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Phorboxazole Synthetic Studies. 1. Construction of a C(3–19) Subtarget Exploiting an Extension of the Petasis–Ferrier Rearrangement

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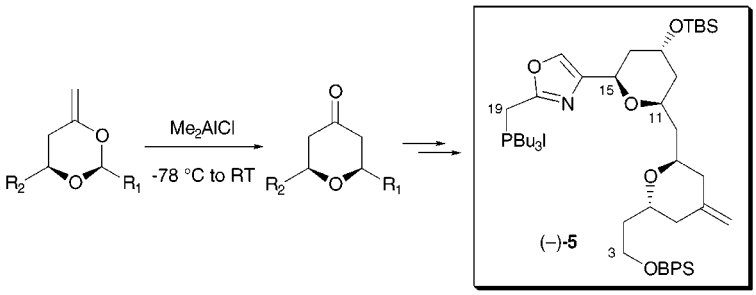
ABSTRACT



In this, the first of two Letters, we outline our overall strategy for the total synthesis of phorboxazoles A (1) and B (2), rare oxazole-containing macrolides possessing extraordinary antimitotic activity, and describe the assembly of a C(3–19) subtarget (–)-5 for the total synthesis of phorboxazole A. The synthesis of (–)-5 was achieved in 15 linear steps (12% overall yield), exploiting a modification of the Petasis–Ferrier rearrangement to construct the C(11–15) *cis*-tetrahydropyran. Dimethylaluminum chloride (Me_2AlCl) proved to be the Lewis acid of choice for the Petasis–Ferrier rearrangement.

Phorboxazoles A (**1**) and B (**2**), rare oxazole-containing macrolides reported in 1995 by Searle and Molinski from the Indian Ocean sponge *Phorbas* sp., are among the most potent antimitotic agents discovered to date, displaying a mean GI_{50} value of 1.58×10^{-9} M against the entire NCI panel of 60 tumor cell lines.[1,2] Although the exact mechanism of action is unknown, studies demonstrate that phorboxazole A (**1**) arrests the cell cycle at the S phase and does not affect microtubules. Given the possibility of a new mechanism of action, the phorboxazoles were recently selected for in vivo trials by the NCI.[2a]

The relative and absolute configurations of the phorboxazoles were established by extensive NMR analysis, in conjunction with degradation and chemical correlation.[2] Not surprisingly the phorboxazoles have attracted wide interest in the synthetic community, leading in 1998 to an elegant total synthesis by Forsyth and co-workers.[3,4] Lured by the architectural complexity, the outstanding antimitotic activity, and their extreme scarcity,[3] we embarked on a total synthesis of these challenging marine natural products. In this Letter, we describe our overall strategy and the assembly of an advanced C(3−19) subtarget **5**.

From the retrosynthetic perspective, disconnection at the C(2−3), C(19−20), and C(28−29) linkages leads to sub-

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

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

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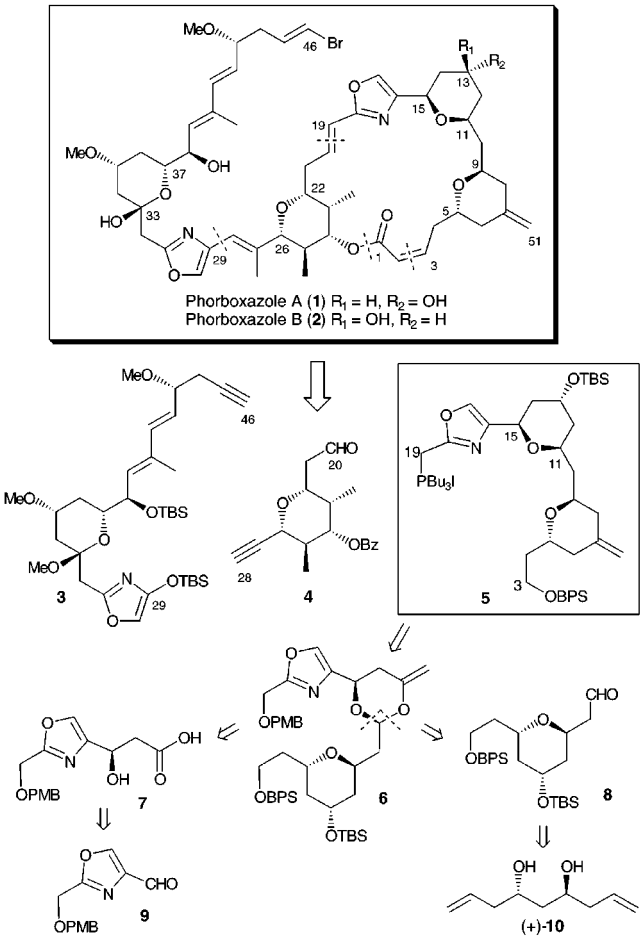
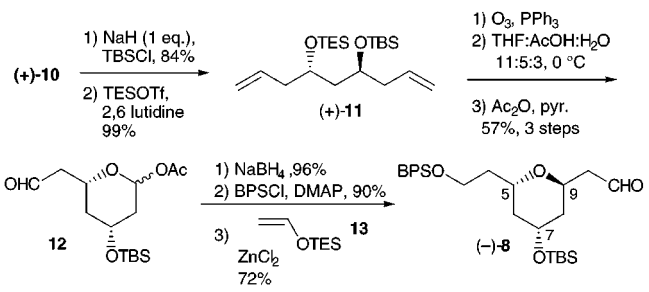
Scheme 1



