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FORMAL TOTAL SYNTHESIS OF HEMIBREVETOXIN B VIA THE INTRAMOLECULAR ALLYLATION FOLLOWED BY RING-CLOSING METATHESIS

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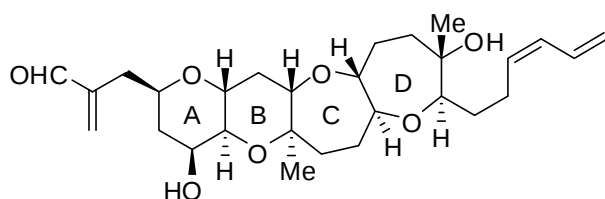
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Dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

Abstract – A formal total synthesis of hemibrevetoxin B (**1**) is described. Intramolecular allylation of α -chloroacetoxy ether **10**, prepared from carboxylic acid **11** and alcohol **12**, was carried out with $\text{MgBr}_2 \cdot \text{OEt}_2$ to give **27**. Ring-closing metathesis of **27** furnished tetracycle **29**, which was converted to a known synthetic intermediate **9**, to complete a formal total synthesis of **1**.

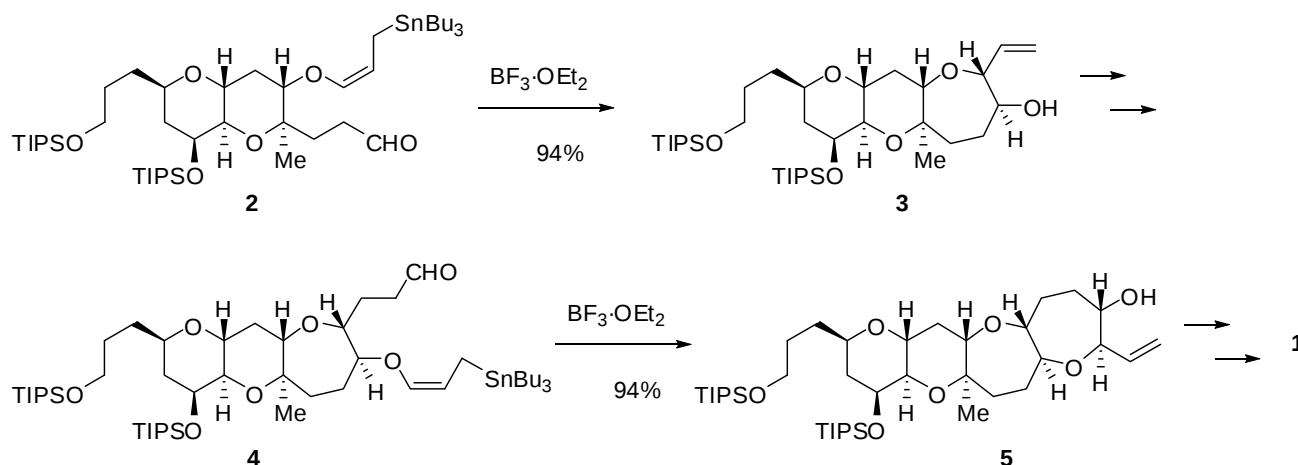
INTRODUCTION

Hemibrevetoxin B (**1**), which has a 6,6,7,7-tetracyclic ether skeleton including ten stereocenters, was isolated from the cultured cells of the red tide organism *Karenia brevis* by Shimizu in 1989.¹ The unique structural features have attracted the attention of synthetic chemists, and a number of strategies have been investigated.²



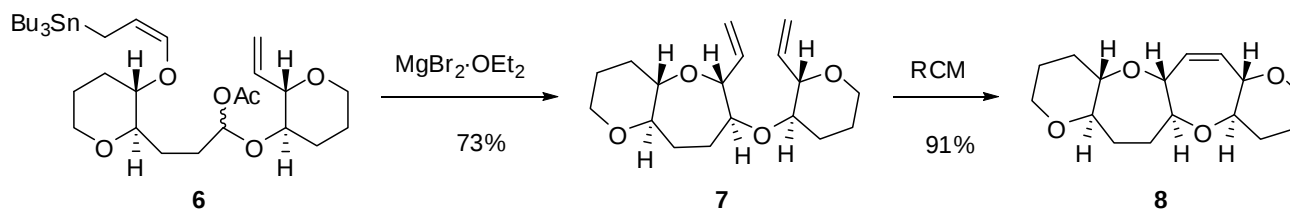
hemibrevetoxin B (**1**)

Previously, we reported a total synthesis of **1** via the Lewis acid mediated intramolecular allylation of aldehydes (Scheme 1).^{2c,e} Treatment of **2** with $\text{BF}_3 \cdot \text{OEt}_2$ gave tricyclic product **3** in 94% yield as a sole product. Similarly, the cyclization of **4** afforded **5**, which was converted to **1** by several steps. Although the target molecule **1** was obtained in relatively high yield (overall 0.75%), the iterative strategy employed makes the synthesis considerably longer (56 steps).



Scheme 1

On the other hand, we recently developed a convergent method for the synthesis of polycyclic ether frameworks via the intramolecular allylation of α -acetoxy ethers and subsequent ring-closing metathesis (RCM).³ A representative result is shown in Scheme 2. Treatment of **6** with $\text{MgBr}_2 \cdot \text{OEt}_2$ gave cyclized product **7**, which was then subjected to ring-closing metathesis (RCM) to furnish 6-7-7-6 fused ring system **8**.

