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Improved Synthesis of the A−G Ring Segment of Brevetoxin B

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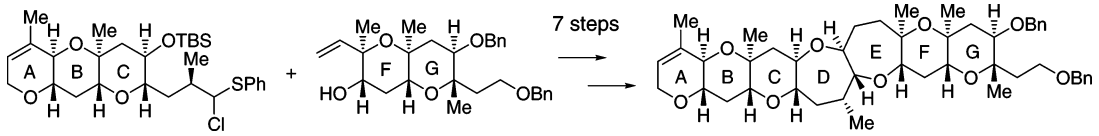

An efficient synthesis of the A−G ring segment **2**, a key intermediate for the total synthesis of brevetoxin B (**1**), was achieved in 37 steps and 5.0% overall yield. The intramolecular allylation of the *O*,*S*-acetal **22**, prepared from the ABC ring segment **15** and the FG ring segment **17**, was carried out using AgOTf as a Lewis acid to give the desired compound **23**, predominantly. Ring-closing metathesis of **23** with the Grubbs catalyst **12** afforded the heptacyclic ether **25**. Selective hydrogenation of the E ring olefin of **25** was performed by diimide reduction to afford **2**.

Introduction

Brevetoxin B (**1**), a potent neurotoxin, was isolated from the red tide organism *Gymnodinium breve* Davis in 1981 as the first example of marine polycyclic ethers (Figure 1).[1] The unique structural features and biological activity of this molecule have attracted significant attention of synthetic chemists.[2,3]

Recently, we have reported a convergent total synthesis of brevetoxin B (**1**).[2d] Scheme 1 illustrates the outline of the synthesis of the A−G ring segment. Coupling of the BC ring segments **3** and FG ring segment **4** was performed via intramolecular allylation and subsequent ring-closing metathesis to give the B−G ring system **5**. The A ring moiety was synthesized by 11 steps based on the Nakata procedure to furnish the A−G ring segment **2**.[2c] However, construction of the A ring after the key segment coupling decreased the convergency of the total synthesis of **1**. To solve this problem, we examined the improved synthesis of **2** starting from the ABC and FG ring segments.

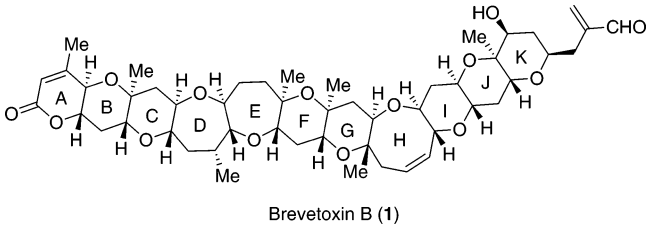

FIGURE 1. Structure of brevetoxin B (**1**).

Results and Discussion

Synthesis of the ABC Ring Segment. Scheme 2 describes the synthesis of the ABC ring segment. Removal of the benzyliden acetal of **6**[2d] under hydrogenation conditions followed by protection of the resulting diol with MPMCl/KH gave **7** in 77% overall yield. Selective cleavage of the primary MPM ether with TMSI/HMDS gave alcohol **8** in quantitative yield.[4] Swern oxidation followed by Grignard reaction with MeMgBr gave methyl carbinol **9**. Swern oxidation of **9** followed by Wittig reaction provided *exo*-methylene **10** in 79% overall yield. Removal of the MPM protection of **10** and allylation of the resulting alcohol gave diene **11** in 88% overall yield. Ring-closing metathesis of **11** with the Grubbs catalyst **12** furnished tricycle **13** in quantitative yield.[5] Selective hydrolysis of the primary TBS ether afforded alcohol **14** in 95% yield. Treatment of **14** with $(PhS)_2/Bu_3P$ gave the ABC ring segment **15** in 91% yield.[6]

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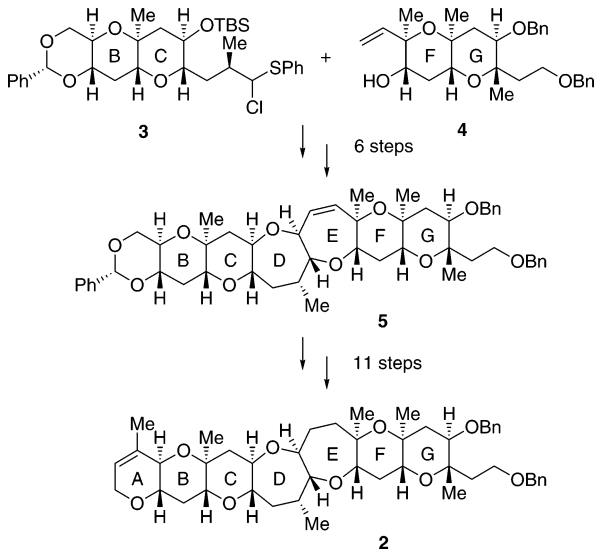
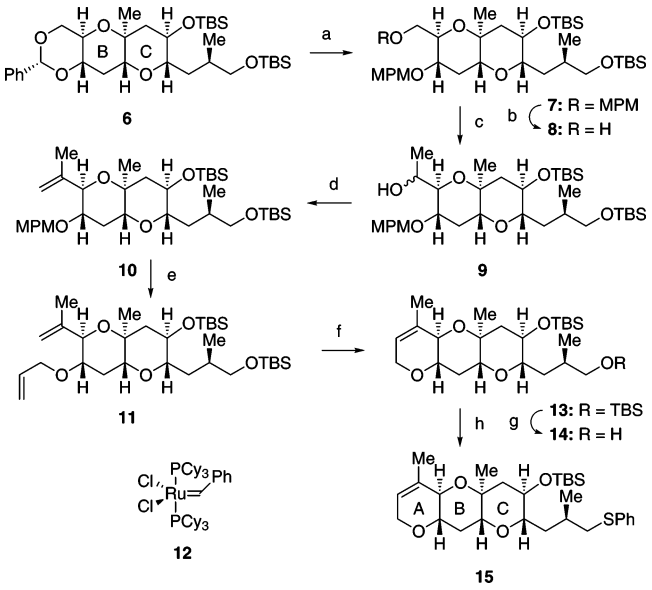
SCHEME 1. Previous Synthesis of A−G Ring Segment of Brevetoxin B



