Macrolide Synthesis

Total Synthesis of Phorboxazole A**

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Phorboxazole A (**1**; see Scheme 1), and its C13 diastereoisomer phorboxazole B, are novel 21-membered macrolides isolated from the rare Indian Ocean sponge *Phorbas* sp.[1] These substances have demonstrated extraordinary potency against the National Cancer Institute (NCI) panel of 60 human tumor cell cultures (mean $GI_{50} < 1.6$ nM).[2] Moreover, phorboxazole A has been shown to arrest the cell cycle in the S phase without affecting tubulin polymerization, suggesting a unique mechanism of action.[2a] While biological studies are severely limited by the scarcity of these natural products, the unprecedented structural features and remarkable antitumor activity have provided the impetus for several synthesis studies.[3] Recently, total syntheses of phorboxazole A[4,5] and phorboxazole B[6] have been reported. Herein, we describe the culmination of our efforts[3d–f] leading to a convergent, enantiocontrolled total synthesis of **1**.

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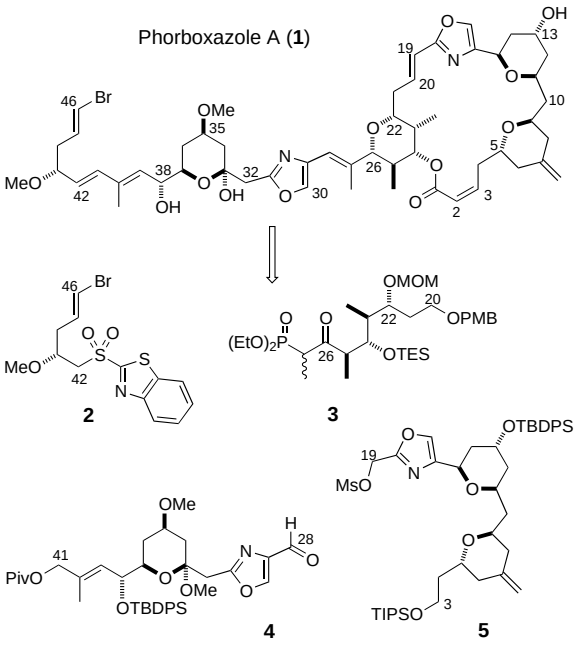
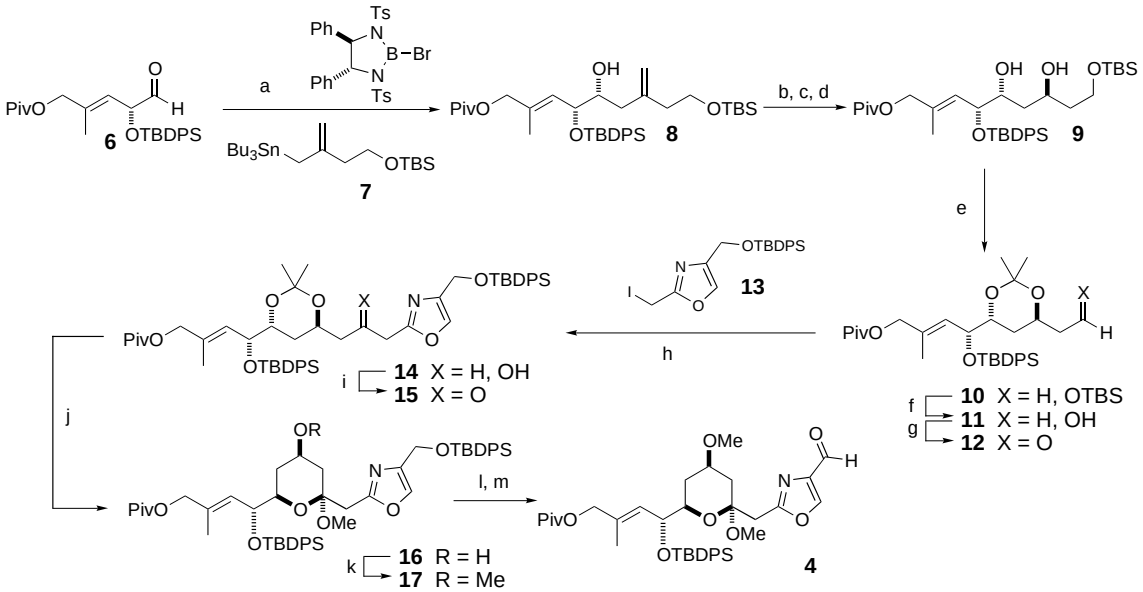
We envisioned in our retrosynthetic analysis the preparation of four nonracemic components **2**–**5** for the convergent assembly of the target macrolide (Scheme 1). Stereoselective formation of the C22–C26 tetrahydropyran moiety of **1** was a central issue for the design strategy that featured the union of components **3** and **4**. Thus, the Horner–Wadsworth–Emmons reaction would precede formation of the fully substituted pyran through retention of the stereochemistry at C22 of component **3** in the π-allyl cation cyclization event. Incorporation of the intact bispyran component **5** utilized the Wittig reaction for construction of the (*E*)-C19–C20 alkene, and was followed by the subsequent attachment of the labile C42–C46 segment by a modified Julia olefination. Finally, our strategy culminated in a late-stage macrocyclization by installation of the (*Z*)-C2–C3 enoate.

