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Asymmetric Synthesis of Phorbosazole B— Part II: Synthesis of the C₁–C₁₉ Subunit and Fragment Assembly**

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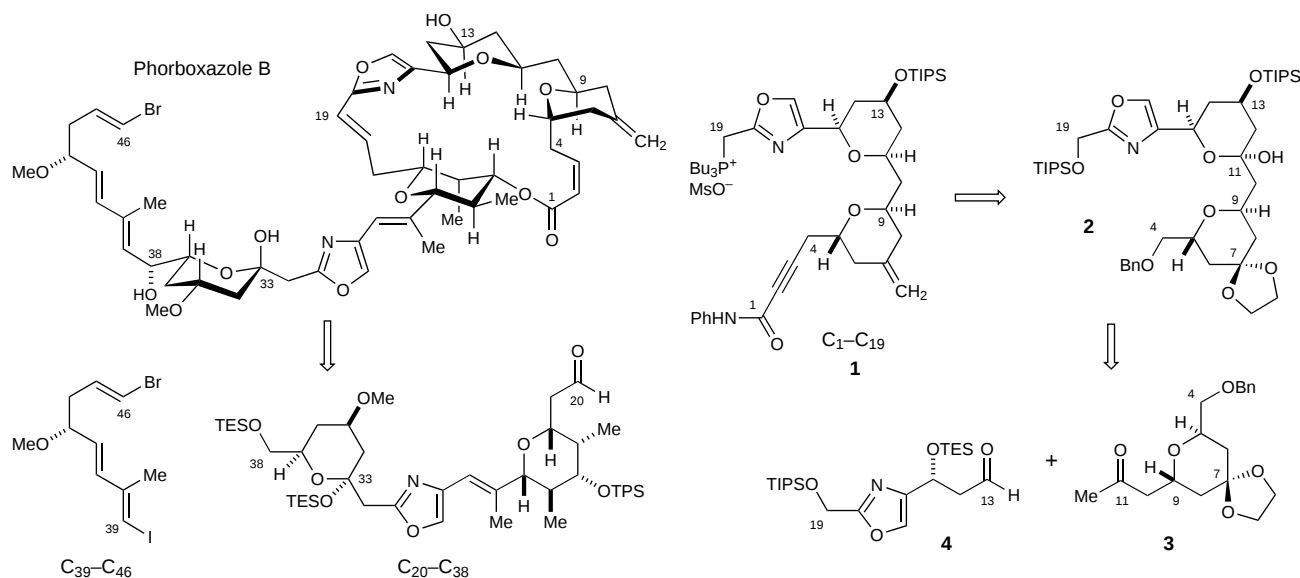
In the preceding communication the syntheses of the C₂₀–C₃₈ and C₃₉–C₄₆ phorbosazole B subunits were presented.^[1] Herein we focus on the synthesis of the final C₁–C₁₉ bispyran subunit **1** and the successful assembly of these fragments into phorbosazole B.

The retrosynthesis of the C₁–C₁₉ region (Scheme 1)^[2] began with disconnection of the peripheral functionality at C₄ and C₁₉, and the masking of leaving groups at these positions as differentially protected primary hydroxyl groups. The C₇ exocyclic olefin was masked as a protected ketone and the C₁₁ stereocenter was envisioned to arrive through reduction of hemiketal **2**. Ring-chain tautomerization of **2** and aldol disconnection of the C₁₂–C₁₃ bond affords the *trans* pyran methylketone fragment **3** and the oxazole aldehyde fragment **4**.

