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Stereoselective Synthesis of the C- and CD-Ring Systems of Hemibrevetoxin B

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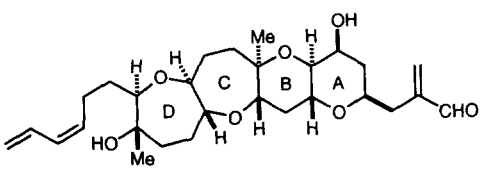
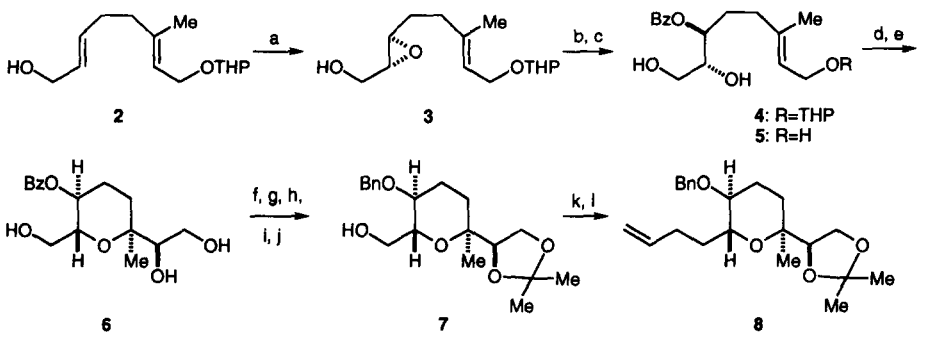
Abstract: The 7, 7-membered CD ring system of hemibrevetoxin B was stereoselectively synthesized. The crucial steps involve the Sharpless asymmetric epoxidation, cyclization to the 6-membered ether, and double rearrangement of the 6, 6-membered bicyclic ether with the simultaneous ring expansion.

Hemibrevetoxin B (**1**),[2] a potent neurotoxin isolated from the red tide organism *Gymnodinium breve*, has a 6,6,7,7-tetracyclic skeleton (ABCD-ring) and contains 10 chiral centers, an α-vinyl aldehyde, and *Z*-diene moieties. Its unique structure and potent activity have attracted the attention of synthetic organic chemists, and recently the total synthesis of **1** was accomplished by the Nicolaou and Yamamoto groups.[3] In a preceding paper,[4] we reported the synthesis of 6- and 7-membered cyclic ethers based on the ring expansion. We now report the stereoselective synthesis of the C- and CD-ring systems of hemibrevetoxin B (**1**) based on the ring expansion of the cyclic ether.



Hemibrevetoxin B (**1**)

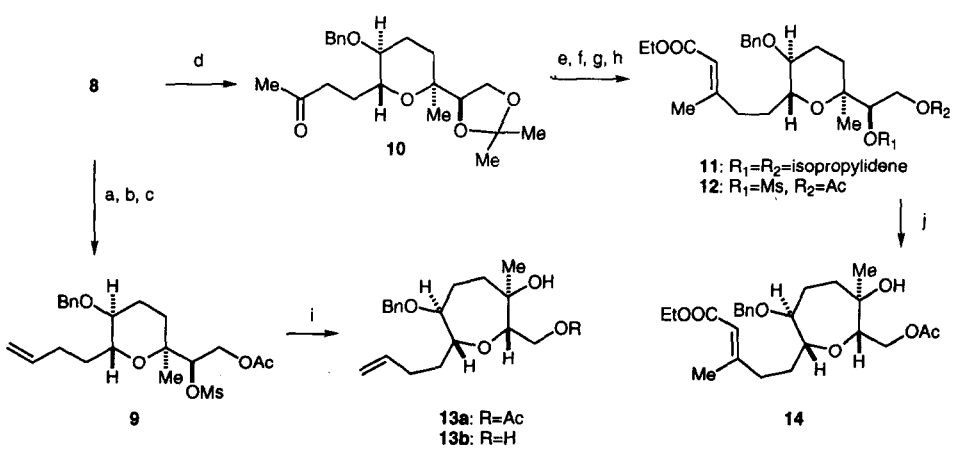
Olefin **2**,[5] prepared from geraniol, was chosen as the starting material. The Sharpless asymmetric epoxidation (AE)[6] of **2** with t-BuOOH in the presence of D-(-)-DIPT and $Ti(O\text{-}iPr)_4$ in CH_2Cl_2 afforded the α-epoxide **3** (98%), which was treated with $Ti(O\text{-}iPr)_4$ and PhCOOH[7] to give the benzoate **4** in 92% yield. After deprotection of the THP ether (86%), the resulting alcohol **5** was again subjected to the Sharpless AE (t-BuOOH, D-(-)-DIPT) and treated with CSA to give the tetrahydrofuran derivative **6** in 69% yield. The triol **6** was then converted into acetonide **7** in 5 steps (74% overall yield); (1) acetonization of the diol, (2) alkaline hydrolysis of the benzoate, (3) protection of the primary alcohol as the TBDPS ether, (4) protection of the secondary alcohol as the benzyl ether, and (5) deprotection of the TBDPS ether. The treatment of **7** with triflic anhydride-pyridine followed by allylmagnesium chloride in the presence of CuI in ether at -50°C



