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Total Synthesis of Brevetoxin-B

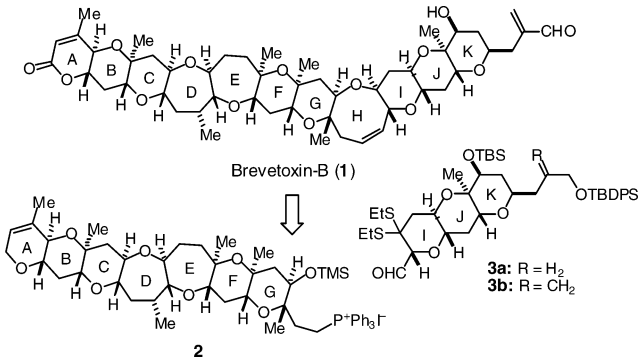
Goh Matsuo, Koji Kawamura, Nobuyuki Hori, Hiroko Matsukura, and Tadashi Nakata*

RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0198, Japan

Received August 23, 2004; E-mail: nakata@rs.kagu.tus.ac.jp

Brevetoxin-B (BTX-B, **1**), produced by the red tide organism, *Gymnodium breve* Davis, is the first member of marine polycyclic ethers to be structurally elucidated and one of the most potent neurotoxins.[1] The structural feature of **1** is a trans-fused polycyclic ether ring system with 23 stereocenters, which contains six-, seven-, and eight-membered ether rings, three carbon−carbon double bonds, one hydroxyl group, and two carbonyl groups. Its unique, complex structure and potent biological activity have attracted the attention of numerous synthetic organic chemists.[2] To date, Nicolaou and co-workers reported the first and only total synthesis of **1** based on a convergent strategy by the coupling of **2** and **3a**.[2a−c] Herein, we report the stereoselective total synthesis of BTX-B (**1**) via the coupling of **2** and **3b**, each ether ring of which was stereoselectively and efficiently constructed on the basis of SmI_2-induced intramolecular cyclization, 6-*endo*-cyclization of hydroxy epoxide, ring-closing olefin metathesis, and SmI_2-induced intramolecular Reformatsky-type reaction. Several kinds of double reactions at the left and right sides were efficiently used through the synthesis.

Scheme 1. Retrosynthetic Plan for BTX-B



A feature of our synthesis of the left segment **2** is a two-directional strategy starting from the D-ring. Commercially available tri-*O*-acetyl-D-glucal (**4**) was converted into α,β-unsaturated ester **6** via alcohol **5**. The first task was stereoselective construction of an α-methyl group on the D-ring. After several attempts to introduce the methyl group into **6**, we found that Kuwajima's conditions[3] smoothly effected the Michael addition: upon treatment with MeMgBr and TMSCl in the presence of Cu(*N*-*i*-Pr−Sal)$_2$ catalyst **7**, the addition reaction efficiently took place only from the α-side to give the desired adduct **8**.[4] Construction of the D-ring was then carried out by our protocol using SmI_2-induced intramolecular cyclization.[5] After conversion of **8** into the requisite aldehyde **9**, treatment with SmI_2 in the presence of MeOH in THF effected radical-induced reductive cyclization with concomitant lactonization to give oxepane **10** with complete stereoselection. Here, we expected that the C- and E-rings would be simultaneously constructed by the two-directional strategy with SmI_2-induced double cyclization. After hydrolysis of the acetal **10** followed by oxidation, treatment of the resultant bis(lactone) with MeLi underwent double methylation to give bis(methyl ketone) **11**. Treatment of **11** with ethyl propiolate[6] effected double hetero-Michael reaction to give bis(β-alkoxy acrylate) **12**. As expected, reaction of **12** with SmI_2 induced double cyclization with complete stereoselection to give trans-fused ester-lactone **13**,[7] corresponding to the CDE-ring, after treatment with *p*-TsOH.