Stereoselective Synthesis of the C3−C17 Bis-Oxane Domain of Phorboxazole A

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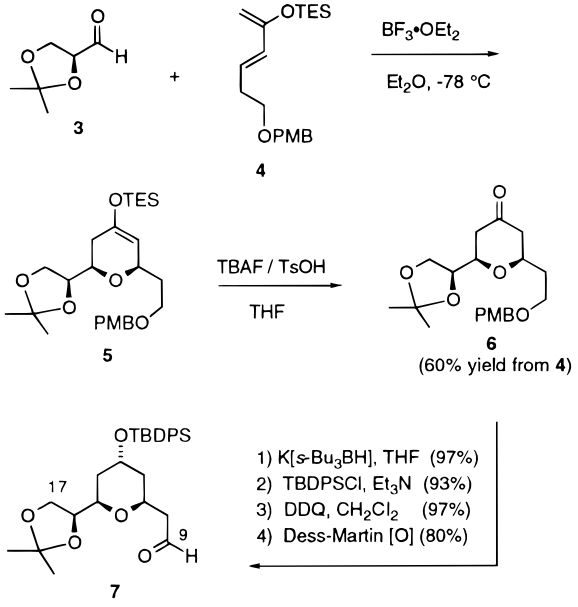
The phorboxazoles are remarkable natural products isolated recently from an Indian Ocean sponge *Phorbas* sp.[1] The structures of phorboxazole A (**1**) and its C13 epimer phorboxazole B have been established by a combination of extensive NMR studies on the natural, derived, and correlation products (Figure 1).[1−3] In addition to an unprecedented structure, phorboxazole A (**1**) has exceptionally potent cytostatic activity against the complete NCI panel of 60 human tumor cell lines.[1] Although the mode of cytostatic activity has not been defined, the arrest of the cell cycle during S phase by **1** distinguishes it from antimitotic natural products.[3] These findings contribute to the recent emergence of the phorboxazoles as premiere synthetic targets. The conformationally rigid macrolide of the phorboxazoles, containing three highly functionalized oxanes and one oxazole, provides a variety of challenges and opportunities for efficient and stereoselective heterocycle synthesis. The C18−C26 portion of the macrolide bears a 2,6-diequatorially substituted oxane, whereas the C1−C17 region contains two methylene-linked, trisubstituted oxanes (C5−C15) that are alternately substituted in a 2,6-trans and 2,6-cis fashion. A convergent synthesis of the central C18−C30 phorboxazole core has been reported.[4] Described here is a stereoselective synthesis of the complementary C3−C17 portion (**2**) of the phorboxazole macrolide (Figure 1). This involves sequential assembly of the C11−C15 and C5−C9 oxanes by hetero Diels−Alder and intramolecular etherification processes, respectively, to construct the unique methylene-linked bis-oxane system of **1**.

The bis-oxane portion of **1** joins the remainder of the natural product through (*Z*)-acrylate and oxazole moieties. Because this terminal functionalization could be elaborated from aldehyde and vicinal amino alcohol precursors at C3 and C16−C17, respectively, a stereoselective synthesis of intermediate **2** was targeted. The synthetic design was to form the C5−C9 oxane by an intramolecular S_N2 displacement of an activated homoallylic hydroxyl at C9. The etherification substrate would derive conveniently from the convergent coupling of a C3−C8 allylic nucleophile and a C9−C17 aldehyde. An initial hetero Diels−Alder reaction between a C15−C17 α-chiral aldehyde and a C9−C14 diene would be relied upon to provide the substituted C11−C15 oxane leading to the C9 aldehyde.