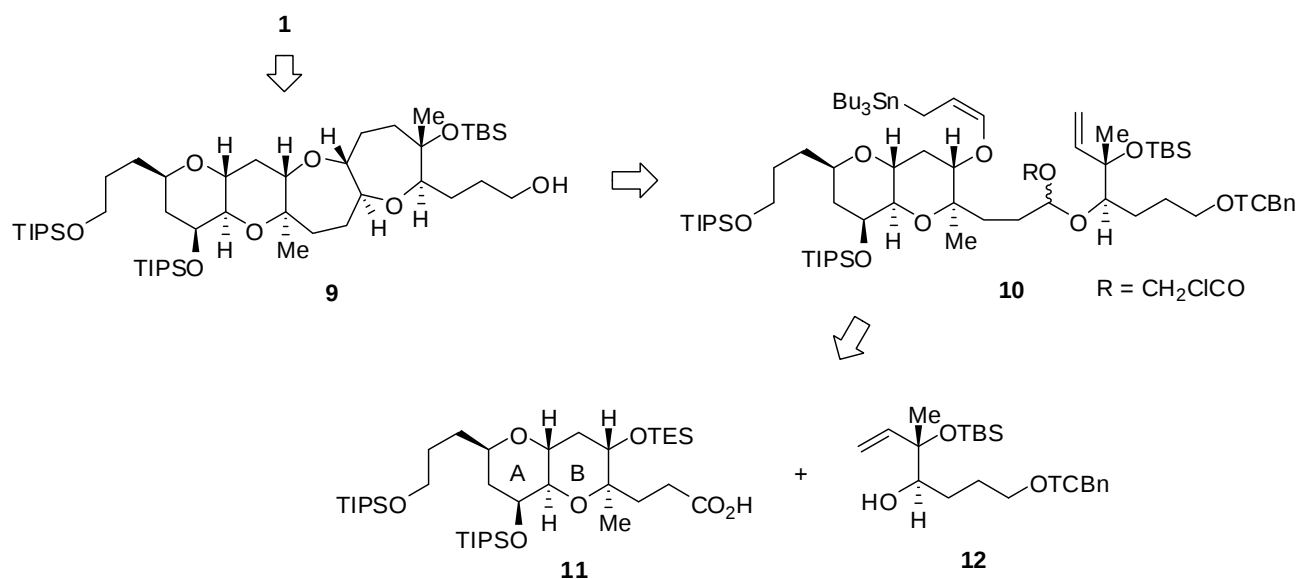


Scheme 2

It was thought that the 6-6-7-7 tetracyclic framework of hemibrevetoxin B (**1**) would be constructed efficiently by using the methodology newly developed. Herein we describe in detail the convergent formal total synthesis of hemibrevetoxin B (**1**).⁴

RESULTS AND DISCUSSION

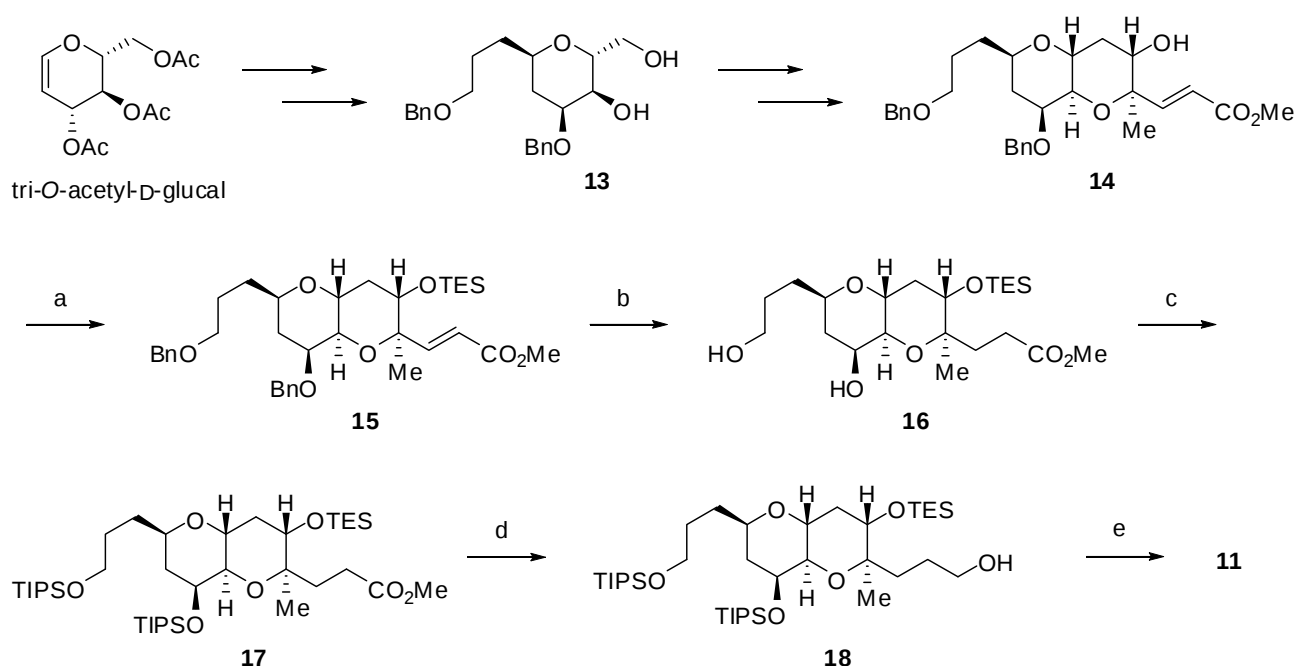
Scheme 3 describes our retrosynthetic analysis of **1**. We focused on the convergent construction of the key intermediate **9**, which was converted to **1** in our previous synthesis, via the intramolecular allylation of α -acetoxy ether **10** followed by ring-closing metathesis. The cyclization precursor **10** would be prepared from carboxylic acid **11** and alcohol **12**.



