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[5] Abbreviations: *dr* = diastereomer ratio; TES = triethylsilyl; TPS = triphenylsilyl; TIPS = triisopropylsilyl; Ms = methanesulfonyl; Bn = benzyl; TMS = trimethylsilyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF = *N*,*N*-dimethylformamide; DMAP = *N*,*N*-dimethylaminopyridine; LDA = lithium diisopropylamide; TMP = 2,2,6,6-tetramethylpiperidide; NBS = *N*-bromosuccinimide; Tr = trityl = triphenylmethyl; Ts = *para*-toluenesulfonyl; DIAD = diisopropylazodicarboxylate; THF = tetrahydrofuran; HMDS = hexamethyldisilazide; pyr = pyridine; TEA = triethylamine; DMSO = dimethyl sulfoxide; Tf = triflate = trifluoromethanesulfonyl.

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

David A. Evans* and Duke M. Fitch

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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[**] Financial support has been provided by the National Institutes of Health (GM-33328) and the National Science Foundation. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities.

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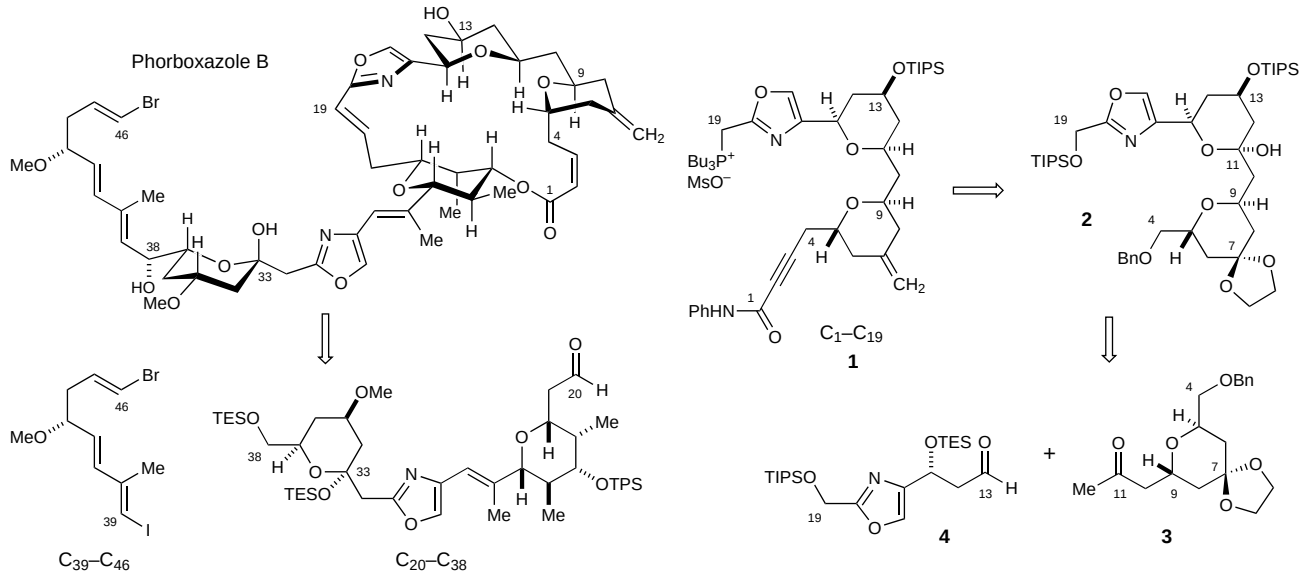
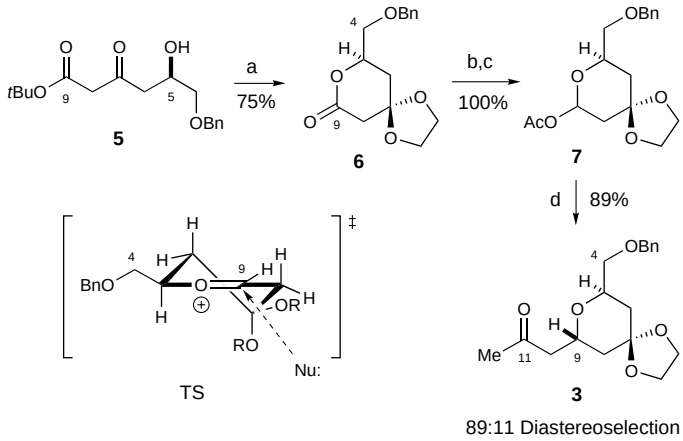


