CHEMISTRY LETTERS, pp. 2143-2146, 1994.

Synthesis of the Tetrahydrofuran Ring Part of a Marine Toxin Polycavernoside-A

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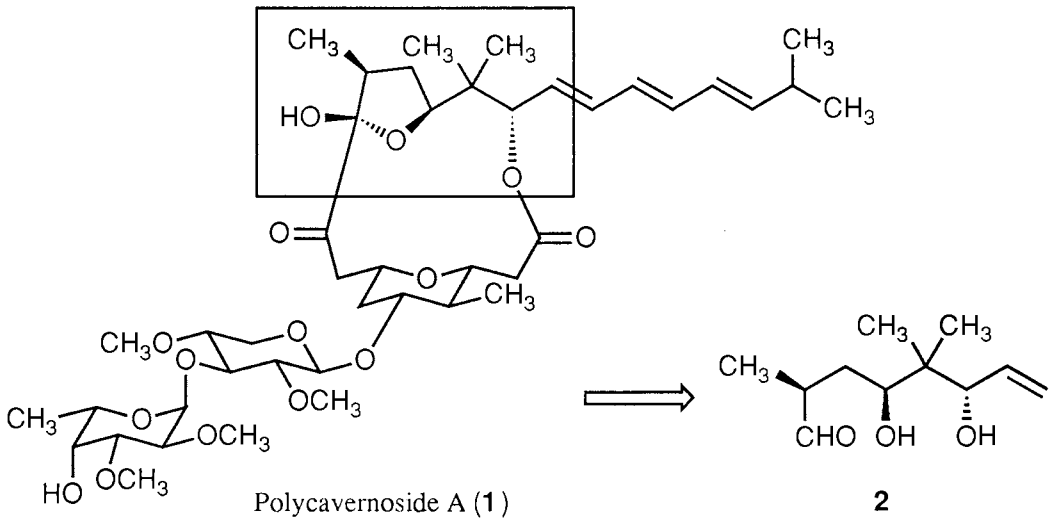
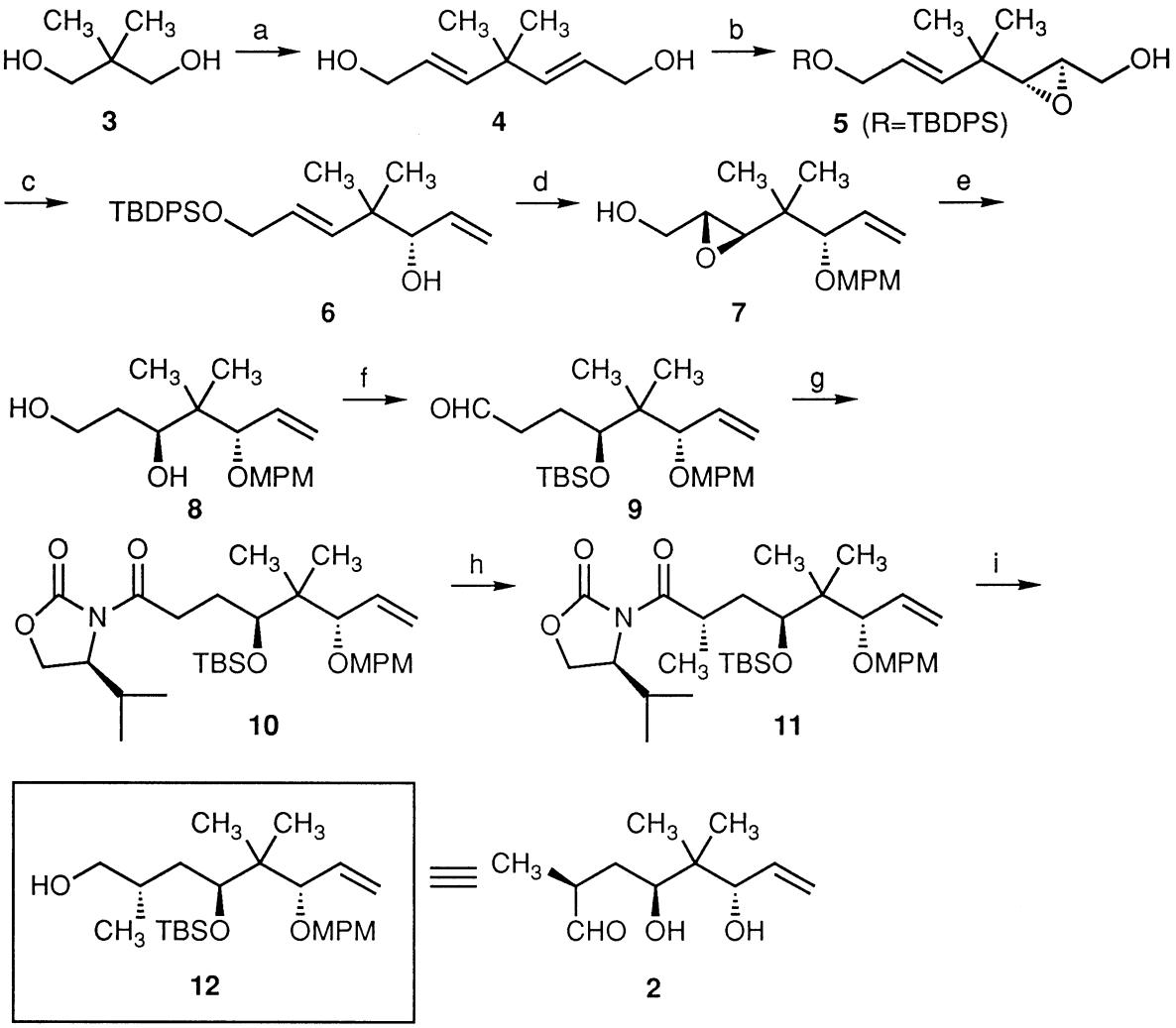
Construction of the tetrahydrofuran ring part of polycavernoside A, which has been isolated as one of toxic principles from the red alga *Polycavernosa tsudai*, is described starting from 2,2-dimethylpropane-1,3-diol. The synthesis involves the Sharpless epoxidation and the Evans procedure for introduction of three chiral centers.

