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Studies on the synthesis of phorboxazole B: stereoselective synthesis of the C28–C46 segment

De Run Li,[a,b] Yong Qiang Tu,[b] Guo-Qiang Lin[a,*] and Wei-Shan Zhou[a]

[a]*Shanghai Institute of Organic Chemistry, 354 Fenglin Road, Shanghai 200032, PR China*
[b]*Department of Chemistry and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China*

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Abstract—A stereoselective synthesis of C28–C46 segment of phorboxazole **B** is described. Key features of the synthetic route involved the use of 1,3-asymmetric induction of Mukaiyama aldol reaction to construct the stereogenic center at C35, and the employment of metalated oxazole chemistry to prepare the ketal **6**.

Phorboxazoles **1** (Fig. 1), which were isolated from the Indian Ocean sponge *Phorbas* sp., are novel 21-membered macrolides accommodating four heavily functionalized oxanes and two 2,4-disubstituted oxazoles.[1] These metabolites have ranked among the most cytostatic natural products known, and exhibit extraordinary potency (mean $GI_{50}<1.6\times10^{-9}$ M) while bioassayed for the 60 human tumor cell strains at the National Cancer Institute (NCI).[2] The unprecedented structural features and remarkable antitumor activity of **1** have inspired wide interest in the synthetic community,[3] and several excellent achievements of total synthesis have been reported.[4] Our retrosynthetic analysis of phorboxazole **B** (**1b**, Figure 1) released the disconnections of the structure at the C2–C3, the C19–C20 and the C27–C28 double bonds, which led to the key building blocks **2**, **3**

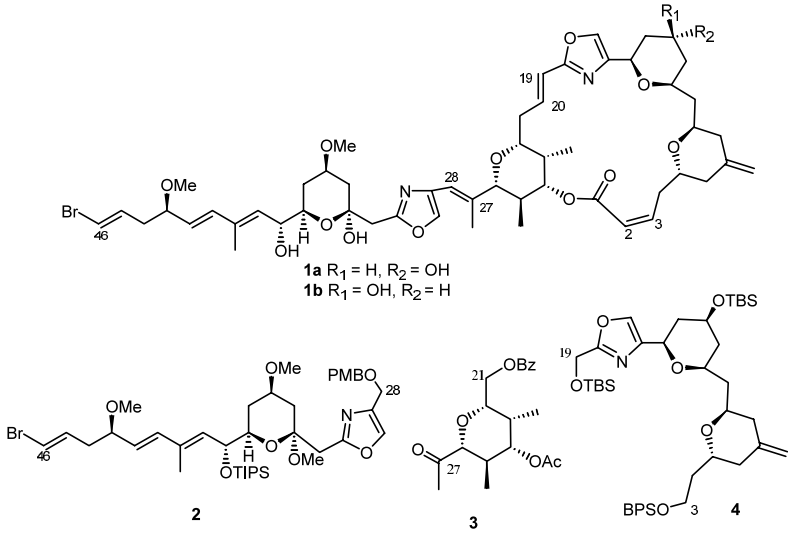

Figure 1. Phorboxazole A (**1a**) and phorboxazole B (**1b**).

Keywords: phorboxazole **B**; synthesis; Mukaiyama aldol reaction; oxazole.
* Corresponding author. Tel.: +86-21-64163223; e-mail: lingq@mail.sioc.ac.cn

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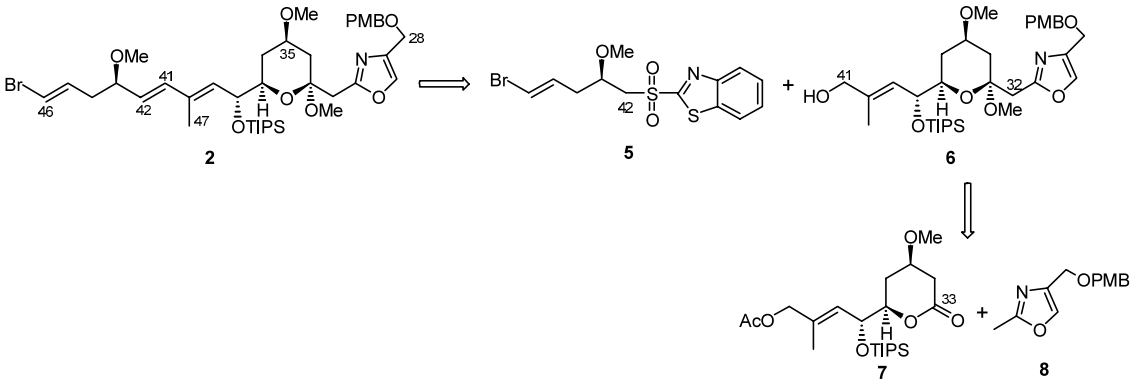


Scheme 1. Retrosynthetic analysis of the segment **2**.