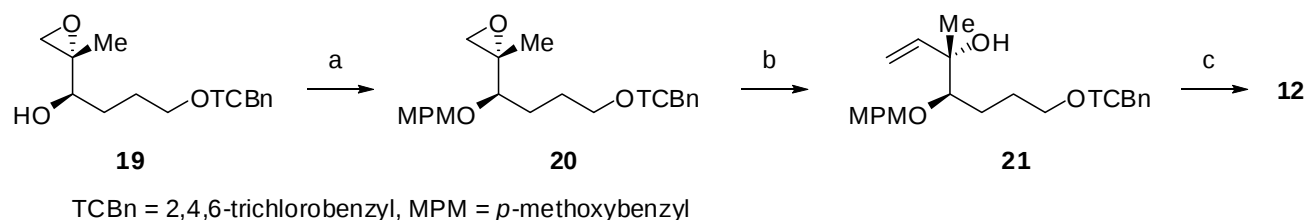
Scheme 3

Synthesis of the AB ring segment **11** is illustrated in Scheme 4. Diol **13**, prepared from tri-*O*-acetyl-D-glucal by the Fujiwara's procedure,^{2j} was converted to the known compound **14** based on a modification of Nicolaou's method.⁵ TES protection of the alcohol **14** gave **15** in quantitative yield. Hydrogenation and debenzoylation of **15** were performed with H₂/Pd(OH)₂-C to give **16**. The resulting diol was protected with TIPSOTf/2,6-lutidine to give **17** in 71% overall yield. Since attempts at the saponification of **17** with aq NaOH gave a complex mixture, preparation of the carboxylic acid **11** was performed stepwisely as shown below. Reduction of the ester **17** with LiAlH₄ afforded alcohol **18** which was subjected to stepwise oxidation to furnish the carboxylic acid **11**, quantitatively.

The D ring precursor **12** was synthesized from epoxide **19** prepared by Fujiwara's procedure (Scheme 3).^{2j} Protection of **19** with MPMCl/NaH gave **20** in 70% yield. Treatment of the epoxide **20** with dimethylsulfonium methylide generated in situ afforded allylic alcohol **21**.⁶ Protection of the resulting tertiary alcohol with TBSOTf/2,6-lutidine followed by removal of the MPM protection provided the alcohol **12** in 41% overall yield (3 steps).



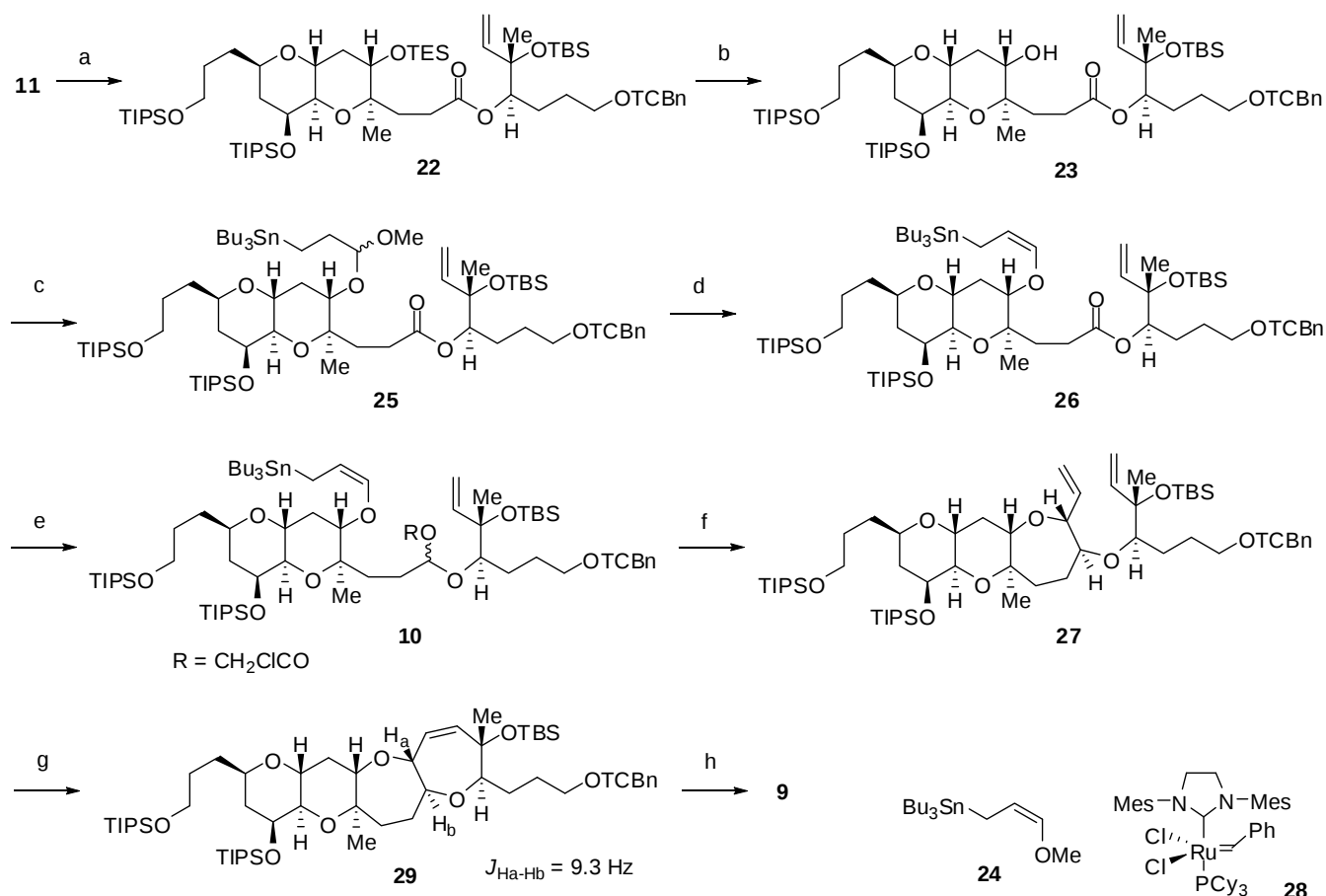
Scheme 4. Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH₂Cl₂, rt, quant; (b) H₂, Pd(OH)₂-C, EtOAc, rt; (c) TIPSOTf, 2,6-lutidine, DMF, rt to 70 °C, 71% (2 steps); (d) LiAlH₄, ether, 0 °C; (e) (i) SO₃·py, DMSO, Et₃N, CH₂Cl₂, 0 °C; (ii) NaClO₂, 2-methyl-2-butene, NaH₂PO₄, THF-H₂O, 0 °C, quant.



