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Published on Web 06/01/2005

Total Synthesis of Brevetoxin B

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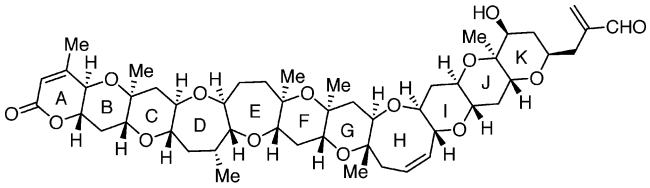
Abstract: The convergent total synthesis of brevetoxin B (**1**) has been achieved. The intramolecular allylation of the *O*,*S*-acetal **20**, prepared from the α-chlorosulfide **17** and the alcohol **5**, was carried out using AgOTf as a Lewis acid to give the diene **21**, predominantly. Ring-closing metathesis of **21** with the Grubbs catalyst **23** afforded the hexacyclic ether **25** which was converted to the A−G ring segment **2** through several steps. The intramolecular allylation of the α-acetoxy ether **42**, prepared from **2** and the J−K ring segment **3**, followed by ring-closing metathesis provided the polycyclic ether framework **44**. A series of reactions of **44**, including oxidation of the A ring, deprotection of the silyl ethers, and selective oxidation of the resulting allylic alcohol, furnished **1**.

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 from synthetic chemists. To date, two total syntheses of **1** have been accomplished using a hydroxy dithioacetal cyclization for the key segment connection.[2] In this paper, we wish to report a convergent total synthesis of **1** based on our own methodology.



Brevetoxin B (**1**)

Figure 1. Structure of Brevetoxin B (**1**).

Results and Discussion

Retrosynthetic Analysis. A brief retrosynthetic analysis of **1** is illustrated in Scheme 1. We have developed a convergent method for the synthesis of polycyclic ether frameworks via the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis.[3] On the basis of this methodology, the polycyclic ether framework of **1** was retrosynthetically broken down into the A−G ring segment **2** and the J−K fragment **3**. The heptacycle **2** would be prepared from **4** and **5** via the same methodology.

Synthesis of the B−C Ring Segment 4. Scheme 2 describes the synthesis of the B−C ring segment **4**. Conversion of the lactone **6**[4] into the corresponding ketene acetal triflate **7** via the standard conditions followed by treatment with the chiral zinc homoenolate **8** in the presence of a palladium catalyst afforded the enol ether **9** in 80% overall yield.[5,6] Hydroboration of the olefin and simultaneous reduction of the ester group gave the corresponding diol, which was converted to the primary alcohol **10** in 66% overall yield via protection and selective deprotection. Stepwise oxidation of **10** afforded the B−C ring segment **4** in 96% overall yield.

Coupling of Segments 4 and 5. The next task of the total synthesis was the convergent construction of the A−G ring framework. The carboxylic acid **4** and the alcohol **5**[4] were connected by Yamaguchi conditions to give the ester **11** in quantitative yield (Scheme 3).[7] Treatment of **11** with TBAF/AcOH gave the alcohol **12** in 88% yield. Acid-catalyzed acetal formation with the γ-methoxyallylstannane **13** followed by acetal cleavage with TMSI/HMDS furnished the allylic stannane **14** in 72% overall yield.[8] The ester **14** was then subjected to the Rychnovsky acetylation. Thus, partial reduction of **14** with DIBAL-H followed by treatment of the resulting aluminum hemiacetal with Ac_2O/DMAP/pyridine afforded the α-acetoxy ether **15**.[9] However, the yield was only 15%, and significant amounts of over-reduced products were obtained.[10] Presumably, the steric repulsion between the diisobutylaluminum moiety and

