Synthesis of the A- and B-Ring System of Hemibrevetoxin-B

Fei Feng and Akio Murai*
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

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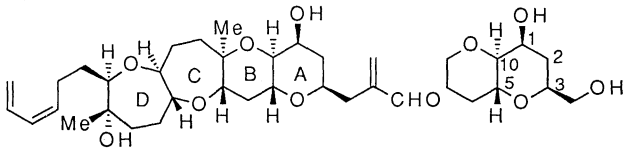
The A- and B-ring system of hemibrevetoxin-B, which has been isolated from the red tide organism, *Gymnodinium breve*, has been synthesized in an optically pure form starting from δ-valerolactone.

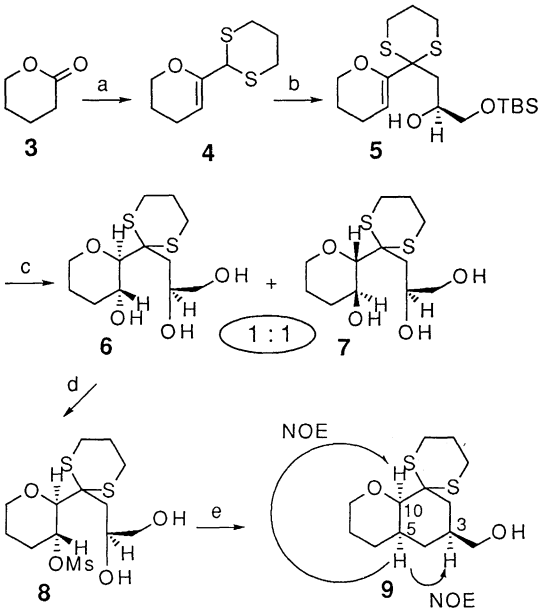
Continuing the previous paper[1] about the synthetic studies on hemibrevetoxin-B (**1**) isolated from the red tide organism, *Gymnodinium breve*,[2] we describe herein the synthesis of **2** corresponding to the A- and B-ring moiety of **1**.



hemibrevetoxin-B (**1**) **2**

The synthesis started with conversion of δ-valerolactone **3** into the corresponding cyclic enol ether **4** via enol trifluoromethanesulfonate (triflate)[3](Scheme 1). Thus, δ-valerolactone **3** was treated with LiHMDS in THF-HMPA and with $PhNTf_2$ to give enol triflate, which was transformed into **4** with 1,3-dithiane and BuLi in an 86% overall yield from **3**. Compound **4** was then allowed to react with BuLi and TBS-ether of (*R*)-(+)-glycidol[4] in THF at -78 °C to -30 °C for 1 h to afford **5** in 90% yield. After desilylation with TBAF, compound **5** was subjected to hydroboration reaction with BH_3·THF in THF at 20 °C for 12 h and treated with 10% NaOH and TBHP to give a separable 1:1 mixture of the triols **6** and **7** in an 82% combined yield. We could not differentiate the stereo-structures of **6** and **7** at this stage. Accordingly, the less polar compound **6** was first chosen and treated successively with $Me_2C(OMe)_2$ and PPTS in MeOH, with MsCl, Et_3N, and DMAP in CH_2Cl_2, and then with 0.4M HCl in THF to yield **8** in a 72% overall yield. Reaction of **8** with *t*-BuOK (1.05 eq) in THF at 0 °C for 3 h effected displacement of the mesyloxy group with inversion of the configuration to afford **9**, mp 109~110 °C, in 80% yield. The NOE experiments of **9** indicated that three protons of the cyclized product at C-3, C-5, and C-10 are mutually *cis*-oriented and we found **9** to be the undesired compound different from **2**.[5]

