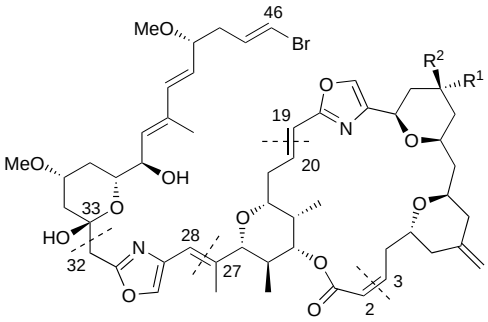
Macrolide Synthesis

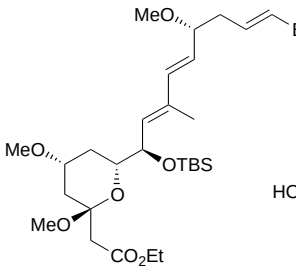
# A Convergent Total Synthesis of Phorboxazole A**

*Miguel A. González and Gerald Pattenden**

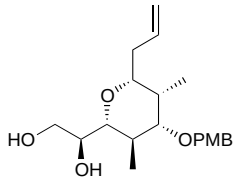
Marine organisms have delivered a fascinating variety of structurally novel and biologically important secondary metabolites in recent years, many of which are now beginning to provide leads for the development of new chemotherapeutic agents. Phorboxazole A (**1**) and B (**2**) are unique oxane–oxazole-based macrolide structures isolated from the Indian Ocean sponge *Phorbas* sp,[1] which exhibit extraordinary cytostatic activity ($GI_{50} < 8 \times 10^{-10}$ M) against the entire panel of human tumor cell lines in the NCI database. Not surprisingly, therefore, these compounds have aroused con-



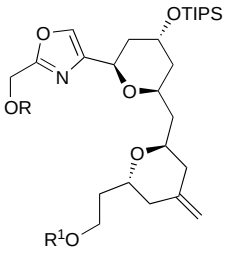

**1**, $R^1$= OH, $R^2$= H
**2**, $R^1$= H, $R^2$= OH




**3**




**4**




**5**

**a** R= PMB, $R^1$= H
**b** R= Ms, $R^1$= TBS

[*] Prof. G. Pattenden, Dr. M. A. González
School of Chemistry, University of Nottingham
Nottingham, NG72RD (UK)
Fax: (+44) 115-951-3535
E-mail: GP@nottingham.ac.uk

