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The Macrocyclic Domain of Phorboxazole A. A Stereoselective Synthesis of the C_1–C_{32} Macrolactone.

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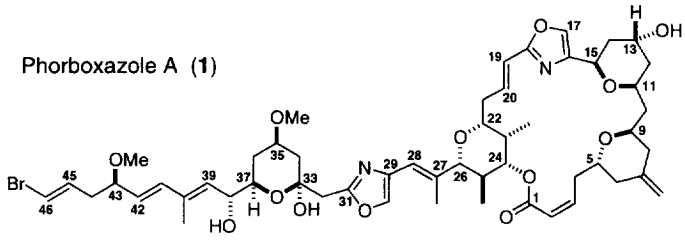
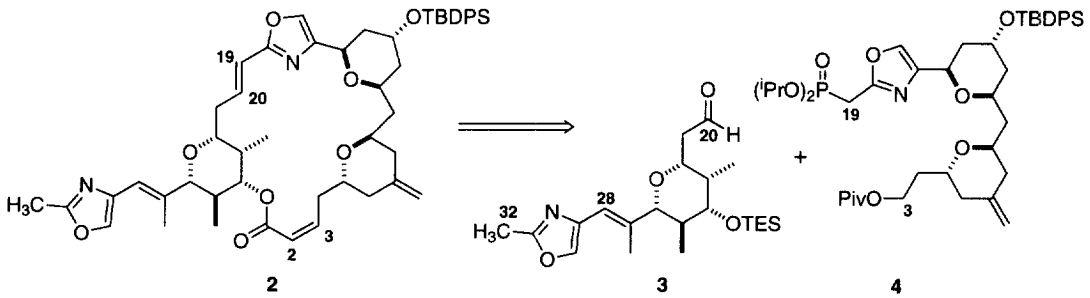
Abstract: A stereoselective synthesis of the C_1–C_{32} macrocyclic domain of phorboxazole A is described. Key steps have examined the convergent linkage of two major components for the formation of the C_{19}–C_{20} (*E*)-alkene, and the subsequent intramolecular (*Z*)-olefination at C_2–C_3 for ring closure of the macrocycle.

The phorboxazoles are exceptionally potent cytostatic agents for the entire panel of sixty NCI human tumor cell lines (GI_{50} < 1.6 nM).[1] The novel macrolide **1** contains a twenty-one membered lactone which features four heterocyclic rings and ten of the fifteen stereogenic centers of the natural product. Since the mechanism of bio-



logical activity for **1** is unclear, considerable efforts will be devoted toward an understanding of structure-activity relationships. The polyoxane-oxazole construction of the rigid macrocyclic array may offer a fundamental structural contribution for the extraordinary antitumor potency exhibited by phorboxazole A.[1a,2] As part of a convergent strategy directed toward the total synthesis of **1**,[3] we have recently developed stereoselective syntheses of the C_3–C_{19} *bis*-tetrahydropyran (**4**) and the C_{20}–C_{32} pentasubstituted tetrahydropyran (**3**).[4] In this communica-



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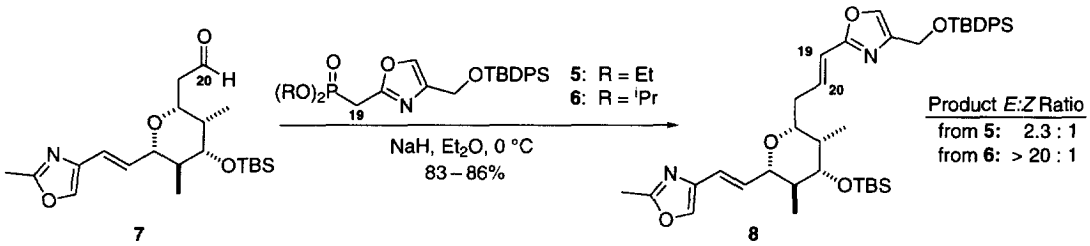
tion, we report the formation of the phorboxazole macrocycle (**2**) via our studies of stereoselective olefination reactions at C_{19}–C_{20} and C_2–C_3 for the coupling of **3** and **4**.

