# Total Synthesis of (+)-Phorboxazole A

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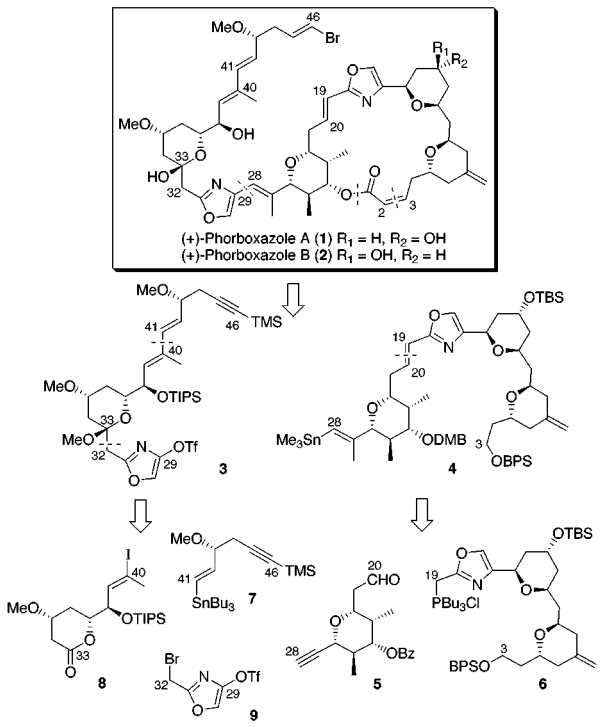
In 1995 Searle and Molinski reported the isolation of phorboxazoles A (**1**) and B (**2**), isomeric oxazole-containing macrolides, from the marine sponge *Phorbas* sp. endemic to the western coast of Australia (Scheme 1).[1] The relative and absolute stereochemistries of the phorboxazoles were secured via a combination of NMR analysis, degradation studies, and synthetic correlation.[2] When tested against the NCI panel of 60 human tumor cell lines, the phorboxazoles displayed virtually unsurpassed cytotoxicity, exhibiting a mean $GI_{50}$ of $1.58 \times 10^{-9}$ M. Although the exact mechanism of action remains unknown, studies demonstrate that phorboxazole A (**1**) arrests the cell cycle at the S phase and does not affect tubulin. Given the potent cytotoxicity and the possibility of a new mechanism of action, the phorboxazoles were selected by the NCI for in vivo trials.[2a]

The combination of the outstanding antimitotic activity, architectural complexity, and extreme scarcity has led to wide interest in the synthetic community.[3] The first total synthesis of phorboxazole A was reported by Forsyth and co-workers in 1998;[4] shortly thereafter Evans and Fitch reported the completion of phorboxazole B.[5] In 1997 we embarked on the synthesis of these challenging marine natural products; subsequently we disclosed assembly of two subtargets exploiting a modified Petasis−Ferrier union-rearrangement tactic for the stereocontrolled construction of the two *cis*-fused tetrahydropyrans.[3n,o] In this communication, we describe the synthesis of the C(3−28) vinyl stannane, the C(33−46) lactone, their union via a bifunctional oxazole linchpin, and completion of the phorboxazole A synthetic venture.

From the retrosynthetic perspective, disconnections of phorboxazole A (**1**) at the C(1) macrolactone, the C(2−3) and C(28−29) linkages led to side chain subtarget **3** and macrolide precursor **4** (Scheme 1). A Wittig transform at C(19−20) further dissected

**Scheme 1**




**4** into aldehyde **5**[6] and salt **6**, the syntheses of which were described previously.[3n,o] Continuing with this analysis, disconnection of subtarget **3** at C(32−33) and C(40−41) revealed vinyl stannane **7**, vinyl iodide **8**, and the bifunctional oxazole **9**. Construction of the C(40−41) linkage would entail a Stille coupling, while oxazole **9**, possessing the pseudobenzylic bromide and the triflate moieties, was envisaged as a novel bidirectional linchpin to unite the side chain with the macrocycle. Importantly, the coupling strategy possessed considerable flexibility from the tactical perspective (vide infra).

