ORGANIC LETTERS

2004
Vol. 6, No. 23
4261−4264

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

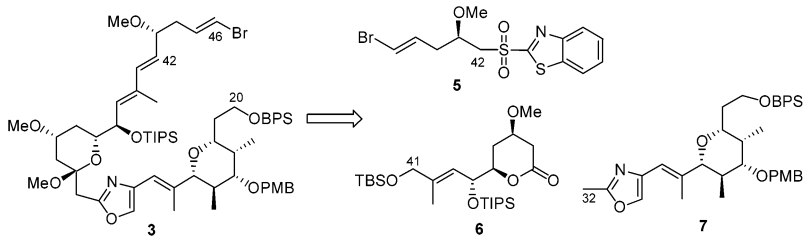
De Run Li, Cai Yun Sun, Ce Su, Guo-Qiang Lin,* and Wei-Shan Zhou

Shanghai Institute of Organic Chemistry, 354 Fenglin Rd, Shanghai 200032, P.R. China

lingq@mail.sioc.ac.cn

Received August 28, 2004

ABSTRACT



An efficient synthesis of the C20–C46 segment of phorboxazole B is described. The key steps involved $Hg(OAc)_2/I_2$-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 $GI_{50} < 1.6 \times 10^{-9}$ M) when bioassayed against 60 human tumor cell strains at the National Cancer Institute (NCI).[1] The unprecedented structural features and remarkable antitumor 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 Evans[5] and Pattenden[7] syntheses and led to the key building blocks

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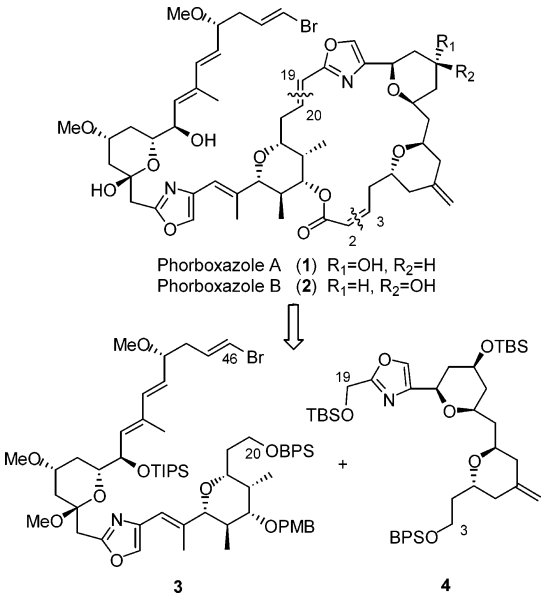
10.1021/ol048275x CCC: $27.50
Published on Web 10/15/2004

Scheme 1. Retrosynthesis of Phorboxazole B

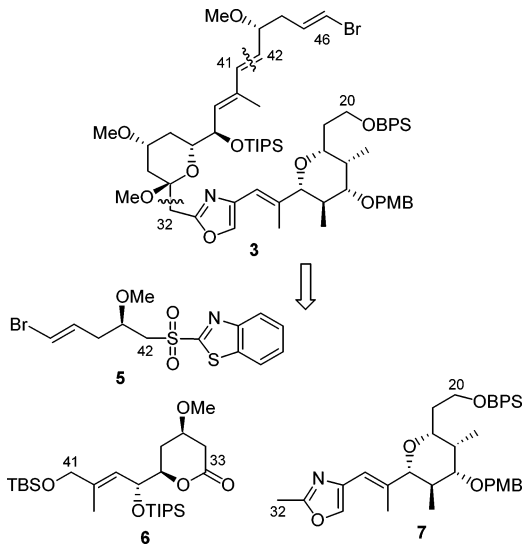


3 and **4**. We envisaged coupling **3** and **4** at C19−C20 using an *E*-selective Wittig reaction. An intramolecular *Z*-selective Wadsworth−Emmons olefination reaction at C2−C3 would then lead to completion of the total synthesis of phorboxazole B.

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

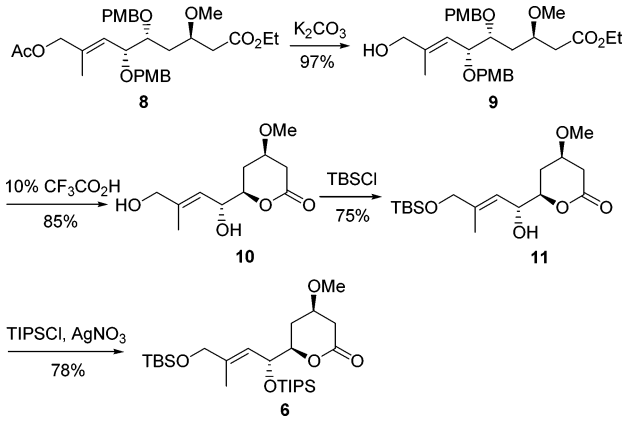
Scheme 2. Retrosynthesis of the C20−C46 Segment **3** of Phorboxazole B



separates **3** into the known sulfone **5**,[3q] lactone **6**, and the tetrahydropyranyl oxazole **7**. It was envisaged that coupling the lactone **6** with **7**, using the procedure described by the Evans group[5] 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 Witttig 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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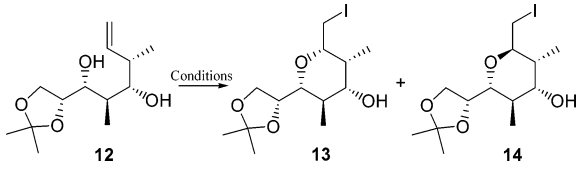
aldehyde by reiterative application of asymmetric crotylation.[3o] To construct the *cis*-tetrahydropyran unit of **7**, the iodocyclization[14] reaction of **12** was first explored. As shown in Table 1, iodocyclization of diol **12** with iodine in

