Natural Product Synthesis

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Total Synthesis of Phorboxazole B**

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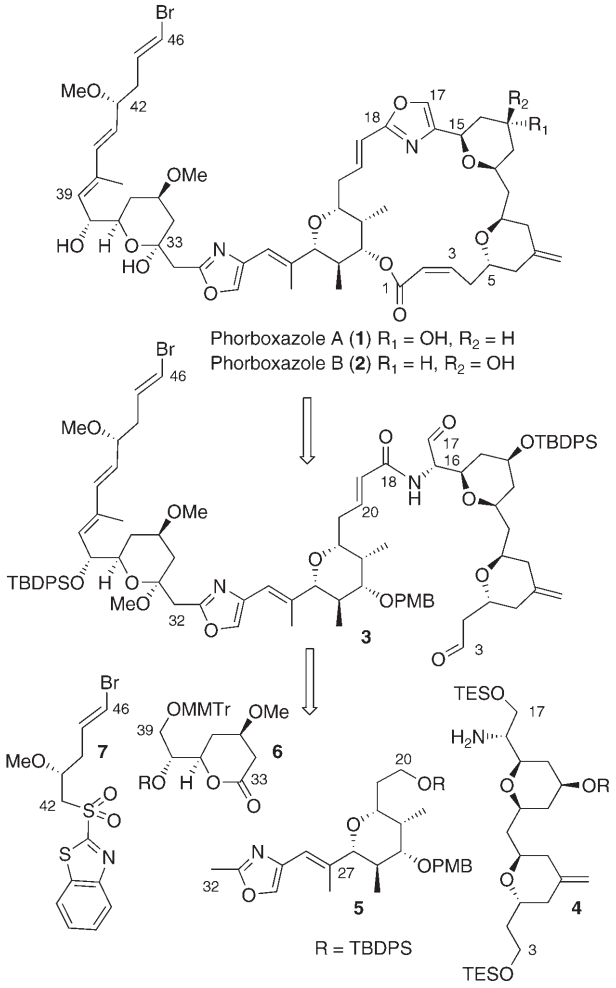
Since their isolation by Molinski and Searle in 1995,[1] the structurally complex phorboxazoles A and B (Scheme 1) have sparked a flurry of interest from the synthetic community. Comprising 15 asymmetric centers, four diversely substituted hydropyran rings, a 21-membered macrolactone, two oxazole rings, and a variety of unsaturations, the phorboxazoles present a considerable challenge. A total of six research groups have reported syntheses of the phorboxazoles, beginning with Forsyth's synthesis of phorboxazole A (**1**) in 1998,[2] followed by Evans's synthesis of phorboxazole B (**2**) in 2000.[3] Subsequent syntheses of phorboxazole A have been completed by the research groups led by Smith (2001,[4] 2005[5]), Pattenden (2003),[6] and Williams (2003),[7] and of phorboxazole B by Zhou et al. (2006).[8] In addition, numerous other synthetic efforts have been described.[9]

The unique biological activity of the phorboxazoles is another driving force for their study. The phorboxazoles are among the most potent cytostatic agents yet discovered, exhibiting a mean $GI_{50} < 1.58 \times 10^{-9}$ M against the NCI panel of 60 tumor cell lines.[10] While it is known that the phorboxazoles induce S-phase cell cycle arrest without interference of the microtubules, the exact mode of activity is not fully understood. Recently, Forsyth, La Clair et al. have shown that fluorescently labeled phorboxazole derivatives induce association of cell-cycle-dependent kinase 4 (cdk4) with extranuclear cytokeratin intermediate filaments (KRT10),[11] and perturbation of cdk4 is known to inhibit cell cycle progression at the G1/S phase.[12] In addition, new, potent analogues are beginning to shed some light on the phorboxazole pharmacophore.[13]

Our interest in the phorboxazoles was kindled by the hidden symmetry we identified in the C5–C15 bis(oxane) segment of the phorboxazoles, for which we pursued a two-directional synthesis/desymmetrization strategy to the C3–C15 cores of phorboxazole A and B.[14] Further investigations led to a functionalized C1–C17 fragment of phorboxazole B,[15] and a catalytic enantioselective hetero-Diels–Alder approach to the stereochemically complex C20–C32 segment.[16] We report herein the culmination of our efforts toward the total synthesis of phorboxazole B.



