ORGANIC LETTERS

2006
Vol. 8, No. 26
6043−6046

Total Synthesis of Phorboxazole A. 2. Assembly of Subunits and Completion of the Synthesis

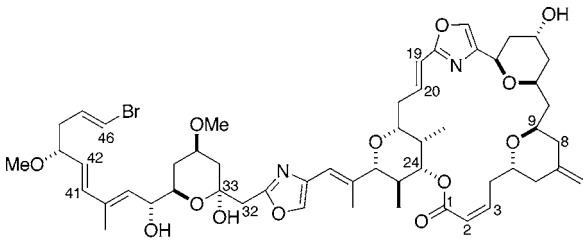
James D. White,* Tae Hee Lee, and Punlop Kuntiyong

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

james.white@oregonstate.edu

Received October 13, 2006

ABSTRACT



Phorboxazole A

Subunits of phorboxazole A containing C1–C2, C3–C8, C9–C19, C20–C32, C33–C41, and C42–C46 were connected in a sequence that first linked C32 with C33 and then C41 with C42. A C3–C8 fragment was joined to C9–C19, and the assembled unit was then joined with the left half of 1. Closure of the macrolide was accomplished by esterification of the C24 alcohol followed by intramolecular Horner–Wadsworth–Emmons condensation to set the (*E*)-C2–C3 alkene.

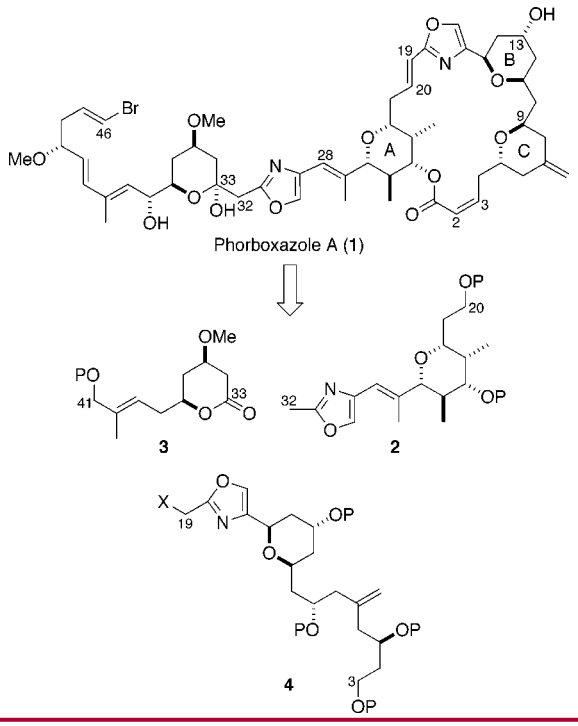
The preceding Letter[1] describes the synthesis of four major subunits of the potent antitumor agent phorboxazole A (**1**).[2] It also reports that attempts to couple two subunits at C32−C33 through addition of the anion from deprotonation of a methyl-substituted oxazole representing C20−C32 with a δ-lactone incorporating C33−C46 encountered difficulties. Specifically, this reaction resulted in a significant quantity of a terminal alkyne arising from elimination of HBr from the bromoalkene. Because we were unsuccessful in attempts to convert the alkyne byproduct to the desired (*E*)-bromoalkene, we decided to adopt a different strategy for assembling the C20−C46 segment of **1**. This Letter reports an assembly sequence that first combines a C20−C32 unit **2** with C33−C41 (**3**), adds the remaining segment (C42−C46) of the phorboxazole side chain, then connects C20 of **2** to a fragment **4** containing C3−C19 before adding the last two carbons and closing the macrolide (Scheme 1). This highly convergent strategy takes advantage of certain features incorporated into other syntheses of phorboxazoles[3−8] and allows us to exploit methodology we developed for the synthesis of subunits containing tetrahydropyrans A and B.[9]

To circumvent the problem of HBr elimination encountered previously in generating the C32−C33 linkage, a truncated version of the phorboxazole side chain was

(1) White, J. D.; Kuntiyoung, P.; Lee, T. H. *Org. Lett.* **2006**, *8*, 6039.
(2) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J .W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879. (d) Molinski, T. F.; Brzezinski, L. J.; Leahy, J .W. *Tetrahedron: Asymmetry* **2002**, *13*, 1013.
(3) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597.
(4) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834.
(5) (a) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1258. (b) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12058.
(6) (a) Gonzalez, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255. (b) Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173.
(7) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.
(8) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.−Eur. J.* **2006**, *12*, 1185.
(9) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Lett.* **2001**, *3*, 4003.