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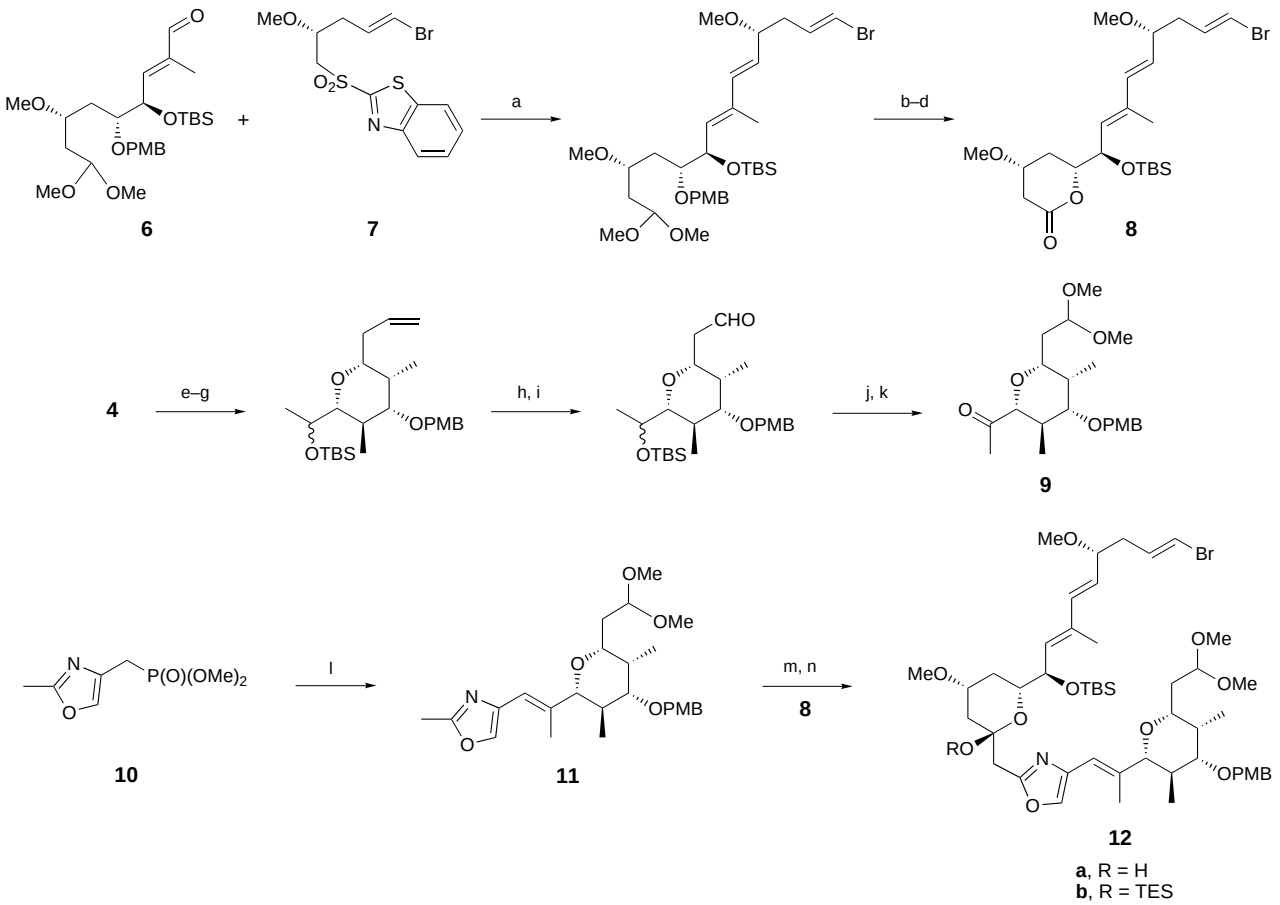
siderable interest within the medicinal and synthetic chemistry communities. Already three total syntheses of the phorboxazoles have been reported,[2–4] and the results of several structure–activity studies are beginning to emerge.[5] In previous publications we described synthetic routes to the key fragments **3**,[6] **4**,[7] and **5a**[8] in phorboxazole A.[9] We now show how we have brought these fragments together, leading to a new and convergent total synthesis of the natural product itself.

With two disubstituted double bonds (C2=C3 and C19=C20), and one trisubstituted double bond (C27=C28), separating the structural units **3, 4**, and **5**, it was clear from the outset of our studies that the ordered, stereocontrolled synthesis of these three double bonds would play a crucial role in any successful synthesis of phorboxazole A. After some initial disappointing forays,[10] we ultimately decided on a strategy to phorboxazole A whereby the C28–C46 side chain was first attached to the oxane **4**, then the bisoxane **5** was added, and finally the macrolide C2–C3 double bond was elaborated in a final key step (see Schemes 1 and 2). To this end, we envisaged coupling the oxane **4** to the phorboxazole side chain via the corresponding oxane–oxazole **11** and the lactone **8** by using the metalated oxazole chemistry developed by Evans et al.[3b]

Thus, the lactone **8** was first elaborated from the known aldehyde **6**[6] and the sulfone **7**[11] in four relatively straightforward steps, and the oxane–oxazole **11** was prepared through an *E*-selective Wadsworth–Emmons olefination between the oxane methyl ketone **9**, derived from **4**,[7] and the oxazole phosphonate ester **10**,[12] as highlighted in Scheme 1. To our satisfaction, when the oxane-substituted 2-methyloxazole **11** was deprotonated with lithium diethylamide generated in situ at −78 °C, and treated with the lactone **8**, the desired cyclic hemiketal **12a** was obtained in high yield and was immediately protected as its corresponding triethylsilyl ketal **12b** in 66% overall yield (Scheme 1). After selective cleavage of the dimethylacetal unit in **12b** with dimethylboron bromide[13] at −78 °C, an *E*-selective Wittig reaction between the resulting aldehyde **13** and the phosphonium salt obtained from the substituted bisoxane **5b**,[8] in the presence of DBU,[14] then led




