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Synthesis of the C22–C26 Tetrahydropyran Segment of Phorboxazole by a Stereoselective Prins Cyclization

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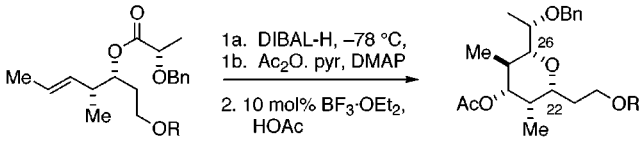
ABSTRACT



Tetrahydropyran rings are found in many complex natural products, and the segment-coupling Prins cyclization is an effective strategy for their synthesis. We report a four-step, stereoselective synthesis of the C20–C27 tetrahydropyran segment of phorboxazole. The key step is a Prins cyclization induced by *catalytic* $BF_3{\cdot}OEt_2$.

Phorboxazoles A and B have attracted the attention of synthetic chemists because of their very high potency in the NCI anticancer screens (mean GI_{50} 1.6 × 10^{-9} M), the difficulty of securing material from natural sources, and their interesting architecture.[1] Forsyth's group led the way with the first total synthesis of phorboxazole A in 1998.[2] A number of other groups have reported work directed toward the total syntheses of the phorboxazoles.[3] Our recent interest in these compounds has focused on the assembly of the four tetrahydropyran rings present in the structures. We describe an enantioselective and stereoselective synthesis of the C22−C26 tetrahydropyran ring of phorboxazole A.

The Prins reaction between a homoallylic alcohol and an aldehyde in acidic solution is a well-established synthesis of tetrahydropyrans.[4] Protic and Lewis acid promoted cy-

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clizations work well in simple cases, and these reactions are often stereoselective.[5] Prins cyclizations have occasionally been used in the synthesis of more complex targets.[6] Our recently reported reductive acetylation of esters to α-acetoxy ethers[7] provides a facile entry into the oxocarbenium ion intermediates that are ideal precursors for segment-coupling Prins cyclizations.[8]

Segment **1**, which includes the C20−C26 tetrahydropyran of the phorboxazoles, is shown in Figure 1. There are a

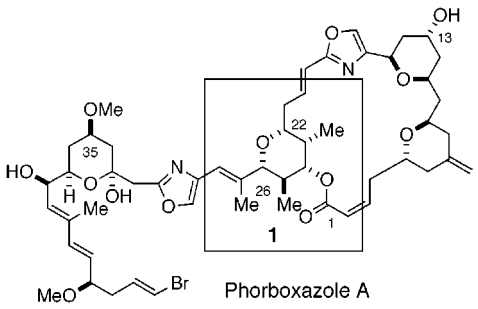
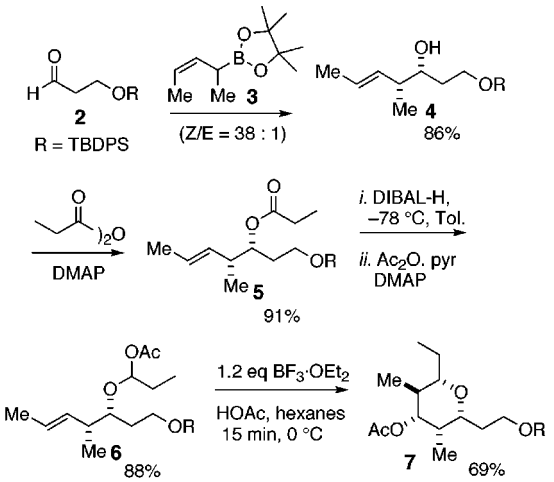


Figure 1. The C22−C26 tetrahydropyran segment of phorboxazole A.

number of possible Prins cyclization precursors for **1**, but none of them are ideal for our strategy because they either involve (a) reductive acetylation of an α,*β*-unsaturated ester or (b) Prins cyclization of an allylic alcohol that might be expected to fragment. To avoid these potential problems, we settled on a strategy in which the trisubstituted alkene would be incorporated after the Prins cyclization. The key elements of this approach were explored in the model study shown in Scheme 1. Aldehyde **2** was coupled with Hoffmann's (*Z*)-

Scheme 1. Prins Cyclization in a Model System



pentenyl boronate **3**[9] to produce homoallylic alcohol **4**.[10] Alcohol **4** incorporates the requisite syn stereochemistry and the (*E*)-alkene geometry that should lead to the correct configuration in the tetrahydropyran. Esterification and reductive acetylation proceeded uneventfully to give α-acetoxy ether **6** in 80% overall yield from alcohol **4**. Activation with $BF_3{\cdot}OEt_2$ and acetic acid in hexanes at 0 °C gave tetrahydropyran **7** as a single isomer in 69% yield. The configuration of **7** was confirmed by NOE measurements and coupling constant analysis (Figure 2). A chair conforma-

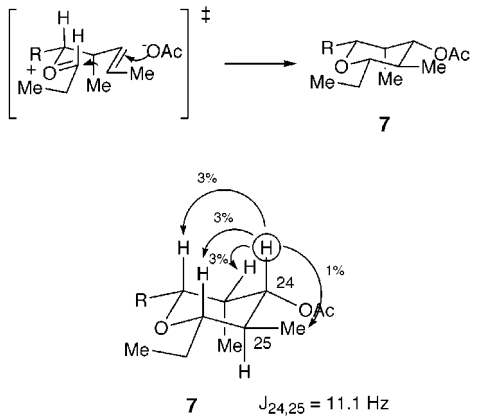
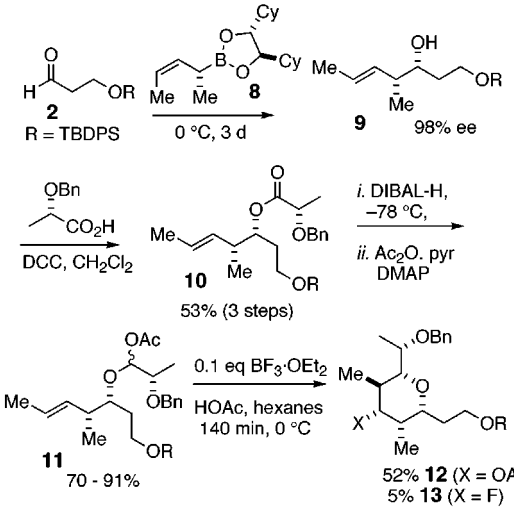


