

Toward the Total Synthesis of Phorboxazole B: An Efficient Synthesis of the C20–C46 Segment

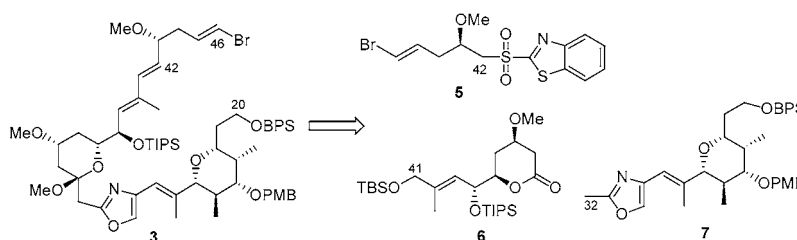
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ABSTRACT



An efficient synthesis of the C20–C46 segment of phorboxazole B is described. The key steps involved $\text{Hg}(\text{OAc})_2/\text{I}_2$ -induced cyclization to construct the *cis*-tetrahydropyran moiety, the coupling of the metalated 2-methyloxazole 7 with lactone 6, and Julia olefination to furnish the conjugated diene moiety.

Phorboxazole A (1) and its epimer phorboxazole B (2), isolated from the sponge *Phorbas* sp. collected in the Indian Ocean, are novel 21-membered macrolides accommodating four heavily functionalized oxanes and two 2,4-disubstituted oxazoles.¹ The relative and absolute stereochemistries of phorboxazoles were determined by extensive NMR analysis, degradation studies, and synthetic correlation.² These metabolites are ranked among the most cytostatic natural products ever known, exhibiting extraordinary potency (mean $\text{GI}_{50} < 1.6 \times 10^{-9}$ M) when bioassayed against 60 human tumor cell strains at the National Cancer Institute (NCI).¹ The unprecedented structural features and remarkable anti-tumor activities of phorboxazoles have attracted great attention in the synthetic community,³ and several excellent achievements of their total synthesis have been reported by Forsyth,⁴ Evans,⁵ Smith,⁶ Pattenden,⁷ and Williams.⁸

Our retrosynthetic analysis of phorboxazole B (Scheme 1) disconnected the structure at the C2–C3 and C19–C20

double bonds, which combined the features of the Evans⁵ and Pattenden⁷ syntheses and led to the key building blocks

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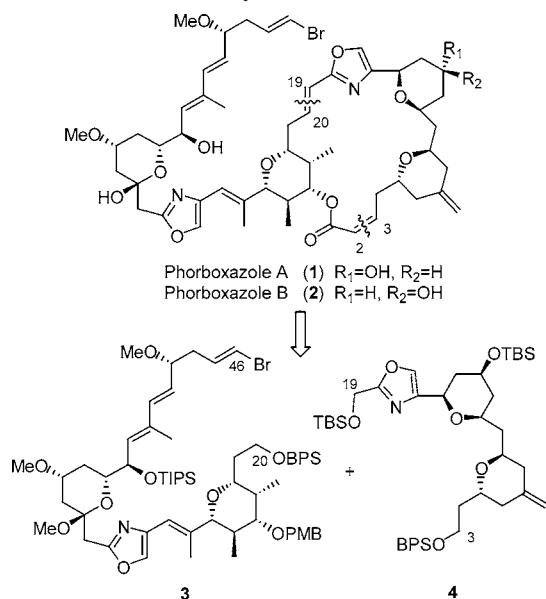
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Scheme 1. Retrosynthesis of Phorboxazole B

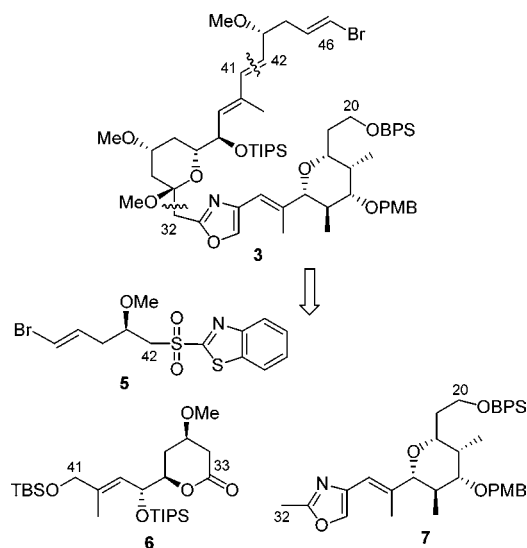


3 and 4. We envisaged coupling 3 and 4 at C19–C20 using an *E*-selective Wittig reaction. An intramolecular *Z*-selective Wadsworth–Emmons olefination reaction at C2–C3 would then lead to completion of the total synthesis of phorboxazole B.