Scheme 1. Phorboxazole retrosynthesis. Protecting groups are defined in Scheme 2.

Our retrosynthesis for phorboxazole B (**2**) is shown in Scheme 1. As in the Forsyth example, the C16–C18 oxazole ring would be constructed by a coupling of a C18 carboxylic acid to a C16 amine, followed by cyclodehydration according to the Wipf procedure.[17] In an effort to minimize steps, the cyclodehydration of **3** would be performed in the presence of a C3 aldehyde. The C2–C3 *Z* double bond would be constructed by a well-precedented intramolecular Horner–Wadsworth–Emmons reaction (HWE),[2,4–8] necessitating a C3–C17 fragment **4**. Application of Evans's conditions for thermodynamic oxazole metalation[3] would serve to join the C20–C32 fragment **5**[16] with a C33–C39 lactone **6**. Julia–Kocienski olefination[18] using sulfone **7**,[19] as in the Wil-

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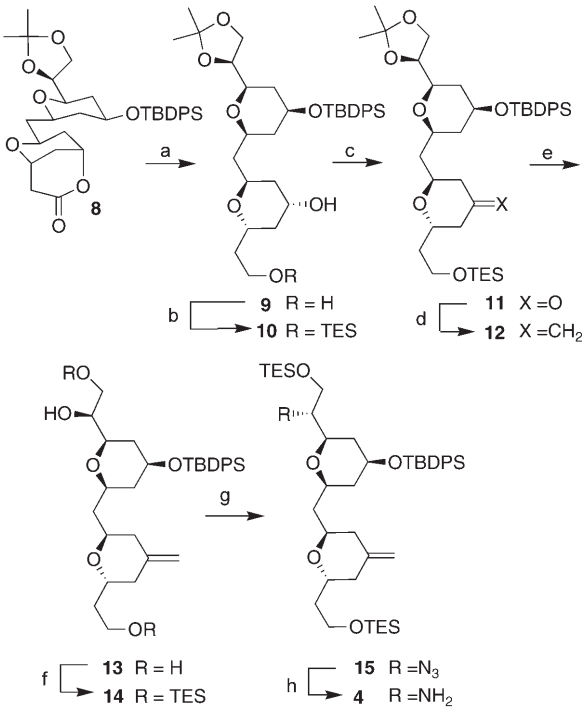
liams,[7] Pattenden,[6] and Zhou[8] examples, would install the C42–C46 side chain.

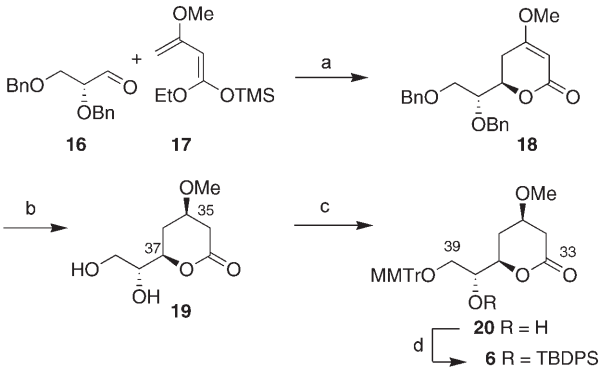
As a result of some late-stage difficulties with our incorporation of the C1–C3 *Z* enoate early on,[20] we revised our synthesis and required a new C3–C17 phorboxazole B fragment **4**. As shown in Scheme 2, the previously constructed



Scheme 2. Synthesis of the C3–C17 fragment **4**. a) $LiBH_4$, THF, 0 °C, 97%; b) TES-Cl, 2,6-lutidine, CH_2Cl_2, −78 °C, 93%; c) Dess–Martin periodinane, CH_2Cl_2, 94%; d) $[Cp_2TiMe_2]$, 1:1 THF/toluene, 80 °C, 77%; e) *p*-TsOH, MeOH, 40 °C, 93%; f) TES-Cl, imidazole, CH_2Cl_2, −78 °C, 76%; g) PPh_3, DEAD, DPPA, 88%; h) PPh_3, H_2O, THF, reflux, 76%. TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl, *p*-TsOH = *p*-toluenesulfonic acid, DEAD = diethylazodicarboxylate, DPPA = diphenylphosphorylazide.

