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Synthesis of the C3–C19 Segment of Phorboxazole B

Justin P. Vitale, Scott A. Wolckenhauer, Nga M. Do, and Scott D. Rychnovsky*

Department of Chemistry, 516 Rowland Hall, University of California—Irvine, Irvine, California 92697-2025

srychnov@uci.edu

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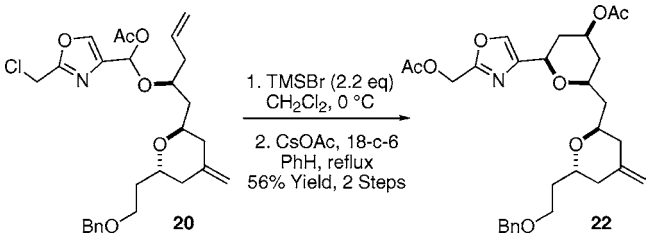
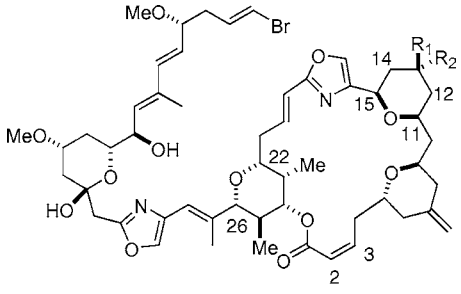
ABSTRACT



Three segment-coupling Prins approaches to the C3–C19 segment of phorboxazole B have been developed. One successful strategy utilized a novel TMSBr-mediated cyclization that proceeded with complete axial selectivity. Displacement of bromide with cesium acetate provided the C13 hydroxyl stereocenter of 22. Additionally, treatment of α-acetoxy ether 20 with TFA enabled a more concise synthesis of the C3–C19 target 13 by allowing direct access to the equatorial alcohol.

Isolated by Molinski from the Indian ocean sponge *Phorbas* sp., phorboxazoles A (**1**) and B (**2**) are a pair of marine macrolides epimeric at C13 (Figure 1).[1a] In addition to their fascinating structures, the phorboxazoles possess antifungal activity and are potent antineoplastic agents.[1a−c] When tested against the National Cancer Institute's (NCI) 60 tumor cell lines, the phorboxazoles displayed high activity across the entire panel (mean GI_{50} 1.58×10^{-9} M) with specific cell lines being inhibited at subnanomolar concentrations. This biological relevance, coupled with their unprecedented architecture, has stimulated a great deal of synthetic interest. Forsyth[2] reported the first synthesis of phorboxazole A in 1998, and since then total syntheses have been reported by Evans[3] (phorboxazole B), Smith,[4] Pattenden,[5] and Williams.[6,7] In addition, numerous approaches to the natural products have also been reported.[8]



Phorboxazole A (1): R_1 = H, R_2 = OH
Phorboxazole B (2): R_1 = OH, R_2 = H

Figure 1. Phorboxazoles.

Our interest in the phorboxazoles stems from a desire to apply our segment-coupling Prins method (Figure 2) to a novel synthesis of phorboxazole B.[9] The strategy utilizes

(1) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126−8131. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422−9423. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879−7880.

(2) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598.

(3) (a) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew Chem., Int. Ed.* **2000**, *39*, 2533−2536. (c) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536−2540.

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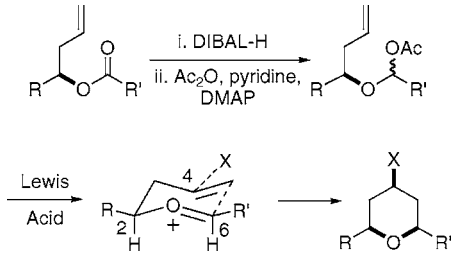
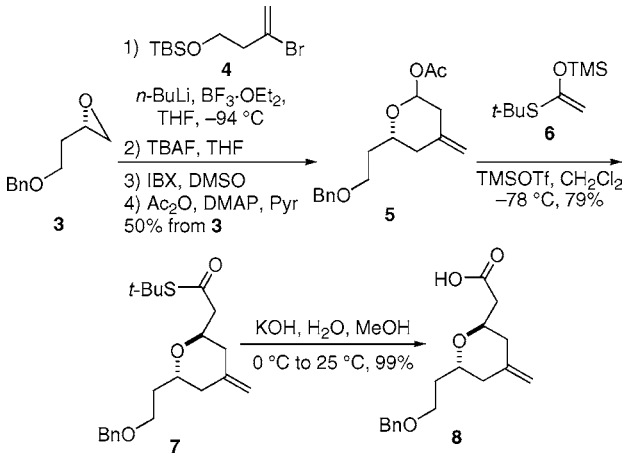


