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# Synthetic Studies Towards Phorboxazole A. A Convergent Synthesis of the C31-C46 Polyene Oxane-Hemiacetal Side Chain

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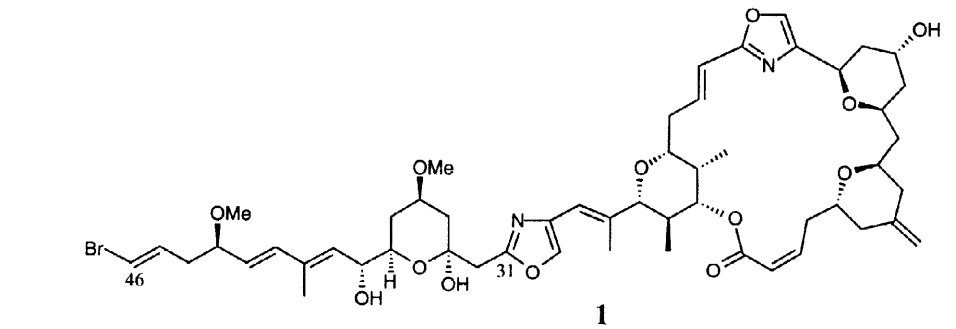
***Abstract:*** A convergent and stereoselective synthesis of the C31-C46 side chain unit in the marine natural product phorboxazole A, which accommodates five asymmetric centres, three carbon-to-carbon double bonds and an oxane-hemiacetal unit, is described. © 1998 Elsevier Science Ltd. All rights reserved.

Phorboxazole A **1** is a unique marine natural product which has been isolated from the Indian Ocean sponge *Phorbas* sp.[1] The molecule exhibits profoundly potent cytostatic activity against human tumour cell lines and it has an unprecedented structure based on a macrolactone core, four oxane and two oxazole rings, and accommodates fifteen asymmetric centres and five *E*- and one *Z*- olefinic bonds. The pronounced biological activity of this novel structure has aroused considerable interest in its total synthesis.[2] In recent work we have disclosed a synthesis of the 2,6-*cis*-oxane unit **3** in phorboxazole A.[3] In this communication we present a concise synthesis of the C31-C46 side chain portion **2**[4] of the natural product which is appropriately functionalised for subsequent connection to the oxane unit **3** *via* an oxazole ring forming sequence.[5]



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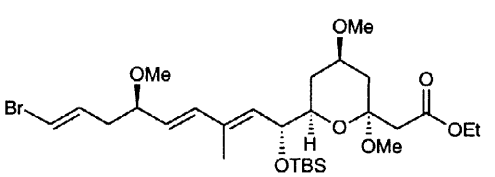

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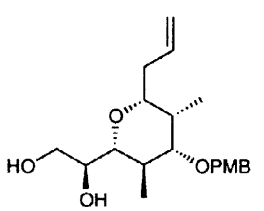

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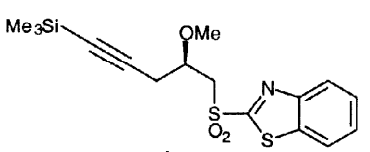

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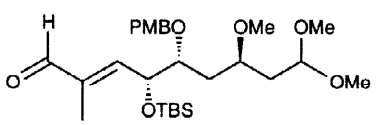

**5**

Our approach to the C31-C46 portion **2** in phorboxazole A was based on a convergent approach using an *E*-selective Julia benzothiazole sulfone olefination reaction[6] between the sulfone **4** and the α,β-unsaturated aldehyde **5** as a key step. Furthermore, we planned to synthesise the sulfone **4** and the aldehyde **5** from the chiral pool compounds *D*-malic acid **6** and *D*-xylose **12** respectively.