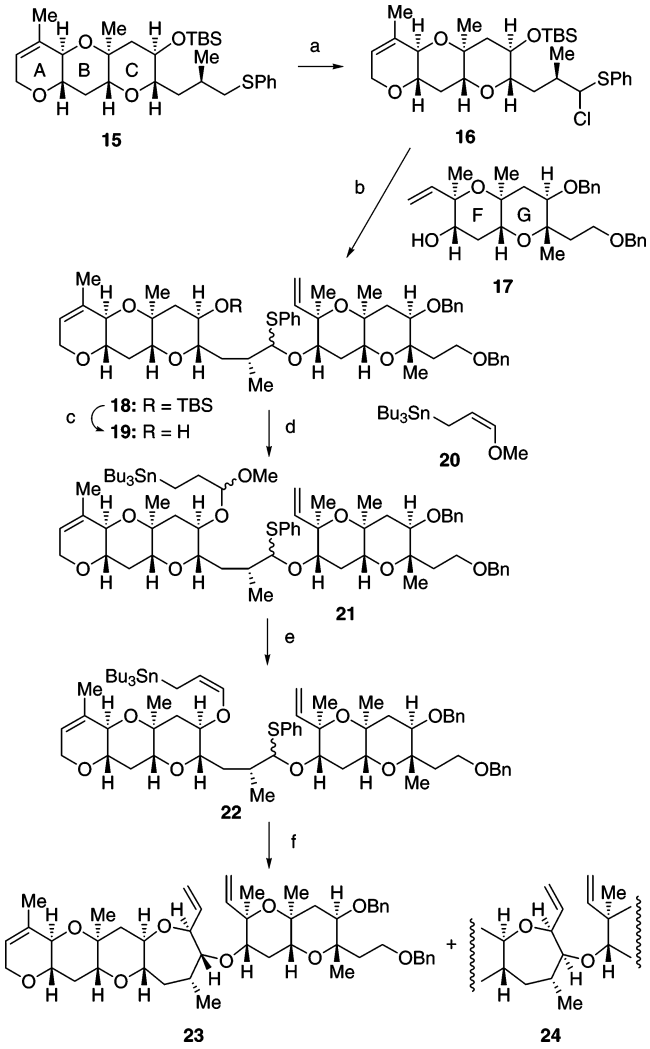
SCHEME 2. Synthesis of ABC Ring Segment[a]



[a] Reagents and conditions: (a) (i) H_2, $Pd(OH)_2$-C, EtOAc, rt; (ii) MPMCl, KH, THF, 35 °C, 77% (2 steps); (b) TMSI, HMDS, CH_2Cl_2, 0 °C, then K_2CO_3, MeOH, 100%; (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C to rt; (ii) MeMgBr, THF, 0 °C; (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C to rt; (ii) $Ph_3PCH_3^+Br^-$, NaHMDS, THF, 0 °C, 79% (4 steps); (e) (i) DDQ, $NaHCO_3$, CH_2Cl_2−H_2O, 35 °C, 88%; (ii) allyl bromide, KH, THF, rt; (f) **12**, CH_2Cl_2, rt, 100% (2 steps); (g) CSA, MeOH, 0 °C, 95%; (h) $(PhS)_2$, Bu_3P, DMF, rt 91%.

Coupling of the ABC and FG Ring Segments. Chlorination of **15** with NCS afforded the α-chlorosulfide **16** (Scheme 3).[7] Acetalization of **16** with the FG ring segment **17**[2d] was performed by the Inoue−Hirama protocol.[8] Thus, treatment of the mixture of **16** and **17** with AgOTf/DTBMP provided the *O,S*-acetal **18** in 91% overall yield.[9] Removal of the TBS protection of **18** with TBAF followed by acid-catalyzed acetal formation with **20** afforded mixed acetal **21** in 97% overall yield. Selective cleavage of the methyl acetal was performed with TMSI/HMDS to give allylic stannane **22** in 89% yield.[10] Treatment of **22** with AgOTf furnished an 87:13 mixture of the desired product **23** and its stereoisomer **24** in 92% yield.

SCHEME 3. Coupling of ABC and FG Ring Segments[a]



[a] Reagents and conditions: (a) NCS, CCl_4, rt; (b) **17**, AgOTf, DTBMP, MS4A, CH_2Cl_2, −78 to −30 °C, 91% based on **17**; (c) TBAF, THF, rt; (d) **20**, CSA, CH_2Cl_2, rt, 97% (2 steps); (e) TMSI, HMDS, CH_2Cl_2, 0 °C, 89%; (f) AgOTf, MS4A, CH_3CN−CH_2Cl_2 (2:1), −78 °C to rt, 92% (**23**:**24** = 87:13).

Synthesis of the A−G Ring Segment. The triene **23** obtained was subjected to ring-closing metathesis using the Grubbs catalyst **12** to give the heptacycle **25** in 84% yield (Scheme 4). The stereochemistry of **25** was determined on the basis of ^1H NMR analysis and NOE experiments as shown in Scheme 4. The next task of the synthesis was the selective hydrogenation of the E ring moiety. After several attempts, we found that the treatment of **25** with diimide provided the A−G ring segment **2** in 87% yield. The trisubstituted olefin on the A ring was totally

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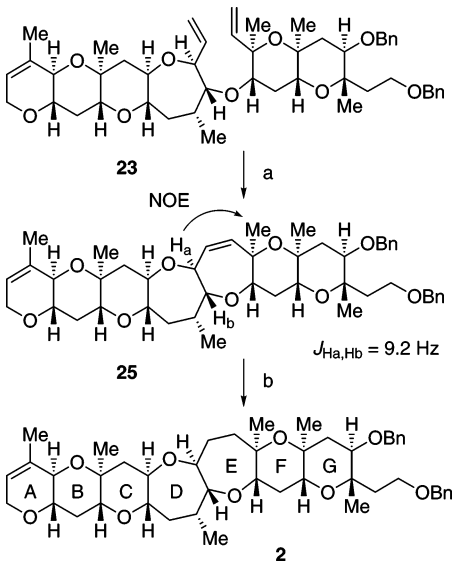
SCHEME 4. Synthesis of A−G Ring Segment[a]