Figure 2. Readily accessible α-acetoxy ethers undergo Prins reaction upon treatment with Lewis acids to afford tetrahydropyrans.

readily accessible α-acetoxy ethers as cyclization substrates.[10] Upon treatment with Lewis acids, α-acetoxy ethers form oxocarbenium ions that undergo Prins cyclization to provide tetrahydropyrans with heteroatoms in the 4-position. Cyclization via a chair transition state with *anti* addition of the nucleophile across the olefin rationalizes the generally high observed selectivity for the *all-cis* product.[9c,11] The utility of this convergent approach for tetrahydropyran construction was demonstrated in a concise synthesis of the central tetrahydropyran (C22−C26) of phorboxazole B.[9b] In this paper, we report the successful application of this methodology to the synthesis of the bis-tetrahydropyran segment (C3−C19) of the natural product.

Our initial approach to the C3−C19 segment of phorboxazole B envisioned Prins cyclization to construct the C11−C12 bond of the natural product and required the synthesis of appropriately functionalized homoallylic alcohol and carboxylic acid coupling partners. Synthesis of carboxylic acid **8** commenced with known optically pure epoxide **3** (Scheme 1).[12] $BF_3{\cdot}OEt_2$-mediated opening of **3** with the vinyllithium reagent derived from vinyl bromide **4** (see the Supporting Information) provided the *tert*-butyldimethylsilyl ether in nearly quantitative yield. Silyl deprotection and primary selective oxidation of the resulting 1,5-diol with IBX provided the lactol, which was acetylated to afford **5** in 50% yield from **3**.[13] Our plan for establishing the 2,6-*trans* stereochemistry of the (C5−C9) pyran ring relied on the stereoelectronic preference for axial addition of nucleophiles to cyclic oxocarbenium ions.[14] In the event, treatment of **5** with TMSOTf in the presence of **6** afforded the *anti*-thioester **7** in 79% yield along with the *syn*-isomer in 14% yield. Hydrolysis of the *anti*-product provided **8** in nearly quantitative yield.

Scheme 1. Synthesis of the Carboxylic Acid Coupling Partner



With the required carboxylic acid in hand, known homoallylic alcohol **10**[15] was accessed in enantiomerically pure form (Scheme 2) by Keck asymmetric allylation[16] of known aldehyde **9**.[15] Following DCC-mediated coupling of **10** and **8**, the resulting ester was converted to α-acetoxy ether **11** by reduction and in situ acetylation.

Having developed an efficient synthesis of α-acetoxy ether **11**, we turned our attention to the key Prins reaction. Despite conducting an extensive screen of cyclization conditions, such as $BF{\cdot}OEt_2$/HOAc, TFAA/HOAc, and TFA/ethylene carbonate, we were unable to affect a high-yielding cyclization. In general, excess Lewis acid was required to induce starting material consumption. This is presumably due to the

(4) (a) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhass, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942−10953. (b) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaus, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834−4836.

(5) (a) Pattenden, G.; Gonzalez, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem* **2003**, *1*, 4173−4208. (b) Gonzalez, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255−1258.

(6) (a) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *PNAS* **2004**, *101*, 12058−12063. (b) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1258−1262.

(7) For a review of the total syntheses, see: Haustedt, L. O.; Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 2711−2716.

(8) For synthetic approaches to the bis-tetrahydropyran segment of the phorboxazoles, see: (a) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026−3038 and references therein. (b) Lucas, B. S.; Luther, L. M.; Burke, S. D. *Org. Lett.* **2004**, *6*, 2965−2968. (c) Zhang, D.-H.; Zhou, W.-S. *Synlett* **2003**, *15*, 1817−1821. (d) Lucas, B. S.; Burke, S. D. *Org. Lett.* **2003**, *5*, 3915−3918. (e) Greer, P. B.; Donaldson, W. A. *Tetrahedron* **2002**, *58*, 6009−6018 and references therein.

(9) (a) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271−7274. (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219. (c) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679−4686. (d) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818. (e) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919−3922. (f) Jasti, R.; Vitale, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904−9905. (g) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1589−1591.

(10) For the preparation of α-acetoxy ethers, see: (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198. (c) Kopecky, D. J.; Rychnovsky, S. D. *Org. Synth.* **2003**, *80*, 177−183.

(11) (a) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960−4961. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580.