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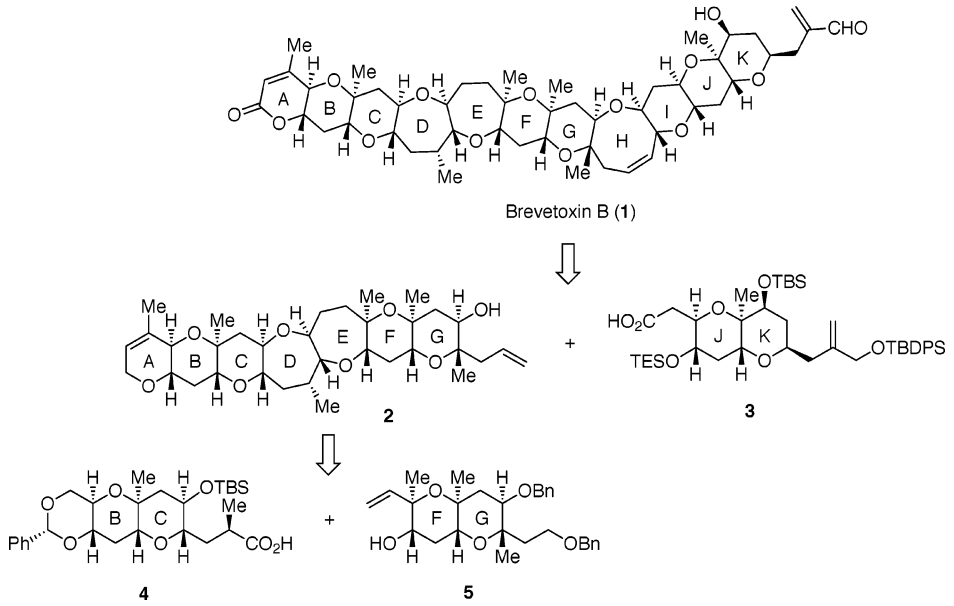
‡ Department of Chemistry.

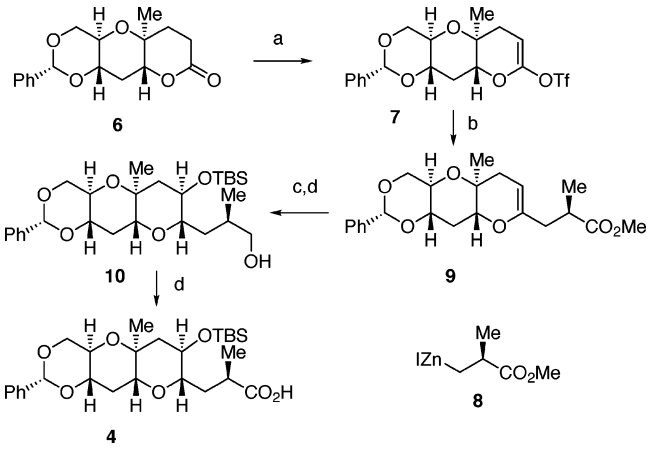
(1) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773−6775.
(2) (a) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173−1174. (b) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 10252−10263. (c) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374−14376.
(3) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 3562−3566.
(4) For the preparation of compounds **5** and **6**, see Supporting Information.
(5) Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3494−3498.
(6) For the palladium-catalyzed coupling of alkylzinc reagents, see: Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821−1823.
(7) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.
(8) Kadota, I.; Sakaihara, T.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 3195−3198.

10.1021/ja051171c CCC: $30.25

Scheme 1. Retrosynthetic Analysis of Brevetoxin B (**1**)

