Pergamon

Tetrahedron Letters, Vol. 37, No. 36, pp. 6449-6452, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01435-9

Synthesis of the Central C18-C30 Core of the Phorboxazole Natural Products

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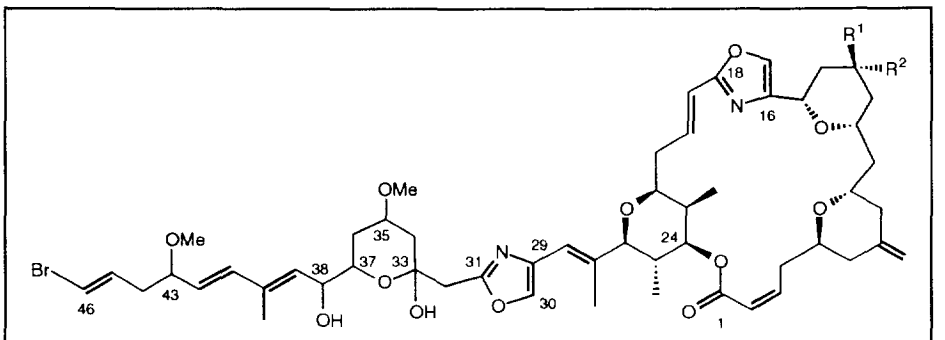
Abstract: A direct synthesis of the central C18-C30 core of the phorboxazole natural products has been developed. This involves construction of an acyclic acrylate using Paterson's (*E*)-enol borinate aldol methodology followed by an intramolecular hetero-Michael addition to form the central pyran ring of the natural products. Copyright © 1996 Elsevier Science Ltd

Phorboxazoles A and B are recently described marine natural products bearing an unprecedented array of structural features and phenomenal levels of cytostatic activity.[1] The relative configuration of the conformationally rigid C1-C26 macrolide portion, as well as the C33-35 oxane ring of the phorboxazoles has been assigned by Searle and Molinski on the basis of extensive NMR analyses, but considerable stereochemical ambiguity remains. As part of a program directed at developing a total synthesis of the phorboxazoles, we report here a concise, enantioselective synthesis of the stereochemically dense central core spanning carbons 18-30 of the natural products.

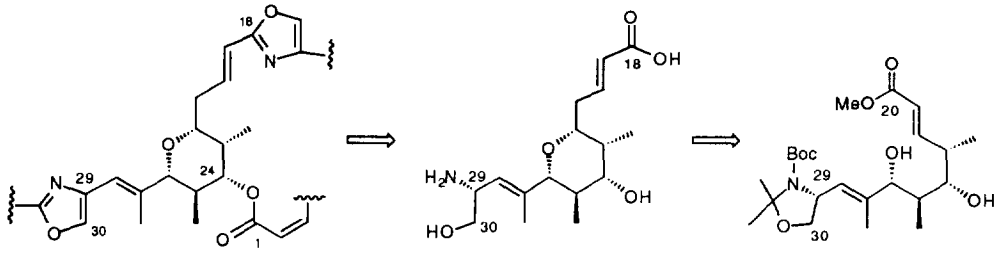


Phorboxazole A $R^1 = OH, R^2 = H$

Phorboxazole B $R^2 = OH, R^1 = H$

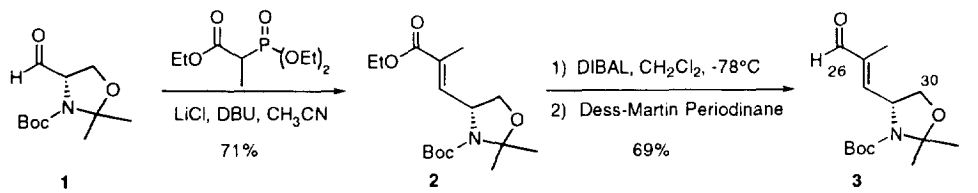
Our approach towards the construction of the highly substituted central pyran moiety of the phorboxazoles was to install four of the five contiguous stereogenic centers in an acyclic C20-C30 intermediate via aldol chemistry, then close the pyran by an intramolecular hetero-Michael addition upon a tethered acrylate. Thermodynamic equilibration in the latter step was expected to establish the

