Total Synthesis of (+)-Phorboxazole A

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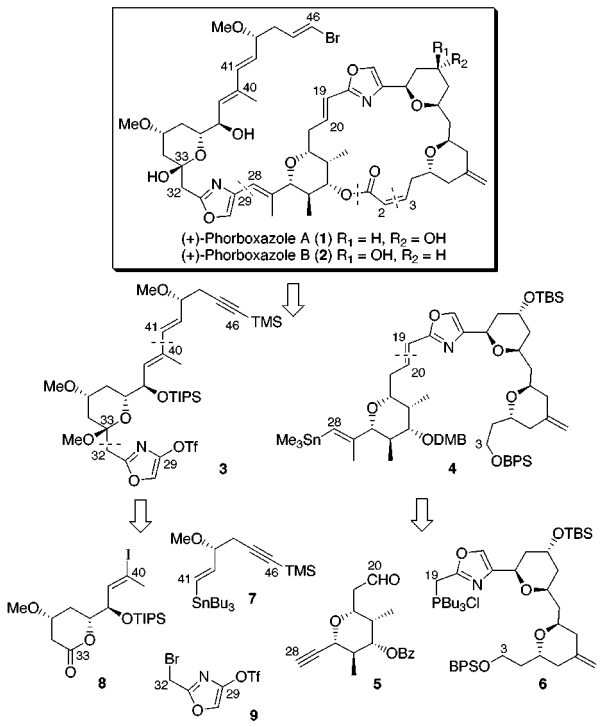
In 1995 Searle and Molinski reported the isolation of phorboxazoles A (**1**) and B (**2**), isomeric oxazole-containing macrolides, from the marine sponge *Phorbas* sp. endemic to the western coast of Australia (Scheme 1).[1] The relative and absolute stereochemistries of the phorboxazoles were secured 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 1.58×10^{-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 β; 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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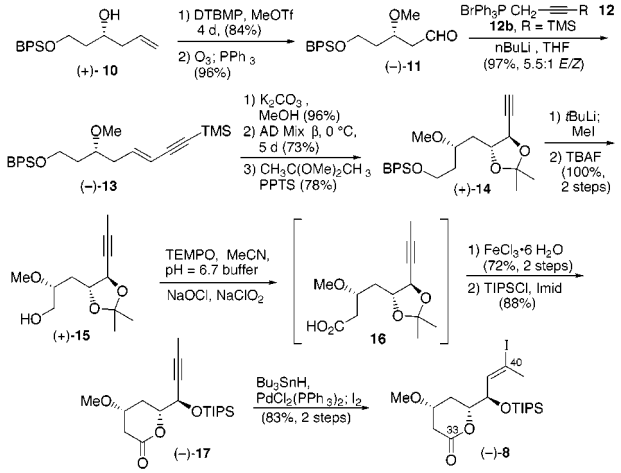
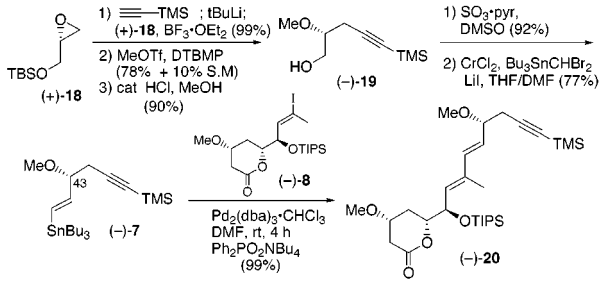
of the alkyne (*t*BuLi; MeI) followed by desilylation (TBAF; 100% yield, 2 steps) next led to alcohol (+)-**15**, which upon TEMPO oxidation[14] afforded an unstable carboxylic acid **16**;[15] immediate hydrolysis of the acetonide with concomitant cyclization ($FeCl_3$·6 H_2O) and protection of the 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



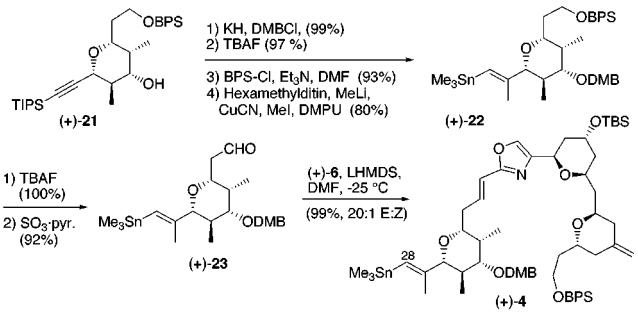
Assembly of the Stille coupling partner (−)-**7** began with known TBS-glycidol (+)-**18** (Scheme 3).[18] Exposure to lithium TMS acetylide in the presence of BF_3·OEt_2,[19] methylation (MeOTf, DTBMP), and selective removal of the TBS group in the presence of the TMS alkyne (cat. HCl, MeOH) furnished 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



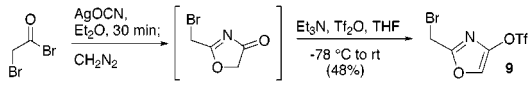
Extensive experimentation demonstrated the necessity of early installation of the C(28) vinyl stannane; thus vinyl stannane **4** was prepared as outlined in Scheme 4. Toward this end, alcohol (+)-**21**[3o] was subjected to hydroxyl protection (DMBCl, KH) and desilylation (TBAF); subsequent exposure 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.

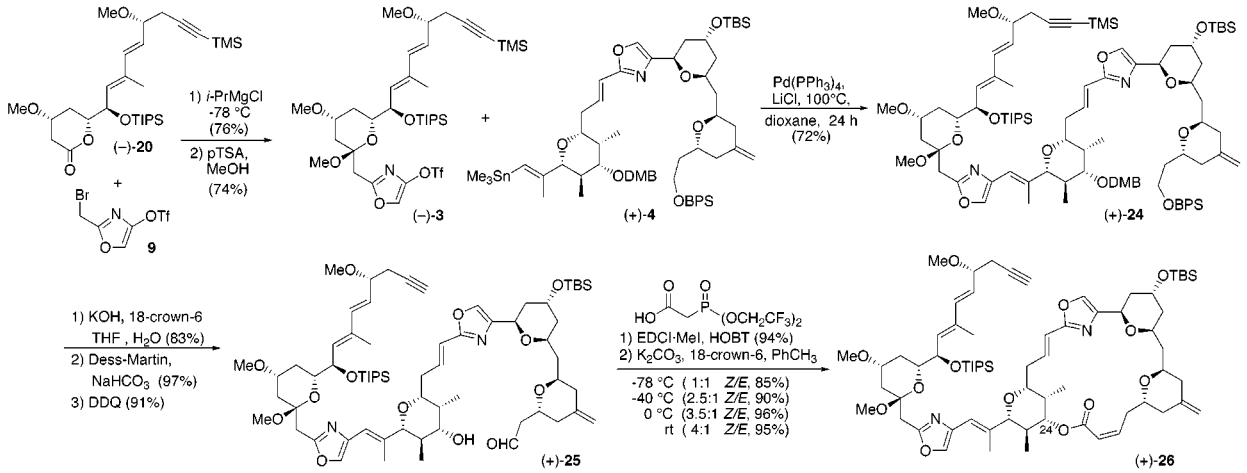
(26) Sheehan, J. C.; Izzo, P. T. *J. Am. Chem. Soc.* **1949**, *71*, 4059.

(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



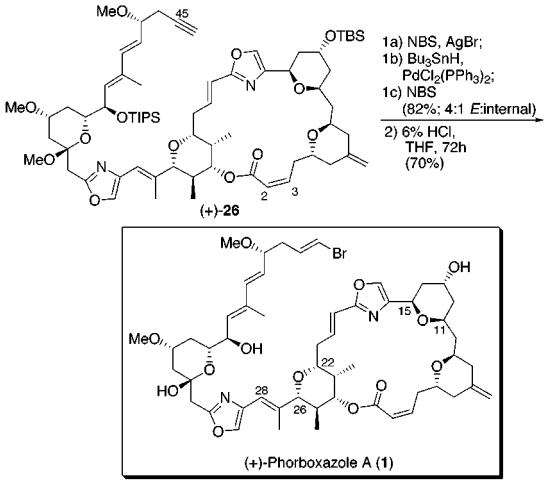
partners before addition of *i*-PrMgCl was required to minimize the dimerization of **9** (arising from the electrophilic nature of unreacted **9**).[30] Methyl ketal formation (*p*TSA, MeOH, 35 °C) completed the synthesis of the C(29−41) side chain triflate (−)-**3**.

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%.

Acknowledgment. Support was provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033. An American Chemical Society, Division of Organic Chemistry Fellowship (funded by DuPont Pharmaceuticals, Inc.) is also gratefully acknowledged (K.P.M.).

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.

Total Synthesis of (+)-Phorboxazole A Exploiting the Petasis−Ferrier Rearrangement

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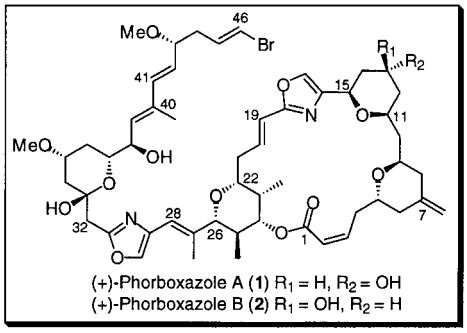
Abstract: A highly convergent, stereocontrolled total synthesis of the potent antiproliferative agent (+)-phorboxazole A (**1**) has been achieved. Highlights of the synthesis include: modified Petasis−Ferrier rearrangements for assembly of both the C(11−15) and C(22−26) *cis*-tetrahydropyran rings; extension of the Julia olefination to the synthesis of enol ethers; the design, synthesis, and application of a novel bifunctional oxazole linchpin; and Stille coupling of a C(28) trimethyl stannane with a C(29) oxazole triflate. The longest linear sequence leading to (+)-phorboxazole A (**1**) was 27 steps, with an overall yield of 3%.

Marine sponges comprise a rich source of architecturally complex, biomedically important natural products; examples include the spongistatins, discodermolide, and the tedanolides.[1] Despite the structural complexity, the scarcity of these molecules in conjunction with their medicinal importance continues to prompt intense synthetic campaigns. During a recent search for novel marine antifungals, Searle and Molinski[2] identified a methanolic extract from the sponge *Phorbas* sp. which displayed significant activity against *Candida albicans.* Bioassay-guided extraction, flash chromatography, and subsequent reverse-phase HPLC afforded two isomeric macrolides termed (+)-phorboxazoles A (**1**) and B (**2**). The structures of the phorboxazoles, including relative and absolute stereochemistry, were determined via a combination of NMR analyses, degradation studies, and synthetic correlations.[3]



The bioactivity profile of the phorboxazoles proved exceptional. In addition to the antifungal activity, the phorboxazoles displayed antibiotic activity against *saccharomyces carlsbergensis.* However, it was the antiproliferative activity that elevated the phorboxazoles to the level of premier medicinal targets. Bioassays against the National Cancer Institute panel of 60 human solid tumor cell lines revealed extraordinary activity *against the entire panel*;[2] the mean GI_{50} value was 1.58×10^{-9} M for both **1** and **2**.[3a] Some cell lines were completely inhibited at the lowest level tested.[2] Particularly noteworthy, phorboxazole A (**1**) inhibited the human colon tumor cell line HCT-116 and the breast cancer cell line MCF7 with GI_{50} values of 4.36×10^{-10} M and 5.62×10^{-10} M, respectively. These data place the phorboxazoles in the company of the spongistatins,[1a] collectively the most potent cytostatic agents discovered to date.

