

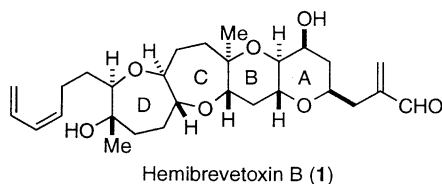
Stereoselective Synthesis of ABC-Ring System of Hemibrevetoxin B

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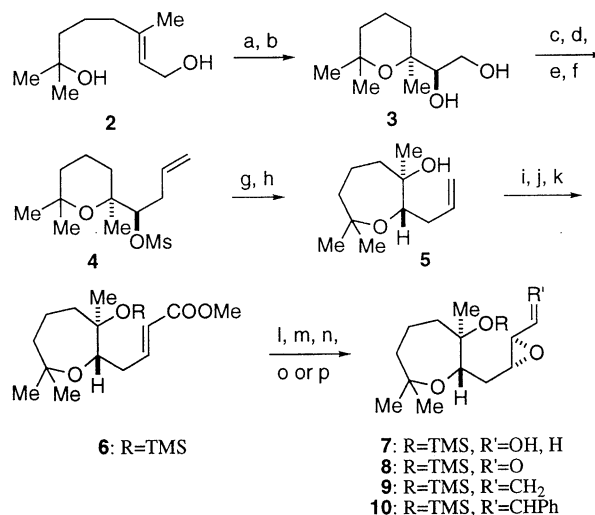
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The 6, 6, 7-membered tricyclic ether ring system (ABC-ring) of hemibrevetoxin B was stereoselectively synthesized. The crucial steps in the present synthesis involve the ring expansion of tetrahydropyran to oxepane, 6-*endo* cyclization of epoxy alcohol, and insertion of a C-4 unit to the A-ring.

Hemibrevetoxin B (**1**),¹ a potent neurotoxin isolated from the red tide organism *Gymnodinium breve*, has a 6, 6, 7, 7-tetracyclic skeleton (ABCD-ring) having 10 chiral centers, an α -vinyl aldehyde and a Z-diene moieties. The unique structure and potent activity have attracted the attention of synthetic organic chemists, and the total syntheses of **1** were accomplished by Nicolaou and Yamamoto groups.² We have recently reported the stereoselective synthesis of the C- and CD-ring systems of hemibrevetoxin B (**1**) based on the ring expansion of cyclic ethers.^{2h} We now report the stereoselective construction of the ABC-ring system of **1** using a model compound **5**.