bicyclic lactone **8**[15] was reduced to diol **9** with $LiBH_4$, followed by selective protection of the primary hydroxy function. Dess–Martin[21] oxidation of the secondary alcohol in **10** yielded ketone **11**, which was olefinated using the Petasis reagent[22] to install the methylene unit in **12**. Acidic removal of the C16–C17 acetonide and the TES ether yielded triol **13**, which was selectively silylated at the primary sites at C3 and C17 to provide bis(TES ether) **14**. Mitsunobu[23] reaction of the free secondary alcohol at C16 with diphenylphosphorylazide (DPPA)[24] yielded azide **15**, which underwent Staudinger reduction[25] to provide the desired C3–C17 amine **4**.

We anticipated that an efficient entry to the C33–C39 lactone **6** could arise from a chelation-controlled hetero-Diels–Alder reaction of the mannitol-derived aldehyde **16**[26] with Brassard diene **17**[27] (Scheme 3). The stereochemical outcome in **18** was predicted based on the work of Midland et al.,[28] although the presence of a β-alkoxy substituent could potentially interfere with the chelation control involving the stereogenic center at the α position.[29] Combination of **16** and



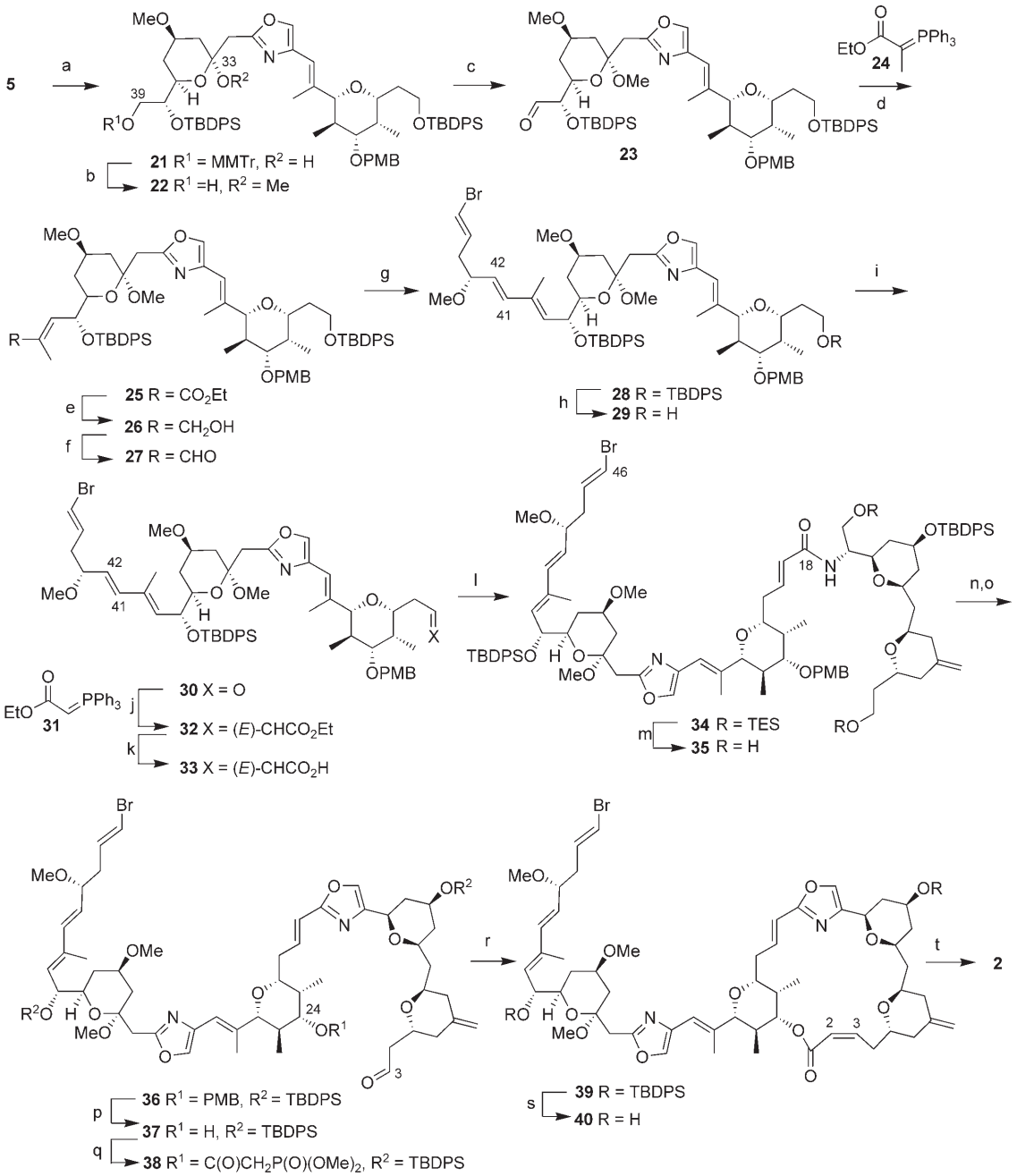
Scheme 3. Synthesis of the C33–C39 lactone **6**. a) $[Eu(fod)_3]$, CH_2Cl_2, 0 °C, 71%; b) Pd/C, H_2, EtOAc, 85%; c) MMTr-Cl, pyridine, DMAP, 100%; d) TBDPS-Cl, $AgNO_3$, pyridine, 50 °C, 71%; fod = tris(6,6,7,7,-8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione), MMTr = monomethoxytriphenylmethyl, DMAP = *N*,*N*-dimethylaminopyridine.

