.32 (td, *J*=9.1, 2.2 Hz, 1H), 3.24 (td, *J*=9.4, 3.6 Hz, 1H), 2.78 (dd, *J*=15.1, 3.4 Hz, 1H), 2.72–2.69 (m, 1H), 2.57 (ddd, *J*=16.0, 8.0, 3.8 Hz, 1H), 2.47–2.30 (m, 3H), 1.51 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 137.4, 136.1, 135.7, 134.2, 133.2, 132.9, 131.5, 128.9, 128.4, 128.2, 127.8, 127.7, 127.5, 126.7, 126.2, 126.1, 126.1, 126.0, 126.0, 125.7, 125.5, 115.8, 101.0, 87.9, 84.5, 80.1, 79.9, 78.8, 76.0, 75.8, 75.4, 75.2, 73.0, 69.5, 67.9, 38.2, 34.5, 29.9; HRMS (ESI TOF) calcd for $C_{39}H_{42}O_9Na$ $(M+Na)^+$ 677.2726, found 677.2718.

4.12. Mixed acetal 19

To a solution of alcohol **17** (43.4 mg, 66.3 mmol) in CH_2Cl_2 (1.0 mL) were added **18** (62.5 μL, 0.199 mmol) and CSA (3.1 mg, 13.3 μmol) at room temperature. After the mixture was stirred for 30 min at the same temperature, the reaction was quenched with Et_3N. Concentration and column chromatography (hexane/EtOAc, 20:1, 8:1, 2:1, including 1% Et_3N) gave mixed acetal **19** (28.0 mg, 42%, 87% based on recovery) and alcohol **17** (22.7 mg, 52% recovery): colorless oil; R_f=0.47 (hexane/EtOAc, 4:1); IR (neat) 3031, 2925, 1742, 1650 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.93 (s, 1H), 7.78–7.72 (m, 2H), 7.68––7.55 (m, 4H), 7.32–7.11 (m, 5H), 6.02–5.94 (m, 1H), 5.90–5.77 (m, 1H), 5.69–5.46 (m, 3H), 5.33–5.15 (m, 4H), 5.05–4.96 (m, 3H), 4.24––4.15 (m, 2H), 4.03–3.88 (m, 3H), 3.77–3.69 (m, 2H), 3.66–3.59 (m, 1H), 3.48–3.25 (m, 6H), 3.16 (s, 3H), 2.75 (dd, *J*=15.9, 9.8 Hz, 1H), 2.66–2.44 (m, 4H), 2.32–2.22 (m, 1H), 2.07–1.85 (m, 2H), 1.61–1.47 (m, 6H), 1.46–1.28 (m, 6H), 1.00–0.76 (m, 15H).

4.13. Allylic stannane 20

To a solution of mixed acetal **19** (43.4 mg, 42.7 μmol) in CH_2Cl_2 (1.0 mL) were added HMDS (90.0 μL, 0.427 mmol) and TMSI (30.4 μL, 0.214 mmol) at 0 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and chromatography (hexane/EtOAc, 12:1, including 1% Et_3N) gave allylic stannane **20** (35.8 mg, 85%): colorless oil; R_f=0.57 (hexane/EtOAc, 4:1); $[\alpha]_D^{27}$ −99.3 (*c* 0.33, $CHCl_3$); IR (neat) 3033, 2925, 1742, 1651 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.97 (s, 1H), 7.78–7.74 (m, 2H), 7.70–7.64 (m, 4H), 7.35–7.12 (m, 5H), 6.17–6.10 (m, 1H), 6.00 (dd, *J*=10.9, 4.8 Hz, 1H), 5.87 (ddd, *J*=17.1, 10.5, 5.3 Hz, 1H), 5.72–5.65 (m, 1H), 5.55–5.42 (m, 2H), 5.25 (s, 1H), 5.20–5.12 (m, 3H), 5.07 (dt, *J*=10.6, 1.6 Hz, 1H), 4.63 (dt, *J*=6.0, 9.0 Hz, 1H), 4.23–4.16 (m, 2H), 4.04–3.89 (m, 4H), 3.75–3.64 (m, 2H), 3.56–3.43 (m, 2H), 3.37–3.24 (m, 3H), 2.96 (dd, *J*=15.2, 2.6 Hz, 1H), 2.69–2.46 (m, 4H), 2.29–2.22 (m, 1H), 1.97–1.85 (m, 2H), 1.67–1.55 (m, 6H), 1.43–1.31 (m, 6H), 1.02–0.86 (m, 15H); ^{13}C NMR (100 MHz, C_6D_6) δ 169.6, 143.2, 138.6, 137.4, 136.4, 135.0, 134.0, 133.5, 132.5, 131.9, 128.9, 126.7, 126.6, 126.4, 126.2, 125.9, 125.6, 115.7, 105.6, 101.0, 88.1, 85.0, 83.6, 80.5, 79.9, 76.5, 76.4, 76.0, 75.9, 75.5, 69.7, 68.1, 60.1, 38.1, 34.9, 30.3, 29.8, 27.9, 14.1, 10.0; HRMS (ESI TOF) calcd for $C_{54}H_{72}O_9SnNa$ $(M+Na)^+$ 1007.4096, found 1007.4056.

4.14. Tetraene 21

To a solution of ester **20** (13.1 mg, 13.3 μmol) in CH_2Cl_2 (1.5 mL) was added DIBAL-H (1.0 M in hexane, 52.2 μL, 52.2 μmol) at −78 °C. After the mixture was stirred for 10 min at the same temperature, to

the resulting mixture were added pyridine (17.4 μL, 0.160 mmol), DMAP (13.0 mg, 0.106 mmol) in CH_2Cl_2 (0.6 mL), and $(ClCH_2CO)_2O$ (54.5 mg, 0.319 mmol) in CH_2Cl_2 (0.7 mL) at −78 °C. After the mixture was allowed to warm up to −20 °C gradually for 1 h, the reaction was quenched with H_2O. The mixture was diluted with EtOAc, and washed with saturated aqueous Rochelle salt, saturated aqueous $CuSO_4$ twice, saturated aqueous $NaHCO_3$, and brine. Dried over Na_2SO_4 and concentration gave the crude α-chloroacetoxy ether **3**, which was used for the next step without further purification.

