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

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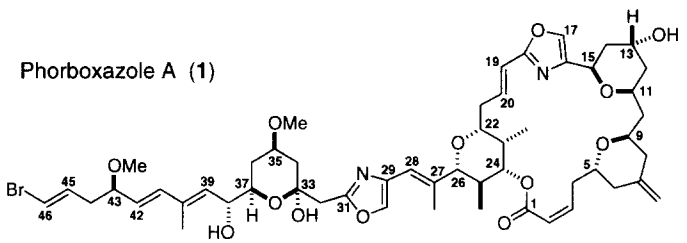
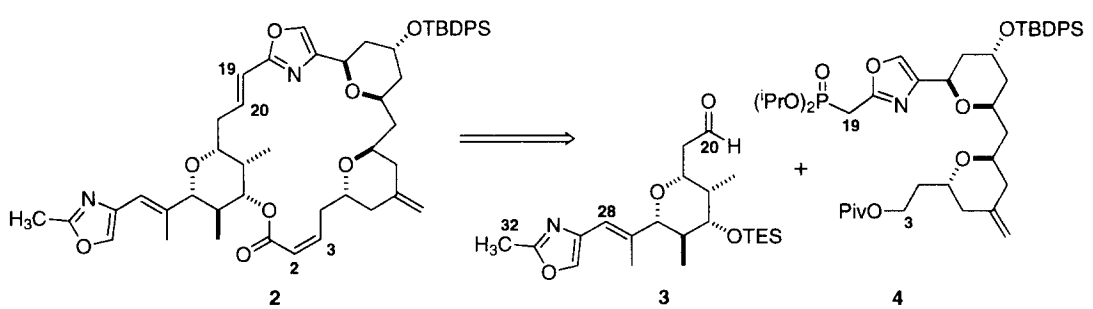
***Abstract:*** A stereoselective synthesis of the $C_1$–$C_{32}$ macrocyclic domain of phorboxazole A is described. Key steps have examined the convergent linkage of two major components for the formation of the $C_{19}$–$C_{20}$ (*E*)-alkene, and the subsequent intramolecular (*Z*)-olefination at $C_2$–$C_3$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




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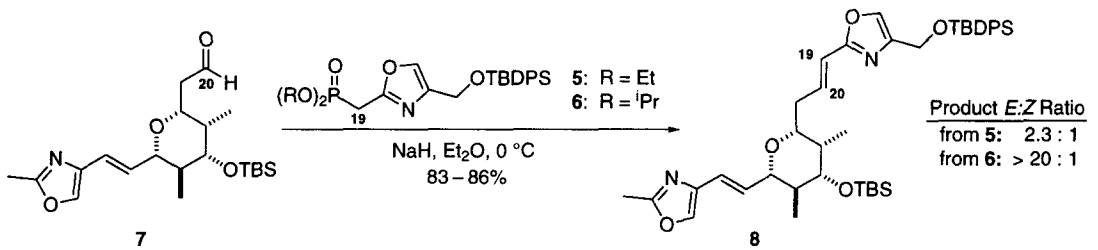
tion, we report the formation of the phorboxazole macrocycle (**2**) via our studies of stereoselective olefination reactions at $C_{19}$–$C_{20}$ and $C_2$–$C_3$ for the coupling of **3** and **4**.

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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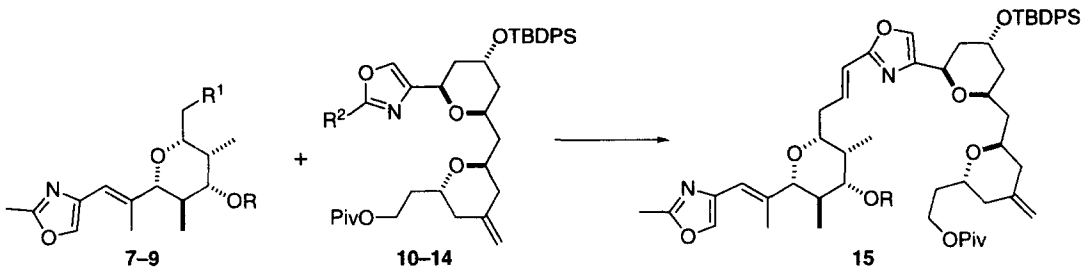
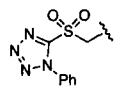
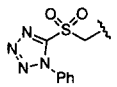
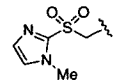
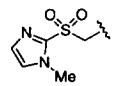
Olefination reactions using the fully elaborated *bis*-pyran oxazole component are summarized in the Table. In comparison to our model studies, these reactions exhibited a surprising trend which provided product enriched in the undesired *Z* alkene. Thus, the Horner-Emmons reaction of ethyl phosphonate **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 ($\delta$ 6.63 for $H_{C_{20}}$ and $\delta$ 6.32 for $H_{C_{19}}$; $J$ = 16 Hz) compared to the corresponding signals observed for the *Z*-olefin ($\delta$ 6.02 for $H_{C_{20}}$ and $\delta$ 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]

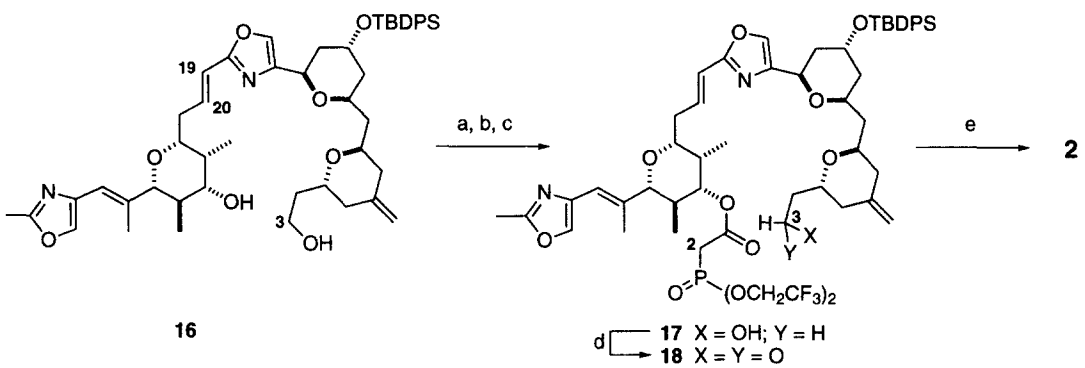
**Table: $C_{19}$–$C_{20}$ Alkene Synthesis[a]**




| 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 $\delta$ 5.92 in the $^1$H NMR spectrum. The corresponding *E*-lactone is characterized by individual multiplets centered at $\delta$ 6.59 and $\delta$ 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.