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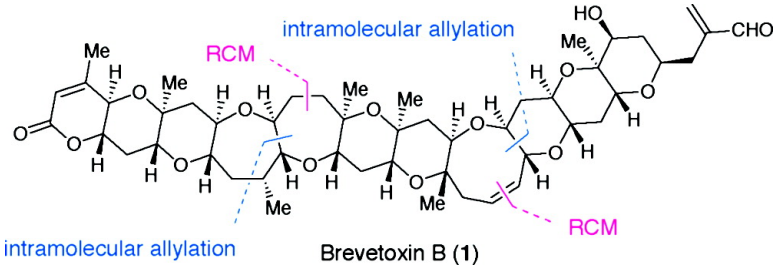
*J. Am. Chem. Soc.*, **2005**, 127 (25), 9246-9250• DOI: 10.1021/ja051171c • Publication Date (Web): 01 June 2005






Brevetoxin B (**1**)

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# Total Synthesis of Brevetoxin B

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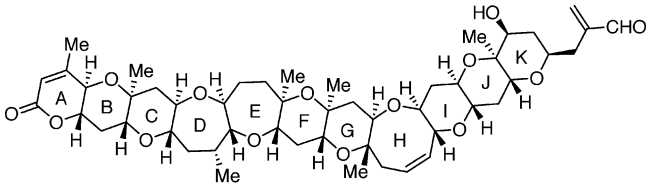
***Abstract:*** The convergent total synthesis of brevetoxin B (**1**) has been achieved. The intramolecular allylation of the *O*,*S*-acetal **20**, prepared from the α-chlorosulfide **17** and the alcohol **5**, was carried out using AgOTf as a Lewis acid to give the diene **21**, predominantly. Ring-closing 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.

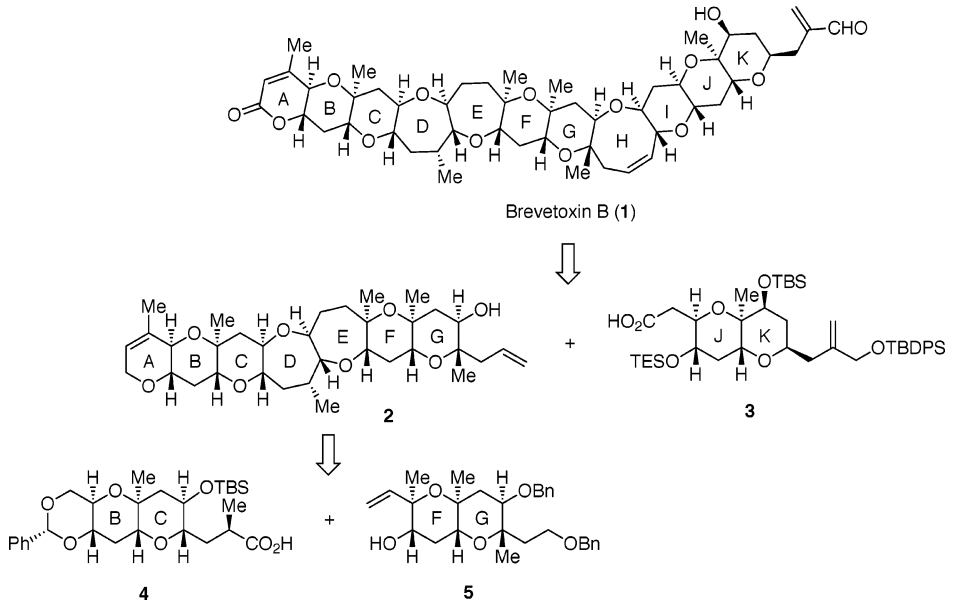
**Coupling of Segments 4 and 5.** The next task of the total synthesis was the convergent construction of the A−G ring framework. The carboxylic acid **4** and the alcohol **5**[4] were connected by Yamaguchi conditions to give the ester **11** in quantitative yield (Scheme 3).[7] Treatment of **11** 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

† Research and Analytical Center for Giant Molecules.
‡ Department of Chemistry.

