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

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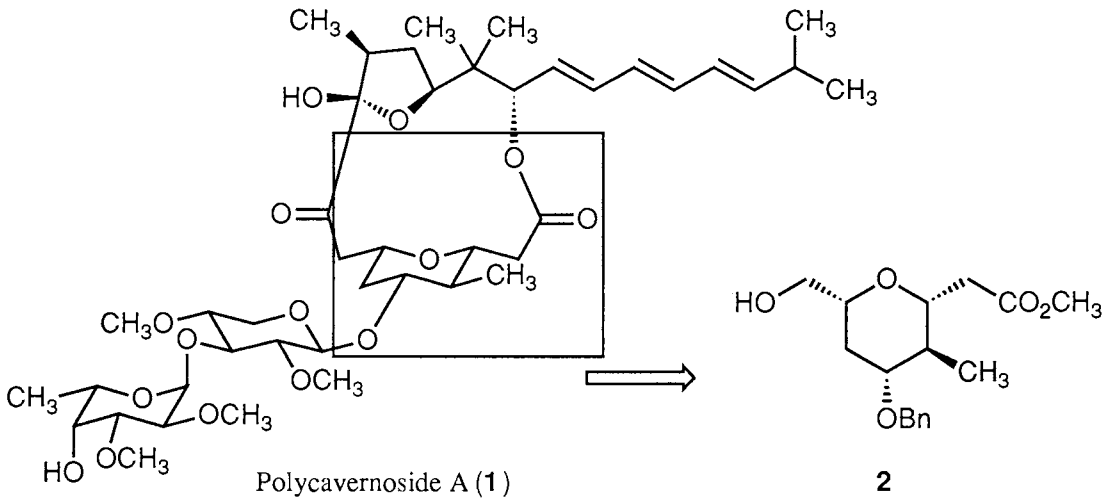
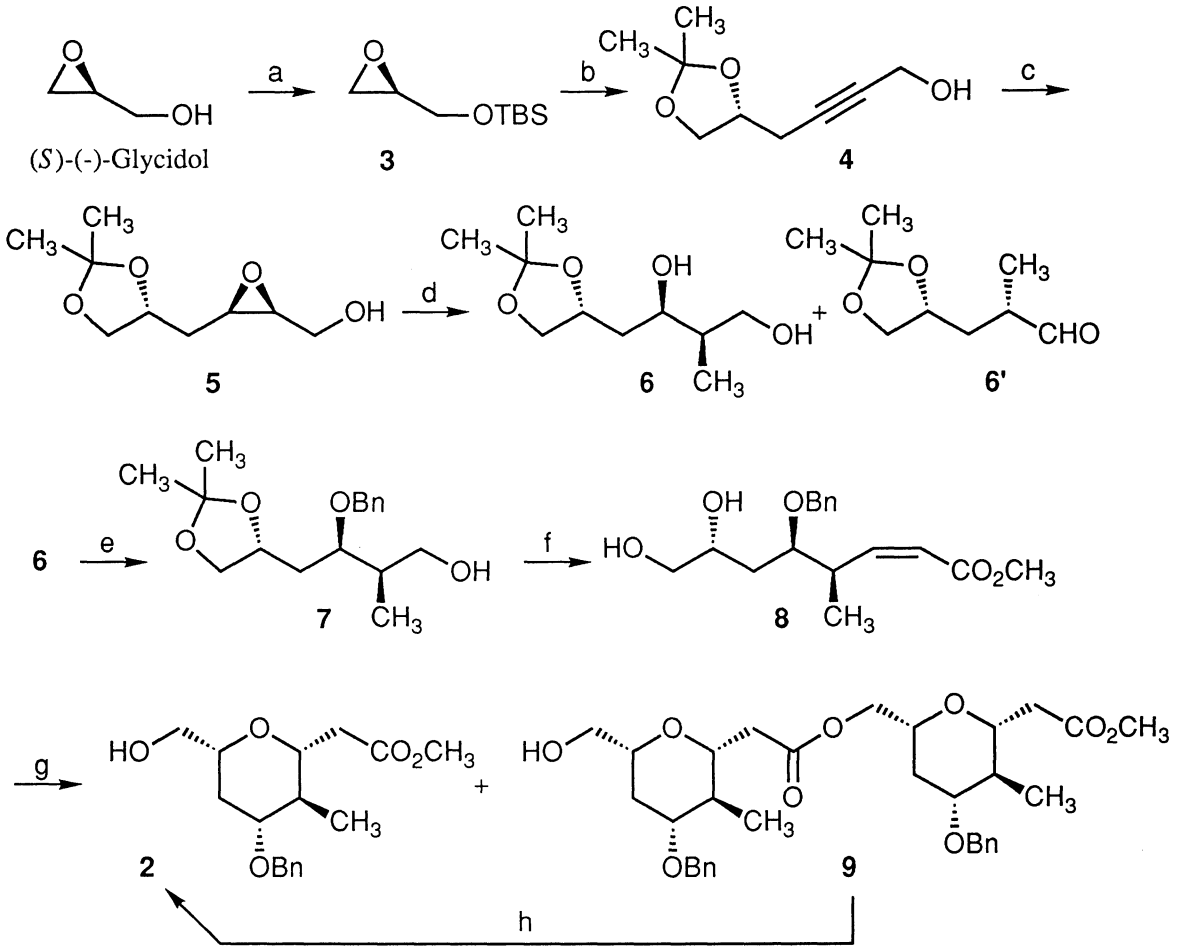
Construction of the tetrahydropyran ring part of polycavernoside A, which has been isolated as one of toxic principles from the red alga *Polycavernosa tsudai*, is described starting from (*S*)-(-)- and (*R*)-(+)-glycidols.

