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Asymmetric Synthesis of Phorboxazole B—Part I: Synthesis of the $C_{20}-C_{38}$ and $C_{39}-C_{46}$ Subunits**

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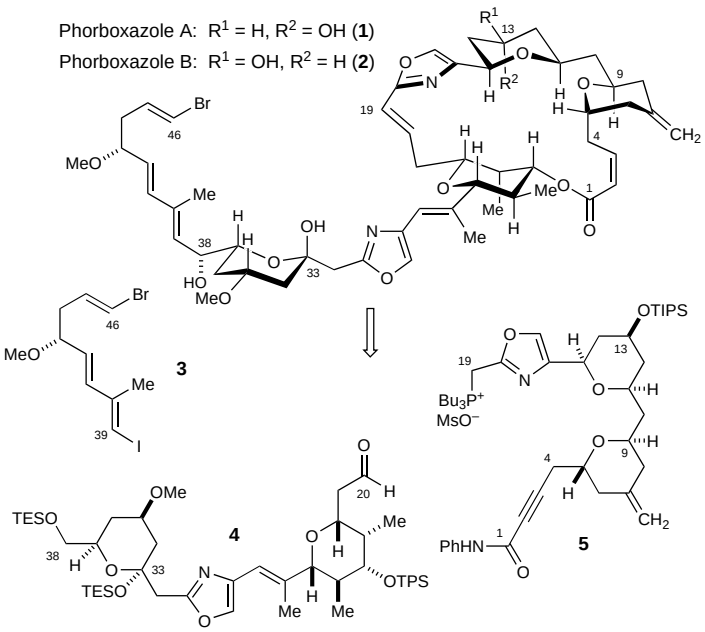
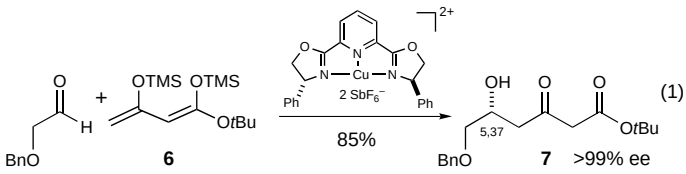
Phorboxazoles A (**1**) and B (**2**) are marine natural products isolated from a newly discovered species of Indian Ocean sponge (genus *Phorbas sp.*).[1] These substances are representatives of a new class of macrolides and are among the most cytostatic natural products known; they inhibit the growth of tumor cells at nanomolar concentrations (mean $GI_{50} = 1.58 \times 10^{-9}$ M).[2] As a result, phorboxazoles A and B have been selected by the National Cancer Institute for in vivo antitumor trials.[1b] The unique structure and impressive biological activity of these molecules have led to widespread efforts to synthesize these substances,[3] and a total synthesis of phorboxazole A has recently been reported.[3u] In this and the following communication[4] we describe our work culminating in the synthesis of phorboxazole B.

The synthesis plan (Scheme 1) calls for an early disconnection of the C_{38}–C_{39} bond to provide the triene side chain **3**, which allows the remainder of the molecule to be divided into fragments of roughly equal complexity. Disconnection through the C_{19}–C_{20} *E* olefin and macrolactone moieties provides the



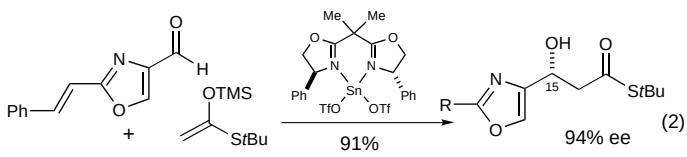
Scheme 1. Retrosynthetic analysis of phorboxazole B. (See ref. [5] for abbreviations.)

