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Synthesis of the C- and D-Ring System of Hemibrevetoxin-B

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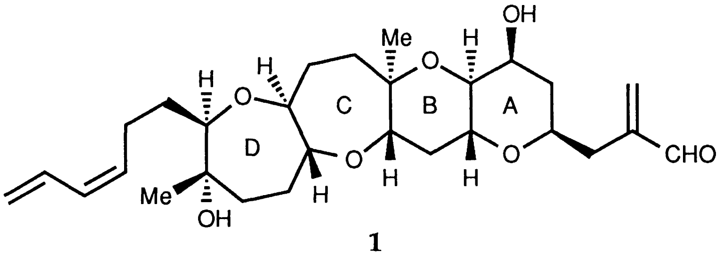
The C- and D-ring system of hemibrevetoxin-B, which has been isolated from the red tide organism, *Gymnodinium breve,* has been synthesized in a racemic form on the basis of our new methodology involving the general conversion of medium sized lactone into the corresponding cyclic ether.

Hemibrevetoxin-B (**1**) is a polycyclic ether isolated from the cultured cells of the red tide organism, *Gymnodinium breve,* by Y. Shimizu et al. in 1989.1) They reported that the compound causes the characteristic rounding of cultured mouse neuroblastoma cells as brevetoxin-A and -B and shows cytotoxicity at a low concentration. In view of its skeletal novelty and biological activity, the compound is an attractive synthetic target, although the absolute configuration has not been determined yet. Recently, we have reported the general synthetic methodology for medium sized cyclic ether starting from the corresponding lactone via its enol trifluoromethanesulfonate (triflate).2,3) In this paper we describe the preliminary synthesis of the racemic C- and D-ring system (**2**) as an application of our synthetic procedure.



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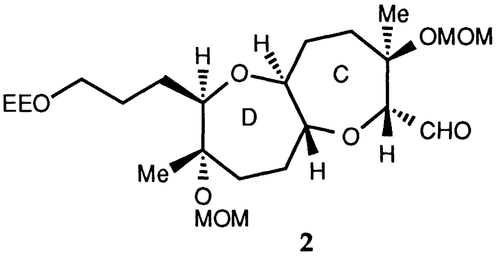
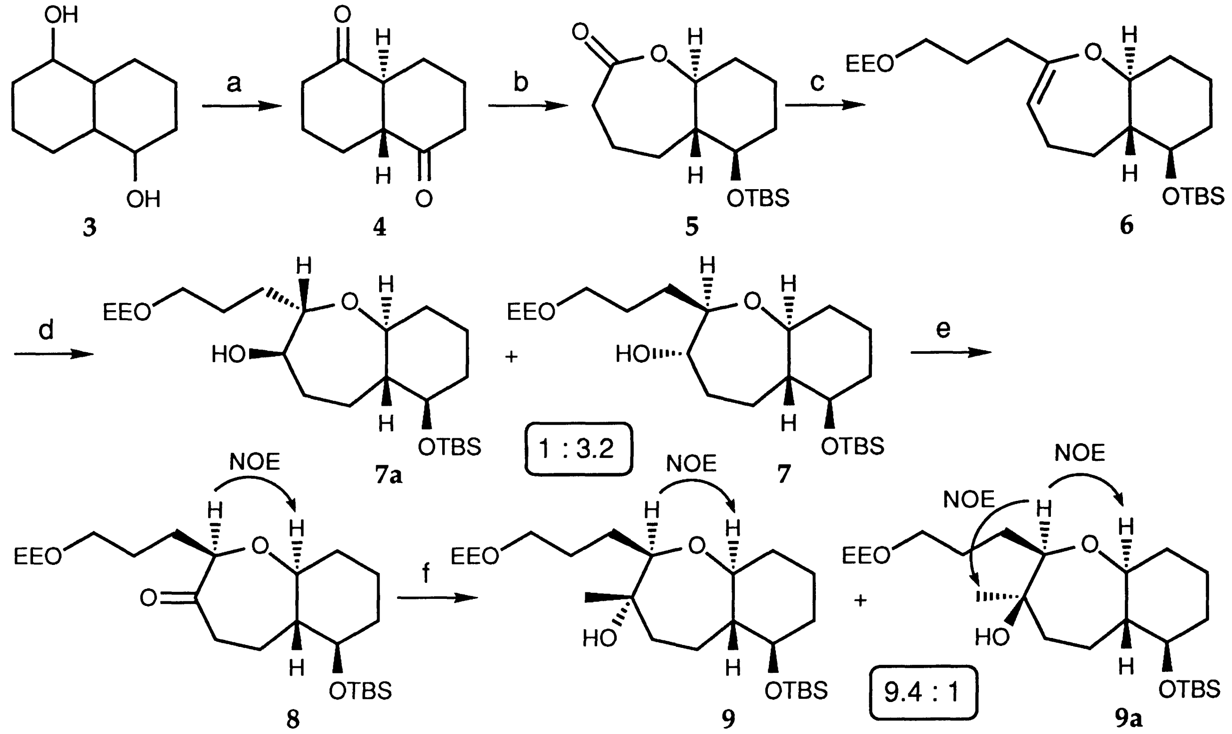


