A Stereoselective Synthesis of the C20–C32 Fragment of the Phorboxazoles

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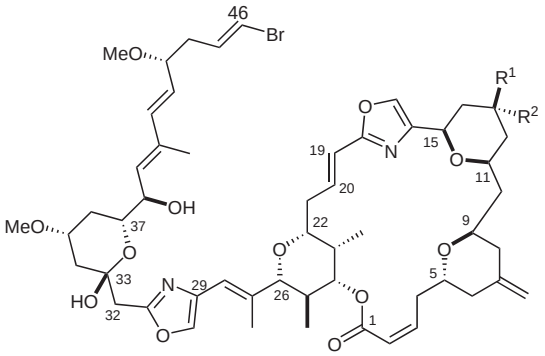
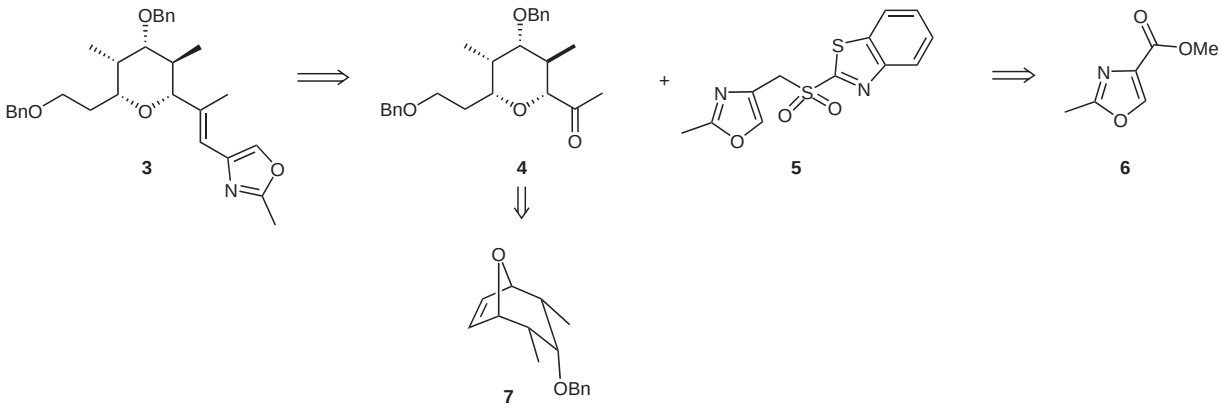
Abstract: The C20–C32 fragment of the phorboxazoles was realized in a stereoconvergent manner utilizing a desymmetrization approach. This successful strategy involves epimerization and modified Julia olefination as key steps.

Keywords: phorboxazole, desymmetrization, epimerization, Julia olefination

Phorboxazoles A (**1**) and B (**2**) are rare marine macrolides isolated from the Indian Ocean sponge *Phorbas sp.* by Searle and Molinski (Scheme 1).[1] Both C13 epimers are comprised of a 21-membered macrolide ring that embodies three oxane rings, one oxazole and subtends a side-chain that contains a second oxazole and a hemiketal oxane ring. These are among the most cytostatic natural products known, inhibiting the growth of tumor cells at nanomolar concentrations with mean $GI_{50} = 1.58 \times 10^{-9}$ M against the NCI panel of 60 tumor cell lines. These scarce natural products arrest cancer cell growth in the S phase at low to subnanomolar concentrations, making them promising candidates for therapeutic development. The tremendous biological activity and the fascinating molecular structure have stimulated synthetic efforts by a number of research groups[2] and seven elegant total syntheses have been reported so far.[3] The remarkable biological activities associated with the phorboxazoles make these compounds important leads for biotherapeutic development.[4] In this letter we describe the synthesis of the C20–C32 fragment.