Assembly of the side chain of phorboxazole began with known Brown allylation[7] adduct (+)-**10** (Scheme 2).[8,9] Methylation of the hydroxyl [MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)],[10] followed by ozonolysis furnished aldehyde (−)-**11** in 81% yield for two steps. Although Wittig olefination of (−)-**11** with methyl alkyne **12a** (R = Me) led to a disappointing mixture of olefins (*E*/*Z* ca. 2.2:1), condensation with the commercially available phosphonate salt **12b** (R = TMS) in THF afforded enyne (−)-**13** in good yield with acceptable selectivity (97%, 5.5:1 *E*/*Z*). The use of a $PhCH_3$/THF (1:1) solvent system improved the *E*/*Z* ratio at the expense of both yield and reproducibility (72%, 7.5:1 *E*/*Z*). Removal of the TMS group ($K_2CO_3$), followed by Sharpless dihydroxylation[11] of the enyne[12,13] (AD-Mix $\beta$; 7:1 dr) and acetonide formation then provided (+)-**14**. Terminal methylation

(1) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126.

(2) (a) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (b) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879.

(3) (a) Lee, C. S.; Forsyth, C. J. *Tetrahedron Lett.* **1996**, *37*, 6449. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672. (c) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998**, *39*, 183. (d) Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319. (e) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099. (f) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185. (g) Wolbers, P.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 1905. (h) Misske, A. M.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 4315. (i) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287. (j) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291. (k) Wolbers, P.; Hoffman, H. M. R. *Synthesis*, **1999**, *5*, 797. (l) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87. (m) Wolbers, P.; Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527. (n) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, 1, 909. (o) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, 1, 913. (p) Wolbers, P.; Hoffman, H. M. R.; Sasse, F. *Synlett* **1999**, *11*, 1808. (q) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469. (r) Pattenden, G.; Plowright, A. T. *Tetrahedron Lett.* **2000**, *41*, 983. (s) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (t) Williams, D. R.; Clark, M. P.; Emde, U.; Berliner, M. A. *Org. Lett.* **2000**, *2*, 3023. (u) Greer, P. B.; Donaldson, W. A. *Tetrahedron Lett.* **2000**, *41*, 3801. (v) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533.

(4) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597.

(5) (a) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536. (b) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

(6) Although aldehyde **5** was the original subtarget for the central pyran, revised aldehyde (+)-**23** was ultimately employed (Scheme 4).

(7) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1991**, *63*, 307.

(8) Clive, D. L. J.; Keshava Murthy, K. S.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914 (see Supporting Information).

(9) The enantiomeric excess (ee) of alcohol (+)-**10** was determined to be 94% via Mosher ester analysis: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(10) The biphenyltertbutyl silyl (BPS) moiety had a tendency to migrate to the secondary hydroxyl when more standard conditions (NaH, MeI) were employed.

(11) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

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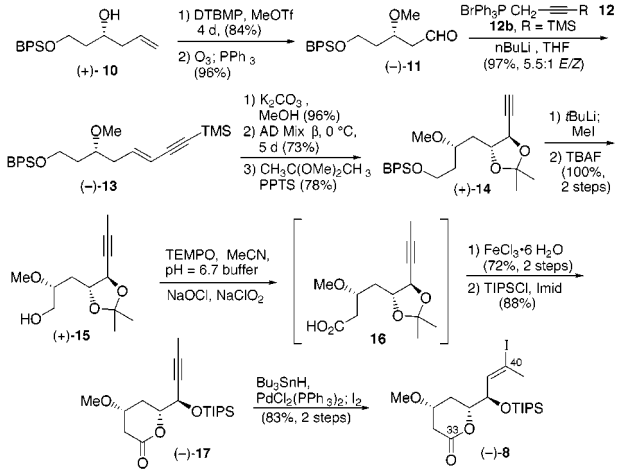
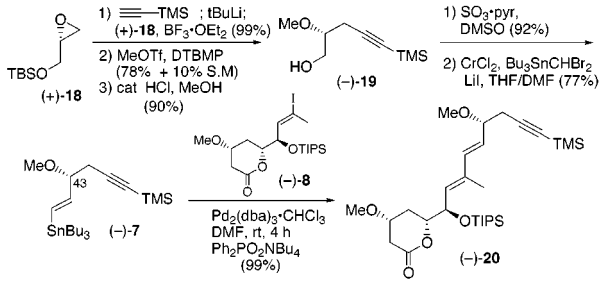
of the alkyne (*t*BuLi; MeI) followed by desilylation (TBAF; 100% yield, 2 steps) next led to alcohol (+)-**15**, which upon TEMPO oxidation[14] afforded an unstable carboxylic acid **16**;[15] immediate hydrolysis of the acetonide with concomitant cyclization ($FeCl_3$·6 $H_2O$) and protection of the remaining secondary hydroxyl (TIPSCl, imid) furnished (−)-**17**. A two-step palladium-promoted hydrostannylation/iodination[16] protocol completed construction of the desired vinyl iodide (−)-**8** (83% yield, 2 steps).[17] Additionally, 10−15% of the internal stannane was recovered after iodination.