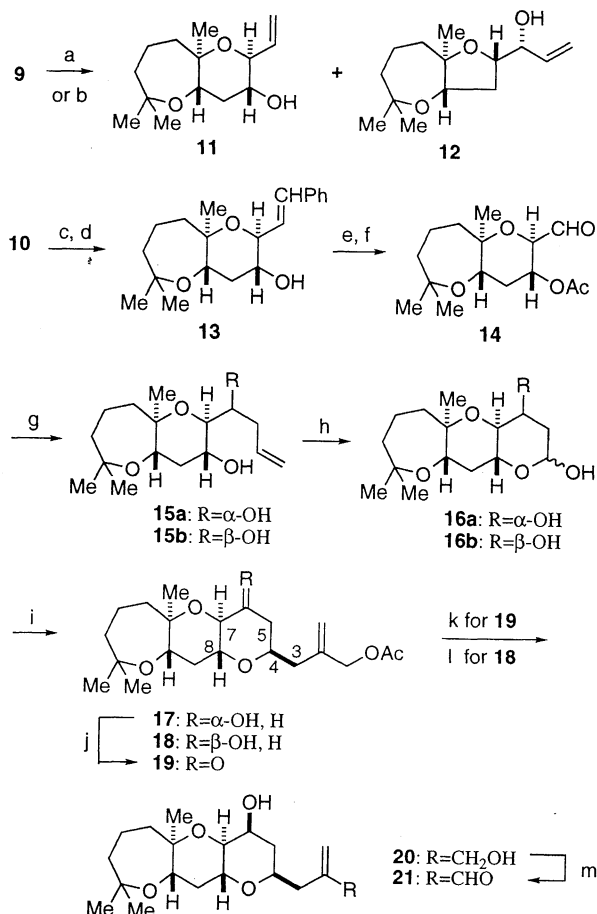
The 7-membered ether **5** corresponding to the C-ring system of **1** was synthesized using the unique rearrangement-ring expansion recently reported by us.³ The Sharpless asymmetric epoxidation (AE)⁴ of **2** with *t*-BuOOH, Ti(O-*i*-Pr)₄, and (-)-DIPT followed by PPTS treatment produced diol **3**, which was converted into mesylate **4** in 4 steps; (1) mesylation of the primary alcohol,⁵ (2) epoxide formation, (3) addition of a vinyl group, and (4) mesylation. Upon treatment of **4** with Zn(OAc)₂ in aq AcOH at 50 °C, the expected rearrangement proceeded smoothly giving the ring expanded 7-membered ether, which was treated with K₂CO₃ to give alcohol **5** in 82% yield. After protection of the tertiary alcohol as a TMS ether, **5** was subjected to ozonolysis and the Wittig reaction to give α,β -unsaturated ester **6** in 89% yield. Reduction of **6** with DIBAH followed by the Sharpless AE using (-)-DET stereoselectively produced α -epoxide **7** in 67% yield. Here we examined the 6-*endo* cyclization of the epoxide **9** using Nicolaou's procedure,⁶ which was expected to give 6-membered ether **11**. The alcohol **7** was converted into olefin **9** via aldehyde **8**. Deprotection of the silyl ether **9** with *n*-Bu₄NF followed by PPTS treatment gave unsatisfactory results producing a 1:1 mixture of 6- and 5-membered ethers, **11** and **12** in 86% yield.⁷ Better result (**11**:**12** = 3.8:1, 78%) for 6-*endo*-cyclization was obtained by treatment of **9** with aq AcOH, in which desilylation and cyclization took place simultaneously. After extensive investigations, we have succeeded in performing 6-*endo* selective cyclization which involved a styryl group next to the epoxide as a controller.⁸



Reagents and conditions: a) *t*-BuOOH, Ti(O-*i*-Pr)₄, (-)-DIPT, MS-4A, CH₂Cl₂, -23 °C; b) PPTS, CH₂Cl₂, rt (74% from **2**); c) MsCl, collidine, CH₂Cl₂, -78 °C ~ rt; d) K₂CO₃, MeOH, rt; e) vinylMgBr, CuI, THF, -20 °C (64% from **3**); f) MsCl, Et₃N, CH₂Cl₂, rt (76%); g) Zn(OAc)₂, AcOH-H₂O (1:1), 50 °C; h) K₂CO₃, MeOH, rt (82% from **4**); i) TMSOTf, 2,6-lutidine, CH₂Cl₂, rt; j) O₃, MeOH, -78 °C; Me₂S, -78 °C ~ rt; k) Ph₃P=CHCO₂Me, PhH, reflux (89% from **5**); l) DIBAH, PhMe, -78 °C (91%); m) *t*-BuOOH, Ti(O-*i*-Pr)₄, (-)-DET, CH₂Cl₂, -23 °C (74%); n) SO₃-pyridine, Et₃N, CH₂Cl₂, DMSO, 0 °C; o) Ph₃P⁺MeI⁻, NaN(TMS)₂, THF, 0 °C (31% from **7**); p) Ph₃P⁺CH₂PhCl⁻, NaN(TMS)₂, THF, 0 °C (72% from **7**).

Scheme 1.

The styryl group was introduced by the Wittig reaction of **8** with Ph₃P=CHPh to give **10** (72%; (*E*)- and (*Z*)-mixture, 1:8). Deprotection of the silyl group of **10** with *n*-Bu₄NF gave an alcohol, and upon treatment with PPTS, 6-*endo*-cyclization took place under virtually complete stereoselection giving the desired 6-membered ether **13** (86%; (*E*)- and (*Z*)-mixture, 1:8). Acetylation of **13** and successive ozonolysis gave aldehyde **14** which was treated with allylmagnesium chloride in the presence of ZnCl₂ to give a separable 1:1.7 mixture of α - and β -diols **15a** and **15b**, quantitatively. The introduction of a C-4 unit into the A-ring was then successfully undertaken. Each ozonolysis of **15a** and **15b** gave lactols **16a** and **16b** which were treated with CH₂=C(CH₂OAc)CH₂TMS in the presence of TMSOTf in MeCN to give **17** (55%) and **18** (60%), respectively. The 6 α -hydroxy acetate **17** was converted into the desired **20** via ketone **19**. Oxidation of **17** with TPAP and NMO provided ketone **19** in 71% yield.⁹ The NMR analysis of **19**¹⁰ suggested the chair conformation of the A-ring with a C4 β axial side chain: the nOe between the protons at C3 and C8, at C5 α and C7 α in **19** and long-range coupling¹¹ (*J*=1.2



Scheme 2.