Scheme 1. Retrosynthetic analysis of the C_1-C_{19} fragment (See reference [2] for abbreviations.)

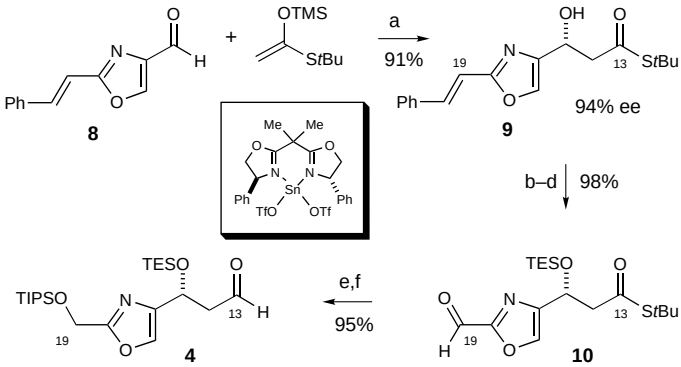


Scheme 2. Synthesis of the C_4-C_{12} *trans*-pyran **3**. a) $HO(CH_2)_2OH$, TMSCl, CH_2Cl_2, RT; 75%; b) DIBAlH, tol, $-78\,^{\circ}C$; 100%; c) Ac_2O, pyr, cat. DMAP, CH_2Cl_2, RT; 100% (92:8 β:α); d) TMSOTf, 2-(trimethylsilyloxy)propene, cat. pyr, CH_2Cl_2, $-78\,^{\circ}C$; 89%. (See ref. [2] for abbreviations.)

yield as a 92:8 mixture of β:α anomers.[5, 6] Treatment of the anomeric acetates with trimethylsilyl trifluoromethanesulfonate[7] and 2-(trimethylsilyloxy)propene resulted in an 89:11 mixture of diastereomeric tetrahydropyrans,[8] with the desired *trans* isomer favored.[9] Axial attack of the nucleophile from the bottom face of the oxocarbenium ion (as depicted in TS) via a chairlike transition structure rationalizes the formation of the major product.[10] This diastereoface is partially hindered by the axial portion of the C_7 ketal, and thus, a minor amount of the undesired *cis* isomer is observed.

The synthesis of the $C_{13}-C_{19}$ oxazole-containing aldehyde began with a Sn^{II}-catalyzed enantioselective aldol addition of the silylketene acetal derived from *tert*-butyl thioacetate to aldehyde **8**[11] (10 mol% [Sn((*S*,*S*)-Ph-box)](OTf)$_2$; box = bisoxazoline) to afford adduct **9** in excellent yield (91%) and enantioselectivity (94% ee; Scheme 3).[12, 13] This reaction is viewed as an extension of analogous aldol reactions with chelating aldehydes that we have reported previously,[14] and the high level of asymmetric induction noted in this transformation provides circumstantial evidence that aldehyde **8** is indeed chelating to the Sn^{II} catalyst. Silylation (TESCl, imidazole), osmium-mediated dihydroxylation,[15] and oxidative cleavage of the derived diol ($Pb(OAc)_4$) provided aldehyde **10** in excellent overall yield. Concomitant DIBAlH reduction of both the C_{19} aldehyde and the C_{13} *tert*-butyl thioester substituents was then accomplished in a single step, while subsequent silylation (TIPSOTf, lut) completed the synthesis of the $C_{13}-C_{19}$ oxazole aldehyde **4** in six steps and 85% overall yield from **8**.

