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Towards the Total Synthesis of Phorboxazoles A and B: Stereocontrolled Synthesis of a C_{20}–C_{32} Subunit

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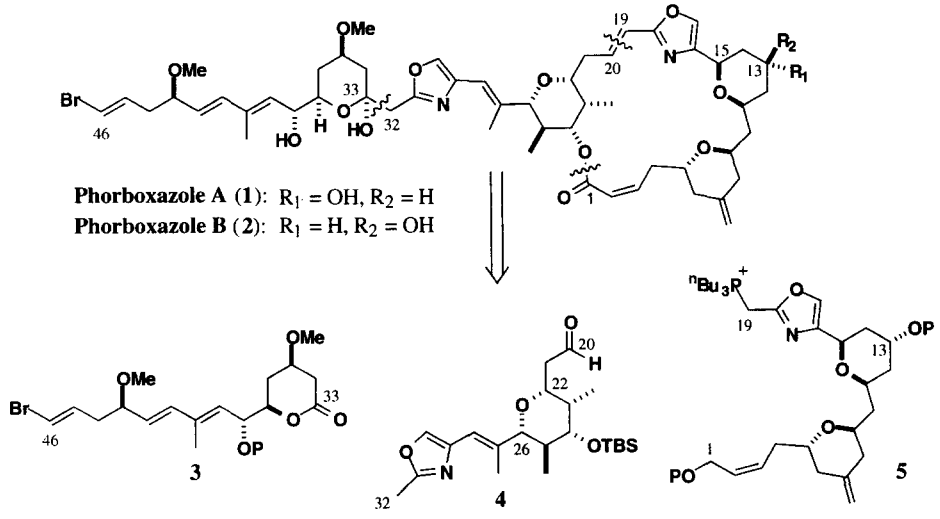
Abstract: The C_{20}–C_{32} phorboxazole subunit **4**, containing 5 stereocentres, was prepared in 8 steps (34%) from ethyl ketone (*S*)-**7**. Key steps included a boron-mediated *anti* aldol reaction and an intramolecular hetero-Michael reaction. Installation of the C_{19}–C_{20} (*E*)-alkene using a Wittig reaction produced a C_{15}–C_{32} fragment, including both oxazoles present in the natural product.

In 1995 Searle and Molinski isolated the marine natural products phorboxazoles A (**1**) and B (**2**) (**Scheme 1**) from a novel Indian Ocean sponge of the genus *Phorbas*.[1] Both C_{13} epimers are potent cytostatic agents (GI_{50} < 0.8 nM). Moreover, the ability of the phorboxazoles to halt the cell cycle in S-phase provides a potential complement to the tubulin-mediated activity of antineoplastic agents causing M-phase arrest (*e.g.* discodermolide).[1,2] Because of their powerful biological activity and structural complexity, the phorboxazoles have inspired considerable interest as synthetic targets,[3,4] including a recent total synthesis by Forsyth.[3a] Salient features of the phorboxazole skeleton include a 25-membered macrolide ring containing three tetrahydropyrans and a 2,4-substituted oxazole; the pendant sidechain comprises a further oxazole, a hemiacetal, diene system, and terminal vinyl bromide.



Scheme 1

In our convergent approach to phorboxazole A (**1**), we envisage three key disconnections, thereby dividing the natural product into subunits **3**-**5**, all of comparable complexity (**Scheme 1**). It is anticipated that the C_{33}–C_{46} segment will be incorporated *via* addition of a C_{32}-metallated methyl oxazole to δ-lactone **3**.[5] We plan to assemble the macrocyclic ring itself by (*E*)-olefination to install the C_{19}–C_{20} double bond, followed by macrolactonisation to close the 25-membered ring. As part of our studies towards the synthesis of phorboxazole A, we now report a stereocontrolled synthesis of the C_{20}–C_{32} subunit **4**. Construction of the pivotal pentasubstituted tetrahydropyran ring (C_{22}–C_{26}) involved three key stereodetermining steps: a boron-