Scheme 5. Reagents and conditions: (a) MPMCl, NaH, TBAI, THF, reflux, 70%; (b) Me₃S⁺T⁻, *n*-BuLi, THF, -10 °C to rt; (c) (i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C to rt, 56% (2 steps); (ii) DDQ, CH₂Cl₂, aq NaHCO₃, 35 °C, 73%.

Coupling of the prepared segments is described in Scheme 6. Esterification of the carboxylic acid **11** and the alcohol **12** under Yamaguchi conditions gave ester **22** in 81% overall yield from **18**.⁷ Selective removal of the TES protective group was performed using catalytic CSA in MeOH to afford **23** in 94% yield. Acetalization of **23** with γ -methoxyallylstannane **24** in the presence of CSA afforded mixed acetal **25** in 81% yield. Treatment of **25** with TMSI/HMDS gave allylic stannane **26** in 91% yield.⁸ Modified Rychnovsky acetylation of the ester **26** provided α -acetoxy ether **10** in 65% yield.^{9,10} Intramolecular allylation of **10** was carried out with MgBr₂·OEt₂ to give **27** as a single stereoisomer in 79% yield. Ring-closing metathesis of the diene **27** with the second generation Grubbs' catalyst **28** furnished **29** in 76% yield.¹¹ The stereochemistry of the 7,7'- system was confirmed by ¹H NMR analysis (*J*_{Ha-Hb} = 9.3

Hz). Finally, hydrogenation of the D ring olefin and deprotection of the 2,4,6-trichlorobenzyl (TCBn) group were performed with $\text{H}_2/\text{Pd-C}$ to give the target compound **9** in 68% yield. The physical and spectroscopic data of **9** were identical with those reported previously.^{2e}



Scheme 6. *Reagents and conditions:* (a) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, rt, then **12**, DMAP, toluene, rt, 81% from **18** (4 steps); (b) CSA, MeOH, 0 °C, 94%; (c) **24**, CSA, CH_2Cl_2 , rt, 81%; (d) HMDS, TMSI, CH_2Cl_2 , 0 °C, 91%; (e) DIBAL-H, -78 °C, CH_2Cl_2 , then $(\text{CH}_2\text{ClCO})_2\text{O}$, DMAP, pyridine, -78 °C, 65%; (f) $\text{MgBr}_2 \cdot \text{OEt}_2$, 4Å MS, CH_2Cl_2 , 0 °C, 79%; (g) **28**, benzene, 80 °C, 76%; (h) H_2 , 10% Pd-C, EtOAc, rt, 68%.

In conclusion, we have achieved a convergent formal total synthesis of hemibrevetoxin B (**1**) via the intramolecular allylation of an α -chloroacetoxy ether and ring-closing metathesis. The longest linear sequence leading to the key synthetic intermediate **9** was 35 steps, while our previous synthesis based on a linear synthetic strategy required 49 steps.^{2c,e,12} Application of the present strategy to the synthesis of other marine natural products is in progress.

EXPERIMENTAL

General Methods. All reactions involving air- and/or moisture-sensitive materials were carried out

under argon with dry solvents purchased from Wako or Kanto chemicals. On workup, extracts were dried over MgSO_4 . Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with Kanto Chemical silica gel 60N (40-100 mesh, spherical, neutral). Yields refer to chromatographically and spectroscopically homogeneous materials.