$C_{20}-C_{38}$ core fragment **4** and the C_1-C_{19} bispyran fragment **5**. The distinctive features of this plan include a Wittig reaction to form the C_{19}–C_{20} olefin, macrolactonization of a C_1-C_{38} seco acid, and late-stage incorporation of the fully functionalized triene side chain. The utilization of our recently developed Cu^{2+}-catalyzed enantioselective aldol reaction[6] [Eq. (1)] provides the foundation for the synthesis of two of



(1)

the polyacetate regions of the molecule (C_4-C_9 and $C_{33}-C_{38}$), while an enantioselective stannous triflate catalyzed aldol reaction has been employed to assemble the $C_{13}-C_{19}$ oxazole-containing subunit [Eq. (2) where R = 2-phenylethene].[4]



(2)

The synthesis of the polypropionate region of the central core fragment **4** began with the addition of the (*E*)-boron enolate of **9**[7] to the known aldehyde **8**,[8] which delivered the desired *anti* aldol adduct in 97% yield (94:6 *dr*) (Scheme 2).[9, 10] Subsequent hydroxyl-directed reduction[11] of the C_{24} ketone provided *anti* diol **10**, which was isolated in 81% yield as a single diastereomer after crystallization.[12] Cyclization of **10** under basic conditions (cat. DBU, CH_2Cl_2) followed by in situ

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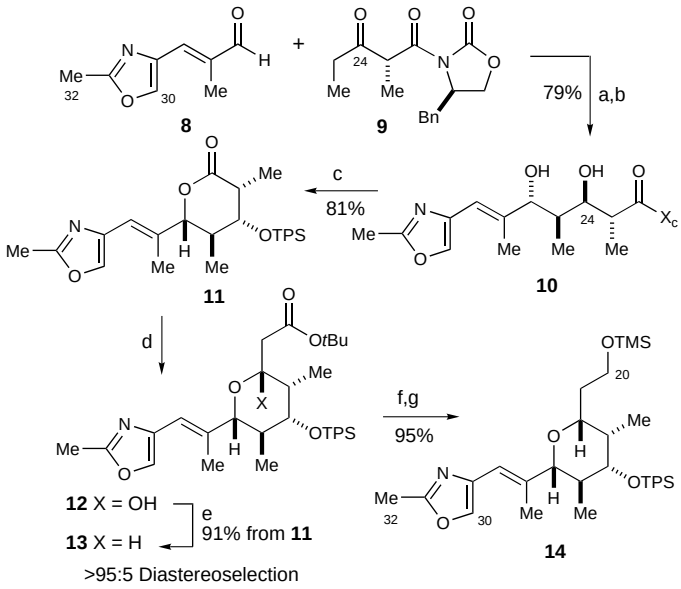


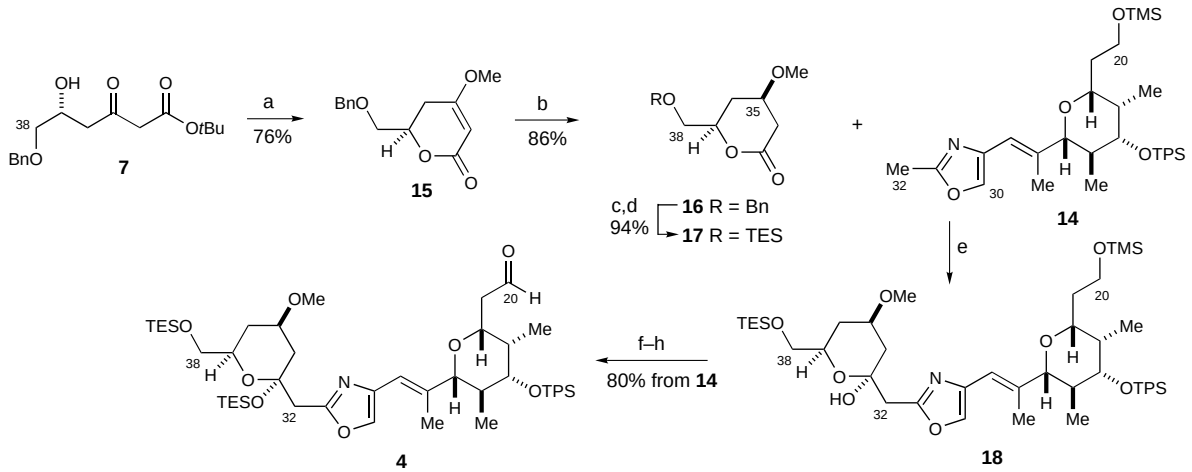
Scheme 2. Synthesis of the $C_{20}-C_{32}$ synthon. a) $(c\text{hex})_2BCl$, $EtNMe_2$, Et_2O, 0 °C; then **8**, −78 → 0 °C; 97 % (94:6 *dr*); b) $Me_4NBH(OAc)_3$, AcOH, 0 °C → RT; 81 % (> 95:5 *dr*); c) cat. DBU, CH_2Cl_2, RT; then imidazole and TPSCl, RT; 81 %; d) *tert*-butyl acetate, LDA, THF, −78 °C; e) $BF_3 \cdot OEt_2$, Et_3SiH, CH_2Cl_2, −78 → −30 °C; 91 % (2 steps); f) $LiAlH_4$, Et_2O/THF, −20 °C; 96 %; g) TMSCl, imidazole, cat. DMAP, DMF, RT; 99 %. X_c = (4R)-4-benzyl-2-oxazolidinone. (See ref. [5] for abbreviations.)