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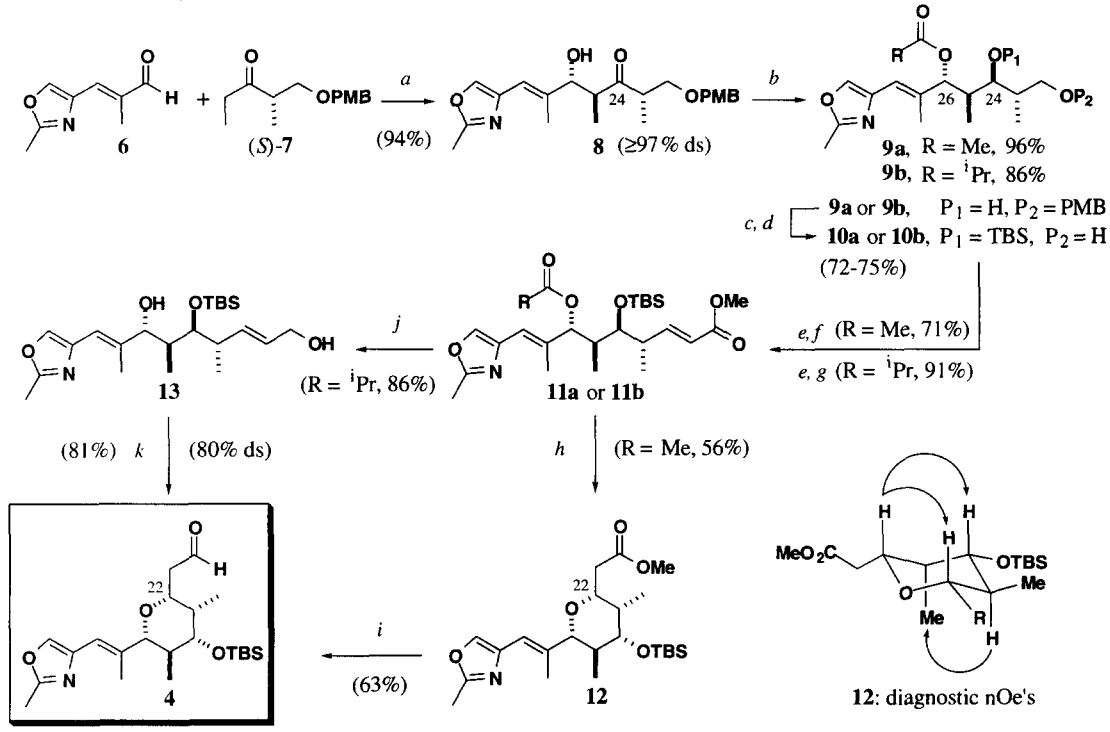
mediated *anti* aldol reaction, substrate-directed 1,3-*anti* reduction, and an intramolecular hetero-Michael reaction. The feasibility of the proposed C_{19}–C_{20} olefination was then demonstrated by the further synthesis of a more elaborate C_{15}–C_{32} fragment of **1**.

The route to the C_{20}–C_{32} subunit **4** is summarised in **Scheme 2**.[6] The synthesis began with a substrate-controlled *anti* aldol reaction between readily available aldehyde **6**[7] and chiral ketone (*S*)-**7**.[8] Following our usual conditions for the generation of the (*E*)-enol borinate of **7**,[8] addition of aldehyde **6** gave the expected *anti* aldol adduct **8** in 94% yield with ≥97% ds. Stereoselective reduction of the C_{24} carbonyl of **8** was then achieved using a modified Evans-Tishchenko reaction,[9] whereby the catalytic species was pre-formed by mixing SmI_2 (30 mol%) and RCHO (R = Me or ^{i}Pr), followed by addition of **8**. This produced the 1,3-*anti* reduction products **9a** (96%) or **9b** (86%) with ≥97% ds and simultaneously allowed differential protection of the C_{24} and C_{26} hydroxyls.



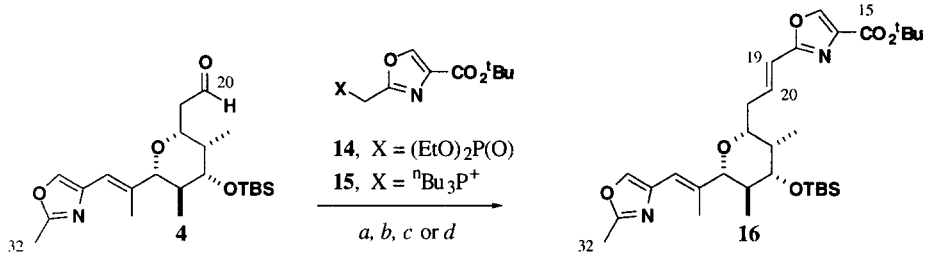
Scheme 2: (a) (*c*-Hex)$_2$BCl, Et_3N, Et_2O, 0 °C, 1 h; **6**, -78 → -20 °C, 18 h; H_2O_2, MeOH, pH 7 buffer; (b) SmI_2 (30 mol%), RCHO, THF, -20 °C, 15 min; **8**, -20 °C, 1 h; (c) TBSCl, Im, DMAP, DMF, 80 °C, 50 h; (d) DDQ, 20:1 CH_2Cl_2/H_2O, 20 °C, 1 h; (e) $(COCl)_2$, DMSO, -78 °C, 10 min; **10a** or **10b**, -78 °C, 1 h; Et_3N, -78 → -40 °C, 40 min; (f) $Ba(OH)_2$, $(MeO)_2P(O)CH_2CO_2Me$, 80:1 THF/H_2O, 20 °C, 1 h; (g) LiCl, DBU, $(MeO)_2P(O)CH_2CO_2Me$, 4:1 CH_3CN/CH_2Cl_2, 20 °C, 2.5 h; (h) K_2CO_3, MeOH, 20 °C, 26 h; (i) DIBAL, CH_2Cl_2, -78 °C, 5 h; (j) DIBAL, CH_2Cl_2, -78 °C, 5 h; (k) SO_3•pyr, Et_3N, 2:1 CH_2Cl_2/DMSO, 0 °C, 2 h.