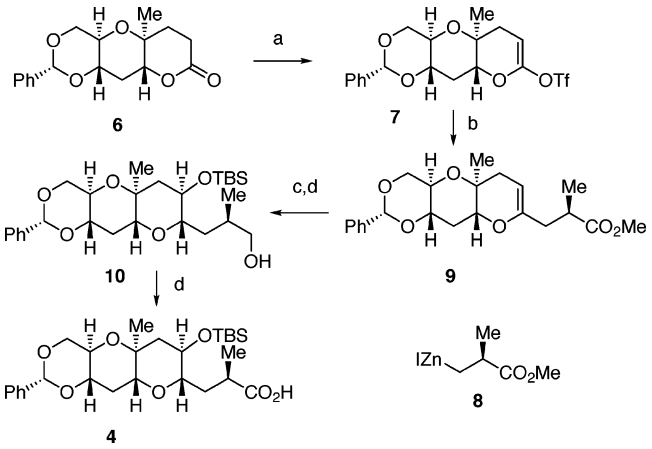
(1) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773−6775.
(2) (a) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173−1174. (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**)

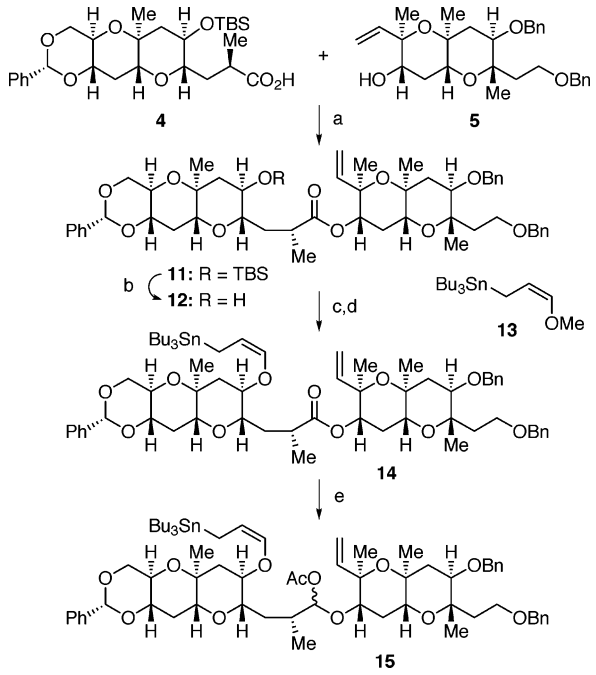



***Scheme 2.*** Synthesis of the B−C Ring Segment **4**[a]




[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]



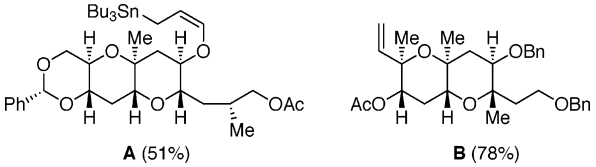

[a] Reagents and conditions: (a) DCC, DMAP, CSA, $CH_2Cl_2$, reflux, 100%; (b) TBAF, AcOH, THF, 50 °C, 88%; (c) **13**, CSA, $CH_2Cl_2$, rt, 93%; (d) TMSI, HMDS, $CH_2Cl_2$, −20 °C, 77%; (e) DIBAL-H, −90 °C, $CH_2Cl_2$, then $Ac_2O$, pyridine, DMAP, −90 °C to room temperature, 15%.

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.

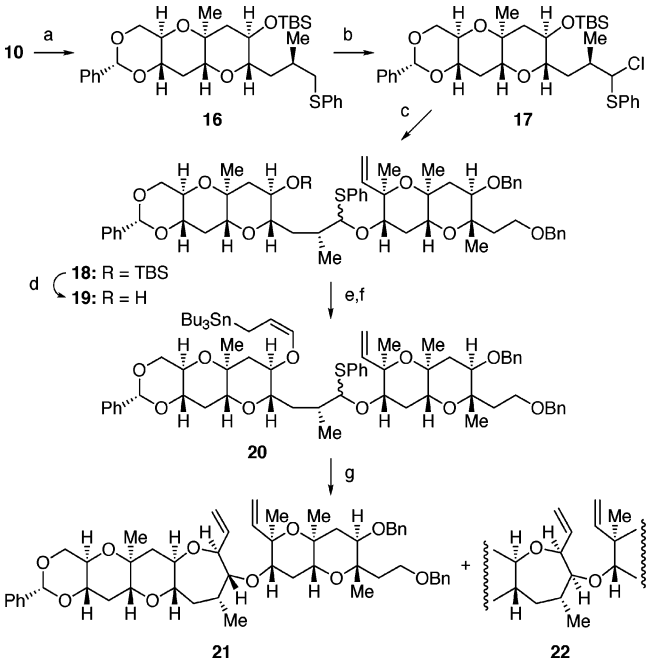



(11) (a) Inoue, M.; Wang, G.-X.; Wang, J.; Hirama, M. *Org. Lett.* **2002**, *4*, 3439−3442. (b) Inoue, M.; Miyazaki, K.; Uehara, H.; Maruyama, M.; Hirama, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12013−12018.

