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Synthesis of the C1–C17 Segment of Phorboxazole B

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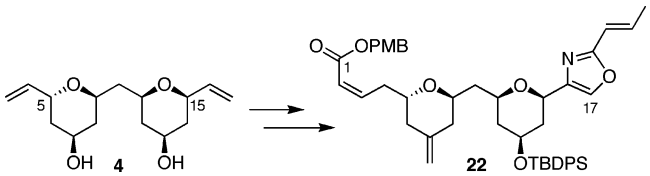
ABSTRACT



The C1–C17 bis-oxane subunit 22 of phorboxazole B is efficiently synthesized by exploiting differential reactivities between similar substituents on the hydropyran rings in 4. Selective dihydroxylation of the equatorial vinyl group, hydroboration of the axial vinyl group, and intramolecular Mitsunobu lactonization serve to fully differentiate the similar hydropyrans.

Recently, we reported a symmetry-based approach to the bis-tetrahydropyran ring systems of phorboxazole A and B, the key step being desymmetrization of *meso* tetraols by palladium-catalyzed, chiral-ligand-mediated double cycloetherification.[1] Although we had achieved the *formal* desymmetrization of these *meso* tetraol chains in greater than 98% ee, we were left with the practical task of regioselectively differentiating between the C5 and C15 vinyl groups, as well as between the C7 and C13 ring hydroxyls, in the course of installing the requisite phorboxazole functional groups. We report herein the successful transformation of bis-tetrahydropyran **4** to a fully functionalized C1−C17 segment of phorboxazole B.

The cytotoxic macrolide phorboxazoles (Figure 1) have been the subject of numerous synthetic efforts. In 1998, the first total synthesis of phorboxazole A was completed by Forsyth,[2] with subsequent total syntheses by Evans[3] (phorboxazole B), Smith,[4] Pattenden,[5] and Williams.[6] The phorboxazoles have been the focus of numerous other efforts,[7] SAR studies,[8] and a recent overview.[9] Discovered by

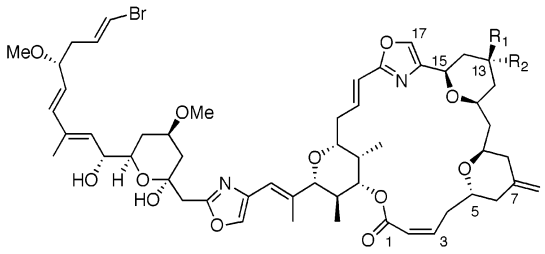


Figure 1. The phorboxazoles.

Molinski in 1995,[10] phorboxazole A and its C13 epimer phorboxazole B exhibit exceptional cytostatic activity. They have shown a mean GI_{50} value of $<1.6 \times 10^{-9}$ M in vitro against the NCI panel of 60 tumor cell lines.[10b]

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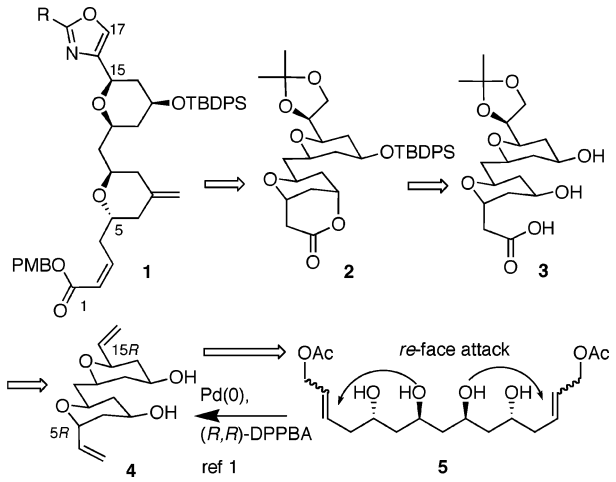
Our retrosynthetic strategy for the C1−C17 subunit of phorboxazole B is outlined in Scheme 1. We anticipated that

