Pergamon

Tetrahedron Letters 39 (1998) 319–322

TETRAHEDRON LETTERS

Synthetic Studies towards Phorboxazole A. A Concise Stereoselective Synthesis of the C20-C26 Pentasubstituted Oxane Ring Unit

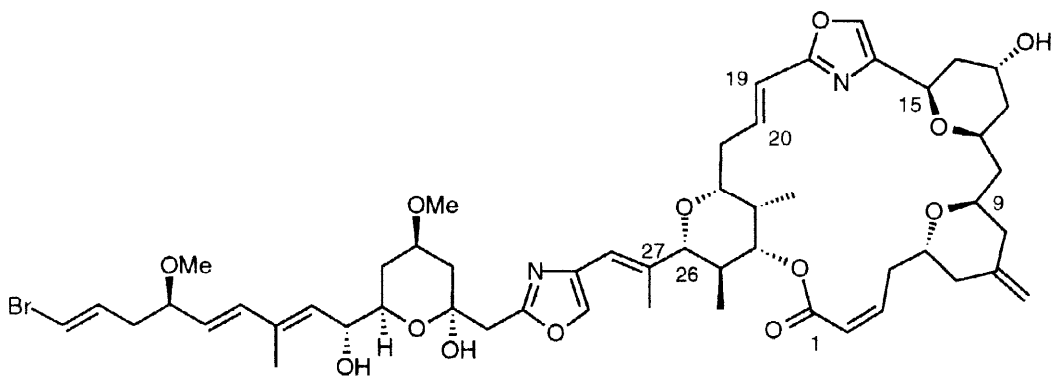
Tao Ye and Gerald Pattenden*

Department of Chemistry, Nottingham University, Nottingham NG7 2RD, England

Received 29 September 1997; accepted 24 October 1997

Abstract: A stereoselective synthesis of the 2,6-*cis* oxane unit, accommodating five contiguous asymmetric centres, found in the novel marine natural product phorboxazole A **1**, is described.

Phorboxazole A **1** is a remarkably novel and structurally interesting marine natural product isolated recently from an extract of the Indian Ocean sponge *Phorbas* sp.[1] The compound exhibits profound and potent cytostatic activity against an astonishing range of human tumour cell lines. The phorboxazole structure is based on a macrolactone core, which accommodates three heavily functionalised oxanes and a 2,4- disubstituted oxazole linked by two alkene units. A side chain containing a second oxazole, further alkene unsaturation, and an oxane hemiacetal unit is attached to the most substituted oxane ring in the macrolactone core. With its unusual ring systems, density of stereochemical detail, and striking biological profile, phorboxazole A has become one of the most sought after targets to challenge and engage the synthetic chemist.[2] In this *Letter* we describe a concise stereoselective synthesis of the novel 2,6-*cis* oxane unit **2** which contains five of the fifteen asymmetric centres in the natural product. Our synthesis starts with the chiral pool compound methyl (*S*)-3-hydroxy-2-methylpropionate **4**,[3] then makes judicious use of Brown's allylboranation[4] and Sharpless asymmetric epoxidation[5] protocols to install the several asymmetric centres, and features an intramolecular epoxide-ring opening process[6] to construct the oxane ring system from the epoxy alcohol **3**, as the key step.