2

The construction of the D ring commenced from the commercially available 1,5-decalindiol (**3**) as a mixture of isomers (Scheme 1). The compound (**4**), obtained from **3** by Jones oxidation,4) was converted to the *t*-butyldimethylsilyloxy lactone (**5**) in a three-step process. Compound **5**, when treated with LiHMDS in a mixture of THF and HMPA, with $PhNTf_2$, and then with $(EEOCH_2CH_2CH_2)_2CuLi$ in THF-HMPA, gave rise to the corresponding cyclic enol ether (**6**) having an ethoxyethyl substituent in a 72% total yield. Compound **6** was reacted with BH_3-THF complex in THF followed by alkaline H_2O_2 to yield a 3.2:1 mixture of alcohols (**7** and **7a**) in a 83% combined yield. Minor product (**7a**) was oxidized and treated with DBU to give **8** in 83% yield, which was identified as the ketone derived directly from **7** by Swern oxidation. Compound **8** was then reacted with MeMgBr in toluene at -78 → -70 °C for 2 h to afford a 9.4:1 mixture of **9** and **9a** in a 95% combined yield. The relative configurations of **8**, **9**, and **9a** were

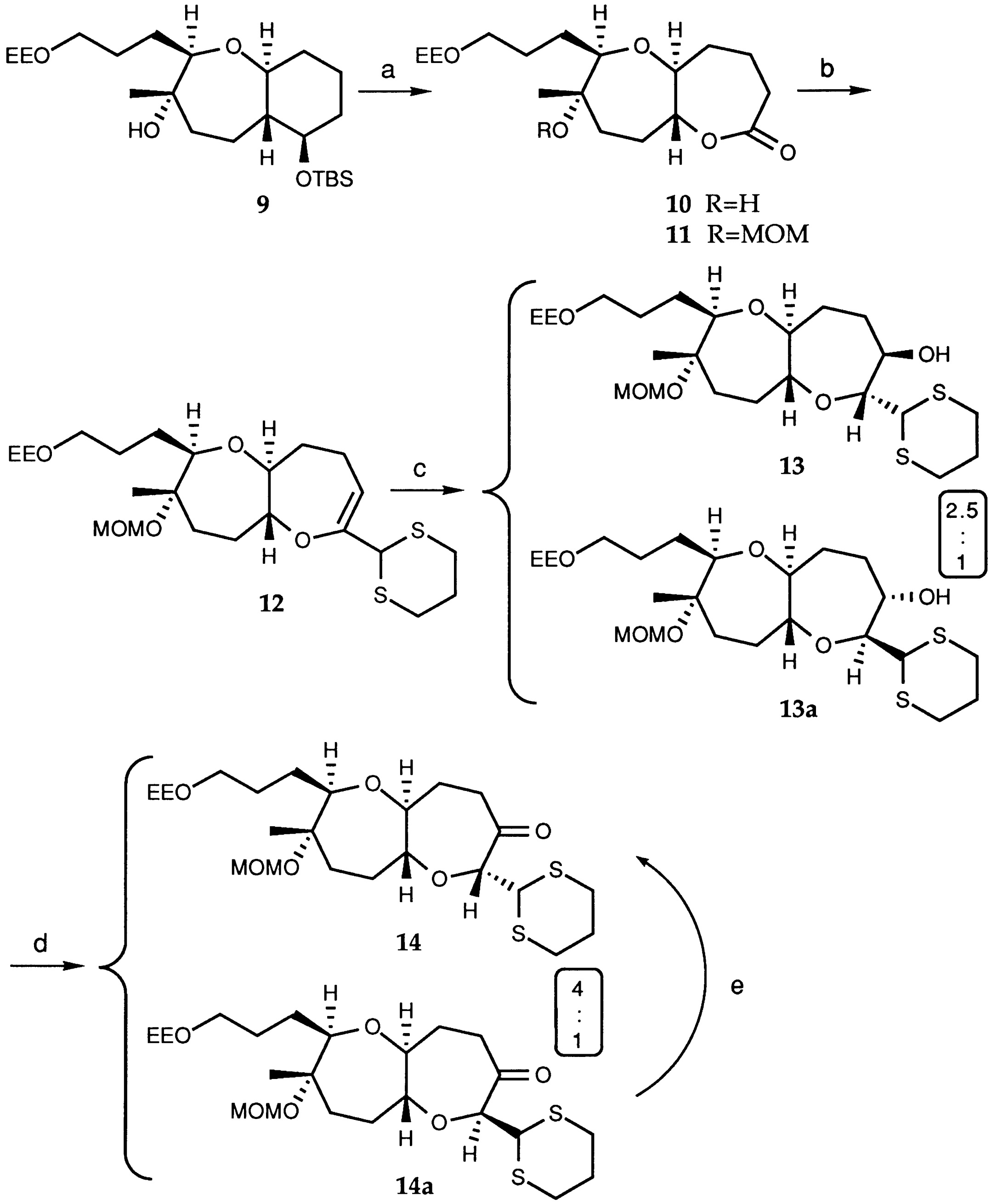


Reagents and conditions: a) Jones' oxid., 20 °C, 12 h, 70%. b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 20 °C, 4 h, 55%; $NaBH_4$, THF-H_2O (4:1), 0 °C, 0.5 h, 72%; TBSCl, imidazole, DMF, 20 °C, 12 h, 95%. c) LiHMDS, THF-HMPA, and then $PhNTf_2$; $(EEOCH_2CH_2CH_2)_2CuMgBr$, THF-HMPA, -20 °C, 12 h, 70%. d) BH_3-THF, THF, 0 °C, 1.5 h; NaOH, H_2O_2, 0 °C, 2 h, 83%. e) Swern oxid., 95%. f) MeMgBr, toluene, -78 °C → -70 °C, 2 h, 95%.

Scheme 1.

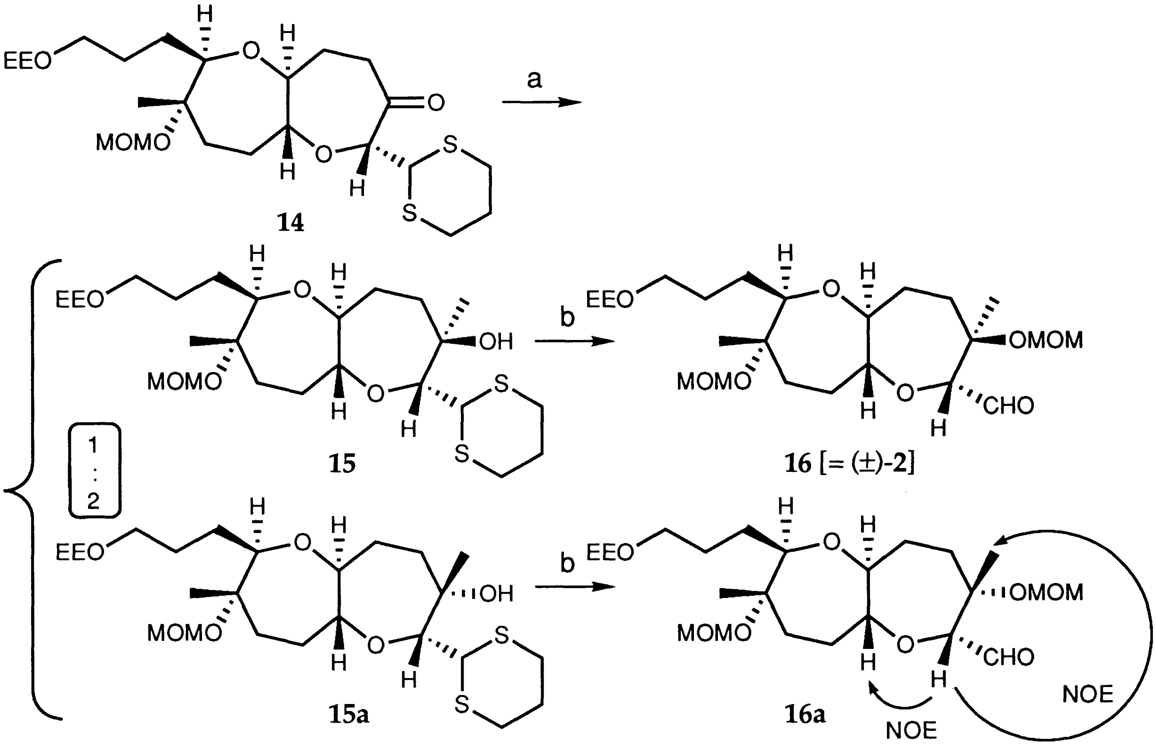
deduced by the NOE experiments.