[a] Reagents and conditions: (a) **12**, benzene, 80 °C, 84%; (b) $KO_2CN{=}NCO_2K$, AcOH, pyridine, MeOH, rt, 87%.

inert under the reaction conditions. The spectroscopic data of **2** obtained are identical with those reported previously.[2]

Conclusion

We have achieved the improved synthesis of the A−G ring segment **2**, a key intermediate for the total synthesis of brevetoxin B (**1**), by using highly convergent strategy. The longest linear sequence leading to **2** was 37 steps with 5.0% overall yield (previous 1.4% by 47 steps). Demonstrated in this study was the power of the intramolecular allylation-RCM methodology as a tool for the convergent synthesis of polycyclic ethers. This approach will make brevetoxin B available in sufficient quantity to perform the further investigation on its biological studies.

Experimental Section

Bis-MPM Ether 7. A mixture of **6** (14.4 g, 23.7 mmol) and 5% $Pd(OH)_2$−C (1.5 g) in EtOAc (250 mL) was stirred for 4 h under H_2 atmosphere. The catalyst was filtered off, and the filtrate was concentrated to give the corresponding diol, which was used for the next reaction directly.

To a suspension of KH (30%, 10 g, 71.2 mmol, prewashed with hexane) in THF (120 mL) at 0 °C were added the crude diol obtained above in THF (0.6 mL) and MPMCl (7.8 mL, 59.3 mmol). After stirring for 2 h at 35 °C, the reaction mixture was quenched with MeOH and water at 0 °C and then extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and chromatography (hexane/EtOAc, 20:1) gave **7** (13.9 g, 77%): oil; R_f = 0.47 (hexane/EtOAc, 4:1); $[\alpha]^{15}_D$ +4.34° (*c* 1.00, $CHCl_3$); IR (neat) 2953 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.21 (m, 2 H), 7.07−7.05 (m, 2 H), 6.83−6.77 (m, 4 H), 4.52−4.22 (m, 3 H), 4.25−4.22 (m, 1 H), 3.75 (s, 6 H), 3.62−3.56 (dd, *J* = 10.4, 4.8 Hz, 1 H), 3.44−3.36 (m, 2 H), 3.31 (dd, *J* = 10, 6.8 Hz, 1 H), 3.14 (ddd, *J* = 9.2, 9.2, 1.2 Hz, 1 H), 3.01 (dd, *J* = 12.6, 4.0 Hz, 1 H), 2.24 (ddd, *J* = 11.6, 4.4, 4.4 Hz, 1 H), 2.08 (dd, *J* = 11.6, 4.8 Hz, 1 H), 1.87−1.80 (m, 1 H), 1.74 (ddd, *J* = 11.2, 8.4, 2.4 Hz, 1 H), 1.52 (s, 3 H), 1.17 (s, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.86 (s, 9 H), 0.82 (s, 9 H), 0.01 (s, 6 H), 0.00 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 159.0, 130.5, 130.1, 129.4, 129.3, 113.8, 113.7, 82.3, 77.9, 77.2, 73.1, 72.9, 72.5, 72.4, 70.9, 70.6, 69.4, 67.8, 55.3, 55.2, 47.5, 36.1, 32.6, 30.5, 26.1, 25.8, 18.5, 18.4, 17.9, 15.7, −3.9, −4.6, −5.2, −5.2; HRMS (ESI TOF) calcd for $C_{42}H_{70}O_8Si_2Na$ (M + Na^+) 781.4507, found 781.4597.

Alcohol 8. To a stirred solution of **7** (437 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added HMDS (0.31 mL, 1.47 mmol) and TMSI (0.1 mL, 0.74 mmol), and the mixture was stirred for 1 h at the same temperature. To the resulting mixture were added MeOH (5 mL) and K_2CO_3 (400 mg). After stirring for 1.5 h at room temperature, the mixture was quenched with water and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and chromatography (hexane/EtOAc, 20:1 to 4:1) gave **8** (316 mg, 100%): oil; R_f = 0.23 (hexane/EtOAc, 4:1); $[\alpha]^{23}_D$ +1.49° (*c* 1.00, $CHCl_3$); IR (neat) 3480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21−7.19 (m, 2 H), 6.85−6.83 (m, 2 H), 4.55−4.34 (m, 2 H), 3.76 (s, 3 H), 3.74−3.71 (m, 1 H), 3.65−3.58 (m, 1 H), 3.52−3.49 (m, 2 H), 3.44−3.35 (m, 2 H), 3.31 (dd, *J* = 9.6, 6.8 Hz, 1 H), 3.14 (ddd, *J* = 9.6, 9.6, 2.0 Hz, 1H), 2.97 (dd, *J* = 12.8, 4.0 Hz, 1 H), 2.26 (ddd, *J* = 12, 4.8, 4.8 Hz, 1 H), 2.02 (dd, *J* = 11.6, 4.8 Hz, 1 H), 1.95 (dd, *J* = 7.6, 4.8 Hz, 1 H), 1.87−1.81 (m, 1 H)1.74 (ddd, *J* = 14, 8.8, 2.0 Hz, 1 H), 1.52 (q, *J* = 11.6 Hz, 1 H), 1.43 (t, *J* = 11.6, 1 H), 1.17 (s, 3 H), 1.16−1.09 (m, 1 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.82 (s, 9 H), 0.00 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 129.9, 129.3, 113.9, 82.4, 78.0, 73.3, 72.6, 72.4, 70.8, 70.5, 67.8, 63.0, 55.3, 47.5, 36.1, 30.2, 26.1, 25.8, 18.5, 18.4, 18.0, 15.9, −3.7, −4.6, −5.1, −5.2; HRMS (ESI TOF) calcd for $C_{34}H_{62}O_7Si_2Na$ (M + Na^+) 661.3932, found 661.3997.