17 to afford **18** proceeded smoothly under Eu^{3+} catalysis.[30] Catalytic hydrogenation, serving to both saturate the ring and liberate the C38 and C39 hydroxy groups, provided crystalline diol **19**, and the stereochemistry at C35 and C37 was unambiguously determined by X-ray crystallography. Selective protection of the primary hydroxy group as the monomethoxytrityl ether (MMTr)[31] was accomplished in quantitative yield to afford **20**, followed by installation of the TBDPS ether at C38 to give the complete C33–C39 lactone **6** in four steps from Brassard's diene **17**.

Phorboxazole B (**2**) was assembled from subunits **4**–**7** as shown in Scheme 4. Coupling of **5** and **6** was achieved by the strategy of Evans for thermodynamic oxazole metalation[3] under conditions of high concentration to afford hemiketal **21** in 75% yield (91% based on recovered starting material **5**). Treatment of **21** with PPTS in MeOH served to cleave the extremely acid-labile MMTr ether at C39[31] and form the mixed methyl ketal **22** in a single operation. Oxidation to the C39 aldehyde **23** using Dess–Martin periodinane[21] was followed by installation of the trisubstituted double bond using the stabilized Wittig reagent **24** to afford *E* (α,β)-unsaturated ethyl ester **25**. Dibal reduction to give the allylic alcohol **26** was followed by careful oxidation yielding the Julia–Kocienski coupling partner **27**. Application of Williams's conditions[19] for olefination using sulfone **7** delivered **28** (86%) as a 92:8 mixture of *E*/*Z* isomers at C41–C42.[32]

Methanolic *p*-TsOH proved suitable for the selective removal of the primary TBDPS ether at C20 in the presence of the secondary allylic TBDPS ether at C38 to provide the primary alcohol **29**. Oxidation to aldehyde **30** was followed by homologation using stabilized Wittig reagent **31** to give ethyl ester **32**. Finally, saponification using LiOH afforded the complete C18–C46 fragment **33**.