Synthesis of the C28–C41 aldehyde **4** began with nonracemic β,γ-unsaturated aldehyde **6** (Scheme 2).[7] Asymmetric allylation of **6** was effected following the tin-to-boron transmetalation of allylstannane **7**[8] using the boron bromide reagent derived from (*R,R*)-1,2-diamino-1,2-diphenylethane bis(sulfonamide) and boron tribromide.[9] Nucleophilic addition provided the homoallylic alcohol **8** as the major component of a mixture (96% yield) of C37 diastereomers (d.r. 7.2:1),[10] demonstrating anti-Felkin stereocontrol as imparted by the chiral auxiliary. Selective oxidative cleavage of the 1,1-disubstituted olefin (OsO_4, $K_3Fe(CN)_6$; $NaIO_4$), and internally directed reduction[11] of the resultant β-hydroxy ketone with $Me_4NBH(OAc)_3$ yielded 1,3-diol **9** with excellent diastereoselectivity (d.r. > 95:5). Protection of **9** as the corresponding acetonide (**10**) led to the expected diagnostic NMR evidence in support of the 1,3-anti relationship.[12]



Scheme 1. Components **2**–**5** of phorboxazole A (**1**). MOM = methoxymethyl, Ms = methanesulfonyl, Piv = pivaloyl, PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsiyl, TIPS = triisopropylsilyl.

Cleavage of the silyl ether and oxidation of the resultant primary alcohol **11** under Swern conditions[13] furnished the aldehyde **12**.