The title compound (**1**) has been isolated as one of the sources of human intoxication from the red alga *Polycavernosa tsudai* by Yasumoto et al. in 1993.[1)] They have proposed the structure of **1**, which is a novel macrolide disaccharide, on the basis of ^{1}H and ^{13}C NMR spectra. However, although the respective relative configurations of the tetrahydrofuran ring, the tetrahydropyran ring, and the sugar moieties have been clarified, the absolute configuration of the whole molecule has not been established yet. We have started the total synthesis of this compound, because of its unusual molecular structure, the significant toxic activity, and the lack of a satisfactory natural source.[1)] We describe herein the construction of **2** corresponding to the tetrahydrofuran ring moiety of **1**.



Polycavernoside A (**1**) **2**

The synthesis commenced with commercially available 2,2-dimethylpropane-1,3-diol **3** (Scheme 1). Successive Swern oxidation and Wittig reaction of **3** followed by DIBAH reduction afforded the symmetric bisallylic alcohol **4** in 56% yield. One of the hydroxyl groups was protected with TBDPSCl and the product was oxidized under the Sharpless conditions[2)] using (-)-diethyl tartrate to give (2*R*,3*R*)-2,3-epoxy alcohol **5** (>99% ee) in a quantitative yield. Compound **5** was treated with I_2, PPh_3, and imidazole[3)] to yield a mixture of the corresponding iodide and olefin alcohol **6**. The mixture was further allowed to react with Zn to provide



Reagents: a) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 1 h, then Et_3N, 20 °C, 30 min; $Ph_3P{=}CHCO_2CH_3$, PhH, reflux, 2.5 days, 56%; DIBAH, CH_2Cl_2, -78 °C, 3.5 h, 84%; b) TBDPSCl, Imid., DMF, 20 °C, 14 h, 57%; (-)-DET, Ti(O-*i*-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, -25 °C, 24 h, 100%; c) I_2, PPh_3, Imid., PhH, 23 °C, 45 min; Zn, NH_4Cl, EtOH, 23 °C, 4 h, 94%; d) MPMCl, NaH, TBAI, THF, 20 °C, 36 h; TBAF, THF, 20 °C, 1.5 h, 69%; (-)-DET, Ti(O-*i*-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, -25 °C, 13 h, 100%; e) Red-Al, THF, 20 °C, 4 h, 100%; f) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 17 h, 98%; TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 40 min; KCN, DMSO, 20 °C, 16 h, 92%; DIBAH, CH_2Cl_2, -78 °C, 3 h; satd Roschelle salt aq, 20 °C, 2 h, 96%; g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (3.75:1), 0 °C, 1 h; PvCl, Et_3N, ether, 0 °C, 1 h, then N-lithio-(4*S*)-4-isopropyl-2-oxazolidone, THF, -78 °C, 15 min → 0 °C, 30 min, 100%; h) LDA, CH_3I, THF, -25 °C, 20 h, 69% (90%); i) $LiAlH_4$, THF, 0 °C, 55 min, 100%.

Scheme 1.