For the important $C_{12}-C_{13}$ aldol fragment coupling, we relied upon methodology developed during our synthesis of altohyrtin C (spongistatin 2),[16] in which boron enolates of β-alkoxy methylketones were added to aldehydes with high



Scheme 3. Synthesis of the $C_{13}-C_{19}$ oxazole aldehyde **4**. a) 10 mol% [Sn((*S*,*S*)-Ph-box)](OTf)$_2$ catalyst, CH_2Cl_2, $-78\,^{\circ}C$; 91%; b) TESCl, imidazole, cat. DMAP, DMF; 100%; c) cat. $K_2OsO_4(H_2O)_2$, cat. quinuclidine, $K_3Fe(CN)_6$, K_2CO_3, methanesulfonamide, *t*BuOH:H_2O (1:1); d) $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, $0\,^{\circ}C$; 98% (2 steps); e) DIBAlH, CH_2Cl_2, $-78\,^{\circ}C$; 95%; f) TIPSOTf, lut, CH_2Cl_2, $0\,^{\circ}C$; 100%. (See ref. [2] for abbreviations.)

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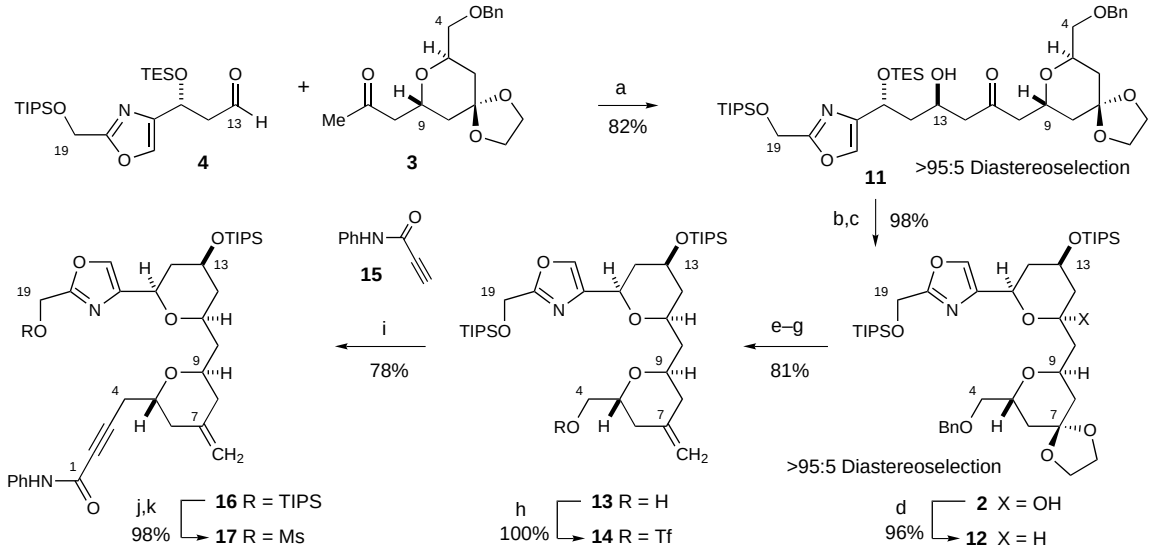
levels of 1,5-*anti* asymmetric induction, regardless of the stereochemistry of the protected β-alkoxyaldehyde substituent.[17] While the methylketones employed in the original study contained either *para*-methoxybenzyl protected β-hydroxyl groups or β-benzylidene acetals, it was unclear whether a methylketone containing a β-tetrahydropyran ring, as in **3**, would exert the same directing effect.[18] In the event (Scheme 4), treatment of the dibutylboron enolate derived from ketone **3** with aldehyde **4** in diethyl ether at $-105\,^{\circ}C$ afforded the aldol adduct **11** in good yield as a single diastereomer.[5, 19] Silylation (TIPSOTf, lut) of the resultant free C_{13} hydroxyl group followed by selective deprotection of the C_{15} triethylsilyl ether provided hemiketal **2**.[20] Axial hydride reduction of the C_{11} hemiketal ($BF_3 \cdot OEt_2$, Et_3SiH)[8] afforded bistetrahydropyran **12** in excellent yield (96%) and diastereoselectivity (>95:5).[5]