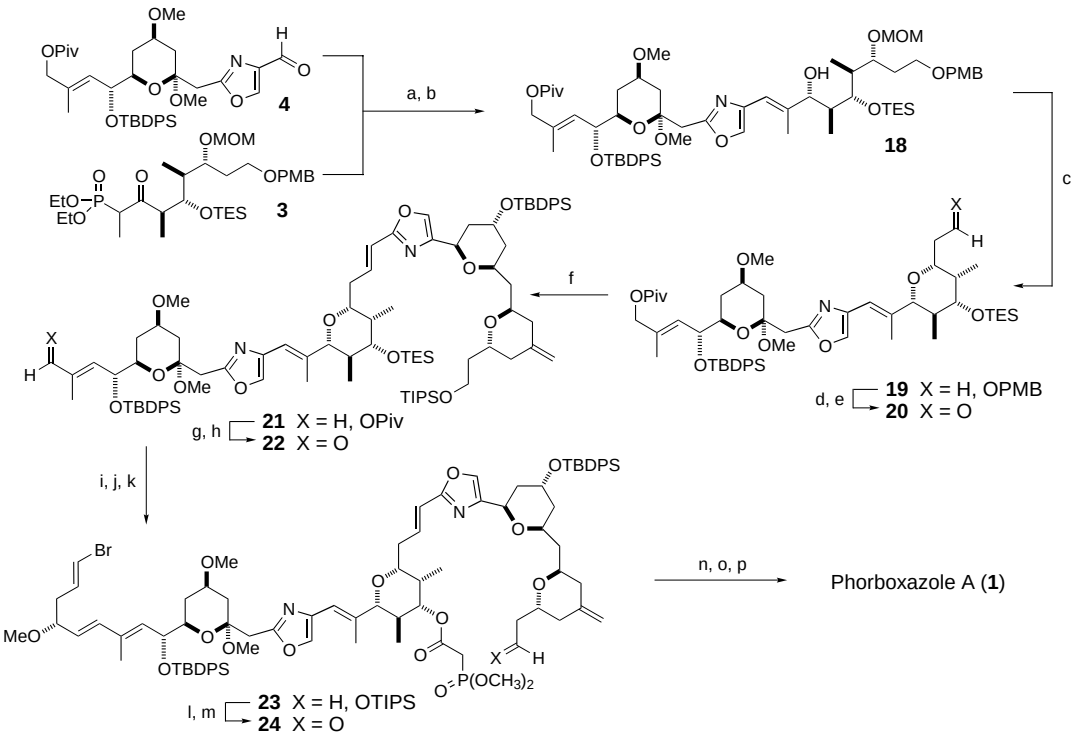


Scheme 2. a) (*S,S*)-1,2-Diamino-1,2-diphenylethane bis(sulfonamide), BBr_3, CH_2Cl_2, 0°C, 1 h; then **7**, RT, 10 h; then **6**, −78°C, 1 h; 96%, 7.2:1 d.r.; b) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, DABCO, *t*BuOH/H_2O (1:1); c) $NaIO_4$, THF/H_2O (1:1); 95% (two steps); d) $Me_4NBH(OAc)_3$, HOAc/CH_3CN (1:1), −20°C, 10 h; 94%, >95:5 d.r.; e) 2,2-dimethoxypropane, cat. CSA, RT, 16 h; f) HF·pyr, THF; 87% for two steps; g) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N; h) **13**, SmI_2, THF, RT; 92% for two steps, 1:1 dr; i) TFAA, DMSO, CH_2Cl_2, −78°C; then acetylacetone, Et_3N, −60° to −40°C; 88%; j) cat. CSA, MeOH, RT, 1.5 h; 82%, 7.2:1 mixture of separable C37 epimers; k) MeI, $CaSO_4$, Ag_2O, 3 d; 90%; l) TBAF, THF, 0°C, 2 h; 92%; m) Dess–Martin periodinane, pyridine, CH_2Cl_2, 1 h; 95%. CSA = camphorsulfonic acid, DABCO = 1,4-diazabicyclo[2.2.2]octane, pyr = pyridine, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TFAA = trifluoroacetic anhydride, Ts = *p*-toluenesulfonyl.

We have previously explored direct incorporation of the intact oxazole nucleus by the use of a Barbier coupling of aldehydes and 2-iodomethyl oxazoles in the presence of SmI_2.[3f] Application of improved conditions using iodide **13** and aldehyde **12** gave the desired alcohol adduct **14** as a 1:1 mixture of diastereomers in 92% yield (over two steps). Oxidation of this mixture using a modification of the trifluoroacetic anhydride–DMSO–NEt_3 protocol[14] provided the corresponding ketone **15** in 88% yield. The inclusion of acetylacetone (3–5 equiv) in the reaction mixture at −60°C immediately prior to addition of triethylamine was necessary to prevent C32-α-methylthiomethylation of the product ketone. In fact, the ease of enolization of **15** was undoubtedly responsible for problems encountered in IBX[15] and Dess–Martin oxidation[16] attempts, which led to varying amounts of further oxidation to aldehydes produced by cleavage of the C32–C33 bond. Subjecting ketone **15** to conditions of acetal exchange with methanol in the presence of a catalytic amount of camphorsulfonic acid provided tetrahydropyran **16** in 82% yield as a 7.2:1 mixture of readily separable C37,C35 epimers, resulting from the original allylation reaction of **6**. Methylation of the C35 alcohol of **16** followed by desilylation of **17** with TBAF and Dess–Martin oxidation delivered the key C28–C41 aldehyde **4** in 39% overall yield from **6**.