Protection of the C_{24} hydroxyl groups of **9a** or **9b** as TBS ethers was best achieved using TBSCl under forcing conditions (1.0 M, 80 °C, >2 days).[10] Unfortunately, some migration of the ester protecting group occurred under the silylation conditions, resulting in limited scrambling of the C_{24} and C_{26} protecting groups. For the acetate series, an inseparable 4:1 regioisomeric mixture was obtained, while the isobutyrate afforded a 9:1 mixture, from which the minor regioisomer could be readily removed by flash column chromatography.[11] Oxidative cleavage of the PMB ether then afforded primary alcohols **10a** or **10b** in good overall yield (R = Me, 69%; R = ^{i}Pr, 64% over 3 steps). Swern oxidation followed by Horner-Wadsworth-Emmons

olefination with trimethylphosphonoacetate, using either $Ba(OH)_2$[12a] (for R = Me) or LiCl/DBU[12b] (for R = ^{i}Pr), gave the required (*E*)-enoates **11a** or **11b.**

With these differentially-protected (*E*)-enoates in hand, two different routes towards the C_{22}–C_{26} tetrahydropyran were pursued. For the acetate series (R = Me), methanolysis of the ester led to concomitant cyclisation to afford a separable mixture of tetrahydropyran **12** (33%) and its C_{22} epimer (22%). Our intention was to correct this lack of kinetic selectivity by equilibration under basic conditions *via* a series of Michael/retro-Michael reactions.[13] However, treatment of the minor C_{22} epimer with Triton-B methoxide failed to induce equilibration to the desired C_{22} isomer. Reduction of desired tetrahydropyran ester **11** with DIBAL resulted in direct conversion to aldehyde **4** in 63% yield: this therefore represents a route to the required C_{20}–C_{32} subunit (10% overall yield from **6**).

In order to achieve better control over the C_{22} stereocentre, an alternative route was pursued with the isobutyrate series. In this approach, enoate **11b** was fully reduced with DIBAL to give diol **13**, followed by selective oxidation of the primary C_{20} hydroxyl under Parikh-Doering conditions.[14] The resulting enal underwent cyclisation during isolation to give aldehyde **4** (81%) as a separable 4:1 mixture of C_{22} epimers. Furthermore, subjecting the minor, undesired tetrahydropyran aldehyde to basic equilibration conditions did indeed result in rapid conversion to give exclusively the all-equatorial C_{22} epimer **4**.[13,15] Thus, recycling of the unwanted epimer increased the net control exerted over the formation of the C_{22} stereocentre. This second route afforded the C_{20}–C_{32} subunit in an improved 34% overall yield over 8 steps.



Scheme 3: (a) **14**, ^{n}BuLi, THF, -78 °C, 30 min; **4**, THF, 0 °C, 1 h; (b) **14**, NaHMDS, THF, 0 °C, 30 min; **4**, THF, 0 °C, 2 h; (c) **14**, KHMDS, THF, 0 °C, 30 min; **4**, THF, 0 °C, 1 h; (d) **15**, LiHMDS, DMF, 0 °C, 30 min; **4**, DMF, 0 °C, 1 h.

Table 1. Optimisation of the C_{19}–C_{20} (*E*)-olefination

Entry	X	Base	Conditions	Yield	Selectivity (*E* : *Z*)
1[a]	$(EtO)_2P(O)$	^{n}BuLi	THF, 0 °C	100%	38:62
2[b]	$(EtO)_2P(O)$	NaHMDS	THF, 0 °C	79%	46:54
3[c]	$(EtO)_2P(O)$	KHMDS	THF, 0 °C	71%	44:56
4[d]	$^n Bu_3P^+$	LiHMDS	DMF, 0 °C	91%	89:11

