Synthetic Studies Towards Phorboxazole B: Stereoselective Synthesis of the C3–C19 Bis-oxane Oxazole Fragment

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Abstract: A convergent and enantioselective synthesis of the C3–C19 bis-oxane oxazole fragment of phorboxazole B has been described. This work features highly efficient substrate-controlled reductions to construct the functionalised *cis*-oxane and a Mukaiyama aldol reaction followed by an intramolecular Williamson reaction leading to a *trans*-oxane.

Key words: enantioselective synthesis, phorboxazole, reduction, Mukaiyama reaction, Williamson reaction

The phorboxazoles (**1a** and **1b**) (see Figure 1), which were isolated from the Indian Ocean sponge *Phorbas* sp., are unique macrolides accommodating four heavily functionalised oxanes and two 2,4-disubstituted oxazoles.[1] These metabolites have ranked among the most potent antibiotic agents discovered to date, displaying exceptional cytostatic activity throughout the panel of 60 NCI human tumor cell lines (mean $GI_{50} < 1.6 \times 10^{-9}$ M).[2] The unprecedented structural features and extraordinary potency of **1** have inspired wide interest in the organic synthetic community,[3,4] and several outstanding achievements of total synthesis have been reported.[5]

Our retrosynthetic analysis of phorboxazole B (**1b**) involved disconnections of the structure at the C2–C3, the C19–C20 and the C27–C28 bonds, which led to the key building blocks **2**–**4**. The stereoselective synthesis of C21–C27 fragment **3** has been reported in a previous publication.[4b] Herein, we describe our synthesis of the C3–C19 bis-oxane oxazole portion **4** of phorboxazole B.

The strategy for constructing the bis-oxane **4** is retrosynthetically outlined in Scheme 1. Disconnection of the structure at the C5–O ether bond followed by sequentially functional group transformations afforded the β-hydroxyl

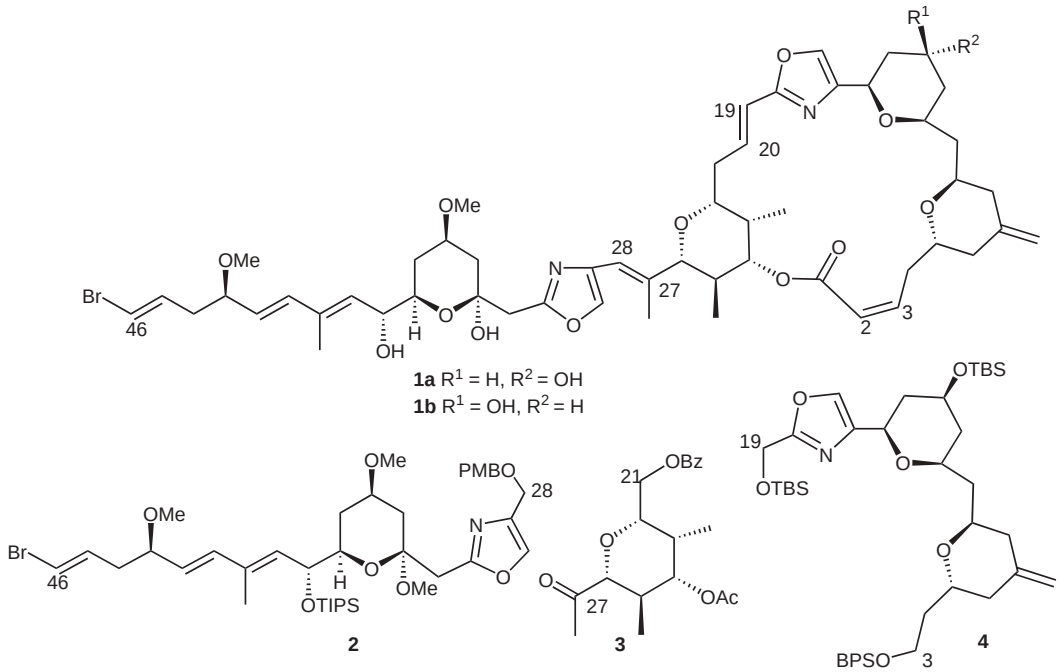

Figure 1 Phorboxazole A (**1a**) and phorboxazole B (**1b**).