Figure 2. Geometry of the Prins cyclization transition state leading to tetrahydropyran **7**; NOE data and coupling constants supports the assignment.

tion of the oxocarbenium ion intermediate and a trans addition across the alkene are consistent with the observed configuration of the product, Figure 2. The successful synthesis of tetrahydropyran **7**, which incorporates the five contiguous stereogenic centers of **1**, led us to investigate the optically active substrate.

A viable precursor to the C20−C26 tetrahydropyran segment of phorboxazole would need to be optically pure and need to incorporate a functional handle for the introduc-

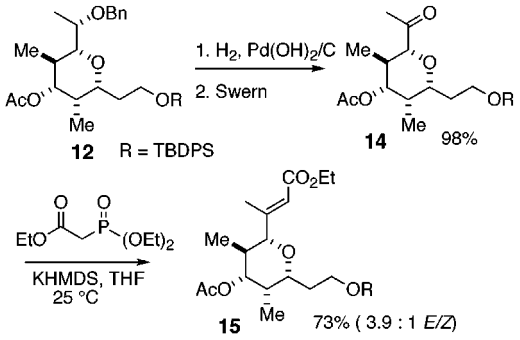
Scheme 2. Synthesis of the Optically Pure Phorboxazole Tetrahydropyran **12**



tion of the C27−C28 trisubstituted alkene. Tetrahydropyran **12** fulfills these requirements, and our approach to **12** is shown in Scheme 2. Aldehyde **2** was coupled with Hoffmann's optically pure (*Z*)-pentenyl boronate **8**[11] to give alcohol **9** with 98% ee.[12] A DCC coupling with *O*-benzyl *S*-lactic acid led to ester **10** as a single diastereomer. The yield of **10** was 53% overall from 3-*O*-(*tert*-butyldiphenylsilyl)propane-1,3-diol, the precursor to aldehyde **2**. Reductive acetylation of **11** worked well on a 100 mg scale and gave α-acetoxy ether **11** in 91% yield. On a 10 g scale, the yield was 70%, and the product was accompanied by 18% of the overreduced product. Normally reductive acetylations scale well,[7] and in this case the problem was probably a too rapid addition of DIBAL-H that led to overreduction. Initial cyclization experiments on a diastereomer of **11** produced significant amount of fluoride trapping along with the desired product. We found that the use of catalytic $BF_3{\cdot}OEt_2$ with acetic acid largely alleviated this problem. Cyclization of α-acetoxy ether **11** with 10 mol % of Lewis acid and 5 equiv of acetic acid gave the desired tetrahydropyran **12** in 52% yield, accompanied by 5% of the corresponding fluoride. This is the first example of which we are aware where a Prins cyclization was *catalyzed* by a Lewis acid. Compound **12** incorporates the five contiguous centers of the C20−C26 ring of phorboxazole and was prepared in four steps and 25% overall yield from aldehyde **2**.

Introduction of the trisubstituted alkene was evaluated as illustrated in Scheme 3. The benzyl ether of **12** was removed

Scheme 3. Synthesis of the Trisubstituted Alkene



by hydrogenation, and the resulting alcohol was oxidized using Swern's conditions.[13] Ketone **14** was isolated as a crystalline solid, mp = 88 °C. X-ray analysis confirmed the relative and absolute configuration of **14**; the structure is shown in Figure 3.[14] Horner−Emmons reaction with the

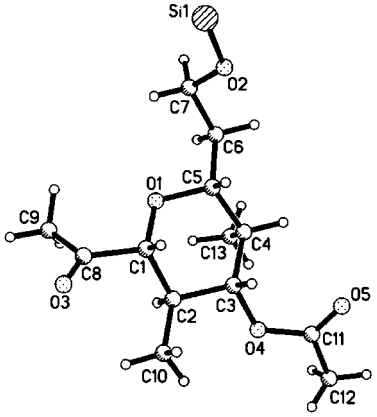


Figure 3. Crystal structure of ketone **14** is shown; the silyl substituents have been omitted for clarity.

triethyl phosphonoacetate anion gave alkene **15** in 73% yield. The desired (*E*)-alkene predominated in a 3.9:1 ratio. Ester **14** has all of the key features of the C20−C26 tetrahydropyran segment **1** from phorboxazole A except for the oxazole ring.

We have described a practical and enantioselective synthesis of the C20−C26 tetrahydropyran of phorboxazole A. This work demonstrates that the segment-coupling Prins cyclization is suitable for the synthesis of highly substituted tetrahydropyran rings.

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Supporting Information Available: Structural information for ketone **14** as a crystallographic information file. Experimental procedures for the preparation of **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Alcohol **9** was analyzed for optical purity by using a Chiralcel OD-H column with 98:2 hexane:*i*-PrOH as the eluent, using the racemate as a standard. The 3*R*,4*R* enantiomer (**9**) eluted first.

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(14) The X-ray data are available as Supporting Information. We thank Dr. Joe Ziller for determining the structure of **14**.