The C-ring system of **2** was prepared from **9** (Scheme 2). Compound **9** was transformed into the corresponding ε-lactone (**10**) in a 77% overall yield, which was protected with methoxymethyl chloride to give **11** in 86% yield. The lactone part of **11** was converted to the enol triflate, which was reacted with $Li^+\ ^-CH(SCH_2CH_2CH_2S)$ in the presence of copper iodide in THF and HMPA at -20 °C to afford the alkylated cyclic enol ether (**12**) in a 60% total yield. The compound was treated with BH_3-THF complex and then with NaOH and *t*-butyl hydroperoxide to give an inseparable 2.5:1 mixture of alcohols (**13** and **13a**) in a 78% combined yield. The mixture, without further separation, was oxidized to the corresponding ketones (**14** and **14a**) in a 77% combined yield. The minor ketone (**14a**) was isomerized to **14** on reaction with DBU in 89% yield. As a result, 1,3-dithianyl group was found to take an equatorial conformation to the C-ring. When compound **14** was reacted with MeMgBr in toluene at -78 °C for 2.5 h, two methylcarbinols (**15** and **15a**) were obtained in a ratio of 1:2[5] in a 80% combined yield (Scheme 3). These alcohols were finally converted in two step process to the corresponding protected aldehydes (**16** and **16a**) in 54% and 72% overall yields, respectively. The stereostructure of these products were



Reagents and conditions: a) TBAF, THF, 20 °C, 36 h, 98%; SO_3-Py, DMSO, TEA, 20 °C, 0.5 h, 82%; *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 20 °C, 2.5 h, 96%; MOM-Cl, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 20 °C, 24 h, 86%. b) LiHMDS, THF-HMPA, -78 °C, 3 h and then $PhNTf_2$, -78 °C → 20 °C, 70%; Li^+ $^-CH(SCH_2CH_2CH_2S)$, CuI, THF-HMPA, -20 °C, 12 h, 81%. c) BH_3-THF, THF, 20 °C, 1.5 h, and then NaOH, TBHP, 0 °C, 1.5 h, 78%. d) SO_3-Py, DMSO, TEA, 20 °C, 1 h, 77%. e) DBU, toluene, 20 °C, 1 h, 89%.

Scheme 2.



Reagents and conditions: a) MeMgBr, toluene, -78 °C, 2.5 h, 80%. b) MOMCl, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 20 °C, 36 h, 90%; CH_3I, $NaHCO_3$, acetone-H_2O (4:1), 20 °C, 5 h (or 2 h), 60% (or 80%).

Scheme 3.

determined from the NOE experiment of **16a**. The compound [**16** (= **2**)] obtained thus is an important synthetic key intermediate for the total synthesis of **1**. These results demonstrate the efficiency of our new methodology.[2] Further studies towards the total synthesis of **1** starting from **2** are now in progress in our laboratory.

References

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

2) K. Tsushima, K. Araki, and A. Murai, *Chem. Lett.*, **1989**, 1313; K. Tsushima and A. Murai, *ibid.*, **1990**, 761. For the application to the total synthesis of (+)-laurencin, see, K. Tsushima and A. Murai, *Tetrahedron Lett.*, in press.

3) For the recent synthetic studies on medium-sized cyclic ethers via transformations of the corresponding lactones, see, K. C. Nicolaou, D. G. McGarry, P. K. Somers, B. H. Kim, W. W. Ogilvie, G. Yiannikouros, C. V. C. Prasad, C. A. Veale, R. R. Hark, *J. Am. Chem. Soc.*, **112**, 6263 (1990), and references cited therein.

4) W. S. Johnson, C. D. Gutsche, and D. K. Banarrjee, *J. Am. Chem. Soc.*, **73**, 5464 (1951).

5) Treatment of **14** with MeMgBr in THF at -78 °C for 2 h gave rise to a 1:2.8 mixture of **15** and **15a** in 90% yield, while the result with MeLi in THF at -78 °C for 2 h provided **15a** exclusively in 80% yield.

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