TES Ether 15. To a mixture of the alcohol **14** (726 mg, 1.42 mmol) in CH_2Cl_2 (15 mL) at 0 °C were added 2,6-lutidine (0.83 mL, 7.1 mmol) and TESOTf (0.81 mL, 3.6 mmol). After stirring for 0.5 h at rt, the mixture was quenched with MeOH, diluted with Et_2O , then washed with water and brine. Concentration and chromatography (hexane/EtOAc, 6:1) gave **15** (885 mg, 100%): oil; $R_f = 0.37$ (hexane/EtOAc, 6:1); $[\alpha]_D^{25} +22.1^\circ$ (c 0.69, CHCl_3); IR (neat) 1725, 1661 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.26 (m, 10 H), 7.12 (d, $J = 15.6$ Hz, 1 H), 6.11 (d, $J = 15.6$ Hz, 1 H) 4.79 (d, $J = 12.4$ Hz, 1H), 4.64 (d, $J = 12.4$ Hz, 1H), 4.50 (s, 2H), 3.87-3.78 (m, 3H), 3.75 (s, 3H), 3.60 (dd, $J = 11.5, 4.4$ Hz, 1 H), 3.51-3.47 (m, 2H), 3.36 (dd, $J = 9.8, 2.4$ Hz, 1 H), 2.30-2.23 (m, 1H), 2.03-1.98 (m, 1H), 1.92-1.91 (m, 2H), 1.72-1.61 (m, 2H), 1.30 (s, 3H), 0.96-0.92 (m, 9H), 0.61-0.55 (m, 6H); HRMS (ESI) calcd for $\text{C}_{36}\text{H}_{52}\text{O}_7\text{SiNa}$ ($\text{M}+\text{Na}$) 647.3375, found 647.3376.

Diol 16. A mixture of **15** (885 mg, 1.42 mmol) and $\text{Pd}(\text{OH})_2\text{-C}$ (100 mg) in EtOAc (75 mL) was stirred vigorously under H_2 . After 3 h, the catalyst was filtered off, and the filtrate was concentrated to give **16** which was used for next reaction without purification.

TIPS Ether 17. To a mixture of the alcohol **16** obtained above in CH_2Cl_2 (15 mL) at 0 °C were added 2,6-lutidine (0.66 mL, 5.7 mmol) and TIPSOTf (0.72 mL, 3.6 mmol), and the mixture was refluxed for 10 h. The mixture was then cooled to 0 °C, quenched with MeOH, diluted with Et_2O , then washed with water and brine. Concentration and chromatography (hexane/EtOAc, 10:1) gave **17** (766 mg, 71%): oil; $R_f = 0.27$ (hexane/EtOAc, 10:1); $[\alpha]_D^{25} +29.8^\circ$ (c 1.02, CHCl_3); IR (neat) 1744 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.36 (d, $J = 2.51$ Hz, 1 H), 3.93-3.82 (m, 1H), 3.72-3.67 (m, 3H), 3.66-3.65 (m, 2H), 3.67 (s, 3H), 3.44 (dd, $J = 11.5, 4.4$ Hz, 1H), 3.11 (dd, $J = 9.9, 2.3$ Hz, 1 H), 2.51-2.30 (m, 2H), 1.865-1.823 (m, 2H), 1.695-1.682 (m, 2H), 1.630 (s, 3H), 1.402-1.345 (m, 4H), 1.06-1.05 (m, 42H), 0.62-0.56 (m, 9H), 0.631-0.562 (m, 6H); HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{82}\text{O}_7\text{Si}_3\text{Na}$ ($\text{M}+\text{Na}$) 781.5261, found 781.5260.

Alcohol 18. To a suspension of LiAlH_4 (25 mg, 0.68 mmol) in Et_2O (5 mL) at 0 °C was added dropwise a solution of **17** (330 mg, 0.43 mmol) in Et_2O (5 mL). After stirring for 1 h at the same temperature, the mixture was quenched with a minimum amount of aq NaCl, and the resulting precipitate was filtered off. Concentration and chromatography (hexane/EtOAc, 6:1) gave **18** (310 mg, 99%): oil; $R_f = 0.27$ (hexane/EtOAc, 6:1); $[\alpha]_D^{24} +32.5^\circ$ (c 0.5, CHCl_3); IR (neat) 3600-3200, 1090 cm^{-1} ; ^1H NMR (400 MHz,

CDCl₃) δ 4.23-4.21 (m, 1 H), 3.80-3.71 (m, 1H), 3.70-3.68 (m, 3H), 3.59-3.58 (m, 2H), 3.46 (dd, J = 10.8, 4.2 Hz, 1H) 3.14 (dd, J = 9.2, 2.3 Hz, 1 H), 2.13-1.95 (m, 2H), 1.80-1.76 (m, 2H), 1.68-1.66 (m, 2H), 1.63 (s, 3H), 1.32-1.27 (m, 6H), 1.12-1.05 (m, 42H), 0.96-0.92 (m, 9H), 0.63-0.56 (m, 6H); HRMS (ESI) calcd for C₃₉H₈₂O₆Si₃Na (M+Na) 753.5311, found 753.5312.

Carboxylic Acid 11. To a mixture of **18** (97 mg, 0.13 mmol), DMSO (0.4 mL), Et₃N (90 μ L, 0.65 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added SO₃·py (63 mg, 0.38 mmol), and the mixture was stirred for 3h. The reaction mixture was diluted with Et₂O, then washed with water and brine. Concentration gave the crude aldehyde, which was used for next reaction directly.

To a mixture of the aldehyde obtained above in *t*-BuOH (1 mL) were added 2-methyl-2-butene (1 mL) and NaClO₂ (45 mg, 0.39 mmol) in 5% NaH₂PO₄ (1 mL), and the mixture was stirred vigorously for 1 h at rt. The mixture diluted with Et₂O, then washed with water and brine. Concentration gave crude **11**, which was used for next esterification directly.