(+)-phorboxazole A (**1**) R^1 = H, R^2 = OH
(+)-phorboxazole B (**2**) R^1 = OH, R^2 = H



Scheme 1

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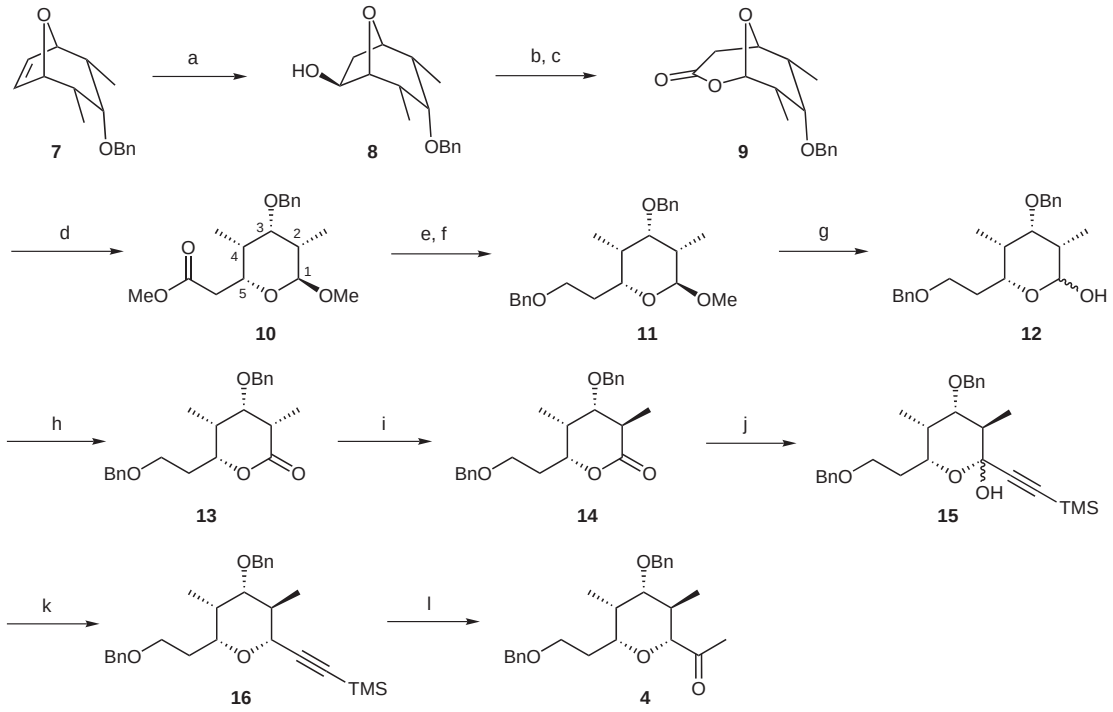


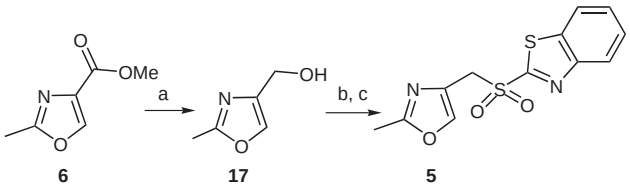
Scheme 2 *Reagents and conditions*: (a) (–)-Ipc$_2$BH, THF, –23 °C, 24 h, NaOH (3 N), 30% H_2O_2, r.t., 6 h; (b) PCC, CH_2Cl_2, r.t., 3 h; (c) MCPBA, $NaHCO_3$, CH_2Cl_2, r.t., 10 h; (d) H_2SO_4–MeOH, 0 °C→r.t., 12 h; (e) $LiAlH_4$, THF, 0 °C→r.t., 6 h; (f) BnBr, NaH, THF, r.t., 12 h; (g) AcOH–H_2O (3:2), 55 °C, 15 h; (h) PCC (1.5 equiv), NaOAc (2 equiv), celite, r.t., 3 h; (i) DBU (1 equiv), THF, r.t., 12 h; (j) *n*-BuLi–trimethylsilylacetylene (3 equiv each), THF, –78 °C, 1.5 h; (k) Et_3SiH–BF_3·Et_2O (10 equiv each), MeCN–CH_2Cl_2 (1:1), –40 °C, 2 h; (l) HgO, H_2SO_4, acetone, 50 °C, 1 h.