Although the precise biochemical mode of action remains undefined, (+)-phorboxazole A (**1**) is known to arrest the cell cycle in S phase but does not inhibit tubulin polymerization or interfere with the integrity of microtubules. Unfortunately, further biological analysis is not possible, because access to the producing sponge is currently restricted.[4] Thus, the phorboxazoles will be only available via total synthesis. Not surprisingly, the novel architecture combined with the impressive bioactivity has attracted wide attention in the synthetic community,[5] including our own interest.[6] In 1998, Forsyth and co-workers[4] published the first total synthesis of (+)-phorboxazole A (**1**); shortly thereafter, Evans and Fitch reported completion of (+)-

(1) (a) Spongistatin: Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (b) Discodermolide: Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. Correction: Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1991**, *56*, 1346. (c) Tedanolide: Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.

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

(3) (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.

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

(5) (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.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905. (h) Misske, A. M.; Hoffmann, 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.; Hoffmann, H. M. R. *Synthesis* **1999**, 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) Wolbers, P.; Hoffmann, H. M. R.; Sasse, F. *Synlett* **1999**, *11*, 1808. (o) Pattenden, G.; Plowright, A. T. *Tetrahedron Lett.* **2000**, *41*, 983. (p) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469. (q) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (r) Williams, D. R.; Clark, M. P.; Emde, U.; Berliner, M. A. *Org. Lett.* **2000**, *2*, 3023. (s) Greer, P. B.; Donaldson, W. A. *Tetrahedron Lett.* **2000**, *41*, 3801. (t) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533. (u) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693.

10.1021/ja011604l CCC: $20.00
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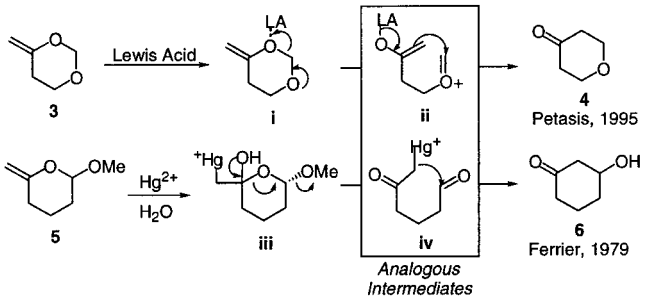
phorboxazole B (**2**).[7] Herein, we disclose a full account of the total synthesis of (+)-phorboxazole A (**1**) recently completed in our laboratory.[6c] A central feature of this synthetic venture was the exploitation of the Petasis−Ferrier rearrangement for the construction of the two 2,6-*cis*-tetrahydropyran rings resident in the phorboxazole macrolide ring.

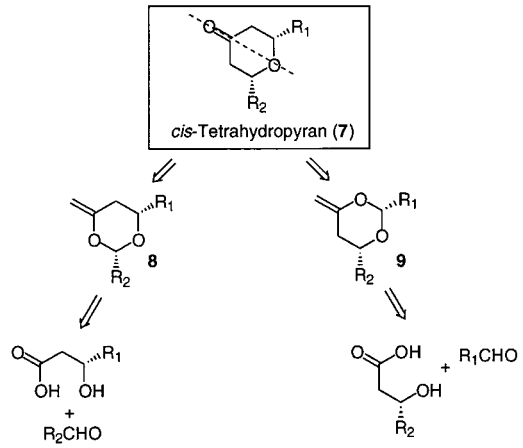
Petasis−Ferrier Rearrangement. In 1996, Petasis reported that the acid-promoted rearrangement of enol acetals to tetrahydropyranones (e.g., **3**→**4**, Scheme 1) proceeds via fragmentation, followed by endo cyclization onto an oxocarbenium (**ii**),[8] a reaction closely related to the earlier Ferrier Type-II[9] enol ether rearrangement (e.g., **5**→**6**) induced by mercuric ion.

Scheme 1



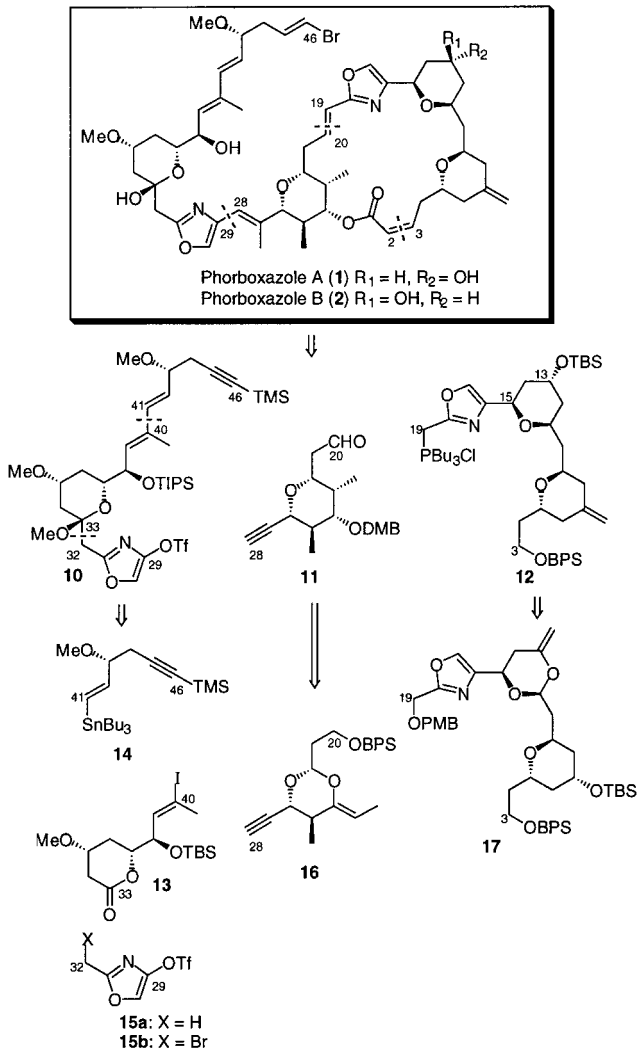
Inspection of the Petasis−Ferrier rearrangement in the context of complex molecule synthesis revealed two important attributes. First, construction of the enol acetal rearrangement substrates comprises an ideal linchpin tactic for complex fragment assembly; second, the latent element of symmetry inherent in the target *cis*-tetrahydropyranones permits rearrangement of either enol acetal **8** or **9** (Scheme 2). Both attributes provide considerable latitude for fragment union and thereby *cis*-tetrahydropyranone construction.

Scheme 2



Synthetic Analysis. In addition to the two 2,6-*cis*-fused tetrahydropyrans (vide supra), the phorboxazoles present a wide array of architectural features, including a 21-membered macrolactone, a *trans*-fused tetrahydropyran, two oxazoles, and six olefinic units: one *Z* and two *E* alkenes, an exomethylene, a diene, and an *E*-vinyl bromide. From the retrosynthetic perspective (Scheme 3), we envisioned disconnection of the phorboxazoles at C(2−3), C(19−20), and C(28−29) to reveal three subtargets (**10**, **11**, and **12**) of comparable structural complexity. In the synthetic sense, fragments **11** and **12** would be united via a Wittig reaction. Continuing with this analysis, disconnection of side chain **10** at C(40−41) and C(32−33) would furnish subtargets **13**, **14**, and **15**. In the forward sense, vinyl stannane **14** and vinyl iodide **13** could be coupled via a Stille reaction. For union of the side chain to the macrocycle, we planned to exploit oxazole triflate **15a**,**b** as a novel bidirectional linchpin (vide infra). Finally, the cornerstone for construction of the central C(20−28) tetrahydropyran, **11**, and bistetrahydropyran **12** would be the Petasis−Ferrier rearrangements, respectively, of vinyl acetals **16** and **17**. Importantly, the overall synthetic strategy held the promise of considerable flexibility for fragment assembly, their union, endgame operations (vide infra), and the construction of analogues.

Scheme 3



Bistetrahydropyran 12: The C(3−19) Subtarget. To implement the first Petasis−Ferrier rearrangement, we sought enol acetal **17**. Our point of departure entailed preparation of *trans*-tetrahydropyran **24** from known aldehyde **18** (Scheme 4).[10]

(6) (a) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913. (c) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834.

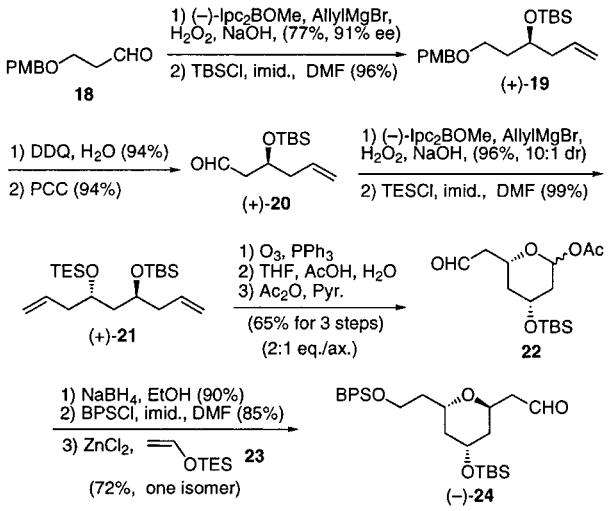
(7) (a) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536. (b) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

(8) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141.

(9) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.