Reagents and conditions: a) t-BuOOH, D-(-)-DIPT, $Ti(O\text{-}iPr)_4$, 4A-MS, CH_2Cl_2, -23°C (98%); b) PhCOOH, $Ti(O\text{-}iPr)_4$, CH_2Cl_2, 0°C ~ rt (92%); c) Dowex (50W-X2), MeOH, rt (86%); d) t-BuOOH, D-(-)-DIPT, $Ti(O\text{-}iPr)_4$, 4A-MS, CH_2Cl_2, -23°C; e) CSA, CH_2Cl_2, rt (69% from **5**); f) p-TsOH, $Me_2C(OMe)_2$, acetone, rt; g) K_2CO_3, EtOH, rt (87% from **6**); h) TBDPSCl, imidazole, DMF, rt (100%); i) NaH, BnBr, n-Bu_4NI, THF, 0°C ~ rt (92%); j) n-Bu_4NF, THF, rt (93%); k) Tf_2O, pyridine, CH_2Cl_2, -10°C; l) allylMgCl, CuI, ether, -50°C (82% from **7**).

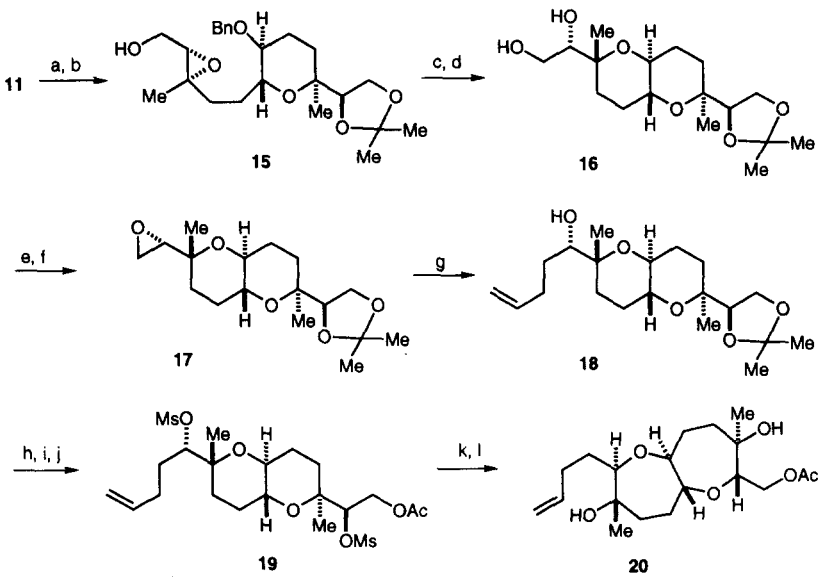
produced olefin **8** in 82% yield.[8]

