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Synthetic Studies Toward Phorboxazole A. Stereoselective Synthesis of the C_3–C_{19} and C_{20}–C_{32} Subunits

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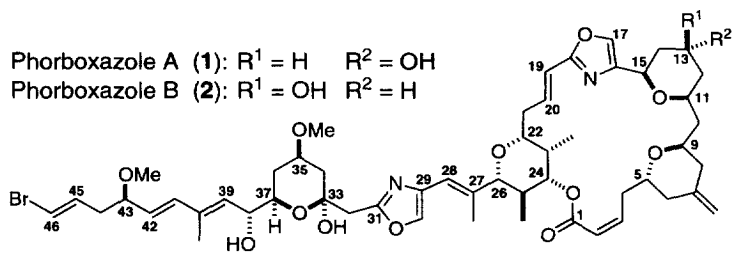
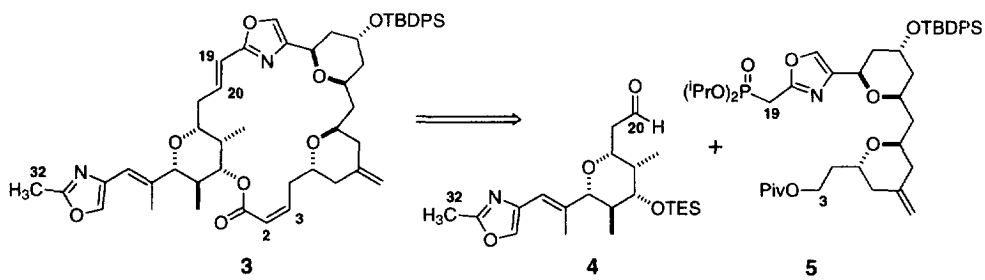
Abstract: A stereocontrolled synthesis of two fragments comprising the macrocyclic core of Phorboxazole A is described. The C_3–C_{19} bis-pyran segment is prepared utilizing reiterative enantioselective allylations from homochiral allylstannanes followed by stereoselective cyclizations. The pentasubstituted tetrahydropyran of the C_{20}–C_{32} fragment is prepared via an intramolecular stereoselective cationic cyclization of a methoxymethyl ether derivative.

Phorboxazoles A (**1**) and B (**2**) are unique macrolides isolated from the Indian Ocean sponge *Phorbas* sp.[1] These metabolites possess exceptional cytostatic activity throughout the panel of sixty NCI human tumor cell lines (mean $GI_{50} < 1.6\times10^{-9}$ M).[2] Selective cytotoxicity at subnanomolar concentrations is found in a number of significant tumor cultures, including leukemia CCRF-CBM, prostate PC-3, breast MCF7, and colon HCT116 and HT29 cell lines.[2c] Moreover, the phorboxazoles do not inhibit tubulin polymerization, and may offer a unique mechanism of action by arresting the cell cycle in S phase.[2] Biological studies are severely limited by the scarcity of natural material. The unprecedented structural features and extraordinary potency of **1** have inspired several synthesis studies,[3] and Forsyth and coworkers[4] have recently reported the first total synthesis.



Herein, we report the stereoselective synthesis of two macrocycle subunits, the C_{20}–C_{32} pentasubstituted tetrahydropyran **4** and the C_3–C_{19} *bis*-tetrahydropyran **5**, which together contain ten of the fifteen stereocenters of



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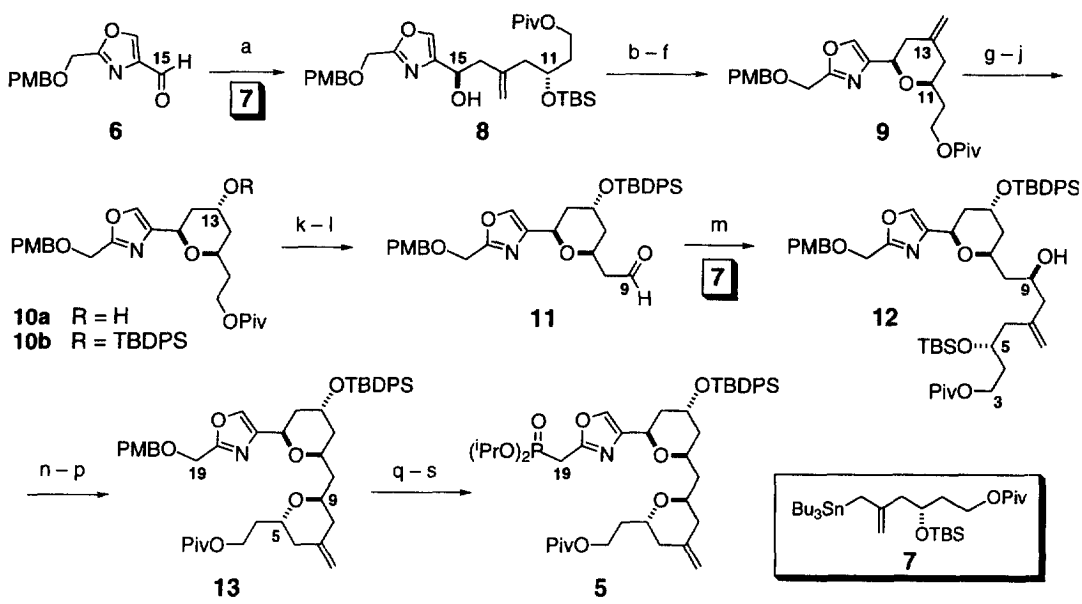
phorboxazole A. Retrosynthetic analysis of macrocycle **3** is envisioned from two bond disconnections, the first at the *trans* C_{19}–C_{20} alkene and the second at the C_2–C_3 olefin of the α,β-unsaturated ester.