Continuing the previous paper[1] about the synthetic studies on polycavernoside A (**1**) isolated from *Polycavernosa tsudai* by Yasumoto,[2] we describe herein the synthesis of **2** corresponding to the tetrahydropyran ring moiety of **1**.



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

The synthesis started with protection of commercially available (*S*)-(-)-glycidol[3] with TBSCl (Scheme 1). By a modification of the Kotsuki procedure,[4] tetrahydropyranyl ether of propargyl alcohol was initially lithiated with BuLi and treated with **3** in the presence of $BF_3 \cdot OEt_2$ to give the coupling product, which was desilylated and then subjected to acetonide formation to yield the acetylene alcohol **4**. The compound **4** was partially reduced with Lindlar catalyst and the product was oxidized under the Sharpless conditions[5] using (+)-diethyl tartrate to give (2*S*,3*R*)-2,3-epoxy alcohol **5** in 75% yield. Compound **5** was treated successively with a mixture of MeLi (7 eq) and CuI (4 eq) in THF-ether (2.3:1)[6] and with $NaIO_4$ to yield an 1,3-diol **6**, along with an oxidized compound **6** , in 69% and 20% overall yields, respectively. The compound **6** was led to the corresponding monobenzyl ether **7** in a three-step process (TBSCl; BnBr; TBAF). The hydroxyl group of **7** was oxidized under the Swern condition to afford the aldehyde, which was immediately allowed to react with $(CH_3O)_2P(O)CH_2CO_2CH_3$, KH, and 18-crown-6 in THF[6,7] to afford a separable 5:1 mixture of (*Z*)- and (*E*)-olefin esters. The (*Z*)-olefin ester was isolated and deprotected with PTS to give a diol **8** in 92% yield.