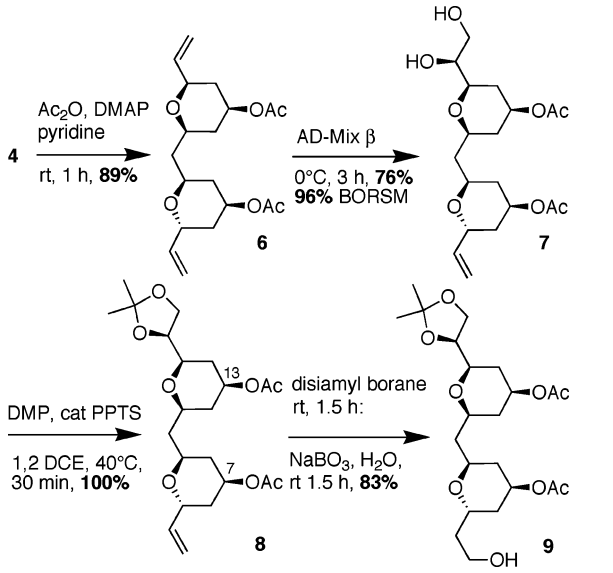
Scheme 1. Retrosynthesis of C1−C17 Segment of Phorboxazole B



an oxazole-containing subunit such as **1** could be obtained from the key 2,6-dioxabicyclo[3.3.1]nonan-3-one intermediate **2**, itself available from an intramolecular Mitsunobu reaction of acid diol **3.** The proximity of the C3 carboxylic acid group to the C7 alcohol in **3** would serve to differentiate the ring hydroxyls. The strategy ultimately relied on finding a suitable way to distinguish between the C5 (axial) and the C15 (equatorial) vinyl groups of bis-tetrahydropyran **4**, previously synthesized in >98% ee and 75% yield from *meso* tetraol **5**.[1]

It is well-known that the reaction rate of functional groups on six-membered rings is influenced by conformation.[11] Examples of the attenuated reactivity of axially disposed groups can be found in studies of conformationally constrained cyclohexanes,[12] as well as in the steroid literature.[13] Our design for achieving the differentiation of the pendant vinyl groups (Scheme 2) was based on the selective dihydroxylation of bis-tetrahydropyran diacetate **6** at the less hindered, equatorial C15 vinyl group.[14] Commercially available AD-mix β[15] yielded diol **7** in 76% yield after 3 h at 0 °C.[16,17] We found that quenching the reaction after 3 h and recycling unreacted **6** avoided exhaustive dihydroxylation to give a 96% yield of **7** based on recovered starting material (BORSM). Protection of the diol using 2,2-dimethoxypropane (DMP) and PPTS in 1,2-dichloroethane afforded the acetonide **8** in quantitative yield. Hydroboration/oxidation of the remaining vinyl group using disiamyl borane/sodium perborate gave the primary alcohol **9,** thereby completing the differential potentiation of the vinyl groups in **4**.

Scheme 2. Differentiation of the C5 and C15 Vinyl Groups



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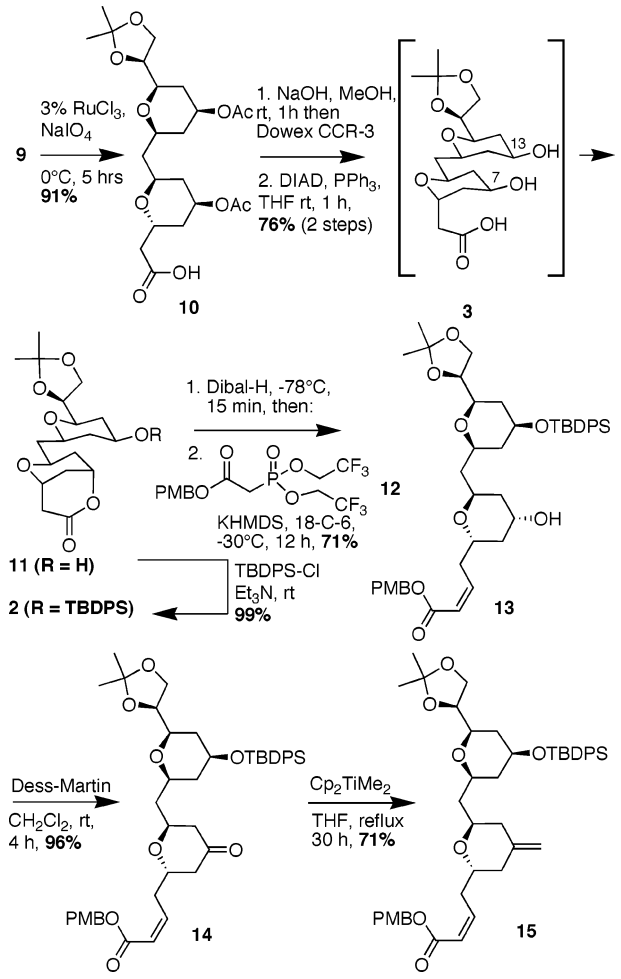
(16) Although the stereochemistry at C16 is ultimately destroyed, a single diastereomer is desirable in the context of a multistep synthesis. AD-Mix β was chosen to provide the matched case of ligand and substrate control as defined by the Sharpless mnemonic (ref 15) and Kishi's empirical rule for dihydroxylation of allylic ether systems. See: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