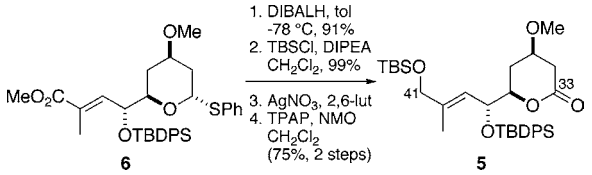
10.1021/ol062531j CCC: $33.50
Published on Web 11/22/2006

Scheme 1. Key Subunits for the C32−C33 and C19−C20 Connections



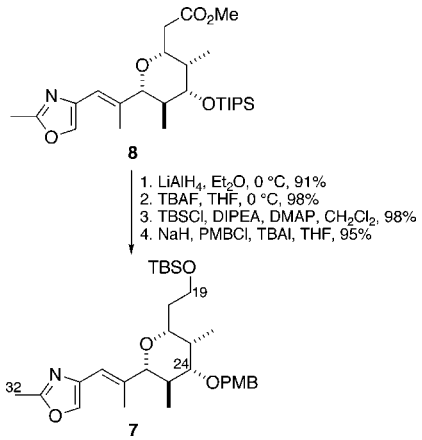
employed for coupling with **2**. This took the form of lactone **5**, obtained in four steps from the previously synthesized

Scheme 2. Synthesis of the C33−C41 Subunit



phenylthio acetal **6**[1] (Scheme 2). The coupling partner **7** for **5** was prepared from tetrahydropyran **8** via a sequence that

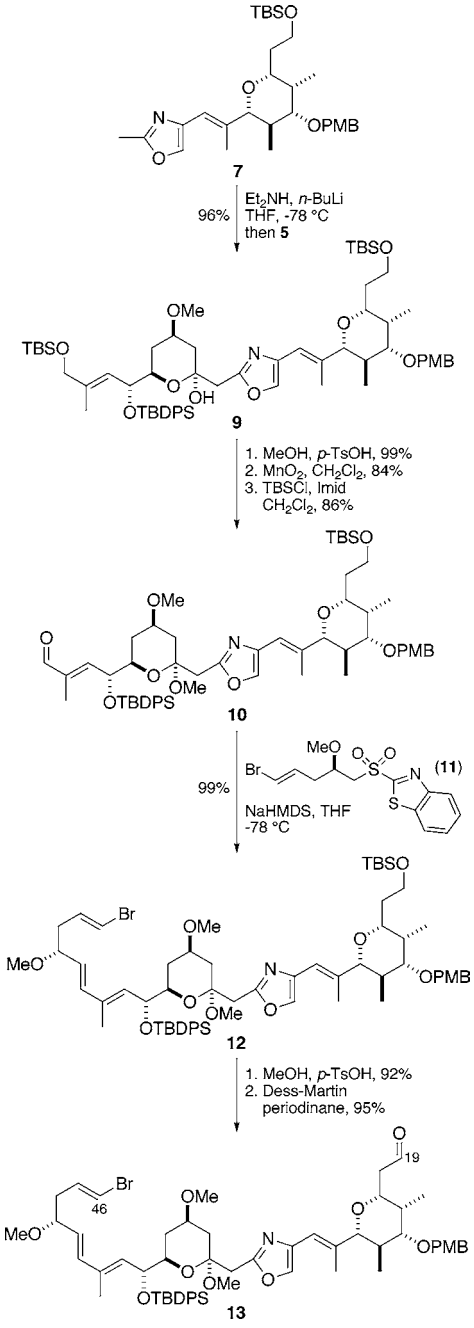
Scheme 3. Synthesis of the C19−C32 Subunit