(10) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

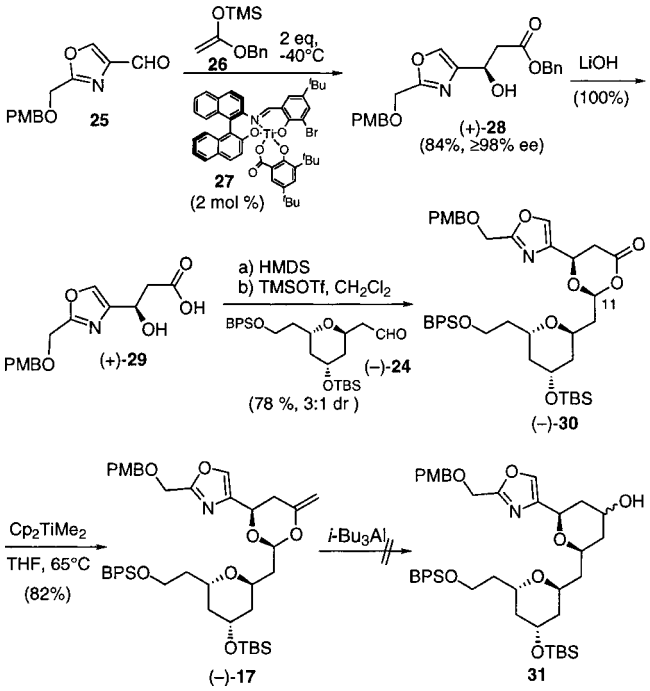
Scheme 4



Toward this end, Brown asymmetric allylation[11] and protection (TBSCl) of the resultant alcohol furnished silyl ether (+)-**19** (91% ee via Mosher ester analysis).[12] Oxidative removal of the PMB ether (DDQ, H_2O)[13] followed by oxidation (PCC) afforded aldehyde (+)-**20**; a second Brown allylation orchestrated the requisite 1,3-trans stereochemical relationship with excellent selectivity (96%, 10:1 diastereomeric ratio, dr). Differential hydroxyl protection (TESCl, imidazole) then furnished silyl ether (+)-**21**, which upon exhaustive ozonolysis generated an unstable bisaldehyde; immediate deprotection (AcOH, THF, H_2O) with concomitant cyclization and acetylation yielded **22** as an inconsequential mixture (2:1 eq/ax) of acetals (65%, 3 steps). Reduction ($NaBH_4$), protection of the resultant alcohols (BPSCl), and axial addition of silyl enol ether **23**[14] then led to aldehyde (−)-**24** as a single isomer (72%). The relative stereochemistry of (−)-**24** was established via two-dimensional NOE experiments.[15]

Construction of β-hydroxyacid **29**, required for elaboration of the Petasis−Ferrier substrate **17** (Scheme 5), entailed condensation of oxazole aldehyde **25**, prepared independently in both the Williams[5i] and our laboratories, with the known benzyl trimethylsilylketene acetal **26**[16,17] exploiting the Carreira enantioselective aldol[18] tactic to afford benzyl ester (+)-**28** in 84% yield with ≥ 98% ee.[12] Removal of the benzyl ester (LiOH; ~100%), followed by dioxanone construction (one-pot), initiated by bis-silylation of (+)-**29** with hexamethyldisilazane (HMDS), followed immediately by TMSOTf -promoted[19] condensation with aldehyde (−)-**24**, afforded *cis*-dioxanone (−)-**30** in 61% yield, along with 18% of the trans isomer, the latter readily removed by flash chromatography. Methylenation exploiting the Petasis−Tebbe reagent (Cp_2TiMe_2)[20] then led to rearrangement substrate (−)-**17**. Unfortunately, all attempts to effect the rearrangement employing the conditions prescribed by Petasis[8] failed to produce the desired 2,6-*cis*-tetrahydropyran.

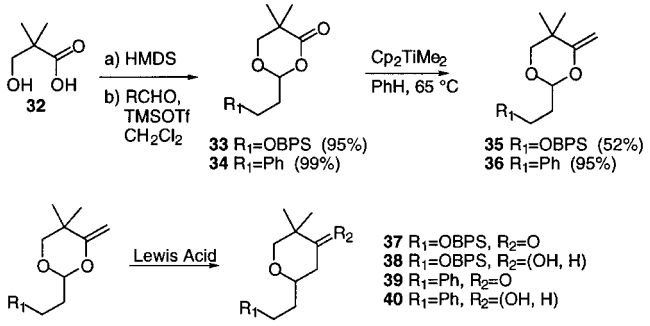
Scheme 5



Improved Conditions for the Petasis−Ferrier Rearrangement. Failure of the prescribed Petasis conditions led us to explore other Lewis acids. Increasing the Lewis acidity was of primary concern. The lack of selectivity of the subsequent carbonyl reduction, inherent with *i*-Bu_3Al, was also identified as a significant liability. Thus, promoters incapable of reducing the initially derived tetrahydropyranone were sought.

To preserve valuable intermediates, we prepared model enol ethers **35** and **36** (Scheme 6). A variety of Lewis acids were

Scheme 6



Lewis Acid	R_1=Ph	R_1=OBPS
i-Bu_3Al	87%	85%
$ZnCl_2$	25%	0%
Me_2AlCl	**95%**	**92%**
$MeAlCl_2$	60%	-
$BF_3{\cdot}Et_2O$	0%	-
$TiCl_4$	0%	-
$TiCl_2(O\text{-}iPr)_2$	0%	-
$SnCl_4$	0%	-

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

(12) (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.

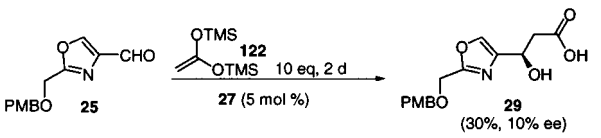
(13) Oikawa, Y.; Yushioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(14) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, 3791.

(15) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546.

(16) Slougui, N.; Rousseau, G.; Conia, J.-M. *Synthesis* **1982**, 58.

(17) The condensation was first attempted using bistrimethylsilyl ketene acetal **122**, to obtain the desired β-hydroxy acid **29** directly; unfortunately, this approach met with little success (30% yield, 10% ee).

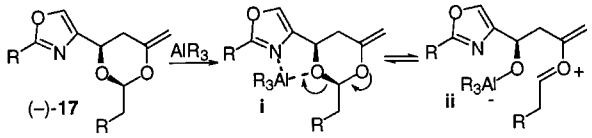


(18) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837.

screened; best results were obtained with Me_2AlCl. Importantly, Me_2AlCl did not reduce the derived ketone. Moreover, the *tert*-butylbiphenyl (BPS) ether moiety (e.g., **35**) was found to tolerate the rearrangement conditions, an important requirement for application of the Petasis−Ferrier transform in complex molecule synthesis.

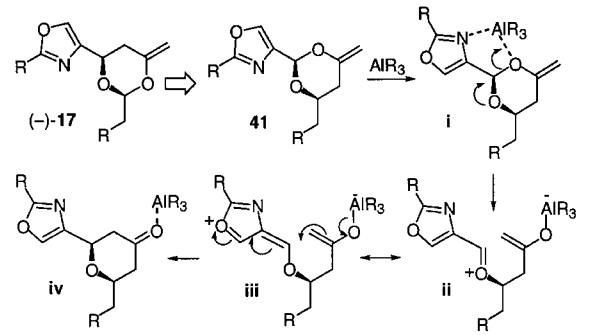
Notwithstanding the improved conditions, enol ether (−)-**17** again failed to undergo rearrangement. We surmised that preferred coordination of the Me_2AlCl promoter with the neighboring oxazole nitrogen precluded productive Lewis acid chelation to the requisite enol ether oxygen in (−)-**17**, thereby preventing rearrangement (Scheme 7).

Scheme 7



Productive Chelation. To circumvent the unproductive chelation, we examined rearrangement substrate **41**, obtained by transposition of the enol ether oxygen permitted by the symmetry inherent in the linchpin construction of tetrahydropyranones (Scheme 8). In this way, initial coordination of bidentate[21] Lewis acid Me_2AlCl with the oxazole nitrogen would allow productive activation of the enol ether oxygen (**i**), liberating the aluminum enolate, which in turn would rearrange to the tetrahydropyranone (**iv**). The transposed substrate (**41**) possessed two additional advantages: the oxazole acetal could lead to a resonance-stabilized oxocarbenium ion (i.e., **iii**), and the rearrangement would proceed via a more facile 6-*exo*-trig ring closure,[22] compared to the 6-*endo* closure required for the unactivated Petasis−Ferrier vinyl acetals.

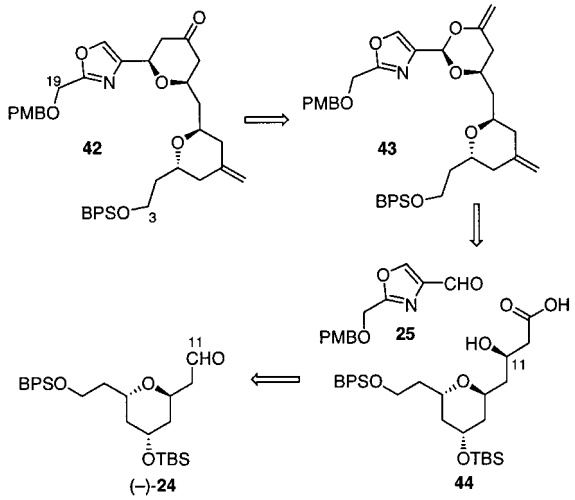
Scheme 8



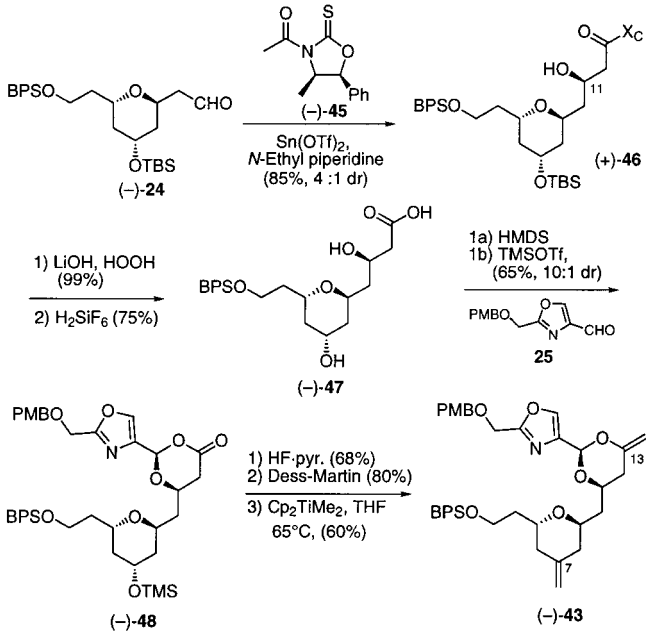
Our attention thus turned to rearrangement substrate **43**, which was readily constructed from previously prepared aldehyde **25** and β-hydroxyacid **44** (Scheme 9). The Nagao acetate aldol[23] protocol was selected to install the C(11) stereocenter in **44** (Scheme 10). Alcohol (+)-**46** was obtained in 85% yield (4:1 dr, unoptimized).

Hydrolytic removal of the auxiliary exploiting basic hydrogen peroxide, followed by selective desilylation (H_2SiF_6),[24] then led

Scheme 9



Scheme 10



to β-hydroxy acid (−)-**47**. The previously developed two-step sequence involving initial bis-silylation (HMDS) of (−)-**47** followed by TMSOTf-catalyzed[19] condensation with aldehyde **25** furnished dioxanone (−)-**48** in 65% yield (10:1 dr). Selective removal of the trimethylsilyl group (HF·pyr), oxidation (Dess−Martin),[25] and treatment with excess Cp_2TiMe_2 (5 equiv) installed both the C(7) exomethylene and the C(13) enol ether to provide rearrangement substrate (−)-**43**.

To our delight, treatment of (−)-**43** with Me_2AlCl at ambient temperature rapidly (2 min) furnished tetrahydropyranone (−)-**42** as a single isomer in 89% yield (Scheme 11). Interestingly, exposure of (−)-**43** to the original Petasis conditions (*i*-Bu_3-Al)[8] led only to recovered starting material. Failure of *i*-Bu_3Al, a monocoordinate Lewis acid, to effect rearrangement supports the bis-chelation model for the rearrangement of (−)-**43** (see Scheme 8).

C(3−19) Subtarget (−)-42: A Second Generation Synthesis. To access (−)-**42** on large scale, a second-generation synthesis was developed (Scheme 12). Asymmetric hetero

(19) (a) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron*, **1981**, *37*, 3899.

(20) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(21) For a discussion of the chelating ability of Me_2AlCl, see: Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457.