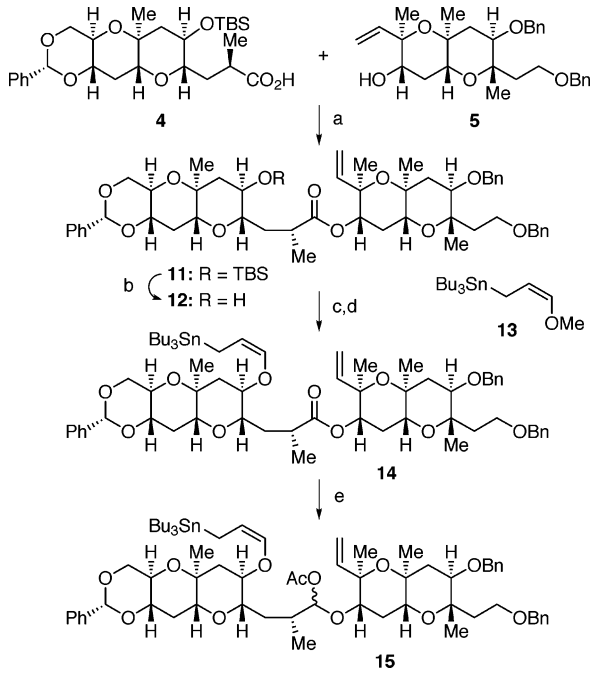


Scheme 2. Synthesis of the B−C Ring Segment **4**[a]



[a] Reagents and conditions: (a) KHMDS, $PhNTf_2$, DMPU, THF, −78 °C, 94%; (b) **8**, $PdCl_2(o\text{-}Tol_3P)_2$, benzene, 40 °C, 85%; (c) (i) $BH_3{\cdot}SMe_2$, THF, 0 °C to room temperature, then NaOH, H_2O_2, 0 °C to room temperature; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 76%; (d) AcOH, H_2O-THF (1:1), 0 °C to room temperature, 87%; (e) (i) $SO_3{\cdot}$py, DMSO, Et_3N, CH_2Cl_2, 0 °C, 100%; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF-*t*-BuOH−H_2O, 0 °C, 96%.

Scheme 3. Coupling of Segments **4** and **5**[a]



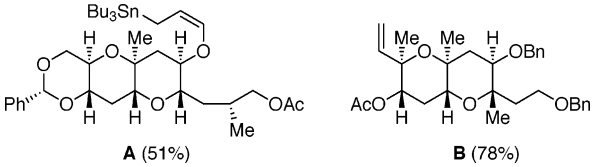
[a] Reagents and conditions: (a) DCC, DMAP, CSA, CH_2Cl_2, reflux, 100%; (b) TBAF, AcOH, THF, 50 °C, 88%; (c) **13**, CSA, CH_2Cl_2, rt, 93%; (d) TMSI, HMDS, CH_2Cl_2, −20 °C, 77%; (e) DIBAL-H, −90 °C, CH_2Cl_2, then Ac_2O, pyridine, DMAP, −90 °C to room temperature, 15%.

the methyl group on the side chain would destabilize the hemiacetal intermediate. Since several attempts for improving the yield of **15** resulted in failure, we next examined an alternative approach.

Intramolecular Allylation of *O,S*-Acetal. Recently, Hirama, Inoue, and co-workers reported the radical cyclization of *O,S*-acetals for the synthesis of polycyclic ethers.[11] It was thought that the use of the *O,S*-acetal as an electrophile for the intramolecular allylation would provide an efficient method for the convergent assembly of cyclic ethers. Scheme 4 describes a new approach for the coupling of the B−C and F−G ring segments. Treatment of **10** with $(PhS)_2/Bu_3P$ gave the sulfide **16** in 90% yield.[12] Chlorination of **16** with NCS afforded the α-chlorosulfide **17**,[13] which was immediately coupled with the

(9) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198. (c) Kopecky, D. J.; Rychnovsky, S. D. *Org. Synth.* **2003**, *80*, 177−183.

(10) The acetates **A** and **B** were obtained in 51 and 79% yields, respectively.