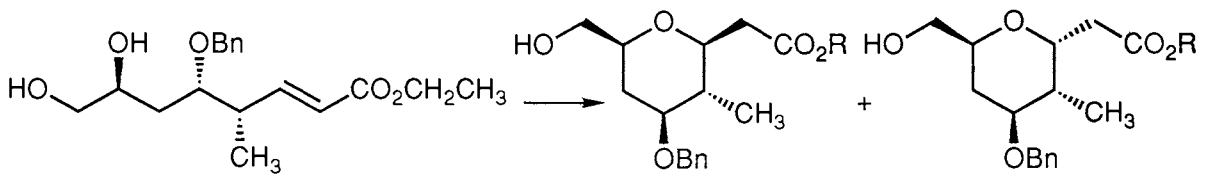


Reagents: a) TBSCl, Imid., DMF, 0 °C, 1 h, 96%; b) propargyl alcohol THP-ether, BuLi, BF_3·OEt_2, THF, -78 °C, 140 min; PTS·H_2O, MeOH, reflux, 9 h; dimethoxypropane, PTS·H_2O, CH_2Cl_2-MeOH (1:4), 20 °C, 25 min, 71%; c) H_2, Lindlar cat., quinoline, EtOH, 20 °C, 3 h, 91%; (+)-DET (1.0 eq), $Ti(O^iPr)_4$ (1.0 eq), TBHP (2.2 eq), MS4A, CH_2Cl_2, -20 °C, 3 days, 75%; d) MeLi (7 eq), CuI (4 eq), THF-ether (2.3:1), -20 °C, 23 h; $NaIO_4$, THF-H_2O (2:1), 20 °C, 26 min, **6** (69%), **6'** (20%); e) TBSCl, DMAP, NEt_3, CH_2Cl_2, 0 °C, 1.5 h, 91%; *t*-BuOK, BnBr, TBAI, THF, 0 °C, 47 min, 95%; TBAF, THF, 20 °C, 80 min, 79%; f) Swern oxid.; $(MeO)_2POCH_2CO_2Me$, KH, 18-crown-6, THF, 0 °C, 1 h, then aldehyde, -78 °C, 225 min, (*Z*)-olefin (78%), (*E*)-olefin (15%); PTS·H_2O, MeOH, 28 °C, 1.5 h, 92%; g) *t*-BuOK (8 mol%), THF, -20 °C, 20 min, 92% (**2**:**9**=6.7:1); h) *t*-BuOK (1 eq), MeOH, 25 °C, 11 h, 91% from **8**.

Scheme 1.

In order to optimize the reaction conditions for the next intramolecular Michael cyclization of the olefin diol **8**, the enantiomeric (*E*)-isomer **10** was subjected to the reaction under the various conditions (Table 1). First of all, *t*-BuOK (1.5 eq) was employed in THF at rather low temp (Run 1).[8] Although the ester part was predominantly hydrolyzed, the desired cyclized compound **11** was obtained in totally 45% yield. It is to be noted that in this case the isomeric cyclized product **12** was not detected in even a trace amount. Next, use of MeONa as a rather weak base led to formation of an 1:1 mixture of **11** and **12** (Run 2). When a catalytic

Table 1.