We have depicted our strategy in Scheme 1, which shows the disconnection approach. The convergent synthesis of the C20–C32 oxazole–oxane **3** is envisaged to be achieved by coupling two subunits, the pentasubstituted oxane **4** and the oxazole sulfone **5** via a modified Julia olefination. The tetrahydropyran moiety **4** is considered to be available by desymmetrization of the bicyclic precursor **7** (Scheme 2).

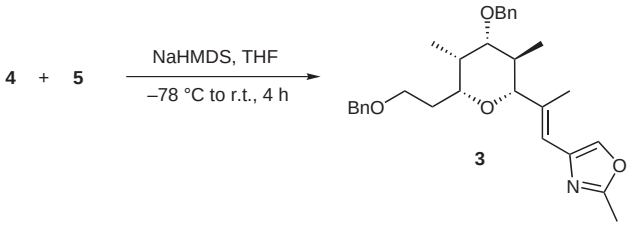
We initiated our synthesis from precursor **7**, which has been previously utilized in the synthesis of rifamycin-S,[5a] (+)-discodermolide,[5b,c] scytofycin C,[5d] prelactone B,[5e] (+)-membrenone and its 7-epimer[5f] wherein we had exploited the desymmetrization approach. Asymmetric hydroboration of the olefin **7** using (–)-diisopinocamphenylborane was carried out to obtain **8** in high optical purity (96%). The alcohol **8** was converted into the lactone **9** by a two-step sequence of pyridinium chlorochromate (PCC) oxidation followed by Baeyer–Villiger oxidation of the resulting ketone. The bicyclic lactone **9** was then subjected to methanolysis in the presence of a catalytic quantity of sulfuric acid in methanol to give acetal ester **10** exclusively in 85% yield, in which three out of five stereocenters of the oxane ring are present. Our subsequent task was to obtain the two further stereocenters at C1 and C2 of the tetrahydropyran unit. With that aim, ester **10** was reduced to the alcohol in quantitative yield using lithium aluminium hydride in tetrahydropyran and the product was protected as its benzyl ether. The dibenzyl methyl acetal **11** was hydrolyzed to give lactol **12** in 55% yield by heating in acetic acid–water (3:2)[6] at 55 °C, PCC oxidation of the lactol provided lactone **13** in quantitative yield. Epimerization[7] of the C2-methyl of **13** was carried out using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran, which furnished epimer **14** in 95% yield and 100% conversion. Epimerization was also effected using catalytic sodium methoxide and catalytic ethanolic potassium hydroxide. This transformation was confirmed by ^{1}H NMR in which the C2-H of **14** resonated upfield (δ 2.5 ppm) relative to the C2-H of **13** (δ 2.8 ppm) and also by the upfield chemical shift of the C3-H proton and modification of the multiplicity of the resonance (triplet to dd) indicating an *anti* relationship between C2-H and C3-H.

Nucleophilic addition of lithiumtrimethylsilyl acetylide to the resulting epi-lactone **14** at –78 °C in tetrahydrofuran provided an inseparable anomeric mixture of hemiketals **15** in 90% yield.[8] Reduction of the hemiketal to pyran was carried out using an excess of triethyl silane and boron trifluoride–diethyl ether complex in dichloromethane–acetonitrile (1:1) at –40 °C for one hour. This gave pentasubstituted pyran **16** exclusively in 85% yield in which the ether linkage between C1 and C5 is in a *syn* configuration (Scheme 2). The stereochemistry of the product was confirmed by ^{1}H NMR and NOE analysis.[9] Desilylation and hydration of the triple bond via oxy-mercuration[10] in a Markownikoff manner was effected in a single step using yellow mercury(II) oxide and aqueous sulfuric acid in refluxing acetone for two hours to give keto tetrahydropyran **4** in 70% yield.

