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Synthetic Studies toward Phorboxazole A. Stereoselective Synthesis of the C_{28}–C_{46} Side Chain Fragment

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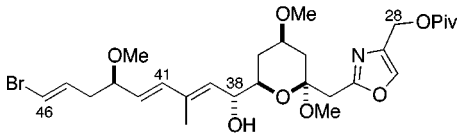
ABSTRACT



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A stereoselective synthesis of the C_{28}–C_{46} fragment (3) of phorboxazole A is described. Key advances include an enantioselective allylation to establish the stereochemistry of the tetrahydropyran unit and a useful SmI_2-mediated modification of the Barbier reaction of iodomethyloxazole 15 with aldehyde 14.

Phorboxazoles A (**1**) and B (**2**) are unique macrolides isolated from the Indian Ocean sponge *Phorbas* sp.[1] These metabolites possess exceptional cytostatic activity throughout the panel of 60 NCI human tumor cell lines (mean $GI_{50} < 1.6 \times 10^{-9}$ M).[2] Selective cytotoxicity at subnanomolar concentrations is found in a number of significant tumor cultures, including leukemia CCRF-CBM, prostate PC-3, breast MCF7, and colon HCT116 and HT29 cell lines.[2c] Moreover, the phorboxazoles do not inhibit tubulin polymerization and may offer a unique mechanism of action by arresting the cell cycle in S phase.[2] Biological studies are severely limited by the scarcity of natural material. The unprecedented structural features and extraordinary potency of **1** have inspired several synthesis studies,[3] and Forsyth and co-workers have reported the first total synthesis.[4a] Very recently, Evans and co-workers have also achieved a total synthesis of this important target.[4b] Previously, we reported the synthesis of the C_1−C_{32} macrolactone of phorboxazole A.[3d,e] Herein, we report the stereoselective synthesis of the C_{28}−C_{46} polyolefinic side chain fragment (**3**). Our retrosynthetic analysis of **3** recognized a bond disconnection which would provide for installation of the C_{39}−C_{42} diene at late stage events (Scheme 1). This strategy suggested sulfone **4** and α,β-unsaturated aldehyde **5** as fully functionalized components of an *E*-selective Julia olefination reaction,[5a] as an extension of our related efforts toward hennoxazole A.[5b]

(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.; Antonio, J. *J. Nat. Prod.* **1993**, *56*, 54. (c) Molinski, T. F. *Tetrahedron Lett.* **1998**, *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) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287. (e) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291. (f) Pattenden, G.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 319. (g) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099. (h) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185. (i) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909. (j) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913. (k) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87. (l) Wolvers, P.; Hoffman, H. M. R. *Synthesis* **1999**, *5*, 797. (m) Wolbers, P.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 1905. (n) Wolbers, P.; Misske, A. M.; Hoffman, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527. (o) Schaus, J.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469. (p) Pattenden, G.; Plowright, A. *Tetrahedron Lett.* **2000**, *41*, 983. (q) Rychnovsky, S.; Thomas, C. *Org. Lett.* **2000**, *2*, 1217.
(4) (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597. (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533. Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536.
(5) (a) Kocienski, P. J.; Blakemore, P. R.; Cole, W. J.; Morley, A. *Synlett.* **1988**, *26*. (b) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924.

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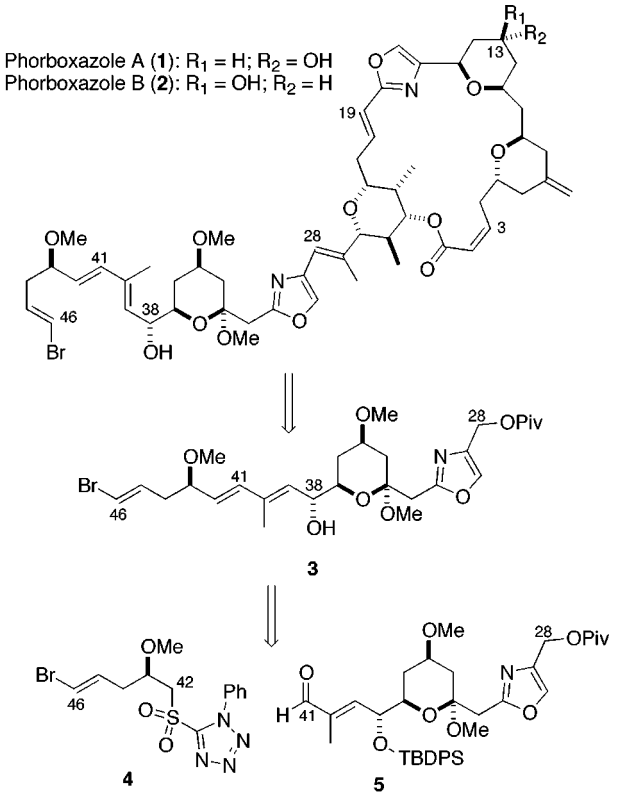
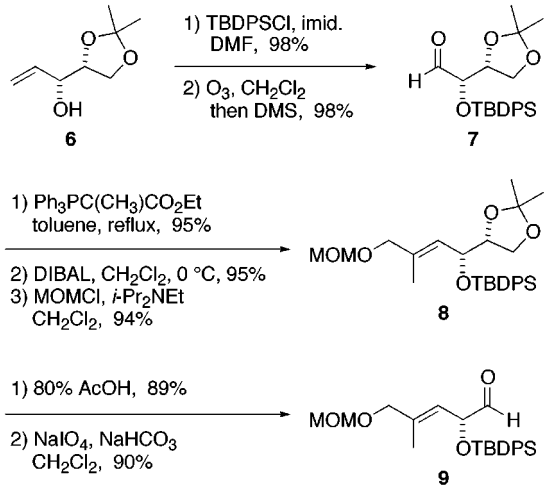
Scheme 1