remaining β-alkoxy ester stereogenic center in the 2,6-diequatorially substituted pyran. The incorporation of a vicinal amino alcohol at C29,C30 should facilitate attachment of the C31-C46 portion of the natural products via C29-C31 oxazole formation. Similarly, a carboxylic acid at C18 may be used to couple the central C18-C30 fragment to the adjoining bispyran moiety of the macrolide by C16-C18 oxazole formation. We chose L-serine as the source of the C29,C30 amino alcohol, and targeted a C18-C20 acrylate as the other terminus of the central phorboxazole fragment.



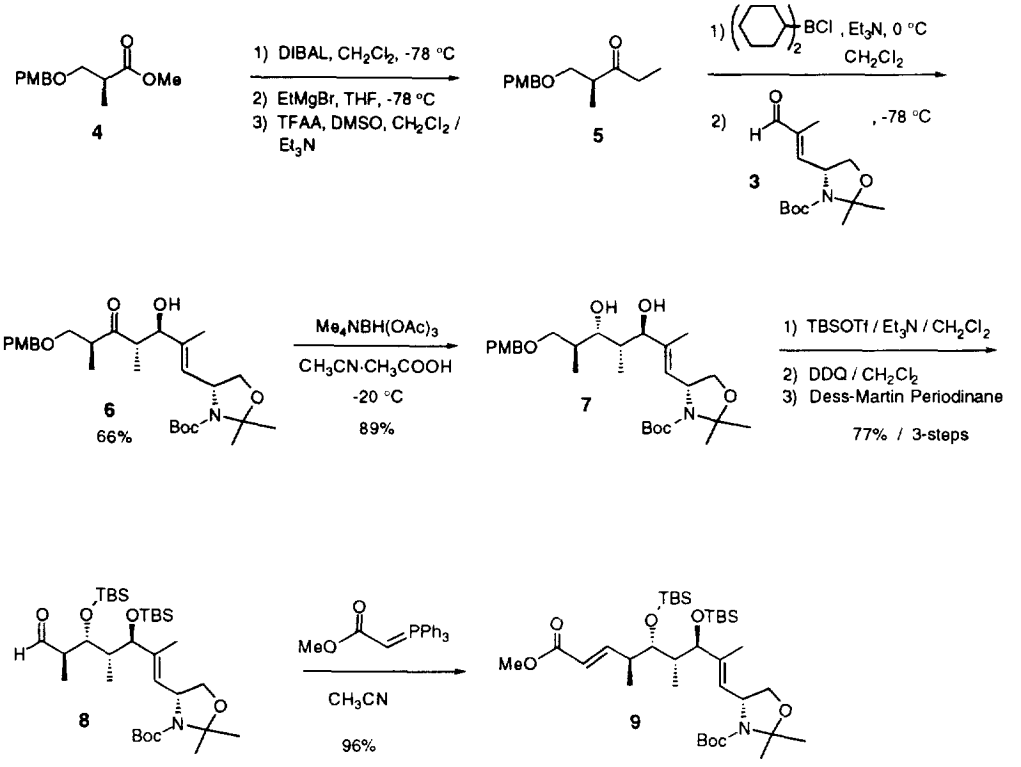
The acyclic stereotetrad present in the intramolecular Michael acceptor was installed smoothly using a combination of Paterson's (*E*)-enol borinate aldol chemistry[2] and Evans' β-hydroxy directed ketone reduction methodology.[3] Condensation of Garner's aldehyde **1**[4] with triethyl 2-phosphonopropionate under Roush-Masamune conditions[5] gave (*E*)-acrylate **2** in 71% yield (scheme 1). Conversion of **2** into the aldehyde **3** required for aldol coupling was accomplished conveniently in a two-step sequence involving diisobutylaluminum hydride reduction to the alcohol, followed by Dess-Martin periodinane oxidation.[6]