silylation (TPSCl, imidazole) yielded lactone **11**, which was subsequently alkylated with the lithium enolate derived from *tert*-butyl acetate to provide hemiketal **12**. Reduction of the unpurified hemiketal ($BF_3 \cdot OEt_2$, Et_3SiH)[13] afforded the desired *cis*-tetrahydropyran **13** (> 95:5 *dr*) in 91 % yield for the two steps.[12] Reduction of the ester ($LiAlH_4$; 96 %) and protection of the resulting primary hydroxyl group (TMSCl, imidazole; 99 %) completed the $C_{20}-C_{32}$ core pyran fragment **14** in 55 % overall yield for the eight-step sequence.

Completion of the $C_{20}-C_{38}$ core fragment **4** required the union of the $C_{33}-C_{38}$ lactone fragment **17** with methyloxazole **14**. The synthesis of the requisite lactone began with aldol adduct **7**, which was cyclized to the unsaturated lactone **15** in 76 % yield under acidic conditions (TMSCl, MeOH, CH_2Cl_2, Scheme 3).[14] Diastereoselective hydrogenation of **15** was accomplished with Raney-nickel[15] to afford methyl ether **16** containing the desired *R* configuration at the C_{35} methoxy residue (86 %; > 95:5 *dr*).[12] In two subsequent steps the benzyl group was replaced with a triethylsilyl group to provide the desired $C_{33}-C_{38}$ lactone **17**.

The plan for coupling lactone **17** with fragment **14** involved metalation of the C_{32} methyl group on the oxazole ring followed by alkylation with the lactone to form the C_{32}–C_{33} bond.[16] Initial attempts to selectively lithiate methyloxazole **14** using common bases (LDA, LiTMP, *n*BuLi) were thwarted by the comparable kinetic acidity of the C_{30} proton. It was eventually discovered that lithium diethylamide possessed the unique ability to provide the desired lithiated species with complete selectivity by an equilibration process that occurred at low temperatures.[3h] Lithiation of **14** with this base followed by addition of lactone **17** afforded the desired hemiketal **18** as a single regio- and stereoisomer. Although stable to silica gel chromatography, this material was carried forth through the subsequent two steps without purification for operational simplicity. While reported methods for hemiketal silylation[17] led to high levels of decomposition when applied to substrate **18**, the use of triethylsilyl trifluoromethanesulfonate and pyridine in a diethyl ether/acetonitrile mixture proved successful, providing the desired mixed-silyl ketal as a single anomer.[18] Selective cleavage of the C_{20} primary trimethylsilyl ether under basic conditions ($NaHCO_3$, MeOH) gave an intermediate alcohol (80 % from **14**), which upon subsequent oxidation with the Dess–Martin periodinane[19] provided the $C_{20}-C_{38}$ core fragment **4** in 44 % overall yield with a longest linear sequence of 12 steps from aldehyde **8**.