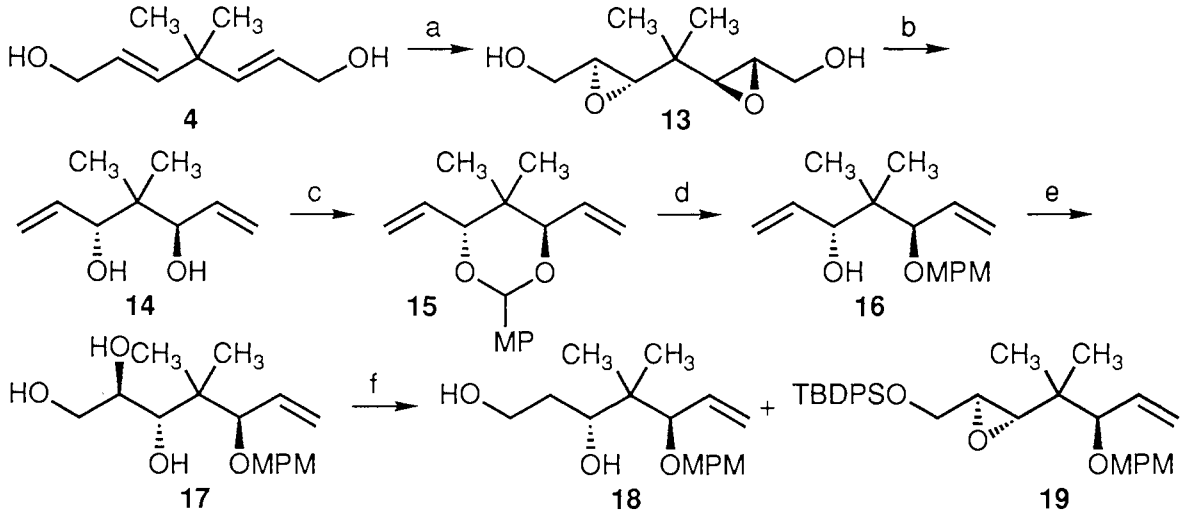
6 in a 94% overall yield from **5**.[4] The hydroxyl group of **6** was protected with MPMCl and then desilylated, followed by Sharpless oxidation with (-)-diethyl tartrate, yielding another epoxy alcohol **7** (>99% de) in a 69% overall yield from **6**. Compound **7** was reduced with Red-Al[5] to give the 1,3-diol **8**[6] quantitatively. Compound

8 was then converted into **9** in a four-step process (TsCl; TBSOTf; KCN; DIBAH) in an 86% overall yield. The aldehyde **9** was oxidized with $NaClO_2$[7] and treated with pivaloyl chloride and then with N-lithio-(4*S*)-4-isopropyl-2-oxazolidone according to the procedure of Evans[8] to give **10** in a quantitative overall yield. The compound **10** was methylated with LDA and CH_3I to afford **11** (>99% de).[9] Compound **11** was reduced with $LiAlH_4$ to the alcohol **12**,[10] which is the synthetic equivalent of **2**.

The construction of the enantiomer **18** corresponding to **8** started with compound **4** in a little different way (Scheme 2). Compound **4** was subjected to Sharpless oxidation involving (+)-diethyl tartrate[2] to give the bisepoxy diol **13** (>98% ee) in 91% yield. Compound **13** was treated with I_2, Ph_3P, and imidazole[3] to afford another bisallyl diol **14** along with the iodinated compound. The mixture was further allowed to react with saturated $Na_2S_2O_3$ aqueous solution to give rise to **14** in an 83% overall yield. The symmetrical diol **14** was then converted to the corresponding *p*-methoxybenzylidene acetal **15** in 93% yield. Compound **15** was reduced quantitatively with DIBAH to the mono-alcohol **16** and oxidized with OsO_4 and NMO at room temperature for 2 h to obtain a triol **17** as a single product in 75% yield (85% yield based on the recovered starting material). The primary hydroxyl group of **17** was protected with TBDPSCl and the less hindered secondary hydroxyl group was removed in the usual manners to give **18** (54%)[11] along with **19** (12%).[12] The diol **18** obtained thus was completely identical with **8** in all respects except optical properties. The synthetic pathway seems to be more efficient than that leading to **8** (Scheme 1). The synthetic route for the enantiomer of **12** has been already established as shown in Scheme 1.

The further synthetic studies involving the connection of these moieties with the other fractions[13] are now in progress in our laboratories.

The authors thank financial support by the Grant-in-Aid for Scientific Research on Priority Areas No. 06225201 from the Ministry of Education, Science and Culture, Japan.