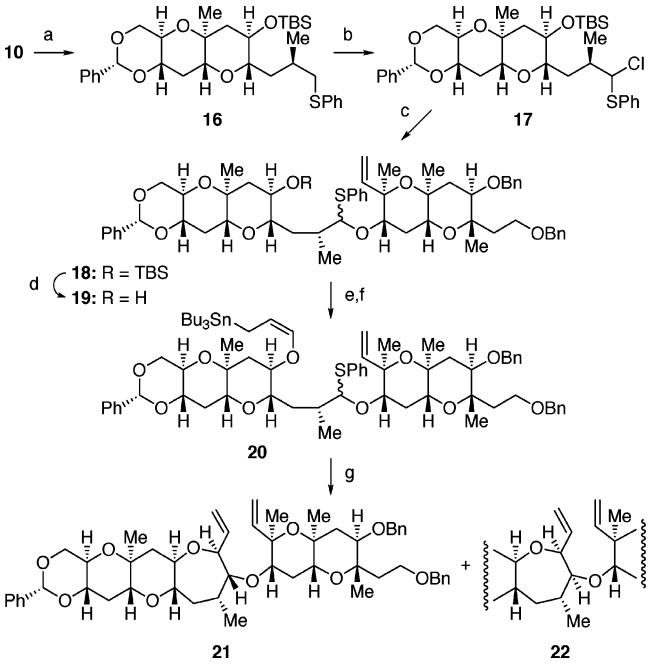


(11) (a) Inoue, M.; Wang, G.-X.; Wang, J.; Hirama, M. *Org. Lett.* **2002**, *4*, 3439−3442. (b) Inoue, M.; Miyazaki, K.; Uehara, H.; Maruyama, M.; Hirama, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12013−12018.

(12) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409−1412.

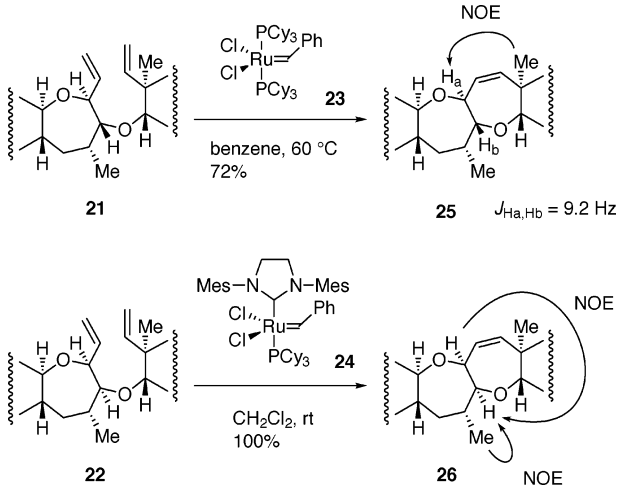
(13) Mukaiyama, T.; Sugaya, T.; Marui, S.; Nakatsuka, T. *Chem. Lett.* **1982**, 1555−1558.

Scheme 4. Alternative Approach[a]



[a] Reagents and conditions: (a) $(PhS)_2$, *n*-Bu_3P, DMF, rt, 90%; (b) NCS, CCl_4, rt; (c) **5**, AgOTf, DTBMP, MS4A, CH_2Cl_2, −78 to −10 °C, 81% based on **5**; (d) TBAF, THF, rt; (e) **13**, CSA, CH_2Cl_2, rt, 81% (2 steps); (f) TMSI, HMDS, CH_2Cl_2, 0 °C, 84%; (g) AgOTf, MS4A, CH_2Cl_2, −78 °C to room temperature, 84% (**21**:**22** = 78:22).