The synthesis of the C3–C19 segment 4 has been reported in a previous publication from our group.^{3p} Herein, we now describe our efficient synthesis of the segment 3 of phorboxazole B.

From a retrosynthetic perspective (Scheme 2), disconnection of the C32–C33 bond and the C41–C42 double bond

Scheme 2. Retrosynthesis of the C20–C46 Segment 3 of Phorboxazole B

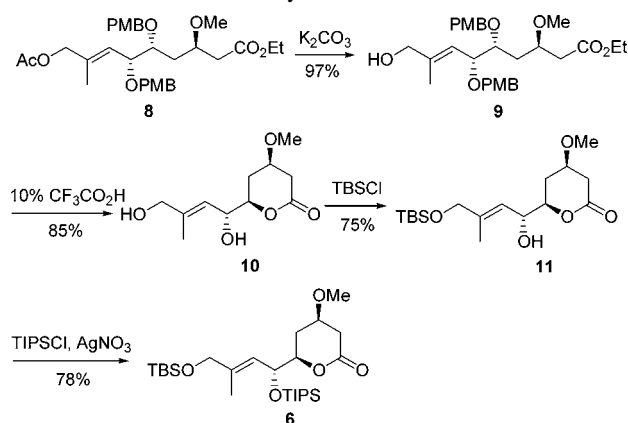


separates 3 into the known sulfone 5,^{3q} lactone 6, and the tetrahydropyran oxazole 7. It was envisaged that coupling

the lactone 6 with 7, using the procedure described by the Evans group⁵ and subsequent Julia olefination reaction with sulfone 5, would lead to the formation of the C20–C46 segment 3.

As shown in Scheme 3, the route to lactone 6 started from our previous reported compound 8, which was synthesized

Scheme 3. Synthesis of Lactone 6



from 1,3-propanediol using a Wittig reaction, a Sharpless AD, and a Mukaiyama aldol reaction as key steps.^{3q} Deprotection of the acetoxy group from 8 with $K_2CO_3/EtOH$ ⁹ afforded alcohol 9 in 97% yield. When compound 9 was treated with 10% CF_3CO_2H in CH_2Cl_2 ,¹⁰ the PMB protecting groups were smoothly removed and the resultant triol concomitantly cyclized to afford the lactone 10. Since lactone 10 is highly soluble in water, the reaction mixture was directly neutralized with Et_3N , concentrated, and purified by SiO_2 flash column chromatography without extraction. Selective protection of the primary hydroxyl group in 10 with $TBSCl/Et_3N$ ¹¹ delivered the mono-TBS ether 11. Protection of 11 with a TIPS (triisopropylsilyl) group under routine conditions ($TIPSCl$, imidazole, cat. DMAP, DMF)¹² was not successful, but the use of $TIPSCl/AgNO_3$ ¹³ afforded the desired lactone 6.

The synthesis of the THP-oxazole segment 7 commenced from diol 12, which was readily accessible from D-glycer-

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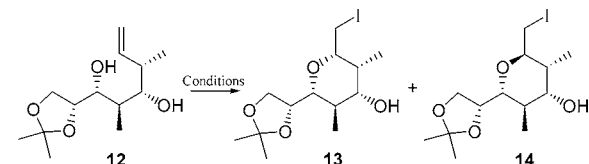
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aldehyde by reiterative application of asymmetric crotylation.³⁰ To construct the *cis*-tetrahydropyran unit of **7**, the iodocyclization¹⁴ reaction of **12** was first explored. As shown in Table 1, iodocyclization of diol **12** with iodine in