Scheme 1



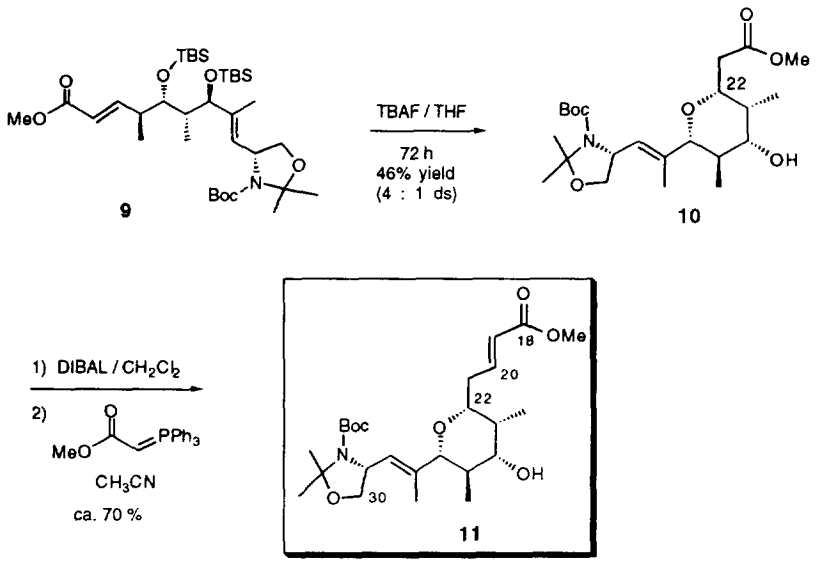
Ethyl ketone **5** was prepared from methyl (S)-3-(*p*-methoxybenzyl)oxy-2-methylpropionate (**4**)[7] by the 3-step sequence illustrated in scheme 2.[8] Conversion of **5** into the (*E*)-dicyclohexylboron enolate at 0 °C, followed by addition of α,β-unsaturated aldehyde **3** at -78 °C gave the anti-anti aldol product[2] **6** in 66% chromatographically isolated yield. β-Hydroxy directed ketone reduction using tetramethylammonium triacetoxyborohydride[3] furnished the 1,3-anti diol **7** in 97% yield. Routine functional group manipulations gave acrylate **9** via aldehyde **8**.

Scheme 2



Pyran formation via intramolecular 1,4-addition was then effected by simply treating **9** with TBAF (1M, THF, 0 °C to room temperature) for 72 h (scheme 3). Under these conditions the bis-equatorially substituted pyran **10** was formed preferentially in a 4:1 ratio of diastereomers, but in modest yield. The use of shorter reaction times allowed the isolation of monosilylated intermediates, as well as the same dihydroxy acrylate and pyran products obtained at longer reaction times. Preliminary attempts to improve the efficiency of the hetero-Michael addition process included the use of elevated temperatures, reaction times longer than 72 h, and stronger bases; however, the net conversion to **10** was not enhanced. Addition of benzyltrimethylammonium methoxide to the TBAF reaction mixture[9] lead to loss of the *N*-Boc protecting group. Thus, without extensive optimization, **10** was elaborated via side chain extension. Sequential treatment of **10** with DIBAL and methyl (triphenylphorphoranylidene)acetate gave (*E*)-acrylate **11** to complete the synthesis of the central C18-C30 phorboxazole fragment. This synthetic sequence provides ready access to the fully functionalized central core of the phorboxazole natural products. As such, it should support continued efforts directed at a convergent total synthesis of this new class of powerfully cytostatic natural products.

Scheme 3



Acknowledgments: We thank the University of Minnesota for a McKnight Land-Grant Professorship (CJF) for partial financial support, and Russell D. Cink and Feryan Ahmed for technical assistance.

References and Notes

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(7) Because the absolute configuration of the phorboxazoles had not been established, we arbitrarily chose the (S)-enantiomer of **4**. This was prepared from methyl (S)-(+)-3-hydroxy-2-methyl-propionate and *p*-methoxybenzyltrichloroacetimidate as described in: Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139-4142.

(8) It has been noted that partial racemization occurred with a similar substrate in this type of reaction sequence: Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585-588. This may be reflected here in the moderate yield of the desired diastereomer **6** obtained from subsequent aldol coupling.

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(*Received in USA* 9 *July* 1996; *accepted* 18 *July* 1996)