[8] For construction of the B- and F-rings, a subtle difference in the reactivity between similar functional groups at the left and right sides was successfully used. Protection of **13** as a TMS ether followed by DIBAH reduction afforded aldehyde-lactol **14**, which was efficiently converted into α,β-unsaturated ketone-ester **15** by one-pot Wittig reaction. Thus, the first Wittig reagent, $Ph_3P{=}C(Me)CO_2Et$, smoothly and predominantly reacted with the lactol at 0 °C−rt, and the second Wittig reagent, $Ph_3P{=}CHCOMe$, reacted with the aldehyde at 100 °C to give ketone-ester **15**, after TMS protection. The CBS asymmetric reduction[9] of the ketone **15** gave the desired β-alcohol **16**,[10] which is the matched isomer for the subsequent Sharpless asymmetric epoxidation (AE)[11] to give the desired α-epoxide. After DIBAH reduction of the ester **16**, the stereoselective epoxidation of the resultant bis(allylic alcohol) **17** was performed by consecutive Sharpless AE; i.e., treatment with TBHP/(−)-DIPT and then TBHP/(+)-DIPT effected epoxidation at the right and left sides, respectively, to afford bis-(α-epoxide) **18**. The first epoxidation gave only α-epoxide, and the stereoselectivity of the second one was ca. 8:1 in favor of α-epoxide. Double oxidation of the diol **18** followed by double Wittig olefination and removal of two TMS groups efficiently afforded bis(vinyl epoxide) **19**. Treatment of **19** with PPTS[12] at 0 °C effected 6-*endo*-cyclization[13] at the right side to give **20**, after TBS protection. Then, PPTS treatment of **20** at room temperature induced 6-*endo*-cyclization at the left side to give the BCDEF-ring **21**.[14] Differentiation of the left and right sides was completely performed at this stage. After O-allylation of **21**, ring-closing olefin metathesis of the resultant **22** with Grubbs reagent[15] smoothly proceeded at room temperature to give **23**.[2d] After removal of the TBS group, Wacker oxidation of **23** took place at the *exo*-methylene position[16] to give aldehyde, which was subjected to the Wittig reaction to give α,β-unsaturated ester **24**. TBS protection of **24**, DIBAH reduction, and MCPBA epoxidation afforded β-epoxide **25** as a single product.[2e,17] Removal of the TBS group followed by PPTS treatment effected 6-*endo*-cyclization[2e,18] to give **26**,[7] which was successfully converted into phosphonium salt **2**,[2c] corresponding to the ABCDEFG-ring.