Table 1. Construction of *cis*-Tetrahydropyran Moiety of **7**



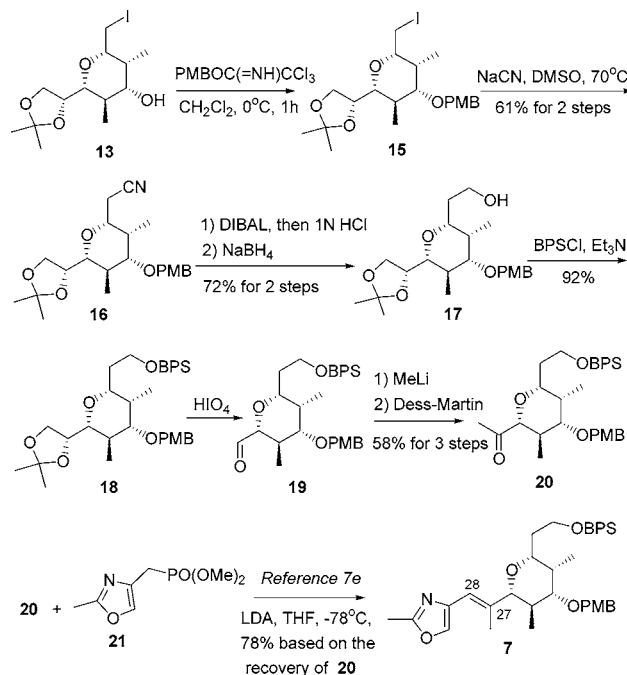
entry	conditions	13/14 ^a	yield ^b (%)
1	I ₂ , CH ₃ CN, −35 °C to 0 °C		^c
2	I ₂ , NaHCO ₃ , CH ₃ CN, 0 °C	2.6:1	46
3	NIS, CH ₂ Cl ₂ , 30 °C	7.7:1	52 ^d
4	Hg(OAc) ₂ , toluene, 0 °C; I ₂ , 30 °C	5:1	86

^a Product ratio was determined by ¹H NMR spectral analysis (300 MHz).
^b Isolated yield. ^c Complex mixture. ^d Based on recovery of 40% starting material.

acetonitrile yielded a complex mixture (entry 1), probably due to the lability of the acetonide to the HI generated during the process of cyclization. Therefore, NaHCO₃ was added to the reaction mixture (entry 2). To our delight, the desired *cis*-tetrahydropyran **13**, along with the minor *trans*-isomer **14**, were obtained in 46% overall yield (**13/14** = 2.6:1). To optimize the stereochemical outcome, NIS (*N*-iodosuccinimide) was used (entry 3). Although the ratio of **13** and **14** increased to 7.7:1, the overall yield was still low (52% based on recovery of 40% starting material). We next turned our attention to Hg(OAc)₂-induced cyclization, which is also a general method for preparing tetrahydropyran systems.¹⁵ After screening various solvents and reaction conditions, we eventually found that when diol **12** was treated with Hg(OAc)₂ in dry toluene at 0 °C and the organomercurial was treated with iodine, the *cis*-tetrahydropyran **13** was formed in 86% yield with 5:1 dr.¹⁶ The configuration of **13** was later confirmed by 2D NOSEY analysis on the oxazole **7**.

Protection of the hydroxyl group in **13** with *p*-methoxybenzyl trichloroacetimidate¹⁷ in the presence of BF₃·OEt₂ gave the PMB ether **15** (Scheme 4). Iodide **15** was converted to the nitrile **16**, and this was successively reduced with DIBAL and NaBH₄ to give the alcohol **17**.¹⁸ Protection of

Scheme 4. Synthesis of Oxazole **7**



the hydroxyl group in **17** with BPSCl (*tert*-butyldiphenylsilyl chloride)¹⁹ gave the ether **18**, which was converted to aldehyde **19** by the action of periodic acid.²⁰ MeLi addition to the aldehyde **19** followed by Dess–Martin oxidation²¹ afforded methyl ketone **20**.

To complete the synthesis of oxazole **7**, an *E*-selective olefination reaction was required to construct the C27–C28-trisubstituted double bond. Although the Wittig reaction²² and Julia olefination²³ have been successfully employed to construct *E*-double bonds, methyl ketone **20** reacted sluggishly under these reaction conditions. Ultimately, we resorted to the procedure described by Pattenden, in which the oxazole phosphonate ester **21** was used.^{7c} We were delighted that, when phosphonate ester **21** was deprotonated with LDA at −78 °C followed by treatment with methyl ketone **20**, the desired THP-oxazole segment **7** was obtained in 78% yield (based on the recovery of 20% starting material).²⁴

With segments **5–7** in hand, the stage was set to complete the synthesis of the C20–C46 segment of phorbaxazole B (Scheme 5). Oxazole **7** was deprotonated with lithium diethylamide at −78 °C^{5a} and treated afterward with lactone **6**, and the desired cyclic hemiketal **22** was obtained in 61% yield as the sole isomer. Selective deprotection of the C41 TBS ether of **22** and spontaneous Fischer glycosidation of the hemiketal was accomplished with PPTS/CH₃OH and

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(16) Compound **13** could be isolated by flash chromatography using silica gel in 71% yield as the major diastereomer.