MPM Ether 20. To a stirred suspension of NaH (110 mg of a 60 % suspension in mineral oil, 2.7 mmol, prewashed with hexane) in THF (3 mL) at rt were added MPMCl (0.18 mL, 1.33 mmol), a solution of **19** (300 mg, 0.88 mmol) in THF (9 mL), and Bu₄NI (400 mg, 1.1 mmol), and the mixture was refluxed for 14 h. After cooling to 0 °C, the reaction mixture was quenched with MeOH, diluted with Et₂O, then washed with water and brine. Concentration and chromatography (hexane/EtOAc, 4:1) gave **20** (380 mg, 70%): oil; R_f = 0.53 (hexane/EtOAc, 10:1); $[\alpha]_D^{23}$ +10.5 ° (c 0.5, CHCl₃); IR (neat) 3040 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (s, 2H), 7.28-7.21 (m, 2H), 6.87-6.84 (m, 2H), 4.67 (s, 2H), 4.58 (d, J = 11.0 Hz, 1H), 4.35 (d, J = 11.0 Hz, 1H), 3.80 (s, 3H), 3.51 (m, 2H), 3.02-3.00 (m, 1H), 2.72 (d, J = 5.1 Hz, 1H), 2.63 (d, J = 5.1 Hz, 1H), 1.86-1.58 (m, 4H), 1.30 (s, 3H); HRMS calcd for C₂₂H₂₅Cl₃O₄SiNa (M+Na) 489.1157, found 489.1155.

Olefine 21. To a suspension of Me₃S⁺I⁻ (400 mg, 1.96 mmol) in THF (2 mL) at -10 °C was added *n*-BuLi (1.56 M in hexane, 1.26 mL, 1.96 mmol), and the mixture was stirred for 30 min at the same temperature. A solution of **20** (180 mg, 0.39 mmol) in THF (3 mL) was introduced to the resulting mixture, and the stirring was continued for 10 h at rt. The reaction mixture was quenched with water and extracted with ether. The organic layer was washed brine, and concentrated to give crude **21** which was used for next reaction directly.

Alcohol 12. To a mixture of the olefine obtained above in CH₂Cl₂ (3 mL) at 0 °C was added 2,6-lutidine (80 μ L, 0.69 mmol) and TBSOTf (82 μ L, 0.46 mmol). After stirring at rt, the reaction mixture was quenched with MeOH at 0 °C, diluted with Et₂O, then washed with water and brine. Concentration and

chromatography (hexane/EtOAc, 40:1) gave the corresponding TBS ether (130 mg, 57%): oil; $R_f = 0.27$ (hexane/EtOAc, 40:1); $[\alpha]_D^{23} +17.3^\circ$ (c 0.6, CHCl_3); IR (neat) 3600-3200, 3030 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (s, 2H), 7.24-7.19 (m, 2H), 6.83-6.81 (m, 2H), 6.00 (dd, $J = 17.7, 10.8$ Hz, 1H), 5.19 (dd, $J = 17.7, 1.1$ Hz, 1H), 5.09 (dd, $J = 10.8, 1.1$ Hz, 1H), 4.65 (s, 2H), 4.62 (d, $J = 10.4$ Hz, 1H), 4.42 (d, $J = 10.4$ Hz, 1H), 3.77 (s, 3H), 3.53-3.41 (m, 2H), 3.18-3.16 (m, 1H), 1.83-1.55 (m, 3H), 1.41-1.33 (m, 1H), 1.27 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H); HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{41}\text{Cl}_3\text{O}_4\text{SiNa}$ ($\text{M}^+ \text{Na}$) 609.1732, found 609.1730.

To a mixture of the TBS ether obtained above (130 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) and aq NaHCO_3 (0.3 mL) was added DDQ (70 mg, 0.33 mmol), and the mixture was stirred for 2 h at rt. The mixture was diluted with Et_2O , then washed with aq NaHCO_3 and brine. Concentration and chromatography (hexane/EtOAc, 10:1) gave **12** (73mg, 73%): oil; $R_f = 0.26$ (hexane/EtOAc, 10:1); $[\alpha]_D^{23} +0.37^\circ$ (c 0.5, CHCl_3); IR (neat) 3600-3200 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (s, 2H), 5.89 (dd, $J = 17.6, 11.0$ Hz, 1H), 5.16 (dd, $J = 17.6, 1.3$ Hz, 1H), 5.12 (dd, $J = 11.0, 1.3$ Hz, 1H), 4.67 (s, 2H), 3.61-3.47 (m, 2H), 3.31-3.27 (m, 1H), 1.83-1.75 (m, 1H), 1.63-1.47 (m, 2H), 1.29 (s, 3H), 1.21-1.13 (m, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{33}\text{Cl}_3\text{O}_3\text{SiNa}$ ($\text{M}^+ \text{Na}$) 489.1157, found 489.1155.

