ORGANIC LETTERS

2001
Vol. 3, No. 11
1693−1696

Formal [4 + 2]-Annulation of Chiral Crotylsilanes: Synthesis of the C19–C28 Fragment of Phorboxazoles

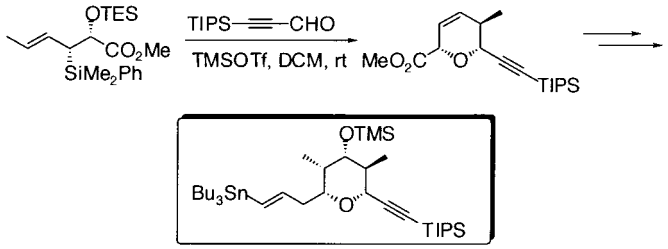
Hongbing Huang and James S. Panek*

Department of Chemistry and Center for Streamlined Synthesis, Metcalf Center for Science and Engineering, 590 Commonwealth Avenue, Boston University, Boston, Massachusetts 02215

panek@chem.bu.edu

Received March 26, 2001

ABSTRACT



A stereoselective synthesis of the C19–C28 fragment of phoborxazole A and B is described. The key step is an enantioselective [4 + 2]-annulation of a crotylsilane 10 with a propargylic aldehyde 11 affording a functionalized dihydropyran 12. A solvent-dependent stereoselective epoxidation of dihydropyrans is also documented.

Isolated from the Indian Ocean sponge *Phorbos* sp., phorboxazoles A and B are among the most cytostatic natural products discovered to date, displaying a mean GI_{50} value of 1.58×10^{-9} M against the entire NCI panel of 60 tumor cell lines.[1] The unique structure and impressive biological activity of the phorboxazoles have attracted wide interest of synthetic chemists.[2] Recently, Forsyth[3] and Evans[4] have reported the first total synthesis of phorboxazoles A and B, respectively. In this letter, we describe a stereoselective synthesis of the C19−C28 tetrahydropyran ring of the phorboxazoles.

We have recently reported our findings concerning the development of a stereoselective [4 + 2]-annulation, which results in the formation of enantiomerically enriched dihydropyrans.[5] The annulation provides stereochemically well-defined dihydropyrans bearing three stereogenic centers and complementary cis or trans stereochemistry across the pyran oxygen. Accordingly, we hope this methodology will find utility in natural product synthesis bearing functionalized pyrans. Further, we anticipate highly substituted tetrahydropyrans can be assembled by functionalization of the double bond.

(1) For isolation and biological data see: (a) Searle, P. A.; Molinski, T. T. *J. Am. Chem. Soc.* **1995**, *117*, 8126−8131. (b) Searle, P. A.; Molinski, T. T. *J. Am. Chem. Soc.* **1996**, *118*, 9422−9423. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879−7880.

(2) Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319−322. (b) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099−6102. (c) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185−7188. (d) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287−2290. (e) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291−2294. (f) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909−912. (g) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913−916. (h) Wolbers, P.; Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527−4530. (i) Wolbers, P.; Hoffmann, H. M. R. *Synthesis* **1999**, 797−802. (j) Wolbers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905−1914. (k) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4315−4324. (l) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219. (m) Donaldson, W. A.; Greer, P. B. *Tetrahedron Lett.* **2000**, *41*, 3801−3803.

(3) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598. (b) Lee, C. S.; Forsyth, C. J. *Tetrahedron Lett.* **1996**, *37*, 6449−6452. (c) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672−5673. (d) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998**, *39*, 183−186.