Olefin 10. To a stirring mixture of DMSO (82 μL, 1.16 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added $(COCl)_2$ (76 μL, 0.87 mmol), and the mixture was stirred for 0.5 h. A solution of alcohol **8** (368 mg, 0.58 mmol) in CH_2Cl_2 (2 mL) was added, and the stirring was continued for 1 h at the same temperature. To the resulting mixture was added Et_3N (0.49 mL, 3.5 mmol), and the mixture was allowed to warm to room temperature. The mixture was diluted with ether and washed with saturated NH_4Cl and brine. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude aldehyde obtained was used for the next reaction directly.

To a mixture of the aldehyde obtained in THF (6 mL) at 0 °C was added MeMgI (1.06 M in ether, 3.3 mL, 3.5 mmol). After stirring for 0.5 h at the same temperature, the mixture was quenched with MeOH, diluted with ether, and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated to give the crude alcohol **9**, which was used for the next reaction directly.

To a stirring mixture of DMSO (82 μL, 1.16 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added $(COCl)_2$ (76 μL, 0.87 mmol), and the mixture was stirred for 0.5 h. A solution the crude alcohol **9** obtained above in CH_2Cl_2 (2 mL) was added, and the strring was continued for 1 h at the same temperature. To the resulting mixture was added Et_3N (0.49 mL, 3.5 mmol), and the mixture was allowed to warm to room temperature. The mixture was diluted with ether and washed with saturated NH_4Cl and brine. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude ketone obtained was used for the next reaction directly.

To a suspension of $Ph_3PCH_3{}^+Br^-$ (608 mg, 0.58 mmol) in THF (4 mL) at 0 °C was added NaHMDS (1.0 M in THF, 1.7 mL, 1.7 mmol), and the mixture was stirred for 20 min at the same temperature. To the resulting mixture was added a solution of crude ketone obtained above in THF (2 mL). After stirring for 1 h at room temperature, the reaction mixture was quenched with water and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and chromatography (hexane/EtOAc, 20:1) gave **10** (298 mg, 79%): oil; R_f = 0.6 (hexane/EtOAc, 4:1); $[\alpha]^{26}_D$ −14.4° (*c* 1.00, $CHCl_3$); IR (neat) 2953 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.19 (m, 2 H), 6.86−6.82 (m, 2 H), 5.09 (s, 1 H), 5.00 (s, 1 H), 4.50−4.37 (m, 2 H), 3.93 (d, *J* = 9.6 Hz, 1 H), 3.78 (s, 3 H), 3.53 (dd, *J* = 9.6, 4.8 Hz, 1 H), 3.40 (ddd, *J* = 10.8, 8.6, 4.8 Hz, 1H), 3.37−3.32 (m, 2 H), 3.17 (ddd, *J* = 9.2, 9.2, 2.0 Hz, 1 H), 3.02 (dd, *J* = 12.8, 3.6 Hz, 1 H), 2.24 (ddd,

J = 11.2, 4.4, 4.4 Hz,1 H), 1.90−1.83 (m, 1 H), 1.76 (ddd, J = 14.8, 8.8, 2.0 Hz, 1 H), 1.70 (s, 3 H), 1.62−1.53 (m, 1 H), 1.49−1.41 (m, 1 H), 1.21 (s, 3 H), 1.15 (ddd, J = 14, 9.6, 4.4 Hz, 1 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.84 (s, 9 H), 0.02 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 143.1, 130.2, 129.3, 115.5, 113.8, 113.7, 82.3, 78.1, 76.8, 74.8, 72.4, 70.9, 70.7, 67.7, 55.3, 47.6, 36.1, 32.6, 30.9, 26.1, 25.8, 18.5, 18.4, 18.1, 17.9, 15.9, −4.0, −4.6, −5.2, −5.2; HRMS (ESI TOF) calcd for $C_{36}H_{64}O_6Si_2Na$ (M + Na^+) 671.4139, found 671.4187.

Tricycle 13. To a solution of **10** (278 mg, 0.43 mmol) in CH_2Cl_2 (4 mL) were added saturated $NaHCO_3$ (1 mL) and DDQ (195 mg, 0.86 mmol), and the mixture was stirred for 1.5 h at 45 °C. The reaction mixture was diluted with ether and then washed with saturated $NaHCO_3$, water, and brine. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and chromatography (hexane/EtOAc, 10:1) gave the corresponding alcohol (188 mg, 84%): oil; R_f = 0.36 (hexane/EtOAc, 4:1); $[\alpha]^{28}_D$ −28.0° (c 0.90, $CHCl_3$); IR (neat) 3448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1 H), 5.04 (t, J = 1.6 Hz, 1 H), 3.80 (d, J = 9.2 Hz, 1 H), 3.53 (dd, J = 9.6, 4.8 Hz, 1 H), 3.49−3.46 (m, 1 H), 3.41 (ddd, J = 10.8, 9.2, 5.2 Hz, 1H), 3.33 (dd, J = 9.6, 6.4 Hz, 1 H), 3.19 (ddd, J = 9.6, 9.6, 2.0 Hz, 1 H), 2.17 (ddd, J = 11.6, 4.4, 4.4 Hz 1 H), 2.09 (dd, J = 11.6, 5.2 Hz, 1 H), 1.90−1.85 (m, 1 H), 1.80−1.73 (m, 1 H), 1.73 (s, 3 H), 1.64−1.55 (m, 2H), 1.50 (t, J = 11.2 Hz, 1 H), 1.23 (s, 3 H), 1.16 (ddd, J = 14, 9.6, 4.4 Hz, 1 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.87 (s, 9 H), 0.84 (s, 9 H), 0.30 (s, 6 H), 0.17 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 115.8, 82.4, 78.8, 78.2, 72.7, 70.9, 67.7, 67.4, 47.5, 36.1, 32.6, 32.5, 26.1, 25.8, 18.5, 18.3, 18.0, 17.1, 15.9, −4.0, −4.6, −5.2, −5.2; HRMS (ESI TOF) calcd for $C_{28}H_{56}O_5Si_2Na$ (M + Na^+) 551.3564, found 551.3584.