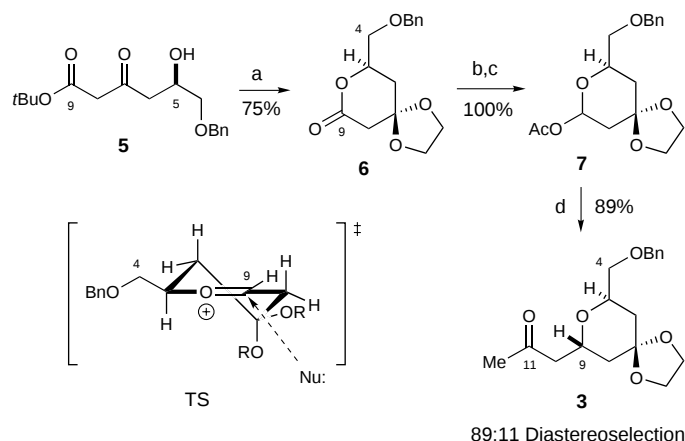
Construction of the C₄–C₁₂ methylketone **3** began from the δ-hydroxy-β-ketoester **5** previously employed in the construction of the C₃₃–C₃₈ lactone (Scheme 2).^[1, 3] Treatment of **5** with ethylene glycol and trimethylsilyl chloride^[4] resulted in a simultaneous cyclization and protection of the ketone to deliver lactone **6** in good yield. Reduction (DIBALH) and acetylation (Ac₂O, pyr, DMAP) provided **7** in quantitative

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



89:11 Diastereoselection

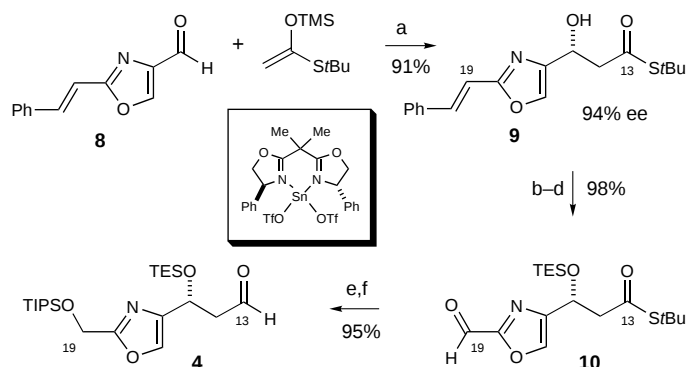
Scheme 2. Synthesis of the C_4-C_{12} *trans*-pyran **3**. a) $\text{HO}(\text{CH}_2)_2\text{OH}$, TMSCl , CH_2Cl_2 , RT; 75%; b) DIBALH, tol , -78°C ; 100%; c) Ac_2O , pyr , cat. DMAP, CH_2Cl_2 , RT; 100% (92:8 β : α); d) TMSOTf , 2-(trimethylsilyloxy)propene, cat. pyr , CH_2Cl_2 , -78°C ; 89%. (See 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 % $[\text{Sn}((S,S)\text{-Ph-box})](\text{OTf})_2$; 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 ($\text{Pb}(\text{OAc})_4$) 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 % $[\text{Sn}((S,S)\text{-Ph-box})](\text{OTf})_2$ catalyst, CH_2Cl_2 , -78°C ; 91%; b) TESCl , imidazole, cat. DMAP, DMF ; 100%; c) cat. $\text{K}_2\text{OsO}_4(\text{H}_2\text{O})_2$, cat. quinuclidine, $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , methanesulfonamide, $t\text{BuOH}:\text{H}_2\text{O}$ (1:1); d) $\text{Pb}(\text{OAc})_4$, K_2CO_3 , CH_2Cl_2 , 0°C ; 98% (2 steps); e) DIBALH, CH_2Cl_2 , -78°C ; 95%; f) TIPSOTf , lut , CH_2Cl_2 , 0°C ; 100%. (See ref. [2] for abbreviations.)