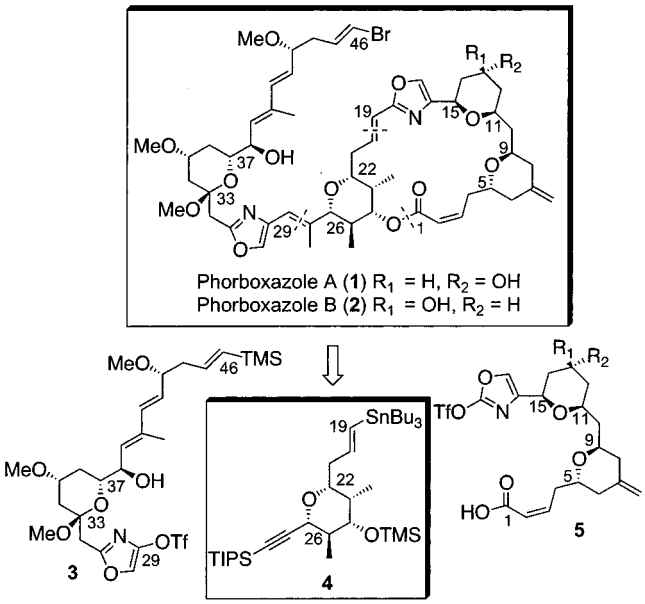
(4) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533−2536. (b) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536−2540. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046

(5) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837.

10.1021/ol015893u CCC: $20.00
Published on Web 04/28/2001

Our retrosynthetic analysis of phorboxazole A leads to subunits **3**, **4**, and **5** (Scheme 1). We envisioned a transition

Scheme 1

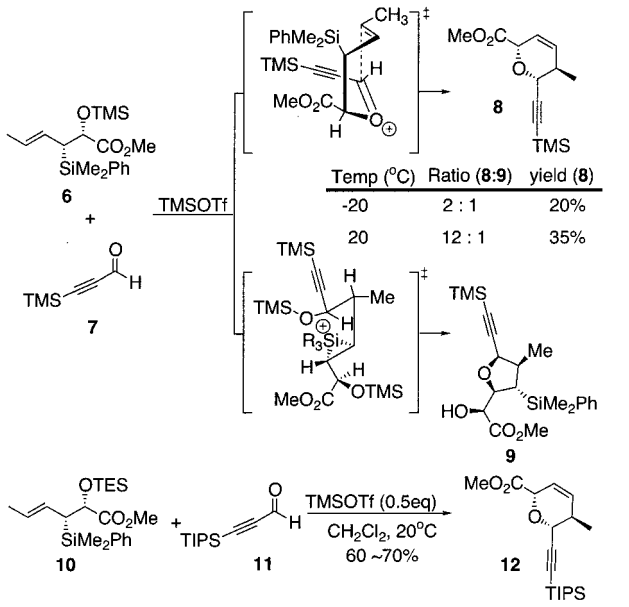


metal catalyzed sp^2-sp^2 coupling strategy for the construction of the C18−C19 and C28−C29 σ-bonds as an efficient and direct route for their assembly.[6] In the synthetic direction, this analysis holds the potential for completion of the macrolide either by lactonization or intramolecular Stille coupling. Focusing on the C19−C28 tetrahydropyran subunit, we explored the use of the dihydropyran annualtion methodology as an effective way to synthesize **4**.

In the presence of a catalytic amount of TMSOTf (−20 °C), trisubstituted dihydropyrans can be obtained with high levels of selectivity from chiral silanes bearing a TMS ether and a range of branched aldehydes.[5] However, under the same conditions, the reaction of siloxy crotylsilane **6** and propargylic aldehyde **7** produced both desired dihydropyran **8** and byproduct furan **9** with low selectivity (Scheme 2).[7] The same reaction, when performed at higher temperature (20 °C), provided dihydropyran as the major product with modest yield. After further experiments, we have learned that silane reagent **10** bearing a triethylsiloxyl (TESO) group adjacent to the ester provided the desired dihydropyran in much higher yield. The enhanced nucleophilic character of a triethylsilyl ether is a subtle but important observation originally documented by Angle.[8] For instance, reaction of **10** and aldehyde **11** afforded dihydropyran **12** in 60−70% yield with no trace of the furan byproduct.