Synthesis of the IJK-ring system **3b** started with the construction of the I-ring. Aldehyde **28** was prepared from commercially available 2-deoxy-D-ribose (**27**) by thioacetalization,[19] benzylidation, hetero-Michael reaction, and deprotection of thioacetal. SmI_2-induced cyclization of **28** gave the desired trans-**29** with complete stereoselection. DIBAH reduction of **29**, Wittig reaction, TBS protection, and DIBAH reduction afforded allylic alcohol **30**. The Sharpless AE of **30** using (−)-DET stereoselectively produced the

* Present address: Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan.

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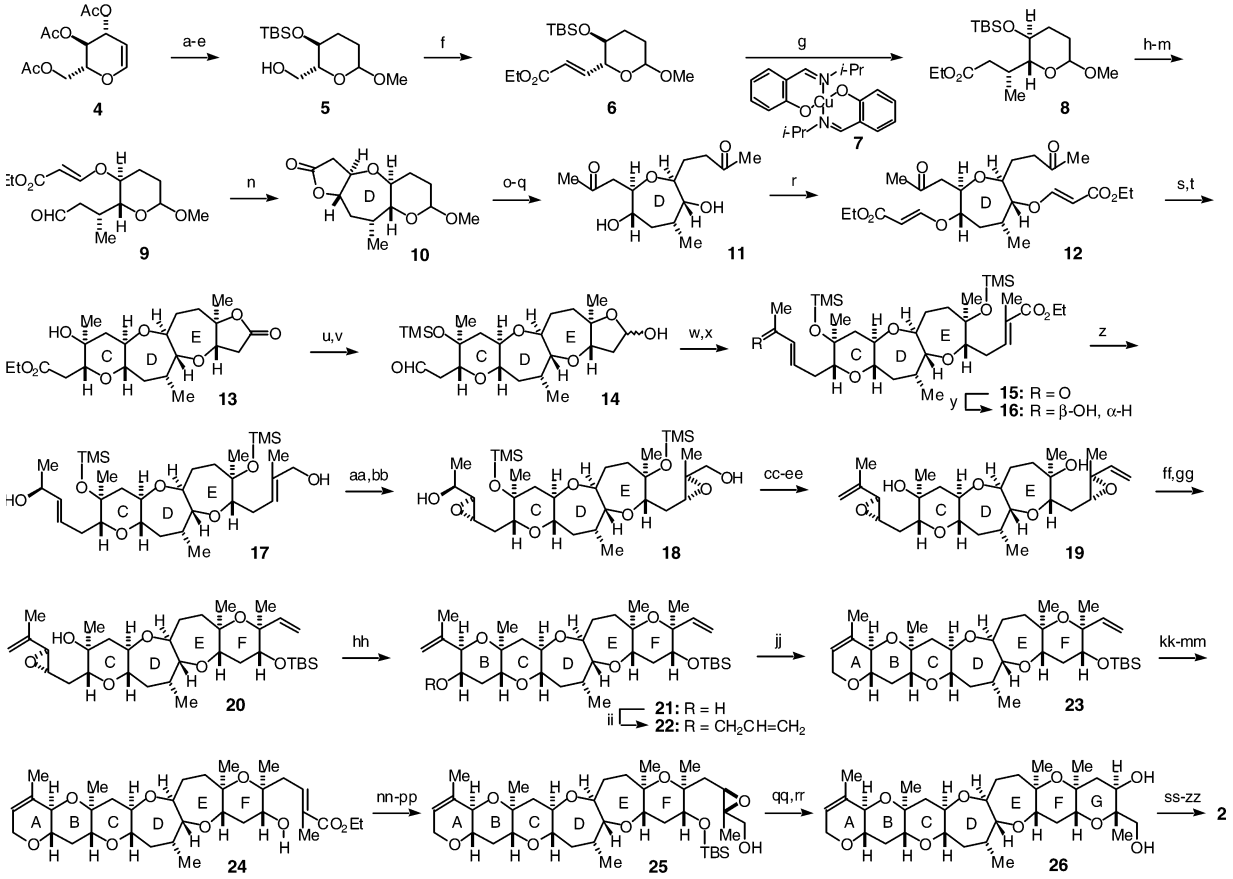
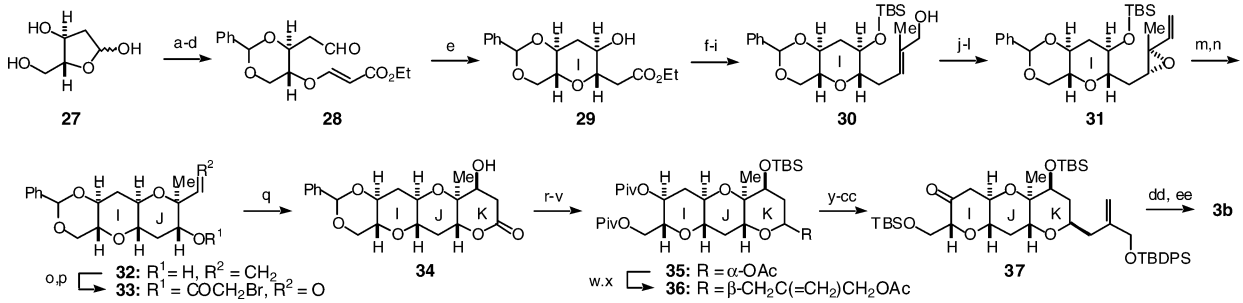
Scheme 2. Synthesis of the ABCDEFG-Ring[a]