Hz) of the diaxial protons at C5 α and C7 α were observed. L-Selectride reduction of **19** proceeded from the less hindered α -side as expected, giving 6 β -alcohol **20** in 71% yield.^{2f} Hydrolysis of the 6 β -hydroxy isomer **18** also gave allyl alcohol **20** (87%), which was finally oxidized with MnO_2 in ether to give aldehyde **21**¹² in 82% yield. The ^1H NMR data for **21** were in good accordance with those of the corresponding positions of hemibrevetoxin B (**1**).

Thus, we have accomplished the stereoselective synthesis of the ABC-ring system of hemibrevetoxin B (**1**). The present synthesis would be also effective for the construction of ether ring systems of other marine polycyclic ethers such as brevetoxin B. The total synthesis of hemibrevetoxin B (**1**) is now in progress.

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- # Visiting scientist from Tanabe Seiyaku Co. Ltd.
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- 7 The cyclisation of the corresponding dibromo olefin ($\text{R}'=\text{CHBr}_2$)⁶ also gave a mixture of 6- and 5-membered ethers ($\text{AcOH-H}_2\text{O}$ at rt, **11:12** = 1:1.6; $\text{CSA-CH}_2\text{Cl}_2$ at -18°C , **11:12** = 1:1.2).
- 8 The present *endo*-cyclization of epoxy alcohols having styryl group are now under investigation. The results will be reported in due course.
- 9 For a review on TPAP oxidation, see: S. V. Ley, J. Norman, W. P. Griffith, and S. P. Marsden, *Synthesis*, **1994**, 639.
- 10 Data for **19**: $[\alpha]_{\text{D}}^{27} +10.4$ (c 0.53, CHCl_3); IR (neat) 1740 cm^{-1} ; ^1H NMR (500MHz; CDCl_3) δ 1.13 (s, 3H), 1.16 (s, 3H), 1.23 (s, 3H), 2.09 (s, 3H), 2.24 (dd, $J=14.7$, 7.0 Hz, 1H), 2.44 (dd, $J=13.7$, 1.2 Hz, 1H), 2.50 (dd, $J=14.7$, 8.2 Hz, 1H), 2.87 (ddd, $J=14.0$, 7.6, 1.2¹¹ Hz, 1H), 3.41 (dd, $J=11.9$, 4.9 Hz, 1H), 3.59 (ddd, $J=11.3$, 10.1, 4.3 Hz, 1H), 4.03 (dd, $J=10.1$, 1.2¹¹ Hz, 1H), 4.51 ~ 4.59 (m, 3H), 5.06 (s, 1H), 5.19 (d, $J=0.9$ Hz, 1H).
- 11 L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford (1969), p.338.
- 12 Data for **21**: $[\alpha]_{\text{D}}^{21} +38.6$ (c 0.57, CHCl_3); IR (neat) 3475 , 1691 cm^{-1} ; ^1H NMR (500 MHz; CD_2Cl_2) δ 1.07 (s, 3H), 1.13 (s, 3H), 1.16 (s, 3H), 2.49 (dd, $J=14.7$, 5.5 Hz, 1H), 3.10 (dd, $J=14.7$, 10.1 Hz, 1H), 3.17 (dd, $J=10.1$, 3.2 Hz, 1H), 3.39 (dd, $J=11.9$, 5.0 Hz, 1H), 3.69 (ddd, $J=11.9$, 10.1, 4.6 Hz, 1H), 3.89 (ddd, $J=10.1$, 5.5, 5.5 Hz, 1H), 3.97 (ddd, $J=3.2$, 3.2, 3.2 Hz, 1H), 6.08 (s, 1H), 6.36 (d, $J=0.9$ Hz, 1H), 9.50 (s, 1H).