Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4933–4935

TETRAHEDRON LETTERS

Stereoselective synthesis of the C21–C27 fragment of the phorboxazoles

Bo Liu and Wei-Shan Zhou*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

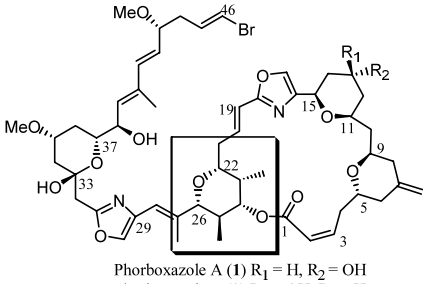
Received 31 December 2002; revised 27 February 2003; accepted 15 April 2003

Abstract—A stereoselective synthesis of the C21–C27 fragment of phorboxazoles A and B was achieved in 12 linear steps via an intramolecular cyclization induced by mercury acetate, to afford a functionalized tetrahydropyran.

Phorboxazoles A (**1**) and B (**2**),[1] isolated from the Indian Ocean sponge *Phorbas* sp., exhibit potent cytostatic activity against human tumor cell lines in the NCI panel.[2] The complex structure consists of four oxane rings, two oxazole rings, fifteen stereogenic centers and a conjugated diene segment (Fig. 1).

The novel structure and potent biological activities of the phorboxazoles have attracted tremendous attention in the synthetic community,[3] and several examples of successful total syntheses have been reported.[4] In this letter, our work on the synthesis of the C21–C27 segment of the phorboxazoles is described.

It has been reported that the intramolecular alkoxymercuration of unsaturated alcohols and phenols provide a general synthesis of five- and six-membered ring ethers.[5] This intramolecular alkoxymercuration chemistry has been employed in the synthesis of carbohydrates.[6] It was further shown that *cis*-2,6-disubstituted tetrahydropyrans could be thus generated in the course of Masamune's synthesis of the bryostatins[7] and Yoshii's synthesis of tetronomycin.[8] Accordingly, we hoped that this methodology would find utility in the synthesis of the phorboxazoles.



Phorboxazole A (**1**) R_1 = H, R_2 = OH
Phorboxazole B (**2**) R_1 = OH, R_2 = H

Figure 1.

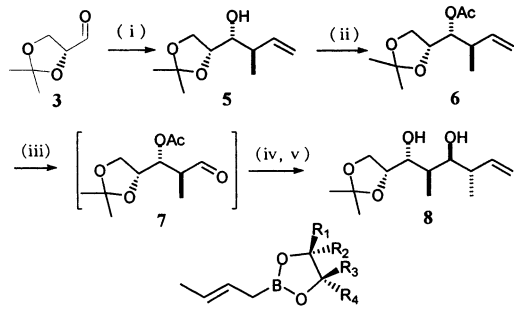
The synthesis of the C21–C27 fragment commenced from D-glyceraldehyde acetonide **3**, which was readily accessible from D-mannitol.[9] Asymmetric crotyl addition to **3** with chiral boronate (–)-**4** under Roush's conditions[10] afforded homoallylic alcohol **5**, which was transformed to its acetate **6** according to the standard procedure.[11] Asymmetric crotylation using (+)-**4** of aldehyde **7** obtained from the ozonolysis of **6**, was followed by treatment with sodium hydroxide. To our surprise, ^{1}H NMR spectroscopy of the product indicated that the B–O bond of the compound from asymmetric crotylation was not cleaved using the usual workup procedure.[10] However this could be achieved by treatment with base overnight in ether instead of toluene, resulting in the simultaneous hydrolysis of the acetate to provide **8** (Scheme 1).

To complete the synthesis of the fully functionalized tetrahydropyran of the phorboxazoles, a stereoselective intramolecular cyclization to construct the stereogenic center of C22 was required. We anticipated that suitable facial bias could be imposed in the transitional state which would result in a stereoselective cyclization.

To our delight, diol **8** was converted to pyran **9** using mercury acetate with good diastereoselectivity and in excellent yield, while compound **10**, the isomer of **9**,

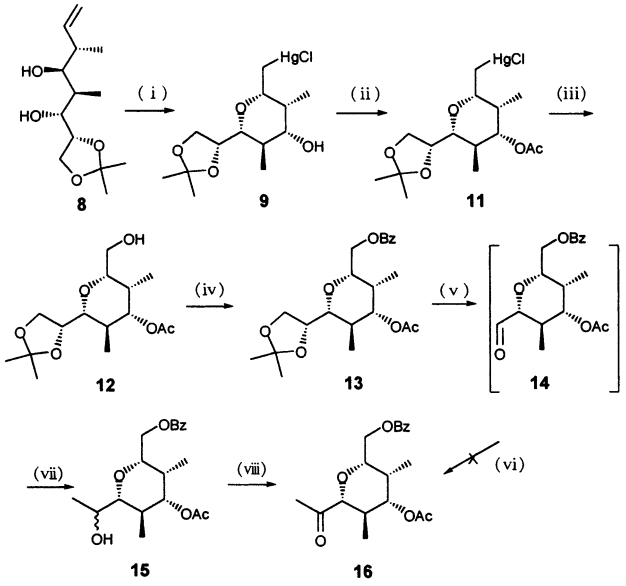
* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail: zhws@pub.sioc.ac.cn