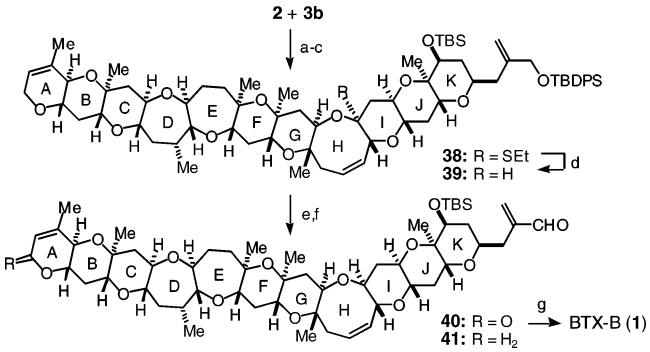
[a] Reagents and conditions: (a) montmorillonite K-10, MeOH−CH_2Cl_2, 40 °C; (b) H_2, 10% Pd/C, MeOH, rt; (c) K_2CO_3, MeOH, rt, 95% (three steps); (d) TBSCl, imidazole, DMF, 50 °C, 100%; (e) CSA, MeOH−CH_2Cl_2, 0 °C, 97%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, *i*-Pr_2NEt, −78 °C → rt, then $Ph_3P{=}CHCO_2Et$, 0 °C → rt, 95%; (g) MeMgBr, TMSCl, **7**, THF, −45 °C, 99%; (h) $LiAlH_4$, Et_2O, 0 °C; (i) TBAF, THF, rt, 97% (two steps); (j) TBSCl, pyridine, CH_2Cl_2, rt, 81%; (k) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt; (l) *p*-TsOH, EtOH, rt, 97% (two steps); (m) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt; (n) SmI_2, MeOH, THF, rt, 83% (two steps); (o) AcOH−H_2O, 80 °C; (p) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 66% (two steps); (q) MeLi, THF, −78 °C, 95%; (r) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt, 95%; (s) SmI_2, MeOH, THF, rt; (t) *p*-TsOH, toluene, 80 °C, 79% (two steps); (u) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 100%; (v) DIBAH, toluene, −78 °C; (w) $Ph_3P{=}C(Me)CO_2Et$, toluene, 0 °C → rt, then $Ph_3P{=}CHCOMe$, 100 °C, 67%, (two steps); (x) TMSOTf, pyridine, CH_2Cl_2, −78 °C, 98%; (y) (*R*)-2-methyl-CBS-oxazaborolidine, cathecholborane, toluene, −78 °C; (z) DIBAH, toluene, −78 °C, 98% (two steps); (aa) TBHP, (−)-DIPT, Ti(O*i*-Pr)$_4$, 4 Å MS, CH_2Cl_2, −30 °C, 92%; (bb) TBHP, (+)-DIPT, Ti(O*i*-Pr)$_4$, 4 Å MS, CH_2Cl_2, −30 °C, 96%; (cc) SO_3·pyridine, Et_3N, DMSO−CH_2Cl_2, rt; (dd) $Ph_3P^+MeBr^-$, NaHMDS, THF, rt; (ee) TBAF, THF, 0 °C, 96% (three steps); (ff) PPTS, CH_2Cl_2, 0 °C; (gg) TBSOTf, pyridine, CH_2Cl_2, −20 → 0 °C, 62% (two steps); (hh) PPTS, CH_2Cl_2, rt, 78%; (ii) allylbromide, NaH, THF, rt; (jj) $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, rt, 96% (two steps); (kk) TBAF, THF, rt; (ll) $PdCl_2$, CuCl, O_2, DMF−H_2O, rt → 60 °C; (mm) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100 °C, 93% (three steps); (nn) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (oo) DIBAH, toluene, −78 °C; (pp) MCPBA, CH_2Cl_2, −20 °C, 87% (three steps); (qq) TBAF, THF, rt; (rr) PPTS, CH_2Cl_2, 0 °C → rt, 79% (two steps); (ss) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, then TBSOTf, −78 → 0 °C; (tt) NaCN, 4 Å MS, DMSO, 80 °C; (uu) DIBAH, CH_2Cl_2, −78 °C, 69% (three steps); (vv) $NaBH_4$, EtOH, 0 °C; (ww) I_2, Ph_3P, imidazole, THF−MeCN, rt, 91% (two steps); (xx) CSA, CH_2Cl_2−MeOH, 70 °C; (yy) TMS-imidazole, CH_2Cl_2, rt, 91% (two steps); (zz) Ph_3P, MeCN, 80 °C, 91%.

Scheme 3. Synthesis of the IJK-Ring[a]