Scheme 5. Ring-Closing Metathesis of **21** and **22**

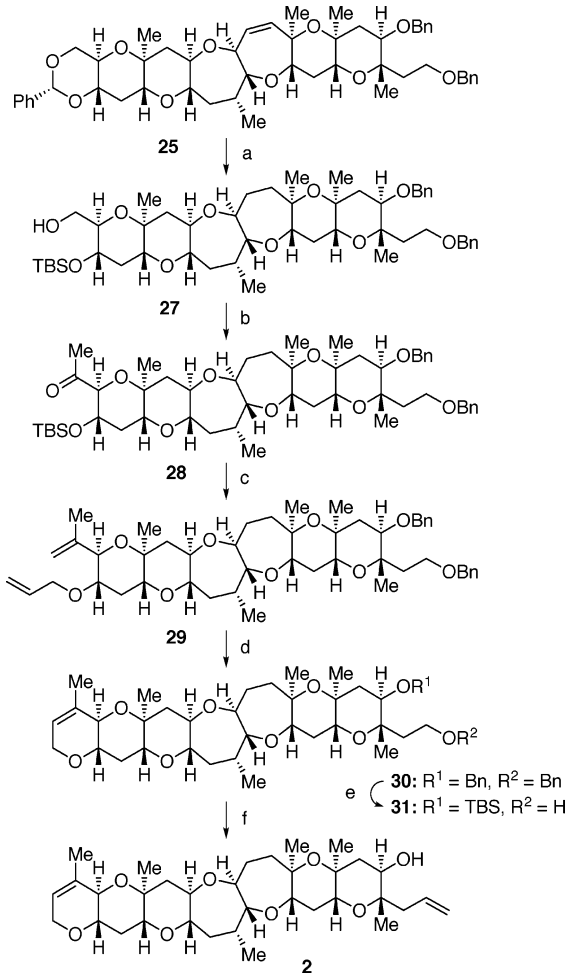


F−G ring segment **5** in the presence of AgOTf/DTBMP to provide the *O*,*S*-acetal **18** in 81% yield.[14,15] A series of reactions, including desilylation with TBAF, acid-catalyzed acetal formation with **13**, and selective cleavage of the methyl acetal with TMSI/HMDS, furnished the allylic stannane **20** in 68% overall yield. The reaction conditions employed did not affect the *O*,*S*-acetal moiety. After several attempts, we found that the intramolecular allylation of the *O*,*S*-acetal **20** proceeded smoothly in the presence of AgOTf to give a 78:22 mixture of the desired product **21** and its stereoisomer **22** in 84% yield.

The diene **21** obtained was subjected to ring-closing metathesis using the Grubbs catalyst **23**, leading to **25** in 72% yield (Scheme 5).[16] On the other hand, the ring-closing metathesis

(14) MacAuliffe, J. C.; Hindsgaul, O. *Synlett* **1998**, 307−309.
(15) The yield is based on the alcohol **5**.

Scheme 6. Synthesis of the A−G Ring Segment **2**[a]



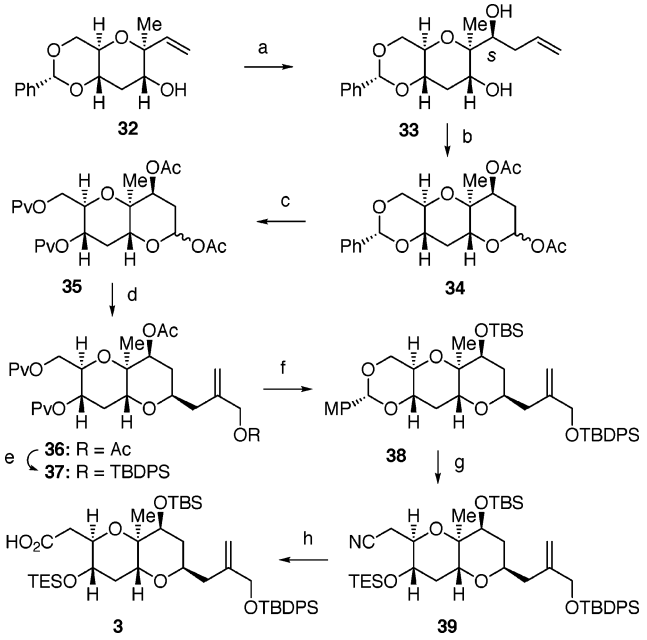
[a] Reagents and conditions: (a) (i) CSA, CH_2Cl_2−MeOH, rt; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to room temperature; (iii) H_2, Pd−C, Et_3N, EtOAc, rt; (iv) CSA, CH_2Cl_2−MeOH, 0 °C, 80%; (b) (i) TPAP, NMO, MS4A, CH_2Cl_2, rt; (ii) MeMgI, THF, 0 °C; (iii) TPAP, NMO, MS4A, CH_2Cl_2, rt, 91%; (c) (i) $Ph_3PCH_3^+Br^-$, NaHMDS, THF, 0 °C to room temperature; (ii) TBAF, THF, 40 °C; (iii) allyl bromide, KH, THF, 0 °C to room temperature, 90%; (d) **23**, CH_2Cl_2, rt, 98%; (e) (i) Li, liquid NH_3, THF, −78 °C; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt; (iii) CSA, CH_2Cl_2−MeOH, 0 °C, 90%; (f) (i) TPAP, NMO, MS4A, CH_2Cl_2, rt; (ii) $Ph_3PCH_3^+Br^-$, NaHMDS, THF, 0 °C to room temperature; (iii) TBAF, THF, 60 °C, 83%.

