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# Stereoselective synthesis of polytetrahydropyrans

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**Abstract**

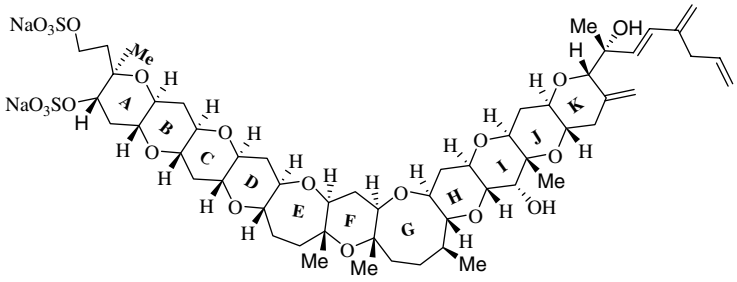
We describe a stereoselective synthesis of a bistetrahydropyran ring system with the same *trans–syn–trans* stereochemistry as is found in the marine polyether ladder yessotoxin.


*Keywords:* Oxacyclic compounds; Toxins; Singlet oxygen; Tetrahydropyrans; Stereoselective synthesis

Yessotoxin **1** is a disulfated polycyclic ether that is produced by the dinoflagellate *Proteceratium reticulatum*[1] and has been isolated from the digestive glands of the scallop *Patinopecten yessoensis*.[2] Due to its highly complex architecture and very interesting biological properties, which include modulation of cytosolic calcium levels in human lymphocytes[3] and cytotoxicity against human tumor cell lines,[4] yessotoxin has attracted the attention of synthetic chemists[5] (Fig. 1).

In recent years we have developed a new method for the synthesis of oxacyclic compounds from either methoxyallene or furan.[6] We have applied this method to the synthesis of chiral butenolides,[7a] natural products,[7b] and polyoxepanes.[7b] Here we report its extension to the stereoselective synthesis of linear polytetrahydropyrans with a view to the eventual synthesis of yessotoxin.

Scheme 1 shows the synthesis of trans-fused bistetrahydropyrans **3** and **4**. The 2,3-trans-disubstituted tetrahydropyran **6** was obtained from the commercially available furan **2** using a previously reported procedure.[6d] Selective protection of its primary hydroxy group afforded **7**[8] in 59% yield, and protection of this secondary alcohol




**1:** Yessotoxin

Fig. 1. Structure of Yessotoxin.

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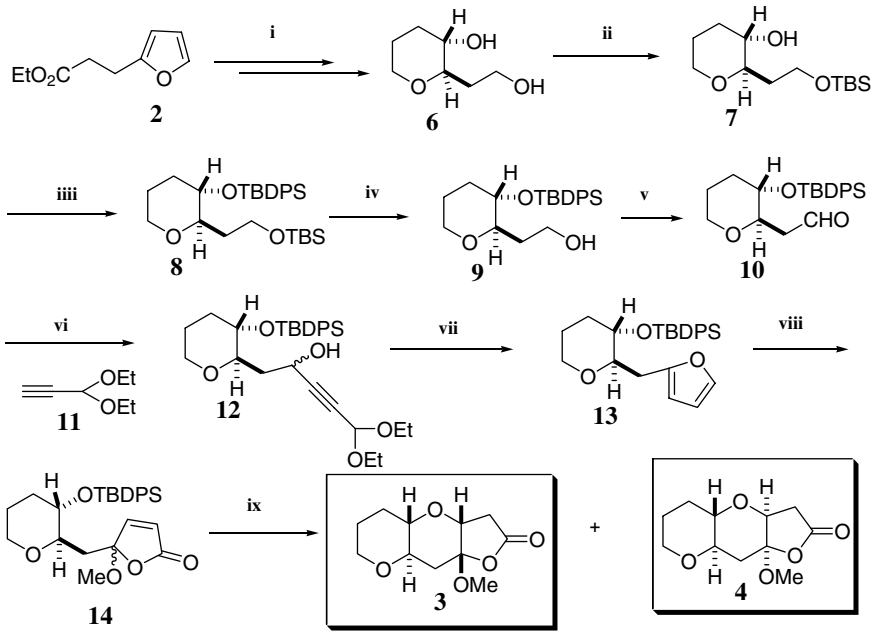