[a] Reagents and conditions: (a) 1,3-propanedithiol, 6N HCl, $CHCl_3$, rt, 90%;[19] (b) $PhCH(OMe)_2$, CSA, EtOAc, rt; (c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt, 84% (two steps); (d) MeI, $NaHCO_3$, MeCN−H_2O, rt, 98%; (e) SmI_2, MeOH, THF, 0 °C, 95%; (f) DIBAH, CH_2Cl_2, −78 °C; (g) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100 °C, 88% (two steps); (h) TBSCl, imidazole, DMF, rt; (i) DIBAH, toluene, −78 °C, 85% (two steps); (j) TBHP, (−)-DET, Ti(O*i*-Pr)$_4$, 4 Å MS, CH_2Cl_2, −20 °C, 98%; (k) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt; (l) $Ph_3P^+MeBr^-$, NaHMDS, THF, 0 °C, 85% (two steps); (m) TBAF, THF, rt; (n) PPTS, CH_2Cl_2, rt, 87% (two steps); (o) $BrCH_2COBr$, pyridine, CH_2Cl_2, 0 °C, 97%; (p) O_3, CH_2Cl_2, −78 °C, then Me_2S, −78 °C → rt; (q) SmI_2, THF, 0 °C, 71% (two steps); (r) TBSOTf, pyridine, CH_2Cl_2, rt, 71%; (s) DIBAH, CH_2Cl_2, −78 °C; (t) Ac_2O, pyridine, rt, 96% (two steps); (u) H_2, $Pd(OH)_2$/C, EtOAc, rt; (v) PivCl, pyridine, rt; (w) $CH_2{=}C(CH_2OAc)CH_2TMS$, TMSOTf, MeCN, −20 °C; (x) TBSOTf, pyridine, CH_2Cl_2, rt, 89% (four steps); (y) K_2CO_3, MeOH, −5 °C; (z) TBDPSCl, imidazole, DMF, rt; (aa) $LiAlH_4$, Et_2O, 0 °C, 88% (three steps); (bb) TBSCl, imidazole, DMF, rt; (cc) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 90% (two steps); (dd) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, then CSA, MeOH, rt, 90%; (ee) SO_3·pyridine, Et_3N, DMSO−CH_2Cl_2, 0 °C, 98%.

Scheme 4. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) **2**, *n*-BuLi, HMPA, THF, −78 °C, then **3b**, −78 °C → rt; (b) PPTS, CH_2Cl_2−MeOH, rt, 68% (two steps); (c) $AgClO_4$, $NaHCO_3$, SiO_2, 4 Å MS, $MeNO_2$, rt; (d) Ph_3SnH, AIBN, toluene, 110 °C; (e) TBAF, THF, rt, 71% (three steps); (f) PCC, benzene, 80 °C, 51% (75%[22] based on oxidation of **41**) for **40**, 38% for **41**; (g) HF·pyridine, CH_2Cl_2, 0 °C, 72%.

α-epoxide, which was converted into the vinyl epoxide **31**. After removal of the TBS group, treatment of **31** with PPTS effected 6-*endo*-cyclization to give **32**, corresponding to the IJ-ring. The remaining construction of the K-ring system was accomplished by the SmI_2-induced intramolecular Reformatsky-type reaction[20] and direct introduction of the side chain.[2f,21] Acylation of **32** with $BrCH_2$-COBr followed by ozonolysis gave the required aldehyde **33**, which was treated with SmI_2 in THF to give the *β*-hydroxy *δ*-lactone **34**[7] as a single product. After conversion of **34** into acetate **35**, the carbon four unit as the side chain was stereoselectively introduced by treatment with $CH_2{=}C(CH_2OAc)CH_2TMS$ in the presence of TMSOTf to give **36**.[7] Methanolysis of the acetate in **36**, TBDPS protection, $LiAlH_4$ reduction, selective TBS protection, and oxidation afforded ketone **37**, which was subjected to thioacetalization, selective removal of the TBS group, and oxidation with SO_3· pyridine to give aldehyde **3b**, corresponding to the IJK-ring.

With both segments **2** and **3b** in hand, our effort turned toward completion of the total synthesis of **1** through their coupling following Nicolaou's procedure.[2c] Treatment of **2** with *n*-BuLi followed by addition of **3b** effected the coupling to give (*Z*)-olefin. Removal of the TMS group followed by $AgClO_4$ treatment induced ring closure to monothioacetal **38**, which was reduced with Ph_3-SnH in the presence of AIBN to give **39**, corresponding to the ABCDEFGHIJK-ring. After removal of the TBDPS group in **39**, treatment with PCC effected double oxidation of alcohol and A-ring methylene at the right and left sides to give lactone-aldehyde **40**, accompanied by monooxidized **41**.[22] Final removal of the TBS group of **40** furnished BTX-B (**1**). The spectral data of synthetic **1** were identical with those reported.[1,2c] Thus, the total synthesis of BTX-B (**1**) has been efficiently achieved with high stereoselectivity in 59 steps as the longest linear sequence (tri-*O*-acetyl-D-glucal (**4**) → BTX-B (**1**)) and in total 90 steps with an average of 93% yield for each step.

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Supporting Information Available: Experimental procedures and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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