targets **3**, **4**, and **5** (Scheme 1). In the synthetic direction, this analysis holds the potential for macrocyclization at either the C(2−3) or the C(19−20) π bonds, after introduction of the C(1−2) moiety. Completion of the carbon skeleton would then entail attachment of the C(29) side chain. Focusing on the C(11−15) cis-fused tetrahydropyran, we explored the Petasis modification[5] of the Ferrier rearrangement[6] of vinyl acetal **6** to assemble **5**. To the best of our knowledge, the Petasis−Ferrier rearrangement has not been utilized in the construction of complex synthetic targets. Continuing with this analysis, disconnection of **6** leads to hydroxy acid **7**, available from known oxazole **9**,[4i] and to *trans*-tetrahydropyran **8**, to arise from known diol (+)-**10**.[7]

Our point of departure entailed construction of the C(3−11) subtarget **8** (Scheme 2). Monoprotection of the symmetrical diol (+)-**10**[7] (NaH, TBSCl, 84% yield) followed by treatment with TESOTf and 2,6-lutidine furnished the differentially protected diol (+)-**11**.[8] Exhaustive ozonolysis, removal of the TES group, and exposure of the resulting lactol to acetic anhydride then led to **12**,[8] a 2:1 mixture of acetates, favoring the equatorial isomer (57% yield, three steps). Reduction of the aldehyde ($NaBH_4$), protection of the resulting alcohol (BPSCl), and treatment with silyl enol ether **13**[9] in the presence of $ZnCl_2$ afforded aldehyde (−)-**8**[8] as the only observed product (62% yield, three steps). The relative configuration of (−)-**8** was established by NOE analysis.[10]

Scheme 2



Construction of vinyl acetal **6**, substrate for the Petasis−Ferrier rearrangement, was achieved as outlined in Scheme 3. Aldol condensation of known oxazole **9**[4i] with silyl ketene acetal **14**[11] in the presence of 2 mol % of the Carreira titanium catalyst[12] derived from (*R*)-(+)-NOBIN (e.g., **15**) furnished (+)-**7**[8] in 84% yield (≥98% ee; determined by Mosher ester analysis).[13] Hydrolysis of the benzyl ester (LiOH, H_2O_2; >99%), bis-silylation with hexamethyldisilazane (HMDS), and condensation with aldehyde (−)-**8** promoted by TMSOTf[14] provided dioxanone (−)-**16**[8] in 61% yield, along with 18% of the C(11) epimer, readily removed by flash chromatography. Methylenation of (−)-**16** with the Petasis−Tebbe reagent (Cp_2TiMe_2)[15] completed construction

(4) For other synthetic efforts, see: (a) Lee, C. S.; Forsyth, C. J. *Tetrahedron Lett.* **1996**, *37*, 6449. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672. (c) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998**, *39*, 183. (d) Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319. (e) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099. (f) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185. (g) Wolbers, P.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 1905. (h) Misske, A. M.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 4315. (i) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287. (j) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291. (k) Wolbers, P.; Hoffman, H. M. R. *Synthesis* **1999**, *5*, 797. (l) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.

(5) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *36*, 141.

(6) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.

(7) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161.