Thus, *D*-malic acid **6** was first converted into the differentially protected triol **7** using six straightforward steps in 43% overall yield as shown in Scheme 1.[7] Deprotection of the PMB ether group in **7**, using DDQ,[8] followed by oxidation of the resulting primary alcohol under Swern conditions next led to the


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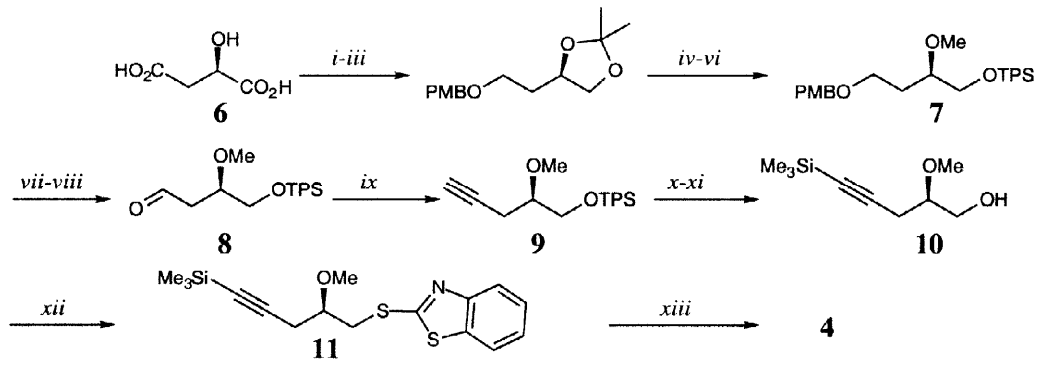
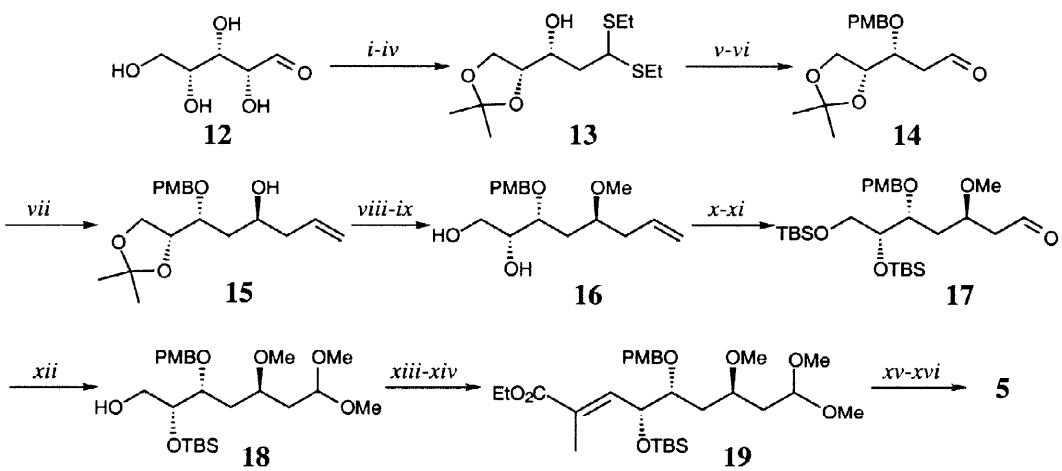
aldehyde **8** which was then converted into the terminal acetylene **9** using Seyferth's reagent.[9] The primary alcohol function in **9** was unmasked and the terminal acetylene residue was then protected as the corresponding trimethylsilane derivative **10**. Treatment of **10** with 2-mercaptobenzothiazole in the presence of $Ph_3P$ - DEAD next gave the sulfide **11**,[6] which on oxidation using *m*-CPBA finally produced the benzothiazole sulfone intermediate **4** as a stable crystalline solid.[7]




***Reagents:*** *i*, $BH_3.SMe_2$, $B(OEt)_3$; *ii*, $Me_2CO$, *p*TSA, $Cu(II)SO_4$, 77% (2 steps); *iii*, PMBCl, $KOBu^t$, $NBu_4I$; *iv*, *p*TSA, MeOH, 69% (2 steps); *v*, TBDPSCl, $Et_3N$, DMAP, 94%; *vi*, NaH, MeI, 87%; *vii*, DDQ, 95%; *viii*, $(COCl)_2$, DMSO, $Et_3N$, 90%; *ix*, $(MeO)_2PCHN_2$, $KOBu^t$, 75%; *x*, TBAF, 96%; *xi*, TMSCl, BuLi, 70%; *xii*, 2-mercaptobenzothiazole, $PPh_3$, DEAD, 94%; *xiii*, *m*-CPBA, $NaHCO_3$, 85%.