The synthesis of conjugated enal **5** began with aldehyde **9**, which was prepared from optically active alcohol **6**[6] in seven steps (Scheme 2). Protection of the alcohol followed

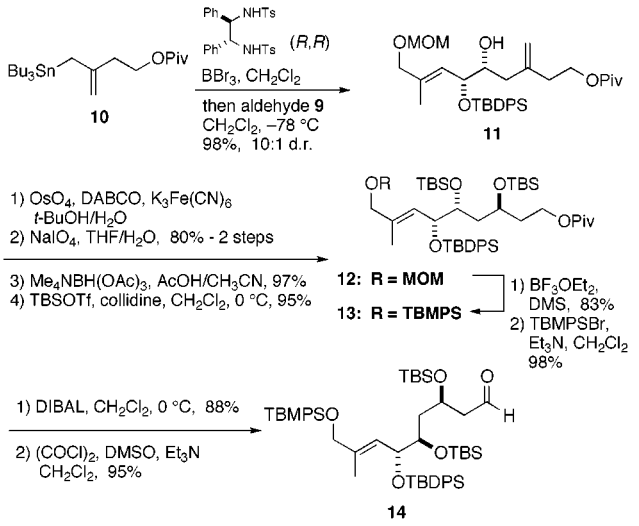
Scheme 2



by reductive ozonolysis led to aldehyde **7**. Wittig olefination was followed by reduction (DIBAL) of the resulting ester, and protection of the resulting allylic alcohol provided **8** in excellent overall yield. Selective removal of the acetonide protecting group with mild acid and cleavage of the diol with sodium periodate gave the desired aldehyde **9**.

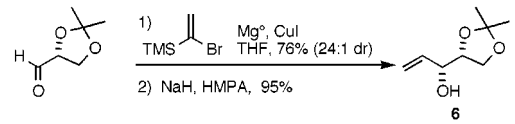
Asymmetric allylation of aldehyde **9** was effected following the tin to boron transmetalation of stannane **10**[7] using the boron bromide reagent derived from (*R,R*)-1,2-diamino-1,2-diphenylethane bis-sulfonamide and boron tribromide (Scheme 3).[8] Formation of the C_{37} homoallylic alcohol was

Scheme 3



achieved in 98% yield (10:1 dr).[9] This is a significant improvement for establishing the correct relative stereochemistry at C_{37}/C_{38} since previous efforts had required a Mitsunobu inversion of the undesired C_{38} diastereomer.[4a] Selective oxidative cleavage of the geminally disubstituted olefin and a directed reduction of the resulting β-hydroxy ketone (>95% de)[10] provided a single diastereomeric product after purification by flash chromatography. Treatment of this diol with TBSOTf and collidine furnished the polyol derivative **12**. Conversion to the fluoride-labile *tert*-butylmethoxyphenylsilyl (TBMPS) ether was necessary at this point in the scheme because our plans for selective deprotection in the corresponding MOM ether of **16** proved unworkable.

(6) Alcohol **6** is available from D-glyceraldehyde acetonide via a stereoselective addition of 1-(trimethylsilyl)vinyl copper, followed by protodesilylation. See: (a) Sato, F.; Kusakabe, M. *Chem. Lett.* **1986**, 1473. (b) Sato, F.; Tanaka, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 165.