Coupling of the β-ketophosphonate **3**, which was synthesized as previously described,[3f] with oxazole carboxaldehyde **4** led to the desired C27-C28 *E*-trisubstituted alkene in 88% yield with excellent selectivity (>95:5 *E*/*Z*; Scheme 3). Reduction of this α,β-unsaturated ketone under Luche conditions gave the C26 alcohol **18** (d.r. 9:1).[17,18] Subsequent treatment of **18** with triflic anhydride (2 equiv) and anhydrous pyridine (5 equiv) in CH_2Cl_2 (−20°C, 12 h) produced a single tetrahydropyran **19** in 55% yield. The mechanism for product formation is consistent with the production of an intermediate transoid allyl cation for internal capture via participation of the β-methoxymethyl ether at C22 with *Re*-face addition followed by dealkylation of the oxonium species.[19] Stereochemical assignments of the fully substituted pyran were supported by one- and two-dimensional NMR experiments (COSY and NOESY). Removal of the PMB ether of **19** followed by Dess–Martin oxidation yielded the C20 aldehyde **20**.

Enantiocontrolled preparation of the C3–C19 bispyran component **5** (Scheme 1) proceeded by a pathway featuring our asymmetric allylation methodology as previously described.[3f] In situ displacement of the reactive mesylate of **5**[20] with tri-*n*-butylphosphane in DMF at room temperature provided an intermediate phosphorane for direct condensation with aldehyde **20** (Scheme 3). The resulting C19–C20 alkene **21** was isolated in nearly quantitative yield with excellent *E* stereoselectivity (*E*:*Z* > 95:5). Reductive removal of the allylic pivaloate and oxidation of the resulting primary



Scheme 3. a) NaH, THF, RT, 0.5 h; 88%, >95:5 *E*:*Z*; b) $NaBH_4$, $CeCl_3 \cdot 7H_20$, MeOH, 0°C, 1 h; 98%, >95:5 d.r.; c) Tf_2O, pyr, CH_2Cl_2, −20°C, 12 h; 55%; d) DDQ, CH_2Cl_2, pH 7 buffer, RT, 1 h; 94%; e) Dess–Martin periodinane, pyr, CH_2Cl_2, RT, 2.5 h; 87%; f) **5**, PBu_3, CH_2Cl_2, RT, 16 h, then add **14**, DBU, RT, 1 h; quant.; g) DIBAL-H, CH_2Cl_2, −78°C, 2 min; 98%; h) Dess–Martin periodinane, pyr, CH_2Cl_2, 1.5 h; 90%; i) **2**, NaHMDS, THF, −78°C to RT; 98%, >95:5 *E*:*Z*; j) CH_2Cl_2/MeOH/HOAc 2:1:1, 2 d, 86%; k) dimethylphosphonoacetic acid, DCC, CH_2Cl_2; l) CSA, MeOH; m) Dess-Martin periodinane, CH_2Cl_2; 76% for three steps; n) K_2CO_3, [18]crown-6, toluene, −20°C, two days; quant., 4:1 *Z*:*E*; o) TBAF, THF; 53%; p) 6% HCl, THF; 80%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminum hydride, HMDS = bis(trimethylsilyl)amide, DCC = *N*,*N*′-dicyclohexylcarbodiimide.