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

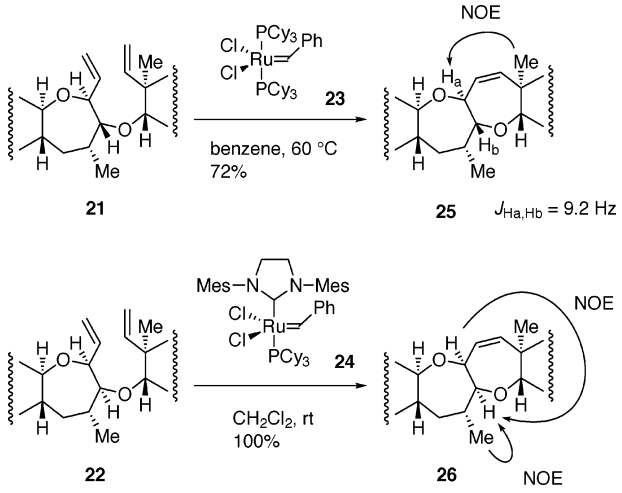
(13) Mukaiyama, T.; Sugaya, T.; Marui, S.; Nakatsuka, T. *Chem. Lett.* **1982**, 1555−1558.

***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**

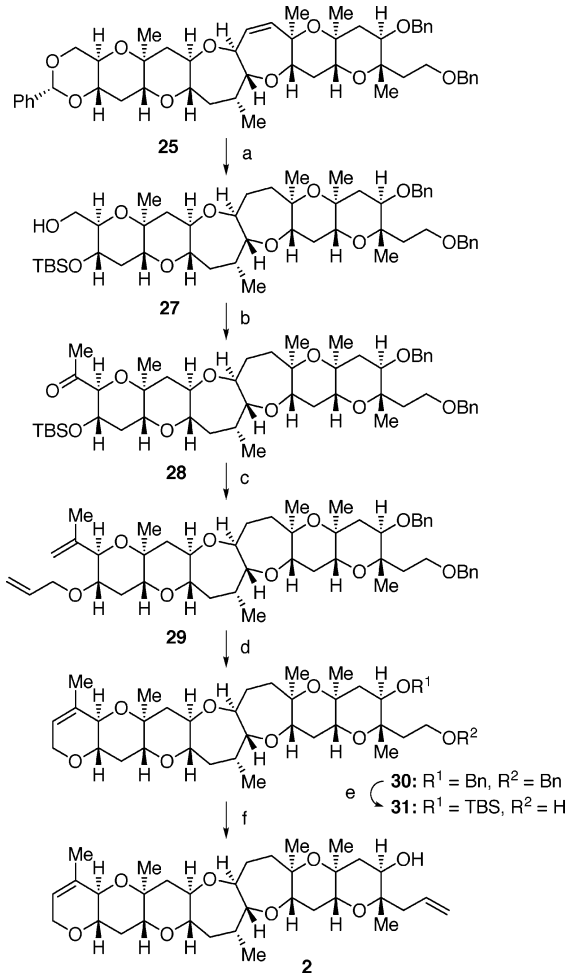


F−G ring segment **5** in the presence of AgOTf/DTBMP to provide the *O*,*S*-acetal **18** in 81% yield.[14,15] A series of reactions, including desilylation with TBAF, acid-catalyzed acetal formation with **13**, and selective cleavage of the methyl acetal with TMSI/HMDS, furnished the allylic stannane **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]



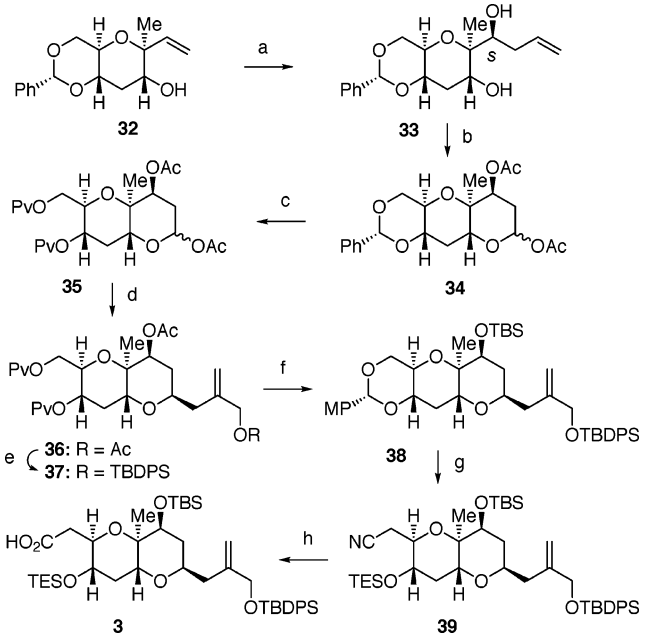
[a] Reagents and conditions: (a) (i) CSA, $CH_2Cl_2$−MeOH, rt; (ii) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C to room temperature; (iii) $H_2$, Pd−C, $Et_3N$, EtOAc, rt; (iv) CSA, $CH_2Cl_2$−MeOH, 0 °C, 80%; (b) (i) TPAP, NMO, MS4A, $CH_2Cl_2$, rt; (ii) MeMgI, THF, 0 °C; (iii) TPAP, NMO, MS4A, $CH_2Cl_2$, 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]