(7) Preparation of stannane **10** is conveniently carried out via deprotonation of 3-methyl-3-buten-1-ol with 2 equiv of Schlosser's base (KOtBu/^{n}BuLi in hexanes) (see (a) Schlosser, M.; Hartmann, J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 508. (b) Collum, D. B.; Mguirk, P. R. *J. Org. Chem.* **1989**, *49*, 843.) and quenching the resulting dianion with tributyltin iodide. Protection of the resulting primary alcohol with trimethylacetyl chloride/pyridine provided stannane **10**.

(8) Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

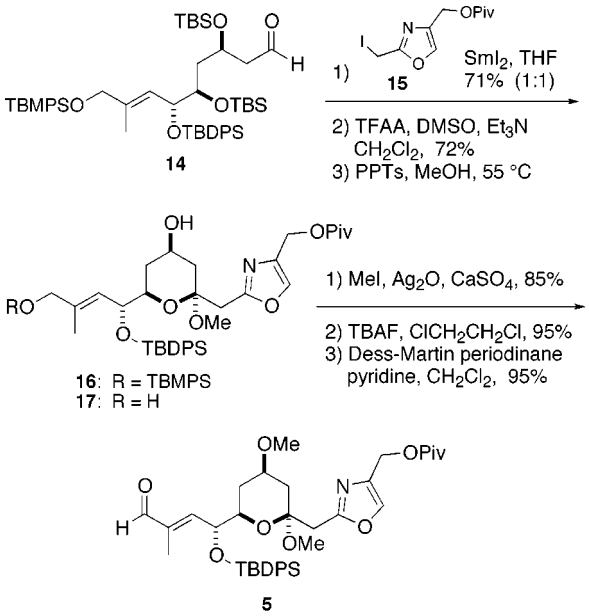
(9) For more examples of asymmetric allylations being used for the synthesis of complex homoallylic alcohols, see: Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P. *Tetrahedron Lett.* **1998**, *39*, 7251.

(10) Evans, D. A.; Carreira, E. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

Subsequent removal of the pivaloate of **13** (DIBAL) and oxidation[11] afforded the desired C_{33} aldehyde (**14**).

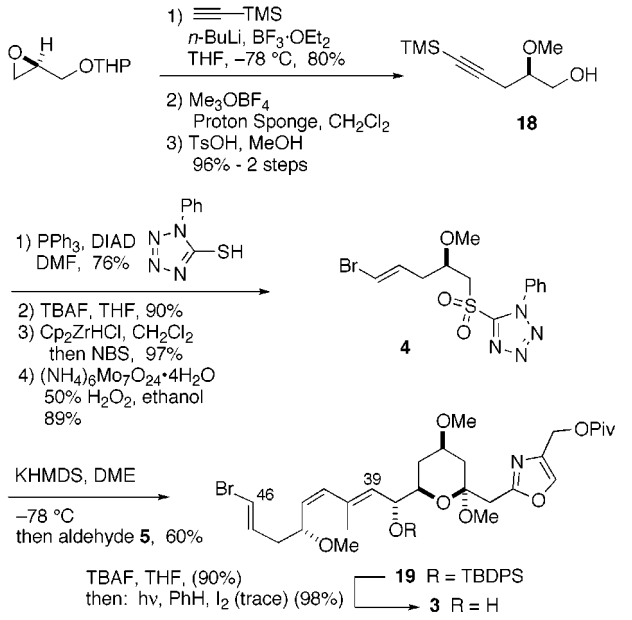
Limited methodology has been described for the successful nucleophilic addition of C-2 metalated oxazoles to carbonyl compounds. These procedures utilize zinc,[12] chromium,[13] or lithium diethylamide[3k] to circumvent issues arising from the instability and reactivity of 5-lithiooxazoles. Herein, we report a new and convenient method for the generation of β-hydroxy ketones from the reaction of iodomethyloxazoles[14] and aldehydes with SmI_2 under Barbier-type conditions.[15] To this end, addition of 4 equiv of SmI_2 to a mixture of aldehyde **14** and iodomethyloxazole **15** proceeded to give the β-hydroxyoxazole as a 1:1 mixture of diastereomers in 71% yield (Scheme 4). This mixture was immediately

Scheme 4



converted to the desired C_{33} ketone using the trifluoroacetic anhydride variant of the Swern oxidation.[16] The β-ketooxazole was directly cyclized under mildly acidic conditions to afford the mixed ketal ring system **16** in 58% yield, along with 23% of the allylic alcohol **17** as single diastereomers.[17] Methylation of the C_{35} alcohol was efficiently carried out

Scheme 5



using silver oxide in methyl iodide, and selective desilylation of the primary TBMPS group[18] followed by oxidation[19] provided the α,β-unsaturated aldehyde fragment **5**.