1

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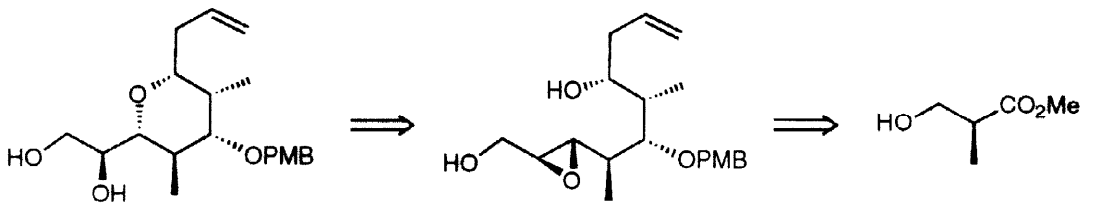
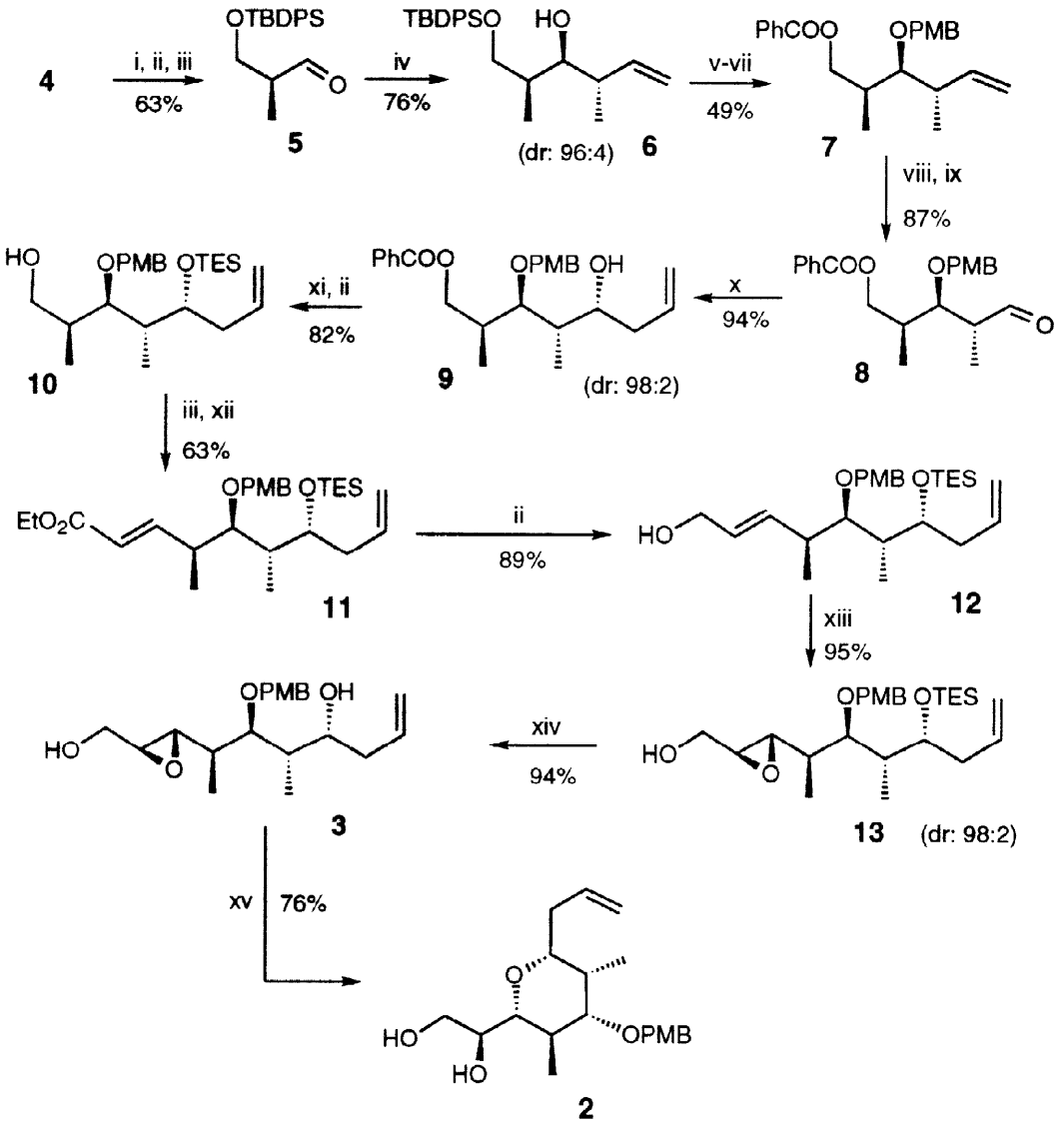
PII: S0040-4039(97)10475-0