(12) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

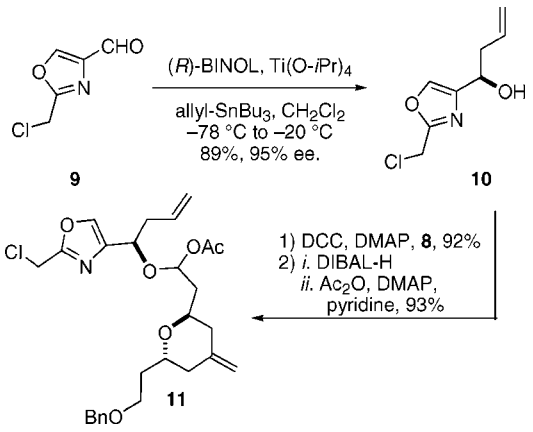
(13) For the primary selective oxidation of 1,4- and 1,5-diols with IBX, see: (a) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *38*, 3485−3488. (b) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945−7948.

(14) Precedent for this stereochemical control element comes from the work of Kishi and Hosomi: (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383−2386.

(15) White, J. D.; Kranemann, C. L.; Kuntyong, P. *Org. Lett.* **2001**, *3*, 4003−4006.

(16) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468.

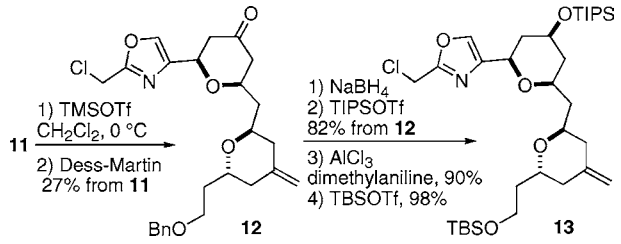
Scheme 2. Synthesis of the First-Generation α-Acetoxy Ether **11**



presence of the Lewis basic oxazole nitrogen. Unfortunately, these forcing conditions often led to intractable mixtures of decomposition products. However, treatment of **11** with TMSOTf (2.2 equiv) in dichloromethane provided, following aqueous workup, a 1:1 mixture of C13 alcohols. Dess−Martin oxidation[17] of the mixture provided ketone **12** in 27% yield over two steps.

Although frustrated by our inability to discover an efficient cyclization, we could access synthetically useful amounts of ketone **12** by this route as shown in Scheme 3. As a result,

Scheme 3. First-Generation Prins Approach



we felt it would be prudent to convert this material to the fully functionalized bis-tetrahydropyran fragment while simultaneously investigating an alternate cyclization substrate. Thus, stereoselective reduction of **12** with $NaBH_4$ gave the equatorial alcohol of phorboxazole B in 82% yield, and this material was then protected as the C13 triisopropylsilyl ether in quantitative yield. Exchange of the C3 hydroxyl protecting group was accomplished by removal of the benzyl ether with aluminum trichloride and *N*,*N*-dimethylaniline followed by treatment of the free alcohol with TBSOTf to provide **13**.[18] This sequence thus provided material suitable for elaboration to the phorboxazole B macrocycle.[19]

It seemed likely that the oxazole was the culprit in this problematic Prins reaction, and we propose that an oxazole stabilized intermediate could account for the unusual reactivity of this substrate. As illustrated in Figure 3, oxocarbenium

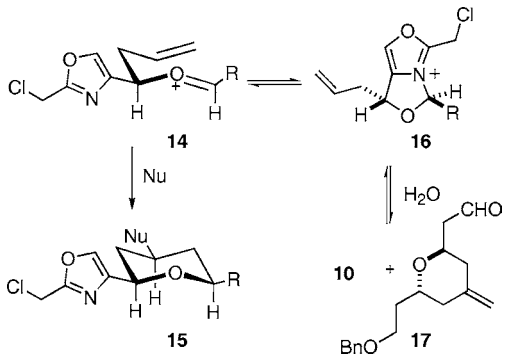
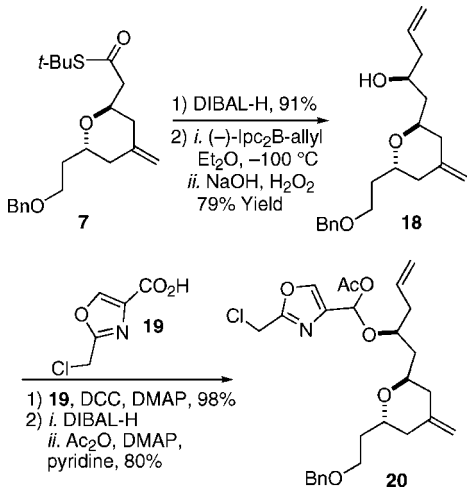


Figure 3. Proposed oxazole-stabilized intermediate **16** that is derived from α-acetoxy ether **11** leads to anomalous reactivity.

ion **14** may undergo Prins cyclization with an appropriate nucleophile to provide desired product **15**. However, formation of intermediate **16** may explain the anomalous reactivity of this substrate. Intermediate **16** would not be productive for cyclization and trapping with adventitious water in the reaction medium or by water introduced upon quench would provide the commonly observed fragmentation products homoallylic alcohol **10** and aldehyde **17**.