To a suspension of KH (214 mg, 1.6 mmol, 30%, prewashed with hexane) in THF (1.5 mL) at 0 °C were added allyl bromide (0.14 mL, 1.6 mmol) and the alcohol obtained above (170 mg, 0.32 mmol) in THF (1.5 mL). After stirring for 1 h at the same temperature, the reaction mixture was quenched with MeOH. The mixture was diluted with ether and then washed with H_2O and brine. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give crude **11**, which was used for the next reaction directly.

To a mixture of the allylic ether **11** in CH_2Cl_2 (64 mL) was added **12** (53 mg, 64 μmol), and the mixture was stirred for 20 h at room temperature. The mixture was filtered through a short silica gel column (ether) and concentrated. The residue was purified by chromatography (hexane/EtOAc, 40:1) to give **13** (176 mg, 100%): oil; R_f = 0.38 (hexane/EtOAc, 10:1); $[\alpha]^{22}_D$ −14.1° (c 1.00, $CHCl_3$); IR (neat) 2953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (dd, J = 3.2, 2 Hz, 1 H), 4.20 (bd, J = 16.4 Hz, 1 H), 4.10 (dd, J = 16.4, 2.8 Hz, 1 H), 3.92 (d, J = 8.8 Hz, 1 H), 3.51 (dd, J = 10, 4.8 Hz, 1H), 3.43 (ddd, J = 10.8, 9.2, 5.2 Hz, 1 H), 3.21−3.14 (m, 2 H), 3.12 (dd, J = 12, 3.6 Hz, 1 H), 2.09−2.03 (m, 2 H), 1.90−1.83 (m, 1 H), 1.75 (ddd, J = 14.4, 9.2, 2.4 Hz, 3 H), 1.68 (s, 3 H), 1.62 (q, J = 12 Hz, 1 H), 1.47 (t, J = 11.2 Hz, 3 H), 1.21 (s, 3 H), 1.15 (ddd, J = 13.6, 10, 4.4 Hz, 1 H), 0.91 (d, J = 6.4 Hz, 3 H), 0.86 (s, 9 H), 0.84 (s, 9 H), 0.04 (s, 6 H), 0.00 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 121.1, 82.6, 79.4, 74.8, 73.5, 71.0, 69.6, 67.7, 66.9, 47.4, 36.2, 32.5, 31.3, 26.1, 25.8, 18.5, 18.3, 17.9, 17.3, 16.3, −3.9, −4.5, −5.2, −5.2; HRMS (ESI TOF) calcd for $C_{29}H_{56}O_5Si_2Na$ (M + Na^+) 563.3564, found 563.3514.

Alcohol 14. To a mixture of **13** (309 mg, 0.57 mmol) in CH_2Cl_2 (6 mL) and MeOH (6 mL) at 0 °C was added CSA (26 mg, 0.11 mmol). After stirring for 2.5 h at the same temperature, the reaction mixture was quenched with Et_3N and filtered through a short silica gel column (ether). Concentration and chromatography (hexane/EtOAc, 4:1) gave **14** (230 mg, 95%): oil; R_f = 0.23 (100% hexane to hexane/EtOAc, 4:1); $[\alpha]^{21}_D$ −2.1° (c 1.00, $CHCl_3$); IR (neat) 3458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (dd, J = 3.6, 2 Hz, 1 H), 4.16 (bd, J = 16.4 Hz, 1 H), 4.05 (dd, J = 16.4, 2.8 Hz, 1 H), 3.88 (d, J = 8.8 Hz, 1 H), 3.47 (ddd, J = 10.8, 8.8, 4.8 Hz, 1H), 3.41−3.38 (m, 2 H), 3.19 (dd, J = 9.2, 2 Hz, 1 H), 3.14 (dd, J = 12.4, 4 Hz, 1 H), 3.11 (dd, J = 11.2, 4.4 Hz, 1 H), 2.06−2.00 (m, 2 H), 1.92−1.86 (m, 1 H), 1.70 (ddd, J = 14.8, 7.6, 2 Hz, 1 H), 1.63 (s, 3 H), 1.58−1.53 (m, 1 H), 1.48−1.41 (m, 2 H), 1.17 (s, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.80 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 121.2, 81.7, 79.5, 74.6, 73.3, 70.0, 69.5, 67.5, 66.9, 47.3, 35.6, 32.6, 31.1, 25.8, 18.0, 17.3, 17.2, 16.2, −3.8, −4.6; HRMS (ESI TOF) calcd for $C_{23}H_{42}O_5SiNa$ (M + Na^+) 449.2699, found 449.2667.

Sulfide 15. To a mixture of **14** (2.55 g, 6.0 mmol) in DMF (60 mL) at 0 °C were added $(PhS)_2$ (2.87 g, 13 mmol) and Bu_3P (3.3 mL, 13 mmol), and the mixture was stirred for 4 h at room temperature. The mixture was diluted with ether and then washed with H_2O and brine. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and chromatography (hexane/EtOAc, 40:1 to 20:1) gave **15** (2.9 g, 95%): oil; R_f = 0.29 (hexane/EtOAc, 10:1); $[\alpha]^{21}_D$ −24.6° (c 0.90, $CHCl_3$); IR (neat) 2952 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.11 (m, 5 H), 5.34 (dd, J = 3.6, 2 Hz, 1 H), 4.23 (bd, J = 16.4 Hz, 1 H), 4.11 (dd, J = 16.4, 2.8 Hz, 1 H), 3.93 (d, J = 7.6 Hz, 1 H), 3.46 (ddd, J = 10.8, 9.2, 5.2 Hz, 1 H), 3.21−3.16 (m, 2 H), 3.12 (dd, J = 8.4, 4 Hz, 1 H), 3.09 (dd, J = 9.6, 4.4 Hz, 1 H), 2.61 (dd, J = 12.8, 8.4 Hz, 1 H), 2.08 (dd, J = 12, 4.8 Hz, 1 H), 2.06−2.00 (m, 2 H), 1.83 (ddd, J = 14.4, 9.2, 2 Hz, 1 H), 1.69 (s, 3 H), 1.61 (q, J = 11.2 Hz, 1 H), 1.49 (t, J = 11.2 Hz, 1 H), 1.35 (ddd, J = 14.4, 10, 4.8 Hz, 1 H), 1.21 (s, 3 H), 1.06 (d, J = 6.8 Hz, 3 H) 0.87 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 134.4, 128.7, 128.7, 125.4, 121.1, 82.2, 79.4, 74.8, 73.4, 70.7, 69.6, 66.9, 47.4, 40.3, 38.9, 31.2, 29.9, 25.8, 20.6, 18.0, 17.3, 16.2, −3.8, −4.6; HRMS (ESI TOF) calcd for $C_{29}H_{46}O_4SSiNa$ (M + Na^+) 541.2784, found 541.2736.