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°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 ($\text{BF}_3 \cdot \text{OEt}_2$, Et_3SiH)^[8] afforded bistetrahydropyran **12** in excellent yield (96 %) and diastereoselectivity ($>95:5$).^[5]

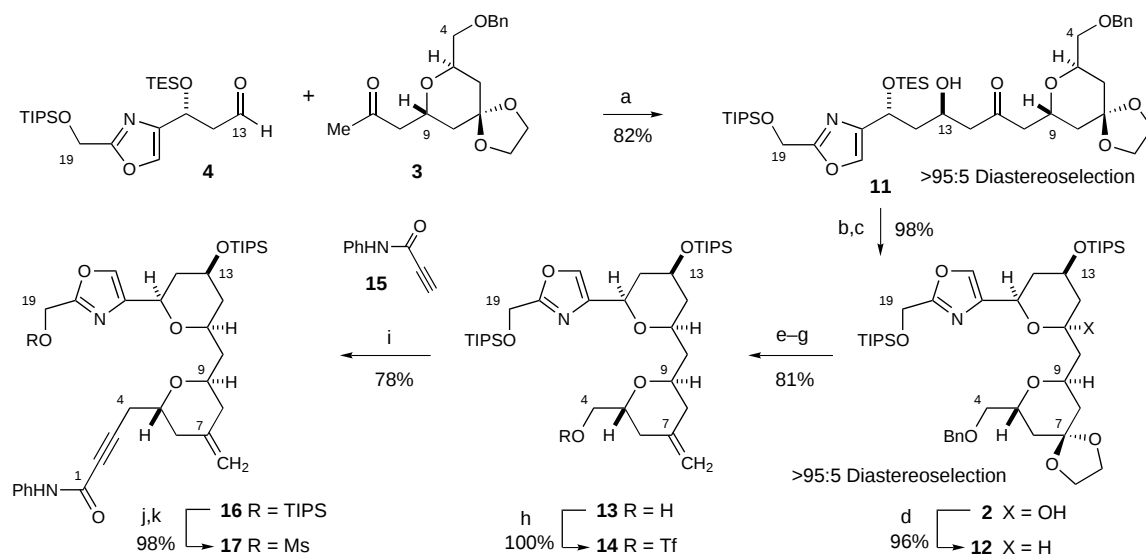
With the requisite stereochemistry incorporated into **12**, some refunctionalization was required to complete the synthesis of this subunit. Ketal hydrolysis ($\text{FeCl}_3 \cdot \text{SiO}_2$)^[21] and debenzoylation were followed by a Wittig olefination to install the C_7 exocyclic olefin. The C_1 – 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°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

