Total Synthesis of Phorboxazole A

Craig J. Forsyth,* Feryan Ahmed, Russell D. Cink, and Chi Sing Lee

Department of Chemistry, University of Minnesota Minneapolis, Minnesota 55455

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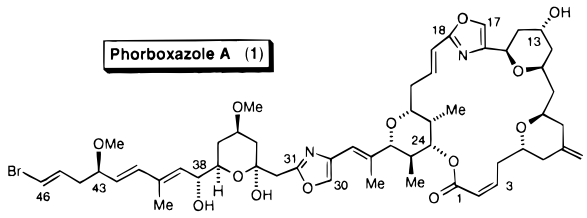
Phorboxazole A (**1**) and its C13 epimer phorboxazole B are remarkable natural products isolated recently from an Indian Ocean sponge *Phorbas* sp.[1] Complete structural assignments for phorboxazoles A and B have resulted from extensive NMR, derivatization, and degradation−correlation studies.[1−3] Their complex and unique structures distinguish the phorboxazoles as a new class of natural products that contain an unprecedented array of oxane, oxazole, macrolide, and polyene moieties. In addition, phorboxazoles A and B have also been selected by the National Cancer Institute for in vivo antitumor trials[2] due to the extraordinary levels of cytostatic activity displayed by **1** against a broad range of human cancer cell lines.[1−3] In contrast to known potent anti-mitotic natural products, **1** appears to halt progression of the cell cycle during the S phase,[3] although the cellular mode of action has apparently not been elucidated. Their novel structures, intriguing biological activity, and limited availability[4] combine to make the phorboxazoles compelling and important targets of total synthesis.[5−8] Reported here is a convergent total synthesis of **1** that culminates our recent work in this area.[5−7]



Strategic disconnections at both of the oxazoles and the acrylate moiety of **1** suggested assembly of the natural product from three fragments, representing carbons 3−17, 18−30, and 31−46. Complementary vicinal amino alcohol and carboxylic acid partners were identified as logical precursors to the two oxazoles. It was anticipated that an intramolecular Horner−Emmons reaction between a C3 aldehyde and a C24 phosphonoacetate could be relied upon to simultaneously install the C1−C3 (*Z*)-acrylate moiety and close the C1−C24 macrolide. Further, it was of interest to explore the effects of macrocyclic conformational constraints on the stereoselectivity of acrylate formation in this manner. Thus, a tricomponent coupling approach was adopted wherein the macrolide domain would be assembled first via sequential formation of the C16−C18 oxazole and bridging acrylate moieties from two halves (C3−C17[6] and C18−C30[7]), and the C31−C46[5] fragment would subsequently be attached by formation of the C29−C31 oxazole. Each of the three key fragments has been synthesized in appropriately functionalized form, as previously reported.[5−7] Merits of this convergent synthetic design include the potential for a concise and rapid assembly, as well as opportunities for the facile construction of structural variants to probe the biological roles of specific functionalities and architectural features of the phorboxazoles.