The synthesis of the $C_{39}-C_{46}$ triene side-chain synthon (Scheme 4) began with a $BF_3 \cdot OEt_2$-promoted alkenyllithium addition to (*R*)-3-(triphenylmethyl)-1,2-epoxypropane[20] to yield alcohol **19**.[21] Methylation of the free hydroxyl group



Scheme 3. Synthesis of the $C_{20}-C_{38}$ synthon **4**. a) TMSCl, MeOH, CH_2Cl_2, 0 °C; 76 %; b) H_2, Raney-Ni, *i*PrOH, RT; 86 % (> 95:5 *dr*); c) H_2, cat. 10 % Pd/C, EtOAc, RT; d) TESCl, imidazole, cat. DMAP, DMF, RT; 94 % (2 steps); e) **14**, $LiNEt_2$, THF, −78 °C; then **17**, −78 °C; f) TESOTf, pyr, Et_2O:CH_3CN (10:1), −50 °C; g) $NaHCO_3$, MeOH, RT; 80 % (3 steps); h) Dess–Martin periodinane, pyr, CH_2Cl_2, RT; 100 %. (See ref. [5] for abbreviations.)

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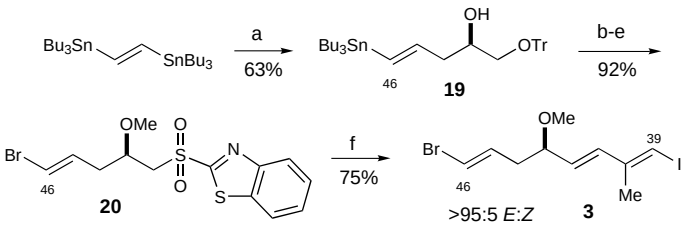
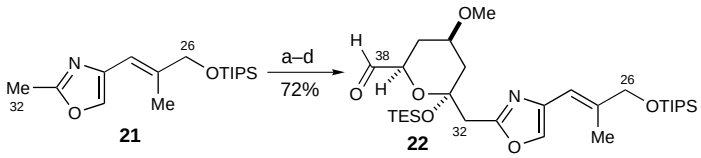


Scheme 4. Synthesis of the $C_{39}-C_{46}$ synthon **3**. a) *n*BuLi, THF, $-78\,^{\circ}C$; then $BF_3\cdot OEt_2$ and (*R*)-3-(triphenylmethyl)-1,2-epoxypropane, $-78\,^{\circ}C$; 63%; b) NaH, DMF, $0\,^{\circ}C$; then MeI, RT; 96%; c) NBS, CH_3CN, $0\,^{\circ}C$; 98%; d) TsOH, Et_2O:MeOH (1:1), RT; 99%; e) 2-mercaptobenzthiazole, Ph_3P, DIAD, THF, RT; then ammonium molybdate, H_2O_2, MeOH, $0\,^{\circ}C$; 99%; f) (*E*)-3-iodo-2-methylprop-2-enal, THF, $-78\,^{\circ}C$; then NaHMDS, $-78\,^{\circ}C \rightarrow$RT; 75% (>95:5 *E*:*Z*). (See ref. [5] for abbreviations.)

(NaH, MeI; 96%), tin–bromine exchange (NBS; 98%), and deprotection of the trityl group (TsOH; 99%) provided an intermediate alcohol which was converted into the benzthiazole sulfone **20** in a one-pot procedure.[22] A subsequent Julia olefination[23] provided the desired $C_{39}-C_{46}$ side chain in 75% yield and >95:5 *E*:*Z* selectivity.[12]

At this point it was necessary to determine the feasibility of the projected late-stage side-chain addition using a model aldehyde. Aldehyde **22** (Scheme 5) was constructed in an

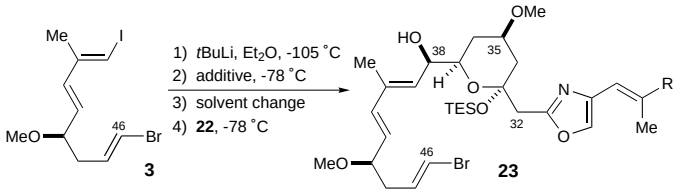


Scheme 5. Construction of a model aldehyde. a) $LiNEt_2$, THF, $-78\,^{\circ}C$; then **17**, $-78\,^{\circ}C$; 79%; b) TESOTf, pyr, 3:2 Et_2O:CH_3CN, $-50\,^{\circ}C$; 98%; c) HF·pyr, pyr, THF, $0\,^{\circ}C$; 93%; d) SO_3·pyr, TEA, DMSO, CH_2Cl_2, $-5\,^{\circ}C$; 100%. (See ref. [5] for abbreviations.)

analogous manner to the parent hemiketal **18** by addition of the lithiated 2-methyloxazole **21**[3h] to lactone **17**. Silylation under the previously described conditions, deprotection of the primary triethylsilyl ether (HF·pyr, pyr), and Parikh–Doering oxidation[24] provided the model aldehyde **22** in four steps and 72% overall yield.