A study of olefination processes was implemented to provide for the formation of the C_{19}–C_{20} (*E*)-alkene of **2**. For example, the Horner-Emmons reaction of the simple derivative, ethyl phosphonate **5**, with aldehyde **7** resulted in a modest preference for the formation of *trans*-2-alkenyloxazole **8** in 83% yield (2.3:1 ratio of *E:Z* isomers).[5] By comparison, the more sterically demanding diisopropyl phosphonate **6** led to substantial improvement in the *E*-selectivity for the reaction process (20:1 ratio of *E:Z* isomers in 86% yield).



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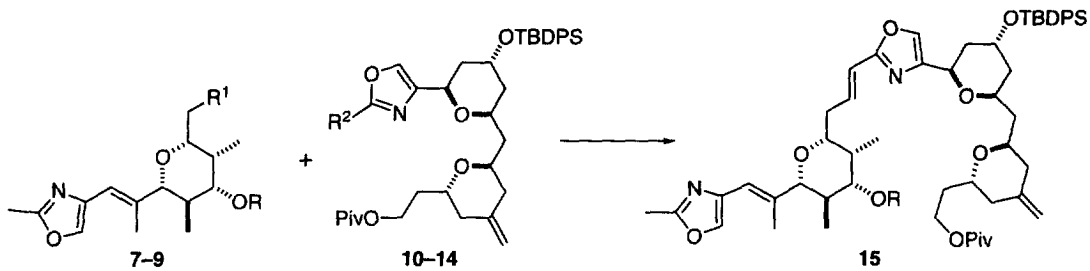
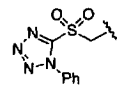
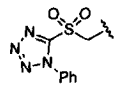
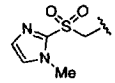
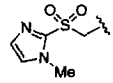
Olefination reactions using the fully elaborated *bis*-pyran oxazole component are summarized in the Table. In comparison to our model studies, these reactions exhibited a surprising trend which provided product enriched in the undesired *Z* alkene. Thus, the Horner-Emmons reaction of ethyl phosphonate **10** and aldehyde **7** (entry 1) led to formation of **15** (R = TBDMS) without stereocontrol. Use of the corresponding diisopropyl phosphonate **11** (entry 2) afforded a mixture of alkenes containing predominantly the desired *trans*-**15** (R = TES; 4:1 ratio of *E:Z*) in 85% yield. Preparative thin-layer chromatography (2:1 hexanes/ethyl acetate) facilitated the separation and individual characterization of the *E* and *Z* isomers. *E*-Alkene **15** was readily identified by the ^{1}H NMR chemical shifts of its characteristic vinylic hydrogens (δ 6.63 for $H_{C_{20}}$ and δ 6.32 for $H_{C_{19}}$; J = 16 Hz) compared to the corresponding signals observed for the *Z*-olefin (δ 6.02 for $H_{C_{20}}$ and δ 6.29 for $H_{C_{19}}$; J = 12 Hz).[6] This tendency was also apparent in Julia olefination reactions for the formation of the C_{19}–C_{20} alkene. Adaptation of the Kocienski modification[7] of the Julia condensation utilized the potassium carbanion of the *N*-phenyltetrazole sulfone **12**[8] for *in situ* elimination, and resulted in unusual *Z*-selectivity (entry 3). When the aldehyde and sulfone functionalities were reversed (entry 4), the reaction proceeded with modest stereocontrol favoring the desired *E*-alkene. Analogous experiments (entries 5 and 6) employed the Kende modification for condensation of carbanions of imidazole sulfones **9** and **14** with subsequent SmI_2-promoted reductive elimination with similar results.[9] Fortunately, our studies demonstrated that the undesired C_{19}–C_{20} *Z*-alkene was completely isomerized to the *E*-alkene upon treatment with excess PPTs (25 equiv) in absolute EtOH (reflux, 2 d). Subsequent hydrolysis of the pivaloate ester (LiOH, aqueous THF/MeOH) provided *E*-alkenyl diol **16** (see Scheme 1) in 63% yield (2 steps). Overall, the Horner-Emmons procedure of entry 2 was the most useful for advancing the synthesis effort.

