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Stereoselective synthesis of the C31–C39 unit of (+)-phorboxazoles from *m*-anisaldehyde☆

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Abstract—A stereoselective route for the synthesis of the C31–C39 fragment of (+)-phorboxazoles is described. The route features Birch reduction, ozonolysis and acid-catalysed cyclisation of enantiopure precursors as key transformations to give the tetrahydropyran ring, starting from *m*-anisaldehyde as a masked β-keto ester to obtain the pyran skeleton of compound **1**.

Phorboxazole A and its C-13 epimer phorboxazole B, isolated from a species of Indian Ocean sponge of the genus *Phorbas* sp.[1] are novel 21-membered macrolides accommodating four heavily functionalised oxanes and two 2,4-disubstituted oxazoles. Phorboxazoles A and B exhibit an extraordinary cytotoxic activity (GI_{50} of 1.58×10^{-9} M) against the entire panel of 60 human tumour cell lines held at the National Cancer Institute. Together with the spongiastatins,[2] the phorboxazoles are, therefore, the most potent naturally occurring cytotoxic agents yet discovered. Although their mechanism of action remains to be established, phorboxazole A has been shown to arrest the cell cycle in the S phase, whilst not inhibiting tubulin polymerisation or interfering with the integrity of microtubules, thereby suggesting a possibly unique mechanism.[1b] Their novel structure and potent biological activity have combined to make the scarcely available phorboxazoles attractive synthetic targets.[3] Forsyth et al.[4] published the first total synthesis of phorboxazole A in 1998; this was followed by a synthesis of phorboxazole B by Evans et al. in 2000.[5]

The phorboxazole skeleton consists of two 2,4-disubstituted oxazoles, four tetrahydropyrans and 15 stereogenic centres organised into a macrolide (C1–C26) and a side-chain substructure (C27–C46). Of the four THP rings, only one, the C31–C39 fragment, possesses a hemiketal functionality and three stereogenic centres. Several groups have reported different strategies for the enantioselective assembly of this THP-hemiketal ring.[6] The first stereoselective approach to this fragment was published by Molinski in 1996,[1c] wherein a derivative (3*R*,5*R*,7*R*,8*S*)-**1**, bearing four stereogenic centres with configuration identical to those present in the natural phorboxazoles, was synthesised using malic acid as the starting material. This synthesis of a model compound and the use of different NMR techniques were pivotal to the elucidation of the absolute configuration of 14 out of the 15 stereocentres in phorboxazoles[1b] (Fig. 1).

The most widely studied region of the phorboxazoles is the C31–C39 tetrahydropyran ring system. This highly-functionalised segment features four asymmetric centres and has been a showcase for various methods of tetrahydropyan synthesis. All approaches hitherto have been dependent on stoichiometric amounts of a chiral source, such as chiral starting materials, auxiliaries, or reagents. In connection with our interest in utilizing a substituted aromatic system as a masked, 1,3-dione or 1,3-diol and 1,5-dione in the synthesis of natural products, we report here a facile synthesis of (−)-**1**. A retrosynthetic strategy for constructing the pyran fragment is outlined in Scheme 1.

Construction of pyran **1** began with the preparation of allylic alcohol **3** from *m*-anisaldehyde (**2**) via a Wittig reaction followed by reduction of the ester with DIBAL-H.[7] Quantitative bromination of the allylic alcohol with PBr_3 in dry diethyl ether, furnished allyl bromide **4** which was coupled with propargyl alcohol using CuI/NaI in *n*-heptanol and acetone (1:1) to give the aromatic