The feasibility of the proposed disconnection of the C_{19}–C_{20} double bond was then tested by conducting a series of olefinations on aldehyde **4** (**Scheme 3**).[16] Metallation of diethyl phosphonate **14** and addition of aldehyde **4** gave the larger C_{15}–C_{32} segment, **16**, as a separable mixture of geometric isomers (**Table 1**, entries 1-3). Notably, using lithium, sodium or potassium cations, the undesired (*Z*)-olefin was obtained as the major isomer in each case. After extensive screening of conditions, it was found that best results were achieved using a Wittig procedure.[16b] Hence, phosphonium salt **15** was formed *in situ* from the corresponding bromide and $^n Bu_3P$ in DMF (60 °C, 5 h), immediately deprotonated with LiHMDS (0 °C, 30 min), and then allowed to react with aldehyde **4** to afford **16** as an 89:11 *E*:*Z* mixture, now in favour of the desired olefin.[6,17]

In conclusion, the C_{20}–C_{32} subunit **4**, containing 5 stereocentres arrayed around the C_{22}–C_{26} tetrahydropyran ring as well as the oxazole-(*E*)-alkene unit of the phorboxazole sidechain, was prepared in 8 steps from ethyl ketone (*S*)-**7** to provide 34% overall yield[15] of the correct diastereomer. High levels of stereocontrol resulted from the key stereodetermining reactions: a boron-mediated *anti* aldol reaction, substrate-directed 1,3-*anti* reduction, and an intramolecular hetero-Michael reaction. Controlled (*E*)-olefination of aldehyde **4** to give the C_{15}–C_{32} fragment **16** has also been achieved. Studies on the C_{32}–C_{33} bond formation and further work towards the total synthesis of the phorboxazoles are currently underway.

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6. All new compounds gave spectroscopic data in agreement with the assigned structures. (*E*)-Olefin **16** had: ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.00 (1H, s, $\underline{H}_{17}$), 7.48 (1H, s, $\underline{H}_{30}$), 6.78 (1H, ddd, *J* = 16.0, 8.3, 6.3 Hz, $\underline{H}_{20}$), 6.35 (1H, d, *J* = 16.1 Hz, $\underline{H}_{19}$), 6.17 (1H, s, $\underline{H}_{28}$), 3.54 (1H, ddd, *J* = 8.0, 5.5, 1.9 Hz, $\underline{H}_{22}$), 3.44 (1H, d, *J* = 10.2 Hz, $\underline{H}_{26}$), 3.42 (1H, dd, *J* = 10.0, 4.8 Hz, $\underline{H}_{24}$), 2.56 (1H, dddd, *J* = 14.8, 7.9, 6.3, 1.8 Hz, $\underline{H}_{21b}$), 2.43 (3H, s, $\underline{H}_{32}$), 2.31 (1H, dddd, *J* = 14.8, 8.3, 5.6, 1.1 Hz, $\underline{H}_{21a}$), 1.91 (3H, d, *J* = 1.1 Hz, $\underline{H}_{48}$), 1.78-1.71 (2H, m, $\underline{H}_{23}$ and $\underline{H}_{25}$), 1.57 (9H, s, $CO_2C\underline{Me}_3$), 0.97 (3H, d, *J* = 6.9 Hz, $C_{23}\underline{Me}$), 0.90 (9H, s, $SiC\underline{Me}_3$), 0.74 (3H, d, *J* = 6.5 Hz, $C_{25}\underline{Me}$), 0.06 (3H, s, Si$\underline{Me}$), 0.04 (3H, s, Si$\underline{Me}$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 161.4, 160.6 (2C), 142.5, 138.4, 138.1, 137.8, 135.6, 135.3, 118.6, 117.6, 88.8, 82.0, 77.4, 77.3, 39.3, 36.5, 34.8, 28.2, 25.8, 18.1, 14.3, 13.9, 13.8, 5.9, -4.1, -4.8.

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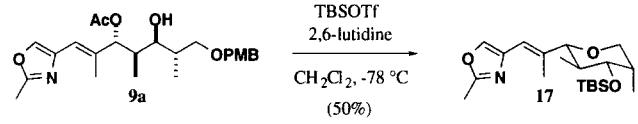
10. Treatment of **9a** with TBSOTf afforded the undesired tetrahydropyran product **17** even at -78 °C, *via* a Lewis acid-promoted cyclisation with precedent in other work performed in this laboratory:



11. For R = Me, the minor regioisomer could not be removed until cyclisation to afford tetrahydropyran ester **12**.

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15. Unfortunately, self-condensation of the aldehyde could not be avoided during equilibration with Triton-B methoxide, leading to a modest 52% recovery of configurationally pure **4**.

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17. The high (*E*)-selectivity is largely attributable to the use of the phosphonium ylid instead of the phosphonate, with the change of solvent from THF to DMF having little effect.