HETEROCYCLES, Vol. 74, 2007, pp. 617 -627. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd August, 2007, Accepted, 12th October, 2007, Published online, 16th October, 2007. COM-7-S(W)39

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

Isao Kadota,[a,*] Takashi Abe,[b] Yukako Ishitsuka,[b] Abeda S. Touchy,[b] Ryoko Nagata,[b] and Yoshinori Yamamoto[b]

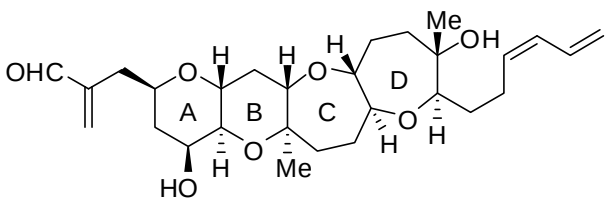
[a]Department of Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Okayama 700-8530, Japan
[b]Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan
kadota-i@cc.okayama-u.ac.jp

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 $MgBr_2 \cdot OEt_2$ 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**.

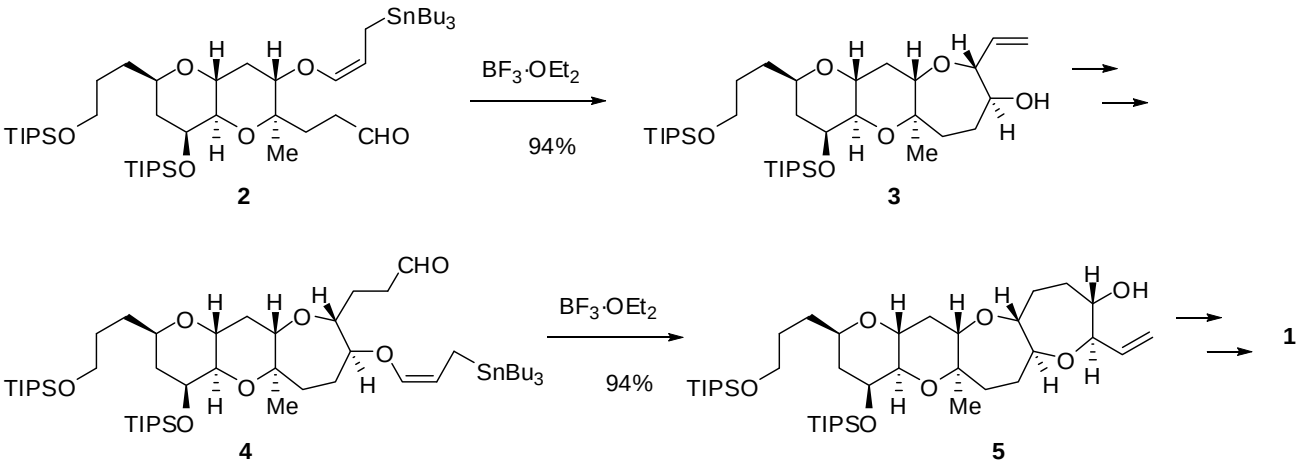
INTRODUCTION

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]



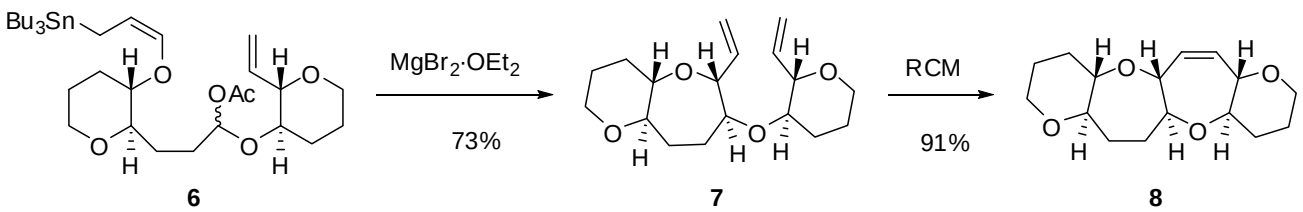
hemibrevetoxin B (**1**)

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 $BF_3{\cdot}OEt_2$ 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 $MgBr_2{\cdot}OEt_2$ gave cyclized product **7**, which was then subjected to ring-closing metathesis (RCM) to furnish 6-7-7-6 fused ring system **8**.