***Scheme 1.*** Synthesis of the side chain **8** and oxazole–pyran **11** and coupling. a) NaHMDS, THF, −78 °C→RT, 93% pure *all-E* isomer; b) $Me_2BBr$, $Et_2O$, −78 °C, 98%; c) DDQ, $CH_2Cl_2/H_2O$ (10:1), 0 °C, 85%; d) TPAP, NMO, powdered 4-Å molecular sieves, $CH_2Cl_2$, 82%; e) Ts–imidazole, NaH, $Et_2O$, −78 °C→0 °C; f) $LiAlH_4$, $Et_2O$; g) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C→RT; h) $OsO_4$, NMO, acetone/water; i) $NaIO_4$ on silica, $CH_2Cl_2$; j) CSA, $MeOH/CH_2Cl_2$; k) DMP, 2,6-lutidine, $CH_2Cl_2$, 43% overall yield from **4**; l) LDA, −78 °C, 30 min, then **9**, 89% (49% conversion); m) $Et_2NH$, *n*BuLi, THF, −78 °C, then **8**; n) TESOTf, pyridine, $MeCN/Et_2O$ (10:1), −47 °C, 36 h, 74% (66% conversion, two steps); HMDS = hexamethyldisilazide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, Ts = *p*-toluenesulfonyl, Tf = Trifluoromethanesulfonyl, CSA = camphorsulfonic acid, DMP = Dess–Martin periodinane, TBS = *tert*-butyldimethylsilyl, LDA = lithium diisopropylamide, TES = triethylsilyl, PMB = *p*-methoxybenzyl

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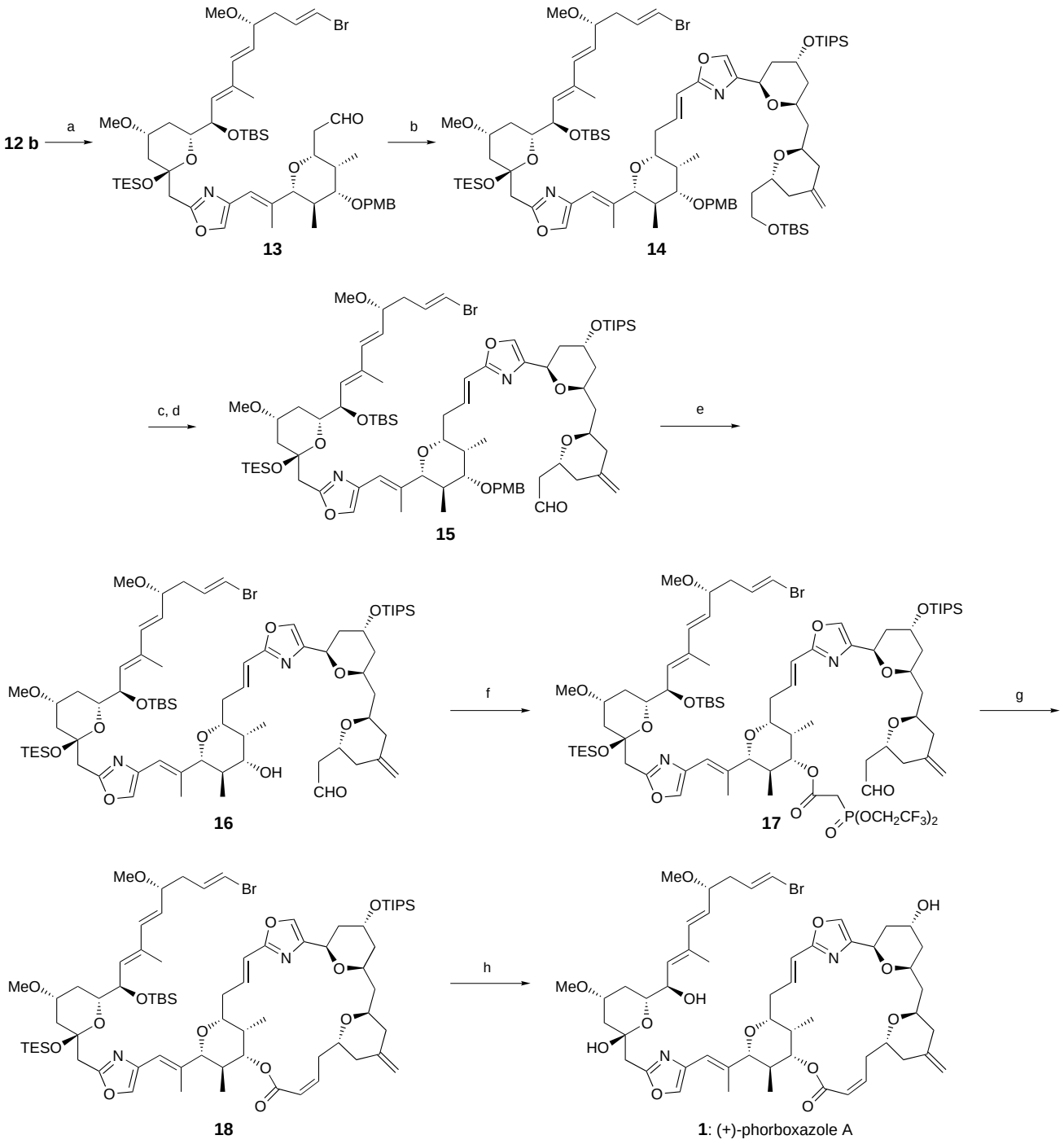
to the advanced bisoxazole–trisoxane intermediate **14**, as a single stereoisomer in excellent overall yield (Scheme 2).

