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Phorboxazole synthetic studies: the C3–C15 bis-oxane segment

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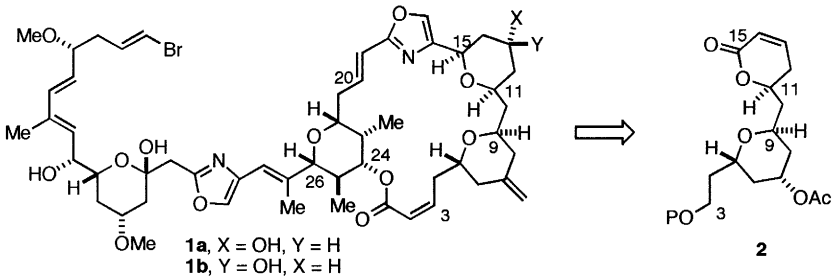
Abstract

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 $GI_{50}s<8\times10^{-10}$ 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**.



1a, X = OH, Y = H
1b, Y = OH, X = H

2

Lewis acid catalysed diene-aldehyde cyclocondensation[4] of **3** with **4** in the presence of $BF_3\cdot Et_2O$, followed by brief treatment with CF_3CO_2H 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 [$LiAlH(OtBu)_3$] and acylation gave **6**. Reaction of **6** with allyl

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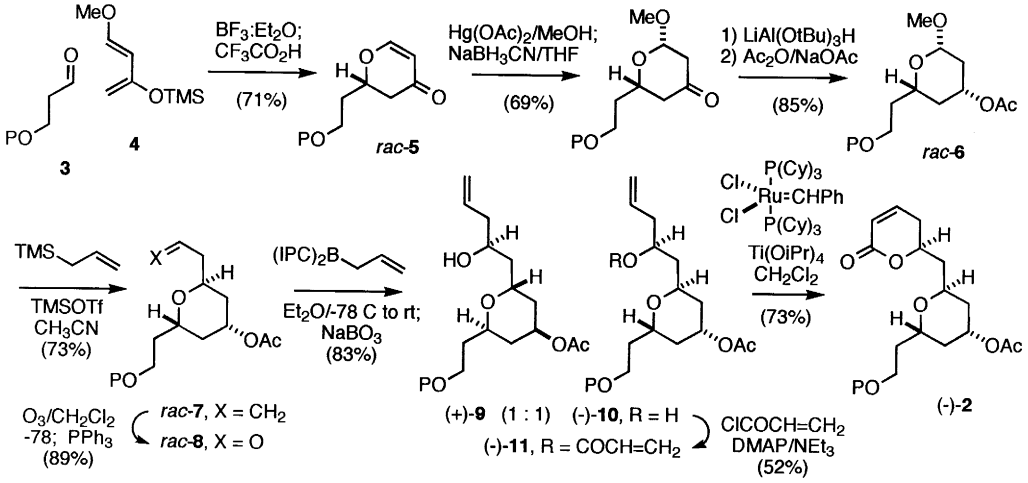
trimethylsilane/TMSOTf/CH_3CN[6] gave the α-C-glucoside **7**, which upon ozonolysis gave the aldehyde *rac*-**8**. The synthesis of a similar aldehyde was reported by Hoffmann's group[2c] beginning from 8-oxabicyclo[3.2.1]octan-3-one (11 steps), and by Smith's group[2d] beginning from 2,4-pentandione (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 metathesis[8] 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, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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.