**Scheme 1**

The *E*-α,β-unsaturated aldehyde **5** required for coupling to the sulfone **4** was elaborated from *D*-xylose as outlined in Scheme 2. Thus, *D*-xylose **12** was first converted into the thioacetal **13** in four steps based on procedures described by Gray *et al.*[10] Protection of the alcohol group in **13** as its PMB ether followed by hydrolysis of the thioacetal next gave the aldehyde **14**. Treatment of the aldehyde **14** with (-)-β-allyl diisopinocampheylborane[11] followed by oxidation with $H_2O_2$ - NaOH led to the homoallylic alcohol **15** which on methylation and deprotection of the acetonide was then converted into the 1,2-diol **16**. After



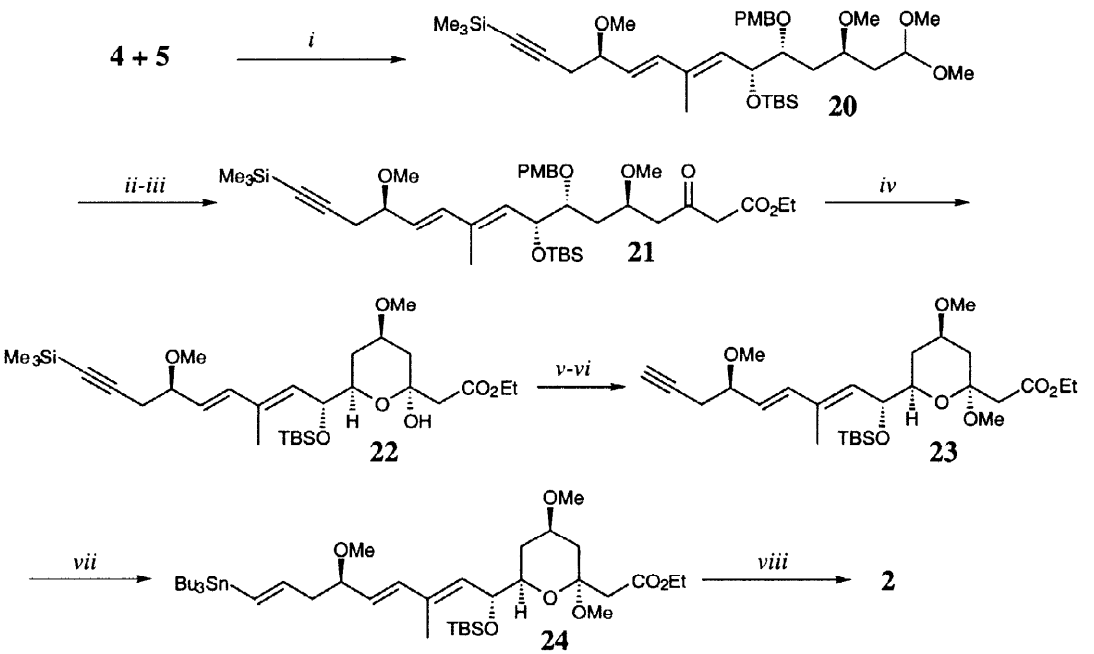

***Reagents:*** *i*, EtSH, HCl, 65%; *ii*, $Me_2CO$, $H_2SO_4$, 90%; *iii*, $KOBu^t$, DMSO, 68%; *iv*, $LiAlH_4$, 92%; *v*, $KOBu^t$, PMBBr, 98%; *vi*, $Hg(ClO_4)_2$, $CaCO_3$, 91%; *vii*, a) (-)-β-allyl diisopinocampheylborane, b) $H_2O_2$, NaOH, 82%; *viii*, $KOBu^t$, MeI, 98%; *ix*, *p*TSA, MeOH, 88%; *x*, TBDMSOTf, $Et_3N$, 98%; *xi*, $OsO_4$, $NaIO_4$, 94% (2 steps); *xii*, CSA, MeOH, 89%; *xiii*, Dess-Martin periodinane, 93%; *xiv*, $CH_3C(PPh_3)CO_2Et$, 91%; *xv*, DIBAL, 89%; *xvi*, Dess-Martin periodinane, 94%.