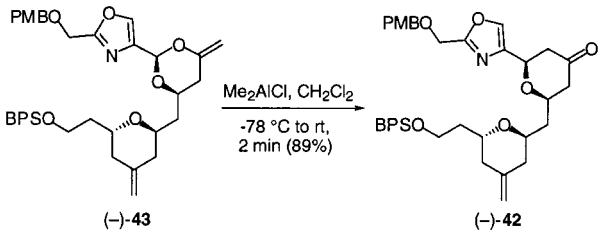
(22) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(23) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418.

(24) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, 58, 5130.

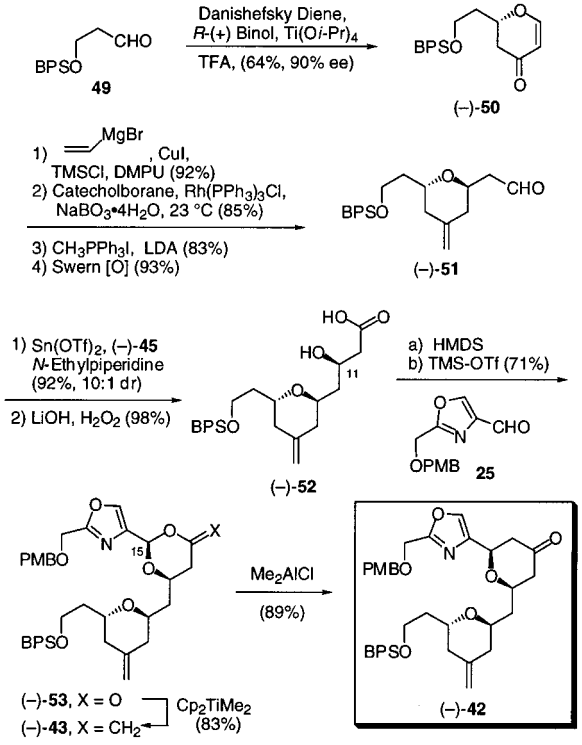
(25) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Scheme 11



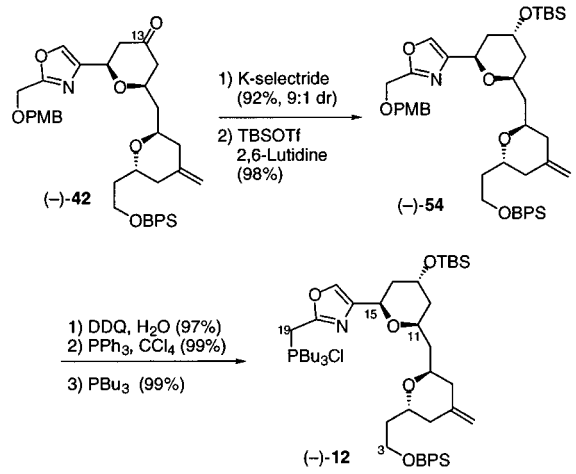
Diels−Alder reaction[26] of aldehyde **49**[27] with Danishefsky's diene,[28] promoted by *R*-(+)-Binol/Ti(O*i*-Pr)$_4$ (10 mol %), furnished enone (−)-**50** in 64% yield (90% ee).[29] Importantly, this reaction could be run on large scale (∼20 g). Axial addition of vinyl cuprate then furnished trans-tetrahydropyranone (30:1 *trans/cis*), which in turn was subjected to chemoselective hydroboration,[30] Wittig olefination, and Swern oxidation to afford aldehyde (−)-**51** (60% yield, 4 steps). A second Nagao aldol reaction, with the tin enolate derived from (−)-**45**,[23] followed by hydrolysis (LiOH, H_2O_2) gave β-hydroxy acid (−)-**52**[31] in 90% yield (2 steps, 10:1 dr). Dioxanone (−)-**53** was then constructed via the now-standard HMDS-promoted bis-silylation of (−)-**52** and condensation with the requisite oxazole aldehyde **25** (71%, 99% BORSM, 10:1 dr). Petasis−Tebbe methylenation (Cp_2TiMe_2) provided enol ether (−)-**43** and, thereby, intersection with the previous synthetic sequence. The second-generation assembly of (−)-**42**, proceeding in 10 steps (21% overall yield), constituted a significant improvement over the initial route (20 steps, 4.5% overall yield).

Scheme 12



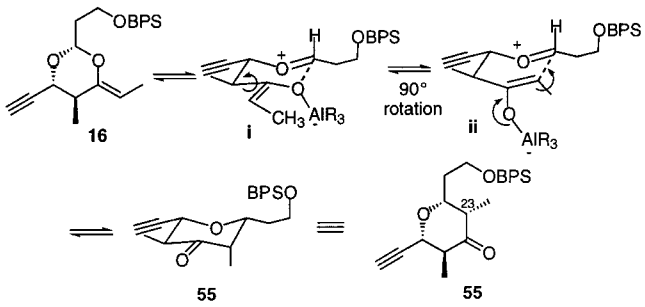
To arrive at the C(3−19) subtarget (−)-**12**, five steps were required (Scheme 13): reduction of the C(13) ketone (K-selectride; 9:1 dr),[32] silylation (TBSOTf, 2,6-lutidine), oxidative removal of the PMB ether (DDQ), generation of the primary chloride (PPh_3, CCl_4),[33] and displacement with tributyl phosphine. Each step proceeded in excellent yield to provide phosphonium salt (−)-**12** in 86% overall yield from (−)-**42**.

Scheme 13



The C(22−26) Central Tetrahydropyran. Although from the outset we envisioned the Petasis−Ferrier rearrangement to be the cornerstone of the (+)-phorboxazole A (**1**) synthetic venture, the fully substituted central tetrahydropyran ring raised the level of synthetic challenge given the requirement of a *Z-exo*-ethylidene acetal, instead of the simpler methylidene acetal employed to construct the C(11−15) tetrahydropyran (Scheme 14). Nonetheless, we envisioned that Lewis acid complexation to the enol ether oxygen in *Z*-enol acetal **16** would trigger ring opening, liberating (reversibly) the aluminum enolate (**i**). A least motion pathway, involving rotation by 90° with intervention of a boat conformation (e.g., **ii**) followed by reclosure of the enolate on the oxocarbenium ion was expected to afford **55**, possessing the C(23) axial methyl. The synthetic challenge in this scenario would be efficient access to *Z*-enol acetal **16**.

Scheme 14



We began with an Oppolzer anti aldol reaction[34] (Scheme 15). Addition of the boron enolate of known propionyl sultam

(26) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

(27) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.

(28) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, *2*, 273.

(29) Enantiomeric excess was determined after Nagao aldol condensation by 500 MHz NMR analysis of the diastereomeric ratio.

(30) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671. Interestingly, when the reaction was performed at 0 °C instead of room temperature, ketone reduction was competitive with hydroboration.

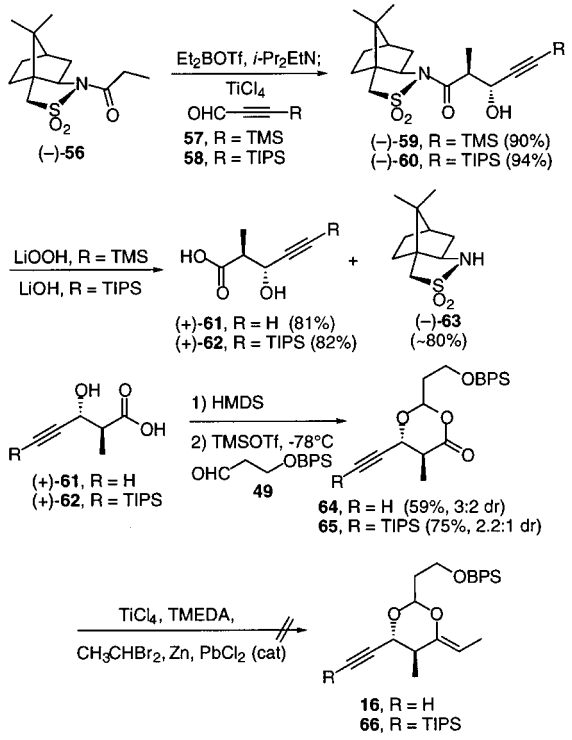
(31) The absolute configuration at C(11) was secured by Mosher ester analysis; see ref 12.

(32) Reduction of the C(13) ketone to the equatorial alcohol ($NaBH_4$) would provide access to (+)-phorboxazole B (**2**).

(33) The corresponding primary iodide was prone to reduction by PBu_3 to afford the corresponding methyl oxazole; thus, the chloride was used.

(34) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321.

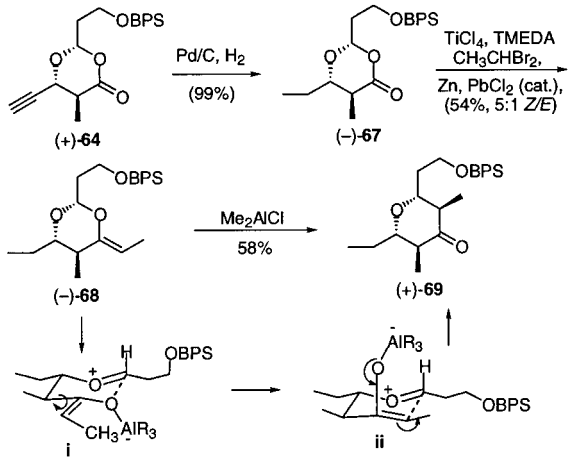
Scheme 15



(−)-**56**[34] to known aldehyde **57** (R = TMS)[35] in the presence of excess $TiCl_4$ furnished (−)-**59** as a single isomer. Oppolzer attributed the anti selectivity to an open transition state.[34] Removal of the sultam with concomitant alkyne desilylation then afforded *β*-hydroxy acid (+)-**61** and recovered sultam (−)-**63**, both in good yield. The two-step condensation of (+)-**61** with aldehyde **49**[27] provided dioxanone **64** in 59% yield, albeit as a disappointing mixture of separable epimers (3:2) favoring the *cis*-dioxanone.[36] The poor selectivity is attributed to the low steric bulk of the alkyne. Ethylidenation à la Takai[37] unfortunately proved unsuccessful, despite exploration of a variety of conditions; only decomposition occurred.[38] To provide the alkyne with a measure of protection, the TIPS-alkyne congener **65** was prepared (Scheme 15).[39] Again, exposure to either the Takai or related carbenoid ethylidenation conditions[40] failed to afford the desired product.

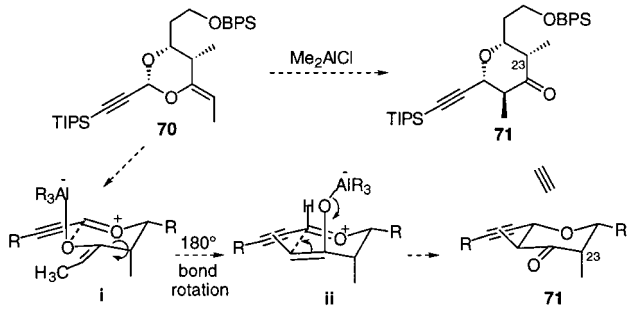
To confirm that the alkyne indeed was prone to decomposition,[38] we prepared the analogous alkane (−)-**67** via hydrogenation (Scheme 16).[41] As expected, (−)-**67** could be converted readily with modest stereoselectivity (5:1 *Z*/*E*)[37] to **68** via the Takai ethylidenation (54%); flash chromatography provided *Z*-alkene (−)-**68**. To our surprise, however, execution of the Petasis−Ferrier rearrangement furnished the all equatorial tetrahydropyran (+)-**69** (58%, unoptimized), the latter assigned via detailed NMR coupling constant analysis in conjunction with 1-D NOE experiments. This unexpected outcome led us to reexamine the proposed rearrangement scenario. Presumably, the least motion pathway of aluminum enolate (**i**) did not occur, because of the increase in steric demands of the corresponding boat conformation (vide infra); instead, rotation by 180° with closure via a chair conformation (**ii**) furnished (+)-**69**.