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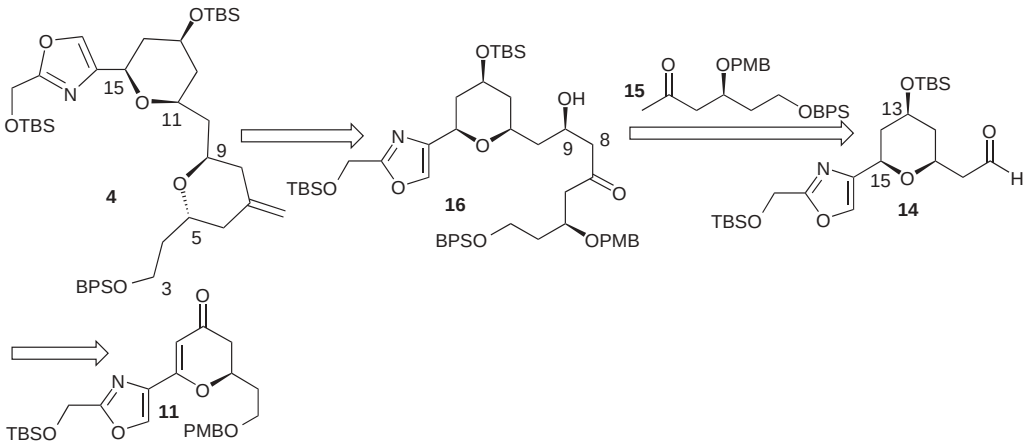
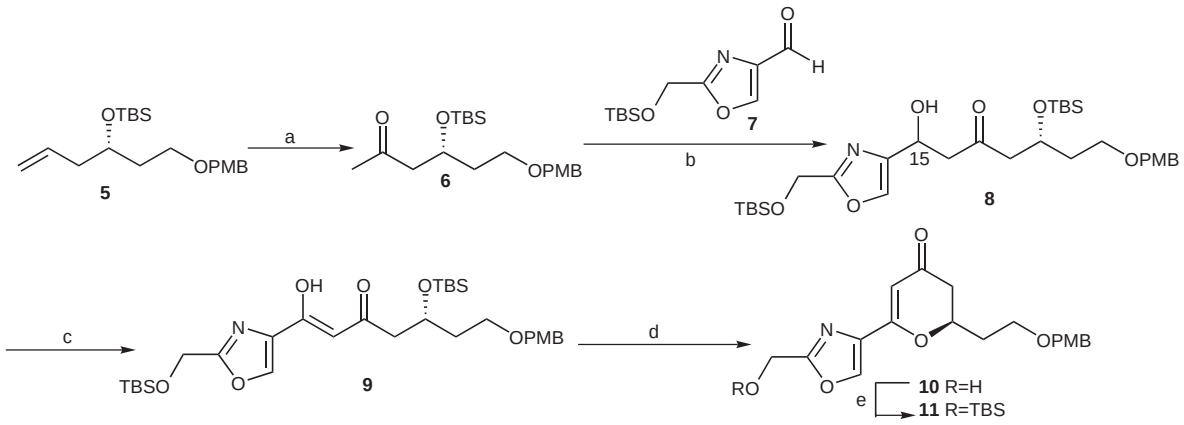


Scheme 1 Retrosynthetic analysis of **4**.

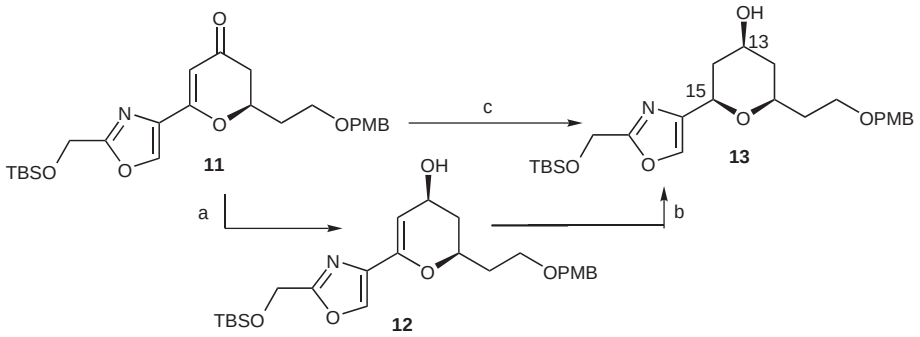
ketone **16**. An aldol disconnection at the C8–C9 bond of compound **16** then let to methyl ketone **15**[6] and aldehyde **14**. The aldehyde **14** could be synthesised from 2*H*-pyranone **11** and the stereochemistry of C13 and C15 was expected to be established via Luche reduction[7] of ketone carbonyl of **11** followed by hydrogenation[8] of the double bond.