Closure of the 21-membered macrolactone is described in Scheme 1. Saponification of the pivaloate ester of *trans*-**15** (R = TES) with LiOH (aqueous THF/MeOH at 22 °C) resulted in concomitant removal of the C_{24} TES ether, affording diol **16** in 92% yield. Installation of the *bis*(2,2,2-trifluoroethyl)phosphonoacetate[10] was effected with excellent conversion via a transesterification which required initial protection of the C_3 primary alcohol of **16**. Subsequent desilylation gave **17** as a key precursor for a mild oxidation[11] to the requisite phosphonate-aldehyde **18**. The Still modification[12] of the intramolecular Horner-Emmons process resulted in efficient formation (85% yield) of the macrocycle as a mixture of *Z*- and *E*-unsaturated esters (ratio 3.5:1 *Z:E*). Our spectral data for the phorboxazole macrolide **2**, as well as its corresponding (*E*)-C_2–C_3 unsaturated ester were completely consistent with ^{1}H NMR spectra kindly supplied by Professor Craig Forsyth.[13]

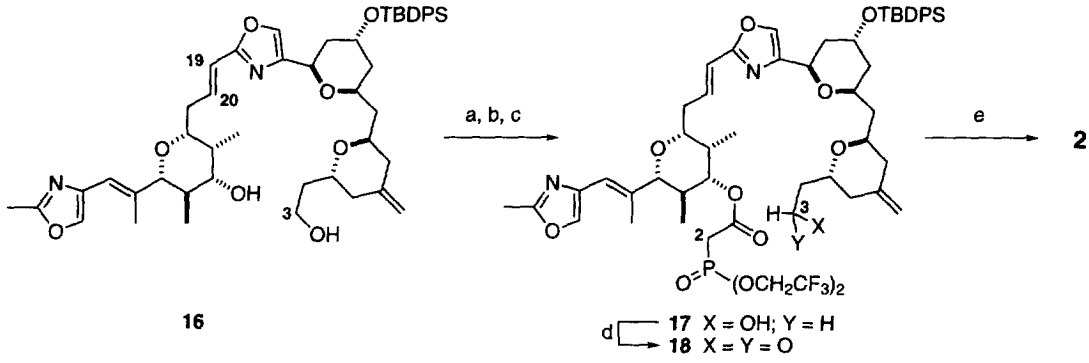
Table: C_{19}–C_{20} Alkene Synthesis[a]



Entry	Pyran (Compound, R^1)		Oxazole *Bis*-Pyran (Compound, R^2)		Reaction Conditions	Yield (%)	Selectivity (*E*:*Z*)
1	**7**	CHO	**10**	$(EtO)_2P(O)$	A	95	1 : 1
2	**7**	CHO	**11**	$(^iPrO)_2P(O)$	A	85	4 : 1
3	**7**	CHO	**12**		B	46	1 : 10
4	**8**		**13**	CHO	B	42	2 : 1
5	**7**	CHO	**14**		C	50	1 : 1
6	**9**		**13**	CHO	C	50	4.5 : 1

a. Conditions: (A) NaH, Et_2O, –10 °C → 0 °C; (B) $KN(SiMe_3)_2$, DME, –65 °C → 0 °C; (C) 1. *n*-BuLi, Et_2O, –78 °C; 2. Ac_2O, CH_2Cl_2; 3. SmI_2, THF.

Scheme 1[a]



[a]Key: (a) TBDMSCl, imid, DMF, 96%; (b) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, DMAP, toluene, reflux, 80%; (c) PPTs, EtOH, 77%; (d) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 70%; (e) K_2CO_3, 18-Crown-6, toluene, 85%.

In summary, two key bond formations have been studies leading to a highly convergent synthesis of the complex macrocyclic domain of phorboxazole A. Further refinements of this approach are underway.

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6. All new compounds were fully characterized and structures are consistent with spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS, $[\alpha]_D$).

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8. The sulfones were prepared from commercially available 1-phenyl-1*H*-tetrazole-5-thiol and 2-mercapto-1-methylimidazole (Aldrich). Mitsunobu conditions were utilized to convert alcohols to the corresponding sulfides (DIAD, Ph_3P, THF). These sulfides were oxidized to the sulfones with ammonium molybdate and 30% aqueous H_2O_2 in EtOH.

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13. The *Z*-unsaturation at C_2–C_3 of **2** is readily identified by the overlapping C_2 and C_3 vinyl hydrogen signals at δ 5.92 in the ^{1}H NMR spectrum. The corresponding *E*-lactone is characterized by individual multiplets centered at δ 6.59 and δ 5.90. We gratefully acknowledge the assistance of Professor Craig Forsyth (Department of Chemistry, University of Minnesota) for supplying proton NMR spectra for our comparisons.