(17) In a related system, OsO_4 alone provided signficantly less regioselectivity and overall yield than AD-Mix; see ref **14**.

The next task was to differentiate the C7 and C13 substituents in **9**, so that the C7 hydroxyl could be transformed into an exo methylene with retention of the C13 hydroxyl. As shown in Scheme 3, after in situ generated

Scheme 3. Differentiation of the C7 and C13 Hydroxyl Groups

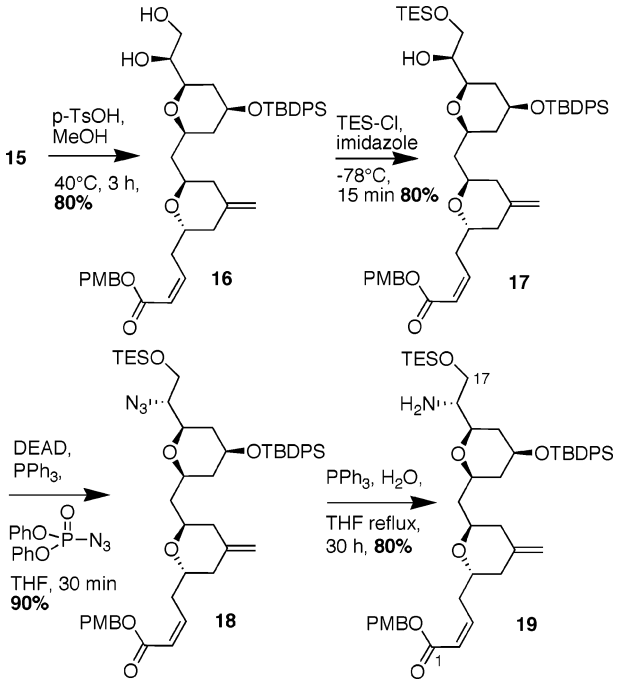


RuO_4 oxidation[18] of the 1° alcohol of **9** to the carboxylic acid **10**, the axially disposed acetic acid substituent was uniquely situated for a intramolecular Mitsunobu[19] reaction with the C7 ring hydroxyl. Although S_N2-type reactions of equatorial leaving groups on six-membered rings are known to be particularly difficult,[20] we surmised that in this intramolecular case, the steric "cost" of the backside approach of the nucleophile had been partially paid via the covalent positioning of the nucleophile. Indeed, after deprotection of the ring hydroxyls using NaOH/MeOH and quenching with the carboxylic acid resin Dowex CCR-3, the crude acid diol[21] **3** yielded the [3.3.1] oxabicyclic lactone **11** when subjected to standard Mitsunobu conditions.[22] Involvement of the C13 hydroxyl, which would lead to a 10-membered lactone ring, was not observed.