of **22** was performed by using the second-generation Grubbs catalyst to afford **26** in quantitative yield.[17] The stereochemistries of **25** and **26** were determined on the basis of ^1H NMR analysis and NOE experiments, as shown in Scheme 5.

Scheme 6 describes the preparation of the A−G ring segment **2**. Removal of the benzylidene acetal of **25**, protection of the resulting diol using TBSOTf/2,6-lutidine, hydrogenation of the olefin with H_2/Pd−C/Et_3N, and selective desilylation of the primary silyl ether afforded the alcohol **27** in 80% overall yield. Oxidation of **27** with TPAP/NMO followed by treatment with MeMgI and subsequent TPAP oxidation of the resulting secondary alcohol gave the methyl ketone **28** in 91% overall yield. Wittig reaction of **28** gave the corresponding *exo*-methylene derivative. The TBS ether was deprotected and

(16) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.
(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

Scheme 7. Synthesis of the J−K Ring Segment **3**[a]

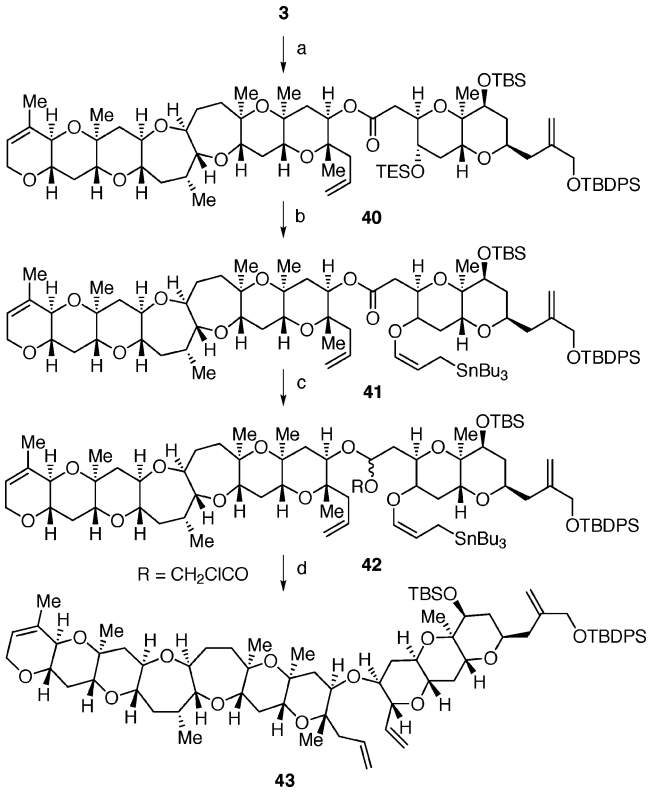


[a] Reagents and conditions: (a) (i) O_3, MeOH, −78 °C, then Me_2S; (ii) allylbromide, Zn powder, saturated NH_4Cl, THF, 0 °C, 93% (*S*:*R* = 2:1); (b) O_3, CH_2Cl_2, −78 °C, then PPh_3; (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 98%; (c) (i) H_2, $Pd(OH)_2$−C, MeOH, rt; (ii) PvCl, pyridine, DMAP, CH_2Cl_2, reflux, 86%; (d) CH_2═$C(CH_2OAc)CH_2TMS$, TMSOTf, CH_3CN, −20 °C, 93%; (e) (i) K_2CO_3, MeOH, 0 °C; (ii) TBDPSCl, imidazole, DMF, rt, 85%; (f) (i) K_2CO_3, MeOH, 40 °C; (ii) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, MS4A, CH_2Cl_2, 0 °C; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 82%; (g) (i) PPTS, MeOH, rt; (ii) I_2, PPh_3, imidazole, Et_2O−benzene, rt; (iii) NaCN, DMSO, 50 °C; (iv) TESCl, 2,6-lutidine, CH_2Cl_2, 0 °C, 86%; (h) DIBAL-H, CH_2Cl_2, −78 °C, 94%; (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF-*t*-BuOH−H_2O, 0 °C, 82%.