Scheme 1. Reagents and conditions: (i) Ref. 6d; (ii) TBSCl, Imid, DMAP, THF, rt (59%); (iii) TBDPSCl, Im, DMF, DMAP (94%); (iv) AcOH, THF, $H_2O$, 0 °C (96%); (v) TPAP, NMO, $CH_2Cl_2$, molecular sieves (61%); (vi) **11**, *n*-BuLi, THF, −78 °C (85%); (vii) $H_2$, Lindlar, MeOH (78%); (viii) (a) $^1O_2$, MeOH, rose Bengal, *hv*; (b) $Ac_2O$, py, DMAP (96%, two steps); (ix) TBAF, THF, rt (60% **3**; 38% **4**).

gave a 94% yield of intermediate **8**.[8] Selective removal of the TBS of **8** using a mixture of acetic acid, THF, and water then afforded a 96% yield of alcohol **9**,[8] which was oxidized to aldehyde **10**[8] in 61% yield using tetrapropylammonium perruthenate (TPAP). Treatment of **10** with the lithium derivative of alkyne **11** gave a mixture of epimeric propynyl alcohols **12**[8] in 85% yield, and the hydrogenation of this mixture over Lindlar catalyst[9] provided a mixture of diastereoisomeric (*Z*)-alkenes that when treated with

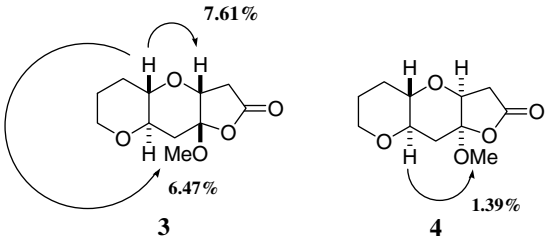
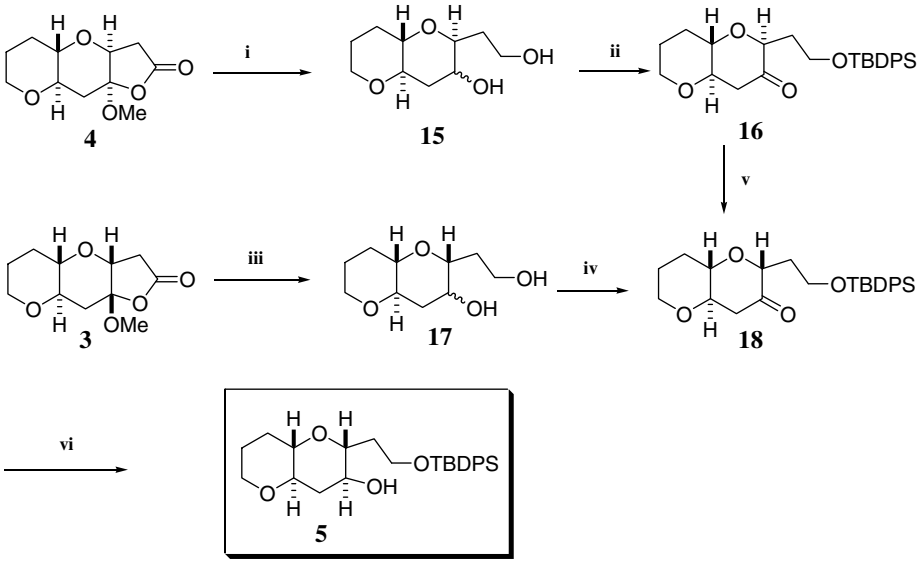
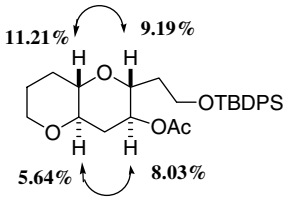


Fig. 2. NOE correlations for **3** and **4**.



Scheme 2. Reagents and conditions: (i) LAH, $BF_3{\cdot}OEt_2$ (84%); (ii) (a) TBDPSCl, Im, DMF, DMAP (65%), (b) TPAP, NMO, $CH_2Cl_2$ (68%); (iii) LAH, $BF_3{\cdot}OEt_2$ (93%); (iv) (a) TBDPSCl, Im, DMF, DMAP (76%), (b) TPAP, NMO, $CH_2Cl_2$ (87%); (v) DBU, $PhCH_3$, 80 °C; (vi) $NaBH_4$, MeOH, $CH_2Cl_2$, −78 °C (85%).




**19**

Fig. 3. NOE correlations for **19**.

catalytic pyridinium *p*-toluene sulfonate (PPTS) gave the desired furan **13**[8] in 78% yield. Oxidation of **13** with singlet oxygen, followed by a treatment with acetic anhydride in pyridine, afforded butenolide **14**[8] in 96% yield (two steps), and the treatment of **14** with TBAF gave the tricyclic lactones **3**[10] and **4**[11] in 60% and 38% yield, respectively.