(8) The structure assigned to each new compound is in accord with its infrared, 500 MHz ^{1}H NMR, and 125 MHz ^{13}C NMR spectra, as well as appropriate ion identification by high-resolution mass spectrometry.

(9) (a) Tino, J. A.; Lewis, M. D.; Kishi, Y. *Heterocycles* **1987**, *25*, 97. (b) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, *43*, 3791.

(10) A nuclear Overhauer enhancement was observed between H(5) and H(7); irradiation of H(5) did not enhance the H(9) resonance.

(11) Slougui, N.; Rousseau, G.; Conia, J.-M. *Synthesis* **1982**, 58.

(12) (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (b) Smrcina, M.; Lorenc, M.; Hanus, V.; Sedmera, P.; Kocovsky, P. *J. Org. Chem.* **1992**, *57*, 1917.

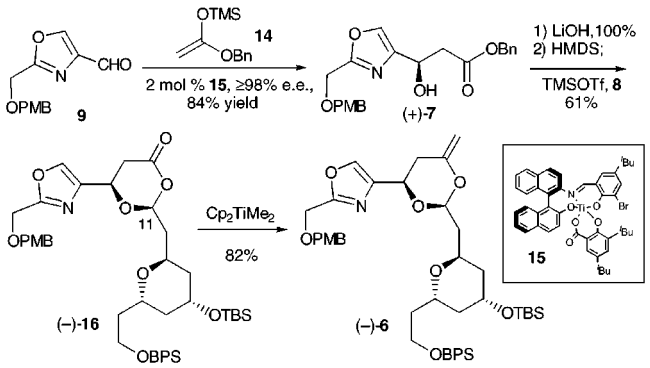
(13) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(14) (a) Harada, T.; Yoshida, T.; Kagamihara, Y.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1367. (b) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.

(15) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

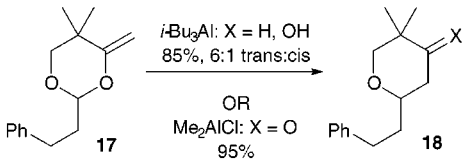
of our initial Petasis−Ferrier substrate (−)-**6**.[8] Unfortunately, all attempts to effect rearrangement with the prescribed[5] *i*-Bu_3Al promoter, employing a variety of temperature, concentration, and solvent regimes failed to produce the desired tetrahydropyran.

Scheme 3



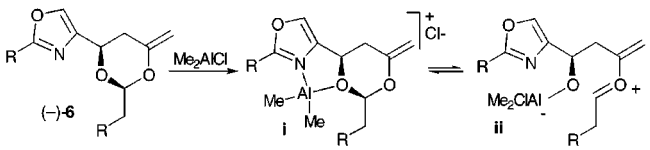
We reasoned that increasing the Lewis acid strength by replacement of one or more alkyl groups in *i*-Bu_3Al with halogens might lead to a more effective promoter. We also sought promoters incapable of Meerwein−Ponndorf−Verley reduction of the initially derived tetrahydropyranone, which often proceeds with variable selectivity. Although many Lewis acids trigger the Petasis−Ferrier rearrangement,[16] the most consistent results with model enol acetal **17**[8,17] (Scheme 4) were obtained with Me_2AlCl. Importantly, Me_2AlCl does not effect Meerwein−Ponndorf−Verley reduction of the initially derived ketone. Moreover, these conditions would appear to tolerate a variety of functionality (e.g., silyl ethers),[18] a clear prerequisite for broad application in natural product total synthesis.

Scheme 4



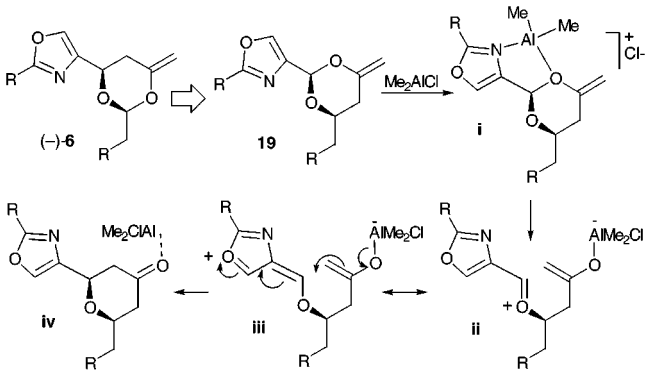
Notwithstanding the improved conditions, enol ether (−)-**6** again failed to undergo rearrangement. That (−)-**6** is unsuited for the Petasis−Ferrier rearrangement may be due to preferred coordination of the Lewis acid with the neighboring oxazole, thereby preventing productive activation of the enol ether and subsequent bond reorganization (Scheme 5).[19]