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



12 **13** **14**

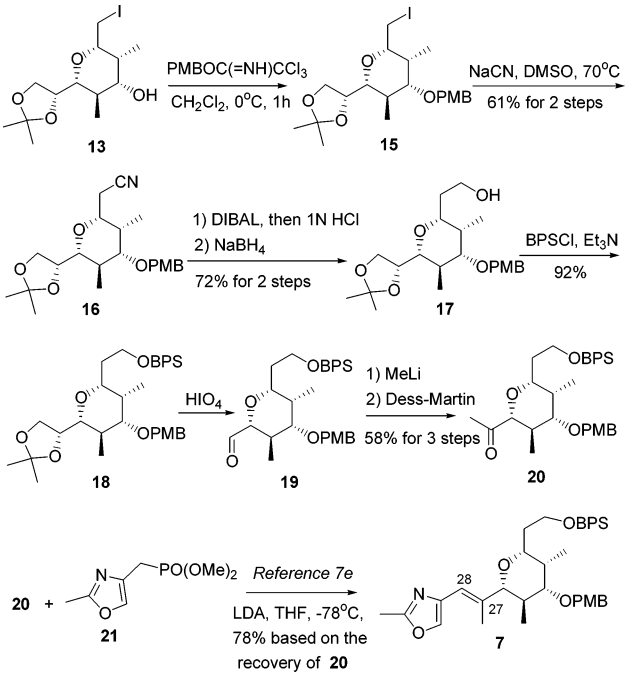
entry	conditions	**13**/**14**[a]	yield[b] (%)
1	I_2, CH_3CN, −35 °C to 0 °C		*c*
2	I_2, $NaHCO_3$, CH_3CN, 0 °C	2.6:1	46
3	NIS, CH_2Cl_2, 30 °C	7.7:1	52[d]
4	$Hg(OAc)_2$, toluene, 0 °C; I_2, 30 °C	5:1	86

[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, $NaHCO_3$ 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 trichloroacetimidiate[17] in the presence of $BF_3{\cdot}OEt_2$ gave the PMB ether **15** (Scheme 4). Iodide **15** was converted to the nitrile **16**, and this was successively reduced with DIBAL and $NaBH_4$ 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 oxidation[21] 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 reaction[22] and Julia olefination[23] have been successfully employed to construct *E*-double bonds, methyl ketone **20** reacted sluggishly under these reaction conditons. Ultimately, we resorted to the procedure described by Pattenden, in which the oxazole phosphonate ester **21** was used.[7e] 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 phorboxazole 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/CH_3OH and

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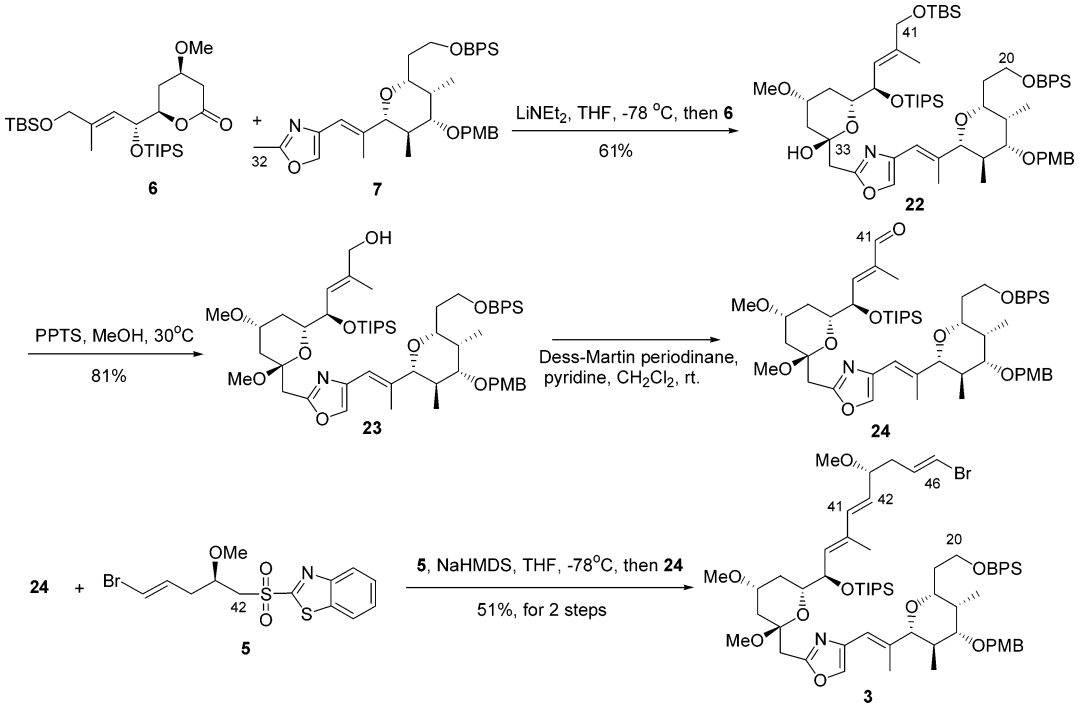
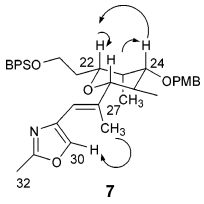
Scheme 5. Synthesis of the C20−C46 Segment of Phorboxazole B



afforded the alcohol **23**. Careful oxidation of the allylic primary alcohol of **23** with Dess−Martin periodinane,[21] followed by Julia olefination[23] 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 $Hg(OAc)_2$/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 phorboxazle 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.

OL048275X