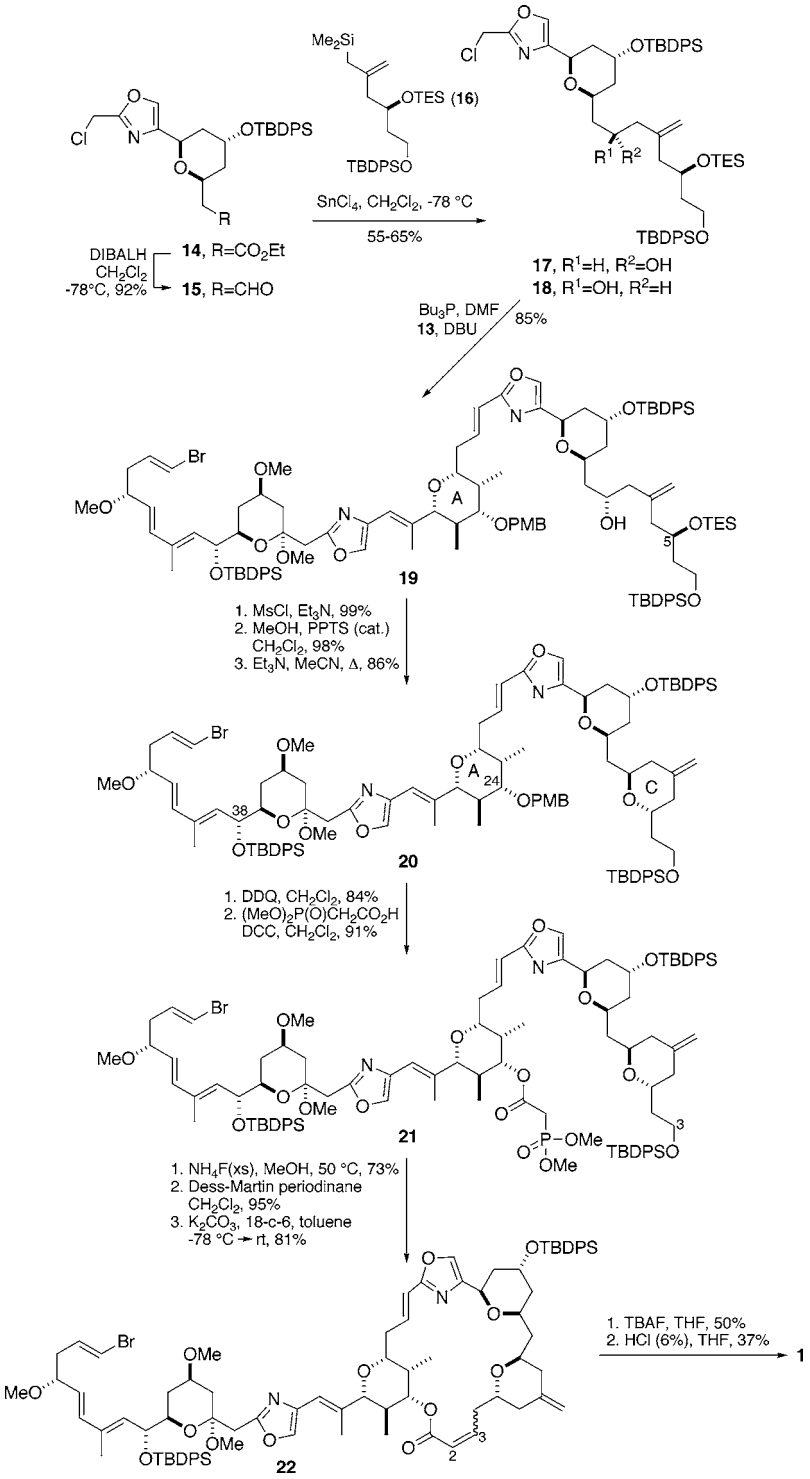
reduced the ester, cleaved the TIPS ether, blocked the primary alcohol as its TBS ether, and then masked the C24 hydroxyl group as a *p*-methoxybenzyl ether (Scheme 3). The last of these moves was found to be necessary to effect clean exposure of the C24 hydroxyl group for esterification prior to the pivotal macrocyclization steps.