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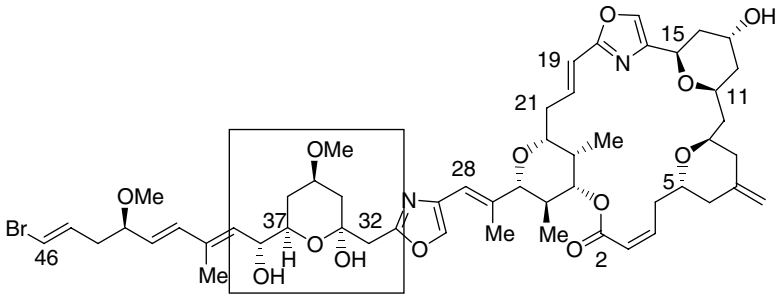
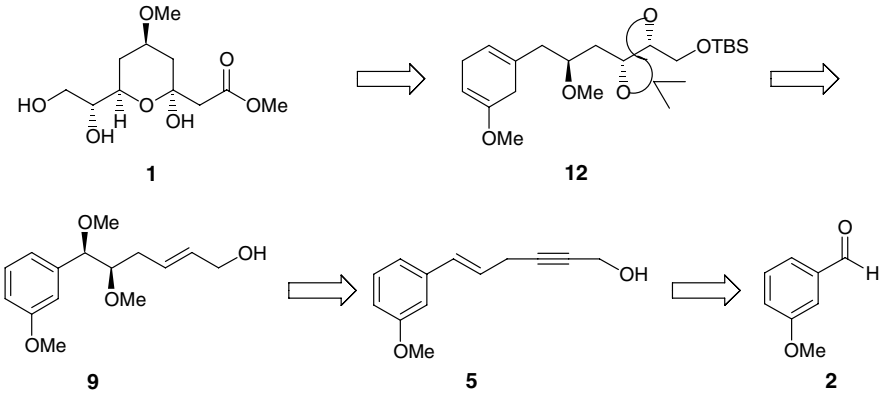


Phorboxazole A

Figure 1.

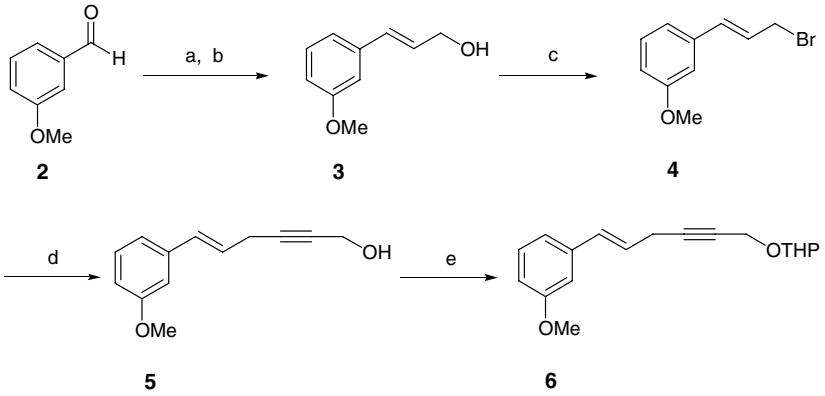


Scheme 1.

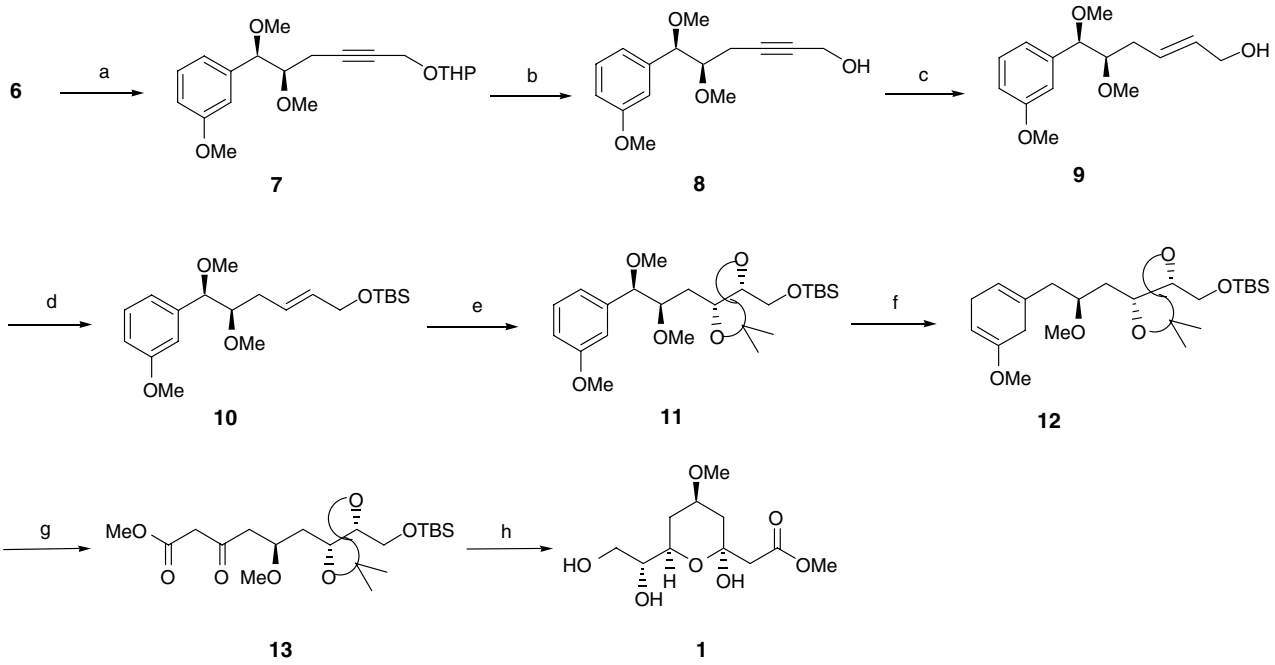
propargyl alcohol **5**.[8] Protection of the primary alcohol with DHP in THF furnished the THP protected alcohol **6** (Scheme 2).