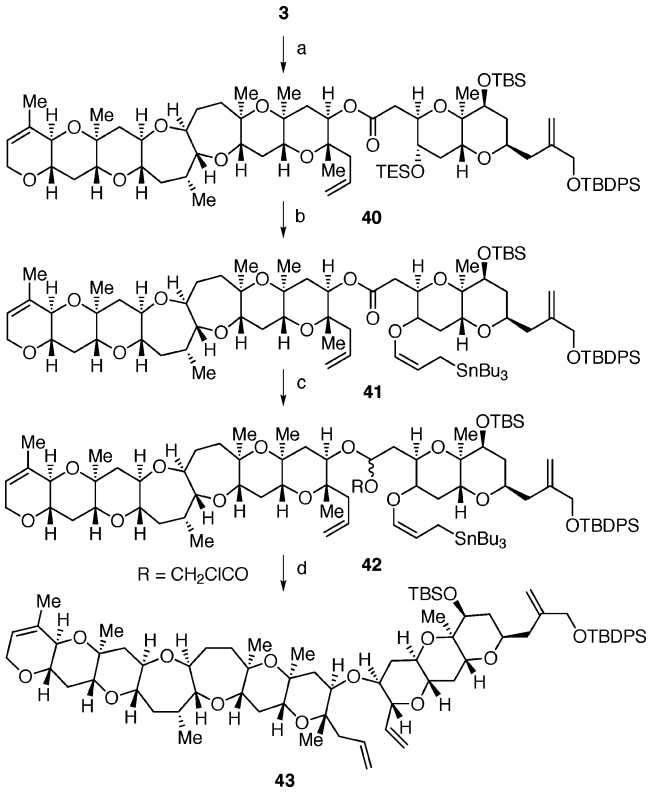


[a] Reagents and conditions: (a) (i) $O_3$, MeOH, −78 °C, then $Me_2S$; (ii) allylbromide, Zn powder, saturated $NH_4Cl$, THF, 0 °C, 93% (*S*:*R* = 2:1); (b) $O_3$, $CH_2Cl_2$, −78 °C, then $PPh_3$; (ii) $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$, rt, 98%; (c) (i) $H_2$, $Pd(OH)_2$−C, MeOH, rt; (ii) PvCl, pyridine, 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]

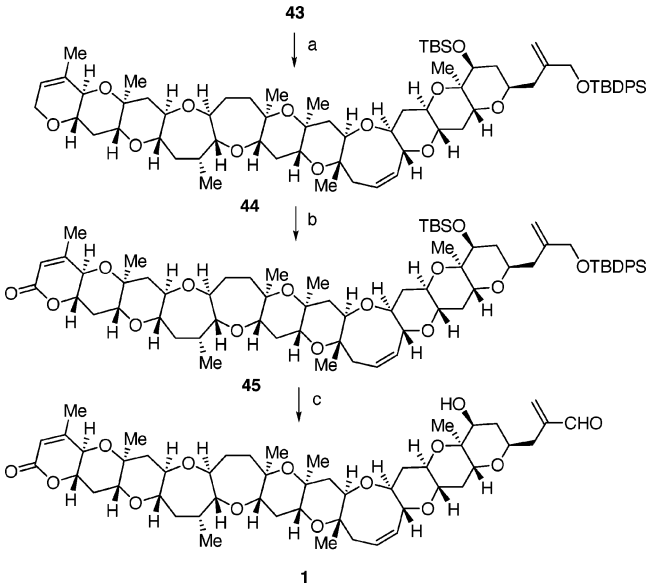


[a] Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF, 40 °C, then **2**, DMAP, toluene, rt, 94%; (b) (i) TBAF, THF, 0 °C; (ii) **13**, CSA, $CH_2Cl_2$, rt; (iii) HMDS, TMSI, $CH_2Cl_2$, 0 °C, 71%; (c) DIBAL-H, $CH_2Cl_2$, −78 °C, then $(CH_2ClCO)_2O$, DMAP, pyridine, $CH_2Cl_2$,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

JA051171C