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Synthetic studies towards phorboxazole A. Stereoselective synthesis of the C3–C19 bis-oxane oxazole portion of the phorboxazole macrolide

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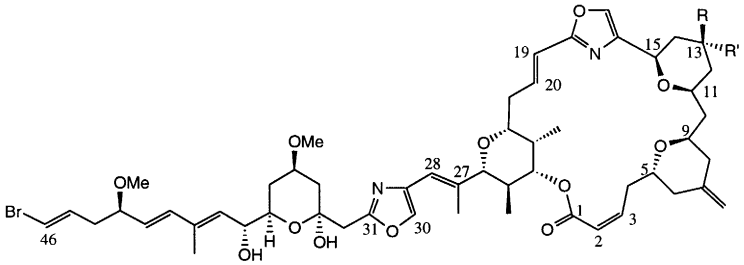
Abstract

A synthesis of the C3–C19 bis-oxane portion of phorboxazole A, involving an oxy anion intramolecular Michael reaction to produce a *cis*-oxane and an intramolecular Williamson reaction leading to a *trans*-oxane, is described.

The phorboxazoles **1** are unique oxane oxazole based macrolides isolated from an Indian Ocean sponge *Phorbas* sp., which show profound cytostatic activity against human tumour cell lines.[1] It is not surprising therefore that the phorboxazoles have attracted wide interest among synthetic chemists[2,3] and, indeed, in 1998 Forsyth and his colleagues[4] described the first total synthesis of phorboxazole A **1a**. In recent publications[2] we have presented our retrosynthetic analysis of phorboxazole, involving disconnections of the structure at the C2–C3, the C19–C20 and the C30–C31/C27–C28 bonds, leading to the key building blocks **2**, **3** and **4**. In the same publications we described stereoselective syntheses of the C20–C27 pentasubstituted oxane ring unit **3** and also the C31–C46 polyene oxane-hemiacetal side chain **2**. In this letter we present a synthesis of the C3–C19 bis-oxane oxazole portion **4** of phorboxazole A, suitably functionalised for connection to the oxane unit **3** en route to the natural product itself.



1a, R=H, R'=OH; **b**, R=OH, R'=H

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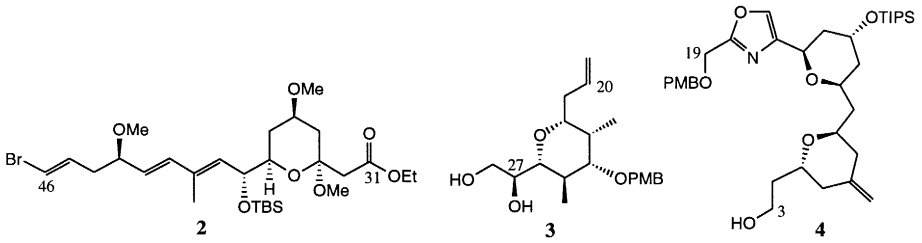
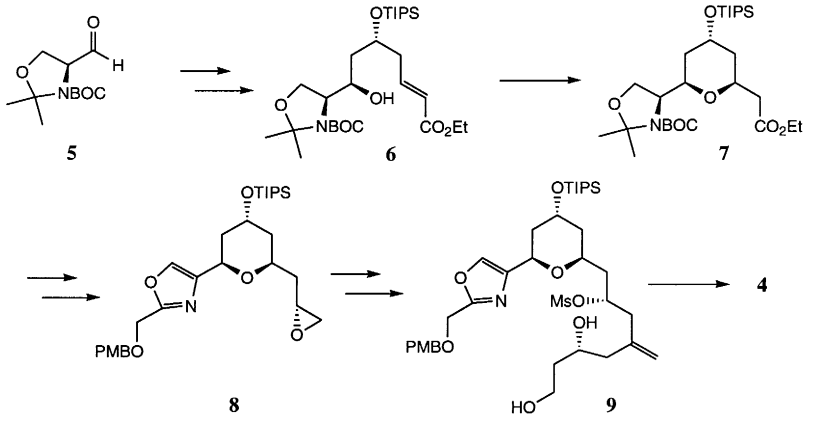