With the requisite stereochemistry incorporated into **12**, some refunctionalization was required to complete the synthesis of this subunit. Ketal hydrolysis ($FeCl_3 \cdot SiO_2$)[21] and debenzylation were followed by a Wittig olefination to install the C_7 exocyclic olefin. The C_1-C_3 fragment was incorporated by displacement of the C_4 primary trifluoromethanesulfonate **14** with the dianion of *N*-phenylpropynamide (**15**).[22] Selective deprotection of the C_{19} triisopropylsilyl ether (TBAF, $-50\,^{\circ}C$) followed by formation of the primary mesylate completed the subunit **17** in 17 steps (longest linear sequence from aldehyde **8**) and 40% overall yield.

With the three phorboxazole subunits **17**, **18**, and **26** in hand,[1] fragment coupling experiments were initiated. After some experimentation it was found that in situ formation of the phosphonium salt of mesylate **17** followed by addition of aldehyde **18** and DBU resulted in the exclusive[5] formation of the desired *E* olefin **19** (Scheme 5).[23] Pursuant to revealing the terminal carboxylic acid residue, *N*-phenylamide **19** was activated through its *N*-Boc imide and hydrolyzed with LiOH.[24] These conditions also resulted in the cleavage of the C_{38} triethylsilyl and C_{24} triphenylsilyl ethers. At this point an effort was made to execute a selective macrolactonization of diol acid **20** in the hope that conformational and entropic effects might favor cyclization onto the desired C_{24} hydroxyl moiety. Unfortunately, cyclization occurred exclusively at the less hindered C_{38} primary hydroxyl group under standard Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, benzene)[25] to provide the undesired 31-membered macrocycle **21**.[26]

Attempts to selectively silylate the C_{38} primary hydroxyl group under standard conditions (TESCl, imidazole, CH_2Cl_2) were complicated by competitive silylation of both the C_1 carboxyl group and the C_{24} secondary hydroxyl moieties. Ultimately, a change in the base from imidazole to 2,6-lutidine led to exclusive silylation of the desired C_{38} primary hydroxyl group (Scheme 6).[27] With the C_{38} hydroxyl group now protected, macrolactonization proceeded smoothly to provide the desired 21-membered macrocycle **23** in excellent yield.[25] Lindlar reduction of the alkynoate (>95:5 *Z*:*E*)[5] led to the formation of the complete C_1-C_{38} macrocyclic region of phorboxazole B.[28] Selective deprotection of the C_{38} primary triethylsilyl ether was followed by Parikh–Doering oxidation[29] to provide the requisite α-alkoxyaldehyde **25**.

For the final fragment coupling, chelate-controlled addition of a fully functionalized $C_{39}-C_{46}$ alkenylmetal species was required. Under the previously optimized conditions,[1] site-selective lithium–halogen exchange of vinyl iodide **26**, transmetalation ($MgBr_2$), and solvent exchange ($Et_2O \rightarrow CH_2Cl_2$), followed by the addition of α-alkoxyaldehyde **25** to the alkenylmagnesium intermediate provided the protected natural product **27** in excellent yield as a single isomer.[5] Deprotection of **27** (TBAF, THF) afforded phorboxazole B in 27 steps (longest linear sequence from aldehyde **8**) and 12.6% overall yield. The synthetic phorboxazole B was identical to the natural material as judged by ^1H NMR spectroscopy (600 MHz, $CDCl_3$), HPLC, TLC R_f values,