Scheme 5



To circumvent the lack of reactivity, we envisioned the transposed enol ether **19** (Scheme 6). In this case, initial coordination of the Lewis acid with the oxazole nitrogen might permit productive activation of the enol ether, liberation of the aluminum enolate, and rearrangement (i.e., **i**−**iv**). Substrate **19** suggested two additional advantages: oxazole acetal **19** should lead to the resonance-stabilized oxocarbenium ion **ii**, and tetrahydropyran formation could proceed via a facile 6 exo-trig ring closure (**iii**).[20]

Scheme 6



This scenario called for assembly of **26** (Scheme 7), a second-generation Petasis−Ferrier substrate. Toward this end, asymmetric hetero-Diels−Alder reaction[21] of aldehyde **20**[22] with the Danishefsky diene,[23] promoted by (+)-(*R*)-Binol/$Ti(OiPr_4)$ (10 mol %), furnished enone (−)-**21**[8] in a 63% yield (88% ee).[24] Conjugate addition of vinyl cuprate then proceeded with high stereocontrol to yield the *trans*-tetrahydropyranone (30:1 trans/cis), which in turn was subjected to chemoselective hydroboration at 23 °C,[25] Wittig olefination, and Swern oxidation to furnish aldehyde (−)-**22**[8] (57% yield, four steps). Aldol reaction of (−)-**22** with the tin enolate derived from (−)-**23** according to Nagao,[26]

(16) Other Lewis acids capable of promoting the Petasis−Ferrier rearrangement included $BF_3{\cdot}OEt_2$, $ZnCl_2$, $TiCl_2(OiPr)_2$, and $MeAlCl_2$.

(17) See Supporting Information.

(18) Rearrangement of related complex substrates with *i*-Bu_3Al proved unsuccessful while use of Me_2AlCl was effective.

(19) For a discussion of the chelating ability of Me_2AlCl, see: Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457.

(20) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(21) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

(22) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.

(23) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, *2*, 273.

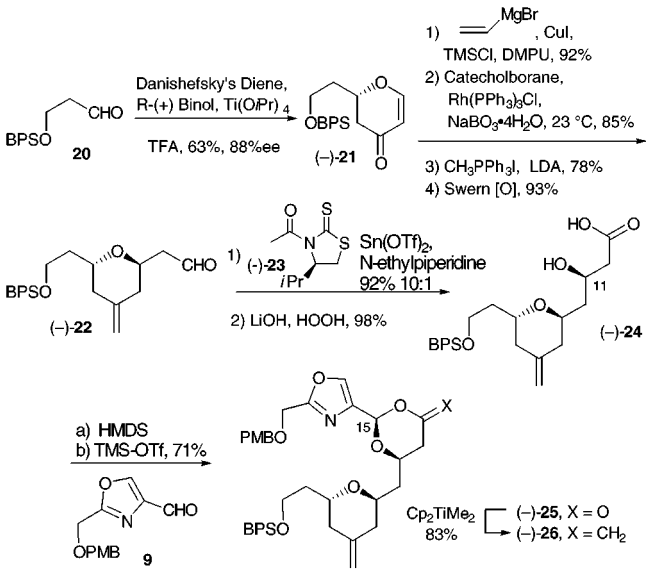
(24) Enantiomeric excess was determined at the level of (−)-**24** by 500 MHz NMR analysis of the diastereomeric ratio.

(25) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671. Interestingly, when the reaction was performed at 0 °C, ketone reduction was competitive with hydroboration.

(26) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc. Chem. Commun.* **1985**, *20*, 1418.