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01099-2



Scheme 1. *Reagents and conditions*: (i) (–)-**4**, 4 Å MS, toluene, –78°C, 7 h, 65%. (ii) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, rt, overnight, 95%. (iii) O_3, CH_2Cl_2, –78°C, 2 h; then Me_2S, rt, overnight. (iv) (+)-**4**, 4 Å MS, toluene, –78°C, 6 h, then rt, overnight. (v) 1 M NaOH, Et_2O, rt, overnight, 60% for three steps.

was obtained in 13% yield. Acetylation of the free hydroxyl group of **9**, followed by oxidative demercuration[7,8,12] led to alcohol **12**. Benzoylation[13]of **12** afforded **13**, which was converted to aldehyde **14** in the presence of periodic acid[14] at 0°C. Although diazomethane had been successfully employed to transform aldehydes to methyl ketones in excellent yield,[15] treatment of **14** with diazomethane provided a mixture of complex products without formation of the desired ketone despite our considerable efforts to optimize the reaction conditions. In the event, we had to resort to



Scheme 2. *Reagents and conditions*: (i) $Hg(OAc)_2$, anhydrous benzene, ice/water bath, 5 h; then brine, 10 min, 87% for **9**. (ii) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, rt, overnight, 96%. (iii) $NaBH_4$, O_2, DMF, rt, 1.5 h, 93%. (iv) BzCl, pyridine, CH_2Cl_2, 0°C to rt, overnight, 83%. (v) H_5IO_6, EtOAc, 0°C, 2 h. (vi) Diazomethane, ether, –25°C. (vii) Me_3Al, CH_2Cl_2, 0°C, 1 h. (viii) Dess–Martin periodinane, CH_2Cl_2, rt, 12 h, 73% for three steps.

the selective methylation of the aldehyde in the presence of the ester with organometallic agents. In fact, methyl addition to aldehyde **14** proved sluggish with dimethyl zinc, and unreactive with methyltripropoxyl titanium, despite both agents having been extensively employed as nucleophilic reagents for addition to aldehydes.[16,17] Ultimately, selective addition was realized using trimethyl aluminum to afford alcohol **15**.[18] Having secured the requisite carbon skeleton, Dess–Martin oxidation afforded the desired ketone, **16** (Scheme 2).[19]

In summary, construction of the C21–C27 subunit **16** for the phorboxazoles has been achieved via a mercury-mediated cyclization. The synthesis proceeded in an efficient and stereocontrolled fashion in 12 linear steps (17% overall yield). The synthesis of other subunits of the phorboxzoles is in progress in our group.

Acknowledgements

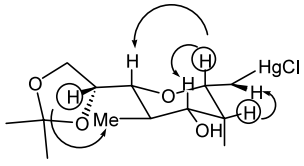
This work was supported by the National Natural Science Foundation of China.

References

1. Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126.
2. (a) Molinski, T. F.; Antonio, J. *J. Nat. Prod.* **1993**, *56*, 54; (b) Molinski, T. F. *Tetrahedron Lett.* **1998**, *37*, 7879; (c) Searle, P. A.; Molinski, T. F.; Brzeainski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422.
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) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099; (d) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998**, *39*, 183; (e) Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319; (f) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185; (g) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287; (h) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291; (i) Wolbers, P.; Misske, A. M.; Hoffman, H. R. *Tetrahedron Lett.* **1999**, *40*, 4527; (j) Wolber, P.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 1905; (k) Misske, A. M.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 4315; (l) Wolbers, P.; Hoffman, H. M. R. *Synthesis* **1999**, *40*, 2291; (m) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiaga, K. J. *Org. Lett.* **1999**, *1*, 87; (n) Smith, A. R., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909; (o) Smith, A. R., 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) Pattenden, G.; Plowright, A. T. *Tetrahedron Lett.* **2000**, *41*, 983; (r) Donaldson, W. A.; Greer, P. B. *Tetrahedron Lett.* **2000**, *41*, 3801; (s) Rychovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217; (t) Williams, D. R.; Clark, M. P.; Emde, V.; Berliner, M. A. *Org. Lett.* **2000**, *2*, 3023; (u) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469; (v) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533; (w) Evans,

D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536; (x) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693; (y) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Lett.* **2001**, *3*, 4003.

