Macrolide Synthesis

A Convergent Total Synthesis of Phorboxazole A**

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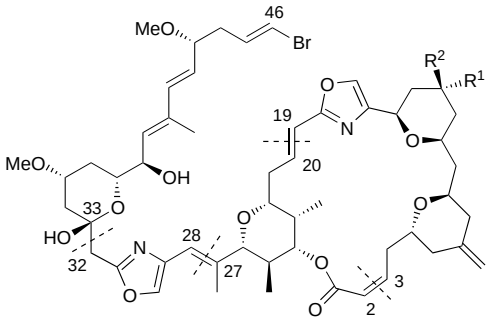
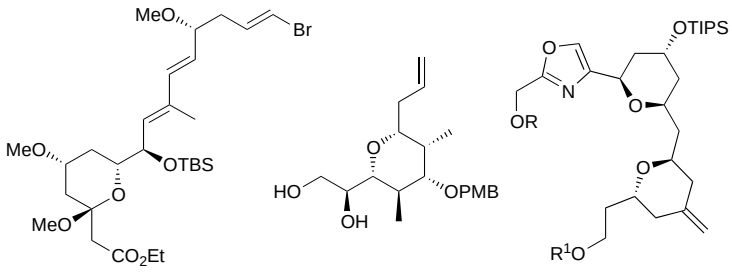
Marine organisms have delivered a fascinating variety of structurally novel and biologically important secondary metabolites in recent years, many of which are now beginning to provide leads for the development of new chemotherapeutic agents. Phorboxazole A (**1**) and B (**2**) are unique oxane–oxazole-based 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

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[**] We thank the EPSRC and The University of Nottingham for support of this work. We also thank Dr. P. Little and Dr. D. S. Millan, in particular, for their contributions, as well as Merck Sharp and Dohme and Pfizer Ltd for continued financial support of our work.

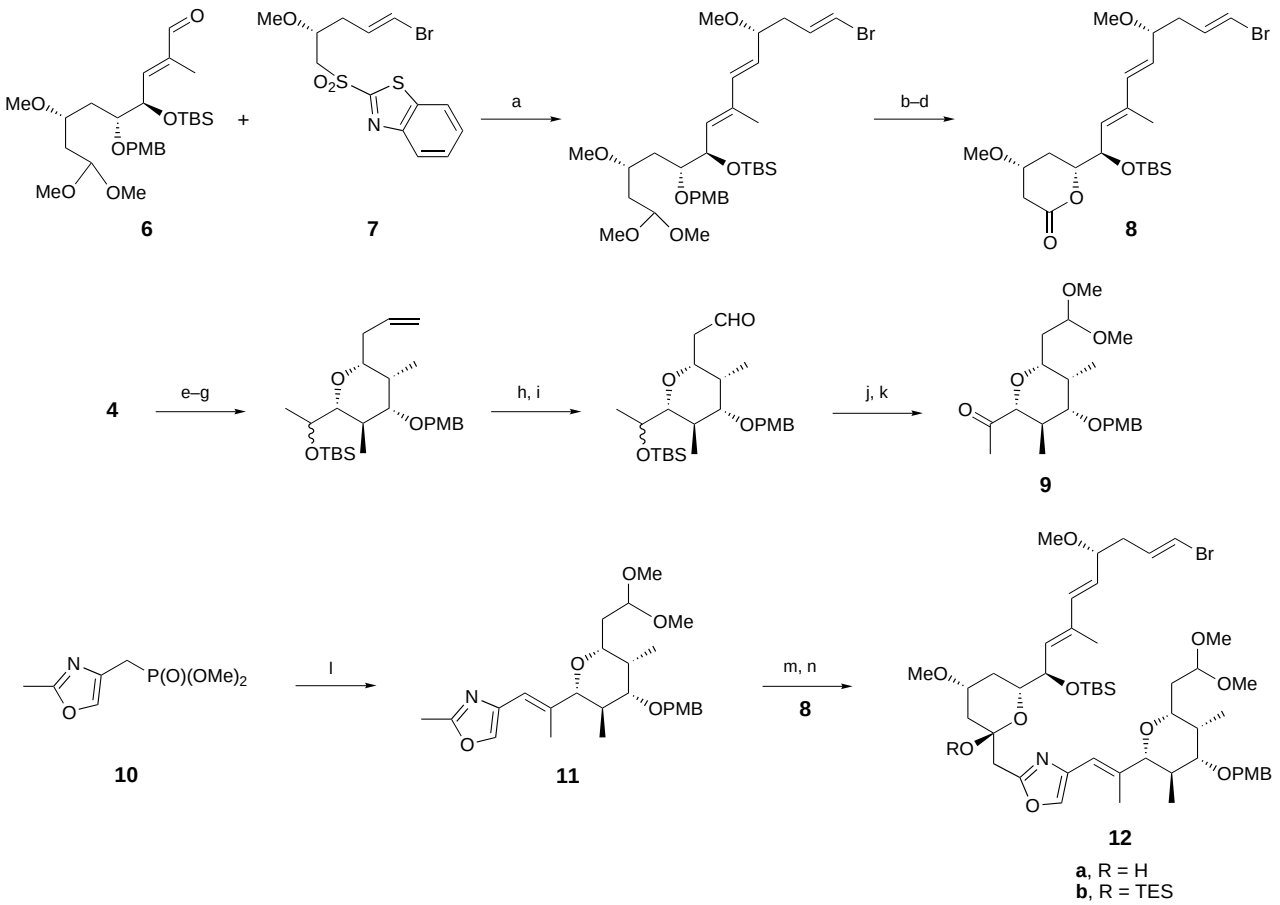
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  0044-8249/03/11511-1293 $ 20.00+.50/0