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allylic alcohol gave the unsaturated aldehyde **22** for attachment of the remaining C42–C46 carbon chain. In this regard, our previous studies have examined the adaptation of the Kocienski modification of the Julia olefination.[21] Intriguingly, use of the corresponding *N*-phenyltetrazole sulfone of **2** resulted predominantly in the formation of the *Z* olefin. On the other hand, the carbanion of the benzothiazole[22] sulfone **2**, previously reported by Evans and co-workers,[6] cleanly reacted with **22** under similar reaction conditions yielding the desired *E,E* diene (98%; >95:5 *E*:*Z*). Removal of the TES ether at C24 (HOAc, CH_2Cl_2, MeOH, 86%) and esterification of the alcohol at C24 with dimethylphosphonoacetic acid (DCC, CH_2Cl_2) provided phosphonate **23**. Selective removal of the TIPS protecting group at C3 under mildly acidic conditions (CSA, MeOH) followed by Dess–Martin oxidation furnished the key aldehyde **24** in 76% yield over three steps. Intramolecular Horner–Wadsworth–Emmons macrocyclization in toluene (K_2CO_3, [18]crown-6, −20°C) gave the macrocycle as a 4:1 mixture of C2–C3 *Z*:*E* olefin isomers. Deprotection of both TBDPS ethers with TBAF in THF provided a diol (53% yield), which permitted the separation of the minor (*E*)-C2–C3 isomer by silica gel chromatography. Finally, hydrolysis of the methyl ketal moiety under acidic conditions (6% aqueous HCl, THF)[4a] furnished phorboxazole A (**1**) in 80% yield. Our synthetic material was identical in all respects with physical and spectroscopic data provided for the natural product.[1]

In summary, we have reported a highly convergent, stereocontrolled total synthesis of phorboxazole A (**1**). Asymmetric allylation reactions of stannyl-derived allyldiazaborolanes are demonstrated as a powerful protocol for the enantiocontrolled assembly of functionally complex components. Key features of the overall scheme include a stereoselective cationic cyclization reaction for formation of the fully substituted C22–C26 tetrahydropyran, and the use of a Julia olefination for incorporation of the sensitive C37–C46 dienyl system. The novel Barbier-type coupling of an iodomethyl oxazole provides a promising methodology for the incorporation of the intact oxazole heterocycle. Full details of this study will be reported in due course.

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[7] The aldehyde **6**, which bears the primary pivaloate, was prepared by the same route as previously described for the corresponding MOM ether in 62% overall yield.[3f]
[8] Stannane **7** is conveniently prepared by deprotonation of 3-methyl-3-buten-1-ol with two equivalents of Schlosser's base, quenching the resulting dianion with tributyltin iodide, and protection of the resultant alcohol (TBSCl, imidazole).
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[10] Small-scale reactions permitted the chromatographic separation of homoallylic alcohol diastereomers for individual characterization. Preparative multigram reactions were conveniently carried forward to acetal **16**, where the desired C37 isomer was easily purified by flash chromatography.
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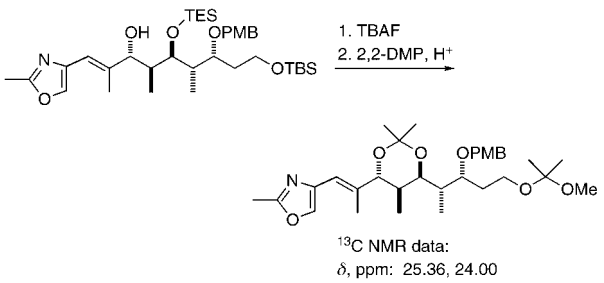
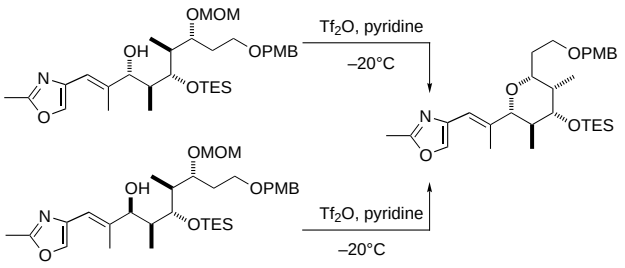
[18] The relative stereocontrol of the reduction was established on a related compound by conversion (2,2′-dimethoxypropane (2,2-DMP)) into the six-membered acetonide and application of ^{13}C NMR spectroscopic analysis.[12]



[19] Model studies had shown that individual diastereomeric allylic alcohols were cyclized under these conditions to afford the same tetrahydropyran product.



[20] Methanesulfonate **5** was prepared from the previously reported C3 pivaloate/C19 PMB ether[3d] by the following four-step sequence: 1) LiOH, THF/MeOH/H_2O; 2) TIPSOTf, 2,6-lutidine; 3) DDQ, CH_2Cl_2/pH 7 buffer; 4) MsCl, Et_3N.

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