Guided by this mechanistic hypothesis, we felt that the problem could be solved by modification of the cyclization precursor. Specifically, we intended to invert the role of the coupling partners and thus construct the C14−C15 bond of

Scheme 4. Synthesis of the Second-Generation α-Acetoxy Ether **20**



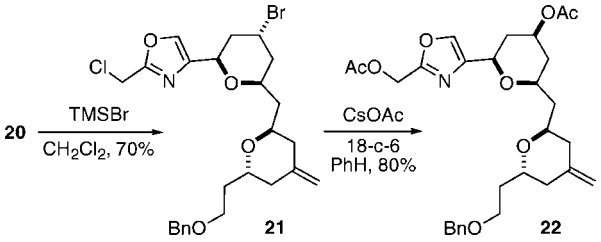
the natural product. Our revised synthetic approach (Scheme 4) commenced with partial reduction of thioester **7**, followed

(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(18) Conditions for benzyl group cleavage were adapted from: Akiyama, T.; Hirofuji, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1321−1324.
(19) Vitale, J. P. Ph.D. Thesis, UC Irvine, 2002.
(20) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439.

by Brown allylation of the resulting aldehyde to afford homoallylic alcohol **18** in 79% yield as a single diastereomer.[20] Synthesis of the second-generation α-acetoxy ether **20** was completed by DCC-mediated coupling of alcohol **18** and carboxylic acid **19** to afford the ester, which was reduced and acetylated without incident.

Upon treatment with TMSBr, α-acetoxy ether **20** underwent efficient Prins cyclization to afford axial bromide **21** as the sole product in good yield (Scheme 5).[21] The complete

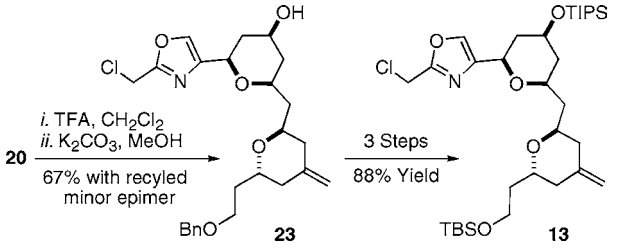
Scheme 5. TMSBr-Mediated Prins Cyclization



axial selectivity of the ring closure was certainly surprising and was not consistent with a mechanism involving concerted cyclization through a chair transition state with approach of the nucleophile from an equatorial trajectory.[22] Nevertheless, we were excited by the efficiency of the transformation. The ultimate success of this approach, however, would depend on our abiltity to displace the axial bromide with an appropriate oxygen nucleophile. Exposure of **21** to cesium acetate and 18-crown-6 in refluxing benzene induced displacement of the axial bromide and the activated C19 chloride to provide **22** in good yield.[23]

Alternatively, treatment of **20** with TFA led to facile Prins cyclization and, following hydrolysis of the C13 trifluoroacetates, afforded a 3.7:1 mixture of chromatographically separable alcohol epimers in 70% yield (Scheme 6).[24] The

Scheme 6. TFA-Mediated Prins Cyclization



minor axial alcohol could be converted to desired product by Dess−Martin oxidation and reduction with $NaBH_4$ to provide **23** in 67% overall yield. This complimentary approach provided direct access to the equatorial alcohol. Compound **23** could be converted to **13** according to the previously optimized conditions.

In summary, three Prins approaches to the C3−C19 segment of phorboxazole B were developed. The success of the first strategy was impeded by the intermediacy of a proposed oxazole stabilized intermediate. Inversion of the coupling partners, however, enabled the development of a novel TMSBr-mediated cyclization, which proceeded with complete axial selectivity. Displacement of bromide with cesium acetate provided the C13 hydroxyl stereocenter. Additionally, direct access to the equatorial alcohol was facilitated by the use of TFA as a cyclization promoter.[25] Clearly, the synthesis of C3−C19 fragment of phorboxazole B underscores the utility of segment coupling Prins reactions in natural product synthesis.

Acknowledgment. The National Institutes of Health (CA-81635) provided financial support. Dupont Pharmaceuticals (J.V.) and Amgen (S.A.W.) provided graduate fellowship support.

Supporting Information Available: Preparation and characterization, including ^1H and ^{13}C spectra of the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) It is noteworthy that treatment of α-acetoxy ether **11** under the same conditions provided solely fragmentation products **10** and **17**.

(22) This phenomenon is general and has been investigated. For a mechanistic rationale, see ref 9f.

(23) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6145−6148.

(24) Conditions for the cyclization were adapted from: Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429−2432.

(25) The second route to **13** using the TFA cyclization was the most concise and proceeded in 13 steps from epoxide **3**. The overall yield for this route, including recycling of the minor epimer of **23**, was 13.2%.