Scheme 5 incorporates the straightforward preparation of the appropriately functionalized sulfone **4**. Thus, the Lewis acid-catalyzed opening of the (*R*)-glycidol derivative with lithium trimethylsilylacetylide and methylation followed by removal of the THP-protecting group gave primary alcohol **18**. Activation of the alcohol and displacement with 1-phenyl-1*H*-tetrazole-5-thiol[20] was followed by introduction of the vinyl bromide functionality via hydrozirconation of the alkyne with Schwartz's reagent[21] and a NBS quench. Oxidation of the heterocyclic sulfide with ammonium molybdate provided the desired sulfone **4**.

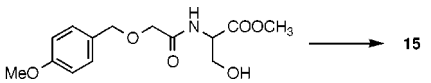
Adaptation of the Kocienski modification[5] of the Julia condensation utilized the potassium carbanion of the *N*-phenyltetrazole sulfone **4** for in situ elimination (Scheme 5). Reaction with aldehyde **5** provided diene **19** in 60% yield[22] and resulted in unexpected *Z*-selectivity (>8:1 *Z*:*E*). This result was surprising considering that our model studies had demonstrated the stereoselective formation of *E*,*E*-dienes

(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2380.

(12) Helquist, P.; Gangloff, A. R.; Akermark, B. *J. Org. Chem.* **1992**, *57*, 4797.

(13) Uguen, D.; Breuilles, P. *Tetrahedron Lett.* **1998**, *39*, 3149.

(14) Oxazole **15** was conveniently prepared from the amide of serine methyl ester shown below in four operations: (a) DAST, K_2CO_3, CH_2Cl_2 (92%); (b) $BrCCl_3$, DBU (81%); (c) DDQ, CH_2Cl_2 (90%); and (d) PPh_3, I_2, imid, CH_2Cl_2 (85%).



(15) For reviews, see: (a) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (b) Kinishima, M.; Hioki, K.; Kono, K.; Sakuma, T.; Tani, S. *Chem. Pharm. Bull.* **1994**, *42*, 2190.

(16) The oxalyl chloride Swern procedure (see ref 12) gave a side product resulting from dichlorination at the C(32) position (72% yield).

(17) The allylic alcohol **17** was easily converted to **16** with TBMPSBr, Et_3N, and CH_2Cl_2 (91% yield).

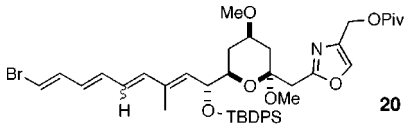
(18) Guindon, Y.; Fortin, R.; Yoakim, C.; Gillard, J. W. *Tetrahedron Lett.* **1984**, *25*, 4717.

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

(20) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(21) Hart, D.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

(22) Additionally, small quantities of tetraene **20** have been observed in the Julia olefination reaction resulting from subsequent elimination of methanol.



when sulfone **4** was reacted with α,β-unsaturated aldehydes.[23] Fortunately, we discovered that the undesired $C_{41}-C_{42}$ *Z*-alkene could be isomerized to the *E*-alkene.[24] Thus, after removal of the C_{38} silyl protecting group, treatment of the *Z,E*-diene **19** with a crystal of iodine followed by irradiation with a sun lamp (250 W) resulted in complete isomerization to the desired *E,E*-diene **3**. Our spectral data for the phorboxazole side chain were consistent with a detailed analyses of ^{1}H and ^{13}C NMR spectra of the natural product.

In summary, we have described an efficient, enantioselective synthesis of the $C_{28}-C_{46}$ side chain of phorboxazole A. Our work features significant methodology for enantiocontrolled allylation and a useful Barbier procedure for a samarium-mediated incorporation of the intact oxazole unit which may have important implications for heterocyclic chemistry. Progress toward the completion of phorboxazole A (**1**) is underway and will be reported in due course.

Acknowledgment. The authors gratefully acknowledge the National Institutes of Health (GM-41560) for generous support of our work. We thank Professor Evans for a preprint of his total synthesis (ref 4b).

Supporting Information Available: Experimental procedures and spectral data for compounds **3**, **11**, and **16** and a listing of ^{1}H NMR data for compounds **4**, **5**, **14**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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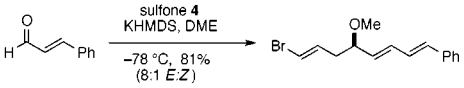
(23) For example, reaction of sulfone **4** with cinnamaldehyde resulted in an 8:1 ratio of (*E*,*E*) to (*E*,*Z*) dienes.



(24) Roelofs, W.; Comeau, A.; Hill, A.; Milicevic, G. *Science* **1971**, *174*, 297.