Sharpless asymmetric dihydroxylation using AD-mix β on the protected alcohol afforded the diol in an 87% yield and 95% de.[9] Subsequent methylation with NaH and MeI in THF yielded dimethoxy compound **7**.[10] Deprotection of the THP group led to the propargyl alcohol **8** in an 85% yield. This compound was elaborated by sequential reduction with LAH followed by the treatment of the resulting allylic alcohol **9**[8] with TBDMSCl in THF to furnish **10** in an 88% yield (Scheme 3).

Sharpless asymmetric dihydroxylation of protected allyl alcohol **10** with AD-mix β afforded the corresponding diol in a 90% yield and 94% de. Protection of the vicinal diol as isopropylidene **11** was accomplished with 2,2-DMP.[11]



Scheme 2. Reagents and conditions: (a) (carbethoxymethylene)triphenylphosphorane, toluene, 80 °C, 82%; (b) DIBAL-H, dry DCM, −78 °C, 90%; (c) PBr_3, dry diethyl ether, 0 °C, 100%; (d) propargyl alcohol, CuI, NaI, K_2CO_3, *n*-heptane:acetone (1:1), rt, 62%; (e) DHP, dry THF, PTSA, 0 °C, 3 h, 68%.



Scheme 3. Reagents and conditions: (a) (i) AD-mix-β, $MeSO_2NH_2$, *t*-butanol:H_2O (1:1), 0 °C, 36 h, 87%; (ii) MeI, NaH, dry THF, 0 °C, 1 h, 100%; (b) cat. PTSA, MeOH + H_2O, 0 °C to rt, overnight, 85%; (c) LAH, dry THF, 0 °C to reflux, 4 h, 95%; (d) TBDMSCl, imidazole, dry THF, 0 °C to rt, 2 h, 88%; (e) (i) AD-mix-β, $MeSO_2NH_2$, *t*-butanol:H_2O (1:1), 0 °C, 40 h, 90%; (ii) 2,2-DMP, dry acetone, cat. PTSA, 5 h, 75%; (f) Li (80 equiv)/liq. NH_3, THF, *t*-butanol, −78 °C, 45 min; (g) O_3, CH_2Cl_2, Sudan-III, −78 °C, Me_2S, 2 h; (h) PPTS, methanol, 0 °C to rt, 3 h (overall yield for three steps, 20%).

The crucial intermediate, β-keto ester **13** was unveiled via a Birch reduction–ozonolysis sequence.[12] When **11** was treated with Li/liq. NH_3, *t*-BuOH,[13] the dihydroanisole intermediate **12** was produced. Ozonolytic cleavage was performed on the unpurified Birch product to give β-keto ester **13**,[14] which was carried to the next step without purification. Treatment of β-keto ester **13** with PPTS[15] in methanol furnished the C31–C39 fragment of phorboxazole (**1**) as a pale yellow semi-solid. The ^{1}H NMR, ^{13}C NMR and other spectral data of the synthetic sample were consistent with those of the reported product.