The stage was now set to complete our synthesis of phorboxazole A through an intramolecular Wadsworth–Emmons reaction of **17** as the penultimate step. Thus, selective cleavage of the primary TBS ether in **14** with HF·pyr[3] at 0 °C proceeded smoothly and the resulting alcohol was then oxidized to the corresponding aldehyde **15** under Dess–Martin conditions[15] (Scheme 2). Removal of the PMB protecting group in **15** with DDQ next led to the secondary alcohol **16**, which was converted into the corresponding fluorophosphonate ester **17**.[2] Intramolecular cyclization of




***Scheme 2.*** Completion of the synthesis of **1**. a) $Me_2BBr$, $Et_2O$, −78 °C, 85 %; b) **5b**, $Bu_3P$, DMF, then **13** and DBU, room temperature or 0 °C, 85–87 %; c) HF·pyr, pyridine, THF, 0 °C→RT, 65–70 %; d) DMP, pyridine, $CH_2Cl_2$, 94 %; e) DDQ, $CH_2Cl_2$–pH 7 buffer, 85 %; f) EDCI·MeI, HOBT, $HO_2CCH_2PO(OCH_2CF_3)_2$, $CH_2Cl_2$, >80 %; g) $K_2CO_3$, [18]crown-6, toluene, room temperature, 82 % (3:1 *Z*/*E*); h) TBAF, THF, 0 °C→RT, 75 %; reversed-phase HPLC purification; DMF = *N*,*N*-dimethylformamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, pyr = pyridine, DMP = Dess–Martin periodinane, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide chloride, HOBT = 1-hydroxybenzotriazole, TBAF = tetrabutylammonium fluoride, TIPS = triisopropylsilyl.

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the aldehyde–phosphonate **17** under the conditions of Still and Gennari[16] gave the *Z*-α,β-unsaturated macrolide **18**, containing approximately 25% of the corresponding *E* isomer.[17] Removal of the three silyl protecting groups in **18** with tetrabutylammonium fluoride in THF at 0°C, followed by chromatography, finally produced (+)-phorboxazole A (**1**), contaminated with its C2–C3 *E* isomer. Further purification by reversed-phase HPLC provided pure (+)-phorboxazole A, whose $^{1}H$ and $^{13}C$ NMR spectra, together with high-resolution mass spectrometric data (calcd for $C_{53}H_{71}N_2O_{13}{}^{79}BrNa$ $[M+Na, {}^{79}Br]^+$: 1045.4037; found: 1045.4053 (100%) (ESI)) and optical rotation data ($[\alpha]_D^{20} = +43.3$, $c = 0.12$, $CHCl_3$) corresponded to those reported for the natural product.[1a,18]

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[17] The *Z*/*E* ratio followed from examination of the absorptions associated with the *Z* ($\delta = 5.92$ ppm) and *E* ($\delta = 6.90$ and 5.85 ppm) olefinic H atoms in the $^{1}H$ NMR spectrum of the mixture.

[18] Naturally derived phorboxazole A had $[\alpha]_D = +44.8°$ ($c = 1.0$, MeOH). All new compounds reported in this study showed satisfactory spectroscopic and mass spectrometric data.

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