The synthesis of 2*H*-pyranone **11** was described in Scheme 2. Wacker oxidation[9] of the chiral building block **5**[5d] gave rise to the methyl ketone **6** in 89% yield. Treatment of the lithium enolate of **6** with aldehyde **7**[10] in THF at –78 °C let to the β-hydroxy ketone **8** in 81% yield as a mixture of two C15 epimeric isomers. These diastereoisomeric substances were used directly in the next step without separation. Thus, oxidation of the mixture of **8** with Dess–Martin periodinane[11] afforded the corresponding β-diketone **9** in 90% yield, which was showed to exist completely in the form of enol-ketone by NMR spectrum. In the following step, it was anticipated that HF acid[12] would immediately catalyse the cyclodehydration reaction after removing the two TBS protecting group in **9**. Indeed, exposure of **9** to 5% solution of HF acid in CH_3CN at room temperature smoothly led to the cyclodehydrated product **10** in an excellent yield (90%). The primary hydroxyl of **10** was reprotected with TBS group to afford 2*H*-pyranone **11** in 97% yield.

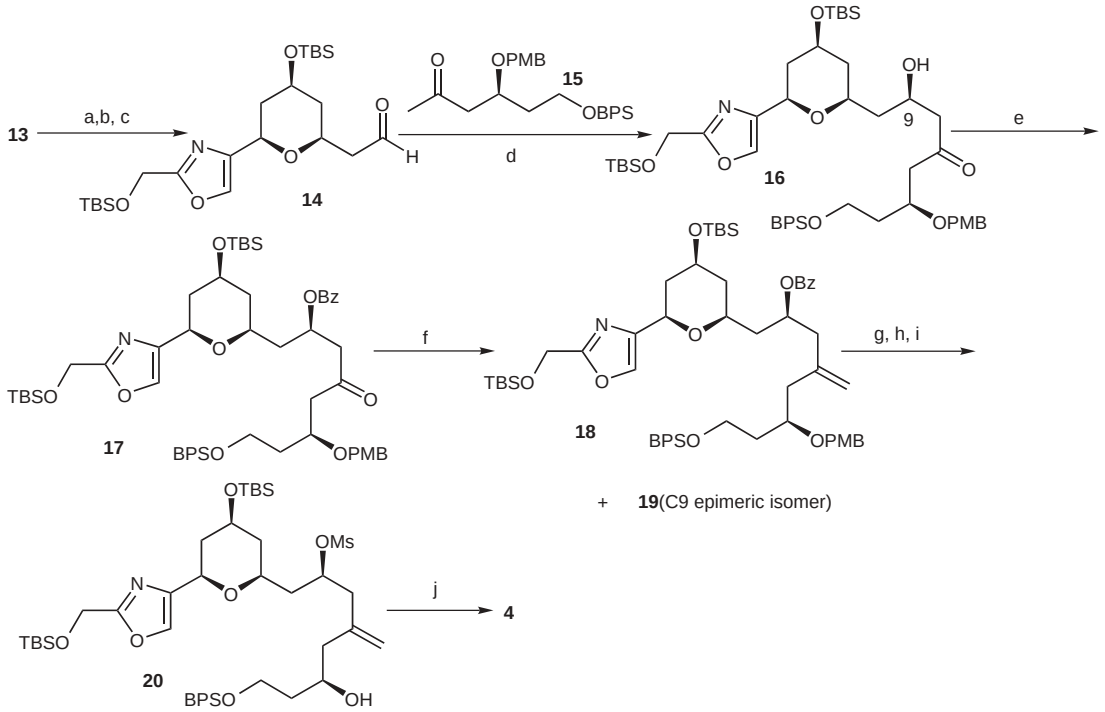
With a quantity of **11** in hand, we focused our attention on the construction of C13 and C15 stereogenic centers (see Scheme 3). Thus, a stereoselective Luche reduction[7] of pyranone **11** in methanol at –78 °C provided 2*H*-pyrane **12** in 95% yield as a single isomer. The next step involved the creation of *cis*-(C11/C15) oxane ring through a stereoselectively substrate-controlled hydrogenation of the C14–C15 double bond.[8] In the presence of a catalytic amount of palladium on charcoal, compound **12** was smoothly hydrogenated to the *cis*-oxane **13** in 95% yield as a single isomer.[13] To our surprise, direct hydrogenation of **11** in EtOAc also delivered compound **13** although the yield was very low. After a lot of trials, it was found that yield was increased to 65% when the reaction was