Ester 22. To a solution of **11** (0.21 mmol) in THF (2 mL) were added Et_3N (89 μL , 0.63 mmol) and 2,4,6-trichlorobenzoyl chloride (78 μL , 0.5 mmol). After stirring for 2 h at rt, the mixture was concentrated under reduced pressures and diluted with toluene (3 mL). A solution of **12** (108 mg, 0.23 mmol) and DMAP (128 mg, 1.05 mmol) in toluene (3 mL) was added, and the mixture was stirred for 0.5 h at rt. The mixture was diluted with ether, then washed with water and brine. Concentration and chromatography (hexane/EtOAc, 15:1) gave **22** (204 mg, 81%): $R_f = 0.21$ (hexane/EtOAc, 15:1); $[\alpha]_D^{25} +19.1^\circ$ (c 1.56, CHCl_3); IR (neat) 1737 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 2H), 5.76 (dd, $J = 17.3, 10.8$ Hz, 1H), 5.09 (dd, $J = 17.3, 1.1$ Hz, 1H), 4.99 (dd, $J = 10.8, 1.1$ Hz, 1H), 4.59 (s, 2H), 4.16-4.13 (m, 1H), 3.73-3.61 (m, 4H), 3.42-3.40 (m, 4H), 3.05 (dd, $J = 9.7, 2.6$ Hz, 1H), 2.33-2.27 (m, 2H), 1.96-1.89 (m, 3H), 1.73-1.69 (m, 3H), 1.60-1.19 (m, 14H), 1.06-0.79 (m, 60 H), 0.55-0.49 (m, 6H), 0.03 (s, 6H); HRMS (ESI) calcd for $\text{C}_{60}\text{H}_{111}\text{Cl}_3\text{O}_9\text{Si}_4\text{Na}$ ($\text{M}^+ \text{Na}$) 1215.6263, found 1215.6272.

Alcohol 23. To a solution of **22** (86 mg, 72 μmol) in MeOH (0.5 mL) and CH_2Cl_2 (0.5 mL) at 0°C was added CSA (3.3 mg, 14 μmol). After stirring for 15 min at the same temperature, the reaction mixture was quenched with Et_3N , diluted with Et_2O , then washed with aq NaHCO_3 and brine. Concentration and chromatography (hexane/EtOAc, 10:1) gave **23** (73 mg, 94%): oil; $R_f = 0.25$ (hexane/EtOAc, 5:1); $[\alpha]_D^{25} +28.7^\circ$ (c 0.6, CHCl_3); IR (neat) 3600-3200, 1739 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 2H), 5.76 (dd, $J = 17.3, 10.7$ Hz, 1 H), 5.10 (dd, $J = 17.3, 1.0$ Hz, 1 H), 5.01 (dd, $J = 10.7, 1.0$ Hz, 1 H),

4.76-4.59 (m, 2H), 4.17-4.13 (m, 1H), 3.74-3.61 (m, 5H), 3.43-3.34 (m, 3H), 3.09 (dd, $J=9.8, 2.4$ Hz, 1 H), 2.29-2.23 (m, 2H), 2.00-1.70 (m, 5H), 1.57-1.45 (m, 9H), 1.37-1.34 (m, 1H), 1.19 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 1.00-0.97 (m, 42H), 0.78 (s, 9H), 0.03-0.01 (m, 6H); HRMS (ESI) calcd for $C_{54}H_{97}Cl_3O_9Si_3Na$ (M+Na) 1101.5398, found 1101.5402.

Mixed Acetal 25. To a mixture of **23** (56 mg, 52 μ mol) and **24** (49 μ L, 0.16 mmol) in CH_2Cl_2 (0.5 mL) at rt was added CSA (2.3 mg, 10 μ mol). After stirring for 2 h, the reaction mixture was quenched with Et_3N and filtered through alumina pad. Concentration and chromatography (hexane/EtOAc, 10:1) gave **25** (63 mg, 81%) as a mixture of stereoisomers: oil; $R_f = 0.31$ (hexane/EtOAc, 10:1); IR (neat) 1737 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 2H), 5.77 (dd, $J=17.3, 10.5$ Hz, 1H), 5.09 (dd, $J=17.3, 1.2$ Hz, 1 H), 5.00 (dd, $J=10.5, 1.2$ Hz, 1 H), 4.813-4.701 (m, 1H), 4.60 (s, 2 H), 4.38-4.33 (m, 1H), 4.15 (s, 1H), 3.63-3.62 (m, 3H), 3.41-3.36 (m, 3H), 3.27-3.07 (m, 5H), 2.56-1.82 (m, 6H), 1.73-1.59 (m, 8H), 1.56-0.73 (m, 92H), 0.07 (s, 6H); HRMS (ESI) calcd for $C_{70}H_{131}Cl_3O_{10}Si_3SnNa$ (M+Na) 1463.7030, found 1463.7041.

Allylic Stannane 26. To a mixture of **25** (63 mg, 43 μ mol) in CH_2Cl_2 (0.5 mL) at 0 °C were added HMDS (90 μ L, 0.43 mmol) and TMSI (30 μ L, 0.22 mmol). After stirring for 1 h at the same temperature, the reaction mixture was quenched with satd aq $NaHCO_3$, and extracted with Et_2O . Concentration and chromatography (hexane/EtOAc, 20:1 containing 1% Et_3N) gave **26** (58 mg, 91%): oil; oil; $R_f = 0.34$ (hexane/EtOAc, 20:1); $[\alpha]_D^{30} +19.0^\circ$ (c 1.00, $CHCl_3$); IR (neat) 1738 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 2H), 5.78-5.67 (m, 2H), 5.10 (dd, $J=17.4, 1.1$ Hz, 1H), 5.00 (dd, $J=10.9, 1.1$ Hz, 1H), 4.75-4.72 (m, 1H), 4.58 (s, 2H), 4.47-4.41 (m, 1H), 4.16-4.15 (m, 1H), 3.76-3.73 (m, 1H), 3.64-3.61 (m, 3H), 3.37-3.18 (m, 3H), 3.11-3.07 (m, 1H), 2.39-2.28 (m, 3H), 2.09-1.91 (m, 3H), 1.73-1.340 (m, 15H), 1.26-1.18 (m, 12H), 1.13 (s, 3H), 1.02-0.73 (m, 66H), 0.01 (s, 6H); HRMS (ESI) calcd for $C_{69}H_{127}Cl_3O_9Si_3SnNa$ (M+Na) 1431.6768, found 1431.6763.