To complete the synthesis of the fully functionalized tetrahydropyran of the phorboxazoles, a stereoselective

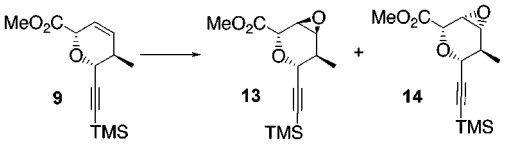
Scheme 2

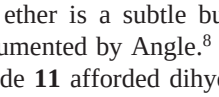


oxygenation of the double bond was required. We anticipated that suitable facial bias could be imposed by the dihydropyran, which would result in a stereoselective epoxidation. Regioselective epoxide ring opening followed by inversion of stereochemistry of the derived alcohol **20** would provide fully functionalized tetralhydropyran containing all of the required stereocenters of subunit **4**.

Our initial studies on the epoxidation of this substrate gave the β-epoxide with poor diastereoselectivity. For the epoxidation of **9**, there appears to be an interesting solvent effect as CH_2Cl_2 and aromatic solvents were less selective in the conversion of **9** to **13** (compare entries 2−4 with 5, Table 1). Thus, the desired β-epoxide **18** was obtained in good yield and selectivity (85%, dr = 13:1) using CCl_4 as the solvent (Scheme 3).

Table 1. Diastereoselective Epoxidation of Dihydropyran **9**



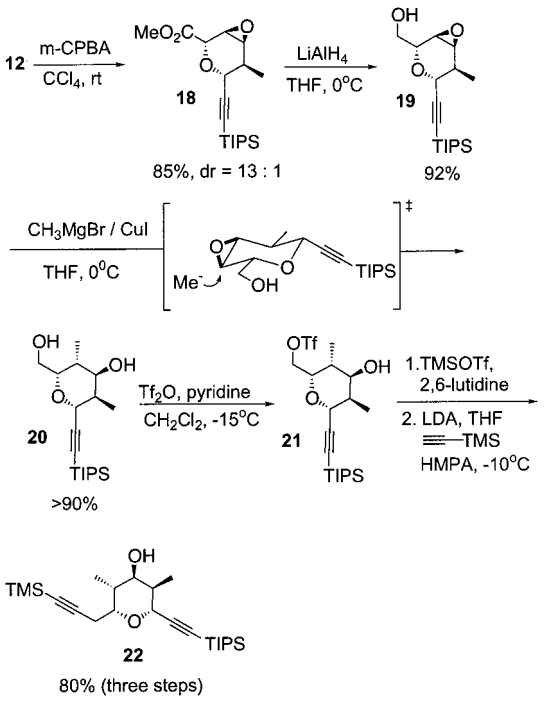
entry	reaction conditions	diastereoselectivity (β/α)[a]
1	 (8eq, CH_3CN, 0°C)	1 : 2
2	m-CPBA (2eq, CH_2Cl_2, rt)	3 : 2
3	m-CPBA (2eq, bezene, rt)	3 : 1
4	m-CPBA (2eq, toluene, rt)	5 : 1
5	m-CPBA (2eq, CCl_4, rt)	10 : 1

[a] Diastereoselectivity was determined by ^1H NMR (400 MHz) analysis.

(6) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469−471.

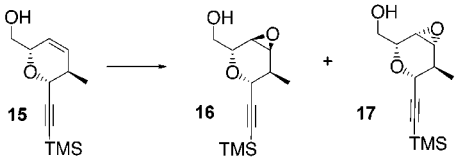
(7) We have reported that enantiomerically enriched tetrahydrofurans can be obtained by the reaction of crotylsilanes and aldehydes; see: (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *26*, 9868−9870. (b) Beresis, R. T.; Panek, J. S. *Bioorg. Med. Chem. Lett.* **1993**, *13*, 1609−1613. (c) For a related tetrahydrofuran synthesis, see: Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461−464.

Scheme 3



The epoxidation on the primary alcohol **15**, derived from the reduction of the ester, was also evaluated as a substrate that may provide useful levels of diastereoselectivity in the introduction of the epoxide. However, $LiAlH_4$ reduction of **9** afforded alcohol **15**, and subsequent reaction with *m*-CPBA under conditions identical to those in Table 1 provided *β*-epoxide as major isomer with lower levels of selectivity (Table 2).[9]

Table 2. Diastereoselective Epoxidation of **15**



entry	reaction conditions	diastereoselectivity (β / α)[a]
1	m-CPBA (2eq, CH_2Cl_2, rt)	1: 1
2	m-CPBA (2eq, bezene, rt)	3 : 1
3	m-CPBA (2eq, toluene, rt)	3 : 1
4	m-CPBA (2eq, CCl_4, rt)	5 : 1