2 **3** **4**

Thus, methyl (*S*)-3-hydroxy-2 methylpropionate **4** was first protected as its *tert*-butydiphenylsilyl ether, which was then converted into the aldehyde **5** *via* the corresponding carbinol.[7] Treatment of the aldehyde **5** with the chiral boron reagent derived from *E*-2-butene, *n*-butyllithium, potassium *tert*-butoxide and (-)-*B*-methoxy diisopinocamphenylborane in the presence of boron trifluoride etherate next gave the secondary alcohol **6** in 76% yield and with excellent diastereoselectivity(92% de).[8] After protection of the alcohol **6** as its *p*-methoxybenzyl ether,[9] exchange of the silyl ether protection for benzoyl then led to the differentially protected 1,3-diol **7** (Scheme 1). Oxidative cleavage of the alkene unit in **7** using OsO_4-$NaIO_4$ next produced the aldehyde **8**, which in a substrate-controlled allylation using allyltributyltin under Lewis acid catalysis gave rise to the homoallylic alcohol **9** in 94% yield and with >95% diastereoselectivity.[10] Protection of **9** as its triethylsilyl ether, followed by deprotection of the primary alcohol benzoate, under reductive conditions, next gave the free primary alcohol **10**. Oxidation of **10** to the corresponding aldehyde, followed by a Wadsworth-Emmons olefination using triethyl phosphonoacetate then led to the *E*-unsaturated ester **11**. The stage was now set to introduce the fifth chiral centre associated with the oxane ring **2** in phorboxazole A, and for this we made use of the ubiquitous Sharpless asymmetric epoxidation protocol.[5] Thus, reduction of **11**, using DIBAL at -78 °C produced the corresponding allylic carbinol **12** which an epoxidation under Sharpless conditions using (+)-diethyl tartarate, gave rise to the epoxide **13** in 94% yield and with excellent diastereoselectivity. Deprotection of the silyl ether group in **13**, next led to the secondary alcohol **3**, which on treatment with titanium tetraisopropoxide in refluxing benzene was smoothly converted into the 2,6-*cis* oxane **2** with the absolute stereochemistry shown.[11] With the completion of the synthesis of **2**, appropriately functioned at C20 and C27 (phorboxazole numbering), further synthetic studies are now in place to link this unit to the other ring systems in **1**, en-route to the natural product itself.



Reagents: i, TBDPS-Cl, DMF, Imid.; ii, DIBAL, hexane, iii, Swern oxidation, iv, (-)-*B*-(*E*)-crotyl isopinocamphenylborane; Et_3N, H_2O_2; v, $PMBOC(NH)CCl_3$, TfOH, ether; vi, TBAF, THF; vii, PhCOCl, DMAP, Py.; viii OsO_4, NMO; ix, $NaIO_4$, THF/H_2O; x, $SnBu_3Allyl$, BF_3 Et_2O, - 78 °C; xi, TESTf, 2,6-lutidine; xii, $(EtO)_2P(O)CH_2CO_2Et$, NaHMDS; xiii, (+)-DET, $Ti(i\text{-}PrO)_4$, TBHP, molecular sieves, -20 °C; xiv, TBAF, THF; xv, $Ti(i\text{-}PrO)_4$, PhH, reflux, 2h.

Scheme 1

Acknowledgements:

We thank the EPSRC for support of this work *via* a ROPA Post-Doctoral Fellowship to TY.

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8. The diastereomeric excess was measured by analysis of the NMR spectra.

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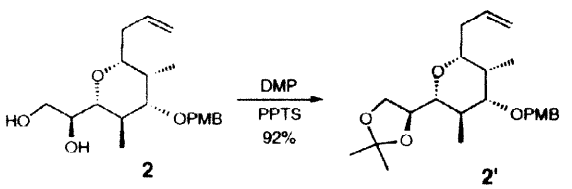
11. The tetrahydropyran **2** was best stored as the corresponding acetonide **2'**. The stereochemistry was assigned using extensive 2D NMR (COSY, TOCSY, HMQC, HMBC and NOESY) studies.



2 **2'**

2': ^{1}H NMR (500 MHz), δ(ppm), 7.26(d, J = 8.2Hz, 2H), 6.87(d, J = 8.2Hz, 2H), 5.75-5.83(m, 1H), 5.09(d, J = 17.2Hz, 1H), 5.04(d, J = 9.8Hz, 1H), 4.56(d, J = 11.0Hz, 1H), 4.26(d, J = 11.0Hz, 1H), 4.17(m, 1H), 3.99(app. d, J = 7.0Hz, 2H), 3.80(s, 3H), 3.35-3.38(m, 1H), 3.15(dd, J = 10.4, 4.3Hz, 1H), 3.12(dd, J = 8.8, 4.6Hz, 1H), 2.37-2.42(m, 1H), 2.13-2.16(m, 1H), 2.08-2.12(m, 1H), 1.48-1.53(m, 1H), 1.40(s, 3H), 1.36(s, 3H), 1.01(d, J = 6.3Hz, 3H), 0.88(d, J = 6.8Hz, 3H); ^{13}C NMR (125 MHz), δ(ppm), 159.19(C), 135.00(CH), 130.58(C), 129.31(CH), 116.69(CH_2), 113.80(CH), 109.20(C), 83.20(CH), 80.99(CH), 77.77(CH), 77.30(CH), 69.68(CH_2), 65.51(CH_2), 55.27(C), 37.26(CH_2), 34.54(CH), 33.48(CH), 26.23(CH_3), 25.97(CH_3), 13.38(CH_3), 5.71(CH_3)