**Scheme 2**

protection of **16** as the corresponding *bis*-TBS derivative, oxidative cleavage of the terminal double bond gave rise to the aldehyde **17**. Treatment of the aldehyde **17** with camphorsulfonic acid in methanol resulted in simultaneous acetal formation and deprotection of the primary alcohol leading to **18**.Oxidation of **18** with

Dess-Martin periodinane[12] followed by a Wittig reaction between the resulting aldehyde and $CH_3C(PPh_3)CO_2Et$ then led to the *E*-unsaturated ester **19**.[13] Finally, reduction of **19** using DIBAL and oxidation of the product alcohol with Dess-Martin periodinane gave the *E*-α,β-unsaturated aldehyde **5**.

Deprotonation of the sulfone **4** using NaHMDS in THF at -78°C in the presence of the *E*-unsaturated aldehyde **5** resulted in stereoselective formation of the *E,E*-diene **20** in a satisfying 74% yield.[13] Deprotection of the dimethyl acetal group in **20**, and treatment of the resulting aldehyde with ethyl diazoacetate next led to the β-keto ester **21**.[14] Removal of the PMB protecting group in **21** using DDQ in $CH_2Cl_2$[8] resulted in spontaneous cyclisation of the intermediate δ-hydroxy ketone producing a single diastereoisomer of the cyclic hemiacetal **22** in 90% yield. The synthesis of the target molecule **2** was then completed following protection of **22** as its methyl ether, deprotection of the terminal acetylene unit, hydrostannylation of **23** and treatment of the resulting vinylstannane with NBS in $CH_3CN$ at 0°C. A significant amount of the p.m.r and c.m.r chemical shift and coupling data recorded for **2** matched, and could be superimposed on corresponding data for the C31-C46 side chain in natural phorboxazole A.[1]




***Reagents:*** *i*, NaHMDS, -78°C, 74%; *ii*, $Me_2BBr$, -78°C, 95%; *iii*, $EtO_2CCHN_2$, $SnCl_2$, 75%; *iv*, DDQ, 90%; *v*, PPTS, MeOH, 50%; *vi*, $AgNO_3$, KCN, 75%; *vii*, $Bu_3SnH$, AIBN, $C_6H_6$, Δ; *viii*, NBS, 60% (2 steps).

**Scheme 3**

**Acknowledgements:** We thank the EPSRC (Fellowship to T.Y.), Merck, Sharp and Dohme and Pfizer Central Research (Studentships to A.T.P. and J.A.T. respectively) for support of this work. We also thank Drs L. Castro (Merck) and C. Barber (Pfizer) for their interest in this study.

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4. During the completion stages of our work, Ahmed and Forsyth described an alternative synthesis of a derivative of **2** using a conceptually different approach; see ref. 2c.

5. For oxazole ring forming reactions applicable to this study see: Chattopadhyay, S.K. and Pattenden, G., *Synlett*, **1997**, *12*, 1342-1343 and references therein.