As illustrated in Scheme 1, phosphonate ester **5** was prepared starting from the readily accessible oxazole carboxaldehyde **6**.[5] Asymmetric allylation of **6** was effected following the tin to boron transmetalation of allylstannane **7**[6] using the boron bromide reagent derived from (*R,R*)-1,2-diamino-1,2-diphenylethane *bis*-sulfonamide/BBr_3 as described by Corey.[7] The diastereofacial selectivity of the addition is primarily determined by the chiral auxiliary, resulting in formation of the *S*-homoallylic alcohol **8** in 98% yield (>95% de).[8] Ring closure to afford the 2,6-*cis*-tetrahydropyran **9** was accomplished by conversion of the C_{11} silyl ether to the corresponding methanesulfonate followed by internal alkoxide displacement.[9] The choice of toluene as solvent was significant, particularly for the minimization of the competing E_2 elimination pathway that leads to diene product. Oxidative cleavage of the C_{13} exocyclic methylene, LS-Selectride® reduction of the intermediate ketone via equatorial hydride delivery, and silylation of the resulting alcohol provided oxane **10** in 75% overall yield from **9**.[10] Hydrolysis of the C_9 pivaloate ester and subsequent oxidation[11] gave aldehyde **11** as the starting point for a second enantioselective allylation using stannane **7**. The reiterative asymmetric allylation process utilized the (*S,S*)-1,2-diamino-1,2-diphenylethane *bis*-sulfonamide controller to produce the complex polyol derivative **12** in 96% yield (85% de). Tosylation of **12** and fluoride removal of the C_5 silyl ether permitted cyclization to the *trans*-substituted tetrahydropyran **13**.[12] Oxidative removal of the *para*-methoxybenzyl ether (PMB) of **13**, and efficient conversion of the resulting alcohol to its C_{19} iodide allowed preparation of the desired diisopropylphosphonate **5** upon treatment with triisopropylphosphite in DMF.[12]

Scheme 1[a]



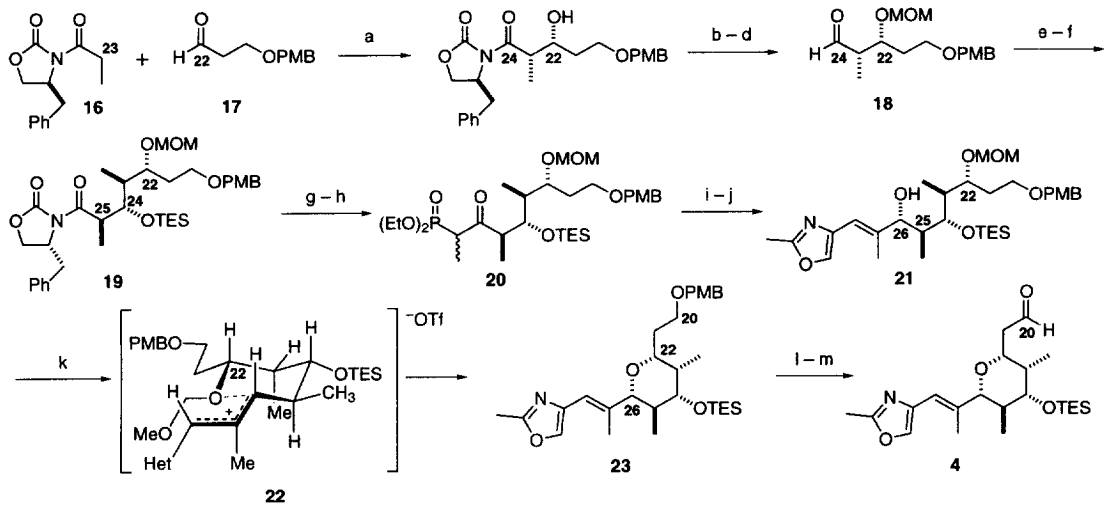
[a]Key: (a) (*R,R*)-1,2-diamino-1,2-diphenylethane *bis*-sulfonamide, BBr_3, CH_2Cl_2, **7**, 12 h, then add **6**, –78 °C, 92%, (dr >20:1); (b) DHP, PPTs, CH_2Cl_2; (c) TBAF, THF, 92% (2 steps); (d) MsCl, Et_3N, CH_2Cl_2; (e) TsOH, MeOH; (f) NaH, $PhCH_3$, 72% (3 steps); (g) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, 1:1 *t*-BuOH/H_2O, 99%; (h) $NaIO_4$, 1:1 THF/H_2O, 98%; (i) LS-Selectride®, THF, –78 °C, 85%; (j) TBDPSCl, imid, DMF, 91%; (k) LiOH, 7:2:2 THF/MeOH/H_2O, 95%; (l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%; (m) (*S,S*)-1,2-diamino-1,2-diphenylethane *bis*-sulfonamide, BBr_3, CH_2Cl_2, **7**, 12 h, then add **11**, –78 °C, 96% (dr 11.8:1); (n) TsCl, DMAP, Et_3N, CH_2Cl_2, 82%; (o) HF-pyr, CH_3CN, 90%; (p) NaH, PhH, reflux, 89%; (q) DDQ, *t*-BuOH, pH 7 buffer, CH_2Cl_2, 91%; (r) Ph_3P, I_2, imid, CH_2Cl_2, 97%; (s) triisopropylphosphite, DMF, 90 °C, 85%.