The configuration of the C_{38} hydroxyl moiety demands that the C_{38}–C_{39} bond construction be executed with chelation control.[25] Accordingly, model studies were undertaken with aldehyde **22** and the triene fragment **3** to address this coupling process (Table 1). It was first determined that site-selective metal–halogen exchange could be implemented on triene **3** at the C_{39} terminus upon treatment with *tert*-butyllithium (1.9 equiv) in ether at $-105\,^{\circ}C$ to give the desired alkenyllithium reagent.[26, 27] Not surprisingly, this organolithium species slightly favored the formation of the undesired diastereomer[12] in reactions with **22** (entry 1, Table 1), which necessitated transmetalation to a more chelate-prone alkenylmetal. The derived alkenylzincate,[28] Grignard, and aluminate,[29] each provided modest levels of diastereoselectivity in ethereal solvents (entries 2 and 4). It was found that chelate-controlled selectivity could be substantially improved by carrying out the addition in methylene chloride (entries 3, 5, and 6).[30] Ultimately, the higher yielding Grignard reagent (entry 5) derived from freshly prepared $MgBr_2$[31] was chosen for the final fragment coupling.[4]

Table 1. Side chain addition experiments.



R = CH_2OTIPS

Entry	Additive	Solvent	Yield [%]	C_{38} diastereoselectivity (*R*:*S*)
1	–	Et_2O	54	1:2
2	Me_2Zn	Et_2O	80	9:1
3	Me_2Zn	CH_2Cl_2	60	20:1
4	$MgBr_2$	Et_2O	77	5:1
5	$MgBr_2$	CH_2Cl_2	79	>20:1
6	Me_3Al	CH_2Cl_2	71	>20:1
7	$CeCl_3$	Et_2O/THF	35	1:7

The preceding discussion describes the stereoselective syntheses of the $C_{39}-C_{46}$ triene side chain and $C_{20}-C_{38}$ core fragment of the phorboxazole skeleton. In addition, a promising procedure for the projected $C_{39}-C_{46}$ side chain fragment coupling was developed on a model system. In the following communication, the synthesis of the C_1-C_{19} bispyran subunit and fragment assembly to phorboxazole B is presented.[4]

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[31] For the preparation of $MgBr_2$ as a solution in Et_2O/benzene, see M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 5583 – 5601.

Asymmetric Synthesis of Phorboxazole B—Part II: Synthesis of the $C_1 - C_{19}$ Subunit and Fragment Assembly**

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In the preceding communication the syntheses of the $C_{20} - C_{38}$ and $C_{39} - C_{46}$ phorboxazole B subunits were presented.[1] Herein we focus on the synthesis of the final $C_1 - C_{19}$ bispyran subunit **1** and the successful assembly of these fragments into phorboxazole B.

The retrosynthesis of the $C_1 - C_{19}$ region (Scheme 1)[2] began with disconnection of the peripheral functionality at C_4 and C_{19}, and the masking of leaving groups at these positions as differentially protected primary hydroxyl groups. The C_7 exocyclic olefin was masked as a protected ketone and the C_{11} stereocenter was envisioned to arrive through reduction of hemiketal **2**. Ring-chain tautomerization of **2** and aldol disconnection of the C_{12}–C_{13} bond affords the *trans* pyran methylketone fragment **3** and the oxazole aldehyde fragment **4**.

Construction of the $C_4 - C_{12}$ methylketone **3** began from the δ-hydroxy-β-ketoester **5** previously employed in the construction of the $C_{33} - C_{38}$ lactone (Scheme 2).[1, 3] Treatment of **5** with ethylene glycol and trimethylsilyl chloride[4] resulted in a simultaneous cyclization and protection of the ketone to deliver lactone **6** in good yield. Reduction (DIBAlH) and acetylation (Ac_2O, pyr, DMAP) provided **7** in quantitative

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