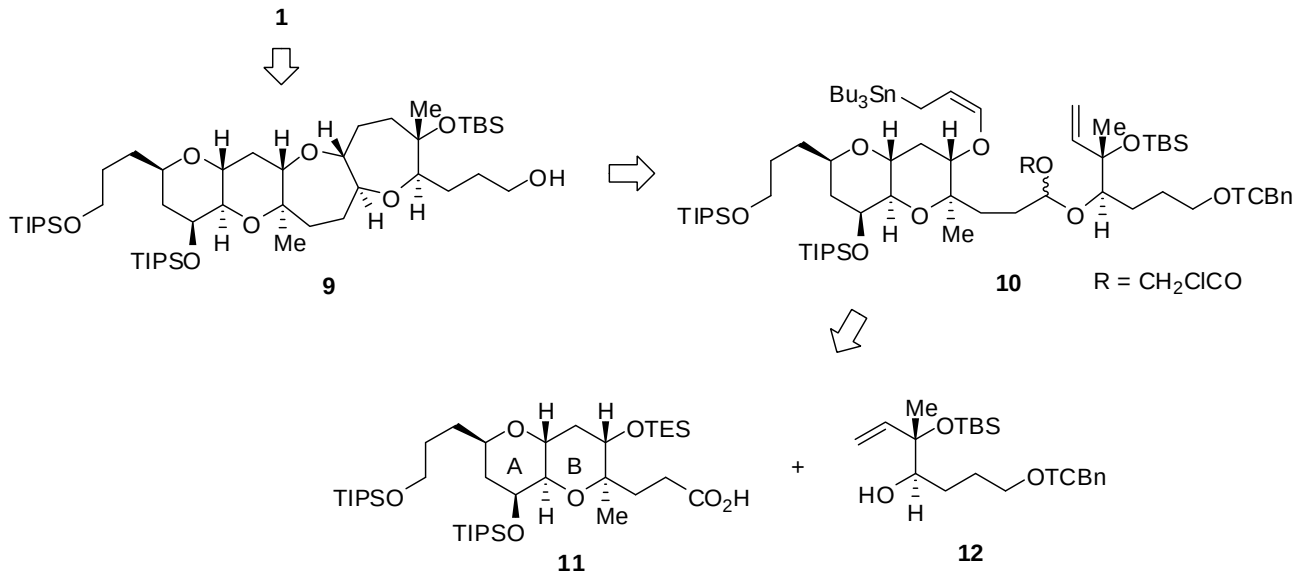


Scheme 2

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

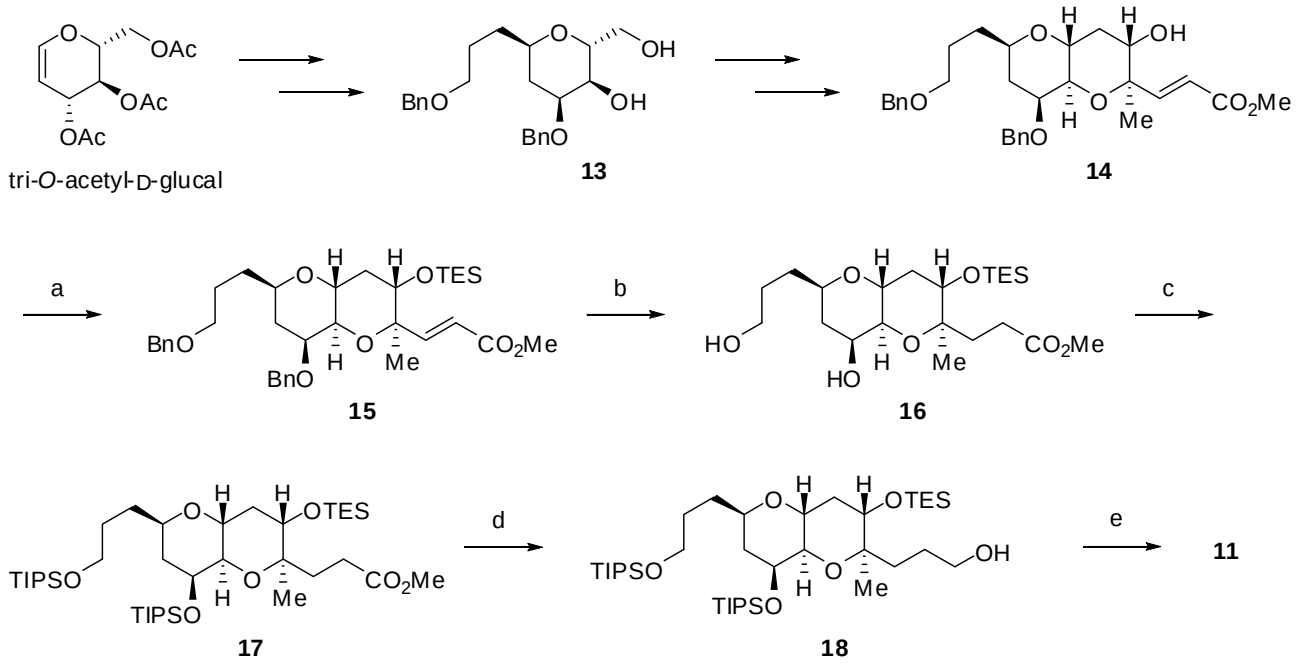
Scheme 3 describes our retrosynthetic analysis of **1**. We focused on the convergent construction of the key intermediate **9**, which was converted to **1** in our previous synthesis, via the intramolecular allylation of α-acetoxy ether **10** followed by ring-closing metathesis. The cyclization precursor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



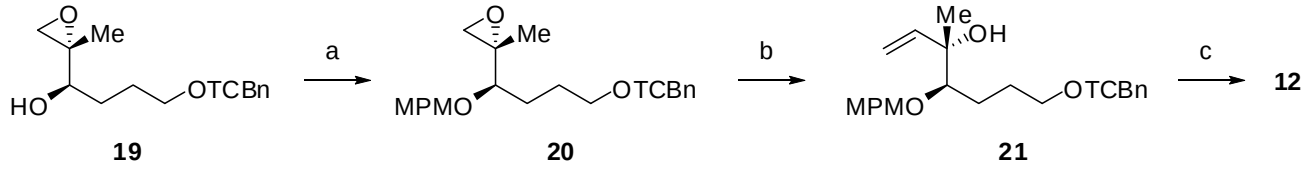
Scheme 3

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 debenzylation of **15** were performed with H_2/$Pd(OH)_2$-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 $LiAlH_4$ 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, CH_2Cl_2, rt, quant; (b) H_2, $Pd(OH)_2$-C, EtOAc, rt; (c) TIPSOTf, 2,6-lutidine, DMF, rt to 70 °C, 71% (2 steps); (d) $LiAlH_4$, ether, 0 °C; (e) (i) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C; (ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, THF-H_2O, 0 °C, quant.