Scheme 4. Synthesis of the C_1-C_{19} bispyran **17**. a) nBu$_2$BOTf, iPr$_2$NEt, Et$_2$O, $-105\,^{\circ}C$; 82%; b) TIPSOTf, lut, CH_2Cl_2, $0\,^{\circ}C$; 99%, c) HF·pyr, pyr, THF, H_2O, $0\,^{\circ}C$; 99%; d) $BF_3 \cdot OEt_2$, Et_3SiH, CH_2Cl_2, $-78 \rightarrow -50\,^{\circ}C$; 96%; e) $FeCl_3 \cdot SiO_2$, $CHCl_3$, acetone, RT; 90%; f) 1 atm H_2, Pd/C, iPrOH; 100%; g) Ph_3PCH_3Br, PhLi, THF, $0\,^{\circ}C$; 90%; h) Tf_2O, pyr, CH_2Cl_2, $-5\,^{\circ}C$; 100%; i) **15**, nBuLi, THF, $-20\,^{\circ}C$; then **14**; 78%; j) TBAF, THF, $-50\,^{\circ}C$; 99%; k) MsCl, iPr$_2$NEt, CH_2Cl_2, $-5\,^{\circ}C$; 99%. (See ref. [2] for abbreviations.)

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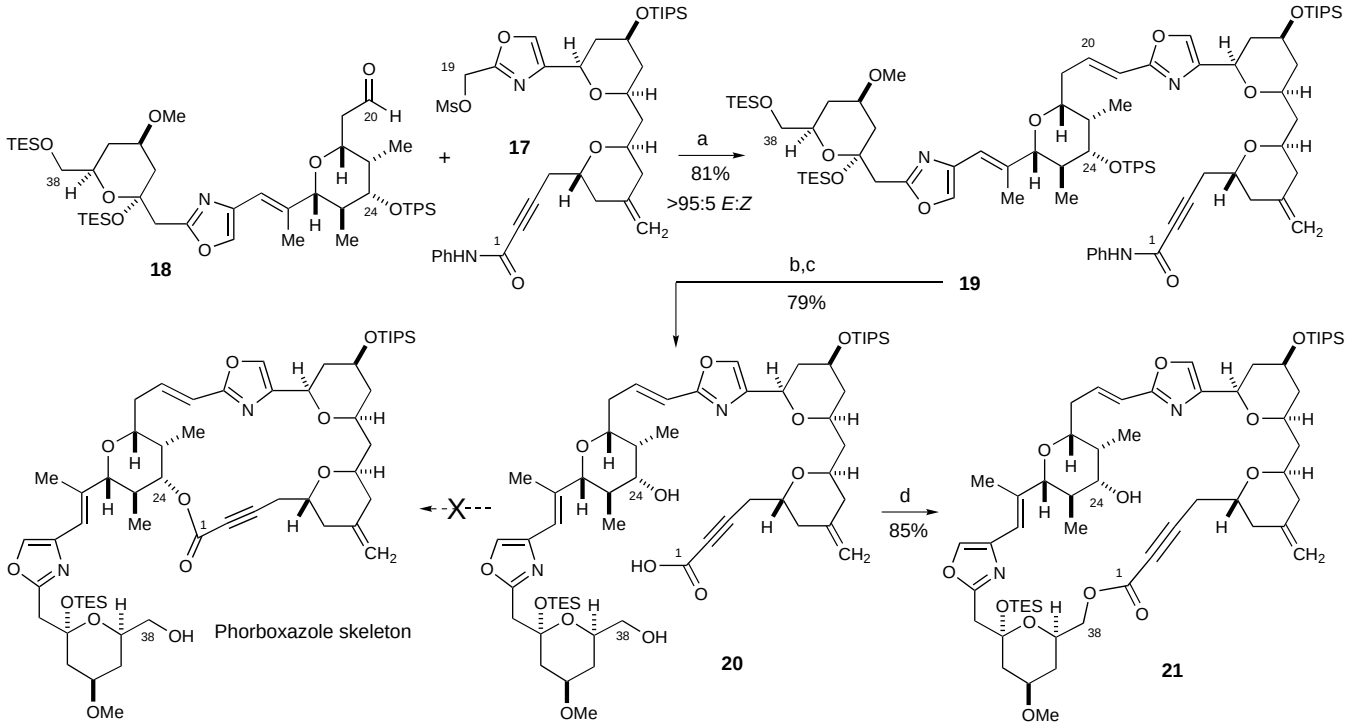
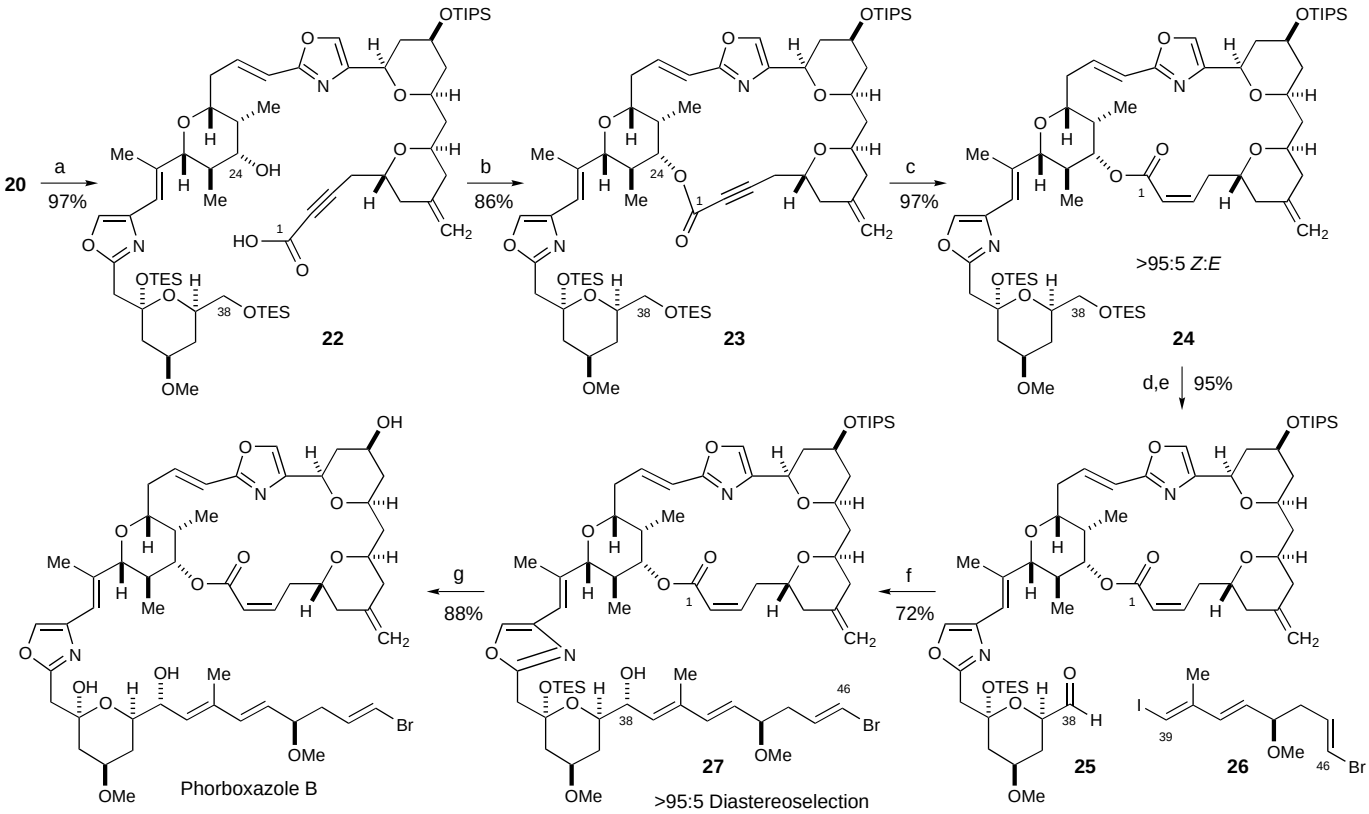


