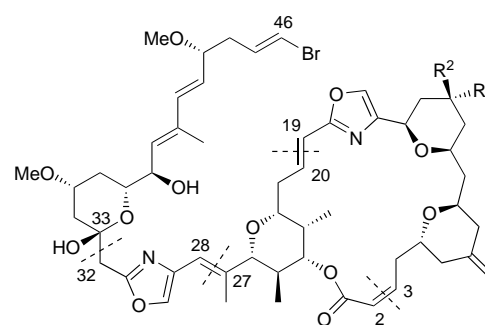




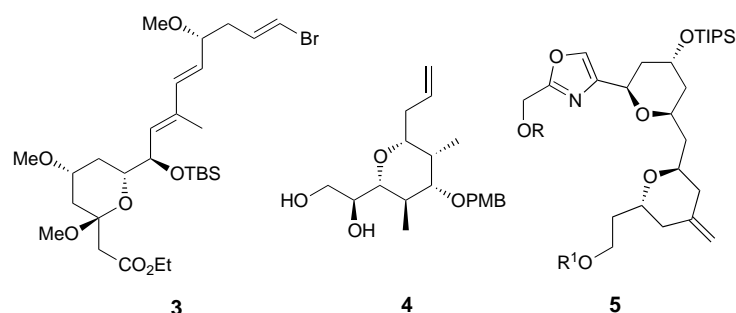
A Convergent Total Synthesis of Phorboxazole A**

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, R¹ = OH, R² = H
2, R¹ = H, R² = OH



a R = PMB, R¹ = H
b R = Ms, R¹ = 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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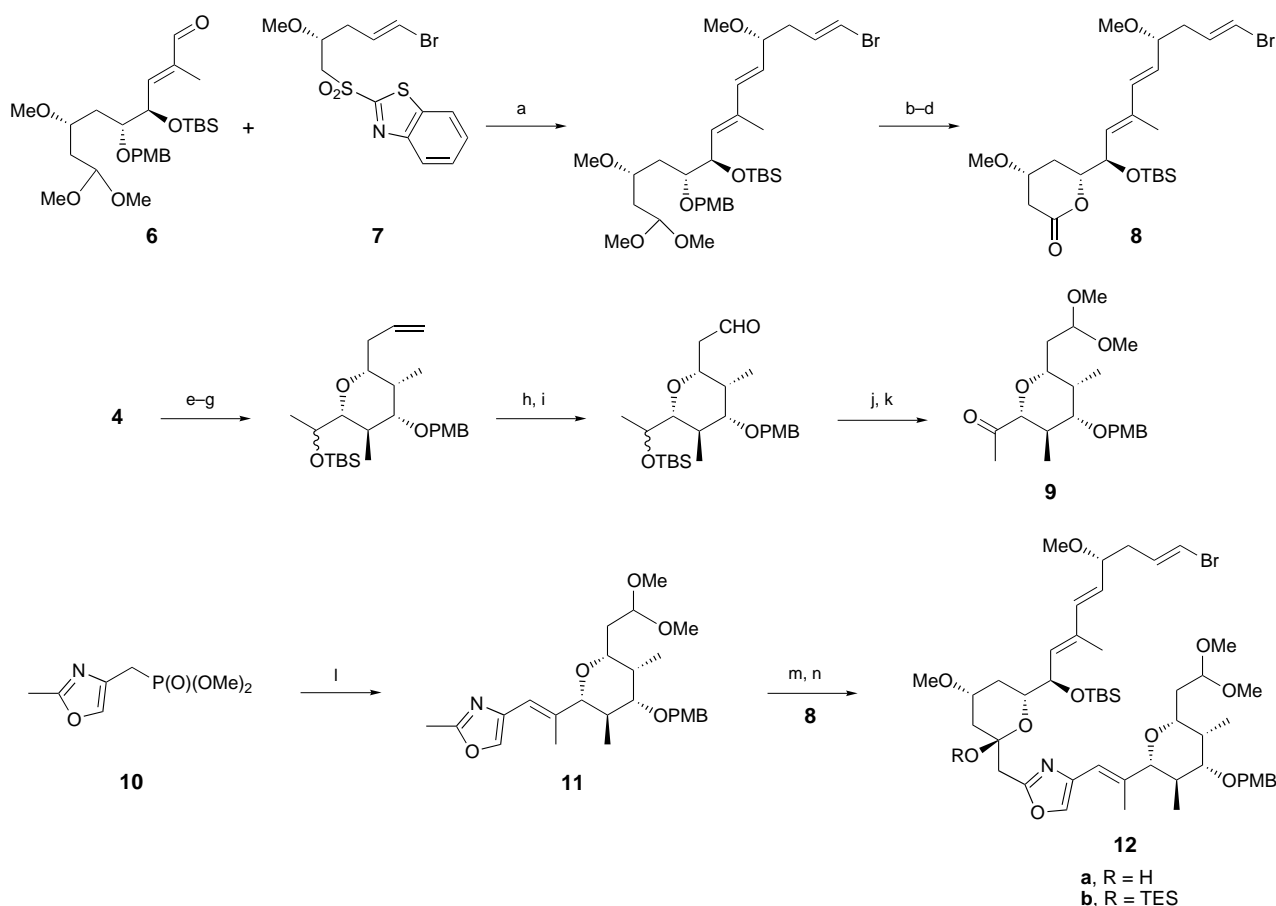
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siderable interest within the medicinal and synthetic chemistry communities. Already three total syntheses of the phorboxazoles have been reported,^[2–4] and the results of several structure–activity studies are beginning to emerge.^[5] In previous 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**,^[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

