A Convergent Synthesis of the C31-C46 Fragment of Phorboxazoles[1]

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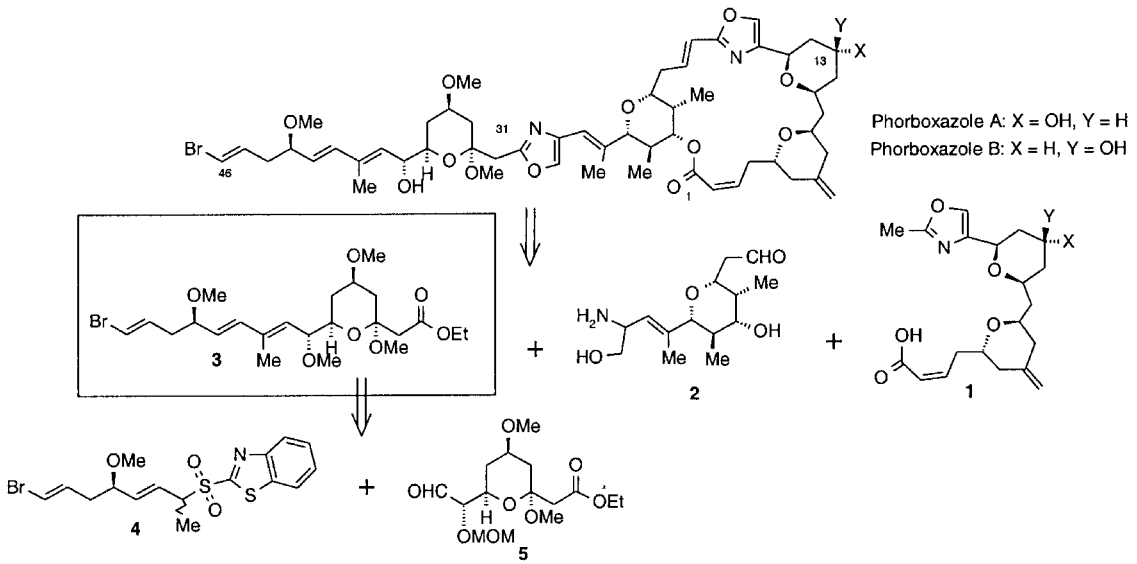
Abstract: A convergent synthesis of the C31-C46 fragment of phorboxazoles has been achieved. This involved the preparation of a C31-C39 aldehyde and a C40-C46 benzothiazole secondary sulfone followed by their coupling, employing modified Julia olefination as a key reaction.

Key words: phorboxazole, Julia olefination, secondary sulfone, sodium formate

Searle and Molinski reported the isolation of phorboxazoles A and B, C-13 epimeric oxazole-containing macrolides, from an Indian Ocean sponge *Phorbas sp.* in 1995 (Scheme 1).[2] Complete structural assignments for phorboxazoles have resulted from the extensive NMR studies.[3] The phorboxazoles were reported to be extremely cytostatic towards the National Cancer Institute's panel of 60 tumor cell lines, and to have potent in vitro antifungal activity against *C. albicans* and *S. carlsbergensis*.[3a] Together with the altohyrtins[4] and the bryostatins,[5] they are amongst the antitumor natural products as they inhibit growth of tumor cells at sub-nanomolar concentrations in vitro (mean GI_{50} $1.58 \cdot 10^{-9}$M).[3b] Unlike antimitotic natural products such as Paclitaxel[6] or the epothilones,[7] the phorboxazoles arrest the cell cycle during S-phase.