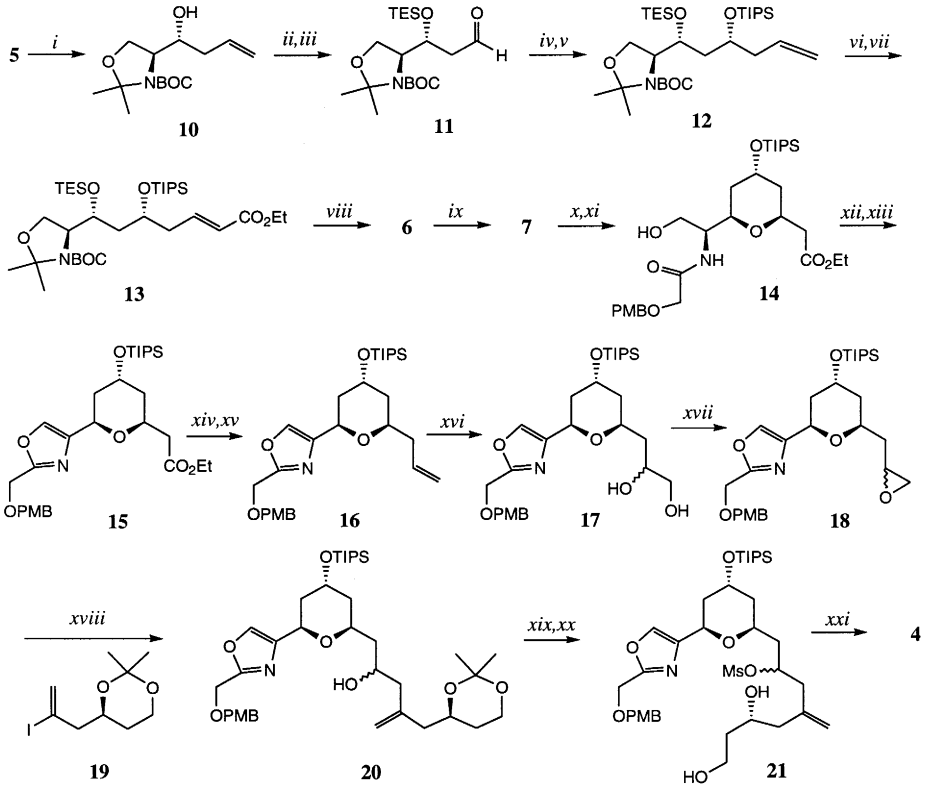
Our synthesis of the C3–C19 bis-oxane oxazole **4** was based on: (i) conversion of the chiral oxazolidine **5**[5] into the 7-hydroxy unsaturated ester **6** using successive Brown allylboration reactions;[6] (ii) oxy anion intramolecular Michael reaction of **6** leading to the *cis*-oxane **7**;[7] (iii) conversion of the oxazolidine unit in **7** to the corresponding oxazole **8**; (iv) introduction of the unsaturated polyol side chain producing **9**; and finally (v) intramolecular cyclisation of **9** to give the *trans*-oxane ring in **4** (Scheme 1).[8]



Scheme 1.

Thus, treatment of the homochiral aldehyde **5**, derived from L-serine,[5] with Brown's (+)-allyl diisopinocampheylborane reagent first led to the homoallylic alcohol **10** in 80% yield and with >92% diastereoselectivity (Scheme 2).[9] After protection of the hydroxyl group in **10**, ozonolysis to **11** followed by a second allylboration reaction and hydroxy group protection led to the corresponding 1,3-dioxy compound **12**. Ozonolysis of the alkene **12** and a Wittig reaction between the resulting aldehyde and (carboethoxymethylene)-triphenylphosphorane next led to **13**, which was then selectively deprotected in the presence of PPTS to reveal the 7-hydroxy unsaturated ester **6**. Treatment of **6** with NaHMDS at −78°C resulted in a selective intramolecular oxy anion Michael addition producing largely the *cis*(C11/C15)-oxane **7** (ca. 14% of the corresponding *trans*-pyran was produced concurrently) in a satisfying 88% yield. The oxazole ring in the target **4** was next elaborated from the oxazolidine **7** following deprotection and conversion of the resulting β-hydroxyamine to the amide **14**. Oxidation of **14** to the corresponding aldehyde and cyclisation, under known literature conditions,[10] produced the oxazole **15**. NOE studies with **15** confirmed the *cis*(C11/C15)-stereochemistry in this oxane intermediate.