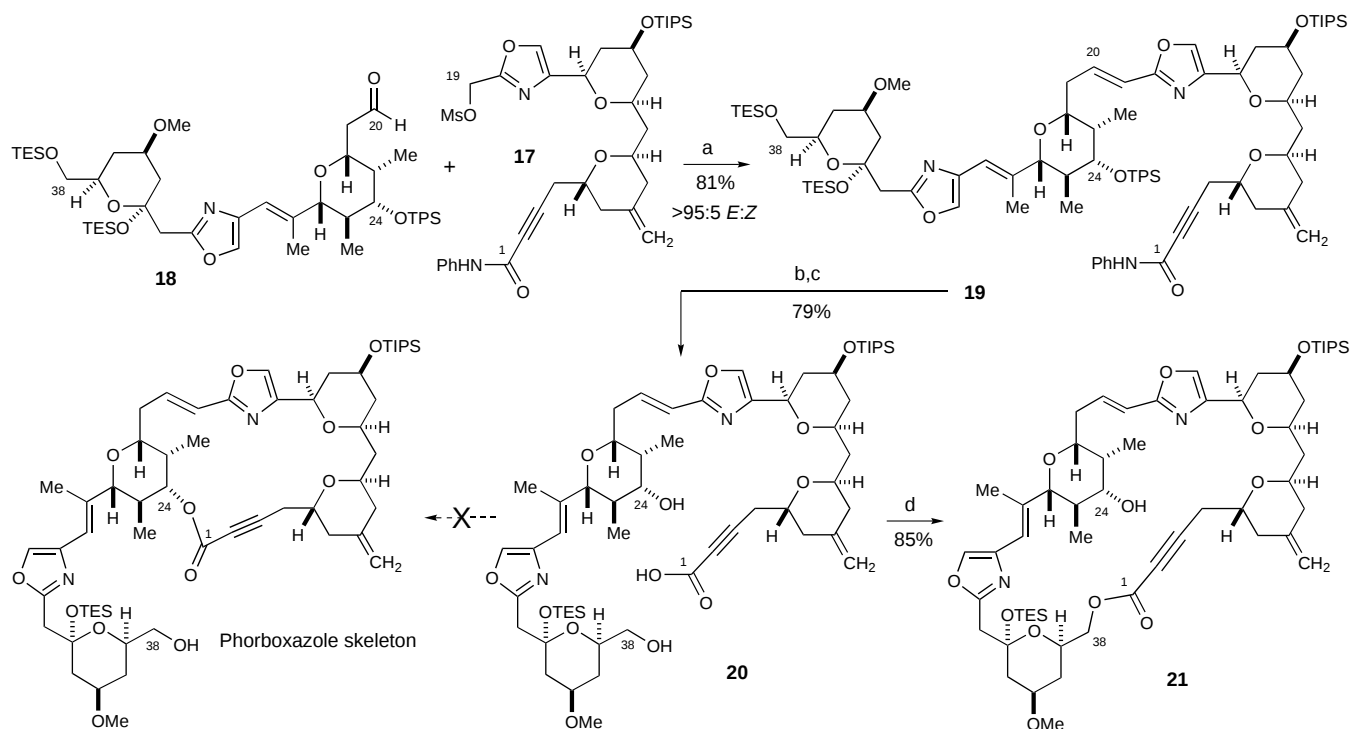
the C_{38} triethylsilyl and C_{24} triphenylsilyl ethers. At this point an effort was made to execute a selective macrolactonization of diol acid **20** in the hope that conformational and entropic effects might favor cyclization onto the desired C_{24} hydroxyl moiety. Unfortunately, cyclization occurred 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**.