The impressive biological activity and the unique structure of phorboxazoles have led to efforts directed towards the synthesis of these compounds. The first total synthesis of phorboxazole A was reported in 1998 by Forsyth and co-workers.[8a] Synthetic studies towards the total synthesis of phorboxazoles have also been published by several groups.[8]

We made the disconnections to reveal the segments, representing C1-C19 (**1**), C20-C30 (**2**) and C31-C46 (**3**) as depicted in Scheme 1. Our route to the C31-C46 fragment **3** in phorboxazoles was based on a convergent approach using an *E*-selective Julia olefination[9] reaction between the secondary sulfone **4** and the aldehyde **5** as a key step. Therefore, we planned to synthesise the sulphone **4** and the aldehyde **5** from the chiral precursors (*R*)-*p*-methoxyphenylmethyl (MPM) glycidol **6** and (*S*)-MPM protected homoallylalcohol epoxide **12**, respectively. The synthesis of sulfone **4** started with the metallation of acetylene (*n*-BuLi, THF, –78 °C)[10] followed by the addition of $BF_3 \cdot OEt_2$ and (*R*)-MPM protected glycidol **6**[13] to provide secondary alcohol in 71% yield. Methylation of the free hydroxyl group with NaH and MeI in THF, at 0 °C yielded **7** in 98%. The terminal alkyne in **7** was hydrostannated under standard conditions (*n*-Bu_3SnH, AIBN, benzene,



Scheme 1

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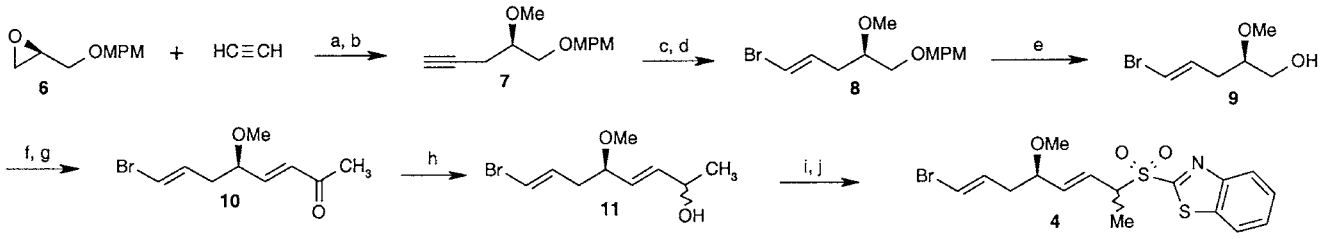
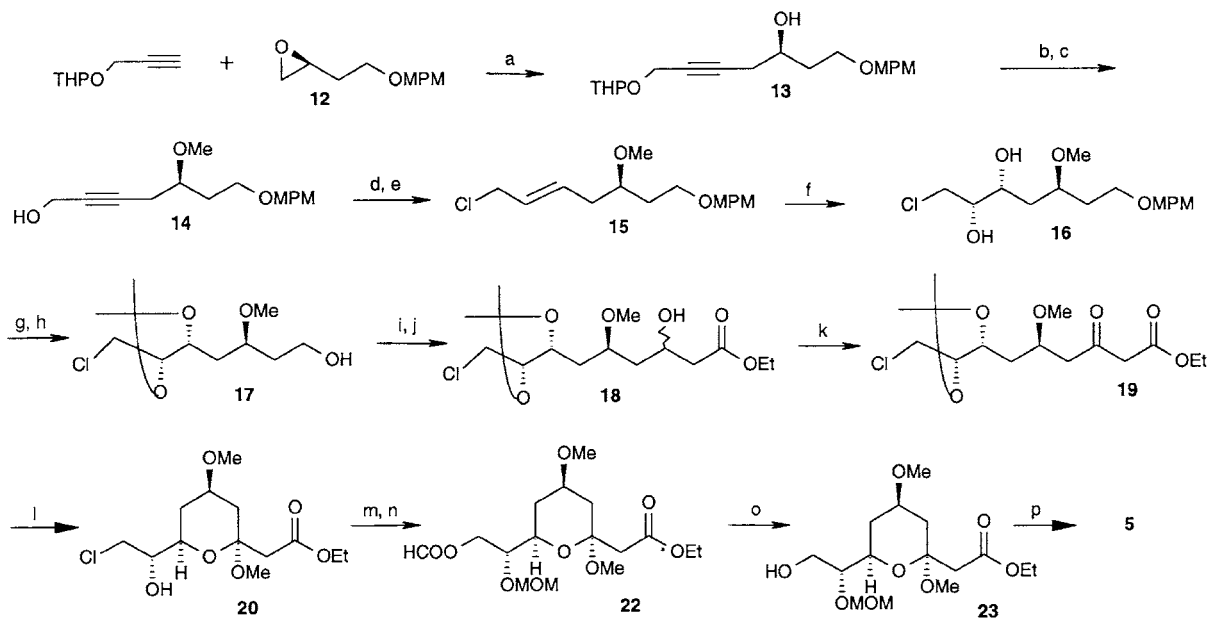
80 °C, 48 h) to give the vinyl stannane in 70% yield as a 5:1 (*E*:*Z*) mixture of geometric isomers, which were separated by flash column chromatography. Facile tin-bromine exchange reaction using NBS in acetonitrile at 0 °C provided vinylic bromide **8** quantitatively. Chiral key intermediate **9**[8d] was obtained by treatment with DDQ (CH_2Cl_2:H_2O = 7:3; r.t.; 10 min) in 95% yield. Alcohol **9** was converted into α,β-unsaturated ketone by employing Swern oxidation followed by Wittig olefination with 1-triphenyl-phosphoranylidene-2-propanone to yield **10** in 72%. The carbonyl functionality in **10** was quantitatively reduced to vinyl carbinol **11** with $NaBH_4$ in MeOH at 0 °C in 15 minutes. The target sulfone **4** was accessed in two steps from the alcohol **11** (Scheme 2). First, compound **11** was converted to thioether under Mitsunobu reaction[11] conditions in 89% yield, which was subsequently oxidised to give the target sulfone **4** in 87% yield.