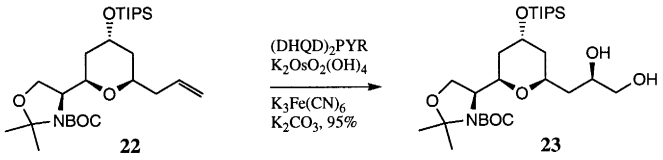
Introduction of the second (*trans*(C5/C9)) oxane ring in the target **4** was accomplished via the protected triol **20**, derived from addition of the cuprate reagent produced from the vinyl iodide **19**[11] to the epoxide intermediate **18**. The oxane epoxide **18** was produced from the oxane ester **15** via vicinal bis-hydroxylation of the alkene intermediate **16** (to **17**) as a key step.[12] Unfortunately we observed no diastereoselectivity in the conversion of **16** into **17**, although the oxazolidine oxane **22** related to the oxazole oxane **16** led to the corresponding vicinal diol **23** with >80% diastereoselectivity.[12] However, addition of the cuprate reagent, produced from the iodide **19**, to the epoxide **18** led to the coupled product



Scheme 2. Reagents: *i*, (a) (+)-α-allyl diisopinocampheylborane, (b) $Et_3N,\cdot H_2O_2$, 80%; *ii*, TESCl, Et_3N, DMAP, 90%; *iii*, (a) O_3, $NaHCO_3$, (b) PPh_3, 92%; *iv*, (a) (+)-α-allyl diisopinocampheylborane, (b) Et_3N, H_2O_2, 76%; *v*, TIPSOTf, 2,6-lutidine, 92%; *vi*, (a) O_3, $NaHCO_3$, (b) PPh_3, 95%; *vii*, Ph_3PCHCO_2Et, 87%; *viii*, PPTS, 84%; *ix*, NaHMDS, −78°C, 88%; *x*, 4 M HCl, dioxane; *xi*, $PMBOCH_2CO_2H$, EDC, HOBt, Et_3N, 75% (two steps); *xii*, Dess–Martin periodinane; *xiii*, (a) 2,6-di-^{t}butylpyridine, PPh_3, $C_2Br_2Cl_4$, (b) DBU, 73% (two steps); *xiv*, DIBAL-H, 87%; *xv*, Ph_3PCH_3Br, *n*-BuLi, 60%; *xvi*, $(DHQD)_2PYR$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, 95% (based on recovered SM); *xvii*, NaH, *N*-tosylimidazole, 76%; *xviii*, ^{t}BuLi, 2-Th-CuCNLi, 60% (based on recovered SM); *xix*, MsCl, Et_3N; *xx*, CSA, MeOH, 60% (two steps); *xxi*, Et_3N, CH_3CN, Δ, 78%

20, as a mixture of C9 epimers. Mesylation of **20** and acetonide deprotection gave rise to the penultimate intermediate **21**. Treatment of **21** with triethylamine in hot acetonitrile resulted in clean intramolecular ether formation involving only the C5 hydroxyl group to produce the six-ring oxane **4** in 78% yield as a 1:1 mixture of *cis*- and *trans*(C5/C9)-diastereoisomers. The diastereoisomers were separated by chromatography to afford the target intermediate bis-oxane oxazole **4**.[13]

Refinements to this strategy, especially to optimise the diastereoselectivity in the conversion of **15** into **18**, either via an oxazole or oxazolidine based *cis*-oxane intermediate, are now in progress in our laboratories.