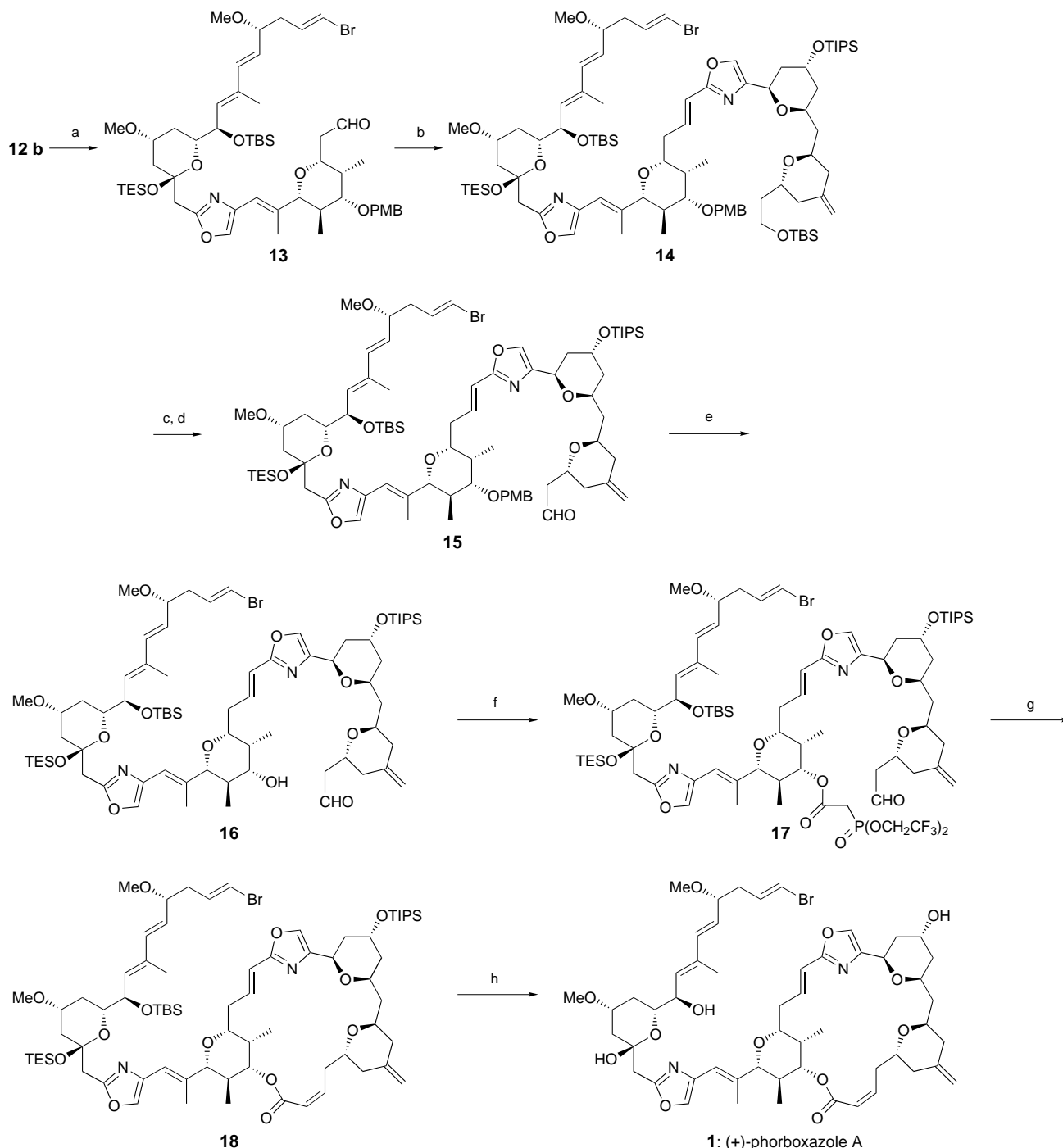


Scheme 1. Synthesis of the side chain **8** and oxazole–pyran **11** and coupling. a) NaHMDS, THF, $-78^{\circ}\text{C} \rightarrow \text{RT}$, 93% pure *all-E* isomer; b) Me_2BBr , Et_2O , -78°C , 98%; c) DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10:1), 0°C , 85%; d) TPAP, NMO, powdered 4-Å molecular sieves, CH_2Cl_2 , 82%; e) Ts–imidazole, Et_2O , $-78^{\circ}\text{C} \rightarrow 0^{\circ}\text{C}$; f) LiAlH_4 , Et_2O ; g) TBSOTf, 2,6-lutidine, CH_2Cl_2 , $-78^{\circ}\text{C} \rightarrow \text{RT}$; h) OsO_4 , NMO, acetone/water; i) NaIO_4 on silica, CH_2Cl_2 ; j) CSA, $\text{MeOH}/\text{CH}_2\text{Cl}_2$; 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 , $n\text{BuLi}$, THF, -78°C , then **8**; n) TESOTf, pyridine, $\text{MeCN}/\text{Et}_2\text{O}$ (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

to the advanced bisoxazole–trioxane 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) Me₂BBr, Et₂O, –78 °C, 85%; b) **5b**, Bu₃P, 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, CH₂Cl₂, 94%; e) DDQ, CH₂Cl₂–pH 7 buffer, 85%; f) EDCl·MeI, HOBT, HO₂CCH₂PO(OCH₂CF₃)₂, CH₂Cl₂, > 80%; g) K₂CO₃, [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, EDCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide chloride, HOBT = 1-hydroxybenzotriazole, TBAF = tetrabutylammonium fluoride, TIPS = triisopropylsilyl.