In conclusion, we have accomplished the synthesis of the C31–C39 fragment of (+)-phorboxazoles using asymmetric dihydroxylation and a Birch reduction–ozonolysis sequence for generating the 3,5-disubstituted 5,6-dihydropyran unit. The use of *m*-anisaldehyde as a masked β-ketoester is advantageous. Spectral data are provided.[16]

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16. Compound **9**: $[\alpha]_D^{25}$ −17.45 (*c* 0.021, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.22 (t, 1H, $J = 8.3$), 6.78 (m, 3H), 5.58 (m, 2H), 4.04 (m, 3H), 3.79 (s, 3H), 3.41 (s, 3H), 3.32 (q, 1H, $J = 10.4$, 5.9), 3.23 (s, 3H), 2.04 (m, 2H), 1.5 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.6, 140.6, 131.5, 129.2, 128.5, 120.1, 113.3, 112.9, 85.2, 83.9, 63.5, 58.7, 57.1, 55.2, 33.3; FABMS (relative intensity) *m*/*z*: 266 (M^+, 15), 235 (10), 195 (13), 165 (10), 151 (55), 121 (20), 69 (70), 57 (100); Anal. Calcd for $C_{15}H_{22}O_4$ (266.333): C, 67.64; H, 8.33; O, 24.03. Found: 266.228: C, 67.62; H, 8.30; O, 24.00. Compound **10**: $[\alpha]_D^{25}$ −22.81 (*c* 0.035, $CHCl_3$); IR (KBr, neat): 2932, 2857, 1693, 1600, 1462, 1257, 1099; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.20 (t, 1H, $J = 8.3$), 6.80 (m, 3H), 5.53 (m, 2H), 4.07 (m, 3H), 3.79 (s, 3H), 3.38 (s, 3H), 3.28 (m, 1H), 3.23 (s, 3H), 2.14 (m, 1H), 1.95 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.6, 140.6, 131.7, 129.1, 126.7, 120.0, 113.3, 112.7, 85.1, 84.1, 63.7, 58.7, 57.0, 55.0, 33.3, 25.9 (3 carbons), 18.3, −5.13 (2 carbons); FABMS (relative intensity) *m*/*z*: 380 (M^+, 40), 349 (5), 323 (10), 249 (7), 195 (20), 151 (80), 121 (20), 89 (40), 73 (100); Anal. Calcd for $C_{21}H_{36}O_4Si$ (380.594): C, 66.27; H, 9.53; O, 16.82. Found: 380.487: C, 66.24; H, 9.49; O, 16.70. Compound **11**: $[\alpha]_D^{25}$ −7.26 (*c* 0.011, $CHCl_3$); IR (KBr, neat): 3443, 2930, 2857, 1603, 1463, 1362, 1315, 1257, 1100; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.20 (t, 1H, $J = 8.5$), 6.80 (m, 3H), 4.09 (d, 1H, $J = 4.68$), 3.94 (m, 1H), 3.80 (s, 3H), 3.64 (t, 1H, $J = 5.2$) 3.52 (m, 3H), 3.38 (s, 3H), 3.26 (s, 3H), 1.41 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 1.25 (m, 1H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.6, 140.8, 129.0, 119.9, 113.2, 112.8, 85.9, 81.6, 81.4, 75.2, 63.4, 59.7, 57.2, 55.1, 35.6, 29.6, 27.3, 26.9, 25.8 (3 carbons), 14.1, −5.4 (2 carbons); FABMS (relative intensity) *m*/*z*: 454 (M^+, 20), 397 (10), 347 (10), 307 (10), 245 (20), 215 (22), 151 (70), 121 (20), 107 (10), 89 (50), 73 (100); Anal. Calcd for $C_{24}H_{42}O_6Si$ (454.672): C, 63.40; H, 9.51; O, 21.11. Found: 454.583: C, 63.36; H, 9.49; O, 21.08. Compound **1**: $[\alpha]_D^{25}$ −52.35 (*c* 0.17, $CHCl_3$); LCMS (relative intensity) *m*/*z*: 264.1 (M^+, 98), 246.0 (65), 203.1 (100), 172.2 (13), 144.2 (12), 117.1 (22); Anal. Calcd for $C_{11}H_{20}O_7$ (264.273): C, 49.99; H, 7.63; O, 42.38. Found: 264.192: C, 49.97; H, 7.60; O, 42.34; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.42 (s, 1H), 4.29 (m, 1H), 3.75 (s, 1H), 3.52 (s, 3H), 3.48 (m, 1H), 3.52 (m, 2H), 3.40 (s, 3H), 2.81 (s, 2H), 1.90 (m, 1H), 1.72 (m, 3H), 1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.96, 98.5, 72.8, 72.0, 68.6, 58.2, 51.9, 48.0, 41.9, 38.7, 32.1.