EDCI-mediated coupling of amine **4** and carboxylic acid **33** produced amide **34** in 85% yield. Removal of the TES ethers at C3 and C17 proceeded in near-quantitative yield to give diol **35**. The key Dess–Martin oxidation[21]/cyclodehydration[17] sequence[2] ultimately afforded oxazole **36** in 71% overall yield with the C3 aldehyde remaining intact. In preparation for the HWE closure of the macrocycle, oxidative



Scheme 4. Completion of the total synthesis of phorboxazole B (**2**). a) $LiNEt_2$, **6**, THF −78 °C 75%, 91% based on recovered starting material; b) PPTS, MeOH, 80%; c) Dess–Martin periodinane, CH_2Cl_2, 92%; d) **24**, toluene, 80 °C, 95%; e) Dibal-H, CH_2Cl_2, −78 °C, 95%; f) Dess–Martin periodinane, 2,6-lutidine, CH_2Cl_2, 92%; g) **7**, NaHMDS, THF, −78 °C to RT, 86% 92:8 *E*/*Z*; h) *p*-TsOH, MeOH, 90% after one recycle; i) Dess–Martin periodinane, CH_2Cl_2, 90%; j) **31**, toluene, 80 °C, 90%; k) LiOH, THF/MeOH/H_2O (4:1:1), 80%; l) **4**, EDCI·MeI, HOBt, CH_2Cl_2, 85%; m) 0.1 N HCl, MeOH, 0 °C, 5 min, 97%; n) Dess–Martin periodinane, CH_2Cl_2; o) 2,6-DBMP, PPh_3, $(CCl_2Br)_2$, CH_2Cl_2, 0 °C then DBU, MeCN, RT, 71% (2 steps); p) DDQ, CH_2Cl_2, pH 7 buffer, 76%; q) DIC, dimethylphosphonoacetic acid, CH_2Cl_2, 93%; r) K_2CO_3, [18]crown-6, toluene, −40 °C to RT, 93% 3:1 *Z*/*E*; s) TBAF, THF, 74%; t) 0.72 N HCl, THF, RT, 60 h, 83%. PPTS = pyridinium *p*-toluenesulfonic acid, Dibal-H = diisobutylaluminum hydride, NaHMDS = sodium bis(trimethylsilyl)amide, EDCI·MeI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide methiodide, HOBt = 1-hydroxybenzotriazole, DBMP = di-*tert*-butyl-4-methylpyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIC = diisopropylcarbodiimide, TBAF = tetrabutylammonium fluoride.

deprotection of the PMB ether at C24 to give secondary alcohol **37** was followed by installation of the dimethylphosphonoacetate moiety in **38** using DIC. Ring closure ensued upon treatment with K_2CO_3/[18]crown-6 to afford **39** as a 3:1 mixture of *Z*/*E* isomers at C2–C3, which were separable by silica gel column chromatography. Lastly, removal of the silyl protecting groups using TBAF gave the C33-methoxy-protected derivative **40** of phorboxazole B which was subsequently hydrolyzed to provide phorboxazole B (**2**) in 83% yield by stirring in 0.72 N HCl[33] for 60 h.[2,4,5,7,8]

In conclusion, modification of our previously reported synthesis of the C1–C17 fragment afforded the required C3–C17 fragment **4**. A rapid synthesis of the C33–C39 lactone **6** by diastereoselective hetero-Diels–Alder reaction facilitated construction of the C18–C46 acid segment **33** from previously reported fragments. Coupling of the subunits **4** and **33** by amidation was followed by a highly efficient oxidation/cyclodehydration sequence to install the C16–C18 oxazole ring. The synthesis of phorboxazole B was thus completed in 28 steps along the longest linear sequence (55 total steps) from readily available starting materials. The phorboxazole B produced by this route provides ^{1}H NMR, HRMS, IR, R_f(TLC), and optical rotation data[1,34] that match those of naturally occurring phorboxazole B.

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[32] The undesired *Z* isomer was most easily removed by preparative HPLC at this stage. See the Supporting Information.
[33] References [2,4,5,7,8] report this as "6% aqueous HCl", which is ambiguous. The concentration of aqueous HCl used in the Forsyth and Williams work can also be described more precisely as 0.72 N. We thank Profs. Forsyth and Williams for clarification.
[34] $[\alpha]_D^{22} = +31\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.1\ \mathrm{g\,cm^{-3}}$, MeOH). The optical rotation of natural phorboxazole B is reported as $[\alpha]_D = +44.4\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 1.0\ \mathrm{g\,cm^{-3}}$, MeOH) (see Ref. [1]).