Scheme 2 a) catalyst $PdCl_2$, CuCl, O_2, DMF–H_2O, r.t., 6 h, 89%; b) LDA, **7**, –78 °C, THF, 81%; c) Dess–Martin periodinane, CH_2Cl_2, r.t., 90%; d) 5% HF in CH_3CN, r.t., 12 h, 90%; e) TBSCl, imidazole, DMF, r.t., 97%.



Scheme 3 a) $NaBH_4$, $CeCl_3$, MeOH, –78 °C, 95%; b) H_2, 10% Pd/C, EtOAc, 8 h, 95%; c) H_2, 5% Pd/C, EtOAc-buffer solution (pH = 1), 8 h, 65%.



Scheme 4 a) TBSCl, imidazole, DMF, r.t., 96%; b) DDQ, CH_2Cl_2–H_2O, r.t., 93%; c) Dess–Martin periodinane, CH_2Cl_2, r.t., 92%; d) 1) LHDMS, TMSCl, THF, –78 °C; 2) **14**, $TiCl_4$, –78 °C, 68%; e) BzCl, py, r.t., 90%; f) Nysted reagent, $TiCl_4$, r.t., 30 min, then **17**, 74%; g) DIBAL-H, CH_2Cl_2, –78 °C; h) MsCl, Et_3N, CH_2Cl_2, 0 °C; i) DDQ, CH_2Cl_2–H_2O, 68% for three steps; j) Et_3N, CH_3CN, reflux, 83%.

conducted in a mild acidic condition. It is particularly noteworthy that the highly stereoselective introduction of the C13 and C15 stereogenic centers together with the *cis*-oxane ring required only conventional manipulations using easily available reagents.

The final completion of this synthesis is described in Scheme 4. Protection of the C13 hydroxy of compound **13** and subsequent removal of the PMB protecting group followed by oxidation of the resulting primary hydroxy afforded the corresponding aldehyde **14** in 82% yield for three steps. Aldol reaction of aldehyde **14** with the silyl enol ether of **15**[6] in the Mukaiyama condition[14] produced the β-hydroxyl ketone **16** as the major component of an inseparable mixture of C9 epimeric isomers (7.8:1).[15] Although it was more convenient to separate these isomers in later step, the mixture were used without difficulties in the ensuing steps. Unfortunately, methylenation of the ketone carbonyl group of **16** did not result in the desired product but a dehydrate one under many conditions, such as Lombardo's condition,[16] Takai's condition,[17] and Petasis's condition.[18] To suppress this undesirable side reaction, the hydroxyl group of **16** was shielded with benzoyl group to provide ketone **17**, which was smoothly methylenated with Nysted reagent {*cyclo*-dibromodi-μ-methylene [μ-(tetrahydrofuran)] trizinc}[19] to give product **18** in

66% yield and **19** in 8% yield. Two isomers were conveniently separated by flash column chromatography on silica gel. With compound **18** in hand, it required only a few steps to complete the synthesis of **4**. Thus, removal of the benzoyl protecting group and subsequent mesylation of the resulting hydroxyl followed by cleavage of the *p*-methoxybenzyl protecting group provided **20** in 68% yield for three steps. According to Forsyth's condition,[3b] finally, when a solution of compound **20** in CH_3CN was treated with excess Et_3N and heated to reflux for 12 hours, the bis-oxane **4** was smoothly produced in 83% yield.[20]

In summary, we have described a convergent and enantioselective synthesis of the bis-oxane oxazole fragment of phorboxazole B. This work features a remarkably efficient strategy for construction of the functionalised *cis*-oxane using stereoselectively substrate-controlled hydrogenation chemistry.

