Pergamon

Tetrahedron Letters 41 (2000) 7673–7676

TETRAHEDRON LETTERS

# Synthetic studies on brevetoxin-B. Part 1: Stereoselective synthesis of the ABC-ring system

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

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

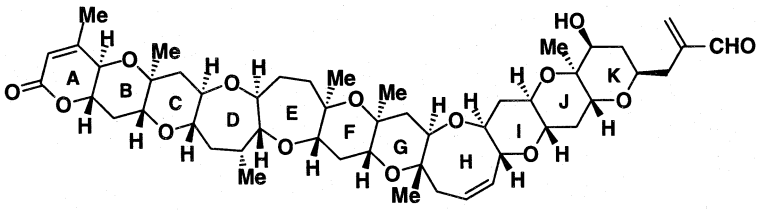
Received 13 July 2000; revised 3 August 2000; accepted 4 August 2000

**Abstract**

The ABC-ring system of brevetoxin-B was stereoselectively synthesized based on the 6-*endo*-cyclization of a hydroxy methylepoxide, ring-closing olefin metathesis and $SmI_2$-induced reductive intramolecular cyclization. 

*Keywords:* brevetoxin-B; *endo*-cyclization; olefin metathesis; radical cyclization; samarium diiodide.

Brevetoxin-B (BTX-B) (**1**),[1] a potent neurotoxin produced by the red tide organism *Gymnodium breve* Davis, has a *trans*-fused polycyclic ether ring system which contains six-, seven- and eight-membered ether rings, 23 stereocenters, three carbon–carbon double bonds and two carbonyl groups. Its unique complex structure and potent biological activity have attracted the attention of synthetic organic chemists, and the first total synthesis of **1** was accomplished by the Nicolaou group.[2] We have recently been investigating the total synthesis of **1** based on our developed synthetic methods. Our synthetic strategy toward BTX-B (**1**) mainly includes four efficient methods for the stereoselective synthesis of *trans*-cyclic ethers: (**a**) the $Zn(OAc)_2$-induced ring-expansion reaction of cyclic ethers **ii** having a chloromethanesulfonate (monochlate) as the leaving group,[3] (**b**) the 6-*endo*-cyclization of styrylepoxide **iv** with CSA, PPTS, or NaH,[4] (**c**) the $SmI_2$-induced reductive intramolecular cyclization of cyclic ethers **vi** having a β-alkoxyacrylate and a carbonyl group,[5] and (**d**) the 6-*endo*-cyclization of the methylepoxide **viii**. In addition to our recently developed methods (**a**–**c**), we included (**d**) the 6-*endo*-cyclization of **viii** as an efficient method for the stereoselective synthesis of *trans*-cyclic ethers. The cyclization of the methylepoxide

