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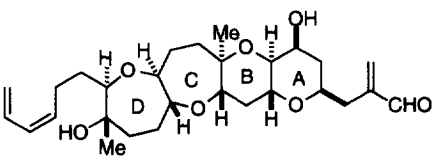
Total Synthesis of Hemibrevetoxin B

Masamichi Morimoto,[1] Hiroko Matsukura, and Tadashi Nakata*

The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-01, Japan

Abstract: Total synthesis of hemibrevetoxin B was stereoselectively accomplished based on a novel double rearrangement-ring expansion of a 6,6-membered ether to a 7,7-membered ether, an exclusive 6-*endo*-cyclization of hydroxy styrylepoxide, and a direct introduction of a C-4 unit as the side chain on the A-ring. Copyright © 1996 Elsevier Science Ltd

The brevetoxins, represented by brevetoxin A and B, are potent neurotoxins produced by the red tide organism *Gymnodium breve* and constitute an important class of marine polycyclic ethers. Hemibrevetoxin B (**1**),[2] whose molecular size is about half that of brevetoxins, was isolated from the cultured cells of *Gymnodinium breve* by Shimizu in 1989. The characteristic structural features of **1** include trans-fused 6, 6, 7, 7-tetracyclic ether rings (ABCD-ring system) having 10 chiral centers, an α-vinyl aldehyde and a (*Z*)-diene moieties. The unique complex structure and potent biological activity have attracted the attention of numerous synthetic organic chemists,[3] and the total syntheses of **1** have recently been accomplished by the Nicolaou[3a,b] and Yamamoto[3c] groups. We have also reported several studies directed toward developing an efficient method for the synthesis of the cyclic ethers and toward the total synthesis of this class of marine polyethers.[4-8] In this paper, we report the stereoselective total synthesis of hemibrevetoxin B (**1**), which features a novel double ring-expansion of the bicyclic ether for the CD-ring formation, an exclusive 6-*endo* cyclization of the hydroxy styrylepoxide for the B-ring formation, and a direct insertion of a C-4 unit as the side chain on the A-ring.



Hemibrevetoxin B (**1**)

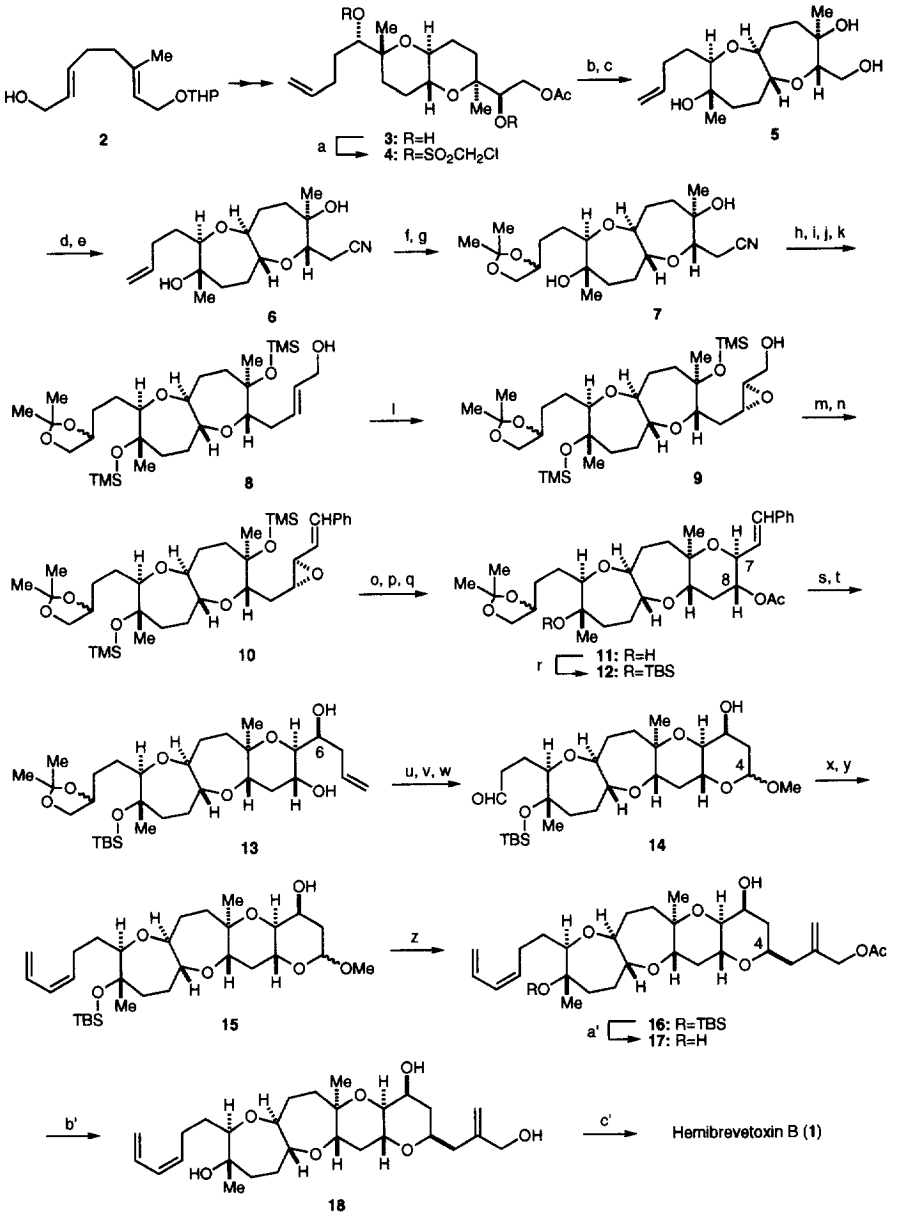
The CD-ring system of **1** was constructed based on the recently developed synthetic method for oxepans by the rearrangement-ring expansion.[4] The synthesis began with the previously reported 6,6-