The construction of the C_{20}–C_{32} component **4** utilized two successive enantioselective boron aldol processes.[13] Reaction of the *Z*(O)-boron enolate of **16** (Scheme 2) with propanal **17**[14] afforded an efficient synthesis of nonracemic aldehyde **18**, and the second Evans aldol reaction incorporating the enantiomeric (*R*)-4-benzyloxazolidinone of **16** led to imide **19**, readily establishing the four contiguous asymmetric carbons in the C_{22}–C_{25} dipropionate segment. Formation of the β-ketophosphonate **20** was completed by cleavage of the auxiliary with the lithium alkoxide of benzyl alcohol[15] and subsequent Claisen condensation of the resulting benzyl ester with the carbanion of ethyl diethylphosphonate.[16]

Horner-Emmons condensation of **20** with 2-methyloxazole-4-carboxaldehyde[17] gave the expected trisubstituted enone (*E*:*Z* ≥ 15:1), and a stereoselective Luche reduction[18] resulted in formation of cyclization precursor **21** as the major product of a 7:1 mixture of erythro:threo diastereomers at C_{25}/C_{26}. When the purified alcohol **21** was treated with Tf_2O (2 equiv) and pyridine (5 equiv) in CH_2Cl_2 (–20 °C, 16 h) a single tetrahydropyran product **23** was isolated in 35–40% yield. Independently the diastereomer of **21** afforded the same result (≥95% de) under identical conditions.[19] The stereochemical assignment of **23** is supported by one and two-dimensional NMR experiments (COSY and NOESY), which also exhibit considerable similarity to data reported for the natural product (C_{22}–C_{32} region).[1] The mechanism of product formation is consistent with a cyclization process through the *transoid*-allyl cation **22** regardless of the configuration of the starting triflate. Nucleophilic capture of the cation via participation of the C_{22} methoxymethyl ether proceeds selectively with *re*-face addition followed by dealkylation of the oxonium species. Finally, removal of the C_{20} PMB ether of **23** and oxidation of the resulting primary alcohol with the Dess-Martin periodinane[11] provided the desired aldehyde **4**.[10]

Further adaptation of our strategy for the synthesis of phorboxazole and related derivatives is underway.

Scheme 2[a]



[a]Key: (a) Bu_2BOTf, Et_3N, CH_2Cl_2, –78 °C, 96%; (b) MOMCl, *i*-Pr_2EtN, 84%; (c) $LiBH_4$, Et_2O/H_2O, 89%; (d) Swern; (e) *ent*-**16**, Bu_2BOTf, Et_3N, CH_2Cl_2, –40 °C, 83% (2 steps); (f) TESCl, imid, CH_2Cl_2, 84%; (g) BnOLi, THF, 89%; (h) $(EtO)_2POEt$, *n*-BuLi (3 equiv), THF, –78 °C, 88%; (i) 2-Methyloxazole-4-carboxaldehyde, NaH, THF, 95% (*E*:*Z* ≥ 15:1); (j) $NaBH_4/CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 80% (7:1 erythro:threo); (k) Tf_2O (2 equiv), pyridine (5 equiv), CH_2Cl_2, –20 °C, 35 – 40%; (l) DDQ, pH 7 buffer, CH_2Cl_2, 78%; (m) Dess-Martin periodinane, pyridine, CH_2Cl_2, 96%.