The stereochemistry of **3** and **4** was established using NOE experiments (Fig. 2).

With lactones **3** and **4** in hand, we aimed to prepare the bicyclic tetrahydropyran **5**, which has the *trans–syn–trans* stereochemistry found in yessotoxin (Scheme 2) and is ready for the addition of a further ring by the above method. To this end, lactones **3** and **4** were opened with LAH, affording diols **15** and **17**. Selective protection of the primary hydroxy groups of **15** and **17**, followed by the oxidation of the resulting secondary alcohols with TPAP, gave ketones **16** and **18**, the former of which was converted to the latter by epimerization with DBU in toluene at 80 °C.[12] Stereoselective reduction of **18** with sodium borohydride in methanol and dichloromethane at −78 °C then afforded the target alcohol **5**.

The relative stereochemistry of **5** was established by NOE experiments on the corresponding acetate, **19** (Fig. 3).

In conclusion, we have shown that the furan approach to oxacycles allows the stereoselective synthesis of a bicyclic tetrahydropyran with the *trans–syn–trans* stereochemistry of yessotoxin. Work is now in progress toward the enantioselective synthesis of polycyclic natural products using this approach.

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10. *Selected data for compound* **3**: White solid. mp: 139 °C; $^{1}H$ NMR ($CDCl_3$, 300 MHz), $\delta$: 3.96 (d, 1H, $J = 4.43$ Hz, CH–C6), 3.85 (d, 1H, $J = 9.88$ Hz, $CH_2$–C3), 3.33 (s, 3H, $CH_3OMe$), 3.32 (m, 1H, $CH_2$–C3), 3.08 (m, 1H, CH–C8), 3.03 (m, 1H, CH–C1), 2.85 (dd, 1H, $J = 4.39$ Hz, $J = 17.32$ Hz, $CH_2$–C10), 2.74 (dd, 1H, $J = 4.20$ Hz, $J = 13.10$ Hz, $CH_2$–C13), 2.35 (dd, 1H, $J = 9.81$ Hz, $J = 17.36$ Hz, $CH_2$–C10), 1.99 (m, 1H, $CH_2$–C5), 1.66 (m, 2H, $CH_2$–C4), 1.59 (m, 1H, $CH_2$–C13), 1.37 (m, 1H, $CH_2$–C5); $^{13}C$ NMR (CDCl3), $\delta$: 175.26 (CO), 106.67 (C-9), 76.69 (CH-6), 75.13 (CH-1), 73.85 (CH-8), 67.93 ($CH_2$-3), 49.80 ($CH_3OMe$), 36.32 ($CH_2$-10), 33.90 ($CH_2$-13), 28.66 ($CH_2$-5), 25.11 ($CH_2$-4); HRMS: calcd for $C_8H_{13}O_3$, 157.0846; found, 157.0843.
11. *Selected data for compound* **4**: yellow solid. mp: 120 °C; $^{1}H$ NMR ($CDCl_3$, 300 MHz), $\delta$: 4.45 (t, 1H, $J = 8.77$ Hz, CH–C1), 3.90 (d, 1H, $J = 12.25$ Hz, $CH_2$–C3), 3.43 (s, 3H, $CH_3OMe$), 3.39 (m, 1H, $CH_2$–C3), 3.31 (m, 1H, CH–C8), 3.14 (m, 1H, CH–C6), 2.90 (dd, 1H, $J = 9.63$ Hz, $J = 17.43$ Hz, $CH_2$–C13), 2.73 (m, 1H, $CH_2$–C13), 2.67 (m, 1H, $CH_2$–C10), 2.00 (m, 1H, $CH_2$–C5), 1.74 (m, 2H, $CH_2$–C4), 1.70 (m, 1H, $CH_2$–C10), 1.48 (m, 1H, $CH_2$–C5); $^{13}C$ NMR ($CDCl_3$), d: 170.94 (CO), 107.24 (C-9), 73.87 (CH-6), 73.67 (CH-1), 71.14 (CH-8), 67.93 ($CH_2$-3), 50.93 ($CH_3OMe$), 35.06 ($CH_2$-10), 32.15 ($CH_2$-13), 28.91 ($CH_2$-5), 25.29 ($CH_2$-4); calcd for $C_8H_{13}O_3$, 157.0857; found, 157.0850.
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