***O,S*-Acetal 18.** To a mixture of **15** (222 mg, 0.43 mmol) in CCl_4 (2 mL) was added NCS (57 mg, 0.43 mmol) in CH_2Cl_2 (0.8 mL). The mixture was stirred for 0.5 h at room temperature to give a solution of α-chlorosulfide **16**, which was used for the next reaction directly.

To a mixture of **17** (100 mg, 0.21 mmol), DTBMP (0.37 mL, 1.7 mmol), and MS4A (1.1 g) in CH_2Cl_2 (8 mL) at −78 °C was added AgOTf (220 mg, 0.86 mmol), and the mixture was stirred for 10 min at the same temperature. To the resulting mixture was added **16** obtained above, and the mixture was allowed to warm to −45 °C over 2 h. The mixture was then filtered through a silica gel pad (ether). Concentration and chromatography (hexane/EtOAc, 40:1 to 4:1 containing 1% Et_3N) gave **18** (134 mg, 91% from reacted **17**) and unreacted **17** (30 mg, 30%). **18**: amorphous; R_f = 0.44 (hexane/EtOAc, 4:1); $[\alpha]^{22}_D$ +8.23° (c 0.98, $CHCl_3$); IR (neat) 2952 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.15 (m, 15 H), 5.81 (dd, J = 17.2, 10.4 Hz, 1 H), 5.25 (s, 1 H), 5.16 (dd, J = 17.2, 1.6 Hz, 1 H), 4.91 (dd, J = 10.8, 1.6 Hz, 1 H), 4.85 (d, J = 4 Hz, 1 H), 4.44 (d, J = 11.6 Hz, 1 H), 4.34 (s, 2 H), 4.28 (d, J = 11.6 Hz, 1 H), 4.13 (bd, J = 14.8 Hz, 1 H), 4.01 (dd, J = 16, 2.4 Hz, 1 H), 3.86 (d, J = 8 Hz, 1 H), 3.76 (dd, J = 10.2, 4.8 Hz, 1 H), 3.54−3.36 (m, 4 H), 3.20 (ddd, J = 9.2, 9.2, 2.0 Hz, 1 H), 3.12 (ddd, J = 12, 8.4, 4.0 Hz, 1 H), 3.06 (dd, J = 12.4, 4.0 Hz, 1 H), 3.00 (dd, J = 12.4, 3.6 Hz, 1 H), 2.22−2.16 (m, 1 H), 2.11 (dd, J = 14.7, 7.6, 2.4 Hz, 1 H), 2.06−1.98 (m, 3 H), 1.87−1.78 (m, 2 H), 1.62 (s, 3 H), 1.58−1.46 (m, 2 H), 1.43−1.35 (m, 2 H), 1.31−1.23 (m, 1 H), 1.20 (s, 3 H), 1.15 (s, 3 H), 1.12 (dd, J = 4.8, 1.6 Hz, 1 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.79 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 138.5, 138.5, 135.8, 134.3, 133.0, 128.8, 128.2, 128.2, 127.6, 127.5, 127.4, 127.4, 127.2, 121.2, 111.9, 93.1, 83.0, 79.6, 77.8, 77.4, 76.9, 76.4, 74.8, 73.4, 73.0, 73.0, 71.3, 71.1, 71.0, 69.6, 66.9, 66.1, 47.5, 40.2, 36.5, 35.4, 31.3, 26.1, 25.9, 23.1, 19.7, 18.1, 17.5, 17.4, 17.3, 16.3, −4.0, −4.4; HRMS (ESI TOF) calcd for $C_{58}H_{82}O_9SSiNa$ (M + Na^+) 1005.5346, found 1005.5369.

Mixed Acetal 21. To a mixture of **18** (174 mg, 177 mmol) in THF (1.8 mL) was added TBAF (1.0 M in THF, 0.47 mL, 470 mmol). After stirring for 20 h at room temperature, the reaction

mixture was filtered through a short silica gel column (ether). Concentration gave the corresponding crude alcohol, which was used for the next reaction directly.

To a solution of the crude alcohol obtained above and **20** (0.17 mL, 0.53 mmol) in CH_2Cl_2 (1.8 mL) was added CSA (8.1 mg, 35 μmol), and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with Et_3N and filtered through a short alumina column (EtOAc). The filtrate was concentrated and purified by chromatography (hexane/EtOAc, 50:1 to 4:1 containing 1% Et_3N) to give **21** as a mixture of diastereoisomers (212 mg, 97%): oil; R_f = 0.41 (hexane/EtOAc, 4:1); IR (neat) 2926 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.78−7.12 (m, 15 H), 6.48−6.39 (m, 1 H), 5.76−5.71 (m1 H), 5.43−5.35 (m, 1 H), 5.25−5.22 (m, 1 H), 5.12 (m, 1 H), 4.63−4.56 (m, 1 H), 4.49−4.44 (m, 3 H), 4.34−4.26 (m, 2 H), 4.12−4.08 (m, 3 H), 3.89−3.83 (m, 1 H), 3.73−3.69 (m, 3 H), 3.64−3.50 (m, 1 H), 3.35−3.22 (m, 6 H), 2.79−2.56 (m, 1 H), 2.31−2.18 (m, 4 H), 2.12−2.04 (m, 2 H), 2.00−1.92 (m, 2 H), 1.89 (m, 3 H), 1.79−1.72 (m, 3 H), 1.70−1.61 (m, 9 H), 1.51−1.43 (m, 6 H), 1.43−1.38 (m, 6 H), 1.32−1.22 (m, 6 H), 1.08−0.96 (m, 18 H); HRMS (ESI TOF) calcd for $C_{68}H_{102}O_{10}SSnNa$ (M + Na^+) 1251.6113, found 1251.5930.