The oxazole unit **6** was synthesized following the published procedure[11] and was reduced to alcohol **17** using DIBAL-H.[12] Oxazole sulfone **5** was accessed in two steps from the oxazole alcohol **17**, which was converted into its corresponding thioether under Mitsunobu reaction conditions[13] in 89% yield and subsequently oxidized with oxone to give the sulfone **5** in 90% yield. Coupling of the sulfone **5** and pentasubstituted tetrahydropyran **4** under the modified Julia olefination conditions[14] gave a separable mixture of *E*/*Z* geometrical isomers in a ratio of 9:1 in 70% yield based on the recovered starting material (Scheme 4).[15]



Scheme 3 (a) DIBAL-H, CH_2Cl_2, –78 °C, 3 h, r.t., 1 h; (b) 2-mercaptobenzothiazole, TPP, DEAD, THF, r.t., 12 h; (c) oxone, THF–MeOH–H_2O (2:1:1), 12 h.



Scheme 4

In summary, the practical synthesis of the central C20–C32 pyran moiety has been developed using a convergent strategy with key steps involving C-2 epimerization and modified Julia olefination. Efforts are in progress to construct the C20–C46 fragment of the phorboxazoles.

Acknowledgment

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(9) The six-membered ring is in the chair form $^5C_2$ conformation. C1-H, C3-H and C5-H have axial orientations confirmed by NOE enhancement between C1-H/C5-H, C1-H/C3-H and C3-H/C5-H and also between C4-Me/C2-H (Figure 1). This arrangement is also strongly supported by the coupling constants $J_{C1\text{-}H\text{–}C2\text{-}H}$ = 10.57 Hz, $J_{C3\text{-}H\text{–}C2\text{-}H}$ = 10.57 Hz and $J_{C3\text{-}H\text{–}C4\text{-}H}$ = 4.53 Hz.