**Scheme 2**



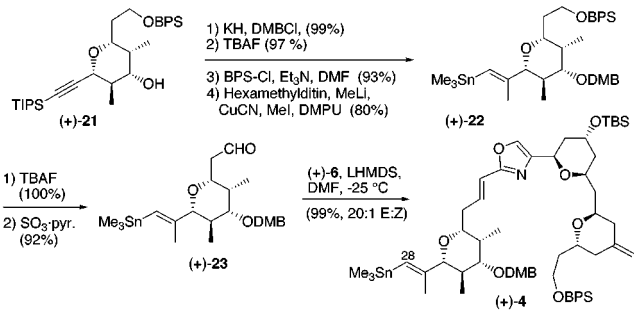

Assembly of the Stille coupling partner (−)-**7** began with known TBS-glycidol (+)-**18** (Scheme 3).[18] Exposure to lithium TMS acetylide in the presence of $BF_3$·$OEt_2$,[19] methylation (MeOTf, DTBMP), and selective removal of the TBS group in the presence of the TMS alkyne (cat. HCl, MeOH) furnished known alcohol (−)-**19**[20] (69% yield, 3 steps). Parikh−Doering[21] oxidation then provided the corresponding aldehyde without epimerization; alternate oxidation protocols (i.e., Swern) led to epimerization at C(43).[22] Hodgson homologation[23] ($CrCl_2$, $Bu_3SnCHBr_2$, LiI, THF/DMF) of the derived aldehyde next afforded vinyl stannane (−)-**7** as a single isomer (77%). The crucial Stille coupling[24] of (−)-**7** and vinyl iodide (−)-**8** was then achieved with $Pd_2(dba)_3$·$CHCl_3$ in the presence of $Ph_2PO_2NBu_4$[25] (DMF, room temperature, 4 h) to furnish (−)-**20** in near quantitative yield.

**Scheme 3**



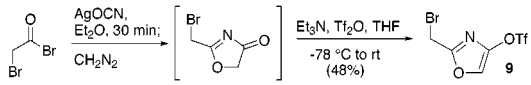

Extensive experimentation demonstrated the necessity of early installation of the C(28) vinyl stannane; thus vinyl stannane **4** was prepared as outlined in Scheme 4. Toward this end, alcohol (+)-**21**[3o] was subjected to hydroxyl protection (DMBCl, KH) and desilylation (TBAF); subsequent exposure to the tin cuprate derived from hexamethylditin (MeLi, CuCN) followed by methylation (MeI, DMPU) provided (+)-**22** in excellent overall yield (71%; 4 steps). Desilylation (TBAF), oxidation ($SO_3$·pyr), and Wittig olefination of the derived aldehyde (+)-**23** with (+)-**6** then proceeded smoothly to afford alkene (+)-**4** (20:1 E:Z). Unfortunately, all attempts to introduce the C(1−2) moiety, involving removal of the BPS group and oxidation to the C(3) aldehyde, proved unsuccessful due presumably to the sensitivity of the trimethyl tin moiety to the oxidative conditions. We therefore turned to the union of the side chain fragment (−)-**20** with (+)-**4**, exploiting the bifunctional oxazole linchpin **9**. This possibility nicely demonstrated the flexibility of the overall coupling strategy.