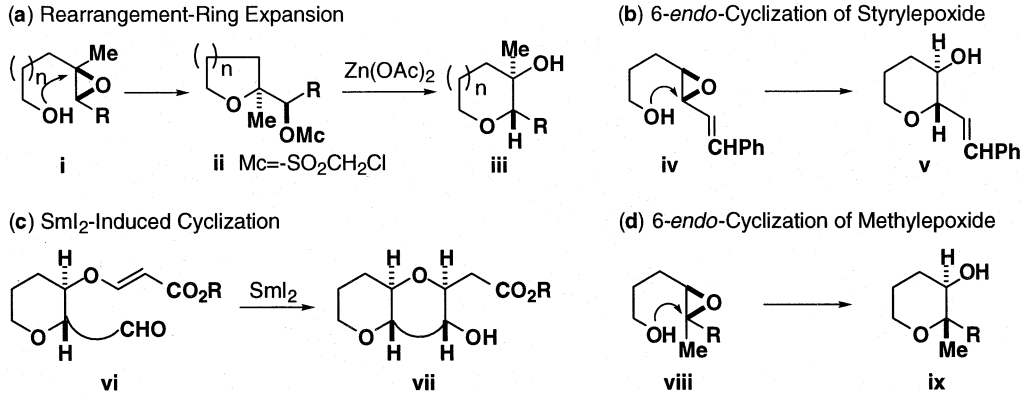



**Brevetoxin B (1)**

* Corresponding author. Fax: +81 48 462 4666; e-mail: nakata@postman.riken.go.jp

0040-4039/00/$ - see front matter 
PII: S0040-4039(00)01341-1

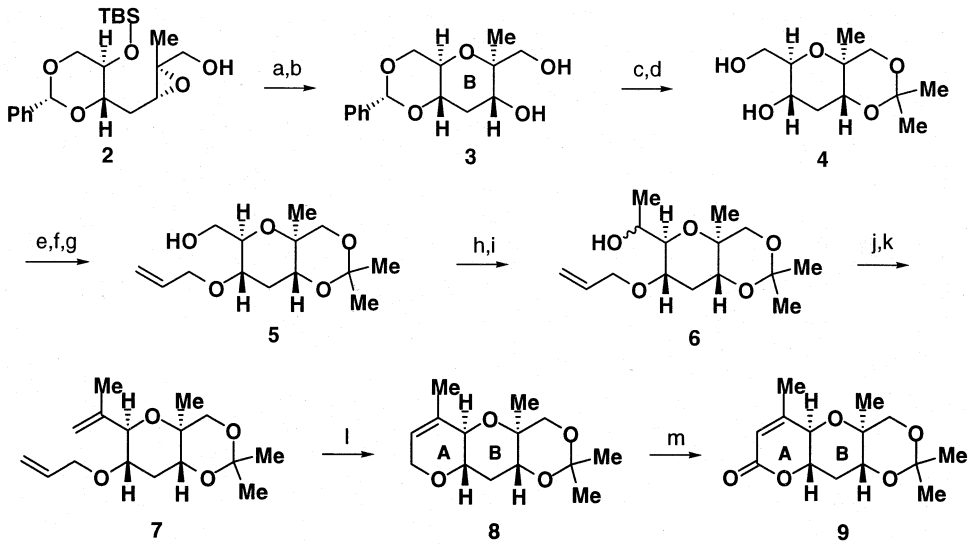
of this type would proceed in the 6-*endo*-mode at the methyl position without any activation.[6] This method might also be useful for the synthesis of the B-, G-, and J-ring systems.




We now report the stereoselective synthesis of the ABC-ring system of BTX-B (**1**) in this paper, and the synthesis of the EFG- and IJK-ring systems in subsequent papers. Our stereoselective synthesis of the ABC-ring system features the 6-*endo*-cyclization of a methylepoxide,[6] ring-closing olefin metathesis,[7] and $SmI_2$-induced reductive intramolecular cyclization,[5] for the construction of the B-, A-, and C-ring systems, respectively.

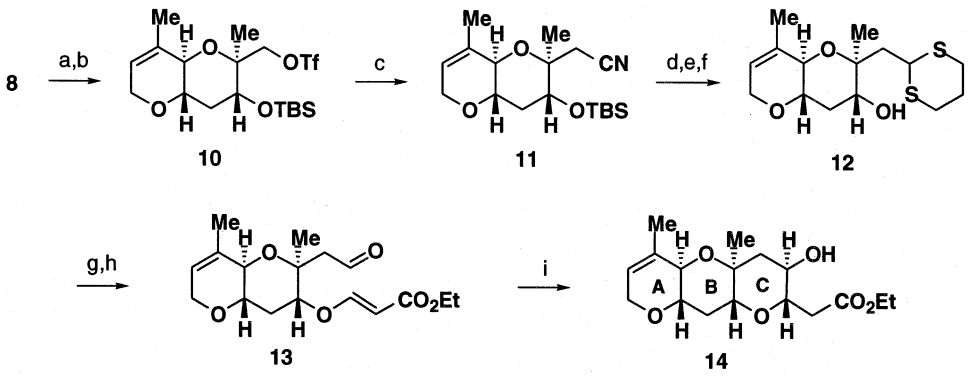
The epoxy alcohol **2**,[8] prepared from 2-deoxy-D-ribose, was chosen as the starting material for the synthesis of the ABC-ring system. Deprotection of the TBS group of **2** followed by the treatment of the resulting hydroxy methylepoxide with PPTS[9] at 0°C effected the 6-*endo*-cyclization to give the 2,3-*trans*-tetrahydropyran **3**, corresponding to the B-ring of **1**, in 93% yield. Thus, the 6-*endo*-cyclization took place at the desired methyl position of the epoxide without any activation; the cyclization using this type of methylepoxide apparently does not need activation by a vinyl[10] or a styryl group[4] next to the epoxide. To construct the dihydropyran ring as an ideal precursor for the A-ring lactone,[2] a ring-closing olefin metathesis[7] would be an efficient protocol. The diol **3** was thus converted into the diene **7** as the substrate for the olefin metathesis via the allyl ether **5**. The acetonide formation of the diol **3** followed by hydrogenolysis of the benzylidene with a catalytic amount of $Pd(OH)_2$ gave the diol **4**, which was then converted into the allyl ether **5** in three steps: (1) selective protection of the primary alcohol as the TBS ether, (2) allylation of the secondary alcohol and (3) deprotection of the TBS group. The oxidation of **5** with TPAP[11] and NMO followed by the Grignard reaction using MeMgBr gave the alcohol **6**, which was subjected to TPAP oxidation and the Wittig reaction using $Ph_3P{=}CH_2$ to give the required diene **7**. Upon treatment of **7** (20 mM in $CH_2Cl_2$) with 0.02 equiv. of Grubbs' reagent,[7] the ring-closing olefin metathesis smoothly proceeded at room temperature for 3 h to give exclusively the desired dihydropyran **8** in 98% yield. The oxidation of **8** with PCC in benzene at reflux afforded the α,β-unsaturated δ-lactone **9**, corresponding to the AB-ring system of **1** (Scheme 1).