Scheme 5. Wittig coupling and hydrolysis. a) PBu_3, DMF; DBU, RT; 81%; b) Boc_2O, DMAP, CH_3CN; 99%; c) LiOH, THF, H_2O, RT; 80%; d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, benzene; 85%. (See ref. [2] for abbreviations.)



Scheme 6. Completion of the synthesis of phorboxazole B. a) TESCl, lut, CH_2Cl_2, $-78\,^{\circ}C$; 97%; b) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, benzene; 86%; c) 1 atm H_2, Lindlar cat., quinoline, 1-hexene, acetone; 97%; d) HF·pyr, pyr, THF, $0\,^{\circ}C$; 95%; e) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2; 100%; f) **26**, *t*BuLi, Et_2O, $-105\,^{\circ}C$; then $MgBr_2$, $-78\,^{\circ}C$; then CH_2Cl_2, **25**; 72%; g) TBAF, THF, $0\,^{\circ}C$; 88%. (See ref. [2] for abbreviations.)

electrospray mass spectrometry, ultraviolet spectroscopy, infrared spectroscopy, and optical rotation values.[30]

Received: April 25, 2000 [Z15025]

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[2] Abbreviations: Ac = acetyl; Ms = methanesulfonyl; TIPS = tiisopropylsilyl; TES = triethylsilyl; TMS = trimethylsilyl; DIBAlH = diisobutylaluminum hydride; Tf = trifluoromethanesulfonyl; Bn = benzyl; DMAP = 4-dimethylaminopyridine; pyr = pyridine; tol = toluene; TBAF = *tetra-n*-butylammonium fluoride; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; lut = 2,6-lutidine; Boc = *tert*-butyloxycarbonyl.

[3] D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669 – 685.

[4] T. H. Chan, M. A. Brook, T. Chaly, *Synthesis* **1983**, 203 – 205.

[5] The product ratio was determined by ^{1}H NMR analysis (500 MHz) of the unpurified reaction mixture.

[6] Although the anomers were separable by chromatography on silica gel, the mixture was generally taken on without purification.

[7] Use of stronger Lewis acids such as $BF_3 \cdot OEt_2$ or $TiCl_4$ led to high levels of decomposition.

[8] For an early example of nucleophilic addition to oxocarbenium ions in the synthesis of *C*-glycosides, see M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976 – 4978.

[9] Optimal results were obtained when buffering the reaction with 20 mol% of pyridine. The diastereoselectivity was determined by HPLC analysis of the unpurified reaction mixture (Zorbax silica gel, 20% EtOAc in hexanes, flow rate = 1.0 mL min^{-1}, 254 nm UV cutoff, major isomer (*trans*) T_r = 11 min, minor isomer (*cis*) T_r = 13 min).

[10] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, chap. 11.

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[12] Dr. David MacMillan is gratefully acknowledged for the development of this reaction.

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[17] D. A. Evans, P. J. Coleman, B. Côté, *J. Org. Chem.* **1997**, *62*, 788 – 789. See also I. Paterson, K. R. Gibson, R. M. Oballa, *Tetrahedron Lett.* **1996**, *37*, 8585 – 8588.

[18] A model aldol reaction with ketone **3** and dihydrocinnamaldehyde under unoptimized conditions (nBu$_2$BOTf, iPr$_2$NEt, Et$_2$O, $-78\,^\circ$C) resulted in a 72% yield of the desired *anti* adduct with > 95:5 diastereoselectivity as determined by ^{1}H NMR analysis (500 MHz) of the unpurified reaction mixture. The relative stereochemistry of this product was determined by X-ray crystallography.