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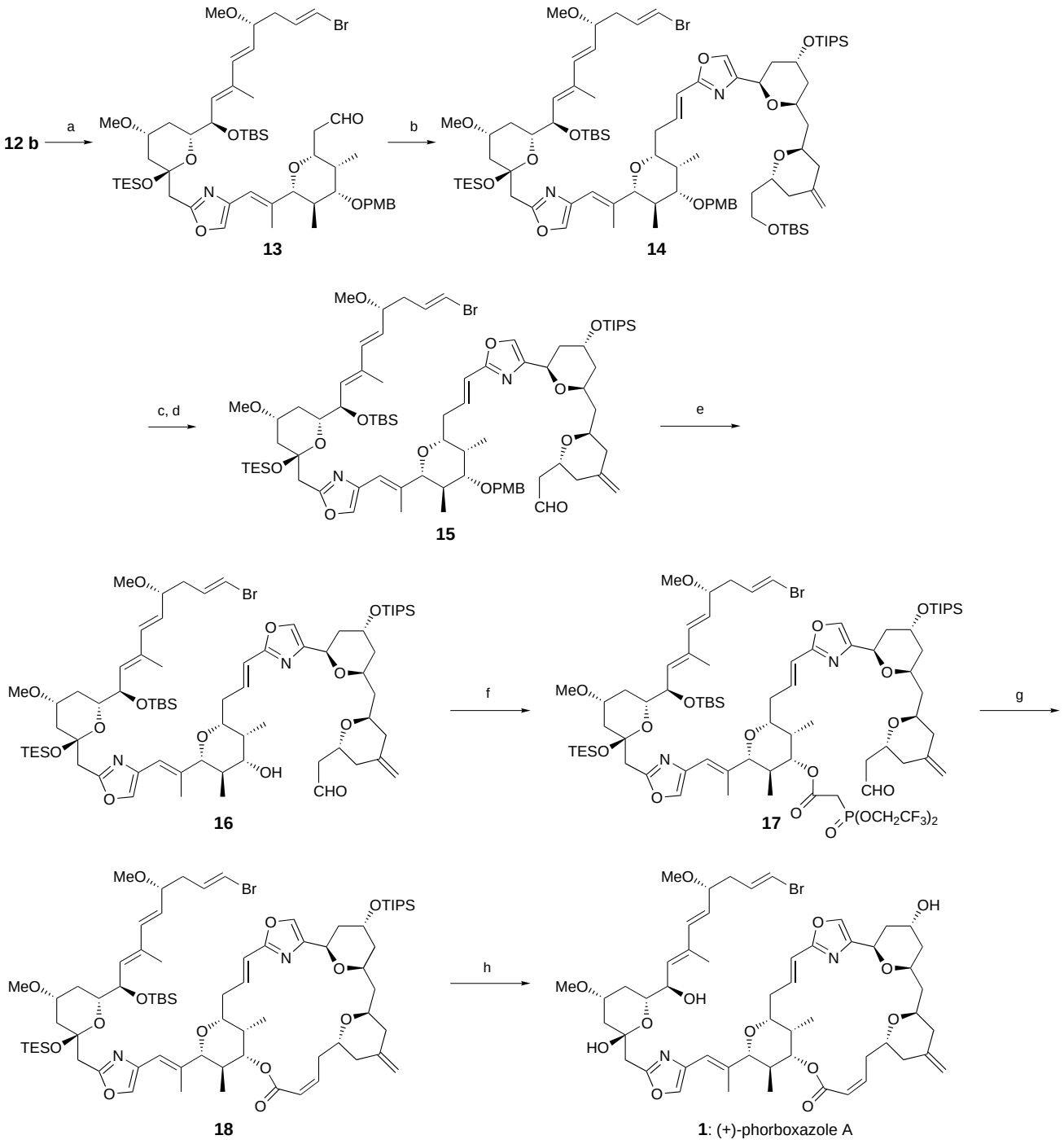
to the advanced bisoxazole–trisoxane intermediate **14**, as a single stereoisomer in excellent overall yield (Scheme 2).

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) EDCl·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, EDCl = 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]

Received: October 28, 2002 [Z50447]

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

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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.

  0044-8249/03/11511-1296 $ 20.00+.50/0