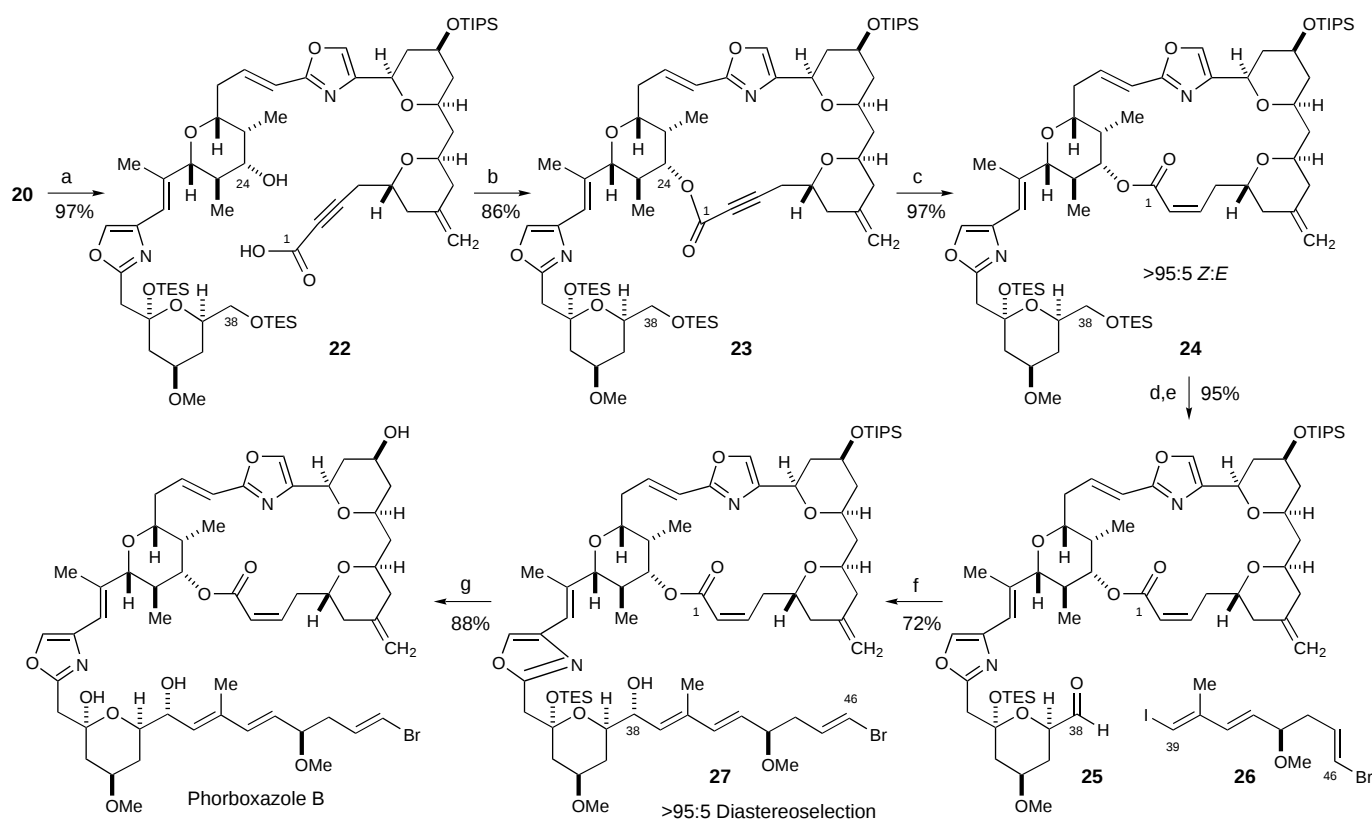
For the final fragment coupling, chelate-controlled addition of a fully functionalized C_{39} – C_{46} alkenylmetal species was required. Under the previously optimized conditions,^[1] site-selective lithium–halogen exchange of vinyl iodide **26**, transmetalation (MgBr_2), and solvent exchange ($\text{Et}_2\text{O} \rightarrow \text{CH}_2\text{Cl}_2$), 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) $n\text{Bu}_2\text{BOTf}$, $i\text{Pr}_2\text{NEt}$, Et_2O , -105°C ; 82%; b) TIPSOTf, lut, CH_2Cl_2 , 0°C ; 99%; c) $\text{HF} \cdot \text{pyr}$, pyr, THF, H_2O , 0°C ; 99%; d) $\text{BF}_3 \cdot \text{OEt}_2$, Et_3SiH , CH_2Cl_2 , $-78 \rightarrow -50^{\circ}\text{C}$; 96%; e) $\text{FeCl}_3 \cdot \text{SiO}_2$, CHCl_3 , acetone, RT; 90%; f) 1 atm H_2 , Pd/C, $i\text{PrOH}$; 100%; g) $\text{Ph}_3\text{PCH}_2\text{Br}$, PhLi , THF, 0°C ; 90%; h) TiF_2O , pyr, CH_2Cl_2 , -5°C ; 100%; i) **15**, $n\text{BuLi}$, THF, -20°C ; then **14**; 78%; j) TBAF, THF, -50°C ; 99%; k) MsCl , $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , -5°C ; 99%. (See ref. [2] for abbreviations.)



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°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) $\text{HF} \cdot \text{pyr}$, pyr, THF, 0°C ; 95%; e) $\text{SO}_3 \cdot \text{pyr}$, Et_3N , DMSO, CH_2Cl_2 ; 100%; f) **26**, $t\text{BuLi}$, Et_2O , -105°C ; then MgBr_2 , -78°C ; then CH_2Cl_2 , **25**; 72%; g) TBAF, THF, 0°C ; 88%. (See ref. [2] for abbreviations.)

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

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