membered bicyclic ether **3** prepared from **2**.[5] The bicyclic ether **3** was treated with chloromethanesulfonyl chloride in the presence of 2,6-lutidine in CH_2Cl_2 to give bis-chloromethanesulfonate **4**.[9] Upon treatment of **4** with $Zn(OAc)_2$ in aq AcOH at 80 °C, the expected double rearrangement-ring expansion took place effectively giving the 7,7-membered bicyclic ether, which was hydrolyzed with K_2CO_3 to give triol **5**[10] corresponding to the CD-ring system in 60% overall yield from **3**.[11,12]

The construction of the AB-ring system was then carried out following the route developed in our model studies.[6] Treatment of the triol **5** with TsCl and then NaCN gave nitrile **6** in 90% yield. Dihydroxylation of olefin **6** with OsO_4 and NMO produced a 1:1 mixture of the diol which was proteced as the acetonide **7** in 93% yield. Reduction of **7** with DIBAH afforded an aldehyde which was further subjected to the Wittig reaction, silylation, and DIBAH reduction to give allyl alcohol **8** in 74% yield. The Sharpless asymmetric epoxidation[13] of **8** with *t*-BuOOH in the presence of (-)-DET and $Ti(Oi\text{-}Pr)_4$ in CH_2Cl_2 stereoselectively afforded α-epoxide **9**. Ring closure of the epoxy alcohol **9** to the 6-membered ether corresponding to the B-ring system was stereoselectively accomplished via the 6-*endo*-cyclization of an epoxy alcohol having a styryl group adjacent to the epoxide.[6,14] Oxidation of **9** with TPAP and NMO[15] followed by the Wittig reaction using $Ph_3P{=}CHPh$ gave a 1:4 mixture of (*E*)- and (*Z*)-styrenes **10** in 67% overall yield from **8**. After deprotection of the TMS ether with TBAF, regio- and stereoselective 6-*endo*-cyclization of the hydroxy styrylepoxide **10** was performed by treatment with CSA, giving the 6-membered ether which was treated with Ac_2O to give **11**[16] in 71% yield. Protection of the tertiary alcohol in **11** with TBSOTf gave **12** in 92% yield. Ozonolysis of the double bond in **12** followed by reaction with allylmagnesium chloride gave 6β-alcohol **13** and its 6α-isomer in 59% and 29% yields, respectively.[17] After ozonolysis of the olefin **13**, treatment with Dowex (50W-X2) in MeOH effected acetalization of the resulting lactol and simultaneous deprotection of the acetonide, giving the diol which was oxidized with $NaIO_4$ to give aldehyde **14**[18] having the ABCD-ring system in 75% yield.

With the ABCD-ring system in hand, we focused our attention on the introduction of the side chains, (*Z*)-diene and α-vinyl propionaldehyde moieties, toward the total synthesis of **1**. The (*Z*)-diene moiety was first introduced according to Nicolaou's procedure:[3a] the Wittig reaction of **14** using $PhSe(CH_2)_3P^+Ph_3I^-$ stereoselectively produced (*Z*)-olefin which was treated with H_2O_2 to give (*Z*)-diene **15** in 71% yield. A C-4 unit as the right side chain was then introduced in one step by treatment of **15** with $CH_2{=}C(CH_2OAc)CH_2TMS$ in the presence of TMSOTf in MeCN to give exclusively 4β-substituted isomers **16** (64%) and **17** (34%).[6] The silyl ether **16** was again treated with TMSOTf in MeCN to give diol **17** in 67% yield.[19] Hydrolysis of the acetate **17** with K_2CO_3 gave allyl alcohol **18** (71%), which was finally oxidized with MnO_2 in ether to give α,β-unsaturated aldehyde **1** in 67% yield. The ^1H and ^{13}C NMR spectra of the synthetic **1** were identical with those of natural hemibrevetoxin B (**1**).