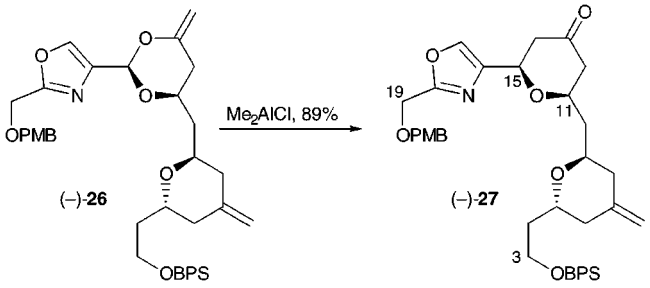
followed by removal of the chiral auxiliary (LiOH, H_2O_2) gave β-hydroxy acid (−)-**24**[8,27] (90% yield, two steps). The diastereoselectivity of the Nagao aldol was 10:1. Bissilylation, followed without isolation by addition of **9**,[4i] led to dioxanone (−)-**25**[8] in 71% yield [99% based on recovered (−)-**24**] and greater than 10:1 selectivity at C(15). Methylenation (Cp_2TiMe_2) completed construction of our second-generation Petasis−Ferrier substrate (−)-**26**.[8]

Scheme 7



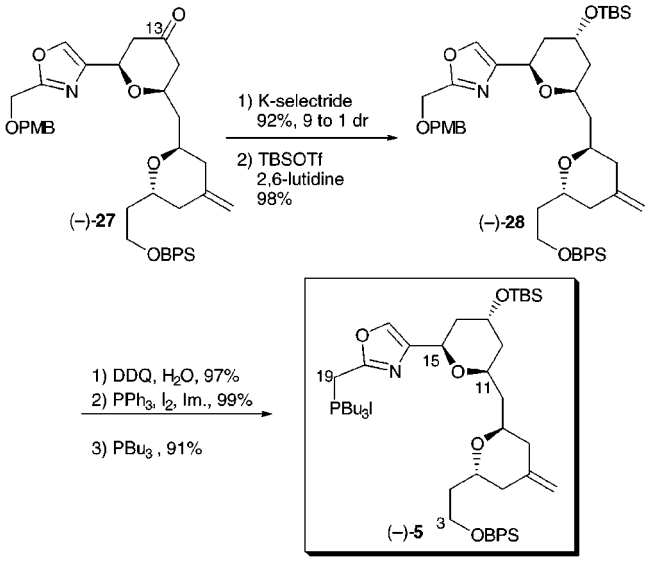
To our delight, treatment of enol ether (−)-**26** with Me_2AlCl at −78 °C (1 equiv), followed by brief warming to room temperature, furnished tetrahydropyranone (−)-**27**[8] as a single isomer in 89% yield (Scheme 8). In contrast, exposure of (−)-**26** to *i*-Bu_3Al led only to recovered starting material. The requisite cis configuration of the newly constructed tetrahydropyran was confirmed by NOESY NMR experiments.[28]

Scheme 8



Having secured the requisite carbon skeleton, five steps were required to complete the C(3−19) subtarget (**5**, Scheme 9): reduction of the C(13) ketone (K-selectride; 9:1 dr),[29] hydroxyl protection (TBSOTf, 2,6-lutidine), oxidative removal of the PMB ether (DDQ), generation of the iodide (PPh_3, I_2, imidazole),[30] and displacement with tributylphosphine. Phosphonium salt (−)-**5**[8] was thus available in 79% for the five steps.

Scheme 9



In summary, construction of the C(3−19) subtarget (−)-**5** for the phorboxazoles has been achieved via a modification of Petasis−Ferrier rearrangement. The synthesis proceeded in a highly efficient, stereocontrolled fashion requiring 15 linear steps (12% overall yield). The Lewis acid of choice for the Petasis−Ferrier rearrangement proved to be Me_2AlCl, obviating reoxidation. Importantly, the ability to transpose the enol ether functionality within Petasis−Ferrier substrates, as illustrated by the construction of (−)-**5**, greatly enhances the utility of this synthetic tactic for tetrahydropyranone assembly. Studies directed toward completion of the phorboxazole synthetic venture continue in our laboratory.

Acknowledgment. Support was provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033.

Supporting Information Available: Spectroscopic and analytical data for compounds **5**−**8**, **11**, **12**, **16**−**18**, **21**, **22**, and **24**−**28** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The absolute configuration at C(11) was secured by Mosher ester analysis; see ref 13.

(28) Mutual nuclear Overhauer enhancements of the H(11) and H(15) resonances indicated the cis relationship in tetrahydropyran (−)-**27**.

(29) It is noteworthy that the reduction of the C(13) ketone to the equatorial alcohol ($NaBH_4$) would provide access to phorboxazole B.

(30) The iodide was moderately unstable and thus used immediately.