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Phorboxazole Synthetic Studies: the C3–C15 Bis-oxane Segment

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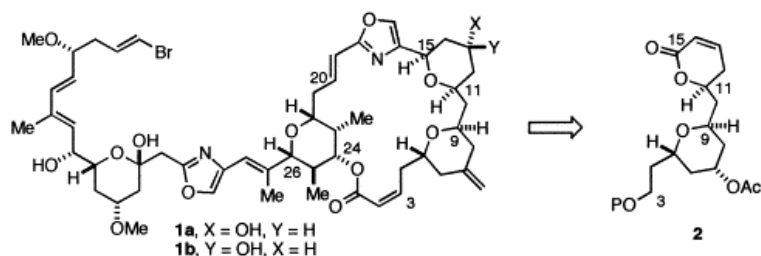
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Abstract

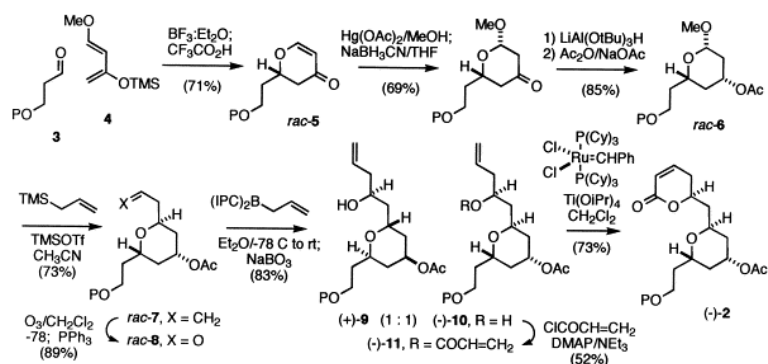
The enantioselective synthesis of the C3–C15 bis-oxane segment of the phorboxazoles has been accomplished from 3-*t*-butyldiphenylsilyloxypropanal in 9 steps (>90% ee).

The phorboxazoles A and B (**1a** and **b**) are isomeric macrolides isolated from the marine sponge *Phorbas* sp.^{1a} In addition to exhibiting antifungal activity against *Candida albicans*, both phorboxazoles gave mean $GI_{50} < 8 \times 10^{-10}$ M against most of the 60 tumor cell lines in the NCI panel. The complex structure of **1** consists of four oxane rings, two oxazole rings, 15 asymmetric centers, and a conjugated diene segment. The complete structure was assigned on the basis of NMR spectral studies, Mosher ester data, degradation, and model synthesis.¹ The outstanding biological activity of **1**, combined with its complex structural architecture, has led to significant activity by a number of research groups,² and a total synthesis by Forsyth's group.³ Recent reports by

Hoffmann,^{2c} Smith^{2d} and Pattenden^{2e} have prompted us to report our own efforts on the synthesis of the C3–C15 bis-oxane segment **2**.



Lewis acid catalysed diene-aldehyde cyclocondensation⁴ of **3** with **4** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, followed by brief treatment with $\text{CF}_3\text{CO}_2\text{H}$ gave dihydropyrone *rac*-**5** (Scheme 1). In our hands attempted asymmetric cyclocondensation by a number of literature procedures proved capricious.⁵ For this reason, establishment of optical activity was deferred to a later stage. Oxymercuration/reduction of **5** followed by reduction [$\text{LiAlH}(\text{OtBu})_3$] and acylation gave **6**. Reaction of **6** with allyl trimethylsilane/TMSOTf/ CH_3CN ⁶ gave the α -C-glucoside **7**, which upon ozonolysis gave the aldehyde *rac*-**8**. The synthesis of a similar aldehyde was reported by Hoffmann's group^{2c} beginning from 8-oxabicyclo[3.2.1]octan-3-one (11 steps), and by Smith's group^{2d} beginning from 2,4-pentandione (12 steps); our route to **8** is significantly shorter (six steps).



Scheme 1. (P=TBDPS)

Chiral allylation of *rac*-**8** with *B*-allyldiisopinocampheylborane (prepared from (-)-(IPC)₂BOMe),⁷ followed by oxidative work up with NaBO_3 , gave a separable mixture of the diastereomers (+)-**9** and (-)-**10** (41 and 42%, respectively). The absolute stereochemistry of each alcohol at C11 was assigned as (*S*) on the basis of the relative chemical shifts of their (*R*)- and (*S*)-Mosher's esters (>90% de each).

Ring closing metathesis⁸ has recently found utility in the preparation of unsaturated δ -lactones.⁹ To this end, esterification of (-)-**10** with acryloyl chloride gave (-)-**11**, which upon treatment with with Grubbs' catalyst (0.3 equivalents) gave the unsaturated pyrone (-)-**2**.¹⁰

In summary, the C3–C15 bis-oxane segment of the phorboxazoles has been prepared in nine steps. Studies directed toward the preparation of other portions of the phorboxazoles continues in our laboratory.

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10. Compound (-)-**2**: $[\alpha]_D -38$ (c 1.0, CHCl₃); ¹H NMR (CDCl₃) δ 7.68–7.61 (m, 4H), 7.46–7.32 (m, 6H), 6.77 (ddd, *J*=3.3, 5.3, 9.6 Hz, 1H), 5.97 (br d, *J*=10.1 Hz, 1H), 5.06 (tt, *J*=4.5, 9.0 Hz, 1H), 4.52 (m, 1H), 4.24 (dq, *J*=4.6, 9.1 Hz, 1H), 3.97 (tt, *J*=4.2 Hz, 8.4 Hz, 1H), 3.81–3.63 (m, 2H), 2.36 (m, 2H), 2.28 (ddd, *J*=5.5, 9.3, 15.3 Hz, 1H), 2.03 (s, 3H), 1.97 (td, *J*=3.1, 12.7 Hz, 1H), 1.86–1.62 (m, 5H), 1.39 (td, *J*=9.2, 12.9 Hz, 1H), 1.02 (s, 9H); ¹³C NMR (CDCl₃) δ 170.3, 164.1, 144.9, 135.5, 133.8, 129.6, 127.7, 121.4, 75.0, 67.2, 66.4, 65.9, 60.2, 38.1, 36.8, 36.2, 34.4, 28.7, 26.8, 21.2, 19.2.