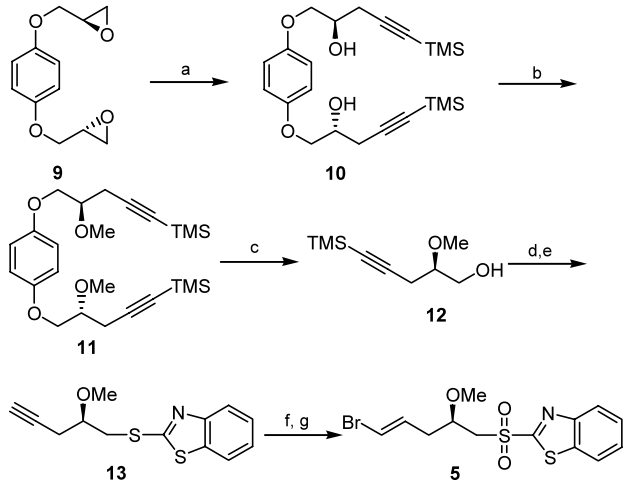
reported in a previous publication.[3bb] Herein, we wish to describe our stereoselective synthesis of the C28–C46 oxane–oxazole segment **2** of phorboxazole **B**.

From the retrosynthetic perspective (Scheme 1), disconnection of C41–C42 double bond separate the unit **2** into the known sulfone **5**[4b,e,f] and oxane–oxazole **6**. We envisaged that coupling the lactone **7** with oxazole **8** by using metalated oxazole chemistry[3m] would lead to formation of **6**.

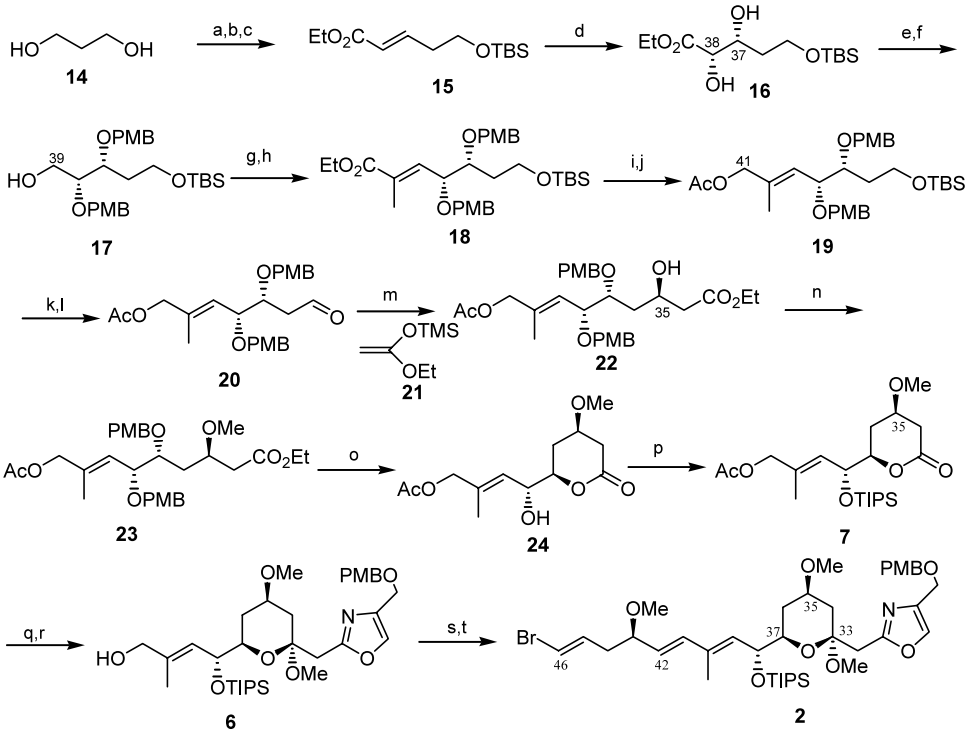
Sulfone **5** was conveniently prepared from the known optically active bis-3C building block **9** (Scheme 2).[5] Ring opening of **9** by lithium TMS acetylide in the presence of $BF_3{\cdot}OEt_2$ gave diol **10**, which was followed by transformation to methyl ether **11** by methylation with Meerwein's salt (Me_3OBF_4).[4b] Removal of hydroquinone from **11** by treatment with CAN[5] produced 2 equiv. of the known alcohol **12**.[4d] Displacement of the primary alcohol of **12** with 2-mercaptobenzothiazole and desilylation of the TMS group furnished the alkyne **13**. Thus, introduction of the vinyl bromide via hydrozirconation of the alkyne and subsequent treatment with NBS,[6] followed by oxidation of the sulfide with ammonium molybdate[4b] afforded the desired sulfone **5**.