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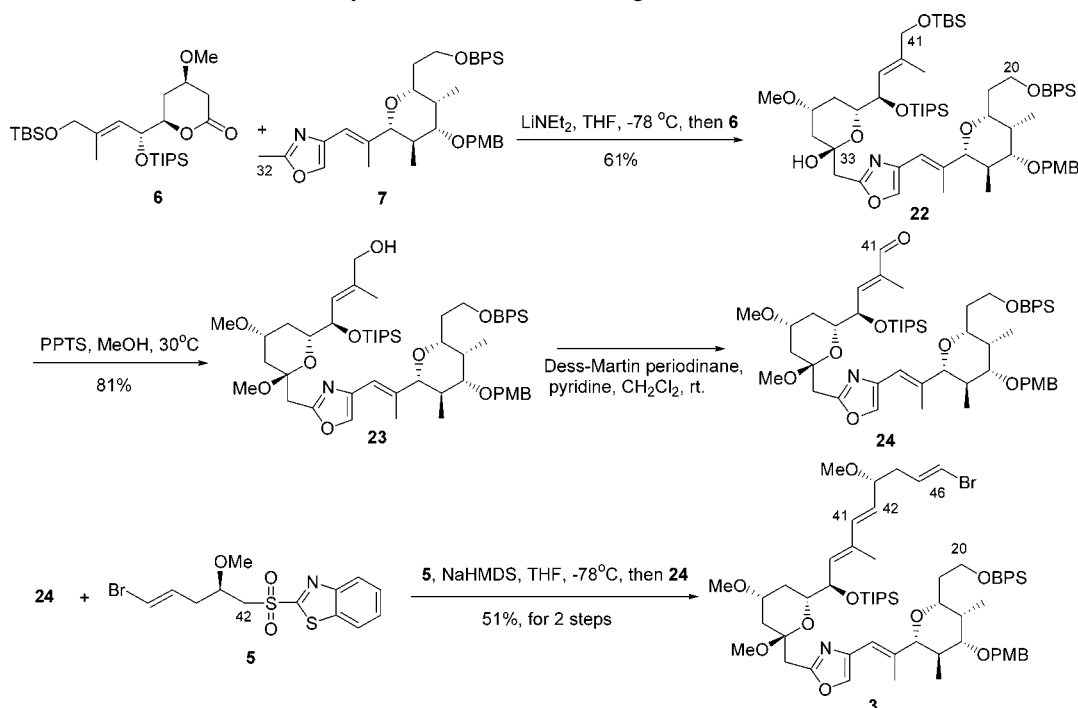
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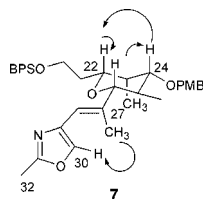
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Scheme 5. Synthesis of the C20–C46 Segment of Phorboxazole B



afforded the alcohol **23**. Careful oxidation of the allylic primary alcohol of **23** with Dess–Martin periodinane,²¹ followed by Julia olefination²³ of the crude aldehyde **24** with sulfone **5**, smoothly furnished the desired *E*-diene moiety (51%, two steps; *E/Z* >95:5). The synthesis of the C20–C46 segment of phorboxazole B was thus completed.

(24) The *cis*-configuration of the tetrahydropyran of the compound **7** was confirmed by the NOE effect among H22, H24, and H26. The NOE effect among C27 methyl group and H30 confirmed *E*-configuration of C27–C28 double bond.



In summary, an efficient synthesis of the C20–C46 segment **3** of phorboxazole B has been developed using a convergent strategy. The key steps involved $\text{Hg}(\text{OAc})_2/\text{I}_2$ -induced cyclization to construct the *cis*-tetrahydropyran unit, the employment of metalated 2-methyl oxazole chemistry to couple lactone **6** with oxazole **7**, and Julia olefination to furnish the conjugated diene moiety. The successful synthesis of the C20–C46 segment **3** has laid a solid foundation for the total synthesis of phorboxazole B, which is in progress in our laboratory and will be reported in due course.

Supporting Information Available: Selected experimental procedures and spectroscopic data of compounds **3**, **5–14**, **16–18**, and **20–23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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