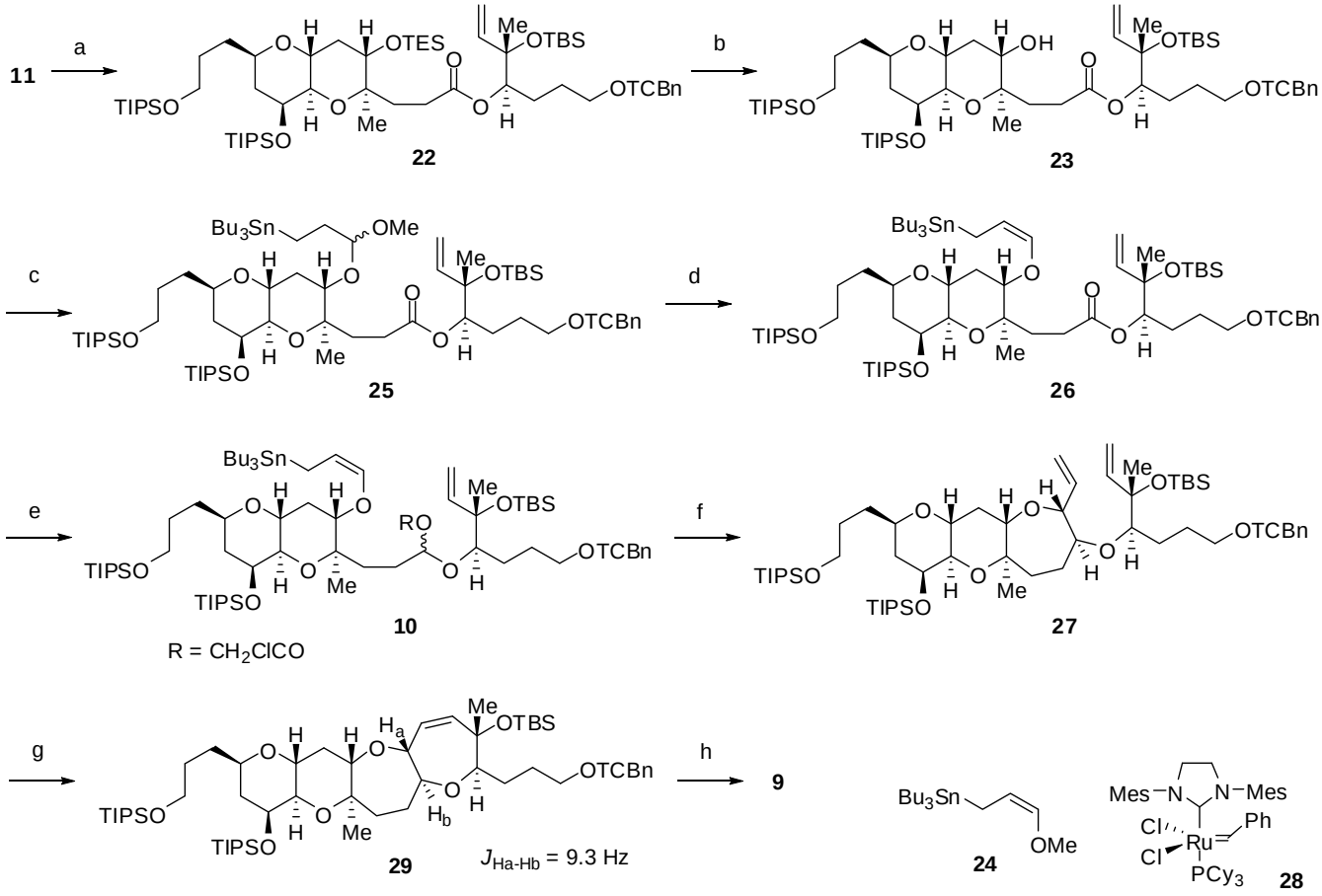


TCBn = 2,4,6-trichlorobenzyl, MPM = *p*-methoxybenzyl

Scheme 5. *Reagents and conditions:* (a) MPMCl, NaH, TBAI, THF, reflux, 70%; (b) $Me_3S^+I^-$, *n*-BuLi, THF, -10 ºC to rt; (c) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC to rt, 56% (2 steps); (ii) DDQ, CH_2Cl_2, aq $NaHCO_3$, 35 ºC, 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 $MgBr_2$·OEt_2 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 ^{1}H NMR analysis ($J_{Ha\text{-}Hb}$ = 9.3

Hz). Finally, hydrogenation of the D ring olefin and deprotection of the 2,4,6-trichlorobenzyl (TCBn) group were performed with H_2/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 ºC, 94%; (c) **24**, CSA, CH_2Cl_2, rt, 81%; (d) HMDS, TMSI, CH_2Cl_2, 0 ºC, 91%; (e) DIBAL-H, -78 ºC, CH_2Cl_2, then $(CH_2ClCO)_2O$, DMAP, pyridine, -78 ºC, 65%; (f) $MgBr_2 \cdot OEt_2$, 4Å MS, CH_2Cl_2, 0 ºC, 79%; (g) **28**, benzene, 80 ºC, 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 imtermediate **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 ºC 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); $[\alpha]^{31}_D$ +22.1 º (*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 $C_{36}H_{52}O_7SiNa$ (M+Na) 647.3375, found 647.3376.