In summary, we have accomplished the stereoselective total synthesis of hemibrevetoxin B (**1**) by a unique synthetic strategy, in which the effectiveness of our recently developed several methods was demonstrated: a novel rearrangement-ring expansion reaction of a cyclic ether having sulfonate on the side chain, an exclusive *endo*-cyclization of hydroxy styrylepoxide, and the effective introduction of α-vinyl propionaldehyde as the side chain. The present synthetic strategy which we have developed should be effectively applicable to the synthesis of other marine polycyclic ethers.



Reagents and conditions: (a) $ClCH_2SO_2Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) $Zn(OAc)_2$, AcOH-H_2O, 60 ~ 80 °C; (c) K_2CO_3, MeOH, rt (60% from **3**); (d) TsCl, pyridine, rt (95%); (e) NaCN, DMSO, 80 °C (95%); (f) OsO_4, NMO, acetone-H_2O, rt; (g) $Me_2C(OMe)_2$, TsOH, acetone, rt (93% from **6**); (h) DIBAH, toluene-CH_2Cl_2, 0 °C; (i) $Ph_3P{=}CHCO_2Me$, benzene, 60 °C; (j) TMSOTf, 2,6-lutidine, CH_2Cl_2, -20 °C (76% from **7**); (k) DIBAH, toluene, -78 °C (98%); (l) t-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$, (-)-DET, 4A-MS, CH_2Cl_2, -23 °C; (m) TPAP, NMO, 4A-MS, CH_2Cl_2, rt; (n) $PhCH_2P^+Ph_3Cl^-$, $(TMS)_2NNa$, THF, 0 °C (67% from **8**); (o) TBAF, THF, rt; (p) CSA, CH_2Cl_2, -40 °C; (q) Ac_2O, pyridine, rt (71% from **10**); (r) TBSOTf, 2,6-lutidine, 0 °C ~ rt (92%); (s) O_3, MeOH-CH_2Cl_2, -78 °C; Me_2S, -78 °C ~ rt; (t) allylMgCl, THF, 0 °C ~ rt (59% for **13** and 29% for α-isomer); (u) O_3, MeOH-CH_2Cl_2, - 78°C; Me_2S, -78 °C ~ rt; (v) Dowex (50W-X2), MeOH, rt; (w) $NaIO_4$, MeOH-H_2O, rt (75% from **13**); (x) $PhSeCH_2CH_2CH_2P^+Ph_3I^-$, *n*-BuLi, THF, HMPA, -78 °C ~ rt; (y) H_2O_2, $NaHCO_3$, THF-H_2O, rt (71% from **14**); (z) $CH_2{=}C(CH_2OAc)CH_2TMS$, TMSOTf, MeCN, 0 °C (64% for **16** and 34% for **17**); (a') TMSOTf, MeCN, 0 °C (67%); (b') K_2CO_3, MeOH, rt (71%); (c') MnO_2, ether, rt (67%).

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8. Nagasawa, K.; Hori, N.; Nakata, T. *Heterocycles*, **1997**, *44*, accepted.
9. We have recently found that the (chloromethylsulfonyl)oxy group served as an efficient leaving group for the inversion of secondary alcohols. (a) Hiranuma, S.; Shimizu, T.; Nakata, T.; Kajimoto, T.; Wong, C.-H. *Tetrahedron Lett.* **1995**, *36*, 8247. (b) Shimizu, T.; Hiranuma. S.; Nakata, T. submitted.
10. The stereostructure of **5** was confirmed by the analyses of the NMR (NOE and HMBC) of the corresponding monoacetate.[5]
11. The yield of the double rearrangement-ring expansion for **3** was improved using bis-chloromethanesulfonate **4** instead of the corresponding bis-mesylate reported in ref 5.
12. The effective rearrangement-ring expansion of cyclic ethers having the (chloromethylsulfonyl)oxy group is now under investigation. The results will be reported in due course.
13. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.
14. Highly stereoselective *endo*-cyclization of hydroxy styrylepoxides will be reported in due course.
15. For a review on TPAP oxidation, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
16. The *axial* configuration of C7 and C8 protons of **11** was confirmed by the ^{1}H NMR spectra: δ 4.40 (t, J=9.5 Hz; C7-H), 4.73 (ddd, J=4.9, 9.5, 11.6 Hz; C8-H).
17. The 6α-hydroxy isomer should be also converted into the desired 6β-alcohol **13** via L-Selectride reduction of the 6-keto derivative as reported in model studies.[6]
18. A 2:1 mixture of 4α- and 4β-methoxy isomers.
19. Deprotection of the TBS ether **16** with HF-pyridine[3b] resulted in decomposition.

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