Scheme 16



Construction of the Central C(22−26) Tetrahydropyran via the Alternate Petasis−Ferrier Rearrangement Substrate. For a second time, we resorted to the pseudosymmetry available in the linchpin construction of the Petasis−Ferrier rearrangement substrates, which dictates that two possible vinyl acetals, related by the transposition of the enol ether oxygen in the substrate, can provide access to the requisite tetrahydropyranone. With this in mind, we envisioned oxygen-transposed enol ether **70** as a viable rearrangement substrate (Scheme 17). Rearrangement involving a 180° bond rotation would lead, now via a chair conformation (**ii**), to **71** possessing the requisite axial methyl substituent at C(23). Critical to this scenario would be the availability of **70** possessing the *Z*-ethylidene geometry.

Scheme 17



Assembly of **70** began with an Evans boron aldol condensation of oxazolidinone (+)-**72**[42] with aldehyde **49** (Scheme 18);[27] removal of the auxiliary (H_2O_2, LiOH) afforded *β*-hydroxy acid (+)-**73** (84%, 2 steps). Silylation followed by TMSOTf-promoted[19] union with aldehyde **58** then furnished dioxanone (+)-**74**. Initial difficulties in the scale-up of this reaction suggested that triflic acid was the actual catalyst; large scale reactions did not proceed until catalytic triflic acid (2−4 mol %) was added. We suspect that advantageous water, more pronounced on a smaller scale, generated triflic acid in situ from TMSOTf (as well as TMS_2O).[43] Yields and diastereoselectivity

(35) Kruithof, K. J. H.; Schmitz, R. F.; Klumpp, G. W. *Tetrahedron* **1983**, *39*, 3073.

(36) At this point, dioxanone **64** was used as a mixture. The *cis*-dioxanone isomer was later purified by crystallization; see ref 41.

(37) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410.

(38) Alkyne reactivity with carbenoid species has been reported. See: Takeda, T.; Shimokawa, H.; Miyachi, Y.; Fujiwara, T. *Chem. Commun.* **1997**, 1055.

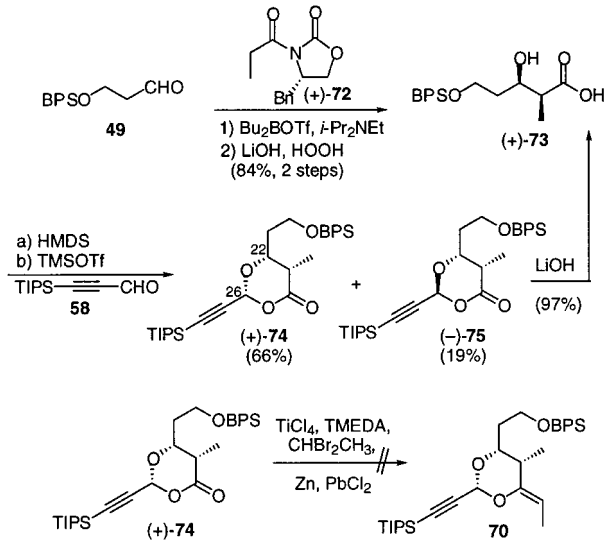
(39) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427.

(40) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.

(41) Alkyne (+)-**64** was prepared in enantiomerically pure form by recrystallization from hexane.

(42) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

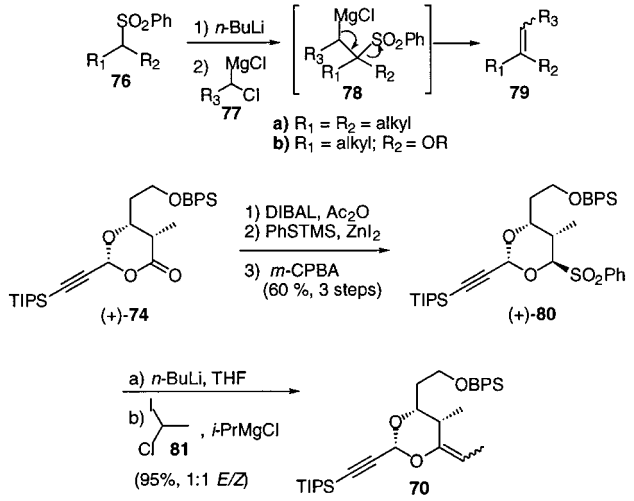
Scheme 18



were similar with the added triflic acid. The *cis*-2,6 stereochemistry was confirmed by two-dimensional NMR data, specifically an NOE between the C(22) and C(26) hydrogens.[15] The trans dioxanone (−)-**75**, recovered in 19% yield, was readily recycled to β-hydroxyacid (+)-**73** (LiOH, 97%). Unfortunately, all direct attempts to install the enol ether for the Petasis−Ferrier rearrangement again proved unrewarding.

Julia Type-II Olefination: A New Tactic for Enol Ether Construction. Our failure to prepare enol ether **70** directly from the lactone provided an opportunity to extend the Type-II Julia olefination[44] to the synthesis of enol ethers. This protocol, which was used to great advantage in our recent total synthesis of the spongistatins,[45] calls for α-alkylation of a sulfone (**76a**; Scheme 19) with an electrophilic α-halo Grignard reagent (**77**); subsequent elimination furnishes the alkene (**79a**). We reasoned that a similar reaction with sulfone **76b** would afford **79b**, contingent on preferential expulsion of phenyl sulfinate over the alkoxide. Toward this end, DIBAL reduction of dioxanone (+)-**74**, followed by in situ acetylation of the alkoxide, furnished the intermediate hemiketal acetate. A two-step sulfone installation

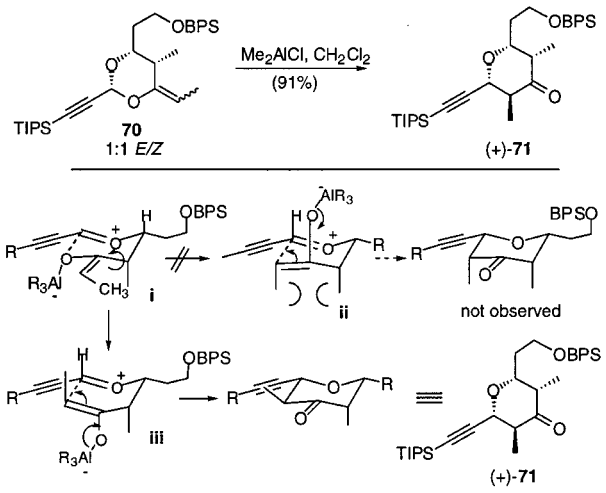
Scheme 19



(PhSTMS, ZnI_2;[46] *m*-CPBA) generated (+)-**80** as a single isomer (60%, 3 steps); presumably, the initial step is under thermodynamic control. Although we were pleased to find that treatment of sulfone (+)-**80** with *n*-BuLi, followed by exposure to 1,1-chloroiodoethane (**81**)[47] and *i*-PrMgCl (a 1:1 mixture) at −78 °C, furnished enol ether **70** in excellent yield (95%), the *E/Z* selectivity was nonexistent.

Petasis−Ferrier Rearrangement of Enol Ether 70: A Pleasant Surprise. Notwithstanding the mixture of enol ethers **70**, treatment with Me_2AlCl afforded *only* the desired tetrahydropyran (+)-**71** in excellent yield (91%). Although the *Z* isomer of **70** rearranges as anticipated presumably via a chair transition state to (+)-**71** (Scheme 17), formation of (+)-**71** from the *E* isomer implies that the unfavorable 1,3-diaxial interactions in transition state **ii** (Scheme 20) preclude a chair conformation and instead favor a boatlike transition state (**iii**).

Scheme 20

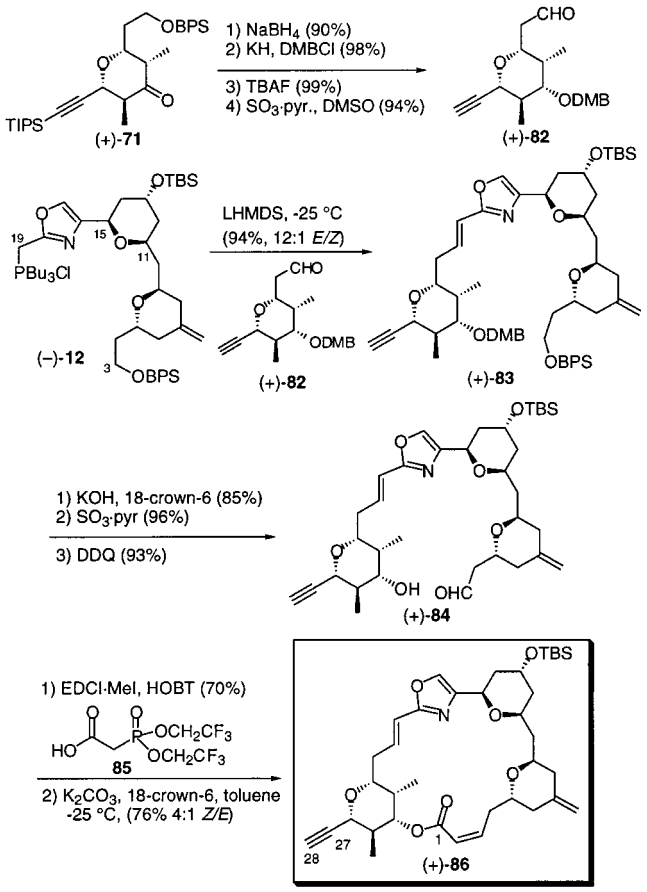


The C(1−28) Macrolide. With access to both (−)-**12** and (+)-**71**, attention turned to the construction of the C(1−28) macrolide. Reduction of (+)-**71** with $NaBH_4$, protection of the resultant alcohol as the 3,4-dimethoxybenzyl (DMB) ether, removal of the silyl groups, and oxidation (SO_3·pyr) furnished aldehyde (+)-**82** (82%, 4 steps). Wittig condensation with (−)-**12** then afforded the trans alkene (+)-**83** both in excellent yield (94%) and with high *E/Z* selectivity (12:1).[5f] In turn, removal of the BPS moiety in the presence of both TBS and DMB groups (KOH, 18-crown-6),[48] oxidation (Dess−Martin),[25] and removal of the DMB group (DDQ) then furnished hydroxyaldehyde (+)-**84** (Scheme 21).