**Scheme 4**




The required oxazole **9** was prepared exploiting a method developed by Sheehan in 1949 (Scheme 5) for the synthesis of oxazolones.[26] Bromoacetyl bromide was exposed to silver isocyanate (30 min, $Et_2O$), filtered, and then subjected to alcohol-free diazomethane;[27] immediate triflation ($Et_3N$, $Tf_2O$, THF, −78 °C to room temperature)[3q] furnished triflate **9** in 48% overall yield.[28]

**Scheme 5**




The stage was now set for the union of (+)-**4** with (−)-**20** utilizing **9**. After optimization we found that *i*-PrMgCl promoted the coupling of bromide **9** with lactone (−)-**20** to afford a single hemiketal[29] in excellent yield (Scheme 6). Presumably, Grignard exchange generates the metalated oxazole that subsequently attacks the lactone. Interestingly, premixing of the coupling

(12) For use of the Sharpless AD reaction with enynes, see: Jeong, K.-S.; Sjo, P.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 3833. Diminished diastereoselectivity with homoallylic enynols has been reported: Caddick, S.; Shanmugathasan, S.; Brasseur, D.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 5735.

(13) Since the *Z* isomer was markedly less reactive than the *E* isomer in the dihydroxylation reaction, the *E/Z* mixture could be used directly.

(14) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, 2564.

(15) Occasionally, the carboxylic acid would undergo cyclization to the corresponding lactone during workup or chromatography.

(16) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(17) Exposure of alkyne (−)-**17** to the Schwartz hydrozirconation and subsequent exposure to NIS, $I_2$, or NBS failed to afford the desired vinyl halide; instead, starting material or decomposition was observed.

(18) Prepared in one step from *S*-glycidol; see: Cywin, C. L.; Webster, F. X.; Kallmerten, J. *J. Org. Chem.* **1991**, *56*, 2953.

(19) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

(20) Alcohol (−)-**19** was first prepared by Pattenden et al. from malic acid in 11 steps (ref 3e); Williams later prepared (−)-**19** (ref 3t).

(21) Parikh, J. R.; v. E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(22) Epimerization was determined by reduction ($BH_3$·THF) to alcohol (−)-**19** and comparison of optical rotations.

(23) Hodgson, D. M.; Boulton, L. T.; Maw, G. N. *Tetrahedron* **1995**, *51*, 3713.

(24) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Organic Reactions*; Wiley: New York, 1997. (b) Stille, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(25) This salt was introduced by Liebeskind to remove $Bu_3SnI$ from the reaction mixture and thereby accelerate the Stille coupling process: Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

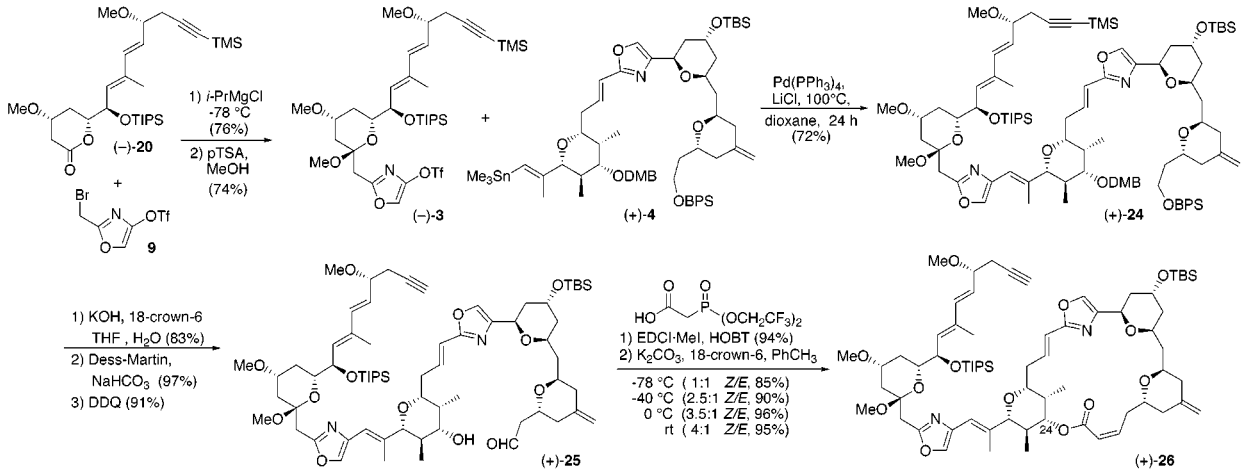
(26) Sheehan, J. C.; Izzo, P. T. *J. Am. Chem. Soc.* **1949**, *71*, 4059.

(27) (a) DeBoer, T. J.; Backer, H. J. *Org. Synth.* **1956**, *36*, 16. (b) Aldrich Technical Bulletin AL-121.

(28) In this three-step process, intermediates were not purified or isolated; thus, the assembly of **9** is possible in a matter of hours.