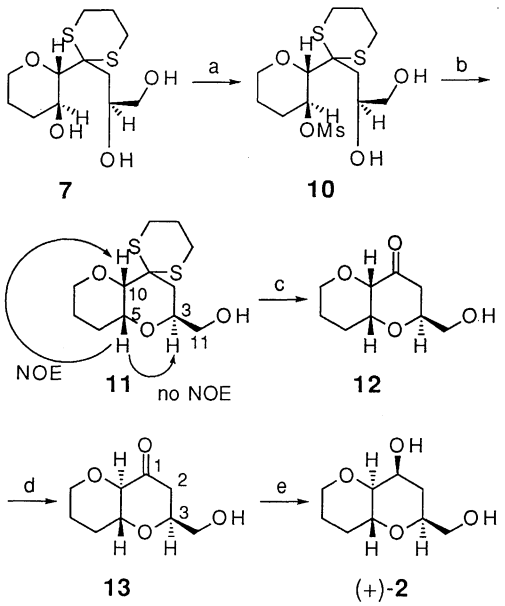
Next, we went back to another compound **7** (Scheme 2). Compound **7** was converted into the monomethanesulfonate **10** in a three step process under the same conditions as above. The compound **10** was allowed to react with *t*-BuOK in THF at 0 °C to 25 °C for 6 h to afford another cyclized product **11**, an oil, as a sole product along with 20% of the unreacted starting material **10**.[6] The NOE experiment of **11** revealed that the protons at C-5 and C-10 on ring junction are *cis*-oriented, but the protons at C-3 and C-5 are *trans*-oriented. The desired compound **11** was then hydrolyzed with MeI and $NaHCO_3$ in acetone-H_2O



Reagents and conditions: a) LiHMDS (1.5 eq), THF-HMPA (1.5 eq), -78 °C, 1.5 h, then $PhNTf_2$, -78 °C → 20 °C, 1.5 h; 1,3-dithiane, BuLi, THF-HMPA (1.8 eq), -20 °C, 12 h, 86%; b) BuLi, TBS-ether of (*R*)-glycidol, THF, -78 °C → -30 °C, 1 h, 90%; c) TBAF, THF, 0 °C, 1 h, ~100%; BH_3·THF (20 eq), THF, 20 °C, 12 h, then 10% NaOHaq, TBHP, 0 °C, 2 h → 20 °C, 2 h, 82% (**6**+**7**); d) $Me_2C(OMe)_2$, PPTS, MeOH, reflux, 4 h, 90%; MsCl, Et_3N, DMAP, CH_2Cl_2, -20 °C → 0 °C, 1 h, ~100%; 0.4M HCl (cat.), THF, 25 °C, 12 h, 90%; e) *t*-BuOK (1.05 eq), THF, 0 °C, 3 h, 80%.

Scheme 1.

(4:1) at 25 °C for 10 h to the *cis*-ketone **12**.[7] The ketone was isomerized quantitatively with DBU in CH_2Cl_2 at 0 °C for 8.5 h to the corresponding *trans*-ketone (+)-**13**, $[\alpha]_D^{20}$ +191.2° (c=0.11, $CHCl_3$). It is to be noted that the ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of **13** shows the A-ring taking the twist-boat conformation with the equatorial CH_2OH group at C-3 as indicated in Figure 1: 2αH, δ2.44 (dd, J=13.9 and 2.6 Hz) and 2βH, δ2.67 (dd, J=13.9 and 11.7 Hz). Furthermore, compound **13** was acetylated on reaction with Ac_2O (5 eq), Et_3N (10 eq), and DMAP (a catalytic amount) in CH_2Cl_2 at -10 °C for 2.5 h to give its acetate **14** in 80.3% yield. The ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of **14** showed that the A-ring would take the twist-chair conformation having the bisectional CH_2OAc group at C-3 as revealed in Figure 1: 2αH, δ2.51 (dd, J=14.6 and 2.9 Hz) and 2βH, δ2.58 (br d, J=14.6 Hz, W_H=1.1 Hz). The reason causing the conformational difference between **13** and **14** has not been clarified at this stage.



Reagents and conditions: a) $Me_2C(OMe)_2$, PPTS, MeOH, reflux, 4 h, 90%; MsCl, Et_3N, DMAP, CH_2Cl_2, -20 °C → 0 °C, 1 h, ~100%; 0.4M HCl (cat.), THF, 25 °C, 12 h, 90%; b) *t*-BuOK (1.1 eq), THF, 0 °C → 25 °C, 6 h, 65%; c) MeI, $NaHCO_3$, acetone-H_2O (4:1), 25 °C, 10 h, 75%; d) DBU (4 eq), CH_2Cl_2, 0 °C, 8.5 h, ~100%; e) L-Selectride (4 eq), THF, -78 °C, 1 h, 94%.