As shown in Scheme 3, monosilylation of **14** and the subsequent oxidation of the alcohol by PCC, followed by olefination of the resultant aldehyde gave the unsaturated ester **15**[7] as a almost single *E* isomer (*E:Z*> 95:5).[8] **15** was subjected to Sharpless asymmetric dihydroxylation to afford the diol **16** in 87% yield (86% ee by chiral GC analysis).[9] Thus, the stereogenic centers at C37 and C38 were smoothly constructed. Protection of hydroxyl groups of **16** by *p*-methoxybenzyl trichloroacetimidiate in the presence of $BF_3{\cdot}OEt_2$,[10] followed by reduction afforded the alcohol **17**. The hydroxyl moieties at C37 and C38 were protected with PMB ether due to the fact that PMB ether gave the best 1,3-stereoinduction of Mukaiyama aldol reaction according to the literature.[11] Swern oxidation[12] of hydroxyl group of **17** and Wittig olefination of the resulting aldehyde with $CH_3C(PPh_3)CO_2Et$ incorporated the *E*-unsaturated ester **18**.[3c] Ester **18** was conveniently transferred to acetate **19** by reduction with DIBAL-H and acylation of the resultant C41 hydroxyl group.[13] Hydrolysis of TBS ether of **19** and oxidation of the alcohol under Dess–Martin condition[14] yielded **20**, which was a -OPMB protected aldehyde and suitable for 1,3-*anti* Mukaiyama aldol reaction.

The aldol coupling of 1-ethoxy-1-[(trimethylsilyl)-oxy]ethane **21**[15] with the aldehyde **20** was found to afford **22** in modest stereoselectivity under standard conditions ($BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$) and neither did the strong Lewis acid such as $TiCl_4$ promote a clean reaction, while the use of the mixed titanium species $TiCl_2(O\textit{i}\text{-}Pr)_2$ (toluene, −78°C) delivered a high-yielding, stereoselective reaction (87%, 4:1 dr)[8] to afford 22,[16] which is consistent with the result reported by Evans et al.[17] The orientation of C35 hydroxyl was assigned to be on the basis of 2D NOSEY spectroscopy of the succeeding lactone **24**. Several methylation methods to protect the free hydroxyl of **22** were proved to be unsuccessful, including NaH/CH_3I[18] and catalyzed diazomethane procedure.[19] Finally, treatment of **22** with



Scheme 2. *Reagents and conditions*: (a) TMSC≡CH, BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, 81%; (b) Me_3OBF_4, Proton Sponge, CH_2Cl_2, rt, 87%; (c) CAN, CH_3CN/H_2O, rt, 91%; (d) 2-mercaptobenzothiazole, PPh_3, DEAD, THF, 0°C, 81%; (e) TBAF, THF, rt, 99%; (f) Cp_2ZrHCl, THF, then NBS; (g) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30% H_2O_2, EtOH, 56%, 2 steps.



Scheme 3. *Reagents and conditions*: (a) NaH, TBSCl, THF, 0°C; (b) PCC, CH_2Cl_2, rt; (c) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 51%, 3 steps; (d) AD-mix , *t*-BuOH/H_2O, rt, 87%; (e) $PMBOC(=NH)CCl_3$, cyclohexane/CH_2Cl_2, $BF_3{\cdot}OEt_2$, 0°C; (f) $LiAlH_4$, Et_2O, rt, 71%, 2 steps; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N; (h) $CH_3C(PPh_3)CO_2Et$, CH_2Cl_2, reflux, 84%, 2 steps; (i) DIBAL-H, CH_2Cl_2, −78°C, 95%; (j) Ac_2O, Et_3N, CH_2Cl_2, rt, 95%; (k) Bu_4NF, THF, rt, 96%; (l) Dess–Martin periodinane, CH_2Cl_2, 91%; (m) $TiCl_2(Oi\text{-}Pr)_2$, toluene, −78°C, then 1-ethoxy-1-[(trimethylsilyl)-oxy]ethane **21**, 87%, 4:1 dr; (n) Me_3OBF_4, Proton Sponge, CH_2Cl_2, rt, 86%; (o) CF_3CO_2H, CH_2Cl_2, rt, 95%; (p) TIPSCl, imidazole, cat. DMAP, DMF, rt, 78%; (q) **8**, $LiNEt_2$, THF, −78°C, then **7**; (r) pTSA, MeOH, rt, 44%, 2 steps; (s) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt; (t) **5**, NaHMDS, THF, −78°C, then aldehyde from **6**, 46%, 2 steps.