[19] The remainder of the material was comprised of cleanly recovered **3** and **4**.

[20] Hemiketal **2** existed as a 92:8 mixture of the closed hemiketal and open hydroxy ketone. This mixture was taken on together in the subsequent reduction.

[21] K. S. Kim, Y. H. Song, B. H. Lee, C. S. Hahn, *J. Org. Chem.* **1986**, *51*, 404 – 407.

[22] The lithium anions of methyl and ethyl propiolate failed to alkylate a model primary trifluoromethanesulfonate derived from the commercial available tetrahydropyran-2-methanol at low temperature ($-78\,^\circ$C) and decomposed upon warming, see M. M. Midland, A. Tramontano, J. R. Cable, *J. Org. Chem.* **1980**, *45*, 28 – 29. Displacement of this model trifluoromethanesulfonate with the dianion of propiolic acid was complicated by O alkylation and double alkylation, which was surpressed through use of the alternative nucleophile **15**. For a complex example of the use of an *N*-phenylamide as a carboxyl surrogate with attenuated nucleophilicity, see D. A. Evans, P. H. Carter, E. M. Carreira, A. B. Charette, J. A. Prunet, M. Lautens, *J. Am. Chem. Soc.* **1999**, *121*, 7540 – 7552. For the synthesis of **15**, see G. M. Coppola, R. E. Damon, *Synth. Commun.* **1993**, *23*, 2003 – 2010. For the alkylation of carbonyl compounds with the dianion of *N*-benzylpropynamide, see G. M. Coppola, R. E. Damon, *J. Heterocycl. Chem.* **1995**, *32*, 1133 – 1139.

[23] Similar conditions have recently appeared in the literature for an oxazole-stablized Wittig coupling, see P. Liu, J. S. Panek, *J. Am. Chem. Soc.* **2000**, *122*, 1235 – 1236.

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[26] The regioselectivity of the cyclization was determined by 1D ^{1}H NMR and 2D COSY experiments.

[27] The difference in the selectivity between the two bases is perhaps a result of the formation of a more active silylating agent derived from the reaction of imidazole with the silyl chloride. Presumably there is no reaction between the silyl chloride and 2,6-lutidine, which simply acts as a base.

[28] The use of 1-hexene as a co-solvent was found to effectively surpress any overreduction. For related conditions, see T.-L. Ho, S.-H. Liu, *Synth. Commun.* **1987**, *17*, 969 – 973.

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[30] We thank Professor T. F. Molinski for kindly providing a sample and copies of ^{1}H NMR spectra of natural phorboxazole B for comparison.

Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A**

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The paraherquamides (**1**, **2**, **5**, **6**),[1–4] marcfortines (**3**, **4**),[5] brevianamides,[6] VM55599 (**9**),[3b] and, most recently, the sclerotamides (**10**)[7] and aspergimides (**8**)[8] are indolic secondary metabolites isolated from various fungi (Scheme 1). The parent and most potent member, paraher-

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[**] This work was supported by the NIH (Grant CA 70375). The Japanese Society for the Promotion of Science (JSPS) is acknowledged for providing support to H.T. Mass spectra were obtained on instruments supported by the NIH Shared Instrumentation Grant (GM 49631). We also wish to thank Dr. Timothy Blizzard (Merck & Co.) for providing an authentic sample of natural paraherquamide A. We also wish to acknowledge Dr. Byung H. Lee (Pharmacia – Upjohn Co.) for providing NMR spectra and an authentic specimen of 14-oxoparaherquamide B. We also wish to thank Dr. Alfredo Vazquez for assistance with purification and characterization of synthetic paraherquamide A.

  1433-7851/00/3914-2540 $ 17.50+.50/0