(29) Presumably, the sterochemical outcome is due to anomeric effects; see: Bonner, W. A. *J. Am. Chem. Soc.* **1959**, *81*, 1448.

**Scheme 6**



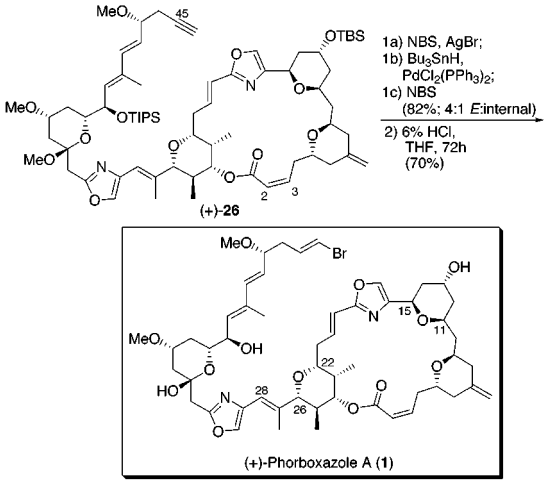

partners before addition of *i*-PrMgCl was required to minimize the dimerization of **9** (arising from the electrophilic nature of unreacted **9**).[30] Methyl ketal formation (*p*TSA, MeOH, 35 °C) completed the synthesis of the C(29−41) side chain triflate (−)-**3**.

Stille coupling of (−)-**3** with vinyl stannane (+)-**4** [$Pd(PPh_3)_4$, LiCl, 100 °C, 24 h] furnished adduct (+)-**24** in a 72% yield (Scheme 6). Selective removal of the BPS group (KOH, 18-cr-6), oxidation (Dess−Martin), and removal of the DMB group (DDQ) then afforded hydroxyaldehyde (+)-**25**. Appendage of a C(1−2) phosphonate moiety[31] at C(24), followed by a Still-modified Horner−Emmons macrocyclization[32] provided (+)-**26**; interestingly the *Z*/*E* selectivity improved with higher temperature.[33]

Having arrived at the complete phorboxazole skeleton, access to the terminal vinyl bromide proved to be an unexpected challenge. Radical promoted hydrostannylation ($Bu_3SnH$, AIBN, Δ; or $Bu_3SnH$, $Et_3B$, room temperature), although providing a mixture of the external to internal vinyl stannanes (4:1), led to isomerization at the C(2−3) olefin. Alternatively, palladium-mediated hydrostannylation [$PdCl_2(PPh_3)_2$, $Bu_3SnH$; NBS] gave predominately the internal [C(45)] bromide, albeit with no C(2,3) isomerization. Success was eventually found in the three-step procedure of Guibe,[16] which exploited the terminal alkynyl bromide for enhanced diastereoselectivity. Global deprotection (6% HCl, THF, 72 h) then afforded (+)-phorboxazole A (**1**), which displayed spectral data identical in all respects to that reported for the natural material [$^1$H NMR (600 MHz), COSY, ROESY, HRMS, UV λ max, optical rotation).

In summary, a highly convergent, stereocontrolled total synthesis of (+)-phorboxazole A (**1**) has been achieved. Highlights

**Scheme 7**




of the synthetic venture include the use of modified Petasis−Ferrier rearrangements for the effective assembly of both the C(11−15) and C(22−26) *cis*-tetrahydropyan rings; the design, synthesis, and application of a novel bifunctional oxazole linchpin; and the preparation and Stille coupling of a C(28) trimethylstannane. The longest linear sequence leading to (+)-phorboxazole A (**1**) was 27 steps, with an overall yield of 3%.

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**Supporting Information Available:** Spectroscopic and analytical data for compounds **1**, **4**, **7**−**9**, **20**, and **22**−**26**, and selected experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0105055

(30) Dimerization was also observed under inverse addition conditions (i.e., slow addition of the oxazole to a −100 °C solution of *t*BuLi).

(31) Pickering, D. A. Ph.D. Thesis, University of Minnesota, 1996.

(32) (a) Stil, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405; (b) For the use of $K_2CO_3$/18-crown-6 in Horner-Emmons reactions, see: Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. Also see: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.

(33) We suspect that higher temperatures accelerate collapse of the intermediate oxaphosphatane, thereby minimizing equilibration to the more stable *E* isomer.