Meerwein's salt (Me_3OBF_4)[4b] and 1,8-bis(dimethylamino)-naphthalene (Proton Sponge) gave the desired compound **23** in 86% yield. Due to the existence of two vicinal PMB ethers, deprotection of the PMB ethers became an obstacle under oxidation procedure,[20] such as DDQ[21] and CAN.[22] Fortunately, when compound **23** was treated with 10% CF_3CO_2H in CH_2Cl_2,[23] the PMB ethers were smoothly removed and the resultant diol was spontaneously cyclized to afford lactone **24** in excellent yield (95%). Protection of C38 free hydroxyl as its triisopropylsilyl ether furnished lactone **7**.[24]

Now it is time to set up the condition for the coupling of 4-(4-methoxy-benzyloxymethyl)-2-methyl-oxazole **8**[25] with lactone **7**. To our delight, when oxazole **8** was deprotonated with lithium diethylamide at −78°C, and treated with lactone **7**, the desired methyl ketal **6** was obtained after methylation (pTSA, CH_3OH).[4d,26] It was noteworthy that the acetoxyl moiety in lactone **7** was also removed in the metalation procedure. Careful oxidation of the allylic primary alcohol of **6** with Dess–Martin periodinane,[14] followed by Julia olefination of the resultant aldehyde with sulfone **5**, according to the similar condition reported by Williams et al.,[4f] furnished the desired *E*, *E* segment **2** (46%, 2 steps; >95:5 *E*:*Z*).[8,27]

In summary, an efficient and enantioselective synthesis of C28–C46 unit **2** of phorboxazole **B** was described. Key features of the synthetic route involved 1,3-induction of Mukaiyama aldol reaction to stereoselectively construct the stereocenter at C35, and the synthesis of the ketal **6** by utilizing metalated oxazole chemistry. Progress toward the completion of phorboxazole **B** is now underway.

Acknowledgements

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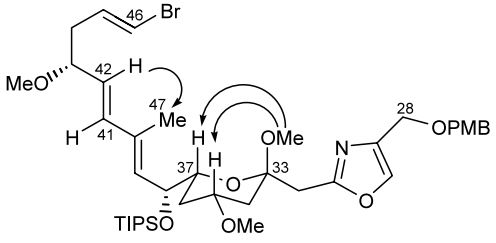
25. Oxazole **8** was conveniently prepared from methyl 2-methyloxazole-4-carboxylate in two operations: (a) DIBAL-H, CH_2Cl_2, −78°C, 68%; (b) PMBCl, NaH, THF, rt, 91%. For the preparation of methyl 2-methyloxazole-4-carboxylate see: Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc*. **1947**, 96.
26. The stereochemistry of C33 in methyl ketal **6** was confirmed by the NOE effect among C33 methoxyl group, H35 and H37 of the compound **2**. That the methyl ketal **6** was obtained as a single diastereoisomer is presumably due to anomeric effects; see: Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.



2

27. The NOE effect between H42 and H47 and the coupling constant between H41 and H42 ($J_{41,42}$ = 15.7 Hz) confirmed *E* configuration of C41–C42 double bond. Physical and spectroscopic data for **2**: colorless oil. $[\alpha]_D^{25}$ = −21.7 (*c* 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.20–6.07 (m, 3H), 5.43 (dd, *J* = 15.7 Hz, 7.7 Hz, 1H), 5.42 (d, *J* = 9.0 Hz, 1H), 4.61 (dd, *J* = 8.8 Hz, 6.2 Hz, 1H), 4.53 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.66–3.53 (m, 3H), 3.33 (s, 3H), 3.30 (d, *J* = 15.0 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 2.96 (d, *J* = 15.0 Hz, 1H), 2.38–2.20 (m, 3H), 1.97 (ddd, *J* = 12.0, 2.2, 2.1 Hz, 1H), 1.76 (s, 3H), 1.37 (dd, J = 12.0, 12.0 Hz, 1H), 1.12–1.04 (m, 22H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 159.3, 138.1, 137.3, 136.4, 133.9, 133.8, 133.1, 130.0, 129.5 (2C), 127.9, 113.8 (2C), 106.3, 99.9, 81.2, 73.9, 73.5, 72.3, 71.7, 63.7, 56.3, 55.5, 55.3, 47.9, 39.2, 39.1, 35.7, 32.1, 18.0 (3C), 17.9 (3C), 13.6, 12.4 (3C). IR (film) 2942, 2867, 1614, 1572, 1515 cm^{-1}. HRMS (ESI) calcd for $C_{40}H_{62}O_8SiNBrNa$ $(M+Na)^+$: 814.3320, found: 814.3332.