The carboxylic acid required for formation of the C16−C18 oxazole was obtained from the C18−C30 intermediate **2**[7] by sequential silylation of the C24 hydroxyl group and saponification of the methyl ester (Scheme 1). The methylene-linked bis-oxane half (C3−C17) of the macrolide was readied for coupling by selective monodesilylation of the bis-silyl ether **4**[6] to give vicinal amino alcohol **5**. Oxazole formation was then initiated by EDCI-mediated coupling[9] of **3** and **5** to yield hydroxy amide **6**. Application of Wipf's improved procedure[10] for 2,4-disubstituted oxazole formation via cyclodehydration of an amide aldehyde[11] involved oxidation of **6** with Dess−Martin periodinane[12] followed by bromooxazoline formation and elimination, which provided oxazole **7** cleanly. Installation of the (*Z*)-acrylate linking the C24 hydroxyl to C3 was preceded by selective removal of the C24 triethylsilyl group of **7** to give secondary alcohol **8**. The liberated hydroxyl was acylated first with diethylphosphonoacetic acid to give **9**, which was then treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[13] to cleave the C3 PMB ether selectively and afford primary alcohol **11**. Oxidation with Dess−Martin periodinane gave the corresponding C24-diethylphosphonoacetate, C3-aldehyde **13**. Rapid cyclization of **13** occurred under Masamune−Roush conditions (LiCl, Et_3N, CH_3CN)[14] to give predominately the (2*E*)-acrylate, (*E*)-**15**. Preliminary attempts to isomerize (*E*)-**15** to (*Z*)-**15** were unrewarding. Alternatively, treatment of **13** with K_2CO_3 and 18-crown-6 in toluene[15] gave a 4:1 ratio of (*Z*)-**15**:(*E*)-**15**, respectively, but a prolonged reaction time was required for substantial conversion at room temperature. A logical attempt to improve the (*Z*)-stereoselectivity[15] and rate of the cyclization involved acylation of **8** with bis-(2,2,2-trifluoroethyl)phosphonoacetic acid to provide the corresponding acetate **10**. Conversion of **10** into aldehyde **14**, followed by intramolecular Horner−Emmons coupling again using Still's conditions (K_2CO_3, 18-crown-6, toluene, −40 to −5 °C, 5 h)[15] markedly enhanced the rate of cyclization, but resulted in the same 4:1 ratio of (*Z*)-**15**:(*E*)-**15**, respectively. Without further optimization or chromatographic separation, the acetonide protecting group was removed from the isomeric mixture of (*E*,*Z*)-**15**. This facilitated separation of the alkene isomers to give the primary alcohol (*Z*)-**16** as a crystalline solid. Gratifyingly, X-ray crystallographic analysis of **16** confirmed that its stereochemistry[2] and conformation[1] are the same as those reported for the C1−C28 portion of **1**.[16]

Final attachment of the C31−C46 fragment necessitated removal of the *t*-Boc group from **16**, which could be accomplished selectively by brief treatment of **16** with 4 N HCl in dioxane. EDCI-mediated coupling[9] of the free amine liberated in situ from **17** with the C31−C46 carboxylic acid (**19**) derived from ester **18**[5] (Scheme 2) gave hydroxy amide **20**. In contrast to the previous smooth formation of the C16−C18 oxazole via a stepwise oxidation−cyclodehydration process,[10] similar conver-

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(16) The X-ray analysis of **16** was performed by Dr. Victor Young of the University of Minnesota Chemistry Department. The use of (*S*)-serine as the source of the C29 stereogenic center defines the absolute stereochemistry of **16**, and the ^1H and ^{13}C NMR spectral data for **16** match well those of the corresponding domain of the natural product.[1] See the Supporting Information.