Allylic Stannane 22. To a mixture of **21** (46 mg, 37 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C were added HMDS (0.21 mL, 1.0 mmol) and TMSI (0.11 mL, 0.78 mmol). After stirring for 1 h at the same temperature, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with ether. The oragnic layer was washed with saturated $NaHCO_3$ and brine. Concentration and chromatography (hexane/EtOAc, 10:1 containing 1% Et_3N) gave **22** (39 mg, 89%): oil; R_f = 0.44 (hexane/EtOAc, 4:1); $[\alpha]^{23}_D$ −0.70° (*c* 0.97, $CHCl_3$); IR (neat) 2926, 1651 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.74−7.12 (m, 15 H), 6.42 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.79 (d, *J* = 6.0 Hz, 1 H), 5.73 (dd, *J* = 17.2, 2.0 Hz, 1 H), 5.23 (dd, *J* = 10.8, 2.0 Hz, 1 H), 5.11 (s, 1 H), 4.76 (ddd, *J* = 8.4, 8.4, 5.6 Hz, 1 H), 4.49−4.43 (m, 3 H), 4.32−4.27 (m, 2 H), 4.20−4.05 (m, 3 H), 3.91−3.85 (m, 1 H), 3.77−3.70 (m, 3 H), 3.58−3.52 (m, 1 H), 3.37 (dd, *J* = 12, 3.6 Hz, 1 H), 3.24 (dd, *J* = 12, 4.0 Hz, 1 H), 3.22−3.18 (m, 1 H), 2.68−2.63 (m, 1 H), 2.58 (ddd, *J* = 14, 6.8, 2.0 Hz, 1 H), 2.46 (dd, *J* = 12, 5.2 Hz, 1 H), 2.30 (dd, *J* = 12, 4.8 Hz, 1 H), 2.28−2.25 (m, 1 H), 2.22−2.18 (m, 2 H), 2.17−2.11 (m, 1 H), 2.02−1.98 (m, 1 H), 1.95−1.79 (m, 5 H), 1.86 (s, 3 H), 1.76−1.65 (m, 8 H), 1.63 (s, 3 H), 1.50 (sext, *J* = 7.2 Hz, 6 H), 1.41 (s, 3 H), 1.40 (d, *J* = 6.0 Hz, 3 H), 1.32 (s, 3 H), 1.23 (s, 3 H), 1.11−1.03 (m, 14 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 140.4, 139.2, 139.0, 136.3, 134.5, 133.2, 129.0, 128.2, 127.6, 127.6, 127.4, 127.3, 127.2, 121.3, 111.3, 106.8, 93.3, 80.9, 79.9, 79.4, 78.3, 77.9, 77.0, 76.5, 74.8, 73.3, 73.1, 73.0, 71.7, 70.9, 70.0, 66.6, 66.3, 40.8, 36.9, 35.5, 31.6, 29.6, 29.5, 27.7, 27.7, 26.5, 23.9, 19.9, 17.5, 17.4, 17.3, 16.0, 13.9, 9.7, 6.5; HRMS (ESI TOF) calcd for $C_{67}H_{98}O_9SSnNa$ (M + Na^+) 1219.5851, found 1219.5614.

Cyclization of 22. To a mixture of **22** (11 mg, 9.2 μmol) and MS4A (90 mg) in MeCN/CH_2Cl_2 (2:1, 0.9 mL) was added AgOTf (19 mg, 74 μmol), and the mixture was stirred vigorously for 7 h at 30 °C. An additional amount of AgOTf (19 mg, 74 μmol) was added, and the stirring was continued for 14 h. The reaction was quenched with Et_3N and filtered through through a short silica gel column (ether). Concentration and chromatography (hexane/EtOAc, 20:1 containing 1% Et_3N) gave a mixture of **23** and **24** (6.8 mg, 92%); the ratio of **23** and **24** (87:13) was determined by ^{1}H NMR spectrum of the mixture. Although careful separation of the mixture gave pure **23**, the stereoisomer **24** was still contaminated with small amounts of **23**. **23**: oil; R_f = 0.41 (hexane/EtOAc, 3:1); $[\alpha]^{23}_D$ +24.5° (*c* 0.38, $CHCl_3$); IR (neat) 2928, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.18 (m, 10 H), 5.83 (dd, *J* = 17.2, 10.4 Hz, 1 H), 5.62 (ddd, *J* = 17.2, 10.8, 5.6 Hz, 1 H), 5.27 (d, *J* = 1.2 Hz, 1 H), 5.27−5.23 (m, 1 H), 5.23−5.18 (m, 1 H), 5.11 (dd, *J* = 10.4, 1.2 Hz, 1 H), 5.06 (ddd, *J* = 10.4, 1.6, 1.6 Hz), 4.48 (d, *J* = 11.6 Hz, 1 H), 4.38 (s, 2 H), 4.32 (d, *J* = 11.6 Hz, 1 H), 4.19 (d, *J* = 5.6 Hz, 1 H), 4.19−4.15 (m, 1 H), 4.09−4.04 (m, 1 H), 3.87 (bd, *J* = 8.0 Hz, 1 H), 3.80 (ddd, *J* = 11.2, 9.2, 5.6 Hz, 1 H), 3.58−3.49 (m, 3 H), 3.29 (dd, *J* = 10.8, 4.4 Hz, 1 H), 3.25 (bs, 1 H), 3.22 (dd, *J* = 12, 3.6 Hz, 1 H), 3.17−3.08 (m, 3 H), 2.10 (dd, *J* = 11.6, 5.2 Hz, 1 H), 2.06−1.98 (m, 2 H), 1.92−1.83 (m, 4 H), 1.71 (q, *J* = 12 Hz, 1 H), 1.62 (s, 3 H), 1.59−1.45 (m, 5 H), 1.41 (q, *J* = 11.2 Hz, 2 H), 1.33 (s, 3 H), 1.19 (s, 3 H), 1.19−1.18 (m, 1 H), 1.18 (s, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 138.4, 137.3, 134.5, 128.2, 128.2, 127.6, 127.5, 127.5, 127.4, 120.9, 115.7, 113.9, 83.6, 81.9, 79.9, 79.7, 78.9, 77.8, 77.1, 74.7, 73.4, 73.2, 73.0, 71.8, 71.1, 69.5, 66.9, 66.0, 45.1, 40.3, 40.2, 34.9, 31.2, 27.6, 26.9, 22.2, 21.7, 19.7, 17.5, 17.2, 15.8, 15.3; HRMS (ESI TOF) calcd for $C_{49}H_{66}O_9Na$ (M + Na^+) 821.4605, found 821.4694.