Final elaboration of the C(1−28) macrolide entailed two steps: attachment of a two-carbon ester fragment (e.g., **85**)[49] (EDCI·MeI, HOBT), followed by an intramolecular Still-modified Horner−Emmons[50] reaction to provide (+)-**86**, as a mixture of C(2−3) olefin isomers (4:1). Although pleased that the C(1−28) macrolide was in hand, we quickly discovered that subsequent installation of the C(27−28) vinyl stannane, em-

(43) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570.
(44) De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133.
(45) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191.
(46) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741.
(47) Simpson, M. *Bull. Soc. Chim. Fr.* **1879**, *31*, 411.
(48) Although we believe these precise conditions are novel for the removal of a BPS group, very similar conditions exist. See: Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1983**, *31*, 2607.
(49) Pickering, D. A. Ph.D. Thesis, University of Minnesota, MN, 1996.
(50) (a) Still, 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.

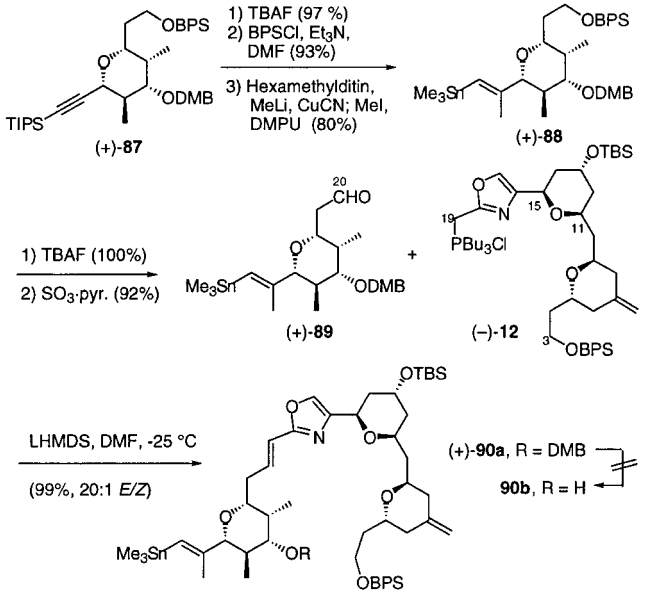
Scheme 21



ploying either cuprate[51] or methylzirconation[52] chemistry, as required to couple with the oxazole linchpin **15** (Scheme 3), was not possible.

Undaunted, we undertook introduction of the C(27−28) vinyl stannane at an earlier stage, again exploiting the inherent flexibility of the overall synthetic design. Toward that end, liberation of the terminal alkyne in (+)-**87** (Scheme 22), followed by addition of trimethylstannyl cuprate (Me_6Sn_2, MeLi, CuCN) and capture of the intermediate vinyl anion with methyl

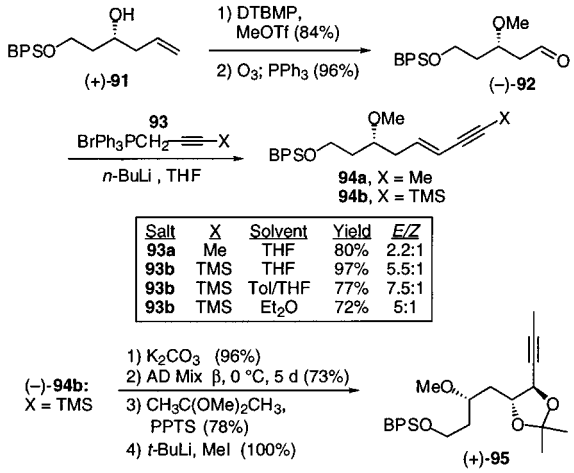
Scheme 22



iodide (DMPU) furnished trisubstituted olefin (+)-**88**. Elaboration of the C(20) aldehyde (+)-**89** (TBAF; SO_3·pyr) followed by Wittig olefination with (−)-**12** then led to trans olefin (+)-**90a** as the sole product. Unfortunately, extensive experimentation demonstrated that the labile trimethylstannane moiety was incompatible with the oxidation conditions to remove the DMB moiety, the required prelude to macrolide construction. Our attention thus turned to the assembly of the C(29−46) side chain, with the intent of attaching this unit prior to construction of the macrolide ring (Scheme 3).

Phorboxazole Side Chain. As outlined earlier (Scheme 3), assembly of the C(29−46) side chain called for lactone **13**, vinyl stannane **14**, and the oxazole triflate linchpin, **15a**,**b**. We began with construction of **13** (Scheme 23). Given that methylation

Scheme 23



Salt	X	Solvent	Yield	E/Z
93a	Me	THF	80%	2.2:1
93b	TMS	THF	97%	5.5:1
93b	TMS	Tol/THF	77%	7.5:1
93b	TMS	Et_2O	72%	5:1

of known homoallylic alcohol (+)-**91**[53] with sodium hydride affords significant silyl migration (∼10−15%), we resorted to the less basic conditions of MeOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).[54] Subsequent ozonolysis followed by reductive workup (PPh_3) furnished aldehyde (−)-**92** (81%, 2 steps). Although Wittig condensation of (−)-**92** with the Wittig salt **93a** possessing the methyl alkyne moiety led to a disappointing mixture (*E*/*Z*) of olefins (∼2.2:1),[55] condensation with the commercially available TMS phosphonate salt **93b** afforded enyne (−)-**94b** with acceptable selectivity (97%, 5.5:1 *E*/*Z*). Improvement in the *E*/*Z* ratio was observed employing toluene/THF (1:1) as the solvent system, albeit at the expense of yield and reproducibility (Scheme 23). Removal of the TMS group, followed by selective Sharpless dihydroxylation[56] of the enyne[57,58] using AD-Mix β, then afforded the corresponding

(51) Presumably, failure of cuprate addition to the alkyne arises from reaction at the existing Michael acceptors (i.e., the unsaturated lactone and vinyl oxazole).

(52) This result did not take us by surprise; during the course of this work, methylzirconation was reported to fail with a similar propargyl ether. See: Barrett, A. G. M.; Bennett, A. J.; Menzer, S.; Smith, M. L.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 162.

(53) 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). The ee of the alcohol prepared in our hands was determined by Mosher ester analysis to be 94%; see ref 12.

(54) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856.

(55) Attempts to improve this ratio using a Horner-type reaction were unsuccessful (50%, 5:3 *E*/*Z*).

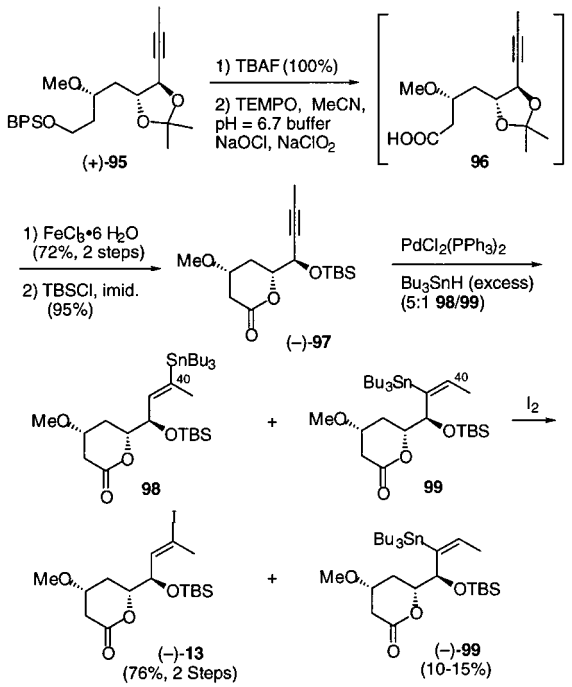
(56) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(57) For use of the Sharpless AD reaction on enynes, see: Jeong, K.-S.; Sjö, P.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 3833.

diol (73%; 7:1 dr).[59] Acetonide formation and alkyne methylation completed assembly of (+)-**95**.

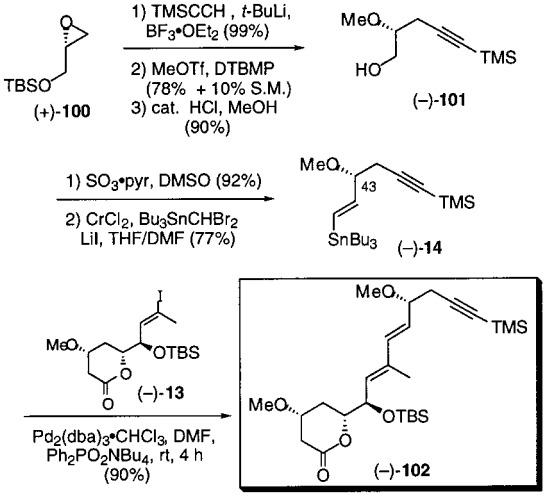
Continuing with construction of lactone **13** (Scheme 24), removal of the BPS group (TBAF) and oxidation via the Merck monophasic TEMPO protocol[60] afforded an unstable[61] acid (**96**) in good yield; other oxidations (PDC/DMF or Dess−Martin; $NaClO_2$) proved less effective. Immediate exposure of the acid (**96**) to $FeCl_3 \cdot 6H_2O$[62] effected acetonide hydrolysis with concomitant lactonization (72%, 2 steps). More conventional acid treatment (AcOH, Δ) resulted in lower yields (~30%). Protection of the secondary hydroxyl then furnished silyl ether (−)-**97**. To access directly vinyl iodide (−)-**13** from alkyne (−)-**97**, we explored Schwartz hydrozirconation;[63] only recovered starting material or decomposition occurred. Fortunately, recourse to a two-step palladium-mediated sequence involving slow addition of excess Bu_3SnH to (−)-**97** in the presence of catalytic $PdCl_2(PPh_3)_2$ yielded a mixture (5:1) of vinyl stannane regioisomers which were not readily separated. Exposure of the mixture to I_2 (0 °C) provided the desired *E*-vinyl iodide (−)-**13** (76% yield, 2 steps), with recovery of 10−15% of internal stannane (−)-**99**; presumably, the lack of reactivity of the internal stannane is due to steric constraints.

Scheme 24



Assembly of vinyl stannane (−)-**14** began with known TBS-glycidol (+)-**100**[64] (Scheme 25). Exposure to the lithium ion derived from TMS acetylene in the presence of $BF_3 \cdot OEt_2$, followed by methylation exploiting again conditions to prevent silyl migration[65] (MeOTf, DTBMP), and, in turn, removal of the TBS group in the presence of the TMS alkyne (cat. HCl, MeOH), furnished known alcohol (−)-**101** (69% yield, 3 steps).[66] Although several oxidation methods (e.g., Swern, Dess−Martin) led to facile epimerization at the C(43) methoxy center, the Parikh−Doering[67] protocol provided the aldehyde as a single isomer (92% yield).[68] Vinyl stannylation à la Hodgson[69] ($CrCl_2$, $Bu_3SnCHBr_2$, THF/DMF) then afforded (−)-**14** (77%). In the event, the critical Stille union[70] of (−)-**14** with vinyl iodide (−)-**13** proceeded in excellent yield to furnish (−)-**102**.[71] The success of this transformation is attributed to the use of $Ph_2PO_2NBu_4$, a salt introduced by Liebeskind[72] to remove Bu_3SnI from the reaction mixture and thereby accelerate the Stille coupling process.