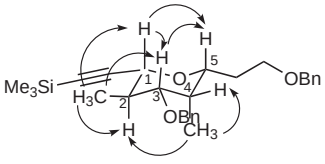

Figure 1

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(15) *Spectral Data*: Compound **1** $[\alpha]_D$ +28.26 (*c* 0.01, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.07 Hz, 3 H), 0.96 (d, *J* = 6.96 Hz, 3 H), 1.60–2.16 (m, 4 H) 1.87 (s, 3 H), 2.42 (s, 3 H), 3.24 (dd, *J* = 5.20, 10.41 Hz, 1 H), 3.44–3.76 (m, 3 H), 4.30–4.68 (m, 5 H), 6.10 (s, 1 H), 7.20–7.34 (m, 10 H), 7.38 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 5.80, 13.23, 13.69, 18.72, 33.02, 33,38, 34.44, 67.03, 69.97, 72.95, 74.46, 76.28, 76.92, 77.56, 79.77, 83.99, 119.46, 127.44, 127.62, 128.26, 135.18, 137.24, 138.49, 138.67; LC–MS: *m*/*z* = 476 [M + H^+].
Compound **10**: $[\alpha]_D$ +57.29 (*c* 1.85, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 7.18 Hz, 3 H), 1.05 (d, *J* = 7.81 Hz, 3 H), 2.0–2.20 (m, 2 H), 2.25–2.36 (dd, *J* = 3.9, 15.6 Hz, 1 H), 2.57–2.70 (m, 1 H), 3.30 (s, 3 H), 3.68 (s, 3 H), 3.84 (m, 1 H), 4.25–4.34 (m, 1 H), 4.47–4.50 (m, 3 H), 7.22–7.30 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.91, 12.89, 35.45, 36.60, 37.31, 51.53, 54.74, 67.34, 69.99, 75.36, 103.42, 127.03, 127.20, 128.14, 172.00; MS (FAB): *m*/*z* = 291 [M^+– OMe].
Compound **13**: colorless oil; $[\alpha]_D$ +50.5 (*c* 1.00, $CHCl_3$); IR (KBr): 3029, 2871, 1743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 7.23 Hz, 3 H), 1.32 (d, *J* = 7.23 Hz, 3 H), 1.72–2.12 (m, 2 H), 2.24–2.40 (m, 1 H), 2.72–2.88 (m, 1 H), 3.52–3.72 (m, 2 H), 3.88 (t, *J* = 5.78 Hz, 1 H), 4.44–4.56 (m, 5 H), 7.24–7.36 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.64, 12.57, 32.41, 35.56, 39.46, 66.24, 73.19, 73.56, 76.26, 127.44, 127.73, 128.40, 137.78, 138.15, 174.34; MS (FAB): *m*/*z* = 369 [M + H^+].
Compound **14**: colorless oil; $[\alpha]_D$ +76.5 (*c* 1.00, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 7.55, 3 H), 1.36 (d, *J* = 6.79 Hz, 3 H), 1.72–1.84 (m, 1 H), 1.96–2.08 (m 1 H), 2.24–2.32 (m, 1 H), 2.44–2.56 (m, 1 H), 3.48 (dd, *J* = 3.77, 9.82 Hz, 1 H), 3.54–3.60 (m, 2 H), 4.32–4.64 (m, 5 H), 7.24–7.32 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.72, 14.61, 33.03, 38.31, 65.92, 70.56, 73.17, 76.15, 80.39, 127.61, 128.43, 137.59, 173.54; MS (FAB): *m*/*z* = 369 [M + H^+].
Compound **16**: colorless oil; $[\alpha]_D$ +54.54 (*c* 0.01, $CHCl_3$); IR (KBr): 2961, 2926, 2179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.17 (s, 9 H), 0.96 (d, *J* = 6.79 Hz, 3 H), 1.04 (d, *J* = 6.79 Hz, 3 H), 1.56–1.68 (m, 1 H), 1.76–2.04 (m, 3 H), 3.09 (dd, *J* = 4.53, 10.57 Hz, 1 H), 3.46–3.60 (m, 2 H), 3.60–3.64 (d, *J* = 10.57 Hz, 1 H), 4.10 (q, *J* = 7.55, 14.35 Hz, 1 H), 4.30 (d, *J* = 11.33 Hz, 1 H), 4.49 (s, 2 H), 4.59 (d, *J* = 12.06 Hz, 1 H), 7.20–7.34 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 5.99, 14.19, 33.33, 34.47, 37.23, 67.02, 69.96, 73.71, 75.98, 83.05, 103.65, 127.74, 128.44, 138.59; LC–MS: *m*/*z* = 450 [M + H^+].
Compound **4**: colorless oil; $[\alpha]_D$ +90.0 (*c* 0.01, $CHCl_3$); IR (KBr): 2969, 2926, 2858, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.98 (m, 6 H), 1.60–2.20 (m, 4 H), 2.11 (s, 3 H) 3.18 (dd, *J* = 4.68, 10.93 Hz, 1 H), 3.32 (d, *J* = 10.93 Hz, 1 H), 3.44–3.64 (m, 3 H), 4.32–4.70 (m, 4 H), 7.28 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.98, 19.44, 26.51, 27.39, 28.40, 60.78, 64.133, 67.09, 69.16, 70.69, 71.11, 71.53, 77.26, 81.76, 121.69, 121.77, 122.44, 122.45, 132.39, 132.49, 201.15; LC–MS: *m*/*z* = 397 [M + H^+].
Compound **5**: IR (KBr): 3029, 2871, 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 4.71 (s, 2 H), 7.54–7.69 (m, 3 H), 7.99 (m, 1 H), 8.24 (m, 1 H); ESI-MS: *m*/*z* 295 [M + H^+].