Stereoselective Synthesis of ABC-Ring System of Hemibrevetoxin B

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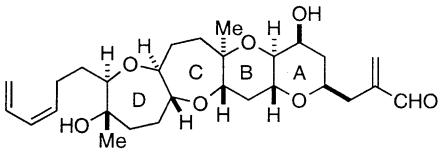
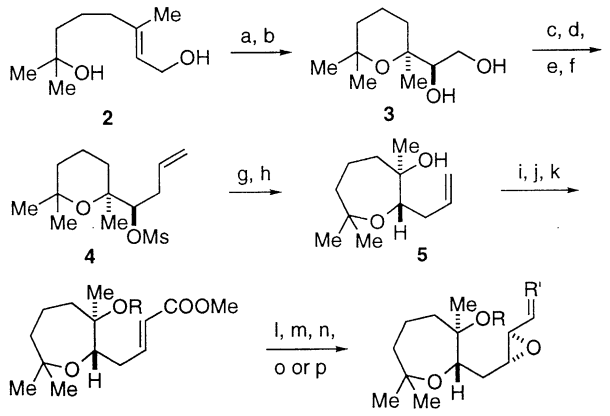
The 6, 6, 7-membered tricyclic ether ring system (ABC-ring) of hemibrevetoxin B was stereoselectively synthesized. The crucial steps in the present synthesis involve the ring expansion of tetrahydropyran to oxepane, 6-*endo* cyclization of epoxy alcohol, and insertion of a C-4 unit to the A-ring.

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**.



Hemibrevetoxin B (**1**)

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 K_2CO_3 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-Bu$_4$NF 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]



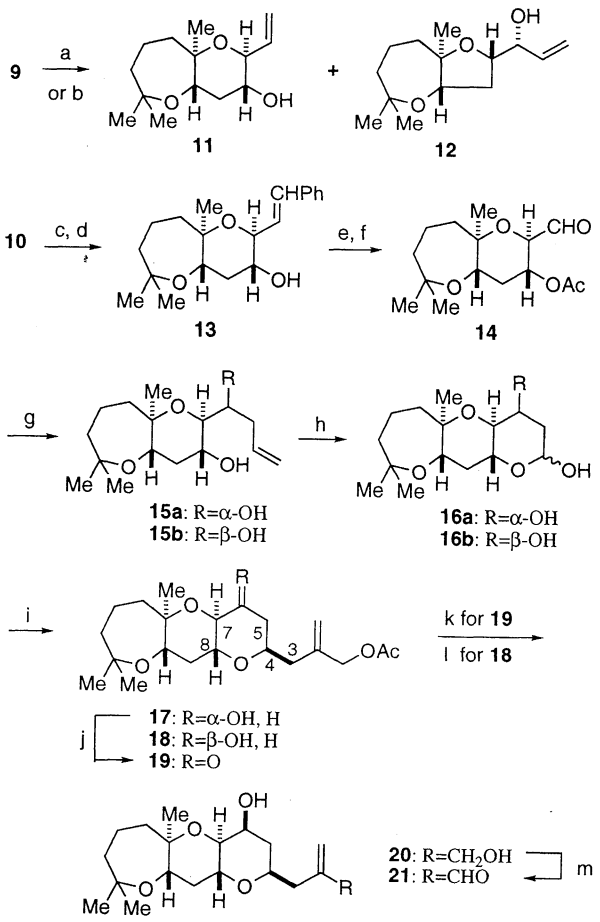
6: R=TMS

7: R=TMS, R'=OH, H
8: R=TMS, R'=O
9: R=TMS, R'=CH_2
10: R=TMS, R'=CHPh

Reagents and conditions: a) t-BuOOH, Ti(O-i-Pr)$_4$, (-)-DIPT, MS-4A, CH_2Cl_2, -23 °C; b) PPTS, CH_2Cl_2, rt (74% from **2**); c) MsCl, collidine, CH_2Cl_2, -78 °C ~ rt; d) K_2CO_3, MeOH, rt; e) vinylMgBr, CuI, THF, -20 °C (64% from **3**); f) MsCl, Et_3N, CH_2Cl_2, rt (76%); g) Zn(OAc)$_2$, AcOH-H_2O (1:1), 50 °C; h) K_2CO_3, MeOH, rt (82% from **4**); i) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt; j) O_3, MeOH, -78 °C; Me_2S, -78 °C ~ rt; k) $Ph_3P{=}CHCO_2Me$, PhH, reflux (89% from **5**); l) DIBAH, PhMe, -78 °C (91%); m) t-BuOOH, Ti(O-i-Pr)$_4$, (-)-DET, CH_2Cl_2, -23 °C (74%); n) SO_3-pyridine, Et_3N, CH_2Cl_2, DMSO, 0 °C; o) $Ph_3P^+MeI^-$, NaN(TMS)$_2$, THF, 0 °C (31% from **7**); p) $Ph_3P^+CH_2PhCl^-$, NaN(TMS)$_2$, THF, 0 °C (72% from **7**).

Scheme 1.

The styryl group was introduced by the Wittig reaction of **8** with $Ph_3P{=}CHPh$ to give **10** (72%; (*E*)- and (*Z*)-mixture, 1:8). Deprotection of the silyl group of **10** with n-Bu$_4$NF 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 $ZnCl_2$ 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 $CH_2{=}C(CH_2OAc)CH_2TMS$ in the presence of TMSOTf in MeCN to give **17** (55%) and **18** (60%), respectively. The 6α-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 C4β axial side chain: the nOe between the protons at C3 and C8, at C5α and C7α in **19** and long-range coupling[11] (J=1.2



Reagents and conditions: a) n-Bu_4NF, THF, rt; PPTS, CH_2Cl_2, rt (86%) b) AcOH-H_2O (10:1), rt (78%); c) n-Bu_4NF, THF, rt; d) PPTS, CH_2Cl_2, rt (86% from **10**); e) Ac_2O, pyridine, rt; f) O_3, MeOH, -78 °C; Me_2S, -78 °C ~ rt; g) allylMgCl, $ZnCl_2$, THF, 0 °C (100% from **13**); h) O_3, CH_2Cl_2, -78 °C; Me_2S, -78 °C ~ rt; i) CH_2=C(CH_2OAc)CH_2TMS, TMSOTf, MeCN, 0 °C (55% for **17** from **15a**, 60% for **18** from **15b**); j) TPAP, NMO, CH_2Cl_2, rt (71%); k) L-Selectride, THF, -78 ~ -30 °C (71%); l) K_2CO_3, MeOH, rt (87%); m) MnO_2, ether, rt (82%).

Scheme 2.

Hz) of the diaxial protons at C5α and C7α were observed. L-Selectride reduction of **19** proceeded from the less hindered α-side as expected, giving 6β-alcohol **20** in 71% yield.[2f] Hydrolysis of the 6β-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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7 The cyclisation of the corresponding dibromo olefin (R'=$CHBr_2$)[6] also gave a mixture of 6- and 5-membered ethers (AcOH-H_2O at rt, **11**:**12** = 1:1.6; CSA-CH_2Cl_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**: $[\alpha]_D^{27}$ +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, 1.2[11] 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, 1.2[11] 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**: $[\alpha]_D^{21}$ +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).