converted to the allyl ether **29** in 90% overall yield by the standard conditions. Ring-closing metathesis of **29** with **23** provided the known compound **30**[2a,b] in 98% yield.[18] Debenzylation of **30** under the Birch conditions, TBS protection of the resulting diol, and selective cleavage of the primary silyl ether afforded the primary alcohol **31** in 90% overall yield. TPAP oxidation of **31** followed by Wittig reaction and desilylation with TBAF gave the A−F ring segment **2** in 83% overall yield.

Synthesis of the J−K Ring Segment. We next examined the synthesis of the J−K ring segment **3** (Scheme 7).[19] Ozonolysis of the known olefin **32**[20] afforded the corresponding aldehyde, which was subjected to the Barbier-type allylation using allyl bromide and Zn powder in the presence of saturated NH_4Cl to give a 2:1 mixture of the desired homoallylic alcohol **33** and its stereoisomer in 93% combined yield.[21,22] Ozonolysis of **33** followed by acetylation of the resulting hemiacetal gave **34** in 98% yield. Removal of the benzylidene acetal of **34** with H_2/$Pd(OH)_2$−C followed by protection of the resulting diol with PvCl/pyridine/DMAP afforded **35** in 86% overall yield.[23] Treatment of **35** with 2-(acetoxymethyl)allyltrimethylsilane and TMSOTf gave **36** as the sole product in 93% yield.[24] Selective removal of the primary acetyl group was carried out with K_2CO_3 in MeOH at 0 °C, and the resulting alcohol was protected with TBDPSCl/imidazole to afford **37** in 85% overall yield. Saponification of **37** with K_2CO_3 in MeOH at 40 °C gave the corresponding triol. Acetalization of the 1,3-diol moiety with *p*-$MeOC_6H_4CH(OMe)_2$/CSA followed by the TBS protection of the remaining secondary alcohol gave **38** in 82% overall yield. Selective hydrolysis of the acetal protection of **38** was carried out with PPTS in MeOH. Selective iodination of the primary alcohol, substitution of the iodide with cyanide, and protection of the remaining secondary alcohol with TESCl/2,6-lutidine furnished the nitrile **39** in 86% overall yield. DIBAL-H reduction of **39** followed by oxidation of the resulting aldehyde gave the carboxylic acid **3** in 77% overall yield.

Scheme 8. Coupling of Segments **2** and **3**[a]