Aldehyde **5** was also prepared in a similarly straightforward manner as indicated in Scheme 3. Condensation of THP protected propargyl alcohol with epoxide **12**[14] following the Yamaguchi protocol afforded the desired alcohol **13** in 76% yield.[11]

Quantitative methylation of alcohol **13** with NaH and MeI in THF at 0 °C and deprotection of THP gave the propargylic alcohol **14** in 94% yield. Compound **15** was accessed by sequential reduction with LAH followed by treatment of the resulting allyl alcohol with TPP in CCl_4 in 86% overall yield. Sharpless asymmetric dihydroxylation reaction conditions using AD-mix β on allylic chloro compound **15** afforded diol **16** in 78% (de 94%) yield.[12] The protection of vicinal diol as isopropylidene with 2,2-DMP and the deprotection of *p*-methoxybenzyl group with DDQ resulted in the chiral alcohol **17** in 86% yield (in two steps). Alcohol **17** was quantitatively oxidised to the aldehyde with IBX, and treated with pre α-metallated CH_3COOEt (LiHMDS, THF; –78 °C; 15 min) to give **18** in 79% yield. The epimeric mixture **18** was oxidised with PDC in DCM to β-keto ester **19** in 80% yield.



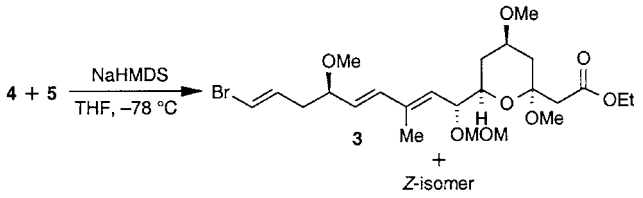
Scheme 2 *Reagents and conditions*: a) BuLi, BF_3·OEt_2, –78 °C; b) NaH, MeI, THF, 0 °C, 1 h; c) *n*-Bu_3SnH, AIBN (cat.), benzene, 80 °C, 48 h; d) NBS, MeCN, 0 °C; e) DDQ, CH_2Cl_2:H_2O (7:3); f) Swern oxidation; g) $CH_3COCH{=}PPh_3$, benzene; h) $NaBH_4$, MeOH, 0 °C; i) 2-mercaptobenzothiazole, DEAD, TPP, THF; j) oxone, MeOH:H_2O:THF (1:1:2), r.t.