The mesylates **9** and **12** required for the rearrangement were then synthesized from **8**. The hydrolysis of the acetonide **8** in aq AcOH, selective acetylation with AcCl-collidine[9] and mesylation produced the mesylate **9** in 36% yield.[10] On the other hand, the Wacker oxidation of **8** effectively afforded ketone **10** (89%) which was subjected to the Wittig-Horner reaction to give the α,β-unsaturated ester **11** in 96% yield. Successive treatment of **11** with aq AcOH, AcCl-collidine, and MsCl-Et_3N gave the mesylate **12** in 78% yield. The reaction of the mesylates **9** and **12** with $Zn(OAc)_2$ in AcOH-H_2O (1:1) at reflux produced the 7-membered ethers **13**[11] and **14**[12] corresponding to the C-ring system in 73% (**13a**; 58% + **13b**; 15%) and 57% yields (after acetylation), respectively. Repeating the same type of reactions on ethers **13** and **14** having the requisite functional groups would construct the D-ring system.

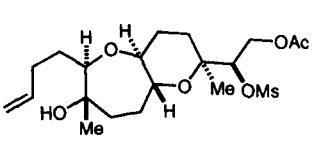


Reagents and conditions: a) aq AcOH, rt ~ 100°C (67%); b) AcCl, collidine, CH_2Cl_2, -78°C (73%); c) MsCl, Et_3N, CH_2Cl_2, rt (73%); d) O_2, $PdCl_2$, CuCl, DMF-H_2O (10 : 1), rt (89%); e) NaH, $(EtO)_2P(O)CH_2COOEt$, benzene, rt (96%); f) aq AcOH, rt (96%); g) AcCl, collidine, CH_2Cl_2, -78°C (98%); h) MsCl, Et_3N, CH_2Cl_2, -16°C (83%); i) $Zn(OAc)_2$, AcOH-H_2O (1:1), reflux (73%); j) $Zn(OAc)_2$, AcOH-H_2O (1:1), reflux; then Ac_2O, pyridine, rt (57%).

Here, we examined the construction of the 7,7-membered CD-ring in one step from the 6,6-membered bicyclic ether **19** via double rearrangement. The reduction of **11** with DIBAH gave the alcohol which was subjected to the Sharpless AE (t-BuOOH, L-(+)-DIPT) giving the α-epoxide **15** in 98% yield. After deprotection of the benzyl group with $H_2/Pd(OH)_2$-C in THF, **15** was treated with PPTS to give the 6,6-membered bicyclic ether **16** in 66% yield. The reaction of **16** with MsCl-collidine[9] followed by K_2CO_3 treatment produced epoxide **17** (85%) which was treated with allylmagnesium chloride in the presence of CuI giving **18** in 77% yield. Olefin **18** was converted into the required dimesylate **19** in 3 steps (68% overall yield); (1) deprotection of the acetonide, (2) selective acetylation of the primary alcohol, and (3) mesylation. Upon treatment of **19** with $Zn(OAc)_2$ in AcOH-H_2O (1:1) at reflux, the required double rearrangement effectively took place giving the 7,7-membered ether **20**[13] in 34% yield[10] (after acetylation), corresponding to the CD-ring system of **1**. In this reaction, the first rearrangement took place on the left ring of **19** producing the 6,7-membered ether **21**, which was then rearranged to the 7,7-membered ether **20**. The stereostructure of the product **20** was confirmed by the NMR analysis (NOE and HMBC) as shown in Fig1.



Reagents and conditions: a) DIBAH, toluene, -78°C (100%); b) t-BuOOH, L-(+)-DIPT, $Ti(O\text{-}iPr)_4$, 4A-MS, CH_2Cl_2, -23°C (98%); c) H_2, $Pd(OH)_2$-C, THF, rt (93%); d) PPTS, CH_2Cl_2, -16°C ~ rt (71%); e) MsCl, collidine, CH_2Cl_2, -78°C ~ rt; f) K_2CO_3, MeOH, rt (85% from **16**); g) allylMgCl, CuI, THF, -20°C (77%); h) aq AcOH, rt (98%); i) AcCl, collidine, CH_2Cl_2,-20°C (90%); j) MsCl, Et_3N, CH_2Cl_2, 0°C ~ rt (77%); k) $Zn(OAc)_2$, AcOH-H_2O (1:1), reflux; l) Ac_2O, pyridine, rt (34% from **19**).