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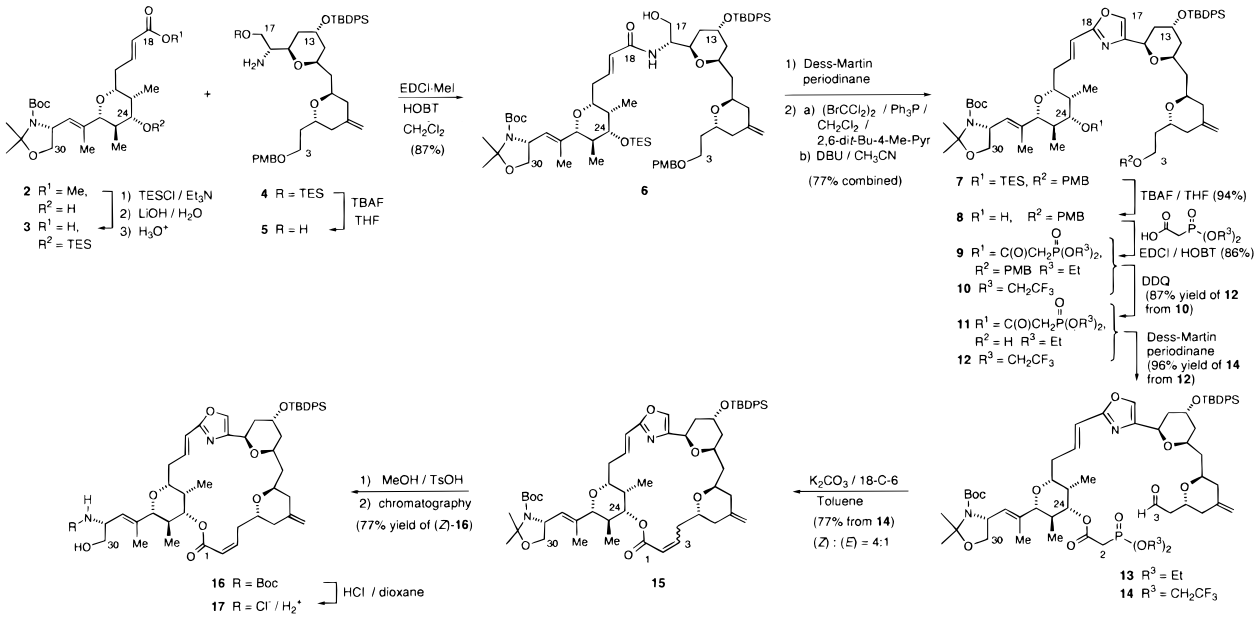
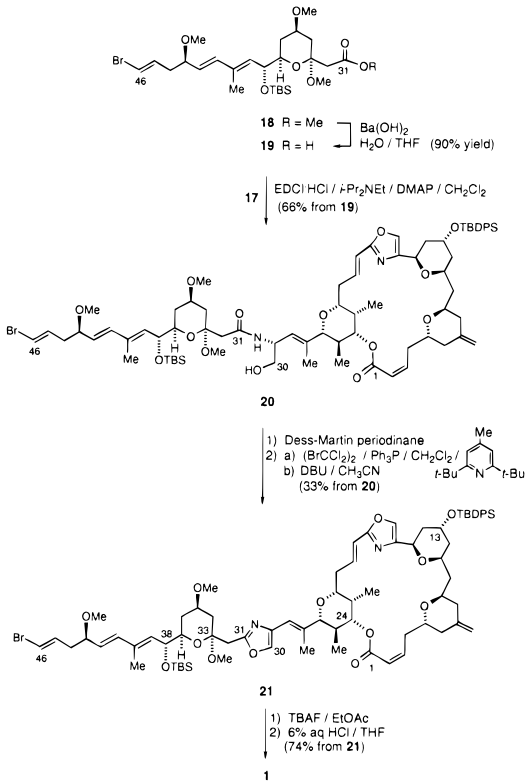
Scheme 1



Scheme 2



sion of **20** into the C29−C31 oxazole **21** has proven, thus far, to be only modest yielding. However, the separate C1−C30 (**17**) and C31−C46 (**19**) domains of **1** were advanced to an intermediate (**21**) representing the trihydroxyl-protected form of **1** in only three steps. The TBDPS ether at C13 resisted initial attempts to remove cleanly all three protecting groups from **21** in one additional step using aqueous HF.[17] However, sequential treatment of **21** with TBAF/EtOAc and 6% aqueous HCl/THF sufficed to cleave both the silyl ethers and the mixed methyl acetal to deliver **1**.[18] Phorboxazole A was thus prepared in only 5 steps from carboxylic acid **19** and amino alcohol **17** and in ca. 34 steps in the longest linear sequence beginning with the synthesis of the C3−C17 intermediate **4**.[6]

This total synthesis represents an alternative source of **1** and should be amenable to the generation of structural variants of phorboxazole A. It relies upon the facile preparation and use of highly functionalized building blocks,[5−7] generally dependable methods for their coupling,[9,10] a late stage, stereoselective[15] installation of the (*Z*)-acrylate, and judicious protecting group deployment. Finally, this work corroborates the structural assignments made for **1**[1−3] and provides an atomic-level definition of the phorboxazole macrolide conformation via the X-ray analysis of intermediate **16**. The latter may prove useful in guiding the rational design of phorboxazole analogues and in studying potential receptor−ligand interactions.

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Supporting Information Available: Experimental procedures for compounds **1**, **3**, **5**−**8**, **10**, **12**, and **14**−**21**; physical and spectral data for compounds **1**−**3**, **5**−**8**, **10**, **12**, **14**−**16**, and **18**−**21**; photocopies of ^{1}H NMR spectra for compounds **1**, **5**−**8**, **10**, **12**, **14**−**16**, and **18**−**21**; photocopies of ^{13}C NMR spectra for compounds **5**−**8**, **10**, **12**, **16**, **18**, and **19**; and X-ray crystallographic data for **16** (59 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(18) The ^{1}H NMR (500 MHz, $CDCl_3$), HRMS (MALDI), and IR data of synthetic **1** match those recorded for the natural product;[1] see the Supporting Information for full experimental details and characterization data.