Preliminary studies indicated that installation of the C16 nitrogen atom was best deferred until after bis-oxane formation was complete. Hence, the synthesis of **2** began with an endo selective, BF_3•OEt_2-mediated[5] hetero Diels−Alder reaction of (*S*)-glyceraldehyde acetonide (**3**)[6] with diene **4**[7] (Scheme 1). This provided the C11−C15 pyranyl

Scheme 1



enol ether **5** as the major diastereomer of a 16:4:1 mixture. Desilylation facilitated the separation of diastereomers, which gave ketone **6** in 60% overall yield from **4**.[8] Selective reduction of **6** to the corresponding axial alcohol was accomplished with potassium tri-*sec*-butylborohydride. Straightforward protecting and functional group manipulations then gave β-pyranyl aldehyde **7** in 70% overall yield from **6**. Initial attempts to form the C5−C9 oxane using a cyclocondensation reaction between **4** and **7** gave unsatisfactory results.[9]

Successful assembly of the C5−C9 oxane was initiated by addition of the organochromium reagent[10,11] derived from allylic bromide **8**[12] to aldehyde **7**. Diastereomeric homoallylic alcohols **9** (9*S*) and **10** (9*R*) were obtained in a 3:2 ratio and 80% combined yield (Scheme 2).[13] The modest coupling diastereoselectivity was compensated for by the ease of conversion of the chromatographically separable **10** into **9** via a simple Mitsunobu[14]-saponification protocol, as well as the overall synthetic convergency of this direct coupling. Activation of the newly generated hydroxyl toward intramolecular displacement was accomplished by mesylation of **9** to give **11**. Selective monodesilylation followed by base treatment led to exceptionally clean S_N2 displacement of the mesylate by the C5

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(6) (a) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981−1983. (b) For a review see: Bednarski, M. D., Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon Press: New York, 1991; Vol. 2, pp 661−706.
(7) Diene **4** was prepared in five steps and 52% overall yield from 1,3-propanediol as described in the Supporting Information.
(8) The minor diastereomers were similarly converted into the corresponding ketones, and analysis of the J_{H-H} values of the α-keto protons indicate that both are exo Diels−Alder adducts. Because cyclocondensations of **3** have been shown previously to be highly Cram selective (ref 6a), it is likely that the major byproduct is the Cram-exo adduct and, hence, the overall Cram selectivity is ca. 20:1.
(9) Hydrolysis of the BF_3•OEt_2-mediated silyl enol ether cyclocondensation products from **4** and **7** gave a mixture of ketones in a 2:1:1:1 ratio and 68% combined yield.
(10) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646.
(11) Takai, K.; Yagashirs, M.; Kuroda, T.; Oshima, T.; Uchimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048−6050.
(12) Bromide **8** was prepared from (*S*)-4-[(4-methoxybenzyl)oxy]butane-1,2-diol as described in the Supporting Information.
(13) Stereochemical assignments for **9** and **10** were made on the basis of Mosher ester analysis as described in the Supporting Information.
(14) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