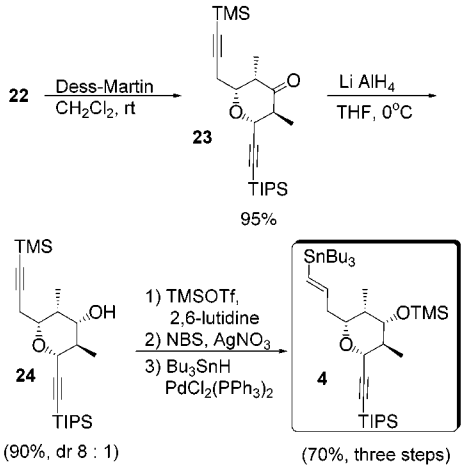
[a] Diastereoselectivity was determined by ^1H NMR (400 MHz) analysis.

Selective reduction of the methyl ester **18** in the presence of the epoxide cleanly provided epoxy-alcohol **19** in high yield. Gratifyingly, regioselective epoxide ring opening provided the diol **20** as a single diastereomer in excellent yield and without the need for purification.[10] It is worth noting that the copper-catalyzed ring opening takes place with complete conversion to the secondary alcohol. The reaction was much less efficient when excess Gilman reagent was used (5 equiv, 8 h). The efficiency of the ring opening leading to the trans-diaxial product **20** ($J^3_{H4,H5}$ = 2.6 Hz) is consistent with Furst−Plattner considerations.[11]

With the epoxide ring opening now solved, the synthesis of fully functionalized pyran was addressed. Treatment of the intermediate diol **20** with triflic anhydride and pyridine afforded the chromatographically stable primary triflate **21** in quantitative yield. Following protection of the secondary alcohol as its TMS ether, displacement of the primary triflate with lithium (trimethylsilyl)acetylide provided alkyne **22** in 80% overall yield.[12]

Completion of the C19−C28 fragment was carried out in a straightforward sequence beginning with a Dess−Martin oxidation[13] of the secondary alcohol, which was followed by a $LiAlH_4$ reduction of the derived ketone **23** producing the equatorial alcohol **24** in 90% overall yield (Scheme 4).

Scheme 4



The vinyl stannane was introduced through a Pd-catalyzed hydrostannation.[14] Accordingly, the secondary alcohol was protected as its TMS ether, which was followed by selective

(8) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 10211−10212.

(9) The lower diastereoselectivity can be attributed to existence of homoallylic acohol which facilitates the formation of α-epoxide. For a review on substrate-directed reaction, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(10) For studies on the mechanism of organocuprate epoxide ring opening, see: (a) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750−3771. (b) Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294−7307.

(11) (a) Furst, A.; Plattner, A. *Helv. Chim. Acta* **1949**, *32*, 275−283. (b) Hewbest, H. B.; Smith, M.; Thomas, A. *J. Am. Chem. Soc.* **1958**, *80*, 3293−3297.

(12) For the similar displacement of primary trifluoromethanesulfonates with the lithium anion of (trimethylsilyl)acetylene, see ref 4

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

(14) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

brominaiton (NBS)[15] of the TMS-protected alkyne, affording the 1-bromoalkyne. This material was treated with tributyltin hydride (2.2 mmol) and catalytic $PdCl_2(PPh_3)_2$ (5% mol) in THF, producing the desired (*E*)-vinyl stannane **4** in 70% overall yield.

In conclusion, we have described an effective and enantioselective synthesis of the fully functionalized C19−C28 tetrahydropyran subunit of phoborxazoles. This work demonstrates that the [4 + 2]-annulation using chiral crotylsilane methodology is suitably versatile for the synthesis of highly substituted tetrahydropyran rings. Further synthetic studies concerning the phoborxazoles will be forthcoming.

Acknowledgment. Financial support was obtained from the NIH/NCI (Grant R01GM55740).

Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015893U

(15) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans.* 1 **1996**, 2417−2419.