Scheme 25



Potential Bidirectional Linchpins: 2-Methyl and 2-Bromomethyl 4-Trifloyloxazoles. With both the side chain lactone (−)-**102** and vinyl stannane (+)-**90** in hand, the stage was set for their union via an appropriate C(29−31) linchpin. We reasoned that either 2-methyl- or 2-bromomethyl-4-trifloyloxazole could serve this purpose.[73] To construct the requisite

(58) Experimentation revealed that an *E/Z* mixture of enynes could be used directly in the dihydroxylation; the *Z* isomer was markedly less reactive than the *E* isomer.

(59) Diminished diastereoselectivity in AD reactions with homoallylic enynols has been reported: Caddick, S.; Shanmugathasan, S.; Brasseur, D.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 5735.

(60) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.

(61) Carboxylic acid **96** in some cases was observed to lactonize in workup or chromatographic purification.

(62) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684.

(63) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(64) Cywin, C. L.; Webster, F. X.; Kallmerten, J. *J. Org. Chem.* **1991**, *56*, 2953.

(65) Again, we found that standard methylation (NaH, MeI) led to a mixture of products.

(66) Alcohol (−)-**101** was prepared previously by Pattenden and coworkers from malic acid; see ref 5e. This alcohol was subsequently prepared by Williams; see ref 5r.

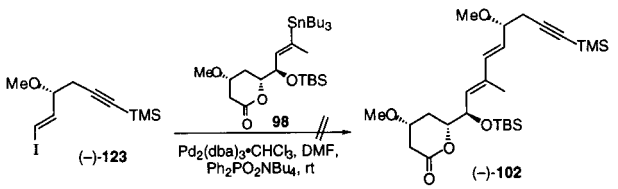
(67) Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(68) The extent of epimerization was determined by reduction ($BH_3 \cdot$ THF) to alcohol (−)-**101** and comparison of optical rotations.

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

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

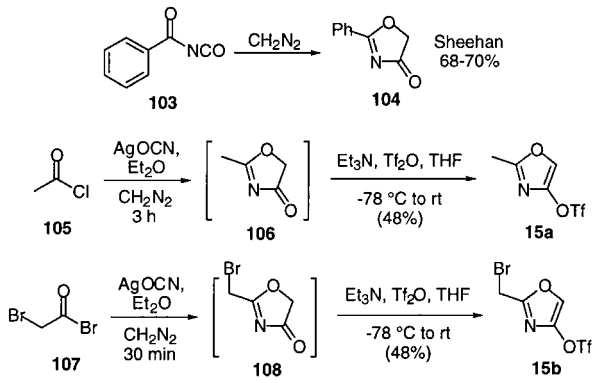
(71) It is noteworthy that vinyl iodide (−)-**123**, prepared by exposure of vinyl stannane (−)-**14** to iodine (97%), did not undergo Stille coupling with the previously prepared vinyl stannane **98** under identical conditions.



(72) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

(73) (a) 4-Trifloyloxazoles have received only modest attention; see ref 5p. (b) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623.

Scheme 26



oxazoles, we turned to a 1949 publication of Sheehan,[74] reporting the conversion of benzoyl isocyanate **103** to oxazolone **104** upon treatment with diazomethane (Scheme 26); enolization and capture as the triflate would furnish the desired linchpins. In the event, dropwise addition of an ethereal solution of diazomethane (alcohol-free)[75] to acetyl isocyanate,[76] readily generated in situ from acetyl chloride, afforded an unstable oxazolone (**106**),[77] which without isolation was converted via conditions developed by Panek[5p] to triflate **15a** in 48% overall yield. Importantly, assembly of **15a** required only a matter of hours and a single purification. An analogous reaction sequence beginning with bromoacetylbromide furnished the corresponding bromide **15b** in identical yield.[78]

Linchpin Model Studies. Initially, we explored the metalation of oxazole **15a** with *t*-BuLi. Unfortunately, only the undesired C(5) adduct **109** formed upon addition to *δ*-valerolactone (64%, Figure 1).[79] The equilibrating conditions specifically developed by the Evans group (e.g., Et_2NLi) to convert the C(5) lithium anion of an oxazole to the C(2) methyl substituent did not alter the reaction outcome. Presumably, the C(5) anion represents both the thermodynamic and the kinetic anion because of the ability of the C(4) triflate (absent in the Evans substrates) to direct lithiation. We thus turned to 2-bromomethyl oxazole **15b**. After considerable experimentation,[80] we discovered that premixing *δ*-valerolactone with **15b** followed by addition of *i*-PrMgCl furnished the desired adduct **110** in 66% yield. Presumably, rapid Grignard exchange[81] occurs to generate the metalated oxazole which attacks the lactone. Premixing was necessary to minimize self-condensation of **15b**.[82]

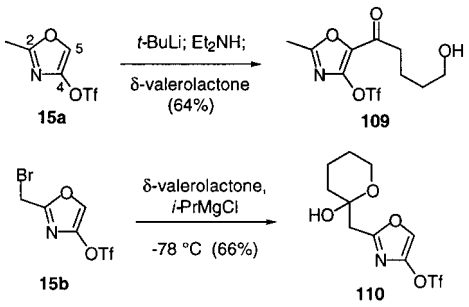


Figure 1. Oxazole metalation studies.

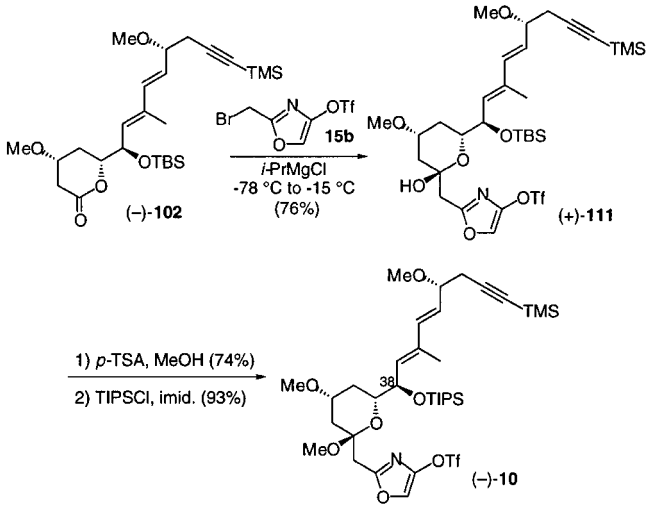
(74) Sheehan, J. C.; Izzo, P. T. *J. Am. Chem. Soc.* **1949**, *71*, 4059.

(75) (a) DeBoer, T. J.; Backer, H. J. *Org. Synth.* **1956**, *36*, 16. (b) Aldrich Technical Bulletin AL-121. The residual ethanol in standard diazomethane reacts with the isocyanate.

(76) For the preparation and isolation of acetyl isocyanate, see: Etienne, A.; Bonte, B.; Druet, B. *Bull. Chim. Soc. Fr.* **1972**, 251. Also see: Scholl, R. *Chem. Ber.* **1890**, *23*, 3505.

Application of this tactic to the (+)-phorboxazole side chain precursor (−)-**102** effected efficient coupling (76%) of **15b** to afford hemiketal (+)-**111** as a single isomer[83] (Scheme 27). Methyl ketal formation (*p*-TSA, MeOH) followed by reprotection of the C(38) hydroxyl as the TIPS ether (TIPSCl, imid) completed construction of the side chain subtarget (−)-**10**.

Scheme 27



Not pleased to have to reprotect the C(38) hydroxyl, we installed the TIPS ether at an earlier stage via an analogous route (Scheme 28). A modest improvement in both the stannylation regioselectivity (6:1) and yield was observed in the TIPS series, presumably because of the increased steric bulk of the TIPS group.[84] Both the Stille coupling and introduction of the oxazole triflate also proceeded smoothly and in excellent yield.

Side Chain Appendage and Macrolide Construction. The plan was now to effect coupling of side chain (−)-**10** with vinyl stannane (+)-**90a**, followed by macrolactone construction (Scheme 29). Initially, we examined $Pd_2dba_3{\cdot}CHCl_3$ as the Stille catalyst;[5p] unfortunately, the desired product (+)-**115** was obtained in less than 20% yield. Exploration of related catalysts and solvent regimes eventually led to $Pd(PPh_3)_4$ in dioxane with excess LiCl (100 °C, sealed tube)[73] as the optimal conditions to promote the Stille coupling; under these conditions, (+)-**115** was obtained in 72% yield.[85] To the best of our knowledge,

(77) Although alternate oxazolone syntheses exist, most require aryl or alkenyl substitution at the C(2) position: (a) Rao, Y. S.; Filler, R. *Chem. Commun.* **1970**, 1622. (b) Troxler, F. *Helv. Chim. Acta* **1973**, *56*, 1815. (c) Rodehorst, R. M.; Koch, T. H. *J. Am. Chem. Soc.* **1975**, *97*, 8. For a discussion of the limitations of such procedures, see ref 73b.

(78) The utility of triflates **15a** and **15b** as linchpins is under further investigation in our laboratories: Smith, A. B., III; Minbiole, K. P.; Freeze, B. S. *Synlett* **2001**, 1543.

(79) Compound **109** is drawn as the open keto-alcohol because of observation of the ^{13}C NMR resonance and infrared absorption (186.8 ppm and 1694 cm^{-1}, respectively). Similarly, compound **110** is drawn as the hemiketal because of observation of a ^{13}C hemiketal NMR resonance and IR hydroxyl absorption [94.7 ppm and 3420 cm^{-1} (br), respectively].

(80) Lithium halogen exchange (*t*-BuLi) in the presence of *δ*-valerolactone afforded **110** in modest yield (∼30%).

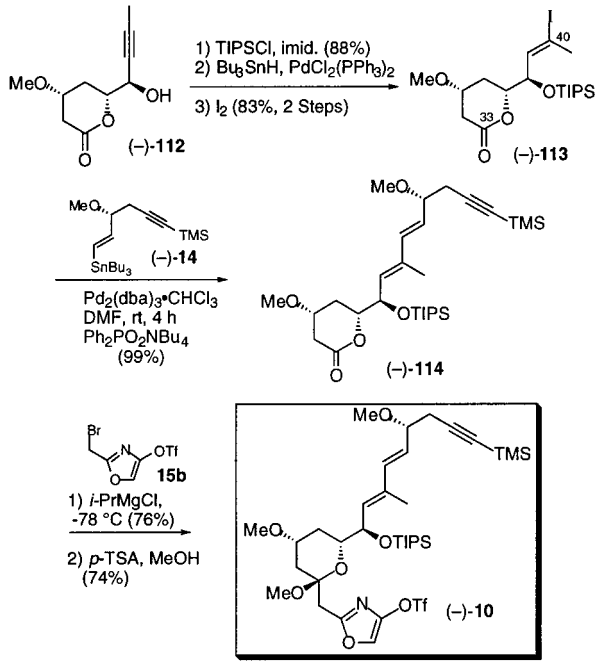
(81) "Grignard exchange" reactions have been demonstrated on vinylic and arylic substrates. See: (a) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428. (b) Delacroix, T.; Berillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108.

(82) Self-condensation arises from the electrophilic nature of unreacted **15b**. Self-condensation was also observed upon inverse addition (i.e., slow addition of bromomethyl oxazole **15b** to a solution of *t*-BuLi at −100 °C).