To a mixture of **3** obtained above and molecular sieves 4 Å (26.0 mg) in CH_3CN (2.7 mL) was added $BF_3\cdot OEt_2$ (0.40 M in CH_2Cl_2, 0.26 mL, 0.104 mmol) at −40 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with Et_3N. Concentration and chromatography (hexane/EtOAc, 10:1, 8:1, 4:1) gave the desired product **21** (4.2 mg, 47% in two steps) and its diastereomer **22** (1.2 mg, 13% in two steps): colorless solid; mp 180 °C (hexane/EtOAc); R_f=0.37 (hexane/EtOAc, 4:1); $[\alpha]_D^{29}$ −35.0 (*c* 0.20, $CHCl_3$); IR (neat) 3035, 2864, 1644 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.96 (s, 1H), 7.74–7.65 (m, 6H), 7.35–7.12 (m, 5H), 6.12–5.93 (m, 3H), 5.63–5.45 (m, 4H), 5.30–5.15 (m, 5H), 5.07 (dt, *J*=10.5, 1.6 Hz, 1H), 4.28–4.24 (m, 2H), 4.17 (dd, *J*=15.6, 4.9 Hz, 1H), 3.86–3.80 (m, 2H), 3.71–3.63 (m, 3H), 3.53–3.26 (m, 6H), 2.96 (ddd, *J*=10.8, 9.5, 4.5 Hz, 1H), 2.86 (ddd, *J*=11.6, 9.5, 4.5 Hz, 1H), 2.66 (ddd, *J*=16.1, 6.6, 3.8 Hz, 1H), 2.51 (ddd, *J*=13.3, 10.6, 2.6 Hz, 1H), 2.41–2.22 (m, 2H), 2.10 (ddd, *J*=13.3, 6.6, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.9, 137.9, 137.8, 136.4, 134.4, 134.2, 133.8, 132.0, 129.2, 128.4, 128.3, 128.1, 127.0, 126.9, 126.9, 126.4, 126.3, 126.0, 116.9, 115.0, 101.4, 88.1, 83.6, 82.7, 82.1, 81.7, 81.2, 80.5, 77.7, 77.6, 76.2, 75.5, 73.5, 70.1, 69.0, 38.3, 35.6, 31.3; HRMS (ESI TOF) calcd for $C_{42}H_{46}O_8Na$ $(M+Na)^+$ 701.3090, found 701.3187.

4.15. Triene 24

To a solution of tetraene **21** (4.1 mg, 6.04 μmol) in benzene (0.7 mL) was added **23** (15.0 mg, 18.1 μmol) at room temperature. After the mixture was stirred for 5 h at 70 °C, the reaction was quenched with Et_3N. Short column chromatography (hexane/EtOAc, 2:1) and concentration gave crude triene. Purification by column chromatography (hexane/EtOAc, 8:1) gave triene **24** (2.9 mg, 74%): colorless solid; mp 195 °C (hexane/EtOAc); R_f=0.36 (hexane/EtOAc, 4:1); $[\alpha]_D^{28}$ −49.0 (*c* 0.22, $CHCl_3$); IR (neat) 3023, 2864, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 4H), 7.53–7.41 (m, 5H), 7.35–7.30 (m, 3H), 5.87–5.71 (m, 5H), 5.62 (dt, *J*=12.6, 2.3 Hz, 1H), 5.45 (s, 1H), 5.03–4.95 (m, 2H), 4.42 (dd, *J*=8.7, 3.0 Hz, 1H), 4.32–4.27 (m, 2H), 4.18 (dd, *J*=8.5, 2.0 Hz, 1H), 4.04–4.00 (m, 1H), 3.81 (dd, *J*=9.0, 1.7 Hz, 1H), 3.65–3.60 (m, 2H), 3.52–3.46 (m, 2H), 3.36 (t, *J*=8.8 Hz, 1H), 3.30–3.20 (m, 2H), 3.11–3.08 (m, 2H), 2.74–2.68 (m, 1H), 2.63 (ddd, *J*=16.2, 7.6, 3.9 Hz, 1H), 2.36–2.25 (m, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 136.6, 134.9, 133.2, 132.9, 131.3, 130.9, 128.9, 128.2, 127.8, 127.8, 127.6, 126.8, 126.7, 126.2, 126.1, 125.8, 125.6, 100.8, 89.2, 87.4, 85.0, 82.1, 81.0, 80.9, 80.5, 79.8, 78.1, 77.2, 76.9, 76.0, 73.2, 68.4, 37.0, 34.7, 32.7; HRMS (ESI TOF) calcd for $C_{40}H_{42}O_8Na$ $(M+Na)^+$ 673.2777, found 673.2753.

4.16. Diol 2

To a solution of benzylidene acetal **24** (2.9 mg, 4.46 μmol) in MeOH (0.30 mL) and CH_2Cl_2 (0.15 mL) was added a trace amount of CSA at room temperature. After the mixture was stirred for 9 h at 40 °C, the reaction was quenched with Et_3N. Concentration and chromatography (hexane/EtOAc, 2:1, 1:2) gave diol **2** (1.9 mg, 76%, 92% based on recovery) and benzylidene acetal **24** (0.5 mg, 17% recovery). The spectroscopic data of **2** obtained are identical with those reported previously.[5d]

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