Acknowledgements

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References

1. (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc*. **1995**, *117*, 8126; (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 9422; (c) Molinski, T. F. *Tetrahedron Lett*. **1996**, *37*, 7879.
2. (a) Pattenden, G.; Ye, T. *Tetrahedron Lett*. **1998**, *39*, 319; (b) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett*. **1998**, *39*, 6099.
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) Paterson, I.; Arnott, E. A. *Tetrahedron Lett*. **1998**, *39*, 7185; (e) Wolbers, P.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 1905; (f) Misske, A. M.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 4315; (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.; Hoffman, H. M. R. *Synthesis* **1999**, *5*, 797; (j) Wolbers, P.; Misske, A. M.; Hoffman, H. M. R. *Tetrahedron Lett*. **1999**, *40*, 4527; (k) Dunkel, R.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 8385; (l) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett*. **1999**, *1*, 87; (m) Smith III, A. B.; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett*. **1999**, *1*, 909; (n) Smith III, A. B.; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett*. **1999**, *1*, 913.
4. Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc*. **1998**, *120*, 5597.
5. McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31.
6. (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc*. **1983**, *105*, 2092; (b) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem*. **1995**, *500*, 1.
7. For some comparative examples, see: (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochem*. **1989**, *19*, 227; (b) Betancort, J. M.; Martin, V. S.; Padron, J. M.; Palazon, J. M.; Ramirez, M. A.; Soler, M. A. *J. Org. Chem*. **1997**, *62*, 4570; (c) Micalizio, G. C.; Roush, W. R. *Tetrahedron Lett*. **1999**, *40*, 3351.
8. For examples of conceptually similar approaches to oxane ring formation see Refs. 3b, g and Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc*. **1992**, *114*, 3162.
9. The diastereoselectivity of each of the allylboration reactions was determined by analysis of the NMR spectra. All new compounds showed satisfactory spectroscopic data together with mass spectrometry and/or combustion analysis. ^{1}H NMR data for compound **7** (360 MHz, C_6D_6, T=340K) δ 4.47–4.39 (1H, m), 4.24 (1H, bd, *J*~8.5), 4.19 (1H, bs), 4.13 (1H, ddd, *J* 10.8, 8.3, 2.0), 4.02–3.93 (1H, m), 3.98 (2H, q, *J* 7.1), 3.68 (1H, dd, *J* 8.6, 5.5), 2.51 (1H, dd, *J* 15.0, 7.3), 2.25 (1H, dd, *J* 15.0, 6.1), 1.90–1.84 (1H, m), 1.75–1.68 (4H, m), 1.61–1.53 (4H, m), 1.44 (9H, s), 1.30 (1H, ddd, *J* 13.6, 11.6, 2.5), 1.17–1.03 (21H, m), 1.00 (3H, t).
10. Wipf, P.; Lim, S. *J. Am. Chem. Soc*. **1995**, *117*, 558.
11. The vinyl iodide **19** was prepared starting from L-malic acid, based on procedures described earlier, see: Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515; Yamaguchi, M.; Hirao, I. *Tetrahedron Lett*. **1983**, *24*, 391; Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett*. **1983**, *24*, 731.
12. Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xu, D.; Sharpless, K. B. *J. Org. Chem*. **1993**, *58*, 3785.
13. The stereochemistry of the bis-oxane **4** was assigned using NOE experiments. ^{1}H NMR data for **4** (360 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* 0.8), 7.27 (2H, d, *J* 8.7), 6.89 (2H, d, *J* 8.7), 4.91 (1H, dd, *J* 11.2, 3.2), 4.77 (1H, s), 4.72 (1H, s), 4.56 (2H, s), 4.55 (2H, s), 4.41–4.39 (1H, m), 4.18–4.04 (2H, m), 4.01–3.95 (1H, m), 3.81 (3H, s), 3.74–3.71 (2H, m), 2.76 (1H, bs), 2.41 (1H, dd, *J* 13.2, 4.8), 2.28 (1H, dd, *J* 13.2, 3.7), 2.08 (1H, bd, *J*~14.0), 2.06 (1H, bd, *J*~13.2), 1.98–1.80 (4H, m), 1.74–1.70 (2H, m), 1.66–1.60 (2H, m), 1.17–1.04 (21H, m).