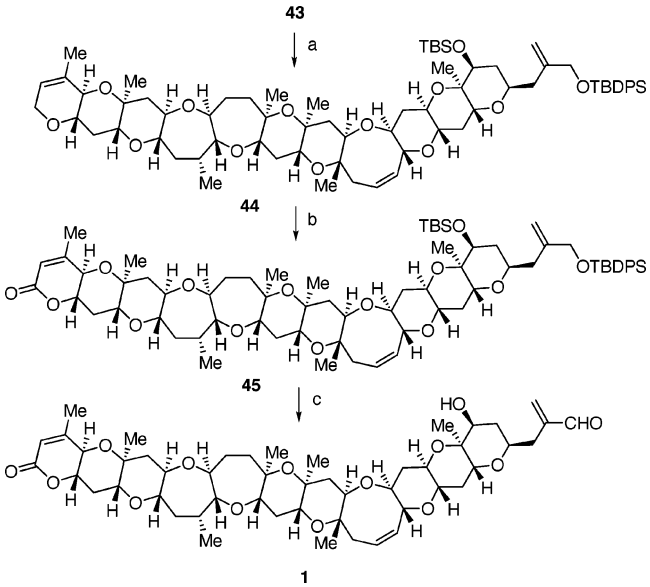


[a] Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 40 °C, then **2**, DMAP, toluene, rt, 94%; (b) (i) TBAF, THF, 0 °C; (ii) **13**, CSA, CH_2Cl_2, rt; (iii) HMDS, TMSI, CH_2Cl_2, 0 °C, 71%; (c) DIBAL-H, CH_2Cl_2, −78 °C, then $(CH_2ClCO)_2O$, DMAP, pyridine, CH_2Cl_2, −78 °C, 68%; (d) $MgBr_2$·OEt_2, CH_3CN, 40 °C, 82%.

Coupling of Segments 2 and 3. Esterification of the A−G ring segment **2** and the J−K segment **3** under the Yamaguchi conditions afforded the ester **40** in 94% yield (Scheme 8). Selective removal of the TES group of **40** was carried out using TBAF to give the corresponding alcohol, which was converted to the allylic stannane **41** via the standard procedure in 71% overall yield. Modified Rychnovsky acetylation of **41** via DIBAL-H reduction followed by treatment with $(CH_2ClCO)_2O$/DMAP/pyridine gave the α-chloroacetoxy ether **42** in 68%

(18) Construction of the A ring moiety via ring-closing metathesis has been reported by Nakata; see ref 2c.
(19) For the preliminary study on the synthesis and coupling of the JK ring fragment, see: Kadota, I.; Nishina, N.; Nishii, H.; Kikuchi, S.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 7929−7932.
(20) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517−4552.
(21) Pétrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910−912.
(22) The Grignard reaction of the hydroxy aldehyde gave poor results.
(23) The benzylidene acetal of **34** was unstable under the reaction conditions which were used in the next C-glycosidation.
(24) The direct introduction of the C4 unit has been reported by Nakata: Matsukura, H.; Hori, N.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 7681−7684.

Scheme 9. Completion of the Total Synthesis of Brevetoxin B (**1**)[a]



[a] Reagents and conditions: (a) **23**, benzene, 40 °C; (b) PCC, benzene, 80 °C, 81% (2 steps); (c) (i) HF·py, CH_2Cl_2, 0 °C; (ii) MnO_2, Et_2O, rt, 84%.

yield.[25] Intramolecular allylation of **42** with $MgBr_2 \cdot OEt_2$ in CH_3CN gave the desired product **43** as a single stereoisomer in 82% yield.

The Final Stage. Completion of the total synthesis is described in Scheme 9. Ring-closing metathesis of **43** with **23** provided the A−K ring skeleton **44**. Oxidation of the A ring moiety of **44** with PCC gave the lactone **45** in 81% overall yield. After removal of the silyl protective groups with HF·py, selective oxidation of the resulting allylic alcohol with MnO_2 provided brevetoxin B (**1**) in 84% overall yield. The synthetic **1** exhibited physical and spectroscopic data identical to those reported previously.[1,2]

(25) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893−11899.

Conclusions

The total synthesis of brevetoxin B (**1**) has been accomplished in a highly convergent manner via the assembly of three fragments. The key steps for the synthesis of **1** are the intramolecular allylation and subsequent ring-closing metathesis. Although an attempt to couple segments **4** and **5** via the α-acetoxy ether **15** resulted in failure (Scheme 3), a new coupling method via the *O*,*S*-acetal **20** proceeded smoothly (Scheme 4). The longest linear sequence leading to **1** was 63 steps with 0.28% overall yield, and the number of the total steps was 108. Further investigation on the convergent synthesis of other marine polycyclic ethers based on the present methodology is in progress.

Acknowledgment. We thank Professor K. Nakanishi (Columbia University) for providing an analytical sample of natural brevetoxin B, and Professor M. Inoue (Tohoku University) for his helpful discussions on the preparation of *O*,*S*-acetals. This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Schemes for the preparation of compounds **5** and **6**. Experimental procedures and characterization data for all new compounds. Copies of ^1H NMR spectra for selected compounds (62 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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