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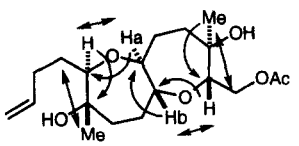

20 $J_{a,b} \approx 9.3$ Hz

NOE

HMBC

Fig 1

Thus, we have accomplished the stereoselective synthesis of the C- and CD-ring systems of hemibrevetoxin B (**1**) based on the ring expansion. Recently, we have succeeded in the stereoselective construction of the ABC-ring system of **1** using a model compound, which will be reported in due course. Based on these results, the synthesis of hemibrevetoxin B (**1**) is now in progress.

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5. The olefin **2** was synthesized from 4-methyl-6-acetoxy-trans-hex-4-enal[14] as follows: (1) $Ph_3P{=}CHCO_2Me$, benzene, reflux (69%); (2) K_2CO_3, MeOH, 0°C ~ rt (84%); (3) DHP, TsOH, ether, 0°C ~ rt (92%); (4) DIBAH, toluene, -65°C (83%).
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10. The yield was not yet optimized.
11. Data for **13a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (s, 3H), 2.06 (s, 3H), 3.30 (td, J=6.7, 3.6 Hz, 1H), 3.40 (ddd, J=9.7, 7.1, 2.7 Hz, 1H), 3.57 (dd, J=8.8, 2.9 Hz, 1H), 4.11 (dd, J=11.5, 9.0 Hz, 1H), 4.28 (dd, J=11.5, 2.7 Hz, 1H), 4.39 (d, J=11.2 Hz, 1H), 4.59 (d, J=11.7 Hz, 1H), 4.96 (d, J=10.2 Hz, 1H), 5.03 (dd, J=17.1, 1.9 Hz, 1H), 5.84 (ddt, J=17.1, 10.3, 6.3 Hz, 1H).
12. Data for **14**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.28 (t, J=7.0 Hz, 3H), 2.07 (s, 3H), 2.15 (d, J=1.0 Hz, 3H), 3.23-3.39 (m, 2H), 3.56 (dd, J=8.9, 2.3 Hz, 1H), 4.08 (dd, J=11.6, 8.9 Hz, 1H), 4.14 (q, J=7.2 Hz, 2H), 4.30 (dd, J=11.6, 2.6 Hz, 1H), 4.38 (d, J=11.6 Hz, 1H), 4.60 (J=11.6 Hz, 1H), 5.66 (d like, J=8.9 Hz, 1H).
13. Data for **20**: $[\alpha]_D$ +13.9° (c 0.36, $CHCl_3$); IR ($CHCl_3$) 3600, 1740, 1240, 1090 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.17 (s, 3H), 2.08 (s, 3H), 3.16-3.31 (m, 3H), 3.56 (dd, J=8.2, 3.4 Hz, 1H), 4.13 (dd, J=11.3, 8.2 Hz, 1H), 4.19 (dd, J=11.3, 3.4 Hz, 1H), 4.98 (d like, J=10.1 Hz, 1H), 5.04 (ddt, J=17.2, 1.9, 1.5 Hz, 1H), 5.83 (dddd, J=17.2, 10.5, 7.3, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 ($CO\underline{C}H_3$), 24.2 (CH_3x2), 28.75 (CH_2), 28.84 (CH_2), 29.8 (CH_2), 31.1 (C=C-$\underline{C}$), 39.38 (CH_2), 39.44 (CH_2), 64.6 ($\underline{C}OC{=}O$), 74.1 (COH), 74.8 (COH), 85.4 (CO), 87.3 (CO), 88.0 (CO), 88.7 (CO), 114.9 ($\underline{C}{=}C$-C), 138.7 (C=$\underline{C}$-C), 171.0 (OC=O).
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