Scheme 3 *Reagents and conditions*: a) *n*-BuLi, BF_3·OEt_2, –78 °C; b) NaH, MeI, THF; c) *p*-TSA, MeOH; d) LAH, THF, reflux, 2 h; e) TPP, CCl_4, reflux, 12 h; f) AD-mix β, 0 °C, 48 h; g) 2,2-DMP, *p*-TSA, acetone; h) DDQ, CH_2Cl_2:H_2O (7:3); i) IBX; j) LiHMDS; CH_3COOEt, –78 °C; k) PDC; l) PPTS, MeOH, 36 h; m) MOMCl, DIPEA; n) HCOONa, NaI, DMF, 80 °C, 3 d; o) $NaBH_4$, MeOH, 0 °C; p) Dess–Martin periodinane oxidation.

The substrate **19** was sonicated for 36 hours using PPTS as the catalyst in MeOH, during which deprotection of the isopropylidene group as well as the cyclisation occurred to yield a single diastereomer of the cyclic acetal methyl ether **20** in 50%. The free alcohol was protected with methoxymethyl chloride and DIPEA in CH_2Cl_2 (in 94% yield), and the chloro functionality was converted to formate **21** with sodium formate in DMF at 80 °C for three days in 70% yield.

Deformylation with $NaBH_4$ in MeOH furnished primary alcohol **23** in 96% yield. The Dess–Martin periodinane oxidation afforded the aldehyde **5** in quatitative yield. Coupling of the secondary sulfone **4** and the aldehyde **5** under the modified Julia olefination conditions gave an inseparable mixture of *E*:*Z* geometrical isomers in 70% yield in a ratio of 1:1 (Scheme 4).



Scheme 4

In conclusion, the practical synthesis of the highly functionalised C31-C46 fragment, achieved in 17 steps (in the longest linear sequence) from MPM protected (*S*)-homoallyl alcohol epoxide **12**,[16] is described. Modified Julia olefination between secondary benzothiazole sulfone **4** and the aldehyde **5** was achieved. Efforts towards the synthesis of the other fragments **1** and **2** and the total synthesis of phorboxazoles are under progress.

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(16) Spectral data for the key fragments: Compound **3** (*E*:*Z* mixture): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.61 (d, *J* = 17.3 Hz, 1 H), 6.27–6.02 (m, 5 H), 5.61–5.42 (m, 2 H), 5.37–5.24 (m, 2 H), 4.58–4.36 (m, 6 H), 4.14 (q, *J* = 14.1 Hz, 4 H), 3.72–3.45 (m, 6 H), 3.34 (s, 6 H), 3.31 (s, 6 H), 3.24 (s, 6 H), 3.23 (s, 6 H), 2.66 (dd, *J* = 14.1 Hz, 4.6 Hz, 4 H), 2.44–2.22 (m, 6 H), 1.90 (s, 3 H), 1.83 (s, 3 H), 1.69–1.55 (m, 2 H), 1.41–1.19 (m, 10 H). IR (neat): 2926, 1736, 1619, 1418, 1376, 1207, 1146, 1089, 1033 cm^{-1}. FAB-MS: *m/z* = 536 [M + 1].
$[\alpha]_D$ = –19.8 (*c* 0.5, $CHCl_3$).
Compound **4** (mixture of diastereomers): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.22–8.18 (m, 2 H), 8.02–7.96 (m, 2 H), 7.67–7.53 (m, 4 H), 6.02–5.44 (m, 8 H), 4.36–4.23 (m, 2 H), 3.56–3.46 (m, 2 H), 3.16 (s, 3 H), 3.02 (s, 3 H), 2.14–1.95 (m, 4 H), 1.64–1.56 (m, 6 H). IR (neat): 2926, 1701, 1469, 1325, 1145, 1093 cm^{-1}. FAB-MS: *m/z* = 418 [M + 2].
$[\alpha]_D$ = –8.20 (*c* 0.8, $CHCl_3$).
Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 4.45 (Abq, *J* = 12.3 Hz, 2 H), 3.81 (s, 3 H), 3.69–3.63 (dd, *J* = 12.5, 6.0 Hz, 1 H), 3.45–3.34 (dd, *J* = 12.5, 6.0 Hz, 1 H), 3.23–3.18 (m, 1 H), 2.76–2.69 (dd, *J* = 12.3, 5.9 Hz, 1 H), 2.57–2.54 (dd, *J* = 12.3, 5.9 Hz, 1 H). IR (neat): 2922, 1512, 1245 cm^{-1}. MS (EI): *m/z* = 194 [M$^+$].
$[\alpha]_D$ = +3.1 (*c* 1.5, $CHCl_3$).
Compound **10**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.64–6.49 (m, 1 H), 6.32–6.08 (m, 3 H), 3.93–3.70 (m, 1 H), 3.29 (s, 3 H), 2.58–2.46 (m, 1 H), 2.38–2.26 (m, 1 H), 2.22 (s, 3 H). IR (neat): 2932, 1735, 1612, 1310 cm^{-1}. MS (EI): *m/z* = 233 [M$^+$].
$[\alpha]_D$ = +2.9 (*c* 0.6, $CHCl_3$).
Compound **12**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 4.40 (s, 2 H), 3.81 (s, 3 H), 3.58–3.53 (m, 2 H), 3.06–2.96 (m, 1 H), 2.76–2.72 (m, 1 H), 2.50–2.43 (m, 1 H), 1.89–1.78 (m, 1 H), 1.72–1.60