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(6) (a) The methyl ketone **15** was conveniently prepared from 1-(*tert*-butyl-diphenyl-silanyloxy)-hex-5-en-3*R*-ol, see: Smith, A. B. III; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675. (b) Protection of 1-(*tert*-butyl-diphenyl-silanyloxy)-hex-5-en-3*R*-ol with PMB protecting group [$Cl_3C(NH)OPMB$, 0.03 equiv $BF_3{\cdot}OEt_2$, CH_2Cl_2–cyclohexane, 0 °C, 87%) followed by Wacker oxidation of the resulting substance (catalyst $PdCl_2$, CuCl, O_2, DMF–H_2O, r.t., 12 h, 86%) provided **6**.

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(13) The configuration of **13** was confirmed by NOE measurements. Compound **13**: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.51 (s, 1 H), 7.14 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 4.73 (s, 2 H), 4.42 (s, 2 H), 4.36 (d, *J* = 10.5 Hz, 1 H), 3.85–3.90 (m, 1 H), 3.80 (s, 3 H), 3.64–3.67 (m, 1 H), 3.60–3.62 (m, 1 H), 3.53–3.56 (m, 1 H), 2.28 (dt, *J* = 12.6, 2.4 Hz, 1 H), 2.01 (dt, *J* = 12.3, 2.4 Hz, 1H), 1.88–1.93 (m, 1 H), 1.78–1.83 (m, 1 H), 1.34 (app q, *J* = 11.7 Hz, 1 H), 1.28 (app q, *J* = 10.5 Hz, 1 H), 0.92 (s, 9 H), 0.10 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 159.1, 141.2, 135.2, 130.5 129.2, 113.7, 73.1, 72.5, 71.0, 67.8, 66.1, 58.3, 55.2, 40.9, 40.0, 36.0, 25.7, 18.3, –5.4.

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(20) The relative stereochemistry between C5 and C9 of **4** was confirmed by NOE experiments. Compound **4**: Colorless oil, $[\alpha]_D^{25} = -14.2$ (c 0.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.65–7.68 (m, 4 H), 7.47 (s, 1 H), 7.37–7.40 (m, 6 H), 4.72 (d, *J* = 5.4 Hz, 2 H), 4.72 (s, 2 H), 4.27 (d, *J* = 10.8 Hz, 1 H), 4.02 (app q, *J* = 6.0 Hz, 1 H), 3.93 (app q, *J* = 6.0 Hz, 1 H), 3.67–3.83 (m, 3 H), 3.49–3.55 (m, 1 H), 2.36 (br s, 1 H), 2.35 (br s, 1 H), 2.12–2.16 (m, 1 H), 1.95–2.07 (m, 3 H), 1.88–1.92 (m, 1 H), 1.79–1.85 (m, 1 H), 1.62–1.70 (m, 1 H), 1.48–1.54 (m, 2 H), 1.20–1.33 (m, 1 H), 1.04 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.09 (s, 6 H), 0.034 (s, 3 H), 0.028 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 142.2, 141.8, 135.7, 135.2, 135.0, 134.0, 129.7, 127.8, 127.7, 110.4, 73.0, 71.4, 69.0, 68.7, 68.6, 60.7, 58.5, 41.2, 40.8, 40.0, 39.6, 39.6, 39.4, 36.5, 27.0, 26.7, 25.9, 19.3 (3 C), 18.5 (3 C), 18.1 (3 C), –4.4 (2 C), –5.3 (2 C). IR (cm^{-1}): 3073, 1655, 1093, 1112. HRMS (ESI) calcd for $C_{46}H_{73}O_6NSi_3Na$ $(M + Na)^+$: 842.4633, found: 842.4638.