Heptacycle 25. To a mixture of **23** (55.7 mg, 71.5 μmol) in benzene (14.3 mL) was added **12** (30 mg, 36 μmol), and the mixture was stirred at 80 °C for 5 h. An additional amount of **12** (120 mg, μ144 mol) was added, and the stirring was continued for 23 h. The mixture was filtered through a short silica gel column (ether), and the filtrate was concentrated. The residue was purified by chromatography (hexane/EtOAc, 20:1) to give **25** (9.6 mg, 83%): amorphous; R_f = 0.38 (hexane/EtOAc, 3:1); $[\alpha]^{26}_D$ −2.24° (*c* 0.48, $CHCl_3$); IR (neat) 2928, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.18 (m, 10 H), 5.66 (dd, *J* = 12.4, 2.4 Hz, 1 H), 5.53 (dd, *J* = 12.4, 2.8 Hz, 1 H), 5.28 (s, 1 H), 4.48 (d, *J* = 11.6 Hz, 1 H), 4.38 (s, 2 H), 4.32 (d, *J* = 11.6 Hz, 1 H), 4.21−4.13 (m, 1 H), 4.12 (ddd, *J* = 9.2, 2.4, 2.4 Hz, 1 H), 4.09−4.04 (m, 1 H), 3.90 (bd, *J* = 9.2 Hz, 1 H), 3.59−3.48 (m, 3 H), 3.42 (dd, *J* = 9.2, 6.0 Hz, 1 H), 3.31−3.21 (m, 3 H), 3.15 (ddd, *J* = 11.6, 8.8, 4.0 Hz, 1 H), 3.09 (dd, *J* = 12.4, 3.6 Hz, 1 H), 3.06−3.00 (m, 1 H), 2.10−1.93 (m, 4 H), 1.91−1.79 (m, 3 H), 1.71−1.60 (m, 2 H), 1.64 (s, 3 H), 1.57−1.47 (m, 2 H), 1.41 (s, 3 H), 1.41−1.34 (m, 1 H), 1.22 (s, 3 H), 1.19−1.17 (m, 1 H), 1.17 (s, 3 H), 1.12 (s, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 138.5, 138.4, 134.5, 131.8, 128.2, 127.6, 127.5, 127.4, 127.4, 121.0, 88.9, 86.2, 84.8, 84.4, 83.6, 80.5, 79.4, 78.1, 77.3, 74.8, 74.0, 73.4, 73.0, 72.9, 71.1, 69.6, 67.0, 66.0, 44.9, 40.3, 40.2, 35.3, 33.5, 31.1, 29.3, 22.7, 20.2, 18.1, 17.6, 17.2, 16.4; HRMS (ESI TOF) calcd for $C_{47}H_{62}O_9Na$ (M + Na^+) 793.4292, found 793.4285.

A−G Ring Segment 2. To a mixture of **25** (9.6 mg, 12.5 μmol), $KO_2CN{=}NCO_2K$ (105 mg, 0.63 mmol), and pyridine (0.86 mL) in MeOH (1 mL) was added AcOH (0.11 mL, 1.9 mmol) slowly via syringe pump (0.04 mL/h). After stirred at room temperature for 3 h, the reaction mixture was quenched with saturated NH_4Cl and filtered with short silica gel column (ether). Concentration and chromatography (hexane/EtOAc, 20:1 to 10:1) gave **2** (8.4 mg, 87%): amorphous; R_f = 0.31 (hexane/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (m, 10 H), 5.34 (brs, 1 H), 4.54 (d, *J* = 11.8 Hz, 1 H), 4.46 (s, 2 H), 4.37 (d, *J* = 11.6 Hz, 1 H), 4.24 (brd, *J* = 16.2 Hz, 1 H), 4.13 (brd, *J* = 16.8 Hz, 1 H), 3.97 (d, *J* = 8.6 Hz, 1 H), 3.66−3.53 (m, 4 H), 3.36 (dd, *J* = 8.3, 5.1 Hz, 1 H), 3.32 (dd, *J* = 11.9, 3.5 Hz, 1 H), 3.28−3.19 (m, 2 H), 3.14 (dd, *J* = 12.4, 3.8 Hz, 1 H), 3.10−3.06 (m, 2 H), 2.13−2.09 (m, 3 H), 2.01−1.90 (m, 4 H), 1.84−1.60 (m, 8 H), 1.70 (s, 3 H), 1.53 (t, *J* = 11.8 Hz, 1 H), 1.40 (t, *J* = 11.5 Hz, 1 H), 1.30 (s, 3 H), 1.27 (s, 3 H), 1.24 (s, 3 H), 1.19 (s, 3 H), 1.03 (d, *J* = 7.1 Hz, 3 H). The ^{1}H NMR data of **2** are identical with those reported previously.[2]

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Supporting Information Available: Copies of ^{1}H NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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