With the C7 hydroxyl group now inverted and protected as the lactone, the differentiation was completed by protecting the C13 hydroxyl as the TBDPS ether **2**. The required *Z*-(α,*β*)-unsaturated ester was installed by a Dibal-H/Still−Gennari olefination sequence[23] using trifluoroethyl phosphonate **12** to give *Z*-**13** in 71% yield. Finally, oxidation at C7 using Dess−Martin periodinane[24] to ketone **14** was followed by selective methylenation of the ketone with dimethyltitanocene,[25] affording the fully differentiated exo methylene **15**.

To install the vicinal amino alcohol functionality and complete the synthesis of the C1−C17 subunit of phorboxazole B, we chose a strategy analogous to that employed by Forsyth in his synthesis of the C3−C17 subunit of phorboxazole A[2b] (Scheme 4). Acidic deprotection of the ac-

Scheme 4. Completion of the C1−C17 Segment of Phorboxazole B



etonide of **15** was followed by monoprotection of the resulting diol **16** to afford 1° TES ether **17**. Mitsunobu inversion of the free 2° alcohol using diphenyl phosphoryl azide[26] proceeded in excellent yield to give the azide **18**. Finally, Staudinger reduction[27] of the azide to the amine

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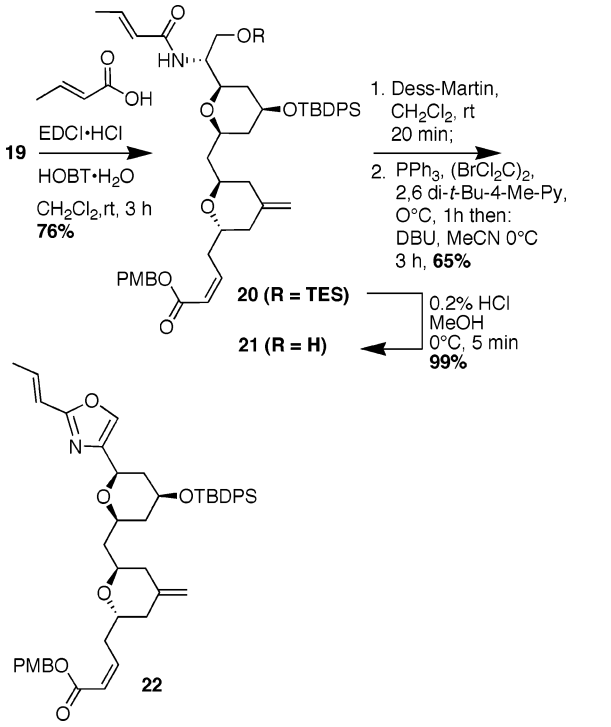
Scheme 5. Subunit Coupling Model Study



produced the fully functionalized C1−C17 subunit of phorboxazole B **19** in 15 steps and 10.8% overall yield from **4**.

Our strategy for future subunit coupling follows the Forsyth precedent of acylation of the C16 amine, followed by oxazole formation using the Wipf procedure.[28] As our subunit has the C1−C3 *Z*-α,*β*-unsaturated ester installed prior to the oxazole formation, we performed a model study to ascertain the stability of the *Z* double bond under the relatively basic Wipf conditions. Scheme 5 illustrates our oxazole formation using *trans*-crotonic acid as a model coupling partner. Acylation of amine **19** using 1.1 equiv of *trans*-crotonic acid gave the amide **20** in 76% yield. Initial attempts at direct oxidation of the 1° TES ether to the C17 aldehyde under Swern conditions[29] were unsuccessful; therefore, we opted for acidic removal of the TES ether to give 1° alcohol **21** followed by oxidation to the aldehyde using Dess−Martin periodinane.[24] The crude amide aldehyde was successfully cyclodehydrated to furnish the desired oxazole **22** using Wipf's conditions.[28]

In conclusion, we have demonstrated that the similar functional groups of bis-tetrahydropyran **4** can be efficiently differentiated by relying on conformational preferences and functional group proximities within the molecule. Selective dihydroxylation of an equatorial vinyl group over an axial vinyl group and intramolecular Mitsunobu lactonization were the key tactics employed in the synthesis of a fully elaborated C1−C17 bis-oxane subunit of phorboxazole B.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2** and **6**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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