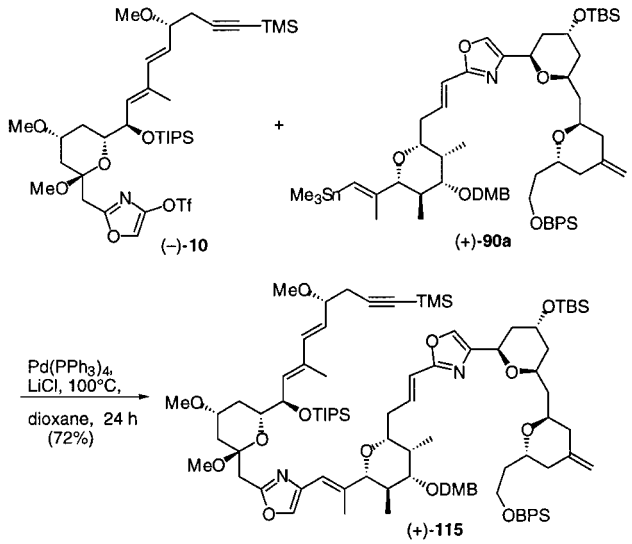
(83) Presumably, the sterochemical outcome is due to the anomeric effect. See: Bonner, W. A. *J. Am. Chem. Soc.* **1959**, *81*, 1448.

(84) The corresponding internal stannane was recovered (∼5−15%).

Scheme 28



Scheme 29

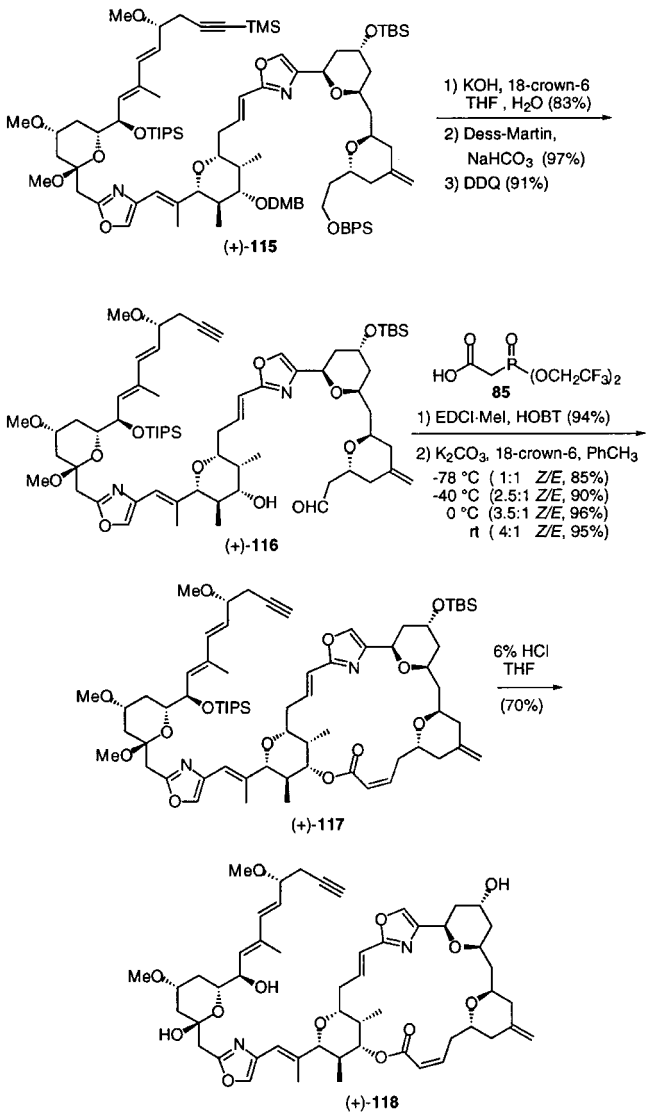


(−)-**10** represents the most complex oxazole triflate employed in a Stille cross coupling.

Macrolide construction followed directly from our earlier synthesis of (+)-**86** (Scheme 21); selective desilylation,[48] oxidation, and DMB removal afforded hydroxyaldehyde (+)-**116** (73%, 3 steps, Scheme 30). Macrocyclization then proceeded in excellent yield to furnish (+)-**117**. Interestingly, the *E*/*Z* selectivity improved with higher temperatures. We attribute the enhanced selectivity to an increase in the rate of oxaphosphatane collapse at the higher temperatures, which minimizes oxaphosphatane equilibration and thereby formation of the trans isomer. Exposure of (+)-**117** to 6% HCl in THF resulted in global deprotection to furnish **118**, the C(45−46) alkyne congener of phorboxazole. The significance of this transformation is twofold: first, alkyne (+)-**118** had been reported to be

(85) The reproducibility of the reaction proved highly dependent on the amount of oxygen present in the system. When a "freeze pump thaw" tactic was employed to deoxygenate the dioxane prior to use, the reaction consistently proceeded in ~68−72% yield.

Scheme 30



equipotent to (+)-phorboxazole A (**1**);[86] and second, the conversion of (+)-**117** to (+)-**118** served to validate the global deprotection conditions needed to arrive at the natural product.

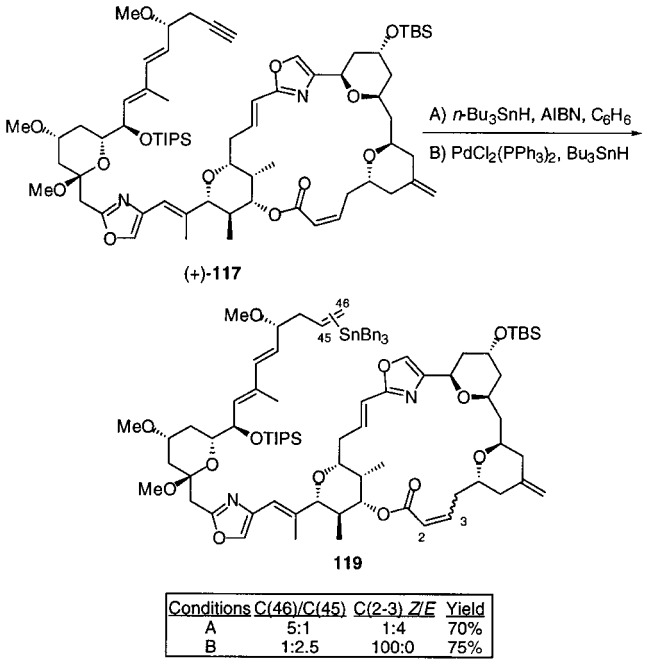
Introduction of the C(46) *E*-Vinyl Bromide: A Non-Trivial Task. The last major synthetic hurdle, namely conversion of alkyne (+)-**117** to the C(46) *E*-vinyl bromide, proved particularly challenging (Scheme 31). Initially, we explored a radical hydrostannylation.[87] Accordingly, treatment of (+)-**117** with Bu_3SnH and AIBN at 80 °C resulted in formation of the desired *E*-vinyl stannane with moderate selectivity (5:1) for the terminal vinyl stannane. Unfortunately, almost complete isomerization of the C(2−3) cis olefin occurred. Alternative radical hydrostannylation conditions (e.g., Bu_3SnH, Et_3B, 0 °C) resulted both in poor yield and selectivity. Palladium catalyzed hydrostannylation [$Cl_2Pd(PPh_3)_2$, Bu_3SnH],[88] known to be unselective with alkynes lacking α branching, actually furnished a prepon-

(86) (a) Hansen, T. M.; Engler, M. M.; Ahmed, F.; Cink, R. D.; Lee, C. S.; Forsyth, C. J. *Abstract of Papers*, 220th National Meeting of the American Chemical Society, Washington, DC; American Chemical Society: Washington, DC, 2000; ORGN-040. (b) Uckun, F. M.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1181.

(87) Leusink, A. J.; Budding, H. A.; Drenth, W. *J. Organomet. Chem.* **1968**, *11*, 541 and references therein.

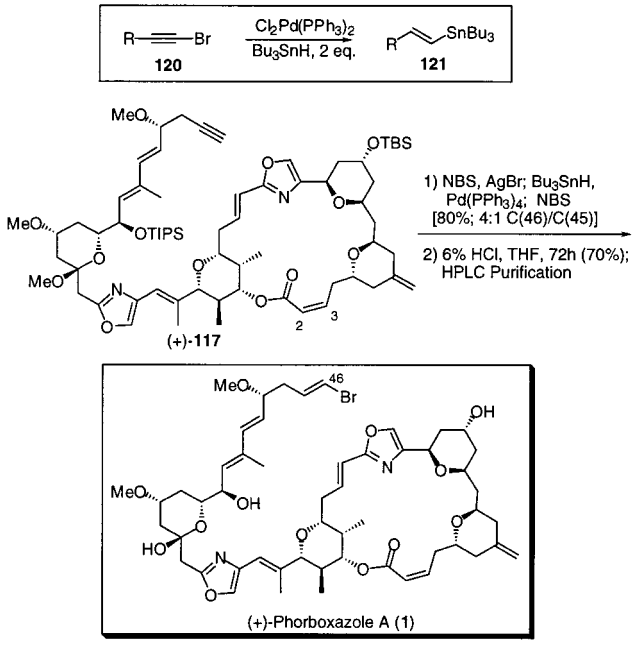
(88) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. Also see: Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417.

Scheme 31



Conditions	C(46)/C(45)	C(2-3) *Z*/*E*	Yield
A	5:1	1:4	70%
B	1:2.5	100:0	75%

Scheme 32



derance of the internal [C(45)] stannane (2.5:1); presumably, chelation of the palladium species to the C(44) methyl ether leads to the internal C(45) stannane. Faced with the failure of other methods (i.e., Schwartz hydrozirconation), we were nonetheless encouraged that palladium-catalyzed hydrostannylation returned the C(2−3) cis olefin geometry intact; thus, the regioselectivity remained the final issue.

Completion of the (+)-Phorboxazole A (1) Synthetic Venture. A careful review of hydrostannylation literature led us to the work of Guibe,[88] who noted improved regioselectivity for the hydrostannylation of alkynyl bromides (e.g., **120**→**121**, Scheme 32). To exploit this precedent, we prepared the alkynyl bromide of (+)-**117** ($AgNO_3$, NBS); palladium catalyzed hydrostannylation afforded the desired *E* vinyl stannane with 4:1 C(46)/C(45) regioselectivity. Without separation, facile tin−bromine exchange (NBS, 95%) followed by treatment with 6% HCl (72 h) furnished a mixture of phorboxazole vinyl bromide isomers [4:1, C(46)/C(45), 70%]. HPLC separation using a Zorbax C_{18} reversed-phase column (55:45 acetonitrile/H_2O) provided pure, totally synthetic (+)-phorboxazole A (**1**), the spectral properties of which were identical in all respects [e.g., ^{1}H NMR, ROESY, COSY (600 MHz), HRMS, and optical rotation] to the corresponding spectral data obtained from natural (+)-phorboxazole A (**1**).

Summary. A highly convergent, stereocontrolled total synthesis of (+)-phorboxazole A (**1**) has been achieved. Highlights of the synthetic venture include the use of modified Petasis−Ferrier rearrangements for the effective linchpin assembly of both the C(11−15) and C(22−26) *cis*-tetrahydropyran rings; extension of the Julia olefination to the synthesis of enol ethers; and the design, synthesis, and application of a novel bifunctional oxazole linchpin. 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: Experimental procedures and analytical data for all compounds (74 pages, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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