(m, 1 H). IR (neat): 2845, 1612, 1513 cm^{-1}. MS (EI): *m/z* = 208 [M^+].
$[\alpha]_D$ = +14.4 (*c* 1.0, $CHCl_3$).
Compound **15**: ^1H NMR (200 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 5.80–5.57 (m, 2 H), 4.40 (s, 2 H), 4.00 (d, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 3.55–3.45 (m, 2 H), 3.40–3.36 (m, 1 H), 3.31 (s, 3 H), 2.34–2.18 (m, 2 H), 1.74–1.68 (m, 2 H). IR (neat): 2935, 1608, 1513, 1252 cm^{-1}. FAB-MS: *m/z* = 298 [M + 1].
$[\alpha]_D$ = –17.6 (*c* 0.75, $CHCl_3$).
Compound **17**: ^1H NMR (200 MHz, $CDCl_3$): δ = 4.09–3.93 (m, 1 H), 3.88–3.71 (m, 3 H), 3.66–3.55 (m, 3 H), 3.41 (s, 3 H), 1.96–1.94 (m, 2 H), 1.77–1.63 (m, 2 H), 1.40 (s, 6 H). IR (neat): 3482, 2921, 1462 cm^{-1}. MS (EI): *m/z* = 252 [M^+].
$[\alpha]_D$ = +12.2 (*c* 2.0, $CHCl_3$).
Compound **20**: ^1H NMR (200 MHz, $CDCl_3$): δ = 4.17 (q, *J* = 6.7 Hz, 2 H), 3.98–3.88 (m, 1 H), 3.75–3.58 (m, 4 H), 3.38 (s, 3 H), 3.28 (s, 3 H), 2.68 (s, 2 H), 2.55–2.48 (m, 1 H), 2.38–2.15 (m, 2 H), 2.05–1.92 (m, 2 H), 1.28 (t, *J* = 6.7 Hz, 3 H). IR (neat): 3447, 2949, 1731, 1319, 1228 cm^{-1}.
FAB-MS: *m/z* = 279 [M – OMe].
$[\alpha]_D$ = –78.6 (*c* 1.0, $CHCl_3$).
Compound **23**: ^1H NMR (200 MHz, $CDCl_3$): δ = 4.71 (Abq, *J* = 10.4 Hz, 2 H), 4.13 (q, *J* = 6.7 Hz, 2 H), 3.79–3.48 (m, 5 H), 3.41 (s, 3 H), 3.32 (s, 3 H), 3.21 (s, 3 H), 2.63 (Abq, *J* = 14.1 Hz, 2 H), 2.38–2.28 (m, 1 H), 1.98–1.88 (m, 1 H), 1.49–1.31 (m, 2 H), 1.27 (t, *J* = 6.7 Hz, 3 H). IR (neat): 3443, 2925, 1733, 1036 cm^{-1}. MS (EI): *m/z* = 336 [M^+].
$[\alpha]_D$ = –19.2 (*c* 1.1, $CHCl_3$).