Reagents: a) (+)-DET, Ti(O-*i*-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, -20 °C, 2 days, 91%; b) I_2, Ph_3P, Imid., THF, 20 °C, 1.5 h, then satd $Na_2S_2O_3$ aq., 20 °C, 2 h, 83%; c) *p*-anisaldehyde, PPTS, PhH, reflux, 3 h, 93%; d) DIBAH, CH_2Cl_2, -20 °C, 3 h, 100%; e) OsO_4, NMO, dioxane-H_2O (3:1), 20 °C, 2 h, 75%; f) TBDPSCl, Imid., DMF, 20 °C, 17 h, 96%; MsCl, Et_3N, CH_2Cl_2, 0 °C, 3 h, $LiAlH_4$, THF, 20 °C, 30 min, **18** (54%), **19** (12%).

Scheme 2.

References

1) M. Y.-Yamashita, R. L. Haddock, and T. Yasumoto, *J. Am. Chem. Soc.*, **115**, 1147 (1993).

2) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).

3) B. Classon, Z. Liu, and B. Samuelsson, *J. Org. Chem.*, **53**, 6126 (1988).

4) The stereochemistry of the hydroxyl group of **6** was determined to be *S* by application of the improved Mosher procedure using the MTPA esters of **6**; I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, **113**, 4092 (1991).

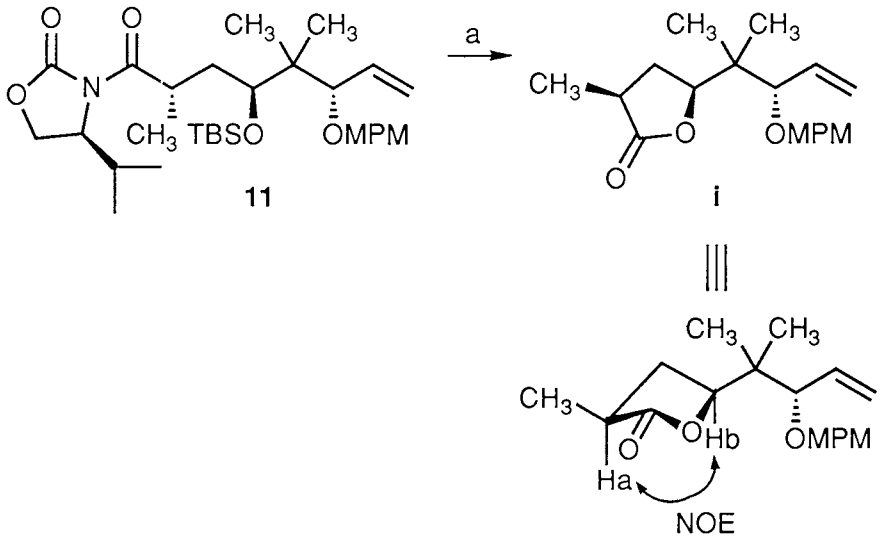
5) S. M. Viti, *Tetrahedron Lett.*, **44**, 4541 (1982); Y. Gao and K. B. Sharpless, *J. Org. Chem.*, **53**, 4081 (1988).

6) **8**; a colorless oil, $[\alpha]_D22$ +16.7° (c=0.78, $CHCl_3$). The stereochemistry of the secondary hydroxyl group in **8** was decided to be *S* by applying the improved Mosher procedure to the MTPA esters of the compound derived from **8** by protecting the primary hydroxyl group with TBDPSCl; see Ref. 4.

7) B. O. Lindgren and T. Nilsson, *Acta Chem. Scan.*, **27**, 888 (1973).

8) D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982).

9) The stereochemistry of the methyl group introduced was determined to be *S* as follows: compound **11** was oxidized in a two-step process [cf. D. A. Evans, T. C. Britton, and J. A. Ellman, *Tetrahedron Lett.*, **28**, 6141 (1987)] and deprotected with HF to yield the butyrolactone (**i**) in a 65% overall yield. The NOE experiment of **i** confirmed the mutual relationship between Ha and Hb.



Reagents: a) H_2O_2, LiOH, THF-H_2O (3:1), 20 °C, 3 h; 1.5M Na_2SO_3 aq., 20 °C, 1.5 h; 46% HF·aq., THF, 20 °C, 14 h, 65%.

10) **12**; a colorless oil, $[\alpha]_D20$ -25.1° (c=0.55, $CHCl_3$).

11) **18**; a colorless oil, $[\alpha]_D22$ -16.0° (c=0.36, $CHCl_3$).

12) Concerning with the configuration of the secondary hydroxyl group at C-2 of **17**, we have postulated to be *R* on the basis of the coupling constant (2.6 Hz) between two oxirane protons at C-2 and C-3 in the ^1H NMR spectrum of compound **19**.

13) K. Fujiwara, S. Amano, T. Oka, and A. Murai, the following paper.

(Received August 22, 1994)