We then examined the stereoselective construction of the C-ring system based on the $SmI_2$-induced reductive intramolecular cyclization[5] (Scheme 2). The removal of the acetonide in **8** with CSA in MeOH and subsequent treatment with triflic anhydride followed by TBSOTf in the presence of 2,6-lutidine in $CH_2Cl_2$[12] gave the triflate **10**, which was treated with NaCN to give the nitrile **11**. After reduction of **11** with DIBAH, the treatment of the resulting aldehyde



Scheme 1. (a) TBAF, THF, rt; (b) PPTS, $CH_2Cl_2$, 0°C (93% from **2**); (c) $Me_2C(OMe)_2$, CSA, DMF, rt (94%); (d) $H_2$, $Pd(OH)_2$, EtOAc, rt (99%); (e) TBSCl, pyridine, rt (93%); (f) allyl bromide, NaH, benzene, reflux (96%); (g) TBAF, THF, rt (95%); (h) TPAP, NMO, MS-4A, $CH_2Cl_2$, rt (86%); (i) MeMgBr, THF, rt (90%); (j) TPAP, NMO, MS-4A, $CH_2Cl_2$, rt (88%); (k) $Ph_3P^+MeBr^-$, NaHMDS, THF, 0°C (96%); (l) $(PCy_3)_2Cl_2Ru{=}CHPh$, $CH_2Cl_2$, rt (98%); (m) PCC, benzene, reflux (53%)

with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ simultaneously allowed the thioacetalization and desilylation to give the thioacetal **12**. The hetero-Michael addition of **12** with ethyl propiolate in the presence of *N*-methylmorpholine followed by dethioacetalization with MeI[13] gave the aldehyde **13**. Upon treatment of **13** with 2.2 equiv. of $SmI_2$ in the presence of 2.2 equiv. of MeOH in THF, a radical-mediated reductive cyclization smoothly proceeded at 0°C for 1 h to exclusively give *trans*-fused tricyclic tetrahydropyran **14** in 91% yield, corresponding to the ABC-ring system of **1**. The stereostructure of **14** was confirmed by the NMR analysis (NOE and HMBC).



Scheme 2. (a) CSA, MeOH, rt (92%); (b) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −78°C, then TBSOTf, −78 ~ 0°C (98%); (c) NaCN, MS-4A, DMSO, 80°C (61%); (d) DIBAH, $CH_2Cl_2$, −78°C; (e) $BF_3{\cdot}Et_2O$, $HS(CH_2)_3SH$, $CH_2Cl_2$, −78 ~ 0°C; (f) TBAF, THF, rt (63% from **11**); (g) ethyl propiolate, *N*-methylmorpholine, $CH_2Cl_2$, rt (70%); (h) MeI, aq. MeCN, rt (100%); (i) 2.2 equiv. of $SmI_2$, 2.2 equiv. of MeOH, THF, 0°C (91%)

In summary, the ABC-ring system of BTX-B (**1**) was efficiently synthesized with complete stereoselection based on the 6-*endo*-cyclization of the methylepoxide, the ring-closing olefin metathesis, and the $SmI_2$-induced cyclization.

## Acknowledgements

This work was supported in part by Special Project Funding for Basic Science (Multibioprobe) from RIKEN. The authors thank Dr. H. Koshino for the NMR spectral measurements and Ms. K. Harata for the mass spectral measurements.

## References

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.
2. (a) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H.-M.; Bleckman, T. *J. Am. Chem. Soc.* **1995**, *117*, 10239. (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.
3. (a) Hori, N.; Nagasawa, K.; Shimizu, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2145. (b) Nakata, T.; Nomura, S.; Matsukura, H. *Tetrahedron Lett.* **1996**, *37*, 213.
4. (a) Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545. (b) Matsukura, H.; Morimoto, M.; Nakata, T. *Chem. Lett.* **1996**, 487.
5. (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099. (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859.
6. Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171.
7. For a review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
8. Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.
9. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
10. (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.
11. For a review, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
12. Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158.
13. Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68.