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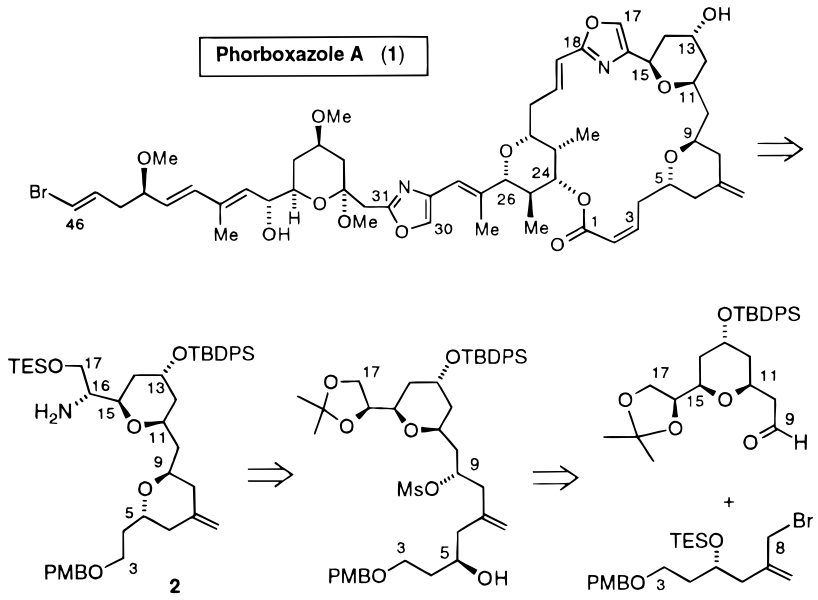
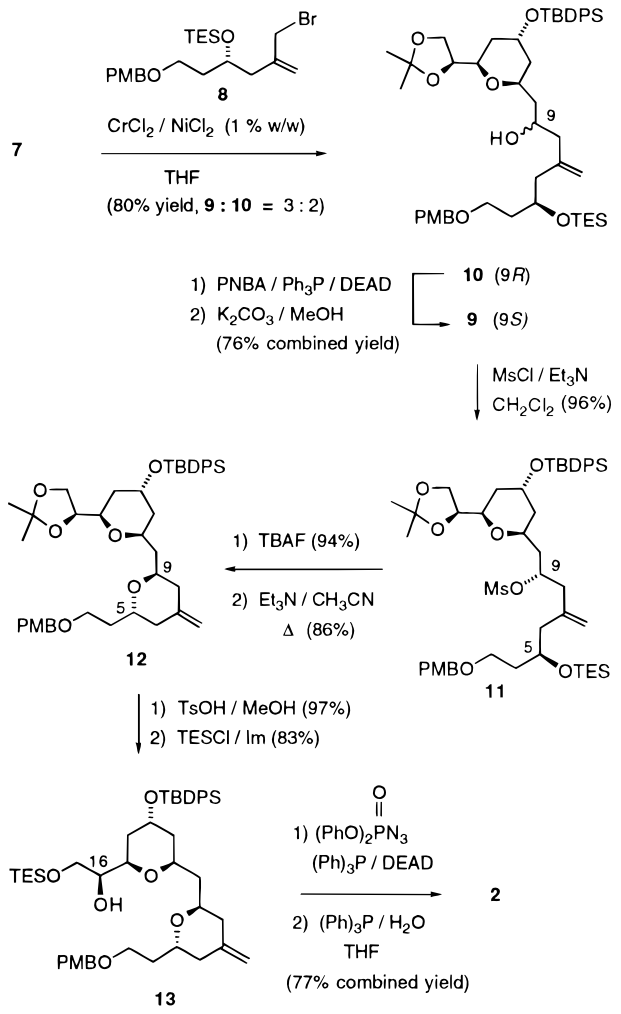


Figure 1.

Scheme 2



hydroxyl group to yield oxane **12**.[15] Although premature elimination of the mesylate to afford a conjugated diene occurred with the use of strong bases (e.g. NaH or KHMDS), this undesirable side reaction could be suppressed by simply using the milder base Et_3N in refluxing CH_3CN. Thus, the stereochemically correct and fully functionalized C5−C9 oxane was generated in only four steps from aldehyde **7**, thereby providing the complete carbon framework of the C3−C17 portion of phorboxazole A.

In preparation for C16−C18 oxazole formation, the acetonide-protected C16−C17 diol of **12** was converted into a vicinal amino alcohol derivative. Acetonide methanolysis, followed by monosilylation gave secondary alcohol **13** (Scheme 2). Azide displacement of the liberated hydroxyl,[16] followed by selective reduction[17] to the amine then completed the preparation of **2** , a synthetically useful fragment representing the C3−C17 domain of phorboxazole A.

Two complementary strategies for the stereocontrolled synthesis of highly substituted oxanes are highlighted in this work. An initial hetero Diels−Alder reaction[5,6] is augmented by a convergent and remarkably efficient intramolecular etherification process. The latter is particularly noteworthy due to the avoidance of competitive elimination and may represent a more general and mild method for substituted oxane formation. In the present context, these sequenced oxane syntheses provide ready access to the C3−C17 domain of **1**, which will facilitate ongoing chemical and biological studies of the phorboxazole natural products.

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Supporting Information Available: Experimental procedures, characterization data, and photocopies of ^1H NMR spectra for all new compounds (32 pages).

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