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 ¹H and ¹³C NMR spectra, together with high-resolution mass spectrometric data (calcd for C₅₃H₇₁N₂O₁₃⁷⁹BrNa [M+Na, ⁷⁹Br]⁺: 1045.4037; found: 1045.4053 (100%) (ESI)) and optical rotation data ([α]_D²⁰ = +43.3, *c* = 0.12, CHCl₃) corresponded to those reported for the natural product.^[1a,18]

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Keywords: antifungal agents · antitumor agents · natural products · olefination · total synthesis

- [14] Similar conditions were used earlier by Evans et al; see reference [3a].
- [15] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
- [16] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408. This macrocyclization tactic had earlier been used by Forsyth et al.^[2] and Smith et al.^[4] in their total synthesis of phorboxazole A.
- [17] The *Z/E* ratio followed from examination of the absorptions associated with the *Z* (δ = 5.92 ppm) and *E* (δ = 6.90 and 5.85 ppm) olefinic H atoms in the ¹H NMR spectrum of the mixture.
- [18] Naturally derived phorboxazole A had [α]_D = +44.8° (*c* = 1.0, MeOH). All new compounds reported in this study showed satisfactory spectroscopic and mass spectrometric data.

- [1] a) P. A. Searle, T. F. Molinski, *J. Am. Chem. Soc.* **1995**, *117*, 8126–8131; b) P. A. Searle, T. F. Molinski, L. J. Brzezinski, J. W. Leahy, *J. Am. Chem. Soc.* **1996**, *118*, 9422–9423; c) T. F. Molinski, *Tetrahedron Lett.* **1996**, *37*, 7879–7880.
- [2] C. J. Forsyth, F. Ahmed, R. D. Cink, C. S. Lee, *J. Am. Chem. Soc.* **1998**, *120*, 5597–5598.
- [3] a) D. A. Evans, D. M. Fitch, T. E. Smith, *J. Am. Chem. Soc.* **2000**, *122*, 10033–10046; b) D. A. Evans, V. J. Cee, T. E. Smith, K. J. Santiago, *Org. Lett.* **1999**, *1*, 87–90.
- [4] a) A. B. Smith III, P. R. Verhoest, K. P. Minbirole, M. Schelhaas, *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953. b) After the submission of this paper another total synthesis of phorboxazole A was completed. See the next paper in this issue: D. R. Williams, A. A. Kiryanov, U. Emde, M. P. Clark, M. A. Berliner, J. T. Reeves, *Angew. Chem.* **2003**, *115*, 1296–1300; *Angew. Chem. Int. Ed.* **2003**, *42*, 1258–1262.
- [5] a) P. Wolbers, H. M. R. Hoffmann, F. Sasse, *Synlett* **1999**, *11*, 1808–1810; b) F. M. Uckun, C. J. Forsyth, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1181–1183; c) T. F. Molinski, L. J. Brzezinski, J. W. Leahy, *Tetrahedron: Asymmetry* **2002**, *13*, 1013–1016.
- [6] G. Pattenden, A. T. Plowright, J. A. Tornos, T. Ye, *Tetrahedron Lett.* **1998**, *39*, 6099–6102.
- [7] G. Pattenden, T. Ye, *Tetrahedron Lett.* **1998**, *39*, 319–322.
- [8] G. Pattenden, A. T. Plowright, *Tetrahedron Lett.* **2000**, *41*, 983–986.
- [9] Several other synthetic approaches to the phorboxazoles have been described by other research groups. For a full bibliography, see: P. B. Greer, W. A. Donaldson, *Tetrahedron* **2002**, *58*, 6009–6018.
- [10] P. Little, D. S. Millan, unpublished results.
- [11] The sulfone was prepared by using similar chemistry to that described earlier in reference [6]. For the use of benzothiazolyl sulfones in olefination reactions, see: a) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357; b) J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878.
- [12] The oxazole phosphonate **10** was prepared by using standard procedures from the known 4-hydroxymethyl-2-methyloxazole; see: D. A. Entwistle, S. I. Jordan, J. Montgomery, G. Pattenden, *Synthesis* **1998**, 603–612.
- [13] Y. Guindon, C. Yoakin, H. E. Morton, *J. Org. Chem.* **1984**, *49*, 3912–3920.