Scheme 2.

Finally, compound **13** was reduced with L-Selectride (4 eq) in THF to (+)-**2**, mp 54~55 °C; $[\alpha]_D^{22}$ +4.2° (c=0.10, $CHCl_3$); LREI-MS, m/z 188 (M^+), 170, 157, 144, 139 129, 111, 100, 84, 71 (100%), 55, and 41; HREI-MS, m/z 188.1055, calculated for $C_9H_{16}O_4$, 188.1049, as a sole product in 94% yield, which constitutes the A- and B-ring part of **1**. The ^{1}H-NMR spectrum (400 MHz, CD_2Cl_2) of **2**[8] showed that the A-ring takes an axial OH group at C-1: 1αH, δ4.05 (q, J=2.9 Hz) and 10αH, δ2.97 (dd, J=9.5 and 2.9 Hz).[9] However, the lack of a long range coupling expected between the protons at C-1 and C-3 would reveal that the A-ring of **2** might deviate slightly from the exact chair conformation. We are now investigating to apply the above results to construction of the whole mother skeleton of **1** aiming at the total synthesis in a chiral form in our laboratory.

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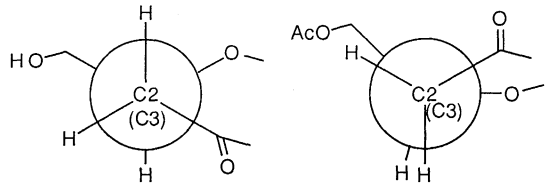

Figure 1. Plausible conformation around C-2 and C-3 of **13** and **14**.

References and Notes

1 F. Feng and A. Murai, *Chem Lett.*, **1992**, 1587.

2 A. V. K. Prasad and Y. Shimizu, *J. Am. Chem. Soc.*, **111**, 6476 (1989).

3 K. Tsushima, K. Araki, and A. Murai, *Chem. Lett.*, **1989**, 1313; K. Tsushima and A. Murai, *Chem. Lett.*, **1990**, 761.

4 The reagent was kindly provided by DAISO Co. Ltd.

5 **9**; ^{1}H-NMR (400 MHz, $CDCl_3$), δ4.07 (1H, br t, J=2.9 Hz, 5-H), 3.95 (1H, m, 3-H), and 3.44 (1H, br s, 10-H).

6 **11**; ^{1}H-NMR (400 MHz, C_6D_6), δ4.12 (2H, m, 3-H and 11-H), 4.02 (1H, br t, J=2.9 Hz, 5-H), and 3.44 (1H, br s, 10-H).

7 **12**; ^{1}H-NMR (400 MHz, $CDCl_3$), δ3.64 (1H, br s, 10-H) and 3.63 (1H, br t, J=2.9 Hz, 5-H).

8 **2**; ^{1}H-NMR (400 MHz, CD_2Cl_2), δ4.05 (1H, q, J=2.9 Hz, 1-H), 3.88 (2H, m, 3-H and 8-H), 3.58 (1H, m, 5-H), 3.55 (1H, dd, J=11.7 and 3.3 Hz, 11-H), 3.43 (1H, m, 8-H), 3.39 (1H, dd, J=11.7 and 6.6 Hz, 11-H), 2.97 (1H, dd, J=9.5 and 2.9 Hz, 10-H), 2.05~1.89 (3H, m, 2 x OH and 6-H), 1.76~1.57 (4H, m, 2-H_2 and 7-H_2), and 1.41 (1H, m, 6-H).

9 These δ-values and splitting patterns are almost coincident with those of compound **1**, which has been totally synthesized by Prof. Nicolaou et al. **1**; ^{1}H-NMR (500 MHz, CD_2Cl_2), δ4.00 (1H, br s) and 3.20 (1H, dd, J=10.1 and 2.1 Hz); cf., Ref. 2 and K. C. Nicolaou, K. R. Reddy, G. Skokotas, F. Sato, X.-Y. Xiao, and C.-K. Hwang, *J. Am. Chem. Soc.*, **115**, 3575 (1993).