4. (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597; (b) Evans, D. A.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033; (c) Smith, A. R., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834; (d) Smith, A. R., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942.
5. (a) Weinberg, N. L.; Wright, G. F. *Can. J. Chem.* **1965**, *43*, 24; (b) Lethbridge, A.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2465; (c) Koning, C. B.; Green, I. R.; Michael, J. P.; Oliveira, J. R. *Tetrahedron* **2001**, *57*, 9623.
6. (a) Pougny, J. R.; Nassr, M. A.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375; (b) Paquet, F.; Sinay, P. *Tetrahedron Lett.* **1984**, *25*, 3071; (c) Martin, O. R.; Xie, F.; Kakarla, R.; Benhamza, R. *Synlett* **1993**, *5*, 165.
7. Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roverts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 2817.
8. Hori, K.; Hikage, N.; Inagaki, A; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888.
9. (a) Schimid, C. R.; Bryant, J. D. *Org. Synth.* **1993**, *72*, 6; (b) Earle, M. J.; Abolur-Rashid, A.; Priestley, N. D. *J. Org. Chem.* **1996**, *61*, 5697.
10. (a) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339; (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
11. Höfle, G.; Steglich, W.; Vorbrügen, H. *Angew. Chem., Int Ed. Engl.* **1978**, *17*, 569.
12. Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.
13. Haines, A. H. *Adv. Carbohydr. Chem Biochem.* **1974**, *33*, 11.
14. Li, L.; Wu, Y.; Wu, Y. *J. Carbohydr. Chem.* **1999**, *18*, 1067.
15. (a) Ravi, B. N.; Marwood, J. F.; Wells, R. J. *Aust. J. Chem.* **1980**, *33*, 2307; (b) Werner, R. M.; Shokek, O.; Davis, J. T. *J. Org. Chem.* **1997**, *62*, 8243.
16. For the use of dimethylzinc, see: Andres, J. M.; Elena, N.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron* **1999**, *55*, 14137.
17. For the use of methyltriisopropoxyltitanium, see: (a) Sutherland, A.; Vederas, J. C. *Chem. Commun.* **1999**, 1739; (b) Furstner, A.; Baumgrarter, J. *Tetrahedron* **1993**, *49*, 8541; (c) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus S. *Chem. Ber.* **1985**, *118*, 1421.
18. (a) Robl, J. A.; Sulsky, R.; Sieber-Mcmaster, E.; Ryono, D. E.; Cimarusti, M. P. *J. Med. Chem.* **1999**, *42*, 305; (b) Robl, J. A.; Cimarusti, M. P. *Tetrahedron Lett.* **1994**, *35*, 1393.
19. Compound **9**: colorless needles; mp 132–134°C; $[\alpha]_D^{20}=+42.7$ (*c* 0.81, $CHCl_3$); IR (KBr) 3505, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.28 (td, $J=6.6$, 2.4 Hz, 1H), 4.03 (s, 1H), 4.00 (d, $J=1.5$ Hz, 1H), 3.76 (td, $J=6.9$, 2.1 Hz, 1H), 3.39–3.46 (m, 1H), 2.99 (dd, $J=9.9$, 2.1 Hz, 1H), 2.16 (d, $J=6.9$ Hz, 2H), 1.82–1.94 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 1.01 (d, $J=6.0$ Hz, 3H), 0.99 (d, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.16, 80.45, 76.61, 76.41, 74.41, 65.40, 40.36, 34.71, 32.94, 26.31, 25.50, 12.52, 5.20. The relative stereochemistry of compound **9** was confirmed by NOE correlation (600 MHz).



9

Compound **16**: colorless oil; $[\alpha]_D^{20}=+94.4$ (*c* 0.54, $CHCl_3$); IR (film) 1719 (shoulder) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01–8.05 (m, 2H), 7.42–7.61 (m, 3H), 4.74 (dd, $J=11.1$, 5.1 Hz, 1H), 4.46 (dd, $J=12.0$, 7.5 Hz, A of AB, 1H), 4.29 (dd, $J=12.0$, 4.5 Hz, B of AB, 1H), 3.93–3.98 (m, 1H), 3.56 (d, $J=14.5$ Hz, 1H), 2.27–2.32 (m, 1H), 2.24 (s, 3H), 2.11 (s, 3H), 1.90–2.05 (m, 1H), 1.03 (d, $J=6.9$ Hz, 3H), 0.86 (d, $J=6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.79, 170.21, 166.14, 133.02, 129.62, 129.50, 128.27, 86.73, 77.24, 75.86, 64.69, 33.48, 31.12, 25.62, 20.85, 12.44, 6.30.