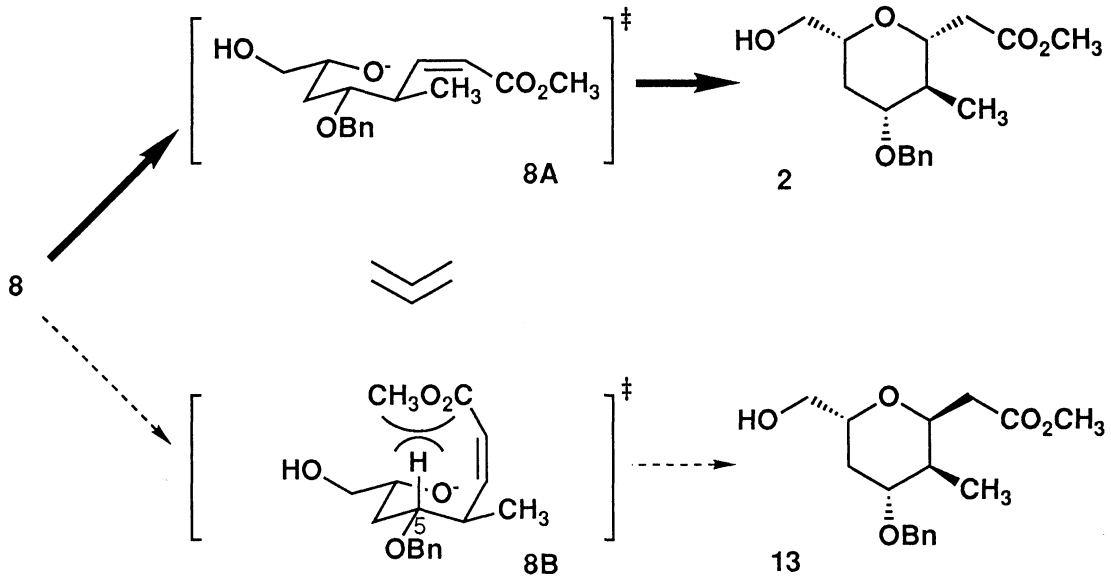
10 **11** **12**

Run	Conditions	Yield of **11** [a]	Yield of **12** [a]
1	**10**, *t*-BuOK (1.5 eq), THF -20 °C, 12 min → 20 °C, 75 min	40% (R=H), [b] 5% ($R=CH_2CH_3$)	———
2	**10**, NaH (1.5 eq), MeOH 20 °C, 15 h → 40 °C, 9.5 h	42% ($R=CH_3$)	42% ($R=CH_3$)
3	**10**, *t*-BuOK (0.1 eq), THF -20 °C, 23 min → 20 °C, 14 min	34% ($R=CH_2CH_3$)[c]	51% ($R=CH_2CH_3$)[c]
4	**12**, *t*-BuOK (1.5 eq), THF -20 °C, 15 min → 20 °C, 1 h	39% (R=H)[b]	13% (R=H)[b]

a) The respective yields of **11** and **12** were estimated by ^{1}H NMR spectra; b) The compound was isolated as its methyl ester on treatment with CH_2N_2 in ether; c) The compound was isolated as its methyl ester on reaction with *t*-BuOK (1.5 eq) in MeOH.

amount of t-BuOK was used, the relative yields of **11** and **12** amounted to 34% and 51%, respectively (Run 3). These results reveal that the comparable ratio of **11** and **12** would be formed kinetically followed by gradual decomposition of the isomer **12** with an excess amount of *t*-BuOK. In fact, treatment of the less stable **12** with *t*-BuOK (1.5 eq) in THF effected equilibration, leading to the 3:1 ratio of **11** and **12** with only a total 52% recovery (Run 4). Eventually, (*E*)-olefin alcohol **10** gave rise to only a limited amount of the desired product **11**. Accordingly, we attempted to check the reaction with the corresponding (*Z*)-olefin diol **8** (Scheme 1). Compound **8** was treated with *t*-BuOK (8 mol%) in THF at -20 °C for 20 min, the intramolecular Michael addition reaction was effected to give a 6.7:1 mixture of the desired cyclized product **2** and its dimer **9** in 92% yield.[9] Compound **9** was smoothly converted to **2** with *t*-BuOK (1 eq) and the overall yield of **2** amounted to 91% from **8**. The exclusive formation of **2** could be rationalized in terms of the transition state closing to the cyclization (Scheme 2). The transition state **8A** leading to **2** might be considerably favored comparing to another rotated isomer **8B** leading to the plausible isomer **13** on the basis of steric repulsion between methoxycarbonyl group and the hydrogen at C-5 position.[10]

The enantioisomer corresponding to **2** has been also synthesized starting from (*R*)-(+)-glycidol.[3,11] The synthetic study on the respective connection of the tetrahydropyran **2** and its enantiomer with the isomers of the tetrahydrofuran moieties[1] is now in progress in our laboratories.



Scheme 2.

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9) **2**; colorless needles, mp 88-89 °C, $[\alpha]_D23$ -50.9 ° (c 1.01, $CHCl_3$).
10) For the intramolecular cyclization leading to tetrahydropyran derivatives from the linear starting compounds having ω-hydroxy-α,β-unsaturated carboxylic esters, see B. Fraser-Reid, R. D. Dawe, and D. B. Tulshian, *Can. J. Chem.*, **57**, 1746 (1979); R. D. Dawe and B. Fraser-Reid, *J. Org. Chem.*, **49**, 522 (1984); V. S. Martin, M. T. Nunez, M. A. Ramirez, and M. A. Soler, *Tetrahedron Lett.*, **31**, 763 (1990); T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, and P. M. Scola, *ibid.*, **33**, 1549 (1992); V. S. Martin and J. M. Palazon, *ibid.*, **33**, 2399 (1992); J. M. Palazon, M. A. Soler, M. A. Ramirez, and V. S. Martin, *ibid.*, **34**, 5467 (1993).
11) Enantiomer of **2**; colorless needles, mp 89-90 °C, $[\alpha]_D24$ +51.0° (c 1.01, $CHCl_3$).

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