The anion derived from **7** with lithium diethylamide under conditions described by Evans[7] was reacted with lactone **5** to afford hemiketal **9** as a single epimer in near quantitative yield (Scheme 4). Treatment of **9** with acidic methanol not only converted this substance to its methyl ketal but simultaneously cleaved both TBS ethers, thus allowing

Scheme 4. Union of the C19−C32, C33−C41, and C42−C46 Subunits



Scheme 5. Union of C3−C19 with C20−C46 and Completion of the Synthesis



selective oxidation of the allylic alcohol to an aldehyde. Reprotection of the remaining primary alcohol then gave **10**. Julia−Kocienski condensation[10] of aldehyde **10** with known sufone **11**[5] afforded a quantitative yield of **12** representing a fully functionalized and protected version of the C19−C46 sector of **1**. In preparation for uniting **12** with a second major fragment of **1**, the primary silyl ether was cleaved and the resulting alcohol was oxidized to aldehyde **13**.

Synthesis of **4** for its linkage to **13** began with reduction of previously prepared ester **14**[1] to aldehyde **15** (Scheme 5). The latter was reacted with allylsilane **16** in the presence of stannic chloride[11] to yield a 1:1 mixture of stereoisomeric alcohols **17** and **18** that were easily separated by chromatography. The (9*S*) configuration of **17** was proven through

(10) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

NMR analysis (^{1}H and ^{19}F) of its Mosher ester,[12] and **18** was converted to **17** by oxidation to a ketone followed by reduction with L-Selectride.

Wittig−Schlosser coupling[13] of the ylide prepared from the tri-*n*-butylphosphonium salt of **17** with aldehyde **13** produced trans C19−C20 alkene **19** accompanied by only a trace of the cis alkene. Alcohol **19** was converted to its mesylate. The TES ether at C5 was cleaved selectively, and the resulting hydroxy mesylate was exposed to triethylamine. This sequence closed tetrahydropyran C to afford **20**. The *p*-methoxybenzyl ether of **20** was cleaved under carefully controlled conditions with DDQ, and the C24 alcohol was esterified with dimethoxyphosphonylacetic acid to give **21**.

At this point, closure of the macrolactone of **1** required formation of a C3 aldehyde which mandated selective cleavage of the primary TBDPS ether in the presence of two secondary TBDPS ethers. The reagent TAS-F was partly successful in this case,[14] giving a mixture of the primary alcohol and two diols, but although it was possible to selectively oxidize the primary alcohol with TEMPO and sodium hypochlorite, we sought an improved method for advancing **21** to a primary alcohol. This was accomplished with an excess of ammonium fluoride in warm methanol; oxidation of the resulting primary alcohol then gave an aldehyde which was lactonized via an intramolecular Horner−Wadsworth−Emmons reaction under conditions described by Williams.[5] The resulting (*E*/*Z*) mixture of alkenes **22** (1:4, respectively) was treated with TBAF to remove the remaining pair of TBDPS ethers and then with aqueous hydrochloric acid to hydrolyze the methyl acetal. After chromatographic purification to remove the minor (*E*) isomer, synthetic phorboxazole A (**1**) was obtained which was identical, by comparison of its ^{1}H NMR spectrum, with natural material isolated by Molinski.[2a] Our synthetic phorboxazole A was further identified by comparison of its ^{13}C NMR spectrum with that published by Williams.[5]

In summary, a highly convergent synthesis of phorboxazole A was completed in which the longest linear sequence is 37 steps and the overall yield is 0.4%. Two of the three tetrahydropyrans within the macrolide framework were formed using intramolecular alkoxycarbonylation in the presence of a palladium(II) species, exemplifying useful methodology for the stereoselective construction of this ubiquitous heterocycle.

Acknowledgment. Financial support from the National Institute of General Medical Science through grants GM-50574 and GM-58889 is gratefully acknowledged.

Supporting Information Available: Detailed experimental procedures and characterization data for new compounds; ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062531J

(11) Dias, L. C.; dos Santos, D. R.; Steil, L. J. *Tetrahedron Lett.* **2003**, *44*, 6861.

(12) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(13) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821.

(14) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750.