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7. All new compounds showed satisfactory spectroscopic data together with mass spectrometry and/or combustion analysis. Selected data; Compound **4**: $\delta_H$ (360MHz) 8.24-8.21 (m, 1H), 8.03-8.00 (m, 1H), 7.66-7.57 (m, 2H), 4.07-4.02 (m, 1H), 3.94 (dd, *J* 14.8, 8.9, 1H), 3.81 (dd, *J* 14.8, 3.0, 1H), 3.25 (s, 3H), 2.66 (dd, *J* 17.0, 4.6, 1H), 2.46 (dd, *J* 17.0, 7.4, 1H), 0.15 (s, 9H); $\delta_C$ (90MHz) 166.8 (s), 152.6 (s), 136.8 (s), 127.9 (d), 127.5 (d), 125.5 (d), 122.2 (d), 100.6 (s), 88.7 (s), 74.5 (d), 58.7 (t), 57.5 (q), 24.1 (t), -0.1 (q); Compound **5**: $\delta_H$ (360MHz) 9.42 (s, 1H), 7.26 (d, *J* 8.7, 2H), 6.87 (d, *J* 8.7, 2H), 6.38 (dbrq, *J* 8.6, 2.3, 1H), 4.71 (dd, *J* 8.6, 5.2, 1H), 4.67 (d, *J* 11.1, 1H), 4.53 (d, *J* 11.1, 1H), 4.48 (t, *J* 5.6, 1H), 3.80 (s, 3H), 3.72 (ddd, *J* 10.2, 5.2, 2.2, 1H), 3.51-3.45 (m, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 3.24 (s, 3H), 1.86 (ddd, *J* 14.2, 6.1, 5.6, 1H), 1.76-1.68 (m, 2H), 1.77 (d, *J* 2.3, 3H), 1.54 (ddd, *J* 13.6, 10.2, 3.2, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.00 (s, 3H); $\delta_C$ (90MHz) 195.1 (d), 159.3 (s), 152.5 (d), 139.2 (s), 130.5 (s), 129.6 (d), 113.8 (d), 101.9 (d), 79.0 (d), 74.2 (d), 73.1 (t), 71.0 (d), 56.1 (q), 55.3 (q), 52.8 (q), 52.6 (q), 37.1 (t), 35.6 (t), 25.8 (q), 18.1 (s), 10.1 (q), -4.6 (q), -4.8 (q); Compound **20**: $\delta_H$ (360MHz) 7.29 (d, *J* 8.6, 2H), 6.88 (d, *J* 8.6, 2H), 6.25 (d, *J* 15.7, 1H), 5.54 (dd, *J* 15.7, 7.8, 1H), 5.46 (d, *J* 9.2, 1H), 4.76 (d, *J* 11.0, 1H), 4.57 (dd, *J* 9.2, 5.8, 1H), 4.51 (d, *J* 11.0, 1H), 4.48 (t, *J* 5.6, 1H), 3.81 (s, 3H), 3.77 (ddd, *J* 10.0, 5.8, 1.8, 1H), 3.63-3.58 (m, 1H), 3.50-3.46 (m, 1H), 3.30 (s, 6H), 3.29 (s, 3H), 3.23 (s, 3H), 2.59 (dd, *J* 16.7, 5.6, 1H), 2.44 (dd, *J* 16.7, 7.1, 1H), 1.87-1.68 (m, 3H), 1.79 (s, 3H), 1.48 (ddd, *J* 13.8, 10.4, 3.3, 1H), 0.89 (s, 9H), 0.14 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); $\delta_C$ (90MHz) 159.1 (s), 137.6 (d), 133.9 (s), 133.0 (d), 131.1 (s), 129.5 (d), 127.5 (d), 113.7 (d), 103.3 (s), 102.0 (d), 86.5 (s), 80.8 (d), 79.8 (d), 74.4 (d), 73.2 (t), 71.7 (d), 56.6 (q), 56.1 (q), 55.3 (q), 52.9 (q), 52.5 (q), 37.3 (t), 35.8 (t), 27.1 (t), 25.9 (q), 18.1 (s), 13.4 (q), 0.1 (q), -4.3 (q), -4.7 (q); Compound **2**: $\delta_H$ (360MHz) 6,19 (d, *J* 16.0, 1H), 6.21-6.17 (m, 1H), 6.10 (d, *J* 13.6, 1H), 5.45 (dd, *J* 15.7, 7.9, 1H), 5.39 (d, *J* 9.2, 1H), 4.42 (d, *J* 9.1, 7.0, 1H), 4.18-4.13 (m, 2H), 3.67-3.54 (m, 2H), 3.48 (ddd, *J* 12.0, 7.1, 1.7, 1H), 3.33 (s, 3H), 3.27 (2xS, 6H), 2.83 (d, *J* 14.0, 1H), 2.57 (d, *J* 14.0, 1H), 2.45-2.41 (m, 1H), 2.37-2.23 (m, 2H), 1.92-1.89 (m, 1H), 1.78 (s, 3H), 1.44 (dd, *J* 12.7, 11.1, 1H), 1.28 (t, *J* 7.2, 3H), 1.05 (dd, *J* 13.6, 11.9, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H).

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13. We obtained no evidence for the co-formation of the *Z*-isomer corresponding to **19** resulting from the Wittig reaction involving $CH_3C(PPh_3)CO_2Et$. The *E,E*- geometry assigned to **20** followed unambiguously from examination of the *J*-values for the relevant olefinic signals in the p.m.r. spectrum (*ie* $J_{VIC}$ 15.7Hz); <5% of the *Z*-olefination product was detected by spectroscopy.

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