Diol 16. A mixture of **15** (885 mg, 1.42 mmol) and $Pd(OH)_2$-C (100 mg) in EtOAc (75 mL) was stirred vigolously 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 ºC 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 ºC, 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); $[\alpha]^{25}_D$ +29.8 º (*c* 1.02, $CHCl_3$) ; IR (neat) 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (d, *J* = 2.51Hz, 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 $C_{40}H_{82}O_7Si_3Na$ (M+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 ºC 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); $[\alpha]^{24}_D$ +32.5 º (*c* 0.5, $CHCl_3$); IR (neat) 3600-3200, 1090 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) 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 $C_{39}H_{82}O_6Si_3Na$ (M+Na) 753.5311, found 753.5312.

Carboxylic Acid 11. To a mixture of **18** (97 mg, 0.13 mmol), DMSO (0.4 mL), Et_3N (90 μL, 0.65 mmol) in CH_2Cl_2 (2 mL) at 0 ºC was added SO_3·py (63 mg, 0.38 mmol), and the mixture was stirred for 3h. The reaction mixture was diluted with Et_2O, then washed with water and brine. Concentration gave the crude aldehyde, which wasa 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 $NaClO_2$ (45 mg, 0.39 mmol) in 5% NaH_2PO_4 (1 mL), and the mixture was stirred vigorously for 1 h at rt. The mixture diluted with Et_2O, 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 Bu_4NI (400 mg, 1.1 mmol), and the mixture was refluxed for 14 h. After cooloing to 0 ºC, the reaction mixture was quenched with MeOH, diluted with Et_2O, 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); $[\alpha]^{23}_D$ +10.5 º (*c* 0.5, $CHCl_3$) ; IR (neat) 3040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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 $C_{22}H_{25}Cl_3O_4SiNa$ (M+Na) 489.1157, found 489.1155.

Olefine 21. To a suspension of $Me_3S^+I^-$ (400 mg, 1.96 mmol) in THF (2 mL) at -10 ºC 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 CH_2Cl_2 (3 mL) at 0 ºC was added 2,6-lutidine (80 μL, 0.69 mmol) and TBSOTf (82 μL, 0.46 mmol). After stirring at rt, the reaction mixture was quenched with MeOH at 0 ºC, diluted with Et_2O, 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); $[\alpha]^{23}_D$ +17.3 º (*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 $C_{29}H_{41}Cl_3O_4SiNa$ (M+ 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); $[\alpha]^{23}_D$ +0.37 º (*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 $C_{21}H_{33}Cl_3O_3SiNa$ (M+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); $[\alpha]^{25}_D$ +19.1 º (*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 $C_{60}H_{111}Cl_3O_9Si_4Na$ (M+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 ºC 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); $[\alpha]^{25}_D$ +28.7 º (*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 μmol) and **24** (49 μL, 0.16 mmol) in CH_2Cl_2 (0.5 mL) at rt was added CSA (2.3 mg, 10 μmol). 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 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C were added HMDS (90 μL, 0.43 mmol) and TMSI (30 μL, 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); $[\alpha]^{30}_D$ +19.0 º (*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 μmol) in CH_2Cl_2 (1.5 mL) at -78 ^oC was added DIBALH (0.94 M in hexane, 0.18 mL, 0.17 mmol), and the mixture was stirred for 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 μL, 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 $MgBr_2 \cdot OEt_2$ (2.5mg, 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 thorght a short silica gel column. Concentration and chromatohraphy (hexane/EtOAc, 6:1) gave **27** (2.1 mg, 79%): oil; R_f = 0.33 (hexane/EtOAc, 6:1); $[\alpha]^{25}_D$ +8.03 º (*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 $C_{57}H_{101}Cl_3O_8Si_3Na$ (M+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 ºC 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); $[\alpha]^{25}_D$ +11.1 º (*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 $C_{55}H_{97}Cl_3O_8Si_3Na$ (M+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.