Acetoxy Ether 10. To a solution of **26** (58 mg, 41 μ mol) in CH_2Cl_2 (1.5 mL) at -78 °C was added DIBALH (0.94 M in hexane, 0.18 mL, 0.17 mmol), and the mixture was stirred for 5 min at the same temperature. A mixture of $(ClCH_2CO)_2O$ (170 mg, 1.0 mmol), DMAP (42 mg, 0.34 mmol) and pyridine (40 μ L, 0.5 mmol) in CH_2Cl_2 (1 mL) was added, and the resulting mixture was allowed to warm to 0 °C. The reaction mixture was then quenched with water and diluted with ether. The organic layer was washed with potassium sodium tartrate, aq $CuSO_4$, satd aq $NaHCO_3$, and brine. Concentration and chromatography (hexane/EtOAc, 20:1 containing 1% Et_3N) gave **10** (40 mg, 65%) as a mixture of stereoisomers: oil; $R_f = 0.29$ (hexane/EtOAc, 20:1); 1H NMR (400 MHz, C_6D_6) δ 6.92 (s, 2H), 5.78-5.64 (m, 2H), 5.05 (dd, $J=17.6, 1.2$ Hz, 1H), 4.97 (dd, $J=10.4, 2.3$ Hz, 1H), 4.91 (dd, $J=10.9, 1.2$ Hz, 1H),

4.68-4.58 (m, 1H), 4.40 (s, 2H), 4.11-4.00 (m, 2H), 3.91-3.86 (m, 1H), 3.77-3.66 (m, 5H), 3.52-3.40 (m, 3H), 3.14-3.11 (m, 1H), 2.55-2.30 (m, 2H), 1.89-0.93 (m, 100H), 0.05-0.03 (m, 6H).

IR and HRMS data for **10** were not collected for lack of stability.

Diene 27. To a stirred suspension of $\text{MgBr}_2 \cdot \text{OEt}_2$ (2.5 mg, 9.7 μmol) and MS4A (10 mg) in CH_2Cl_2 (0.5 mL) at 0 °C was added **10** (3.6 mg, 2.4 μmol) in CH_2Cl_2 (0.5 mL). After stirring for 40 min at the same temperature, the mixture was quenched with Et_3N and filtered through a short silica gel column. Concentration and chromatography (hexane/EtOAc, 6:1) gave **27** (2.1 mg, 79%): oil; $R_f = 0.33$ (hexane/EtOAc, 6:1); $[\alpha]_D^{25} +8.03^\circ$ (c 0.235, CHCl_3); IR (neat) 2941, 1096 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.29 (s, 2H), 5.87 (dd, $J = 17.3, 10.3$ Hz, 1H), 5.63-5.59 (m, 1H), 5.19-4.93 (m, 4H), 4.64 (s, 2H), 4.24-4.23 (m, 1H), 4.11-4.10 (m, 1H), 3.86-3.68 (m, 1H), 3.66-3.60 (m, 4H), 3.52-3.43 (m, 3H), 3.10-3.01 (m, 2H), 1.93-1.90 (m, 3H), 1.76-1.72 (m, 3H), 1.58-1.23 (m, 16H), 1.14-1.02 (m, 42H), 0.88-0.80 (m, 9H), 0.03-0.01 (m, 6H); HRMS (ESI) calcd for $\text{C}_{57}\text{H}_{101}\text{Cl}_3\text{O}_8\text{Si}_3\text{Na}$ ($\text{M}+\text{Na}$) 1125.5762, found 1125.5727.

Tetracycle 29. A mixture of **27** (4.6 mg, 4.2 μmol) and **28** (18 mg, 21 μmol) in benzene (0.5 mL) was stirred at 80 °C in a sealed vial. After 18 h, the mixture was filtered through a short silica gel column. Concentration and chromatography (hexane/EtOAc, 20:1) gave **29** (3.2 mg, 76%): oil; $R_f = 0.33$ (hexane/EtOAc, 10:1); $[\alpha]_D^{25} +11.1^\circ$ (c 0.38, CHCl_3); IR (neat) 2926, 1096 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.26 (s, 2H), 5.57 (dd, $J = 13.2, 2.6$ Hz, 1H), 5.36 (dd, $J = 13.2, 1.8$ Hz, 1H), 4.62 (s, 2H), 4.13-4.11 (m, 1H), 3.86 (Ha, ddd, $J = 9.3, 2.3, 2.3$ Hz, 1H), 3.73-3.60 (m, 4H), 3.49-3.44 (m, 2H), 3.29-3.19 (m, 3H), 3.13 (dd, $J = 9.8, 2.4$ Hz, 1H), 2.28-2.22 (m, 2H), 1.96-1.86 (m, 4H), 1.71-1.49 (m, 10H), 1.18-0.95 (m, 57H), 0.75 (s, 6H); HRMS (ESI) calcd for $\text{C}_{55}\text{H}_{97}\text{Cl}_3\text{O}_8\text{Si}_3\text{Na}$ ($\text{M}+\text{Na}$) 1097.5449, found 1097.5455.

Alcohol 9. A mixture of **29** (1.8 mg, 1.7 μmol) and 10% Pd-C (20 mg) in AcOEt (1.5 mL) was stirred under H_2 . After 4 h, the catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to give **9** (1.0 mg, 68%). The ^1H NMR data of **9** is identical with that reported previously.

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