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5. Aldehyde **6** was prepared in four steps from *p*-methoxybenzyloxy acetic acid. Condensation of the acid with serine methyl ester and cyclization of the resulting amide using DAST (92%) directly provided the oxazoline precursor (see Lellouche, J.P.; Lafargue, P.; Guenot, P. *Heterocycles* **1995**, *41*, 947). The oxazoline was oxidized to the oxazole (81%) using $BrCCl_3$/DBU (see Williams, D.R.; Lowder, P.D.; Gu, Y.G.; Brooks, D.A. *Tetrahedron Lett.* **1997**, *38*, 331). Reduction of the ester with DIBAL (CH_2Cl_2, –78 °C, 10 min) provided the desired aldehyde **6** (90%).
6. Preparation of allylstannane **7** is conveniently carried out via copper-catalyzed addition of the Grignard reagent generated from 2-bromo-3-trimethylsilylpropene (see Nishiyama, H.; Yokoyama, H.; Harimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267) to the nonracemic terminal epoxide generated from (*S*)-malic acid. Following protection of the resulting secondary alcohol, a two-step protocol (1. NBS, CH_2Cl_2, –78 °C, 4h; 2. $Bu_3SnCuLi$, THF, –78 °C to –40 °C) was utilized to convert the allylsilane to allylstannane **7**.
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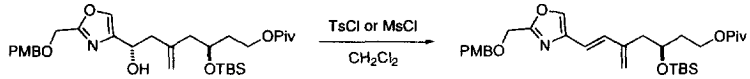
9. Attempted synthesis of the mesylate or tosylate of alcohol **14** resulted in formation of substantial amounts of diene **15**. Attempted desilylation of the crude mesylate of alcohol **14** with TBAF prior to cyclization resulted in formation of diene **15** as the major product.



14 **15**

10. ^1H NMR data for selected compounds: **10a** ($CDCl_3$, 500 MHz) δ 7.56 (s, 1H), 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.87 (dd, J = 11.0, 2.0 Hz, 1H), 4.54 (s, 2H), 4.53 (s, 2H), 4.36 (d, J = 2.0 Hz, 1H), 4.17 (ddd, J = 17.0, 11.0, 6.5 Hz, 1H), 4.07 (ddd, J = 23.5, 11.0, 6.5 Hz, 1H), 3.80 (s, 3H), 1.99–1.86 (m, 3H), 1.82–1.72 (m, 2H), 1.63–1.58 (m, 2H), 1.19 (s, 9H); **13** (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4H), 7.56 (s, 1H), 7.46–7.35 (m, 6H), 7.28 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.03 (d, J = 10.0 Hz, 1H), 4.77 (d, J = 14.0 Hz, 2H), 4.53 (s, 4H), 4.31 (m, 1H), 4.23–3.98 (m, 4H), 3.87 (dddd, J = 12.4, 12.4, 6.2, 6.2 Hz, 1H), 3.80 (s, 3H), 2.40 (dd, A of ABX, J_{AB} = 13.6 Hz, J_{AX} = 5.7 Hz, 1H); 2.33 (dd, B of ABX, J_{BA} = 13.6 Hz, J_{BX} = 6.1 Hz, 1H), 2.05–1.83 (m, 4H), 1.78–1.70 (m, 2H), 1.62 (d, J = 13.6 Hz, 1H), 1.48 (ddd, J = 13.2, 6.0, 6.0 Hz, 1H), 1.41–1.33 (m, 1H), 1.26–1.21 (m, 1H), 1.18 (s, 9H), 1.10 (s, 9H); **4** (400 MHz, $CDCl_3$) δ 9.75 (t, J = 1.6 Hz, 1H), 7.47 (s, 1H), 6.17 (s, 1H), 4.03 (dddd, J = 8.8, 1.6, 1.6, 1.6 Hz, 1H), 3.53–3.48 (m, 2H), 2.72 (ddd, J = 16.8, 8.8, 2.0 Hz, 1H), 2.44 (s, 3H), 2.38 (ddd, J = 16.8, 8.0, 2.0 Hz, 1H), 1.89 (s, 3H), 1.82–1.69 (m, 2H), 0.98 (d, J = 6.4 Hz, 1H), 0.97 (t, J = 8.0 Hz, 9H), 0.77 (d, J = 6.4 Hz, 1H), 0.61 (q, J = 8.0 Hz, 1H).
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19. (a) No improvement was obtained with changes in solvent, or amine bases, such as Et_3N, *i*-Pr_2EtN, lutidine or DMAP. (b) No desired product was obtained when **21** was treated with MsCl/pyridine.