ACKNOWLEDGEMENTS

This work was financially supported by the Novartis Foundation for the Promotion of Science, the Kurata Memorial Hitachi Science and Technology Foundation, the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

REFERENCES AND NOTES

1. A. V. K. Prasad and Y. Shimizu, *J. Am. Chem. Soc.,* 1989, **111**, 6476.
2. For total syntheses of hemibrevetoxin B, see: (a) K. C. Nicolaou, K. R. Reddy, G. Skokotas, F. Sato, and X.-Y. Xiao, *J. Am. Chem. Soc.,* 1992, **114**, 7935. (b) K. C. Nicolaou, K. R. Reddy, G. Skokotas, F. Sato, X.-Y. Xiao, and C.-K. Hwang, *J. Am. Chem. Soc.,* 1993, **115**, 3558. (c) I. Kadota, J.-Y. Park, N. Koumura, G. Pollaud, Y. Matsukawa, and Y. Yamamoto, *Tetrahedron Lett.,* 1995, **36**, 5777. (d) M. Morimoto, H. Matsukura, and T. Nakata, *Tetrahedron Lett.,* 1996, **37**, 6365. (e) I. Kadota and Y. Yamamoto, *J. Org. Chem.,* 1998, **63**, 6597. (f) A. Zakarian, A. Batch, and R. A. Holton, *J. Am. Chem. Soc.,* 2003, **125**, 7822. For formal syntheses, see: (g) Y. Mori, K. Yaegashi, and H. Furukawa, *J. Am. Chem. Soc.,* 1997, **119**, 4557. (h) Y. Mori, K. Yaegashi, and H. Furukawa, *J. Org. Chem.,* 1998, **63**, 6200. (i) J. D. Rainier, S. P. Allwein, and J. M. Cox, *J. Org. Chem.,* 2001, **66**, 1380. (j) K. Fujiwara, D. Sato, M. Watanabe, H. Morishita, A. Murai, H. Kawai, and T. Suzaki, *Tetrahedron Lett.,* 2004, **45**, 5243.
3. I. Kadota, A. Ohno, K. Matsuda, and Y. Yamamoto, *J. Am. Chem. Soc.,* 2002, **124**, 3562.
4. For a preliminary communication, see: I. Kadota, T. Abe, Y. Ishitsuka, A. S. Touchy, R. Nagata, and Y. Yamamoto, *Tetrahedron Lett*., 2007, **48**, 219.
5. K. C. Nicolaou, C.-K. Hwang, and M. E. Duggan, *J. Am. Chem. Soc.,* 1989, **111**, 6682.
6. L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Le Gall, D.-S. Shin, and J. R. Falck, *Tetrahedron Lett.,* 1994, **35**, 5449.
7. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.,* 1979, **52**, 1989.
8. I. Kadota, T. Sakaihara, and Y. Yamamoto, *Tetrahedron Lett*., 1996, **37**, 3195.
9. I. Kadota, H. Takamura, K. Sato, A. Ohno, K. Matsuda, and Y. Yamamoto, *J. Am. Chem. Soc.,* 2003, **125**, 46.
10. For the original conditions, see: (a) V. H. Dahanukar and S. D. Rychnovsky, *J. Org. Chem.,* 1996, **61**, 8317. (b) D. J. Kopecky and S. D. Rychnovsky, *J. Org. Chem.,* 2000, **65**, 191. (c) D. J. Kopecky, and S. D. Rychnovsky, *Org. Synth.,* 2003, **80**, 177
11. M. Scholl, S. Ding, C. W. Lee, and R. H. Grubbs, *Org. Lett.,* 1999, **1**, 953.
12. Seven steps are required to complete the total syntheis of **1** from **9**.